

Supporting Information

Silver-Mediated Oxidative Trifluoromethylation of Alcohols to Alkyl Trifluoromethyl Ethers

Jian-Bo Liu, Xiu-Hua Xu, and Feng-Ling Qing

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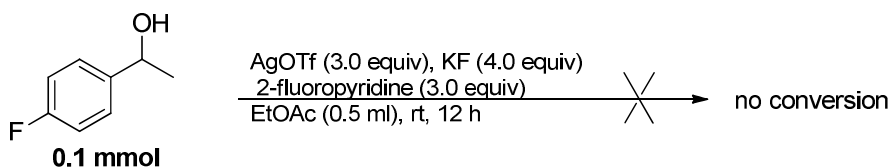
1. General Information

All reactions were carried out under an inert argon atmosphere unless otherwise indicated. Substrates were purchased from commercial sources (Aldrich, Alfa and Chemical Reagent Companies of China) and used as received. Anhydrous ethyl acetate was purchased from J&K. Spray-dried KF was dried at 170°C for 12 h under vacuum prior to use. Unless otherwise noted, all reagents were obtained commercially and used without further purification. ^1H NMR (TMS as the internal standard) and ^{19}F NMR spectra (CFCl_3 as the outside standard and low field is positive) were recorded on a Bruker AM300 or Bruker AM400 spectrometer. ^{13}C NMR was recorded on a Bruker AM400 spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

2. Experimental data

2.1 Preliminary Investigation of Reaction Mechanism

1) No conversion was observed when **1a** was treated with AgOTf, KF, and 2-fluoropyridine, which excluded the formation of alkoxy silver complex



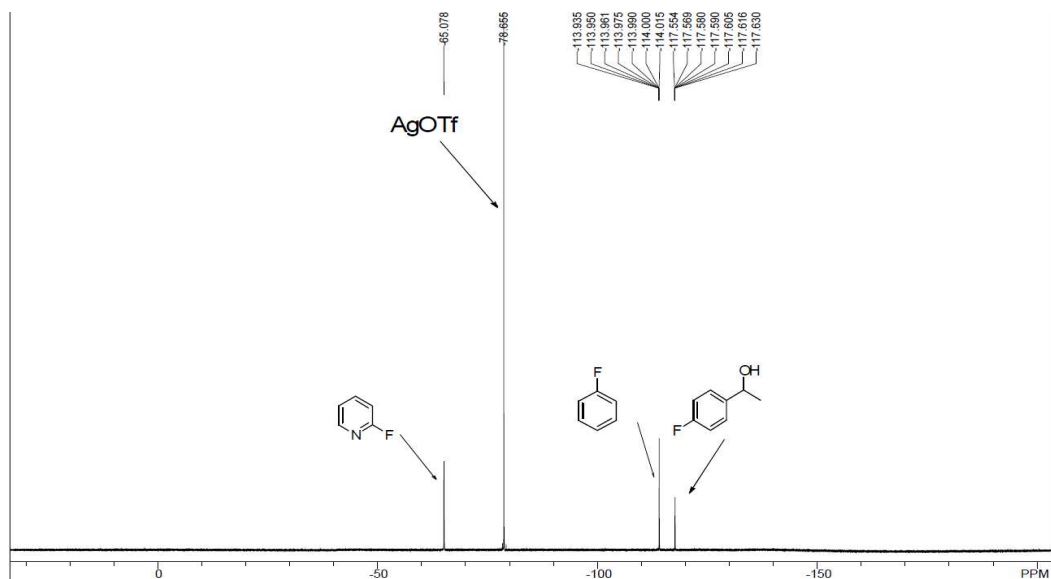
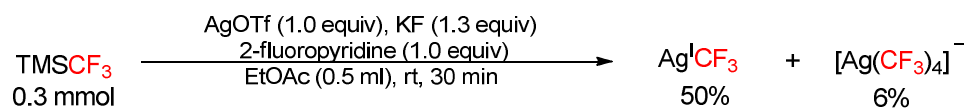


Fig. S1. ^{19}F NMR spectrum of the reaction mixture that **1a** was treated with AgOTf, KF, and 2-fluoropyridine in EtOAc at room temperature for 12 h.

2) Preparation of $\text{Ag}^{\text{I}}\text{CF}_3$ (^{19}F NMR (376 MHz, CDCl_3) δ -22.6 (br, 3F))^{1,2}



1. Tyrra, W.; Naumann, D. *J. Fluorine Chem.* **2004**, *125*, 823.

2. Ye, Y.; Lee, S. H.; Sanford, M. *Org. Lett.* **2011**, *13*, 5464.

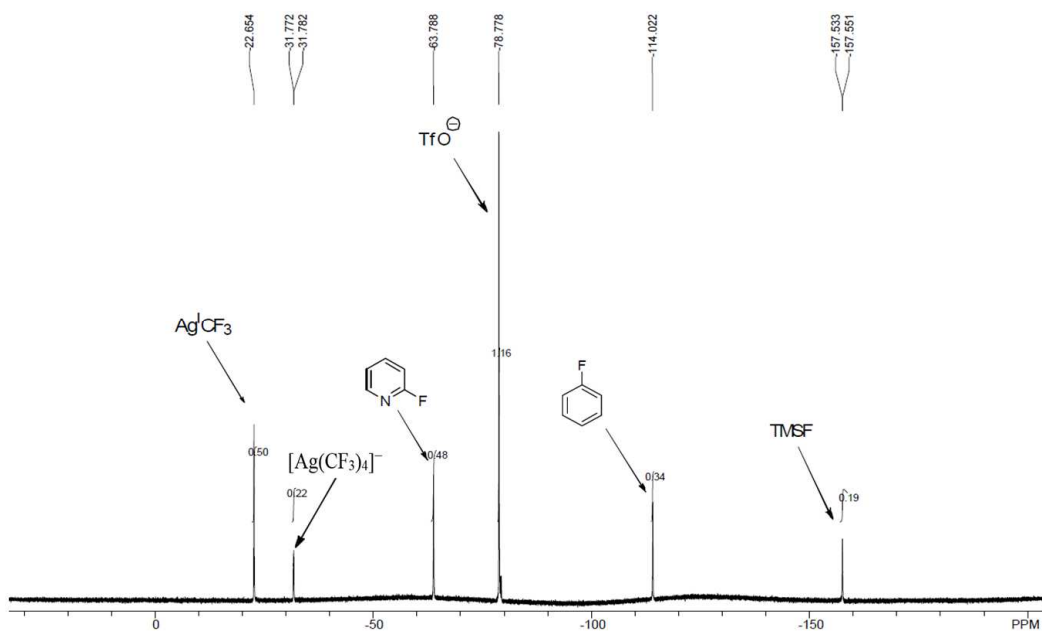


Fig. S2. ^{19}F NMR spectrum of the preparation of Ag^+CF_3^-

3) Oxidative *O*-trifluoromethylation of 1-(4-fluorophenyl)ethanol (**1a**) with pre-generated Ag^+CF_3^- in the presence of selectfluor.

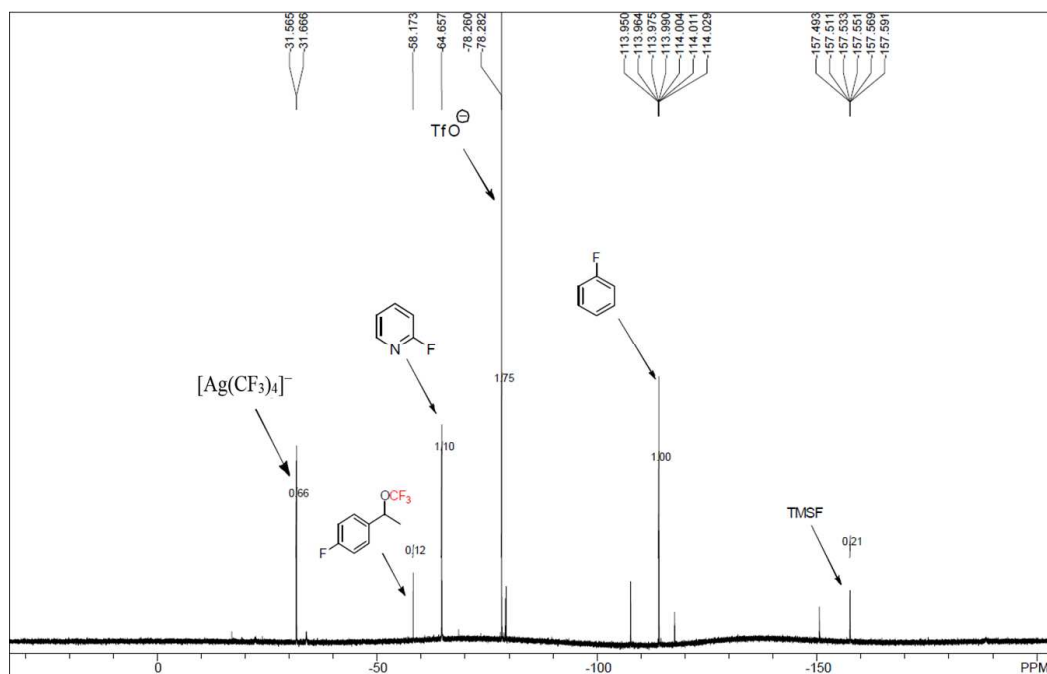
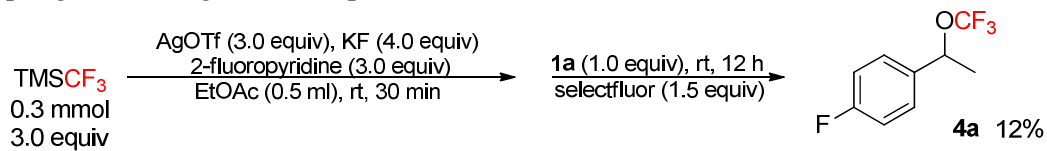


Fig. S3. ^{19}F NMR spectrum of the crude reaction mixture of $\text{Ag}^{\text{I}}\text{CF}_3$ with 1-(4-fluorophenyl)ethanol (**1a**)

4) Preparation of $[\text{Ag}(\text{CF}_3)_4]^-$ (^{19}F NMR (376 MHz, CDCl_3) δ -31.6 (d, $J = 36.8$ Hz, 3F))³

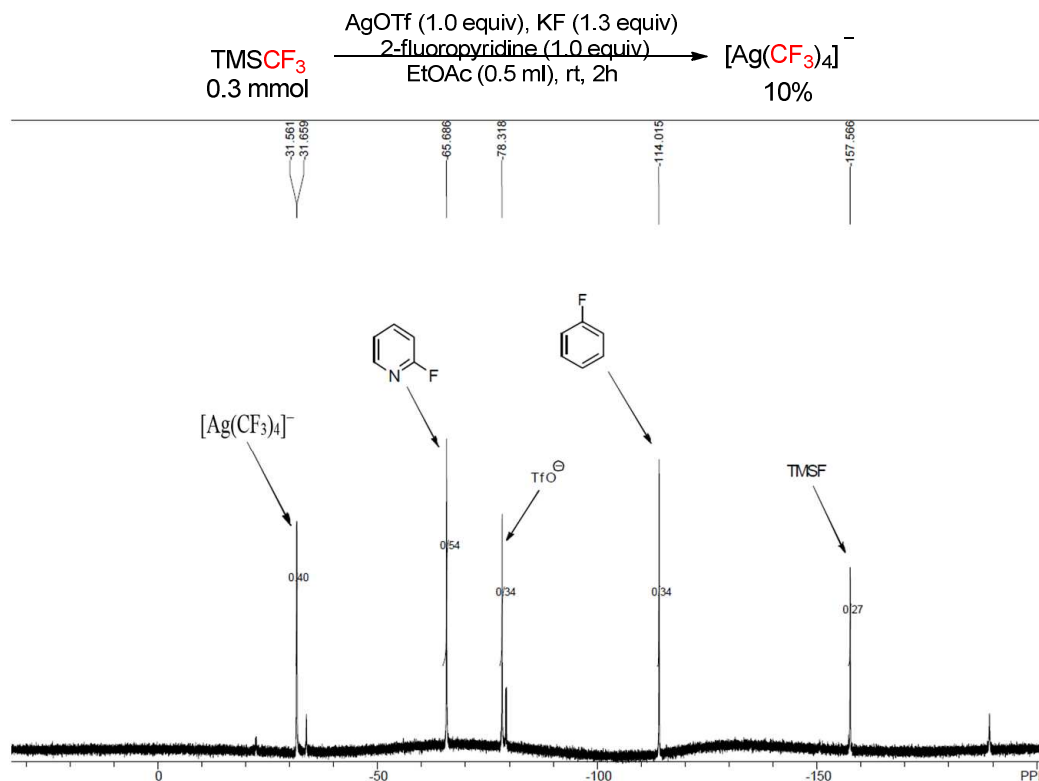
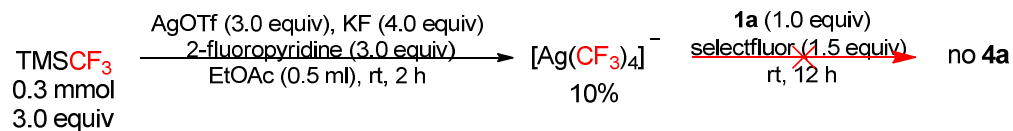


Fig. S4. ^{19}F NMR spectrum of the preparation of $[\text{Ag}(\text{CF}_3)_4]^-$ that TMSCF_3 and $\text{Ag}^{\text{I}}\text{CF}_3$ were totally converted.

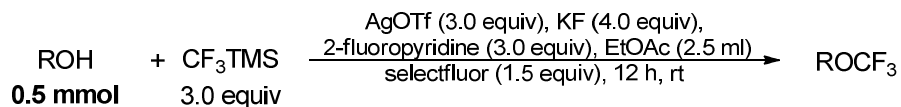
3. Dukat, W.; Naumann, D. *Rev. Chim. Miner.* **1986**, 23, 589.

5) Oxidative trifluoromethylation of 1-(4-fluorophenyl) ethanol (**1a**) with $[\text{Ag}(\text{CF}_3)_4]^-$



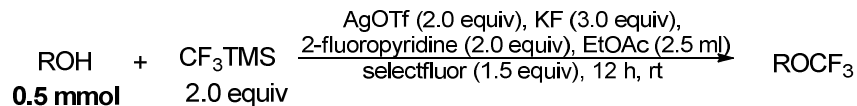
2.2 General Procedure for Silver-mediated Trifluoromethylation of Alcohols

General Procedure A



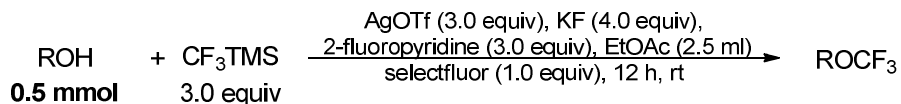
To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (265.7 mg, 0.75 mmol, 1.5 equiv), KF (116.2 mg, 2.0 mmol, 4.0 equiv), alcohol (0.5 mmol, 1.0 equiv) were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) and CF₃TMS (213.3 mg, 1.5 mmol, 3.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether.

General Procedure B



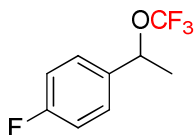
To a reaction tube that was equipped with a stirring bar, AgOTf (256.9 mg, 1.0 mmol, 2.0 equiv), Selectfluor (265.7 mg, 0.75 mmol, 1.5 equiv), KF (87.1 mg, 1.5 mmol, 3.0 equiv), alcohol (0.5 mmol, 1.0 equiv) were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), 2-fluoropyridine (97.1 mg, 1.0 mmol, 2.0 equiv) and CF₃TMS (142.2 mg, 1.0 mmol, 2.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether.

General Procedure C



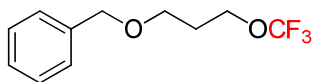
To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (177.1 mg, 0.5 mmol, 1.0 equiv), KF (116.2 mg, 2.0 mmol, 4.0 equiv), alcohol (0.5 mmol, 1.0 equiv) were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) and CF₃TMS (213.3 mg, 1.5 mmol, 3.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with Ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether.

2.3 Characterization Data for Products



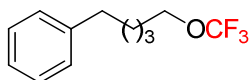
1-Fluoro-4-(1-(trifluoromethoxy)ethyl)benzene (4a).

4a was prepared according to **the general procedure A** in 62% yield as a colourless oil. (*R*_f = 0.75 in hexane). ¹H NMR (400 MHz, CDCl₃) δ 1.62 (d, *J* = 5.6 Hz, 3H), 5.29 (q, *J* = 6.4 Hz, 1H), 7.02-7.10 (m, 2H), 7.30-7.36 (m, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -58.1 (s, 3F), -113.6 (m, 1F). ¹³C NMR (100 MHz, CDCl₃) δ 23.3, 76.5 (q, *J* = 2.4 Hz), 115.6 (d, *J* = 21.2 Hz), 121.6 (q, *J* = 253.8 Hz), 127.6 (d, *J* = 8.8 Hz), 136.3 (d, *J* = 2.9 Hz), 162.7 (d, *J* = 245.8 Hz). IR (neat) ν 2954, 2924, 2853, 1457, 1285, 1242, 1163, 913, 744 cm⁻¹. MS (EI): *m/z* (%) 208 (M⁺, 38.2), 193 (100). HRMS Calculated for C₉H₈OF₄ 208.0511, found [M]⁺ 208.0518.



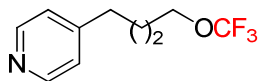
((3-(Trifluoromethoxy)propoxy)methyl)benzene (4b).

4b was prepared according to **the general procedure B** in 70% yield as a colourless oil ($R_f = 0.4$ in hexane). ^1H NMR (400 MHz, CDCl_3) δ 1.92-2.01 (m, 2H), 3.56 (t, $J = 6.0$ Hz, 2H), 4.09 (t, $J = 6.4$ Hz, 2H), 4.50 (s, 2H), 7.27-7.36 (m, 4H). ^{19}F NMR (376 MHz, CDCl_3) δ -60.8 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 29.2, 64.5 (q, $J = 3.2$ Hz), 65.8, 73.2, 121.7 (q, $J = 252.3$ Hz), 127.6, 127.7, 128.4, 138.2. IR (neat) ν 3032, 2866, 2359, 1480, 1455, 1410, 1359, 1330, 1208, 1049, 859, 737, 698, 610 cm^{-1} . MS (EI): m/z (%) 234 (M^+ , 13.4), 91 (100). HRMS Calculated for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{F}_3$ 234.0868, found $[\text{M}]^+$ 234.0866.



(3-(Trifluoromethoxy)propyl)benzene (4c).

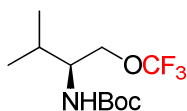
4c was prepared according to **the general procedure B** in 92% yield as a colourless oil ($R_f = 0.75$ in hexane). ^1H NMR (400 MHz, CDCl_3) δ 1.42-1.52 (m, 2H), 1.63-1.78 (m, 4H), 2.66 (t, $J = 8.0$ Hz, 2H), 3.97 (t, $J = 6.4$ Hz, 2H), 7.18-7.35 (m, 5H). ^{19}F NMR (376 MHz, CDCl_3) δ -60.7 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 25.2, 28.7, 31.1, 35.9, 67.5 (q, $J = 3.2$ Hz), 121.9 (q, $J = 251.8$ Hz), 125.9, 128.48, 128.52, 142.4. IR (neat) ν 3064, 3028, 2939, 2862, 1604, 1496, 1454, 1408, 1274, 1138, 1069, 1045, 839, 747, 699 cm^{-1} . MS (EI): m/z (%) 232 (M^+ , 41.2), 91 (100). HRMS Calculated for $\text{C}_{12}\text{H}_{15}\text{OF}_3$ 232.1075, found $[\text{M}]^+$ 232.1072.



4-(3-(Trifluoromethoxy)propyl)pyridine (4d).

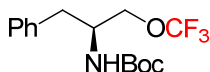
4e was prepared according to **the general procedure A** in 53% yield as a yellow oil ($R_f = 0.6$ in hexane/EtOAc = 1/1). ^1H NMR (400 MHz, CDCl_3) δ 1.66-1.77 (m, 4H), 2.63 (t, $J = 7.2$ Hz, 2H), 3.96 (t, $J = 6.0$ Hz, 2H), 7.09 (dd, $J = 4.4$ Hz, $J = 1.6$ Hz, 2H), 8.48 (dd, $J = 4.4$ Hz, $J = 1.6$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -60.8 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 26.2, 28.1, 34.5, 66.9 (q, $J = 2.9$ Hz), 121.7 (q, $J = 252.6$ Hz), 123.8, 149.8, 150.6. IR (neat) ν 2948, 1603, 1415, 1268, 1220, 1138, 808 cm^{-1} .

MS (EI): m/z (%) 219 (M^+ , 100). HRMS Calculated for $C_{10}H_{12}NOF_3$ 219.0871, found $[M]^+$ 219.0874.



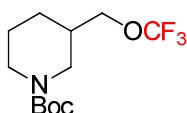
(S)-tert-Butyl (3-methyl-1-(trifluoromethoxy)butan-2-yl)carbamate (4e).

4e was prepared according to **the general procedure B** in 85% yield as a white solid (R_f = 0.8 in hexane/EtOAc = 5/1), mp 56 °C. 1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 6.4 Hz, 6H), 1.41 (s, 9H), 1.75-1.87 (m, 1H), 3.54 (br, 1H), 3.90-4.05 (m, 2H), 4.62 (br, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.0 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.3, 28.3, 28.9, 54.6, 67.3, 79.6, 121.7 (q, J = 252.3 Hz), 155.6. IR (neat) ν 3303, 2974, 2933, 2881, 1681, 1535, 1469, 1391, 1368, 1248, 1217, 1175, 1136, 1051, 1031, 865 cm^{-1} . MS (EI): m/z (%) 271 (M^+ , 0.1), 57 (100). HRMS Calculated for $C_{11}H_{20}NO_3F_3$ 271.1395, found $[M]^+$ 271.1396.



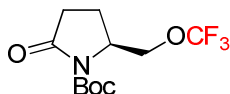
(S)-tert-Butyl (1-phenyl-3-(trifluoromethoxy)propan-2-yl)carbamate (4f).

4f was prepared according to **the general procedure B** in 75% yield as a white solid (R_f = 0.8 in hexane/EtOAc = 5/1), mp 80 °C. 1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.78-2.94 (m, 2H), 3.82-4.08 (m, 3H), 4.76 (br, 1H), 7.16-7.34 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 37.1, 50.6, 67.2, 79.9, 121.7 (q, J = 253.0 Hz), 126.9, 128.7, 129.3, 136.8, 155.1. IR (neat) ν 3367, 3030, 2978, 2934, 1686, 1528, 1451, 1371, 1326, 1283, 1222, 1169, 1136, 1016, 849, 741, 700, 618 cm^{-1} . MS (EI): m/z (%) 319 (M^+ , 1.7), 57 (100). HRMS Calculated for $C_{15}H_{20}NO_3F_3$ 319.1395, found $[M]^+$ 319.1401.



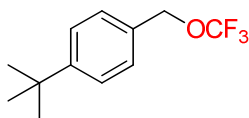
tert-Butyl 3-((trifluoromethoxy)methyl)piperidine-1-carboxylate (4g).

4g was prepared according to **the general procedure B** in 78% yield as a colourless oil ($R_f = 0.7$ in hexane/Et₂O = 4/1). ¹H NMR (400 MHz, CDCl₃) δ 1.20-1.90 (m, 14H), 2.50-3.00 (m, 2H), 3.74-4.10 (m, 4H). ¹⁹F NMR (376 MHz, CDCl₃) δ -61.1 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 23.9, 26.7, 28.3, 35.1, 44.4, 46.1, 68.9, 79.6, 121.6 (q, $J = 252.3$ Hz), 154.8. IR (neat) ν 2977, 2935, 2862, 1697, 1475, 1422, 1367, 1270, 1149, 1041, 970, 858, 770 cm⁻¹. MS (EI): m/z (%) 283 (M⁺, 26.5), 57 (100). HRMS Calculated for C₁₂H₂₀NO₃F₃ 283.1395, found [M]⁺ 283.1398.



(S)-tert-Butyl 2-oxo-5-((trifluoromethoxy)methyl)pyrrolidine-1-carboxylate (4h).

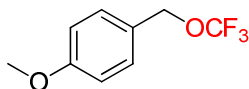
4h was prepared according to **the general procedure A** in 70% yield as colourless oil ($R_f = 0.4$ in hexane/EtOAc = 5/1). ¹H NMR (400 MHz, CDCl₃) δ 1.44 (s, 9H), 2.00-2.09 (m, 1H), 2.21-2.44 (m, 2H), 2.56-2.70 (m, 1H), 4.07-4.25 (m, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -56.8 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 22.2, 27.6, 30.2, 55.5, 66.7, 83.0, 119.3 (q, $J = 262.0$ Hz), 153.0, 173.9. IR (neat) ν 2983, 1751, 1460, 1372, 1292, 1157, 970, 858, 792, 654, 599 cm⁻¹. MS (EI): m/z (%) 268 ([M-CH₃]⁺, 5.1), 152 (100). HRMS Calculated for C₁₀H₁₃NO₄F₃ [M-CH₃]⁺ 268.0797, found [M]⁺ 268.0800.



1-(tert-Butyl)-4-((trifluoromethoxy)methyl)benzene (4i).

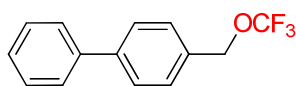
4i was prepared according to **the general procedure B** in 74% yield as a colourless oil ($R_f = 0.75$ in hexane). ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 9H), 4.97 (s, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -60.3 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 31.3, 34.7, 69.5 (q, $J = 3.7$ Hz), 121.7 (q, $J = 253.8$ Hz), 125.7, 128.1, 130.9, 152.2. IR (neat) ν 2966, 2907, 2872, 1618, 1519, 1468, 1396, 1277, 1208, 1144, 1017, 850, 827, 614 cm⁻¹. MS (EI): m/z (%) 232 (M⁺,

17.8), 217 (M^+ , 100). HRMS Calculated for $C_{12}H_{15}OF_3$ 232.1075, found $[M]^+$ 232.1079.



1-Methoxy-4-((trifluoromethoxy)methyl)benzene (4j).

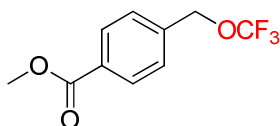
To a reaction tube that was equipped with a stirring bar, AgOTf (256.9 mg, 1.0 mmol, 2.0 equiv), Selectfluor (265.7 mg, 0.75 mmol, 1.5 equiv), KF (87.1 mg, 1.5 mmol, 3.0 equiv), 2,6-di-*tert*-butylphenol (51.5 mg, 0.25 mmol, 0.5 equiv) were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), alcohol **1j** (69.1mg, 0.5 mmol, 1.0 equiv), 2-fluoropyridine (97.1 mg, 1.0 mmol, 2.0 equiv) and CF_3TMS (142.2 mg, 1.0 mmol, 2.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of silica (eluted with Ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether **4j** in 82% yield as a yellow oil (R_f = 0.4 in hexane). 1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.91 (s, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.1 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 69.1 (q, J = 3.4 Hz), 141.1, 121.6 (q, J = 257.4 Hz), 125.9, 130.1, 160.2. IR (neat) ν 2963, 2910, 2840, 1615, 1518, 1466, 1395, 1250, 1176, 1140, 1035, 843, 824, 609 cm^{-1} . MS (EI): m/z (%) 206 (M^+ , 50.2), 121 (M^+ , 100). HRMS Calculated for $C_9H_9O_2F_3$ 206.0555, found $[M]^+$ 206.0559.



4-((Trifluoromethoxy)methyl)-1,1'-biphenyl (4k).

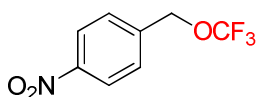
4k was prepared according to the general procedure B in 76% yield as a white solid (R_f = 0.7 in hexane), mp 64 °C. 1H NMR (300 MHz, $CDCl_3$) δ 5.05 (s, 2H), 7.36-7.53 (m, 5H), 7.59-7.68 (m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.6 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.9 (q, J = 3.4 Hz), 121.8 (q, J = 253.8 Hz), 127.2, 127.5, 127.7,

128.6, 128.9, 132.8, 140.5, 142.0. IR (neat) ν 3059, 3034, 2969, 2910, 1568, 1489, 1403, 1267, 1234, 1208, 1128, 1008, 909, 882, 826, 762, 734, 691, 650 cm^{-1} . MS (EI): m/z (%) 252 (M^+ , 100). HRMS Calculated for $\text{C}_{14}\text{H}_{11}\text{OF}_3$ 252.0762, found $[\text{M}]^+$ 252.0763.



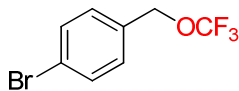
Methyl 4-((trifluoromethoxy)methyl)benzoate (4l).

4l was prepared according to **the general procedure C** in 68% yield as a colourless oil (R_f = 0.75 in hexane/EtOAc = 7/1). ^1H NMR (300 MHz, CDCl_3) δ 3.92 (s, 3H), 5.03 (s, 2H), 7.42 (d, J = 8.1 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -61.0 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 52.2, 68.2 (q, J = 3.7 Hz), 121.7 (q, J = 254.5 Hz), 127.4, 130.0, 130.6, 138.7, 166.6. IR (neat) ν 2957, 2907, 2847, 1725, 1618, 1514, 1438, 1392, 1278, 1204, 1146, 1110, 1020, 845, 804, 758, 707, 612 cm^{-1} . MS (EI): m/z (%) 234 (M^+ , 32.3), 203 (M^+ , 100). HRMS Calculated for $\text{C}_{10}\text{H}_9\text{O}_3\text{F}_3$ 234.0504, found $[\text{M}]^+$ 234.0505.



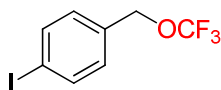
1-Nitro-4-((trifluoromethoxy)methyl)benzene (4m).

4m was prepared according to **the general procedure C** in 44% yield as a yellow oil (R_f = 0.7 in hexane/EtOAc = 7/1). ^1H NMR (300 MHz, CDCl_3) δ 5.11 (s, 2H), 7.56 (d, J = 8.4 Hz, 2H), 8.27 (d, J = 8.7 Hz, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -61.2 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 67.4 (q, J = 3.7 Hz), 121.6 (q, J = 255.2 Hz), 124.0, 128.1, 140.9, 148.2. IR (neat) ν 3086, 2865, 1610, 1526, 1350, 1267, 1204, 1147, 1016, 861, 841, 739, 701 cm^{-1} . MS (EI): m/z (%) 221 (M^+ , 100). HRMS Calculated for $\text{C}_8\text{H}_6\text{NO}_3\text{F}_3$ 221.0300, found $[\text{M}]^+$ 221.0296.



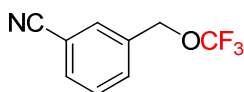
1-Bromo-4-((trifluoromethoxy)methyl)benzene (4n).

4n was prepared according to **the general procedure B** in 80% yield as a colourless oil ($R_f = 0.8$ in hexane). ^1H NMR (300 MHz, CDCl_3) δ 4.93 (s, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -60.9 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 68.3 (q, $J = 3.7$ Hz), 121.7 (q, $J = 253.8$ Hz), 123.1, 129.6, 131.9, 132.9. IR (neat) ν 2968, 2908, 1901, 1598, 1491, 1468, 1388, 1271, 1204, 1146, 1072, 1013, 830, 805, 610 cm^{-1} . MS (EI): m/z (%) 254 (M^+ , 54.9), 175 (M^+ , 100). HRMS Calculated for $\text{C}_8\text{H}_6\text{OF}_3\text{Br}$ 253.9554, found $[\text{M}]^+$ 253.9548.



1-Iodo-4-((trifluoromethoxy)methyl)benzene (4o).

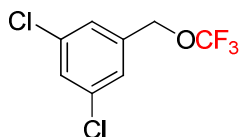
4o was prepared according to **the general procedure B** in 82% yield as a colourless oil ($R_f = 0.8$ in hexane). ^1H NMR (400 MHz, CDCl_3) δ 4.91 (s, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 7.72 (d, $J = 7.6$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -60.5 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 68.3 (q, $J = 3.7$ Hz), 94.7, 121.6 (q, $J = 254.5$ Hz), 129.7, 133.5, 137.9. IR (neat) ν 2966, 2906, 1902, 1594, 1488, 1467, 1384, 1267, 1203, 1145, 1009, 827, 801, 602 cm^{-1} . MS (EI): m/z (%) 302 (M^+ , 100). HRMS Calculated for $\text{C}_8\text{H}_6\text{OF}_3\text{I}$ 301.9416, found $[\text{M}]^+$ 301.9424.



3-((Trifluoromethoxy)methyl)benzonitrile (4p).

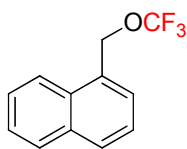
4p was prepared according to **the general procedure C** in 61% yield as a colourless oil ($R_f = 0.6$ in hexane/EtOAc = 7/1). ^1H NMR (300 MHz, CDCl_3) δ 5.01 (s, 2H), 7.50-7.68 (m, 4H). ^{19}F NMR (282 MHz, CDCl_3) δ -61.1 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 67.6 (q, $J = 3.6$ Hz), 113.1, 118.2, 121.6 (q, $J = 253.3$ Hz), 129.7, 131.1, 131.9, 132.4, 135.5. IR (neat) ν 2968, 2234, 1487, 1396, 1273, 1215, 1147, 1027, 797,

690 cm^{-1} . MS (EI): m/z (%) 201 (M^+ , 100). HRMS Calculated for $\text{C}_9\text{H}_6\text{NOF}_3$ 201.0401, found $[\text{M}]^+$ 201.0406.



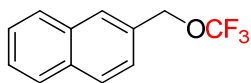
1,3-Dichloro-5-((trifluoromethoxy)methyl)benzene (4q).

4q was prepared according to **the general procedure C** in 56% yield as a colourless oil (R_f = 0.8 in hexane). ^1H NMR (300 MHz, CDCl_3) δ 4.92 (s, 2H), 7.25 (d, J = 0.9 Hz, 2H), 7.36 (s, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ -61.2 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 67.2 (q, J = 3.6 Hz), 121.6 (q, J = 255.3 Hz), 126.0, 129.0, 135.4, 137.1. IR (neat) ν 3083, 2927, 2359, 1596, 1574, 1438, 1388, 1266, 1241, 1150, 1032, 850, 801, 669 cm^{-1} . MS (EI): m/z (%) 244 (M^+ , 49.9), 209 (100). HRMS Calculated for $\text{C}_8\text{H}_5\text{OF}_3\text{Cl}_2$ 243.9670, found $[\text{M}]^+$ 243.9668.



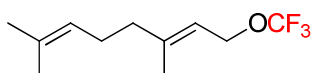
1-((Trifluoromethoxy)methyl)naphthalene (4r).

4r was prepared according to **the general procedure B** in 73% yield as a colourless oil (R_f = 0.75 in hexane). ^1H NMR (300 MHz, CDCl_3) δ 5.41 (s, 2H), 7.42-7.58 (m, 4H), 7.87 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.4 Hz, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ -60.7 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 67.6 (q, J = 3.7 Hz), 121.6 (q, J = 254.5 Hz), 123.2, 125.2, 126.2, 127.0, 127.7, 128.9, 129.4, 130.2, 131.4, 133.8. IR (neat) ν 3053, 2971, 2934, 1514, 1407, 1264, 1214, 1141, 1008, 852, 798, 775, 584 cm^{-1} . MS (EI): m/z (%) 226 (M^+ , 100). HRMS Calculated for $\text{C}_{12}\text{H}_9\text{OF}_3$ 226.0605, found $[\text{M}]^+$ 226.0596.



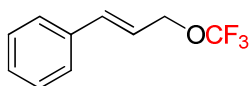
2-((Trifluoromethoxy)methyl)naphthalene (4s).

4s was prepared according to **the general procedure B** in 80% yield as a white solid ($R_f = 0.75$ in hexane), mp 54 °C. ^1H NMR (300 MHz, CDCl_3) δ 5.16 (s, 2H), 7.44-7.58 (m, 3H), 7.82-7.92 (m, 4H). ^{19}F NMR (282 MHz, CDCl_3) δ -60.6 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 69.3 (q, $J = 3.7$ Hz), 121.8 (q, $J = 253.7$ Hz), 125.3, 126.6, 126.7, 127.4, 127.8, 128.1, 128.7, 131.3, 133.1, 133.4. IR (neat) ν 3062, 2962, 1601, 1509, 1406, 1259, 1204, 1125, 1024, 857, 823, 756, 740, 667 cm^{-1} . MS (EI): m/z (%) 226 (M^+ , 100). HRMS Calculated for $\text{C}_{12}\text{H}_9\text{OF}_3$ 226.0605, found $[\text{M}]^+$ 226.0599.



(E)-3,7-Dimethyl-1-(trifluoromethoxy)octa-2,6-diene (4t).

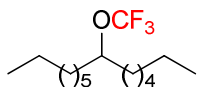
4t was prepared according to **the general procedure B** in 75% yield as a colourless oil ($R_f = 0.8$ in hexane). ^1H NMR (300 MHz, CDCl_3) δ 1.61 (s, 3H), 1.69 (s, 3H), 1.71 (s, 3H), 2.02-2.15 (m, 4H), 4.49 (d, $J = 7.2$ Hz, 2H), 5.08 (br, 1H), 5.37 (t, $J = 7.2$ Hz, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ -60.1 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 16.4, 17.6, 25.6, 26.1, 39.4, 64.1 (q, $J = 3.6$ Hz), 116.8, 121.8 (q, $J = 253.0$ Hz), 123.5, 132.1, 144.1. IR (neat) ν 2970, 2925, 2859, 1672, 1447, 1385, 1262, 1140, 1005, 882, 841 cm^{-1} . MS (EI): m/z (%) 222 (M^+ , 6.1), 69 (100). HRMS Calculated for $\text{C}_{11}\text{H}_{17}\text{OF}_3$ 222.1232, found $[\text{M}]^+$ 222.1237.



(E)-(3-(Trifluoromethoxy)prop-1-en-1-yl)benzene (4u).

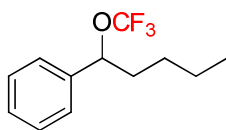
4u was prepared according to **the general procedure B** in 50% yield as a colourless oil ($R_f = 0.8$ in hexane). ^1H NMR (300 MHz, CDCl_3) δ 4.62 (dd, $J = 6.3$ Hz, $J = 1.2$ Hz, 2H), 6.20-6.31 (m, 1H), 6.70 (d, $J = 15.9$ Hz, 1H), 7.22-7.44 (m, 5H). ^{19}F NMR (282 MHz, CDCl_3) δ -60.5 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 68.0 (q, $J = 3.7$ Hz), 121.4, 121.8 (q, $J = 253.8$ Hz), 126.8, 128.5, 128.7, 135.2, 135.7. IR (neat) ν 3030, 2960, 1497, 1464, 1398, 1265, 1216, 1142, 1014, 967, 875, 746, 692 cm^{-1} . MS (EI):

m/z (%) 202 (M^+ , 90.3), 117 (M^+ , 100). HRMS Calculated for $C_{10}H_9OF_3$ 202.0605, found $[M]^+$ 202.0608.



4-(Trifluoromethoxy)heptane (4v).

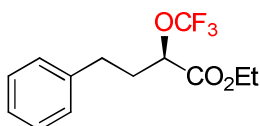
4v was prepared according to **the general procedure A** in 51% yield as a colourless oil (R_f = 0.8 in hexane). 1H NMR (400 MHz, $CDCl_3$) δ 0.83-0.90 (m, 6H), 1.24-1.38 (m, 18H), 1.55-1.64 (m, 4H), 4.10-4.20 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.00, 14.02, 22.55, 22.62, 24.71, 24.75, 29.10, 29.14, 29.40, 31.7, 31.8, 34.2, 80.3, 121.8 (q, J = 251.6 Hz). IR (neat) ν 2956, 2929, 2859, 1467, 1380, 1283, 1218, 1134, 840, 724 cm^{-1} . MS (EI): m/z (%) 196 ($[M-CF_3OH]^+$, 9.4), 69 (M^+ , 100). HRMS Calculated for $C_{14}H_{28}$ ($[M-CF_3OH]^+$) 196.2191, found $[M]^+$ 196.2196.



(1-(Trifluoromethoxy)pentyl)benzene (4w).

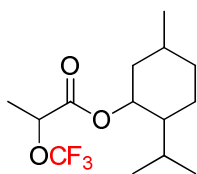
To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (265.7 mg, 0.75 mmol, 1.5 equiv), KF (116.2 mg, 2.0 mmol, 4.0 equiv), 2,6-di-*tert*-butylphenol (51.5mg, 0.25 mmol, 0.5equiv) were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), alcohol **1w** (82.1 mg, 0.5 mmol, 1.0 equiv), 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) and CF_3TMS (213.3 mg, 1.5 mmol, 3.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature. After 12 h, the reaction mixture was filtered through a plug of silica (eluted with Ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether **4w** in 87% yield as a colourless oil (R_f

= 0.8 in hexane). ^1H NMR (300 MHz, CDCl_3) δ 0.90 (t, J = 6.9 Hz, 3H), 1.24-1.40 (m, 4H), 1.78-1.86 (m, 1H), 1.92-2.02 (m, 1H), 5.08 (t, J = 6.9 Hz, 1H), 7.30-7.43 (m, 5H). ^{19}F NMR (282 MHz, CDCl_3) δ -58.2 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 13.8, 22.3, 27.4, 37.1, 81.2, 121.8 (q, J = 253.8 Hz), 126.1, 128.3, 128.5, 139.8. IR (neat) ν 3035, 2960, 2866, 1457, 1275, 1211, 1142, 1045, 1003, 852, 760, 699 cm^{-1} . MS (EI): m/z (%) 232 (M^+ , 16.3), 175 (M^+ , 100). HRMS Calculated for $\text{C}_{12}\text{H}_{15}\text{OF}_3$ 232.1075, found $[\text{M}]^+$ 232.1068.



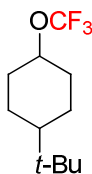
(R)-Ethyl 4-phenyl-2-(trifluoromethoxy)butanoate (4x).

To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (265.7 mg, 0.75 mmol, 1.5 equiv), KF (116.2 mg, 2.0 mmol, 4.0 equiv), 2,6-di-*tert*-butylphenol (51.5mg, 0.25 mmol, 0.5equiv) were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), alcohol **1x** (104.1 mg, 0.5 mmol, 1.0 equiv), 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) and CF_3TMS (213.3 mg, 1.5 mmol, 3.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature. After 12 h, the reaction mixture was filtered through a plug of silica (eluted with Ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether. **4x** in 54% yield as a yellow oil (R_f = 0.65 in hexane/EtOAc = 20/1). ^1H NMR (400 MHz, CDCl_3) δ 1.28 (t, J = 7.2 Hz, 3H), 2.17 (q, J = 7.6 Hz, 2H), 2.70-2.80 (m, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.56 (t, J = 6.0 Hz, 1H), 7.15-7.32 (m, 5H). ^{19}F NMR (376 MHz, CDCl_3) δ -59.5 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 30.7, 33.7, 61.8, 74.9, 121.5 (q, J = 255.0 Hz), 126.4, 128.4, 128.6, 139.8, 169.0. IR (neat) ν 3030, 2984, 2940, 2871, 1763, 1743, 1604, 1498, 1456, 1370, 1281, 1225, 1150, 1088, 1030, 877, 854, 745, 700 cm^{-1} . MS (EI): m/z (%) 276 (M^+ , 36.5), 172 (M^+ , 100). HRMS Calculated for $\text{C}_{13}\text{H}_{15}\text{O}_3\text{F}_3$ 276.0973, found $[\text{M}]^+$ 276.0967.



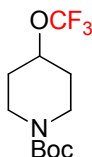
2-Isopropyl-5-methylcyclohexyl 2-(trifluoromethoxy)propanoate (4y).

4y was prepared according to **the general procedure A** in 68% yield as a yellow oil ($R_f = 0.8$ in hexane/EtOAc = 20/1). ^1H NMR (400 MHz, CDCl_3) δ 0.74 (d, $J = 7.2$ Hz, 3H), 0.84-1.07 (m, 9H), 1.37-1.54 (m, 5H), 1.60-2.00 (m, 4H), 4.63 (q, $J = 6.8$ Hz, 1H), 4.75 (td, $J = 11.2$ Hz, $J = 4.8$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -59.8 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 16.1, 18.1, 20.6, 21.9, 23.4, 26.3, 31.3, 34.1, 40.4, 46.9, 72.1 (q, $J = 2.9$ Hz), 75.9, 121.4 (q, $J = 255.3$ Hz), 169.0. IR (neat) ν 2958, 2873, 1763, 1740, 1458, 1389, 1371, 1282, 1232, 1150, 1121, 1047, 981, 959, 916, 900, 846 cm^{-1} . MS (EI): m/z (%) 295 ($[\text{M}-\text{H}]^+$, 0.1), 95 (M^+ , 100). HRMS Calculated for $\text{C}_{14}\text{H}_{22}\text{O}_3\text{F}_3$ ($[\text{M}-\text{H}]^+$) 295.1521, found $[\text{M}]^+$ 295.1518.



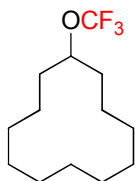
1-(tert-Butyl)-4-(trifluoromethoxy)cyclohexane (4z).

4z was prepared according to **the general procedure A** in 85% yield (dr = 73 : 27) as a colourless oil ($R_f = 0.8$ in hexane). ^1H NMR (300 MHz, CDCl_3) δ 0.85 (s, 9H), 0.96-1.70 (m, 5.5H), 1.80- 2.15 (m, 3.5H), 4.00-4.14 (m, 0.75H), 4.50 (s, 0.2H). ^{19}F NMR (282 MHz, CDCl_3) δ -58.0 (s, 3F), -58.1 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 21.0, 22.6, 25.4, 27.4, 27.5, 29.7, 31.4, 31.6, 32.2, 32.5, 32.9, 46.7, 47.4, 74.6 (q, $J = 2.2$ Hz), 78.6, 121.7 (q, $J = 252.3$ Hz), 121.9 (q, $J = 251.6$ Hz). IR (neat) ν 2955, 2870, 1480, 1470, 1455, 1367, 1335, 1290, 1216, 1133, 1048, 1028, 860 cm^{-1} . MS (EI): m/z (%) 224 (M^+ , 1.3), 57 (M^+ , 100). HRMS Calculated for $\text{C}_{11}\text{H}_{19}\text{OF}_3$ 224.1388, found $[\text{M}]^+$ 224.1380.



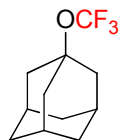
tert-Butyl 4-(trifluoromethoxy)piperidine-1-carboxylate (4aa).

4aa was prepared according to **the general procedure A** in 60% yield as a colourless oil ($R_f = 0.7$ in hexane/Et₂O = 4/1). ¹H NMR (300 MHz, CDCl₃) δ 1.46 (s, 9H), 1.70-1.95 (m, 4H), 3.22-3.33 (m, 2H), 3.64-3.75 (m, 2H), 4.36-4.46 (m, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ -58.4 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 28.8, 31.8, 40.9, 74.9 (q, $J = 2.9$ Hz), 80.4, 122.1 (q, $J = 253.0$ Hz), 155.1. IR (neat) ν 2975, 2872, 1698, 1479, 1423, 1367, 1285, 1241, 1218, 1171, 1135, 1032, 993, 861, 843, 770 cm⁻¹. MS (EI): m/z (%) 269 (M⁺, 17.7), 57 (M⁺, 100). HRMS Calculated for C₁₁H₁₈NO₃F₃ 269.1239, found [M]⁺ 269.1243.



(Trifluoromethoxy)cyclododecane (4ab).

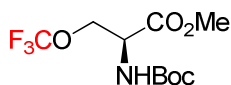
4ab was prepared according to **the general procedure A** in 81% yield as a colourless oil ($R_f = 0.8$ in hexane). ¹H NMR (400 MHz, CDCl₃) δ 1.30-1.50 (m, 18H), 1.52-1.65 (m, 2H), 1.71-1.83 (m, 2H), 4.30-4.38 (m, 1H). ¹⁹F NMR (376 MHz, CDCl₃) δ -57.7 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 20.5, 23.1, 23.3, 23.8, 24.0, 29.8, 77.9, 121.8 (q, $J = 251.6$ Hz). IR (neat) ν 2935, 2866, 1471, 1448, 1285, 1211, 1131, 1004, 834 cm⁻¹. MS (EI): m/z (%) 252 (M⁺, 3.2), 83 (M⁺, 100). HRMS Calculated for C₁₃H₂₃OF₃ 252.1701, found [M]⁺ 252.1708.



(3s,5s,7s)-1-(Trifluoromethoxy)adamantane (4ac).

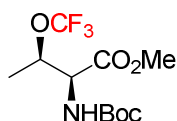
4ac was prepared according to **the general procedure A** in 41% yield as a yellow oil

(R_f = 0.8 in hexane). ^1H NMR (400 MHz, CDCl_3) δ 1.63 (s, 6H), 2.00 (s, 6H), 2.19 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -49.1 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 30.9, 35.7, 42.3, 83.4, 121.5 (q, J = 254.5 Hz). IR (neat) ν 2919, 2857, 1456, 1325, 1317, 1259, 1200, 1181, 1132, 1059, 840, 651 cm^{-1} . MS (EI): m/z (%) 220 (M^+ , 81), 163 (100). HRMS Calculated for $\text{C}_{11}\text{H}_{15}\text{OF}_3$ 220.1075, found $[\text{M}]^+$ 220.1069.



(S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-(trifluoromethoxy)propanoate (4ad).

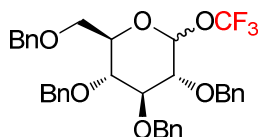
4ad was prepared according to **the general procedure A** in 56% yield as a colourless oil (R_f = 0.6 in hexane/EtOAc = 5/1). ^1H NMR (400 MHz, CDCl_3) δ 1.44 (s, 9H), 3.78 (s, 3H), 4.20-4.37 (m, 2H), 4.54 (d, J = 8.0 Hz, 1H), 5.35 (d, J = 7.2 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -61.2 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 28.2, 52.8, 52.9, 67.1, 80.6, 121.4 (q, J = 253.8 Hz), 155.1, 169.2. IR (neat) ν 3375, 2981, 1754, 1719, 1507, 1440, 1369, 1254, 1220, 1163, 1062, 1036, 867 cm^{-1} . MS (EI): m/z (%) 287 (M^+ , 0.04), 57 (M^+ , 100). HRMS Calculated for $\text{C}_{10}\text{H}_{16}\text{NO}_5\text{F}_3$ 287.0981, found $[\text{M}]^+$ 287.0987.



(2S,3R)-Methyl 2-((tert-butoxycarbonyl)amino)-3-(trifluoromethoxy)butanoate (4ae).

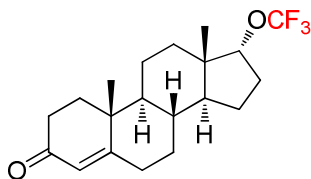
4ae was prepared according to **the general procedure A** in 31% yield as a colourless oil (R_f = 0.6 in hexane/EtOAc = 5/1). ^1H NMR (400 MHz, CDCl_3) δ 1.39 (d, J = 6.4 Hz, 3H), 1.44 (s, 9H), 3.75 (s, 3H), 4.43 (d, J = 9.6 Hz, 1H), 4.85 (q, J = 6.4 Hz, 1H), 5.19 (d, J = 10.0 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -58.7 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 17.8, 28.2, 52.7, 57.4, 75.8, 80.5, 121.4 (q, J = 253.8 Hz), 155.9, 169.7. IR (neat) ν 3376, 2982, 1758, 1720, 1508, 1439, 1369, 1284, 1225, 1165, 1063,

1000, 859 cm^{-1} . MS (EI): m/z (%) 301 (M^+ , 0.04), 57 (M^+ , 100). HRMS Calculated for $\text{C}_{11}\text{H}_{18}\text{NO}_5\text{F}_3$ 301.1137, found $[\text{M}]^+$ 301.1135.



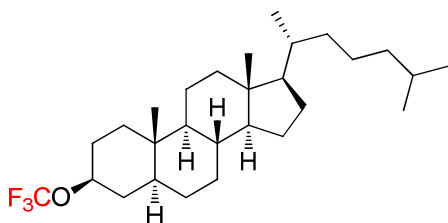
(2*R*,3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-(trifluoromethoxy)tetrahydro-2*H*-pyran (4af).

To a reaction tube that was equipped with a stirring bar, AgOTf (385.4 mg, 1.5 mmol, 3.0 equiv), Selectfluor (265.7 mg, 0.75 mmol, 1.5 equiv), KF (116.2 mg, 2.0 mmol, 4.0 equiv), 2,6-di-*tert*-butylphenol (51.5 mg, 0.25 mmol, 0.5 equiv), were added successively in a nitrogen-filled glovebox. Then ethyl acetate (2.5 mL), alcohol **1af** (270.3 mg, 0.5 mmol, 1.0 equiv), 2-fluoropyridine (145.5 mg, 1.5 mmol, 3.0 equiv) and CF_3TMS (213.3 mg, 1.5 mmol, 3.0 equiv) were added successively under Ar atmosphere. The reaction mixture was stirred at room temperature. After 12 h, the reaction mixture was filtered through a plug of silica (eluted with Ethyl acetate). The filtrate was concentrated, and the product was purified by column chromatography on silica gel to give the alkyl trifluoromethyl ether **4af** in 41% yield as a colourless oil (R_f = 0.8 in hexane/EtOAc = 2/1, dr = 5:1). ^1H NMR (300 MHz, CDCl_3) δ 3.50-4.00 (m, 6H), 4.58-5.56 (m, 9H), 7.15-7.37 (m, 20H). ^{19}F NMR (282 MHz, CDCl_3) δ -57.9 (s, 3F), -58.3 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 67.8, 68.1, 72.5, 73.6, 75.1, 75.4, 75.8, 75.9, 76.7, 77.0, 77.1, 77.4, 78.4, 80.8, 81.2, 84.3, 98.9, 121.4 (q, J = 257.4 Hz), 127.7, 127.8, 127.84, 127.90, 127.96, 128.05, 128.3, 128.4, 128.47, 128.51, 137.4, 137.5, 137.7, 137.9, 138.00, 138.04, 138.3, 138.5. IR (neat) ν 3064, 3031, 2914, 2870, 1497, 1454, 1360, 1263, 1167, 1088, 1028, 736, 698 cm^{-1} . MS (EI): m/z (%) (M^+ ,), (100). HRMS Calculated for CHO_5F_3 , found $[\text{M}]^+$.



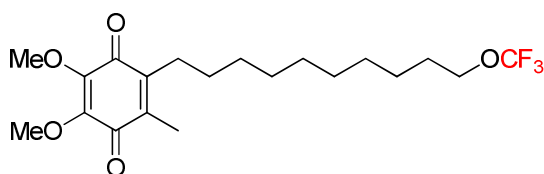
(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-17-(trifluoromethoxy)-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (4ag).

4ag was prepared according to **the general procedure A** in 54% yield as colourless oil ($R_f = 0.5$ in hexane/EtOAc = 5/1). ^1H NMR (300 MHz, CDCl_3) δ 0.86 (s, 3H), 0.85-1.20 (m, 4H), 1.20 (s, 3H), 1.35-2.46 (m, 15H), 4.04 (t, $J = 8.4$ Hz, 1H), 5.74 (s, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ -58.5 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 11.4, 17.4, 20.4, 23.2, 27.8, 31.4, 32.6, 33.9, 35.4, 35.7, 36.0, 38.6, 42.4, 49.8, 53.7, 86.5, 121.8 (q, $J = 251.4$ Hz), 124.0, 170.6, 199.4. IR (neat) ν 2944, 2855, 1676, 1616, 1450, 1285, 1229, 1203, 1133, 1068, 1019, 883, 863 cm^{-1} . MS (EI): m/z (%) 356 (M^+ , 50.3), 314 (M^+ , 100). HRMS Calculated for $\text{C}_{20}\text{H}_{27}\text{O}_2\text{F}_3$ 356.1963, found $[\text{M}]^+$ 356.1965.



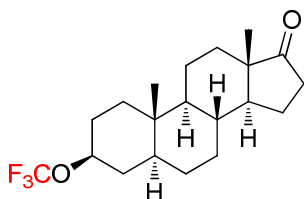
(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-3-(trifluoromethoxy)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene (4ah).

4ah was prepared according to **the general procedure A** in 72% yield as a white solid ($R_f = 0.8$ in hexane), mp 92 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 0.64 (s, 3H), 0.80-1.97 (m, 43H), 4.06-4.16 (m, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -57.5 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 12.0, 12.1, 18.7, 21.2, 22.5, 22.8, 23.9, 24.2, 28.0, 28.2, 28.4, 28.6, 32.0, 34.9, 35.2, 35.4, 35.8, 36.2, 36.7, 39.5, 40.0, 42.6, 44.7, 54.2, 56.3, 56.4, 78.6, 121.7 (q, $J = 252.3$ Hz). IR (neat) ν 2951, 2872, 1468, 1446, 1373, 1365, 1284, 1217, 1131, 1020, 908, 852, 736 cm^{-1} . MS (EI): m/z (%) 456 ($[\text{M}]^+$, 31.9), 301 (M^+ , 100). HRMS Calculated for $\text{C}_{28}\text{H}_{47}\text{OF}_3$ $[\text{M}]^+$ 456.3579, found $[\text{M}]^+$ 456.3583.



2,3-Dimethoxy-5-methyl-6-(10-(trifluoromethoxy)decyl)cyclohexa-2,5-diene-1,4-dione (4ai).

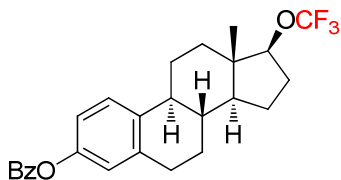
4ai was prepared according to **the general procedure B** in 64% yield as a yellow oil ($R_f = 0.6$ in hexane/Et₂O = 3/1). ¹H NMR (300 MHz, CDCl₃) δ 1.24-1.45 (m, 14H), 1.58-1.72 (m, 2H), 1.99 (s, 3H), 2.42 (t, $J = 7.2$ Hz, 2H), 3.88-3.98 (m, 8H). ¹⁹F NMR (282 MHz, CDCl₃) δ -61.1 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 11.8, 25.4, 26.3, 28.7, 29.0, 29.26, 29.31, 29.34, 29.8, 61.1, 67.5 (q, $J = 2.9$ Hz), 121.7 (q, $J = 252.0$ Hz), 138.7, 143.0, 144.3, 184.1, 184.7. IR (neat) ν 3286, 2930, 2856, 1767, 1651, 1611, 1456, 1408, 1380, 1268, 1139, 1070, 1007, 948, 874, 745, 704 cm⁻¹. MS (EI): m/z (%) 406 (M⁺, 52.7), 197 (M⁺, 100). HRMS Calculated for C₂₀H₂₉O₅F₃ 406.1968, found [M]⁺ 406.1967.



(3S,5S,8R,9S,10S,13S,14S)-10,13-Dimethyl-3-(trifluoromethoxy)tetradecahydro-1H-cyclopenta[*a*]phenanthren-17(2H)-one (4aj).

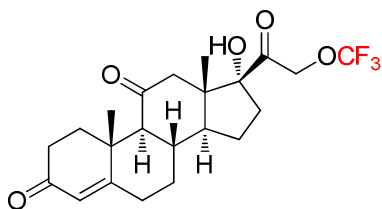
4aj was prepared according to **the general procedure A** in 91% yield as a white solid ($R_f = 0.6$ in hexane/EtOAc = 7/1), mp 125 °C. ¹H NMR (400 MHz, CDCl₃) δ 0.62-0.70 (m, 1H), 0.82 (s, 3H), 0.83 (s, 3H), 0.90-1.35 (m, 8H), 1.43-2.09 (m, 12H), 2.36-2.46 (m, 1H), 4.05-4.15 (m, 1H). ¹⁹F NMR (376 MHz, CDCl₃) δ -57.5 (s, 3F). ¹³C NMR (100 MHz, CDCl₃) δ 12.1, 13.8, 20.4, 21.7, 28.2, 28.3, 30.7, 31.5, 34.8, 35.0, 35.4, 35.8, 36.6, 44.6, 47.7, 51.4, 54.3, 78.3, 121.7 (q, $J = 251.9$ Hz), 221.0. IR (neat) ν 2942, 2858, 1740, 1472, 1453, 1373, 1336, 1284, 1216, 1132, 1059, 1017,

872, 855 cm^{-1} . MS (EI): m/z (%) 358 (M^+ , 100). HRMS Calculated for $\text{C}_{20}\text{H}_{29}\text{O}_2\text{F}_3$ 358.2120, found $[\text{M}]^+$ 358.2121.



(8R,9S,13S,14S,17S)-13-Methyl-17-(trifluoromethoxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl benzoate (4ak).

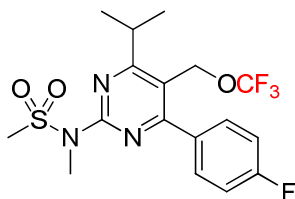
4ak was prepared according to **the general procedure A** in 80% yield as a white solid (R_f = 0.4 in hexane/EtOAc = 2/1), mp 185 °C. ^1H NMR (400 MHz, CDCl_3) δ 0.85 (s, 3H), 1.20-1.52 (m, 6H), 1.72-2.36 (m, 7H), 2.86-2.92 (m, 2H), 4.12 (t, J = 8.4 Hz, 1H), 6.91-6.99 (m, 2H), 7.32 (d, J = 8.8 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 8.18 (d, J = 7.6 Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -58.0 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 11.5, 23.0, 25.9, 27.0, 28.0, 29.5, 36.3, 38.2, 42.9, 44.0, 49.4, 86.7, 118.8, 121.7, 121.8 (q, J = 252.3 Hz), 126.5, 128.5, 129.8, 130.2, 133.5, 137.7, 138.2, 148.8, 165.5. IR (neat) ν 2947, 2915, 2854, 1732, 1560, 1491, 1450, 1435, 1398, 1299, 1270, 1251, 1206, 1171, 1127, 1024, 895, 714 cm^{-1} . MS (EI): m/z (%) 444 ($[\text{M}]^+$, 11.5), 105 (M^+ , 100). HRMS Calculated for $\text{C}_{26}\text{H}_{27}\text{O}_3\text{F}_3$ $[\text{M}]^+$ 444.1912, found $[\text{M}]^+$ 444.1909.



(8S,9S,10R,13S,14S,17R)-17-Hydroxy-10,13-dimethyl-17-(2-(trifluoromethoxy)acetyl)-7,8,9,10,12,13,14,15,16,17-decahydro-1H-cyclopenta[a]phenanthrene-3,11(2H,6H)-dione (4al).

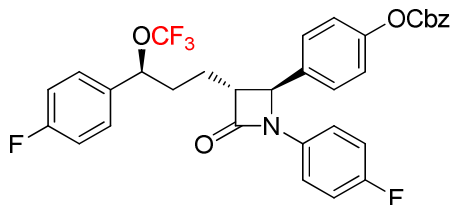
4al was prepared according to **the general procedure A** in 65% yield as a white solid (R_f = 0.6 in hexane/EtOAc = 2/1), mp 145 °C. ^1H NMR (400 MHz, CDCl_3) δ 0.59 (s,

3H), 1.20-1.73 (m, 7H), 1.86- 2.06 (m, 5H), 2.20-2.50 (m, 5H), 2.70-2.77 (m, 2H), 2.89 (d, $J = 12.4$ Hz, 1H), 3.95 (s, 1H), 4.58 (d, $J = 18.0$ Hz, 1H), 5.01 (d, $J = 17.6$ Hz, 1H), 5.67 (s, 1H), . ^{19}F NMR (376 MHz, CDCl_3) δ -60.8 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3) δ 15.6, 17.1, 23.1, 32.2, 32.3, 33.6, 34.5, 35.0, 36.4, 38.3, 49.8, 50.2, 51.4, 62.4, 69.9, 88.8, 121.5 (q, $J = 254.6$ Hz), 124.2, 170.6, 201.1, 202.9, 209.1. IR (neat) ν 3495, 3247, 2939, 2854, 1736, 1690, 1658, 1435, 1375, 1354, 1282, 1216, 1196, 1147, 1092, 1050, 912, 882, 780, 734, 604 cm^{-1} . MS (EI): m/z (%) 428 (M^+ , 84.0), 258 (M^+ , 100). HRMS Calculated for $\text{C}_{22}\text{H}_{27}\text{O}_5\text{F}_3$ 428.1811, found $[\text{M}]^+$ 428.1806.



***N*-(4-(4-Fluorophenyl)-6-isopropyl-5-((trifluoromethoxy)methyl)pyrimidin-2-yl)-*N*-methylmethanesulfonamide (4am).**

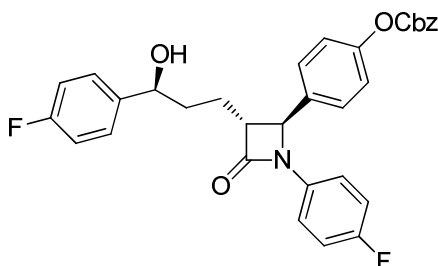
4am was prepared according to **the general procedure A** in 76% yield as a white solid ($R_f = 0.8$ in hexane/EtOAc = 5/1), mp 107 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.33 (d, $J = 6.8$ Hz, 6H), 3.30-3.38 (m, 1H), 3.49 (s, 3H), 3.56 (s, 3H), 4.94 (s, 2H), 7.17 (t, $J = 8.4$ Hz, 2H), 7.61-7.66 (m, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -60.9 (s, 3F), -110.4 (s, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 22.0, 31.7, 33.1, 42.4, 42.5, 62.7 (q, $J = 3.7$ Hz), 114.6, 115.7 (d, $J = 21.2$ Hz), 121.2 (q, $J = 255.9$ Hz), 131.2 (d, $J = 8.0$ Hz), 133.3 (d, $J = 2.9$ Hz), 158.8, 163.9 (d, $J = 248.6$ Hz), 167.6, 178.6. IR (neat) ν 2976, 2935, 2876, 2259, 1607, 1554, 1512, 1481, 1444, 1409, 1377, 1342, 1258, 1157, 998, 965, 894, 847, 815, 773, 734, 621, 562, 522 cm^{-1} . MS (EI): m/z (%) 421 (M^+ , 5.0), 342 (M^+ , 100). HRMS Calculated for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{F}_4\text{S}$ 421.1083, found $[\text{M}]^+$ 421.1087.



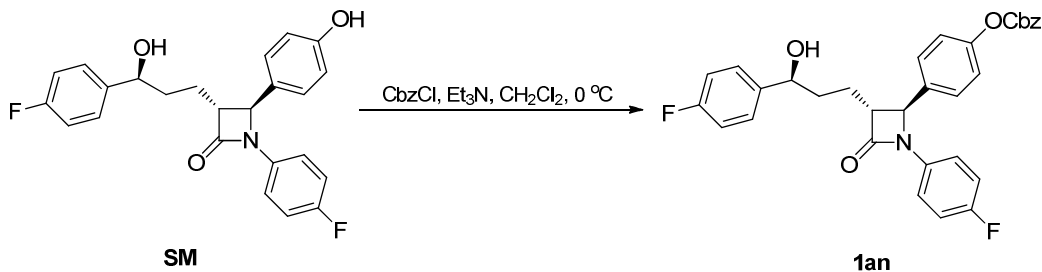
Benzyl (4-((2*S*,3*R*)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-(trifluoromethoxy)propyl)-4-oxoazetidin-2-yl)phenyl) carbonate (4an).

4an was prepared according to **the general procedure A** in 52% yield as a colourless oil ($R_f = 0.8$ in hexane/EtOAc = 3/1). ^1H NMR (300 MHz, CDCl_3) δ 1.90-2.10 (m, 4H), 3.03 (br, 1H), 4.62 (s, 1H), 5.09 (t, $J = 6.0$ Hz, 1H), 5.27 (s, 2H), 6.93 (t, $J = 8.4$ Hz, 2H), 7.05 (t, $J = 8.4$ Hz, 2H), 7.18-7.43 (m, 13H). ^{19}F NMR (282 MHz, CDCl_3) δ -58.2 (s, 3F), -113.3 (m, 1F), -118.0 (m, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 24.8, 34.8, 60.0, 60.6, 70.6, 79.9, 115.8 (d, $J = 21.1$ Hz), 116.0 (d, $J = 22.6$ Hz), 118.4 (d, $J = 8.0$ Hz), 121.6 (q, $J = 254.5$ Hz), 121.1, 127.0, 127.8 (d, $J = 8.0$ Hz), 128.6, 128.8, 128.9, 133.6 (d, $J = 2.2$ Hz), 134.6, 134.8 (d, $J = 2.9$ Hz), 135.2, 151.3, 153.5, 159.1 (d, $J = 242.1$ Hz), 162.8 (d, $J = 246.5$ Hz), 166.5. IR (neat) ν 3037, 2953, 1754, 1607, 1509, 1385, 1225, 1143, 1016, 835, 737 cm^{-1} . MS (EI): m/z (%) 611 (M^+ , 0.02), 137 (100). HRMS Calculated for $\text{C}_{33}\text{H}_{26}\text{NO}_5\text{F}_5$ 611.1731, found $[\text{M}]^+$ 611.1724.

2.4 Preparation of substrate 1an



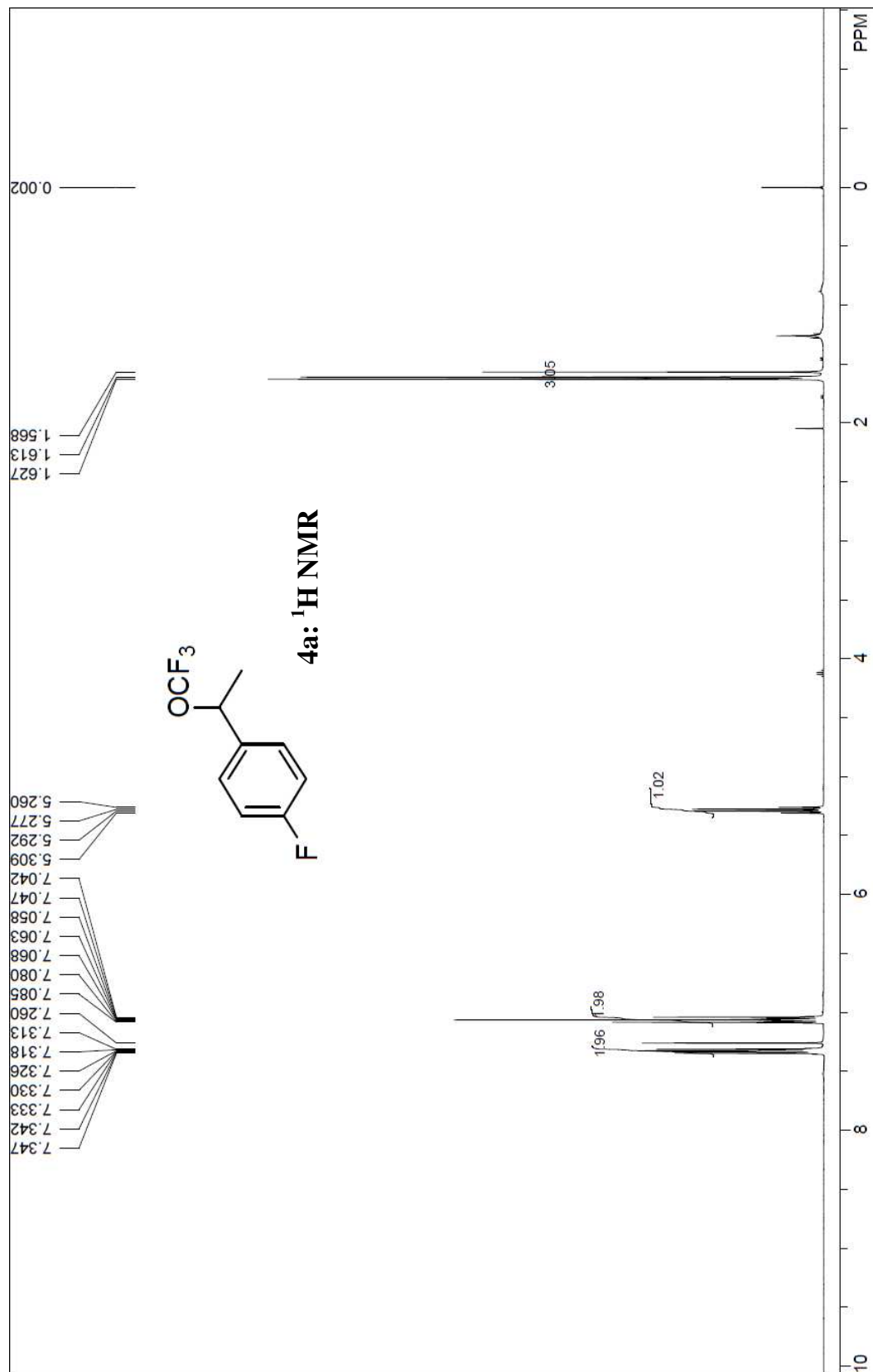
Benzyl (4-((2*S*,3*R*)-1-(4-fluorophenyl)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-oxoazetidin-2-yl)phenyl) carbonate (1an**).**

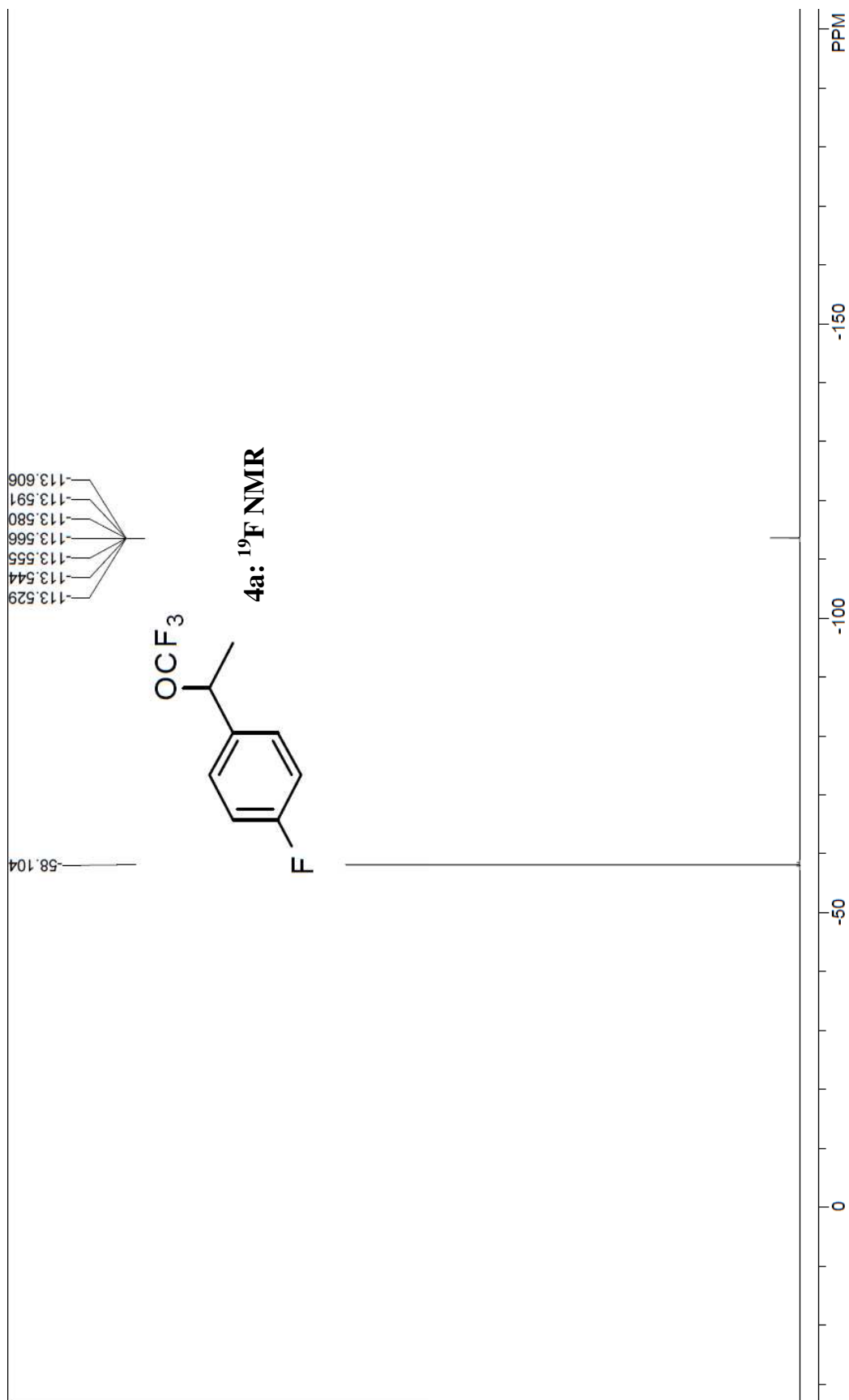


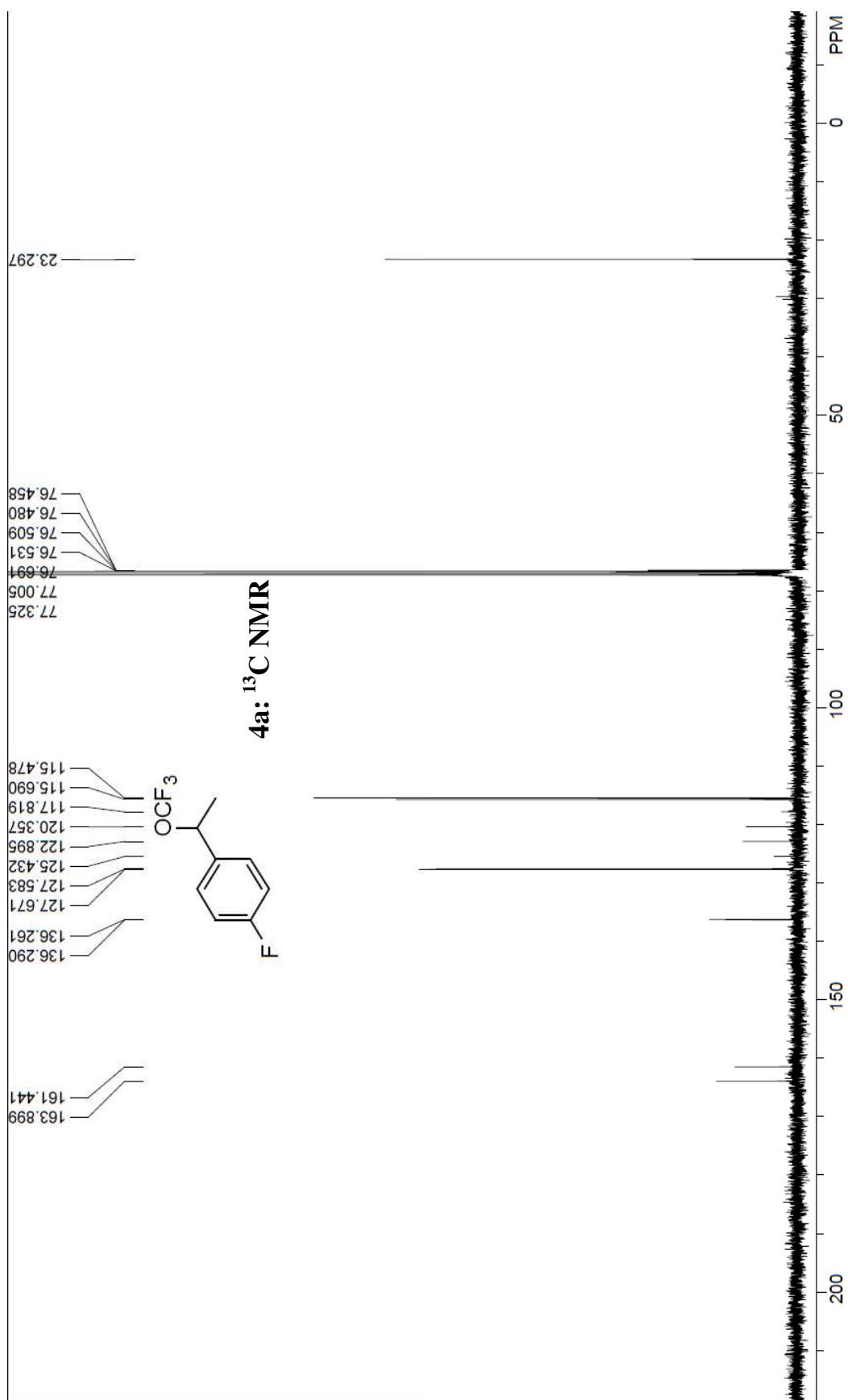
CbzCl (308 mg, 1.8 mmol) was added to a mixture of **SM** (500 mg, 1.2 mmol) and Et₃N (666 mg, 6 mmol) in CH₂Cl₂ (56 mL) at 0 °C was added CbzCl (308 mg, 1.8 mmol). The reaction mixture was stirred at 0 °C for 30 min and then water (3 mL) was added to quench the reaction. The reaction mixture was added EtOAc (30 mL), and the mixture was washed with water (10 mL) and brine (10 mL) and dried over Na₂SO₄. The solvent was removed and the mixture was purified by Column chromatography on silica gel with eluting PE/EtOAc = 1/1 to give the **1an** (580 mg, 92% yield).

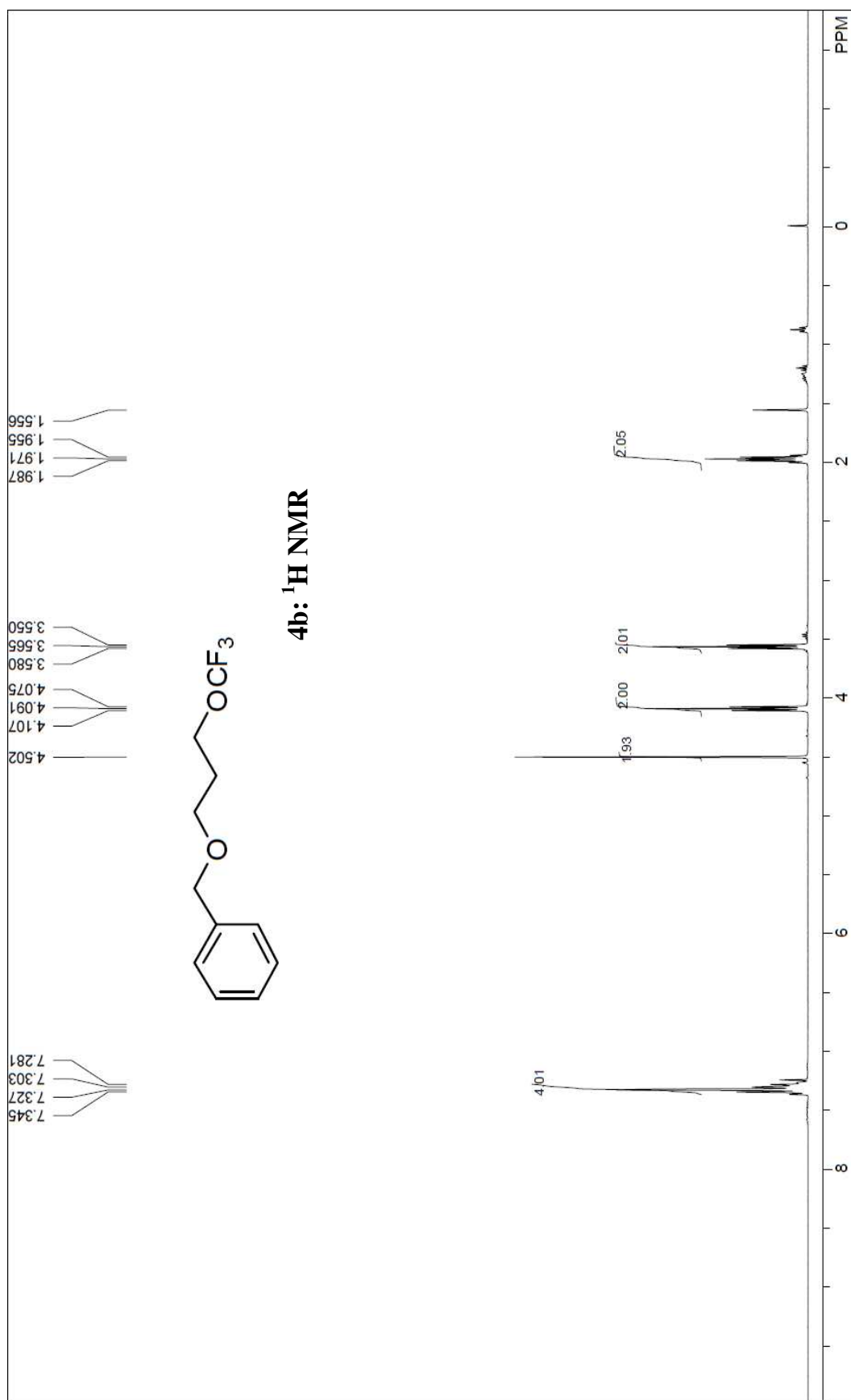
¹H NMR (300 MHz, CDCl₃) δ 1.70-2.60 (m, 5H), 3.00-3.15 (m, 1H), 4.60-4.75 (m, 2H), 5.26 (s, 2H), 6.85-7.05 (m, 4H), 7.08-7.45 (m, 13H). ¹⁹F NMR (282 MHz, CDCl₃) δ -115.3 (m, 1F), -118.0 (m, 1F). ¹³C NMR (100 MHz, CDCl₃) δ 25.0, 36.6, 60.4, 60.8, 70.6, 73.1, 115.4 (d, *J* = 21.9 Hz), 116.0 (d, *J* = 22.6 Hz), 118.4 (d, *J* = 7.3 Hz), 122.0, 127.0, 127.4 (d, *J* = 8.0 Hz), 128.6, 128.8, 128.9, 133.7 (d, *J* = 2.0 Hz), 134.6, 135.4, 140.1 (d, *J* = 2.9 Hz), 151.2, 153.5, 159.1 (d, *J* = 242.1 Hz), 162.2 (d, *J* = 244.3 Hz), 167.3. IR (neat) ν 3434 (br), 2934, 2251, 1751, 1604, 1509, 1385, 1221, 1156, 1016, 911, 835, 736, 698 cm⁻¹. MS (EI): *m/z* (%) 543 (M⁺, 5.0), 344 (100). HRMS Calculated for C₃₂H₂₇NO₅F₂ 543.1857, found [M]⁺ 543.1864.

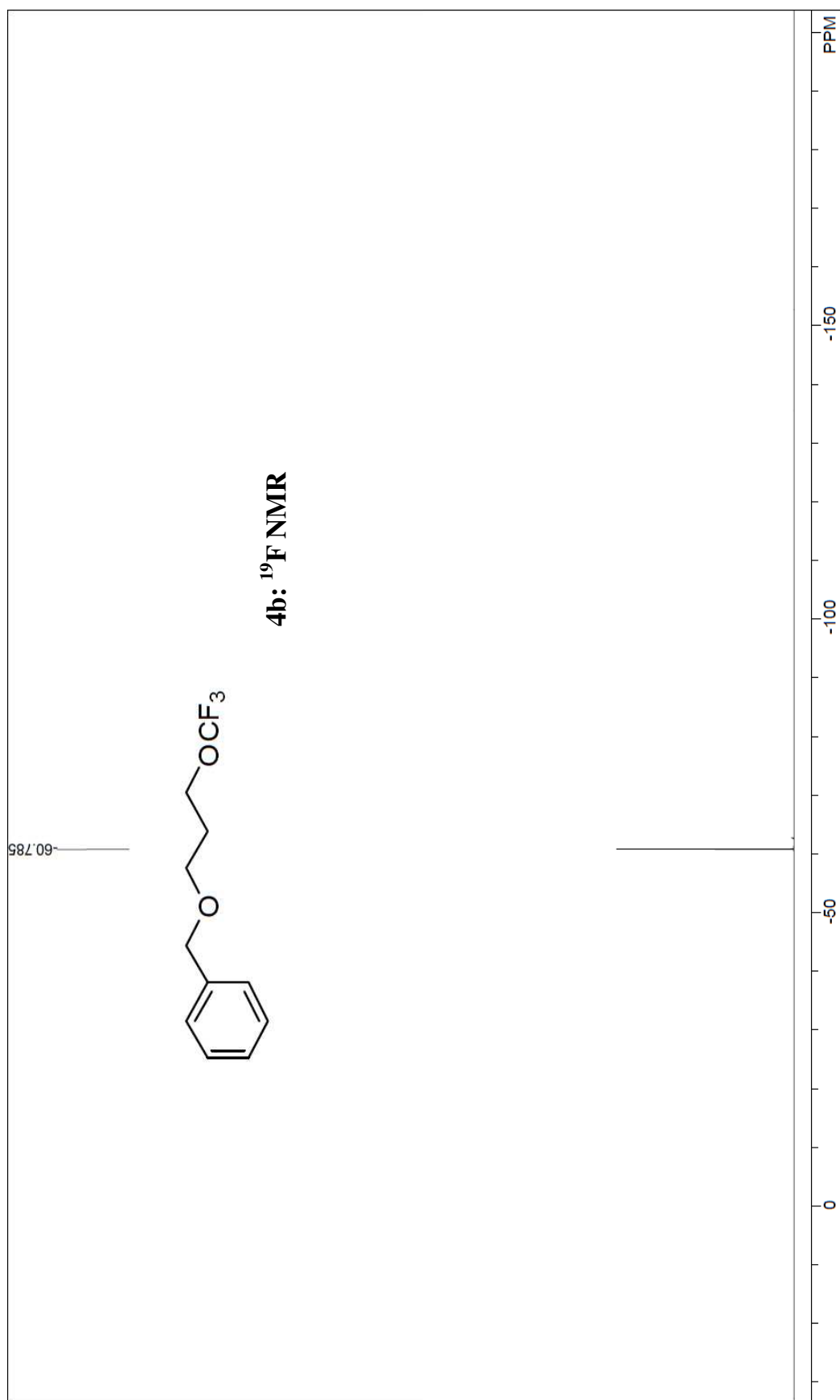
3. NMR Spectra for New Compounds



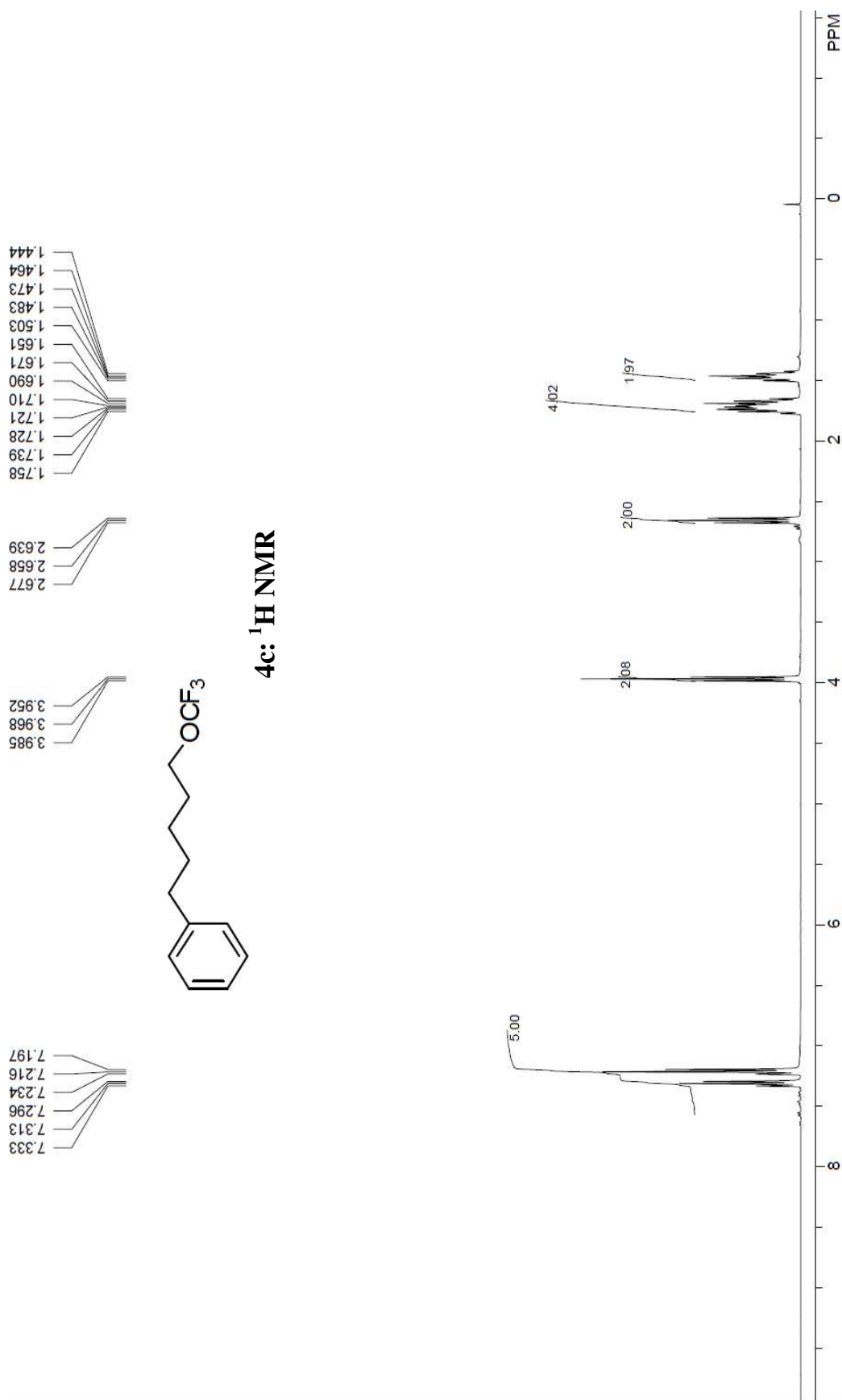


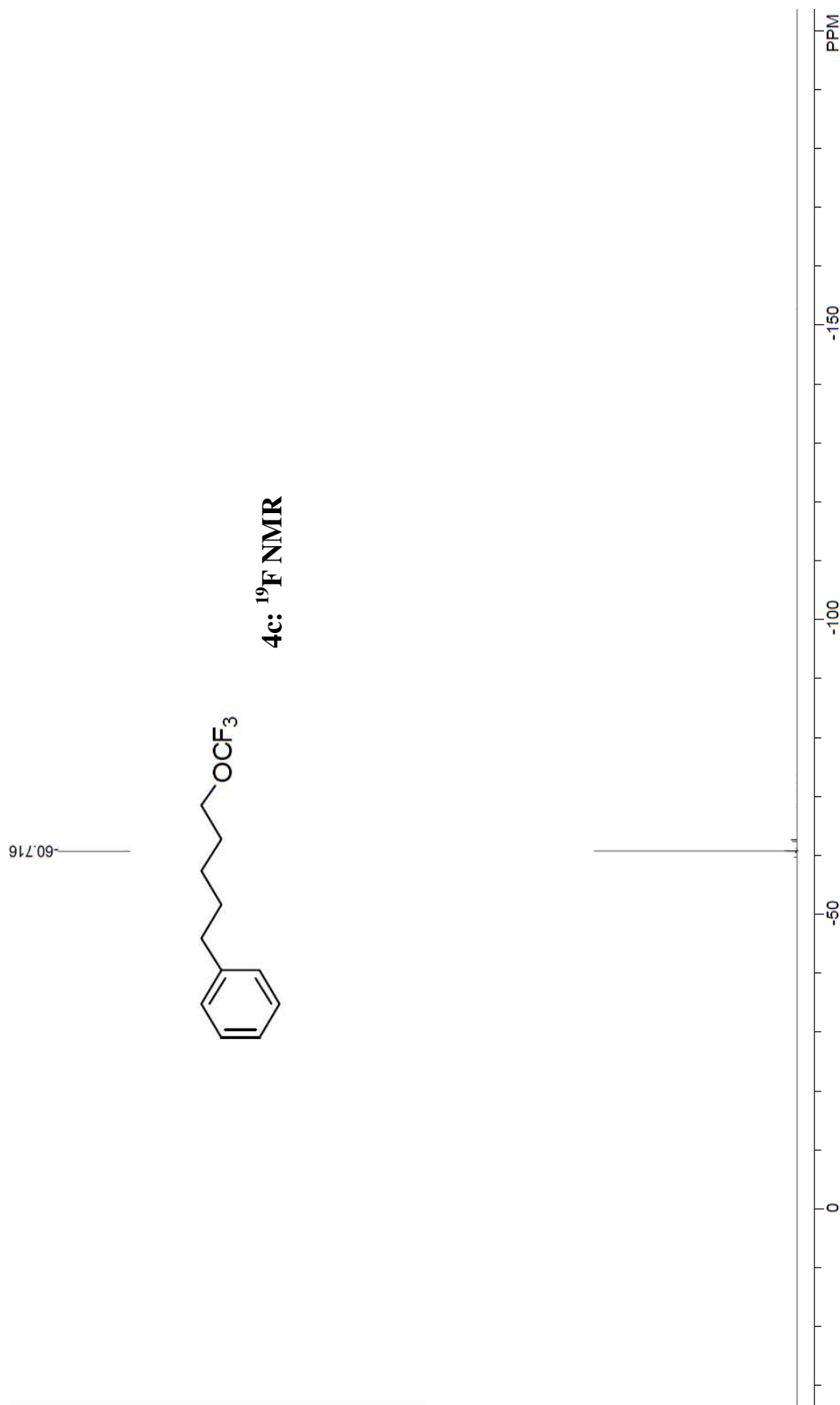


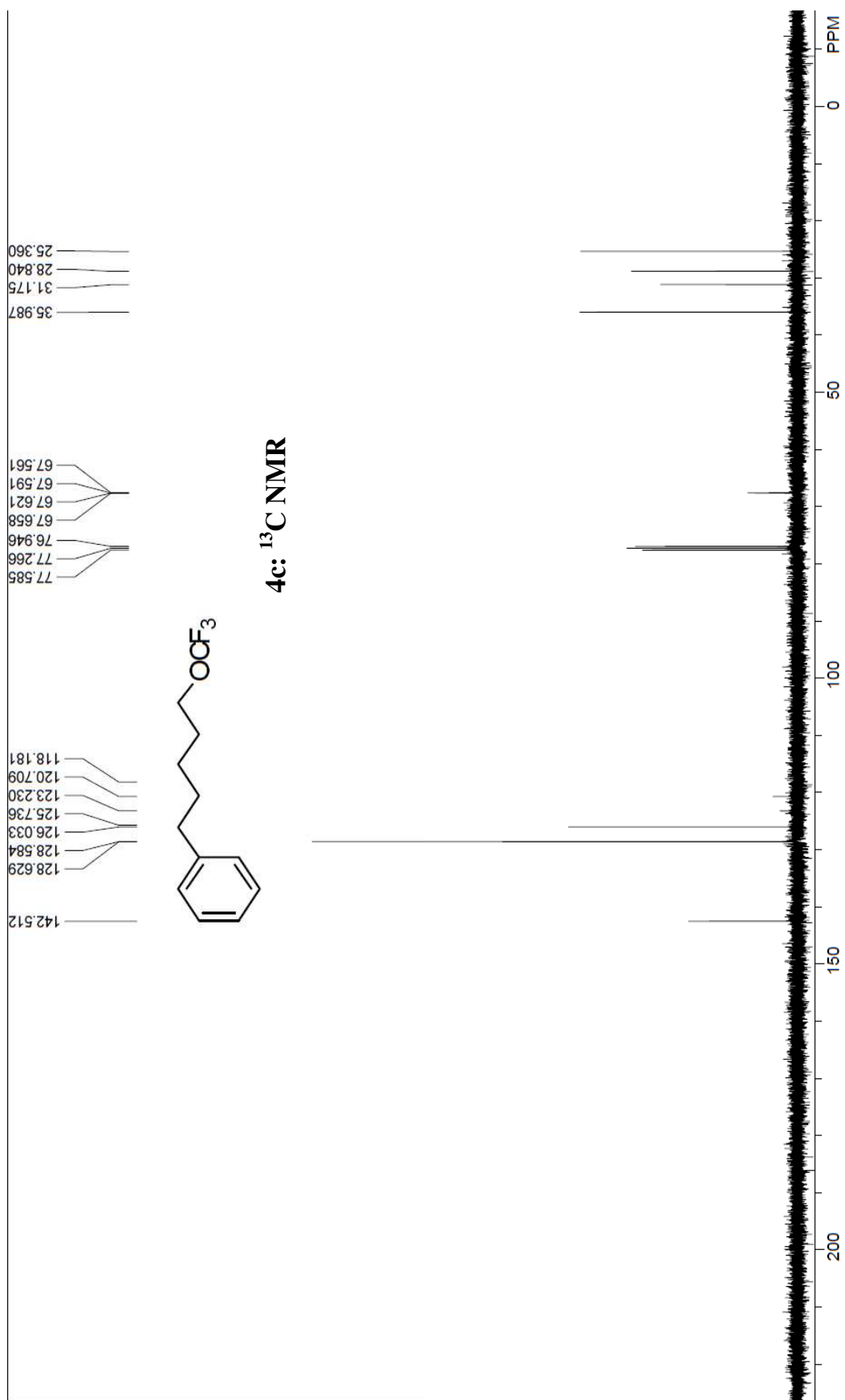


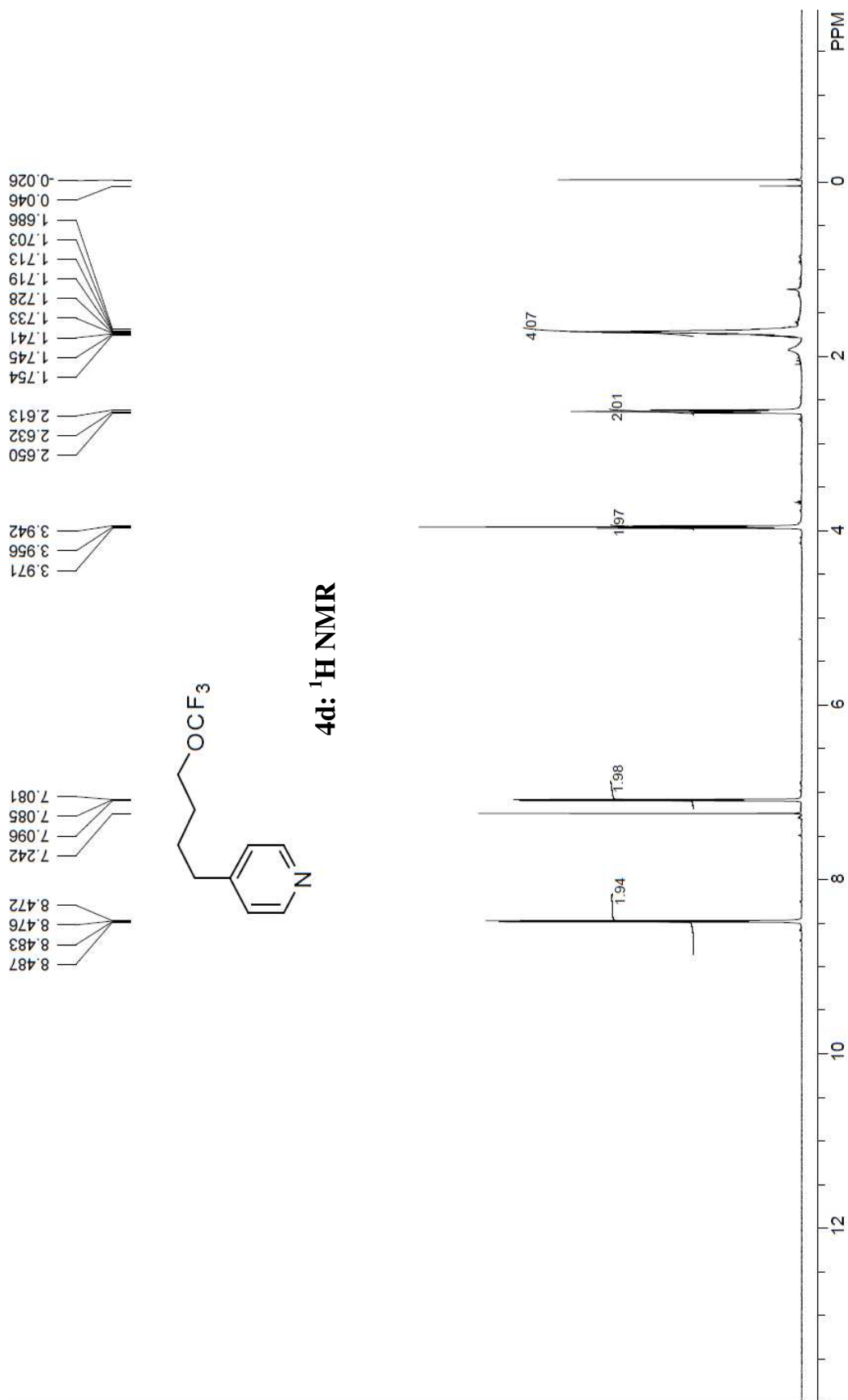


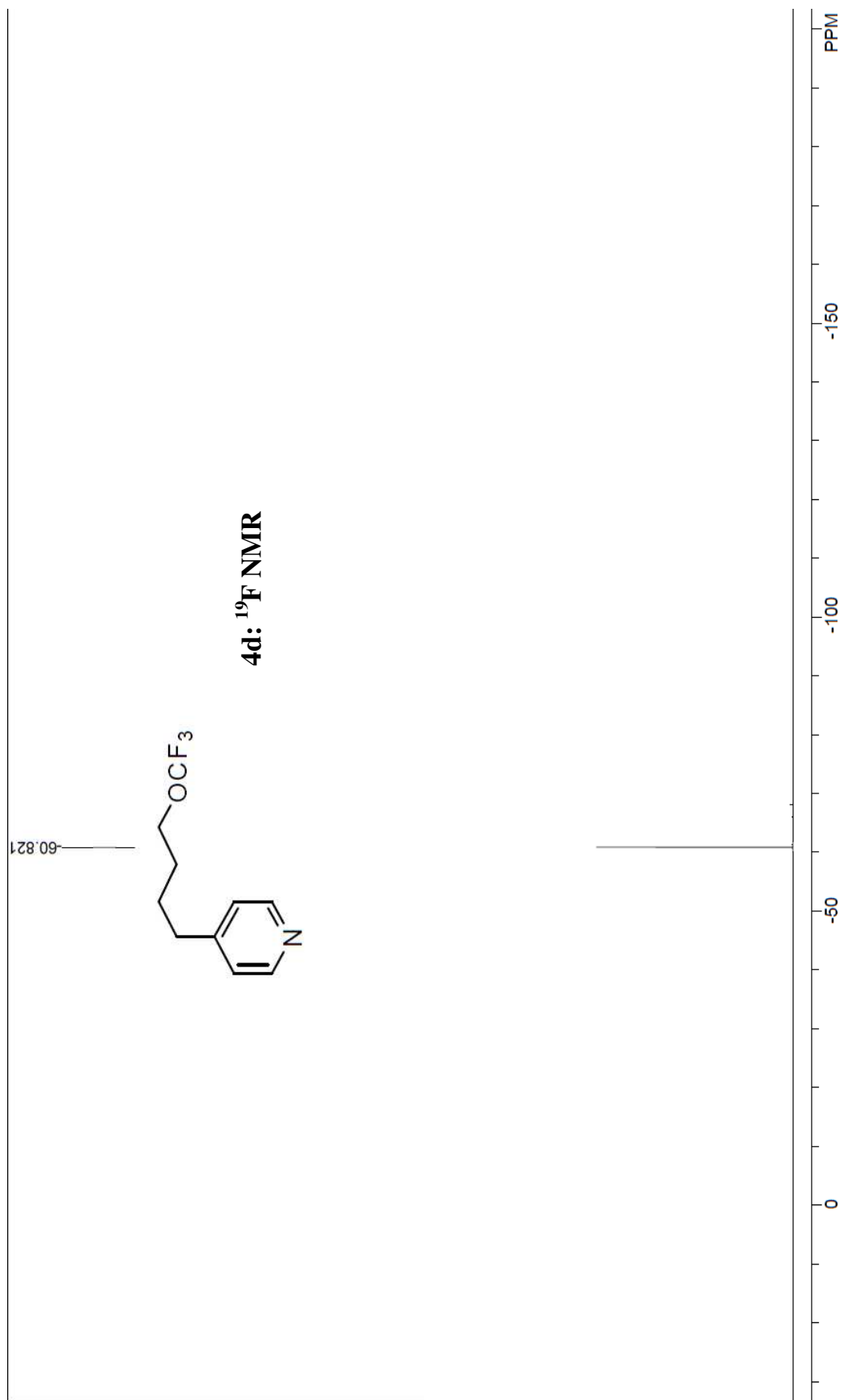


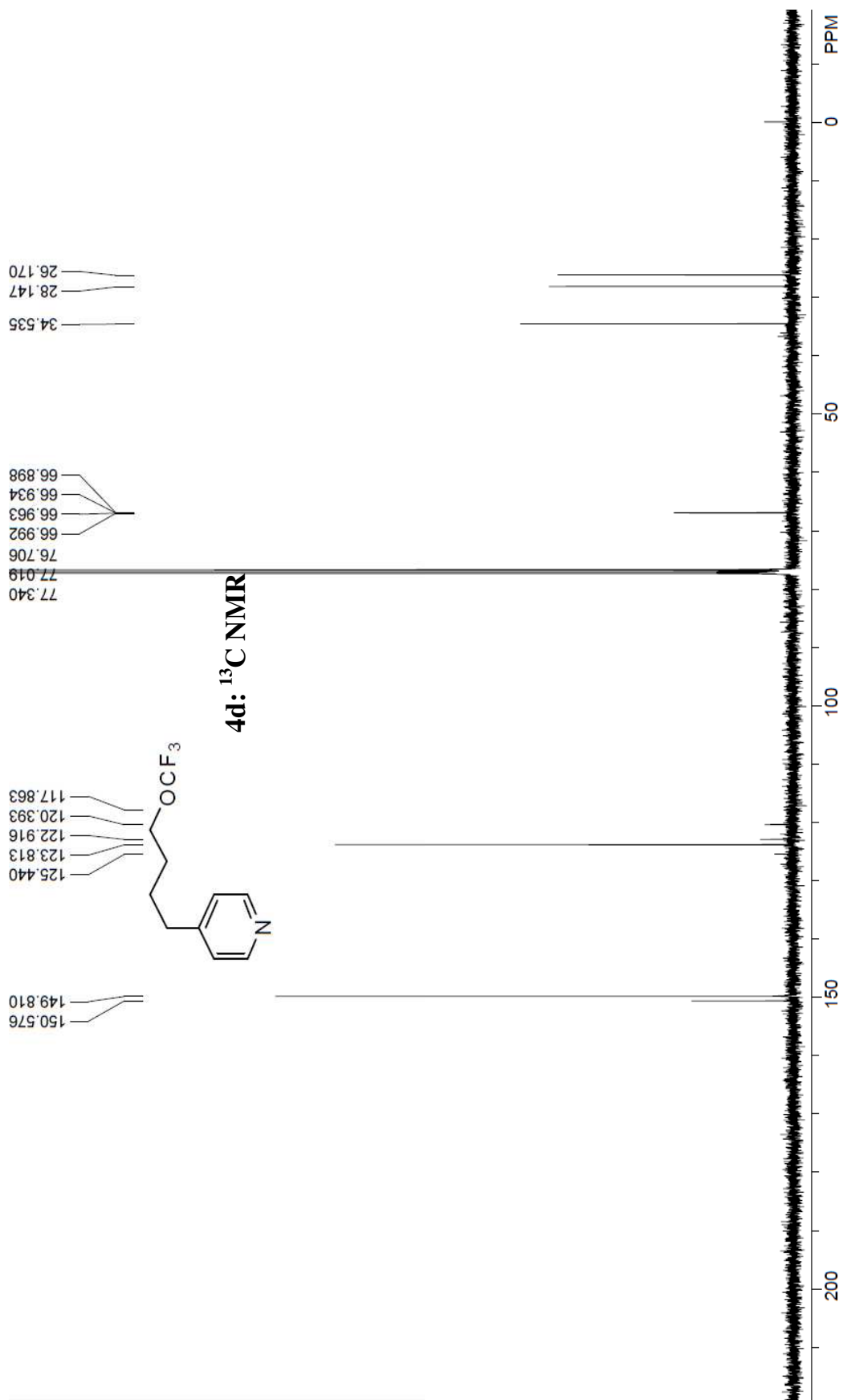


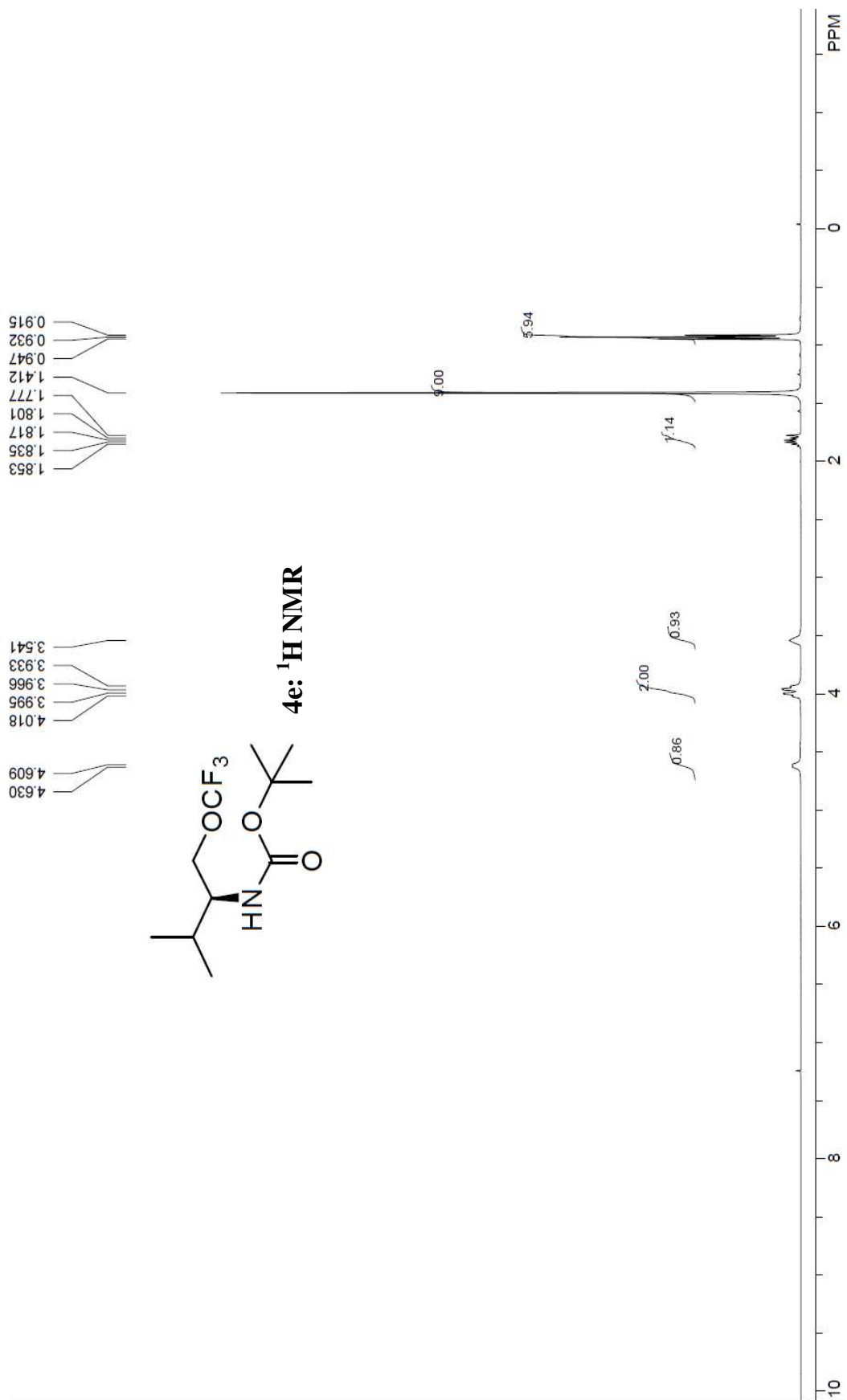


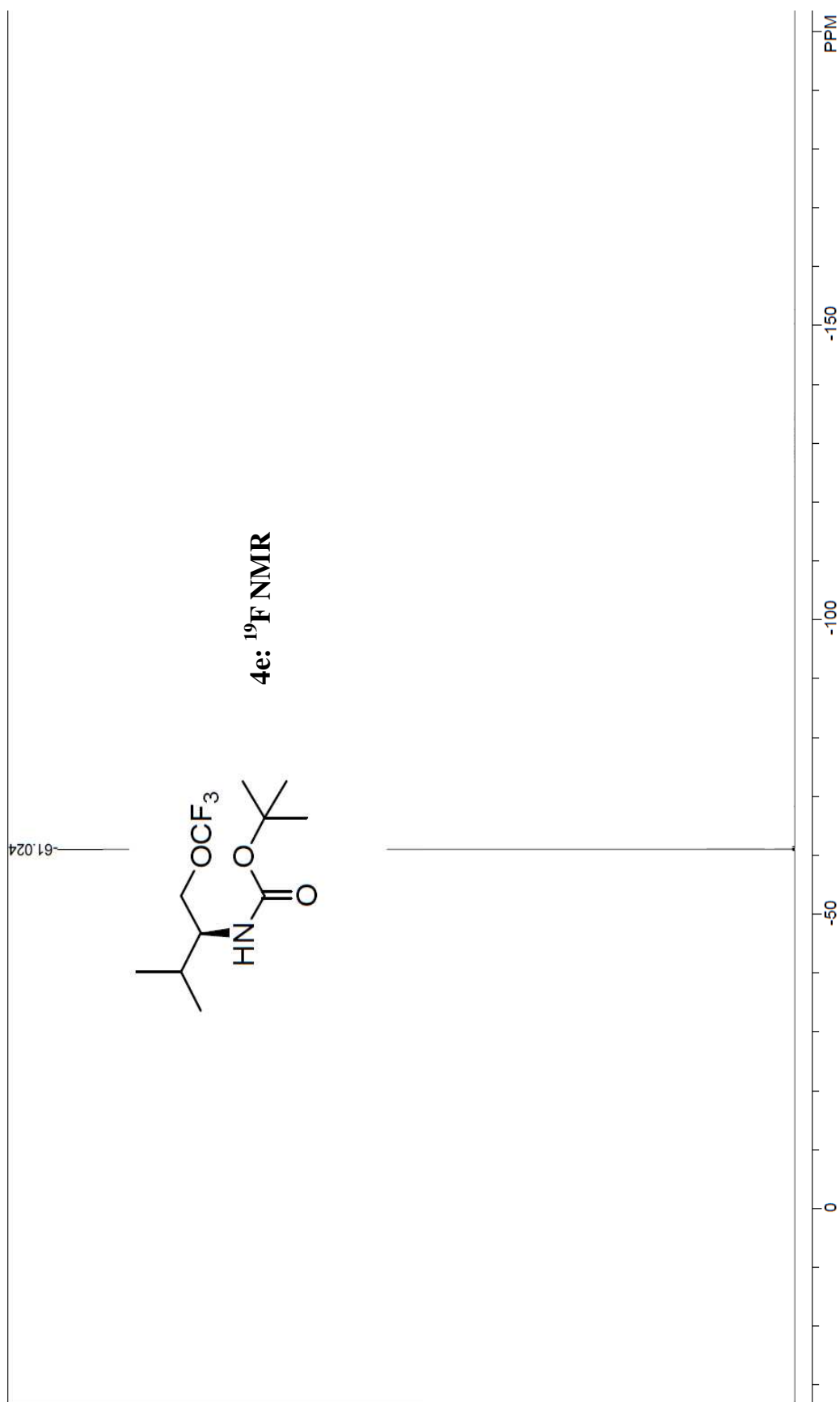


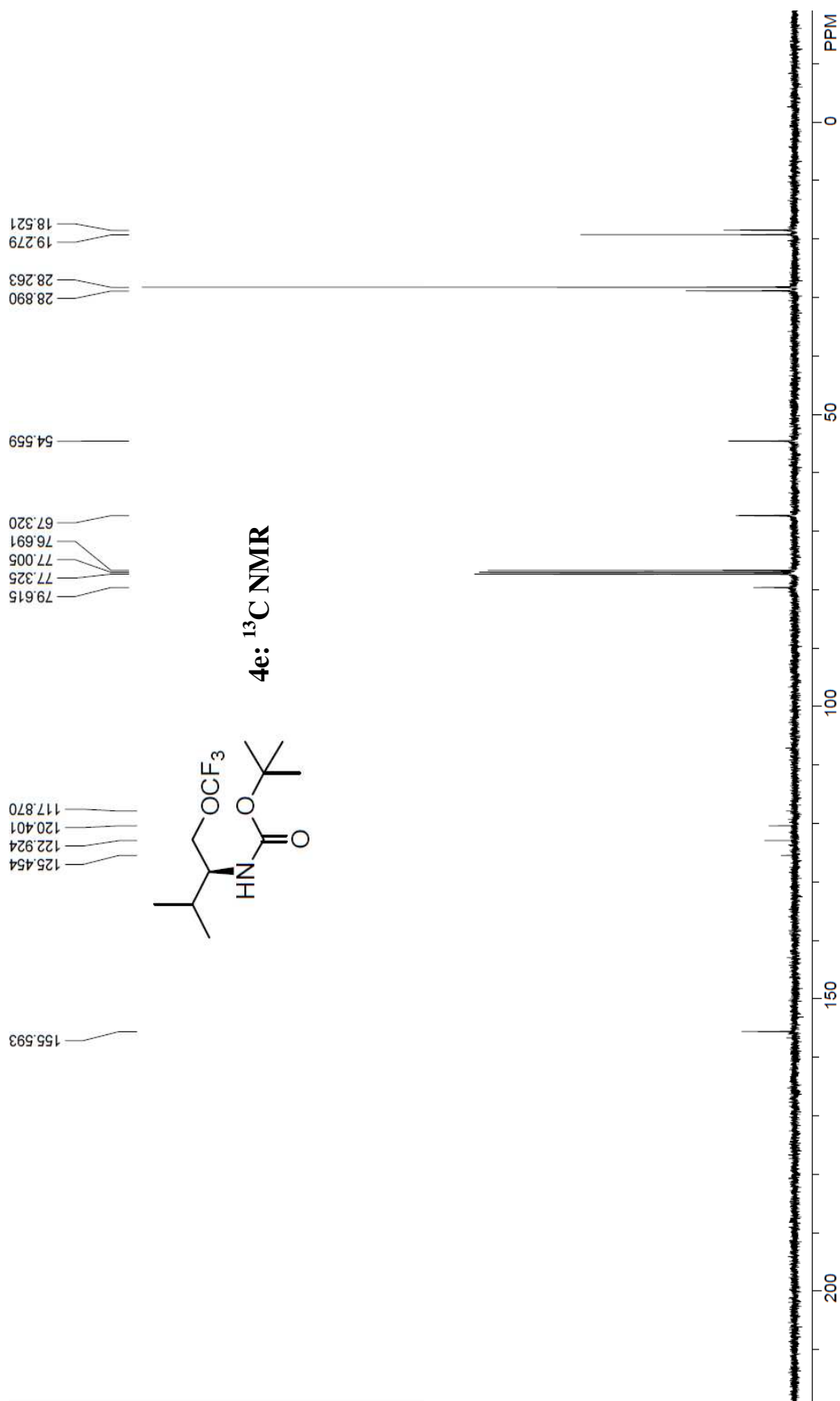


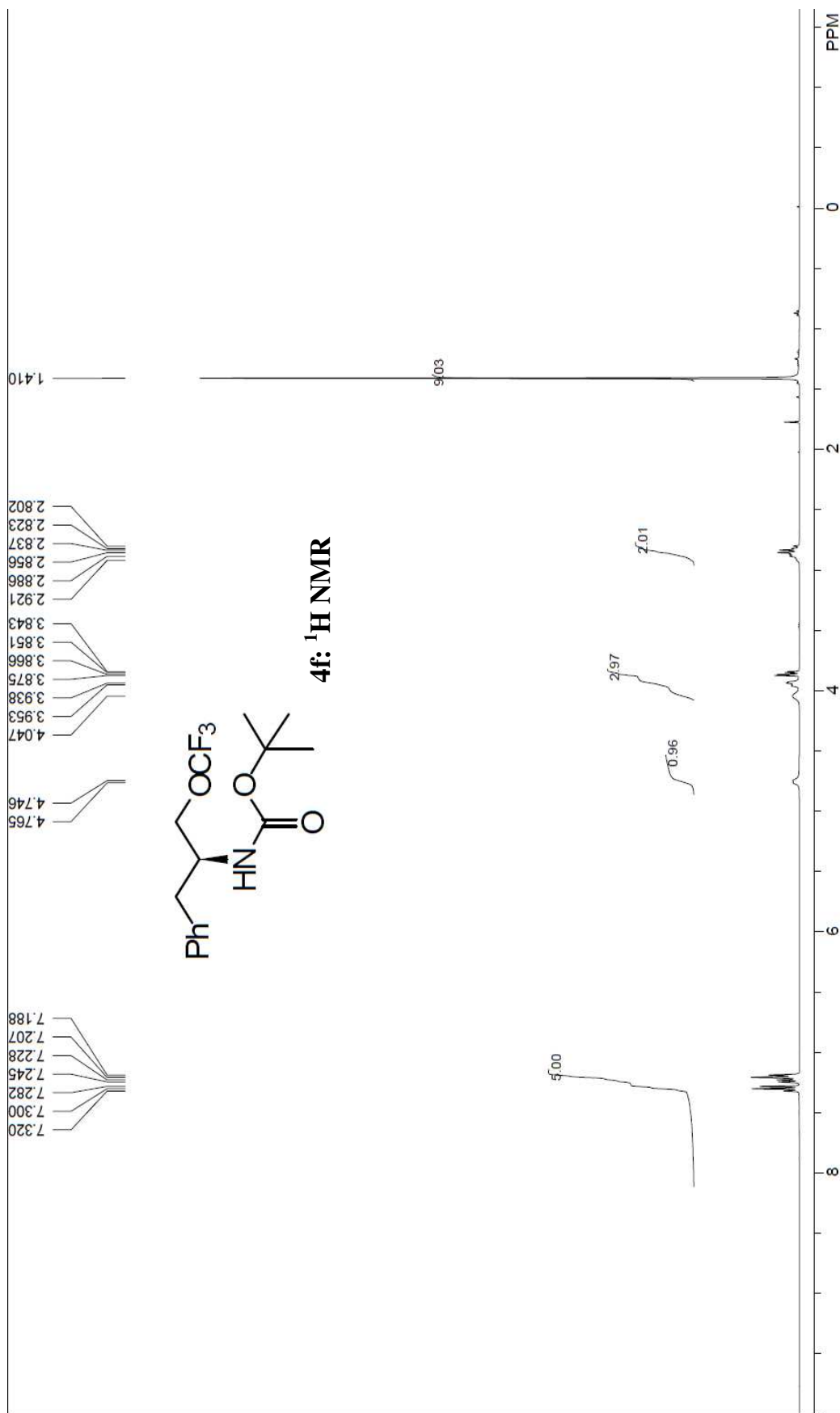


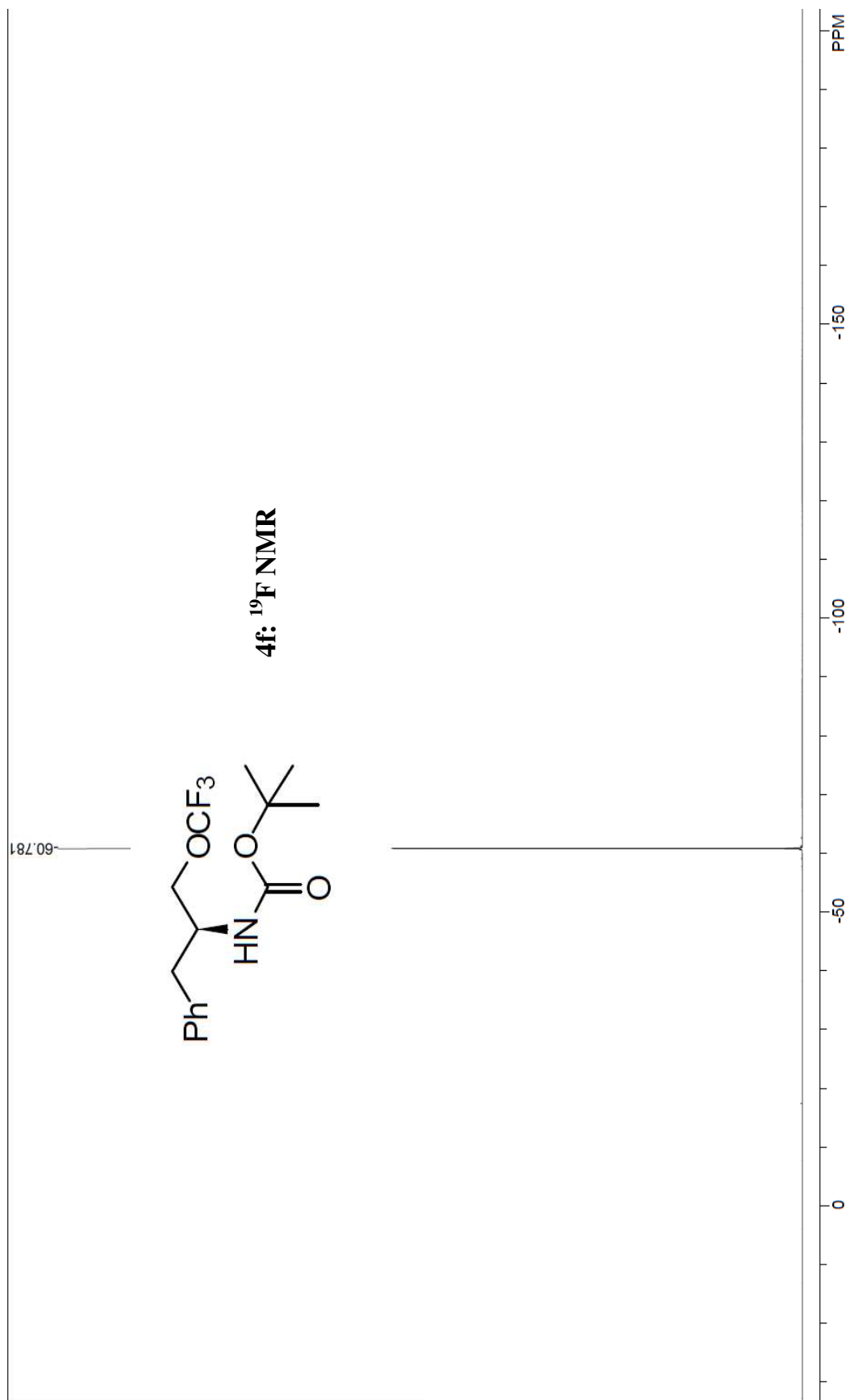


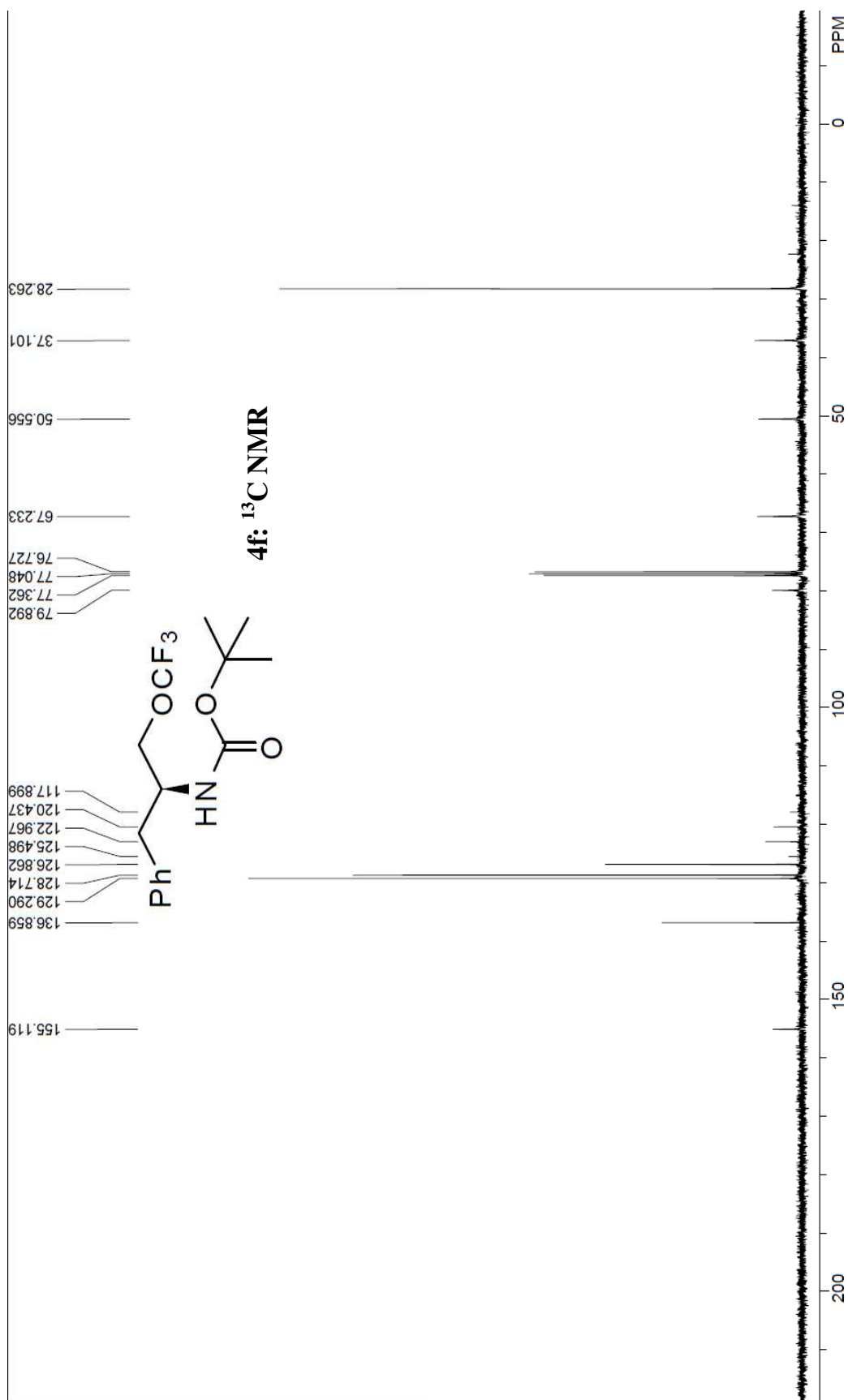


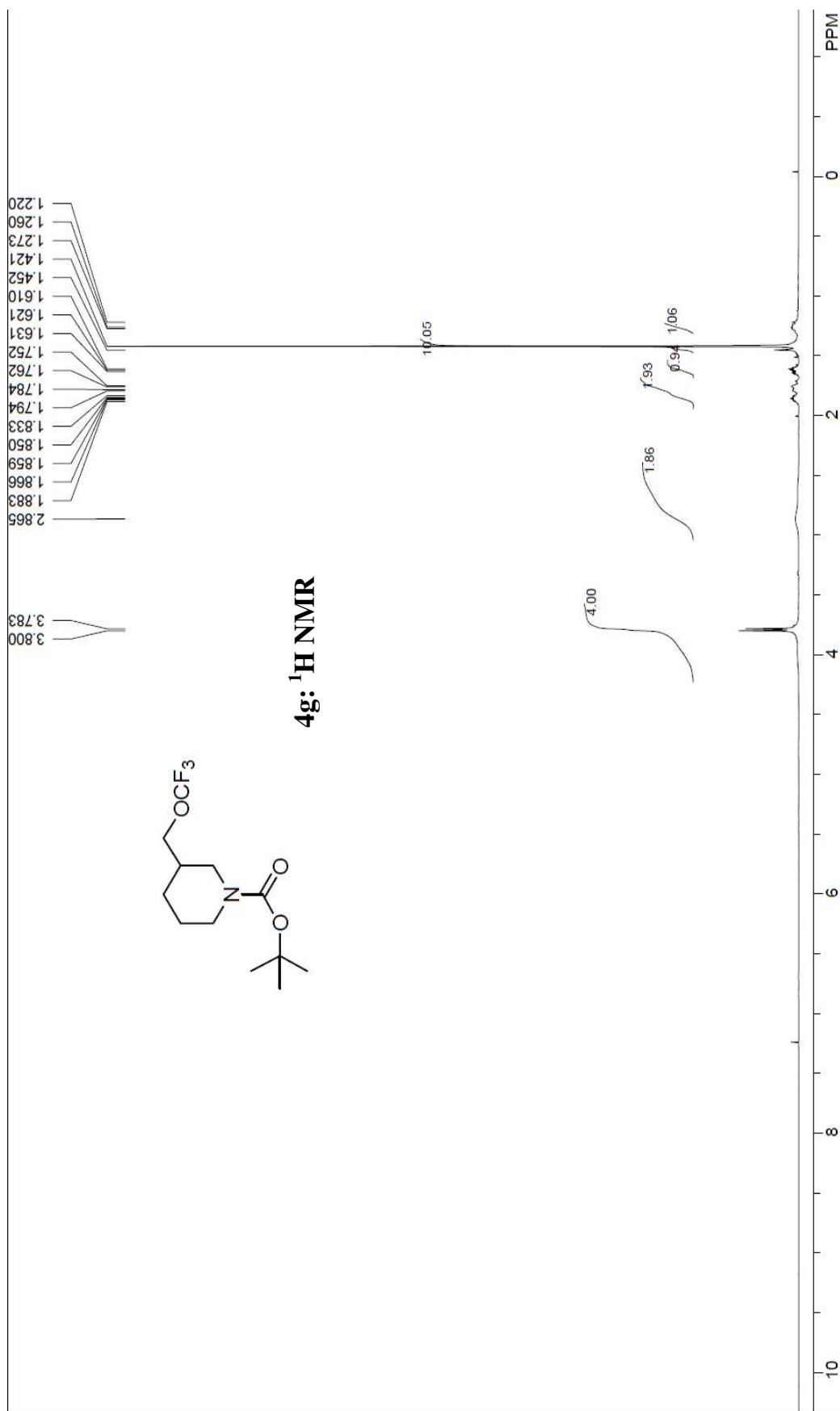


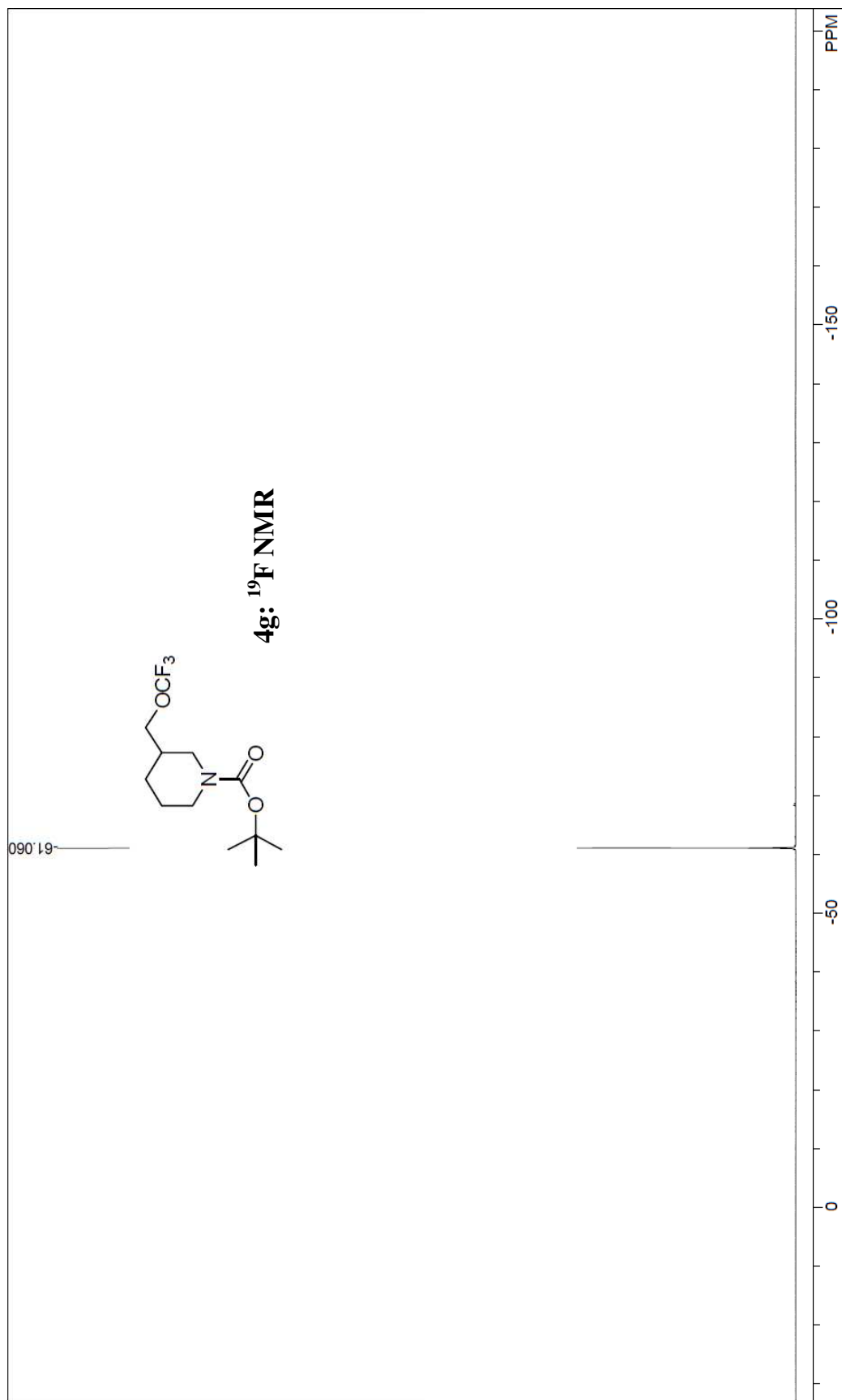


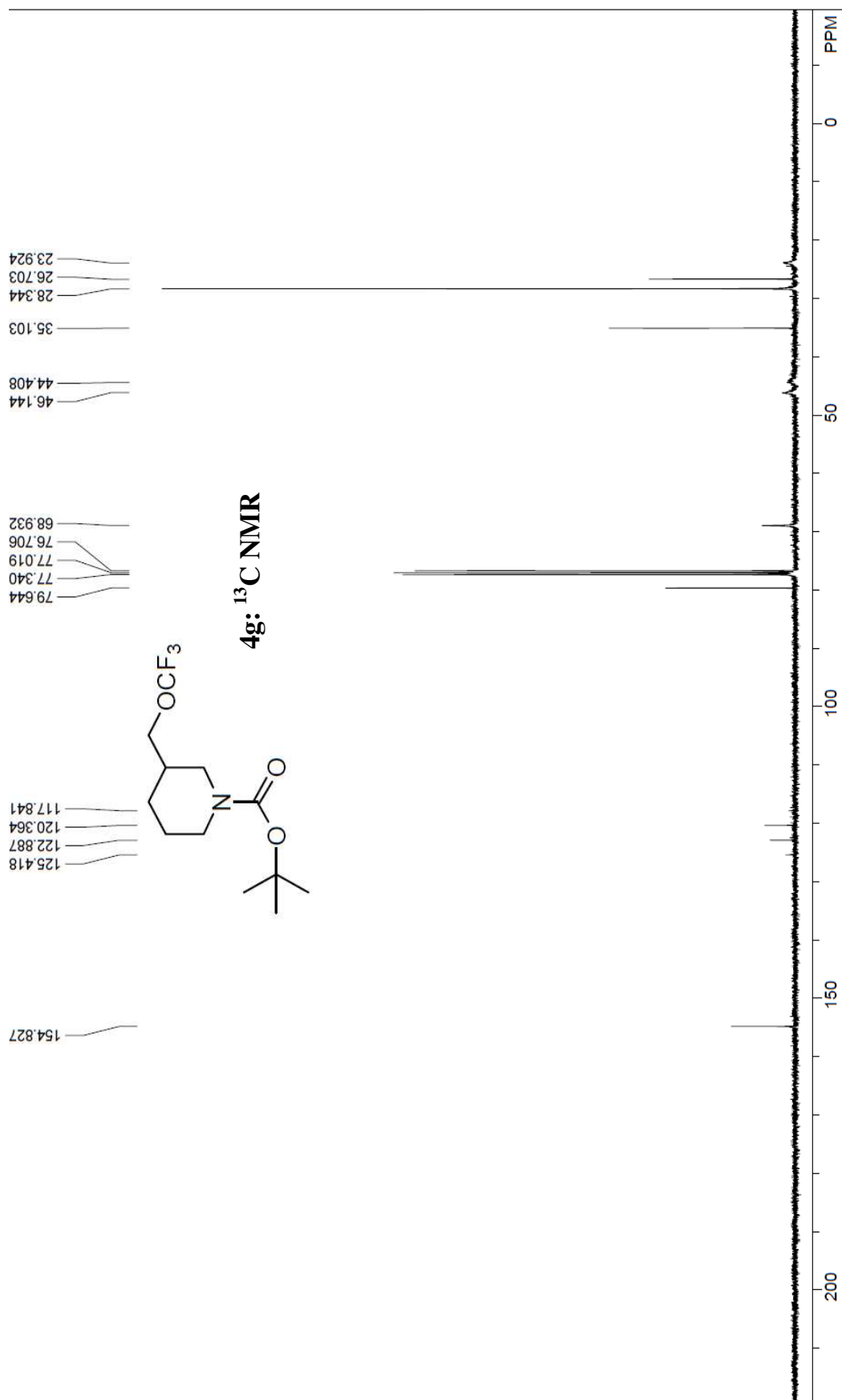


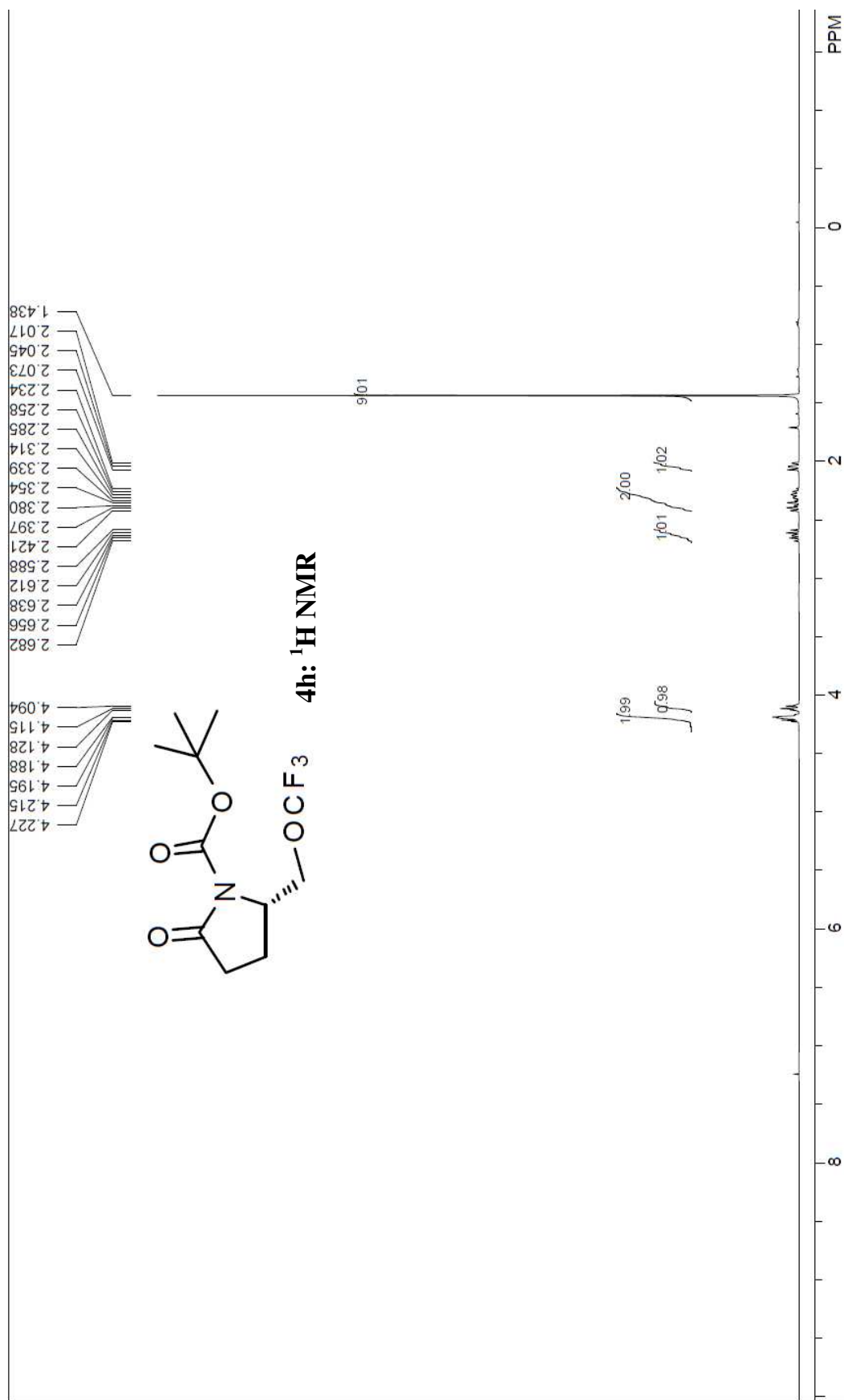


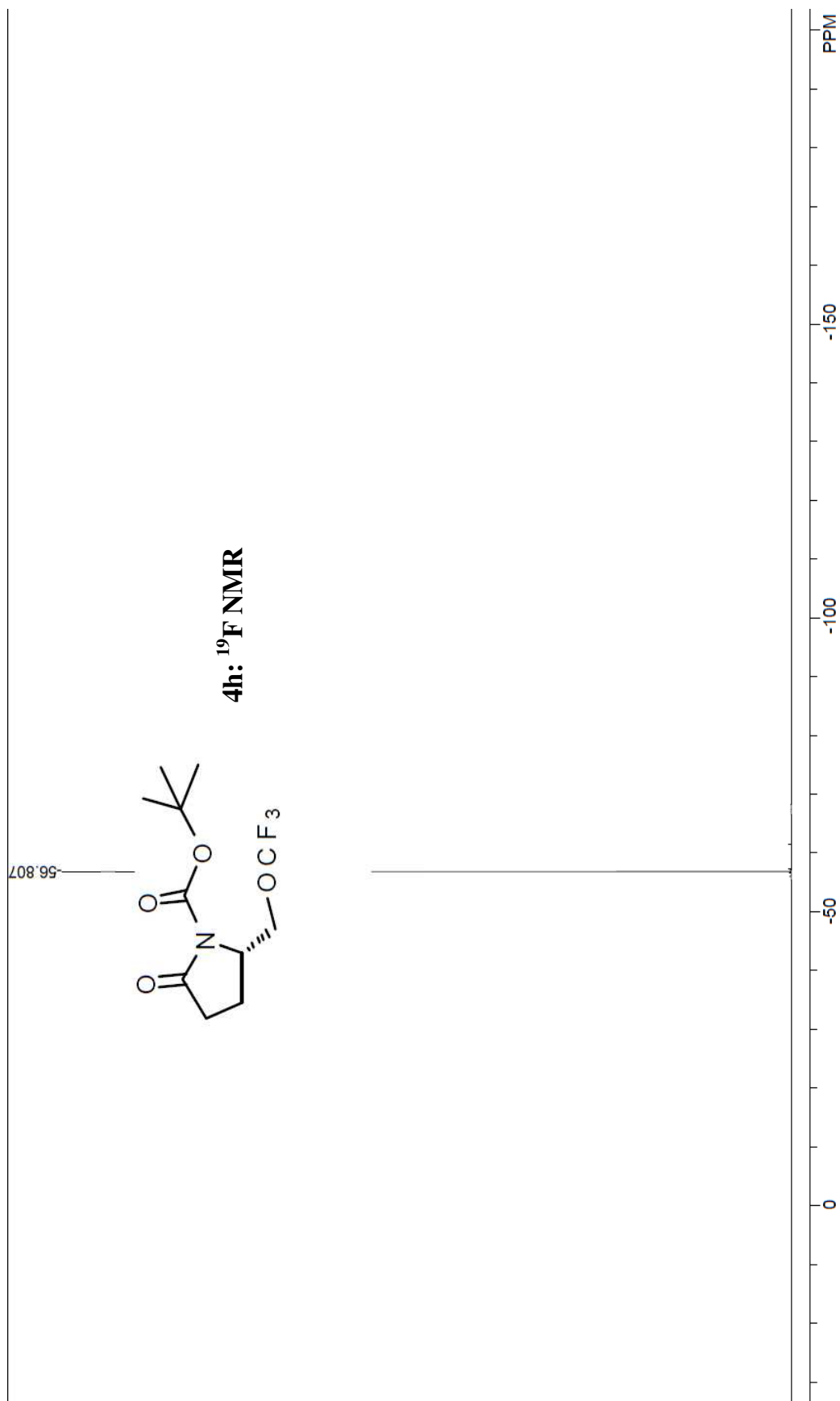


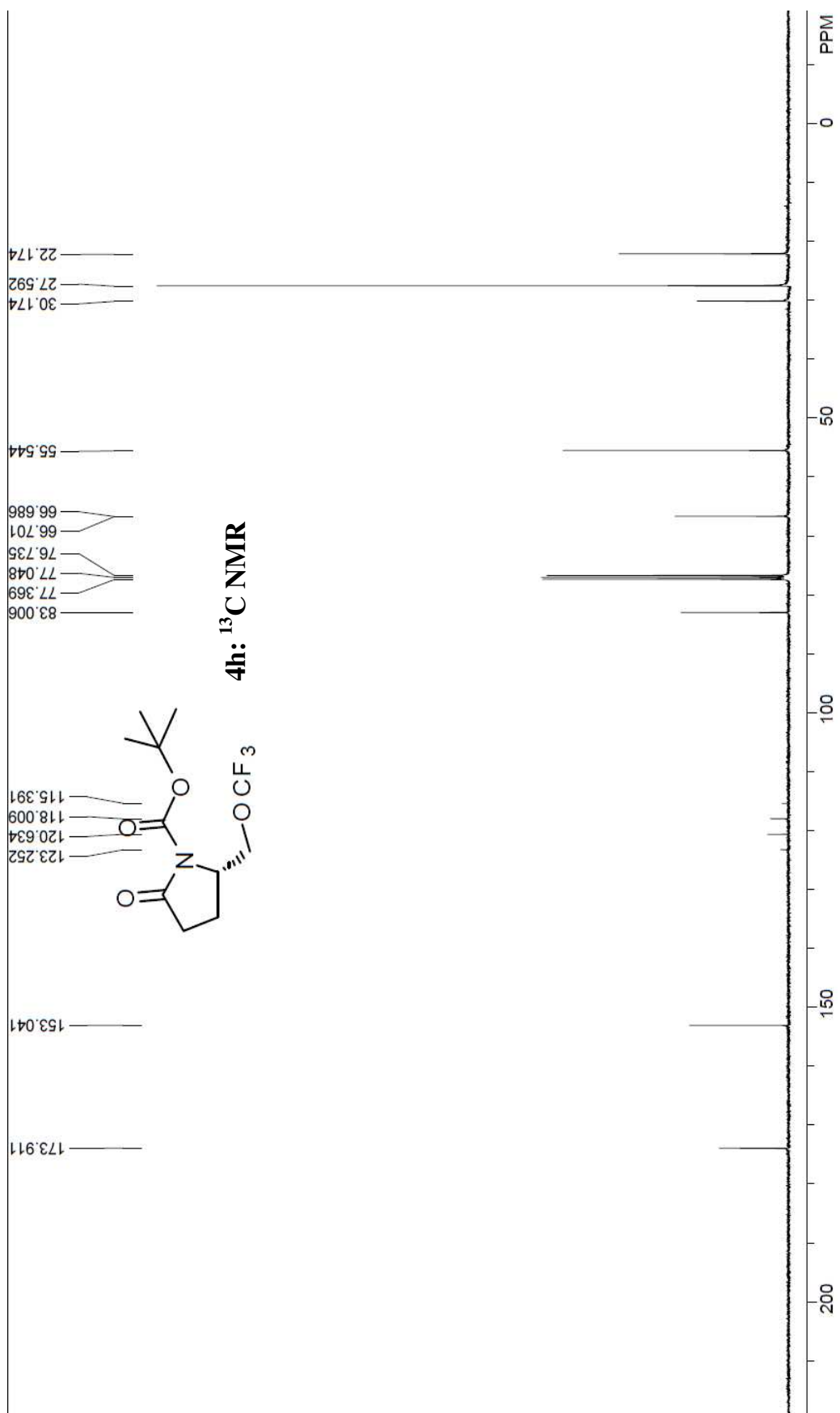


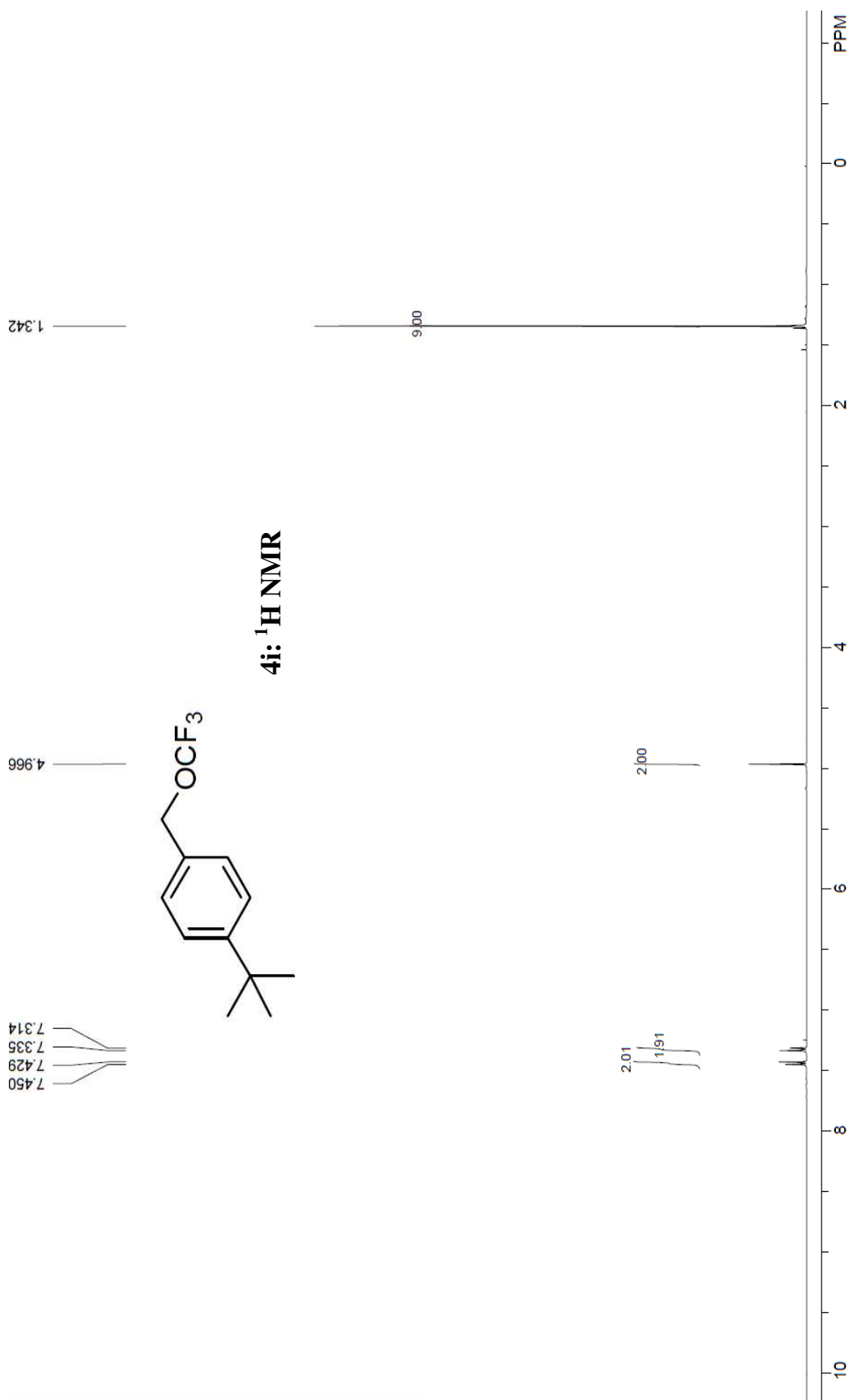


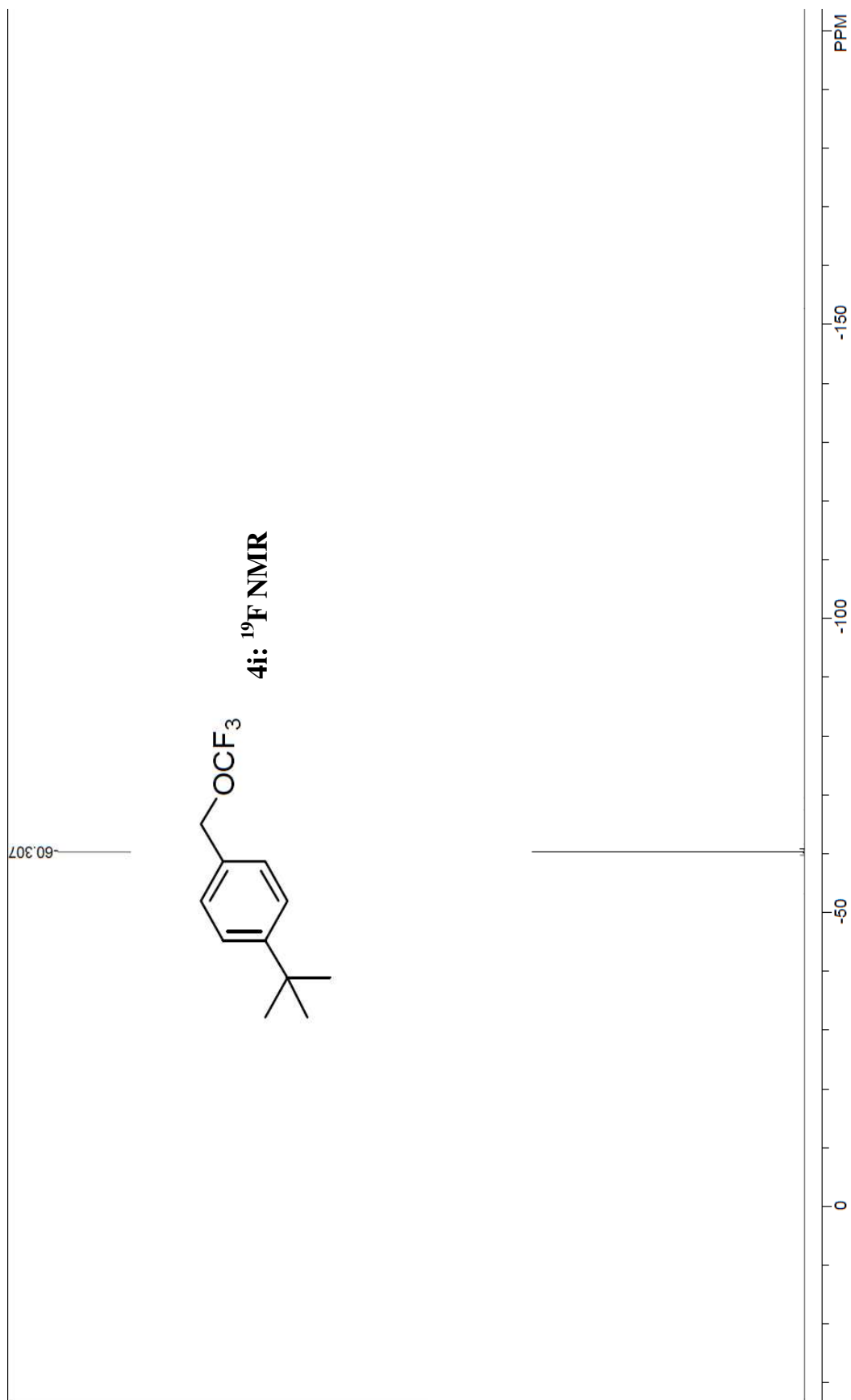


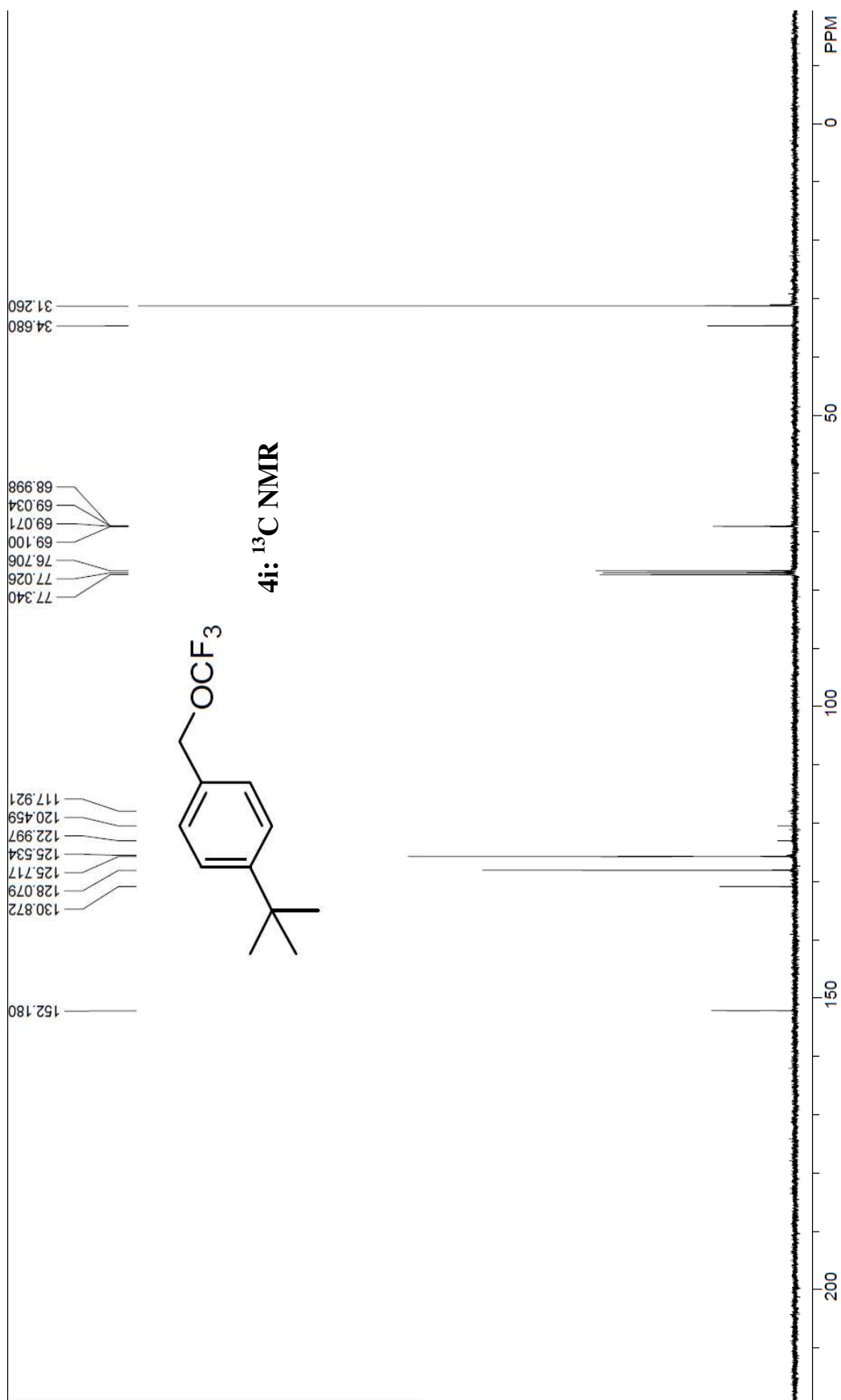


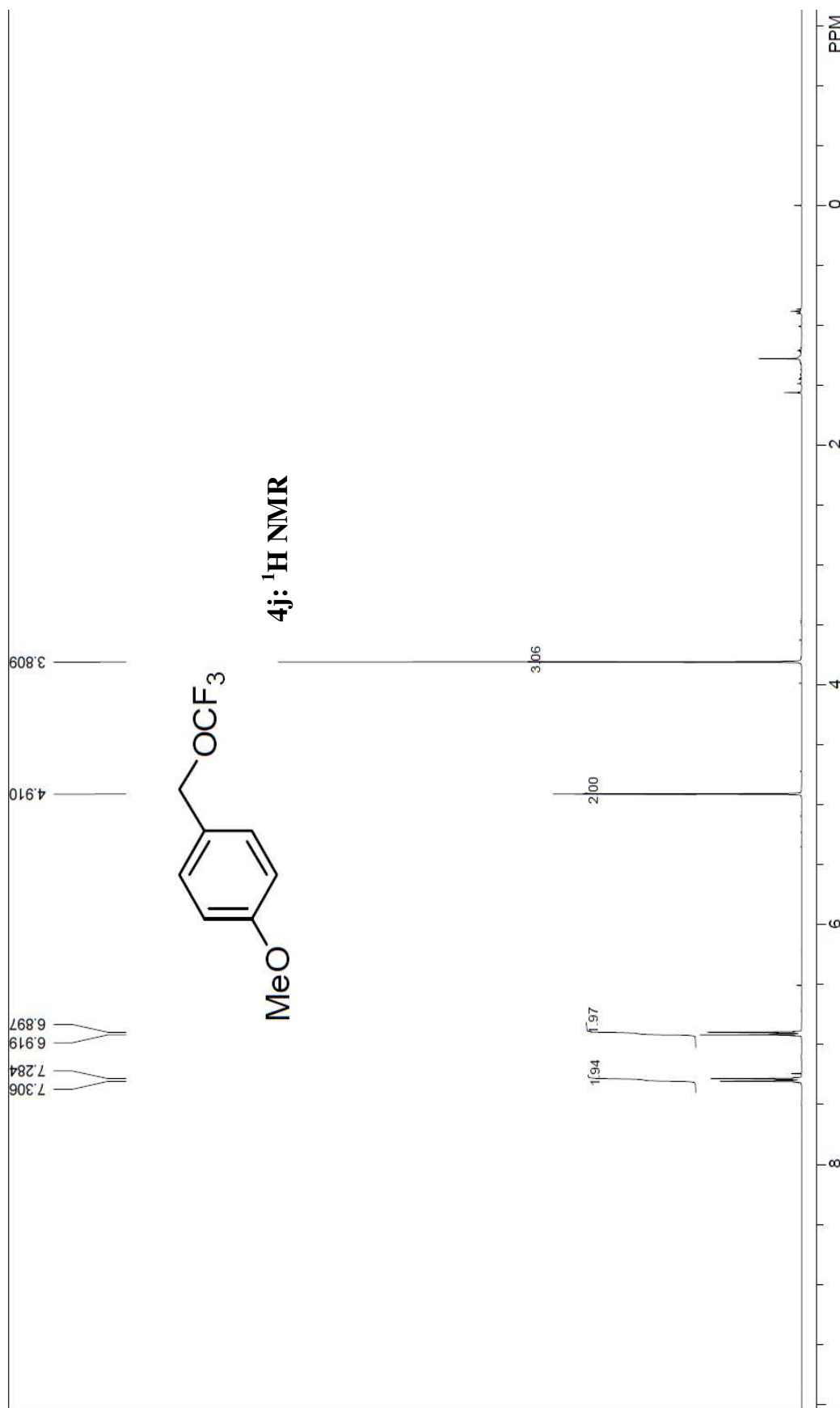




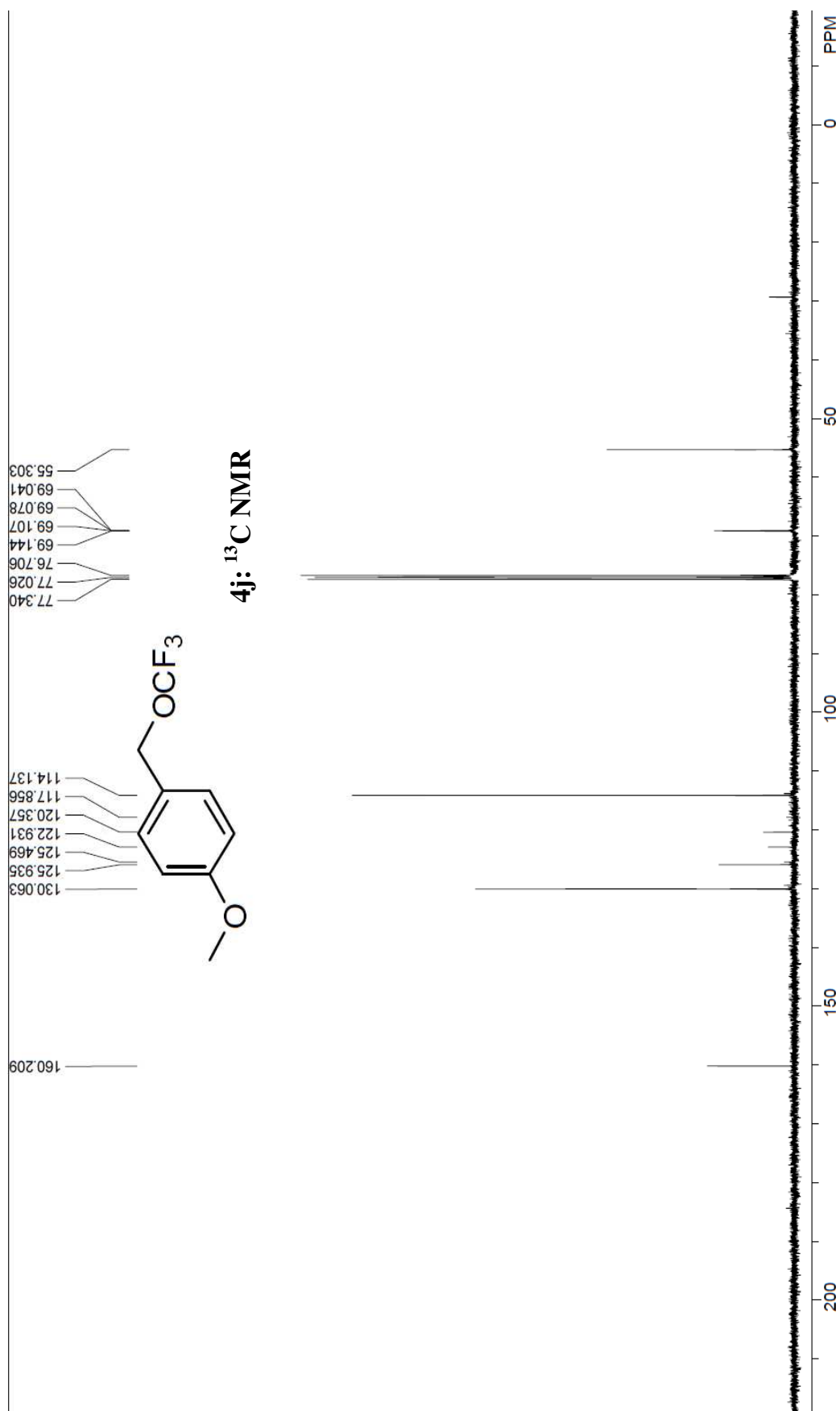




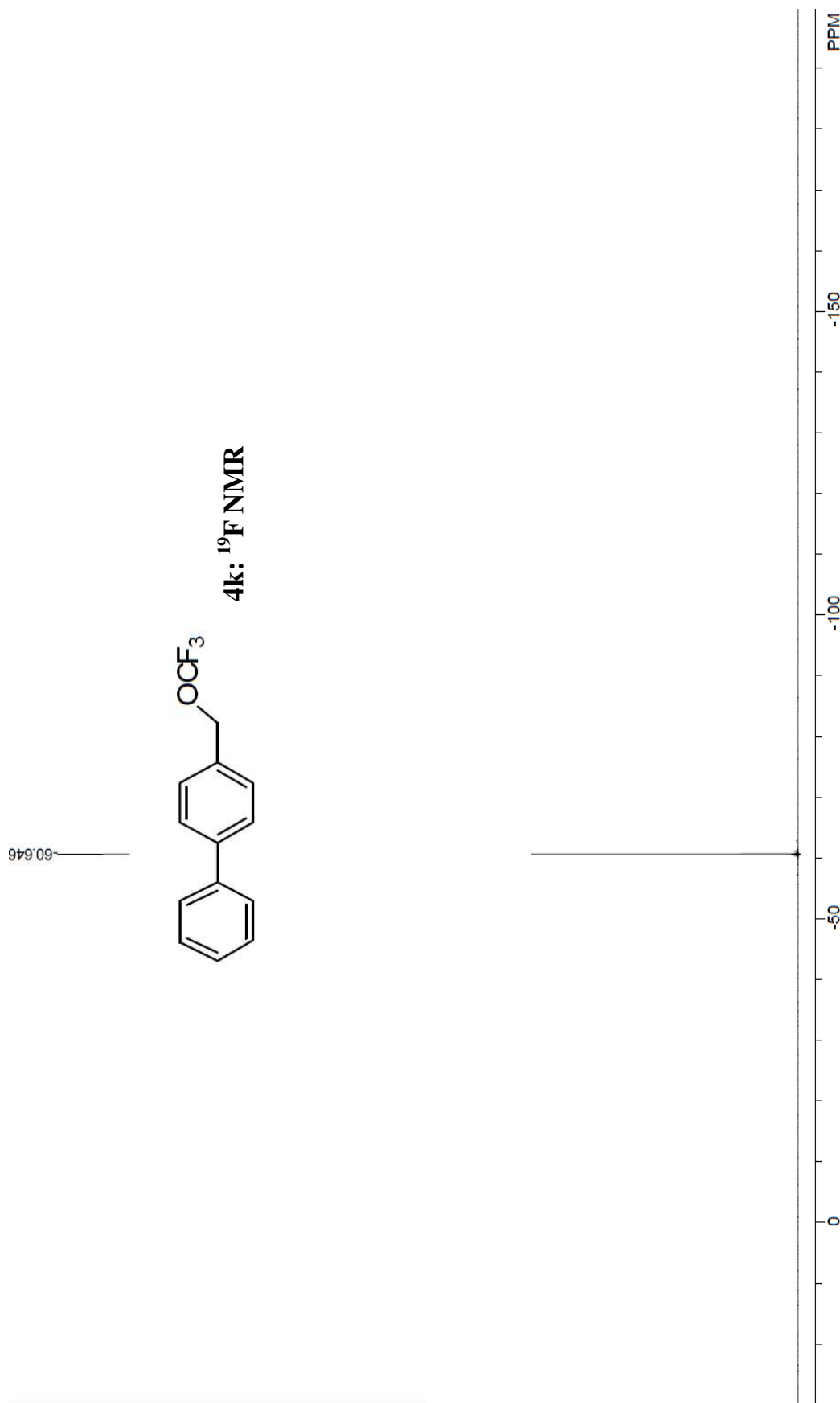




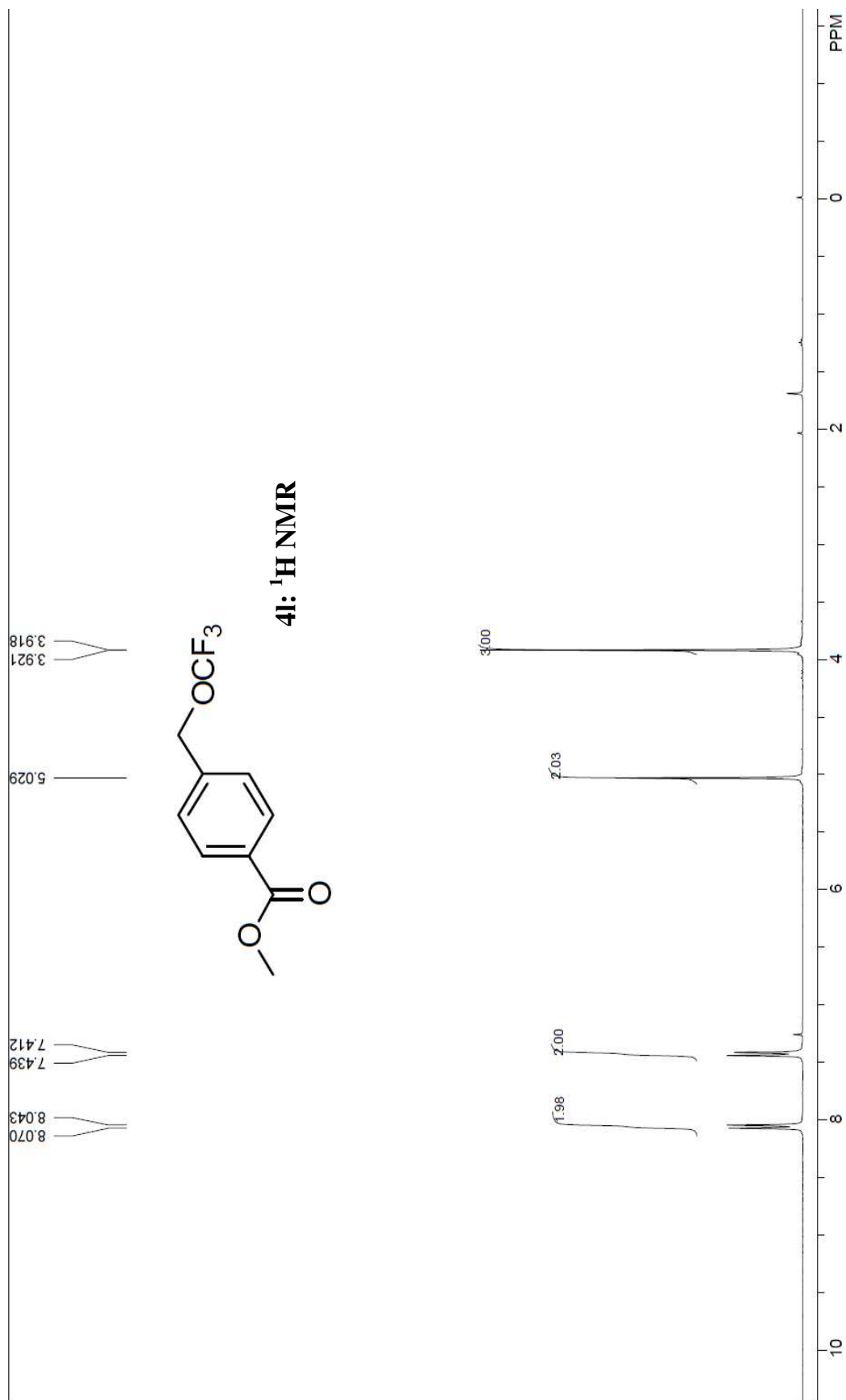


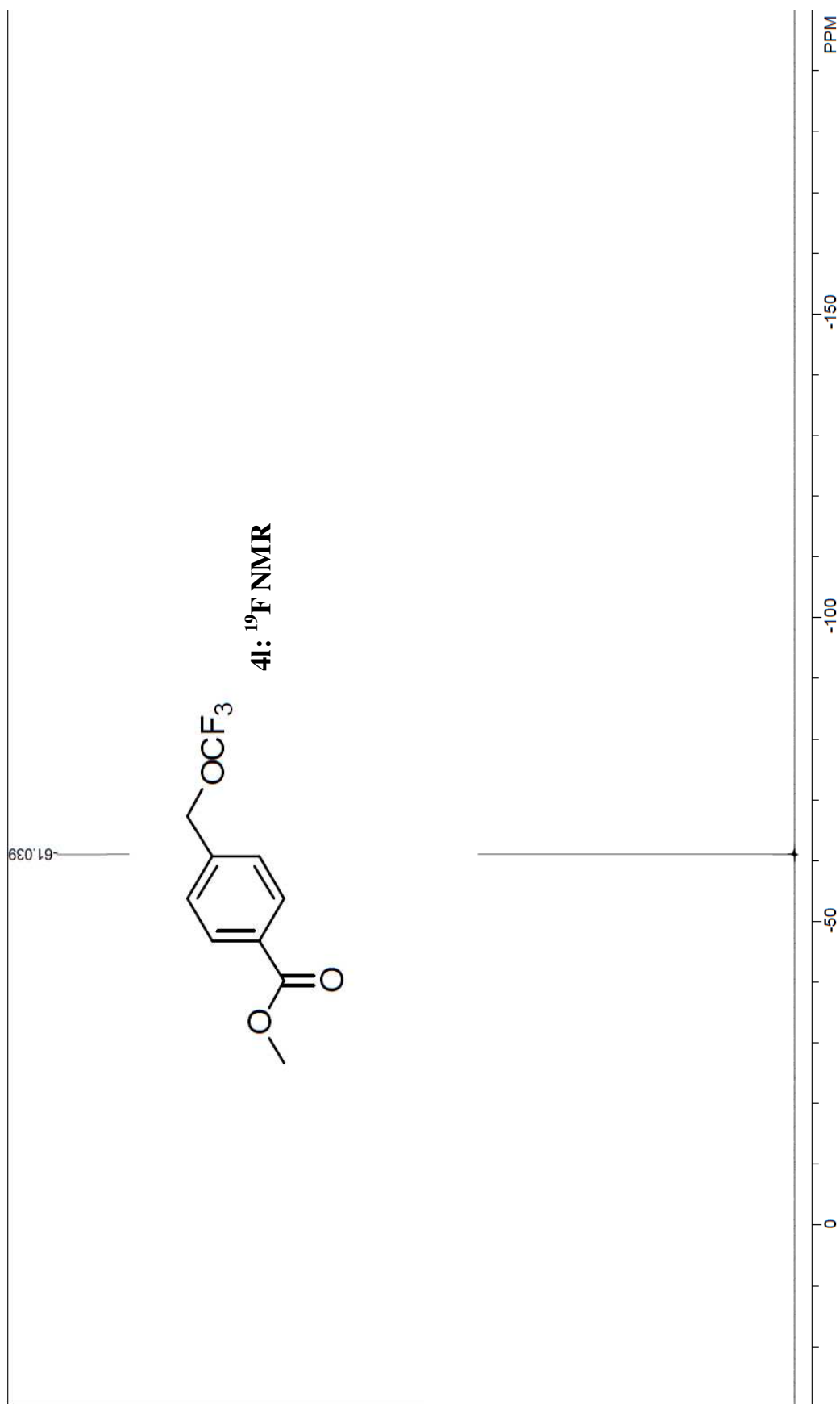




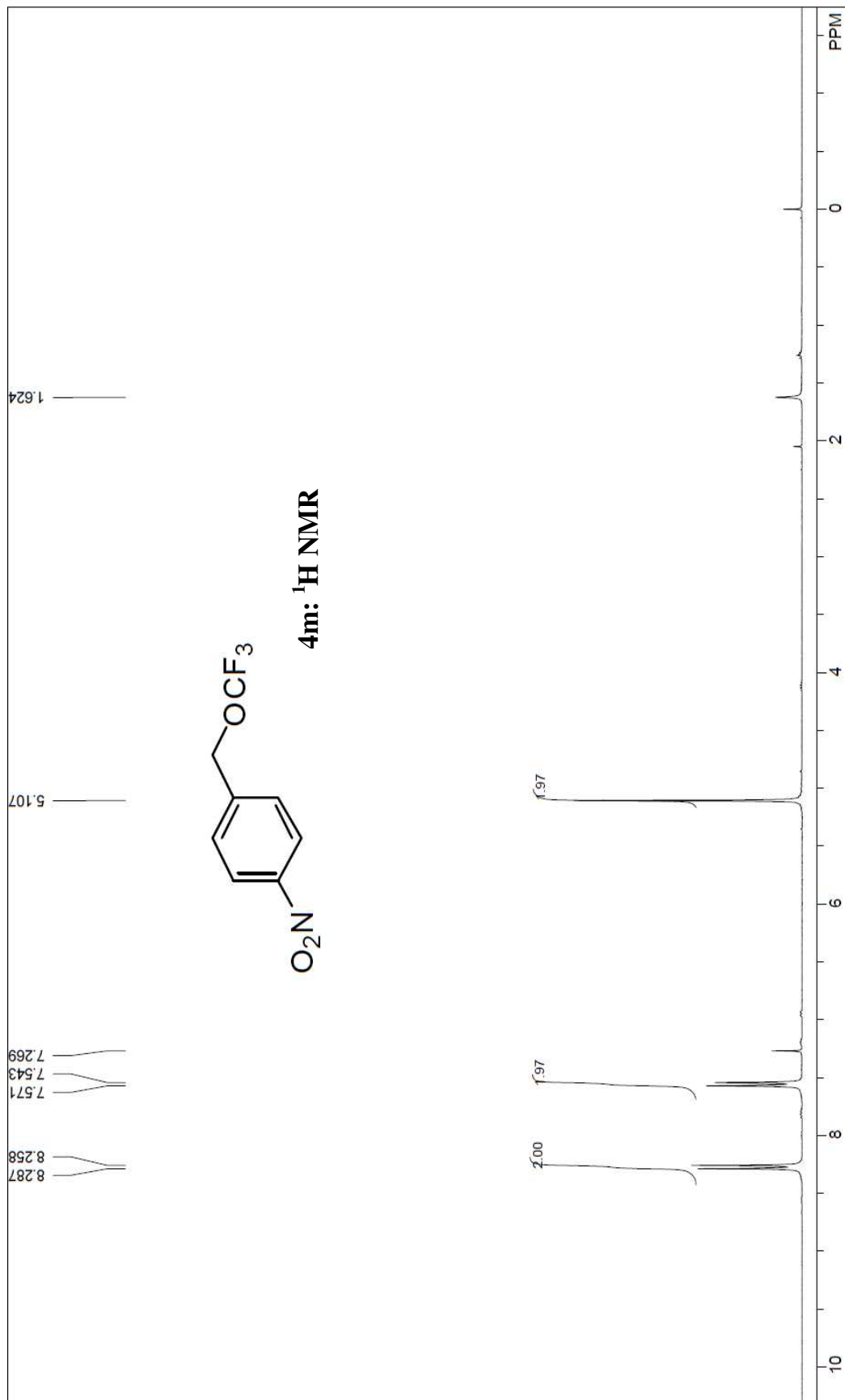


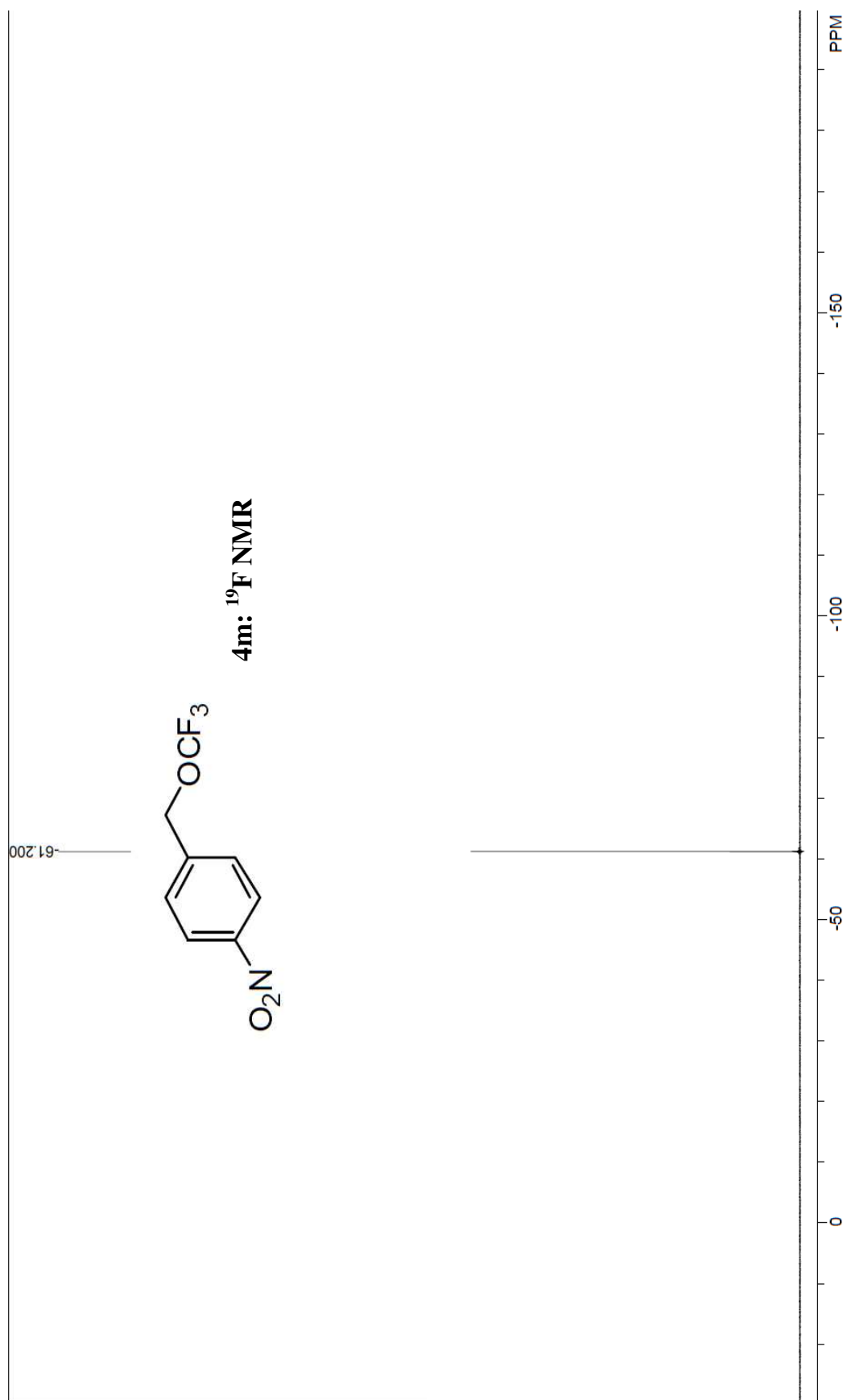


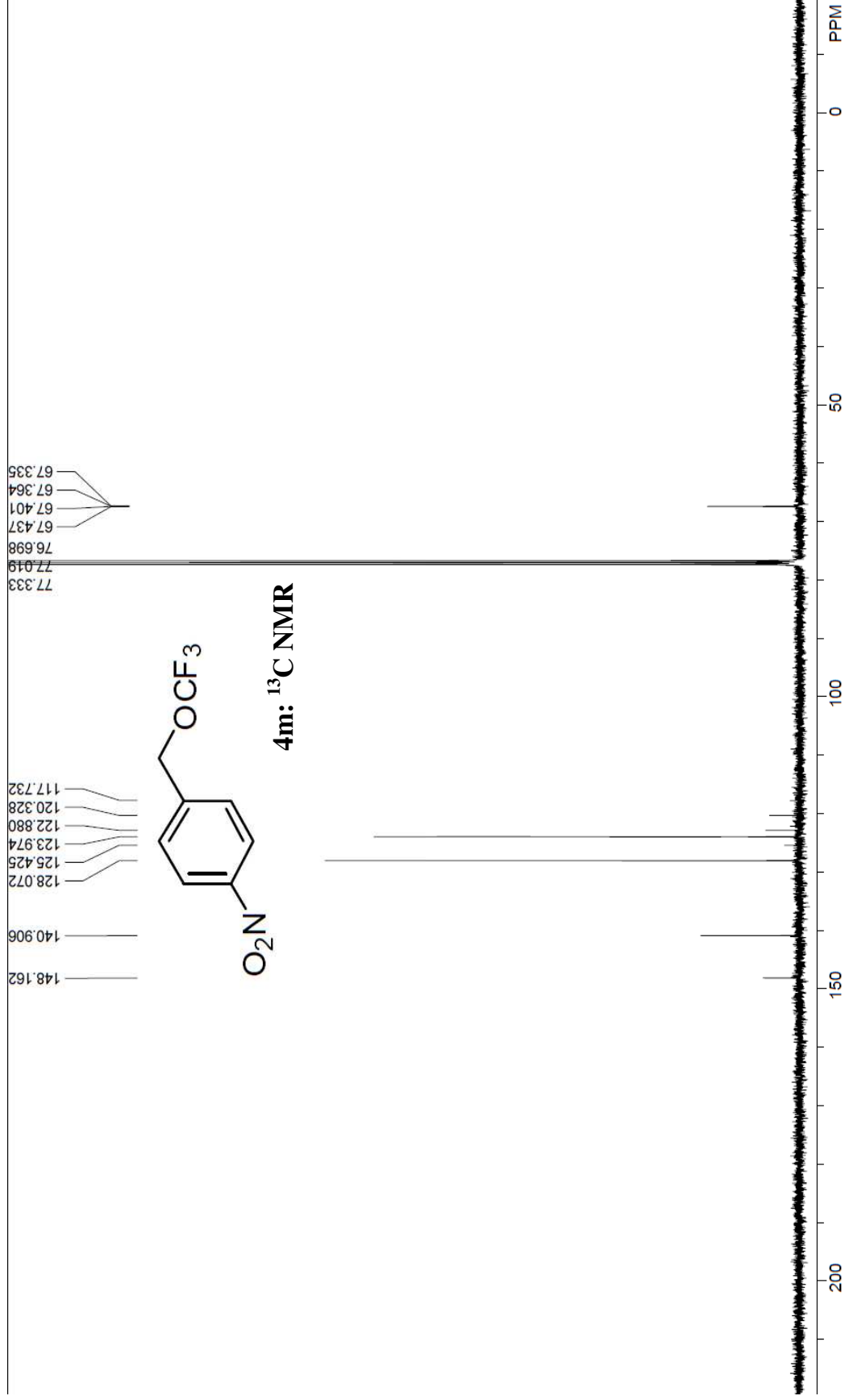


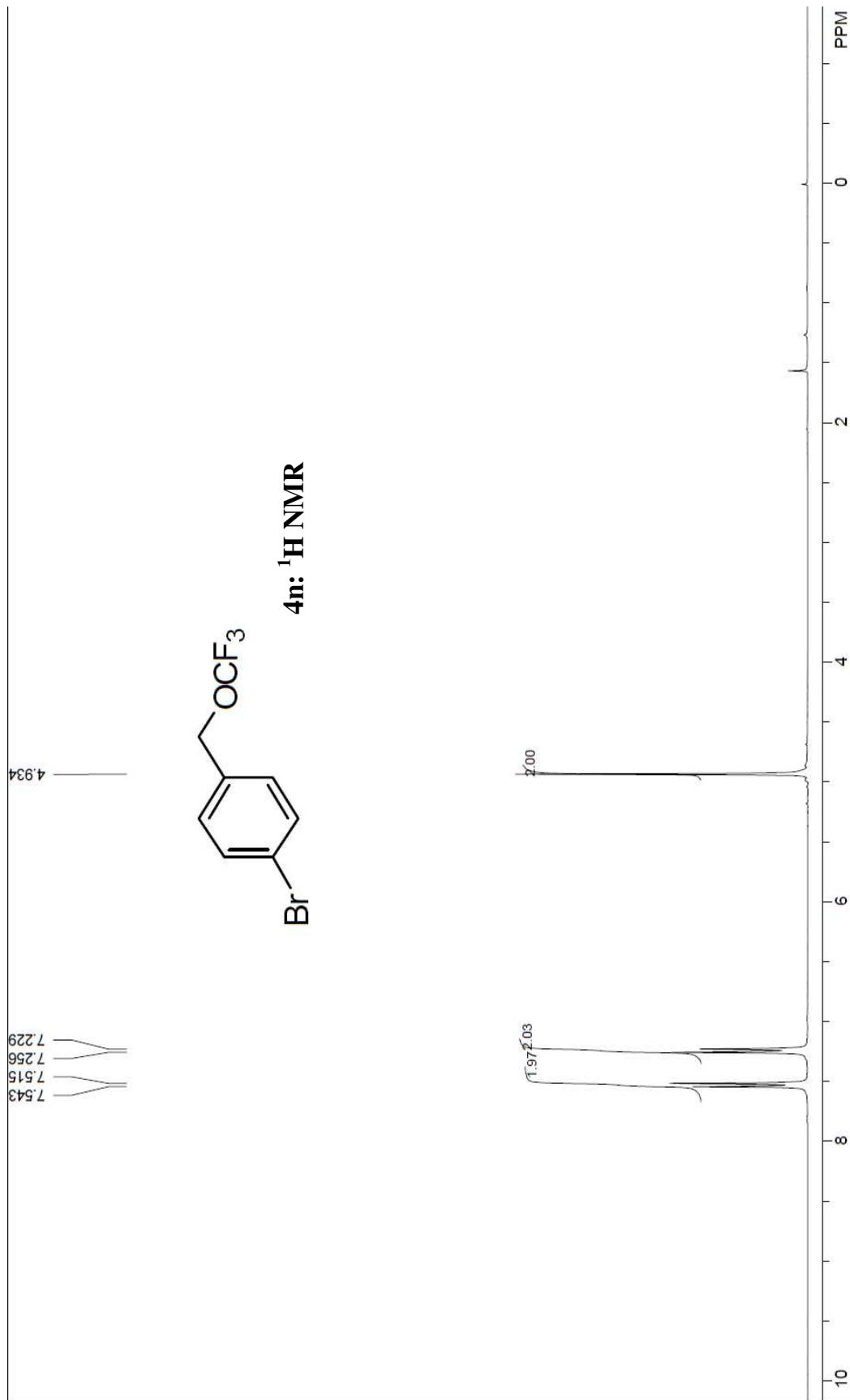


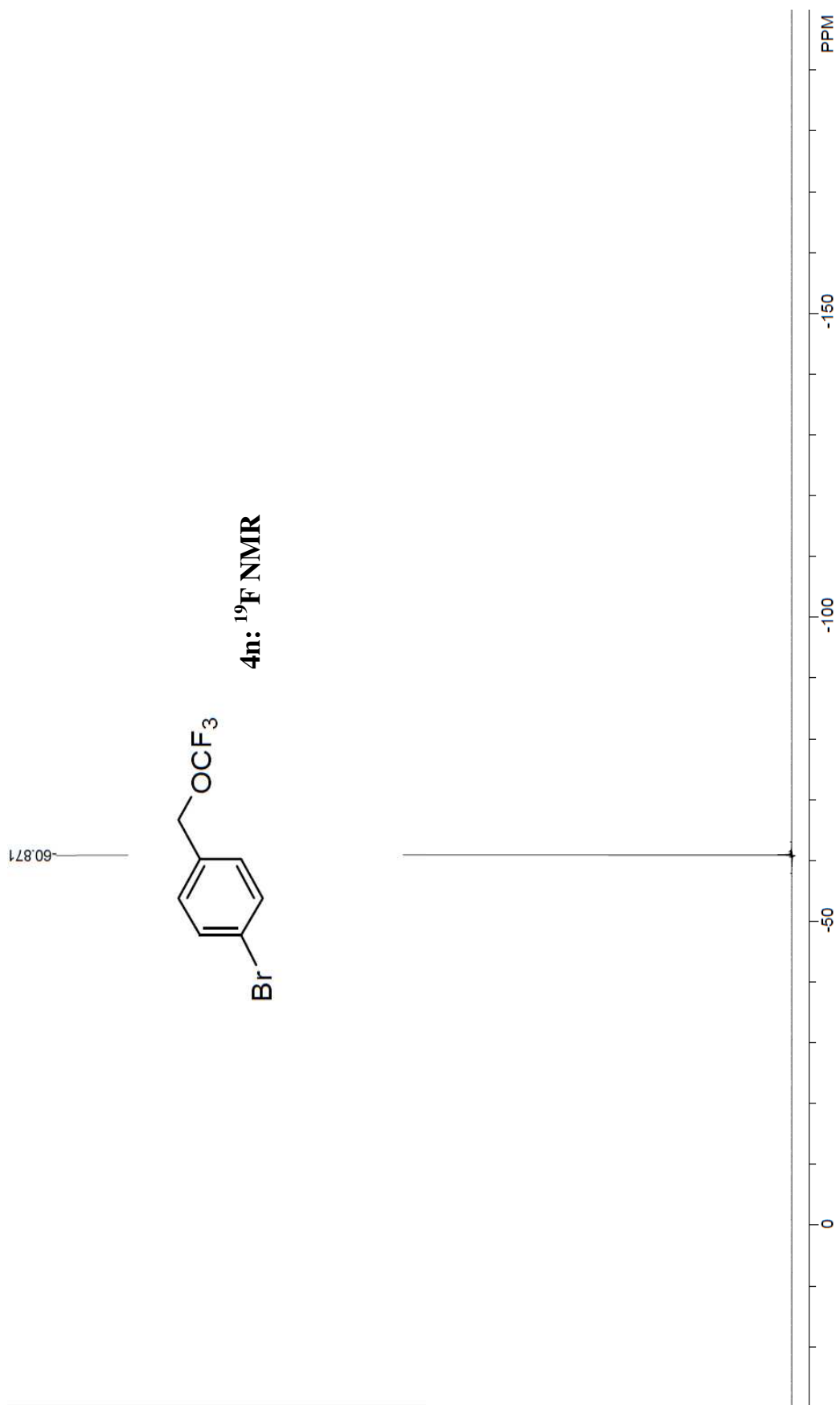


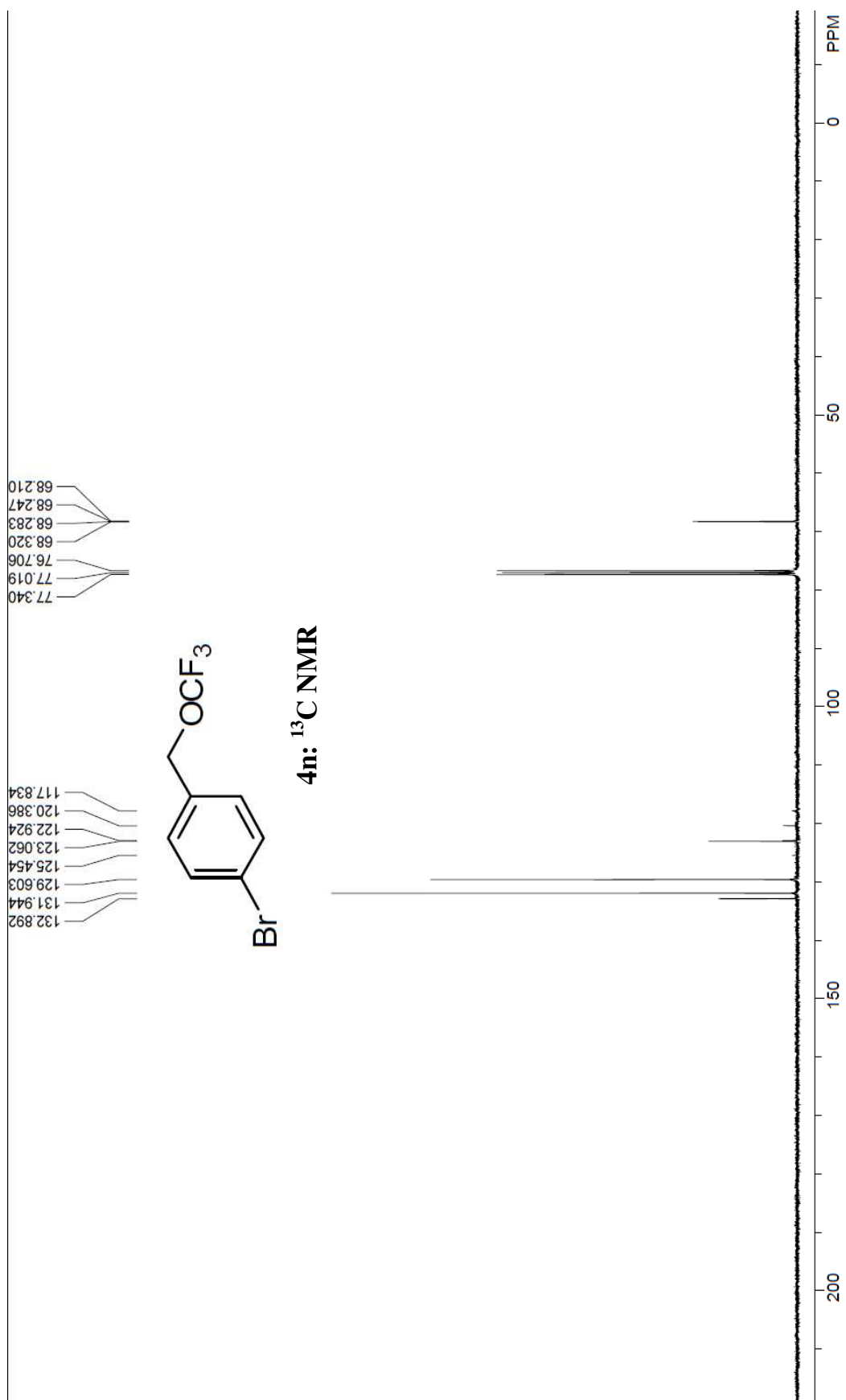


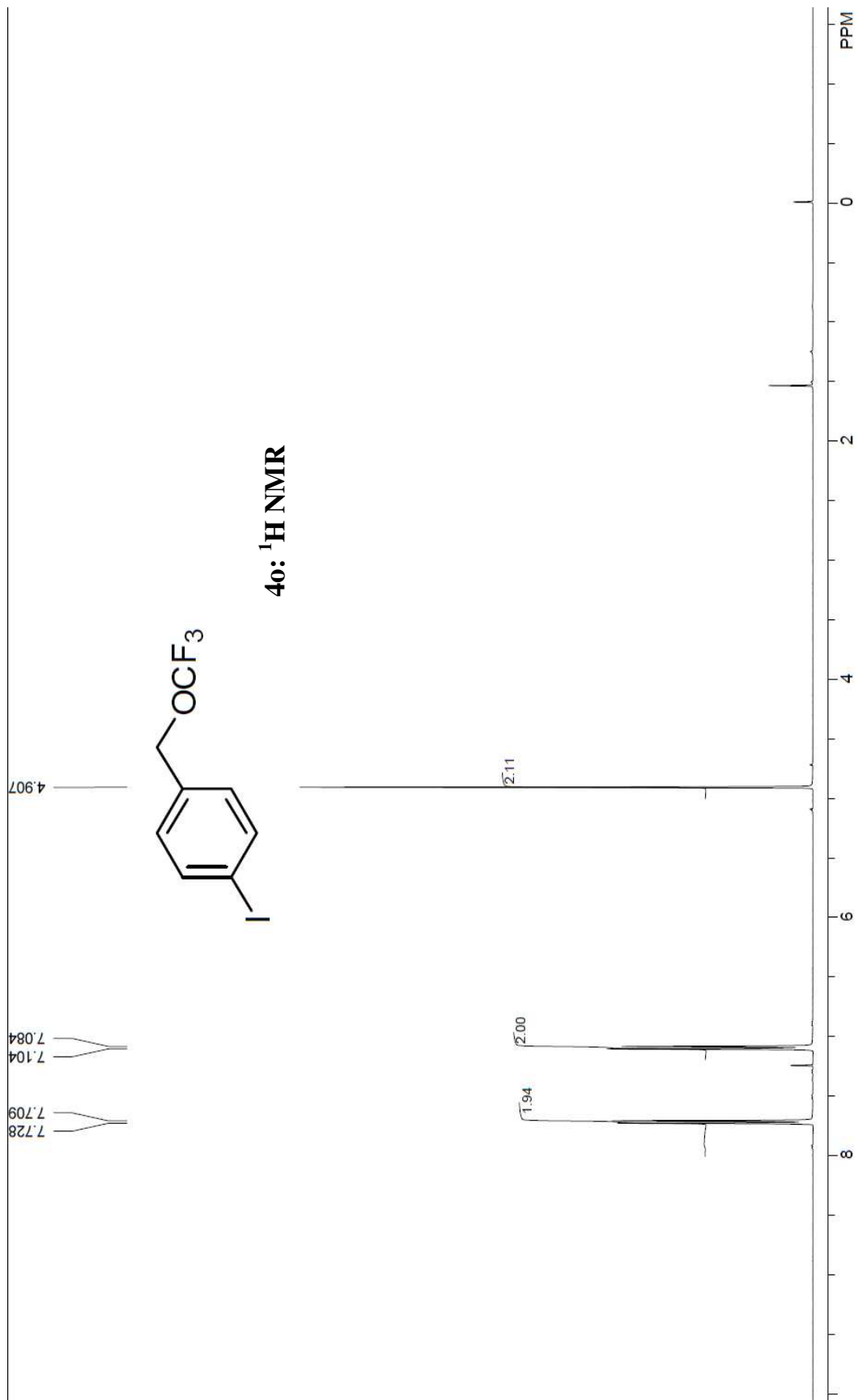


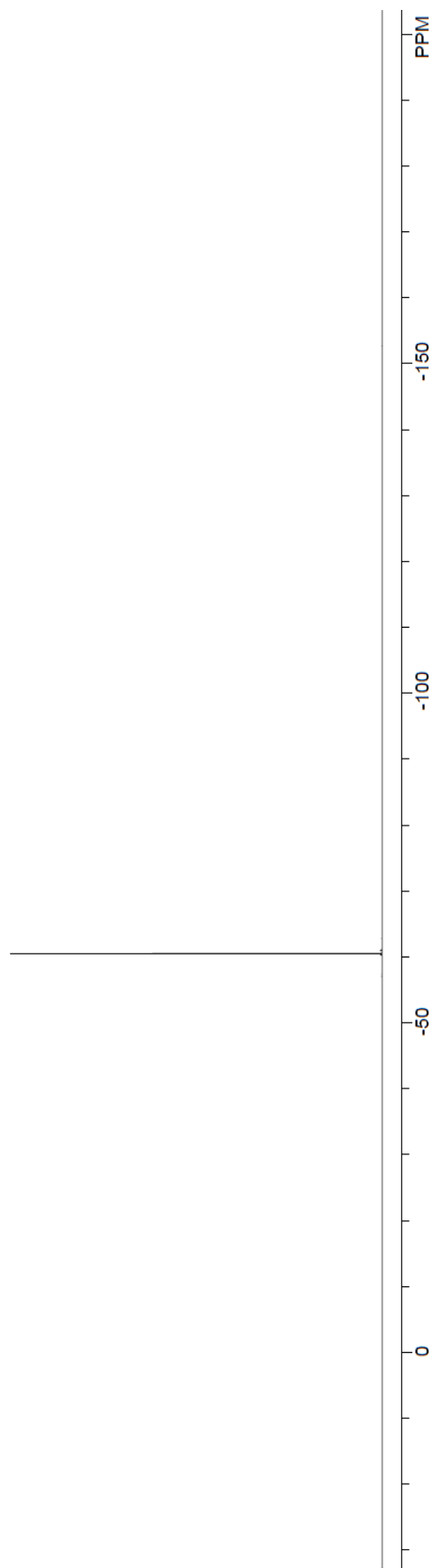
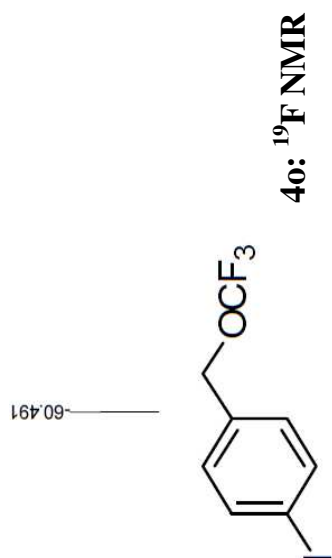


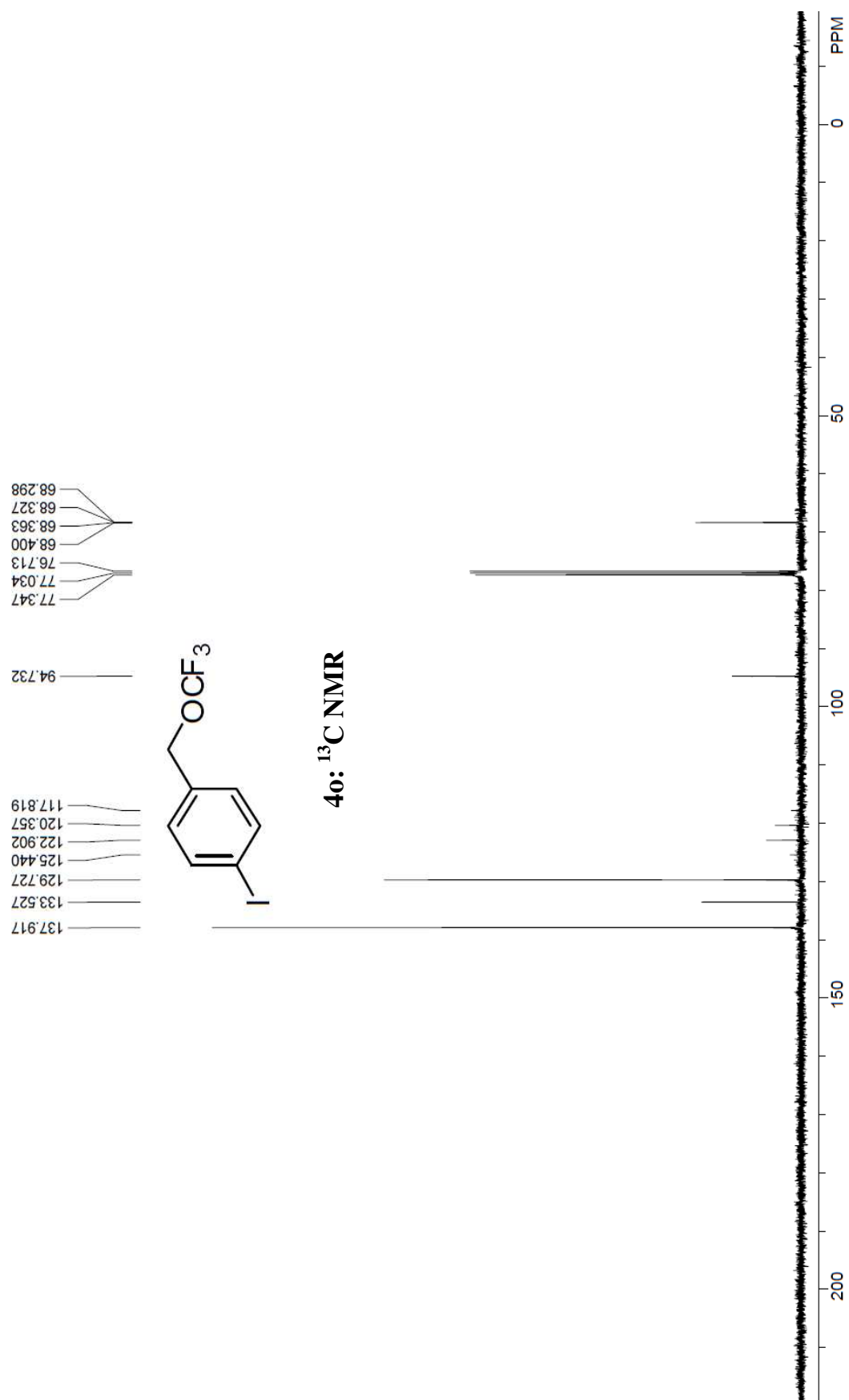


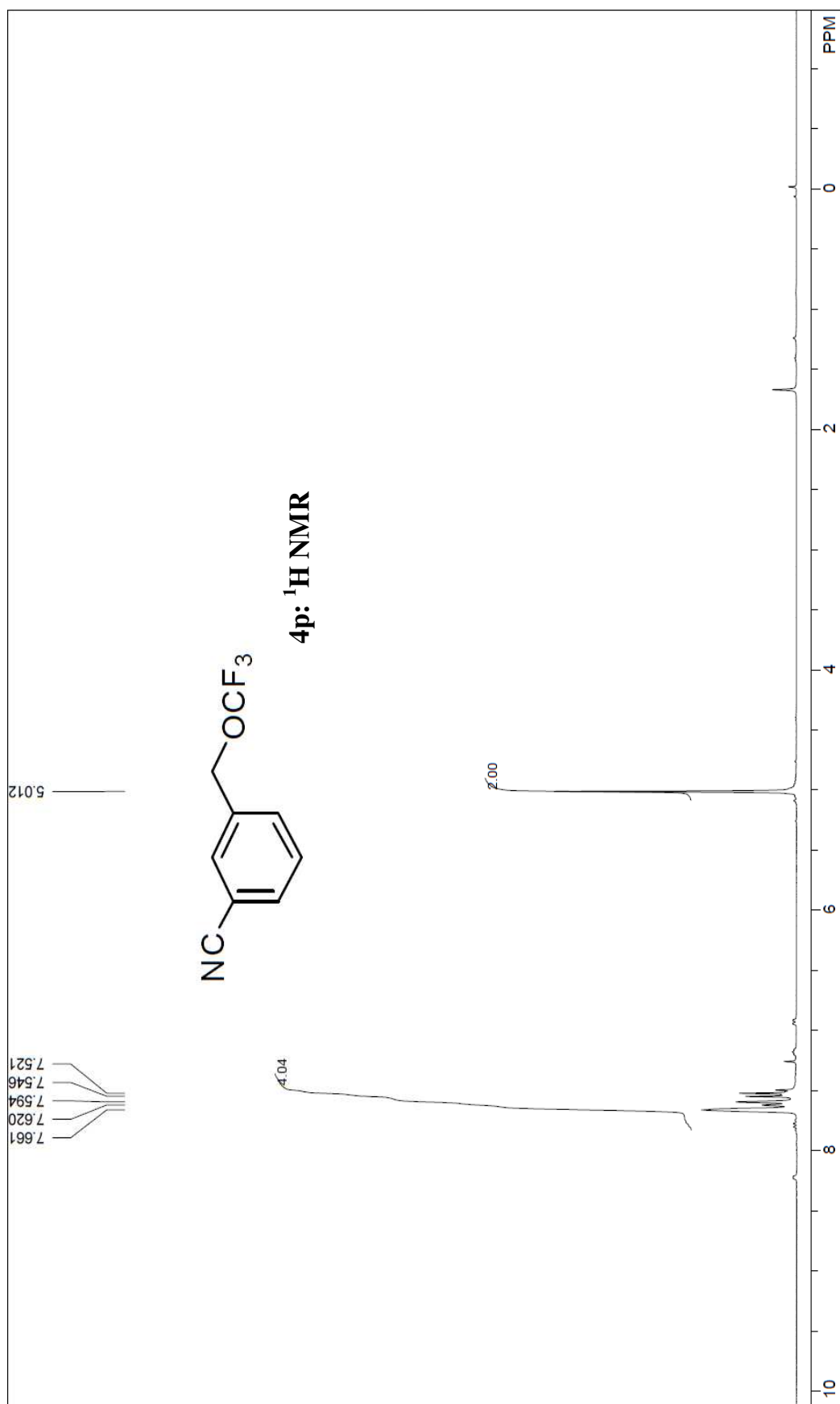


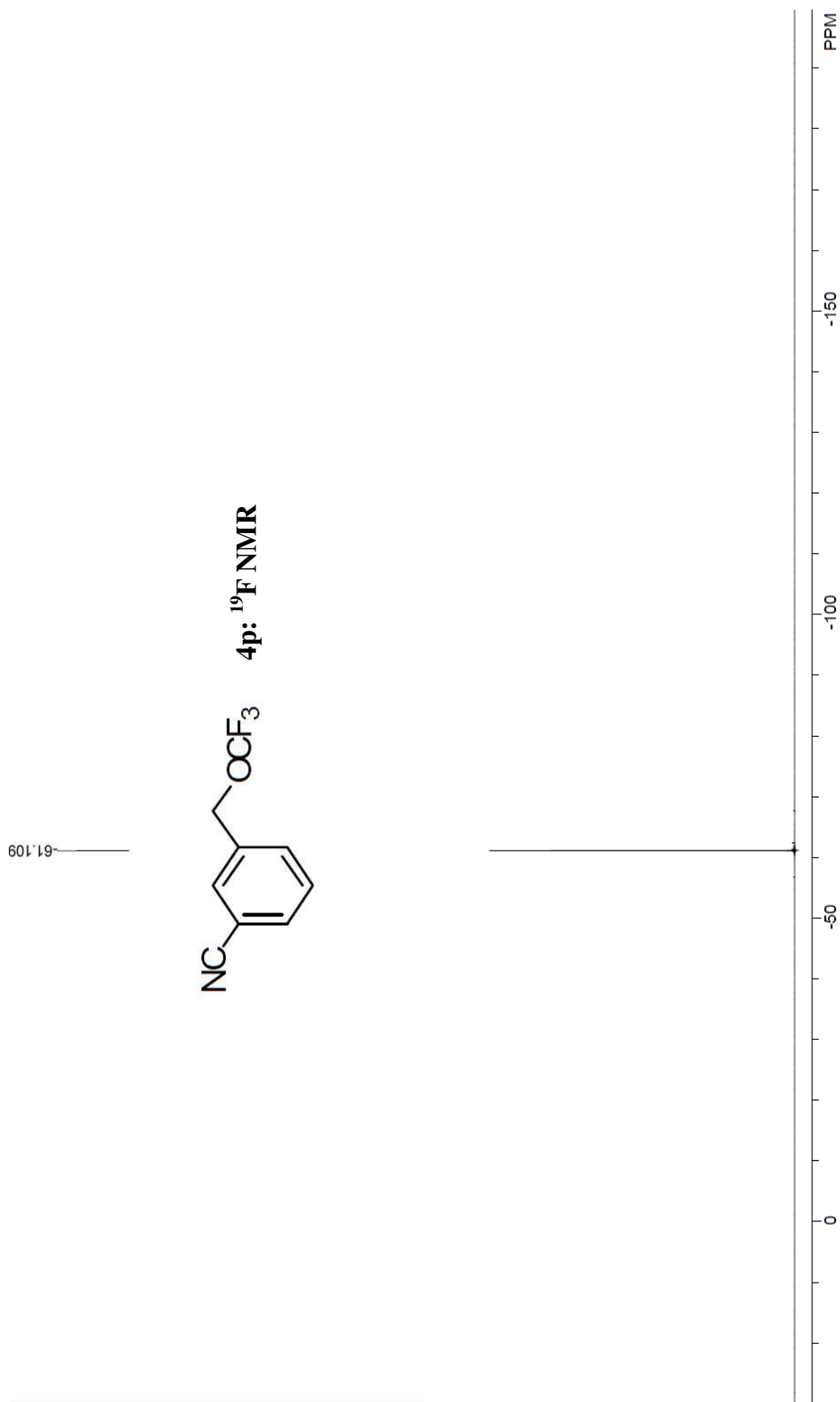


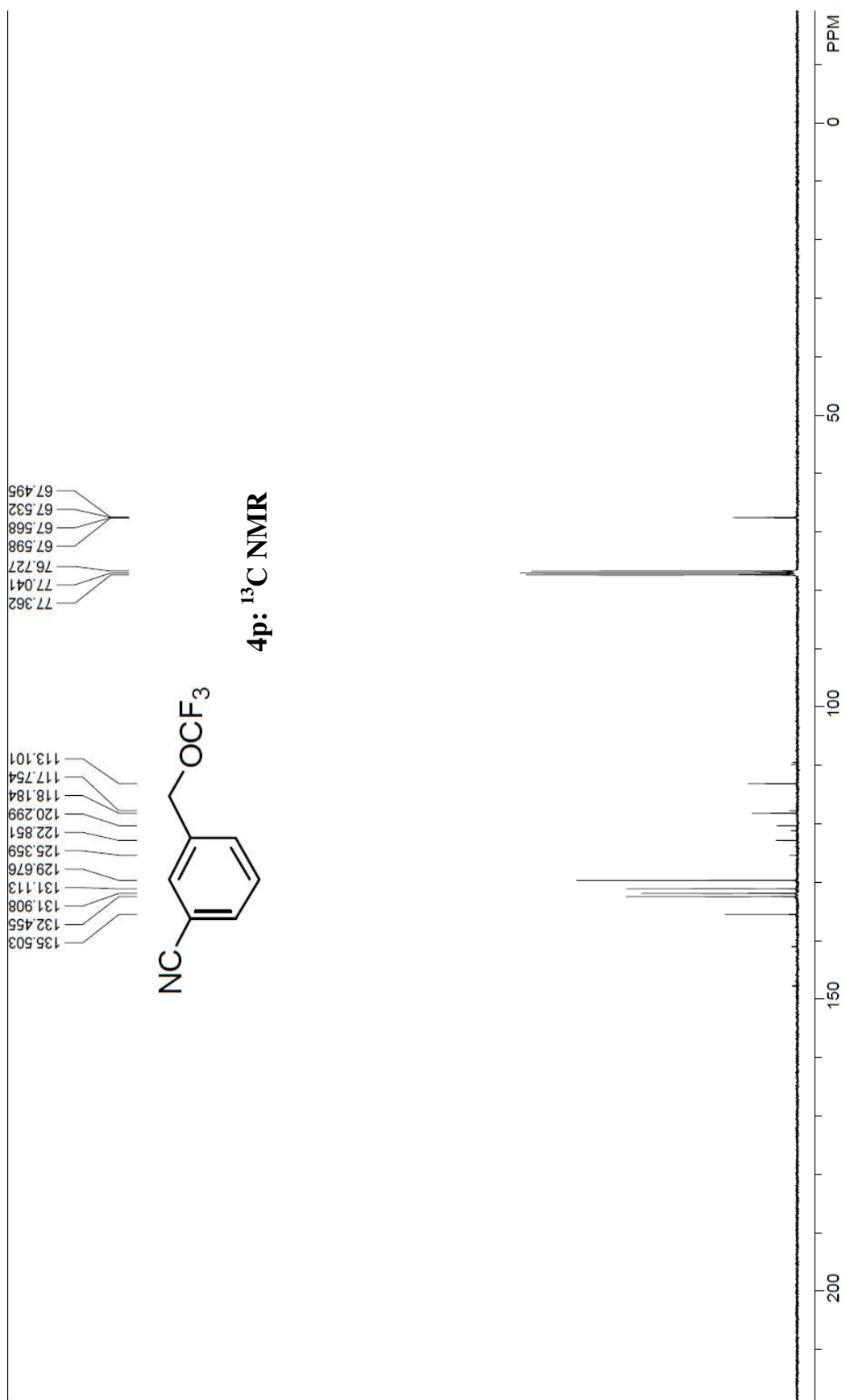


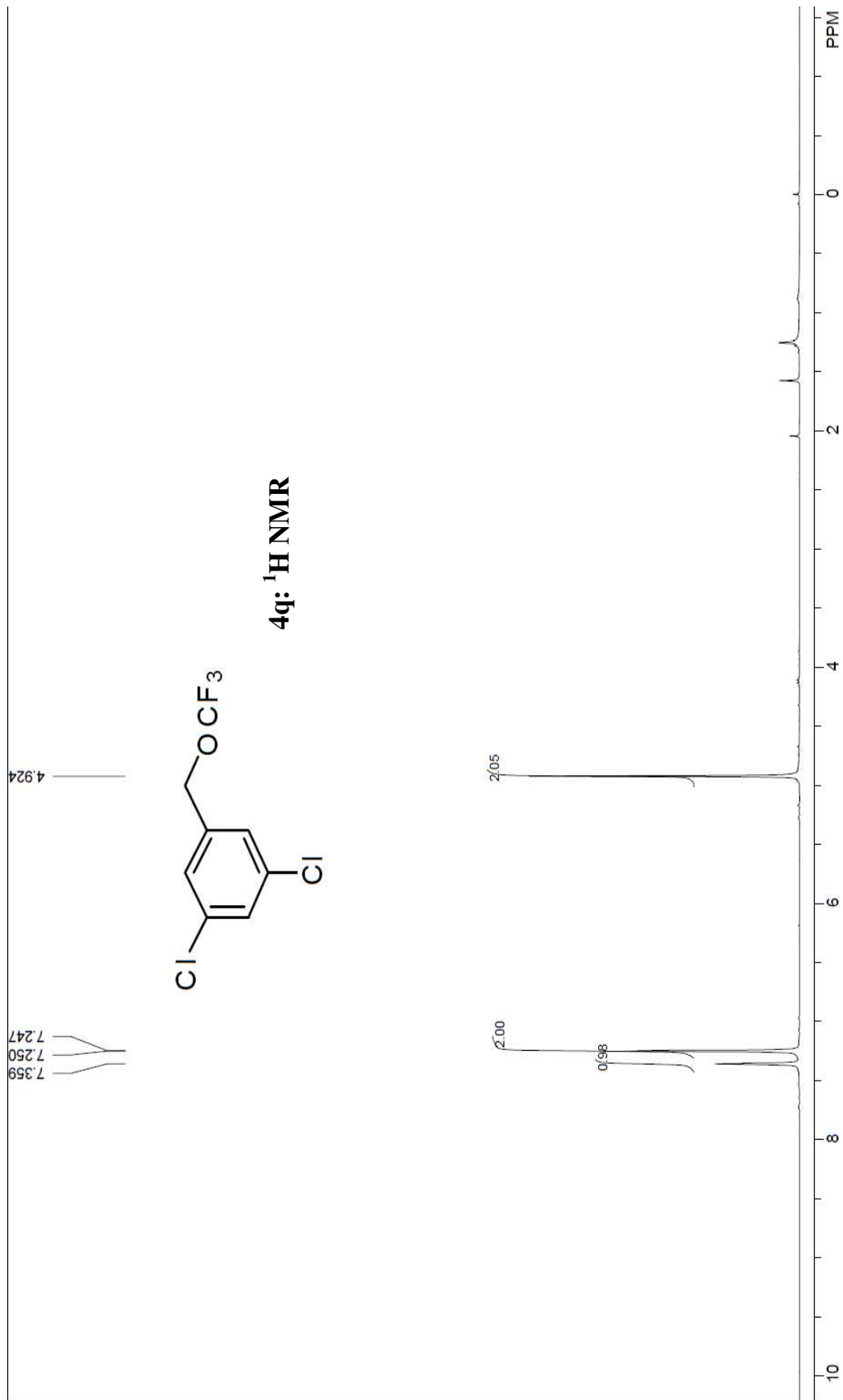


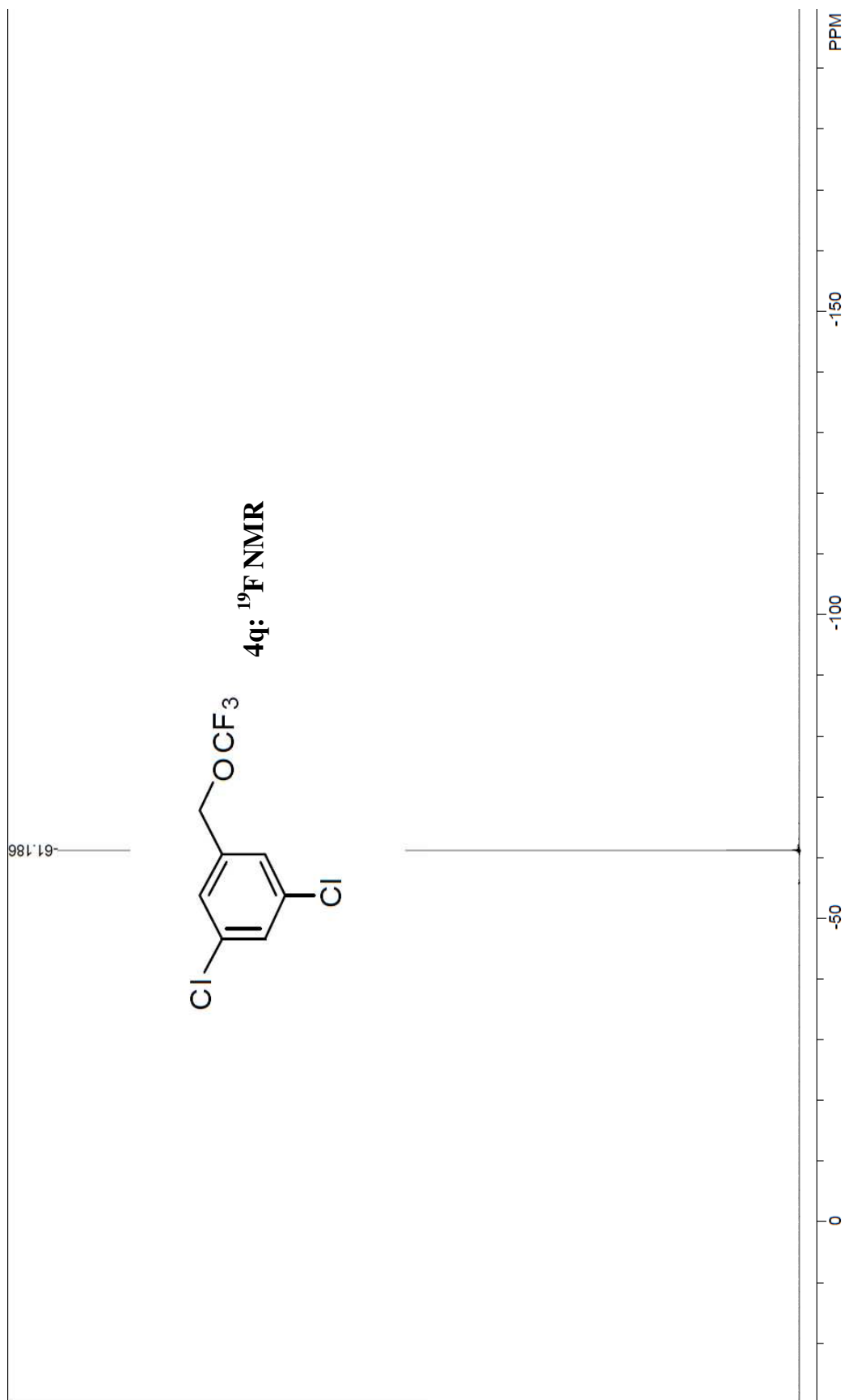


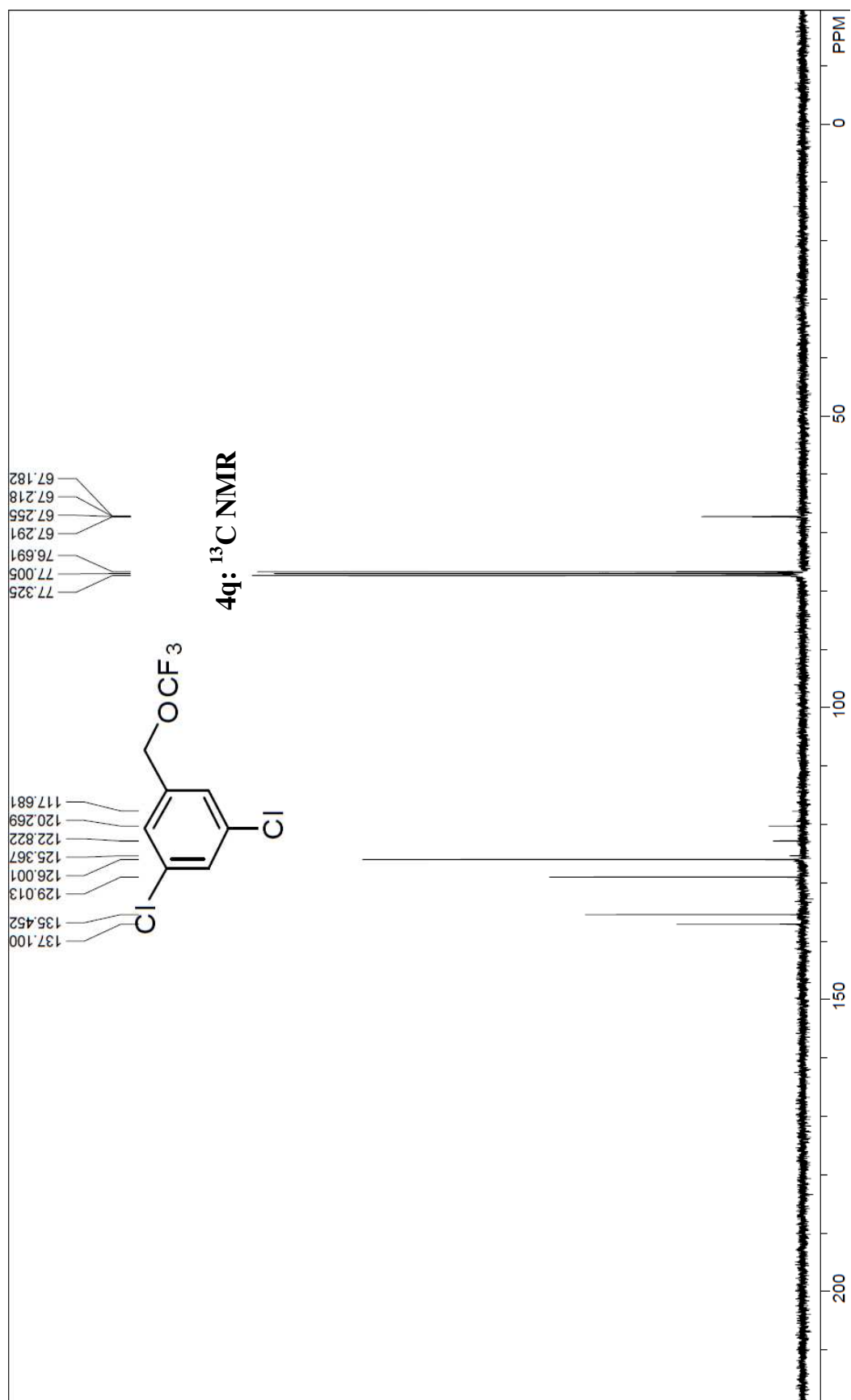


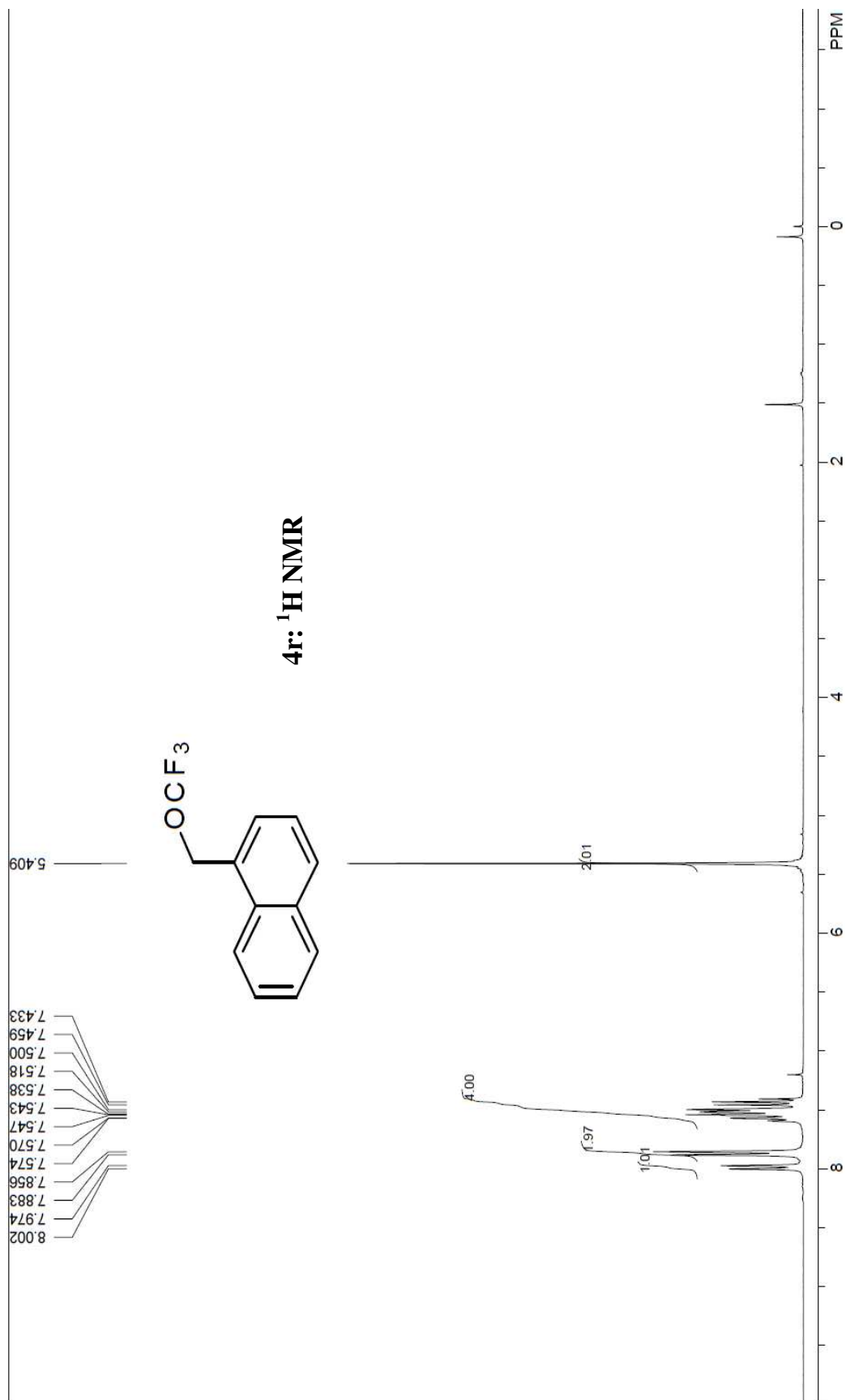


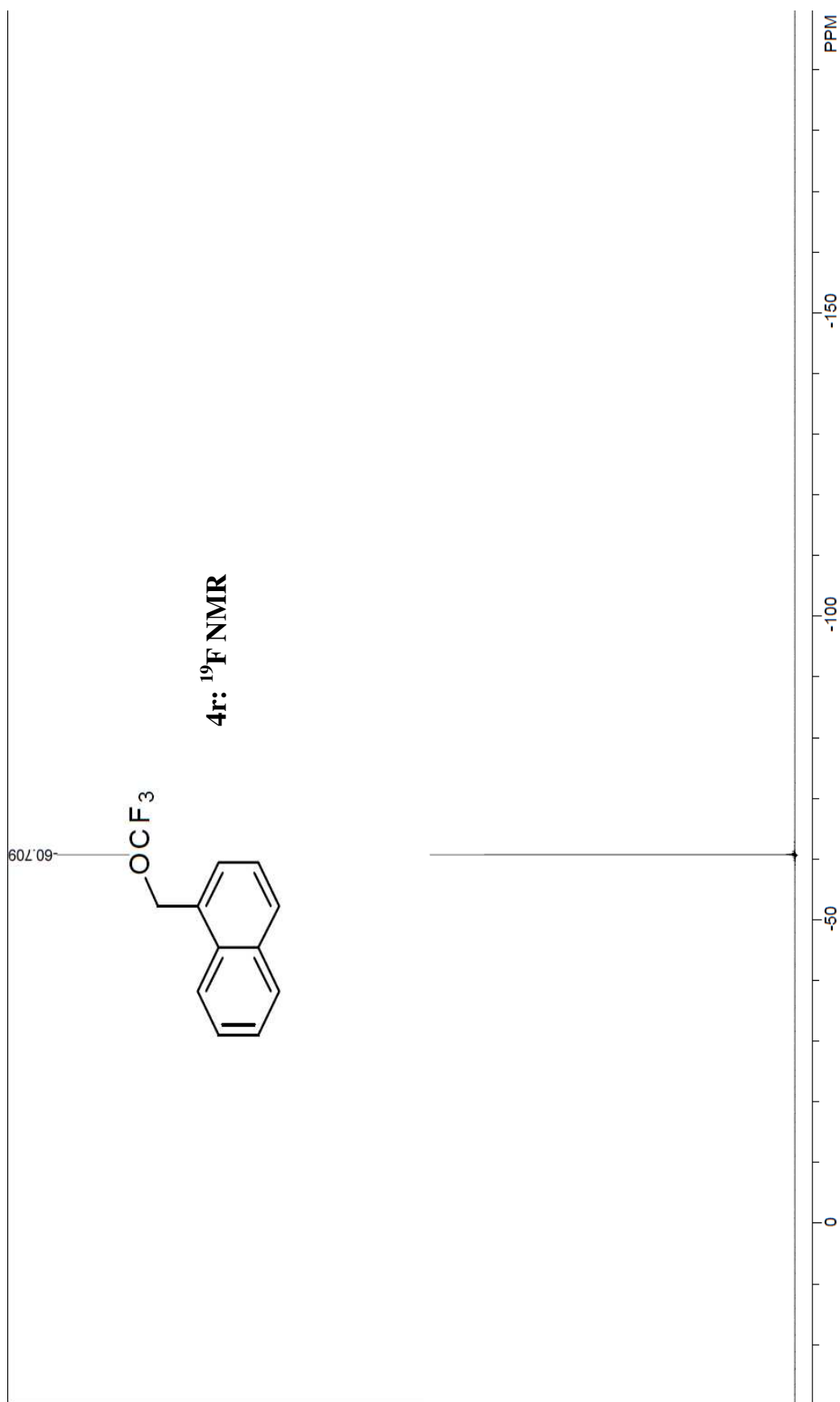


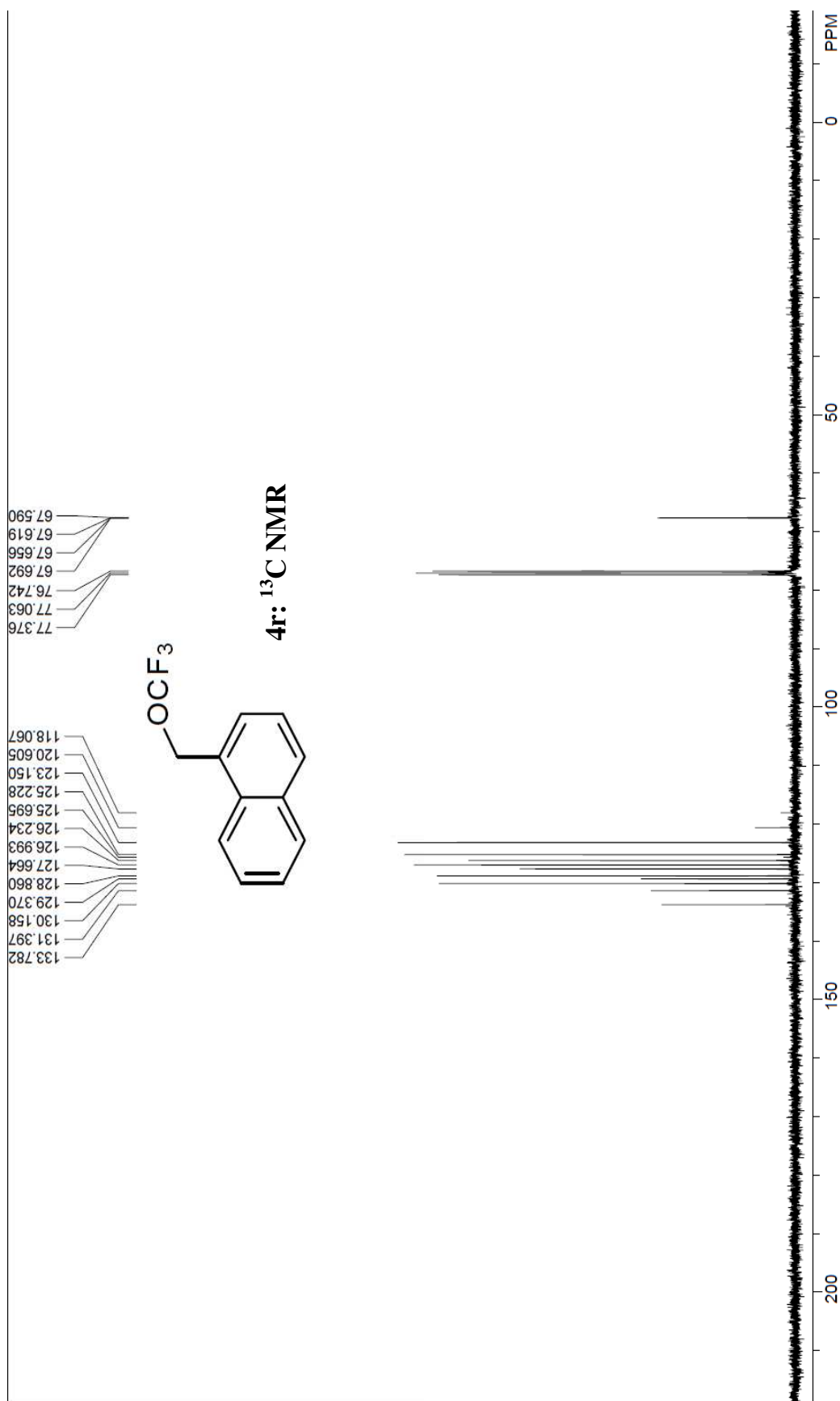


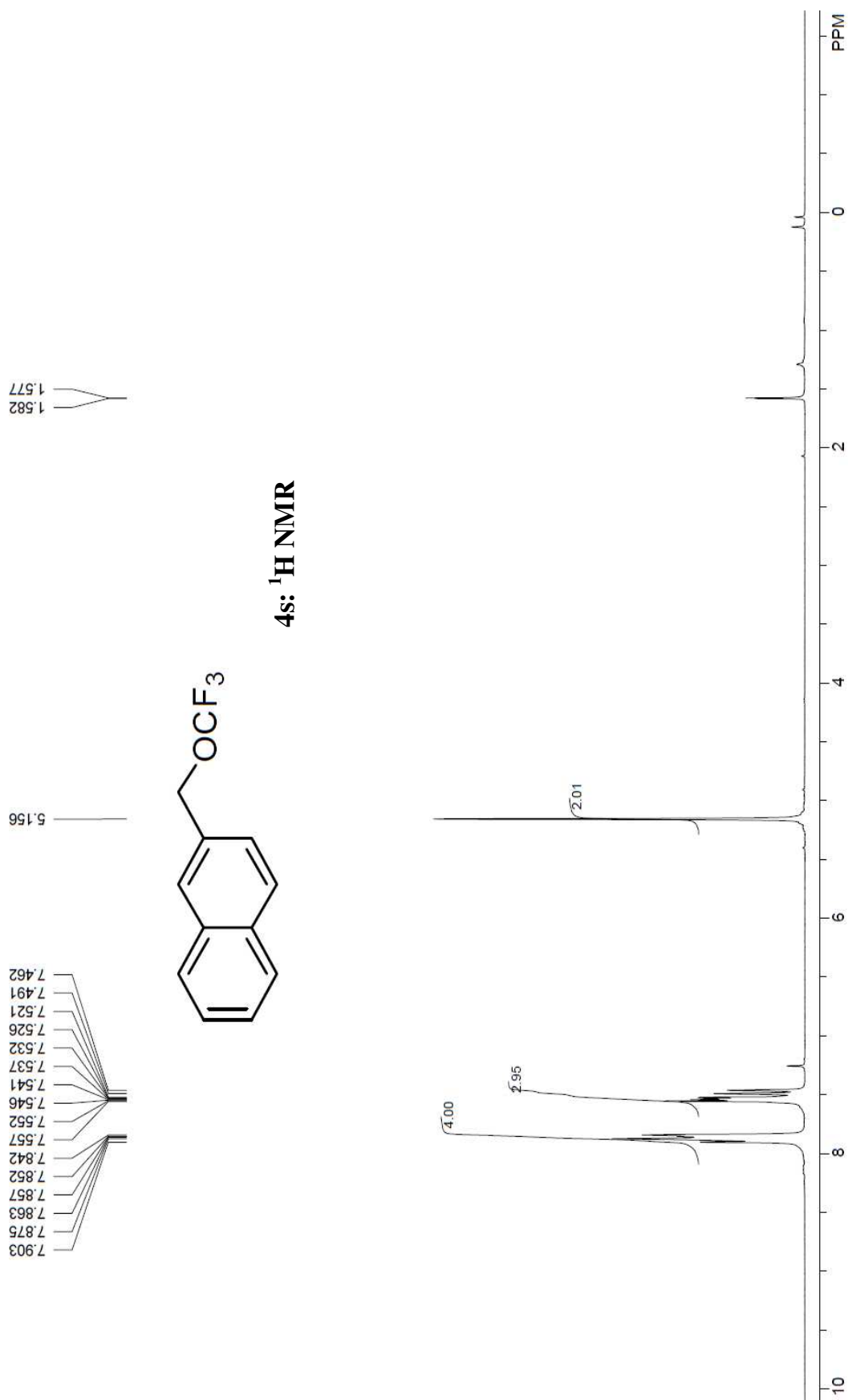


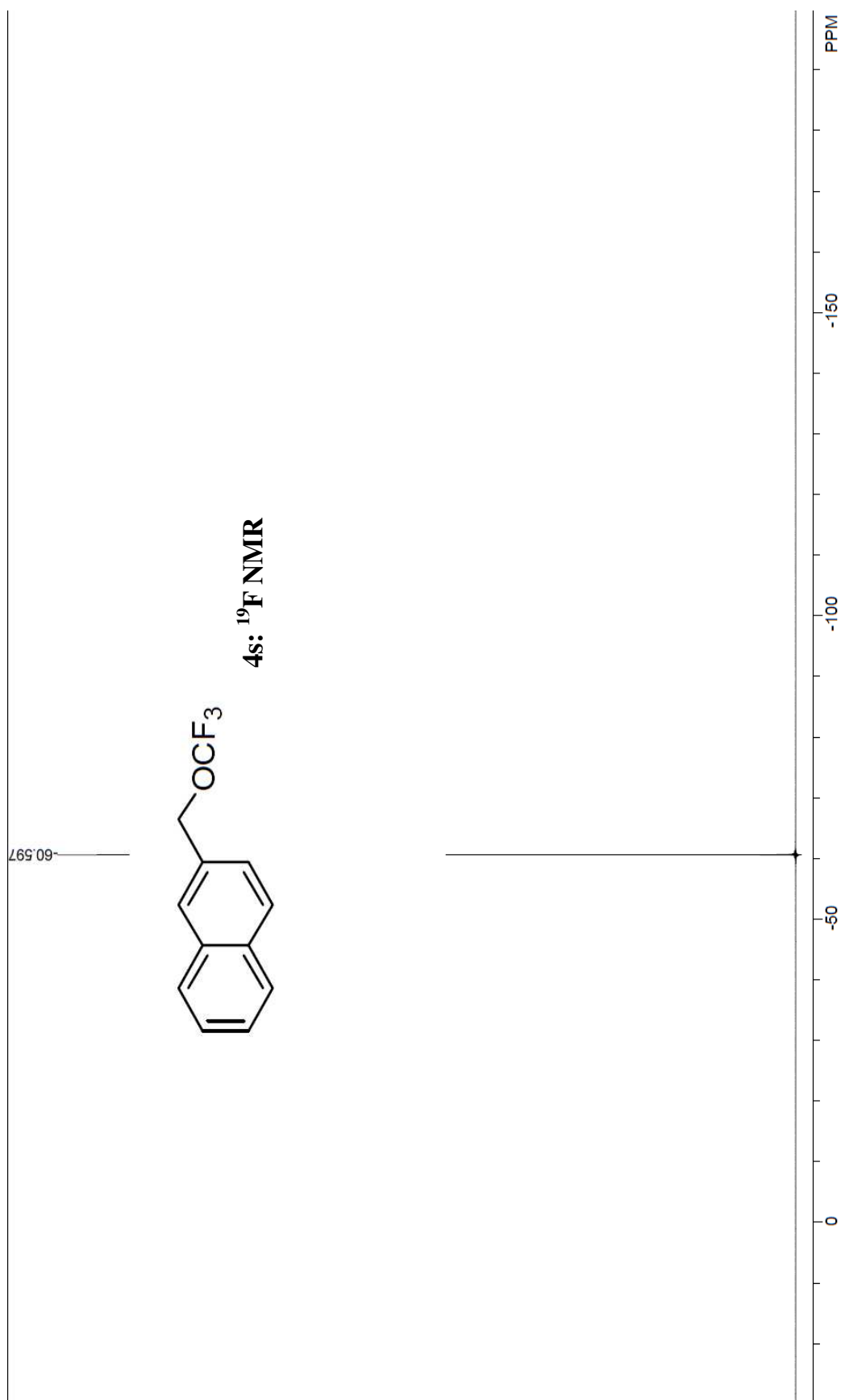


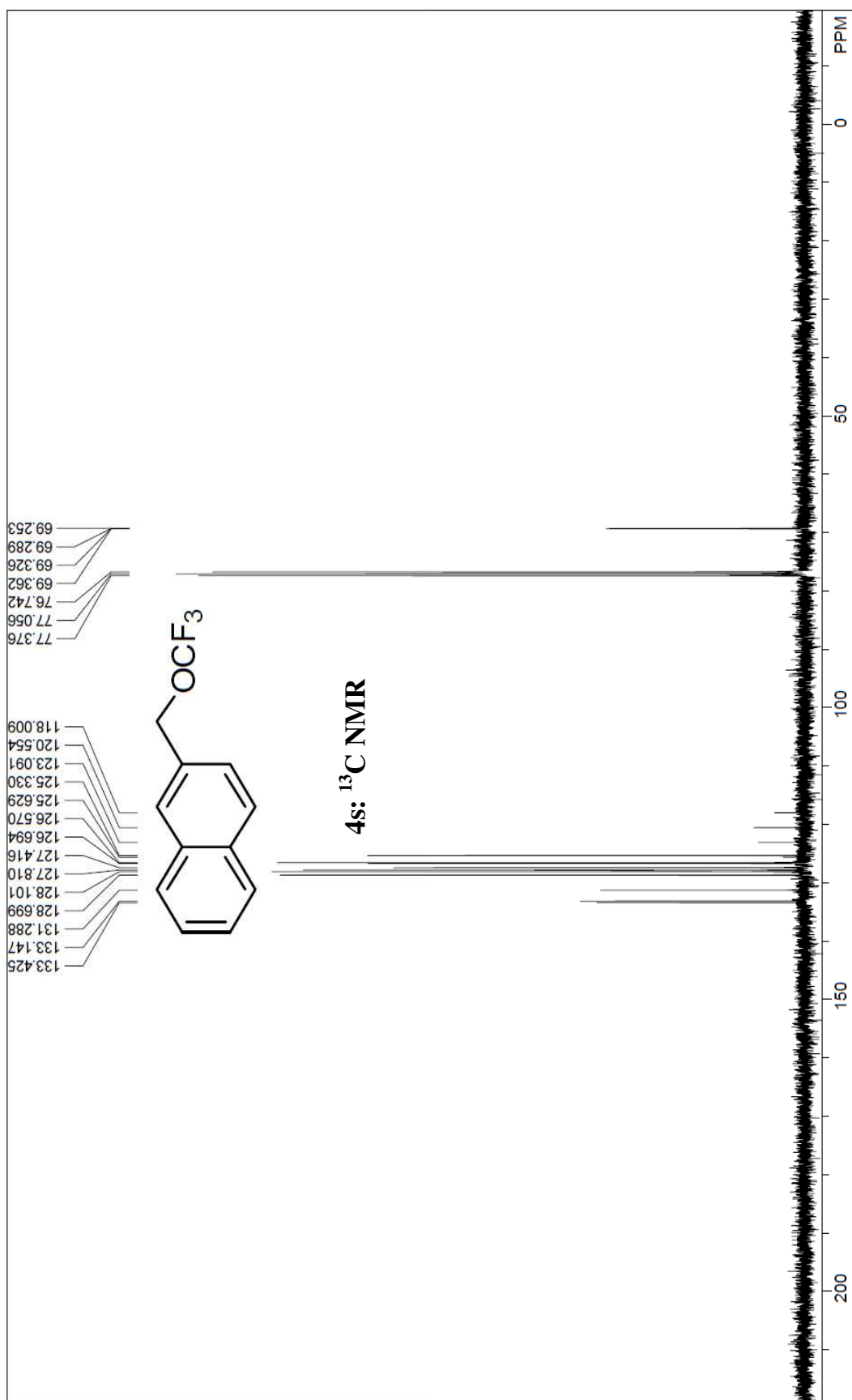


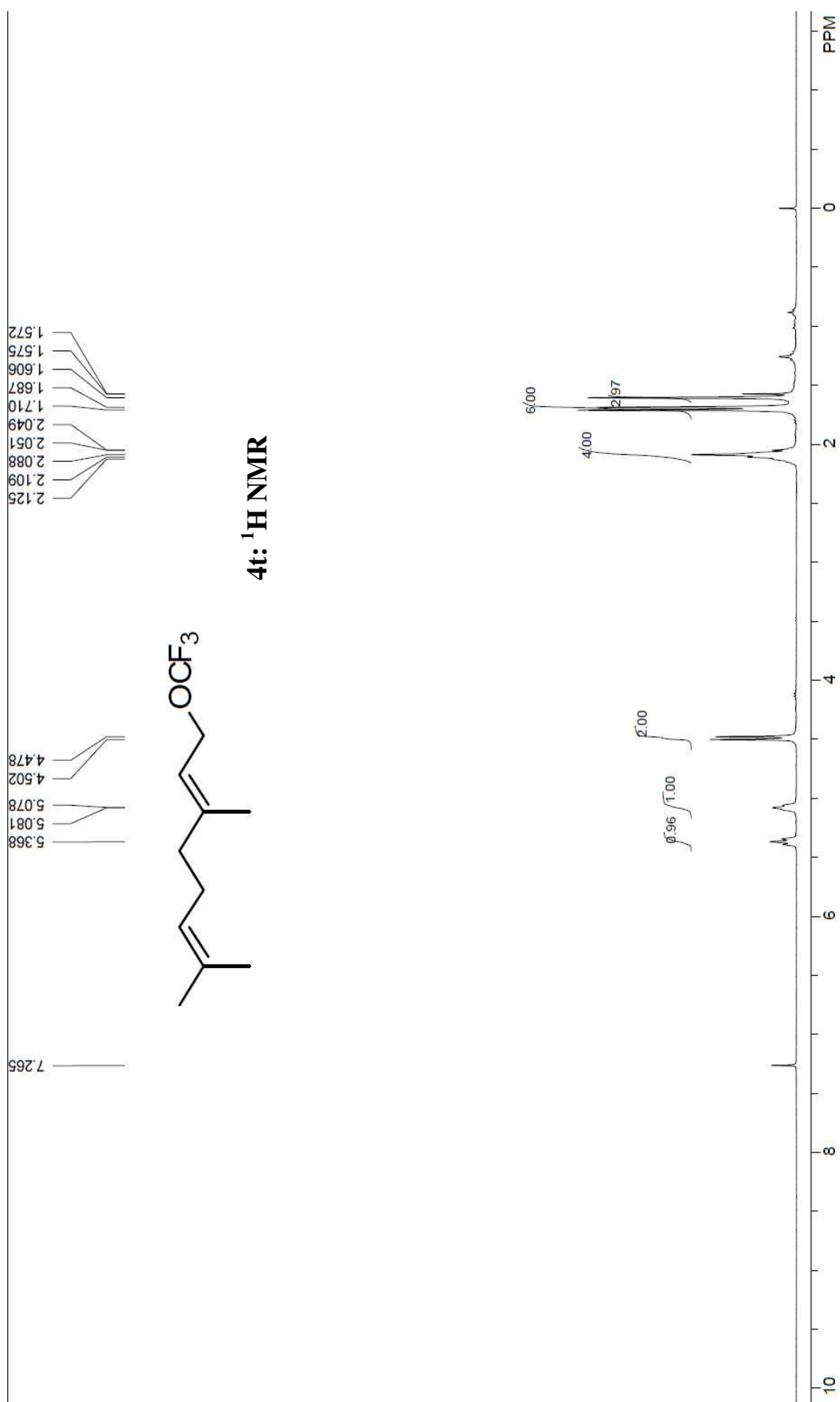


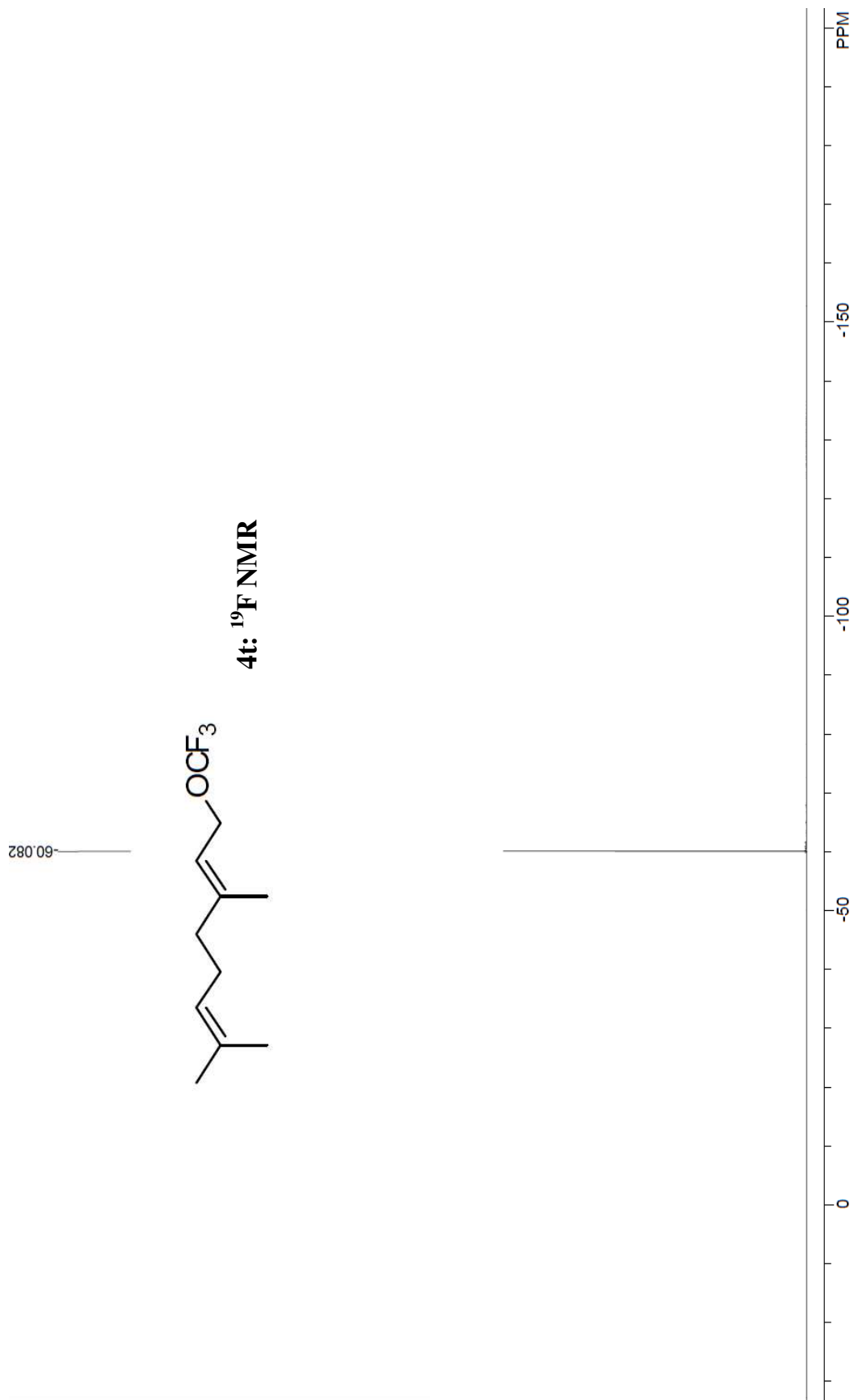


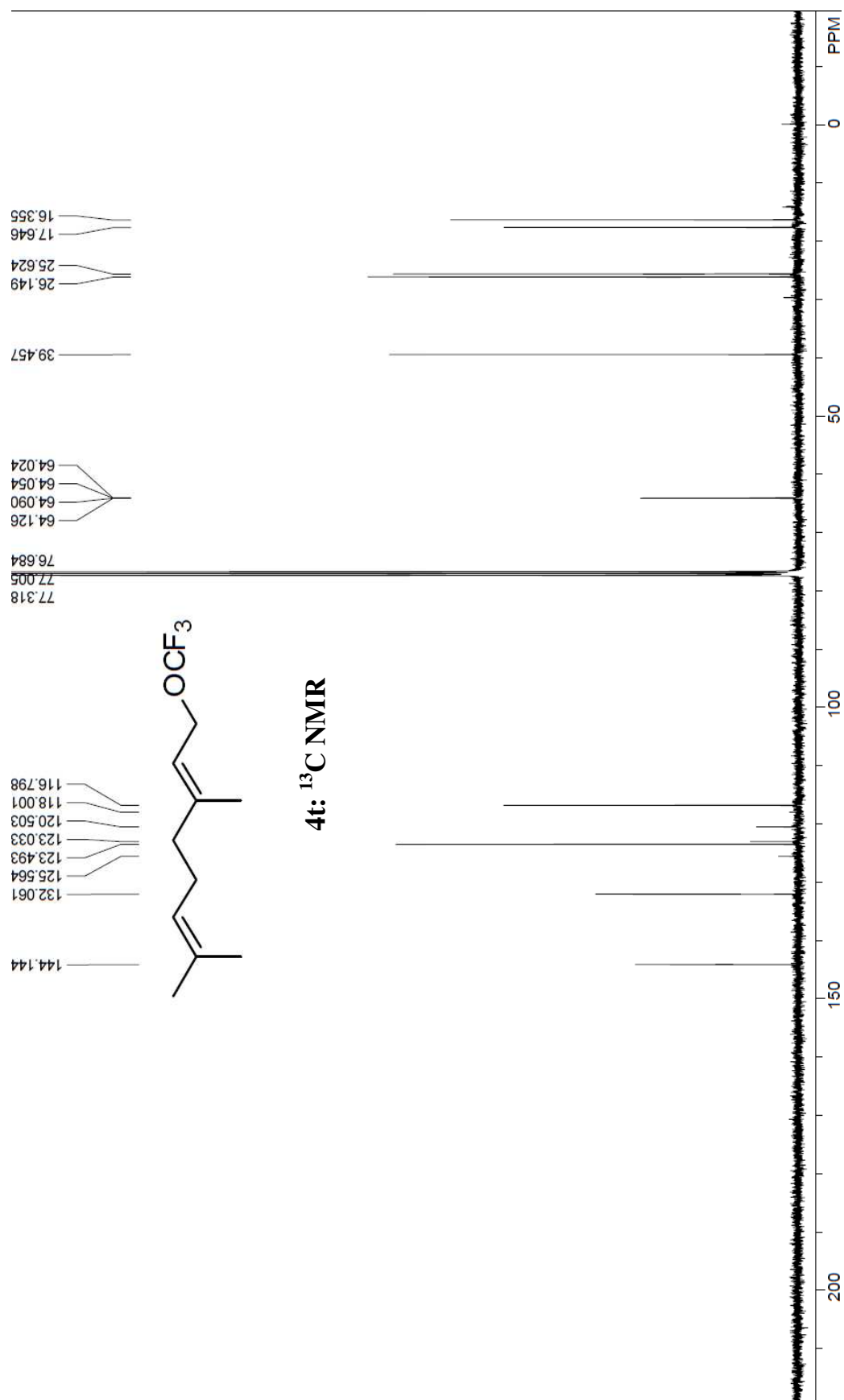


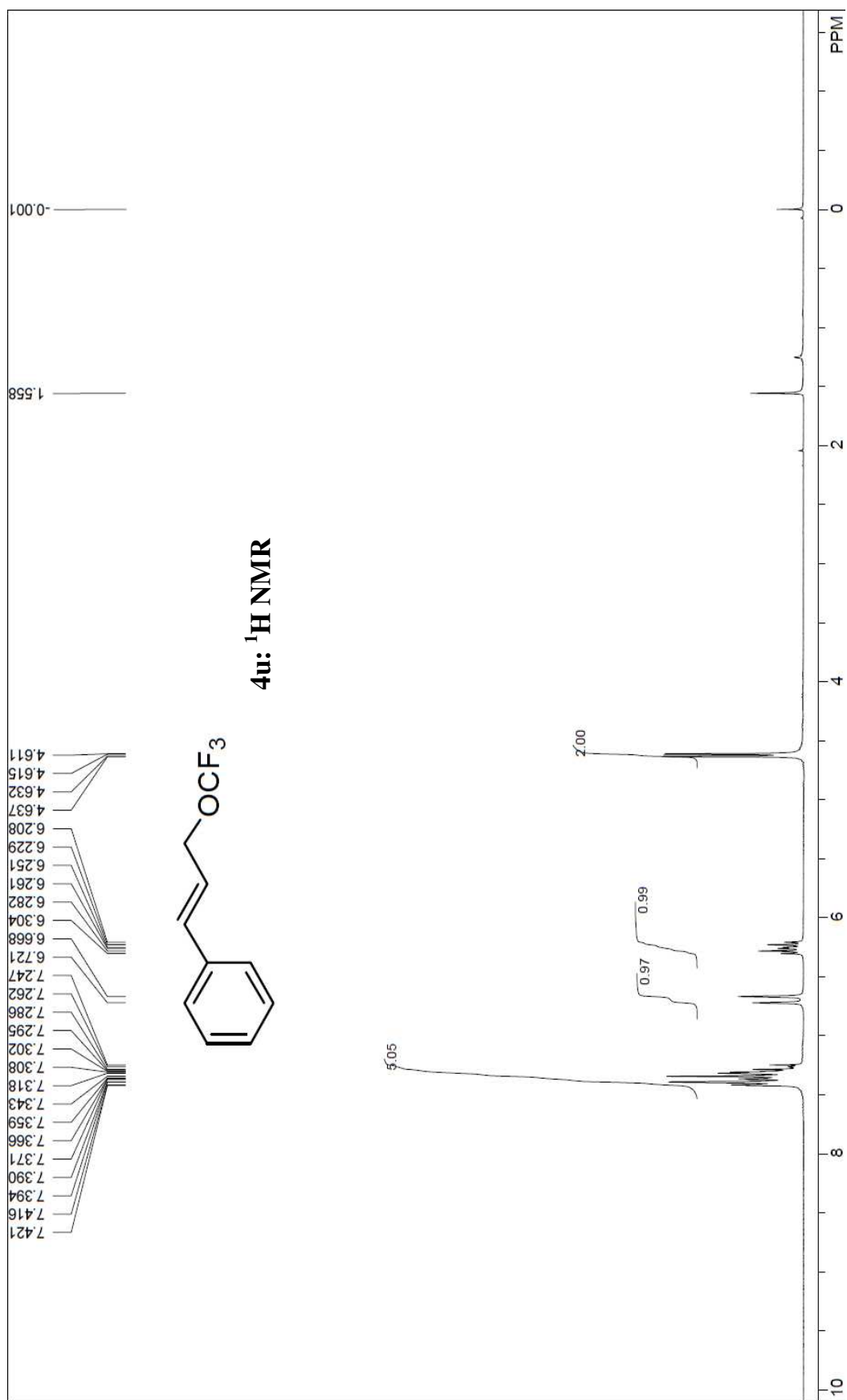


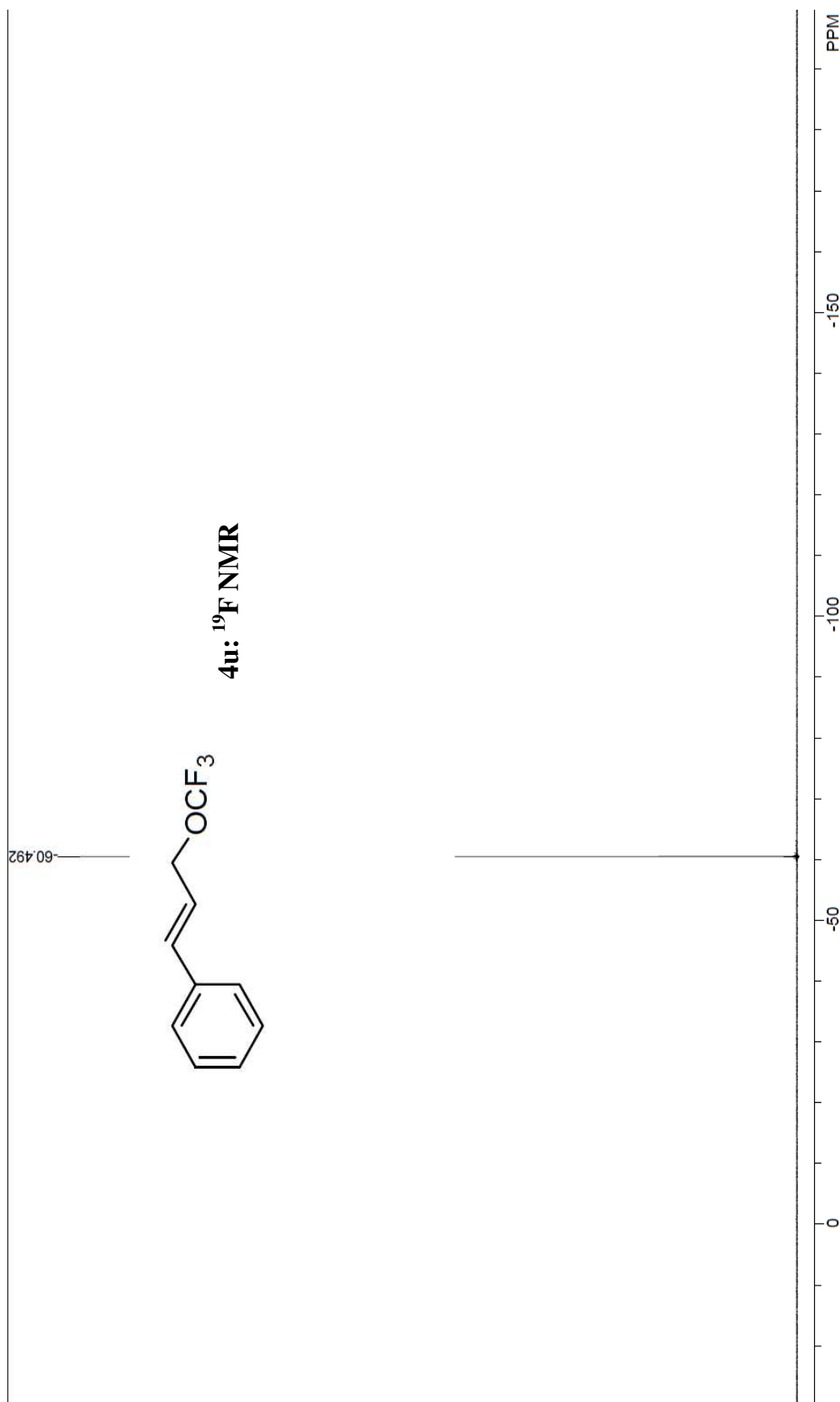


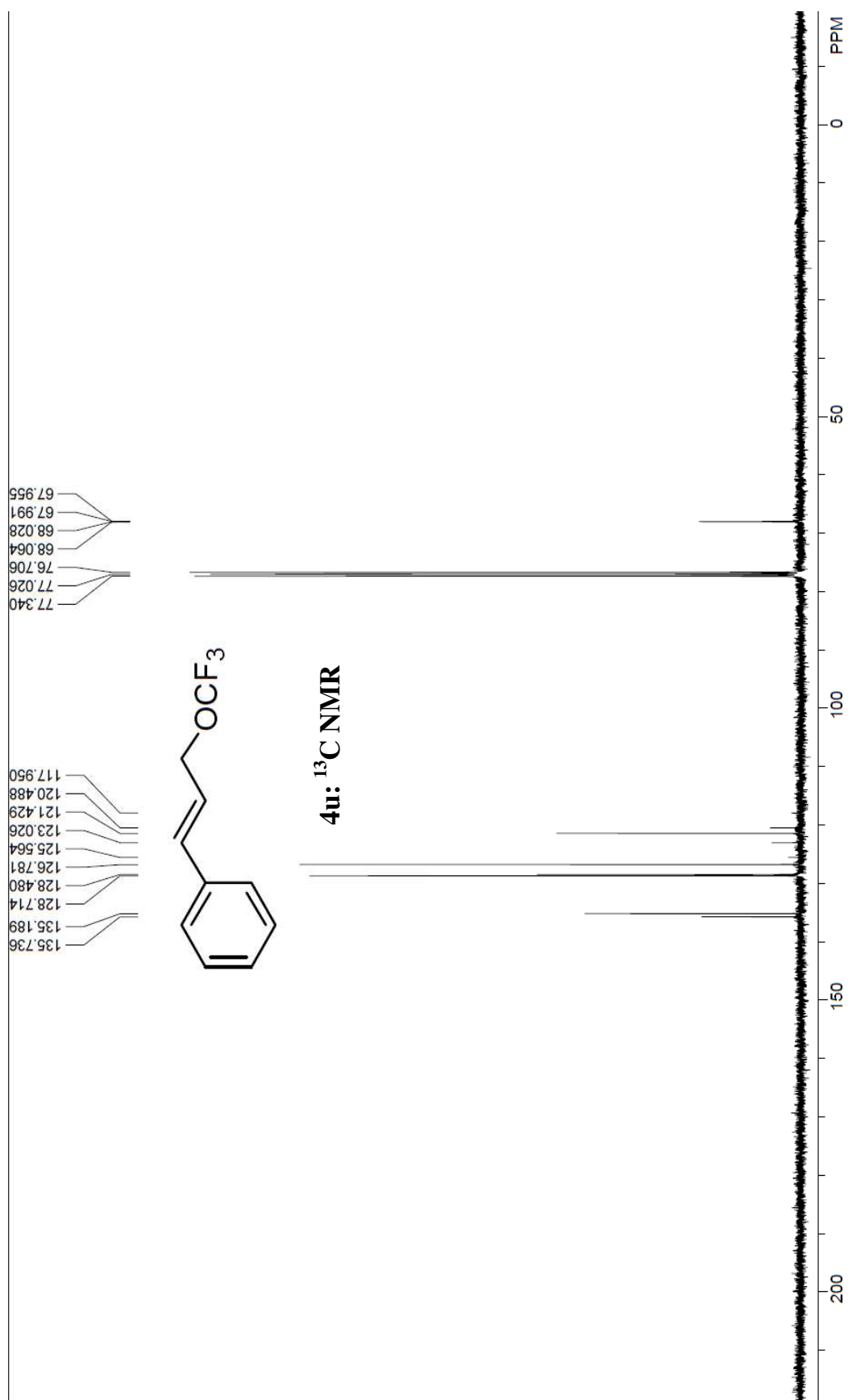


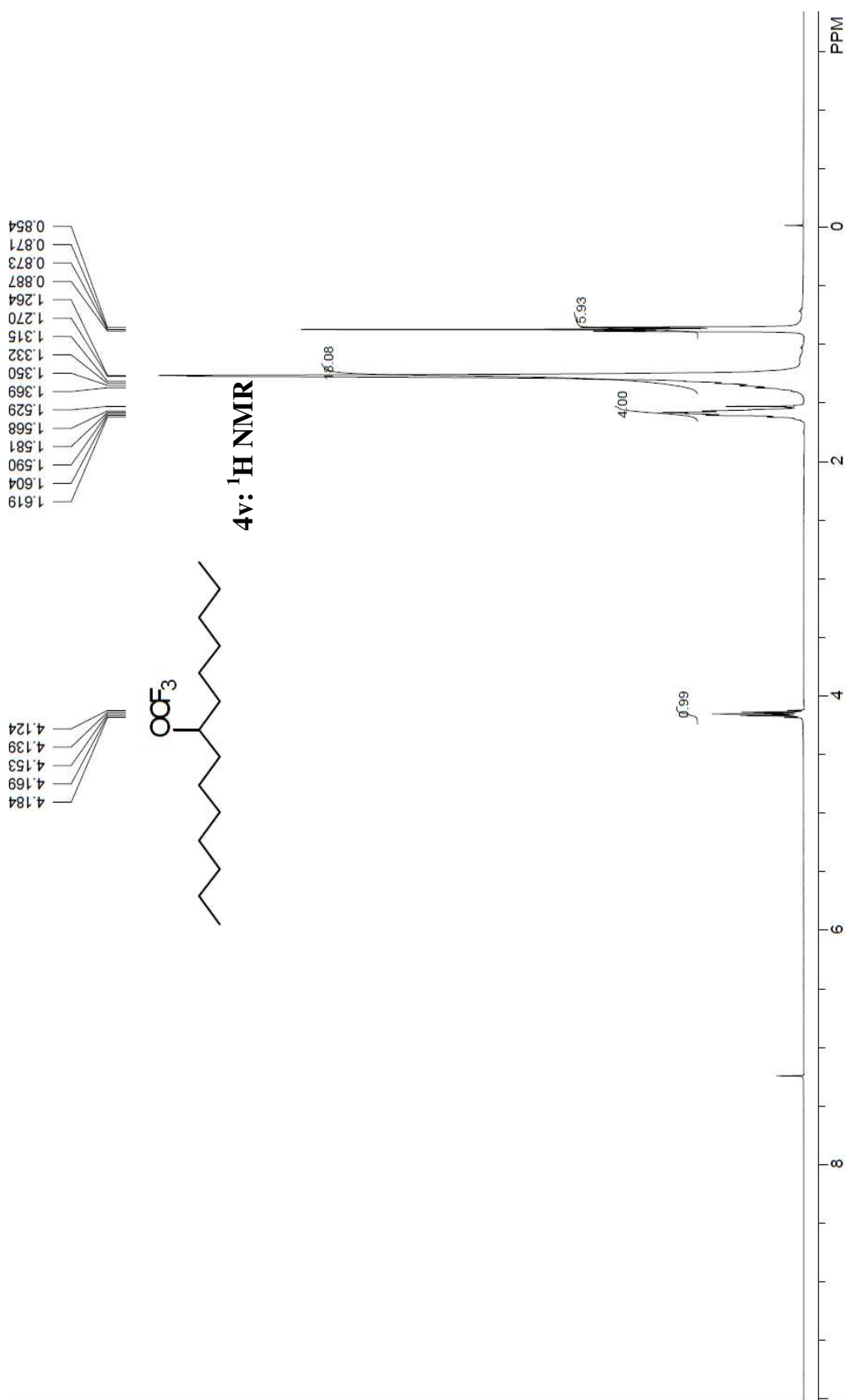


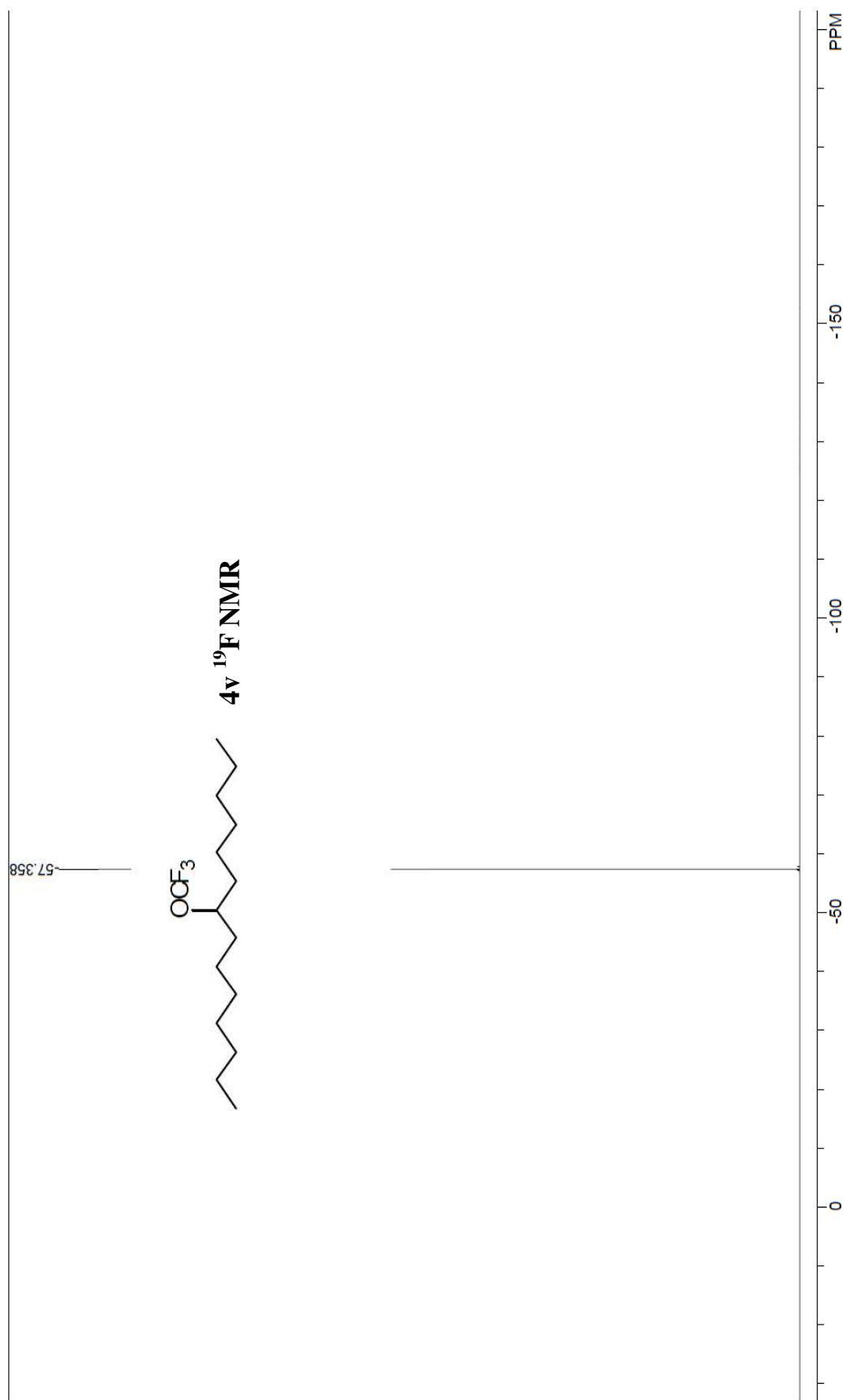




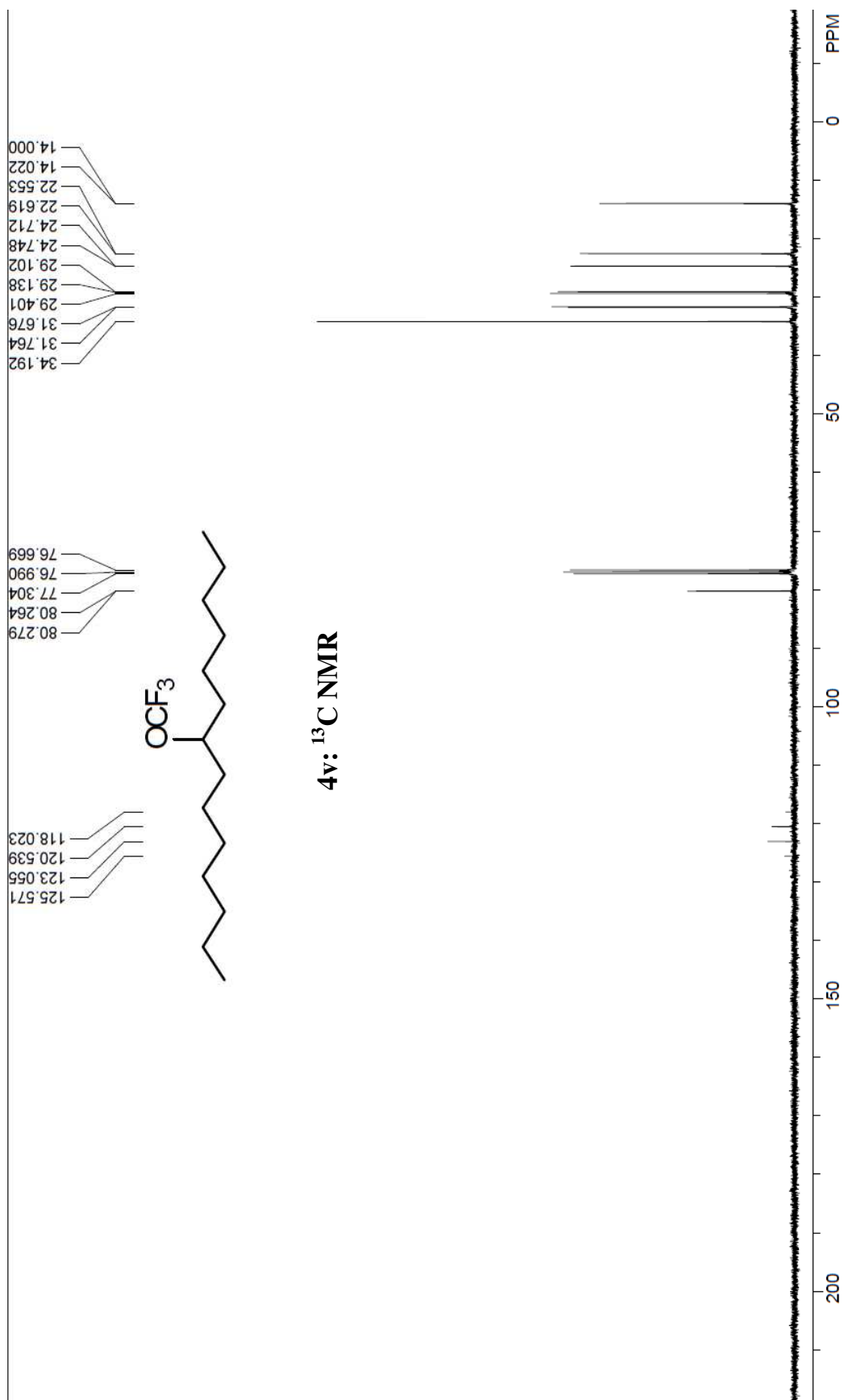


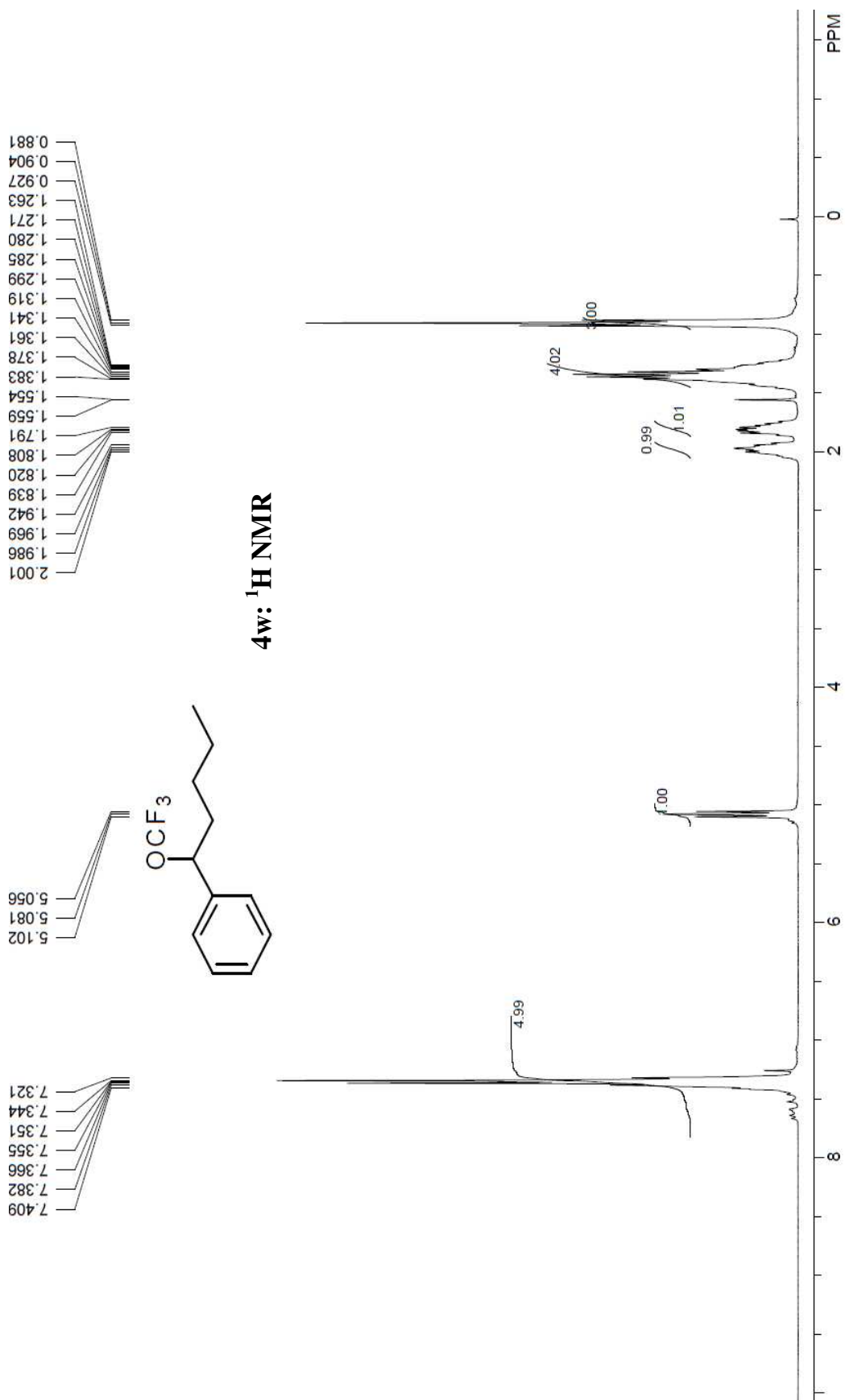


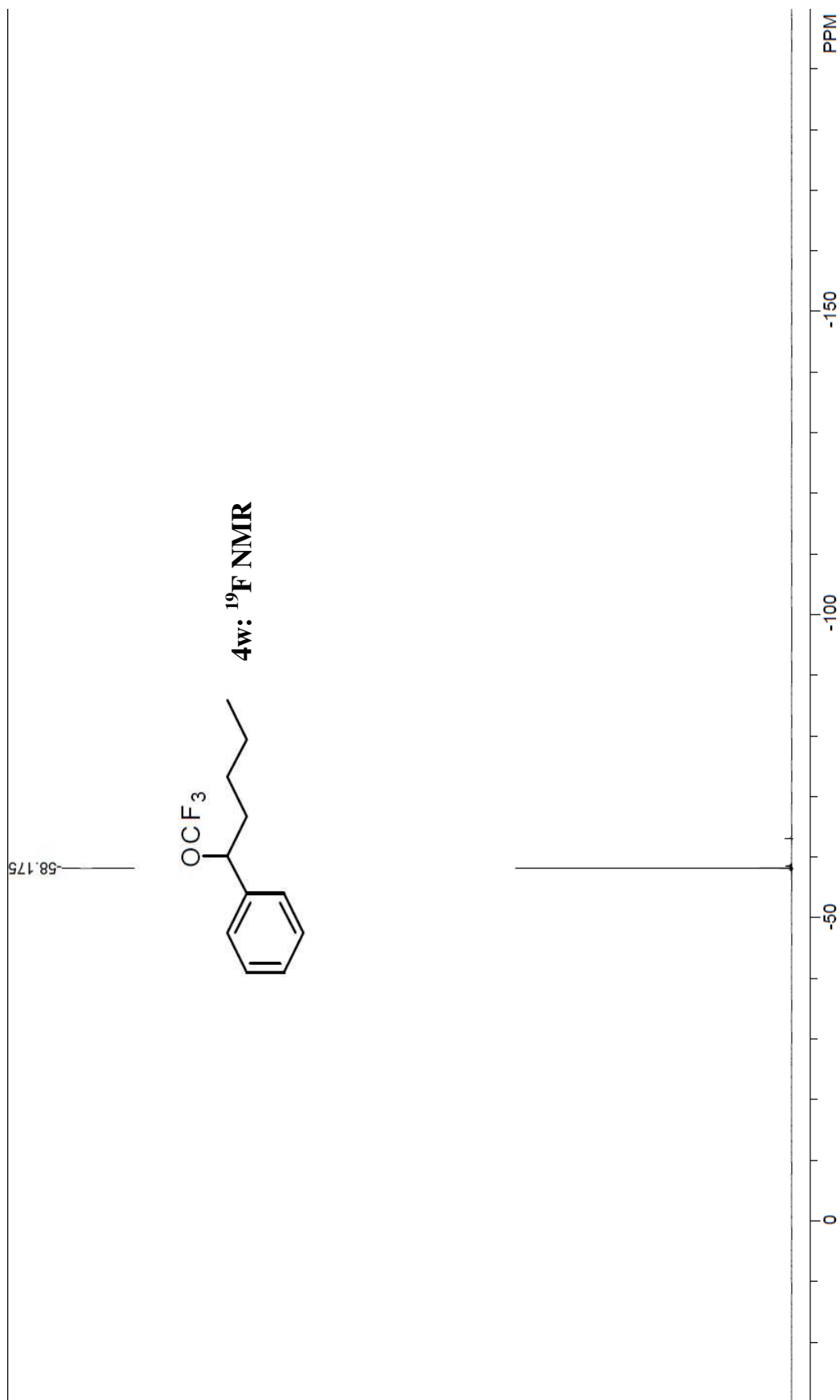


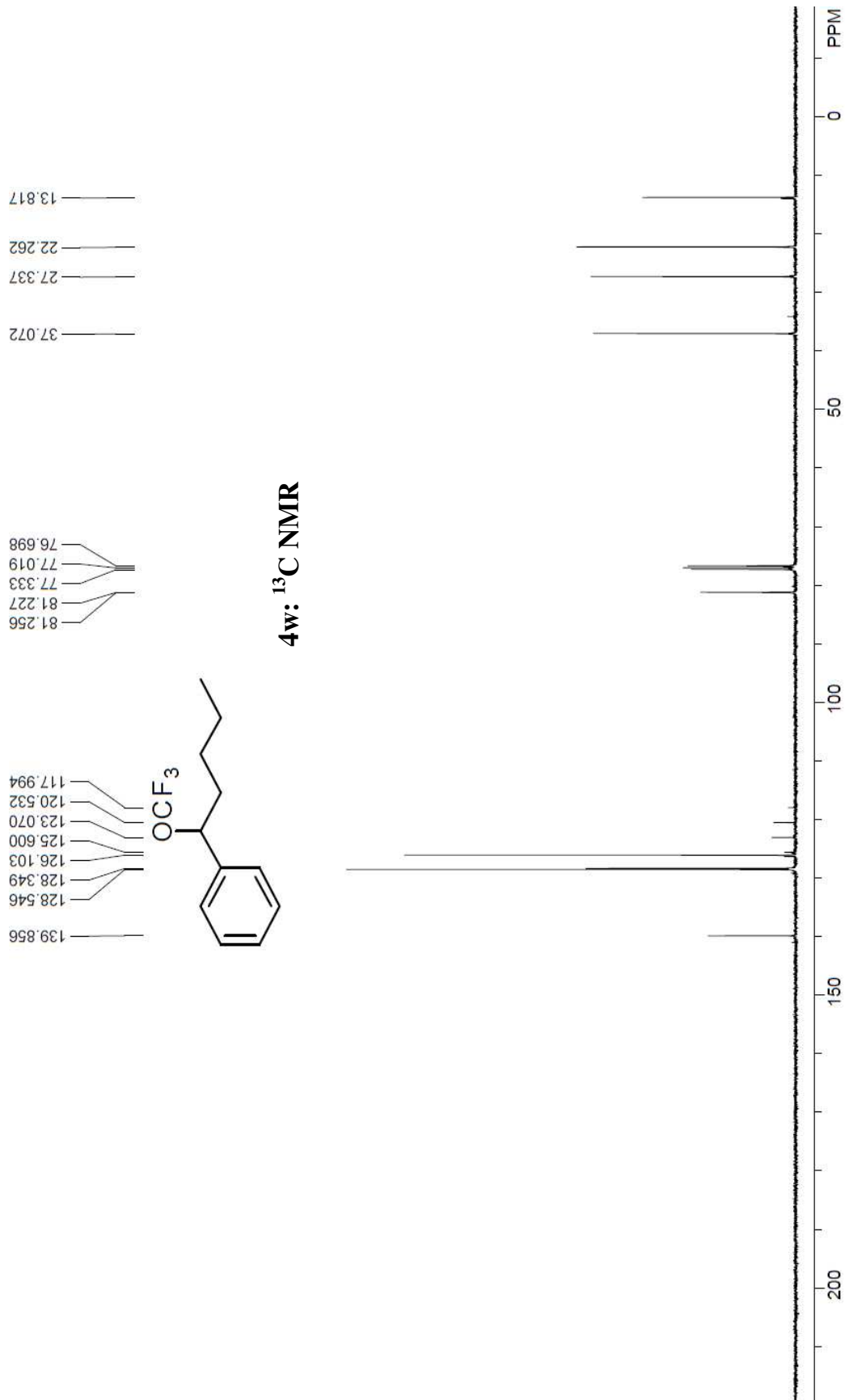


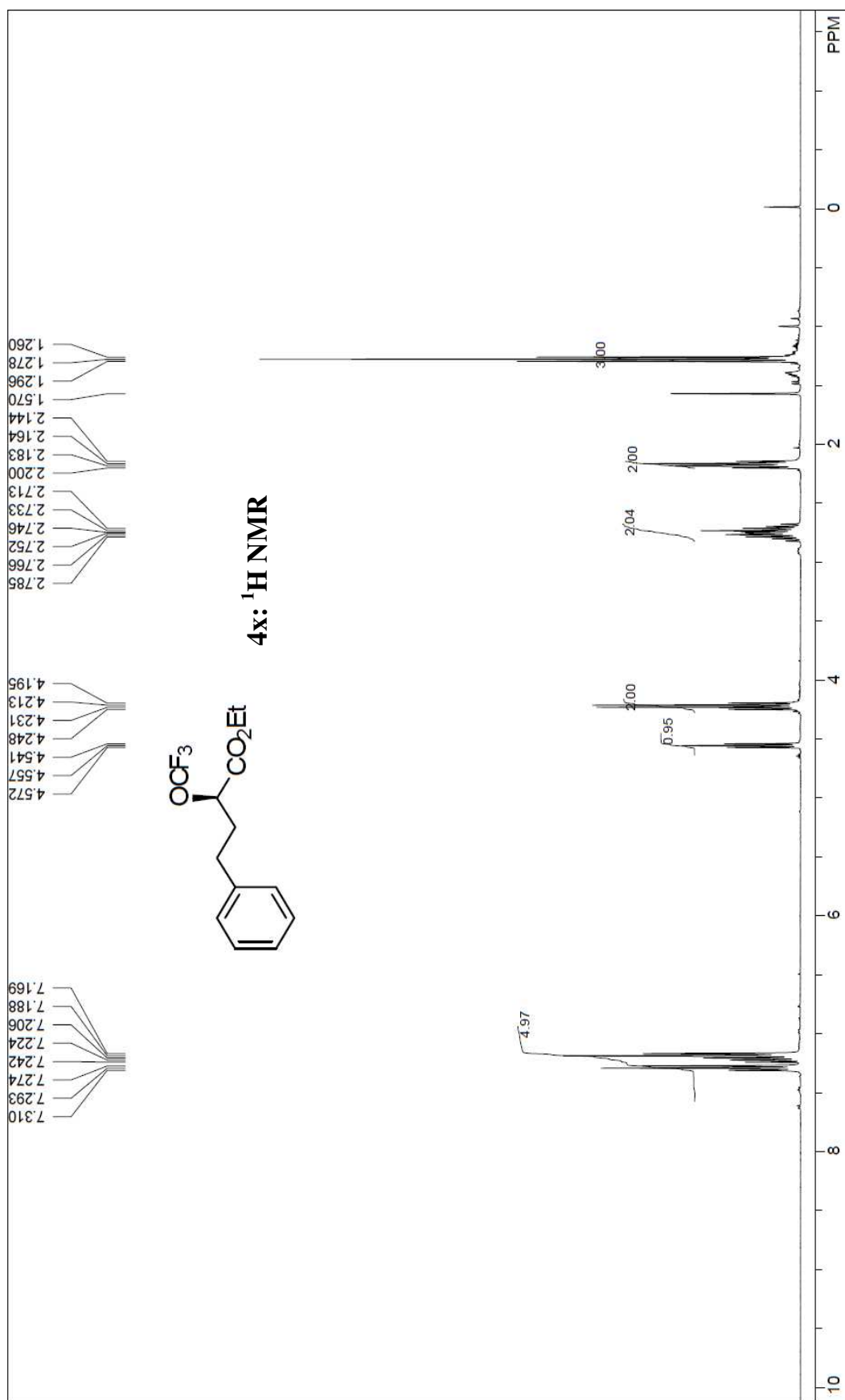
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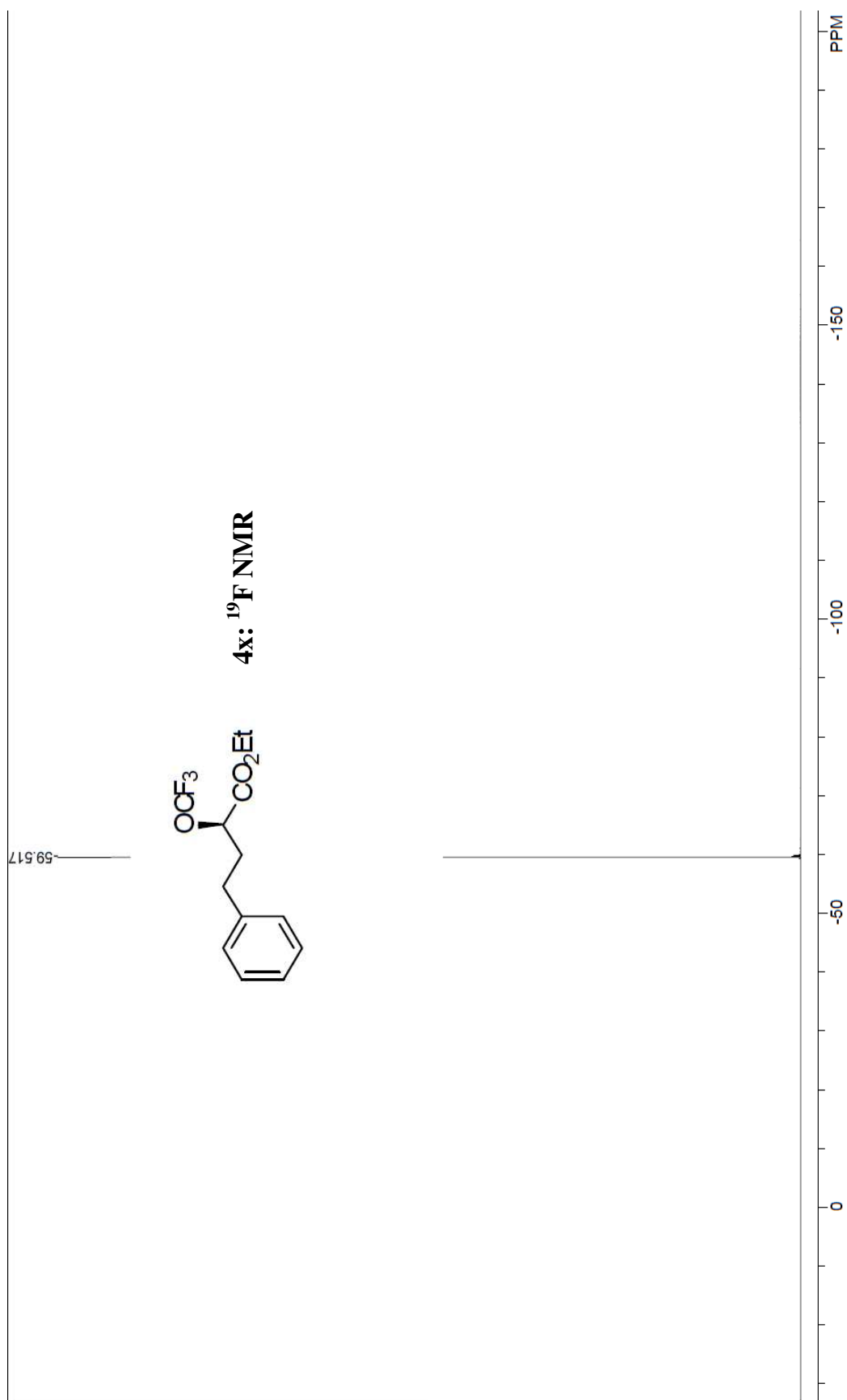


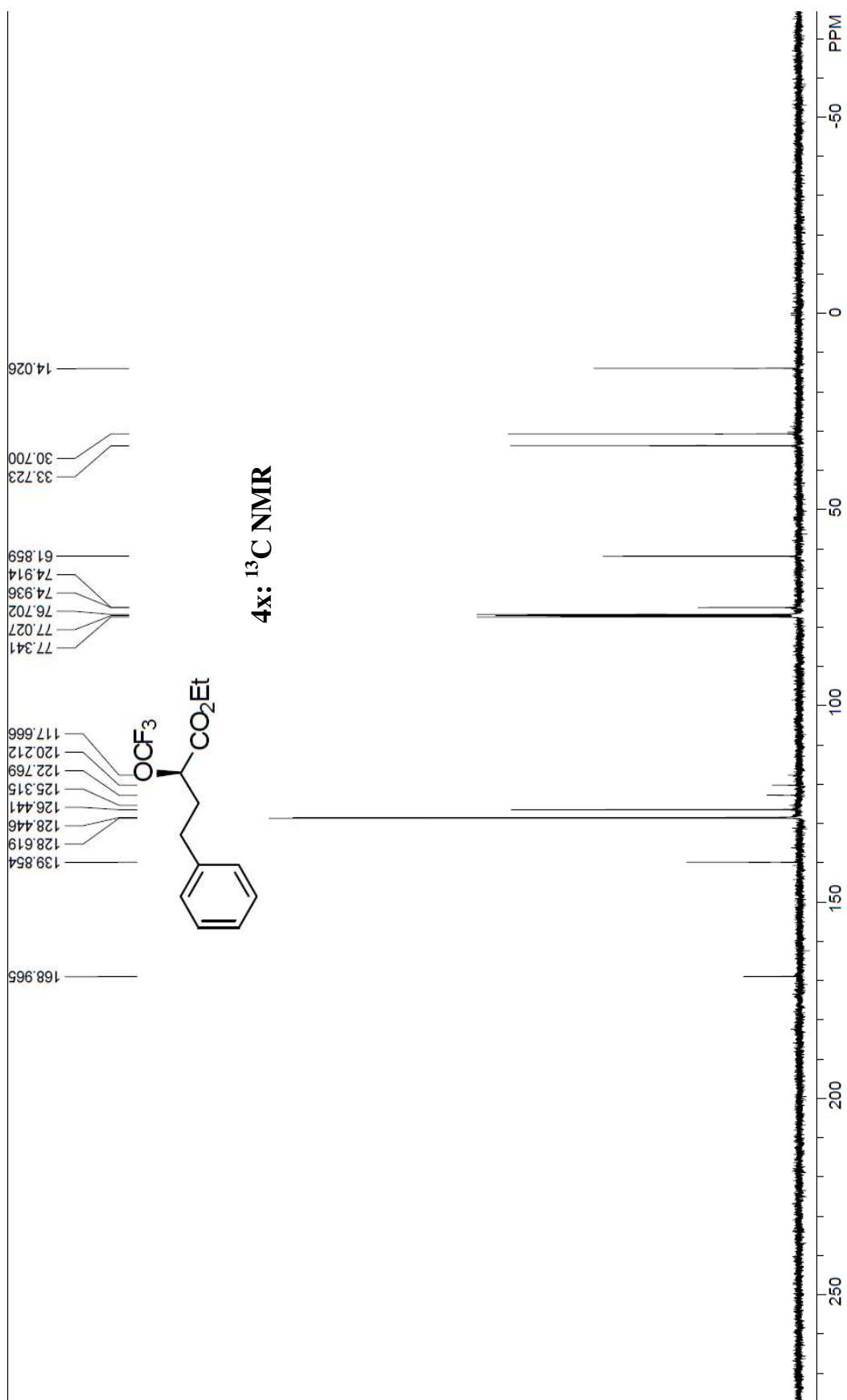


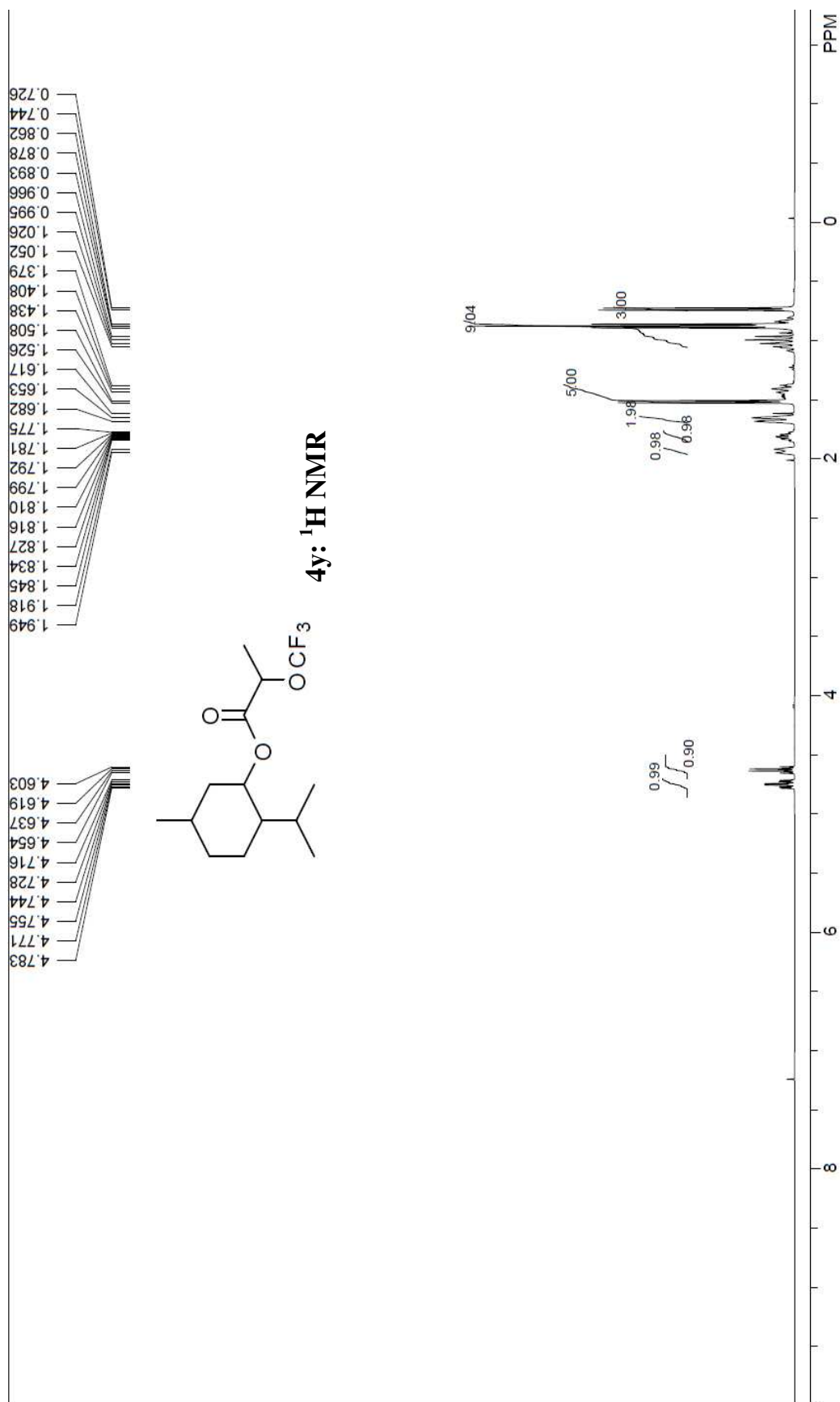


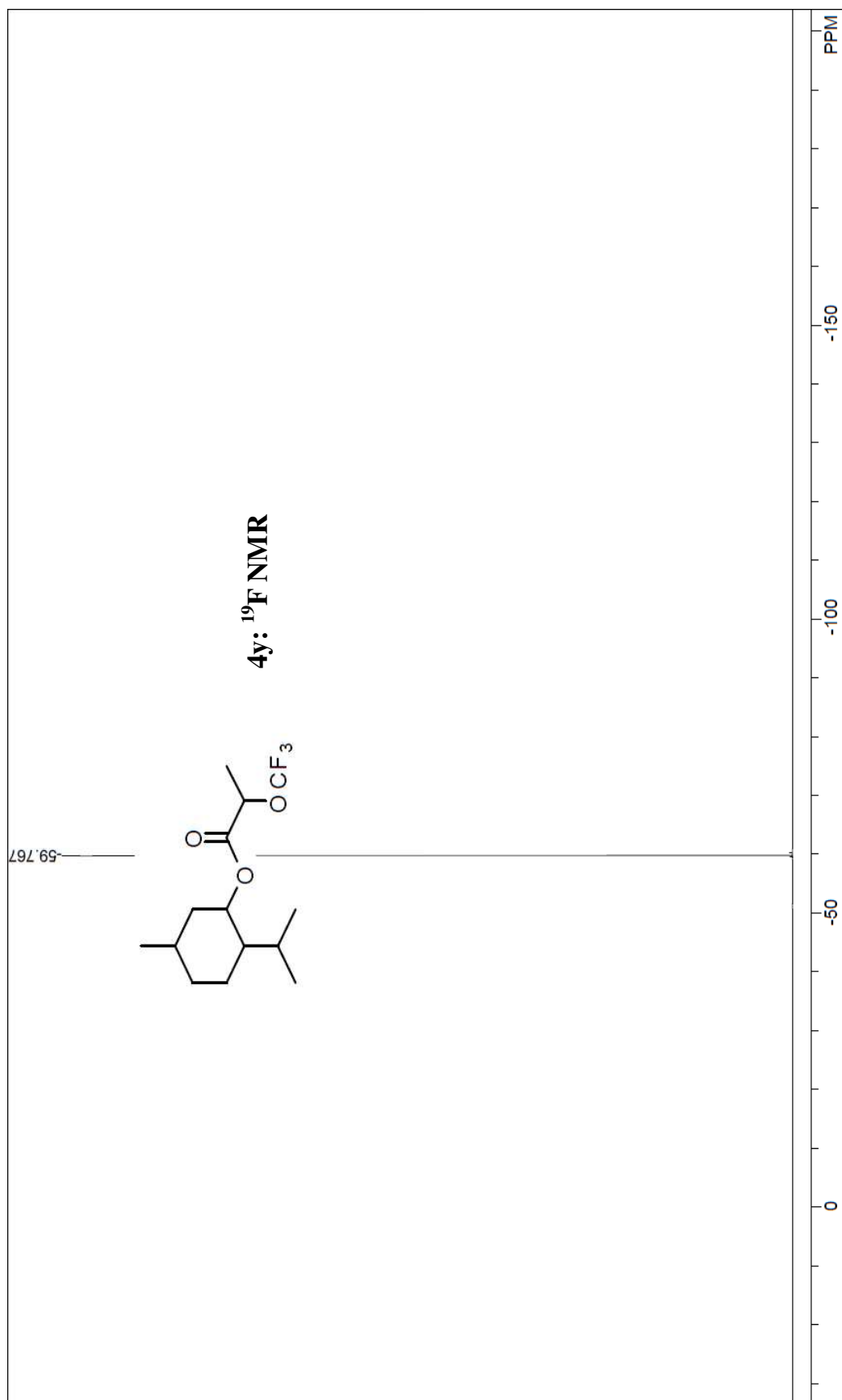


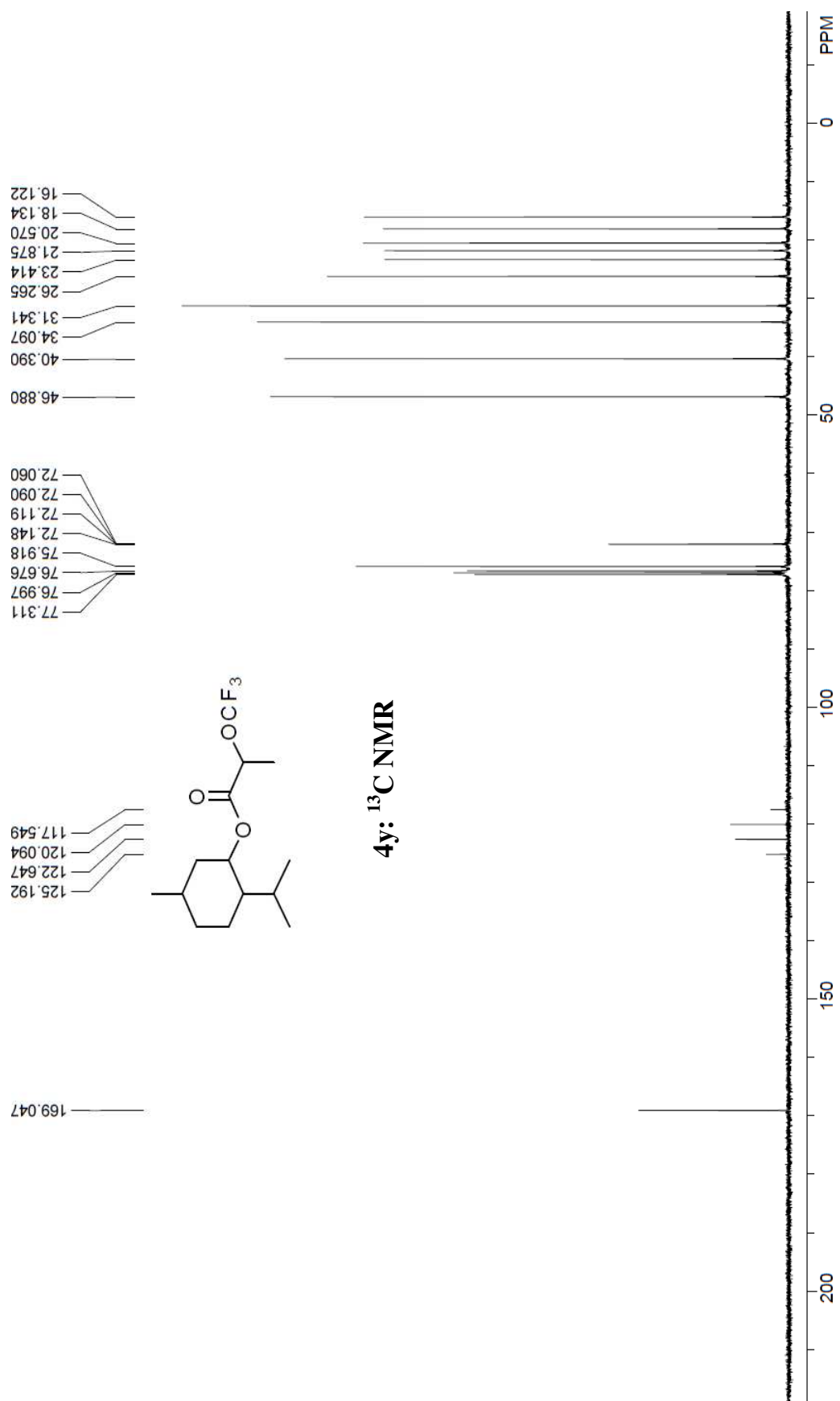


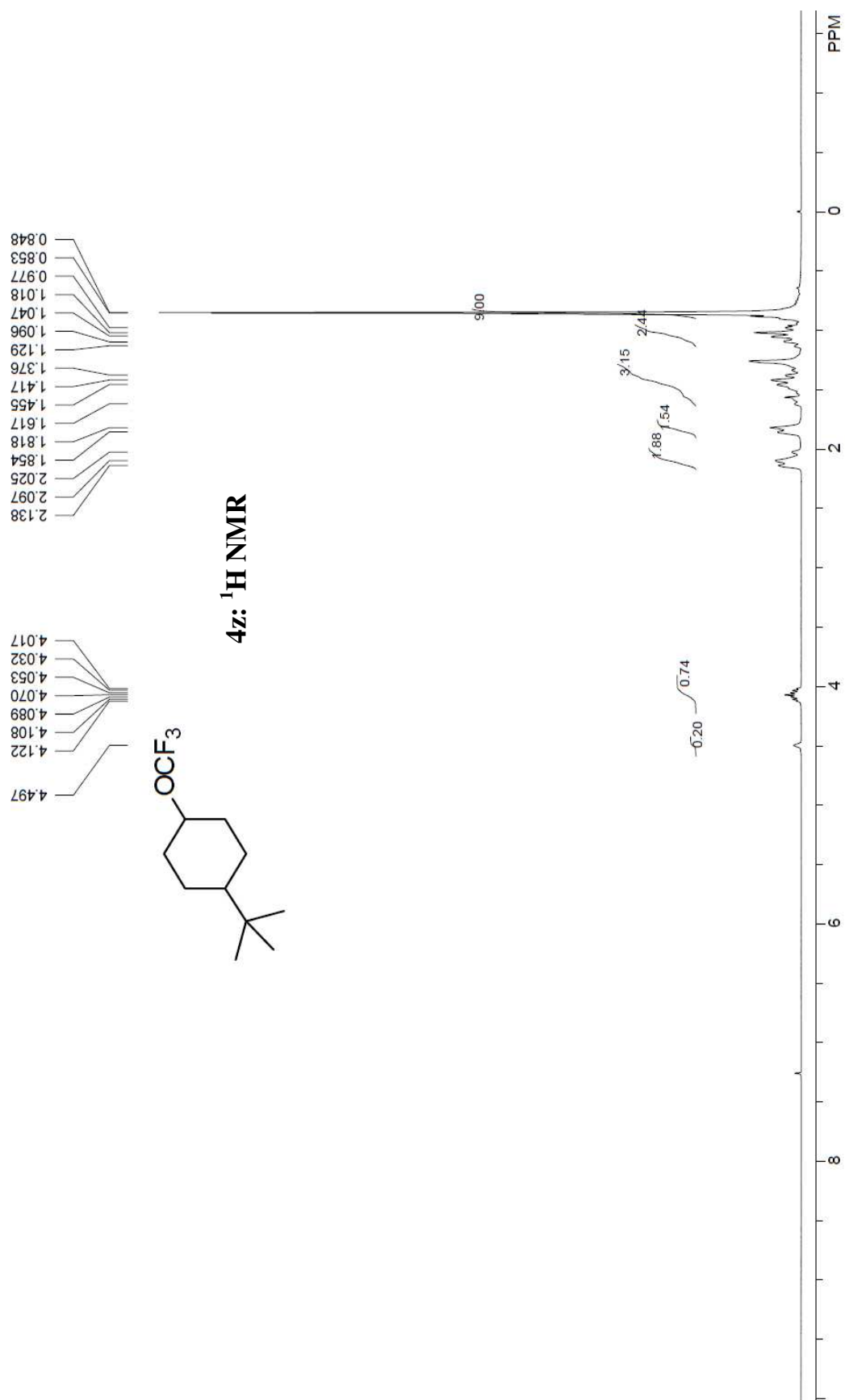


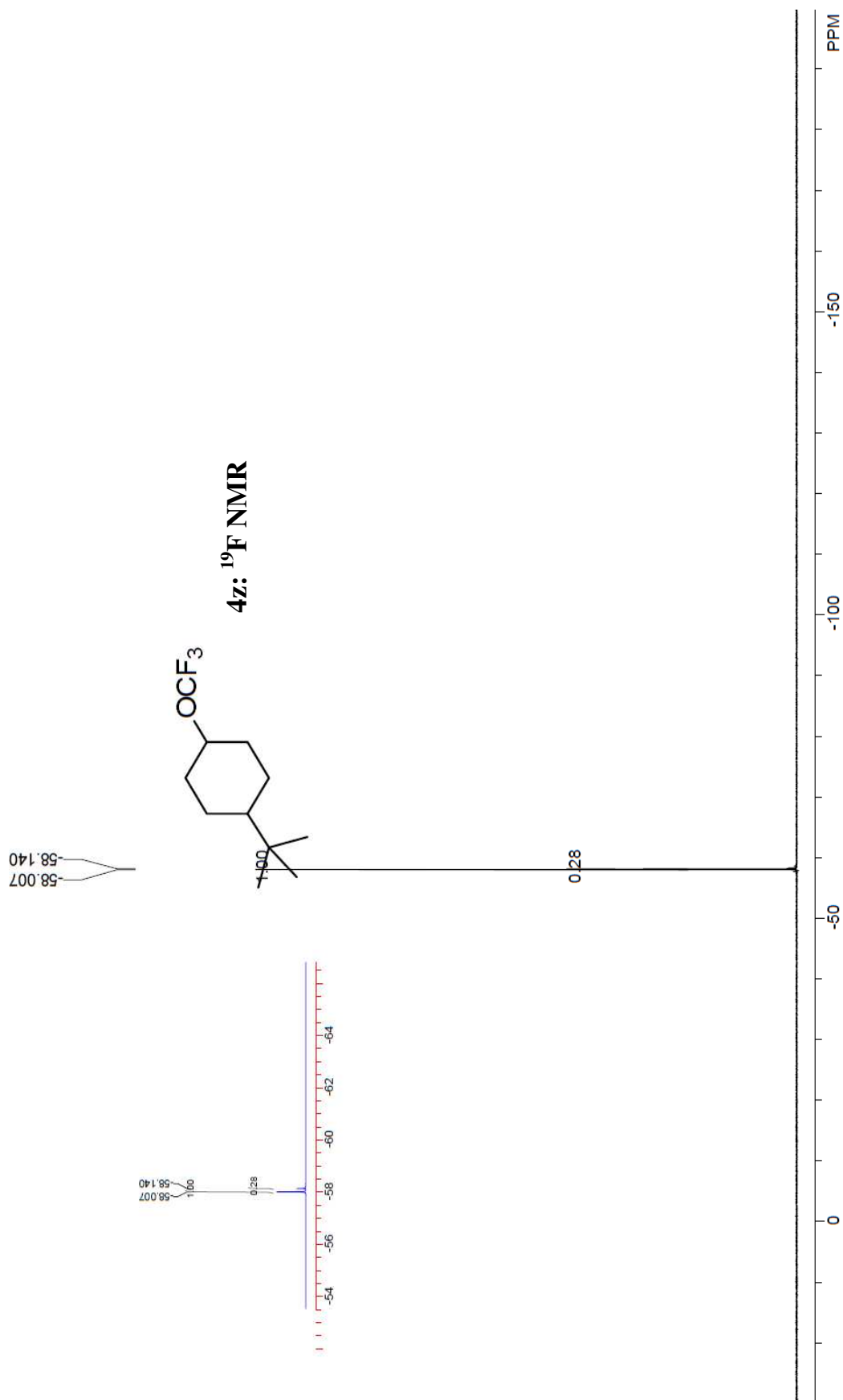


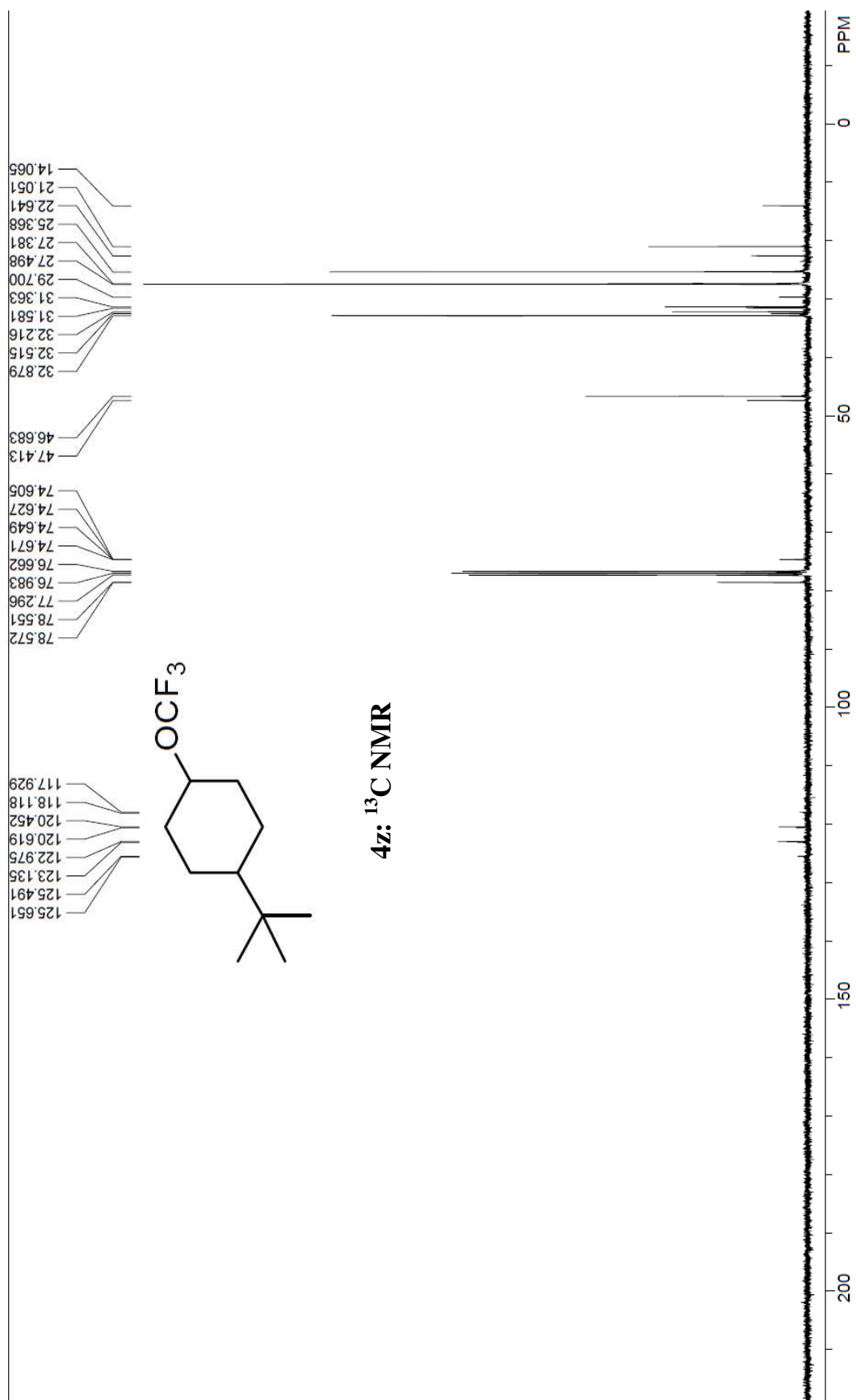


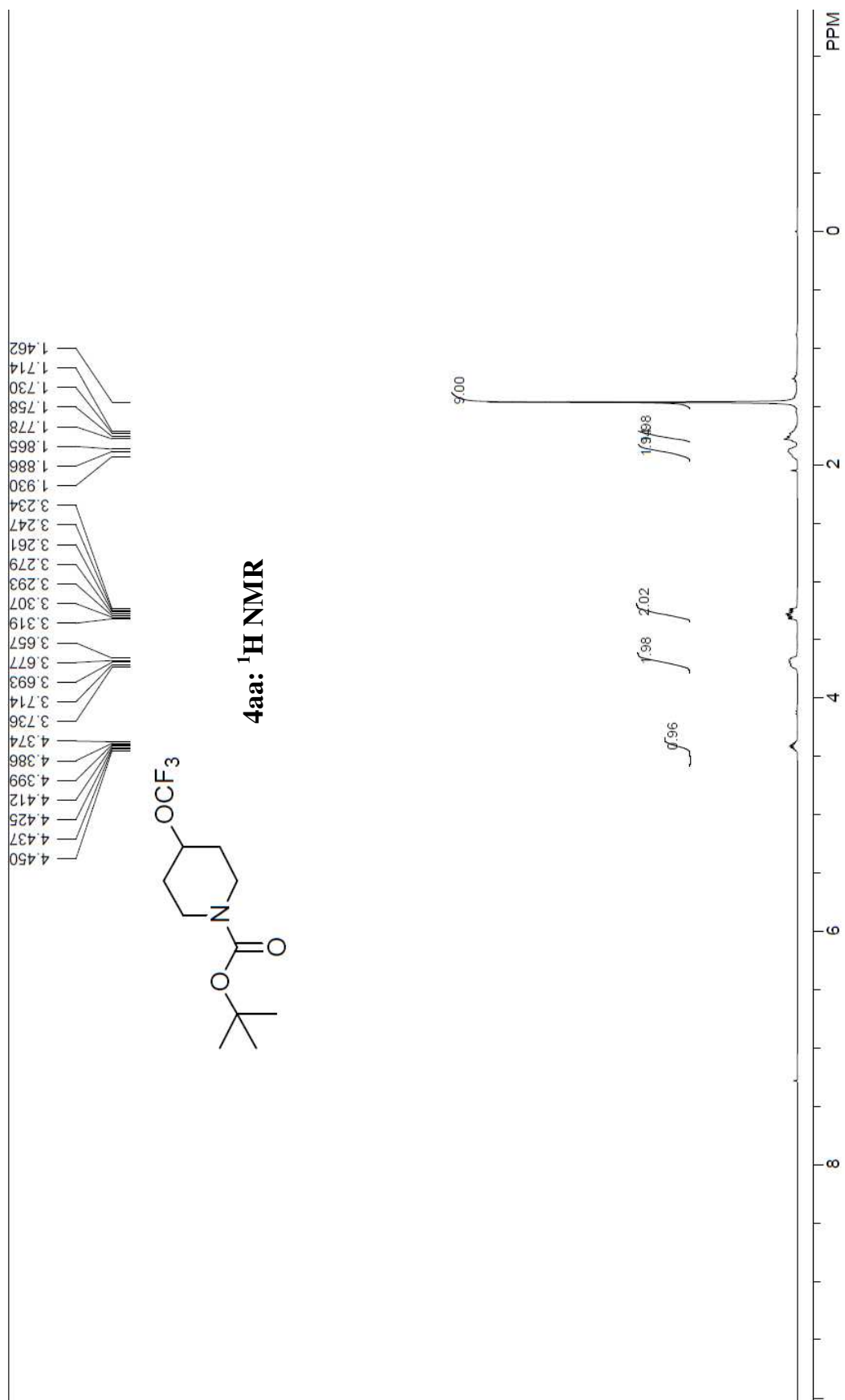


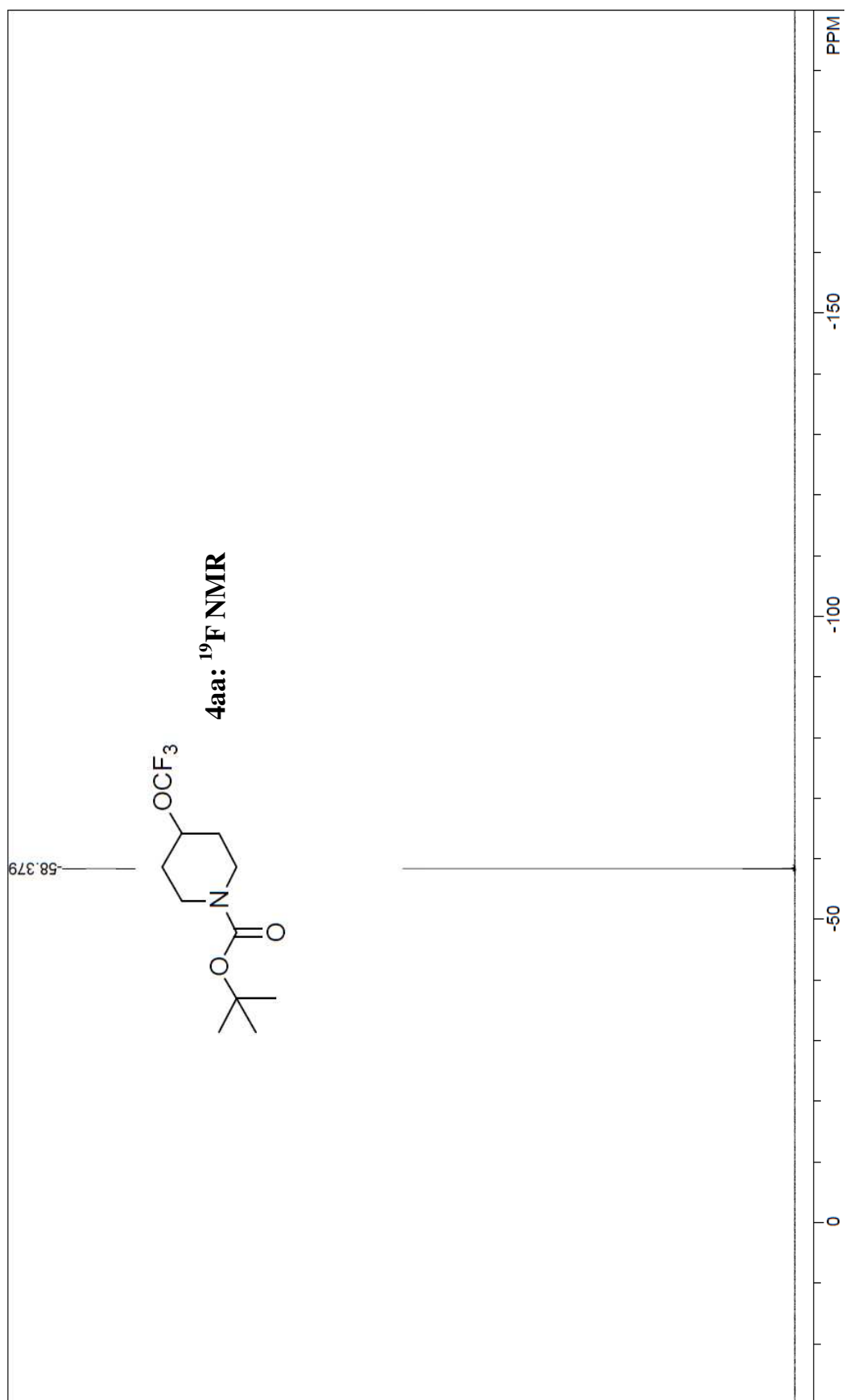


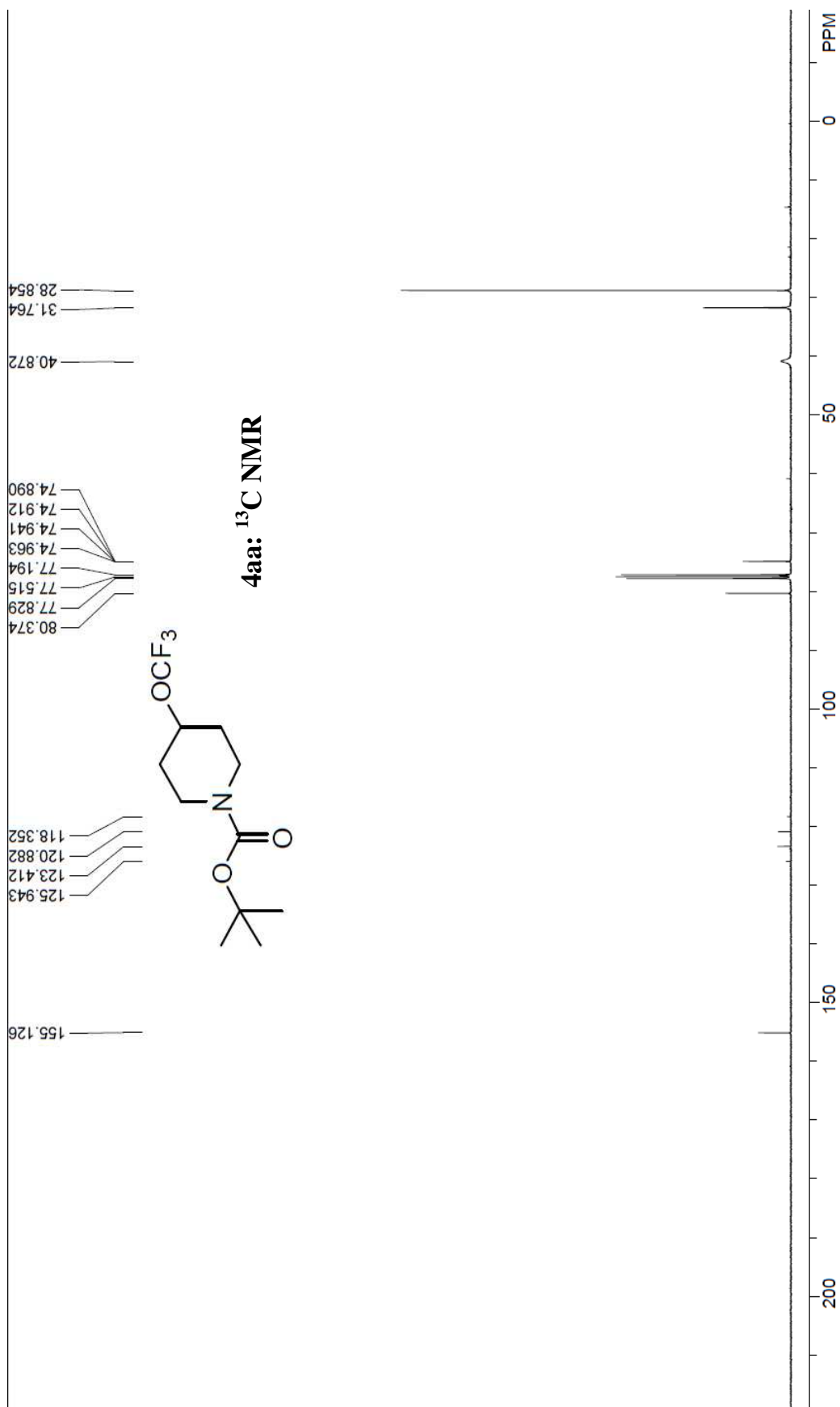


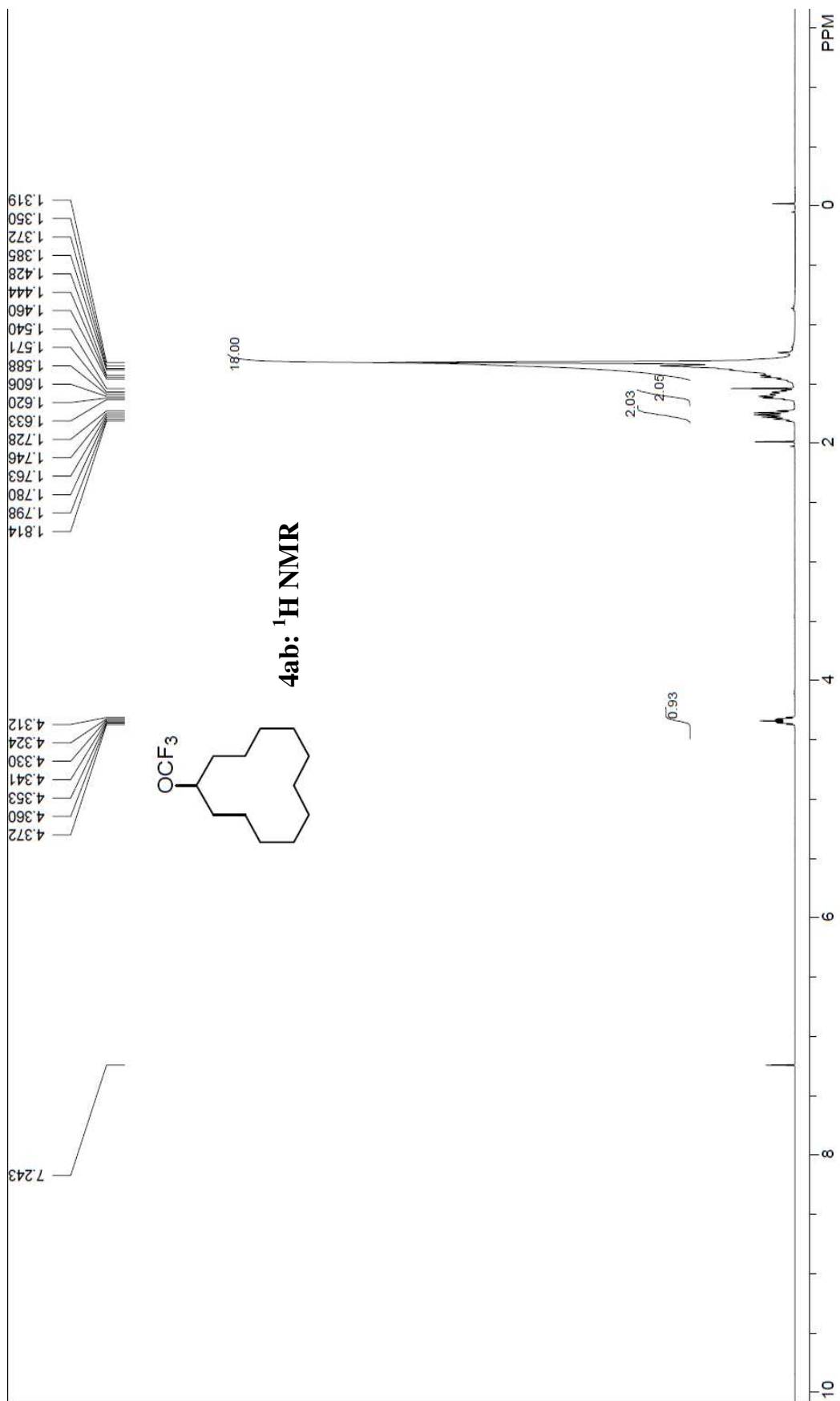


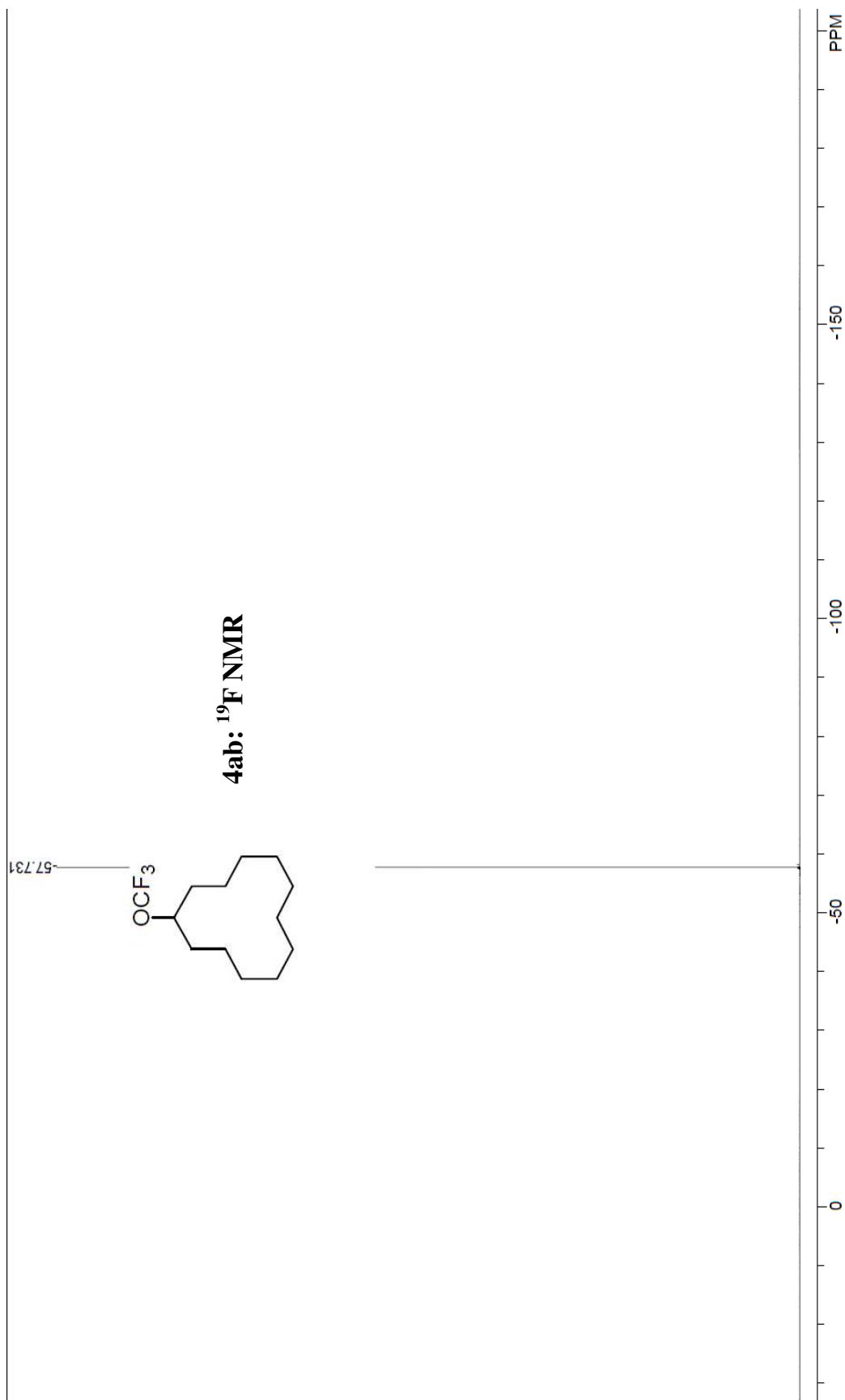


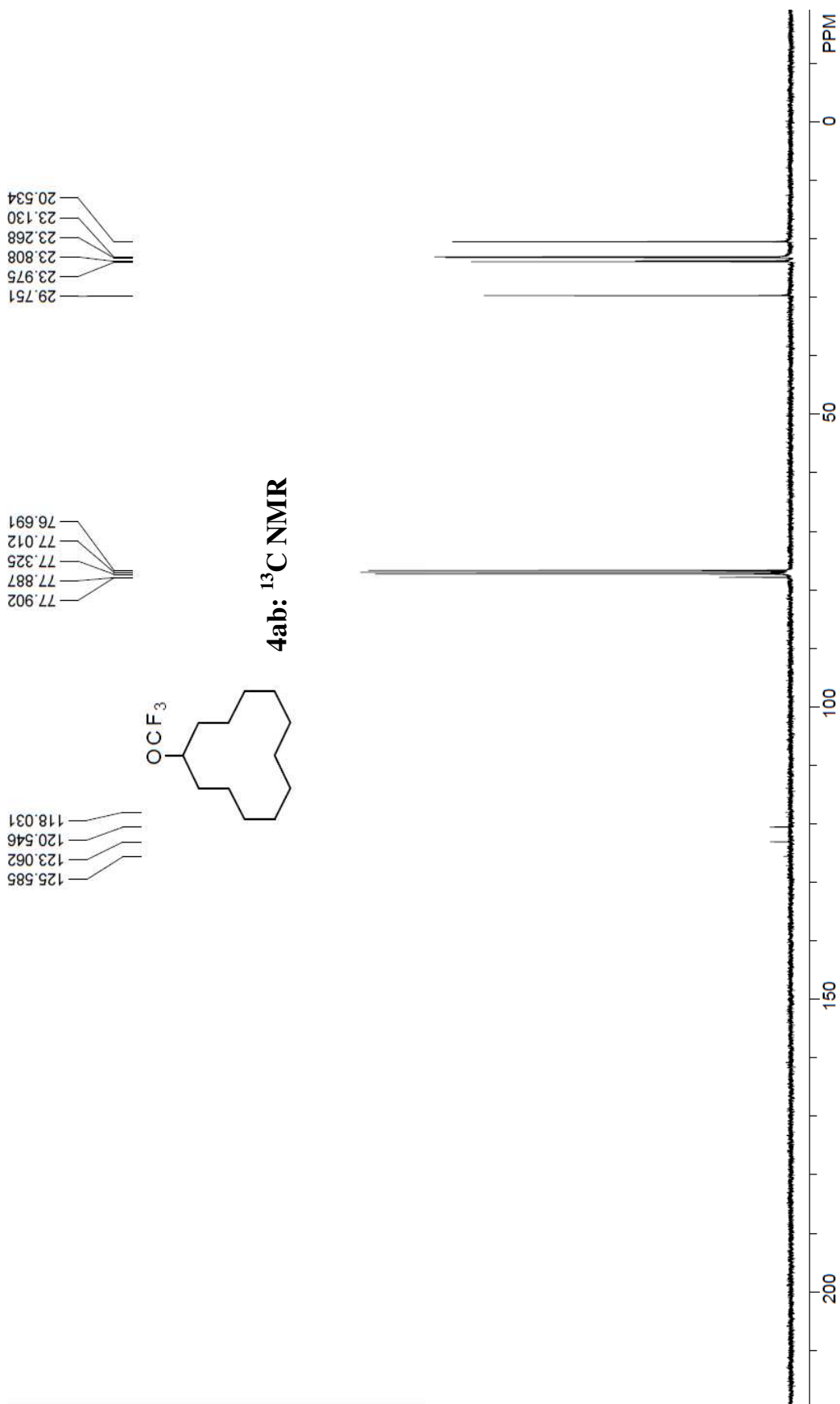


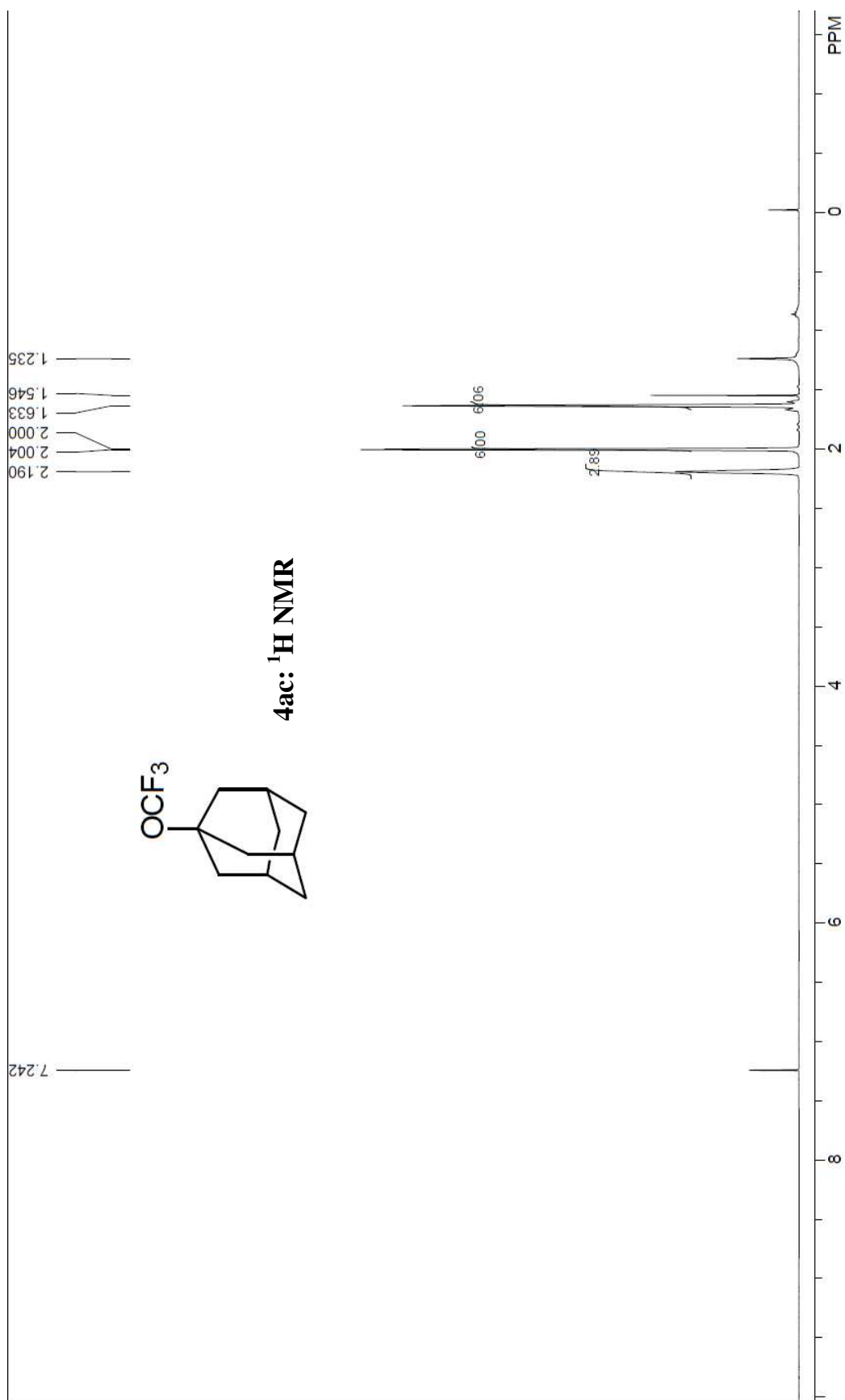


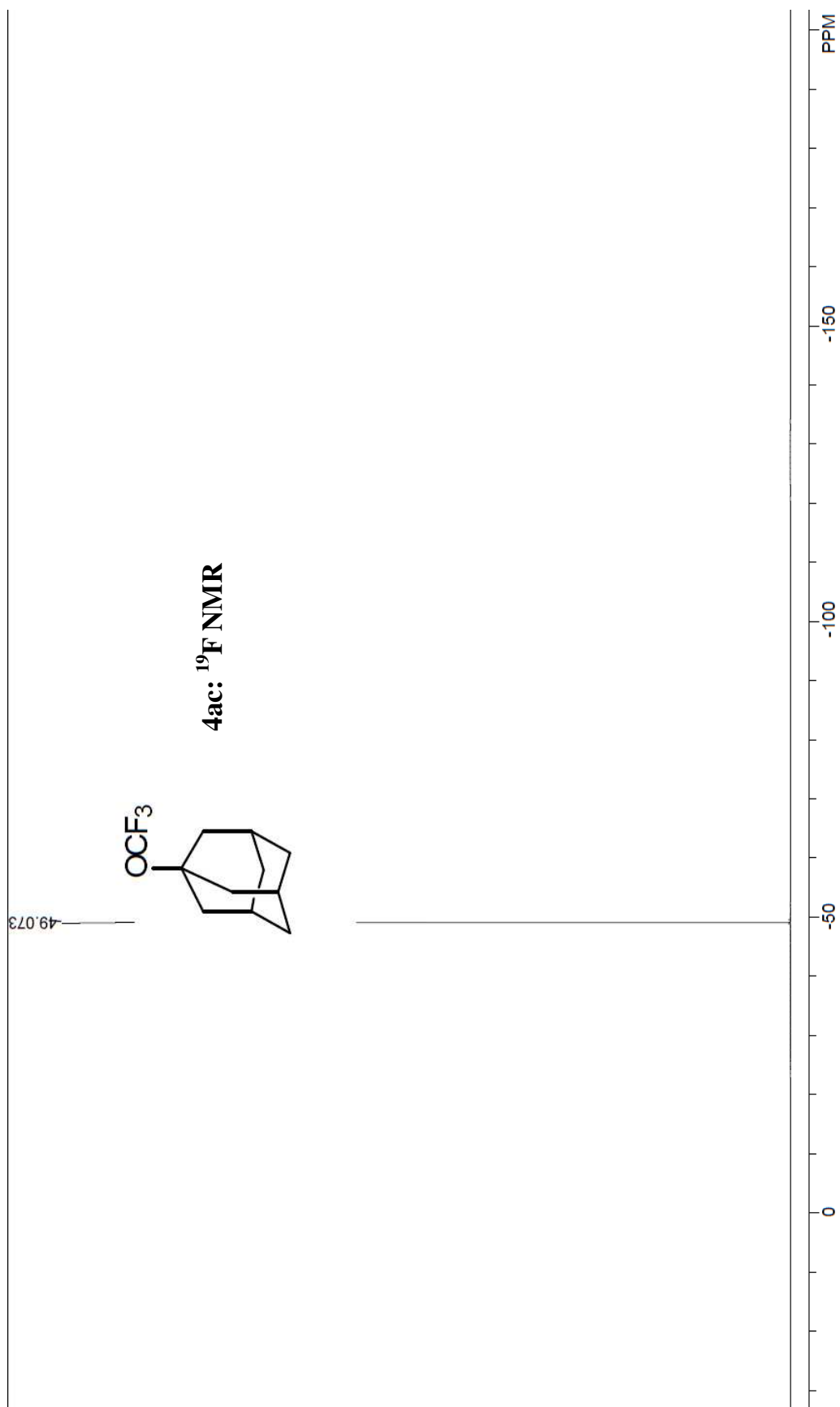


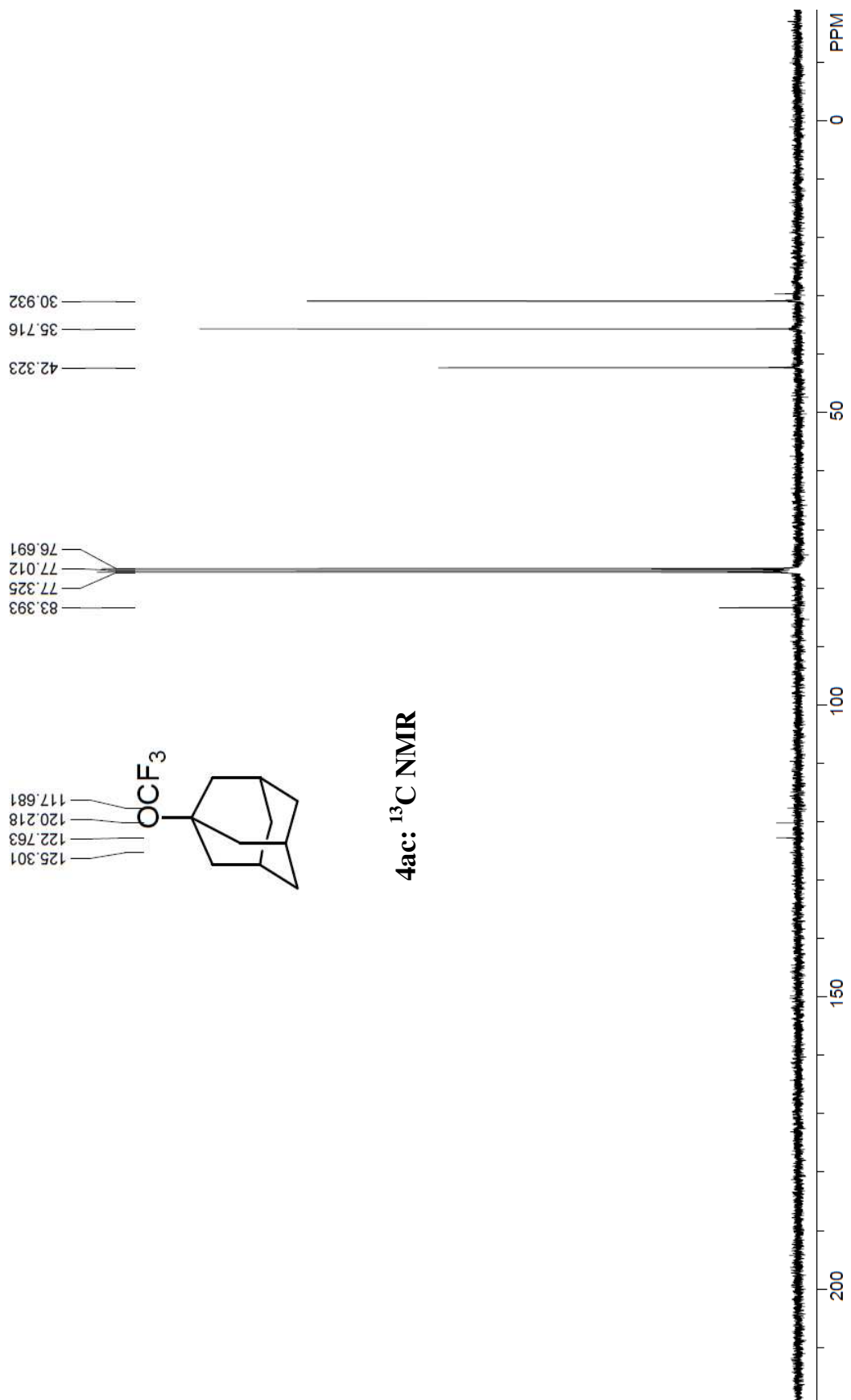


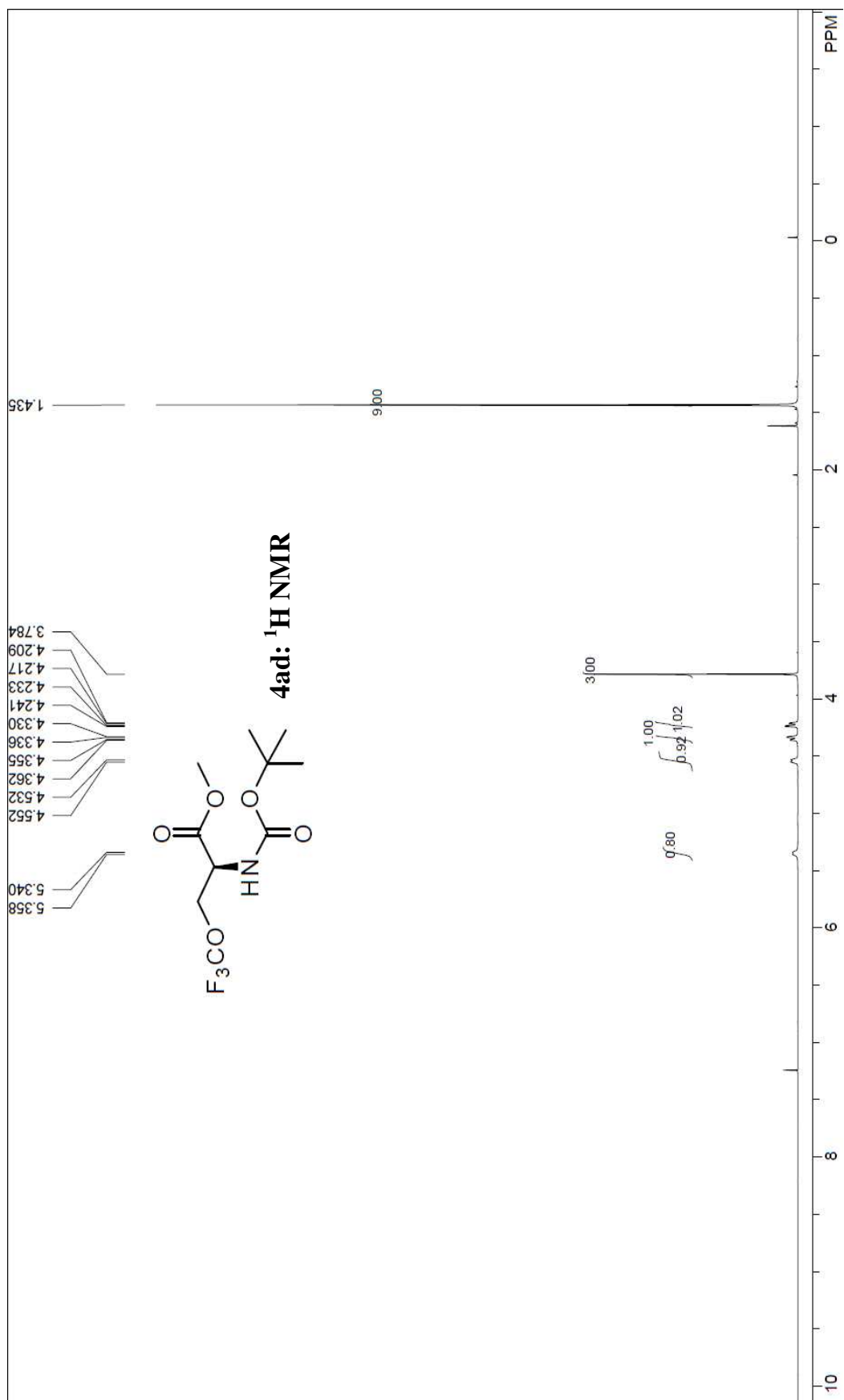


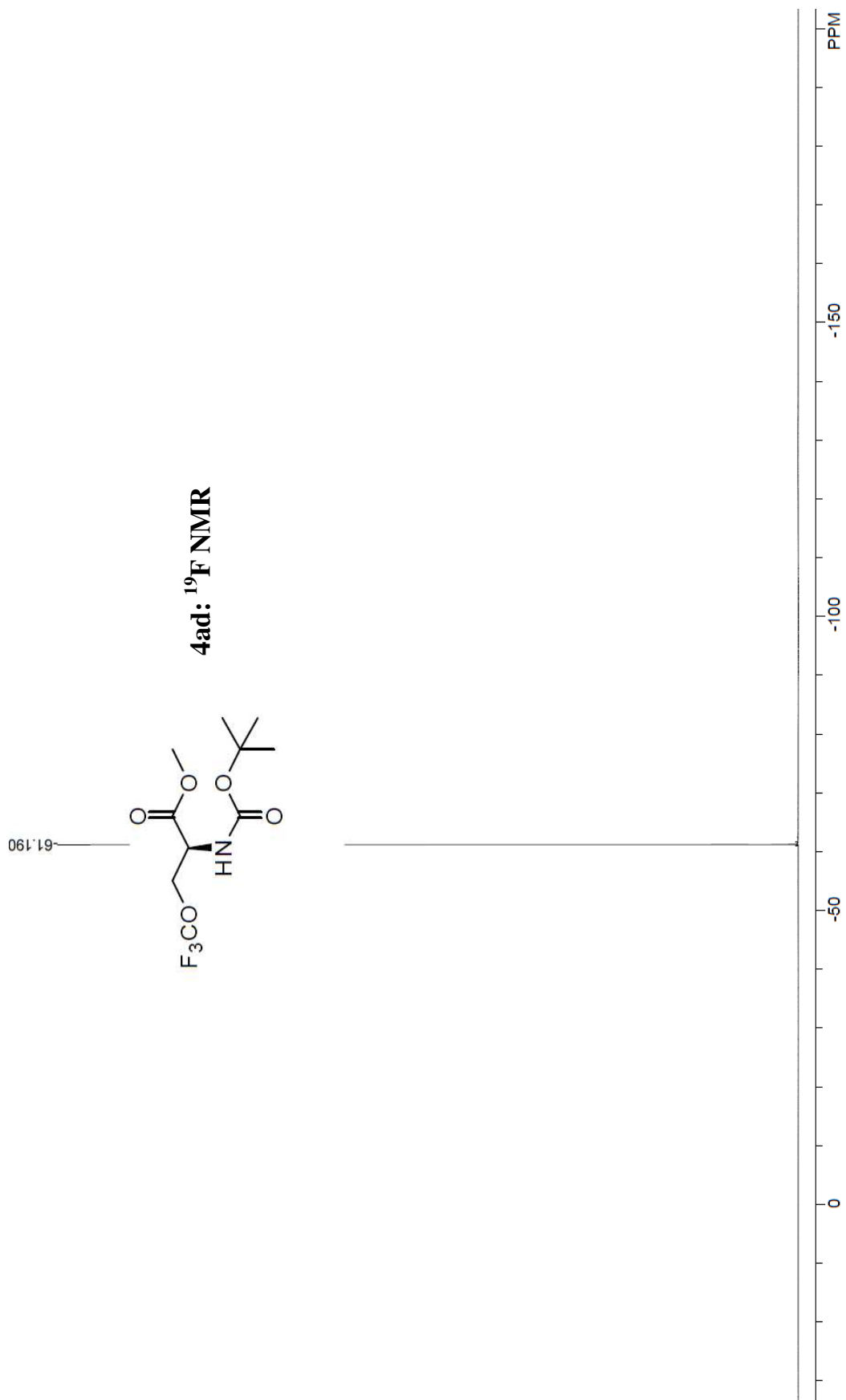


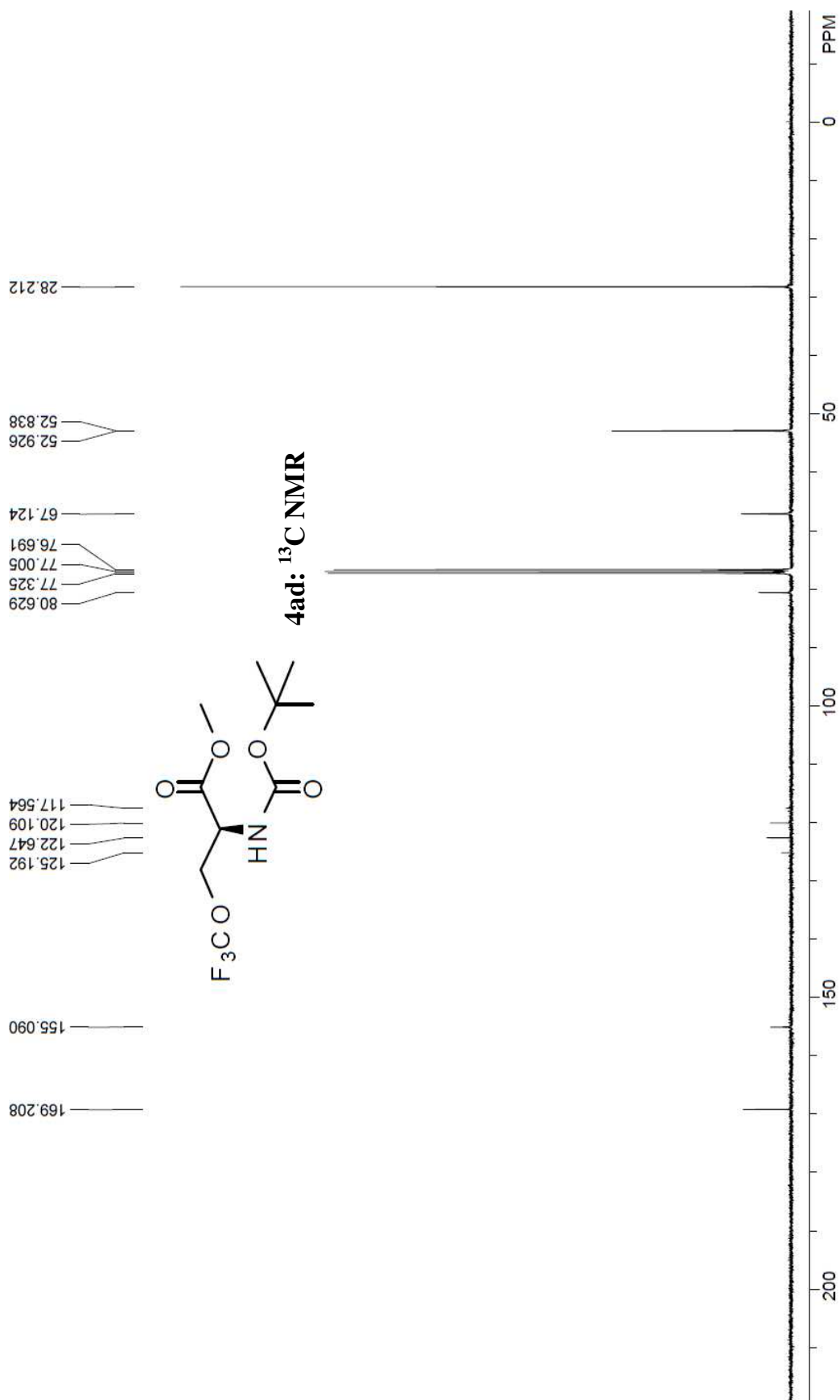


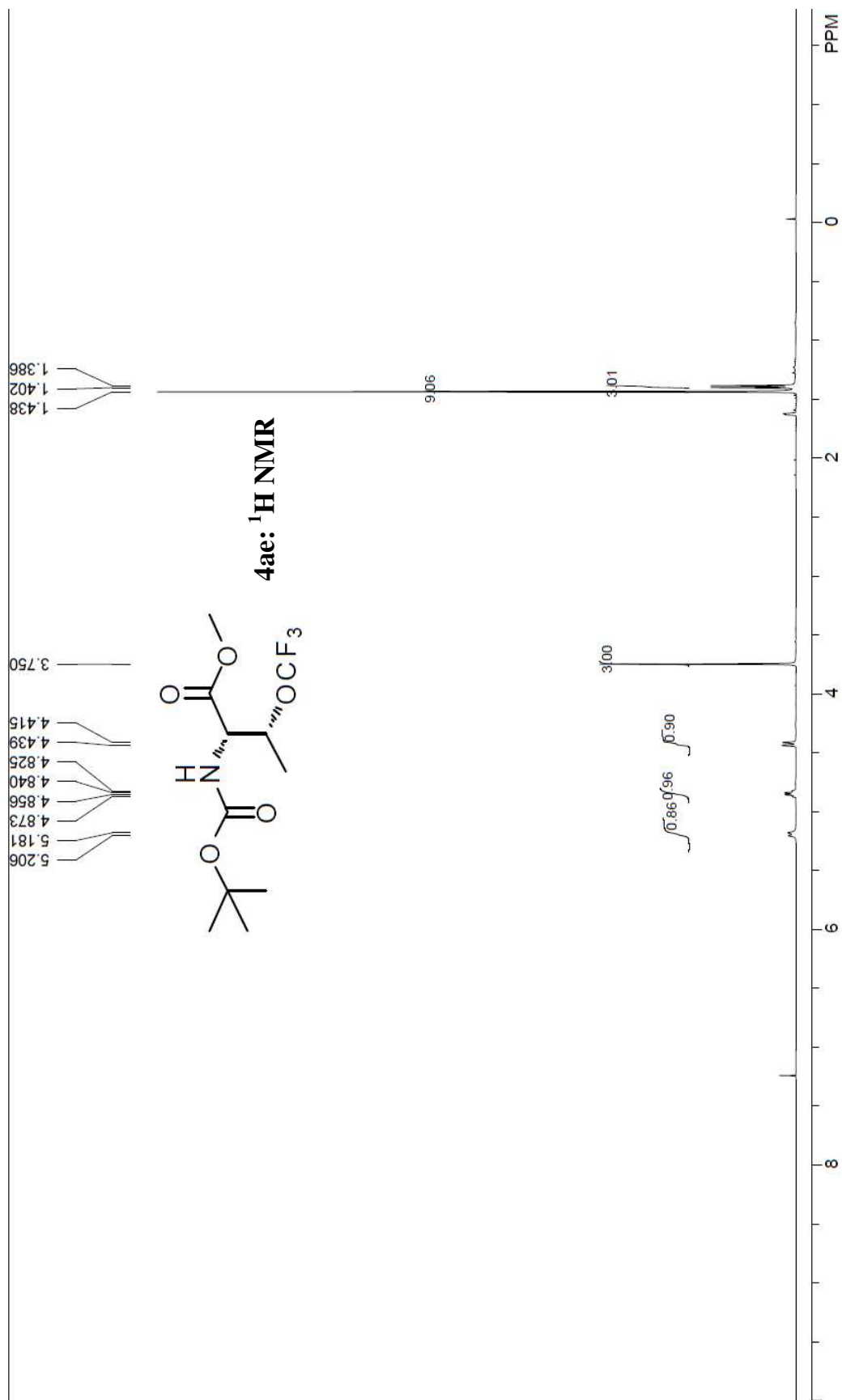


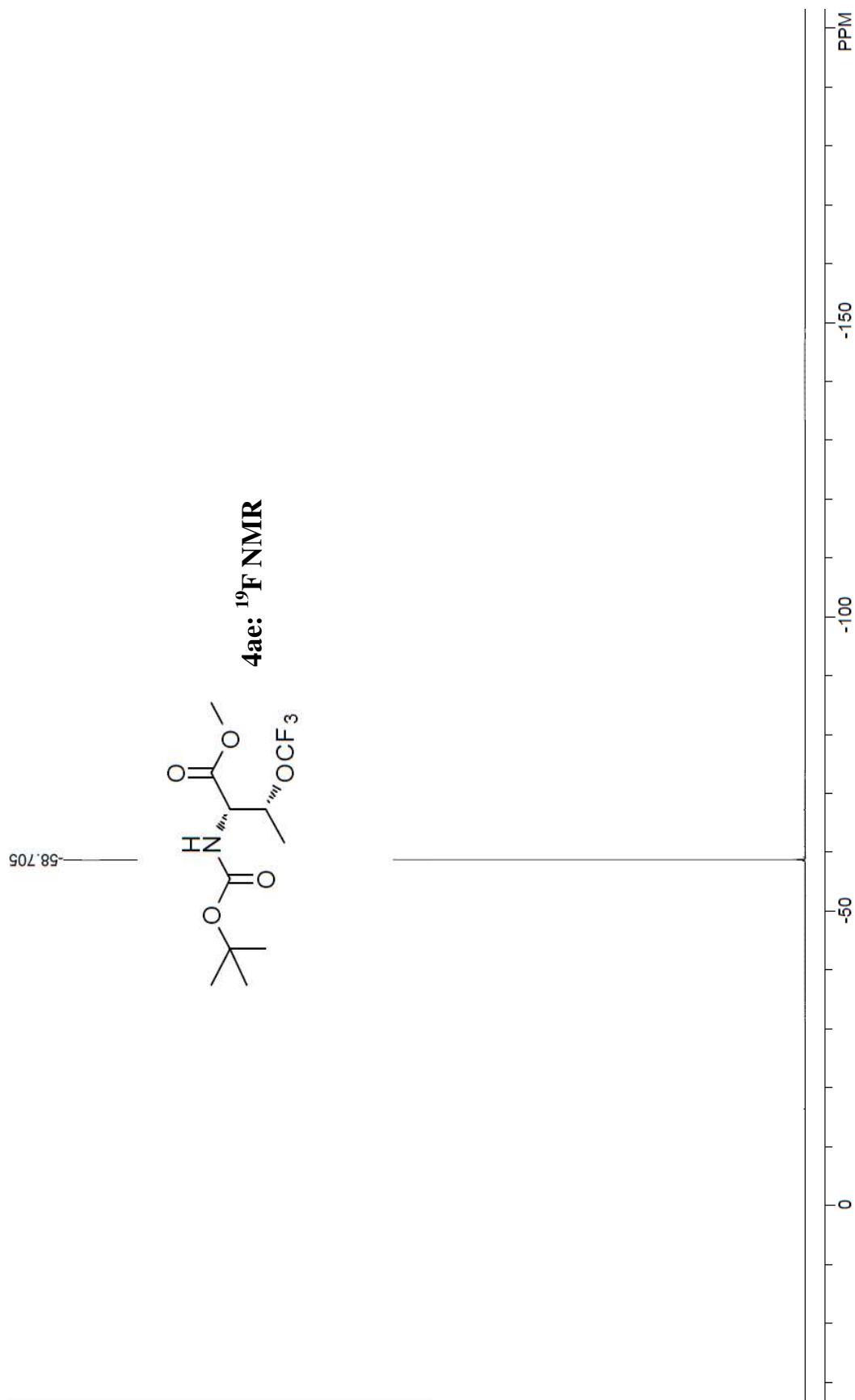


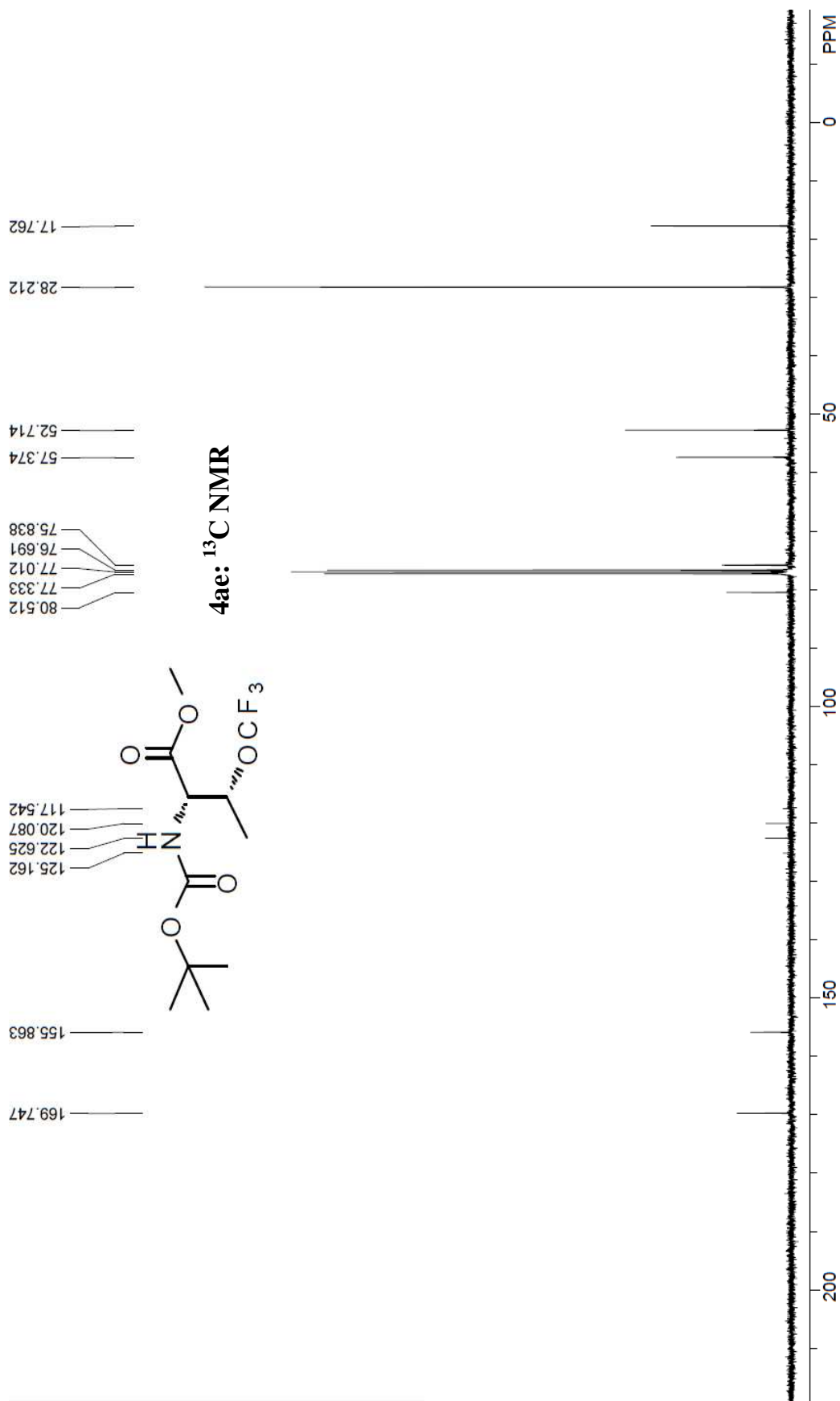


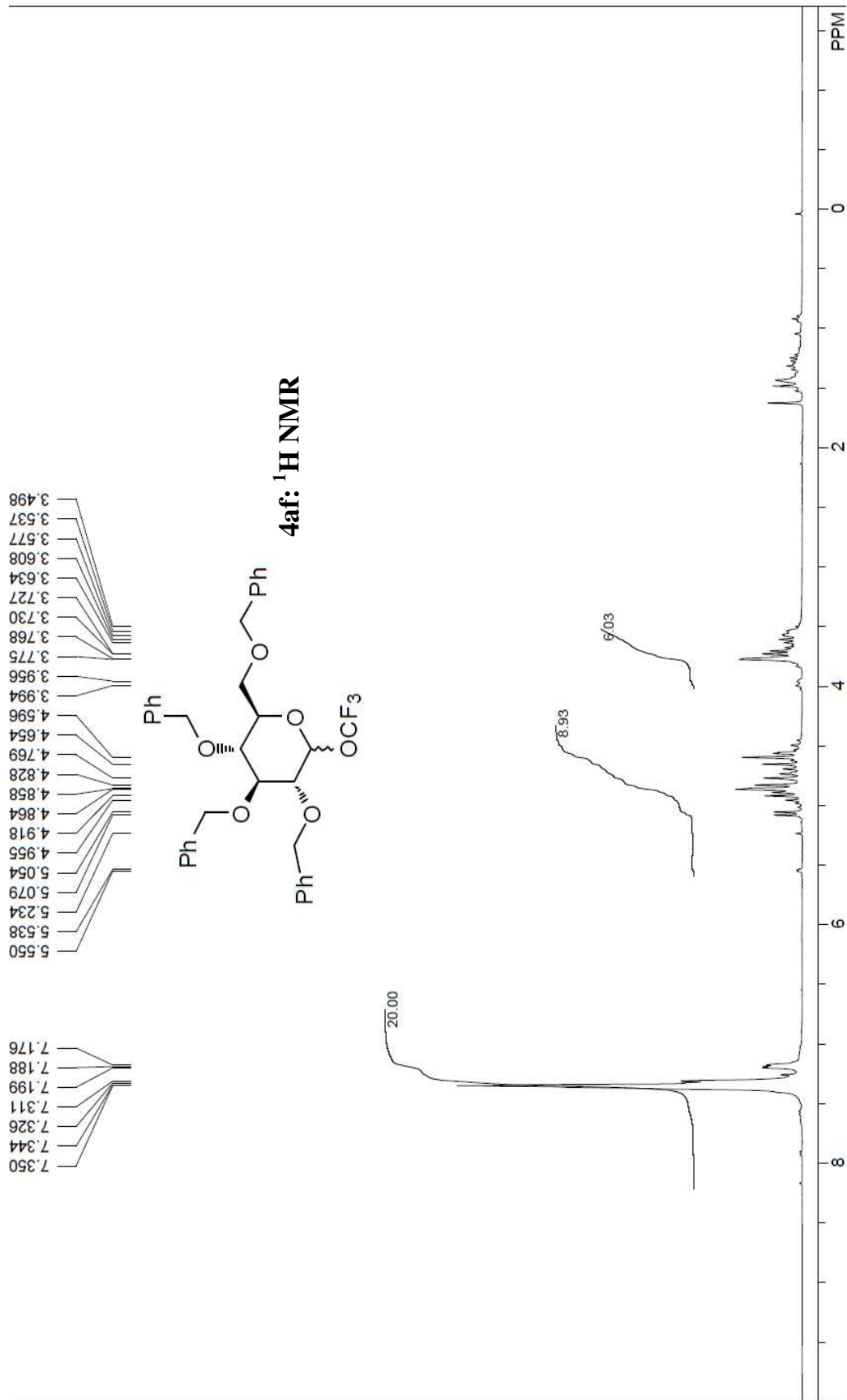


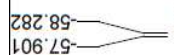






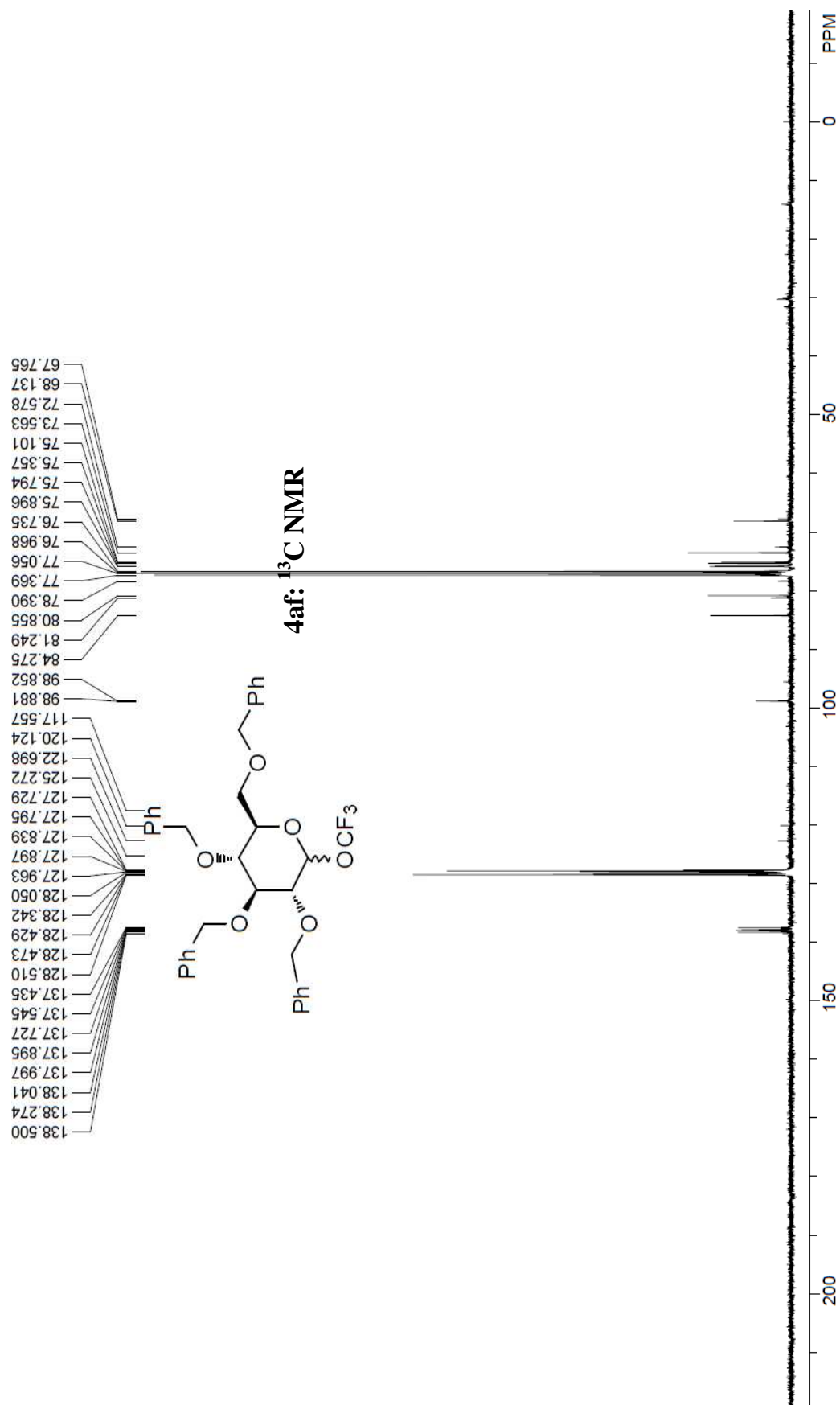


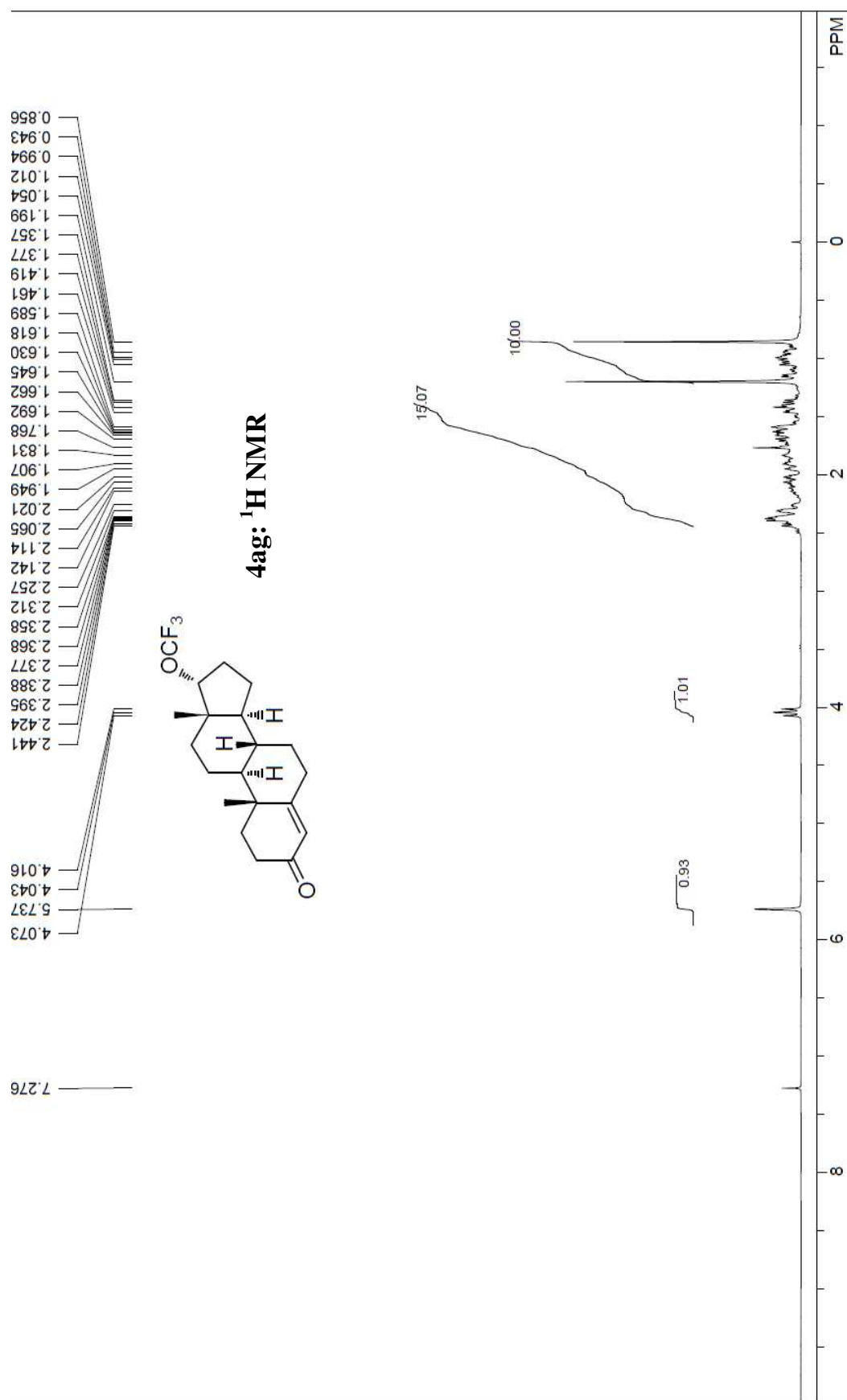


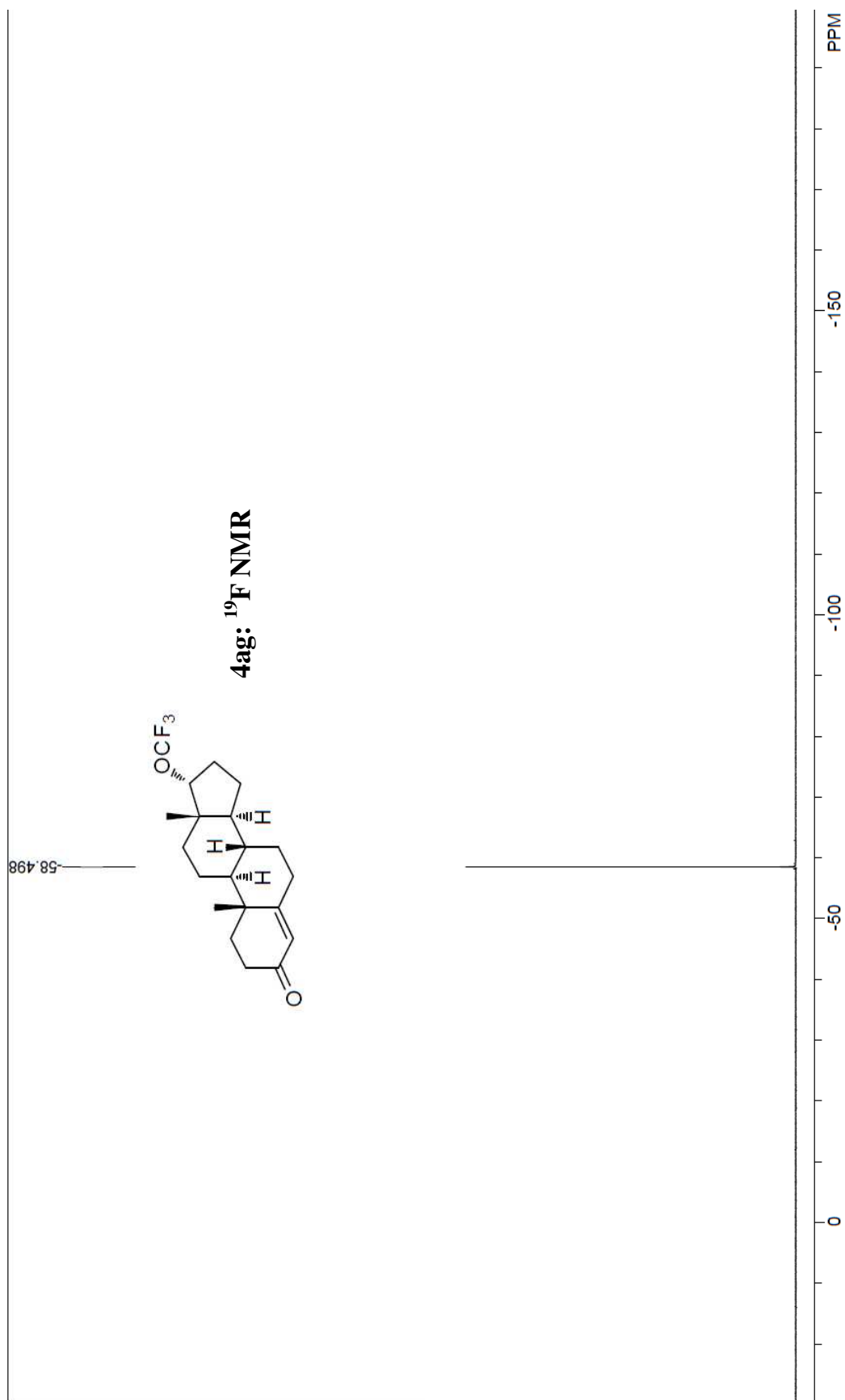


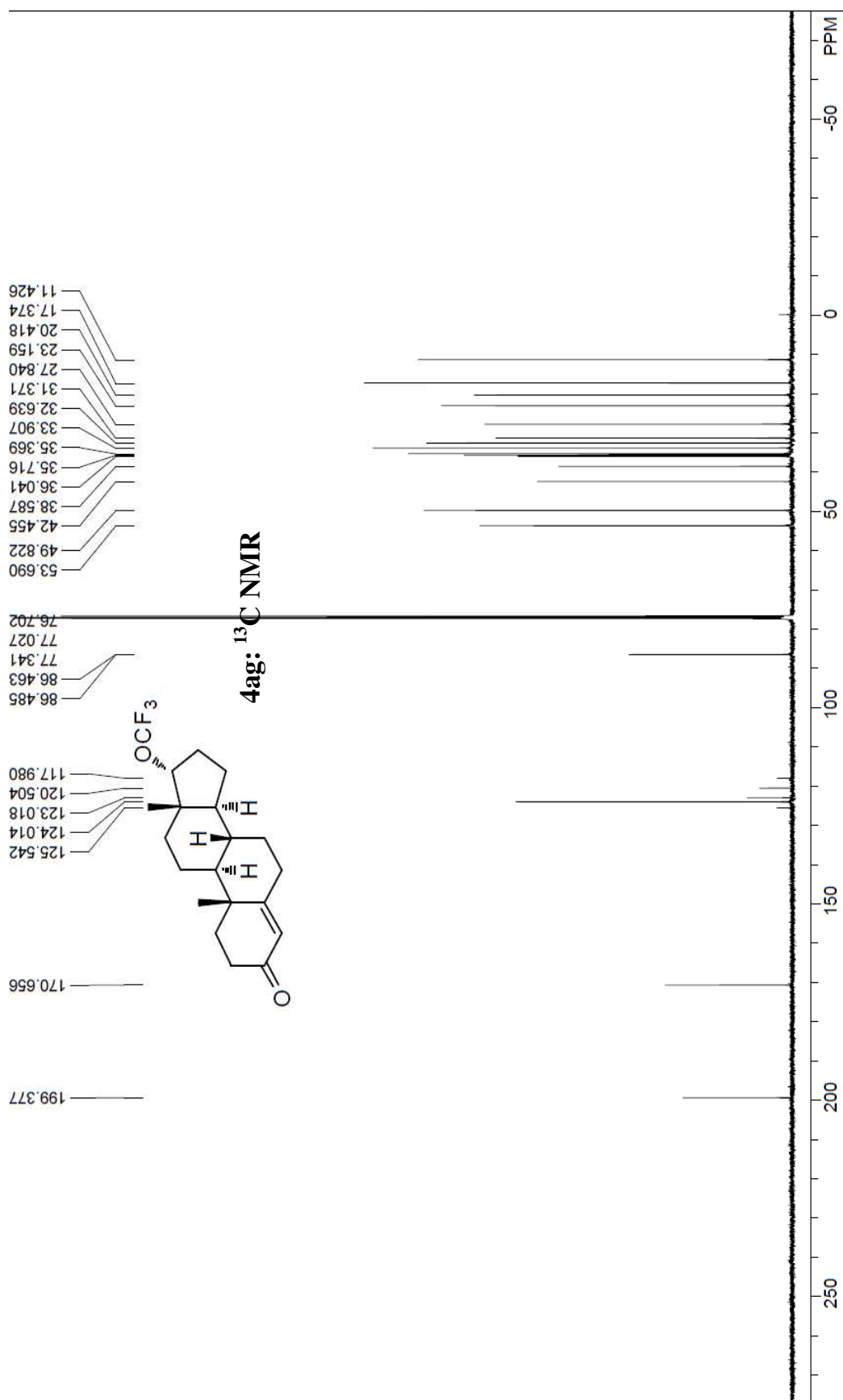
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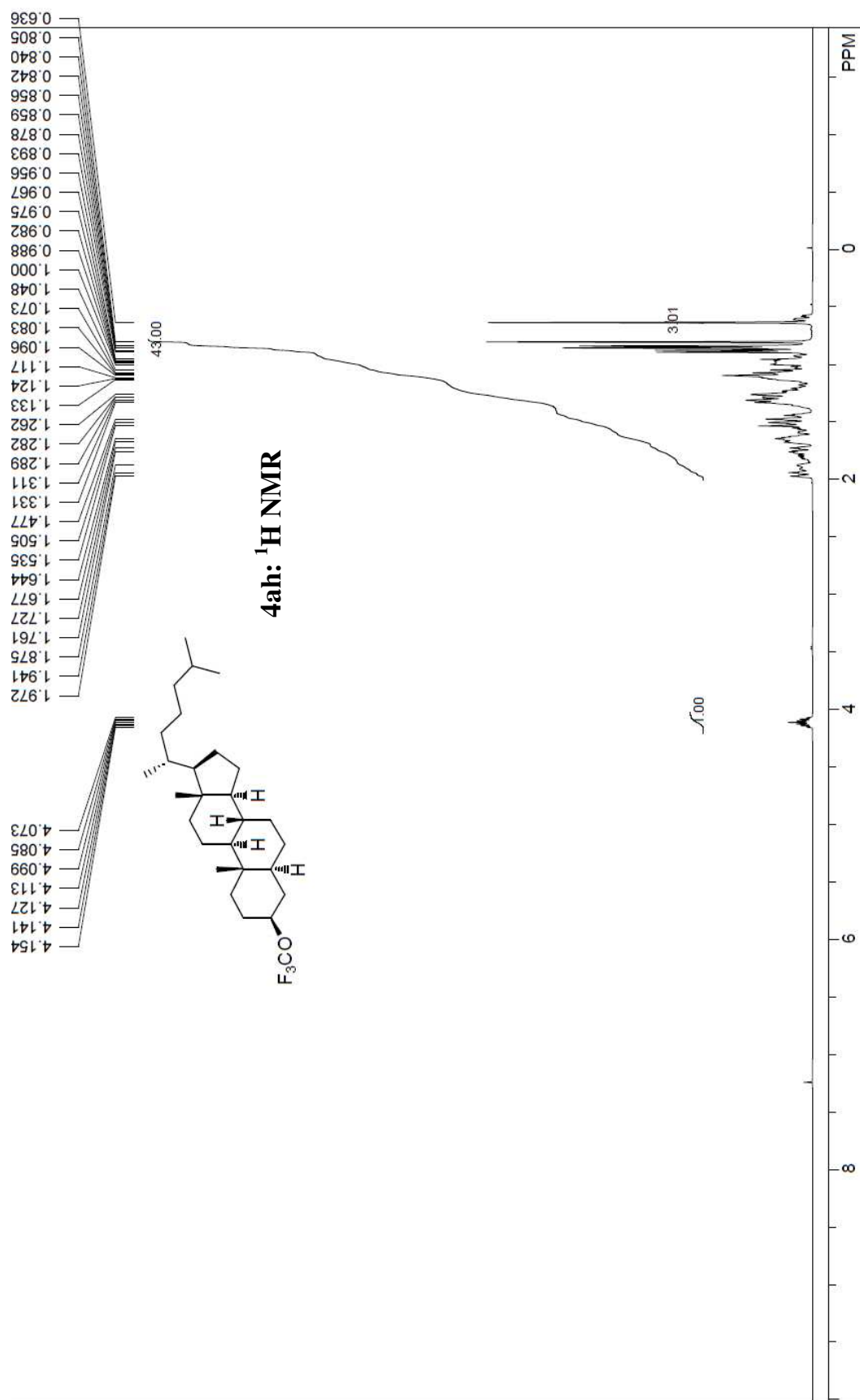


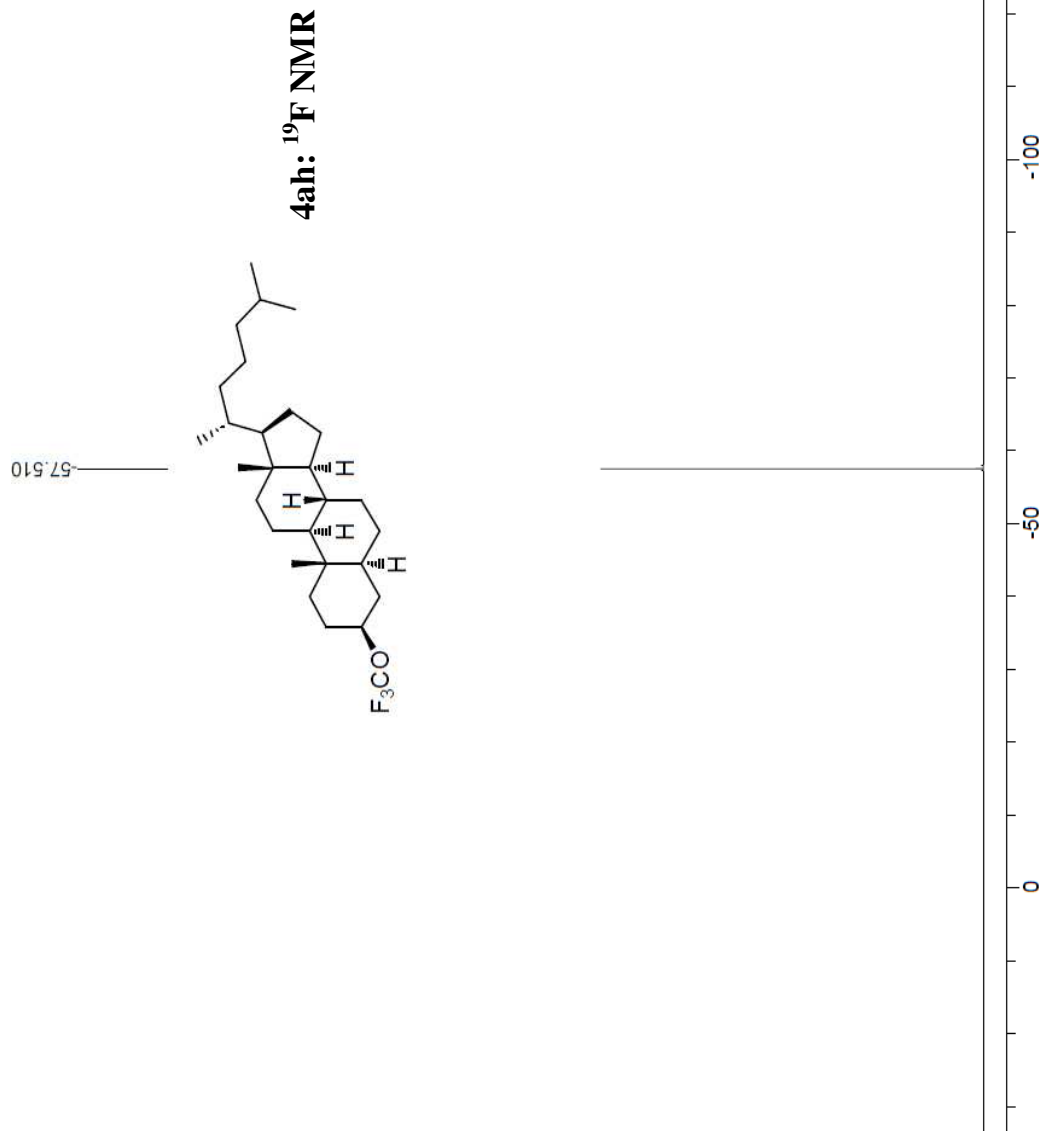


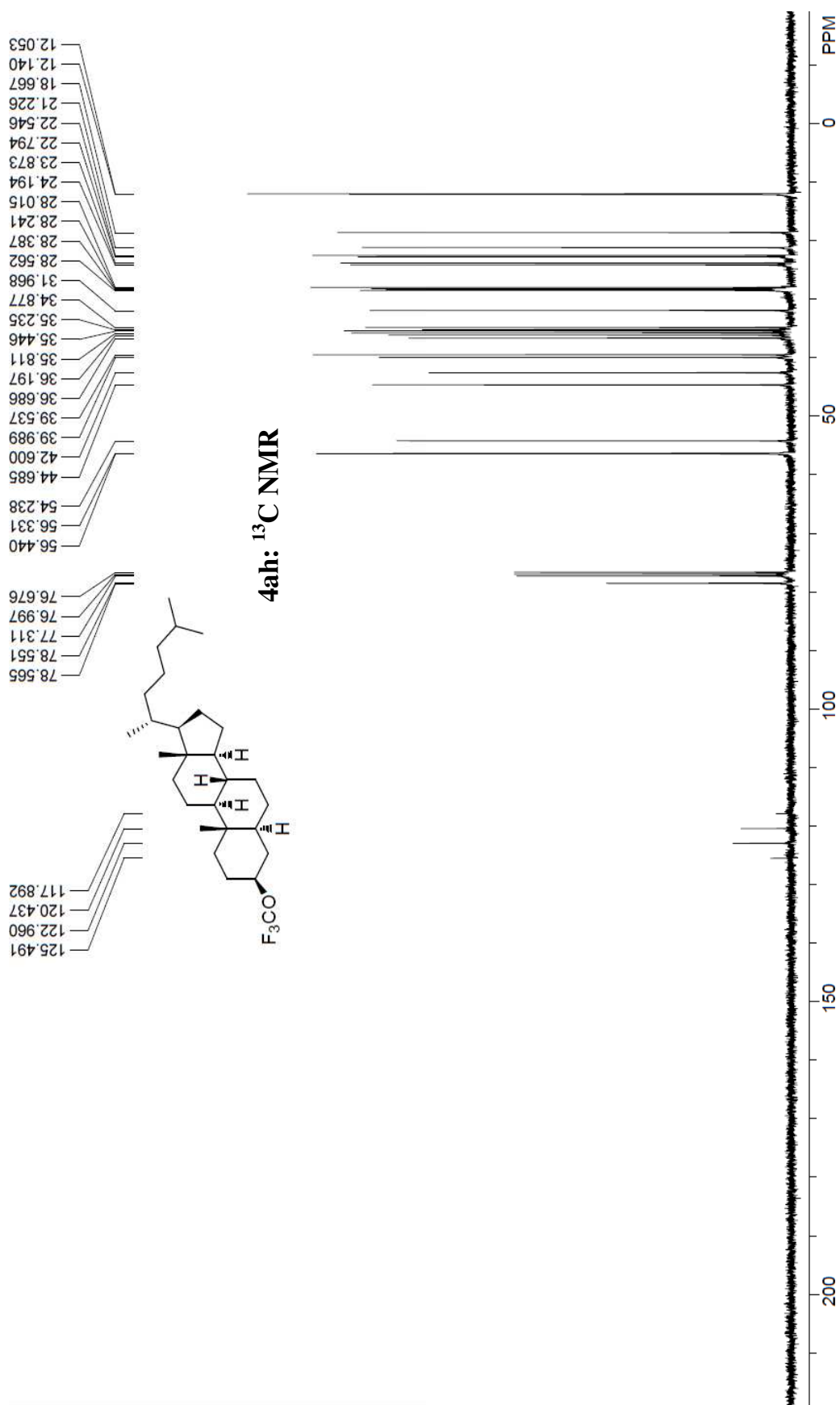


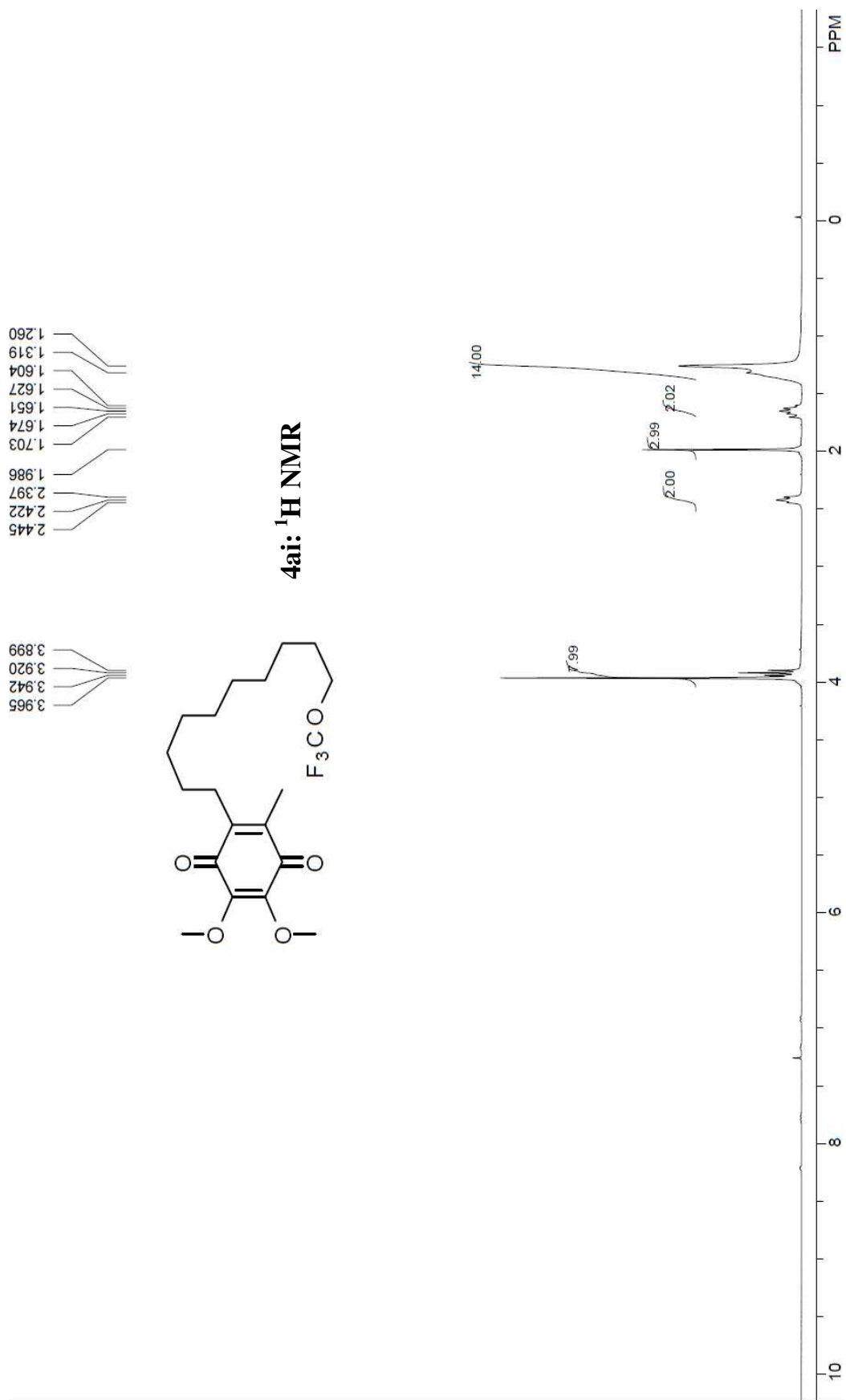


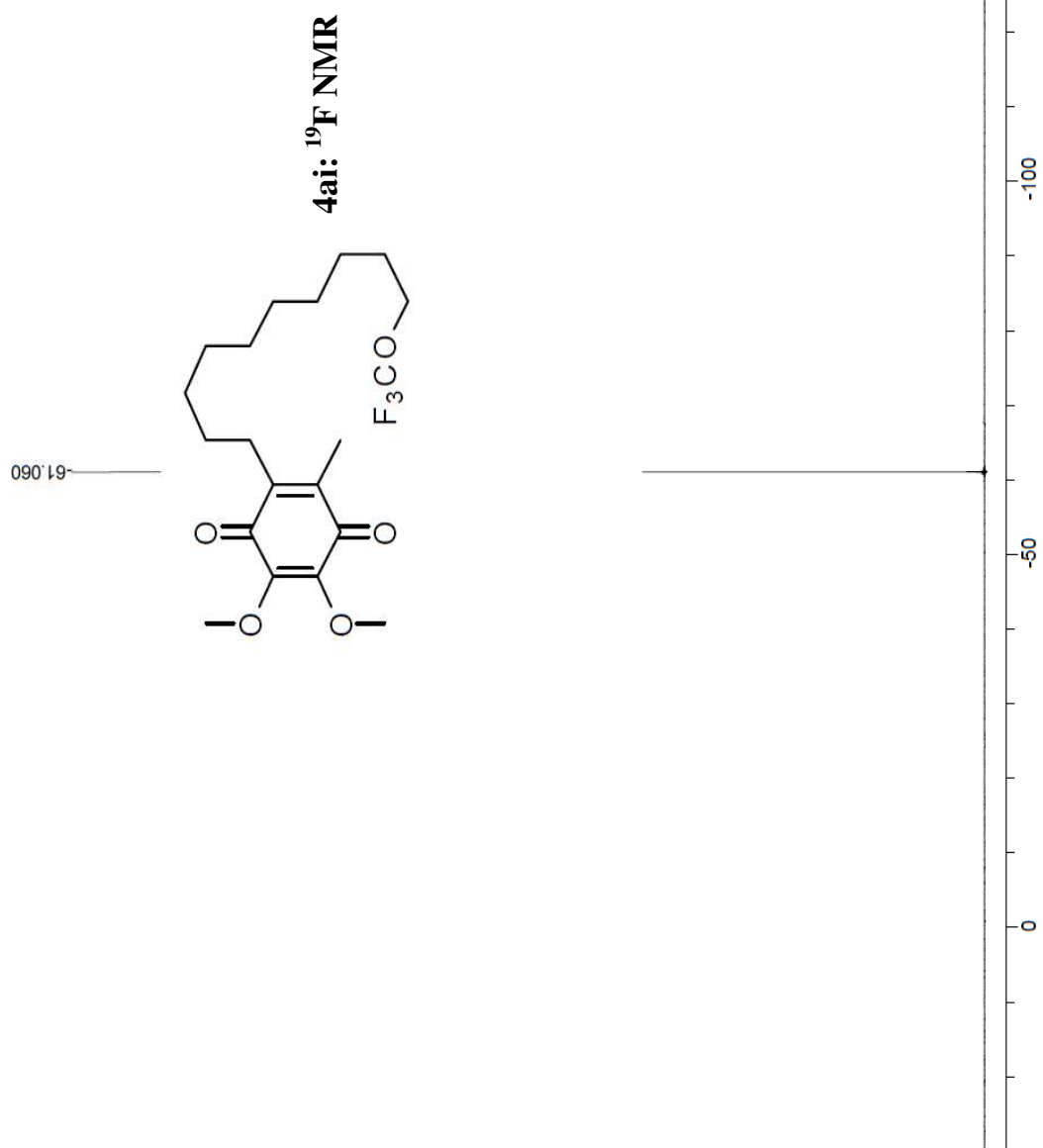


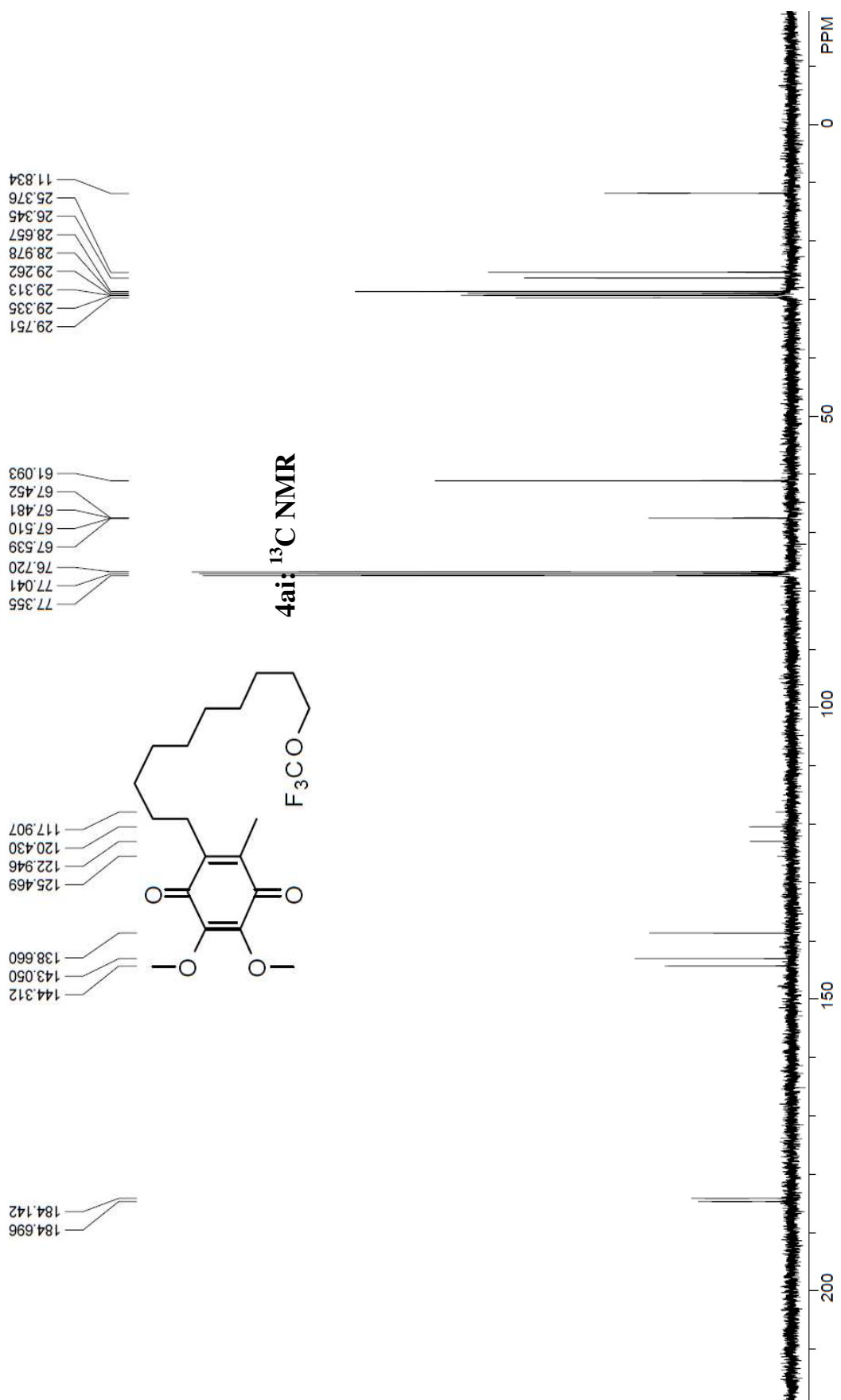


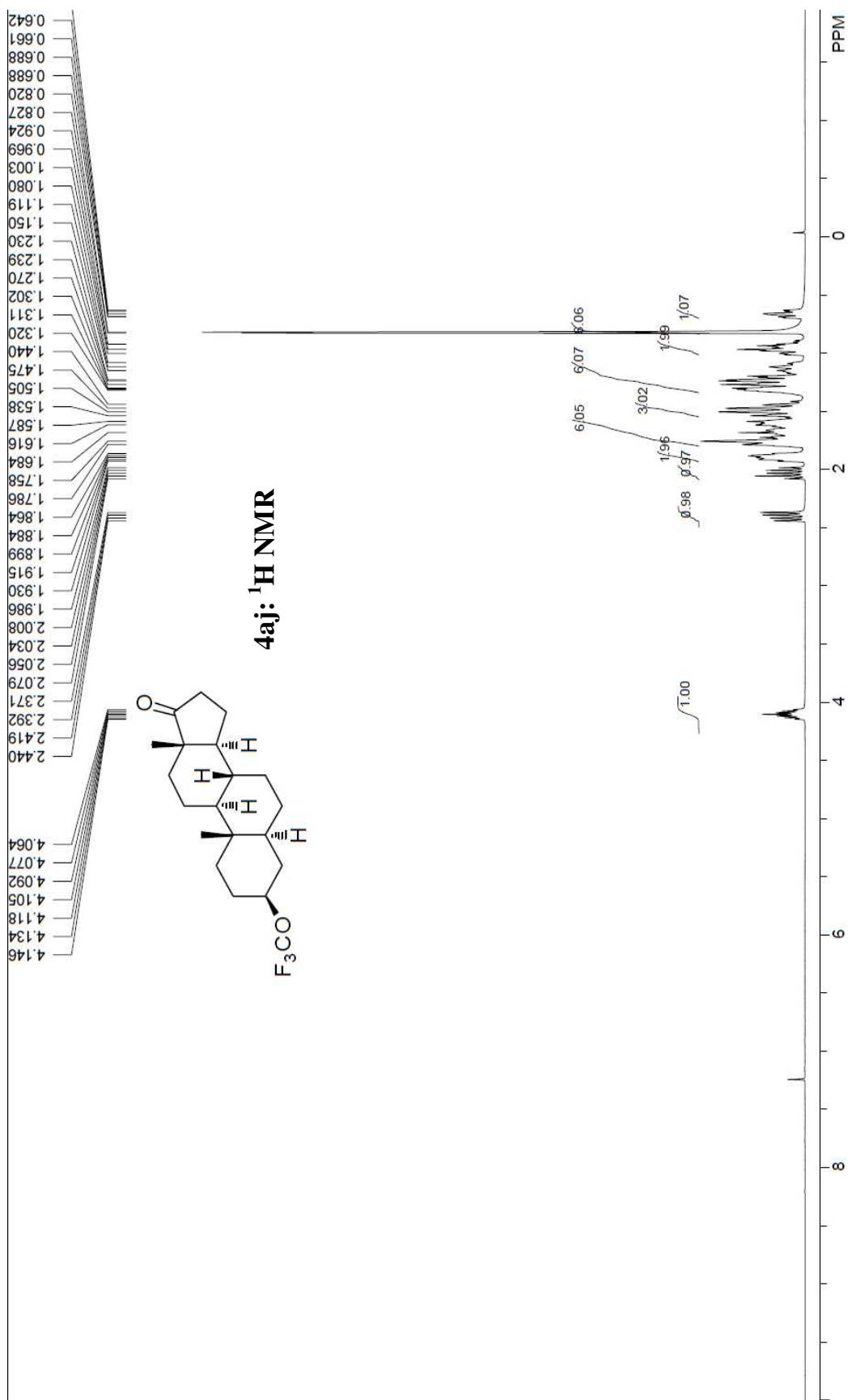


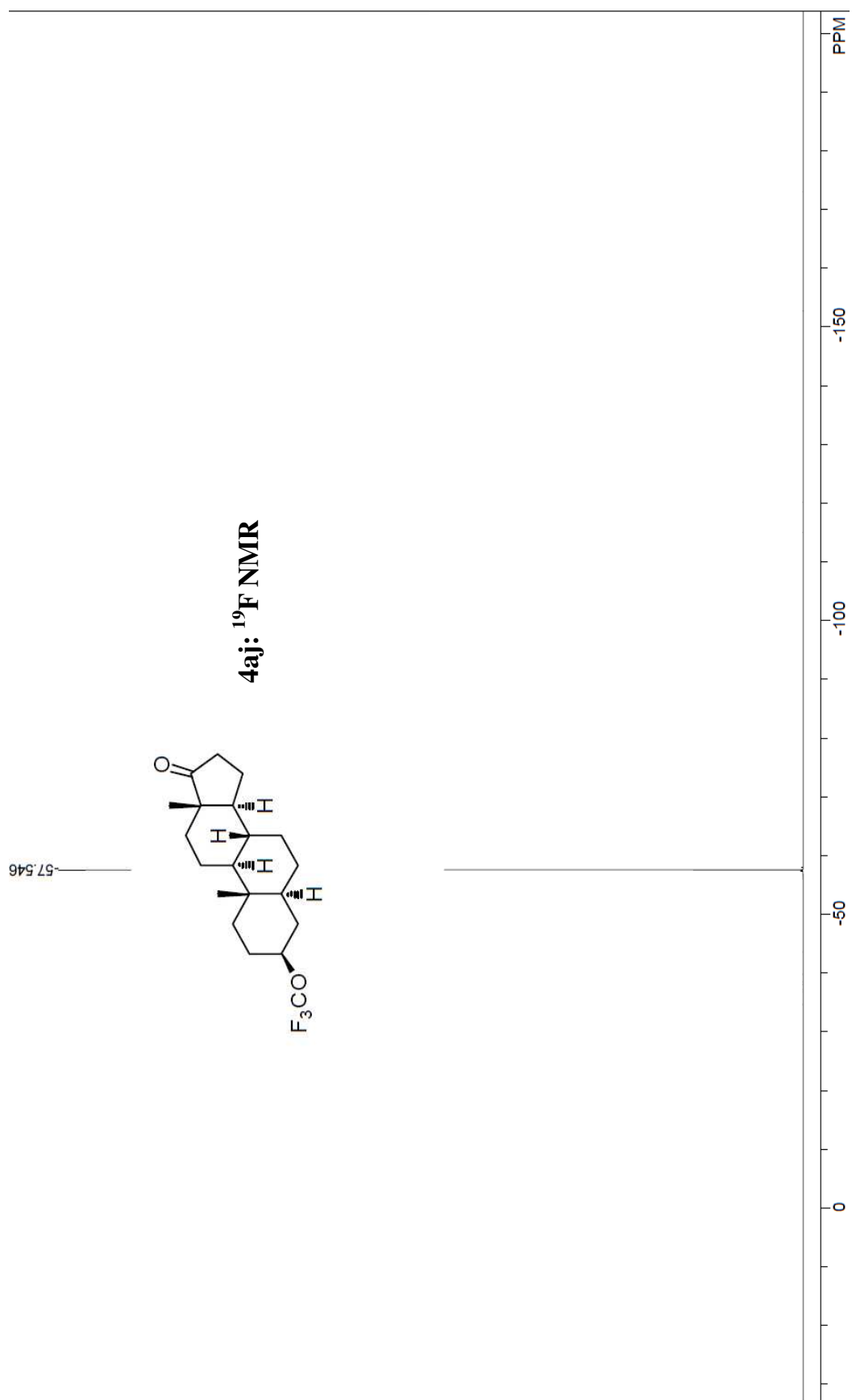


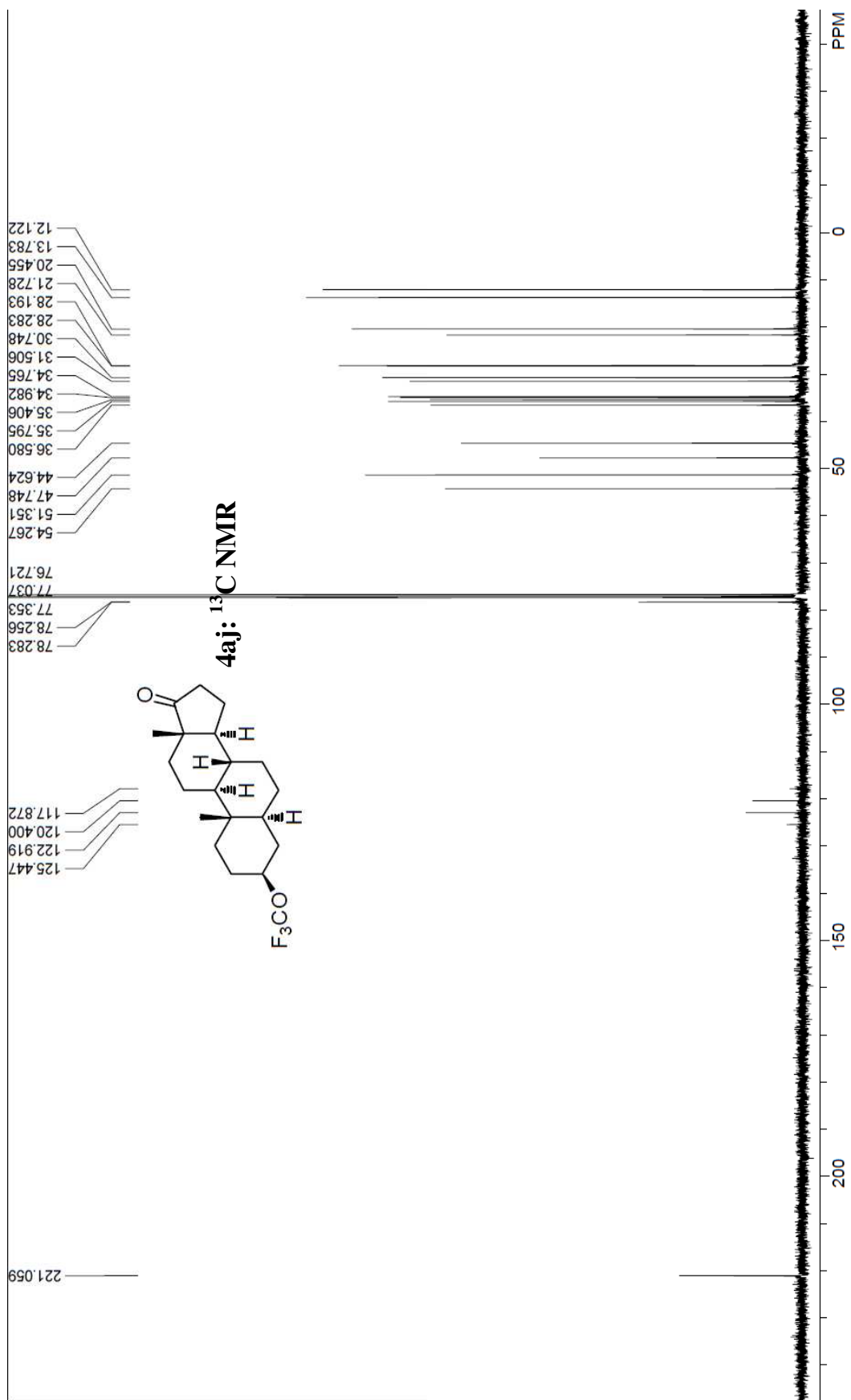


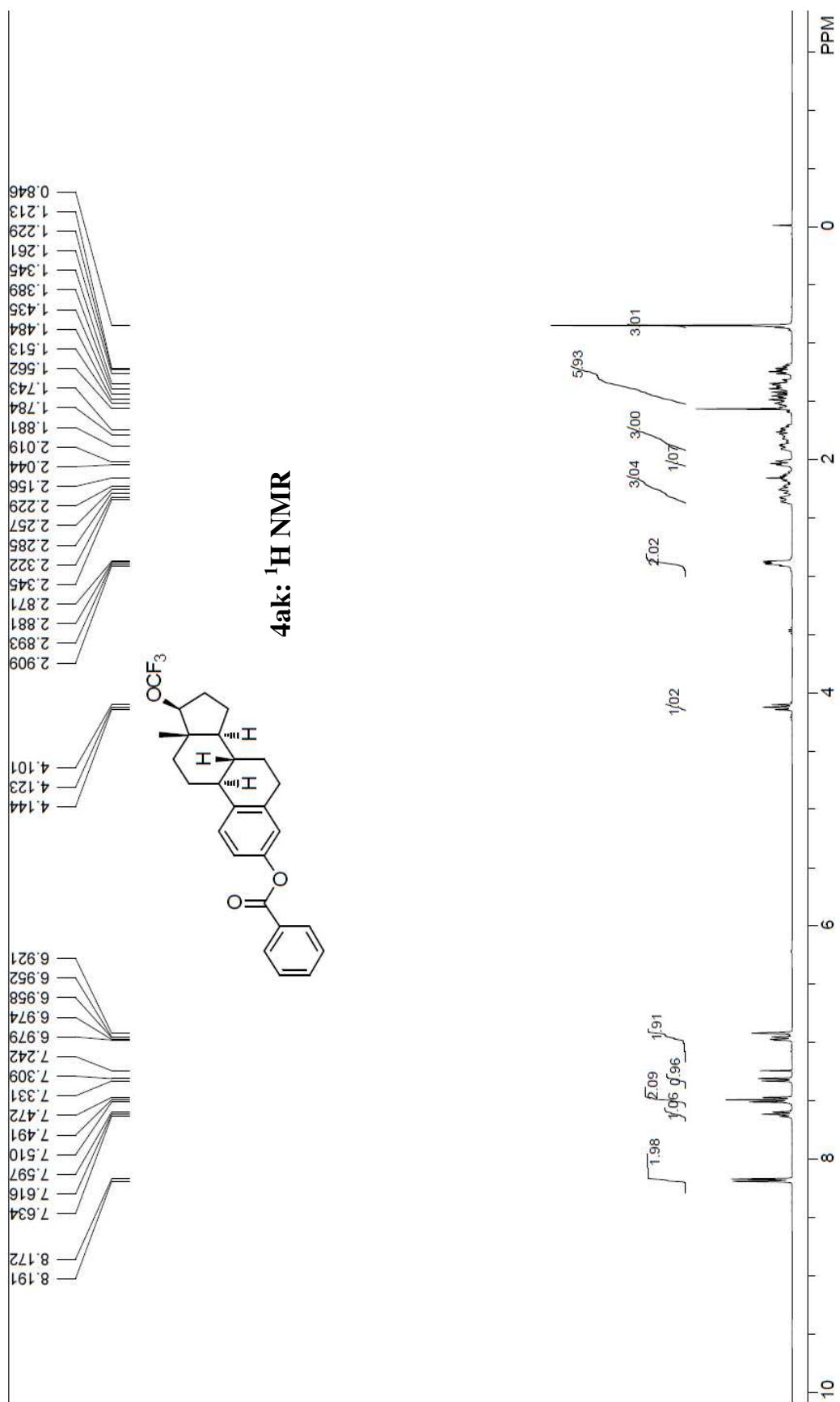


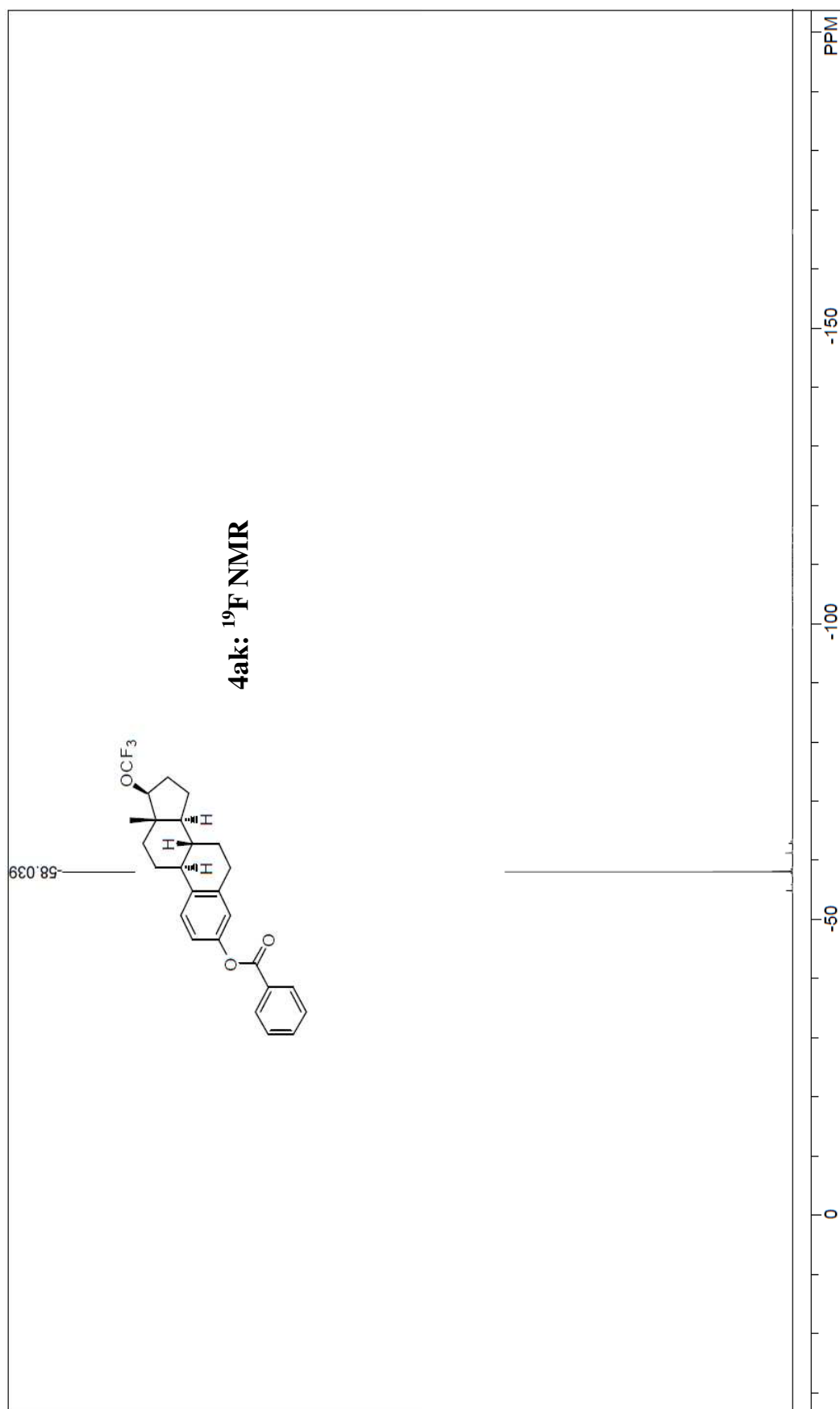


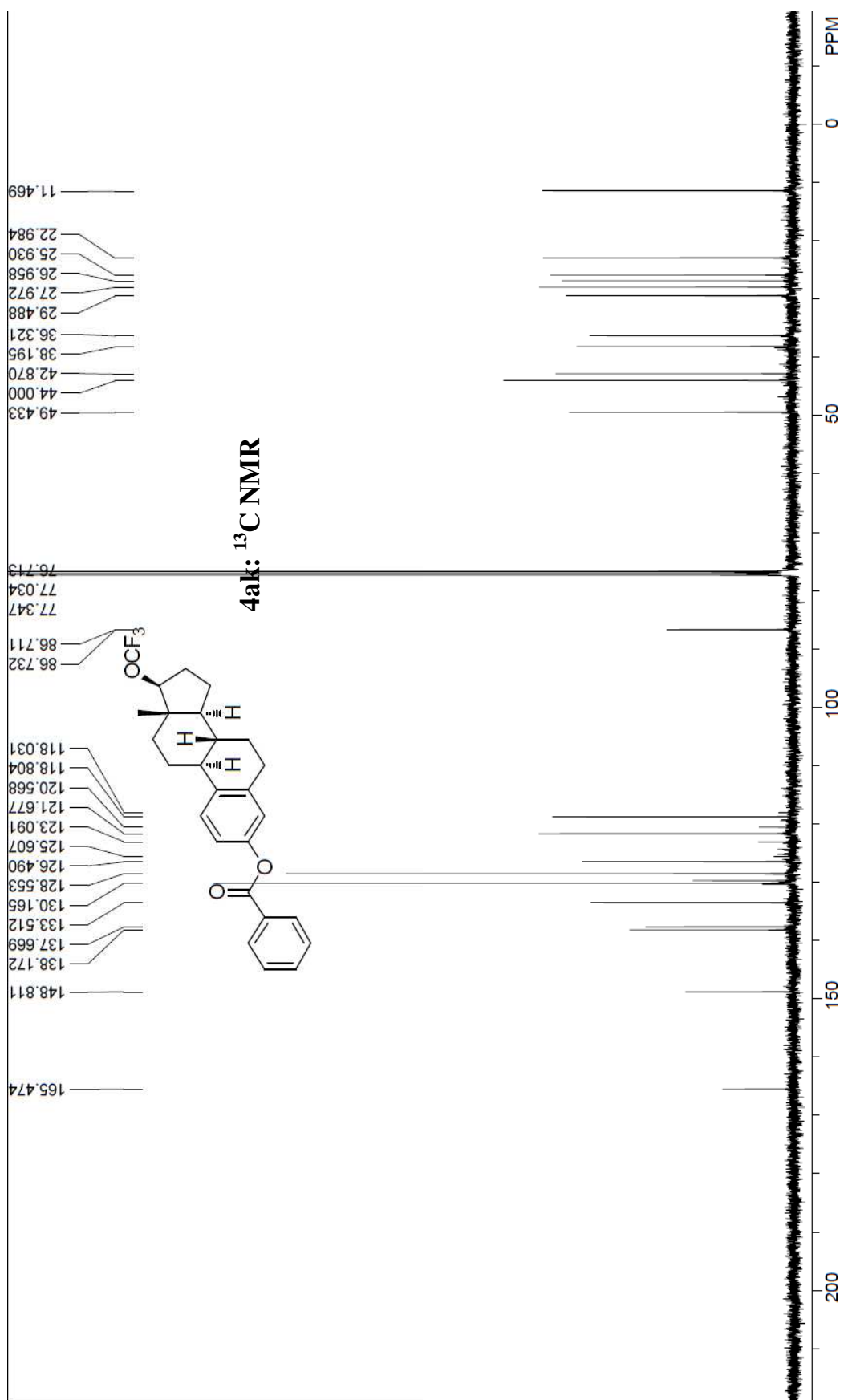


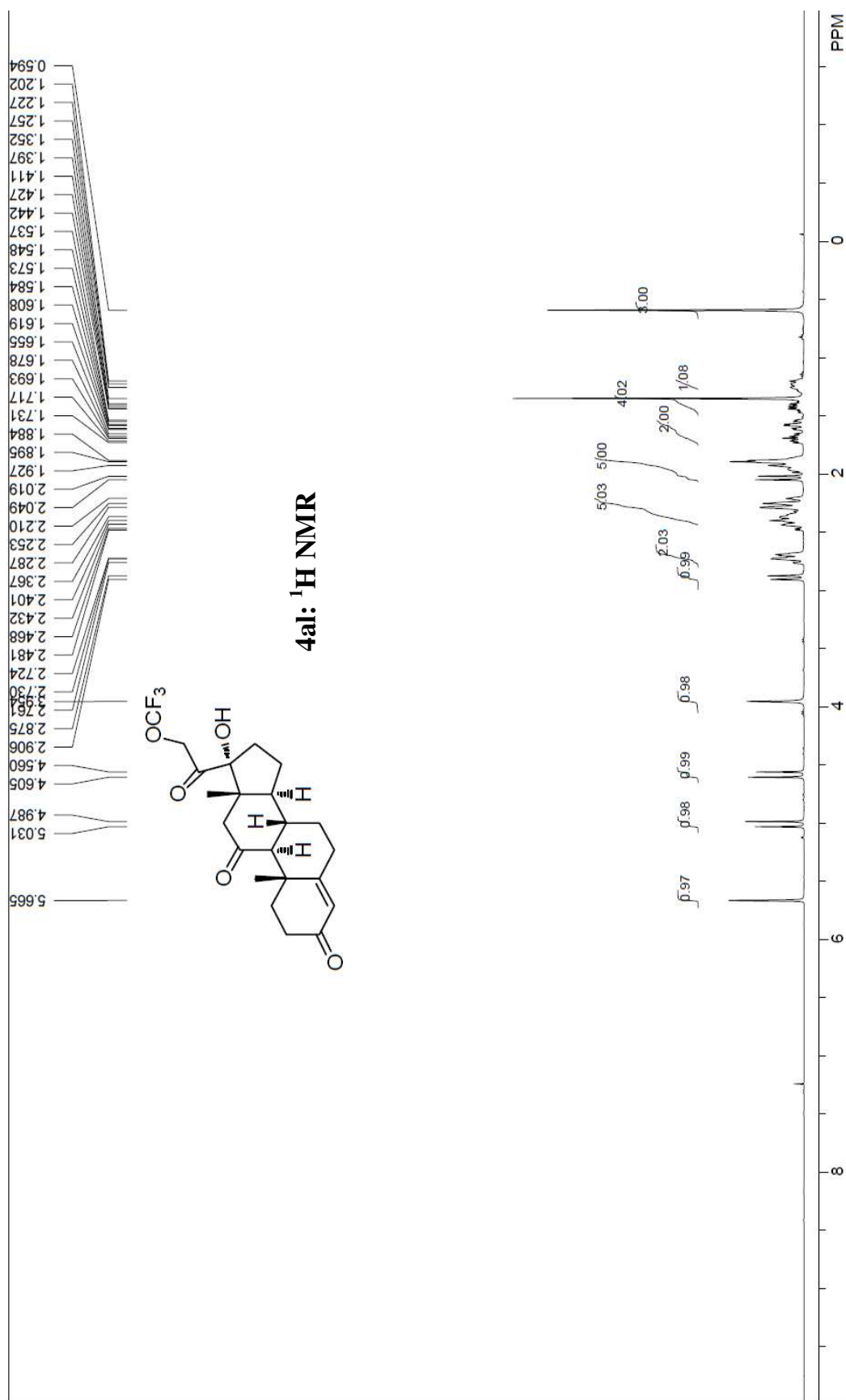


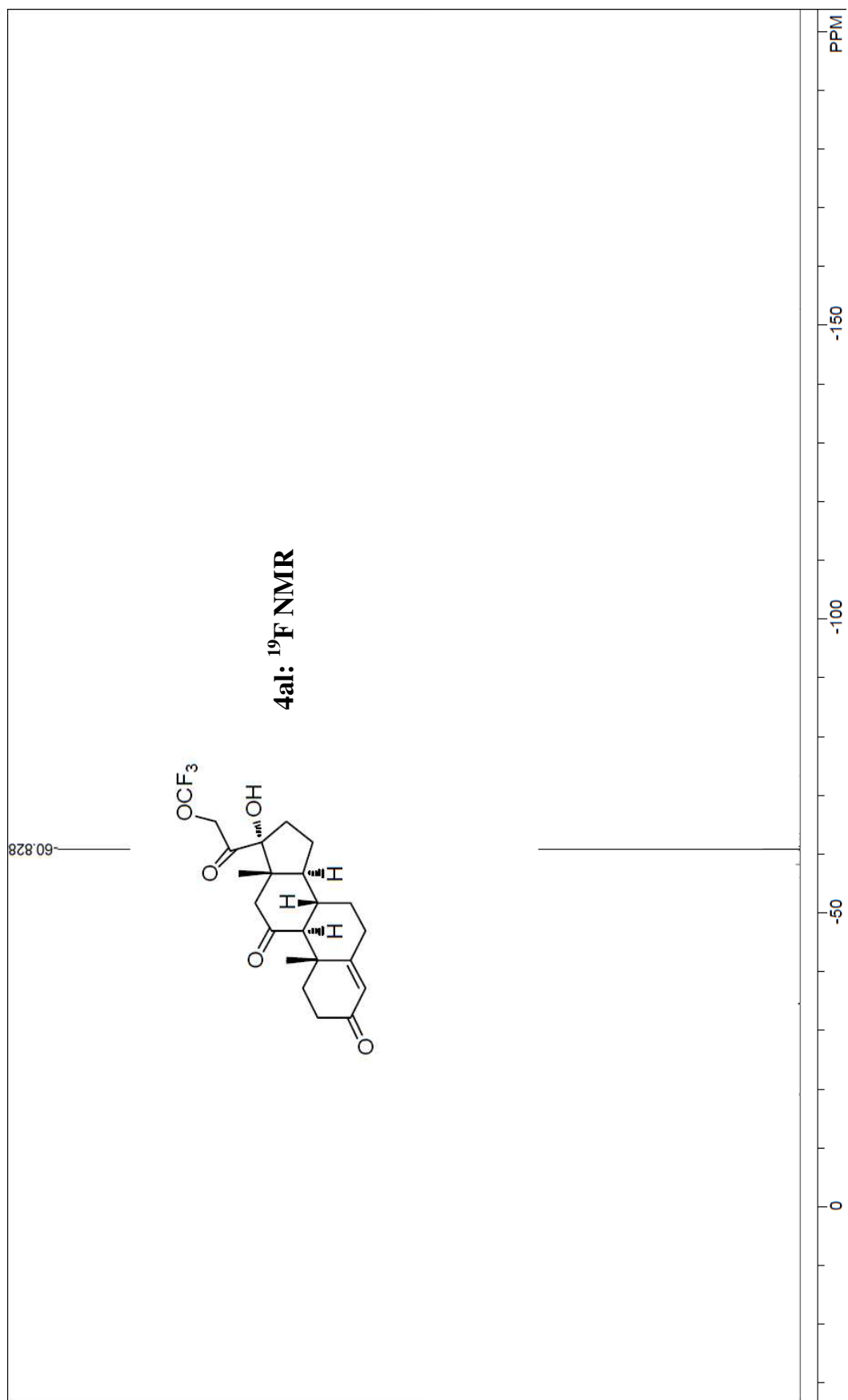


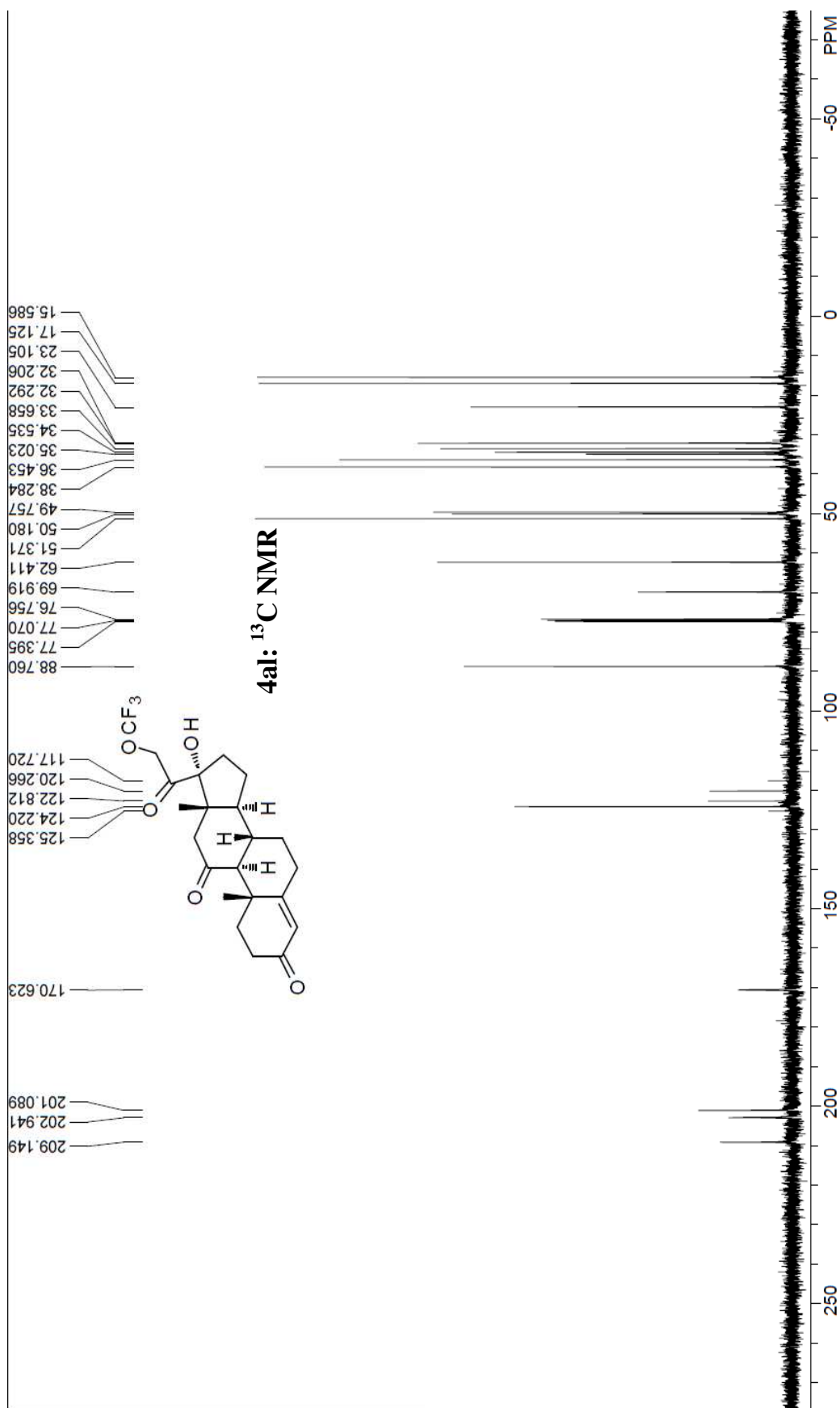


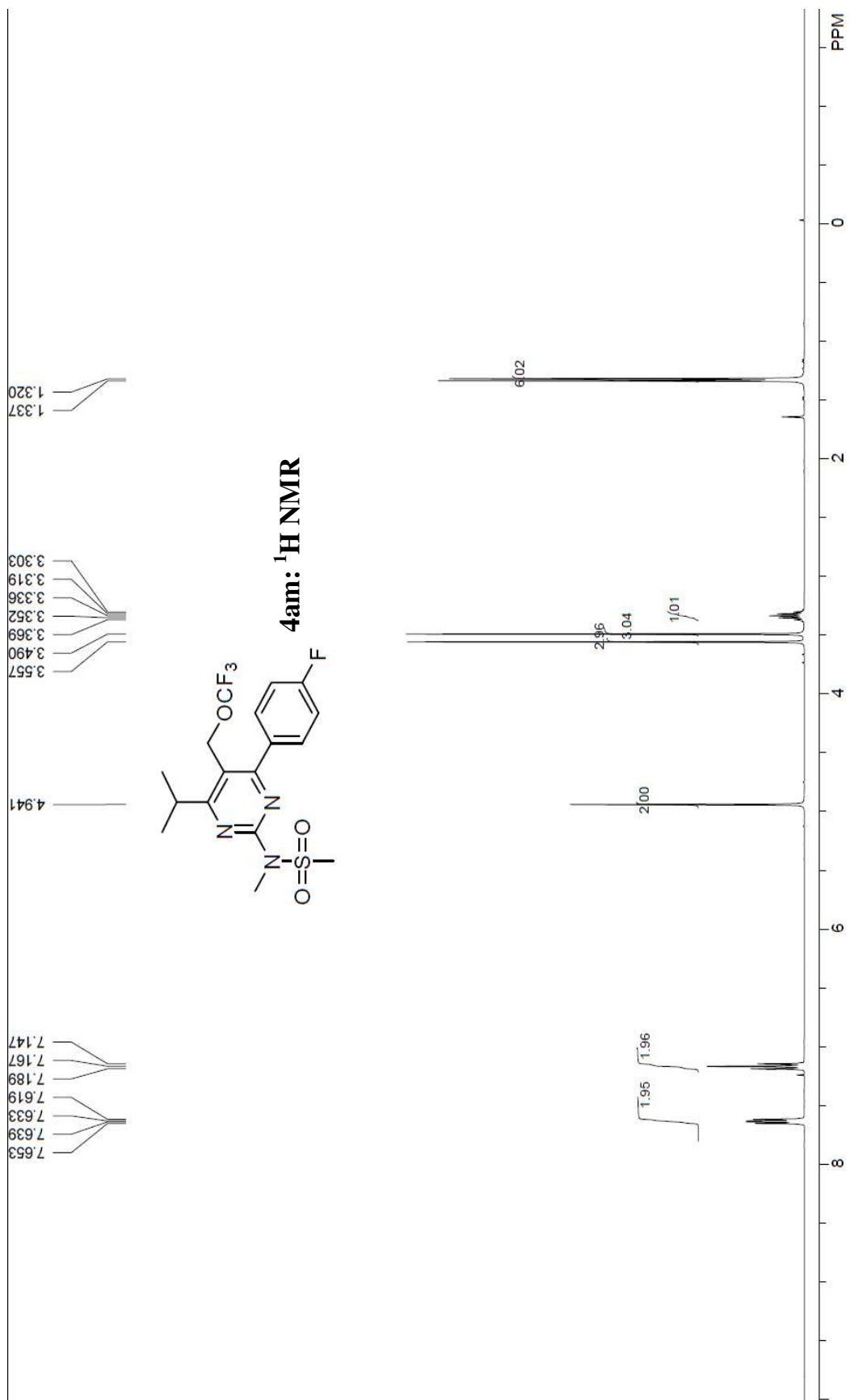


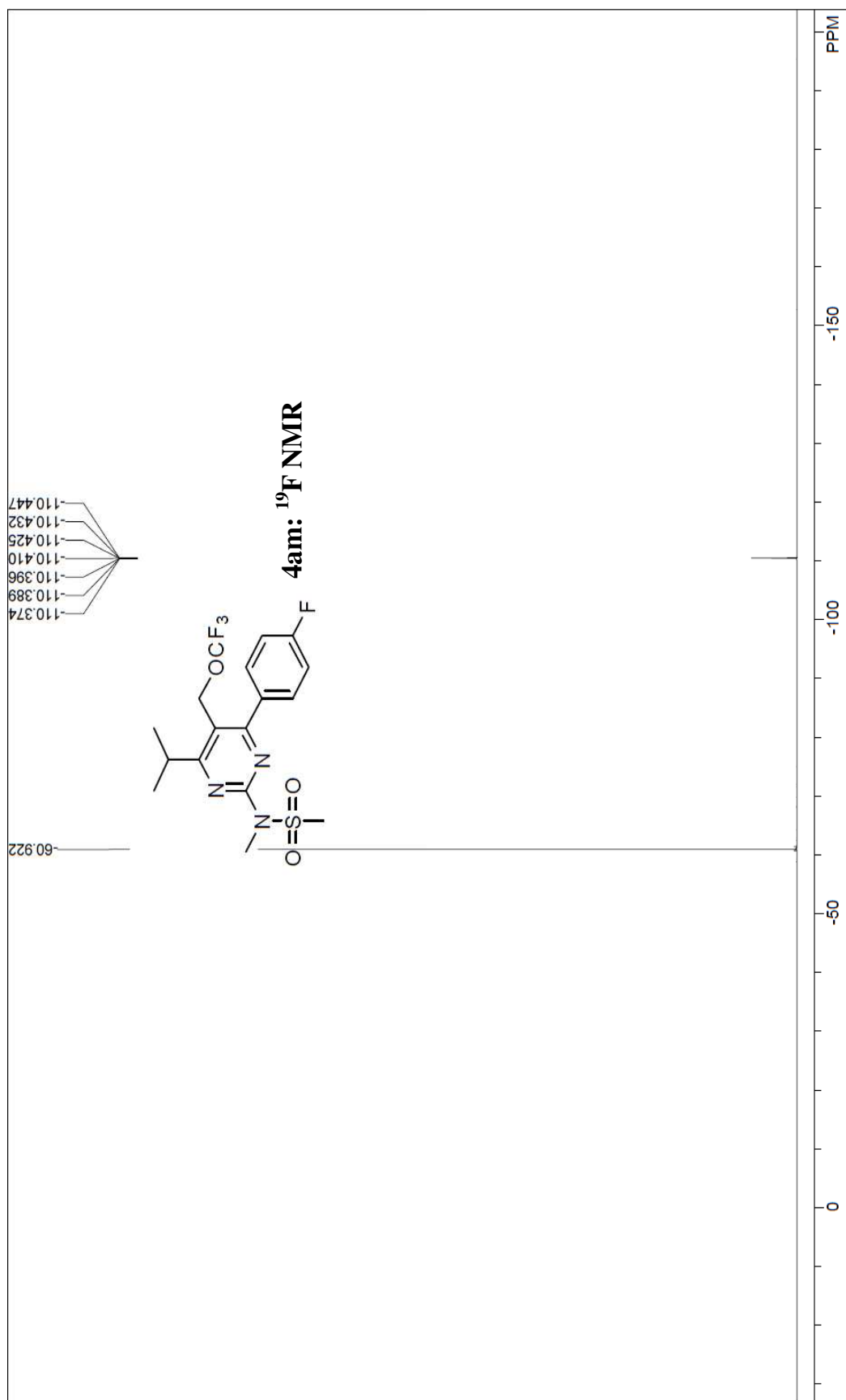


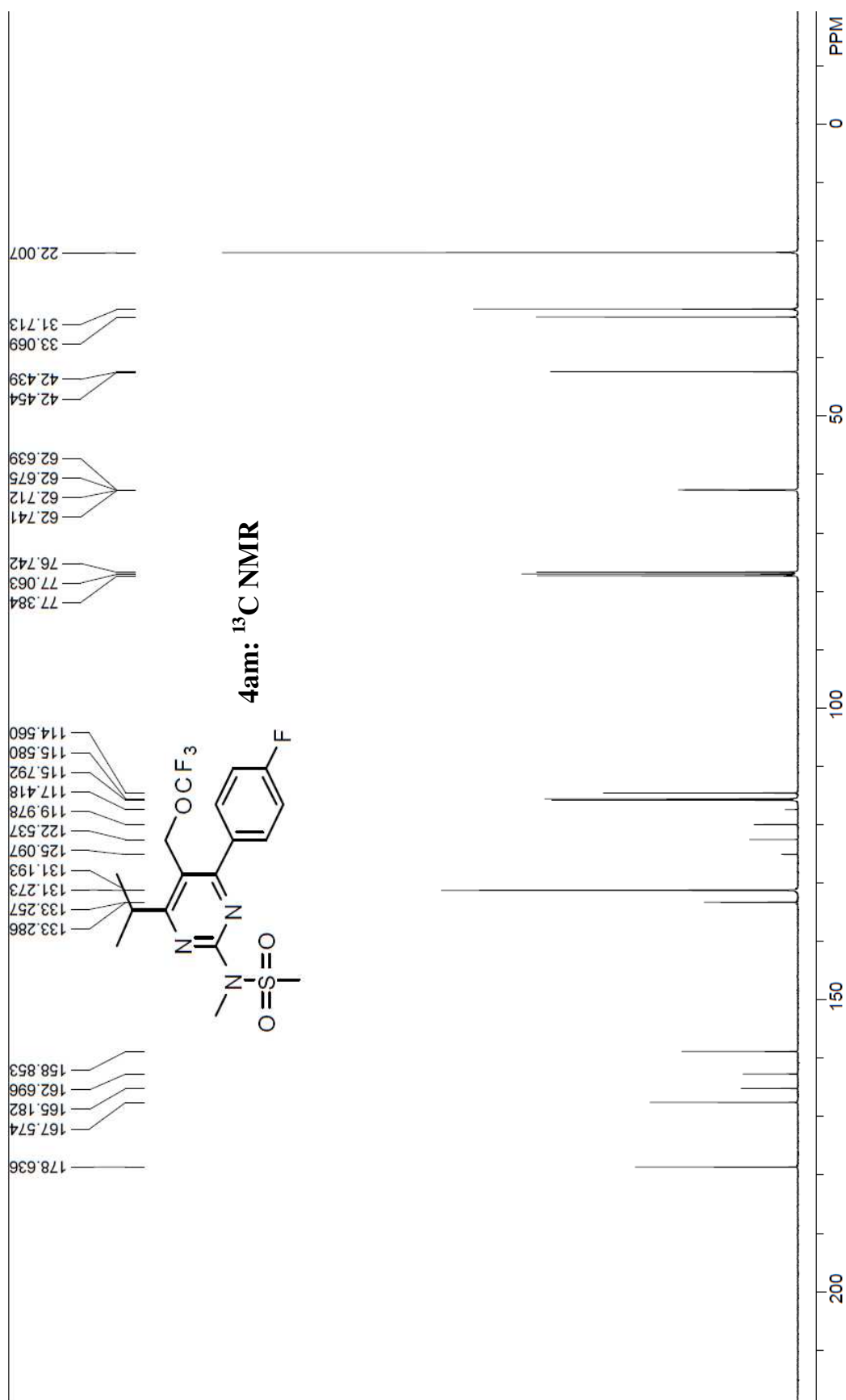


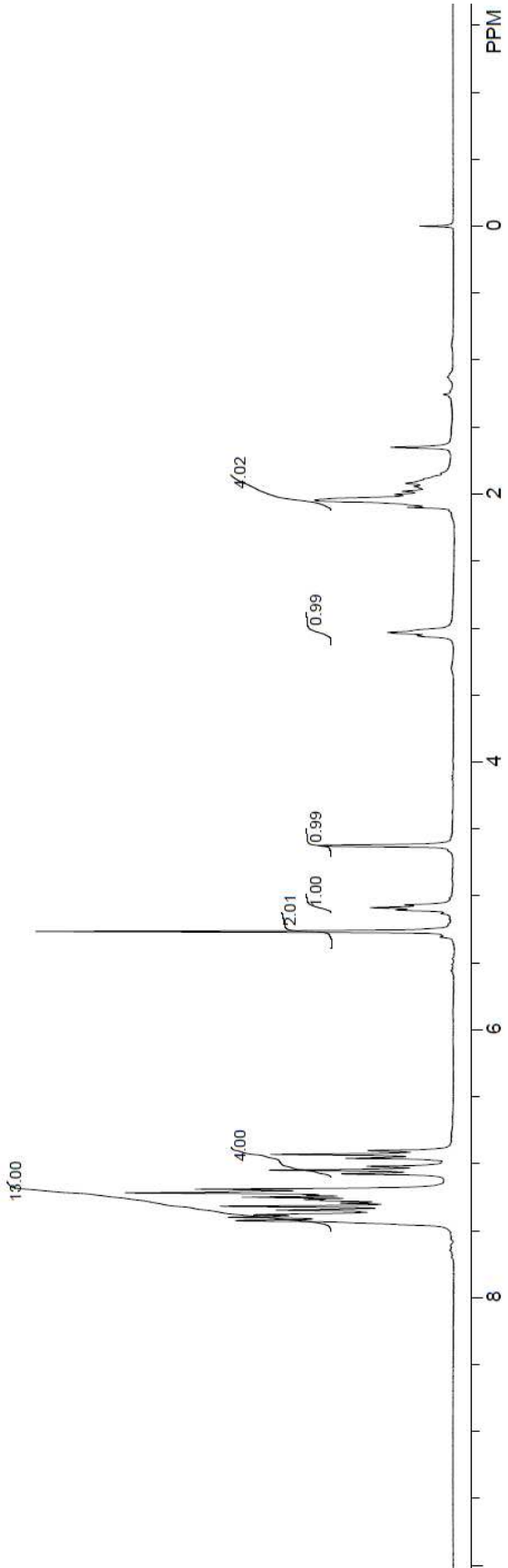












4an: ¹H NMR

