Enantiopure α-Trifluoromethylated Aziridine-2-Carboxylic Acid (α-TfmAzy) : Synthesis and Peptide Coupling

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Supporting Information

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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. Microwave irradiated reactions were Performed on a CEM Discover S. Class apparatus in sealed reaction vessels (10 or 35 mL) using the dynamic control mode. This mode applies a specified amount of power, defined by the user, to reach the temperature control point. It modulates this set power automatically, based on the Infrared sensor feedback data, to ensure the control point is reached rapidly, but with limited error. ^{1}H NMR (400.0 MHz), ^{13}C NMR (100.5 MHz) and ^{19}F (376.2 MHz) were measured on a JOEL EXC400 spectrometer. Chemical shifts of ^{1}H 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 BRUCKER TENSOR 27, wave numbers are given in cm^{-1}. Optical rotations were determined using a Anton Paar MCP 200 polarimeter. HRMS analyses were performed by either the IMAGIF/ICSN-CNRS or

IRCGN/DCPC Dpt or BIOCIS laboratory. Melting Points were measured on a Büchi apparatus and uncorrected.

The compounds **(*R*)-2** and **(*S*)-2** were prepared using a previously described procedure.[1]

(*R*)-2-benzylamino-2-trifluoromethyl-3-hydroxybenzylpropanoate (*R*)-5 and

(*R*)-2-amino-2-trifluoromethyl-3-hydroxybenzylpropanoate (*R*)-5'

To a solution of **(*R*)-2** (0.410 g, 1.9 mmol, 1 equiv) in DMF (5 mL) was added $PhCH_2Br$ (0.46 mL, 3.9 mmol, 2 equiv) and K_2CO_3 (0.538 g, 3.9 mmol, 2 equiv). The resulting mixture was stirred at room temperature for 2 hours (TLC and ^{19}F NMR monitoring) and quenched with water (30 mL). The organic layer was separated and the resulting aqueous phase was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient 90:10 to 70:30 cyclohexane/ethyl acetate) to give **(*R*)-5** (0.401 g, 58 %) and **(*R*)-5'** (0.120 g, 23%). **(*R*)-5**: white solid; mp 113°C; R_f = 0.53 (80:20 cyclohexane/ethyl acetate); $[\alpha]_D$ +3.3 (c 0.5, $CHCl_3$); IR (neat) 3450, 3316, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (bs, 2H), 3.78 (d, *J* = 12.1 Hz, 1H), 3.85 (d, *J* = 12.1 Hz, 1H), 3.98 (d, *J* = 11.5 Hz, 1H), 4.09 (d, *J* = 11.5 Hz, 1H), 5.29 (s, 2H), 7.25-7.37 (m, 10H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 47.9, 61.0, 68.3, 69.4 (q, *J* = 24.9 Hz), 123.5 (q, *J* = 287.5 Hz), 127.6, 128.2, 128.3, 128.6, 128.7, 134.5, 138.6, 167.5; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -73.9 (s). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{19}F_3NO_3$ 354.1317; found 354.1303. **(*R*)-5'**: yellow oil; R_f = 0.27 (60:40 cyclohexane/ethyl acetate); $[\alpha]_D$ + 52.9 (c 1.0, $CHCl_3$); IR (neat): 3365, 3310, 3174, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.55 (bs, 3H), 3.73 (d, *J* = 11.2 Hz, 1H), 4.11 (d, *J* = 11.2 Hz, 1H), 5.26 (s, 2H), 7.32-7.39 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 62.3, 65.8 (q, *J* = 25.9 Hz), 68.4, 123.9 (q, *J* = 285.6 Hz), 127.9, 128.6, 134.5, 167.7; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -78.7 (s). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{13}F_3NO_3$ 264.0848; found 264.0838.

(*S*)-2-benzylamino-2-trifluoromethyl-3-hydroxybenzylpropanoate (*S*)-5 and (*S*)-2-amino-2-trifluoromethyl-3-hydroxybenzylpropanoate (*S*)-5'

(*S*)-5 (0.380 g, 56%) and **(*S*)-5'** (0.150 g, 30%) were obtained from **(*S*)-2** (0.402 g, 1.9 mmol) following the procedure used for (*R*)-5. **(*S*)-5**: $[\alpha]_D$ −3.1 (c 0.5, $CHCl_3$); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{19}F_3NO_3$ 354.1317; found 354.1311. **(*S*)-5'**: $[\alpha]_D$ −51.8 (c 1.0, $CHCl_3$); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{13}F_3NO_3$ 264.0848; found 264.0851. The other spectroscopic data of **(*S*)-5** and **(*S*)-5'** were similar to those of **(*R*)-5** and **(*R*)-5'** respectively.

(*R*)-2-benzylamino-2-trifluoromethyl-3-methylsulfonylbenzylpropanoate (*R*)-6

Methanesulfonyl chloride (0.09 mL, 1.2 mmol, 2 equiv) was slowly added at 0°C to a stirred solution of **(*R*)-5** (0.216 g, 0.61 mmol, 1 equiv) and triethylamine (0.33 mL, 2.4 mmol, 4 equiv) in CH_2Cl_2 (10 mL). The resulting mixture was warmed up to room temperature and stirred for 30 min (TLC and ^{19}F NMR monitoring). After complete consumption of starting material, the solution was quenched with saturated NH_4Cl aqueous solution (50 mL). The organic layer was separated and the resulting aqueous phase is extracted using CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was

[1] Simon, J.; Nguyen, T. T.; Chelain, E.; Lensen, N.; Pytkowicz, J.; Chaume, G.; Brigaud, T. *Tetrahedron: Asymmetry* **2011**, *22*, 309–314.

purified by silica gel chromatography (gradient 90:10 to 70:30 cyclohexane/ethyl acetate) to give **(*R*)-6** (0.209 g, 79%) as a pure isolated compound. **(*R*)-6**: Colorless oil; *Rf* = 0.55 (80:20 cyclohexane/ethyl acetate); $[\alpha]_D$ +10.6 (c 0.5, $CHCl_3$); IR (neat): 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.90 (s, 3H), 3.79 (d, *J* = 12.2 Hz, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 4.65 (s, 2H), 5.26 (d_{AB}, *J*=13.2 Hz, 1H), 5.33 (d_{AB}, *J* = 13.2 Hz, 1H), 7.25-7.38 (m, 10H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 37.6, 47.6, 65.5, 68.0 (q, *J* = 25.9 Hz), 68.8, 123.5 (q, *J* = 278.5 Hz), 127.5, 128.3, 128.5, 128.6, 128.7, 128.9, 134.3, 138.5, 165.6; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -74.3 (s); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}F_3NO_5S$ 432.1092; found 432.1082.

(*S*)-2-benzylamino-2-trifluoromethyl-3-methylsulfonylbenzylpropanoate (*S*)-6

(*S*)-6 (0.200 g, 82%) was obtained from (*S*)-5 (0.200 g, 0.57 mmol) following the procedure used for (*R*)-8. **(*S*)-6**: $[\alpha]_D$ -9.6 (c 0.5, $CHCl_3$); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}F_3NSO_2$ 432.1092; found 432.1083. The other spectroscopic data of **(*S*)-6** were similar to those of **(*R*)-6**.

(*R*)-*N*-benzyl-2-benzyloxycarbonyl-2-trifluoromethylaziridine (*R*)-7

To a solution of (*R*)-**6**-(0.100 g, 0.23 mmol, 1 equiv) in CH_3CN (10 mL) was added benzylamine (0.08 mL, 0.42 mmol, 2 equiv) and the reaction mixture was stirred at room temperature for 15 min. Then the mixture was stirred under microwave irradiation (140 W) at 80°C. After 15 min the reaction mixture was washed with saturated brine (20 mL), organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give **(*R*)-7** (0.060 g, 78%) as colorless oil. **(*R*)-7**: *Rf* = 0.90 (90:10 cyclohexane/ethyl acetate); $[\alpha]_D$ +14.3 (c 0.5, $CHCl_3$); IR (neat): 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (bs, 1H), 2.48 (bs, 1H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.89 (d, *J* = 13.3 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 7.16-7.45 (m, 10H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 37.7, 44.2 (q, *J* = 24.0 Hz), 55.7, 67.9, 122.7 (q, *J* = 278.3 Hz), 127.5, 127.8, 128.1, 128.3, 128.4, 128.7, 134.6, 137.2, 163.9; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ -73.7 (s); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_2$ 336.1211; found 336.1205.

(*S*)-*N*-benzyl-2-benzyloxycarbonyl-2-trifluoromethylaziridine (*S*)-7

(*S*)-7 (0.055 g, 79%) was obtained from (*S*)-6 (0.090 g, 0.21 mmol) following the procedure used for (*R*)-7. **(*S*)-7**: $[\alpha]_D$ −13.8 (c 0.5, $CHCl_3$); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_2$ 336.1211; found 336.1208. The other spectroscopic data of **(*S*)-7** were similar to those of **(*R*)-7**.

The compound **8** was prepared using a previously described procedure.[2]

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

To a 70:30 dr mixture of oxazolidine **8** (2.0 g, 8.10 mmol, 1.0 equiv) in dichloromethane (20 mL) under argon atmosphere at 0° C was added Et_3N (4.5 mL, 32.4 mmol, 4.0 equiv) and MsCl (1.26 mL, 16.2 mmol, 2 equiv). The reaction was stirred for 1 hour at room temperature, and then quenched with water (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2×30 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. After filtration through a short pad of silica gel, the *O*-mesylated oxazolidinone **4** (2.596 g, 98%) was obtained in good yield as a yellow oil (63:37 diastereoismeric mixture). **4**: *Rf* = 0.45 (70:30 cyclohexane/ethyl acetate); IR (neat): 3300 cm^{-1}

[2] Simon, J.; Chelain, E.; Brigaud, T. *Org. Lett.* **2012**, *14*, 604–607.

(*majo*)-4 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.68 (s, 1H), 3.82 (t, *J* = 8.5 Hz, 1H), 4.42 (t, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.60 (dd, *J* = 7.3, 8.5 Hz, 1H), 7.30-7.43 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 38.0, 62.0, 66.9, 74.8, 94.1 (q, *J* = 29.7 Hz), 123.7 (q, *J* = 288.5 Hz), 127.0, 128.7, 129.2, 137.2; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ: -83.9 (s).

(*mino*)-4: ^{1}H NMR (400 MHz, $CDCl_3$) δ : 3.14 (s, 3H), 3.68 (s, 1H), 3.82 (t, *J* = 8.3 Hz, 1H), 4.42 (t, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.70 (dd, *J* = 7.3, 8.5 Hz, 1H), 7.30-7.43 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 31.6, 61.2, 67.5, 75.5, 92.9 (q, *J* = 33.5 Hz), 123.8 (q, *J* = 287.5 Hz), 126.9, 128.3, 128.7, 138.0; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ -84.2 (s); HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{15}F_3NO_4S$ 326.0674; Found 326.0675.

(2R)-2-phenyl-5-trifluoromethyl-1-aza-4-oxa-bicyclo[3.1.0] hexane (9)

To a solution of *O*-mesylated oxazolidine **4** (0.100 g, 0.307 mmol, 1 equiv) in CH_3CN (10 mL) was added benzylamine (0.067 mL, 0.614 mmol, 2 equiv) and the reaction mixture was stirred at room temperature for 15 min. Then the mixture was stirred under microwave irradiation (140 W) at 80°C. After 20 min the reaction mixture was washed with saturated brine (20 mL), organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give **9** as a 70/30 mixture of 2 diastereoisomers (64 mg, 91% yield). An analytical fraction of each diastereoisomer was isolated for characterization. **(*majo*)-9** : White solid; mp 48°C; *Rf*= 0.36 (80:20 cyclohexane/ethylacetate); $[\alpha]_{21}^{D}$ = +59 (c 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22 (d, *J* = 1.7 Hz,1H), 2.24 (d, *J* = 1.7 Hz, 1H), 3.73 (t, *J* = 9.9, 1H), 4.63 (dd, *J* = 9.9, 8.0 Hz, 1H), 4.72 (dd, *J* = 9.9, 8.0 Hz, 1H), 7.30-7.35 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 28.4, 63.8, 69.5, 79.8 (q, *J* = 41.2 Hz), 121.1 (q, *J* = 274.1), 126.7, 128.0, 128.8, 136.1; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ: -79.6 (s). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{11}H_{10}F_3NO$ 229.0714; Found 229.0710. **(*mino*)-9**: Yellow oil; *Rf*= 0.33 (80:20 cyclohexane/ethyl acetate); $[\alpha]_{21}^{D}$ = −39.2 (c 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (d, *J* = 2.1 Hz, 1H), 2.42 (d, *J* = 2.1 Hz, 1H), 4.29-4.38 (m, 3H), 7.30-7.40 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.4, 63.8, 69.5, 80.7 (q, *J* = 41.2 Hz), 122.3 (q, *J* = 275.1 Hz), 126.7, 128.0, 128.8, 136.2; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ -78.9 (s). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{11}H_{10}F_3NO$ 229.0714; Found 229.0719.

3-methylsulfonyl-2-trifluoro-2-[(1*R*)-2-hydroxy-1-phenylamino]propanenitrile (*R*,*R*)- and (*R*,*S*)-10

To a 70:30 dr mixture of *O*-Mesylated oxazolidine **4** (10.721 g, 32.95 mmol, 1 equiv) in dichloromethane (50 mL) at 0°C under an argon atmosphere were successively added TMSCN (8.2 mL, 65.91 mmol, 2 equiv) and $BF_3.OEt_2$ (8.1 mL, 65.91 mmol, 2 equiv). The corresponding mixture was stirred at room temperature for 30 min. The reaction mixture was stirred at room temperature over 3 hours, poured into a saturated $NaHCO_3$ aqueous solution (200 mL) and stirred vigorously for 1 hour. The layers were separated and the aqueous layer was extracted with dichloromethane (2×100 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A fraction of the crude material (2.0 g) was then purified by silica gel chromatography with an elution gradient (80:20 and 70/30 cyclohexane/ethyl acetate) gave 0.530 g (27%) of a pure fraction of the **(*R*,*S*)-10** 0.480 g (24%) of mixture of both diastereoisomer and 0.705 mg (36%) of a pure fraction of the major diastereoisomer **(*R*,*R*)-10**. **(*R*,*S*)-10**: yellow oil; *Rf* = 0.14 (70:30 cyclohexane/ethyl acetate); $[\alpha]_{21}^{D}$= −86.5 (c 1.4, $CHCl_3$); IR (neat): 3573, 3345, 2356 cm^{-}

[1]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (br s, 1H), 2.92 (s,3H), 3.02 (br s,1H), 3.52 (dd, *J* = 11.5 Hz, 9.2 Hz, 1H), 3.77 (dd, *J* = 11.5, 5.7 Hz, 1H), 4.18 (dd, *J* = 9.2, 5.7 Hz, 1H), 4.18 (m, 2H), 7.32-7.41 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 37.7, 61.5, 62.7 (q, *J* = 29.5 Hz), 65.7, 66.7, 112.6, 122.1 (q, *J* = 287.3 Hz), 127.1, 128.6, 128.9, 138.9; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ -78.0 (s). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}F_3N_2O_4S$ 353.0783; Found 353.0787. **(*R*,*R*)-10**: White solid; mp 125°C; *Rf* = 0.19 (70:30 cyclohexane/ethyl acetate); $[\alpha]_{21}^{D}$= -5.98 (c 0.5, $CHCl_3$); IR (neat): 3573, 3345, 2361 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (br s, 1H), 2.90 (s, 3H), 3.02 (br s,1H), 3.48-3.58 (m, 1H), 3.75-3.82 (m, 1H), 4.18-4.73 (m, 3H), 7.34-7.42 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 38.4, 61.8, 66.2, 67.1, 62.5 (q, *J* = 29.1 Hz), 112.8, 121.9 (q, *J* = 286.6Hz), 127.1, 128.1, 128.7, 139.1; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ -77.4 (s, 3F, CF_3). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}F_3N_2O_4S$ 353.0783; Found 353.0778.

(2*S*)-*N*-((1*R*)-2-hydroxy-1-phenylethyl)-2-cyano-2-trifluoromethylaziridine (*R*,*S*)-11

To a solution of aminonitrile **(*R*,*R*)-10** (590 mg, 1.67 mmol, 1.0 equiv) in acetonitrile (15 mL) was added Et_3N (0.93 mL, 6.69 mmol, 4 equiv) at room temperature. The resulting mixture was warmed to reflux for 48 hours. The reaction was monitored by TLC (70:30 cyclohexane/ethyl acetate eluent). The reaction was cooled down to room temperature and concentrated under reduced pressure. The crude mixture was washed with a saturated solution of NH_4Cl (50 mL) and extracted with AcOEt (3×20 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was then purified by silica gel chromatography with an elution gradient (80:20 to 70:30 cyclohexane/ethyl acetate) to give **(*R*,*S*)-11** (0.393 g, 91%) as a pure isolated compound. **(*R*,*S*)-11**: White oil; R_f = 0.70 (80:20 cyclohexane/ethyl acetate); $[\alpha]_{20}^{D}$= −291.7 (c 0.5, $CHCl_3$); IR (neat): 3418, 2250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (br s, 1H, OH), 2.60 (s, 1H), 2.84 (s, 1H), 3.35 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.86 (dd, *J*=11.3, 4.3 Hz, 1H), 3.96 (dd, *J*=11.3, 7.8 Hz, 1H), 7.35-7.40 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 32.8 (q, *J* = 42.3 Hz), 39.2, 67.7 , 72.1, 112.5, 121.2 (q, *J* = 275.8 Hz); ^{19}F NMR (376.2 MHz, $CDCl_3$) δ -75.1 (s, 3F, CF_3). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{12}F_3N_2O$ 257.0902; Found 257.0909.

(*2R*,*6R*)-2-phenyl-6-trifluoromethyl-4-oxa-1-azabicyclo[4.1.0] heptan-5-one (*R*,*R*)-12

To a solution of aminonitrile **(*R*,*S*)-10** (0.663 g, 1.88 mmol, 1.0 equiv) in acetonitrile (15 mL) was added Et_3N (1.05 mL, 7.52 mmol, 4 equiv) at room temperature. The resulting mixture was warmed to reflux for 48 hours. The reaction was monitored by TLC (70:30 cyclohexane/ethyl acetate eluent). The reaction was cooled down to room temperature and concentrated under reduced pressure. The crude mixture was washed with a saturated solution of NH_4Cl (50 mL) and extracted with AcOEt (3×20 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was then purified by silica gel chromatography with an elution gradient (80:20 and 70:30 cyclohexane/ethyl acetate) to give **(*R*,*R*)-12** (0.347 g, 72%) as a pure isolated compound. White solid; mp 242°C; R_f=0.70 (80:20 cyclohexane/ethyl acetate); $[\alpha]_{20}^{D}$= −19.0 (c 1.0, $CHCl_3$); IR (neat): 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 1H,), 2.70 (s, 1H), 3.90 (dd, *J* = 6.7, 4.4 Hz, 1H), 4.41-4.48 (m, 2H), 7.37-7.47 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 35.8, 38.0 (q, *J* = 36.9 Hz), 61.9 , 70.7, 122.3 (q, *J* = 276.2 Hz), 127.1, 128.9, 129.1, 136.4, 162.2; ^{19}F

NMR (376.2 MHz, $CDCl_3$) δ -74.9 (s, 3F, CF_3). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{11}F_3NO_2$ 258.0742; Found 258.0743.

(2*S*)-*N*-((1*R*)-2-hydroxy-1-phenylethyl)-2-trifluoromethylaziridine-2-carboxylic acid (*R,S*)-13

To a solution of aziridine **(*R,S*)-11** (0.988 g, 3.85 mmol, 1.0 equiv) in a mixture of THF/H_2O (1/1) (15 mL), was added LiOH (0.185 g, 7.71 mmol, 2 equiv) at room temperature. The solution was stirred for 40 hours under reflux. The reaction was cooled to room temperature and the crude mixture was washed with a solution of HCl (1N) (20 mL) and extracted with AcOEt (2×50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the acid **(*R,S*)-13** (0.932 g, 88%) as a white solid directly engaged without further purification. **(*R,S*)-13**: White solid; mp 140°C; $[\alpha]_{20}^{D}$= −46.5 (c 0.7, H_2O); IR (neat): 3400,1714 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 2.67 (br s, 1H), 2.68 (br s, 1H), 3.69-3.88 (m, 3H), 7.26-7.38 (m, 5H); ^{13}C NMR (100.5 MHz, D_2O) δ 37.7, 45.0 (q, *J* = 33.8 Hz), 66.2, 67.5, 123.8 (q, *J* = 284.6 Hz), 127.9, 128.2, 128.5, 138.1, 167.2; ^{19}F NMR (376.2 MHz, D_2O) δ -73.7 (s, 3F, CF_3). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{13}F_3NO_3$ 276.0848; Found 276.0853.

(*2S*)-*N*-((*1R*)-2-hydroxy-1-phenylethyl)-2-((*3S*)-3-methyl-4-tert-butyloxycarbamide)-2-trifluoromethyl aziridine (*R,S,S*)-14

To a solution of aziridine carboxylic acid **(*R,S*)-13** (209 mg, 0.76 mmol, 1.0 equiv) in tetrahydrofurane (10 mL), were successively added L-alanine tert-butyl ester hydrochloride (0.276 g, 1.52 mmol, 2 equiv), Et_3N (0.32 mL, 2.28 mmol, 3 equiv) and after 15 minutes stirring at room temperature BOP-Cl (0.386 g, 1.52 mmol, 2 equiv). The reaction mixture was stirred overnight at room temperature, and then quenched with water (20 mL). The layers were separated and the aqueous phase was extracted with AcOEt (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was then purified by silica gel chromatography with an elution gradient (80:20 and 70:30 cyclohexane/ethyl acetate) to give **(*R,S,S*)-14** (244 mg, 80%) as a pure isolated compound. **(*R,S,S*)-14**: Viscous oil; R_f=0.70 (80:20 cyclohexane/ethyl acetate); $[\alpha]_{20}^{D}$= −97.1 (c 2.9, $CHCl_3$); IR (neat): 3429, 1733, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.0 Hz, 3H), 1.39 (br s, 9H), 1.64 (br s, 1H), 2.56 (s, 1H), 2.77 (s, 1H), 3.55 (m, 1H), 3.84 (d, *J* = 5.0 Hz, 2H), 4.14-4.22 (m, 1H), 6.20 (br s, 1H, NH), 7.28-7.36 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 17.6, 27.9, 36.1, 44.3 (q, *J* = 35.3 Hz), 49.4, 67.2, 68.1, 82.4, 123.9 (q, *J* = 282.7 Hz), 127.6, 128.0, 128.5, 139.1, 160.4, 170.9; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ -71.9 (s, 3F, CF_3). HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{26}F_3N_2O_4$ 403.1845; Found 403.1843.

(*2S*)-2-((*3S*)-3-methyl-4-tert-butyloxycarbamide)-2-trifluoromethyl aziridine (*S,S*)-15

To a solution of dipeptide **(*R,S,S*)-14** (0.186 g, 0.46 mmol, 1.0 equiv) in MeOH (5 mL) was added $Pd(OH)_2$ 10% (232 mg 0.5 equiv.). The resulting mixture was stirred under a 5 bars atmosphere of H_2 for 48 hours (TLC and ^{19}F RMN monitoring). After completion, the mixture was directly filtered off cotton and celite, the solvent was removed under reduced pressure and the resulting crude product was purified by silica gel chromatography (90:10 cyclohexane/ethyl acetate) to give **(*S,S*)-15** (0.066 g, 51%) as white solid. **(*S,S*)-15**: white solid; mp 90-92°C; $[\alpha]_{20}^{D}$= -47 (c 0.2, MeOH); IR (neat): 3284, 2980, 2930, 1734, 1658, 1520, 1370, 1147 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) (two rotamers 1/1) δ 1.31 (d, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 18H), 1.92 (brs, 1H), 2.11 (brs, 1H), 2.24 (brs, 1H), 2.40 (brs, 1H), 4.22 (q, *J* = 6.9 Hz, 1H), 4.31 (q, *J* = 6.9Hz, 1H); ^{13}C NMR (100.5 MHz, CD_3OD) (two rotamers 1/1) δ 17.2, 17.5, 28.1, 29.7, 40.3 (q, *J* = 33.5 Hz), 41.3 (q, *J* = 36.4 Hz), 49.9,

51.1, 83.0, 125.2 (q, J = 277.0 Hz), 165.7, 167.0, 172.7; ^{19}F NMR (376.2 MHz, CD_3OD) (two rotamers 1/1) δ -74.1 (s, 3F, CF_3), -74.8 (s, 3F, CF_3). HRMS (ESI) m/z: $[M+NH_4]^+$ calcd for $C_{11}H_{21}F_3N_3O_3$ 300.1535; Found 300.1535.

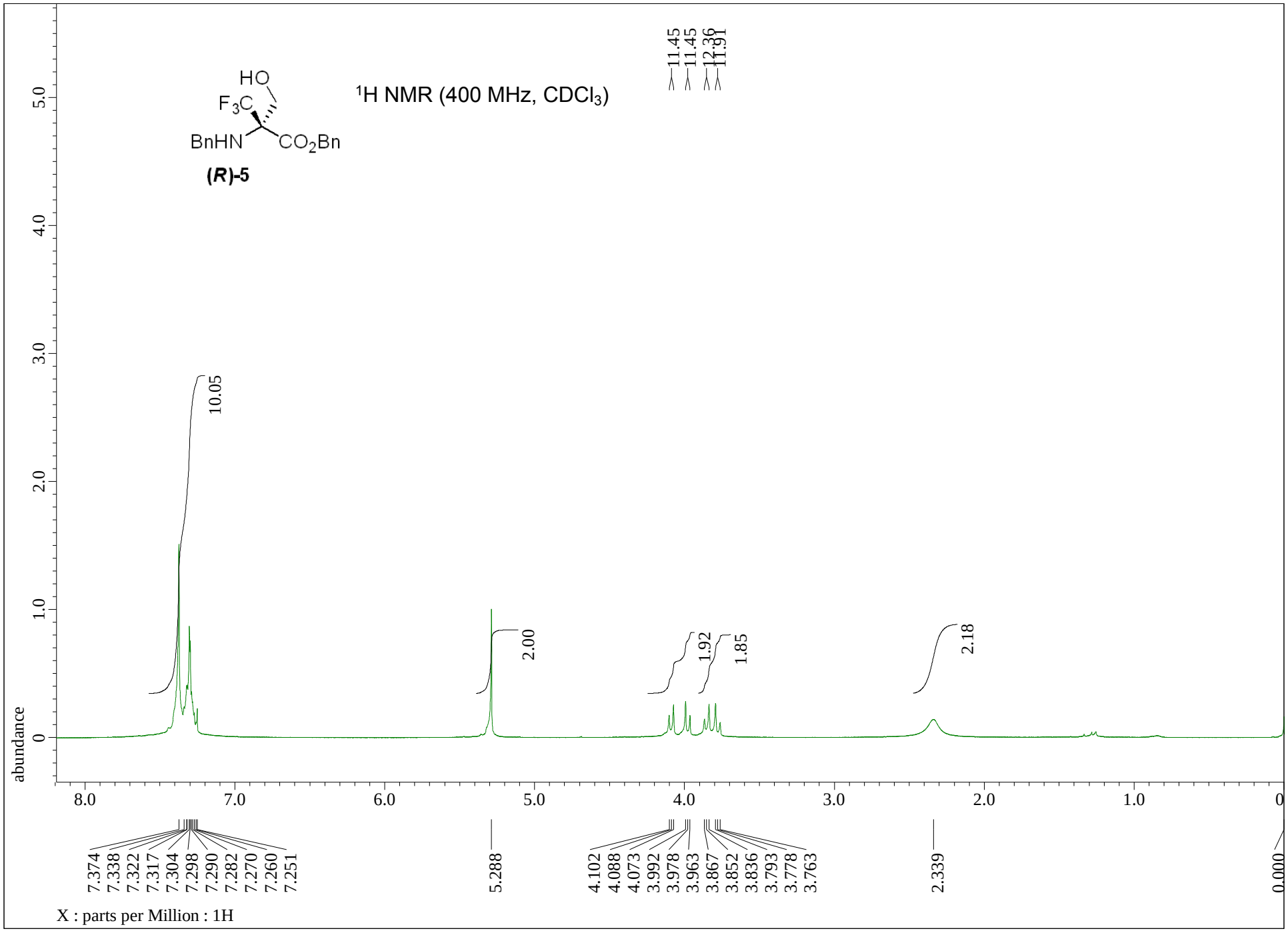
(*2S*)-*N*-Acetyl-2-((*3S*)-3-methyl-4-tert-butyloxycarbamide)-2-trifluoromethyl aziridine (*S,S*)-16

To a solution of dipeptide **(*S,S*)-15** (0.044 g, 0.16 mmol, 1.0 equiv) was added acetic anhydride $(Ac)_2O$ (0.5 mL 34 equiv.). The reaction was stirred at ambient temperature under argon for 16 hours and at 100°C for 2h (TLC monitoring). After completion, the crude product was evaporated to dryness under high vacuum to give **(*S,S*)-16** (0.047 g, 93%) as a colorless thick oil. **(*S,S*)-16**: colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 1.42 (d, J = 7.3 Hz, 3H), 1.49 (s, 9H), 2.20 (s, 3H), 2.80 (brs, 1H), 2.88 (brs, 1H), 4.34 (q, J = 7.3 Hz, 1H); ^{13}C NMR (100.5 MHz, CD_3OD) δ 17.1, 24.1, 28.1 (3C), 33.3, 46.4 (q, J = 35.7 Hz), 50.9, 83.1, 123.8 (q, J = 276.9 Hz), 162.9, 172.4, 179.9; ^{19}F NMR (376.2 MHz, CD_3OD) δ -70.5 (s, 3F, CF_3); MS (ESI) m/z: $[M+H]^+$ 325.15.

tert-butyl removal of **(*S,S*)-16**

To a solution of **(*S,S*)-**16 (0.027 g, 0.08 mmol, 1.0 equiv) in dichloromethane (1 mL) was added trifluoroacetic acid (0.2 mL) at room temperature. The reaction was stirred at room temperature for 2h and the crude evaporated to dryness under vacuum. The removal of the *tert*-butyl group was comfirmed by NMR (^{1}H, ^{13}C and ^{19}F) and HPLC-MS. ^{1}H NMR (400 MHz, CD_3OD) (major) δ 1.44 (d, J = 7.3 Hz, 3H), 2.16 (s, 3H), 2.78 (brs, 1H), 2.87 (brs, 1H), 4.44 (p, J = 7.3 Hz, 1H), 8.21 (d, J = 7.1 Hz, 1H); (minor) δ 1.39 (d, J = 7.3 Hz, 3H), 2.17 (s, 3H), 2.78 (brs, 1H), 2.85 (brs, 1H), 4.44 (p, J = 7.3 Hz, 1H), 8.43 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100.5 MHz, CD_3OD) (major) δ 15.3, 22.0, 31.5, 44.3 (q, J = 35.9 Hz), 48.1, 83.1, 121.8 (q, J = 276.8 Hz), 160.9, 172.9, 178.1; ^{19}F NMR (376.2 MHz, CD_3OD) (major) δ -70.4 (s, 3F, CF_3) (minor) δ -70.5 (s, 3F, CF_3); MS (ESI) m/z: $[M+H]^+$ 269.10.

3. NMR spectra


HO
F3C
BnHN
CO2Bn
(R)-5
1H NMR (400 MHz, CDCl3)
11.45
11.45
12.36
11.91
10.05
2.00
1.92
1.85
2.18
abundance
X : parts per Million : 1H
7.374
7.338
7.322
7.317
7.304
7.298
7.290
7.282
7.270
7.260
7.251
5.288
4.102
4.088
4.073
3.992
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3.836
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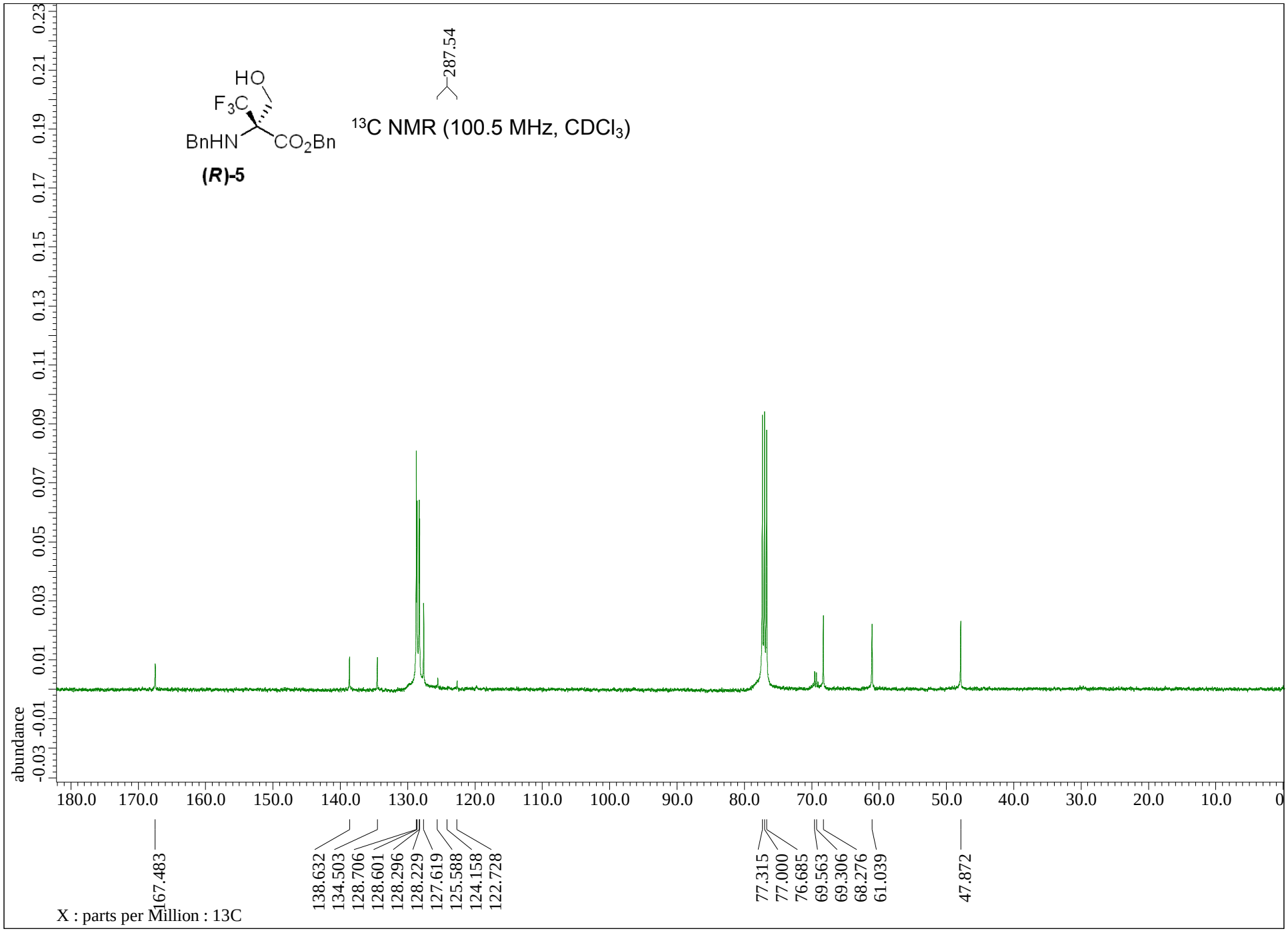
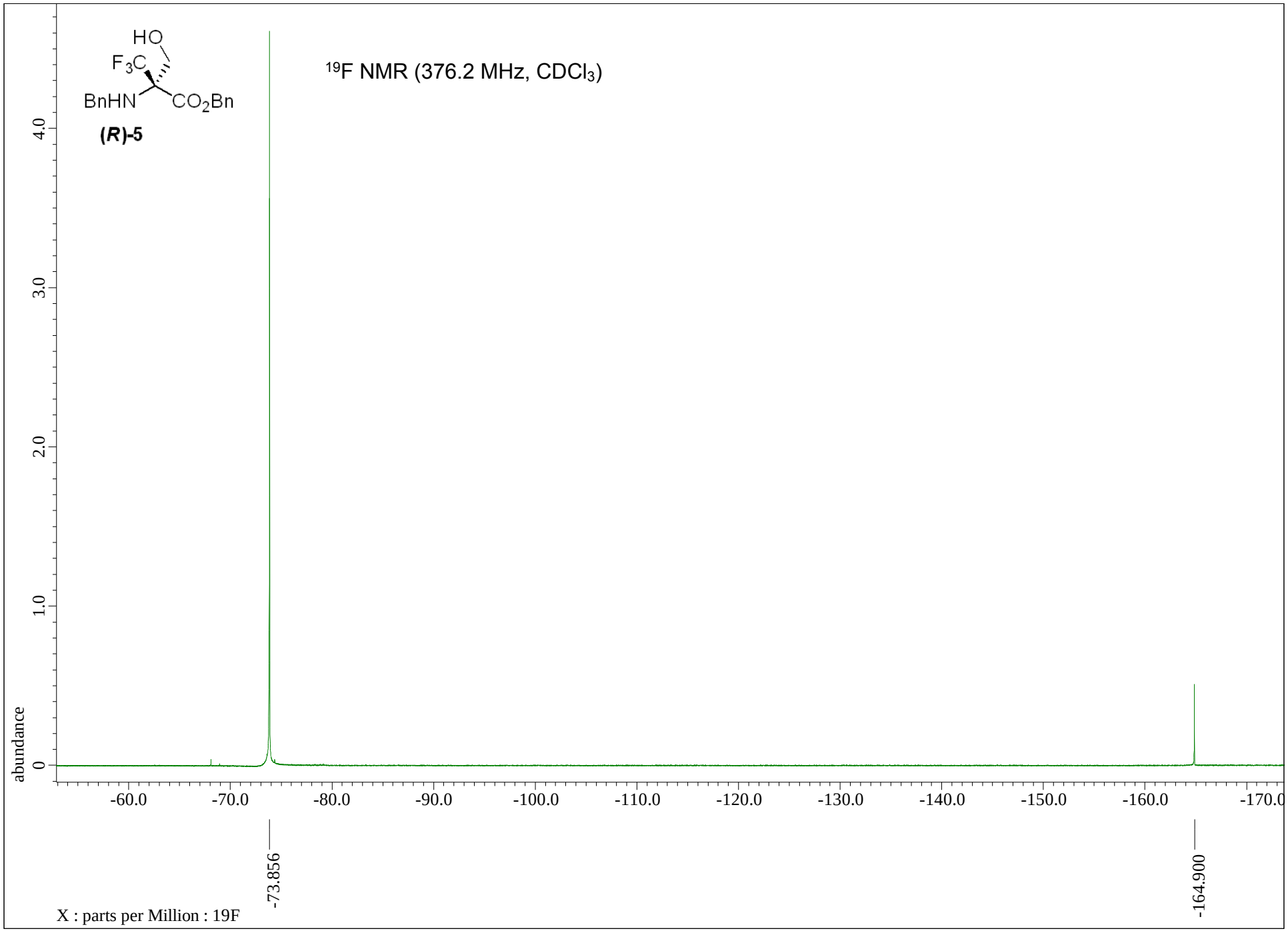
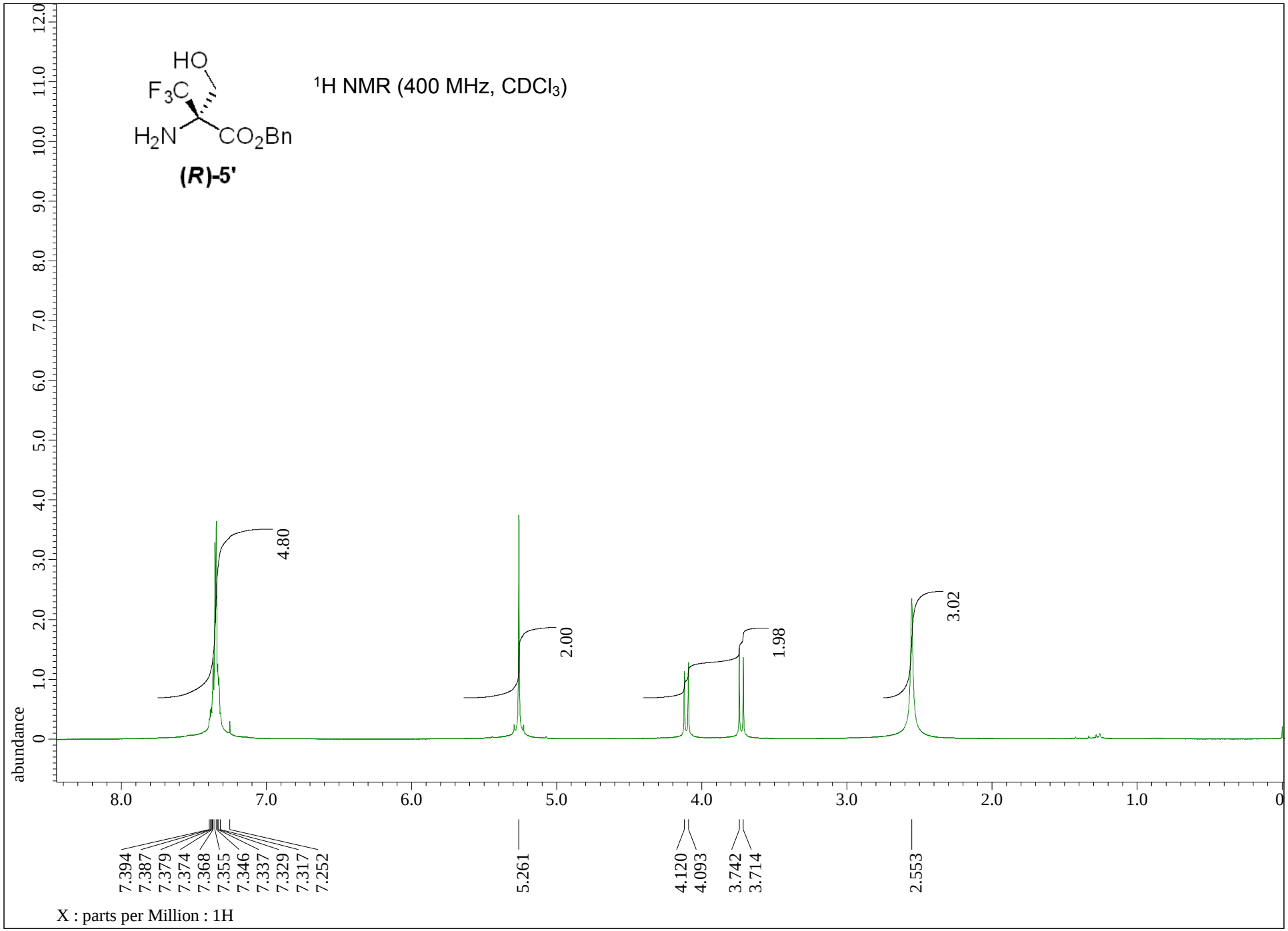
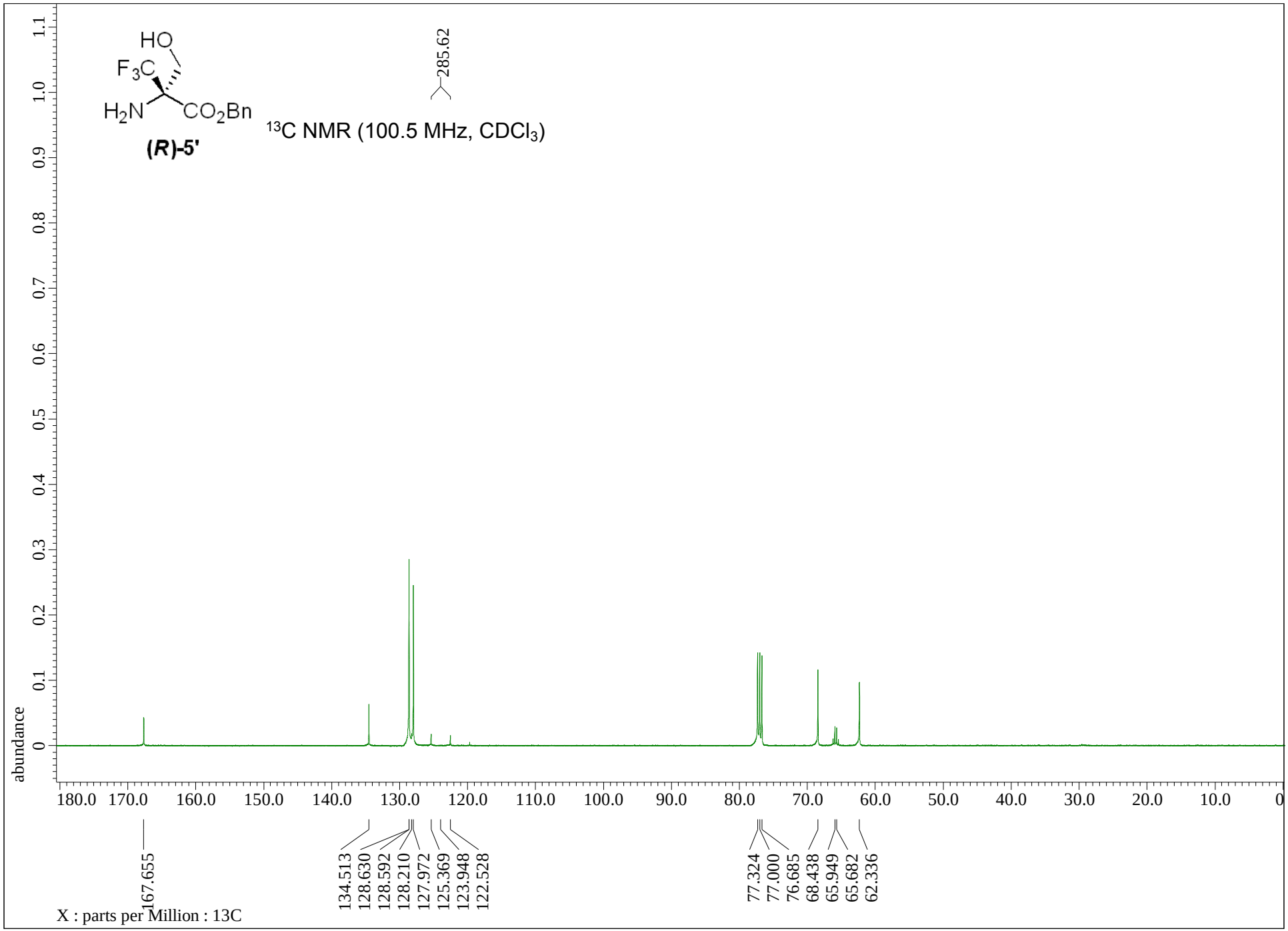
0.000


HO
F3C
BnHN
CO2Bn
(R)-5
13C NMR (100.5 MHz, CDCl3)
287.54
abundance
-0.03 -0.01 0.01 0.03 0.05 0.07 0.09 0.11 0.13 0.15 0.17 0.19 0.21 0.23
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
167.483
138.632
134.503
128.706
128.601
128.296
128.229
127.619
125.588
124.158
122.728
77.315
77.000
76.685
69.563
69.306
68.276
61.039
47.872
X : parts per Million : 13C


HO
F3C
BnHN
CO2Bn
(R)-5
19F NMR (376.2 MHz, CDCl3)
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
-73.856
-164.900
X : parts per Million : 19F


HO
F3C
H2N
CO2Bn
(R)-5'
1H NMR (400 MHz, CDCl3)
abundance
4.80
2.00
1.98
3.02
7.394
7.387
7.379
7.374
7.368
7.355
7.346
7.337
7.329
7.317
7.252
5.261
4.120
4.093
3.742
3.714
2.553
X : parts per Million : 1H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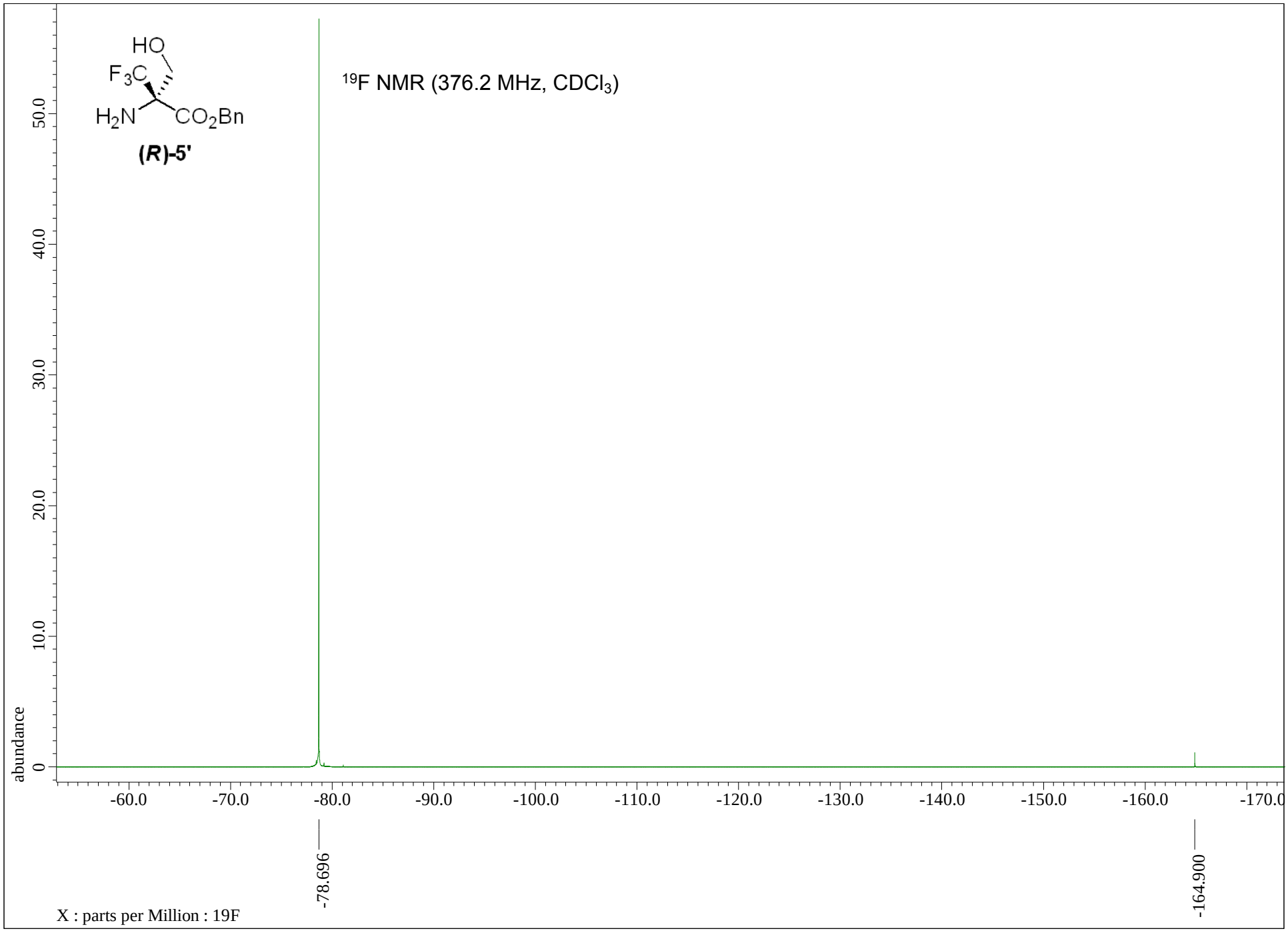
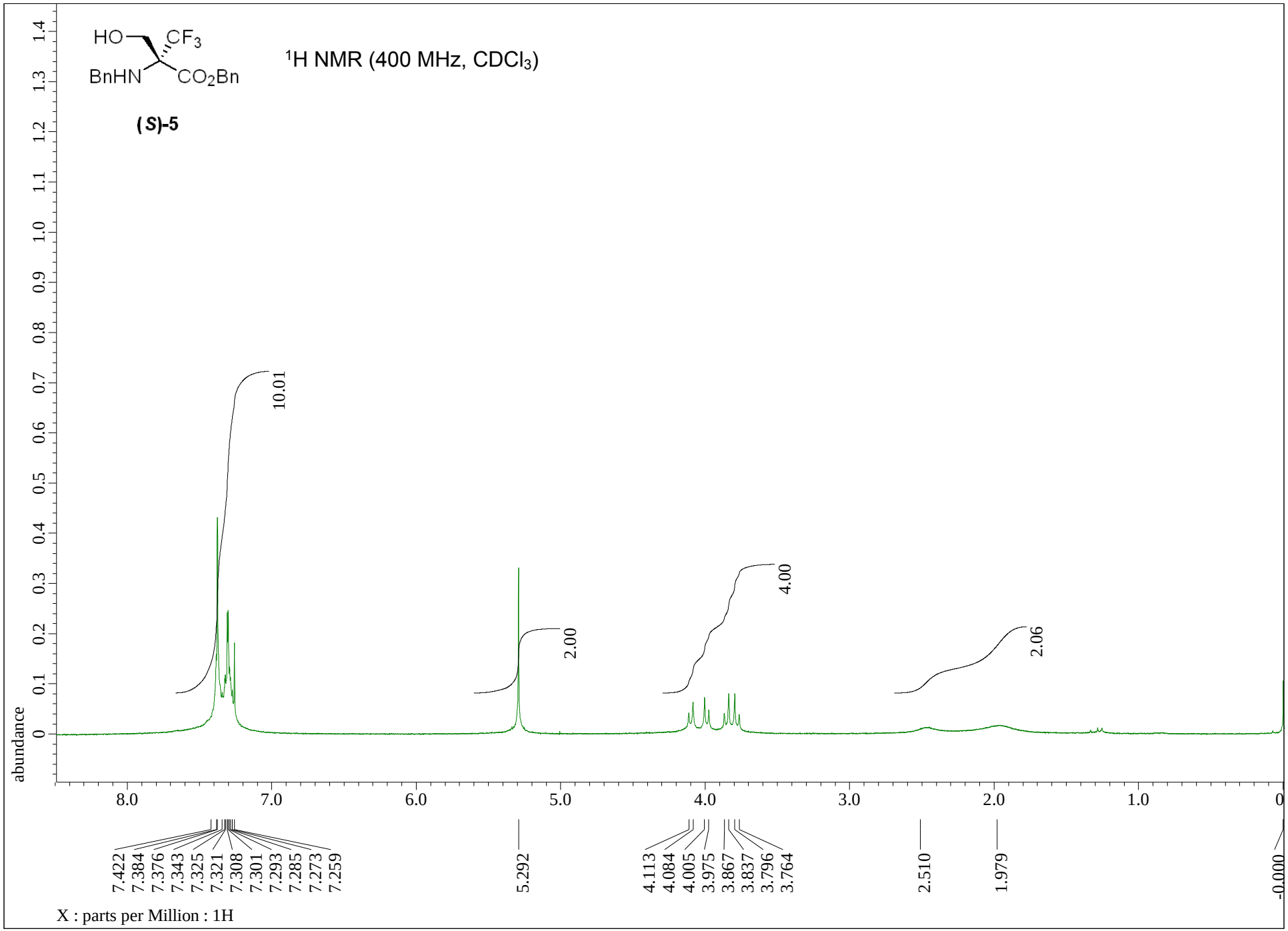
F3C
H2N
CO2Bn
(R)-5'
13C NMR (100.5 MHz, CDCl3)
285.62
abundance
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
167.655
134.513
128.630
128.592
128.210
127.972
125.369
123.948
122.528
77.324
77.000
76.685
68.438
65.949
65.682
62.336
X : parts per Million : 13C


HO
F3C
H2N
CO2Bn
(R)-5'
19F NMR (376.2 MHz, CDCl3)
50.0
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
-78.696
-164.900
X : parts per Million : 19F


HO
CF3
BnHN
CO2Bn
(S)-5
1H NMR (400 MHz, CDCl3)
abundance
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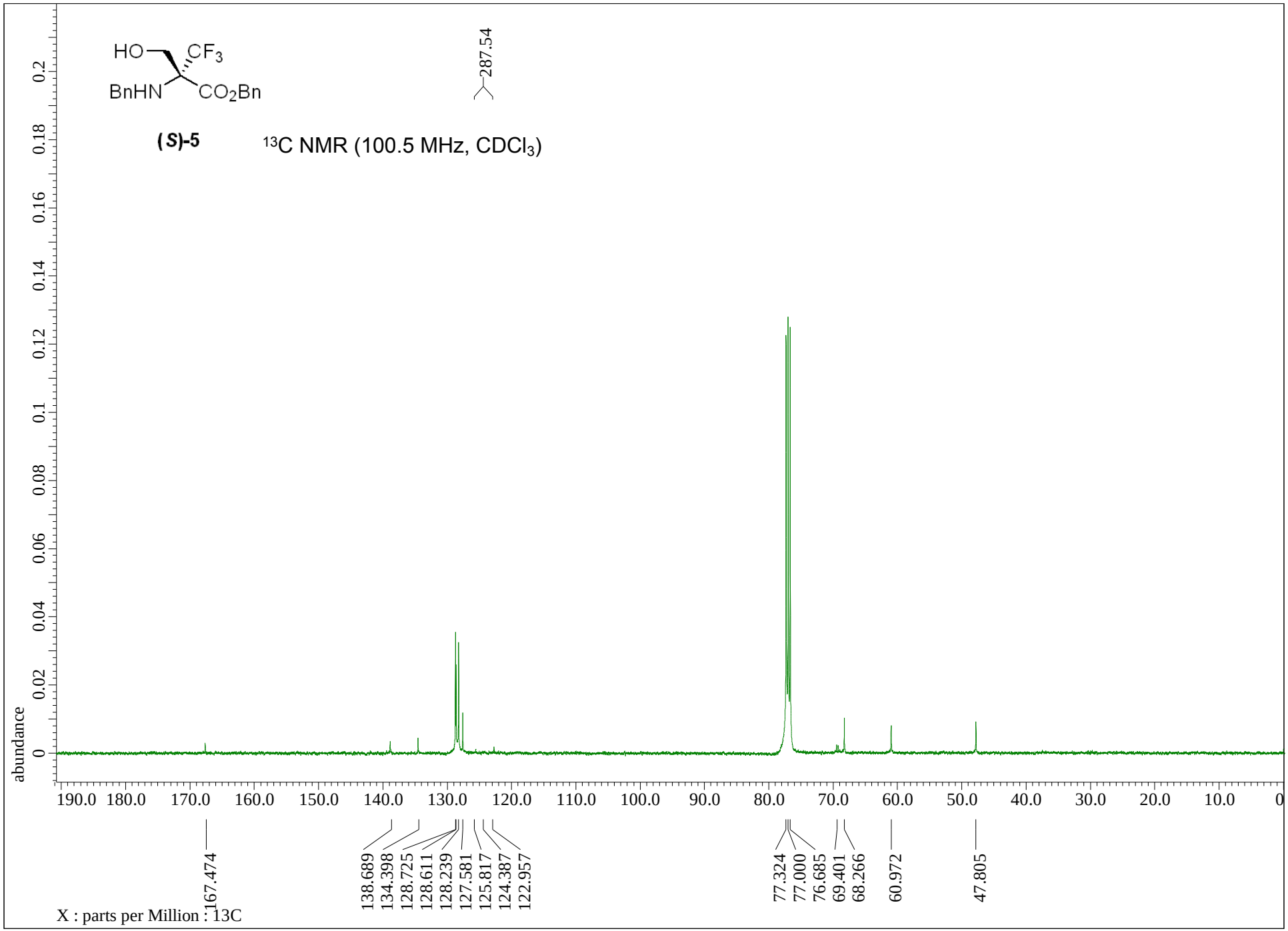
2.00
4.00
2.06
7.422
7.384
7.376
7.343
7.325
7.321
7.308
7.301
7.293
7.285
7.273
7.259
5.292
4.113
4.084
4.005
3.975
3.867
3.837
3.796
3.764
2.510
1.979
-0.000
X : parts per Million : 1H


HO
CF3
BnHN
CO2Bn
(S)-5
13C NMR (100.5 MHz, CDCl3)
287.54
abundance
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
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
167.474
138.689
134.398
128.725
128.611
128.239
127.581
125.817
124.387
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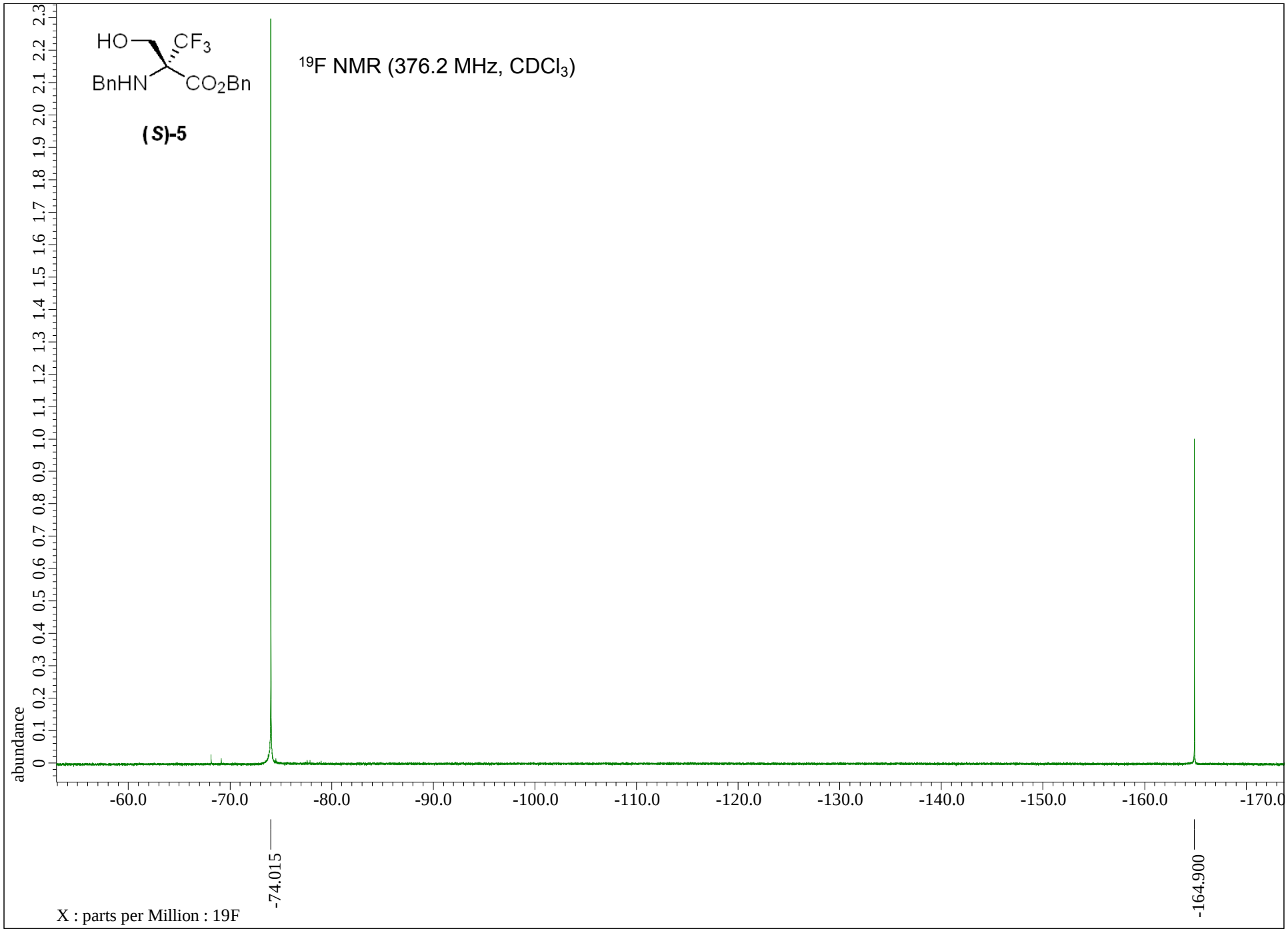
77.324
77.000
76.685
69.401
68.266
60.972
47.805
X : parts per Million : 13C


HO
CF3
BnHN
CO2Bn
(S)-5
19F NMR (376.2 MHz, CDCl3)
abundance
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-60.0 -70.0 -80.0 -90.0 -100.0 -110.0 -120.0 -130.0 -140.0 -150.0 -160.0 -170.0
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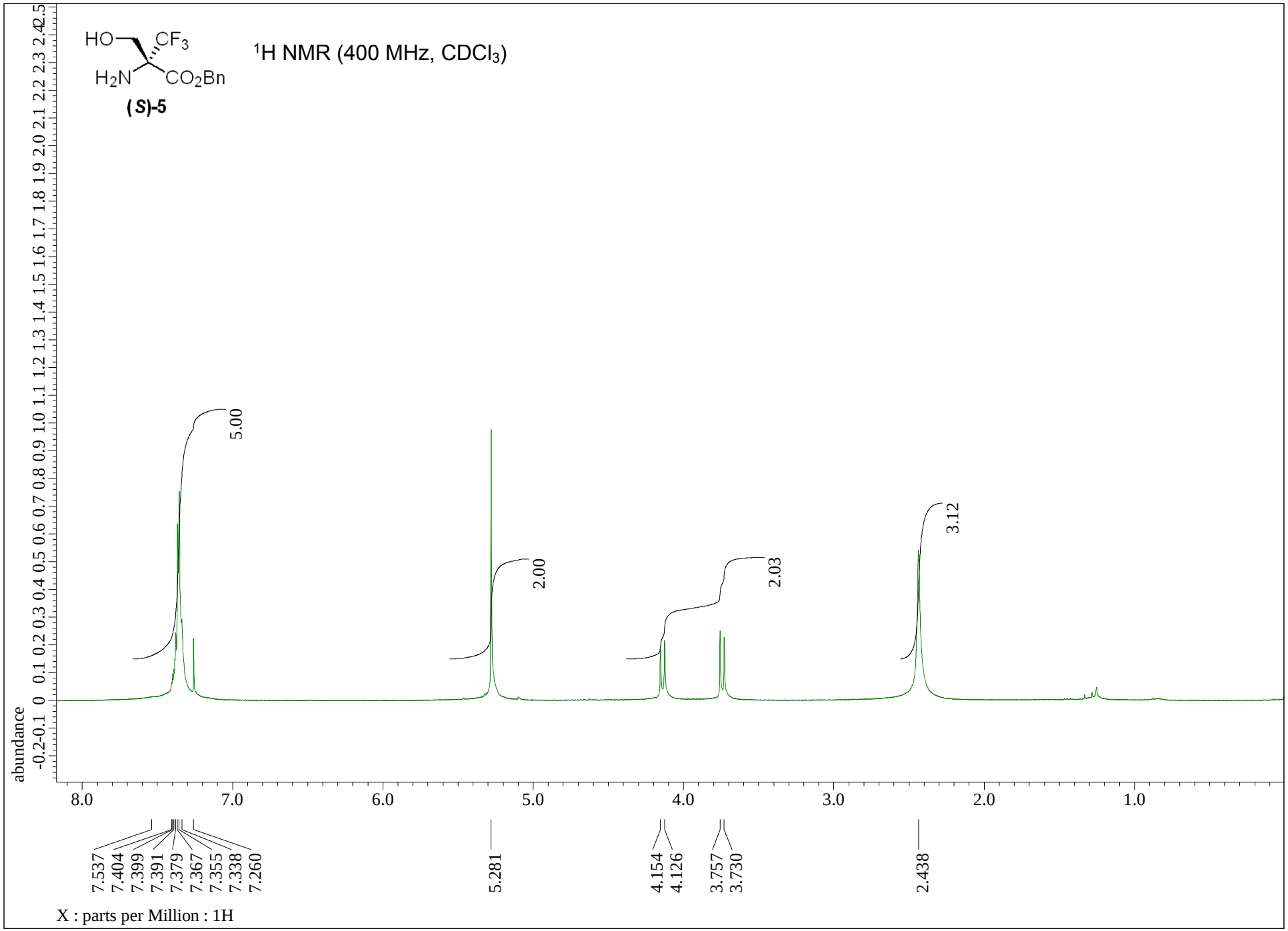
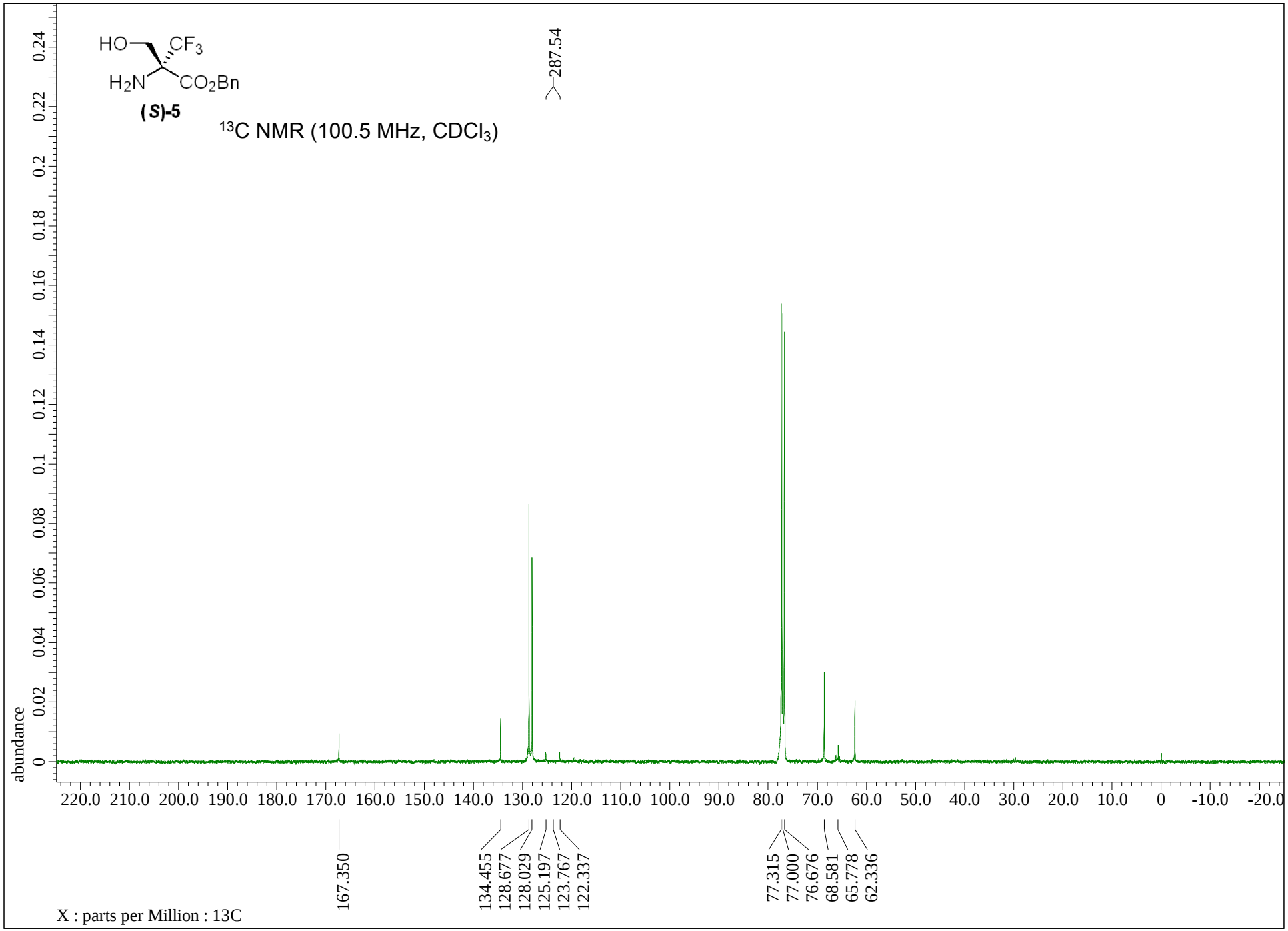
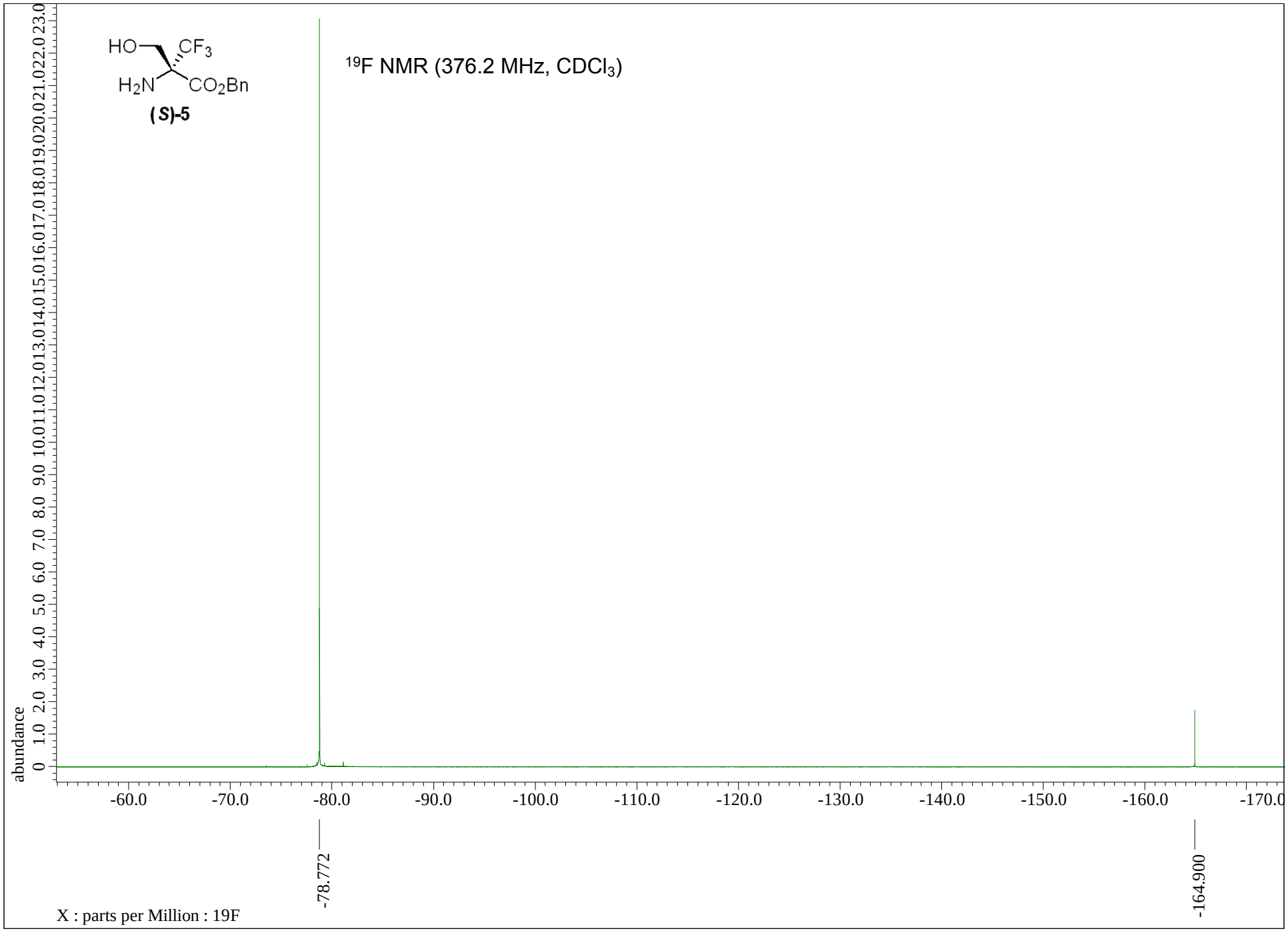
-164.900
X : parts per Million : 19F


HO
CF3
H2N
CO2Bn
(S)-5
1H NMR (400 MHz, CDCl3)
abundance
5.00
2.00
2.03
3.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.537
7.404
7.399
7.391
7.379
7.367
7.355
7.338
7.260
5.281
4.154
4.126
3.757
3.730
2.438
X : parts per Million : 1H


HO
CF3
H2N
CO2Bn
(S)-5
13C NMR (100.5 MHz, CDCl3)
287.54
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
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
167.350
134.455
128.677
128.029
125.197
123.767
122.337
77.315
77.000
76.676
68.581
65.778
62.336
X : parts per Million : 13C


HO
CF3
H2N
CO2Bn
(S)-5
19F NMR (376.2 MHz, CDCl3)
abundance
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
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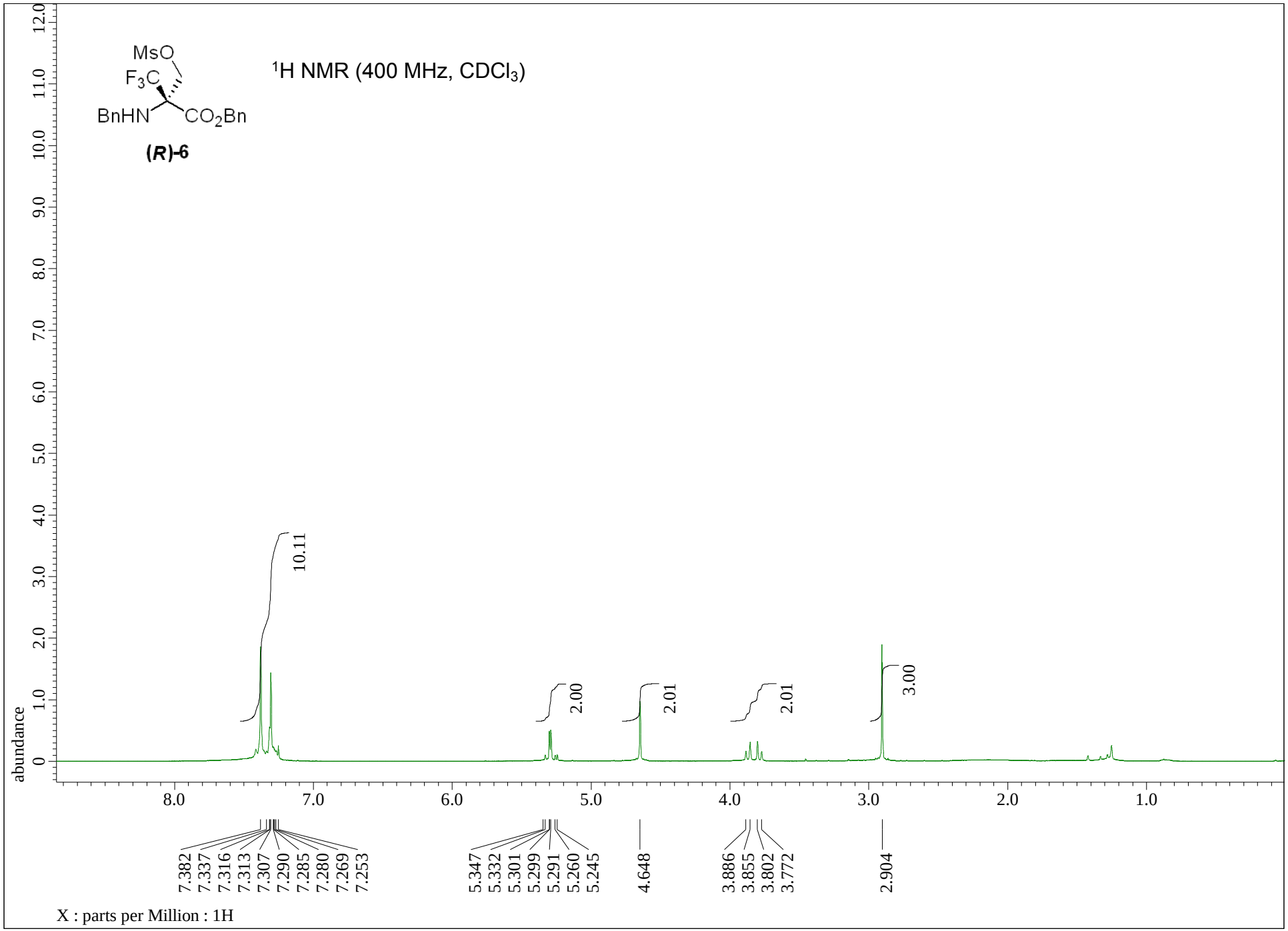
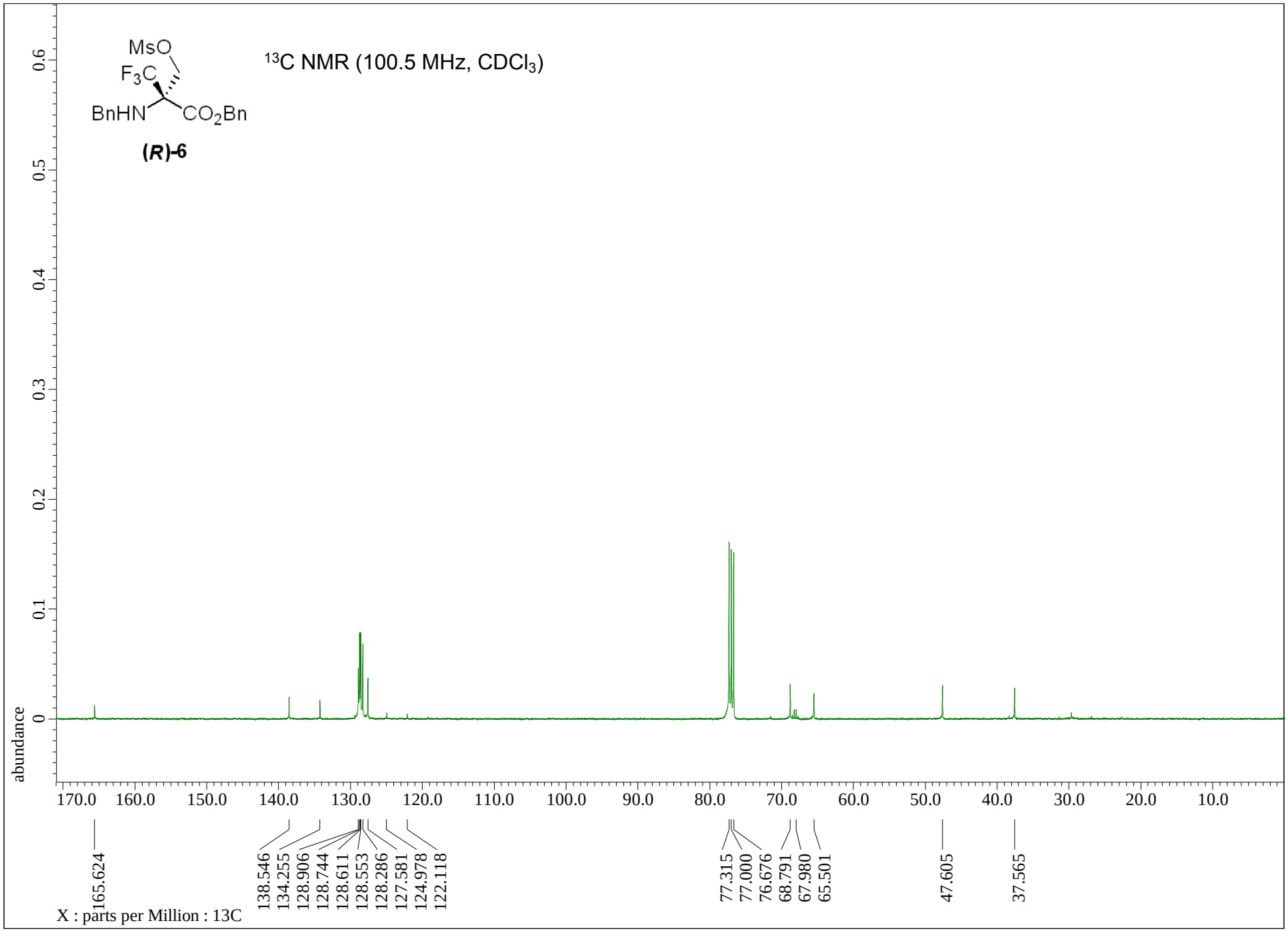
-170.0
-78.772
-164.900
X : parts per Million : 19F


MsO
F3C
BnHN
CO2Bn
(R)-6
1H NMR (400 MHz, CDCl3)
abundance
10.11
2.00
2.01
2.01
3.00
7.382
7.337
7.316
7.313
7.307
7.290
7.285
7.280
7.269
7.253
5.347
5.332
5.301
5.299
5.291
5.260
5.245
4.648
3.886
3.855
3.802
3.772
2.904
X : parts per Million : 1H


MsO
F3C
BnHN
CO2Bn
(R)-6
13C NMR (100.5 MHz, CDCl3)
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
165.624
138.546
134.255
128.906
128.744
128.611
128.553
128.286
127.581
124.978
122.118
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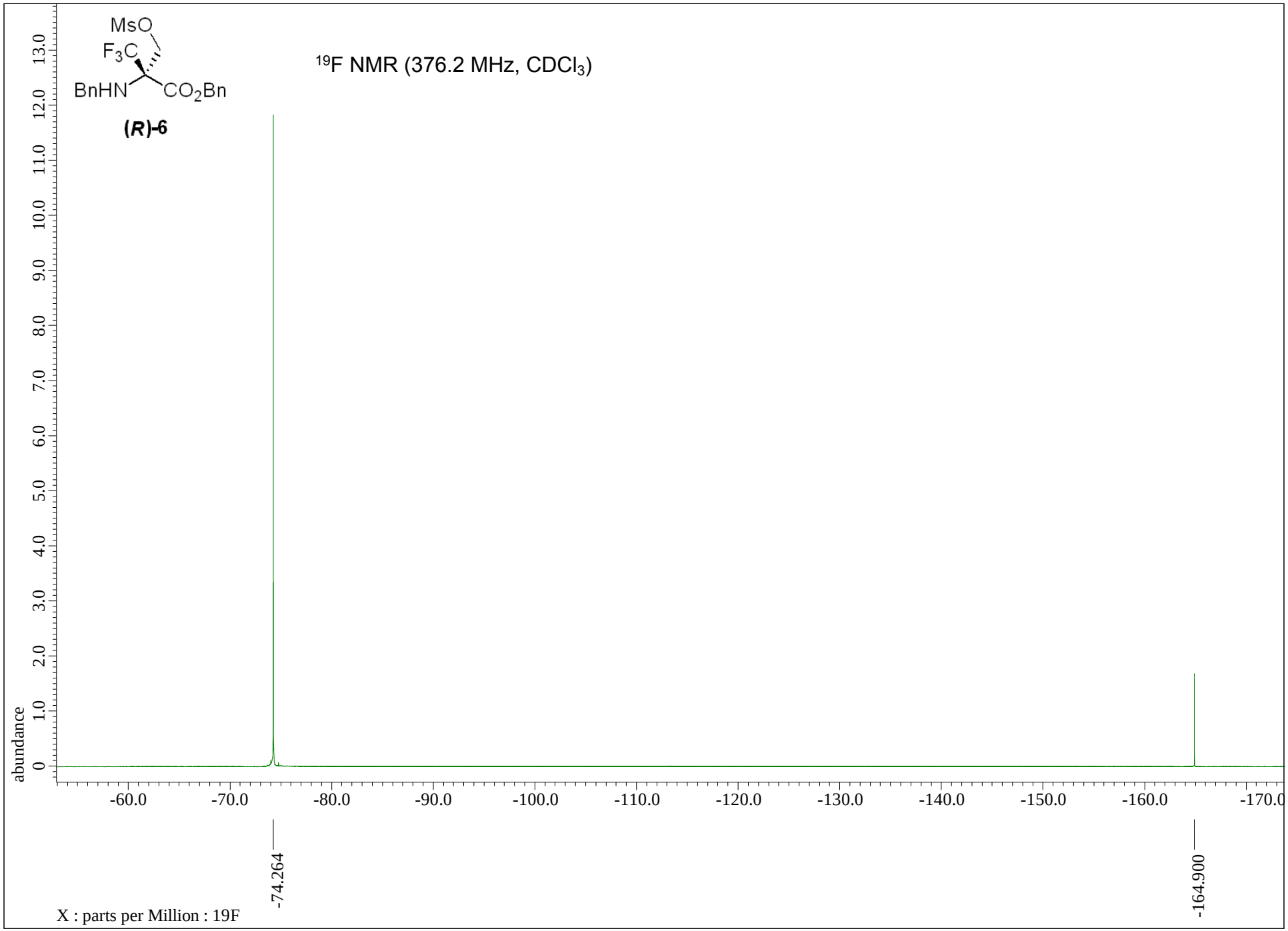
67.980
65.501
47.605
37.565
X : parts per Million : 13C


MsO
F3C
BnHN
CO2Bn
(R)-6
19F NMR (376.2 MHz, CDCl3)
abundance
13.0
12.0
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
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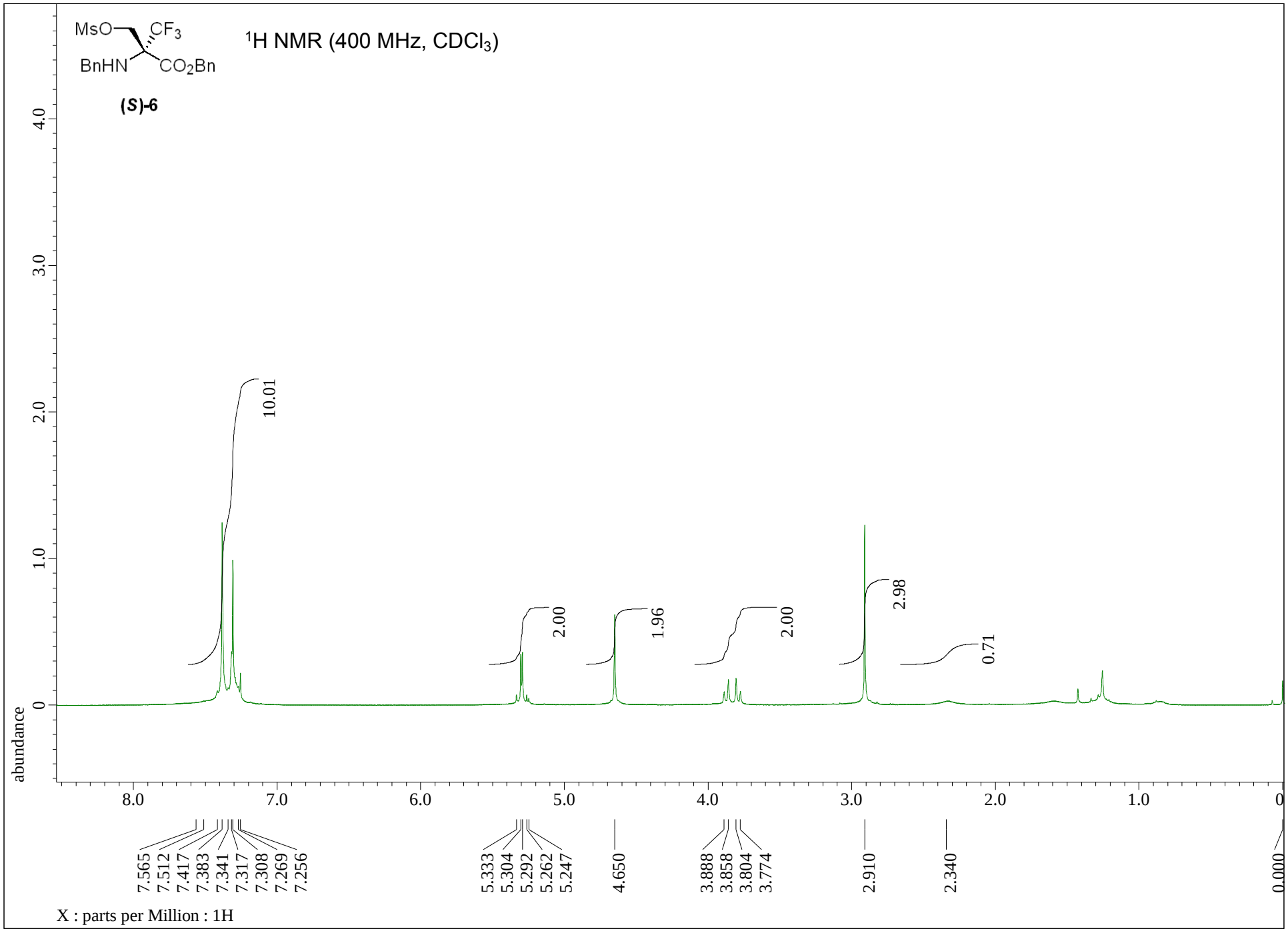
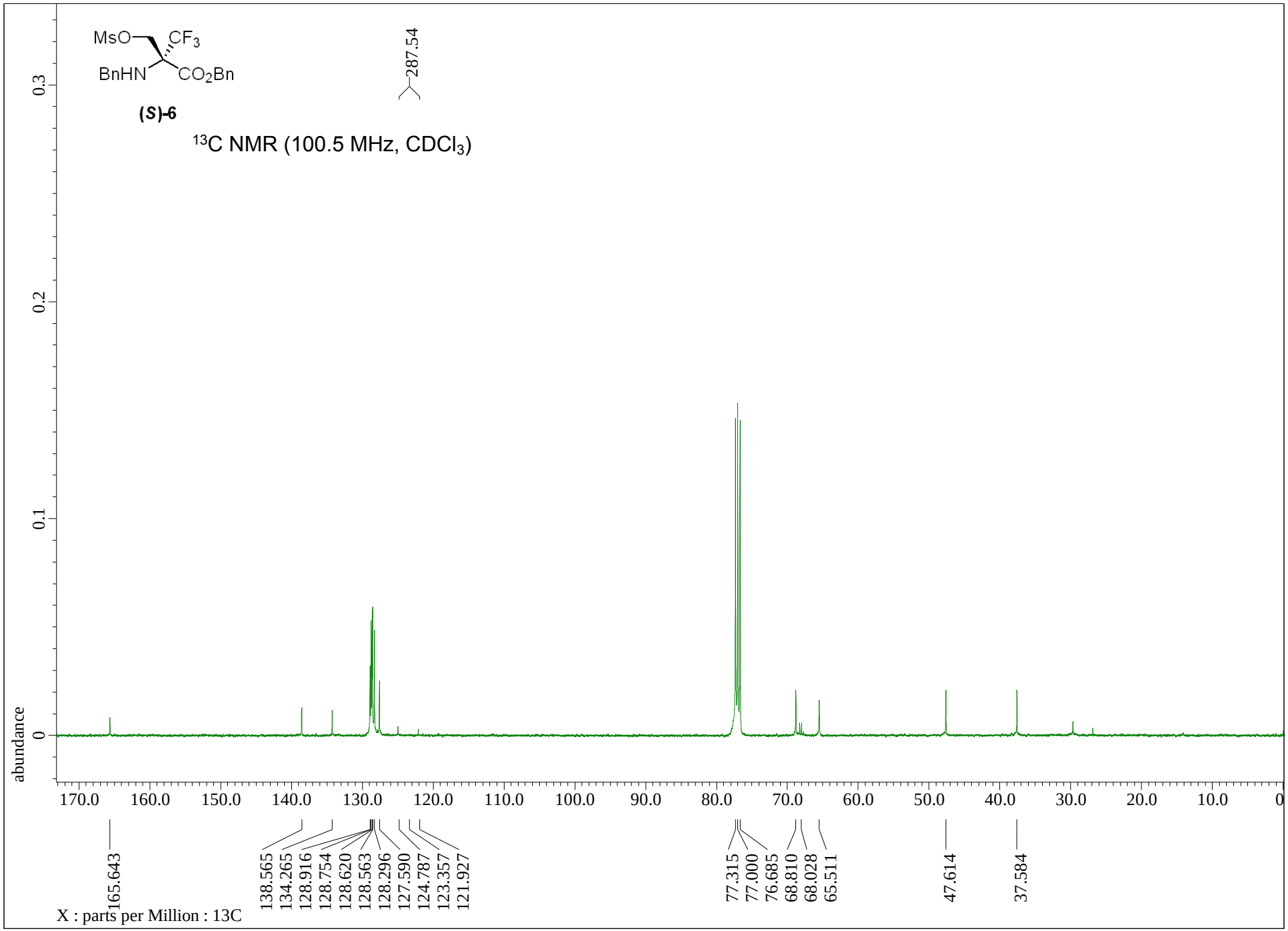
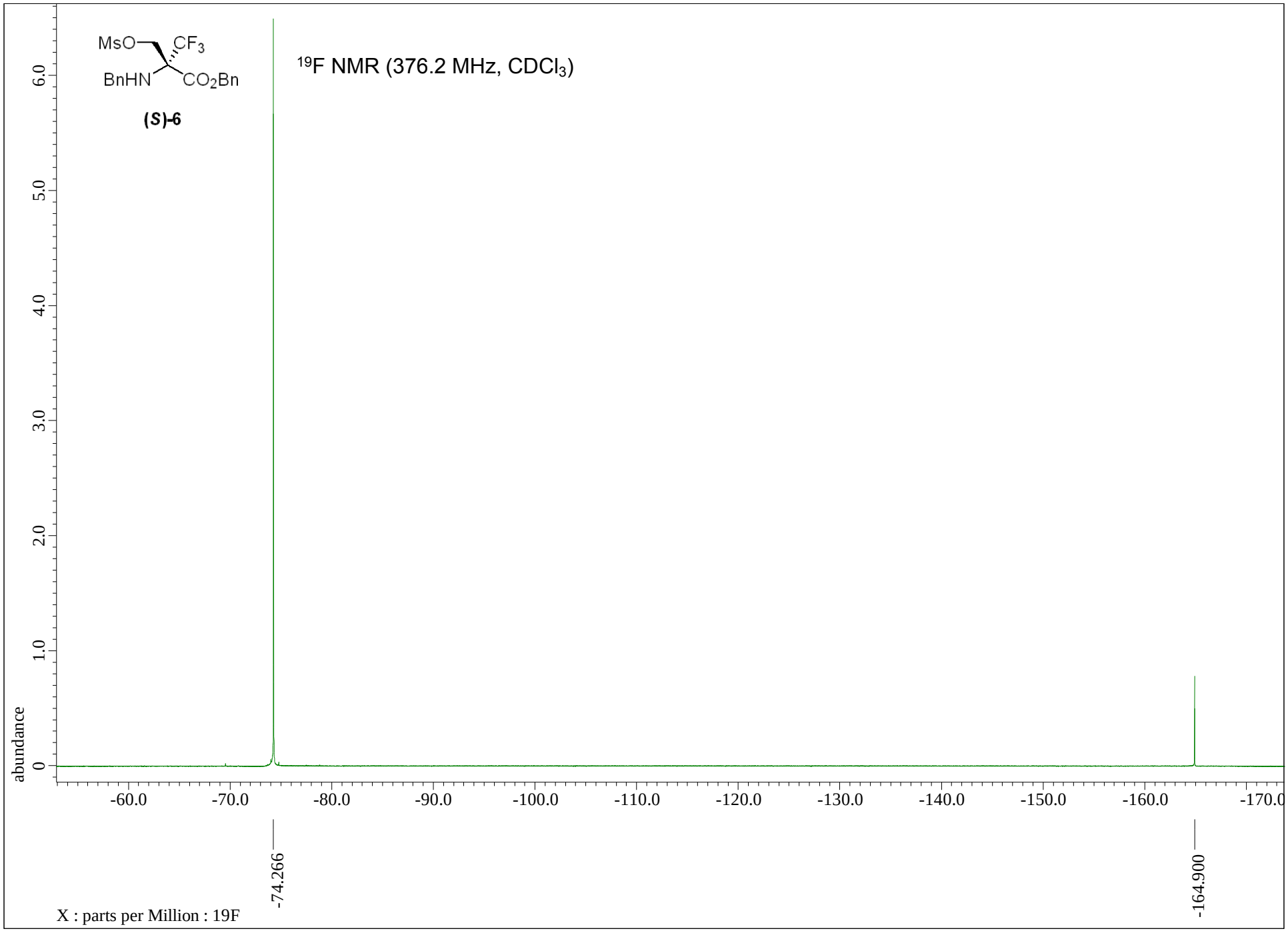
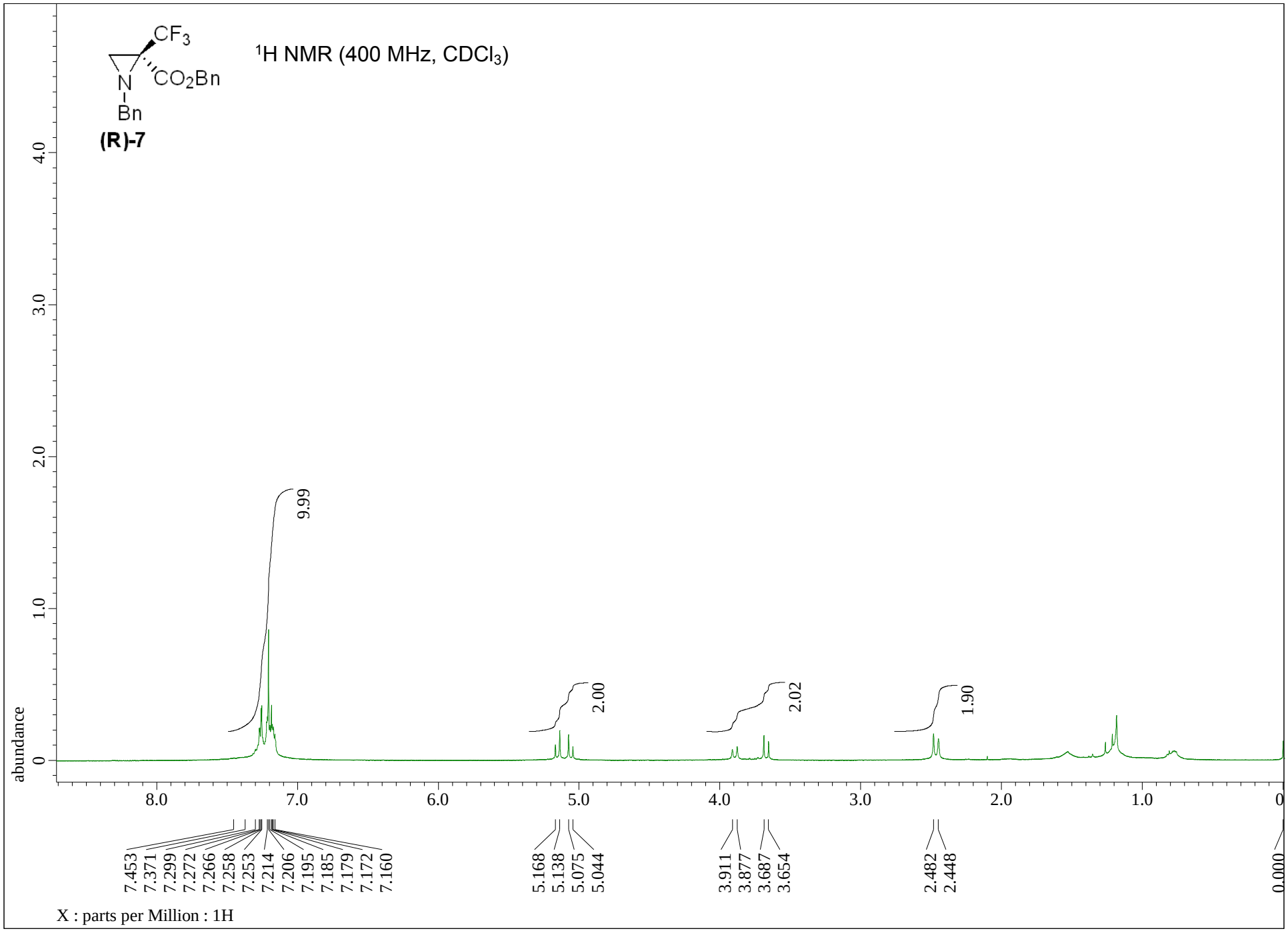
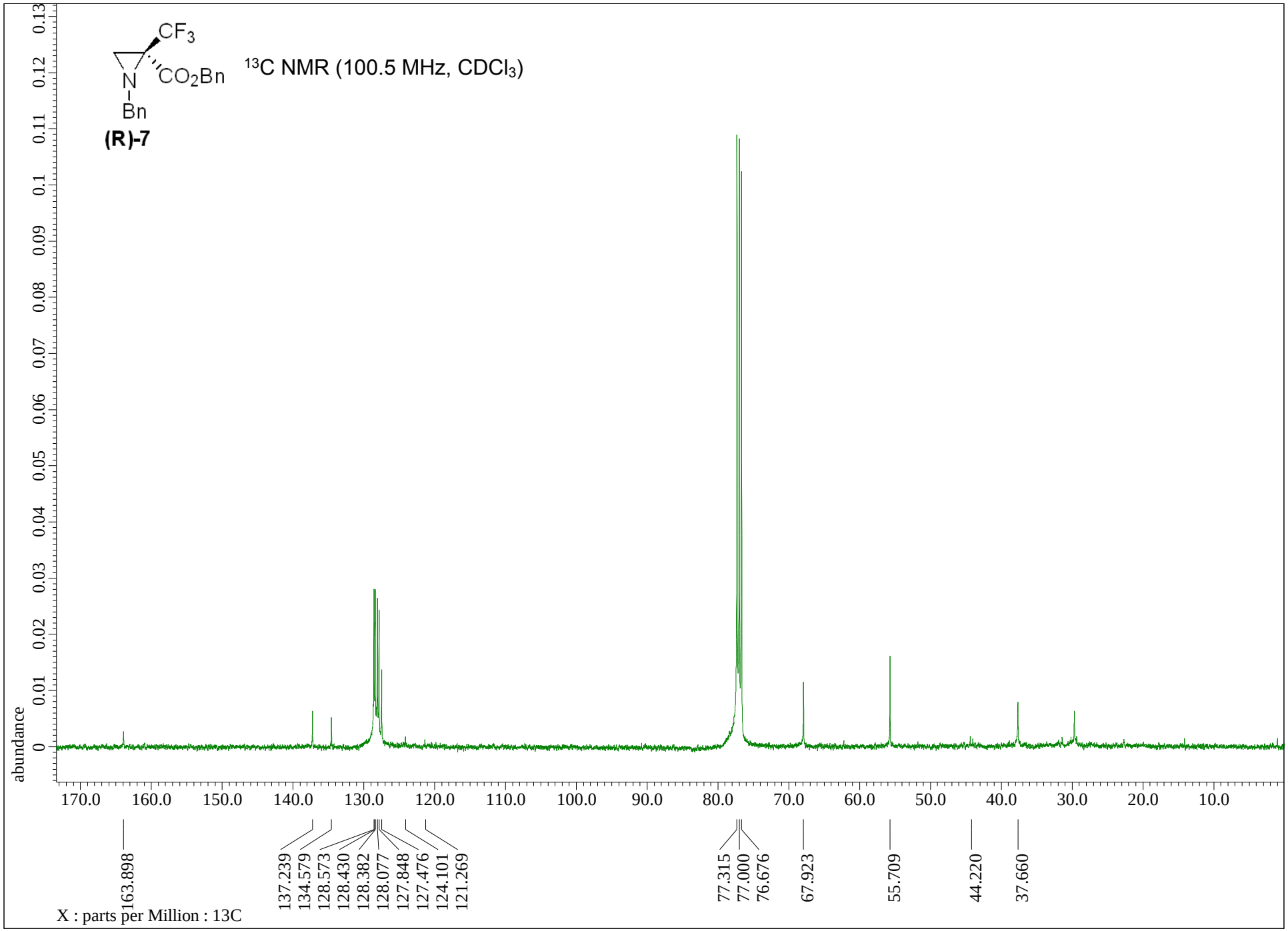
X : parts per Million : 19F

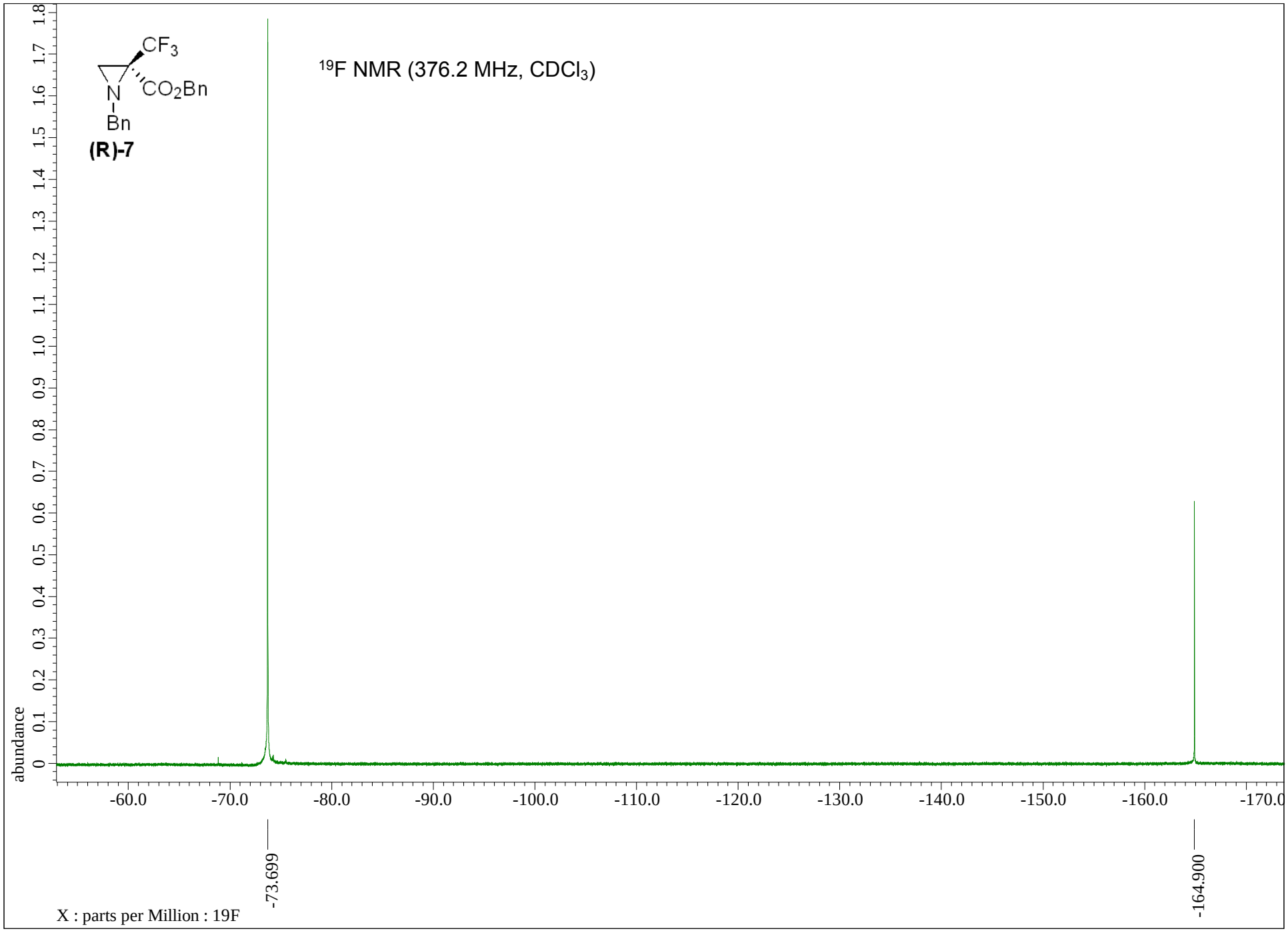

MsO
CF3
BnHN
CO2Bn
(S)-6
1H NMR (400 MHz, CDCl3)
abundance
10.01
2.00
1.96
2.00
2.98
0.71
7.565
7.512
7.417
7.383
7.341
7.317
7.308
7.269
7.256
5.333
5.304
5.292
5.262
5.247
4.650
3.888
3.858
3.804
3.774
2.910
2.340
0.000
X : parts per Million : 1H

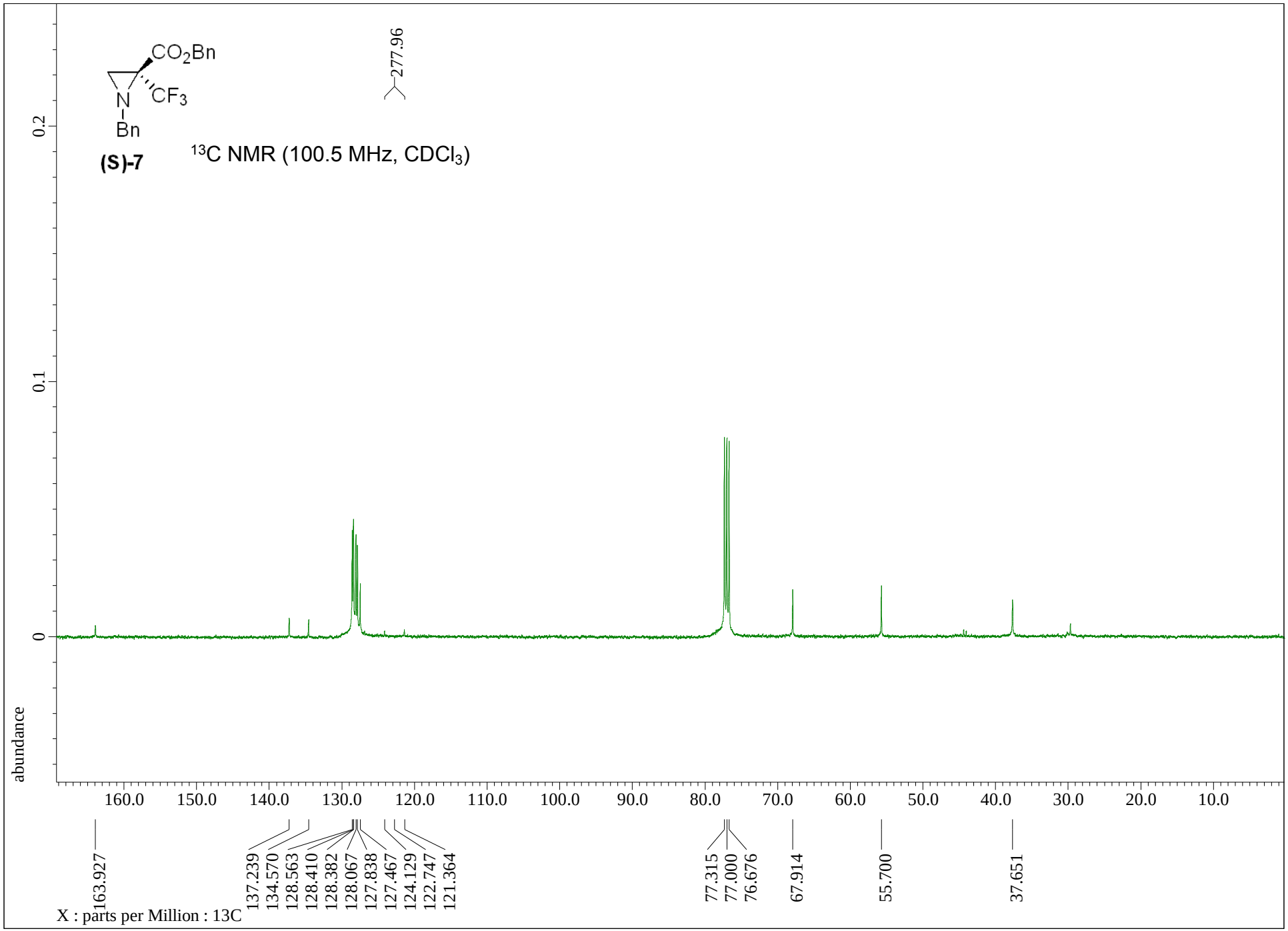

MsO
CF3
BnHN
CO2Bn
(S)-6
287.54
13C NMR (100.5 MHz, CDCl3)
abundance
0.3
0.2
0.1
0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
165.643
138.565
134.265
128.916
128.754
128.620
128.563
128.296
127.590
124.787
123.357
121.927
77.315
77.000
76.685
68.810
68.028
65.511
47.614
37.584
X : parts per Million : 13C

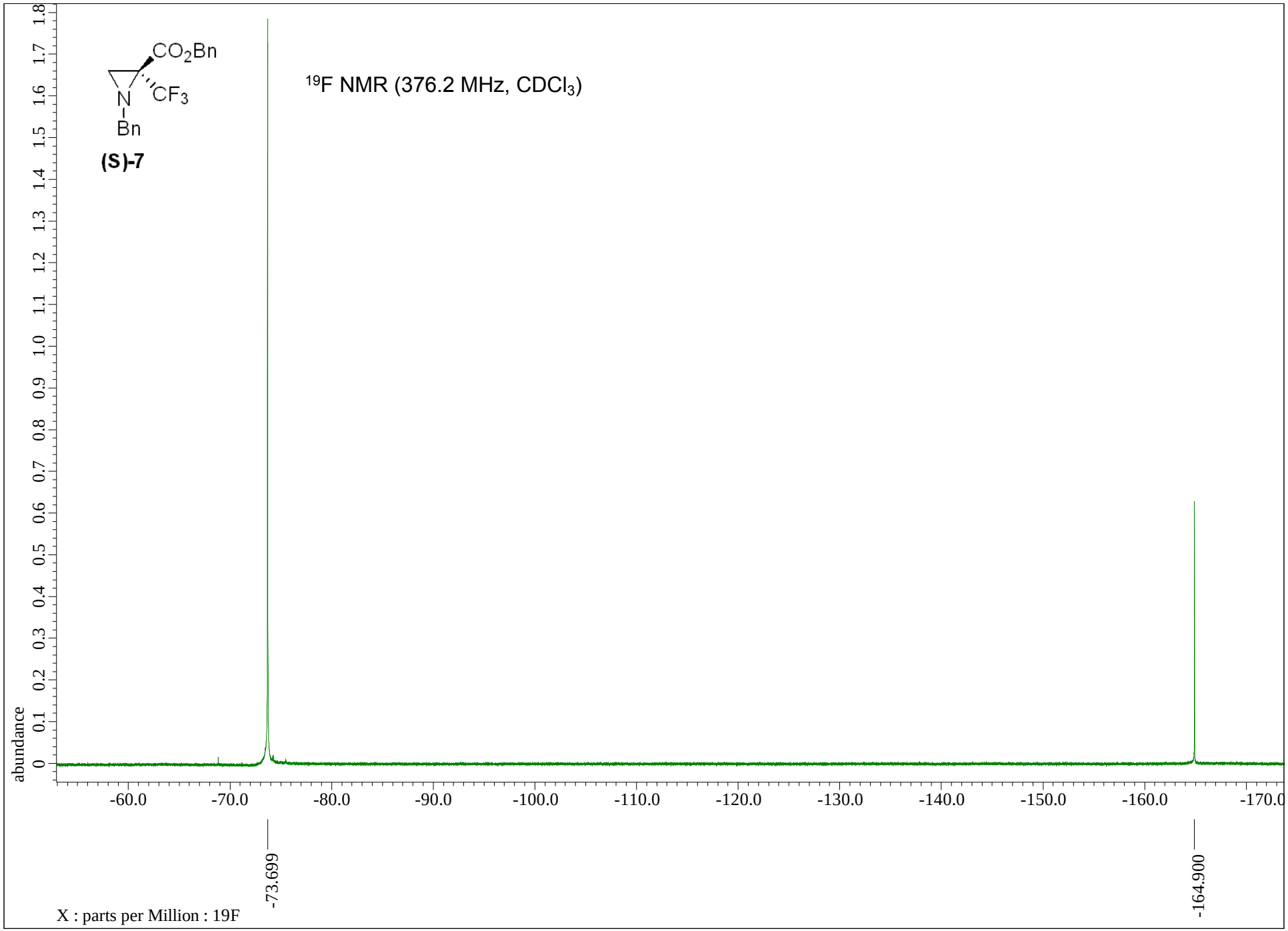

MsO
CF3
BnHN
CO2Bn
(S)-6
19F NMR (376.2 MHz, CDCl3)
abundance
6.0
5.0
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-74.266
-164.900
X : parts per Million : 19F

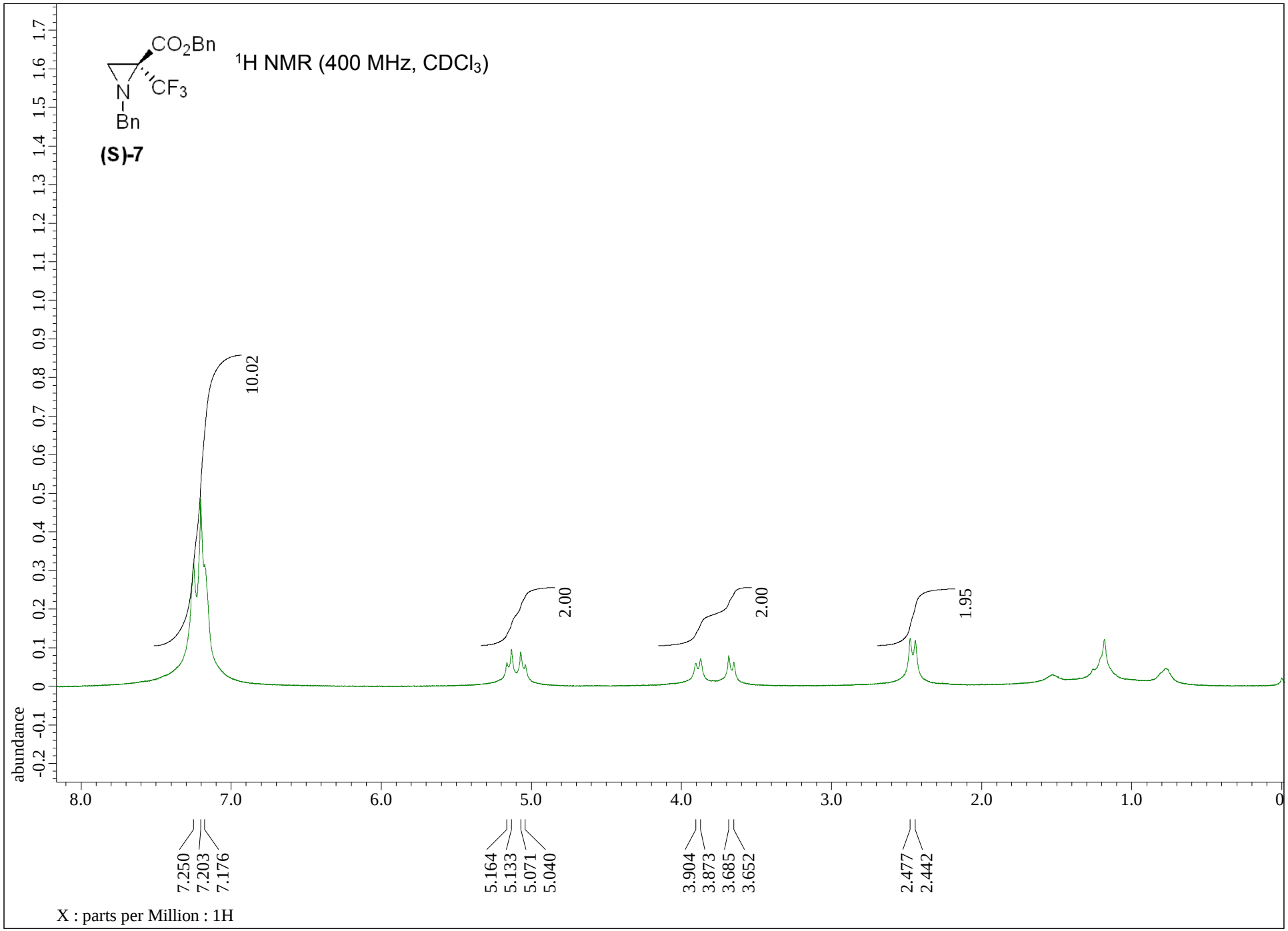

CF3
CO2Bn
N
Bn
(R)-7
1H NMR (400 MHz, CDCl3)
abundance
9.99
2.00
2.02
1.90
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.453
7.371
7.299
7.272
7.266
7.258
7.253
7.214
7.206
7.195
7.185
7.179
7.172
7.160
5.168
5.138
5.075
5.044
3.911
3.877
3.687
3.654
2.482
2.448
0.000
X : parts per Million : 1H

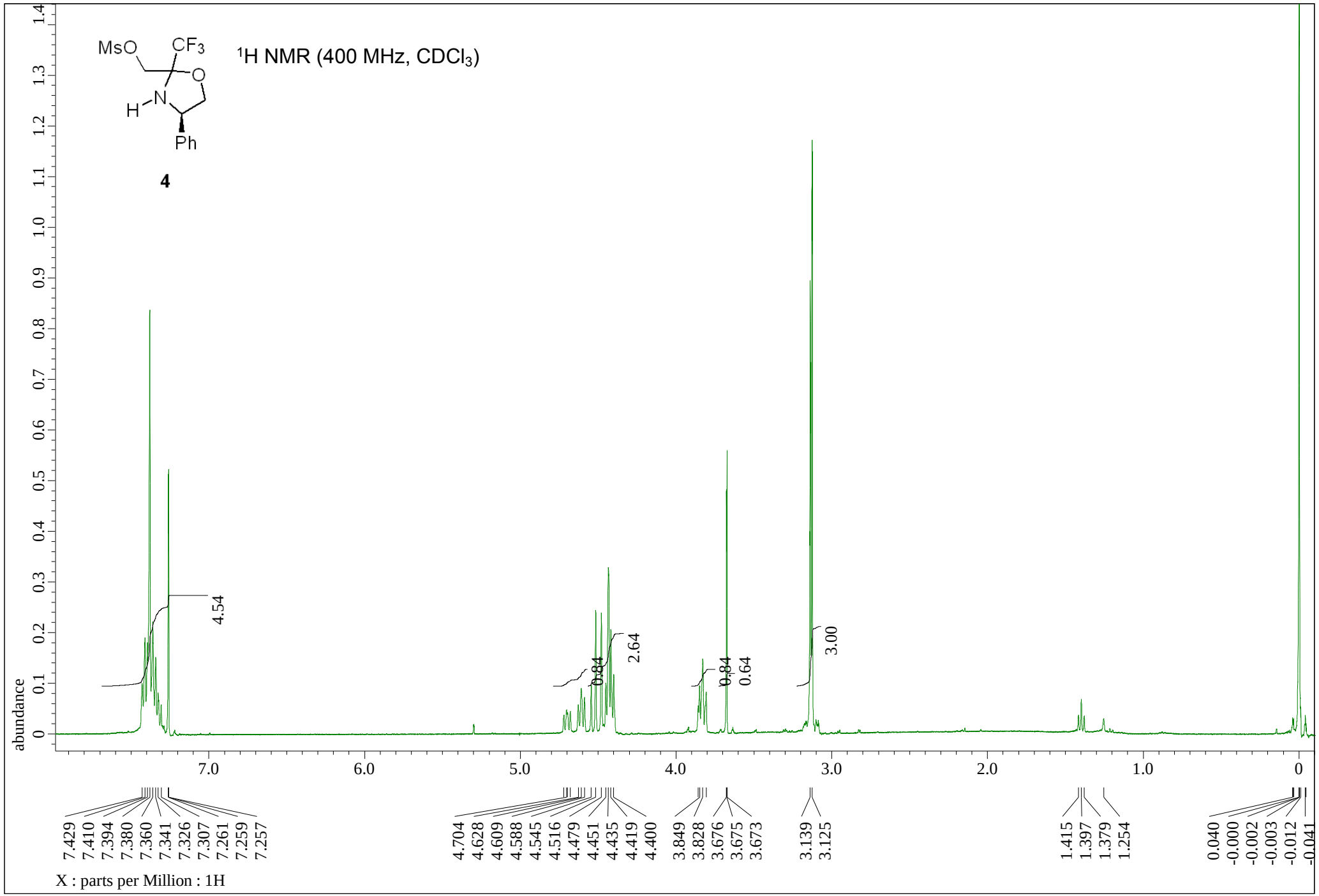

CF3
CO2Bn
N
Bn
(R)-7
13C NMR (100.5 MHz, CDCl3)
abundance
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.1
0.11
0.12
0.13
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
163.898
137.239
134.579
128.573
128.430
128.382
128.077
127.848
127.476
124.101
121.269
77.315
77.000
76.676
67.923
55.709
44.220
37.660
X : parts per Million : 13C

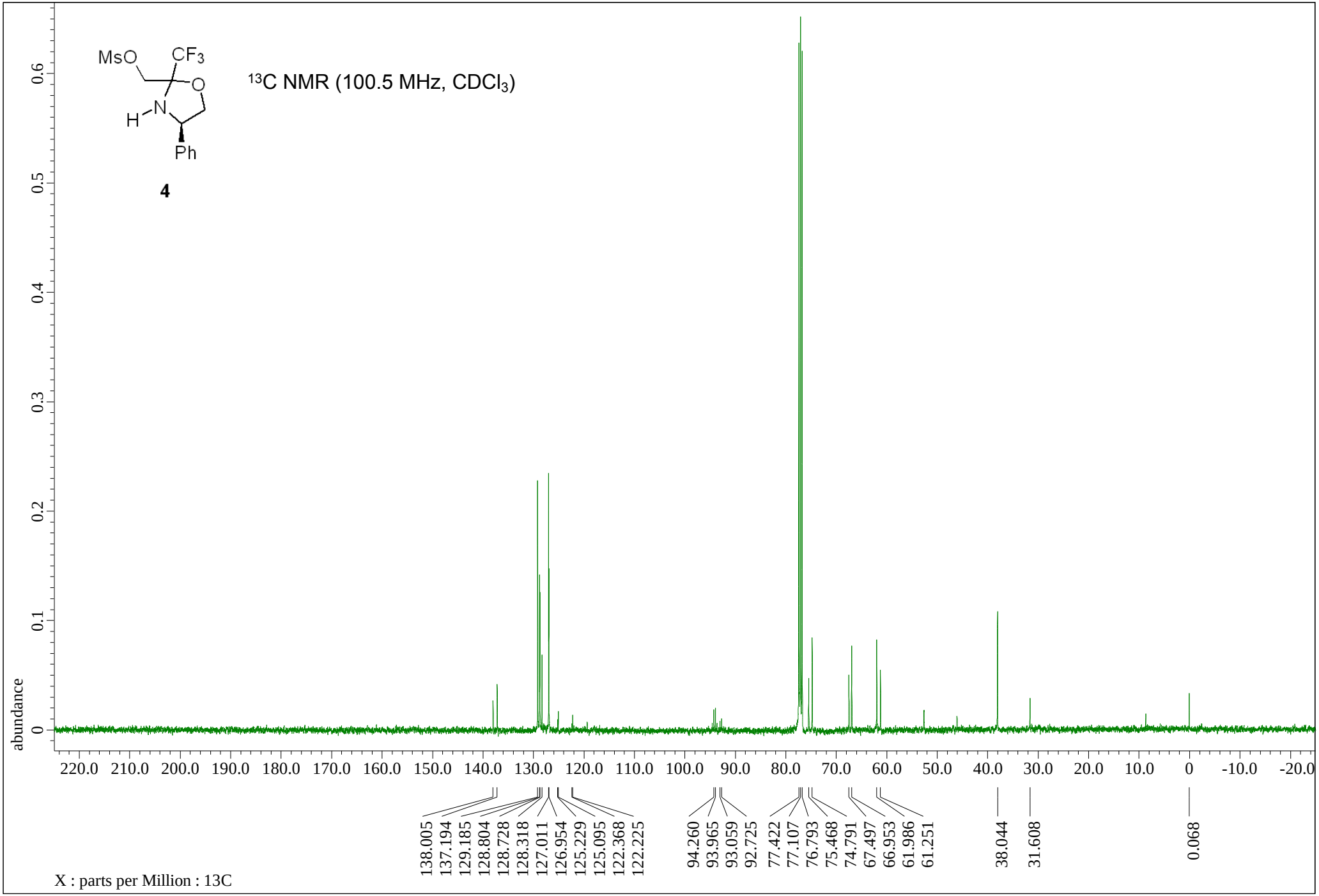

CF3
CO2Bn
N
Bn
(R)-7
19F NMR (376.2 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-73.699
-164.900
X : parts per Million : 19F

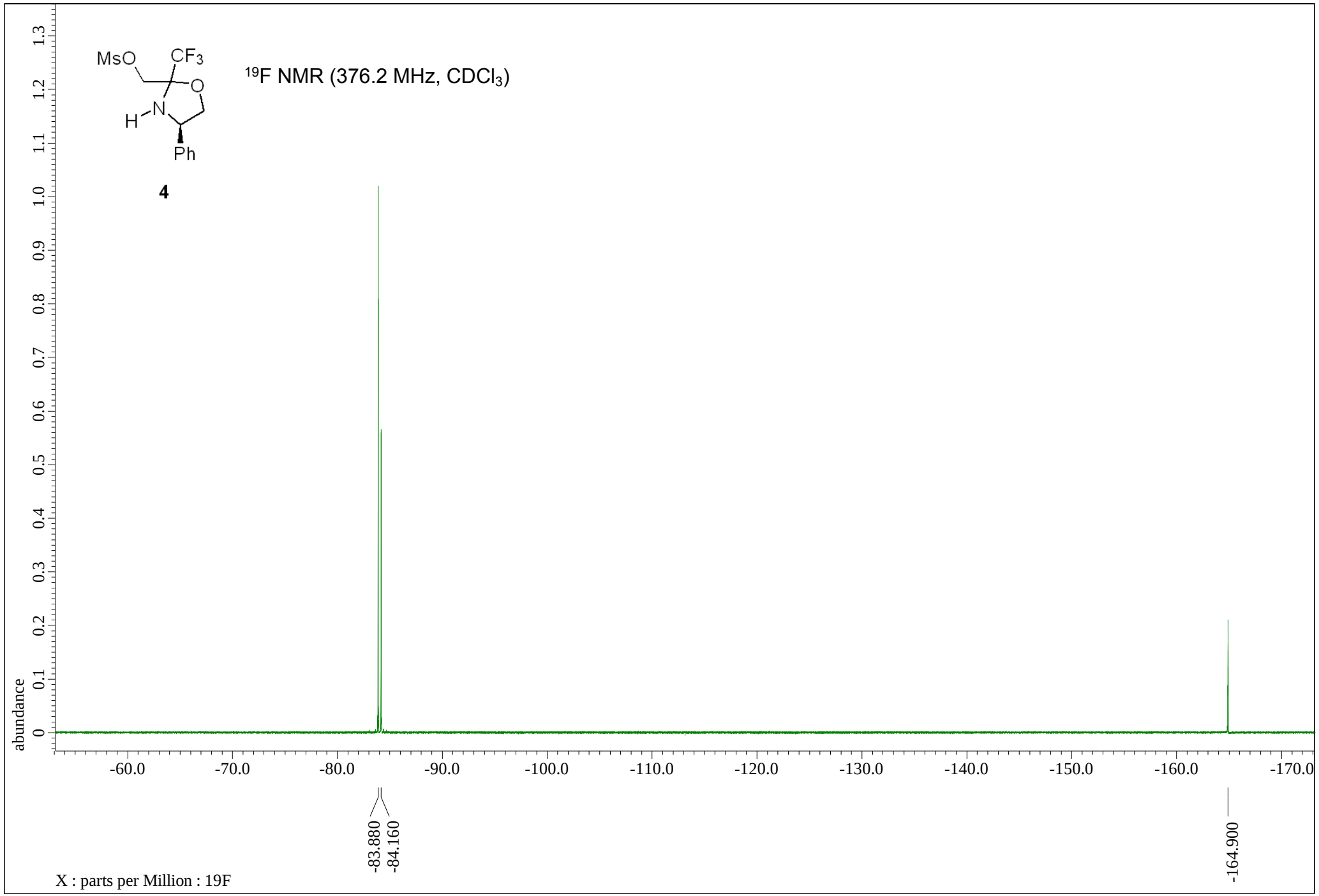

CO2Bn
CF3
N
Bn
(S)-7
277.96
13C NMR (100.5 MHz, CDCl3)
0.2
0.1
0
abundance
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
163.927
137.239
134.570
128.563
128.410
128.382
128.067
127.838
127.467
124.129
122.747
121.364
77.315
77.000
76.676
67.914
55.700
37.651
X : parts per Million : 13C

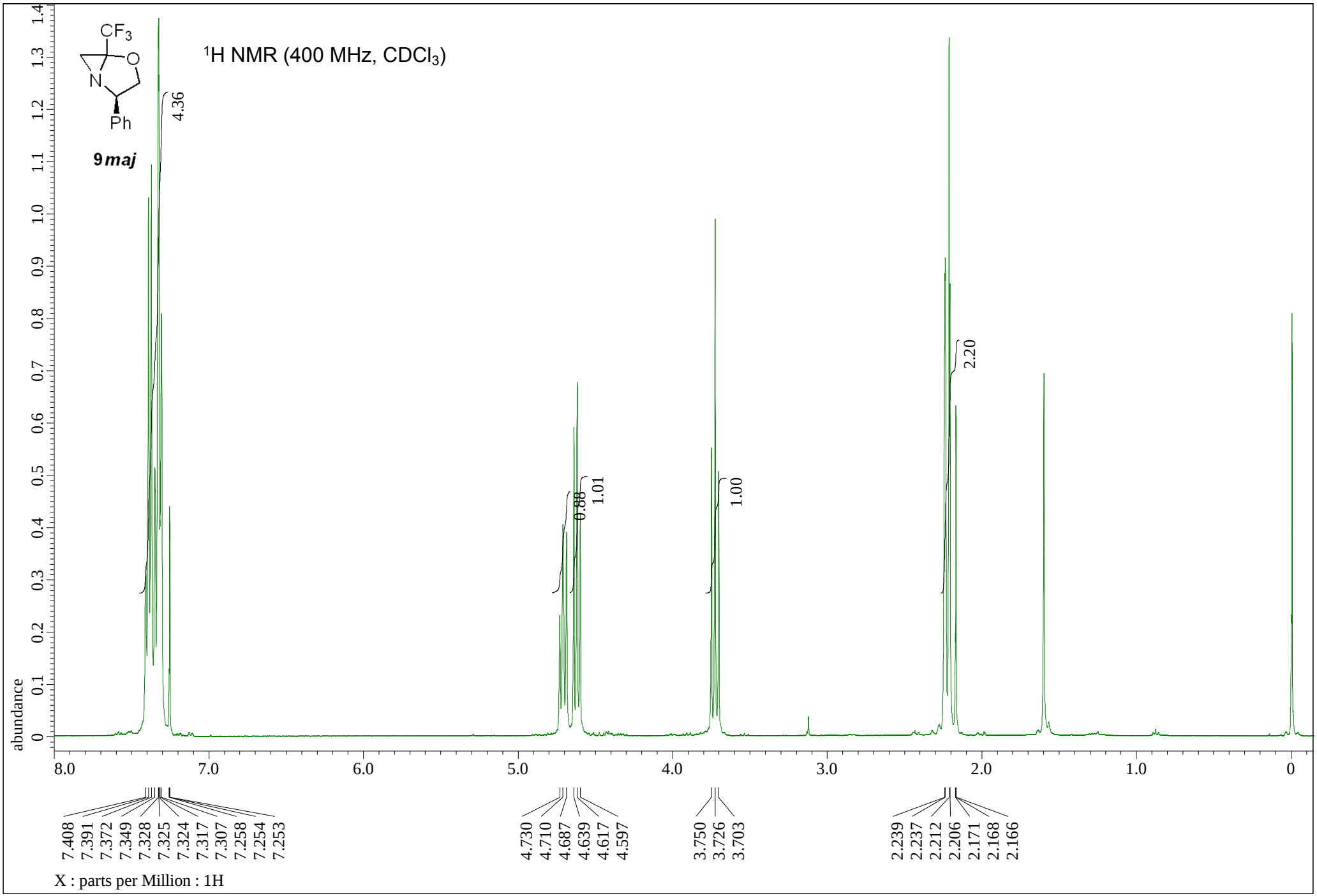

CO2Bn
CF3
N
Bn
(S)-7
19F NMR (376.2 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-73.699
-164.900
X : parts per Million : 19F

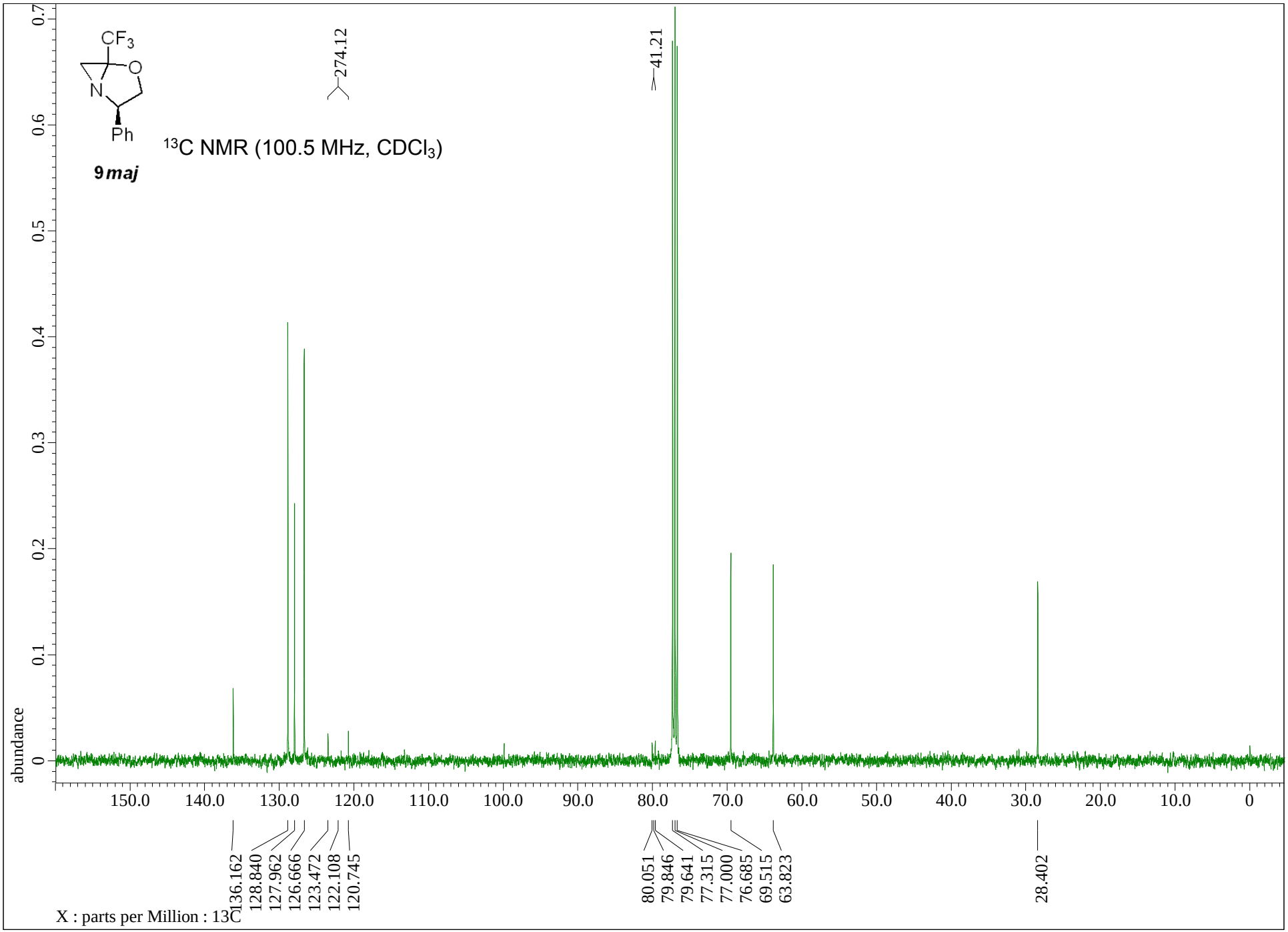

CO2Bn
CF3
N
Bn
(S)-7
1H NMR (400 MHz, CDCl3)
10.02
2.00
2.00
1.95
abundance
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.250
7.203
7.176
5.164
5.133
5.071
5.040
3.904
3.873
3.685
3.652
2.477
2.442
X : parts per Million : 1H

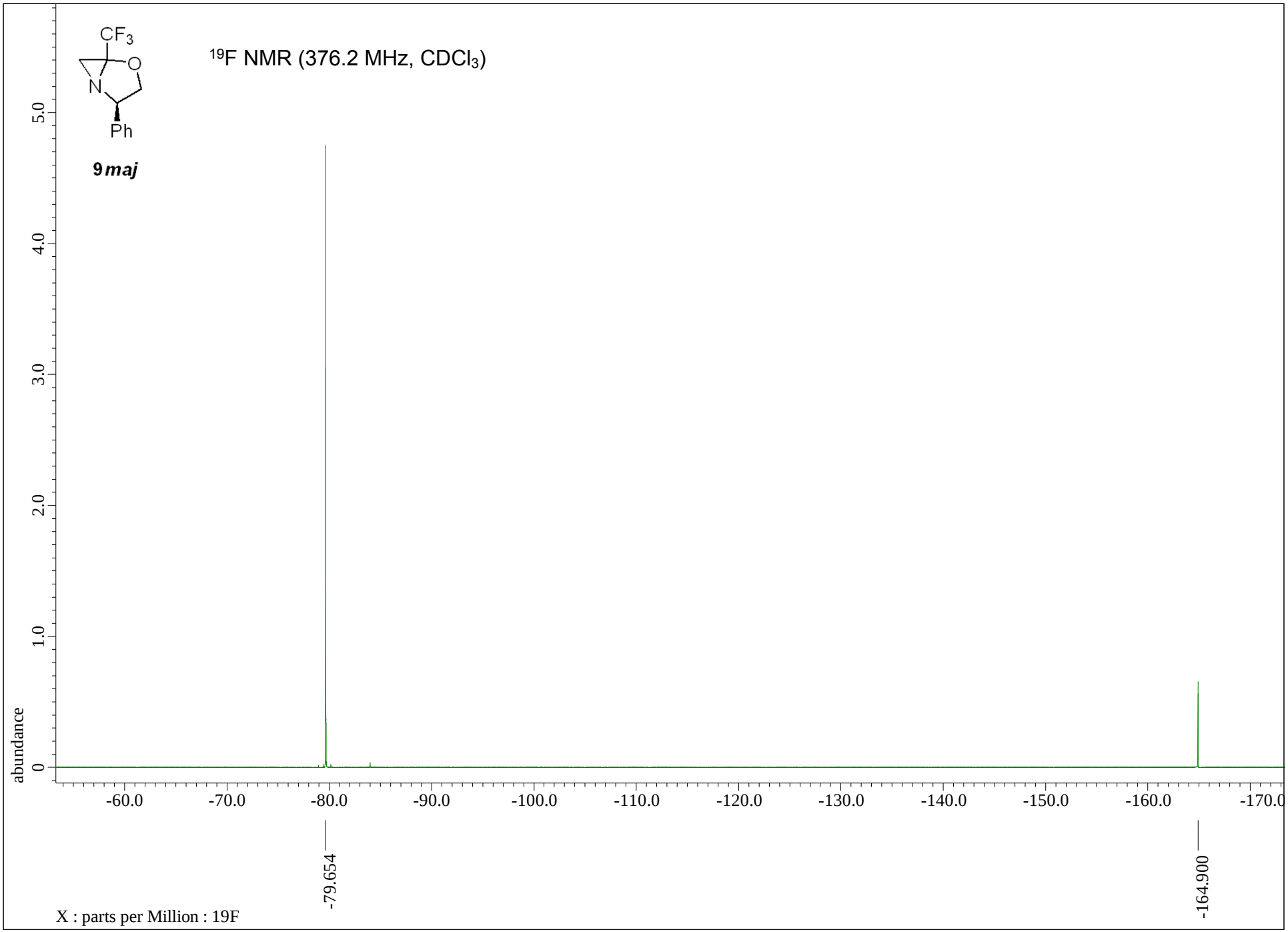

MsO
CF3
O
N
H
Ph
4
1H NMR (400 MHz, CDCl3)
abundance
4.54
0.84
2.64
0.84
0.64
3.00
7.429
7.410
7.394
7.380
7.360
7.341
7.326
7.307
7.261
7.259
7.257
4.704
4.628
4.609
4.588
4.545
4.516
4.479
4.451
4.435
4.419
4.400
3.849
3.828
3.676
3.675
3.673
3.139
3.125
1.415
1.397
1.379
1.254
0.040
-0.000
-0.002
-0.003
-0.012
-0.041
X : parts per Million : 1H

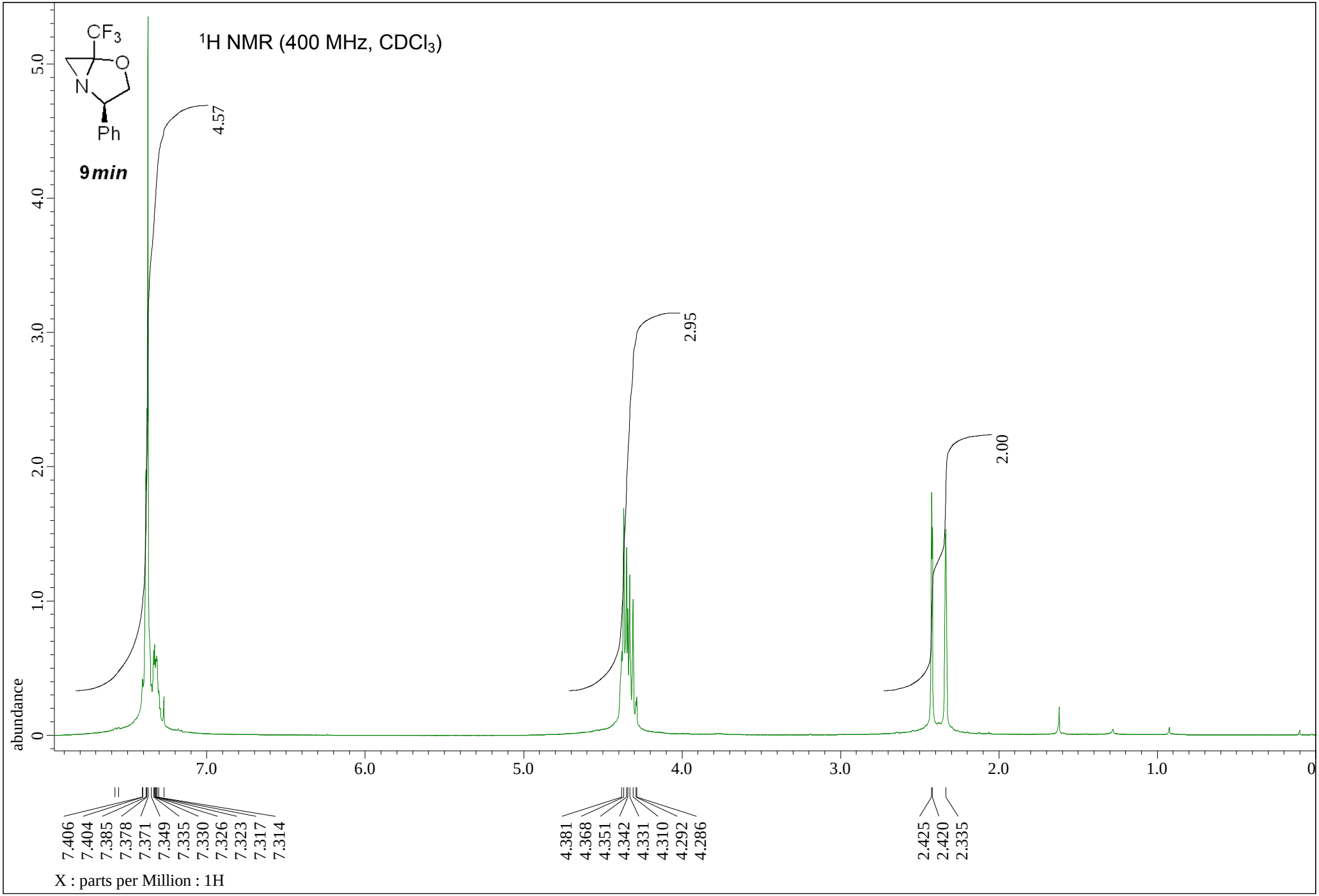

MsO
CF3
O
N
H
Ph
4
13C NMR (100.5 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
138.005
137.194
129.185
128.804
128.728
128.318
127.011
126.954
125.229
125.095
122.368
122.225
94.260
93.965
93.059
92.725
77.422
77.107
76.793
75.468
74.791
67.497
66.953
61.986
61.251
38.044
31.608
0.068
X : parts per Million : 13C

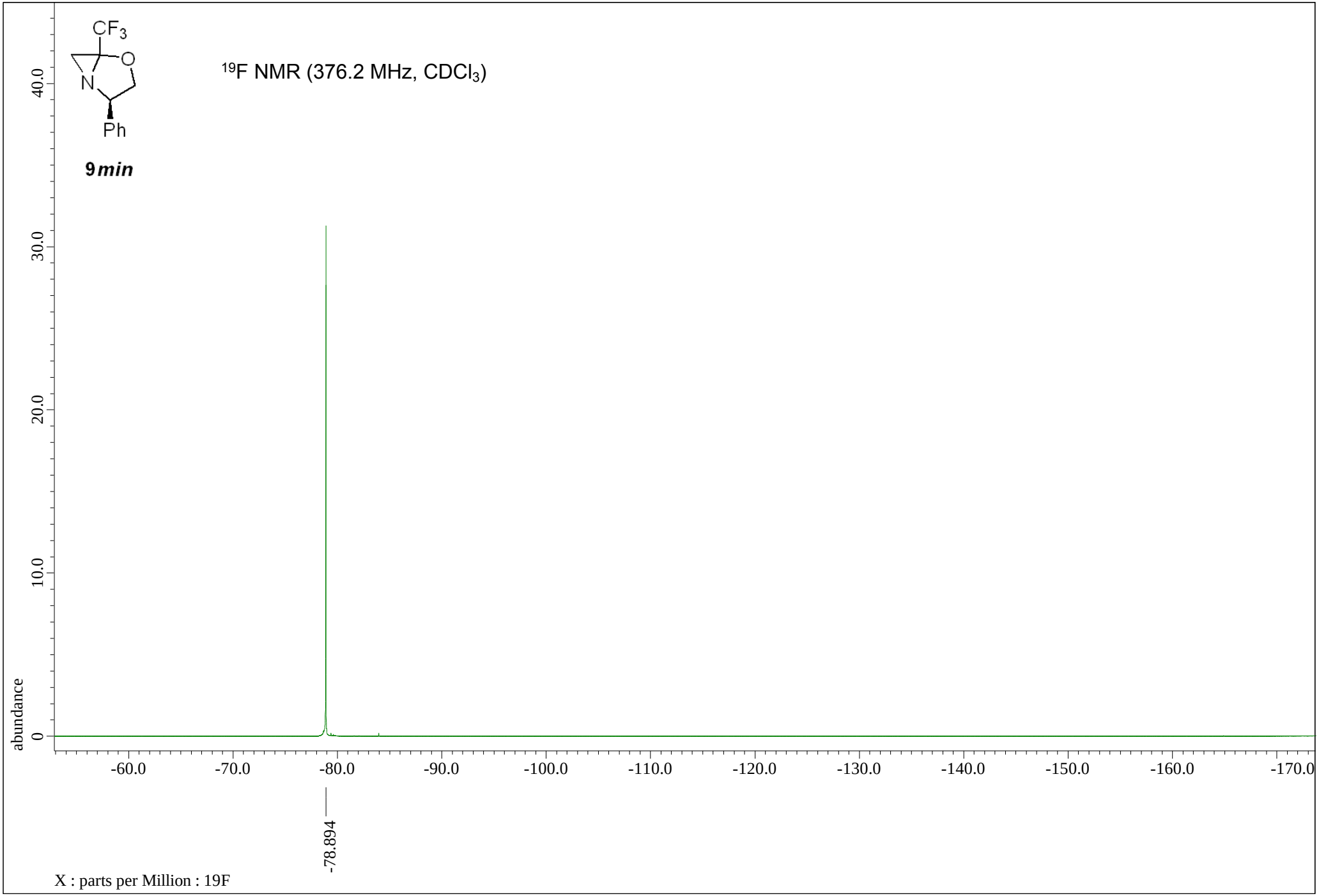

MsO
CF3
O
H
N
Ph
4
19F NMR (376.2 MHz, CDCl3)
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-83.880
-84.160
-164.900
X : parts per Million : 19F

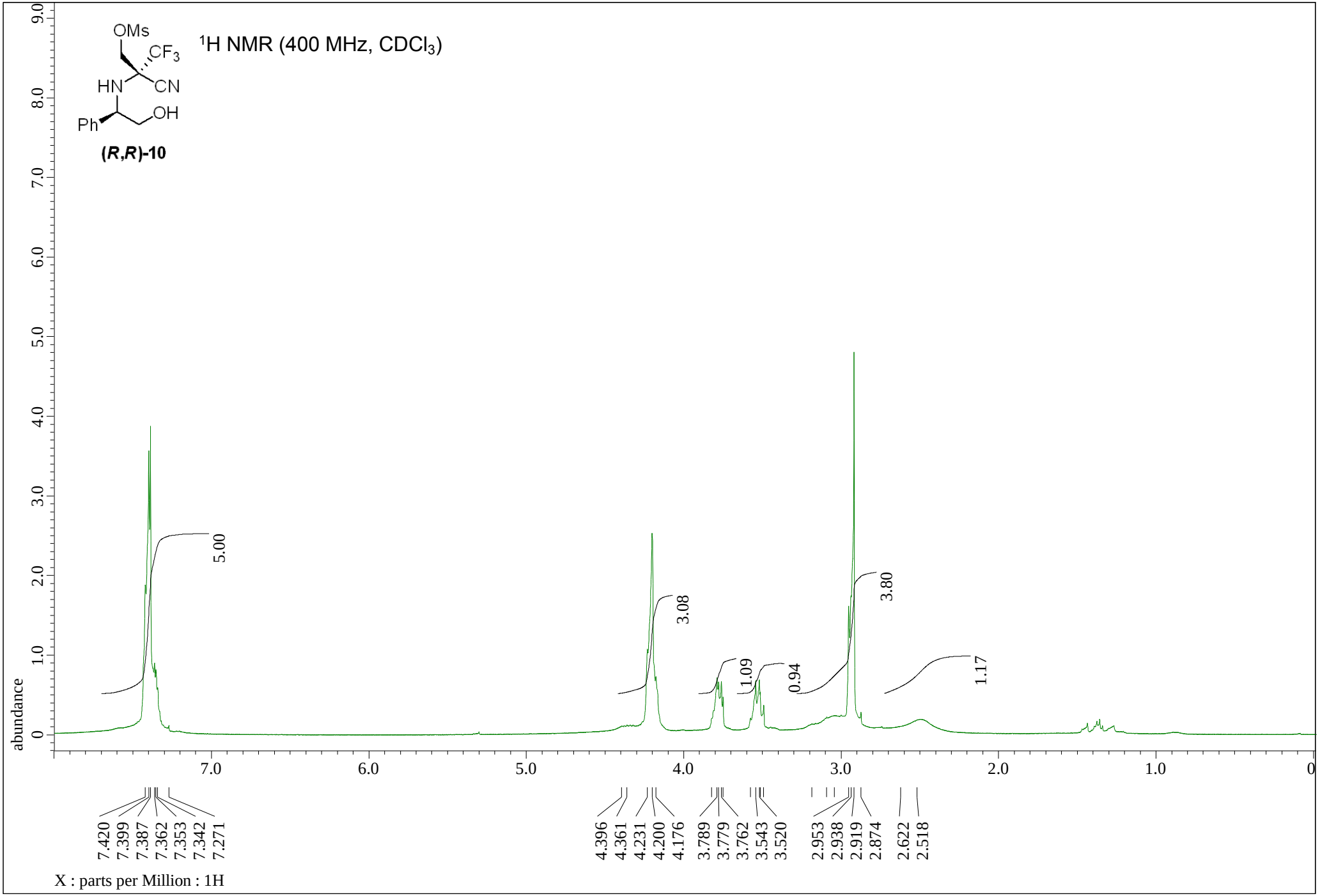

^{1}H NMR (400 MHz, $CDCl_3$)
CF_3
O
N
Ph
9*maj*
4.36
0.88
1.01
1.00
2.20
abundance
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.408
7.391
7.372
7.349
7.328
7.325
7.324
7.317
7.307
7.258
7.254
7.253
4.730
4.710
4.687
4.639
4.617
4.597
3.750
3.726
3.703
2.239
2.237
2.212
2.206
2.171
2.168
2.166
X : parts per Million : 1H

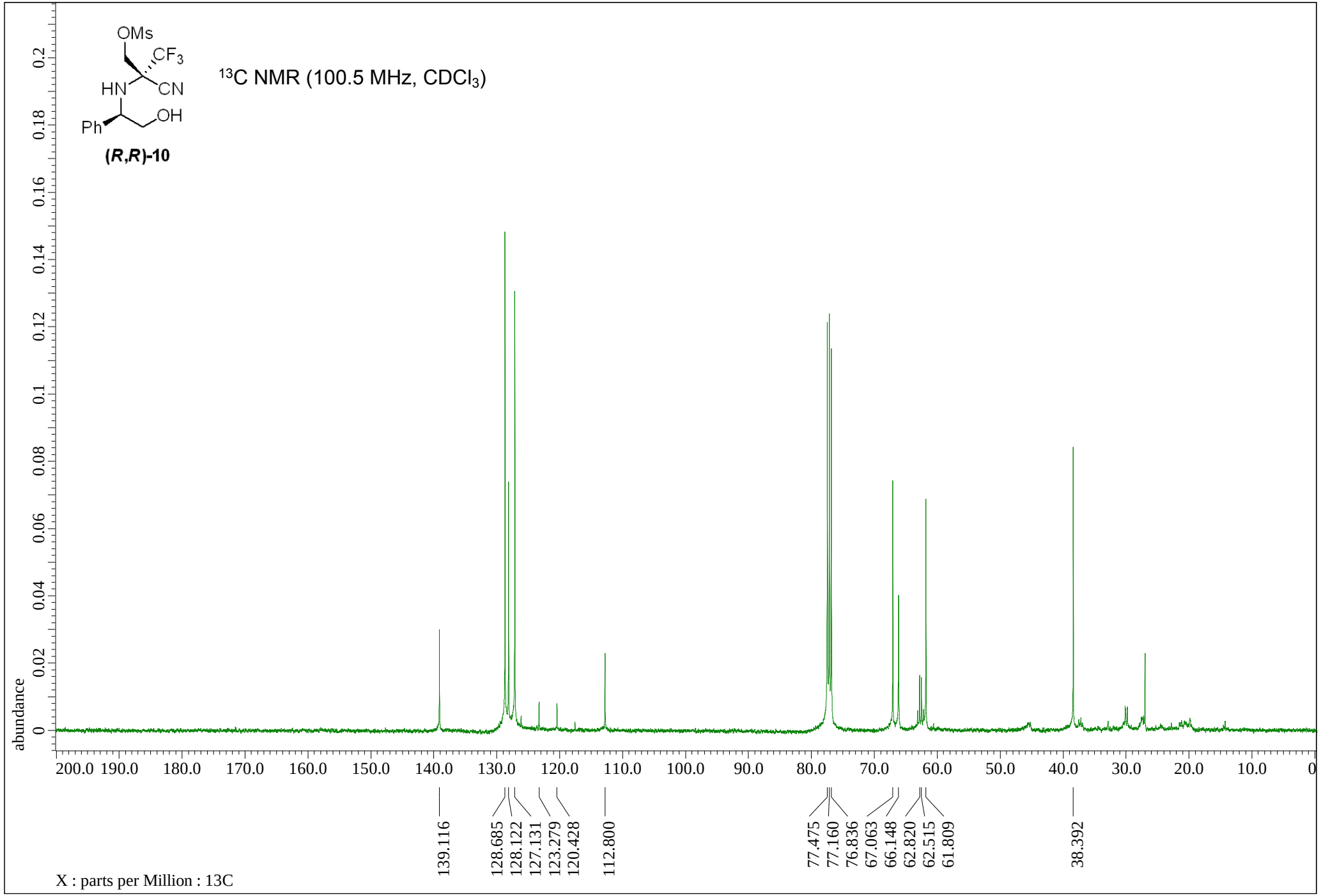

CF3
O
N
Ph
9maj
13C NMR (100.5 MHz, CDCl3)
274.12
41.21
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
136.162
128.840
127.962
126.666
123.472
122.108
120.745
80.051
79.846
79.641
77.315
77.000
76.685
69.515
63.823
28.402
X : parts per Million : 13C

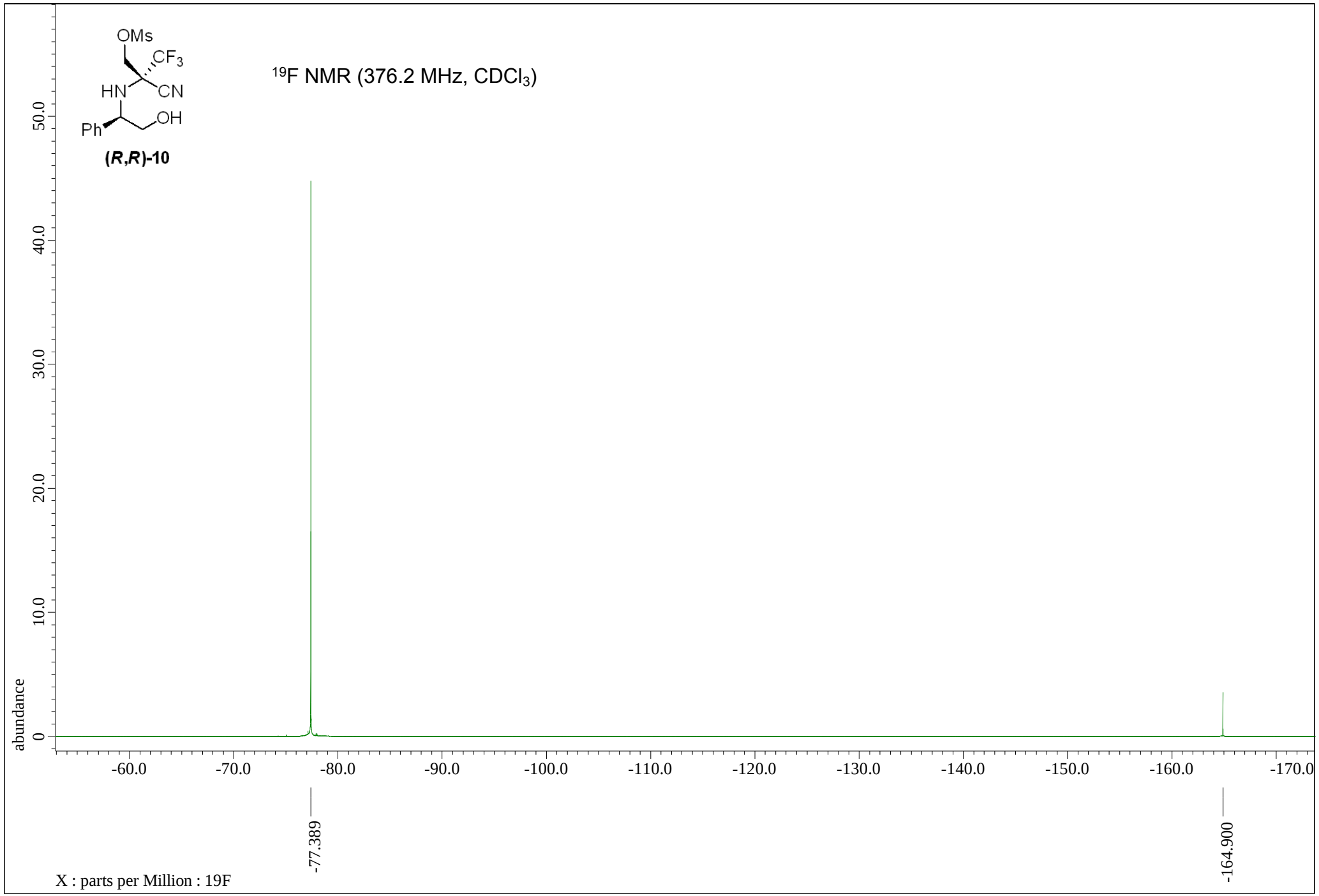

CF3
O
N
Ph
9maj
19F NMR (376.2 MHz, CDCl3)
abundance
5.0
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-79.654
-164.900
X : parts per Million : 19F

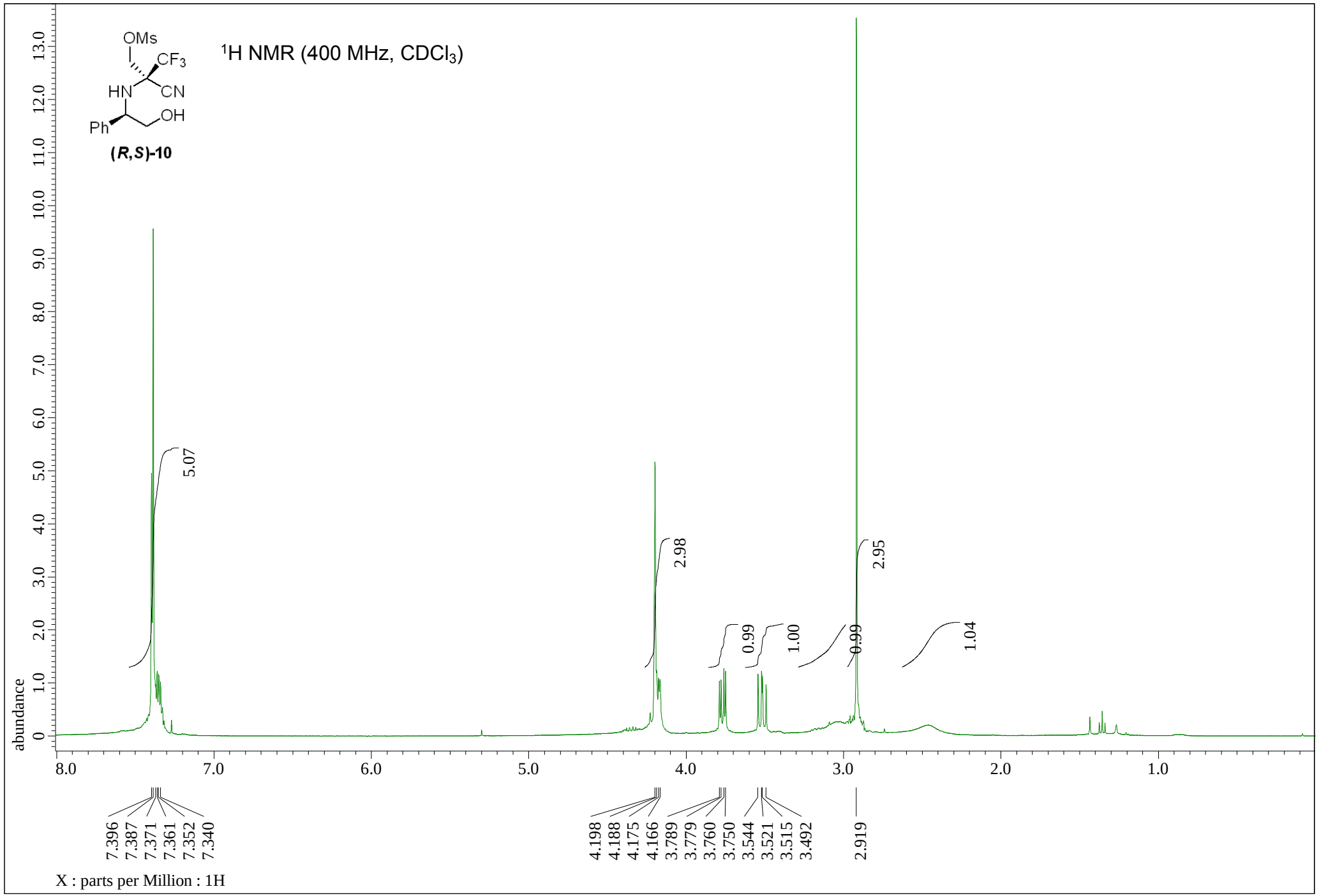

^{1}H NMR (400 MHz, $CDCl_3$)
CF_3
O
N
Ph
9*min*
4.57
2.95
2.00
abundance
5.0
4.0
3.0
2.0
1.0
0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.406
7.404
7.385
7.378
7.371
7.349
7.335
7.330
7.326
7.323
7.317
7.314
4.381
4.368
4.351
4.342
4.331
4.310
4.292
4.286
2.425
2.420
2.335
X : parts per Million : 1H

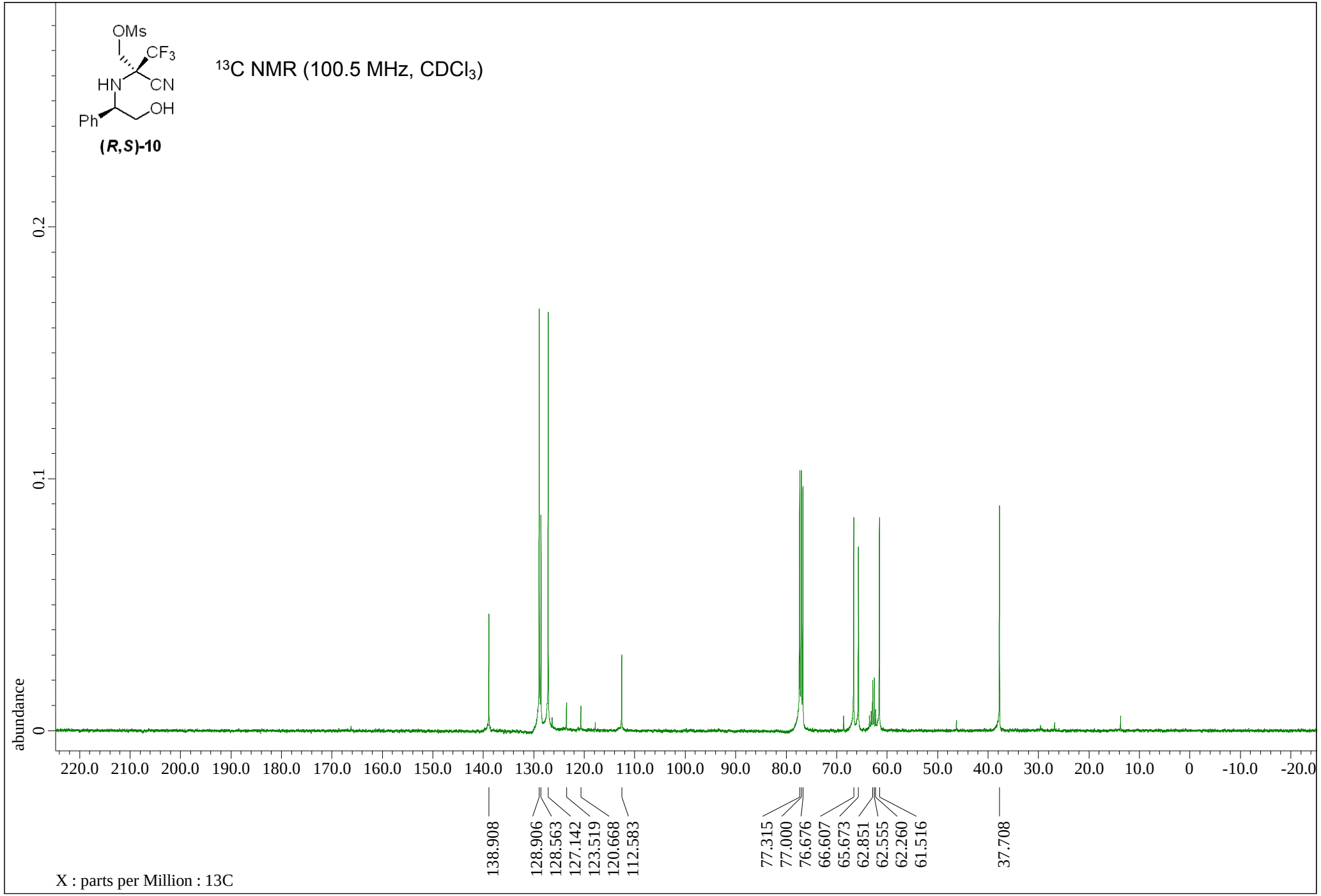

CF3
O
N
Ph
9 min
19F NMR (376.2 MHz, CDCl3)
40.0
30.0
20.0
10.0
0
abundance
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-78.894
X : parts per Million : 19F

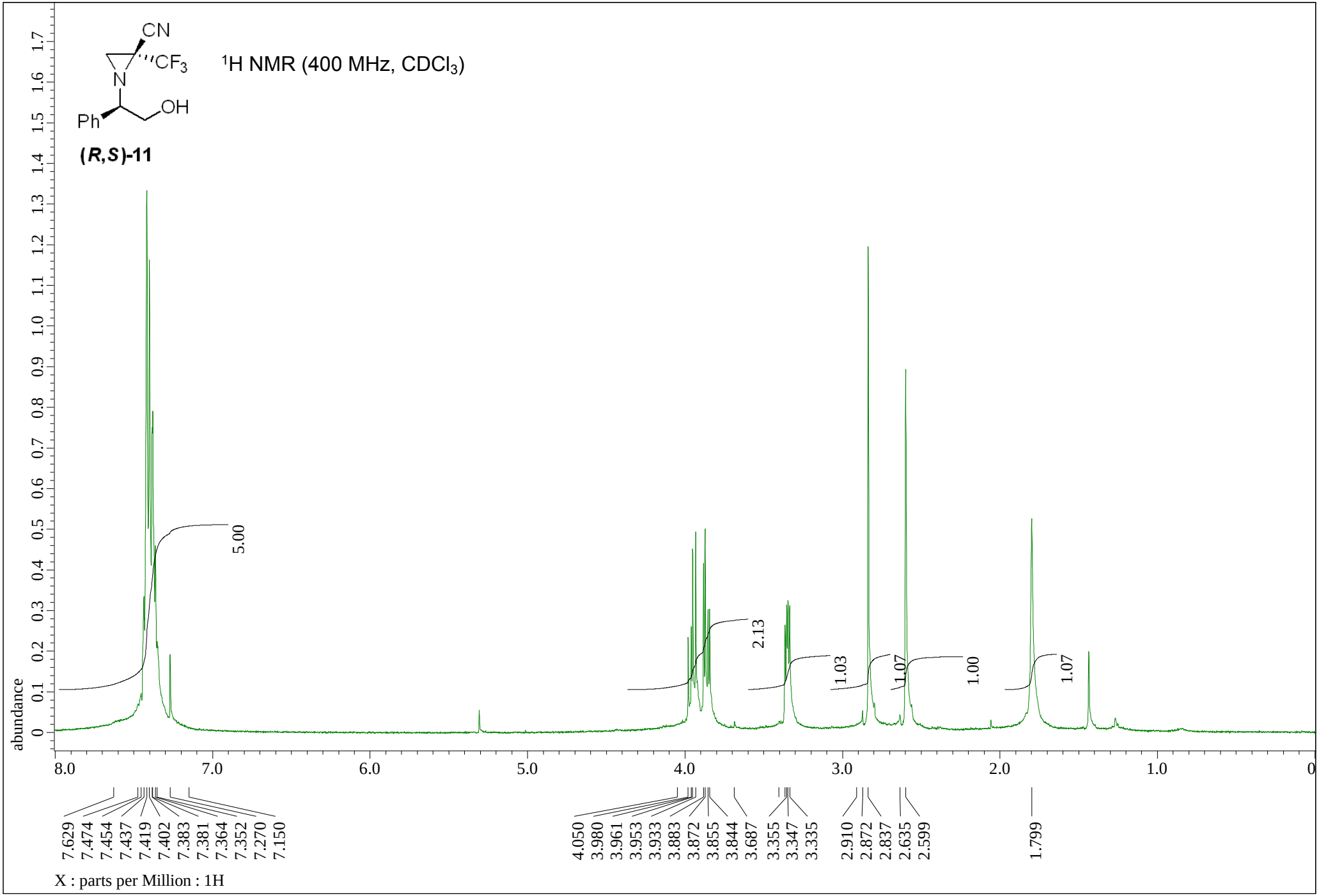

OMs
CF3
HN
CN
OH
Ph
(R,R)-10
1H NMR (400 MHz, CDCl3)
abundance
5.00
3.08
1.09
0.94
3.80
1.17
7.420
7.399
7.387
7.362
7.353
7.342
7.271
4.396
4.361
4.231
4.200
4.176
3.789
3.779
3.762
3.543
3.520
2.953
2.938
2.919
2.874
2.622
2.518
X : parts per Million : 1H

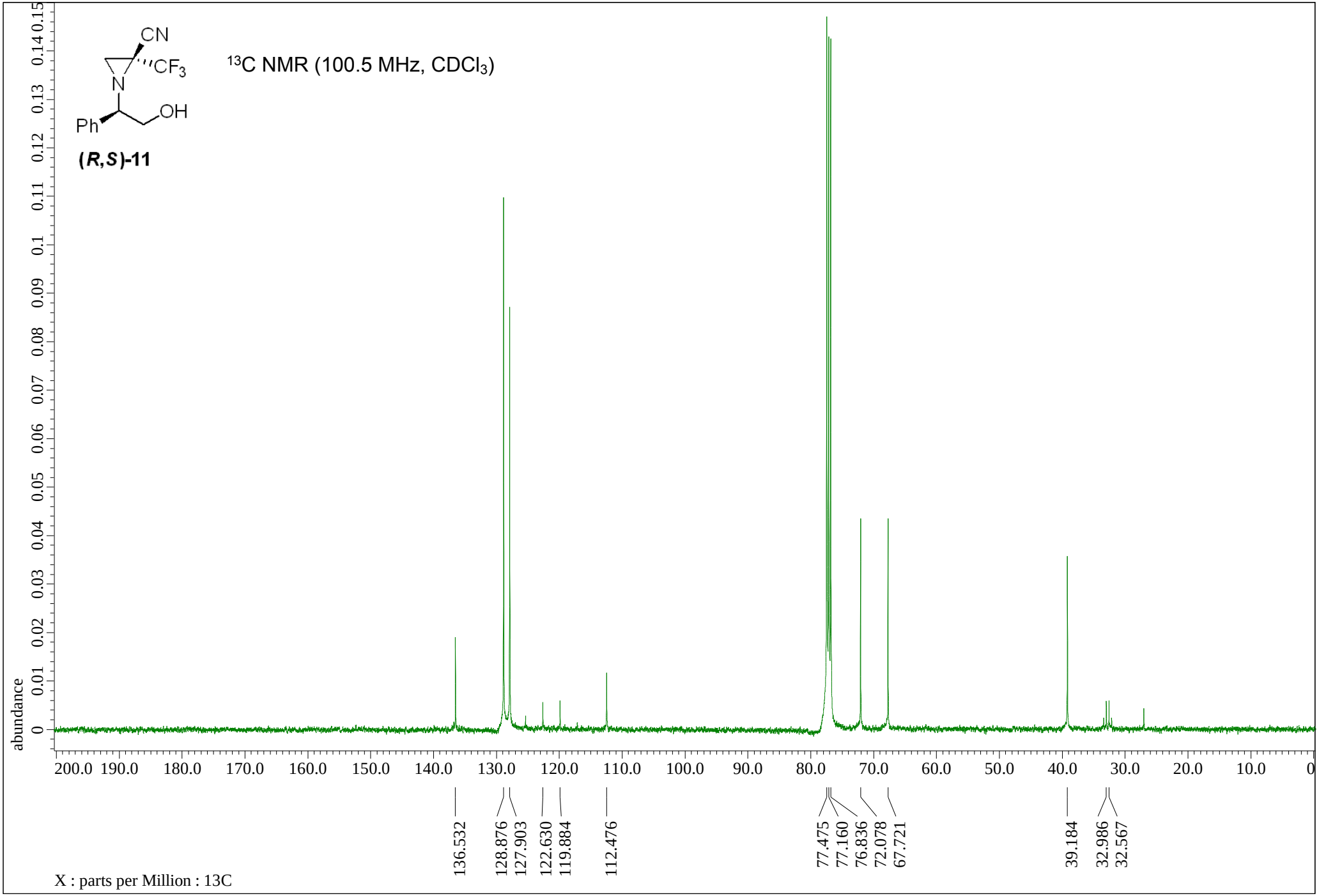

OMs
CF3
HN
CN
OH
Ph
(R,R)-10
13C NMR (100.5 MHz, CDCl3)
abundance
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
139.116
128.685
128.122
127.131
123.279
120.428
112.800
77.475
77.160
76.836
67.063
66.148
62.820
62.515
61.809
38.392
X : parts per Million : 13C

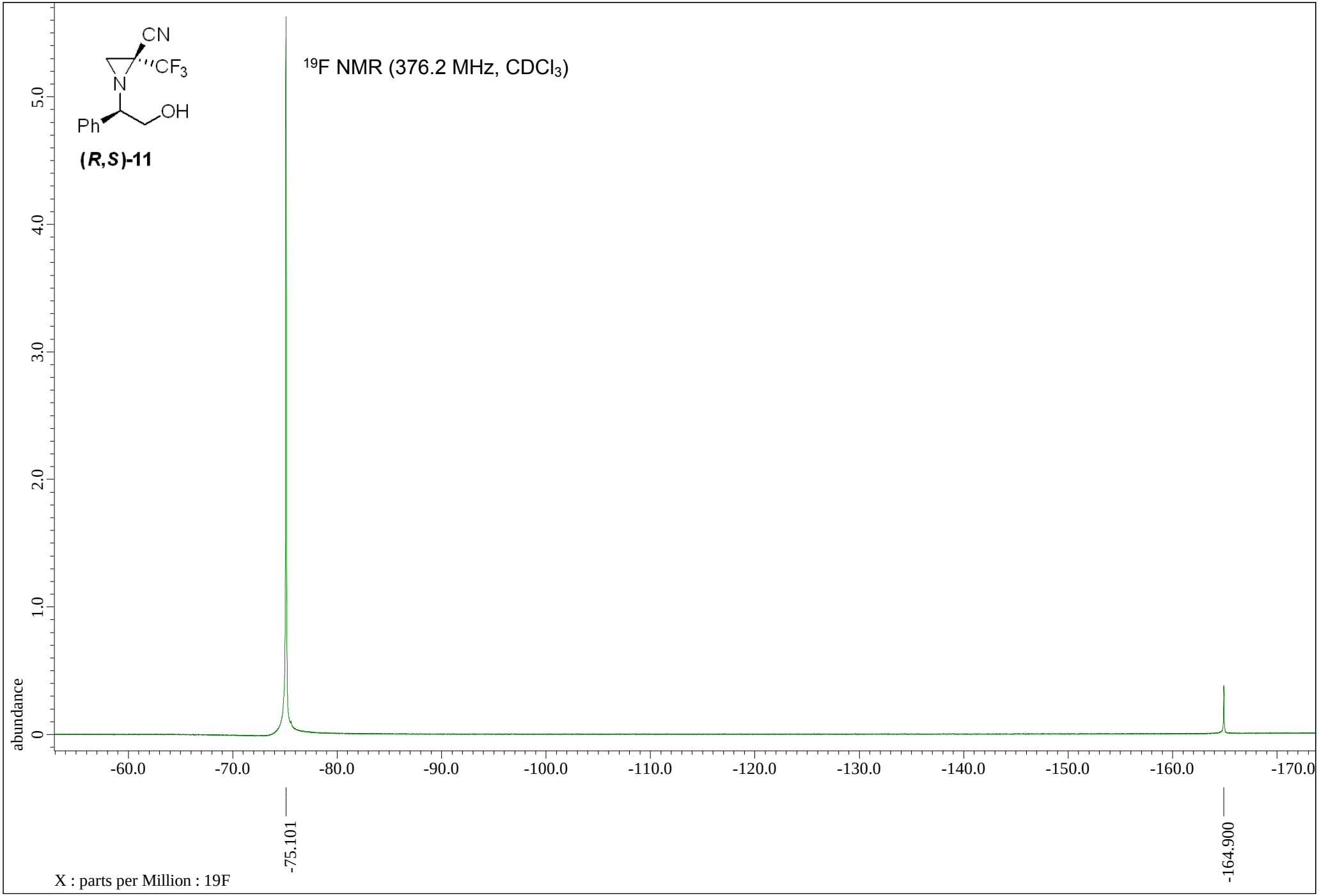

OMs
CF3
HN
CN
OH
Ph
(R,R)-10
19F NMR (376.2 MHz, CDCl3)
50.0
40.0
30.0
20.0
10.0
0
abundance
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-77.389
-164.900
X : parts per Million : 19F

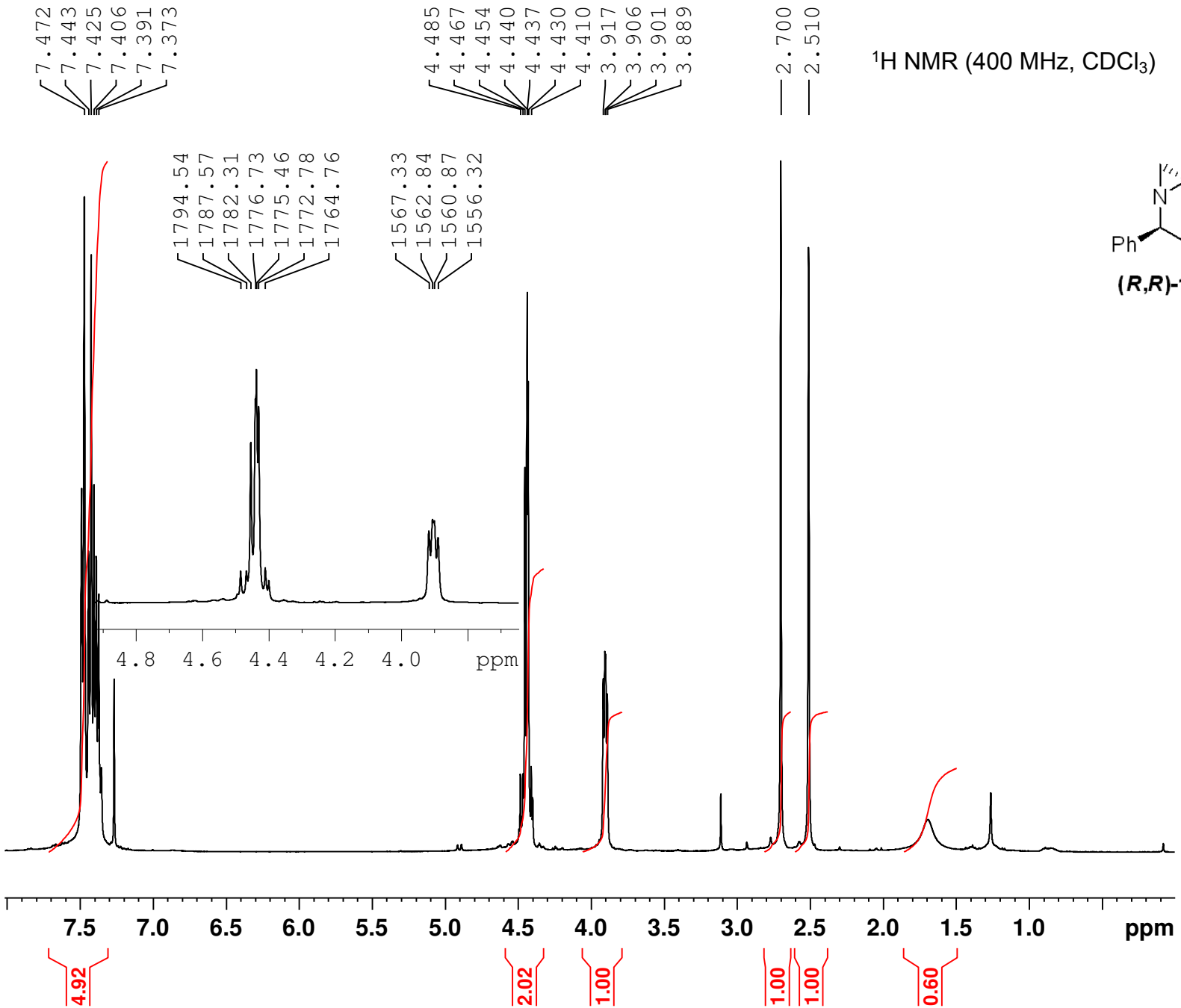

OMs
CF3
HN
CN
OH
Ph
(R,S)-10
1H NMR (400 MHz, CDCl3)
abundance
5.07
2.98
0.99
1.00
0.99
2.95
1.04
7.396
7.387
7.371
7.361
7.352
7.340
4.198
4.188
4.175
4.166
3.789
3.779
3.760
3.750
3.544
3.521
3.515
3.492
2.919
X : parts per Million : 1H


OMs
CF3
HN
CN
OH
Ph
(R,S)-10
13C NMR (100.5 MHz, CDCl3)
abundance
0
0.1
0.2
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
138.908
128.906
128.563
127.142
123.519
120.668
112.583
77.315
77.000
76.676
66.607
65.673
62.851
62.555
62.260
61.516
37.708
X : parts per Million : 13C


CN
CF3
N
OH
Ph
(R,S)-11
1H NMR (400 MHz, CDCl3)
abundance
5.00
2.13
1.03
1.07
1.00
1.07
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.629
7.474
7.454
7.437
7.419
7.402
7.383
7.381
7.364
7.352
7.270
7.150
4.050
3.980
3.961
3.953
3.933
3.883
3.872
3.855
3.844
3.687
3.355
3.347
3.335
2.910
2.872
2.837
2.635
2.599
1.799
X : parts per Million : 1H

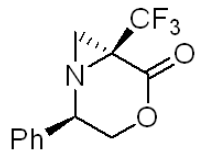

CN
CF3
N
OH
Ph
(R,S)-11
13C NMR (100.5 MHz, CDCl3)
abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0
136.532
128.876
127.903
122.630
119.884
112.476
77.475
77.160
76.836
72.078
67.721
39.184
32.986
32.567
X : parts per Million : 13C


CN
CF3
N
OH
Ph
(R,S)-11
19F NMR (376.2 MHz, CDCl3)
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
-75.101
-164.900
X : parts per Million : 19F



^{1}H NMR (400 MHz, $CDCl_3$)

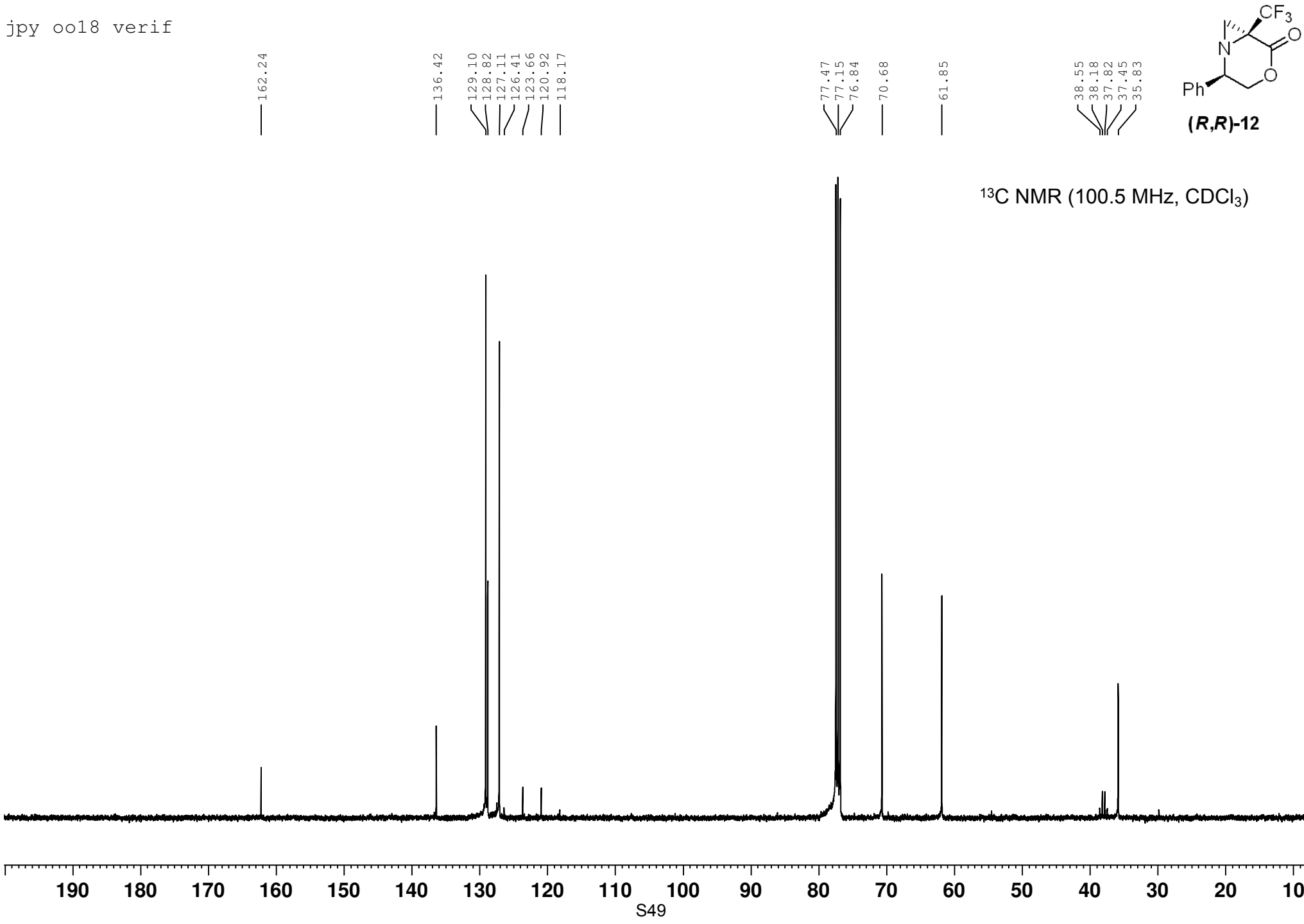
jpy oo18 verif

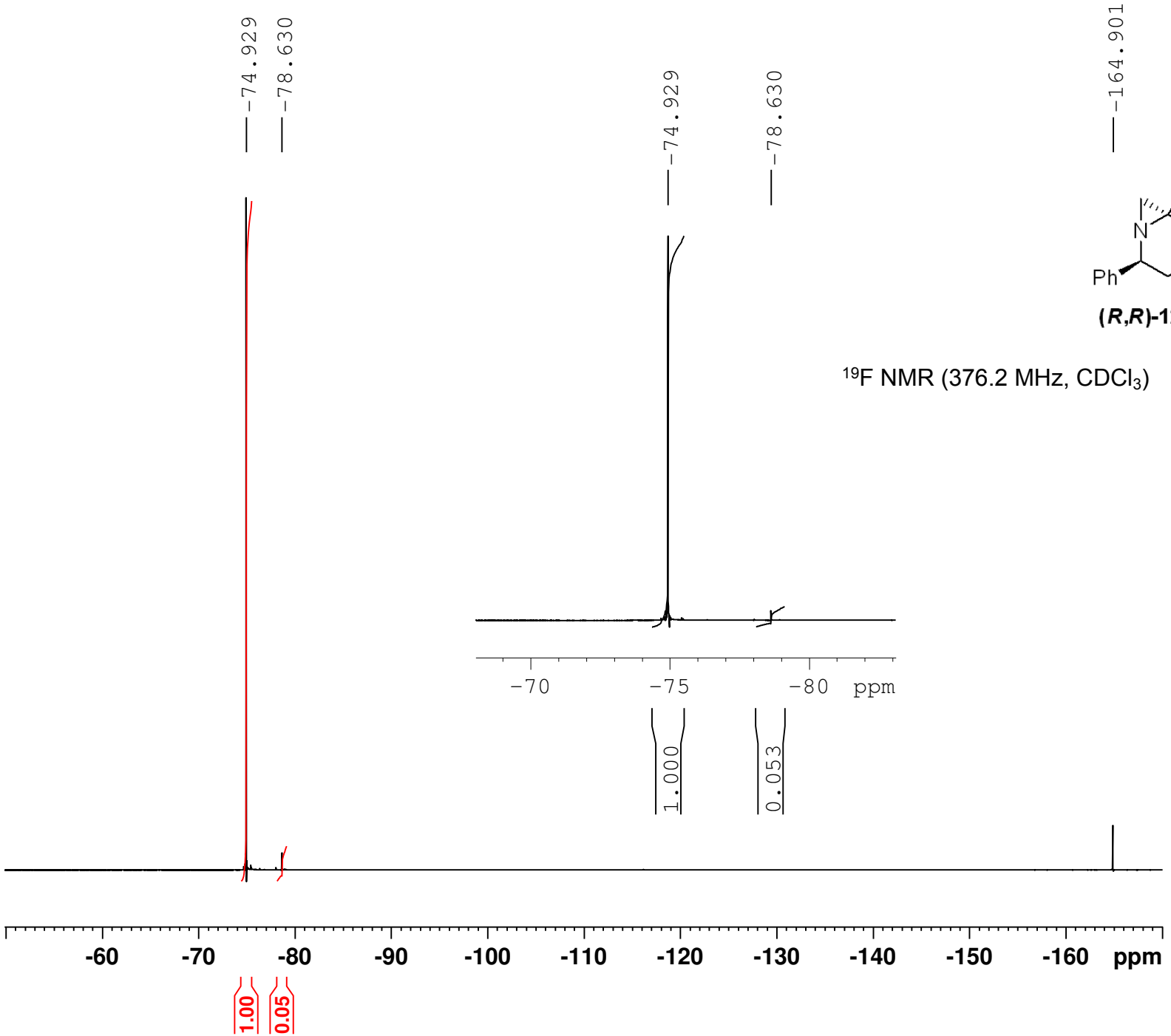


(*R*,*R*)-12

```
Current Data Parameters
NAME      jpy oo18 verif
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20191115
Time              13.48 h
INSTRUM  Avance Neo 400
PROBHD   Z163739_0087 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8196.722 Hz
FIDRES          0.250144 Hz
AQ              3.9976959 sec
RG                   101
DW                61.000 usec
DE                13.89 usec
TE                293.1 K
D1           1.00000000 sec
TD0                    1
SFO1         400.1424709 MHz
NUC1                  1H
P0                 2.67 usec
P1                 8.00 usec
PLW1         24.04299927 W

F2 - Processing parameters
SI                 65536
SF           400.1400070 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

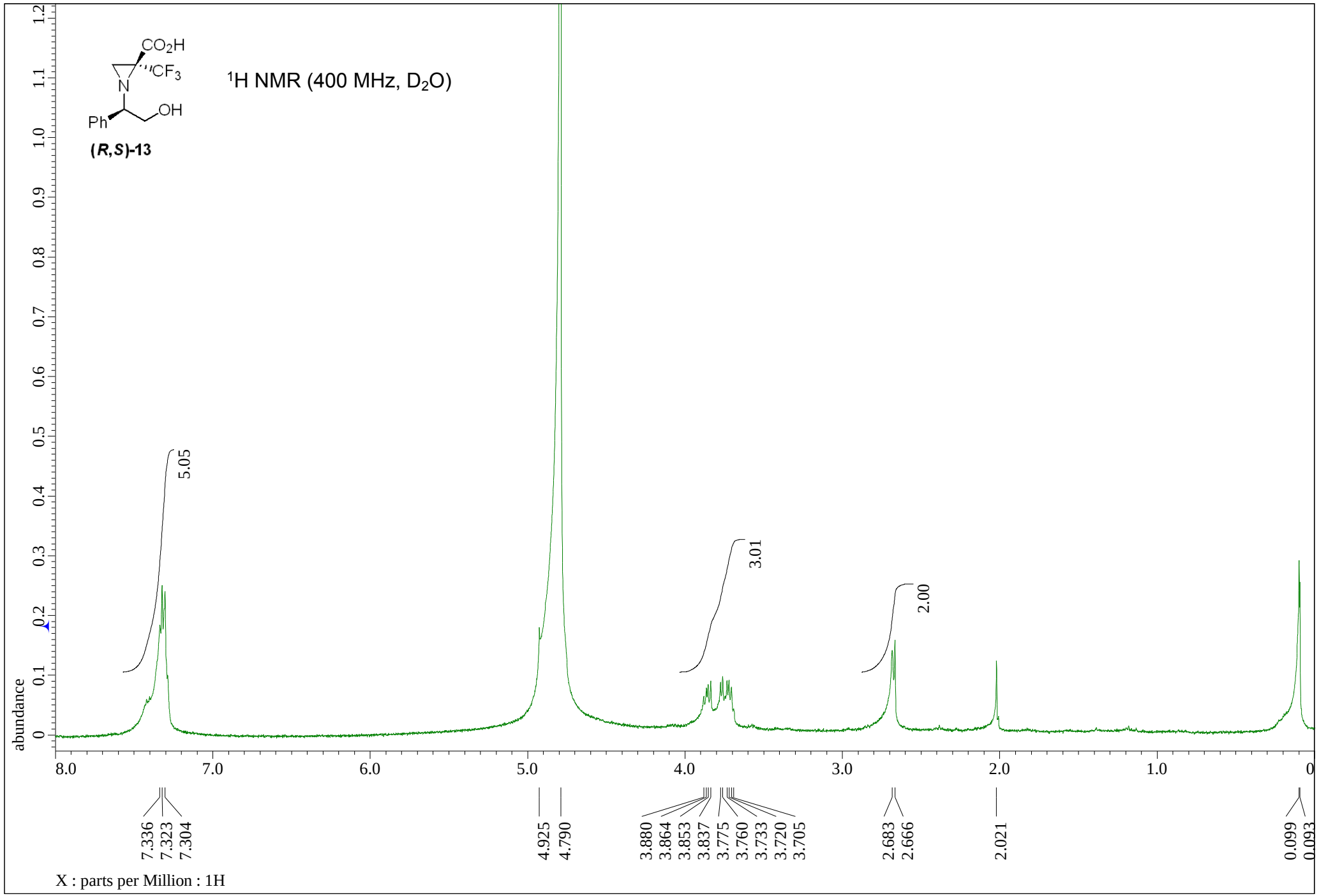
jpy oo18 verif

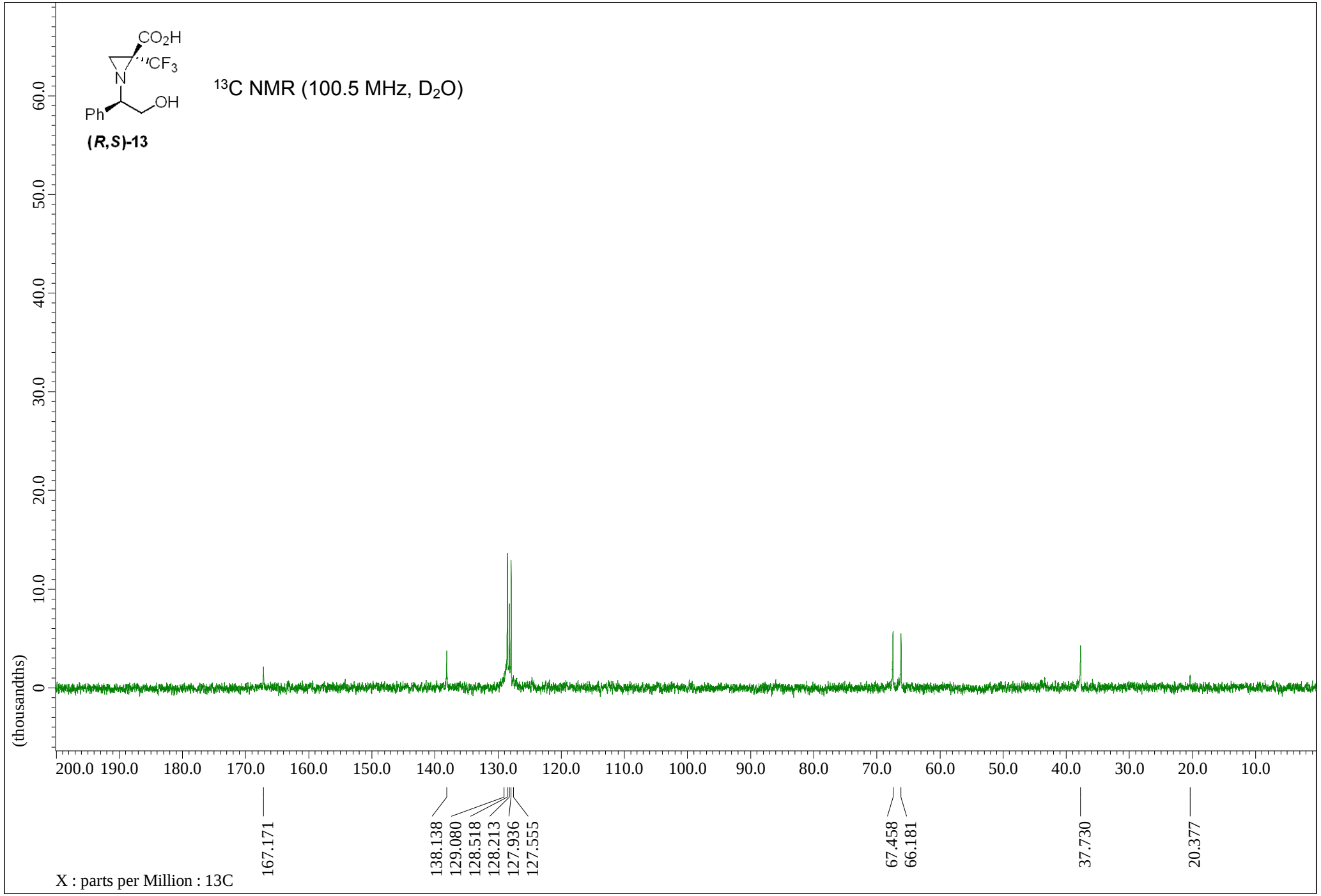


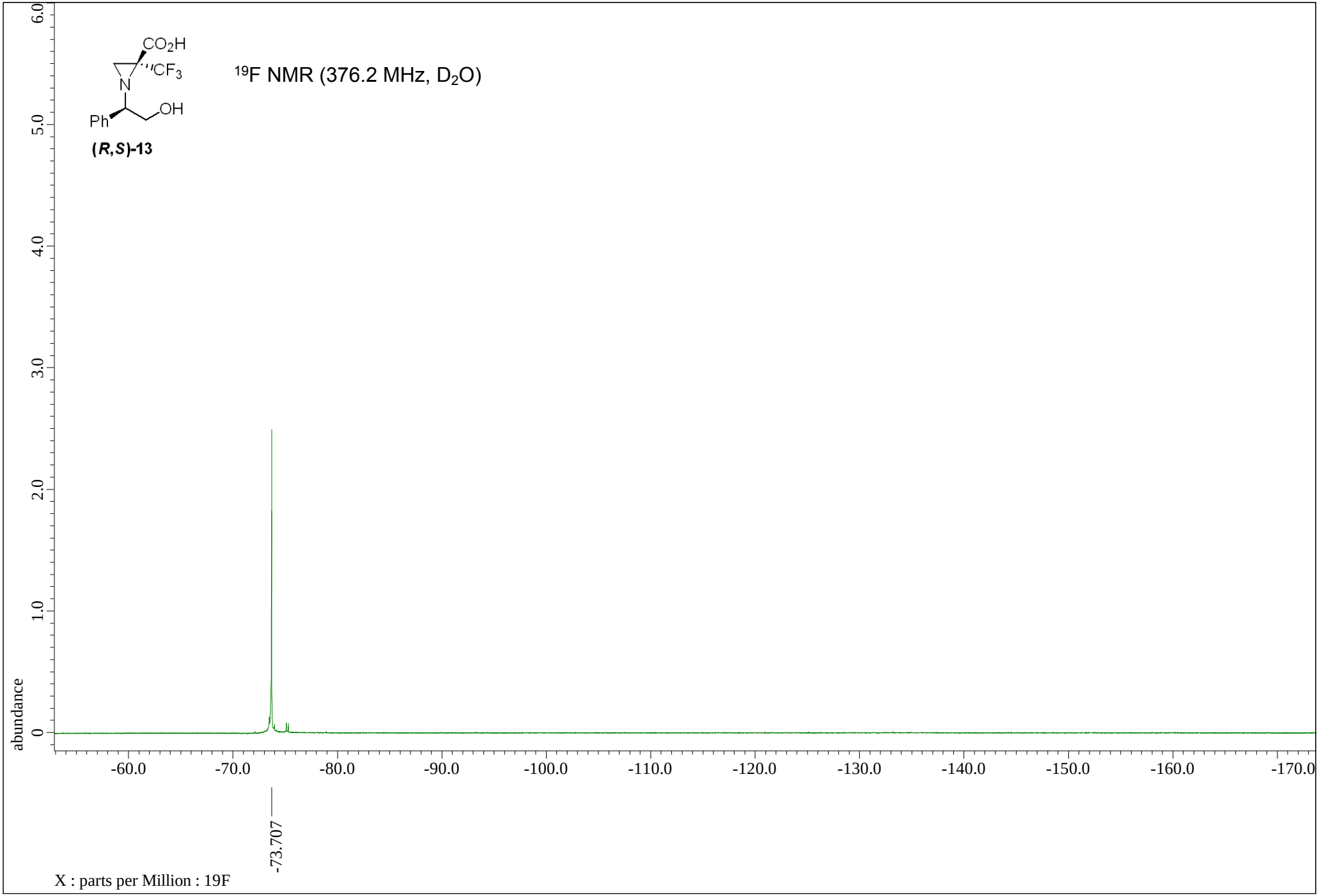


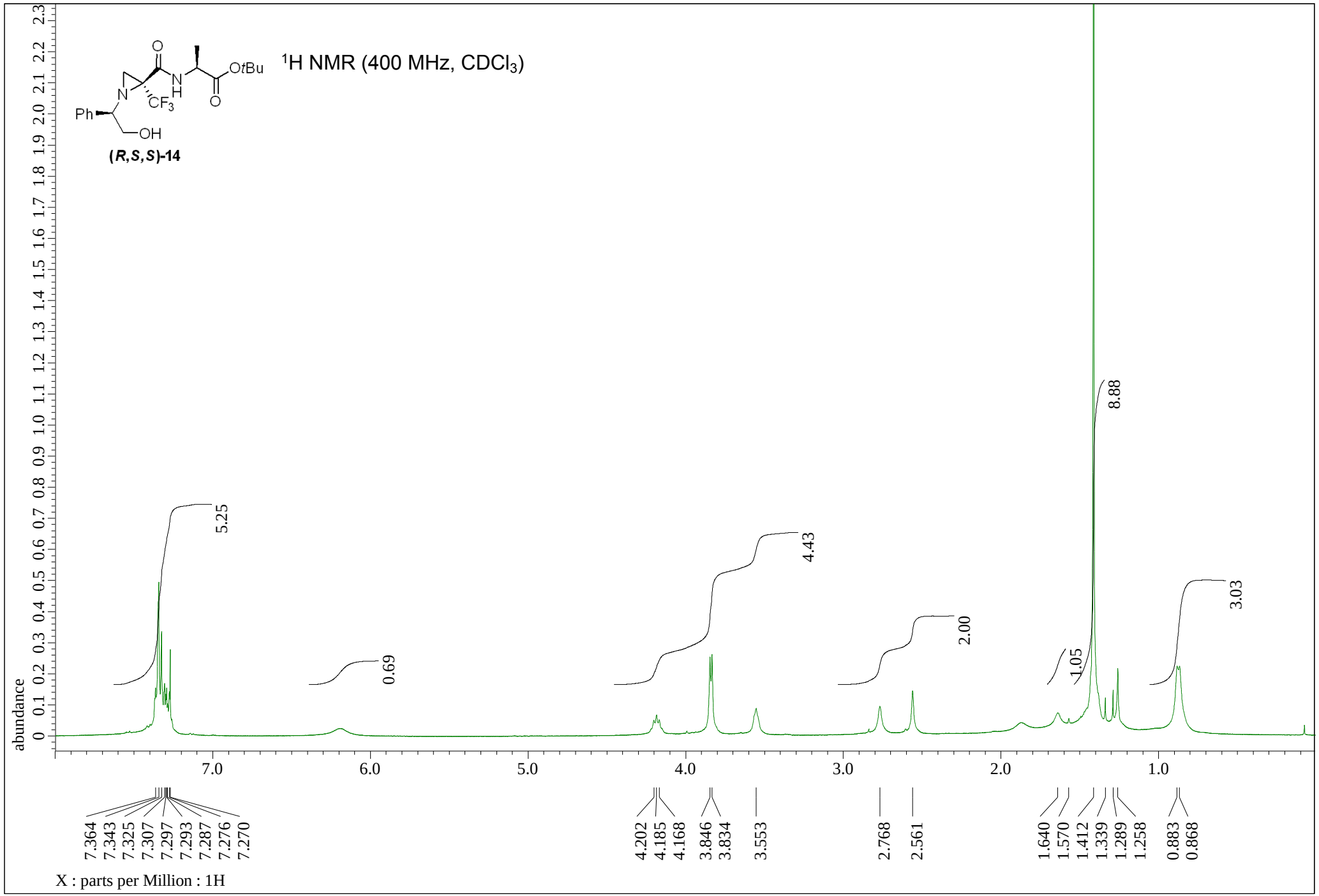
jpy oo18 verif

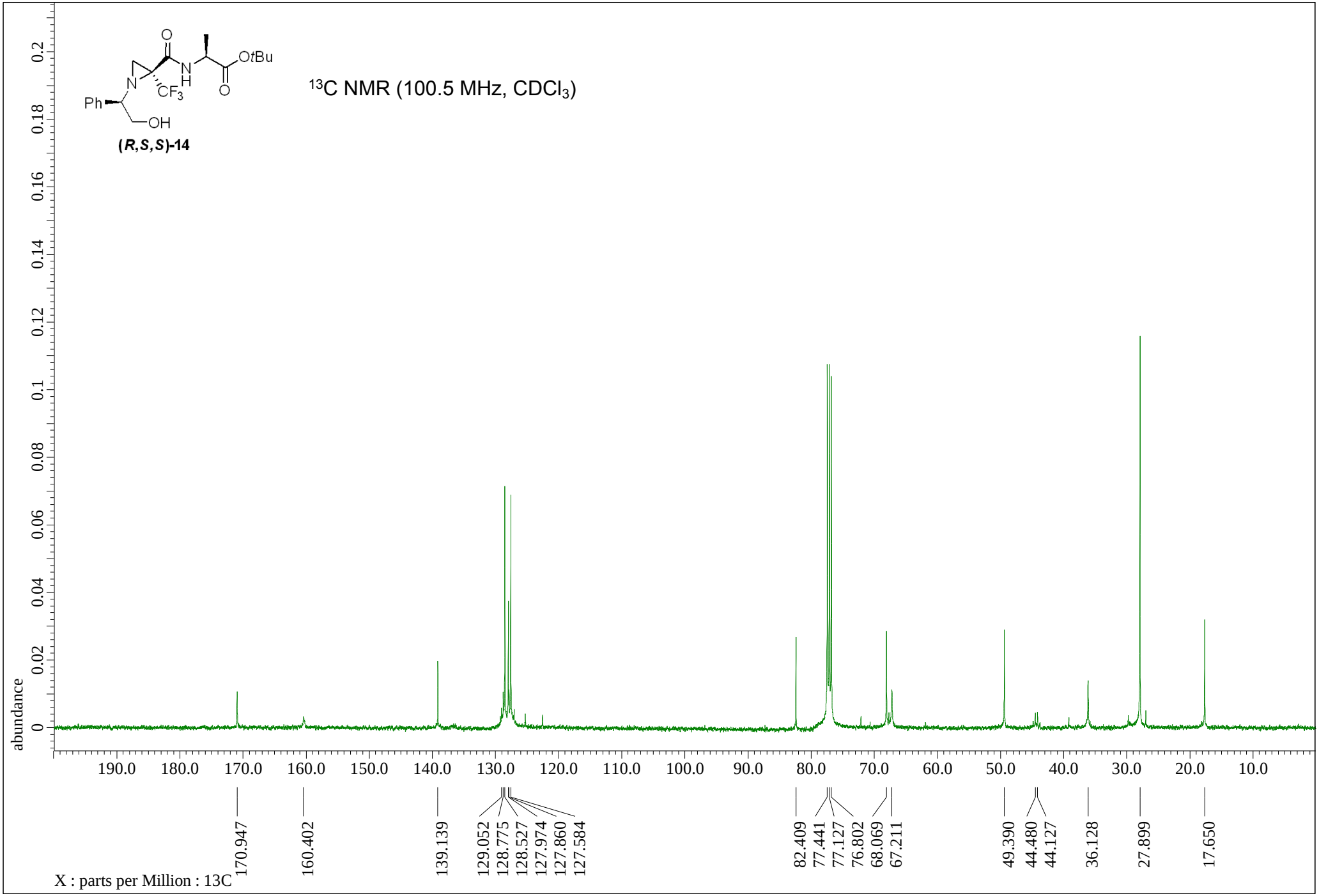
```
Current Data Parameters
NAME      jpy oo18 verif
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20191115
Time              13.50 h
INSTRUM  Avance Neo 400
PROBHD   Z163739_0087 (
PULPROG            zgig
TD               131072
SOLVENT            CDCl3
NS                    16
DS                     4
SWH           90909.094 Hz
FIDRES         1.387163 Hz
AQ             0.7208960 sec
RG                   101
DW                 5.500 usec
DE                 6.50 usec
TE                293.2 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1
SFO1         376.4701248 MHz
NUC1                 19F
P1                12.00 usec
PLW1         34.92499924 W
SFO2         400.1416006 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         24.04299927 W
PLW12         0.18997000 W

F2 - Processing parameters
SI                 65536
SF           376.5089825 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

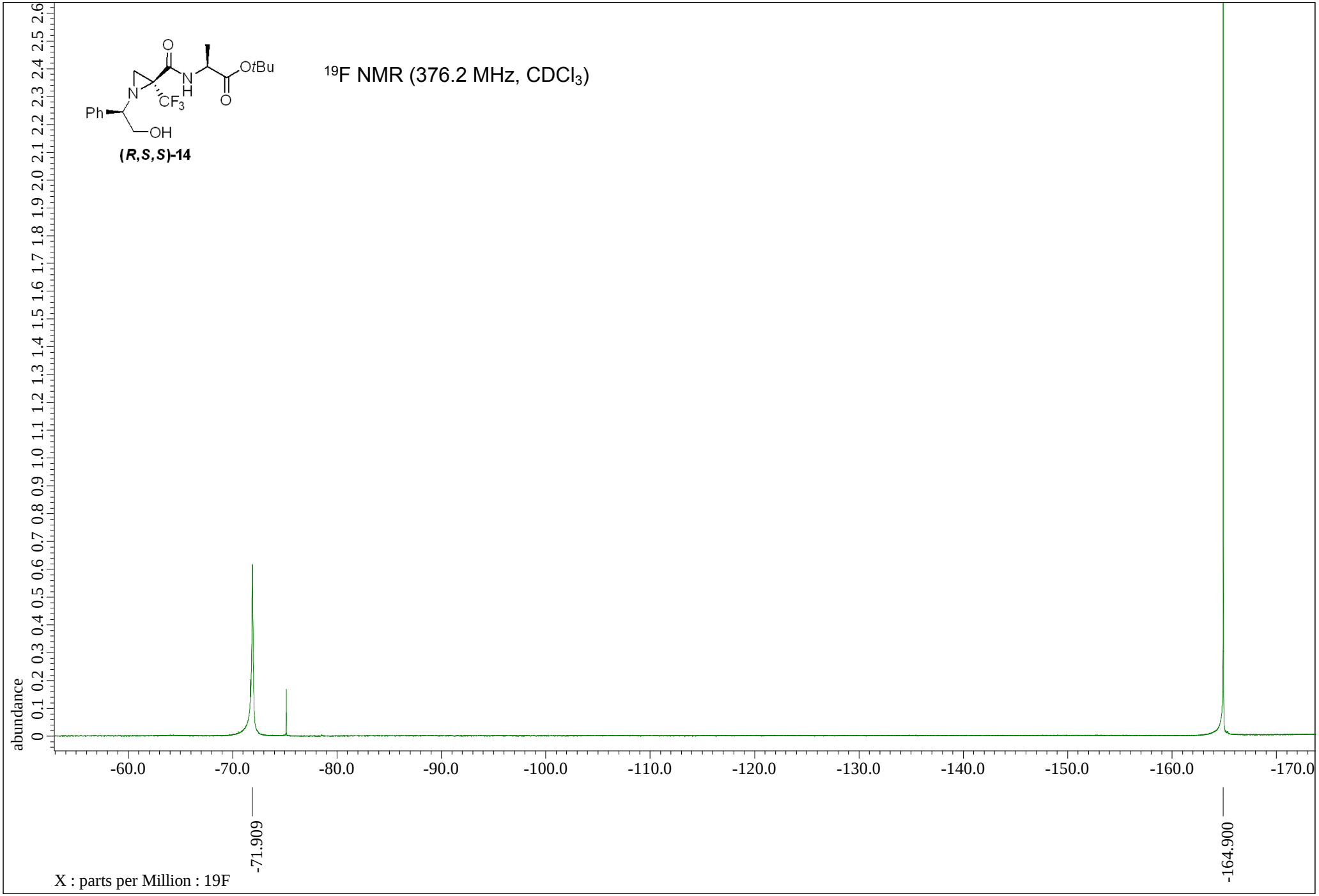

CO2H
CF3
N
Ph
OH
(R,S)-13
1H NMR (400 MHz, D2O)
abundance
5.05
3.01
2.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.336
7.323
7.304
4.925
4.790
3.880
3.864
3.853
3.837
3.775
3.760
3.733
3.720
3.705
2.683
2.666
2.021
0.099
0.093
X : parts per Million : 1H

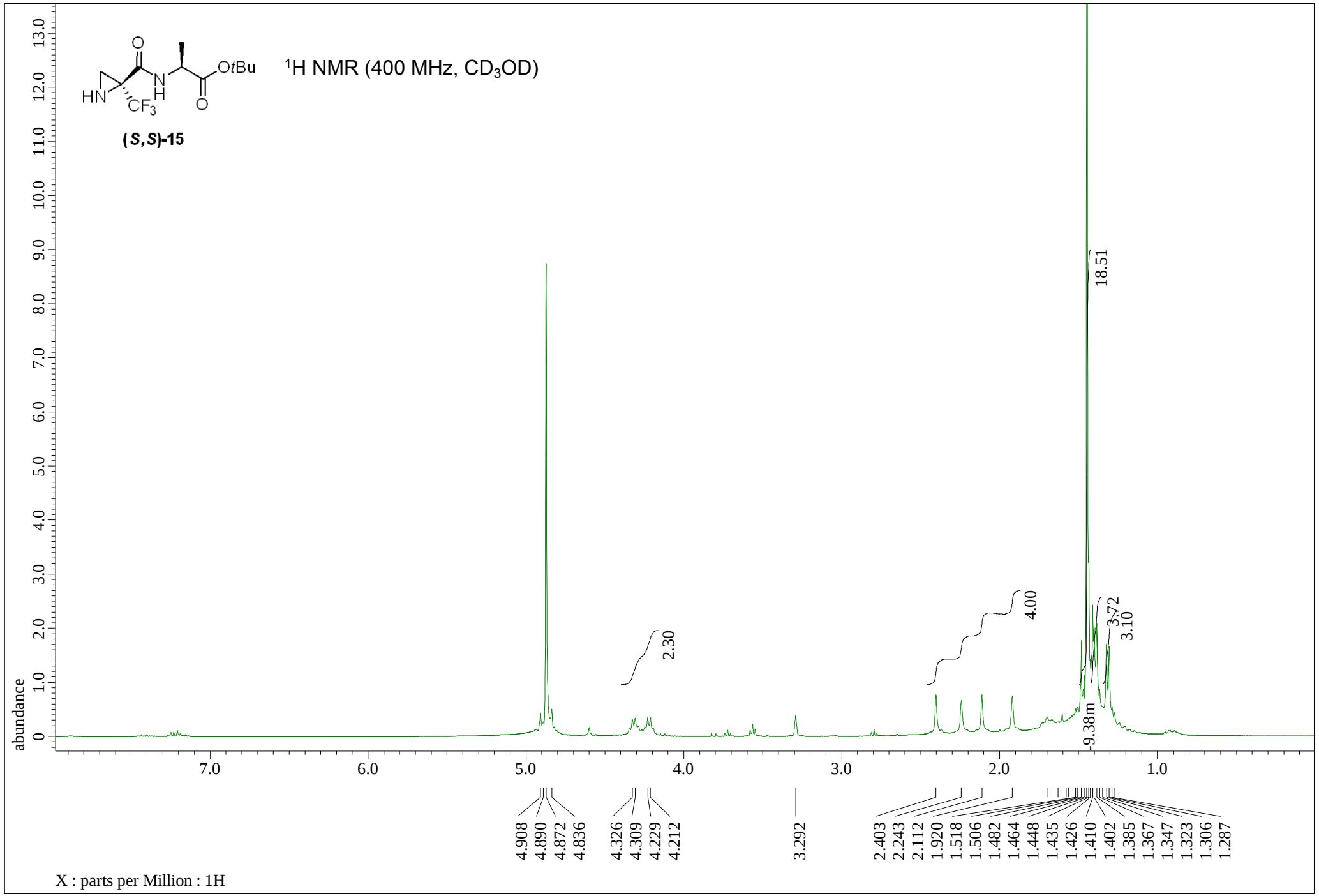

CO2H
CF3
N
OH
Ph
(R,S)-13
13C NMR (100.5 MHz, D2O)
(thousandths)
60.0
50.0
40.0
30.0
20.0
10.0
0
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0
167.171
138.138
129.080
128.518
128.213
127.936
127.555
67.458
66.181
37.730
20.377
X : parts per Million : 13C

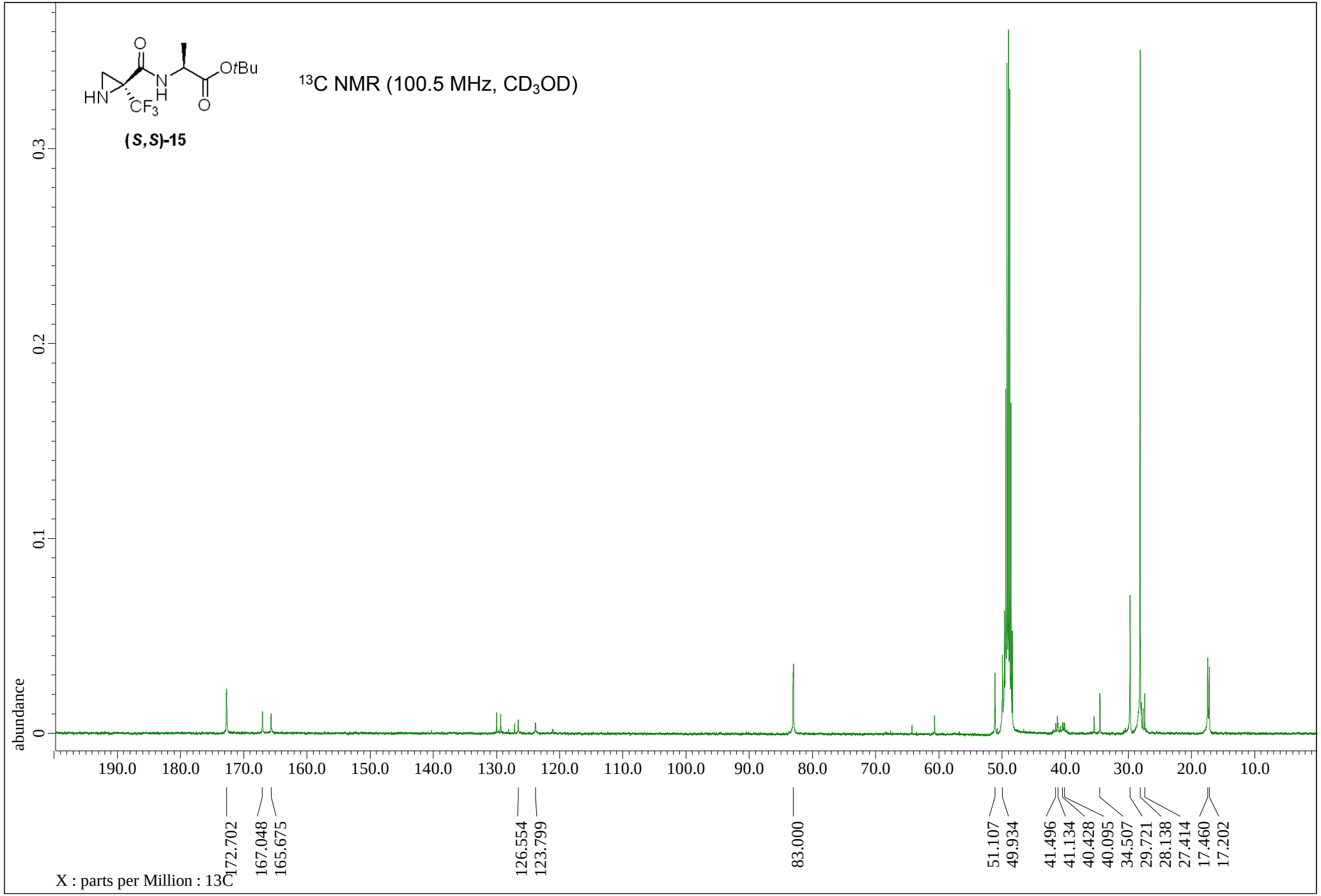

CO2H
CF3
N
OH
Ph
(R,S)-13
19F NMR (376.2 MHz, D2O)
abundance
6.0
5.0
4.0
3.0
2.0
1.0
0
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-73.707
X : parts per Million : 19F

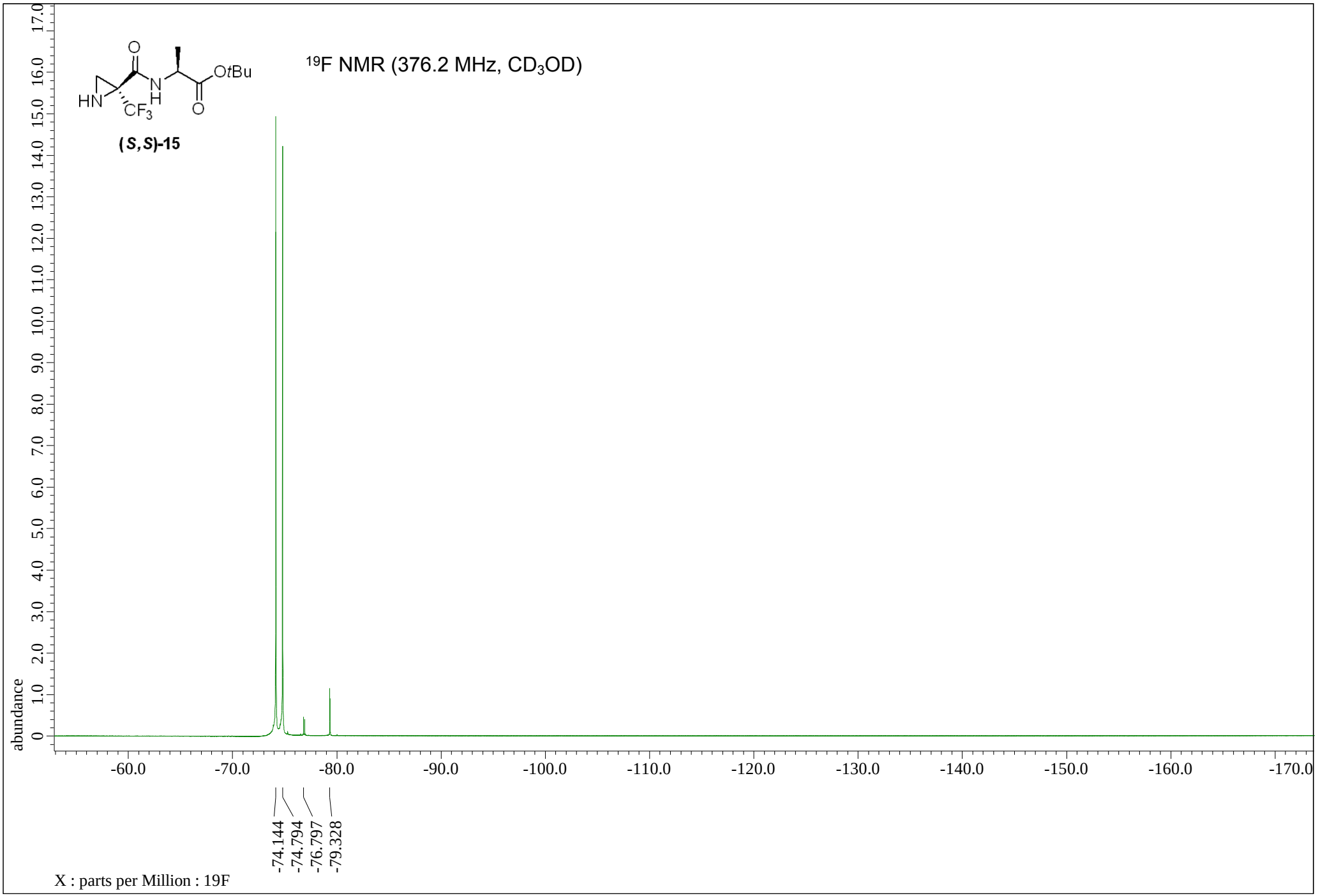

(R,S,S)-14
1H NMR (400 MHz, CDCl3)
abundance
X : parts per Million : 1H
5.25
0.69
4.43
2.00
1.05
8.88
3.03
7.364
7.343
7.325
7.307
7.297
7.293
7.287
7.276
7.270
4.202
4.185
4.168
3.846
3.834
3.553
2.768
2.561
1.640
1.570
1.412
1.339
1.289
1.258
0.883
0.868

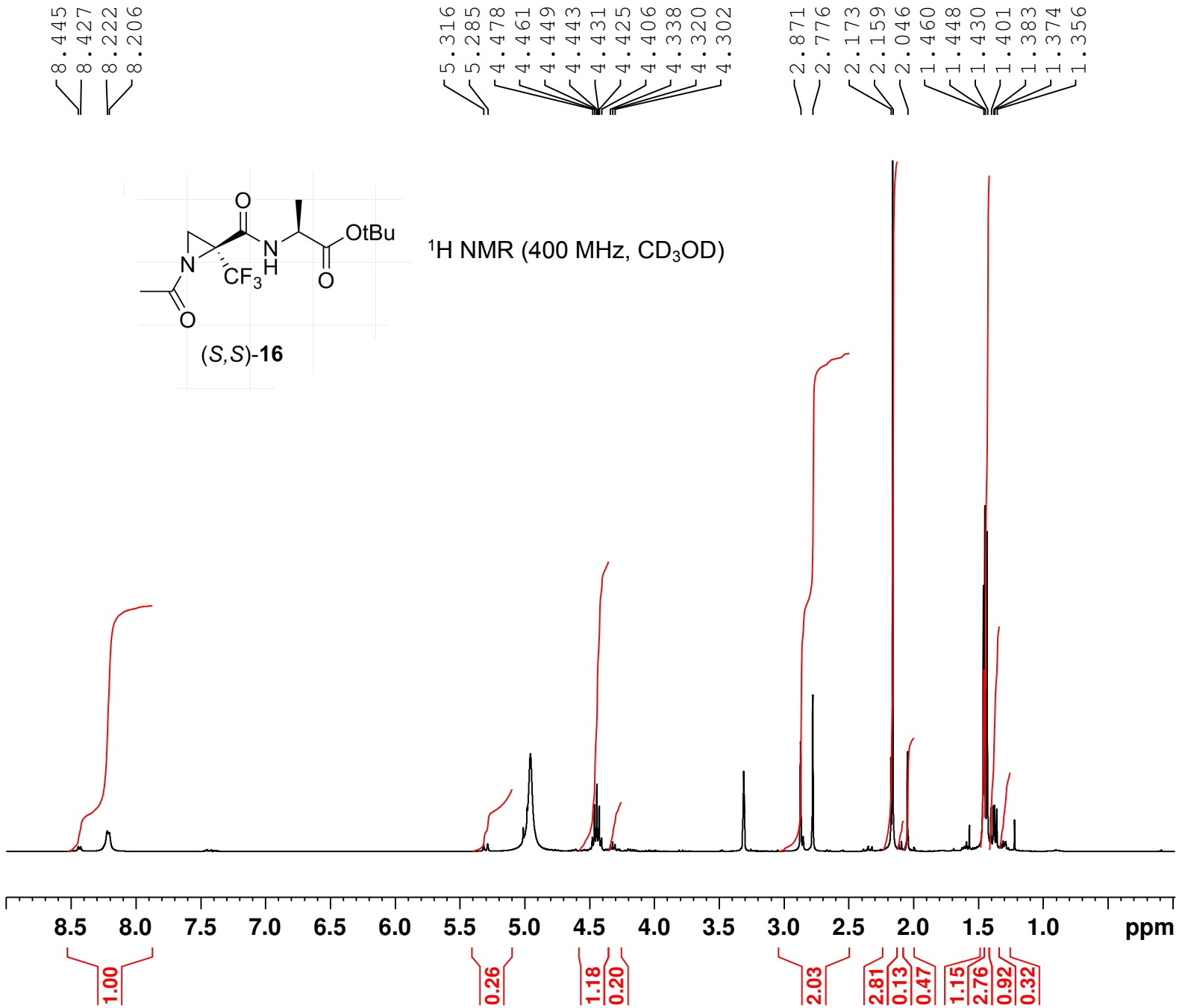

(R,S,S)-14
13C NMR (100.5 MHz, CDCl3)
abundance
X : parts per Million : 13C
170.947
160.402
139.139
129.052
128.775
128.527
127.974
127.860
127.584
82.409
77.441
77.127
76.802
68.069
67.211
49.390
44.480
44.127
36.128
27.899
17.650


(R,S,S)-14
19F NMR (376.2 MHz, CDCl3)
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
-71.909
-164.900
X : parts per Million : 19F


(S,S)-15
1H NMR (400 MHz, CD3OD)
abundance
18.51
9.38m
4.00
2.30
3.72
3.10
4.908
4.890
4.872
4.836
4.326
4.309
4.229
4.212
3.292
2.403
2.243
2.112
1.920
1.518
1.506
1.482
1.464
1.448
1.435
1.426
1.410
1.402
1.385
1.367
1.347
1.323
1.306
1.287
X : parts per Million : 1H


(S,S)-15
13C NMR (100.5 MHz, CD3OD)
abundance
0
0.1
0.2
0.3
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
172.702
167.048
165.675
126.554
123.799
83.000
51.107
49.934
41.496
41.134
40.428
40.095
34.507
29.721
28.138
27.414
17.460
17.202
X : parts per Million : 13C


(S,S)-15
19F NMR (376.2 MHz, CD3OD)
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
-74.144
-74.794
-76.797
-79.328
X : parts per Million : 19F

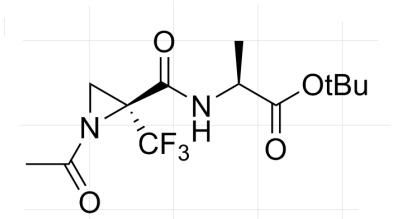


jpy 426 b

```
Current Data Parameters
NAME                 jpy 426 b
EXPNO                       10
PROCNO                       1

F2 - Acquisition Parameters
Date_               20200311
Time                    16.07 h
INSTRUM         Avance Neo 400
PROBHD          Z163739_0087 (
PULPROG                  zg30
TD                      65536
SOLVENT                  MeOD
NS                         16
DS                          2
SWH                  8196.722 Hz
FIDRES               0.250144 Hz
AQ                   3.9976959 sec
RG                         101
DW                      61.000 usec
DE                      13.89 usec
TE                      293.2 K
D1                   1.00000000 sec
TD0                         1
SFO1               400.1424709 MHz
NUC1                       1H
P0                      2.67 usec
P1                      8.00 usec
PLW1               24.04299927 W

F2 - Processing parameters
SI                      65536
SF                 400.1400076 MHz
WDW                        EM
SSB             0
LB                      0.30 Hz
GB              0
PC                      1.00
```

jpy 426 b

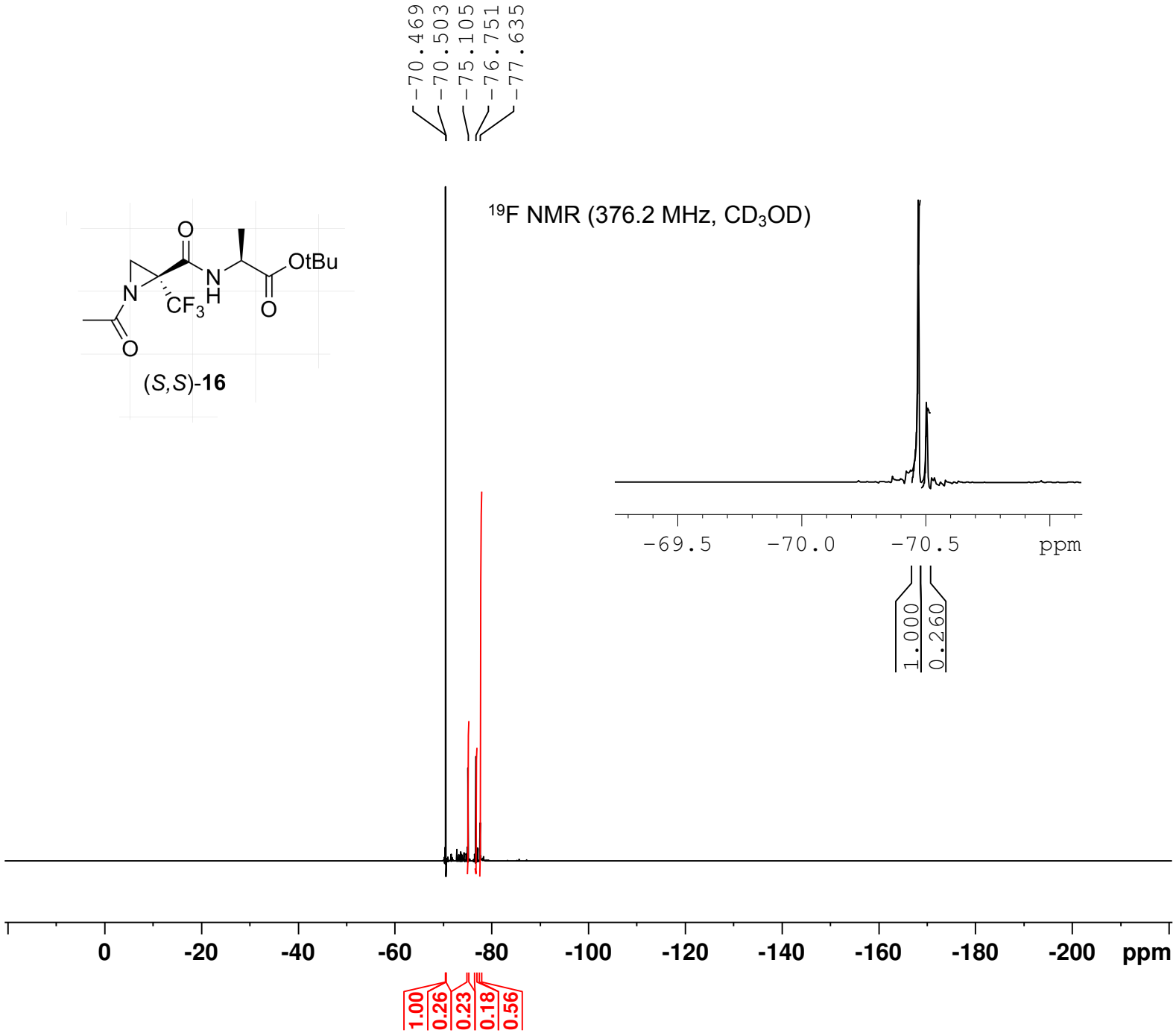
178.09
172.87
160.88
125.95
123.20
120.45
117.70
81.12
58.90
31.51
31.49
26.11
21.98
15.30



(*S*,*S*)-**16**

^{13}C NMR (100.5 MHz, CD_3OD)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



jpy 426 b

```
Current Data Parameters
NAME                 jpy 426 b
EXPNO                       11
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20200311
Time                     16.09 h
INSTRUM          Avance Neo 400
PROBHD           Z163739_0087 (
PULPROG                   zgig
TD                      131072
SOLVENT                   MeOD
NS                          16
DS                           4
SWH                  90909.094 Hz
FIDRES                1.387163 Hz
AQ                    0.7208960 sec
RG                          101
DW                        5.500 usec
DE                        6.50 usec
TE                        293.2 K
D1                  1.00000000 sec
D11                 0.03000000 sec
TD0                          1
SFO1                376.4701248 MHz
NUC1                        19F
P1                       12.00 usec
PLW1                34.92499924 W
SFO2                400.1416006 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    90.00 usec
PLW2                24.04299927 W
PLW12                0.18997000 W

F2 - Processing parameters
SI                       65536
SF                  376.5077756 MHz
WDW                         EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```

3. X-Ray single crystal data for (*R*,*R*)-12

Crystal data and structure refinement for (*R*,*R*)-**12** (CCDC-1953801)

Identifier	OO18
Formula	C_{12} H_{10} F_3 N O_2
Space Group	P 2_1 2_1 2_1
Cell Lengths	**a** 6.1057(3) **b** 8.7390(4) **c** 21.1275(10)
Cell Angles	**α** 90 **β** 90 **γ** 90
Cell Volume	1127.32
Z, Z'	**Z**: 4 **Z'**: 0
R-Factor (%)	3.48
Temperature (K)	Room Temp.(283-303)
Reduced Cell Lengths	**a** 6.1057 **b** 8.739 **c** 21.1275
Reduced Cell Angles	**α** 90 **β** 90 **γ** 90
Reduced Cell Volume	1127.32
Radiation Probe	x-ray
Radiation Source	micro-focus sealed X-ray tube
Density (CCDC)	1.515
Absolute Configuration	yes

Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	C1	0	C.3	-0.0063(3)	0.6017(2)	0.33580(8)	x,y,z
2	H1	0	H	-0.156878	0.581041	0.322201	x,y,z
3	C2	0	C.3	-0.0002(4)	0.7655(2)	0.35985(10)	x,y,z
4	H2A	0	H	-0.026361	0.835147	0.324906	x,y,z
5	H2AB	0	H	-0.115799	0.780259	0.390758	x,y,z
6	O3	0	O.3	0.2086(3)	0.80028(15)	0.38849(7)	x,y,z
7	C4	0	C.2	0.3112(3)	0.6979(2)	0.42363(10)	x,y,z
8	C5	0	C.3	0.2083(3)	0.5441(2)	0.43166(8)	x,y,z
9	N6	0	N.3	0.0473(2)	0.48944(16)	0.38527(7)	x,y,z
10	O7	0	O.2	0.4864(3)	0.7283(2)	0.44617(9)	x,y,z
11	C9	0	C.3	-0.0264(3)	0.5263(3)	0.44872(9)	x,y,z
12	H9A	0	H	-0.065955	0.442105	0.476382	x,y,z

13	H9AB	0	H	-0.112621	0.618493	0.454342	x,y,z
14	C8	0	C.3	0.3619(3)	0.4235(3)	0.45602(10)	x,y,z
15	C10	0	C.2	0.1392(3)	0.5816(2)	0.27838(8)	x,y,z
16	C11	0	C.2	0.3242(3)	0.4902(2)	0.27819(9)	x,y,z
17	H11	0	H	0.361431	0.434849	0.314214	x,y,z
18	C12	0	C.2	0.4545(4)	0.4807(3)	0.22464(10)	x,y,z
19	H12	0	H	0.578830	0.419307	0.225134	x,y,z
20	C13	0	C.2	0.4024(4)	0.5605(3)	0.17112(11)	x,y,z
21	H13	0	H	0.491556	0.554506	0.135522	x,y,z
22	C14	0	C.2	0.2179(5)	0.6493(2)	0.17032(10)	x,y,z
23	H14	0	H	0.180643	0.703074	0.133881	x,y,z
24	C15	0	C.2	0.0874(4)	0.6595(2)	0.22311(10)	x,y,z
25	H15	0	H	-0.038127	0.719720	0.221810	x,y,z
26	F16	0	F	0.4299(3)	0.4545(3)	0.51433(6)	x,y,z
27	F17	0	F	0.2681(3)	0.28713(19)	0.45720(8)	x,y,z
28	F18	0	F	0.54027(19)	0.40753(17)	0.42043(6)	x,y,z