Synthesis of enantiopure α-Tfm-Proline and α-Tfm-Pipecolic Acid from oxazolo-pyrrolidines and -piperidines

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Supporting Information

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1. General information

Unless otherwise mentioned, all reagents were purchased from commercial source. All glassware was dried in an oven at 70°C prior to use. THF was distilled under nitrogen from sodium/benzophenone prior to use. CH_2Cl_2 was distilled under nitrogen from CaH_2 prior to use. Heated reactions were performed using an oil bath and a magnetic stirrer connected to a temperature controller. ^1H NMR (400.0 MHz), ^{13}C NMR (100.5 MHz) and ^{19}F (376.2 MHz) were measured on a JEOL EXC400 or a BRUKER AVANCE NEO 400 MHz spectrometer. Chemical shifts of ^1H NMR were reported in ppm downfield from Me_4Si (δ 0.0 ppm), $CDCl_3$ (δ 77.16 ppm) or C_6F_6 (δ −164.9 ppm) as internal standard. Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constant (Hz), integration. Column chromatography was performed on SDS 60A, (40-63 μm.) silica gel, employing mixture of specified solvent as eluent. Thin-

layer chromatography (TLC) was performed on Merck silica gel (Merck 60 PF254) plates. Silica TLC plates were visualized under UV light, by a 10% solution of phosphomolybdic acid in ethanol followed by heating. Infrared spectra (IR) were obtained by Fourier-transformation on BRUKER TENSOR 27, wave numbers are given in cm^{-1}. Optical rotations were determined using a Anton Paar MCP 200 polarimeter. HRMS were obtained using a QTOF 6530 Agilent Technologies, source ESI, resolution 12000. Melting Points were measured on a Büchi apparatus and uncorrected. An Agilent 1200 series high performance liquid chromatograph coupled to an ELSD detector and a chiral column CHIRALPAK AS-H (250 x 4.6 mm) were used to determine the enantiopurity of **(*R*)-15** and **(*S*)-15**.

2. Synthesis and analytical data of new compounds

(4*R*)-2-(3-carboethoxyethyl)-2-trifluoromethyl-4-phenyl-1,3-oxazolidine **4**

In a screw-capped vial, a solution of **1** (2.07 g, 10.65 mmol, 1 equiv) in toluene (10 mL) was added (*R*)-phenylglycinol (1.51 g, 11.18 mmol, 1.05 equiv) and PPTS (0.1 g, 0.4 mmol, 0.04 equiv).The mixture was heated for 12 h until the disappearance of the starting compound. The reaction mixture was then cooled down to room temperature, toluene was evaporated and CH_2Cl_2 (15 mL) was added. The organic phase was washed with $NaHCO_3$ (2×15 mL) then with a saturated solution of NaCl (15 mL), dried over $MgSO_4$ and evaporated under vacuum. The crude product could be used without further purification in the next step or purified by silica gel chromatography (90/10 cyclohexane/ethyl acetate) to give **4** (3.20 g, 94%) as colorless oil. *Rf* 0.40 (80/20, cyclohexane / ethyl acetate); IR (neat, cm^{-1}): 2980, 1730, 1165, 700 ; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.26 (t, *J* = 6.9 Hz, 3H), 2.20-2.34 (m, 2H), 2.52-2.67 (m, 2H), 2.76 (d, *J* = 7.8 Hz, 1H), 3.70 (t, *J* = 8.2 Hz, 1H), 4.10-4.18 (m, 2H), 4.39 (t, *J* = 7.3 Hz, 1H), 4.64 (q, *J* = 7.8 Hz, 1H), 7.29-7.39 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) : δ 14.3, 27.5, 27.8, 61.0, 61.3, 74.8, 126.0 (q, $^1J_{CF}$ = 271 Hz), 127.0, 128.4, 129.0, 138.5, 173.4; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -84.99; HRMS (ESI-TOF): $[M+H]^+$ calculated for $C_{15}H_{19}F_3NO_3$ 318.1317, found 318.1313.

(4*R*)-2-(3-carboethoxypropyl)-2-trifluoromethyl-4-phenyl-1,3-oxazolidine **5**

In a screw-capped vial, **2** (0.90 g, 4.23 mmol, 1 equiv) was dissolved in toluene (5 mL) with (*R*)-phenylglycinol (0.62 g, 4.44 mmol, 1.05 equiv). PPTS (0.05 g, 0.12 mmol, 0.05 equiv) was added in catalytic portion. The mixture was heated for 24 h until the disappearance of the starting compound. The reaction mixture was then cooled to rt, toluene was evaporated and

AcOEt (20 mL) was added. The organic phase was washed with $NaHCO_3$ (2×15 mL) then with NaCl (20 mL) and dried over $MgSO_4$. The crude mixture was purified by flash chromatography (90/10 cyclohexane / ethyl acetate). A mixture of two inseparable diastereoisomers **5** (85/15 *dr*) was obtained (1 g, 3.02 mmol) in 71% yield. Yellow oil; *Rf* 0.78 (70/30 cyclohexane / ethyl acetate); IR (neat, cm^{-1}): 2985, 1730, 1162, 700; ^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 1.27 (t, J = 7.3 Hz, 3H), 1.80-2.08 (m, 3H,), 2.34-2.48 (m, 3H), 3.73 (t, J = 8.2 Hz, 1H), 4.14 (q, J = 7.3 Hz, 2H), 4.39 (t, J = 7.3 Hz, 1H), 4.61 (t, J = 7.3 Hz, 1H),7.26-7.43 (m, 5H); (minor isomer) δ 1.27 (t, J = 7.3 Hz, 3H), 1.80-2.08 (m, 3H), 2.34-2.48 (m, 3H), 3.82 (t, J = 9.2 Hz, 1H), 4.14 (q, J = 7.3, 2H), 4.39 (t, J = 7.3 Hz, 1H), 4.61 (t, J = 7.3 Hz, 1H),7.26-7.43 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): (major isomer) δ 14.3, 17.8, 31.7, 33.7, 60.5, 61.7, 74.5, 95.8 (q, J = 28.8 Hz), 125, 1 (q, J = 288.5 Hz), 126.9 , 128.4, 129.0, 138.4, 173.1; (minor isomer) δ 14.3, 17.3, 32.4, 33.3, 60.5, 61.7, 75.4, 94.7 (q, J = 29.7 Hz), 125.1 (q, J = 281.8 Hz), 126.8, 127.8, 128.6, 139.4,173.2; ^{19}F NMR (376.2 MHz, $CDCl_3$): (major isomer) -85.0, (minor isomer) δ -85.2; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{16}H_{21}F_3NO_3$ 332.1474, found 332.1468.

(*R*)-2-(3-carboxypropyl)-2-trifluoromethyl-4-phenyl-1,3-oxazolidine **6**

In a screw-capped vial, **3** (10.00 g, 54.32 mmol, 1 equiv) was dissolved in toluene (60 mL) with (*R*)-(-)-phenylglycinol (7.84 g, 57.04 mmol, 1.05 equiv). PPTS (6.84 g, 2.72 mmol, 0.05 equiv) was added. The mixture was heated for 1h. After cooling, toluene was evaporated and DCM (70 mL) was added for dilution. The organic extract was washed with $NaHCO_3$ (1×70 mL). The aqueous phase was acidified with HCl 1M until pH = 4 and extracted with dichloromethane (2 ×70 mL). Organic phase was successively washed with staturated NaCl (20 mL) and dried over $MgSO_4$. Two inseparable diastereomers **6** were obtained (95/5 *dr*). The crude compound was obtained in 82% yield (13.60 g, 44.85 mmol) and used without purification in the next step. Yellow oil; *Rf* 0.58 (50/50 cyclohexane / ethyl acetate); IR (neat, cm^{-1}): 3224, 2983, 1705, 1168; ^1H NMR (400 MHz, $CDCl_3$): (major isomer) δ 1.91-2.1 (m, 3H), 2.37-2.53 (m, 3H), 3.75 (t, J = 7.8 Hz), 4.40 (t, J = 7.8 Hz), 4.62 (t, J = 7.8 Hz, 1H),7.26-7.40 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): (major isomer) δ 18.7, 31.0, 33.5, 61.7, 74.6, 95.8 (q, J = 29.7 Hz), 125.0 (q, J = 288.5 Hz), 127.0, 128.5, 129.1, 138.4, 178.6; ^{19}F NMR (376.2 MHz, $CDCl_3$): (major isomer) δ -85.0. HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{14}H_{17}F_3NO_3$ 304.1161, found 304.1152.

(4*R*)-2-(3-hydroxypropyl)-2-trifluoromethyl-4-phenyl-1,3-oxazolidine **7**

To a solution of oxazolidine **4** (26.8 g, 84.4 mmol, 1.0 equiv) in a mixture of ethanol/THF (300 mL/150 mL) under argon atmosphere at 0 °C was added $NaBH_4$ (38.3 g, 1.013 mol, 12.0 equiv)

and very slowly $CaCl_2$ (65.6 g, 0.591 mol, 7.0 equiv). The reaction was stirred for 1 h at room temperature, then quenched with saturated NH_4Cl aqueous solution (100 mL). Methanol was removed under reduced pressure and the corresponding aqueous solution was taken up with ethyl acetate (150 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. After filtration through a short pad of silica gel, and precipitation in pentane followed by filtration the pure reduced oxazolidine **7** (22.0 g, 95%) was obtained as a white solid. m.p. 62-64°C; *Rf* 0.56 (80/20, cyclohexane / ethyl acetate); IR (neat, cm^{-1}): 3411, 3349 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) : δ 1.67-1.72 (m, 2H), 1.88-1.88 (m, 1H), 1.95-2.03 (m, 1H), 2.58 (s, 1H), 3.53-3.67 (m, 3H), 4.30 (t, J = 7.3 Hz, 1H), 4.53 (t, J = 7.3 Hz, 1H), 7.22-7.31 (m, 5H, H_{Ar}); ^{13}C NMR (100.5 MHz $CDCl_3$) : δ 25.3, 29.2, 61.8, 62.5, 74.6, 96.0 (q, $^2J_{CF}$ = 29.6 Hz), 125.2 (q, $^1J_{CF}$ = 288.3 Hz), 127.0, 128.5, 129.1, 138.4; ^{19}F NMR (376.2 MHz $CDCl_3$) : δ -84.86; HRMS (ESI-TOF): $[M+H]^+$ calculated for $C_{13}H_{17}F_3NO_2$ 276.1211, found 276.1207.

Oxazolopyrrolidine **8**

To a solution of oxazolidine **7** (11.7 g, 42.8 mmol) in CH_2Cl_2 (200 mL) under argon atmosphere were added triphenylphosphine (16.8 g, 64.2 mmol, 1.5 equiv.) and imidazole (9.3 g, 136.9mmol, 3.2 equiv.). Then iodine (16.3 g, 64.2 mmol, 1.5 equiv.) was added slowly and the mixture was stirred for 2 h under aluminum foil. The crude mixture was washed with H_2O (100 mL) and brine (100 mL) and the organic phase was dried over $MgSO_4$. Purification by flash chromatography (80/20 cyclohexane/ethyl acetate) gave **8** as a diastereoisomerically pure compound in 73% yield (8.031 g, 31 mmol) as a colorless oil. *Rf* 0.8 (80/20, cyclohexane / ethyl acetate); IR (neat, cm^{-1}): 2945, 1145; ^1H NMR (400 MHz $CDCl_3$): δ 1.75-1.82 (m, 2H), 1.92-2.00 (m, 1H), 2.41-2.47 (m, 1H), 2.53-2.59 (m, 1H), 2.64-2.69 (m, 1H), 4.12 (dd, J = 7.8, 10.1 Hz, 1H), 4.30 (dd, J = 6.4, 7.8 Hz, 1H), 4.71 (dd, J = 6.4, 10.1 Hz, 1H), 7.31-7.37 (m, 5H, H_{Ar}); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 24.9, 34.4, 49.4, 64.4, 67.1, 103.7 (q, $^2J_{CF}$ = 30.7 Hz), 124.9 (q, $^1J_{CF}$ = 284.7 Hz), 126.7, 128.5, 128.7, 135.0; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -84.6; HRMS (ESI-TOF): $[M+H]^+$ calculated for $C_{13}H_{15}F_3NO$ 258.1106, found 258.1102.

Oxazolopiperidinone **9 maj** and **9 min**.

To the acid **6** (1.74 g, 5.74 mmol, 1 equiv) dissolved in toluene (70 mL) was added a small amount of p-toluenesulfonic acid (0.13 g, 0.86 mmol, 0.15 equiv) and the mixture was heated

with a Dean-Stark trap for 24h. After cooling, the mixture was diluted with ethyl acetate (30 mL) and washed with NaOH 2N (40 mL). The organic extract was dried on $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (90/10 to 80/20 cyclohexane / ethyl acetate) gave the major isomer **9 maj** (1.05 g, 3.68 mmol, 63%) and, the minor isomer **9 min** (0.13 g, 0 .43 mmol, 7%). **9 maj**: Colorless oil; *Rf* 0.41 (70/30 cyclohexane / ethyl acetate); $[\alpha]^{19.9}_D$: 140 ° (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}): 2915, 1674, 1157; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74-1.82 (m, 1H), 1.93-1.96 (m, 1H), 2.01-2.13 (m, 1H), 2.50-2.60 (m, 2H), 2.62-2.70 (m, 1H), 4.15 (td, *J* = 8.7, 2.3 Hz, 1H), 4.62 (td, *J* = 8.7, 2.3 Hz), 5.49 (t, *J* = 8.7 Hz, 1H), 7.37-7.17 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): 15.3, 29.5, 30.0, 60.5, 72.5, 92.7 (q, *J* = 30.7 Hz), 124.5 (q, *J* = 291.4 Hz), 125.4, 127.5, 128.7, 138.5, 171.7; NMR ^{19}F (376.2 MHz, $CDCl_3$): δ -80.1; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{14}H_{15}F_3NO_2$ 286.1055, found 286.1052.

9 min: White solid; m.p.112-114°C; *Rf* 0.44 (70/30 cyclohexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): δ 1.87-1.96 (m, 1H), 1.98-2.07 (m, 1H), 2.10-2.18 (m, 1H), 2.26-2.44 (m, 2H), 2.50-2.57 (m, 1H), 4.01-4.05 (m, 1H), 4.66 (t, *J* = 8.3 Hz, 1H), 5.10 (dd, *J* = 9.7 Hz, 8.3 Hz, 1H), 7.26-7.36 (m, 5H), ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 16.4, 28.5, 30.5, 60.3, 75.1, 91.8 (q, *J* = 30.7 Hz), 125.0 (q, *J* = 287.5 Hz), 126.4, 128.1, 128.9, 140.5, 169.1; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -81.7. HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{14}H_{15}F_3NO_2$ 286.1055, found 286.1052.

Oxazolopiperidine **10 maj and 10 min**

To a solution of **9 maj** (2 g, 7 mmol, 1 equiv) in THF (20 mL) cooled to 0°C was slowly added BH_3/THF 1M (19.53 mmol, 21.7 mL, 2.8 equiv). The resulting mixture was stirred during 2h until disappearance of the starting materiel checked by ^{19}F NMR. MeOH (20 mL) was added and the reaction mixture was stirred for 30 minutes. MeOH was evaporated. The crude colorless oil obtained was purified by flash chromatography (90/10 cyclohexane / ethyl acetate). The compound **10 maj** was obtained in 71% yield (1.359 g, 5.01 mmol) as a colorless oil.

10 maj: Colorless oil; *Rf* 0.88 (90/10 cyclohexane / ethyl acetate); $[\alpha]^{19.9}_D$: -226 ° (c 1.1, $CHCl_3$); IR (neat, cm^{-1}): 2952, 1147; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41-1.46 (m, 1H), 1.71-1.81 (m, 4H) 2.03-2.10 (m, 1H), 2.75-2.81 (m, 1H), 2.87-2.94 (m, 1H), 3.79 (t, *J* = 9.1 Hz, 1H), 4.25 (dd, *J* = 7.8, 6.9 Hz, 1H), 4.36 (dd, *J* = 10 Hz, 6.4 Hz, 1H), 7.28-7.44 (m); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 17.0, 18.1, 26.7, 41.7, 65.2, 74.1, 92.4 (q, *J* = 29.7), 125.6 (q, *J* = 288.5 Hz), 127.8, 128.2, 128.7, 138.4; NMR ^{19}F (376.2 MHz, $CDCl_3$): δ -85.2; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{14}H_{17}F_3NO$ 272.1262, found 272.1258.

To a solution of **9 min** (1.00 g, 3.5 mmol, 1 equiv) in THF (10 mL) cooled to 0°C was slowly added BH_3/THF 1M (12.25 mmol, 12.25 mL, 3.5 equiv). The resulting mixture was stirred during 2h until disappearance of the starting materiel checked by ^{19}F NMR. MeOH (10 mL) was added and the reaction mixture was stirred for 30 minutes. MeOH was evaporated. The crude colorless oil obtained was purified by flash chromatography (90/10 cyclohexane/AcOEt). The compound (*S*)-**10** was obtained in 32% yield (0.304 g, 1.12 mmol) as a white solid.

10 min: *Rf* 0.70 (90/10 cyclohexane / ethyl acetate); IR (neat, cm^{-1}): 2952, 1147; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26-1.32 (m, 1H), 1.42-1.46 (m, 1H), 1.56-1.59 (m, 1H), 1.60-1.62 (m, 1H), 1.68-1.75 (m, 1H), 2.20-2.25 (m, 1H), 2.59-2.64 (m, 1H), 2.75-2.83 (m, 1H), 3.65-3.70 (m, 1H), 4.30-4.33 (m, 2H), 7.24-7.31 (m, 5H-arom); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 20.3, 24.4, 30.6, 41.1, 63.2, 74.5, 90.7, 125.8, 128.0, 128.2, 128.9, 140.1; NMR ^{19}F (376.2 MHz, $CDCl_3$): δ -75.5 (s, CF_3).

1-(2-hydroxy-1-phenylethyl)-2-carbonitrile-2-trifluoromethylpyrolidine **11**

To a solution of oxazolidine **8** (13.68 g, 53.23 mmol, 1 equiv) in CH_2Cl_2 (300 mL) was added, dropwise, trimethylsilyl cyanide (9.9 mL, 79.84 mmol, 1.5 equiv) at room temperature and under argon atmosphere. Then BF_3-Et_2O (10.1 mL, 79.84 mmol, 1.5 equiv) was added, dropwise, at 0°C. The mixture was stirred at room temperature for 1h, until the disappearance of the starting material checked by ^{19}F NMR. Then, $NaHCO_3$ (200 mL) was added and the mixture was stirred at room temperature for 30 minutes. The aqueous phase was extracted with DCM (3×200 mL) and organics extracts were gathered and dried on $MgSO_4$. The crude product could be used without further purification in the next step. A mixture of diastereomers (38/62) **11** (15.2 g, 99%) was obtained as colorless oil. A pure analytical sample of each diastereoisomer (*R*)-**11** and (*S*)-**11** was isolated by flash chromatography (90/10 cyclohexane/ethyl acetate).

(*R*)-**11**: Oil; *Rf* 0.40 (90/10, pentane/Et_2O); $[\alpha]^{19.9}_D$: +20.04° (c 0.7, $CHCl_3$); IR (neat, cm^{-1}): 3487, 2949, 2250, 1140; ^1H NMR (400 MHz, $CDCl_3$): δ 1.80-1.91 (m, 2H), 2.29-2.35 (m, 1H), 2.46-2.49 (m, 1H), 2.76 (t, J = 8.0 Hz, 1H), 2.18 (d, J = 8.0 Hz, 1H), 3.76-3.80 (m, 1H), 3.94-3.99 (m, 1H), 4.52 (t, J = 8.0 Hz, 1H), 7.33-7.43 (m, 5H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 22.8, 35.5, 47.6, 63.1, 63.8, 65.0 (q, $^2J_{CF}$ = 31.6 Hz), 116.6, 127.0 (q, $^1J_{CF}$ = 284.6 Hz), 128.6, 128.7, 129.9, 134.5; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -79.5; HRMS (ESI-TOF): $[M+H]^+$ calculated for $C_{14}H_{16}F_3N_2O$ 285.1215, found 285.1221.

(*S*)-**11**: Oil; *Rf* 0.28 (90/10, pentane/Et_2O); $[\alpha]^{19.9}_D$: +31.32° (c 1, $CHCl_3$); IR (neat, cm^{-1}): 3531, 2948, 2248, 1149; ^1H NMR (400 MHz, $CDCl_3$): δ 1.97-2.05 (m, 2H), 2.49-2.55 (m, 2H), 3.26-

3.31 (m, 1H), 3.34-3.40 (m, 1H), 3.94-4.04 (m, 1H), 4.09-4.15 (m, 1H), 4.48-4.54 (m, 1H), 7.26-7.36 (m, 5H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 23.6, 35.0, 47.2, 62.7, 63.8, 66.9 (q, $^{2}J_{CF}$ = 32.6 Hz), 117.9, 123.7 (q, $^{1}J_{CF}$ = 285.6 Hz), 126.8, 127.5, 128.7, 139.2; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -80.5; HRMS (ESI-TOF): $[M+H]^+$ calculated for $C_{14}H_{16}F_3N_2O$ 285.1215, found 285.1220.

1-(2-hydroxy-1-phenylethyl)-2-carbonitrile-2-trifluoromethylpiperidine- (*R*)-**12** and (*S*)-**12**

To a solution of oxazolidine **10 maj** and **10 min** (2.3 g, 8.49 mmol, 1 equiv) in CH_2Cl_2 (65 mL) was added, dropwise, trimethylsilyl cyanide (1.61 mL, 12.73 mmol, 1.5 equiv) at room temperature and under argon atmosphere. Then BF_3-Et_2O (1.57 mL, 12.73 mmol, 1.5 equiv) was added, dropwise, at 0°C. The mixture was stirred at room temperature for 1h, until the disappearance of the starting material checked by ^{19}F NMR. Then, $NaHCO_3$ (40 mL) was added and the mixture was stirred at room temperature for 30 minutes. The aqueous phase was extracted with DCM (3×30 mL) and organics extracts were gathered and dried on $MgSO_4$. A mixture of diastereomers (50/50) (*R*)-**12** and (*S*)-**12** was obtained; they were separated by flash chromatography (90/10 to 80/20 cyclohexane / ethyl acetate). (*R*)-**12** (894 mg, 3.00 mmol) and (*S*)-**12** (848 mg, 2.84 mmol) were obtained in respectively 41% and 39% yield, as an oil for (*R*)-**12** and a white solid for (*S*)-**12**.

(*R*)-**12**: Oil; *Rf* 0.46 (80/20 cyclohexane / ethyl acetate); $[\alpha]^{19.9}_D$: -15.2° (c 1, $CHCl_3$); IR (neat, cm^{-1}): 3507, 2949, 2252, 1146 ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.25-1.40 (m, 1H), 1.55-1.59 (m, 1H), 1.65-1.74 (m, 1H), 1.83-1.87 (m, 1H), 1.99 (td, *J* = 12.0 Hz, 4Hz, 1H), 2.21 (d, *J* = 13.0 Hz, 1H), 2.80 (t, *J* = 12.0 Hz, 1H), 2.95 (d, *J* = 12.0 Hz, 1H) 4.21-4.27 (m, 1H), 4.35 (dd, *J* = 11.9 Hz, 5.0 Hz, 1H), 4.41 (dd, *J* = 11.9 Hz, 6.0 Hz, 1H), 7.26-7.45 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): *δ* 20.4, 24.8, 32.6, 43.6, 59.4, 63.1, 64.4 (q, *J* = 27.8 Hz), 115.7, 123.6 (q, *J* = 286.6 Hz), 127.4, 128.0, 128.5, 138.8; ^{19}F NMR (376.2 MHz, $CDCl_3$): *δ* -73.5; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{15}H_{17}F_3N_2O$ 299.1371, found 299.1362.

(*S*)-**12**: white solid; m.p. 118-120°C; *Rf* 0.26 (80/20 cyclohexane / ethyl acetate); $[\alpha]^{19.9}_D$: +58.9° (C = 1, $CHCl_3$); IR (neat, cm^{-1}): 3470, 2949, 1170; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.48-1.62 (m, 2H), 1.74-1.98 (m, 3H), 2.21 (d, *J* = 12.8 Hz, 1H), 2.37 (t, *J* = 12 Hz, 1H), 3.23 (d, *J* = 12.8 Hz, 1H), 3.61 (dd, *J* = 11.5Hz, 5.5 Hz, 1H), 4.04 (t, *J* = 10.5 Hz, 1H), 4.47 (m, 1H), 7.32-7.38 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): *δ* 20.4, 25.0, 33.1, 43.3, 61.4, 63.9, 64.0 (q, *J* = 27.8 Hz) 113.4, 123.5 (q, *J* = 286.6 Hz), 128.3, 128.9, 130.0, 132.9; ^{19}F NMR (376.2 MHz,

$CDCl_3$): δ -71.9; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{15}H_{17}F_3N_2O$ 299.1371, found 299.1363.

Morpholinones (*R*)-**13** and (*S*)-**13**

To a mixture of nitriles diastereomers (38/62) (*R*)-**11** and (*S*)-**11** (15.2 g, 53.23 mmol, 1 equiv) dissolved in toluene (500 mL) was added a small amount of p-toluenesulfonic acid (5.08 g, 26.74 mmol, 0.5 equiv) and the mixture was heated with a Dean-Stark trap for 24h. After cooling, the resulting mixture was filtered, toluene was evaporated and CH_2Cl_2 (150 mL) was added. The organic phase was washed with HCl 1M (2×150 mL) then with a saturated solution of NaCl (150 mL), dried over $MgSO_4$ and evaporated under vacuum Purification by flash chromatography (80/20 cyclohexane / ethyl acetate) gave the minor isomer (*R*)-**13** (4.72 g, 16.5 mmol, 31%) and the major isomer (*S*)-**13** (6.02 g, 21.1 mmol, 39%).

Spectroscopic data of (*R*)-**13** and (*S*)-**13** are in accordance with the literature reported data[8c]

α-Trifluoromethylproline (*R*)-**14** and (*S*)-**14**

The pure (*R*)-**13** diastereoisomer (2.55 g, 8.94 mmol) in a mixture of absolute ethanol / TFA (30 mL / 1 mL) was hydrogenated over 20% $Pd(OH)_2/C$ (500 mg) at room temperature for 48 h under 5 bars pressure of hydrogen. The reaction mixture was filtered and evaporated under reduced pressure. The residue was taken up with HCl (1M, 30 mL), concentrated under reduced pressure and loaded onto DOWEX 50W8-400 column to afford the pure (*R*)-α-Tfm-proline (*R*)-**14** (1.20 g, 74%) as a white solid.

The pure (*S*)-**13** diastereoisomer (4.15 g, 14.65 mmol) in absolute ethanol (150 mL) was hydrogenated over 20% $Pd(OH)_2/C$ (850 mg) at room temperature for 48 h under 5 bars pressure of hydrogen. The reaction mixture was filtered, evaporated under reduced pressure and washed with ether to afford (*S*)-α-Tfm-proline (*S*)-**14** (2.09 g, 78%) as a white solid.

Spectroscopic data of **14** are in accordance with the literature reported data.[8c] (*R*)-**14**: $[\alpha]^{19.9}_D$: +54° (c 1, H_2O); (*S*)-**14**: $[\alpha]^{19.9}_D$: -59° (c 1, H_2O).

2-carboxamide-2-(trifluoromethyl)piperidine- (*R*)-**15** and (*S*)-**15**

In a screw-capped vial, compound (*R*)-**12** (0.598 g, 2.0 mmol, 1 equiv) or (*S*)-**12** (0.579 g, 1.9 mmol, 1 equiv) was dissolved in H_2SO_4 (95%) (2 mL) and refluxed until the disappearance of the starting material, monitored by ^{19}F NMR. The crude mixture was neutralized with K_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and organics extracts were dried over

$MgSO_4$. Purification by flash chromatography (97/3 to 30/70 cyclohexane / ethyl acetate) gave compound (*R*)-**15** in 55% yield (0,200 g, 1.05 mmol) and (*S*)-**15** in 32% yield (0,116 g, 0.61mmol) as a white solid.

(*R*)-15: White solid; m.p. 133-135°C; *Rf* 0.57 (30/70 ethyl acetate / cyclohexane); $[\alpha]^{19.9}_D$= + 2.29 (c 1, MeOH); IR (neat, cm^{-1}): 3341, 3291, 3169, 1668; 1622, 1128; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (tt, *J* = 11.7 Hz, 4 Hz, 1H), 1.45 (tt, *J* = 12.7 Hz, 3 Hz, 1H), 1.51-1.59 (m, 2H), 1.75-1.82 (m, 2H), 2.41 (dt, *J* = 12.7 Hz, 3.5 Hz, 1H), 2.71 (td, *J* = 12.6 Hz, 3 Hz, 1H), 3.03 (d, *J* = 13.5 Hz, 1H), 6.03 (s, 1H), 7.17 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 20.5, 25.5, 26.4, 42.6, 65.1 (q, *J* = 25.2 Hz), 124.9 (q, *J* = 284.8 Hz), 169.5; NMR ^{19}F (376.2 MHz, $CDCl_3$): δ -81.0; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_7H_{12}F_3N_2O$ 197.0902, found 197.0901.

(*S*)-15: White solid; m.p. 133-135°C; *Rf* 0.57 (30/70 ethyl acetate / cyclohexane); $[\alpha]^{19.9}_D$= **-** 2.78 (c 1, MeOH); IR (neat, cm^{-1}): 3341, 3291, 3168, 1668, 1622, 1129; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (tt, *J* = 11.7 Hz, 4 Hz, 1H), 1.46 (tt, *J* = 12.3 Hz, 3.2 Hz, 1H), 1.51-1.60 (m, 2H), 1.76-1.83 (m, 2H), 2.41 (dt, *J* = 13.1 Hz, 3.2 Hz, 1H), 2.71 (td, *J* = 12.5 Hz, 2.2 Hz, 1H), 3.03 (d, *J* = 13.6 Hz, 1H), 5.95 (s, 1H), 7.17 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 20.5, 25.5, 26.4, 42.7, 65.1 (q, *J* = 25.3 Hz), 124.9 (q, *J* = 284.8 Hz), 169.5; NMR ^{19}F (376.2 MHz, $CDCl_3$): δ -81.0; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_7H_{12}F_3N_2O$ 197.0902 , found 197.0904.

HPLC conditions: Chiral column CHIRALPAK IA-3 (250 x 4.6 mm) hexane/isopropanol = 9/1, flow rate = 1mL.min^{-1}, wavelength = 206 nm; tr **(*S*)-15** = 5.749 min; tr **(*R*)-15** = 6.067 min.

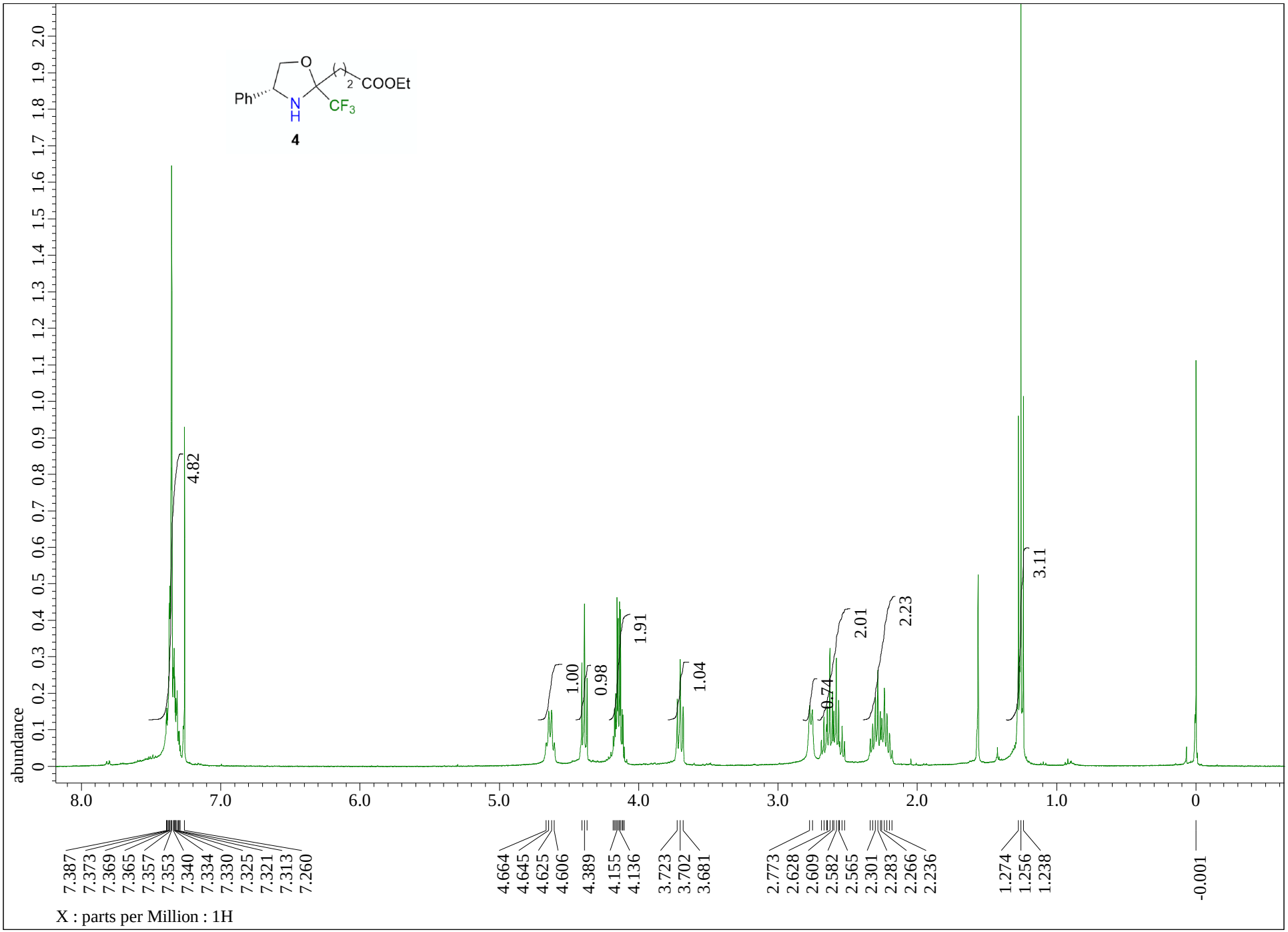
2-carboxy-2-trifluoromethylpiperidine hydrobromide (*R*)-**16** and (*S*)-**16**

In a screw-capped vial, compound (*R*)-**15** or (*S*)-**15** (0.100 g, 0.51 mmol, 1 equiv) was dissolved in HBr (48%) (2mL) and refluxed until the disappearance of the starting material, monitored by ^{19}F NMR. The solution was then concentrated under reduced pressure to obtain the compound (*R*)-**16** or (*S*)-**16** in a quantitative yield as a brown solid. (0.140 g, 0.51mmol) (*R*)-**16**: brown solid; m.p.253-255°C; $[\alpha]^{19.9}_D$= +1.03 (c 0.5, MeOH); IR (neat, cm^{-1}): 3099, 2939, 2798, 1754; ^{1}H NMR (400 MHz, D_2O): δ 1.31-1.44 (m, 1H), 1.53-1.65 (m, 1H), 1.78-1.87 (m, 3H), 2.43 (d, 1H, J = 14.4 Hz), 3.23 (td, 1H, *J* = 13.2 Hz, 3.4 Hz), 3.38 (d, 1H, *J* = 13.5 Hz); ^{13}C NMR (100.5 MHz, D_2O): δ 18.3, 20.7, 24.8, 43.4, 66.8(q, *J* = 27.6 Hz), 122.8 (q, *J* = 285 Hz), 165.4; ^{19}F NMR (376.2 MHz, D_2O): δ -75.9; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_7H_{11}F_3NO_2$ 198.0742, found 198.0745.

(*S*)-**16**: brown solid; m.p.253-255°C; $[\alpha]^{19.9}_{D}$= -1.01 (c 0.5, MeOH); IR (neat, cm^{-1}): 3099, 2939, 2798, 1754; ^{1}H NMR (400 MHz, D_2O): ^{1}H NMR (400 MHz, H_2O): δ 1.30-1.42 (m, 1H), 1.52-1.65 (m, 1H), 1.77-1.87 (m, 3H), 2.42 (d, 1H, *J* = 14.2 Hz), 3.22 (td, 1H, *J* = 13.2 Hz, 3.2 Hz), 3.38 (d, 1H, *J* = 12.1 Hz); ^{13}C NMR (100.5 MHz, D_2O): δ 18.3, 20.7, 24.8, 43.4, 66.8 (q, *J* = 27.7 Hz), 122.8 (q, *J* = 284 Hz), 165.4; ^{19}F NMR (376.2 MHz, D_2O): δ -75.9; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_7H_{11}F_3NO_2$ 198.0742, found 198.0740.

H-Pip-Ala-OBn **17**

To a solution of **(*R*)-16** (0.05 g, 0.18 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added Et_3N (0.08 mL, 0.58 mmol, 3.2 equiv). The mixture was stirred at room temperature during 20 minutes and then poured dropwise in a solution of H-Ala-OBn.HCl (48.5 mg, 0.225 mmol, 1.25 equiv) and BOP-Cl (60 mg, 0.234 mmol, 1.3 equiv) in DCM (5 mL). This mixture was stirred at room temperature overnight. The organic phase was washed with NH_4Cl (2 x 10 mL), $NaHCO_3$ (2 x 10 mL), NaCl (1 x 10 mL), dried over $MgSO_4$ and concentrated under vacuo. The crude product was purified by automatic flash chromatography (ethyl acetate in cyclohexane, 3% to 100% in 10', 100% to 100% in 10') to obtain the pure dipeptide (30 mg, 0.08 mmol) with a yield of 47% as a colorless oil. *Rf* 0.67 (100% ethyl acetate); $[\alpha]^{19.9}_{D}$= - 9.95 (c 1, $CHCl_3$); IR (neat, cm^{-1}): 3362; 2943; 2361; 2342; 1740; 1684; 1512; 1453; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26-1.44 (m, 2H), 1.46 (d, *J* = 7.1 Hz, 3H), 1.49-1.64 (m, 2H), 1.73-1.80 (m, 1H), 2.38 (d, *J* = 13.5 Hz, 1H), 2.61 (td, *J* = 12.4 Hz, 3.1 Hz, 1H), 3.02 (d, *J* = 13.8 Hz, 1H), 4.66 (p, J = 7.34 Hz, 1H), 5.14 (d, J = 12.3 Hz, 1H) , 5.21 (d, J = 12.3 Hz, 1H), 7.32-7.38 (m, 5H), 7.77 (d, J = 7.2 Hz, 1H, NH_2); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 18.3, 20.4, 25.3, 26.5, 42.5, 48.6, 64.8 (q, *J* = 25.4 Hz), 67.3, 124.9 (q, *J* = 285.3 Hz), 128.3, 128.6, 128.7, 135.4, 166.4, 172.2; NMR ^{19}F (376.2 MHz, $CDCl_3$): δ -80.7; HRMS (ESI-TOF): $[M+H]^+$ calcd for $C_{17}H_{22}F_3N_2O_3$ 359.1577, found 359.1575.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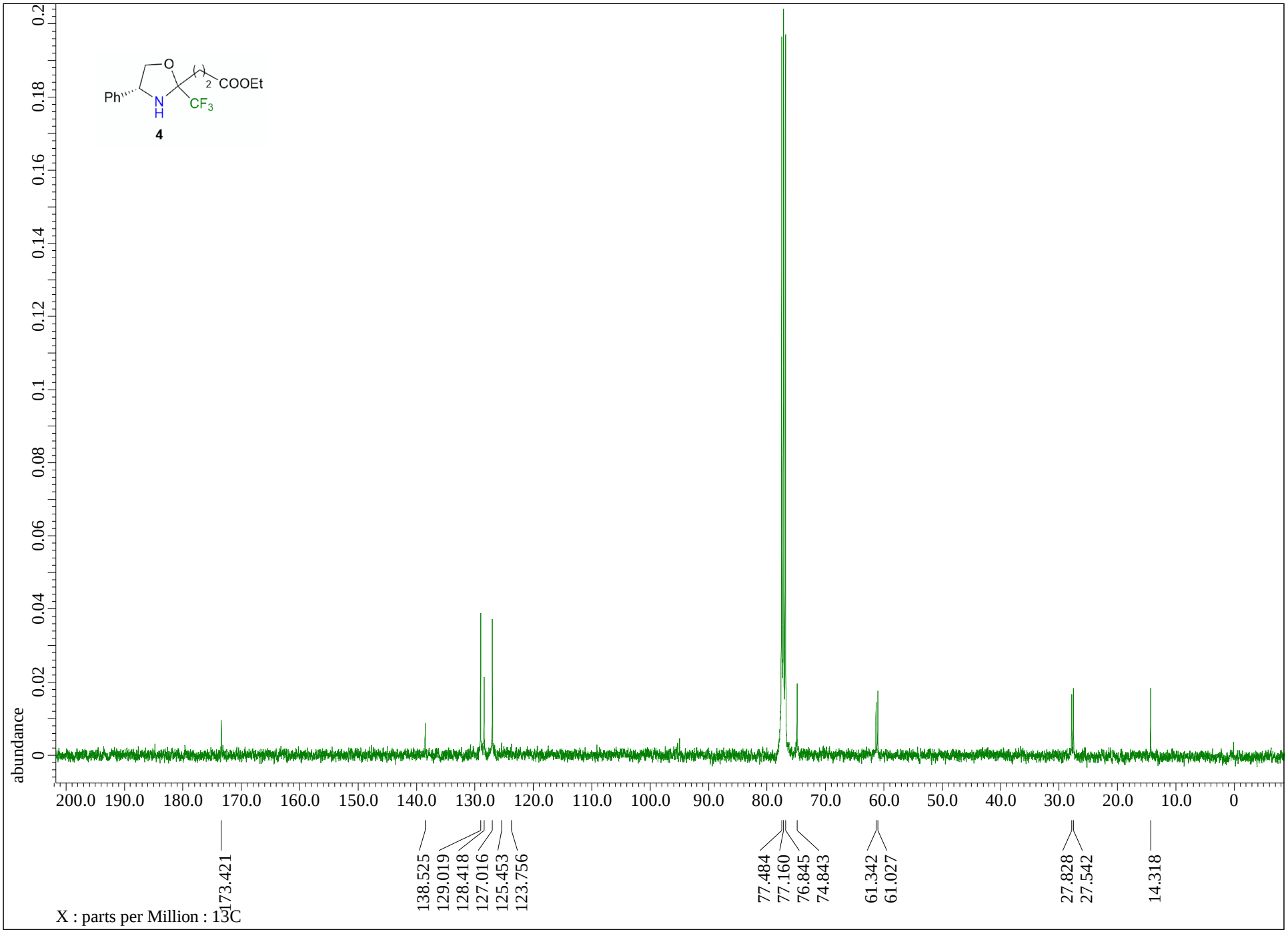
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0.18
0.2
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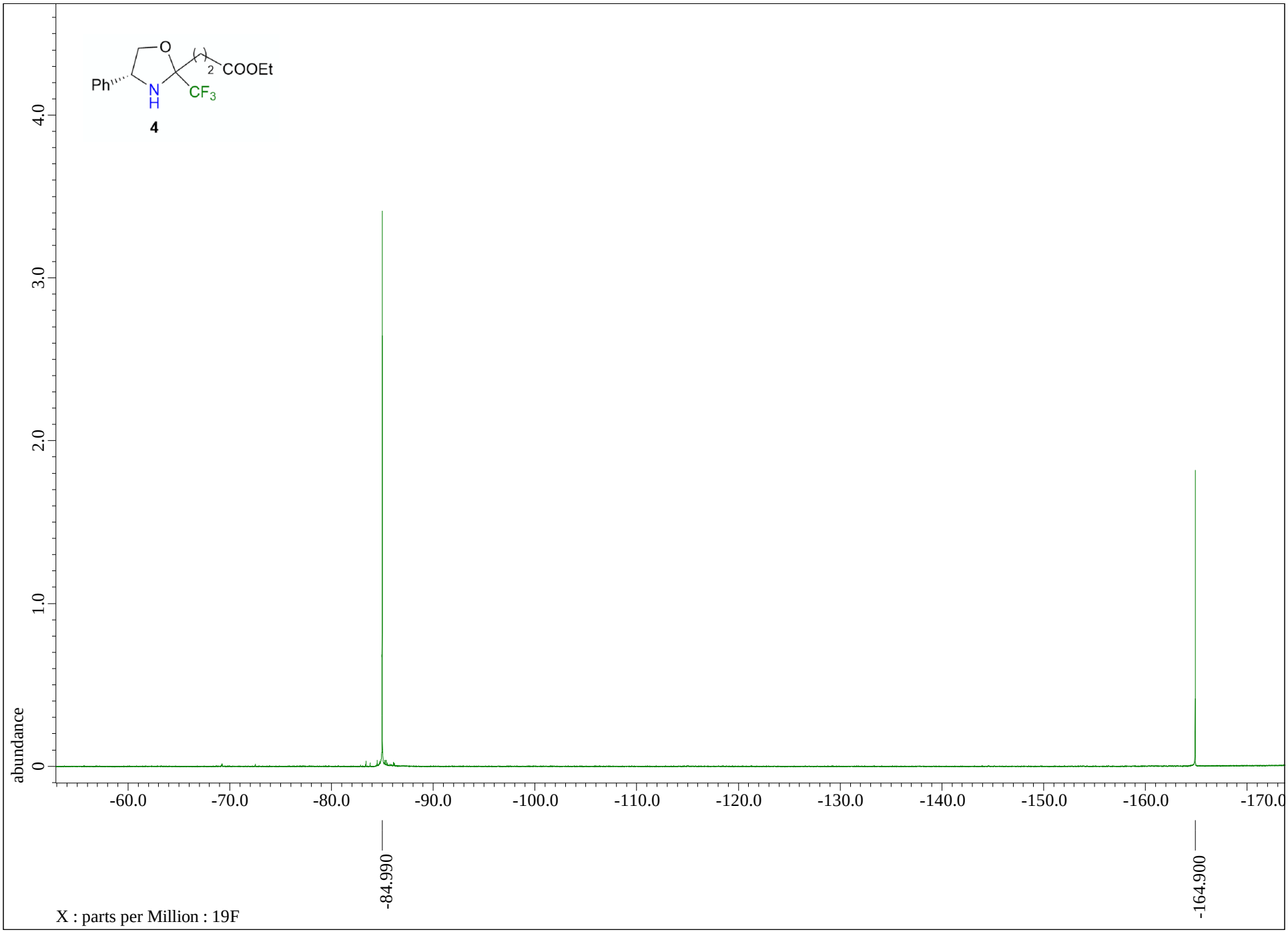
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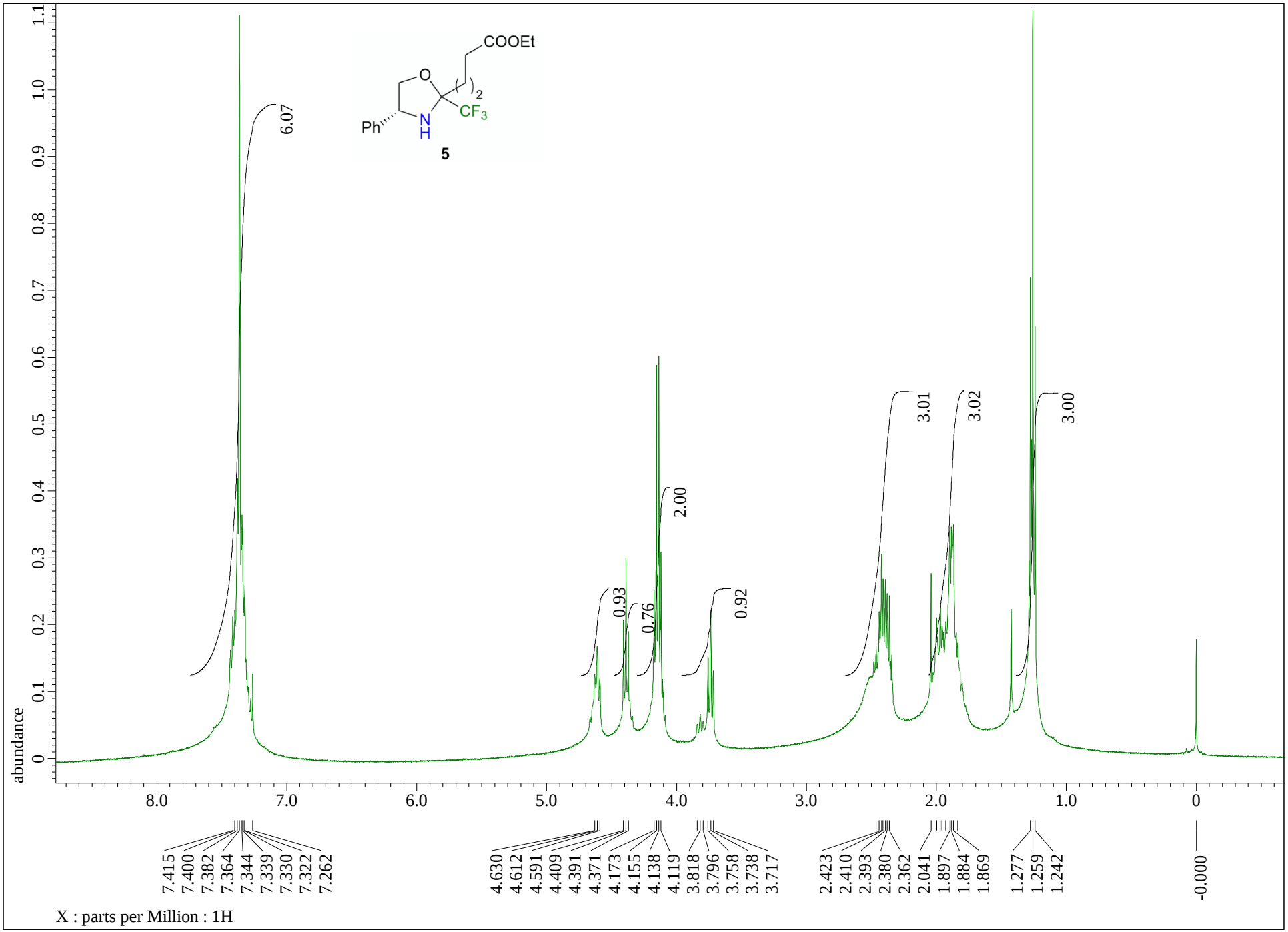
X : parts per Million : 19F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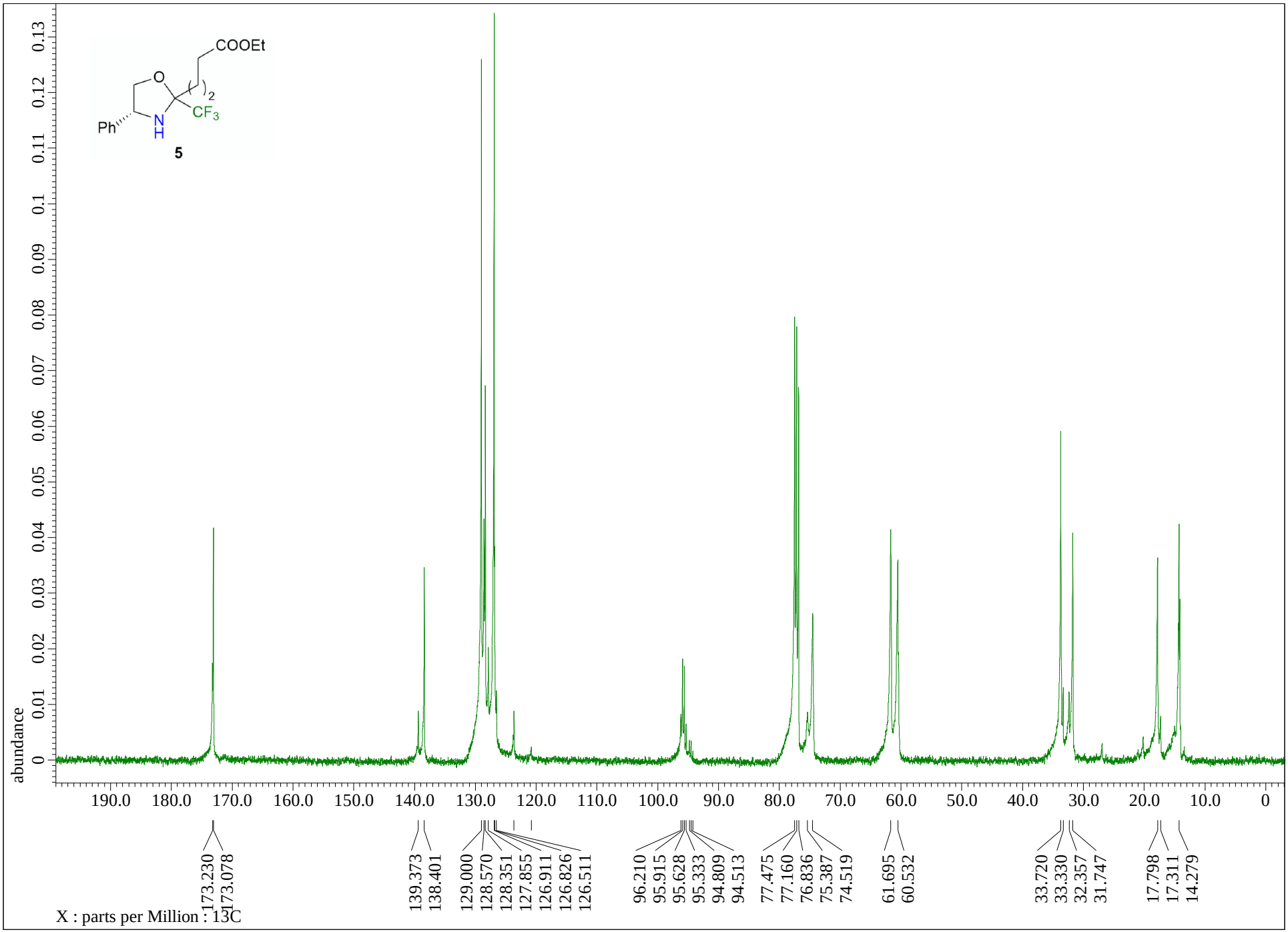
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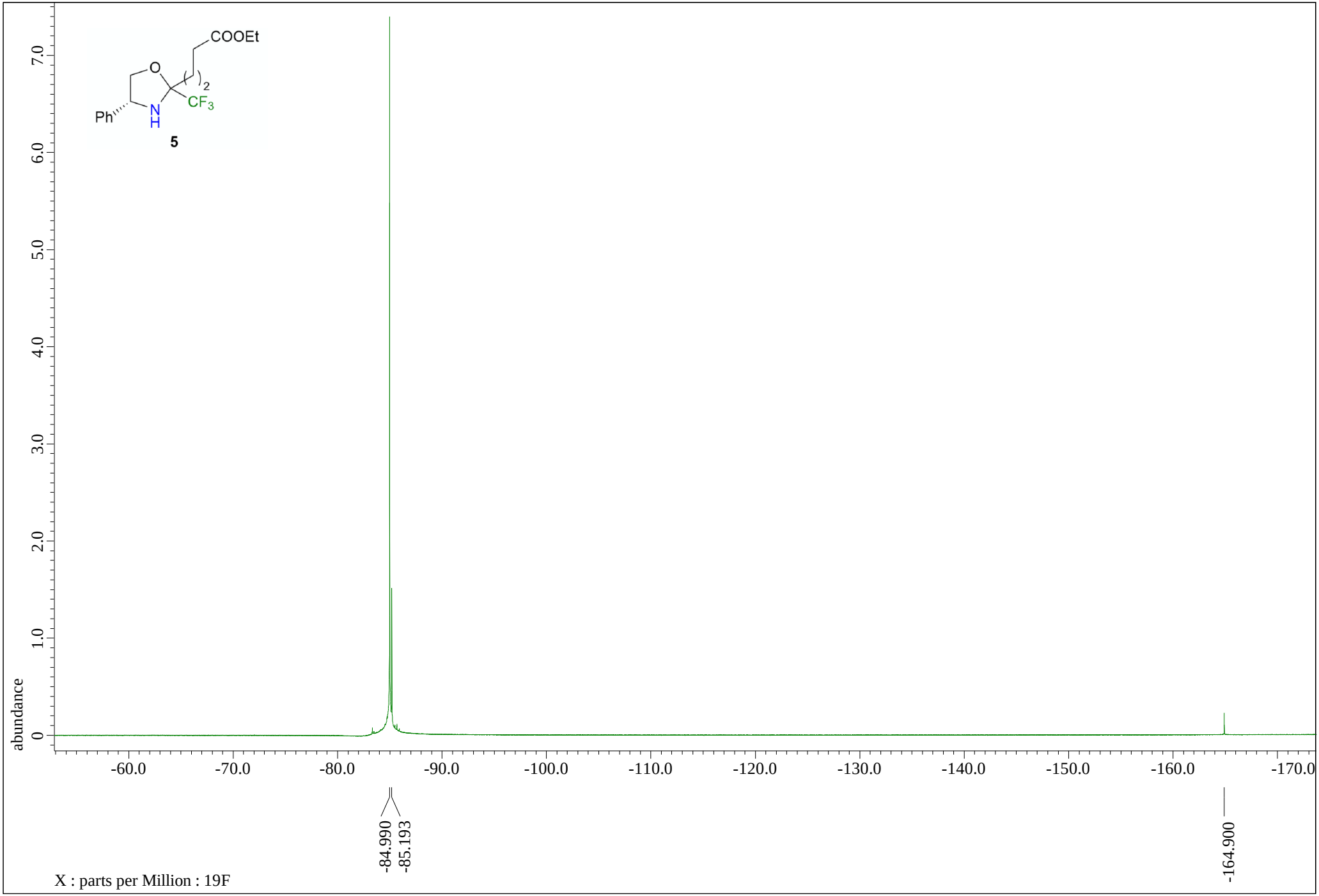
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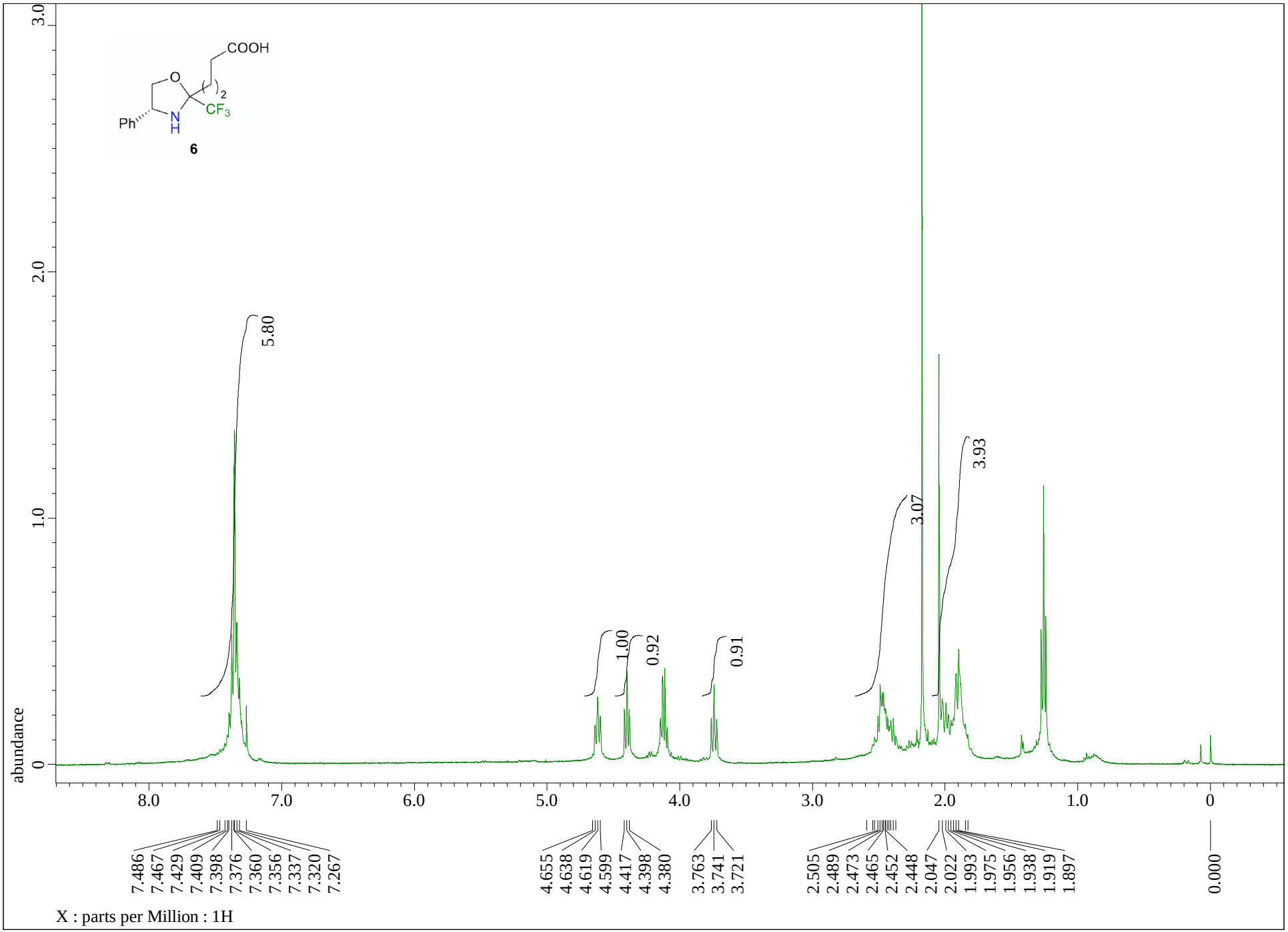
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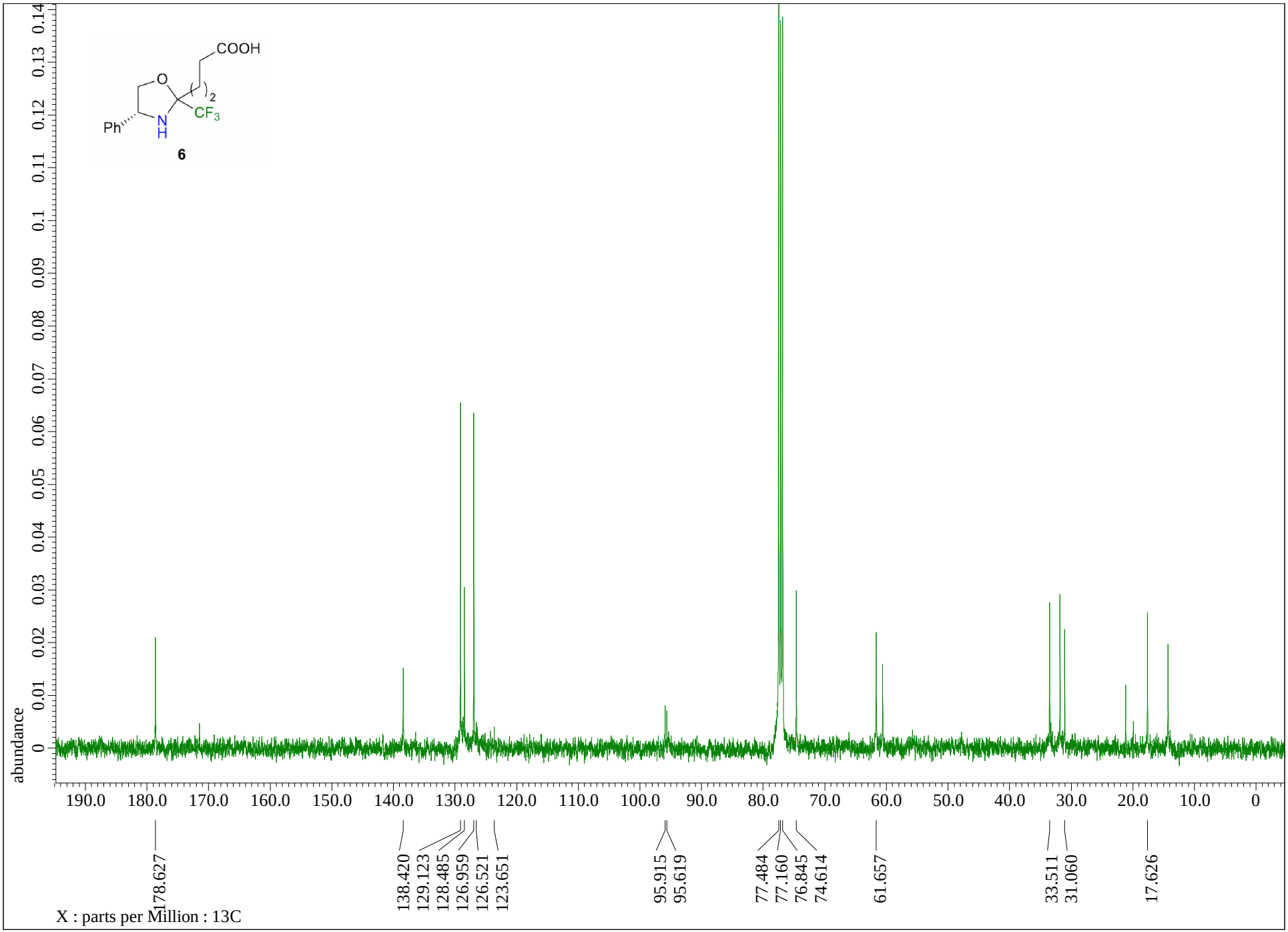
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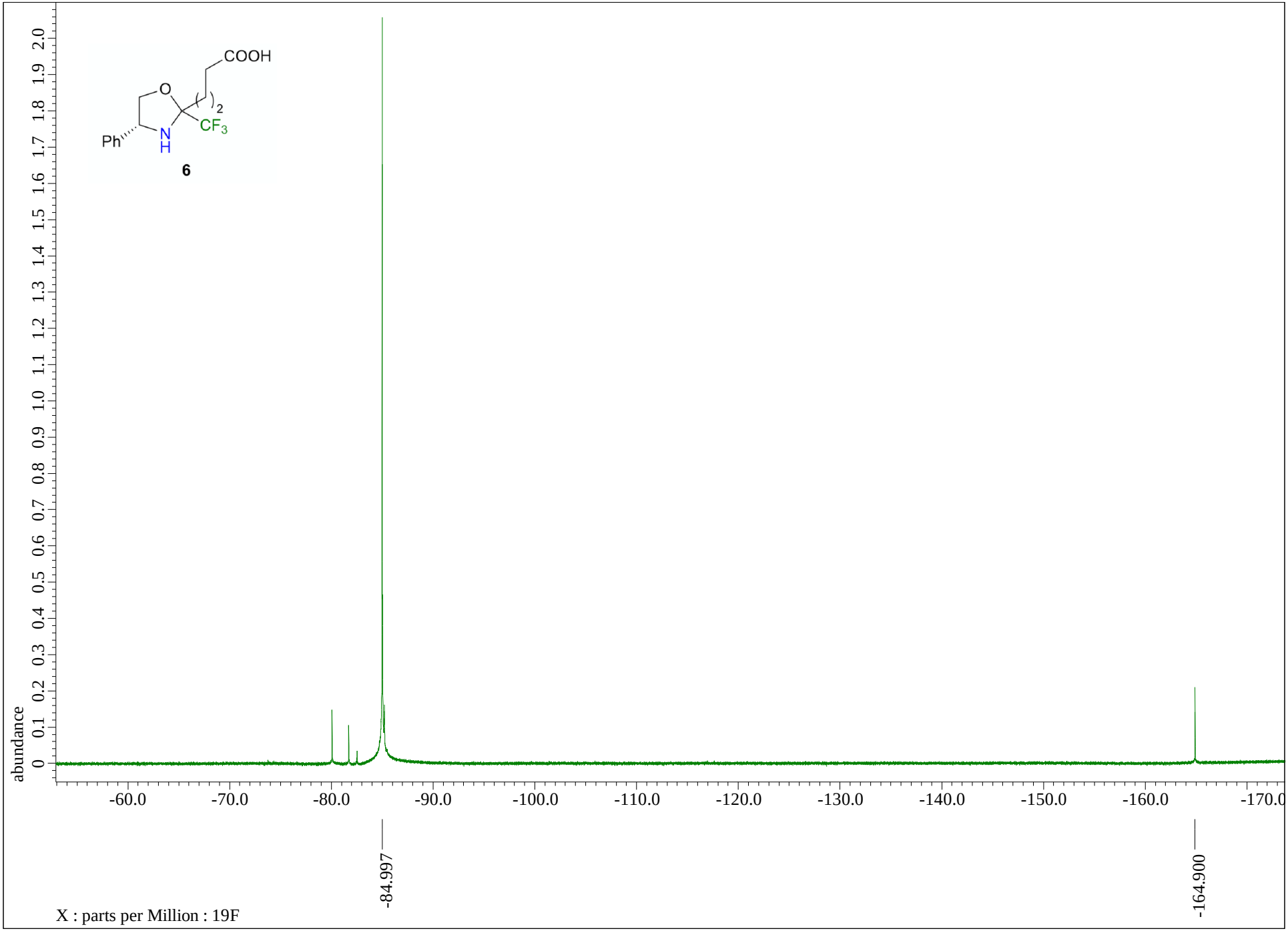
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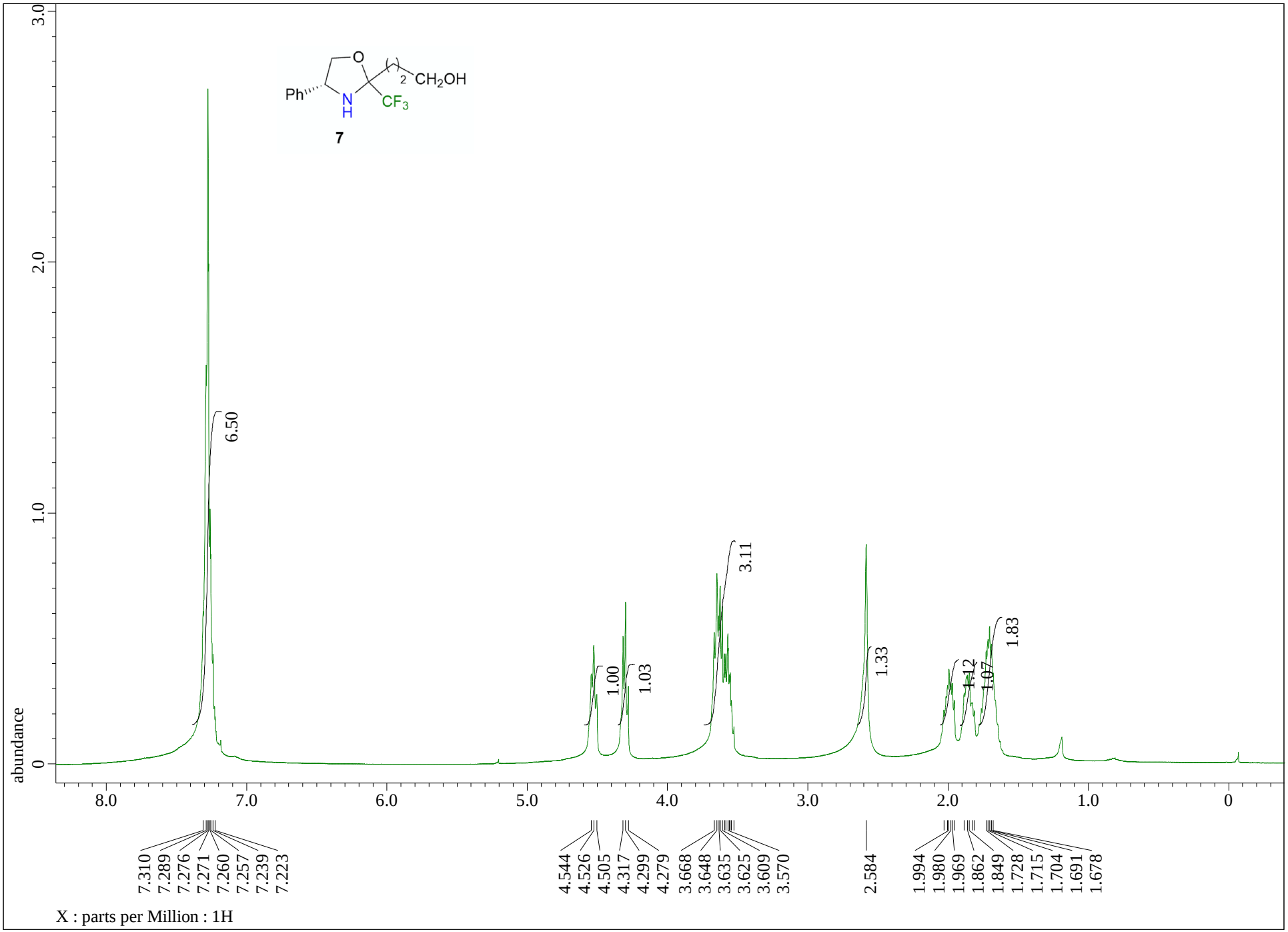
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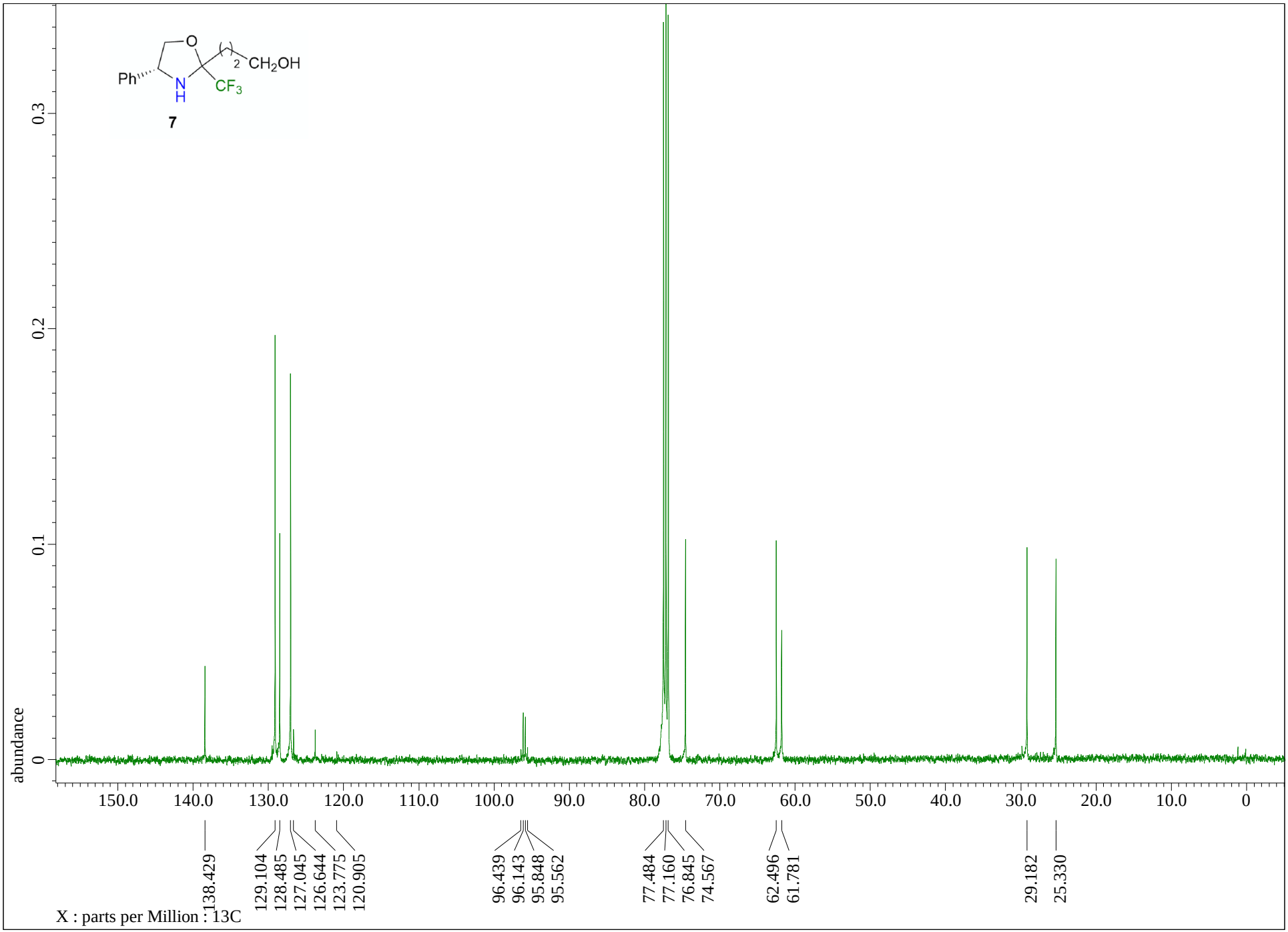
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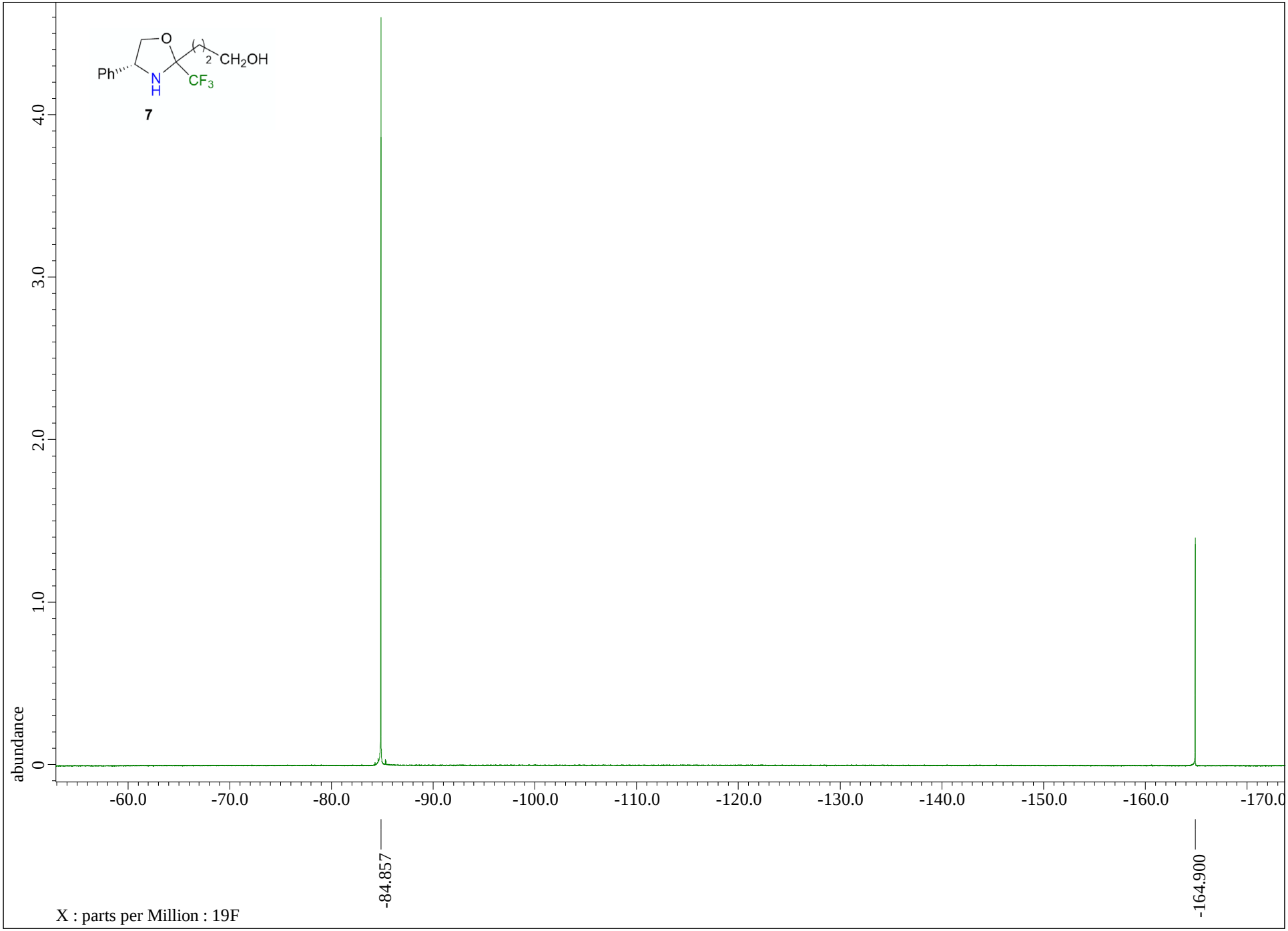
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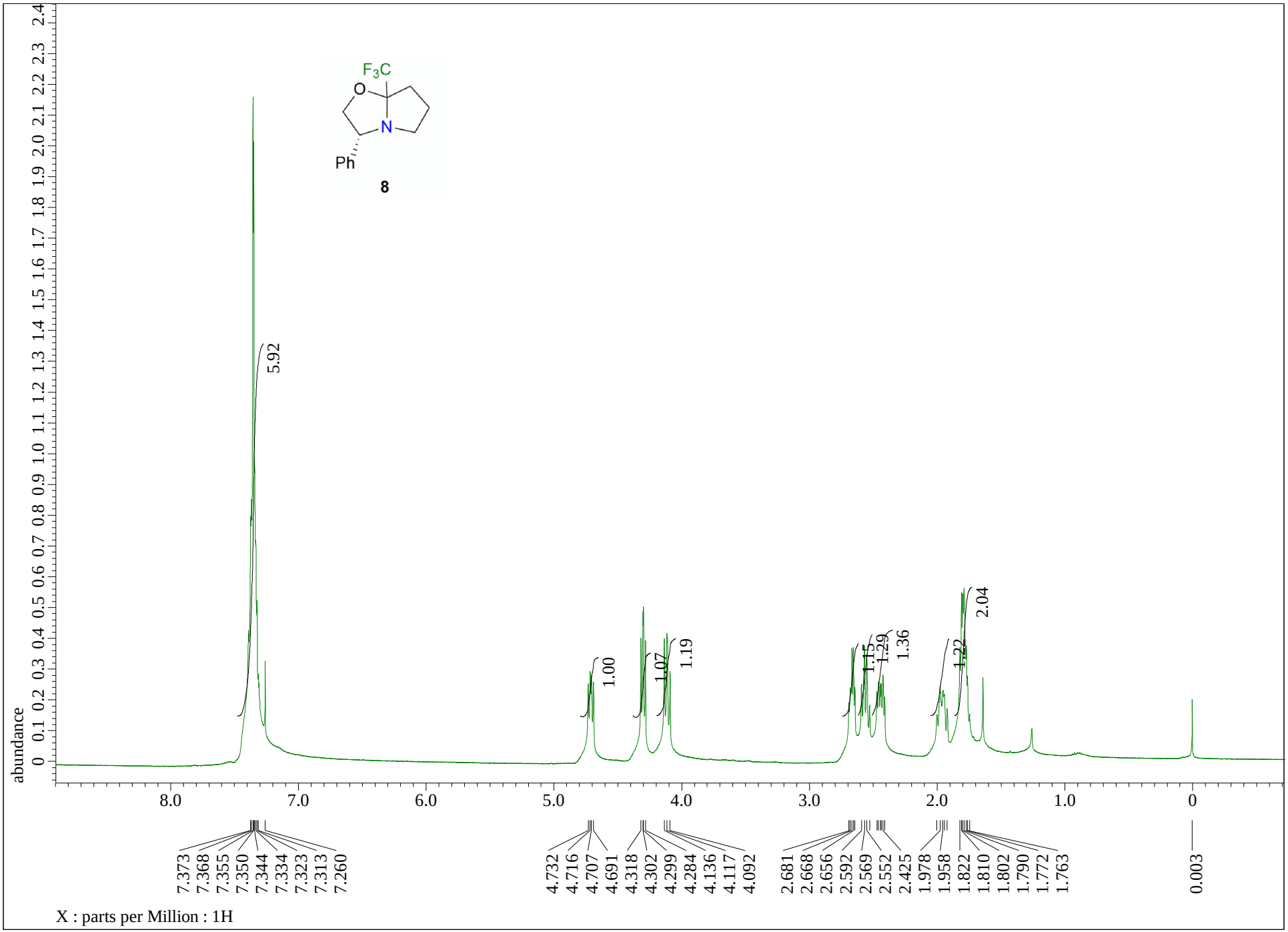
X : parts per Million : 19F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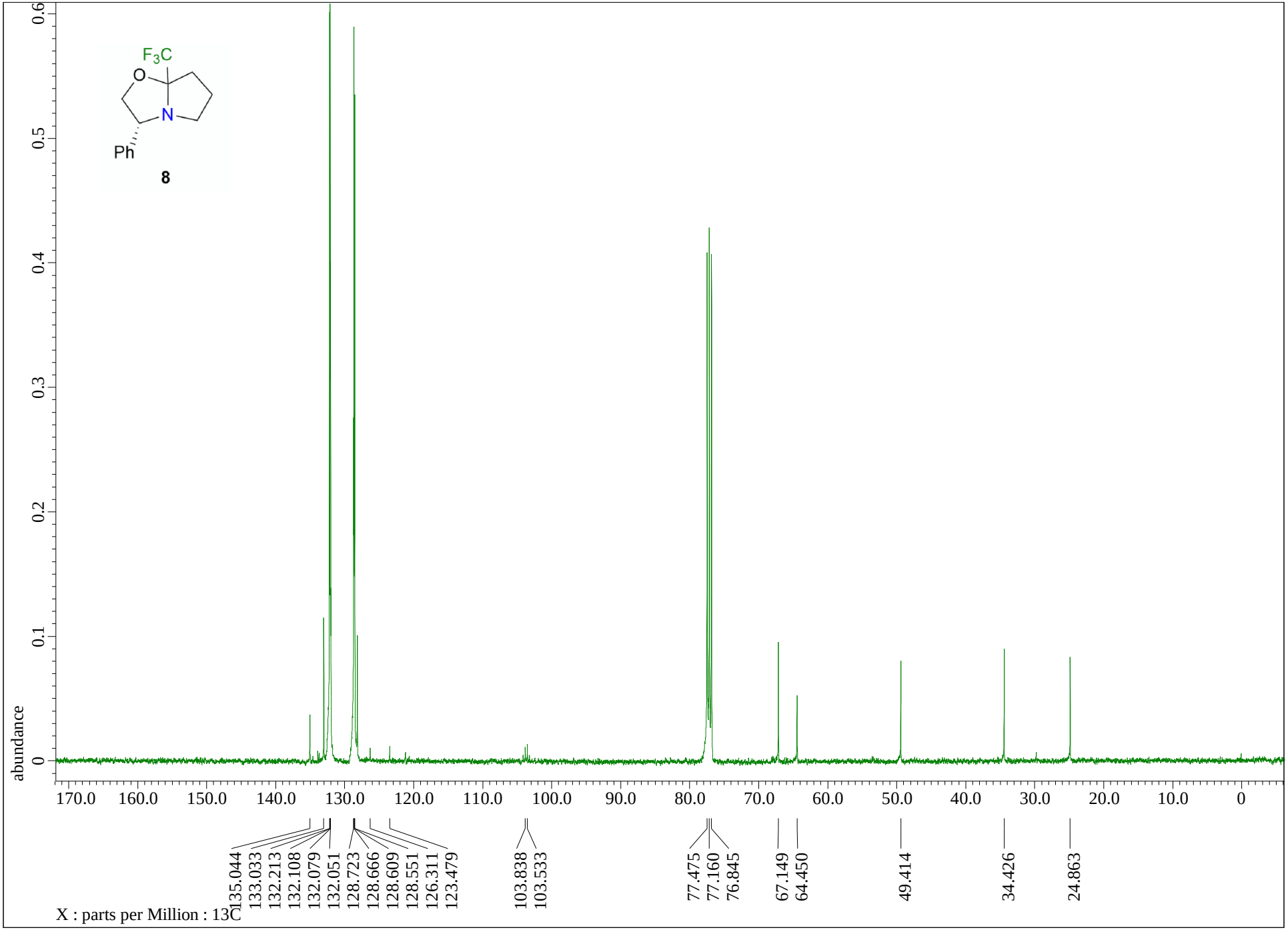
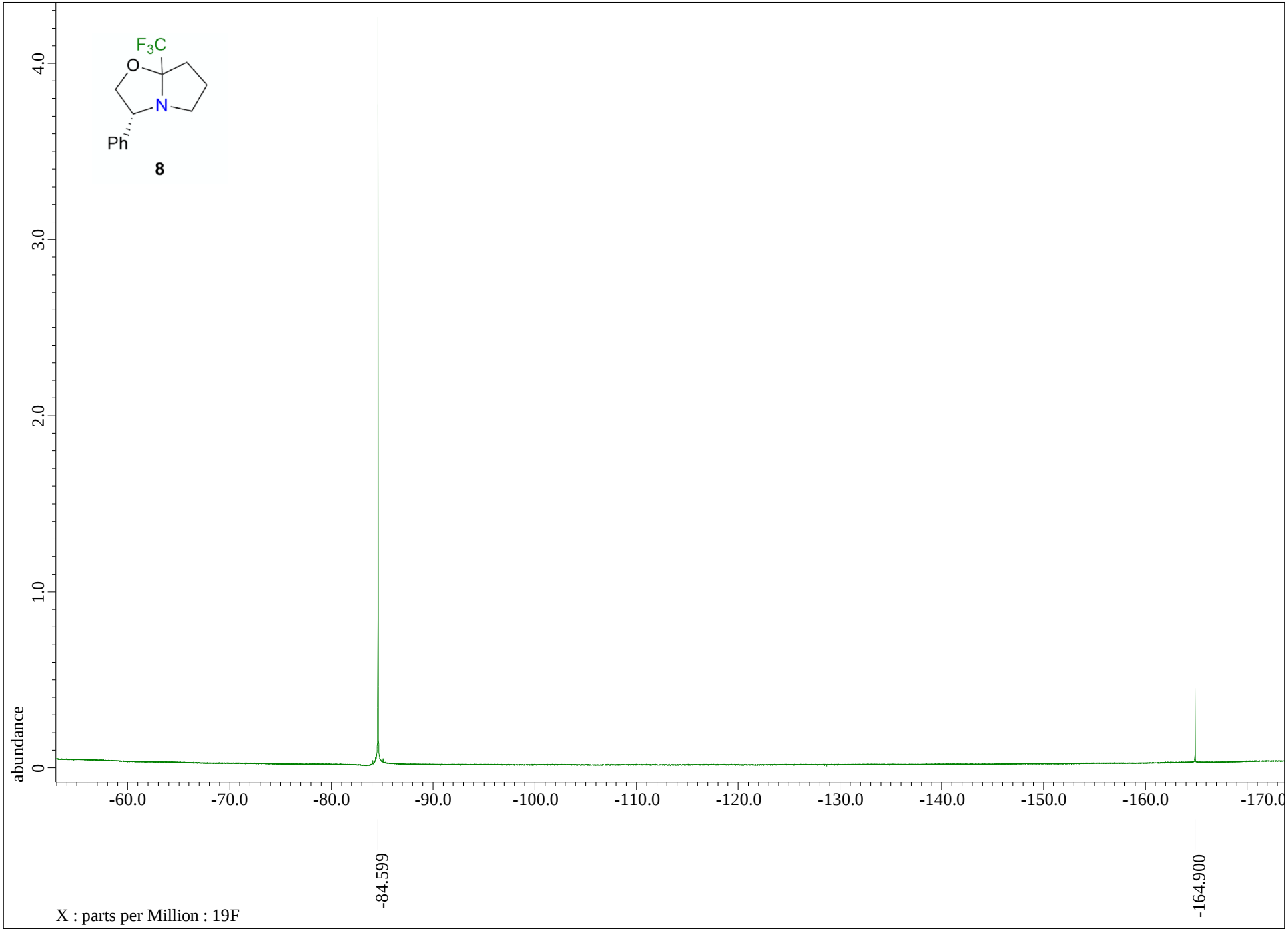
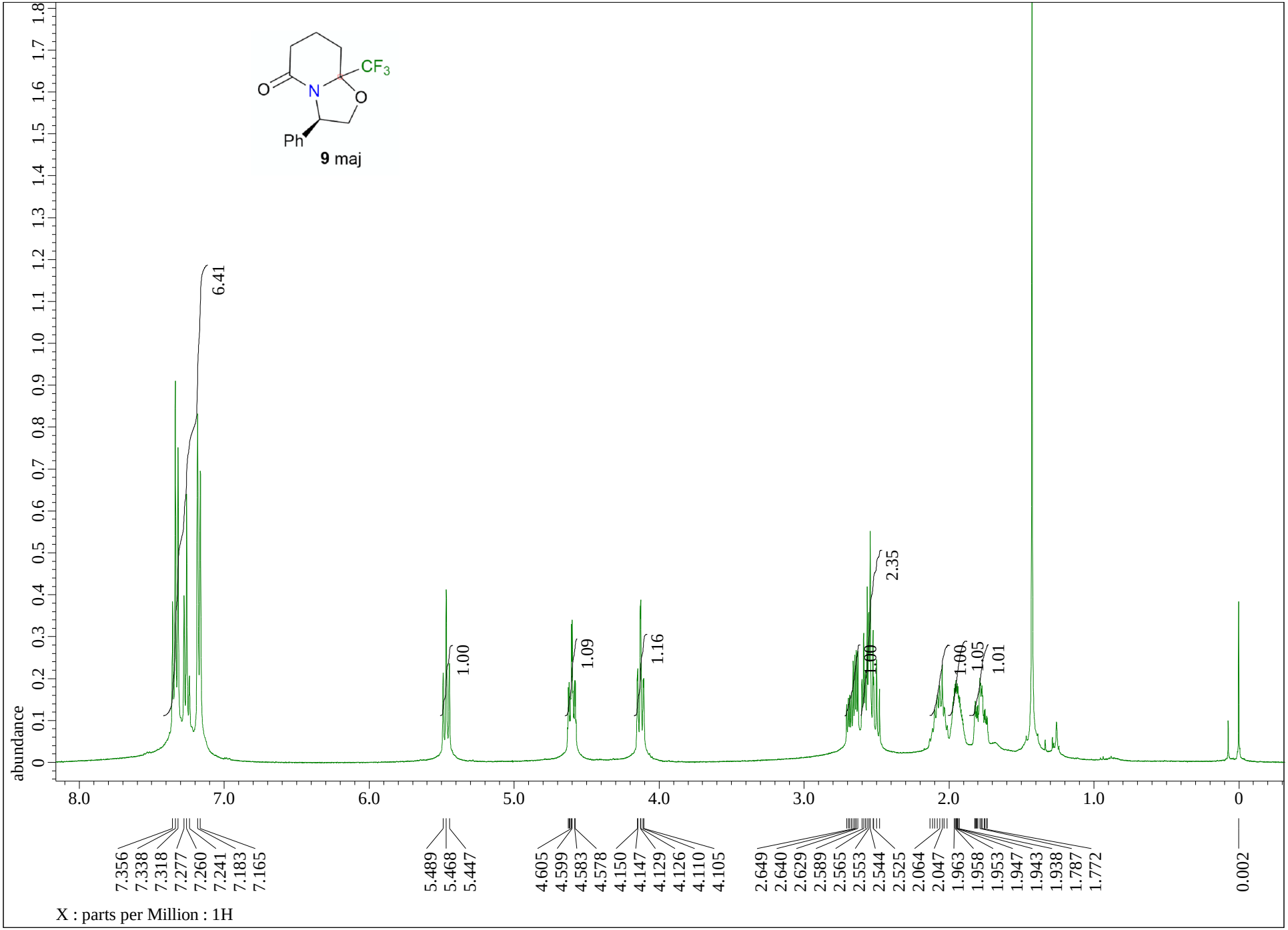
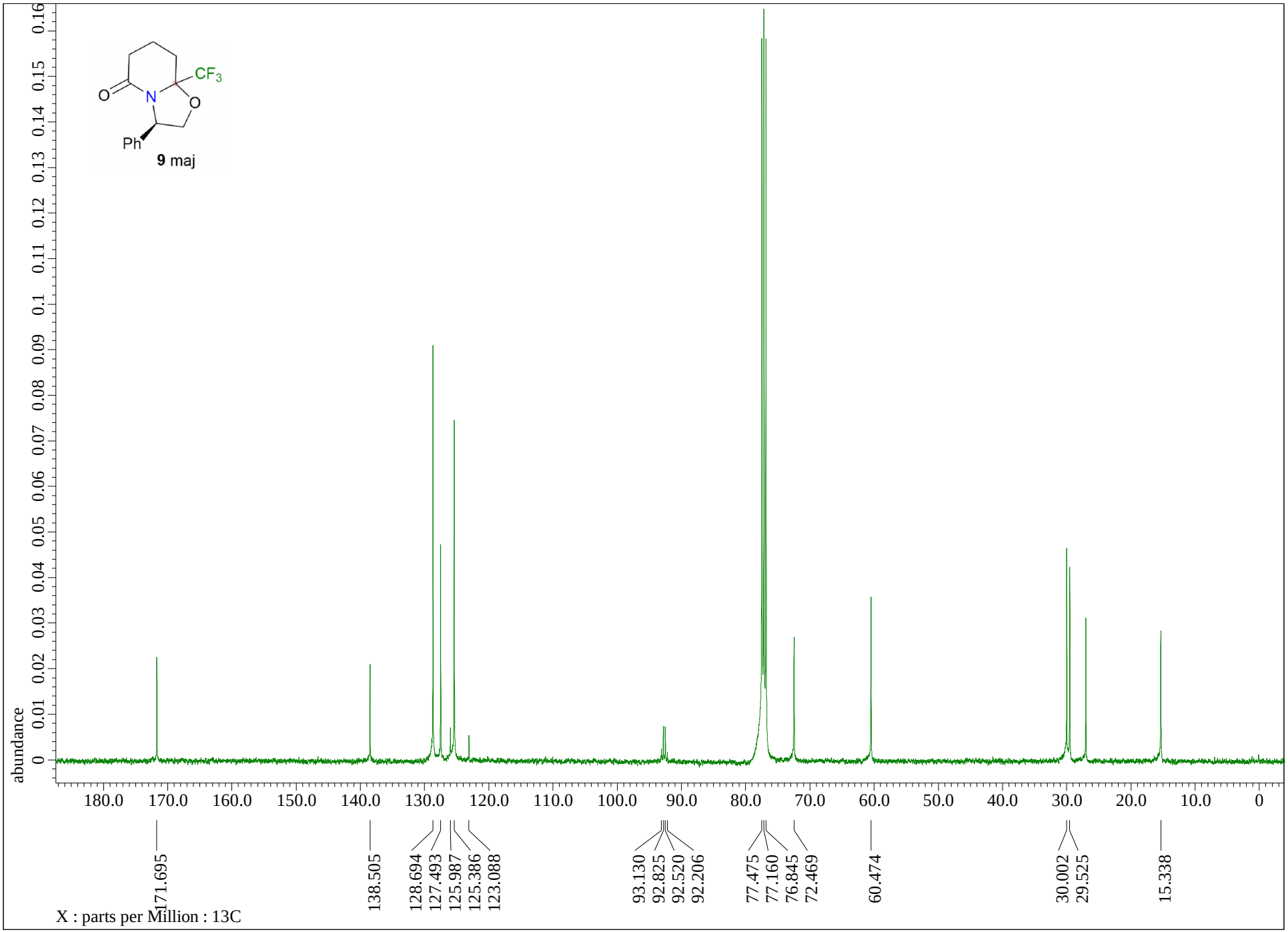
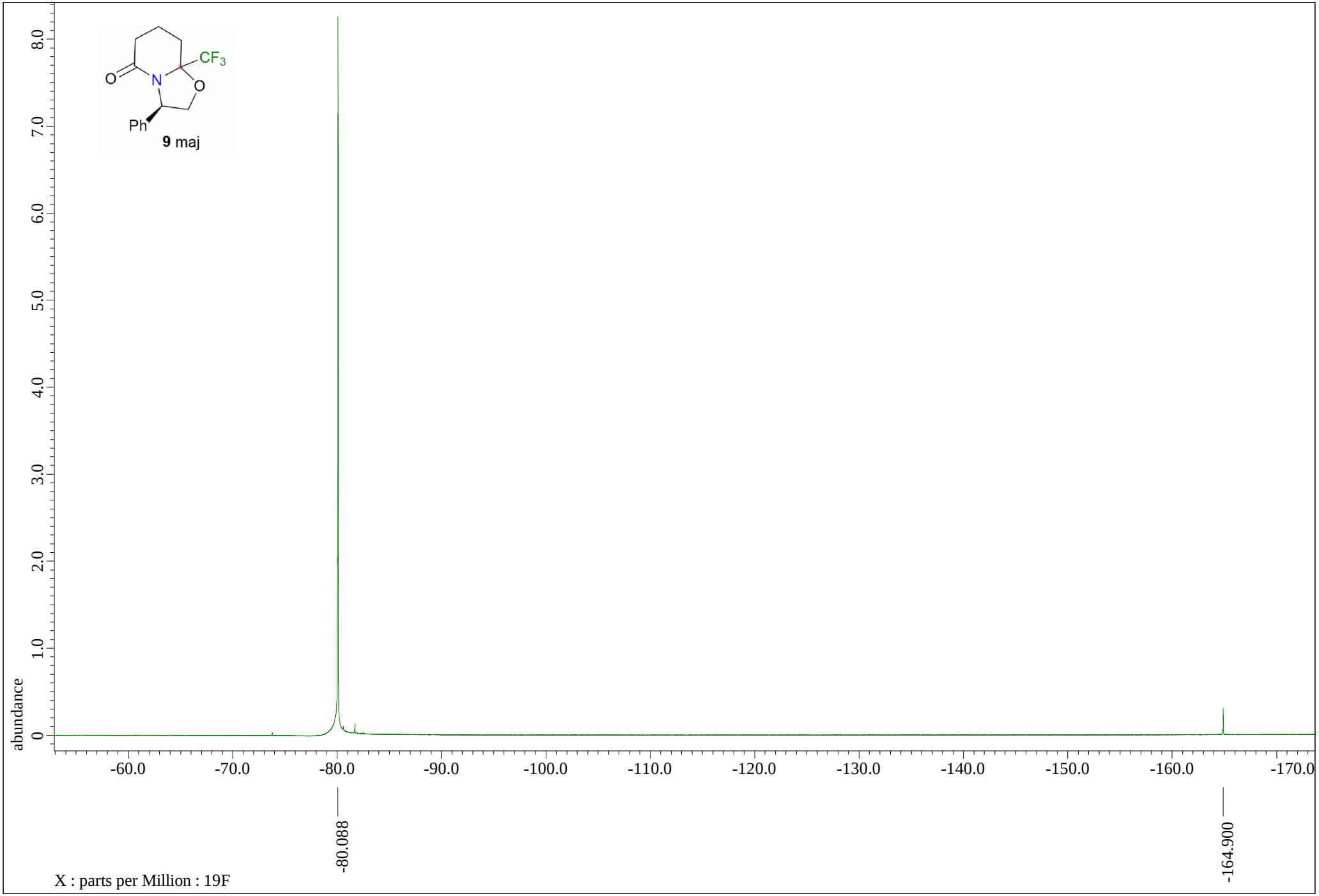
7.355
7.350
7.344
7.334
7.323
7.313
7.260
4.732
4.716
4.707
4.691
4.318
4.302
4.299
4.284
4.136
4.117
4.092
2.681
2.668
2.656
2.592
2.569
2.552
2.425
1.978
1.958
1.822
1.810
1.802
1.790
1.772
1.763
0.003

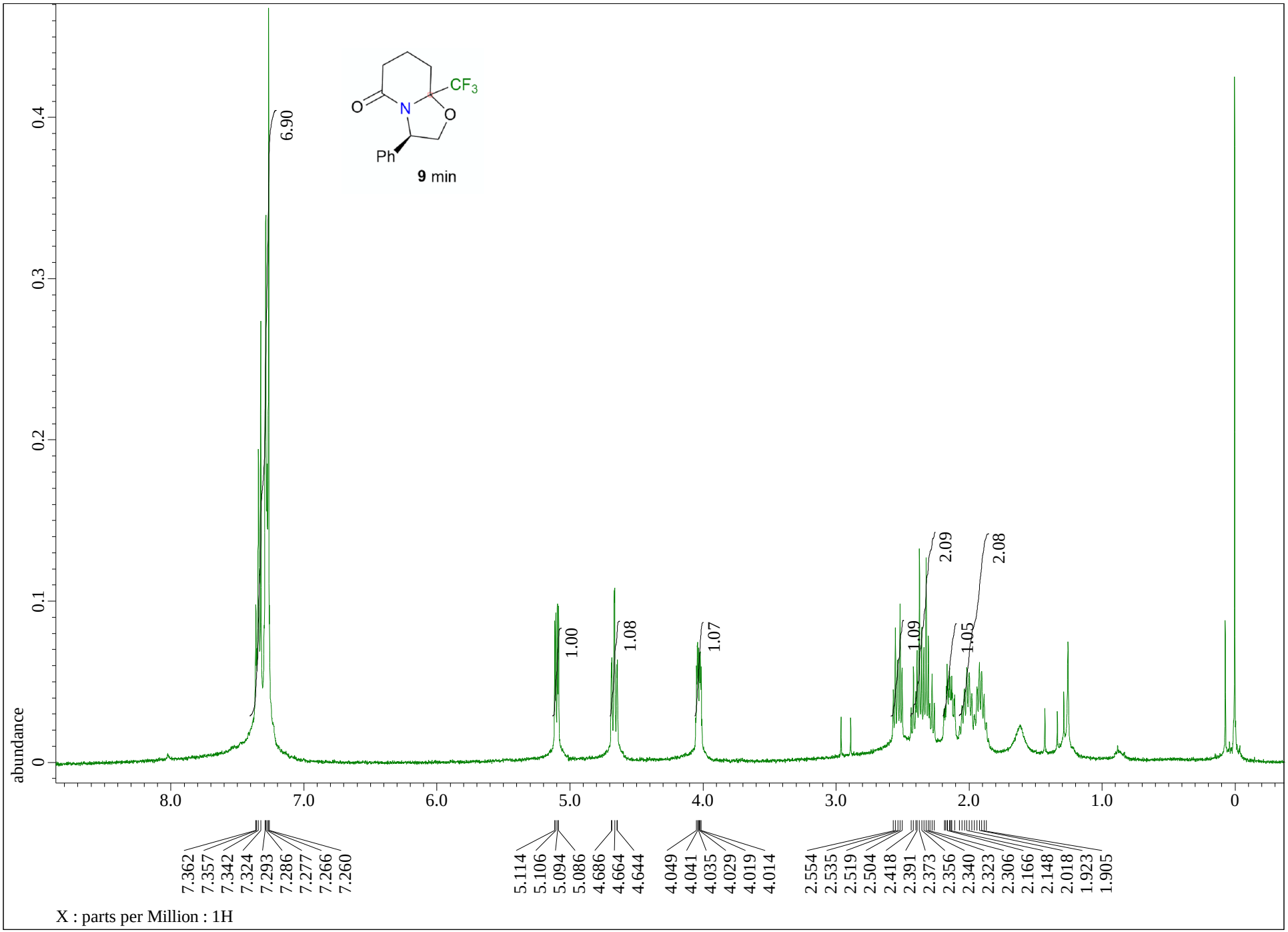

F3C
O
N
Ph
8
abundance
0.6
0.5
0.4
0.3
0.2
0.1
0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
135.044
133.033
132.213
132.108
132.079
132.051
128.723
128.666
128.609
128.551
126.311
123.479
103.838
103.533
77.475
77.160
76.845
67.149
64.450
49.414
34.426
24.863
X : parts per Million : 13C

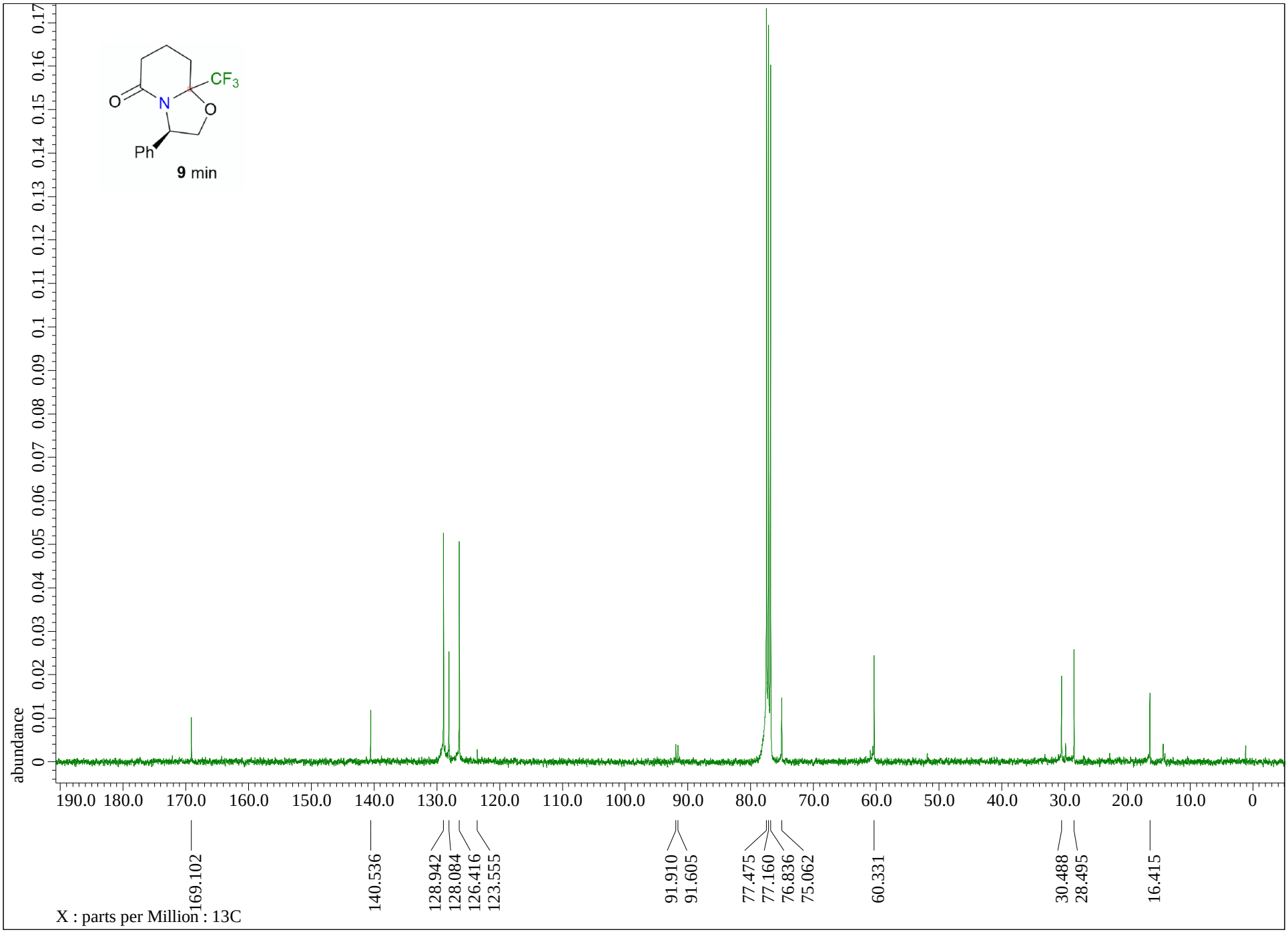

F3C
O
N
Ph
8
abundance
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-84.599
-164.900
X : parts per Million : 19F

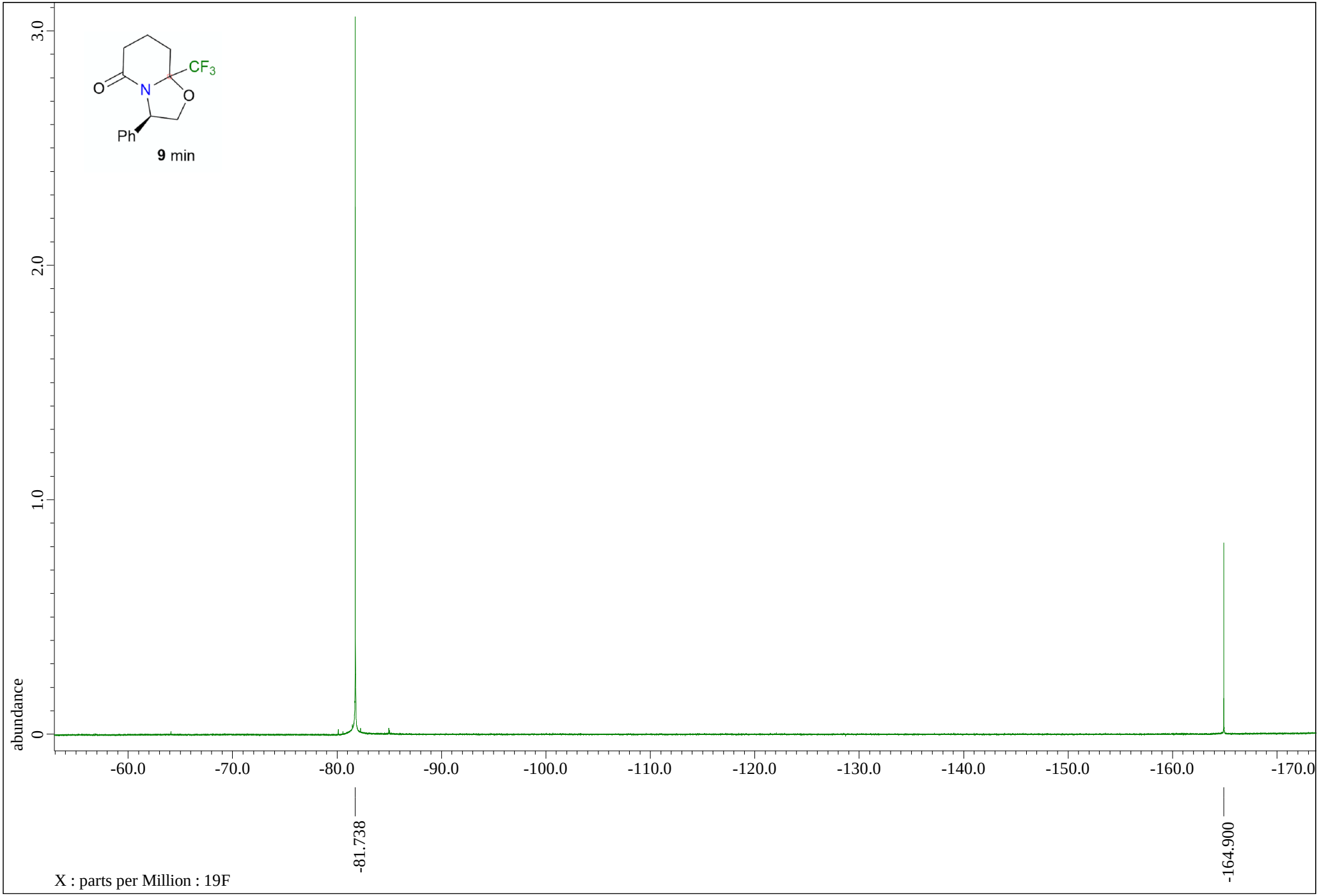

CF3
O
N
O
Ph
9 maj
abundance
6.41
1.00
1.09
1.16
2.35
1.00
1.00
1.05
1.01
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.356
7.338
7.318
7.277
7.260
7.241
7.183
7.165
5.489
5.468
5.447
4.605
4.599
4.583
4.578
4.150
4.147
4.129
4.126
4.110
4.105
2.649
2.640
2.629
2.589
2.565
2.553
2.544
2.525
2.064
2.047
1.963
1.958
1.953
1.947
1.943
1.938
1.787
1.772
0.002
X : parts per Million : 1H

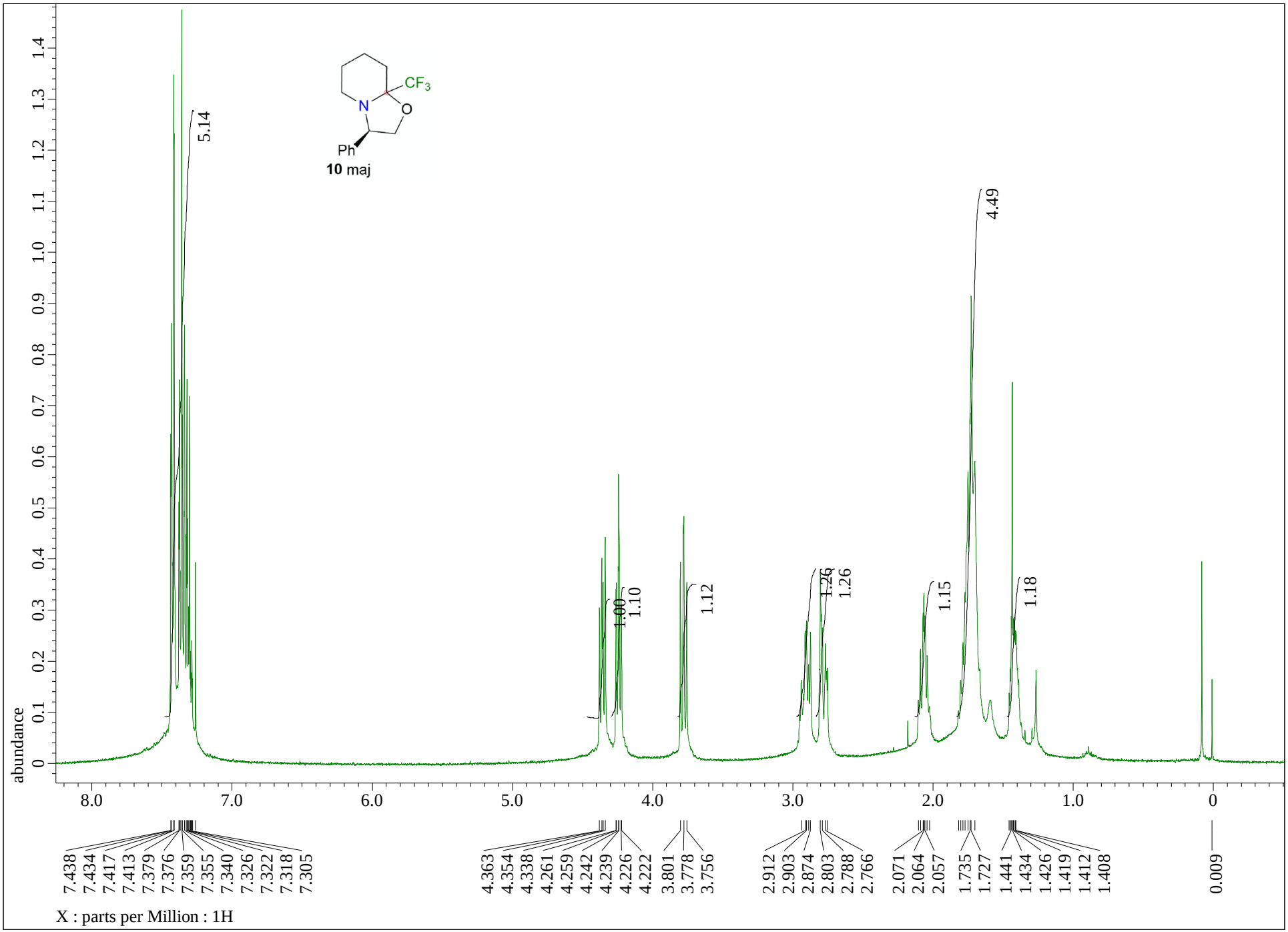

CF3
O
N
O
Ph
9 maj
abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16
180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
171.695
138.505
128.694
127.493
125.987
125.386
123.088
93.130
92.825
92.520
92.206
77.475
77.160
76.845
72.469
60.474
30.002
29.525
15.338
X : parts per Million : 13C

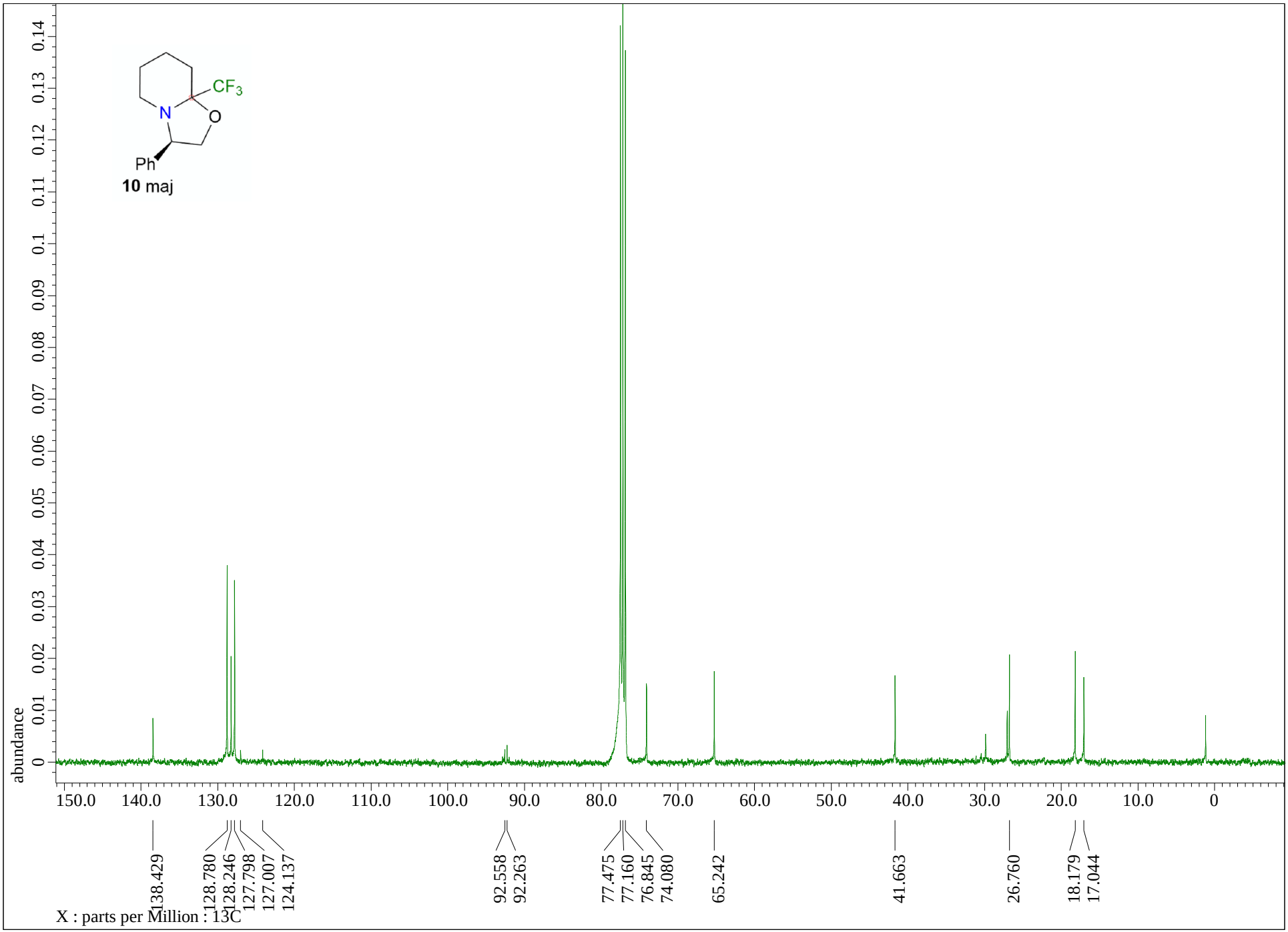

CF3
O
N
O
Ph
9 maj
abundance
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-80.088
-164.900
X : parts per Million : 19F

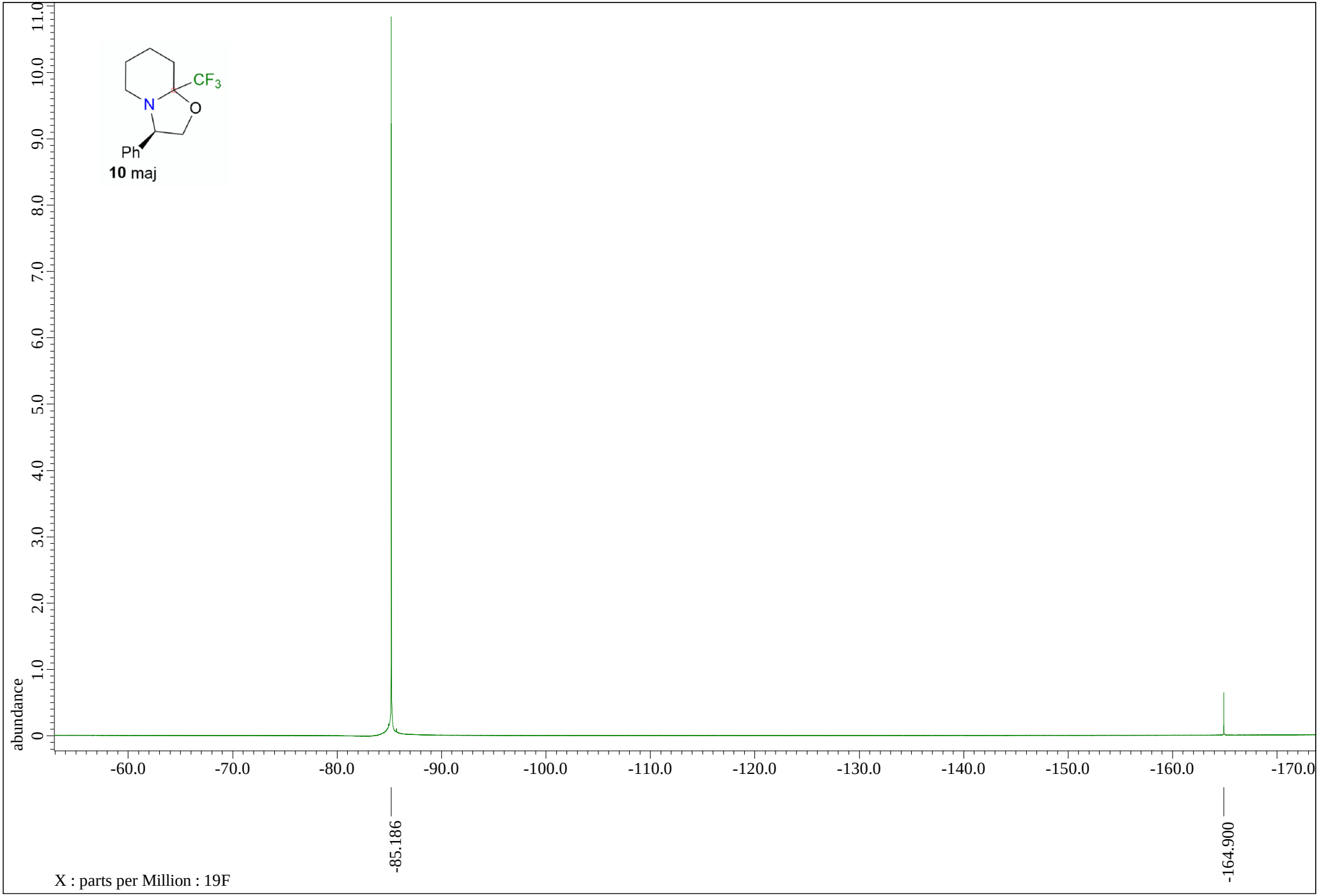

CF3
O
N
O
Ph
9 min
6.90
1.00
1.08
1.07
1.09
2.09
1.05
2.08
abundance
0
0.1
0.2
0.3
0.4
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.362
7.357
7.342
7.324
7.293
7.286
7.277
7.266
7.260
5.114
5.106
5.094
5.086
4.686
4.664
4.644
4.049
4.041
4.035
4.029
4.019
4.014
2.554
2.535
2.519
2.504
2.418
2.391
2.373
2.356
2.340
2.323
2.306
2.166
2.148
2.018
1.923
1.905
X : parts per Million : 1H

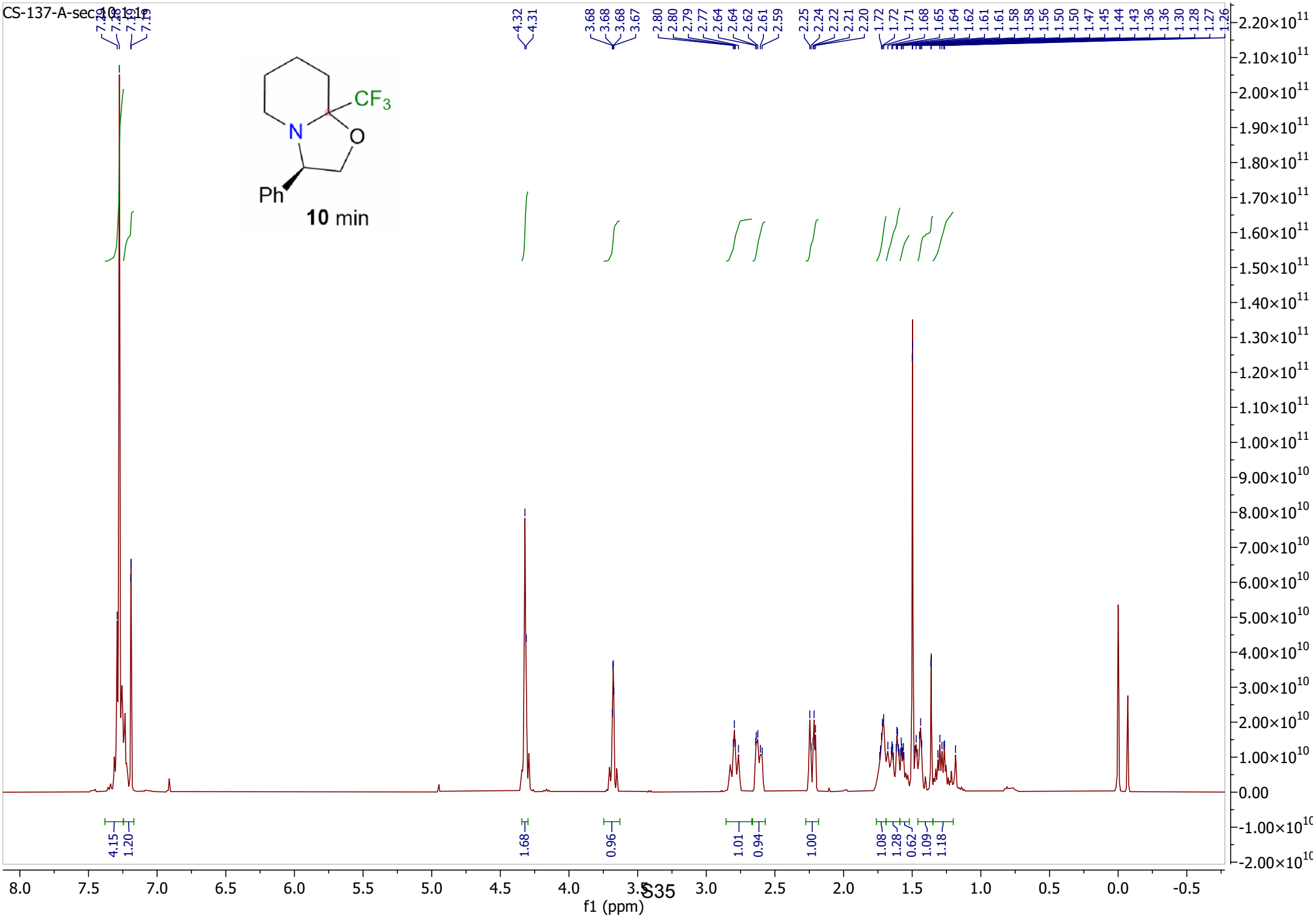

CF3
O
N
O
Ph
9 min
abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16 0.17
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
169.102
140.536
128.942
128.084
126.416
123.555
91.910
91.605
77.475
77.160
76.836
75.062
60.331
30.488
28.495
16.415
X : parts per Million : 13C

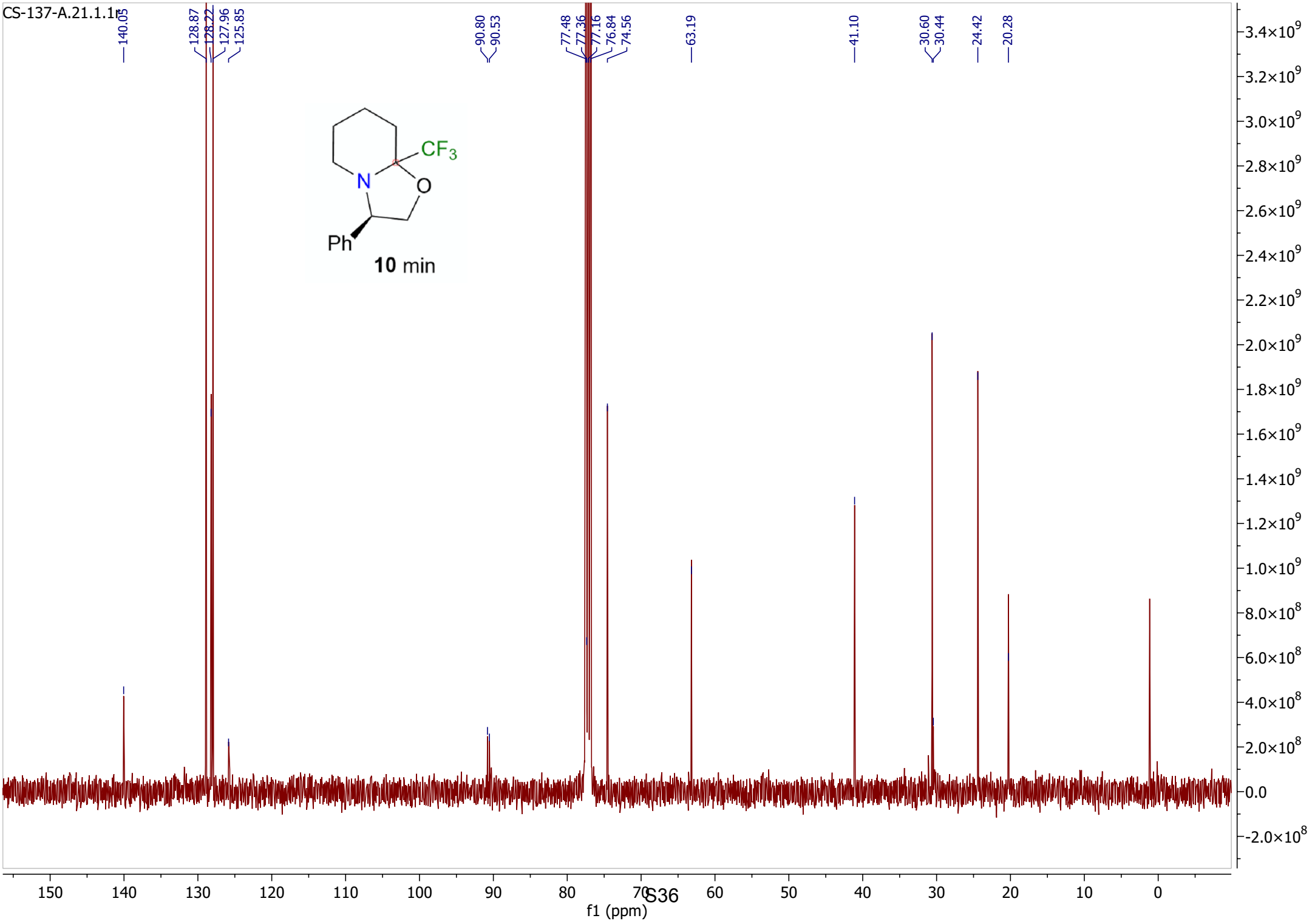

CF3
O
N
O
Ph
9 min
3.0
2.0
1.0
0
abundance
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-81.738
-164.900
X : parts per Million : 19F

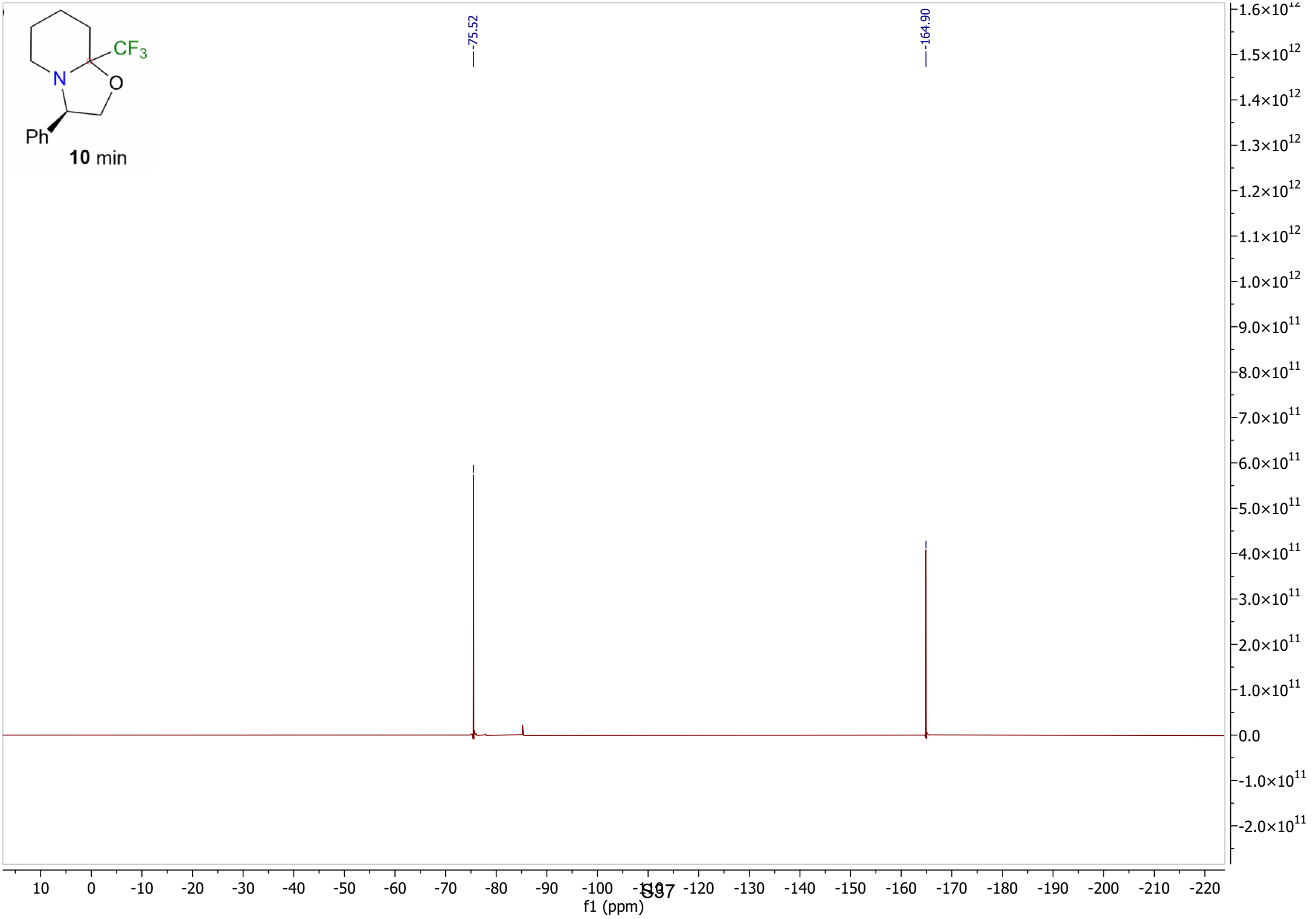

CF3
N
O
Ph
10 maj
abundance
X : parts per Million : 1H
5.14
4.49
1.00
1.10
1.12
1.26
1.26
1.15
1.18
7.438
7.434
7.417
7.413
7.379
7.376
7.359
7.355
7.340
7.326
7.322
7.318
7.305
4.363
4.354
4.338
4.261
4.259
4.242
4.239
4.226
4.222
3.801
3.778
3.756
2.912
2.903
2.874
2.803
2.788
2.766
2.071
2.064
2.057
1.735
1.727
1.441
1.434
1.426
1.419
1.412
1.408
0.009

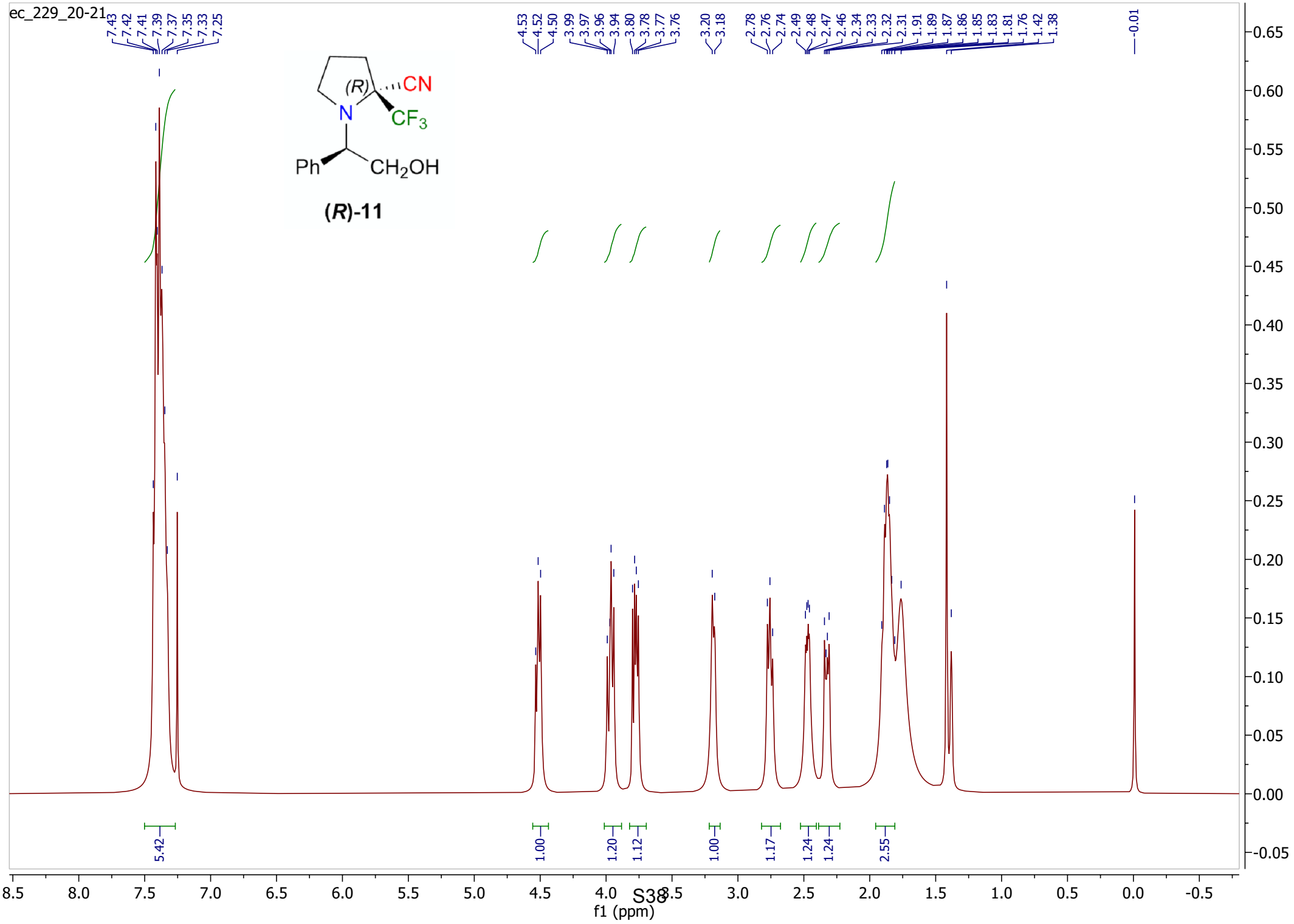

CF3
N
O
Ph
10 maj
abundance
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.1
0.11
0.12
0.13
0.14
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
138.429
128.780
128.246
127.798
127.007
124.137
92.558
92.263
77.475
77.160
76.845
74.080
65.242
41.663
26.760
18.179
17.044
X : parts per Million : 13C

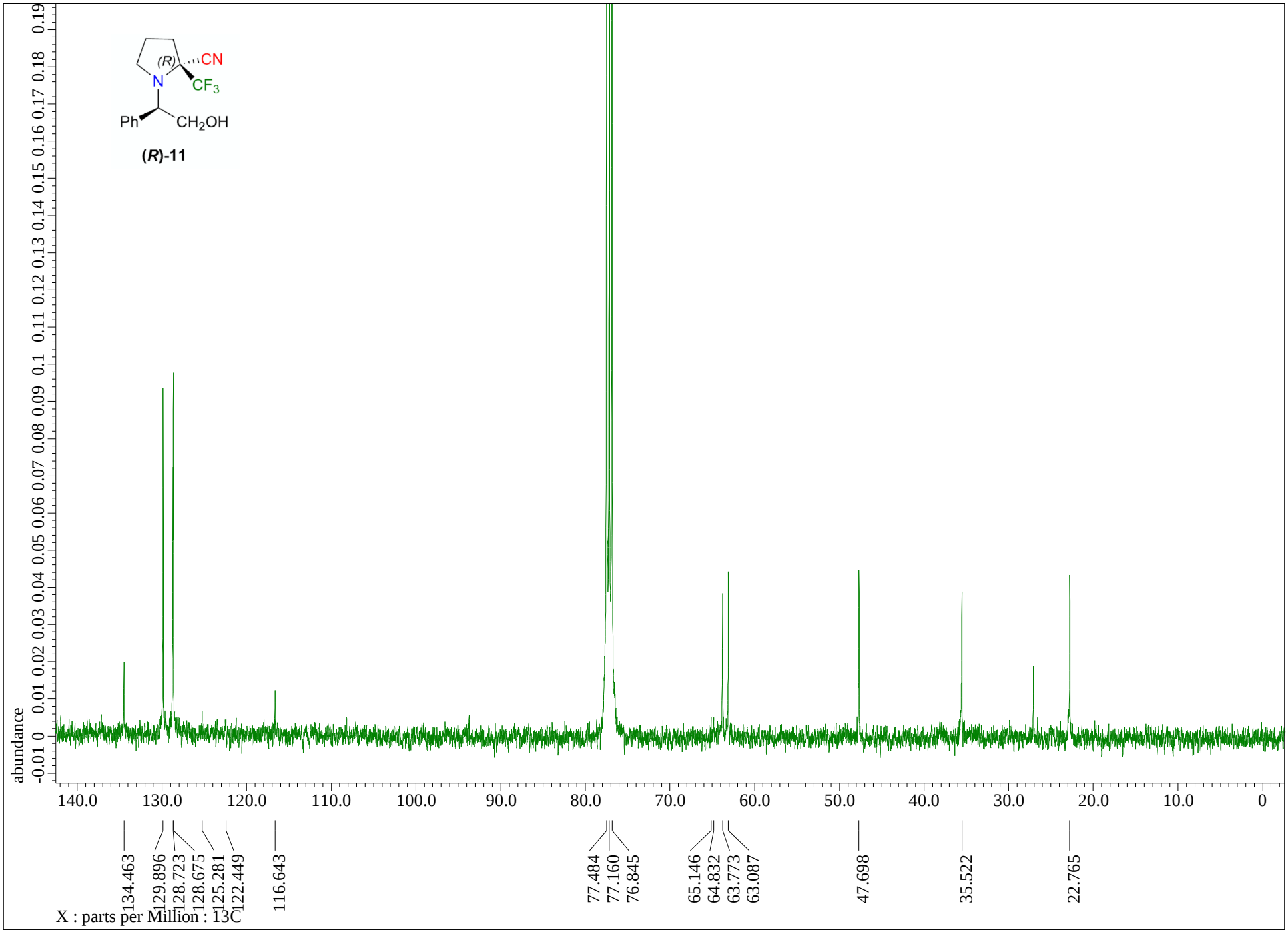

CF3
N
O
Ph
10 maj
abundance
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-85.186
-164.900
X : parts per Million : 19F

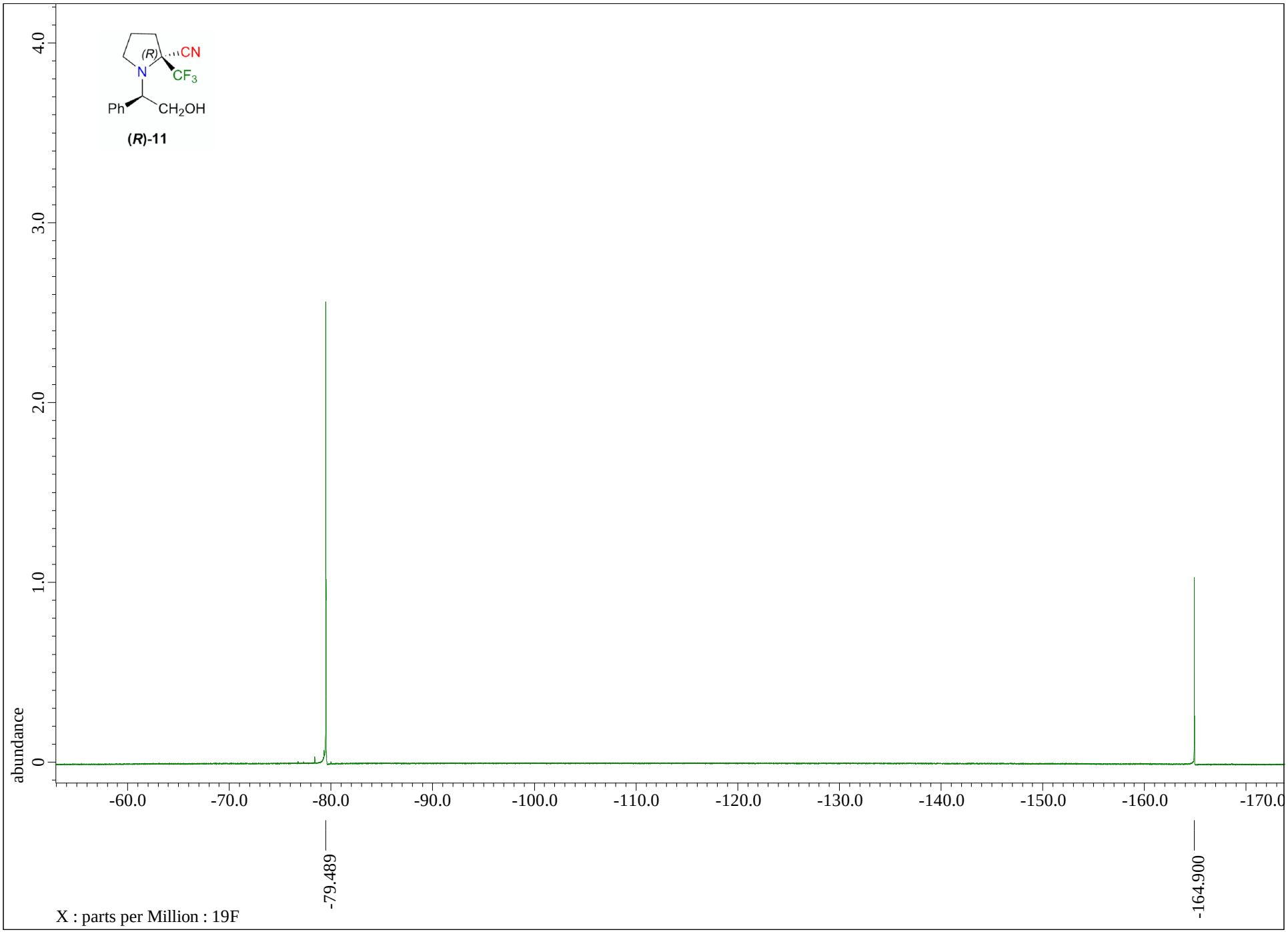

CS-137-A-sec-10-1e
7.40
7.25
7.24
7.19
4.32
4.31
3.68
3.68
3.68
3.67
2.80
2.80
2.79
2.77
2.64
2.64
2.62
2.61
2.59
2.25
2.24
2.22
2.21
2.20
1.72
1.72
1.71
1.68
1.65
1.64
1.62
1.61
1.61
1.58
1.58
1.56
1.50
1.50
1.47
1.45
1.44
1.43
1.36
1.36
1.30
1.28
1.27
1.26
CF3
N
O
Ph
10 min
4.15
1.20
1.68
0.96
1.01
0.94
1.00
1.08
1.28
0.62
1.09
1.18
f1 (ppm)

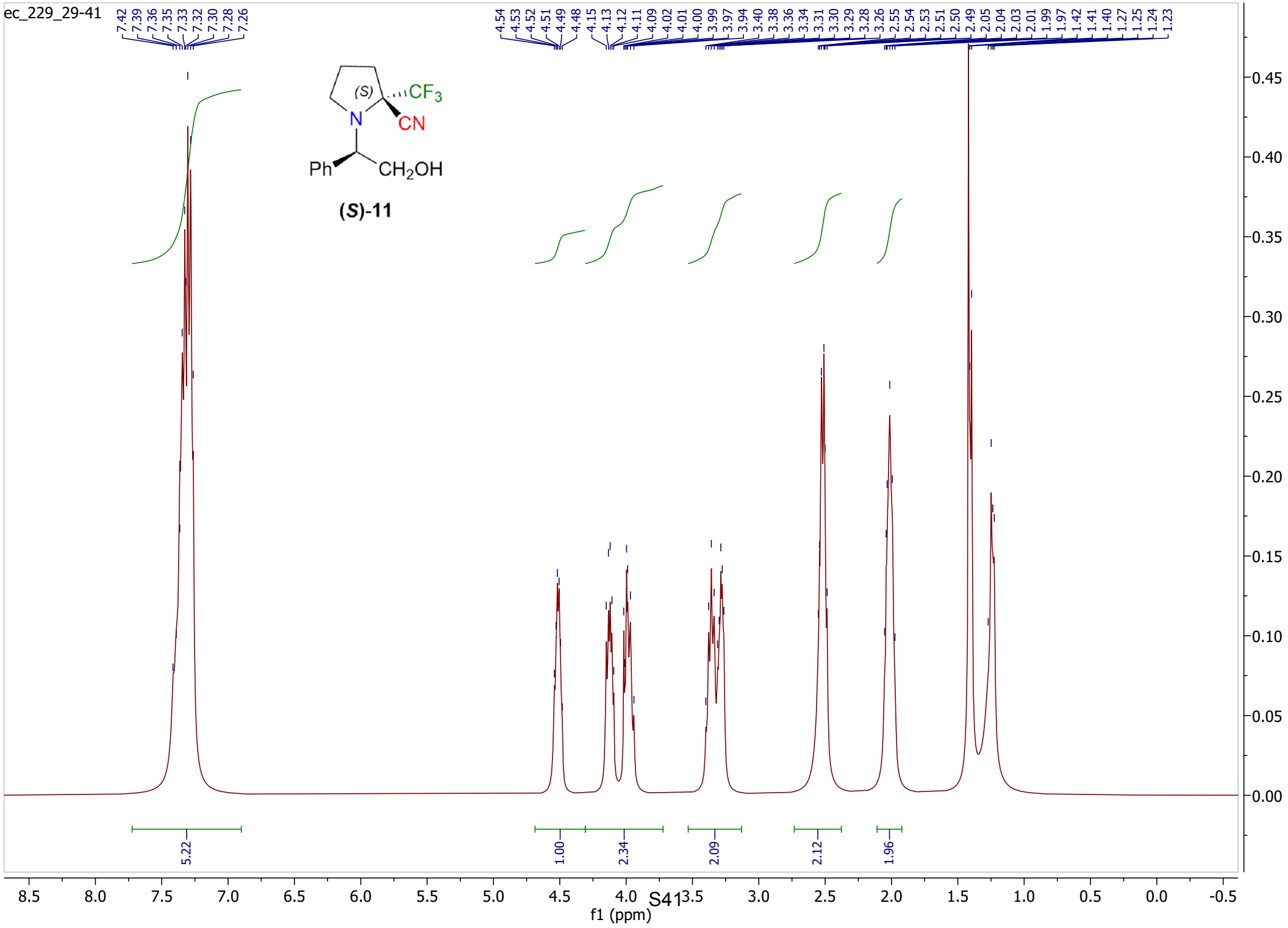

CS-137-A.21.1.1r
140.05
128.87
128.22
127.96
125.85
90.80
90.53
77.48
77.36
77.16
76.84
74.56
63.19
41.10
30.60
30.44
24.42
20.28
CF3
N
O
Ph
10 min
3.4×10^9
3.2×10^9
3.0×10^9
2.8×10^9
2.6×10^9
2.4×10^9
2.2×10^9
2.0×10^9
1.8×10^9
1.6×10^9
1.4×10^9
1.2×10^9
1.0×10^9
8.0×10^8
6.0×10^8
4.0×10^8
2.0×10^8
0.0
-2.0×10^8
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

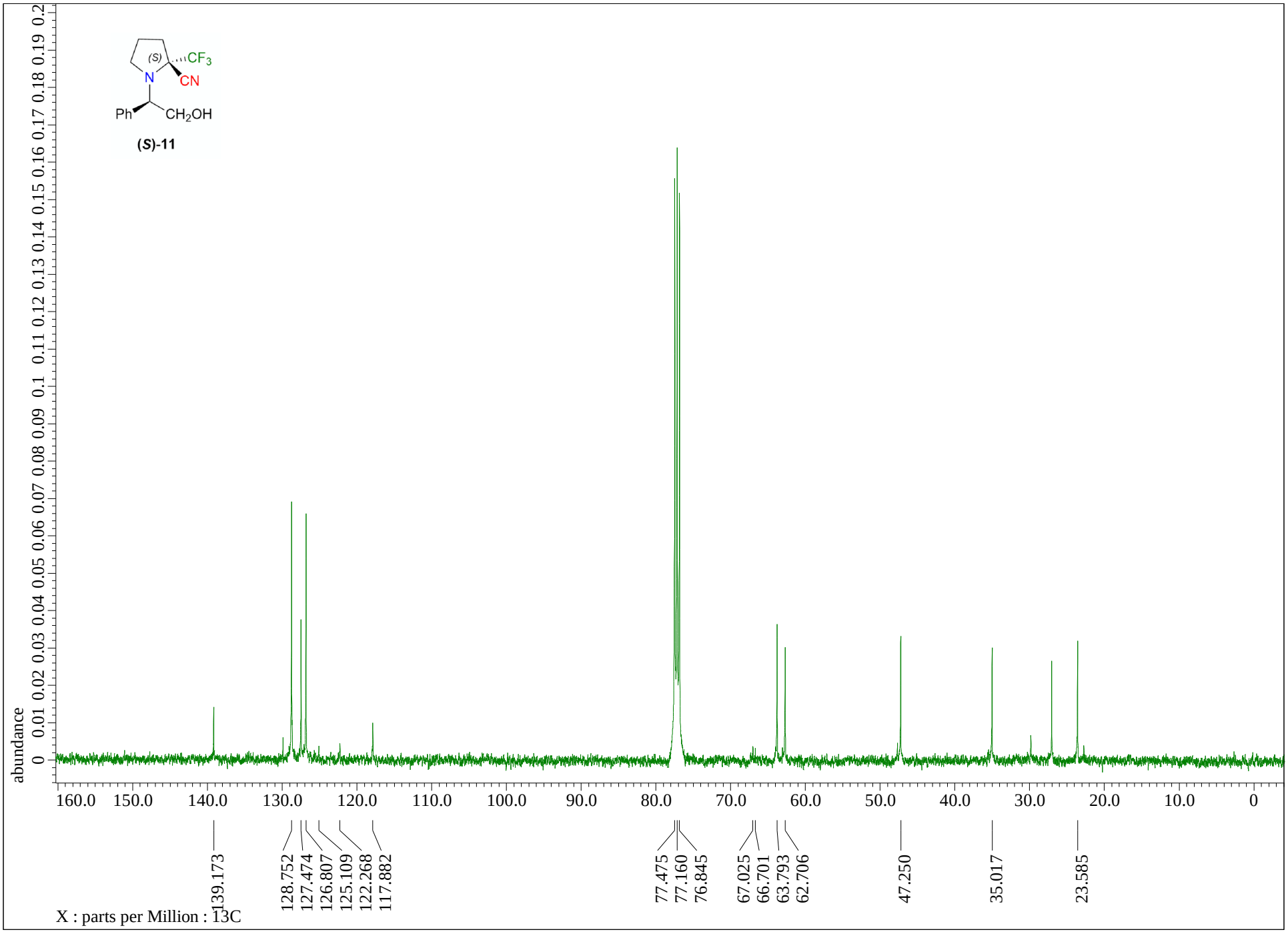

CF3
N
O
Ph
10 min
-75.52
-164.90
1.6×10^12
1.5×10^12
1.4×10^12
1.3×10^12
1.2×10^12
1.1×10^12
1.0×10^12
9.0×10^11
8.0×10^11
7.0×10^11
6.0×10^11
5.0×10^11
4.0×10^11
3.0×10^11
2.0×10^11
1.0×10^11
0.0
-1.0×10^11
-2.0×10^11
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

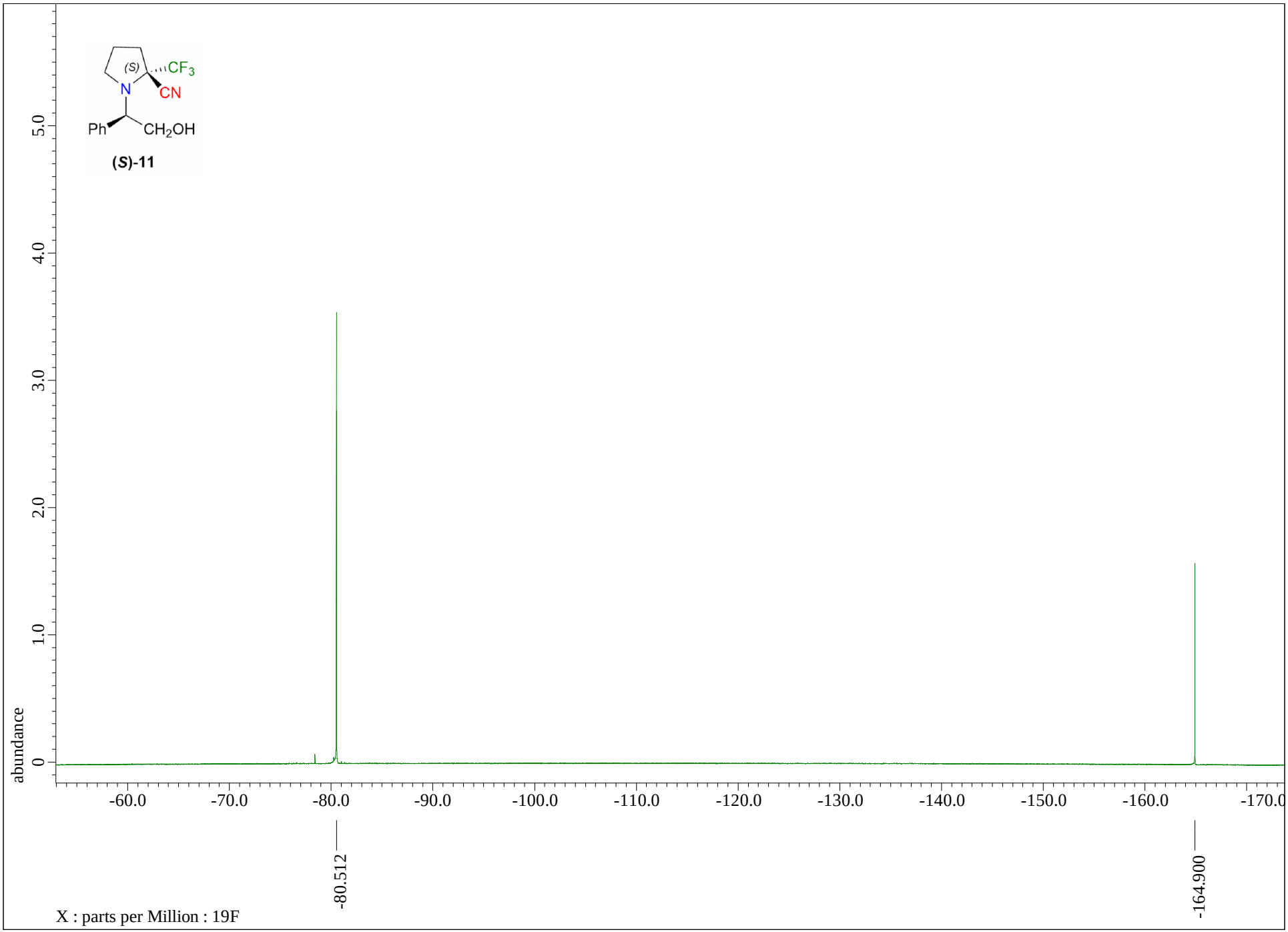

ec_229_20-21
7.43 7.42 7.41 7.39 7.37 7.35 7.33 7.25
4.53 4.52 4.50 3.99 3.97 3.96 3.94 3.80 3.78 3.77 3.76 3.20 3.18 2.78 2.76 2.74 2.49 2.48 2.47 2.46 2.34 2.33 2.32 2.31 1.91 1.89 1.87 1.86 1.85 1.83 1.81 1.76 1.42 1.38
-0.01
(R)
CN
N
CF3
Ph
CH2OH
(R)-11
5.42
1.00
1.20
1.12
1.00
1.17
1.24
1.24
2.55
f1 (ppm)

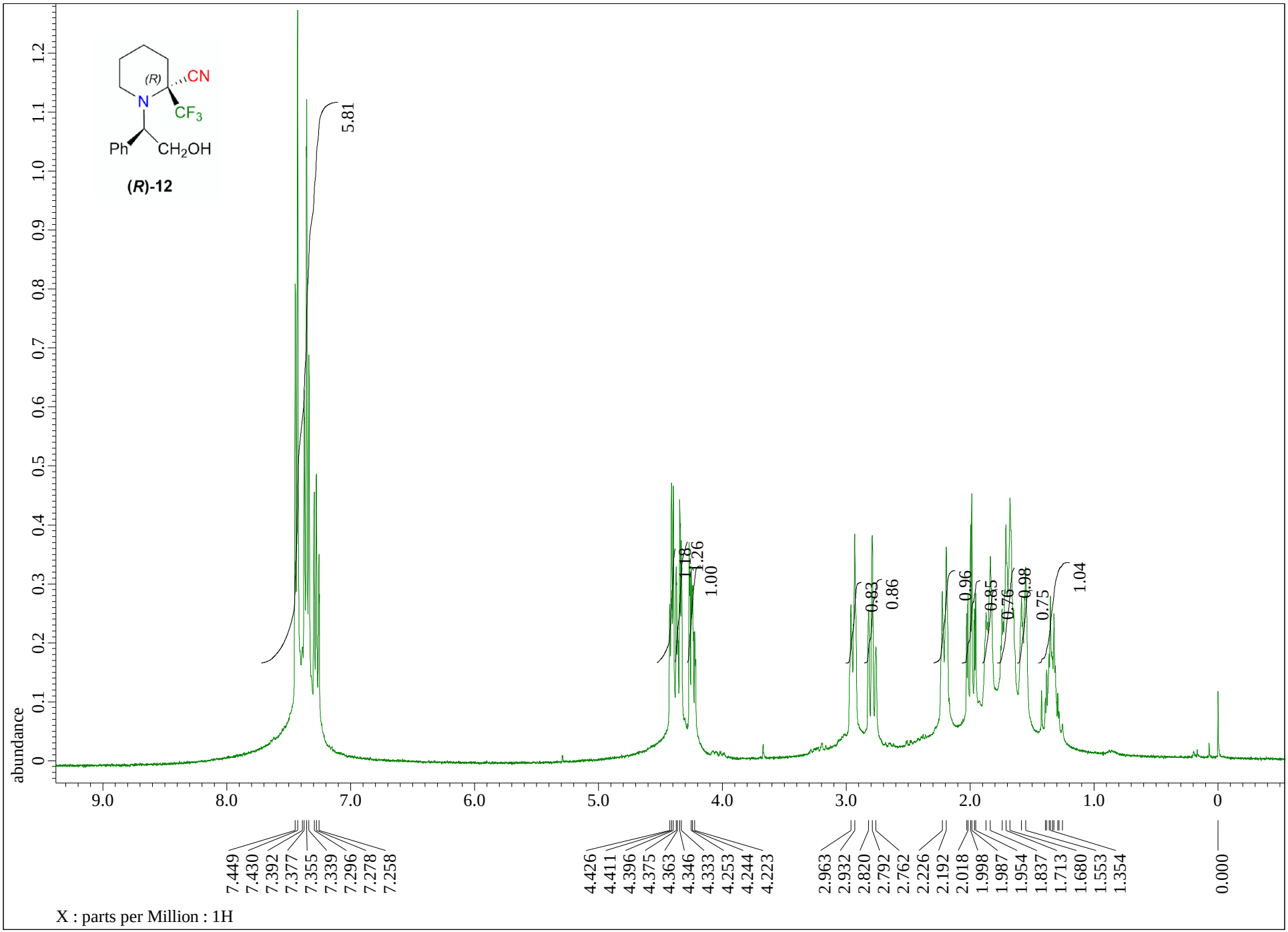

(R)
CN
N
CF3
Ph
CH2OH
(R)-11
abundance
-0.01 0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16 0.17 0.18 0.19
140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
134.463
129.896
128.723
128.675
125.281
122.449
116.643
77.484
77.160
76.845
65.146
64.832
63.773
63.087
47.698
35.522
22.765
X : parts per Million : 13C

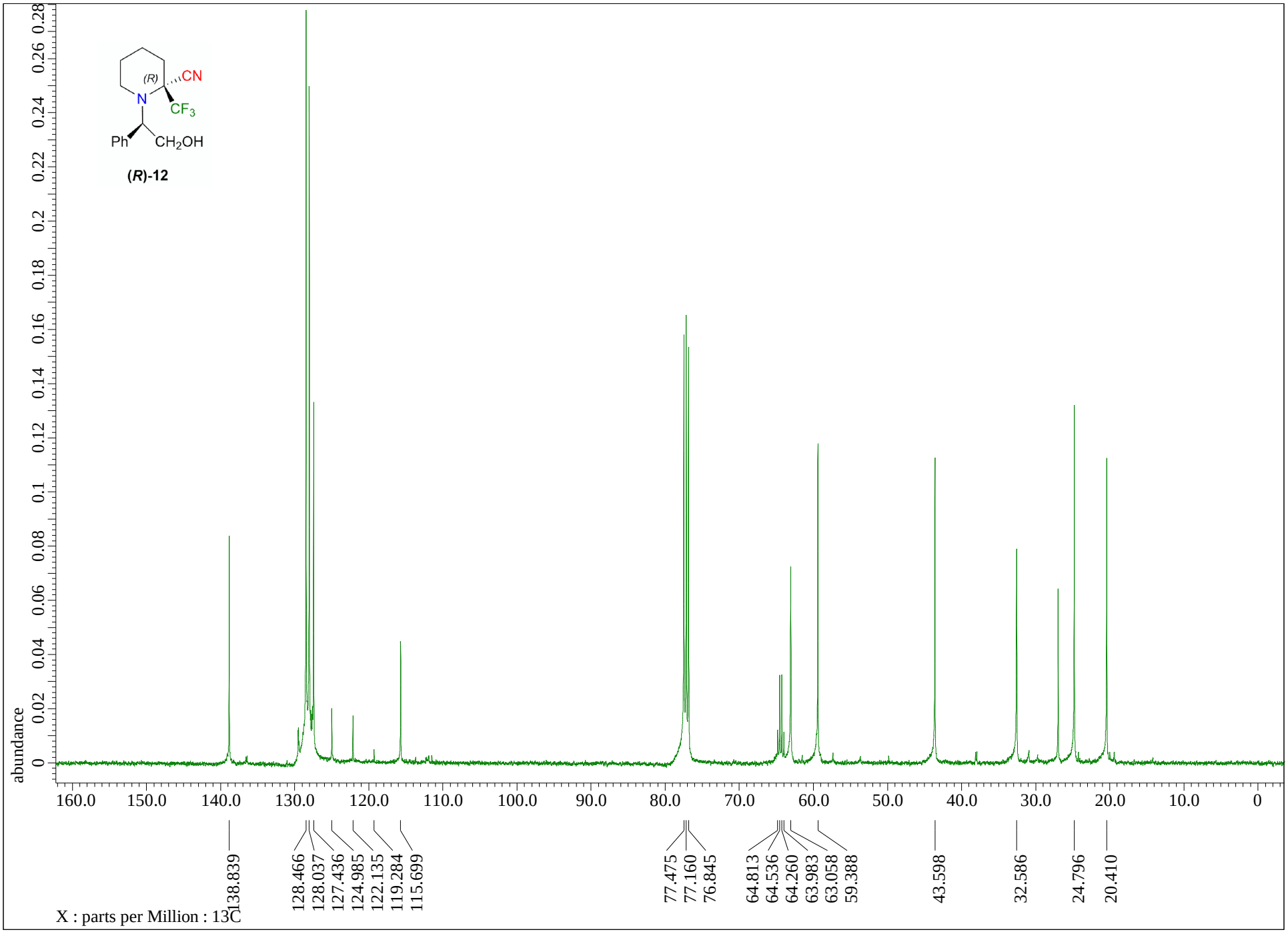

(R)
CN
N
CF3
Ph
CH2OH
(R)-11
4.0
3.0
2.0
1.0
0
abundance
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-79.489
-164.900
X : parts per Million : 19F

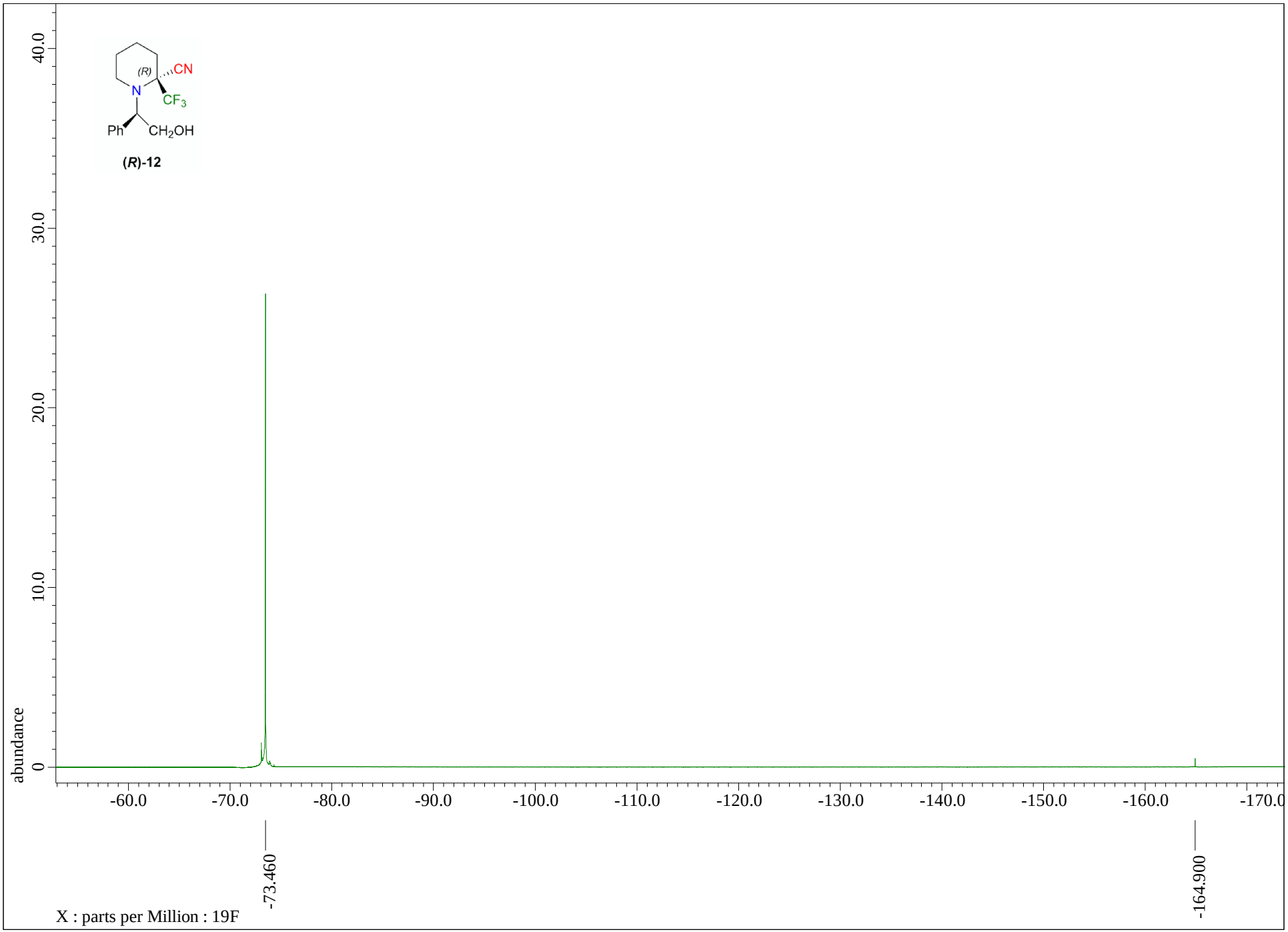

ec_229_29-41
7.42 7.39 7.36 7.35 7.33 7.32 7.30 7.28 7.26
4.54 4.53 4.52 4.51 4.49 4.48 4.15 4.13 4.12 4.11 4.09 4.02 4.01 4.00 3.99 3.97 3.94 3.40 3.38 3.36 3.34 3.31 3.30 3.29 3.28 3.26 2.55 2.54 2.53 2.51 2.50 2.49 2.05 2.04 2.03 2.01 1.99 1.97 1.42 1.41 1.40 1.27 1.25 1.24 1.23
(S)
CF3
N
CN
Ph
CH2OH
(S)-11
5.22
1.00
2.34
2.09
2.12
1.96
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

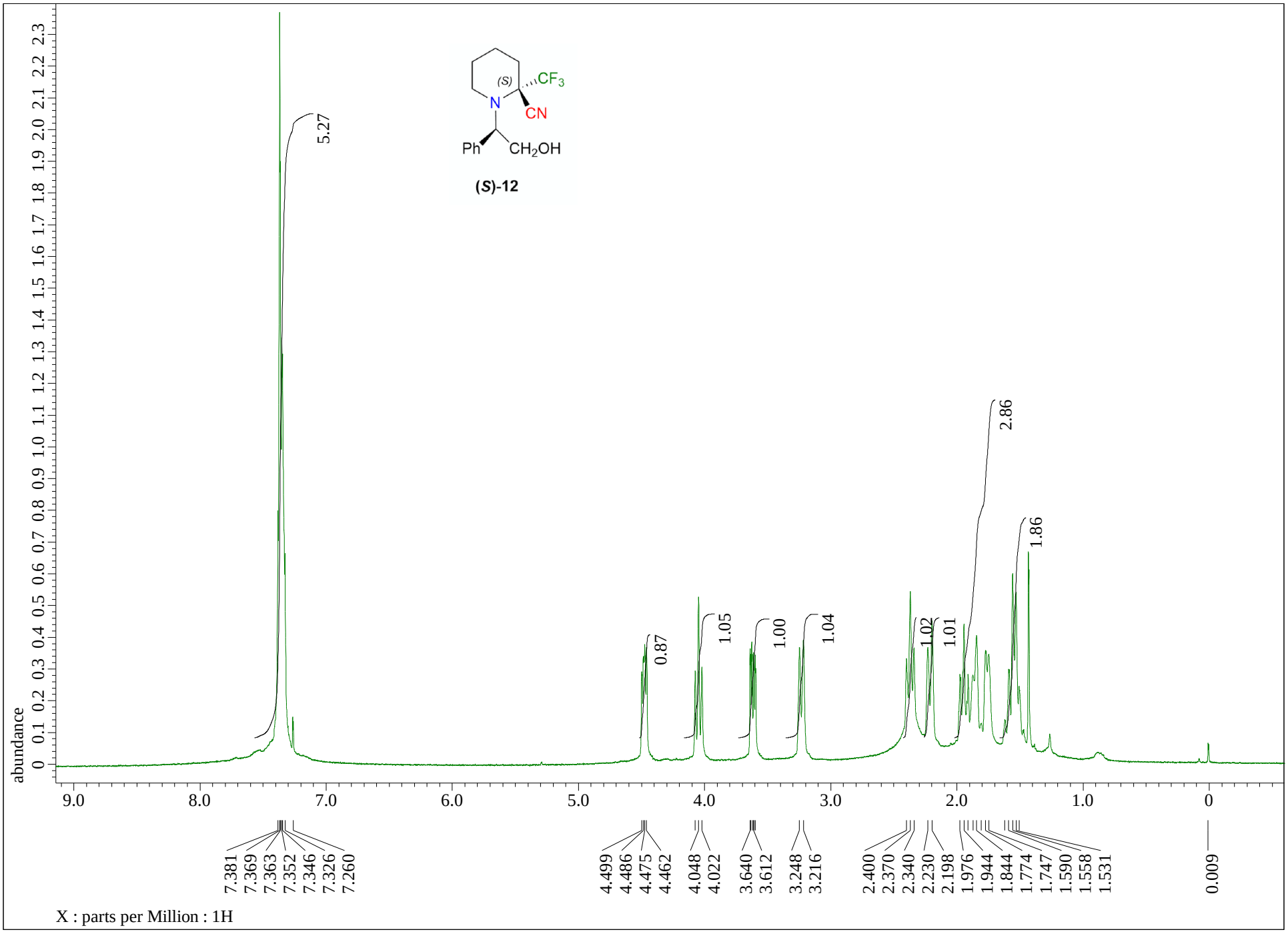

(S)
CF3
N
CN
Ph
CH2OH
(S)-11
abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16 0.17 0.18 0.19 0.2
160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
139.173
128.752
127.474
126.807
125.109
122.268
117.882
77.475
77.160
76.845
67.025
66.701
63.793
62.706
47.250
35.017
23.585
X : parts per Million : 13C

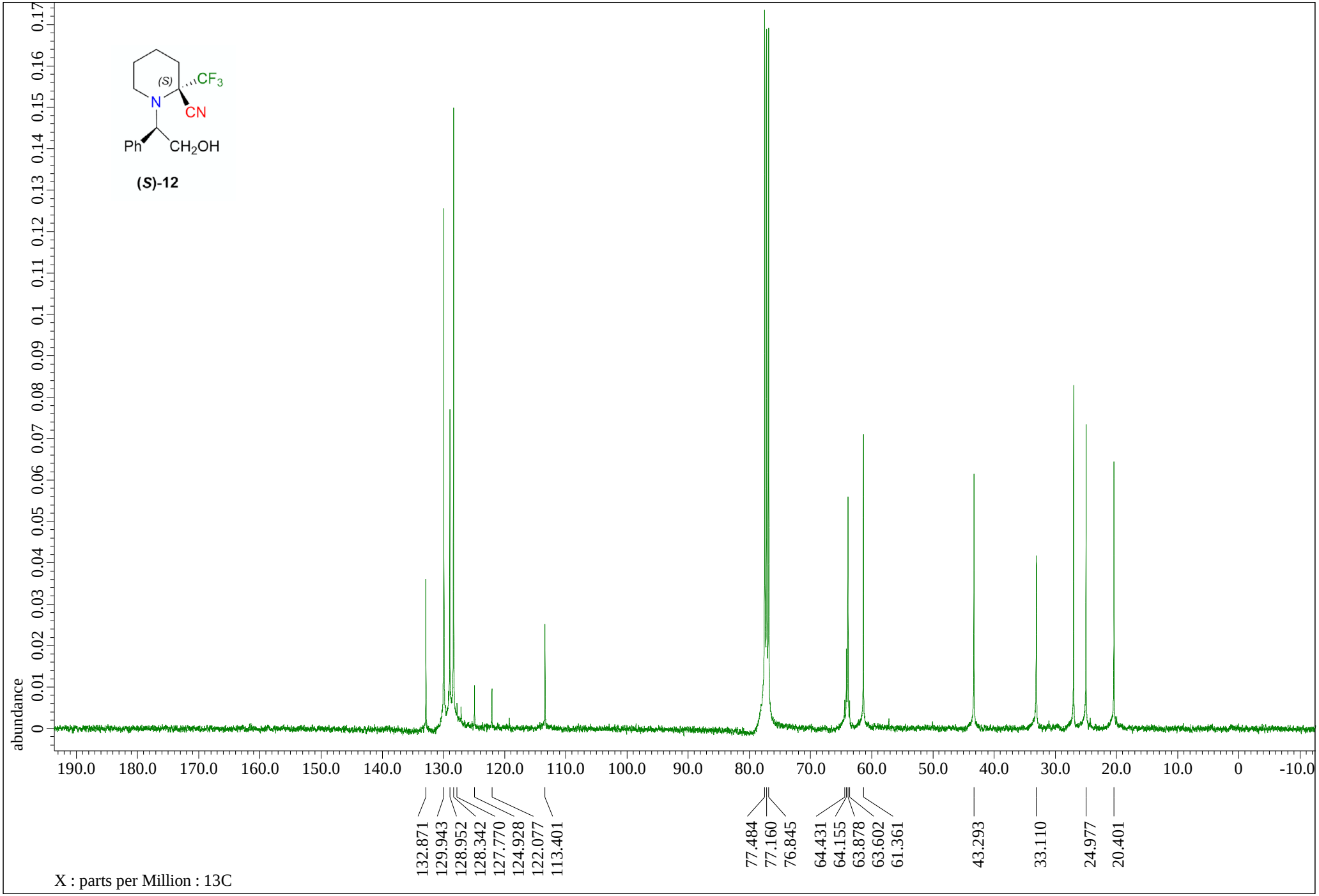

(S)
CF3
N
CN
Ph
CH2OH
(S)-11
abundance
5.0
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-80.512
-164.900
X : parts per Million : 19F

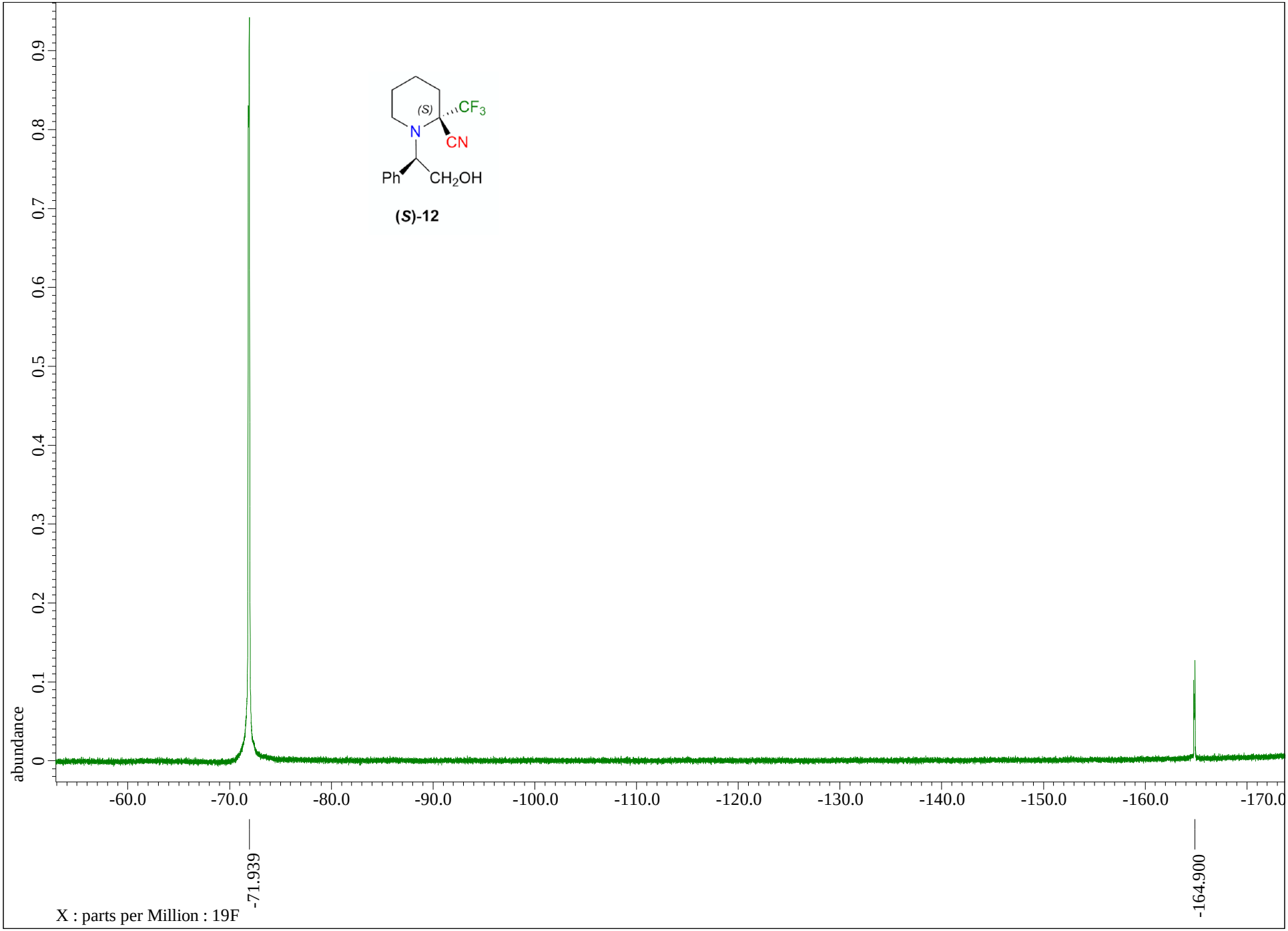

(R)
CN
N
CF3
Ph
CH2OH
(R)-12
abundance
X : parts per Million : 1H
5.81
1.18
1.26
1.00
0.83
0.86
0.96
0.85
0.76
0.98
0.75
1.04
7.449
7.430
7.392
7.377
7.355
7.339
7.296
7.278
7.258
4.426
4.411
4.396
4.375
4.363
4.346
4.333
4.253
4.244
4.223
2.963
2.932
2.820
2.792
2.762
2.226
2.192
2.018
1.998
1.987
1.954
1.837
1.713
1.680
1.553
1.354
0.000

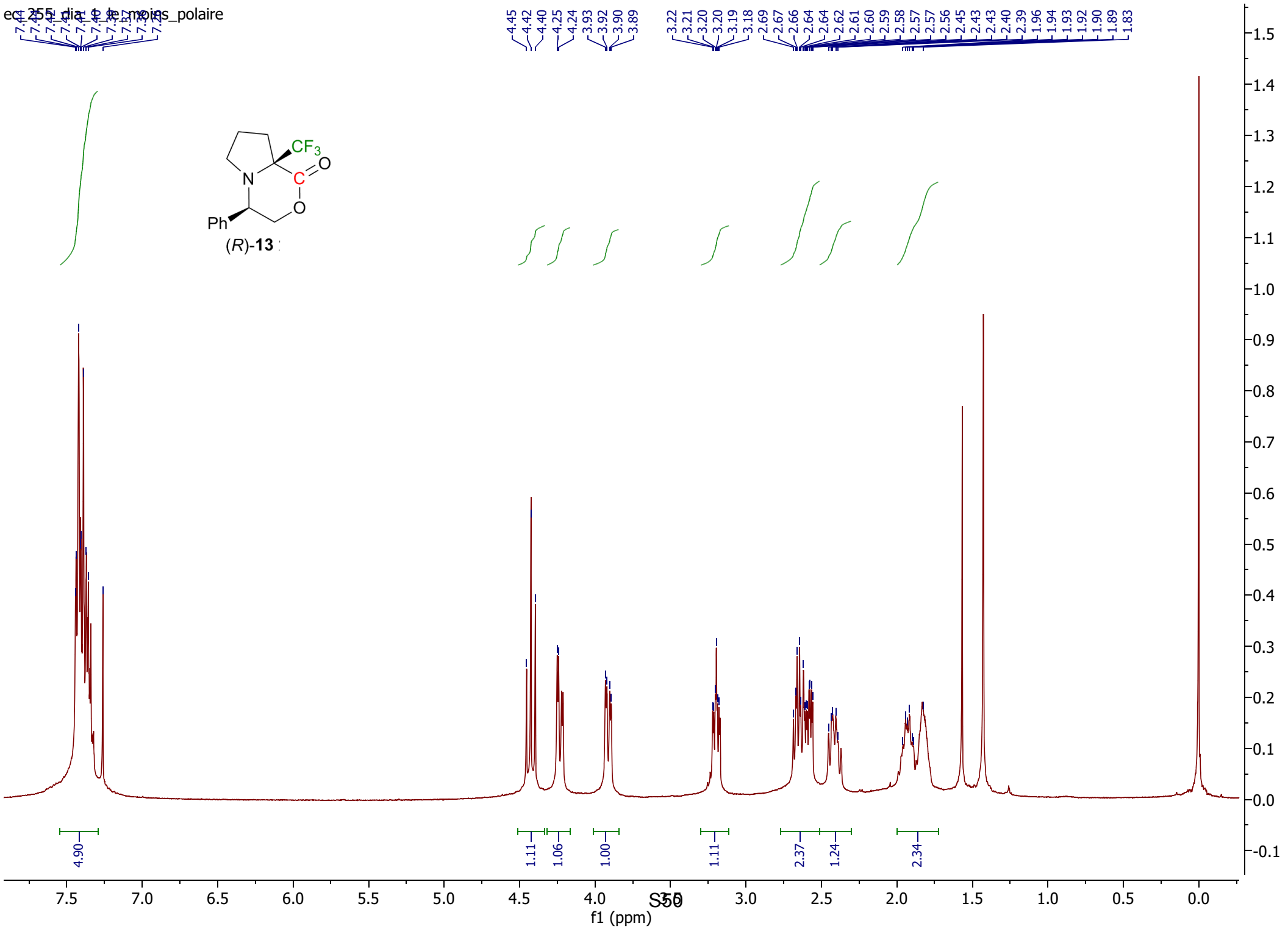

(R)
CN
N
CF3
Ph
CH2OH
(R)-12
abundance
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
0.22
0.24
0.26
0.28
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
138.839
128.466
128.037
127.436
124.985
122.135
119.284
115.699
77.475
77.160
76.845
64.813
64.536
64.260
63.983
63.058
59.388
43.598
32.586
24.796
20.410
X : parts per Million : 13C


(R)
CN
N
CF3
Ph
CH2OH
(R)-12
40.0
30.0
20.0
10.0
0
abundance
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-73.460
-164.900
X : parts per Million : 19F

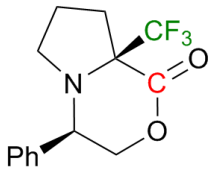

(S)
CF3
N
CN
Ph
CH2OH
(S)-12
abundance
X : parts per Million : 1H
5.27
0.87
1.05
1.00
1.04
1.02
1.01
2.86
1.86
7.381
7.369
7.363
7.352
7.346
7.326
7.260
4.499
4.486
4.475
4.462
4.048
4.022
3.640
3.612
3.248
3.216
2.400
2.370
2.340
2.230
2.198
1.976
1.944
1.844
1.774
1.747
1.590
1.558
1.531
0.009


(S)
CF3
N
CN
Ph
CH2OH
(S)-12
abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16 0.17
190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0
132.871
129.943
128.952
128.342
127.770
124.928
122.077
113.401
77.484
77.160
76.845
64.431
64.155
63.878
63.602
61.361
43.293
33.110
24.977
20.401
X : parts per Million : 13C

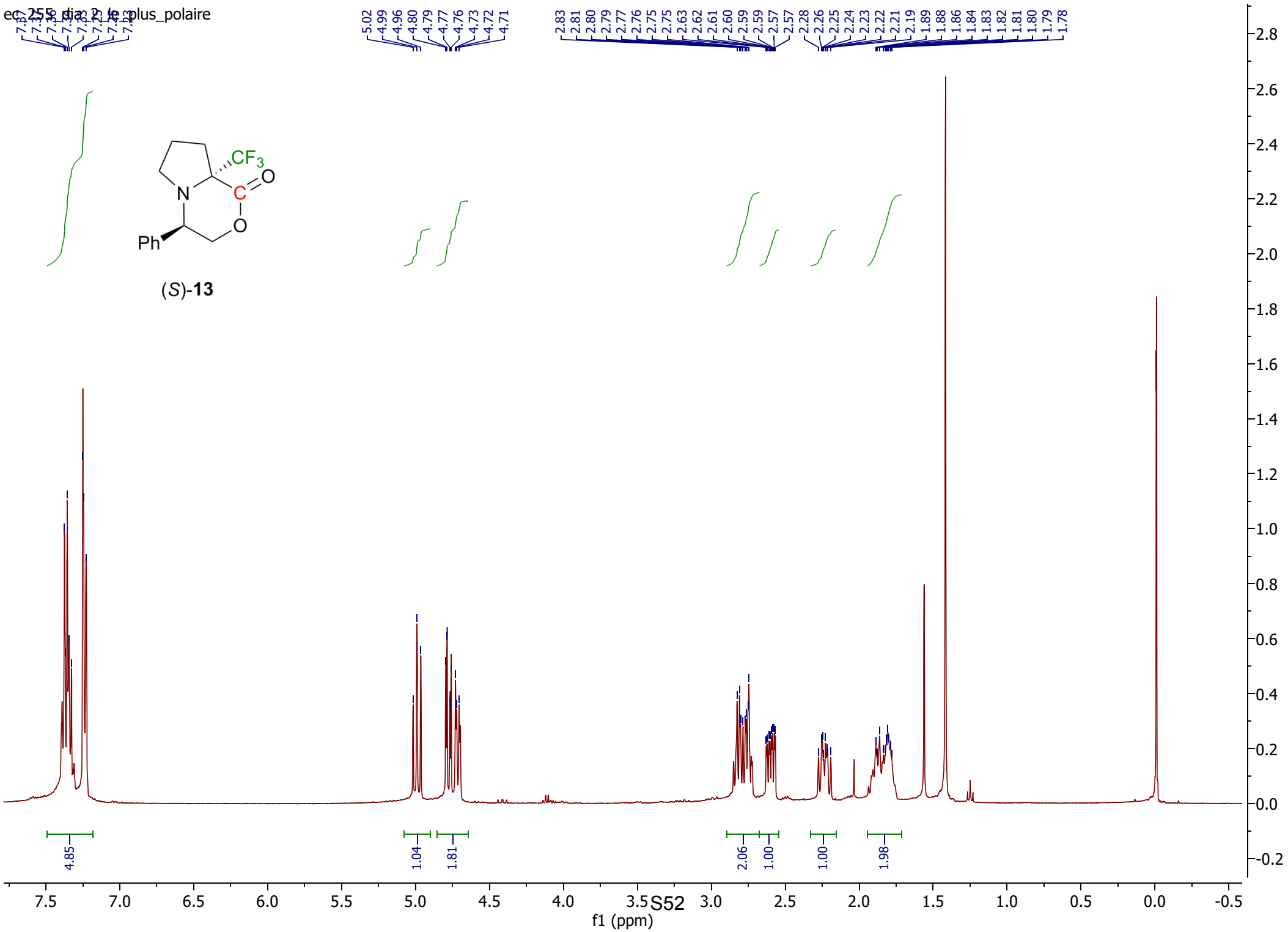

(S)
CF3
N
CN
Ph
CH2OH
(S)-12
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-71.939
-164.900
X : parts per Million : 19F


ec_255_dia_e_le_moins_polaire
CF3
O
N
C
O
Ph
(R)-13
f1 (ppm)

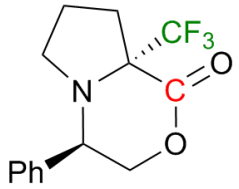
ec_255_dia_1_le_moins_polaire



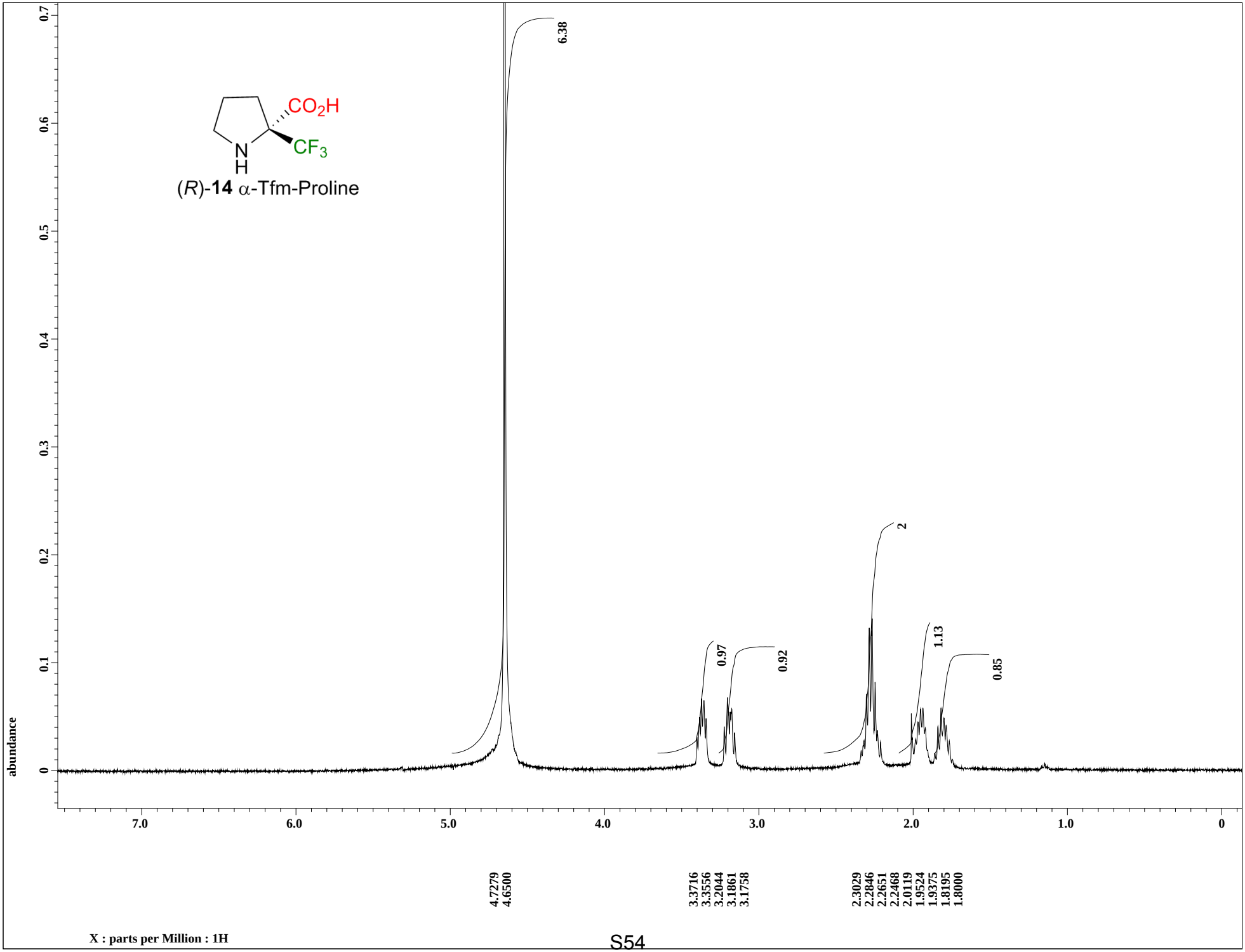
(*R*)-**13**

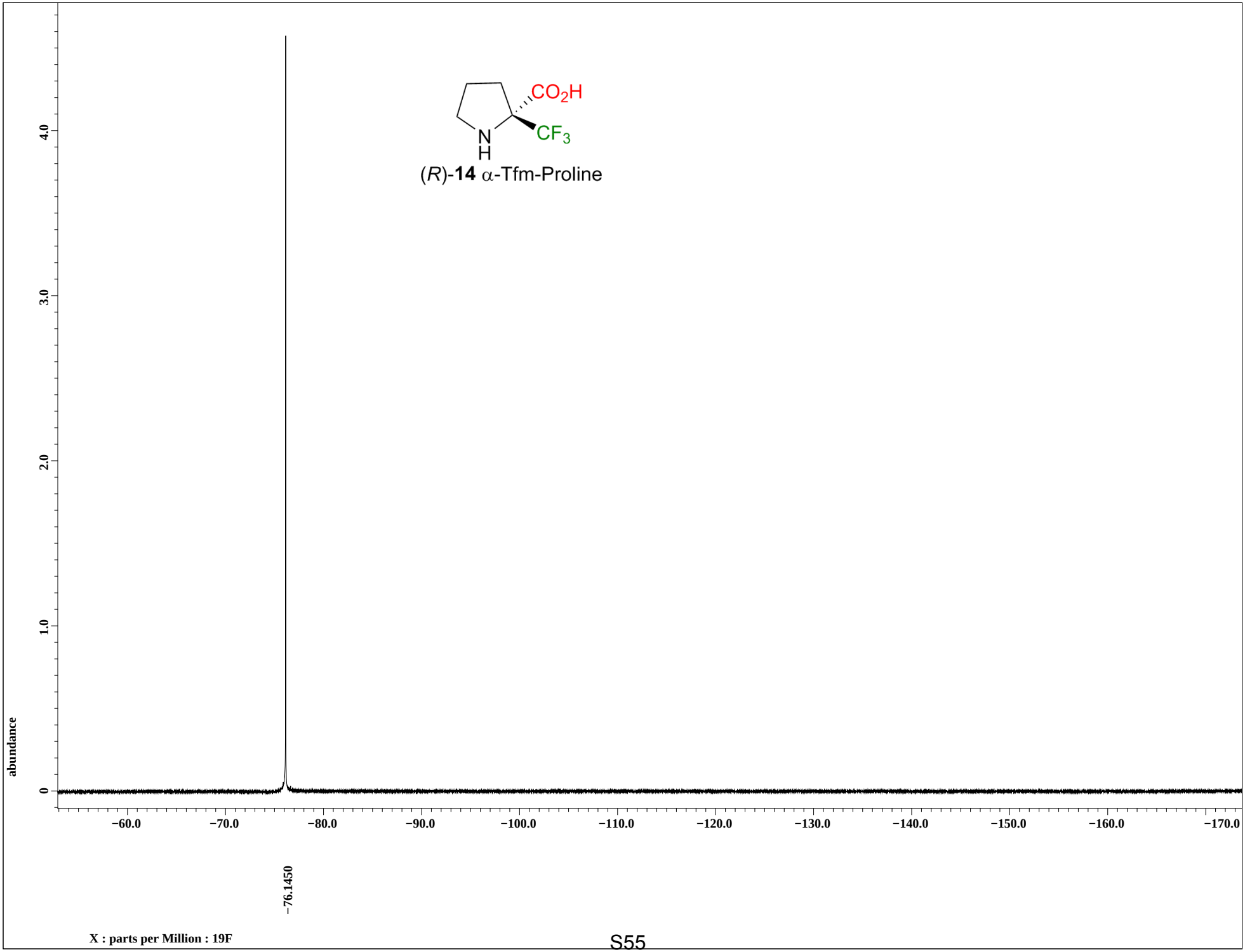

ec_255_dia_2_le_plus_polaire
CF3
O
C
N
O
Ph
(S)-13
f1 (ppm)

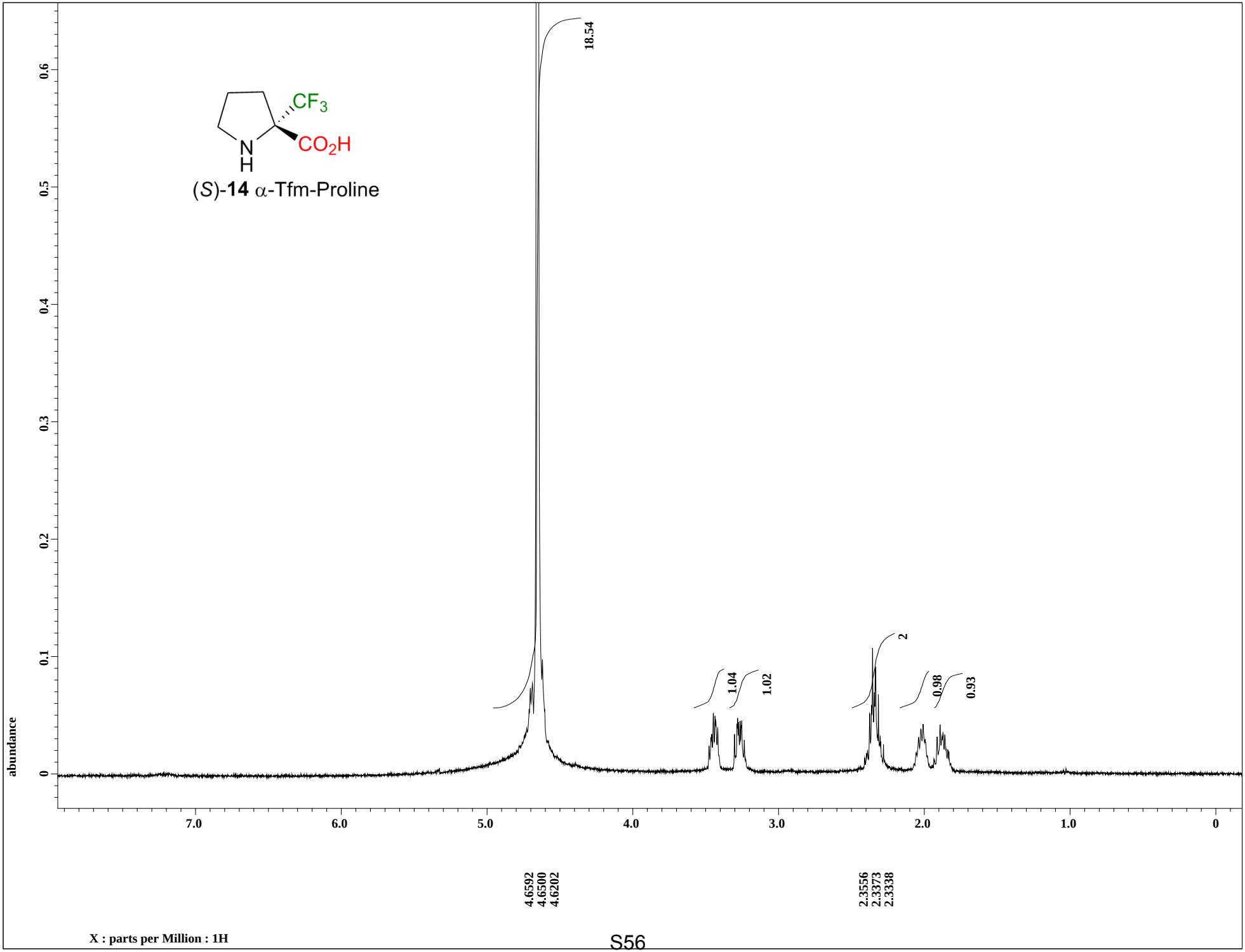
ec_255_dia_2_le_plus_polaire

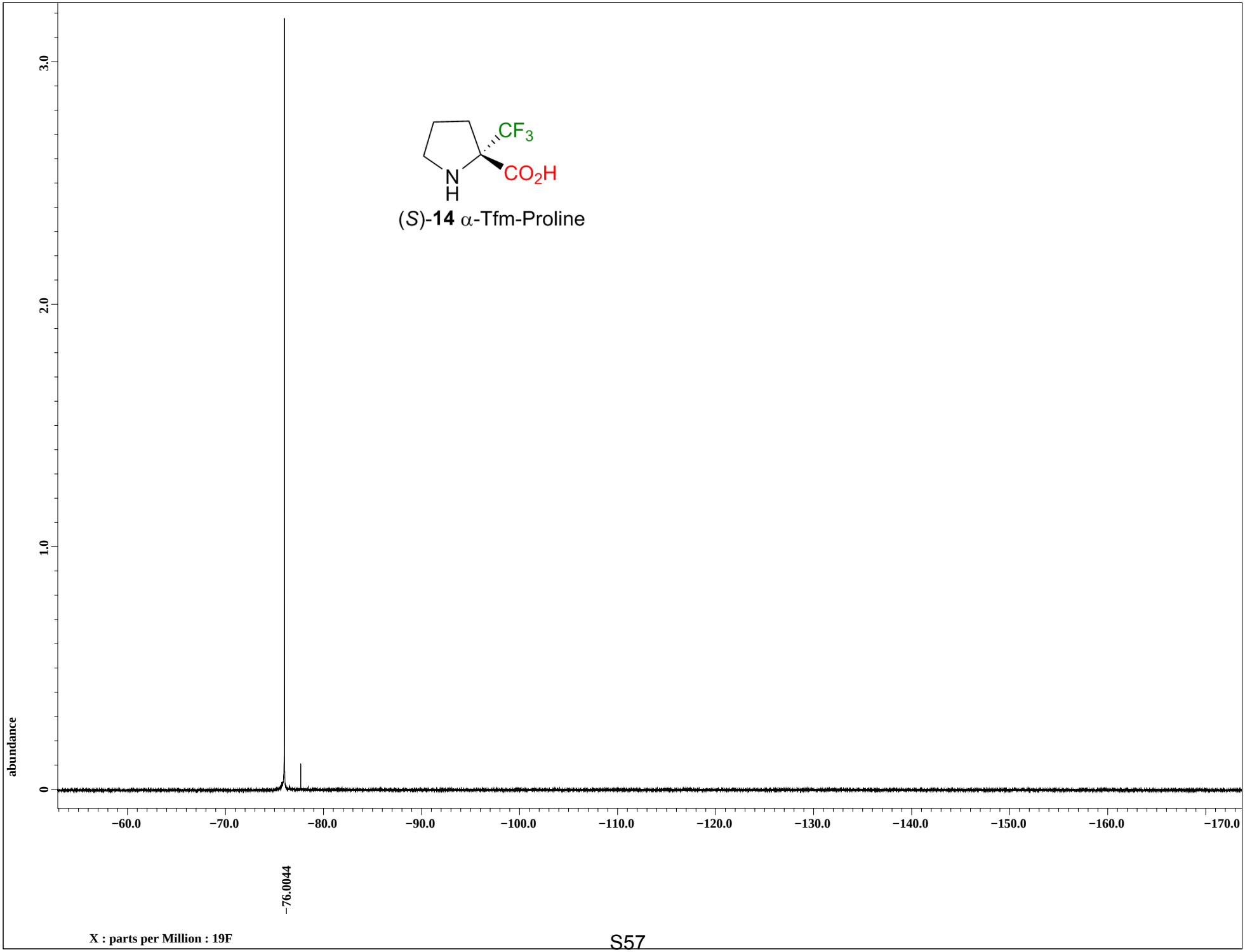


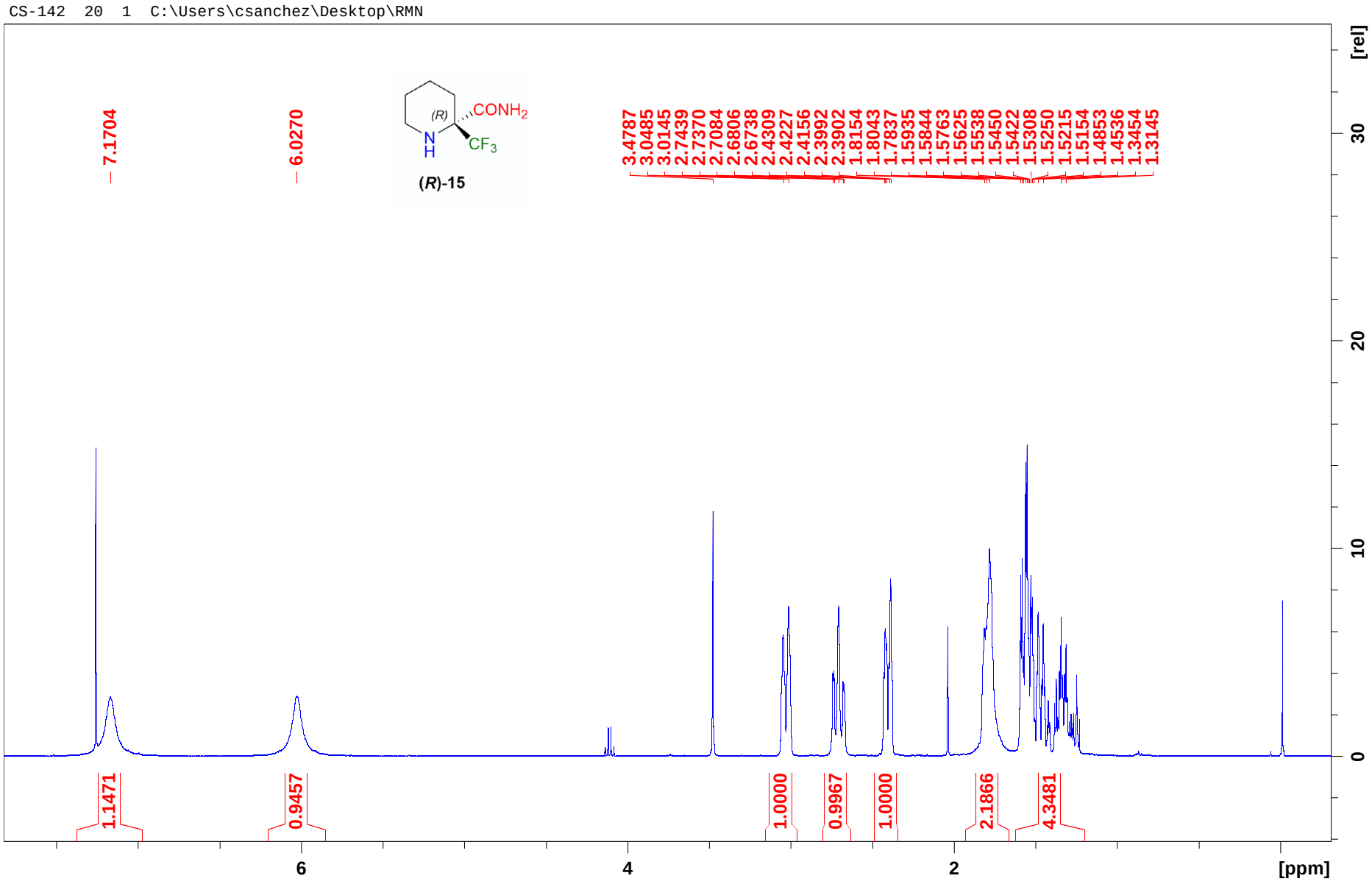
(*S*)-**13**

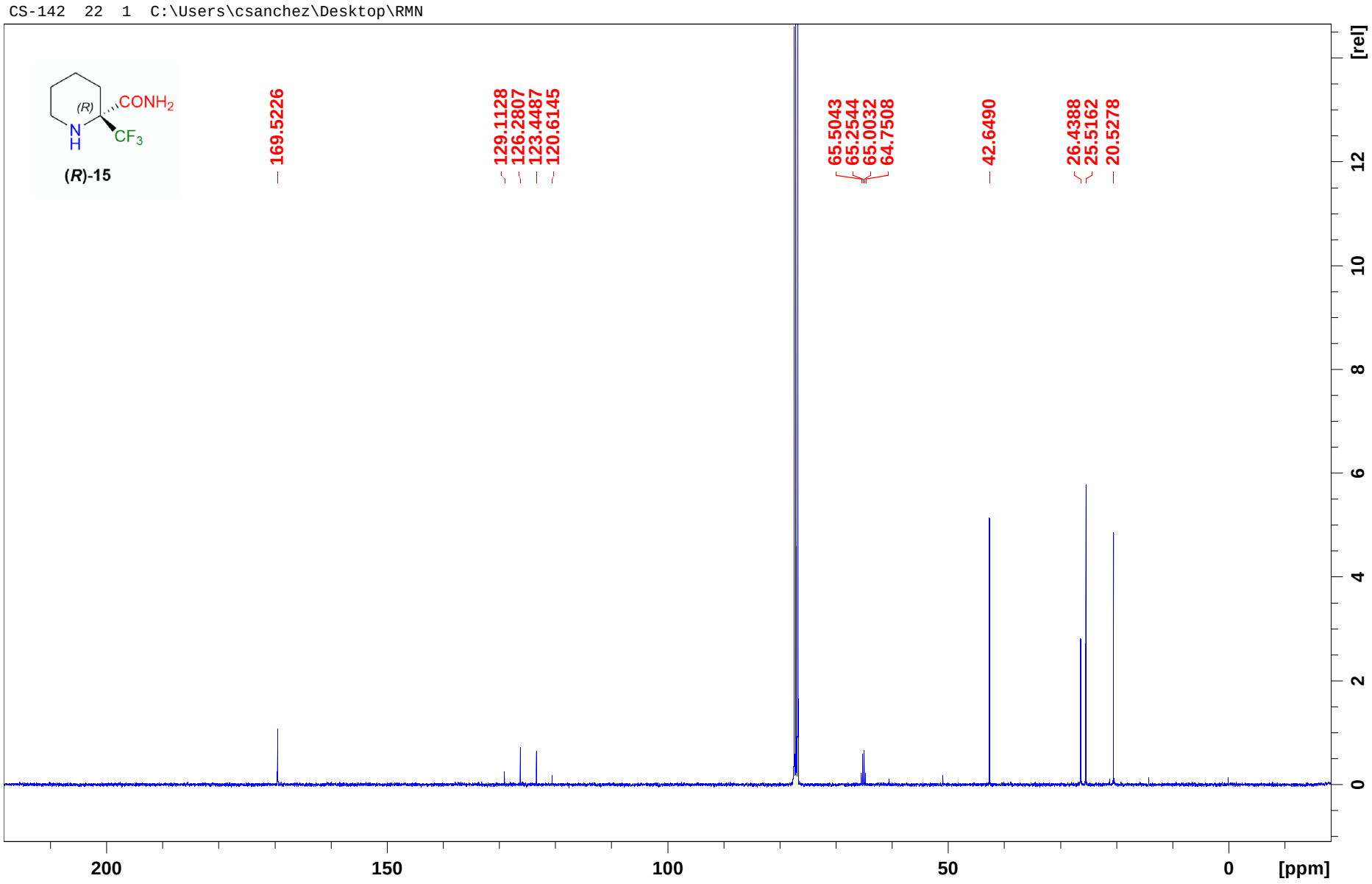

CO2H
CF3
N
H
(R)-14 α-Tfm-Proline
6.38
0.97
0.92
2
1.13
0.85
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
4.7279
4.6500
3.3716
3.3556
3.2044
3.1861
3.1758
2.3029
2.2846
2.2651
2.2468
2.0119
1.9524
1.9375
1.8195
1.8000
X : parts per Million : 1H

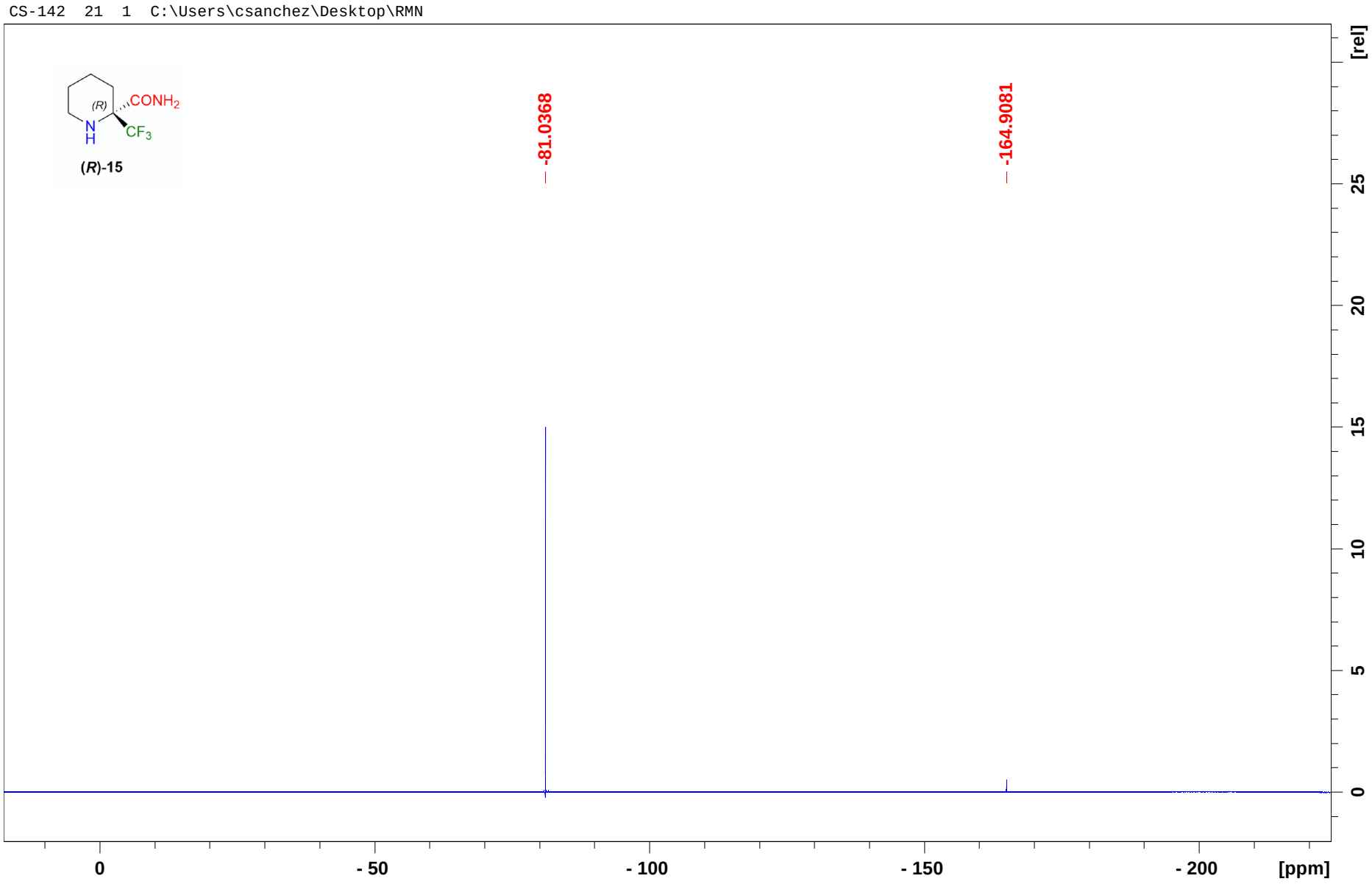

CO2H
CF3
N
H
(R)-14 α-Tfm-Proline
abundance
4.0
3.0
2.0
1.0
0
−60.0
−70.0
−80.0
−90.0
−100.0
−110.0
−120.0
−130.0
−140.0
−150.0
−160.0
−170.0
−76.1450
X : parts per Million : 19F

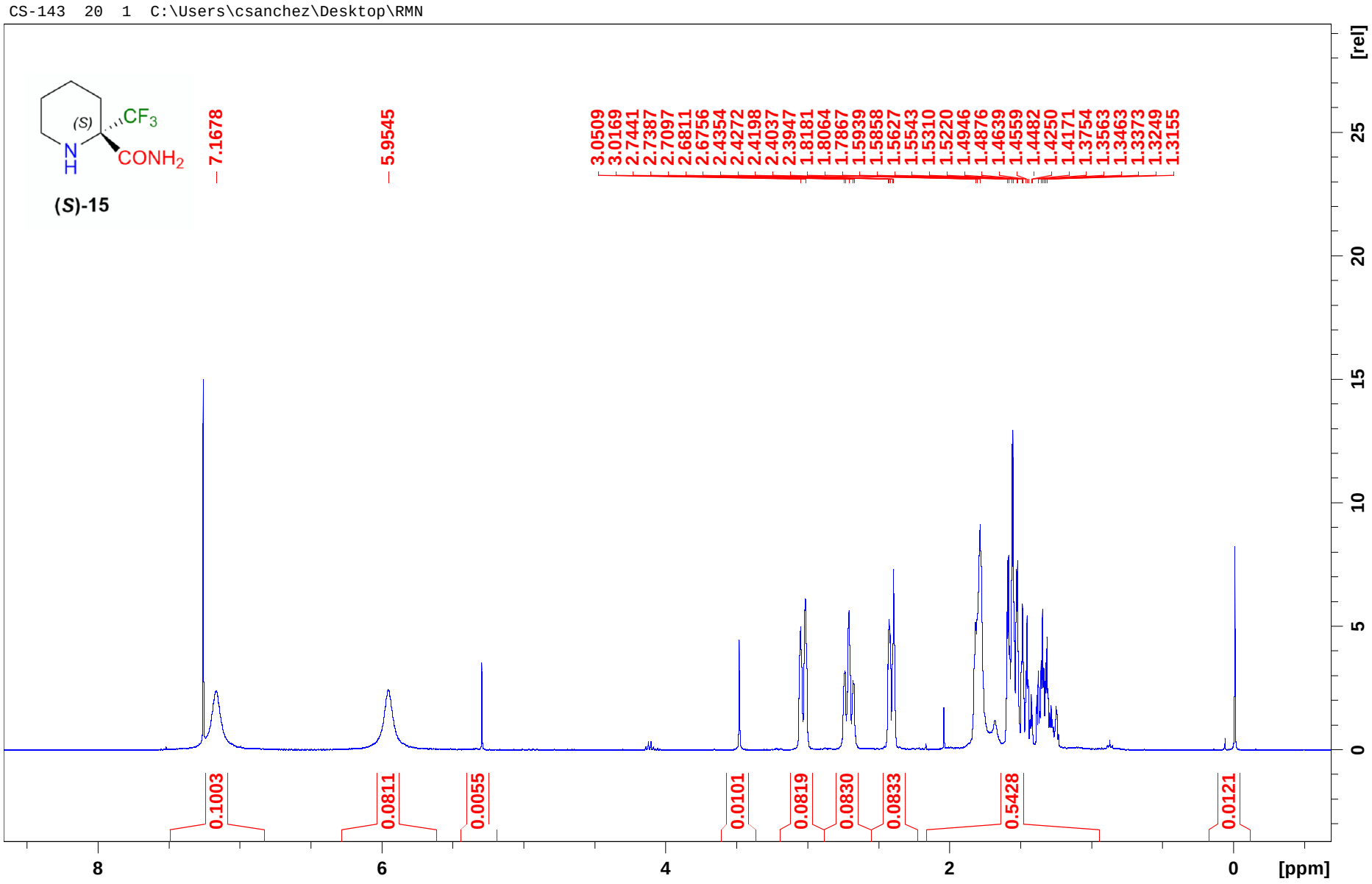

CF3
CO2H
N
H
(S)-14 α-Tfm-Proline
18.54
1.04
1.02
2
0.98
0.93
abundance
0.6
0.5
0.4
0.3
0.2
0.1
0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
4.6592
4.6500
4.6202
2.3556
2.3373
2.3338
X : parts per Million : 1H

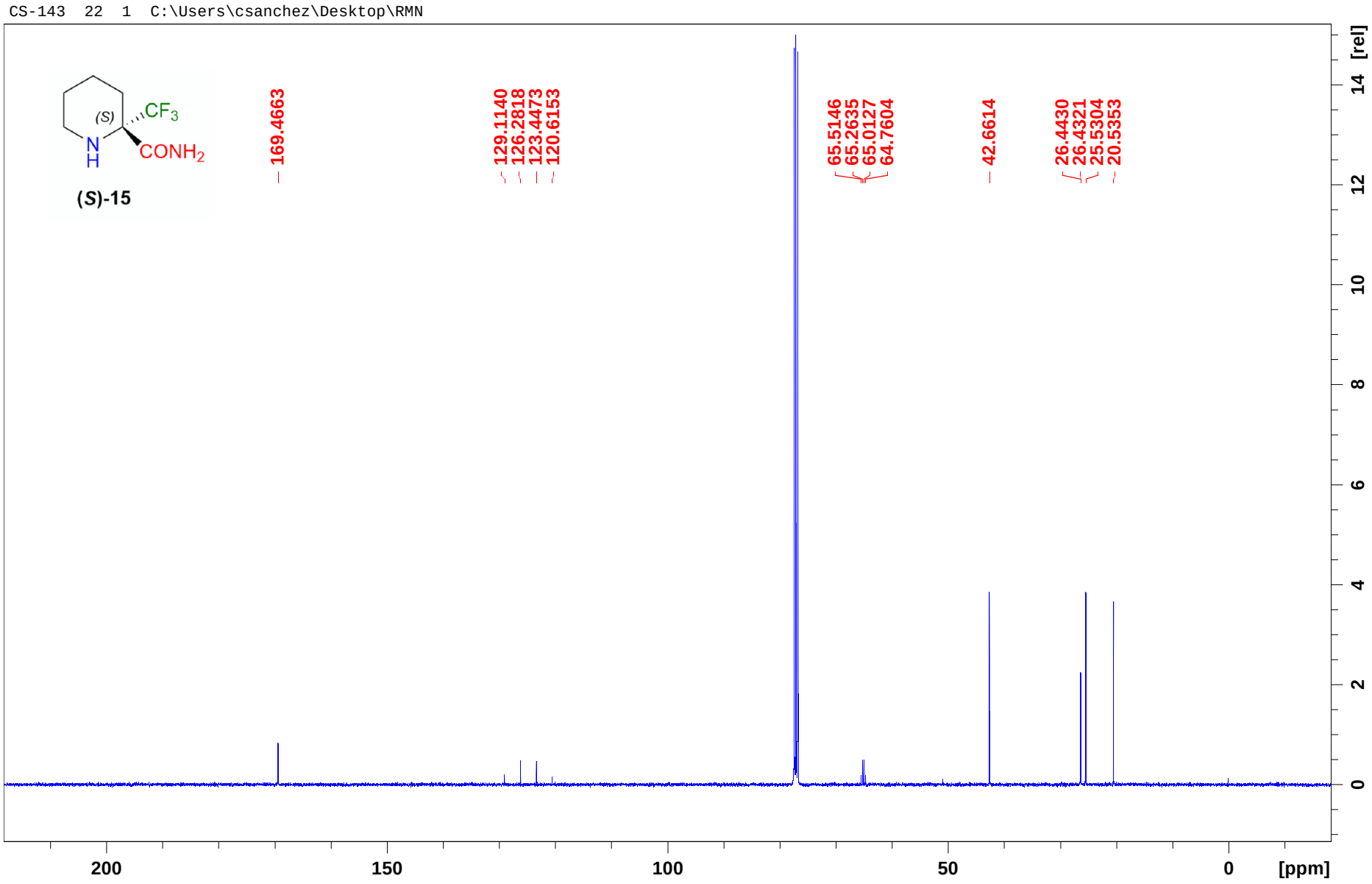

CF3
CO2H
N
H
(S)-14 α-Tfm-Proline
abundance
3.0
2.0
1.0
0
−60.0
−70.0
−80.0
−90.0
−100.0
−110.0
−120.0
−130.0
−140.0
−150.0
−160.0
−170.0
−76.0044
X : parts per Million : 19F


CS-142 20 1 C:\Users\csanchez\Desktop\RMN
7.1704
6.0270
3.4787
3.0485
3.0145
2.7439
2.7370
2.7084
2.6806
2.6738
2.4309
2.4227
2.4156
2.3992
2.3902
1.8154
1.8043
1.7837
1.5935
1.5844
1.5763
1.5625
1.5538
1.5450
1.5422
1.5308
1.5250
1.5215
1.5154
1.4853
1.4536
1.3454
1.3145
(R)
CONH2
CF3
N
H
(R)-15
1.1471
0.9457
1.0000
0.9967
1.0000
2.1866
4.3481
6
4
2
[ppm]
[rel]
0
10
20
30

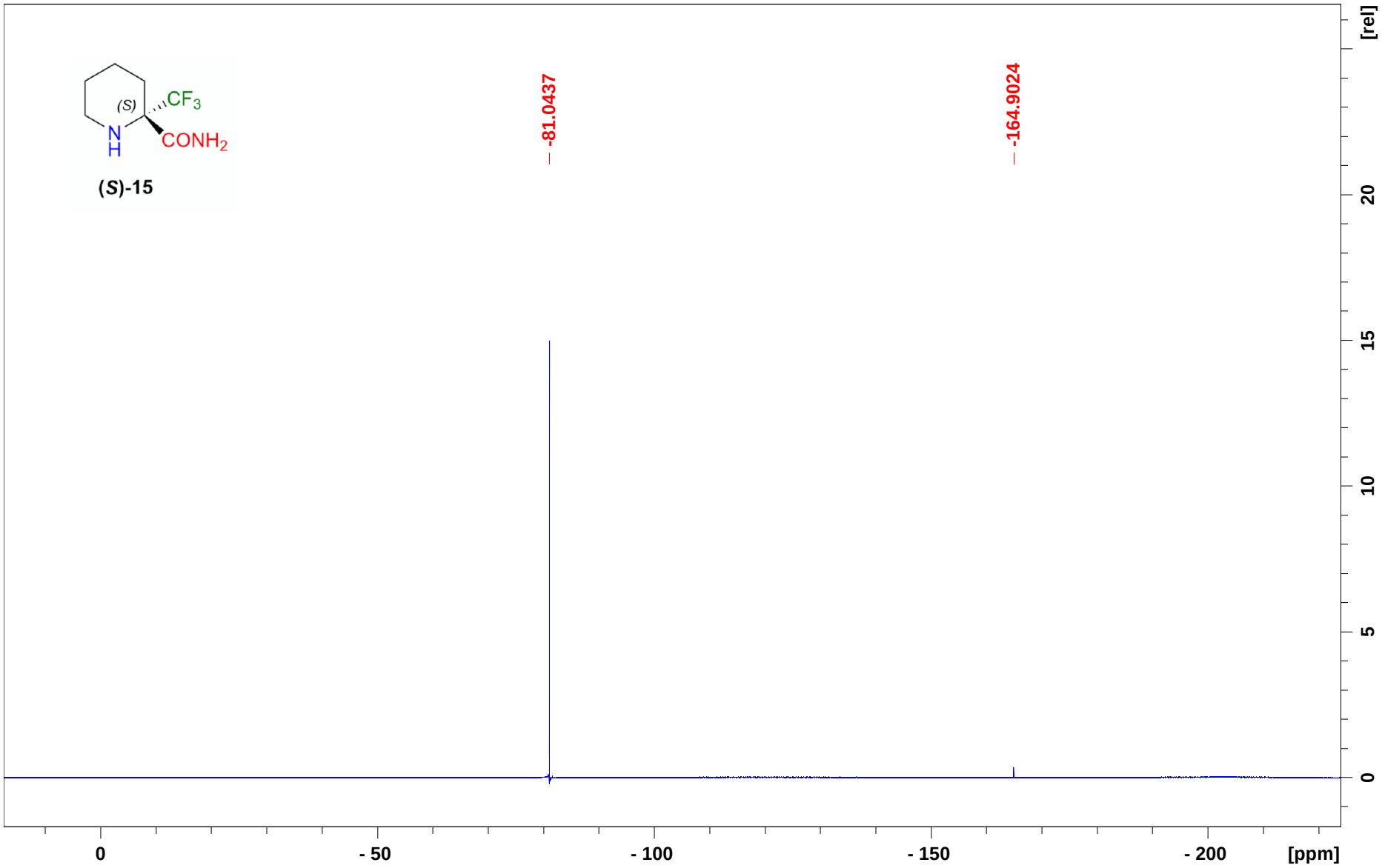

CS-142 22 1 C:\Users\csanchez\Desktop\RMN
(R)
CONH2
N
H
CF3
(R)-15
169.5226
129.1128
126.2807
123.4487
120.6145
65.5043
65.2544
65.0032
64.7508
42.6490
26.4388
25.5162
20.5278
[rel]
0
2
4
6
8
10
12
200
150
100
50
0
[ppm]

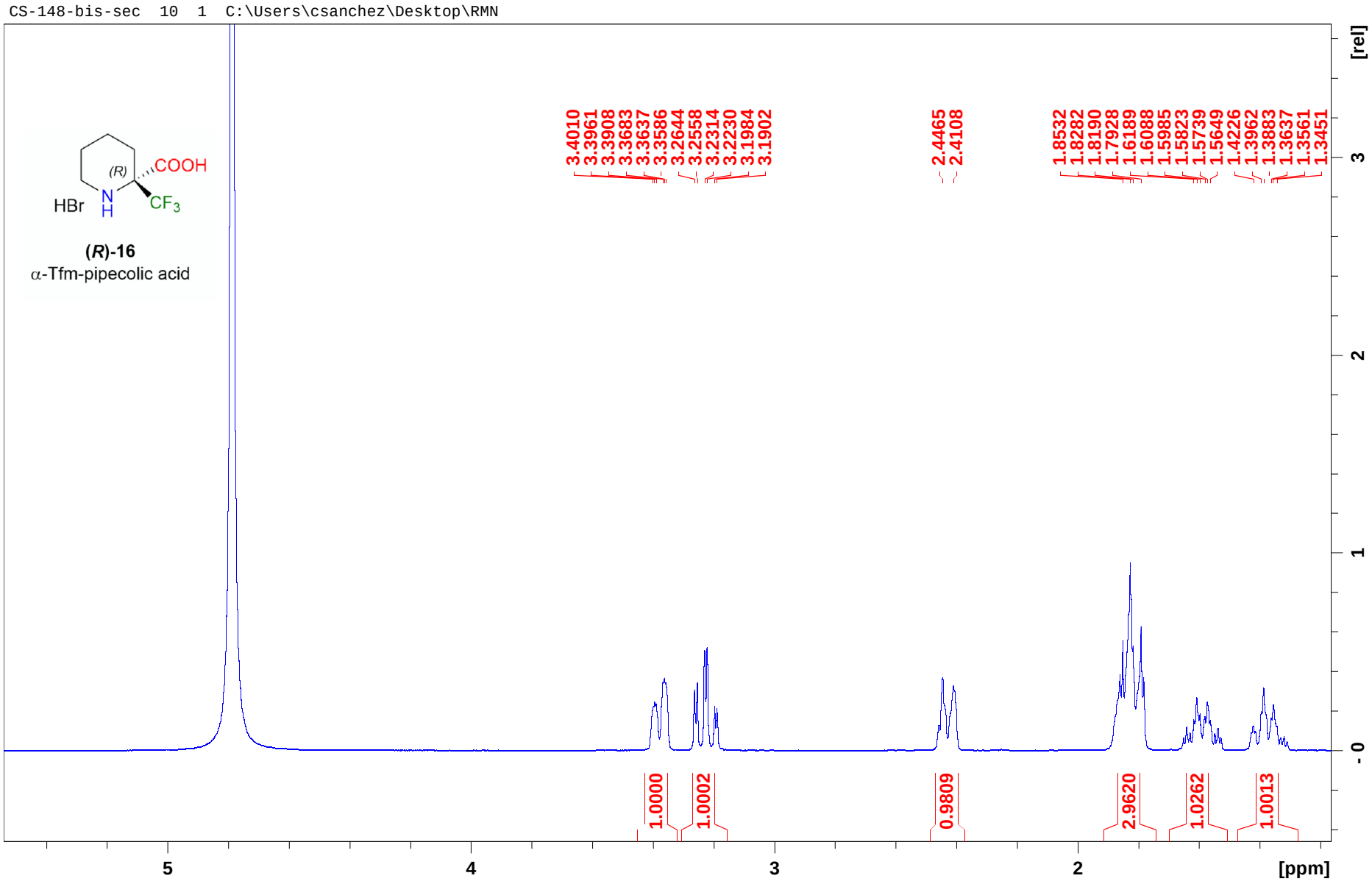

CS-142 21 1 C:\Users\csanchez\Desktop\RMN
(R)
CONH2
N
H
CF3
(R)-15
-81.0368
-164.9081
[rel]
25
20
15
10
5
0
0
- 50
- 100
- 150
- 200
[ppm]


CS-143 20 1 C:\Users\csanchez\Desktop\RMN
(S)
CF3
CONH2
N
H
(S)-15
7.1678
5.9545
3.0509
3.0169
2.7441
2.7387
2.7097
2.6811
2.6756
2.4354
2.4272
2.4198
2.4037
2.3947
1.8181
1.8064
1.7867
1.5939
1.5858
1.5627
1.5543
1.5310
1.5220
1.4946
1.4876
1.4639
1.4559
1.4482
1.4250
1.4171
1.3754
1.3563
1.3463
1.3373
1.3249
1.3155
[rel]
0
5
10
15
20
25
0.1003
0.0811
0.0055
0.0101
0.0819
0.0830
0.0833
0.5428
0.0121
8
6
4
2
0
[ppm]

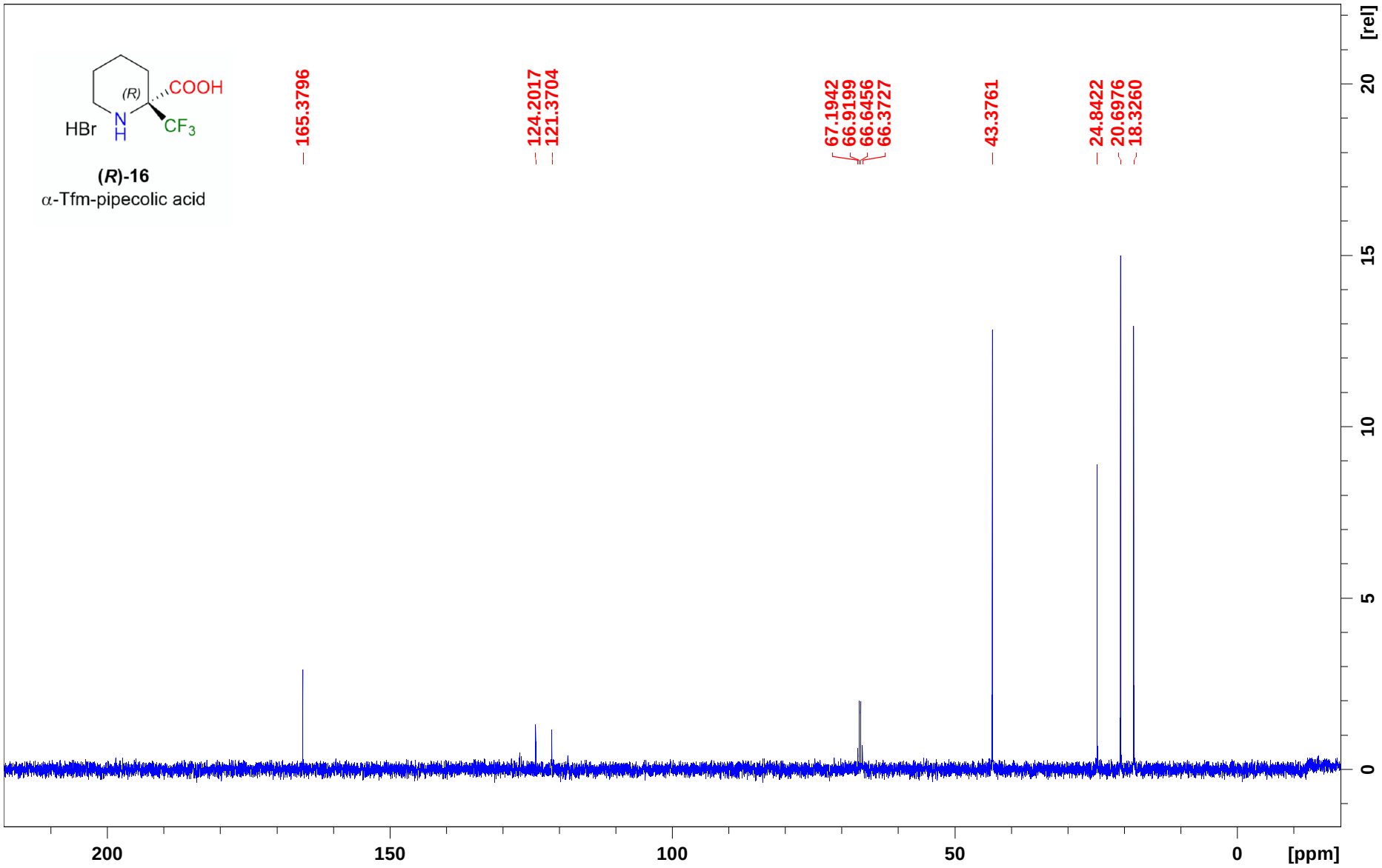

CS-143 22 1 C:\Users\csanchez\Desktop\RMN
(S)
CF3
CONH2
N
H
(S)-15
169.4663
129.1140
126.2818
123.4473
120.6153
65.5146
65.2635
65.0127
64.7604
42.6614
26.4430
26.4321
25.5304
20.5353
14 [rel]
12
10
8
6
4
2
0
200
150
100
50
0
[ppm]

CS-143 21 1 C:\Users\csanchez\Desktop\RMN

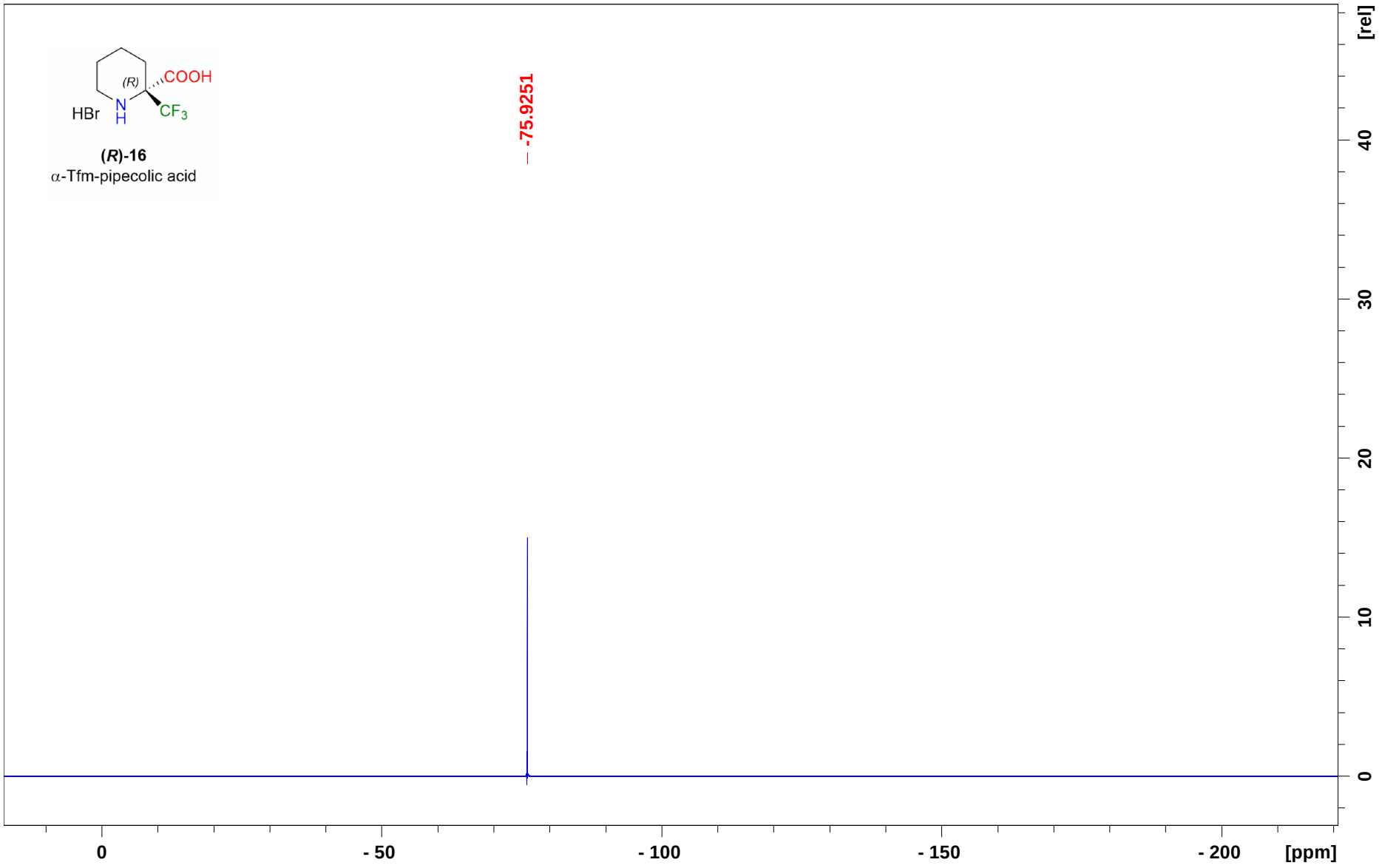



CS-148-bis-sec 10 1 C:\Users\csanchez\Desktop\RMN
(R)
COOH
HBr
N
H
CF3
(R)-16
α-Tfm-pipecolic acid
3.4010
3.3961
3.3908
3.3683
3.3637
3.3586
3.2644
3.2558
3.2314
3.2230
3.1984
3.1902
2.4465
2.4108
1.8532
1.8282
1.8190
1.7928
1.6189
1.6088
1.5985
1.5823
1.5739
1.5649
1.4226
1.3962
1.3883
1.3637
1.3561
1.3451
1.0000
1.0002
0.9809
2.9620
1.0262
1.0013
[rel]
[ppm]

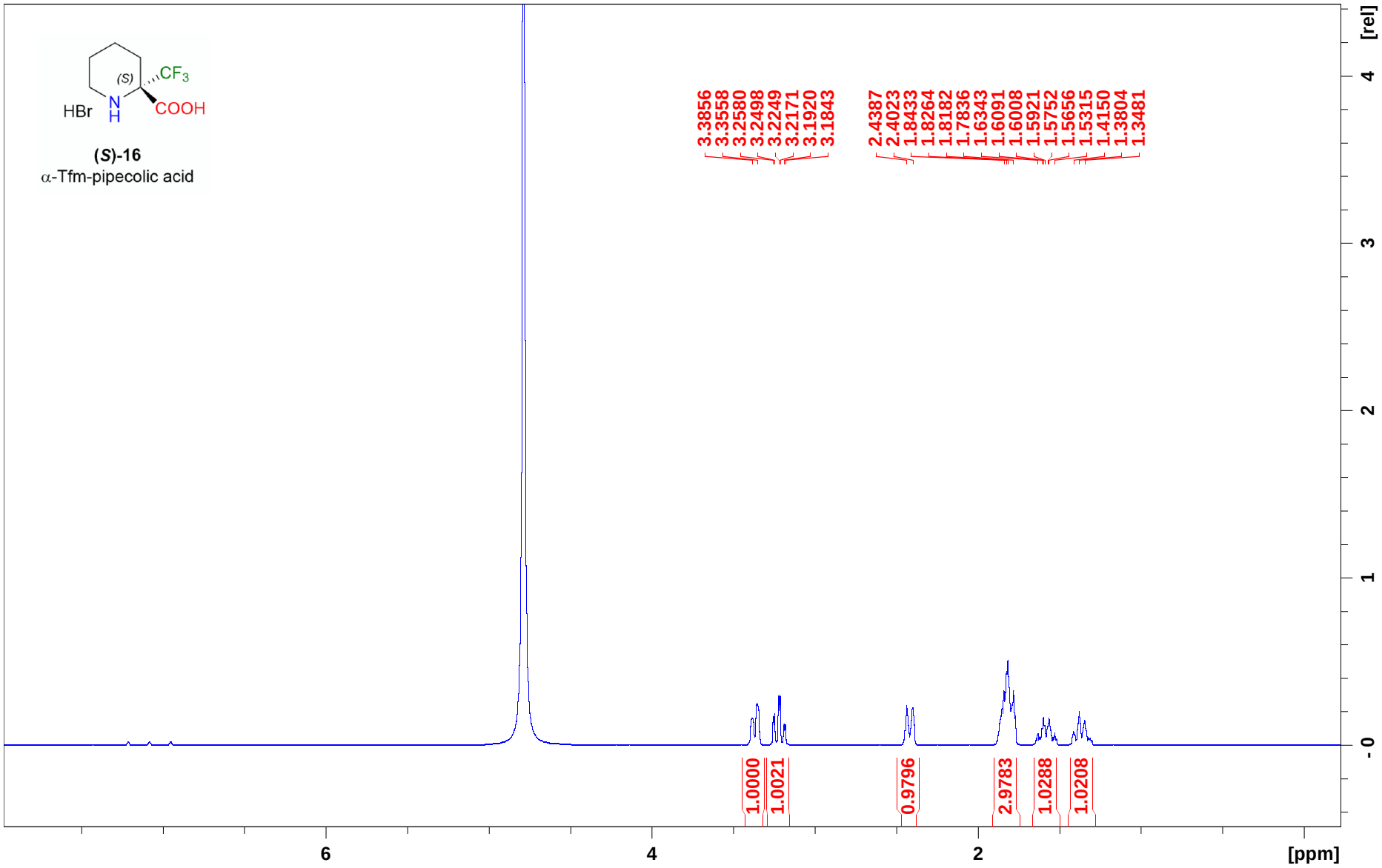
CS-148-bis-sec 12 1 C:\Users\csanchez\Desktop\RMN



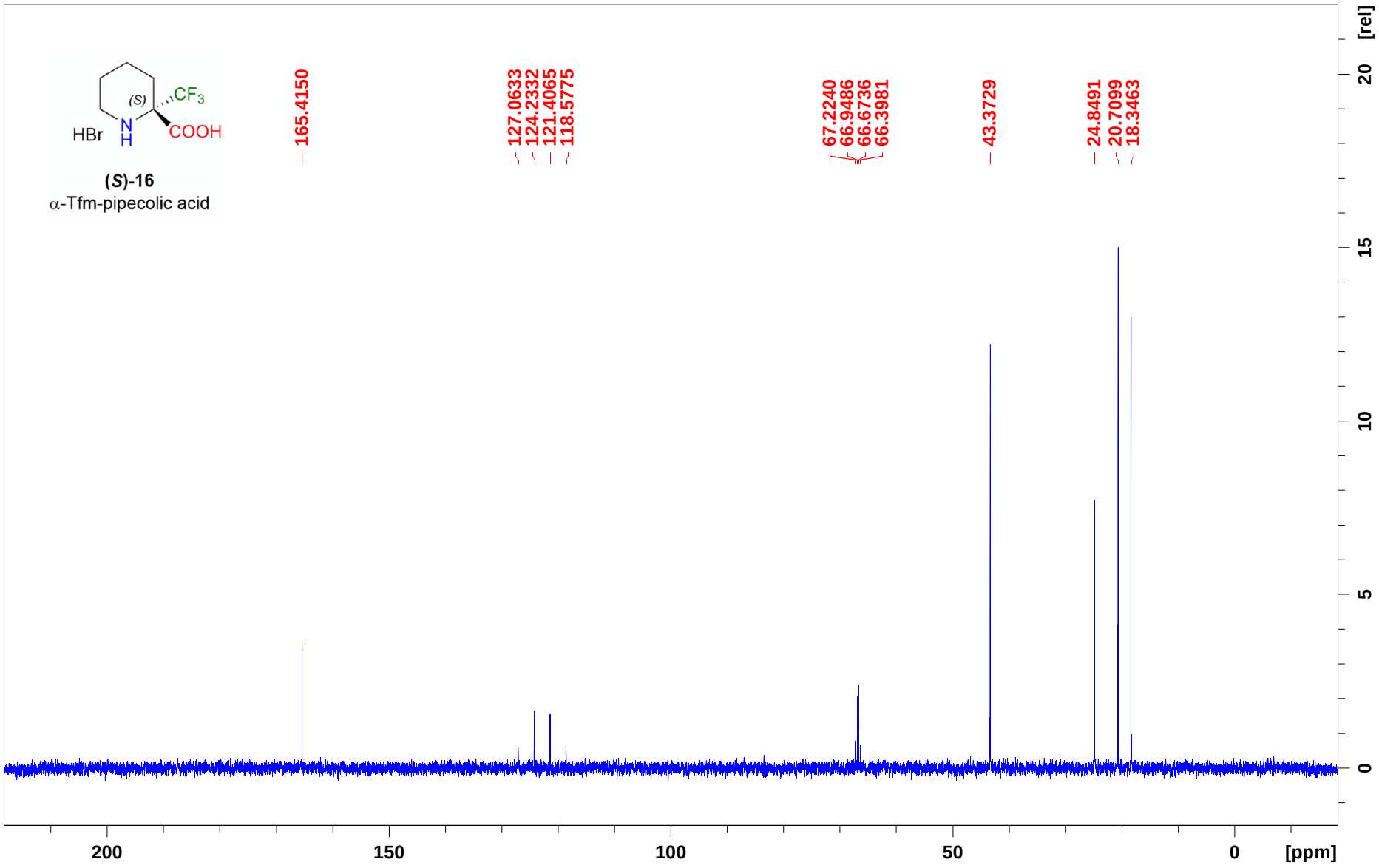
CS-148-bis-sec 11 1 C:\Users\csanchez\Desktop\RMN



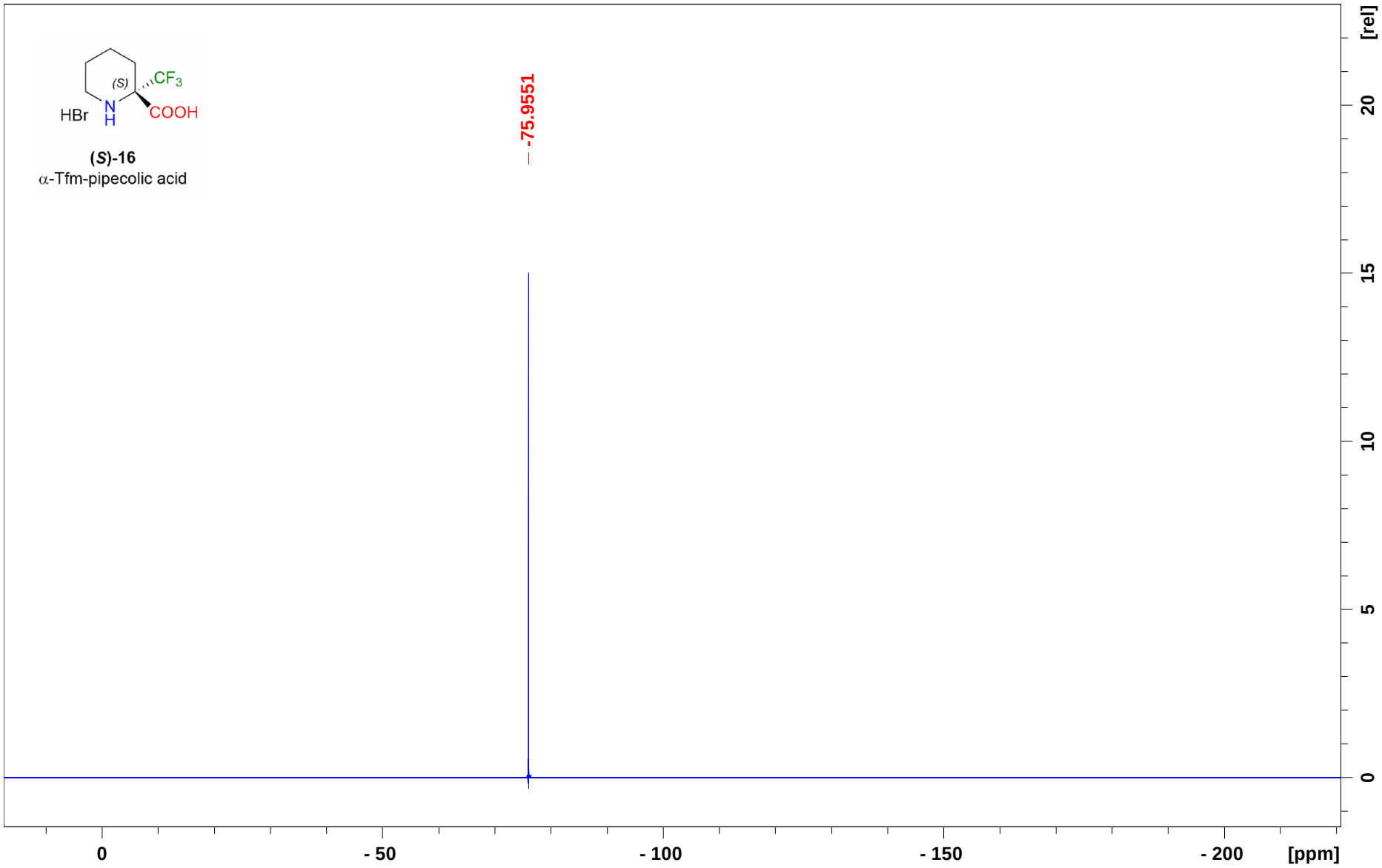
CS-149-bis-sec 10 1 C:\Users\csanchez\Desktop\RMN



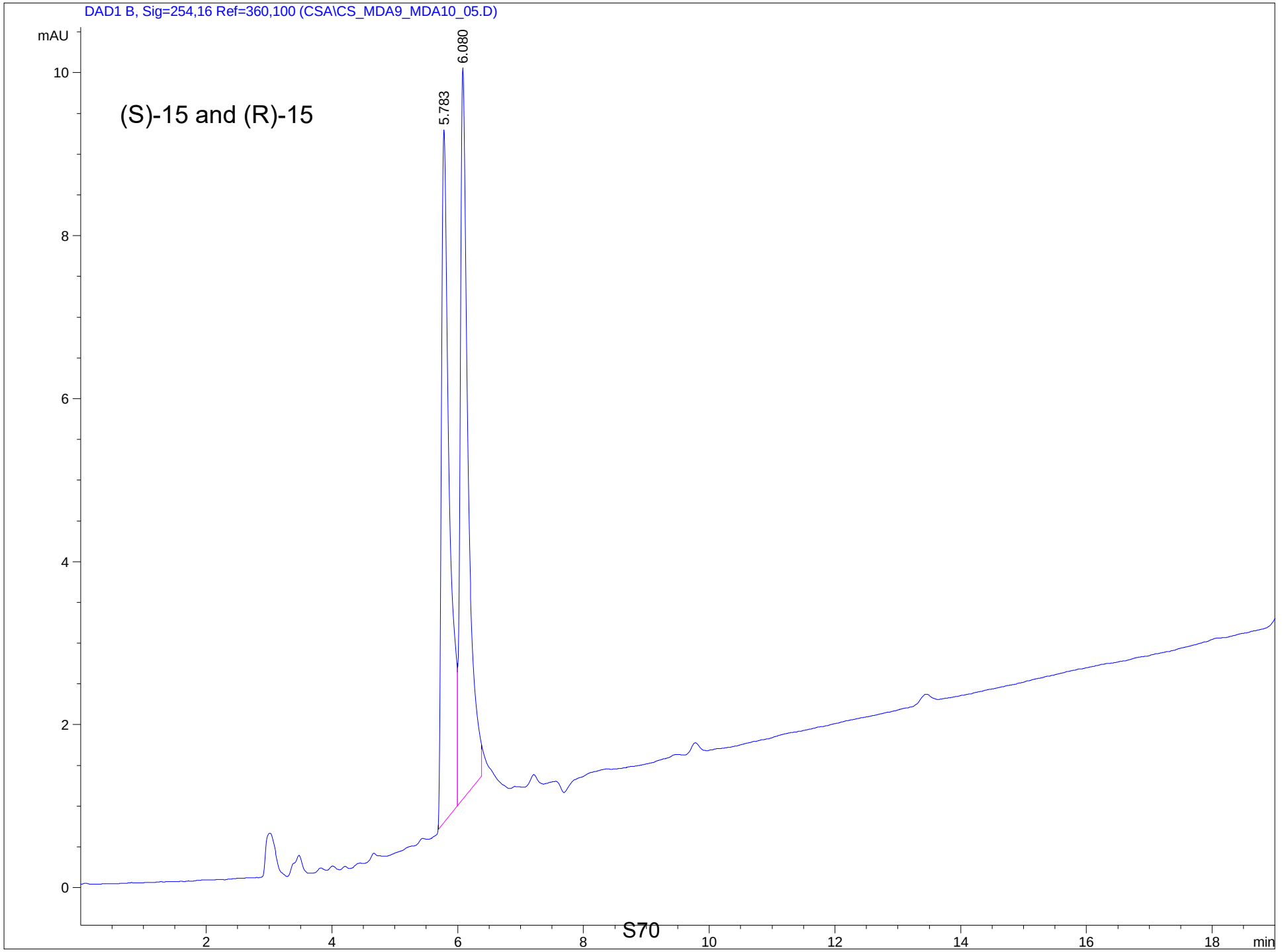
CS-149-bis-sec 12 1 C:\Users\csanchez\Desktop\RMN



CS-149-bis-sec 11 1 C:\Users\csanchez\Desktop\RMN



Current Chromatogram(s)



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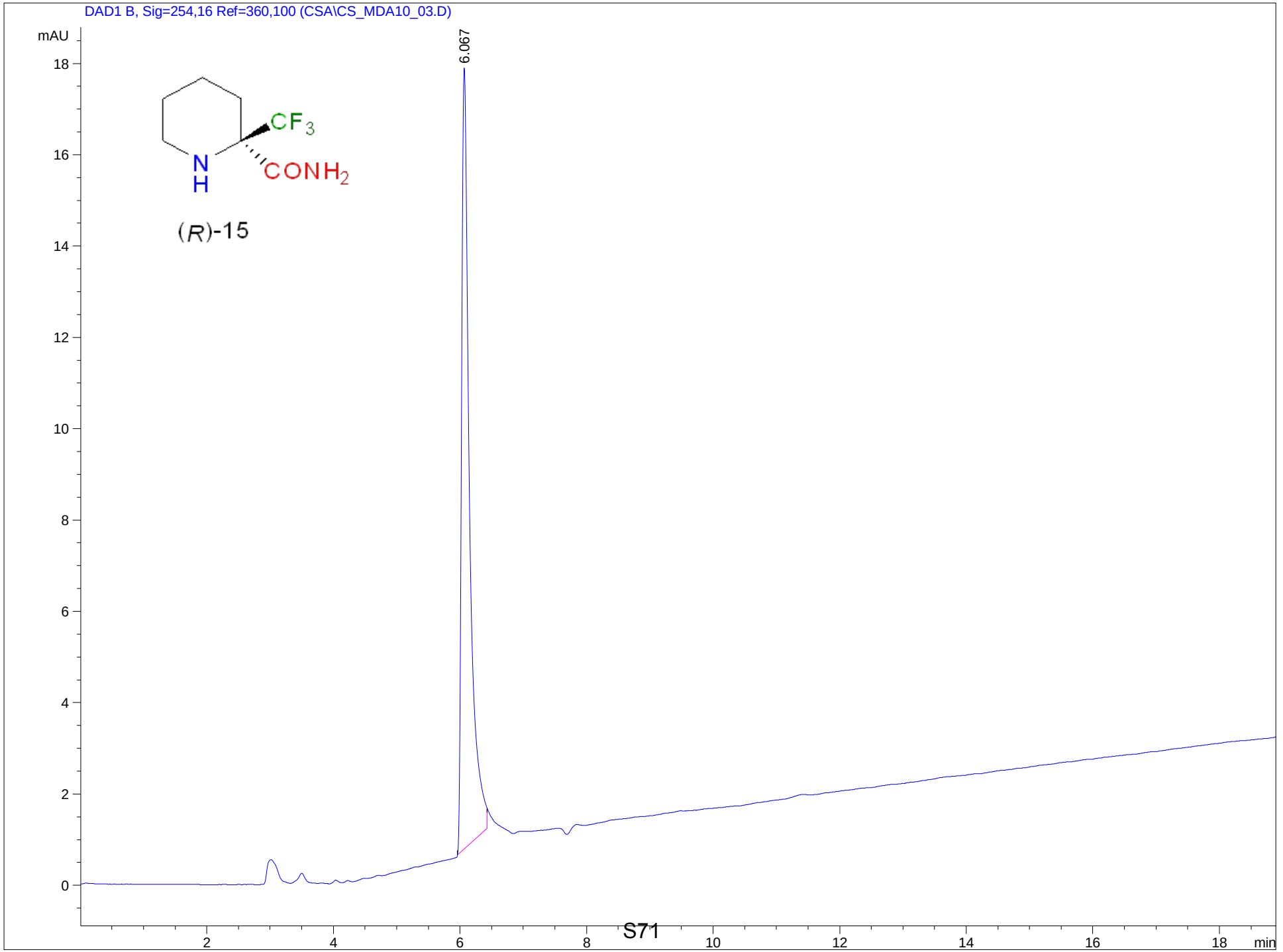
Current Chromatogram(s)



Current Chromatogram(s)