Supporting Information

Efficient and Direct Nucleophilic Difluoromethylation of Carbonyl Compounds and Imines with Me_3SiCF_2H at Ambient or Low Temperature

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General Methods:

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. The solvent DMF was distilled from CaH_2, and the solvent THF and DME were distilled from sodium. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz or 300 MHz NMR spectrometer. ^1H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. Me_3SiCF_2H, and $PhMe_2SiCF_2H$ were prepared according to known procedures.[1a, b] $Me_3SiCF_2CH_3$ was prepared according to known procedures as a mixture of $Me_3SiCF_2CH_3$ and $Me_3SiOSiMe_3$ (molar ratio = 6:1, determine by ^1H NMR), and was used directly without further purification. [1c]

Typical procedure for difluoromethylation of aldehydes (2a-k) and 1,1-difluoroethylation of aldehyde 2a (for difluoroethylation of aldehyde 2a, 76 mg CsF was used):

Under N_2 atmosphere, CsF (10 mg, 0.07 mmol) was added to a solution of 4-methoxybenzaldehyde **2a** (68 mg, 0.50 mmol) and (difluoromethyl)trimethylsilane Me_3SiCF_2H (**1**) (124 mg, 1.0 mmol) in 2 mL of DMF, then the mixture was stirred at room temperature overnight. A solution of TBAF (1.0 ml, 1 M in THF) was then added, and the whole mixture was stirred for another 1h. After extraction with Et_2O and H_2O, the organic phase was washed with brine, and then dried over anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **3a**. (82 mg, 0.455 mmol, yield: 91%). Colorless oil. ^1H NMR: δ 7.30 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 7.9 Hz, 2H), 5.71 (td, J = 56.2 Hz, J = 4.6 Hz, 1H), 4.70 (td, J =10.3 Hz, J =

4.7 Hz, 1H), 3.78 (s, 3H), 2.88 (b, 1H). ^{19}F NMR: δ 128.20 (dd, *J* = 56.2 Hz, *J* = 10.5 Hz, 2F). MS (EI, m/z): 188 (M^+, 6.4), 137 (100.0), 109 (48.5), 77 (23.5). The characterization data was consistent with the previous report.[2]

3b: Colorless oil. IR (film): 3405, 2978, 1477, 1443, 1202, 1149, 1122, 1062, 752, 711 cm^{-1}. ^{1}H NMR: δ 7.51 (d, *J* = 7.1 Hz, 1H), 7.15–7.34 (m, 3H), 5.83 (t, *J* = 55.8 Hz, 1H), 5.29 (dd, *J* =15.1 Hz, *J* = 6.9 Hz, 1H), 2.68 (b, 1H). ^{19}F NMR: δ −127.00 (ddd, *J* = 281.3 Hz, *J* = 54.7 Hz, *J* = 6.9 Hz, 1F), −132.27 (ddd, *J* = 281.2 Hz, *J* = 55.6 Hz, *J* = 15.1 Hz, 1F). ^{13}C NMR: δ 133.4 (t, *J* = 3.7 Hz), 132.7, 130.0, 129.5, 128.6, 127.3, 114.7 (t, *J* = 246.6 Hz), 69.9 (dd, *J* = 25.1Hz, *J* = 22.5 Hz). MS (EI, m/z): 192 (M^+, 9.7), 141 (100.0), 113 (19.6), 77 (86.7), 51 (20.1). HRMS (EI): m/z calcd. For $C_8H_7ClF_2O$ (M^+) 192.0153, found 192.0157.

3c: Colorless oil. IR (film): 3589, 3394, 2977, 1702, 1601, 1578, 1480, 1434, 1383, 1202, 1142, 1076, 790, 765, 722, 706, 694, 448 cm^{-1}. ^{1}H NMR: δ 7.45 (s, 1H), 7.28–7.40 (m, 3H), 5.74 (td, *J* = 56.3 Hz, *J* = 4.7 Hz ,1H), 4.82 (td, *J* =10.2 Hz, *J* = 4.6 Hz, 1H), 2.54 (b, 1H). ^{19}F NMR: δ −128.27 (dd, *J* = 55.8 Hz, *J* = 10.4 Hz, 2F). ^{13}C NMR: δ 137.7, 134.6, 129.9, 129.1, 127.2 (d, *J* = 1.4 Hz), 125.2 , 115.4 (t, *J* = 246.1 Hz), 72.9 (t, *J* = 24.8Hz). MS (EI, m/z): 192 (M^+, 25.2), 141 (99.4), 113 (42.7), 77 (100.0), 51(19.0). HRMS (EI): m/z calcd. For $C_8H_7ClF_2O$ (M^+) 192.0153, found 192.0157.

3d: Colorless oil. IR (film): 3400, 2982, 1593, 1565, 1475, 1385, 1199, 1149, 1108, 1062, 1042, 896, 868, 854, 824, 778, 571 cm^{-1}. ^{1}H NMR: δ7.54 (d, *J* = 8.4 Hz , 1H), 7.45 (s, 1H), 7.41 (d, *J* = 2.1 Hz,1H), 7.32 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1H), 5.88 (td, *J* = 55.5 Hz, *J* = 3.3 Hz, 1H) 5.34 (ddd, *J* = 15.3 Hz, *J* = 6.9 Hz, *J* = 3.0 Hz, 1H), 2.88 (b, 1H). ^{19}F NMR: δ −127.70 (ddd, *J* = 281.9 Hz, *J* = 54.9 Hz, *J* = 7.3 Hz , 1F), −132.61 (ddd, *J* = 281.9 Hz, *J* = 55.8 Hz, *J* = 14.6 Hz , 1F). ^{13}C NMR: δ 135.3, 133.4, 132.1 (t, *J* = 3.0 Hz), 129.3, 127.7, 114.4 (t, *J* = 185.2 Hz), 69.5 (dd *J* = 19.0 Hz, *J* = 17.2 Hz). MS (EI, m/z): 226 (M^+, 9.1), 175 (100.0), 111 (50.3), 75 (16.6), 51 (6.7). HRMS (EI): m/z calcd. For $C_8H_6Cl_2F_2O$ (M^+) 225.9764, found 225.9774.

3e: Yellow oil. IR (film): 3096, 1533, 1482, 1354, 1206, 1139, 1072, 809, 730, 689 cm^{-1}. ^{1}H NMR: δ 8.31 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.1 Hz,1H), 7.58 (t, *J* =8.1 Hz, 1H), 5.79 (td, *J* = 55.8 Hz, *J* = 4.8 Hz, 1H), 4.99 (dt, *J* = 10.5, *J* = 4.5 Hz, 1H), 3.10 (b, 1H). ^{19}F NMR: δ −127.53 (ddd, *J* = 285.9 Hz, *J* = 55.2Hz, *J* =10.2 Hz , 1F), −129.18 (ddd, *J* = 286.5 Hz, *J* = 54.7 Hz, *J* = 10.2 Hz , 1F). ^{13}C NMR: δ 148.2, 137.8 (dd, *J* = 3.3 Hz, *J* = 1.7 Hz), 133.3 (d, *J* = 1.4 Hz), 129.6, 123.8, 122.1, 115.1 (t, *J* = 184.7 Hz), 72.4 (t, *J* = 18.4 Hz). MS (EI, m/z): 203 (M^+, 3.5), 152 (100.0), 105 (24.7), 77 (20.1), 51(12.0). HRMS (EI): m/z calcd. For $C_8H_7F_2NO_3$ (M^+) 203.0394, found 203.0398.

3f: Yellow oil. ^{1}H NMR: δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.72(td, *J* = 55.8 Hz, *J* = 4.5 Hz ,1H), 4.79 (td, *J* =10.2 Hz, *J* = 4.5 Hz, 1H), 2.60 (b, 1H). ^{19}F NMR: δ −127.28 (ddd, *J* = 285.7 Hz, *J* = 56.4 Hz, *J* = 10.4 Hz, 1F), −128.29 (ddd, *J* = 285.7 Hz, *J* = 56.4 Hz, *J* = 10.4 Hz, 1F). MS (EI, m/z): 236 (M^+, 19.6), 185 (100.0), 157 (18.4) , 77 (72.0) , 51 (16.7). The characterization data was consistent with the previous report.[3]

3g: Yellow solid. ^{1}H NMR: δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.71 (td, *J* = 56.1 Hz, *J* = 4.2 Hz, 1H), 4.64 (td, *J* =10.2 Hz, *J* = 4.5Hz, 1H), 2.93 (s, 6H), 2.67 (b, 1H). ^{19}F NMR: δ −127.49 (dt, *J* = 56.4 Hz, *J* = 10.4 Hz, 2F). MS (EI, m/z): 201 (M^+, 37.6), 164 (10.8), 150 (100.0) , 120 (18.7) , 77 (8.7). The characterization data was consistent with the previous report.[4]

3h: White solid. ^{1}H NMR: δ 7.27−7.42 (m, 2H), 6.99 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.4Hz, 1H), 5.95 (td, *J* = 56.4 Hz, *J* = 3.6 Hz ,1H), 5.02 (ddd, *J* =14.4 Hz, *J* = 6.9 Hz, *J* = 3.6 Hz, 1H), 3.84 (s, 3H), 3.23 (b, 1H). ^{19}F NMR: δ −125.80 (ddd, *J* = 280.9 Hz, *J* = 56.1 Hz, *J* = 7.6 H, 1F), −130.48 (ddd, *J* = 280.9 Hz, *J* = 56.7 Hz, *J* = 15.2 Hz, 1F). MS (EI, m/z): 188 (M^+, 21.6), 137 (100.0), 121 (20.2) , 107 (58.9) , 77 (24.3), 51 (10.0). The characterization data was consistent with the previous report.[4]

3i: White solid. ^{1}H NMR: δ 7.76–7.87(m, 4H), 7.41–7.53 (m, 3H), 5.81 (td, *J* = 55.8 Hz, *J* = 4.5 Hz ,1H), 4.91 (td, *J* =10.2 Hz, *J* = 4.5 Hz, 1H), 2.69 (b, 1H). ^{19}F NMR: δ −126.89 (ddd, *J* = 283.4 Hz, *J* = 55.4 Hz, *J* = 10.2 Hz, 1F), −128.09 (ddd, *J* = 283.7 Hz, *J* = 55.2 Hz, *J* = 10.4 Hz, 1F). MS (EI, m/z): 208 (M^+, 54.9), 157 (86.4), 129 (100.0). The characterization data was consistent with the previous report.[2]

3j: Yellow oil. ^{1}H NMR: δ 7.10–7.37 (m, 5H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9 Hz, *J* = 6.0 Hz, 1H), 5.61 (td, *J* = 56.7 Hz, *J* = 3.6 Hz ,1H), 4.26–4.42 (m, 1H), 2.56 (b, 1H). ^{19}F NMR: δ −128.03 (ddd, *J* = 285.1 Hz, *J* = 57.5 Hz, *J* = 12.1 Hz, 1F), −129.43 (ddd, *J* = 285.1 Hz, *J* = 55.8 Hz, *J* = 10.4Hz, 1F). MS (EI, m/z): 184 (M^+, 29.6), 133 (100.0), 115 (38.1) , 105 (15.9) , 77 (20.8), 55 (26.4). The characterization data was consistent with the previous report.[2]

3k: Yellow oil. ^{1}H NMR: δ 7.06–7.28 (m, 5H), 5.52 (td, *J* = 55.8 Hz, *J* = 4.2 Hz ,1H), 3.55–3.75 (m, 1H), 2.74–2.90 (m, 1H), 2.56–2.74 (m, 1H), 2.05 (b, 1H), 1.60–1.95 (m, 2H). ^{19}F NMR: δ −129.72 (dd, *J* = 56.4 Hz, *J* = 10.9 Hz, 2F). MS(EI, m/z): 186 (M^+, 28.7), 117 (51.2), 105 (18.0), 91 (100.0). The characterization data was consistent with the previous report.[5]

3l: Yellow oil: IR (film): 3428, 2956, 2838, 1612, 1514, 1301, 1247, 1179, 1139, 1065, 1035, 831. ^{1}H NMR: δ 7.12 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.60 (td, *J* = 56.4 Hz, *J* = 3.9 Hz, 1H), 3.78 (s, 3H), 3.78-1.62 (m, 1H) , 2.90-2.75 (m, 1H), 2.75-2.57 (m, 1H), 2.15 (b, 1H), 1.97-1.69 (m, 2H). ^{19}F NMR: δ −129.91 (dd, *J* = 55.6 Hz, 10.2 Hz, 2F). ^{13}C NMR: δ 157.9, 132.9, 129.4, 116.3 (t, *J* = 244.2 Hz), 113.1, 70.2 (t, *J* = 23.3 Hz), 55.2, 31.6 (t, *J* = 2.9 Hz), 30.0. MS (EI, m/z): 216 (M^+, 22.6), 170 (9.0), 154 (10.8) , 121 (100.0) . HRMS (EI): m/z calcd. For $C_{11}H_{14}F_2O_2$ (M^+) 216.0962, found 216.0964 .

11: ^{1}H NMR: δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.80 (t, *J* = 9.6 Hz, 1H), 3.82 (s, 3H), 2.05 (b, 1H), 1.50 (t, *J* = 18.9 Hz, 3H). ^{19}F NMR: δ −101.50 (qd, *J* = 18.0 Hz, *J* = 9.3 Hz, 2F). MS (EI, m/z): 202 (M^+, 9.2), 137 (100.0), 109 (27.1) , 94 (22.2) , 77 (21.3), 65 (17.2). HRMS (EI): m/z calcd. For $C_{11}H_{14}F_2O$ (M^+) 200.1013, found 200.1012. The characterization data was consistent with the previous report.[1c]

Typical procedure for *t*BuOK-mediated difluoromethylation of ketones (4a, 4b, 8) and 1,1-difluoroethylation of ketone 4a:

Under N_2 atmosphere, *t*BuOK (100 mg, 0.89 mmol) in 1.5 mL THF was added to a solution of 9H-fluoren-9-one **4a** (55 mg, 0.305 mmol) and (difluoromethyl)-trimethylsilane Me_3SiCF_2H (**1**) (108 mg, 0.87 mmol) in 2 mL THF at −78 °C, then the mixture was slowly warmed to room temperature. After extraction with Et_2O and H_2O, the organic phase was s dried over anhydrous $MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **5a** (67 mg, 0.289 mmol, yield: 95%). White solid. Mp: 103−105 °C. IR (KBr): 3374, 3065, 3044, 2955, 1450, 1349, 1205, 1143, 1088, 1070, 1056, 925, 806, 778, 768, 751, 740, 731, 675, 625, 576. ^{1}H NMR: δ 7.56−7.66 (m, 4H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 5.82 (t, *J* = 55.5 Hz, 1H), 2.62 (b, 1H). ^{19}F NMR: δ −129.26 (d, *J* = 55.6 Hz, 2F). ^{13}C NMR: δ 142.1 (t, *J* = 1.7 Hz), 140.7, 130.3, 128.2, 125.3 (t, *J* = 1.7 Hz), 120.2, 115.6 (t, *J* = 249.5 Hz) , 81.2 (t, *J* = 21.7 Hz). MS (EI, m/z): 232 (M^+, 17.5), 181 (100.0), 152 (40.6), 76 (8.6). HRMS (EI): m/z calcd. For $C_{14}H_{10}F_2O$ (M^+) 232.0700, found 232.0702.

5b: Yellow oil. IR (film): 3568, 2974, 1910, 1596, 1577, 1493, 1406, 1139, 1096, 1077, 1015, 910, 827, 800, 758, 528, 501 cm^{-1}. ^{1}H NMR: δ 7.39 (d, *J* = 9.0 Hz, 4H), 7.34 (d, *J* = 8.7 Hz, 4H), 6.12 (t, *J* = 55.5 Hz, 1H), 2.90 (b, 1H). ^{19}F NMR: δ −127.35 (d, *J* = 55.8 Hz, 2F). ^{13}C NMR: δ 138.4, 134.5, 128.6, 128.5 (t, *J* = 1.7 Hz), 116.5 (t, *J* = 251.7 Hz), 77.4 (t, *J* = 21.5Hz). MS (EI, m/z): 302 (M^+, 2.7), 251 (100.0), 197 (96.2), 139 (76.2), 105 (58.8), 77 (23.7). HRMS (EI): m/z calcd. For $C_{14}H_{10}Cl_2F_2O$ (M^+) 302.0077, found 302.0075.

9: White solid. Mp: 130–132 ^{o}C. IR (KBr): 3446, 2952, 2920, 2896, 1591, 1493, 1438, 1250, 1130, 1073, 1040, 864, 835, 808, 773 cm^{-1}. ^{1}H NMR: δ 8.23 (d, *J* =4.5 Hz,1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.64 (s, 1H), 7.29 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.93 (dd, *J* = 7.8 Hz, *J* = 5.1 Hz, 1H), 5.71 (d, *J* = 10.5 Hz, 1H), 5.59 (t, *J* = 56.4 Hz, 1H), 5.53 (d, *J* = 10.5 Hz, 1H), 3.64 (dd, *J* = 9.3 Hz, *J* = 7.2 Hz, 2H), 3.49 (b, 1H), 0.96 (dd, *J* = 9.3 Hz, *J* = 7.5 Hz, 2H), –0.04 (s, 9H). ^{19}F NMR: δ –130.30 (dd, *J* = 247.7 Hz, *J* = 55.3 Hz, 1F), –131.50 (dd, *J* = 247.4 Hz, *J* = 56.1 Hz, 1F). ^{13}C NMR: δ 149.7, 148.5, 137.0, 136.9, 130.0, 127.1, 127.0, 121.9, 117.2, 116.3, 115.7 (t, *J* = 251.3 Hz), 114.0, 72.6, 70.7 (t, *J* = 21.8 Hz), 65.3, 18.0, –1.52. MS (EI, m/z): 412 (M^+, 8.5), 361 (44.8), 303 (90.), 73 (100.0). HRMS (EI): m/z calcd. For $C_{19}H_{23}ClF_2N_2O_2Si$ (M^+) 412.1185, found 412.1183.

12: Yellow oil. IR (film): 3550, 3441, 3064, 3008, 1608, 1452, 1386, 1190, 1146, 1109, 1057, 933, 917, 890, 753, 734. ^{1}H NMR: δ 7.73-7.58 (m, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 2.77 (b, 1H), 1.25 (t, *J* = 18.6 Hz, 3H). ^{19}F NMR: δ –103.13 (q, *J* = 18.6 Hz, 2F). ^{13}C NMR: δ 143.5, 143.2, 130.0, 128.2, 125.2, 124.0 (t, *J* = 248.0 Hz), 120.1, 83.8 (t, *J* = 24.0 Hz), 19.5 (t, *J* = 26.4 Hz). MS (EI, m/z): 246 (M^+, 7.6), 181 (100.0), 152 (42.2) , 65 (8.1). HRMS (EI): m/z calcd. For $C_{15}H_{12}F_2O$ (M^+) 246.0856, found 246.0854.

Typical procedure for difluoromethylation of N-*tert*-butanesulfinimines (6a-h) and 1,1-difluoroethylation of N-*tert*-butanesulfinimine 6a:

Under N_2 atmosphere, *t*BuOK (100 mg, 0.89 mmol) in 1.5 mL THF was added to a solution of (E)-N-(4-methoxybenzylidene)-2-methylpropane-2-sulfinamide **6a** (72 mg, 0.300 mmol) and (difluoromethyl)trimethylsilane Me_3SiCF_2H **1** (108 mg, 0.87 mmol) in 2 mL THF at –78 ^{o}C, then the mixture was slowly warmed to room temperature. After extraction with Et_2O and H_2O, the organic phase was s dried over anhydrous

$MgSO_4$. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **7a** (80 mg, 0.274 mmol, yield: 91%). White solid. Mp: 51–52 °C. IR (KBr): 3453, 3102, 2962, 1612, 1516, 1243, 1180, 1062, 1050, 1029, 835 cm^{-1}. ^1H NMR: δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.92 (td, *J* = 55.5 Hz, *J* = 3.6 Hz, 1H), 4.50–4.65 (m, 1H), 3.78 (s, 3H), 3.63 (d, *J* = 5.7 Hz, 1H), 1.22 (s, 9H). ^{19}F NMR: δ −124.55 (ddd, *J* = 281.5 Hz, *J* = 55.3 Hz, *J* = 12.4 Hz, 1F), −126.68 (ddd, *J* = 281.5 Hz, *J* = 55.6 Hz, *J* = 12.4 Hz, 1F). ^{13}C NMR: δ 159.9, 129.2, 126.8, 115.3 (t, *J* = 246.1 Hz), 114.3, 60.0 (dd, *J* = 23.5 Hz, *J* = 22.3 Hz), 56.6, 55.2, 22.4. MS (ESI, m/z): 292.0 ($M+H^+$). HRMS (ESI): calcd. For $C_{13}H_{20}F_2NO_2S$ ($M+H^+$) 292.11773, found 292.11905.

7b: White solid. Mp: 109–111 °C. IR (KBr): 3331, 3027, 2985, 2964, 2916, 2868, 1249, 1068, 1017, 756 cm^{-1}. ^1H NMR: δ 7.23–7.38 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.96 (td, *J* = 56.4 Hz, *J* = 4.5 Hz, 1H), 4.69–4.86 (m, 1H), 4.24 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 1.23 (s, 9H). ^{19}F NMR: δ −121.52 (ddd, *J* = 277.2 Hz, *J* = 56.1 Hz, *J* = 8.7 Hz, 1F), −127.21 (ddd, *J* = 277.5 Hz, *J* = 56.4 Hz, *J* = 16.1 Hz, 1F). ^{13}C NMR: δ 149.8, 149.0, 138.6, 136.2, 130.7, 123.7, 114.6 (t, *J* = 247.0 Hz), 58.5 (t, *J* = 23.0 Hz), 57.0, 22.3. MS (ESI, m/z): 292.2 ($M+H^+$), 314.1 ($M+Na^+$). HRMS (ESI): calcd. For $C_{13}H_{19}F_2NNaO_2S$ ($M+Na^+$) 314.09968, found 314.10033.

7c: White solid. Mp: 119–121 °C. IR (KBr): 3445, 3117, 2991, 2979, 2924, 2864, 1363, 1071, 815, 535 cm^{-1}. ^1H NMR: δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 5.93 (td, *J* = 55.5 Hz, *J* = 3.6 Hz, 1H), 4.52–4.68 (m, 1H), 3.67 (d, *J* = 5.7 Hz, 1H), 2.34 (s, 3H), 1.22 (s, 9H). ^{19}F NMR: δ −124.42 (ddd, *J* = 281.4 Hz, *J* = 55.6 Hz, *J* = 12.1 Hz, 1F), −126.67 (ddd, *J* = 280.6 Hz, *J* = 55.6 Hz, *J* = 12.4 Hz, 1F). ^{13}C NMR: δ 138.8, 131.8, 129.6, 127.7, 115.3 (t, *J* = 246.4 Hz), 60.3 (dd, *J* = 23.0 Hz, *J* = 21.9 Hz), 56.6, 22.3, 21.0. MS (ESI, m/z): 276.0 ($M+H^+$). HRMS (ESI): calcd. For $C_{13}H_{20}F_2NOS$ ($M+H^+$) 276.12282, found 314.12357.

7d: White solid. Mp: 117–119 °C. IR (KBr): 3448, 3112, 2991, 2955, 2925, 2900, 2866, 1491, 1363, 1070, 1056, 749 cm^{-1}. ^{1}H NMR: δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.95 (td, *J* = 55.2 Hz, *J* = 3.0 Hz, 1H), 4.53-4.70 (m, 1H), 3.82 (d, *J* = 6.6 Hz, 1H), 1.23 (s, 9H). ^{19}F NMR: δ −125.33 (ddd, *J* = 282.3 Hz, *J* = 55.3 Hz, *J* = 14.9 Hz, 1F), −126.50 (ddd, *J* = 282.0 Hz, *J* = 55.3 Hz, *J* = 10.2 Hz, 1F). ^{13}C NMR: δ 133.7, 132.0, 129.7, 123.1, 114.8 (t, *J* = 242.8 Hz), 59.8 (t, *J* = 23.0 Hz), 56.8, 22.3. MS (ESI, m/z): 340.1 ($M+H^+$). HRMS (ESI): calcd. For $C_{12}H_{16}BrF_2NNaOS$ ($M+Na^+$) 361.99962, found 362.00041.

7e: Yellow oil. IR (film): 3435, 3184, 2961, 2928, 2869, 1476, 1429, 1365, 1075, 712 cm^{-1}. ^{1}H NMR: δ 8.66 (s, 1H), 8.61 (d, *J* = 4.5 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 7.5 Hz, *J* = 4.8 Hz, 1H), 6.04 (td, *J* = 55.2 Hz, *J* = 2.7 Hz, 1H), 4.63-4.80 (m, 1H), 4.24 (d, *J* = 6.9 Hz, 1H), 1.24 (s, 9H). ^{19}F NMR: δ −124.96 (ddd, *J* = 283.7Hz, *J* = 56.1 Hz, *J* = 12.4 Hz, 1F), −126.84 (ddd, *J* = 282.5 Hz, *J* = 55.0 Hz, *J* = 13.5 Hz, 1F). ^{13}C NMR: δ 149.8, 149.0, 136.2, 130.7, 123.7, 114.6 (t, *J* = 246.7 Hz), 58.5 (t, *J* = 23.0 Hz), 57.0, 22.3. MS (ESI, m/z): 263.4 ($M+H^+$). HRMS (ESI): calcd. For $C_{11}H_{16}F_2N_2NaOS$ ($M+Na^+$) 285.08436, found 285.08513.

7f: White solid. Mp: 81–83 °C. IR (KBr): 3253, 2959, 2874, 1479, 1368, 1151, 1051, 1015, 907, 872 cm^{-1}. ^{1}H NMR: δ 5.91 (t, *J* = 54.9 Hz, 1H), 3.36 (d, *J* = 8.7 Hz, 1H), 3.17 (dt, *J* = 22.2 Hz, *J* = 9.3 Hz, 1H), 1.23 (s, 9H), 1.04 (s, 9H). ^{19}F NMR: δ −119.42 (ddd, *J* = 286.8 Hz, *J* = 53.6 Hz, *J* = 10.2 Hz, 1F), −127.97 (ddd, *J* = 288.5 Hz, *J* = 55.8 Hz, *J* = 23.1 Hz, 1F). ^{13}C NMR: δ 114.5 (t, *J* = 243.5 Hz), 66.8 (t, *J* = 17.0 Hz), 57.1, 33.1 (d, *J* = 6.1 Hz), 26.9, 22.5. MS (ESI, m/z): 242.1 ($M+H^+$). HRMS (ESI): calcd. For $C_{10}H_{22}F_2NOS$ ($M+H^+$) 242.13847, found 242.13942.

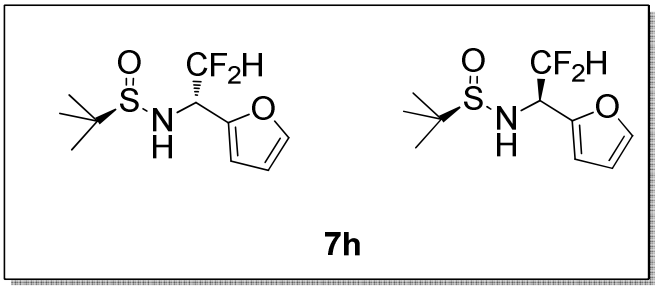
7g: White solid. Mp: 123–124 °C. IR (KBr): 3448, 3115, 3032, 2987, 2968, 2926, 2905, 2866, 1449, 1382, 1361, 1123, 1065, 1048, 970, 752, 694 cm^{-1}. ^{1}H NMR: δ 7.41 (d, *J* = 6.9 Hz, 2H), 7.22-7.37 (m, 3H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.23 (dd, *J* = 15.9 Hz, *J* = 6.6 Hz, 1H), 5.83 (td, *J* = 55.8 Hz, *J* = 3.0 Hz, 1H), 4.16-4.35 (m, 1H),

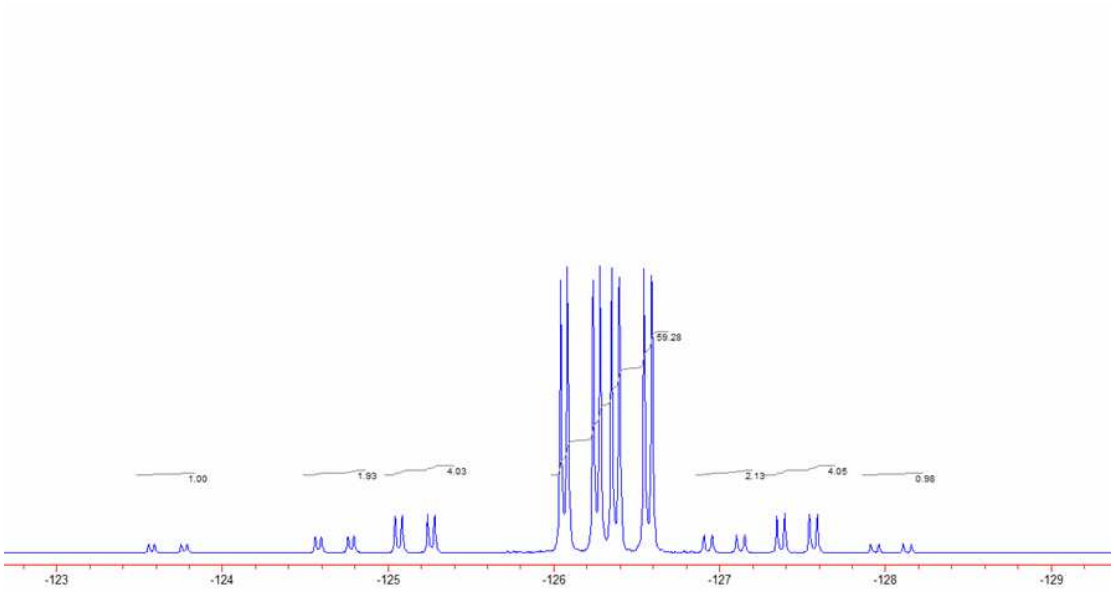
3.54 (d, *J* = 7.5 Hz, 1H), 1.23 (s, 9H). ^{19}F NMR: δ −125.94 (ddd, *J* = 282.8 Hz, *J* = 55.6 Hz, *J* = 12.1 Hz, 1F), −127.46 (ddd, *J* = 281.2 Hz, *J* = 56.4 Hz, *J* = 13.8 Hz, 1F). ^{13}C NMR: δ 136.0, 135.6, 128.6, 128.4, 126.8, 121.5 (t, *J* = 3.9 Hz), 115.1 (t, *J* = 246.8 Hz), 59.8 (t, *J* = 22.8 Hz), 22.4. MS (ESI, m/z): 288.0 ($M+H^+$). HRMS (ESI): calcd. For $C_{14}H_{20}F_2NOS$ ($M+H^+$) 288.12282, found 288.12334.

7h: Yellow oil. IR (film): 3203, 2962, 1504, 1472, 1366, 1234, 1151, 1072, 1014, 885, 742, 598 cm^{-1}. ^{1}H NMR: δ 7.44 (s, 1H), 6.47 (d, *J* = 3.0 Hz, 1H), 6.36-6.40 (m, 1H), 6.00 (td, *J* = 55.5 Hz, *J* = 3.0 Hz, 1H), 4.63-4.78 (m, 1H), 3.80 (d, *J* = 7.5 Hz, 1H), 1.25 (s, 9H). ^{19}F NMR: δ −124.86 (ddd, *J* = 280.6 Hz, *J* = 55.8 Hz, *J* = 8.7 Hz, 1F), −127.67 (ddd, *J* = 282.6 Hz, *J* = 55.6 Hz, *J* = 13.2 Hz, 1F). ^{13}C NMR: δ 133.7, 132.0, 129.7, 123.1, 114.8 (t, *J* = 247.0 Hz), 59.8 (t, *J* = 23.0 Hz), 56.8, 22.3. MS (ESI, m/z): 252.0 ($M+H^+$). HRMS (ESI): calcd. For $C_{10}H_{16}F_2NO_2S$ ($M+H^+$) 252.08643, found 252.08740.

13: White solid. Mp: 106-108 ^{o}C. IR (KBr): 3227, 2998, 2961, 2940, 1615, 1520, 1409, 1257, 1233, 1186, 1129, 1062, 1024, 922, 827, 803, 558. ^{1}H NMR: δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.55-4.40 (m, 1H), 3.78 (s, 3H), 3.66 (d, *J* = 6.6 Hz, 1H), 1.52 (t, *J* = 18.6 Hz, 3H), 1.22 (s, 9H). ^{19}F NMR: δ −96.88 (dqd, *J* = 245.6 Hz, *J* = 18.9 Hz, *J* = 10.4 Hz, 1F), δ −100.77 (dqd, *J* = 243.9 Hz, *J* = 19.1 Hz, *J* = 19.0 Hz 1F). ^{13}C NMR: δ 159.8, 129.3, 128.6, 122.9 (t, *J* = 244.9 Hz), 114.2, 63.5 (t, *J* = 25.3 Hz), 56.6, 55.2, 22.4, 21.4 (t, *J* = 26.9 Hz). MS (ESI, m/z): 306.1 ($M+H^+$), 328.1 ($M+Na^+$). HRMS (MALDI): calcd. For $C_{14}H_{22}F_2NO_2S$ ($M+H^+$) 306.1334, found 306.1347.

An example of determination of diastereomeric ratio of 7a-7h (reaction mixture after saturated NaCl water solution and EtOAc was added) by ^{19}F NMR:

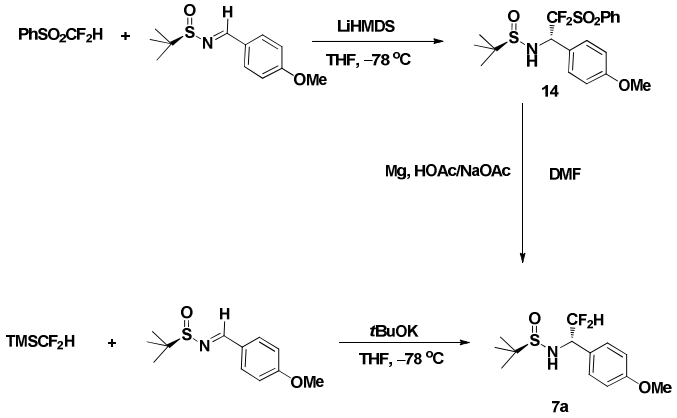




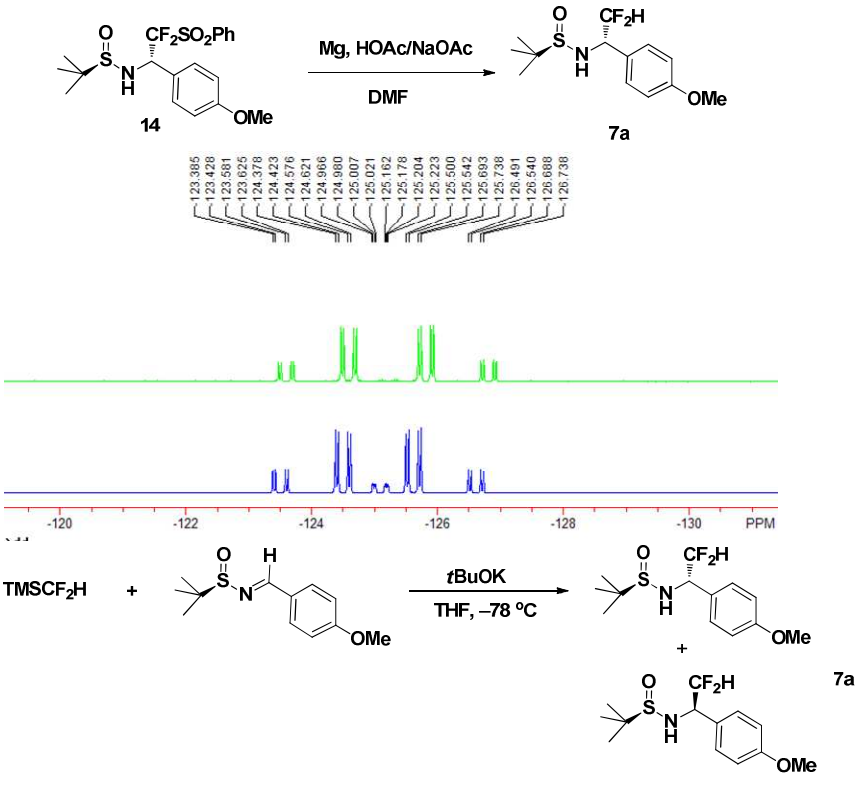
dr ratio = (4.03 + 59.28 + 4.05)/(1.00 + 1.93 + 2.13 + 0.98) = 92:8

Determination the relative configuration of the main isomer of product 7a. Compound **14** was synthesized according to known procedure.[6] After desulfonation of compound **14** with Mg/HOAc/NaOAc, we compared the ^{19}F NMR spectrum of product and compound **7a** synthesized from our direct difluoromethylation with

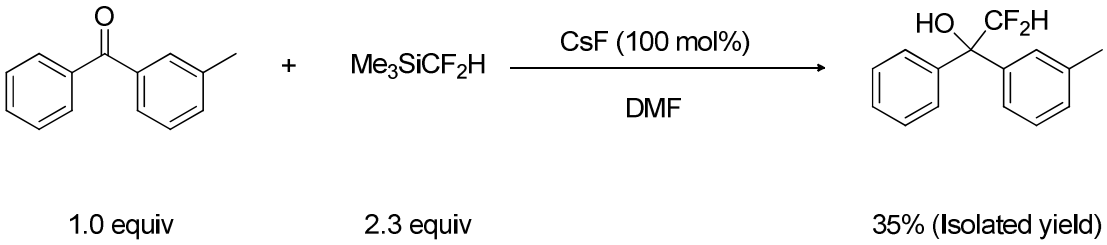
Me_3SiCF_2H. The relative configuration of the main isomer of product **7a** obtained from these two ways is the same.



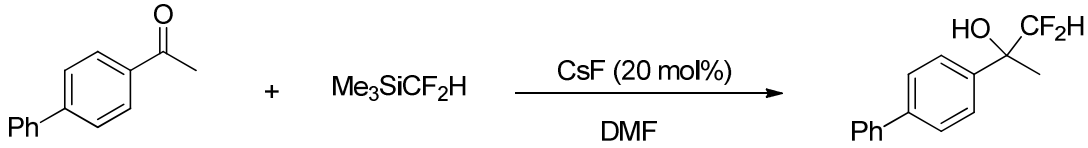
^{19}F NMR



Difluoromethylation of ketones in DMF.

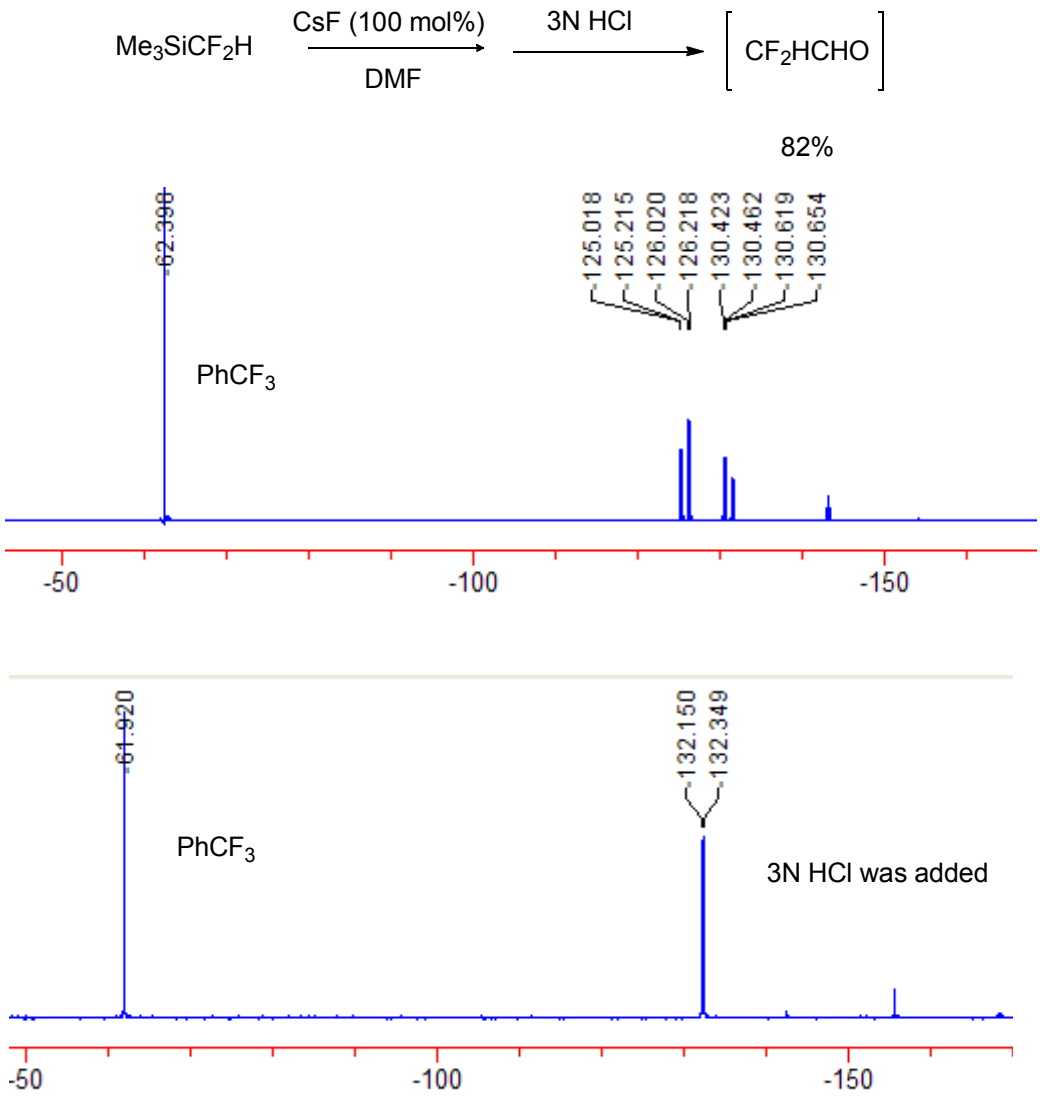


1.0 equiv | 2.3 equiv | 35% (Isolated yield)



1.0 equiv | 2.9 equiv | 39% (Isolated yield)

Difluoromethylation of DMF in absence of carbonyl compound.



Reference:

1. a) Prakash, G. K. S.; Hu, J; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457. b) Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 717. c) Mogi, R.; Morisaki, K.; Hu, J; Prakash, G. K. S.; Olah, G. A. *J. Fluorine Chem.* **2007**, *128*, 1098.
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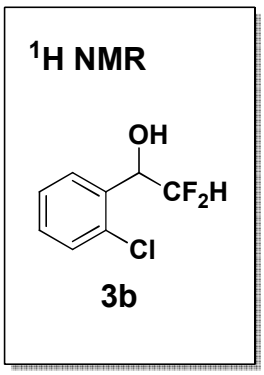
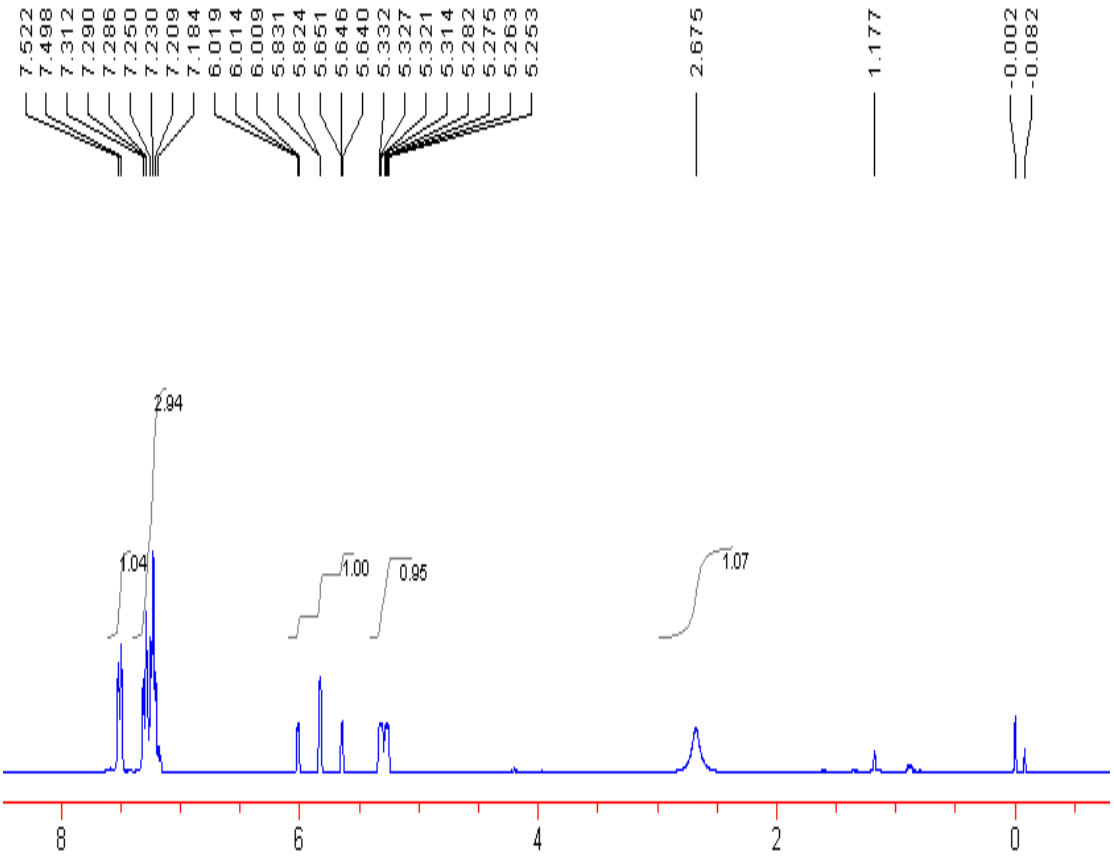
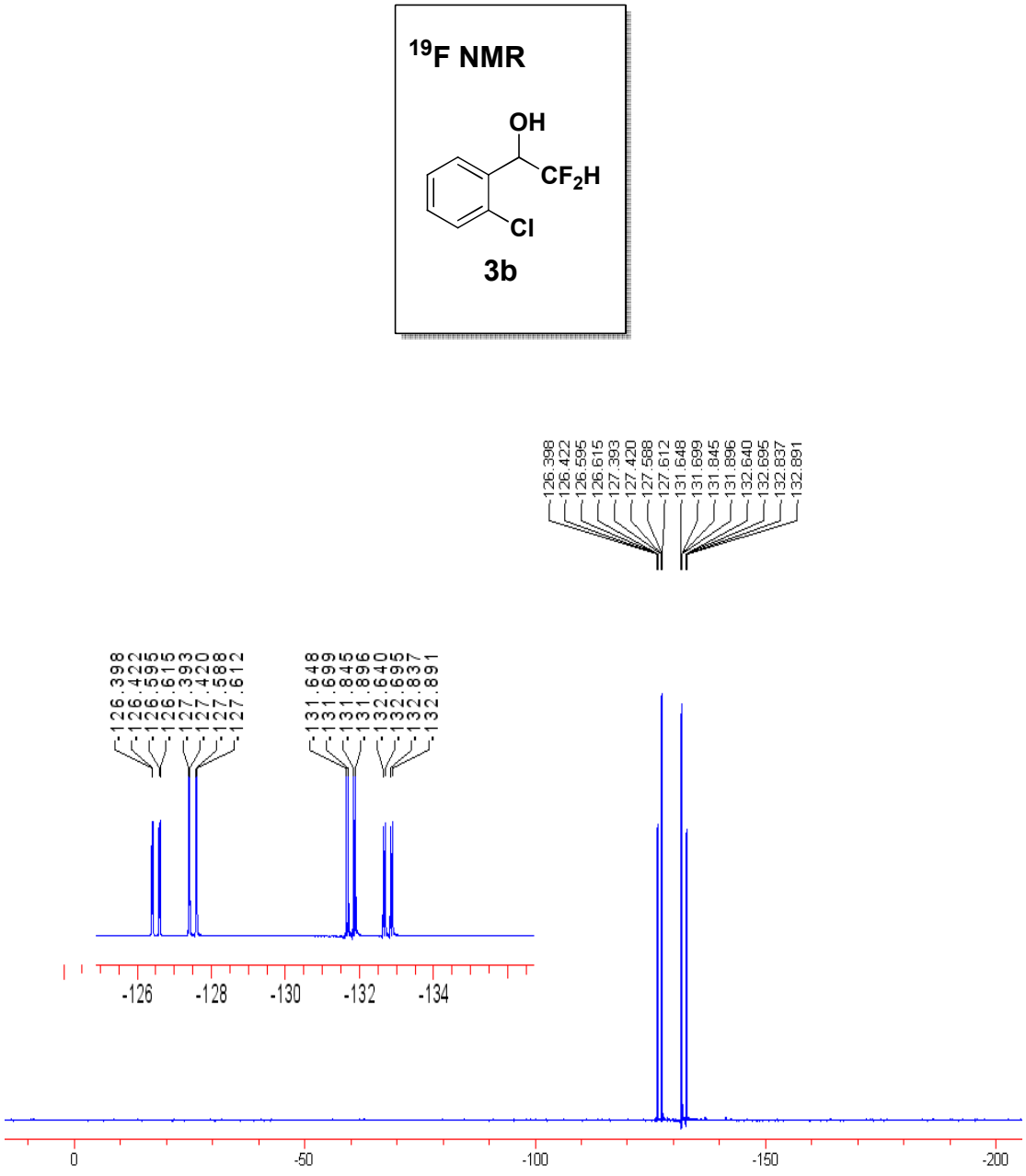
3. Isabel, E.; Bateman, K. P.; Chauret, N.; Cromlish, W.; Desmarais, S.; Duong, L. T.; Falgueyret, J.-P.; Gauthier, J. Y.; Lamontagne, S.; Lau, C. K.; Léger, S.; LeRiche, T.; Lévesque, J.-F.; Li, C. S.; Massé, F.; McKay, D. J.; Mellon, C.; Nicoll-Griffith, D. A.; Oballa, R. M.; Percival, M. D.; Riendeau, D.; Robichaud, J.; Rodan, G. A.; Rodan, S. B.; Seto, C.; Thérien, M.; Truong, V. L.; Wesolowski, G.; Young, R. N.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 887.
4. Liu, J.; Ni, C. ; Li, Y.; Zhang, L.; Wang, G. Y.; Hu, J. *Tetrahedron Lett.* **2006**, *47*, 6753.
5. Prakash, G. K. S.; Hu, J. ; Wang, Y.; Olah, G. A. *Eur. J. Org. Chem.* **2005**, 2218.
6. Li, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5882.

^{1}H, ^{19}F, and ^{13}C NMR spectra of all new products:



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CF2H
Cl
3b
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131.699
131.845
131.896
132.640
132.695
132.837
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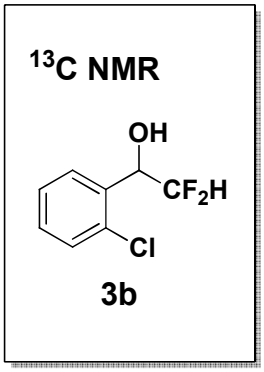
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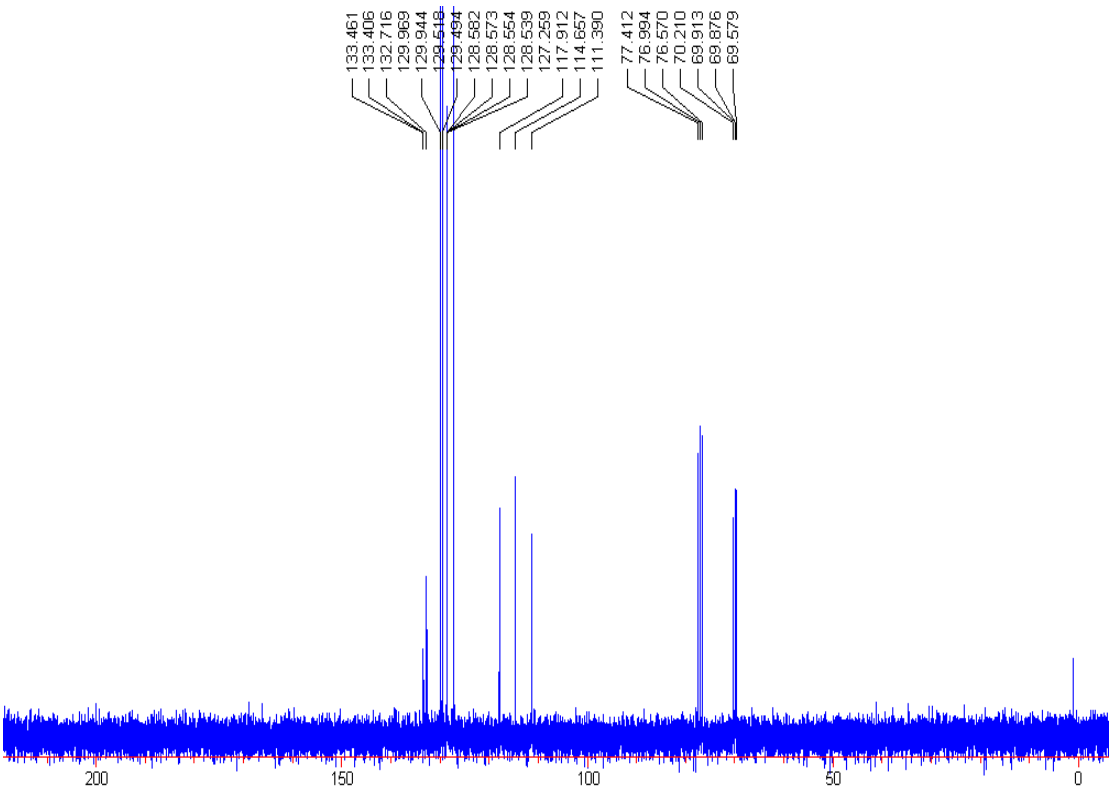
OH
CF2H
Cl
3b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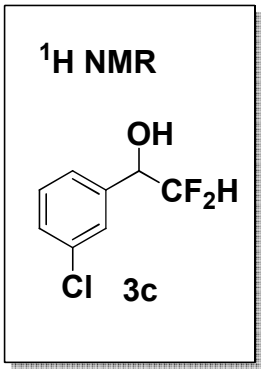
0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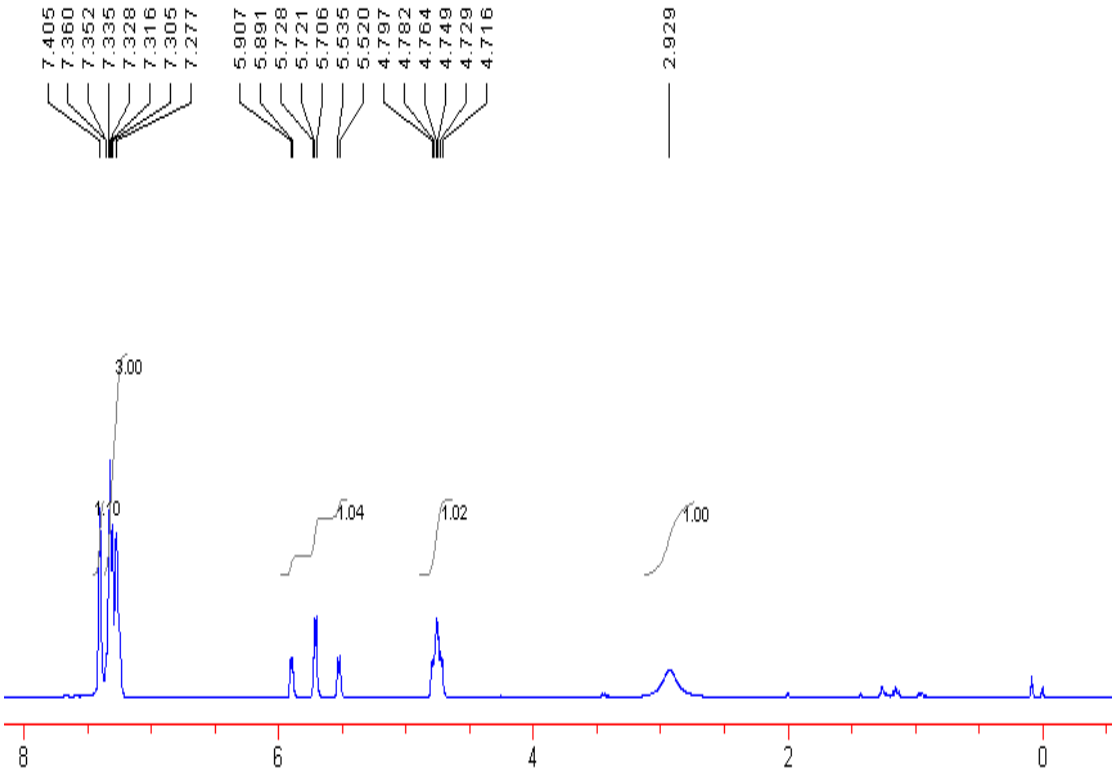
OH
CF2H
Cl
3c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5.520
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1.02
1.00
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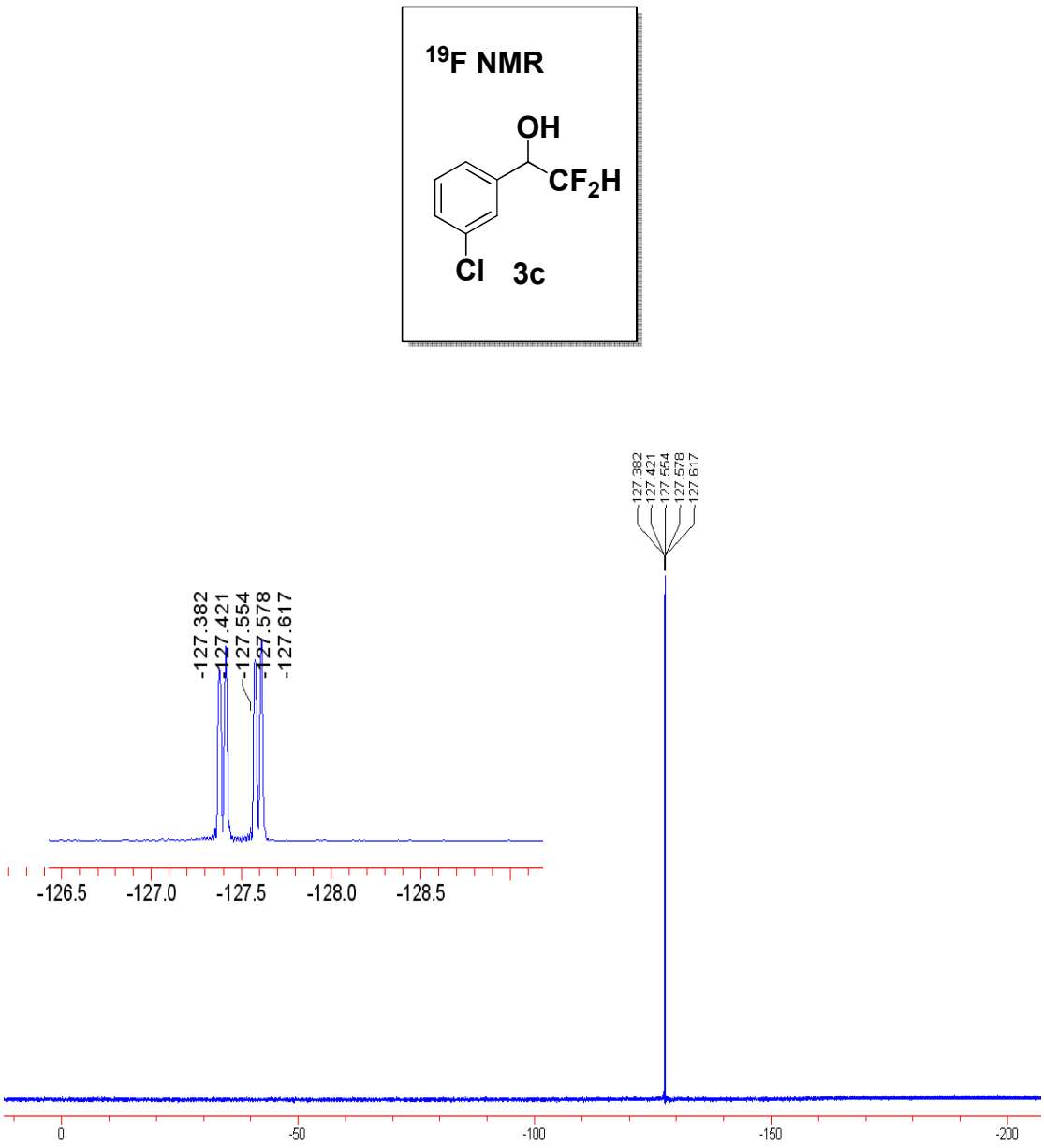
6
4
2
0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CF2H
Cl
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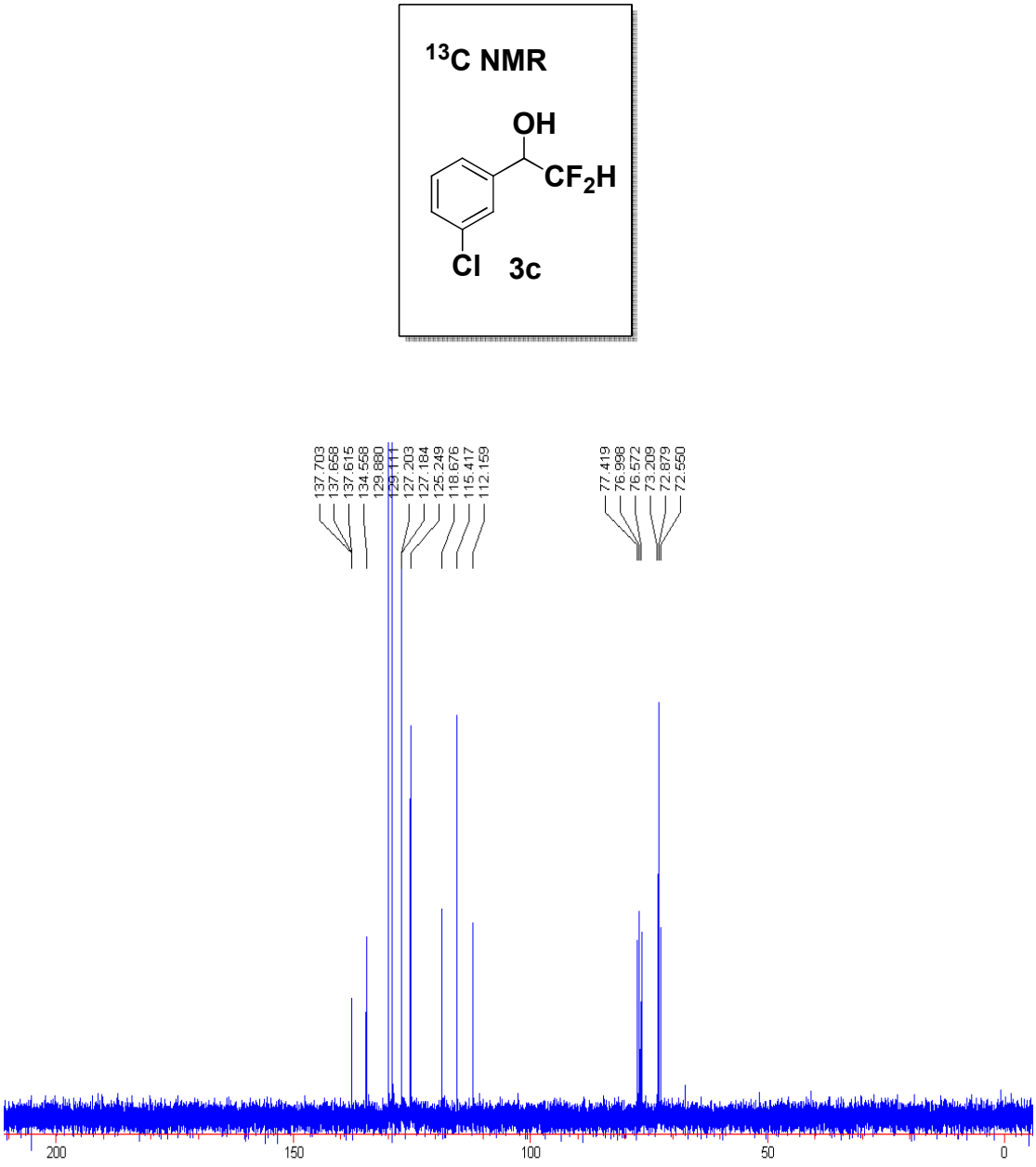
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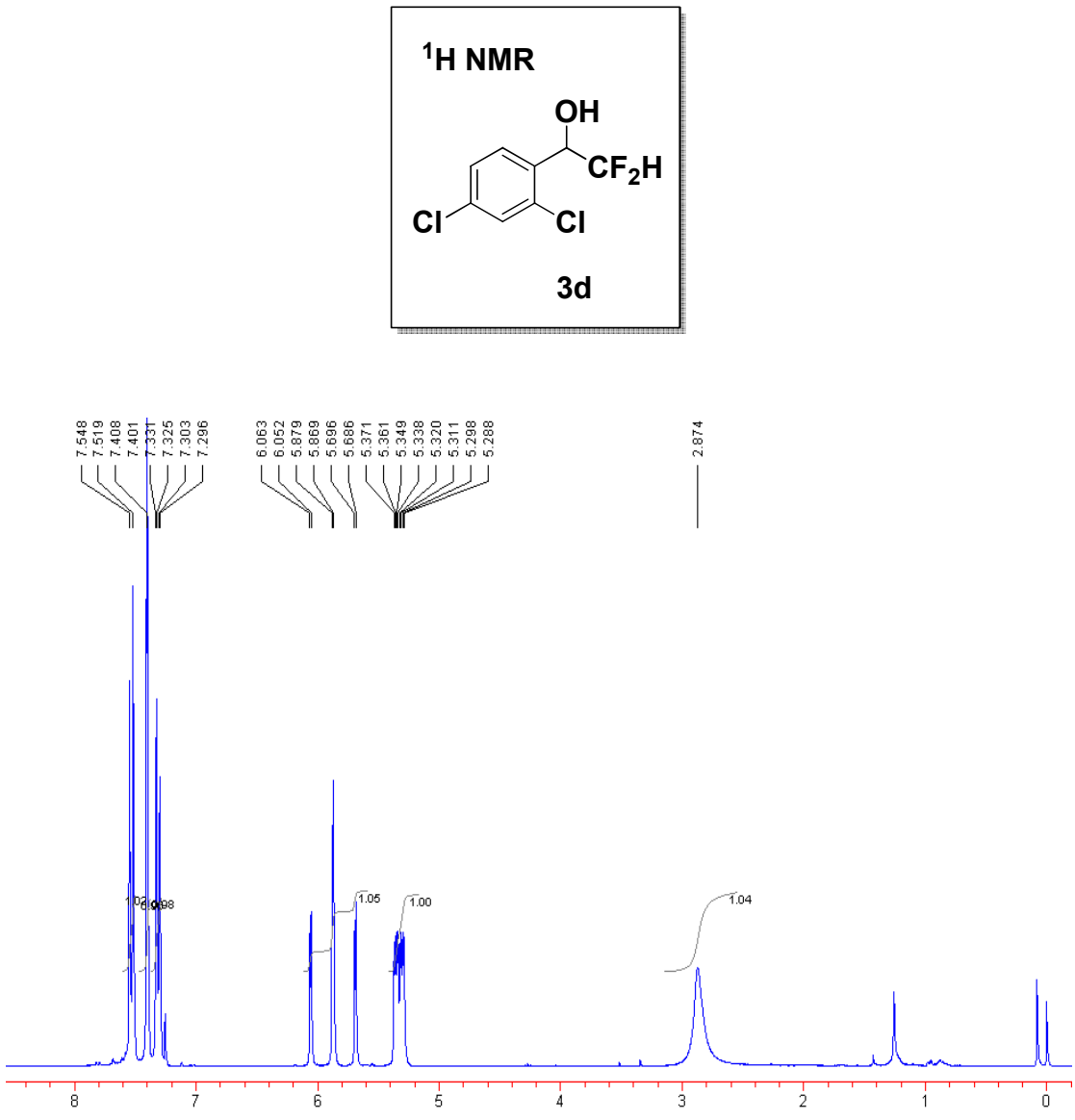
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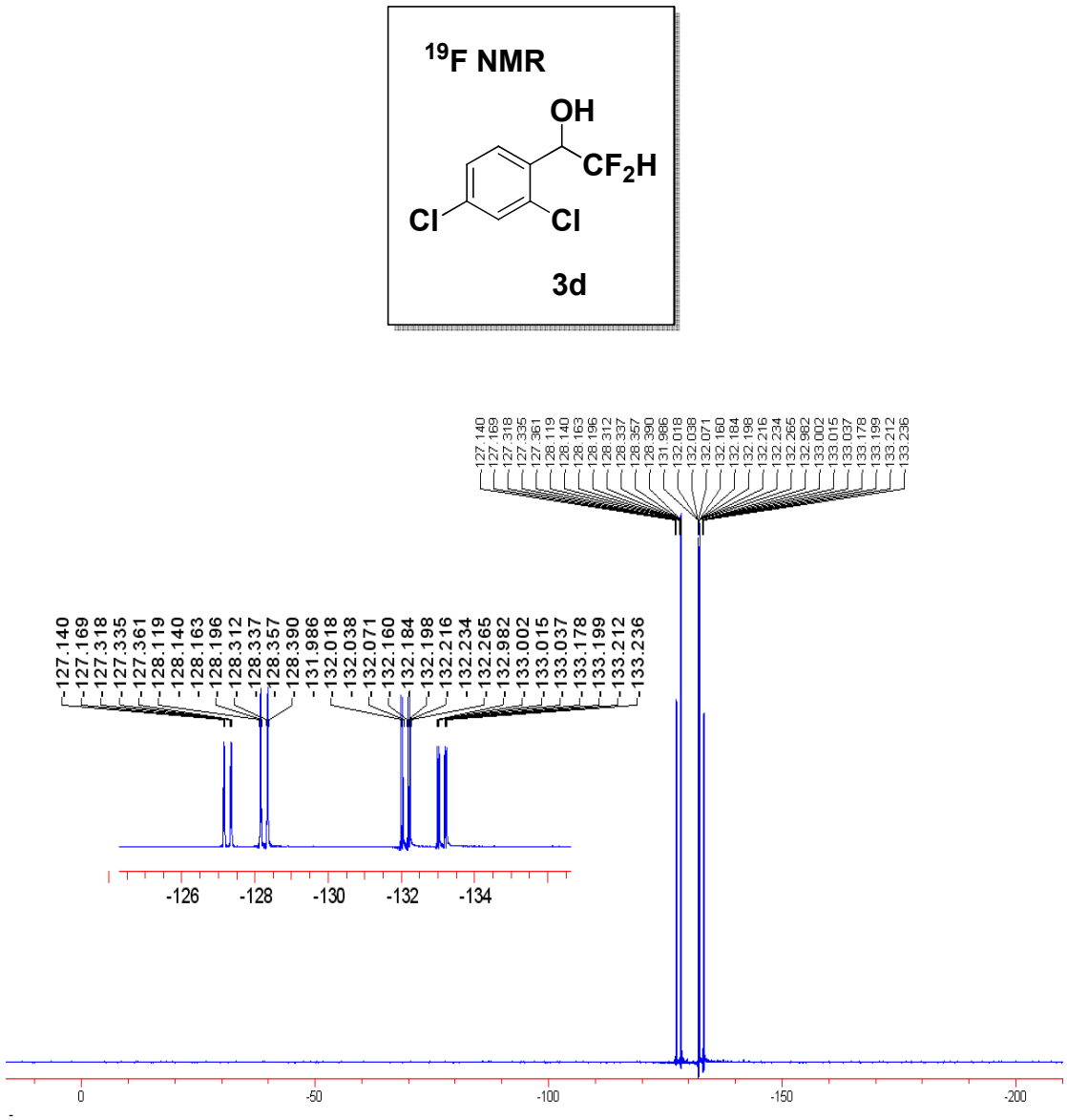
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CF2H
Cl
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133.002
133.015
133.037
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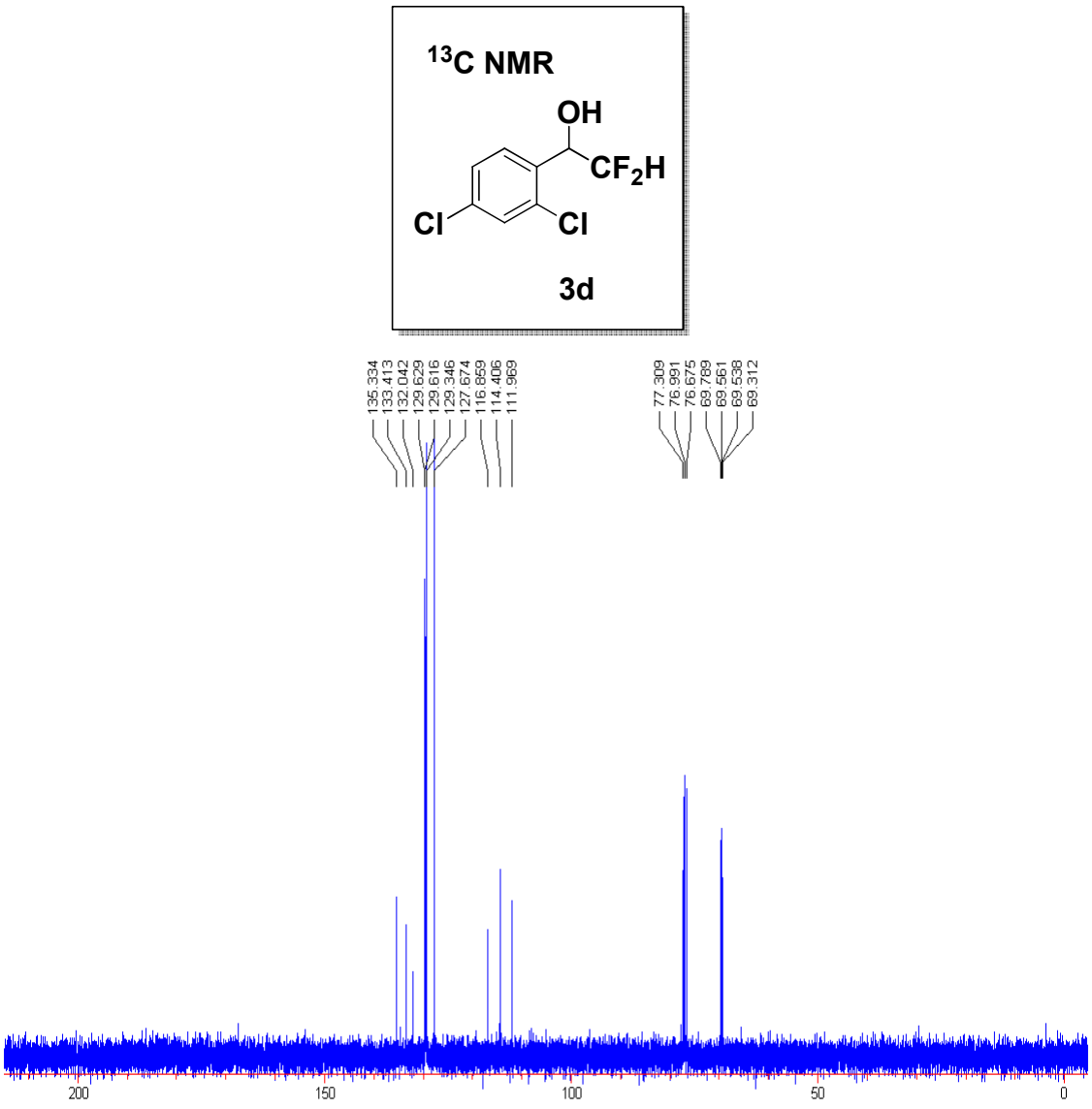
-200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50
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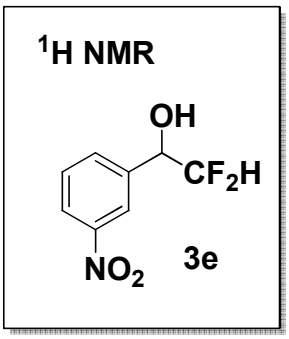
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NO2
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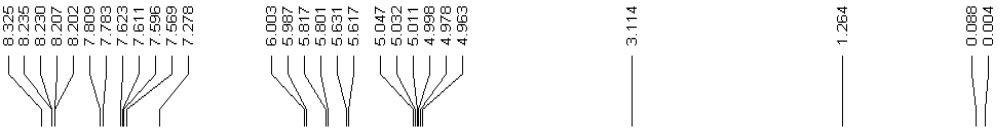
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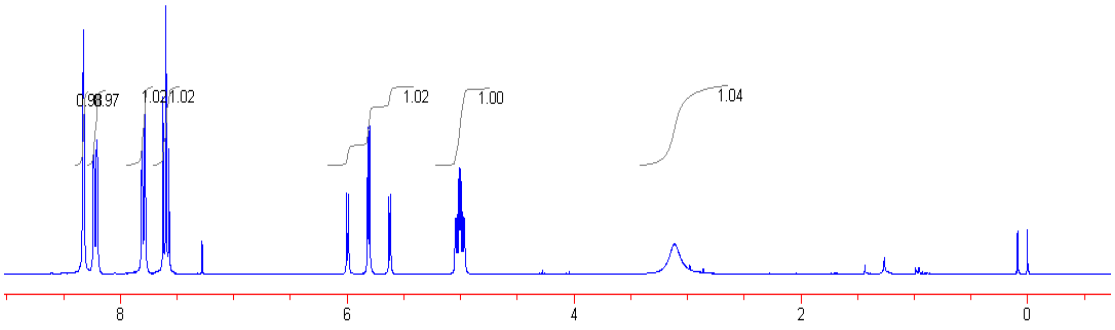
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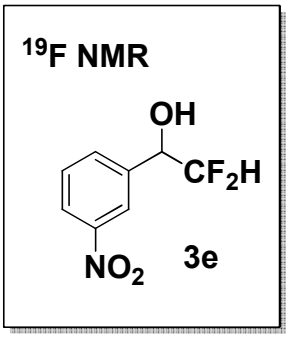
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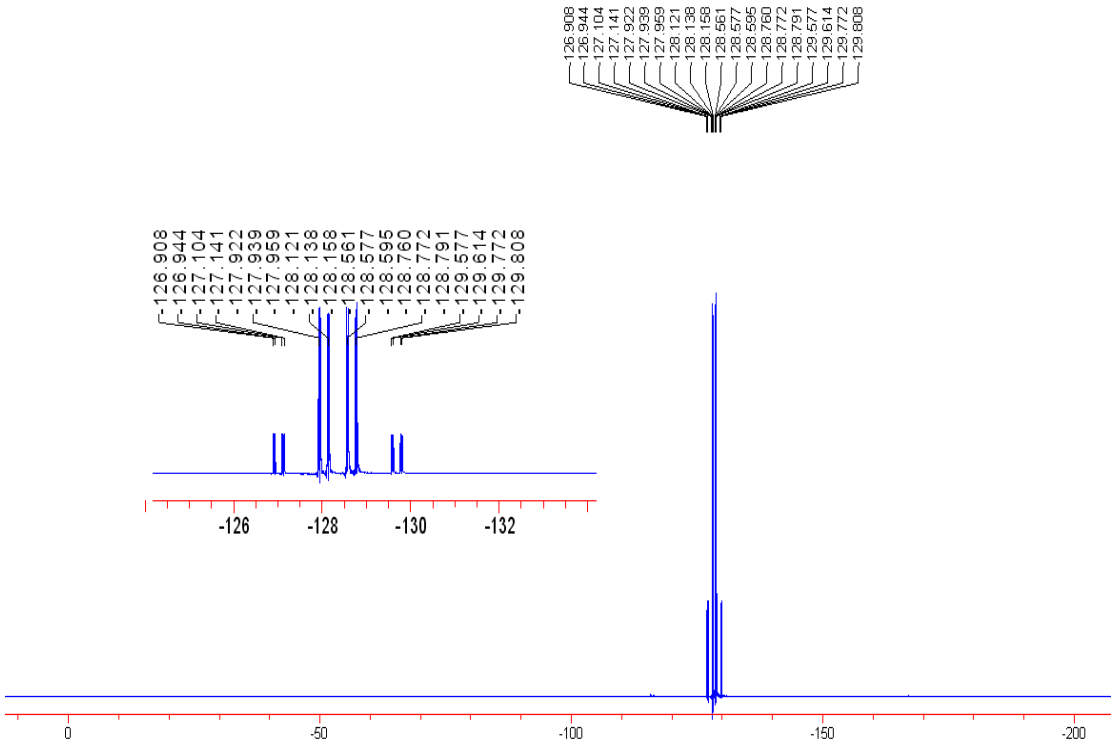
OH
CF2H
NO2
3e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-127.104
-127.141
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-128.138
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-128.561
-128.577
-128.595
-128.760
-128.772
-128.791
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-129.808
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-128
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-132
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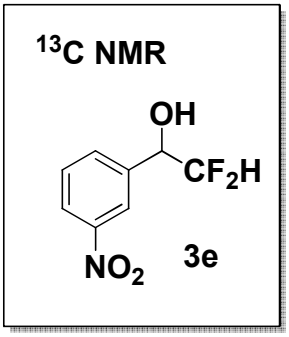
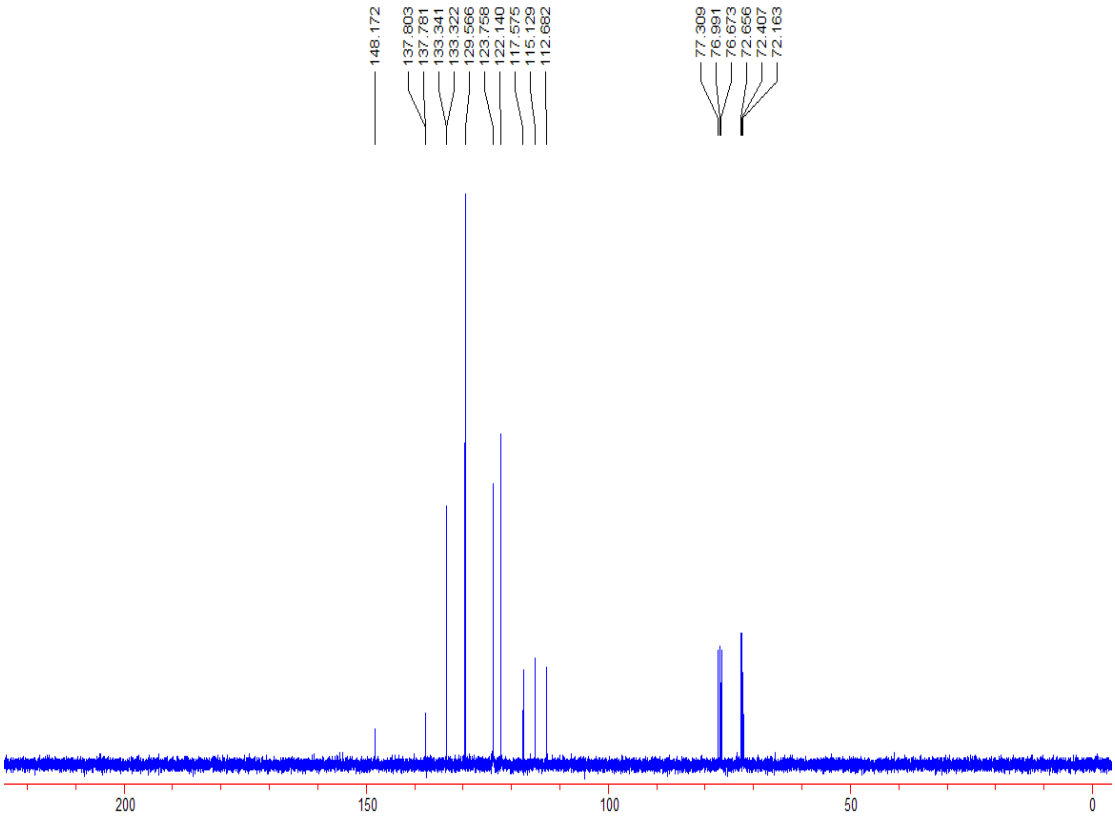
-150
-200


13C NMR
OH
CF2H
NO2
3e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122.140
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72.407
72.163
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150
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50
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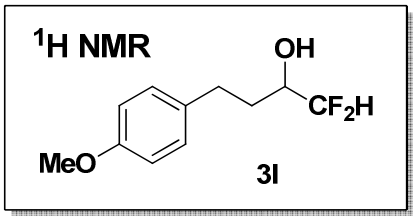
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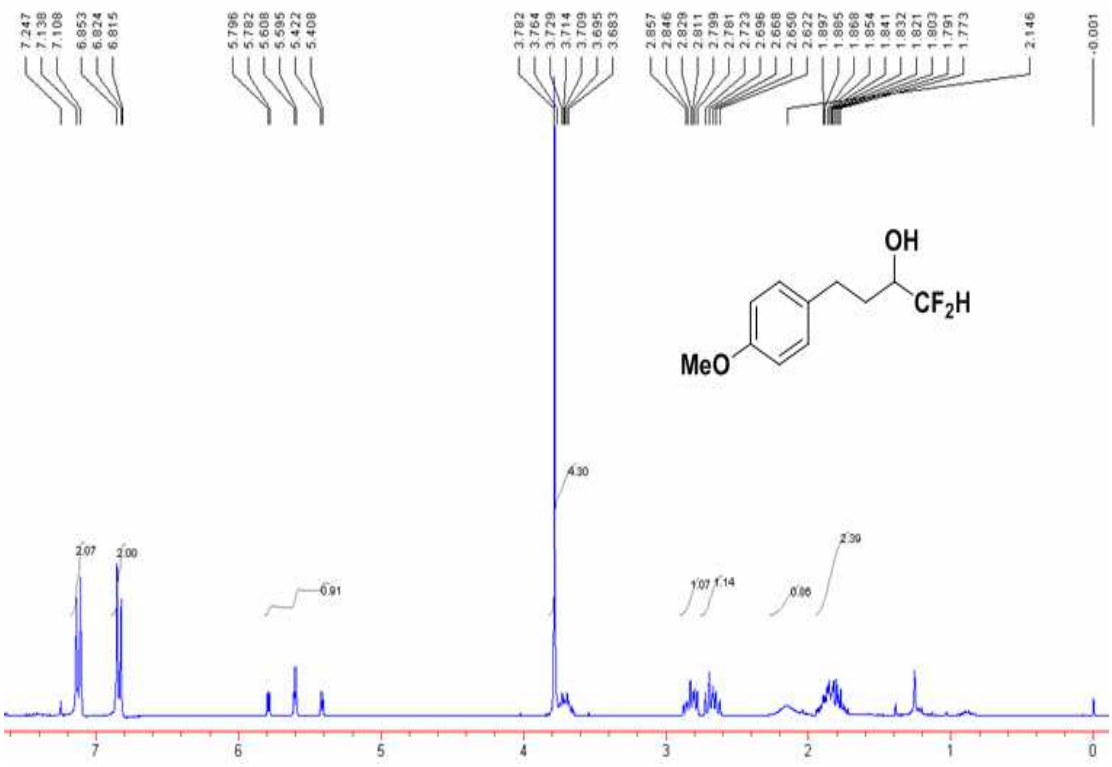
CF2H
MeO
3l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5.408
3.782
3.764
3.729
3.714
3.709
3.695
3.683
2.857
2.846
2.829
2.811
2.799
2.781
2.723
2.696
2.668
2.650
2.622
1.897
1.885
1.868
1.854
1.841
1.832
1.821
1.803
1.791
1.773
2.146
0.001
OH
CF2H
MeO
4.30
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2.39
7
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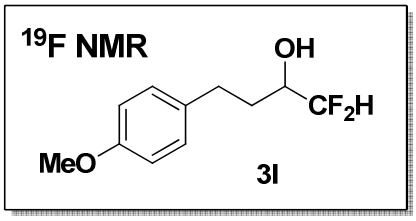
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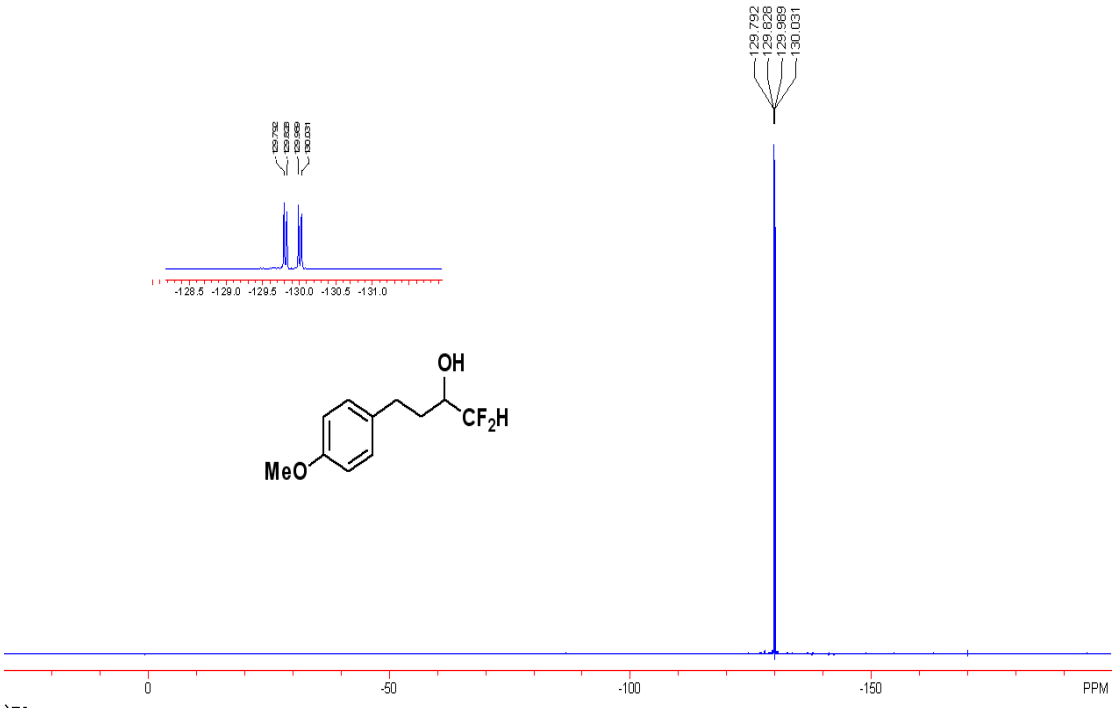
OH
CF2H
MeO
3l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129.828
129.989
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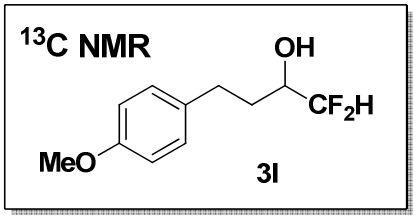
MeO
0
-50
-100
-150
PPM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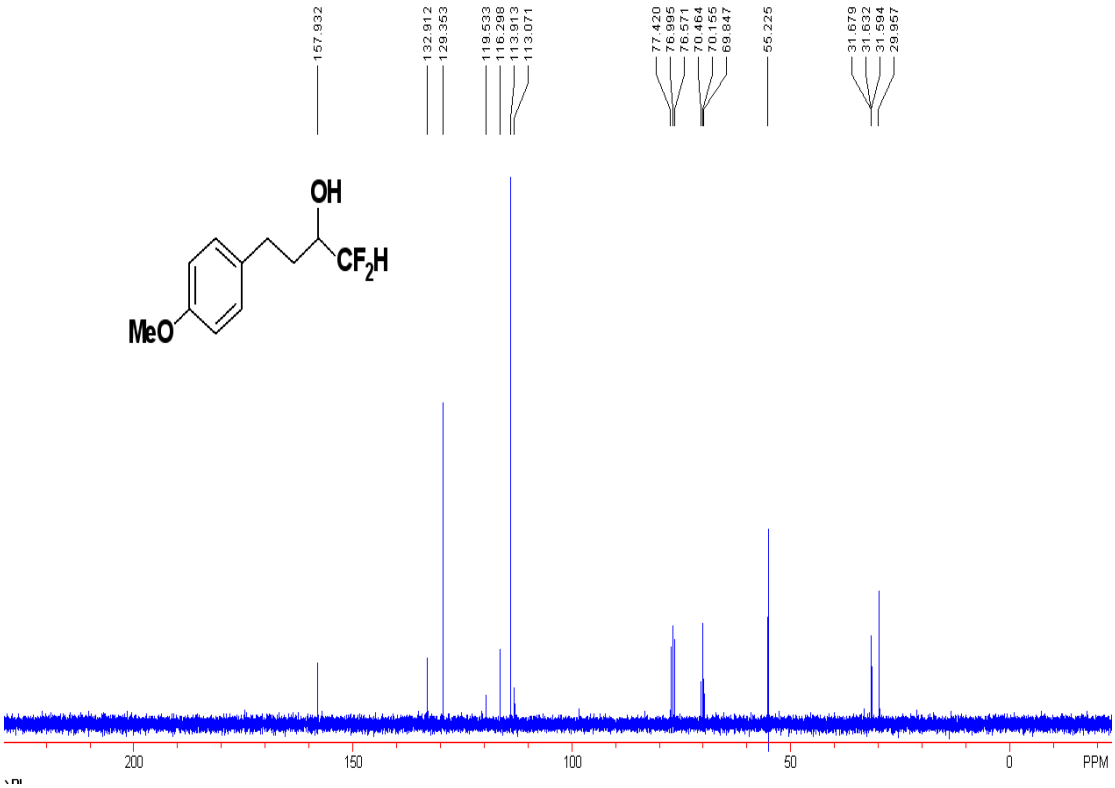
OH
CF2H
MeO
3l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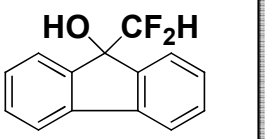
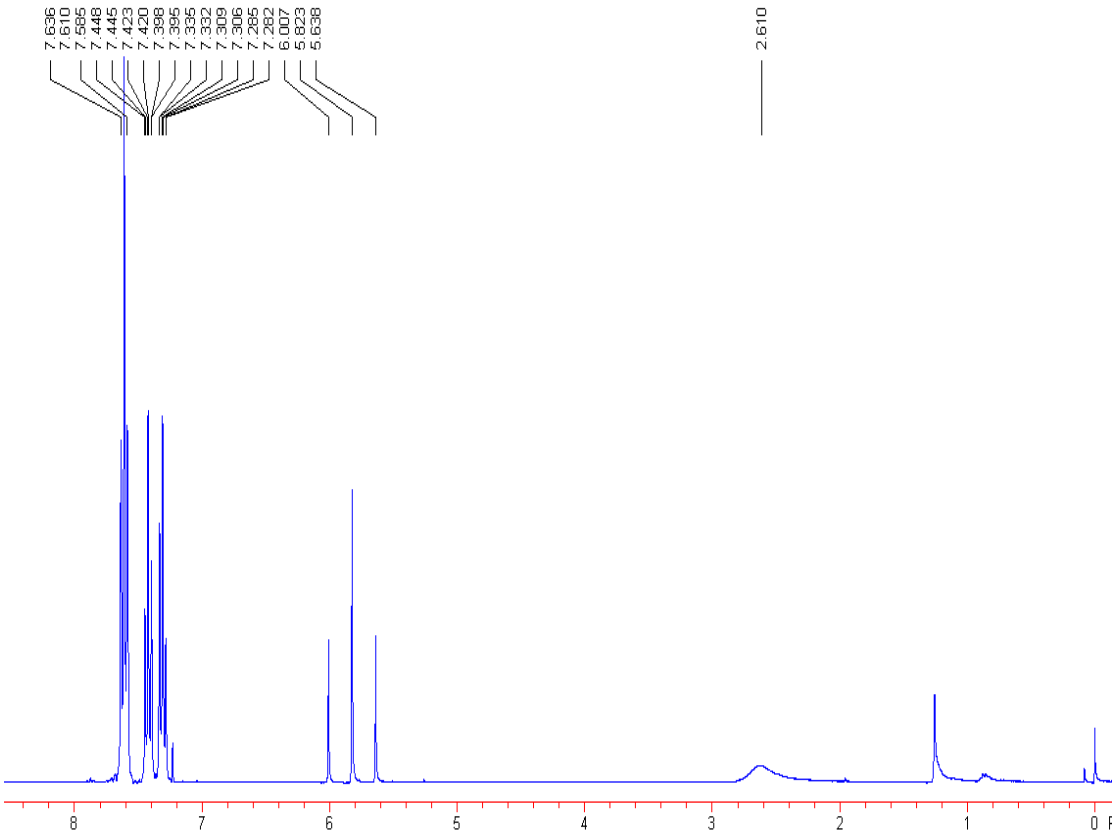
129.353
119.533
116.298
113.913
113.071
77.420
76.995
76.571
70.464
70.155
69.847
55.225
31.679
31.632
31.594
29.957
OH
CF2H
MeO
200
150
100
50
0
PPM

^{19}F NMR


HO
CF2H

5a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7.585
7.448
7.445
7.423
7.420
7.398
7.395
7.335
7.332
7.309
7.306
7.285
7.282
6.007
5.823
5.638
2.610
8
7
6
5
4
3
2
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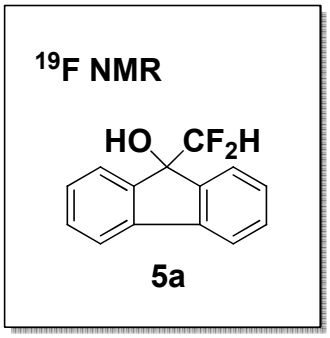
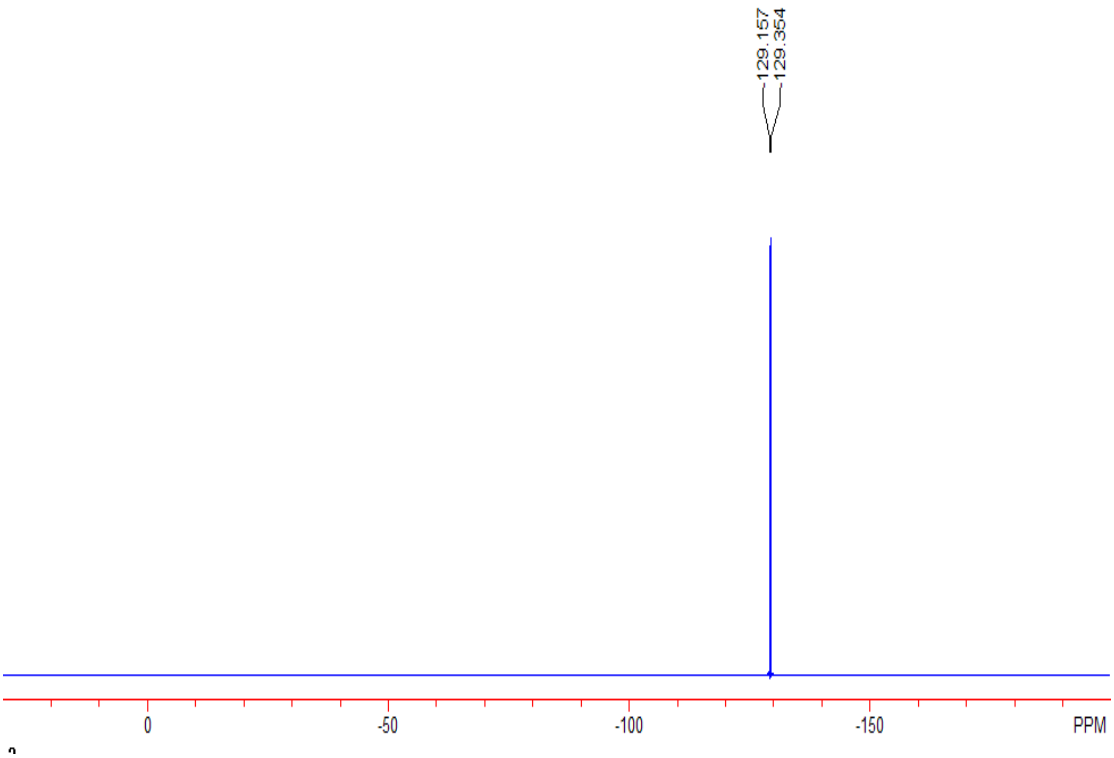

19F NMR
HO
CF2H
5a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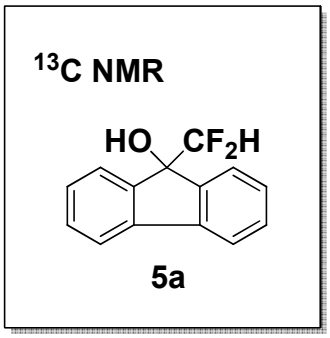
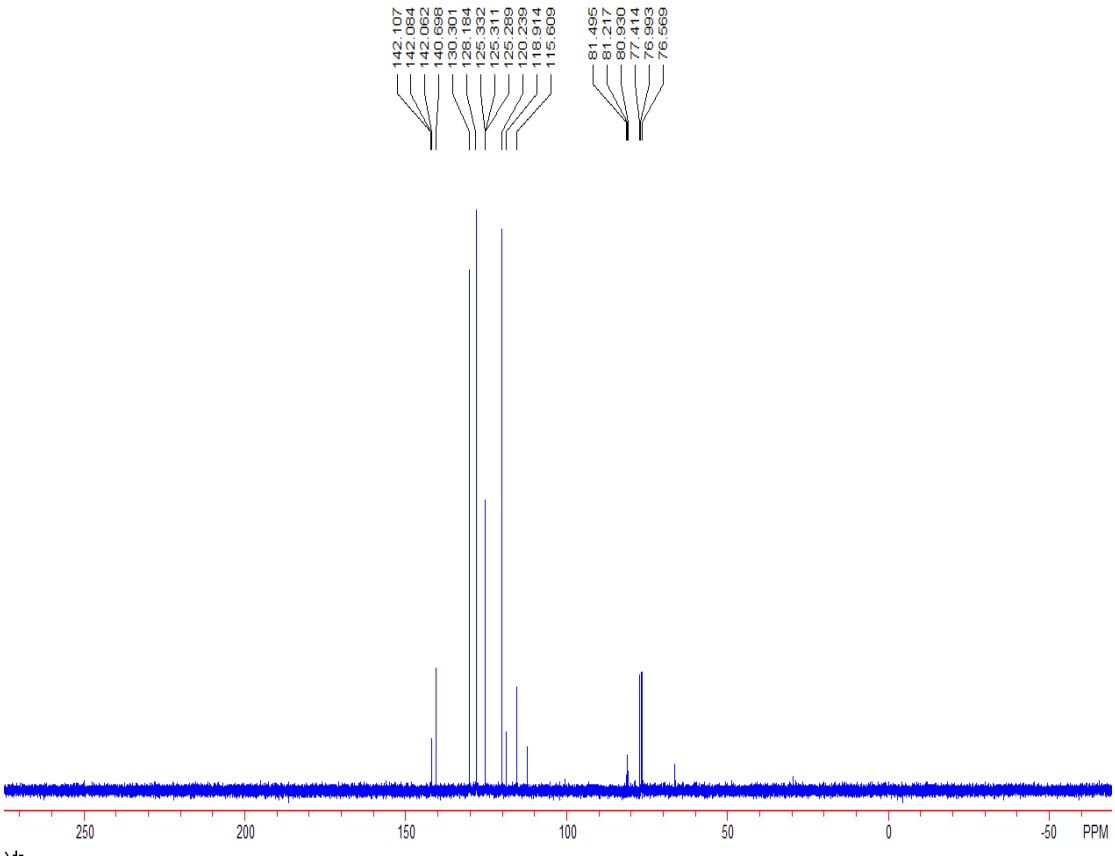
129.354
0
-50
-100
-150
PPM


13C NMR
HO
CF2H
5a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125.332
125.311
125.289
120.239
118.914
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80.930
77.414
76.993
76.569
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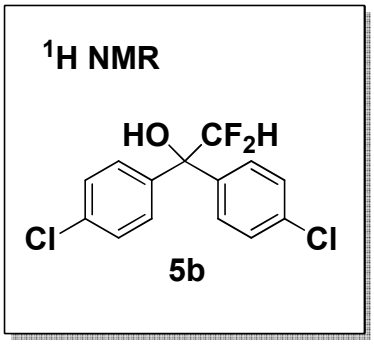
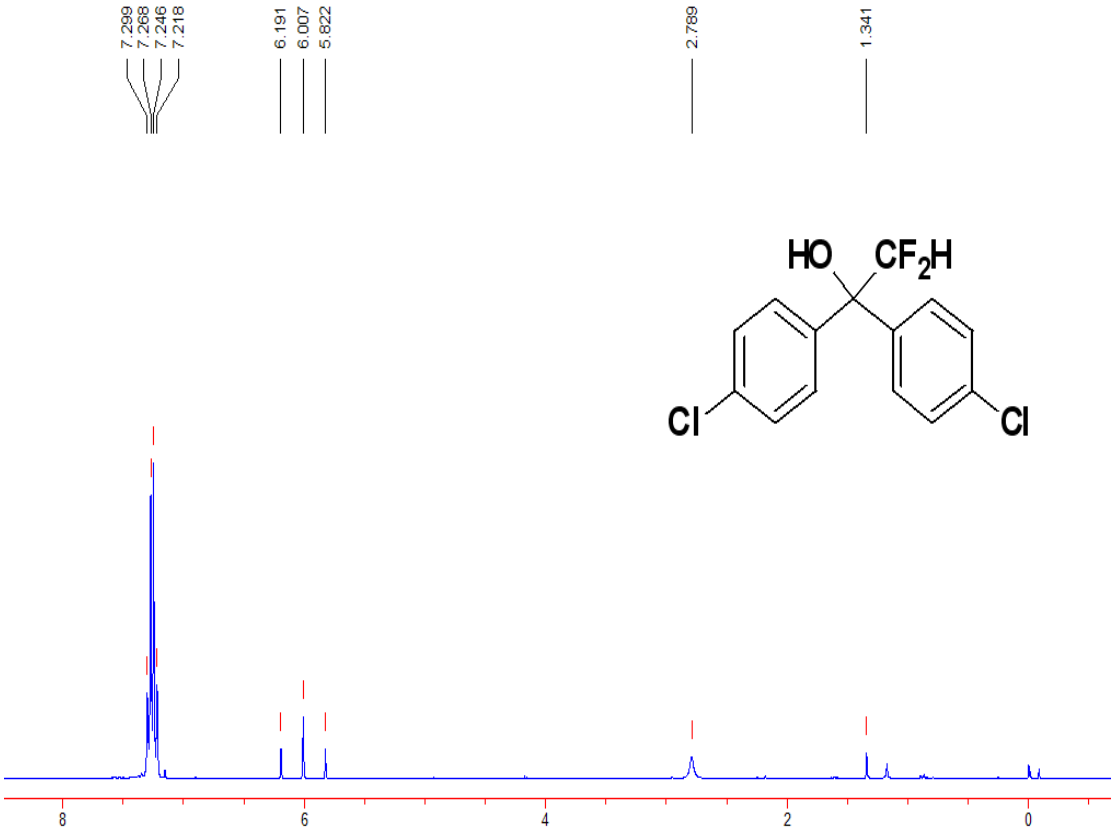
200
150
100
50
0
-50
PPM


^{1}H NMR
HO
CF_2H
Cl
Cl
5b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7.268
7.246
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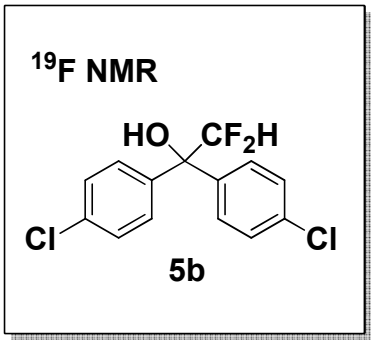
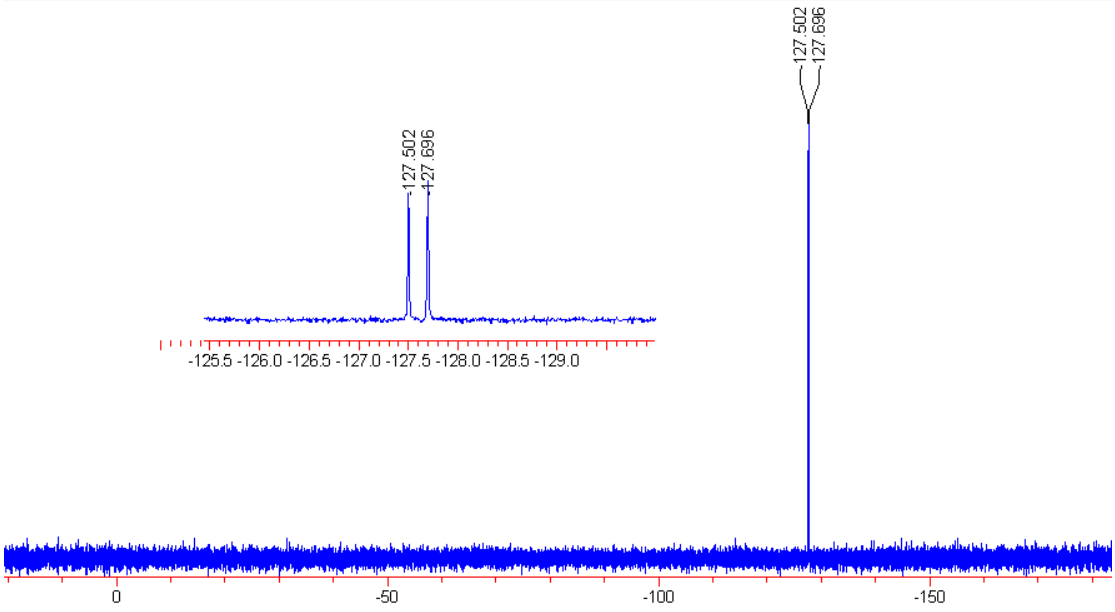
6.191
6.007
5.822
2.789
1.341
HO
CF_2H
Cl
Cl
8
6
4
2
0


19F NMR
HO
CF2H
Cl
Cl
5b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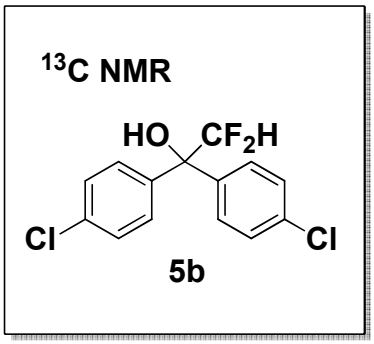
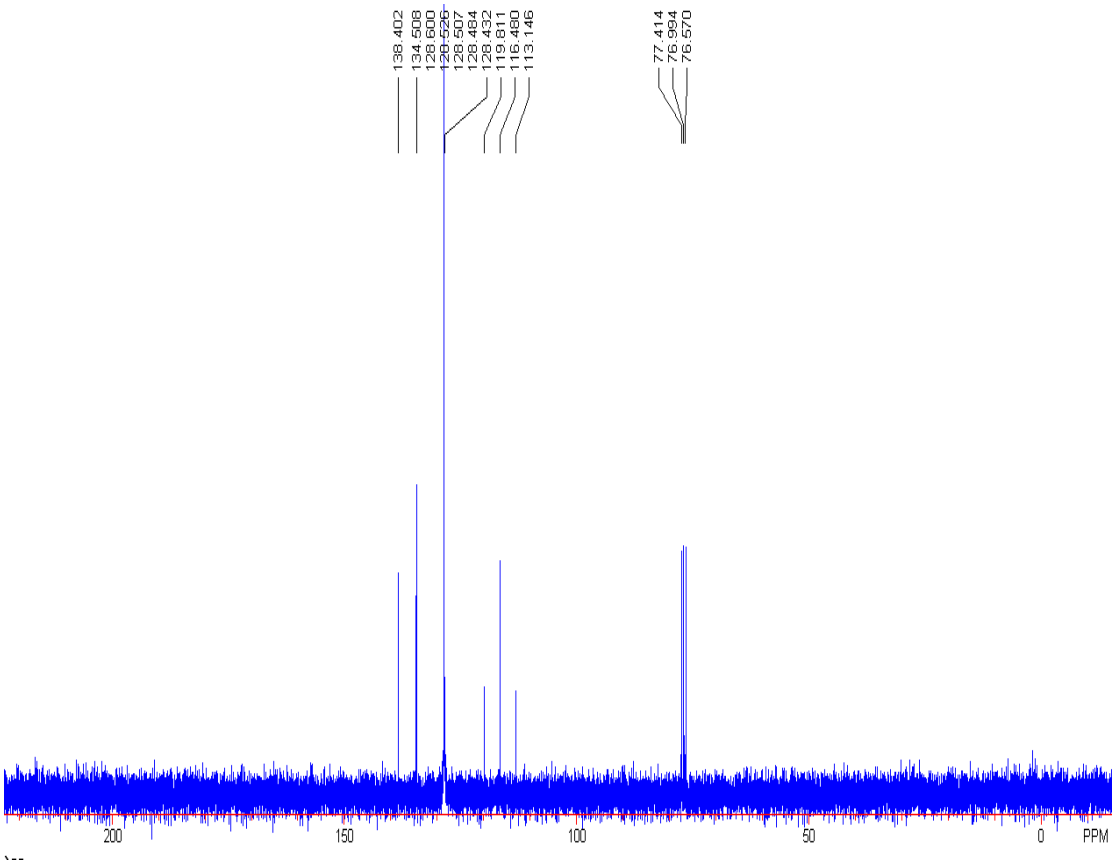
127.696
127.502
127.696
-125.5 -126.0 -126.5 -127.0 -127.5 -128.0 -128.5 -129.0
0
-50
-100
-150


13C NMR
HO
CF2H
Cl
Cl
5b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128.526
128.507
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76.570
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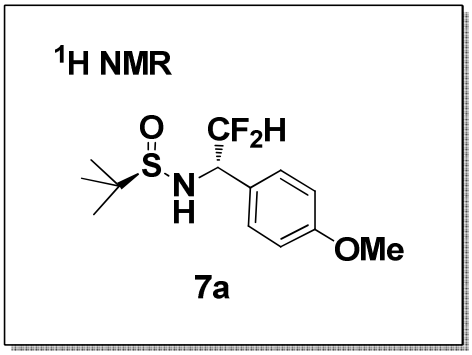
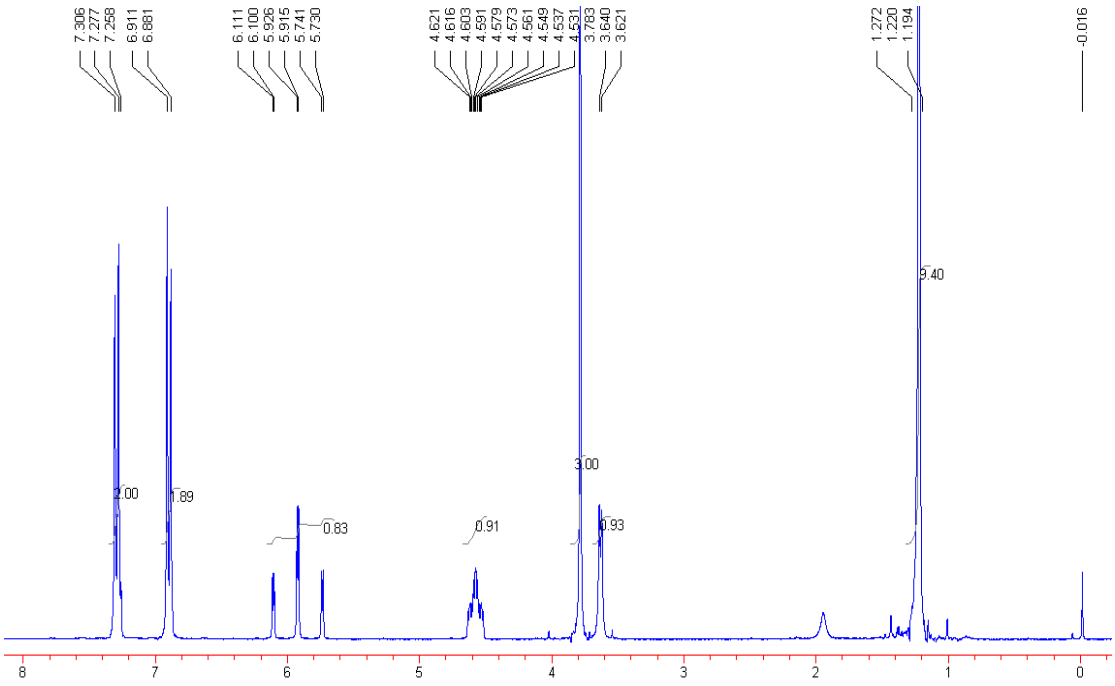
150
100
50
0
PPM


1H NMR
O
S
N
H
CF2H
OMe
7a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5.741
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4.616
4.603
4.591
4.579
4.573
4.561
4.549
4.537
4.531
3.783
3.640
3.621
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1.220
1.194
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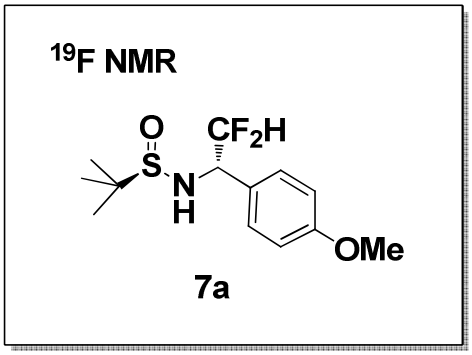
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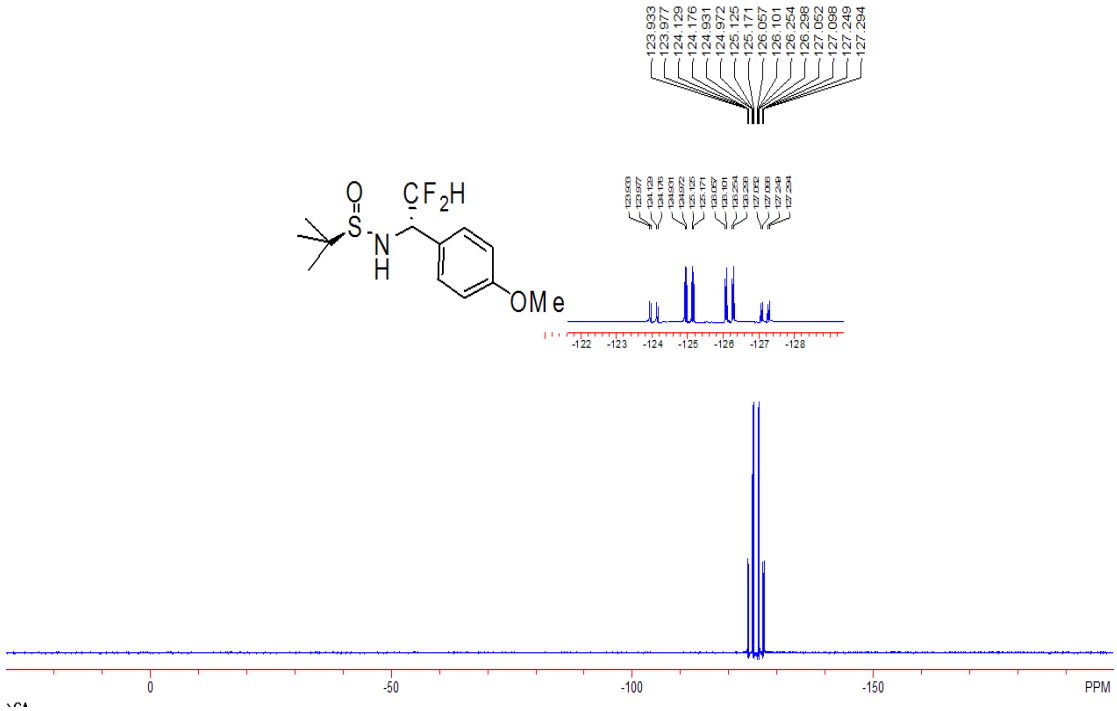
H
CF2H
OMe
7a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127.098
127.249
127.294
O
S
N
H
CF2H
OMe
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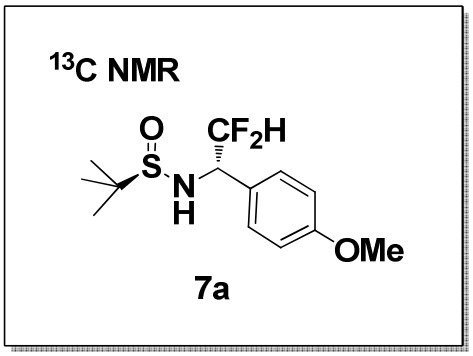
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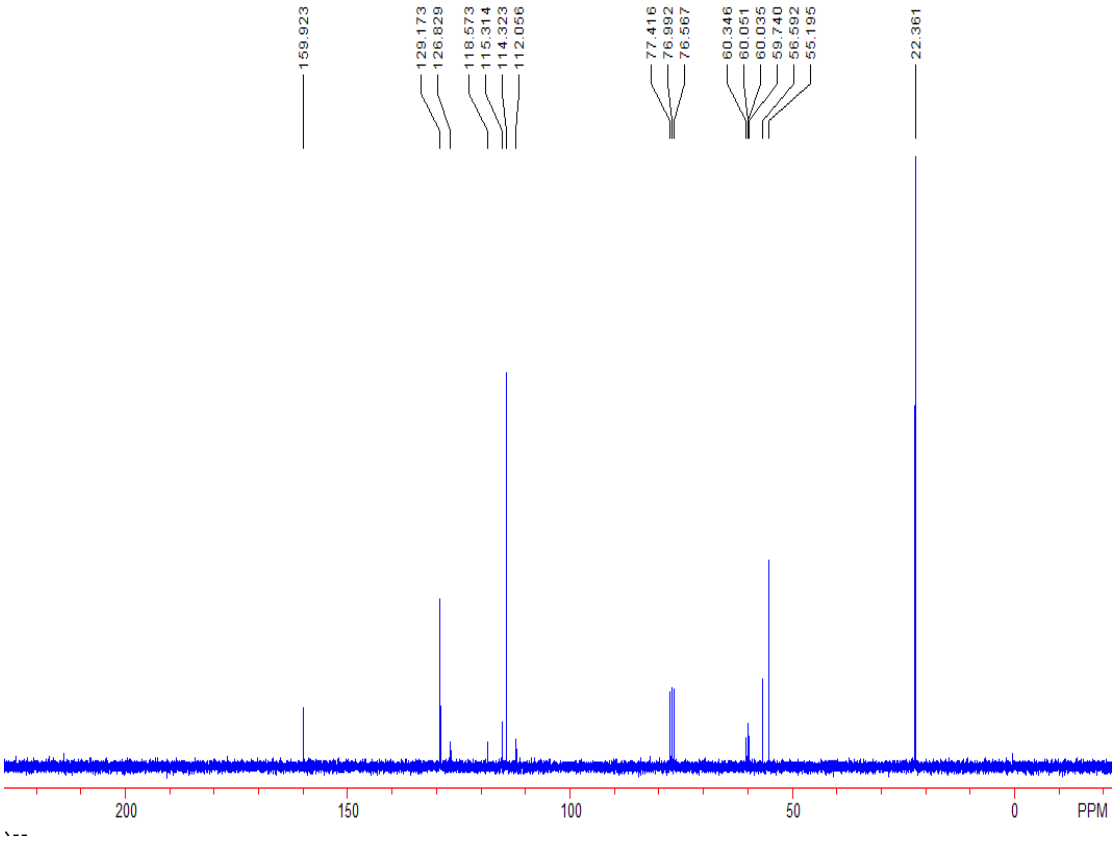
H
CF2H
OMe
7a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114.323
112.056
77.416
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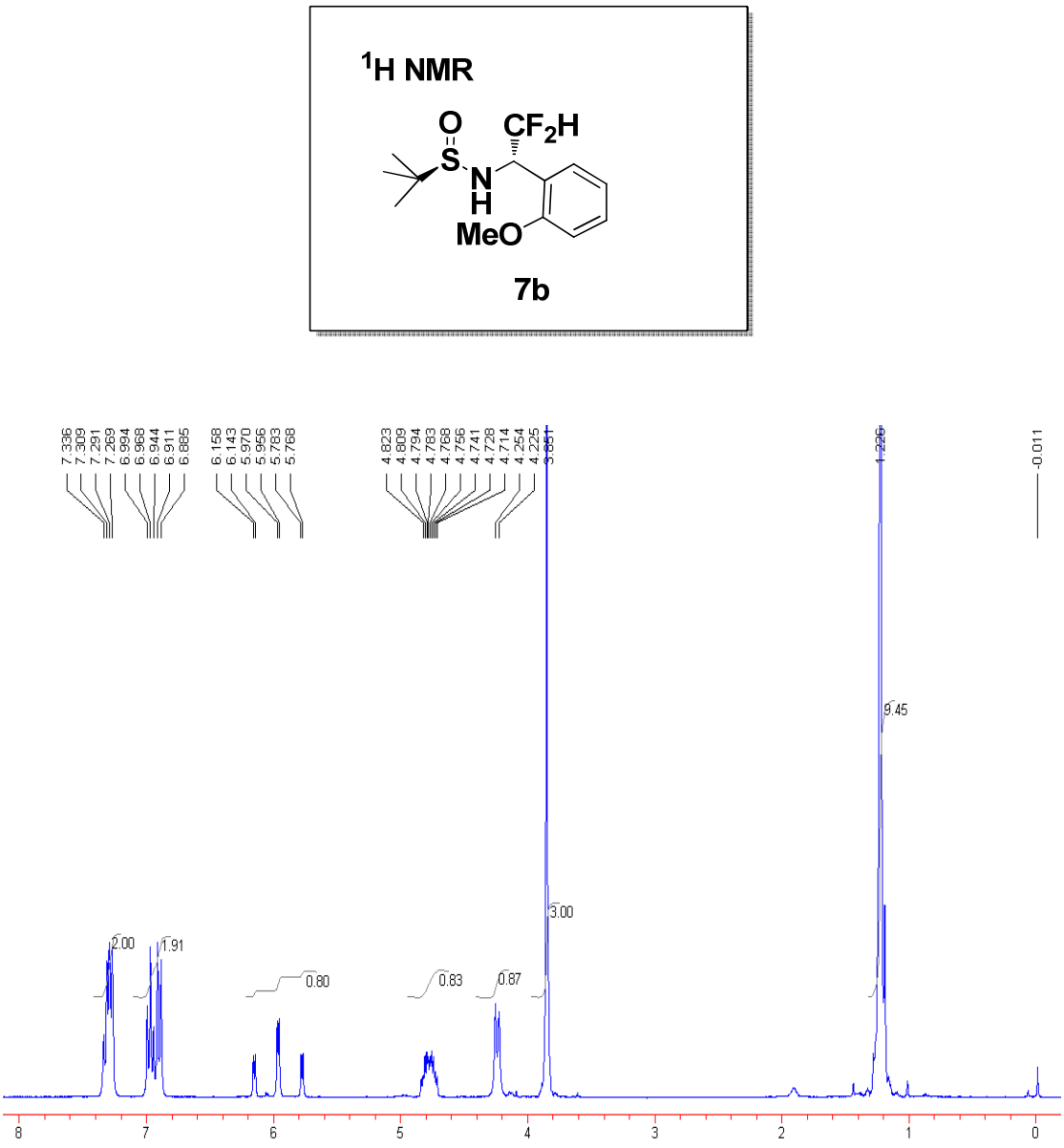
PPM


1H NMR
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CF2H
MeO
7b
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6.911
6.885
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5.783
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4.741
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4.714
4.254
4.225
3.851
1.226
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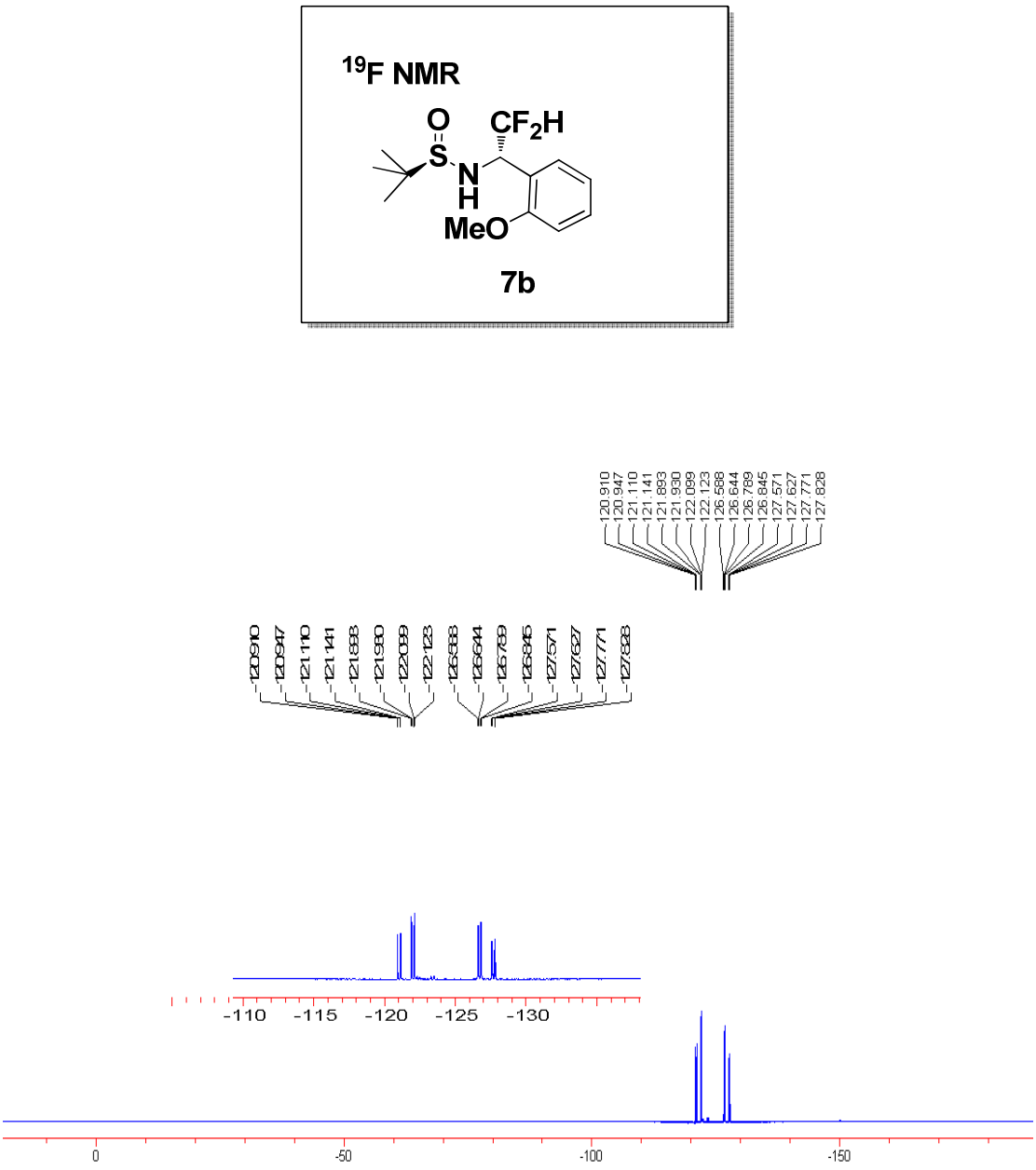
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H
MeO
CF2H
7b
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122.123
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126.644
126.789
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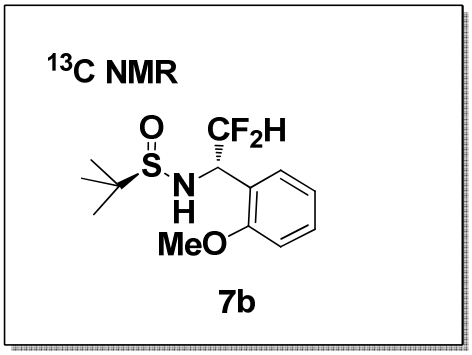
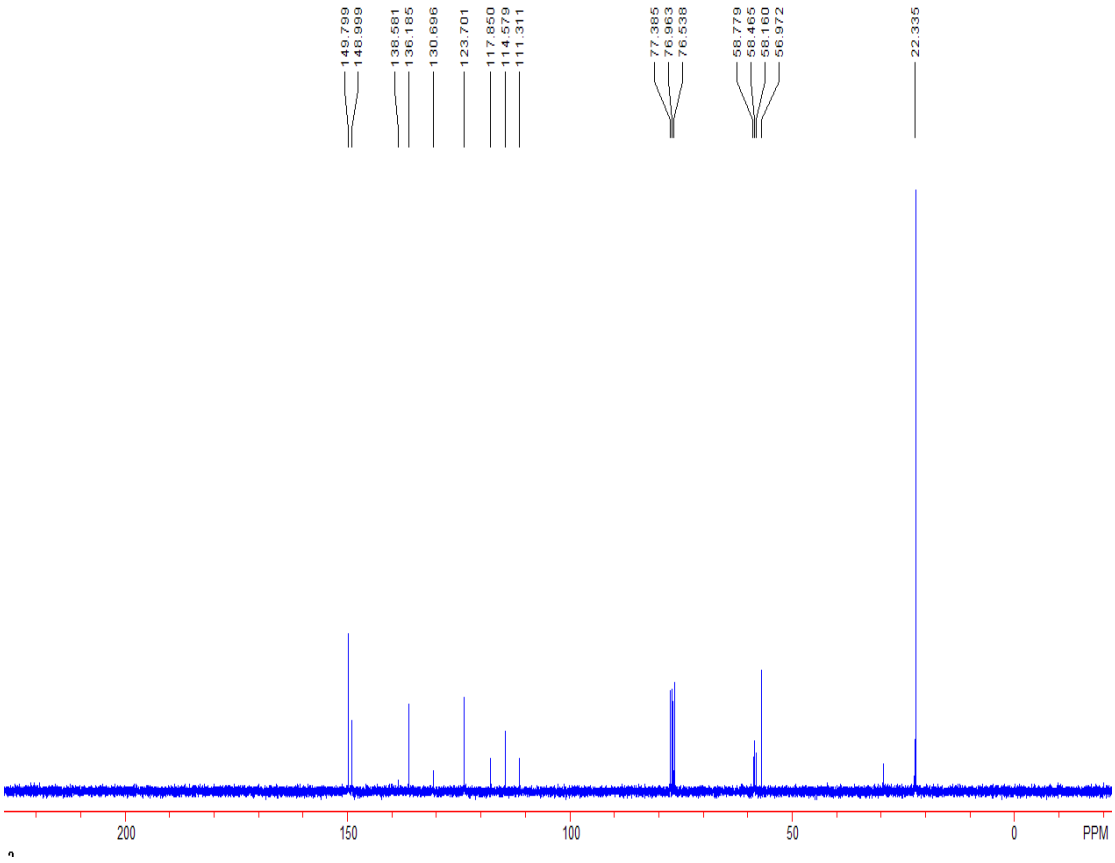

13C NMR
O
S
N
H
MeO
CF2H
7b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114.579
111.311
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76.538
58.779
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58.160
56.972
22.335
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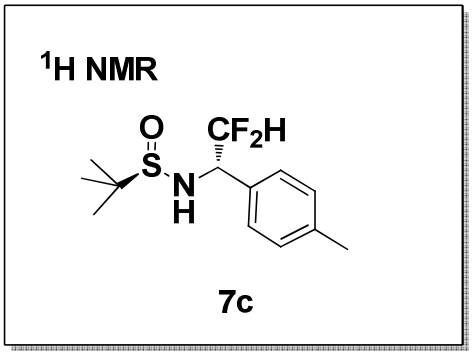
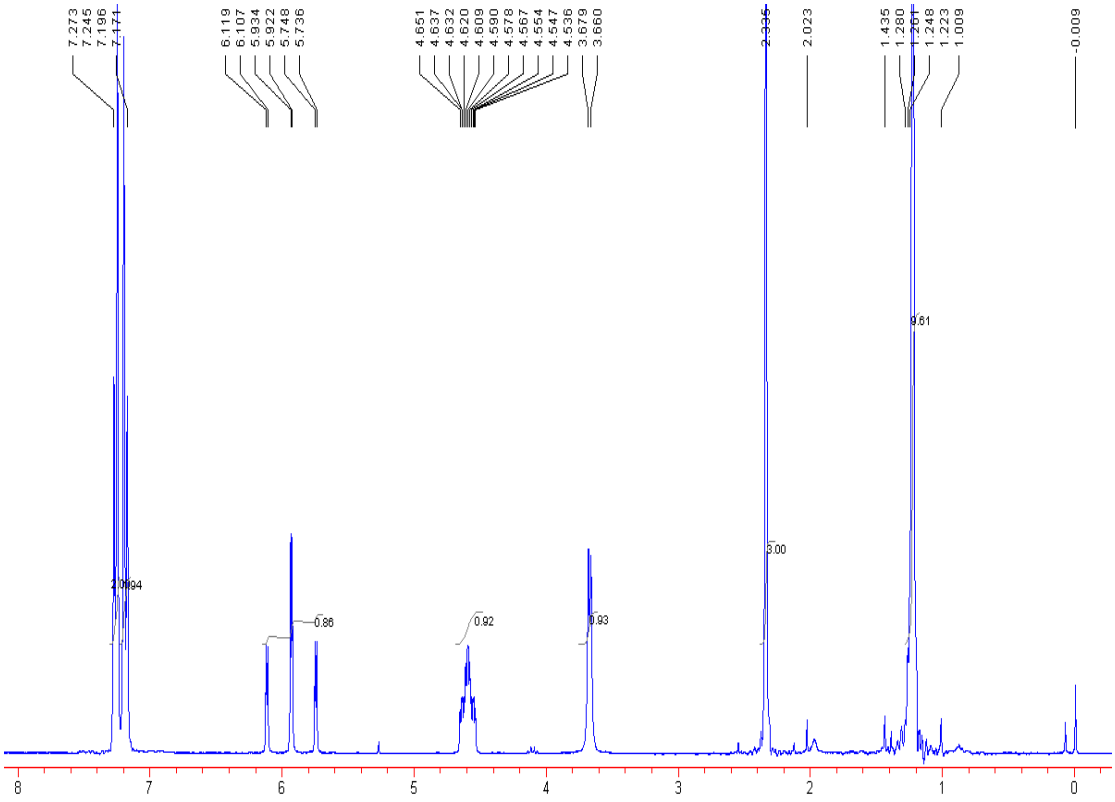
100
50
0
PPM


1H NMR
O
S
N
H
CF2H
7c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4.637
4.632
4.620
4.609
4.590
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4.547
4.536
3.679
3.660
2.336
2.023
1.435
1.280
1.261
1.248
1.223
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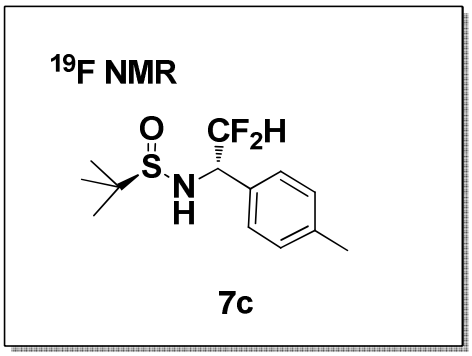
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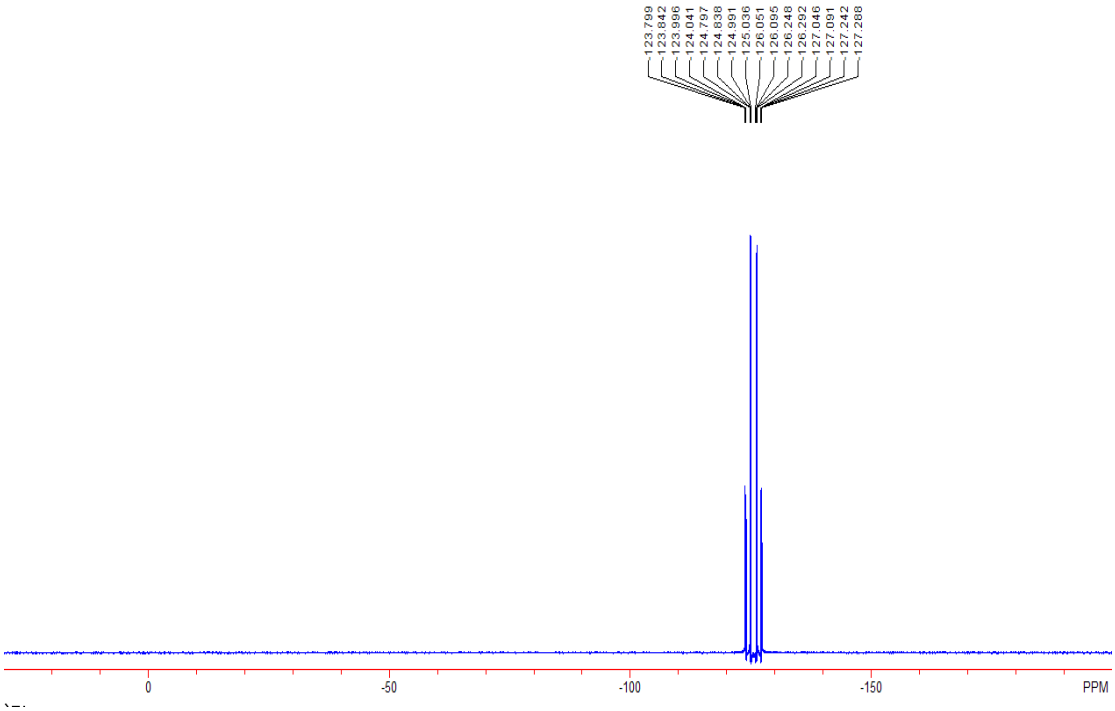
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127.288
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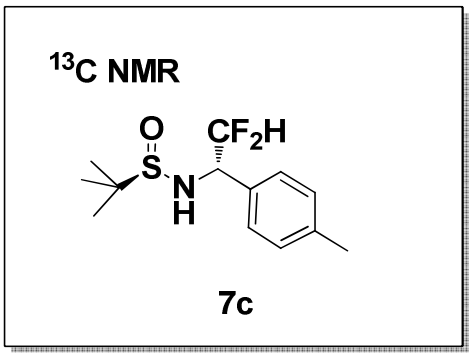
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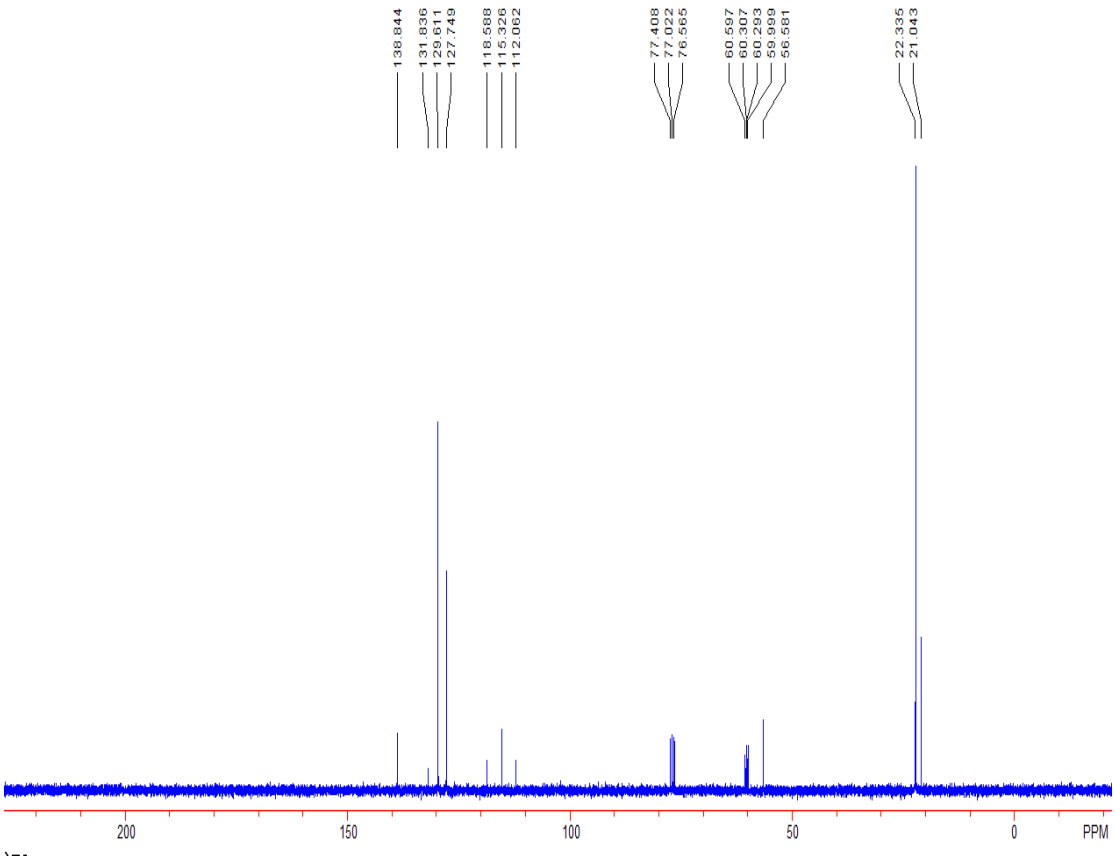
O
S
N
H
CF2H
7c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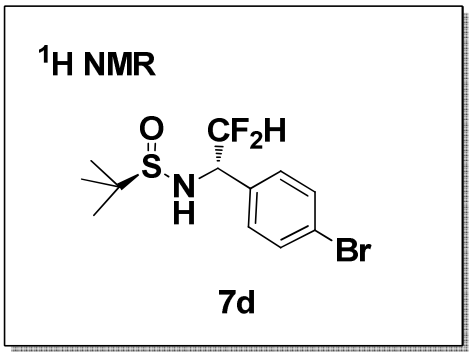
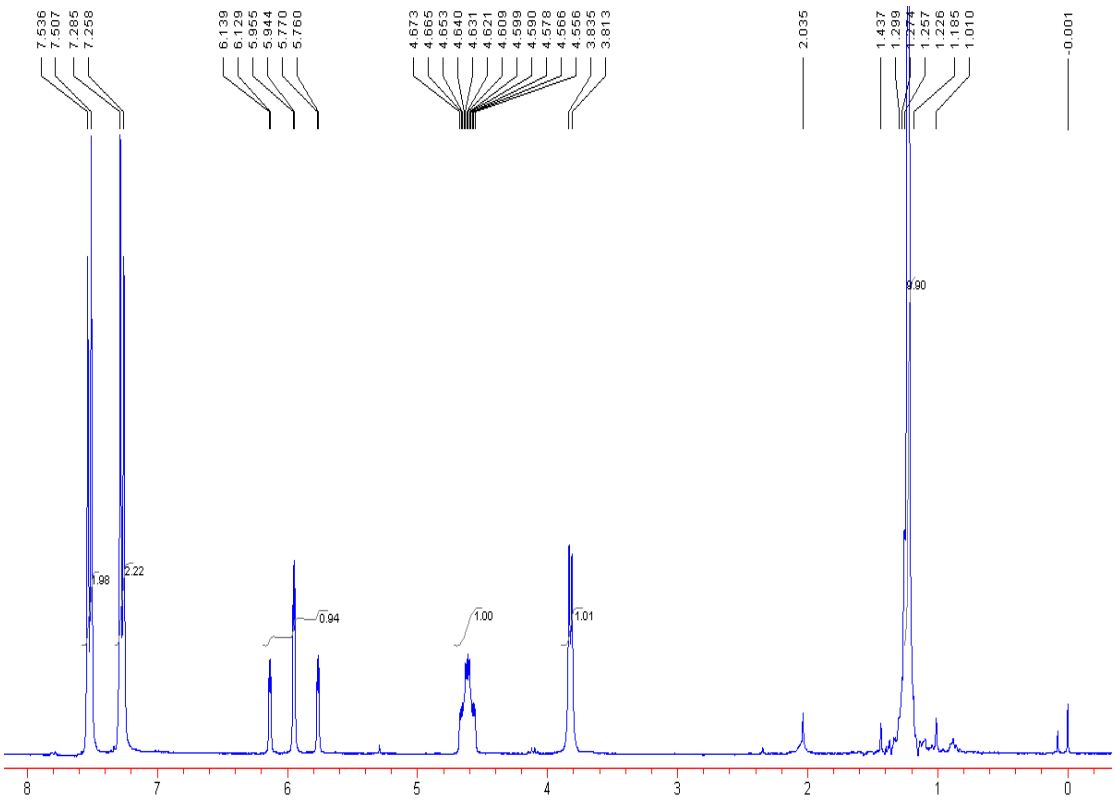
PPM


1H NMR
O
S
N
H
CF2H
Br
7d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4.653
4.640
4.631
4.621
4.609
4.599
4.590
4.578
4.566
4.556
3.835
3.813
2.035
1.437
1.299
1.274
1.257
1.226
1.185
1.010
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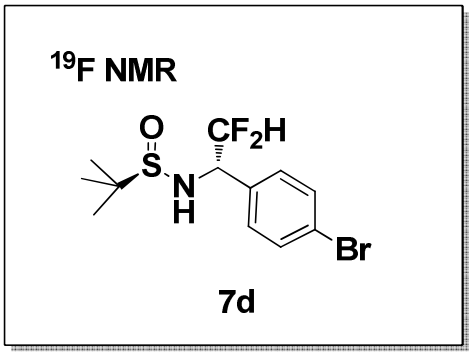
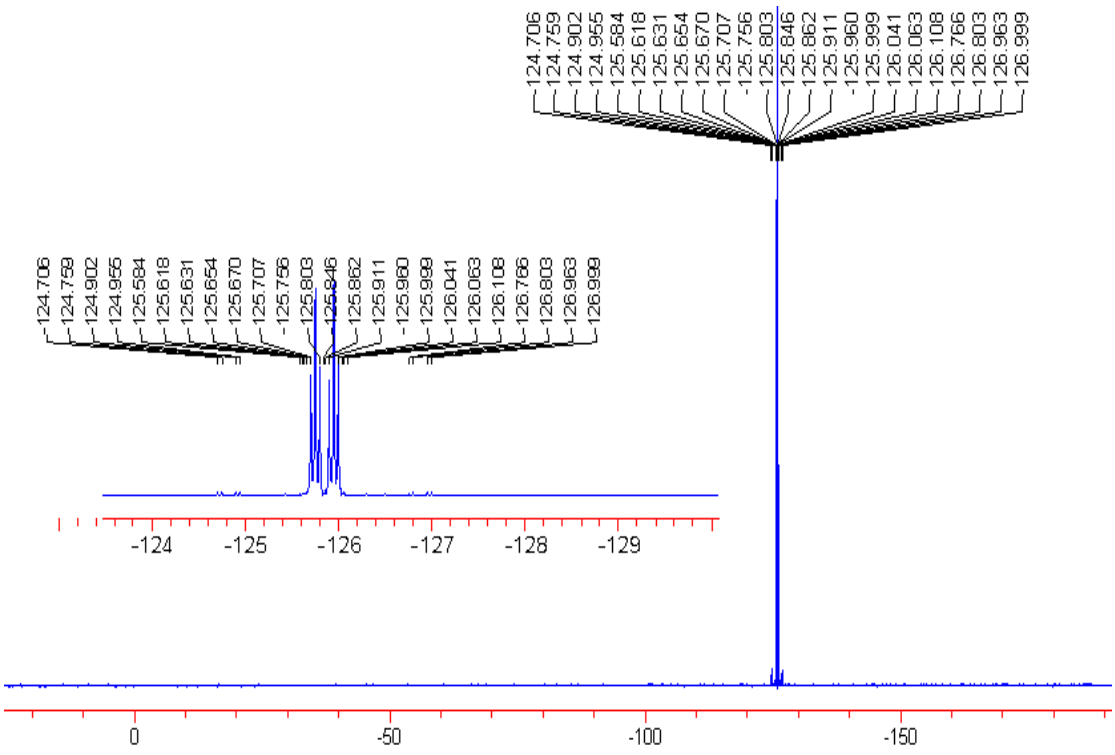

19F NMR
O
S
N
H
CF2H
Br
7d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125.960
125.999
126.041
126.063
126.108
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126.963
126.999
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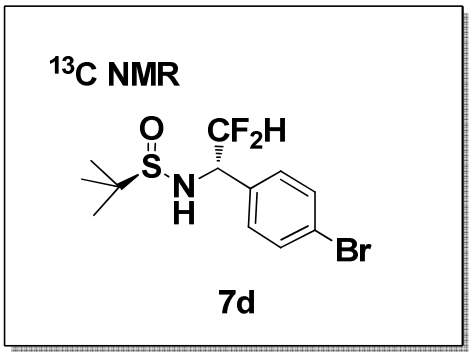
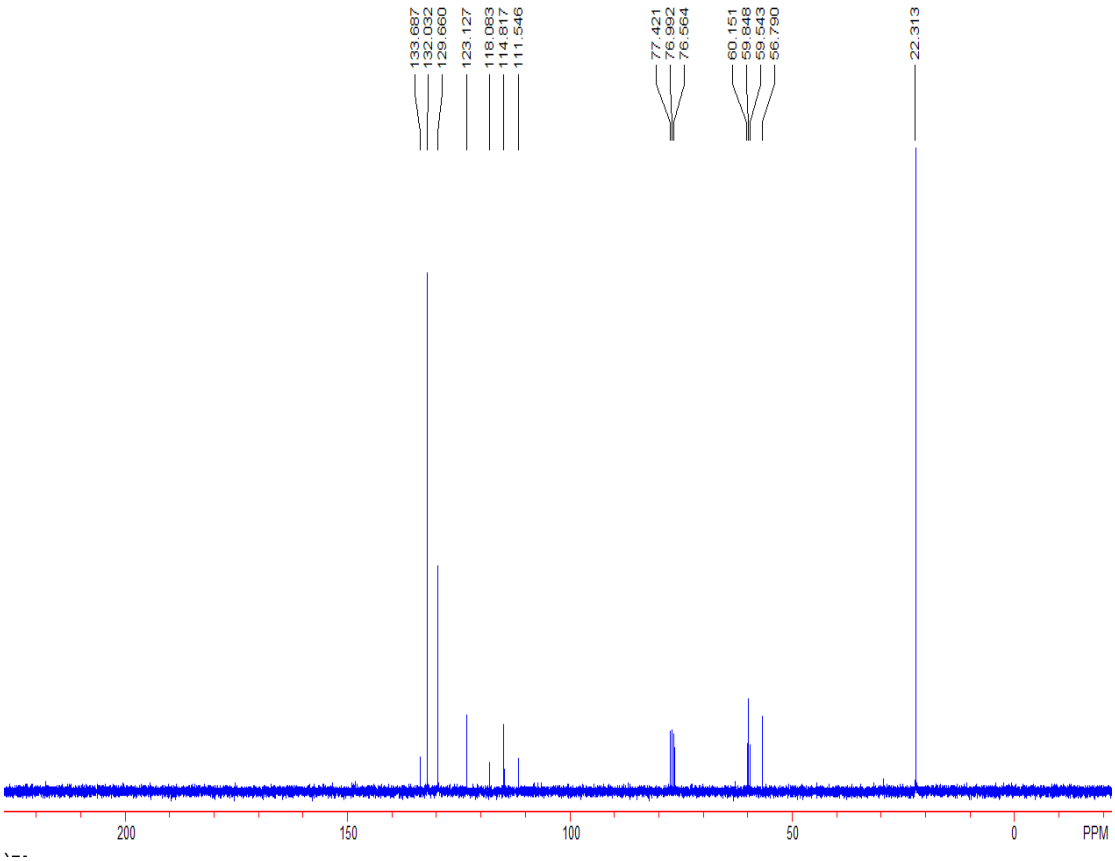

13C NMR
O
S
N
H
CF2H
Br
7d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123.127
118.083
114.817
111.546
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60.151
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22.313
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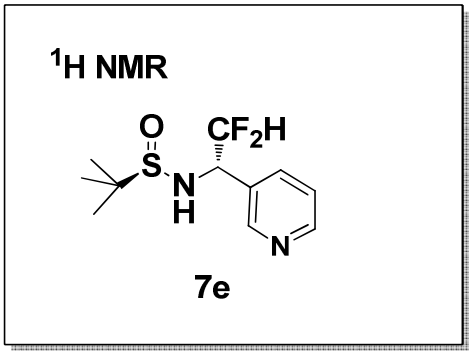
PPM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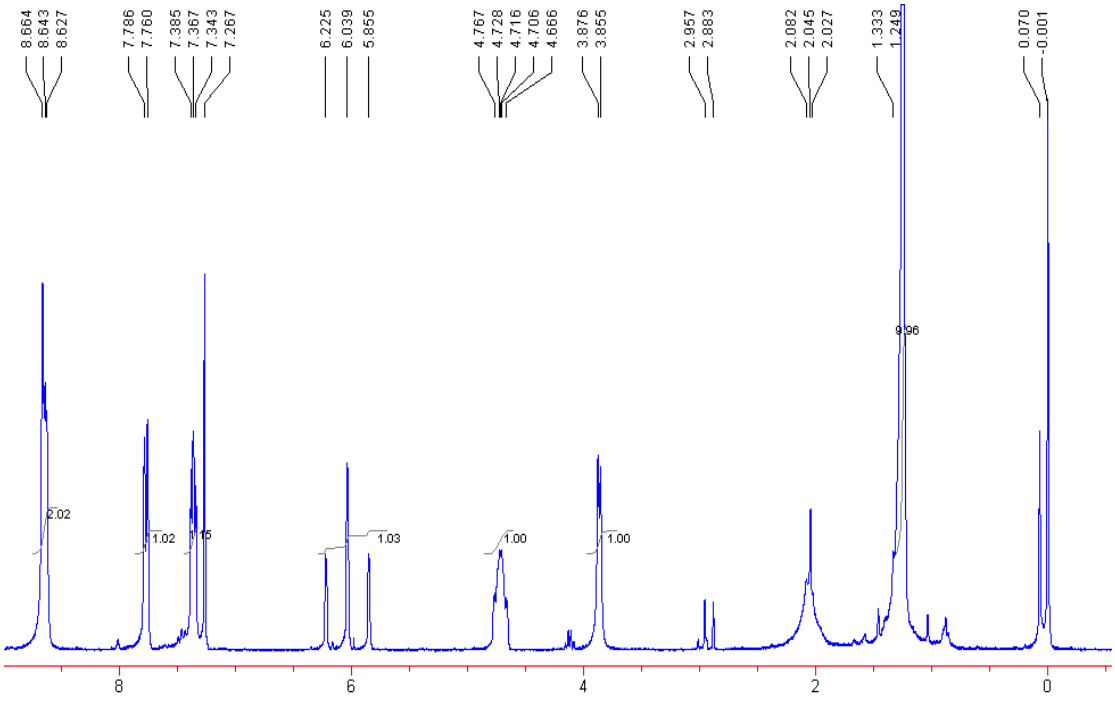
CF_2H
N
7e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7.343
7.267
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6.039
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4.767
4.728
4.716
4.706
4.666
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3.855
2.957
2.883
2.082
2.045
2.027
1.333
1.249
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1.00
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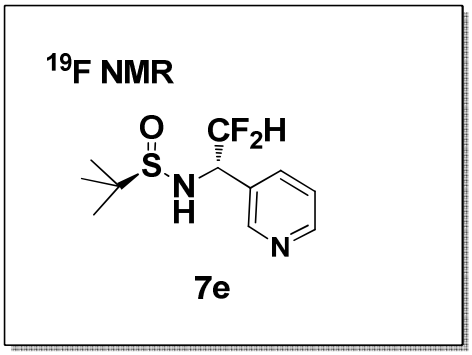
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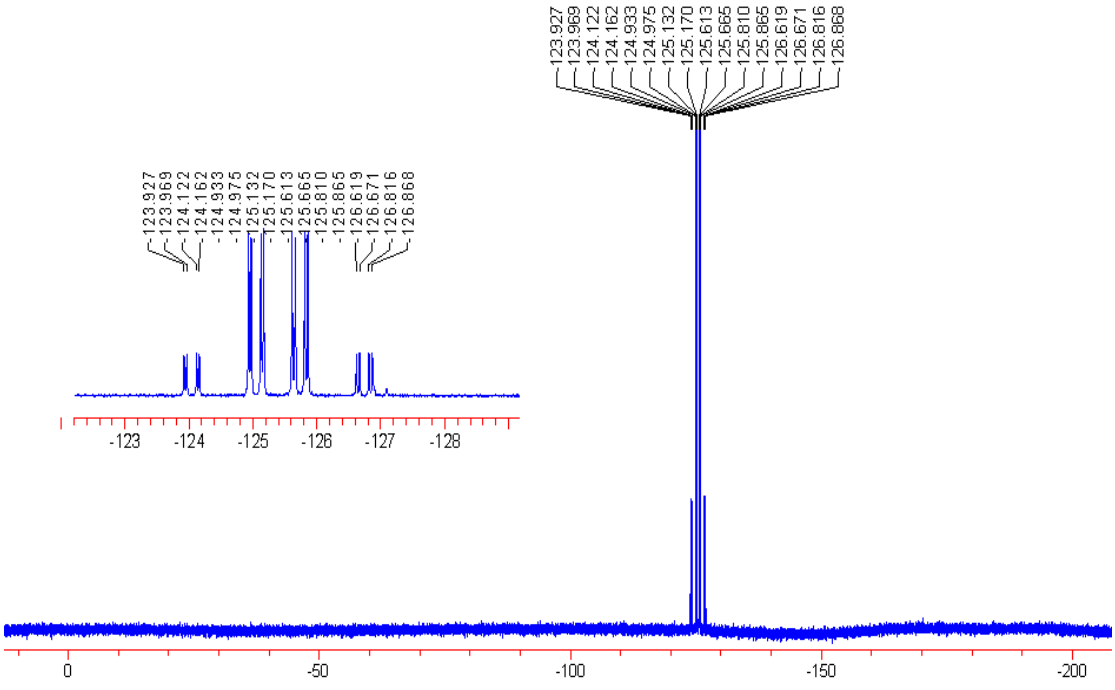
S
N
H
CF2H
N
7e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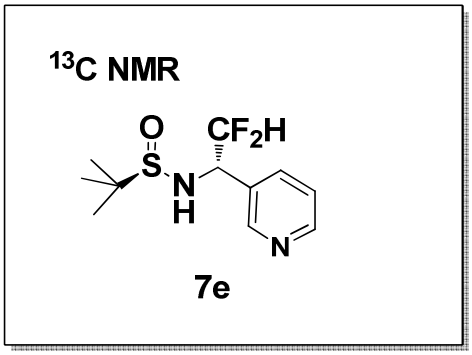
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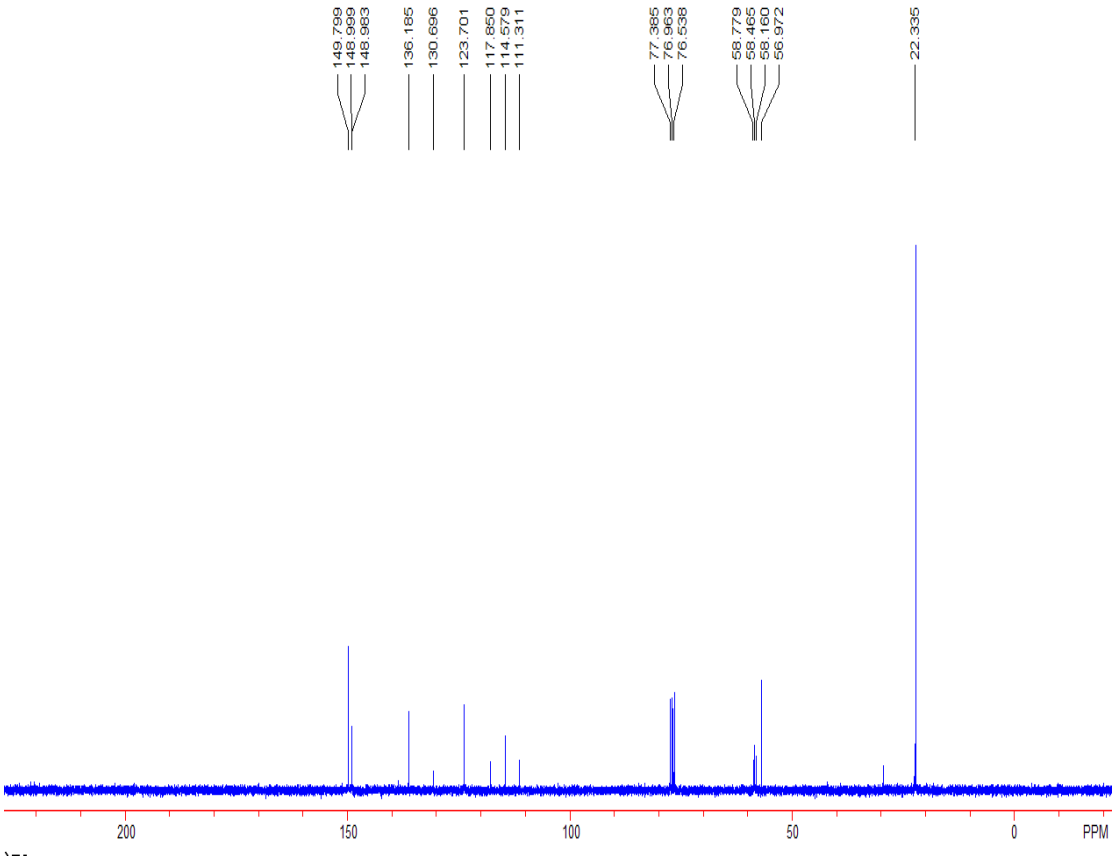
S
N
H
CF2H
N
7e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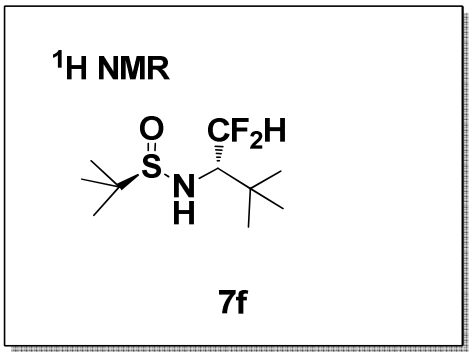
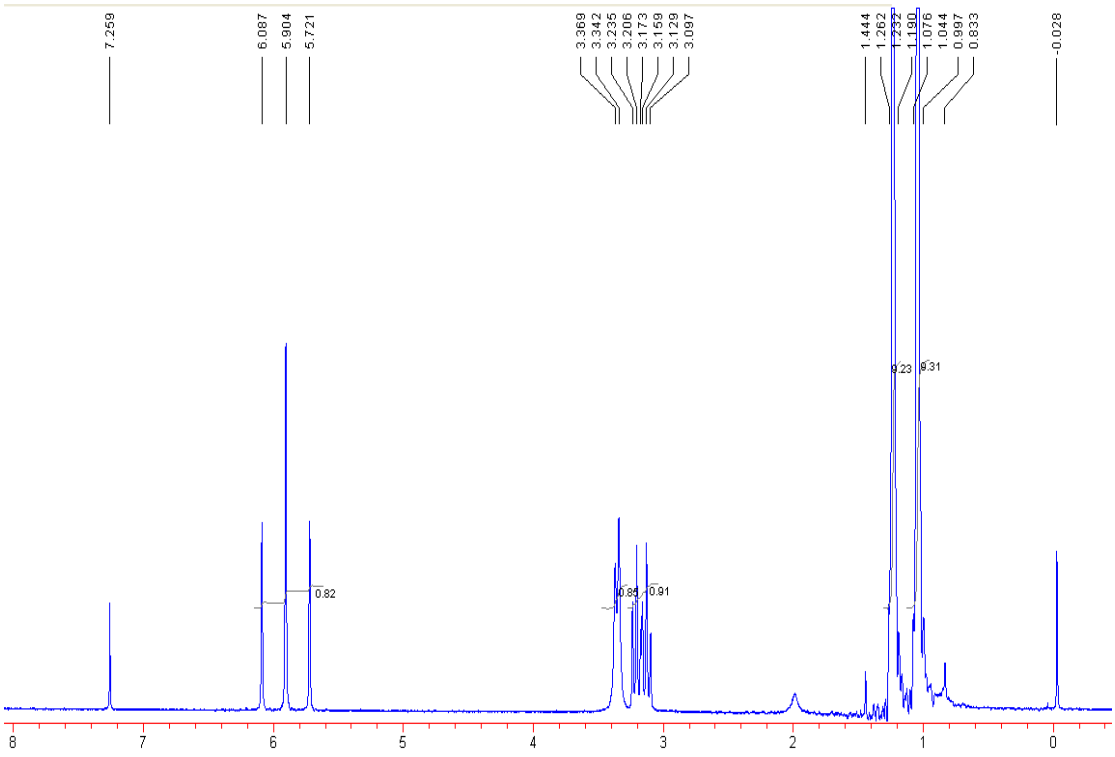
PPM


1H NMR
O
S
N
H
CF2H
7f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5.721
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3.342
3.235
3.206
3.173
3.159
3.129
3.097
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1.262
1.232
1.190
1.076
1.044
0.997
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0.85
0.91
9.23
9.31
8
7
6
5
4
3
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1
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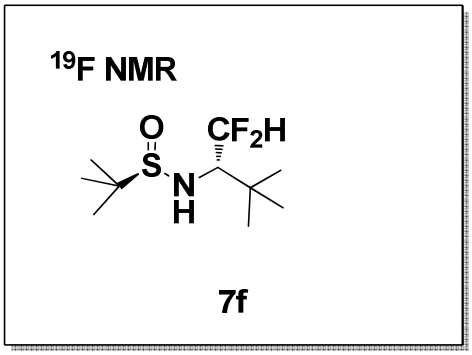
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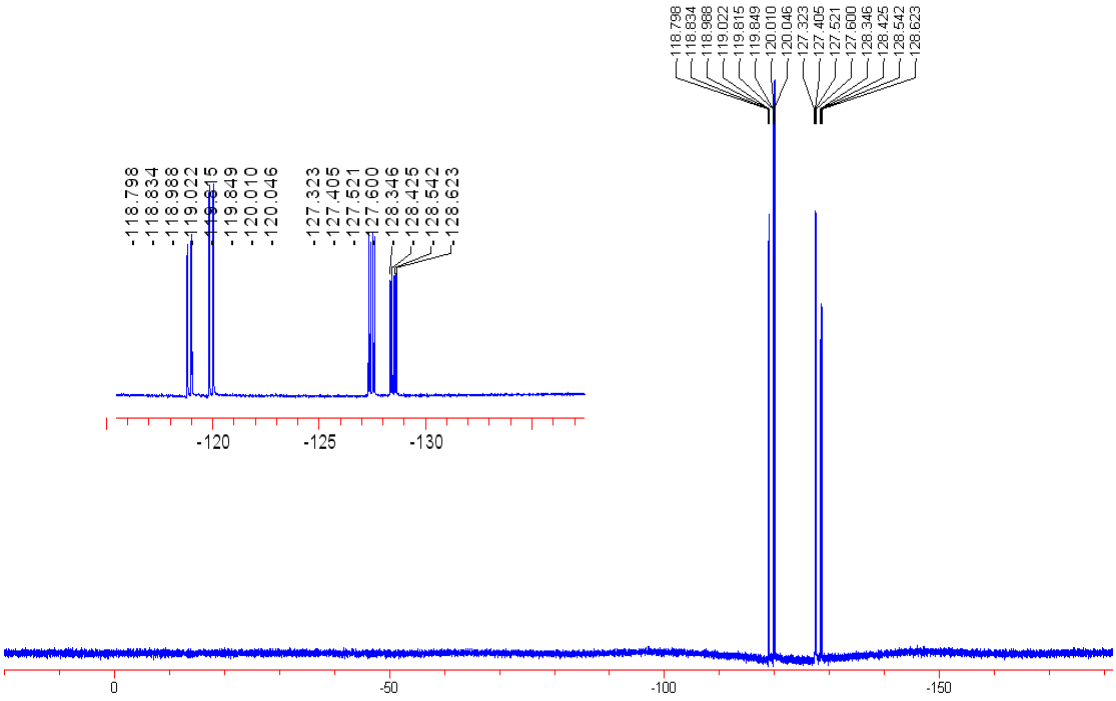
O
S
N
H
CF2H
7f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-118.988
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-120.010
-120.046
-127.323
-127.405
-127.521
-127.600
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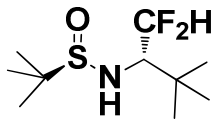
-128.542
-128.623
-120
-125
-130
0
-50
-100
-150

^{13}C NMR



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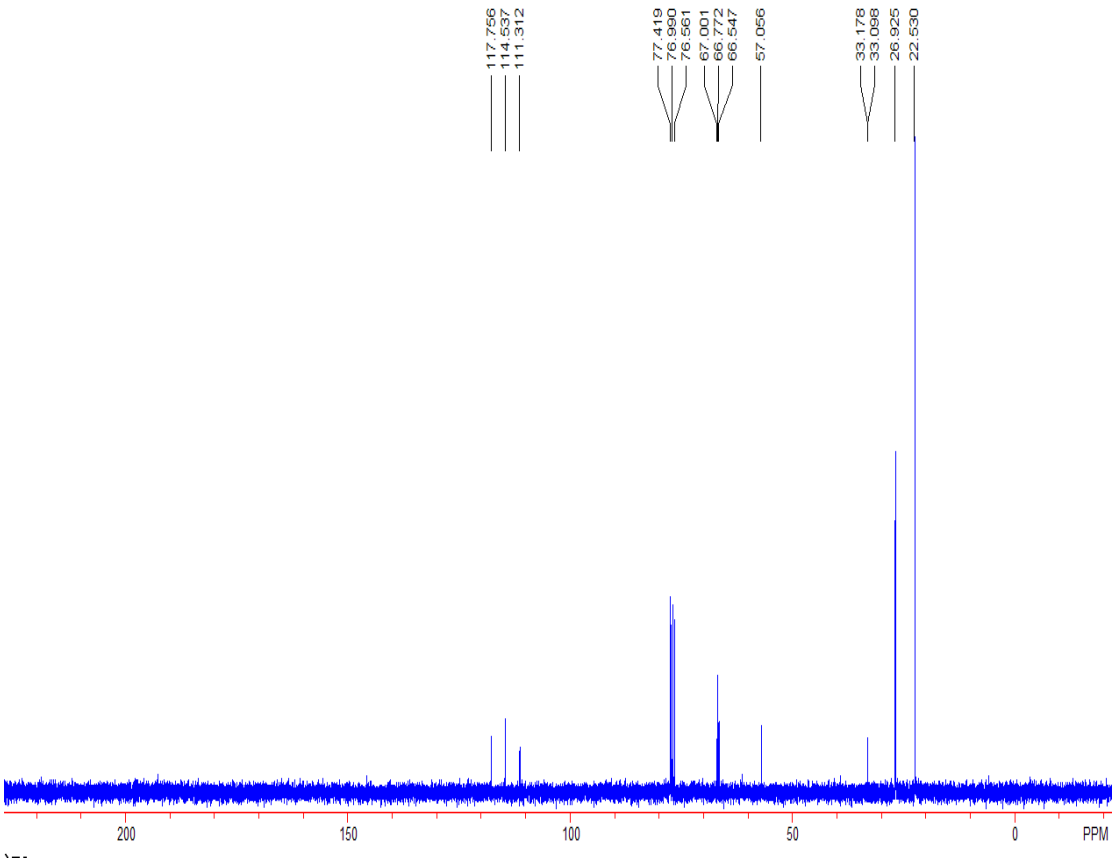
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100
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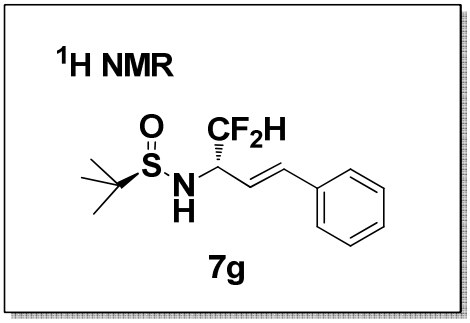
PPM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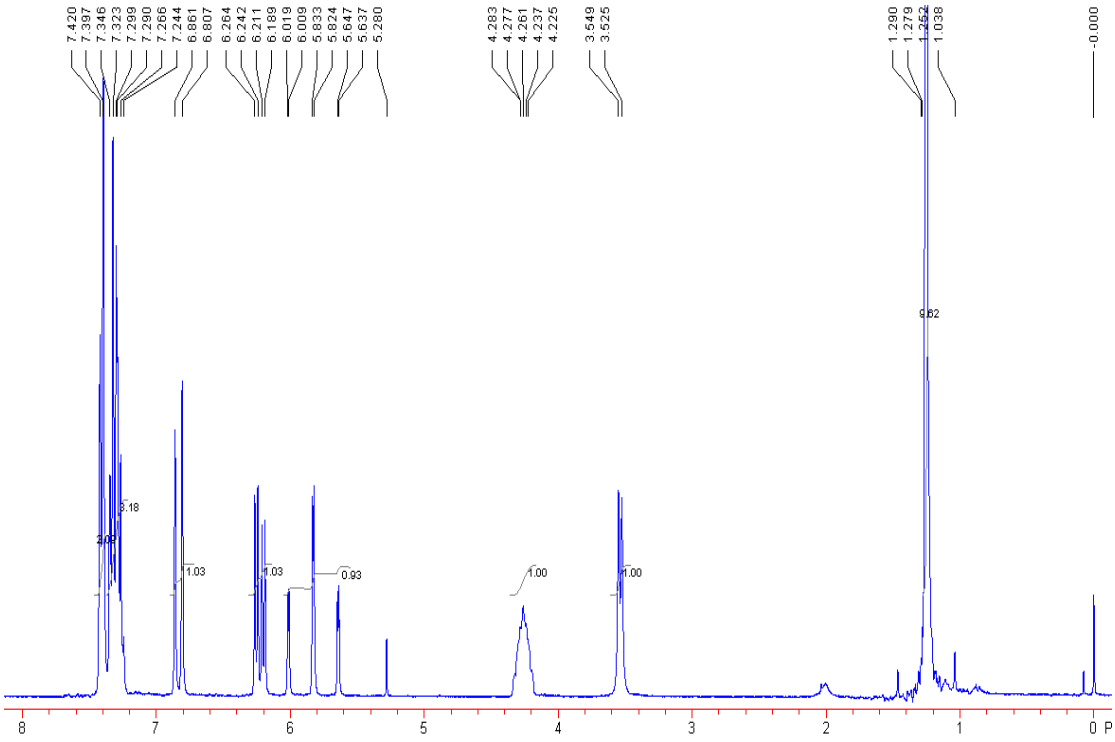
O
S
N
H
CF2H
7g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6.211
6.189
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5.833
5.824
5.647
5.637
5.280
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4.277
4.261
4.237
4.225
3.549
3.525
1.290
1.279
1.252
1.038
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1.00
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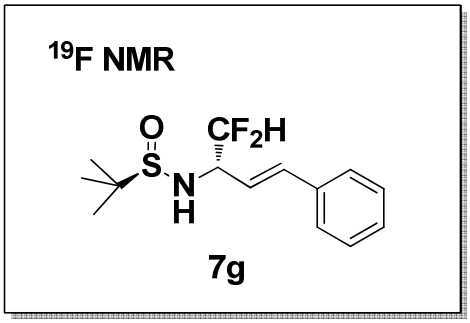
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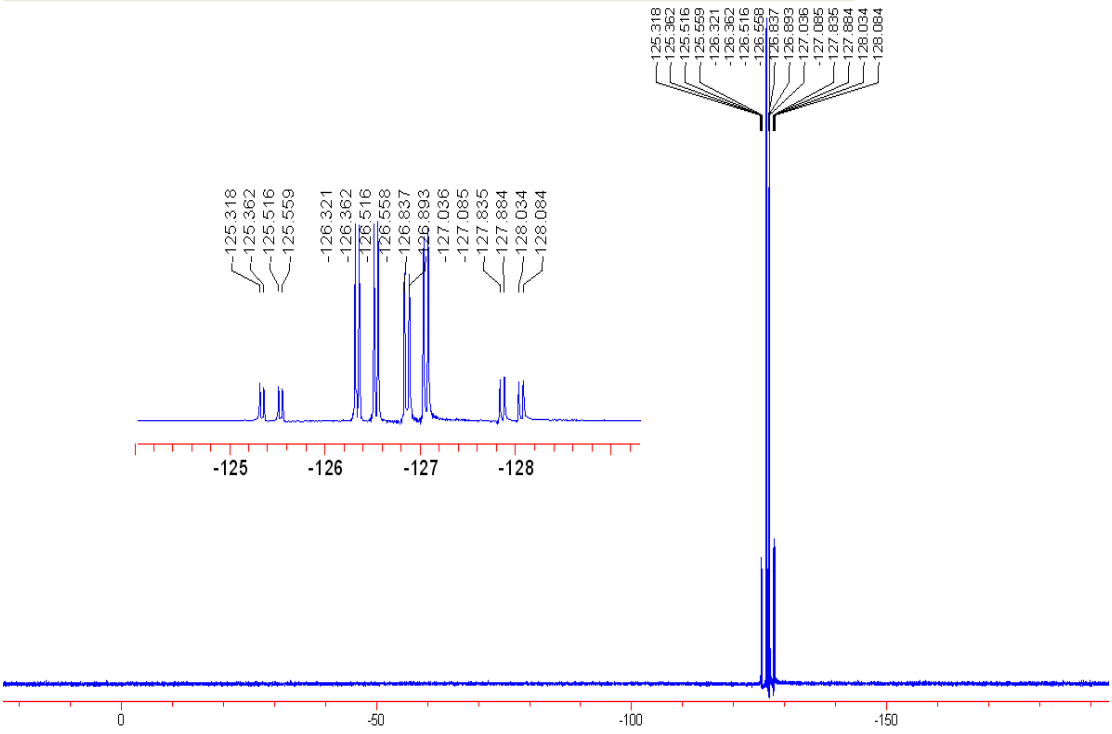
S
N
H
CF2H
7g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-125.516
-125.559
-126.321
-126.362
-126.516
-126.558
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-127.036
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-127
-128
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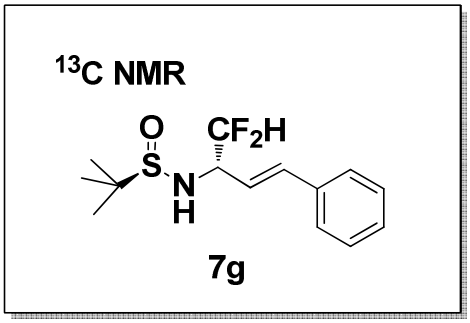
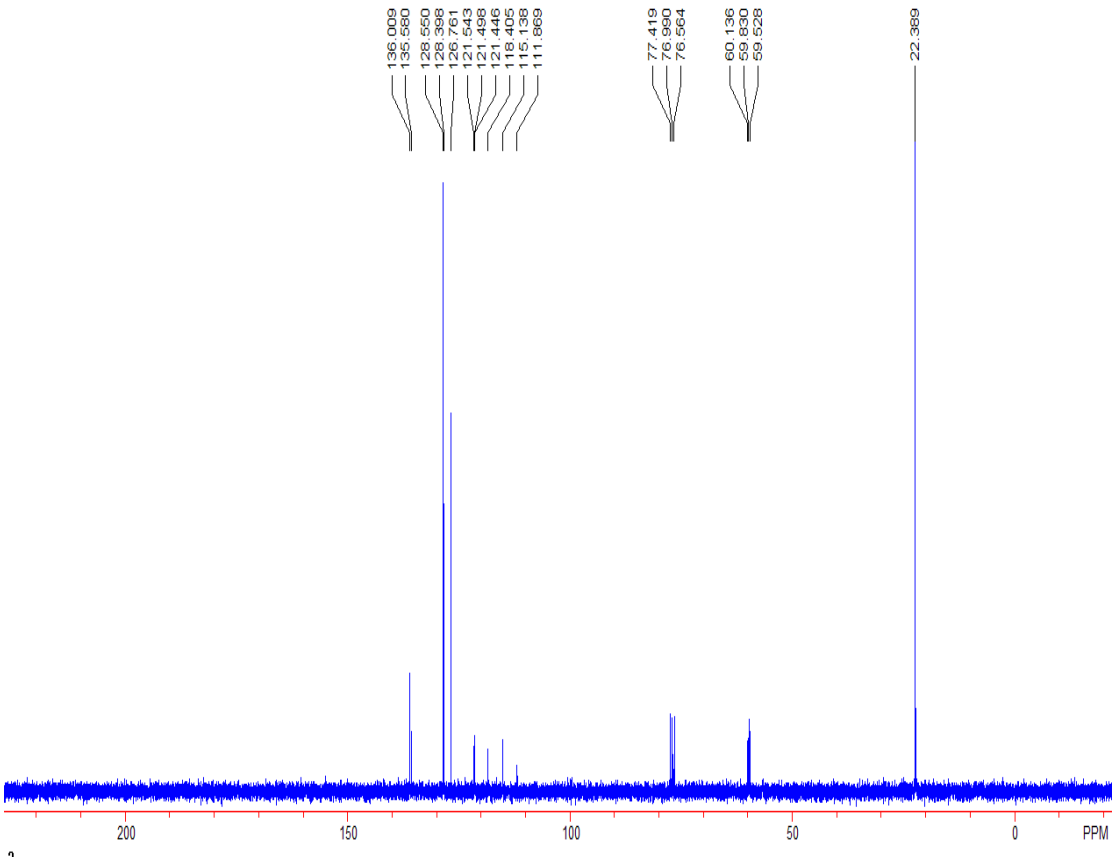
-100
-150


13C NMR
O
S
N
H
CF2H
7g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115.138
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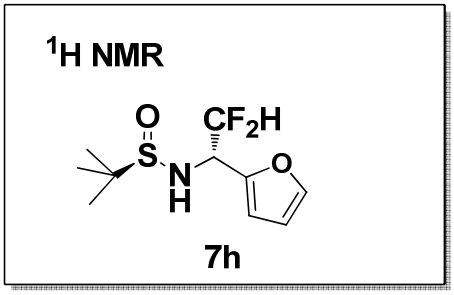
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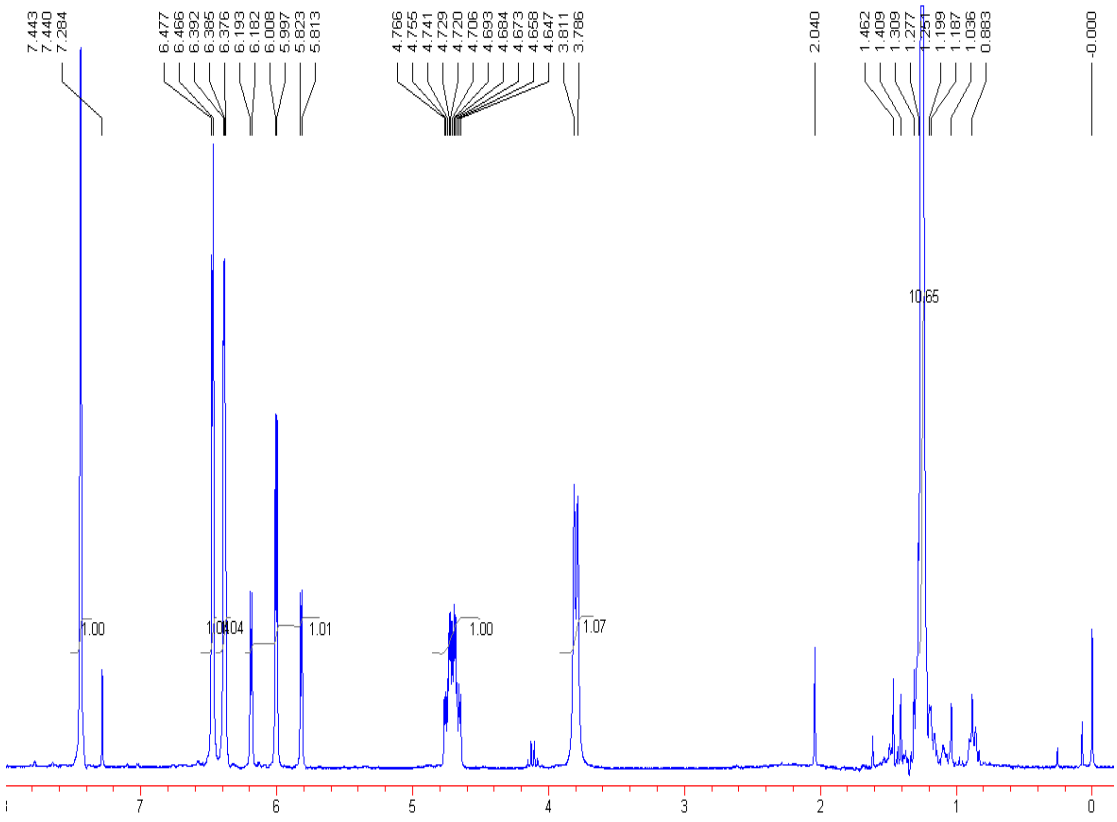
S
N
H
CF2H
O
7h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5.823
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1.187
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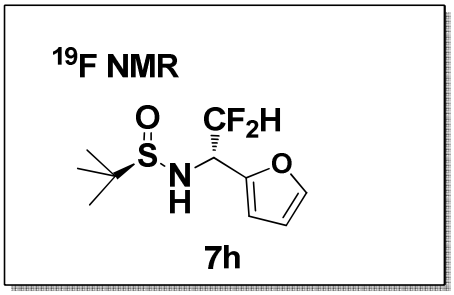
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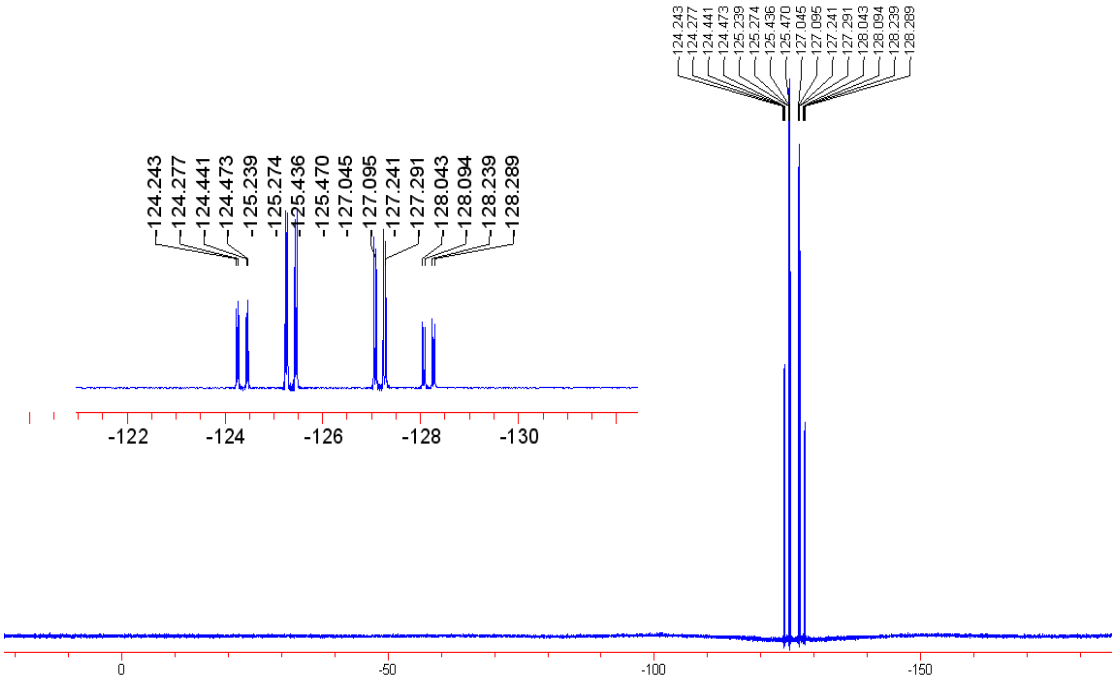
CF2H
O
7h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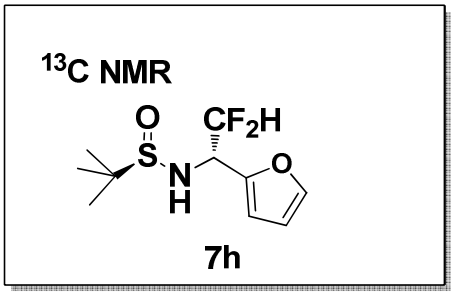
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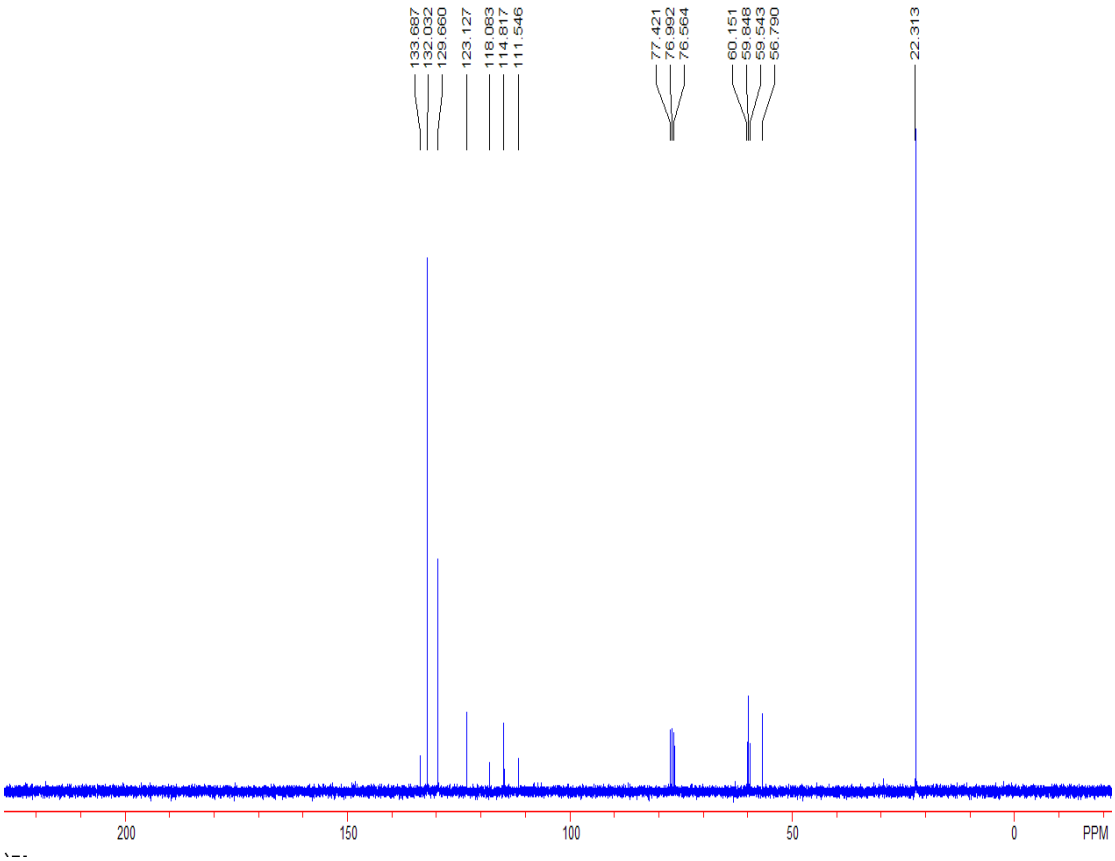
H
CF2H
O
7h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118.083
114.817
111.546
77.421
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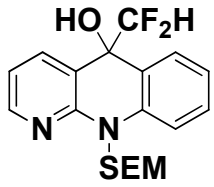
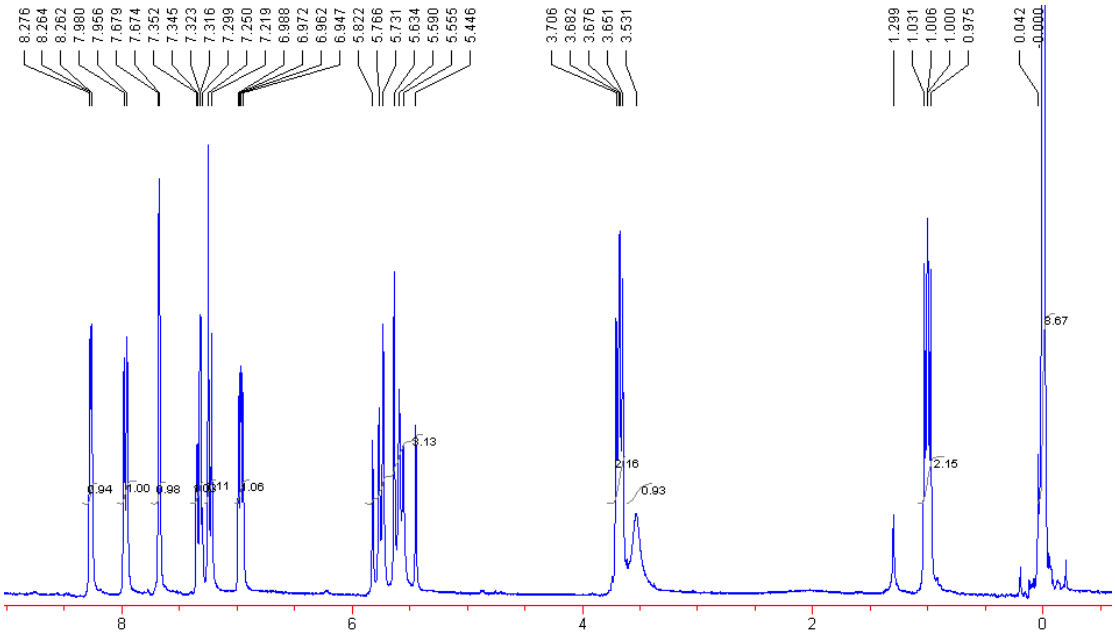
59.543
56.790
22.313
200
150
100
50
0
PPM

^{1}H NMR


HO
CF2H
N
N
SEM

9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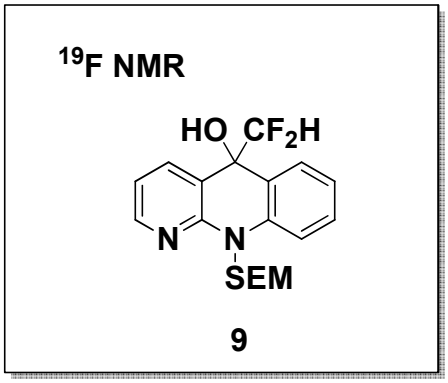
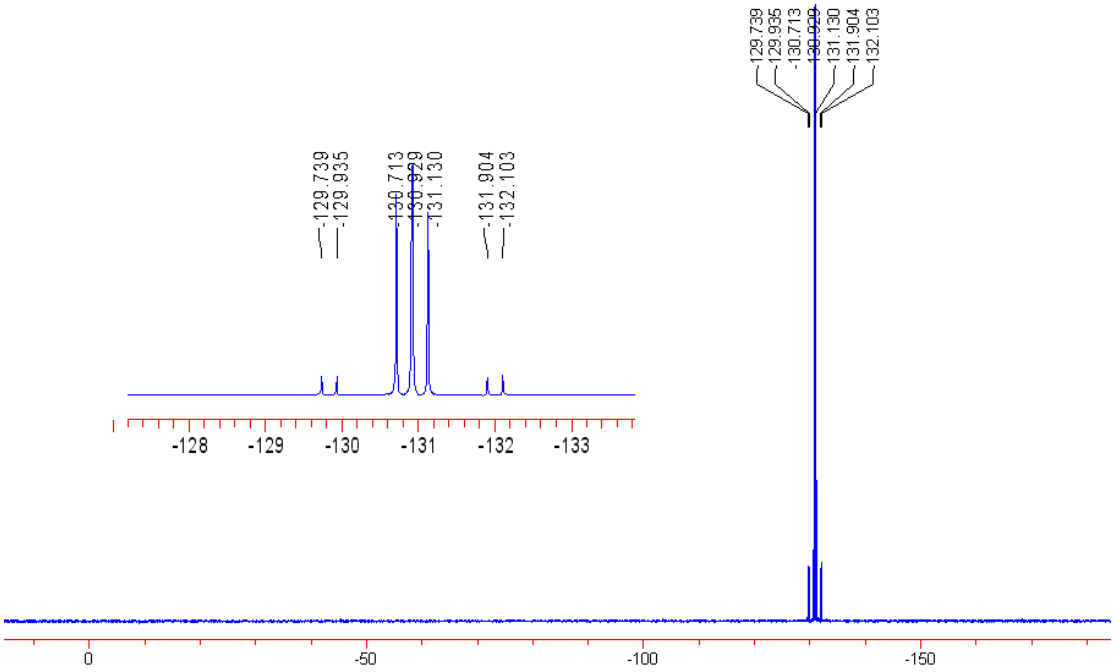

19F NMR
HO CF2H
N
N
SEM
9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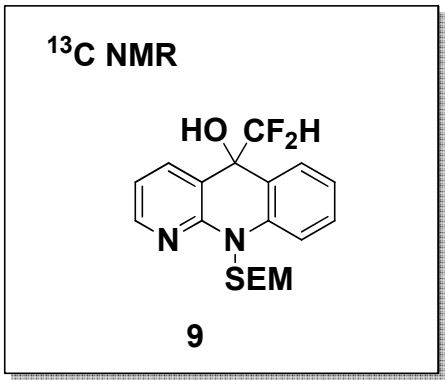
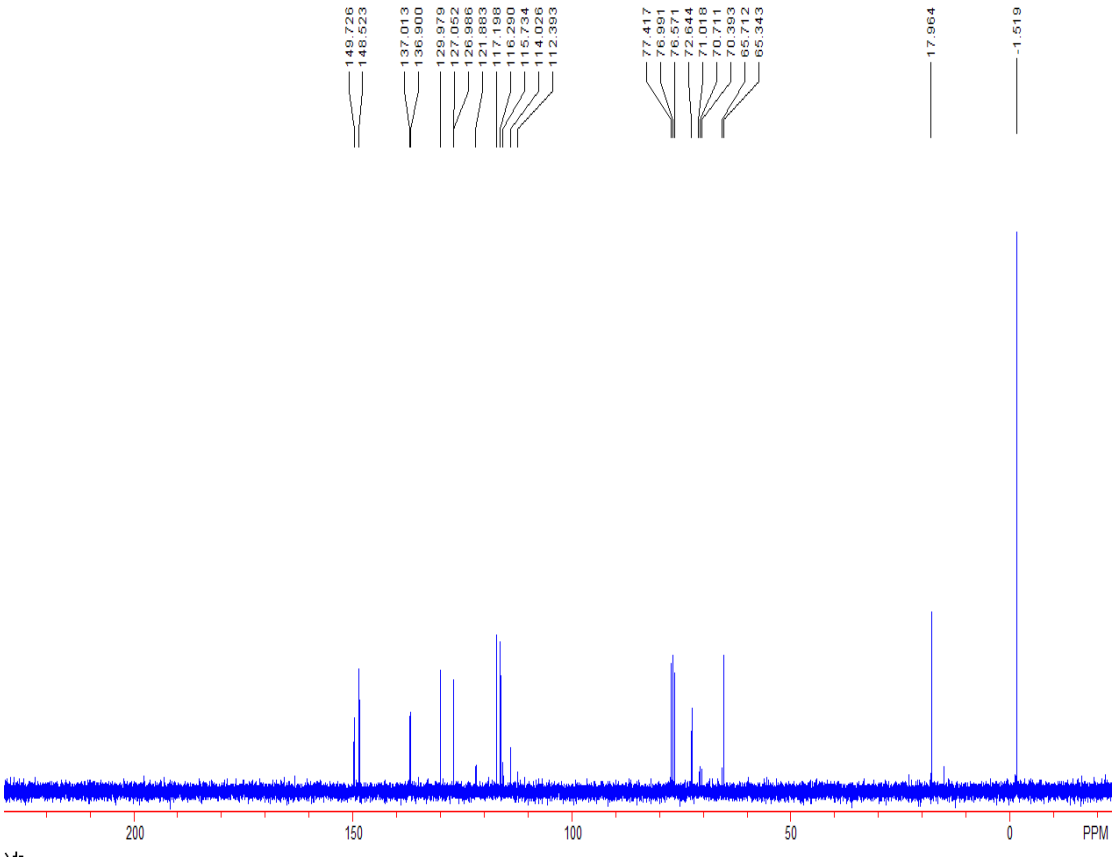

13C NMR
HO
CF2H
N
N
SEM
9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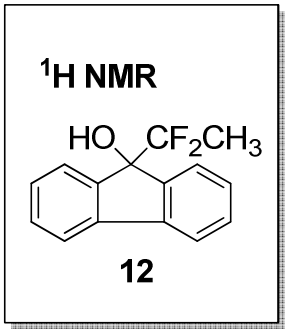
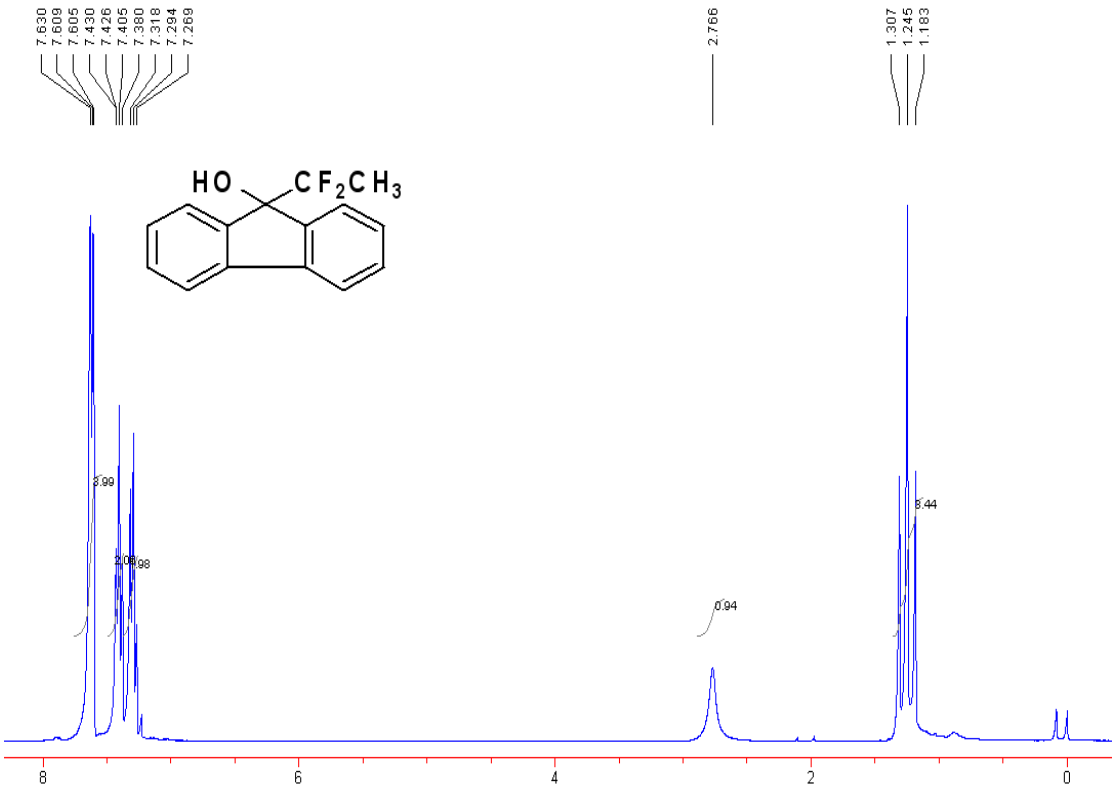
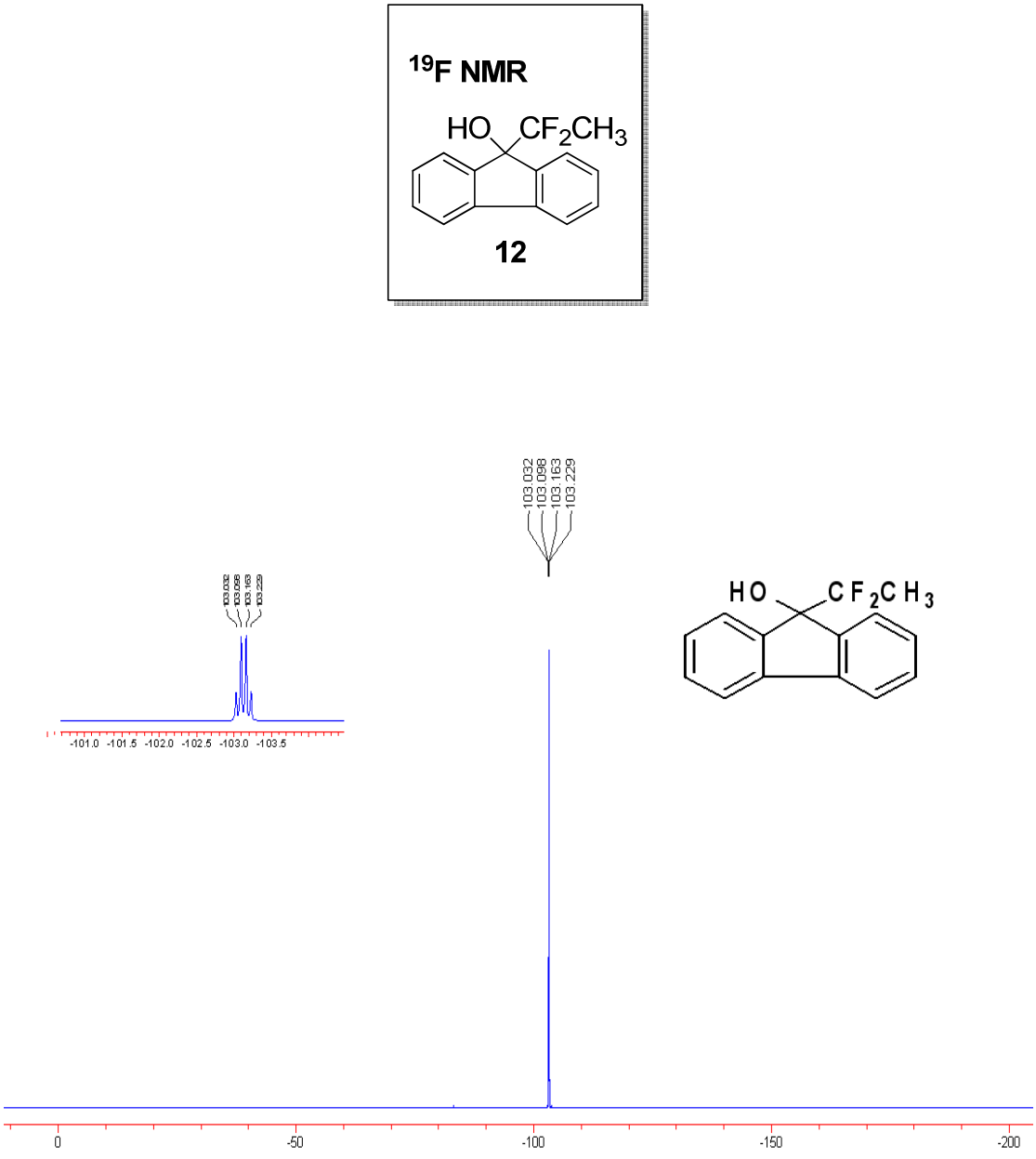
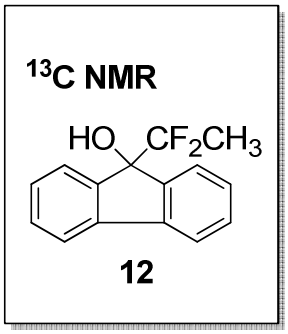
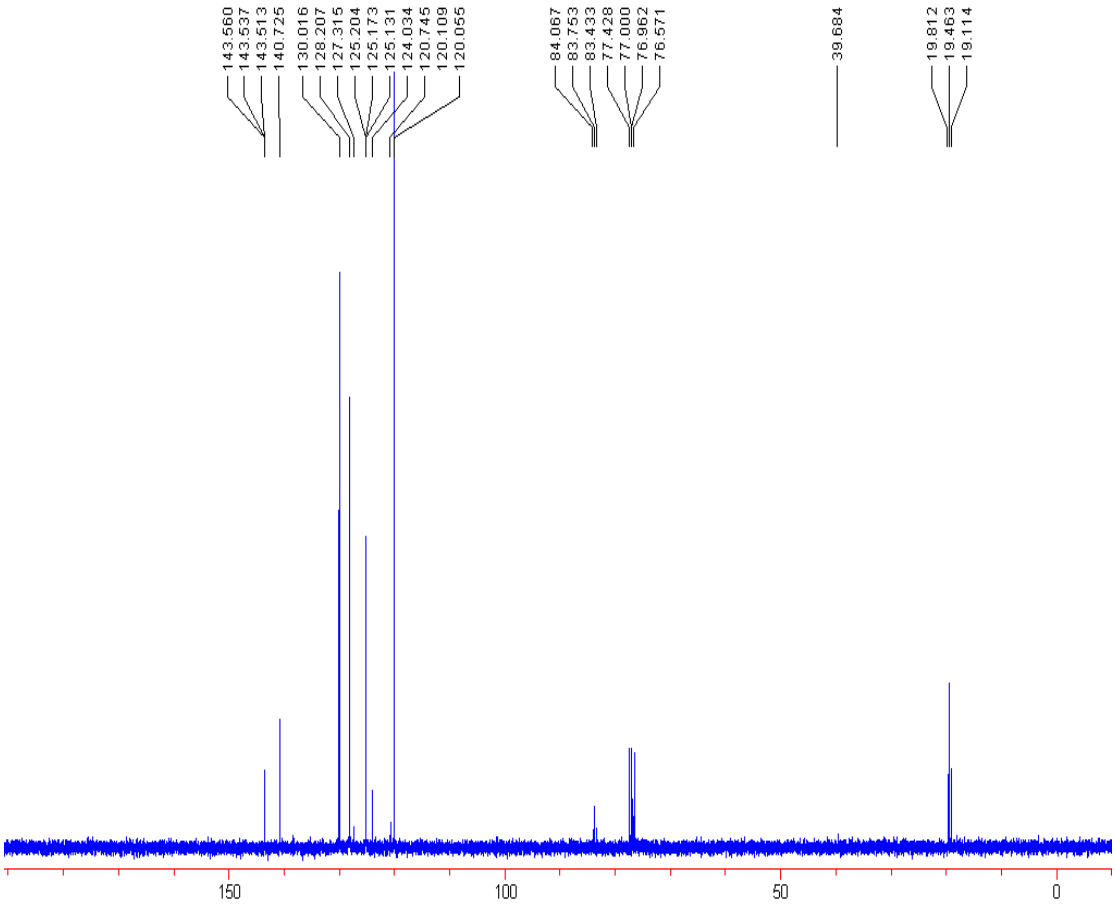
112.393
77.417
76.991
76.571
72.644
71.018
70.711
70.393
65.712
65.343
17.964
1.519
200
150
100
50
0
PPM

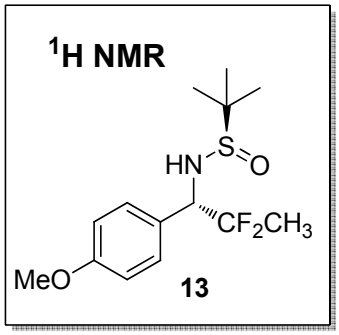

^{1}H NMR
HO
CF_2CH_3
12

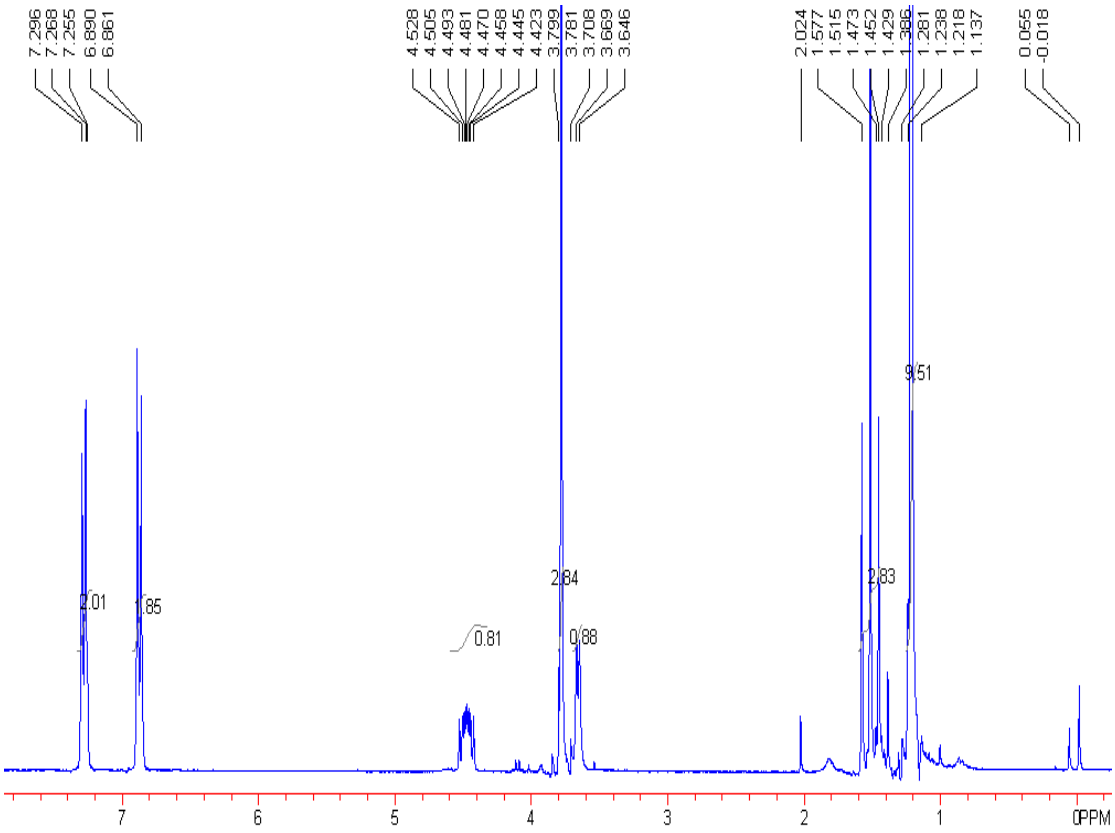

7.630
7.609
7.605
7.430
7.426
7.405
7.380
7.318
7.294
7.269
2.766
1.307
1.245
1.183
HO
CF_2CH_3
3.99
2.08
1.98
0.94
8.44
8
6
4
2
0

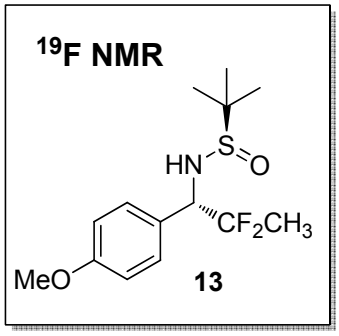

19F NMR
HO
CF2CH3
12
103.032
103.098
103.163
103.229
HO
CF2CH3
-101.0
-101.5
-102.0
-102.5
-103.0
-103.5
0
-50
-100
-150
-200

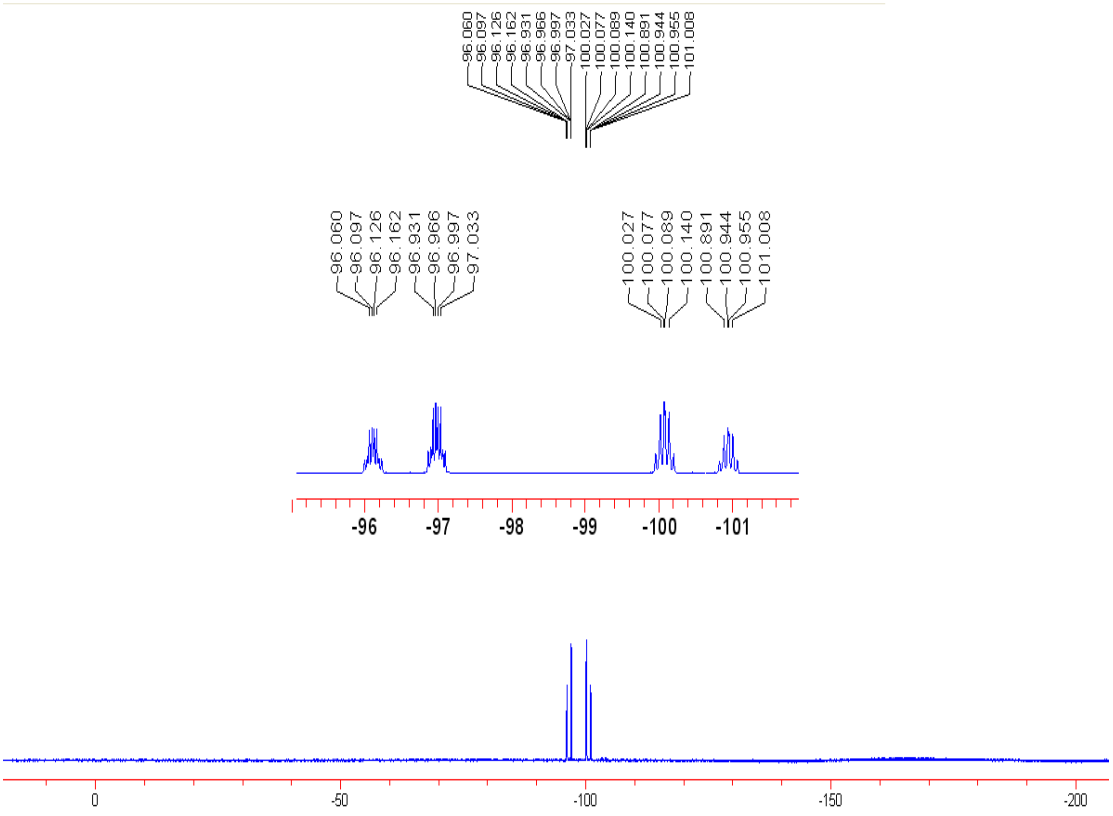

13C NMR
HO
CF2CH3
12


143.560
143.537
143.513
140.725
130.016
128.207
127.315
125.204
125.173
125.131
124.034
120.745
120.109
120.055
84.067
83.753
83.433
77.428
77.000
76.962
76.571
39.684
19.812
19.463
19.114
150
100
50
0


1H NMR
HN
S
O
CF2CH3
MeO
13


7.296
7.268
7.255
6.890
6.861
4.528
4.505
4.493
4.481
4.470
4.458
4.445
4.423
3.799
3.781
3.708
3.669
3.646
2.024
1.577
1.515
1.473
1.452
1.429
1.386
1.281
1.238
1.218
1.137
0.055
-0.018
2.01
1.85
0.81
2.84
0.88
2.83
9.51
7
6
5
4
3
2
1
0PPM


19F NMR
HN
S
O
CF2CH3
MeO
13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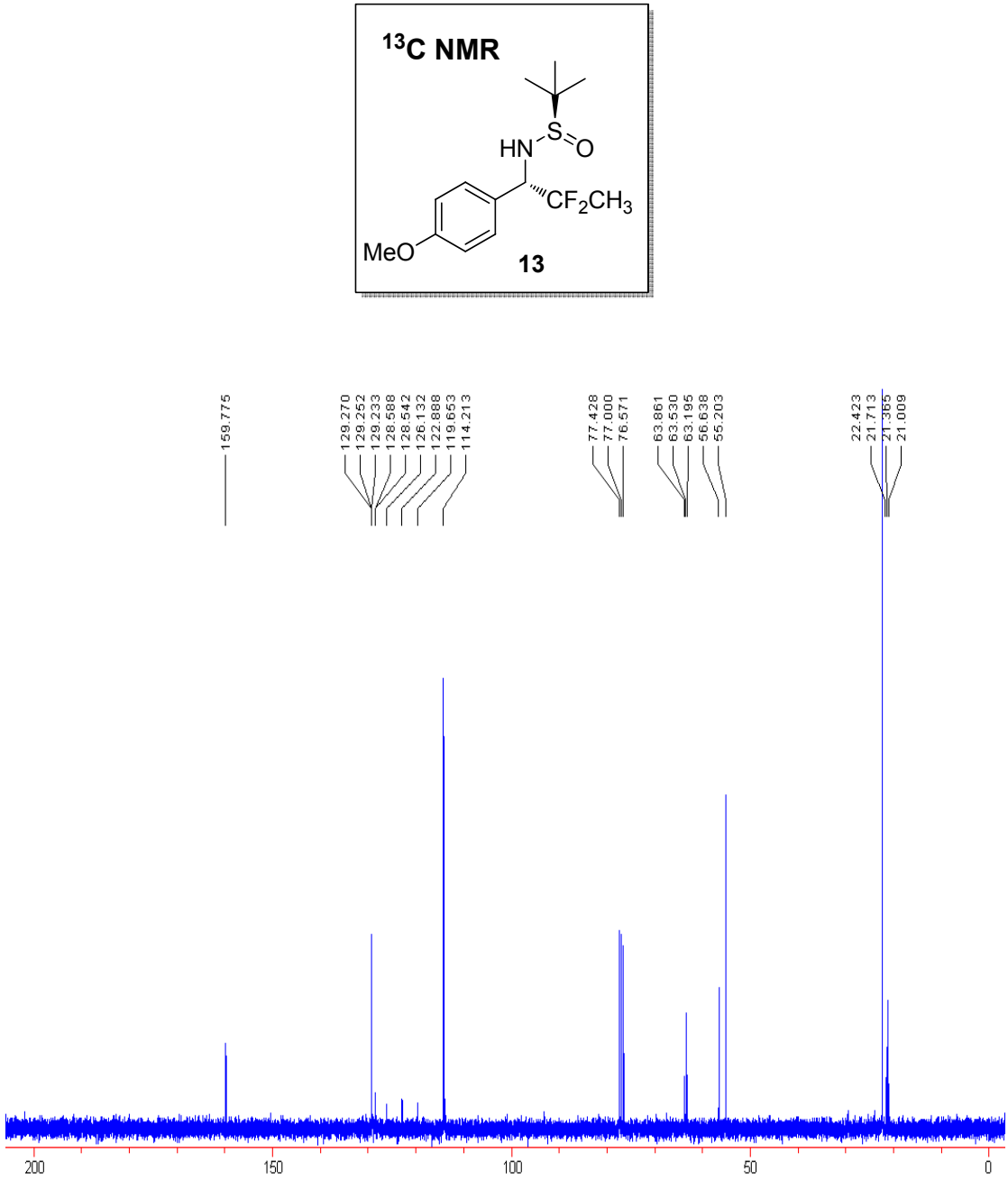
96.097
96.126
96.162
96.931
96.966
96.997
97.033
100.027
100.077
100.089
100.140
100.891
100.944
100.955
101.008
-96
-97
-98
-99
-100
-101
0
-50
-100
-150
-200


13C NMR
HN
S
O
CF2CH3
MeO
13
159.775
129.270
129.252
129.233
128.588
128.542
126.132
122.888
119.653
114.213
77.428
77.000
76.571
63.861
63.530
63.195
56.638
55.203
22.423
21.713
21.365
21.009
200
150
100
50
0