

Supporting Information for

Conversion of Methyl Ketones and Methyl Sulfones into α -Deutero- α,α -Difluoromethyl Ketones and α -Deutero- α,α -Difluoromethyl Sulfones in Three Synthetic Steps

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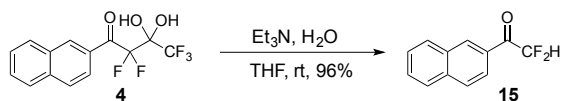
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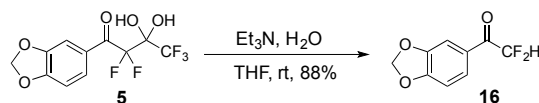
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Experimental Procedures and Characterization Data

Representative Reaction Procedure for Preparation of α,α -Difluoromethyl Ketones. A solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **4**¹ (73 mg, 0.23 mmol) in H₂O/THF (2 mL/0.5 mL) was treated with Et₃N (130 μ L, 0.91 mmol), and the resultant mixture was stirred for 10 min at rt. The organics were extracted with CH₂Cl₂ (3 \times 5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. SiO₂ flash chromatography (CHCl₃) afforded the product **15** as a colorless solid (45 mg) in 96% yield.²

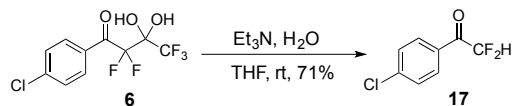


2,2-Difluoro-1-(naphthalen-2-yl)ethanone 15. See representative reaction procedure. All spectral and characterization data matched the reported data.³

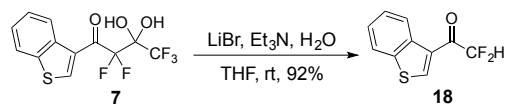


1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoroethanone 16. See representative reaction procedure. 1-(Benzo[*d*][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **5**¹ (80 mg, 0.26 mmol), Et₃N (140 μ L, 0.73 mmol), and H₂O/THF (2 mL/0.5 mL) were used. The title compound **16** was isolated as a colorless solid (45 mg) in 88% yield: mp 61–62 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.70 (ddt, *J* = 8.3, 1.8, 1.0 Hz, 1H), 7.49 (d, *J* = 1.5 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.24 (t, *J* = 53.6 Hz, 1H), 6.08 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 185.6 (t, *J* = 25.1 Hz, 1C),

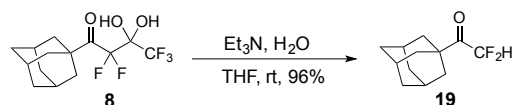
153.4, 148.5, 126.8, 126.0, 111.3 (t, $J = 253$ Hz, 1C), 108.8, 108.4, 102.2; ^{19}F NMR (282 MHz, CDCl_3) $\delta -122.1$ (d, $J = 53.3$ Hz, 2F); IR (film) ν_{max} 1694, 1451, 1259, 1036 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_9\text{H}_6\text{F}_2\text{O}_3$ (M) $^+$ 200.0285, found 200.0286.²



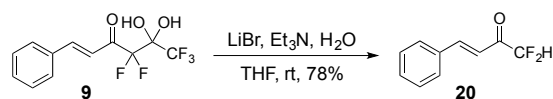
1-(4-Chlorophenyl)-2,2-difluoroethanone 17. See representative reaction procedure. 1-(4-Chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **6**¹ (100 mg, 0.33 mmol), Et_3N (185 μL , 1.31 mmol), and $\text{H}_2\text{O}/\text{THF}$ (2 mL/0.5 mL) were used. The title compound **17** was isolated as a colorless oil (45 mg) in 71% yield.² All spectral and characterization data matched the reported data.³



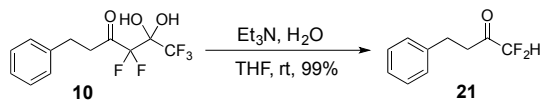
1-(Benzothiophen-3-yl)-2,2-difluoroethanone 18. See representative reaction procedure. 1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **7**⁴ (25 mg, 0.08 mmol), LiBr (40 mg, 0.46 mmol), and Et_3N (21 μL , 0.15 mmol) were used. SiO_2 flash chromatography (17:3 hexanes/ Et_2O) afforded the title compound **18** as a colorless oil (15 mg) in 93% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.78–8.73 (m, 1H), 8.69 (t, $J = 1.5$ Hz, 1H), 7.95–7.89 (m, 1H), 7.55 (m, 1H), 7.48 (m, 1H), 6.22 (t, $J = 53.8$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 182.4 (t, $J = 25.4$ Hz, 1C), 141.4 (t, $J = 6.1$ Hz, 1C), 139.0, 136.6, 128.6, 126.4, 126.0, 125.1, 122.2, 111.6 (t, $J = 255$ Hz, 1C); ^{19}F NMR (282 MHz, CDCl_3) $\delta -121.1$ (d, $J_{\text{HF}} = 53.8$ Hz, 2F); IR (film) ν_{max} 1679, 1491, 1462, 1424, 1135, 1109, 1055 cm^{-1} ; HRMS (CI) m/z calcd for $\text{C}_{10}\text{H}_6\text{F}_2\text{OS}$ (M) $^+$ 212.0107, found 212.0109.



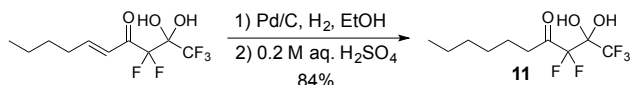
1-(Adamantan-1-yl)-2,2-difluoroethanone 19. See representative reaction procedure. 1-(Adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **8**¹ (47 mg, 0.14 mmol), Et_3N (80.0 μL , 0.57 mmol), $\text{H}_2\text{O}/\text{THF}$ (2 ml/0.5 ml) were used. The reaction mixture was stirred for 1 h at rt. The title compound **19** was isolated in 96% yield (30 mg) as a colorless oil.² All spectral and characterization data matched the reported data.⁵



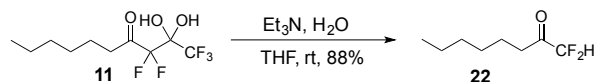
(E)-1,1-Difluoro-4-phenylbut-3-en-2-one 20. See representative reaction procedure. (*E*)-4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one **9**⁴ (50 mg, 0.17 mmol), LiBr (87 mg, 1.01 mmol), Et_3N (50 μL , 0.4 mmol), and $\text{H}_2\text{O}/\text{THF}$ (1.7 ml/1.7 ml) were used. The reaction mixture was stirred for 30 min at rt. SiO_2 flash chromatography (1:3 $\text{Et}_2\text{O}/\text{Hexanes}$) afforded the title compound **20** in 78% yield (24 mg) as a colorless oil. All spectral and characterization data matched the reported data.³



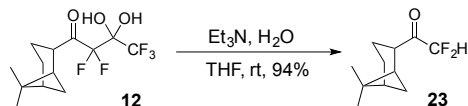
1,1-Difluoro-4-phenylbutan-2-one 21. See representative reaction procedure. 4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one **10**⁴ (35.7 mg, 0.120 mmol), Et₃N (67 μ L, 0.48 mmol), and H₂O/THF (1.5 mL/1.5 mL) were used. The title compound **21** was isolated as a colorless oil in 99% yield (22 mg). All spectral and characterization data matched the reported data.⁶



1,1,1,3,3-Pentafluoro-2,2-dihydroxydecan-4-one 11. To a solution of 1,1,1,3,3-pentafluoro-2,2-dihydroxydec-5-en-4-one¹ (500 mg, 1.8 mmol) in EtOH (15 mL) was added Pd/C (28.7 mg, 0.243 mmol), and the mixture was stirred under a H₂ atmosphere for 24 h at rt. Next, the mixture was diluted with CH₂Cl₂ (5 mL), filtered through Celite, and concentrated under reduced pressure. The residue was dissolved in 1:1 THF/0.2 M aqueous H₂SO₄ (10 mL) and stirred for 16 h at rt. SiO₂ flash chromatography (9:1 hexanes/EtOAc) afforded the desired product **11** as a colorless oil in 83% yield (418 mg): ¹H NMR (300 MHz, CDCl₃) δ 4.62 (br s, 2H), 2.82 (t, *J* = 4.5 Hz, 2H), 1.64 (m, 2H), 1.30 (m, 6H), 0.89 (t, *J* = 4.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 204.0 (t, *J* = 27.5 Hz, 1C), 120.6 (q, *J* = 288 Hz, 1C), 109.5 (t, *J* = 266 Hz, 1C), 92.4 (m, 1C), 37.9, 31.4, 28.3, 22.4, 22.1, 13.9; ¹⁹F NMR (282 MHz, CDCl₃) δ -82.87 (t, *J* = 11.3 Hz, 3F), -121.44 (q, *J* = 11.3 Hz, 2F); IR (film) ν_{\max} 3424, 2963, 2933, 2887, 1710, 1200, 1178, 1071 cm⁻¹; HRMS (EI) *m/z* calcd for C₁₀H₁₄F₅O₂ (M+H-H₂O)⁺ 261.0914, found 261.0917.

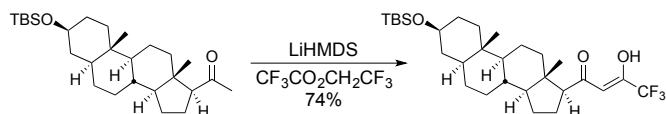


1,1-Difluoro-octan-2-one 22. See representative reaction procedure. 1,1,1,3,3-Pentafluoro-2,2-dihydroxydecan-4-one **11** (44.8 mg, 0.161 mmol), Et₃N (91 μ L, 0.64 mmol), and H₂O/THF (1.6 mL/1.5 mL) were used. The title compound **22** was isolated as a colorless oil in 88% yield (23 mg). All spectral and characterization data matched the reported data.⁶

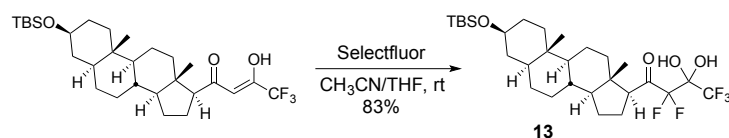


2,2-Difluoro-1-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)ethanone 23. See representative reaction procedure. 1-((1*S*,2*S*,5*S*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **12**¹ (49.1 mg, 0.155 mmol), Et₃N (87 μ L, 0.62 mmol), and H₂O/THF (1.5 mL/0.3 mL) were used. The title compound **23** was isolated as a colorless oil in 94% yield (30 mg): ¹H NMR (500 MHz, CDCl₃) δ 5.76 (t, *J* = 53.8 Hz, 1H), 3.43 (t, *J* = 8.6 Hz, 1H), 2.13 (m, 3H), 1.91 (m, 3H), 1.62 (m, 1H), 1.42 (d, *J* = 10.4 Hz, 1H), 1.25 (s, 3H), 0.92 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 201.44 (t, *J* = 23.8 Hz, 1C), 109.90 (t, *J* = 254 Hz, 1C), 43.1, 42.0, 39.9, 39.4, 26.4, 23.6, 23.4, 20.3, 14.4; ¹⁹F NMR (282 MHz, CDCl₃) δ -126.8 (dd, *J* = 318, 53.8 Hz, 1F), -128.4 (dd, *J* = 318, 53.8 Hz, 1F); IR (film) ν_{\max} 2974, 2950, 2918, 1718, 1123, 1077,

958 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{16}\text{F}_2\text{O}$ (M)⁺ 202.1169, found 202.1168; $[\alpha]_{\text{D}}^{26} +36^\circ$ (c 1.2, CHCl_3).

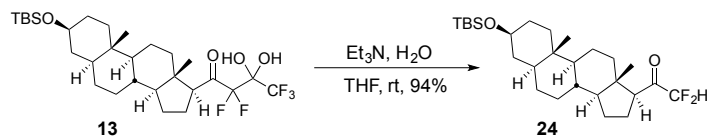


3-(*tert*-Butyldimethylsilyl)-21-(trifluoroacetyl)pregnenolone. To -78°C solution of *n*-BuLi (120 μL , 1.56 M in hexanes) in THF (6 mL) was added hexamethyldisilazane (303 mg, 1.88 mmol) dropwise. The mixture was stirred at -78°C for 20 min, and then, 3-(*tert*-butyldimethylsilyl)pregnenolone⁷ (678 mg, 1.57 mmol) was added. The resultant mixture was stirred for 45 min at -78°C . Next, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (461 mg, 2.35 mmol) was added dropwise and the mixture was stirred for 15 min at -78°C . The reaction mixture was quenched with 1 M aqueous H_2SO_4 (10 mL) and stirred for 10 min. The resultant mixture was extracted with CH_2Cl_2 (10 mL \times 3), and the organics were dried over Na_2SO_4 . Concentration under reduced pressure afforded the title compound in 74% yield (610 mg) as a solid: mp $96\text{--}98^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 5.86 (s, 1H), 3.55 (tt, $J = 10.8, 4.7$ Hz, 1H), 2.43 (t, $J = 9.0$ Hz, 1H), 2.18–2.07 (m, 1H), 1.89 (dd, $J = 8.2, 2.6$ Hz, 1H), 1.82–1.72 (m, 2H), 1.71–1.63 (m, 3H), 1.62–1.56 (m, 1H), 1.49–1.41 (m, 2H), 1.38 (dt, $J = 18.3, 4.9$ Hz, 1H), 1.35–1.22 (m, 7H), 1.20–1.13 (m, 1H), 1.07 (m, 1H), 0.98–0.91 (m, 3H), 0.88 (s, 9H), 0.80 (s, 3H), 0.65 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.6, 174.8 (q, $J = 36.0$ Hz, 1C), 117.2 (q, $J = 218.3$ Hz, 1C), 96.4, 72.0, 59.3, 56.7, 54.3, 46.5, 45.0, 38.6, 38.5, 37.1, 35.7, 35.6, 32.1, 31.9, 28.6, 26.0 (3), 24.4, 22.8, 21.1, 18.3, 13.4, 12.4, -4.6 (2); ^{19}F NMR (282 MHz, CDCl_3) δ -75.8 (s, 3F); IR (film) ν_{max} 2930, 2855, 1593, 1200, 1157, 1107, 1090, 836 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{29}\text{H}_{47}\text{F}_3\text{O}_3\text{SiNa}$ ($\text{M}+\text{Na}$)⁺ 551.3144, found 551.3149; $[\alpha]_{\text{D}}^{23} +70^\circ$ (c 1.03, CHCl_3).

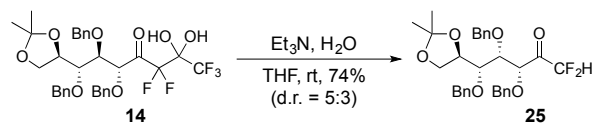


3-(*tert*-Butyldimethylsilyl)-21,21-difluoro-21-(2,2,2-trifluoro-1,1-dihydroxyethyl)pregnenolone 13. A solution of 3-(*tert*-butyldimethylsilyl)-21-(trifluoroacetyl)pregnenolone (277 mg, 0.52 mmol) in CH_3CN (2 mL) and THF (2 mL) was treated with Selectfluor (464 mg, 1.31 mmol). After 24 h, Selectfluor (300 mg, 0.98 mmol) was added and the mixture was stirred for an additional 24 h. Next, the reaction was diluted with EtOAc (50 mL) and filtered through Celite. The residue was concentrated *in vacuo*, dissolved in CH_2Cl_2 (20 mL), and washed with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound **13** in 83% yield (252 mg) as a solid: mp $108\text{--}111^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 4.68 (br s, 2H), 3.55 (tt, $J = 10.8, 4.8$ Hz, 1H), 3.18 (t, $J = 8.8$ Hz, 1H), 2.18–2.09 (m, 1H), 1.93 (d, $J = 12.3$ Hz, 1H), 1.84–1.71 (m, 2H), 1.71–1.63 (m, 3H), 1.58 (dt, $J = 9.7, 3.1$ Hz, 1H), 1.48–1.23 (m, 11H), 1.07 (m, 1H), 0.99–0.90 (m, 2H), 0.88 (s, 9H), 0.80 (s, 3H), 0.70 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 207.0 (t, $J = 28.6$ Hz, 1C), 120.9 (q, $J = 283.3$ Hz, 1C), 108.5 (t, $J = 266$ Hz, 1C), 92.8 (qt, $J = 29.8, 1.0$ Hz, 1C), 72.1, 57.3 (2), 54.0, 48.3, 44.9, 38.5, 38.3, 37.1, 35.8, 35.5, 32.1, 31.8, 28.6, 25.9 (3), 24.6, 24.4, 21.2, 18.3, 13.7, 12.3, -4.6 (2); ^{19}F NMR (282 MHz,

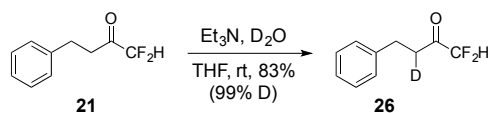
CDCl₃) δ -80.8 (t, J = 8.0 Hz, 3F), -119.5 (dq, J = 116, 8.4 Hz, 2F); IR (film) ν_{\max} 3436, 2931, 2858, 1717, 1386, 1209, 1087, 837, 775 cm⁻¹; HRMS (ESI) m/z calcd for C₂₉H₄₄F₅O₃Si (M-H-H₂O)⁻ 563.2980, found 563.2973; $[\alpha]_D^{26}$ +83° (c 2.08, CHCl₃).



3-(*tert*-Butyldimethylsilyl)-21,21-difluoropregnenolone 24. See representative reaction procedure. 3-(*tert*-Butyldimethylsilyl)-21,21-difluoro-21-(2,2,2-trifluoro-1,1-dihydroxyethyl)-pregnenolone **13** (30 mg, 0.05 mmol), Et₃N (29 μ L, 0.21 mmol), H₂O/THF (500 μ L/100 μ L) were used. The reaction mixture was stirred for 1 h at rt. The title compound **24** was isolated as a solid in 94% yield (23 mg): mp 116–118 °C; ¹H NMR (500 MHz, CDCl₃) δ 5.63 (t, J = 54.2 Hz, 1H), 3.55 (ddd, J = 15.7, 10.8, 4.8 Hz, 1H), 2.94 (t, J = 8.9 Hz, 1H), 2.17 (m, 1H), 1.88 (d, J = 12.7 Hz, 1H), 1.80–1.63 (m, 5H), 1.58 (dq, J = 13.6, 3.9 Hz, 1H), 1.49–1.17 (m, 11H), 1.13–1.02 (m, 1H), 0.94 (ddd, J = 27.5, 14.0, 4.5 Hz, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.67 (s, 3H), 0.05 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 201.3 (t, J = 24.9 Hz, 1C), 109.9 (t, J = 251 Hz, 1C), 72.1, 57.0, 56.9, 54.2, 46.4, 45.0, 38.6 (2), 37.2, 35.7, 35.5, 32.1, 31.9, 28.6, 26.0 (3), 24.6, 23.6, 21.2, 18.3, 13.9, 12.3, -4.6 (2); ¹⁹F NMR (282 MHz, CDCl₃) δ -128.4 (d, J_{HF} = 54.1 Hz, 2F); IR (film) ν_{\max} 2931, 1732, 1252, 1091 cm⁻¹; HRMS (EI) m/z calcd for C₂₆H₄₃F₂O₂Si (M-CH₃)⁺ 453.3000, found 453.2994; $[\alpha]_D^{23}$ +77° (c 0.16, CHCl₃).

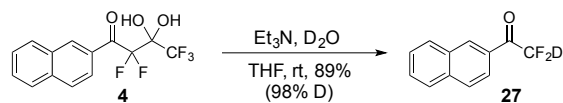


(4*S*,5*R*)-3,4,5-Tris(benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,1-difluoropentan-2-one 25. To a solution of (5*R*,6*S*,7*R*)-5,6,7-tris(benzyloxy)-7-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,1,1,3,3-pentafluoro-2,2-dihydroxyheptan-4-one **14**⁸ (65 mg, 0.10 mmol) in H₂O/THF (1.5 mL/1.5 mL) was added LiBr (26 mg, 0.30 mmol), followed by Et₃N (55 μ L, 0.40 mmol), and the resultant mixture was stirred for 15 min at rt. The organics were extracted with CH₂Cl₂ (3 \times 5 mL), dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound **25** (40 mg, colorless oil) as an inseparable mixture of diastereomers (d.r. = 5:3) in 74% yield: ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.51–7.23 (m, 15H), 6.29* (t, J = 54.1 Hz, 1H), 6.28 (dd, J = 53.9, 52.8 Hz, 1H), 4.85 (dd, J = 13.6, 11.2 Hz, 1H), 4.75–4.55 (m, 5H), 4.37–4.12 (m, 3H), 4.05–3.90 (m, 3H), 1.35* (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 198.3* (dd, J = 23.5, 21.5 Hz, 1C), 195.7 (dd, J = 25, 20 Hz, 1C), 139.3*, 138.9, 138.8*, 138.7, 138.4*, 138.3, 129.5* (2C), 129.5 (2C), 129.4* (2C), 129.4 (2C), 129.3, 129.2* (2C), 129.2* (2C), 129.1, 129.1 (2C), 129.0*, 129.0 (2C), 128.9* (2C), 128.9* (2C), 128.8 (2C), 128.8 (2C), 128.7*, 128.6*, 128.5, 111.0* (dd, J = 251, 240 Hz, 1C), 109.7 (t, J = 247 Hz, 1C), 109.3*, 108.6, 82.6, 82.4*, 82.1, 80.2*, 78.6*, 78.0, 77.8, 76.8*, 75.2*, 75.0*, 74.6, 74.3, 74.0*, 73.8, 67.1*, 66.6, 26.9*, 26.8, 25.3*, 25.2; ¹⁹F NMR (376 MHz, (CD₃)₂CO) δ -126.1 (dd, J = 299, 52.3 Hz, 1F), -130.2* (ddd, J = 310, 53.0, 2.2 Hz, 1F), -132.8* (dd, J = 310, 53.7 Hz, 1F), -134.5 (ddd, J = 299, 56.0, 1.5 Hz, 1F); IR (film) ν_{\max} 3028, 2988, 2869, 1752, 1498, 1455, 1380, 1374, 1209, 1156, 1058 cm⁻¹; HRMS (ESI) m/z calcd for C₃₁H₃₄F₂O₆Na (M+Na)⁺ 563.2221, found 563.2210. *denotes minor diastereomer.

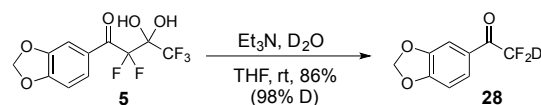


1,1-Difluoro-3-deutero-4-phenylbutan-2-one 26. To a solution of 1,1-difluoro-4-phenylbutan-2-one **21** (40.0 mg, 0.217 mmol) in D₂O/THF (2.1 mL/0.7 mL) was added Et₃N (122 μL, 0.869 mmol) dropwise. After 24 h, the reaction was extracted with CH₂Cl₂ (2.5 mL × 2). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. SiO₂ flash chromatography (CHCl₃) afforded the title compound **26** as a colorless solid (34 mg) in 83% yield: ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.28 (m, 2H), 7.25–7.18 (m, 3H), 5.68 (tt, *J* = 54.0, 0.9 Hz, 1H), 3.05–2.93 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.9 (tt, *J* = 26.5, 7.5 Hz, 1C), 139.8, 128.6 (2C), 128.3 (2C), 126.5, 109.8 (t, *J* = 251 Hz, 1C), 37.4 (t, *J* = 20.0 Hz, 1C), 28.21 (t, *J* = 6.3 Hz, 1C); ¹⁹F NMR (282 MHz, CDCl₃) δ –127.9 (dt, *J* = 53.9, 9.4 Hz, 2F); IR (film) ν_{max} 3066, 3031, 2930, 1747, 1497, 1456, 1162, 1110, 955 cm⁻¹; HRMS (EI) *m/z* calcd for C₁₀H₉DF₂O (M)⁺ 185.0762, found 185.0732.

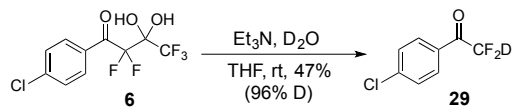
Representative Reaction Procedure for α-Deutero-α,α-difluoromethyl Ketone. To a solution of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one **4**¹ (100 mg, 0.31 mmol) in D₂O/THF (2 mL/0.5 mL) was added Et₃N (175 μL, 1.25 mmol), and the resultant mixture was stirred for 15 min at rt. The organics were extracted with CH₂Cl₂ (3 × 5 mL), dried over Na₂SO₄, and concentrated under reduced pressure. SiO₂ flash chromatography (100% CHCl₃) afforded the product **27** as a colorless solid (58 mg) in 89% yield (98% deuterium incorporation).



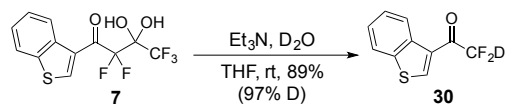
2-Deutero-2,2-difluoro-1-(naphthalen-2-yl)ethanone 27. See representative reaction procedure: mp 58–60 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.64 (s, 1H), 8.07 (m, 1H), 8.00 (m, 1H), 7.96–7.86 (m, 2H), 7.67 (m, 1H), 7.60 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 187.5 (t, *J* = 24.8 Hz, 1C), 136.2, 132.4, 132.2, 130.0, 129.6, 128.9, 128.7, 127.8, 127.2, 124.0, 110.9 (tt, *J* = 251, 29.3 Hz, 1C); ¹⁹F NMR (282 MHz, CDCl₃) δ –123.1 (t, *J* = 8.2 Hz, 2F); IR (film) ν_{max} 1707, 1108, 801 cm⁻¹; HRMS (EI) *m/z* calcd for C₁₂H₈DF₂O (M+H)⁺ 208.0684, found 208.0681.



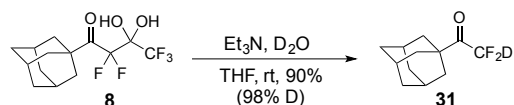
1-(Benzo[d][1,3]dioxol-5-yl)-2-deutero-2,2-difluoroethanone 28. See representative reaction procedure. 1-(Benzo[d][1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **5**¹ (79 mg, 0.25 mmol), Et₃N (140 μL, 1.01 mmol), and D₂O/THF (2 mL/0.5 mL) were used. The title compound **28** was isolated as a colorless solid (43 mg) in 86% yield (98% deuterium incorporation): mp 61–63 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.71 (ddt, *J* = 8.3, 1.7, 1.1 Hz, 1H), 7.49 (d, *J* = 1.5 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.09 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 185.6 (t, *J* = 25.4 Hz, 1C), 153.4, 148.5, 126.9 (t, *J* = 3.1 Hz, 1C), 126.0, 111.0 (tt, *J* = 250, 28.8 Hz, 1C), 108.8, 108.4, 102.2; ¹⁹F NMR (282 MHz, CDCl₃) δ –122.8 (t, *J* = 8.2 Hz, 2F); IR (film) ν_{max} 1694, 1447, 1239, 1095, 1035 cm⁻¹; HRMS (EI) *m/z* calcd for C₉H₅DF₂O₃ (M)⁺ 201.0348, found 201.0345.



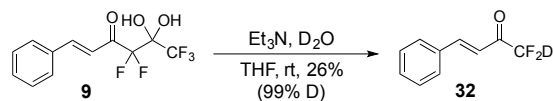
1-(4-Chlorophenyl)-2-deutero-2,2-difluoroethanone 29. See representative reaction procedure. 1-(4-Chlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **6**¹ (68.5 mg, 0.23 mmol), Et₃N (125 μ L, 0.90 mmol), and D₂O/THF (2 ml/0.5 ml) were used. The title compound **29** was isolated as a colorless oil (20 mg) in 47% yield (96% deuterium incorporation): ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 186.6 (t, J = 56.4 Hz, 1C), 141.7, 131.0 (2), 129.6, 129.4 (2), 111.0 (tt, J = 566, 64.9 Hz, 1C); ¹⁹F NMR (282 MHz, CDCl₃) δ -123.2 (t, J = 8.2 Hz, 2F); IR (film) ν_{max} 1711, 1591, 1172, 1094 cm⁻¹; HRMS (EI) m/z calcd for C₈H₄DCIF₂O (M)⁺ 191.0060, found 191.056.



1-(Benzo[b]thiophen-3-yl)-2-deutero-2,2-difluoroethanone 30. See representative reaction procedure. 1-(Benzo[b]thiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **7**⁴ (10 mg, 0.03 mmol), LiBr (16 mg, 0.18 mmol) and Et₃N (9 μ L, 0.06 mmol) was used. The title compound **30** was isolated as a colorless oil (5.7 mg) in 86% yield (97% deuterium incorporation): ¹H NMR (400 MHz, CDCl₃) δ 8.74 (d, J = 8.1 Hz, 1H), 8.69 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 182.4 (t, J = 25.6 Hz, 1C), 141.4 (t, J = 6.1 Hz, 1C), 139.0, 136.6, 128.5, 126.4, 126.1, 125.2, 122.3, 111.2 (tt, J = 252, 28.8 Hz, 1C); ¹⁹F NMR (376 MHz, CDCl₃) δ -121.72 (t, J = 8.1 Hz, 2F); IR (film) ν_{max} 3110, 1678, 1490, 1462, 1424, 1375, 1245, 1106 cm⁻¹; HRMS (EI) m/z calcd for C₁₀H₅DF₂OS (M)⁺ 213.0170, found 213.0162.

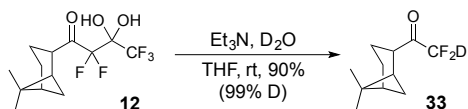


1-(Adamantan-1-yl)-2-deutero-2,2-difluoroethanone 31. See representative reaction procedure. 1-(Adamantan-1-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **8**¹ (30.0 mg, 0.09 mmol), Et₃N (100 μ L, 0.73 mmol), D₂O (600 μ L) were used. The title compound **31** was isolated as a colorless oil (18 mg) in 90% yield (98% deuterium incorporation): ¹H NMR (500 MHz, CDCl₃) δ 2.08 (s, 3H), 1.94 (d, J = 2.7 Hz, 6H), 1.83–1.69 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 201.9 (t, J = 21.8 Hz, 1C), 108.8 (tt, J = 566, 62.0 Hz, 1C), 45.2, 37.1 (3), 36.2 (3), 27.5 (3); ¹⁹F NMR (282 MHz, CDCl₃) δ -126.4 (t, J_{DF} = 8.2 Hz, 2F); IR (film) ν_{max} 2910, 1732, 1454, 1109 cm⁻¹; HRMS (EI) m/z calcd for C₁₂H₁₆DF₂O (M+H)⁺ 216.1301, found 216.1312.

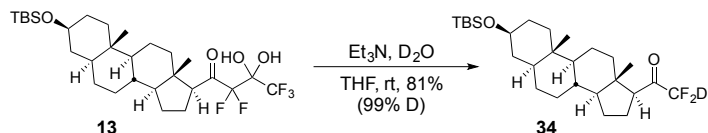


(E)-1-Deutero-1,1-difluoro-4-phenylbut-3-en-2-one 32. See representative reaction procedure. (E)-4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one **9**⁴ (100 mg, 0.34 mmol) and Et₃N (90 μ L, 0.67 mmol) were used. SiO₂ flash chromatography (17:3 hexanes/EtOAc) afforded

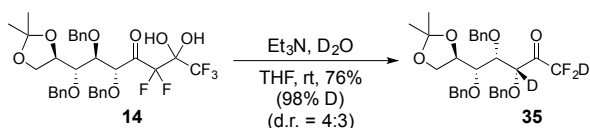
the title compound **32** as a colorless oil (16 mg) in 26% yield (99% deuterium incorporation): ^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, $J = 16.1$ Hz, 1H), 7.69–7.61 (m, 2H), 7.51–7.41 (m, 3H), 7.05 (dt, $J = 16.1, 1.2$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 187.7 (t, $J = 25.8$ Hz, 1C), 148.1, 133.6, 131.7, 129.1 (2C), 128.9 (2C), 117.8, 110.1 (tt, $J = 25.8, 27.5$ Hz, 1C); ^{19}F NMR (282 MHz, CDCl_3) δ -127.44 (t, $J = 8.2$ Hz, 2F); IR (film) ν_{max} 3064.22, 3031.15, 2931.99, 2262.84, 1703.98, 1607.18, 1577.24, 1496.63, 1451.50, 1343.70 cm^{-1} ; HRMS (EI/CI) m/z calcd for $\text{C}_{10}\text{H}_7\text{DF}_2\text{O}$ (M^+) 183.0606, found 183.0603.



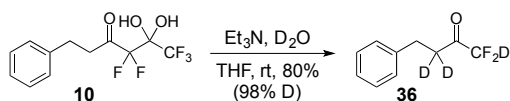
2-Deutero-2,2-difluoro-1-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)ethanone 33. See representative reaction procedure. 1-((1*S*,2*S*,5*S*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **12**¹ (67.1 mg, 0.268 mmol) and Et_3N (151 μL , 1.07 mmol) were used. The title compound **33** was isolated as a colorless oil (49 mg) in 90% yield (99% deuterium incorporation): ^1H NMR (500 MHz, CDCl_3) δ 3.43 (t, $J = 8.6$ Hz, 1H), 2.17 (m, 3H), 1.90 (m, 3H), 1.62 (m, 1H), 1.42 (d, $J = 10.4$ Hz, 1H), 1.25 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.5 (t, $J = 23.8$ Hz), 109.6 (tt, $J = 25.0, 28.8$ Hz), 43.0, 42.0, 39.9, 39.4, 26.4, 23.6, 23.4, 20.2, 14.4; ^{19}F NMR (282 MHz, CDCl_3) δ -127.43 (dt, $J = 319, 8.2$ Hz, 1F), -129.1 (dt, $J = 319, 8.2$ Hz, 1F); IR (film) ν_{max} 2974, 2951, 2918, 1718, 1463, 1123, 958 cm^{-1} ; HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{16}\text{DF}_2\text{O}$ ($\text{M}+\text{H}^+$) 203.1232, found 203.1229; $[\alpha]_{\text{D}}^{26} +34^\circ$ (c 0.9, CHCl_3).



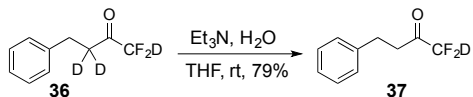
3-(*tert*-Butyldimethylsilyl)-21-deutero-21,21-difluoropregnenolone 34. See representative reaction procedure. 3-(*tert*-Butyldimethylsilyl)-21,21-difluoro-21-(2,2,2-trifluoro-1,1-dihydroxyethyl)-pregnenolone **13** (30 mg, 0.05 mmol) and Et_3N (58 μL , 0.41 mmol) were used. The reaction mixture was stirred for 12 h at rt. The title compound **34** was isolated as a colorless solid (20 mg) in 81% yield (99% deuterium incorporation): mp 130–131 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 3.55 (ddd, $J = 15.7, 10.8, 4.8$ Hz, 1H), 2.95 (t, $J = 8.9$ Hz, 1H), 2.17 (m, 1H), 1.87 (d, $J = 12.0$ Hz, 1H), 1.80–1.63 (m, 5H), 1.57 (dq, $J = 13.5, 3.5$ Hz, 1H), 1.49–1.17 (m, 11H), 1.13–1.03 (m, 1H), 0.92 (ddd, $J = 28.5, 14.5, 4.5$ Hz, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.66 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.3 (t, $J = 24.8$ Hz, 1C), 109.5 (tt, $J = 25.0, 28.9$ Hz, 1C), 72.0, 57.0, 54.1, 46.4 (2C), 44.9, 38.6, 37.1, 35.6, 35.5, 32.1, 31.9, 28.6, 25.9 (3), 24.6, 23.6, 23.5, 21.1, 18.3, 13.9, 12.3, -4.6 (2); ^{19}F NMR (282 MHz, CDCl_3) δ -129.0–129.1 (m, 2F); IR (film) ν_{max} 2931, 1730, 1252 cm^{-1} ; HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{46}\text{DF}_2\text{O}_2\text{Si}$ ($\text{M}+\text{H}^+$) 470.3376, found 470.3372; $[\alpha]_{\text{D}}^{23} +59^\circ$ (c 0.18, CHCl_3).



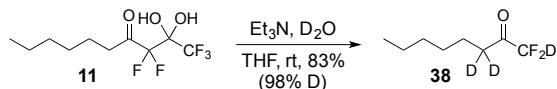
(4*S*,5*R*)-3,4,5-Tris(benzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-deutero-1,1-difluoropentan-2-one 35. To a solution of (5*R*,6*S*,7*R*)-5,6,7-tris(benzyloxy)-7-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,1,1,3,3-pentafluoro-2,2-dihydroxyheptan-4-one **14**⁸ (116 mg, 0.177 mmol) in D₂O/THF (2.75 mL/2.75 mL) was added LiBr (47 mg, 0.53 mmol) followed by Et₃N (98 μL, 0.71 mmol), and the resultant mixture was stirred for 30 min at rt. The organics were extracted with CDCl₃ (3 × 1 mL), dried over Na₂SO₄, and concentrated under reduced pressure to afford the title compound **35** (51 mg, colorless oil) as an inseparable mixture of diastereomers (d.r. = 4:3) in 53% yield (98% deuterium incorporation): ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.53–7.22 (m, 15H), 4.92–4.81(m, 1H), 4.76 (m, 4H), 4.40–3.91 (m, 6H), 1.36* (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ¹³C NMR (100 MHz, (CD₃)₂CO) δ 198.2* (dd, *J* = 23.5, 21.6 Hz, 1C), 195.6 (dd, *J* = 24.6, 20.2, 1C), 139.1*, 138.8, 138.7*, 138.6, 138.2*, 138.1, 129.4* (2C), 129.3 (2C), 129.2* (2C), 129.2* (2C), 129.2, 129.1 (2C), 129.0* (2C), 128.9, 128.9 (2C), 128.8*, 128.8 (2C), 128.8* (2C), 128.7* (2C), 128.7 (2C), 128.7 (2C), 128.6*, 128.4*, 128.3, 110.7* (m, 1C), 109.2*, 109.0 (m, 1C), 108.5, 82.4, 82.2*, 81.5 (t, *J* = 22 Hz, 1C), 80.8*, 78.0* (t, *J* = 22 Hz, 1C), 77.8, 77.6, 76.6*, 75.0*, 74.8*, 74.4, 74.1, 73.7*, 73.6, 67.0*, 66.4, 26.7*, 26.7, 25.2*, 25.0; ¹⁹F NMR (376 MHz, (CDCl₃) δ –126.9 (dt, *J* = 300, 6.8 Hz, 1F), –130.4* (dt, *J* = 311, 7.5 Hz, 1F), –133.6* (dt, *J* = 311, 8.3 Hz, 1F), –135.0 (dt, *J* = 300, 7.9 Hz, 1F); IR (film) ν_{max} 3035, 2990, 2934, 2878, 1749, 1457, 1384, 1214, 1067, 1053 cm⁻¹; HRMS (ESI) *m/z* calcd for C₃₁H₃₂D₂F₂O₆ (M)⁺ 542.2449, found 542.2459. *denotes minor diastereomer.



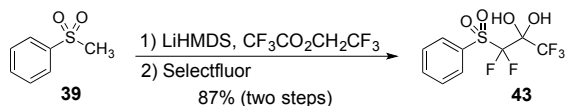
1,1-Difluoro-1,3,3-trideutero-4-phenylbutan-2-one 36. See representative reaction procedure. 4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhexan-3-one **10** (57.0 mg, 0.191 mmol), Et₃N (107 μL, 0.765 mmol), and D₂O/THF (1.9 mL/1.9 mL) were used. The title compound **36** was isolated as a colorless oil (30 mg) in 80% yield (98% deuterium incorporation): ¹H NMR (500 MHz, CDCl₃) δ 7.32–7.28 (m, 2H), 7.25–7.18 (m, 3H), 2.96 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 199.0 (t, *J* = 26.5 Hz, 1C), 139.8, 128.6 (2C), 128.3 (2C), 126.5, 109.5 (tt, *J* = 251, 29.0 Hz, 1C), 37.0 (m, 1C), 28.2; ¹⁹F NMR (282 MHz, CDCl₃) δ –128.7 (t, *J* = 7.9 Hz, 2F); IR (film) ν_{max} 3066, 3031, 2930, 2870, 2918, 1747, 1605, 1498, 1456, 1163, 1110, 955 cm⁻¹; HRMS (EI) *m/z* calcd for C₁₀H₇D₃F₂O (M)⁺ 187.0888, found 187.0868.



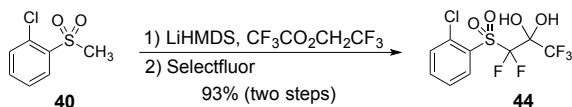
1-Deutero-1,1-difluoro-4-phenylbutan-2-one 37. To a solution of 1,1-difluoro-1,3,3-trideutero-4-phenylbutan-2-one **36** (10.1 mg, 0.054 mmol) in H₂O/THF (0.5 mL/0.5 mL) was added Et₃N (20 μL, 0.22 mmol) dropwise. After 24 h, the reaction was extracted with CH₂Cl₂ (3 mL × 2). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. The title compound **37** was isolated as a colorless oil (7.9 mg) in 79% yield: ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.27 (m, 2H), 7.25–7.18 (m, 3H), 3.03–2.95 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 198.9 (tt, *J* = 251, 28.9 Hz), 139.8, 128.6 (2C), 128.3 (2C), 126.5, 109.5 (t, *J* = 28.9 Hz, 1C), 37.7, 28.3; ¹⁹F NMR (282 MHz, CDCl₃) δ –128.7 (t, *J* = 7.9 Hz, 2F); IR (film) ν_{max} 3065, 3030, 2958, 2918, 2950, 1742, 1660, 1605, 956 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₀H₈DF₂O (M–H)⁻ 184.0679, found 184.0690.



1-Deutero-1,1-difluoro-3,3-deutero-octan-2-one 38. 1,1,1,3,3-Pentafluoro-2,2-dihydroxydecan-4-one **38**⁴ (59.2 mg, 0.213 mmol), Et₃N (120 μ L, 0.85 mmol), and D₂O/THF (2.0 mL/0.6 mL) were used. The reaction mixture was stirred for 18 hr at rt. The title compound **38** was isolated as a colorless oil (29 mg) in 83% yield (98% deuterium incorporation): ¹H NMR (300 MHz, CDCl₃) δ 1.66–1.58 (m, 2H), 1.35–1.25 (m, 6H), 0.88 (t, J = 4.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 200.1 (tt, J = 26.3, 7.5 Hz, 1C), 109.5 (tt, J = 250, 28.8 Hz, 1C), 35.7 (t, J = 18.8 Hz, 1C), 31.4, 28.6, 22.4, 22.2 (t, J = 5.0 Hz, 1C), 13.9; ¹⁹F NMR (282 MHz, CDCl₃) δ –128.7 (t, J = 8.5 Hz, 2F); IR (film) ν_{max} 2955, 2924, 1713, 1464, 1097, 805 cm⁻¹; HRMS (CI) m/z calcd for C₈H₁₂D₃F₂O (M+H)⁺ 168.1279, found 168.1286.

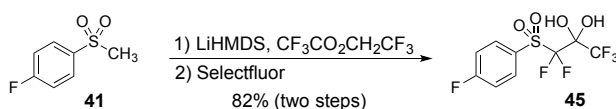


1,1,1,3,3-Pentafluoro-3-(phenylsulfonyl)propane-2,2-diol 43. To a –78 °C solution of *n*-BuLi (452 μ L, 1.7 M in hexanes) in THF (3 mL) was added hexamethyldisilazane (161 μ L, 0.768 mmol). After stirring the reaction for 20 min at –78 °C, a solution of methyl phenyl sulfone **39** (100 mg, 0.64 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (129 μ L, 0.960 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature, the reaction was warmed to rt, quenched with 1 M aqueous H₂SO₄ (3 mL) and then stirred for 60 min. The resultant mixture was extracted with CH₂Cl₂ (5 mL \times 3). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in CH₃CN (10 mL) and treated with Selectfluor[®] (1.13 g, 3.20 mmol). The reaction mixture was heated to 80 °C with stirring for 24 h. Next, the reaction was diluted with EtOAc (50 mL), filtered through Celite, and concentrated under reduced pressure to afford the title compound **43** in 87% yield (170 mg) as a colorless solid: mp 84–86 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, J = 7.8 Hz, 2H), 7.81 (t, J = 7.5 Hz, 1H), 7.65 (t, J = 7.9 Hz, 2H), 5.17 (br s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 136.3, 132.3, 130.9 (2C), 129.5 (2C), 121.8 (q, J = 289 Hz, 1C), 116.1 (t, J = 302 Hz, 1C), 93.2 (qt, J = 33.0, 8.0 Hz, 1C); ¹⁹F NMR (564 MHz, CDCl₃) δ –82.5 (t, J = 10.8 Hz, 3F), –111.2 (q, J = 10.8 Hz, 2F); IR (film) ν_{max} 3442, 2925, 2853, 1336, 1177, 1151, 1072 cm⁻¹; HRMS (ESI) m/z calcd for C₉H₇ClF₅O₄S (M+Cl)⁻ 340.9674, found 340.9645.

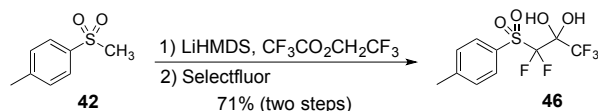


1-((2-Chlorophenyl)sulfonyl)-1,1,3,3,3-pentafluoropropane-2,2-diol 44. To a –78 °C solution of *n*-BuLi (370 μ L, 1.7 M in hexanes) in THF (4 mL) was added hexamethyldisilazane (132 μ L, 0.629 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 2-chlorophenyl methyl sulfone **40** (100 mg, 0.525 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (106 μ L, 0.788 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature, the reaction was warmed to room temperature, quenched with 1 M aqueous H₂SO₄ (3 mL) and then

stirred for 60 min. The resultant mixture was extracted with CH₂Cl₂ (5 mL × 3). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in CH₃CN (10 mL) and treated with Selectfluor[®] (930 mg, 263 mmol). The reaction mixture was heated to 80 °C with stirring for 24 h. Next, the reaction was diluted with EtOAc (50 mL), filtered through Celite, and concentrated under reduced pressure to afford the title compound **44** in 93% yield (166 mg) as a colorless solid: mp 118–120 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 4.16 (br s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 137.0, 136.1, 134.6, 132.9, 131.0, 127.7, 116.7 (t, *J* = 306 Hz, 1C), 120.3 (q, *J* = 288 Hz, 1C), 93.0 (qt, *J* = 33.0, 8.0 Hz, 1C); ¹⁹F NMR (376 MHz, CDCl₃) δ –82.4 (t, *J* = 10.9 Hz, 3F), –109.0 (q, *J* = 10.9 Hz, 2F); IR (film) ν_{max} 3470, 3099, 1345, 1208, 1180, 1076 cm⁻¹; HRMS (EI) *m/z* calcd for C₉H₄ClF₅O₃S (M–H₂O)⁻ 321.9490, found 321.9493.



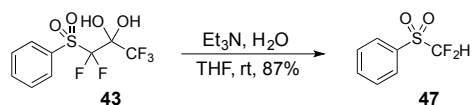
1,1,1,3,3-Pentafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol 45. To a –78 °C solution of n-BuLi (680 μL, 2 M in hexanes) in THF (5 mL) was added hexamethyldisilazane (288 μL, 1.38 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 4-fluorophenyl methyl sulfone **41** (200 mg, 1.15 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (231 μL, 1.72 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature, the reaction was warmed to room temperature and quenched with 1 M aqueous H₂SO₄ (5 mL) and then stirred for 60 min. The resultant mixture was extracted with CH₂Cl₂ (10 mL × 3). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in CH₃CN (15 mL) and treated with Selectfluor[®] (2.03 mg, 5.74 mmol). The reaction mixture was heated to 80 °C with stirring for 24 h. Next, the reaction was diluted with EtOAc (50 mL), filtered through Celite, and concentrated under reduced pressure to afford the title compound **45** in 82% yield (306 mg) as a colorless solid: mp 74–75 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.00 (dd, *J* = 8.7, 4.9 Hz, 2H), 7.25 (app t, *J* = 8.5 Hz, 2H), 5.07 (br s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5 (d, *J* = 260 Hz, 1C), 134.0 (d, *J* = 10.3 Hz, 2C), 128.3 (d, *J* = 3.1 Hz, 1C), 120.9 (q, *J* = 289 Hz, 1C), 116.9 (t, *J* = 301 Hz), 116.9 (d, *J* = 23.1 Hz, 2C), 93.3 (qt, *J* = 25.0, 9.0 Hz, 1C); ¹⁹F NMR (376 MHz, CDCl₃) δ –82.5 (t, *J* = 10.9 Hz, 3F), –99.1 (tt, *J* = 8.2, 5.0 Hz, 1F), –111.0 (q, *J* = 10.9 Hz, 2F); IR (film) ν_{max} 3445, 3110, 1342, 1177, 1154, 1075 cm⁻¹; HRMS (ESI) *m/z* calcd for C₉H₅F₆O₄S (M–H)⁻ 322.9818, found 322.9822.



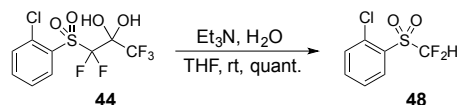
1,1,1,3,3-Pentafluoro-3-tosylpropane-2,2-diol 46. To a –78 °C solution of n-BuLi (420 μL, 1.7 M in hexanes) in THF (4 mL) was added hexamethyldisilazane (149 μL, 0.708 mmol). After stirring the reaction for 20 min at –78 °C, a solution of 4-(methylsulfonyl)toluene **42** (100 mg, 0.590 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 90 min at –78 °C, and then 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (119 μL, 0.855 mmol) was added dropwise. After an additional 60 min of stirring at the same temperature, the reaction was warmed to room

temperature and quenched with 1 M aqueous H₂SO₄ (3 mL) and then stirred for 60 min. The resultant mixture was extracted with CH₂Cl₂ (5 mL × 3). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in CH₃CN (10 mL) and treated with Selectfluor[®] (1.05 mg, 2.95 mmol). The reaction mixture was heated to 80 °C with stirring for 24 h. Next, the reaction was diluted with EtOAc (50 mL), filtered through Celite, and concentrated under reduced pressure to afford the title compound **46** in 71% yield (134 mg) as a colorless solid: mp 73–74 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 5.20 (br s, 2H), 2.49 (br s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 148.0, 130.9 (1C), 130.2 (2C), 129.2, 120.4 (q, *J* = 287 Hz), 116.4 (t, *J* = 301 Hz), 93.2 (qt, *J* = 25.0, 8.0 Hz, 1C), 21.9; ¹⁹F NMR (564 MHz, CDCl₃) δ -82.49 (t, *J* = 10.8 Hz), -111.55 (q, *J* = 10.9 Hz); IR (film) ν_{max} 3433, 3073, 2930, 1338, 1177, 1153, 1074 cm⁻¹; HRMS (ESI) *m/z* calcd for C₁₀H₉F₅NaO₄S (M+Na)⁺ 343.0034, found 343.0012.

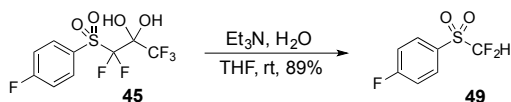
Representative Reaction Procedure for α,α-Difluoromethyl Sulfoxes. A solution of 1,1,1,3,3-pentafluoro-3-(phenylsulfonyl)propane-2,2-diol **43** (30 mg, 0.1 mmol) in H₂O/THF (0.3 mL/0.3 mL) was treated with Et₃N (55 μL, 0.39 mmol) and stirred for 30 min at rt. The reaction mixture was quenched with saturated aqueous NH₄Cl (1 mL) then extracted with CH₂Cl₂ (5 mL × 3). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. SiO₂ flash chromatography (19:1 hexanes/EtOAc) afforded the product **47** as a solid (17 mg) in 89% yield.



((Difluoromethyl)sulfonyl)benzene 47. See representative reaction procedure. All spectral and characterization data matched the reported data.⁹

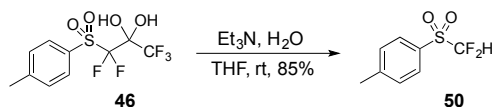


1-Chloro-2-((difluoromethyl)sulfonyl)benzene 48. See representative reaction procedure. 1-((2-Chlorophenyl)sulfonyl)-1,1,3,3,3-pentafluoropropane-2,2-diol **44** (30 mg, 0.09 mmol), Et₃N (49 μL, 0.35 mmol), and H₂O/THF (0.5 mL/0.5 mL) were used. The title compound **48** was isolated as a solid (19.5 mg) in 98% yield: mp 47–49 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.69 (td, *J* = 7.9, 1.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.2 Hz, 1H), 6.52 (t, *J* = 53.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 136.6, 134.3, 133.9, 132.4, 131.4, 127.8, 114.3 (t, *J* = 287 Hz, 1C); ¹⁹F NMR (376 MHz, CDCl₃) δ -122.9 (d, *J* = 53.8 Hz, 2F); IR (film) ν_{max} 3087, 2924, 1349, 1172, 1096, 1039 cm⁻¹; HRMS (ESI) *m/z* calcd for C₇H₅ClF₂NaO₂S (M+Na)⁺ 248.9559, found 248.9540.



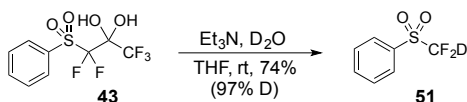
1-((Difluoromethyl)sulfonyl)-4-fluorobenzene 49. See representative reaction procedure.

1,1,1,3,3-Pentafluoro-3-((4-fluorophenyl)sulfonyl)propane-2,2-diol **45** (50 mg, 0.15 mmol) and Et₃N (107 μ L, 0.771 mmol) were used. The title compound **49** was isolated as a solid (28 mg) in 89% yield: mp 51–52 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (dd, J = 7.8, 4.6 Hz, 2H), 7.32 (app t, J = 8.3 Hz, 2H), 6.21 (t, J = 53.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3 (d, J = 258 Hz, 1C), 133.7 (d, J = 10.2 Hz, 1C), 127.6 (d, J = 3.1 Hz, 1C), 117.2 (d, J = 22.9 Hz, 1C), 114.6 (t, J = 286 Hz, 1C); ¹⁹F NMR (376 MHz, CDCl₃) δ -100.3 (tt, J = 8.1, 4.9 Hz, 1F), -122.4 (d, J = 53.4 Hz, 2F); IR (film) ν_{max} 2921, 2849, 1347, 1156, 1108, 1077 cm⁻¹; HRMS (EI) m/z calcd for C₇H₅F₃O₂S (M)⁺ 209.9962, found 209.9975.

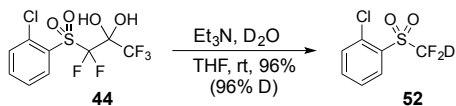


1-((Difluoromethyl)sulfonyl)-4-methylbenzene 50. See representative reaction procedure. The title compound **50** was isolated as a solid (22 mg) in 85% yield: mp 68–69 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 6.17 (t, J = 53.5 Hz, 1H), 2.50 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 130.6 (2C), 130.3 (2C), 128.7, 114.6 (t, J = 285 Hz, 1C), 21.9; ¹⁹F NMR (376 MHz, CDCl₃) δ -122.7 (d, J = 53.6 Hz, 2F); IR (film) ν_{max} 2924, 2854, 1343, 1167, 1159, 1077 cm⁻¹; HRMS (ESI) m/z calcd for C₈H₈F₂NaO₂S (M+Na)⁺ 229.0103, found 229.0104.

Representative Reaction Procedure for α -Deutero- α,α -difluoromethyl Sulfoxes. A solution of 1,1,1,3,3-pentafluoro-3-(phenylsulfonyl)propane-2,2-diol **43** (85 mg, 0.28 mmol) in D₂O/THF (0.5 mL/0.5 mL) was treated with Et₃N (155 μ L, 1.11 mmol) and stirred for overnight at rt. The reaction mixture was extracted with CH₂Cl₂ (5 mL \times 3). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. SiO₂ flash chromatography (19:1 hexanes/EtOAc) afforded the product **51** as a colorless oil (54 mg) in 74% yield (97% deuterium incorporation).

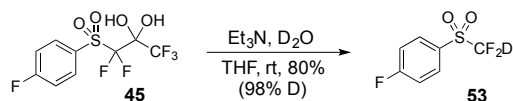


1-((Deuterodifluoromethyl)sulfonyl)benzene 51. See representative reaction procedure. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 7.6 Hz, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 135.8, 131.7, 130.5, 129.5, 114.2 (tt, J = 284, 30.8 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -123.5 (t, J = 8.1 Hz, 2F); IR (film) ν_{max} 2992, 2916, 1327, 1167, 1121, 1073 cm⁻¹; HRMS (ESI) m/z calcd for C₇H₅DF₂NaO₂S (M+Na)⁺ 216.0012, found 216.0038.

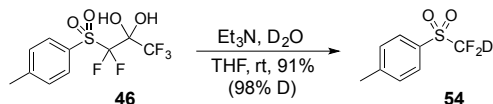


1-Chloro-2-((deuterodifluoromethyl)sulfonyl)benzene 52. See representative reaction procedure. The title compound **52** was isolated as a solid (20 mg) in 96% yield (96% deuterium incorporation): mp 49–50 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 136.6, 134.4, 133.9, 132.4, 131.5, 127.8, 114.0 (t, J = 284, 31.5 Hz), ¹⁹F NMR (376 MHz,

CDCl₃) δ -123.6 (t, J = 8.4 Hz, 2F); IR (film) ν_{\max} 2921, 2851, 1346, 1191, 1124, 1093 cm⁻¹; HRMS (EI) m/z calcd for C₇H₄DCIF₂O₂S (M)⁺ 226.9730, found 226.9738.



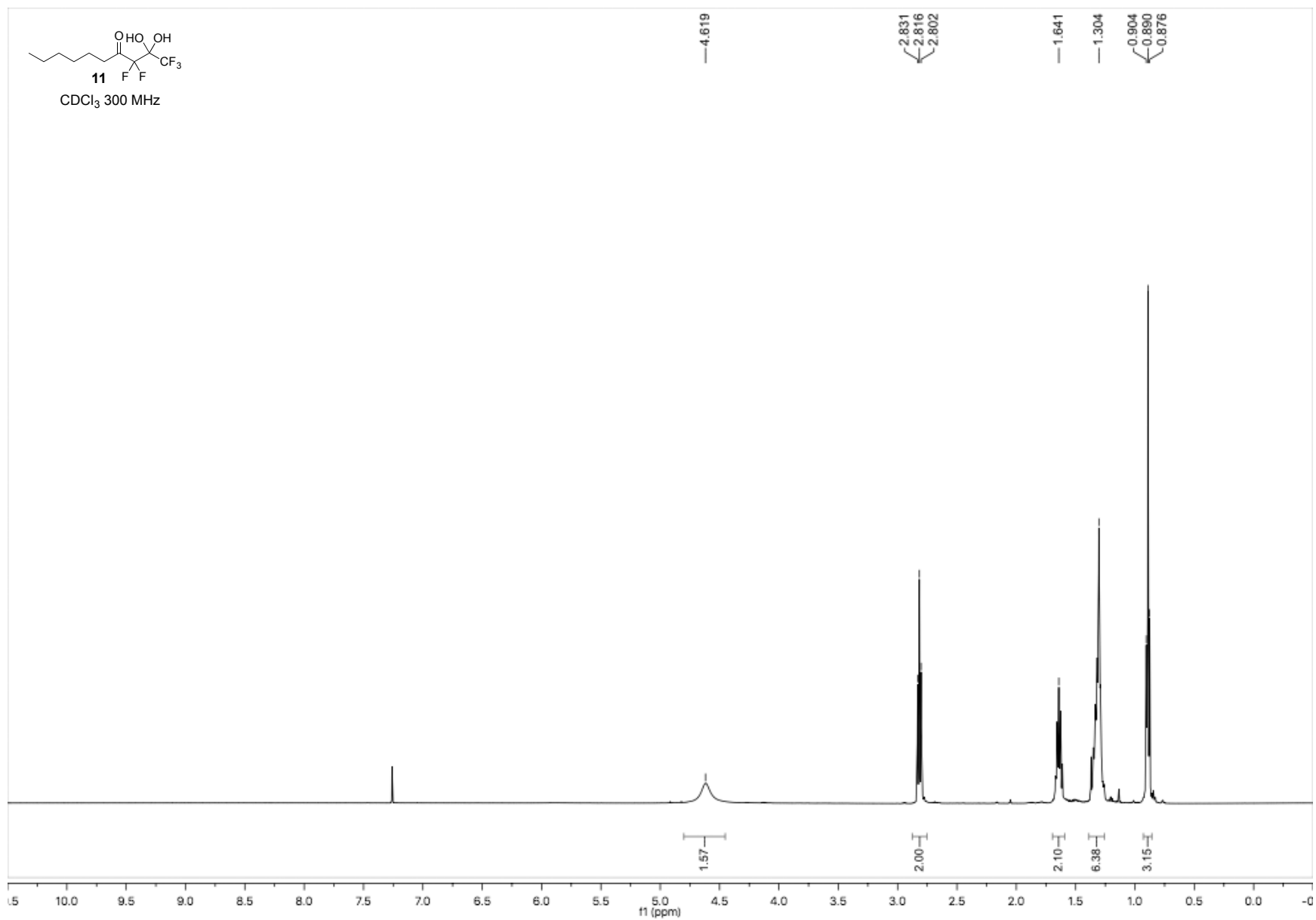
1-((Deuterodifluoromethyl)sulfonyl)-4-fluorobenzene 53. See representative reaction procedure. The title compound **53** was isolated as a solid (26 mg) in 80% yield (98% deuterium incorporation): mp 50–51 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (dd, J = 8.8, 5.0 Hz, 1H), 7.33 (app t, J = 8.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5 (d, J = 260 Hz, 1C), 133.7 (d, J = 11.0 Hz, 1C), 127.6 (d, J = 4.0 Hz, 1C), 117.2 (d, J = 23.0 Hz, 1C), 114.2 (tt, J = 284, 31.1 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -100.3 (tt, J = 8.1, 5.0 Hz, 1F), -123.0 (t, J = 7.9 Hz, 2F); IR (film) ν_{\max} 2922, 2853, 1345, 1191, 1125, 1075 cm⁻¹; HRMS (EI) m/z calcd for C₇H₄DF₃O₂S (M)⁺ 211.0025, found 211.0035.

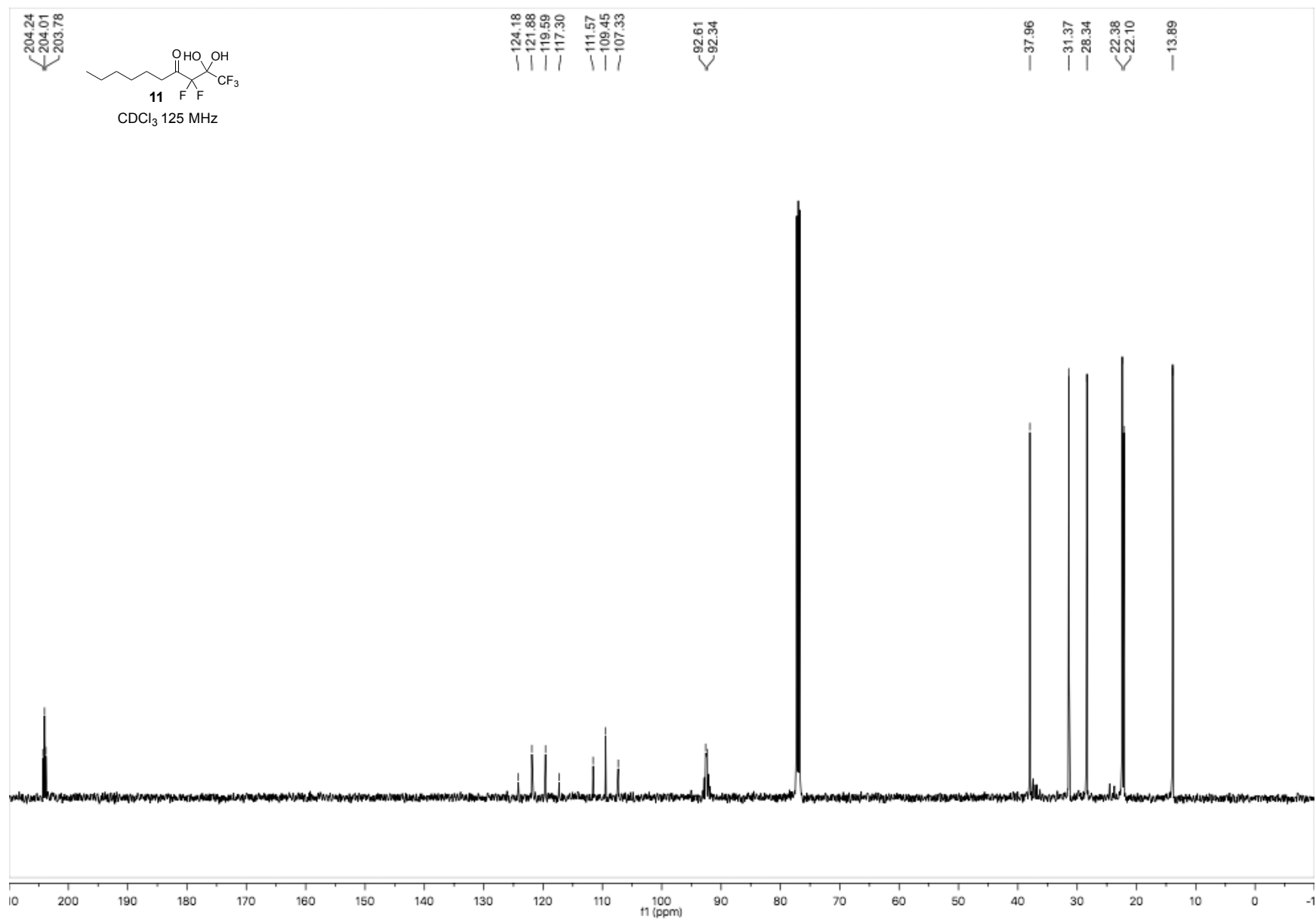


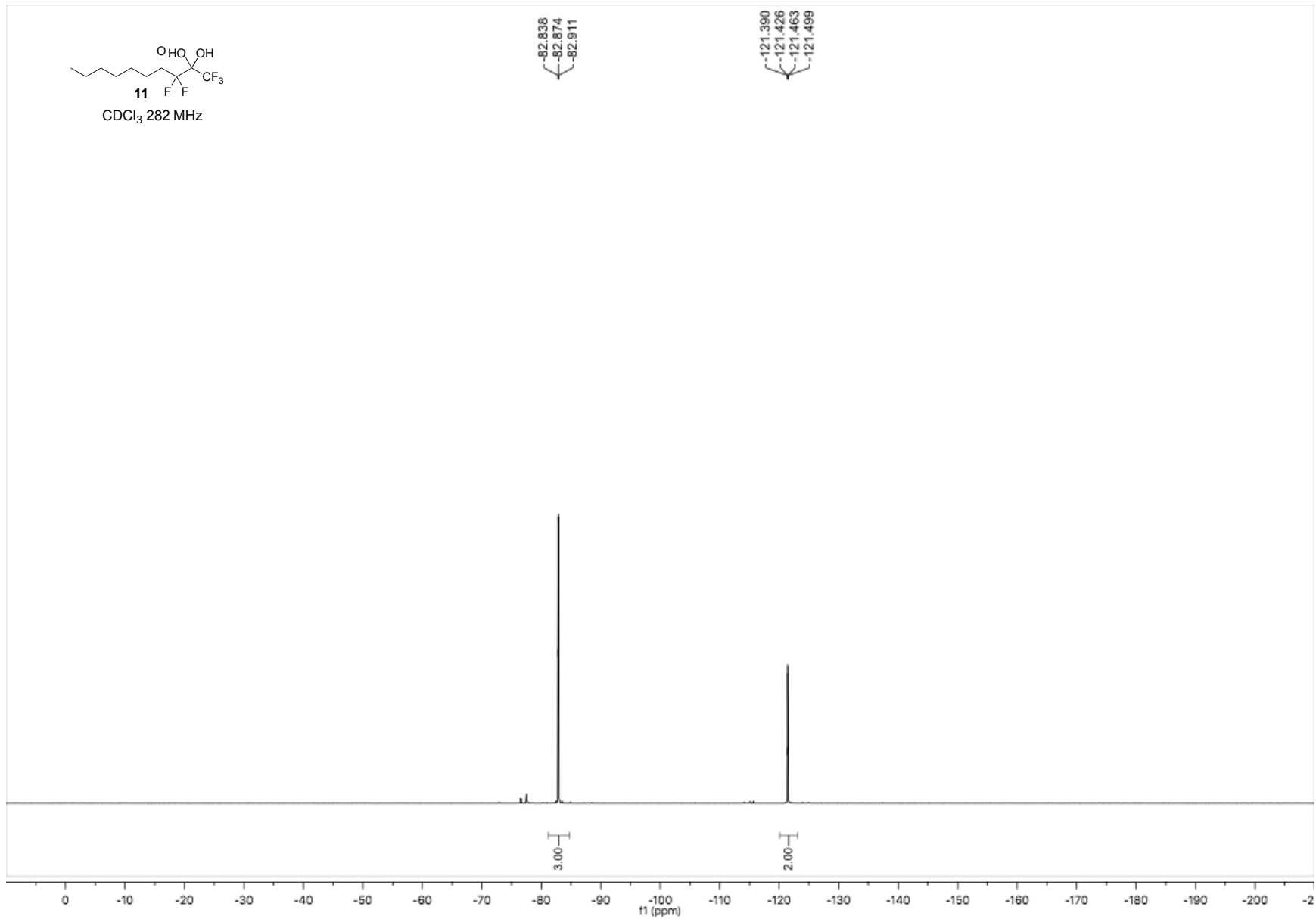
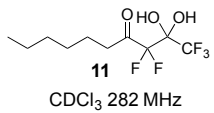
1-((difluoromethyl-d)sulfonyl)-4-methylbenzene 54. See representative reaction procedure. The title compound **54** was isolated as a solid (29 mg) in 91% yield (98% deuterium incorporation): mp 70–71 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 2.49 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.4, 130.5, 130.2, 128.6, 114.2 (tt, J = 282, 30.2 Hz), 21.8; ¹⁹F NMR (376 MHz, CDCl₃) δ -123.6 (t, J = 8.4 Hz, 2F); IR (film) ν_{\max} 2924, 2849, 1339, 1180, 1123, 1075 cm⁻¹; HRMS (ESI) m/z calcd for C₈H₈DF₂O₂S (M+H)⁺ 208.0354, found 208.0351.

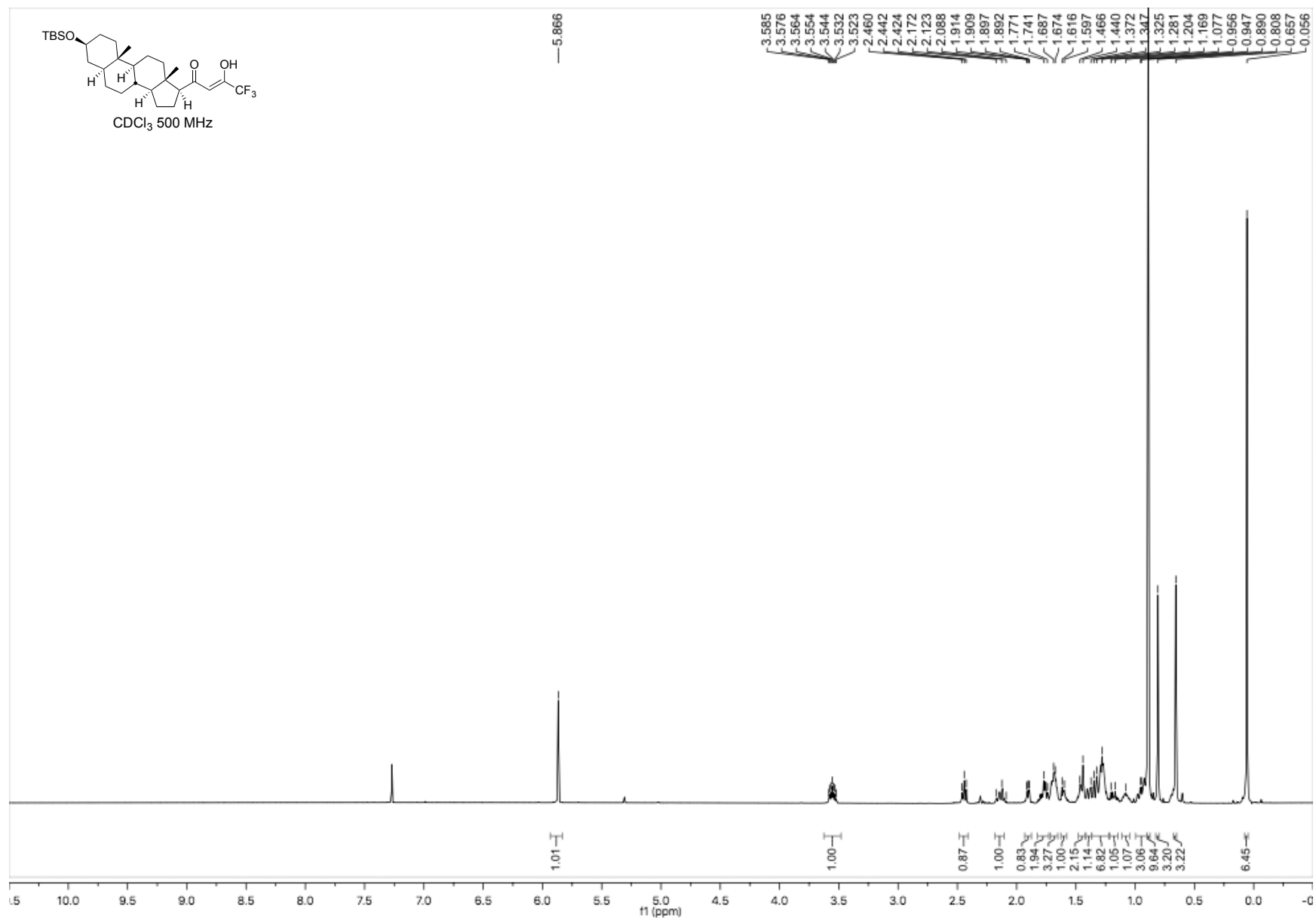
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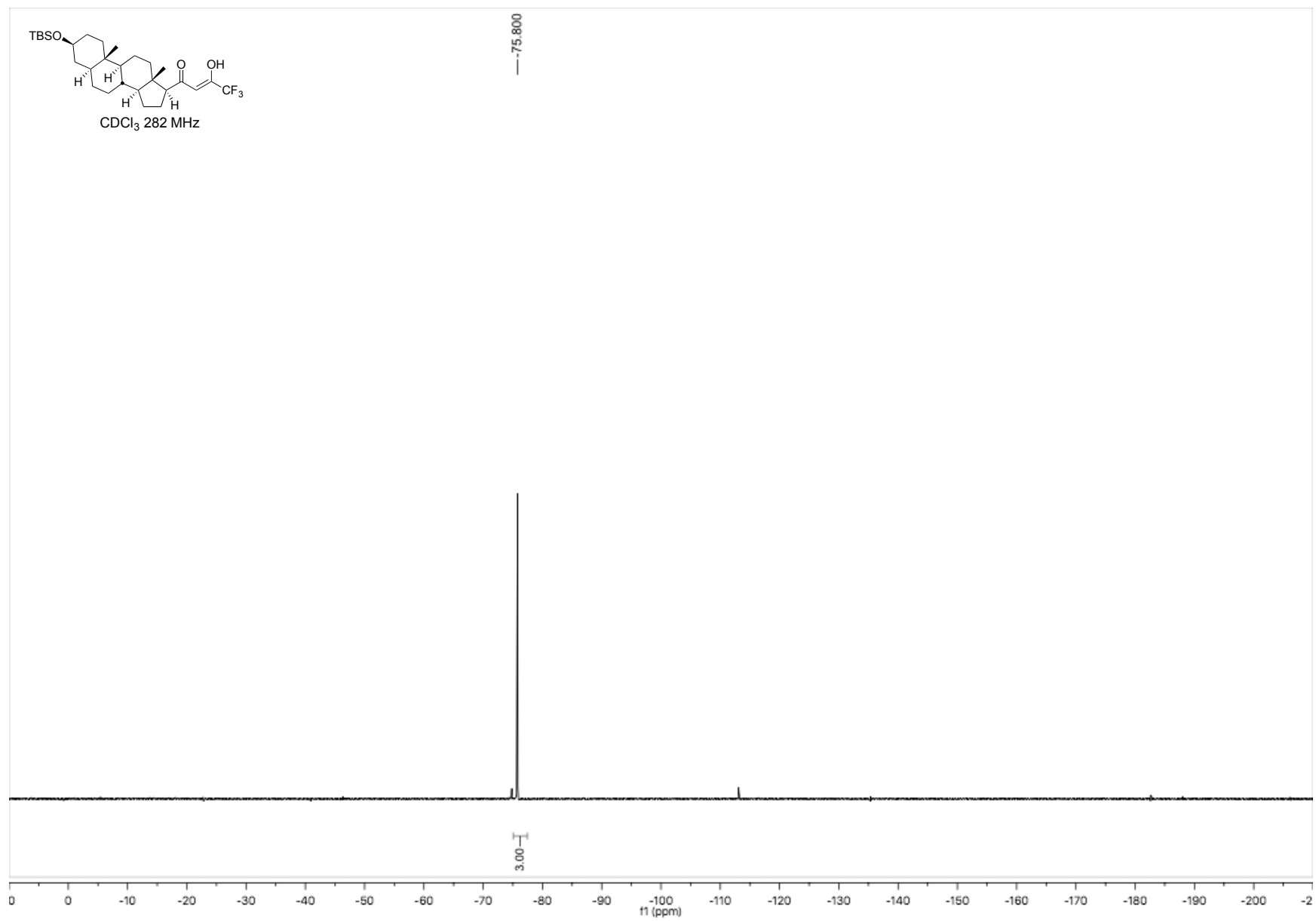
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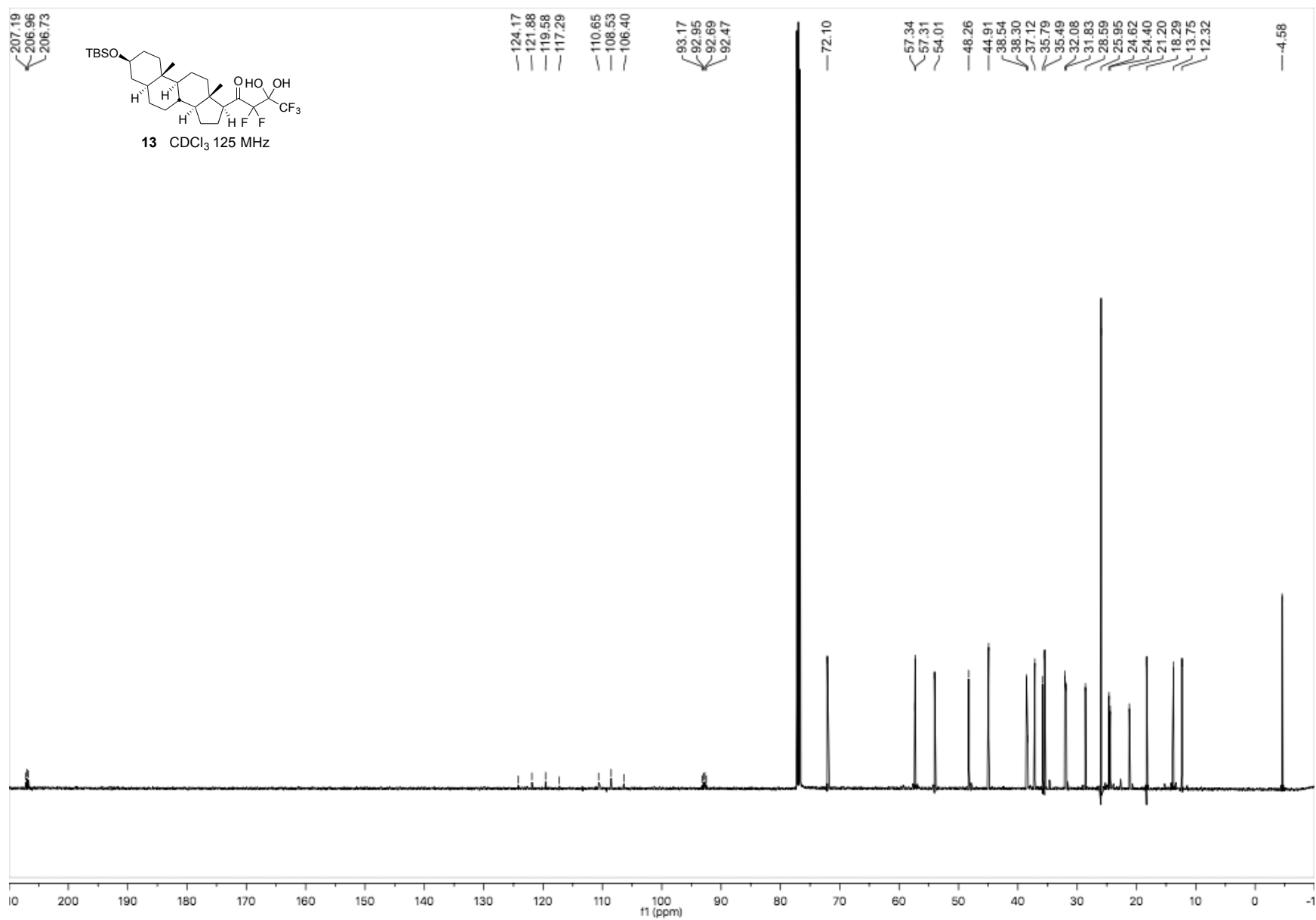


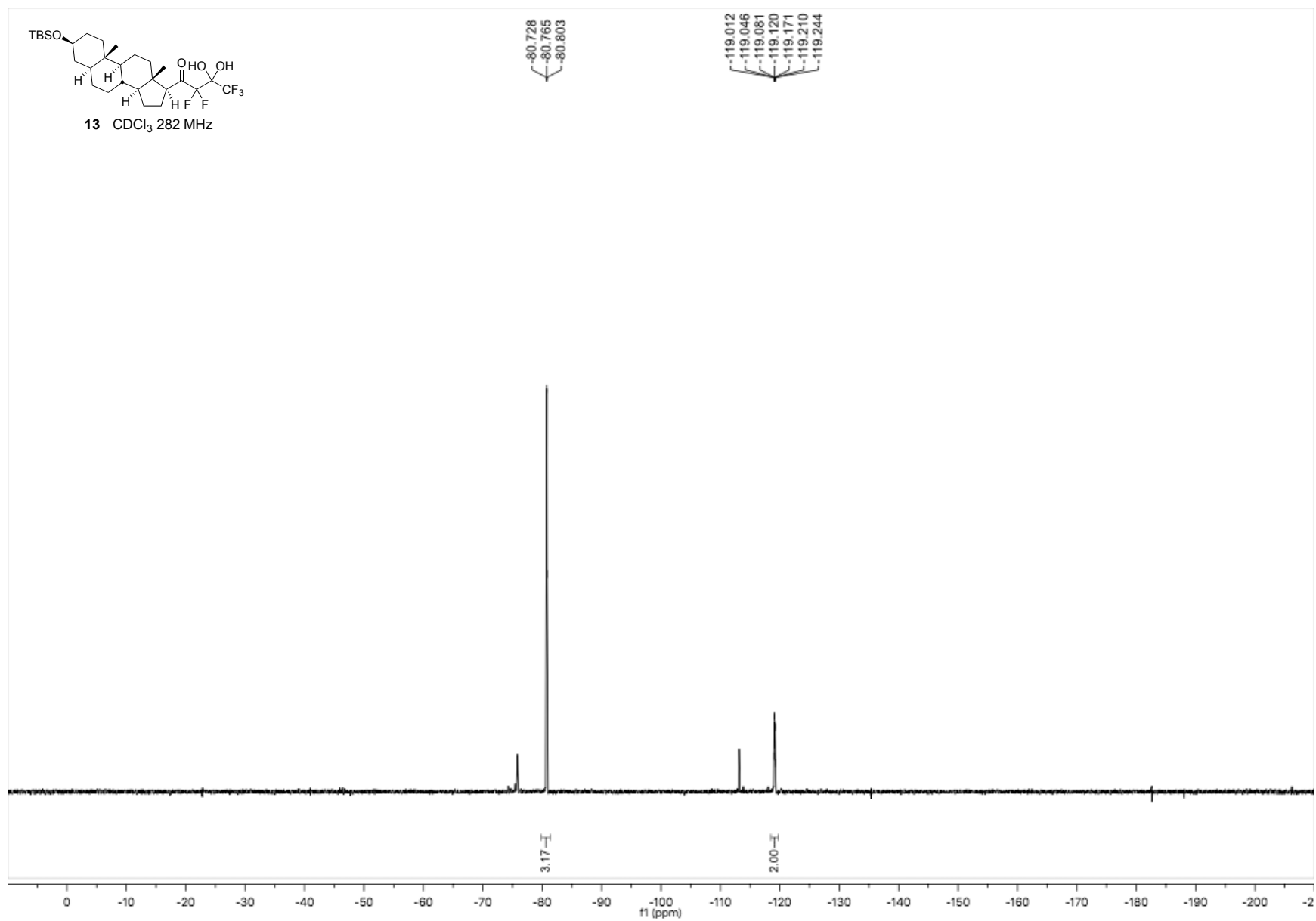


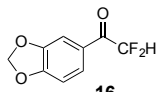




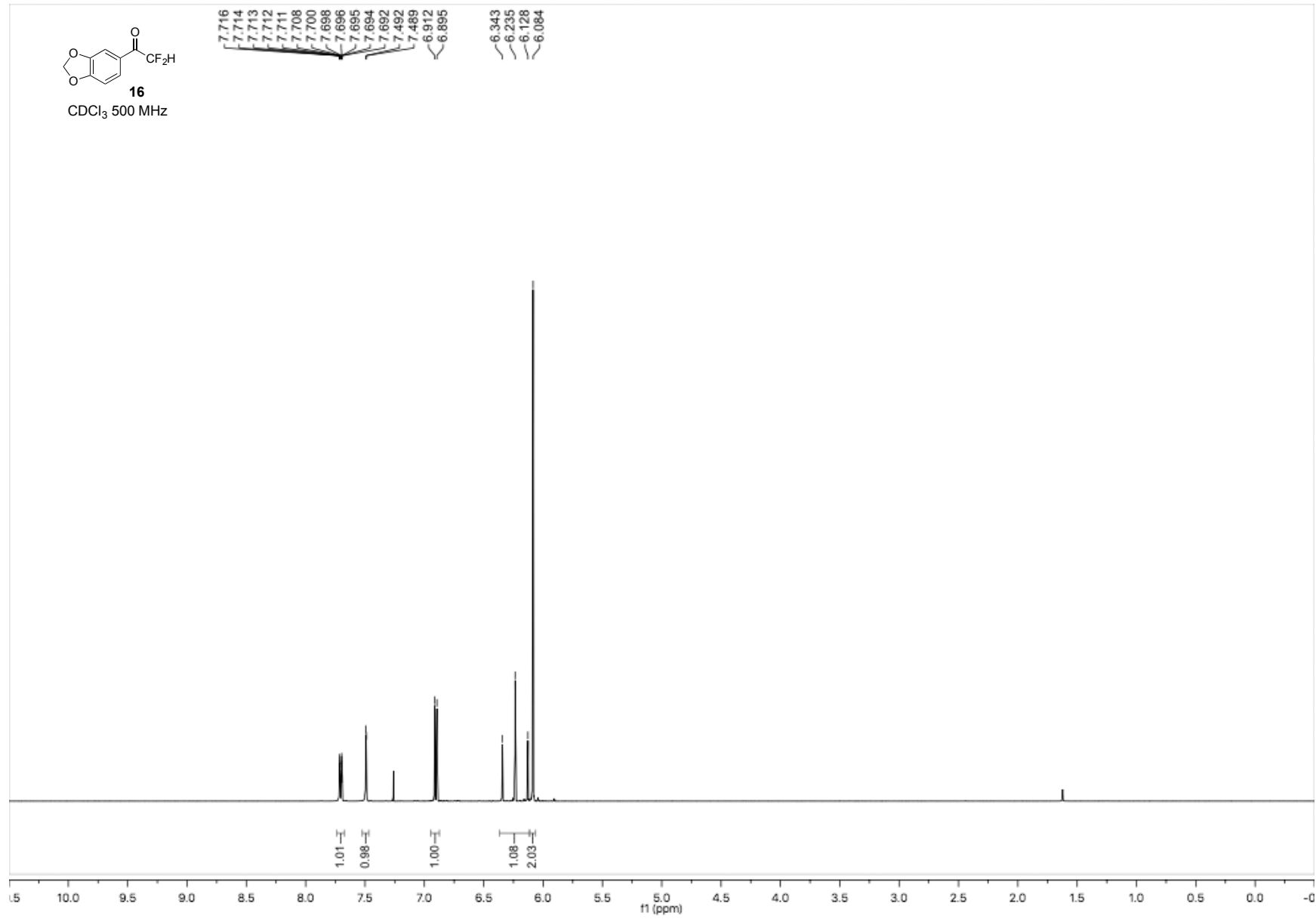


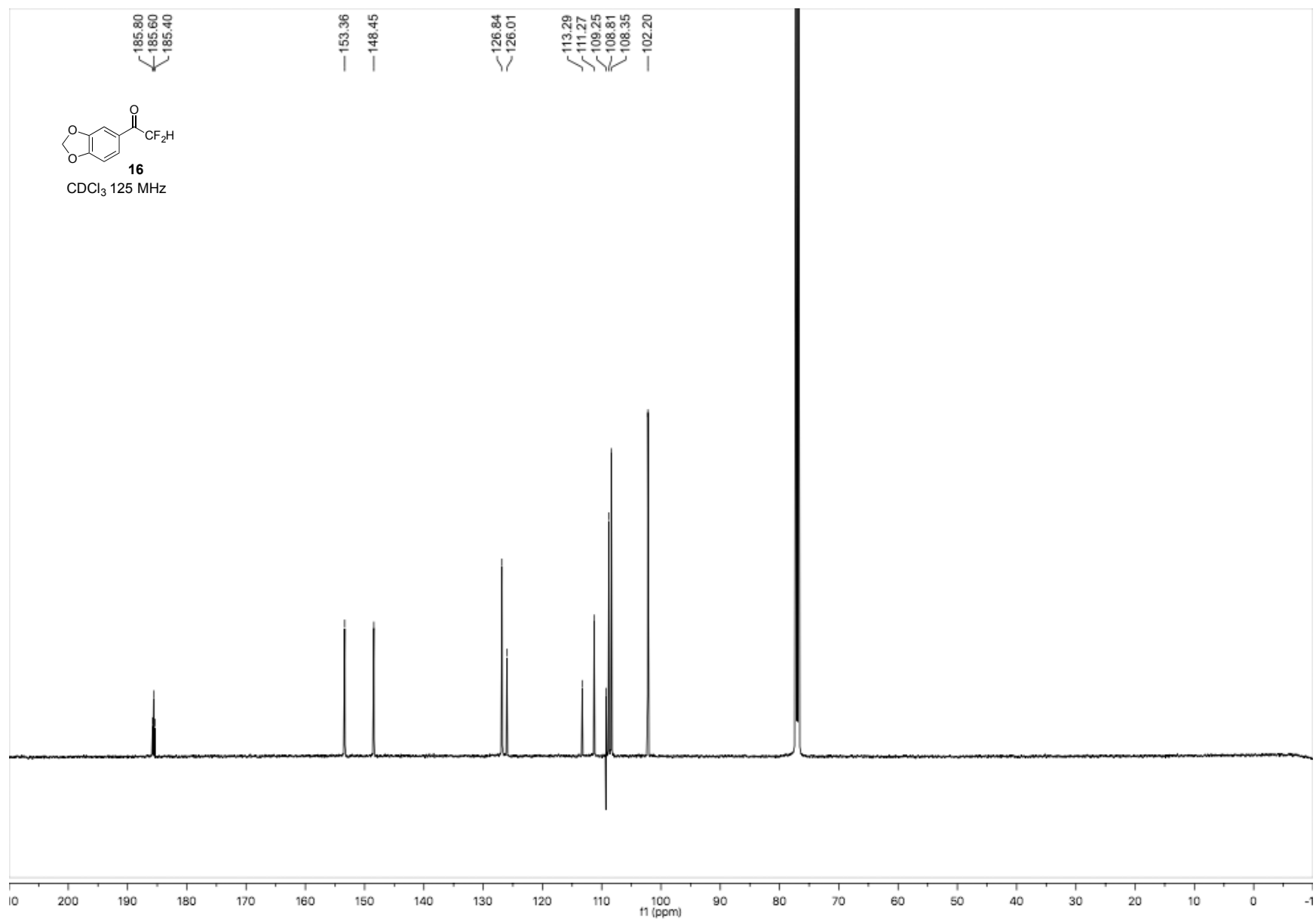


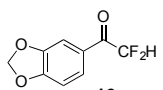




CDCl₃ 500 MHz

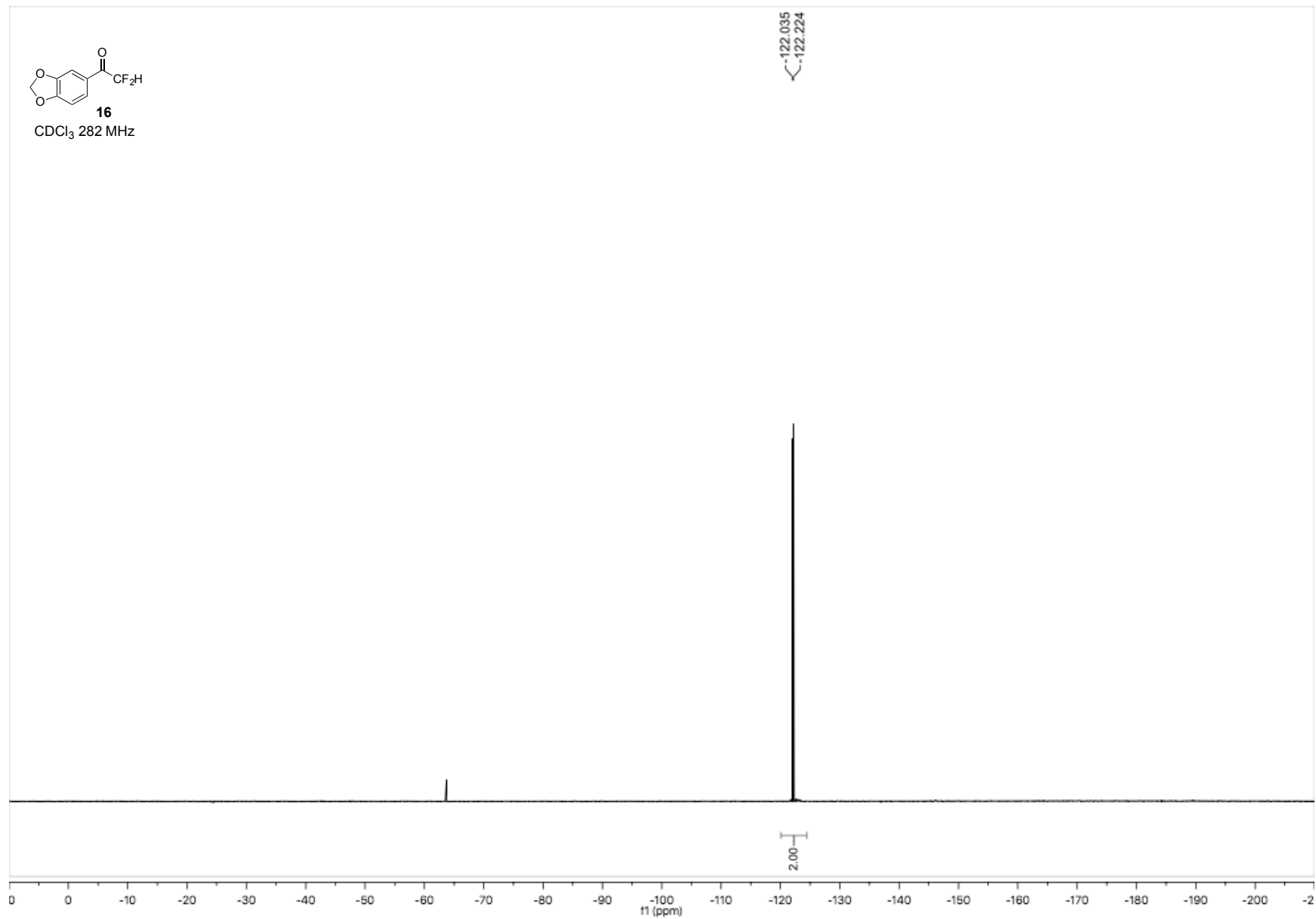


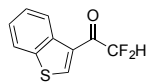




16

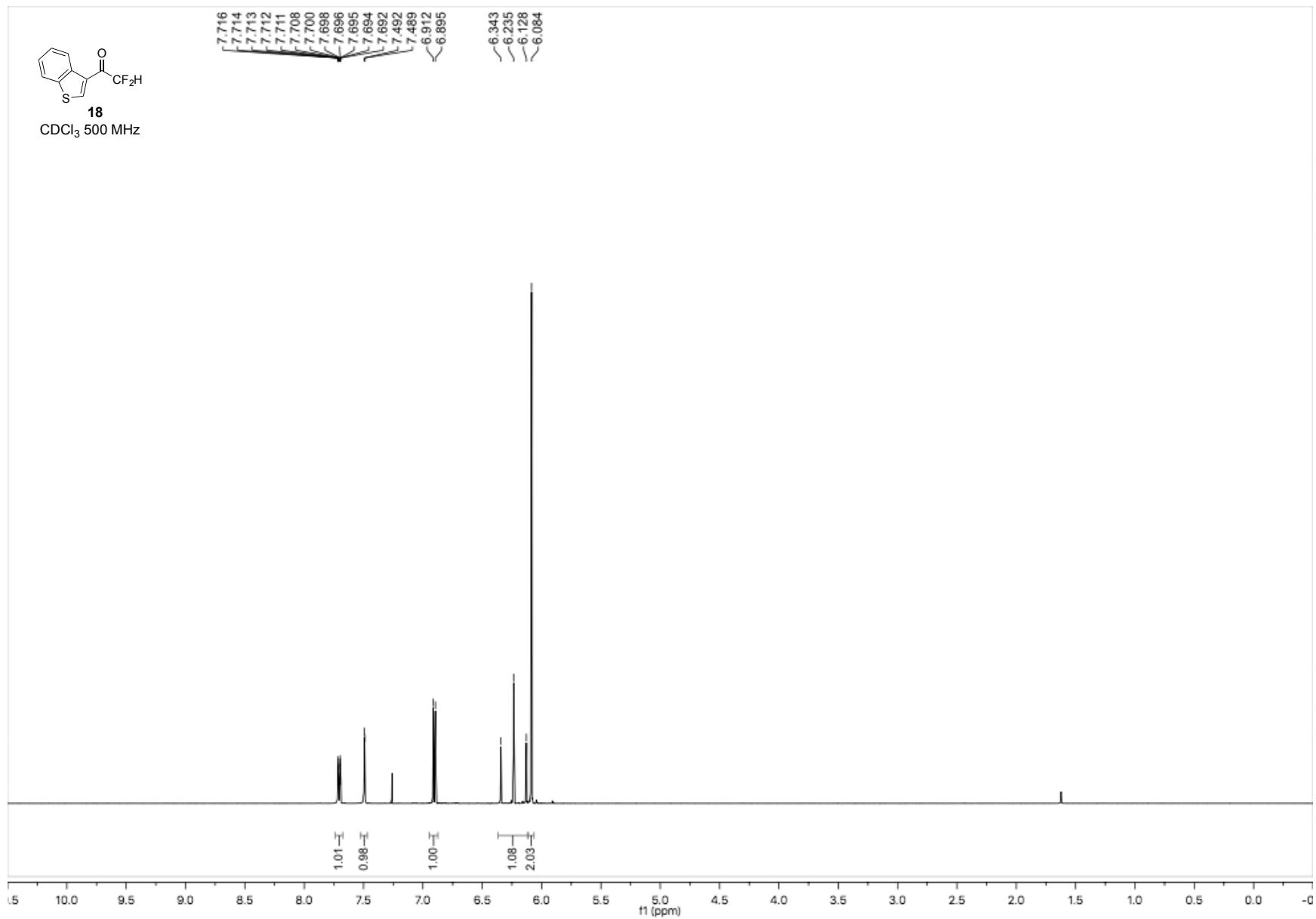
CDCl₃ 282 MHz

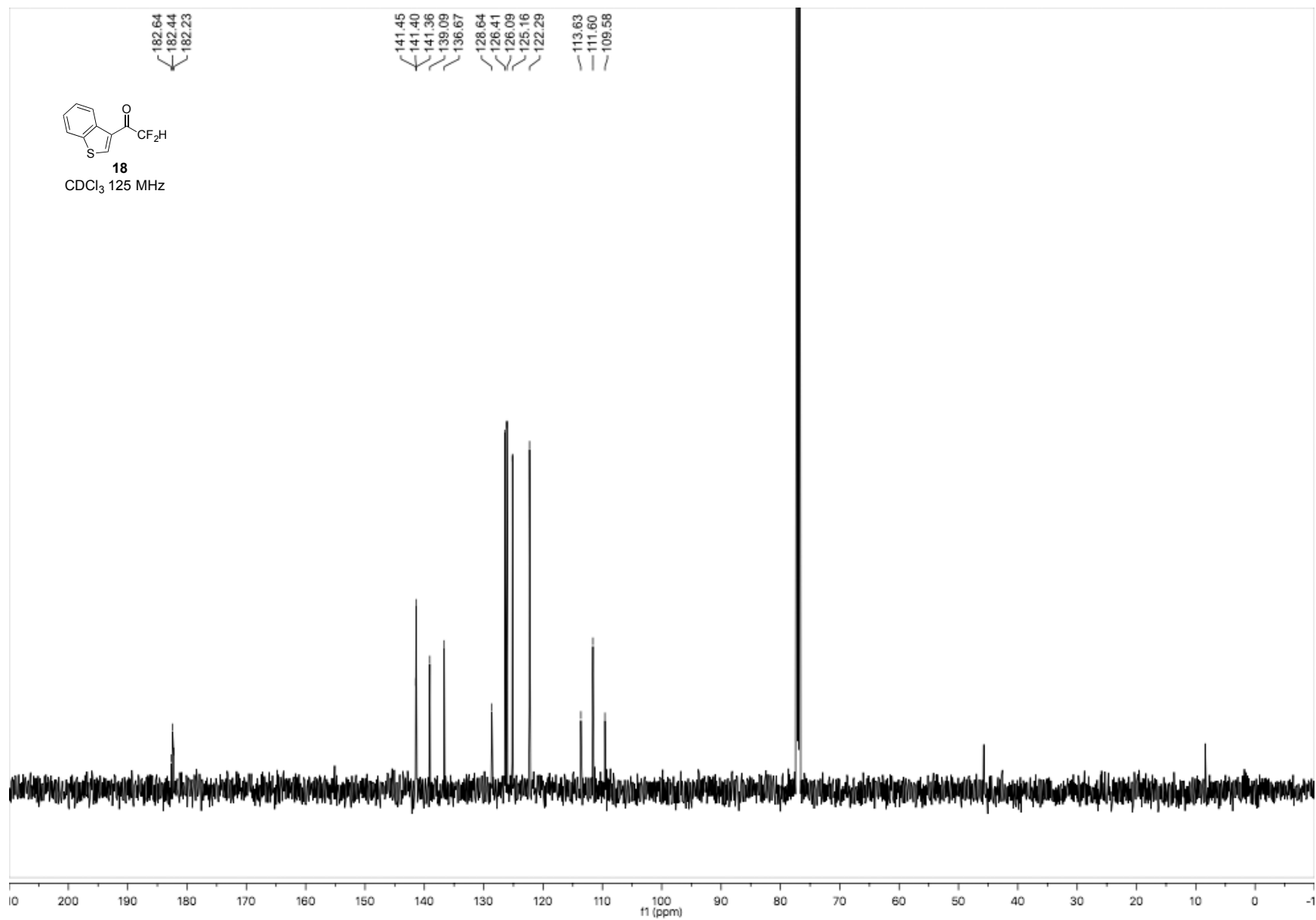


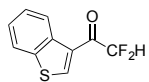


18

CDCl₃ 500 MHz

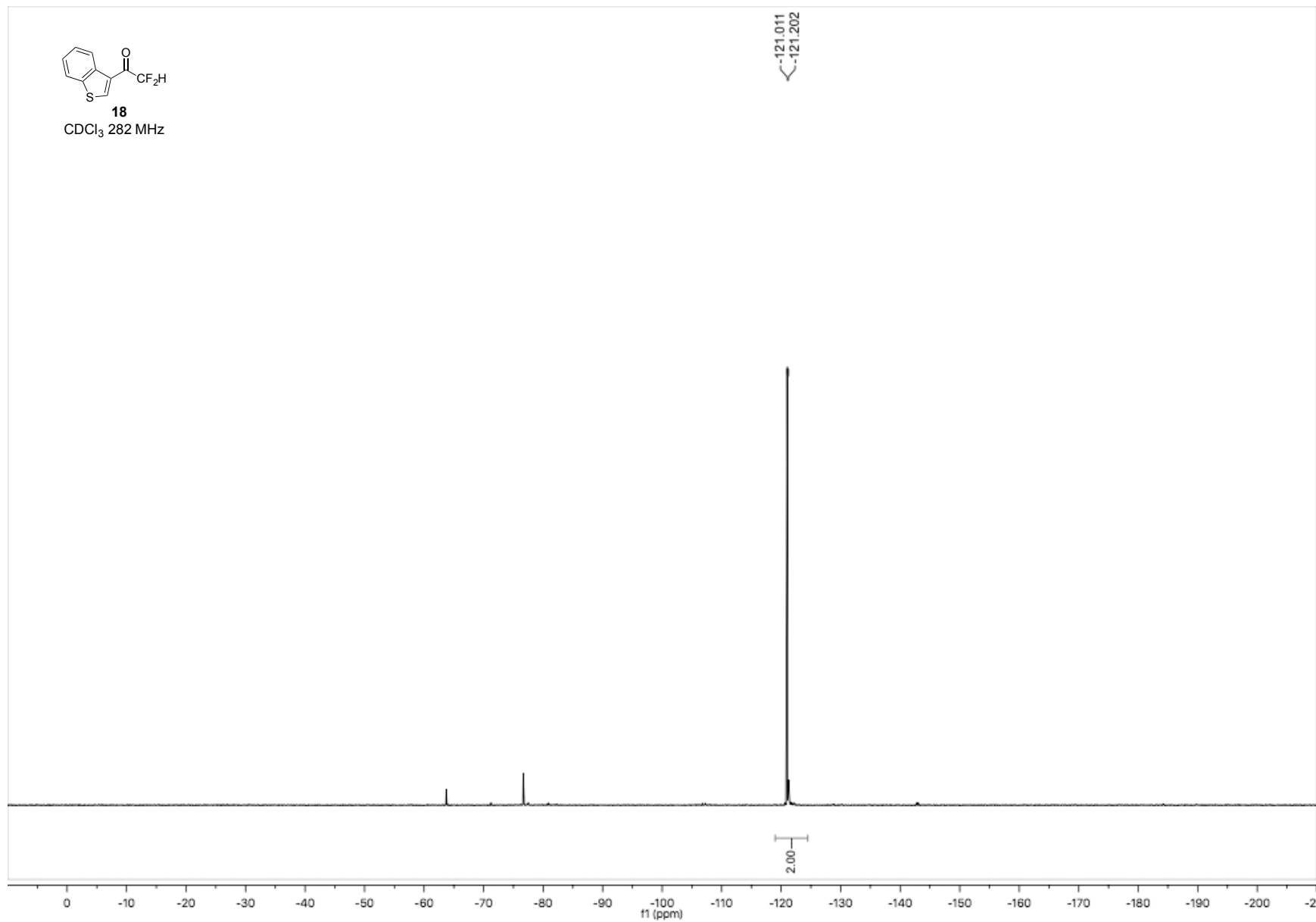


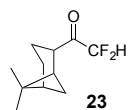




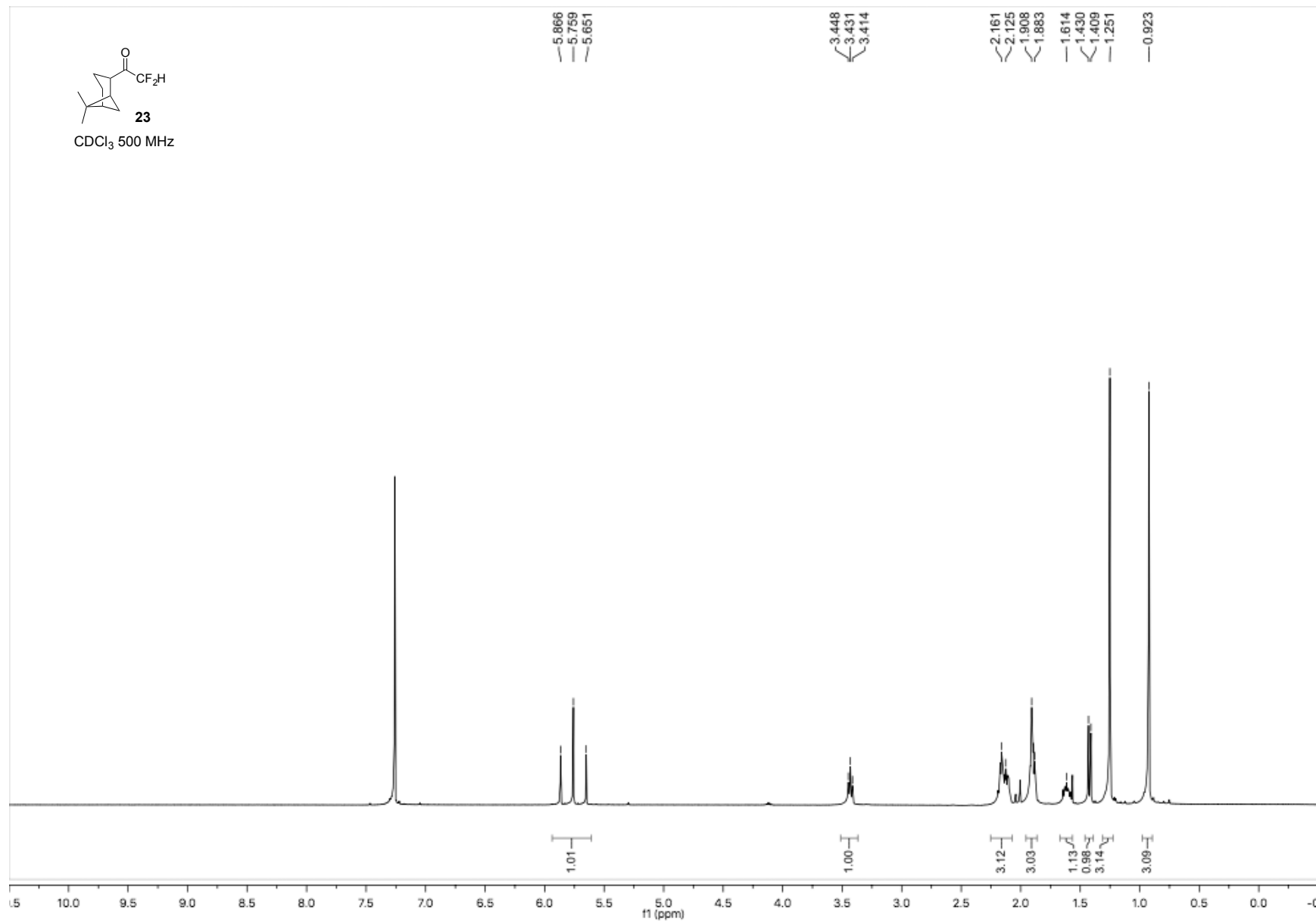
18

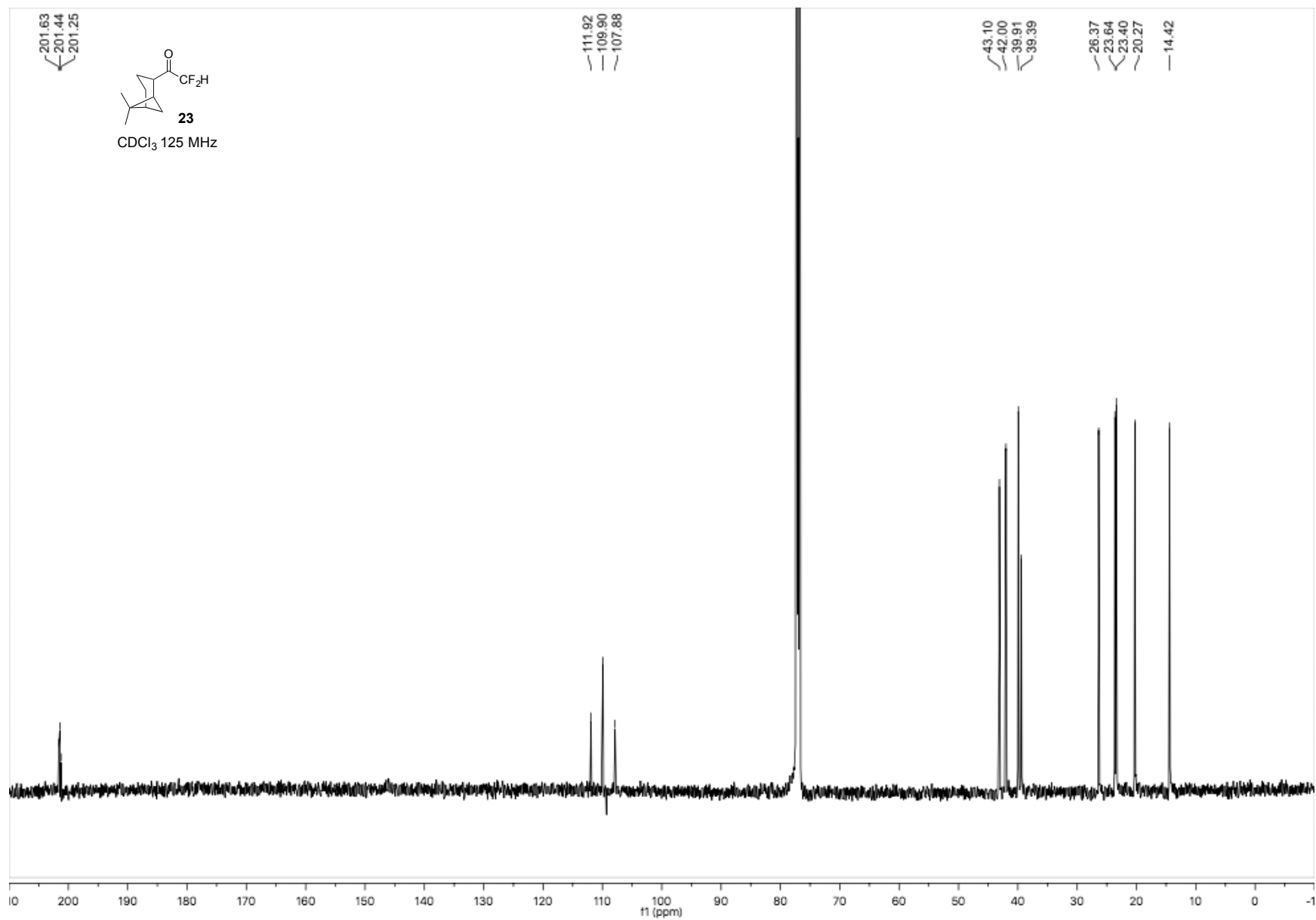
CDCl₃ 282 MHz

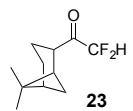




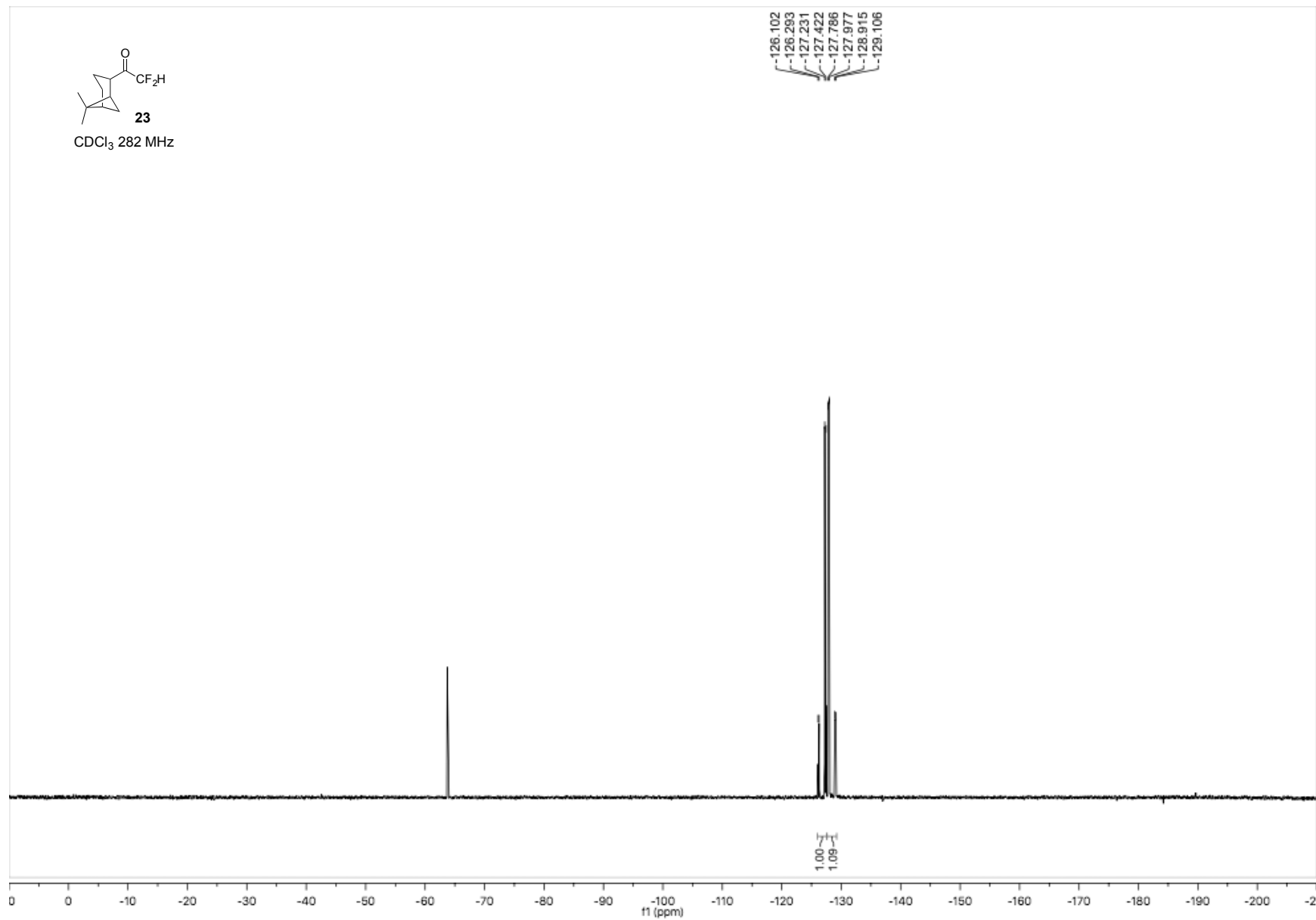
CDCl₃ 500 MHz

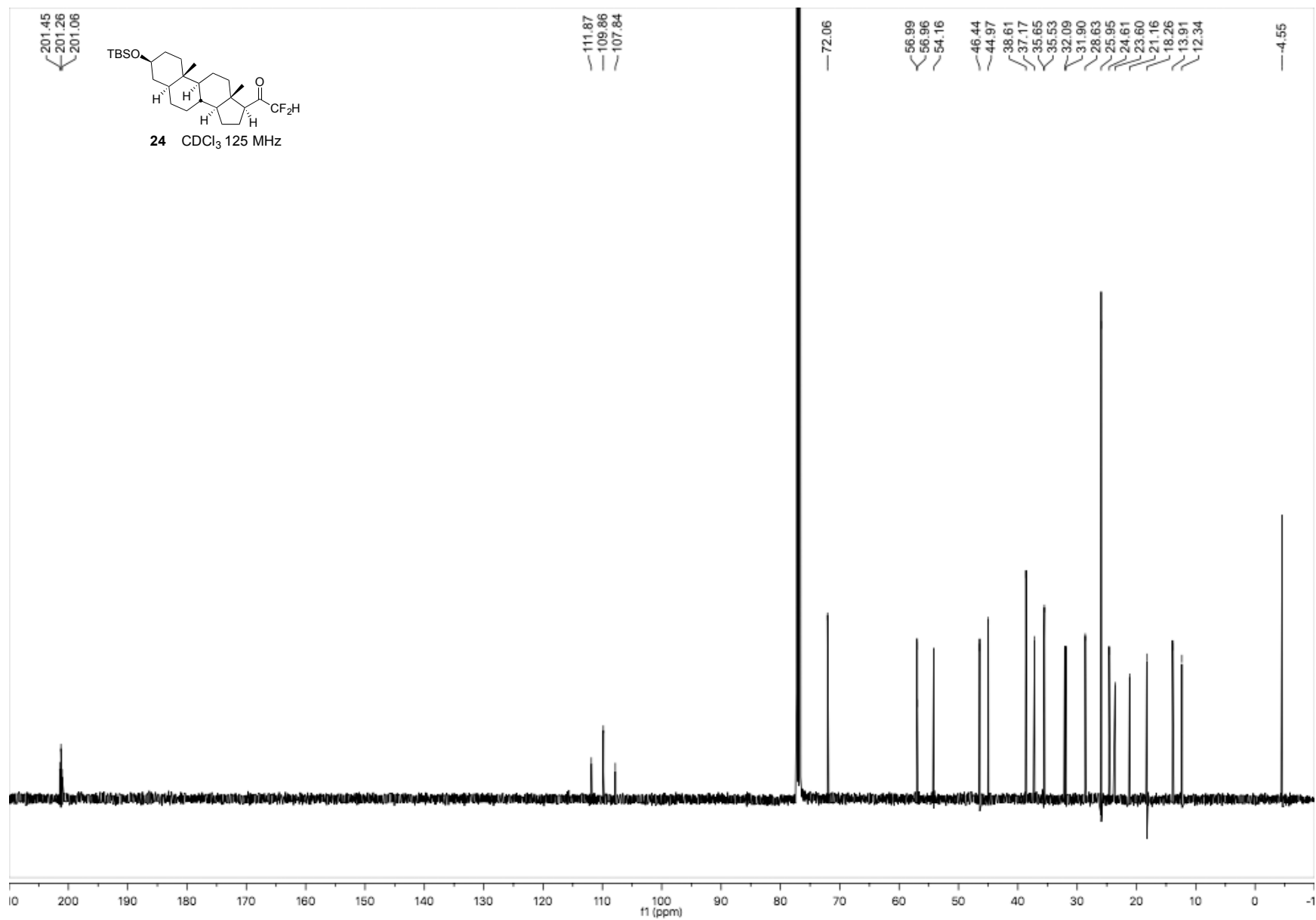


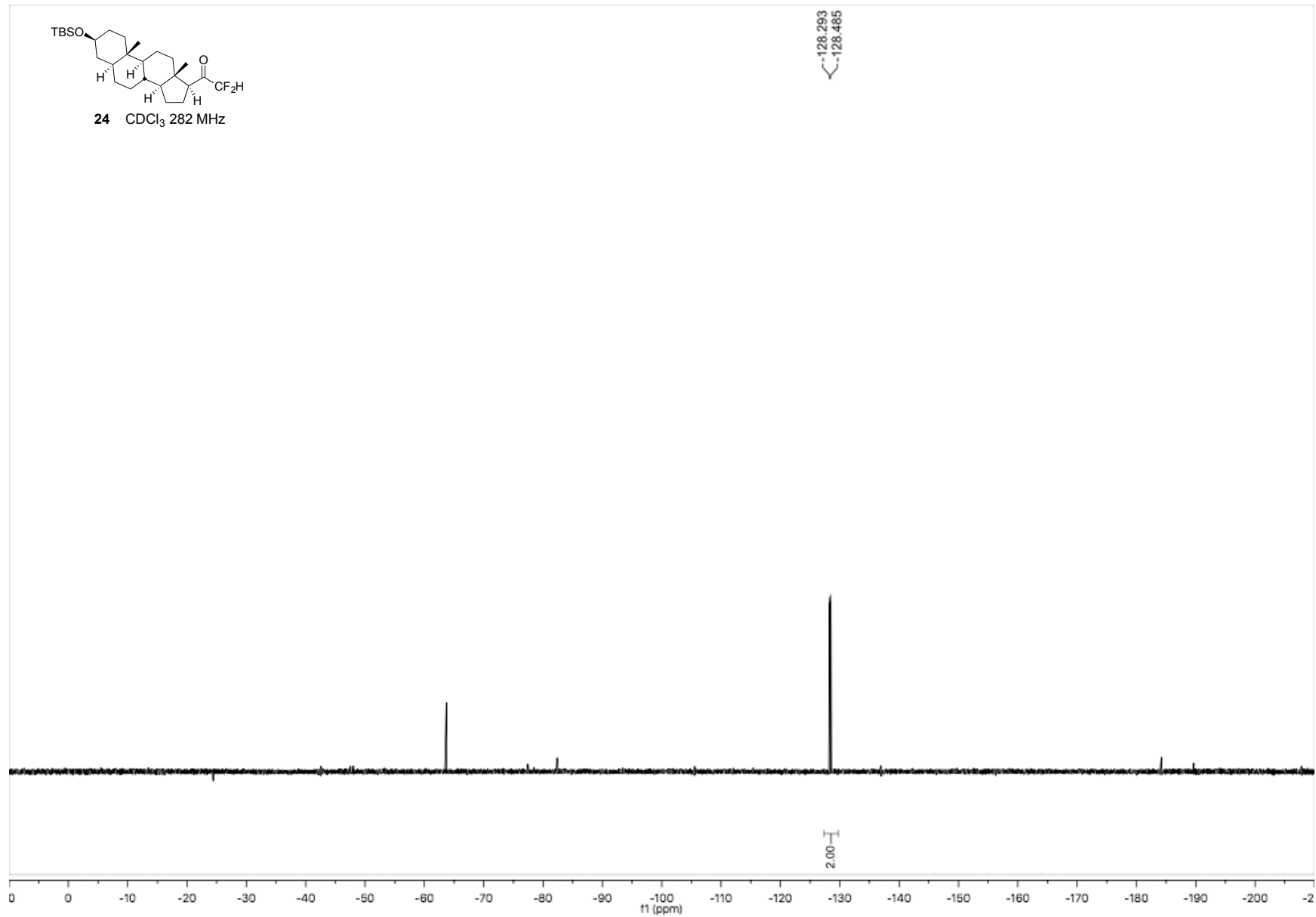
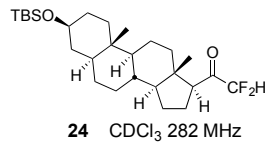


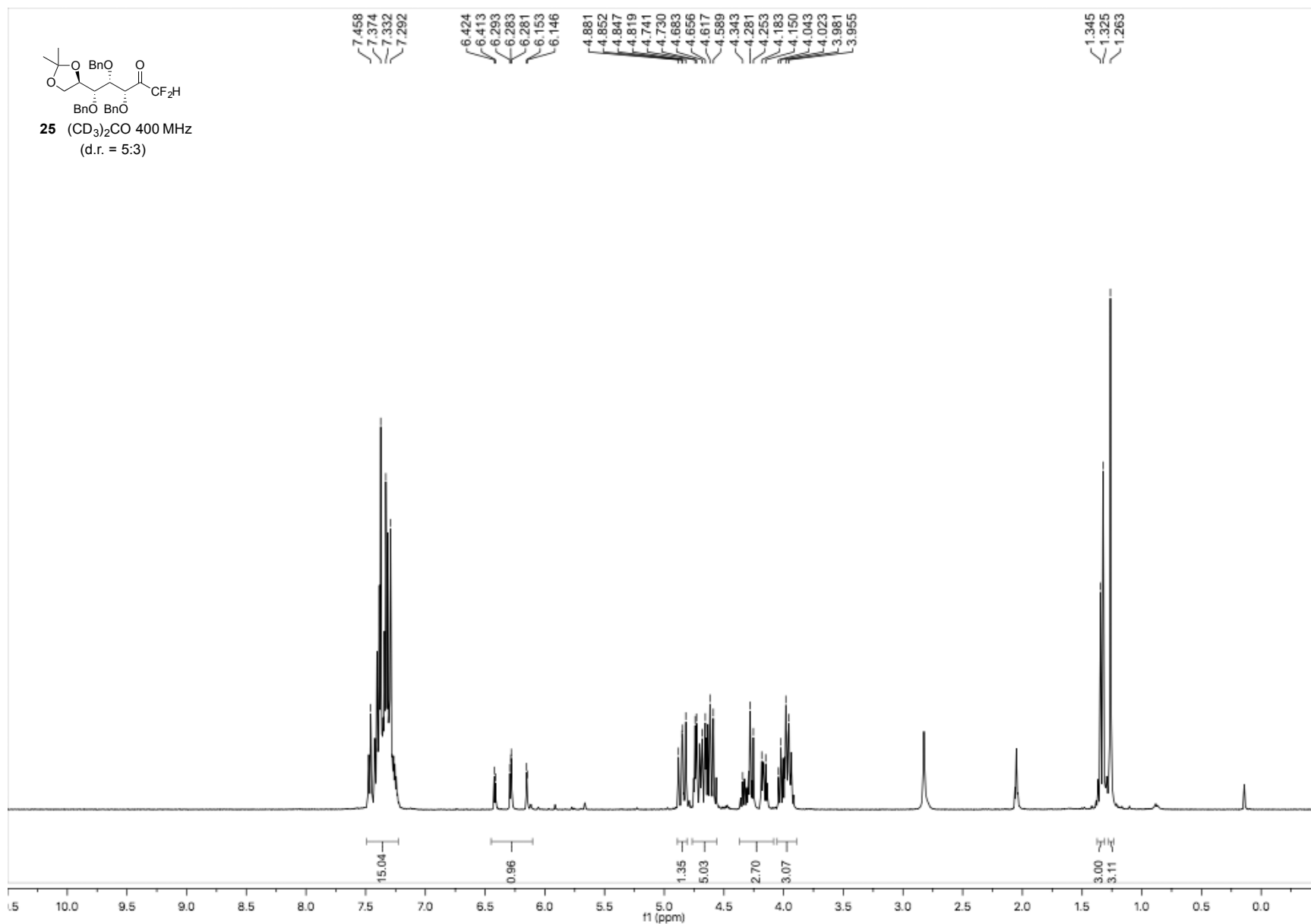


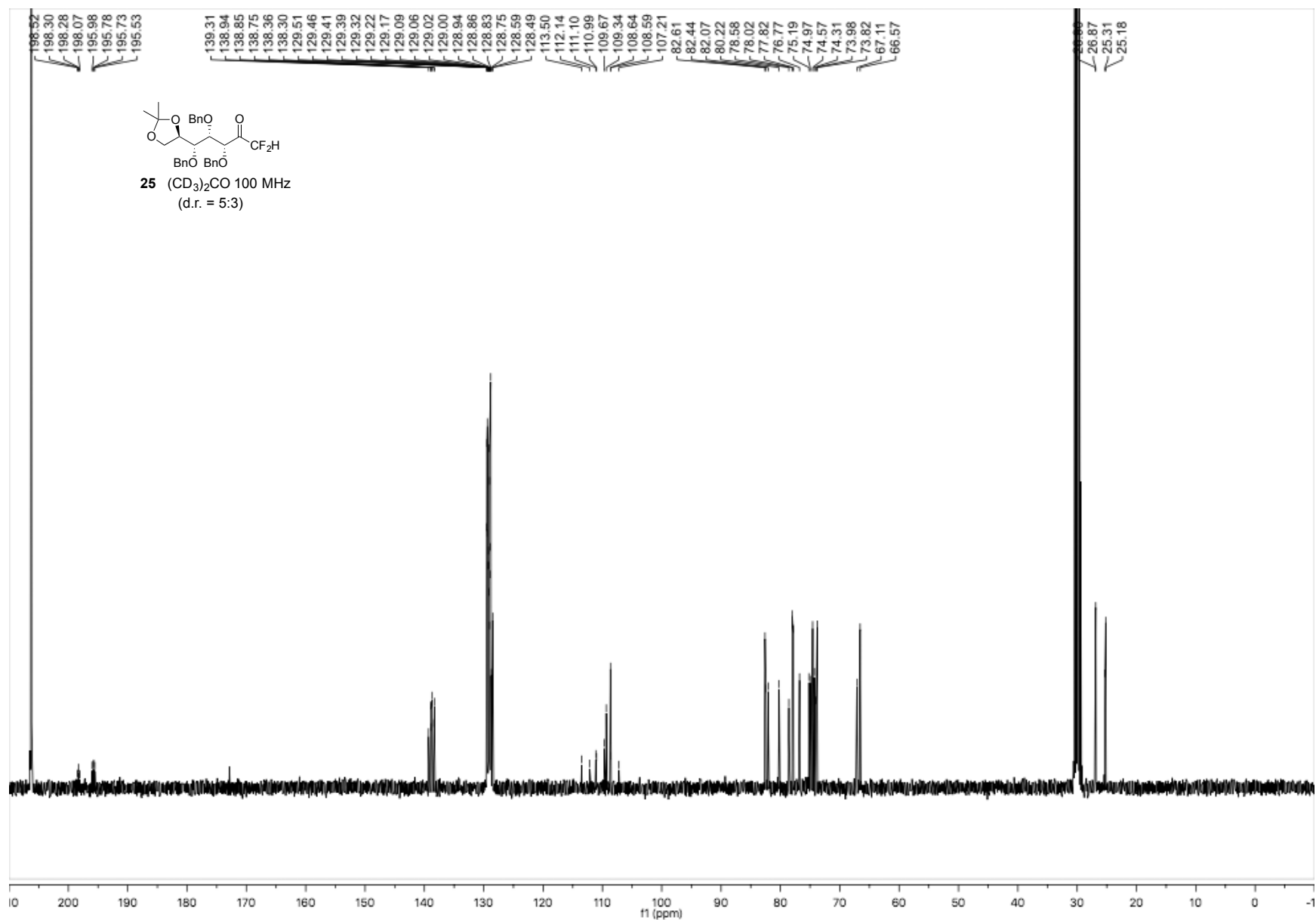
CDCl₃ 282 MHz

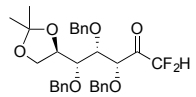




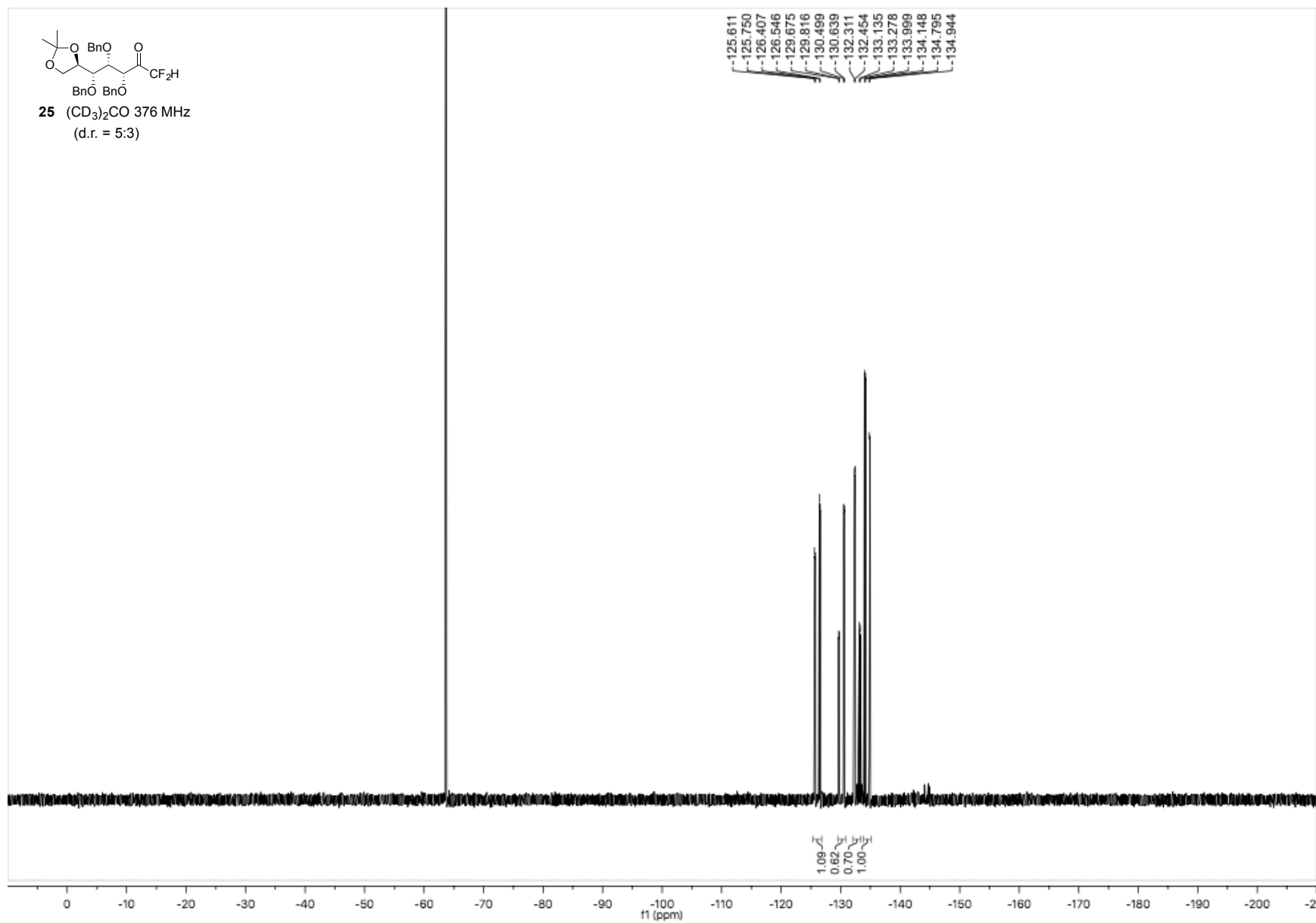


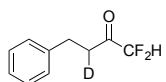




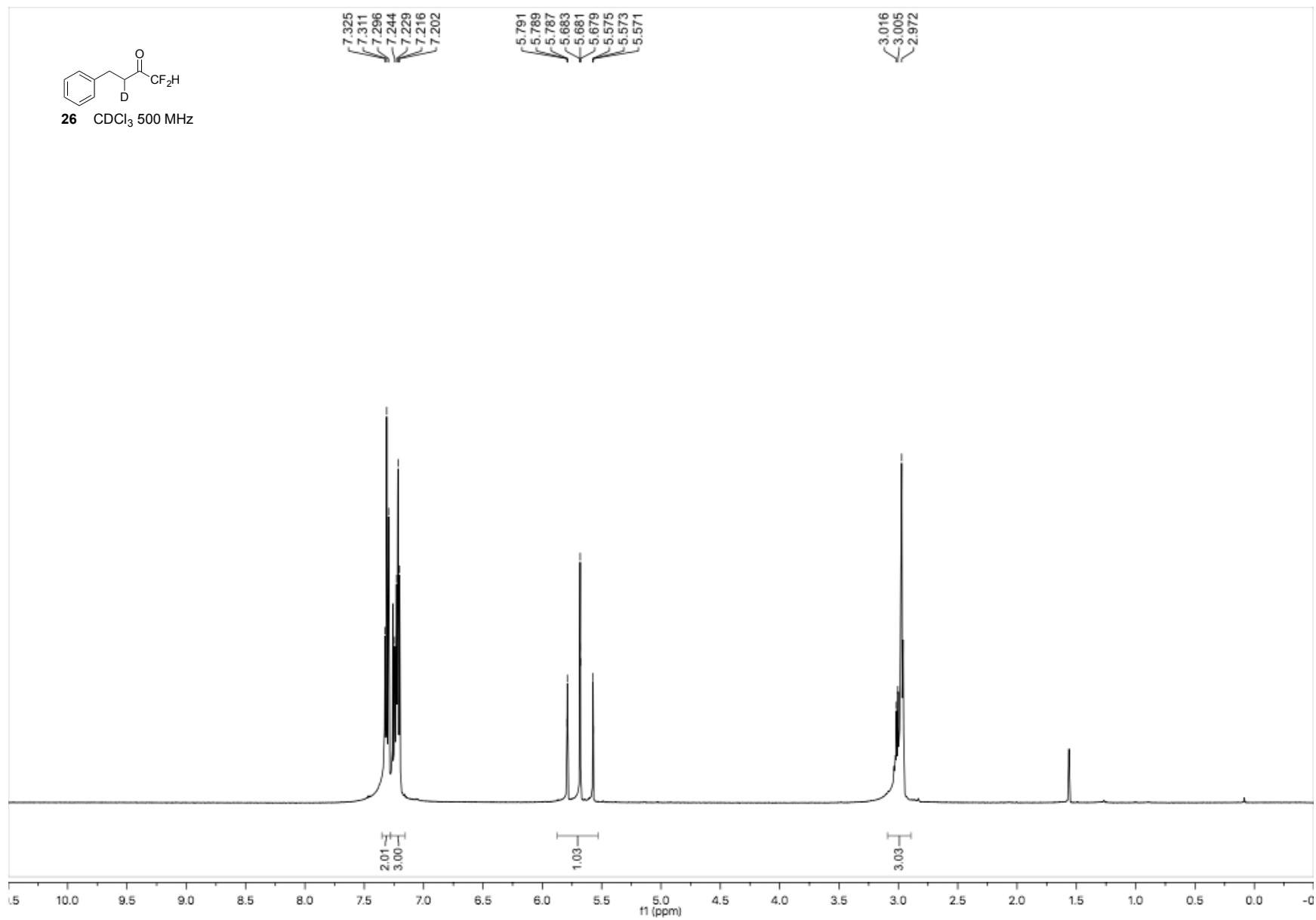


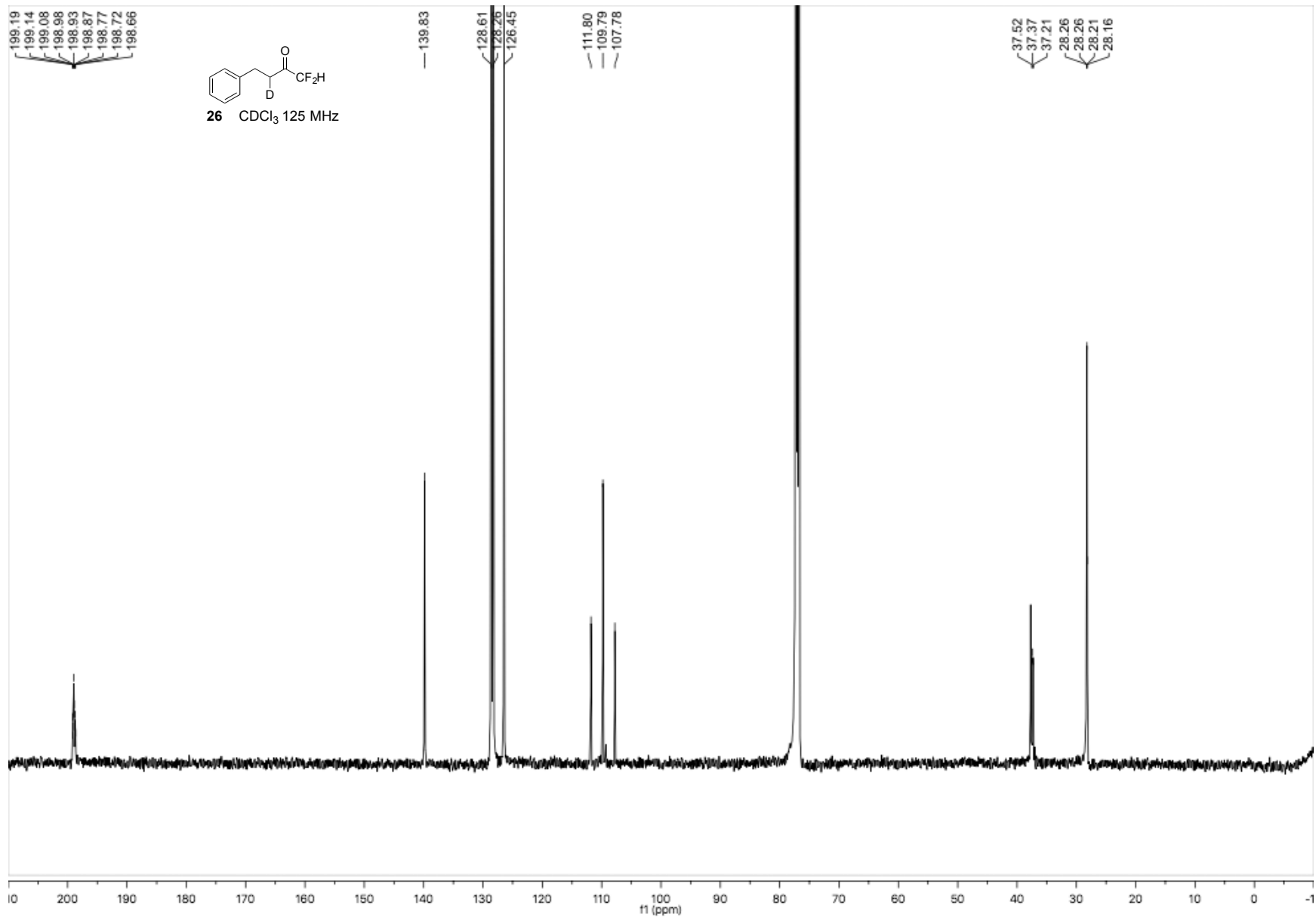
25 (CD₃)₂CO 376 MHz
(d.r. = 5:3)

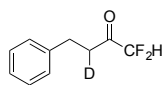




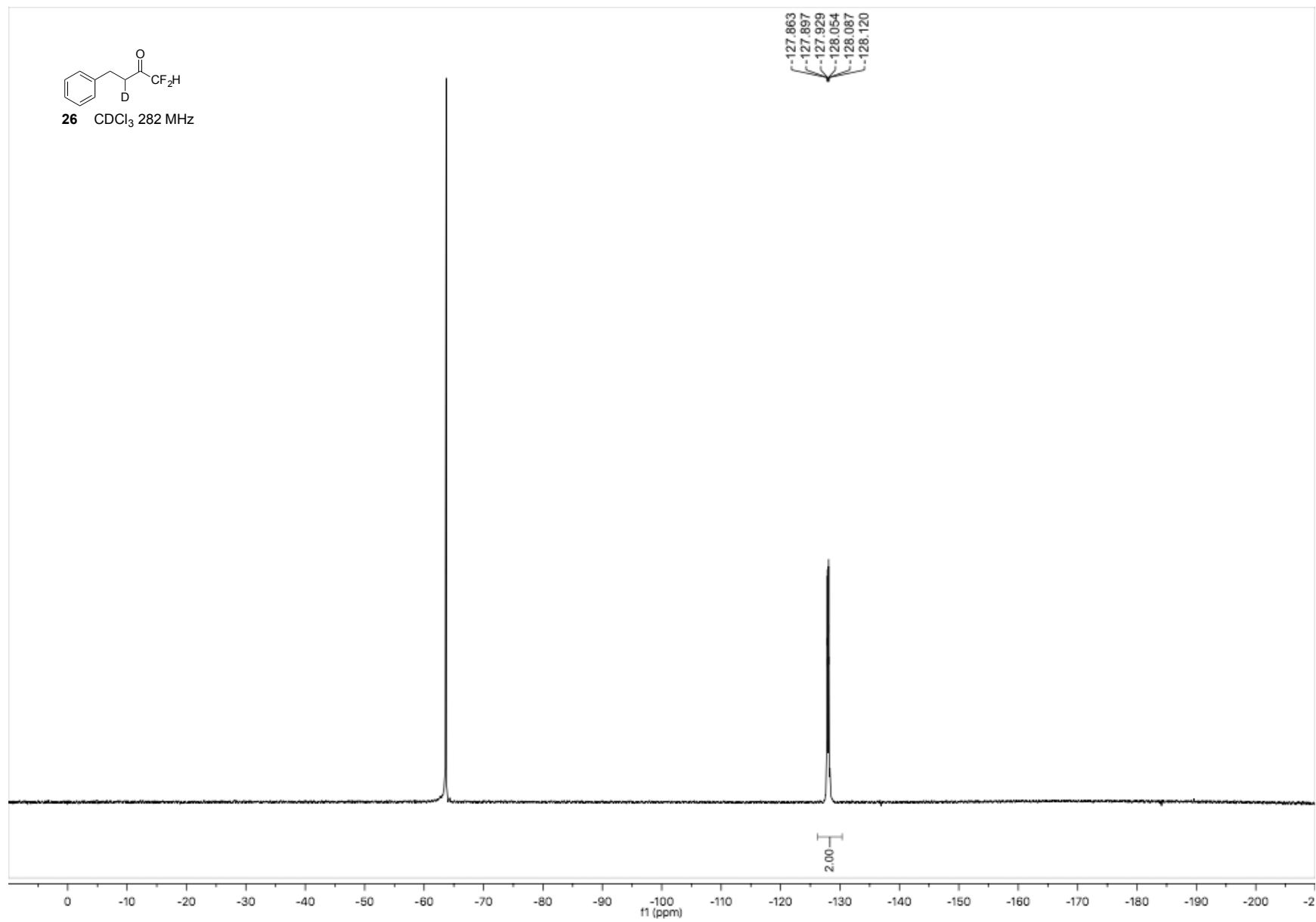
26 CDCl₃ 500 MHz

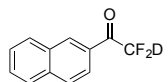






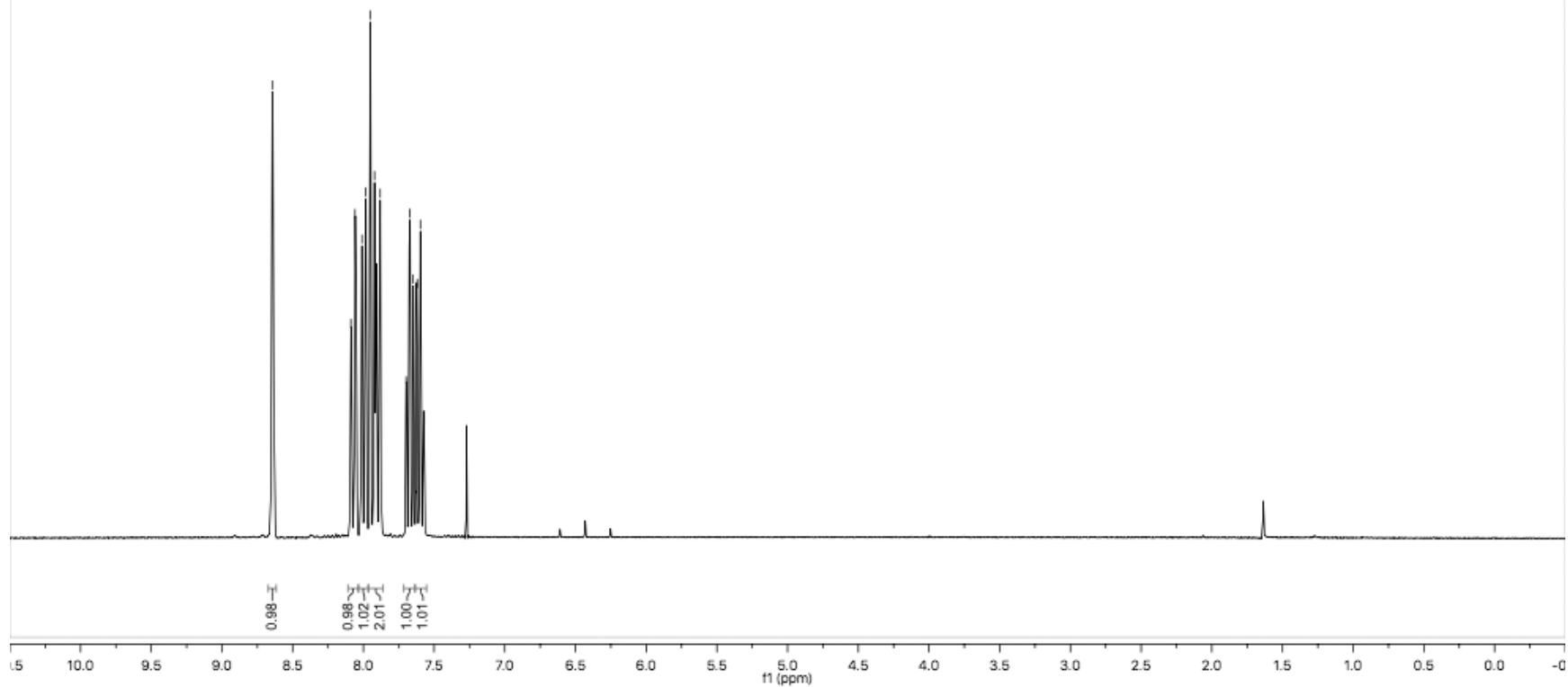
26 CDCl₃ 282 MHz

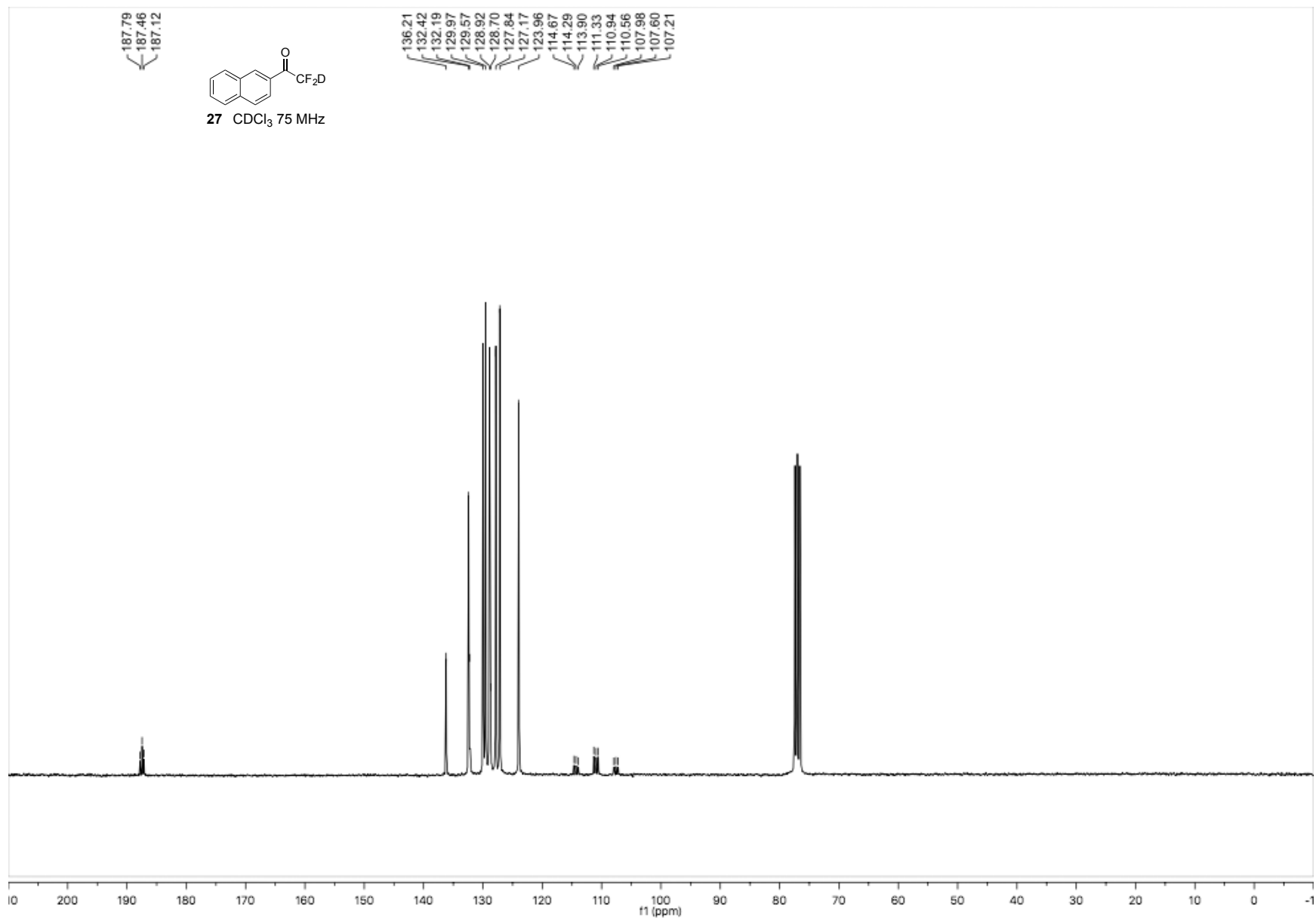


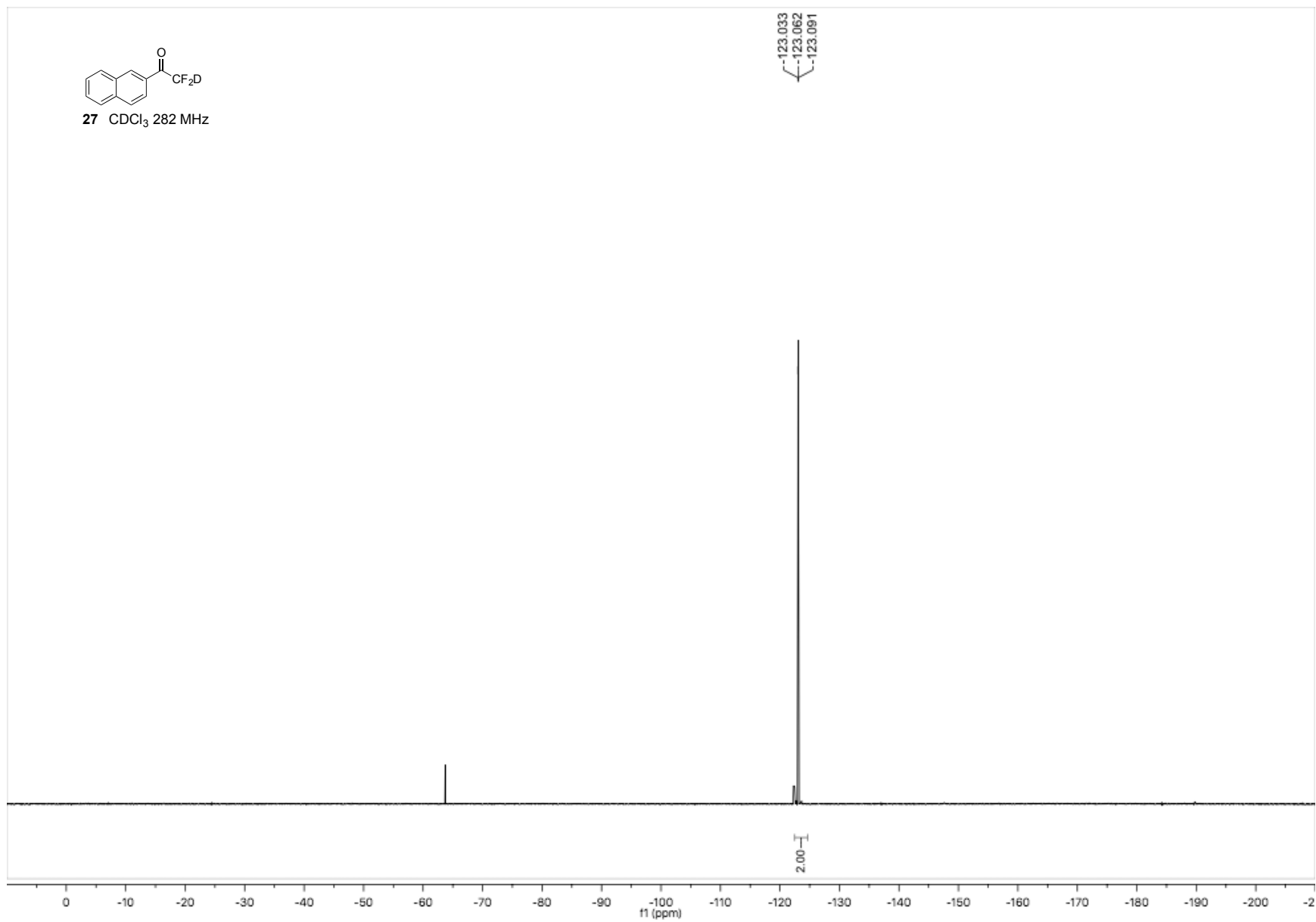
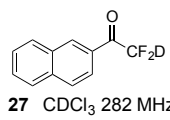


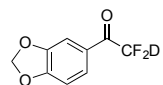
27 CDCl₃ 300 MHz

8.642
8.088
8.059
8.010
7.983
7.950
7.921
7.881
7.698
7.670
7.648
7.619
7.597
7.570

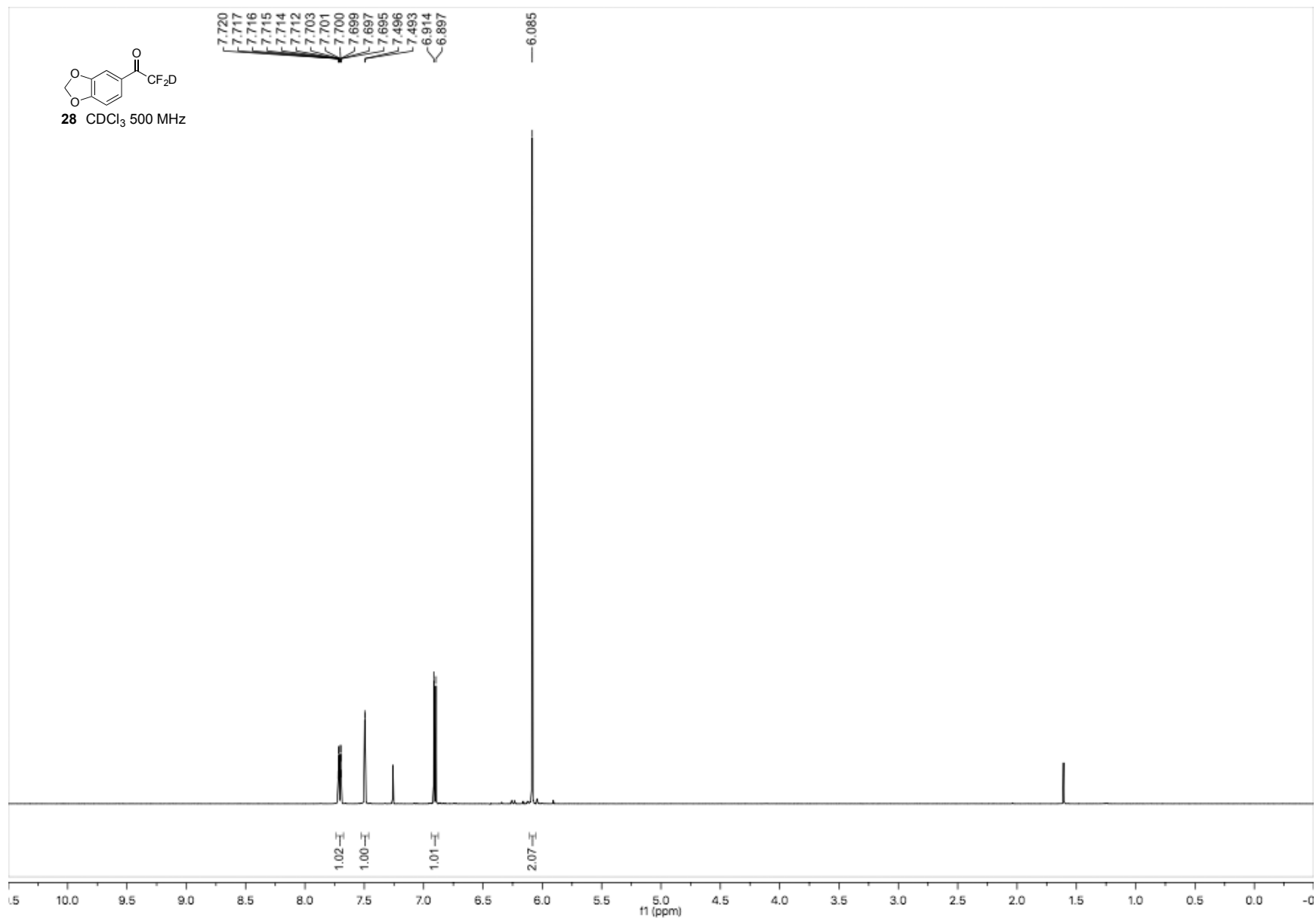


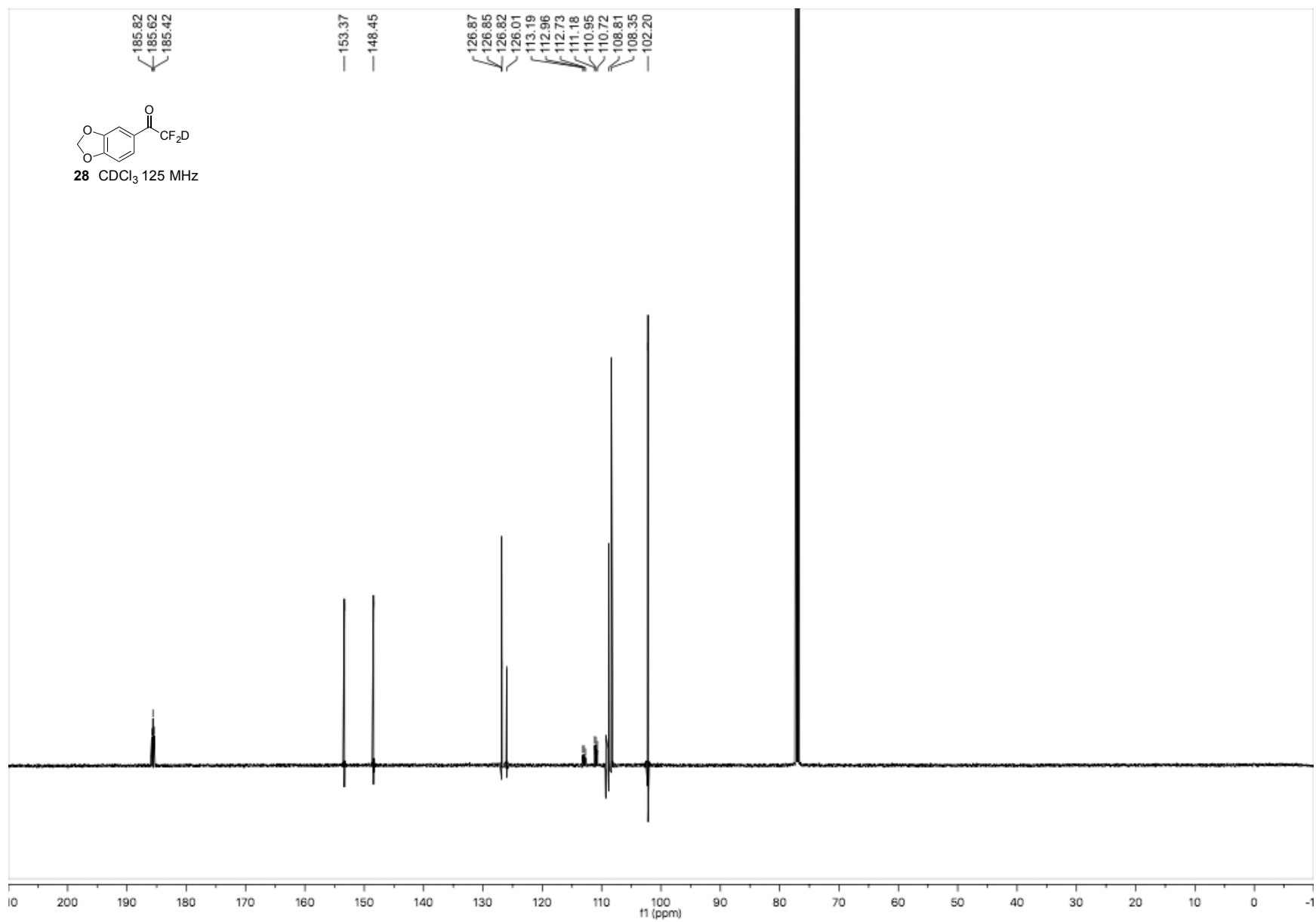


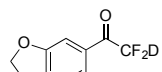




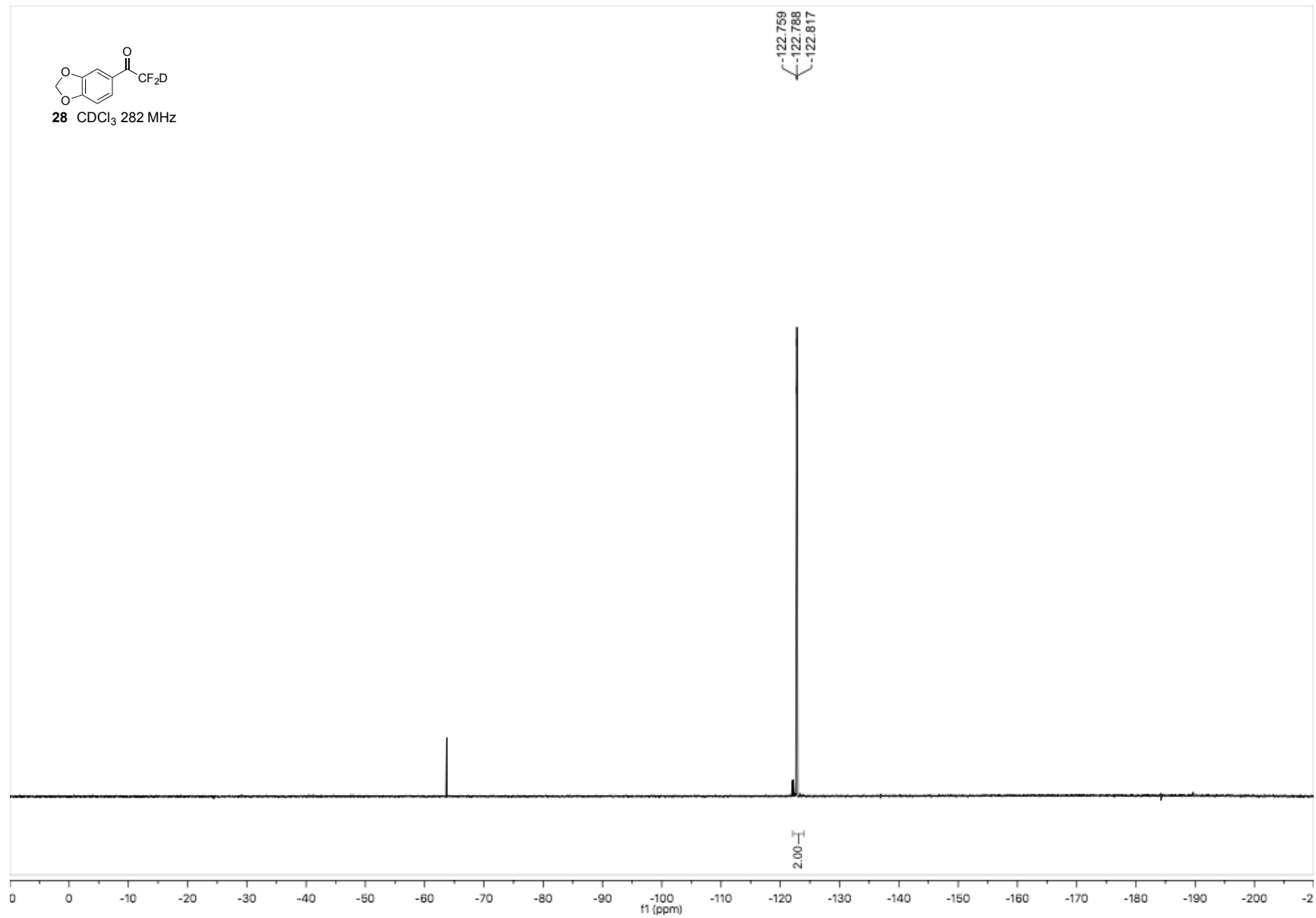
28 CDCl₃ 500 MHz

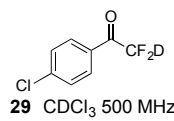






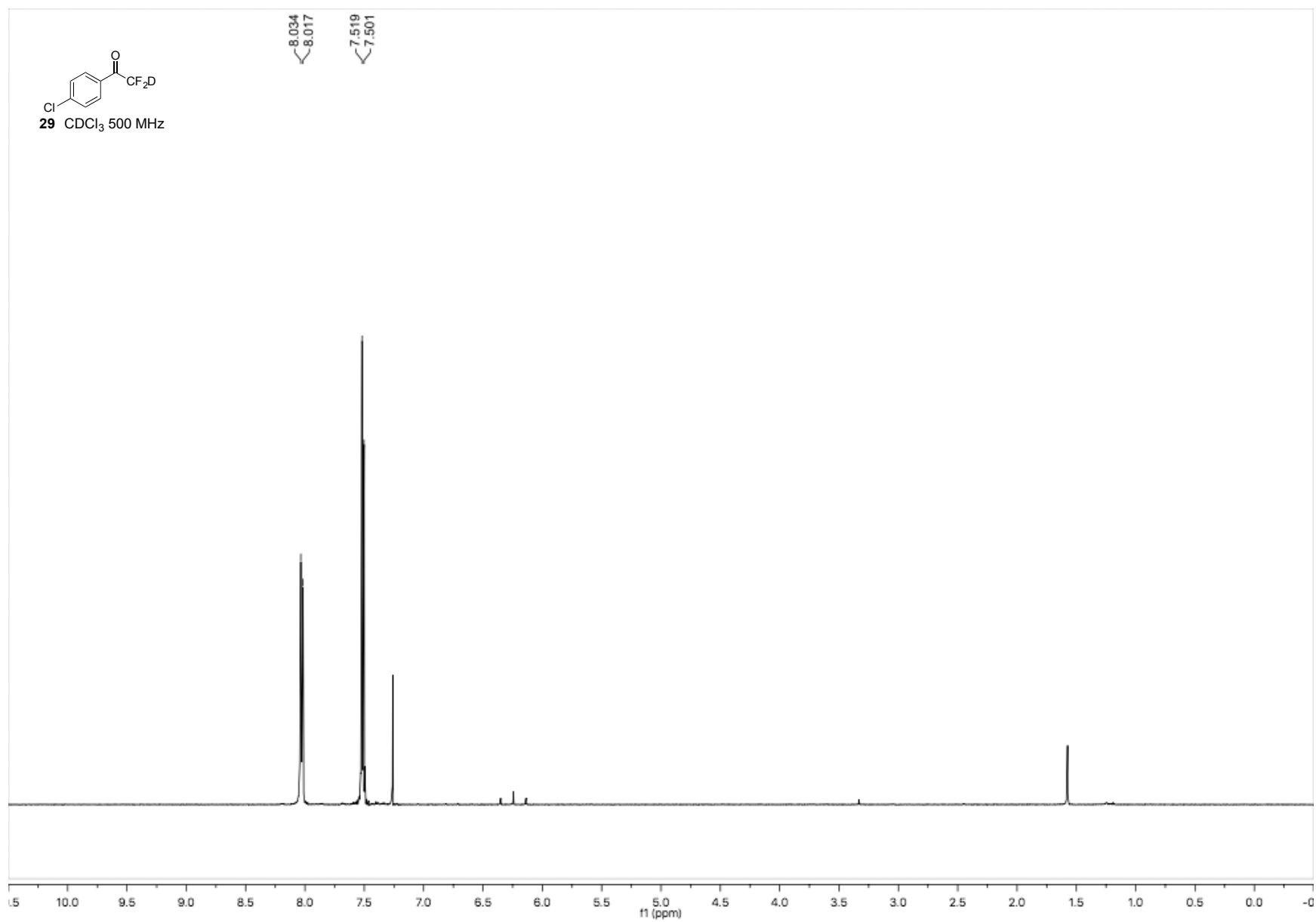
28 CDCl₃ 282 MHz

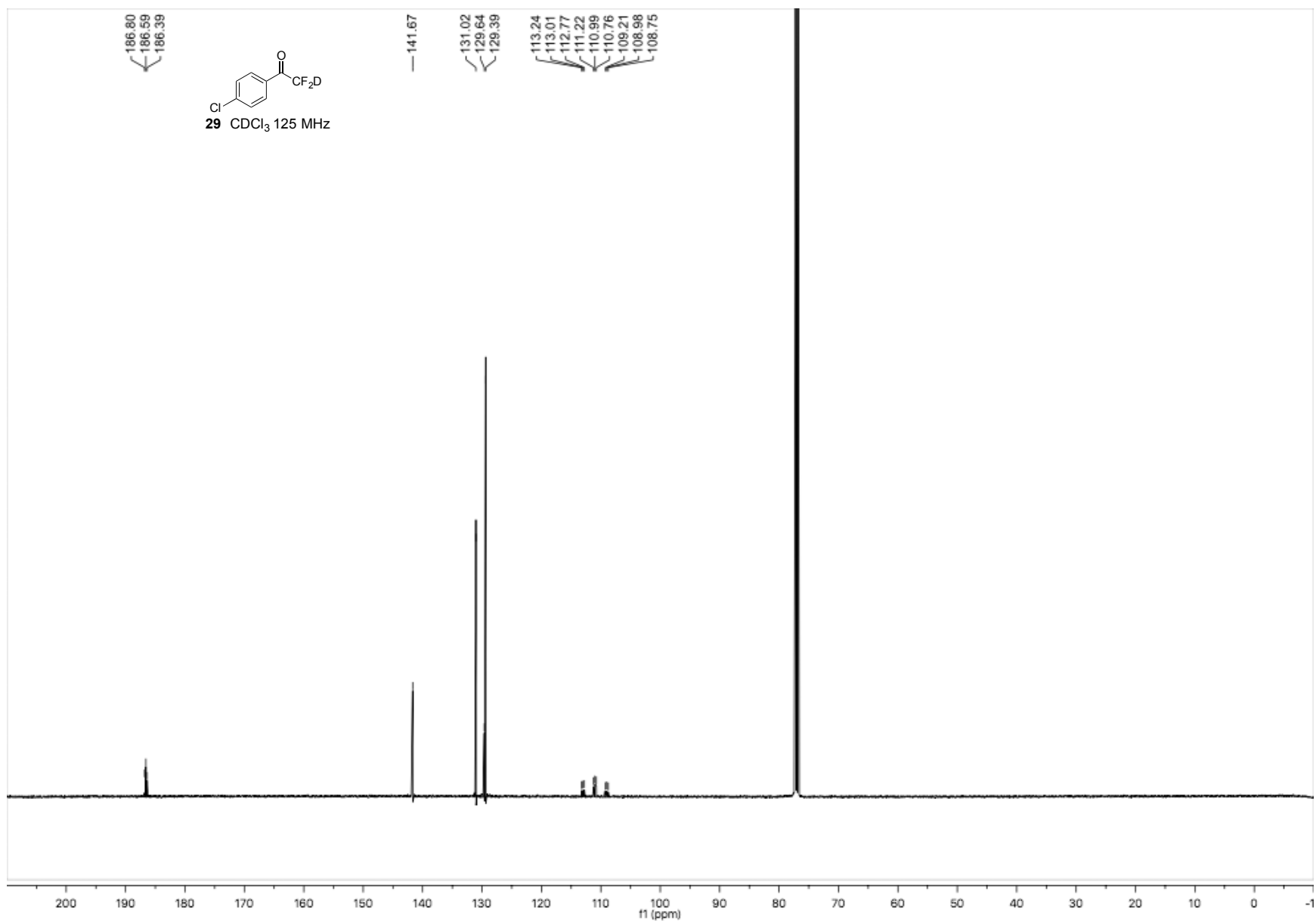


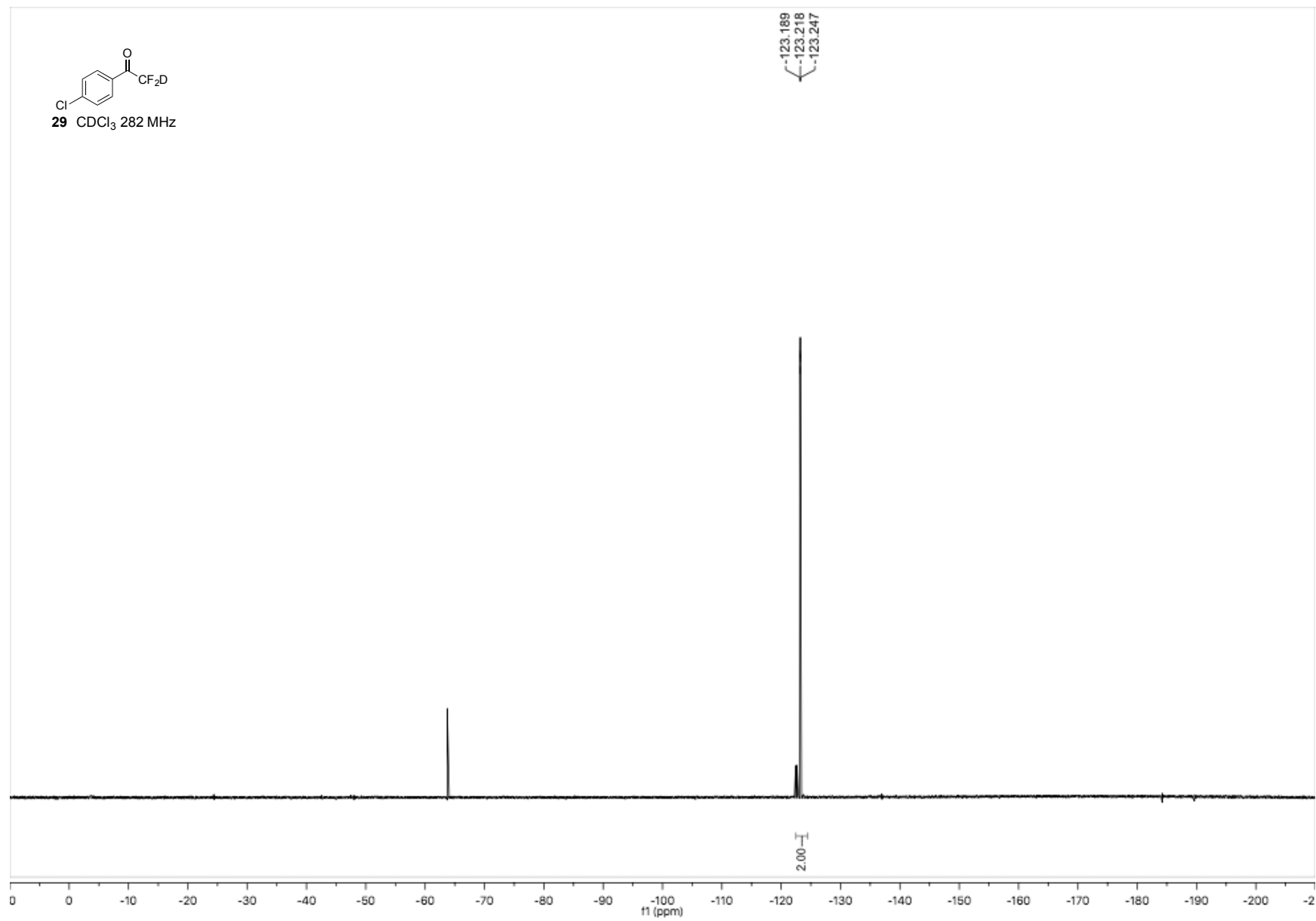
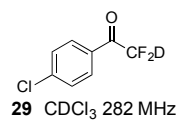


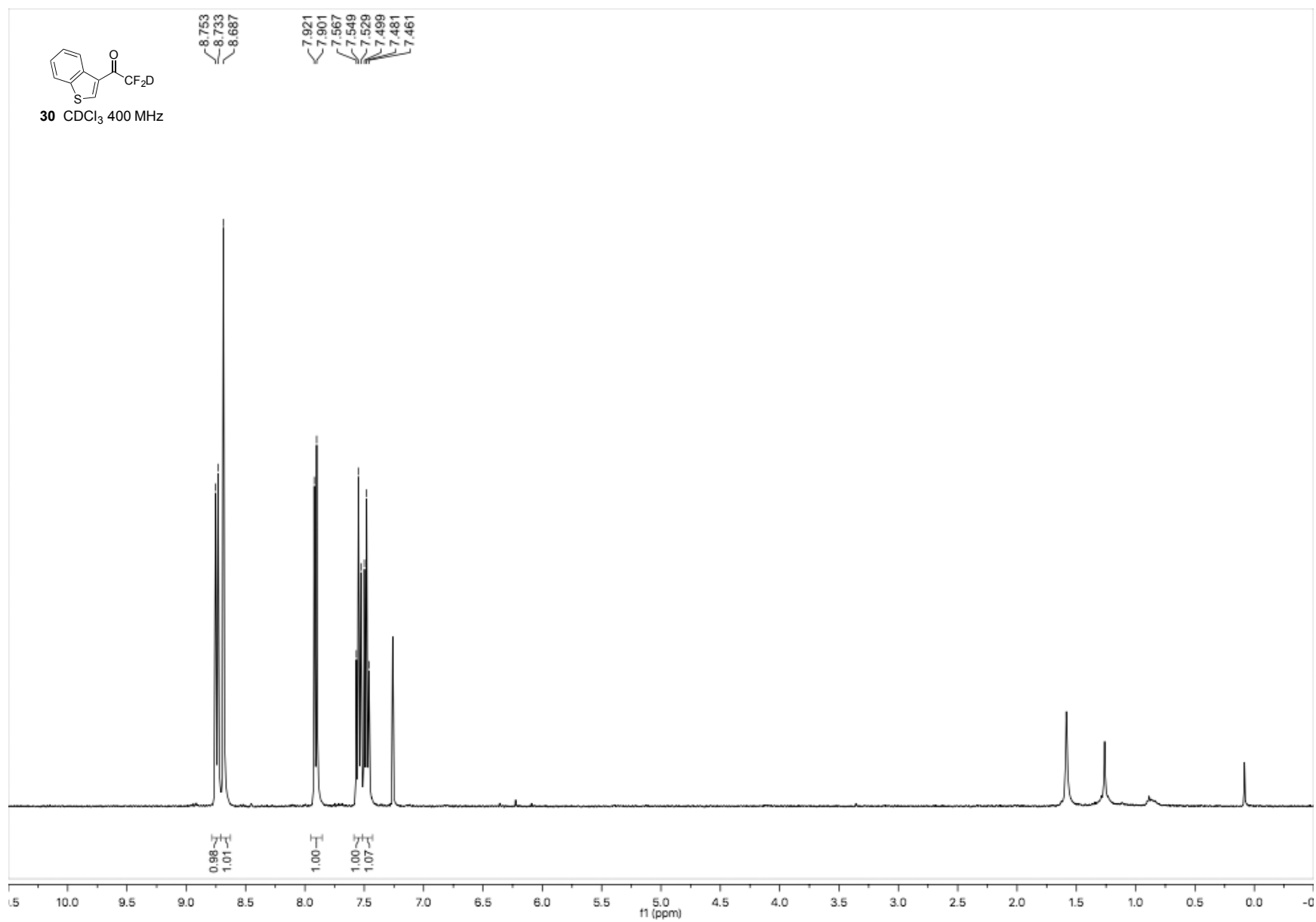
8.034
8.017

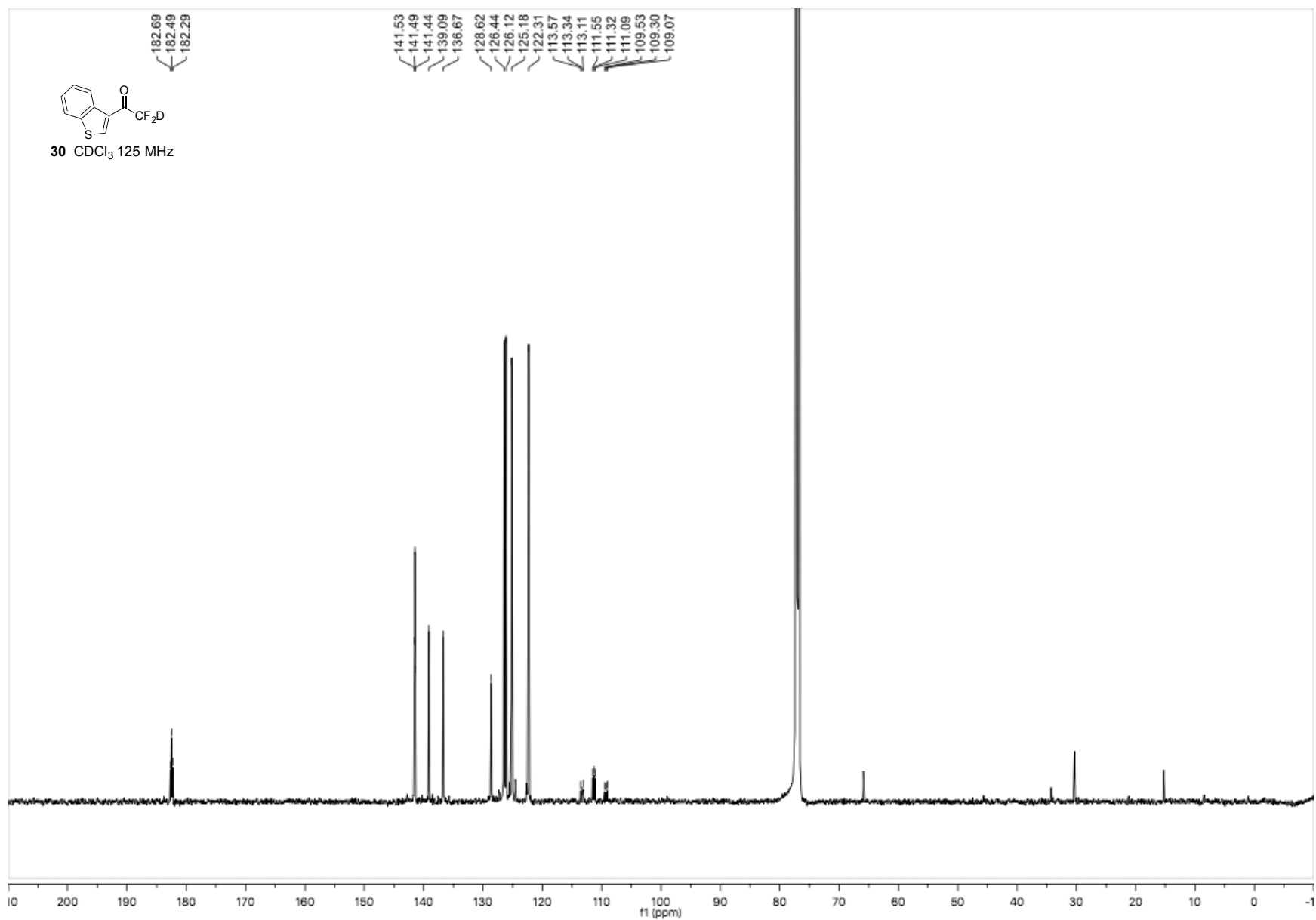
7.519
7.501

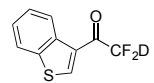






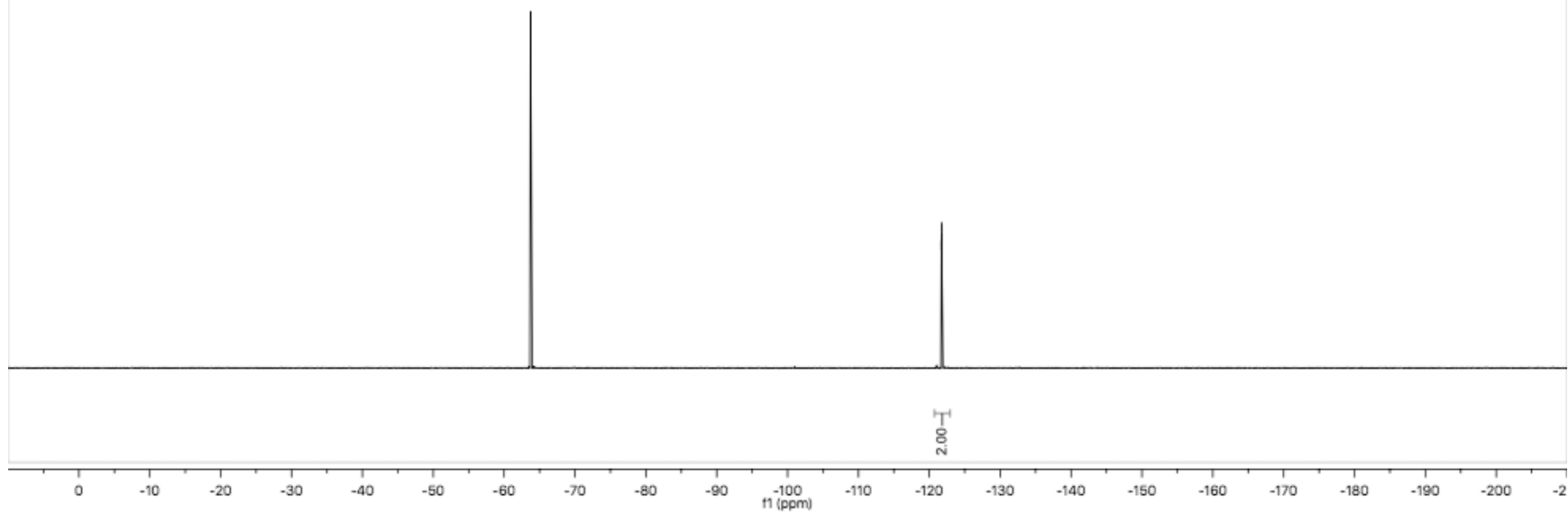


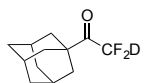




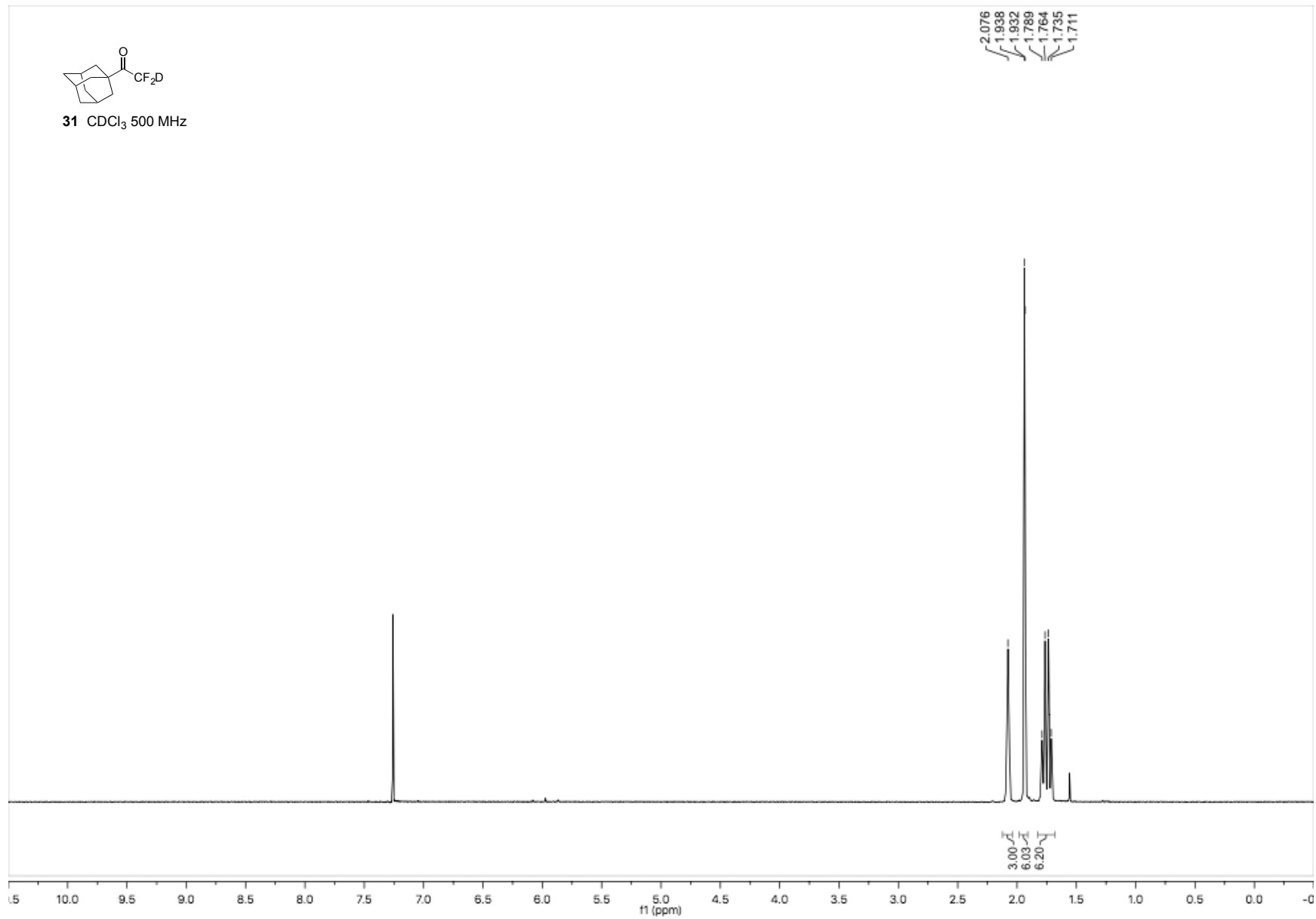
30 CDCl₃ 376 MHz

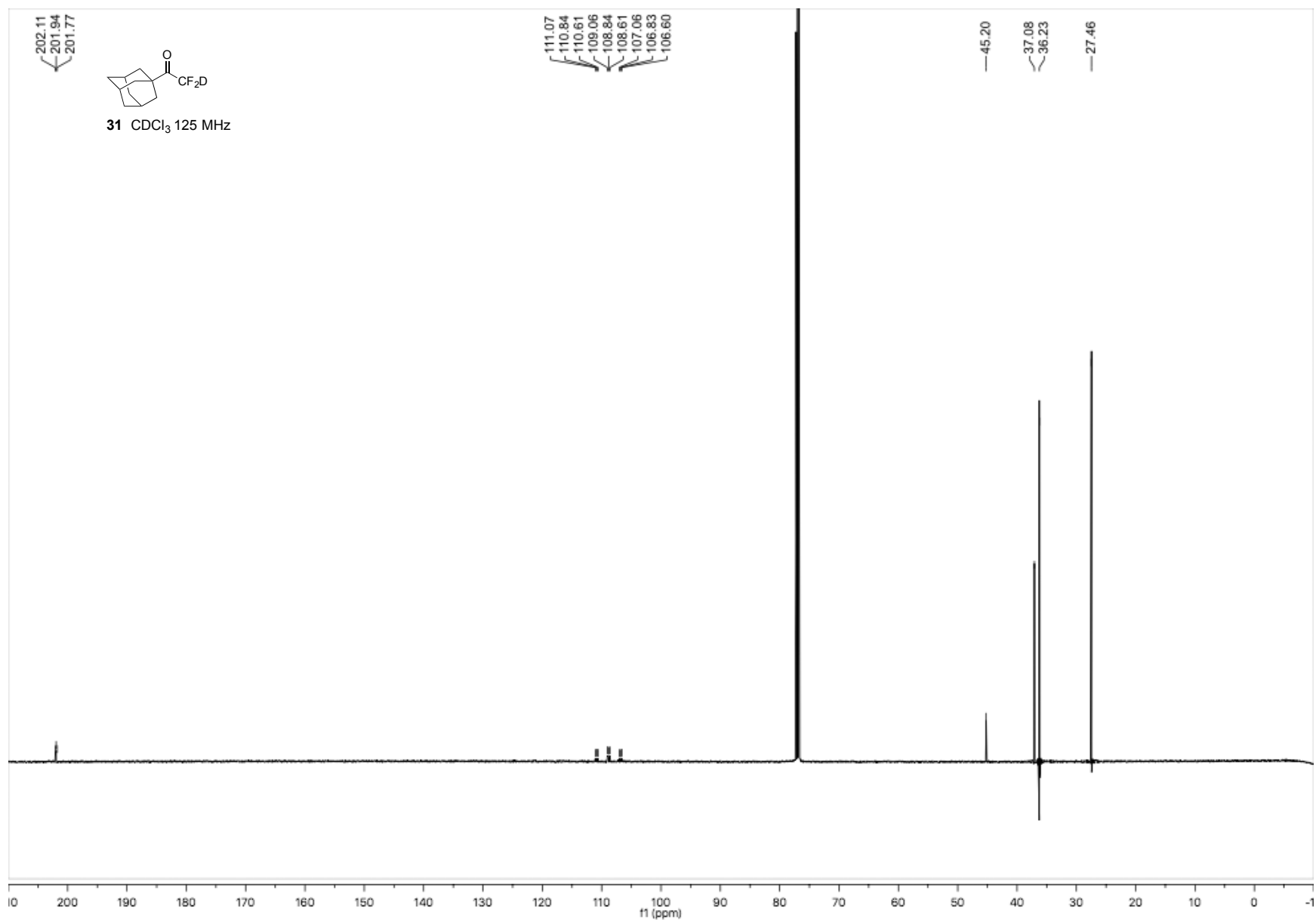
-121.700
-121.722
-121.744

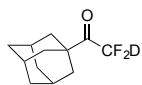




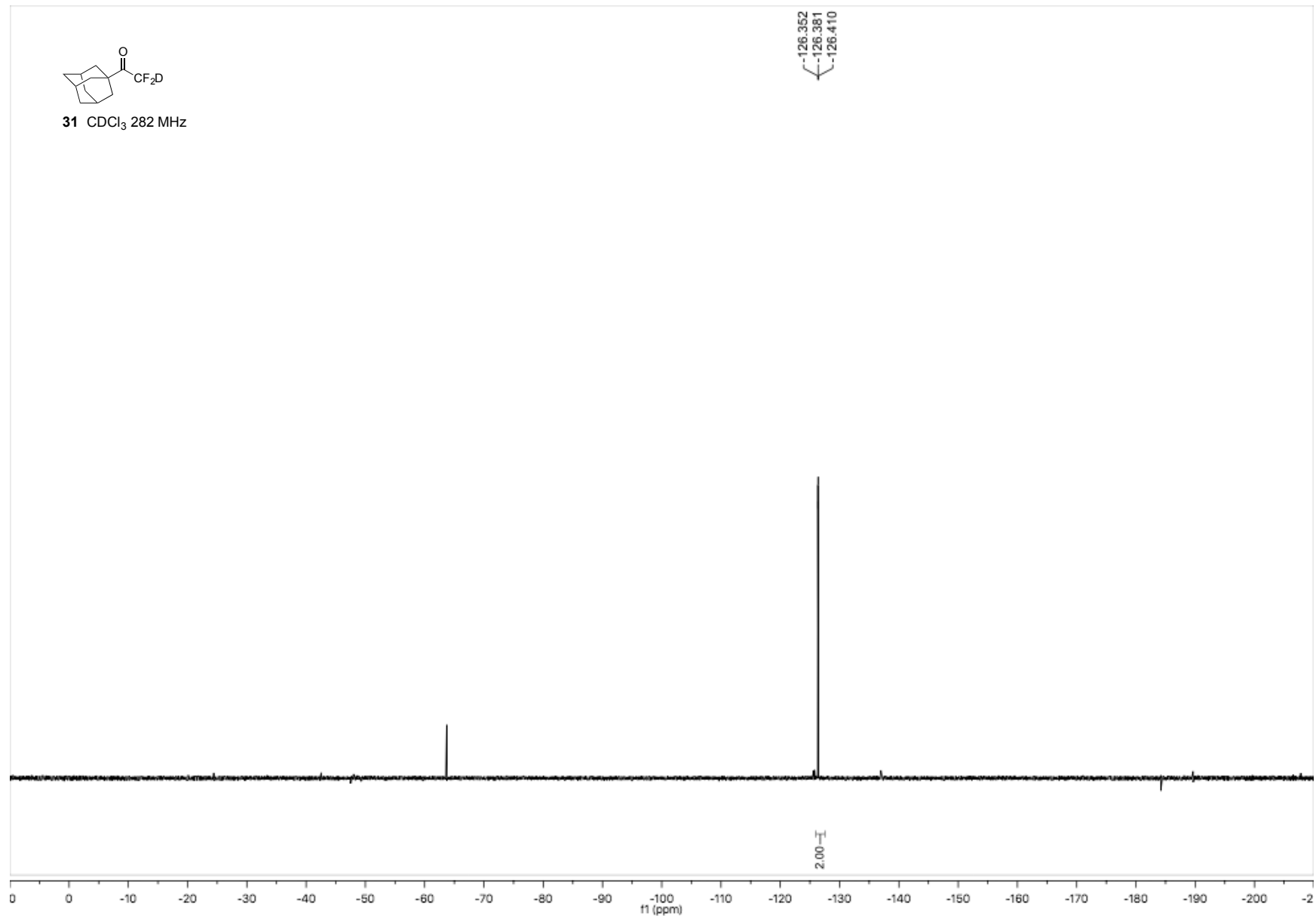
31 CDCl₃ 500 MHz

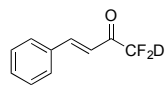






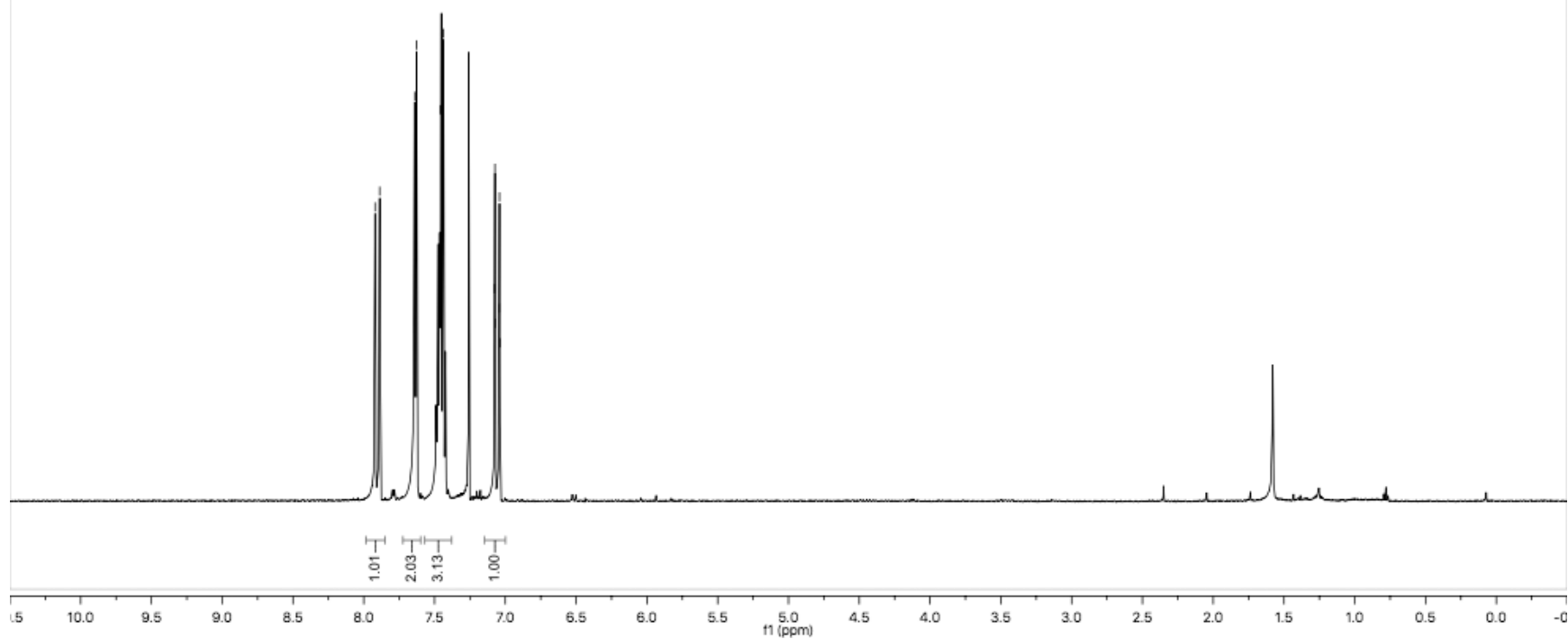
31 CDCl₃ 282 MHz

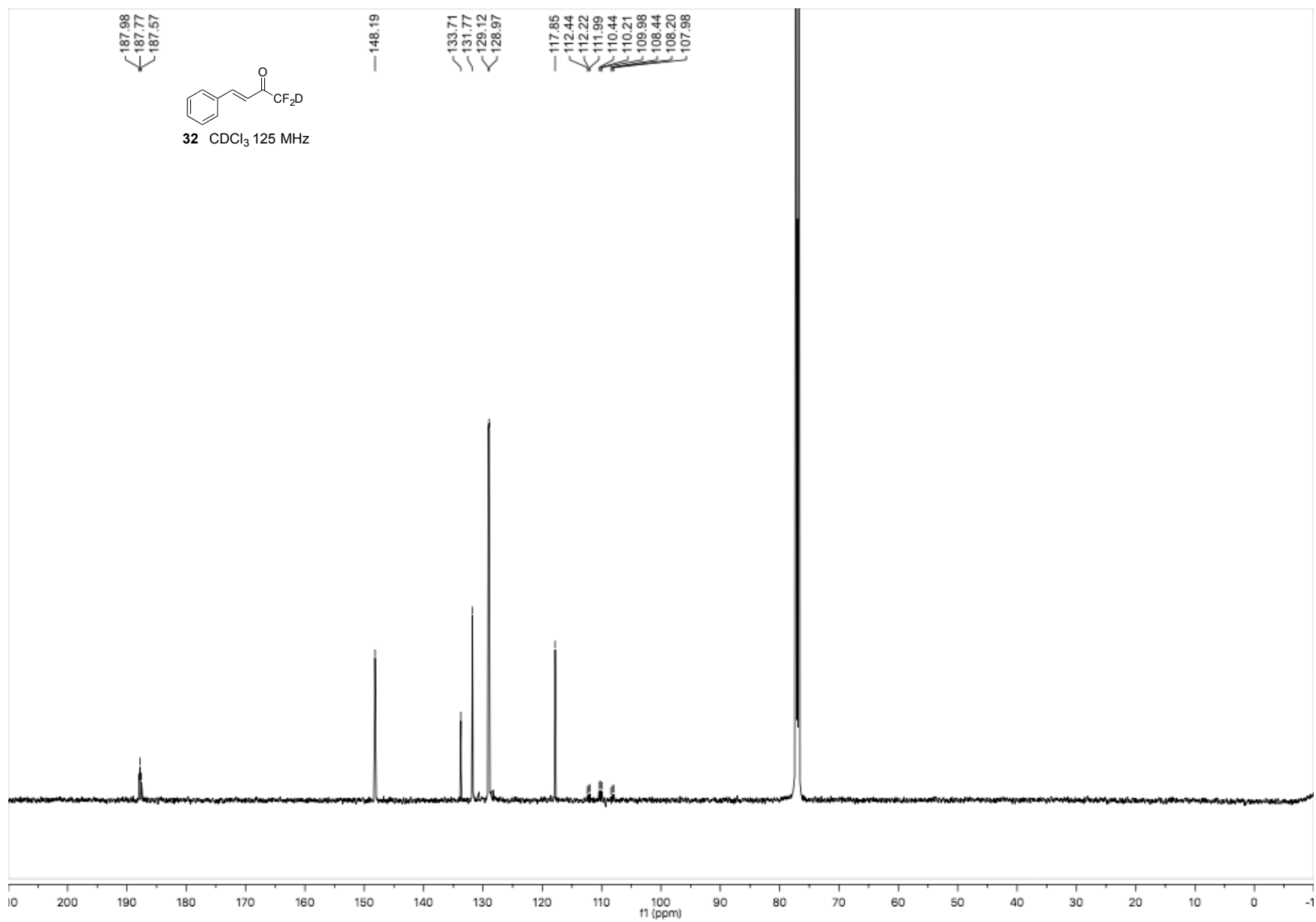


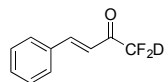


32 CDCl₃ 500 MHz

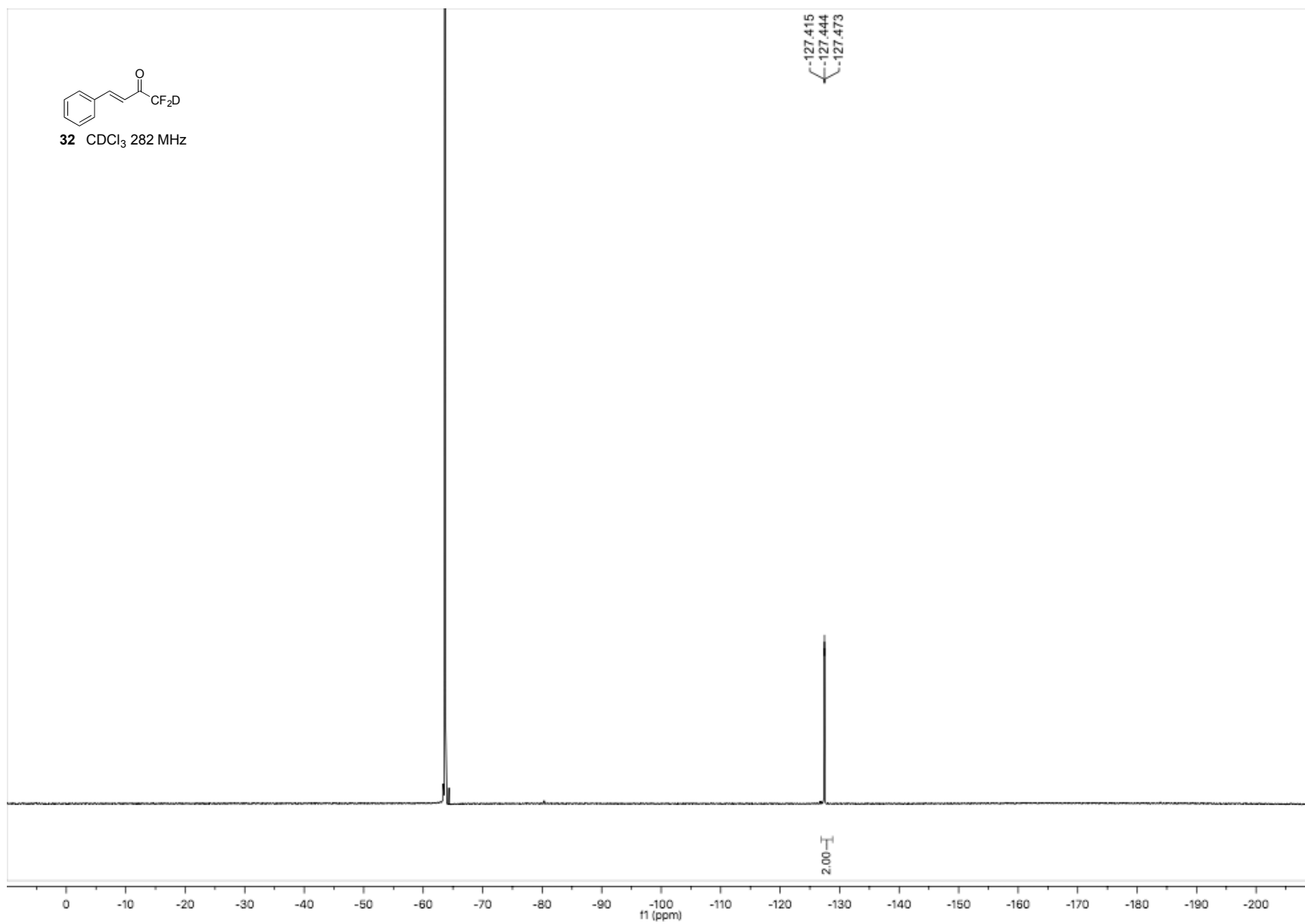
7.920
7.888
7.641
7.627
7.461
7.437
7.076
7.074
7.071
7.044
7.041
7.039

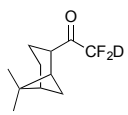




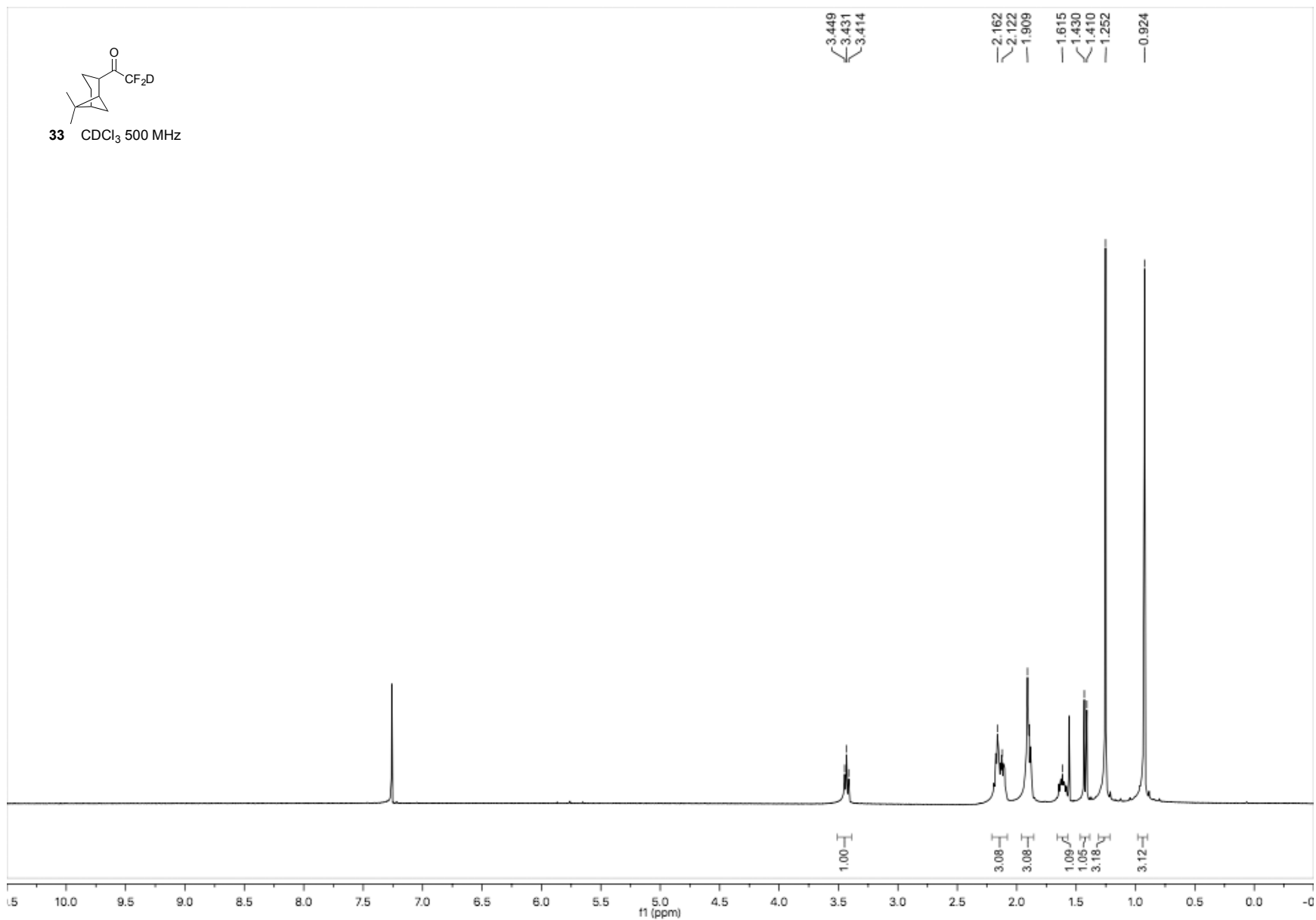


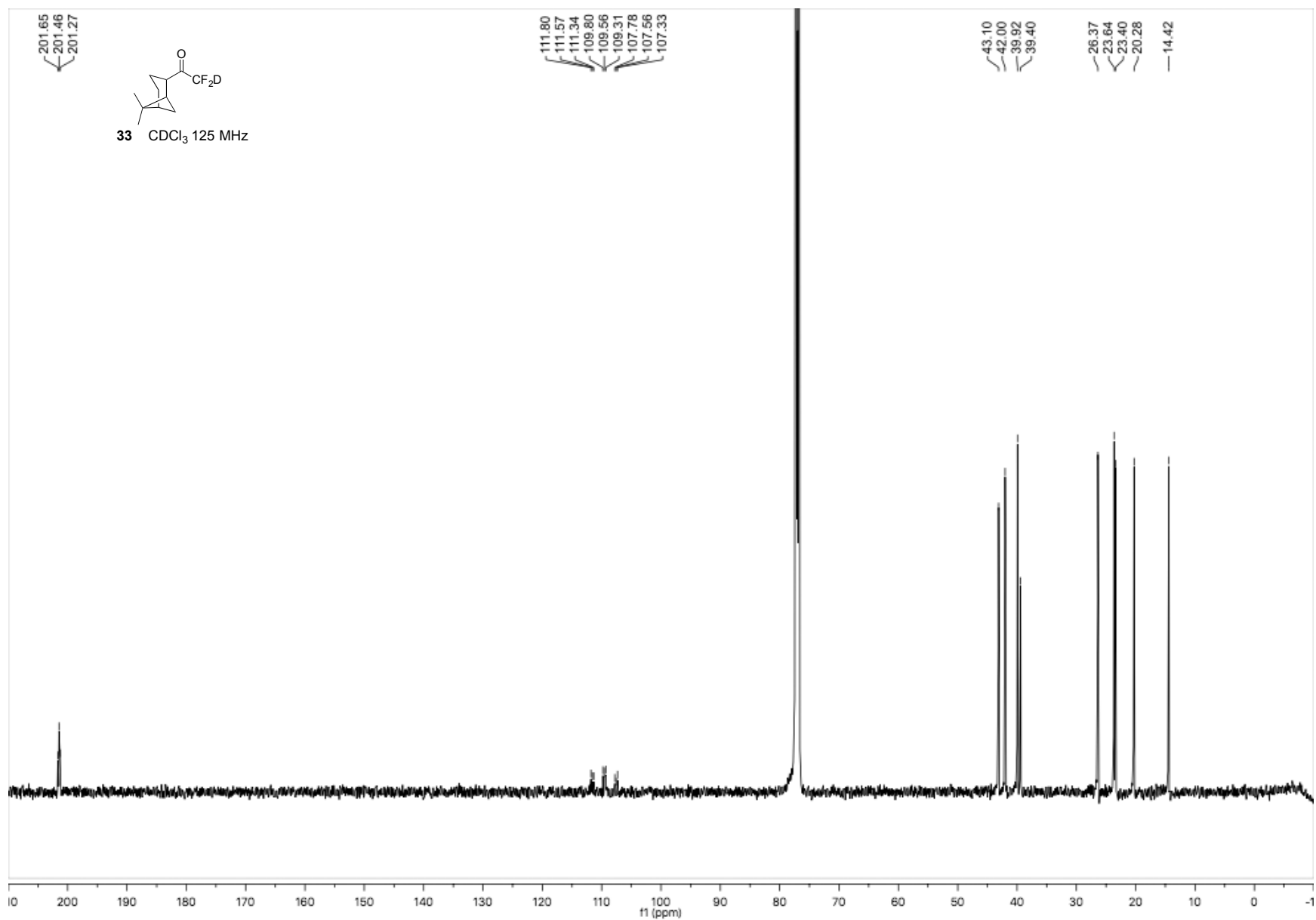
32 CDCl₃ 282 MHz

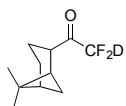




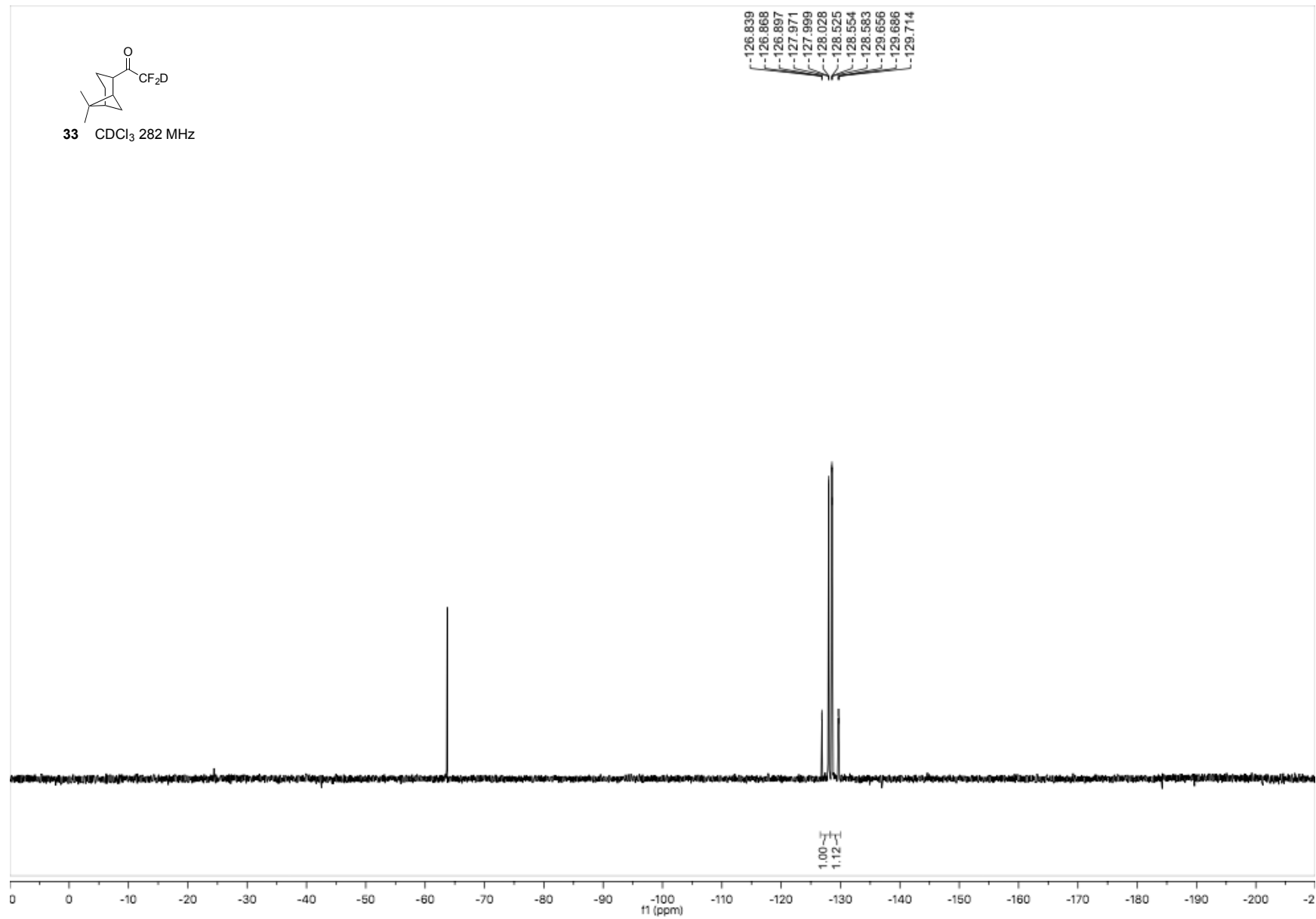
33 CDCl₃ 500 MHz

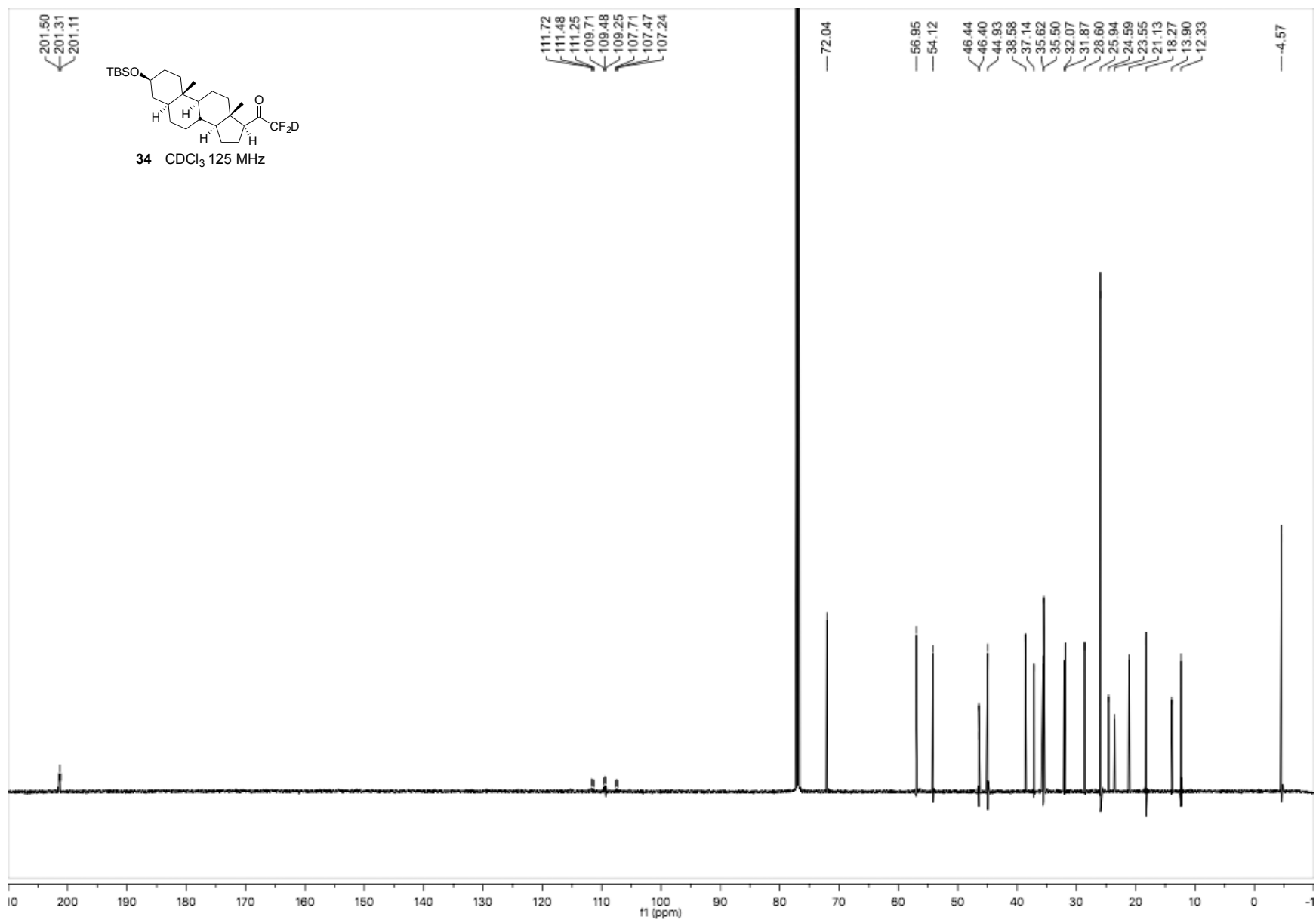


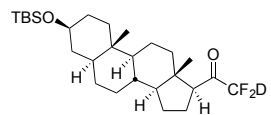




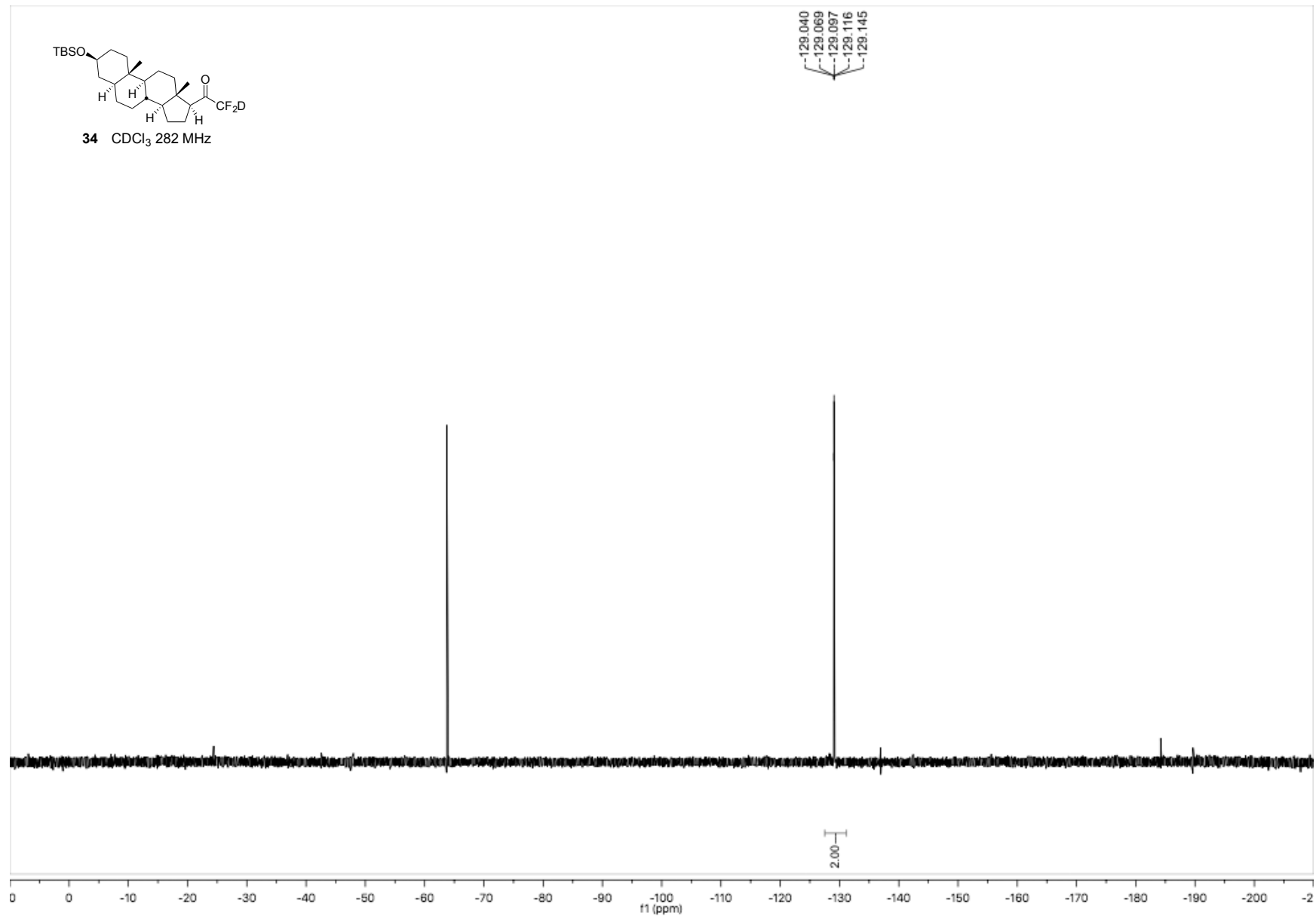
33 CDCl₃ 282 MHz

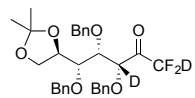




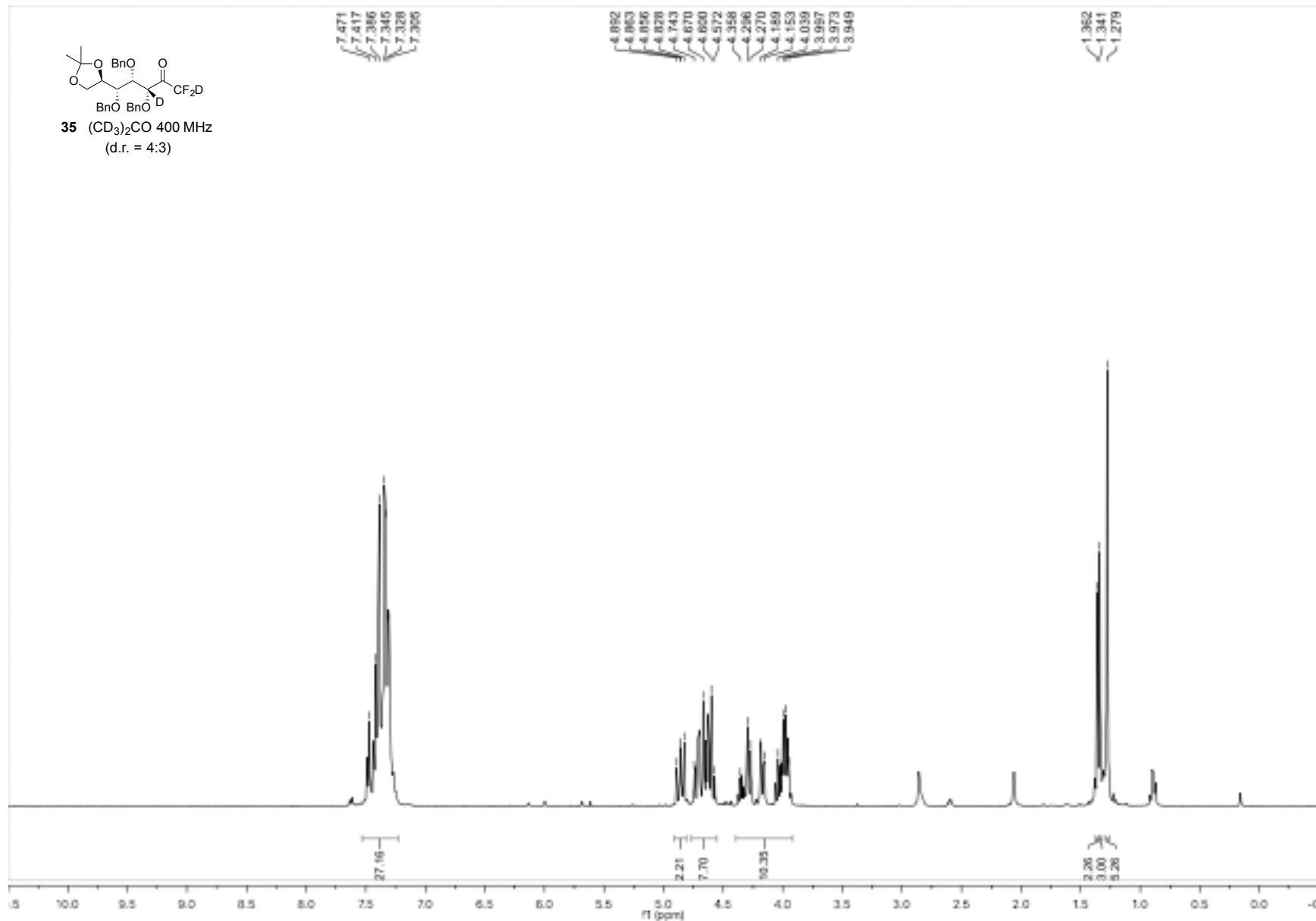


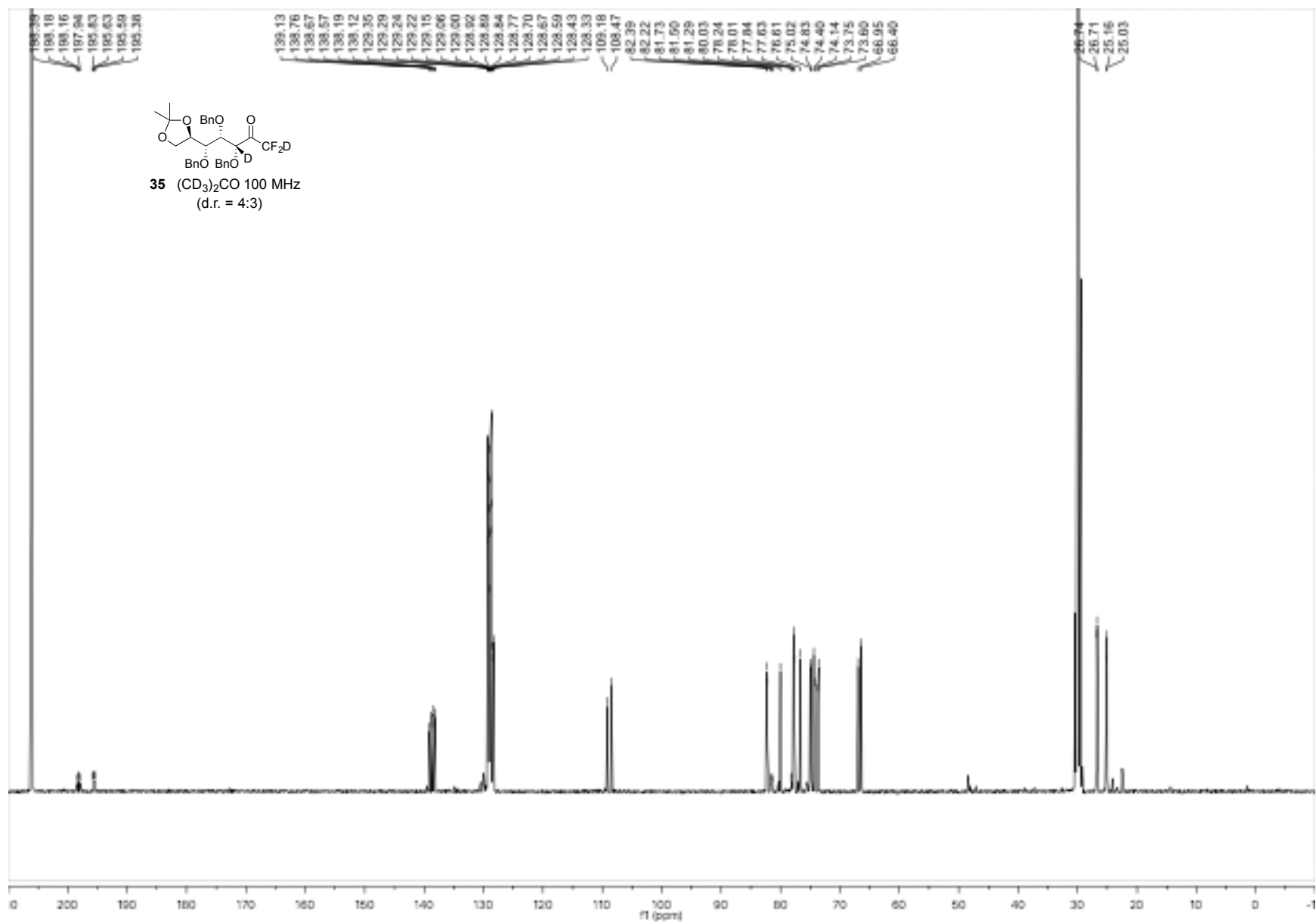
34 CDCl₃ 282 MHz

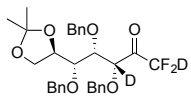




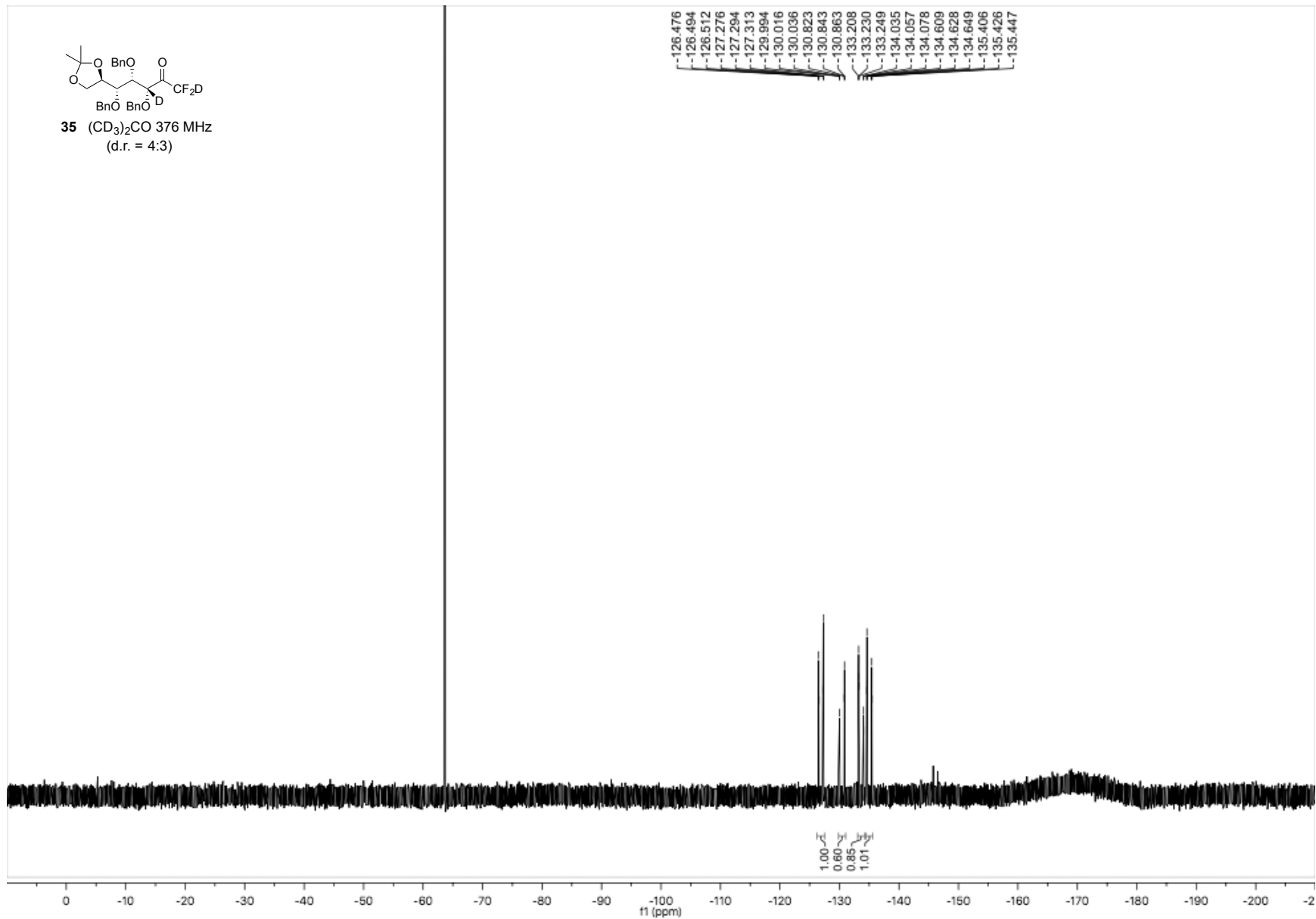
35 (CD₃)₂CO 400 MHz
(d.r. = 4:3)

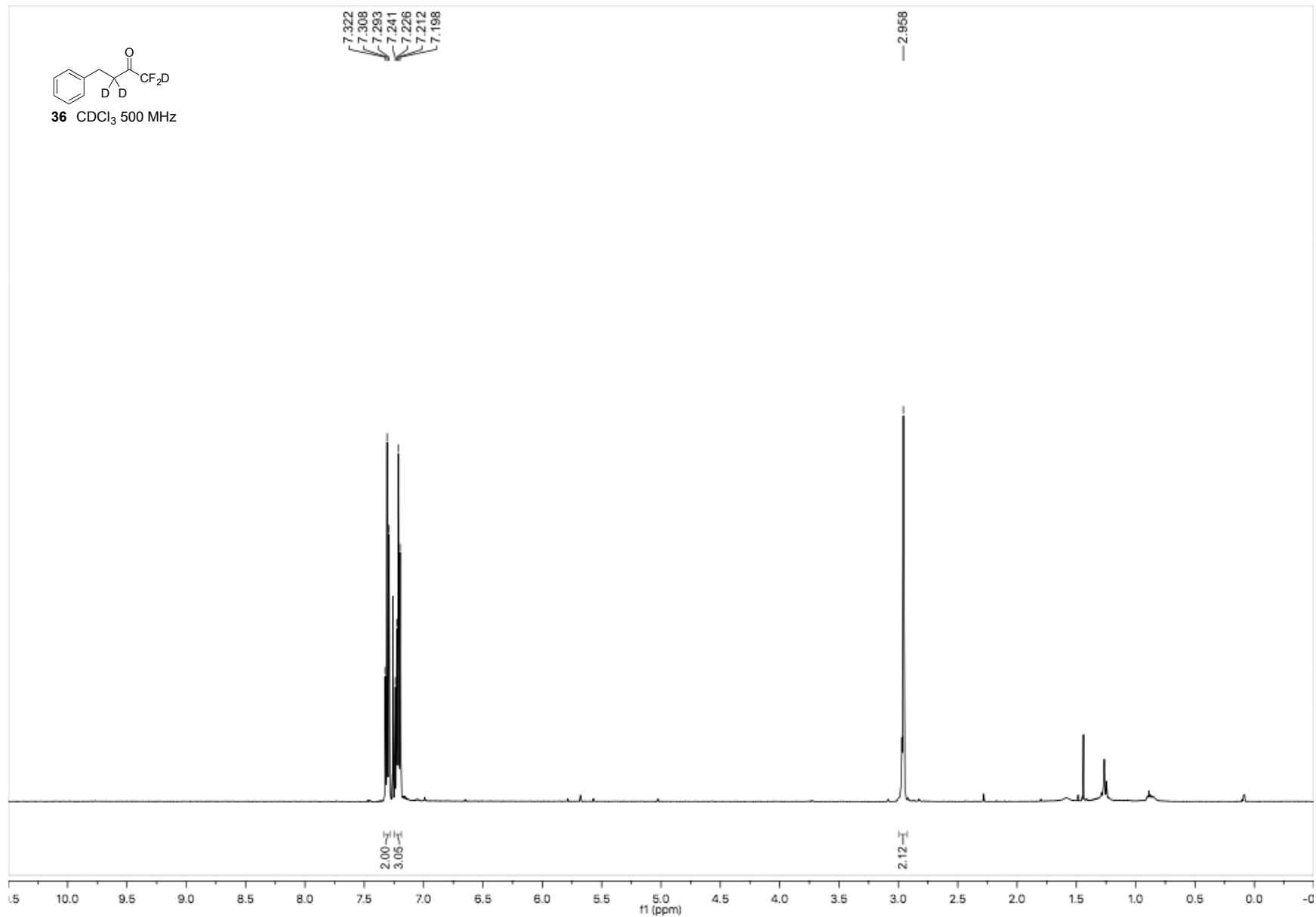
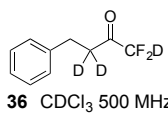


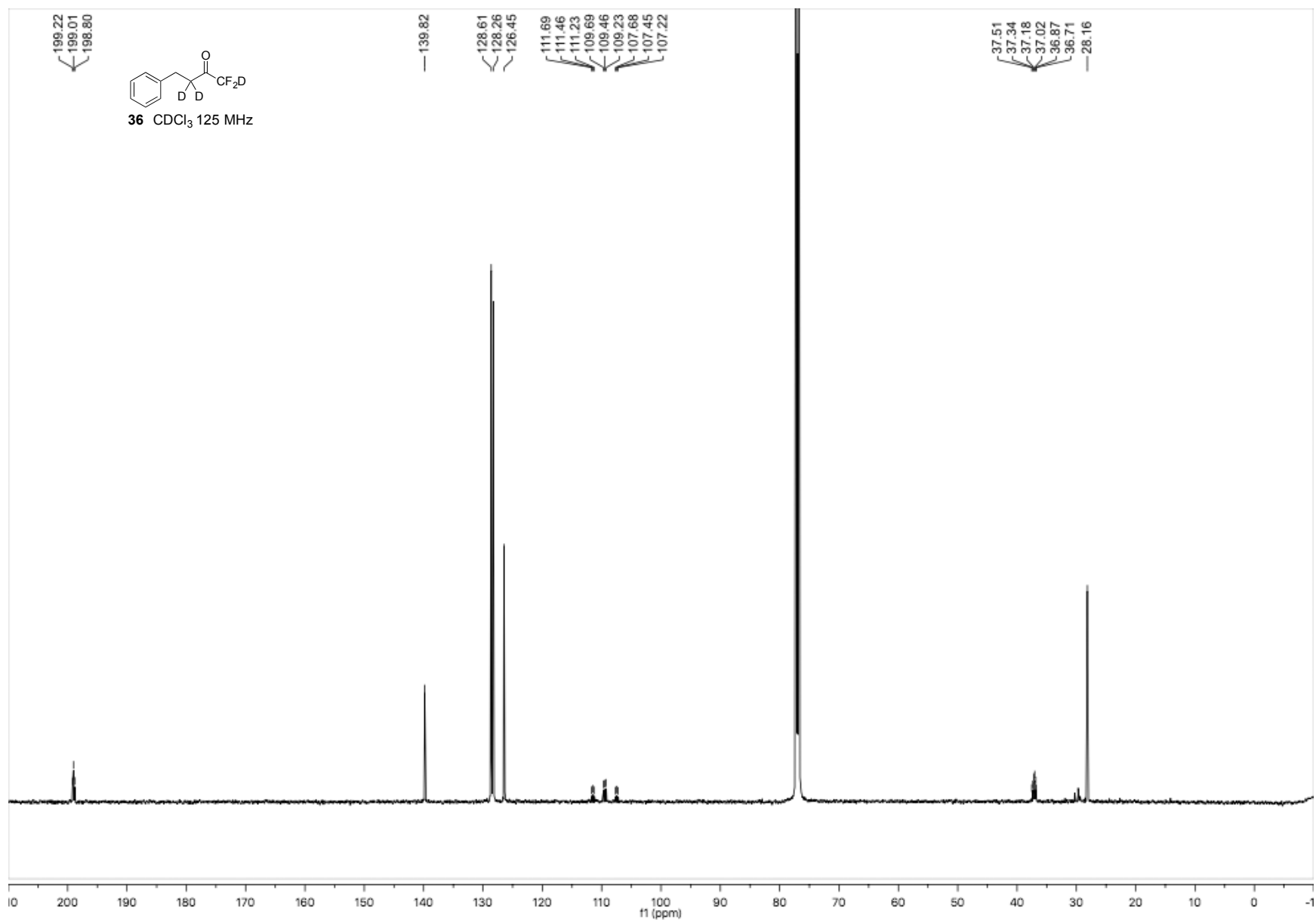


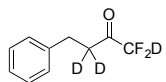


35 (CD₃)₂CO 376 MHz
(d.r. = 4:3)

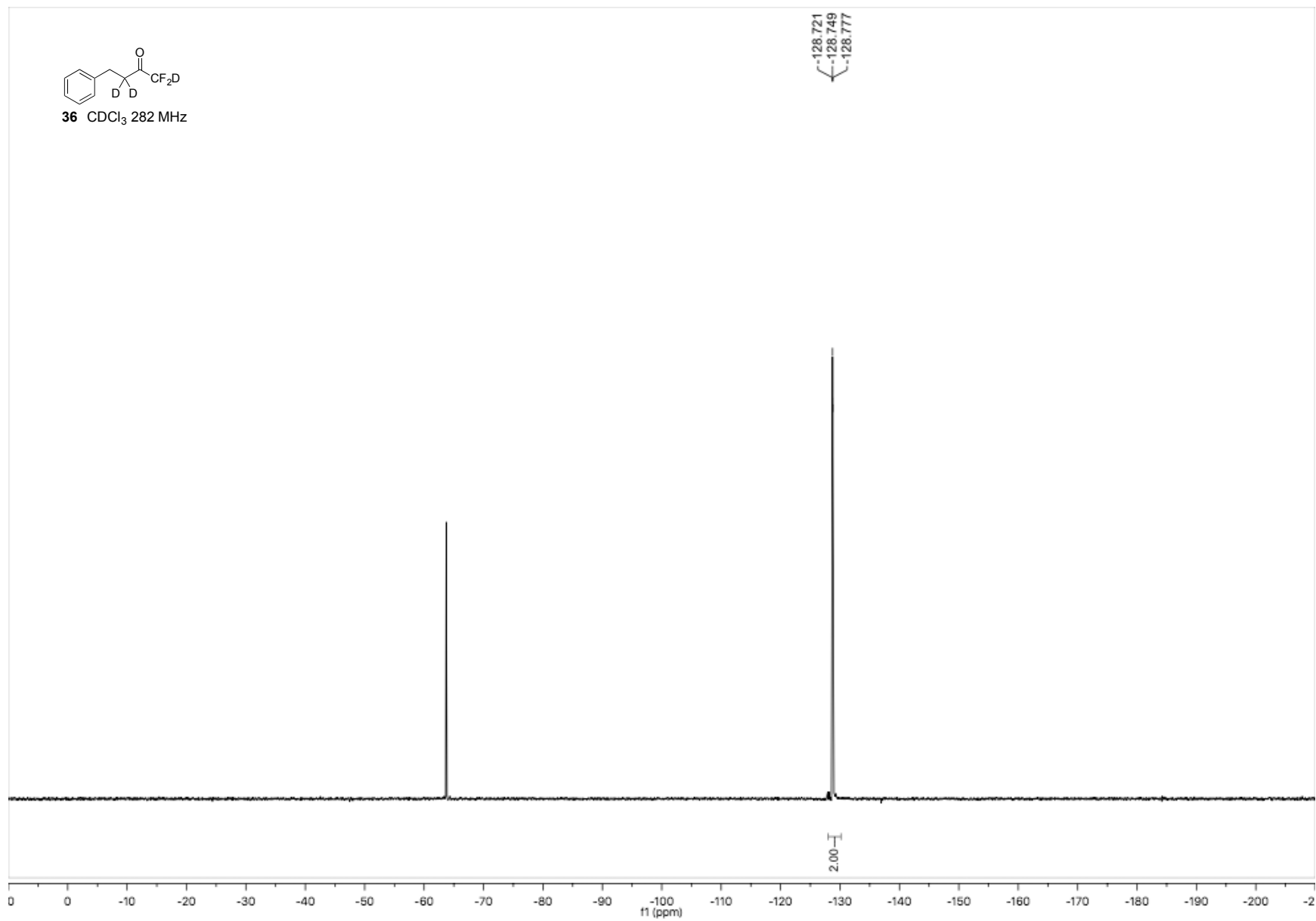


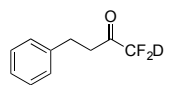




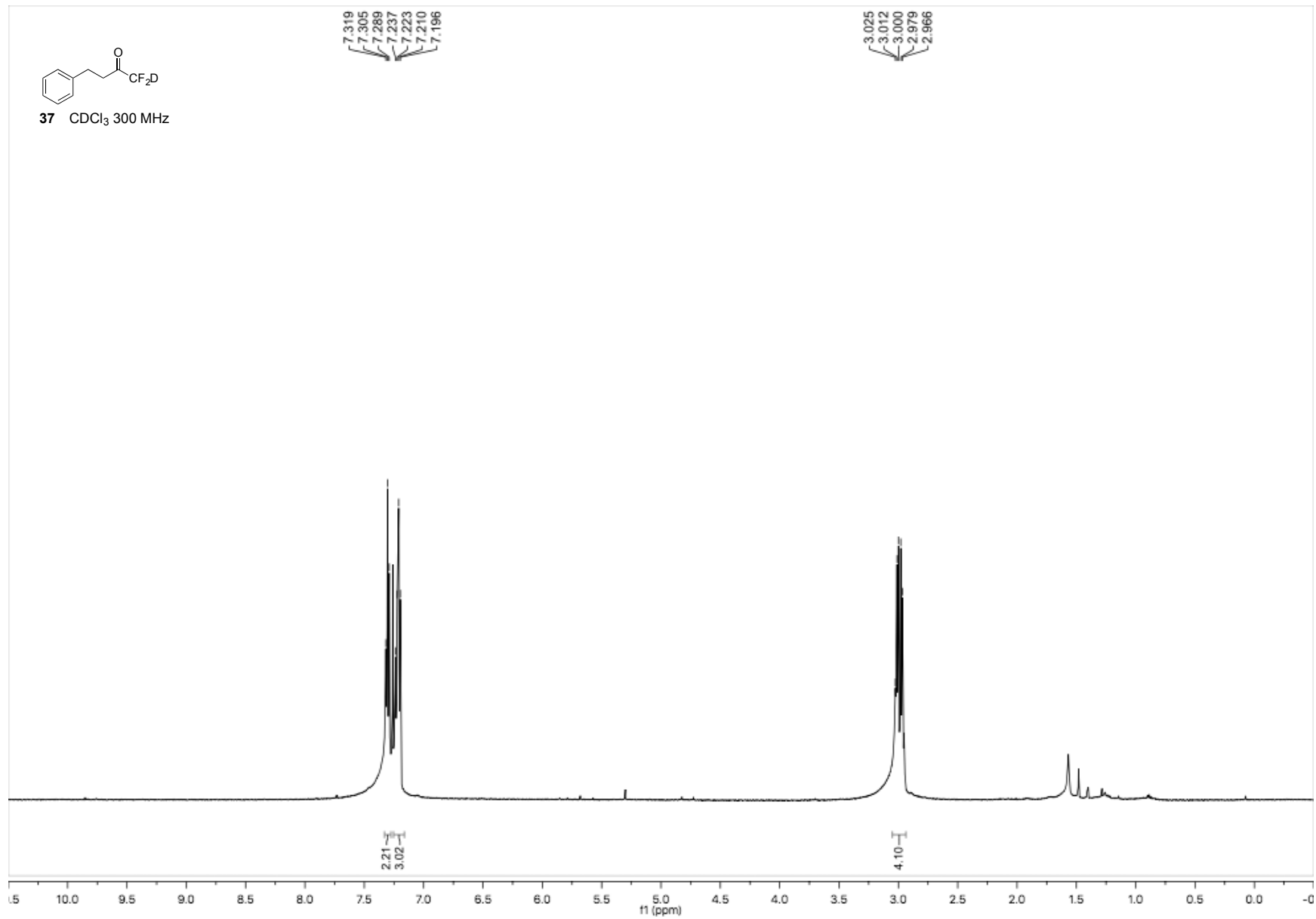


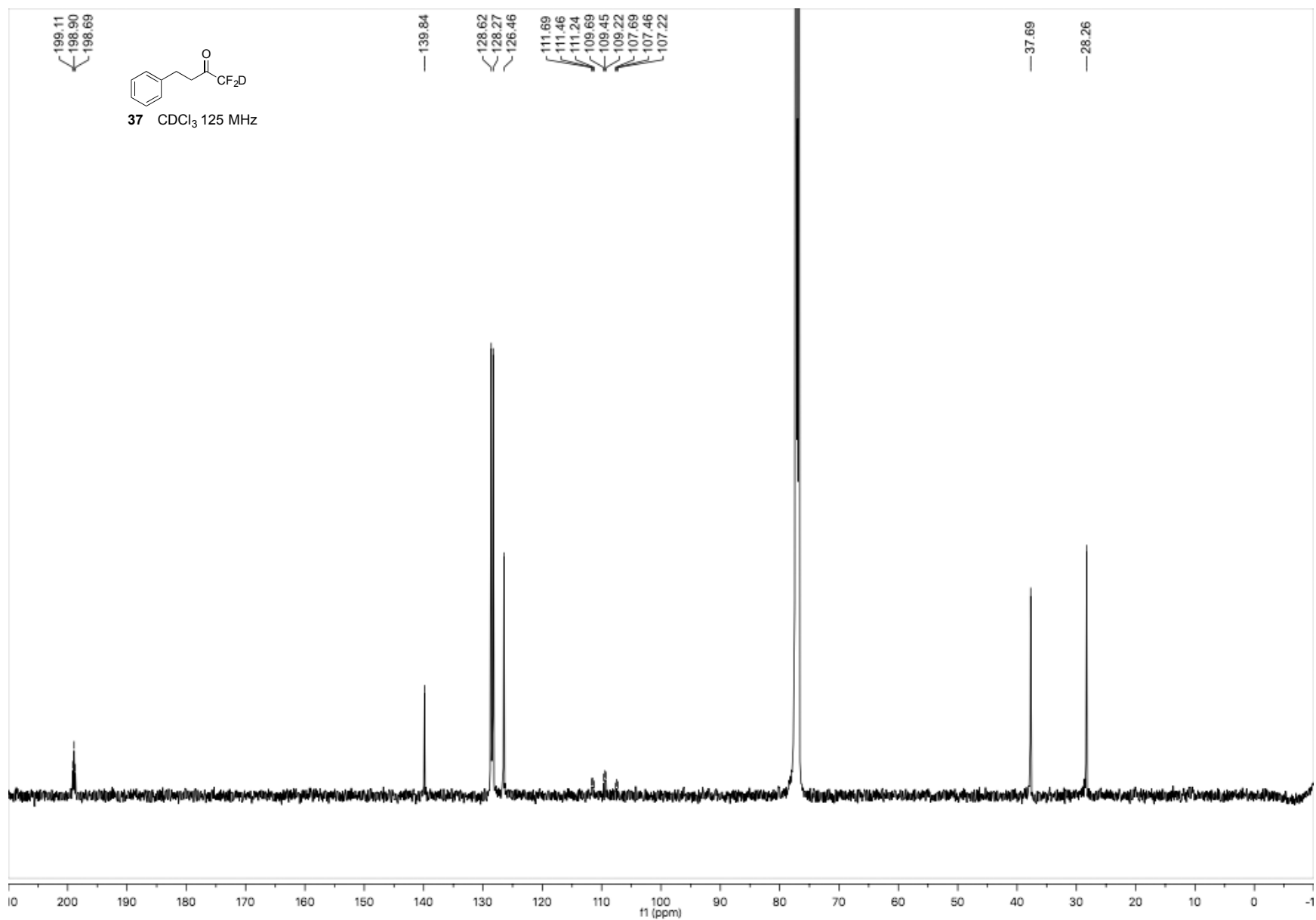
36 CDCl₃ 282 MHz

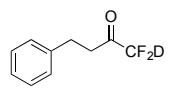




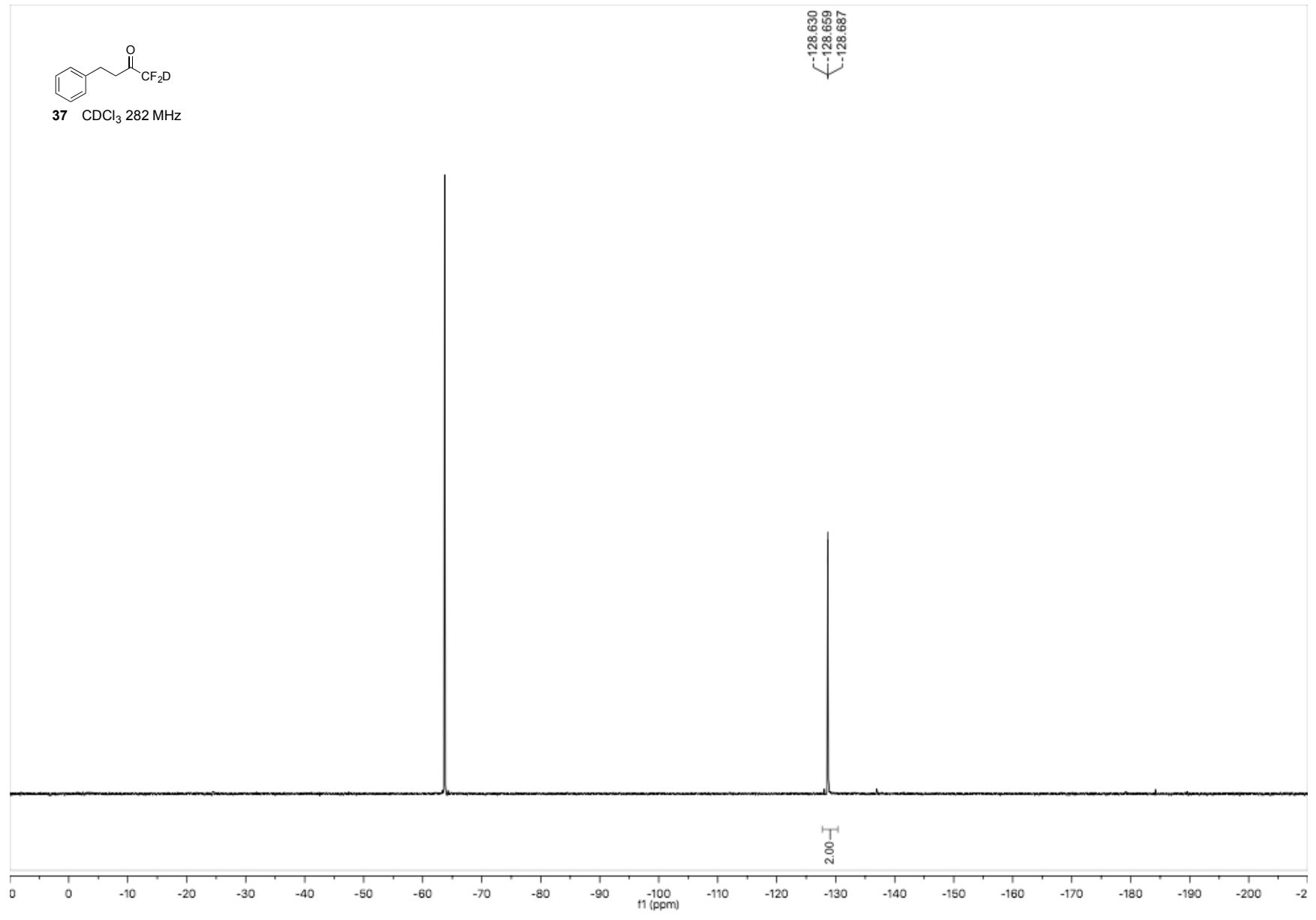
37 CDCl₃ 300 MHz

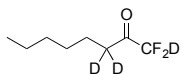




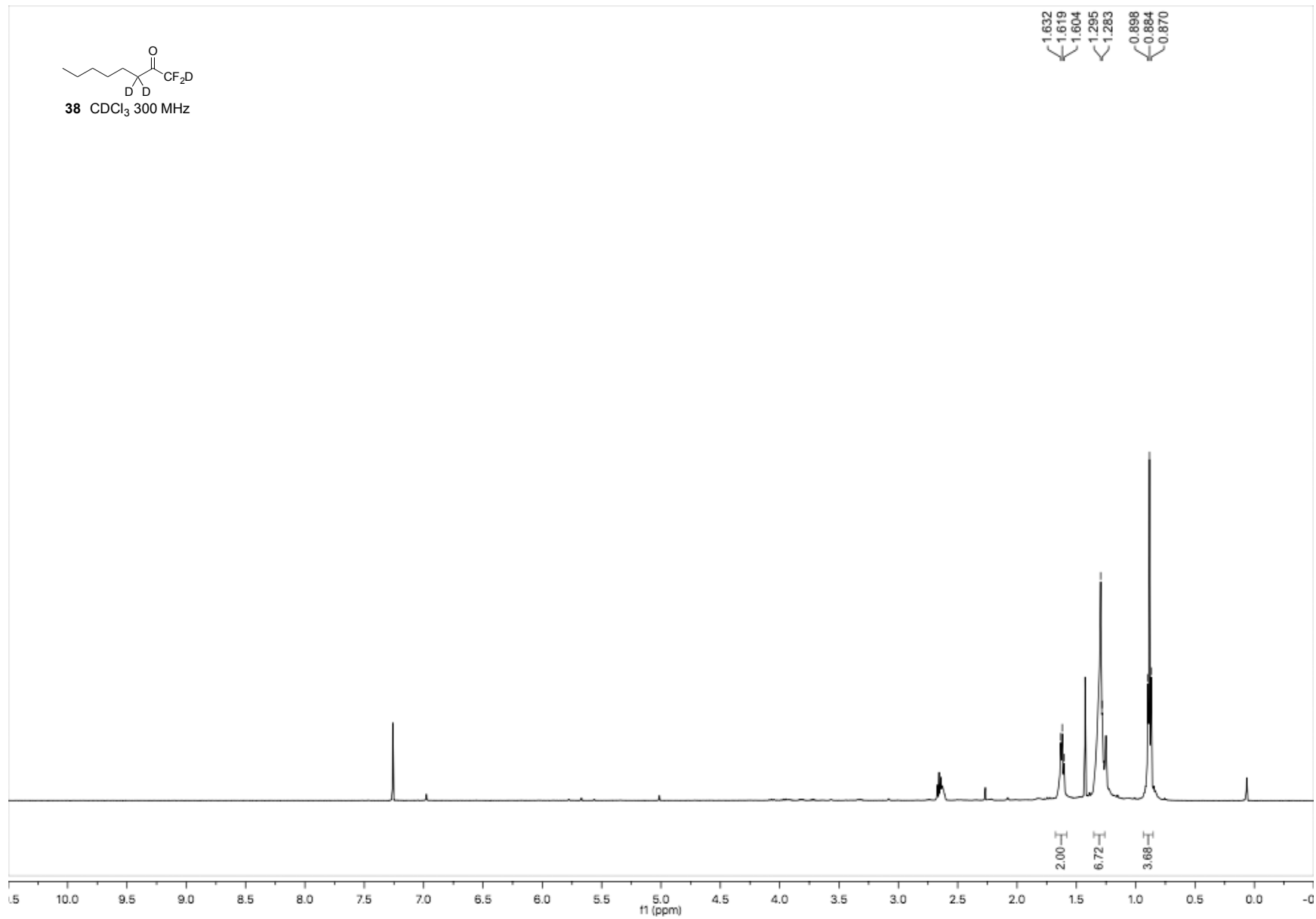


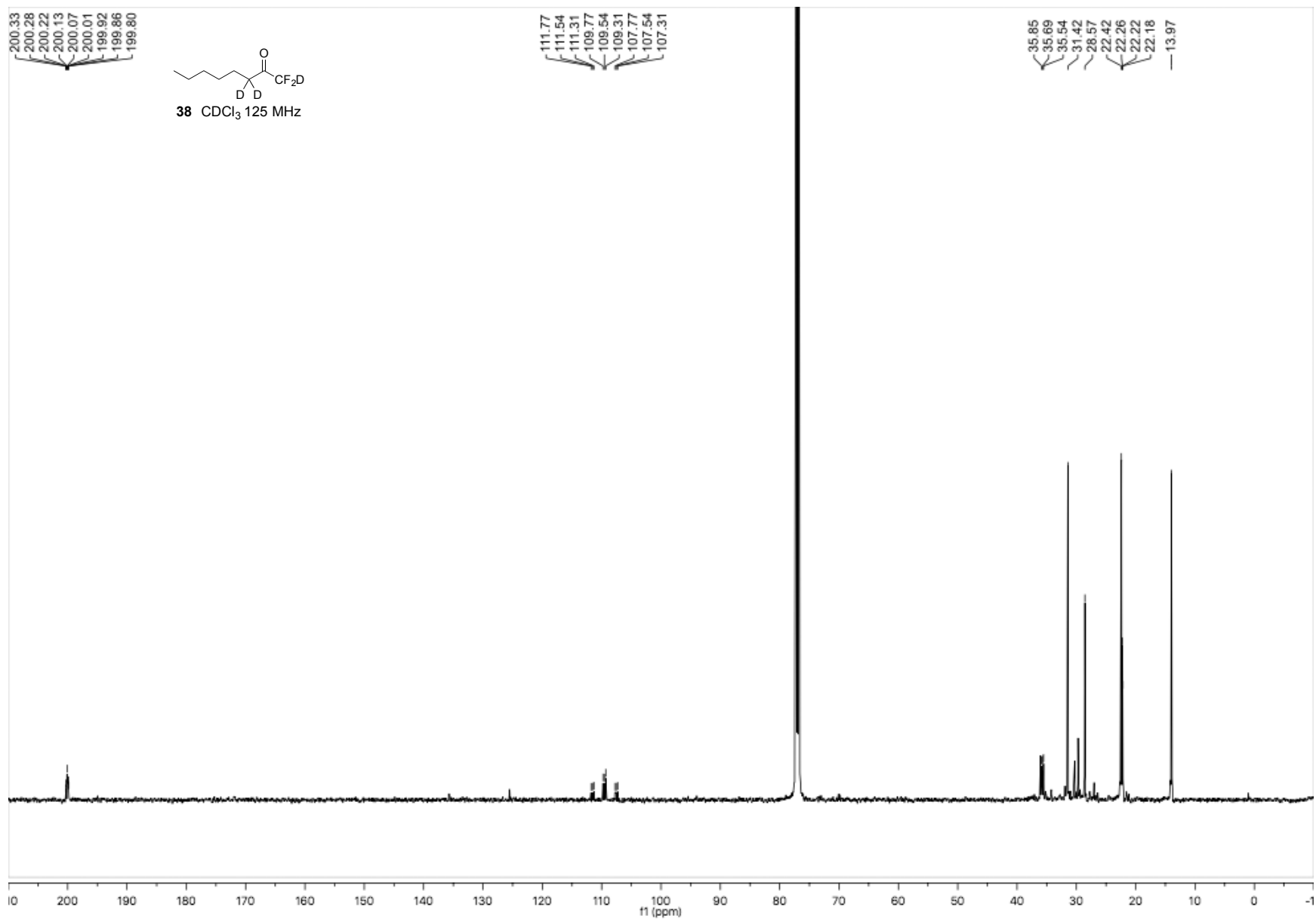
37 CDCl₃ 282 MHz

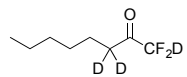




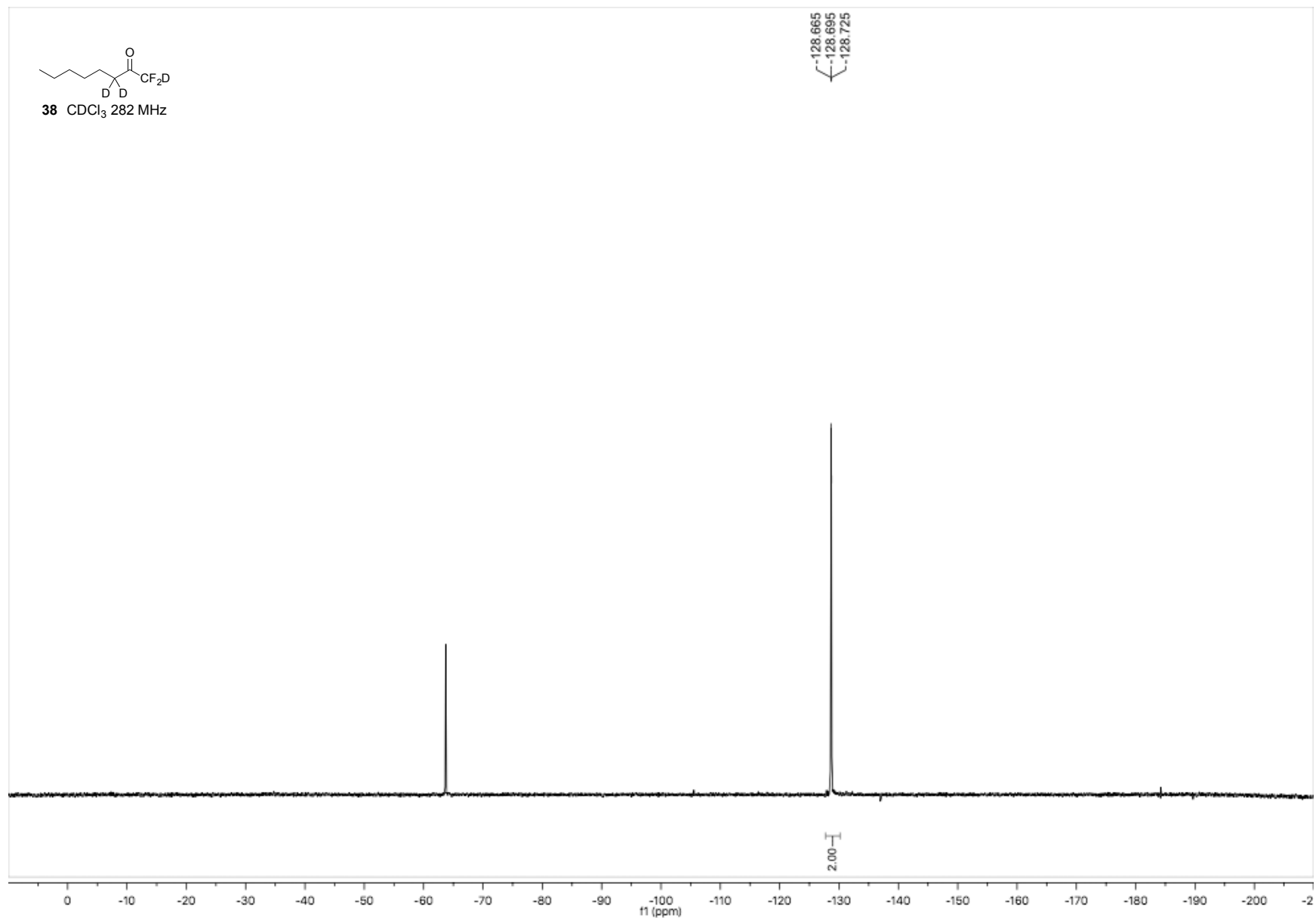
38 CDCl₃ 300 MHz

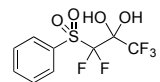






38 CDCl₃ 282 MHz

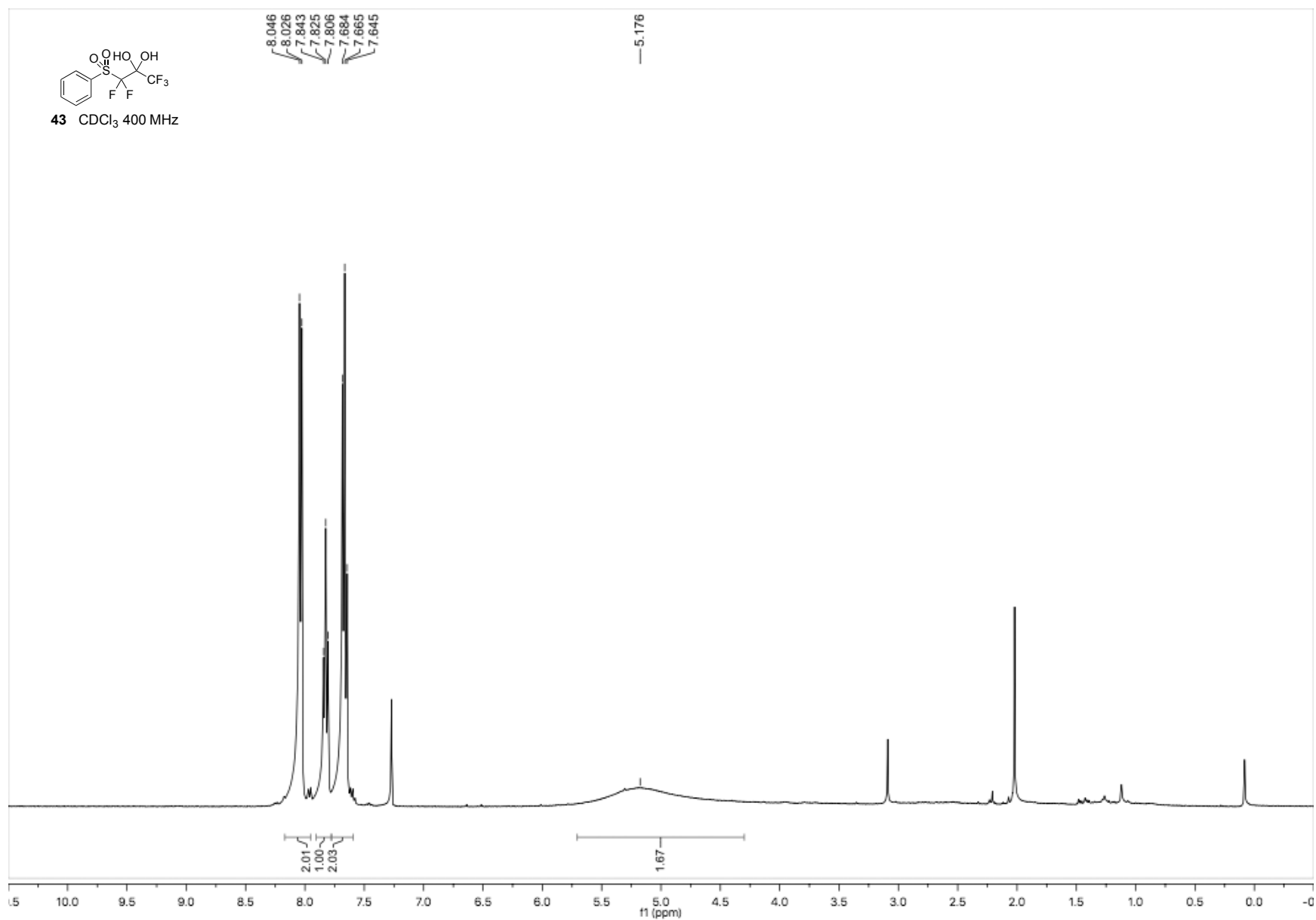


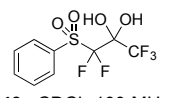


43 CDCl₃ 400 MHz

8.046
8.026
7.843
7.825
7.806
7.684
7.665
7.645

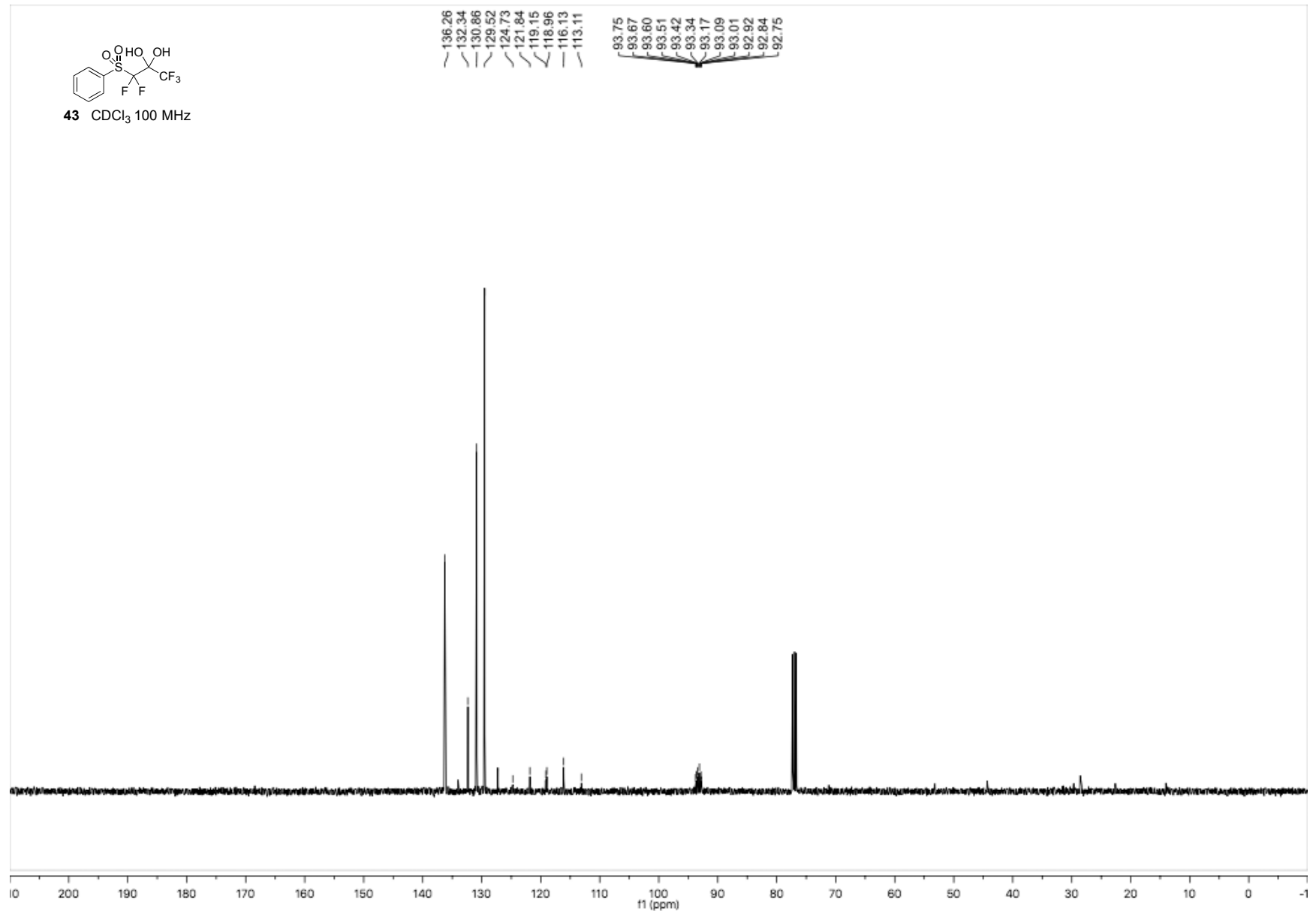
5.176

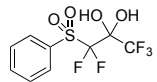




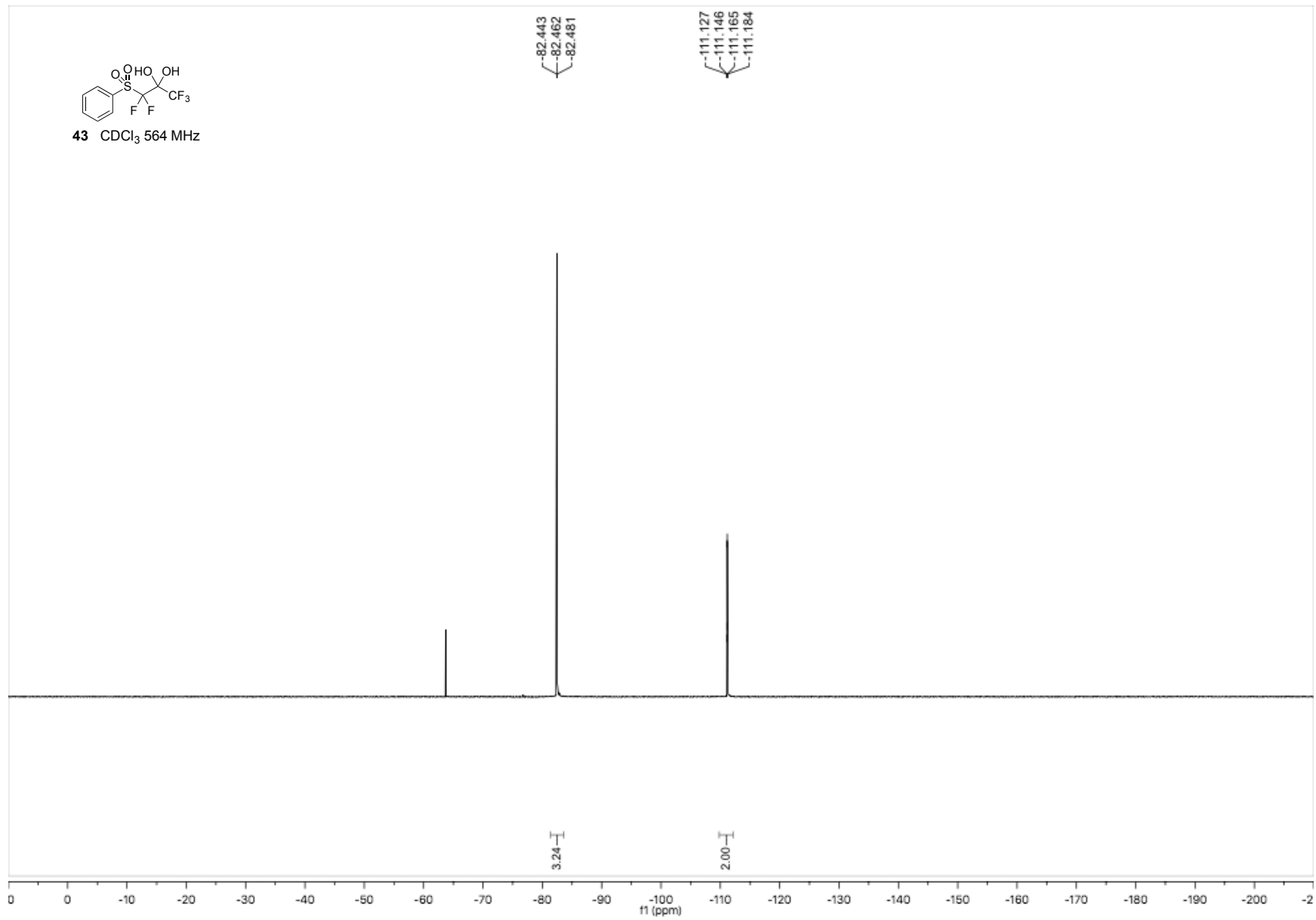
43 CDCl₃ 100 MHz

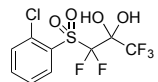
136.26
132.34
130.86
129.52
124.73
121.84
119.15
118.96
116.13
113.11
93.75
93.67
93.60
93.51
93.42
93.34
93.17
93.09
93.01
92.92
92.84
92.75





43 CDCl₃ 564 MHz

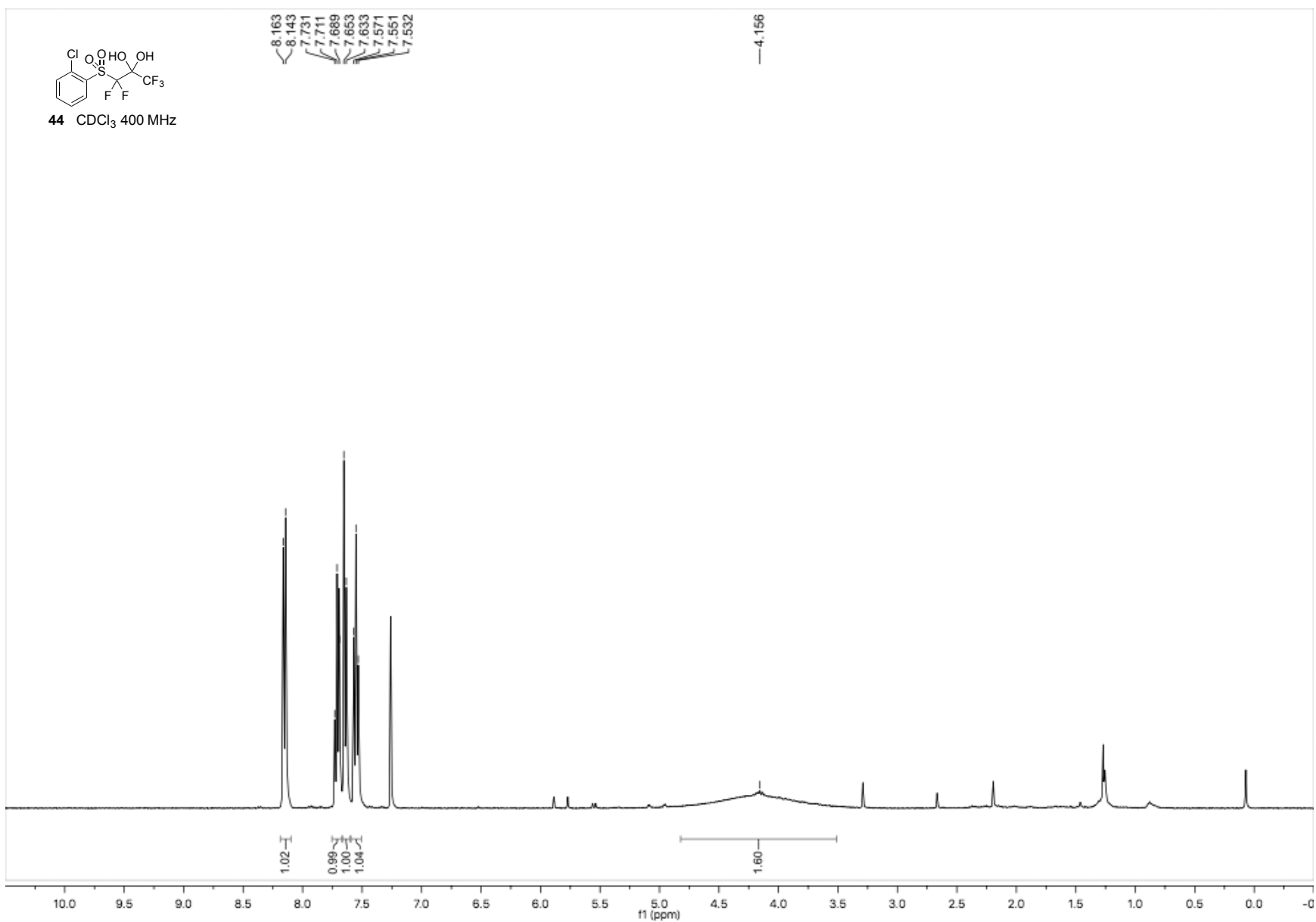


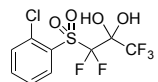


44 CDCl₃ 400 MHz

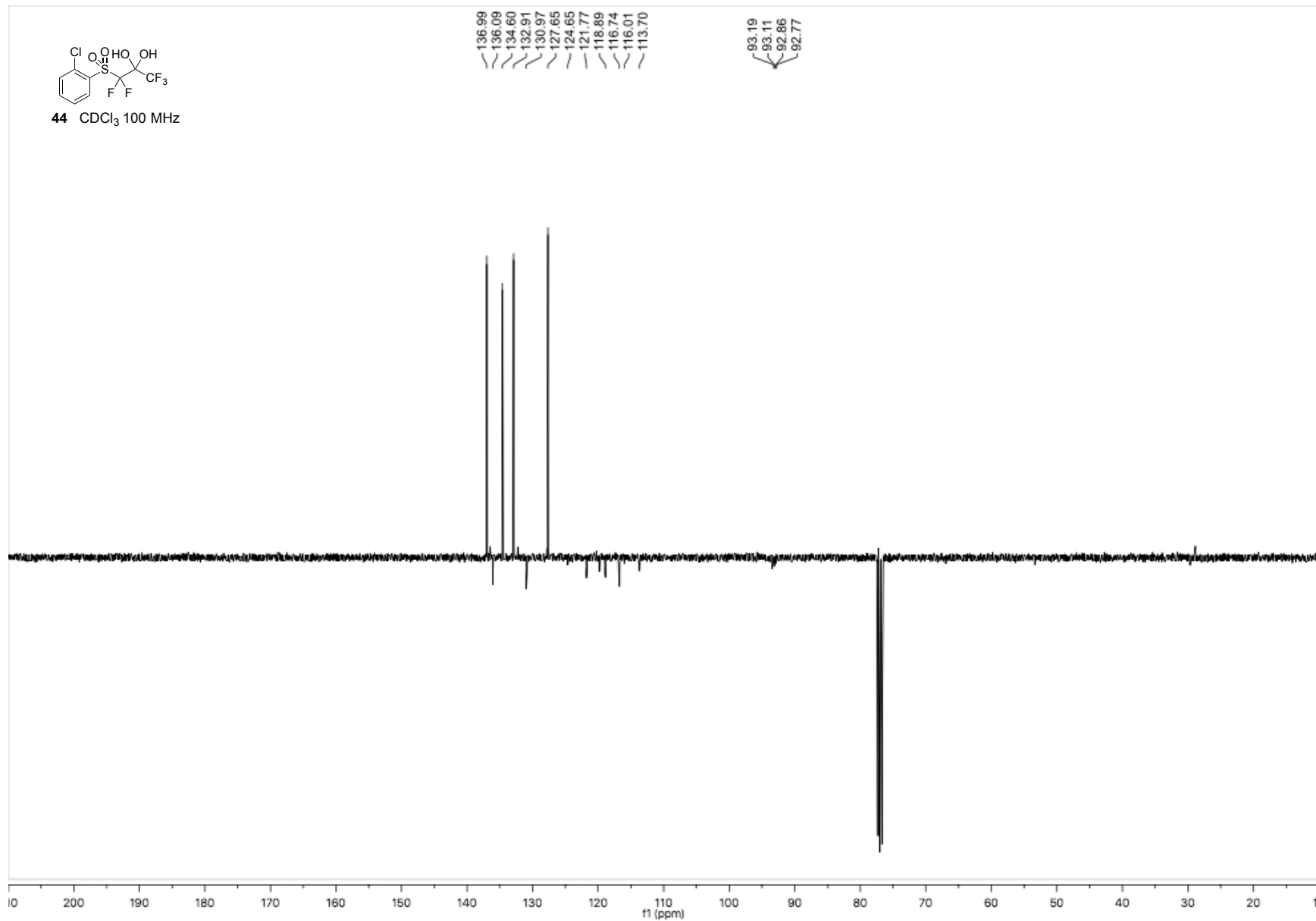
8.163
8.143
7.731
7.711
7.689
7.653
7.633
7.571
7.551
7.532

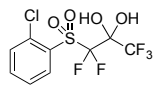
4.156



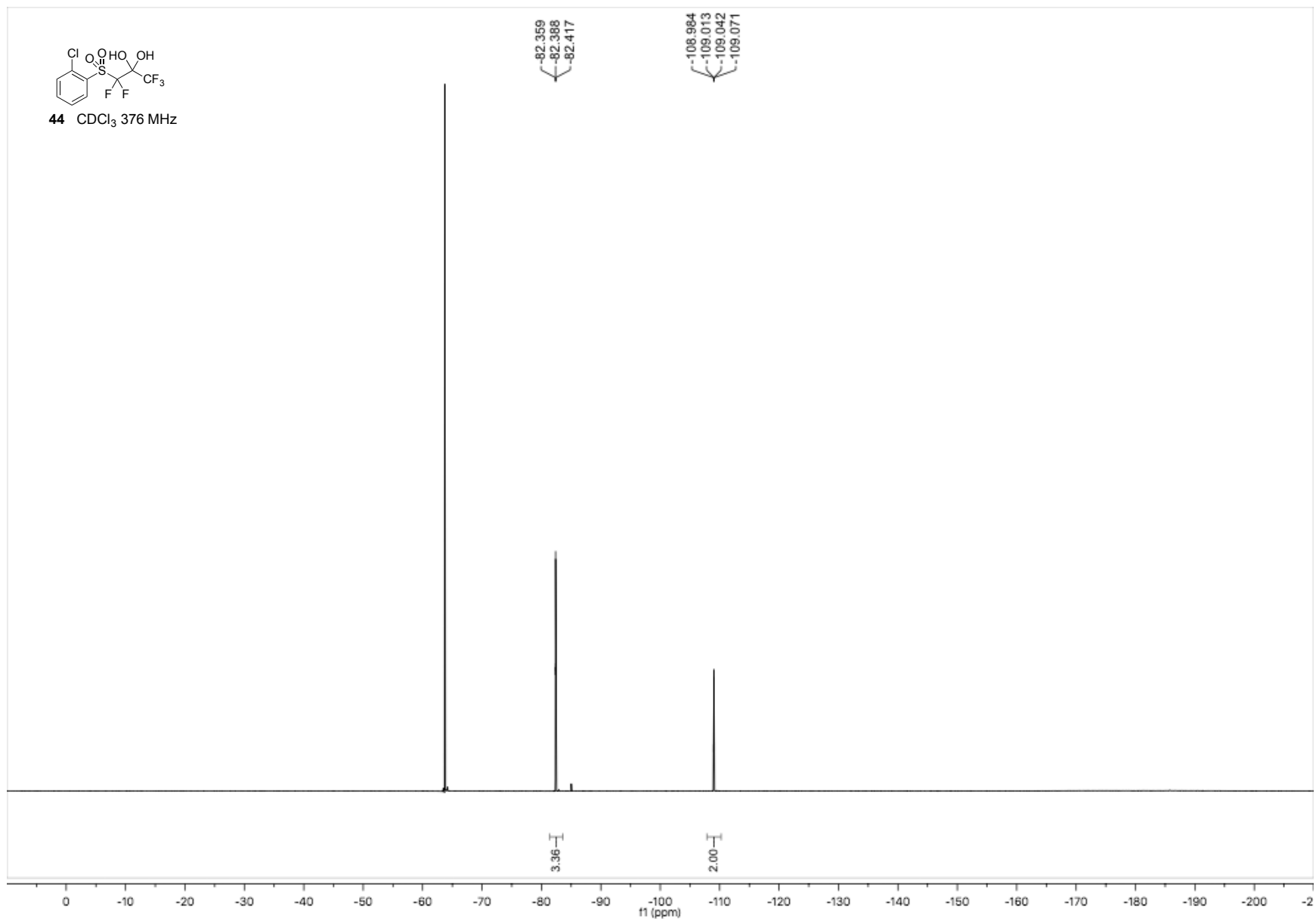


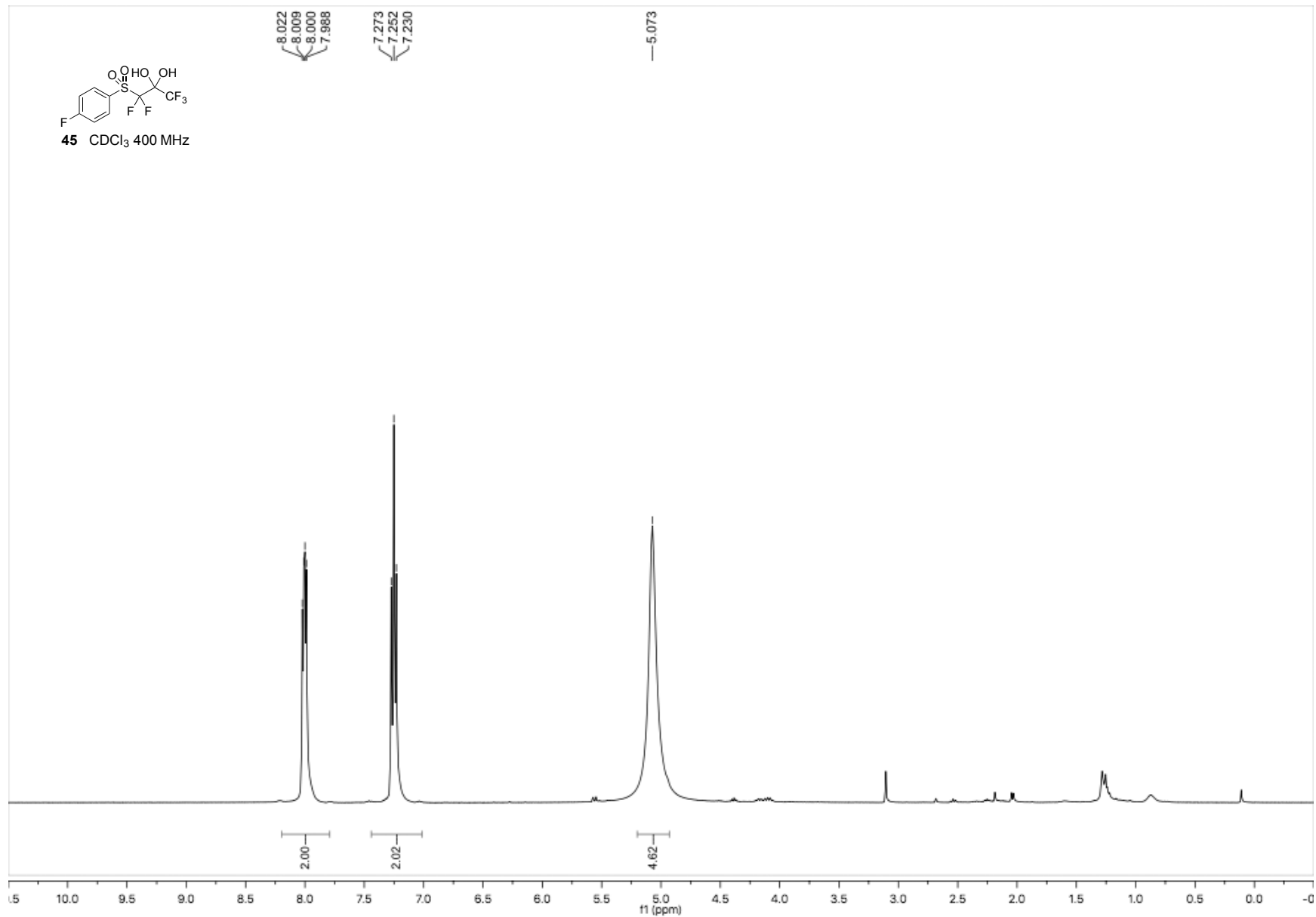
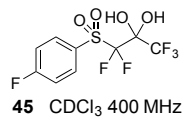
44 CDCl₃ 100 MHz

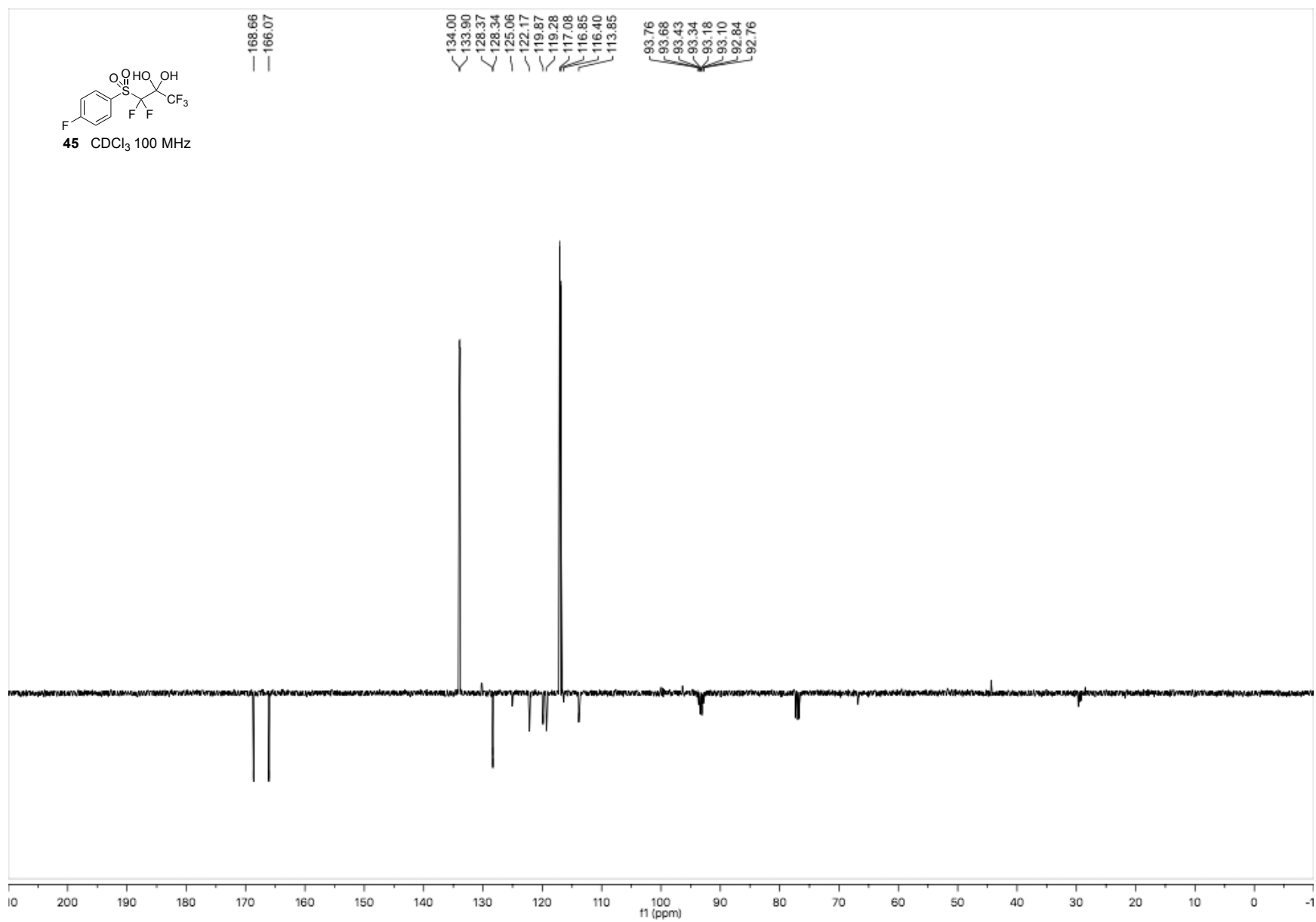


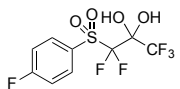


44 CDCl₃ 376 MHz

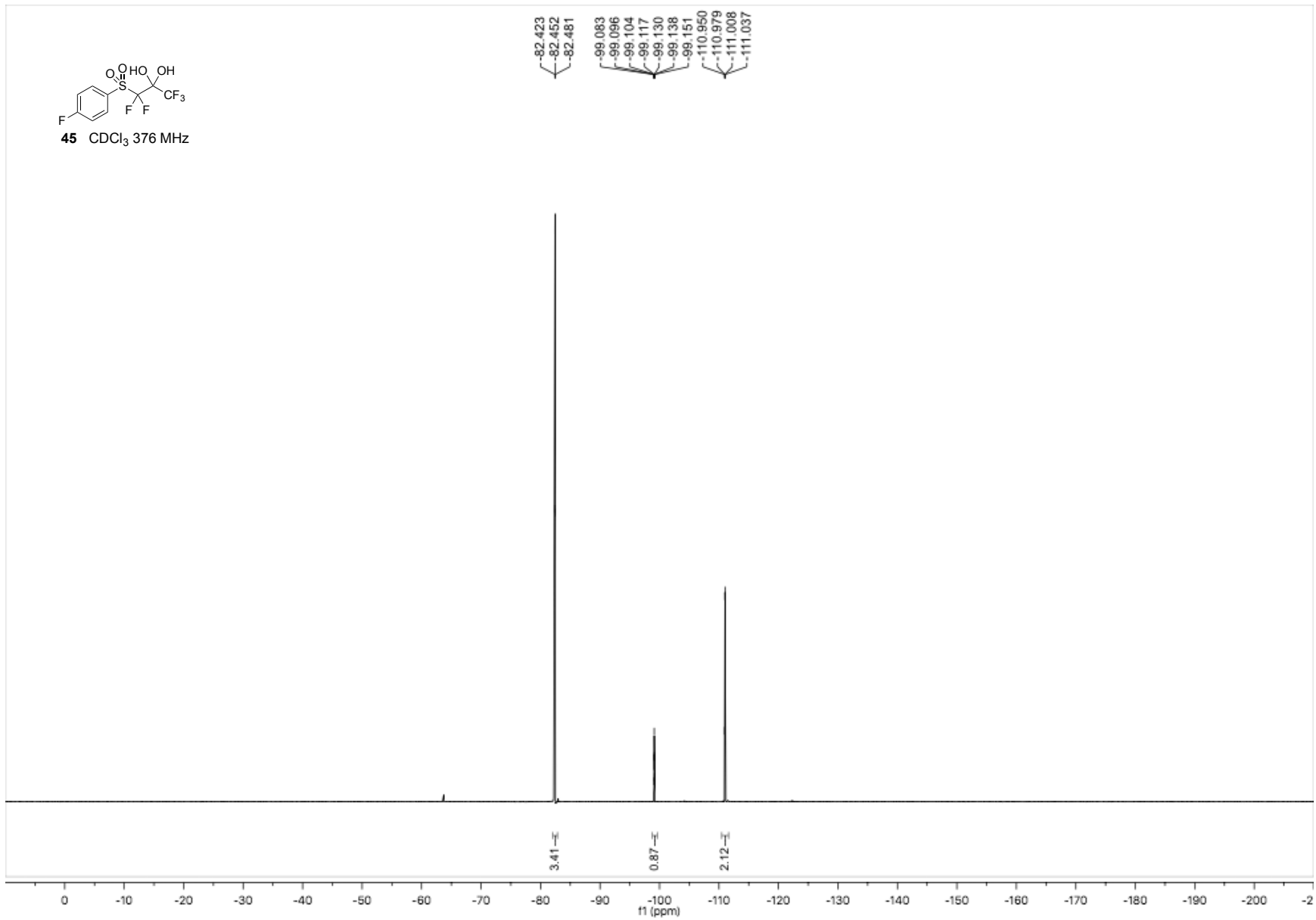


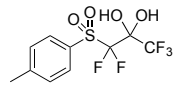




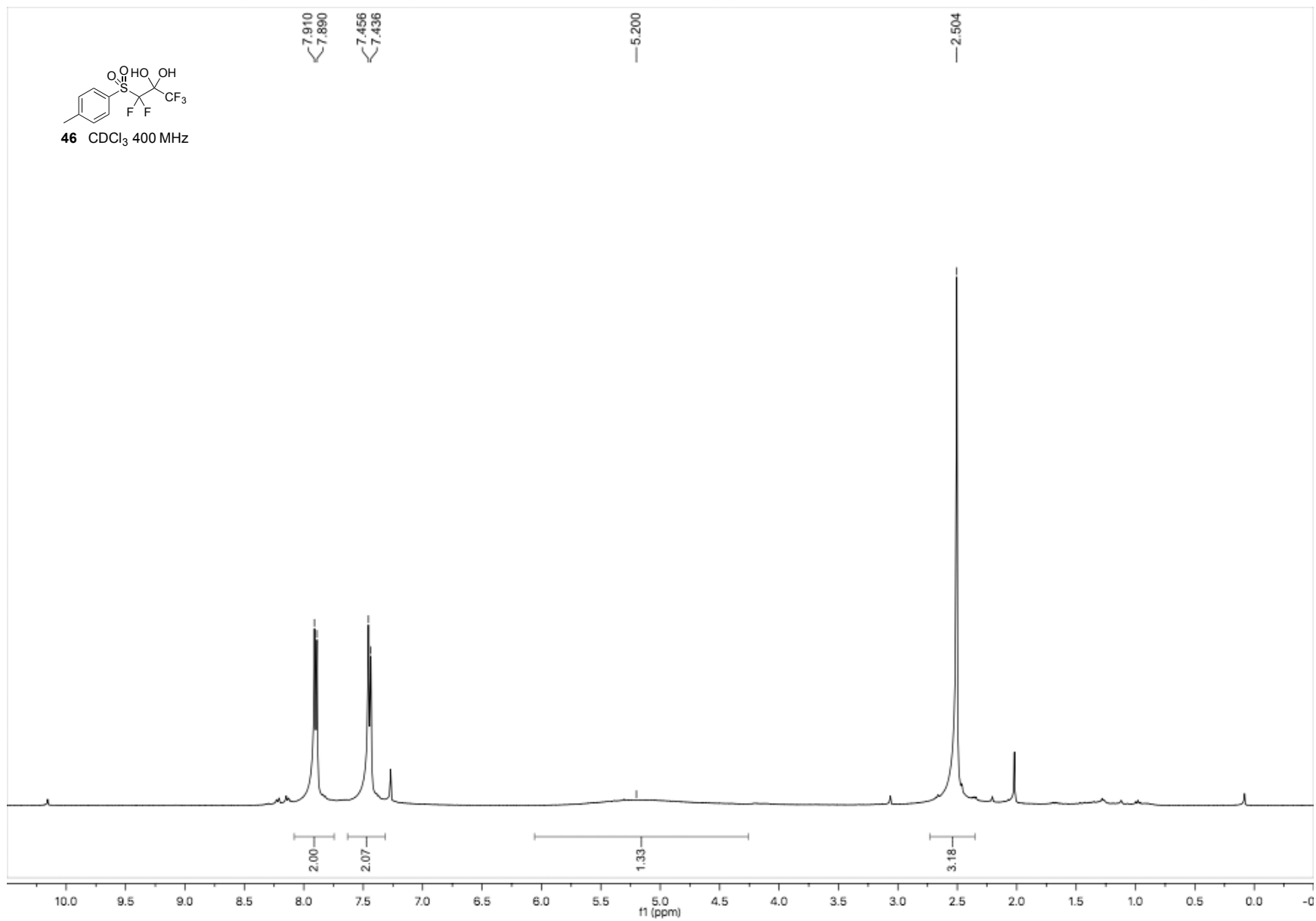


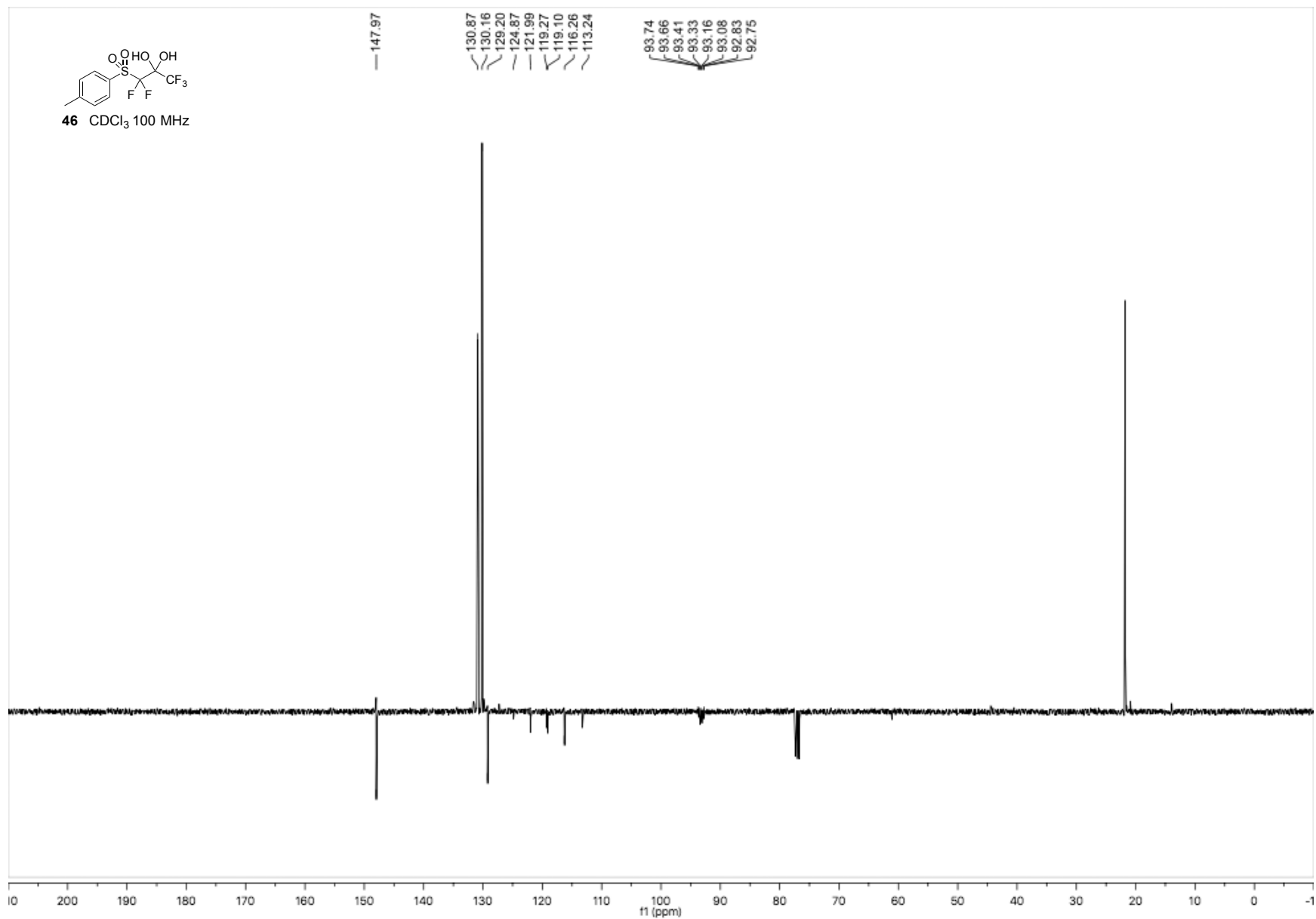
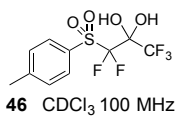
45 CDCl₃ 376 MHz

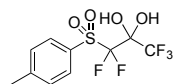




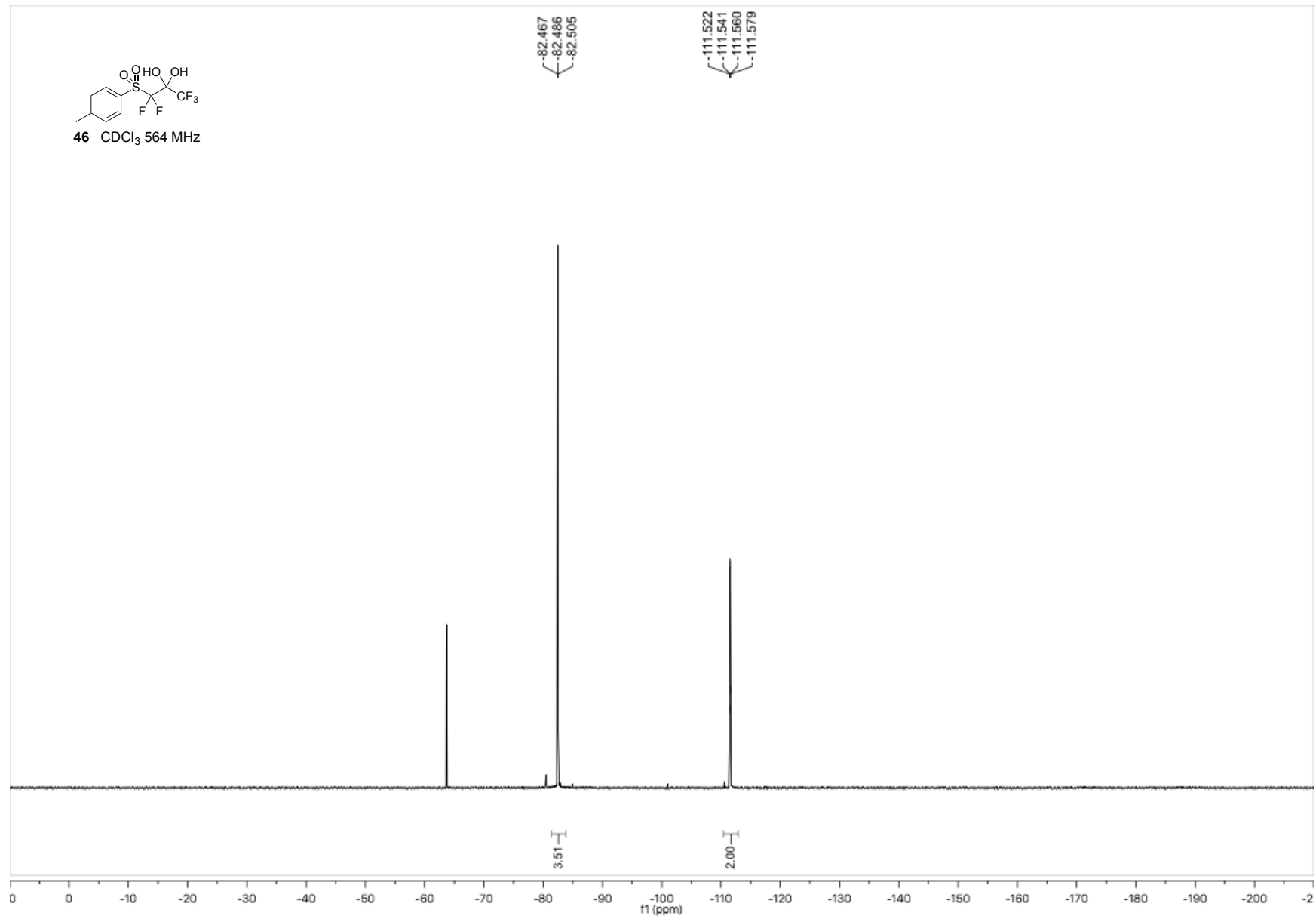
46 CDCl₃ 400 MHz

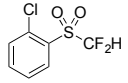






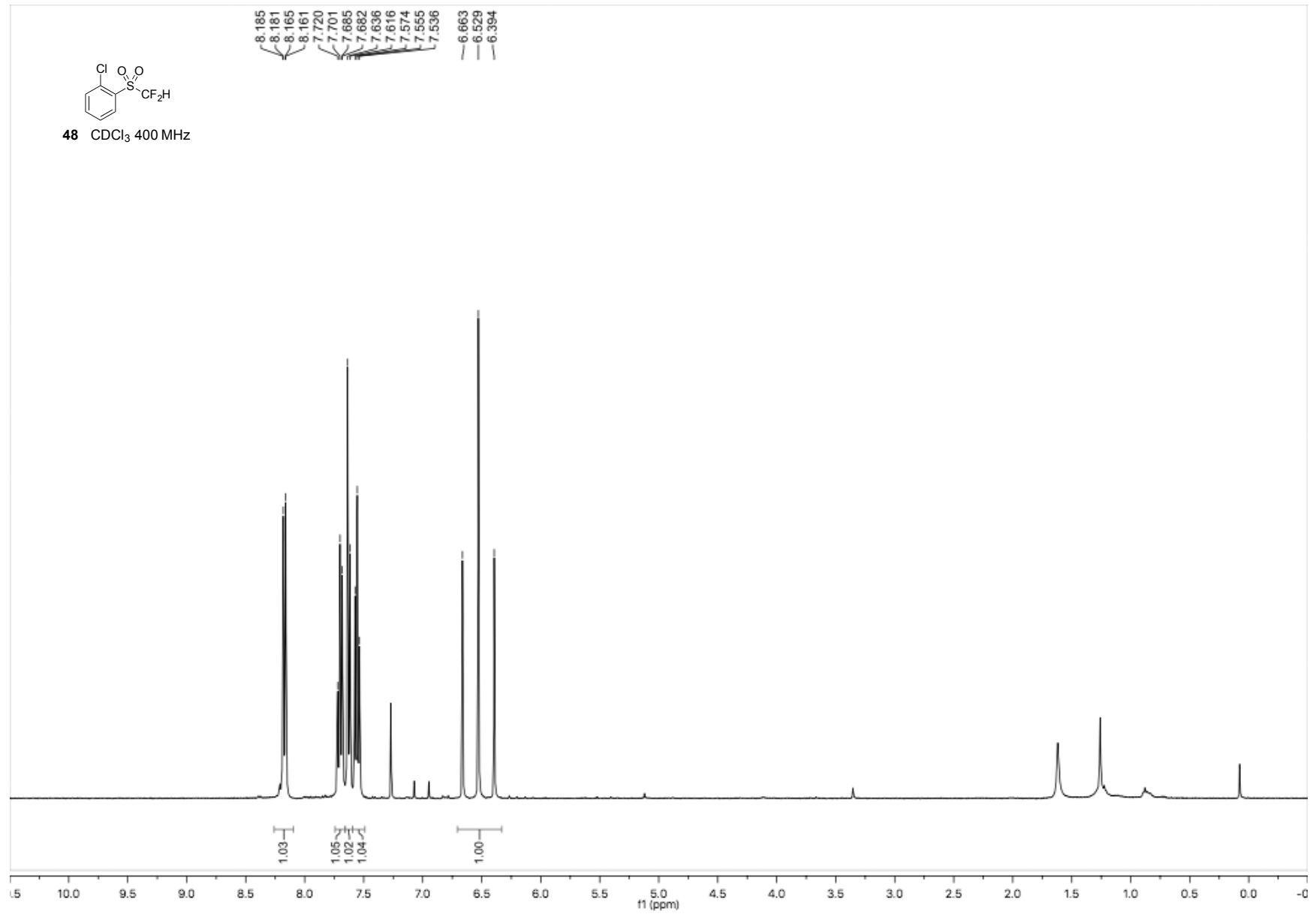
46 CDCl₃ 564 MHz

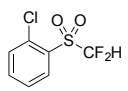




48 CDCl₃ 400 MHz

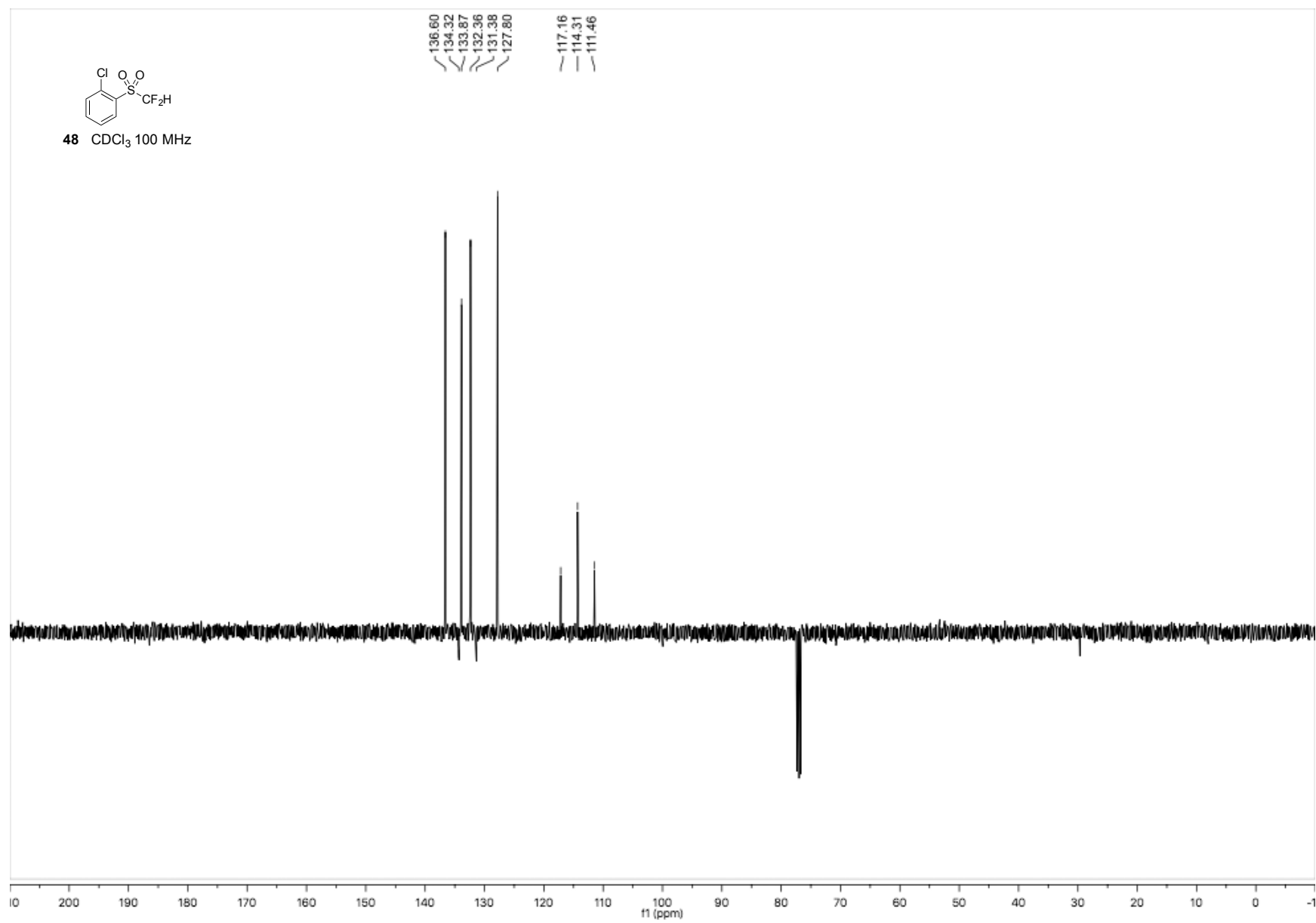
8.185
8.181
8.165
8.161
7.720
7.701
7.685
7.682
7.636
7.616
7.574
7.555
7.536
6.663
6.529
6.394

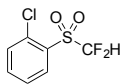




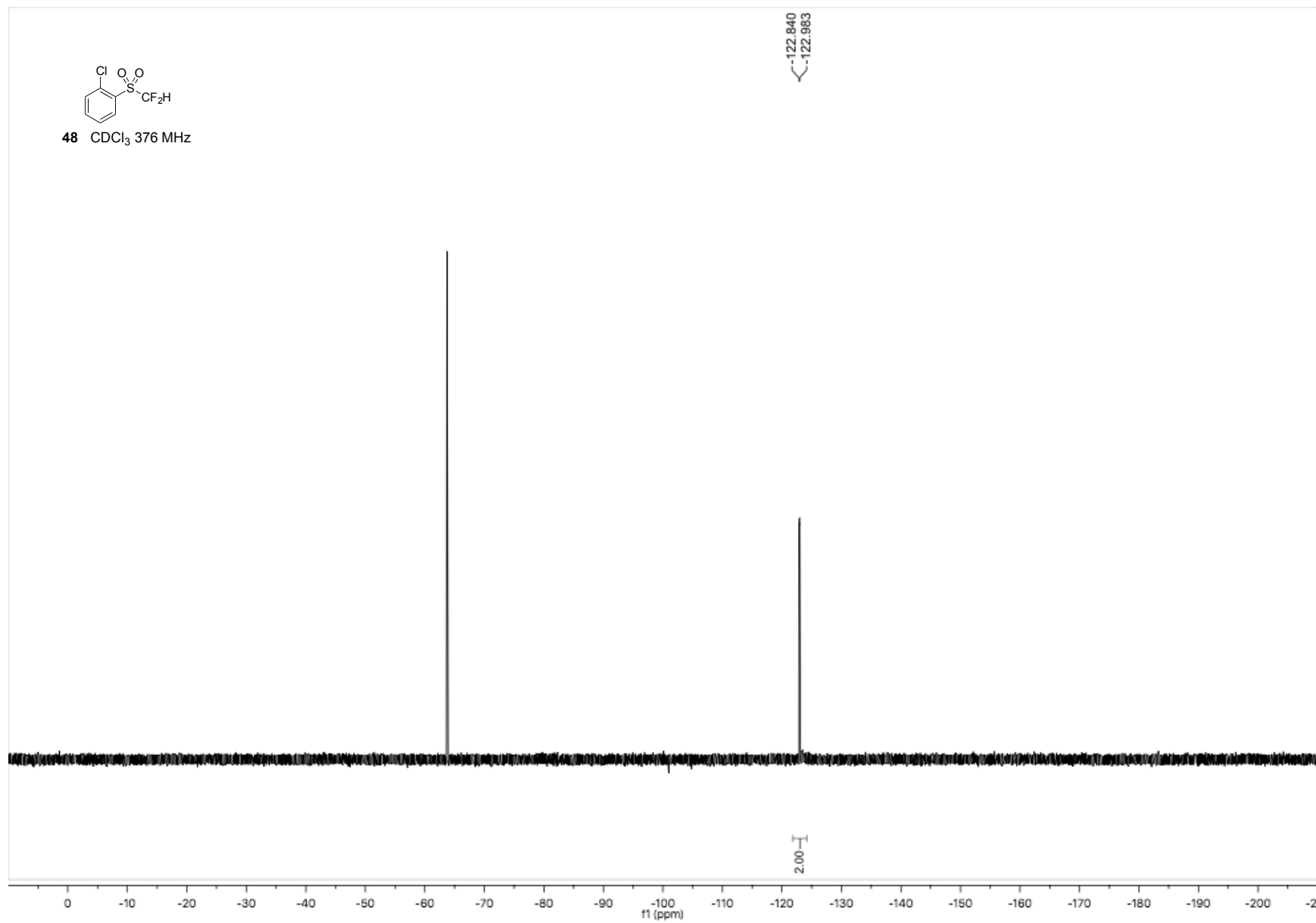
48 CDCl₃ 100 MHz

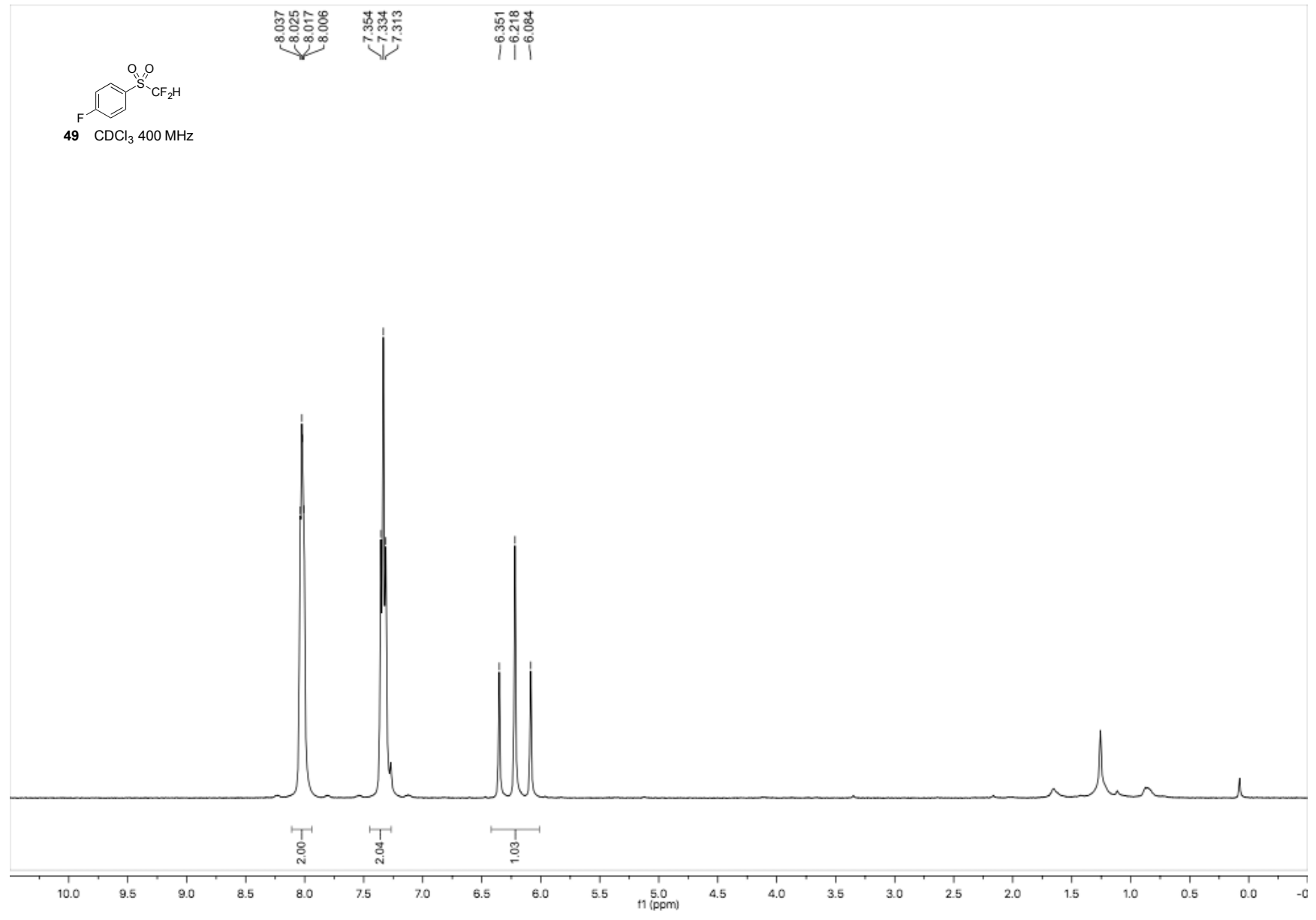
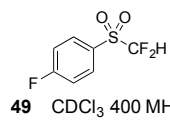
136.60
134.32
133.87
132.36
131.38
127.80
117.16
114.31
111.46

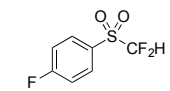




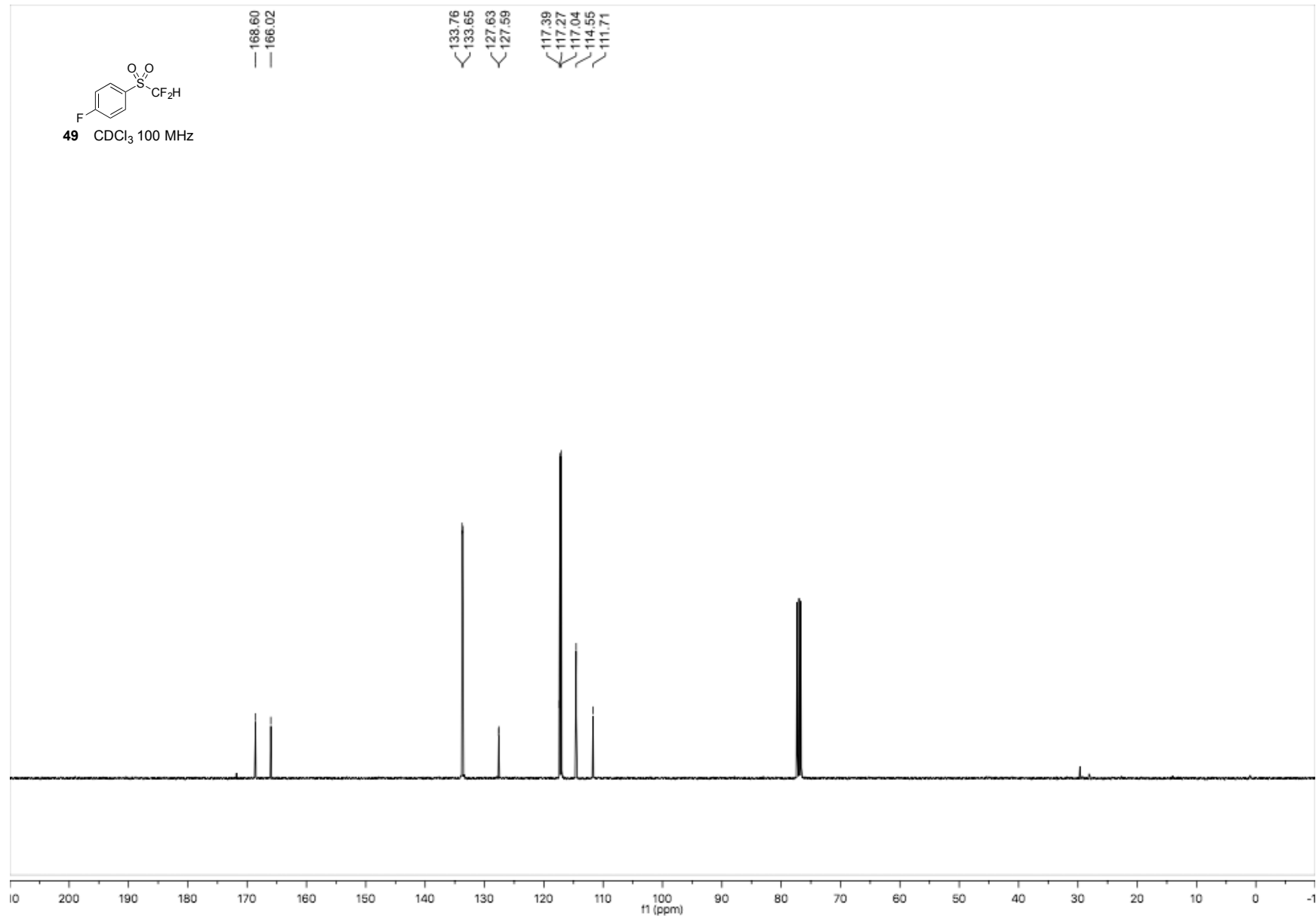
48 CDCl₃ 376 MHz

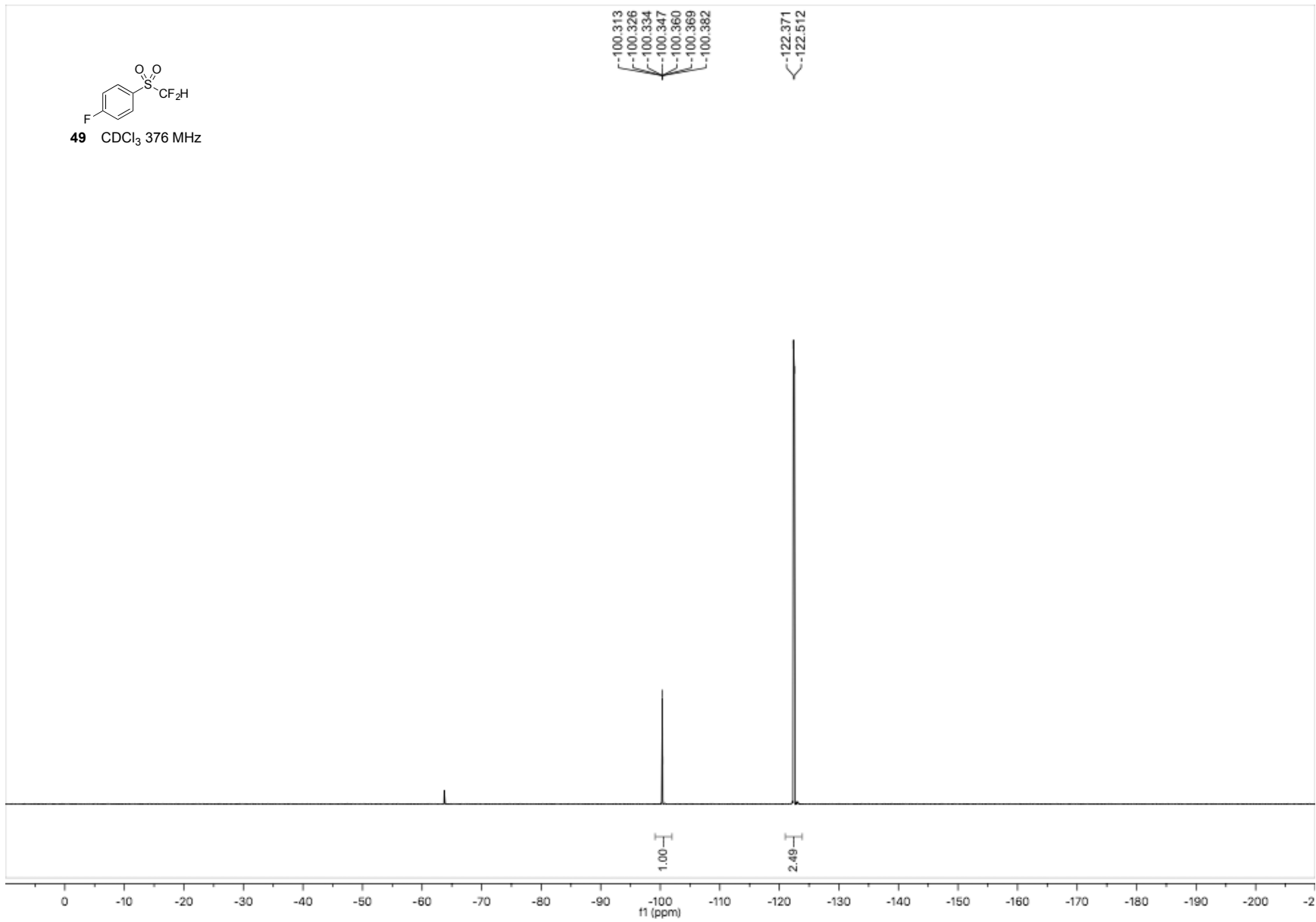
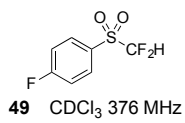


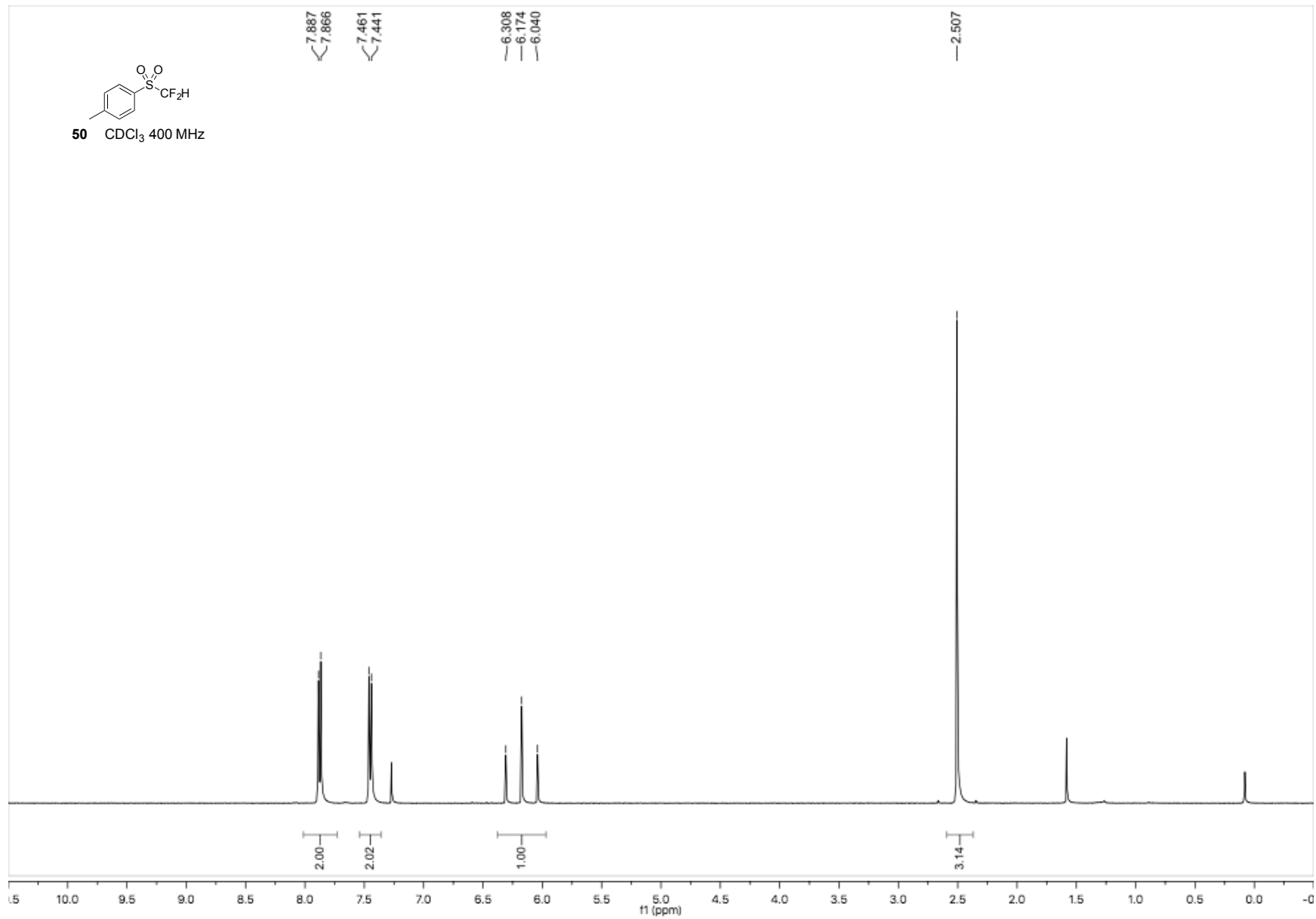
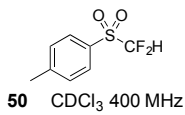


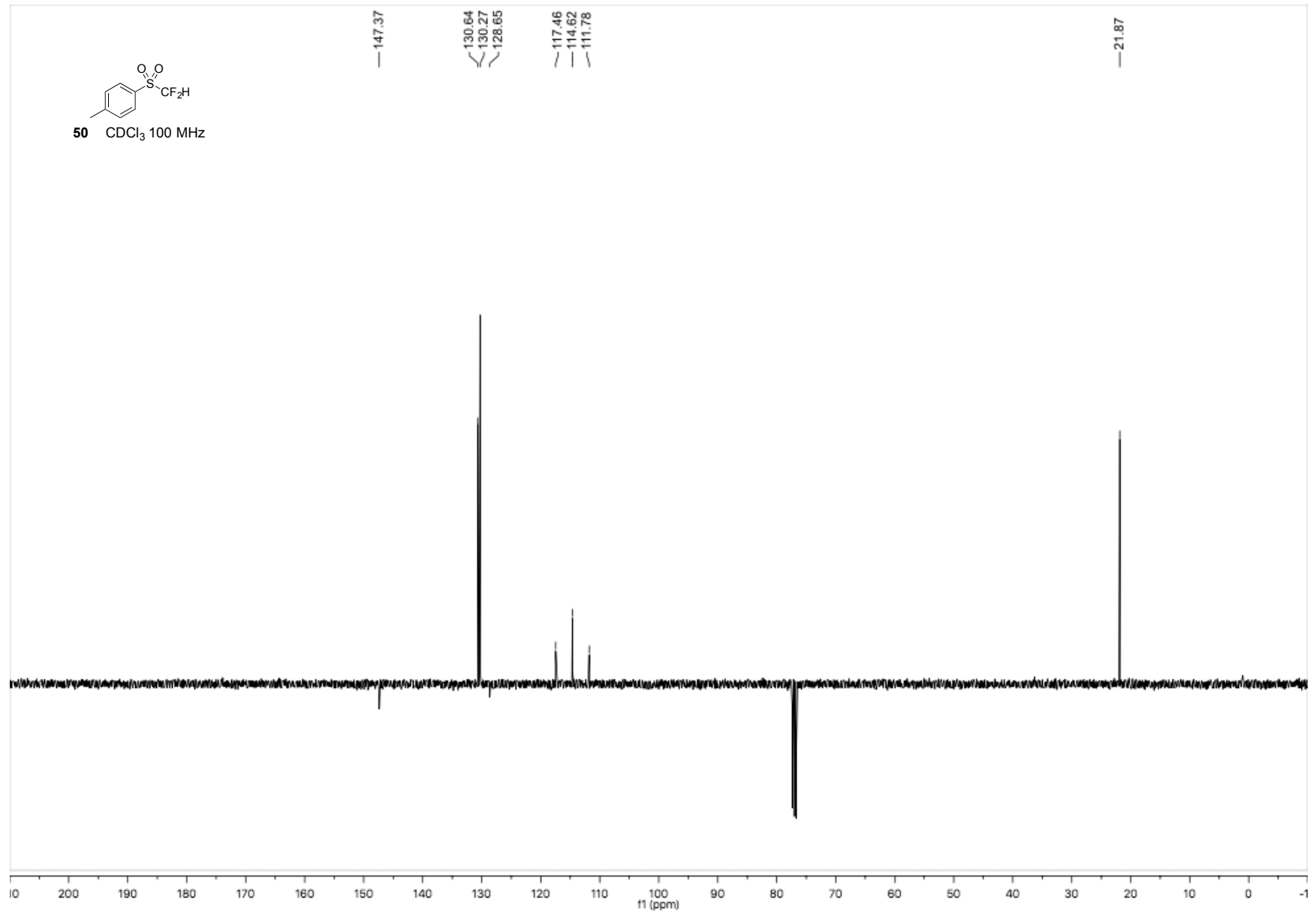
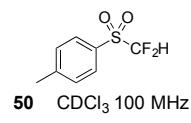


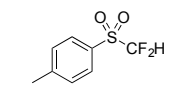
49 CDCl₃ 100 MHz



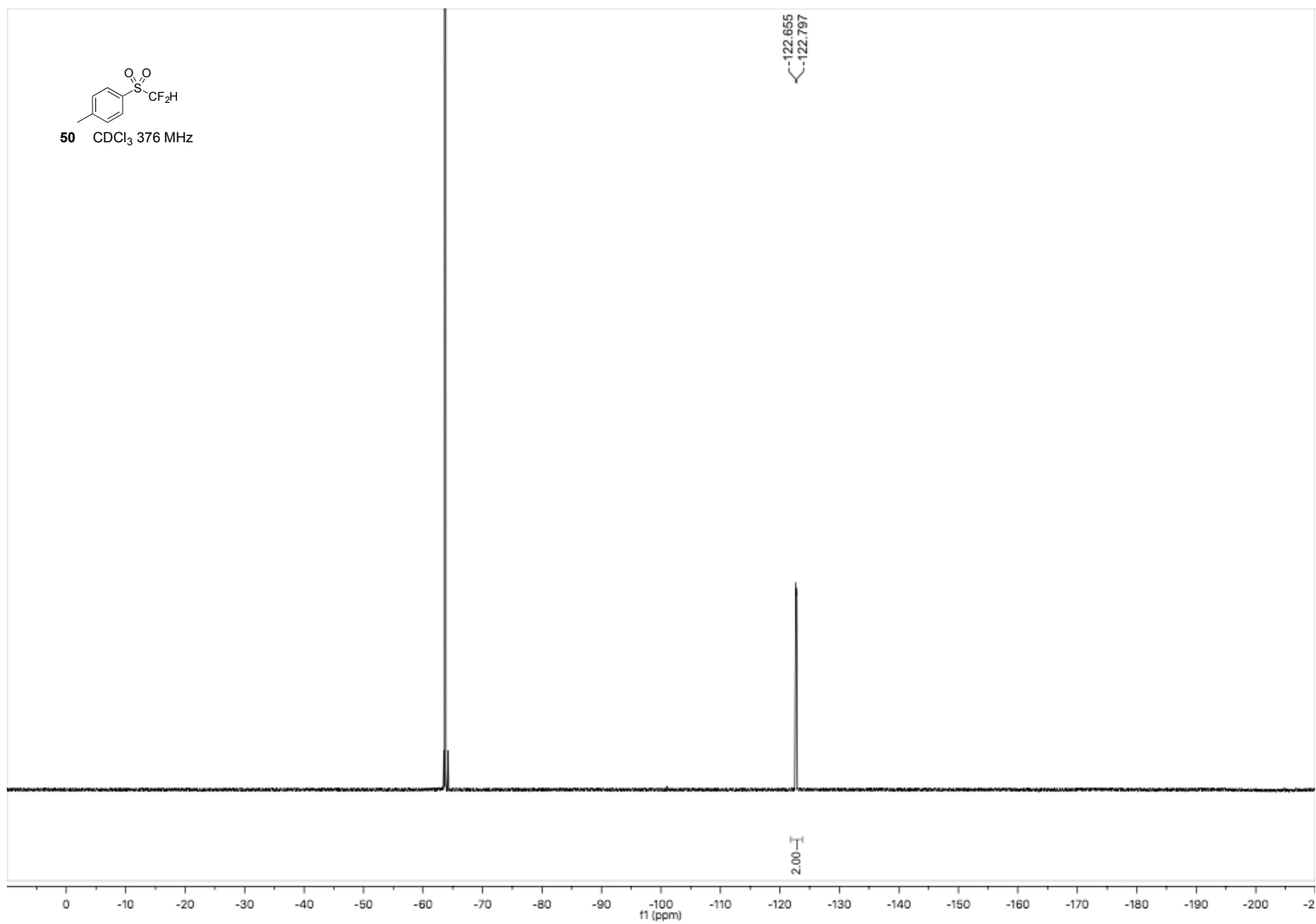


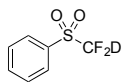






50 CDCl₃ 376 MHz

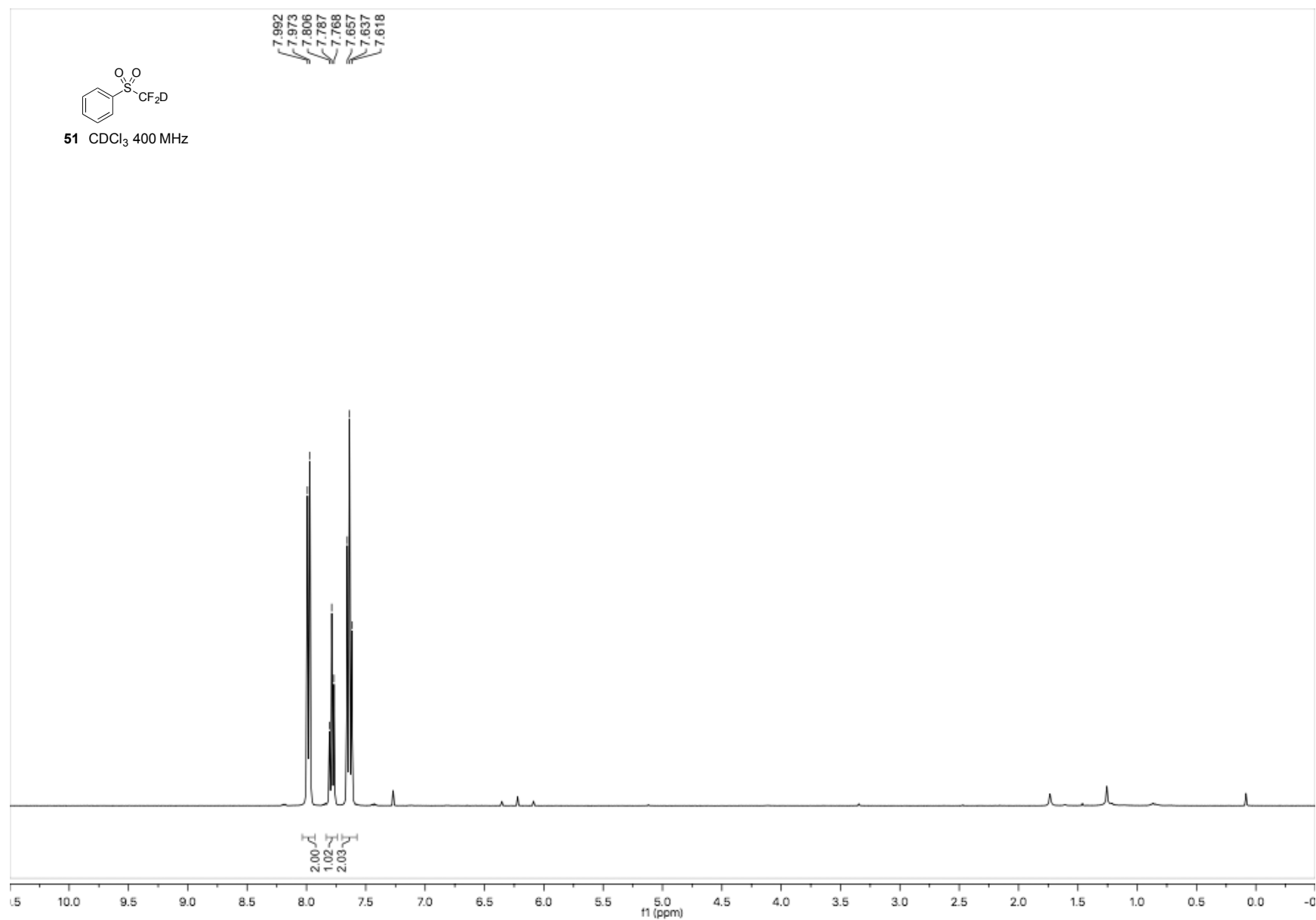


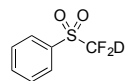


51 CDCl₃ 400 MHz

7.992
7.973
7.806
7.787
7.768
7.657
7.637
7.618

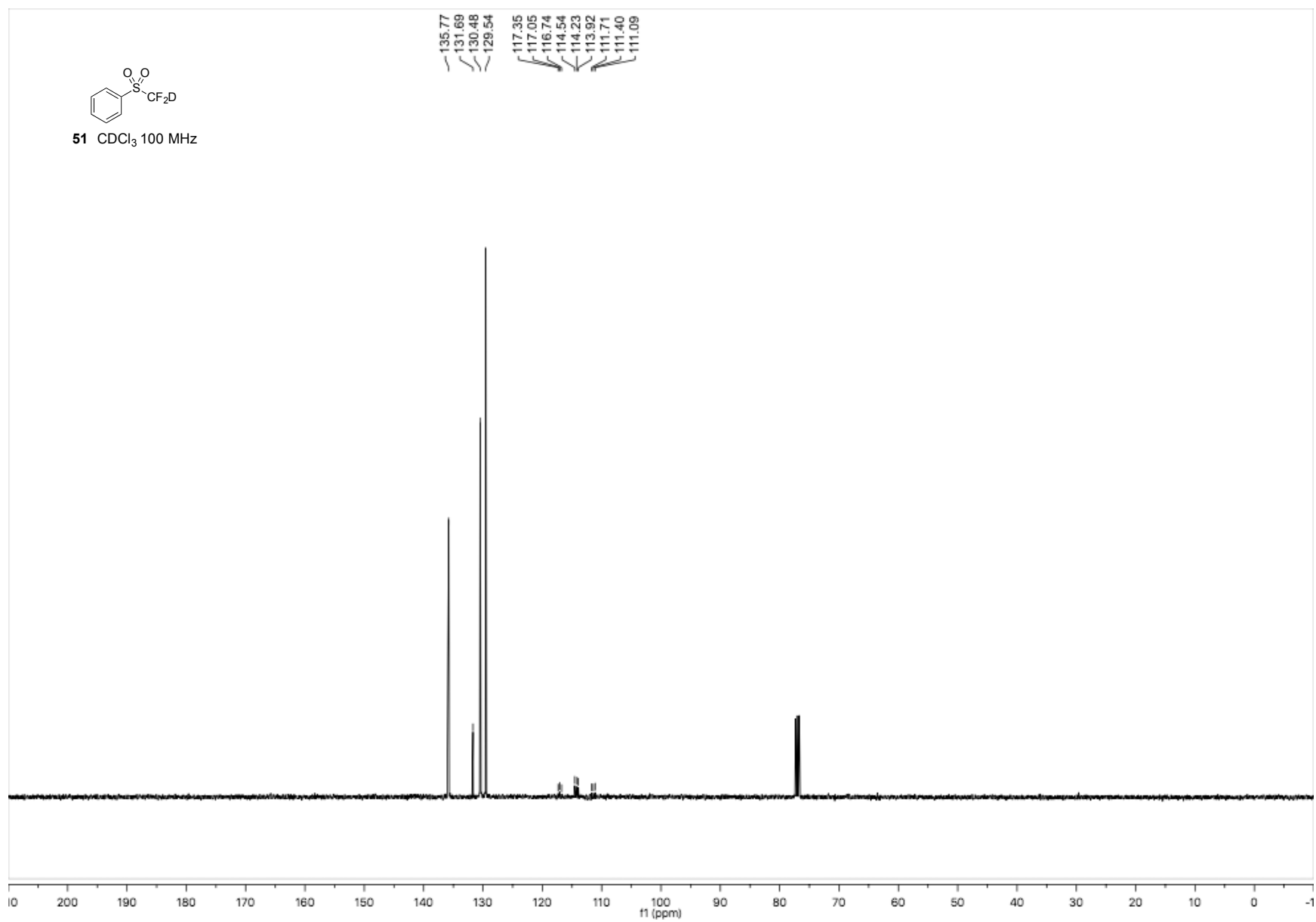
2.00
1.02
2.03

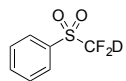




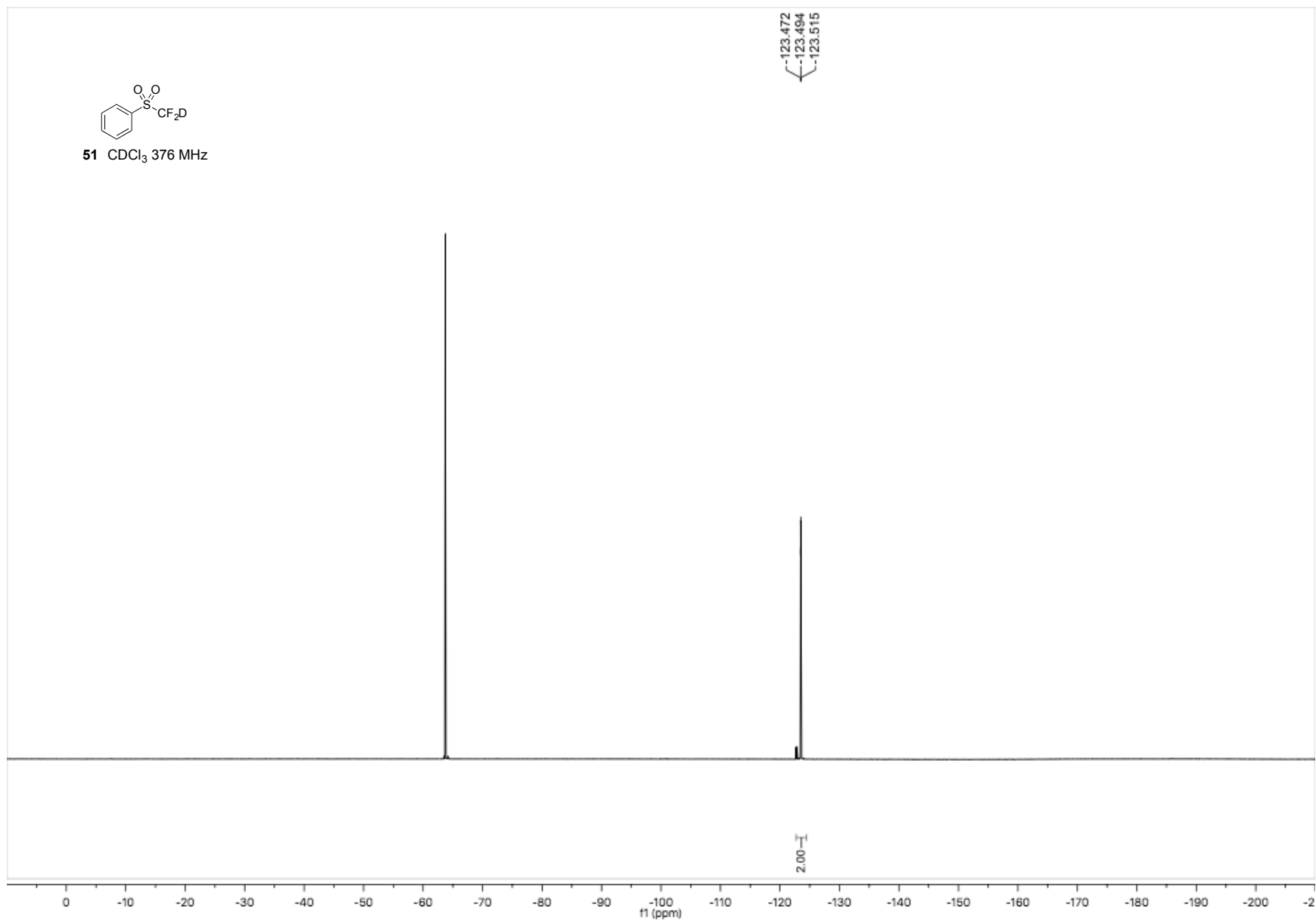
51 CDCl₃ 100 MHz

135.77
131.69
130.48
129.54
117.35
117.05
116.74
114.54
114.23
113.92
111.71
111.40
111.09

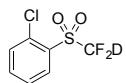




51 CDCl₃ 376 MHz

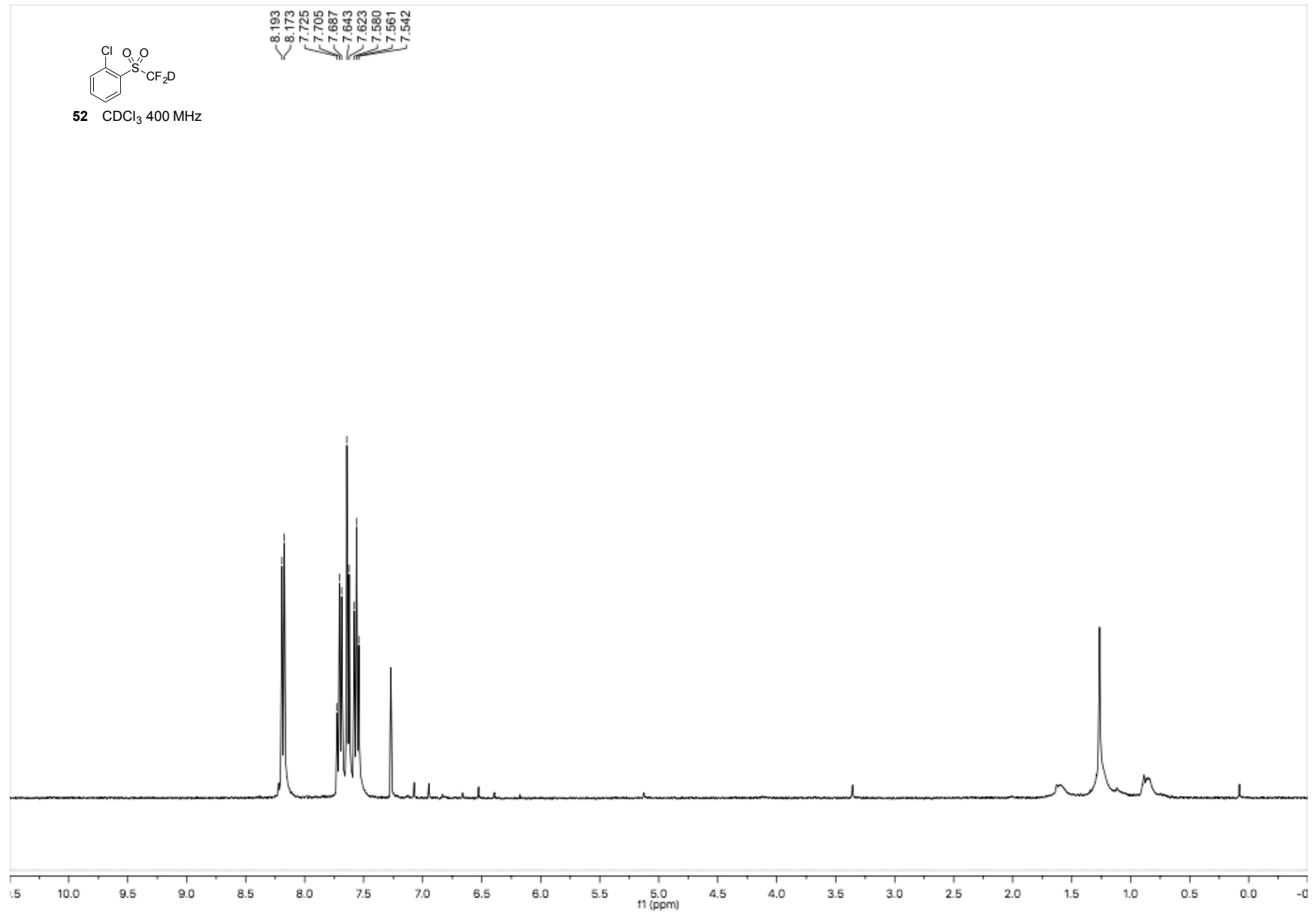


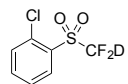
S101



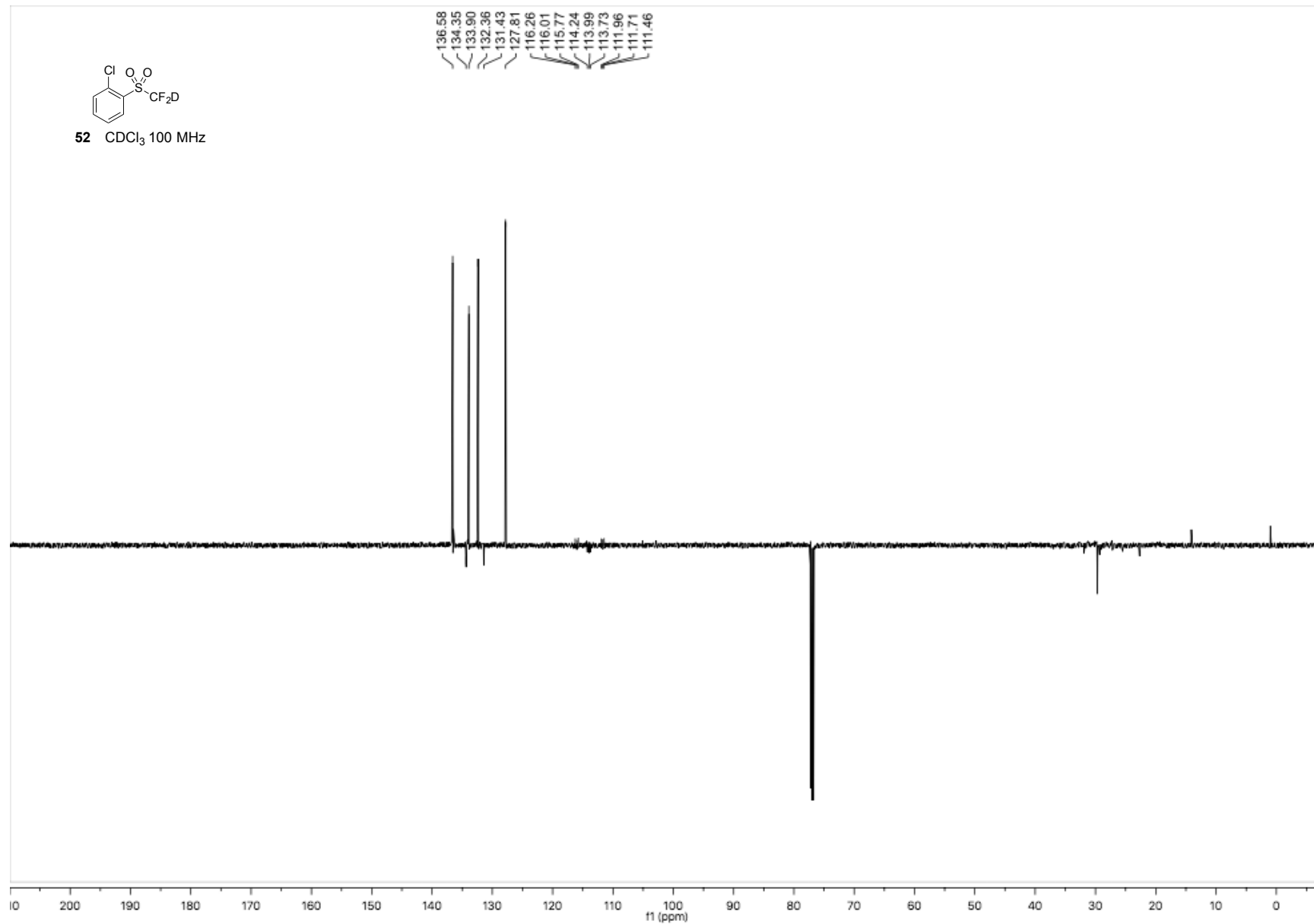
52 CDCl₃ 400 MHz

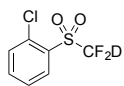
8.193
8.173
7.725
7.705
7.687
7.643
7.623
7.580
7.561
7.542



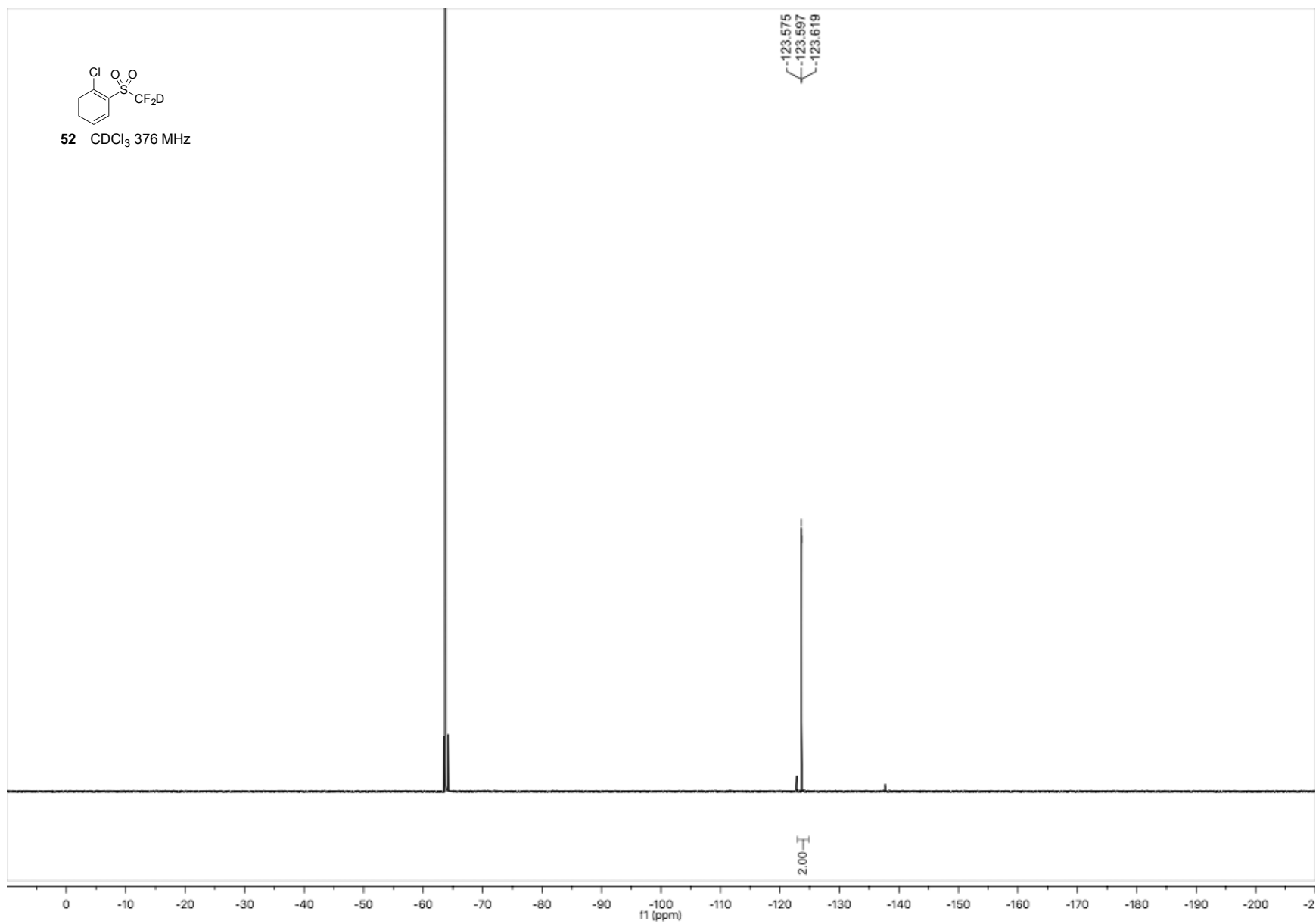


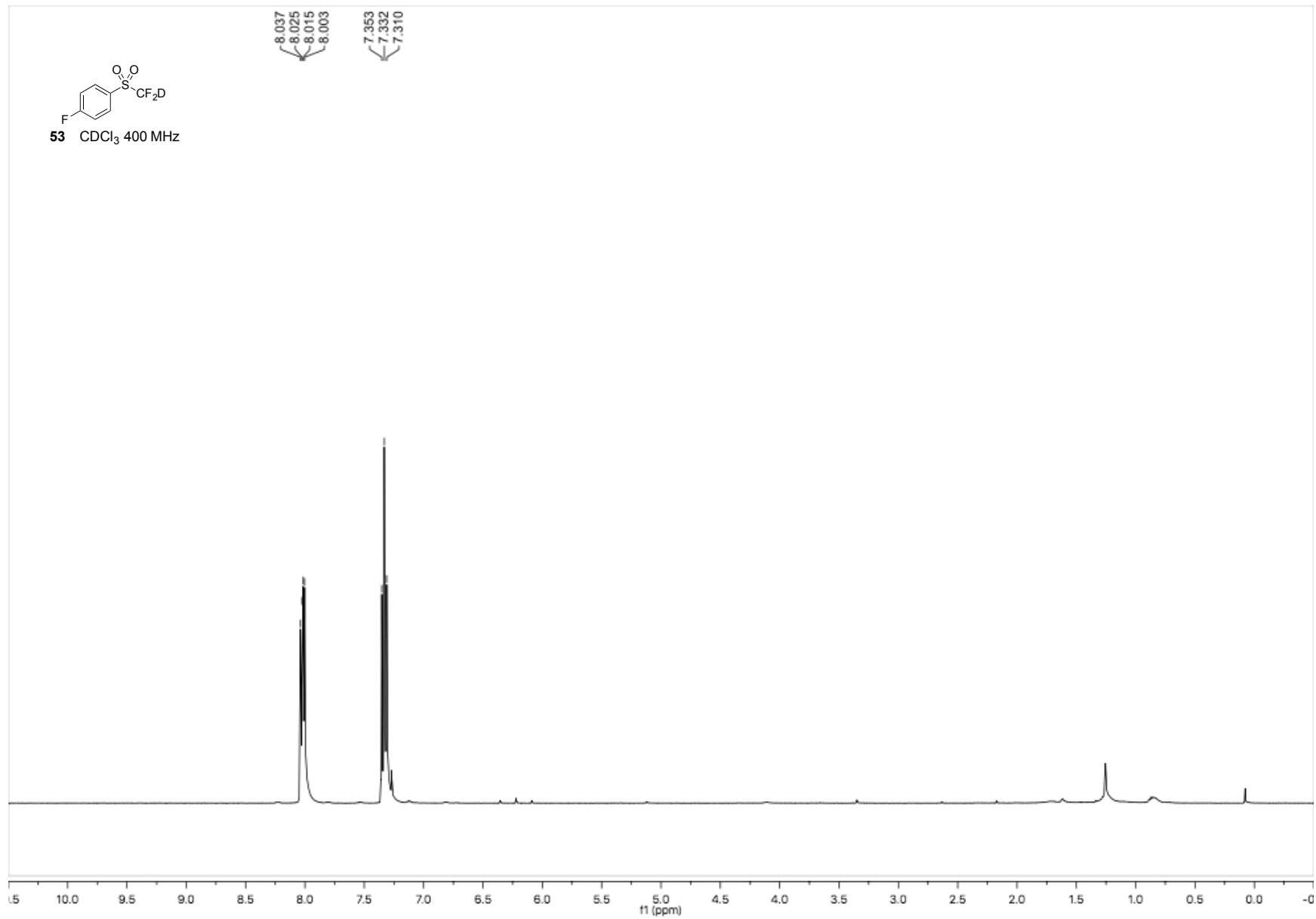
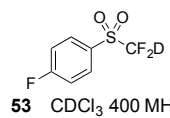
52 CDCl₃ 100 MHz

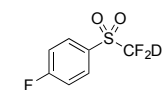




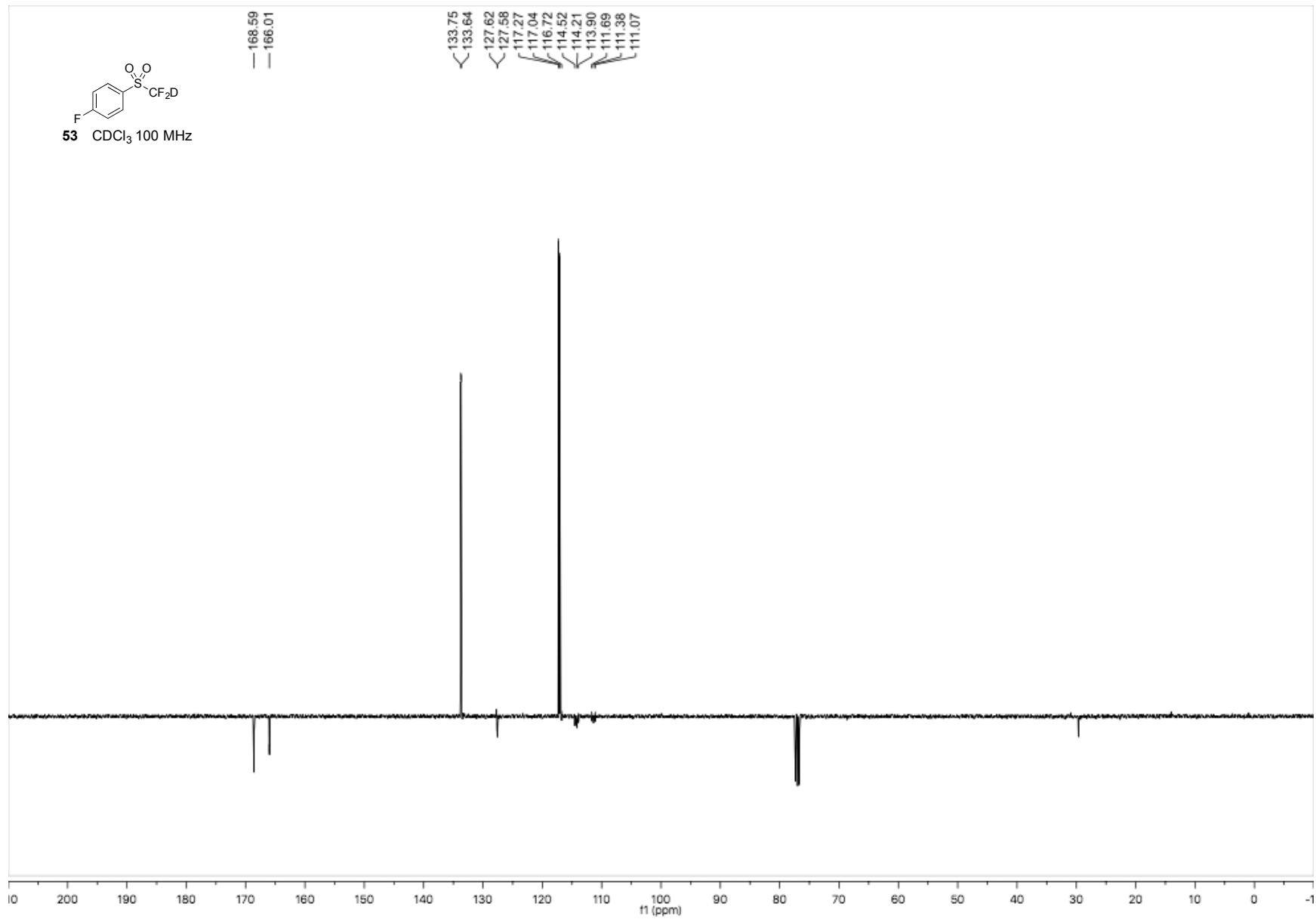
52 CDCl₃ 376 MHz

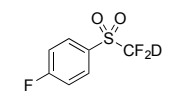




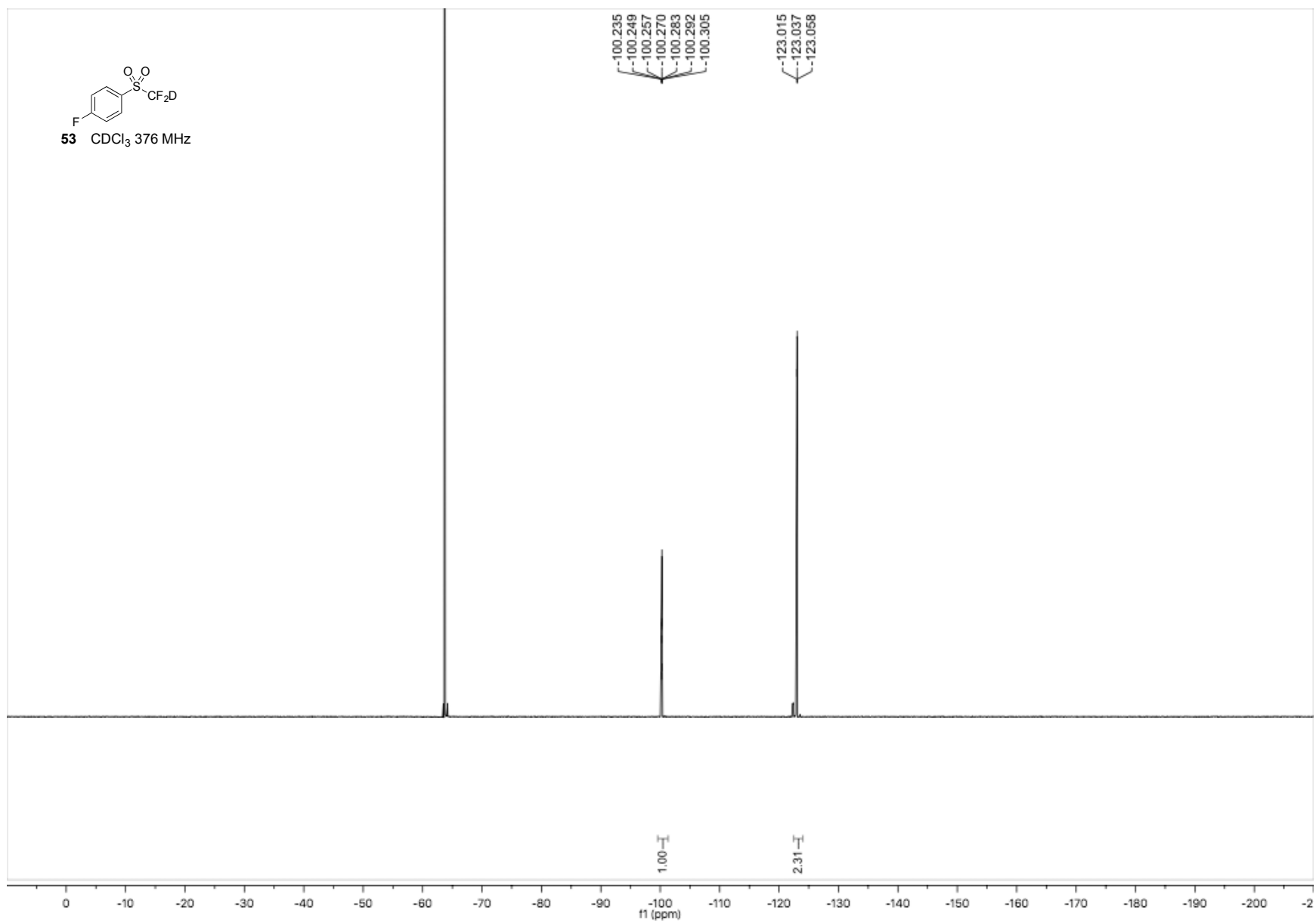


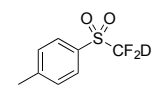
53 CDCl₃ 100 MHz



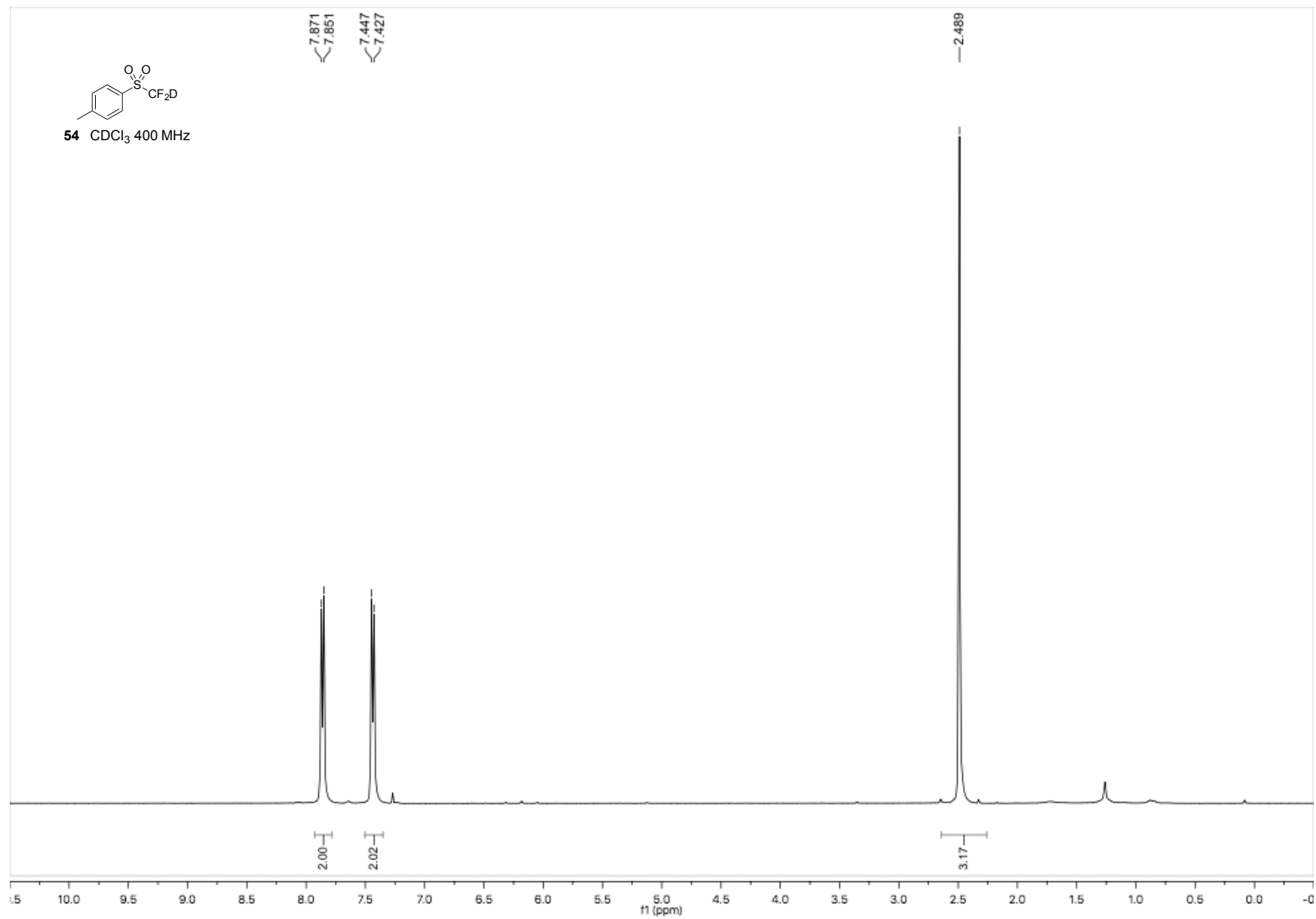


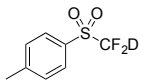
53 CDCl₃ 376 MHz



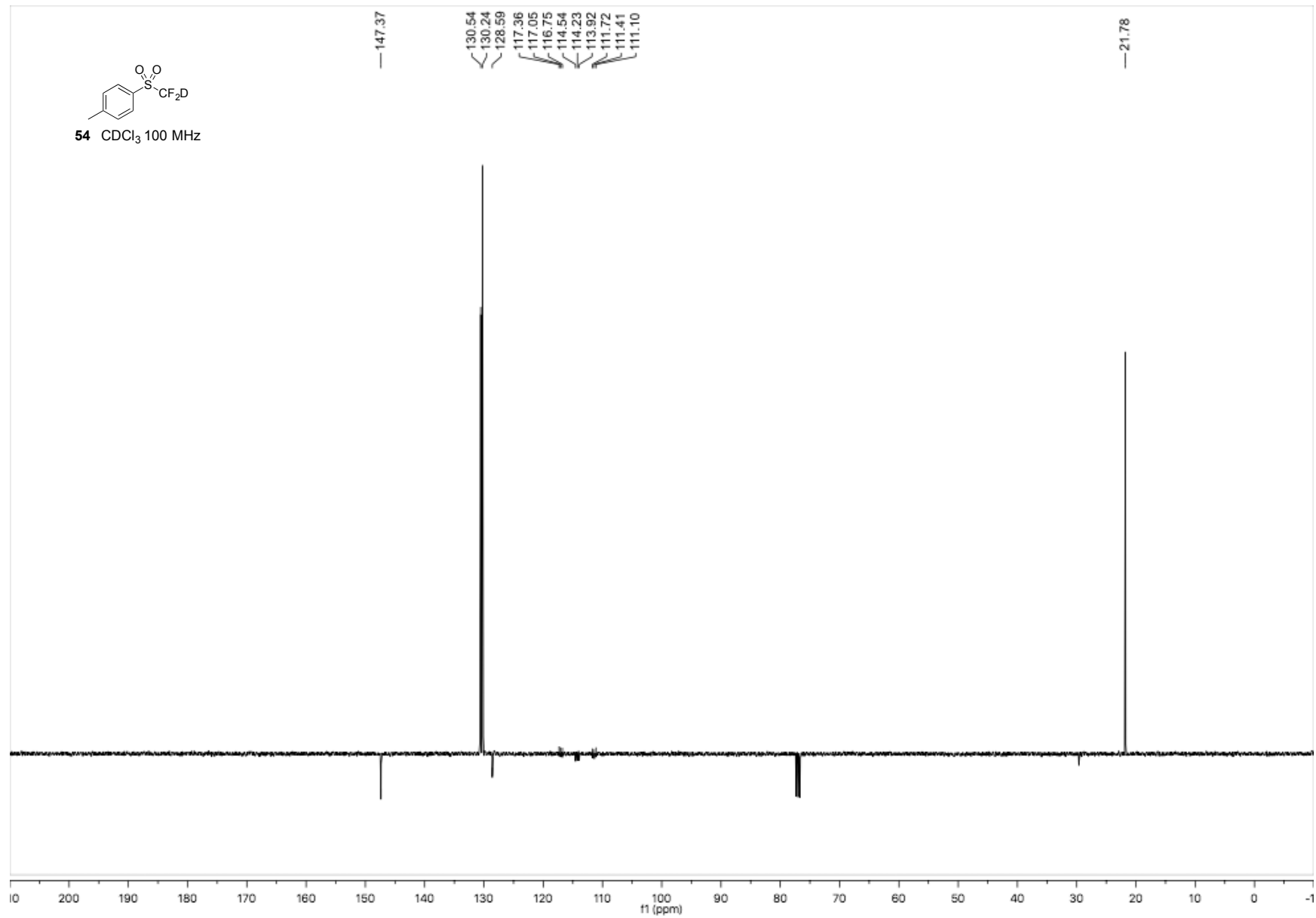


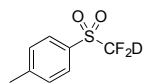
54 CDCl₃ 400 MHz





54 CDCl₃ 100 MHz





54 CDCl₃ 376 MHz

