Supplementary Information for

Synthesis of Fluorinated Leucines and Valines for Use in Protein NMR

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Contents

Cell-free protein synthesis, protein mass spectrometry and NMR measurements

Sample preparation of GB1 with fluorinated amino acids

Samples of GB1 with fluorinated amino acids were produced using cell-free protein synthesis. The GB1 construct used contained an N-terminal MASMTG tag and a C-terminal tobacco etch virus (TEV) protease recognition site followed by a His_6 tag (Figure S1). Each cell-free reaction was conducted at 30 °C for 16 h in a dialysis system with 4 mL inner reaction mixture and 40 mL outer buffer following a published protocol,[1] where leucine, valine or alanine was excluded from both the inner reaction mixture and outer buffer and 2 mM of the desired fluoroleucine, fluorovaline or fluoroalanine was added, respectively, where 3-fluoroalanine was purchased as racemate from abcr GmBH (Karlsruhe, Germany). The proteins were purified using a 1 mL His GraviTrap column (Cytiva, USA) according to the manufacturer's protocol. Afterwards, the buffer was exchanged to the NMR buffer (20 mM MES, 100 mM NaCl, pH 6.5) using an Amicon ultrafiltration centrifugal tube with a 3 kDa molecular weight cut-off (Merck Millipore, USA). The average yield was about 0.75-1.5 mg of purified protein per mL cell-free inner reaction mixture.

MASMTGMTYK LILNGKTLKG ETTTEAVDAA TAEKVFKQYA
NDNGVDGEWT YDDATKTFTV TEENLYFQGH HHHHH

Figure S1. Amino acid sequence of the GB1 construct used. The N-terminal MASMTG tag and the C-terminal TEV protease recognition site are shown in blue and red, respectively.

Intact protein mass spectrometry

Intact protein analysis was performed on an Orbitrap Fusion™ Tribrid™ mass spectrometer (Thermo Fisher Scientific, USA) connected to a Thermo Fisher Scientific UltiMate 3000 HPLC system equipped with a ZORBAX 300SB-C3, 3.5 µm, 4.6 x 50 mm HPLC column (Agilent Technologies, USA). Approximately 20 pmol of sample was injected using a 500 mL/min linear gradient of solvent A (0.1% (v/v) formic acid in water) and solvent B (0.1% (v/v) formic acid in acetonitrile), ramping solvent B from 5% at the start to 80% after 12 min. Data were collected using an electrospray ionization (ESI) source in positive ion mode. Protein intact mass was determined by deconvolution using the program Xcalibur 3.0.63 (Thermo Fisher Scientific, USA).

NMR measurements

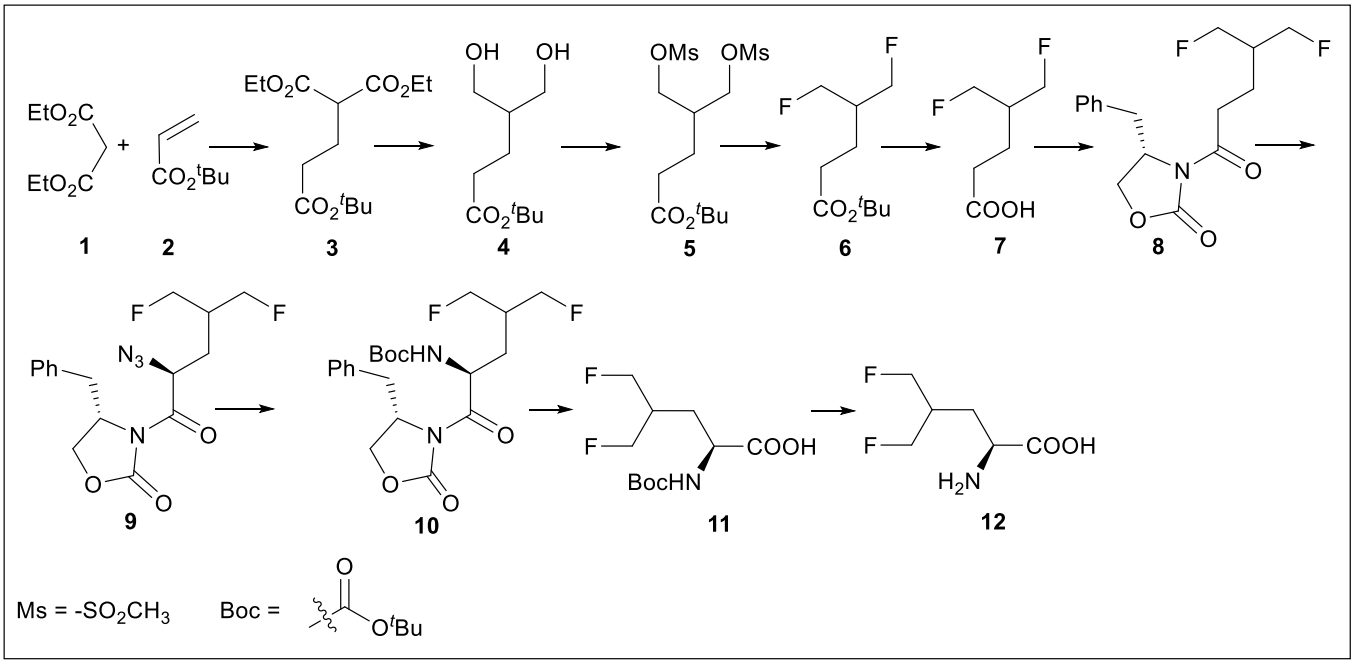
All ^{19}F-NMR spectra were acquired at 25 °C on a Bruker 400 MHz NMR spectrometer equipped with a room temperature broadband probe. Parameters used: 109-218 ms acquisition time, ^{1}H decoupling during acquisition, recovery delay 1 s, exponential window multiplication with 3 Hz line broadening prior to Fourier transformation.

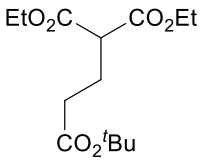
References

1. Apponyi, M., Ozawa, K., Dixon, N. and Otting, G. (2008). Cell-free protein synthesis for analysis by NMR spectroscopy. In B. Kobe, M. Guss & T. Huber (Eds.), *Structural Proteomics* (Vol. 426, pp. 257–268): Humana Press.

Experimental Procedures and Characterization

Scheme 1: 5,5'-difluoro-*L*-leucine (12)





3-(*tert*-Butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (3) was prepared according to the literature procedure: K. R. Prabhu, N. Pillarsetty, H. Gali, K. V. Katti, *J. Am. Chem. Soc.*, 2000, **122**, 1554.

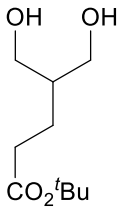
An Ace pressure tube was charged with diethylmalonate (1.00 g; 6.24 mmol), *tert*-butyl acrylate (800 mg; 6.24 mmol), dry toluene (25 mL), potassium carbonate (862 mg; 6.24 mmol) and tetrabutylammonium hydrogen sulfate (30 mg; 0.08 mmol). The reaction vessel was sealed and heated to 100 °C (oil bath temperature) for 4 hours. GC indicated complete conversion at this point. The reaction was diluted with EtOAc (200 mL) and washed with water (2 x 200 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. 1.72 g (96%) of yellowish oil was obtained. Crude product was used directly in the next step. The analytical sample was obtained by short-path vacuum distillation (160 °C bath temperature / 0.1 mbar).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.19 (q, *J* = 7.1 Hz, 4H), 3.41 (t, *J* = 7.4 Hz, 1H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.16 (q, *J* = 7.3 Hz, 2H), 1.44 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 6H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 171.86, 169.22, 80.76, 61.57, 51.02, 32.86, 28.22, 24.07, 14.21 ppm.

HRMS (*m/z*): calculated for $C_{14}H_{24}O_6Na$ [M+Na$^+$] 311.1487, found 311.1471.

IR (ATR): 3443 (w), 2981 (s), 2938 (m), 1733 (s), 1730 (s), 1448 (m), 1369 (m), 1252 (m), 1152 (s), 1030 (m), 848 (w) cm^{-1}.



***tert*-Butyl 5-hydroxy-4-(hydroxymethyl)pentanoate (4)**

A solution of 3-(*tert*-butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (**3**) (1.65 g; 5.72 mmol) and LiCl (640 mg; 15 mmol) in MeOH (50 mL) was cooled to 0 °C. $NaBH_4$ (830 mg; 22 mmol) was added portion-wise over the period of 30 minutes. The reaction mixture was stirred at 0 °C for another 2 hours. TLC indicated complete conversion. The reaction mixture

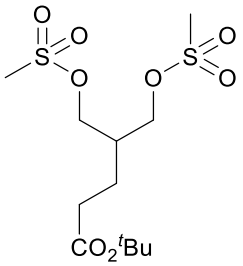
was diluted with water (50 mL) and brine (50 mL) and stirred at room temperature for 2 hours. Methanol was distilled off under reduced pressure. The remaining suspension was saturated with NaCl and extracted with EtOAc (6 x 50 mL). The combined organic solutions were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by a flash column chromatography (mobile phase hexanes/EtOAc with gradient 4/1 to 0/1). 1.02 g (87%) of colourless oil was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 – 3.73 (m, 2H), 3.64 (m, 2H), 2.81-2.76 (br. s, 2H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.65 (m, 1H), 1.62 (q, *J* = 6.8 Hz, 2H), 1.44 (s, 9H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 173.73, 80.84, 65.31, 42.04, 33.20, 28.20, 22.51 ppm.

IR (ATR): 3442 (s), 2978 (m), 2930 (m), 2878 (m), 1728 (s), 1368 (w), 1255 (w), 1153 (s), 1038 (m), 844 (w) cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87; N, 0. Found: C, 58.48; H, 9.94; N, 0.



tert-Butyl 5-((methylsulfonyl)oxy)-4-(((methylsulfonyl)oxy)methyl)pentanoate (5)

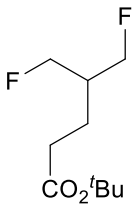
A solution of *tert*-butyl 5-hydroxy-4-(hydroxymethyl)pentanoate (**4**) (1.00 g; 4.90 mmol) and DIPEA (2.6 mL; 15 mmol) in dry toluene (30 mL) was cooled to -20 °C. Mesyl chloride (0.85 mL; 11 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to warm to 0 °C and stirred at this temperature for 2 hours. The reaction mixture was applied directly to a 50 g silica gel column. The column was eluted with hexanes/EtOAc (with gradient 4/1 to 0/1). Fractions containing product were evaporated under reduced pressure. 1.65 g (94%) of yellow oil was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (dd, *J* = 10.2, 4.3 Hz, 2H), 4.20 (dd, *J* = 10.2, 6.3 Hz, 2H), 3.04 (s, 6H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.22 (m, 1H), 1.72 (q, *J* = 7.3 Hz, 2H), 1.44 (s, 9H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 171.87, 81.13, 67.93, 37.63, 37.48, 32.33, 28.20, 22.53 ppm.

HRMS (*m/z*): calculated for $C_{12}H_{24}O_8S_2Na$ [M+Na$^+$] 383.0810, found 383.0825.

IR (ATR): 3028 (w), 2929 (m), 2941 (m), 1723 (s), 1458 (w), 1355 (s), 1256 (w), 1175 (s), 964 (s), 944 (s), 832 (m), 754 (w) cm^{-1}.



tert-Butyl 5-fluoro-4-(fluoromethyl)pentanoate (6)

An Ace pressure tube was charged with dry *tert*-butanol (50 mL), anhydrous CsF (13.7 g; 90 mmol) and *tert*-butyl 5-((methylsulfonyl)oxy)-4-(((methylsulfonyl)oxy)methyl)pentanoate (**4**) (1.62 g; 4.49 mmol). The reaction vessel was sealed and heated to 95 °C (oil bath temperaturte) overnight. The reaction mixture was partitioned between brine (150 mL) and EtOAc (150 mL). The aqueous phase was extracted with additional EtOAc (3 x 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. 876 mg (94%) of yellow liquid was obtained (about 80% purity). Crude product was used directly in the next step. The analytical sample (~30 mg) was obtained by short path vacuum distillation.

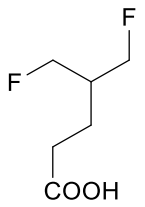
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.57 – 4.36 (multiple peaks, J^{H-F} = 47.4, 4H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.05 (m, 1H), 1.69 (q, *J* = 7.4 Hz, 2H), 1.45 (s, 9H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -228.51 (td, *J* = 47.1, 22.3 Hz) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 172.38, 82.56 (dd, *J* = 169.6, 5.33 Hz), 80.74, 39.85 (t, *J* = 18.2 Hz), 32.82, 28.23, 21.81 (t, *J* = 5.8 Hz) ppm.

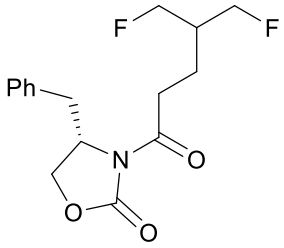
GC-MS (EI, 75 eV): m/z 206.8 ([M-H]$^+$, 1%), 153 (15%), 135 (84%), 87.1 (25%), 57.1 (100%).

IR (ATR): 3439 (w), 2979 (s), 2910 (m), 1729 (s), 1476 (w), 1368 (m), 1257 (m), 1157 (s), 1015 (m), 846 (w) cm^{-1}.



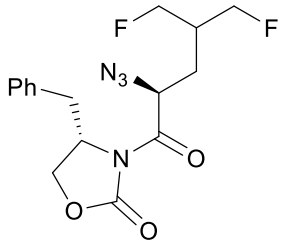
5-Fluoro-4-(fluoromethyl)pentanoic acid (7)

It is advisable not to use trifluoroacetic acid for this step as it is very difficult to remove TFA from the reaction product. A few drops of concentrated sulfuric acid were added to the DCM (20 mL) solution of *tert*-butyl 5-fluoro-4-(fluoromethyl)pentanoate (**6**) (840 mg; 4.03 mmol). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction was partitioned between brine (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (bath temperature 40 °C; 50 mbar). 550 mg (90 %) of yellow oil was obtained. Crude product was used in the next step without further purification. The analytical sample was obtained by short-path vacuum distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ:4.53 – 4.29 (multiple peaks, J^{H-F} = 47.1, 4H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.16 – 1.90 (m, 1H), 1.69 (q, *J* = 7.4 Hz, 2H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -228.51 (td, *J* = 47.1, 22.2 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 178.98, 82.20 (dd, *J* = 169.5, 5.4 Hz), 39.53 (t, *J* = 18.3 Hz), 31.14, 21.41 (t, *J* = 5.8 Hz) ppm.
HRMS (TOF ES$^-$ *m/z*): calculated for $C_6H_9O_2F_2$ [M-H$^+$] 151.0571, found: 151.0569.
IR (ATR): 3473 (broad w), 3086 (broad s), 2981 (broad w) 2913 (broad w), 2654 (broad m), 1733 (s), 1423 (s), 1292 (m), 1225 (m), 1180 (w), 1018 (m), 948 (w) cm^{-1}.



(*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (8)

Pivaloyl chloride (0.45 mL; 3.7 mmol) was added dropwise to the solution of 5-fluoro-4-(fluoromethyl)pentanoic acid (**7**) (500 mg; 3.29 mmol) and DIPEA (0.87 mL; 5.0 mmol) in dry THF (30 mL) at 0 °C. In a separate flask to a solution of (*S*)-4-benzyloxazolidin-2-one (0.89 g; 5.0 mmol) in dry THF (30 mL) was added BuLi (2 M; 2.5 mL) at -78 °C. After 2 hours the solution of mixed anhydride was cannulated into the solution of lithium (*S*)-4-benzyl-2-oxooxazolidin-3-ide at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (250 mL) and aq. HCl (1 M; 150 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 938 mg (92%) of colourless oil was obtained.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 2H), 7.21 (m, 1H), 7.13 (m, 2H), 4.60 (m, 1H), 4.54 – 4.32 (multiple peaks, 4H), 4.19 – 4.07 (multiple peaks, 2H), 3.22 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.09 – 2.87 (multiple peaks, 2H), 2.70 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.17 – 1.94 (m, 1H), 1.75 (multiple peaks, 2H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -228.31 (td, *J* = 48.1, 12.1 Hz, 1F), -228.36 (td, *J* = 46.5, 11.7 Hz, 1F) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 172.52, 153.59, 135.29, 129.52, 129.11, 127.54, 82.61 (dd, *J* = 169.1, 5.3 Hz two diastereotopic carbons –CH_2F with matching shifts and multiplicities), 66.46, 55.27, 39.80 (t, *J* = 18.3 Hz), 38.03, 33.00, 21.02 (t, *J* = 5.8 Hz) ppm.
HRMS (*m/z*): calculated for $C_{16}H_{20}NO_3F_2$ [M+H$^+$] 312.1411, found: 312.1419.
IR (ATR): 3547 (w), 3384 (w), 3030 (w), 2969 (s), 2914 (m), 1780 (s), 1700 (s), 1604 (w), 1480 (w), 1455 (w), 1394 (m), 1356 (m), 1213 (m), 1103 (m), 1011 (m), 842 (w), 747 (m), 704 (m) cm^{-1}.
$[\alpha]_D^{20}$ 47.3 (*c* 0.90, $CHCl_3$).



(*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (9)

A cooled (-78 °C) solution of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**7**) (900 mg; 2.89 mmol) in dry THF (10 mL) was cannulated into a cooled (-78 °C) solution of KHMDS (3.2 mmol) in THF (~18 mL). After 30 minutes a cooled (-78 °C) solution of trysil azide (1.1 g; 3.5 mmol) in THF (12 mL) was cannulated into the solution of previously prepared potassium enolate at -78 °C. After 2 minutes the reaction was quenched with acetic acid (0.9 mL). The reaction mixture was warmed to 35 °C and stirred at this temperature for 40 minutes. The volatiles were removed under reduced pressure (bath temperature ~35 °C). The residue was partitioned between EtOAc (250 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 826 mg (81%) of colorless oil was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.32 (m, 2H), 7.30 (m, 1H), 7.25 – 7.19 (m, 2H), 5.10 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.76 – 4.41 (multiple peaks, 5H), 4.33 – 4.21 (multiple peaks, 2H), 3.34 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.86 (dd, *J* = 13.5, 9.4 Hz, 1H), 2.43 – 2.24 (m, 1H), 2.03 – 1.85 (multiple peaks, 2H) ppm.

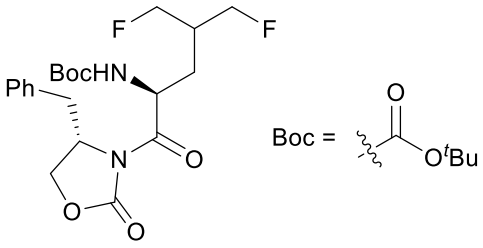
^{19}F NMR (376 MHz, $CDCl_3$) δ: -227.75 (td, *J* = 47.5, 21.9 Hz, 1F), -227.92 (td, *J* = 46.3, 21.9 Hz, 1F) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 170.31, 152.91, 134.60, 129.42, 129.13, 127.63, 82.87 (dd, *J* = 170.0, 5.8 Hz), 81.78 (dd, *J* = 170.0, 5.9 Hz), 66.78, 58.56, 55.45, 37.88, 37.60 (t, *J* = 9.3 Hz), 28.40 (t, *J* = 5.3 Hz) ppm.

HRMS (*m/z*): calculated for $C_{16}H_{19}N_2O_3F_2$ [M-N_2+H$^+$] 325.1364, found: 325.1378.

IR (ATR): 3030 (w), 2969 (m), 2915 (m), 2115 (s), 1783 (s), 1706 (s), 1479 (m), 1445 (m), 1393 (s), 1213 (s), 1112 (m), 1010 (m), 705 (m) cm^{-1}.

$[\alpha]_D^{20}$ 67.96 (*c* 0.90, $CHCl_3$).



(*S*)-3-((*S*)-2-(Boc-amino)-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (10)

Pd/C (10%; 150 mg) was added to a solution of (*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**9**) (800 mg; 2.27 mmol) and Boc_2O (5.0 g; 23 mmol) in EtOAc (25 mL). The resulting suspension was stirred under 3 bars of hydrogen for 4 hours. The volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 20/1 to 1/1). 874 mg (90%) of white solid was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 2H), 7.29 (m, 1H), 7.21 (m, 2H), 5.48 (ddd, *J* = 10.8, 9.3, 2.8 Hz, 1H), 5.27 (d, *J* = 7.5 Hz, 1H), 4.76 – 4.35 (multiple peaks, 5H), 4.27 – 4.17 (multiple peaks, 2H), 3.32 (d, *J* = 12.0 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.43 – 2.16 (m, 1H), 1.95 – 1.76 (m, 1H), 1.68 – 1.53 (m, 1H), 1.46 (s, 9H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -228.48 (multiple peaks, 2F) ppm.

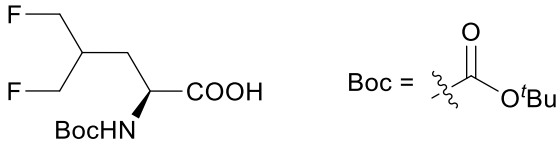
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 173.04, 155.67, 152.76, 134.95, 129.45, 129.07, 127.48, 83.19 (dd, *J* = 169.2, 4.7 Hz), 81.45 (dd, *J* = 168.8, 5.7 Hz), 80.34, 66.61, 55.49, 51.51, 37.53, 37.41 (t, *J* = 18.04 Hz), 29.83, 28.28 ppm.

HRMS (*m/z*): calculated for $C_{21}H_{28}N_2O_5F_2Na$ [M+Na$^+$] 449.1864, found: 449.1883.

IR (ATR): 3378 (m), 2979 (m), 2918 (w), 1784 (s), 1703 (s), 1500 (m), 1455 (w), 1392 (s), 1368 (s), 1246 m), 1165 (m), 1111 (m), 1015 (m), 761 (m), 703 (m) cm^{-1}.

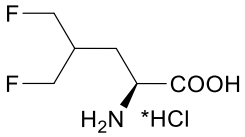
$[\alpha]_D^{20}$ 33.2 (*c* 0.9, $CHCl_3$).

M.p.: 123 °C.



(*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (11)

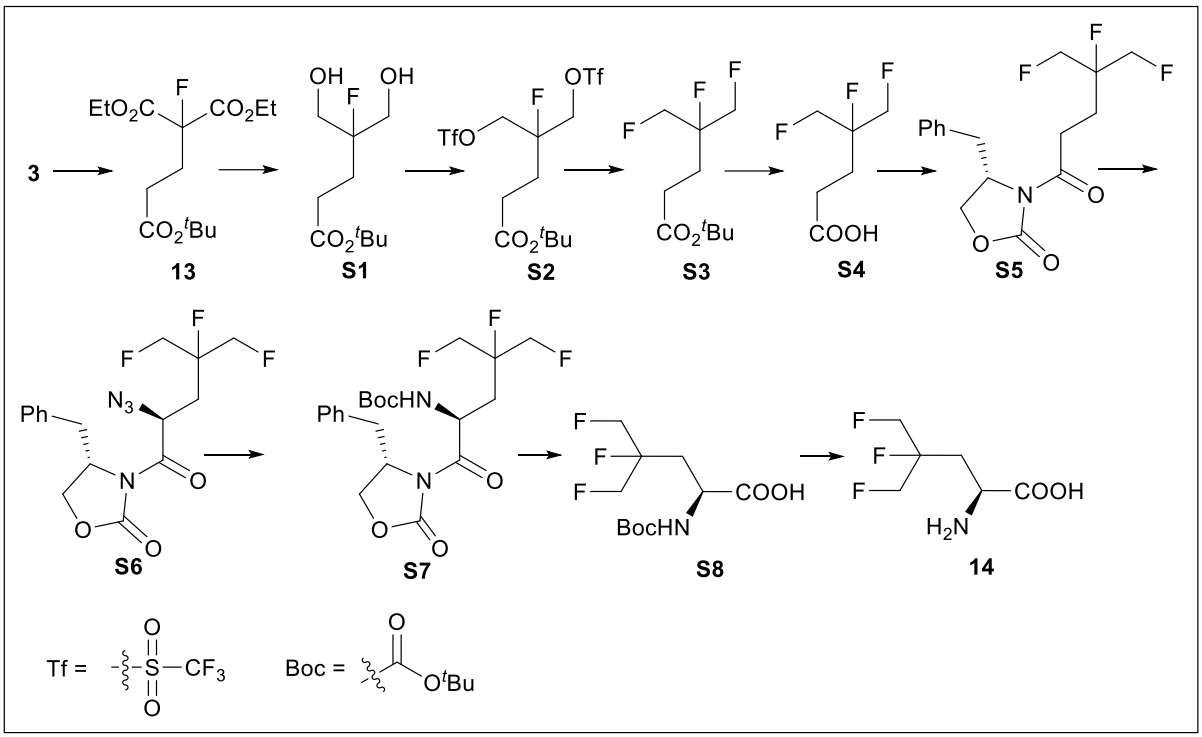
LiOH (48 mg; 2.0 mmol) in water (3 mL) was added to a cooled (0 °C) solution of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5-fluoro-4-(fluoromethyl)-1-oxopentan-2-yl)carbamate (**10**) (530 mg; 1.24 mmol) in THF (10 mL). The reaction mixture was stirred for 1 hour at 0 °C. The reaction mixture was acidified to pH 2…3 by careful addition of aq. HCl (1M). THF was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and brine (50 mL). Aqueous phase was extracted with additional EtOAc (4 x 20 mL). Combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 5/1 to 0/1). 273 mg (82%) of amorphous glassy solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.63 – 4.34 (multiple peaks, 4H), 4.20 (dd, *J* = 10.1, 4.4 Hz, 1H), 2.15 (m, 1H), 2.00 – 1.81 (m, 1H), 1.79 – 1.60 (m, 1H), 1.45 (s, 9H) ppm.
^{19}F NMR of major conformer (376 MHz, CD_3OD) δ: -225.28 (td, *J* = 47.1, 20.9 Hz, 1F), -228.41 (td, *J* = 47.3, 24.0 Hz, 1F) ppm. **^{19}F NMR** of minor conformer δ: -225.71 (td, *J* = 46.8, 21.3 Hz, 1F), -227.53 (td, *J* = 47.4, 23.4 Hz, 1F) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 178.36, 160.72, 86.38 (dd, *J* = 168.5, 5.1 Hz), 85.23 (dd, *J* = 168.3, 5.3 Hz), 83.20, 55.16, 41.28 (t, *J* = 18.4 Hz), 32.01 (t, *J* = 5.3 Hz), 31.23 ppm.
HRMS (TOF ES$^-$ *m/z*): calculated for $C_{11}H_{18}NO_4F_2$ [M-H$^+$] 266.1204, found: 266.1211.
IR (ATR): 3384 (broad m), 2981 (m), 2909 (w), 1718 (s), 1520 (m), 1396 (m), 1253 (w), 1164 (m), 1013 (m) cm^{-1}.
$[\alpha]_D^{20}$ -6.5 (*c* 1.0, $CHCl_3$).

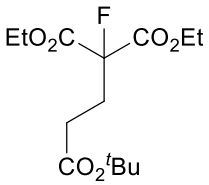


(*S*)-2-Amino-5-fluoro-4-(fluoromethyl)pentanoic acid hydrochloride (12)

TFA (5 mL) was added to a DCM (15 mL) solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (**11**) (220 mg; 0.82 mmol). The reaction mixture was stirred at ambient temperature 3 hours. The volatiles were removed under reduced pressure. The residue was dissolved in MeCN (15 mL) and anhydrous HCl (2M in ether; 3 mL) was added. The volatiles were removed under reduced pressure and HCl treatment was repeated 3 times. Finally, the crystalline residue was suspended in EtOAc (15 mL), sonicated 5 minutes and then collected by filtration. The reaction product was washed with EtOAc (3 x 3 mL). After drying in vacuum 143 mg (85%) of white microcrystalline solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.68 – 4.39 (multiple peaks, 4H), 4.11 (t, *J* = 7.1 Hz, 1H), 2.54 – 2.25 (m, 1H), 2.10 (m, 1H), 1.93 (m, 1H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -230.36 (td, *J* = 46.8, 20.5 Hz, 1F), -230.50 (td, *J* = 46.3, 21.8 Hz, 1F) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 171.58, 83.58 (dd, *J* = 168.4, 5.8 Hz), 83.25 (dd, *J* = 168.1, 6.2 Hz), 51.88, 38.25 (t, *J* = 18.7 Hz), 29.07 (t, *J* = 5.6 Hz) ppm.
HRMS (*m/z*): calculated for $C_6H_{12}NO_2F_2$ [M+H$^+$] 168.0836, found: 168.0839.
IR (ATR): 3451 (broad w), 3024 (broad s), 2527 (w), 2272 (broad s), 1738 (s), 1476 (w), 1386 (m), 1218 (m), 1031 (m), 1031 (m), 961 (m), 831 (m) cm^{-1}.
$[\alpha]_D^{20}$ 14.30 (*c* 1.0, CH_3OH).
M.p.: 152 °C.

Scheme 2: 4,5,5'-trifluoro-*L*-leucine (14) and 4,5,5'-trifluoro-*L*-leucine-^{15}N





3-(*tert*-Butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (13)

3-(*tert*-Butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (**3**) (9.00 g; 31.2 mmol) in dry THF (30 mL) was added dropwise to a NaH (1.60 g; 60% dispersion in mineral oil; ca. 40 mmol) suspension in dry THF (300 mL) while maintaining internal temperature below 5 °C. Resulting suspension was stirred at 0 °C 1 hour. *N*-Fluorobenzenesulfonimide (12.6 g; 40.0 mmol) was added in small portions at a rate to maintain internal temperature below 5 °C. The reaction mixture was allowed to warm to ambient temperature and stirring was continued overnight. The volatiles were removed under reduced pressure. The residue was suspended in ether (300 mL) and filtered. Ether solution was washed with aq $NaHCO_3$ (2 x 100 mL), water (200 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 8.87 g (93%) of product was obtained in a form of colorless oil. Crude product was used directly in the next step. The analytical sample was obtained by a flash column chromatography (mobile phase hexanes/EtOAc with gradient 20/1 to 8/1).

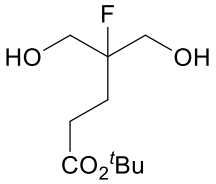
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (q, *J* = 7.1 Hz, 4H), 2.59 – 2.27 (multiple peaks, 4H), 1.43 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 6H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -167.26 (t, *J* = 22.2 Hz) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 171.28, 166.01 (d, *J* = 25.5 Hz), 93.96 (d, *J* = 198.6 Hz), 81.03, 62.84, 29.54 (d, *J* = 21.3 Hz), 29.11 (d, *J* = 3.6 Hz), 28.17, 14.10 ppm.

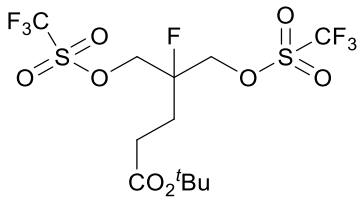
HRMS (*m/z*): calculated for $C_{14}H_{23}O_6FNa$ [M+Na$^+$] 329.1376, found 329.1385.

IR (ATR): 2981 (s) 2939 (m), 1753 (s), 1457 (m), 1369 (s), 1247 (s), 1155 (s), 1095 (m), 1031 (m), 848 (m) cm^{-1}.



tert-Butyl 4-fluoro-5-hydroxy-4-(hydroxymethyl)pentanoate (S1)

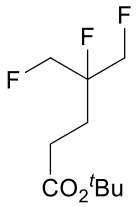
Solution of 3-(*tert*-butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (**13**) (8.50 g; 27.7 mmol) and LiCl (2.54 g; 60.0 mmol) in MeOH (200 mL) was cooled to 0 °C. $NaBH_4$ (5.30 g; 140 mmol) was added portion wise over the period of 30 minutes. The reaction mixture was stirred at 0 °C for 2 hours. TLC indicated complete conversion. The reaction mixture was diluted with water (100 mL) and brine (100 mL) and stirred at room temperature 2 hours. Methanol was distilled off under reduced pressure. Remaining suspension was saturated with NaCl and extracted with EtOAc (4 x 100 mL). Combined organic solutions were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by a flash column chromatography (mobile phase hexanes/EtOAc with gradient 4/1 to 1/1). 5.36 g (87%) of white solid was obtained. The analytical sample was obtained by crystallization from MTBE/hexane.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 – 3.59 (multiple peaks, 4H), 3.03 (t, *J* = 6.6 Hz, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.97 (dt, *J* = 21.4, 7.1 Hz, 2H), 1.44 (s, 9H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -173.98 (m) ppm.
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 173.85, 97.19 (d, *J* = 173.2 Hz), 81.37, 63.89 (d, *J* = 27.5 Hz), 28.73 (d, *J* = 5.2 Hz), 28.12, 26.29 (d, *J* = 21.4 Hz) ppm.
IR (ATR): 3395 (broad s), 2981 (s), 2935 (s), 1733 (s), 1454 (s), 1370 (s), 1251 (m), 1157 (s), 1055 (s), 949 (w), 915 (w), 885 (m), 850 (m) cm^{-1}.
Anal.: Calcd for $C_{10}H_{19}FO_4$: C, 54.04; H, 8.62; N, 0. Found: C, 54.47; H, 8.73; N, 0.
M.p.: 76 °C.



tert-Butyl 4-fluoro-5-((triflyl)oxy)-4-(((triflyl)oxy)methyl)pentanoate (S2)

Corresponding bis-mezylate is very inert towards substitution with fluoride (CsF; ^{t}BuOH). For this reason, bis-triflate (**S2**) was used instead.

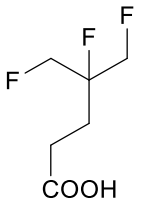
Solution of *tert*-butyl 4-fluoro-5-hydroxy-4-(hydroxymethyl)pentanoate (**S1**) (4.70 g; 21.1 mmol) and 2,6-lutidine (6.2 mL; 53 mmol) in dry DCM (150 mL) was cooled to -78 °C. Triflic anhydride (8.1 mL; 48 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to warm to 0 °C and stirred at this temperature for 1 hour. The reaction mixture was washed with aq. $KHSO_4$ (3 x 100 mL; 5% solution) and water (2 x 100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 9.86 g (96%) of white solid was obtained. The reaction product is quite unstable in solution which prevented characterization. It was used immediately in the next step.



tert-Butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (S3)

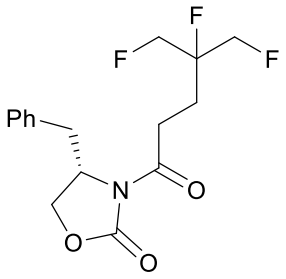
An Ace pressure tube was charged with dry *tert*-butanol (70 mL), anhydrous CsF (21.2 g; 140 mmol) and *tert*-butyl 4-fluoro-5-((triflyl)oxy)-4-(((triflyl)oxy)methyl)pentanoate (**S2**) (6.00 g; 12.3 mmol). The reaction vessel was sealed and heated to 95 °C (oil bath temperature) overnight. The reaction mixture was partitioned between water (300 mL) and

EtOAc (300 mL). The organic phase was washed with water (4 x 100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. 2.63 g (94 %) of yellow liquid was obtained (about 90% purity). Crude product was used directly in the next step. The analytical sample was obtained by short path vacuum distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.79 – 4.15 (m, 4H), 2.51 – 2.27 (m, 2H), 2.15 – 1.87 (m, 2H), 1.44 (s, 9H) ppm.
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 171.77, 93.91 (dt, *J* = 177.5, 18.6 Hz), 81.93 (ddd, *J* = 176.4, 29.7, 5.3 Hz), 81.02, 28.60 (d, *J* = 5.2 Hz), 28.12, 26.19 (dt, *J* = 21.3, 3.5 Hz) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -175.13 – -177.86 (m, 1F), -234.16 (td, *J* = 47.4, 12.0 Hz, 2F) ppm.
HRMS (*m/z*): calculated for $C_{10}H_{17}O_2F_3Na$ [M+Na$^+$] 249.1078, found 249.1081.
IR (ATR): 2981 (s), 2937 (m), 1734 (s), 1458 (m), 1369 (m), 1327 (m), 1249 (m), 1160 (s), 1039 (s), 951 (w), 929 (w), 900 (m), 848 (m), 759 (w), 609 (w) cm^{-1}.



4,5-Difluoro-4-(fluoromethyl)pentanoic acid (S4)

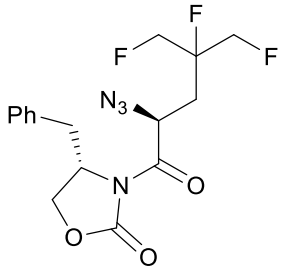
It is advisable not to use TFA for this step as it is very difficult to remove TFA from the reaction product.
A few drops of concentrated sulfuric acid were added to the DCM (50 mL) solution of *tert*-butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (**S3**) (2.50 mg; 11.0 mmol). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction was partitioned between brine (50 mL) and ether (50 mL). The aqueous phase was extracted with additional ether (3 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (bath temperature 40 °C; 50 mbar). 1.65 g of yellowish solid was obtained. Crude product was used in the next step without further purification. The analytical sample was obtained by short-path vacuum distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.51 (broad s, 1H), 4.70 – 4.32 (m, 4H), 2.64 – 2.50 (m, 2H), 2.23 – 1.99 (m, 2H) ppm.
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 179.04, 93.65 (dt, *J* = 177.8, 18.7 Hz), 81.91 (ddd, *J* = 176.7, 29.7, 5.2 Hz), 27.30 (d, *J* = 5.5 Hz), 25.81 (dt, *J* = 21.3, 3.6 Hz) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -176.28 (m, 1F), -234.00 (td, *J* = 46.9, 12.2 Hz, 2F) ppm.
HRMS (ESI$^-$ *m/z*): calculated for $C_6H_8O_2F_3$ [M-H$^+$] 169.0476, found 169.0474.
IR (ATR): 2980 (broad s), 1714 (s), 1458 (m), 1419 (w), 1294 (w), 1226 (w), 1164 (w), 1045 (s), 960 (w), 931 (s), 890 (s), 803 (m), 759 (m), 617 (m) cm^{-1}.
Mp: 39-40 °C.



(*S*)-4-Benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (S5)

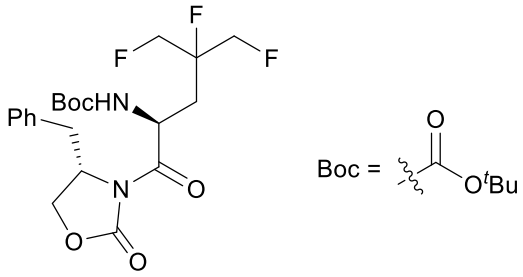
Pivaloyl chloride (1.73 mL; 13.0 mmol) was added dropwise to a solution of 4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S4**) (1.60 g; 9.40 mmol) and DIPEA (2.9 mL; 16 mmol) in dry THF (60 mL) at 0 °C. In a separate flask to a solution of (*S*)-4-benzyloxazolidin-2-one (3.54 g; 20.0 mmol) in dry THF (100 mL) was added BuLi (2 M; 8.5 mL) at -78 °C. After 2 hours the solution of mixed anhydride was cannulated into the solution of lithium (*S*)-4-benzyl-2-oxooxazolidin-3-ide at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (350 mL) and aq. HCl (1 M; 150 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 2.95 g (95%) of amorphous solid was obtained.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 2H), 7.27 (m, 1H), 7.20 (m, 2H), 4.71 – 4.42 (multiple peaks, 5H), 4.24 – 4.14 (multiple peaks, 2H), 3.29 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.22 – 3.01 (multiple peaks, 2H), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.26 – 2.10 (multiple peaks, 2H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 171.86, 153.51, 135.23, 129.46, 129.05, 127.47, 93.91 (dt, *J* = 177.7, 18.7 Hz), 81.92 (ddd, *J* = 176.3, 29.6, 5.3 Hz; overlapping diastereotopic $-CH_2F$ signals), 66.45, 55.25, 37.86, 28.95 (d, *J* = 5.3 Hz), 25.26 (dt, *J* = 21.3, 3.7 Hz) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -175.48 (m, 1F), -234.03 (apparent tt, *J* = 47.5, 11.9 Hz, 2F) ppm.
HRMS (*m/z*): calculated for $C_{16}H_{18}F_3NO_3Na$ [M+Na$^+$] 352.1131, found 352.1146.
IR (ATR): 3029 (w), 2964 (m), 2924 (w), 1784 (s), 1706 (s), 1604 (w), 1454 (m), 1394 (s), 1355 (s), 1213 (s), 1108 (s), 1030 (s), 900 (m), 763 (m), 746 (m), 703 (s) cm^{-1}.
$[\alpha]_D^{20}$ 42.00 (*c* 1.1, $CHCl_3$).



(*S*)-3-((*S*)-2-Azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (S6)

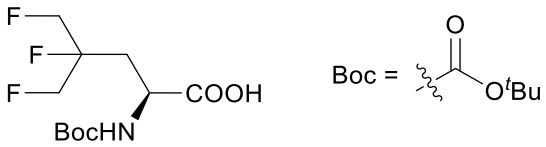
A cooled (-78 °C) solution of (*S*)-4-Benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**S5**) (1.90 g; 5.77 mmol) in dry THF (20 mL) was cannulated into a cooled (-78 °C) solution of KHMDS (7.2 mmol) in THF (ca. 25 mL). After 30 minutes a cooled (-78 °C) solution of trysil azide (2.2 g; 7.2 mmol) in THF (20 mL) was cannulated into the solution of previously prepared potassium enolate at -78 °C. After 2 minutes the reaction was quenched by the addition of acetic acid (1 mL). The reaction mixture was warmed to 35 °C and stirred at this temperature for 40 minutes. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (350 mL) and sat. aq. $NaHCO_3$ (200 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 10/1 → 3/1). 1.83 g (86%) of amorphous solid was obtained.
^1H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 2H), 7.30 (m, 1H), 7.22 (m, 2H), 5.34 (dd, *J* = 7.7, 5.5 Hz, 1H), 4.76 – 4.46 (multiple peaks, 5H), 4.33 – 4.20 (multiple peaks, 2H), 3.31 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.87 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.50 – 2.19 (multiple peaks, 2H) ppm.
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 169.39, 153.05, 134.67, 129.53, 129.22, 127.73, 93.53 (dt, *J* = 179.2, 18.7 Hz), 82.31 (ddd, *J* = 177.6, 26.7, 5.2 Hz), 81.87 (ddd, *J* = 176.7, 30.8, 6.2 Hz), 66.86, 55.53, 55.21 (d, *J* = 4.7 Hz), 37.73, 32.15 (dt, *J* = 20.9, 3.4 Hz) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -173.42 (m, 1F), -232.97 (td, *J* = 46.8, 12.8 Hz, 1F), -233.88 (td, *J* = 46.7, 12.5 Hz, 1F) ppm.
HRMS (*m/z*): calculated for $C_{16}H_{17}F_3N_4O_3Na$ [M+Na$^+$] 393.1150, found 393.1151.
IR (ATR): 3030 (w), 2962 (w), 2924 (w), 2115 (s), 1781 (s), 1705 (s), 1455 (w), 1393 (m), 1214 (s), 1112 (m), 1039 (s), 907 (w), 762 (m), 705 (m) cm^{-1}.
$[\alpha]_D^{20}$ 59.7 (*c* 1.1, $CHCl_3$).



(*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (S7)

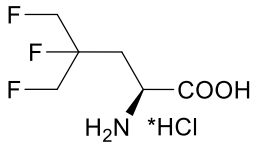
Pd/C (10%; 200 mg) was added to a solution of (*S*)-3-((*S*)-2-azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**7**) (600 mg; 1.62 mmol) and Boc_2O (5 g; 23 mmol) in EtOAc (25 mL). The resulting suspension was stirred under 3 bars of hydrogen overnight. The volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 20/1 to 1/1). 670 mg (93%) of white solid was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (multiple peaks, 5H), 5.42 (broad s, 1H), 5.34 (broad s, 1H), 4.82 – 4.40 (multiple peaks, 5H), 4.29 – 4.04 (multiple peaks, 2H), 3.25 (d, *J* = 12.6 Hz, 1H), 2.71 (dd, *J* = 13.1, 9.9 Hz, 1H), 2.32 – 1.98 (multiple peaks, 2H), 1.38 (s, 9H) ppm.
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 172.14, 155.32, 153.12, 135.05, 129.54, 129.15, 127.56, 94.59 (dt, *J* = 175.9, 22.0 Hz), 83.56–81.62 (m), 83.29–81.12 (m), 80.64, 66.84, 55.63, 49.43, 37.62, 32.93 (d, *J* = 21.7 Hz), 28.36 ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -170.09 (broad s, 1F), -234.55 (td, *J* = 45.9, 11.3 Hz, 1F), -235.24 (td, *J* = 45.9, 11.3 Hz, 1F) ppm.
HRMS (*m/z*): calculated for $C_{21}H_{27}F_3N_2O_5Na$ [M+Na$^+$] 467.1770, found 467.1779.
IR (ATR): 3393 (broad m), 2980 (m), 2932 (w), 1780 (s), 1704 (s), 1499 (m), 1455 (w), 1394 (m), 1368 (m), 1247 (m), 1166 (m), 1112 (m), 1048 (m), 907 (w), 762 (m), 704 (m) cm^{-1}.
$[\alpha]_D^{20}$ 35.2 (*c* 1.1, $CHCl_3$).
Mp: 95-96 °C.



(*S*)-2-((*tert*-Butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (S8)

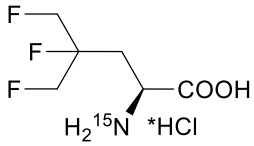
LiOH (72 mg; 3.0 mmol) in water (3 mL) was added to a cooled (0 °C) solution of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**) (500 mg; 1.13 mmol) in THF (10 mL). The reaction mixture was stirred for 1 hour at 0 °C. The reaction mixture was acidified to pH 2…3 by careful addition of aq. HCl (1 M). THF was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and brine (50 mL). The aqueous phase was extracted with additional EtOAc (4 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 5/1 to 0/1). 264 mg (82%) of amorphous glassy solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.77 – 4.41 (multiple peaks, 4H), 4.26 (dd, *J* = 9.2, 2.6 Hz, 1H), 2.42 (apparent t, *J* = 16.3 Hz, 1H), 2.10 (apparent ddd, *J* = 24.7, 15.3, 10.2 Hz, 1H), 1.45 (s, 9H) ppm.
^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ: 175.11, 157.82, 95.46 (dt, *J* = 178.3, 18.2 Hz), 83.46 (ddd, *J* = 174.7, 28.2, 6.6 Hz), 83.23 (ddd, *J* = 174.3, 28.1, 5.5 Hz), 80.82, 50.11 (d, *J* = 4.5 Hz), 33.70 (dt, *J* = 21.5, 3.5 Hz), 28.69 ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -174.11 (m, 1F), -236.16 (td, *J* = 47.1, 12.4 Hz, 1F), -236.95 (td, *J* = 47.0, 12.2 Hz, 1F) ppm.
HRMS (ESI$^-$ *m/z*): calculated for $C_{11}H_{17}NO_6F_3$ [M-H$^+$] 284.1110, found 284.1117.
IR (ATR): 3361 (broad w), 2992 (w), 1718 (s), 1687 (s), 1522 (s), 1373 (w), 1284 (s), 1254 (m), 1166 (s), 1066 (s), 1035 (s), 935 (s), 895 (m), 867 (m), 782 (s), 622 (s) cm^{-1}.
$[\alpha]_D^{20}$ -14.8 (*c* 1.1, $CHCl_3$).
Mp: 113-115 °C.



(*S*)-2-Amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (14)

TFA (5 mL) was added to a DCM (15 mL) solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S8**) (240 mg; 0.84 mmol). The reaction mixture was stirred at ambient temperature for 3 hours. The volatiles were removed under reduced pressure. The residue was dissolved in MeCN (15 mL) and anhydrous HCl (2 M in ether; 3 mL) was added. The volatiles were removed under reduced pressure and the HCl treatment was repeated 3 times. Finally, the crystalline residue was suspended in EtOAc (15 mL), sonicated 5 minutes and then collected by filtration. The reaction product was washed with EtOAc (3 x 3 mL). After drying under vacuum 166 mg (89%) of white microcrystalline solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.89 – 4.66 (m, 2H), 4.65 (ddd, *J* = 47.0, 20.5, 1.8 Hz, 2H), 4.32 (dd, *J* = 8.6, 4.2 Hz, 1H), 2.59 (ddd, *J* = 29.2, 15.9, 4.1 Hz, 1H), 2.47 – 2.29 (m, 1H) ppm.
^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ: 171.10, 95.90 (dt, *J* = 178.2, 18.2 Hz), 83.84 (ddd, *J* = 176.0, 25.2, 6.2 Hz), 83.18 (ddd, *J* = 174.2, 27.7, 6.3 Hz), 49.94 (broad s), 32.42 (ddd, *J* = 20.4, 5.1, 3.7 Hz) ppm.

^{19}F NMR (376 MHz, CD_3OD) δ: -174.81 – -176.97 (m), -236.60 (td, *J* = 46.9, 11.6 Hz), -237.10 (td, *J* = 46.7, 11.9 Hz) ppm.
HRMS (*m/z*): calculated for $C_6H_{11}NO_2F_3$ [M+H$^+$] 186.0742, found 186.0747.
IR (ATR): 3010 (broad s), 2565 (m), 1749 (broad s), 1558 (s), 1488 (s), 1457 (m), 1220 (m), 1136 (m), 1032 (s), 1016 (s), 954 (m), 897 (m), 789 (m), 716 (m), 653 (s) cm^{-1}.
$[\alpha]_D^{20}$ 5.2 (*c* 0.9, CH_3OH).
Mp: 165-168 °C.



(*S*)-2-Amino-4,5-difluoro-4-(fluoromethyl)pentanoic-^{15}*N* acid hydrochloride was prepared as above, following the procedure described for (*S*)-2-amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**14**), except using sodium azide-1-^{15}*N* as the ^{15}N source. Starting with 500 mg of sodium azide-1-^{15}*N*, 193 mg of final product was obtained.

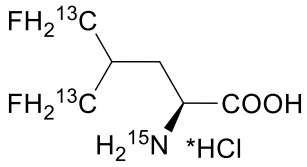
2,4,6-Triisopropylbenzenesulfonyl azide-^{15}*N* (**17**) was prepared as described in the literature: J. E. Leffler, Y. Tsuno, *J. Org. Chem.,* 1963, **28**, 902.

^{1}H NMR (400 MHz, CD_3OD) δ: 4.90 – 4.62 (m, 2H), 4.65 (ddd, *J* = 47.0, 20.6, 1.8 Hz, 2H), 4.33 (dd, *J* = 8.6, 4.1 Hz, 1H), 2.59 (ddd, *J* = 29.3, 16.4, 4.0 Hz, 1H), 2.46 – 2.23 (m, 1H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -175.54 (m, 1F), -236.62 (td, *J* = 46.8, 11.5 Hz, 1F), -237.12 (td, *J* = 46.6, 11.9 Hz, 1F) ppm.
^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ: 171.08, 95.89 (dt, *J* = 178.1, 18.1 Hz), 83.84 (ddd, *J* = 175.9, 25.2, 6.3 Hz), 83.17 (ddd, *J* = 174.1, 27.7, 6.3 Hz), 49.90 (broad s), 32.43 (ddd, *J* = 20.6, 5.3, 3.7 Hz) ppm.
HRMS (*m/z*): calculated for $C_6H_{11}{}^{15}NO_2F_3$ [M+H$^+$] 186.0712, found 187.0721.
IR (ATR): 2980 (broad s), 2563 (m), 1757 (s), 1559 (m), 1499 (s), 1417 (m), 1225 (s), 1131 (s), 1033 (s), 957 (w), 896 (m), 827 (m), 790 (m), 719 (m), 654 (s) cm^{-1}.
$[\alpha]_D^{20}$ 5.1 (c 1.1, CH_3OH).
Mp: 165-168 °C.

Scheme 3: 5,5'-difluoro-*L*-leucine- 5,5'-$^{13}C_2$-^{15}N (18)

5,5'-difluoro-*L*-leucine- 5,5'-$^{13}C_2$-^{15}N (**18**) was prepared according to the Scheme 1. See the previous section for experimental procedures. Starting with 1 g of diethyl malonate-1,3-$^{13}C_2$ and 500 mg of sodium azide-1-^{15}N, **260 mg** of **18** was obtained.

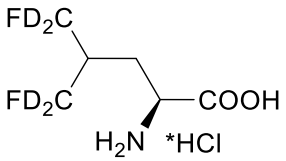
2,4,6-Triisopropylbenzenesulfonyl azide-^{15}N (**17**) was prepared as described in the literature: J. E. Leffler, Y. Tsuno, *J. Org. Chem.,* 1963, **28**, 902.



^{1}H NMR (400 MHz, CD_3OD) δ: 4.83 – 4.23 (m, 4H), 4.12 (t, *J* = 7.1 Hz, 1H), 2.53 – 2.25 (m, 1H), 2.18 – 2.02 (m, 1H), 1.99 – 1.88 (m, 1H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -230.01 – -231.02 (m, 2F) ppm.
^{19}F NMR (376 MHz, D_2O) δ: -227.41 (dtdd, *J* = 165.0, 46.6, 22.3, 6.5 Hz), -228.01 (dtdd, *J* = 165.3, 46.9, 23.3, 6.4 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 171.54, 83.60 (dd, *J* = 168.8, 6.3 Hz, high intensity signal), 83.28 (dd, *J* = 168.9, 6.3 Hz, high intensity signal), 51.85, 38.21 (tt, *J* = 37.9, 18.7 Hz), 29.03 (t, *J* = 5.2 Hz) ppm.
^{15}N NMR (41 MHz, CD_3OD) δ: 36.02 (s) ppm.
HRMS (*m/z*): calculated for $^{12}C_4{}^{13}C_2H_{12}{}^{14}NO_2F_2$ [M+H$^+$] 170.0903, found: 170.0908, calculated for $^{12}C_4{}^{13}C_2H_{12}{}^{15}NO_2F_2$ [M+H$^+$] 171.0874, found: 171.0881.
IR (ATR): 3457 (broad w), 3010 (broad s), 2603 (w), 2529 (w), 1968 (broad w), 1740 (s), 1486 (s), 1361 (w), 1216 (s), 1012 (m), 942 (m), 801 (m) cm^{-1}.
$[\alpha]_D^{20}$ 14.4 (*c* 1.0, CH_3OH).
M.p.: 151 °C.

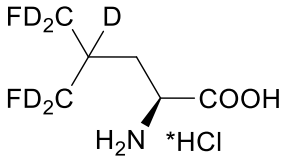
Scheme 4: deuterated 4,4'-difluoro-*L*-leucines 20 and 22

Deuterated 4,4'-difluoro-*L*-leucines **20** and **22** were prepared according to Scheme 1. See the previous section for experimental procedures. Starting with 5 g of $NaBD_4$ **590 mg** of difluoroleucine (**20**) was obtained. Starting with 2 g of $NaBD_4$ **63 mg** of difluoroleucine (**22**) was obtained.



(*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-5,5-d_2 acid hydrochloride (20)

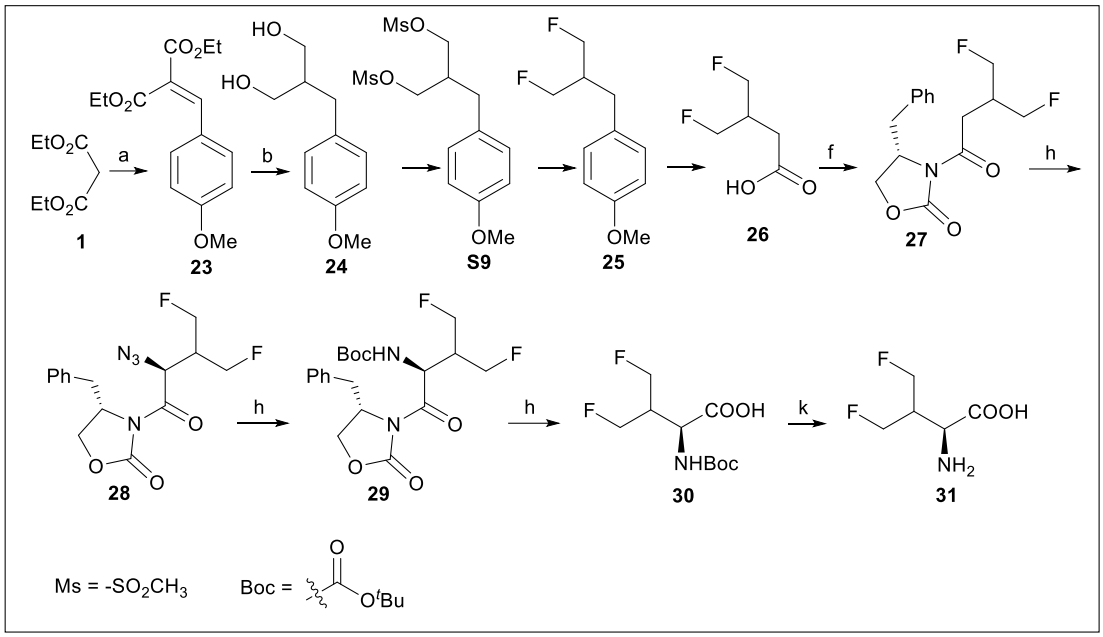
^{1}H NMR (400 MHz, CD_3OD) δ: 4.12 (t, *J* = 7.2 Hz, 1H), 2.39 (tt, *J* = 21.6, 6.9 Hz, 1H), 2.09 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.94 (dt, *J* = 14.2, 7.1 Hz, 1H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -231.7 (m) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 171.56, 86.58 – 77.70 (multiple signals, both -CD_2F groups), 51.87, 37.85 (t, *J* = 18.7 Hz), 28.92 (t, *J* = 5.5 Hz) ppm.
HRMS (*m/z*): calculated for $C_6H_8D_4NO_2F_2$ [M+H$^+$] 172.1087, found: 1721091.
IR (ATR): 3017 (broad s), 2558 (w), 2013 (w), 1985 (w), 1743 (s), 1491 (m), 1384 (m), 1233 (s), 1214 (s), 969 (m), 935 (m), 819 (m) cm^{-1}.
cm^{-1}.
M.p.: 149-151 °C.
$[\alpha]_D^{20}$ 13.7 (*c* 1.0, CH_3OH).

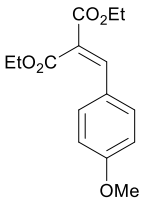


(*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-4,5,5-d_3 acid hydrochloride (22)

^{1}H NMR (400 MHz, CD_3OD) δ: 4.11 (t, *J* = 6.9 Hz, 1H), 2.08 (dd, *J* = 14.5, 6.9 Hz, 1H), 1.94 (dd, *J* = 14.5, 6.6 Hz, 1H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -231.85 (broad s), -231.96 (broad s) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 171.68, 84.73 – 81.05 (multiple peaks: two diastereotopic -CD_2F groups), 51.93, 38.88 – 36.46 (m), 28.82 (t, *J* = 5.5 Hz) ppm.
HRMS (*m/z*): calculated for $C_6H_7D_5NO_2F_2$ [M+H$^+$] 173.1150, found: 173.1156.
IR (ATR): 3019 (broad s), 2559 (w), 2136 (w), 2013 (w), 1984 (w), 1738 (s), 1607 (w), 1490 (s), 1237 (m), 1211 (s), 1001 (m), 955 (s), 807 (s) cm^{-1}.
$[\alpha]_D^{20}$ 14.0 (*c* 1.0, CH_3OH).
M.p.: 150-152 °C.

Scheme 5: 4,4'-difluoro-L-valine (31)





Diethyl 2-(4-methoxybenzylidene)malonate (23) was prepared according to the literature procedure: Herschel Mukherjee, Carlos A. Martinez, *ACS Catalysis*, 2011, **1**, 1010.

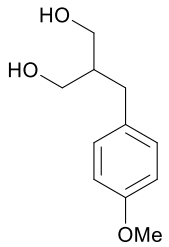
A solution of diethylmalonate (**1**) (4.8 g; 30 mmol), 4-anisaldehyde (4.1 g; 30 mmol), piperidine (0.3 mL; 3 mmol) and acetic acid (0.17 mL; 3.0 mmol) in heptane (200 mL) was refluxed with a Dean-Stark trap overnight. The reaction mixture was partitioned between EtOAc (150 mL) and aq. $NaHCO_3$ (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (mobile phase hexanes/EtOAc with gradient 20/1 to 4/1). 7.31 g (88%) of yellow oil was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.36 – 1.28 (multiple peaks, 6H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 167.32, 164.62, 161.71, 141.91, 131.71, 125.54, 123.74, 114.41, 61.74, 61.57, 55.50, 14.30, 14.09 ppm.

HRMS (*m/z*): calculated for $C_{15}H_{18}O_5Na$ [M+Na$^+$] 301.1052, found 301.1053.

IR (ATR): 3442 (w), 2982 (m), 2938 (w), 2906 (w), 2840 (w), 1733 (s), 1604 (s), 1514 (s), 1466 (m), 1379 (w), 1307 (w), 1258 (m), 1213 (m), 1180 (m), 1065 (m), 1026 (m), 831 (m) cm^{-1}.



2-(4-Methoxybenzyl)propane-1,3-diol (24)

A solution of diethyl 2-(4-methoxybenzylidene)malonate (**23**) (4.50 g; 16.2 mmol) and LiCl (850 mg; 20 mmol) in MeOH (150 mL) was cooled to 0 °C. $NaBH_4$ (3.0 g; 80 mmol) was added portion-wise over a period of 45 minutes. The reaction

mixture was stirred at 0 °C for another 2 hours. TLC indicated complete conversion. The reaction mixture was diluted with water (50 mL) and brine (50 mL) and stirred at room temperature for 2 hours. Methanol was distilled off under reduced pressure. The remaining suspension was saturated with NaCl and extracted with EtOAc (6 x 50 mL). The combined organic solutions were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (mobile phase hexanes/EtOAc with gradient 4/1 to 0/1). 2.57 g (81%) of white solid was obtained.

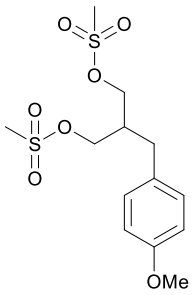
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.84 – 3.75 (multiple peaks, 5H), 3.67 (dd, *J* = 10.6, 6.9 Hz, 2H), 2.57 (d, *J* = 7.5 Hz, 2H), 2.22 – 2.09 (br. s, 2H), 2.08 – 1.96 (m, 1H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.16, 131.94, 130.03, 114.02, 65.88, 55.42, 44.17, 33.49 ppm.

IR (ATR): 3279 (broad s), 2933 (m), 2910 (m), 2850 (w), 1584 (w), 1512 (m), 1457 (w), 1322 (m), 1242 (m), 1111 (s), 1042 (s), 972 (m), 836 (m), 802 (m) cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; N, 0. Found: C, 67.38; H, 8.23; N, 0.

M.p.: 71 °C.



2-(4-Methoxybenzyl)propane-1,3-diyl dimethanesulfonate (S9)

A solution of *tert*-butyl 2-(4-methoxybenzyl)propane-1,3-diol (**24**) (2.30 g; 11.7 mmol) and DIPEA (5.2 mL; 30 mmol) in dry toluene (50 mL) was cooled to -20 °C. Mesyl chloride (1.9 mL; 25 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to warm to 0 °C and stirred at this temperature for 2 hours. The reaction mixture was applied directly to a 100 g silica gel column. The column was eluted with hexanes/EtOAc with gradient from 4/1 to 0/1. Fractions containing product were evaporated under reduced pressure. 3.42 g (83%) of yellowish solid was obtained.

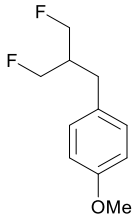
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.27 (dd, *J* = 10.0, 4.3 Hz, 2H), 4.17 (dd, *J* = 10.0, 6.2 Hz, 2H), 3.79 (s, 3H), 3.04 (s, 6H), 2.70 (d, *J* = 7.7 Hz, 2H), 2.46 – 2.36 (m, 1H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.73, 130.11, 129.15, 114.42, 67.92, 55.42, 40.41, 37.44, 32.62 ppm.

HRMS (*m/z*): calculated for $C_{13}H_{20}O_7S_2Na$ $[M+Na^+]$ 375.0548, found 375.0555.

IR (ATR): 3030 (m), 2940 (m), 2839 (w), 1613 (w), 1514 (m), 1467 (w), 1354 (s), 1248 (m), 1174 (s), 1033 (w), 962 (s), 833 (m), 751 (w), 529 (m) cm^{-1}.

M.p.: 87 °C.



1-(3-Fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (25)

An Ace pressure tube was charged with dry *tert*-butanol (70 mL), anhydrous CsF (22.8 g; 150 mmol) and 2-(4-methoxybenzyl)propane-1,3-diyl dimethanesulfonate (**3**) (3.30 g; 9.36 mmol). The reaction vessel was sealed and heated to 95 °C (oil bath temperaturte) overnight. The reaction mixture was partitioned between brine (200 mL) and EtOAc (250 mL). The aqueous phase was extracted with additional EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 1.75 g (94%) of yellow liquid was obtained (about 80% purity). Crude product was used directly in the next step.

The analytical sample was obtained as follows: a sample of crude product was dissolved in DCM (10 mL) and a few drops of concentrated sulfuric acid were added. The emulsion was stirred at ambient temperature for 1 hour. The DCM emulsion was partitioned between ether (50 mL) and water (25 mL). The organic phase was washed with water (10 mL)

and brine (30 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (mobile phase hexanes/ether 20/1) to afford pure compound **25**.

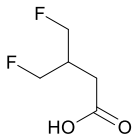
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.57 – 4.34 (multiple peaks, J^{HF}= 47.1 Hz, 4H), 3.80 (s, 3H), 2.66 (d, *J* = 7.7 Hz, 2H), 2.24 (m, 1H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -229.66 (td, *J* = 47.1, 22.3 Hz) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.40, 130.50, 130.19, 114.16, 82.21 (dd, *J* = 168.8, 4.9 Hz), 55.41, 42.74 (t, *J* = 18.1 Hz), 31.50 (t, *J* = 5.8 Hz) ppm.

IR (ATR): 2965 (s), 2907 (s), 2838 (w), 2057 (w), 1998 (w), 1900 (w), 1612 (s), 1514 (s), 1467 (m), 1302 (m), 1249 (s), 1179 (s), 1036 (s), 1009 (s), 847 (m), 808 (m) cm^{-1}.

GC-MS (EI, 75 eV): m/z 200.1 ([M]$^+$, 24%), 121.1 (100%).



4-Fluoro-3-(fluoromethyl)butanoic acid (26)

A suspension of 1-(3-fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (**25**) (1.54 g; 7.69 mmol), $RuCl_3$ (166 mg; 0.80 mmol) and $NaIO_4$ (32 g; 150 mmol) in EtOAc (60 mL), MeCN (60 mL) and water (60 mL) was stirred intensively overnight. The reaction mixture was filtered through a pad of celite. The filtrate was partitioned between ether (200 mL) and aq. HCl (1 M; 200 mL). The aqueous phase was extracted with additional ether (4 x 50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure (bath temperature 35 °C; 60 mBar). 776 mg (73%) of yellow liquid was obtained. The crude product was used in the next step without further purification. The analytical sample (colourless liquid) was obtained by short-path vacuum distillation.

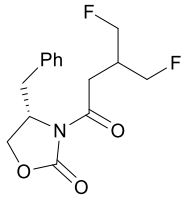
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.61 – 4.46 (multiple peaks, J^{HF} = 47.0 Hz, 4H), 2.72 – 2.44 (multiple peaks, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 177.79, 81.98 (dd, *J* = 170.0, 5.4 Hz), 36.98 (t, *J* = 19.0 Hz), 30.81 (t, *J* = 6.0 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -228.94 (td, *J* = 46.6, 21.2 Hz) ppm.

HRMS (TOF ES$^-$ *m/z*): calculated for $C_5H_7O_2F_2$ [M-H$^+$] 137.0414, found 137.0416.

IR (ATR): 2978 (broad s), 2915 (broad s), 2631 (broad m), 1714 (s), 1417 (m), 1292 (m), 1241 (m), 1188 (w), 1016 (m), 949 (w) cm^{-1}.



(*S*)-4-Benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (27)

Pivaloyl chloride (0.48 mL; 4.0 mmol) was added dropwise to a solution of 4-fluoro-3-(fluoromethyl)butanoic acid (**26**) (520 mg; 3.77 mmol) and DIPEA (0.87 mL; 5.0 mmol) in dry THF (30 mL) at 0 °C. In a separate flask to a solution of (*S*)-4-benzyloxazolidin-2-one (0.89 g; 5.0 mmol) in dry THF (30 mL) was added BuLi (2 M; 2.5 mL) at -78 °C. After 2 hours the solution of mixed anhydride was cannulated into the solution of lithium (*S*)-4-benzyl-2-oxooxazolidin-3-ide at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (250 mL) and aq. HCl (1 M; 150 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 851 mg (76%) of colourless oil was obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.23 – 7.18 (m, 2H), 4.73 – 4.65 (m, 1H), 4.65 – 4.46 (m, 4H), 4.23 (ddd, *J* = 9.0, 7.5, 0.5 Hz, 1H), 4.19 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.30 (dd, *J* = 13.4, 3.4 Hz, 1H), 3.12 (ddd, *J* = 17.9, 6.7, 0.8 Hz, 1H), 3.04 (ddd, *J* = 17.9, 6.8, 0.6 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.75 – 2.64 (m, 1H) ppm.

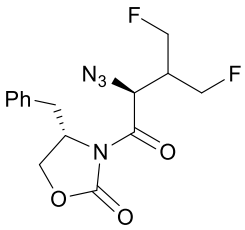
^{19}F NMR (376 MHz, $CDCl_3$) δ: -228.21 (td, *J* = 46.5, 22.0 Hz, 1F), -228.42 (td, *J* = 48.2, 22.0 Hz, 1F) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 170.98, 153.40, 135.11, 129.39, 129.04, 127.46, 82.30 (dd, *J* = 169.5, 5.5 Hz), 82.23 (dd, *J* = 169.6, 5.6 Hz), 66.42, 55.21, 37.90, 36.62 (t, *J* = 19.0 Hz), 32.35 (t, *J* = 5.9 Hz) ppm.

HRMS (*m/z*): calculated for $C_{15}H_{18}NO_3F_2$ [M+H$^+$] 298.1255, found: 298.1262.

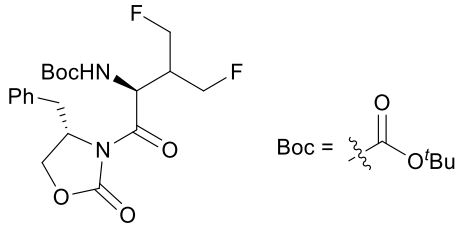
IR (ATR): 2971 (w), 2913 (w), 1780 (s), 1702 (s), 1390 (m), 1352 (m), 1214 (m), 1102 (w), 1015 (m) cm^{-1}.

$[\alpha]_D^{20}$ 42.7 (*c* 1.1, $CHCl_3$).



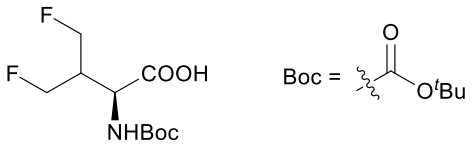
(*S*)-3-((*S*)-2-Azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (28)

A cooled (-78 °C) solution of (*S*)-4-benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (**27**) (830 mg; 2.79 mmol) in dry THF (10 mL) was cannulated into a cooled (-78 °C) solution of KHMDS (3.2 mmol) in THF (~18 mL). After 30 minutes a cooled (-78 °C) solution of trysil azide (1.0 g; 3.2 mmol) in THF (12 mL) was cannulated into the solution of previously prepared potassium enolate at -78 °C. After 2 minutes the reaction was quenched with acetic acid (0.9 mL). The reaction mixture was warmed to 35 °C and stirred at this temperature for 40 minutes. The volatiles were removed under reduced pressure (bath temperature ~35 °C). The residue was partitioned between EtOAc (250 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 785 mg (83%) of colourless oil was obtained.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.20 (multiple peaks, 3H), 7.18 – 7.13 (m, 2H), 5.36 (d, *J* = 7.1 Hz, 1H), 4.74 – 4.39 (multiple peaks, 5H), 4.22 (ddd, *J* = 9.3, 7.4, 0.5 Hz, 1H), 4.18 (dd, *J* = 9.2, 3.3 Hz, 1H), 3.25 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.81 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.78 – 2.60 (m, 1H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -227.39 (td, *J* = 47.0, 18.1 Hz), -228.52 (td, *J* = 46.6, 23.0 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 168.45, 153.18, 134.71, 129.55, 129.22, 127.74, 81.12 (dd, *J* = 170.2, 6.0 Hz), 80.23 (dd, *J* = 169.3, 5.9 Hz), 66.92, 58.43 (dd, *J* = 5.1, 3.9 Hz), 55.71, 42.50 (t, *J* = 18.9 Hz), 37.78 ppm.
HRMS (*m/z*): calculated for $C_{15}H_{17}N_2O_3F_2$ [M-N_2+H^+] 311.1207, found: 311.1198.
IR (ATR): 2980 (w), 2917 (w), 2114 (s), 1784 (s), 1706 (s), 1394 (s), 1213 (m), 1016 (m), 762 (w) cm^{-1}.
$[\alpha]_D^{20}$ 20.2 (*c* 1.1, $CHCl_3$).



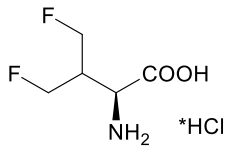
tert-Butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (29)

Pd/C (10%; 150 mg) was added to a solution of (*S*)-3-((*S*)-2-Azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (**28**) (560 mg; 1.66 mmol) and Boc_2O (5.4 g; 25 mmol) in EtOAc (25 mL). The resulting suspension was stirred under 3 bars of hydrogen for 4 hours. The volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 20/1 to 1/1). 594 mg (87%) of white solid was obtained.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 2H), 7.28 (m, 1H), 7.25 – 7.18 (m, 2H), 5.65 – 5.46 (multiple peaks, 2H), 4.83 – 4.42 (multiple peaks, 5H), 4.28 – 4.15 (multiple peaks, 2H), 3.36 (dd, *J* = 13.4, 2.9 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.82 – 2.64 (m, 1H), 1.46 (s, 9H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -225.75 (td, *J* = 46.8, 15.8 Hz), -227.23 (td, *J* = 46.6, 25.4 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ:171.28, 155.62, 153.10, 135.12, 129.56, 129.19, 127.59, 81.43 (dd, *J* = 169.8, 7.3 Hz), 80.66 (dd, *J* = 167.2, 4.6 Hz), 80.62, 66.83, 55.94, 52.08 (m), 42.71 (t, *J* = 16.9 Hz), 37.67, 28.37 ppm.
HRMS (*m/z*): calculated for $C_{20}H_{26}N_2O_5F_2Na$ [M+Na^+] 435.1707, found: 435.1726.
IR (ATR): 3425 (broad m), 2980 (m), 2918 (m), 1786 (s), 1704 (s), 1500 (s), 1392 (s), 1368 (s), 1245 (m), 1165 (m), 1013 (m), 762 (m), 705 (m) cm^{-1}.
$[\alpha]_D^{20}$ 47.6 (*c* 1.1, $CHCl_3$).
M.p.: 112 °C.



(*S*)-2-((*tert*-Butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (30)

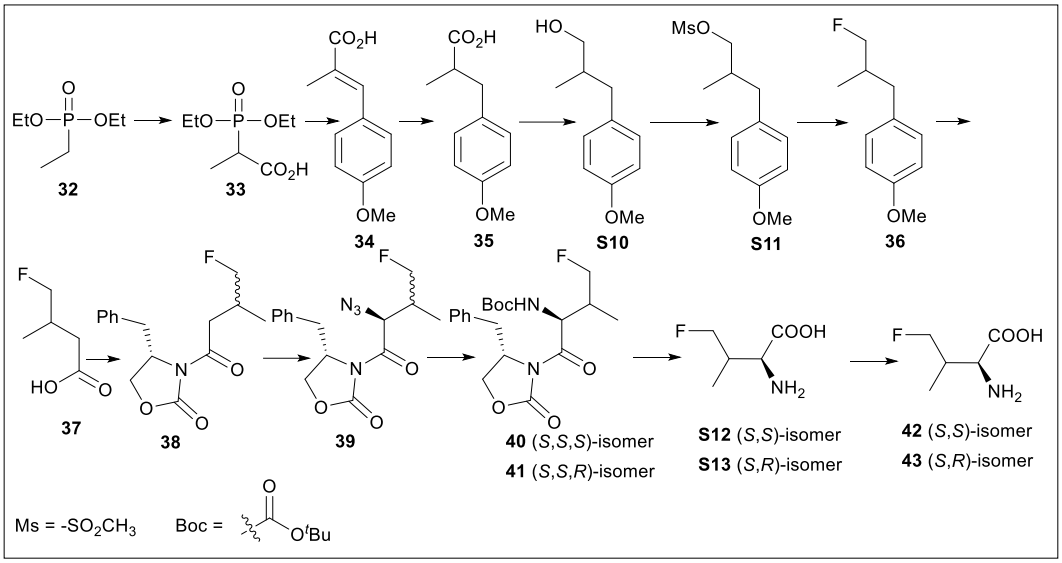
LiOH (48 mg; 2.0 mmol) in water (3 mL) was added to a cooled (0 °C) solution of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (**29**) (400 mg; 0.97 mmol) in THF (10 mL). The reaction mixture was stirred for 1 hour at 0 °C. The reaction mixture was acidified to pH 2…3 by a careful addition of aq. HCl (1 M). The THF was removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and brine (50 mL). The aqueous phase was extracted with additional EtOAc (4 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 5/1 to 0/1). 218 mg (89%) of amorphous glassy solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.73 – 4.44 (multiple peaks, 4H), 4.38 (d, *J* = 5.3 Hz, 1H), 2.75 – 2.47 (m, 1H), 1.45 (s, 9H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -229.34 (td, *J* = 47.0, 19.7 Hz, 1F), -230.39 (td, *J* = 47.0, 21.8 Hz, 1F) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ:174.18, 157.94, 81.82 (dd, *J* = 168.7, 6.8 Hz), 81.66 (dd, *J* = 167.1, 7.0 Hz), 80.91 (bs), 52.77, 43.99 (t, *J* = 18.7 Hz), 28.64 ppm.
HRMS (TOF ES$^-$ *m/z*): calculated for $C_{10}H_{16}NO_4F_2$ [M-H$^+$] 252.1047, found: 252.1058.
IR (ATR): 3447 (m), 3318 (broad m), 2981 (s), 2925 (w), 2553 (broad w), 1717 (broad s), 1527 (m), 1396 (m), 1252 (w), 1163 (m), 1069 (w), 1024 (m), 858 (w), 763 (m) cm^{-1}.
$[\alpha]_D^{20}$ -9.1 (*c* 1.1, $CHCl_3$).

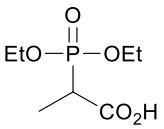


(*S*)-2-Amino-4-fluoro-3-(fluoromethyl)butanoic acid hydrochloride (31)

TFA (5 mL) was added to a DCM (15 mL) solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (**30**) (208 mg; 0.82 mmol). The reaction mixture was stirred at ambient temperature for 3 hours. The volatiles were removed under reduced pressure. The residue was dissolved in MeCN (15 mL) and anhydrous HCl (2 M in ether; 3 mL) was added. The volatiles were removed under reduced pressure and the HCl treatment was repeated 3 times. The crystalline residue was suspended in EtOAc (15 mL), sonicated 5 minutes and then collected by filtration. The reaction product was washed with EtOAc (3 x 3 mL). After drying under vacuum 144 mg (93%) of white microcrystalline solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.86 – 4.59 (m, 4H), 4.27 (d, *J* = 4.0 Hz, 1H), 2.97 – 2.73 (m, 1H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -223.93 (td, *J* = 46.7, 20.8 Hz), -225.72 (td, *J* = 46.4, 23.6 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 172.67, 84.02 (dd, *J* = 168.5, 3.9 Hz), 83.97 (dd, *J* = 168.1, 3.7 Hz), 55.03 (t, *J* = 3.7 Hz), 45.31 (t, *J* = 19.1 Hz) ppm.
HRMS (*m/z*): calculated for $C_5H_{10}NO_2F_2$ [M+H$^+$] 154.0680, found: 154.0681.
IR (ATR): 3447 (broad w), 2981 (broad s), 2548 (w), 2253 (broad s), 2042 (m), 1958 (w), 1733 (s), 1487 (m), 1405 (m), 1216 (m), 1165 (m), 1060 (m), 961 (m), 822 (w) cm^{-1}.
$[\alpha]_D^{20}$ 17.1 (*c* 1.1, CD_3OD).
M.p.: 158 °C.

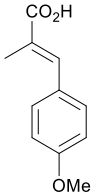
Scheme 6: 4-fluoro-*L*-valines 42 and 43





2-(Diethoxyphosphoryl)propanoic acid (33) was obtained using a slightly modified literature procedure: P. Coutrot, A. Ghribi, *Synthesis*, 1986, **8**, 661.

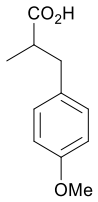
The reaction was performed in a 250 mL Schlenk flask under argon atmosphere. BuLi (21.0 mL; 2.5 M in THF) was added dropwise to a cooled solution of diethylethanephosphonate (**32**) (8.00 g; 48.15 mmol) in THF (150 mL) while maintaining the internal temperature below -55 °C. The resulting solution was stirred at -50 °C for 1 hour. The headspace of the reaction flask was evacuated and refilled with CO_2 from a balloon attached to the sidearm of the flask. The internal temperature briefly spiked to -37 °C. The reaction mixture was allowed to warm to 0 °C. Aqueous sat. $NaHCO_3$ (150 mL) was added and THF was removed under reduced pressure. The aqueous suspension was extracted with MTB (3 x 50 mL) and the organic phase was discarded. The aqueous phase was acidified to pH 2 with aq. HCl (1 M). The resulting suspension was extracted with EtOAc (3 x 100 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 5.27 g (52% based on diethylethanephosphonate) of colourless oil was obtained. Crude reaction product was used in the next step without further purification and characterization.
When the reaction was performed with $^{13}CO_2$, diethylethanephosphonate/BuLi was used in 2-fold excess over $^{13}CO_2$ and a yield of 90% based on $^{13}CO_2$ was obtained.



(*E*)-3-(4-Methoxyphenyl)-2-methylacrylic acid (34)

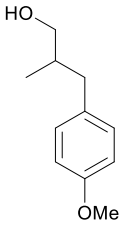
2-(Diethoxyphosphoryl)propanoic acid (**33**) (5.00 g; 23.8 mmol) in THF (20 mL) was added dropwise to a solution of BuLi (2.5 M, 20 mL) in THF (150 mL) while maintaining the internal temperature below -50 °C. The reaction mixture was stirred for 1 h at -50 °C. *p*-Anisaldehyde (3.16 mL; 26 mmol) in THF (10 mL) was added dropwise at -50 °C. The reaction mixture was warmed to 50 °C and stirred at this temperature for 1 h. Aqueous sat. $NaHCO_3$ (150 mL) was added to the reaction mixture and THF was removed under reduced pressure. The aqueous suspension was extracted with MTB (3 x 50 mL) and the organic phase was discarded. The remaining aqueous solution was acidified to pH 3 with aq. HCl (1 M). The resulting suspension was extracted with EtOAc (3 x 100 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 3.86 g (84%) of white crystalline solid was obtained. NMR analysis showed that the obtained product was sufficiently pure for further transformation.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.18 (broad s, 1H), 7.80 (s, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.17 (s, 3H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 174.78, 160.16, 140.97, 131.91, 128.35, 125.30, 114.08, 55.46, 13.88 ppm.
HRMS (ESI$^-$ *m/z*): calculated for $C_{11}H_{11}O_3$ [M-H$^+$] 191.0708, found 191.0708.
IR (ATR): 2946 (broad w), 1661 (s), 1601 (s), 1512 (m), 1423 (w), 1319 (w), 1280 (m), 1253 (s), 1180 (s), 1131 (w), 1030 (w), 825 (w) cm^{-1}.
Mp: 155-156 °C.



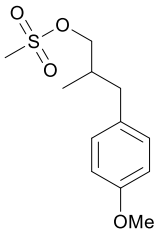
3-(4-Methoxyphenyl)-2-methylpropanoic acid (**35**)

(*E*)-3-(4-Methoxyphenyl)-2-methylacrylic acid (**34**) (3.80 g; 19.8 mmol) was dissolved in EtOH (70 mL). Pd/C (300 mg; 10%) was added and the resulting suspension was stirred intensively overnight under 6 bars of hydrogen. LC-MS analysis indicated clean and complete conversion at this point. The suspension was filtered through a pad of celite and evaporated under reduced pressure. 3.82 g (99%) of a colourless oil was obtained. The reaction product was used in the next step without further purification and characterization.



3-(4-Methoxyphenyl)-2-methylpropan-1-ol (S10)

Borane (1M in THF; 32 mL) was added dropwise to the solution of 3-(4-methoxyphenyl)-2-methylpropanoic acid (**35**) (3.80 g; 19.6 mmol) in dry THF (150 mL). The reaction mixture was stirred for 3 h at ambient temperature. LC-MS indicated complete and clean conversion at this point. The volatiles were removed under reduced pressure. The residue was dissolved in MeOH (100 mL) and the solution was evaporated again. The evaporation of the MeOH solution was repeated 3 times to remove all boric acid derivatives in the form of volatile $B(OMe)_3$. 3.34 g (95%) of colourless oil was obtained. TLC analysis indicated almost pure product. Crude product was used in the next step without further purification. The analytical sample was obtained by silica-gel column chromatography (hexanes/EtOAc with gradient 10/1 to 1/1).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.52 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.46 (dd, *J* = 10.6, 6.1 Hz, 1H), 2.69 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.37 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.90 (m, 1H), 1.61 (broad s, 1H), 0.91 (d, *J* = 6.8 Hz, 3H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 157.91, 132.75, 130.12, 113.78, 67.72, 55.34, 38.87, 38.00, 16.53 ppm.
HRMS (ESI *m/z*): calculated for $C_{11}H_{15}O$ [M-OH]$^+$ 163.1123, found 163.1127.
GC-MS (EI, 75 eV): m/z 180.2 ([M$^+$], 10%), 121.1 (100%).
IR (ATR): 3366 (broad s), 2954 (s), 2913 (s), 2872 (s), 2835 (s), 2059 (w), 1882 (w), 1612 (m), 1512 (s), 1464 (m), 1300 (m), 1247 (s), 1179 (m), 1114 (w), 1036 (s), 986 (w), 843 (m), 804 (m), 753 (w) cm^{-1}.



3-(4-Methoxyphenyl)-2-methylpropyl methanesulfonate (S11)

A solution of 3-(4-methoxyphenyl)-2-methylpropan-1-ol (**S10**) (3.10 g; 17.2 mmol) and DIPEA (4.7 mL; 27 mmol) in dry toluene (50 mL) was cooled to -20 °C. Mesyl chloride (1.8 mL; 23 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to warm to 0 °C and stirred at this temperature 2 hours. TLC analysis showed complete conversion. The reaction mixture was applied directly to a 100 g silica gel column. The column was eluted with hexanes/EtOAc with gradient 4/1 to 1/1. The fractions containing product were evaporated under reduced pressure. 4.15 g (93%) of colourless oil was obtained.

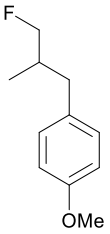
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.07 (dd, *J* = 9.5, 5.7 Hz, 1H), 4.02 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.79 (s, 3H), 2.98 (s, 3H), 2.69 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.47 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.15 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 158.25, 131.23, 130.16, 113.98, 73.85, 55.37, 38.32, 37.31, 35.24, 16.46 ppm.

GC-MS (EI, 75 eV): m/z 258.1 ([M]$^+$, 16%), 162.1(13%), 147.1 (20%), 121.1 (100%), 91.1 (9%).

HRMS (ESI *m/z*): calculated for $C_{12}H_{18}O_4SNa$ [M+Na$^+$] 281.0823, found 281.0820.

IR (ATR): 3029 (m), 2963 (s), 2937 (s), 2838 (m), 1613 (m), 1514 (s), 1466 (m), 1354 (s), 1301 (w), 1247 (s), 1174 (s), 1117 (w), 1034 (m), 962 (s), 833 (s), 753 (m) cm^{-1}.



1-(3-Fluoro-2-methylpropyl)-4-methoxybenzene (36)

An Ace pressure tube was charged with dry *tert*-butanol (70 mL), anhydrous CsF (30.4 g; 200 mmol) and 3-(4-methoxyphenyl)-2-methylpropyl methanesulfonate (**S11**) (4.05 g; 15.7 mmol). The reaction vessel was sealed and heated to 95 °C (oil bath temperaturte) overnight. The reaction mixture was partitioned between brine (200 mL) and EtOAc (250 mL). The aqueous phase was extracted with additional EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 2.63 g (92%) of yellowish liquid was obtained (about 90% purity). Crude product was used directly in the next step. The analytical sample was obtained by a short-path vacuum distillation.

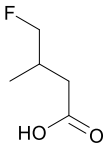
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.27 (apparent dd, *J* = 47.5, 5.6 Hz, 2H), 3.80 (s, 3H), 2.71 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.43 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.07 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -224.31 (td, *J* = 47.4, 20.4 Hz) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 157.98, 131.89, 130.11, 113.74, 87.42 (d, *J* = 168.7 Hz), 55.25, 37.76 (d, *J* = 5.5 Hz), 36.24 (d, *J* = 18.2 Hz), 15.63 (d, *J* = 6.0 Hz) ppm.

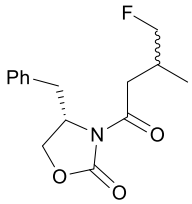
GC-MS (EI, 75 eV): m/z 182.1 ([M]$^+$, 20%), 121.1 (100%), 91.1 (7%), 77.1 (6%).

IR (ATR): 2962 (s), 2909 (m), 2836 (w), 1613 (m), 1514 (s), 1464 (m), 1301 (m), 1247 (s), 1178 (m), 1037 (m), 1008 (m), 843 (m), 799 (m) cm^{-1}.



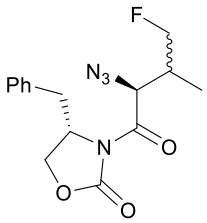
4-Fluoro-3-methylbutanoic acid (37)

A suspension of 1-(3-fluoro-2-methylpropyl)-4-methoxybenzene (**36**) (2.44 g; 13.4 mmol), $RuCl_3$ hydrate (290 mg; 1.3 mmol) and $NaIO_4$ (32 g; 150 mmol) in EtOAc (60 mL), MeCN (60 mL) and water (60 mL) was stirred vigorously overnight. The reaction mixture was filtered through a pad of celite. The filtrate was partitioned between ether (200 mL) and aq. HCl (1 M; 200 mL). The aqueous phase was extracted with additional ether (4 x 50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure (bath temperature 35 °C; 60 mbar). The residue was dissolved in sat. aq. $NaHCO_3$ (50 mL). The aqueous solution was washed with MTB (50 mL) and the organic phase was discarded. The aqueous phase was acidified to pH 2 with aq. HCl (1 M) and then extracted with EtOAc (3 x 50 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 1.22 g (76%) of yellowish liquid was obtained. Crude product was used in the next step without further purification. The analytical sample (colourless liquid) was obtained by short-path vacuum distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.85 (broad s, 1H), 4.30 (ddd, *J* = 47.3, 9.0, 5.0 Hz, 1H), 4.21 (ddd, *J* = 47.4, 9.0, 6.0 Hz, 1H), 2.48 (dd, *J* = 15.5, 5.8 Hz, 1H), 2.39 – 2.24 (m, 1H), 2.20 (ddd, *J* = 15.3, 7.6, 0.8 Hz, 1H), 0.98 (dd, *J* = 6.8, 1.1 Hz, 3H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -223.65 (td, *J* = 46.6, 19.2 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 178.99, 87.12 (d, *J* = 170.0 Hz), 37.16 (d, *J* = 5.3 Hz), 31.21 (d, *J* = 18.7 Hz), 15.73 (d, *J* = 6.6 Hz) ppm.
HRMS (ESI$^-$ *m/z*): calculated for $C_5H_8O_2F$ [M-H$^+$] 119.0508, found 119.0503.
IR (ATR): 3090 (broad s), 2974 (s), 1713 (s), 1415 (m), 1299 (m), 1247 (m), 1206 (m), 1015 (m), 939 (m) cm^{-1}.



(4*S*)-4-Benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (38)

Pivaloyl chloride (1.1 mL; 8.5 mmol) was added dropwise to the solution of 4-fluoro-3-methylbutanoic acid (**37**) (800 mg; 6.66 mmol) and DIPEA (2.0 mL; 11.0 mmol) in dry THF (40 mL) at 0 °C. In a separate flask to a solution of (*S*)-4-benzyloxazolidin-2-one (2.66 g; 15.0 mmol) in dry THF (50 mL) was added BuLi (2 M; 6.0 mL) at -78 °C. After 2 hours the solution of mixed anhydride was cannulated into the solution of lithium (*S*)-4-benzyl-2-oxooxazolidin-3-ide at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (250 mL) and aq. HCl (1 M; 150 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 1.49 g (80%) of colourless amorphous solid was obtained.
NMR signals of both diastereomers are poorly resolved and therefore the spectra are reported for a mixture. In the ^{13}C NMR spectrum almost all peaks of the diastereomers overlap so that the total number of signals is not 26 but 17.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 – 7.24 (m, 4H), 7.23 – 7.19 (m, 2H), 7.16 – 7.12 (m, 4H), 4.61 (m, 2H), 4.42 – 4.30 (m, 2H), 4.29 – 4.18 (m, 2H), 4.17 – 4.07 (m, 4H), 3.23 (m, 2H), 3.02 (m, 2H), 2.88 – 2.73 (m, 2H), 2.69 (m, 2H), 2.53 – 2.30 (m, 2H), 1.00 (m, 6H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -222.60 (td, *J* = 47.7, 20.0 Hz, 1F), -222.86 (td, *J* = 46.3, 20.1 Hz, 1F) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 171.86, 153.45, 135.28, 129.42, 128.99, 127.39, 87.35 (d, *J* = 170.0 Hz), 87.29 (d, *J* = 169.5 Hz), 66.25, 55.21, 38.33 (d, *J* = 5.3 Hz), 38.28 (d, *J* = 5.4 Hz), 37.96, 37.89, 30.73 (d, *J* = 18.9 Hz), 16.00 (d, *J* = 6.9 Hz), 15.91 (d, *J* = 6.6 Hz) ppm.
HRMS (ESI *m/z*): calculated for $C_{15}H_{19}NO_3F$ [M+H$^+$] 280.1349, found 280.1345.
IR (ATR): 2968 (m), 2930 (w), 1780 (s), 1702 (s), 1390 (s), 1352 (m), 1210 (s), 1003 (m), 750 (m), 702 (m) cm^{-1}.



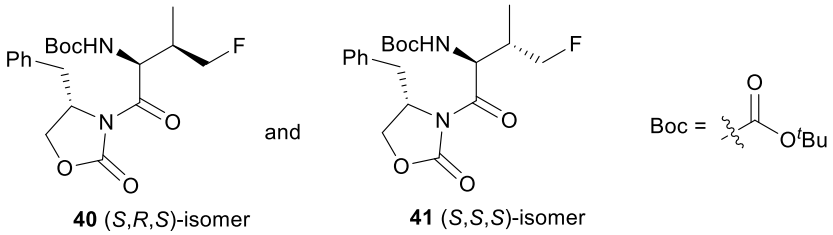
(4*S*)-3-((2*S*)-2-Azido-4-fluoro-3-methylbutanoyl)-4-benzyloxazolidin-2-one (39)

To -78 °C cooled solution of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**38**) (1.20 g; 4.30 mmol) in dry THF (15 mL) was cannulated into a cooled (-78 °C) solution of KHMDS (5.0 mmol) in THF (~18 mL). After 30 minutes a cooled (-78 °C) solution of trysil azide (1.70 g; 5.50 mmol) in THF (12 mL) was cannulated into a solution of previously prepared potassium enolate at -78 °C. After 2 minutes reaction was quenched with acetic acid (2 mL). The reaction mixture was warmed to 35 °C and stirred at this temperature 40 minutes. The volatiles were removed under reduced pressure (bath temperature ~35 °C). The residue was partitioned between EtOAc (250 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 10/1 to 3/1). 1.06 g (77%) of colourless oil was obtained. The NMR signals of the mixture of diastereomers of **39** are not well resolved and the spectra are reported for the mixture.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.32 (m, 4H), 7.32 – 7.26 (m, 2H), 7.25 – 7.21 (m, 4H), 5.23 (d, *J* = 6.8 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 4.75 – 4.64 (m, 2H), 4.62 – 4.33 (m, 4H), 4.31 – 4.18 (m, 4H), 3.39 - 3.28 (m, 2H), 2.94 – 2.77 (m, 2H), 2.65 – 2.33 (m, 2H), 1.11 - 1.05 (m, 6H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -225.25 (td, *J* = 47.2, 15.2 Hz), -228.35 (td, *J* = 46.9, 22.7 Hz) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 169.85, 169.14, 153.14, 153.07, 134.84, 134.76, 129.55, 129.46, 129.18, 129.08, 127.66, 127.57, 85.14 (d, *J* = 170.9 Hz), 84.20 (d, *J* = 169.1 Hz), 66.76, 66.75, 62.37 (d, J = 2.5 Hz), 61.52, 55.72, 55.64, 37.79, 37.62, 36.67 (d, *J* = 17.7 Hz), 36.60 (d, J = 18.8 Hz), 13.49 (d, J = 6.6 Hz), 11.44 (d, *J* = 7.4 Hz) ppm.



40 (*S*,*R*,*S*)-isomer **41** (*S*,*S*,*S*)-isomer

tert-Butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (40) and *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (41)

Pd/C (10%; 200 mg) was added to a solution of (4*S*)-3-((2*S*)-2-azido-4-fluoro-3-methylbutanoyl)-4-benzyloxazolidin-2-one (**39**) (1.06 g; 3.31 mmol) and Boc_2O (5.0 g; 23 mmol) in EtOAc (15 mL). The resulting suspension was stirred under 3 bars of hydrogen for 4 hours. The volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc with gradient 20/1 to 1/1). 1.16 g (89%) of white solid was obtained. The mixture of diastereomers obtained was separated by preparative HPLC on a Chiralpak IC column with DCM as mobile phase. **40** elutes first followed by **41**. 450 mg of **40** (80% from azide) and 530 mg of **41** (94% from azide) was obtained.

Analytical data for **40**:

^{1}H NMR (400 MHz, $CDCl_3$) δ: (t, *J* = 7.1 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 6.8 Hz, 2H), 5.52 (dd, *J* = 9.1, 4.0 Hz, 1H), 5.49 (broad d, *J* = 9.1 Hz, 1H), 4.62 (ddt, *J* = 9.9, 6.6, 3.3 Hz, 1H), 4.39 (apparent dd, *J* = 47.1, 5.1 Hz, 2H), 4.26 – 4.07 (m, 2H), 3.35 (dd, *J* = 13.4, 2.5 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.9 Hz, 1H), 2.45 (broad d, *J* = 22.1 Hz, 1H), 1.46 (s, 9H), 1.09 (dd, *J* = 7.0, 0.9 Hz, 3H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ: -220.59 (td, *J* = 47.1, 23.6 Hz) ppm.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 172.38, 155.92, 153.04, 135.28, 129.55, 129.11, 127.48, 84.81 (d, *J* = 168.5 Hz), 80.18, 66.65, 55.96, 55.32, 37.66, 36.89 (d, *J* = 17.8 Hz), 28.37, 13.36 (d, *J* = 7.7 Hz) ppm.

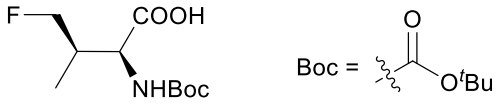
HRMS (ESI *m/z*): calculated for $C_{20}H_{27}N_2O_5FNa$ [M+Na$^+$] 417.1802, found 417.1802.

IR (ATR): 3404 (broad m), 2978 (m), 2932 (w), 1783 (s), 1700 (s), 1497 (m), 1390 (s), 1367 (s), 1242 (m), 1166 (m), 1108 (w), 1013 (w), 762 (w), 703 (w) cm^{-1}.

$[\alpha]_D^{20}$ 58.2 (*c* 0.9, $CHCl_3$).

M.p.: 104-105 °C.

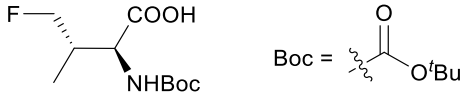
Analytical data for **41**:
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.31 (m, 2H), 7.30 – 7.25 (m, 1H), 7.22 (d, *J* = 6.8 Hz, 2H), 5.60 (dd, *J* = 9.2, 4.2 Hz, 1H), 5.38 – 5.10 (broad d, *J* = 8.4 Hz, 1H), 4.64 (ddt, *J* = 10.2, 6.7, 3.3 Hz, 1H), 4.62 – 4.41 (m, 1H), 4.31 (ddd, *J* = 47.2, 9.2, 6.6 Hz, 1H), 4.23 – 4.15 (multiple peaks, 2H), 3.32 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.39 (m, 1H), 1.46 (s, 9H), 0.96 (dd, *J* = 7.0, 0.9 Hz, 3H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -221.01 (td, *J* = 47.0, 13.4 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 172.32, 155.57, 152.93, 135.23, 129.56, 129.18, 127.57, 85.89 (d, *J* = 170.7 Hz), 80.34, 66.62, 55.80, 53.91, 37.68, 36.83 (d, *J* = 18.0 Hz), 28.41, 10.42 (d, *J* = 6.3 Hz) ppm.
HRMS (ESI *m/z*): calculated for $C_{20}H_{27}N_2O_5FNa$ [M+Na$^+$] 417.1802, found 417.1805.
IR (ATR): 3385 (broad m), 2978 (m), 2932 (w), 1785 (s), 1700 (s), 1499 (m), 1391 (s), 1368 (s), 1213 (m), 1166 (m), 1109 (w), 1012 (w), 761 (w), 702 (w) cm^{-1}.
$[\alpha]_D^{20}$ 64.6 (*c* 1.0, $CHCl_3$).
M.p.: 127-128 °C.



S12 (*S*,*R*)-isomer

(2*S*,3*R*)-*N*-Boc-4-fluorovaline (S12)

LiOH (32 mg; 1.3 mmol) in aq. hydrogen peroxide (7 mL, 10% v/v) was added to a cooled (0 °C) solution of *tert*-butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**40**) (400 mg; 1.01 mmol) in THF (10 mL). The reaction mixture was stirred for 1 hour at 0 °C. LCMS analysis indicated complete conversion. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) and THF was removed under reduced pressure. The aqueous solution was extracted with DCM (3 x 10 mL). The organic phase was discarded. The aqueous phase was acidified to pH 2 by a careful addition of aq. HCl (1 M). The aqueous suspension was extracted with EtOAc (4 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 203 mg (85%) of amorphous glassy solid was obtained. The reaction product was used in the next step without further purification.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.47 – 4.13 (multiple peaks, 2H), 4.09 (d, *J* = 5.6 Hz, 1H), 2.33 – 2.09 (m, 1H), 1.35 (s, 9H), 0.91 (d, *J* = 7.0 Hz, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -225.75 (td, *J* = 47.3, 20.0 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 174.82, 158.07, 85.85 (d, *J* = 167.9 Hz), 80.70, 56.33 (d, *J* = 4.3 Hz), 37.76 (d, *J* = 18.5 Hz), 28.67, 13.06 (d, *J* = 6.3 Hz) ppm.
HRMS (ESI$^-$ *m/z*): calculated for $C_{10}H_{17}NO_4F$ [M-H$^+$] 234.1142, found 234.1150.
IR (ATR): 3322 (broad m), 2979 (m), 2932 (w), 1717 (s), 1514 (m), 1398 (m), 1254 (m), 1165 (s), 1019 (m) cm^{-1}.
$[\alpha]_D^{20}$ -7.3 (*c* 1.0, $CHCl_3$).

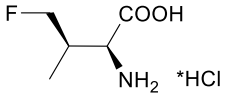


S13 (*S*,*S*)-isomer

(2*S*,3*S*)-*N*-Boc-4-fluorovaline (S13)

LiOH (36 mg; 1.5 mmol) in aq hydrogen peroxide (7 mL, 10% v/v) was added to a cooled (0 °C) solution of *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**41**) (486 mg; 1.23 mmol) in THF (10 mL). The reaction mixture was stirred for 1 hour at 0 °C. LCMS analysis indicated complete conversion. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) and THF was removed under reduced pressure. The aqueous solution was extracted with DCM (3 x 10 mL). The organic phase was discarded. The aqueous phase was acidified to pH 2 by careful addition of aq. HCl (1 M). The aqueous suspension was extracted with EtOAc (4 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 243 mg (84%) of white crystalline solid was obtained. The reaction product was used in the next step without further purification.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.49 – 4.09 (multiple peaks, 3H), 2.44 (m, 1H), 1.45 (s, 9H), 0.92 (dd, *J* = 7.1, 1.4 Hz, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -222.82 (td, *J* = 47.2, 15.6 Hz) ppm.

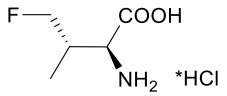
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ: 174.97, 158.24, 85.75 (d, *J* = 169.0 Hz), 80.69, 55.26 (d, *J* = 4.4 Hz), 37.56 (d, *J* = 18.6 Hz), 28.68, 10.89 (d, *J* = 7.4 Hz) ppm.
HRMS (ESI$^-$ *m/z*): calculated for $C_{10}H_{17}NO_4F$ [M-H$^+$] 234.1142, found 234.1149.
IR (ATR): 3328 (broad m), 2979 (m), 2934 (w), 1720 (s), 1520 (m), 1400 (m), 1369 (m), 1165 (s), 1012 (m) cm^{-1}.
$[\alpha]_D^{20}$ 0.86 (*c* 1.05, $CHCl_3$).
M.p.: 104-105 °C.



42 (*S*,*R*)-isomer

(2*S*,3*R*)-4-Fluorovaline hydrochloride (42)

TFA (5 mL) was added to a DCM (10 mL) solution of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S12**) (176 mg; 0.75 mmol). The reaction mixture was stirred at ambient temperature for 3 hours. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (15 mL) and anhydrous HCl (2 M in ether; 3 mL) was added. The volatiles were removed under reduced pressure and the HCl treatment was repeated 3 times. The crystalline residue was suspended in MeCN (5 mL), sonicated 5 minutes and then collected by centrifugation. The reaction product was washed with additional MeCN (2 x 2 mL). After drying under vacuum 102 mg (79%) of white microcrystalline solid was obtained.
^1H NMR (400 MHz, CD_3OD) δ: 4.56 (ddd, *J* = 47.0, 9.6, 7.2 Hz, 1H), 4.50 (ddd, *J* = 46.7, 9.6, 5.4 Hz, 1H), 4.10 (d, *J* = 3.7 Hz, 1H), 2.70 – 2.41 (m, 1H), 1.08 (d, *J* = 7.1 Hz, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -222.17 (td, *J* = 46.5, 15.5 Hz) ppm.
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ: 170.34, 85.28 (d, *J* = 169.2 Hz), 55.13 (d, *J* = 4.5 Hz), 36.73 (d, *J* = 18.6 Hz), 11.06 (d, *J* = 7.5 Hz) ppm.
HRMS (ESI *m/z*): calculated for $C_5H_{11}NO_2F$ [M+H$^+$] 136.0774, found 136.0768.
IR (ATR): 3391 (broad s), 2986 (broad s), 2563 (w), 2489 (w), 2430 (w), 2234 (s), 2054 (w), 1737 (s), 1584 (m), 1522 (s), 1437 (m), 1405 (m), 1353 (w), 1219 (s), 1183 (m), 1161 (m), 1000 (s), 839 (s), 668 (s), 547 (m), 508 (m) cm^{-1}.
M.p.: >180 °C with decomposition.
$[\alpha]_D^{20}$ 37.9 (*c* 1.1, CH_3OH).



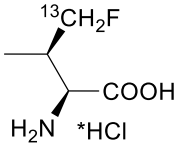
43 (*S*,*S*)-isomer

(2*S*,3*S*)-4-Fluorovaline hydrochloride (43)

TFA (5 mL) was added to a DCM (10 mL) solution of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S13**) (213 mg; 0.90 mmol). The reaction mixture was stirred at ambient temperature for 3 hours. The volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (15 mL) and anhydrous HCl (2 M in ether; 3 mL) was added. The volatiles were removed under reduced pressure and the HCl treatment was repeated 3 times. The crystalline residue was suspended in MeCN (5 mL), sonicated 5 minutes and then collected by centrifugation. The reaction product was washed with additional MeCN (2 x 2 mL). After drying under vacuum 132 mg (85%) of white microcrystalline solid was obtained.
^1H NMR (400 MHz, CD_3OD) δ: 4.62 (ddd, *J* = 46.6, 9.7, 4.5 Hz, 1H), 4.47 (ddd, *J* = 47.2, 9.7, 7.2 Hz, 1H), 4.14 (d, *J* = 3.7 Hz, 1H), 2.73 - 2.57 (m, 1H), 1.10 (dd, *J* = 7.3, 1.3 Hz, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -224.55 (td, *J* = 47.1, 20.5 Hz) ppm.
$^{13}C\{^1H\}$ NMR (101 MHz, CD_3OD) δ: 170.85, 85.54 (d, *J* = 168.6 Hz), 55.59 (d, *J* = 3.0 Hz), 36.35 (d, *J* = 18.4 Hz), 10.94 (d, *J* = 7.3 Hz) ppm.
HRMS (ESI *m/z*): calculated for $C_5H_{11}NO_2F$ [M+H$^+$] 136.0774, found 136.0770.
IR (ATR): 3355 (broad s), 2974 (broad s), 2579 (w), 2523 (w), 2430 (w), 2107 (w), 1994 (w), 1743 (s), 1623 (m), 1587 (m), 1528 (s), 1422 (s), 1219 (s), 1159 (m), 1134 (m), 999 (s), 885 (m), 835 (s), 663 (m), 584 (m) cm^{-1}.
$[\alpha]_D^{20}$ 9.5 (*c* 1.1, CH_3OH).
M.p.: >180 °C with decomposition.

Scheme 7: 4-fluorovalines-4-^{13}C 46 and 47

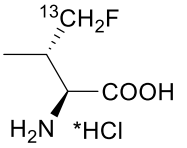
62 mg of (2*S*,3*R*)-4-fluorovaline-4-^{13}*C* hydrochloride (**46**) and **57 mg** of (2*S*,3*S*)-4-fluorovaline-4-^{13}*C* hydrochloride (**47**) were prepared according to Scheme 6. See the previous section for experimental procedures.



46 (*S*,*S*)-isomer

(2*S*,3*R*)-4-Fluorovaline-4-^{13}*C* hydrochloride (46)

^{1}H NMR (400 MHz, CD_3OD) δ: 4.56 (dddd, *J* = 152.9, 47.0, 9.6, 7.9 Hz, 1H), 4.49 (dddd, *J* = 153.1, 46.7, 9.6, 5.4 Hz, 1H), 4.10 (apparent t, *J* = 3.9 Hz, 1H), 2.63 – 2.45 (m, 1H), 1.08 (ddd, *J* = 7.3, 6.1, 1.3 Hz, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -222.31 (dtd, *J* = 169.0, 46.8, 16.3 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 170.35, 85.29 (high intensity d, *J* = 169.2 Hz), 55.15 (d, *J* = 4.4 Hz), 37.16 (dd, *J* = 38.9, 18.1 Hz), 11.06 (d, *J* = 6.7 Hz) ppm.
HRMS (ESI *m/z*): calculated for $^{12}C_4{}^{13}CH_{11}NO_2F$ [M+H$^+$] 137.0807, found 137.0805.
IR (ATR): 3350 (broad m), 2992 (broad s), 2560 (w), 2427 (w), 2003 (w), 1967 (w), 1751 (s), 1525 (m), 1490 (m), 1417 (m), 1219 (s), 975 (m), 821 (s) cm^{-1}.
$[\alpha]_D^{20}$ 35.4 (*c* 1.0, CH_3OH).
M.p.: >180 °C with decomposition.

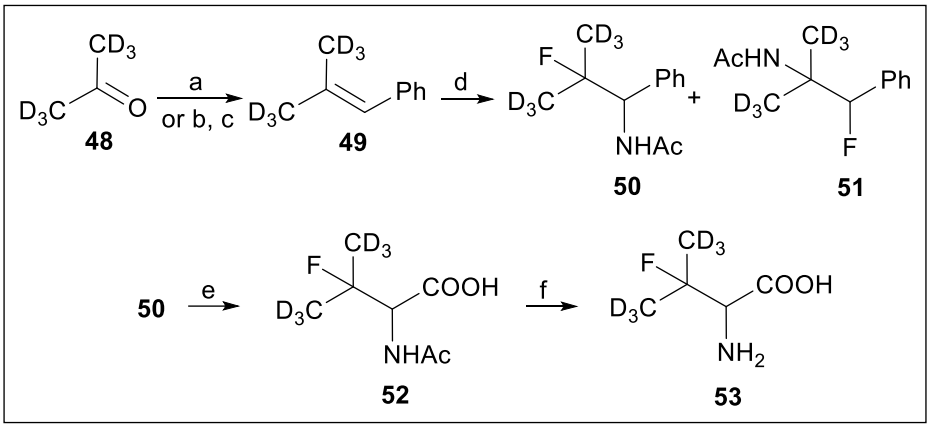


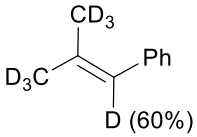
47 (*S*,*R*)-isomer

(2*S*,3*S*)-4-Fluorovaline-4-^{13}*C* hydrochloride (47)

^{1}H NMR (400 MHz, CD_3OD) δ: 4.61 (dddd, *J* = 153.3, 46.7, 9.8, 4.5 Hz, 1H), 4.48 (dddd, *J* = 152.0, 47.3, 9.8, 7.7 Hz, 1H), 4.14 (apparent t, *J* = 3.7 Hz, 1H), 2.86 – 2.39 (m, 1H), 1.10 (ddd, *J* = 7.0, 5.8, 1.0 Hz, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ: -224.65 (dtd, *J* = 168.4, 47.0, 20.6 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ: 170.83, 85.54 (high intensity d, *J* = 168.5 Hz), 55.59 (d, *J* = 2.5 Hz), 36.34 (dd, *J* = 37.6, 18.4 Hz), 10.97 ppm.
HRMS (ESI *m/z*): calculated for $^{12}C_4{}^{13}CH_{11}NO_2F$ [M+H$^+$] 137.0807, found 137.0807.
IR (ATR): 3013 (broad s), 2910 (broad s), 2557 (w), 2428 (w), 1992 (w), 1961 (w), 1737 (s), 1607 (w), 1496 (s), 1219 (s), 993 (s), 835 (m), 793 (w) cm^{-1}.
$[\alpha]_D^{20}$ 9.6 (*c* 1.0, CH_3OH).
M.p.: >180 °C with decomposition.

Scheme 8: 3-fluorovaline-3,3,3,3',3',3'-d_6 (55)





(2-(Methyl-d_3)prop-1-en-1-yl-3,3,3-d_3)benzene (49) was obtained following a literature procedure with modifications: R. Zhou, H. Liu, H. Tao, X. Yu, J. Wu, *Chem. Sci.*, 2017, **8**, 4654.

Benzyltriphenylphosphonium bromide (56.6 g, 130 mmol) suspension in dry THF (350 mL) was cooled to -70 °C under argon atmosphere. BuLi (55 mL, 2.5 M) was added dropwise with intensive stirring. The resulting orange suspension was warmed to 0 °C over the period of two hours. Acetone-d_6 (10.4 mL, 140 mmol) was added dropwise to the suspension at 0 °C. The reaction mixture was heated to 50 °C overnight. The precipitate was filtered of and washed with several portions of THF. The filtrate was evaporated under reduced pressure (50 mbar, 35 °C bath temperature). The residue was suspended in hexanes and applied to a 100 g silica gel column eluting with hexanes. After evaporation of hexanes 6.15 g (36%) of colourless, volatile liquid was obtained. NMR and GC-MS analysis showed that the 1-position contains 60% deuterium resulting from an H/D exchange between acetone-d_6 and phosphonium ylide.

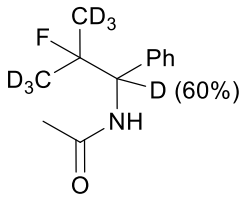
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (t, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.4 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.18 (s, 0.4H), 1.77(m, 0.12H), 1.72 (m, 0.12H) ppm.

^{2}H NMR (61 MHz, $CDCl_3$) δ: 6.34 (s, 0.6D), 1.89 (s, 3D), 1.86 (s, 3D) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 138.76 (d, *J* = 7.2 Hz), 135.29 (d, *J* = 8.9 Hz), 128.80, 128.11, 125.85, 125.30, 28.13 – 24.40 (m), 20.35 – 16.86 (m) ppm.

GC-MS (EI, 75 eV): m/z 139.2 ([M$^+$], 70%), 138.2 ([M$^+$], 80%), 121.2 (100 %), 120.2 (86%), 94.1 (20%), 93.1 (20%).

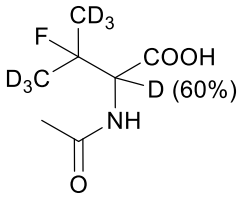
IR (ATR): 3080 (s), 3056 (s), 3023 (s), 2956 (w), 2913 (w), 2226 (s), 2192 (s), 2113 (m), 2052 (m), 1645 (m), 1598 (m), 1493 (s), 1443 (m), 1270 (w), 1047 (m), 9112 (m), 862 (m), 759 (s), 697 (s) cm^{-1}.



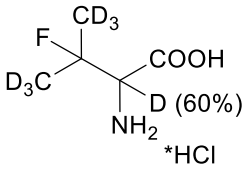
***N*-(2-Fluoro-2-(methyl-d_3)-1-phenylpropyl-3,3,3-d_3)acetamide (50)**

A suspension of K_2CO_3 (7.60 g, 55 mmol) and 2-methyl-1-phenyl-1-propene (**49**) (3.20 g, 24.2 mmol) in dry MeCN (150 mL) was cooled to -10 °C under argon atmosphere. Selectfluor (8.50 g, 24.0 mmol) was added in one portion and the resulting suspension was stirred at -5 °C for 5 hours. GC-MS indicated complete conversion of the 2-methyl-1-phenyl-1-propene at this point. Sat. aq. $NaHCO_3$ (100 mL) was added to the suspension and the volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (200 mL) and water (100 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography (hexanes/EtOAc with gradient from 5/1 to 1/1). First eluted *N*-(1-fluoro-2-methyl-1-phenylpropan-2-yl)acetamide (**51**) which was isolated as a white solid (835 mg, 16%), followed by *N*-(2-fluoro-2-methyl-1-phenylpropyl)acetamide (**50**) also a white solid (2.13 g, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.27 (multiple peaks, 5H), 6.41 (broad s, 1H), 4.95 (dd, *J* = 27.8, 9.5 Hz, 0.4H), 2.01 (s, 3H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ -156.02 (d, *J* = 26.7 Hz, species containing H in the benzylic position), -156.19 (s, deuterated species) ppm.
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 169.38, 138.62 (d, *J* = 4.9 Hz), 128.48, 128.37, 127.81, 97.16 (d, *J* = 173.1 Hz), 59.62 (d, *J* = 17.9 Hz), 26.11 – 23.41 (m, overlapping CD_3 groups), 23.34 ppm.
HRMS (*m/z*): calculated for $C_{12}H_{10}D_6NOFNa$ [M+Na$^+$] 238.1490, found 238.1499.
IR (ATR): 3270 (s), 3065 (m), 2837 (w), 2241 (w), 1636 (s), 1548 (s), 1376 (w), 1295 (w), 1118 (m), 1052 (w), 790 (w), 723 (s), 701 (m) cm^{-1}.
M.p.: 123-126 °C.

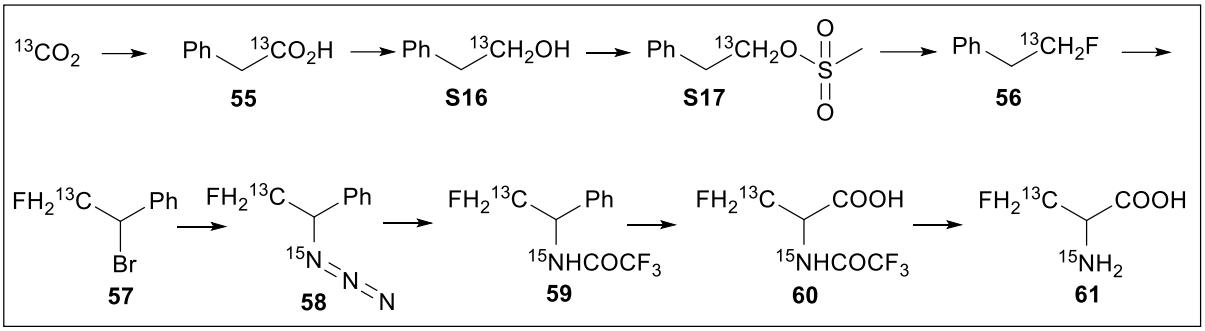


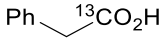
2-Acetamido-3-fluoro-3-(methyl-*d*$_3$)butanoic-4,4,4-*d*$_3$ acid (52)
N-(2-Fluoro-2-methyl-1-phenylpropyl)acetamide (**50**) (1.22 g; 5.83 mmol) was dissolved in a mixture of EtOAc (50 mL), MeCN (50 mL) and water (100 mL). $RuCl_3$ (100 mg, 0.48 mmol) and $NaIO_4$ (25.7g, 120 mmol) were added and the resulting suspension was stirred intensively for 48 hours at ambient temperature. UPLC analysis indicated complete conversion of the starting material at this point. The precipitate was filtered off and washed with several portions of acetonitrile. The volume of the filtrate was reduced to approximately 35 mL under reduced pressure. The remaining aqueous solution was acidified to pH 3 with aq. HCl and applied to 120 g C18 reverse-phase column. The column was eluted first with 600 mL 3% MeCN in water followed by 600 mL 6% MeCN in water. Fractions containing the product were evaporated under reduced pressure. After drying in vacuum 840 mg (81%) of white solid was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.59 (d, *J* = 18.7 Hz, 0.4H), 2.03 (s, 3H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ -148.60 (d, *J* = 17.3 Hz, species containing H in the α position), -148.77 (s, α-deuterated species) ppm.
^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ: 173.39, 172.12 (d, *J* = 3.6 Hz), 95.36 (d, *J* = 175.3 Hz), 60.49 (d, *J* = 23.5 Hz), 25.05 – 23.24 (multiple peaks, two overlapping -CD_3 groups), 22.27 ppm.
HRMS (*m/z*): calculated for $C_7H_6D_6NO_3FNa$ [M+Na$^+$] 206.1076, found 206.1074.
IR (ATR): 3342 (m), 2812 (broad w), 2242 (w), 1729 (m), 1616 (s), 1539 (s), 1438 (m), 1340 (w), 1304 (m), 1222 (w), 1129 (w), 1046 (w), 1001 (w), 687 (m) cm^{-1}.
M.p.: 140-142 °C.



3-Fluorovaline-4,4,4,4',4',4'-*d*$_6$ hydrochloride (53)
2-Acetamido-3-fluoro-3-methylbutanoic acid (**52**) (800 mg, 4.51 mmol) was heated to 80 °C in 20 mL of aq. HCl (4 M; 6 mL). After 24 h full conversion was reached. The solution was filtered and evaporated under reduced pressure. The remaining solid was suspended in MeCN (30 mL), filtered and washed with MeCN (3 x 5 mL). After drying in vacuum 581 mg (75%) of white powder was obtained.
^{1}H NMR (400 MHz, CD_3OD) δ: 4.22 (d, *J* = 10.7 Hz, 0.4H) ppm.
^{19}F NMR (376 MHz, CD_3OD) δ -144.70 (broad s, species containing H in the alfa position), -144.85 (s, species containing D in the α-position) ppm.
^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ: 168.55 (d, *J* = 8.6 Hz), 94.40 (d, *J* = 175.4 Hz), 61.10 (d, *J* = 21.9 Hz), 25.83 – 24.42 (m), 22.83 – 20.53 (m) ppm.
HRMS (ESI$^-$, *m/z*): calculated for $C_5H_3D_6NO_2F$ [M-H$^+$] 140.0994, found 140.0988.
IR (ATR): 2969 (broad s), 2589 (w), 2241 (w), 2002 (m), 1744 (s), 1595 (s), 1496 (s), 1405 (m), 1234 (s), 1181 (s), 1102 (s), 1045 (s), 770 (s), 694 (s), 683 (s) 544 (s) cm^{-1}.
M.p.: 200 °C with decomposition.

Scheme 9: 3-fluoroalanine-3-^{13}C-^{15}N (63)





2-Phenylacetic-1-^{13}C acid (55)

Benzylmagnesium chloride (1 M in ether; 100 mL) was cannulated into a 250 mL Schlenk flask and cooled to -78 °C under nitrogen. A balloon filled with $^{13}CO_2$ (approx. 2L; ca. 89 mmol) was attached to the sidearm of the reaction flask. $^{13}CO_2$ completely condensed into the reaction mixture over the period of 1 hour. The reaction was quenched by slow addition of aq. HCl (2 M; 150 mL). The organic phase was separated and washed with brine (100 mL). The combined aqueous phase was extracted with additional ether (4 x 100 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The remaining solid was suspended in hexanes (150 mL) and filtered. After drying 11.0 g (91% based on $^{13}CO_2$) of white solid was obtained. The reaction product was used in the next step without further purification.

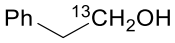
^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.13 (s, 1H), 7.40 – 7.27 (multiple peaks, 5H), 3.67 (d, *J* = 7.8 Hz, 2H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 178.28 (high intensity peak), 133.35 (d, *J* = 2.9 Hz), 129.51 (d, *J* = 1.7 Hz), 128.78, 127.49, 41.19 (d, *J* = 55.2 Hz) ppm.

HRMS (*m/z* ESI^-): calculated for $C_7{}^{13}CH_7O_2$ [M-H$^+$] 136.0480, found 136.0477.

IR (ATR): 3065 (broad s), 3033 (broad s), 1659 (s), 1499 (w), 1454 (w), 1408 (m), 1270 (m), 1220 (m), 1133 (m), 907 (broad m), 751 (s), 701 (s) cm^{-1}.

M.p.: 71-72 °C.



2-Phenylethan-1-ol-1-^{13}C (S16)

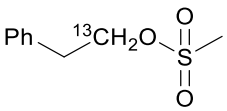
$LiAlH_4$ (3.80 g; 100 mmol) was suspended in dry THF (250 mL) at 0 °C. 2-Phenylacetic-1-^{13}C acid (**57**) (10.5 g; 77.1 mmol) was added portion-wise with intensive stirring. The cooling bath was removed and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was cooled to -20 °C and quenched by slow addition of aq. HCl (4 M; 120 mL). The resulting mixture was saturated with solid NaCl and then extracted with ether (4 x 150 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (bath temperature 40 °C; pressure 35 mbar). 8.76 g (93%) of colourless liquid with a rose smell was obtained. The reaction product was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (m, 2H), 7.18 – 7.10 (multiple peaks, 3H), 3.71 (dt, *J* = 143.1, 6.7 Hz, 2H), 2.75 (apparent q, *J* = 6.6 Hz, 2H), 2.33 (broad s, 1H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 138.63 (d, *J* = 1.8 Hz), 129.05 (d, *J* = 1.6 Hz), 128.54, 126.41, 63.56 (high intensity peak), 39.16 (d, *J* = 35.9 Hz) ppm.

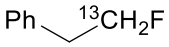
GC-MS (EI, 75 eV): m/z 123.0 ([M$^+$], 30%), 91.0 (100%), 78.0 (7%), 65.0 (16%).

IR (ATR): 3328 (broad s), 3086 (w), 3063 (w), 3028 (m), 2942 (s), 2866 (s), 1947 (w), 1869 (w), 1808 (w), 1700 (w), 1497 (m), 1454 (m), 1080 (w), 1030 (s), 854 (w), 746 (s), 699 (s) cm^{-1}.



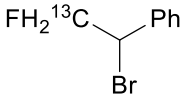
2-Phenylethyl-1-^{13}C methanesulfonate (S17)

To a solution of 2-phenylethan-1-ol-1-^{13}C (**S16**) (5.00 g; 40.9 mmol) in dry toluene (120 mL) was added DIPEA (9.9 mL; 55 mmol) followed by mesyl chloride (3.6 mL; 47 mmol) at -20 °C. The reaction mixture was allowed to warm to 0 °C and stirred for 2 hours at this temperature. TLC and GC control showed complete conversion. The reaction mixture was diluted with ether (200 mL) and then washed with aq. $KHSO_4$ (5% w/v; 2 x 150 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. 7.97 g (97%) of yellowish liquid was obtained. The reaction product was used in the next step without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (m, *J* = 7.1 Hz, 2H), 7.20 – 7.12 (multiple peaks, 3H), 4.32 (dt, *J* = 151.1, 6.9 Hz, 2H), 2.96 (td, *J* = 6.8, 5.4 Hz, 2H), 2.73 (s, 3H) ppm.
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 136.42 (d, *J* = 1.3 Hz), 129.06 (d, *J* = 2.0 Hz), 128.77, 127.13, 70.45 (high intensity signal), 37.28, 35.64 (d, *J* = 37.3 Hz) ppm.
GC-MS (EI, 75 eV): m/z 105.1 ([M-MsOH$^+$], 100%), 91.0 (40%), 79.0 (14%), 65.1 (9%).
IR (ATR): 3567 (broad w), 3064 (w), 3030 (m), 2940 (m), 1604 (w), 1498 (m), 1455 (m), 1351 (s), 1173 (s), 949 (s), 803 (s), 752 (m), 701 (s) cm^{-1}.



(2-Fluoroethyl-2-^{13}C)benzene (56)

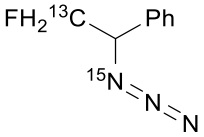
An Ace pressure tube was charged with 2-phenylethyl-1-^{13}C methanesulfonate (**S17**) (7.60 g; 40.0 mmol), anhydrous CsF (27.3 g; 180 mmol) and dry ^{t}BuOH (60 mL). The reaction was heated overnight at 95 °C (oil bath temperature). GC-MS showed complete conversion of the starting material. The reaction mixture was partitioned between ether (200 mL) and water (250 mL). The phases were separated and the aqueous phase was extracted with 3 additional portions of ether (100 mL each). The combined organic phase was washed with brine (150 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (bath temperature 35 °C; pressure 50 mbar). The remaining liquid was short-path distilled (bath temperature 110 °C; pressure 40 mbar). 2.63 g (56%) of colourless liquid was obtained. NMR analysis showed some impurities. Nonetheless, the reaction product was used in the next step without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 – 7.19 (m, 2H), 7.17 – 7.10 (multiple peaks, 3H), 4.53 (ddt, *J* = 151.6, 47.1, 6.6 Hz, 2H), 2.92 (dq, *J* = 23.0, 6.5 Hz, 2H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -214.82 – -215.90 (m) ppm.
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 137.21 (dd, *J* = 6.2, 1.4 Hz), 129.10 (d, *J* = 1.7 Hz), 128.69, 126.81, 84.23 (high intensity d, *J* = 168.9 Hz), 37.05 (dd, *J* = 37.3, 20.3 Hz) ppm.
GC-MS (EI, 75 eV): m/z 125.0 ([M$^+$], 40%), 91.0 (100%), 78.0 (7%), 65.0 (13%).
IR (ATR): 3388 (broad s), 3063 (w), 2936 (s), 2869 (s), 1692 (m), 1604 (w), 1497 (m), 1454 (m), 1362 (m), 1235 (w), 1175 (m), 1030 (s), 940 (w), 747 (m), 700 (s) cm^{-1}.



(1-Bromo-2-fluoroethyl-2-^{13}C)benzene (57)

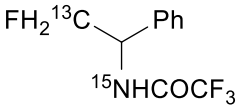
A solution of (2-fluoroethyl-2-^{13}C)benzene (**56**) (2.10g; 16.9 mmol), NBS (7.1 g; 40 mmol) and AIBN (330 mg; 2.0 mmol) in MeCN (60 mL) was refluxed for 3 hours. GC-MS indicated complete conversion at this point. The reaction mixture was evaporated under reduced pressure (bath temperature 40 °C; pressure 50 mbar). The residue was suspended in ether (30 mL) and hexanes (70 mL). The resulting suspension was filtered through a pad of silica (50 g) which was washed with additional ether/hexanes (200 mL; 1/3, v/v). Almost colourless filtrate was evaporated under reduced pressure (bath temperature 40 °C; pressure 30 mbar). 3.28 g (96%) of yellowish liquid was obtained. The reaction product was used in the next step without further purification. The analytical sample (as a colourless liquid) was obtained by short-path distillation (bath temperature 80 °C; pressure 7 mbar).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (m, 2H), 7.41 – 7.32 (multiple peaks, 3H), 5.11 (m, 1H), 5.10 - 4.47 (multiple peaks, 2H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -204.44 (dtd *J* = 180.5, 46.2, 12.1 Hz) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 137.29 (d, *J* = 3.5 Hz), 129.31, 129.07, 128.10 (d, *J* = 1.8 Hz), 84.83 (high intensity signal d, *J* = 179.9 Hz), 49.97 (dd, *J* = 41.2, 22.0 Hz) ppm.
GC-MS (EI, 75 eV): m/z 204.9 ([M^+], 5%), 202.9 ([M^+], 5%), 124.0 (100%), 104.0 (65%), 77.0 (15%).
IR (ATR): 3388 (broad s), 3063 (w), 3028 (m), 2936 (s), 2869 (s), 1692 (m), 1604 (w), 1497 (m), 1454 (m), 1362 (m), 1235 (w), 1175 (m), 1030 (s), 940 (w), 748 (m), 700 (s) cm^{-1}.



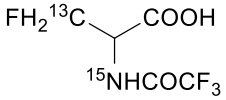
(1-(Azido-^{15}N)-2-fluoroethyl-2-^{13}C)benzene (58)

A solution of (1-bromo-2-fluoroethyl-2-^{13}C)benzene (**57**) (1.60 g; 7.88 mmol) and sodium azide-1-^{15}N (500 mg; 7.7 mmol) in DMF (20 mL) was stirred at ambient temperature for 3 hours. GC-MS indicated complete conversion at this point. The reaction mixture was partitioned between water (300 mL) and ether (200 mL). The aqueous phase was extracted with an additional portion of ether (200 mL). The combined organic phases were washed with water (200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (bath temperature 40 °C; pressure 50 mbar). 1.21 g (95%) of yellowish liquid was obtained. Crude product was used in the next step without further purification. The analytical sample was obtained by column chromatography (hexanes/EtOAc with gradient 1/0 to 10/1, v/v).
^1H NMR (400 MHz, $CDCl_3$) δ: 7.45 – 7.37 (multiple peaks, 3H), 7.37 – 7.32 (m, 2H), 4.89 – 4.22 (multiple peaks, 3H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -217.43 (dtd, *J* = 178.8, 47.0, 14.2 Hz) ppm.
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 134.58 (d, *J* = 7.1 Hz), 129.15, 127.34, 127.33, 85.50 (high intensity d, *J* = 179.0 Hz), 65.16 (dd, *J* = 41.2, 19.5 Hz) ppm.
GC-MS (EI, 75 eV): m/z 167.0 ([M^+], 5%), 133.0 (55%), 104.0 (60%), 77.1 (100%).
IR (ATR): 3066 (w), 3034 (w), 2946 (w), 2899 (w), 2105 (s), 1493 (w), 1455 (m), 1313 (m), 1260 (s), 997 (s), 869 (m), 757 (m), 700 (s) cm^{-1}.



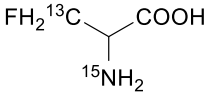
***N*-(2-Fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}N (59)**

A suspension of (1-(azido-^{15}N)-2-fluoroethyl-2-^{13}C)benzene (**58**) (1.13g; 6.84 mmol) and Pd/C (10%; 150 mg) in MeOH (30 mL) and aq. HCl (12 M; 1 mL) was stirred under 4 bars of hydrogen overnight. The suspension was filtered through a pad of celite and evaporated under reduced pressure. The amorphous residue was dissolved in EtOH (50 mL) and toluene (100 mL) and evaporated again. The residue was dissolved in dry MeCN (100 mL). DIPEA (5.5 mL; 30 mmol) was added and solution was cooled to -20 °C. TFAA (1.9 mL; 14 mmol) was added dropwise. The solution was allowed to warm to room temperature over a period of 2 hours. The volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (300 mL) and aq. HCl (1 M; 200 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc with gradient 1/0 to 8/1, v/v). 1.05 g (65%) of white solid was obtained.
^1H NMR (400 MHz, $CDCl_3$) δ: 7.54 – 7.30 (multiple peaks, 5H), 6.95 (dd, *J* = 92.5, 8.1 Hz, 1H), 5.28 (dsx, *J* = 23.4, 3.8 Hz, 1H), 5.10 – 4.29 (multiple peaks, 2H) ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ: -75.74 (s, 3F), -227.00 (dtd, *J* = 177.1, 47.7, 24.3 Hz, 1F) ppm.
^{15}N NMR (41 MHz, $CDCl_3$) δ: 114.08 ppm (from $^1H/^{15}N$ HSQC).
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 156.91 (qd, *J* = 36.8, 18.7 Hz), 135.64 (d, *J* = 3.4 Hz), 129.20, 128.87, 126.92, 115.72 (qd, *J* = 288.0, 10.8 Hz), 83.86 (high intensity d, *J* = 177.0 Hz), 53.82 (ddd, *J* = 39.4, 19.0, 10.2 Hz) ppm.
HRMS (*m/z* ESI^-): calculated for $C_9{}^{13}CH_8{}^{15}NOF_4$ [M-H^+] 236.0546, found 236.0557.
IR (ATR): 3255 (broad s), 3093 (m), 2896 (m), 1694 (s), 1548 (m), 1457 (w), 1186 (s), 1090 (w), 986 (m), 762 (m), 700 (m) cm^{-1}.
M.p.: 92-93 °C.



3-Fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (60)

A suspension of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}N (**59**) (1.00 g; 4.25 mmol), $RuCl_3$ (180 mg; 0.87 mmol) and $NaIO_4$ (15 g; 70 mmol) in EtOAc (30 mL), MeCN (30 mL) and water (30 mL) was stirred intensively overnight. The reaction mixture was filtered through a pad of celite. The filtrate was partitioned between EtOAc (200 mL) and aq. HCl (1 M; 200 mL). The aqueous phase was extracted with additional EtOAc (4 x 50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc with gradient 10/1 to 0/1, v/v). TLC was developed with 5% MeOH in EtOAc (R_f ~ 0.35). 560 mg (65%) of white solid was obtained.
^{1}H NMR (400 MHz, acetone-d_6) δ: 8.78 (dd, *J* = 94.7, 7.9 Hz, 1H), 5.11 – 4.41 (multiple peaks, 3H) ppm.
^{19}F NMR (376 MHz, acetone-d_6) δ: -76.32 (s, 3F), -229.01 (dtd, *J* = 171.1, 47.1, 27.5 Hz, 1F) ppm.
^{15}N NMR (41 MHz, acetone-d_6) δ: 108.70 ppm (from ^{1}H/^{15}N HSQC).
^{13}C{^{1}H} NMR (100 MHz, acetone-d_6) δ: 168.71 (d, *J* = 7.1 Hz), 157.92 (qd, *J* = 37.5, 17.3 Hz), 116.91 (qd, *J* = 286.9, 11.6 Hz), 82.72 (high intensity d, *J* = 171.8 Hz), 54.24 (ddd, *J* = 39.5, 20.3, 12.1 Hz) ppm.
HRMS (*m/z* ESI$^-$): calculated for $C_4{}^{13}CH_4{}^{15}NO_3F_4$ [M-H$^+$] 204.0131, found 204.0134.
IR (ATR): 3286 (s), 3077(w), 2954 (w), 1705 (s), 1550 (m), 1464 (w), 1448 (w), 1189 (s), 1165 (s), 1011 (m), 922 (w), 900 (w) cm^{-1}.
M.p.: 98-99 °C.



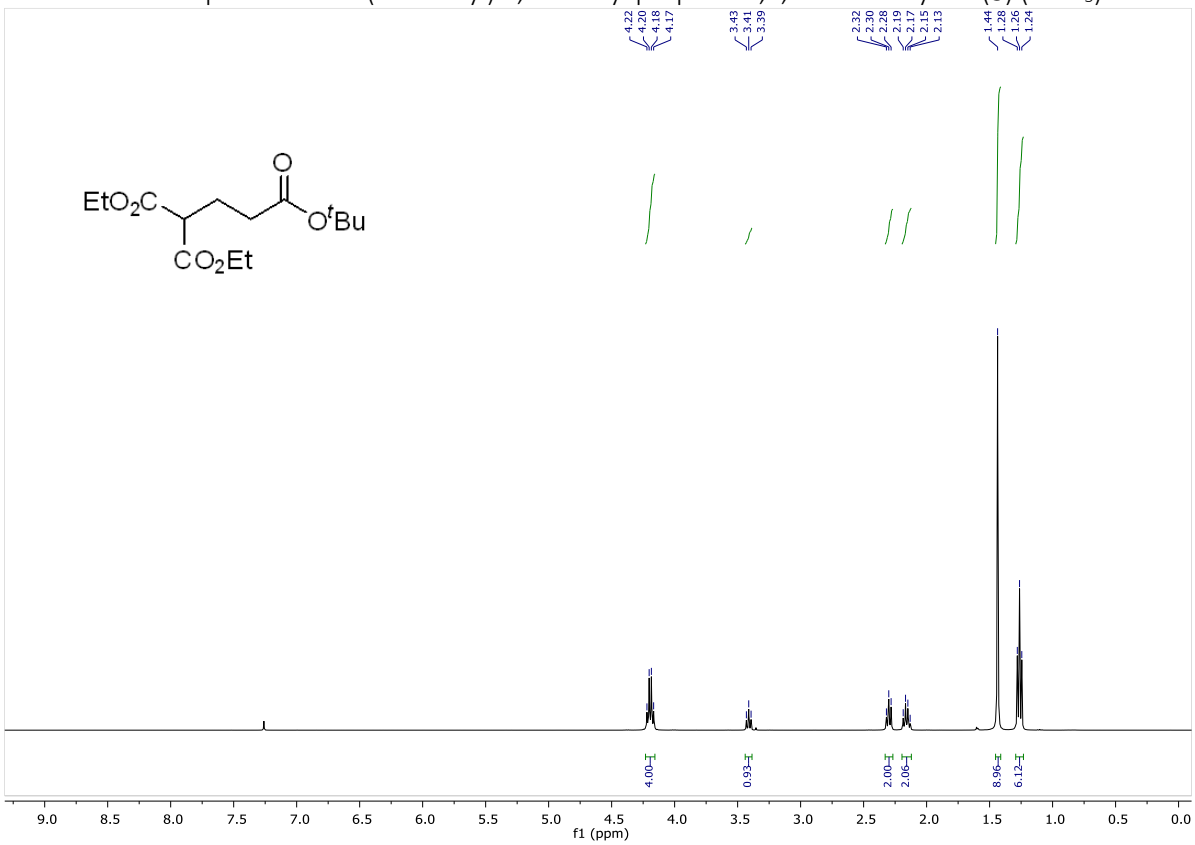
3-Fluoro-alanine-3-^{13}C-^{15}N (61)

3-Fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**) (530 mg; 2.61 mmol) was refluxed for 3 hours in aq. HCl (4 M; 20 mL). The volatiles were removed under reduced pressure. The amorphous residue was dissolved in water (20 mL). The resulting solution was carefully neutralized with aq. $NaHCO_3$ to pH 5.5 … 6. The neutralized solution was filtered and evaporated under reduced pressure. The crystalline residue was suspended in anhydrous MeOH (~5 mL) and sonicated for 5 minutes. The reaction product was collected by filtration, washed with methanol (2 x 2 mL) and dried under reduced pressure. 258 mg (92%) of bright white solid was obtained. NMR analysis of the product showed that no further purification was required.
^{1}H NMR (400 MHz, D_2O) δ: 5.22 – 4.58 (multiple peaks, 2H), 4.11 (apparent ddt, *J* = 29.8, 4.9, 2.6 Hz, 1H) ppm.
^{19}F NMR (376 MHz, D_2O) δ: -229.23 (dtd, *J* = 169.5, 46.7, 29.7 Hz) ppm.
^{13}C{^{1}H} NMR (100 MHz, D_2O) δ: 170.51 (d, *J* = 6.2 Hz), 82.03 (high intensity d, *J* = 169.3 Hz), 54.93 (ddd, *J* = 38.7, 19.7, 5.0 Hz) ppm.
HRMS (*m/z* ESI$^-$): calculated for $C_2{}^{13}CH_5{}^{15}NO_2F$ [M-H$^+$] 108.0308, found 108.0306.
IR (ATR): 3063 (broad s), 2910 (w), 2747 (w), 2612 (w), 2107 (m), 1610 (s), 1419 (m), 1353 (m), 1305 (m), 1244 (w), 1166 (m), 1090 (m), 1012 (m), 955 (m), 903 (m), 846 (m), 638 (m), 564 (m)cm^{-1}.
M.p.: 150 °C with decomposition.

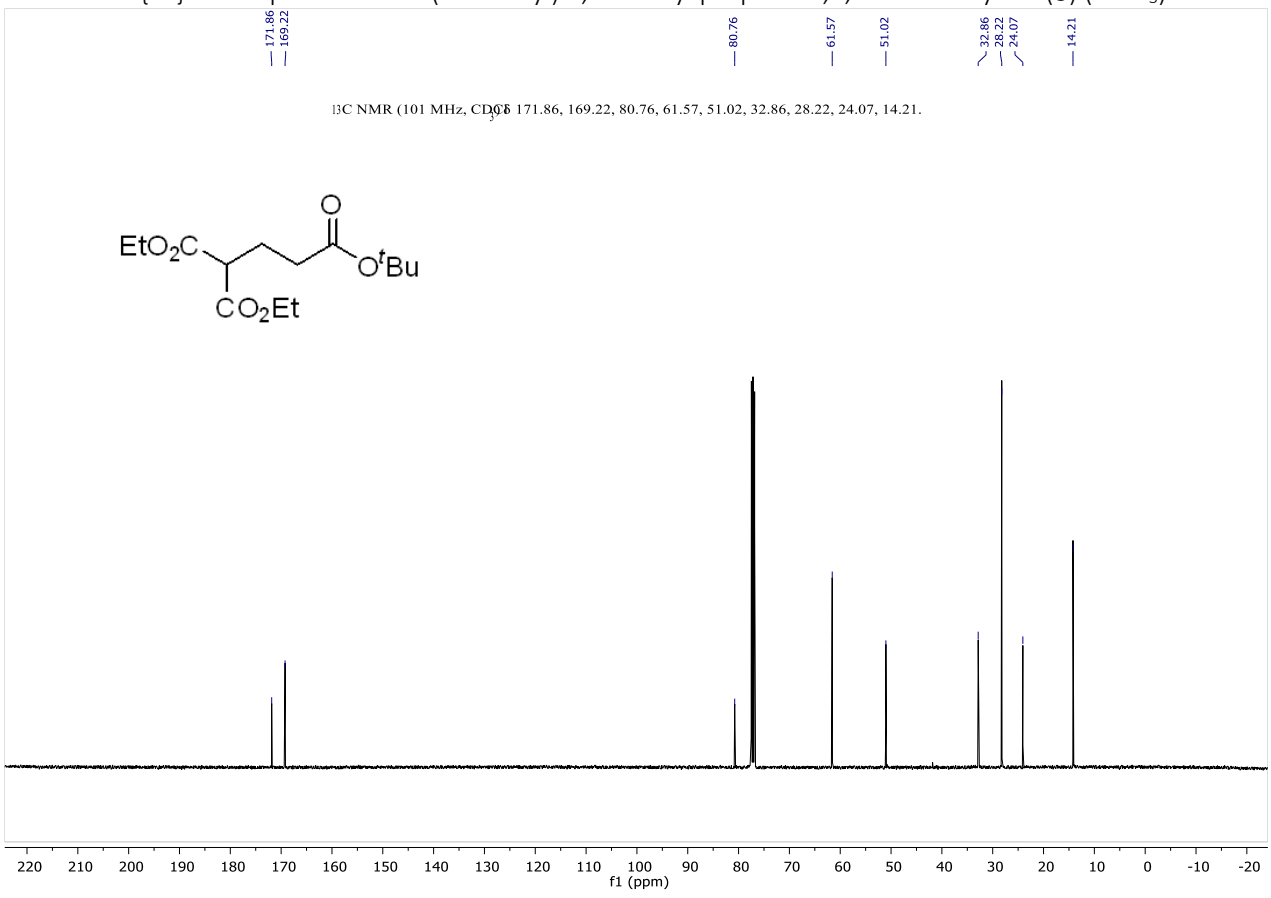
NMR, HRMS and IR Spectra for Intermediates and Products

Spectra of compounds in Scheme 1

^{1}H NMR spectrum of 3-(*tert*-butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (**3**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of 3-(*tert*-butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (**3**) ($CDCl_3$)



HRMS of 3-(*tert*-butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (**3**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

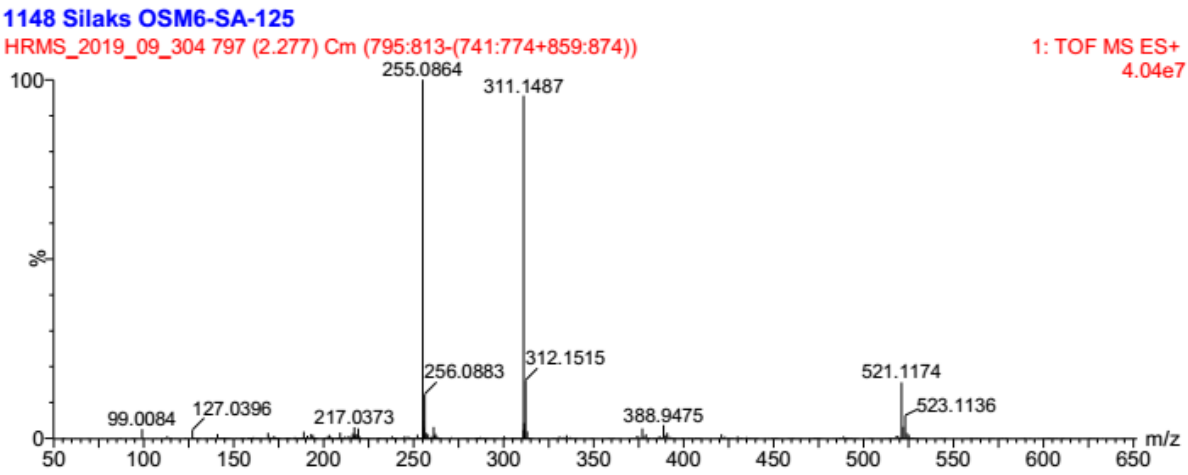
HRMS_2019_09_304	1148 Silaks OSM6-SA-125				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	2:B,3	1.000000	MS_Tune	Col#43

Elemental Composition Report:

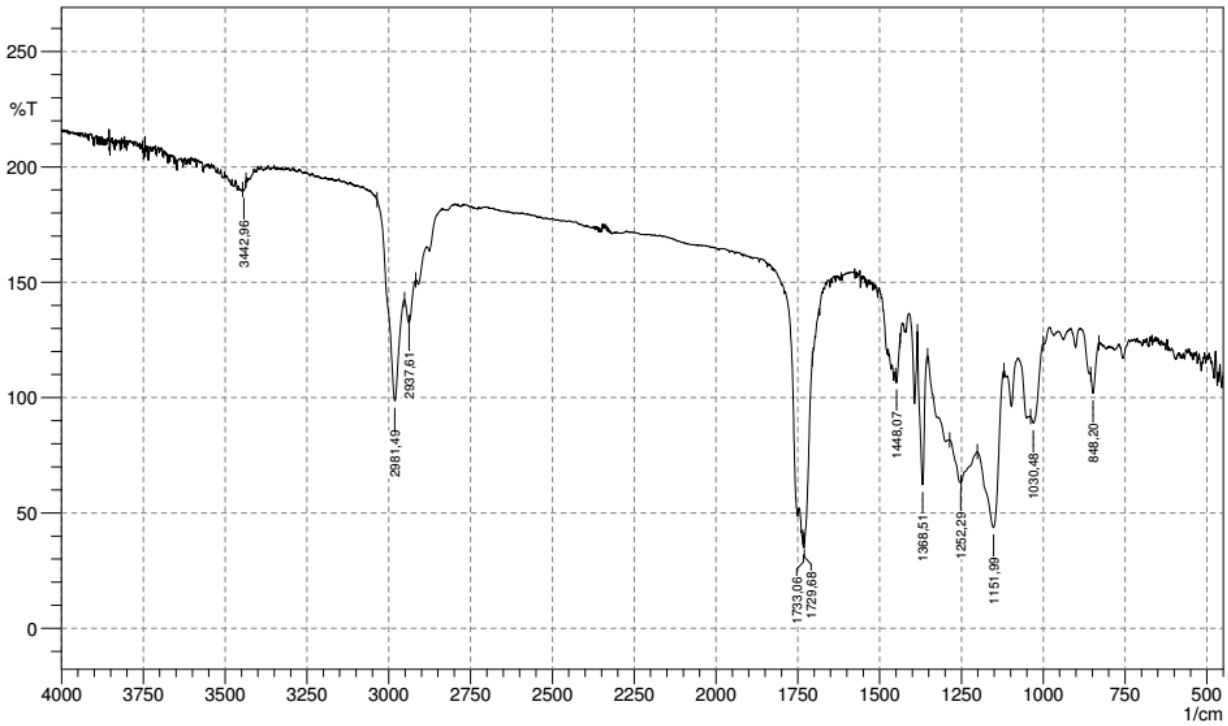
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
34 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-50 H: 1-60 O: 0-10 Na: 1-1

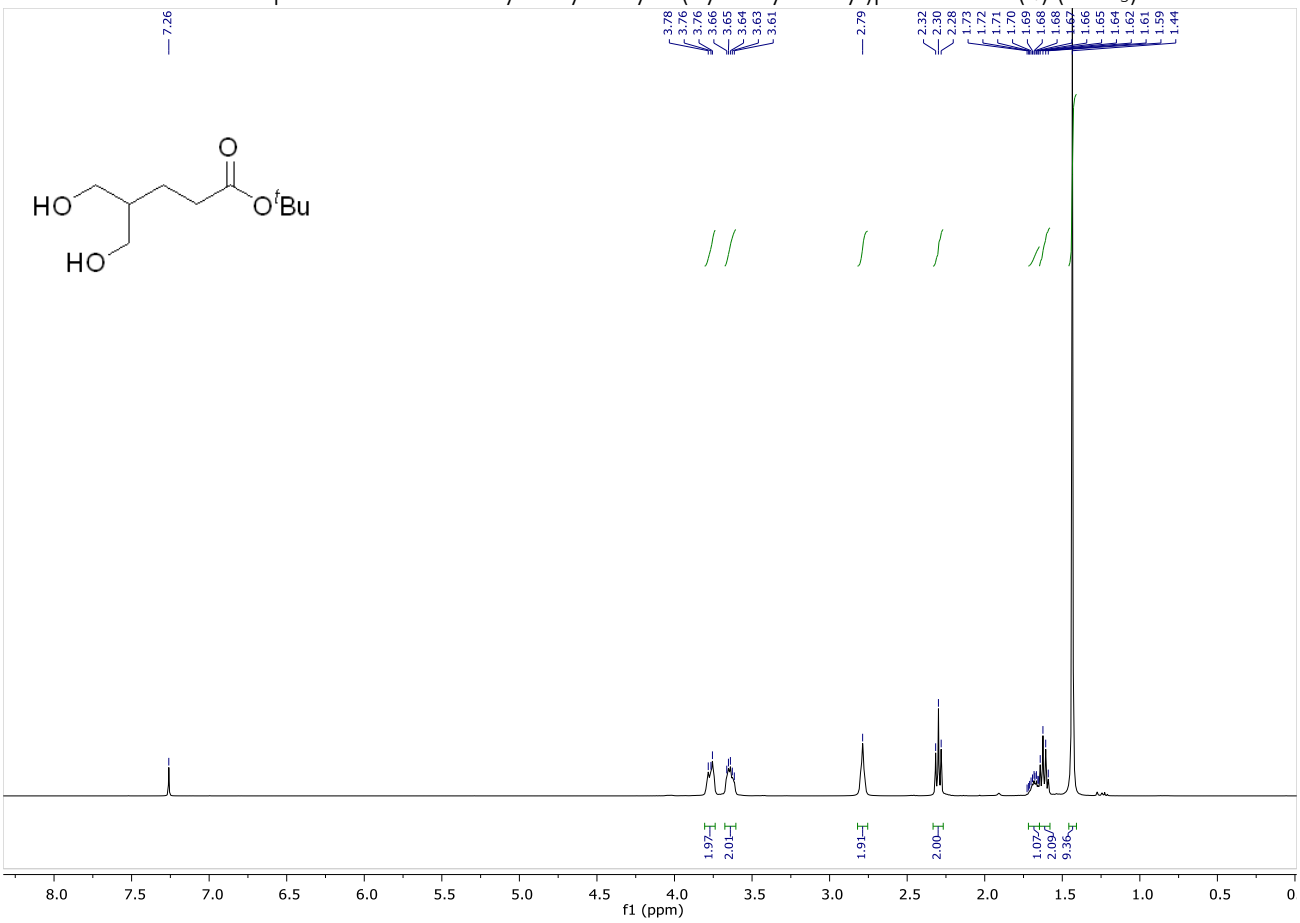
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
311.1487	100.00	311.1471	1.6	5.1	2.5	545.4	n/a	n/a	C14 H24 O6 Na



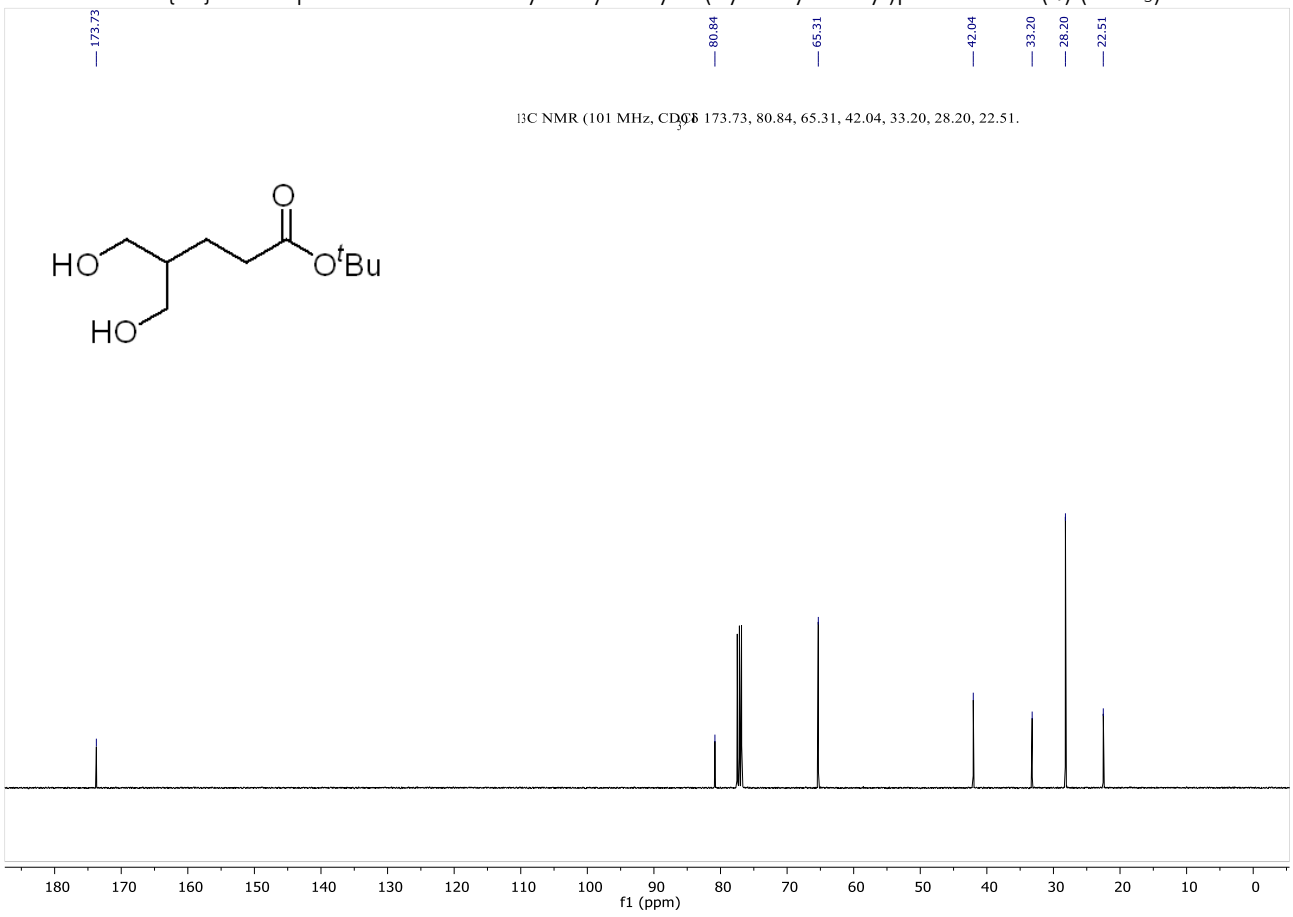
IR(ATR) spectrum of 3-(*tert*-butyl) 1,1-diethyl propane-1,1,3-tricarboxylate (**3**)



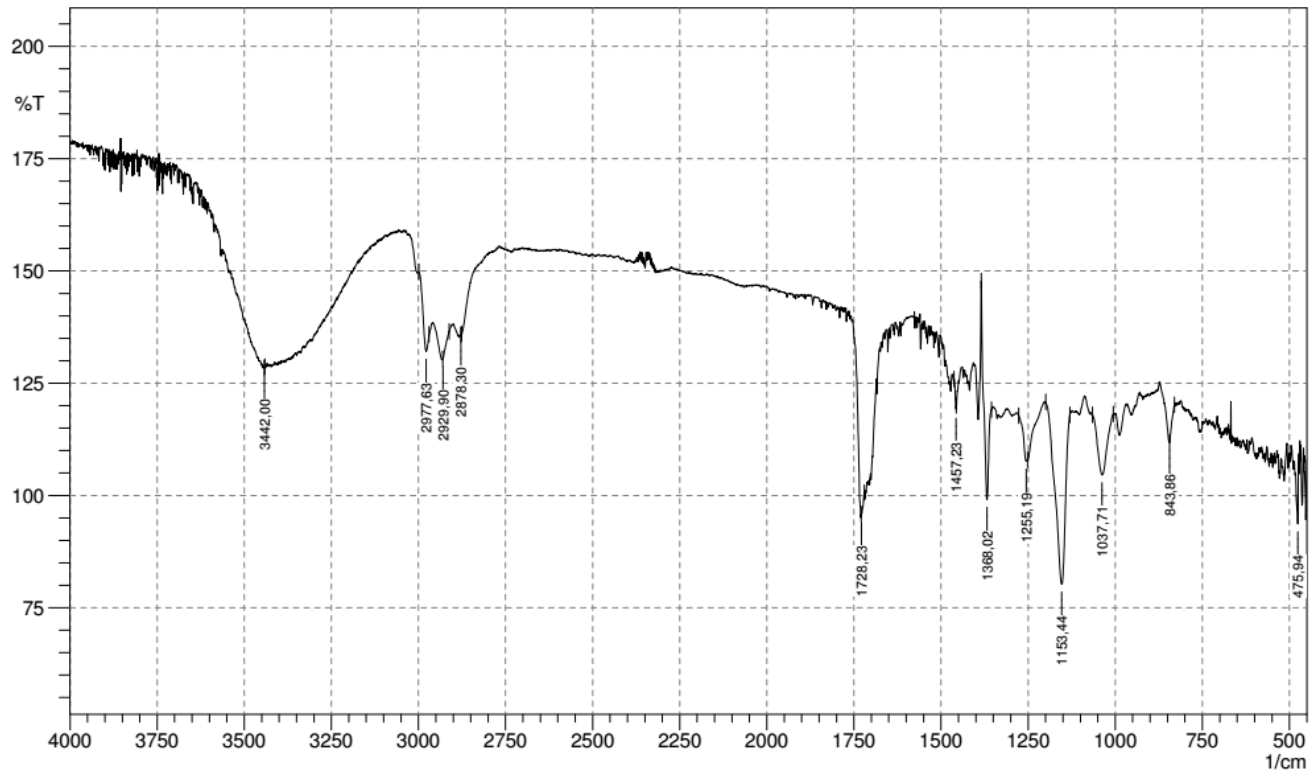
^{1}H NMR spectrum of *tert*-Butyl 5-hydroxy-4-(hydroxymethyl)pentanoate (**4**) ($CDCl_3$)



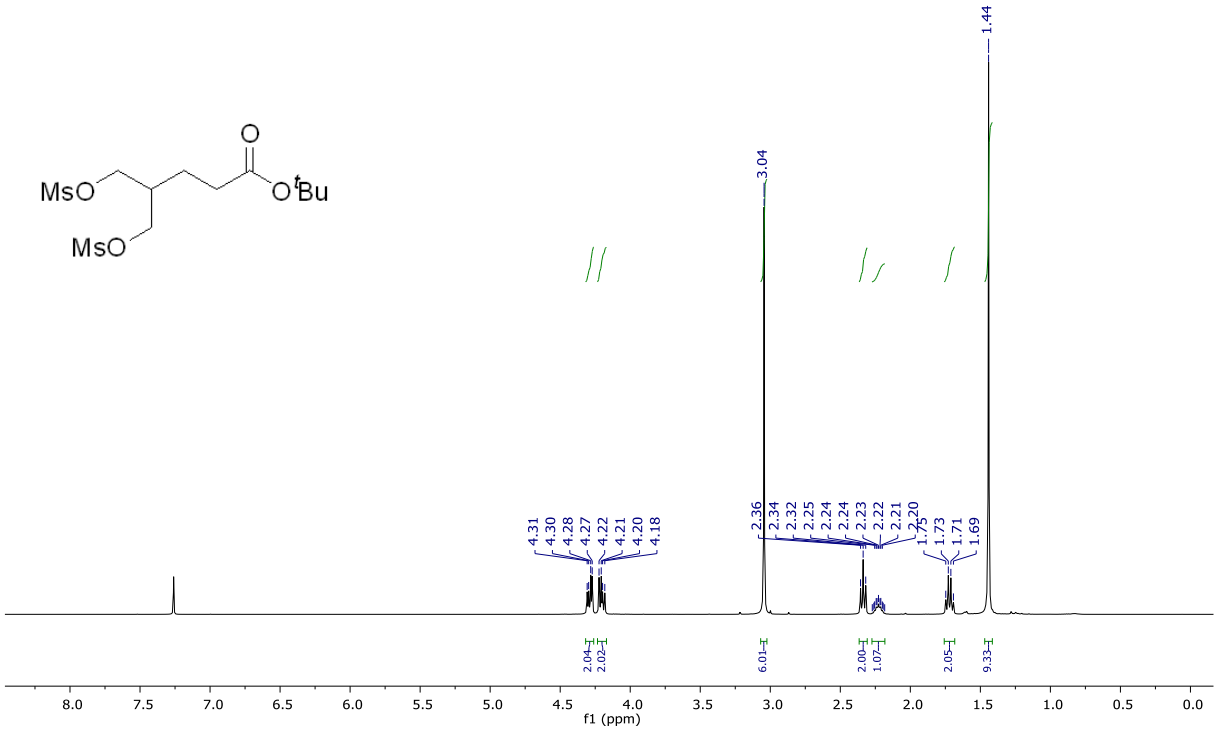
^{13}C{^{1}H} NMR spectrum of *tert*-Butyl 5-hydroxy-4-(hydroxymethyl)pentanoate (**4**) ($CDCl_3$)



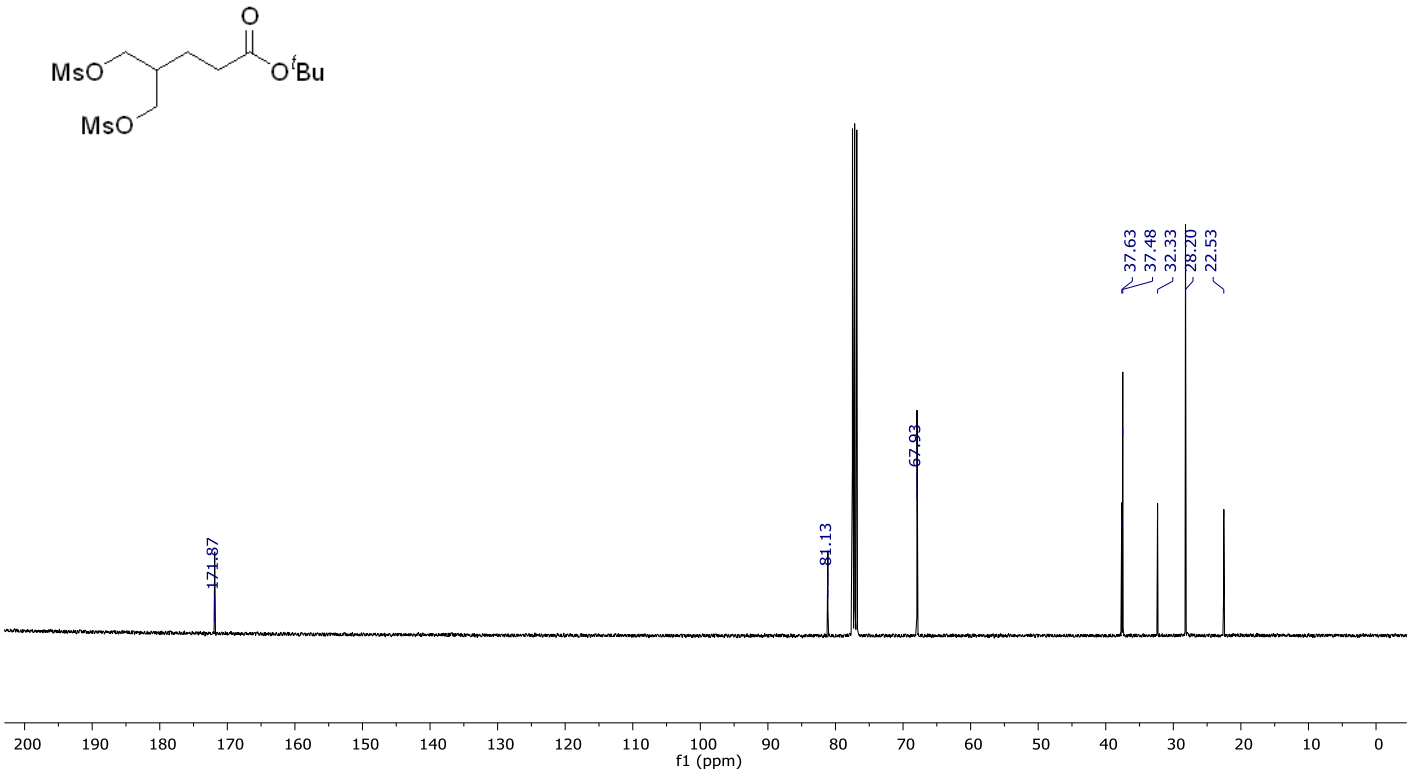
IR(ATR) spectrum of *tert*-Butyl 5-hydroxy-4-(hydroxymethyl)pentanoate (**4**)



^{1}H NMR spectrum of *tert*-Butyl 5-((methylsulfonyl)oxy)-4-(((methylsulfonyl)oxy)methyl)pentanoate (**5**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of *tert*-Butyl 5-((methylsulfonyl)oxy)-4-(((methylsulfonyl)oxy)methyl)pentanoate (**5**) ($CDCl_3$)



HRMS of *tert*-Butyl 5-((methylsulfonyl)oxy)-4-(((methylsulfonyl)oxy)methyl)pentanoate (**5**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

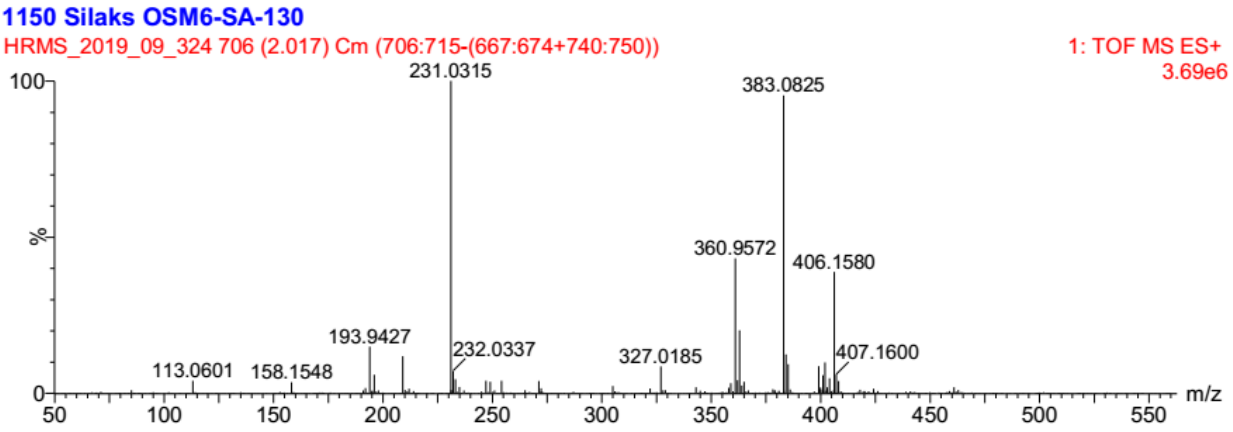
HRMS_2019_09_324	1150 Silaks OSM6-SA-130				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	1:F,7	1.000000	MS_Tune	Col#43

Elemental Composition Report:

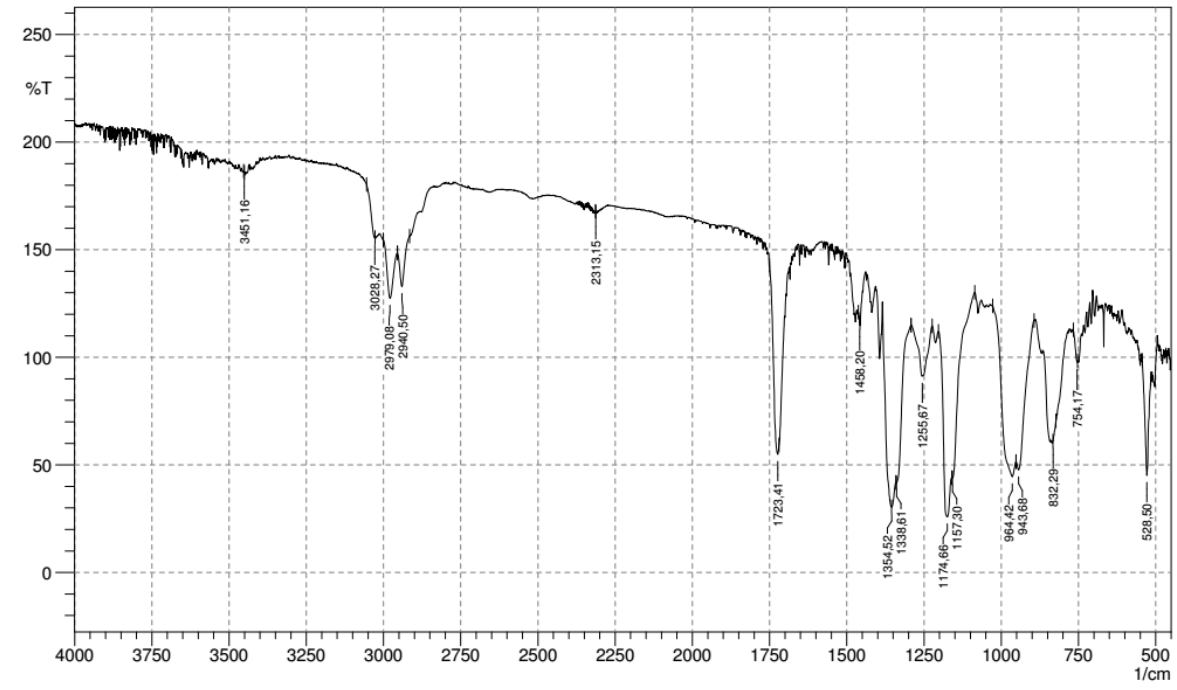
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 90.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
159 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-50 H: 1-60 O: 0-10 Na: 0-1 S: 1-2

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
383.0825	100.00	383.0810	1.5	3.9	0.5	281.8	0.044	95.67	C12 H24 O8 Na S2
		383.0834	-0.9	-2.3	3.5	284.8	3.139	4.33	C14 H23 O8 S2

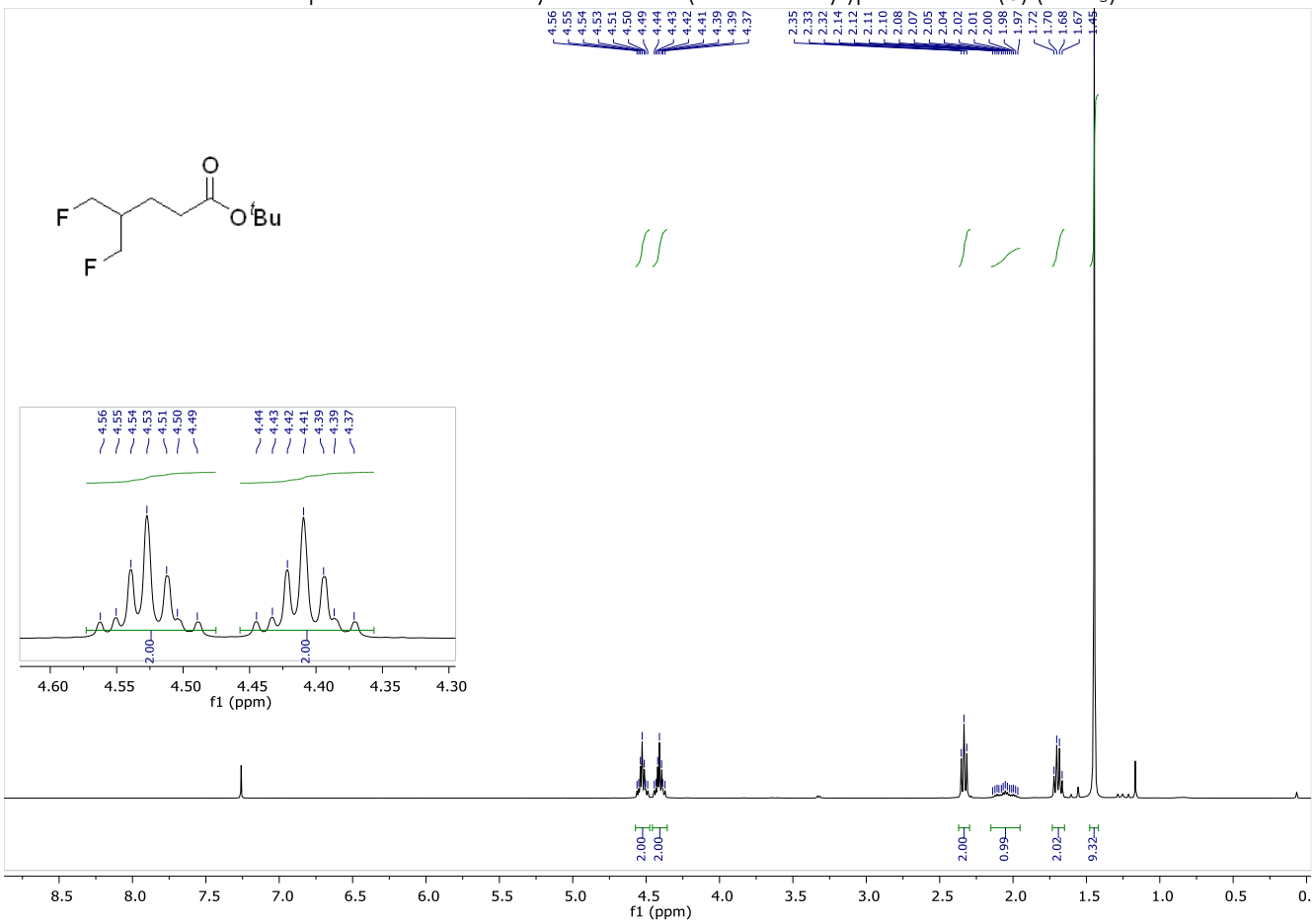


IR(ATR) spectrum of *tert*-Butyl 5-((methylsulfonyl)oxy)-4-(((methylsulfonyl)oxy)methyl)pentanoate (**5**)

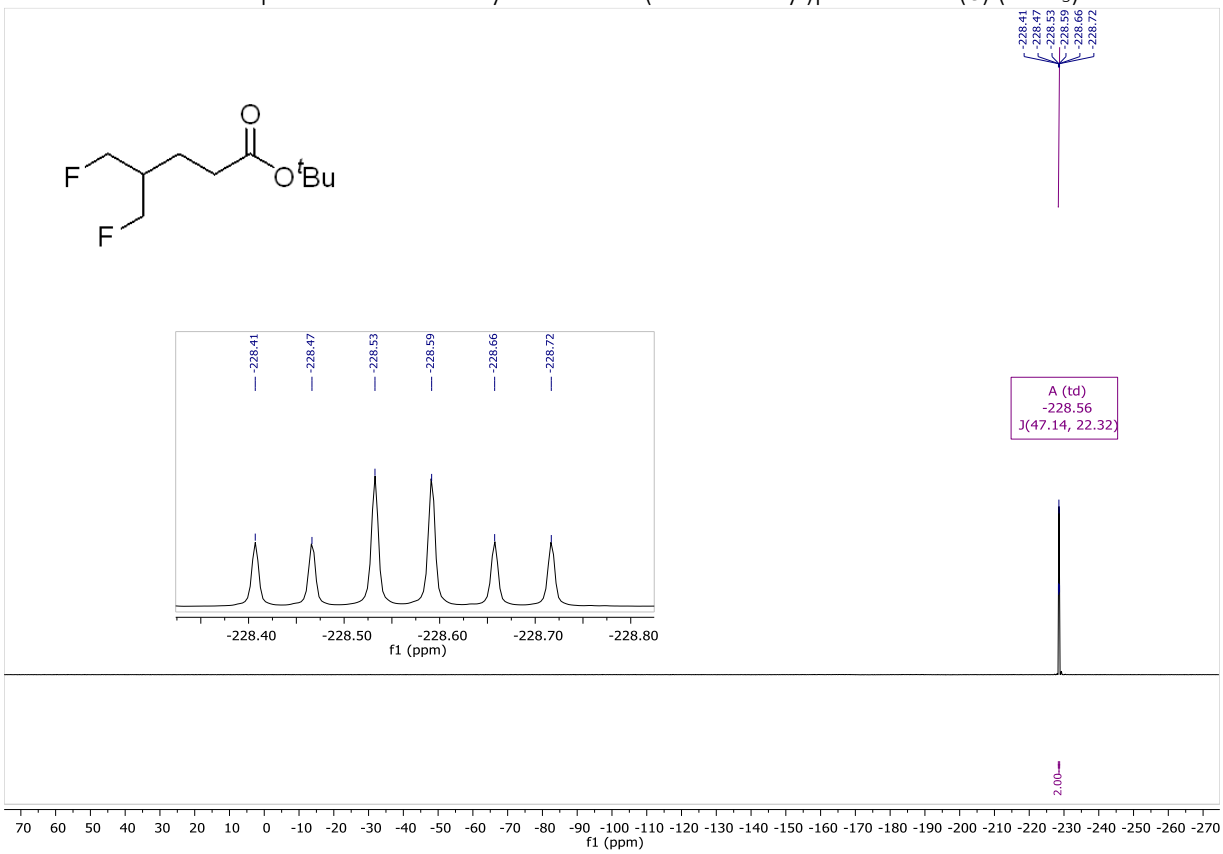


OSM6-SA_130

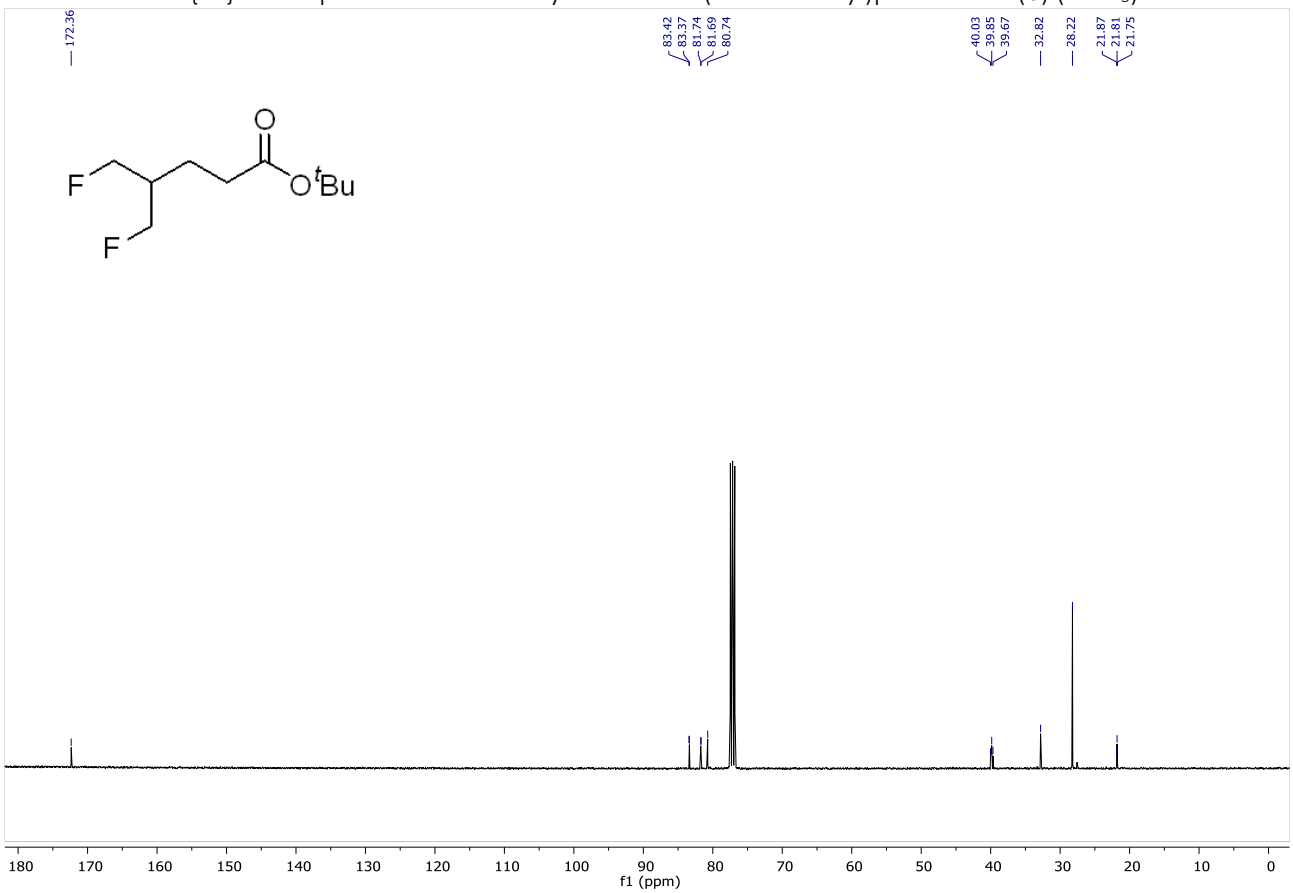
^{1}H NMR spectrum of *tert*-butyl 5-fluoro-4-(fluoromethyl)pentanoate (**6**) ($CDCl_3$)



^{19}F NMR spectrum of *tert*-butyl 5-fluoro-4-(fluoromethyl)pentanoate (**6**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl 5-fluoro-4-(fluoromethyl)pentanoate (**6**) ($CDCl_3$)



GC-MS of *tert*-butyl 5-fluoro-4-(fluoromethyl)pentanoate (**6**)

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File       :D:\DATA_2019\10_Okt_2019\14_14524.D
Operator   : E
Acquired   : 14 Oct 2019  14:47     using AcqMethod LAURA.M
Instrument :     GCMS
Sample Name: Silaks OSMG-SA-138
Misc Info  :
Vial Number: 6
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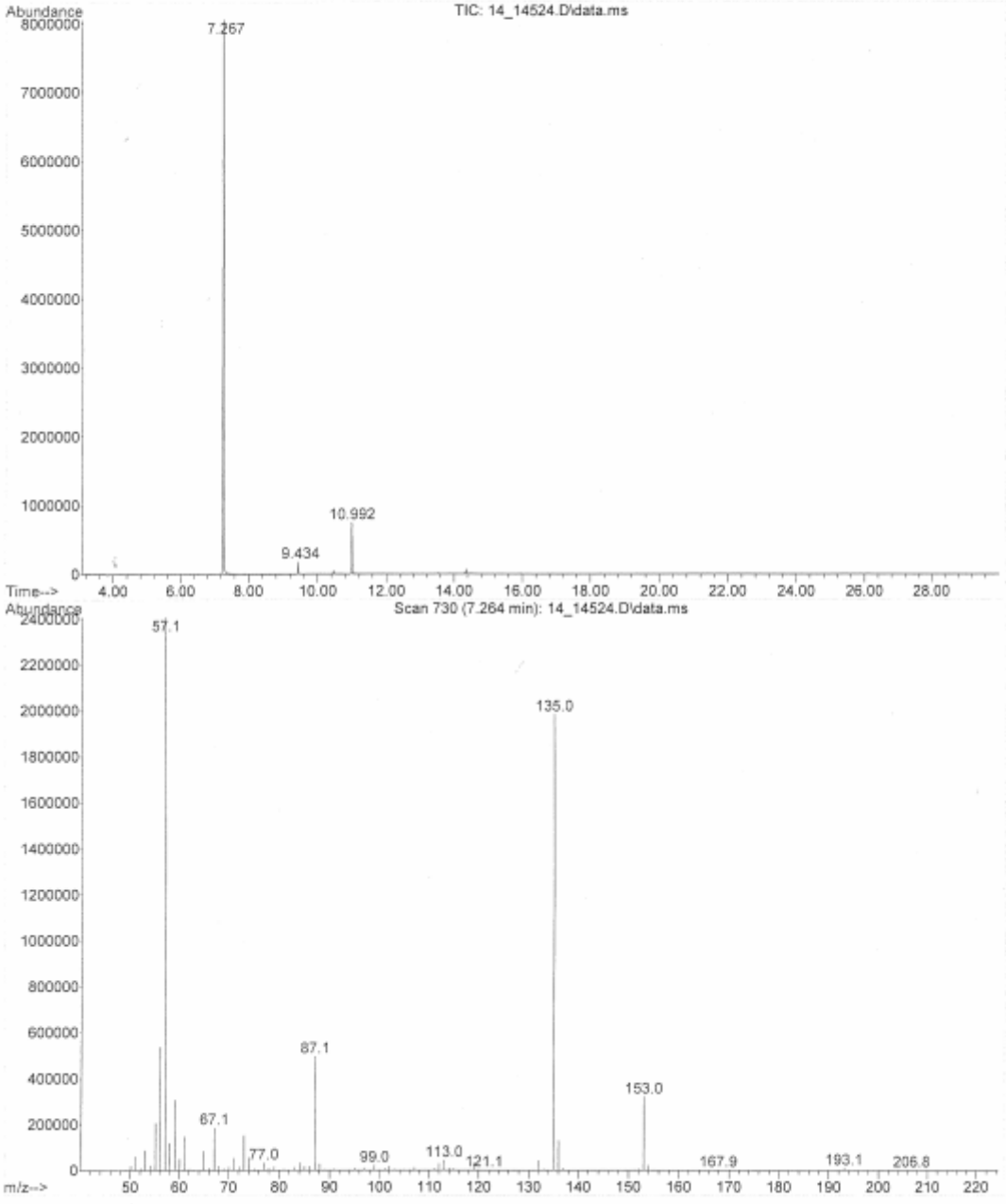
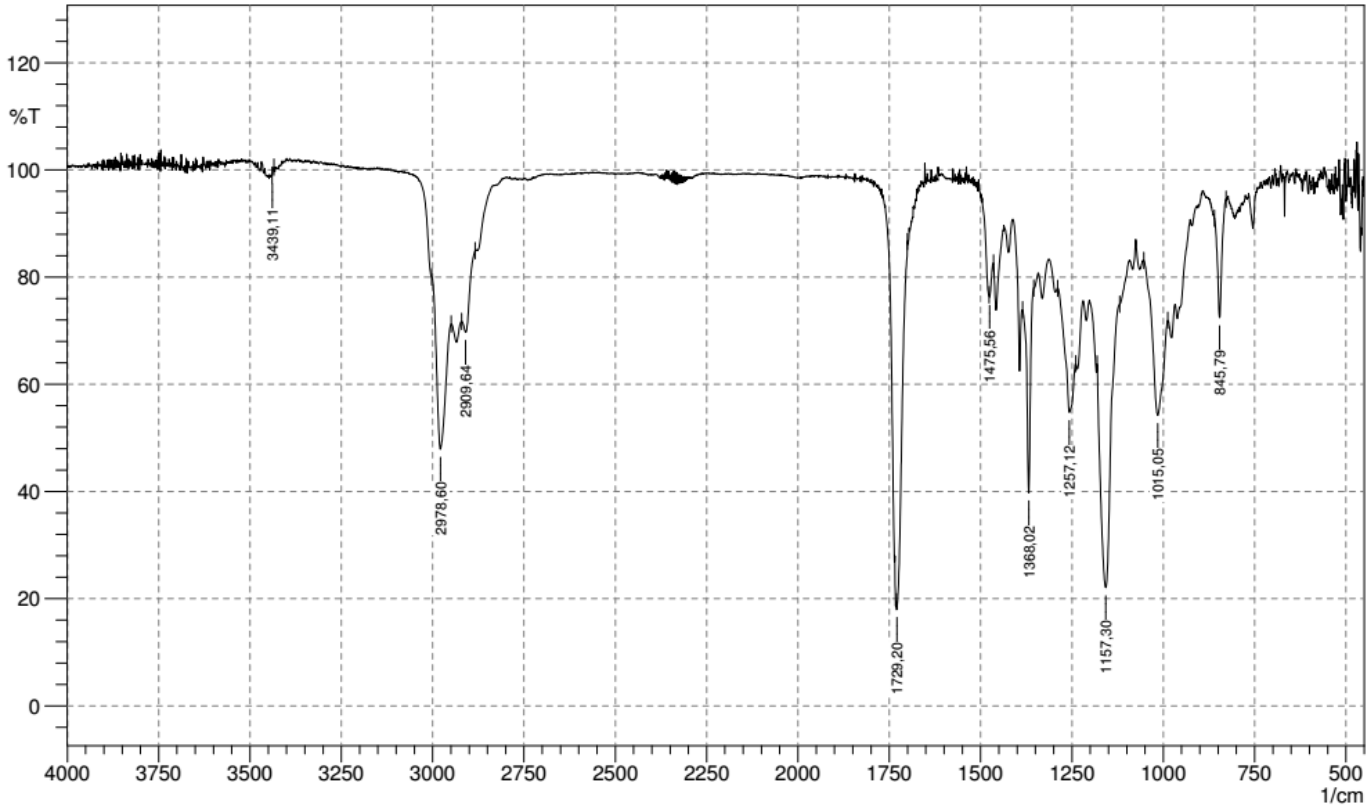
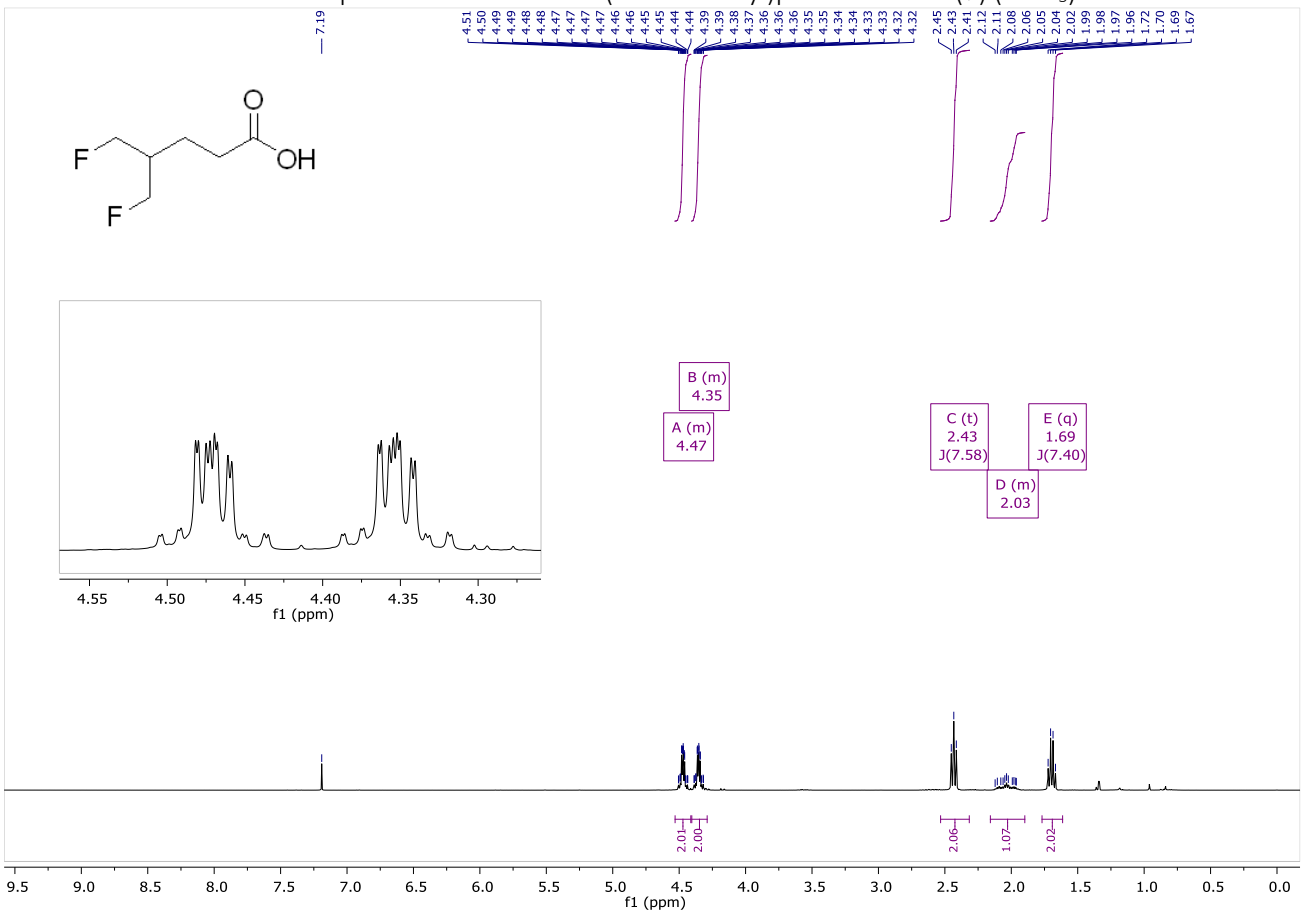


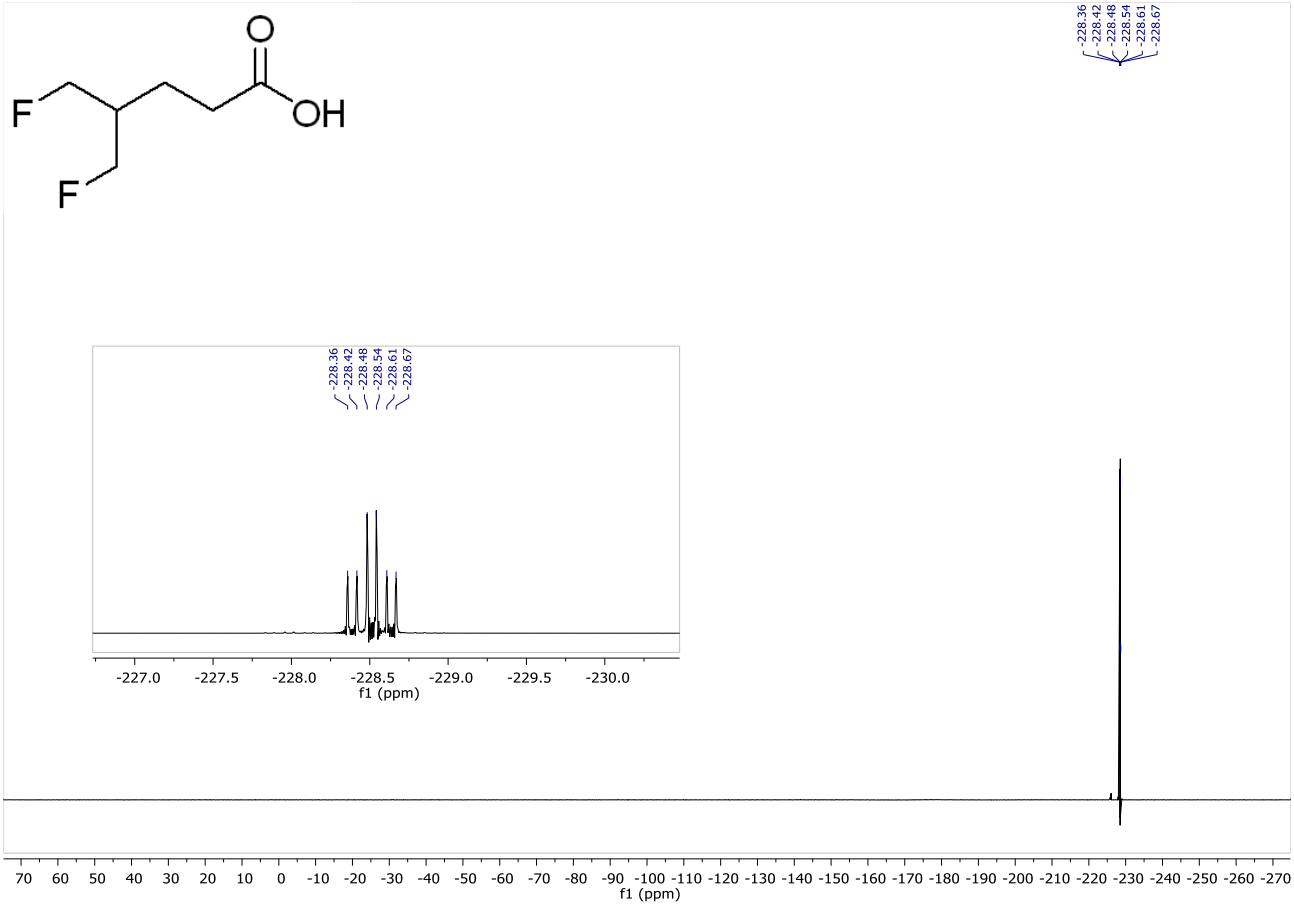
IR(ATR) spectrum of *tert*-butyl 5-fluoro-4-(fluoromethyl)pentanoate (**6**)



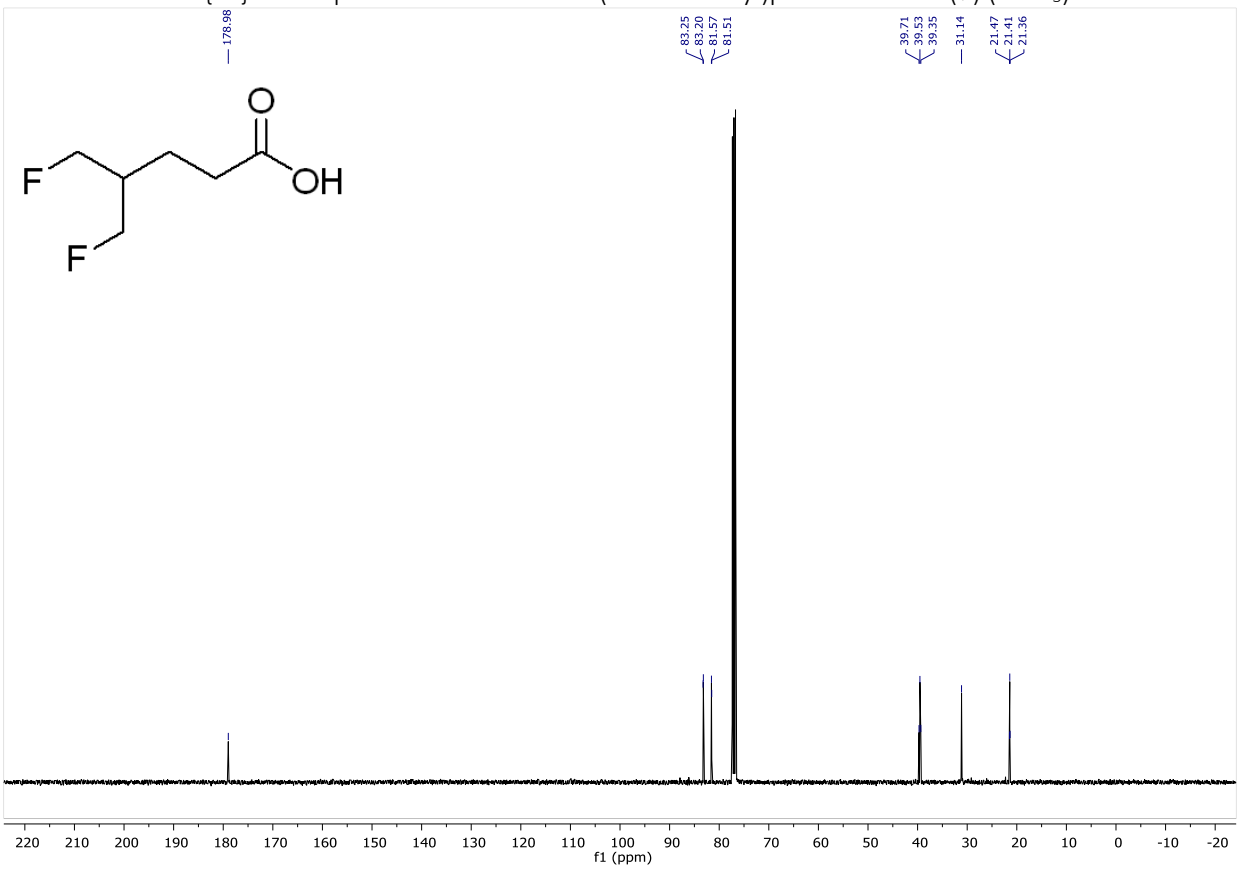
^{1}H NMR spectrum of 5-fluoro-4-(fluoromethyl)pentanoic acid (**7**) ($CDCl_3$)



^{19}F NMR spectrum of 5-fluoro-4-(fluoromethyl)pentanoic acid (**7**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 5-fluoro-4-(fluoromethyl)pentanoic acid (**7**) ($CDCl_3$)



HRMS of 5-fluoro-4-(fluoromethyl)pentanoic acid (**7**)

MS: Waters Synapt G2-Si	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18	
ESI-	Cone, V:	40			2.1x50mm, 1.7µm	

Sample:

HRMS_2019_10_322 1215 Silaks OSM-SA-143

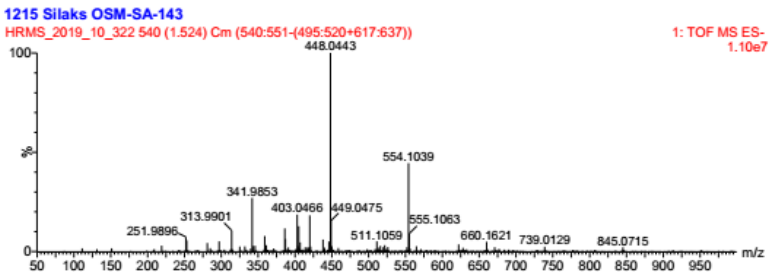
MS_NEG_RES_4min ACN_Form_5-98_040_4min 2:C,2 3.000000 MS_Tune Col#43

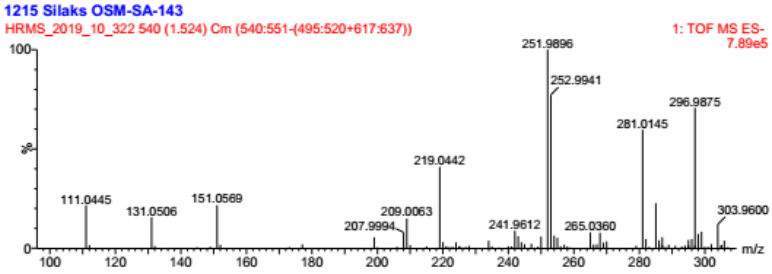
Elemental Composition Report:

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 90.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

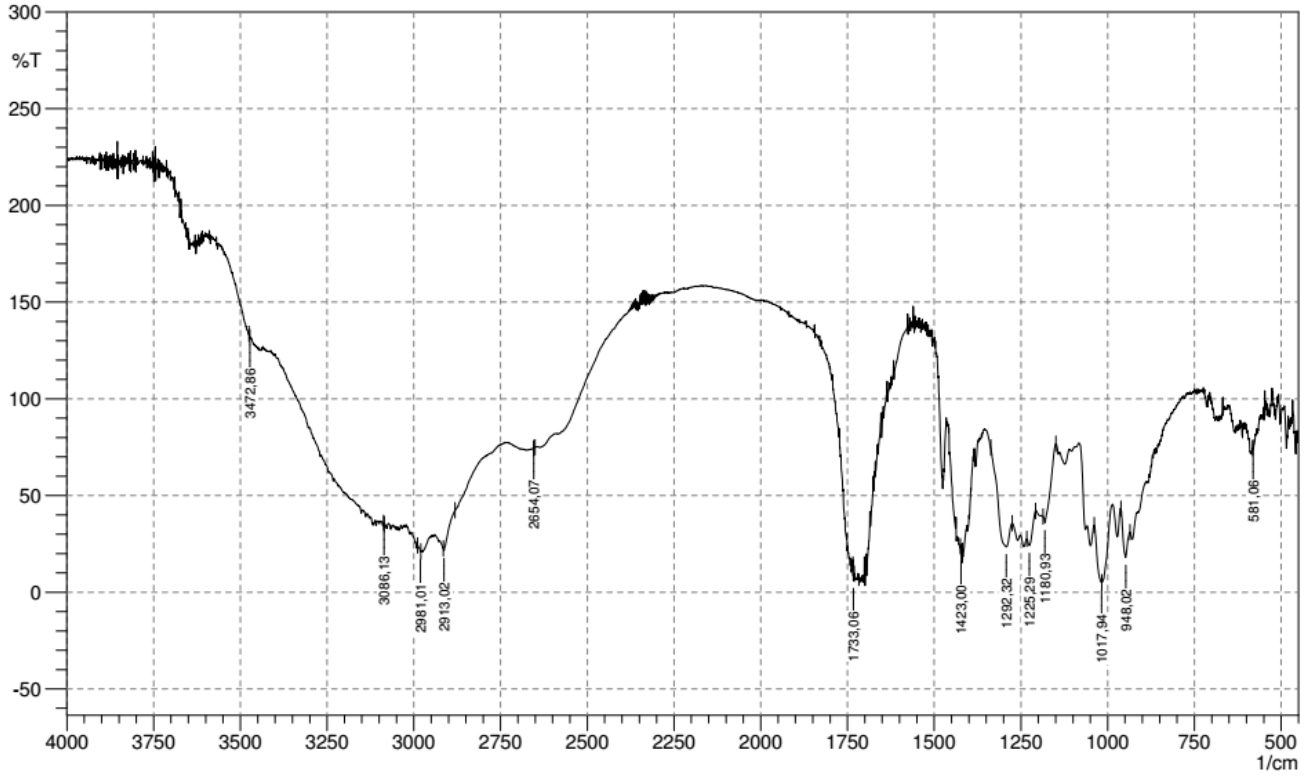
Monoisotopic Mass, Even Electron Ions
51 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 0-10 O: 0-10 F: 2-2

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
151.0569	100.00	151.0571	-0.2	-1.3	1.5	145.7	n/a	n/a	C6 H9 O2 F2



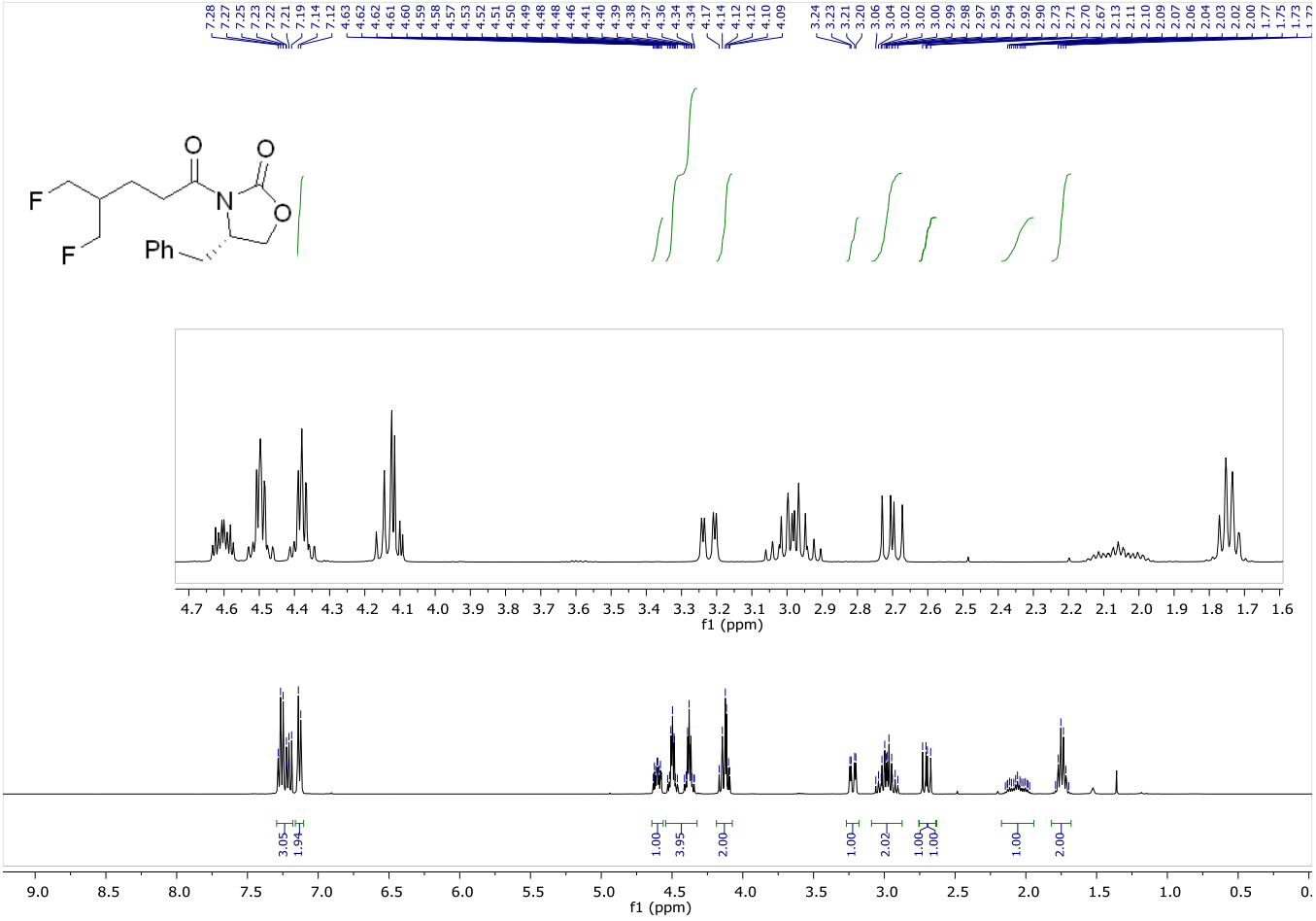


IR(ATR) spectrum of 5-fluoro-4-(fluoromethyl)pentanoic acid (**7**)

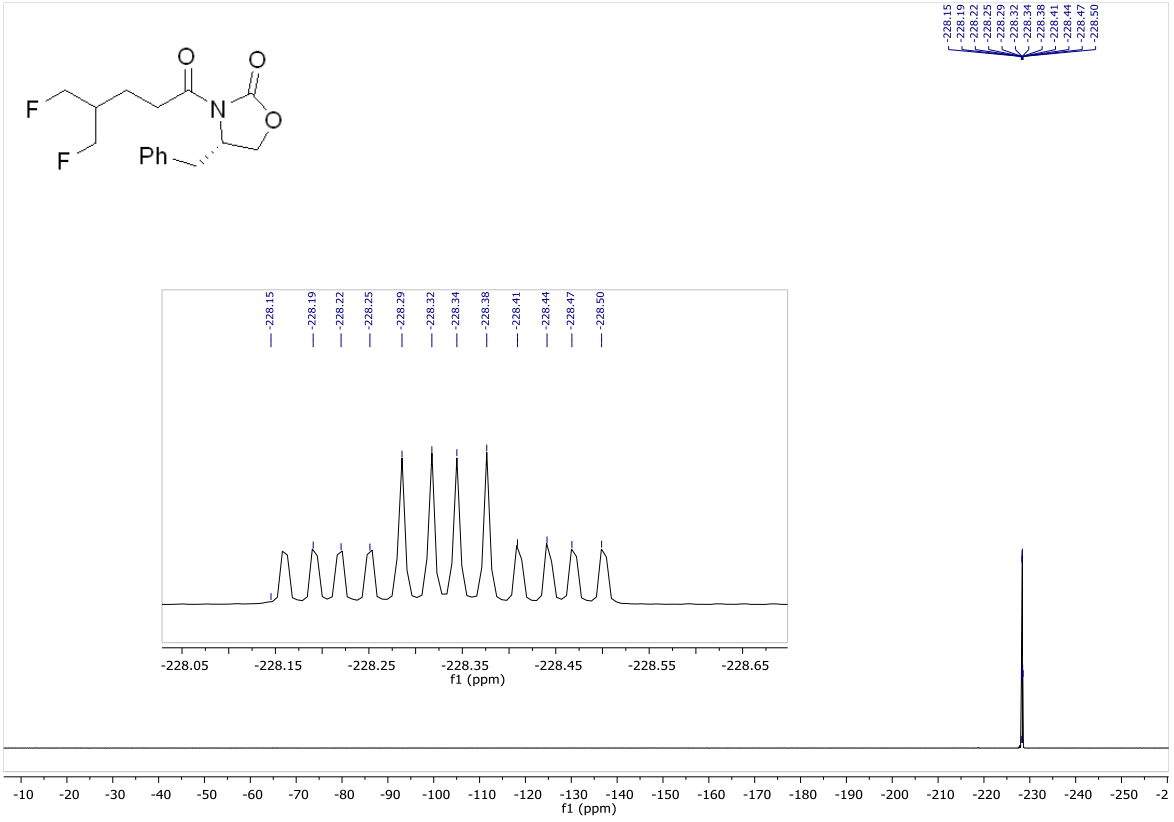


OSM6-AM-PENtF2

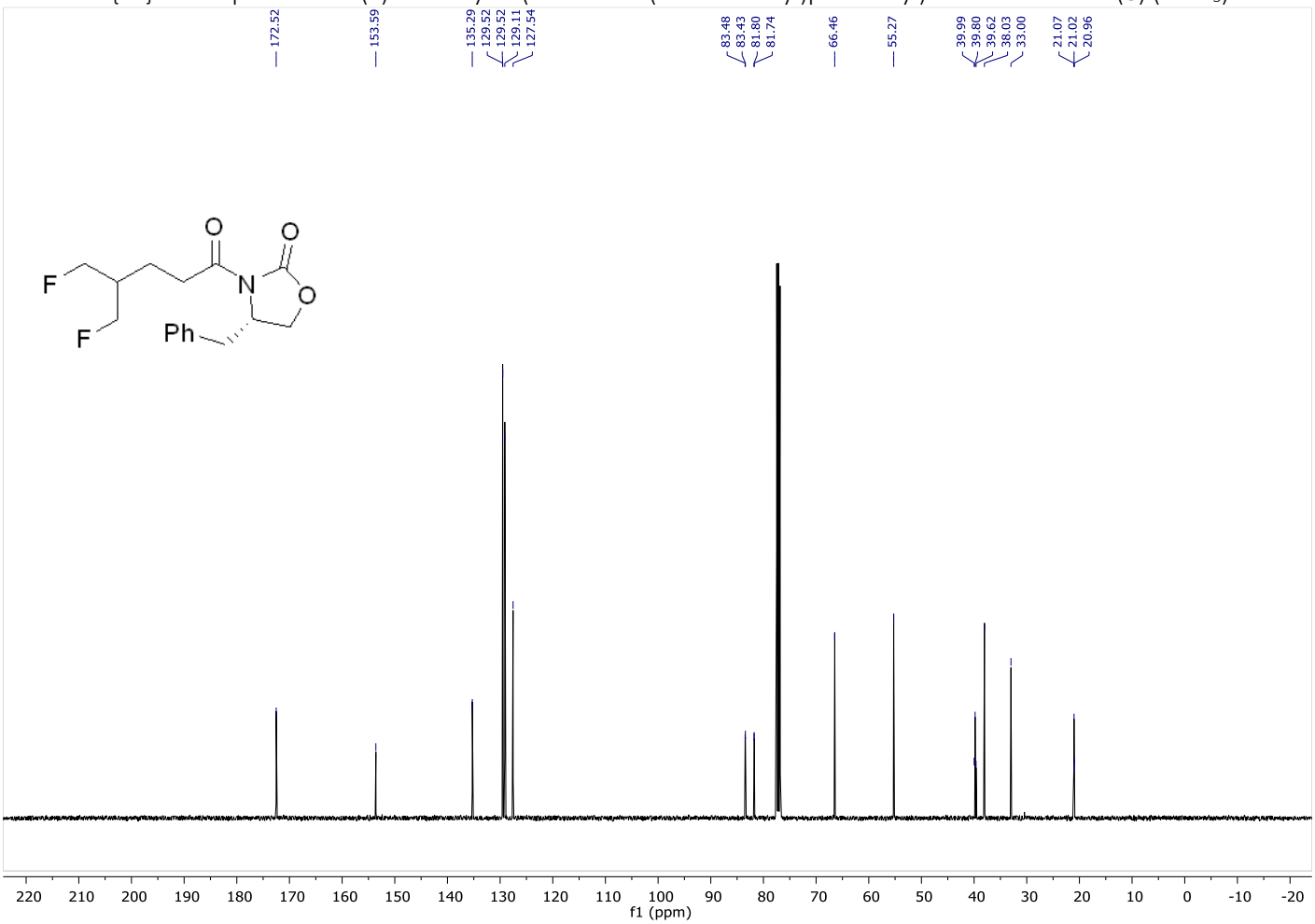
^{1}H NMR spectrum of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**8**) ($CDCl_3$)



^{19}F NMR spectrum of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**8**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**8**) ($CDCl_3$)



HRMS of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**8**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

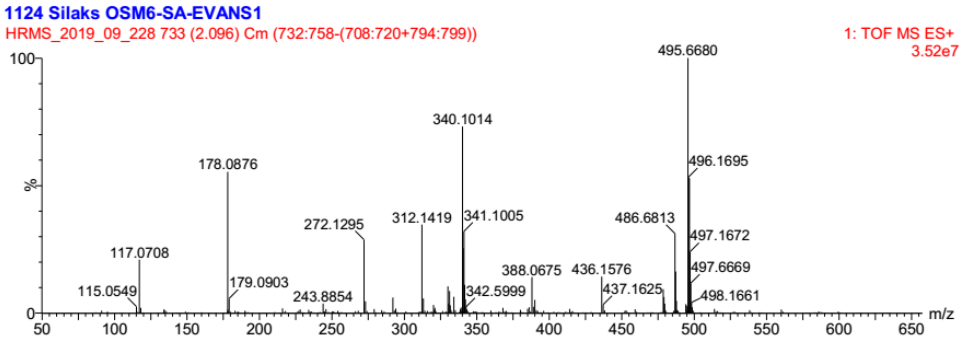
HRMS_2019_09_228	1124 Silaks OSM6-SA-EVANS1				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	1:E,2	1.000000	MS_Tune	Col#43

Elemental Composition Report:

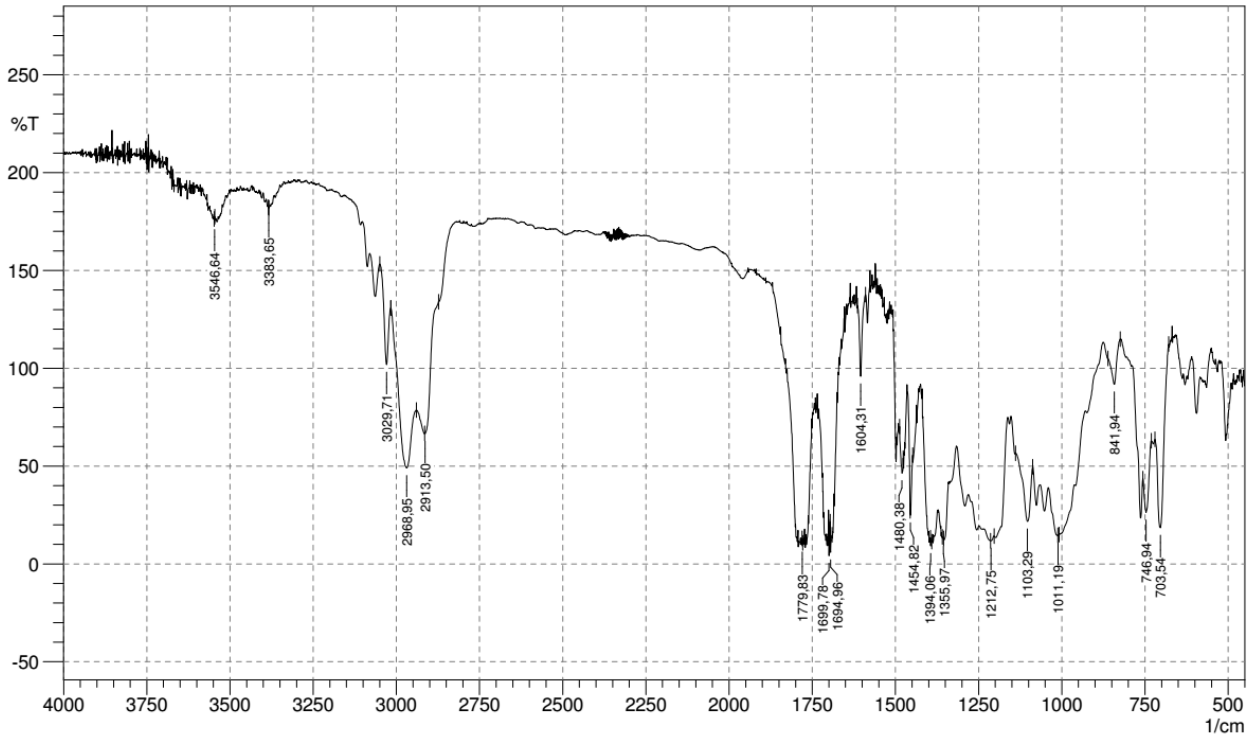
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
240 formula(e) evaluated with 1 results within limits (up to 3 closest results for each mass)
Elements Used:
C: 0-65 H: 1-140 N: 0-6 O: 0-16 F: 2-2

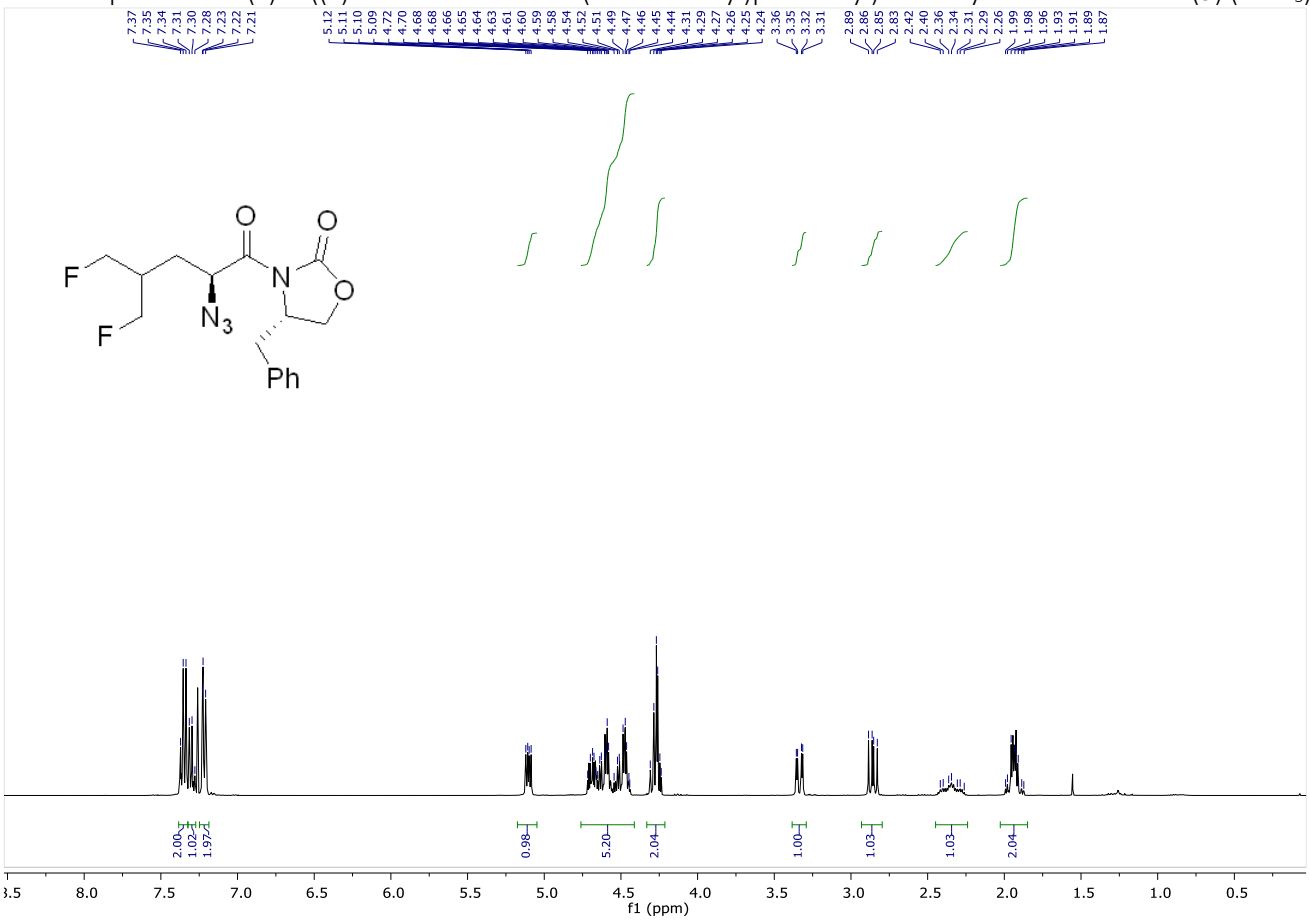
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
312.1419	100.00	312.1411	0.8	2.6	6.5	851.3	n/a	n/a	C16 H20 N O3 F2



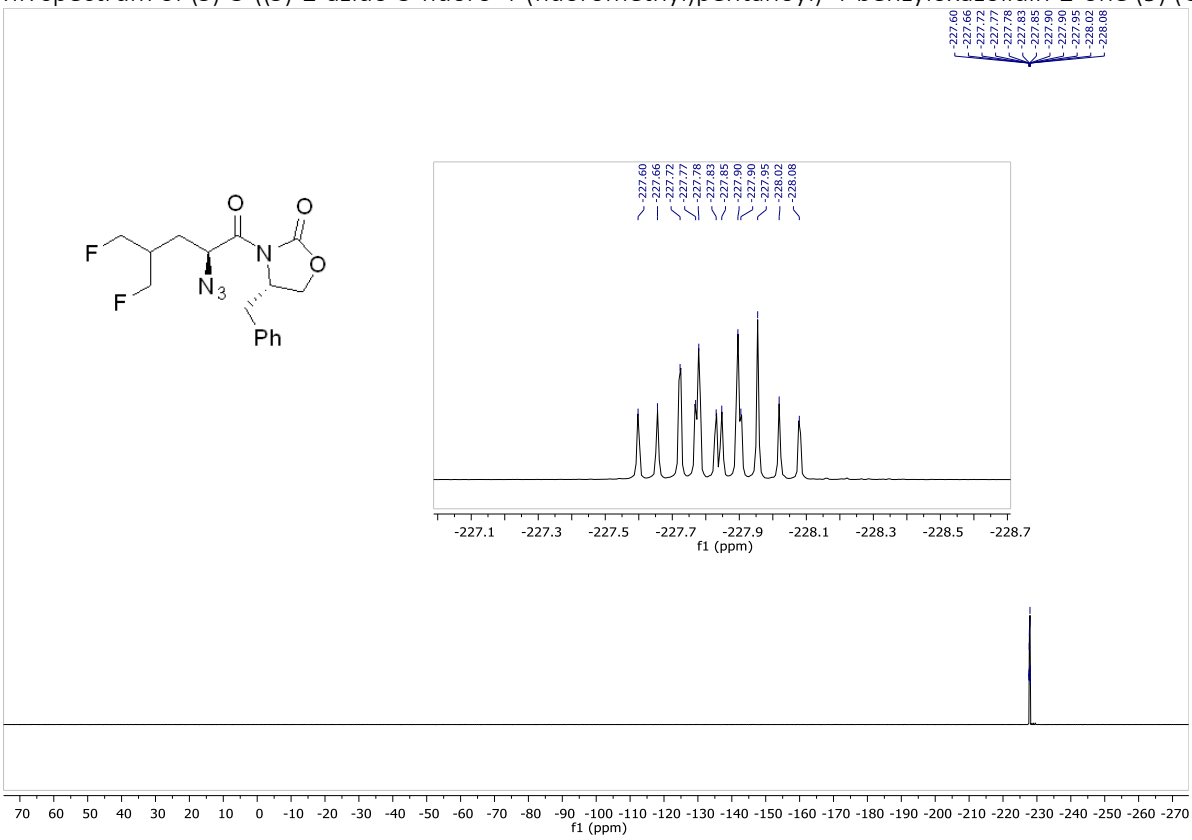
IR(ATR) spectrum of (*S*)-4-benzyl-3-(5-fluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**8**)



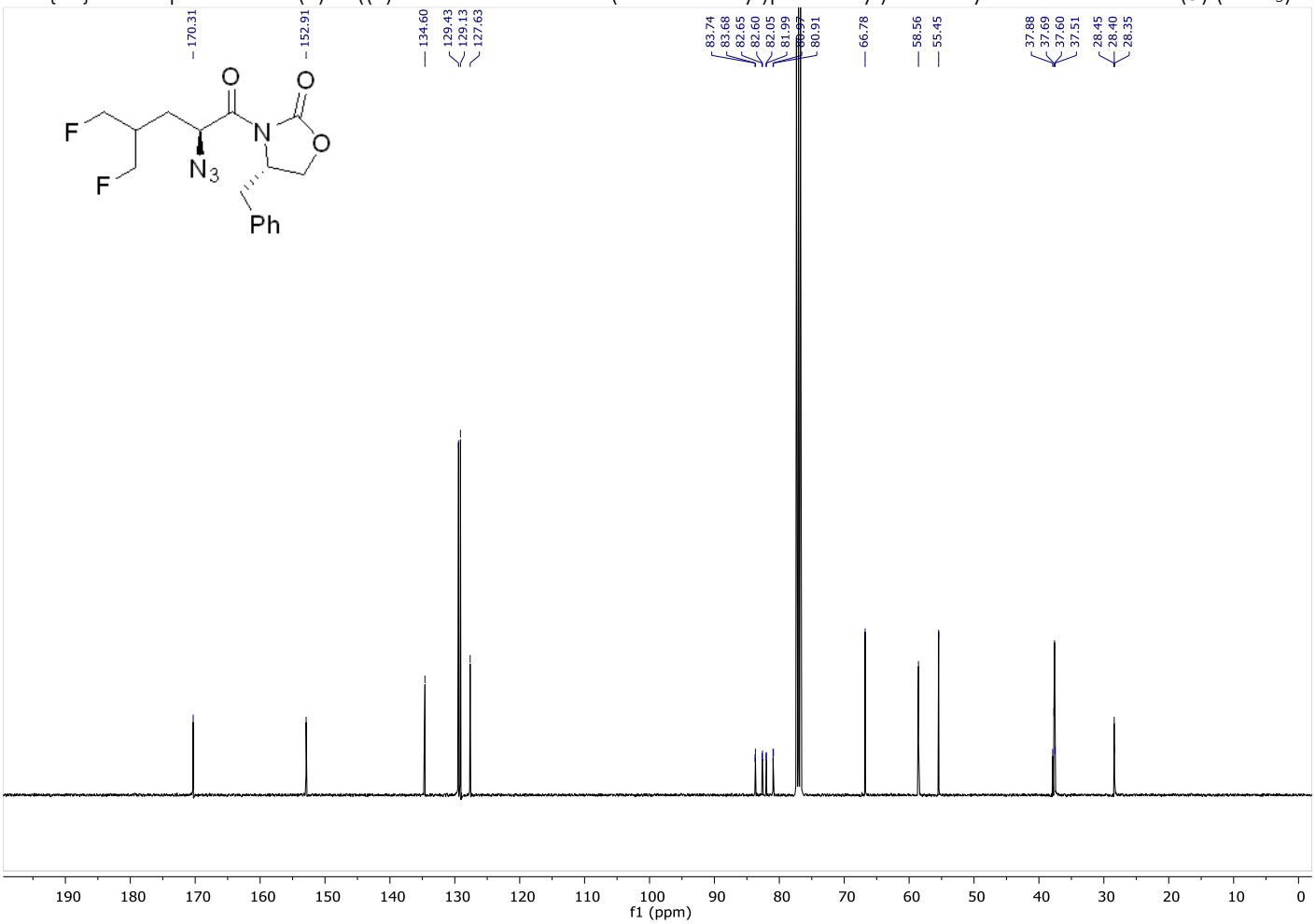
^{1}H NMR spectrum of (*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**9**) ($CDCl_3$)



^{19}F NMR spectrum of (*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**9**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**9**) ($CDCl_3$)



HRMS of (*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**9**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2019_11_297 1485 Maleckis OSM6-AF-F180

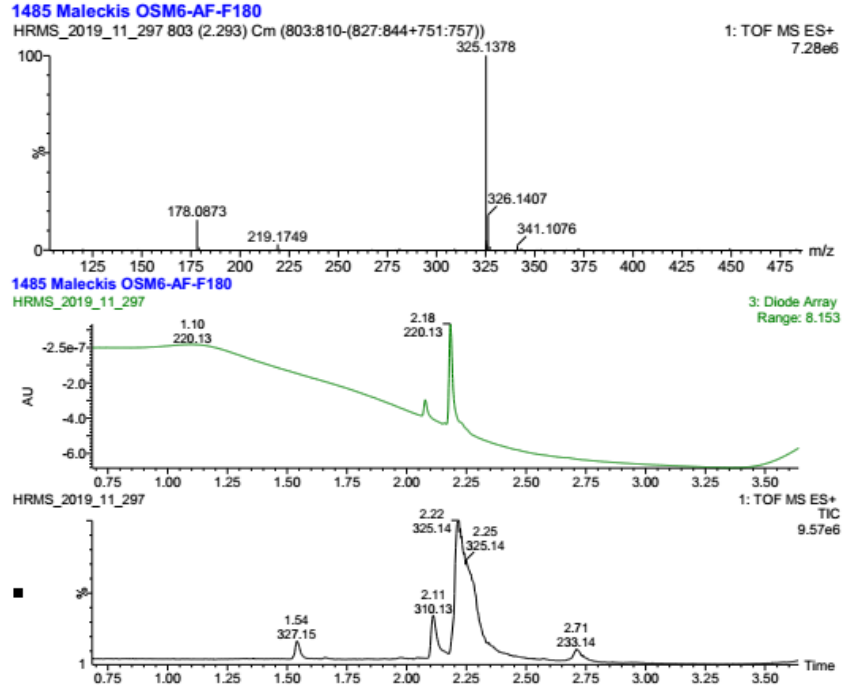
MS_POS_RES_4min ACN_Form_5-98_040_4min 2:F,7 1.000000 MS_Tune Col#43

Elemental Composition Report:

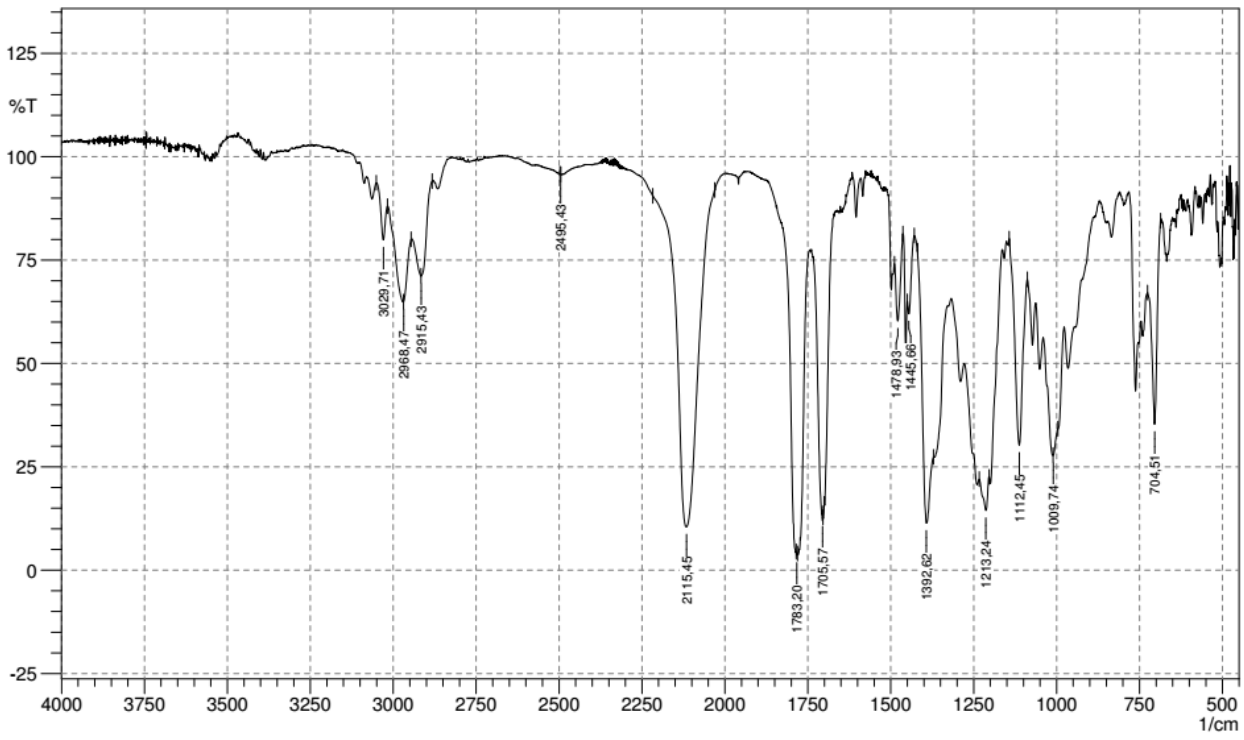
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
250 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 1-10 O: 1-10 F: 2-2

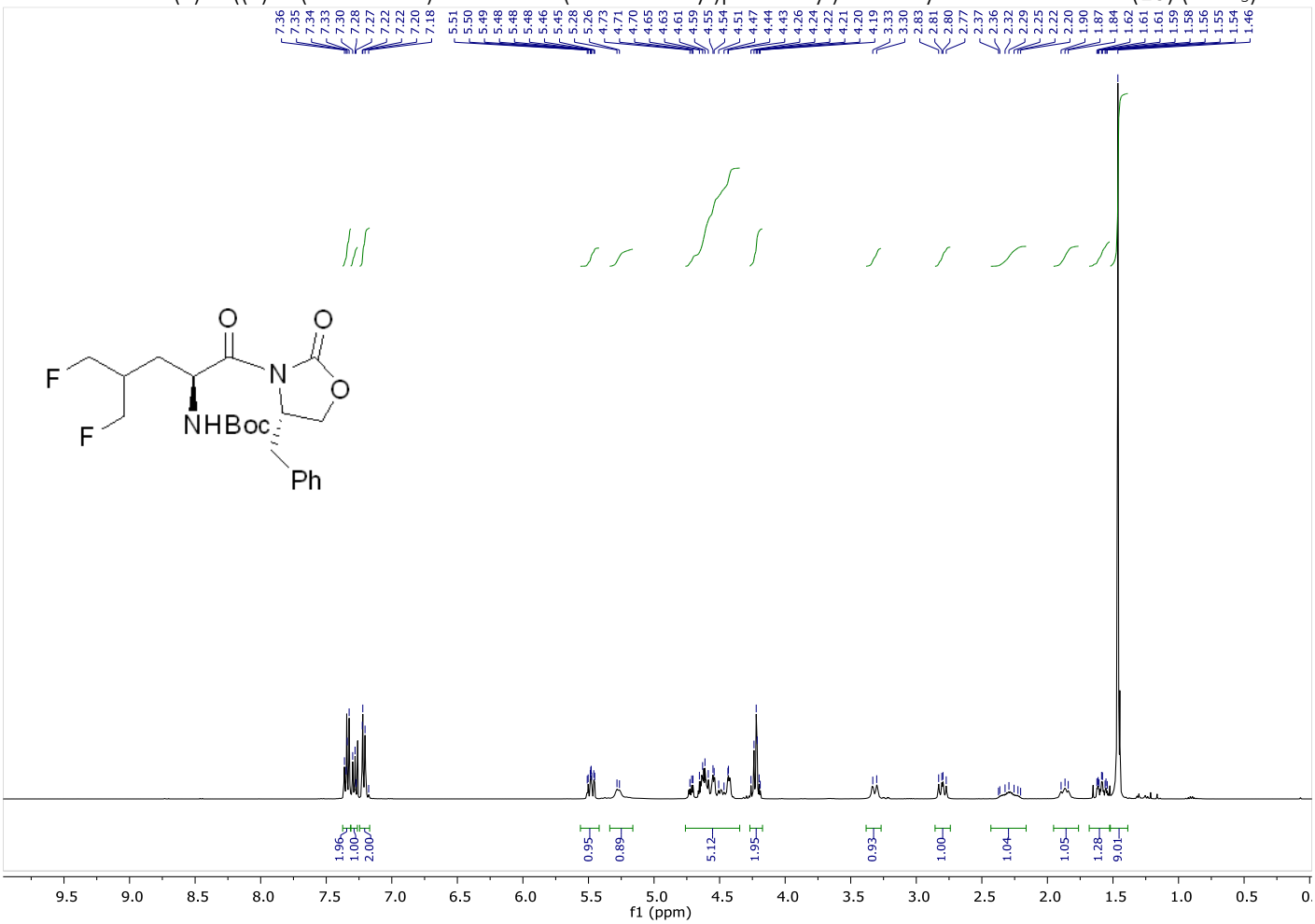
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
325.1378	100.00	325.1364	1.4	4.3	7.5	388.2	n/a	n/a	C16 H19 N2 O3 F2



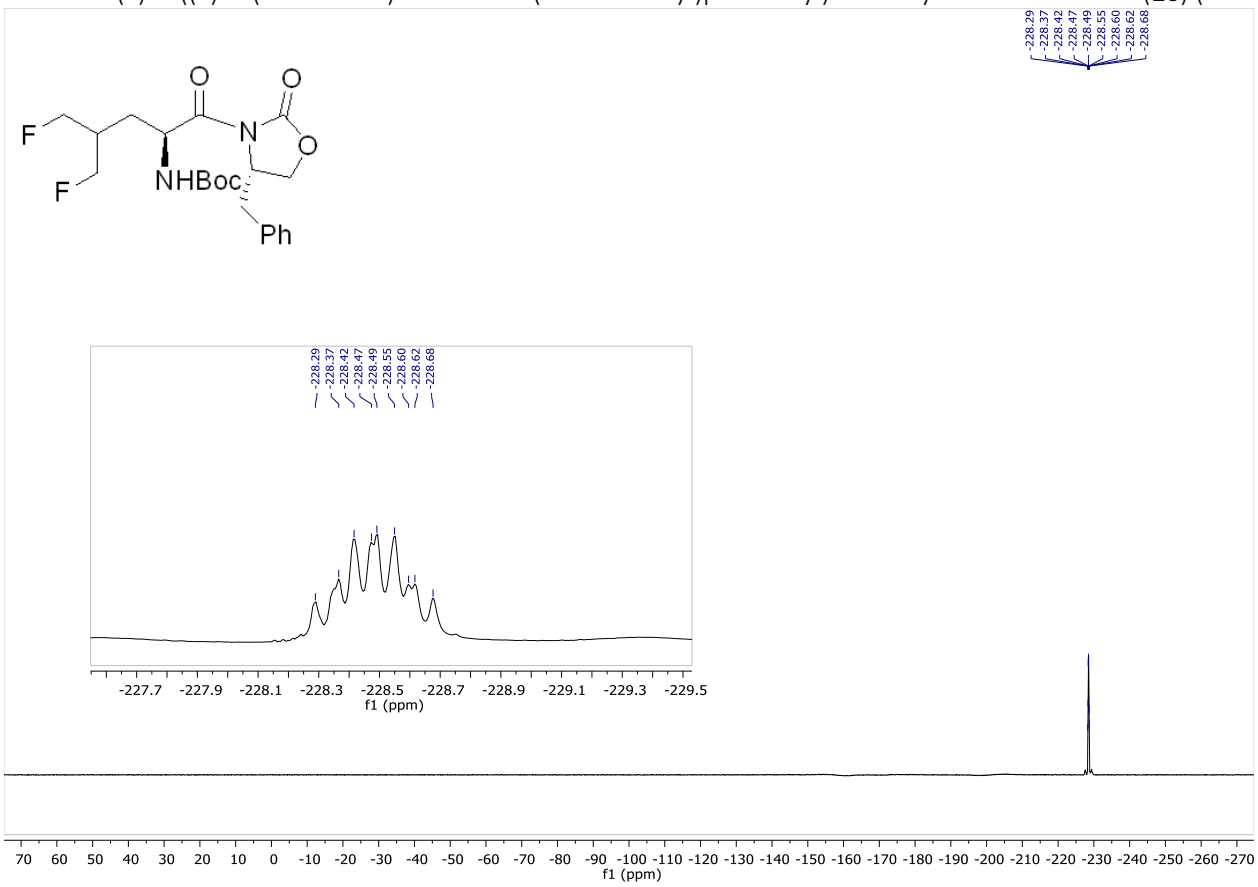
IR(ATR) spectrum of (*S*)-3-((*S*)-2-azido-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**9**)



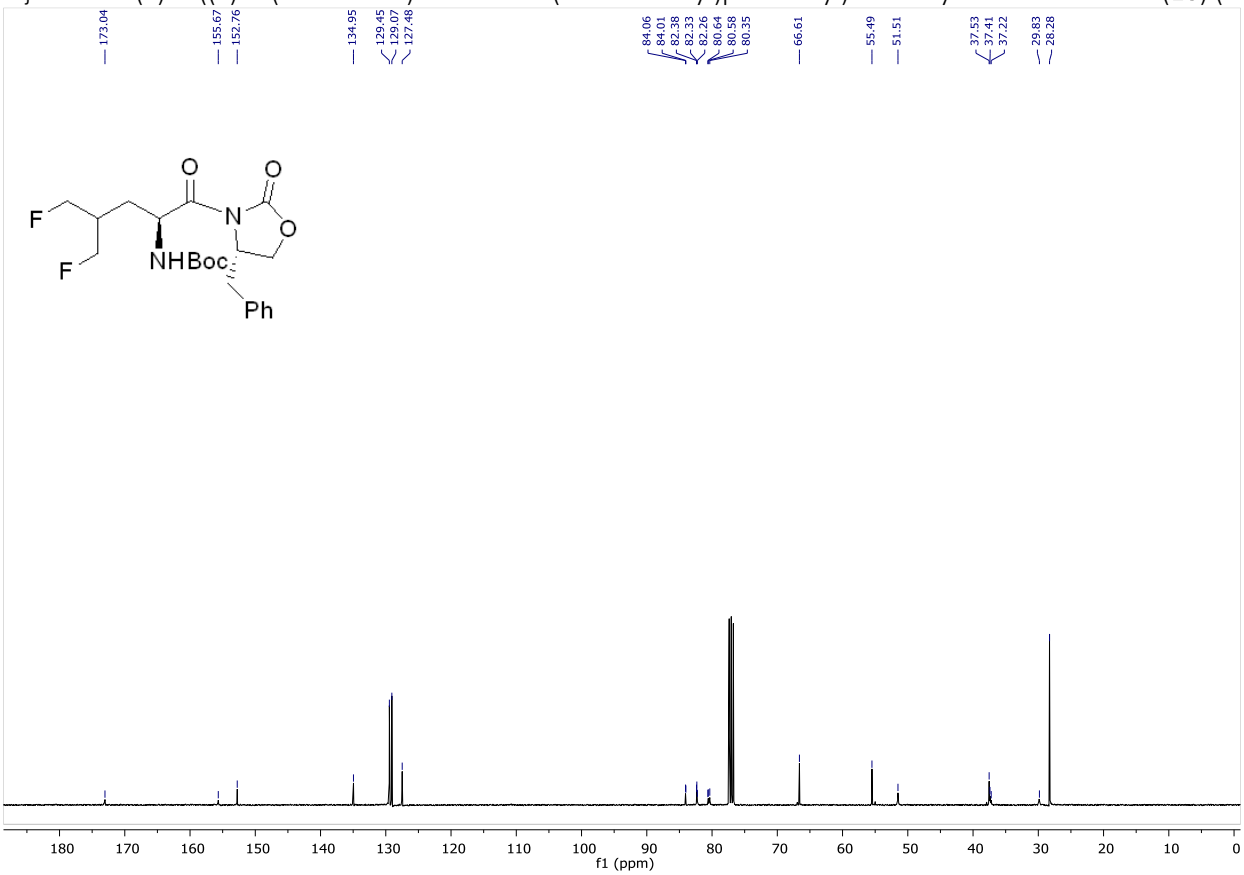
^{1}H NMR of (*S*)-3-((*S*)-2-(Boc-amino)-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**10**) ($CDCl_3$)



^{19}F NMR of (*S*)-3-((*S*)-2-(Boc-amino)-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**10**) ($CDCl_3$)



$^{13}C\{1H\}$ NMR of (*S*)-3-((*S*)-2-(Boc-amino)-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**10**) ($CDCl_3$)



HRMS of (*S*)-3-((*S*)-2-(Boc-amino)-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**10**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

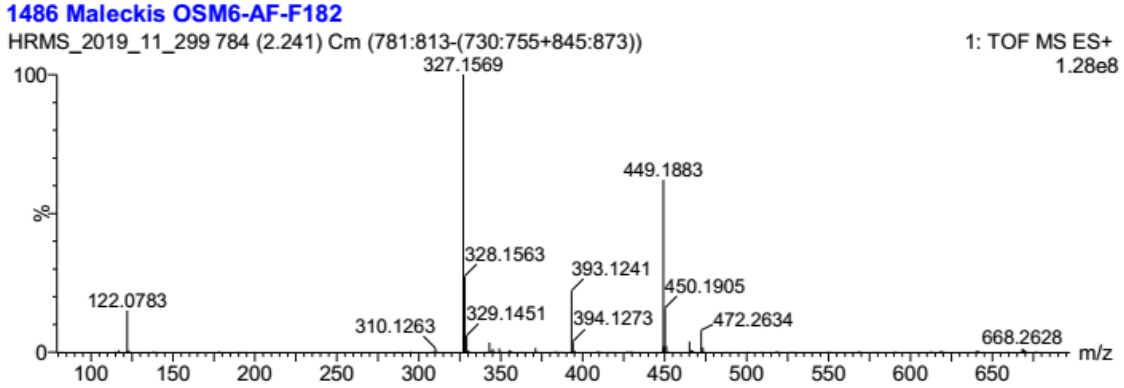
HRMS_2019_11_299	1486 Maleckis OSM6-AF-F182				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	2:F,8	1.000000	MS_Tune	Col#43

Elemental Composition Report:

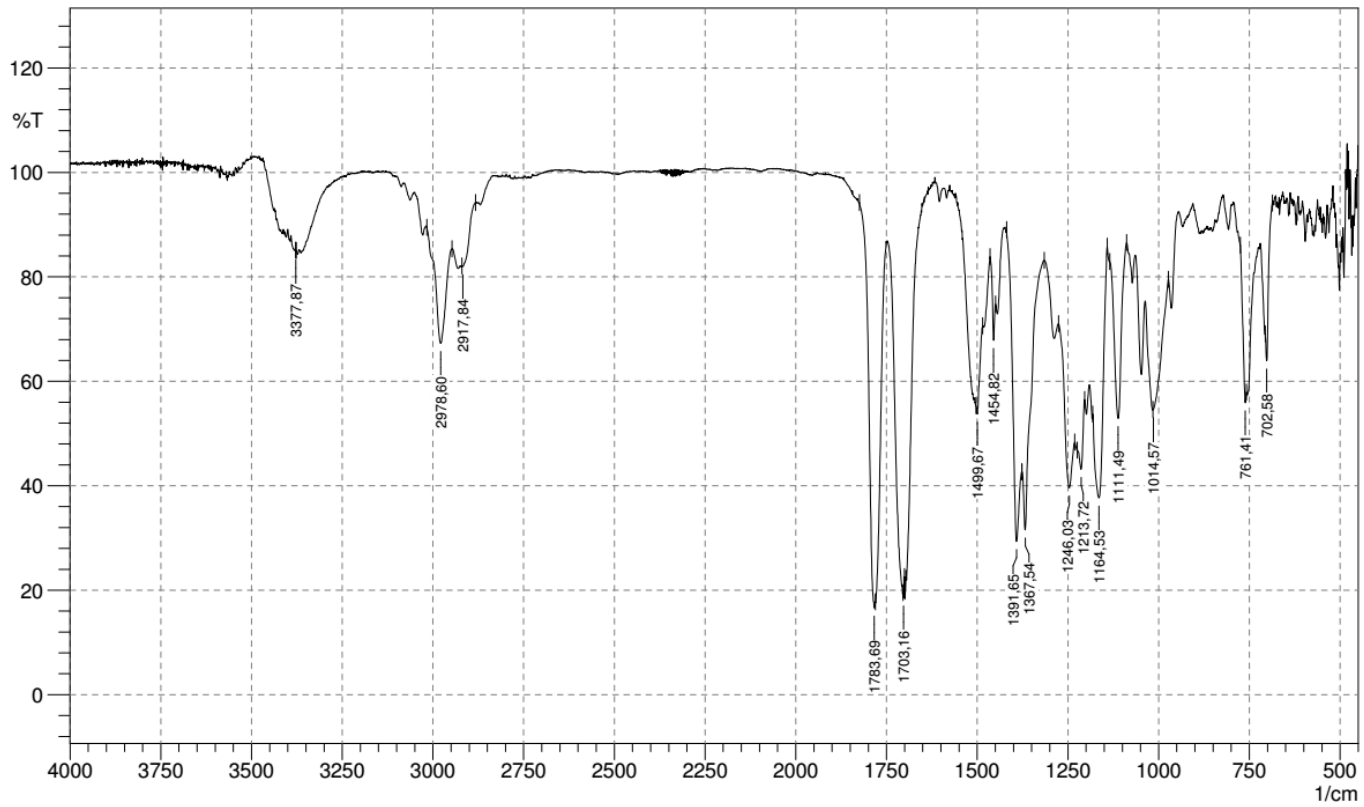
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
361 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 1-10 O: 1-10 F: 2-2 Na: 1-1

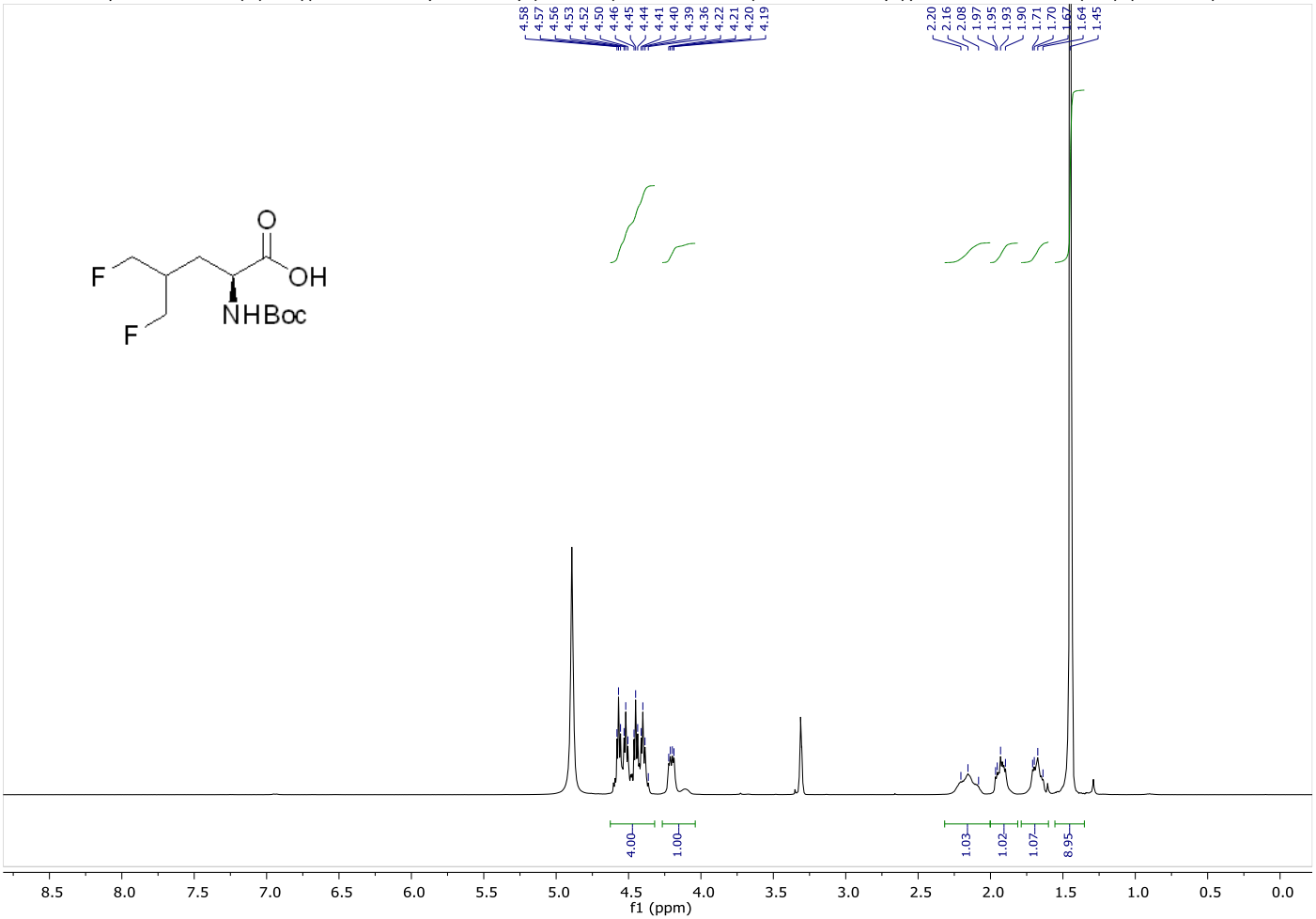
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
449.1883	100.00	449.1864	1.9	4.2	7.5	898.2	4.038	1.76	C21 H28 N2 O5 F2 Na
		449.1877	0.6	1.3	12.5	894.2	0.018	98.22	C22 H24 N6 O F2 Na
		449.1896	-1.3	-2.9	-0.5	902.7	8.577	0.02	C10 H28 N8 O8 F2 Na



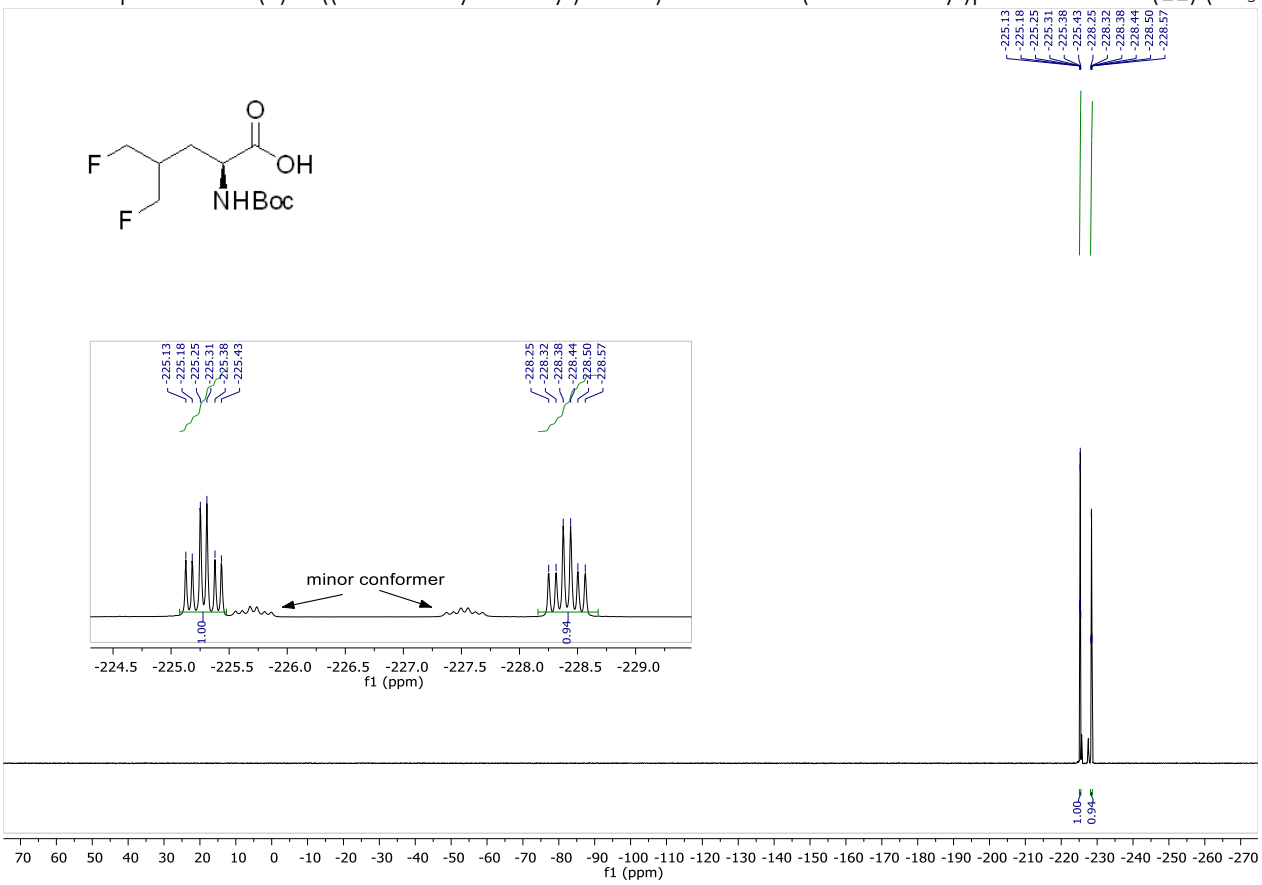
IR(ATR) of (*S*)-3-((*S*)-2-(Boc-amino)-5-fluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**10**)



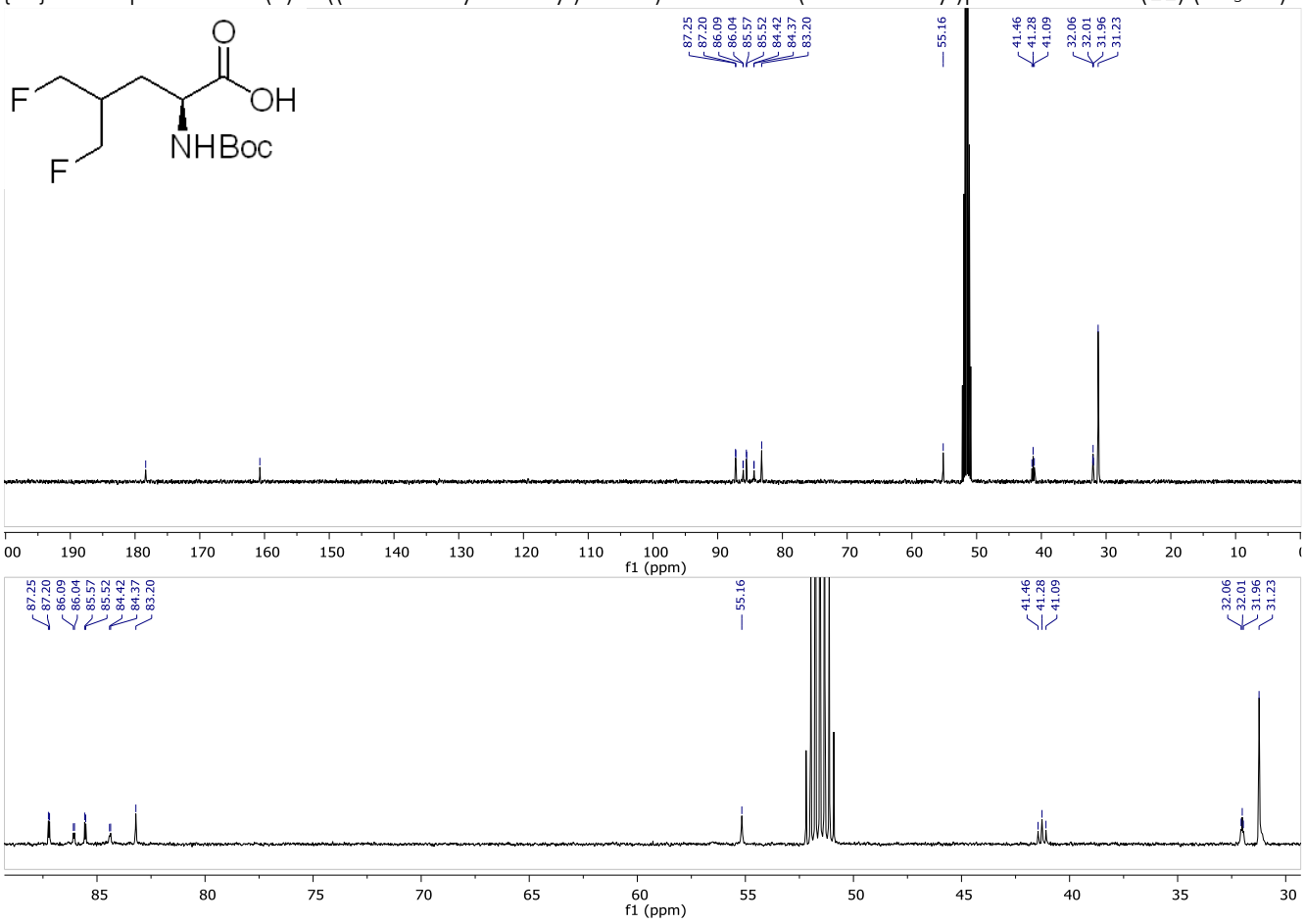
^{1}H NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (**11**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (**11**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (**11**) (CD_3OD)



HRMS of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (**11**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:
HRMS_2019_12_213 1515 Maleckis OSM6-AM-186
MS_NEG_RES_4min ACN_Form_5-98_040_4min 2:E,3 5.000000 MS_Tune Col#43

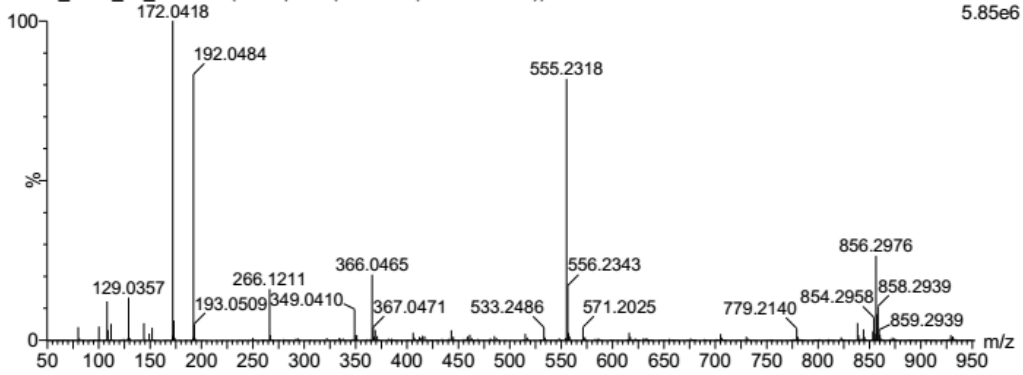
Elemental Composition Report:

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

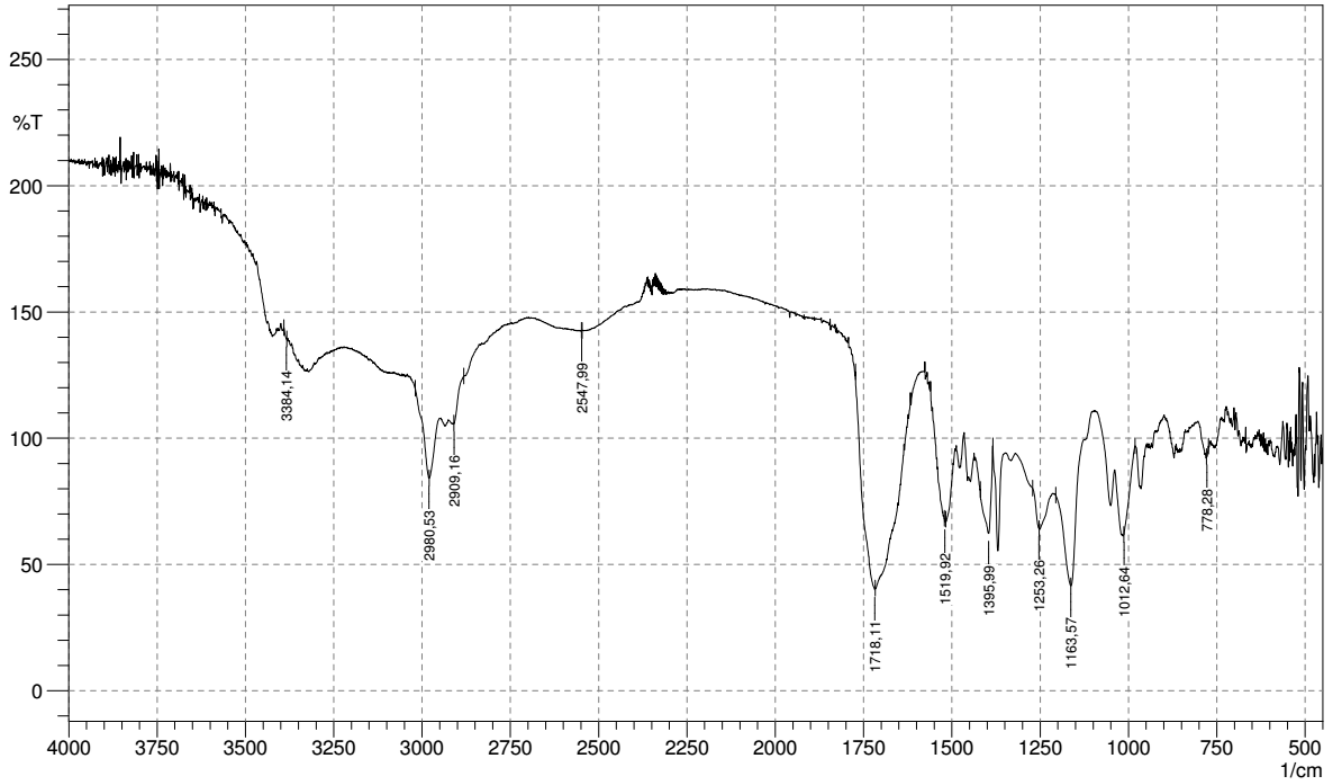
Monoisotopic Mass, Even Electron Ions
157 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-30 H: 1-100 N: 1-10 O: 1-10 F: 2-2

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
266.1211	100.00	266.1204	0.7	2.6	2.5	176.1	n/a	n/a	C11 H18 N O4 F2

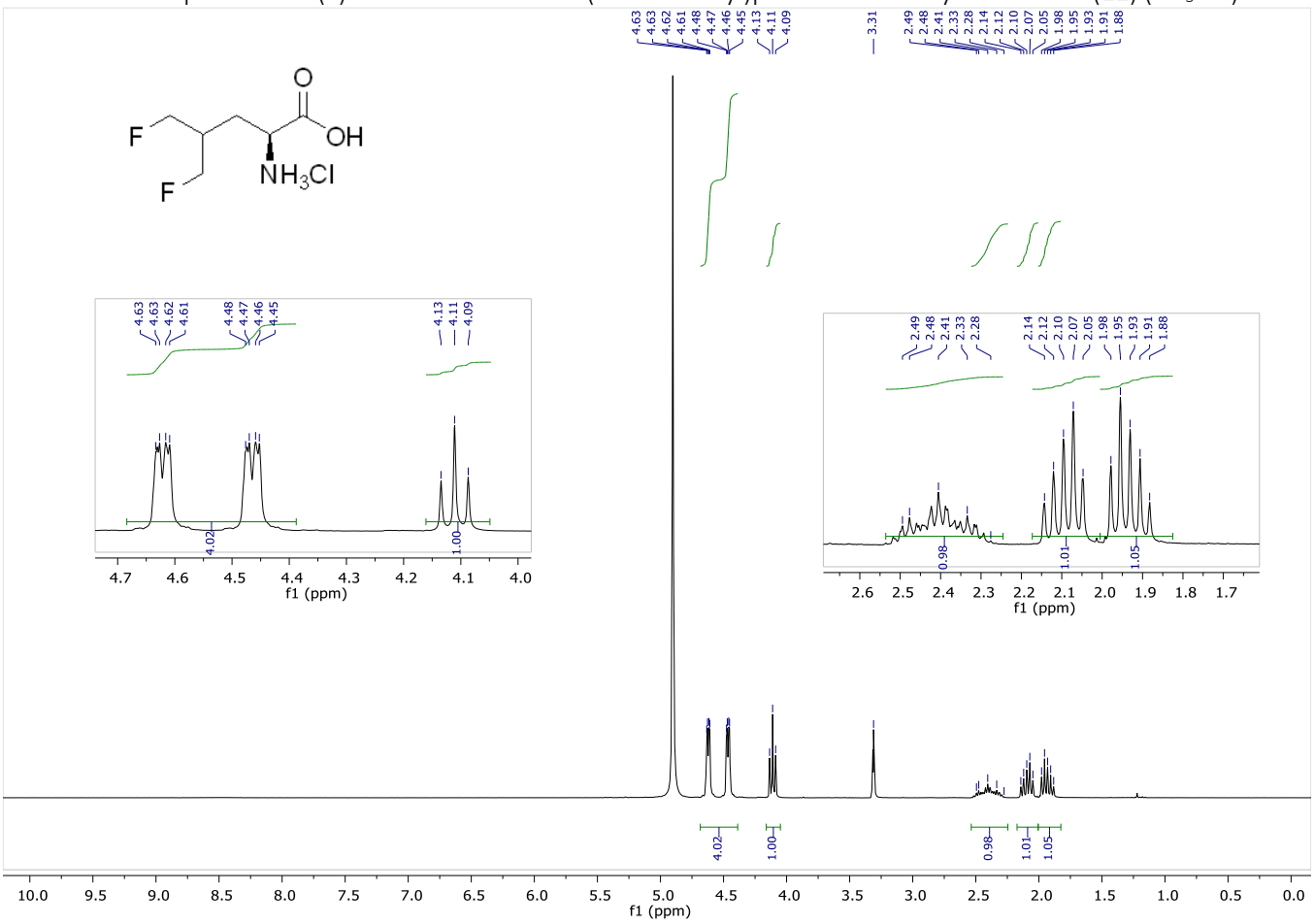
1515 Maleckis OSM6-AM-186
HRMS_2019_12_213 677 (1.904) Cm (677:686-(721+617:645))
1: TOF MS ES-
5.85e6



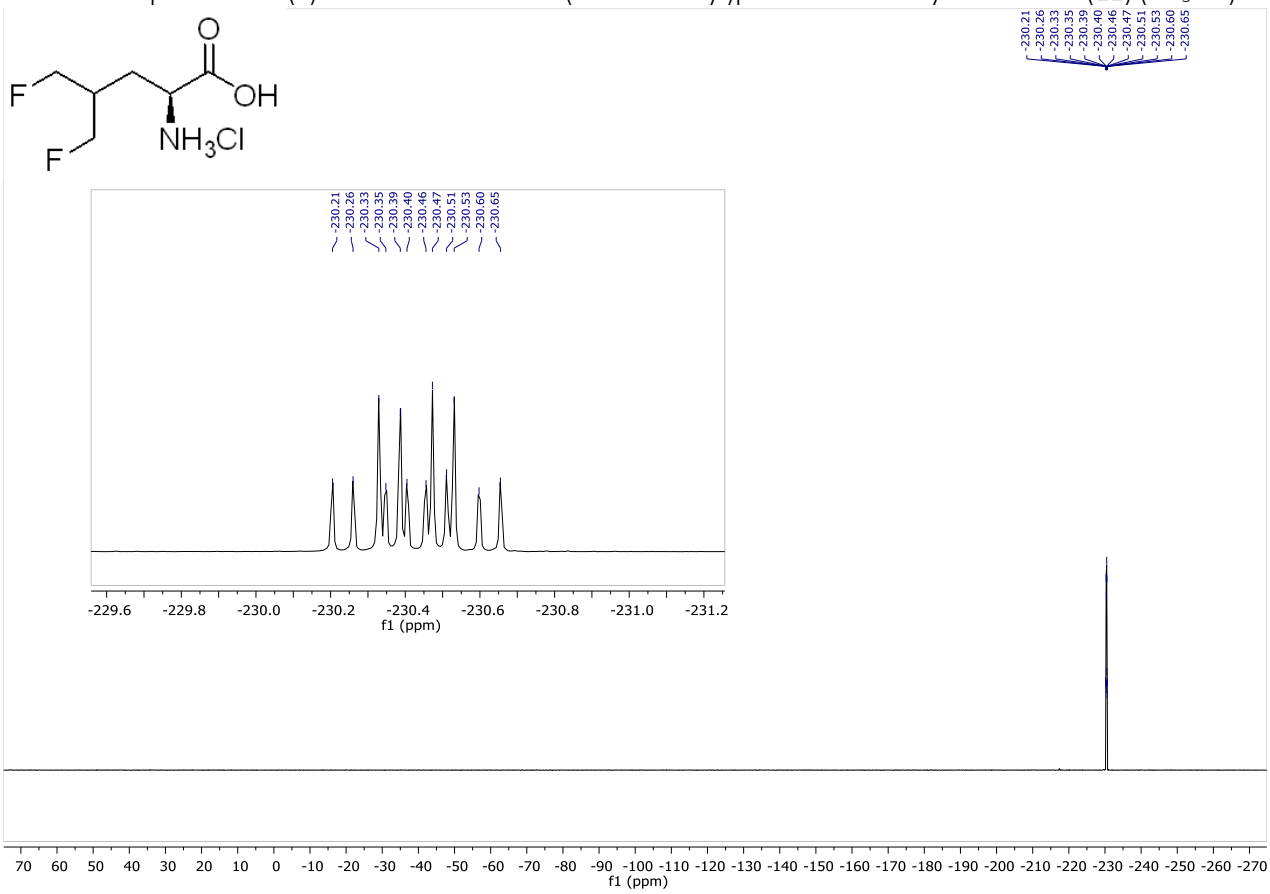
IR(ATR) spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-5-fluoro-4-(fluoromethyl)pentanoic acid (**11**)



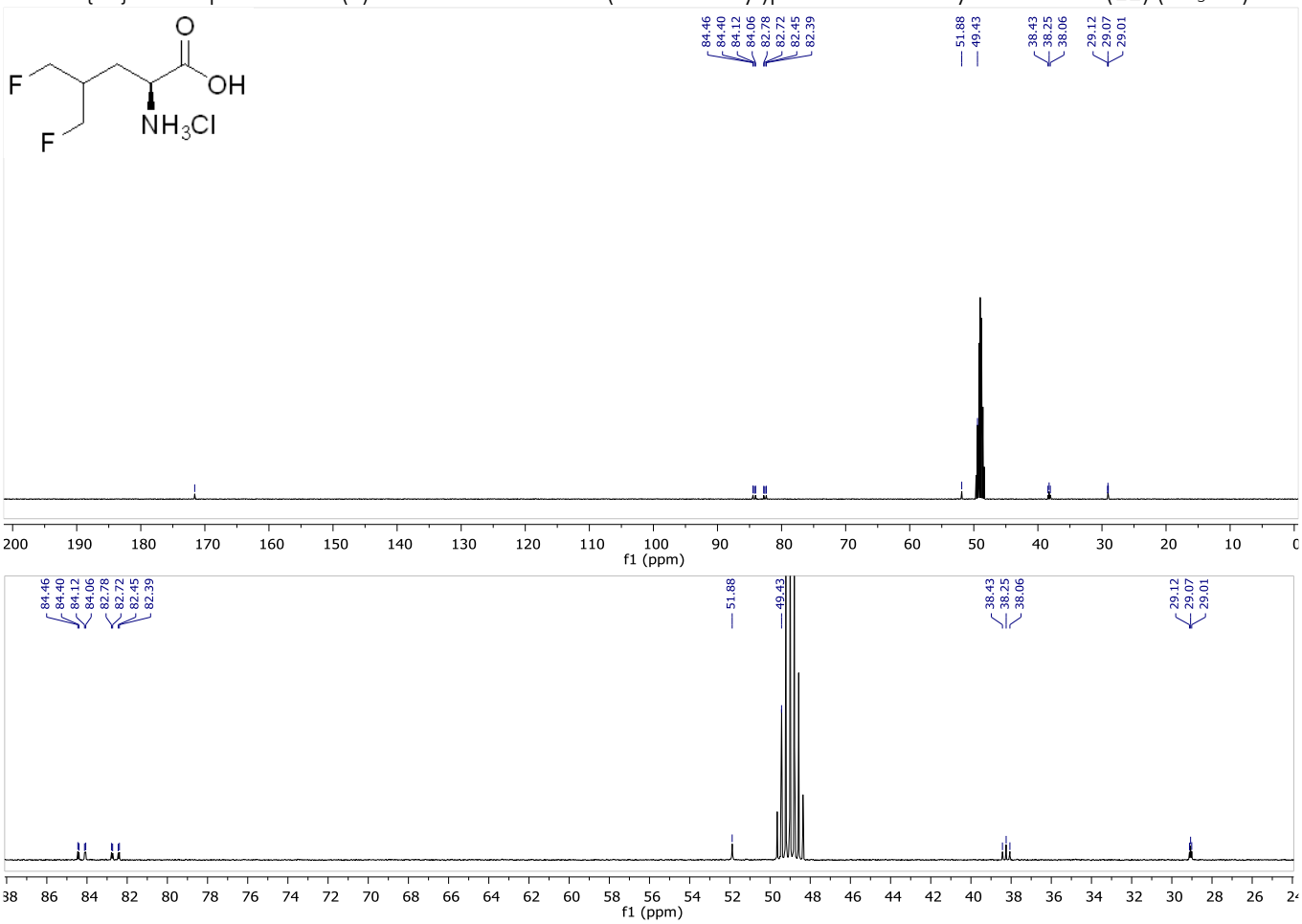
^{1}H NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**12**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**12**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**12**) (CD_3OD)



HRMS of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**12**) (CD_3OD)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

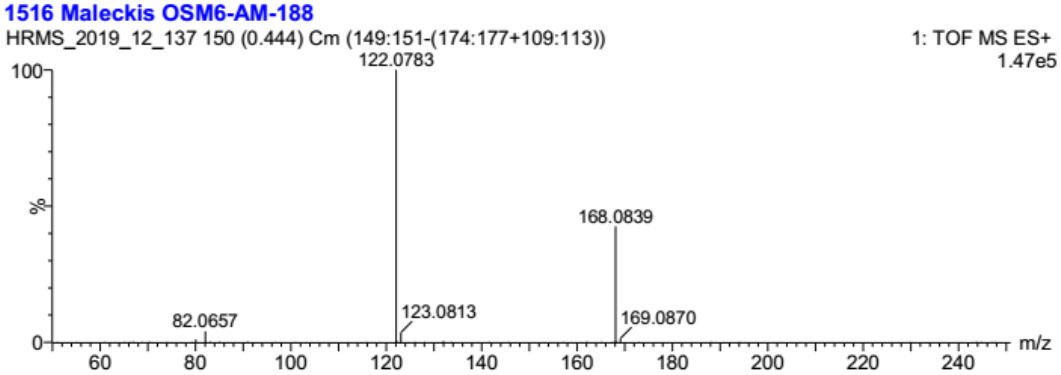
HRMS_2019_12_137 1516 Maleckis OSM6-AM-188
MS_POS_RES_4min ACN_Form_5-98_040_4min 2:E,4 5.000000 MS_Tune Col#43

Elemental Composition Report:

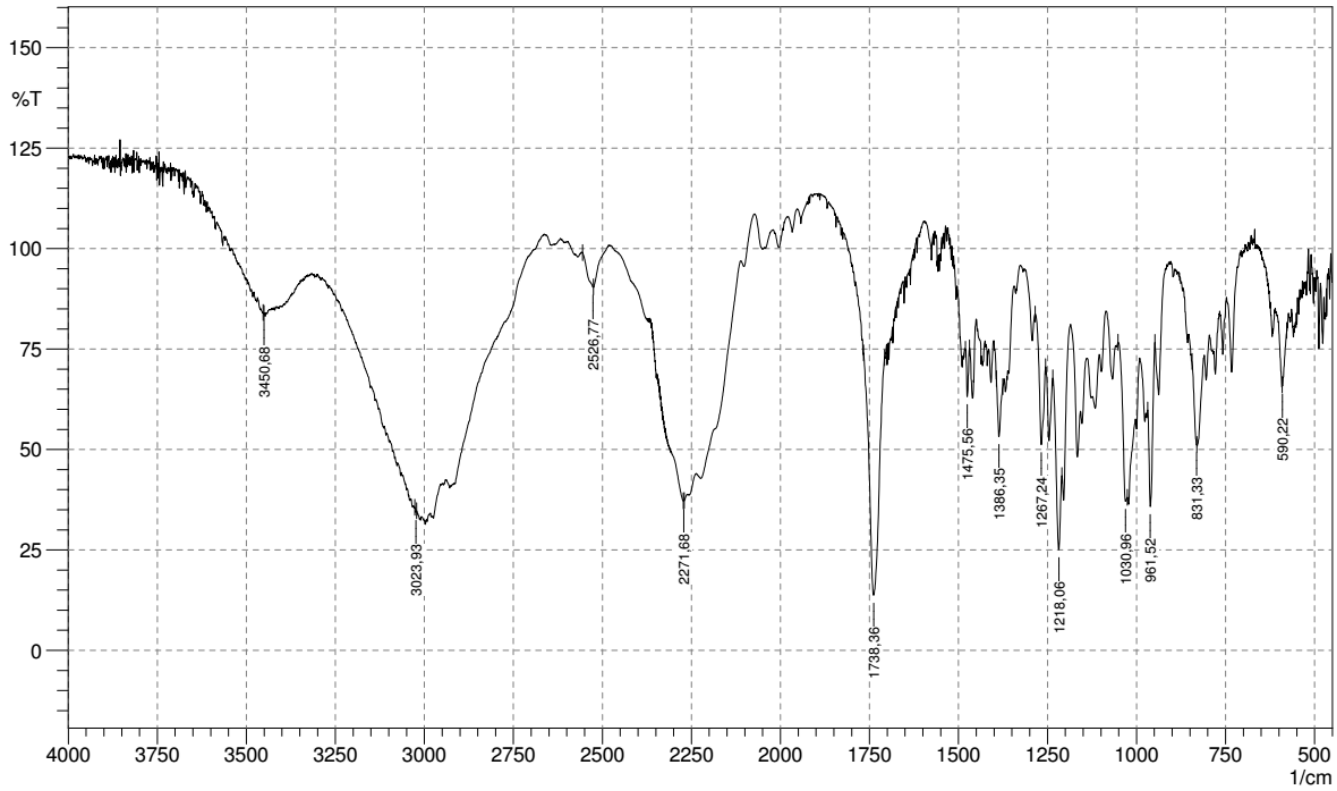
Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
35 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-60 N: 1-10 O: 1-10 F: 2-2

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
168.0839	168.0836	0.3	1.8	0.5	96.0	n/a	n/a	C6 H12 N O2 F2

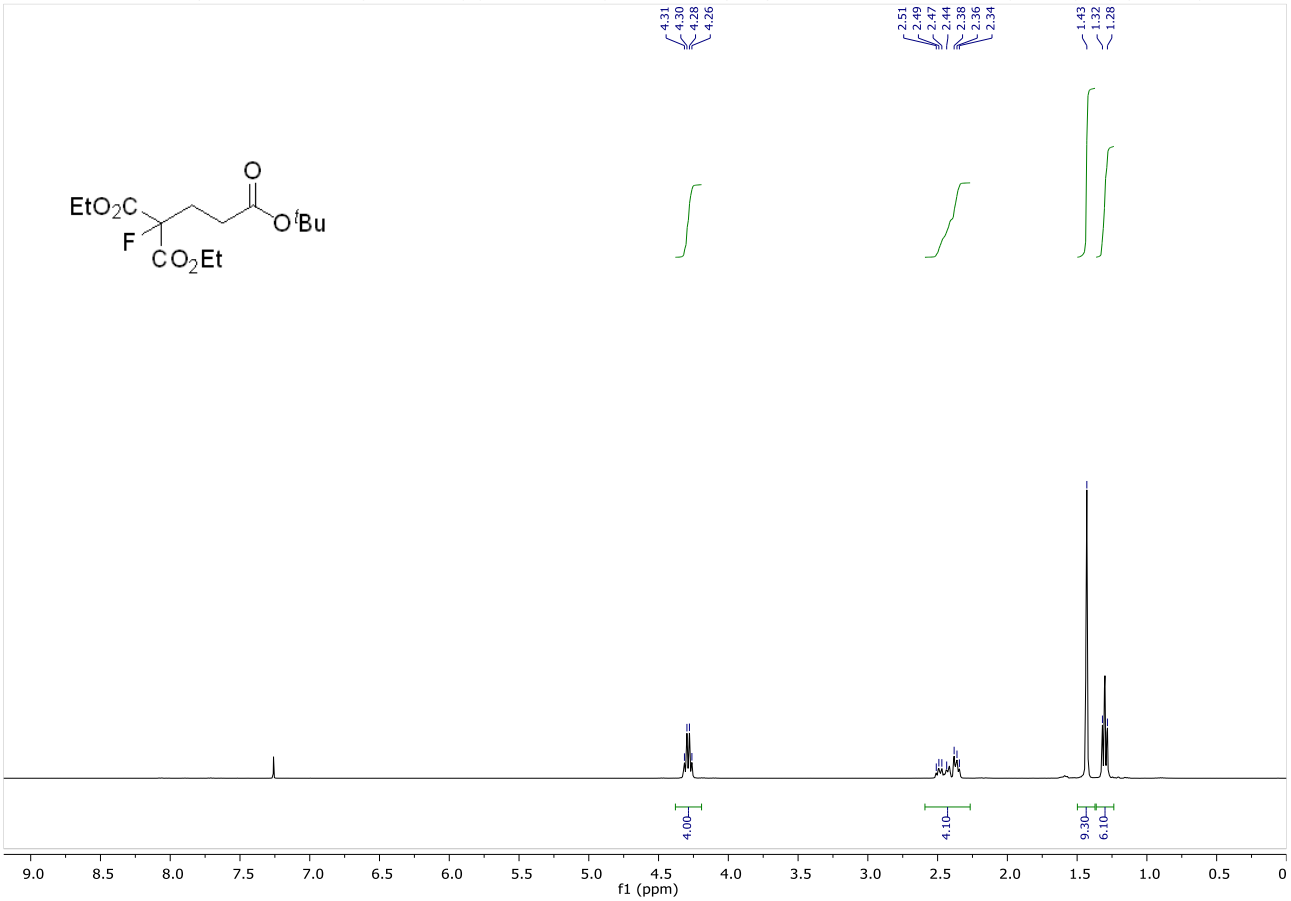


IR(ATR) spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**12**) (CD_3OD)

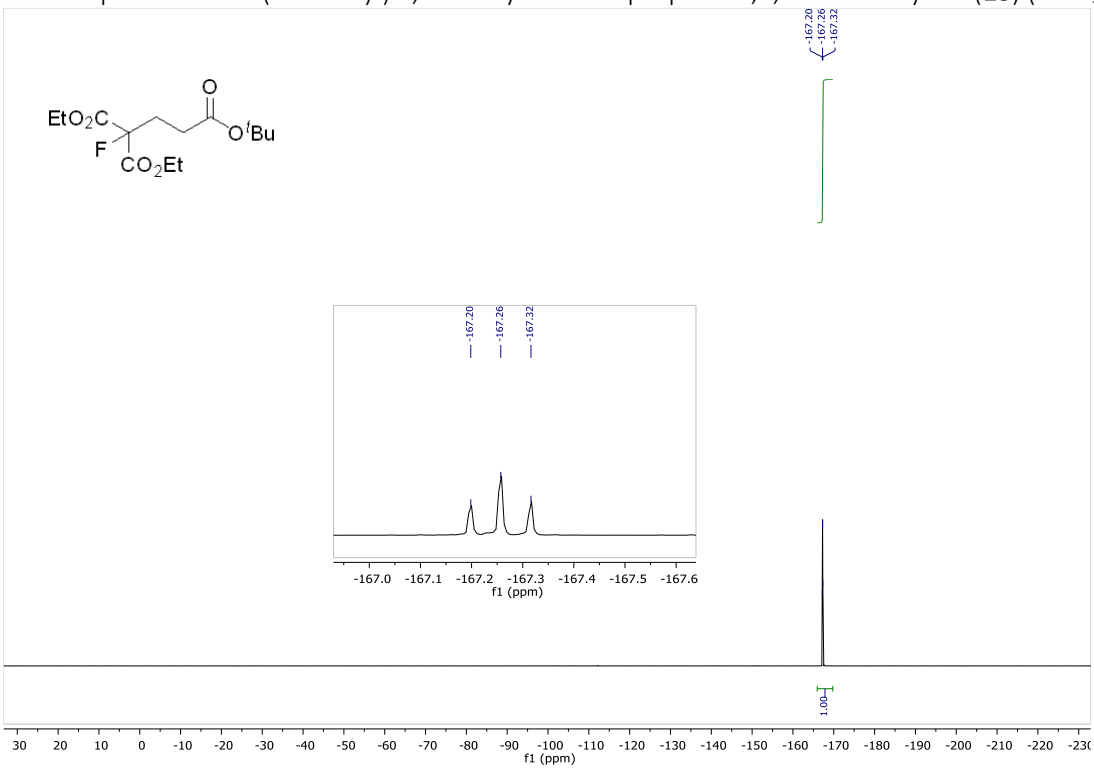


Spectra of compounds in Scheme 2

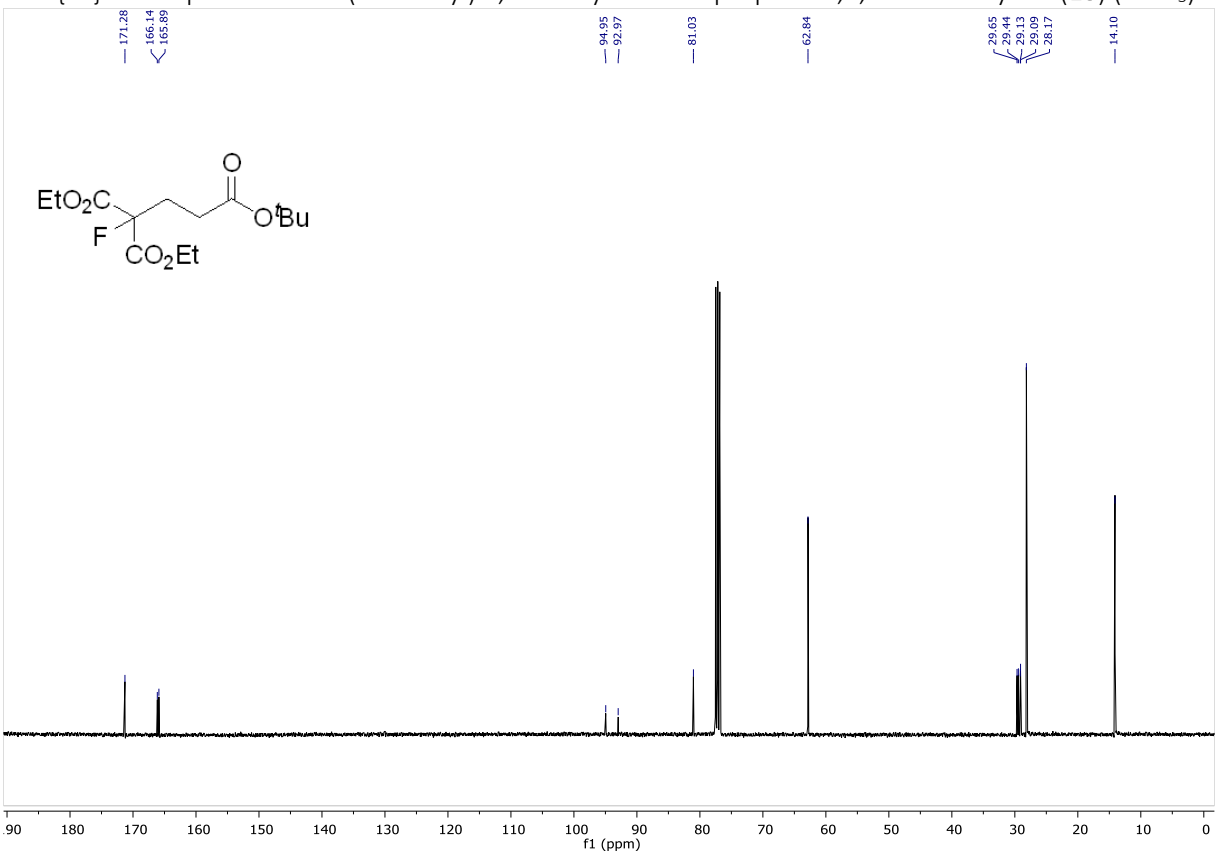
^{1}H NMR spectrum of 3-(*tert*-butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (**13**) ($CDCl_3$)



^{19}F NMR spectrum of 3-(*tert*-butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (**13**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 3-(*tert*-butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (**13**) ($CDCl_3$)



HRMS of 3-(*tert*-butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (**13**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2019_11_293	1483 Maleckis OSM6-AF-ASF				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	2:F,5	1.000000	MS_Tune	Col#43

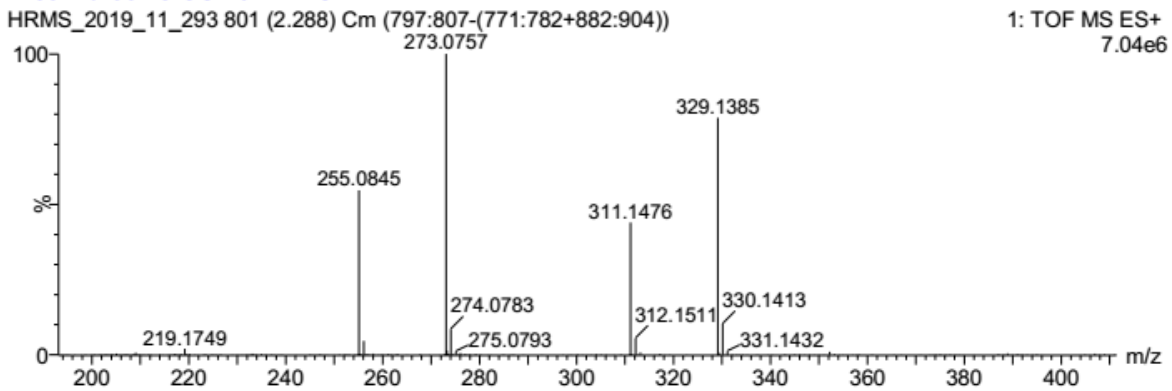
Elemental Composition Report:

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

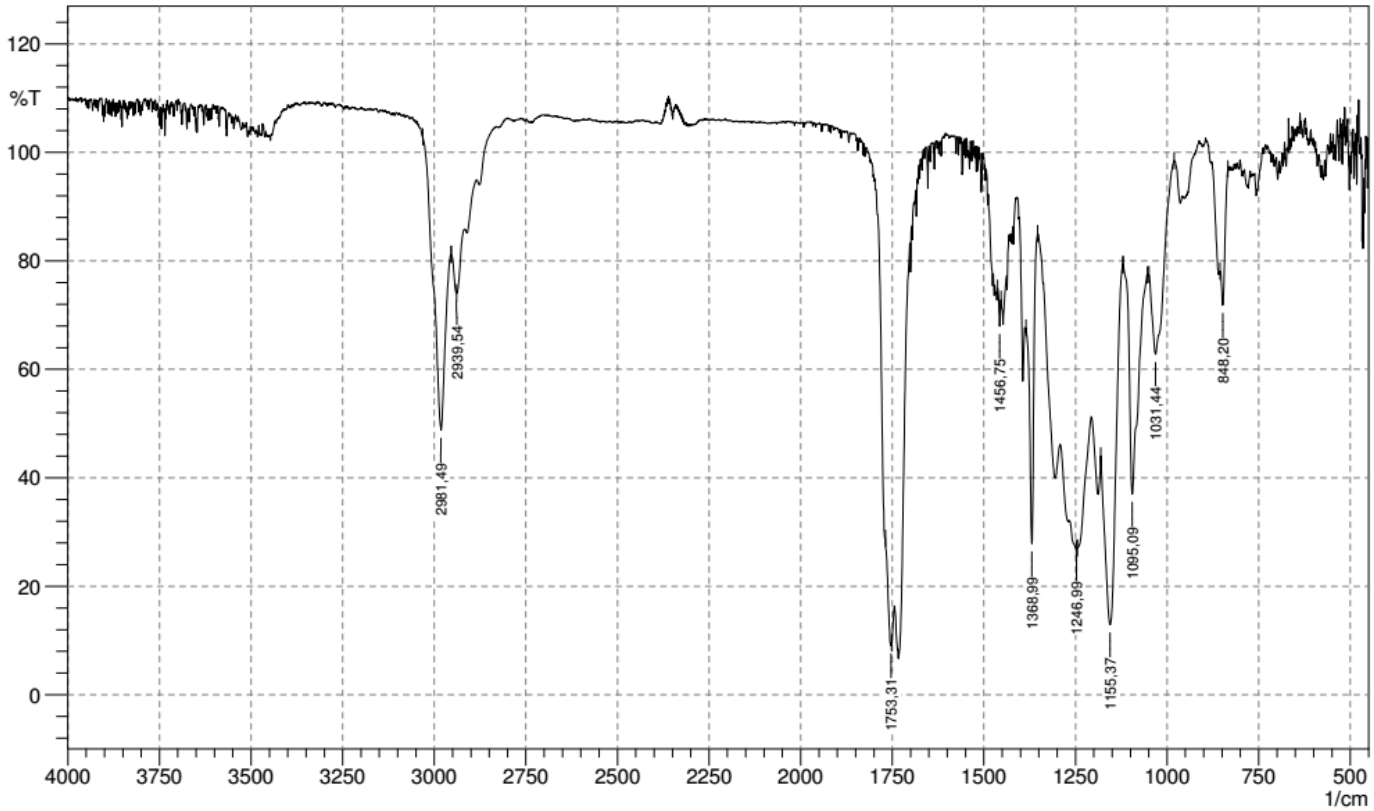
Monoisotopic Mass, Even Electron Ions
30 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 O: 1-10 F: 1-1 Na: 1-1

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
329.1385	100.00	329.1376	0.9	2.7	2.5	183.5	n/a	n/a	C14 H23 O6 F Na

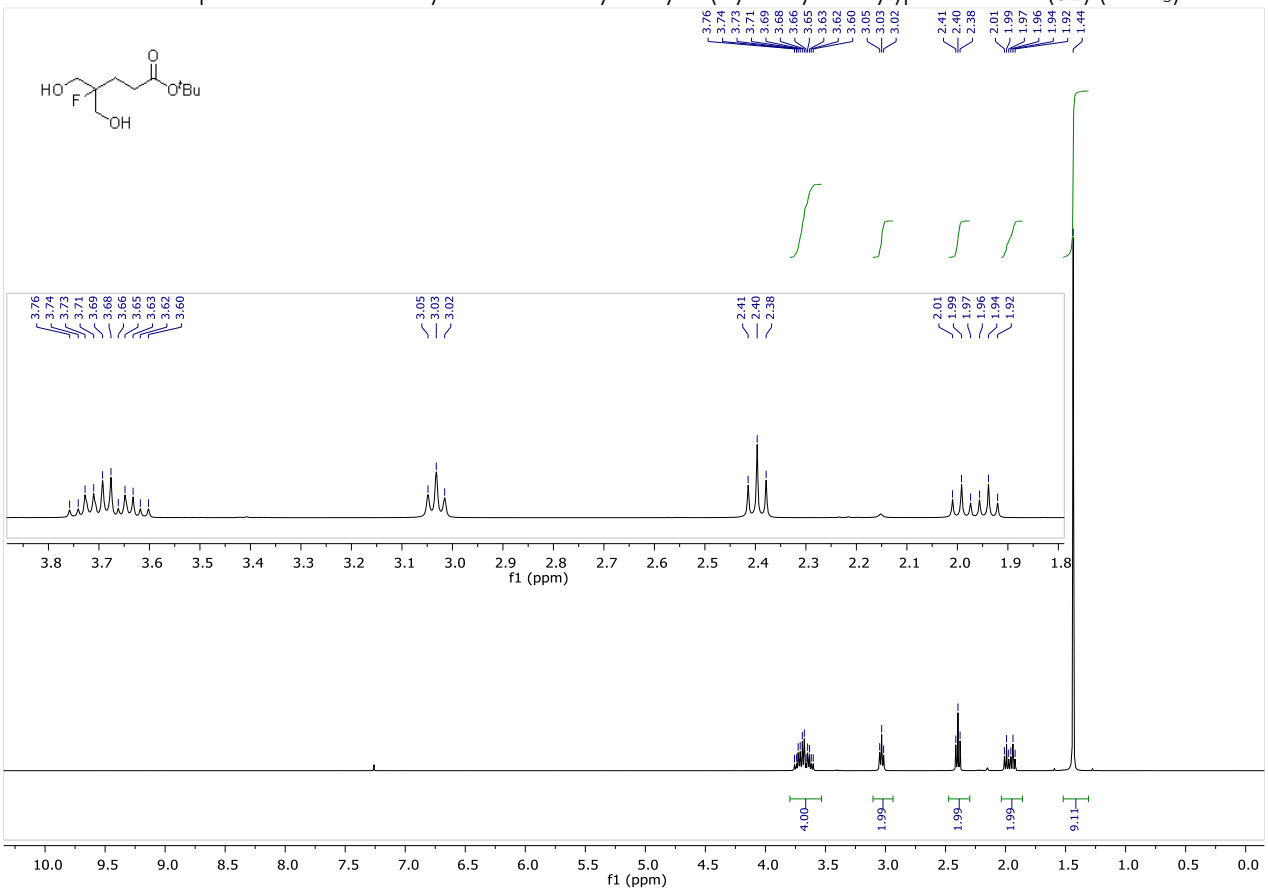
1483 Maleckis OSM6-AF-ASF



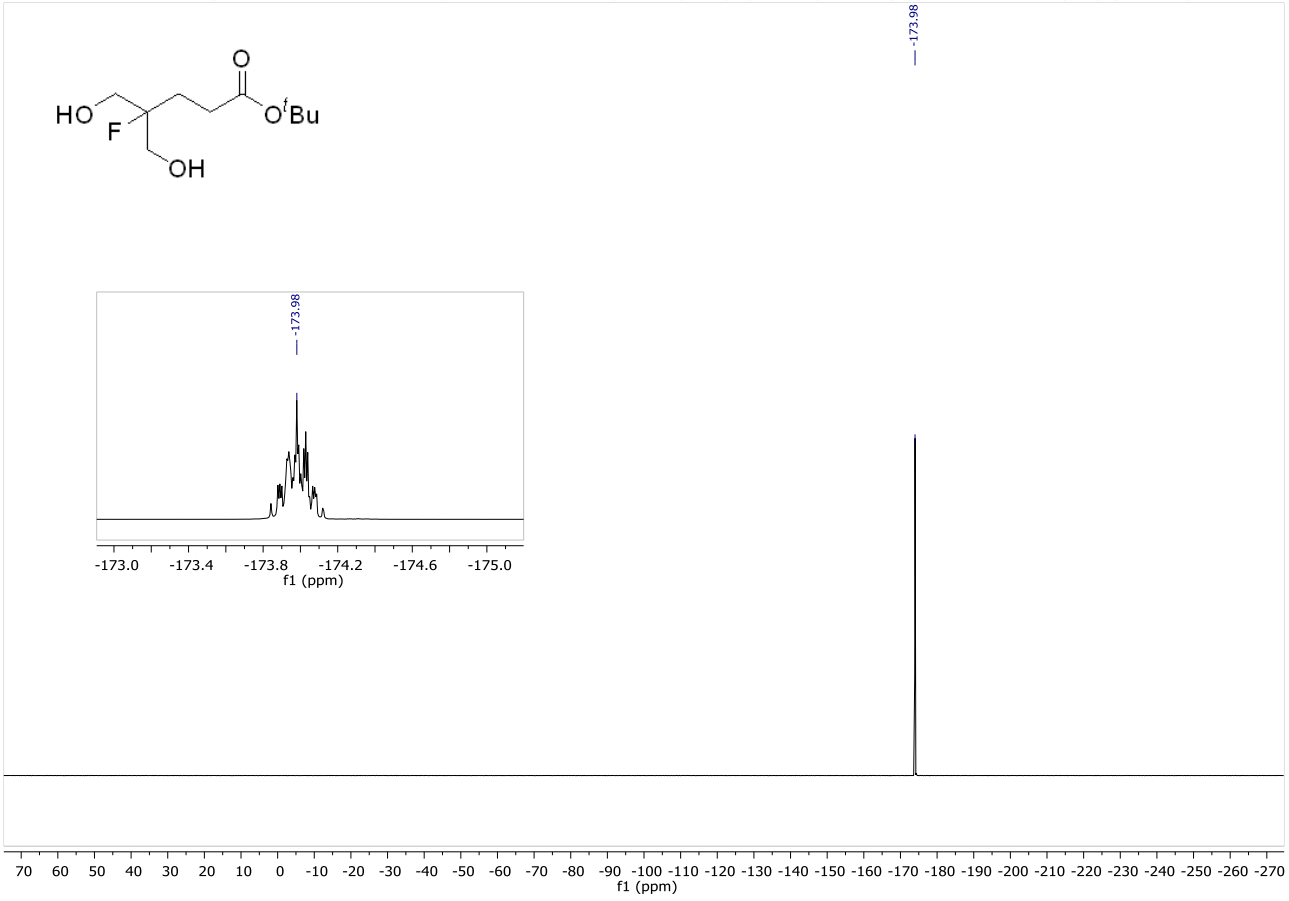
IR(ATR) spectrum of 3-(*tert*-butyl) 1,1-diethyl-1-fluoropropane-1,1,3-tricarboxylate (**13**)



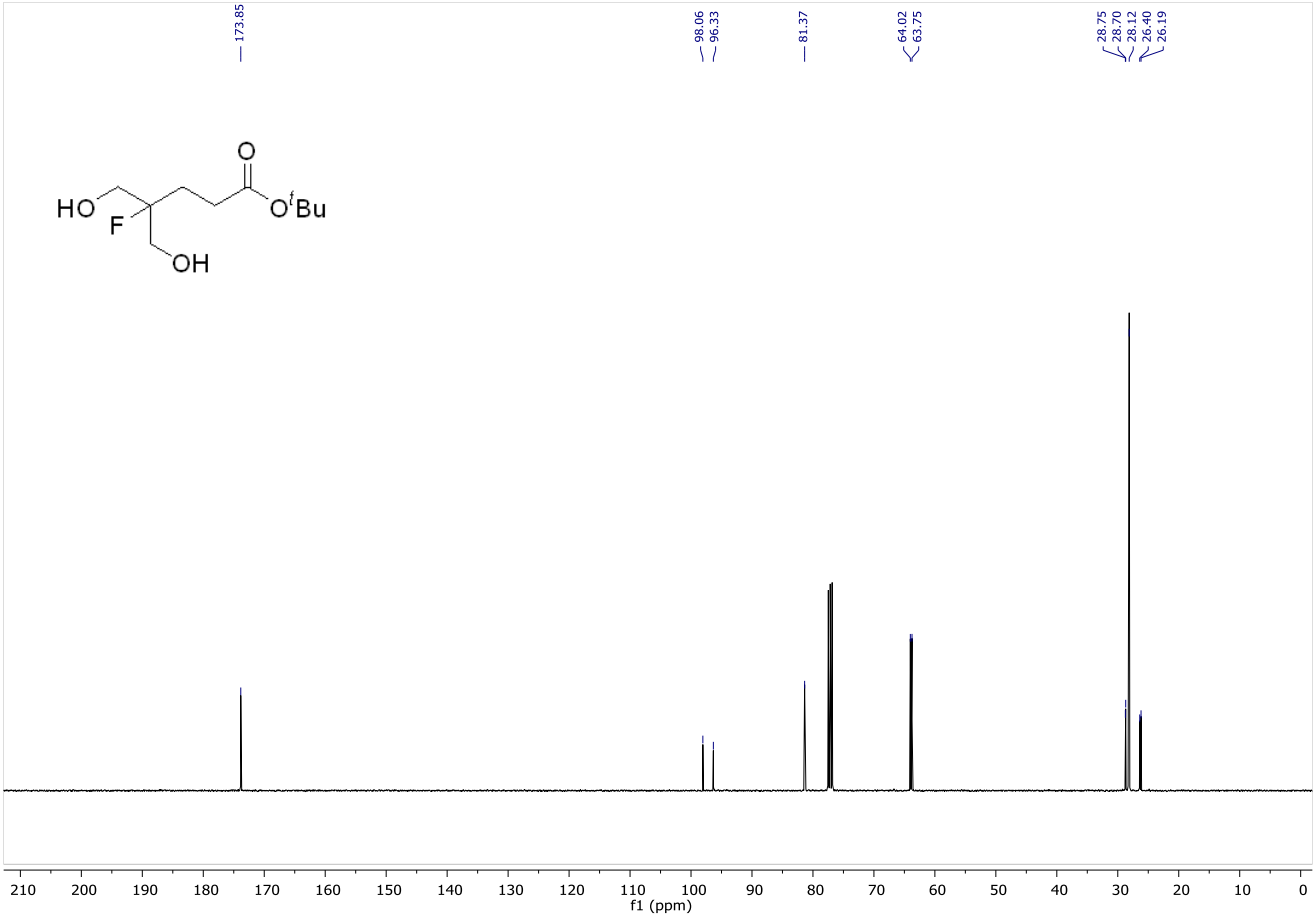
^{1}H NMR spectrum of *tert*-butyl 4-fluoro-5-hydroxy-4-(hydroxymethyl)pentanoate (**S1**) ($CDCl_3$)



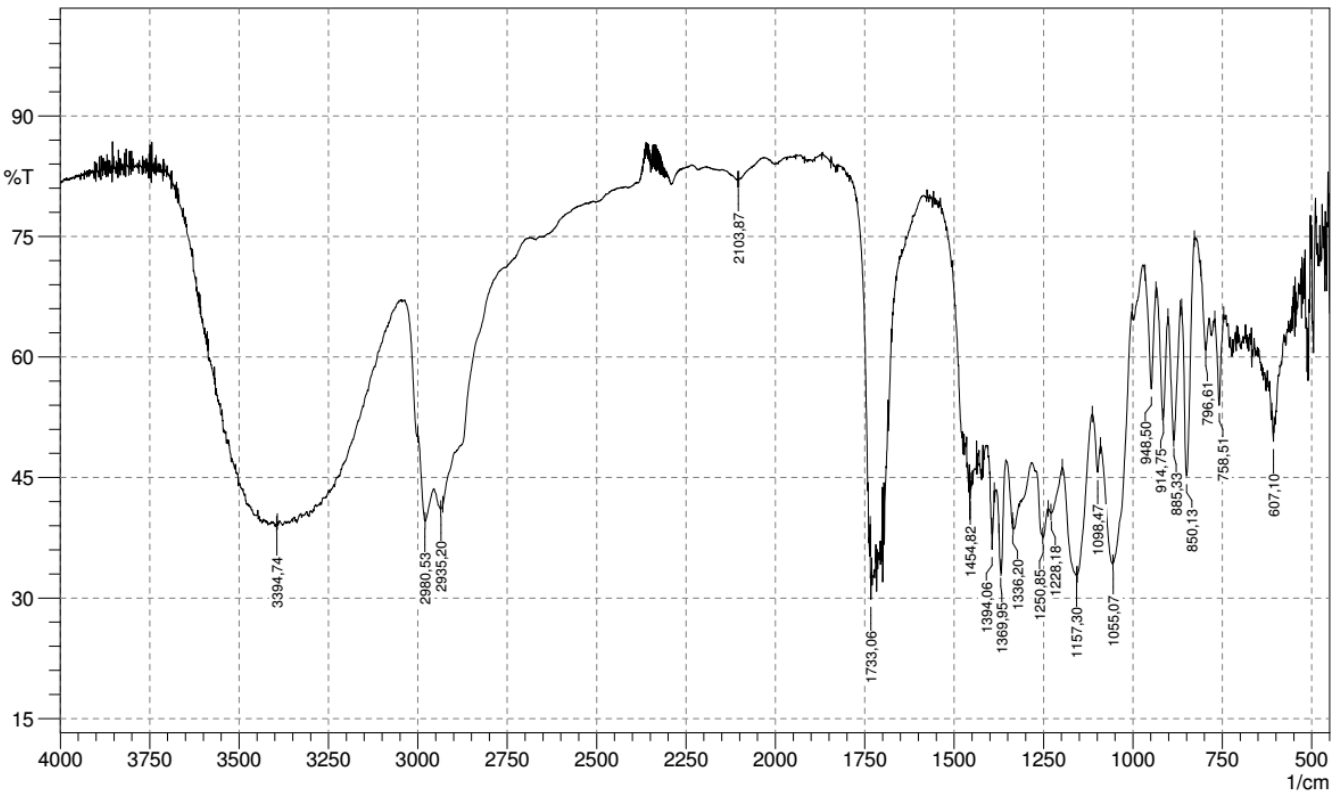
^{19}F NMR spectrum of *tert*-butyl 4-fluoro-5-hydroxy-4-(hydroxymethyl)pentanoate (**S1**) ($CDCl_3$)



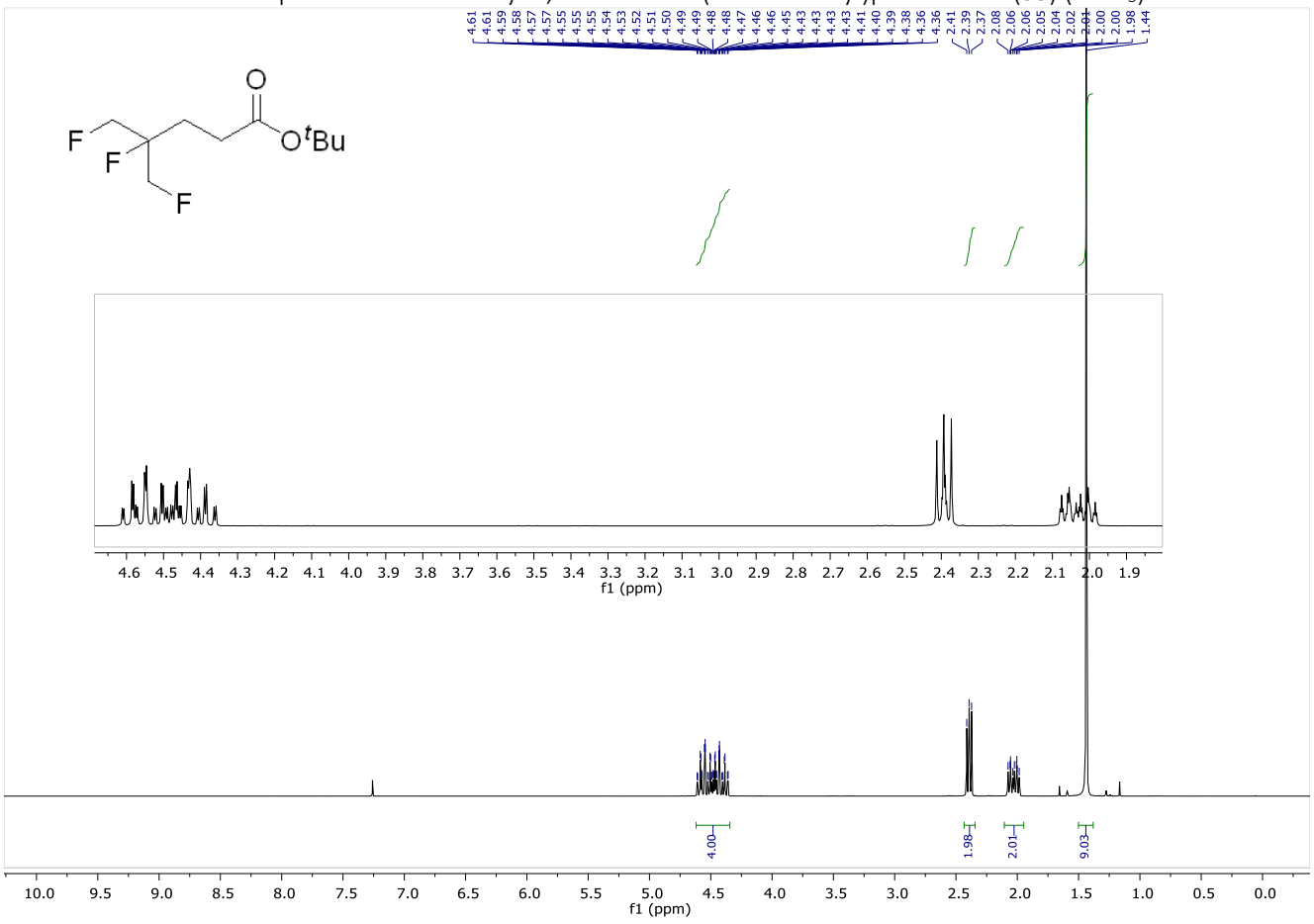
$^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl 4-fluoro-5-hydroxy-4-(hydroxymethyl)pentanoate (**S1**) ($CDCl_3$)



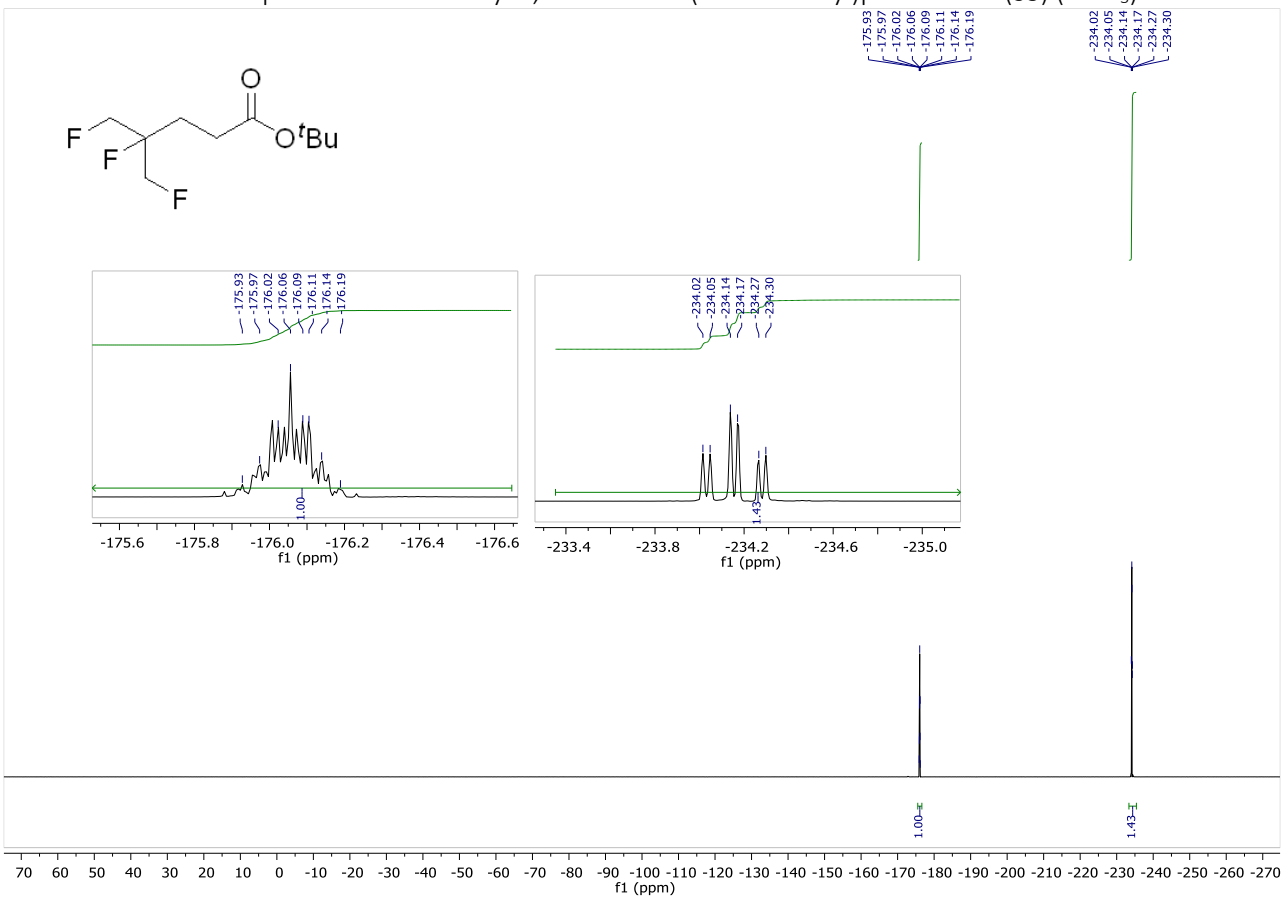
IR(ATR) spectrum of *tert*-butyl 4-fluoro-5-hydroxy-4-(hydroxymethyl)pentanoate (**S1**)



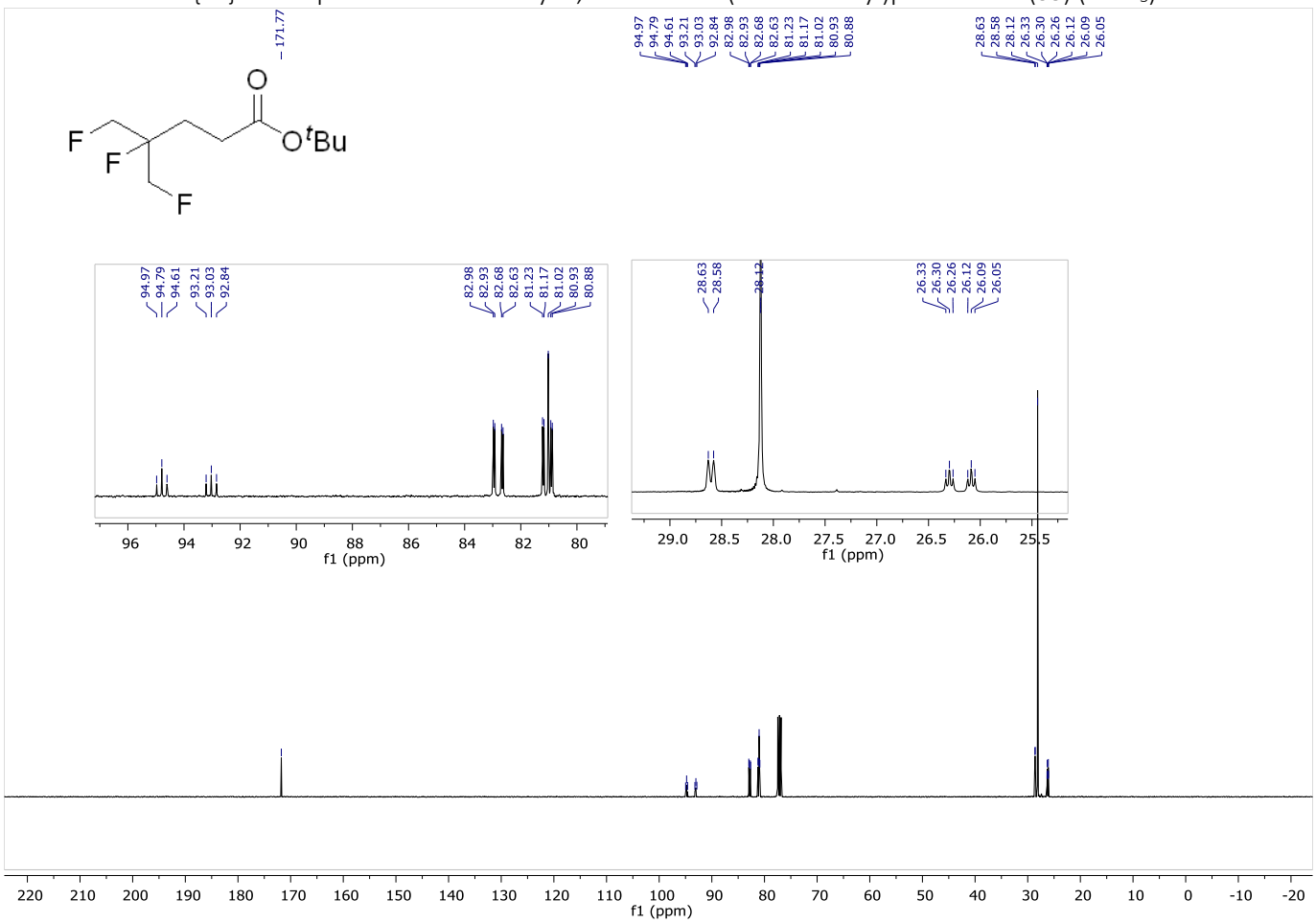
^{1}H NMR spectrum of *tert*-butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (**S3**) ($CDCl_3$)



^{19}F NMR spectrum of *tert*-butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (**S3**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (**S3**) ($CDCl_3$)



HRMS of *tert*-butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (**S3**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	4.0	**LC: Acquity UPLC H-Class**	Column:	-
ESI+	Cone, V:	40			

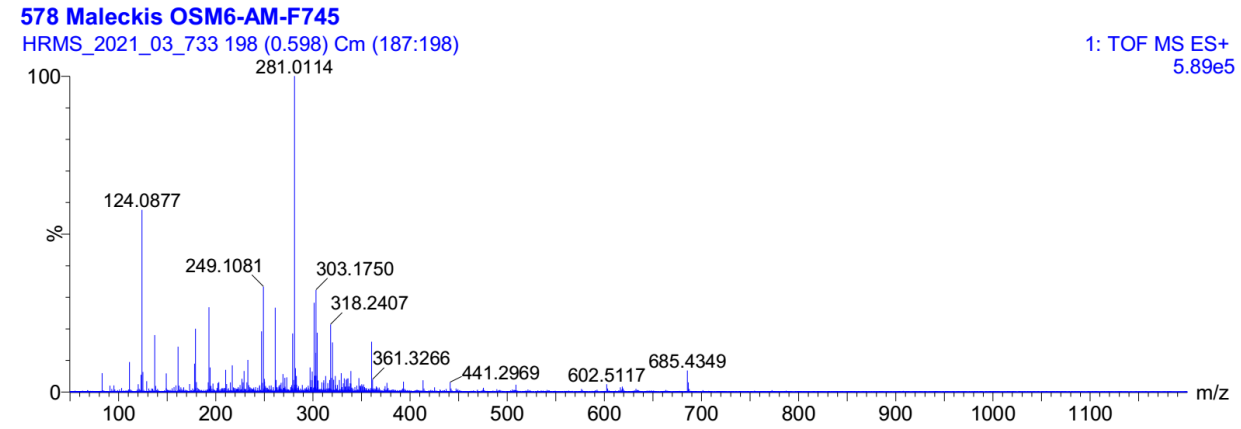
Sample:
HRMS_2021_03_733 578 Maleckis OSM6-AM-F745
MS_POS_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune_4kV

Elemental Composition Report:

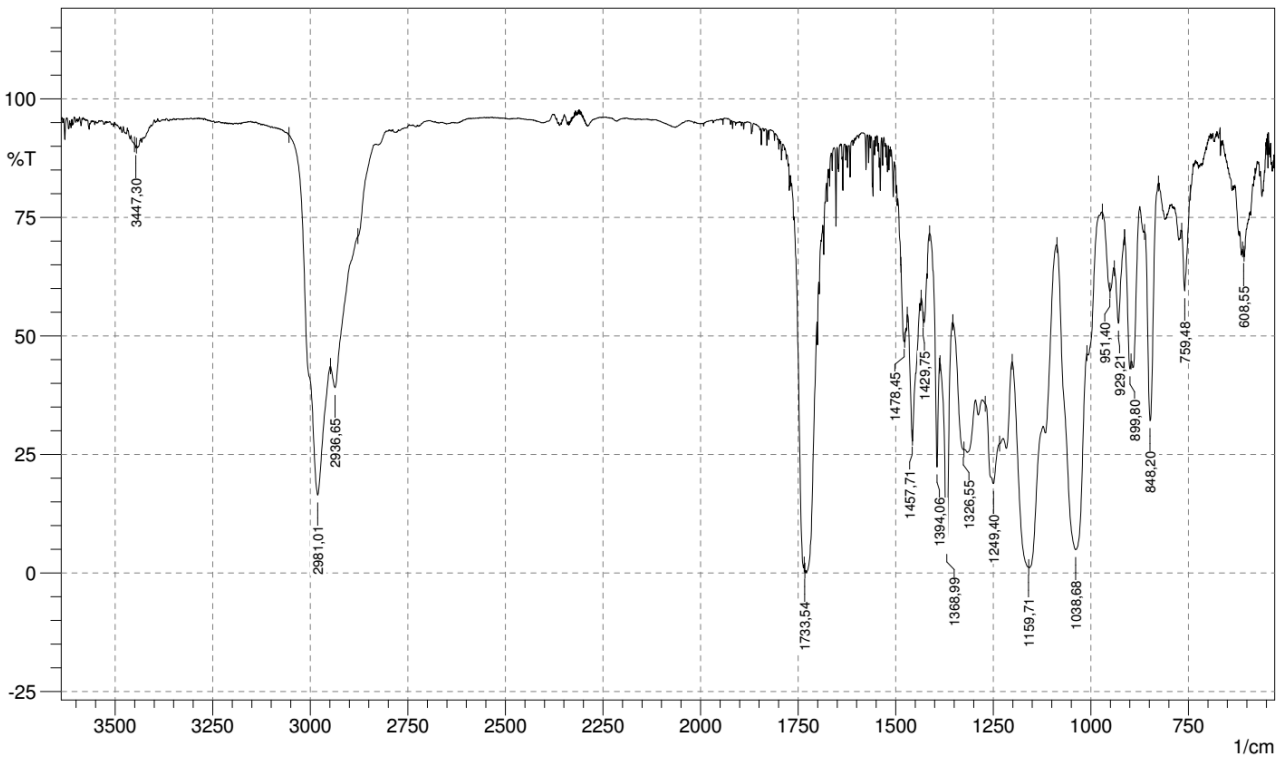
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
132 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-20 O: 0-20 F: 3-3 Na: 1-1

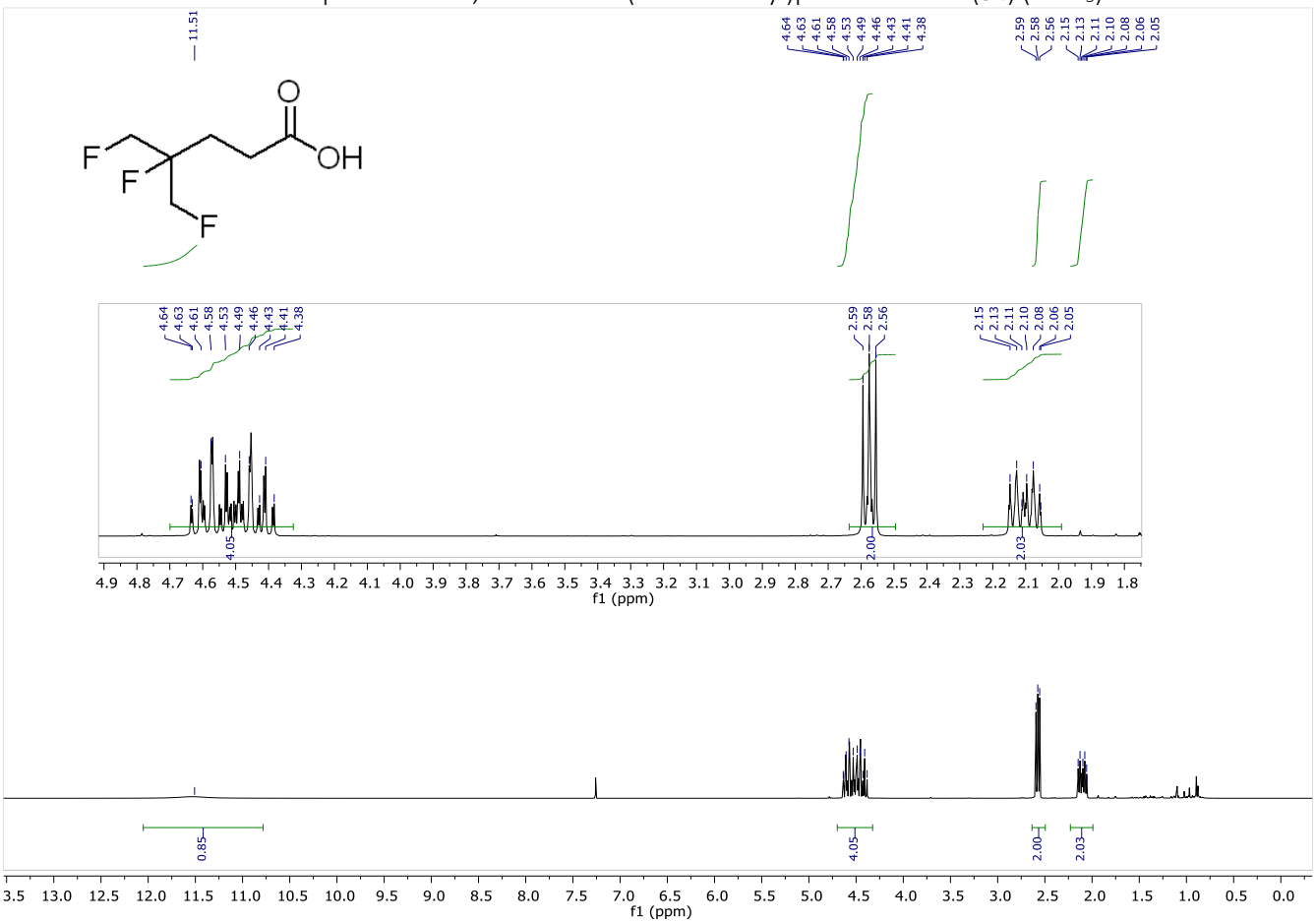
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
249.1081	100.00	249.1078	0.3	1.2	0.5	1092.3	n/a	n/a	C10 H17 O2 F3 Na



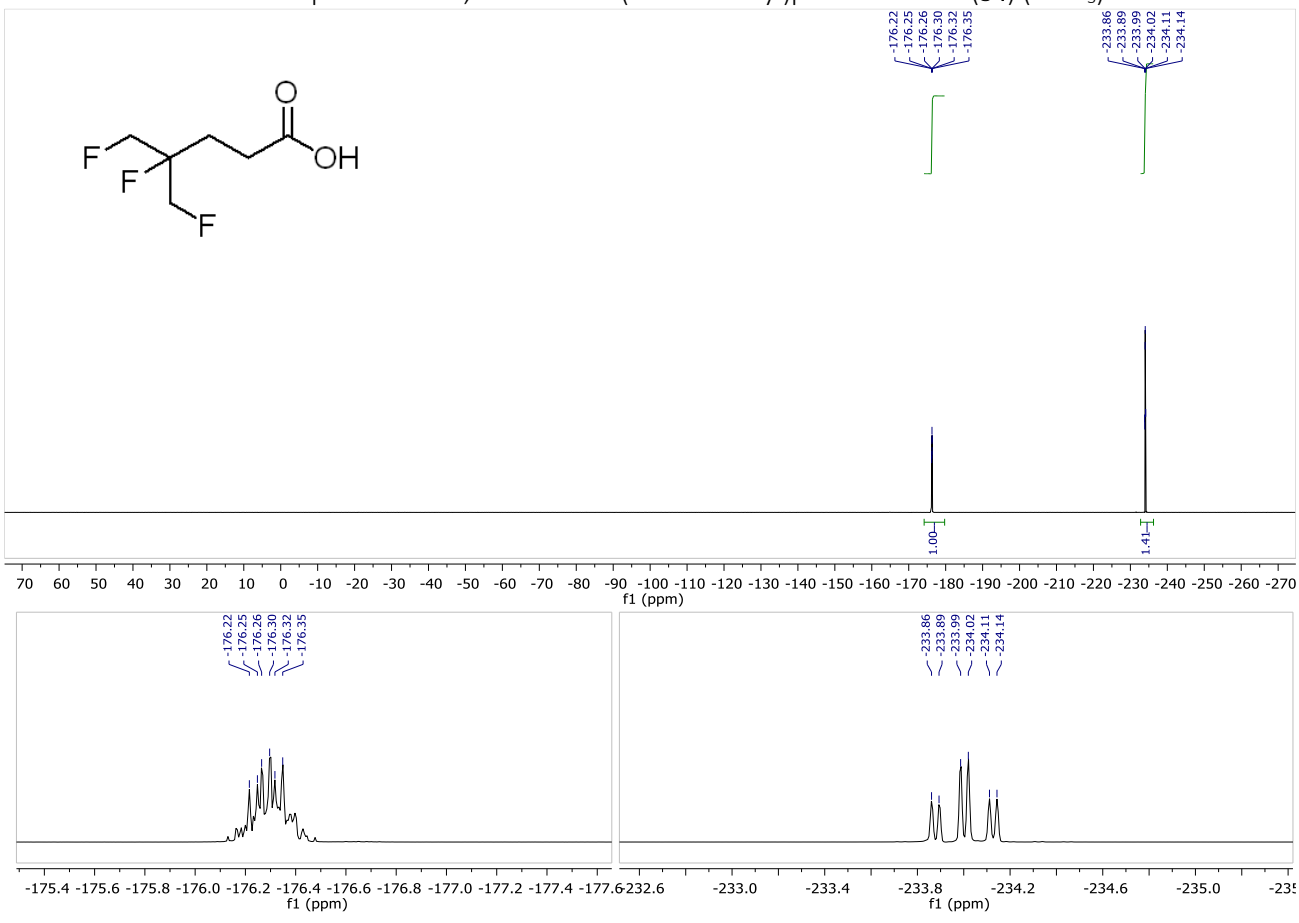
IR(ATR) spectrum of *tert*-butyl 4,5-difluoro-4-(fluoromethyl)pentanoate (**S3**)



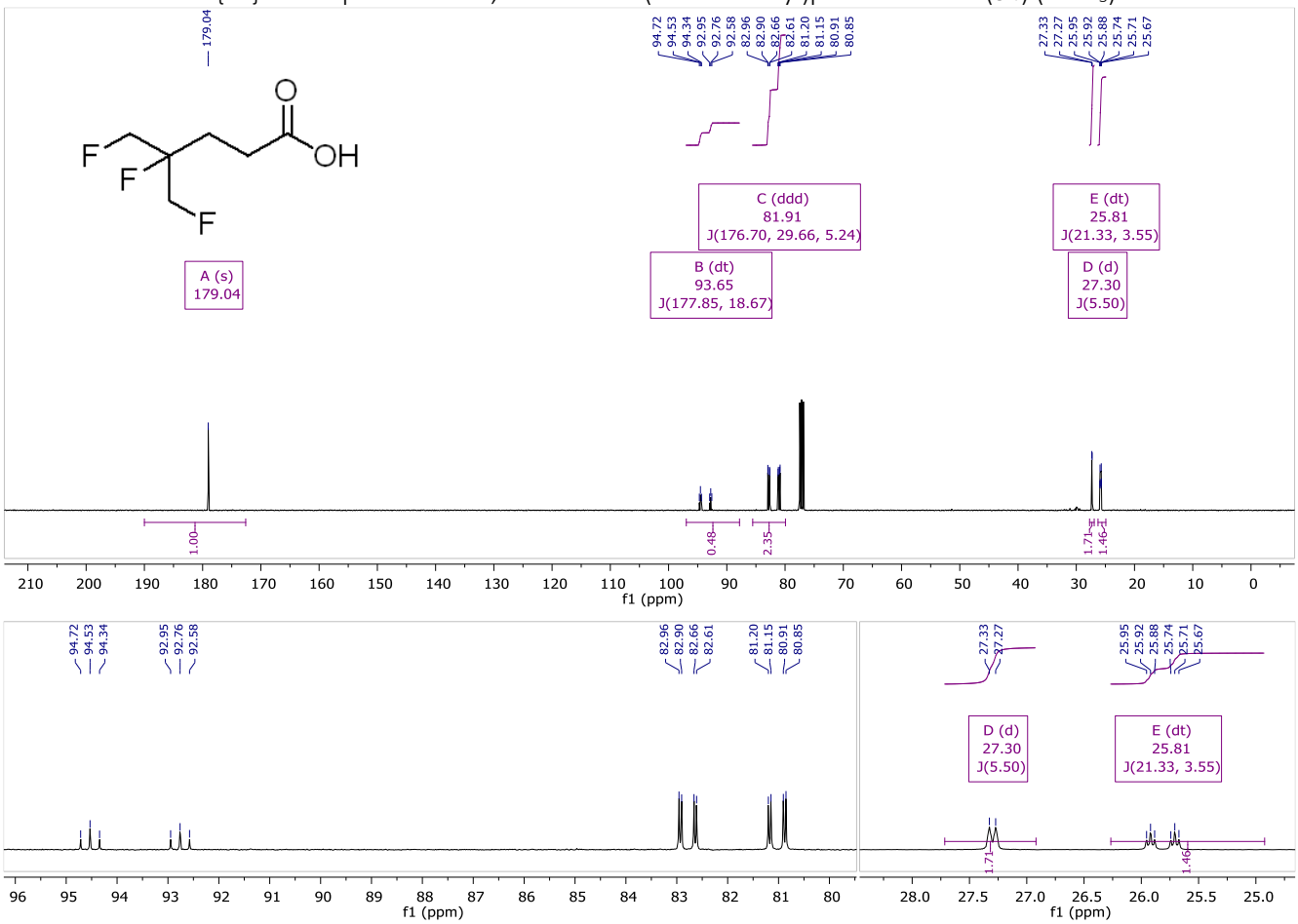
^{1}H NMR spectrum of 4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S4**) ($CDCl_3$)



^{19}F NMR spectrum of 4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S4**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S4**) ($CDCl_3$)



HRMS of 4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S4**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column: -
ESI-	Cone, V:	40		

Sample:

HRMS_2021_03_734 579 Maleckis OSM6-AM-F748

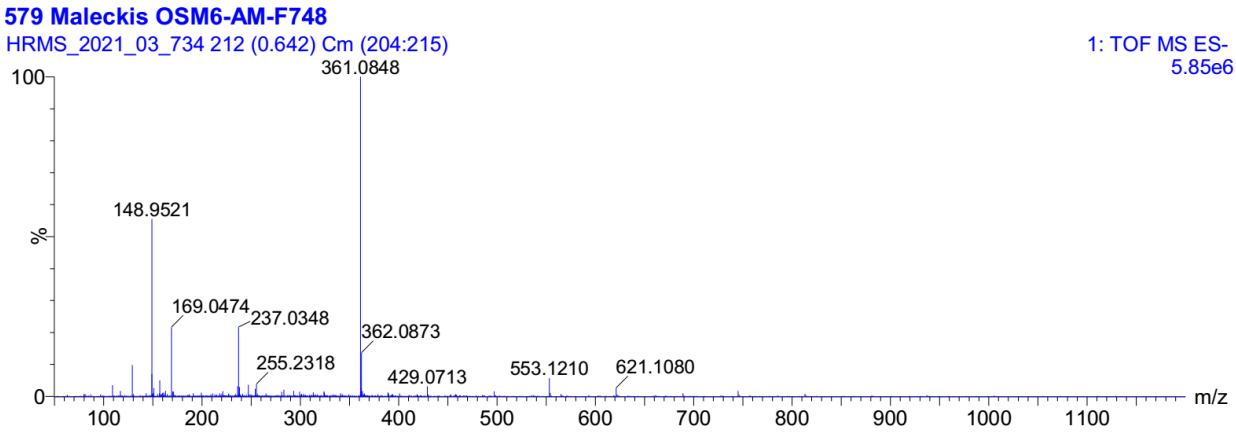
MS_NEG_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

Elemental Composition Report:

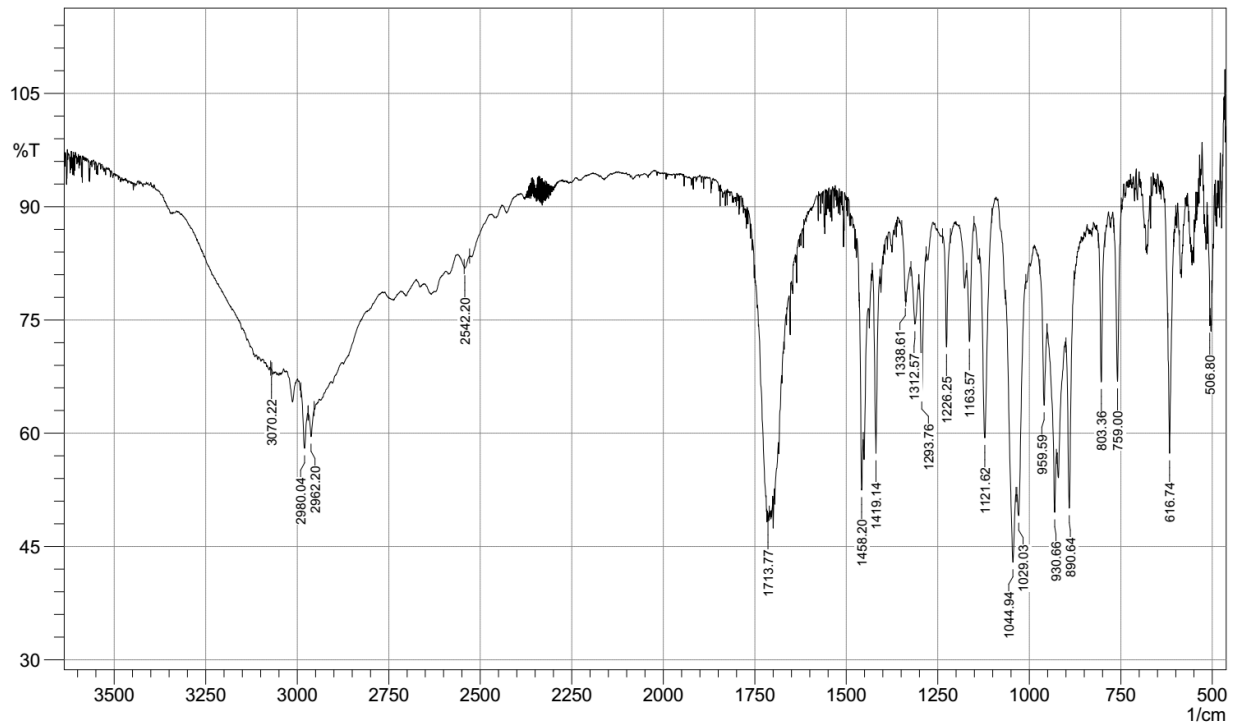
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
56 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-20 O: 0-20 F: 3-3

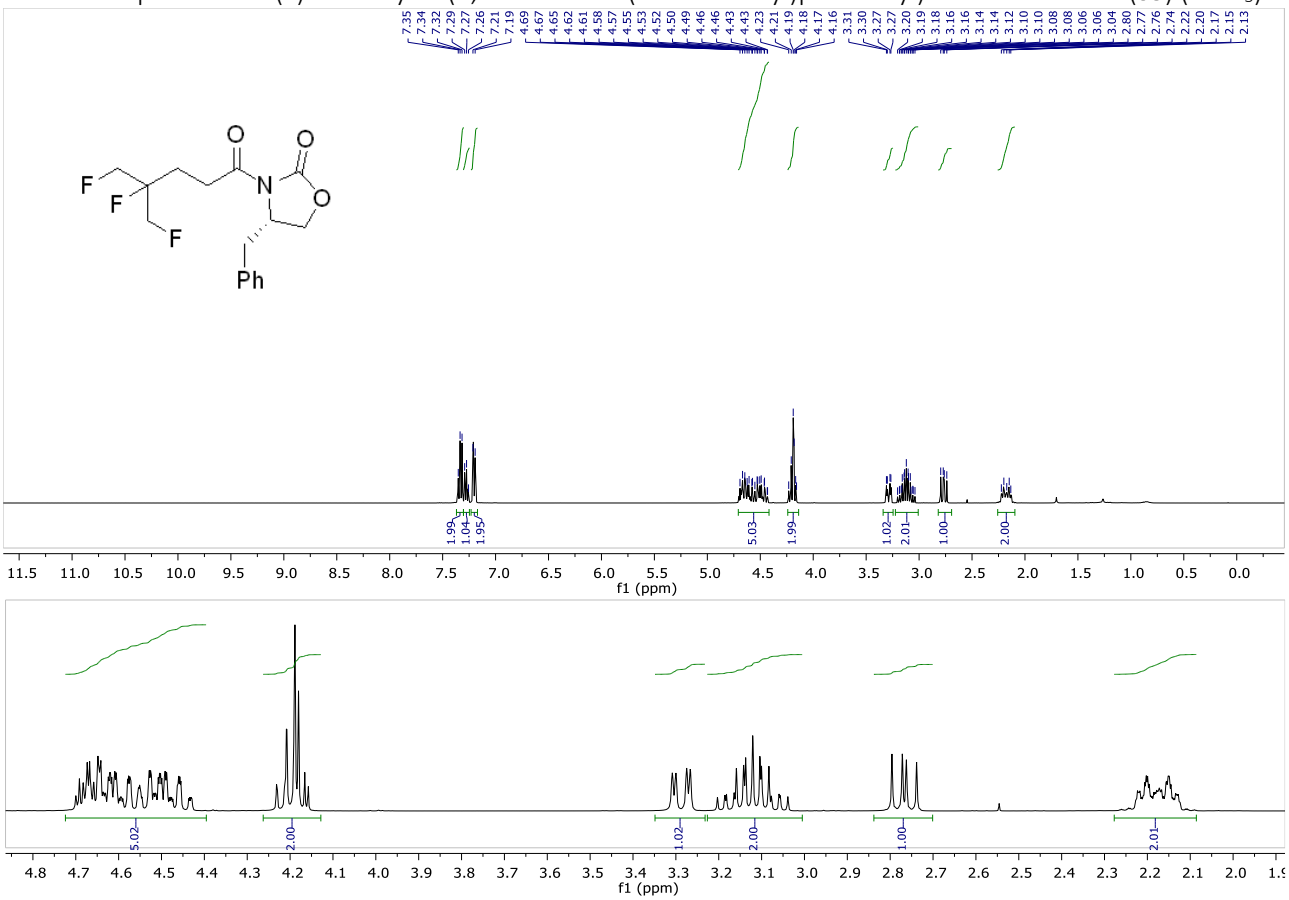
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
169.0474	100.00	169.0476	-0.2	-1.2	1.5	1357.5	n/a	n/a	C6 H8 O2 F3



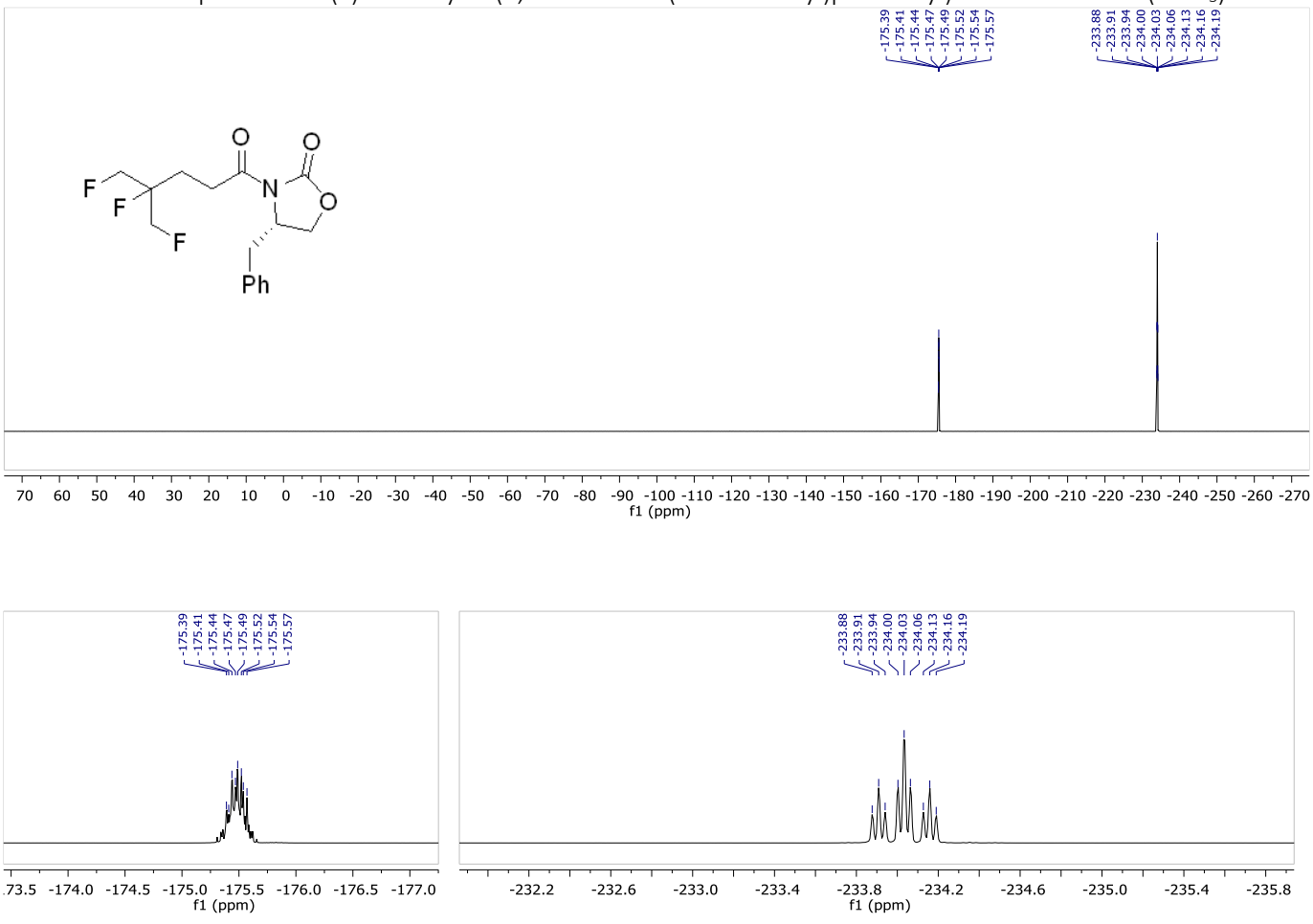
IR(ATR) spectrum of 4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S4**)



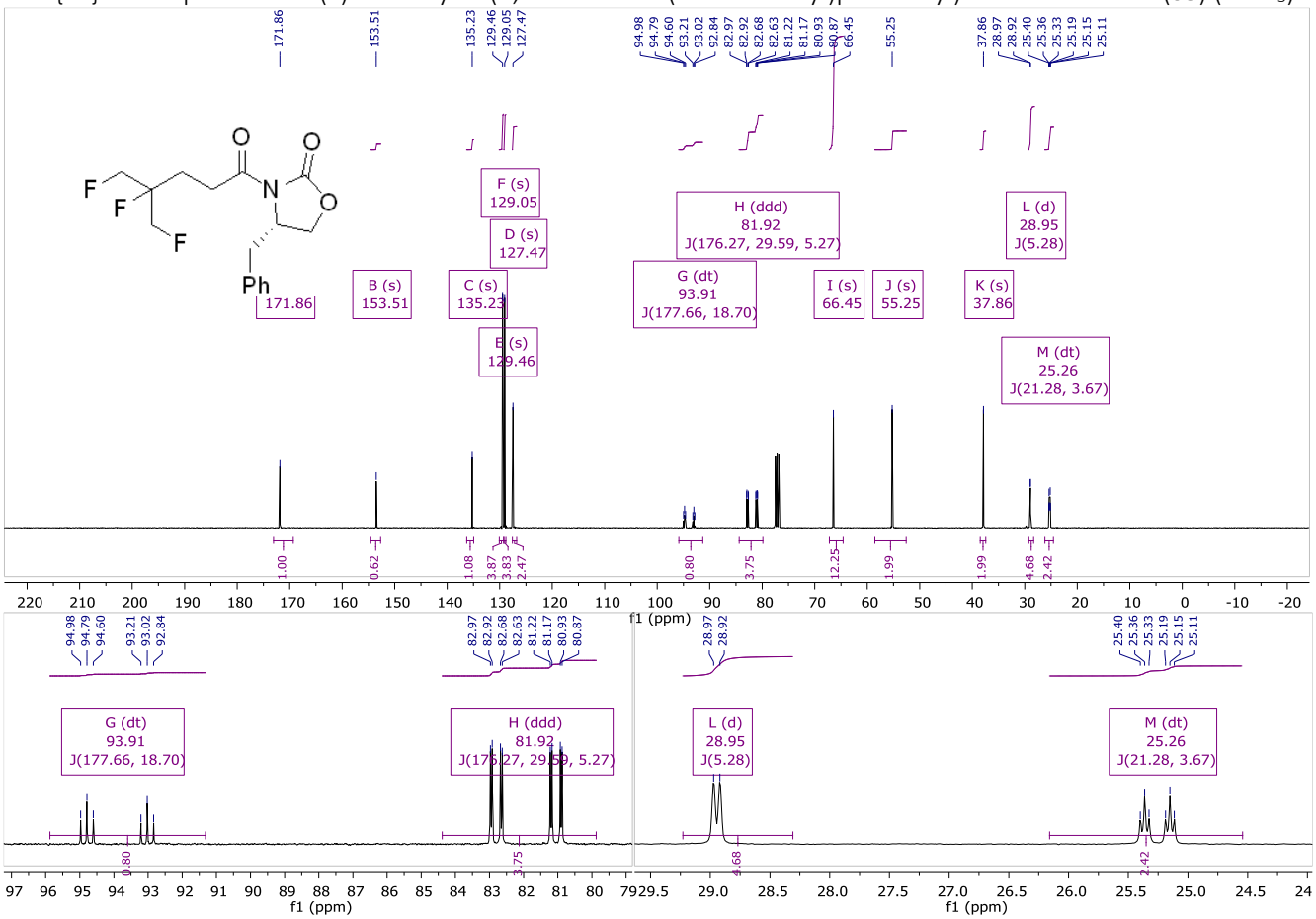
^{1}H NMR spectrum of (*S*)-4-benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**S5**) ($CDCl_3$)



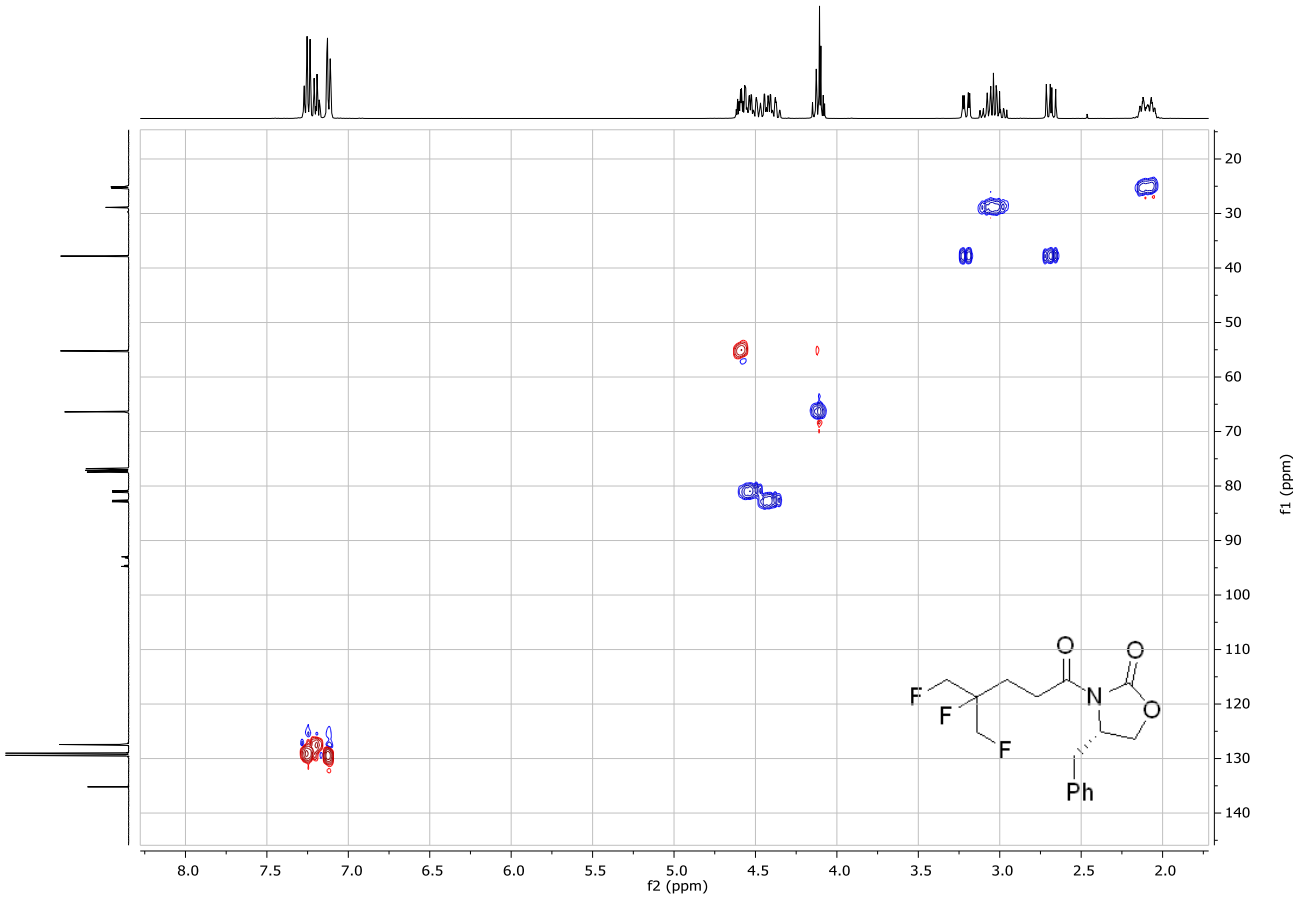
^{19}F NMR spectrum of (*S*)-4-benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-4-benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**S5**) ($CDCl_3$)



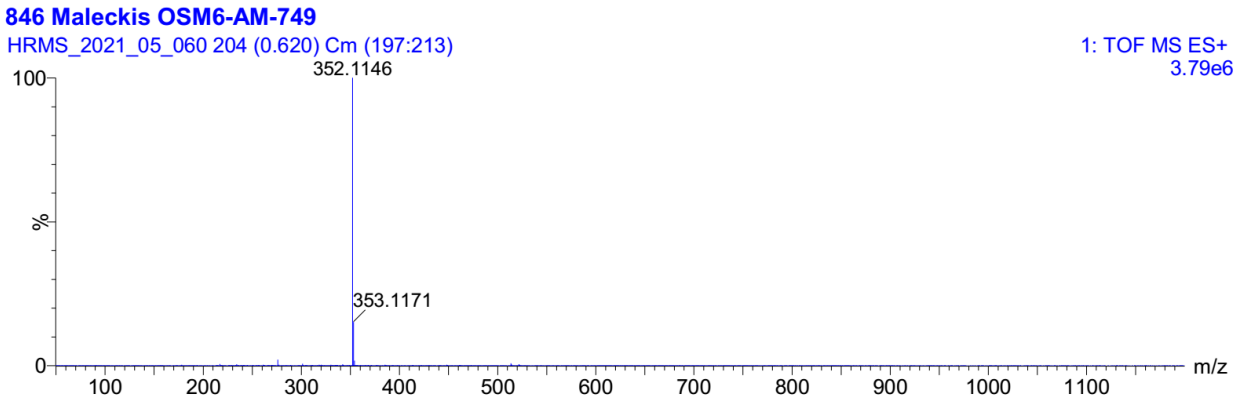
$^{1}H/^{13}C$ HSQC NMR spectrum of (*S*)-4-benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**S5**) ($CDCl_3$)



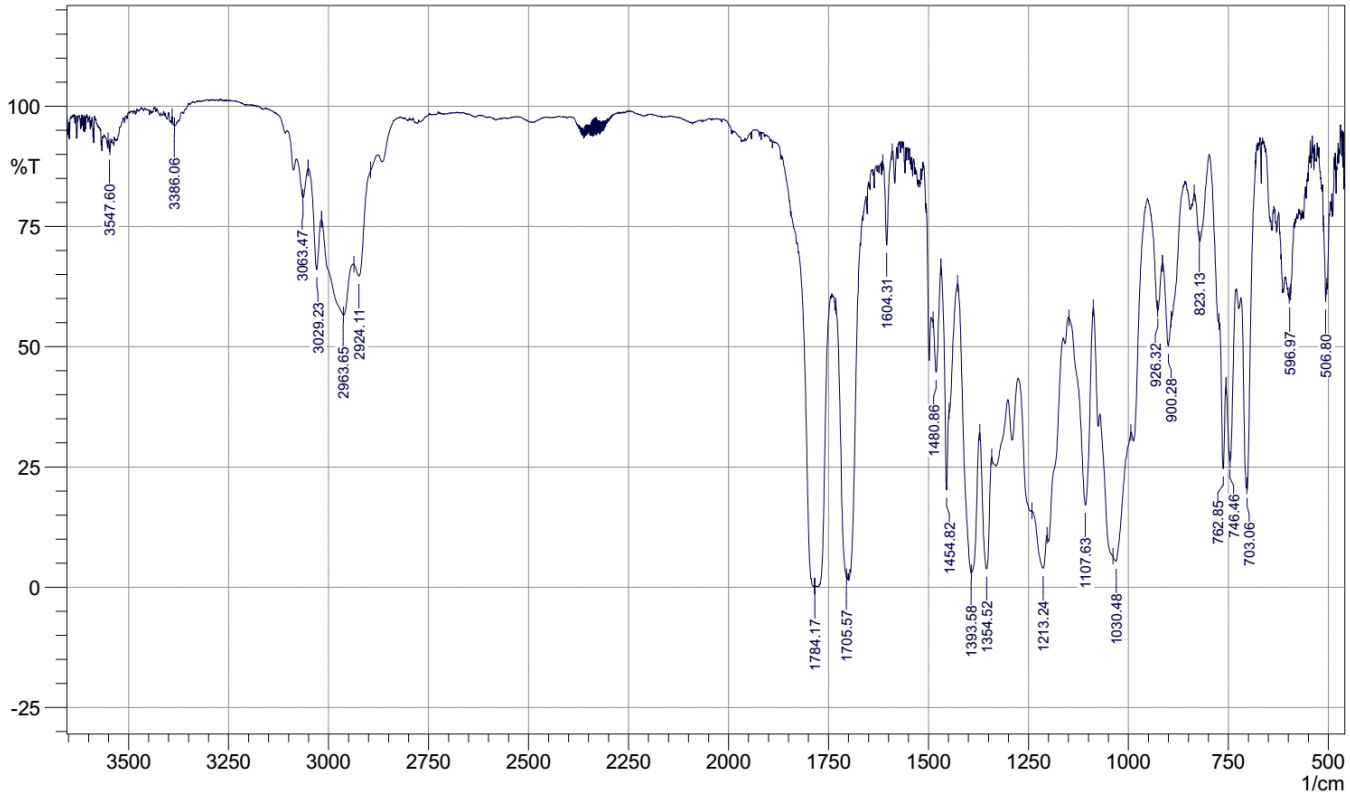
HRMS of (*S*)-4-benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**S5**)

MS: Waters Synapt G2-Si ESI+	Capillary, kV: Cone, V:	0.7 40	**LC: Acquity UPLC H-Class**	Column: -

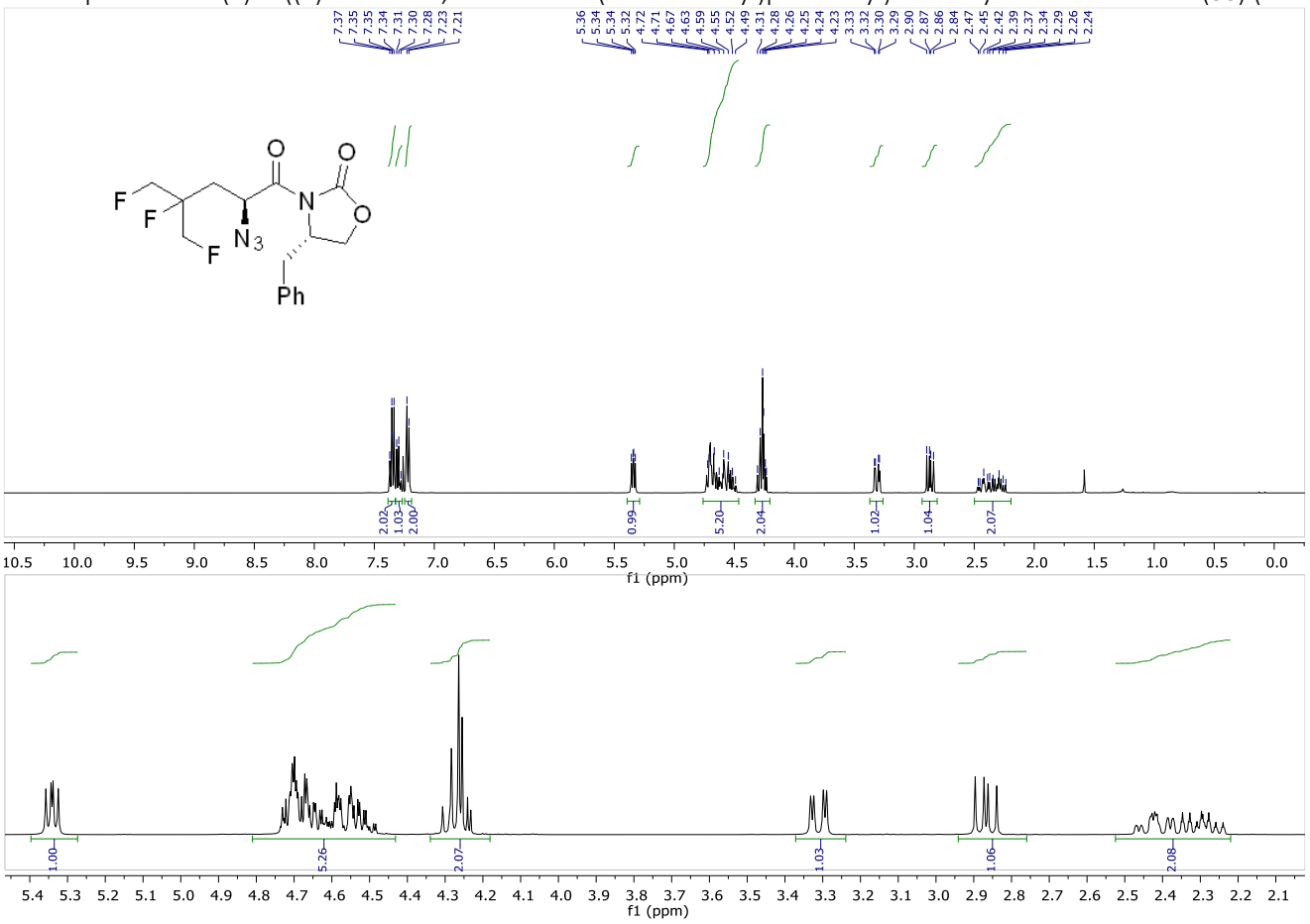
Sample:
HRMS_2021_05_060 846 Maleckis OSM6-AM-749
MS_POS_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune



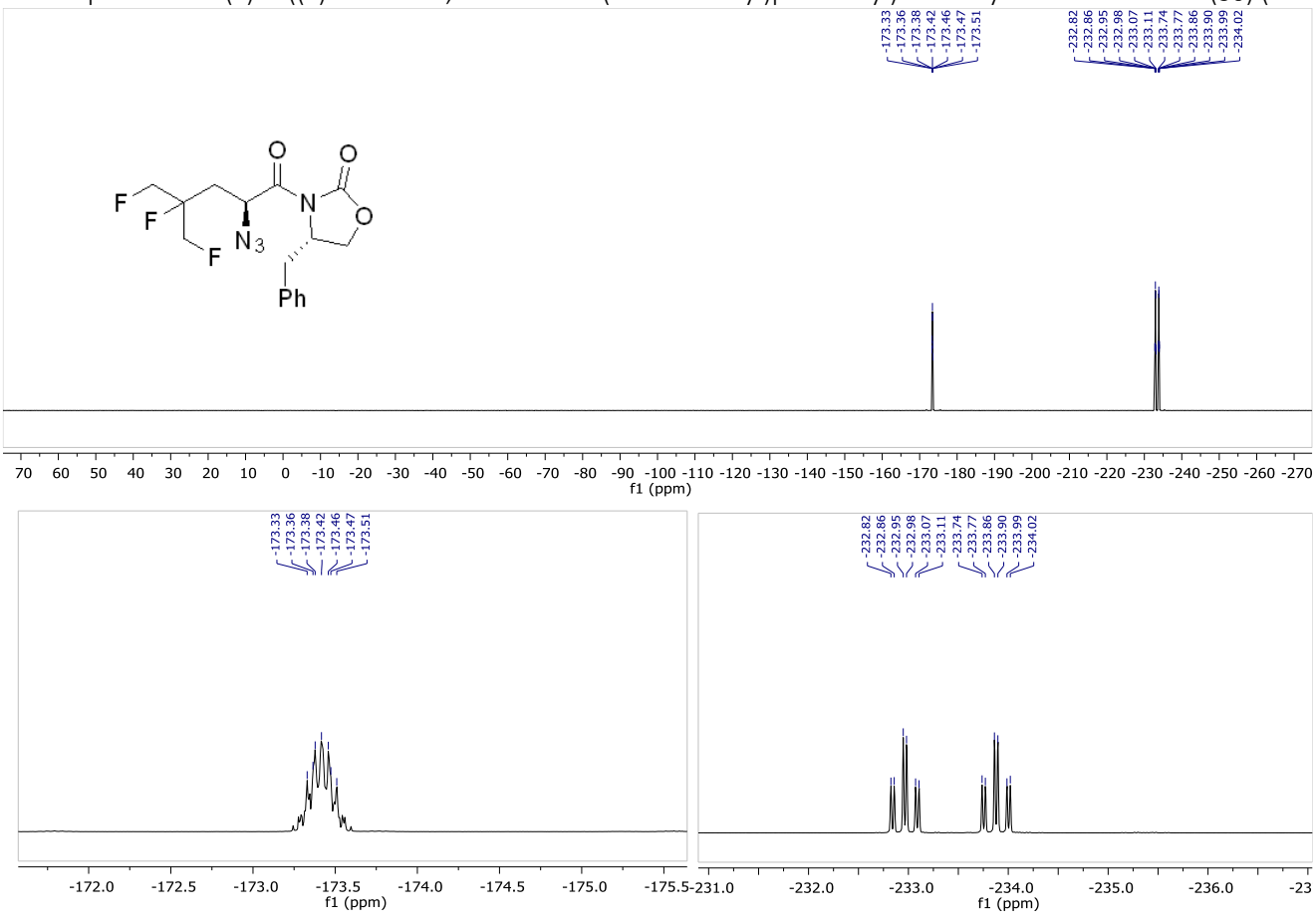
IR(ATR) spectrum of (*S*)-4-benzyl-3-(4,5-difluoro-4-(fluoromethyl)pentanoyl)oxazolidin-2-one (**S5**)



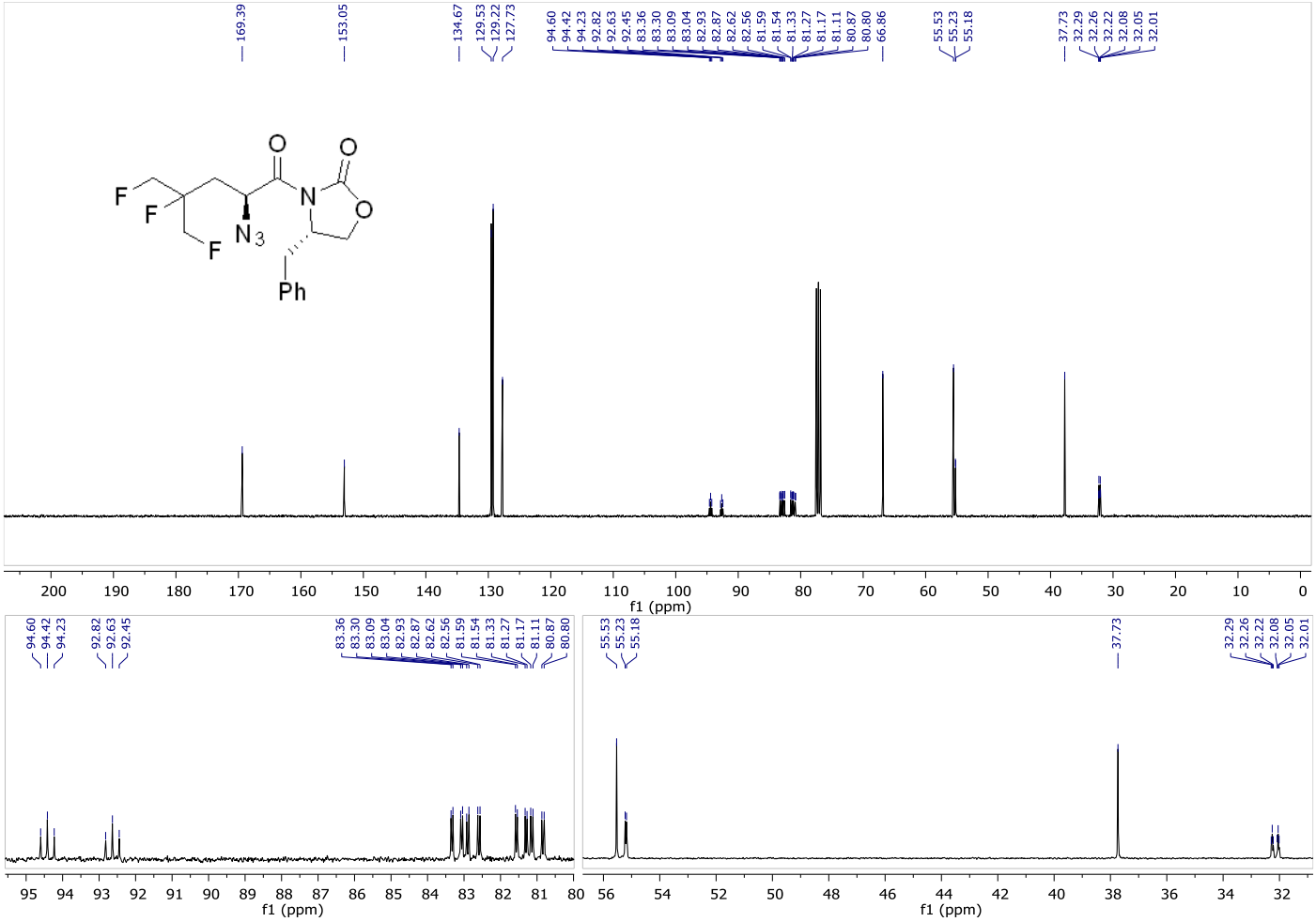
^{1}H NMR spectrum of (*S*)-3-((*S*)-2-azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S6**) ($CDCl_3$)



^{19}F NMR spectrum of (*S*)-3-((*S*)-2-azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S6**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR of (*S*)-3-((*S*)-2-azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S6**) ($CDCl_3$)



HRMS of (*S*)-3-((*S*)-2-azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S6**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	-
ESI+	Cone, V:	40			

Sample:

HRMS_2021_05_061 847 Maleckis OSM6-AM-752

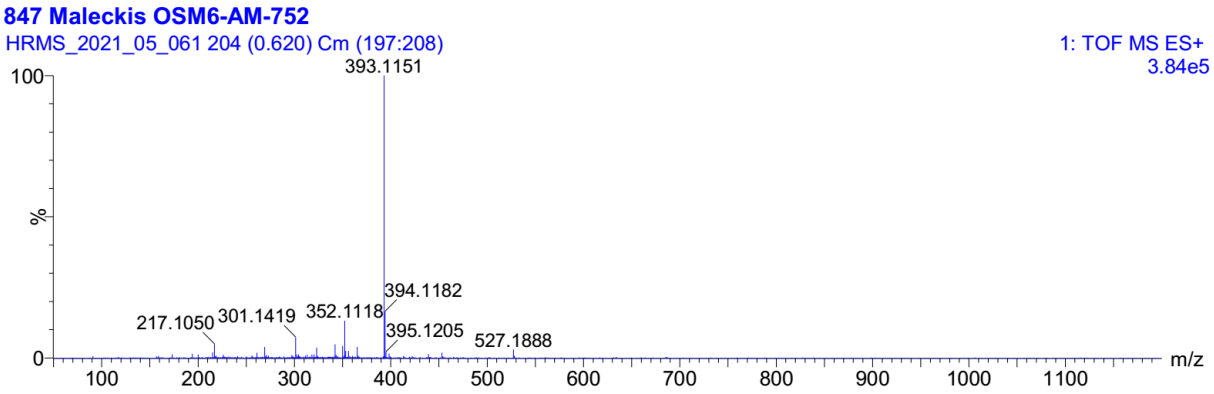
MS_POS_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

Elemental Composition Report:

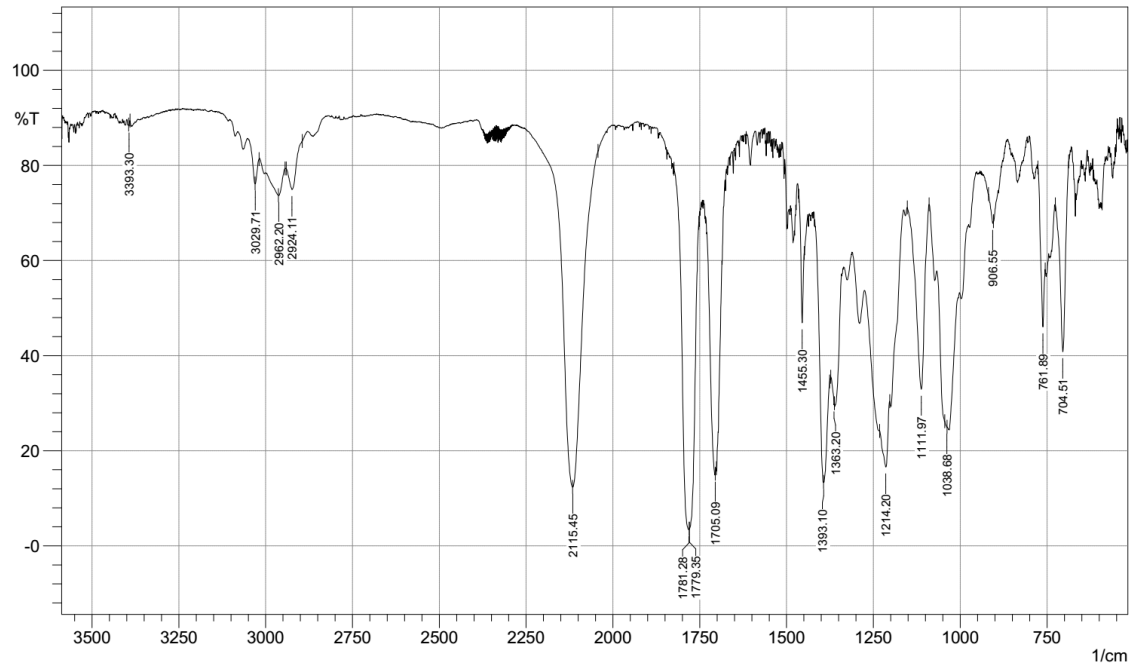
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
545 formula(e) evaluated with 2 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-15 O: 0-15 Na: 1-1 F: 3-3

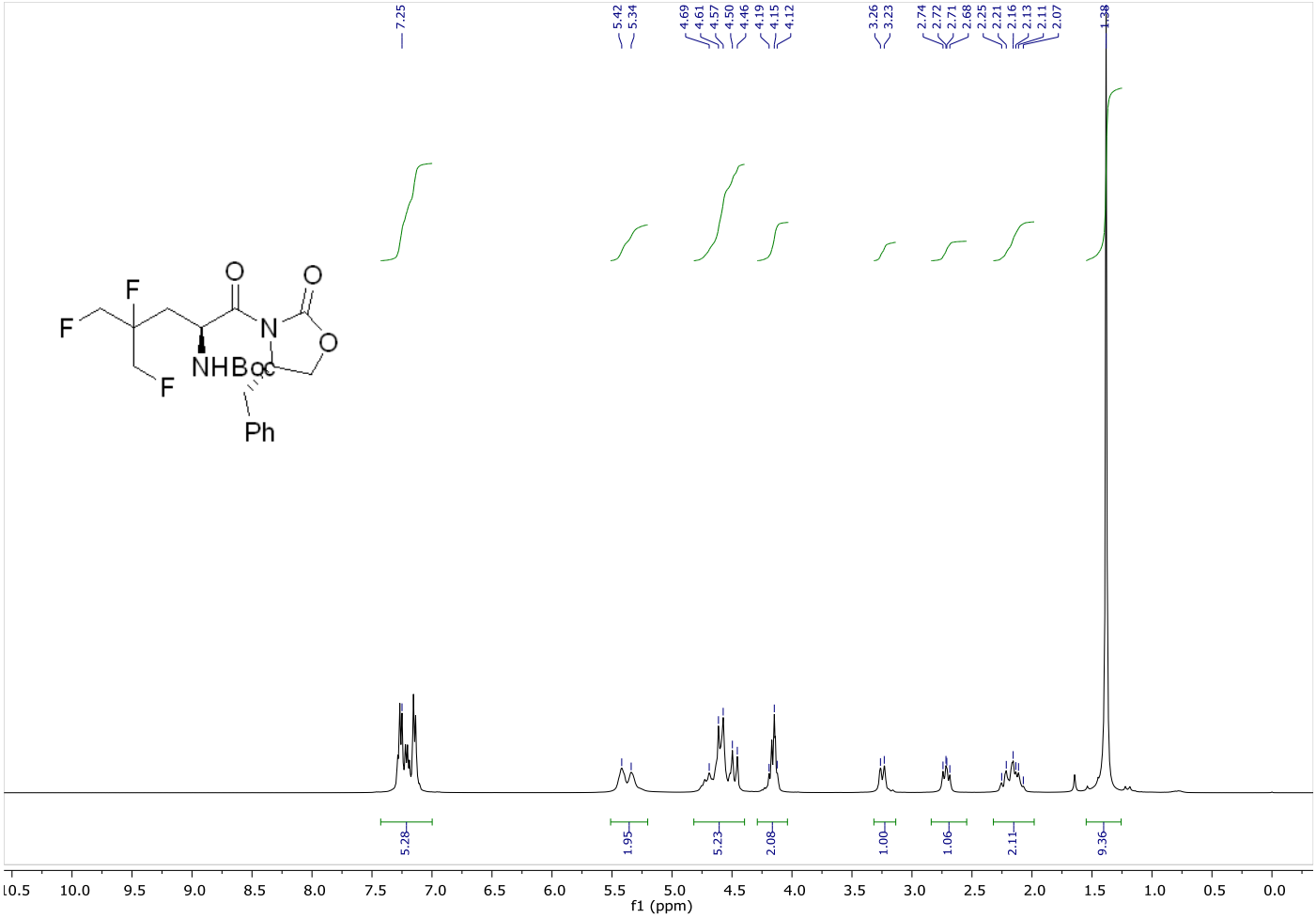
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
393.1151	100.00	393.1150	0.1	0.3	8.5	602.2	1.742	17.52	C16 H17 N4 O3 Na F3
		393.1137	1.4	3.6	3.5	600.7	0.193	82.48	C15 H21 O7 Na F3



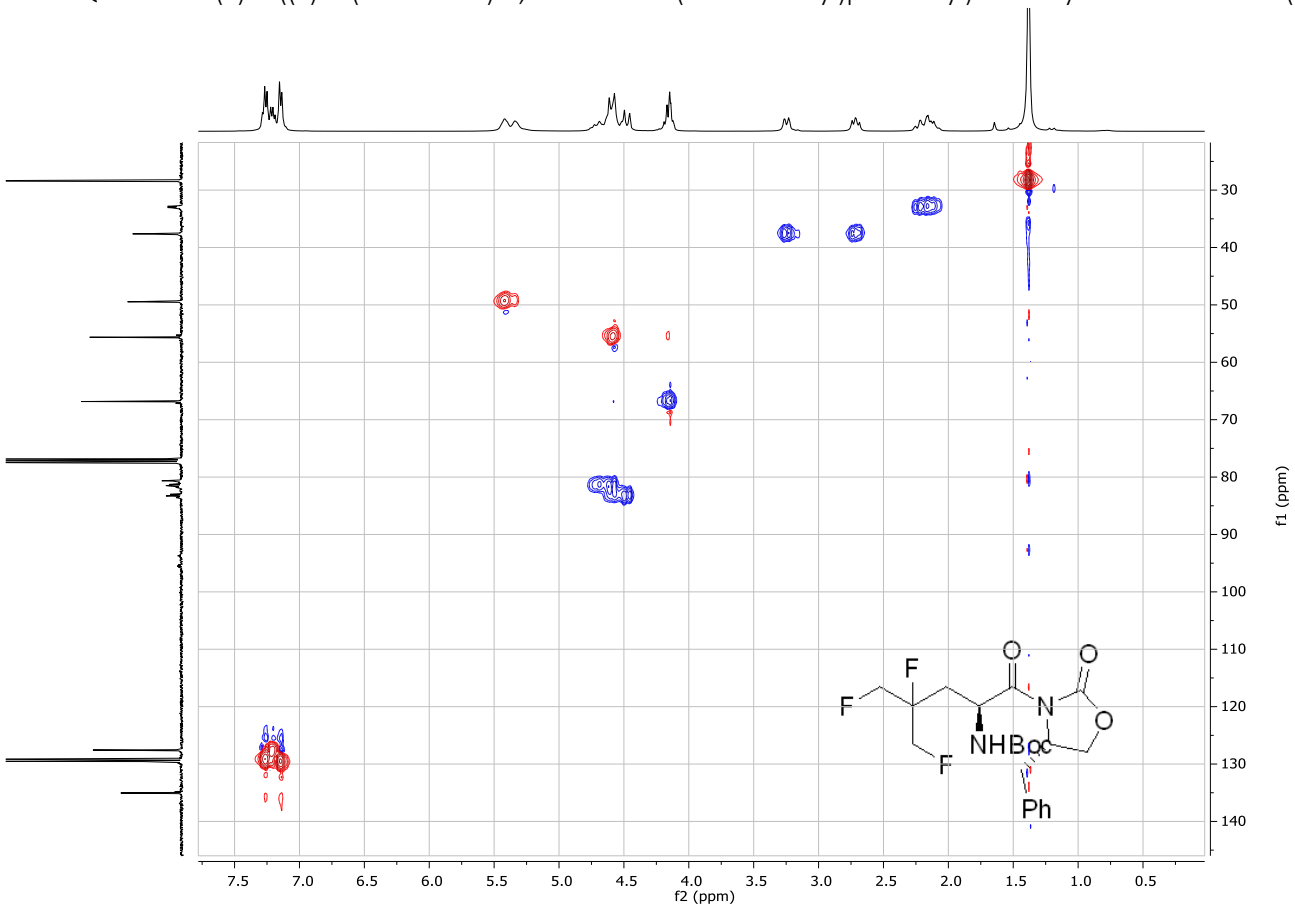
IR(ATR) spectrum of (*S*)-3-((*S*)-2-azido-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S6**)



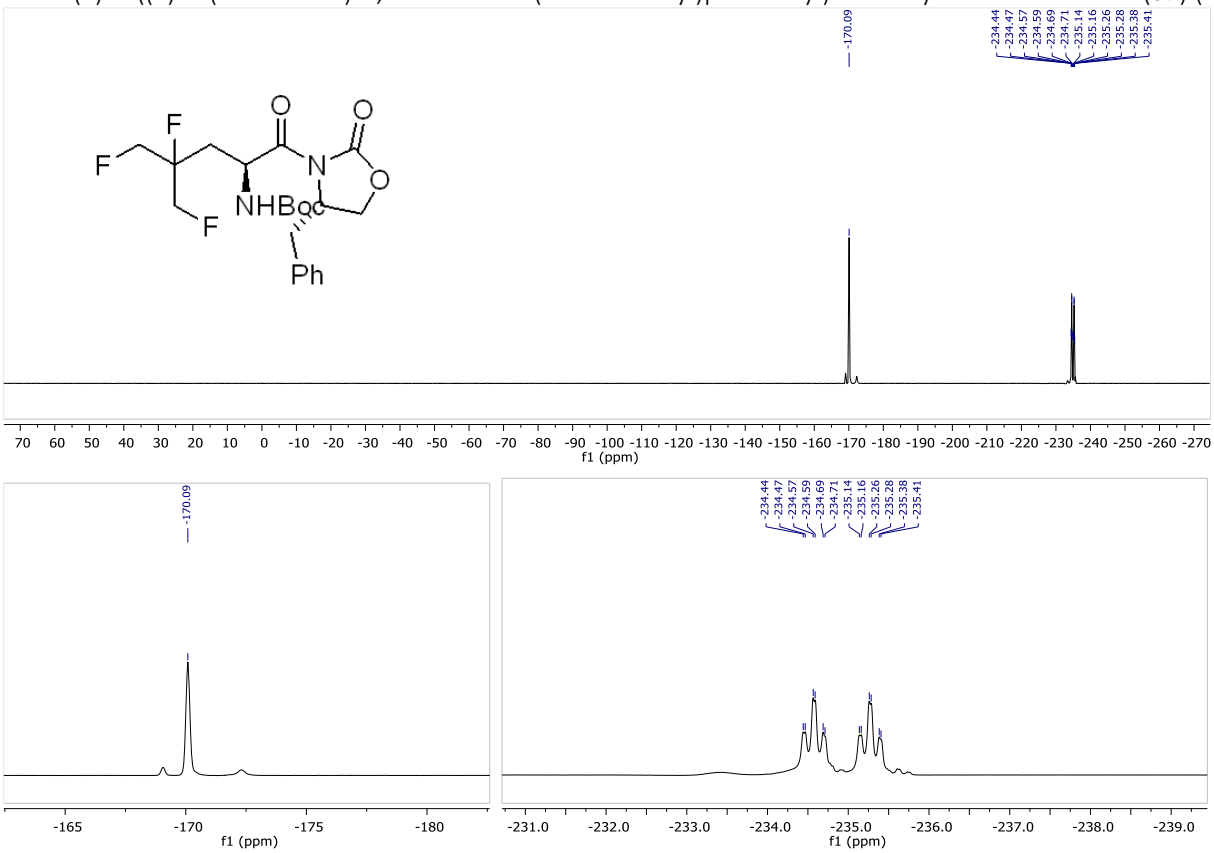
^{1}H NMR of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**) ($CDCl_3$)



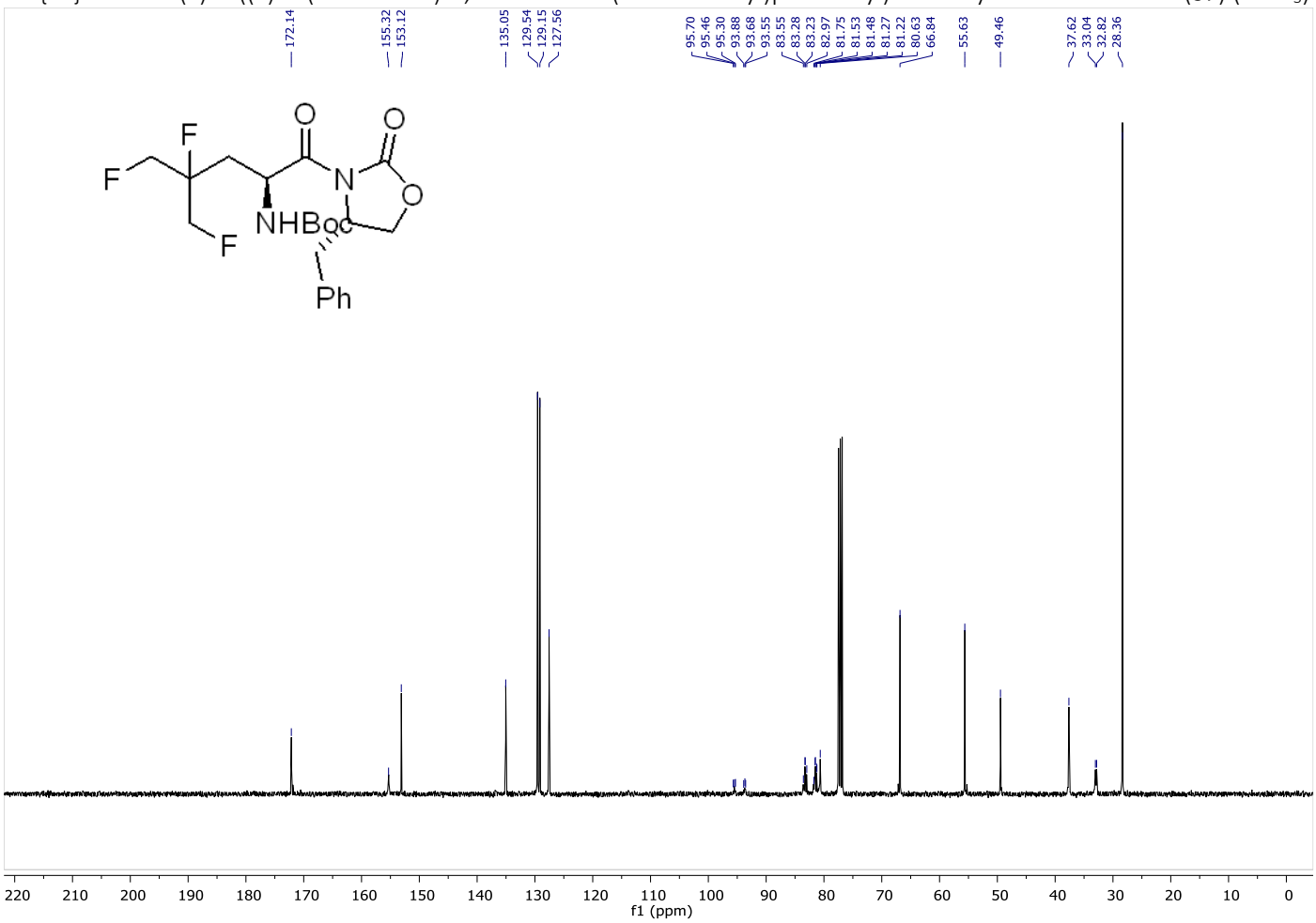
^{1}H/^{13}C HSQC NMR of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**)



^{19}F NMR of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**) ($CDCl_3$)



^{13}C{^{1}H} NMR of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**) ($CDCl_3$)



HRMS of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

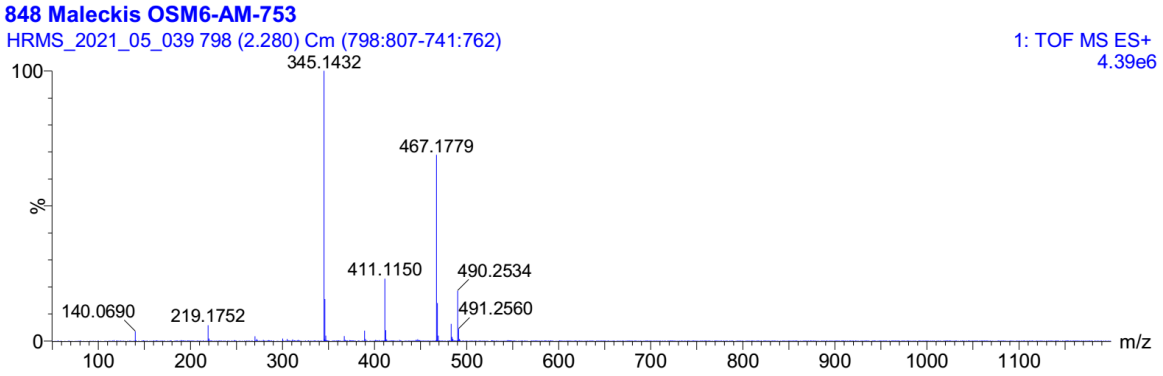
HRMS_2021_05_039	848 Maleckis OSM6-AM-753				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	1:D,1	1.000000	MS_Tune	Col#66

Elemental Composition Report:

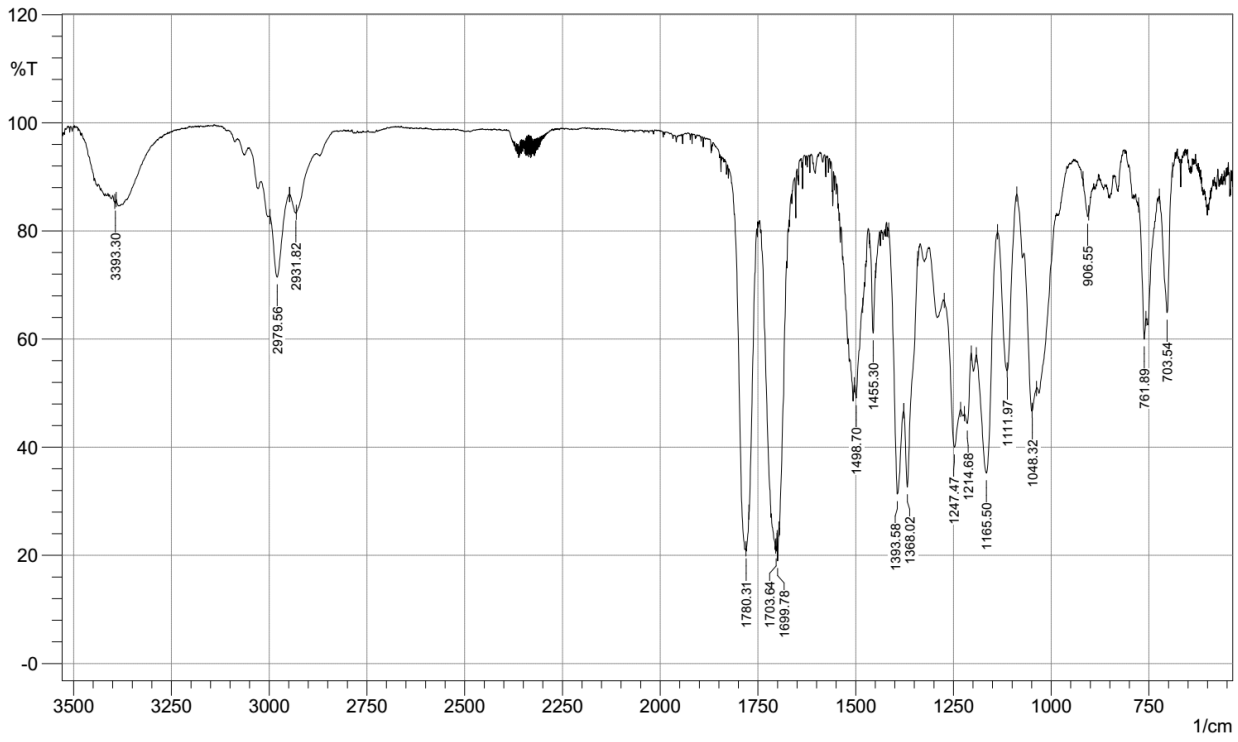
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
803 formula(e) evaluated with 4 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-15 O: 0-15 F: 3-3 Na: 1-1

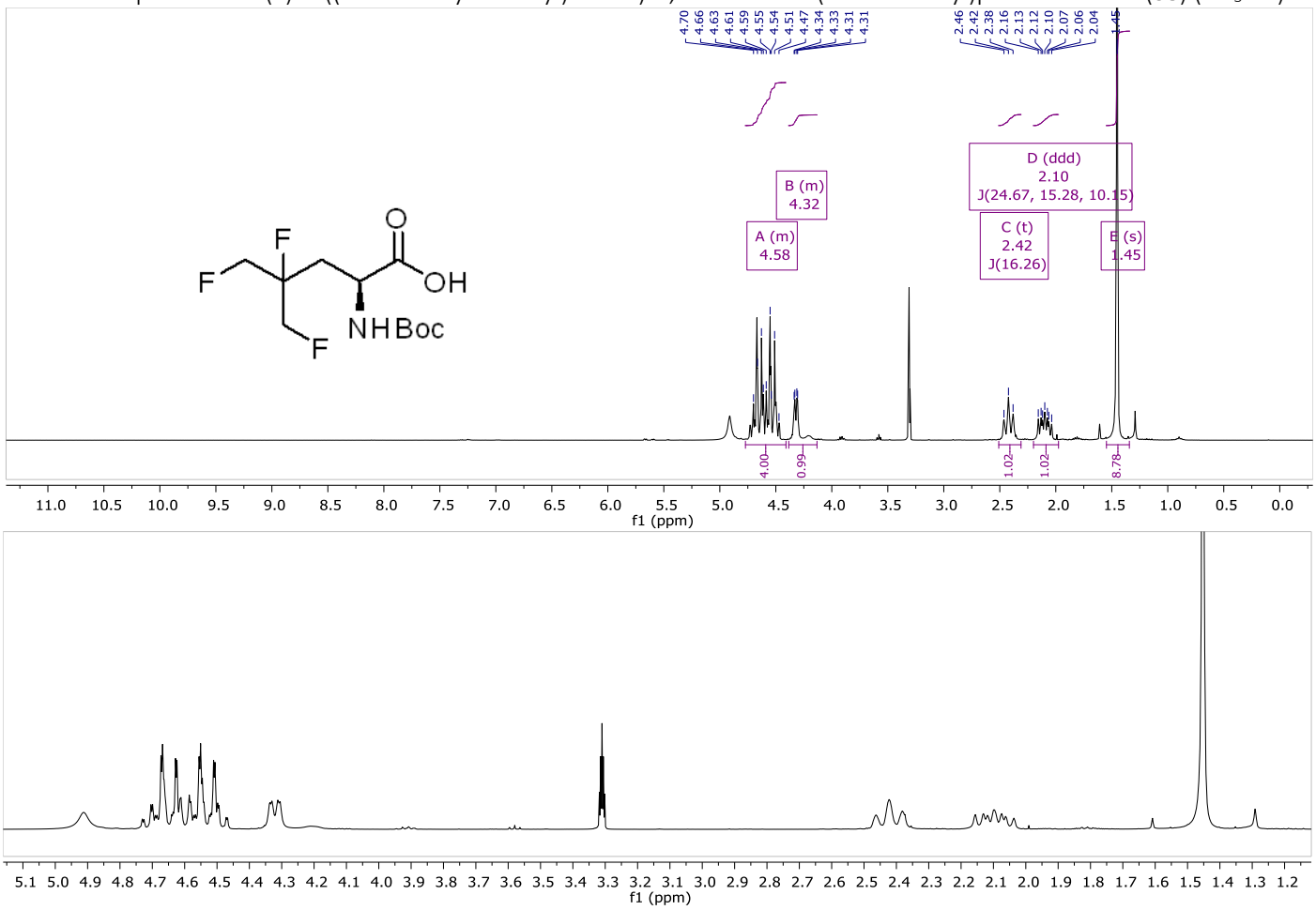
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
467.1779	100.00	467.1775	0.4	0.9	0.5	379.0	2.386	9.20	C6 H23 N14 O6 F3 Na
		467.1783	-0.4	-0.9	12.5	376.9	0.276	75.89	C22 H23 N6 O F3 Na
		467.1770	0.9	1.9	7.5	379.9	3.264	3.82	C21 H27 N2 O5 F3 Na
		467.1802	-2.3	-4.9	-0.5	378.9	2.200	11.08	C10 H27 N8 O8 F3 Na



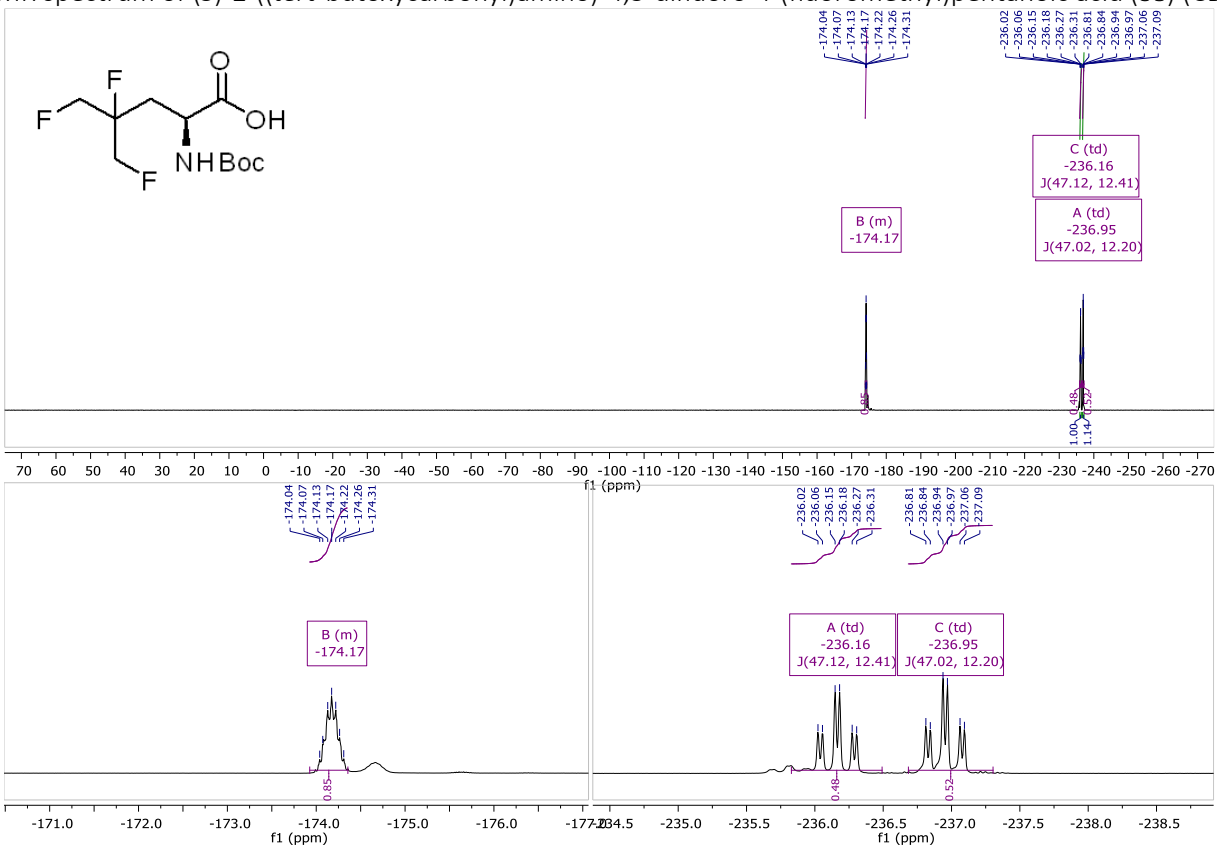
IR(ATR) spectrum of (*S*)-3-((*S*)-2-(Boc-amino)-4,5-difluoro-4-(fluoromethyl)pentanoyl)-4-benzyloxazolidin-2-one (**S7**)



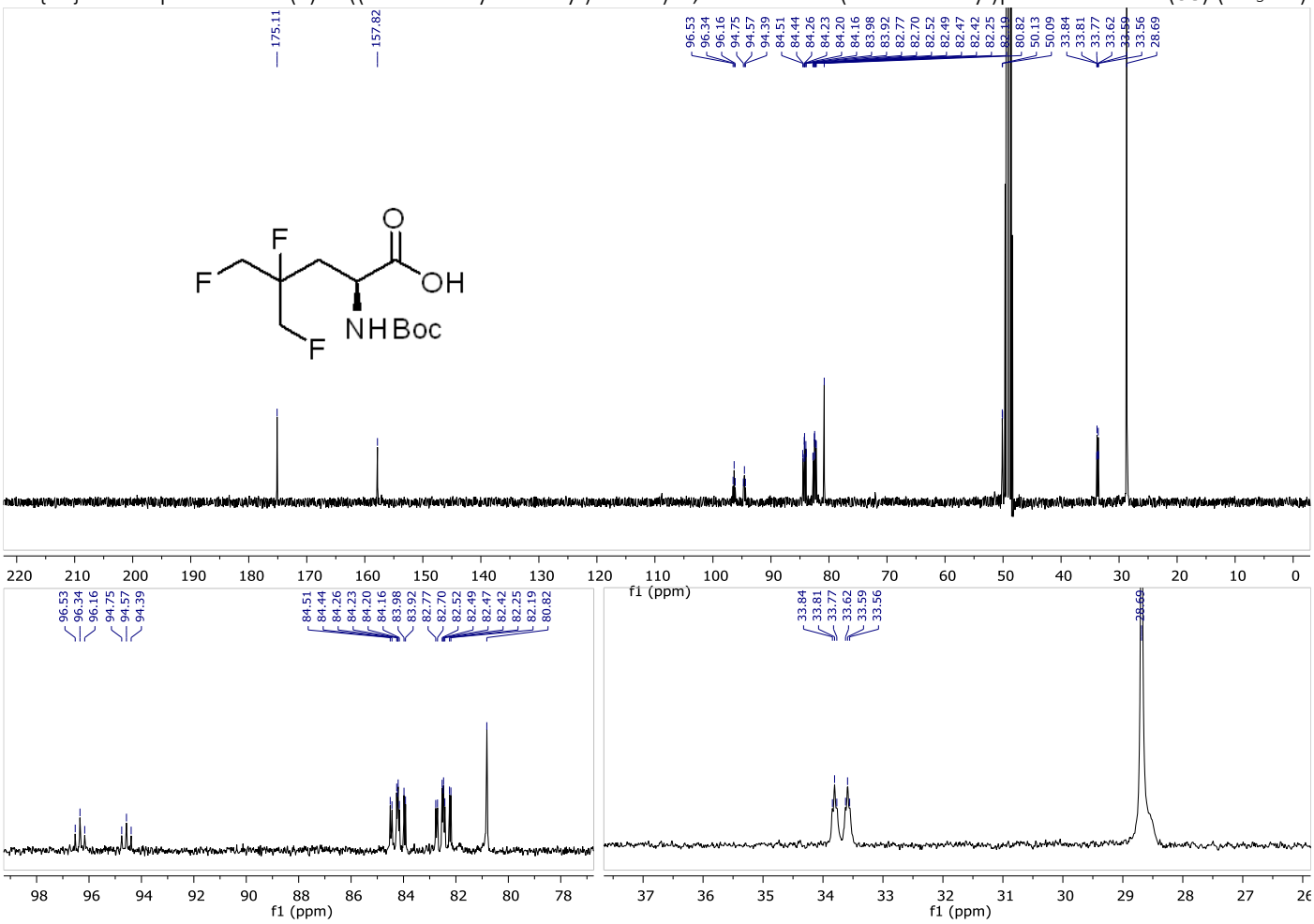
^{1}H NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S8**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S8**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S8**) (CD_3OD)



HRMS of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S8**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

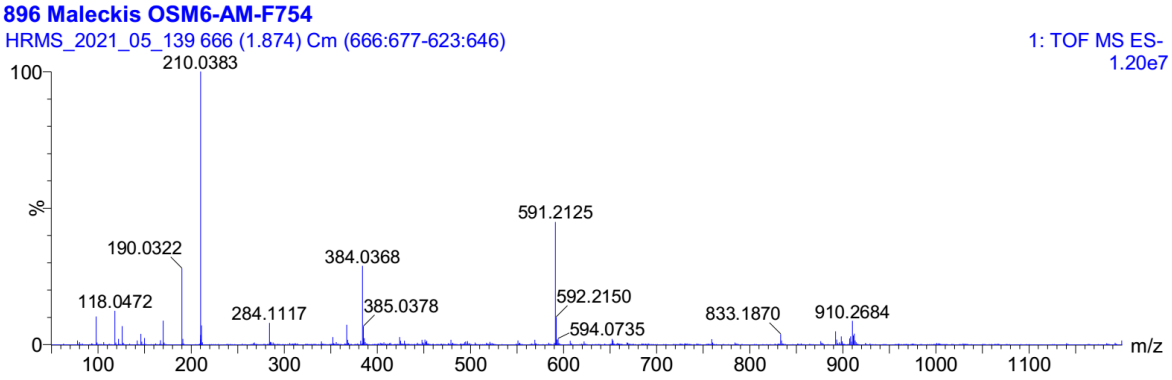
HRMS_2021_05_139	896 Maleckis OSM6-AM-F754				
MS_NEG_RES_4min	ACN_Form_5-98_040_4min	1:E,3	1.000000	MS_Tune	Col#66

Elemental Composition Report:

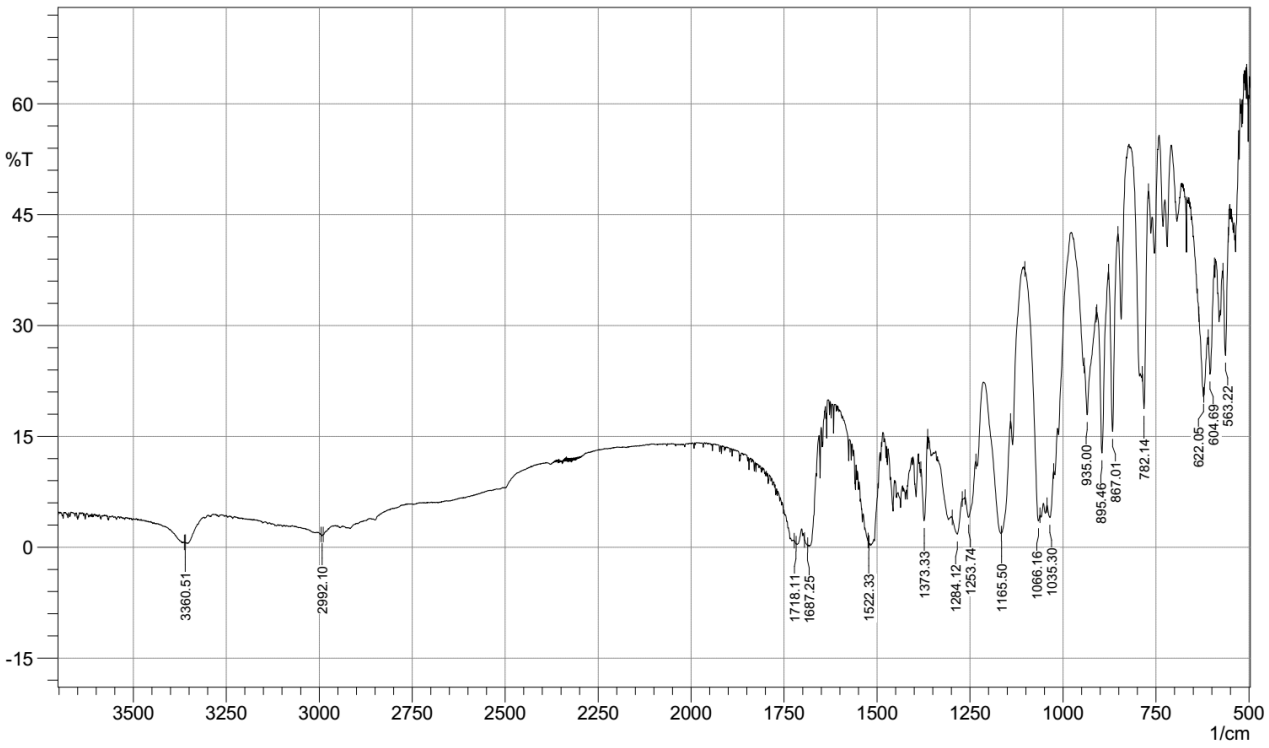
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
276 formula(e) evaluated with 2 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-15 O: 0-15 F: 3-3

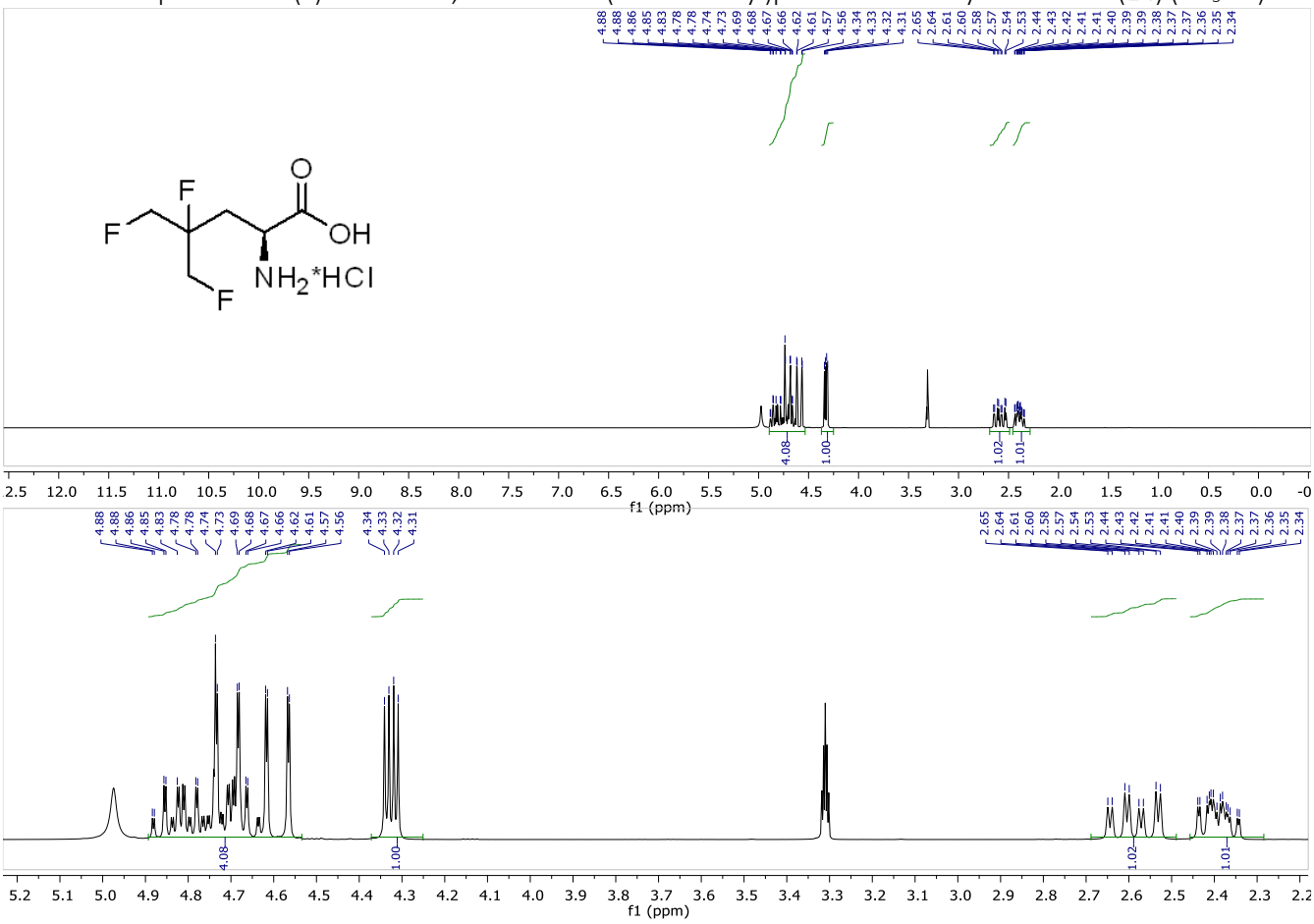
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
284.1117	100.00	284.1123	-0.6	-2.1	7.5	744.7	0.014	98.57	C12 H13 N5 F3
		284.1110	0.7	2.5	2.5	749.0	4.246	1.43	C11 H17 N O4 F3



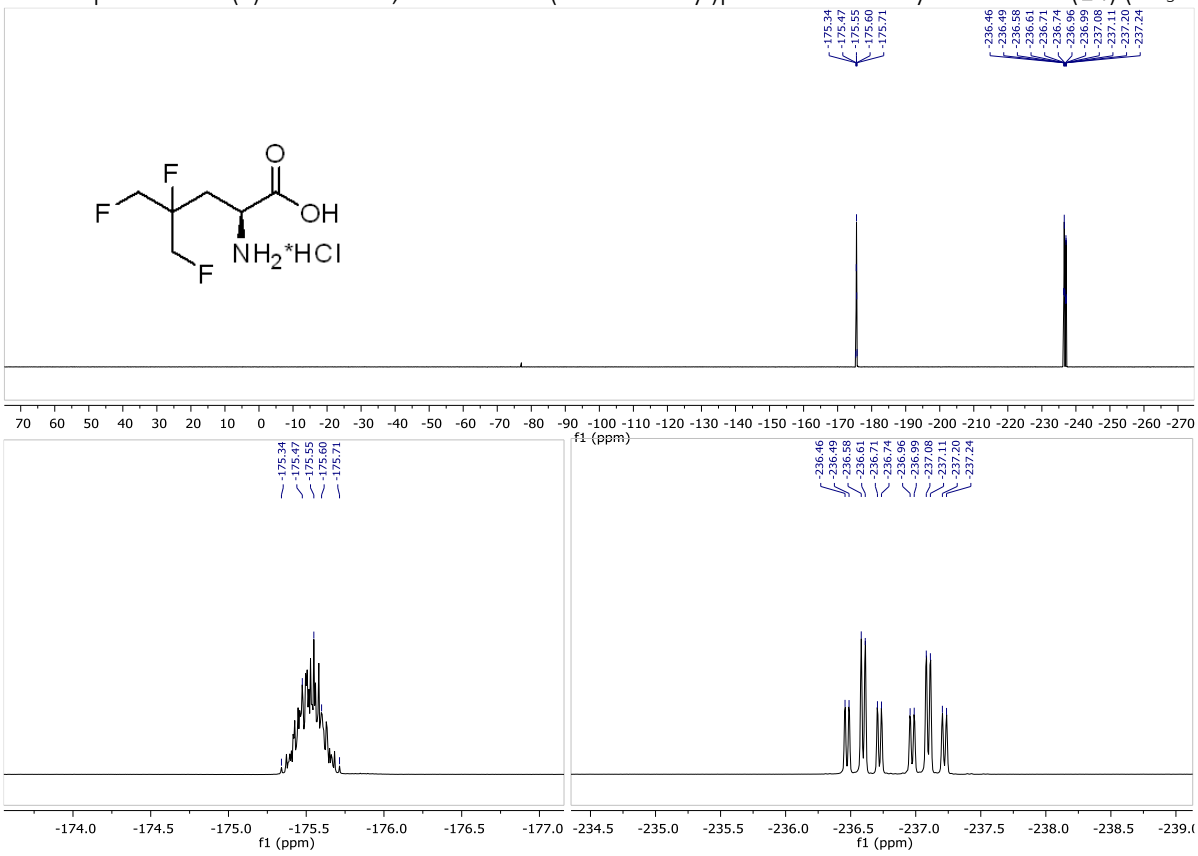
IR(ATR) spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4,5-difluoro-4-(fluoromethyl)pentanoic acid (**S8**)



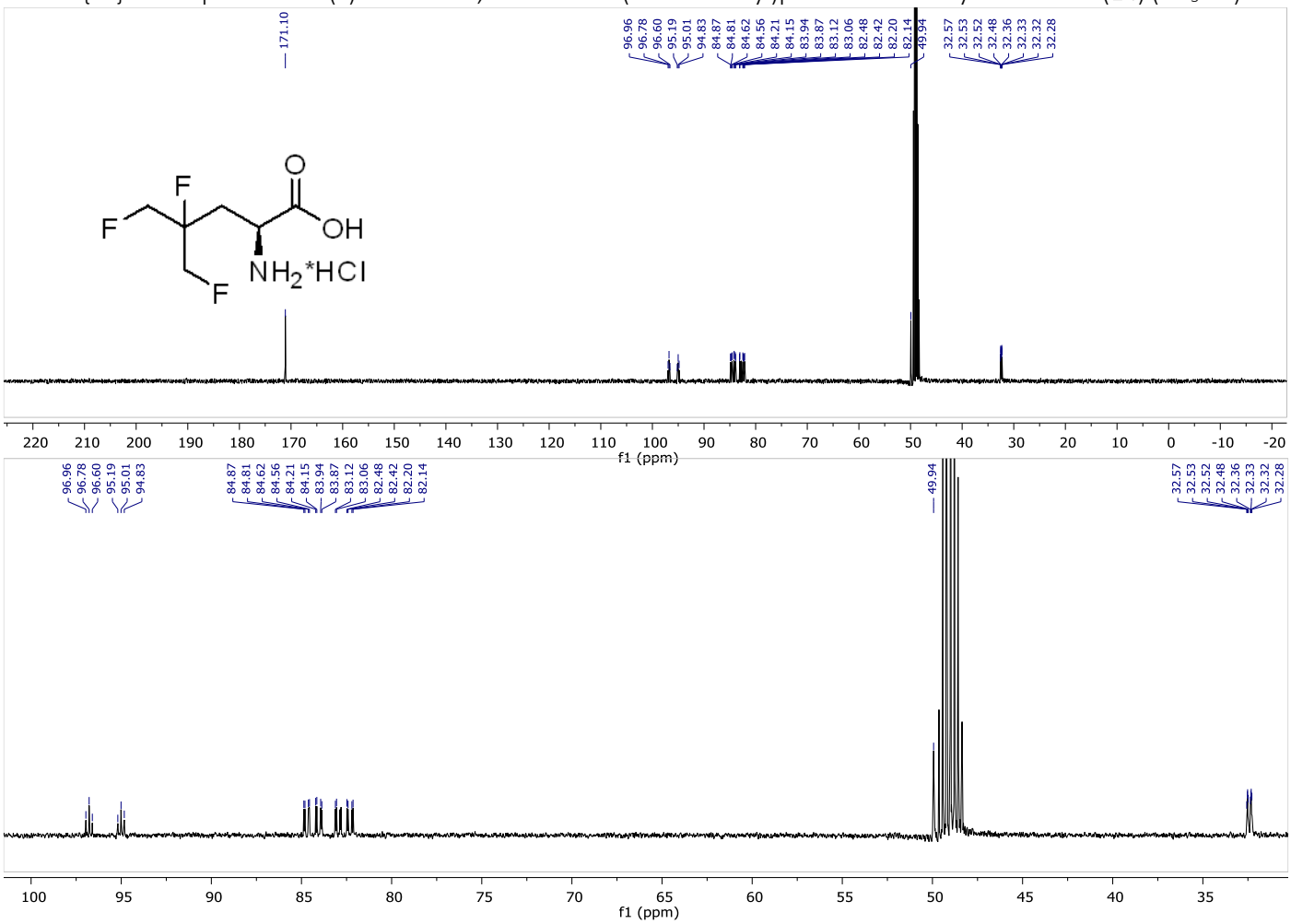
^{1}H NMR spectrum of (*S*)-2-amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**14**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**14**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**14**) (CD_3OD)



HRMS of (*S*)-2-amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**14**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

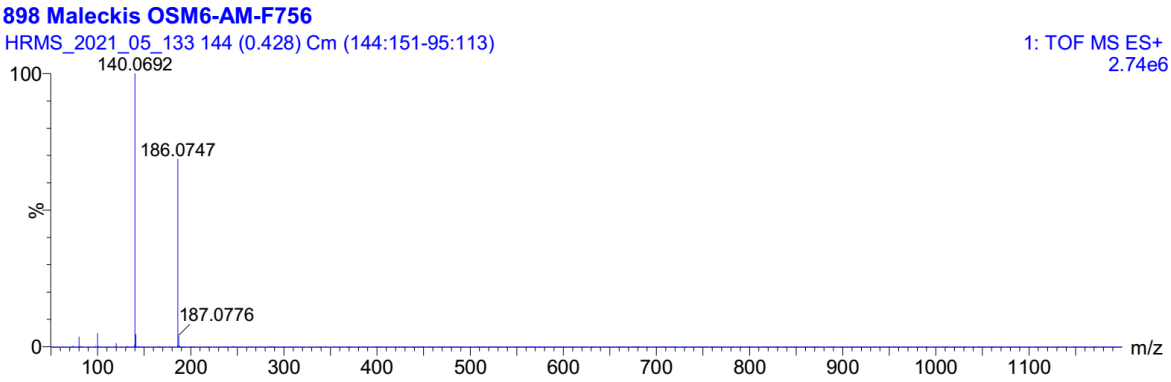
HRMS_2021_05_133	898 Maleckis OSM6-AM-F756				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	1:E,5	1.000000	MS_Tune	Col#66

Elemental Composition Report:

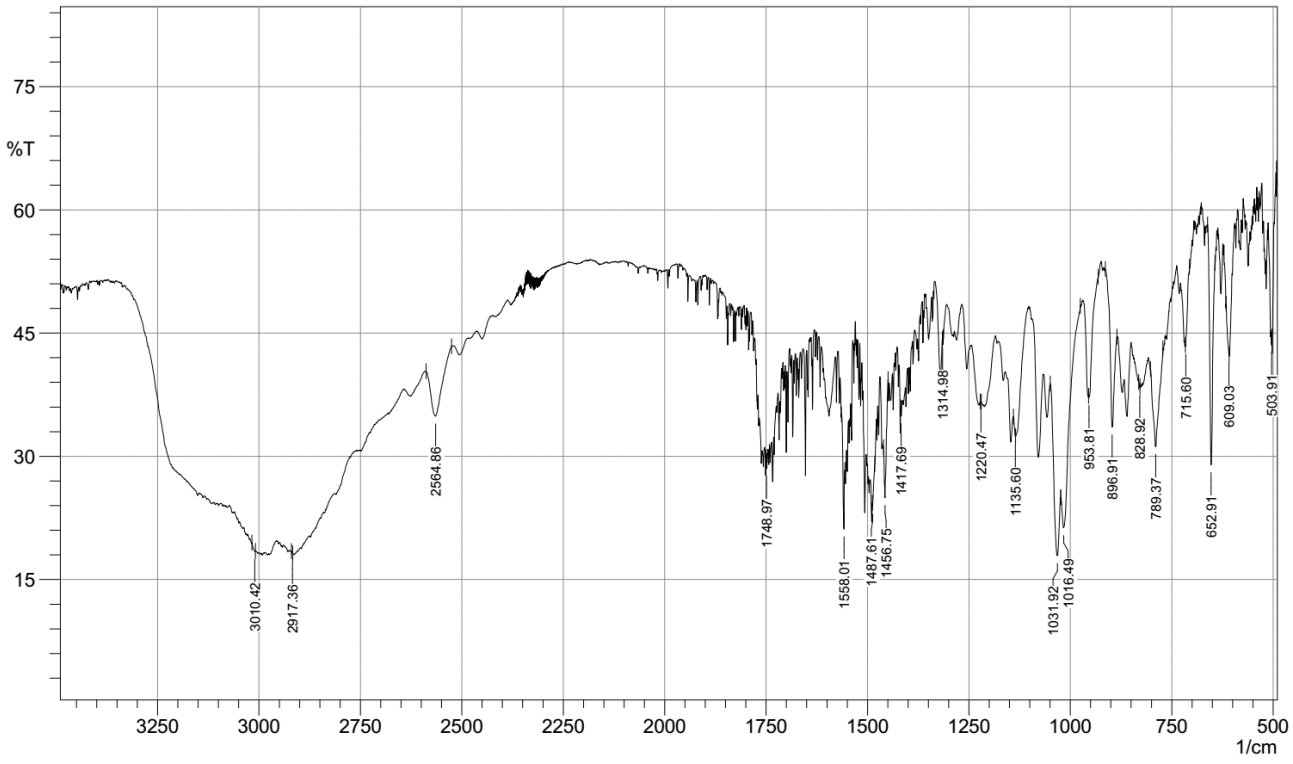
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
73 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-15 O: 0-15 F: 3-3

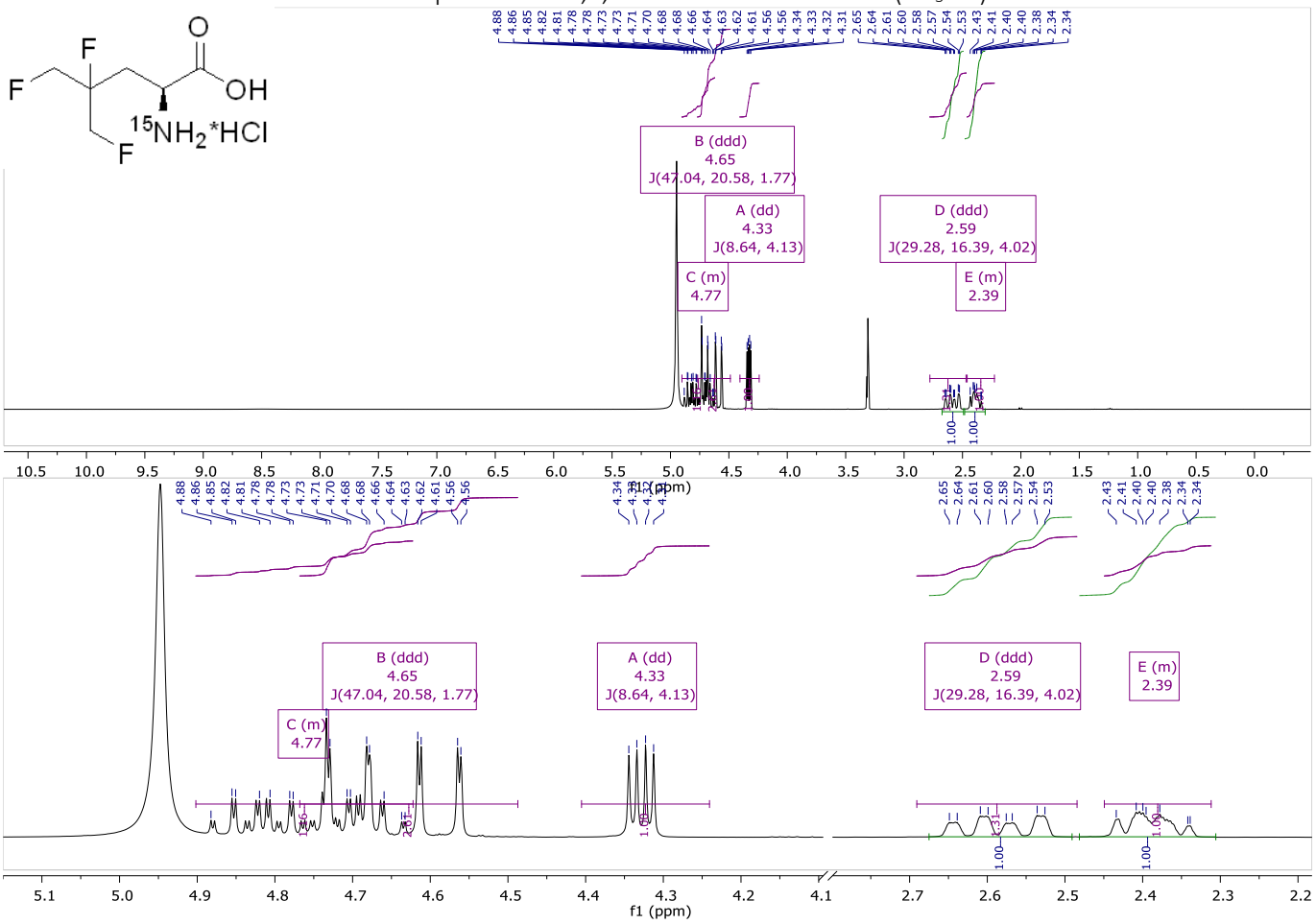
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
186.0747	100.00	186.0742	0.5	2.7	0.5	314.3	n/a	n/a	C6 H11 N O2 F3



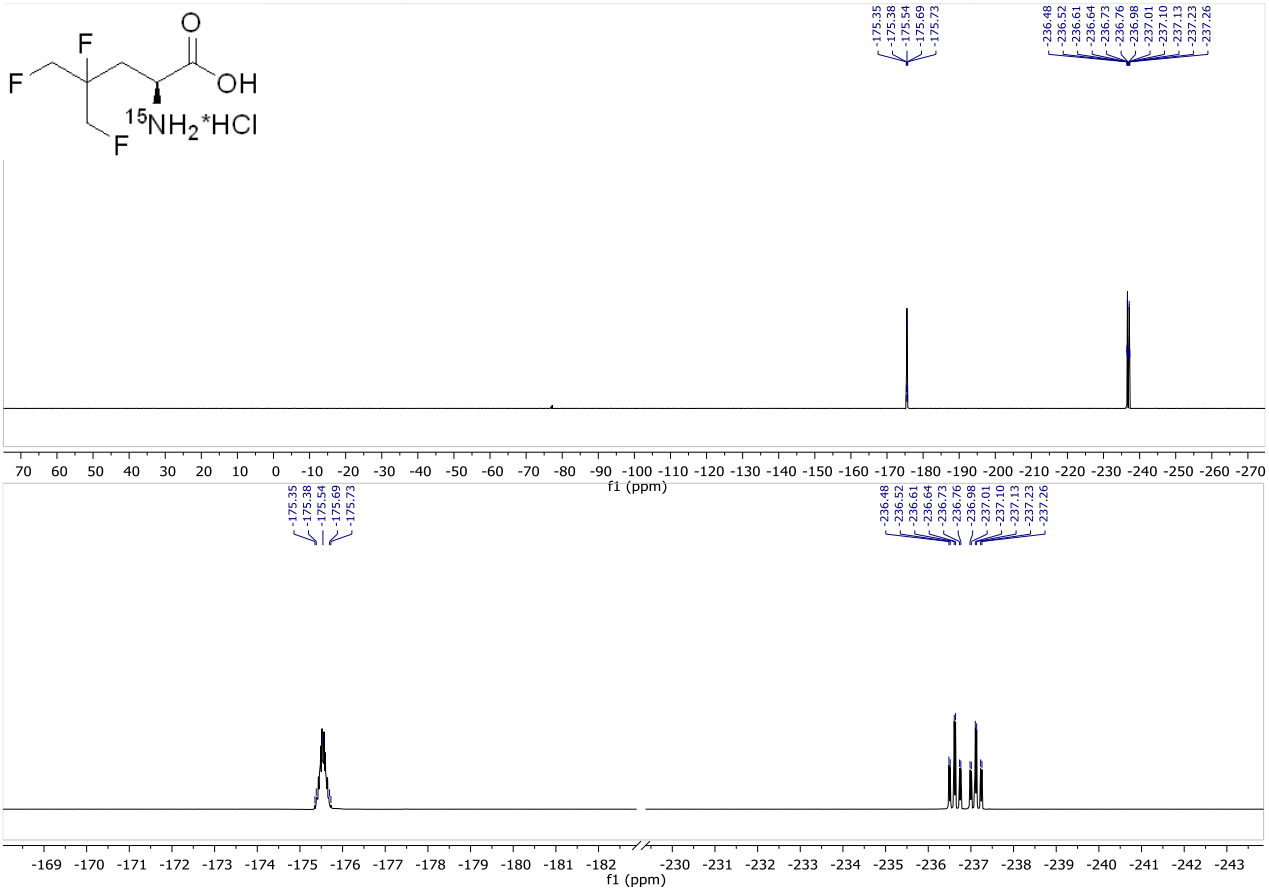
IR(ATR) spectrum of (*S*)-2-amino-4,5-difluoro-4-(fluoromethyl)pentanoic acid hydrochloride (**14**)



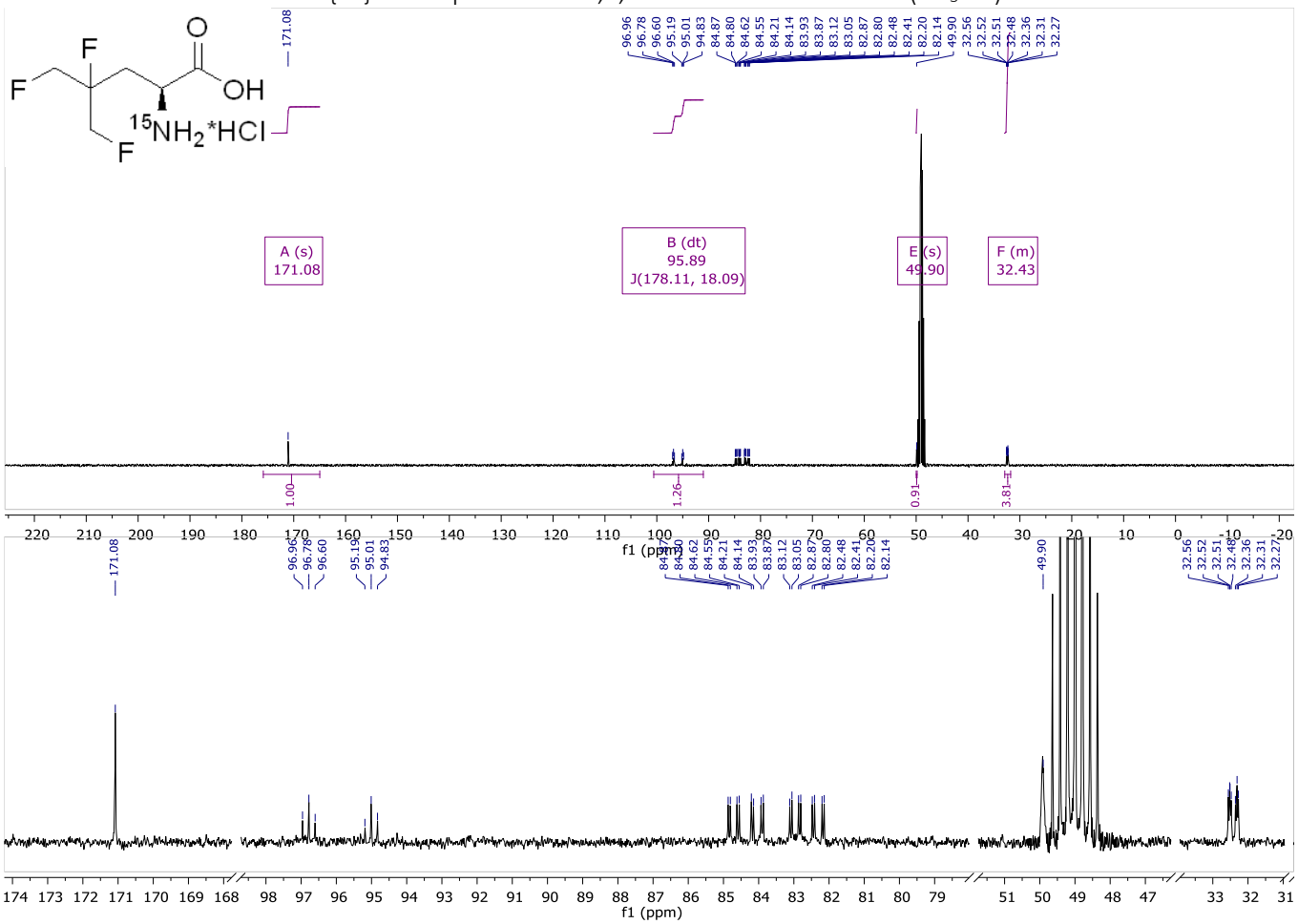
^{1}H NMR spectrum of 4,5,5’-trifluoro-*L*-leucine-^{15}N (CD_3OD)



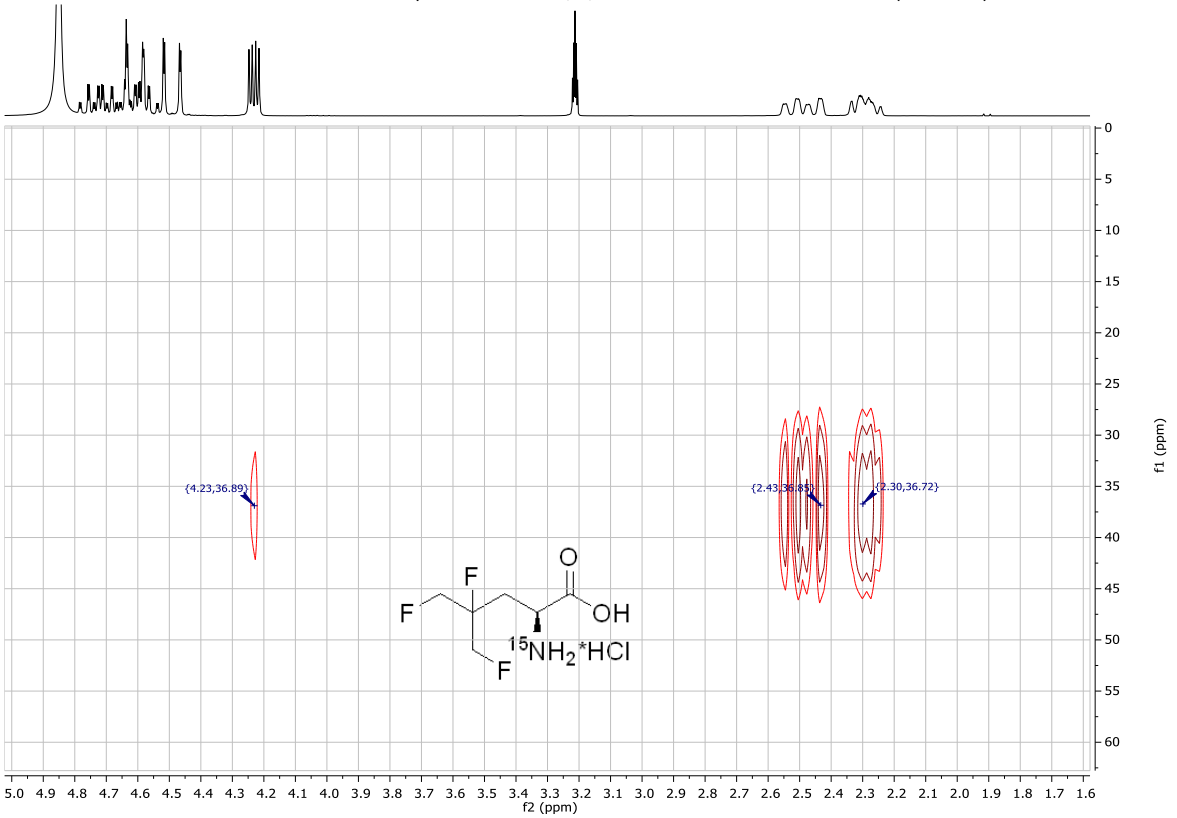
^{19}F NMR spectrum of 4,5,5’-trifluoro-*L*-leucine-^{15}N (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of 4,5,5'-trifluoro-*L*-leucine-^{15}N (CD_3OD)



$^{1}H/^{15}N$ HSQC NMR spectrum of 4,5,5'-trifluoro-*L*-leucine-^{15}N (CD_3OD)



MS: Waters Synapt G2-Si ESI+	Capillary, kV: Cone, V:	0.7 40	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18 2.1x50mm, 1.7µm

Sample:

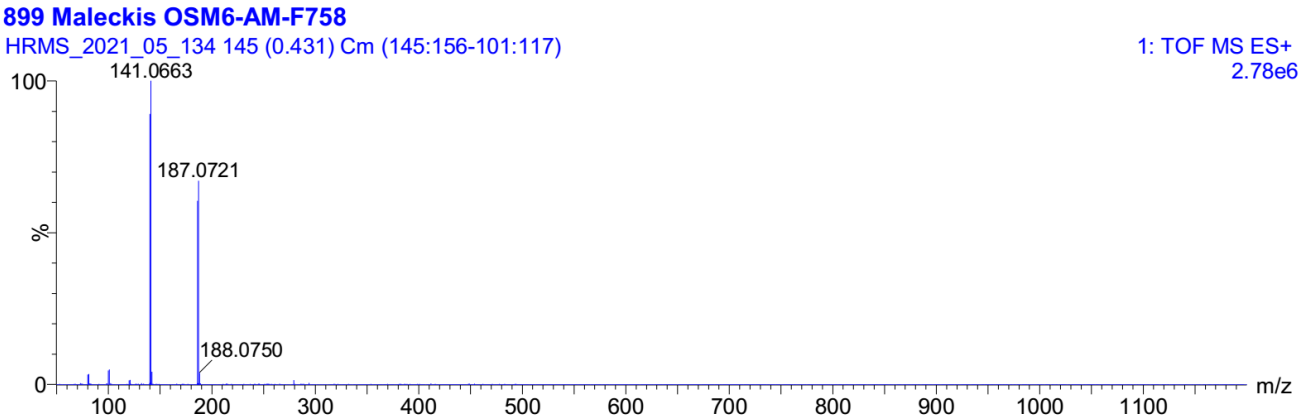
HRMS_2021_05_134 899 Maleckis OSM6-AM-F758
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:E,6 1.000000 MS_Tune Col#66

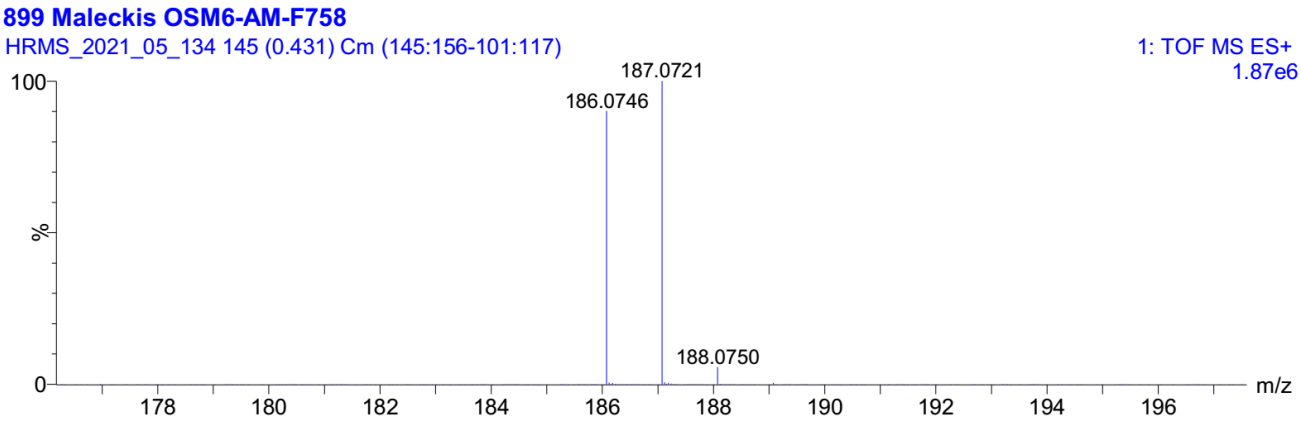
Elemental Composition Report:

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

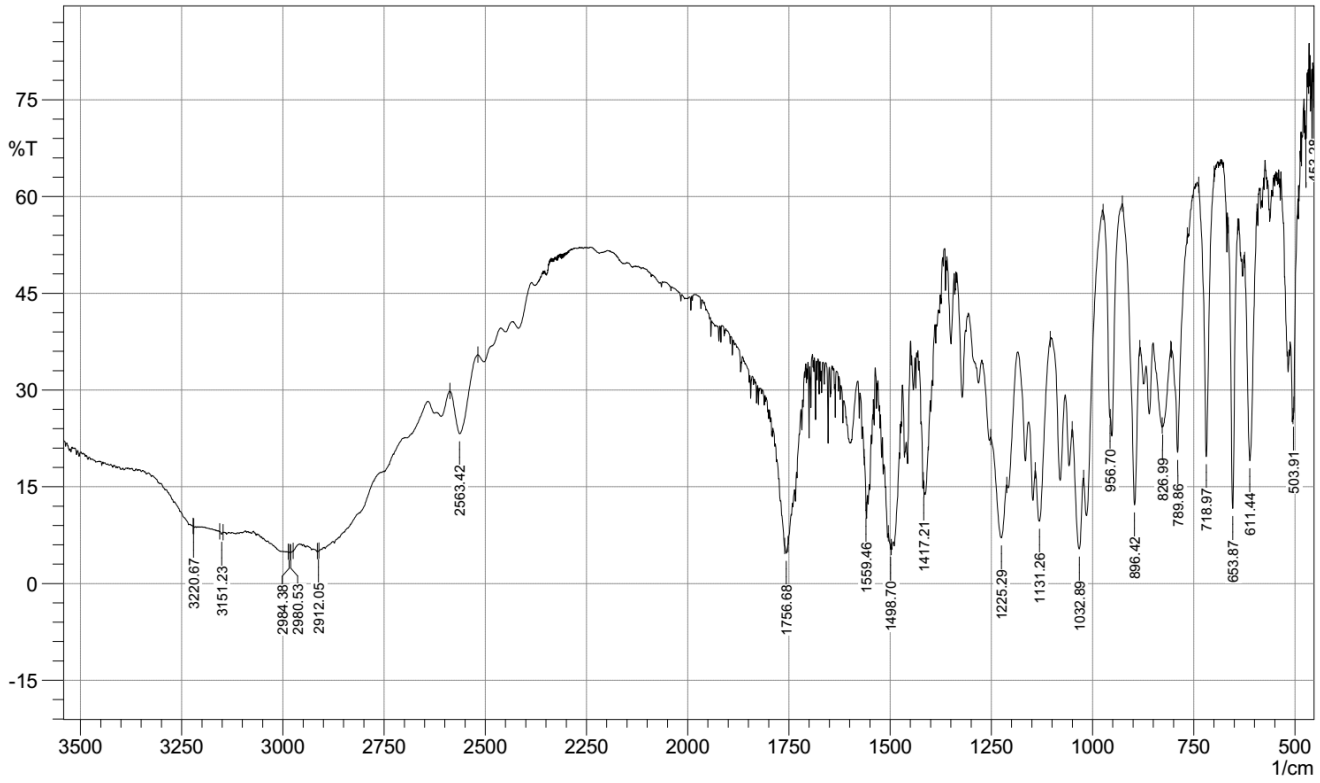
Monoisotopic Mass, Even Electron Ions
273 formula(e) evaluated with 2 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 O: 0-15 F: 3-3 14N: 0-10 15N: 0-10

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
187.0721	100.00	187.0721	0.0	0.0	1.5	628.6	2.499	8.21	C4 H9 F3 14N2 15N3
		187.0712	0.9	4.8	0.5	626.2	0.086	91.79	C6 H11 O2 F3 15N



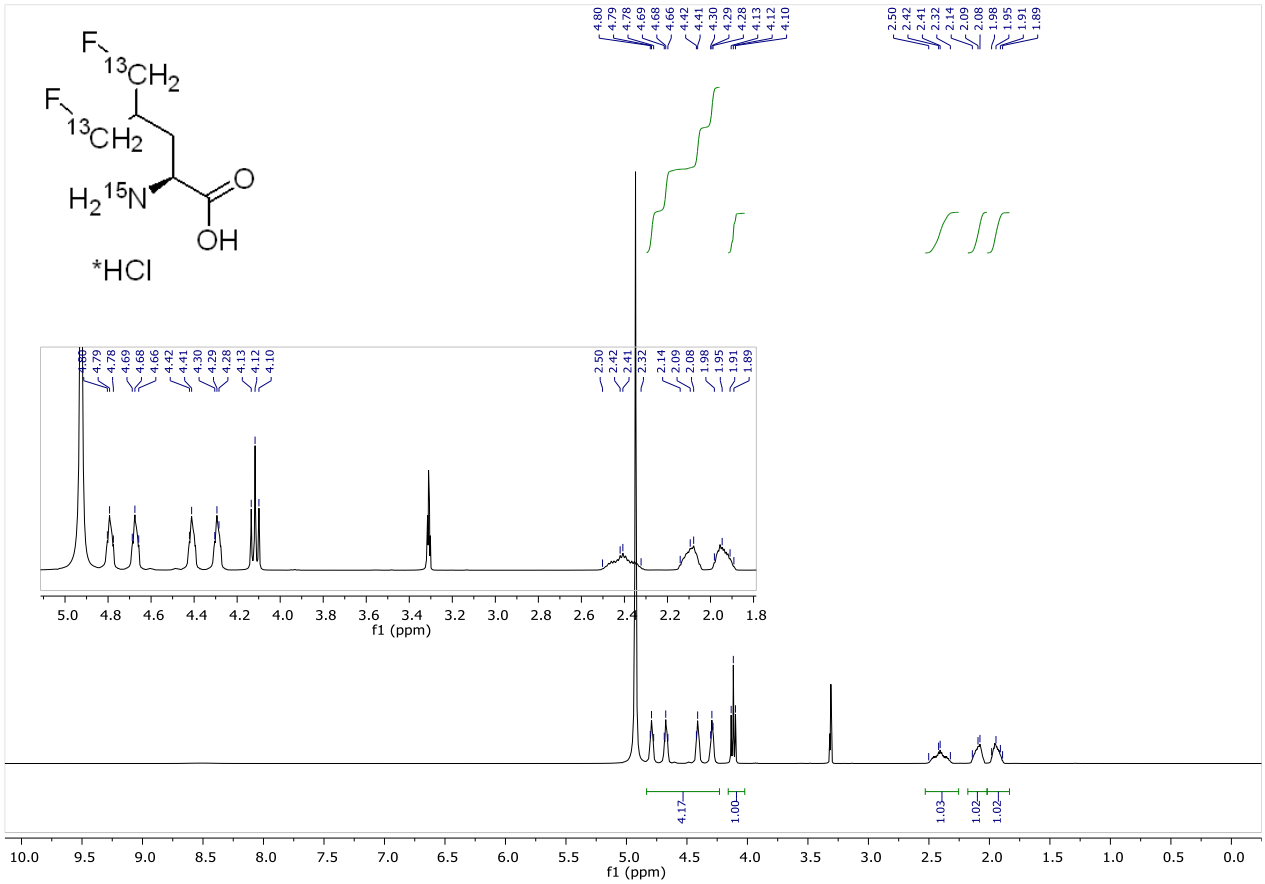


IR(ATR) spectrum of 4,5,5’-trifluoro-*L*-leucine-^{15}N (CD_3OD)

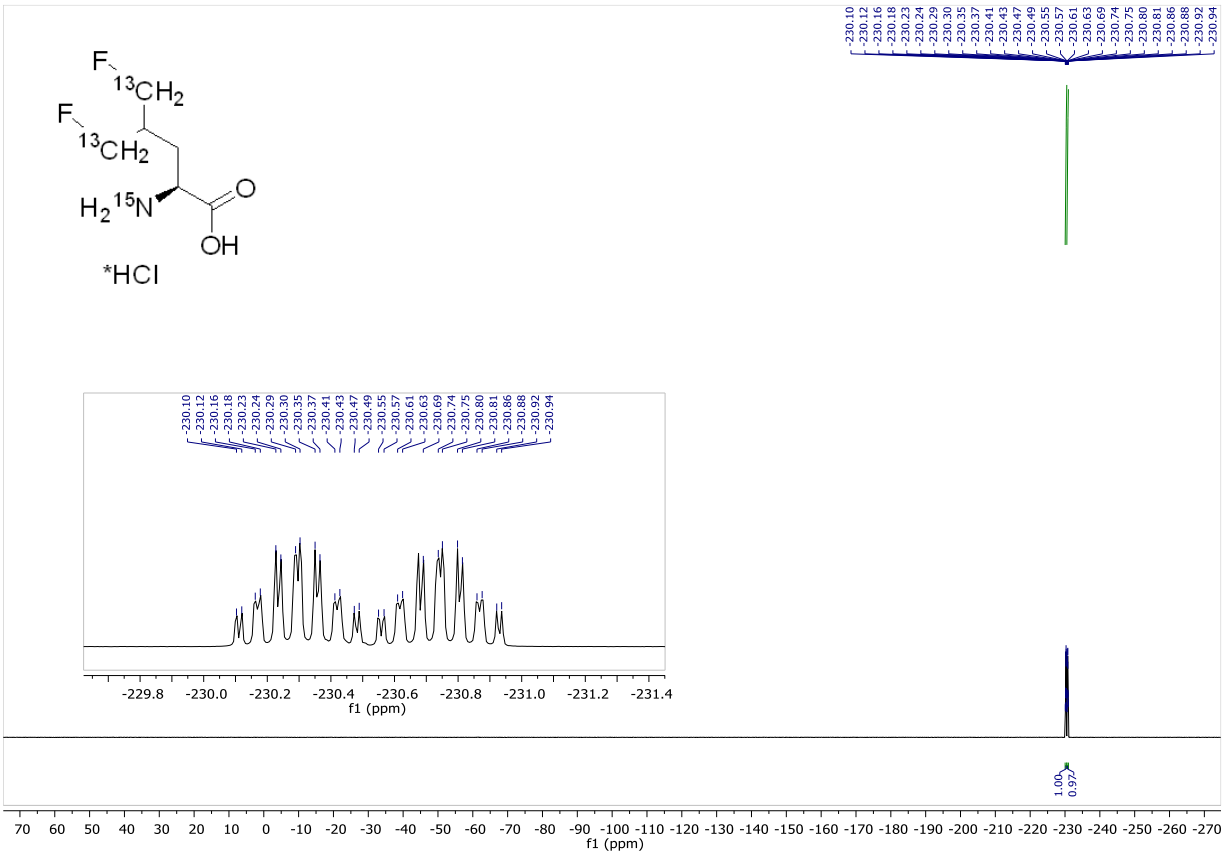


Spectra of compounds in Scheme 3

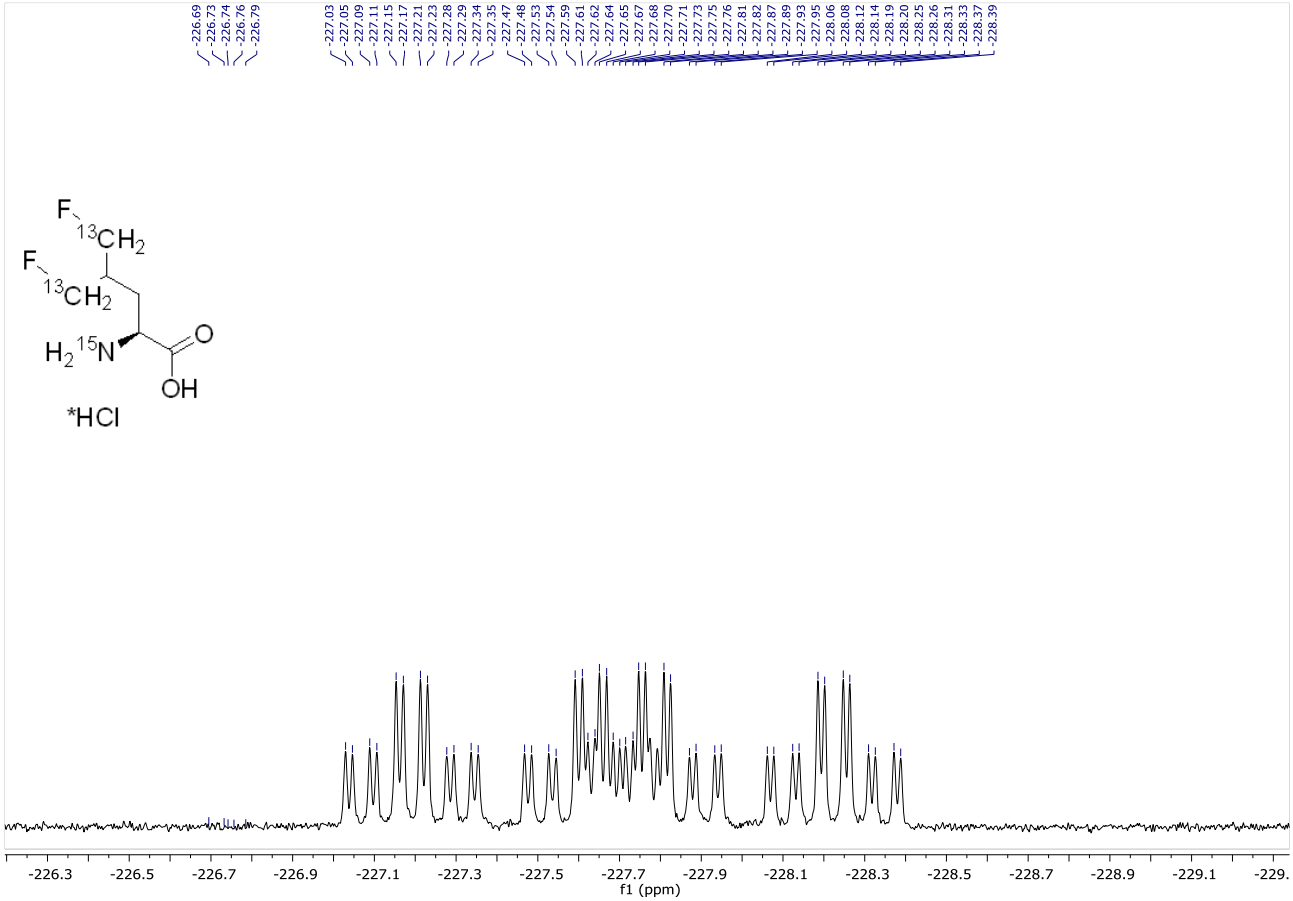
^{1}H NMR spectrum of 5,5’-difluoro-*L*-leucine- 5,5’-$^{13}C_2$-^{15}N (**18**) (CD_3OD)



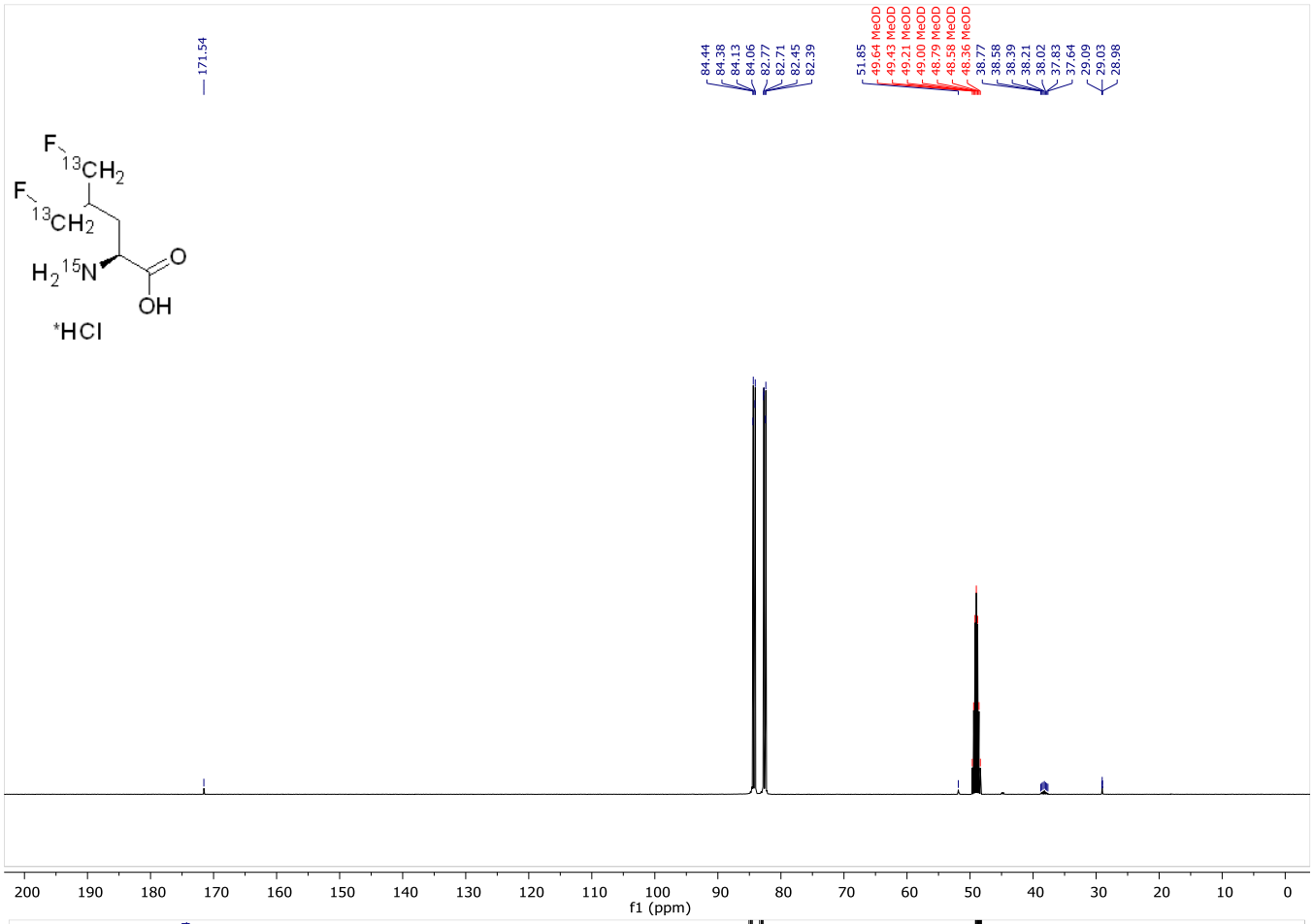
^{19}F NMR spectrum of 5,5’-difluoro-*L*-leucine- 5,5’-$^{13}C_2$-^{15}N (**18**) (CD_3OD)

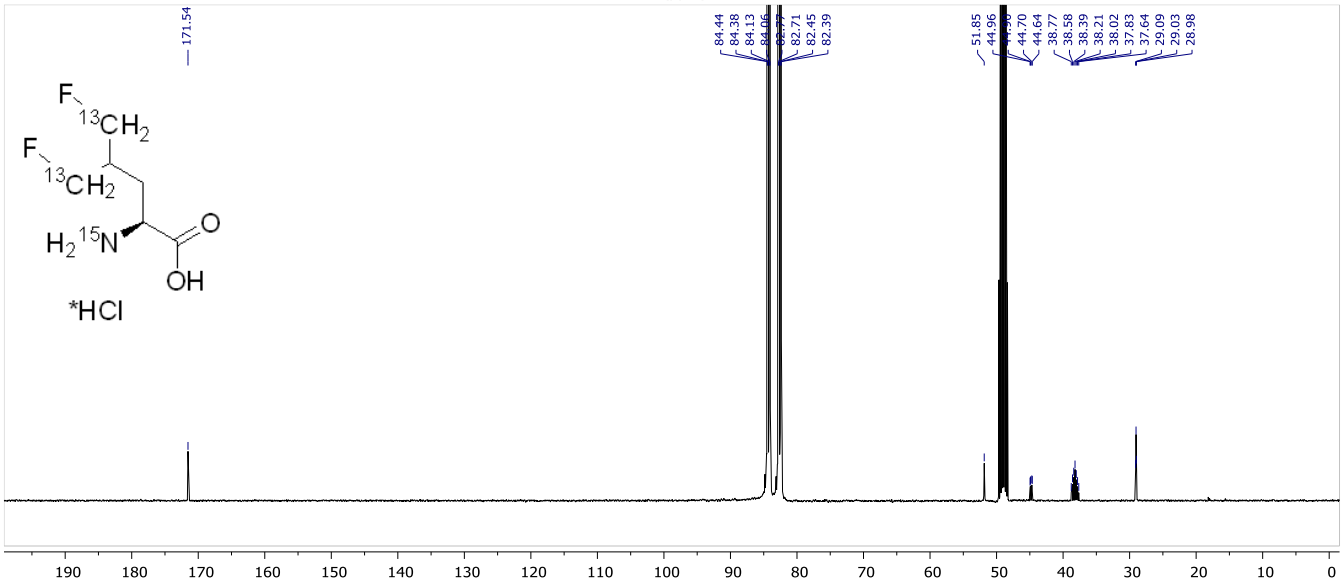


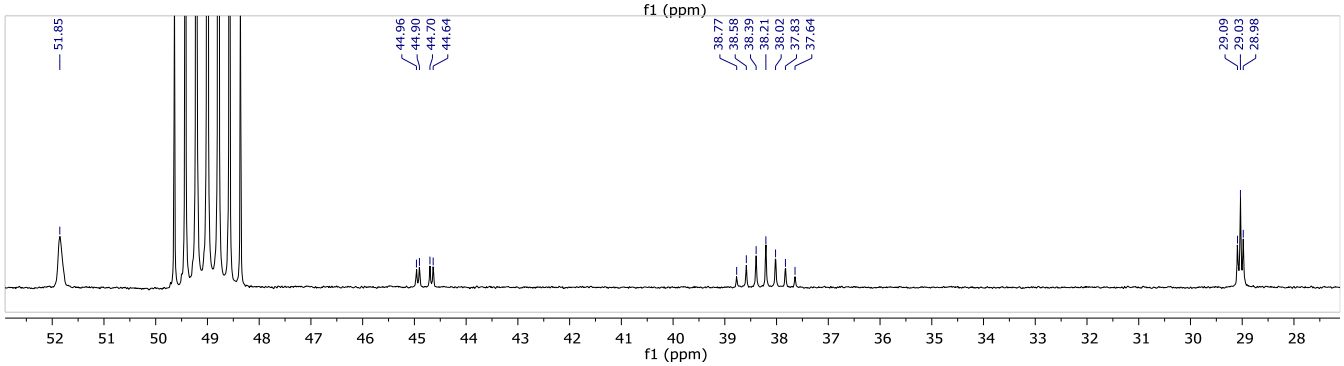
^{19}F NMR spectrum of 5,5’-difluoro-*L*-leucine- 5,5’-$^{13}C_2$-^{15}N (**18**) (D_2O)



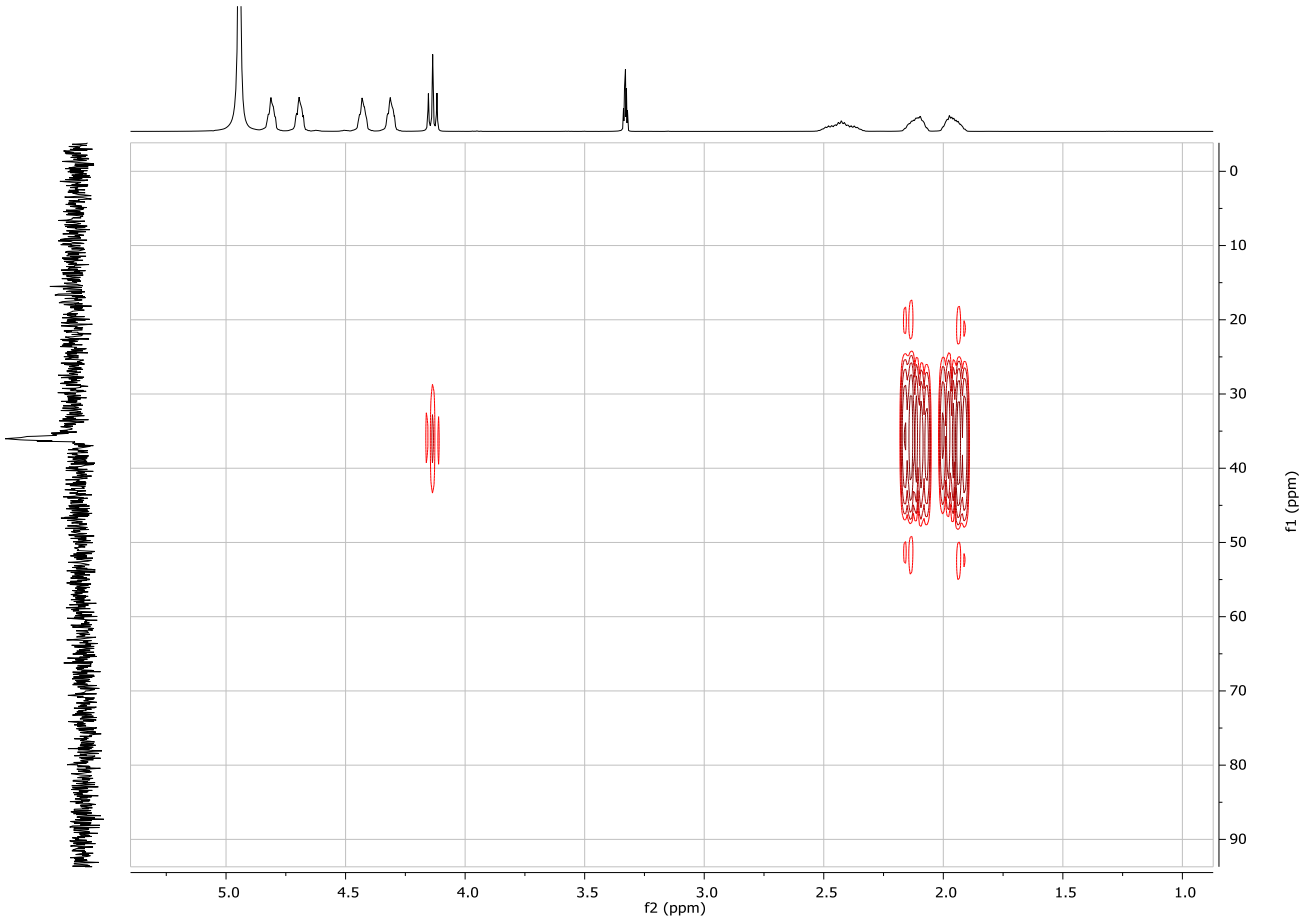
$^{13}C\{^{1}H\}$ NMR spectrum of 5,5'-difluoro-*L*-leucine- 5,5'-$^{13}C_2$-^{15}N (**18**) (CD_3OD)







$^{1}H/^{15}N$ HMBC NMR spectrum of 5,5'-difluoro-*L*-leucine- 5,5'-$^{13}C_2$-^{15}N (**18**) (CD_3OD)



HRMS of 5,5’-difluoro-*L*-leucine- 5,5’-$^{13}C_2$-^{15}N (**18**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2020_01_020 1639 Maleckis OSM6-AM-ValF2C13

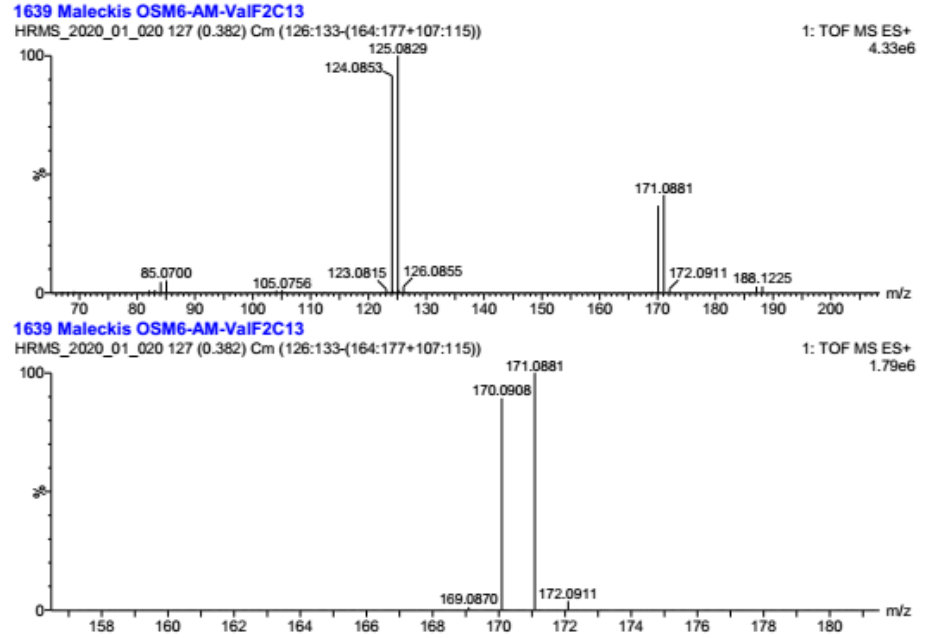
MS_POS_RES_4min ACN_Form_5-98_040_4min 2:E,5 1.000000 MS_Tune Col#43

Elemental Composition Report:

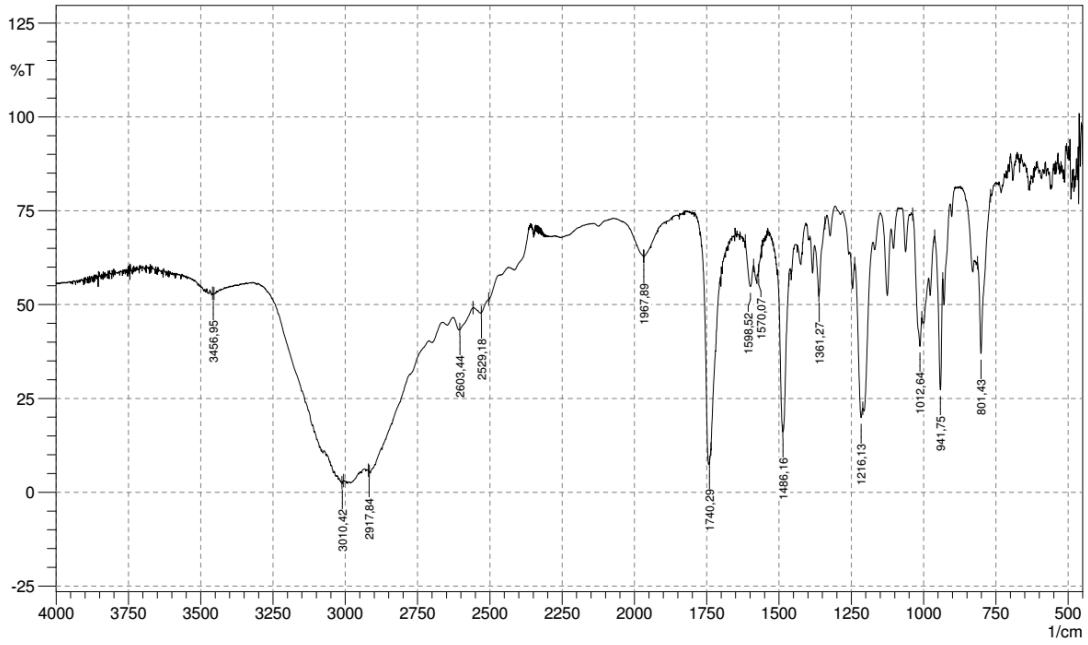
Multiple Mass Analysis: 2 mass(es) processed
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2132 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
12C: 1-50 13C: 0-2 H: 1-100 14N: 0-10 15N: 0-10 O: 0-10 F: 2-2

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
170.0908	89.30	170.0903	0.5	2.9	0.5	408.1	0.146	86.45	12C4 13C2 H12 14N O2 F2
		170.0912	-0.4	-2.4	1.5	409.9	1.999	13.55	12C2 13C2 H10 14N3 15N2 F2
171.0881	100.00	171.0874	0.7	4.1	0.5	309.5	0.570	56.53	12C4 13C2 H12 15N O2 F2
		171.0887	-0.6	-3.5	0.5	309.8	0.847	42.88	12C2 13C H10 14N5 O F2
		171.0882	-0.1	-0.6	1.5	314.1	5.143	0.58	12C2 13C2 H10 14N2 15N3 F2

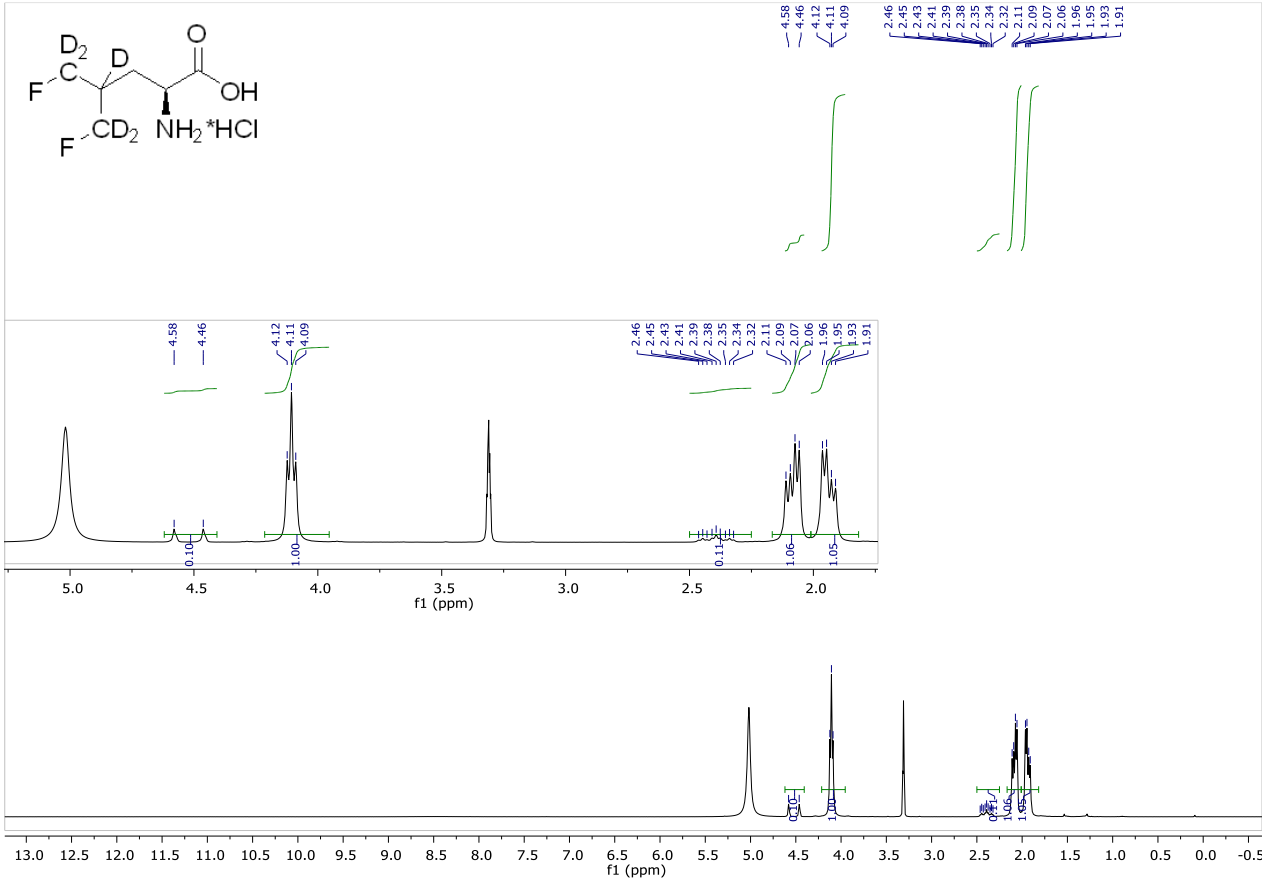


IR(ATR) spectrum of 5,5’-difluoro-*L*-leucine- 5,5’-$^{13}C_2$-^{15}N (**18**)

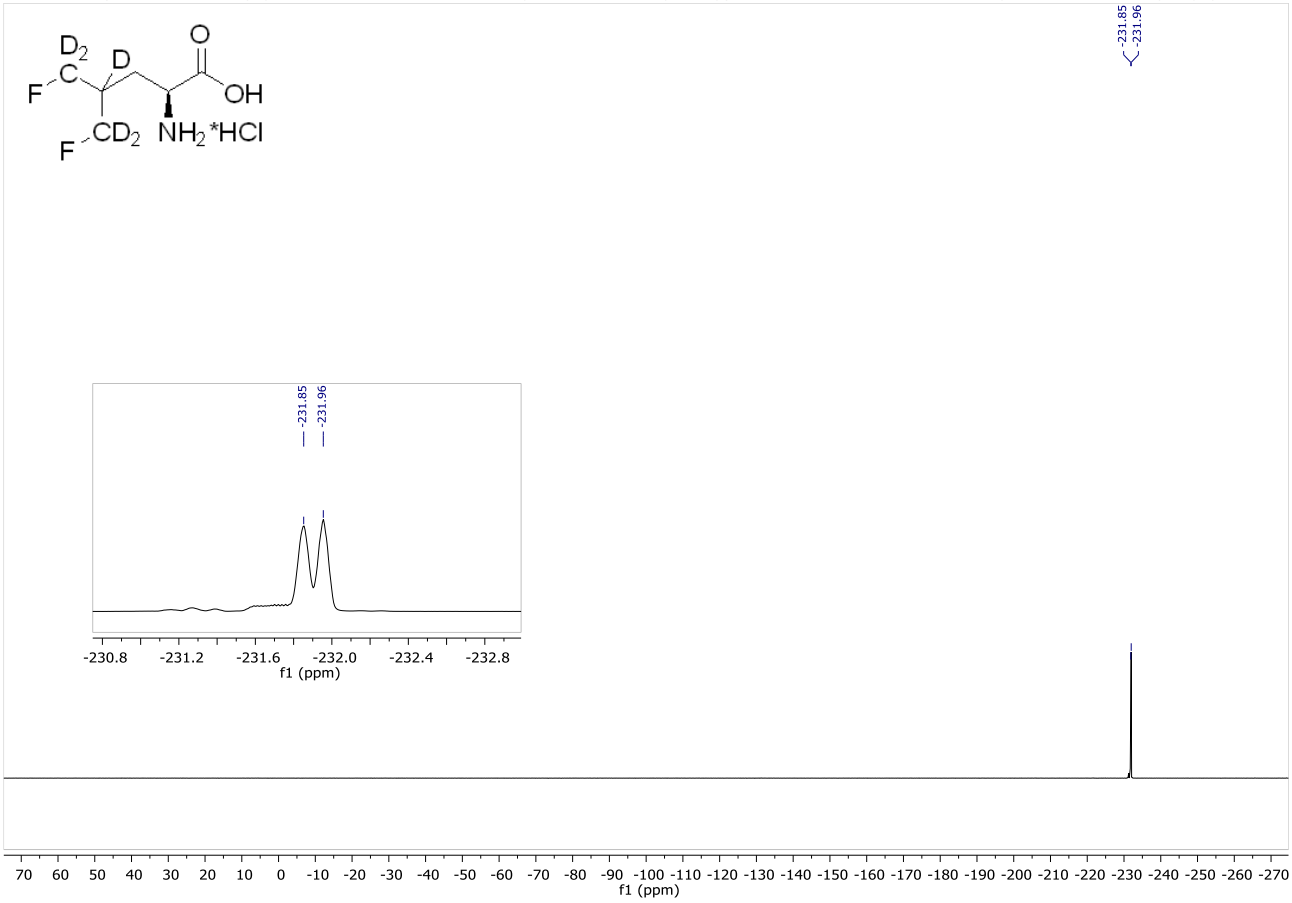


Spectra of compounds in Scheme 4

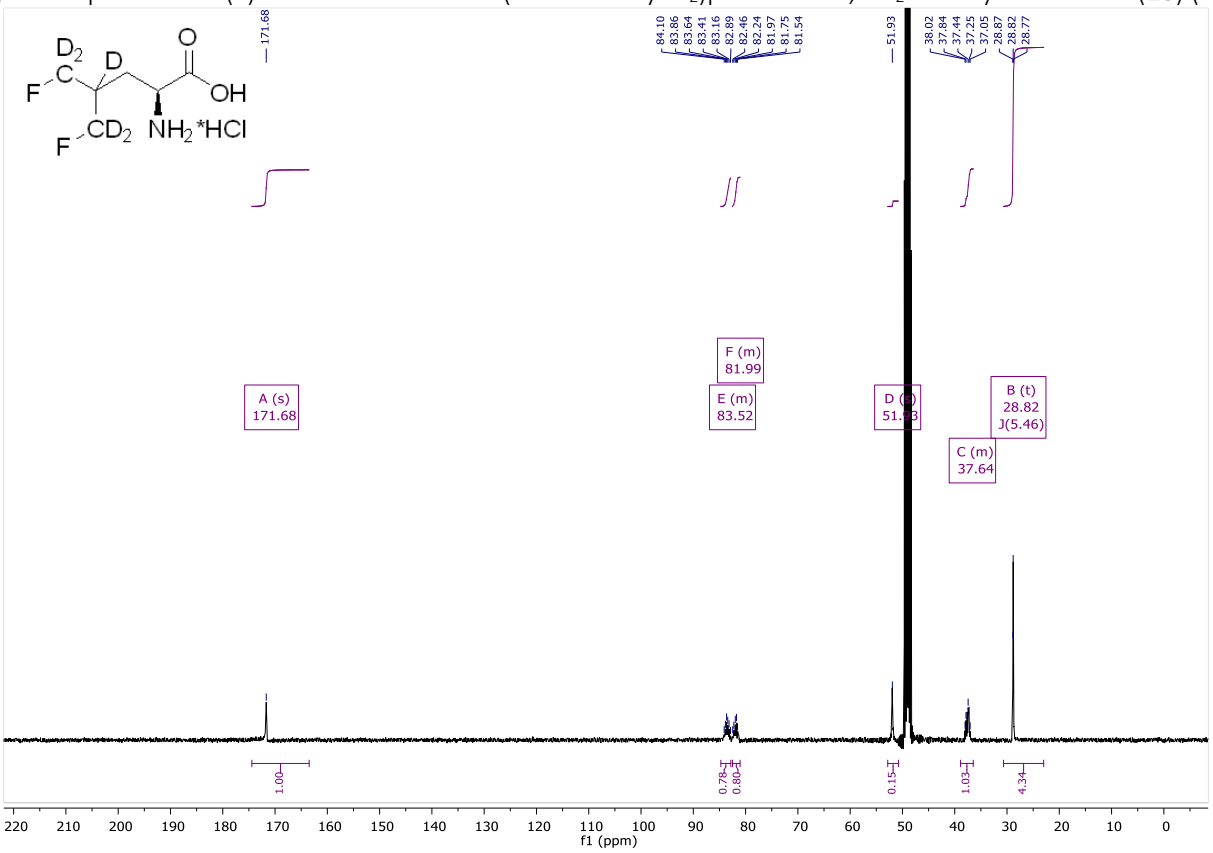
^{1}H NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d$_2$)pentanoic-5,5-d$_2$ acid hydrochloride (**20**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d$_2$)pentanoic-5,5-d$_2$ acid hydrochloride (**20**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-5,5-d_2 acid hydrochloride (**20**) (CD_3OD)



HRMS of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-5,5-d_2 acid hydrochloride (**20**) (CD_3OD)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

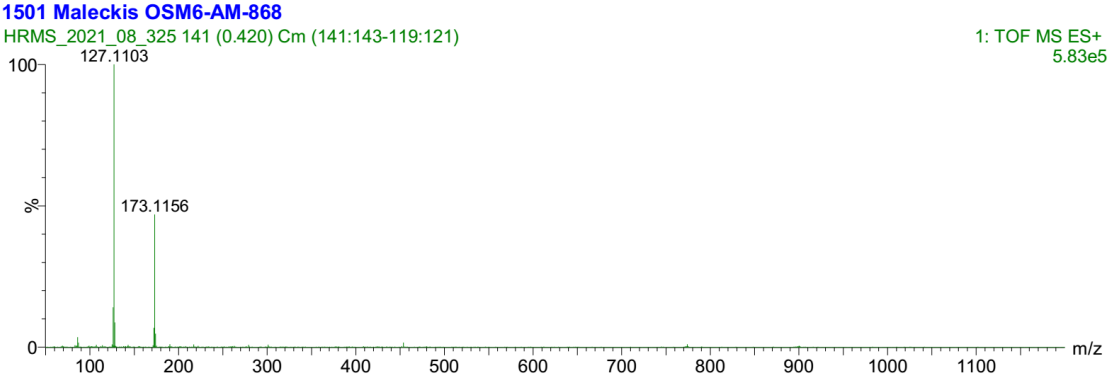
HRMS_2021_08_325 1501 Maleckis OSM6-AM-868
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:E,8 1.000000 MS_Tune Col#66

Elemental Composition Report:

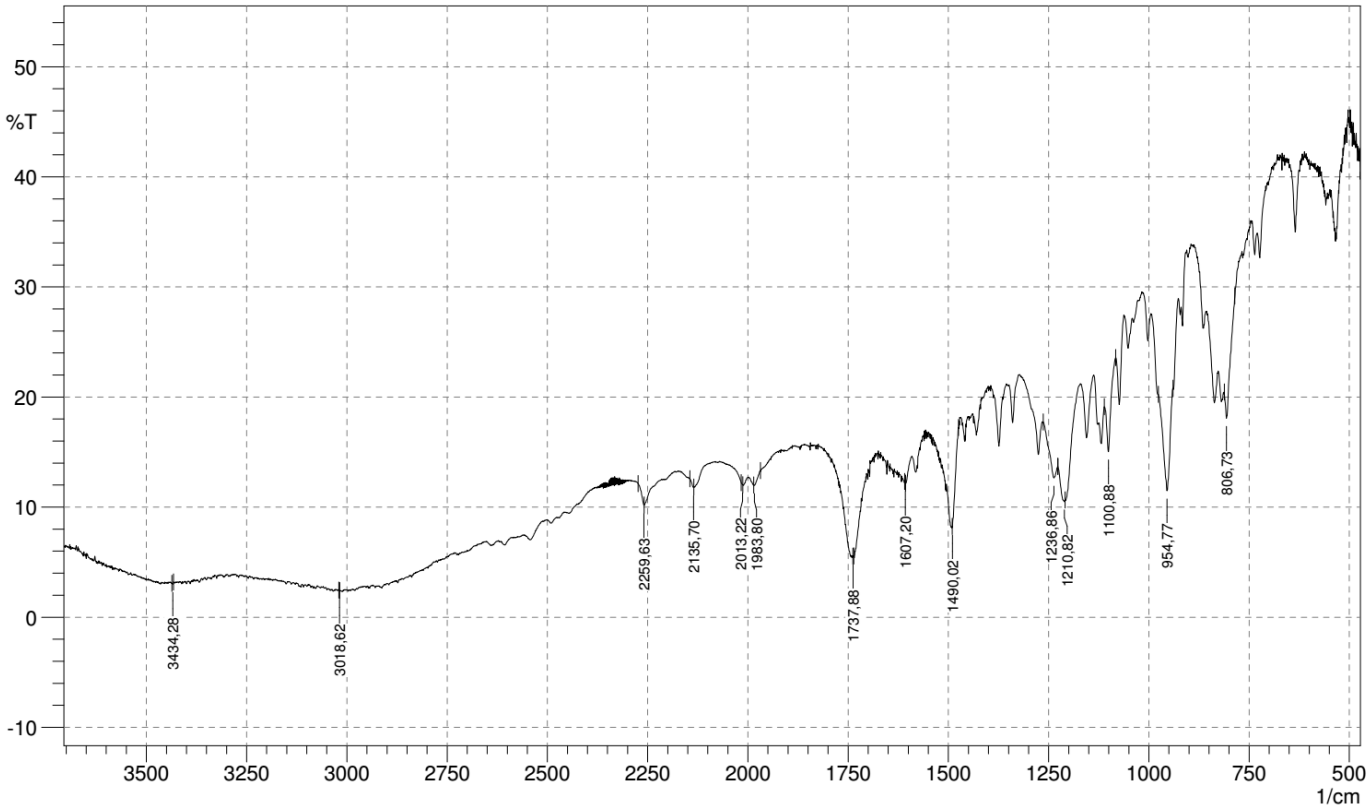
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
4729 formula(e) evaluated with 3 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 1H: 1-105 2H: 1-10 N: 0-10 O: 0-10 F: 2-2 Na: 0-1

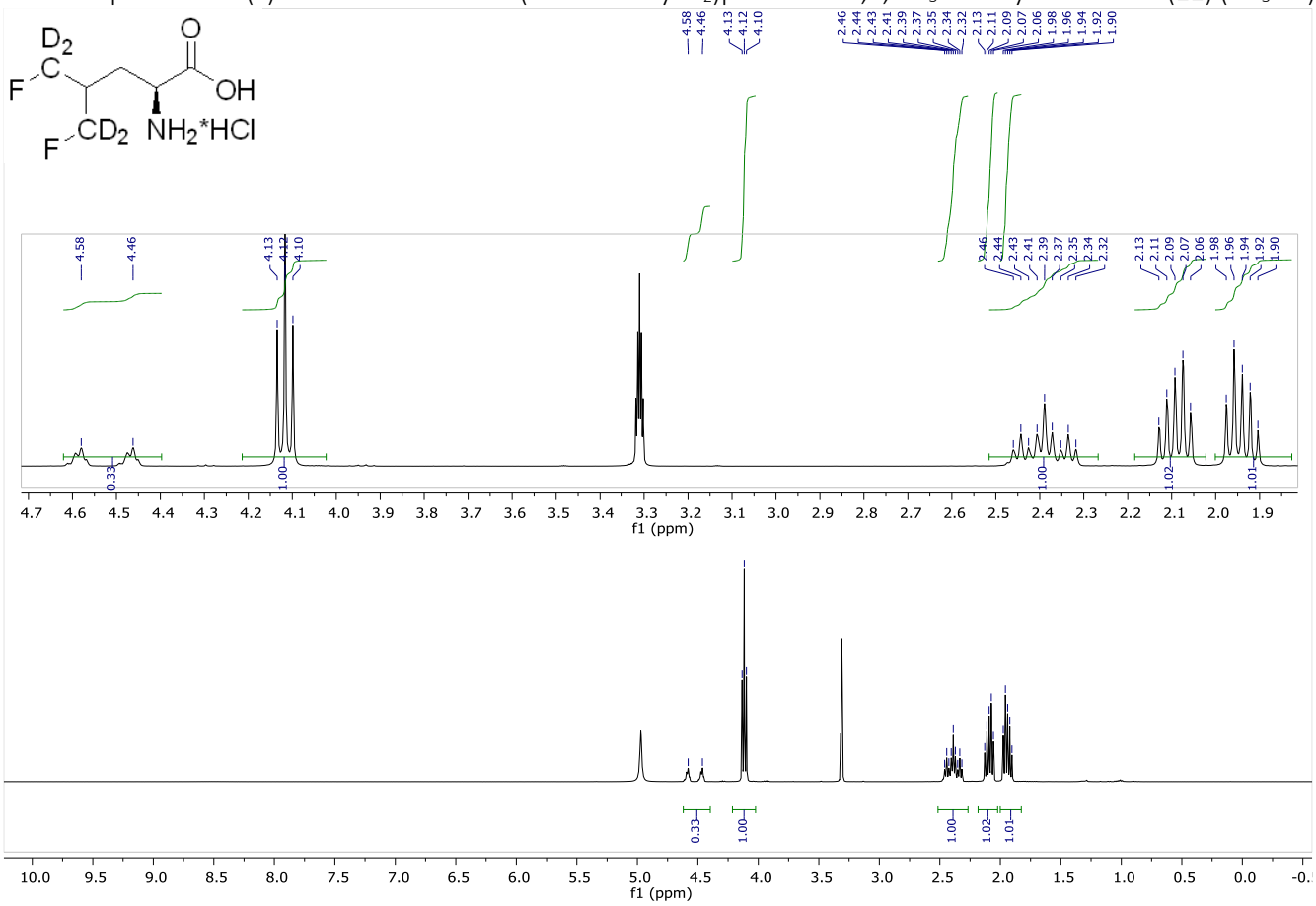
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
173.1156	100.00	173.1154	0.2	1.2	0.5	575.5	2.457	8.57	C2 1H7 2H3 N7 F2
		173.1152	0.4	2.3	0.5	575.0	1.876	15.31	C4 1H7 2H4 N4 O F2
		173.1150	0.6	3.5	0.5	573.4	0.273	76.12	C6 1H7 2H5 N O2 F2



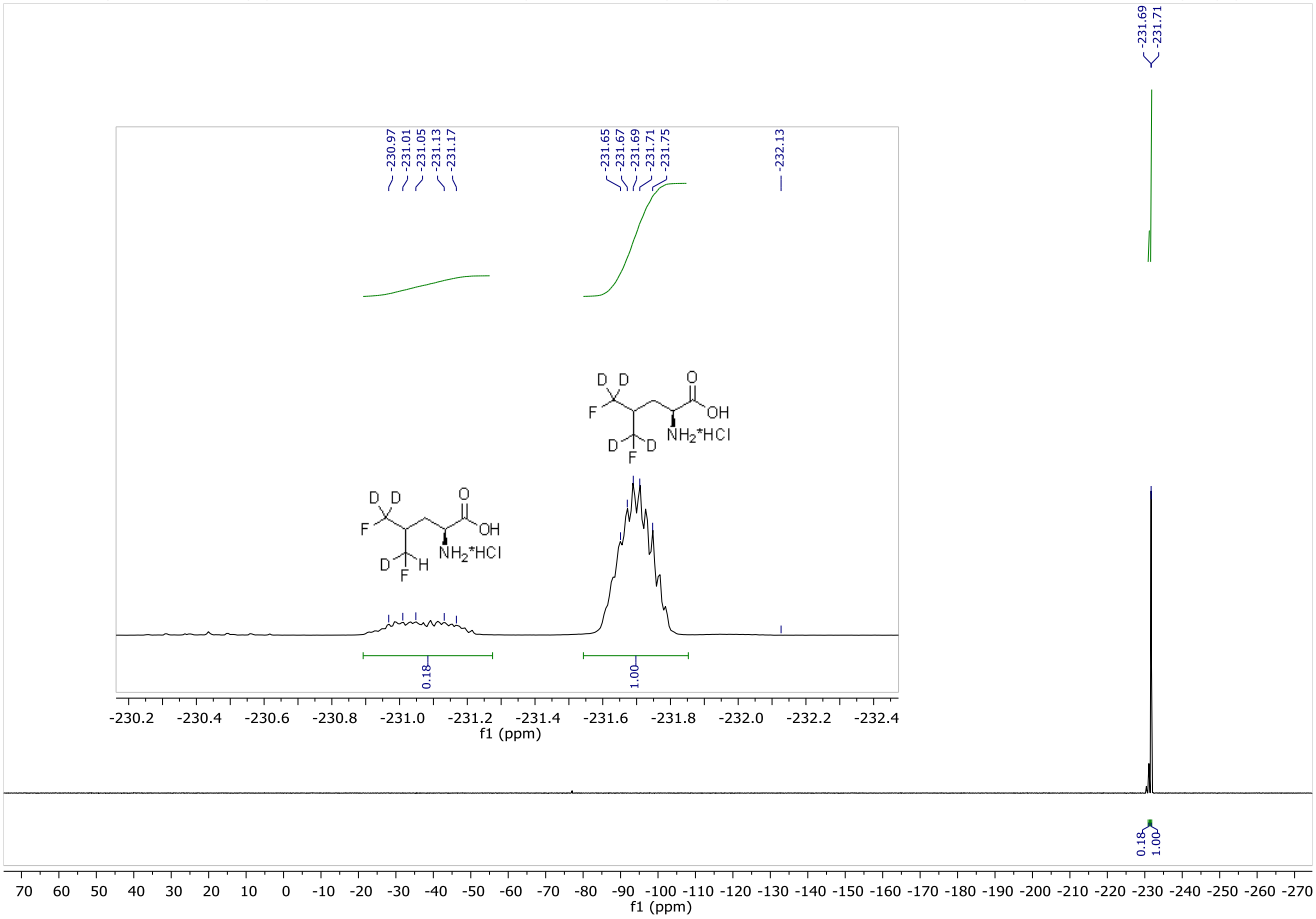
IR(ATR) spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-5,5-d_2 acid hydrochloride (**20**) (CD_3OD)



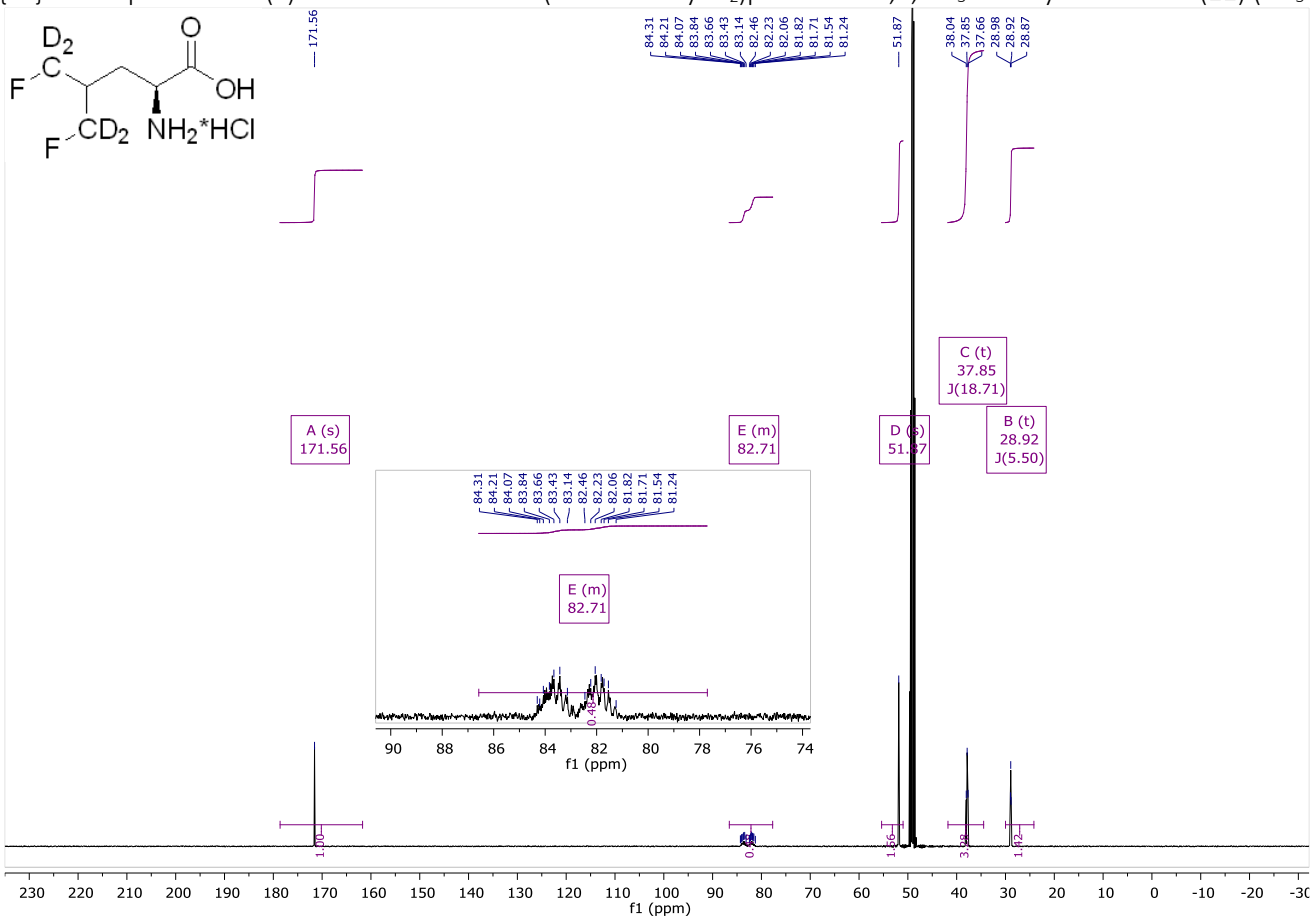
^{1}H NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d$_2$)pentanoic-4,5,5-d$_3$ acid hydrochloride (**22**) (CD$_3$OD)



^{19}F NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d$_2$)pentanoic-4,5,5-d$_3$ acid hydrochloride (**22**) (CD$_3$OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-4,5,5-d_3 acid hydrochloride (**22**) (CD_3OD)



HRMS of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-4,5,5-d_3 acid hydrochloride (**22**) (CD_3OD)

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

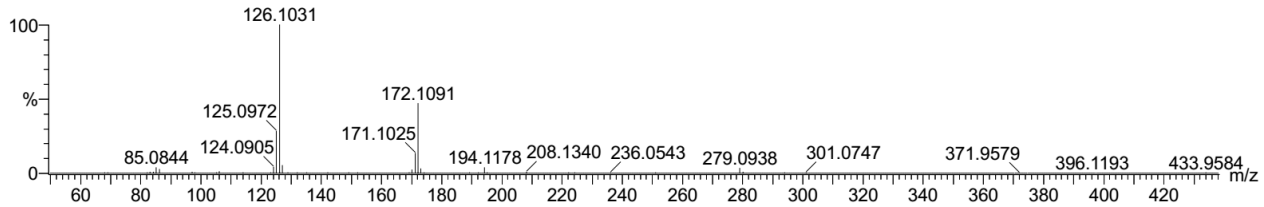
Monoisotopic Mass, Even Electron Ions
247 formula(e) evaluated with 3 results within limits (up to 3 best isotopic matches for each mass)
Elements Used:
C: 1-80 1H: 0-10 2H: 0-4 N: 1-3 O: 1-3 F: 0-2

1772 Maleckis OSM6-AM-F-928
20-Oct-2021

HRMS_2021_10_303 133 (0.398) Cm (132:137-154:157)

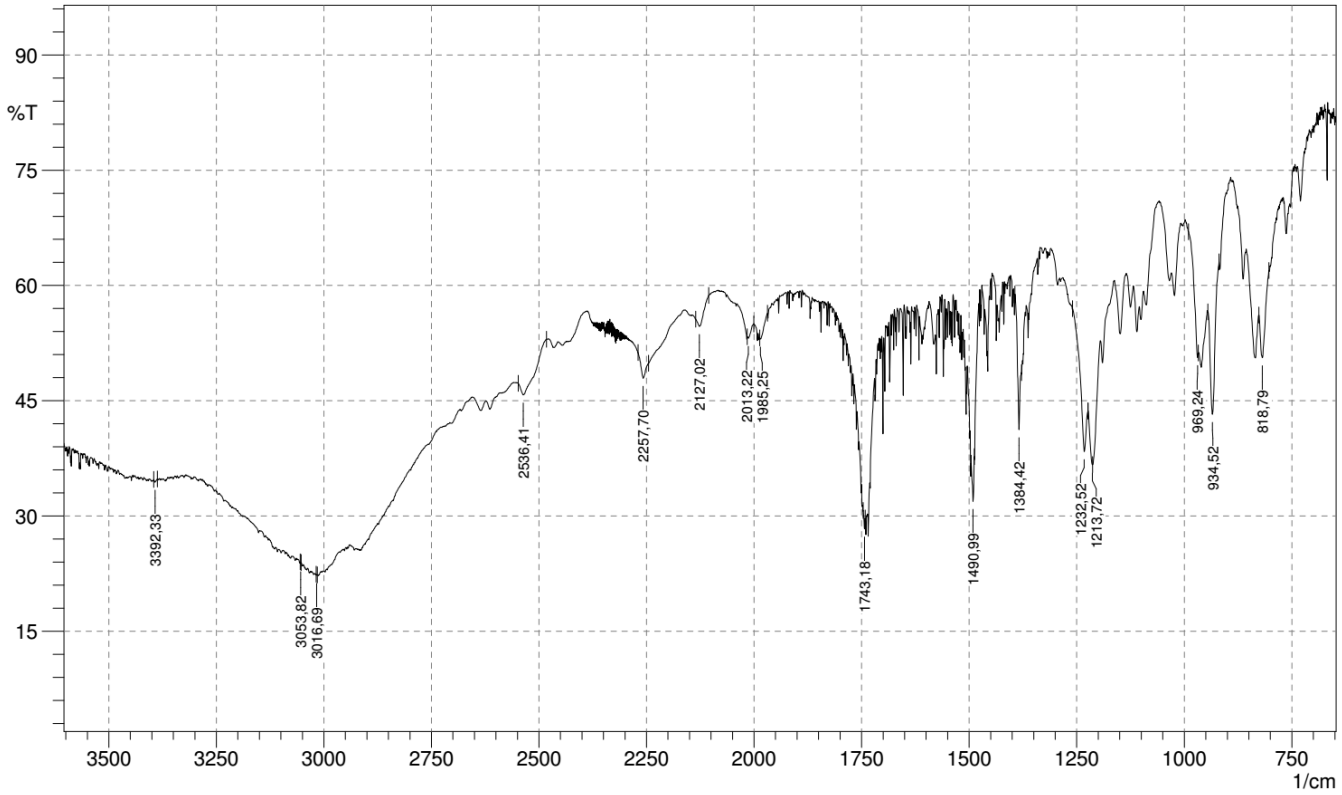
OSI/FOKL-MS
Synapt G2-Si

1: TOF MS ES+
3.02e+006



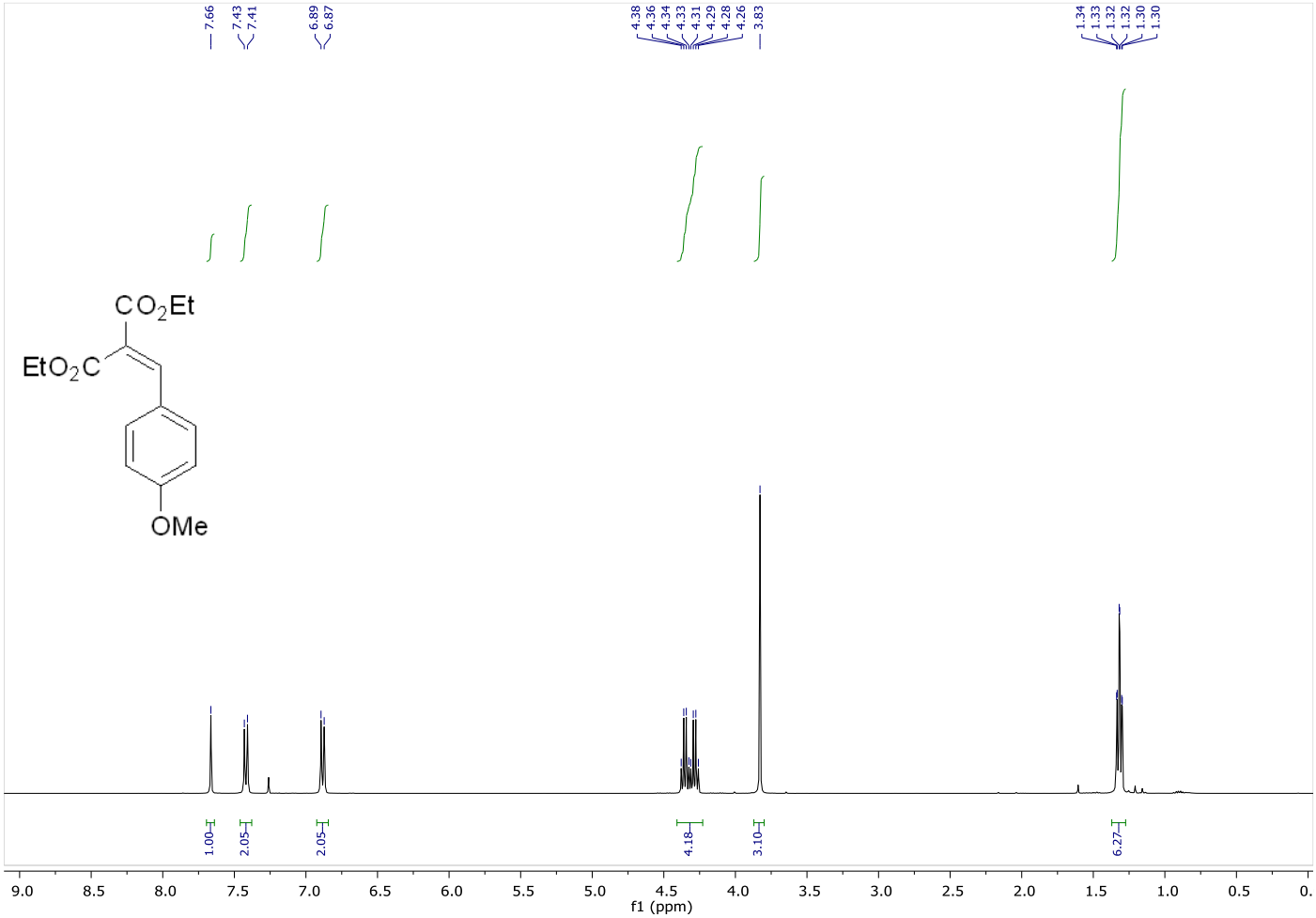
Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Conf(%)	Formula
172.1091	172.1087	0.4	2.3	0.5	98.88	C6 1H8 2H4 N O2 F2
	172.1055	3.6	20.9	3.5	1.10	C7 1H10 2H2 N3 O2
	172.1076	1.5	8.7	4.5	0.02	C9 1H7 2H4 N O F

IR(ATR) spectrum of (*S*)-2-Amino-5-fluoro-4-(fluoromethyl-d_2)pentanoic-4,5,5-d_3 acid hydrochloride (**22**) (CD_3OD)

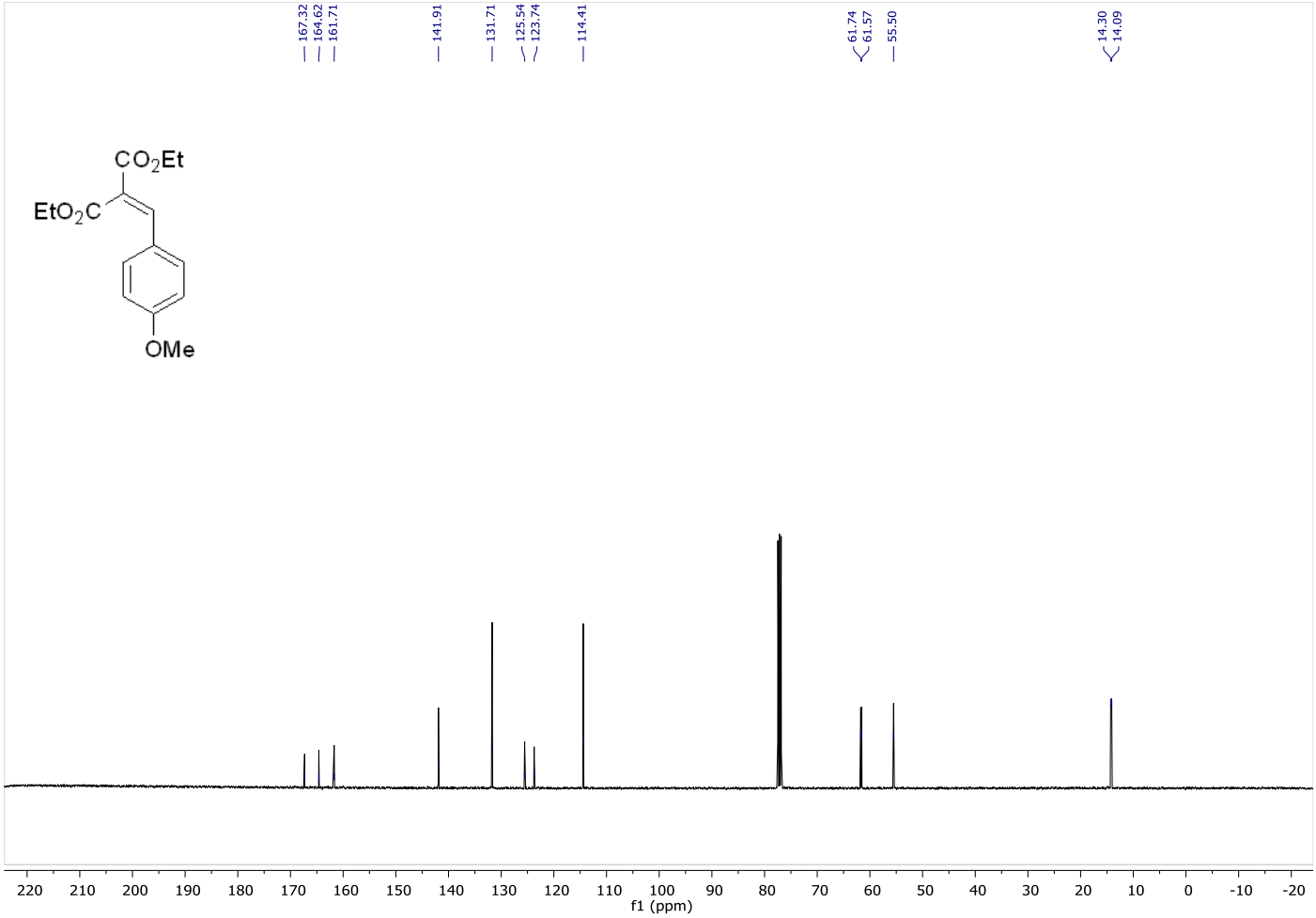


Spectra of compounds in Scheme 5

^{1}H NMR spectrum of diethyl 2-(4-methoxybenzylidene)malonate (**23**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of diethyl 2-(4-methoxybenzylidene)malonate (**23**) ($CDCl_3$)



HRMS of diethyl 2-(4-methoxybenzylidene)malonate (**23**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18		
ESI+	Cone, V:	40			2.1x50mm, 1.7µm		

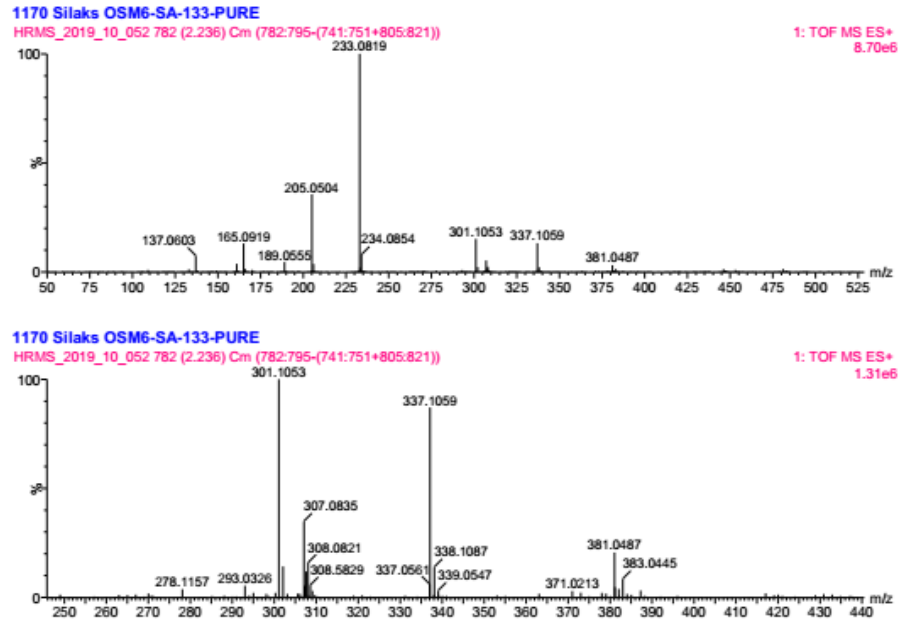
Sample:
HRMS_2019_10_052 1170 Silaks OSM6-SA-133-PURE
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:D,2 0.500000 MS_Tune Col#43

Elemental Composition Report:

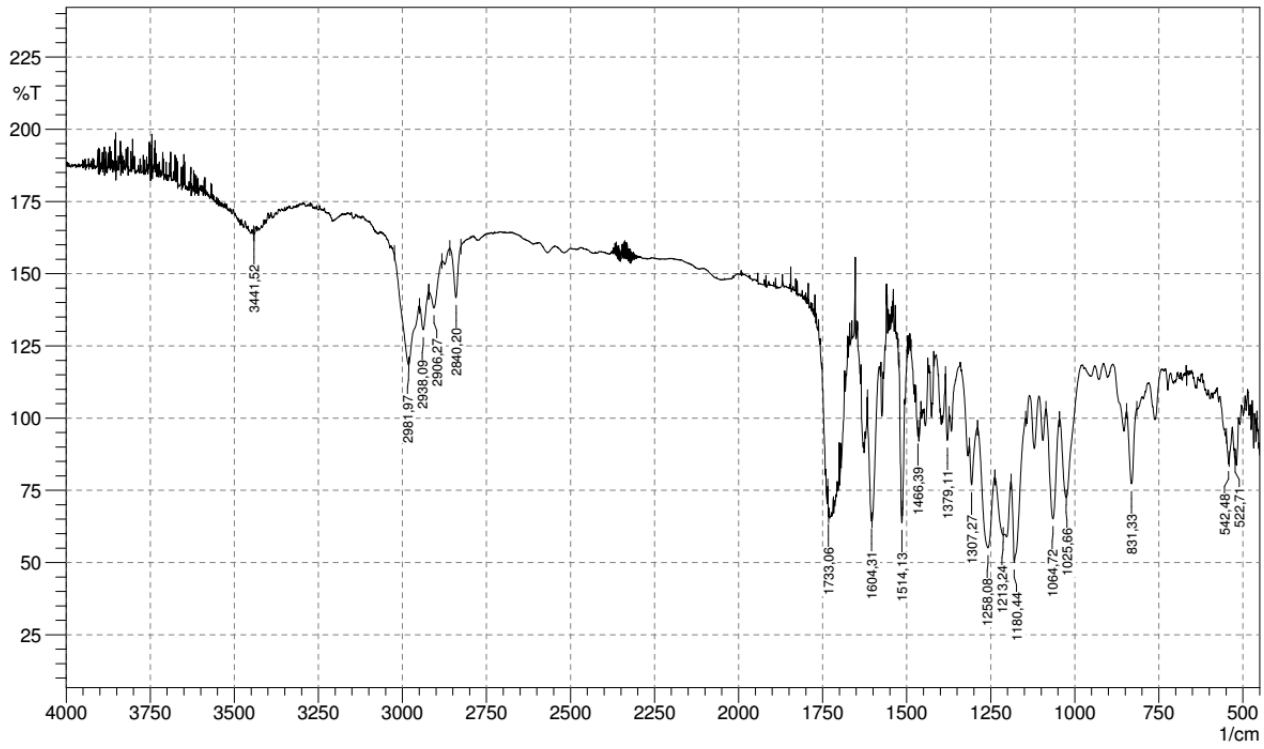
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 90.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
31 formula(e) evaluated with 1 results within limits (up to 3 closest results for each mass)
Elements Used:
C: 0-50 H: 1-60 O: 1-10 Na: 1-1

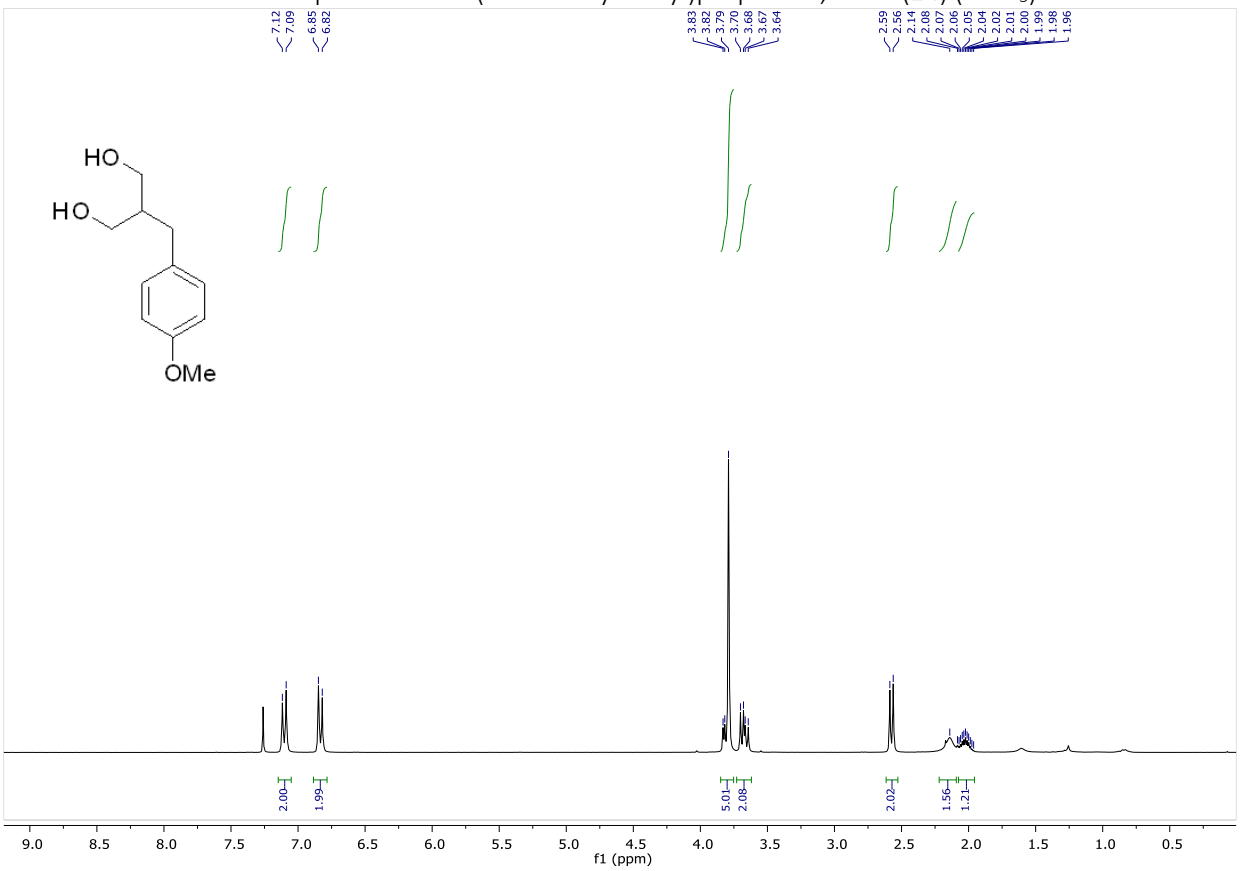
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
301.1053	100.00	301.1052	0.1	0.3	6.5	120.9	n/a	n/a	C15 H18 O5 Na



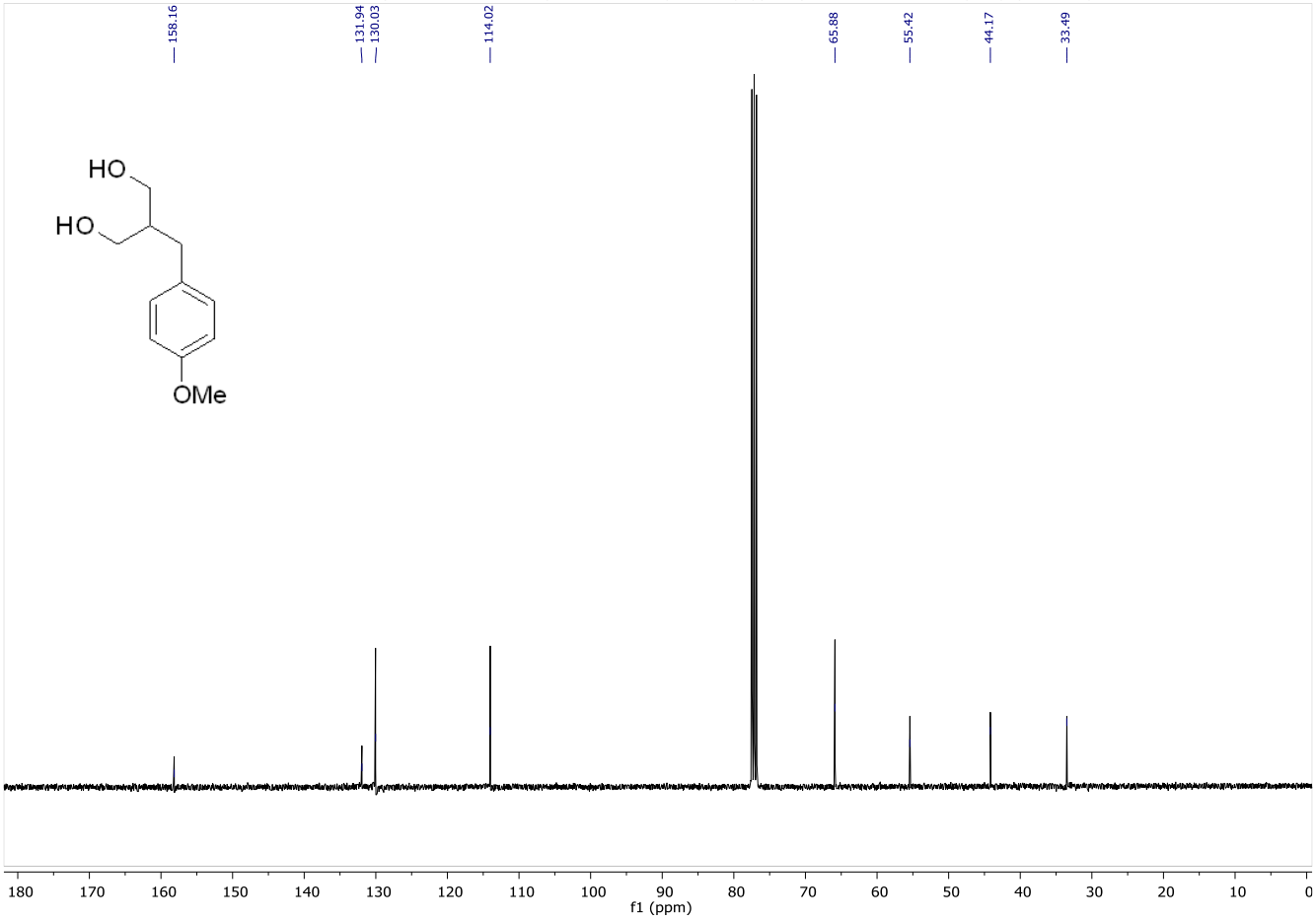
IR(ATR) spectrum of diethyl 2-(4-methoxybenzylidene)malonate (**23**)



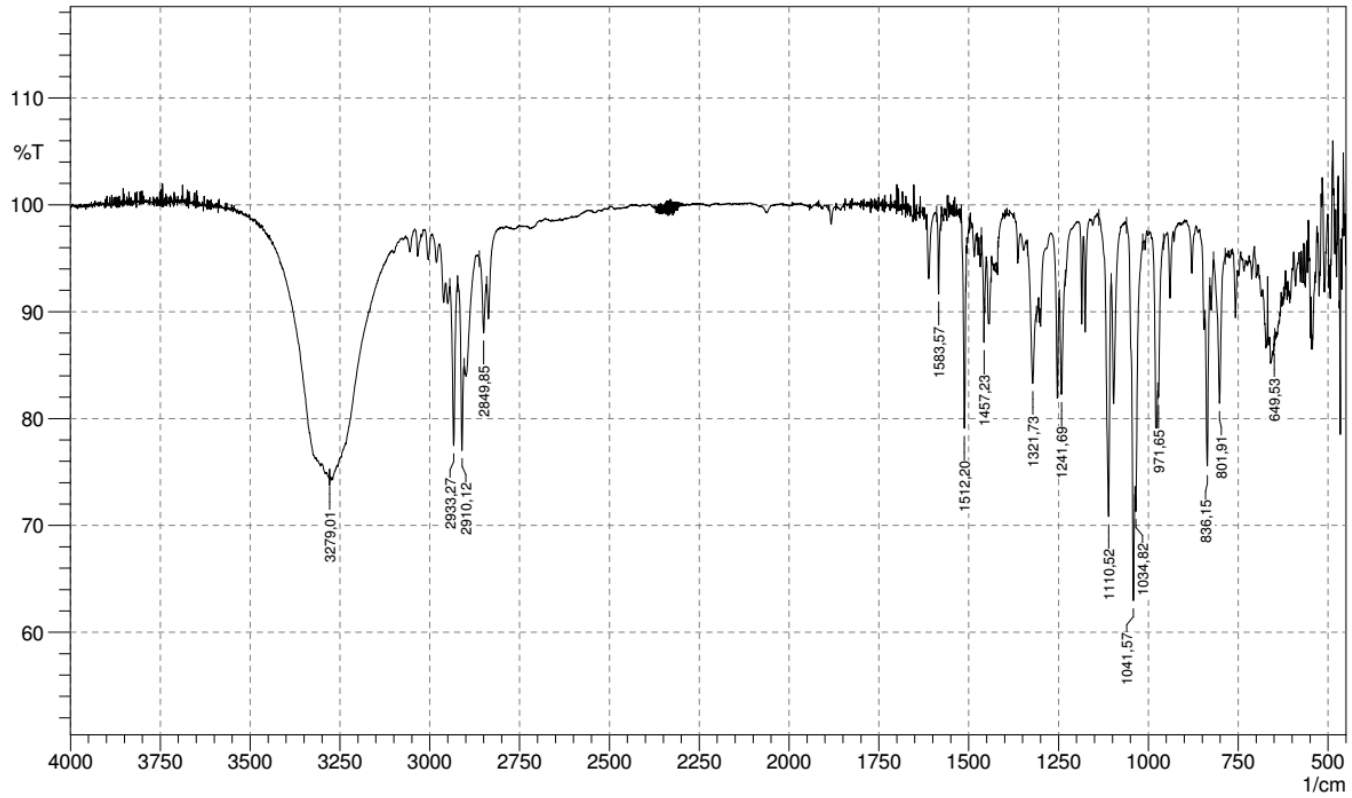
^{1}H NMR spectrum of 2-(4-methoxybenzyl)propane-1,3-diol (**24**) ($CDCl_3$)



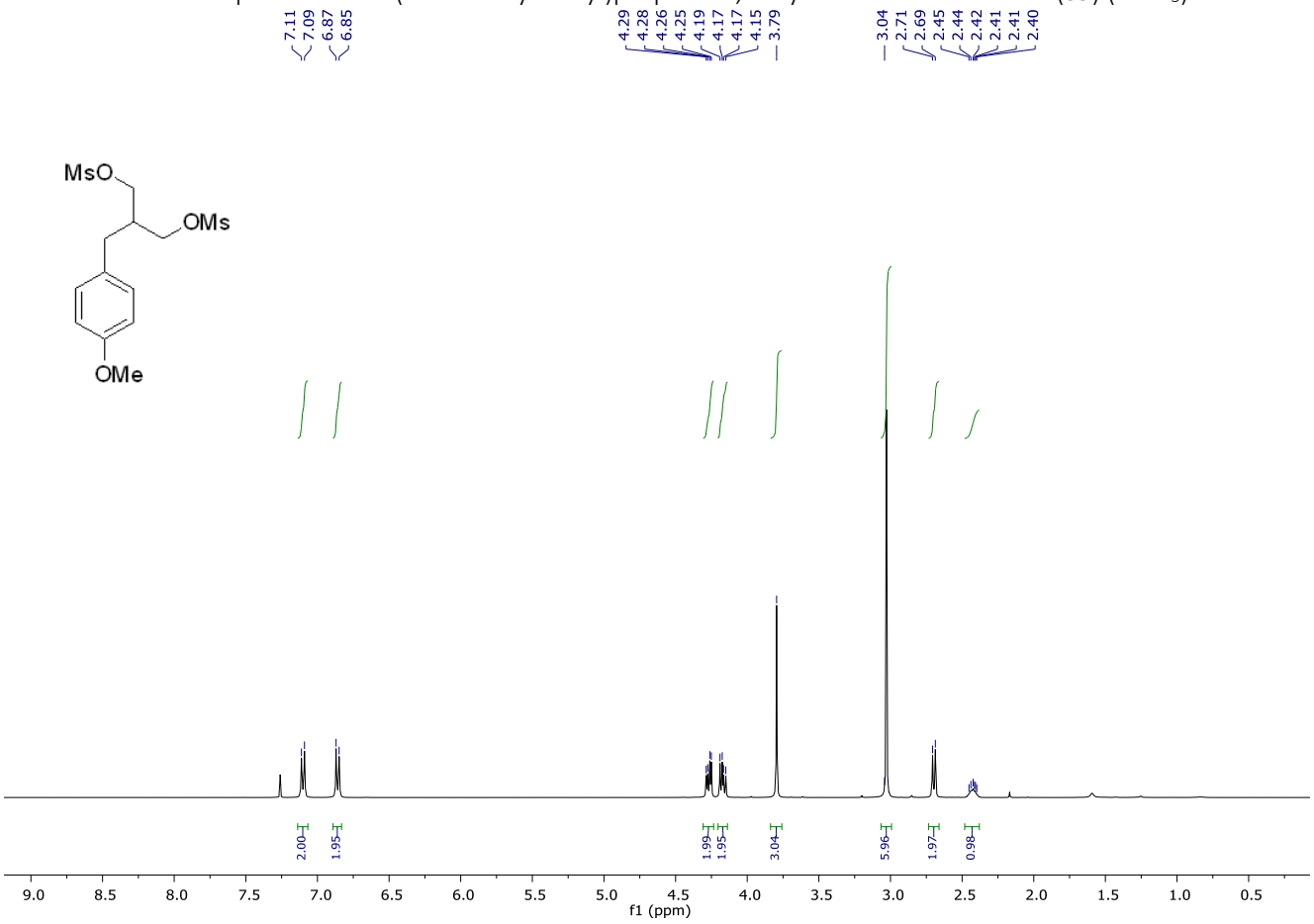
^{13}C{^{1}H} NMR spectrum of 2-(4-methoxybenzyl)propane-1,3-diol (**24**) ($CDCl_3$)



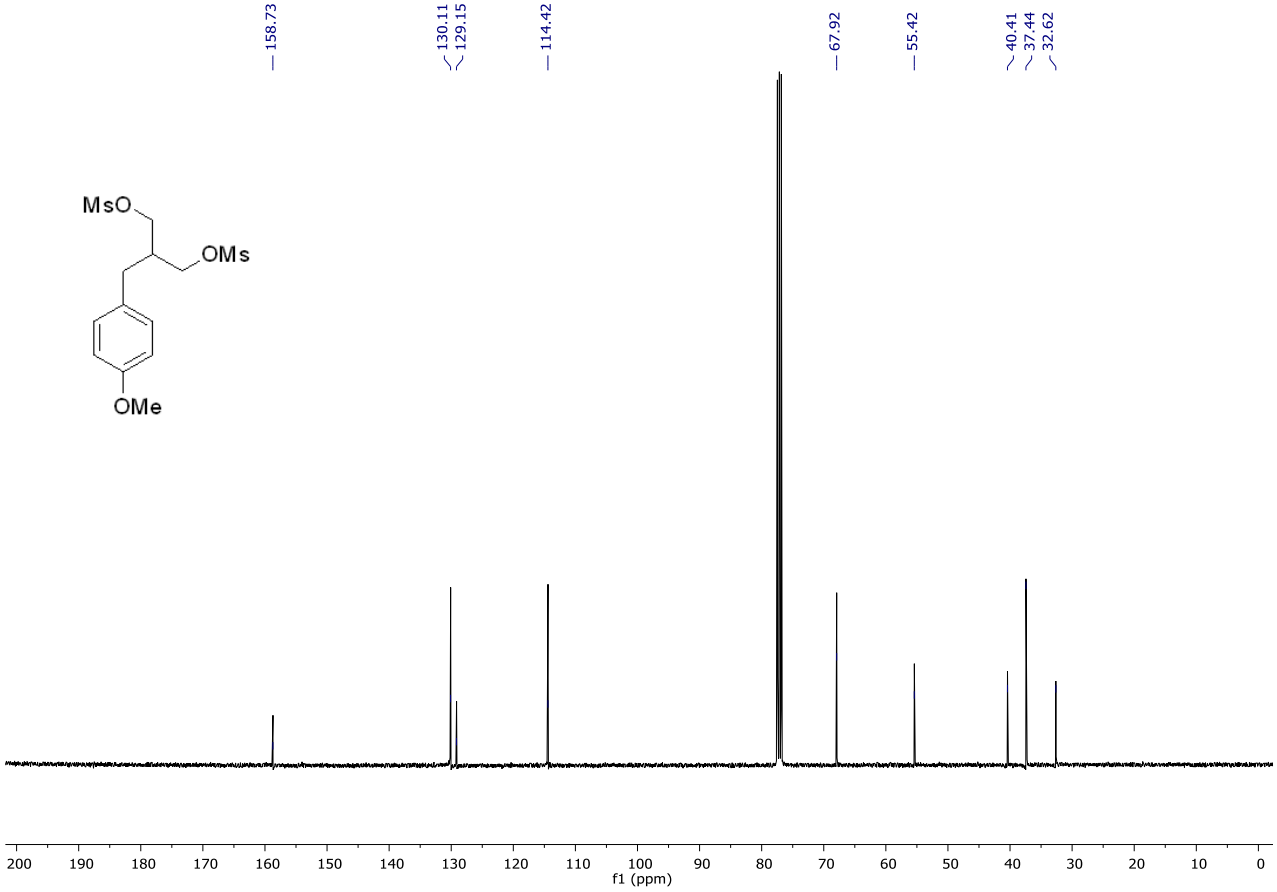
IR(ATR) spectrum of 2-(4-methoxybenzyl)propane-1,3-diol (**24**)



^{1}H NMR spectrum of 2-(4-methoxybenzyl)propane-1,3-diyl dimethanesulfonate (**S9**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of 2-(4-methoxybenzyl)propane-1,3-diyl dimethanesulfonate (**S9**) ($CDCl_3$)



HRMS of diethyl 2-(4-methoxybenzyl)propane-1,3-diyl dimethanesulfonate (**S9**) (**23**)

MS: Waters Synapt G2-Si	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2019_10_095 1171 Silaks OSM6-SA-ANSIS-OSM

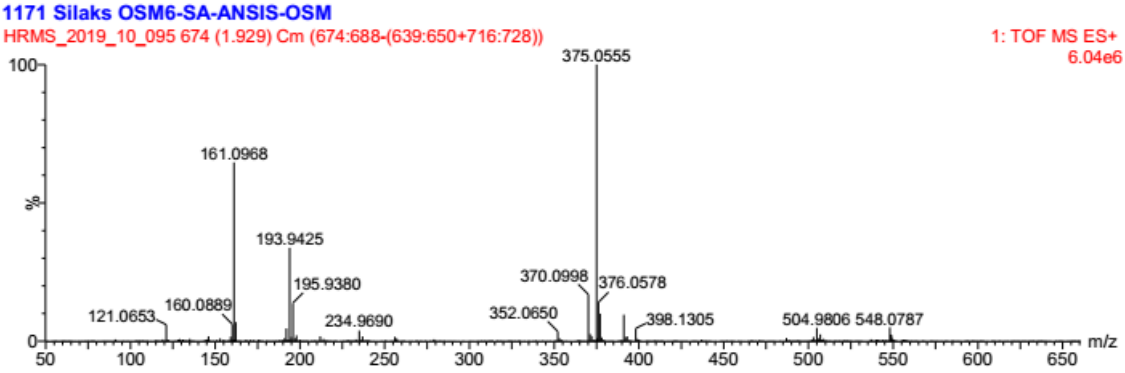
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:D,3 1.000000 MS_Tune Col#43

Elemental Composition Report:

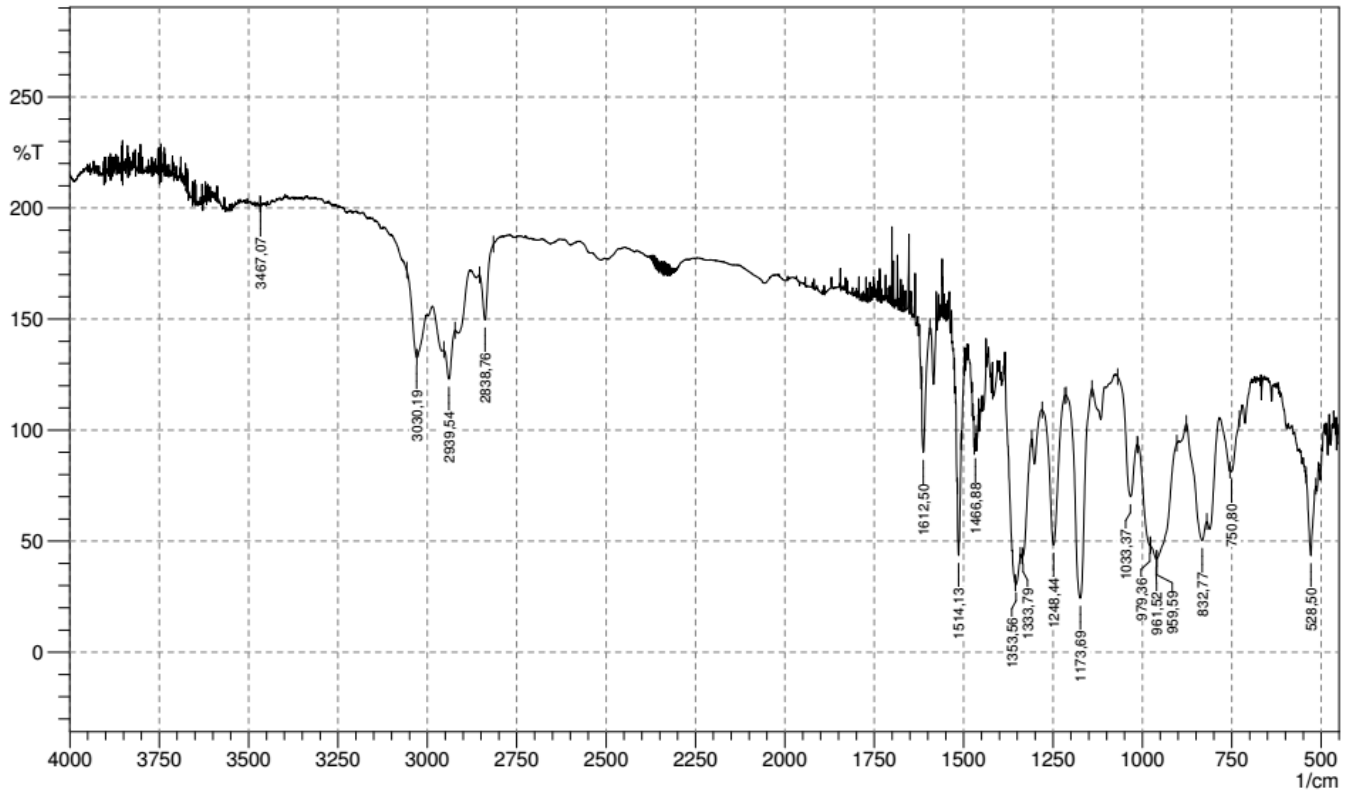
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 90.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
30 formula(e) evaluated with 1 results within limits (up to 3 closest results for each mass)
Elements Used:
C: 0-50 H: 1-60 O: 1-10 S: 2-2 Na: 1-1

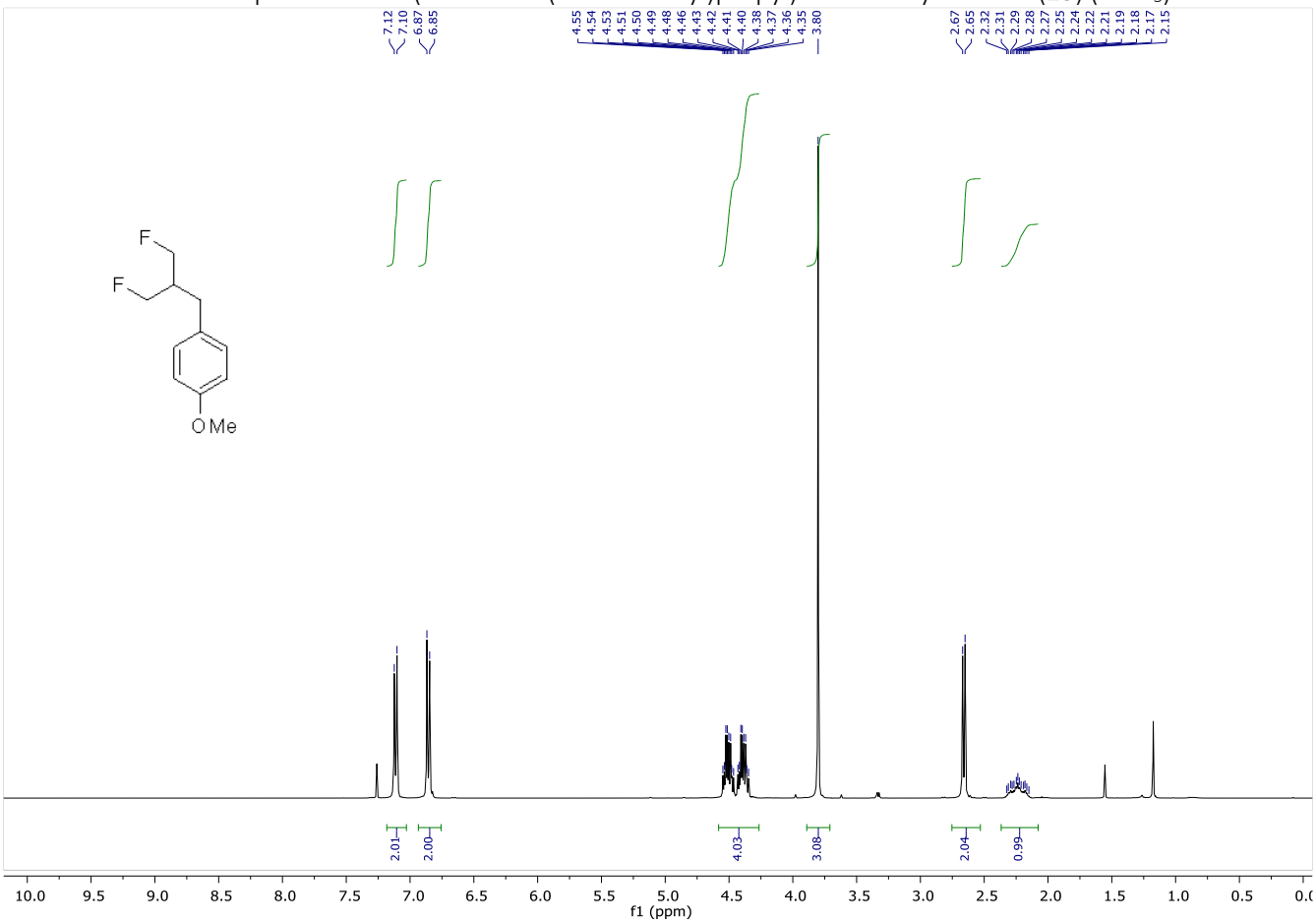
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
375.0555	100.00	375.0548	0.7	1.9	3.5	267.3	n/a	n/a	C13 H20 O7 S2 Na



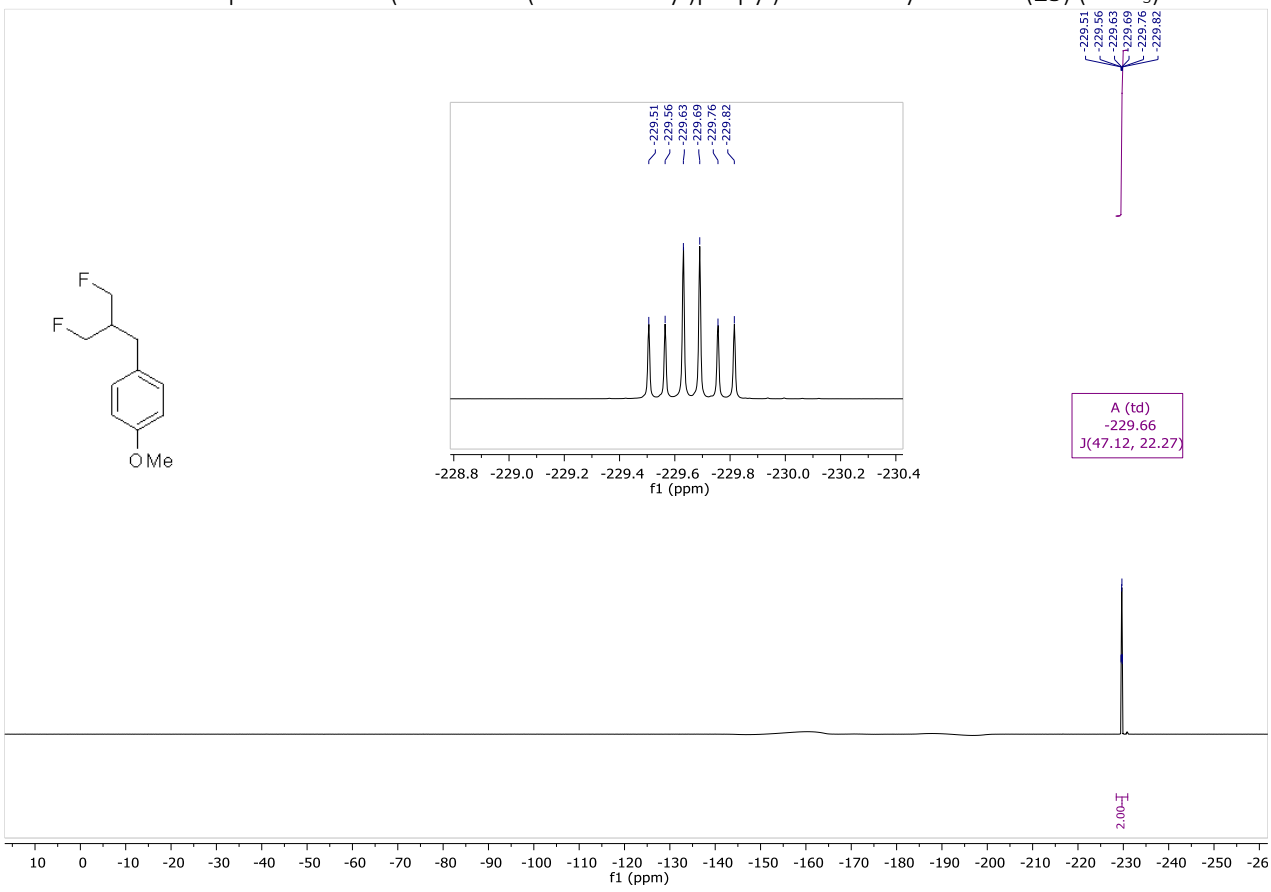
IR(ATR) spectrum of 2-(4-methoxybenzyl)propane-1,3-diyl dimethanesulfonate (**S9**) (**23**)



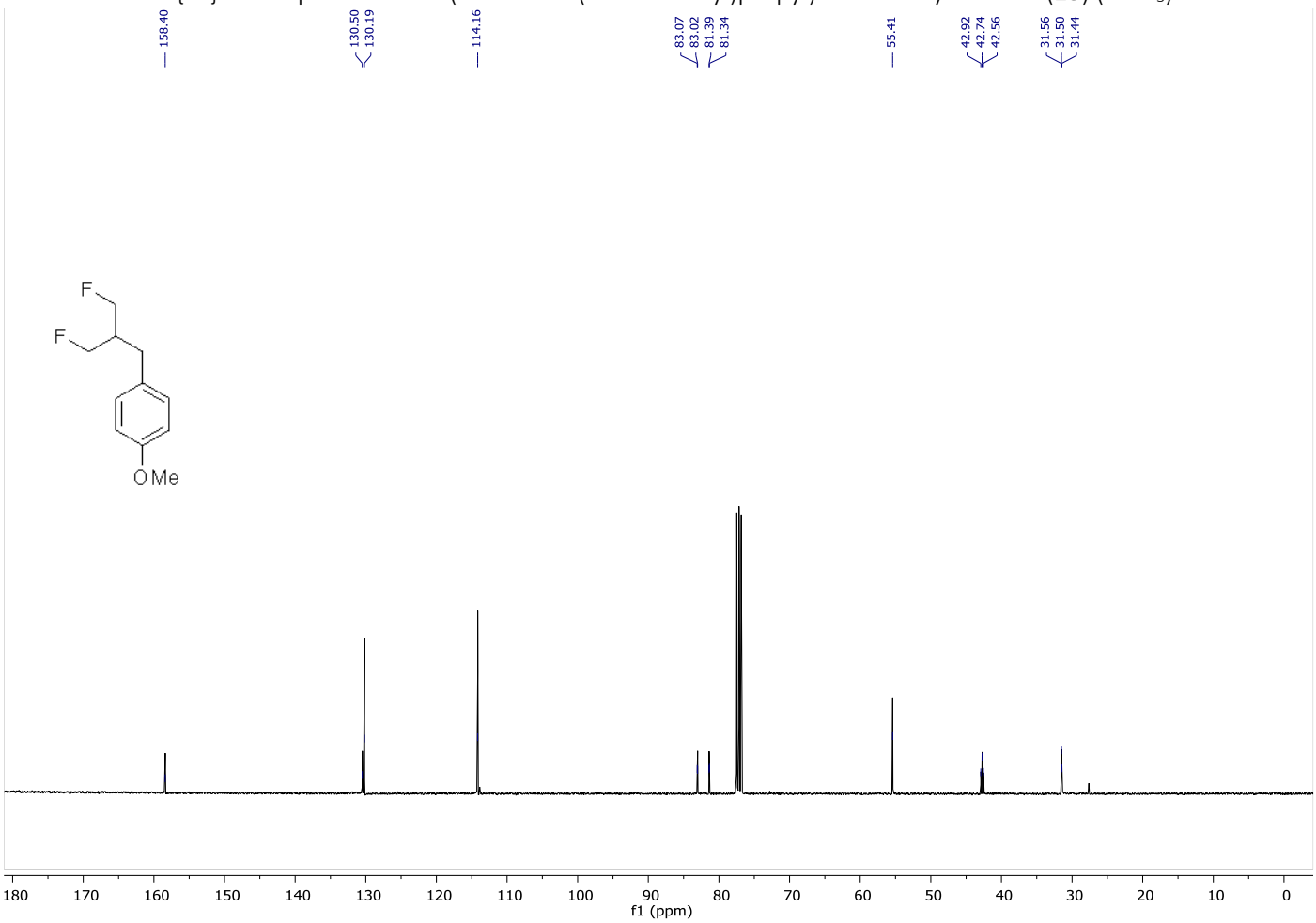
^{1}H NMR spectrum of 1-(3-fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (**25**) ($CDCl_3$)



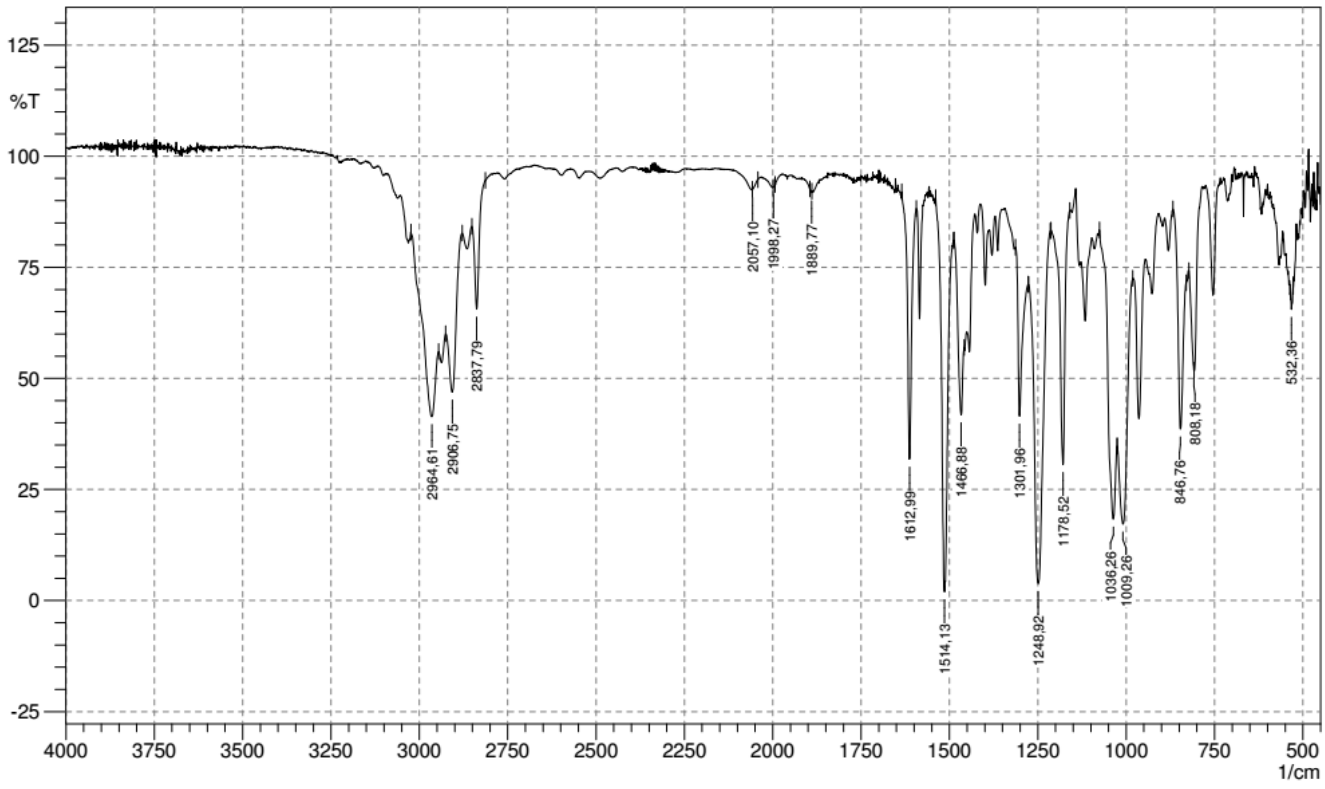
^{19}F NMR spectrum of 1-(3-fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (**25**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 1-(3-fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (**25**) ($CDCl_3$)

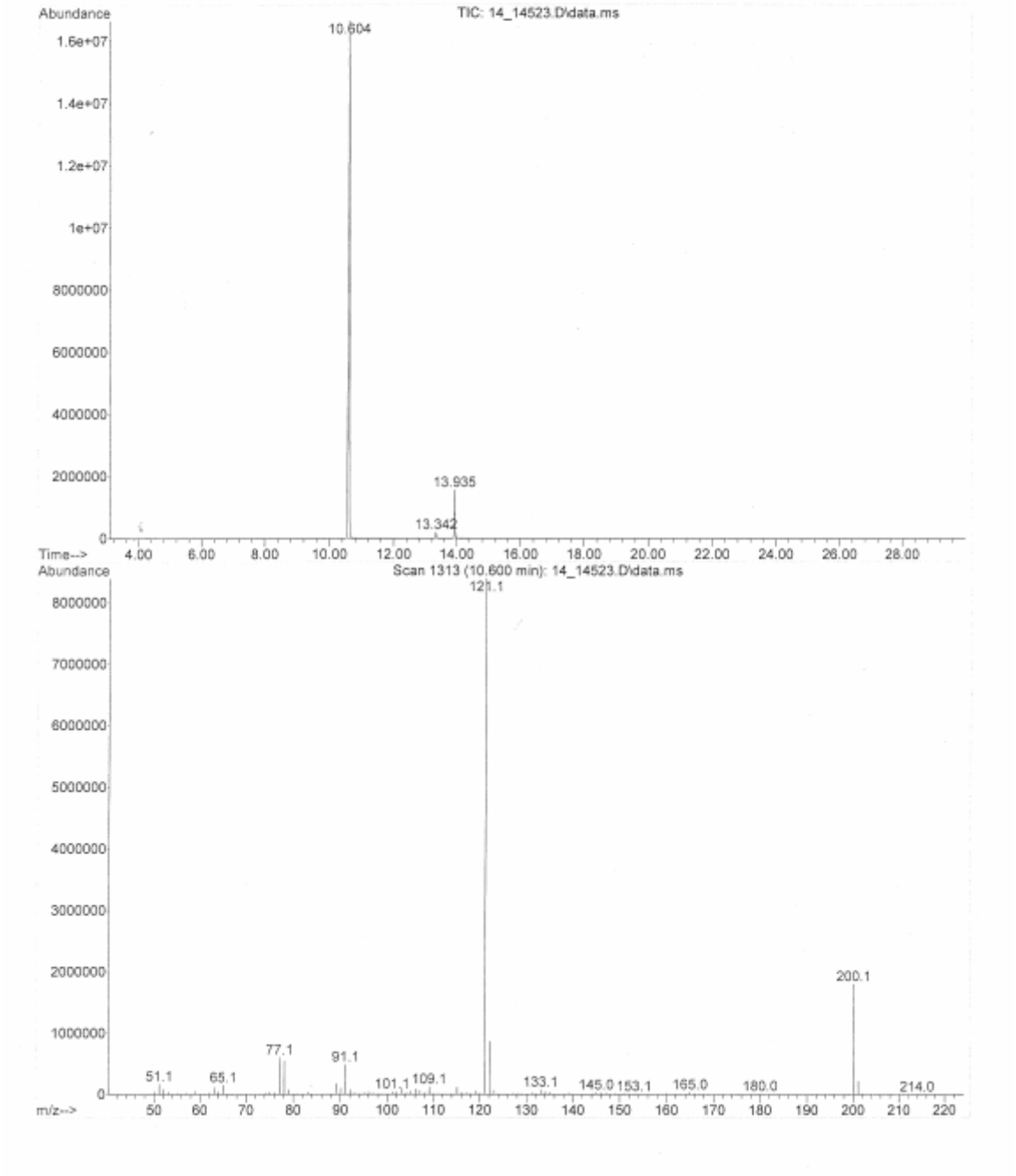


IR(ATR) spectrum of 1-(3-fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (**25**)

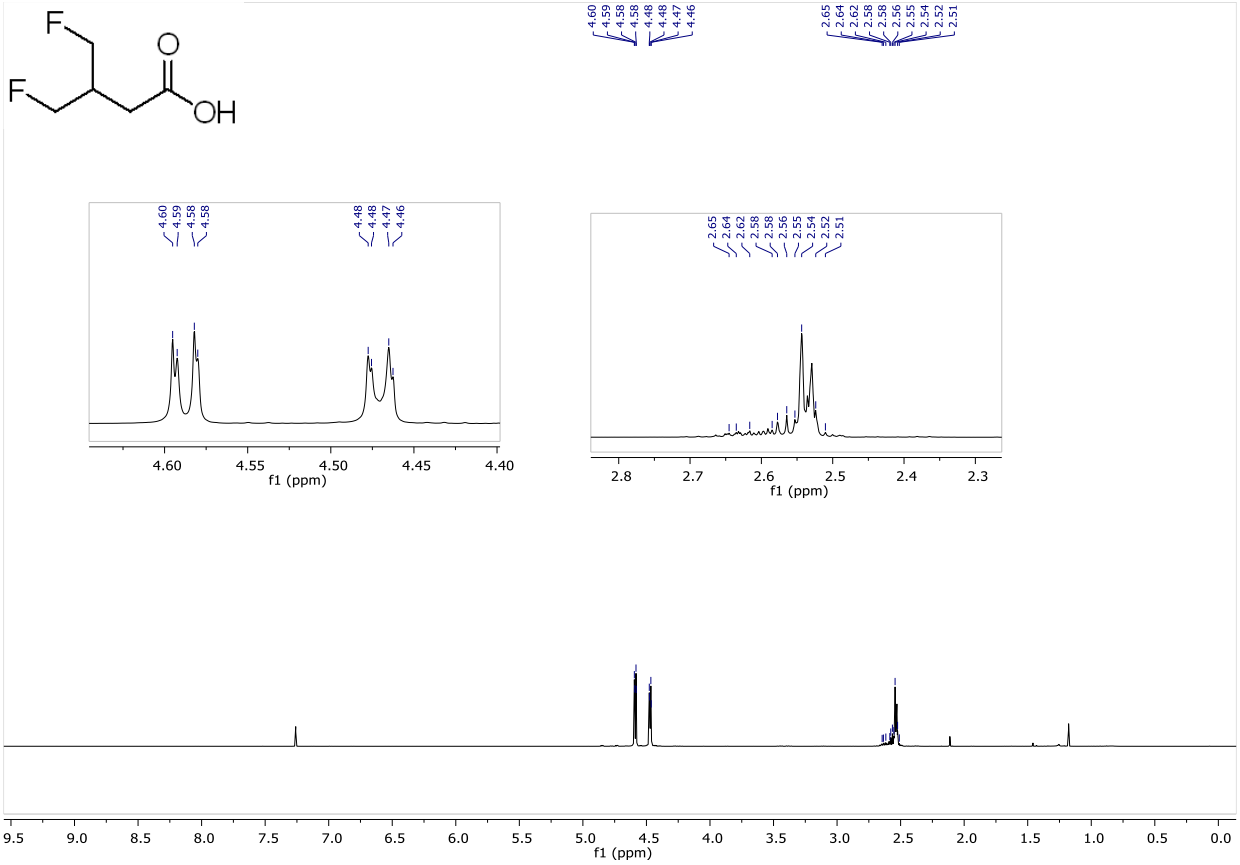


GC-MS of 1-(3-fluoro-2-(fluoromethyl)propyl)-4-methoxybenzene (**25**)

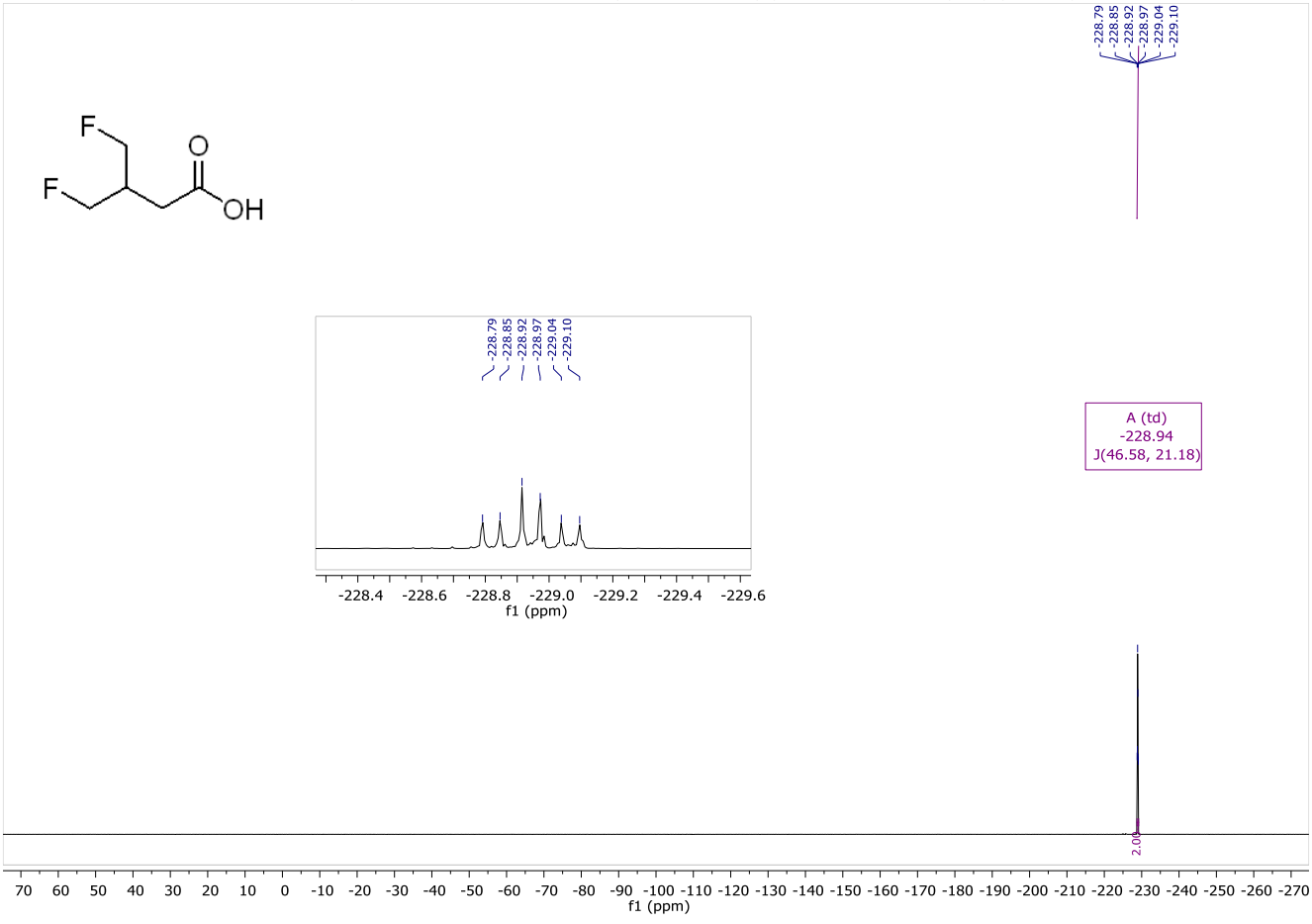
```
File        :D:\DATA_2019\10_Okt_2019\14_14523.D
Operator    : E
Acquired    : 14 Oct 2019  14:14      using AcqMethod LAURA.M
Instrument :    GCMS
Sample Name: Silaks OSMG-SA-136
Misc Info  :
Vial Number: 5
```



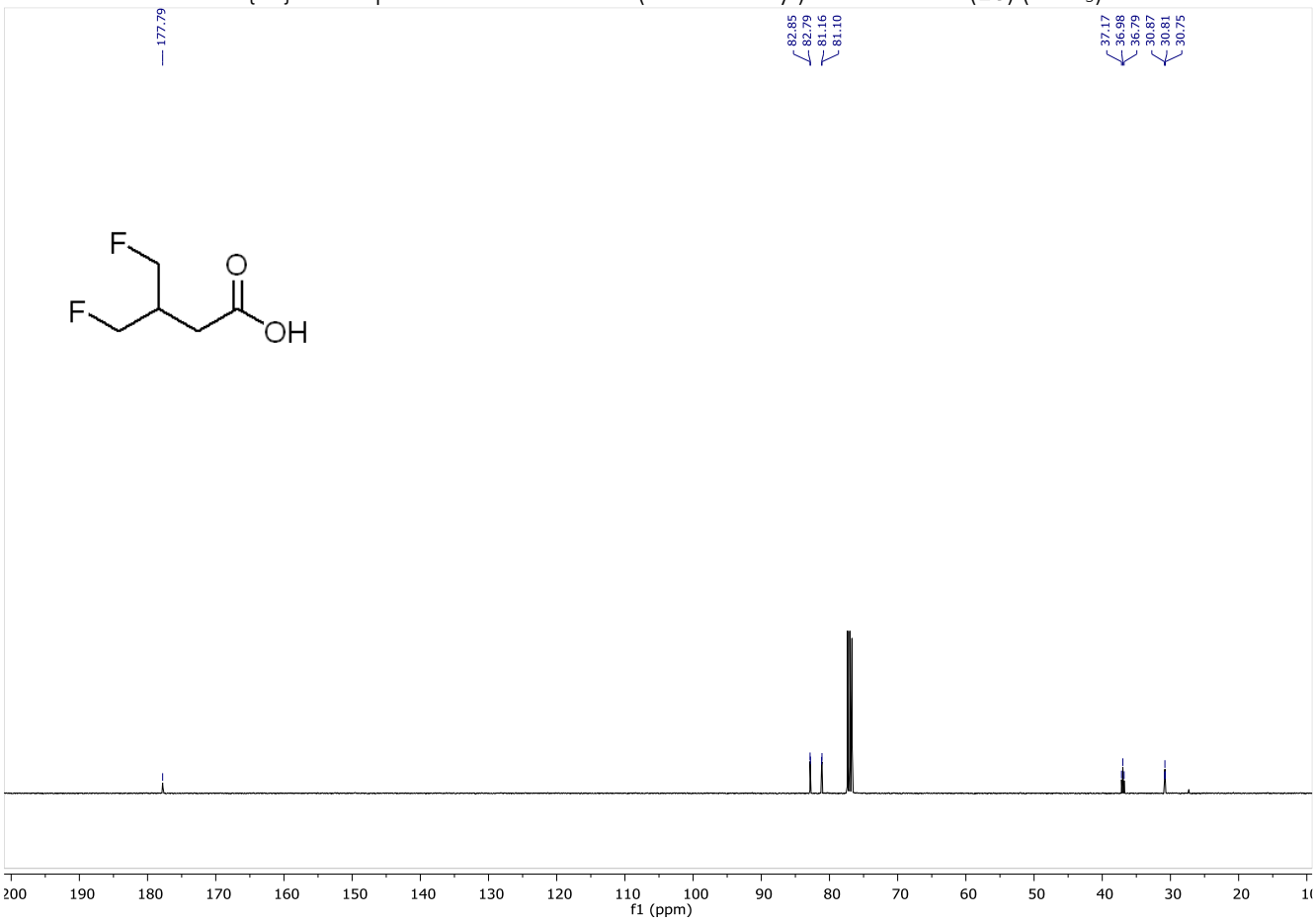
^{1}H NMR spectrum of 4-fluoro-3-(fluoromethyl)butanoic acid (**26**) ($CDCl_3$)



^{19}F NMR spectrum of 4-fluoro-3-(fluoromethyl)butanoic acid (**26**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 4-fluoro-3-(fluoromethyl)butanoic acid (**26**) ($CDCl_3$)



HRMS of 4-fluoro-3-(fluoromethyl)butanoic acid (**26**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

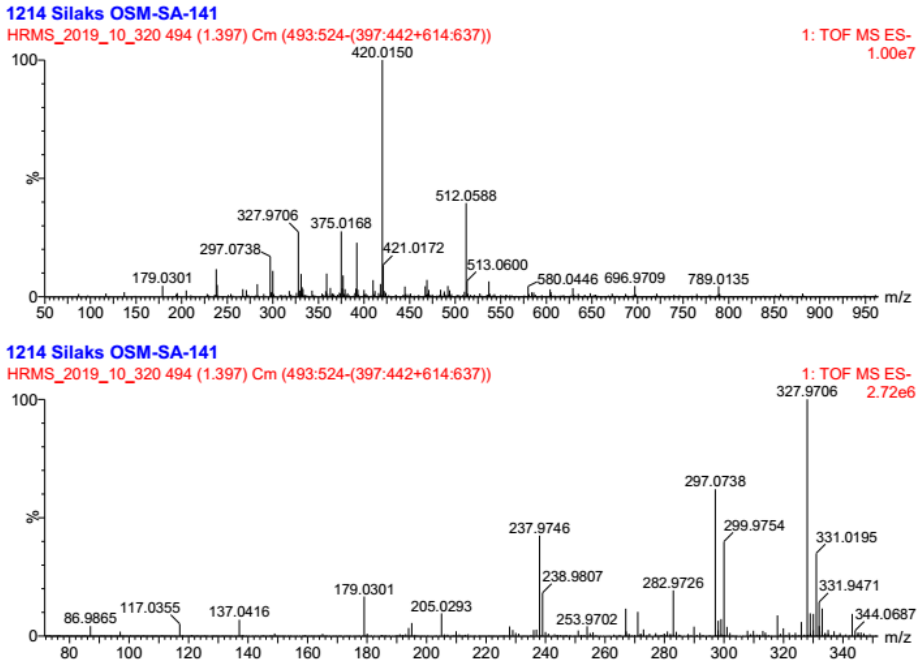
HRMS_2019_10_320 1214 Silaks OSM-SA-141
MS_NEG_RES_4min ACN_Form_5-98_040_4min 2:C,1 3.000000 MS_Tune Col#43

Elemental Composition Report:

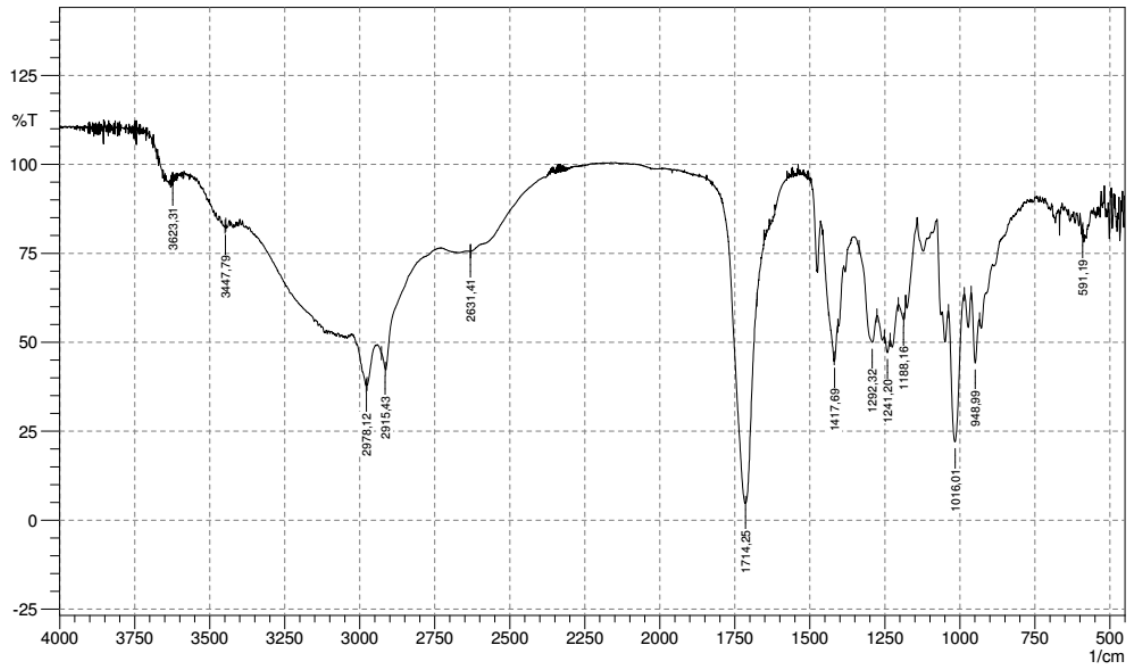
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 90.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
36 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 0-10 O: 0-10 F: 2-2

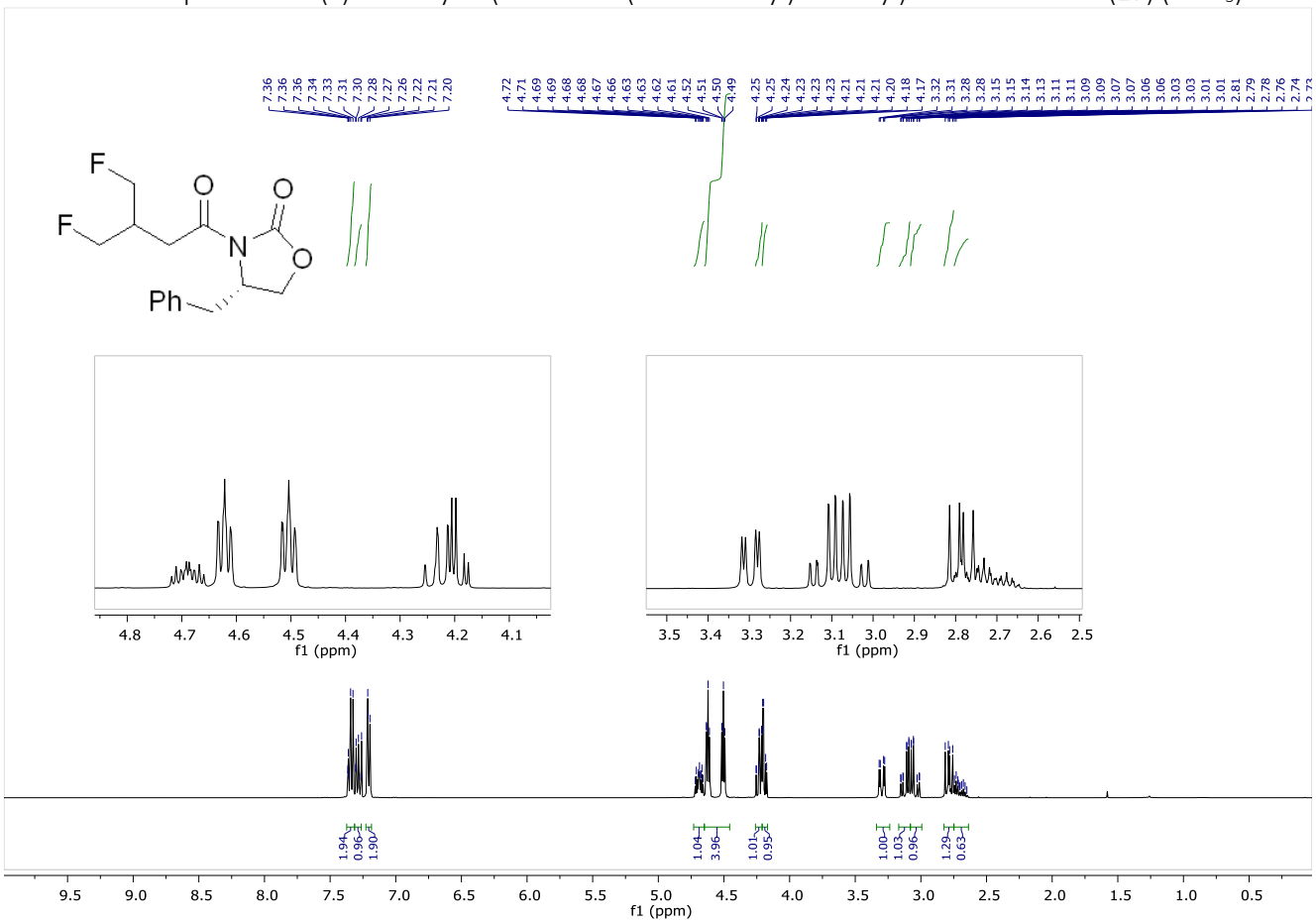
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
137.0416	100.00	137.0414	0.2	1.5	1.5	487.8	n/a	n/a	C5 H7 O2 F2



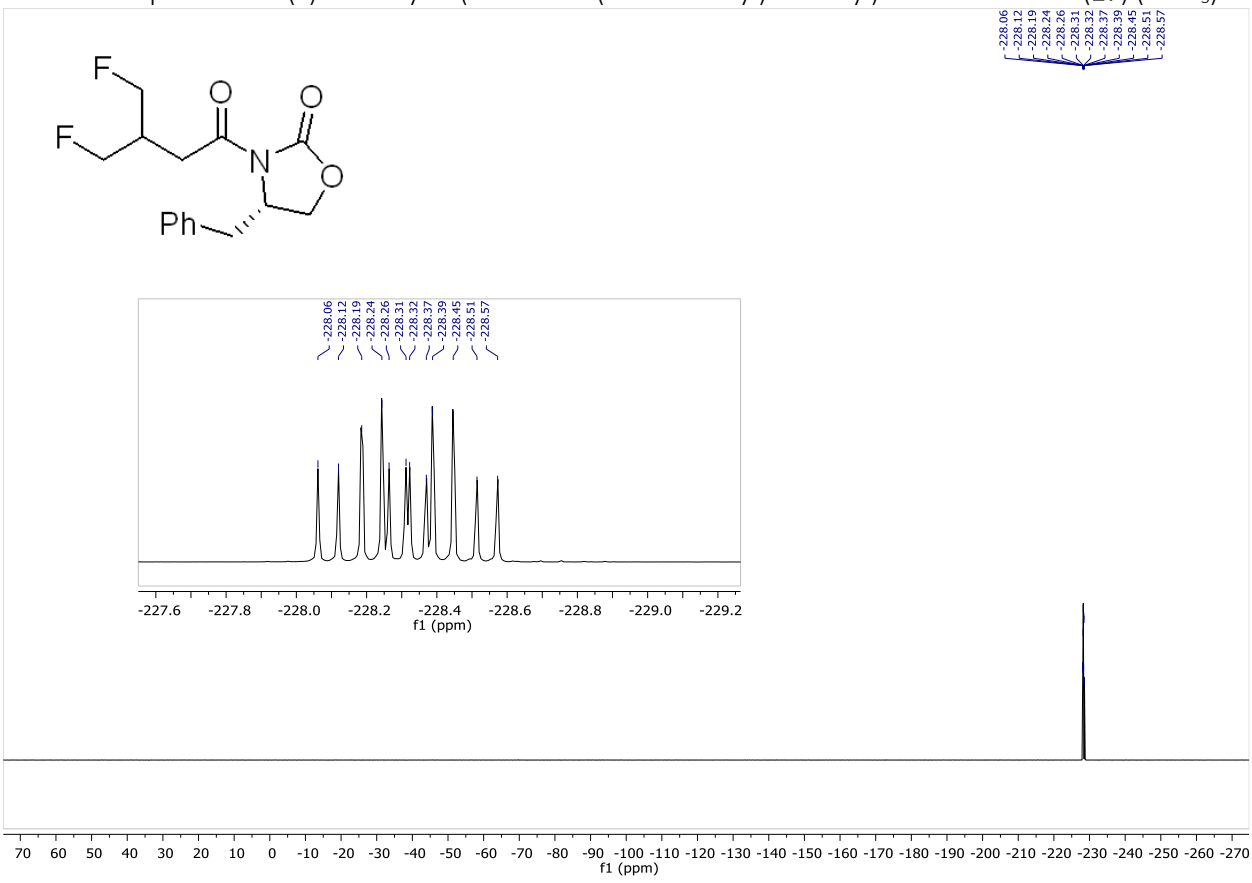
IR(ATR) spectrum of 4-fluoro-3-(fluoromethyl)butanoic acid (**26**)



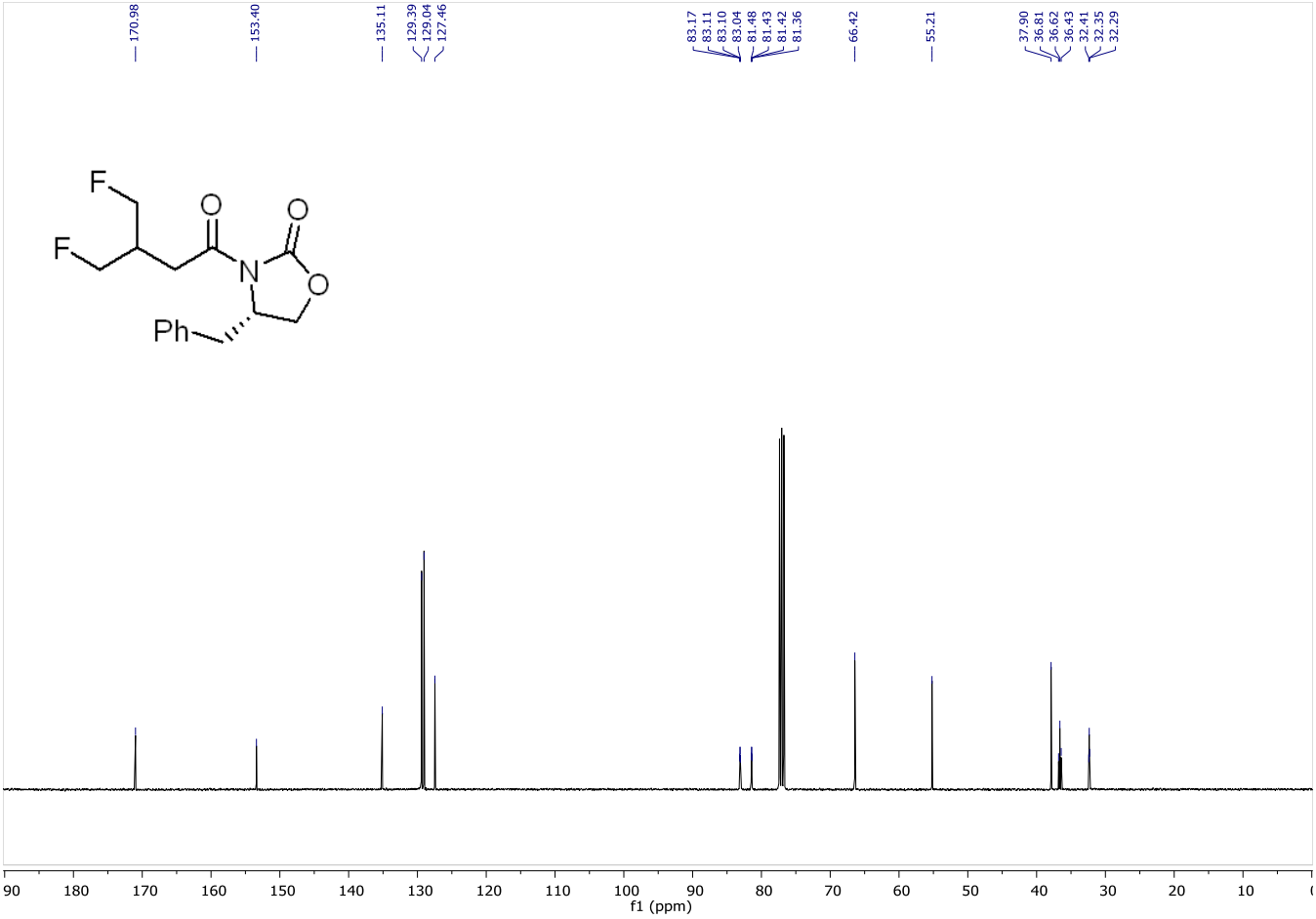
^{1}H NMR spectrum of (*S*)-4-benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (**27**) ($CDCl_3$)



^{19}F NMR spectrum of (*S*)-4-benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (**27**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-4-benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (**27**) ($CDCl_3$)



HRMS of (*S*)-4-benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (**27**)

MS: Waters Synapt G2-Si	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2019_11_295	1484 Maleckis OSM6-AF-F179				
MS_POS_RES_4min	ACN_Form_5-98_040_4min	2:F,6	1.000000	MS_Tune	Col#43

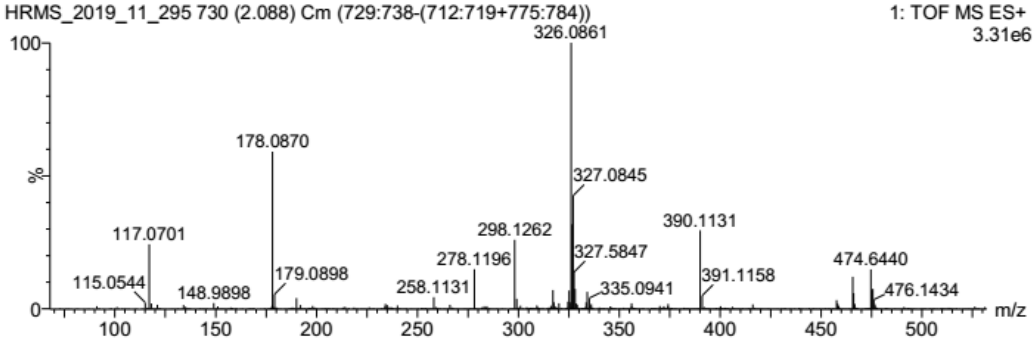
Elemental Composition Report:

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

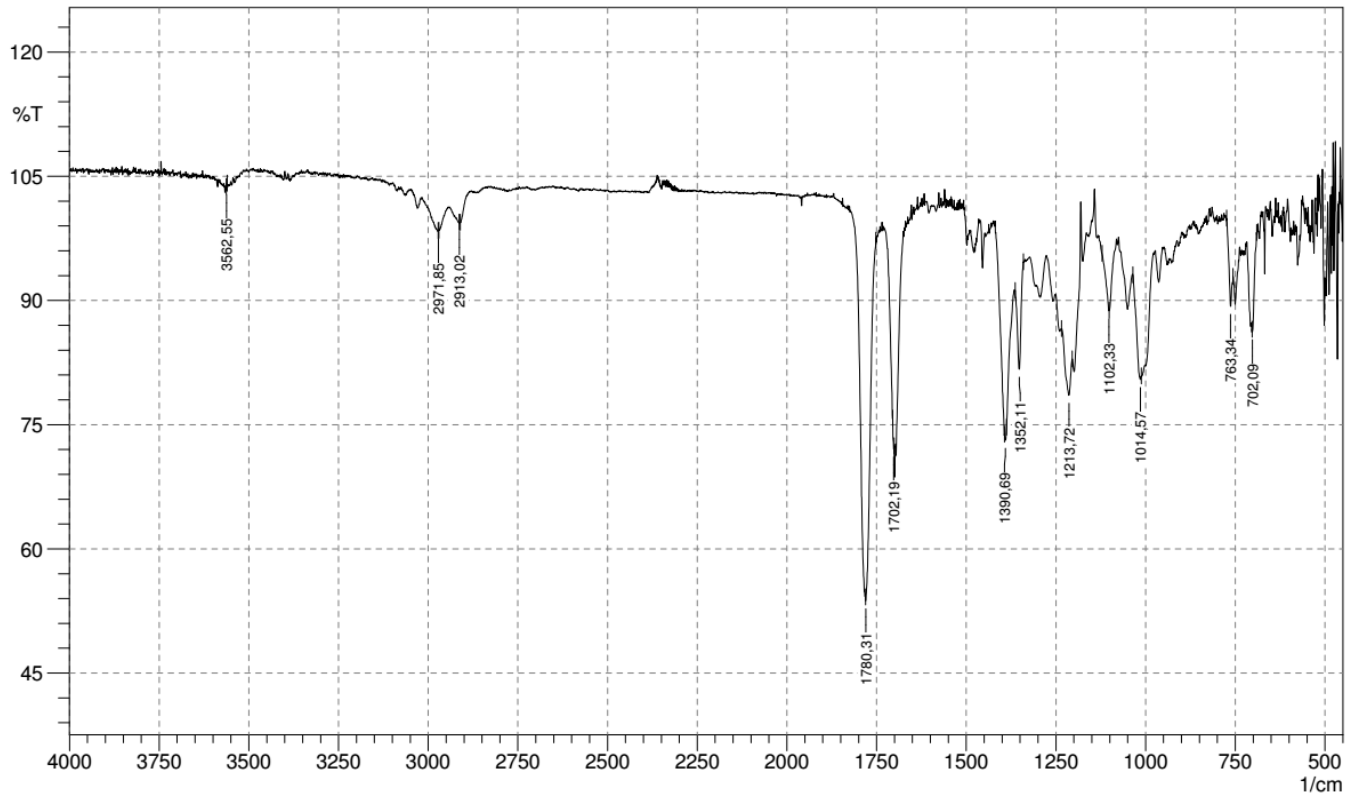
Monoisotopic Mass, Even Electron Ions
204 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 1-10 O: 1-10 F: 2-2

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
298.1262	100.00	298.1255	0.7	2.3	6.5	320.0	n/a	n/a	C15 H18 N O3 F2

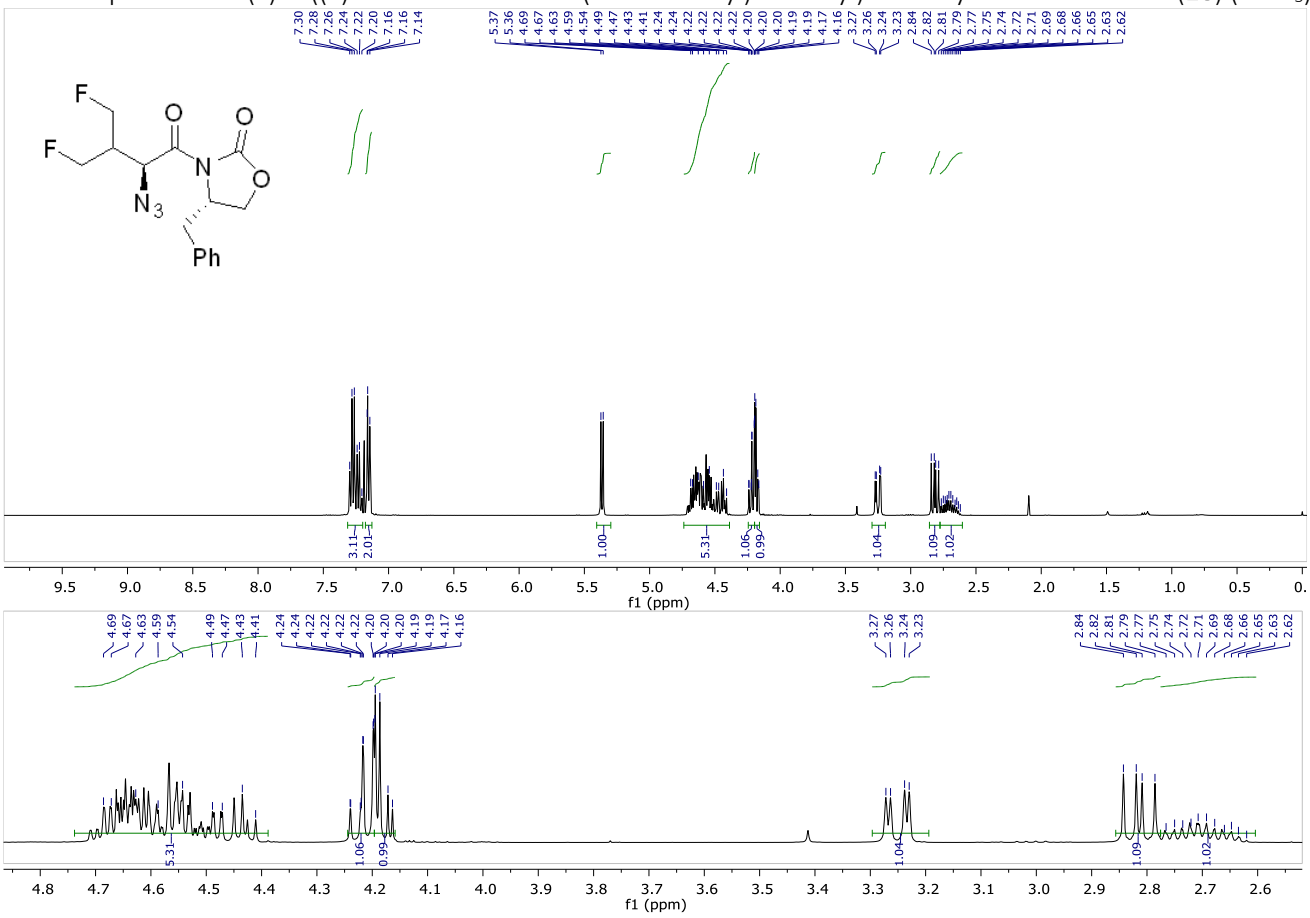
1484 Maleckis OSM6-AF-F179



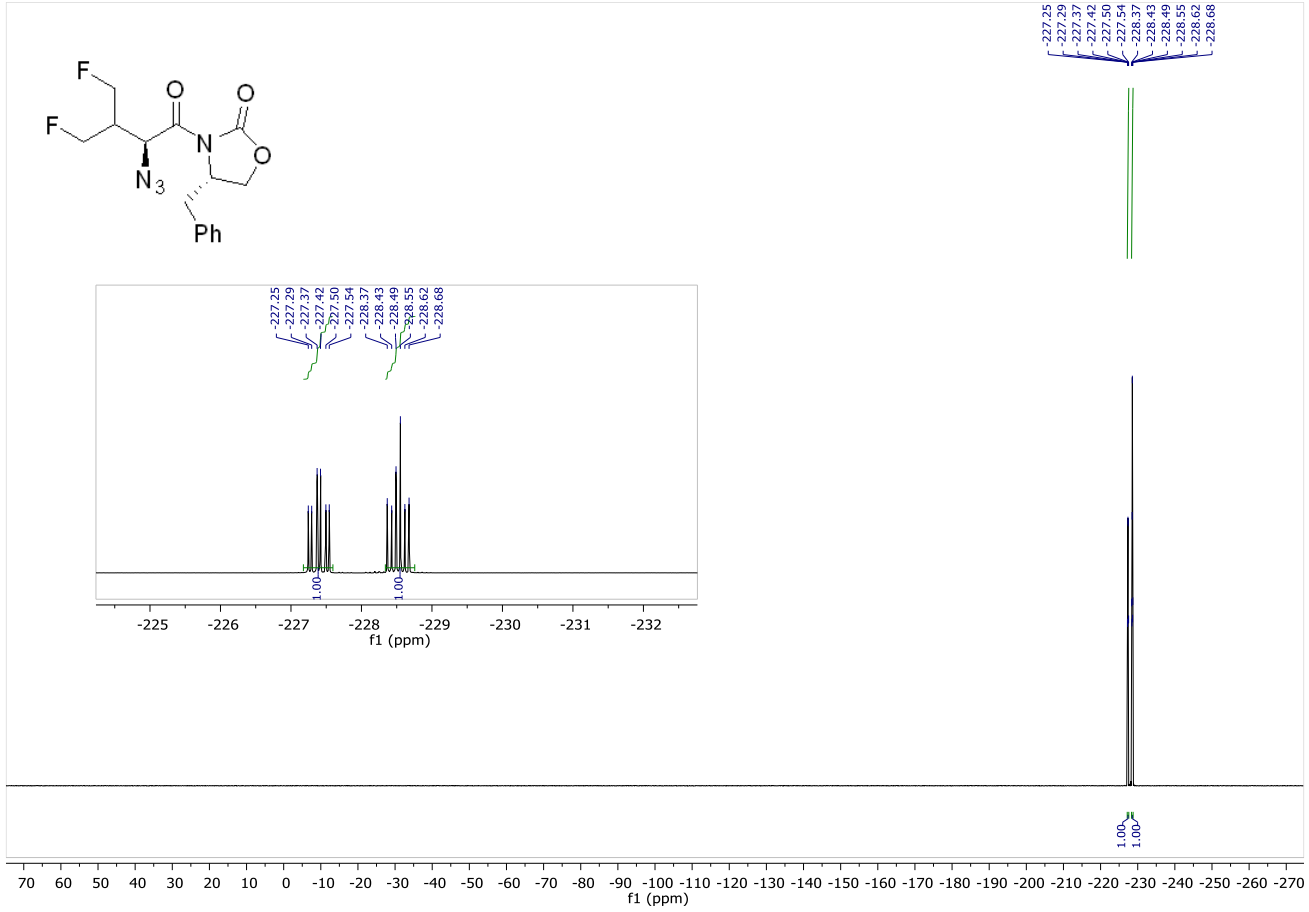
IR(ATR) spectrum of (*S*)-4-benzyl-3-(4-fluoro-3-(fluoromethyl)butanoyl)oxazolidin-2-one (**27**)



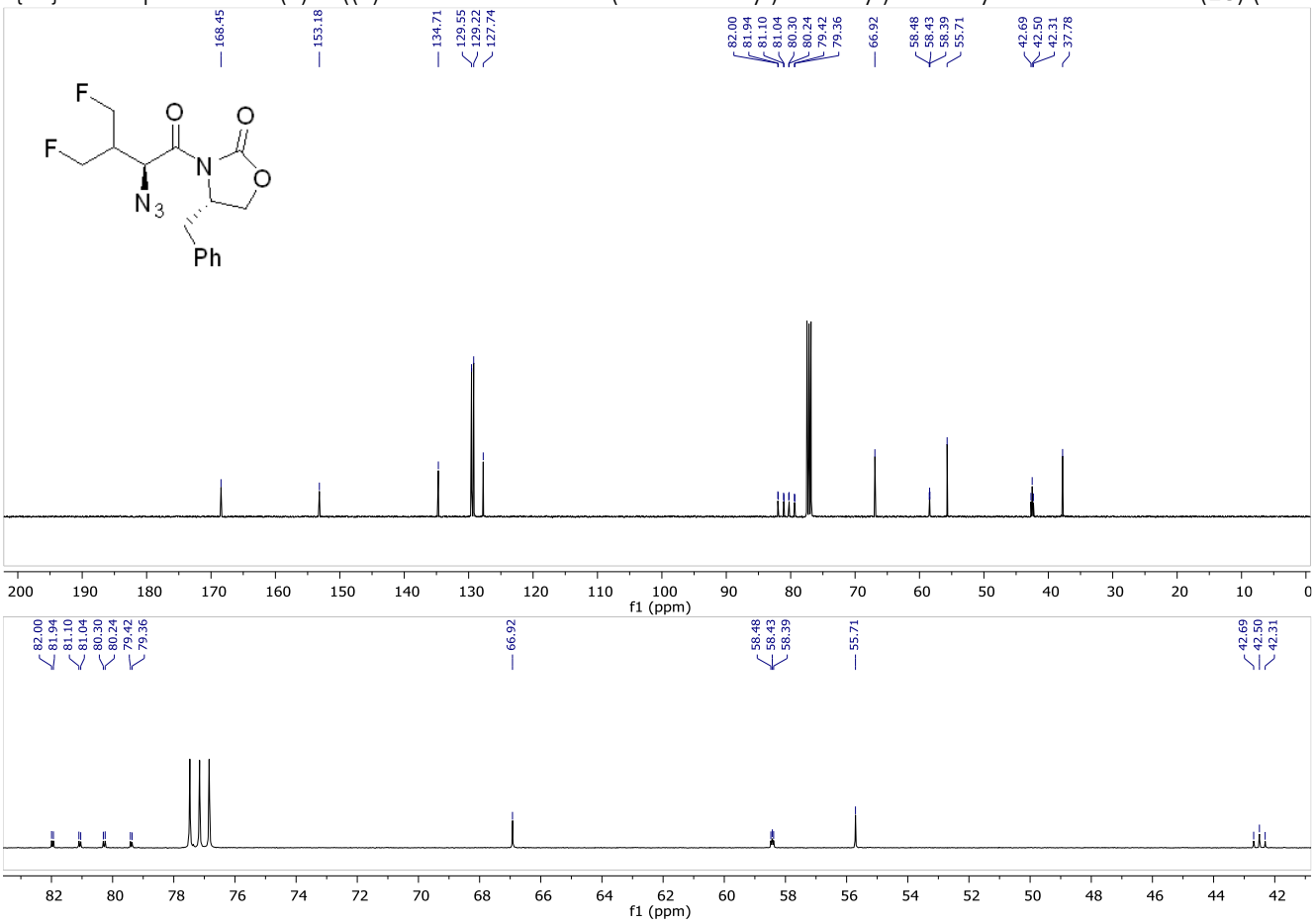
^{1}H NMR spectrum of (*S*)-3-((*S*)-2-azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (**28**) ($CDCl_3$)



^{19}F NMR spectrum of (*S*)-3-((*S*)-2-azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (**28**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-3-((*S*)-2-azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (**28**) ($CDCl_3$)



HRMS of (*S*)-3-((*S*)-2-azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (**28**)

Latvijas Organiskās sintēzes institūts
Fizikāli organiskās ķīmijas laboratorija

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

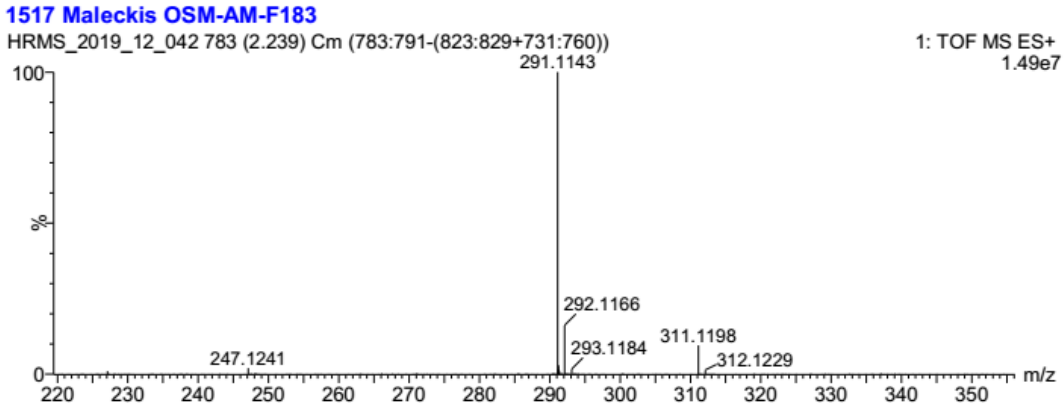
Sample:
HRMS_2019_12_042 1517 Maleckis OSM-AM-F183
MS_POS_RES_4min ACN_Form_5-98_040_4min 2:E,5 1.000000 MS_Tune Col#43

Elemental Composition Report:

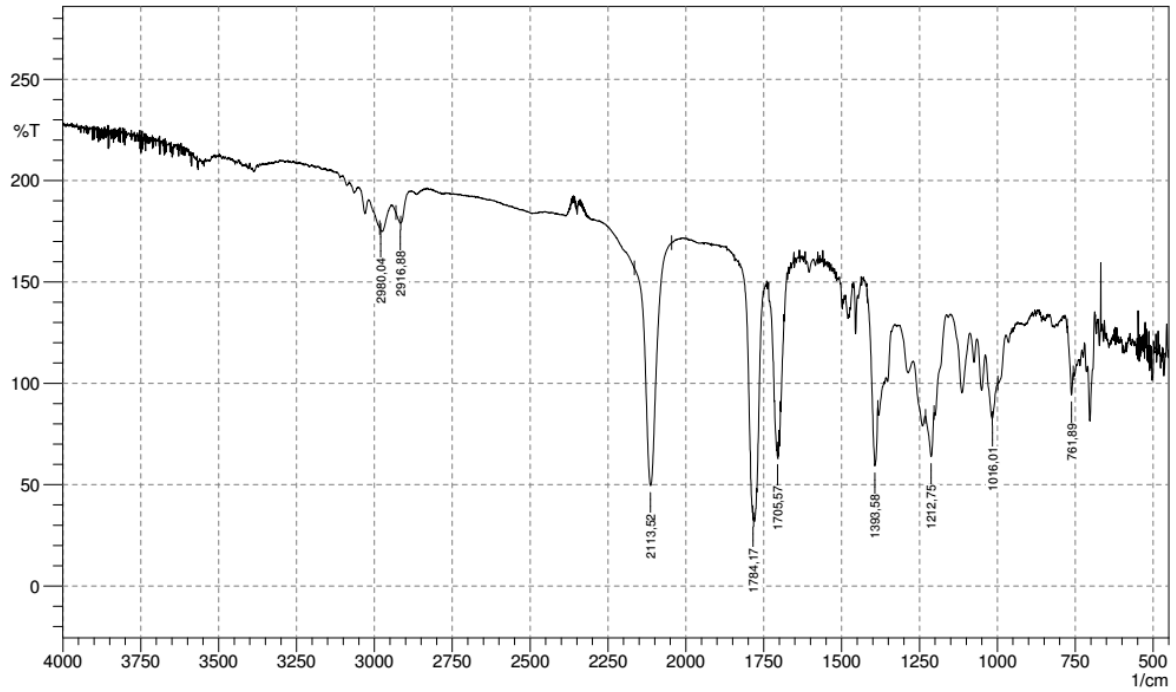
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
230 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-60 N: 1-10 O: 1-10 F: 2-2

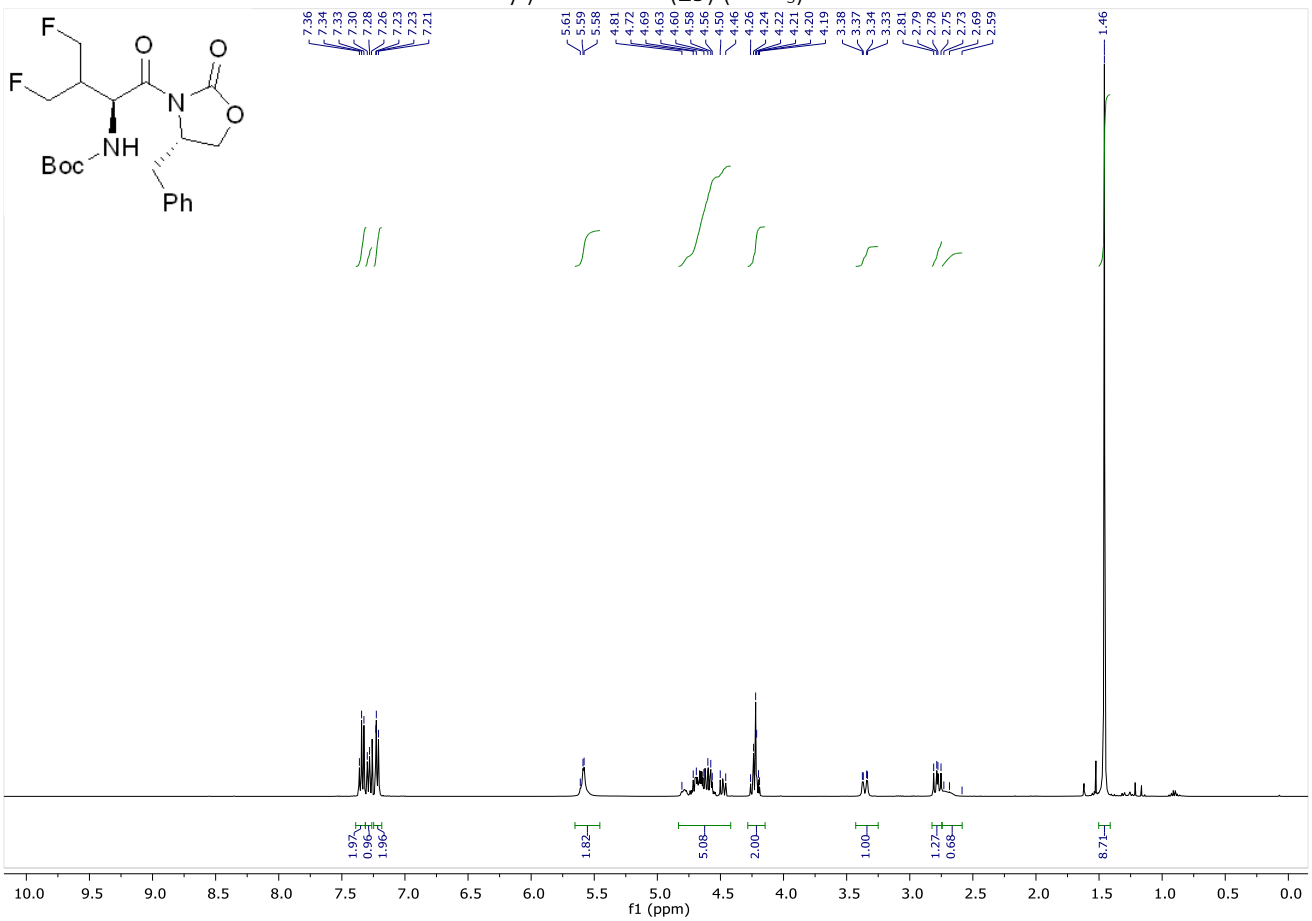
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
311.1198	311.1207	-0.9	-2.9	7.5	127.9	0.271	76.29	C15 H17 N2 O3 F2
	311.1180	1.8	5.8	8.5	129.3	1.695	18.37	C11 H13 N8 O F2
	311.1167	3.1	10.0	3.5	130.6	2.930	5.34	C10 H17 N4 O5 F2



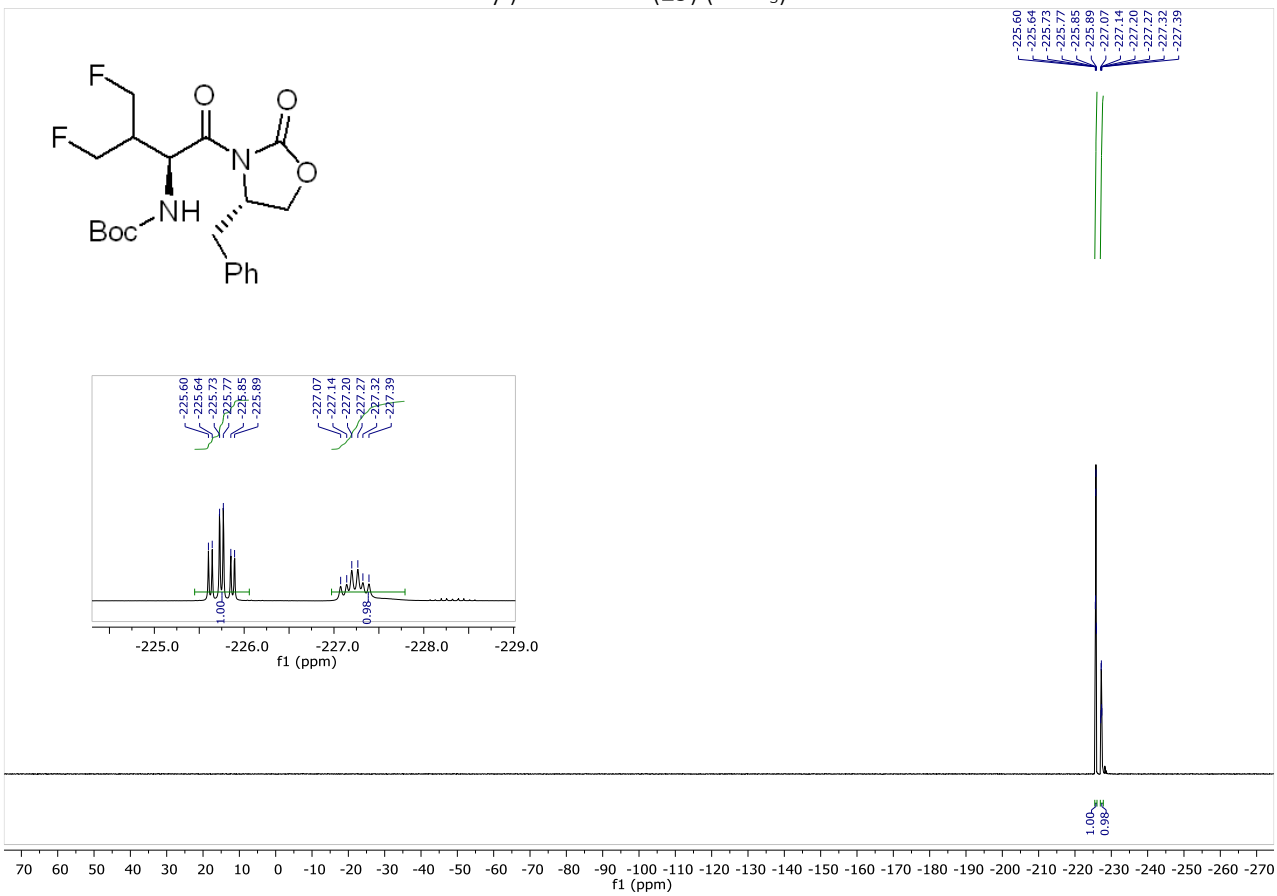
IR(ATR) spectrum of (*S*)-3-((*S*)-2-azido-4-fluoro-3-(fluoromethyl)butanoyl)-4-benzyloxazolidin-2-one (**28**)



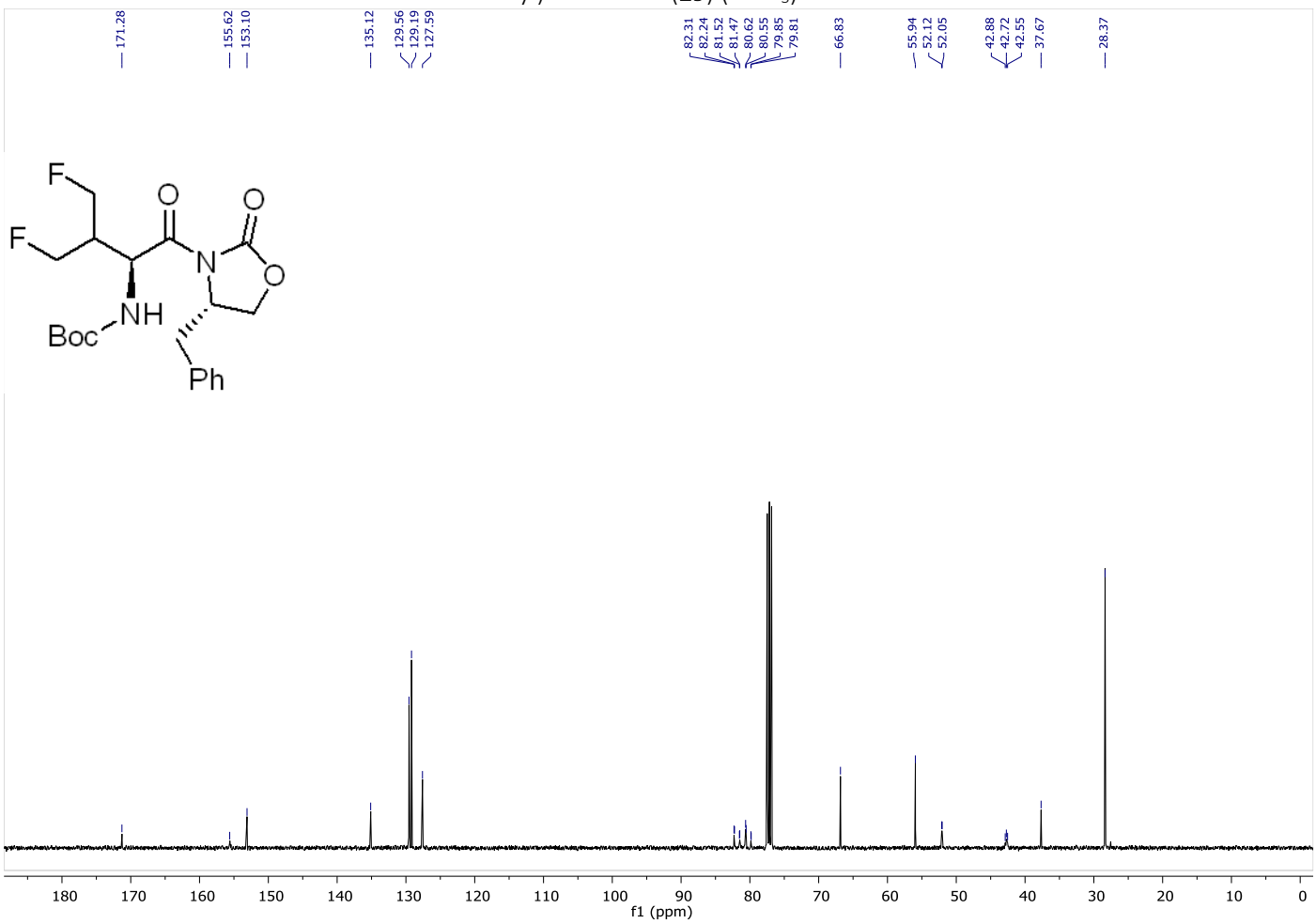
^{1}H NMR spectrum of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (**29**) ($CDCl_3$)



^{19}F NMR spectrum of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (**29**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (**29**) ($CDCl_3$)



HRMS of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (**29**)

MS: Waters Synapt G2-Si	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2019_12_044 1518 Maleckis OSM6-AM-F189

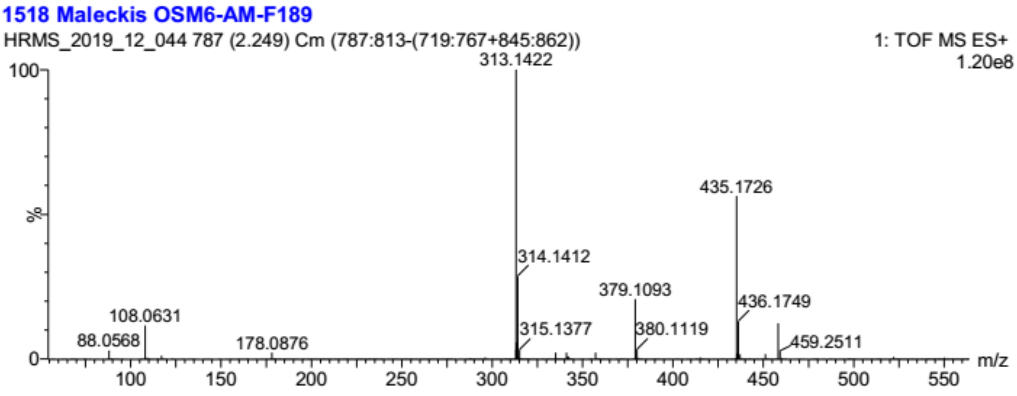
MS_POS_RES_4min ACN_Form_5-98_040_4min 2:E,6 1.000000 MS_Tune Col#43

Elemental Composition Report:

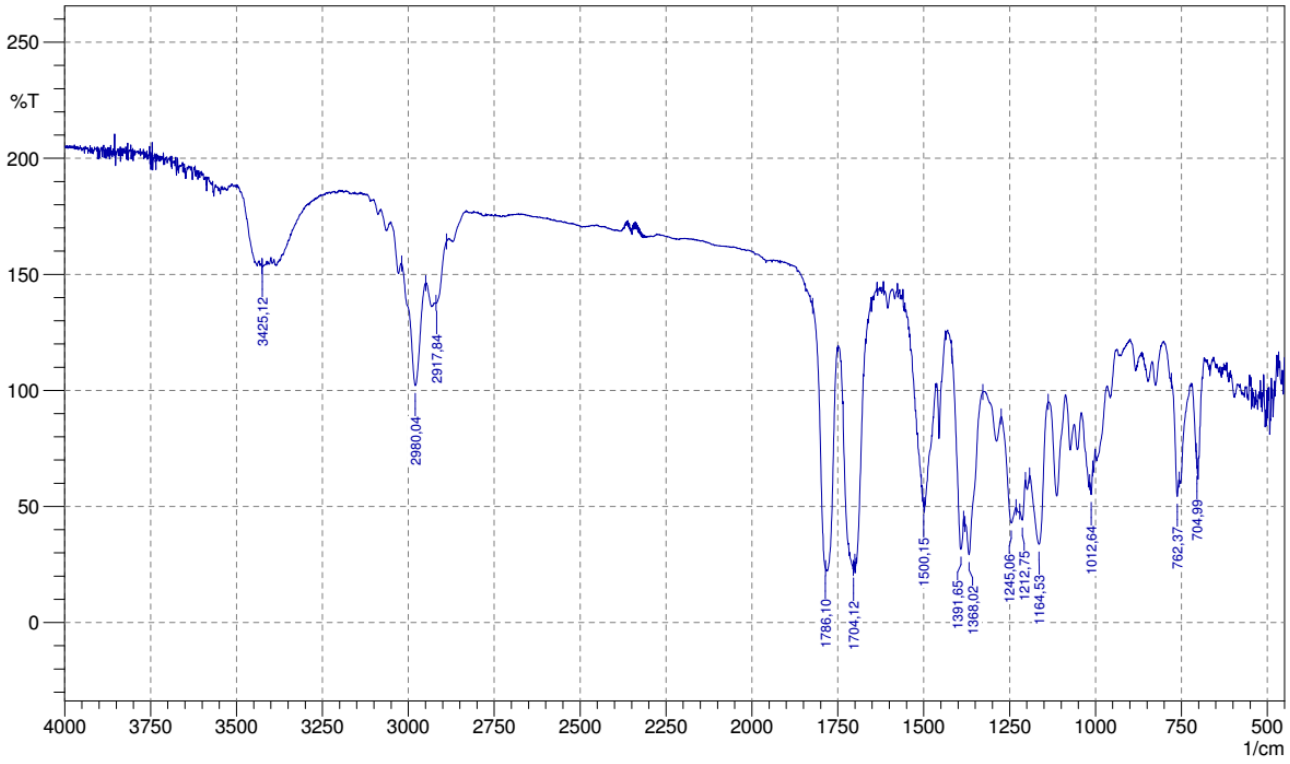
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
345 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-60 N: 1-10 O: 1-10 F: 2-2 Na: 1-1

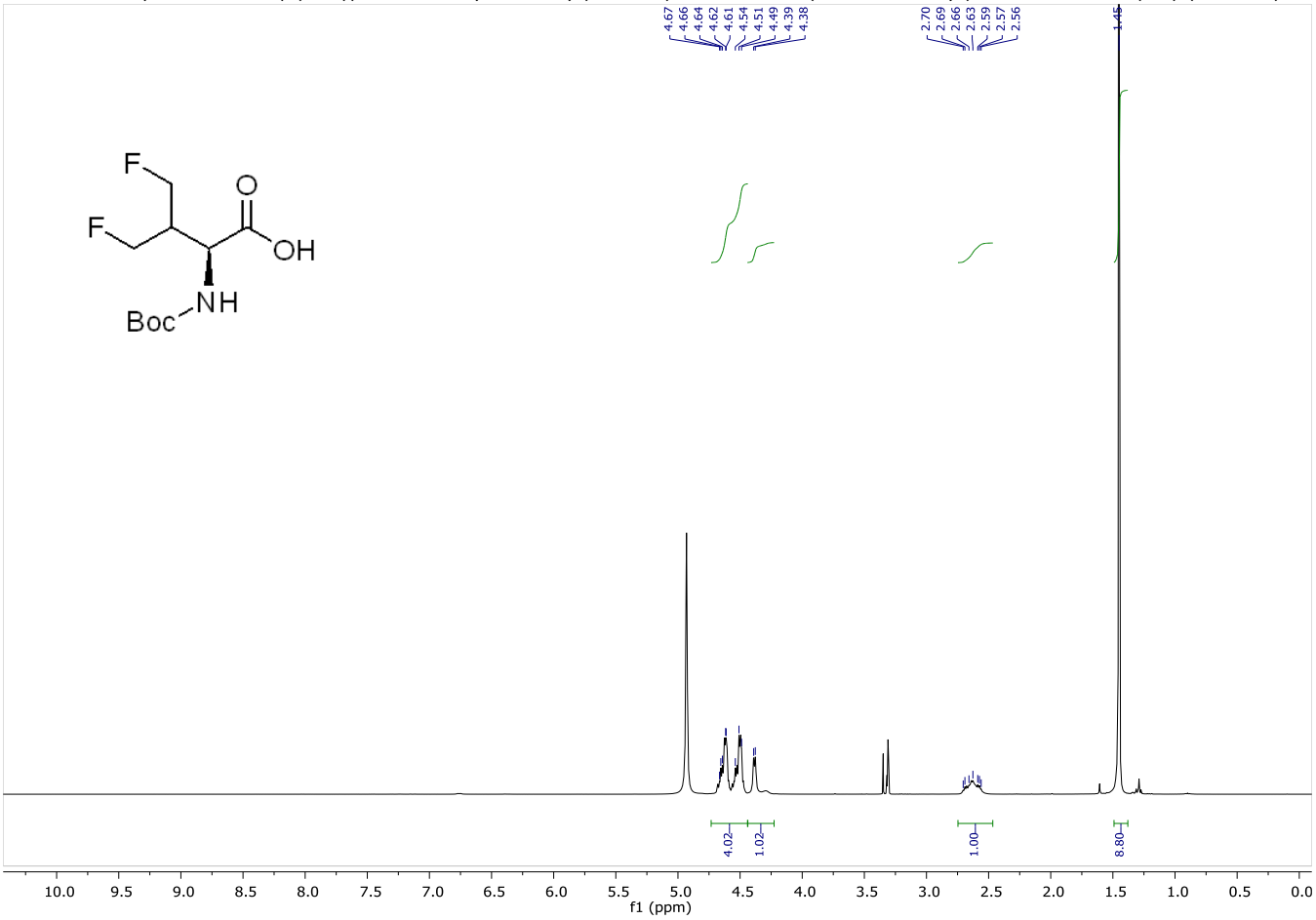
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
435.1726	100.00	435.1721	0.5	1.1	12.5	807.7	0.267	76.55	C21 H22 N6 O F2 Na
		435.1739	-1.3	-3.0	-0.5	815.7	8.232	0.03	C9 H26 N8 O8 F2 Na
		435.1707	1.9	4.4	7.5	808.9	1.452	23.41	C20 H26 N2 O5 F2 Na
		435.1766	-4.0	-9.2	-1.5	816.2	8.770	0.02	C13 H30 N2 O10 F2 Na



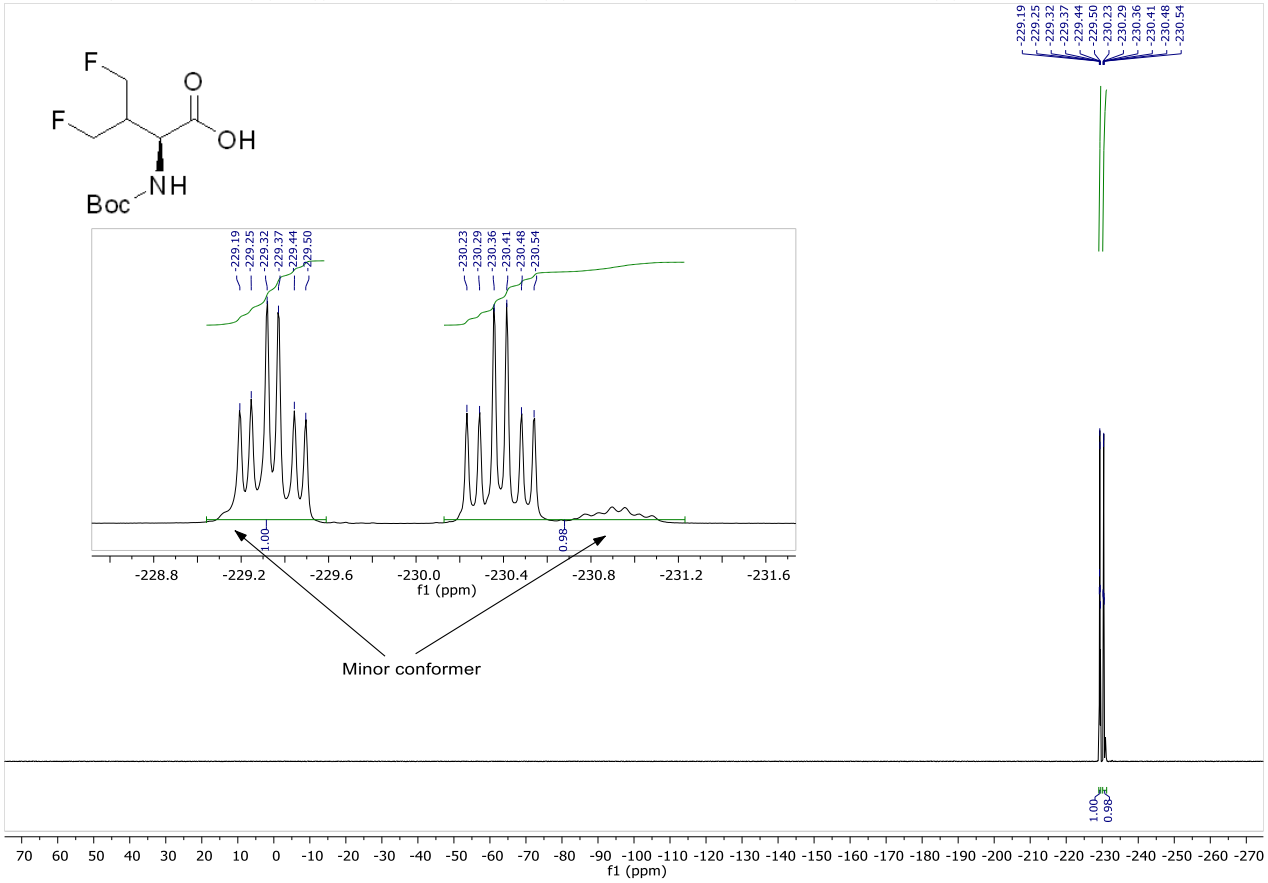
IR(ATR) spectrum of *tert*-butyl ((*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-(fluoromethyl)-1-oxobutan-2-yl)carbamate (**29**)



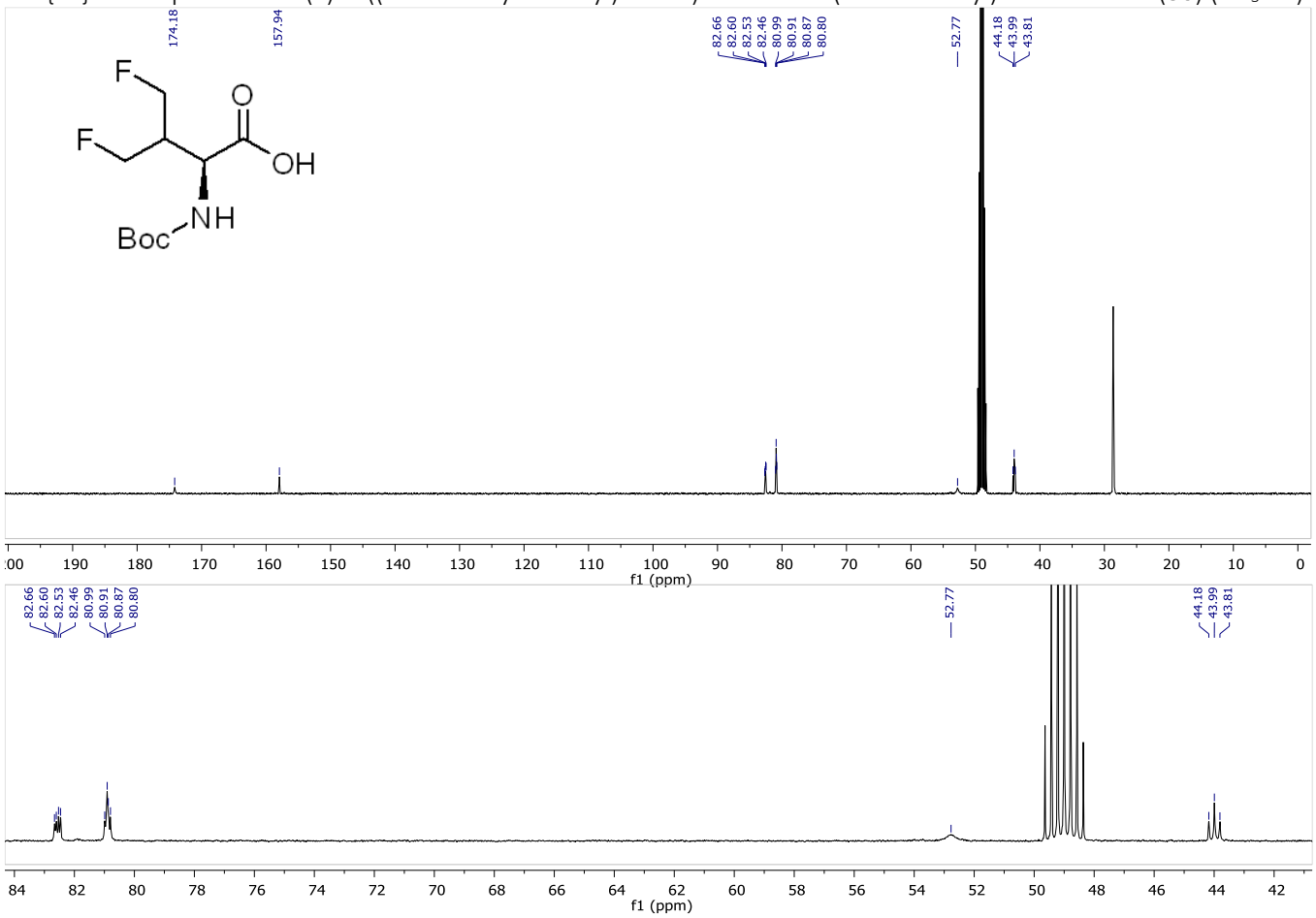
^{1}H NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (**30**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (**30**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (**30**) (CD_3OD)



HRMS of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (**30**)

MS: Waters Synapt G2-Si	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

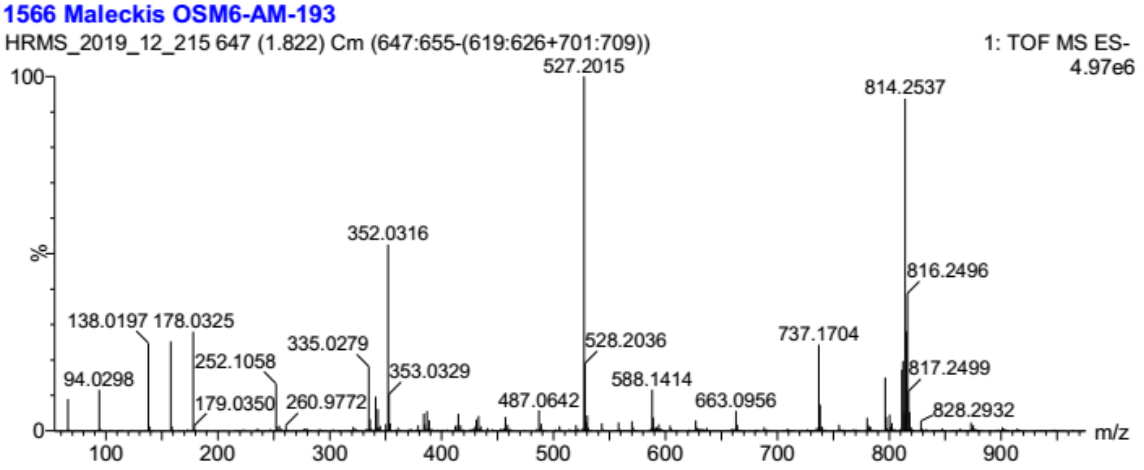
Sample:
HRMS_2019_12_215 1566 Maleckis OSM6-AM-193
MS_NEG_RES_4min ACN_Form_5-98_040_4min 2:C,1 5.000000 MS_Tune Col#43

Elemental Composition Report:

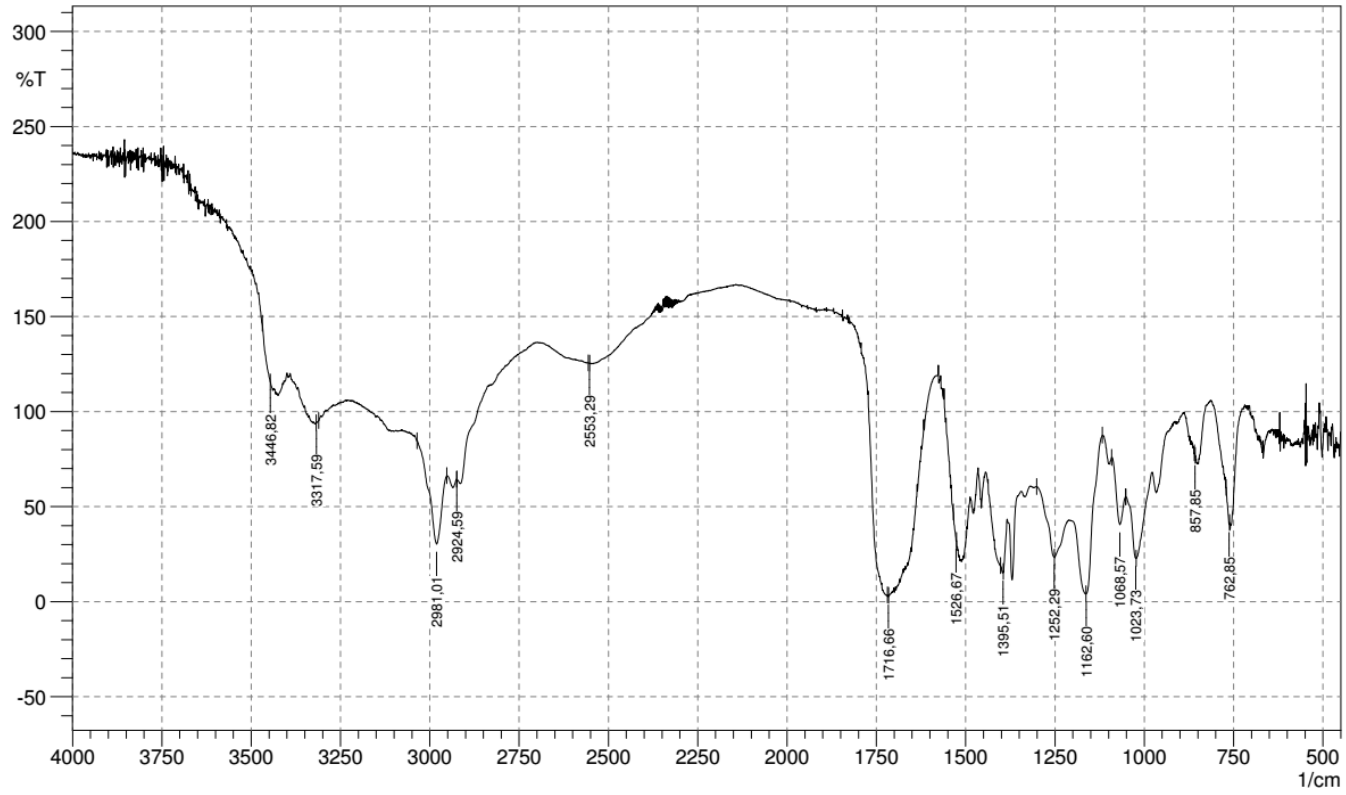
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
137 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-30 H: 1-100 N: 1-10 O: 1-10 F: 2-2

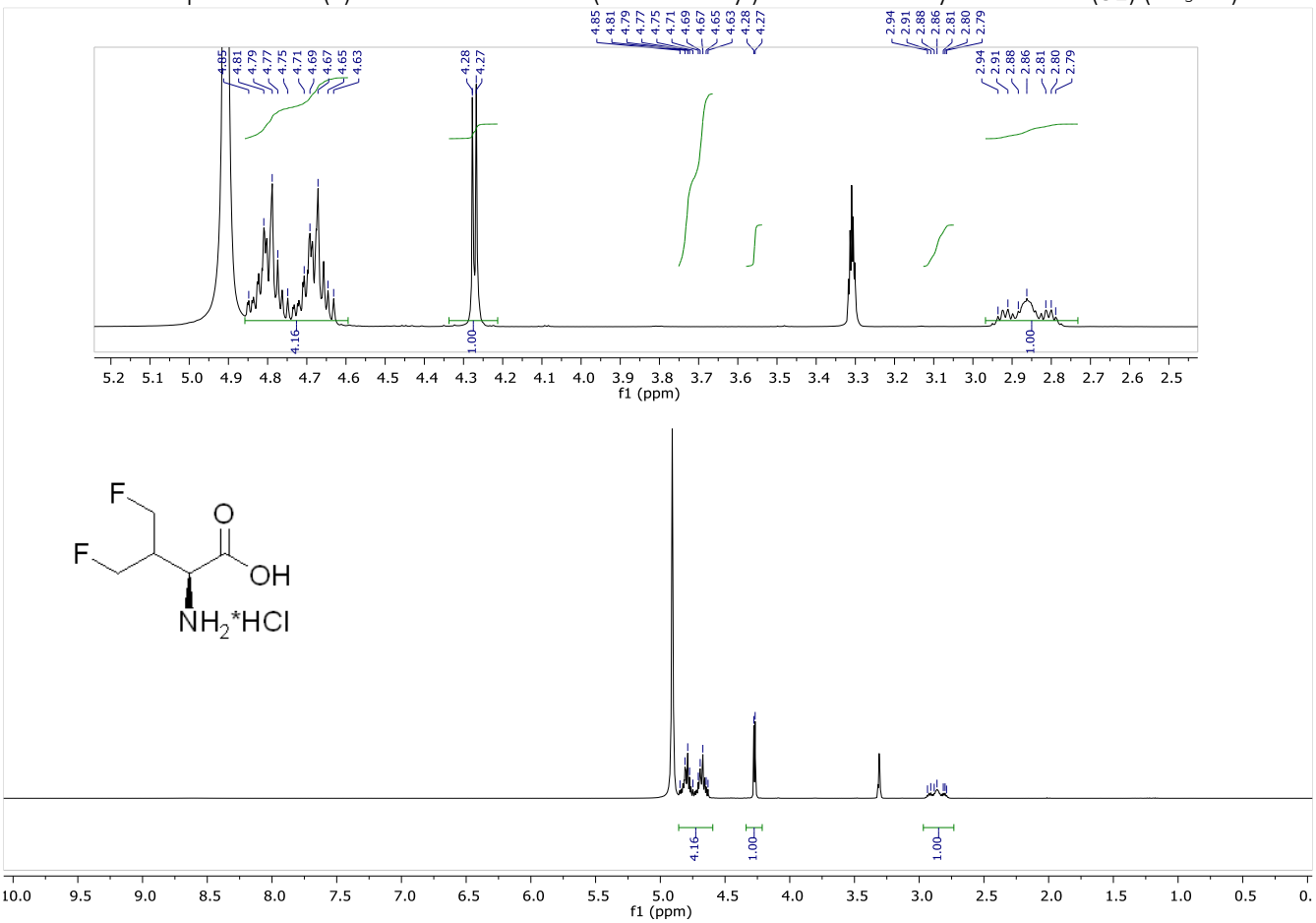
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
252.1058	100.00	252.1047	1.1	4.4	2.5	189.5	n/a	n/a	C10 H16 N O4 F2



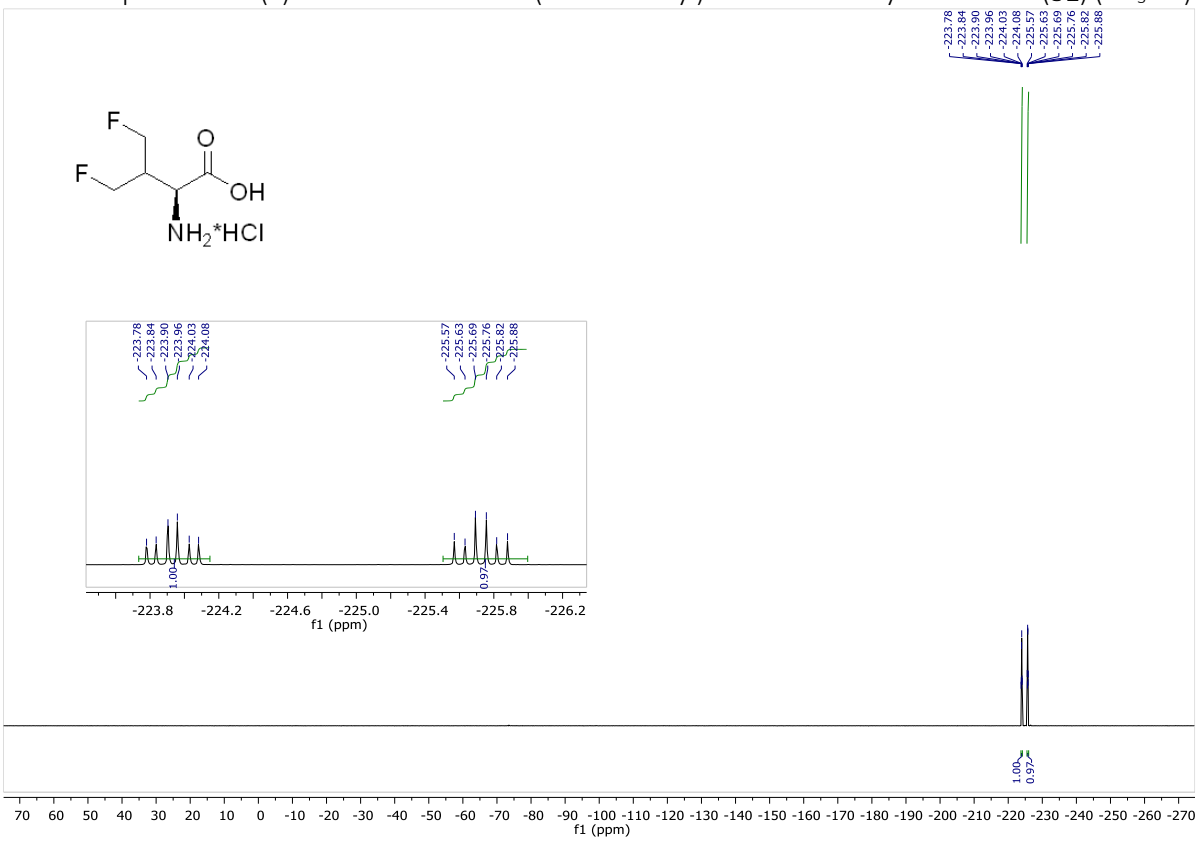
IR(ATR) spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-4-fluoro-3-(fluoromethyl)butanoic acid (**30**)



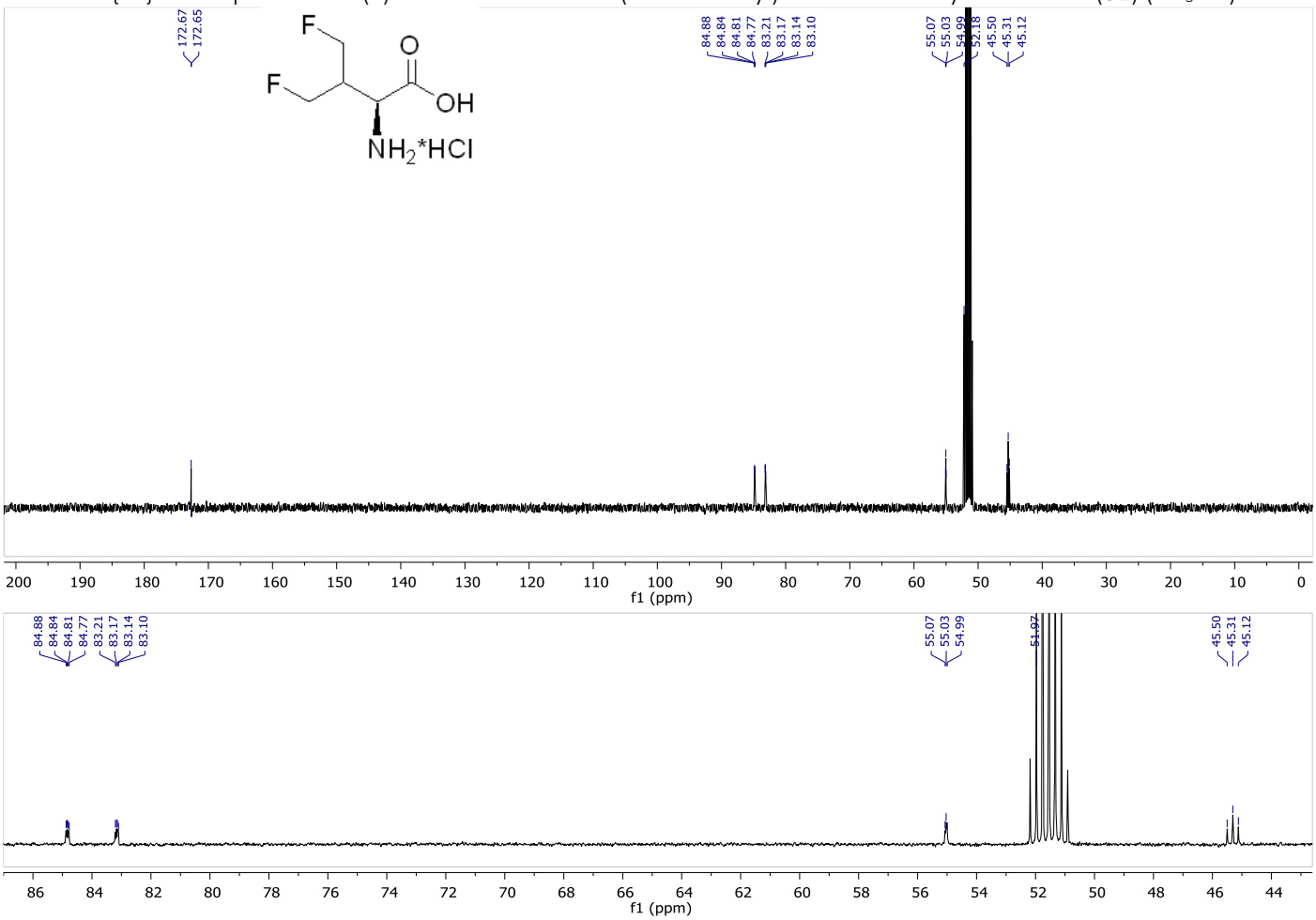
^{1}H NMR spectrum of (*S*)-2-amino-4-fluoro-3-(fluoromethyl)butanoic acid hydrochloride (**31**) (CD_3OD)



^{19}F NMR spectrum of (*S*)-2-amino-4-fluoro-3-(fluoromethyl)butanoic acid hydrochloride (**31**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (*S*)-2-amino-4-fluoro-3-(fluoromethyl)butanoic acid hydrochloride (**31**) (CD_3OD)



HRMS of (*S*)-2-amino-4-fluoro-3-(fluoromethyl)butanoic acid hydrochloride (**31**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2019_12_184 1567 Maleckis OSM6-AM-ValF2

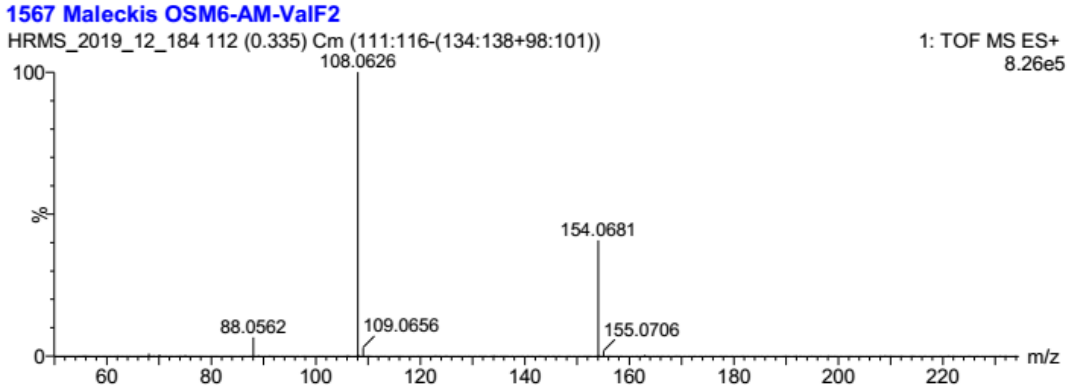
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:A,8 1.000000 MS_Tune Col#43

Elemental Composition Report:

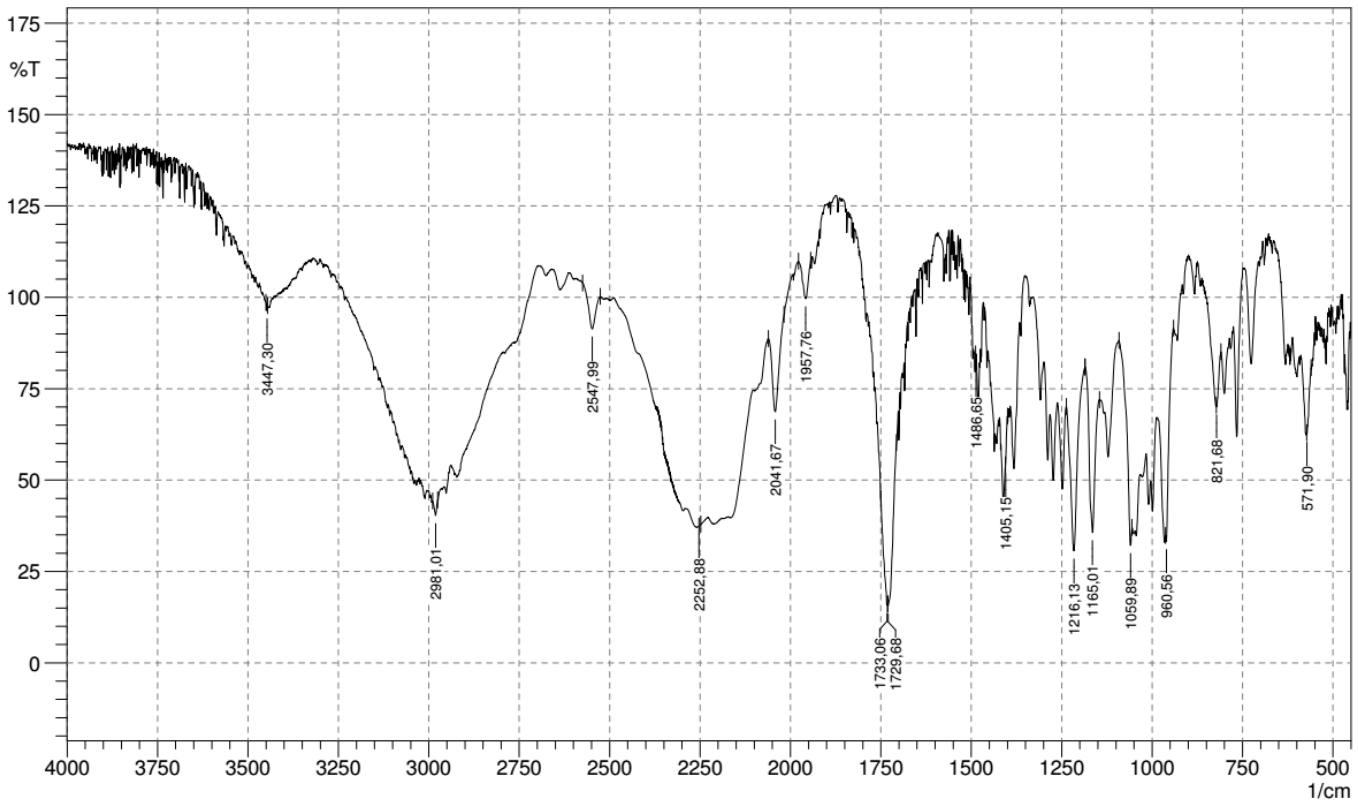
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
23 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-50 H: 1-100 N: 1-10 O: 1-10 F: 2-2

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
154.0681	100.00	154.0680	0.1	0.6	0.5	294.8	n/a	n/a	C5 H10 N O2 F2

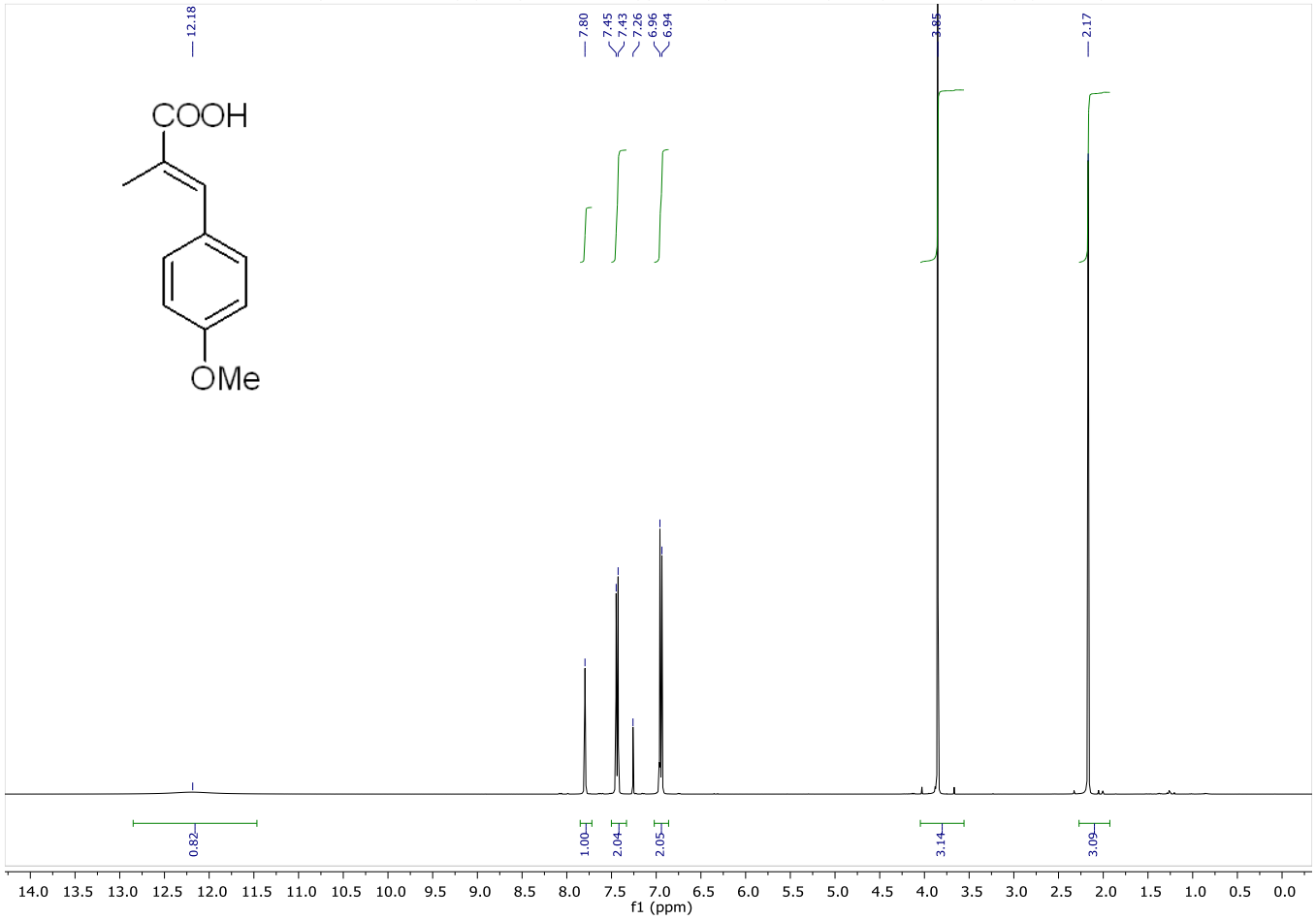


IR(ATR) spectrum of (*S*)-2-amino-4-fluoro-3-(fluoromethyl)butanoic acid hydrochloride (**31**)

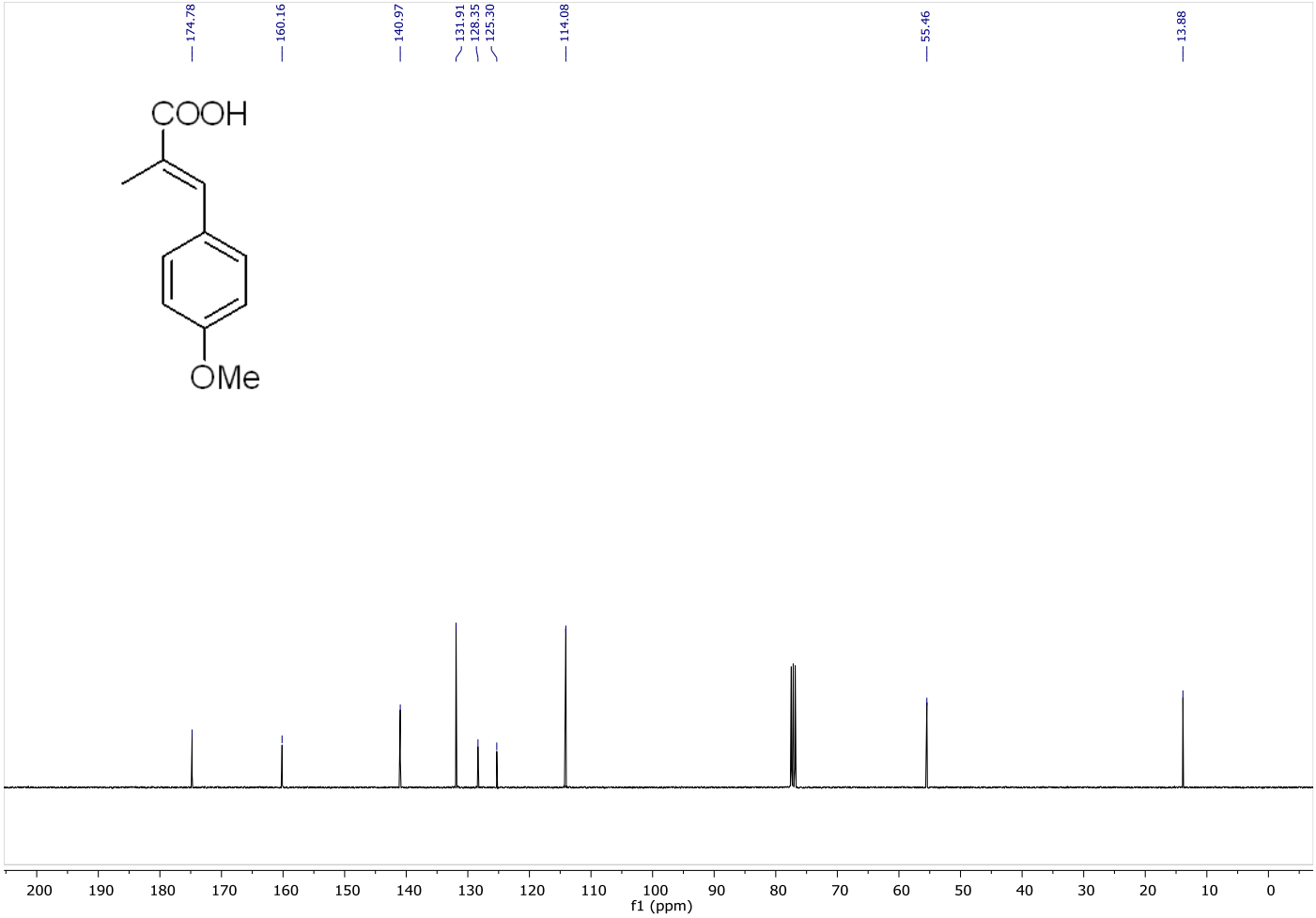


Spectra of compounds in Scheme 6

^{1}H NMR spectrum of (*E*)-3-(4-methoxyphenyl)-2-methylacrylic acid (**34**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (*E*)-3-(4-methoxyphenyl)-2-methylacrylic acid (**34**) ($CDCl_3$)



HRMS of (*E*)-3-(4-methoxyphenyl)-2-methylacrylic acid (**34**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	-
ESI-	Cone, V:	40			

Sample:

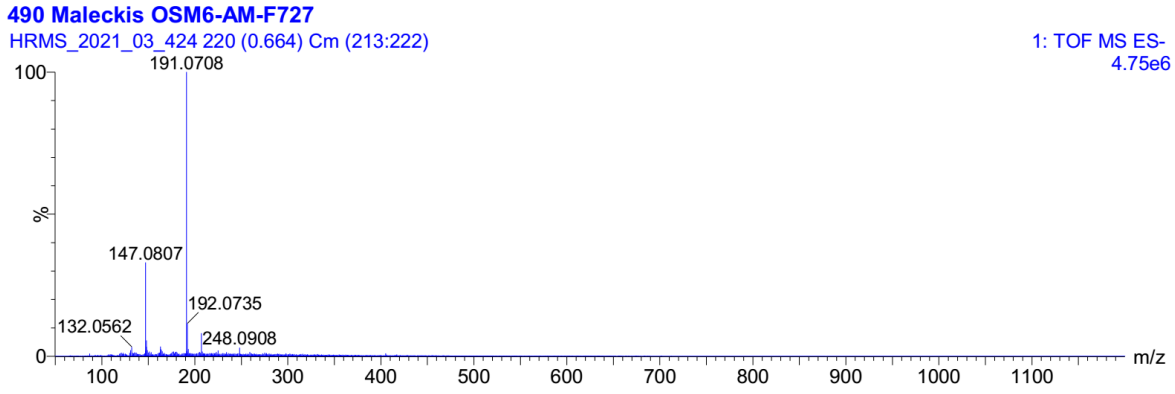
HRMS_2021_03_424 490 Maleckis OSM6-AM-F727
MS_NEG_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

Elemental Composition Report:

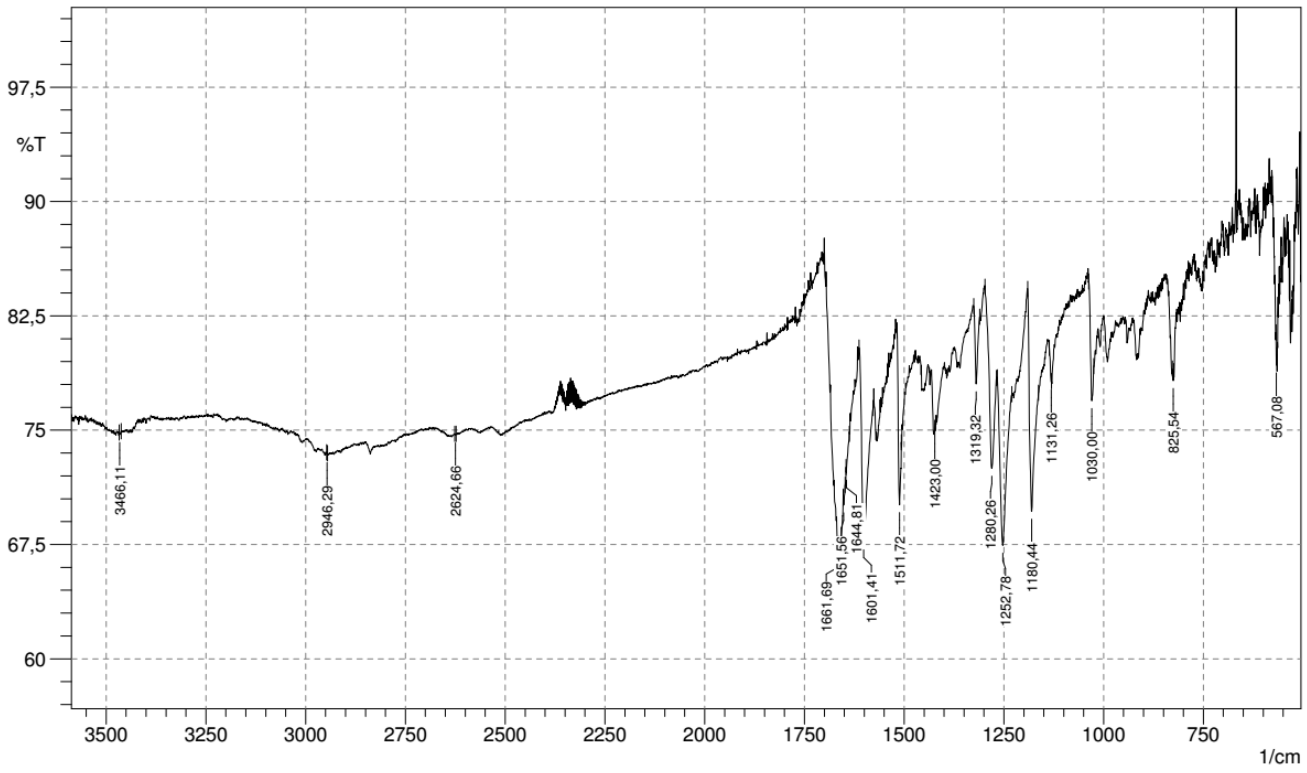
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
204 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-20 O: 0-20

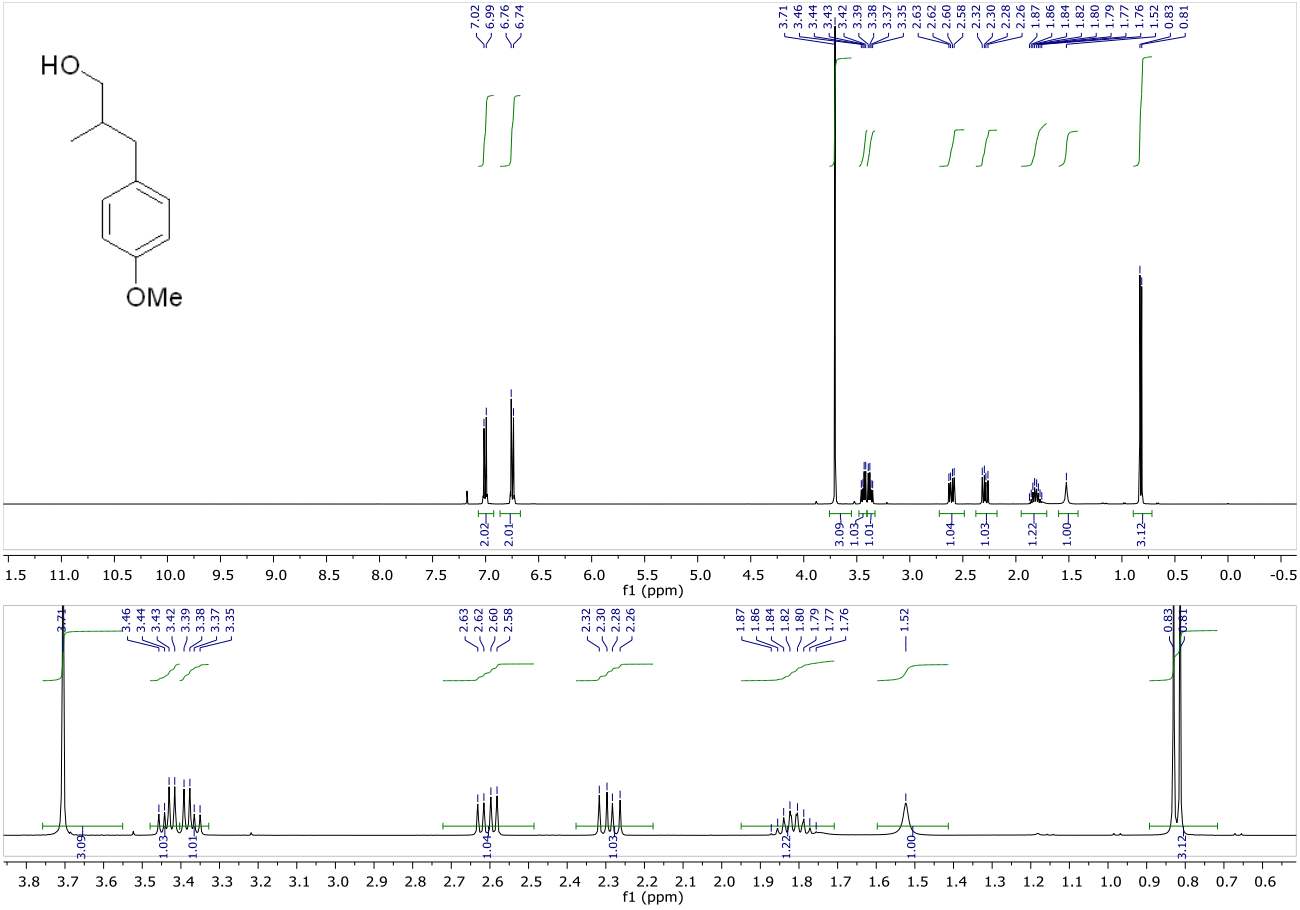
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
191.0708	100.00	191.0708	0.0	0.0	6.5	1389.5	n/a	n/a	C11 H11 O3



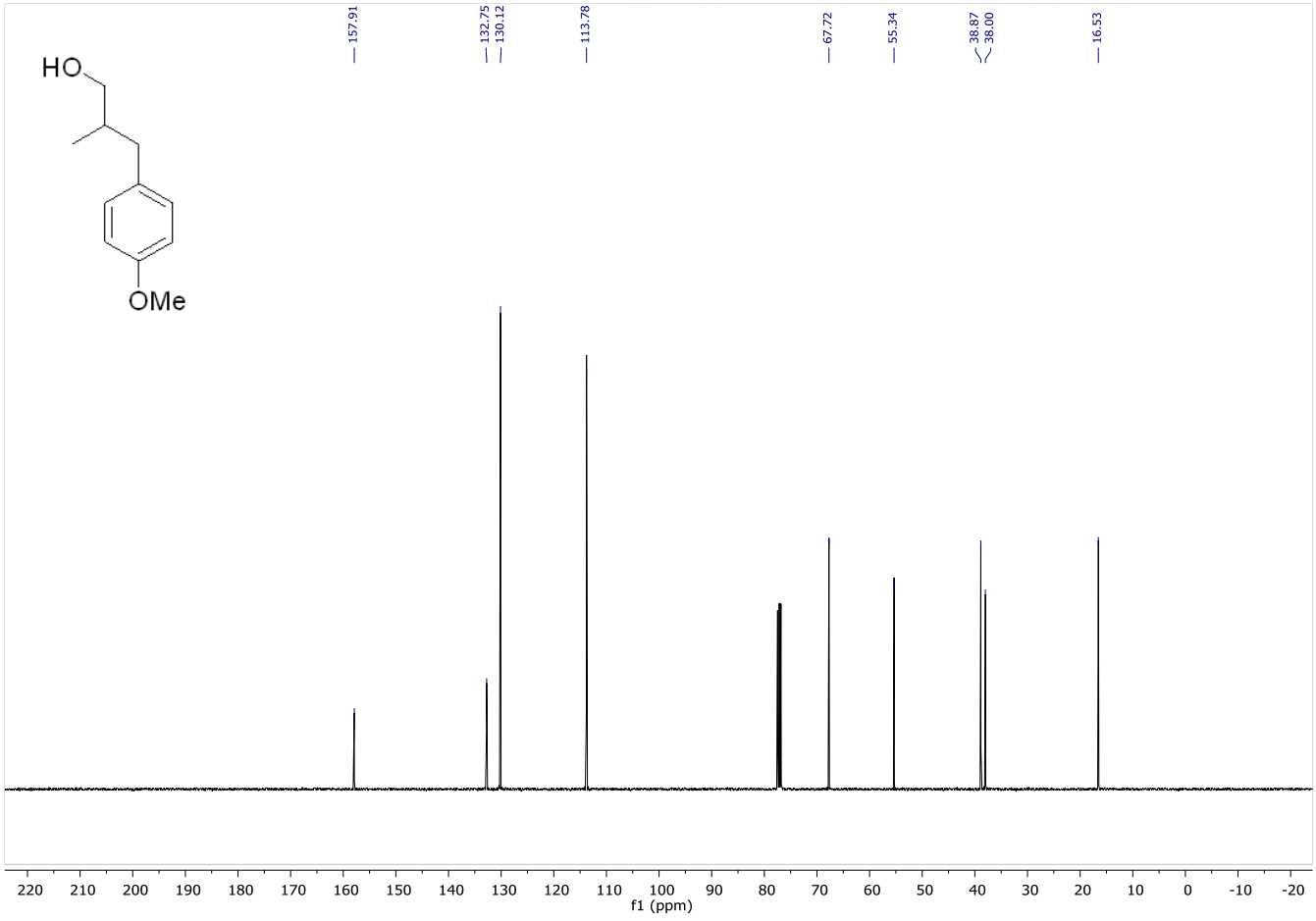
IR(ATR) spectrum of (*E*)-3-(4-methoxyphenyl)-2-methylacrylic acid (**34**)



^{1}H NMR spectrum of 3-(4-methoxyphenyl)-2-methylpropan-1-ol (**S10**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of 3-(4-methoxyphenyl)-2-methylpropan-1-ol (**S10**) ($CDCl_3$)



HRMS of 3-(4-methoxyphenyl)-2-methylpropan-1-ol (**S10**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

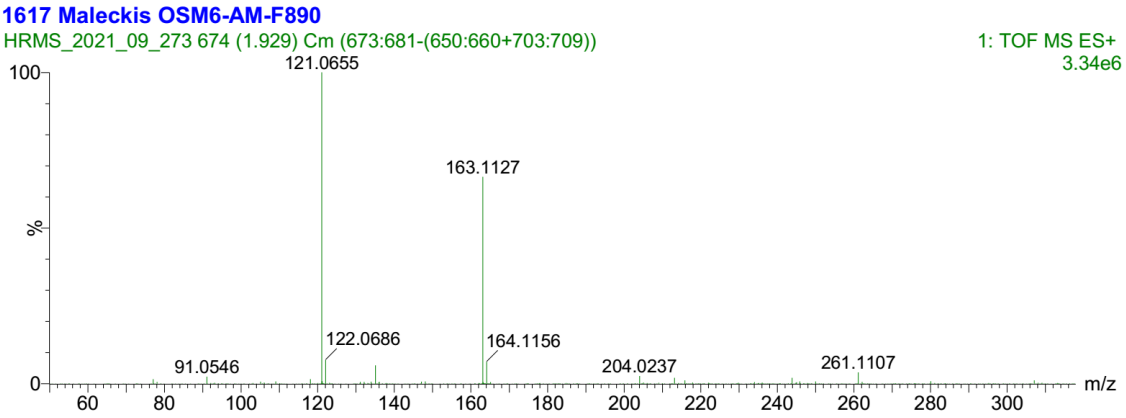
HRMS_2021_09_273 1617 Maleckis OSM6-AM-F890
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:D,6 1.000000 MS_Tune Col#66

Elemental Composition Report:

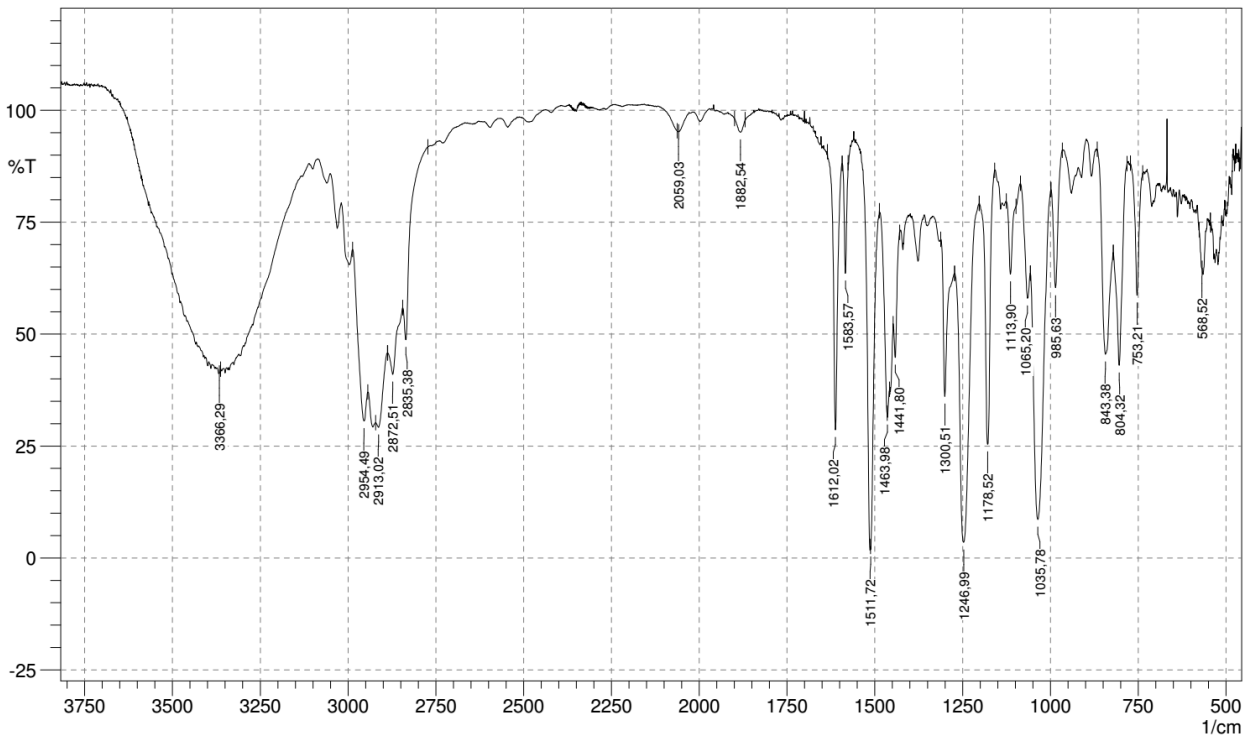
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
23 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-120 O: 0-10

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
163.1127	100.00	163.1123	0.4	2.5	4.5	401.4	n/a	n/a	C11 H15 O



IR(ATR) spectrum of 3-(4-methoxyphenyl)-2-methylpropan-1-ol (**S10**)



OSM6_AM-F890

GC-MS of 3-(4-methoxyphenyl)-2-methylpropan-1-ol (**S10**)

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File        :D:\DATA_2021\09-Sept-2021\21_15151.D
Operator    : E
Acquired    : 21 Sep 2021  11:28      using AcqMethod LAURA.M
Instrument :    GCMS
Sample Name: Maleckis OSM6-AM-F891-2
Misc Info  :
Vial Number: 8
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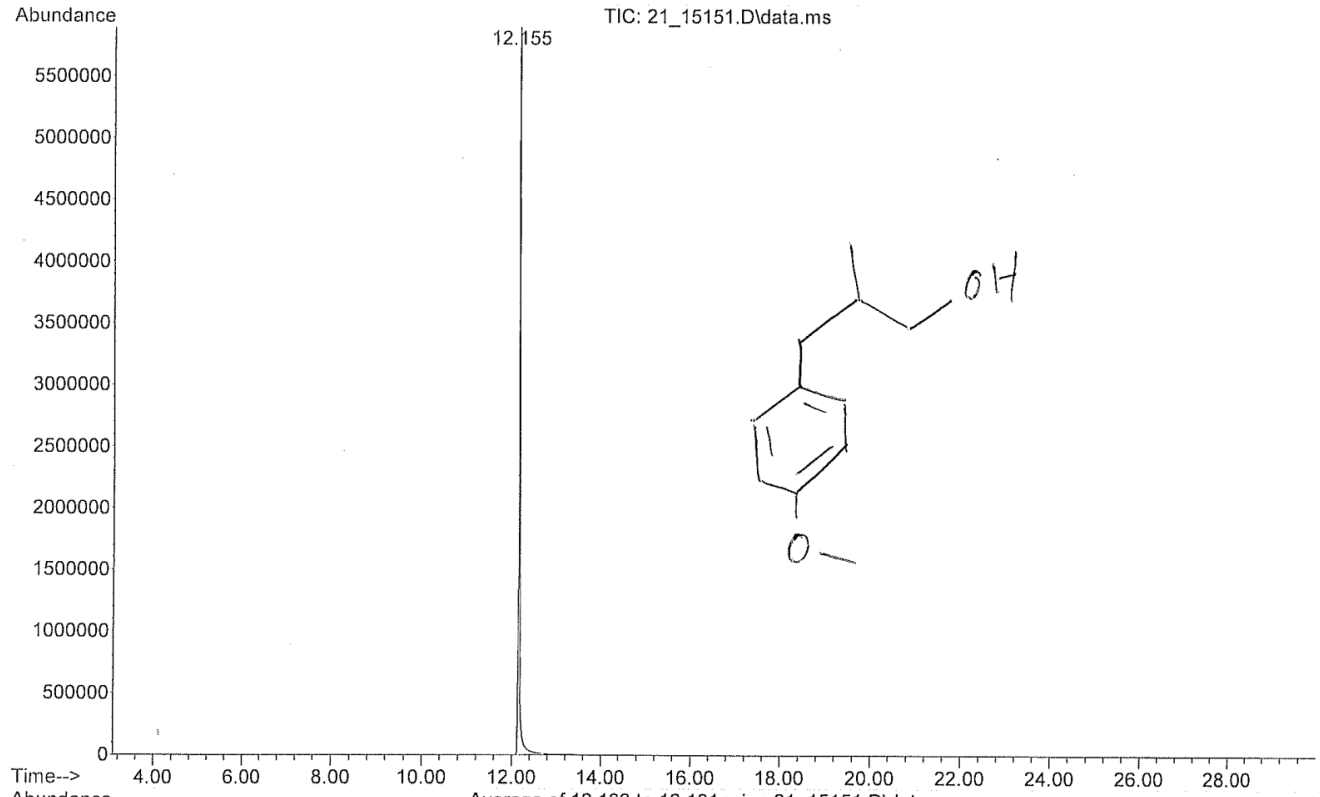
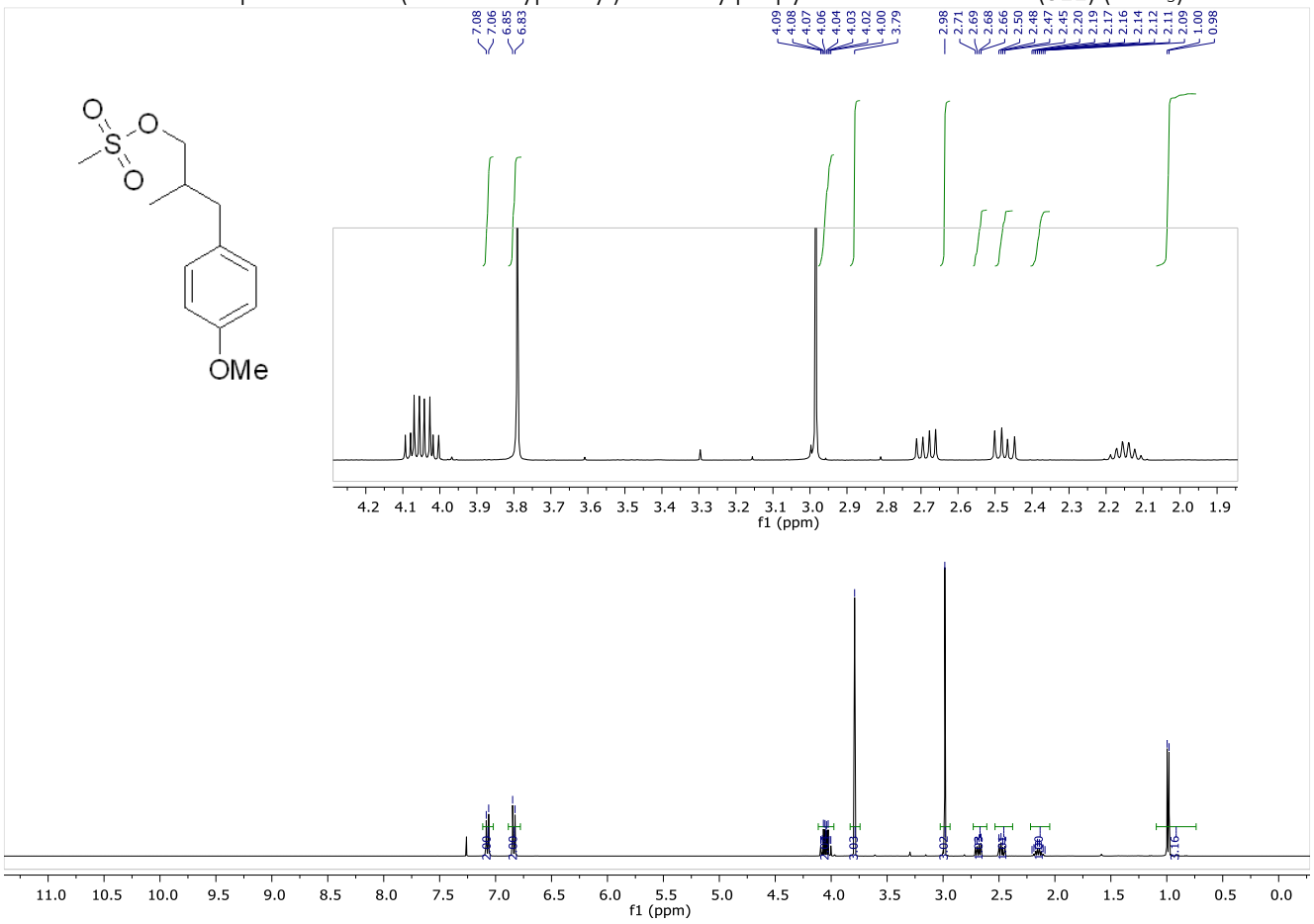
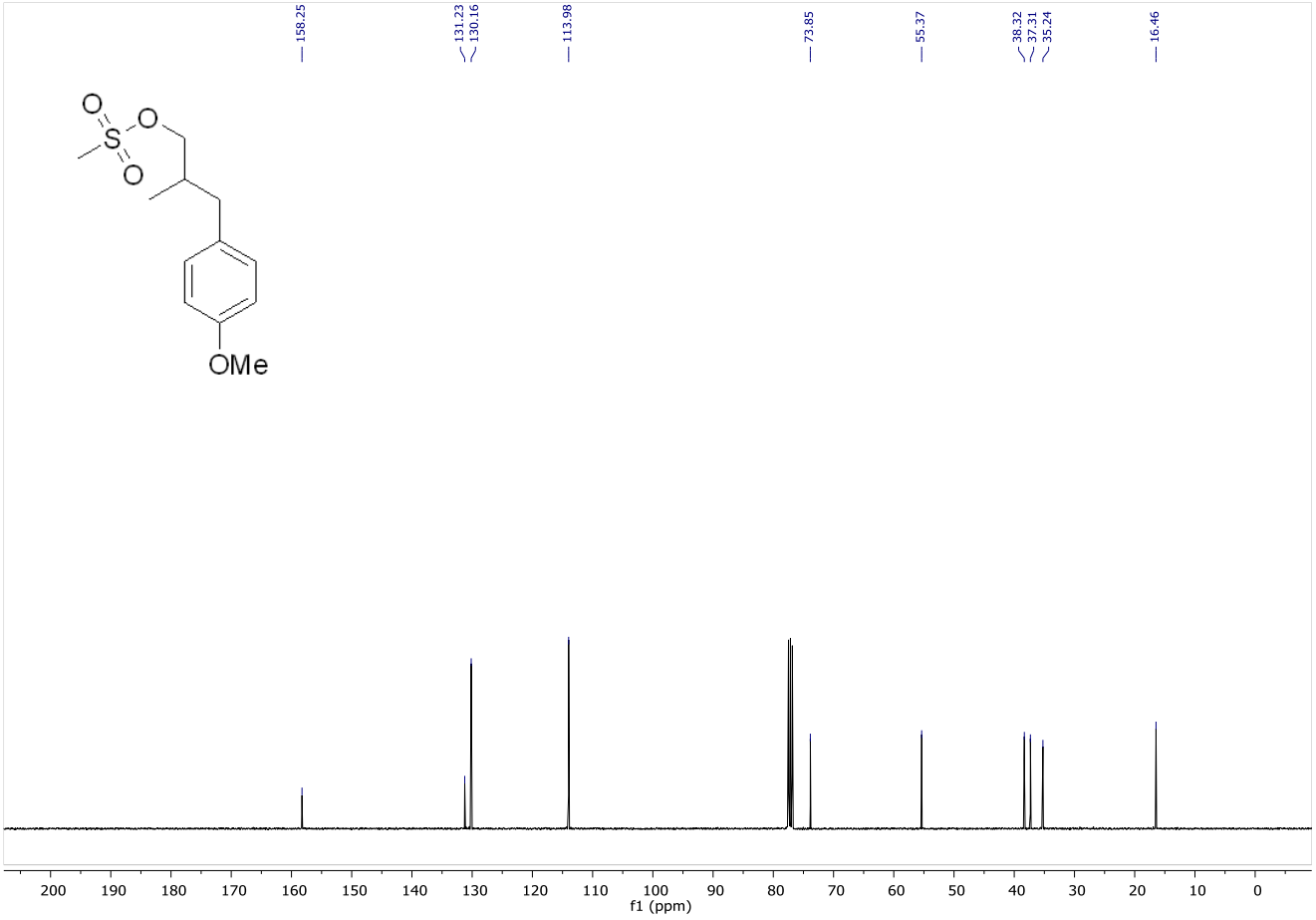


^{1}H NMR spectrum of 3-(4-methoxyphenyl)-2-methylpropyl methanesulfonate (**S11**) ($CDCl_3$)



^{13}C{^{1}H} NMR 3-(4-methoxyphenyl)-2-methylpropyl methanesulfonate (**S11**) ($CDCl_3$)



GC-MS of 3-(4-methoxyphenyl)-2-methylpropyl methanesulfonate (**S11**)

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File        :D:\DATA_2021\03-Mar-2021\15_15033.D
Operator    : E
Acquired    : 15 Mar 2021  14:50      using AcqMethod LAURA.M
Instrument :    GCMS
Sample Name: Maleckis OSM6-AM-F735
Misc Info  :
Vial Number: 9
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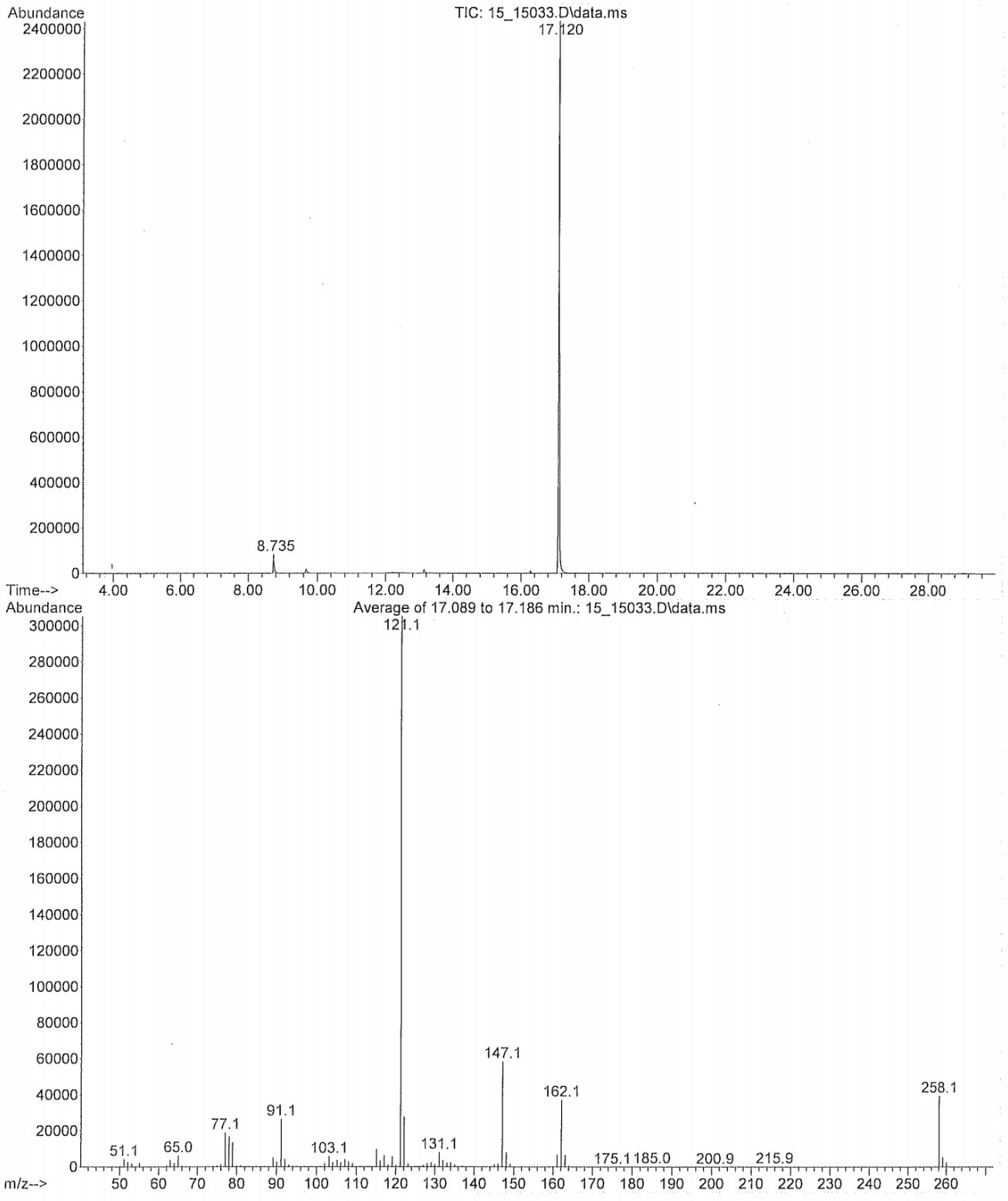


HRMS of 3-(4-methoxyphenyl)-2-methylpropyl methanesulfonate (**S11**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column: -
ESI+	Cone, V:	40		

Sample:

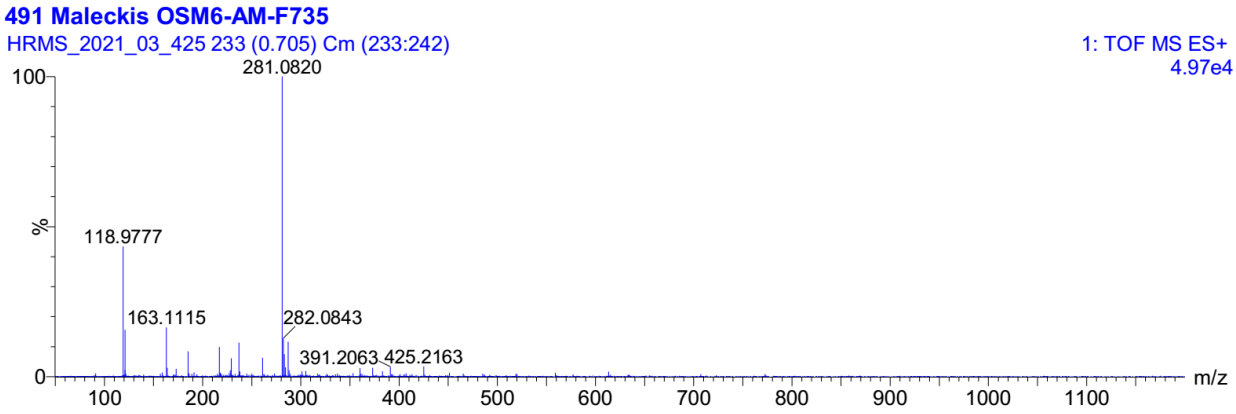
HRMS_2021_03_425 491 Maleckis OSM6-AM-F735
MS_POS_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

Elemental Composition Report:

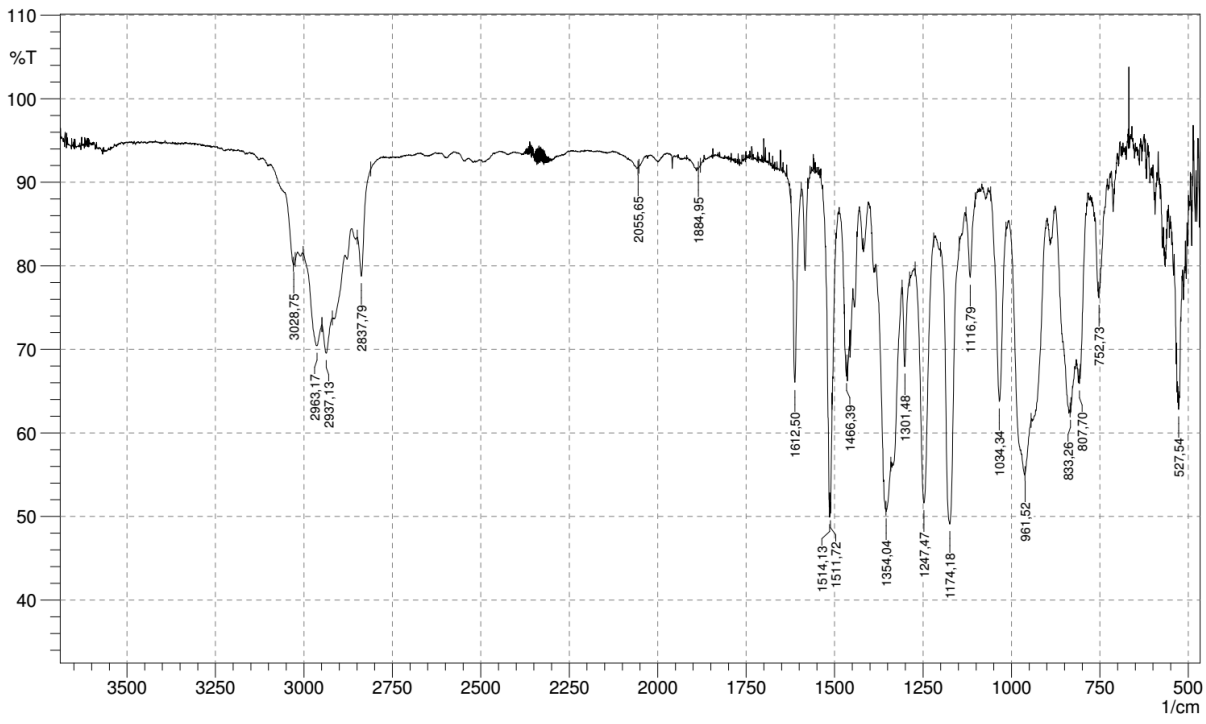
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
279 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-20 O: 0-20 S: 1-1 Na: 1-1

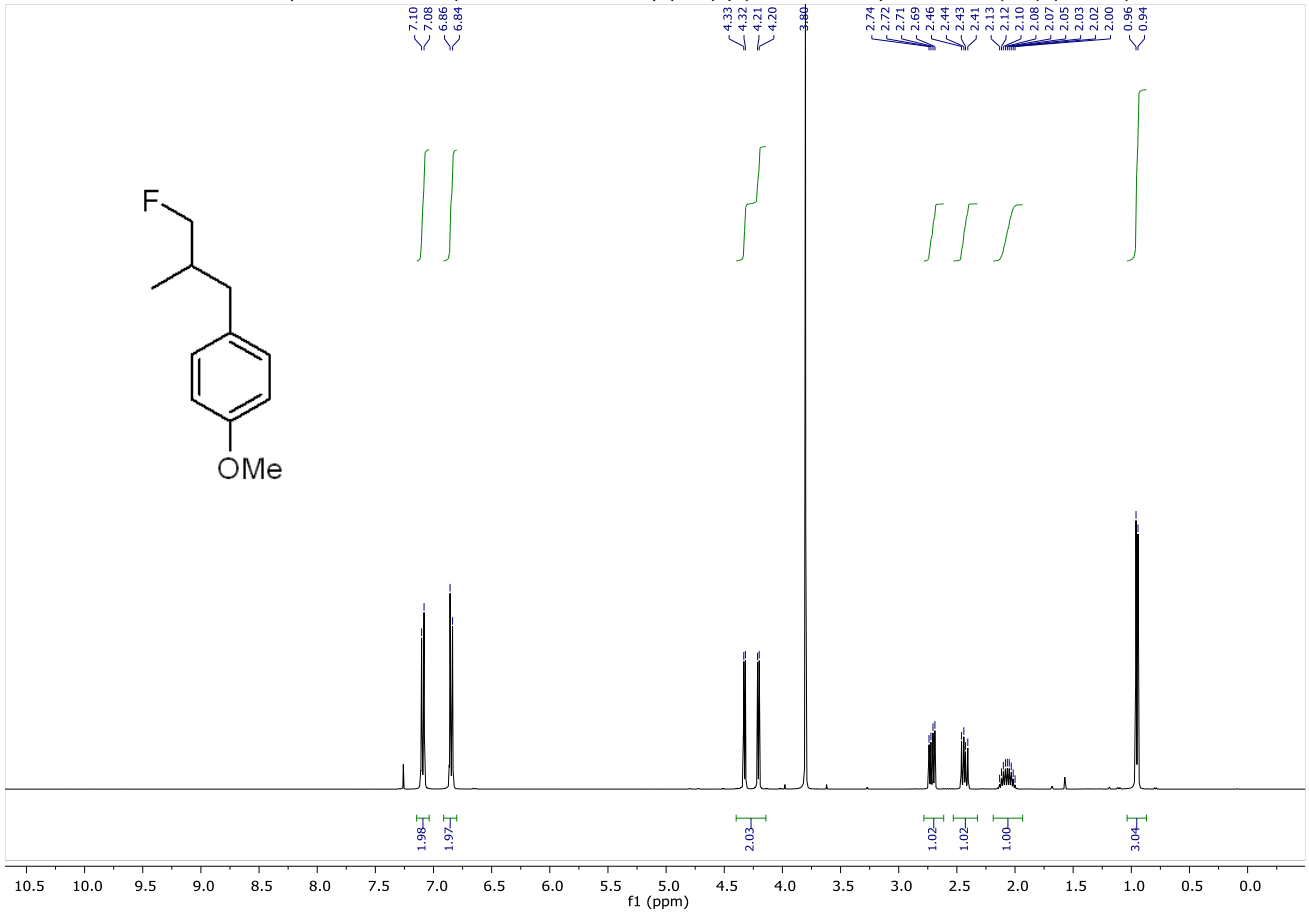
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
281.0820	100.00	281.0823	-0.3	-1.1	3.5	255.4	n/a	n/a	C12 H18 O4 S Na



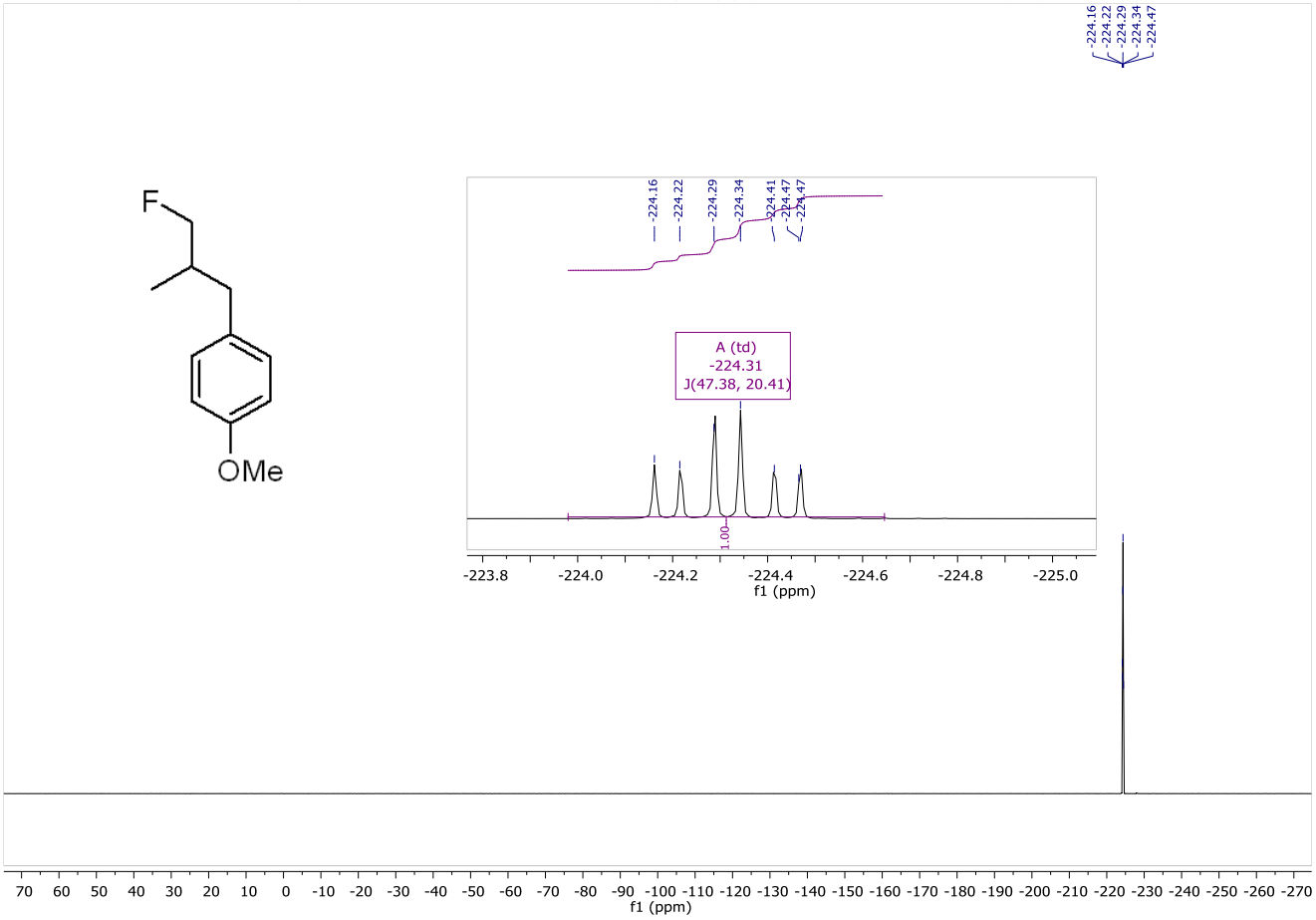
IR(ATR) spectrum of 3-(4-methoxyphenyl)-2-methylpropyl methanesulfonate (**S11**)



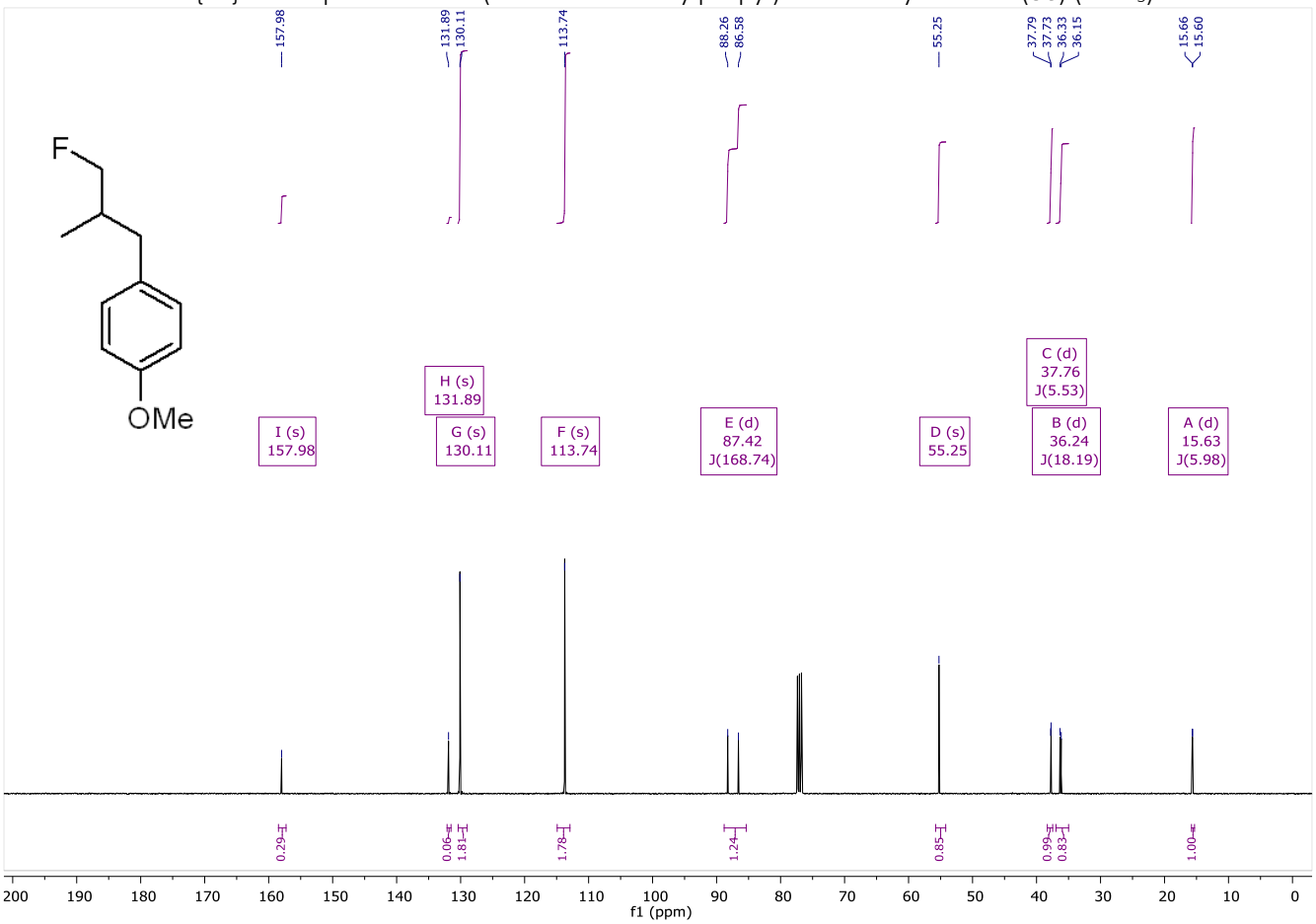
^{1}H NMR spectrum of 1-(3-fluoro-2-methylpropyl)-4-methoxybenzene (**36**) ($CDCl_3$)



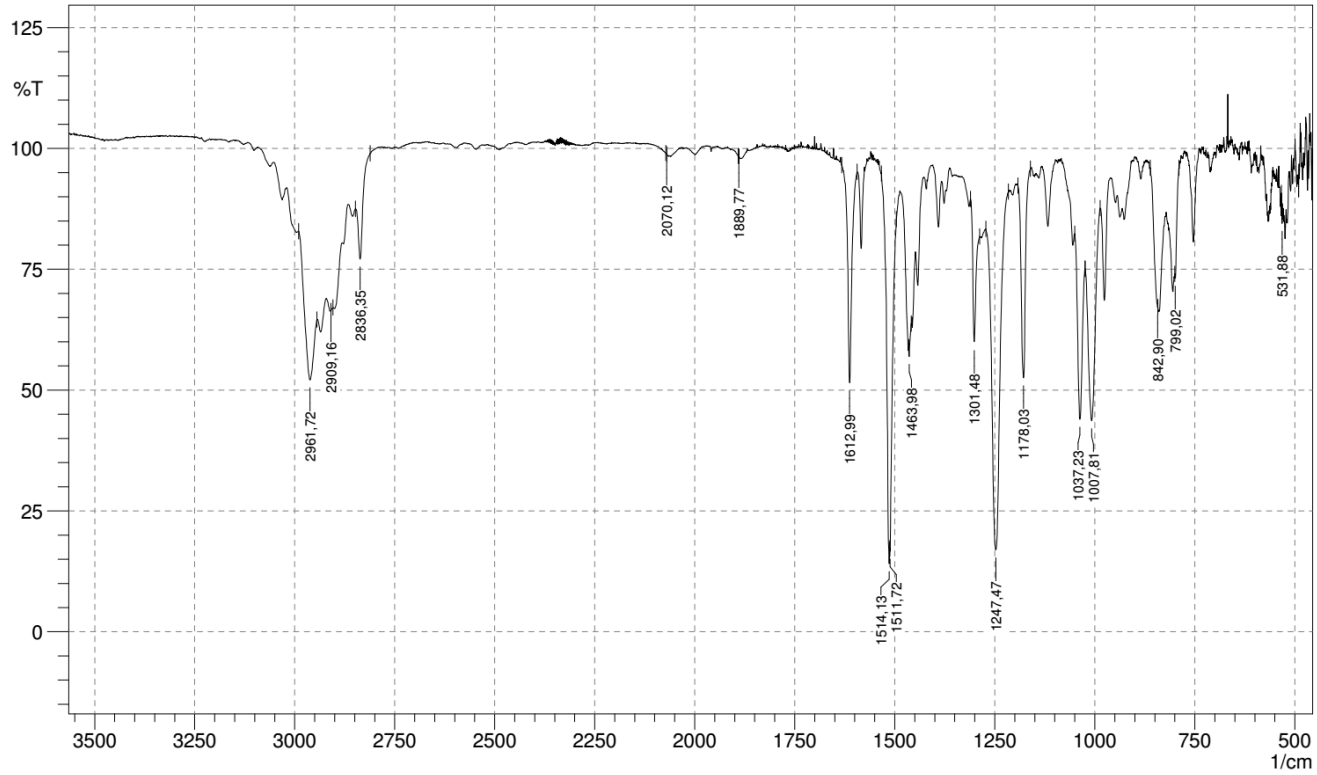
^{19}F NMR spectrum of 1-(3-fluoro-2-methylpropyl)-4-methoxybenzene (**36**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 1-(3-fluoro-2-methylpropyl)-4-methoxybenzene (**36**) ($CDCl_3$)



IR(ATR) spectrum of 1-(3-fluoro-2-methylpropyl)-4-methoxybenzene (**36**)



GC-MS of 1-(3-fluoro-2-methylpropyl)-4-methoxybenzene (**36**)

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Operator    : E
Acquired    : 15 Mar 2021  15:56      using AcqMethod LAURA.M
Instrument :    GCMS
Sample Name: Maleckis OSM6-AM-F737
Misc Info  :
Vial Number: 11
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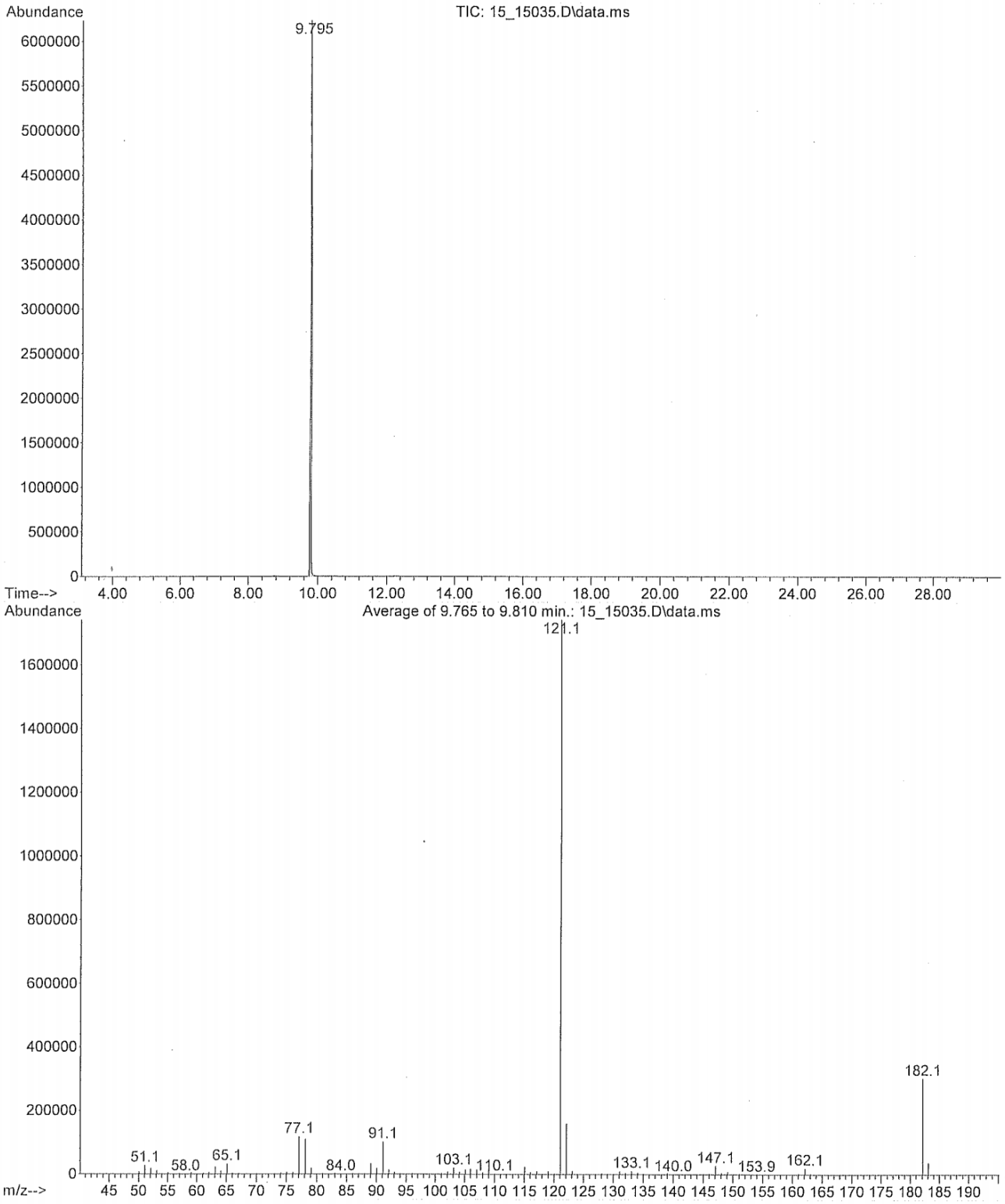
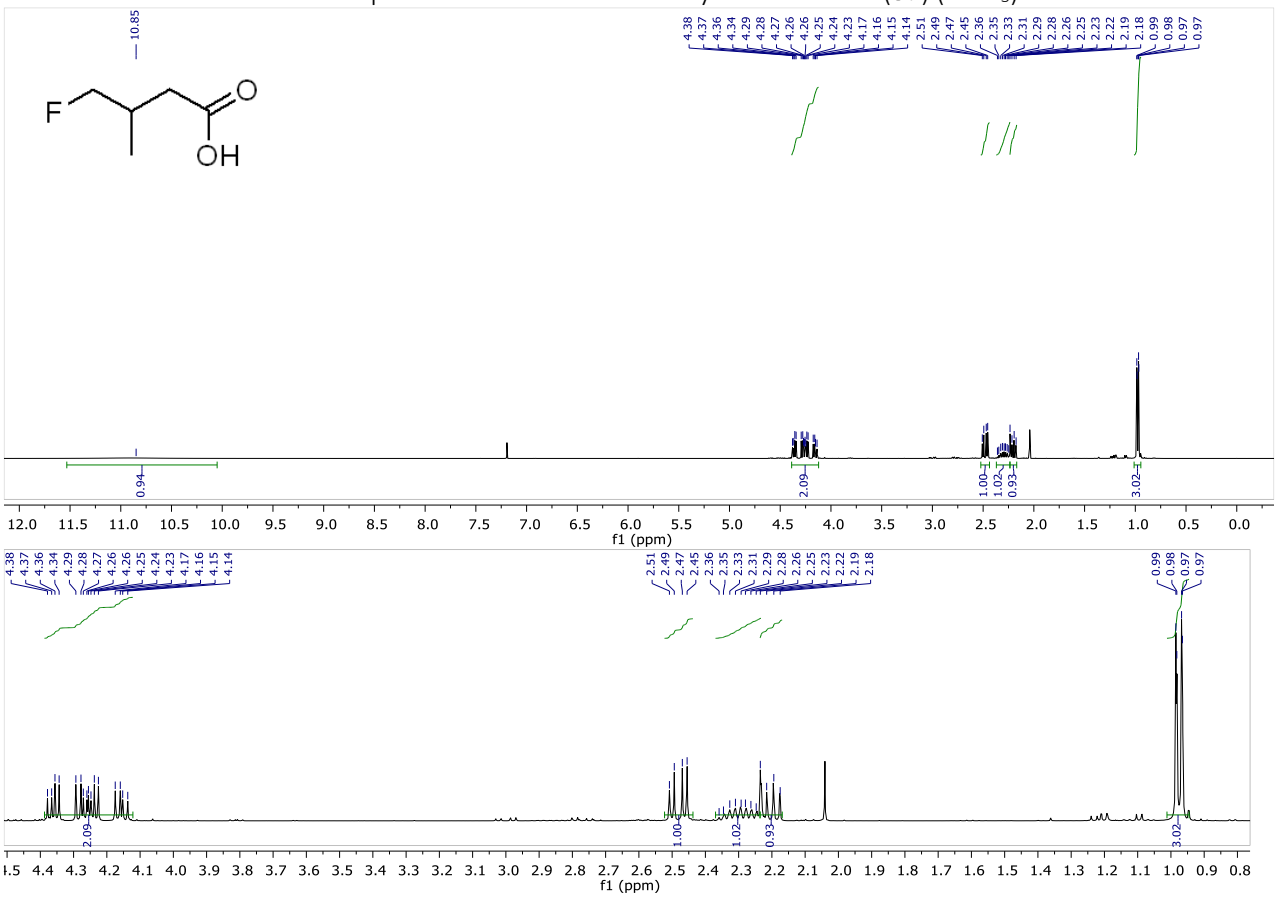
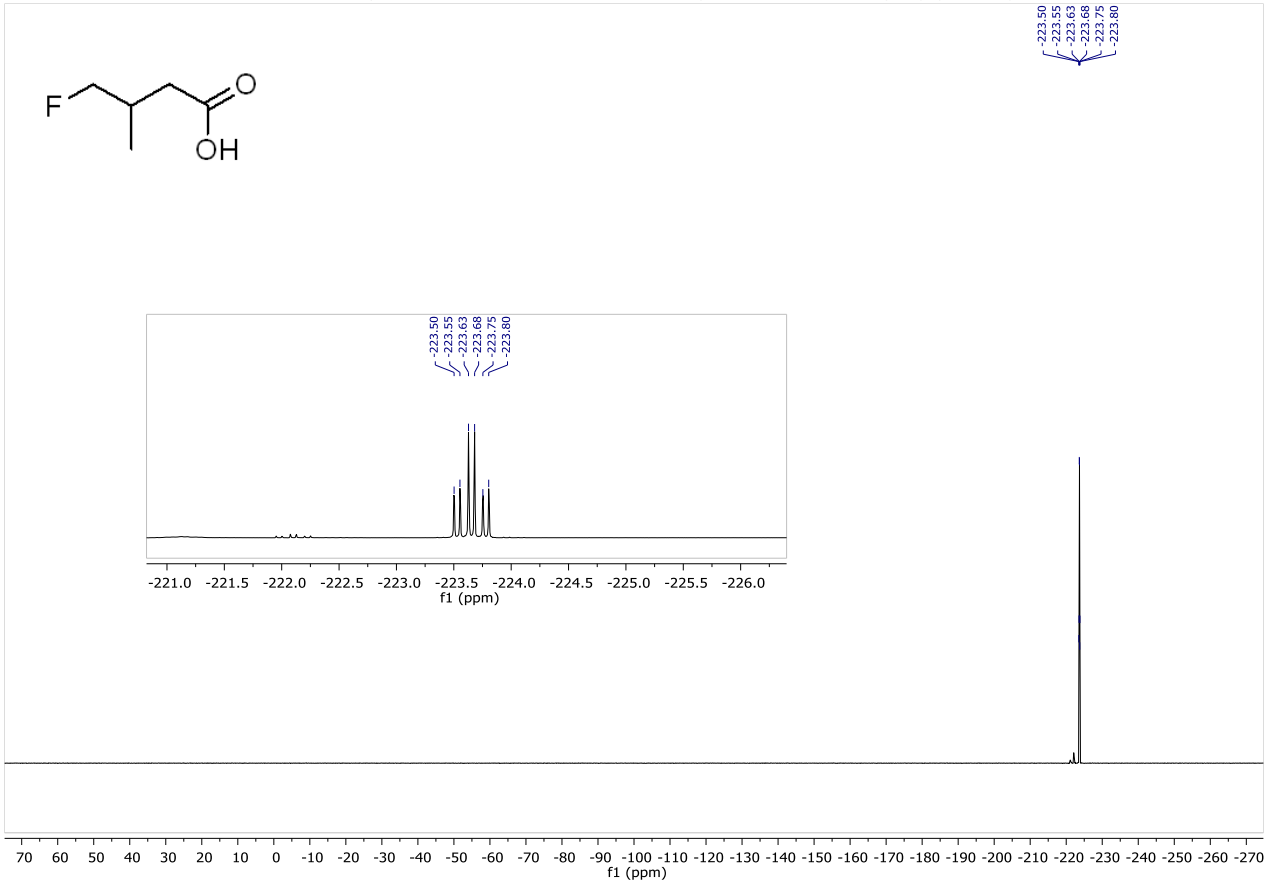


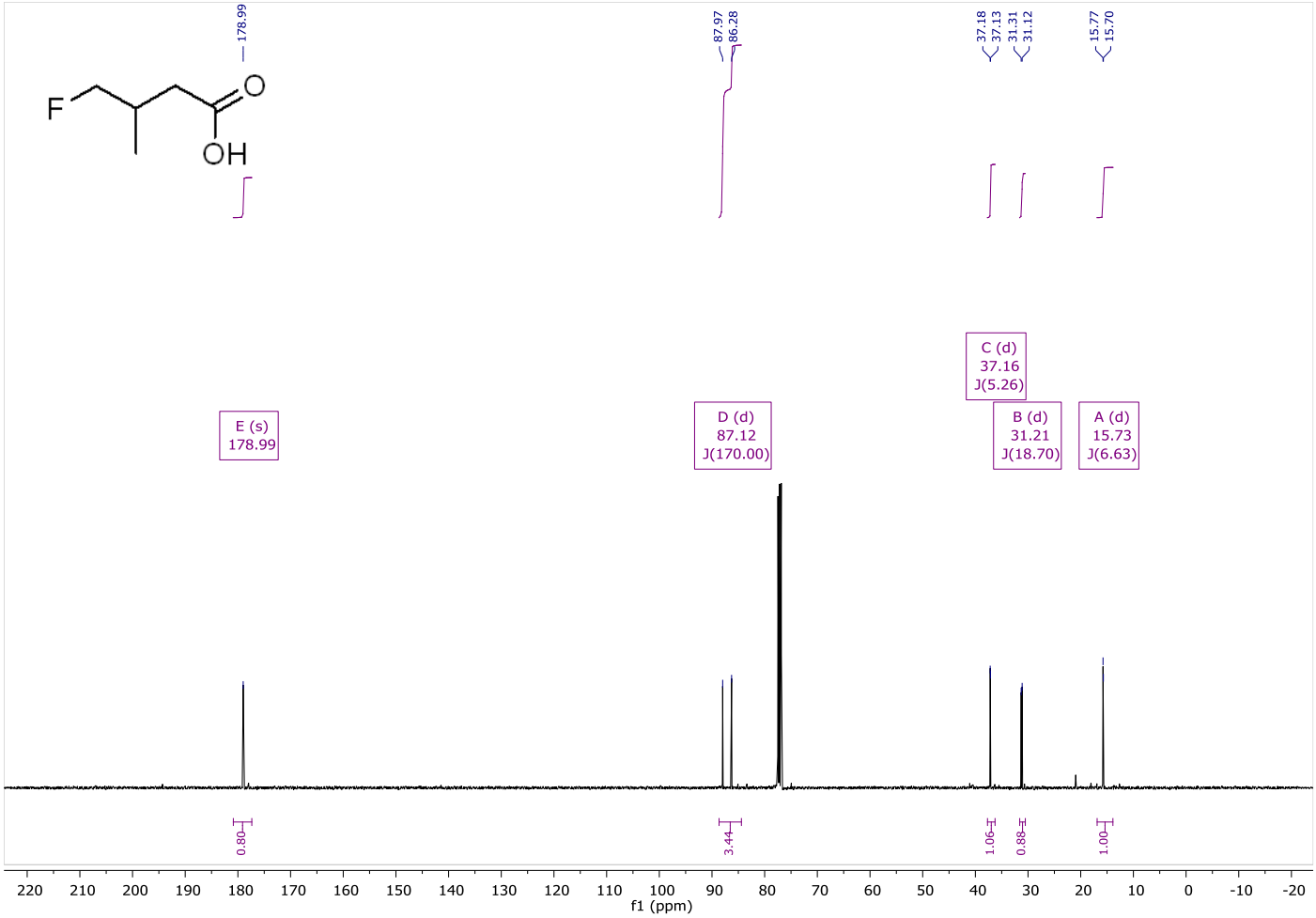
^{1}H NMR spectrum of 4-fluoro-3-methylbutanoic acid (**37**) ($CDCl_3$)



^{19}F NMR spectrum of 4-fluoro-3-methylbutanoic acid (**37**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of 4-fluoro-3-methylbutanoic acid (**37**) ($CDCl_3$)



HRMS of 4-fluoro-3-methylbutanoic acid (**37**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	-
ESI-	Cone, V:	40			

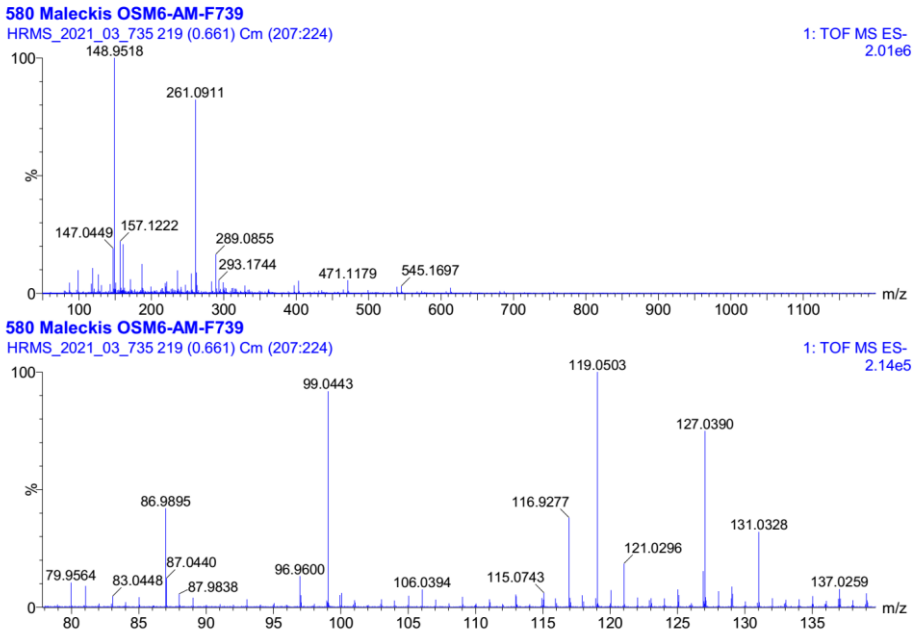
Sample:
HRMS_2021_03_735 580 Maleckis OSM6-AM-F739
MS_NEG_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

Elemental Composition Report:

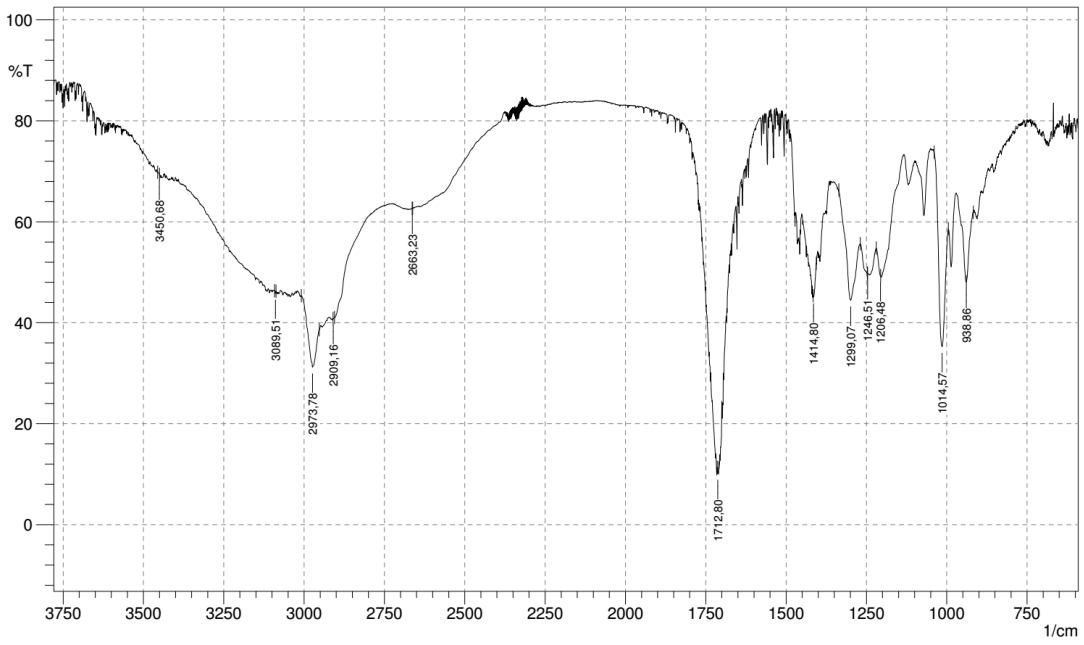
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
95 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 H: 0-110 N: 0-20 O: 0-20 F: 1-3

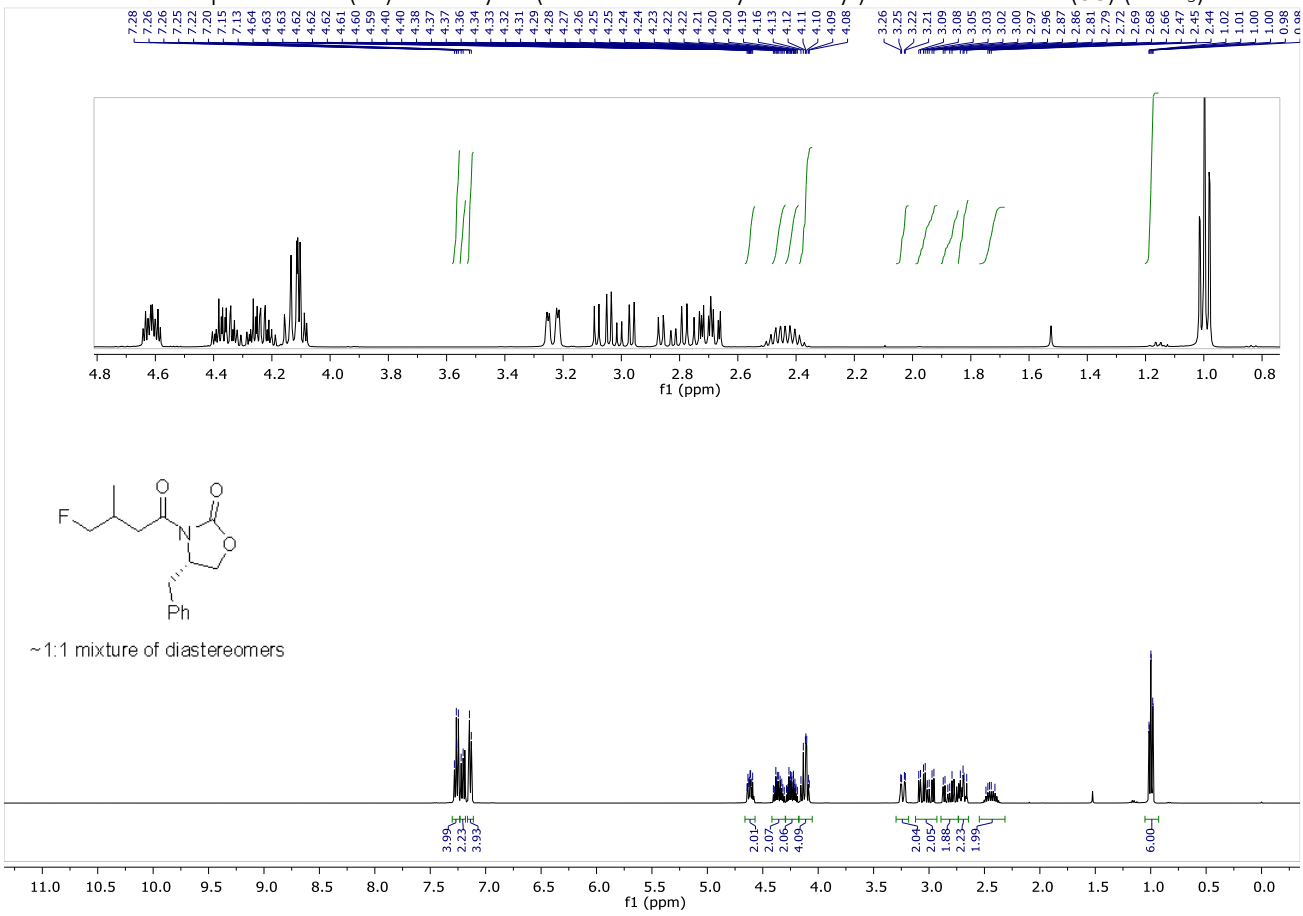
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
119.0503	100.00	119.0508	-0.5	-4.2	1.5	1331.6	n/a	n/a	C5 H8 O2 F



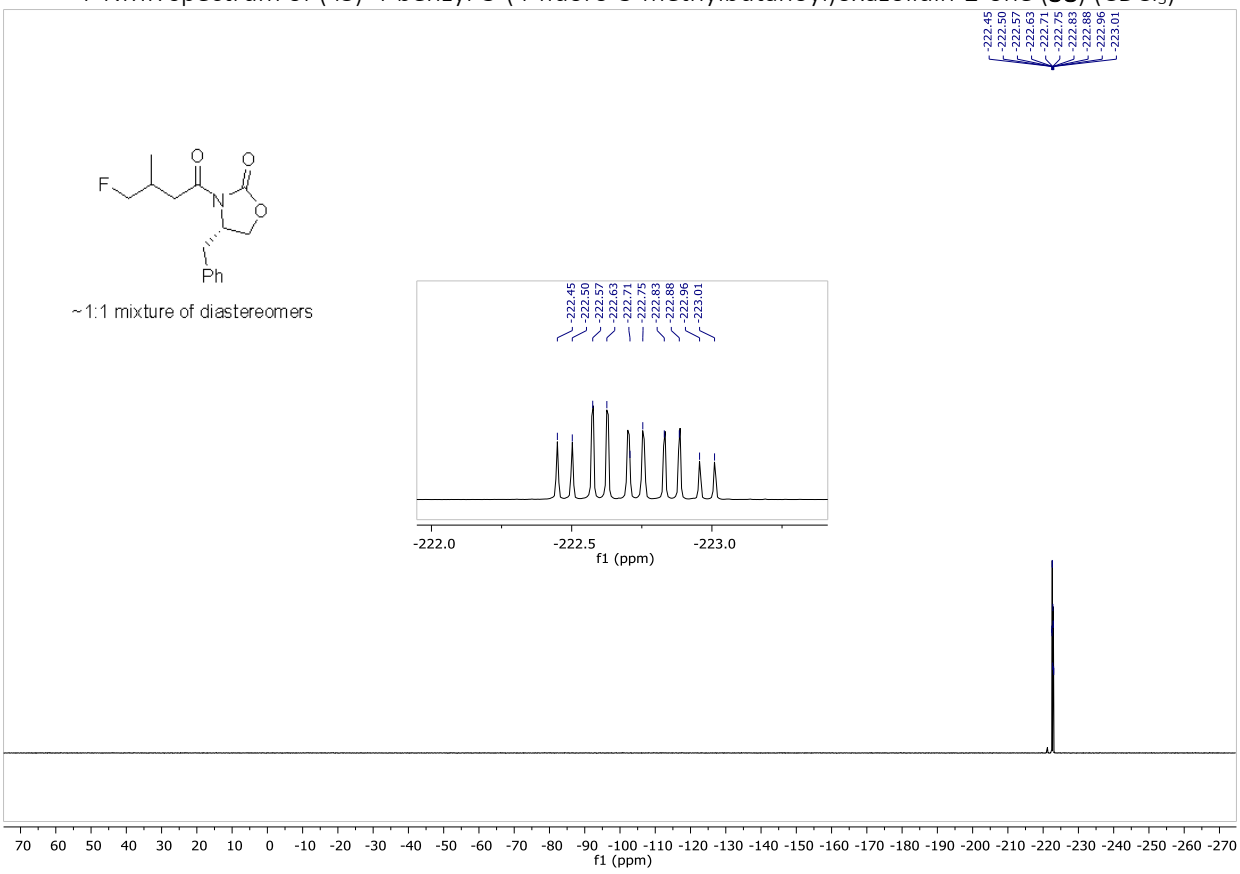
IR(ATR) spectrum of 4-fluoro-3-methylbutanoic acid (**37**)



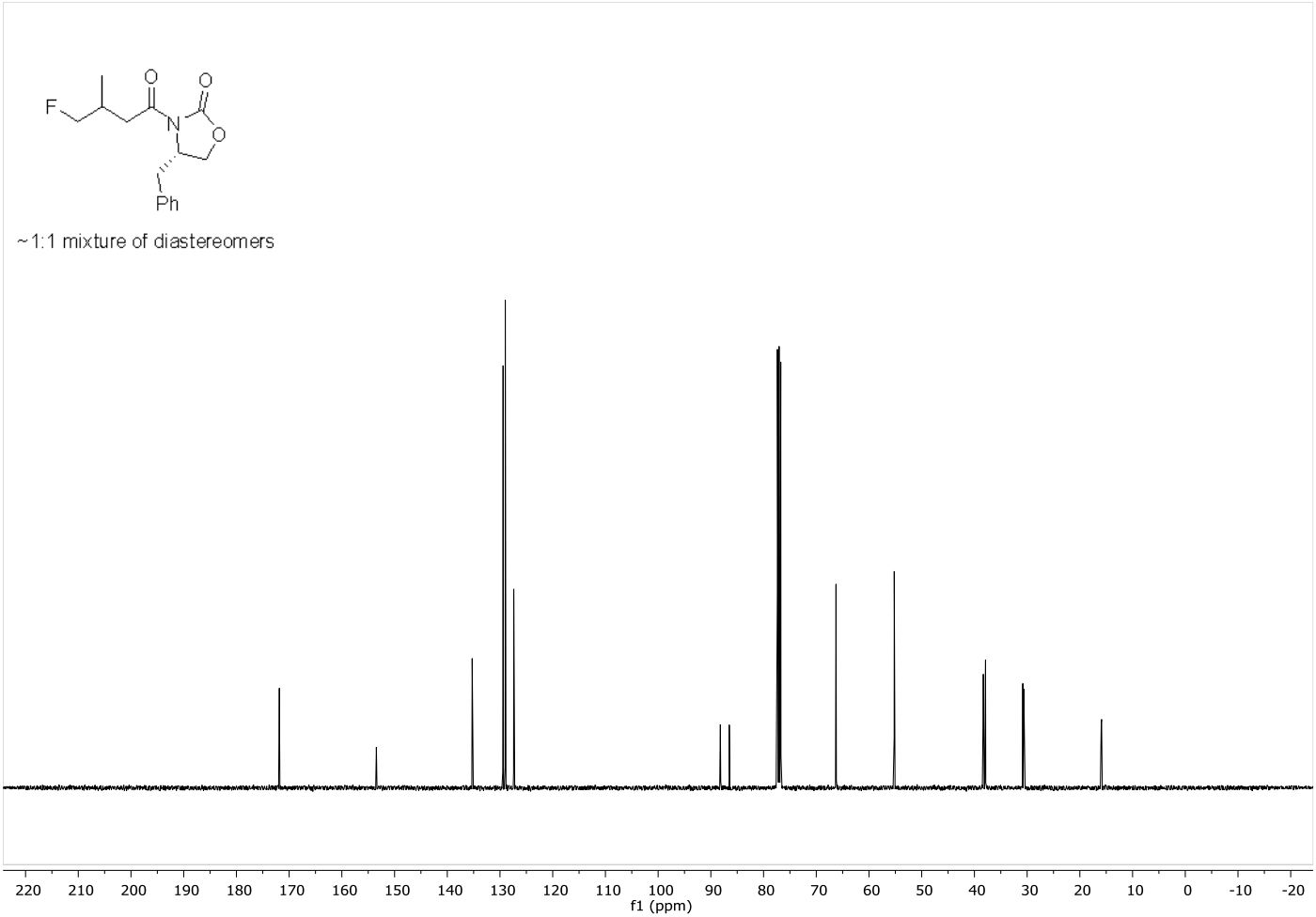
^{1}H NMR spectrum of (4*S*)-4-benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (**38**) ($CDCl_3$)



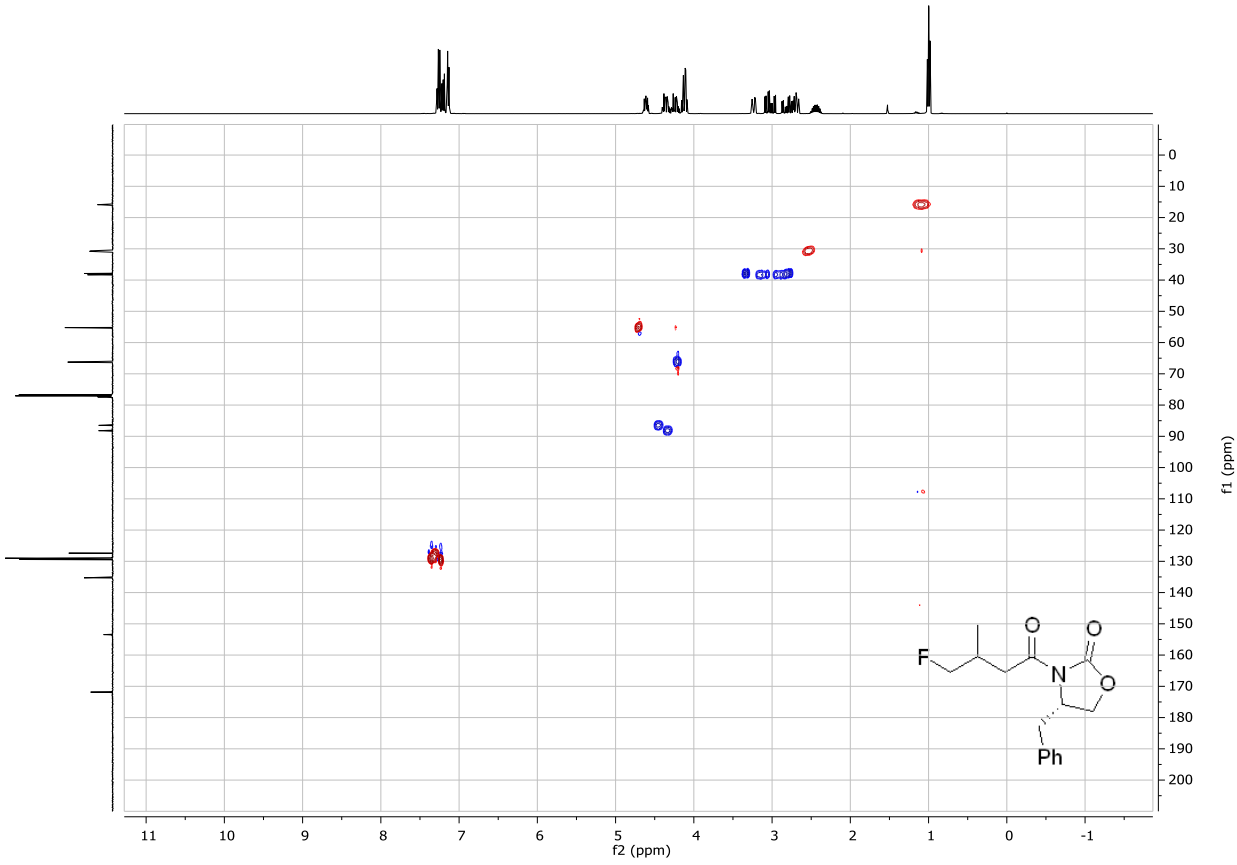
^{19}F NMR spectrum of (4*S*)-4-benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (**38**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (4*S*)-4-benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (**38**) ($CDCl_3$)



$^{1}H/^{13}C$ HSQC NMR spectrum of (4*S*)-4-benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (**38**) ($CDCl_3$)



HRMS of (4*S*)-4-benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (**38**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

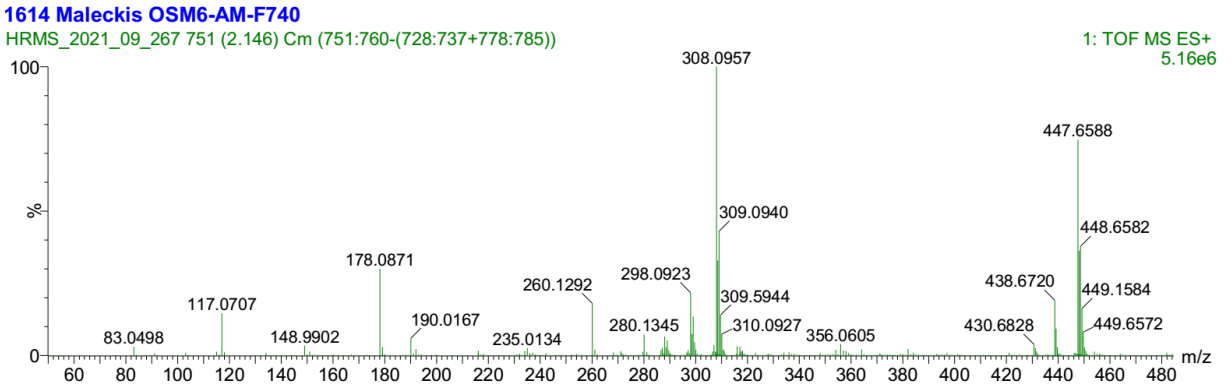
HRMS_2021_09_267 1614 Maleckis OSM6-AM-F740
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:D,3 1.000000 MS_Tune Col#66

Elemental Composition Report:

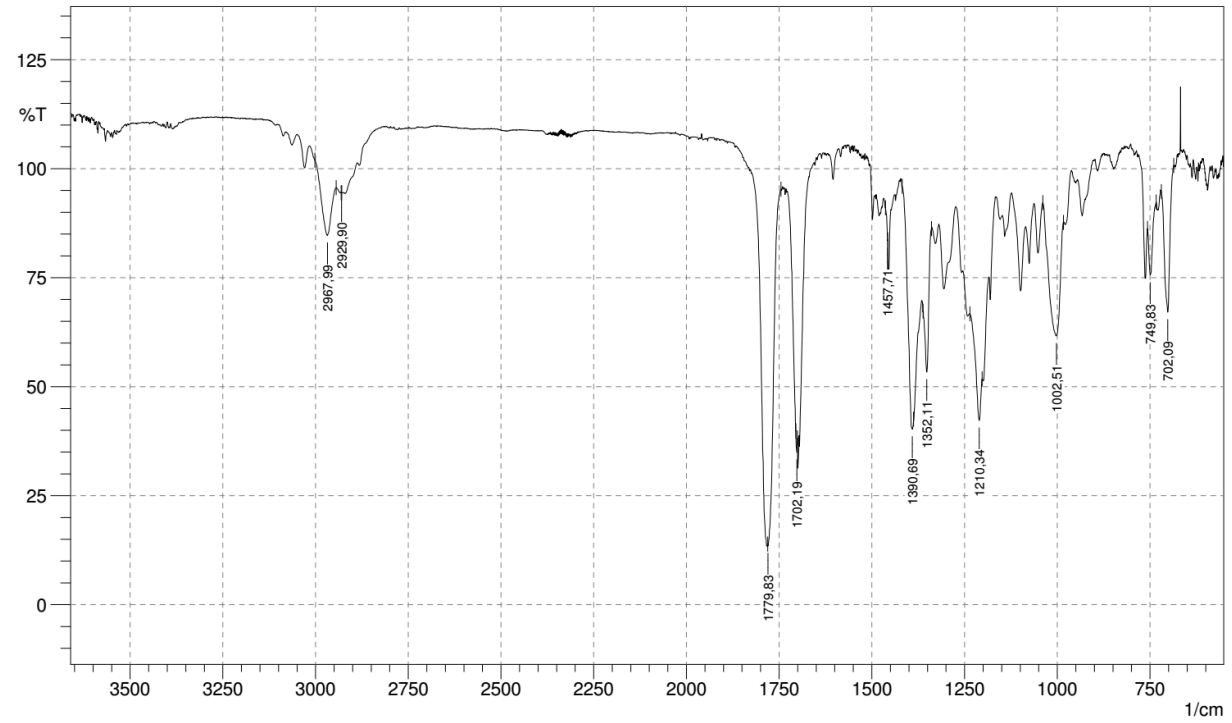
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
399 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-120 N: 0-5 O: 0-10 F: 0-1

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
280.1345	100.00	280.1349	-0.4	-1.4	6.5	425.5	0.000	99.98	C15 H19 N O3 F
		280.1338	0.7	2.5	10.5	434.1	8.596	0.02	C18 H18 N O2

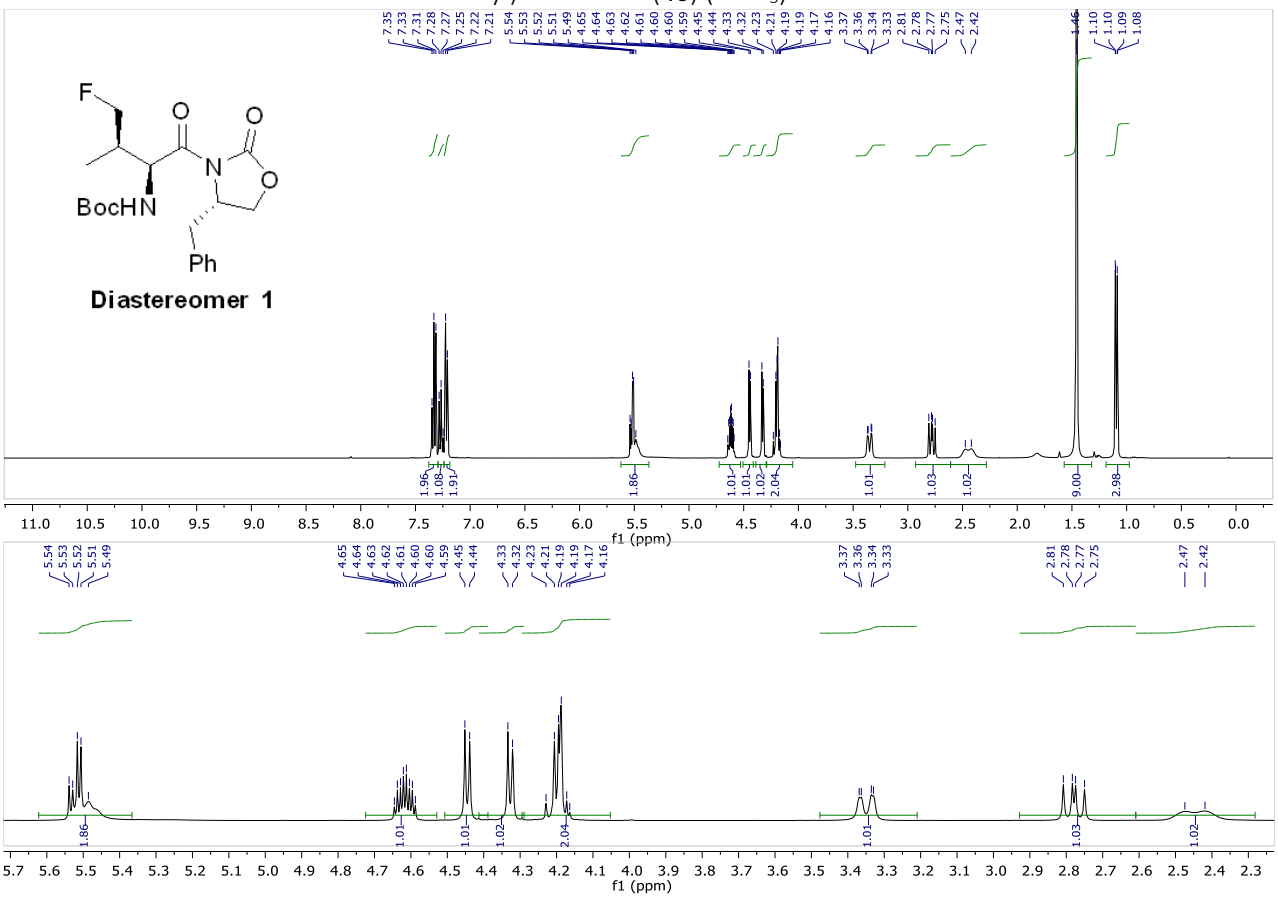


IR(ATR) spectrum of (4*S*)-4-benzyl-3-(4-fluoro-3-methylbutanoyl)oxazolidin-2-one (**38**)

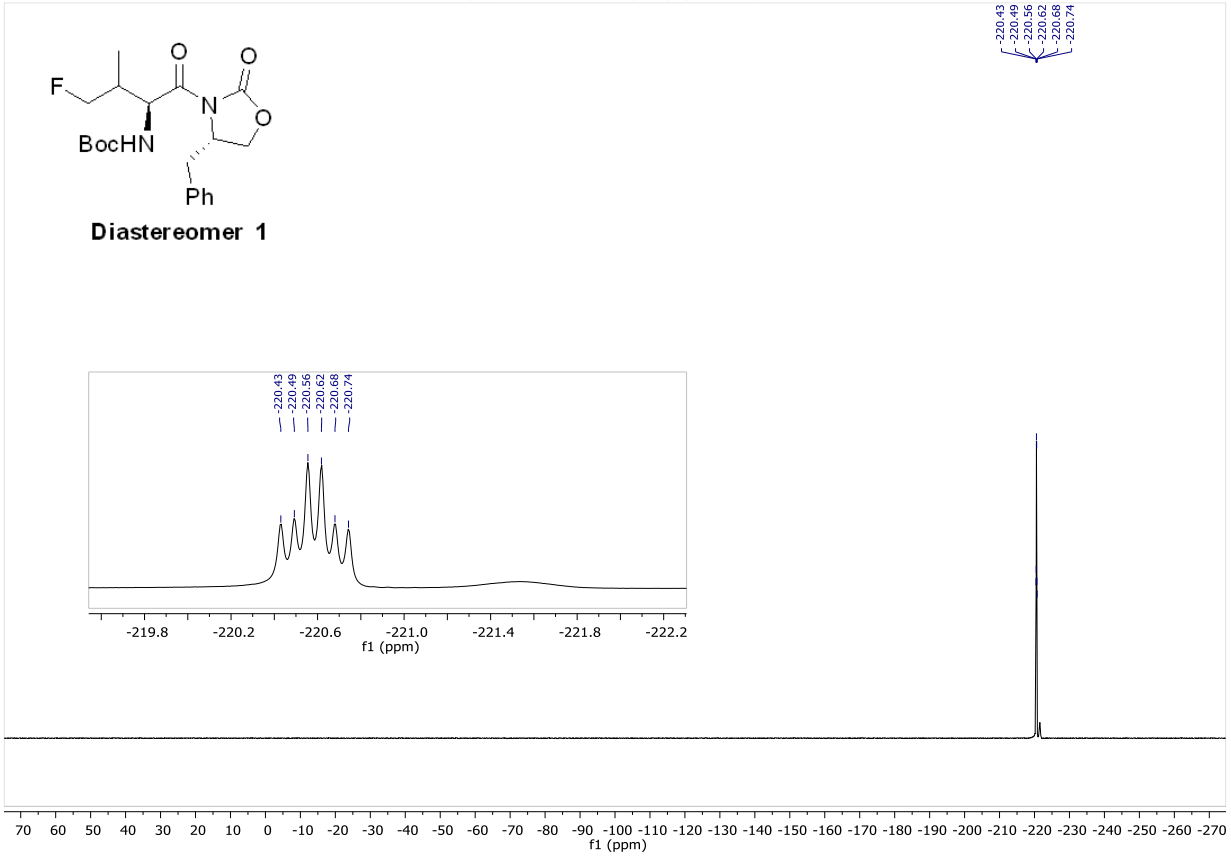


OSM6-AM-F740

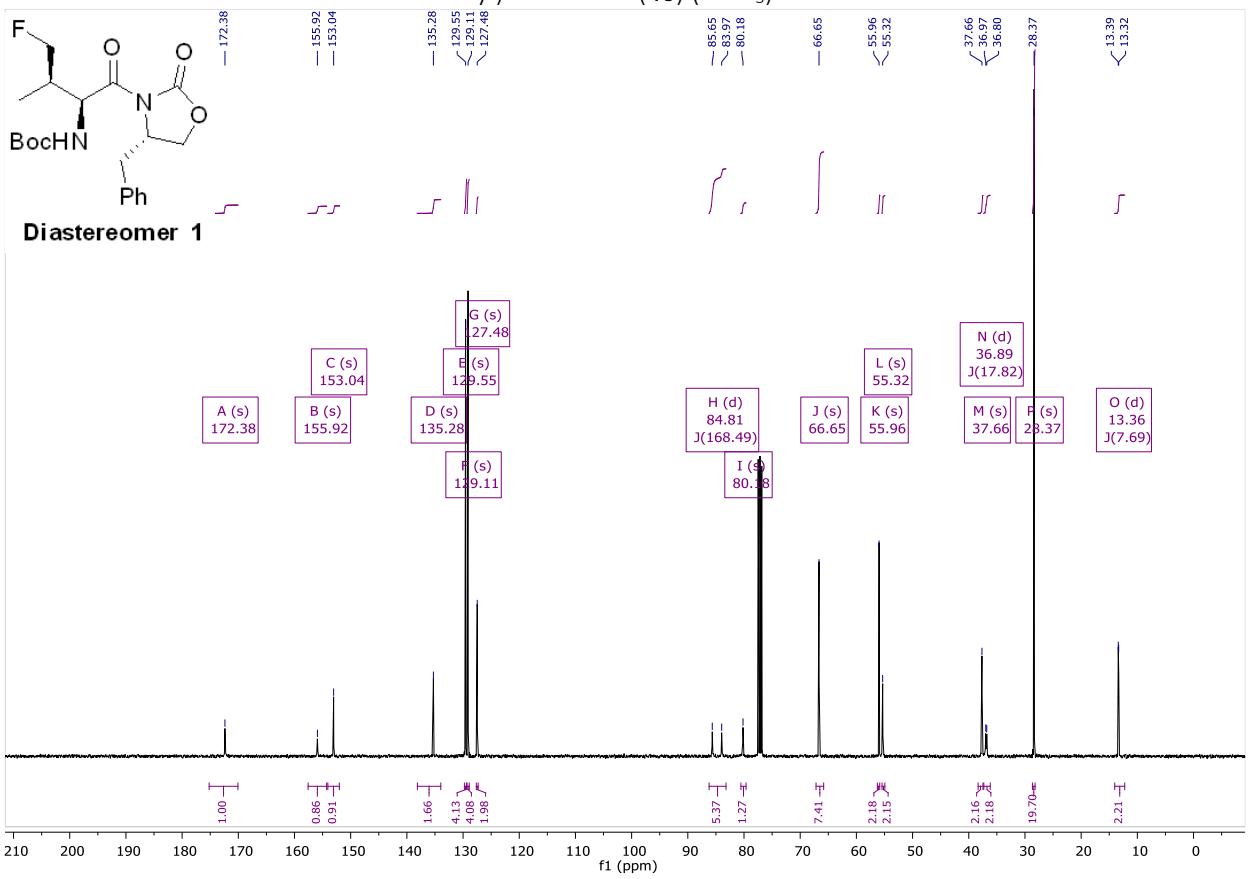
^{1}H NMR spectrum of *tert*-butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**40**) ($CDCl_3$)



^{19}F NMR spectrum of *tert*-butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**40**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**40**) ($CDCl_3$)



HPLC of mixture of **40** and **41**

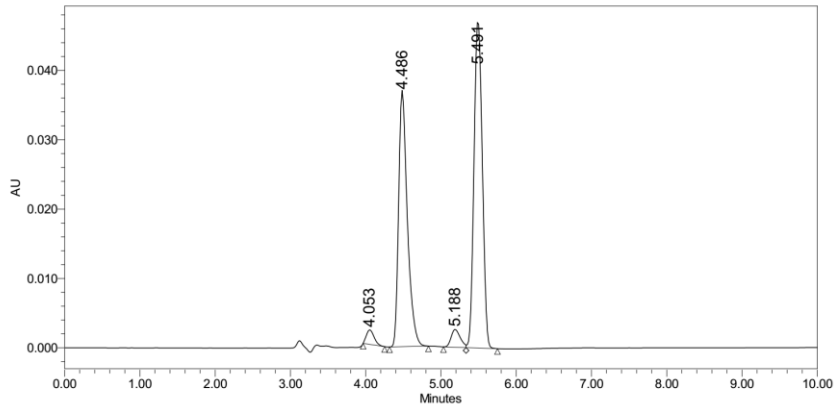
Empower 2 software

Chiralpak IC_1 100%DCM

SAMPLE INFORMATION

Sample Name:	704-Ch393-OSM6-AM-F746_IC		
Sample Type:	Unknown	Sample Set Name:	31082021 Ch393
Vial:	24	Acq. Method Set:	Iz_210_254_F1_100B
Injection #:	1	Processing Method	Chiralpak IC 1
Injection Volume:	10.00 ul	Channel Name:	W2489 ChB
Run Time:	40.0 Minutes	Proc. Chnl. Descr.:	W2489 ChB 254nm
Date Acquired:	8/31/2021 10:39:37 AM EET	Acquired By:	System
Date Processed:	8/31/2021 12:13:59 PM EET		

Chiralpak IC-1 (4.6x250 mm)
100% DCM stab amyl; F=1 mL/min; T=25oC



c = 1.0 mg/ml in 10%ipa/hex

	RT	Area	% Area	Height	EP Plate Count	Resolution	Selectivity	Width @ 50%	K Prime
1	4.053	14796	2.14	2091	6720			0.116	0.287
2	4.486	296297	42.82	36849	7891	2.170	1.479	0.119	0.424
3	5.188	21528	3.11	2585	8603	3.309	1.526	0.132	0.647
4	5.491	359366	51.93	47316	11193	1.409	1.149	0.122	0.743

HRMS of *tert*-butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**40**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2021_09_269 1615 Maleckis OSM6-AM-F746-1

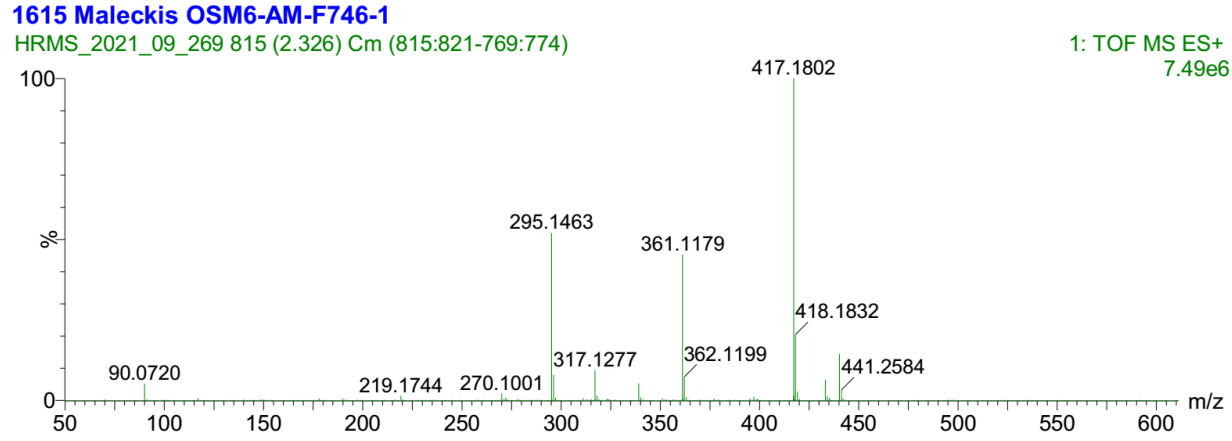
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:D,4 1.000000 MS_Tune Col#66

Elemental Composition Report:

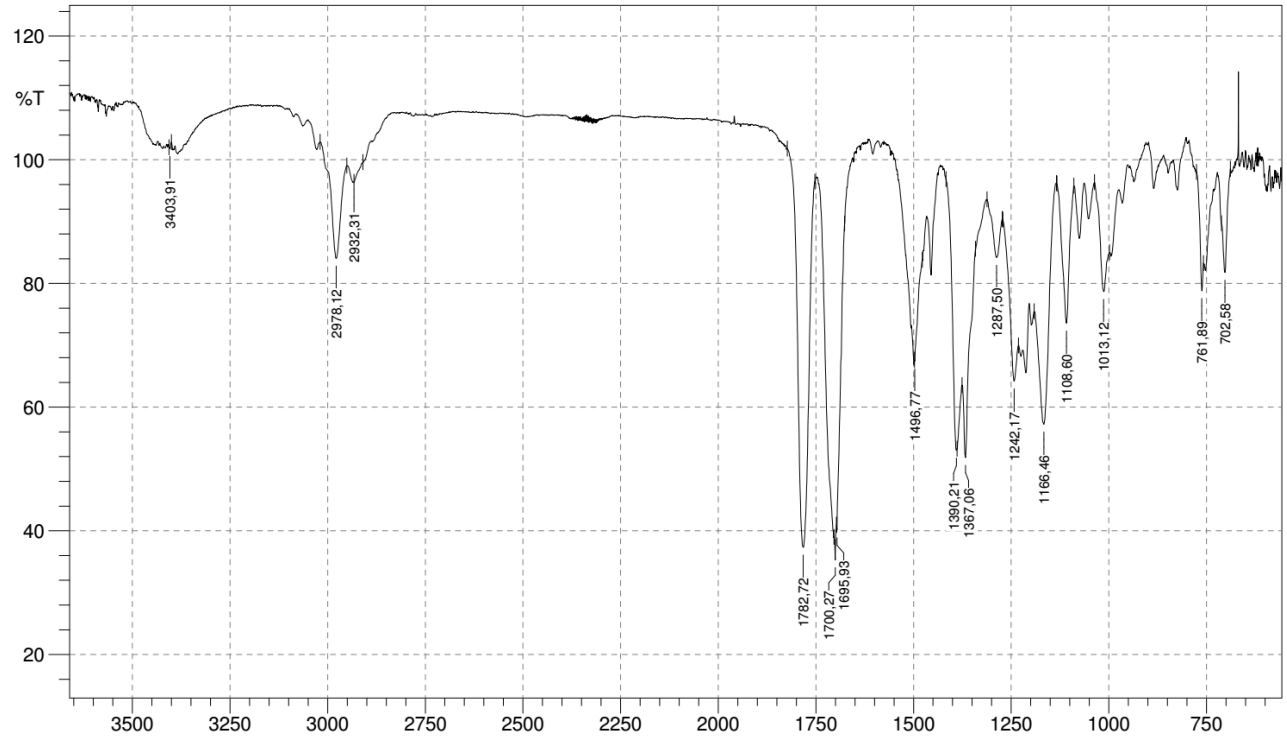
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
815 formula(e) evaluated with 3 results within limits (up to 2 closest results for each mass)
Elements Used:
C: 0-100 H: 0-120 N: 0-5 O: 0-6 F: 0-1 Na: 0-1

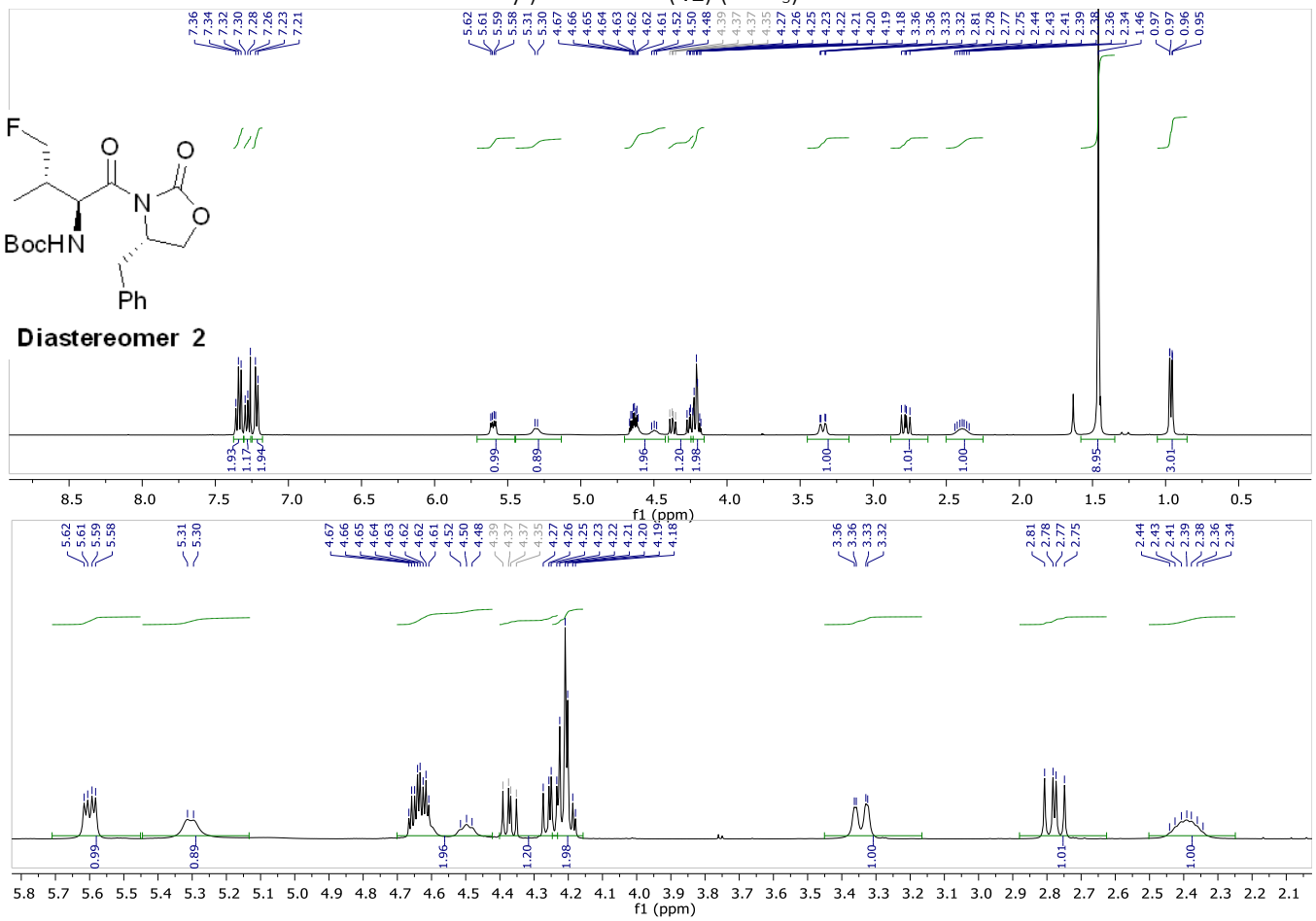
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
417.1802	100.00	417.1802	0.0	0.0	7.5	954.9	0.006	99.44	C20 H27 N2 O5 F Na
		417.1790	1.2	2.9	11.5	960.0	5.182	0.56	C23 H26 N2 O4 Na



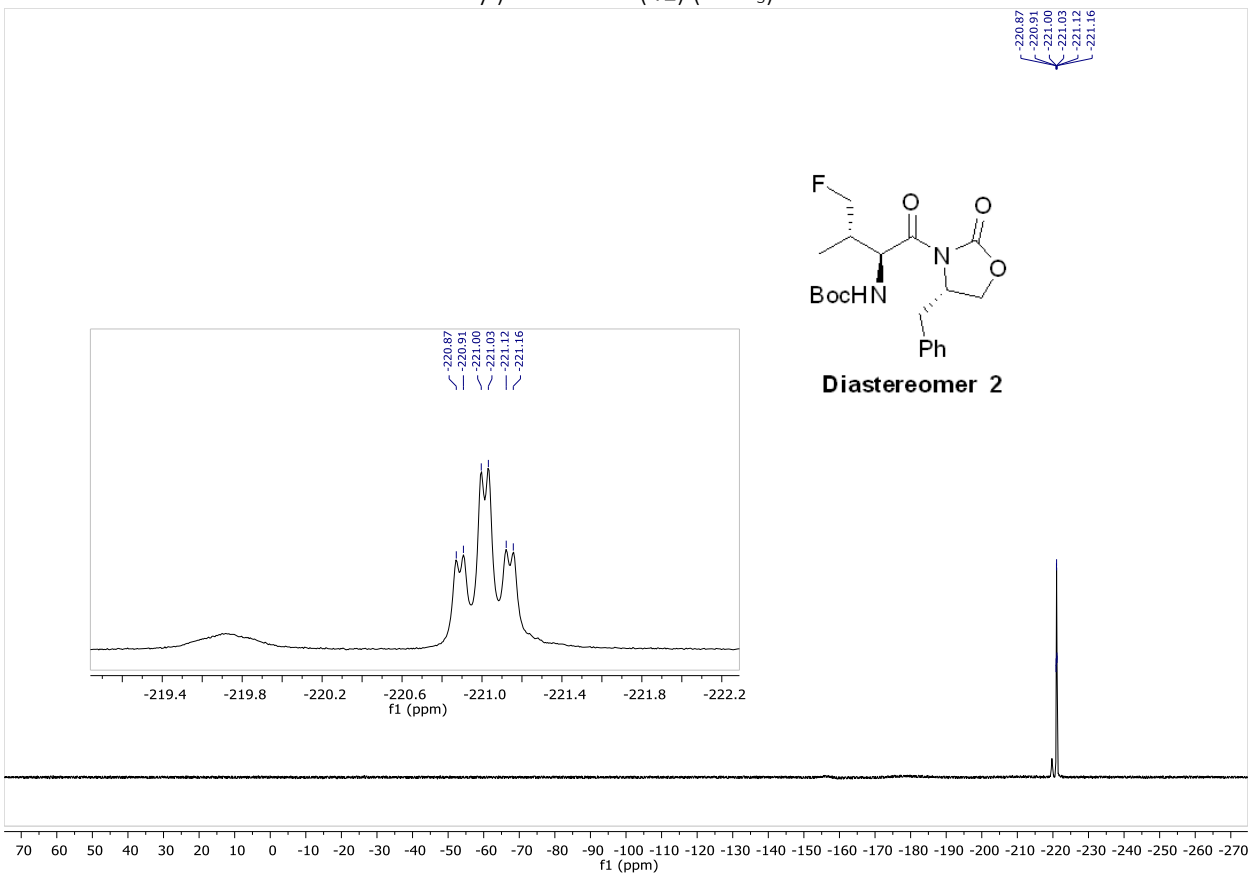
IR(ATR) *tert*-butyl ((2*S*,3*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**40**)



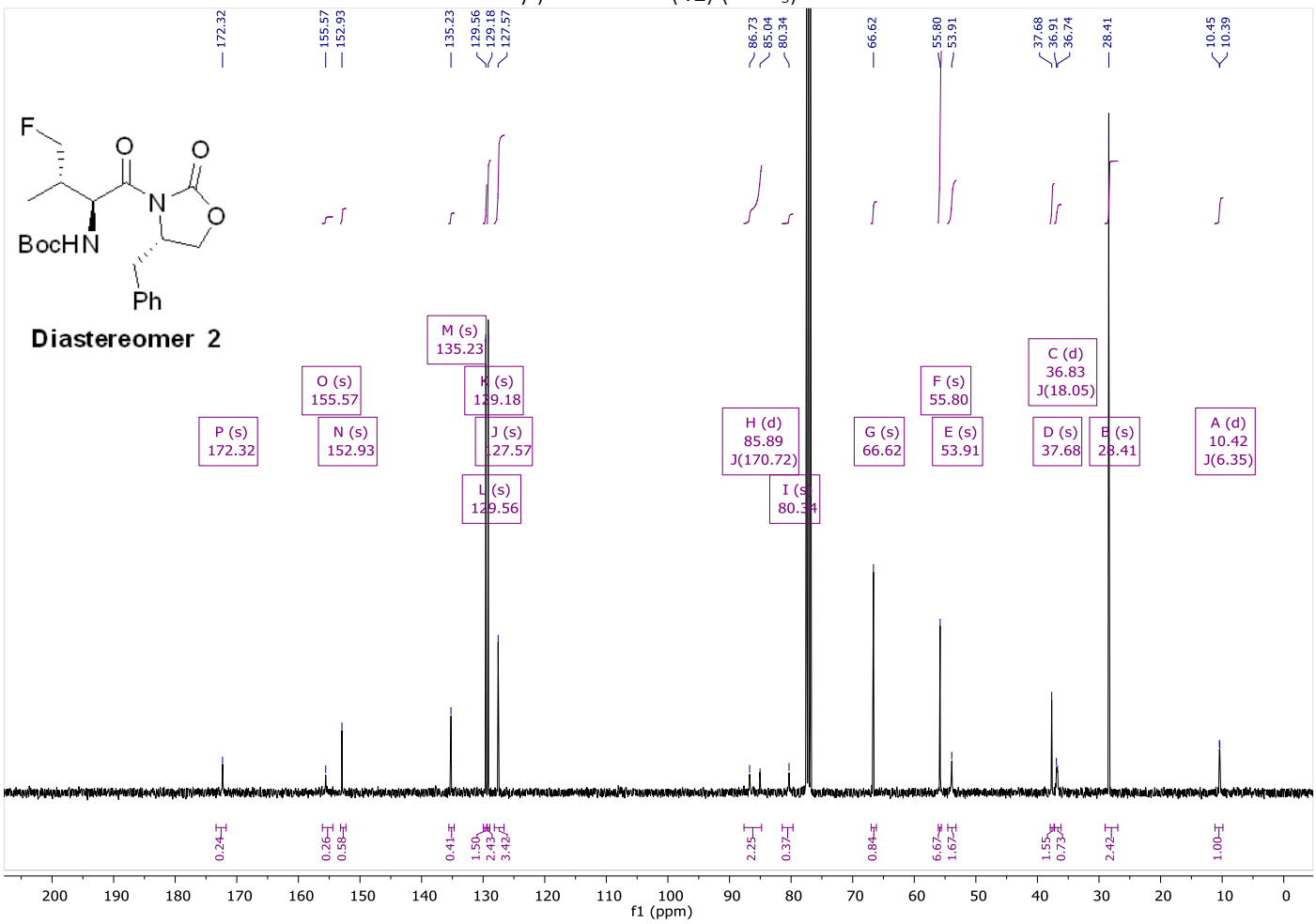
^{1}H NMR spectrum of *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**41**) ($CDCl_3$)



^{19}F NMR spectrum of *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**41**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**41**) ($CDCl_3$)



HRMS of *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**41**)

MS: Waters Synapt G2-Si ESI+	Capillary, kV: Cone, V:	0.7 40	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18 2.1x50mm, 1.7µm

Sample:

HRMS_2021_09_271 1616 Maleckis OSM6-AM-F746-2

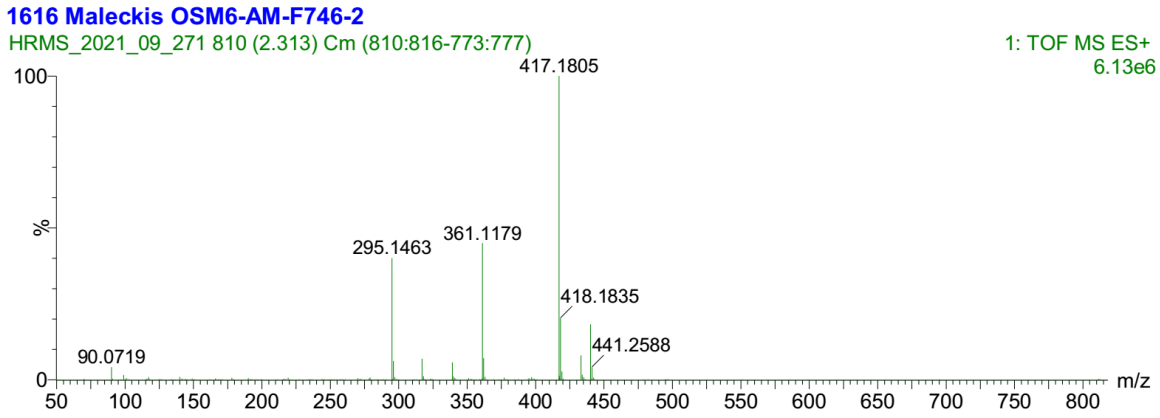
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:D,5 1.000000 MS_Tune Col#66

Elemental Composition Report:

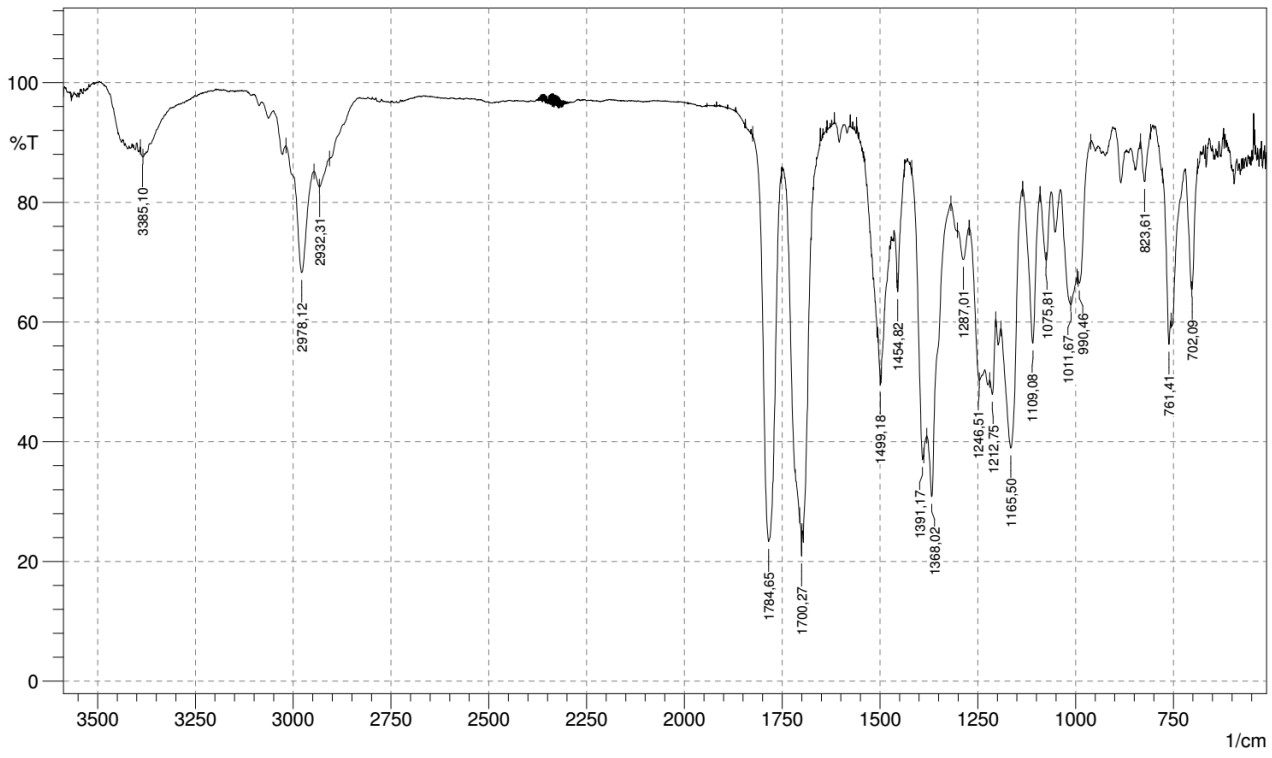
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
815 formula(e) evaluated with 4 results within limits (up to 2 closest results for each mass)
Elements Used:
C: 0-100 H: 0-120 N: 0-5 O: 0-6 F: 0-1 Na: 0-1

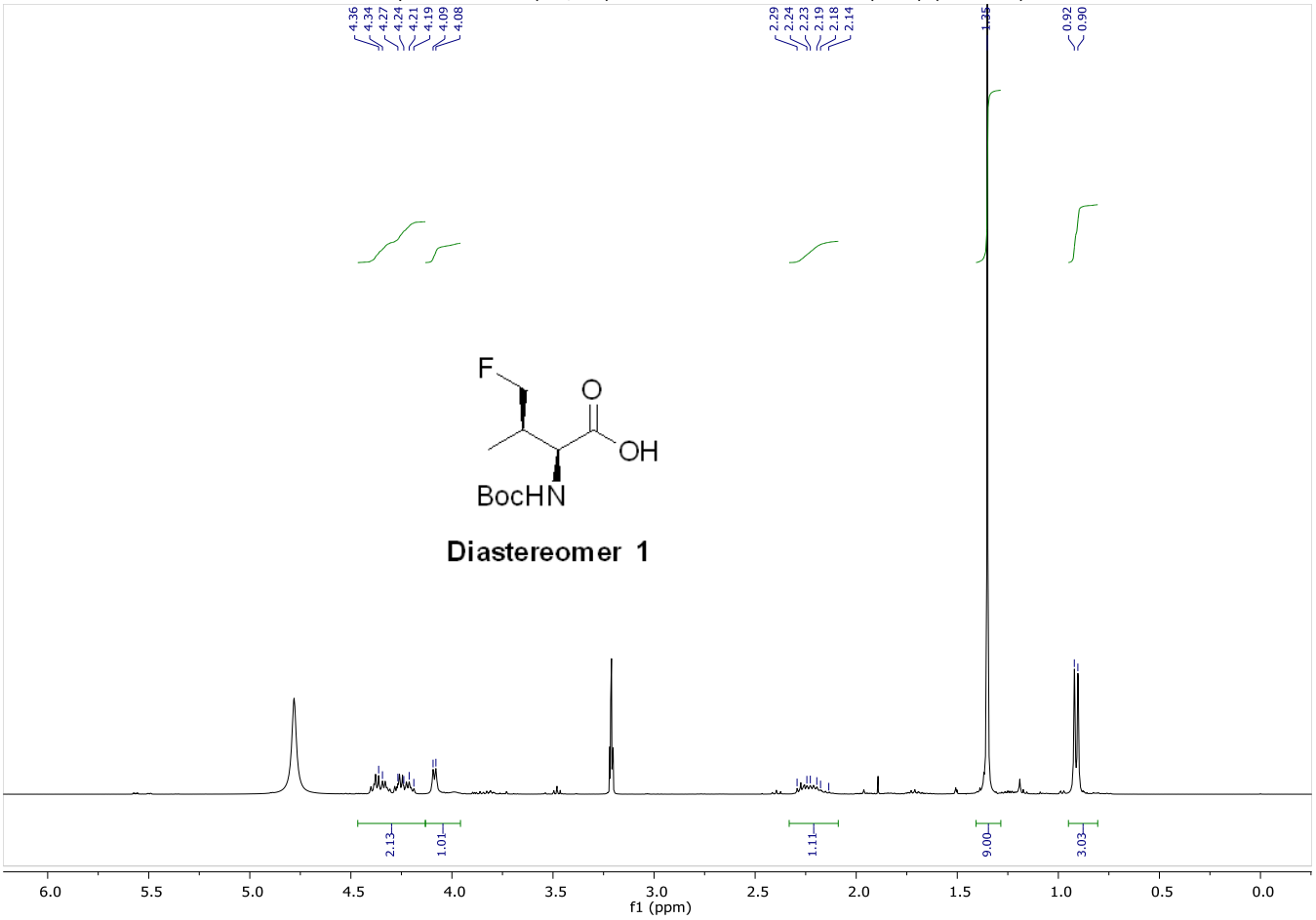
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
417.1805	100.00	417.1802	0.3	0.7	7.5	1004.2	0.002	99.83	C20 H27 N2 O5 F Na
		417.1814	-0.9	-2.2	14.5	1010.5	6.369	0.17	C25 H25 N2 O4



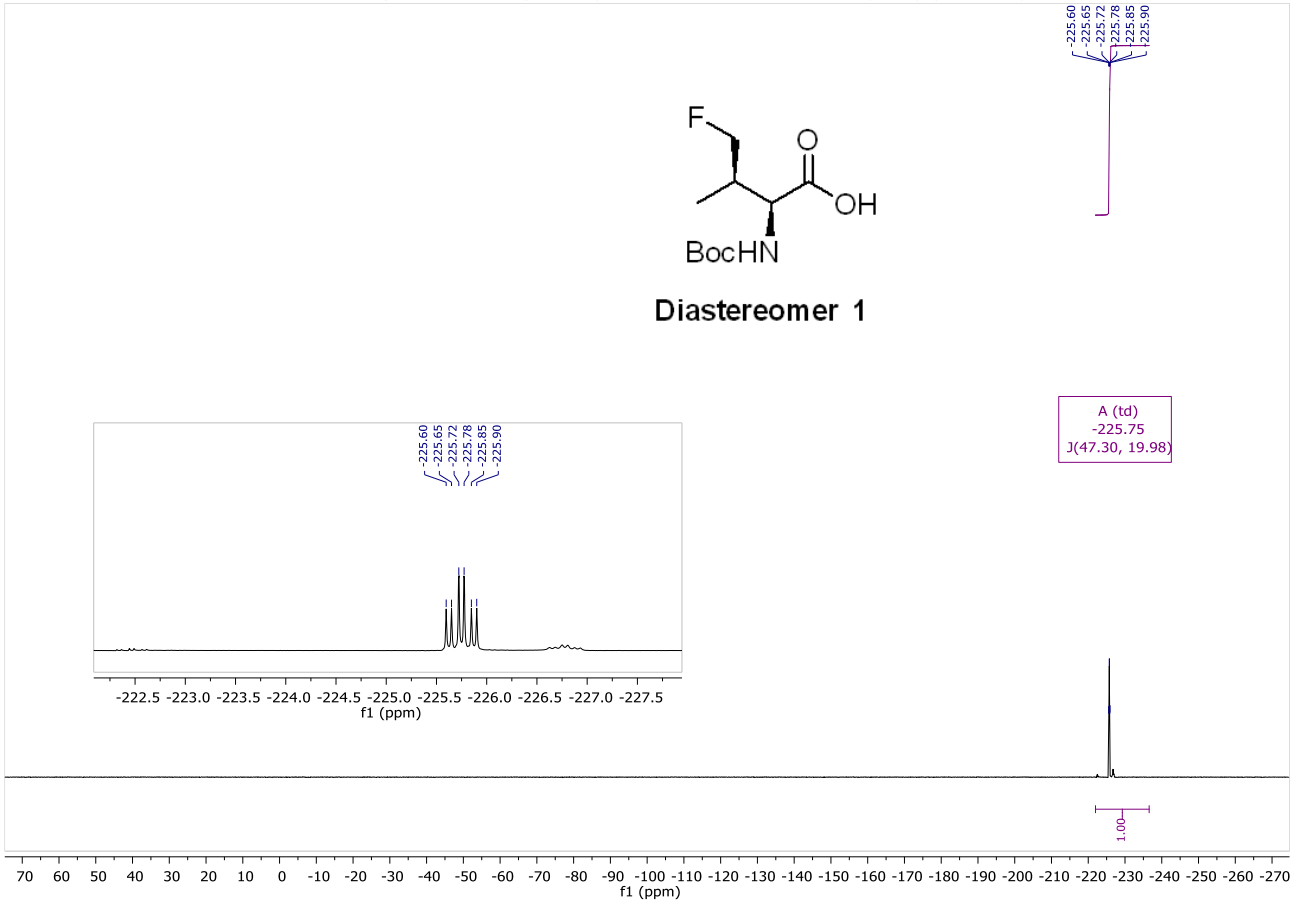
IR(ATR) of *tert*-butyl ((2*S*,3*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-4-fluoro-3-methyl-1-oxobutan-2-yl)carbamate (**41**)



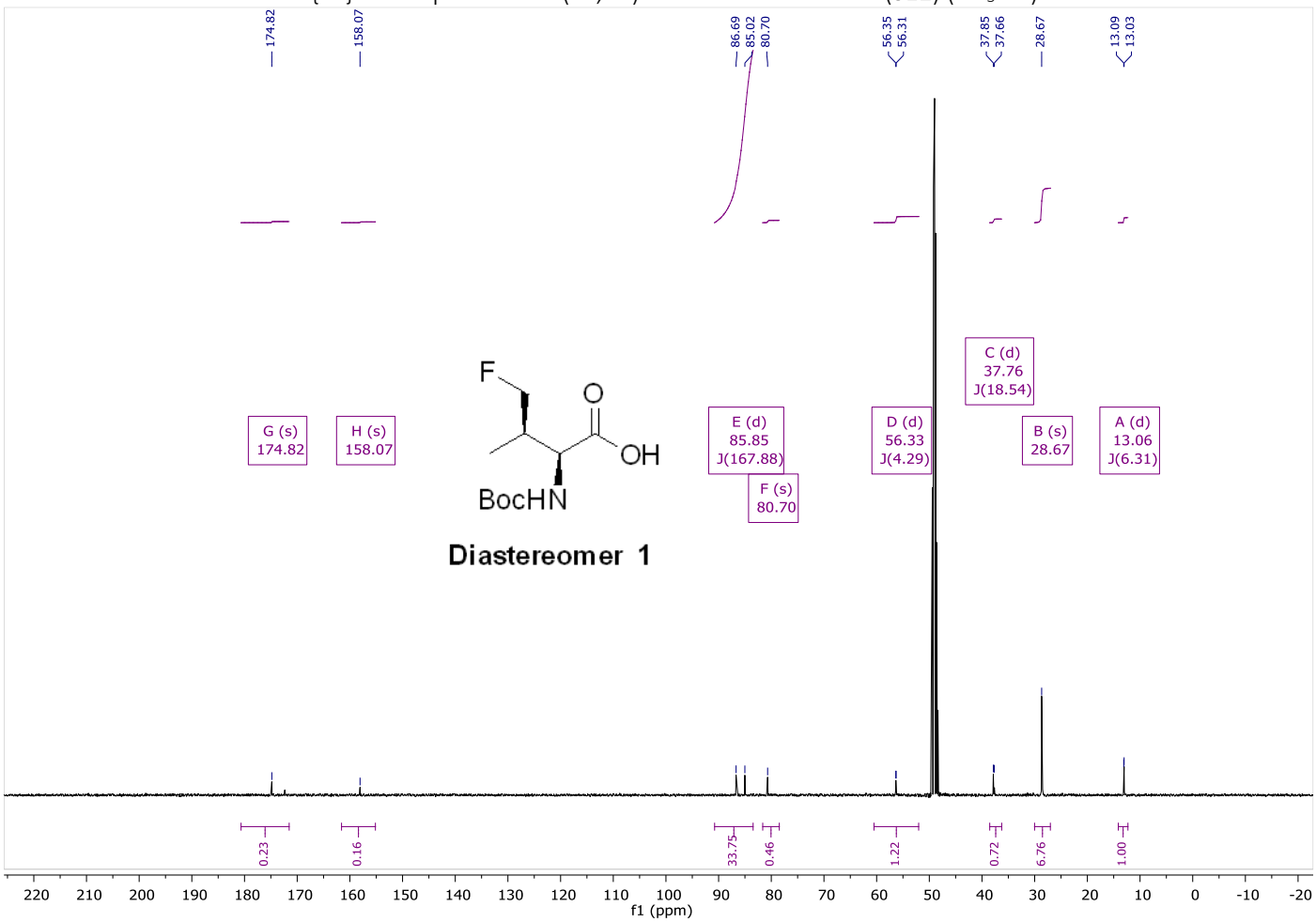
^{1}H NMR spectrum of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S12**) (CD_3OD)



^{19}F NMR spectrum of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S12**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S12**) (CD_3OD)



HRMS of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S12**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2021_09_280 1619 Maleckis OSM6-AM-F893-1

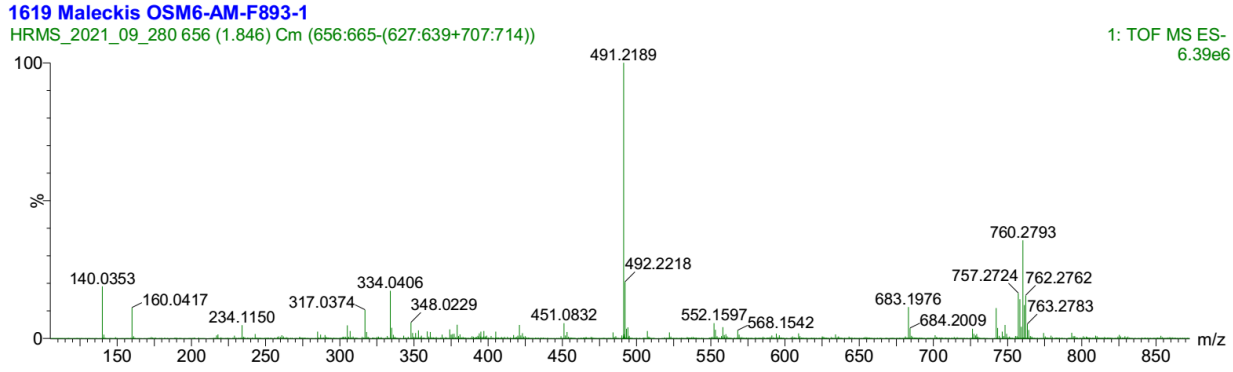
MS_NEG_RES_4min ACN_Form_5-98_040_4min 1:D,8 1.000000 MS_Tune Col#66

Elemental Composition Report:

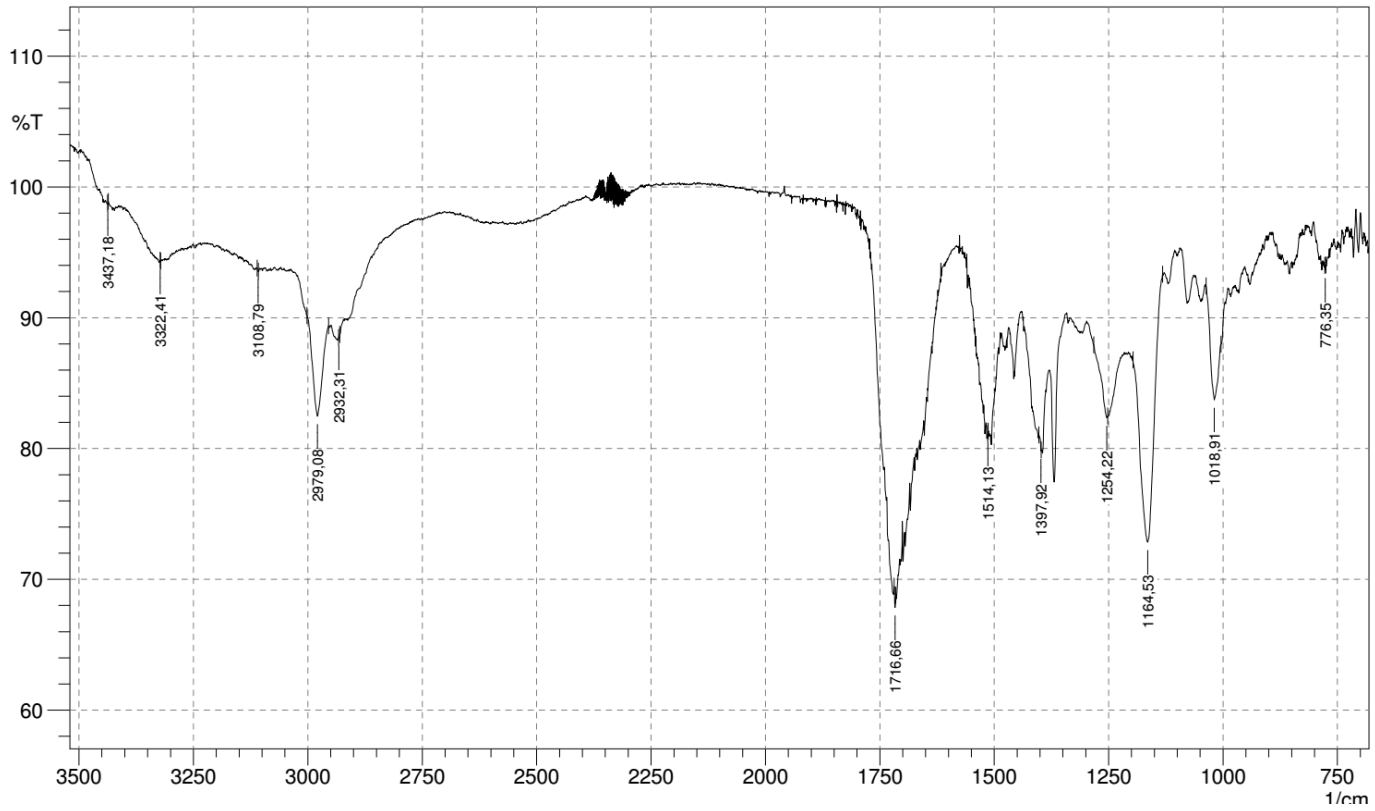
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
130 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-120 N: 1-5 O: 1-5 F: 0-1

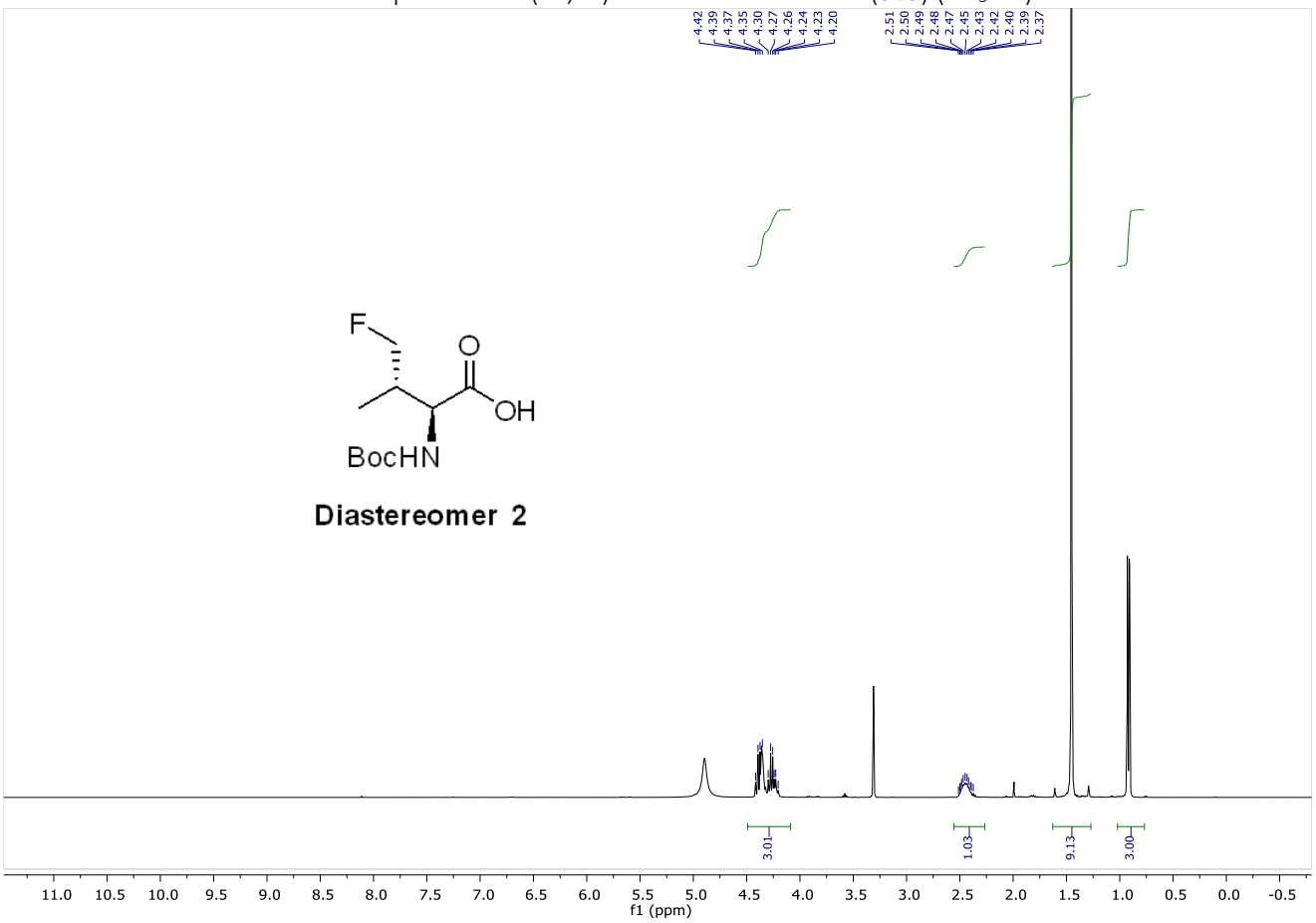
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
234.1150	100.00	234.1142	0.8	3.4	2.5	460.2	n/a	n/a	C10 H17 N O4 F



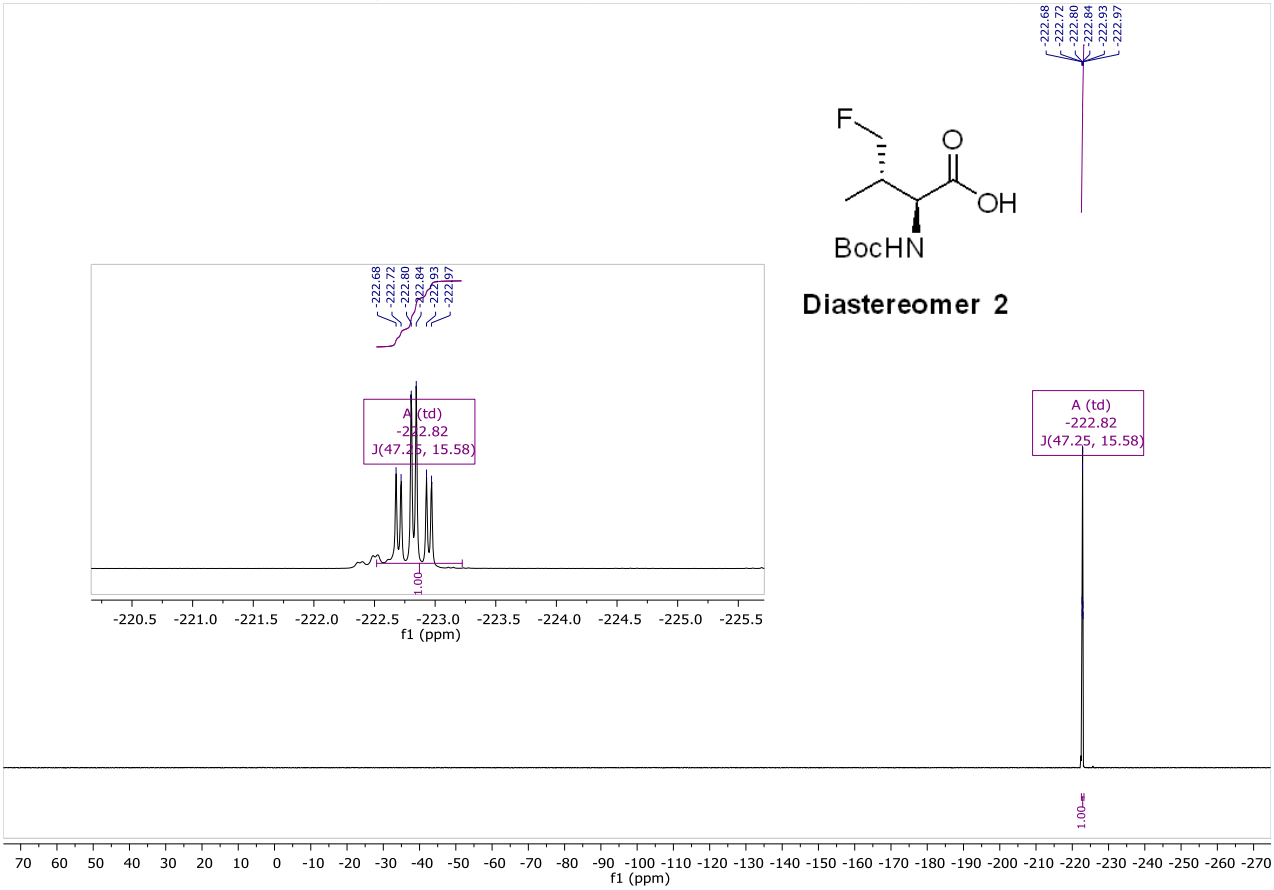
IR(ATR) spectrum of (2*S*,3*R*)-*N*-Boc-4-fluorovaline (**S12**)



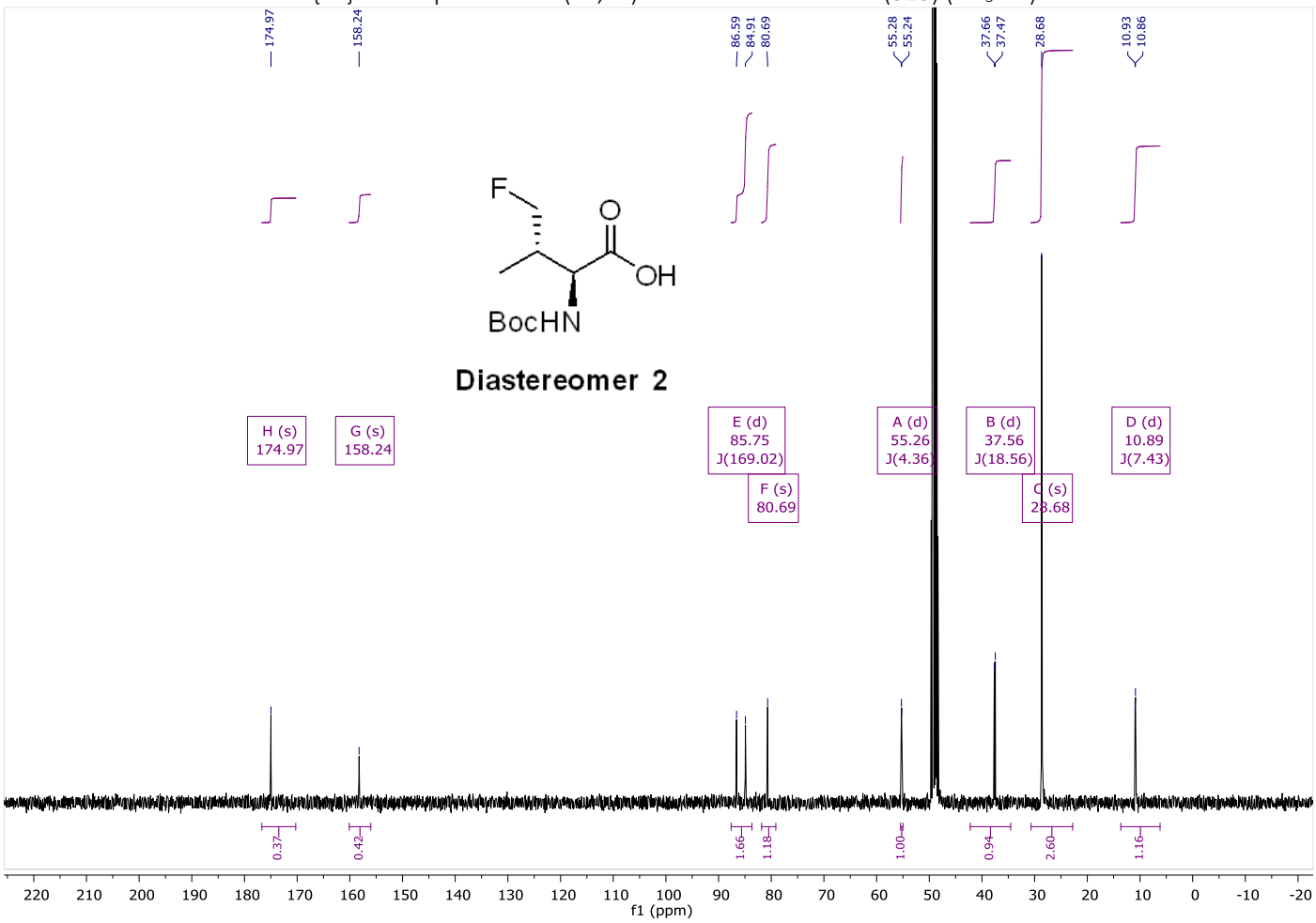
^{1}H NMR spectrum of (2*S*,3*S*)-*N*-Boc-4-fluorovaline (**S13**) (CD_3OD)



^{19}F NMR spectrum of (2*S*,3*S*)-*N*-Boc-4-fluorovaline (**S13**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (2*S*,3*S*)-*N*-Boc-4-fluorovaline (**S13**) (CD_3OD)



HRMS of (2*S*,3*S*)-*N*-Boc-4-fluorovaline (**S13**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2021_09_277 1618 Maleckis OSM6-AM-F891-2

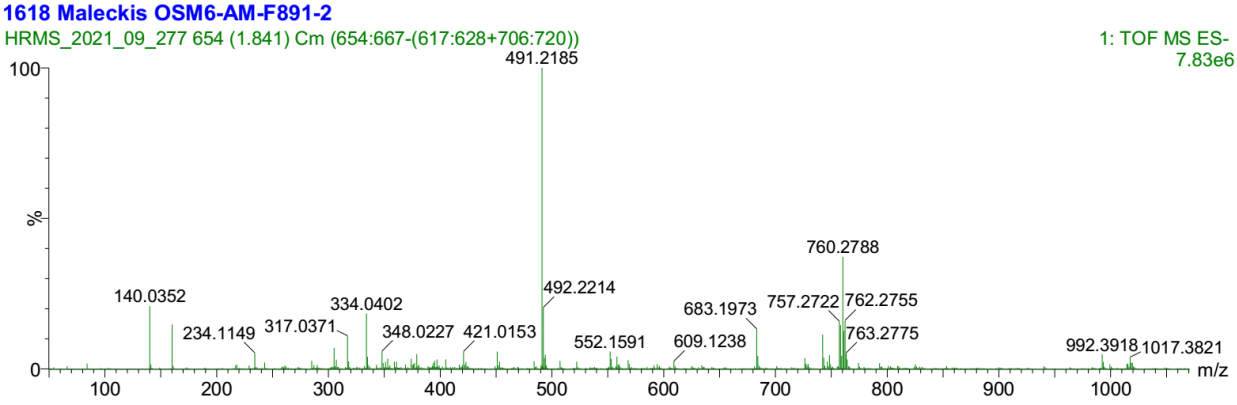
MS_NEG_RES_4min ACN_Form_5-98_040_4min 1:D,7 5.000000 MS_Tune Col#66

Elemental Composition Report:

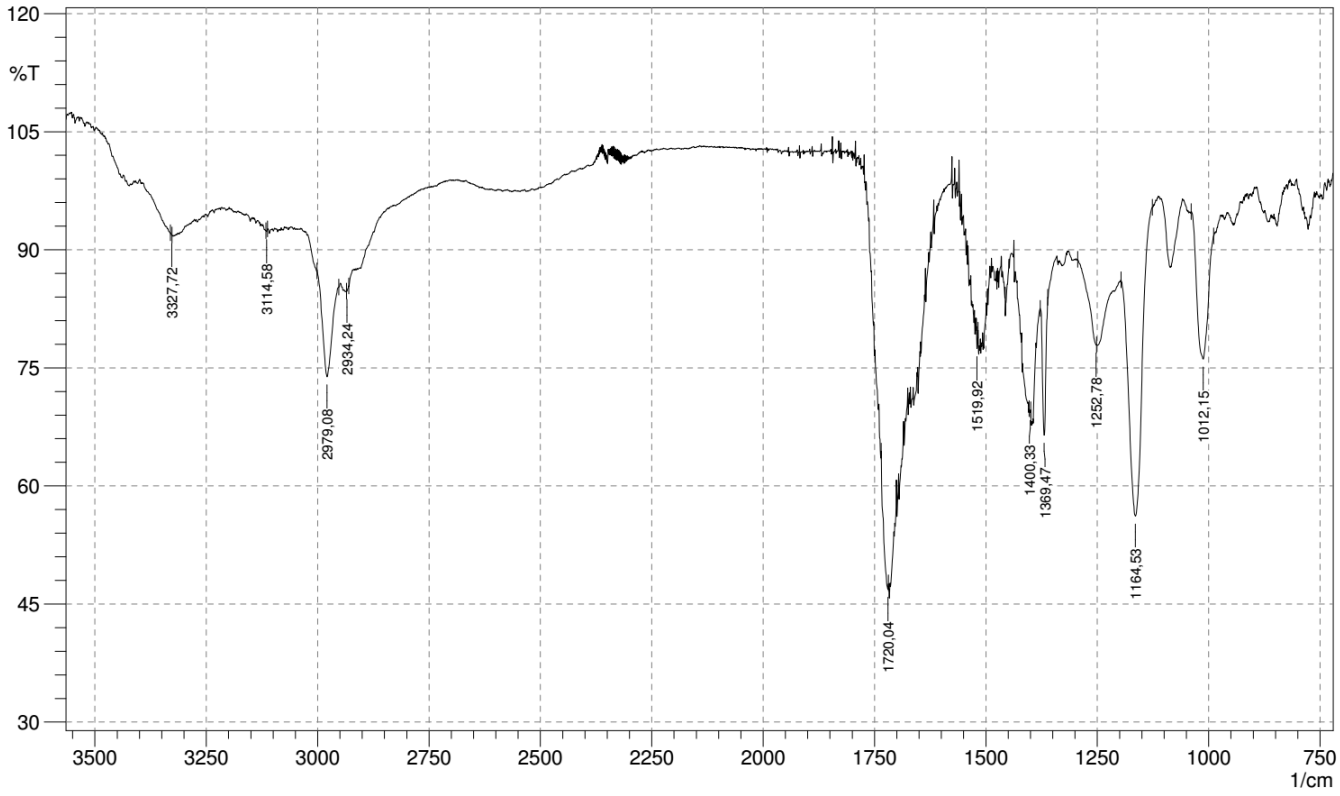
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
130 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-120 N: 1-5 O: 1-5 F: 0-1

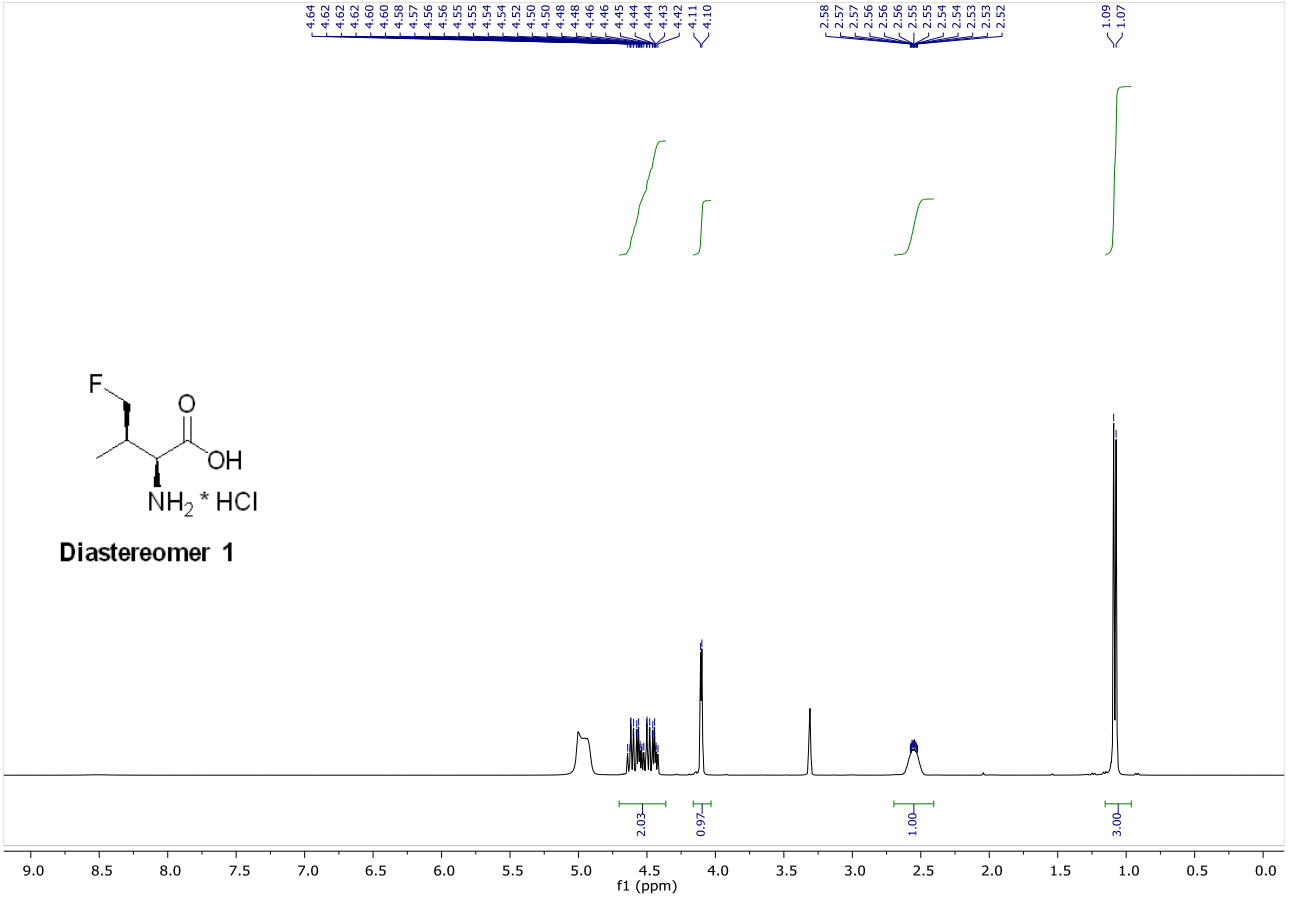
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
234.1149	100.00	234.1142	0.7	3.0	2.5	523.9	n/a	n/a	C10 H17 N O4 F



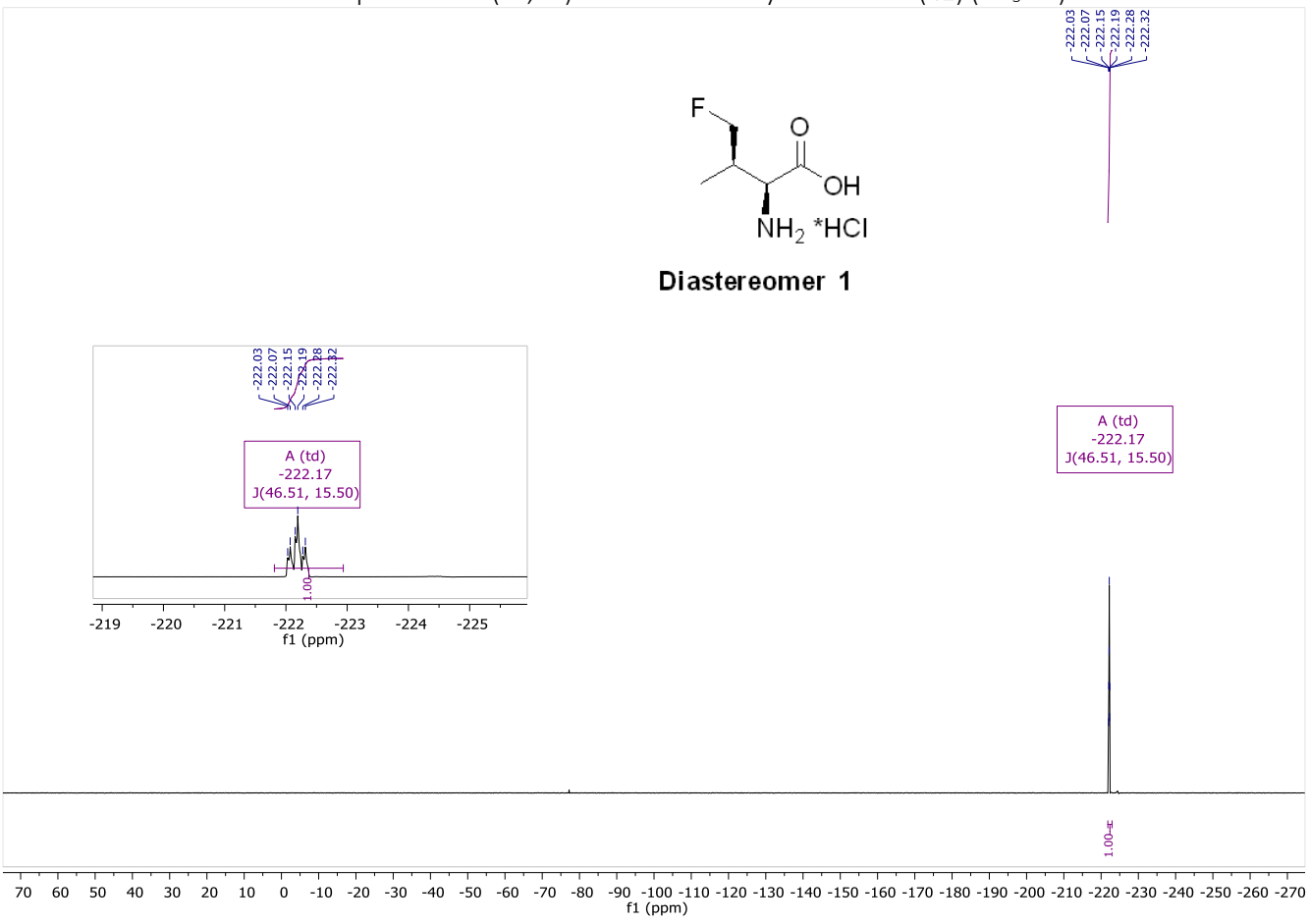
IR(ATR) spectrum of (2*S*,3*S*)-*N*-Boc-4-fluorovaline (**S13**)



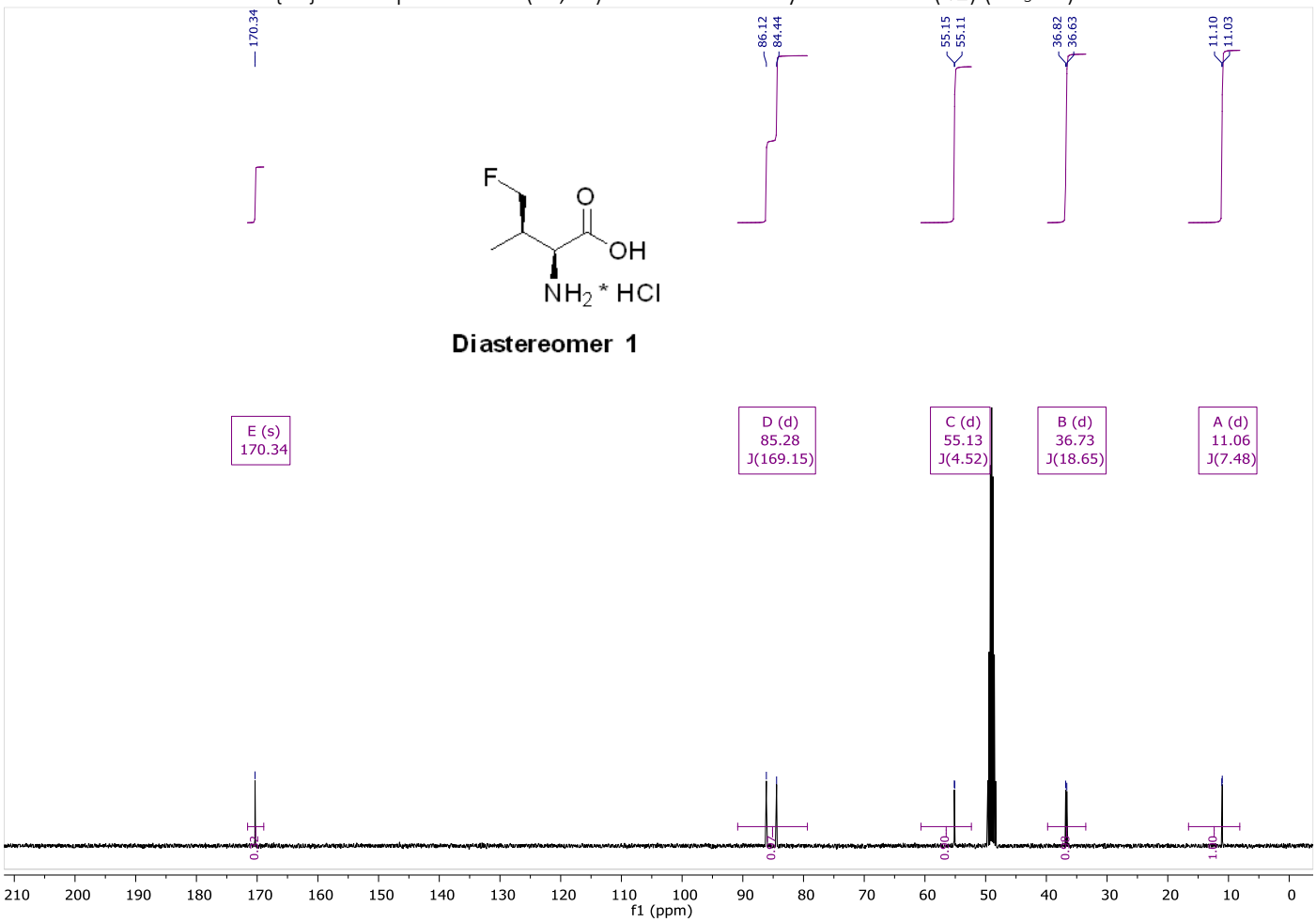
^{1}H NMR spectrum of (2*S*,3*R*)-4-fluorovaline hydrochloride (**42**) (CD_3OD)



^{19}F NMR spectrum of (2*S*,3*R*)-4-fluorovaline hydrochloride (**42**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (2*S*,3*R*)-4-fluorovaline hydrochloride (**42**) (CD_3OD)



HRMS of (2*S*,3*R*)-4-fluorovaline hydrochloride (**42**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2021_09_298 1621 Maleckis OSM6-AM-F896-1

MS_POS_RES_4min ACN_Form_5-98_040_4min 1:E,4 10.000000 MS_Tune Col#66

Elemental Composition Report:

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

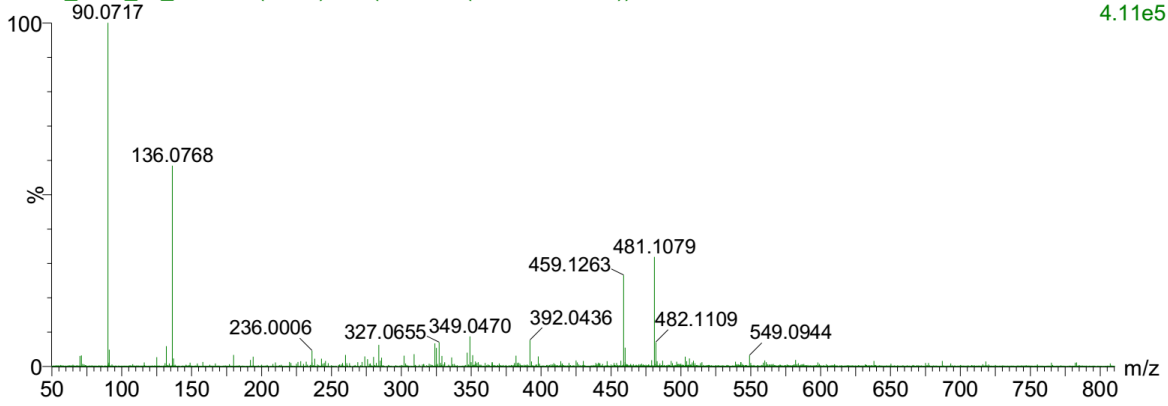
Monoisotopic Mass, Even Electron Ions
56 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-120 N: 1-5 O: 1-5 F: 0-1

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
136.0768	100.00	136.0774	-0.6	-4.4	0.5	658.9	0.010	99.03	C5 H11 N O2 F
		136.0762	0.6	4.4	4.5	663.5	4.640	0.97	C8 H10 N O

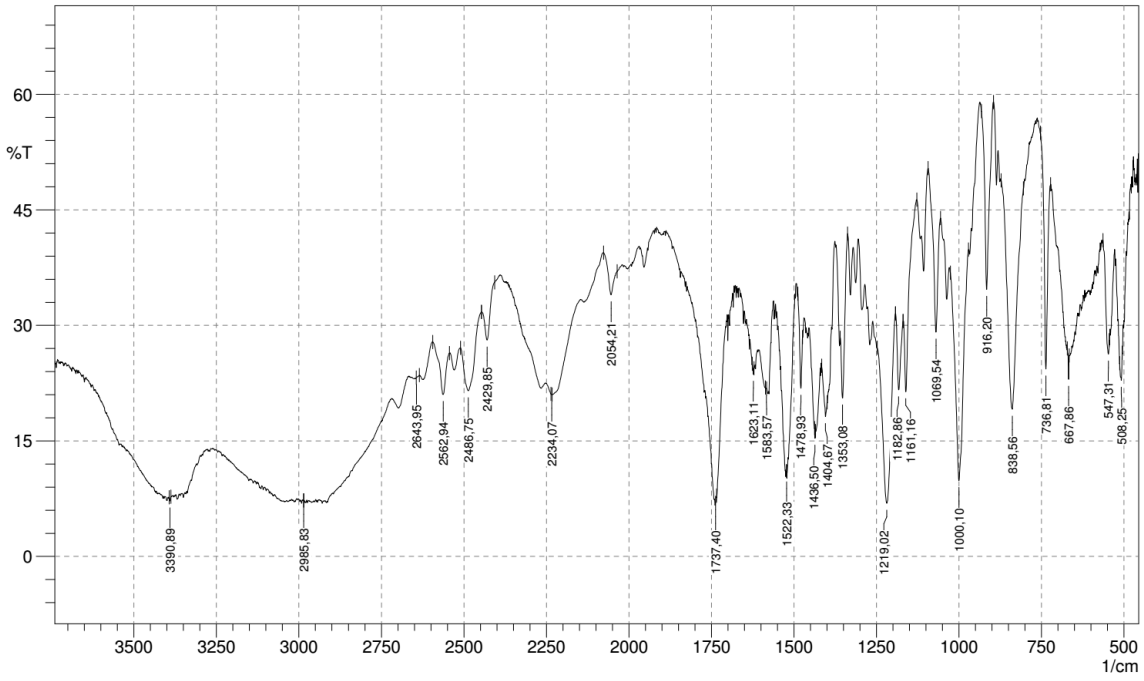
1621 Maleckis OSM6-AM-F896-1

HRMS_2021_09_298 125 (0.376) Cm (121:148-(203:229+55:74))

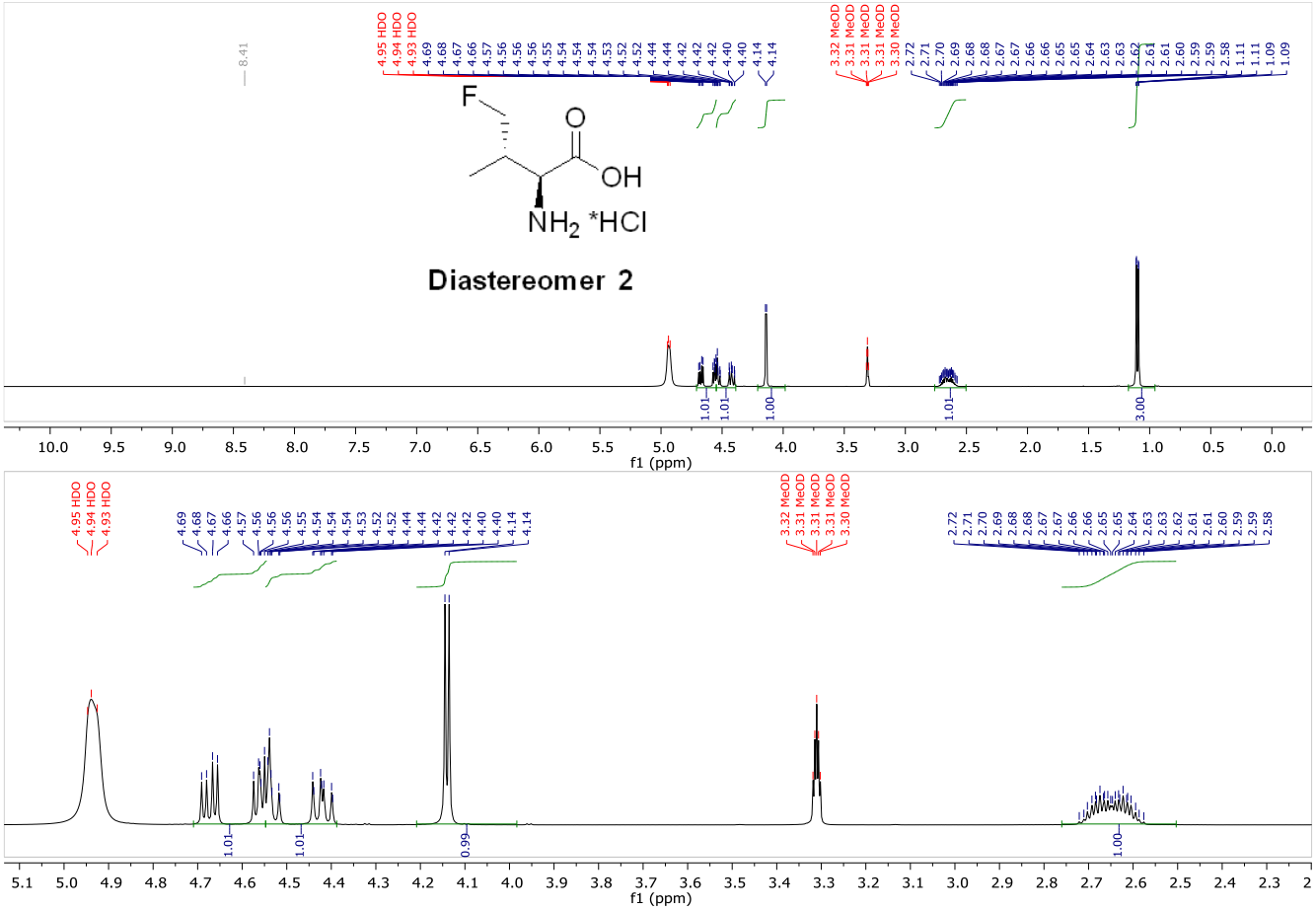
1: TOF MS ES+
4.11e5



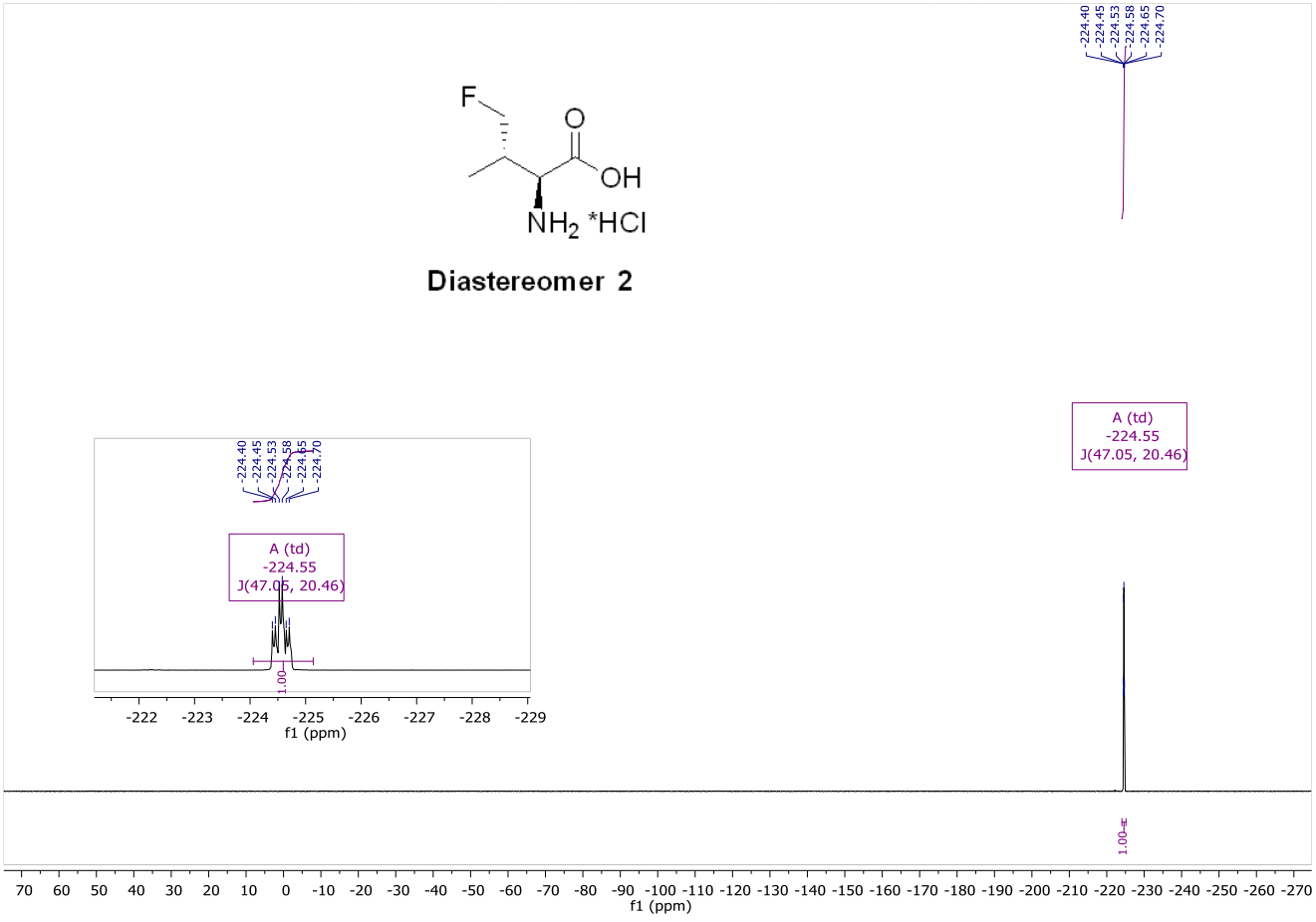
IR(ATR) spectrum of (2*S*,3*R*)-4-fluorovaline hydrochloride (**42**)



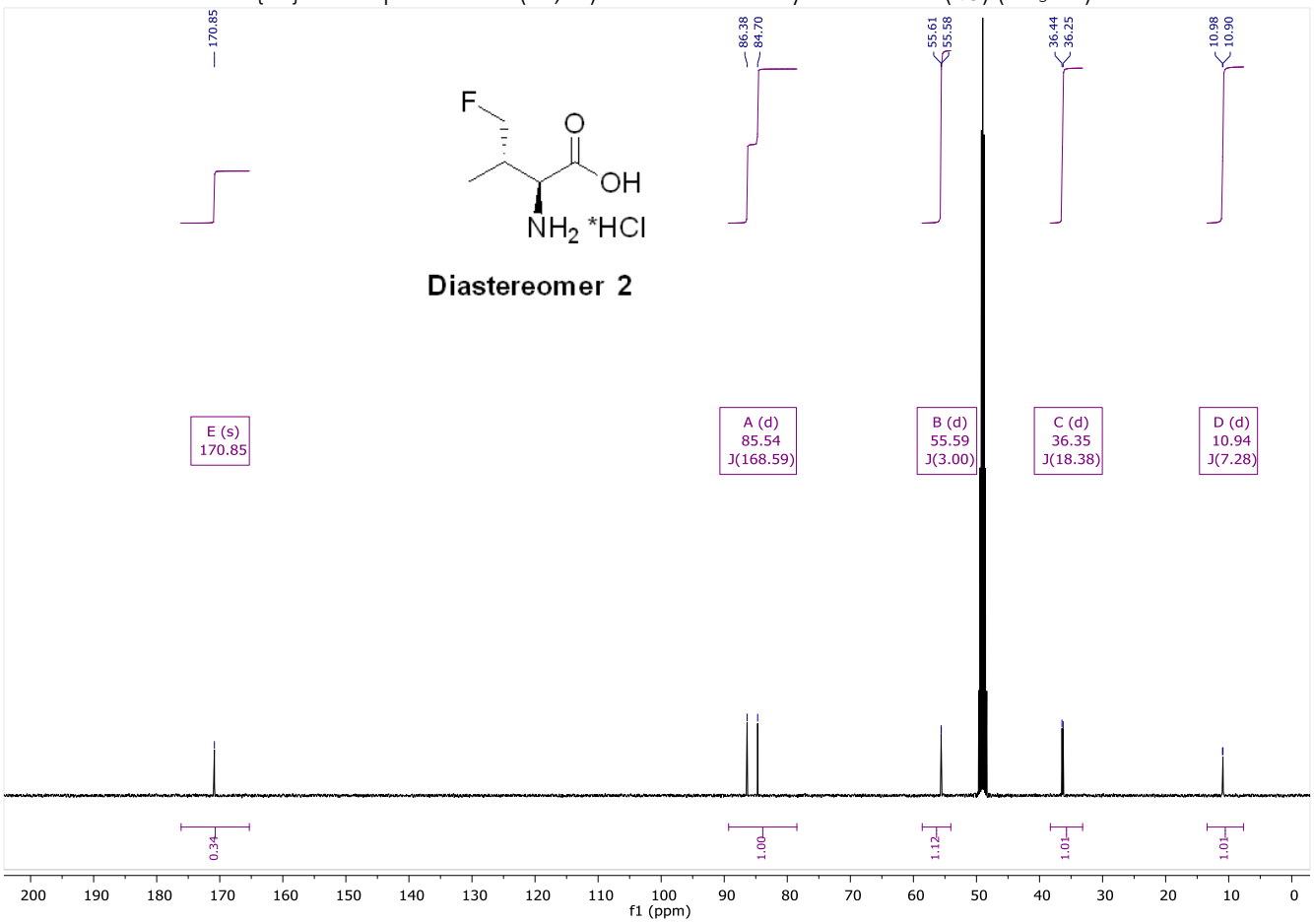
^{1}H NMR spectrum of (2*S*,3*S*)-4-fluorovaline hydrochloride (**43**) (CD_3OD)



^{19}F NMR spectrum of (2*S*,3*S*)-4-fluorovaline hydrochloride (**43**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of (2*S*,3*S*)-4-fluorovaline hydrochloride (**43**) (CD_3OD)



HRMS of (2*S*,3*S*)-4-fluorovaline hydrochloride (**43**)

MS: Waters Synapt G2-S*i*	Capillary, kV:	0.7	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

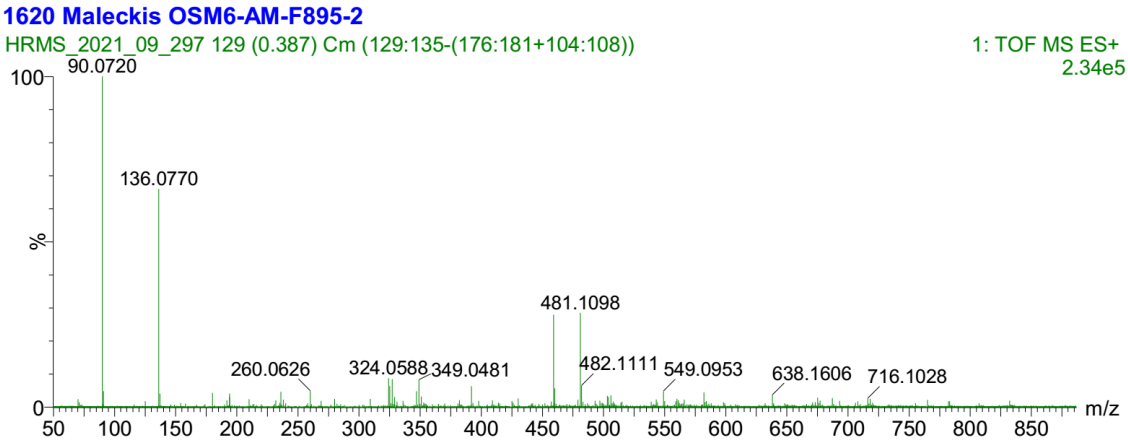
HRMS_2021_09_297 1620 Maleckis OSM6-AM-F895-2
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:E,3 10.000000 MS_Tune Col#66

Elemental Composition Report:

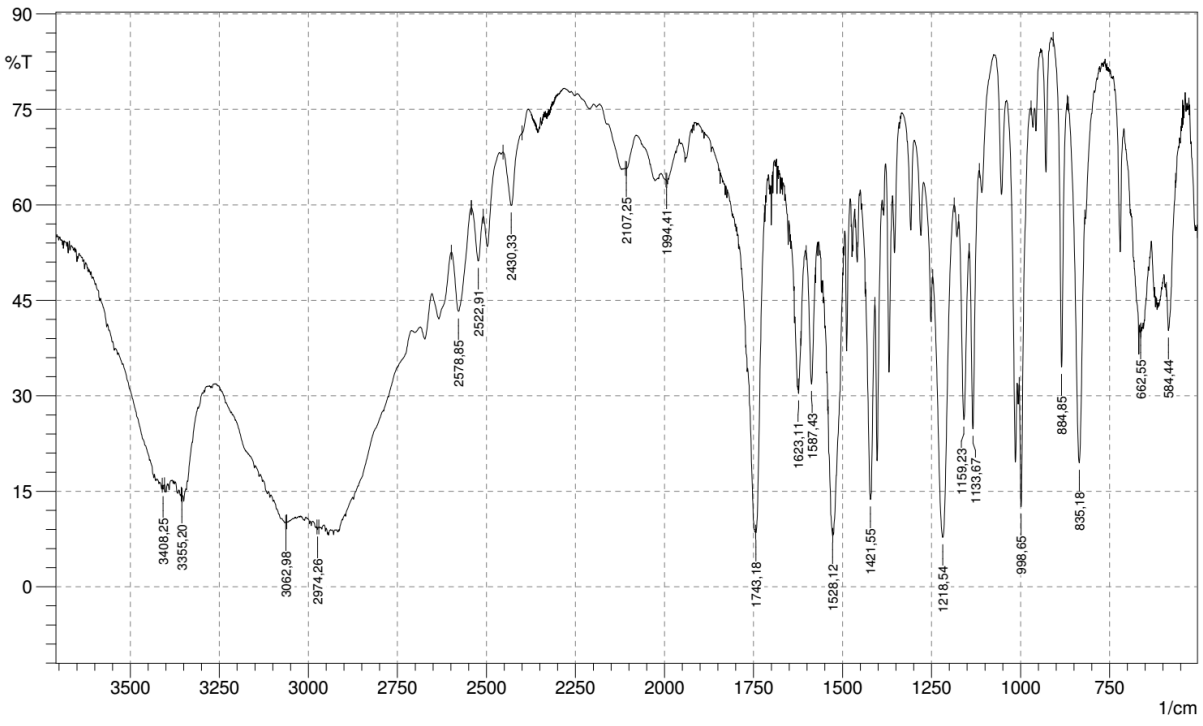
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
56 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-100 H: 1-120 N: 1-5 O: 1-5 F: 0-1

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
136.0770	100.00	136.0774	-0.4	-2.9	0.5	788.6	n/a	n/a	C5 H11 N O2 F

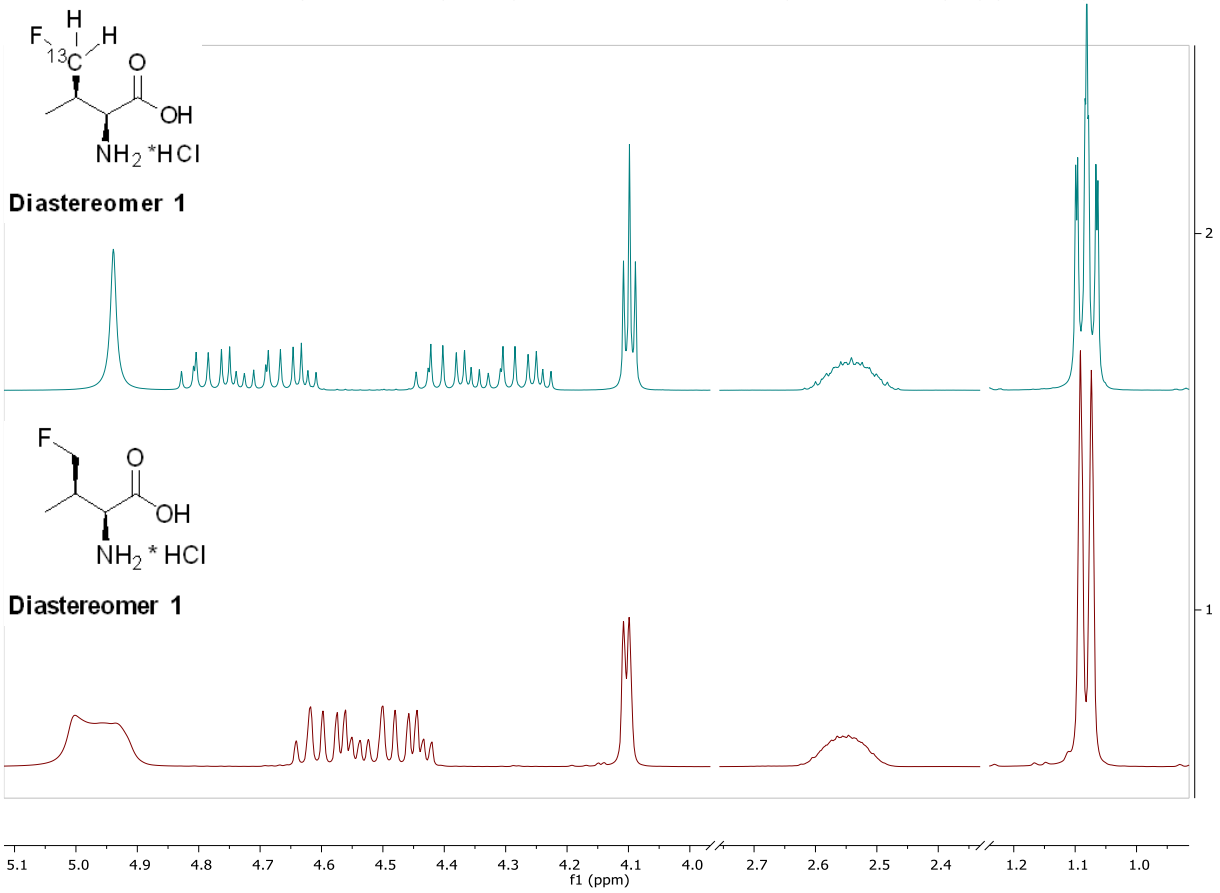


IR(ATR) spectrum of (2*S*,3*S*)-4-fluorovaline hydrochloride (**43**)

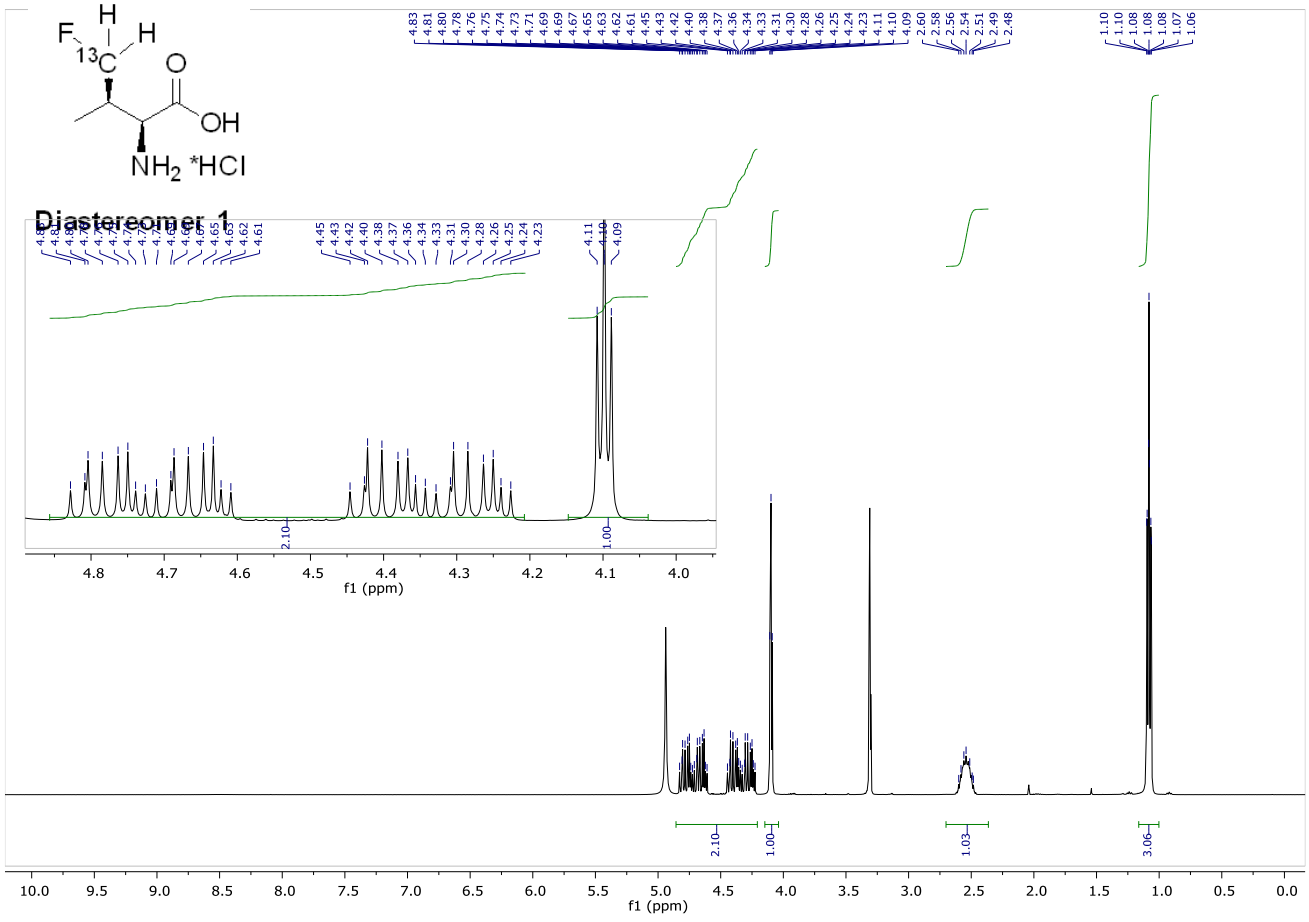


Spectra of compounds in Scheme 7

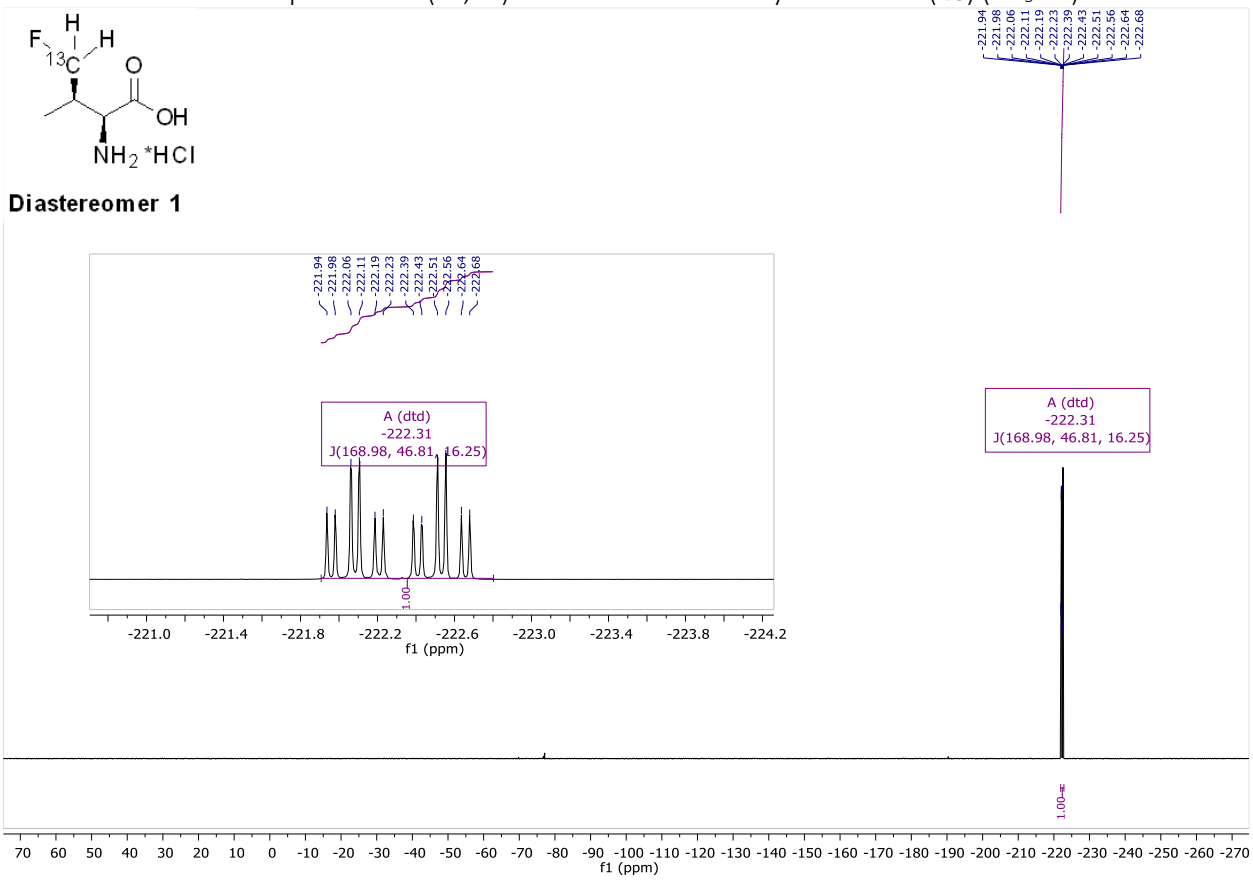
^{1}H NMR spectrum of (2*S*,3*R*)-4-fluorovaline-4-^{13}*C* hydrochloride (**46**) (CD_3OD)



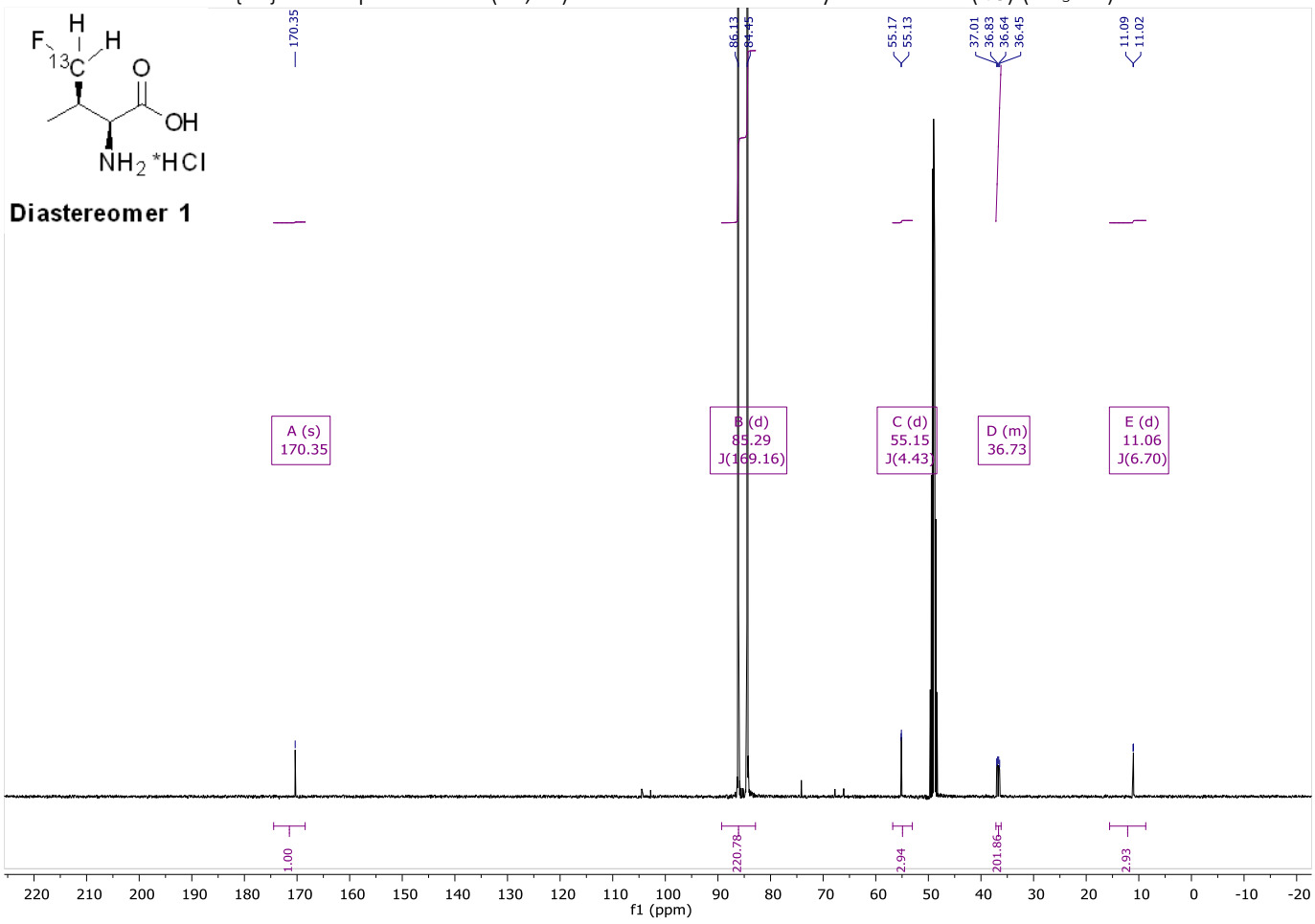
^{1}H NMR spectrum of (2*S*,3*R*)-4-fluorovaline-4-^{13}*C* hydrochloride (**46**) (CD_3OD)



^{19}F NMR spectrum of (2*S*,3*R*)-4-fluorovaline-4-^{13}*C* hydrochloride (**46**) (CD_3OD)



^{13}C{^{1}H} NMR spectrum of (2*S*,3*R*)-4-fluorovaline-4-^{13}*C* hydrochloride (**46**) (CD_3OD)



HRMS of (2*S*,3*R*)-4-fluorovaline-4-^{13}C hydrochloride (**46**)

Elemental Composition Report **Page 1**

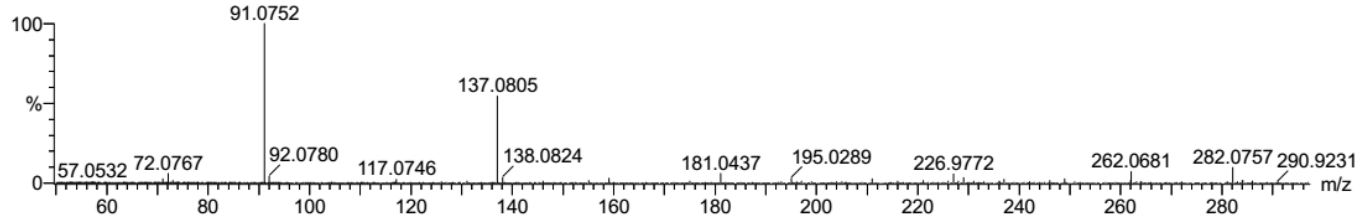
Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
193 formula(e) evaluated with 5 results within limits (up to 3 best isotopic matches for each mass)
Elements Used:
12C: 1-10 13C: 1-5 H: 0-100 N: 1-3 O: 1-3 F: 0-1

1774 Maleckis OSM6-AM-F-940-1
20-Oct-2021

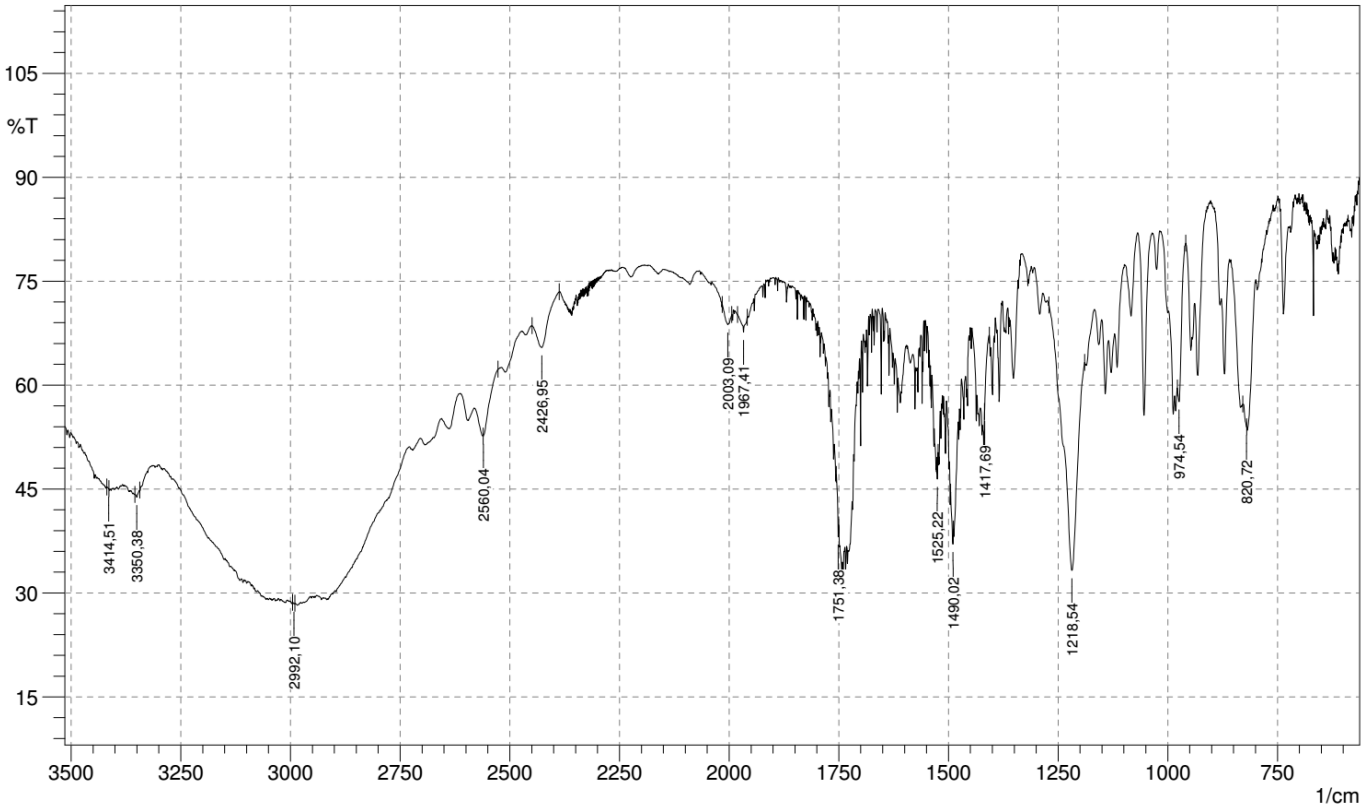
HRMS_2021_10_307 119 (0.360) Cm (119:121-(105:108+149:152))

OSI/FOKL-MS
Synapt G2-Si
1: TOF MS ES+
1.17e+005

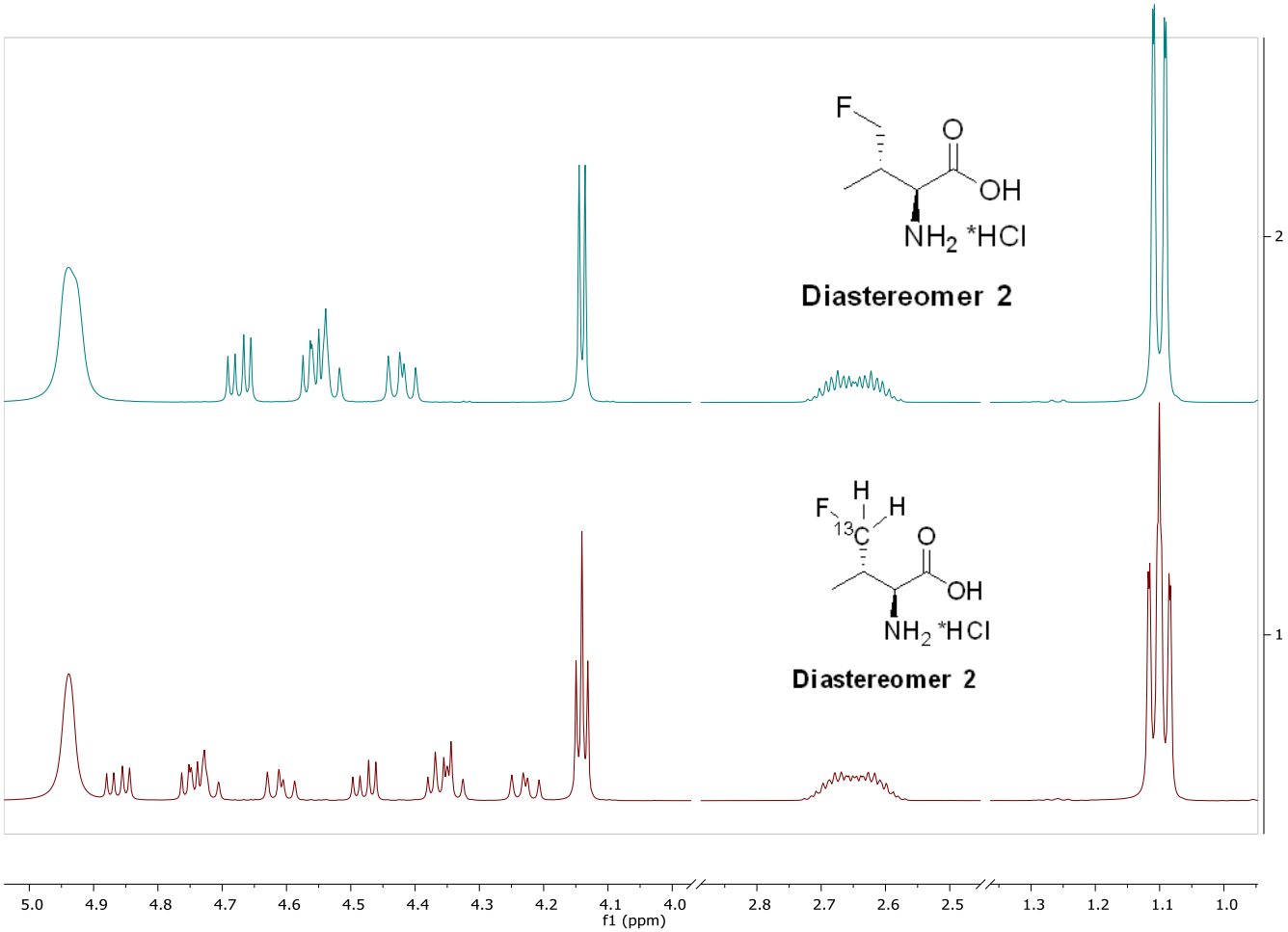


Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Conf(%)	Formula
137.0805	137.0807	-0.2	-1.5	0.5	49.81	12C4 13C H11 N O2 F
	137.0796	0.9	6.6	4.5	30.16	12C7 13C H10 N O
	137.0837	-3.2	-23.3	0.5	20.03	12C2 13C2 H11 N2 O3

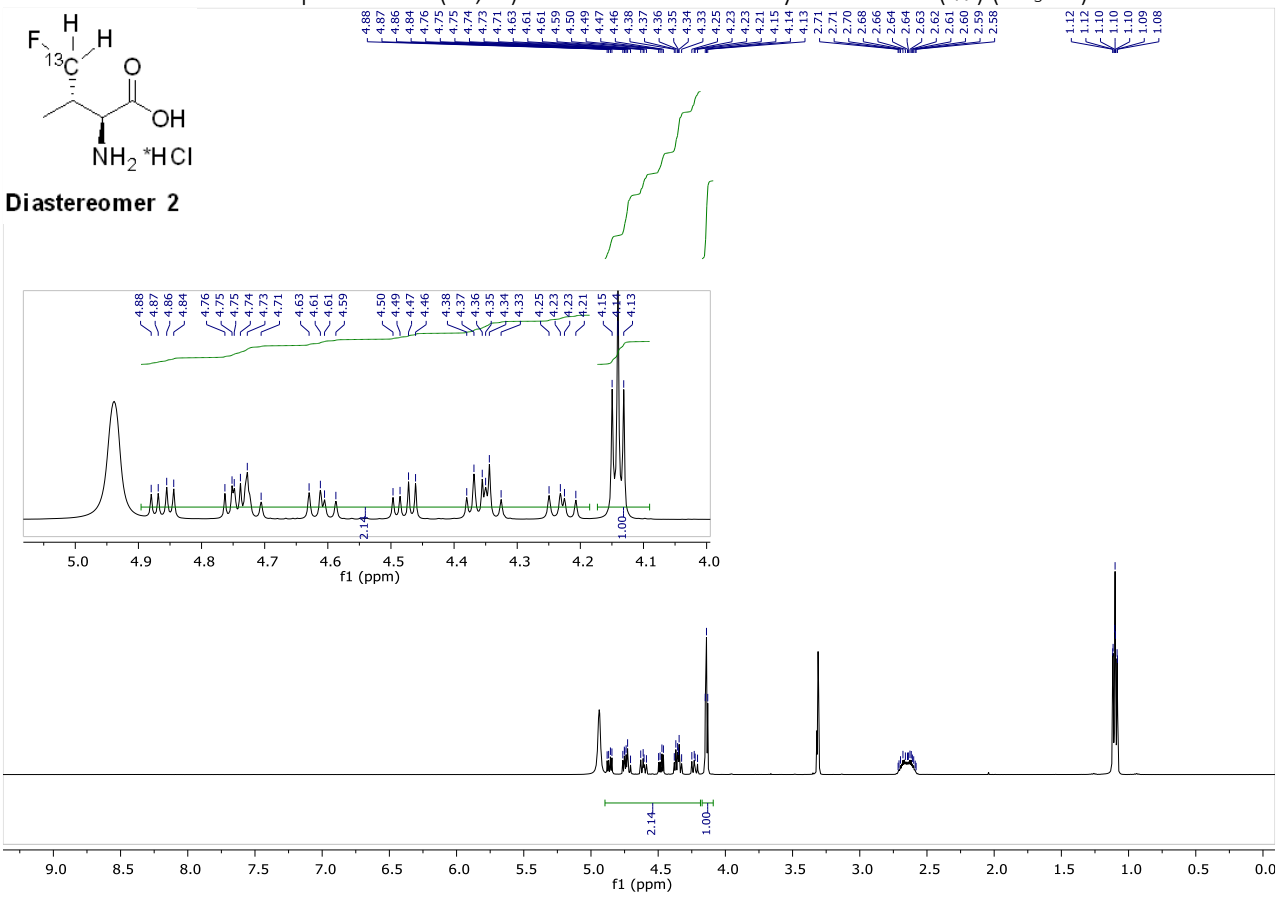
IR(ATR) spectrum of (2*S*,3*R*)-4-fluorovaline-4-^{13}C hydrochloride (**46**)



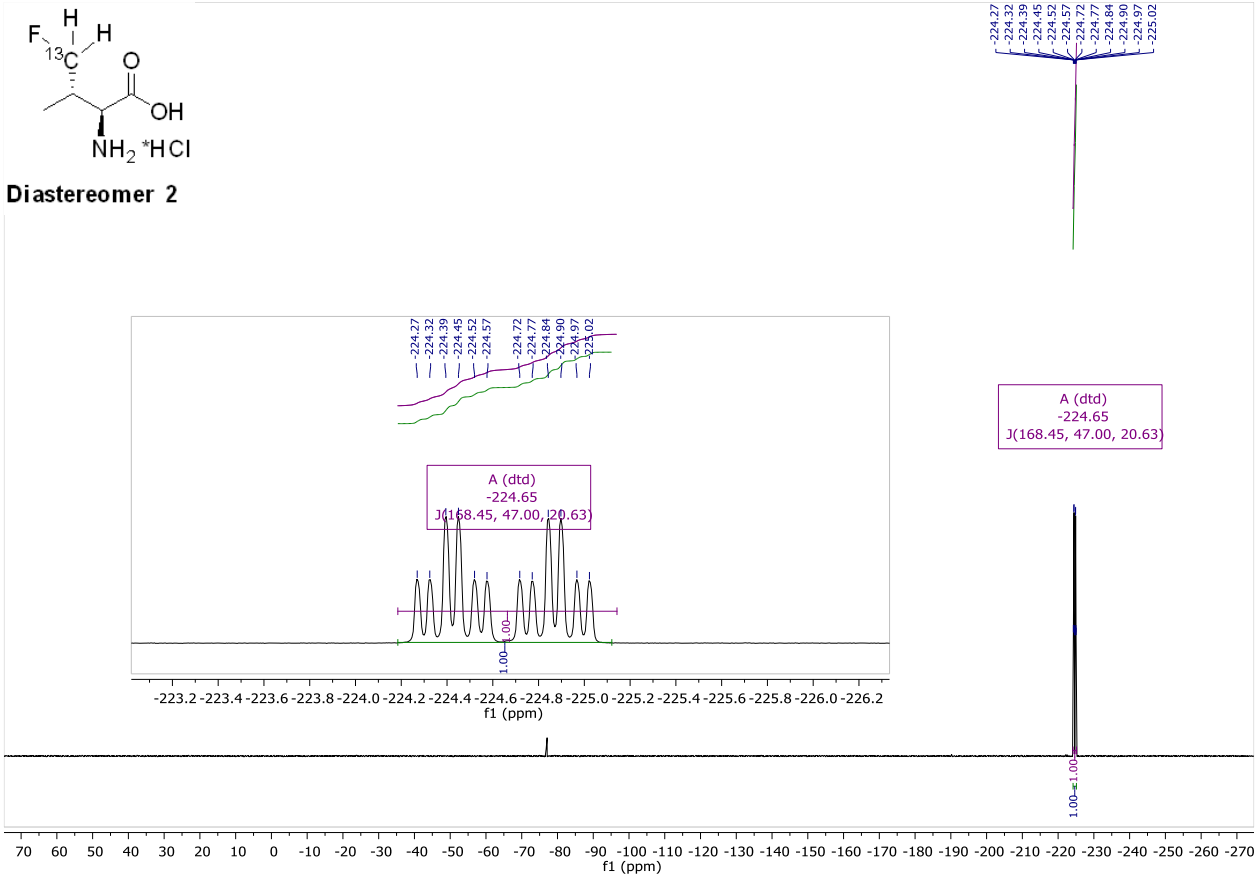
^{1}H NMR spectrum of (2*S*,3*S*)-4-fluorovaline-4-^{13}*C* hydrochloride (**47**) (CD_3OD)



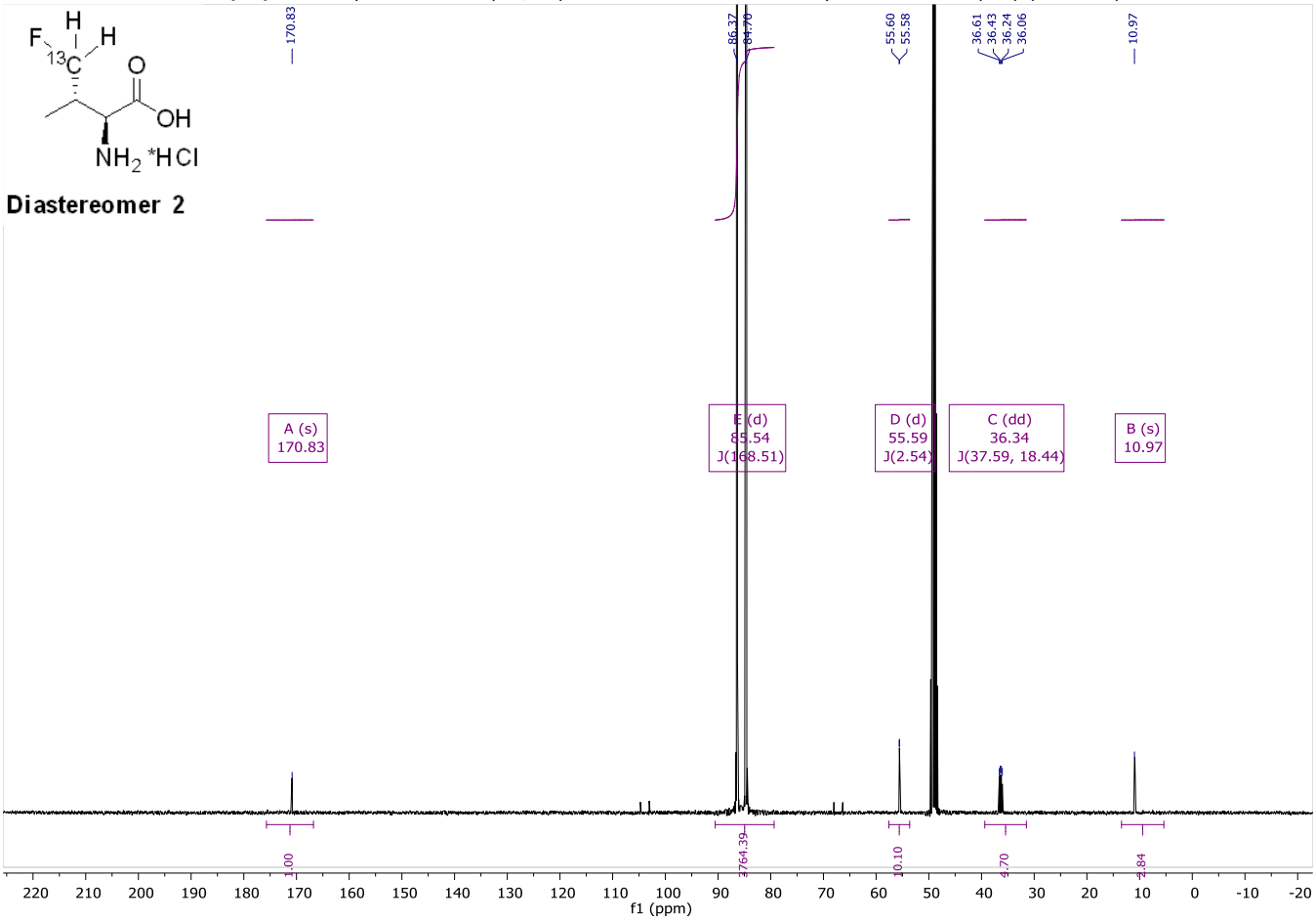
^{1}H NMR spectrum of (2*S*,3*S*)-4-fluorovaline-4-^{13}*C* hydrochloride (**47**) (CD_3OD)



^{19}F NMR spectrum of (2*S*,3*S*)-4-fluorovaline-4-^{13}*C* hydrochloride (**47**) (CD_3OD)



^{13}C{^{1}H} NMR spectrum of (2*S*,3*S*)-4-fluorovaline-4-^{13}*C* hydrochloride (**47**) (CD_3OD)



HRMS of (2*S*,3*S*)-4-fluorovaline-4-^{13}C hydrochloride (**47**)

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

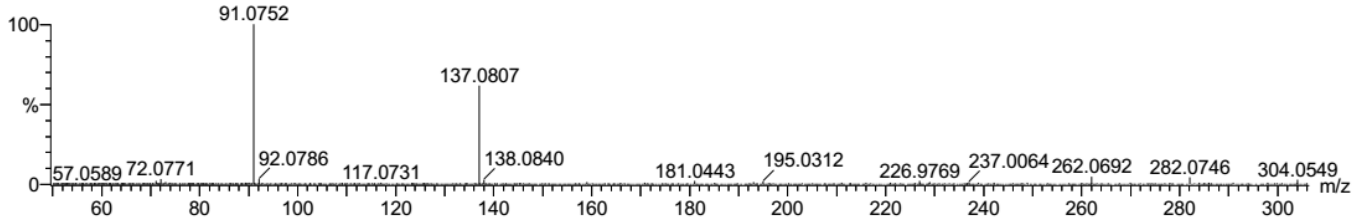
Monoisotopic Mass, Even Electron Ions
193 formula(e) evaluated with 4 results within limits (up to 3 best isotopic matches for each mass)
Elements Used:
H: 0-100 N: 1-3 O: 1-3 F: 0-1 12C: 1-10 13C: 1-5

1773 Maleckis OSM6-AM-F-940-1
20-Oct-2021

HRMS_2021_10_305 119 (0.360) Cm (119:120-(106:108+147:149))

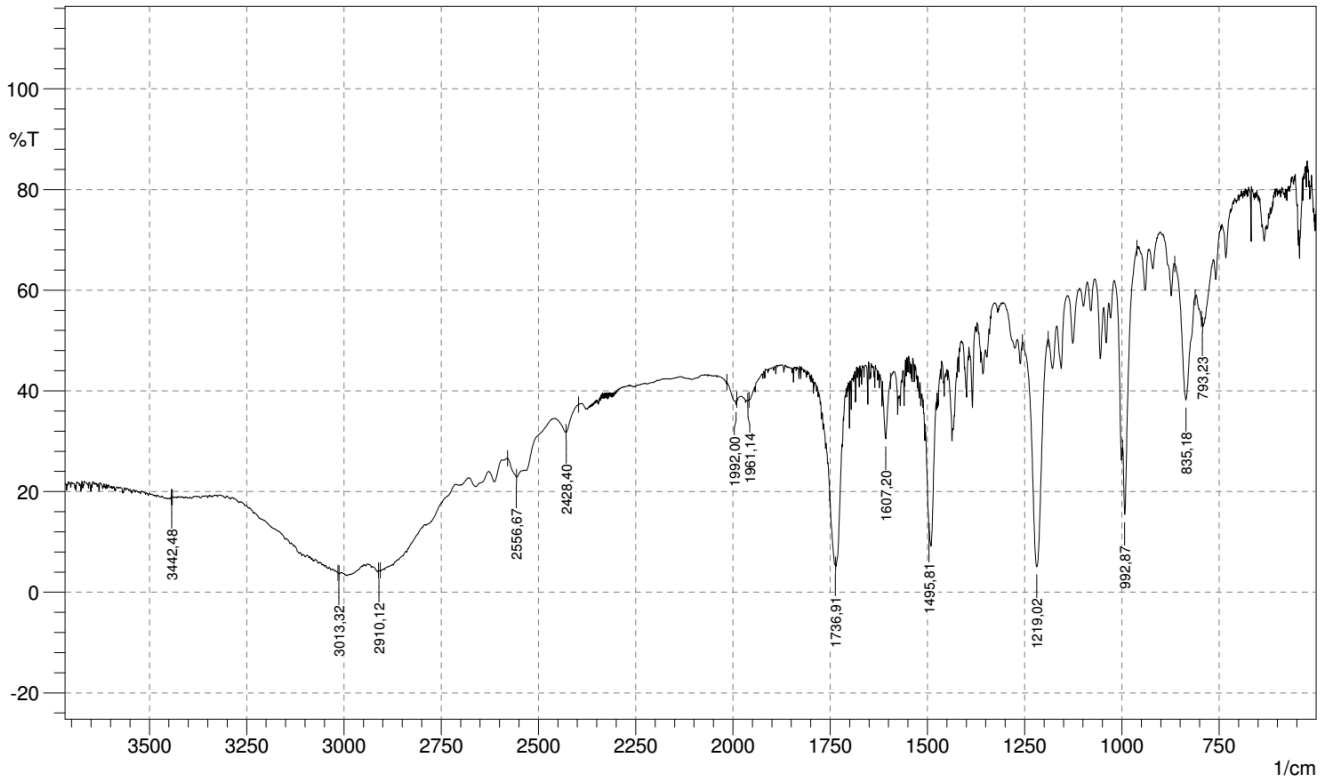
OSI/FOKL-MS
Synapt G2-Si

1: TOF MS ES+
7.40e+004



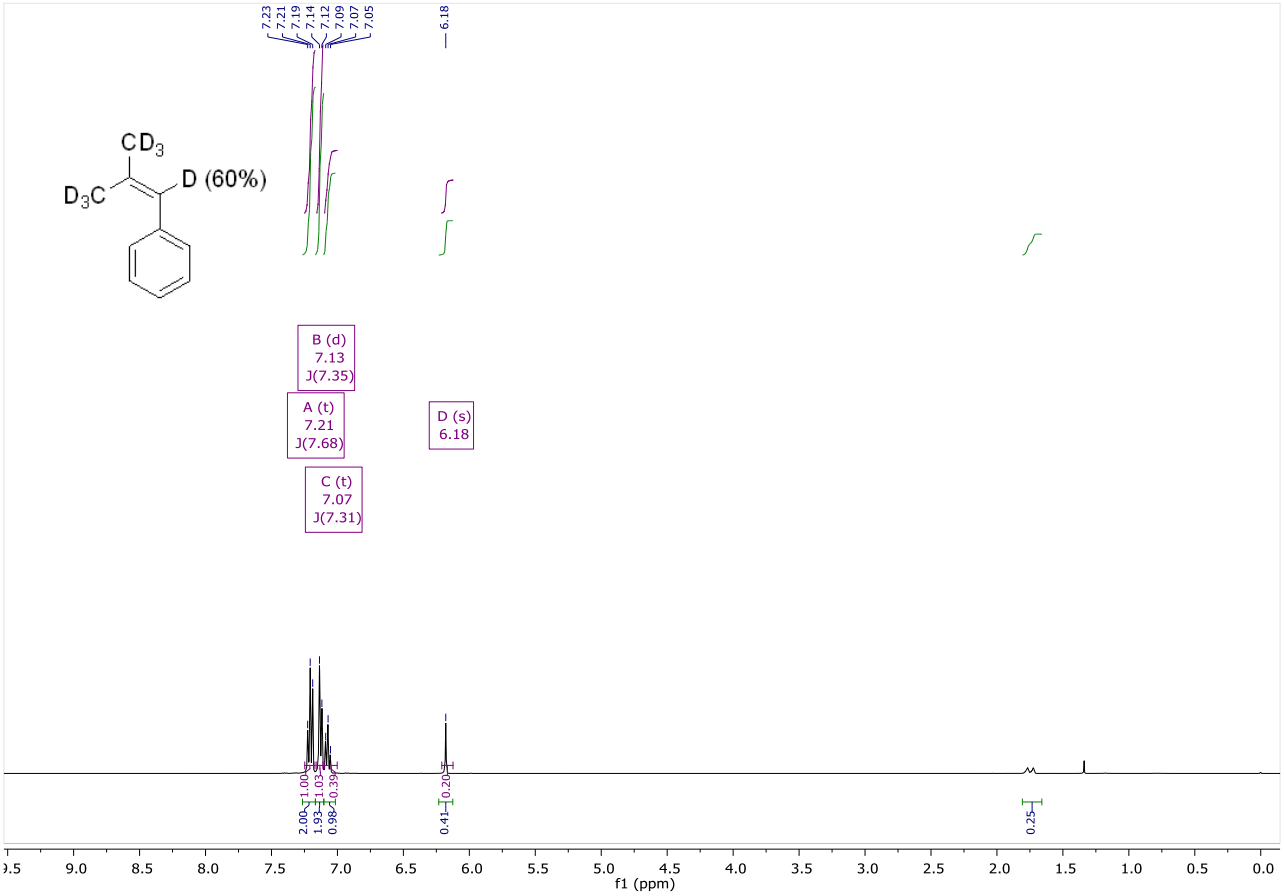
Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Conf(%)	Formula
137.0807	137.0807	0.0	0.0	0.5	30.29	H11 N O2 F 12C4 13C
	137.0830	-2.3	-16.8	1.5	32.66	H9 N3 O F 12C 13C3
	137.0837	-3.0	-21.9	0.5	37.05	H11 N2 O3 12C2 13C2

IR(ATR) spectrum of (2*S*,3*S*)-4-fluorovaline-4-^{13}C hydrochloride (**47**)

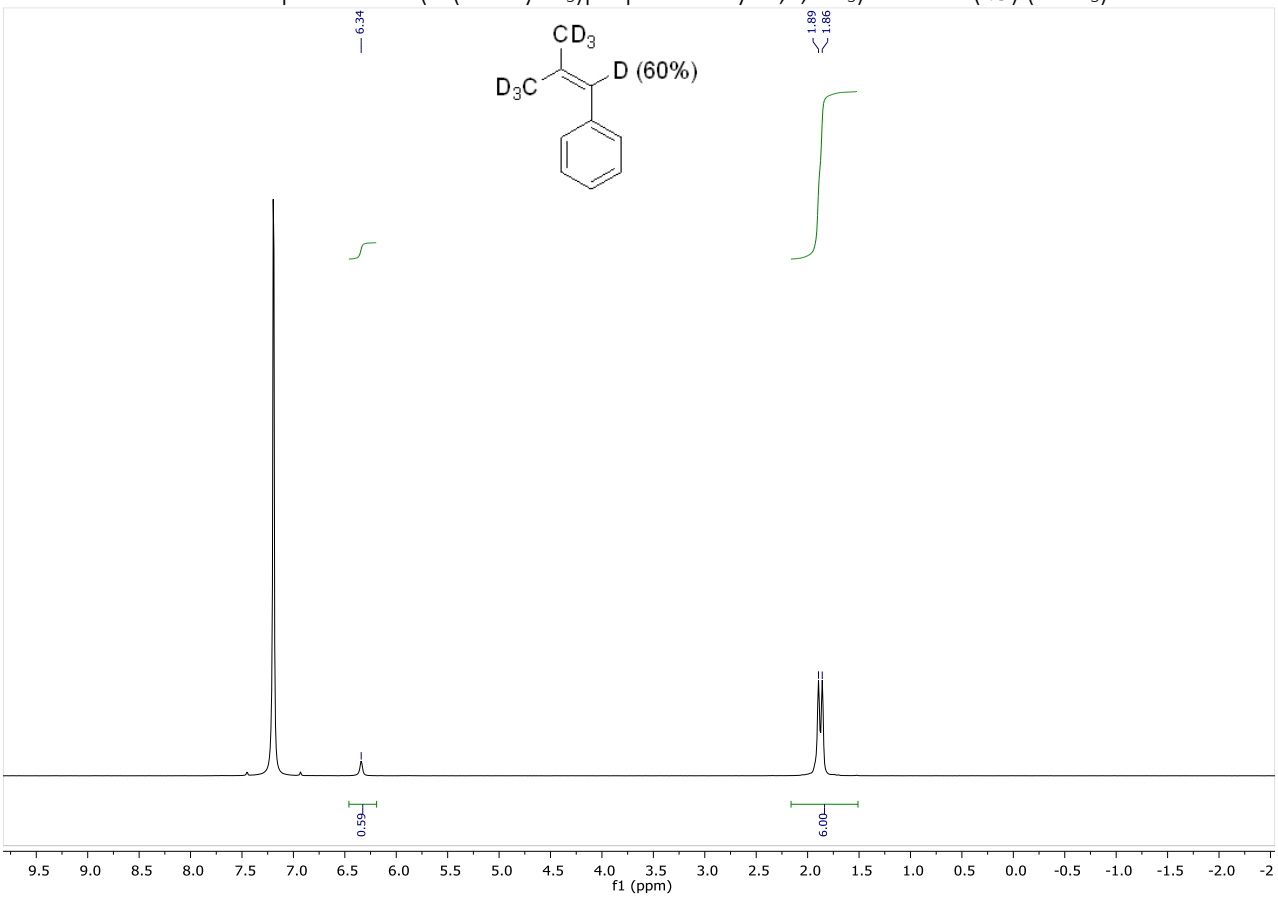


Spectra of compounds in Scheme 8

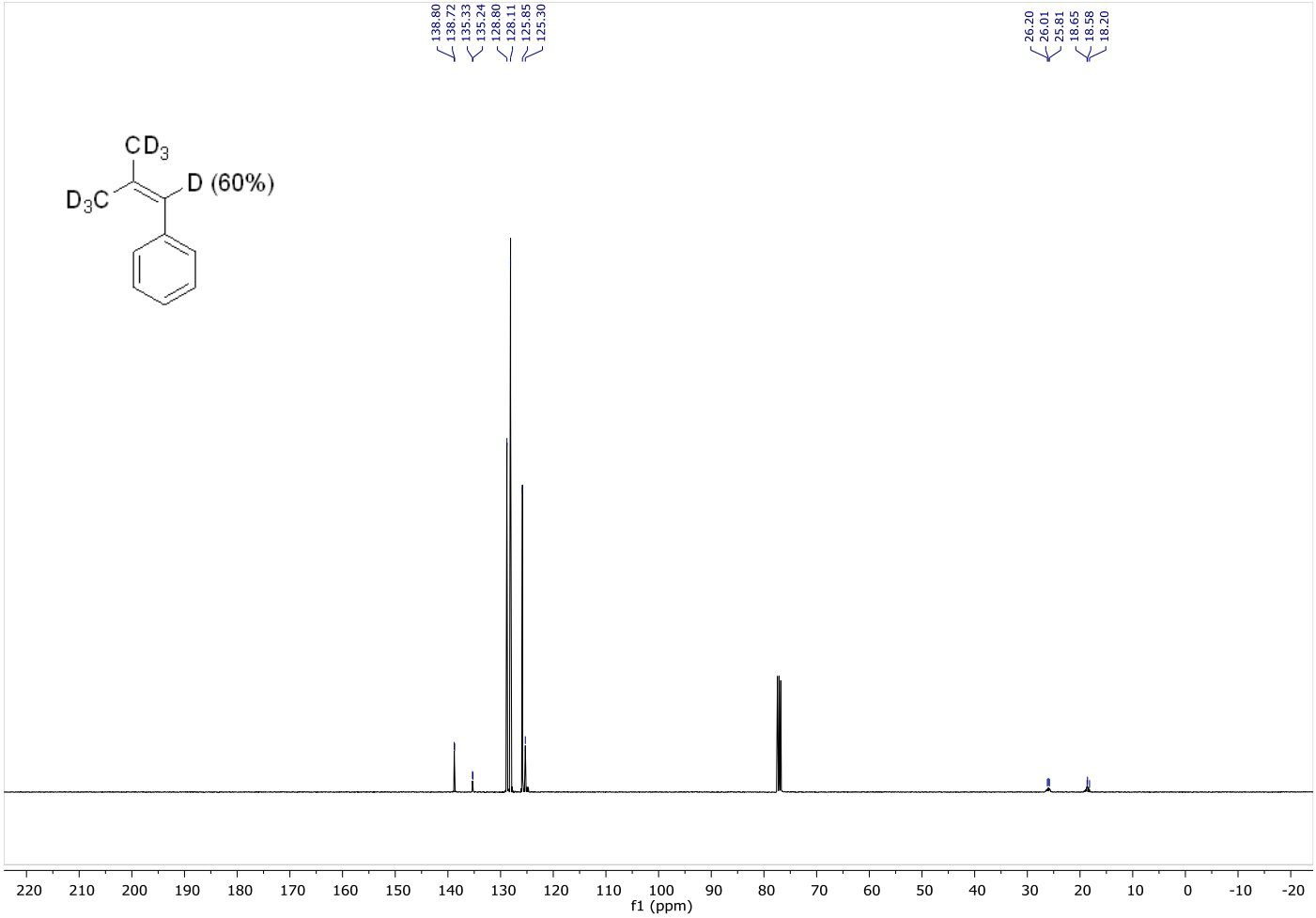
^{1}H NMR spectrum of (2-(methyl-d_3)prop-1-en-1-yl-3,3,3-d_3)benzene (**49**) ($CDCl_3$)



^{2}H NMR spectrum of (2-(methyl-d_3)prop-1-en-1-yl-3,3,3-d_3)benzene (**49**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (2-(methyl-d_3)prop-1-en-1-yl-3,3,3-d_3)benzene (**49**) ($CDCl_3$)



GC-MS of (2-(methyl-d_3)prop-1-en-1-yl-3,3,3-d_3)benzene (**49**)

```
File        :D:\DATA_2021\08-Aug-2021\24_15143.D
Operator    : E
Acquired    : 24 Aug 2021  14:19      using AcqMethod LAURA.M
Instrument :     GCMS
Sample Name: Maleckis OSM6-AM-851
Misc Info  :
Vial Number: 23
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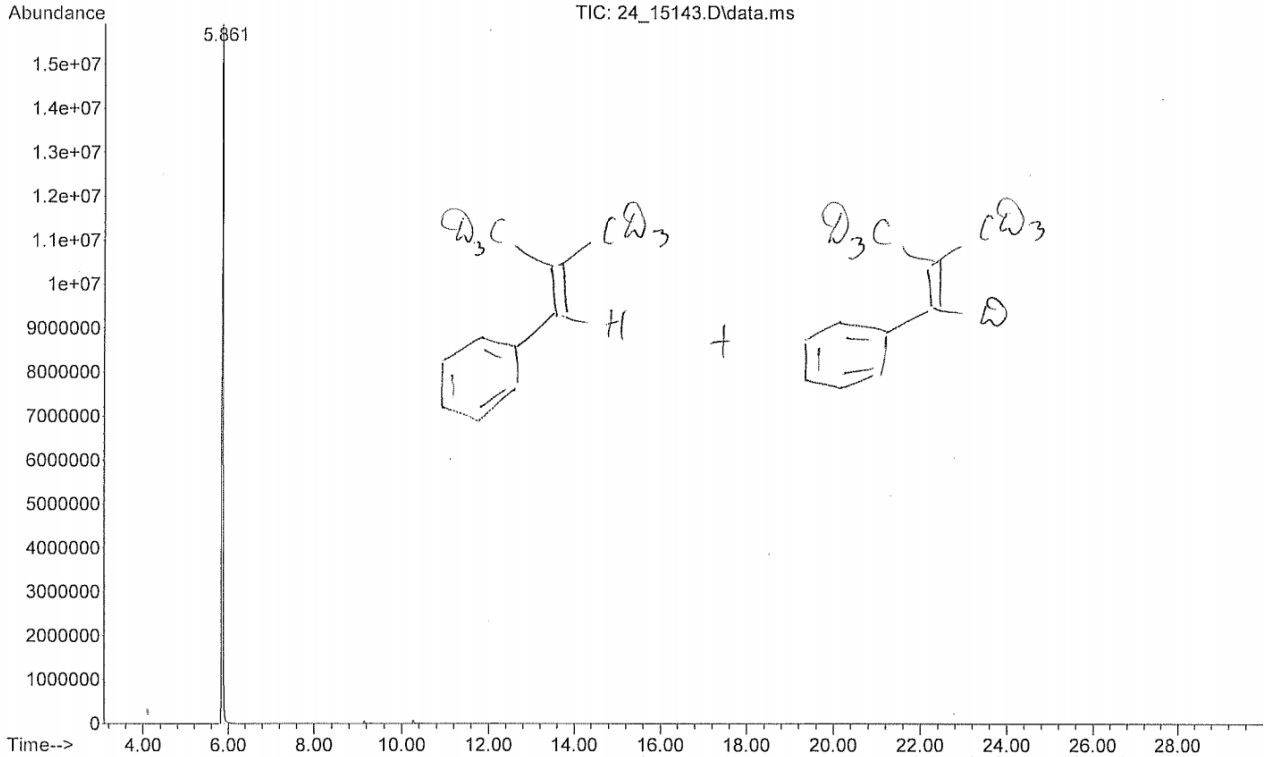
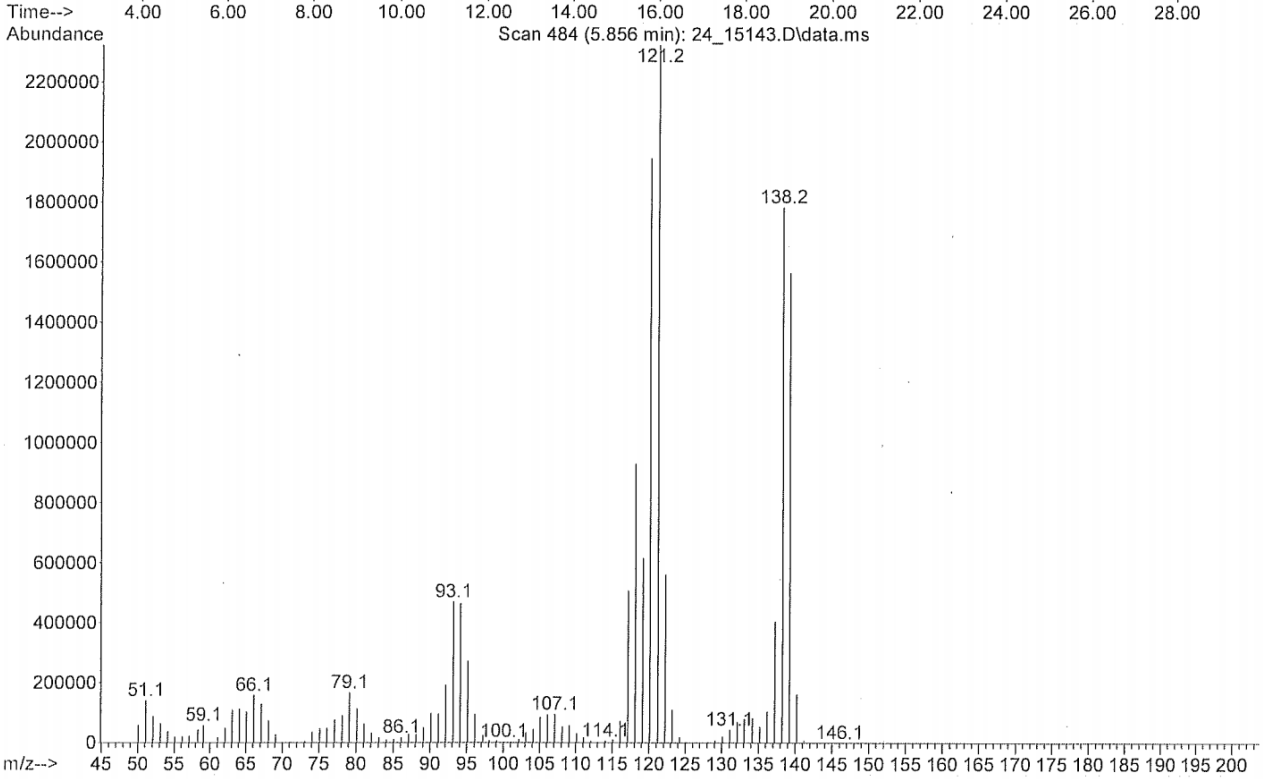
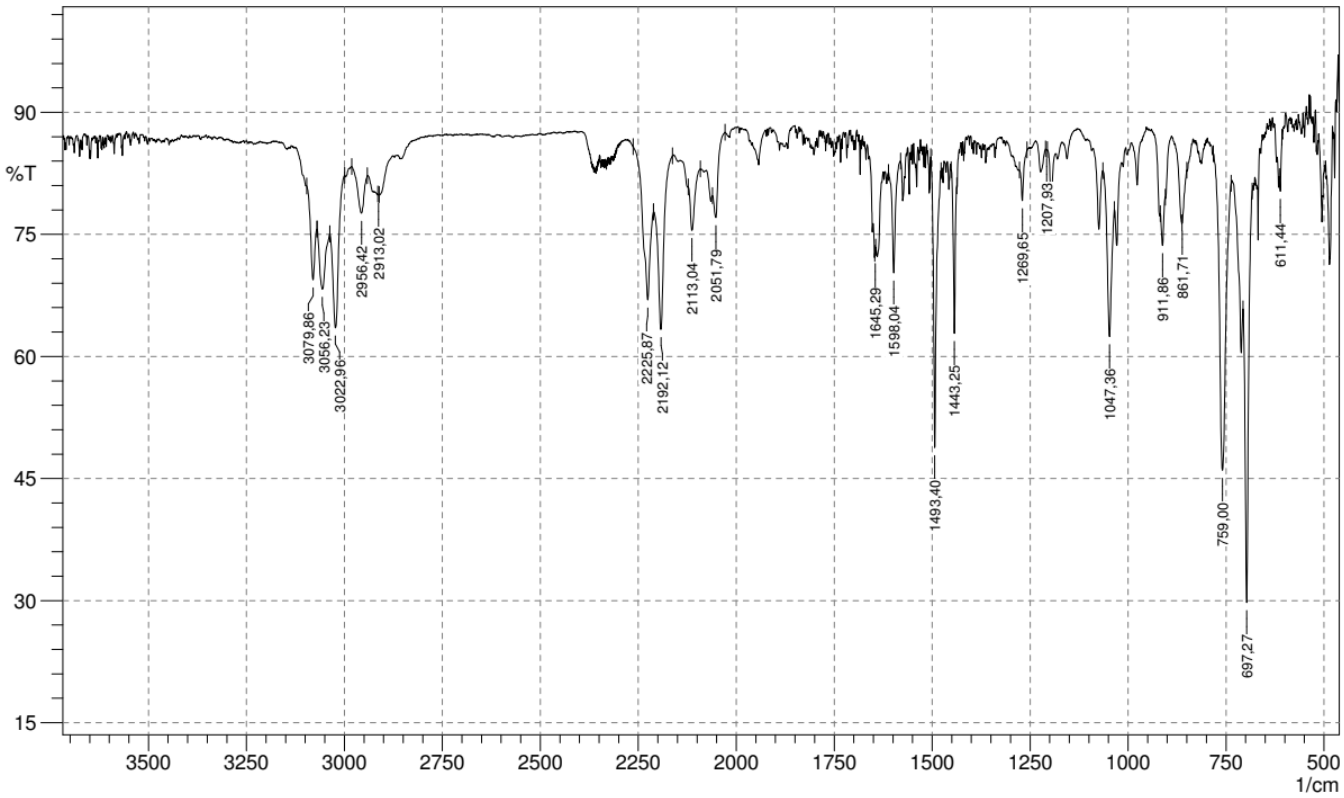
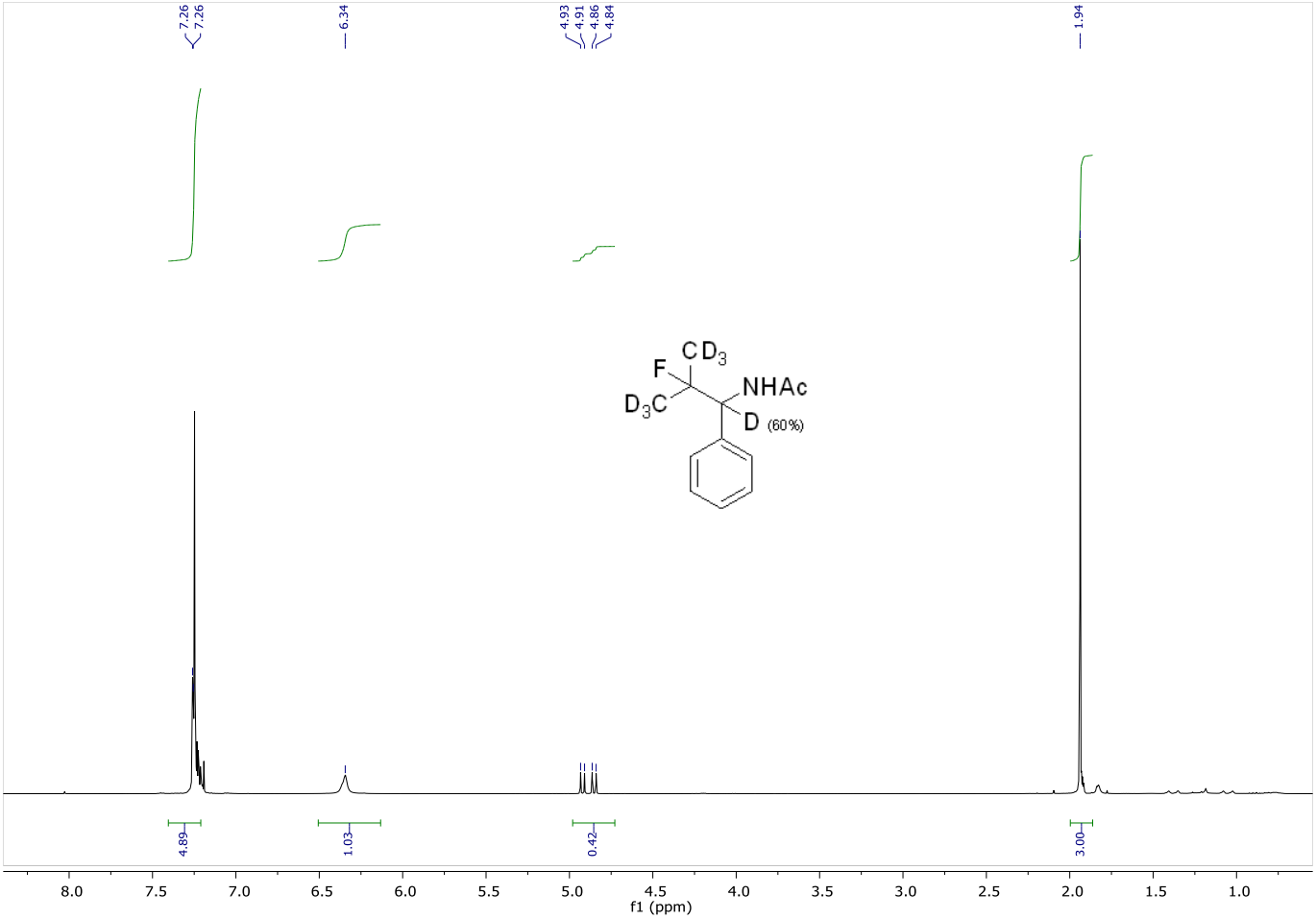




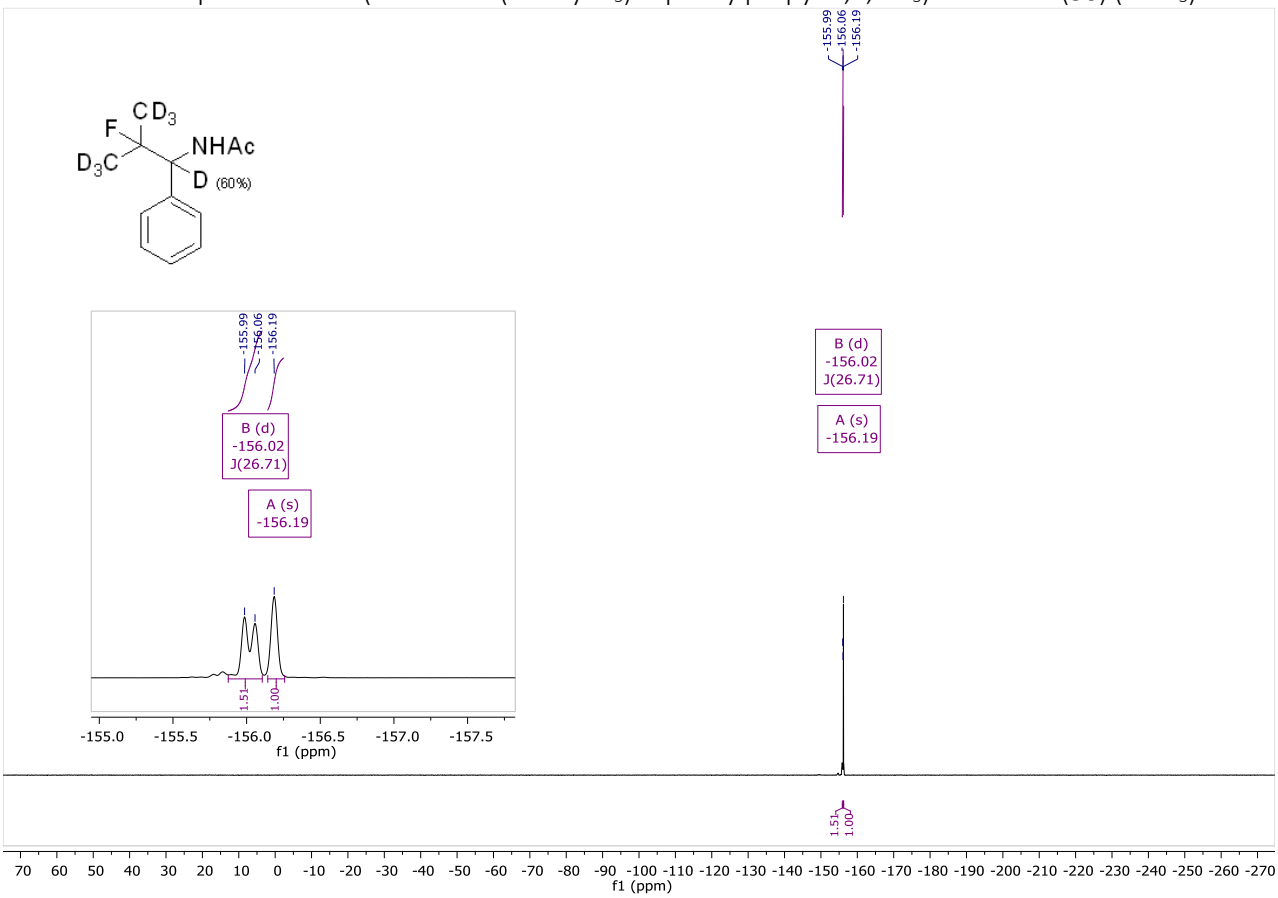
IR(ATR) spectrum of (2-(methyl-d_3)prop-1-en-1-yl-3,3,3-d_3)benzene (**49**)



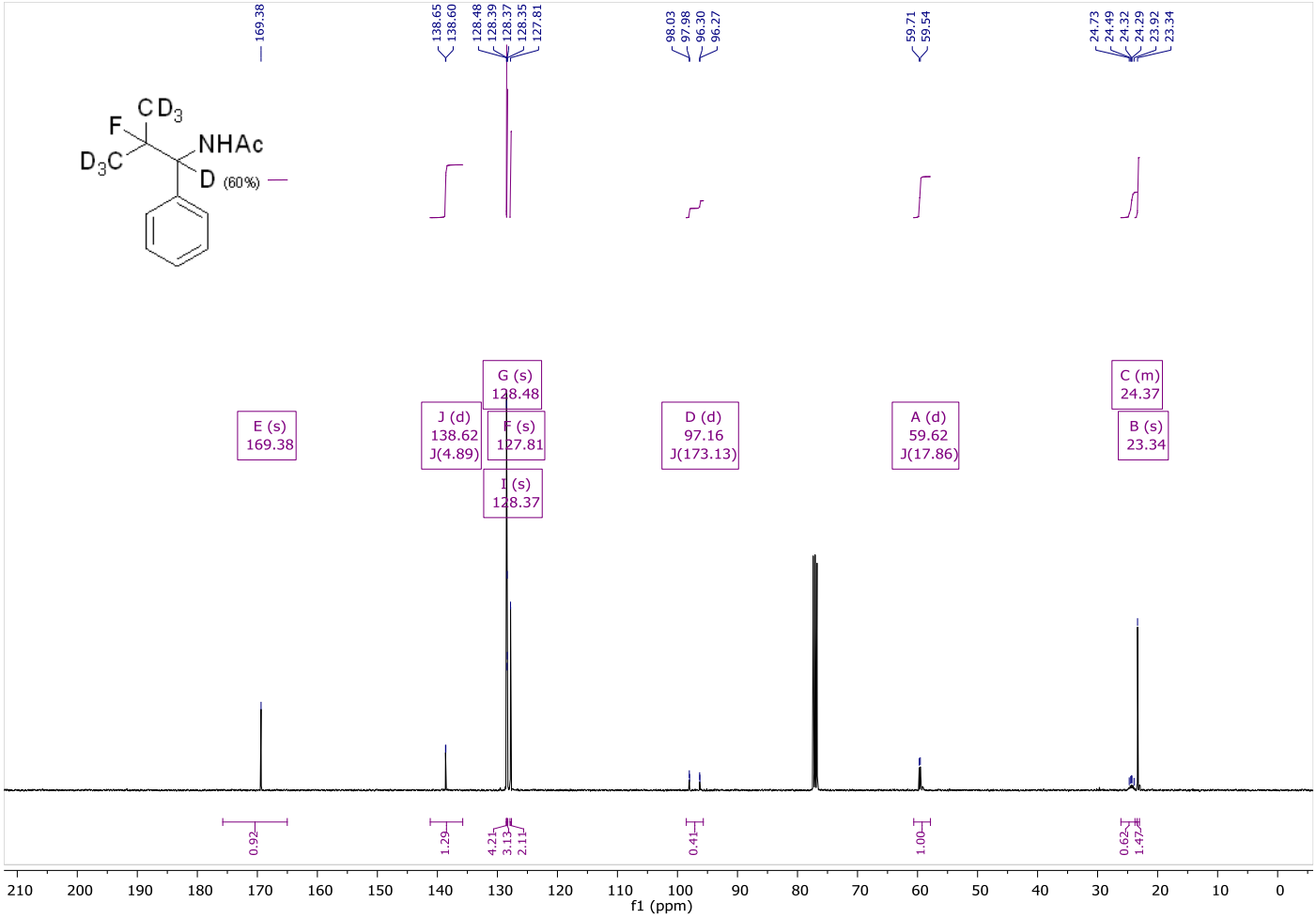
^{1}H NMR spectrum of *N*-(2-fluoro-2-(methyl-d_3)-1-phenylpropyl-3,3,3-d_3)acetamide (**50**) ($CDCl_3$)



^{19}F NMR spectrum of *N*-(2-fluoro-2-(methyl-d_3)-1-phenylpropyl-3,3,3-d_3)acetamide (**50**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of *N*-(2-fluoro-2-(methyl-d_3)-1-phenylpropyl-3,3,3-d_3)acetamide (**50**) ($CDCl_3$)



HRMS of *N*-(2-fluoro-2-(methyl-d_3)-1-phenylpropyl-3,3,3-d_3)acetamide (**50**)

MS: Waters Synapt G2-Si **ESI+**	Capillary, kV: Cone, V:	0.7 40	**LC: Acquity UPLC H-Class**	Column:	-

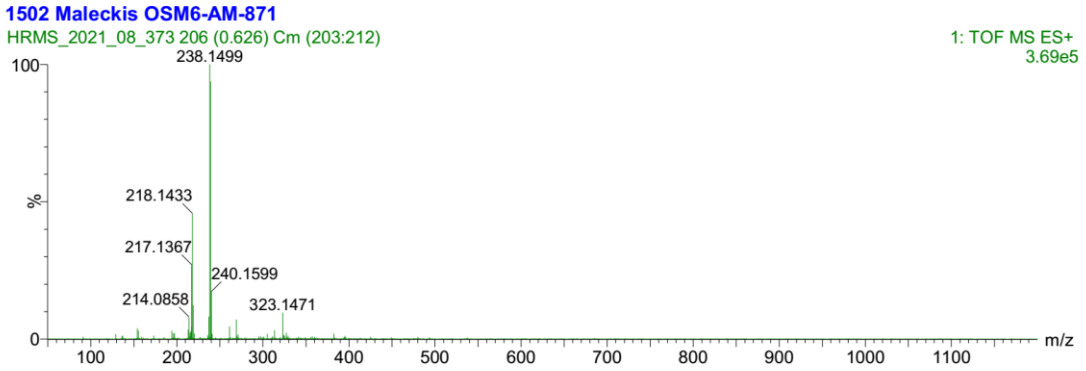
Sample:
HRMS_2021_08_373 1502 Maleckis OSM6-AM-871
MS_POS_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

Elemental Composition Report:

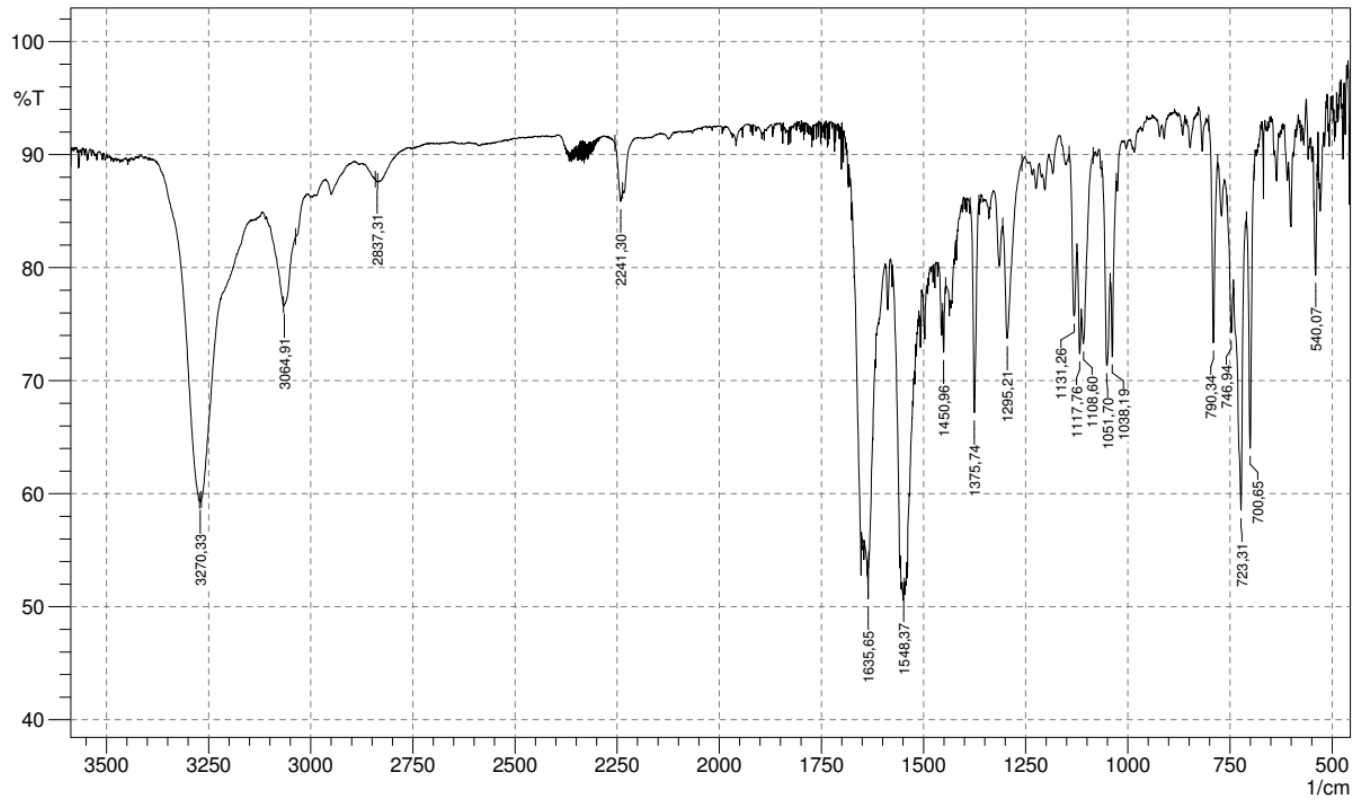
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
19173 formula(e) evaluated with 9 results within limits (up to 7 closest results for each mass)
Elements Used:
C: 0-100 1H: 1-105 2H: 1-10 N: 0-10 O: 0-10 F: 1-1 Na: 0-1

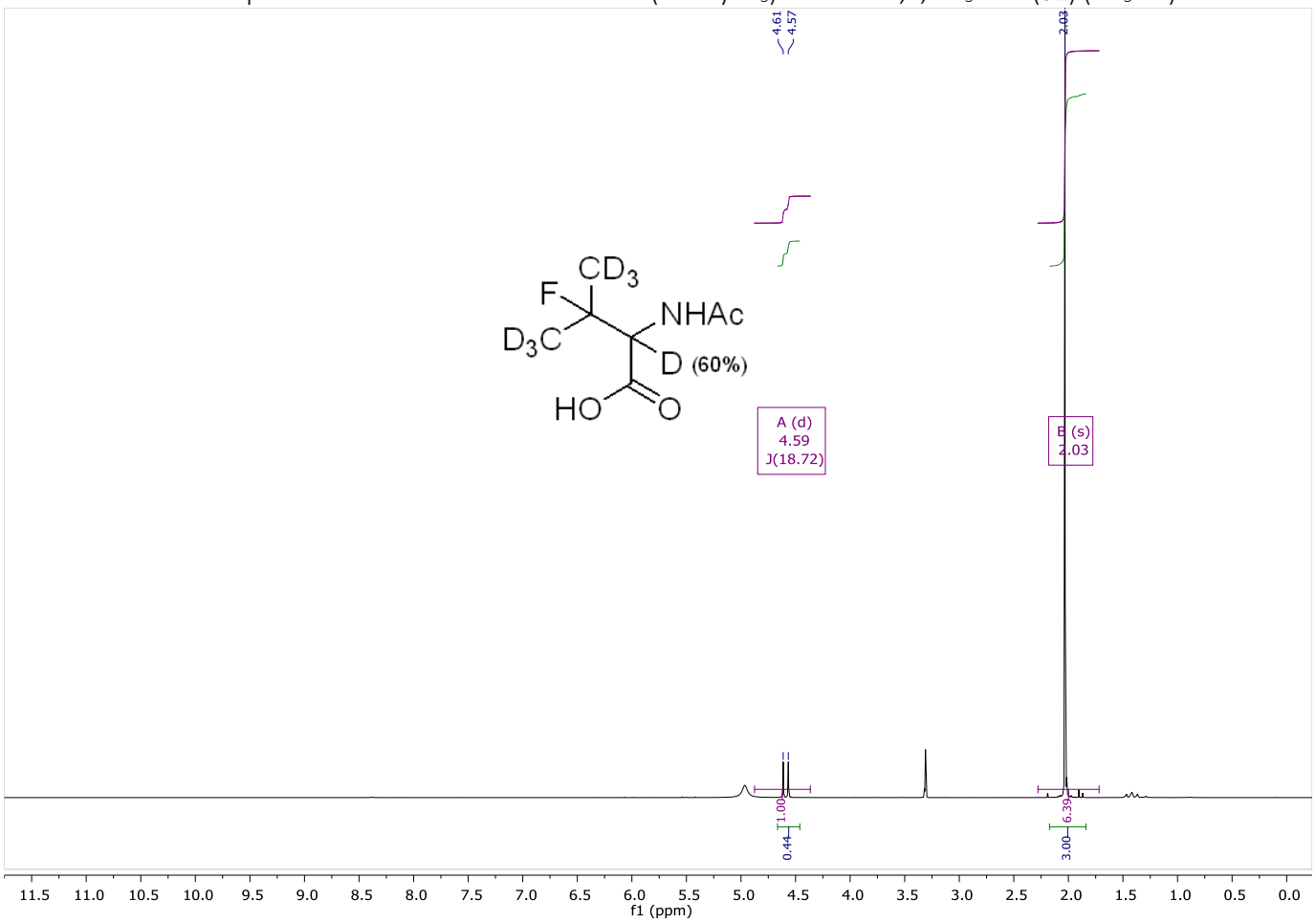
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
238.1499	100.00	238.1500	-0.1	-0.4	2.5	707.0	3.444	3.19	C6 1H2 2H10 N5 O2 F Na
		238.1502	-0.3	-1.3	2.5	708.5	4.953	0.71	C4 1H2 2H9 N8 O F Na
		238.1503	-0.4	-1.7	2.5	704.9	1.343	26.12	C11 1H13 2H5 O4 F
		238.1505	-0.6	-2.5	2.5	705.8	2.232	10.74	C9 1H13 2H4 N3 O3 F
		238.1492	0.7	2.9	4.5	705.5	2.019	13.27	C10 1H10 2H5 N4 F Na
		238.1507	-0.8	-3.4	2.5	706.8	3.298	3.70	C7 1H13 2H3 N6 O2 F
		238.1490	0.9	3.8	4.5	704.4	0.861	42.28	C12 1H10 2H6 N O F Na



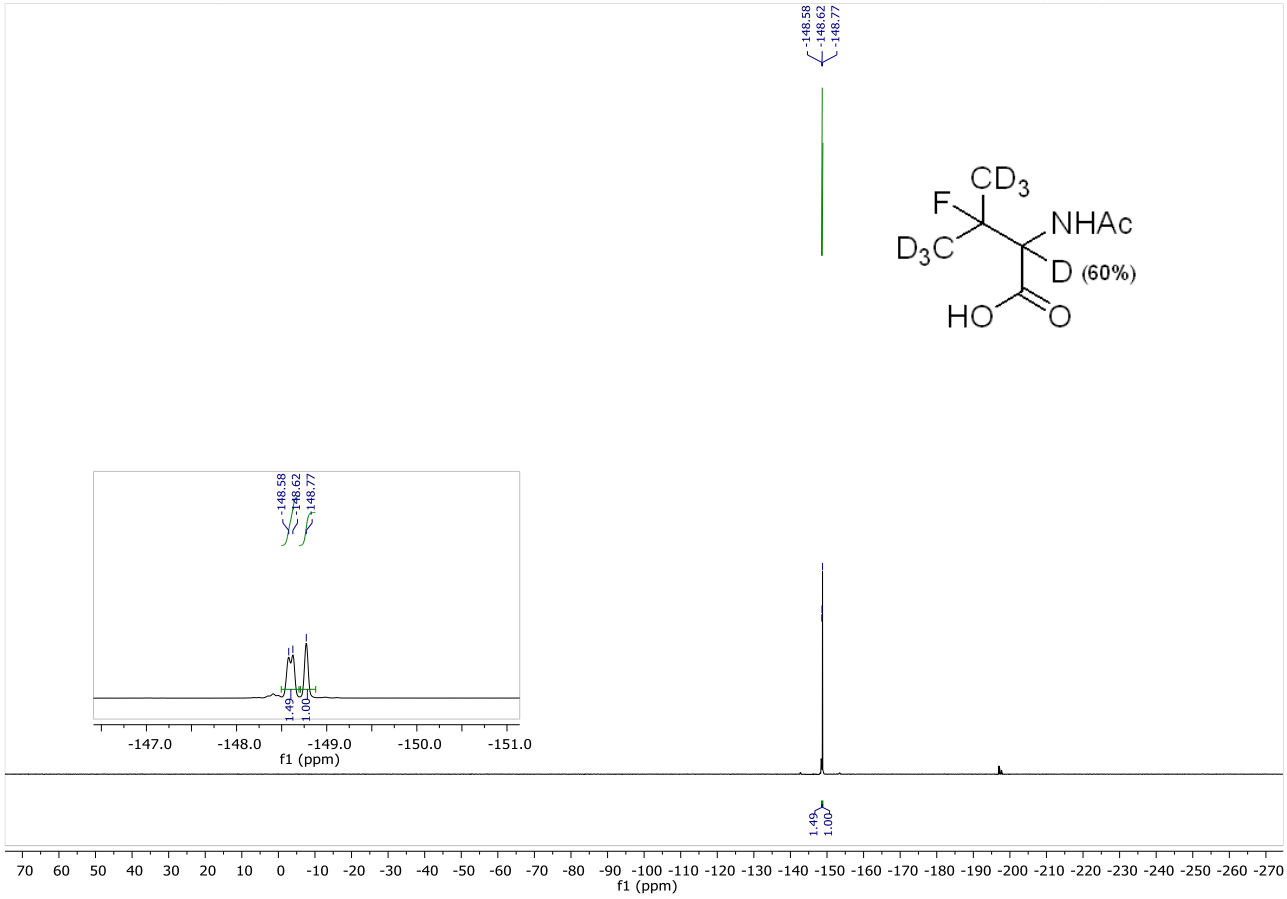
IR(ATR) spectrum of *N*-(2-fluoro-2-(methyl-d_3)-1-phenylpropyl-3,3,3-d_3)acetamide (**50**)



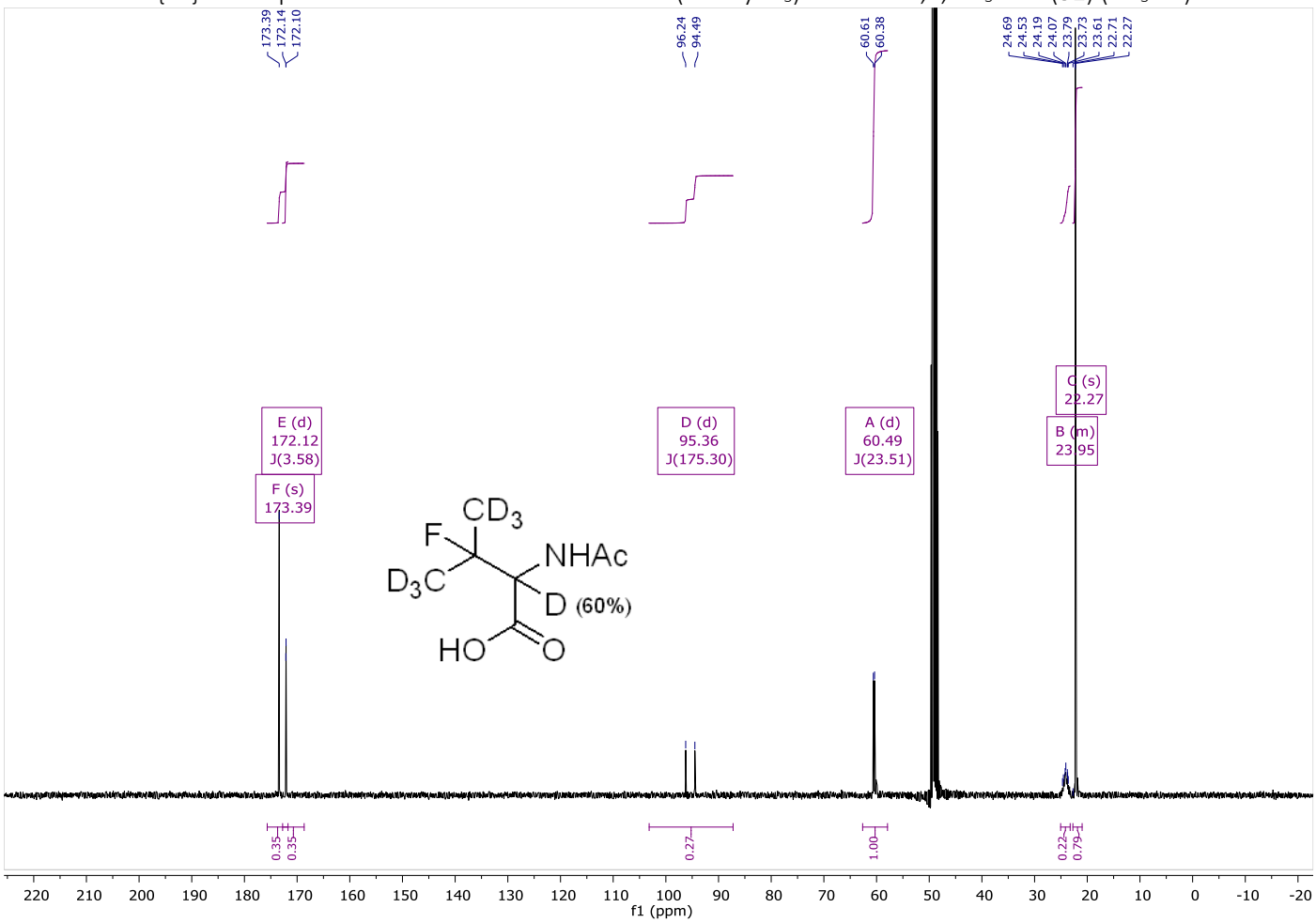
^{1}H NMR spectrum of 2-acetamido-3-fluoro-3-(methyl-d_3)butanoic-4,4,4-d_3 acid (**52**) (CD_3OD)



^{19}F NMR spectrum of 2-acetamido-3-fluoro-3-(methyl-d_3)butanoic-4,4,4-d_3 acid (**52**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of 2-acetamido-3-fluoro-3-(methyl-d_3)butanoic-4,4,4-d_3 acid (**52**) (CD_3OD)



HRMS of 2-acetamido-3-fluoro-3-(methyl-d_3)butanoic-4,4,4-d_3 acid (**52**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	4.0	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI+	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

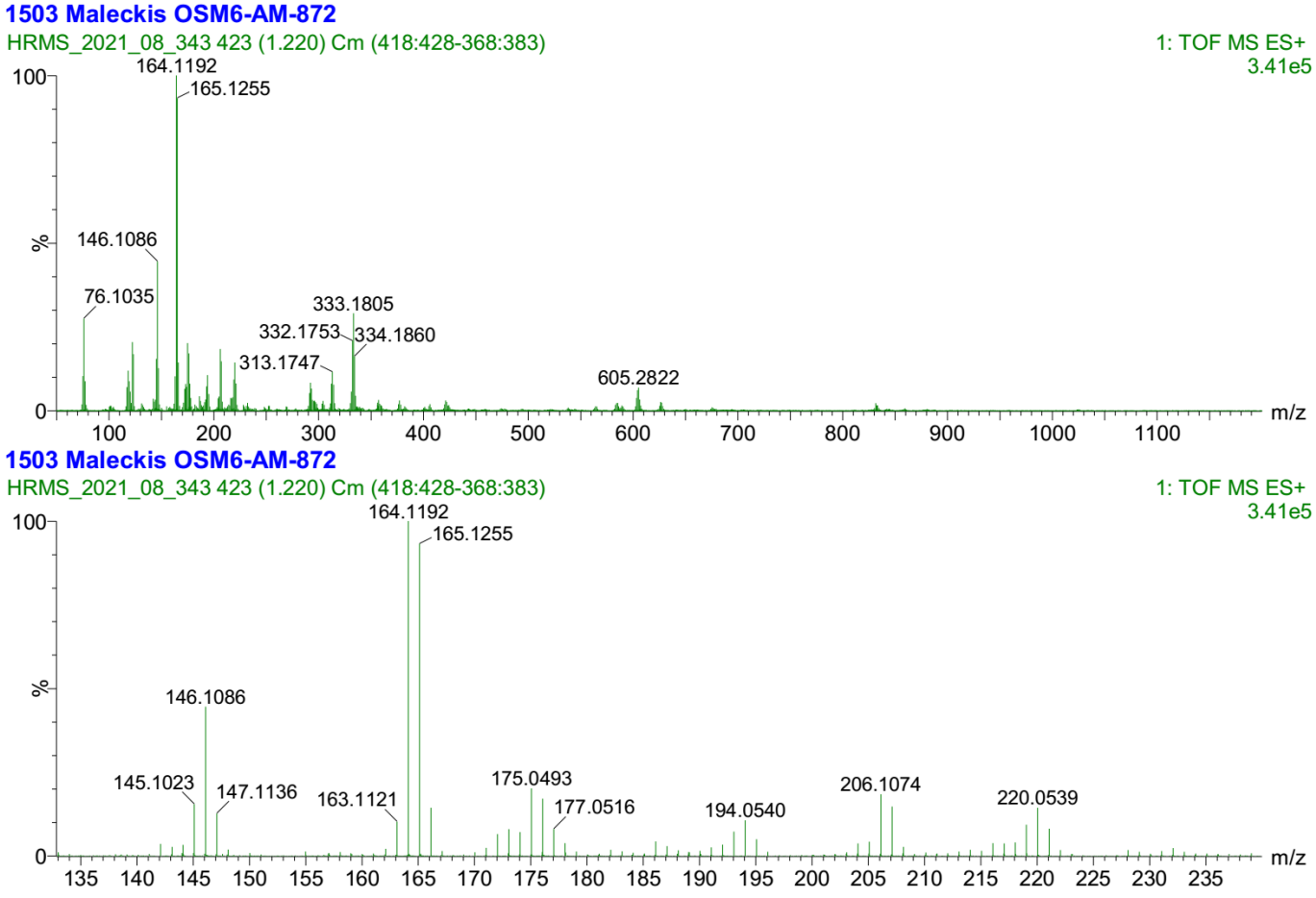
HRMS_2021_08_343 1503 Maleckis OSM6-AM-872
MS_POS_RES_4min ACN_Form_5-98_040_4min 1:F,2 1.000000 MS_Tune_4kV Col#66

Elemental Composition Report:

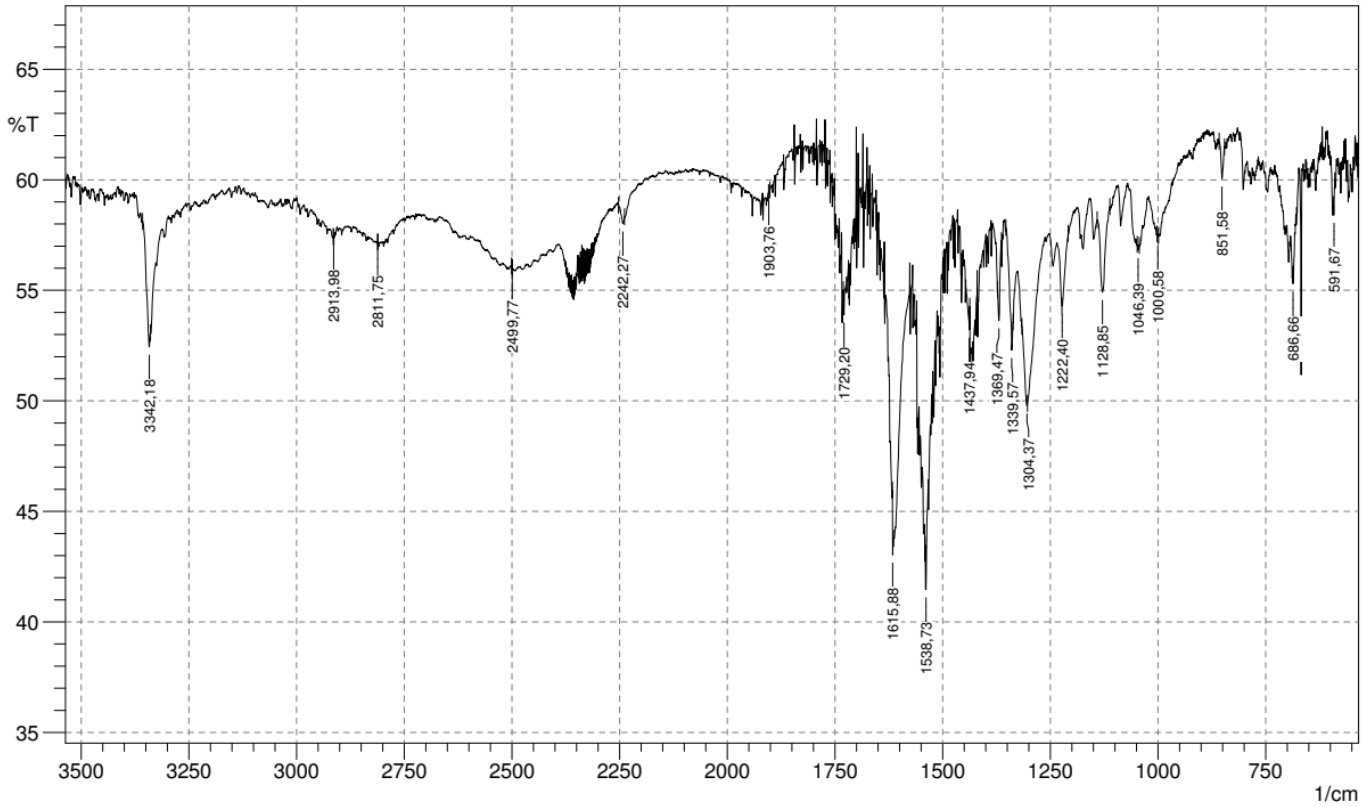
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
12630 formula(e) evaluated with 9 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 1H: 1-105 2H: 1-10 N: 0-10 O: 0-10 F: 1-1 Na: 0-1

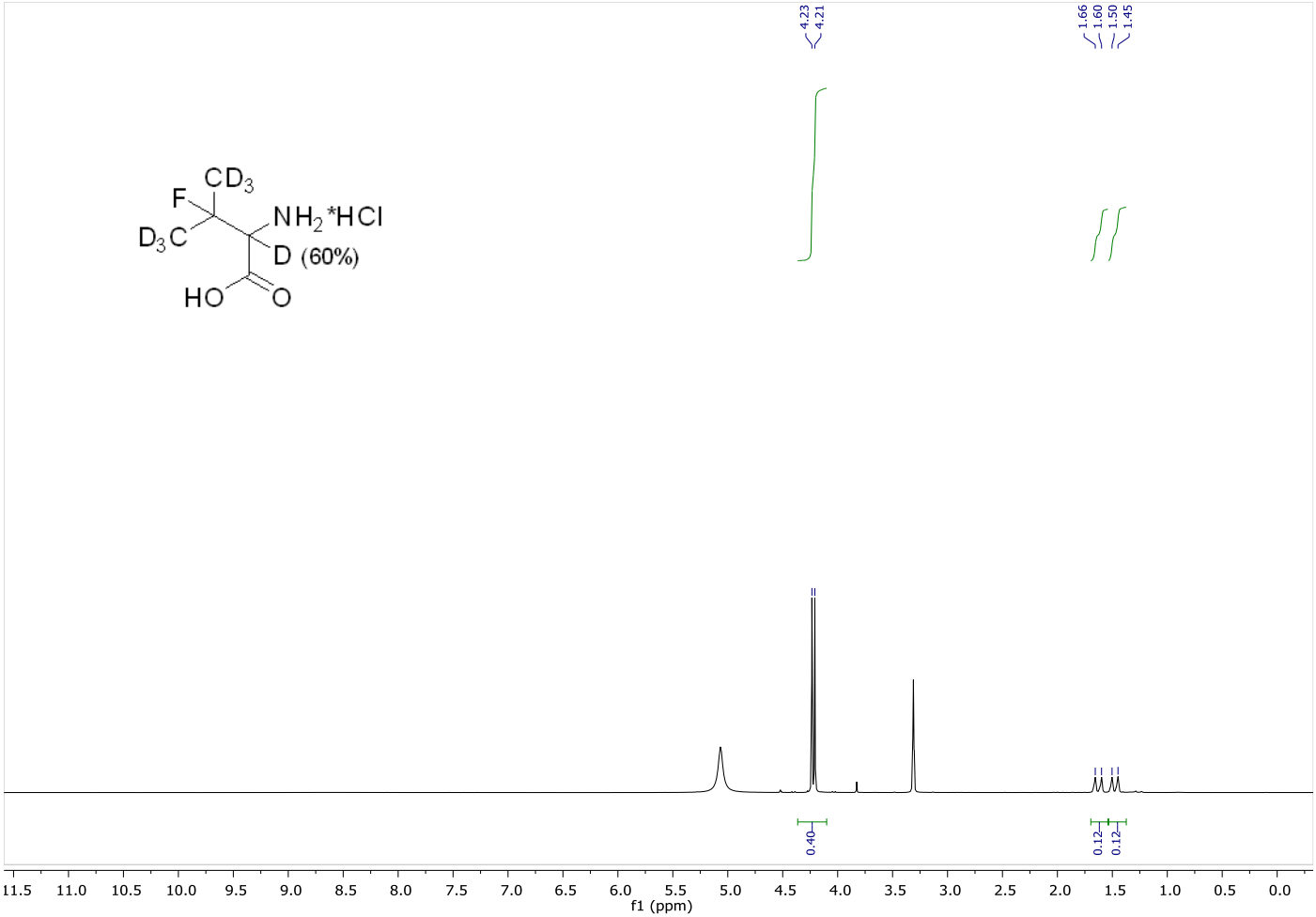
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
206.1074	100.00	206.1075	-0.1	-0.5	5.5	626.6	0.566	56.76	C3 1H 2H5 N10 F
		206.1073	0.1	0.5	5.5	628.0	1.972	13.92	C5 1H 2H6 N7 O F
		206.1076	-0.2	-1.0	1.5	628.5	2.435	8.76	C7 1H6 2H6 N O3 F Na
		206.1071	0.3	1.5	5.5	628.3	2.221	10.85	C7 1H 2H7 N4 O2 F
		206.1078	-0.4	-1.9	1.5	628.4	2.331	9.72	C5 1H6 2H5 N4 O2 F Na



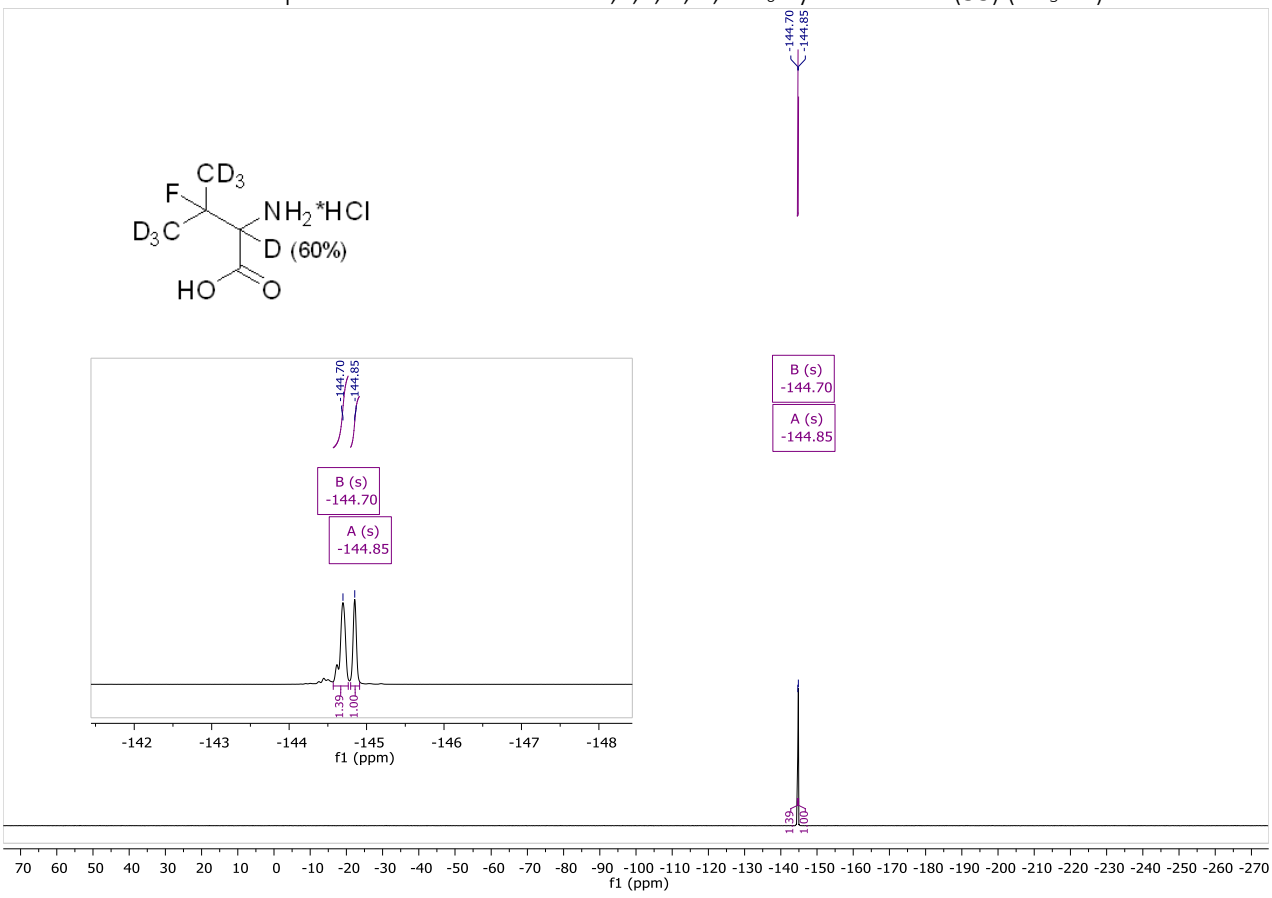
IR(ATR) spectrum of 2-acetamido-3-fluoro-3-(methyl-d_3)butanoic-4,4,4-d_3 acid (**52**)



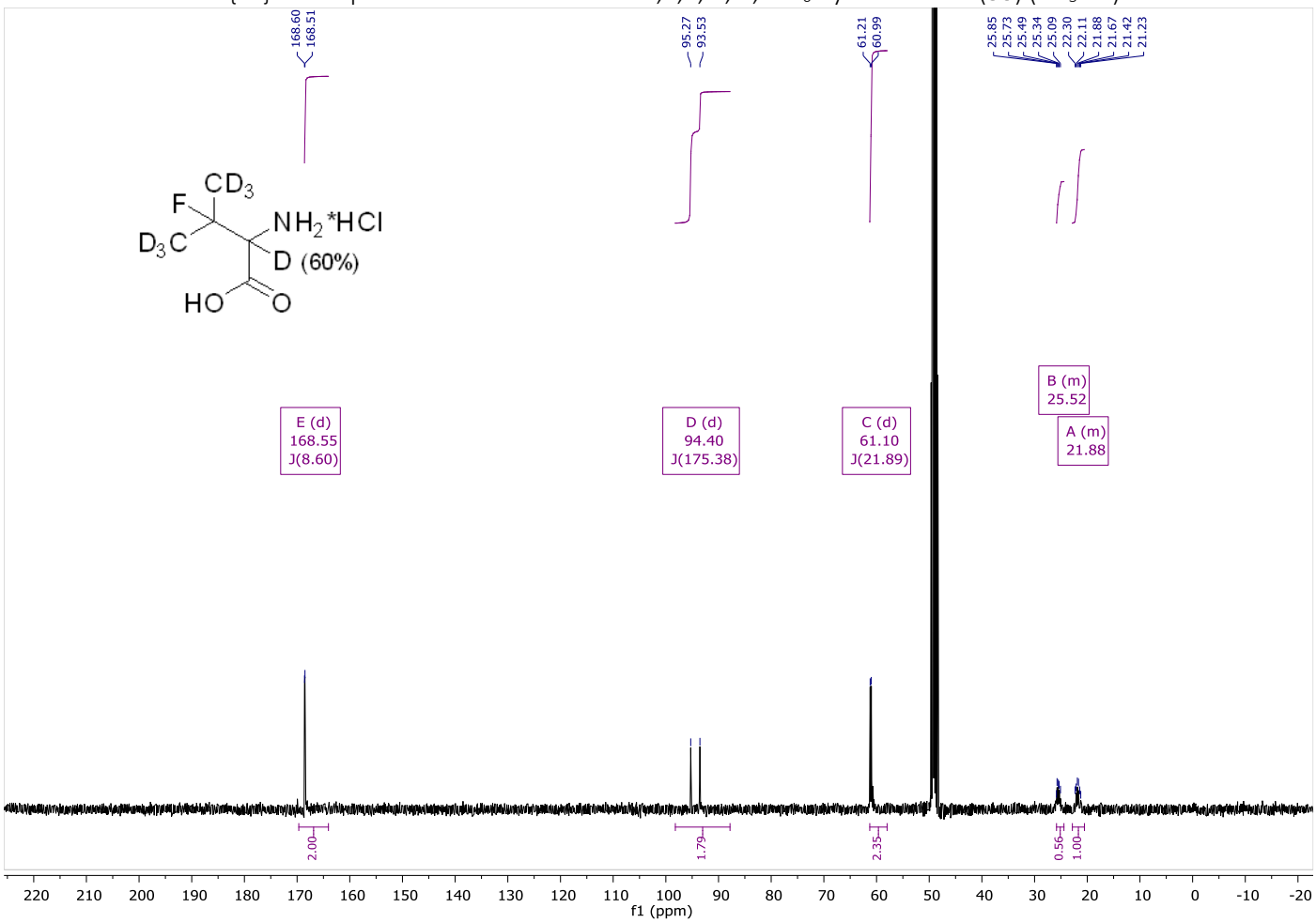
^{1}H NMR spectrum of 3-fluorovaline-4,4,4,4',4',4'-d_6 hydrochloride (**53**) (CD_3OD)



^{19}F NMR spectrum of 3-fluorovaline-4,4,4,4',4',4'-d_6 hydrochloride (**53**) (CD_3OD)



$^{13}C\{^{1}H\}$ NMR spectrum of 3-fluorovaline-4,4,4,4',4',4'-d_6 hydrochloride (**53**) (CD_3OD)



HRMS of 3-fluorovaline-4,4,4,4',4',4'-d_6 hydrochloride (**53**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	-
ESI-	Cone, V:	40			

Sample:

HRMS_2021_08_368 1505 Maleckis OSM6-AM-878

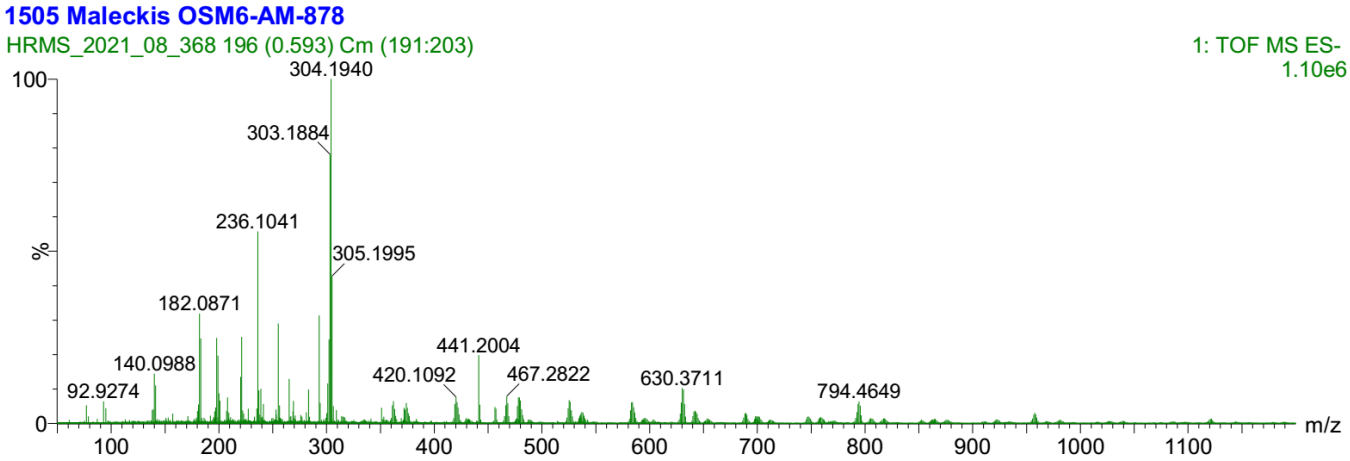
MS_NEG_RES_1min_infusion_bez_mob_f 0.000000 MS_Tune

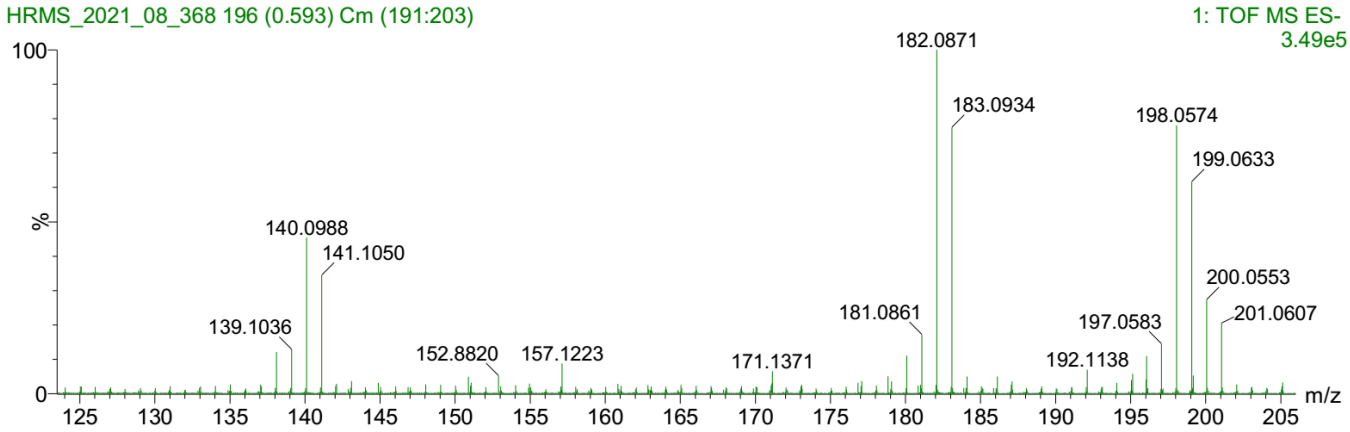
Elemental Composition Report:

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

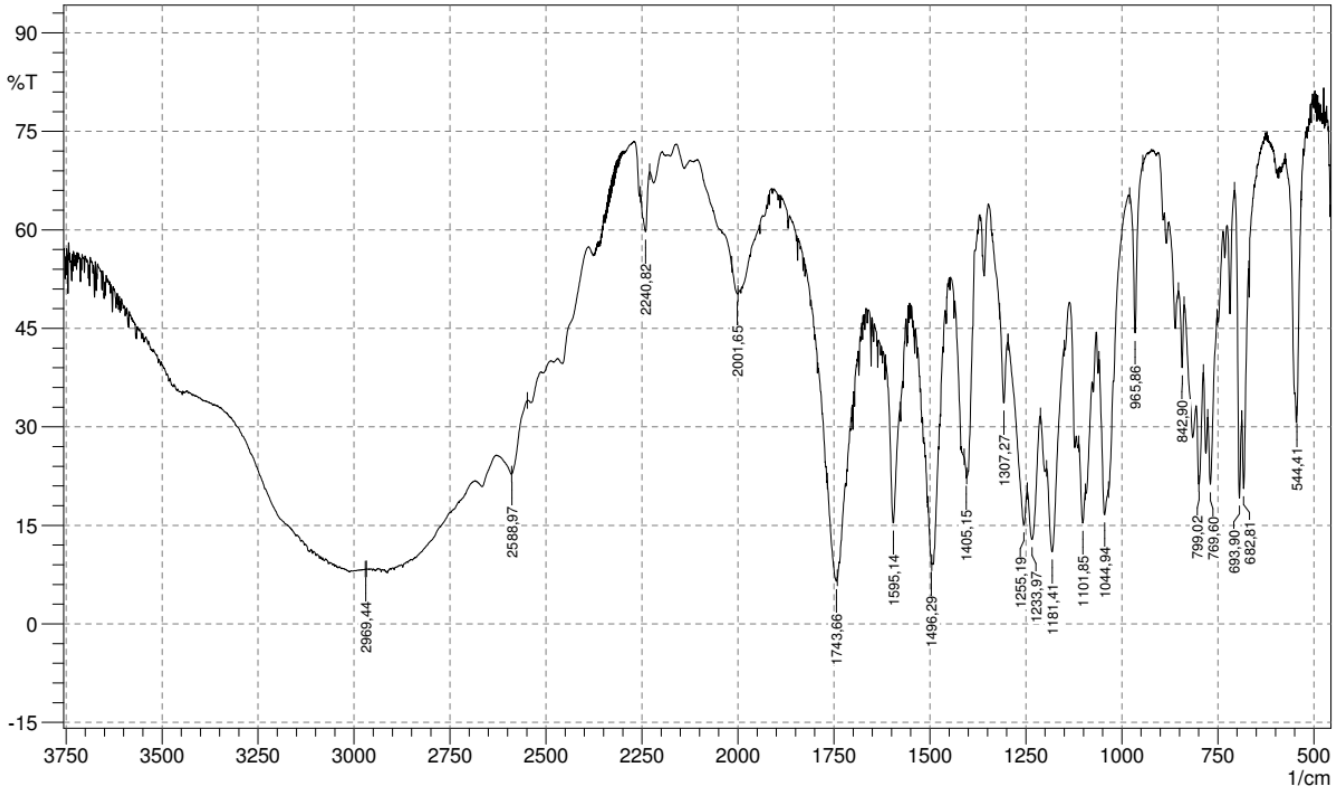
Monoisotopic Mass, Even Electron Ions
3315 formula(e) evaluated with 2 results within limits (up to 5 closest results for each mass)
Elements Used:
C: 0-100 N: 0-10 O: 0-10 F: 1-1 Na: 0-1 1H: 1-105 2H: 1-10

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
140.0988	100.00	140.0986	0.2	1.4	3.5	1420.8	0.915	40.06	C9 F 1H11 2H
		140.0994	-0.6	-4.3	1.5	1420.4	0.512	59.94	C5 N O2 F 1H3 2H6



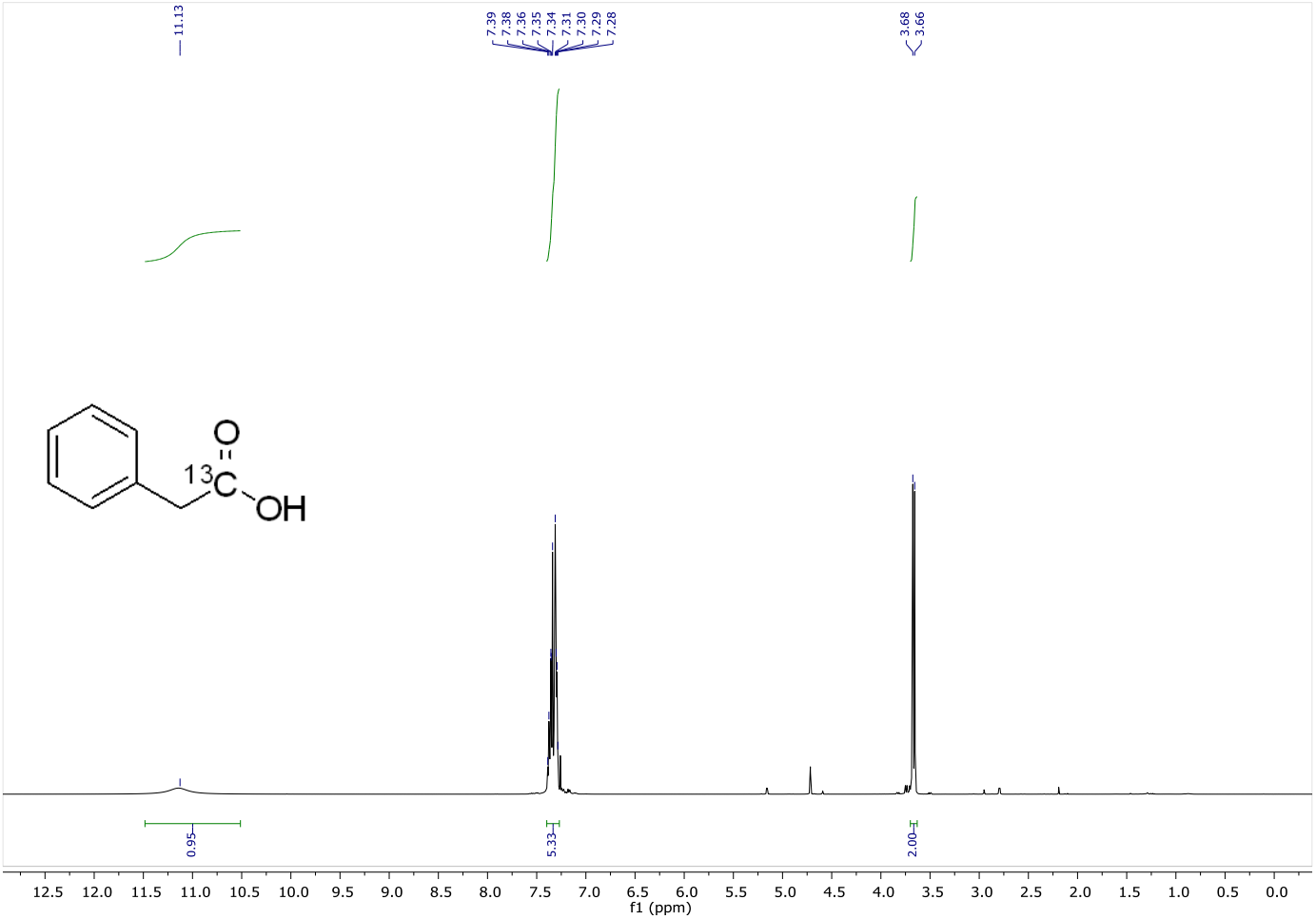


IR(ATR) spectrum of 3-fluorovaline-4,4,4,4',4',4'-d_6 hydrochloride (**53**)

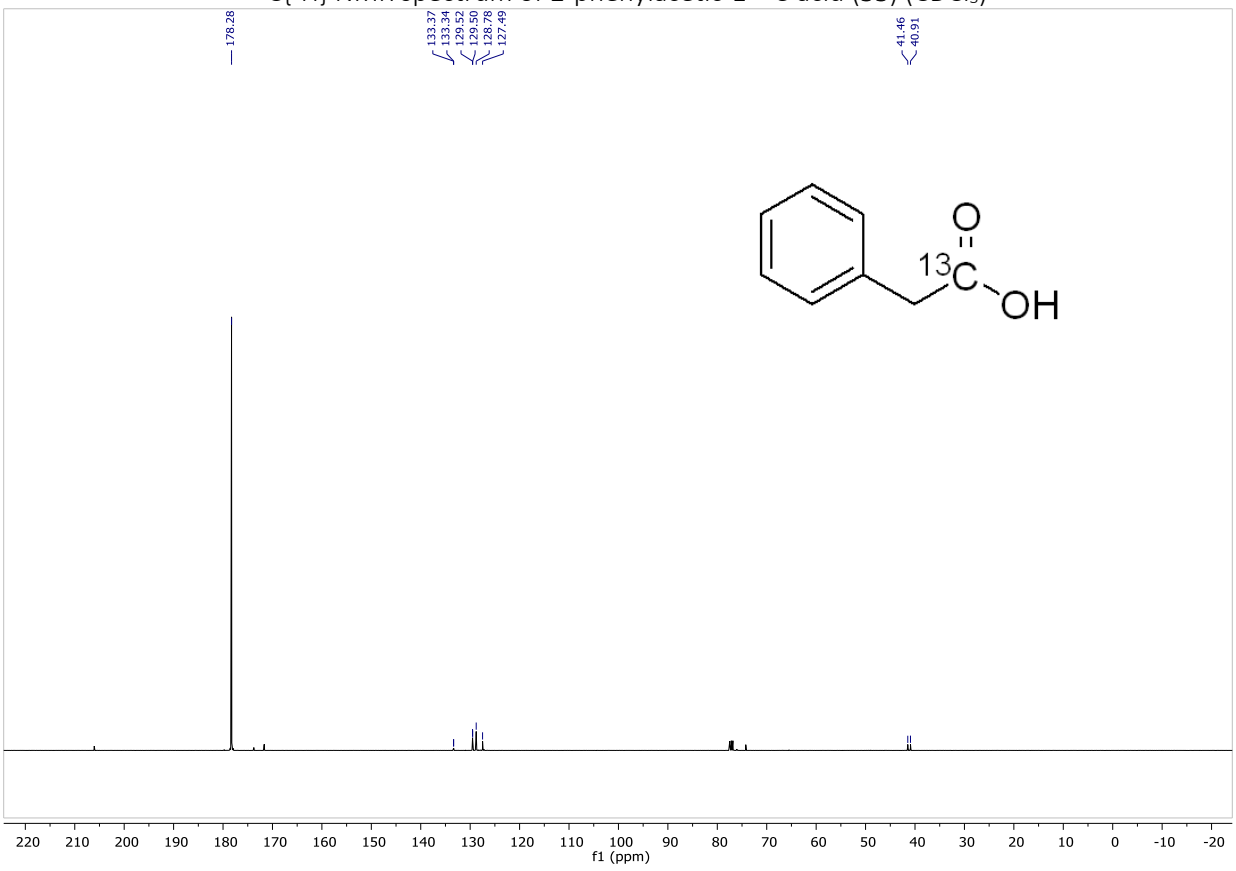


Spectra of compounds in Scheme 9

^{1}H NMR spectrum of 2-phenylacetic-1-^{13}*C* acid (**55**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of 2-phenylacetic-1-^{13}*C* acid (**55**) ($CDCl_3$)



HRMS of 2-phenylacetic-1-^{13}C acid (**55**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

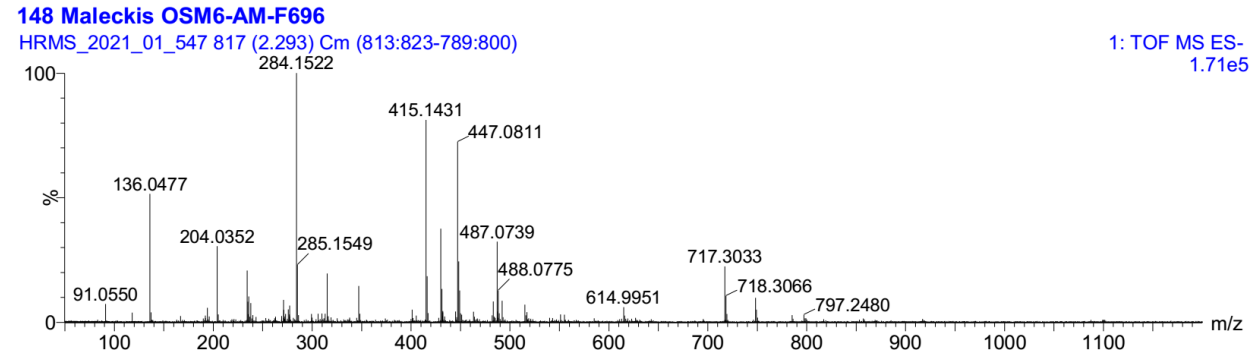
HRMS_2021_01_547	148 Maleckis OSM6-AM-F696				
MS_NEG_RES_4min	ACN_Form_5-98_040_4min	1:F,2	1.000000	MS_Tune	Col#66

Elemental Composition Report:

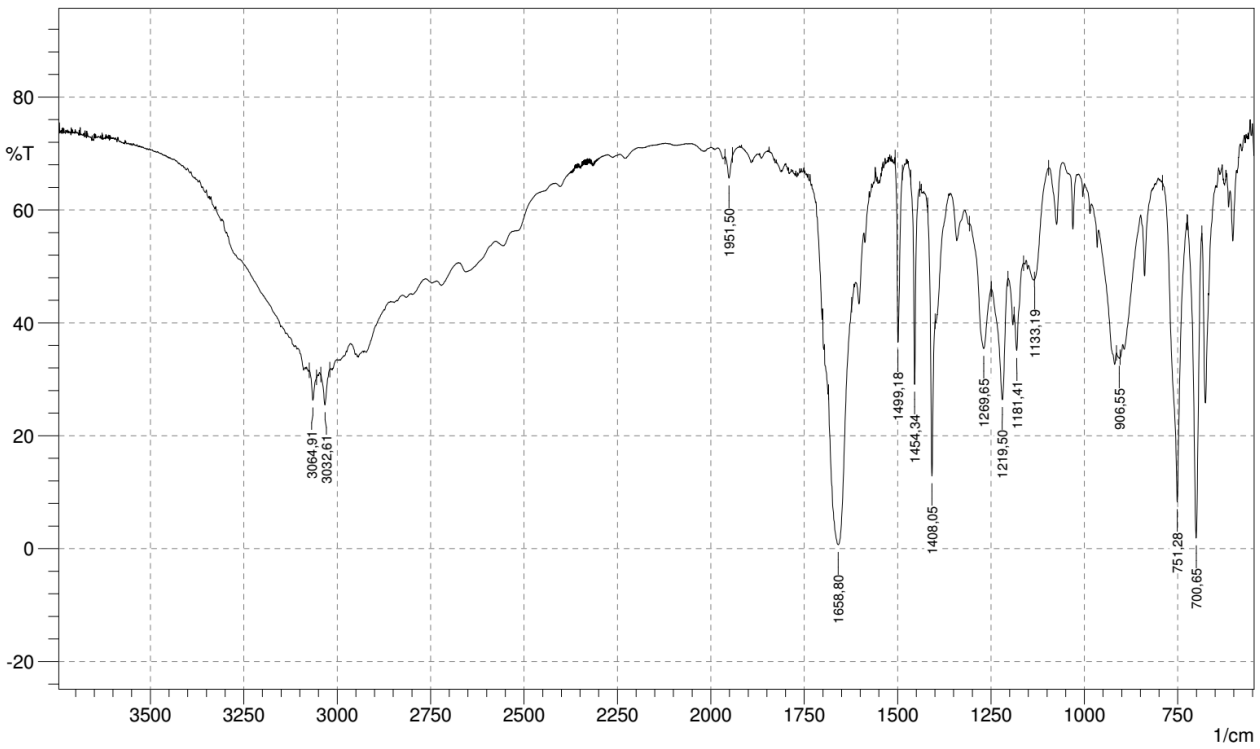
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
439 formula(e) evaluated with 2 results within limits (up to 5 closest results for each mass)
Elements Used:
H: 0-100 N: 0-15 O: 0-30 12C: 1-50 13C: 0-2

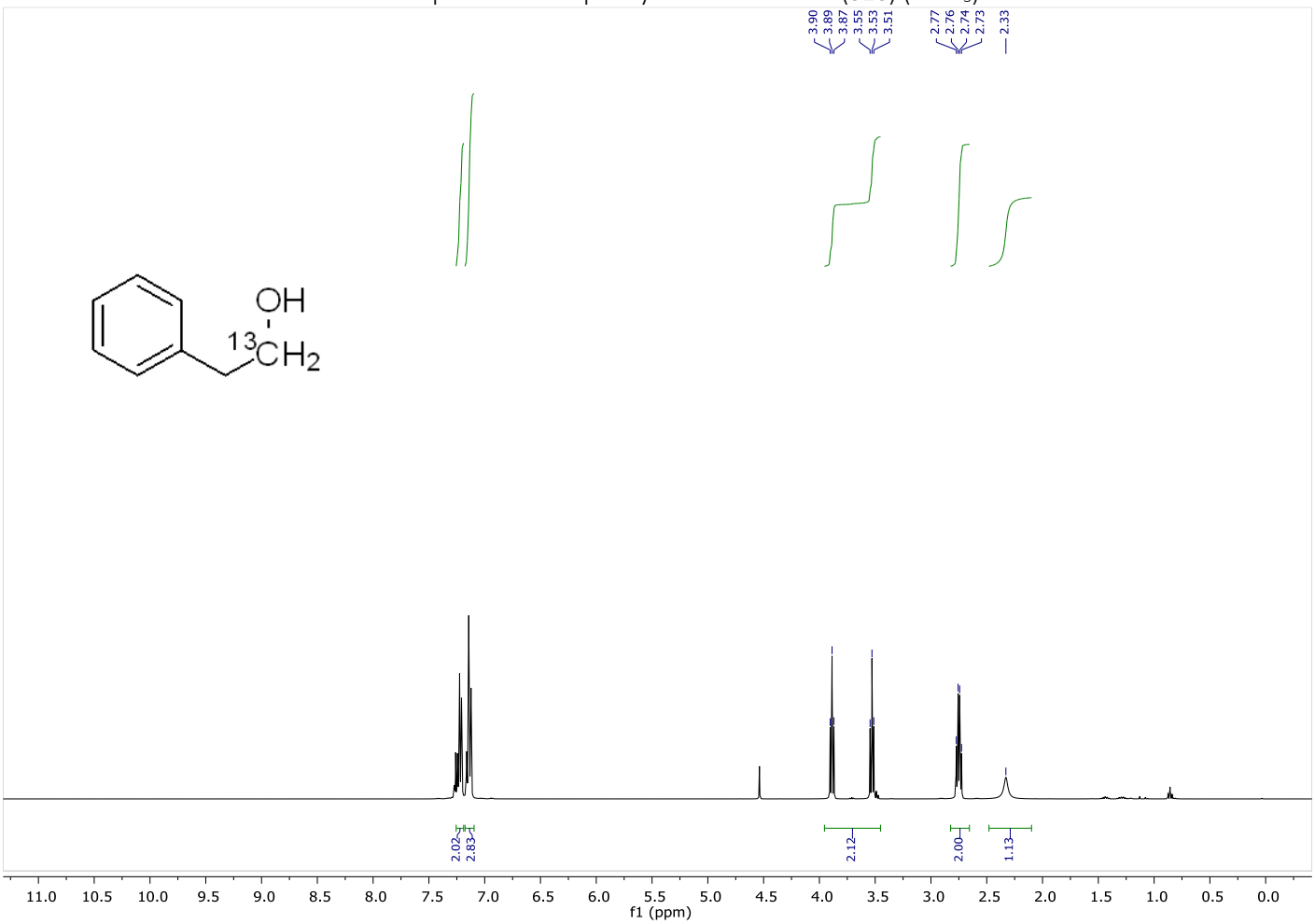
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
136.0477	100.00	136.0480	-0.3	-2.2	5.5	655.6	0.534	58.64	H7 O2 12C7 13C
		136.0471	0.6	4.4	1.5	655.9	0.883	41.36	H6 N5 O3 12C



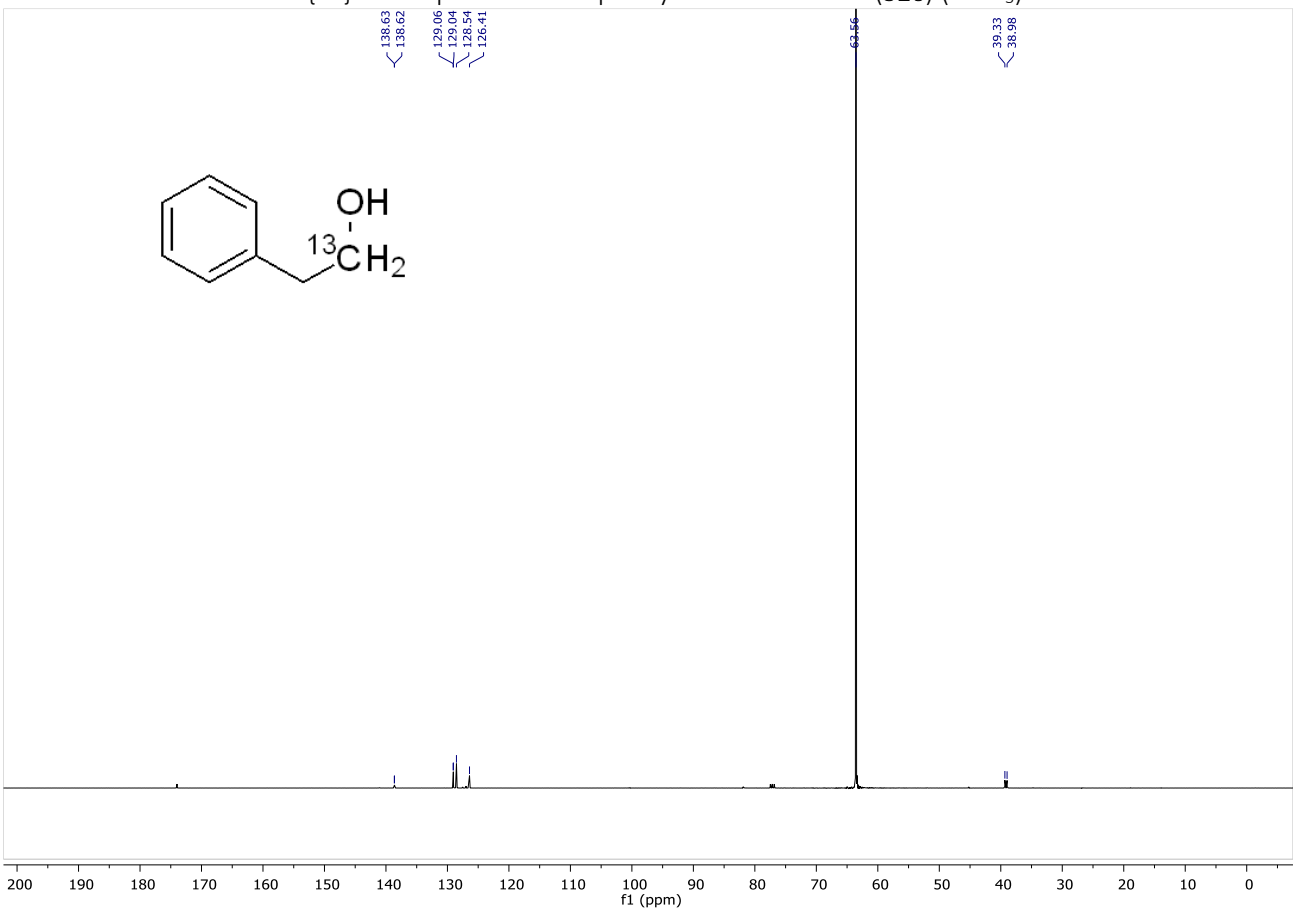
IR(ATR) spectrum of 2-phenylacetic-1-^{13}C acid (**55**)



^{1}H NMR spectrum of 2-phenylethan-1-ol-1-^{13}*C* (**S16**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of 2-phenylethan-1-ol-1-^{13}*C* (**S16**) ($CDCl_3$)



GC-MS of 2-phenylethan-1-ol-1-^{13}C (**S16**)

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File        :D:\DATA_2021\01-Jan-2021\28_14985.D
Operator    : E
Acquired    : 28 Jan 2021  14:19      using AcqMethod LAURA.M
Instrument :    GCMS
Sample Name: Maleckis OSM6-AM-F697
Misc Info  :
Vial Number: 26
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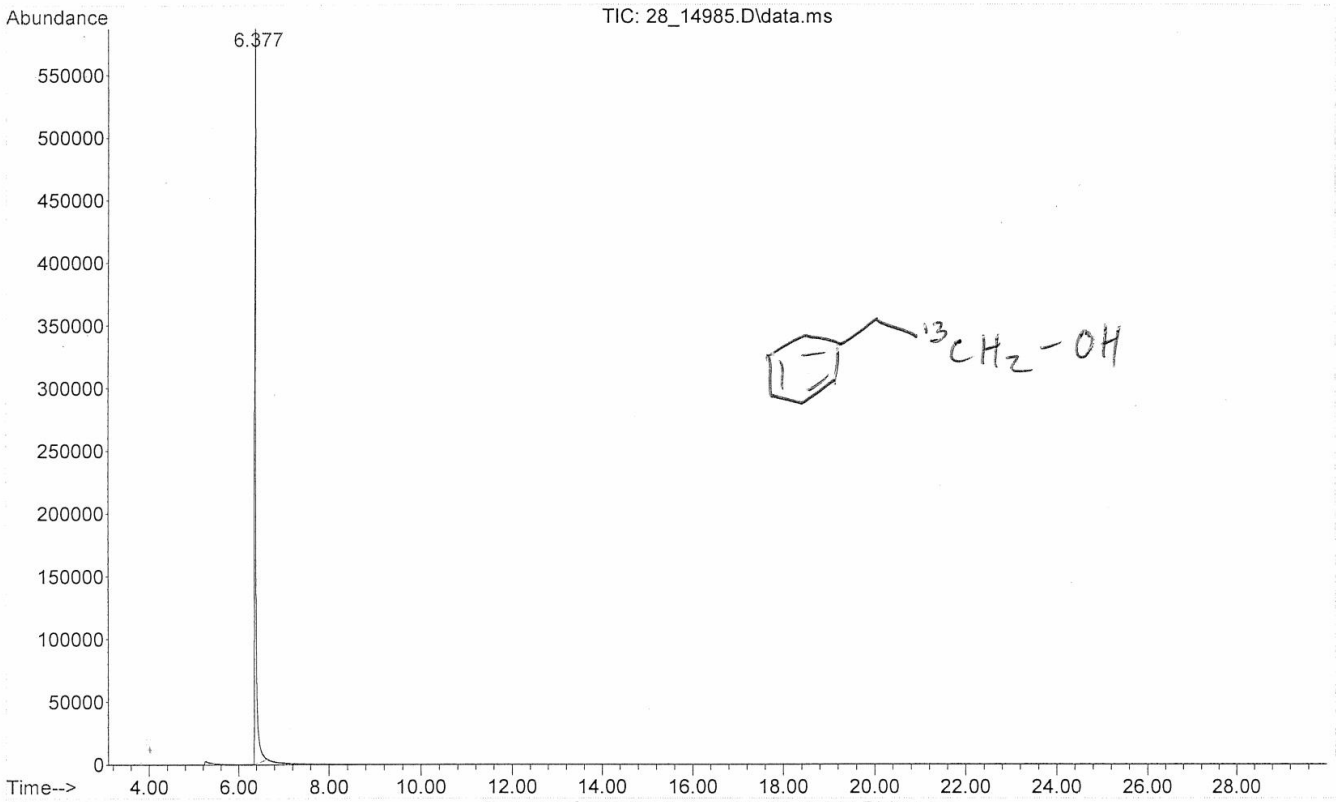
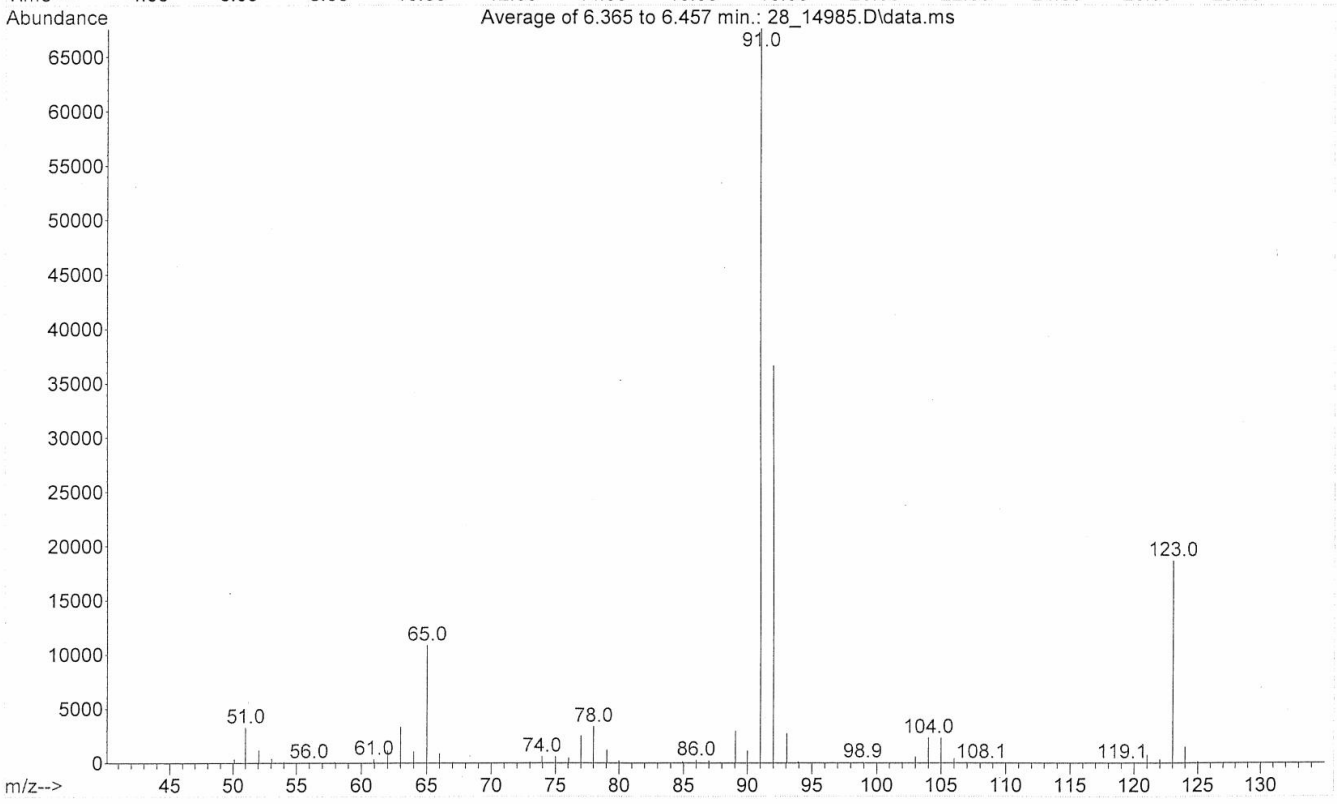
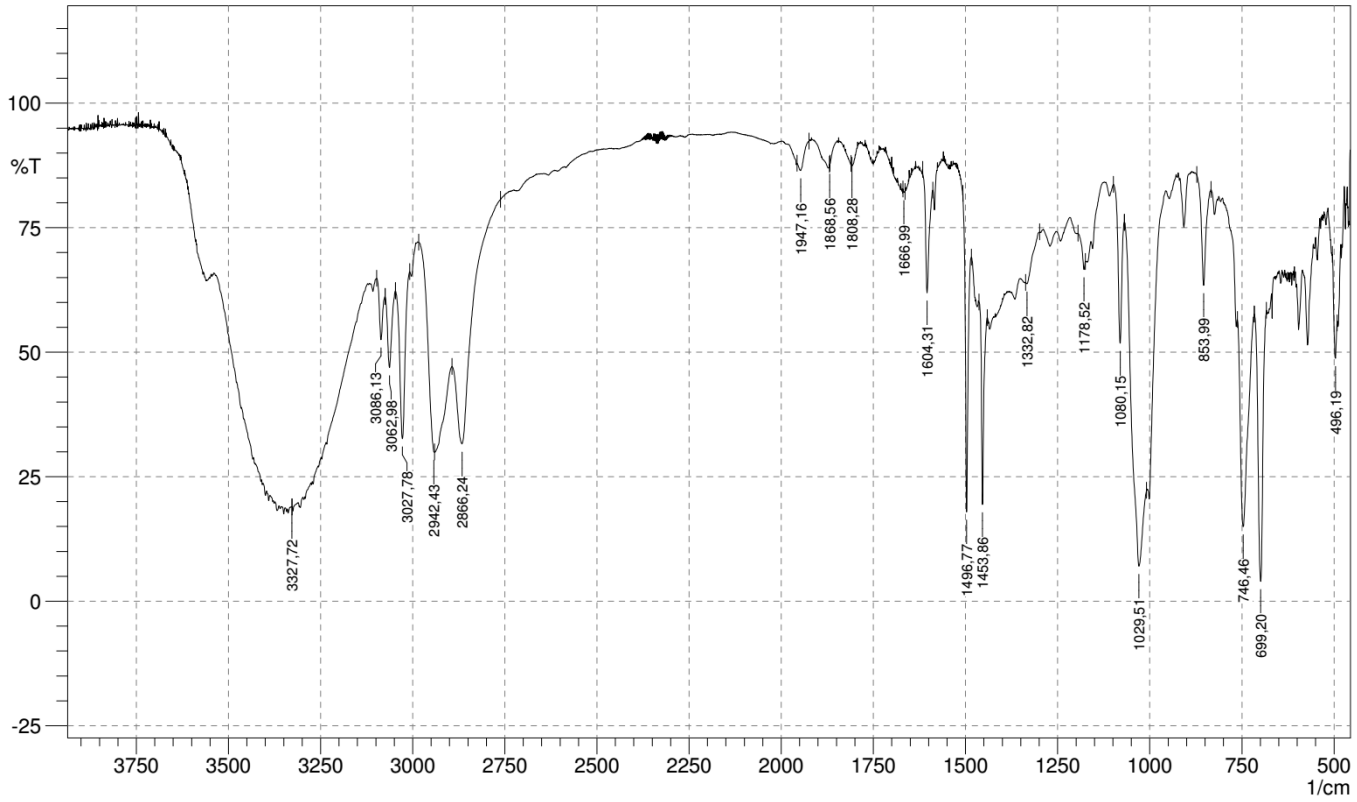
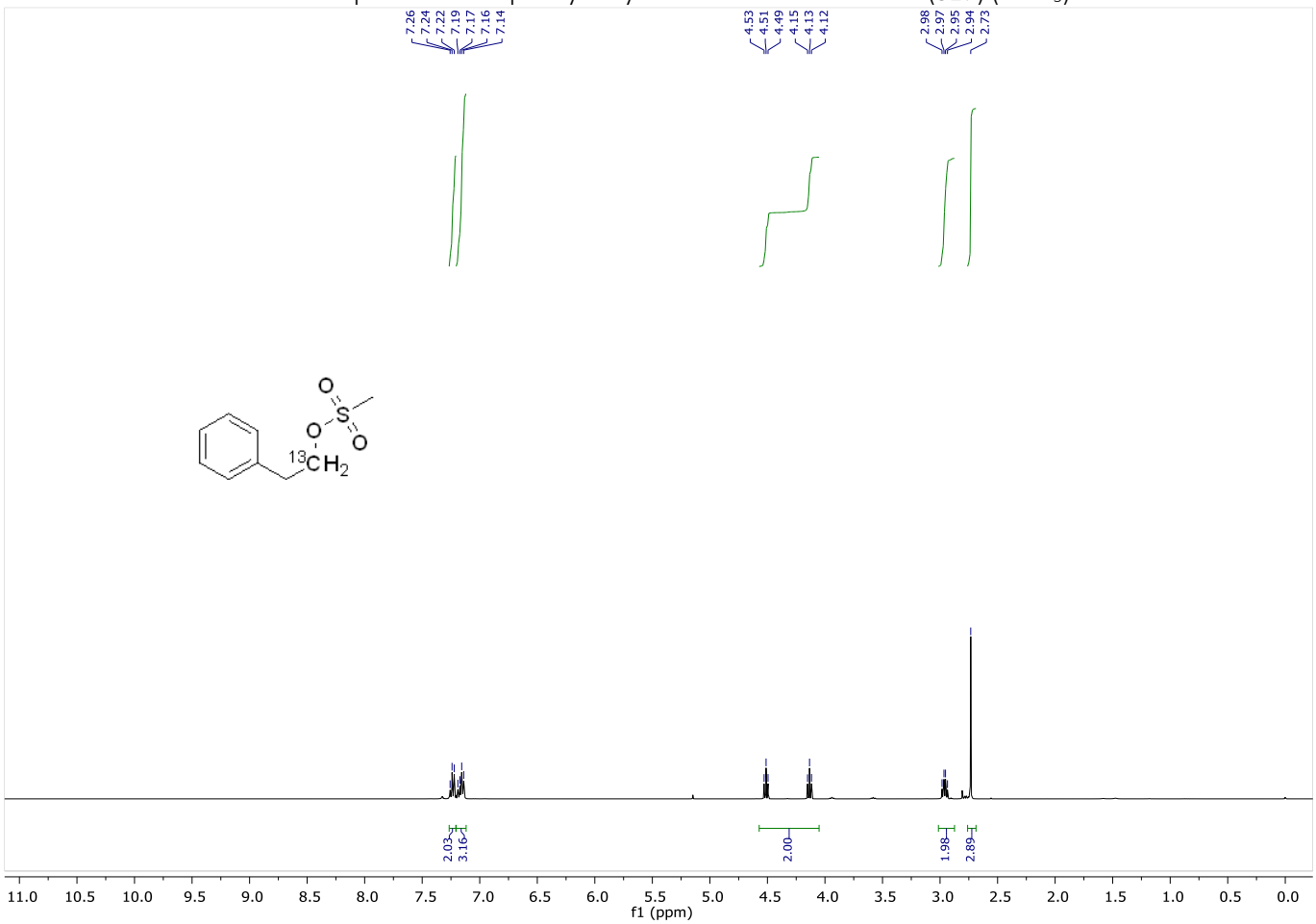




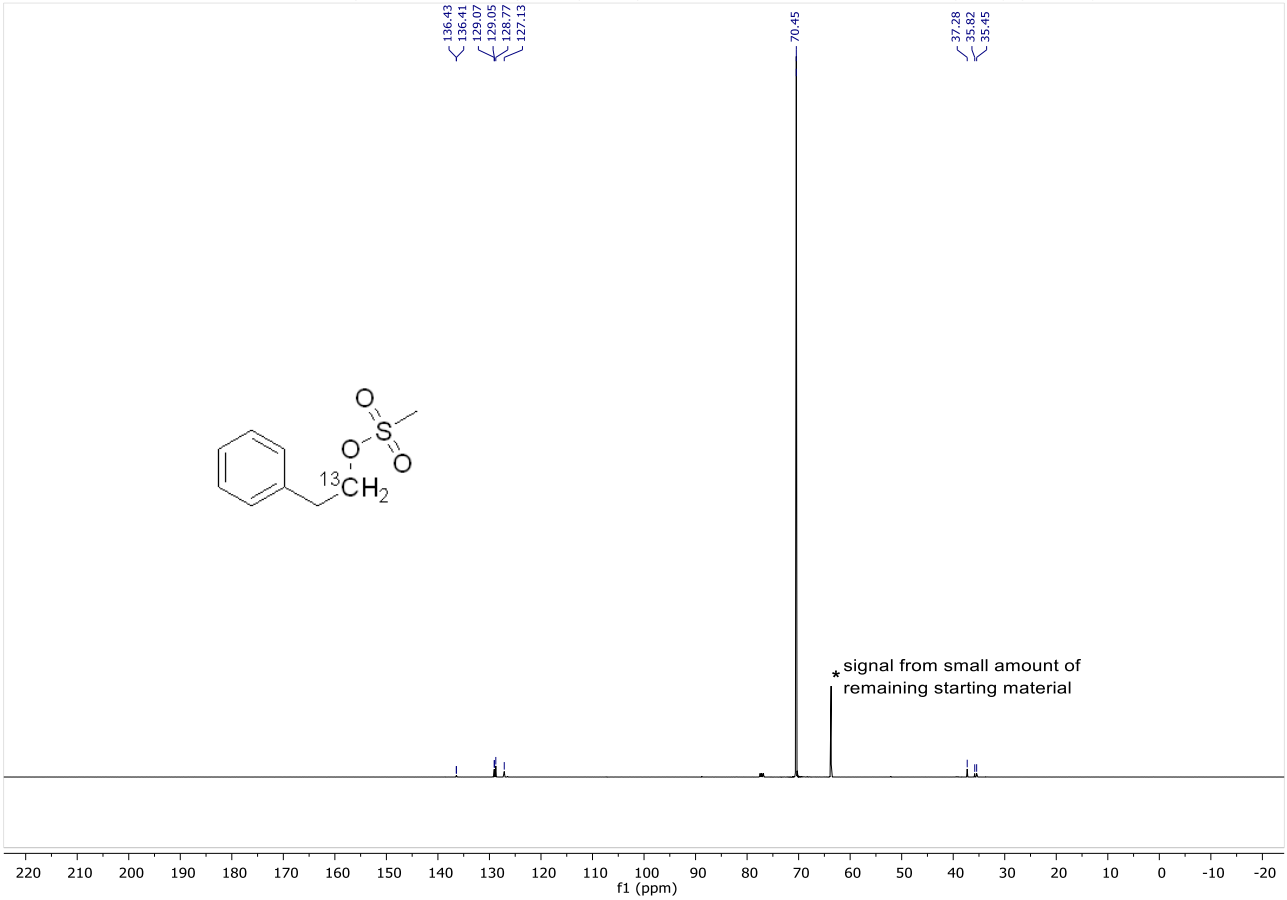
IR(ATR) spectrum of 2-phenylethan-1-ol-1-^{13}C (**S16**)



^{1}H NMR spectrum of 2-phenylethyl-1-^{13}*C* methanesulfonate (**S17**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of 2-phenylethyl-1-^{13}*C* methanesulfonate (**S17**) ($CDCl_3$)



GC-MS of 2-phenylethyl-1-^{13}C methanesulfonate (**S17**)

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Acquired    :  4 Feb 2021  13:10      using AcqMethod LAURA.M
Instrument  :    GCMS
Sample Name: Maleckis OSM6-AM-F699
Misc Info   :
Vial Number: 43
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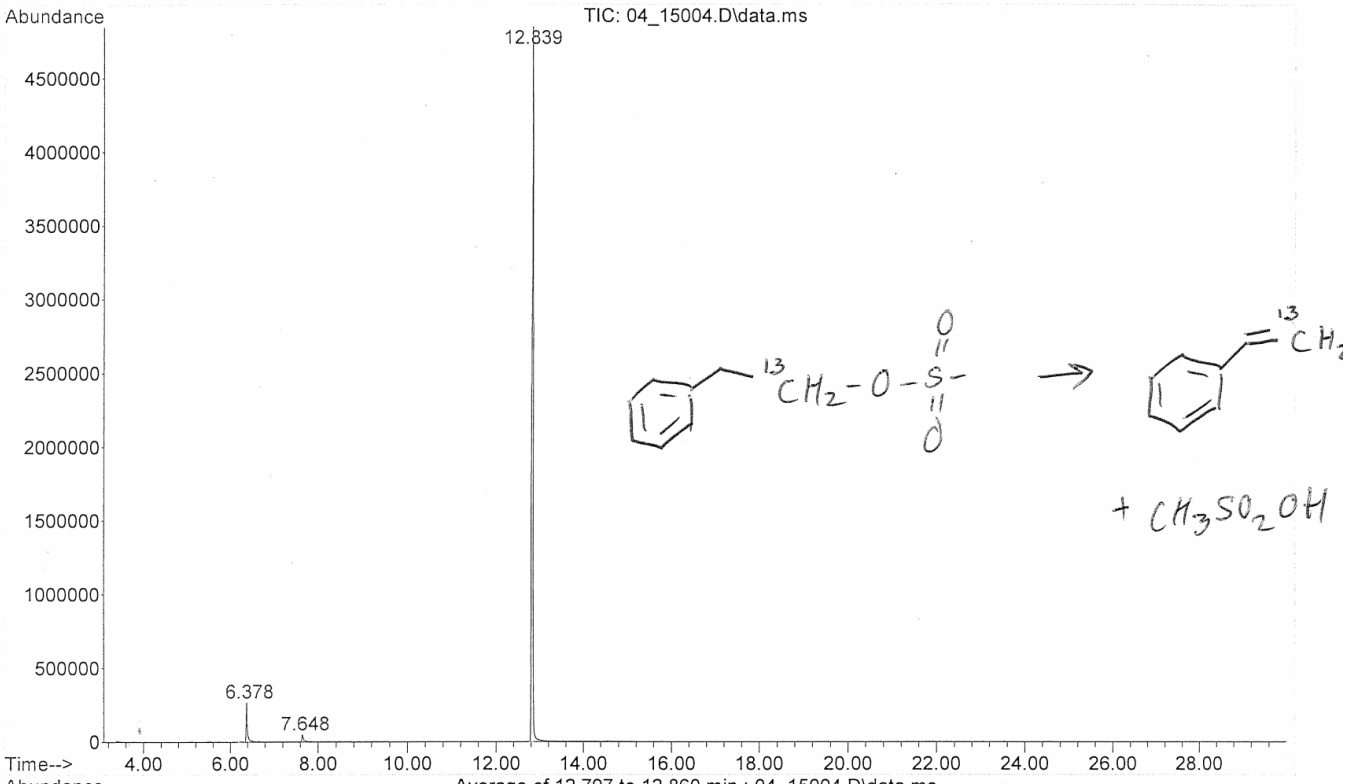
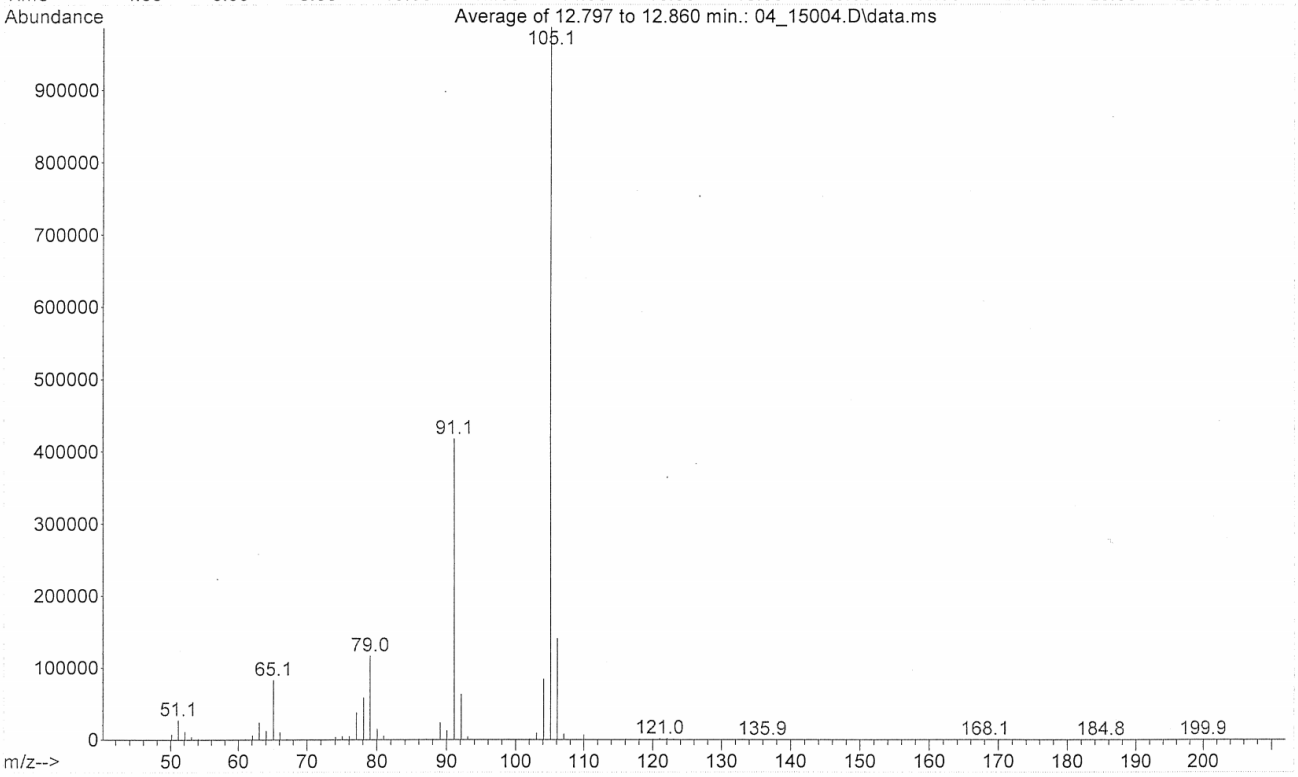
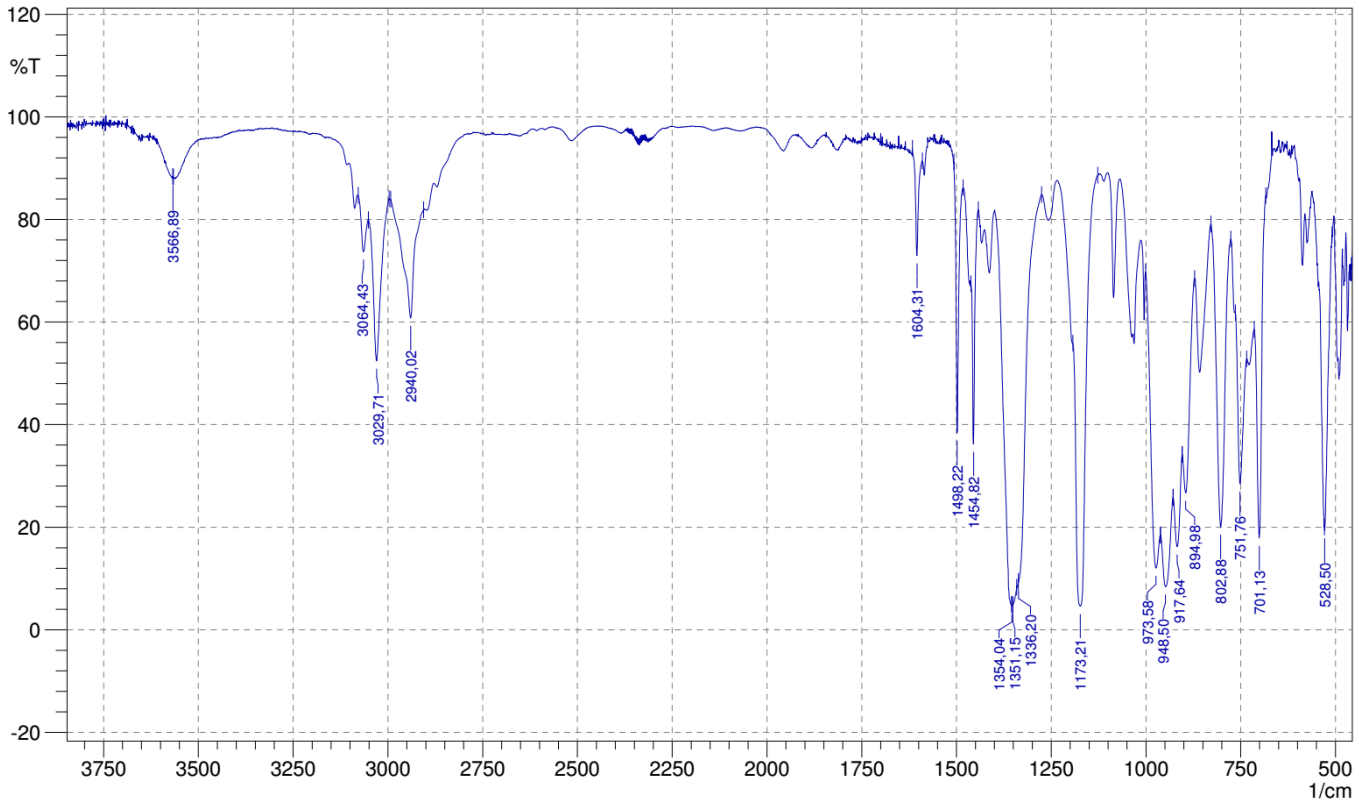
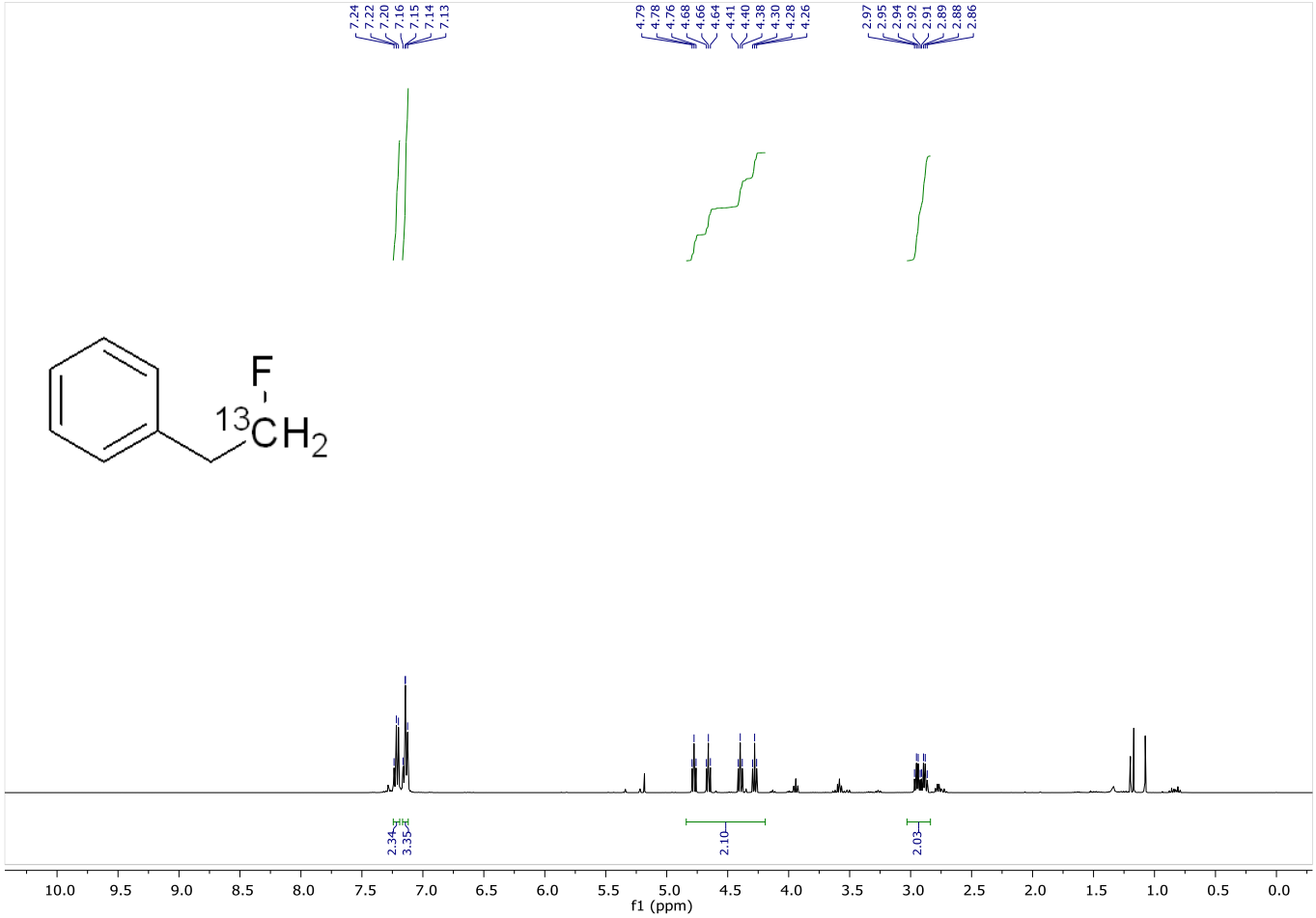




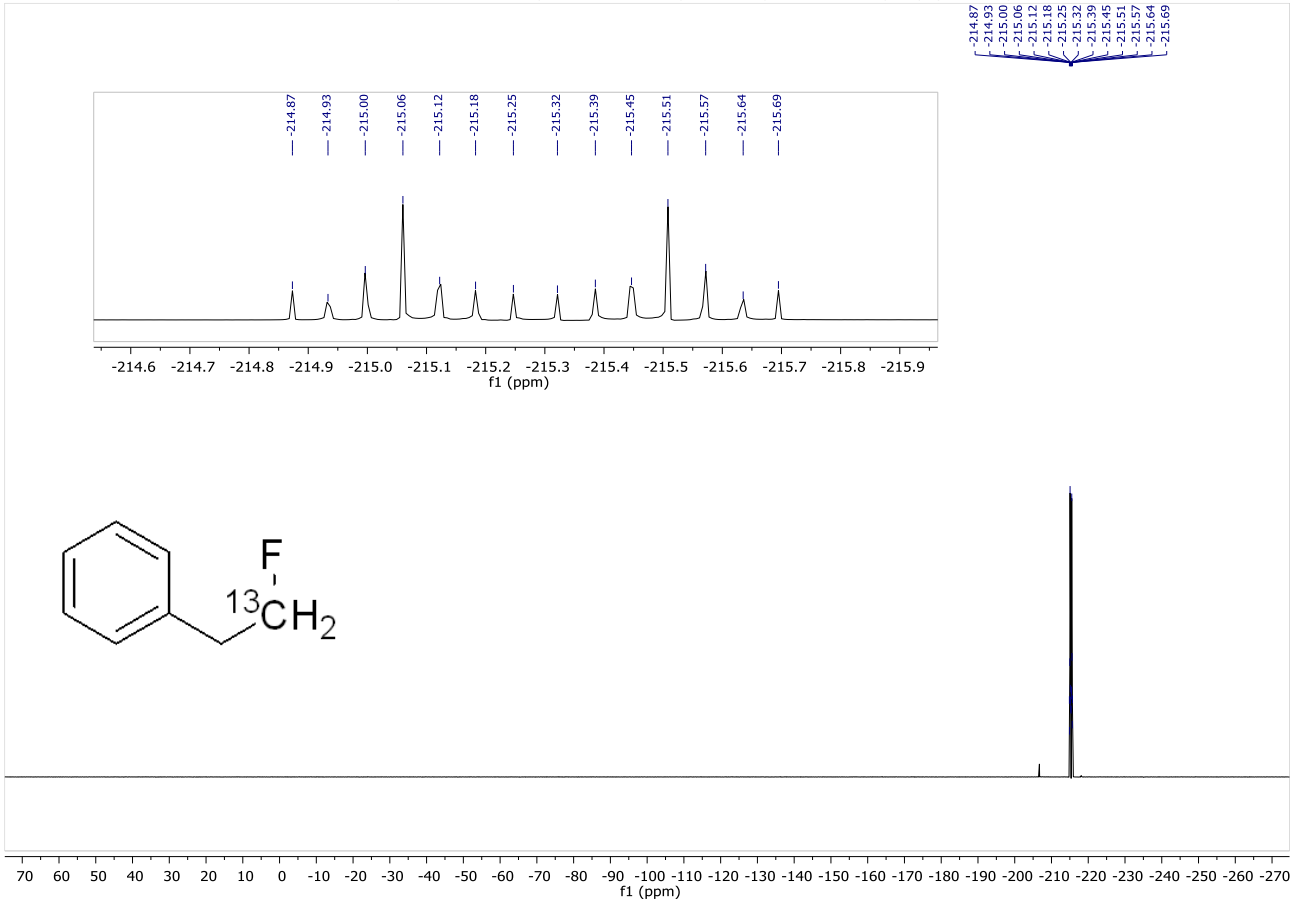
IR(ATR) spectrum of 2-phenylethyl-1-^{13}C methanesulfonate (**S17**)



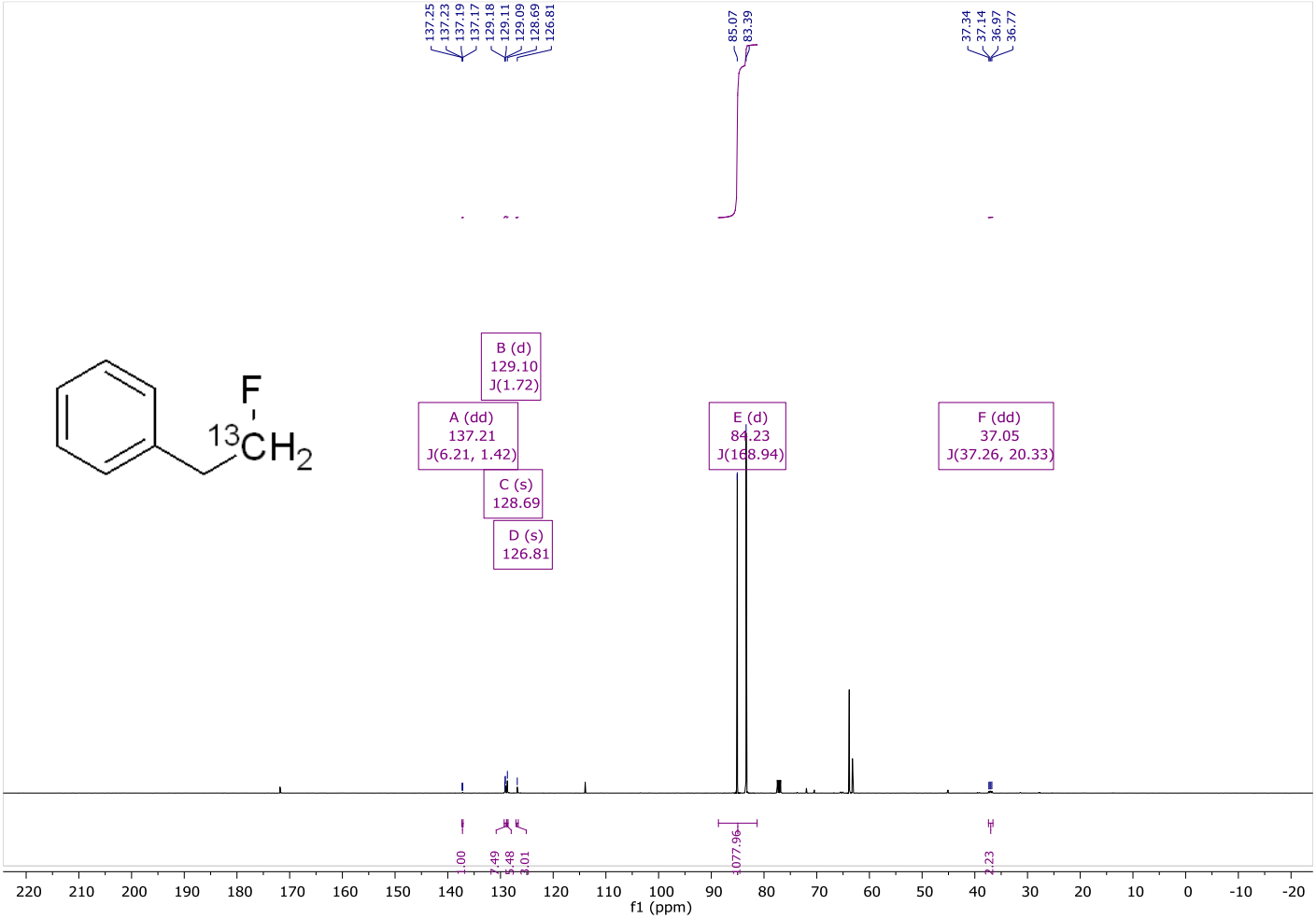
^{1}H NMR spectrum of (2-fluoroethyl-2-^{13}*C*)benzene (**56**) ($CDCl_3$)



^{19}F NMR spectrum of (2-fluoroethyl-2-^{13}*C*)benzene (**56**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (2-fluoroethyl-2-^{13}C)benzene (**56**) ($CDCl_3$)



GC-MS of (2-fluoroethyl-2-^{13}C)benzene (**56**)

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File        :D:\DATA_2021\01-Jan-2021\28_14987.D
Operator    : E
Acquired    : 28 Jan 2021  15:26     using AcqMethod LAURA.M
Instrument :    GCMS
Sample Name: Maleckis OSM6-AM-F700
Misc Info  :
Vial Number: 28
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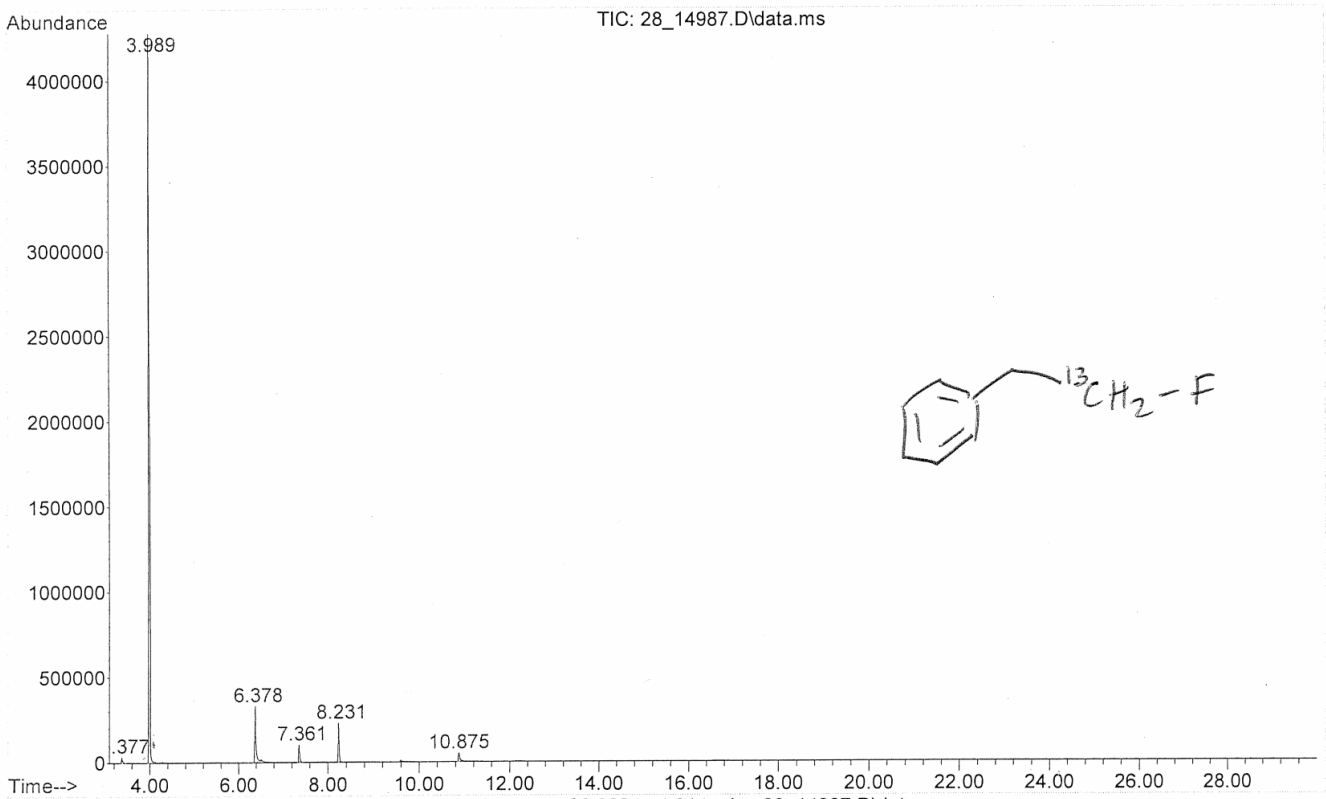
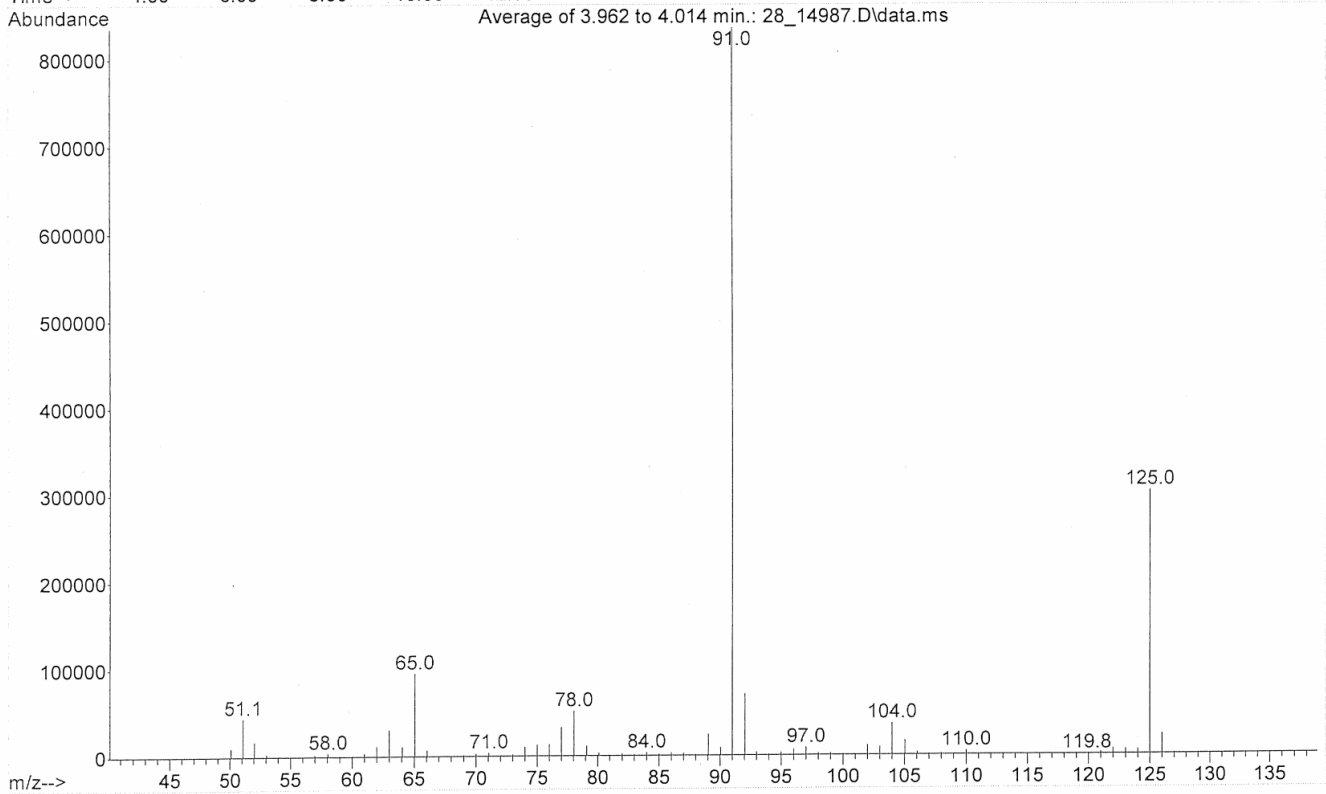
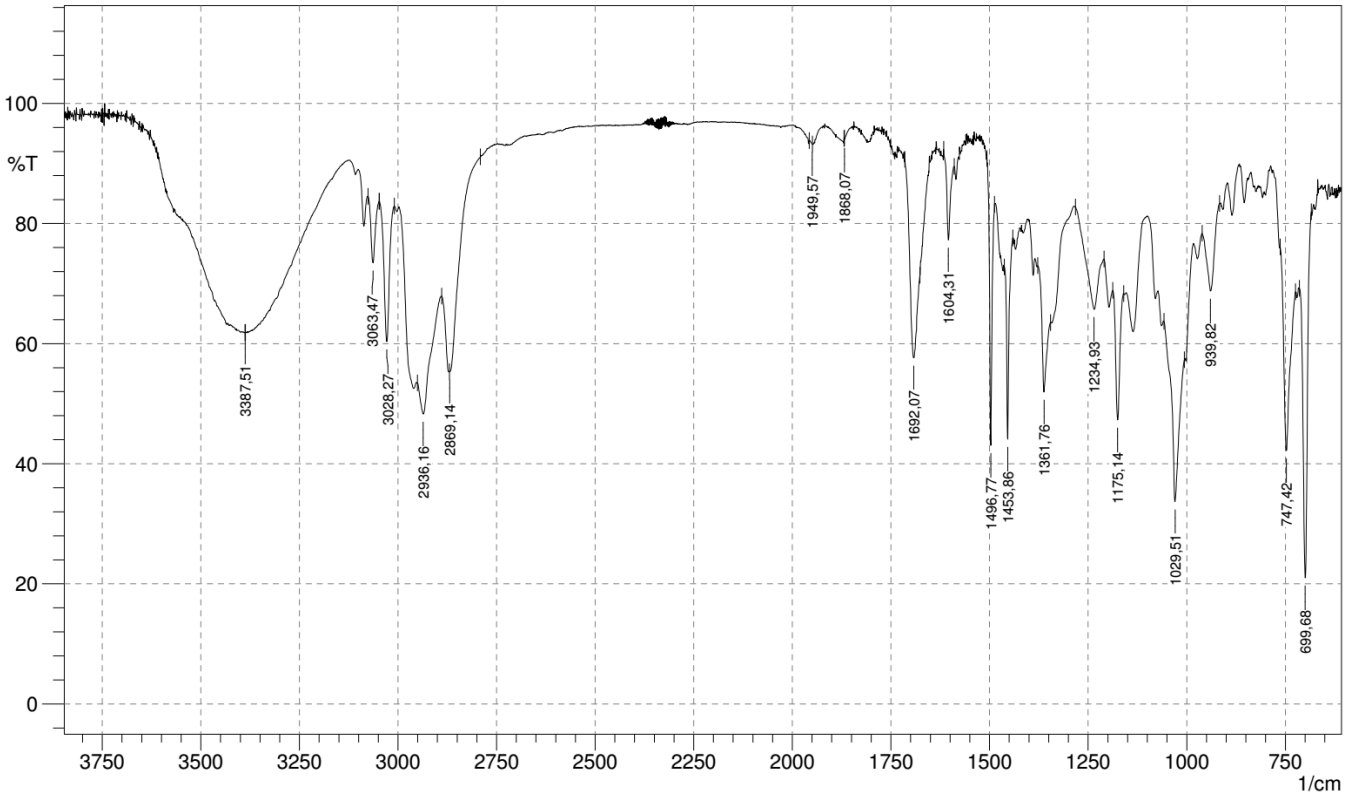
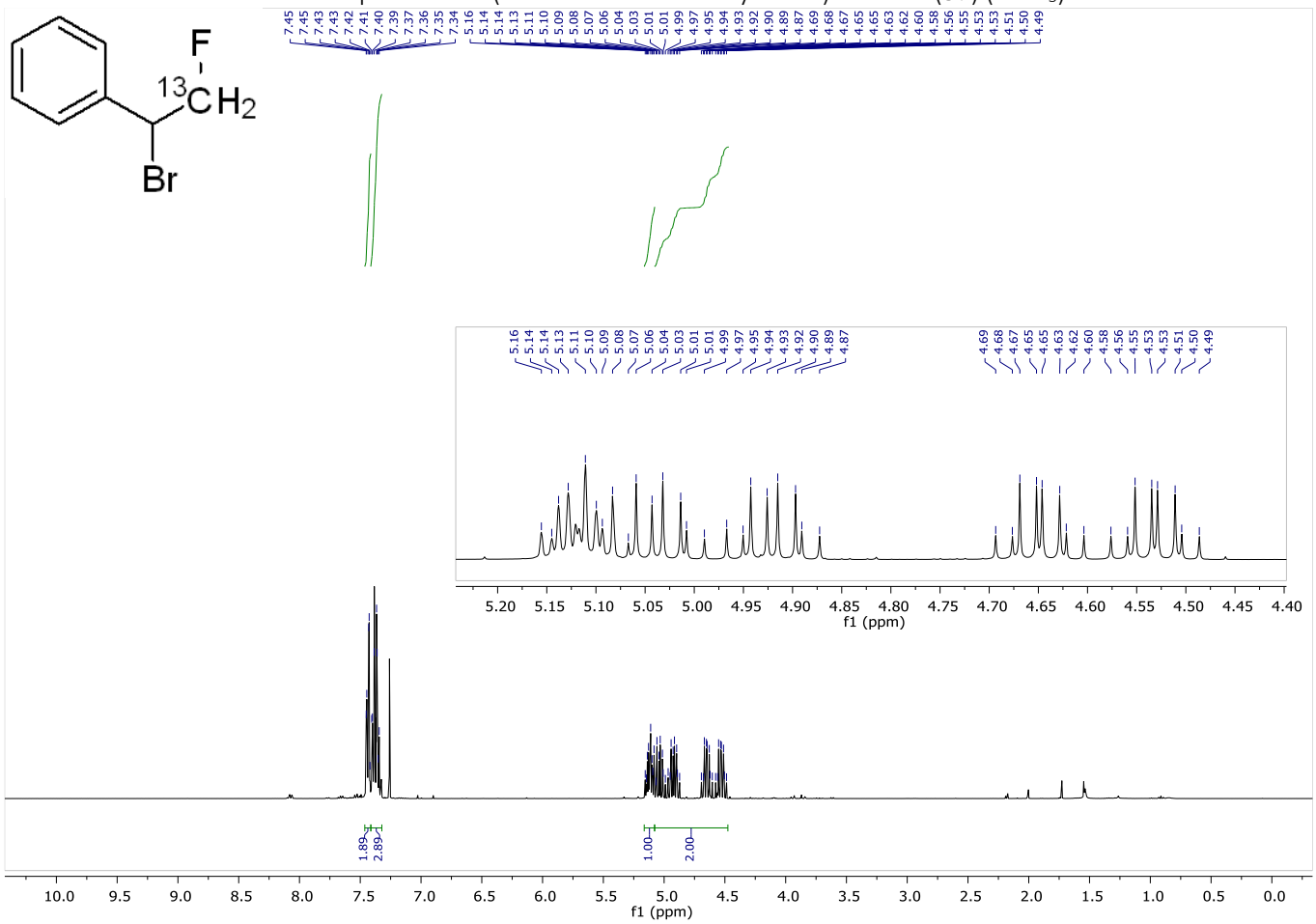




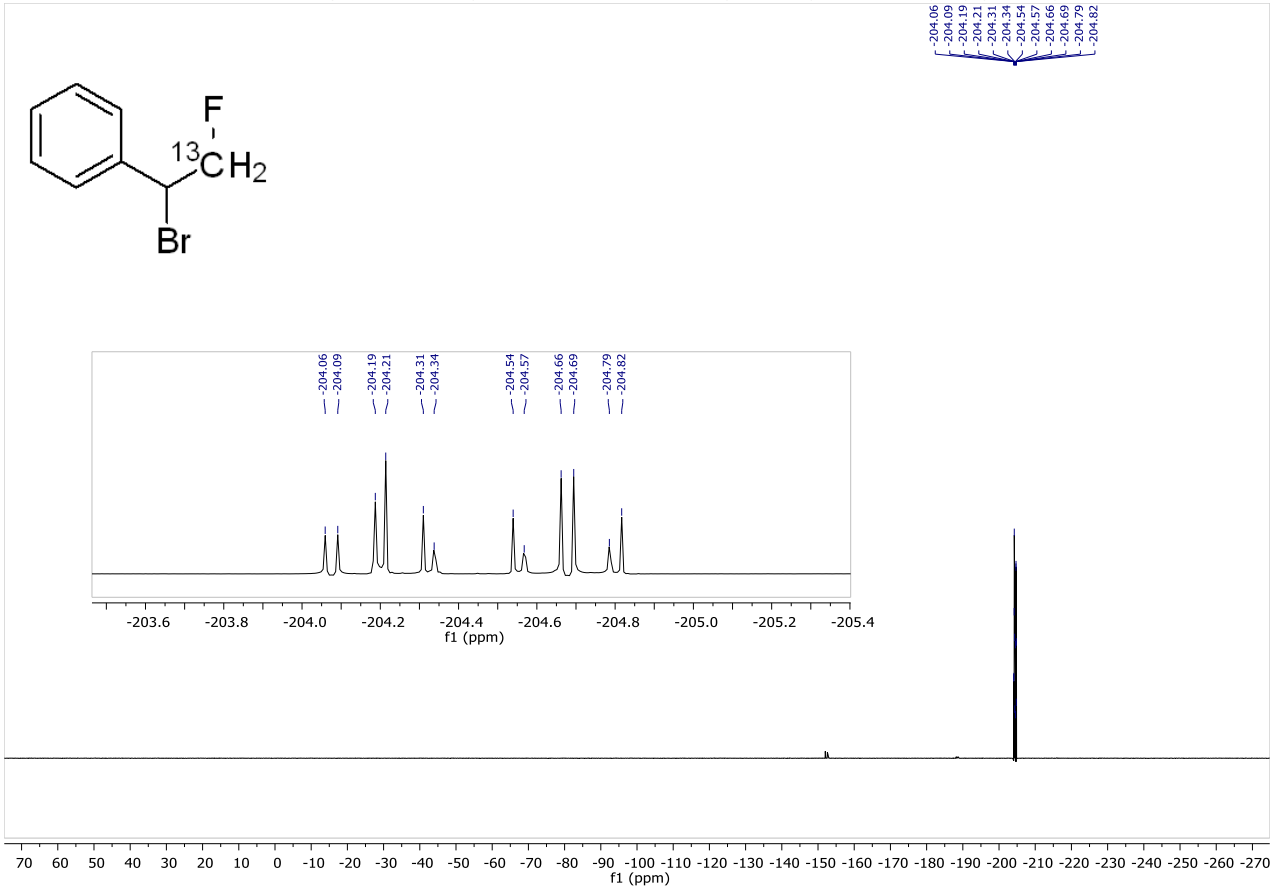
IR(ATR) spectrum of (2-fluoroethyl-2-^{13}C)benzene (**56**)



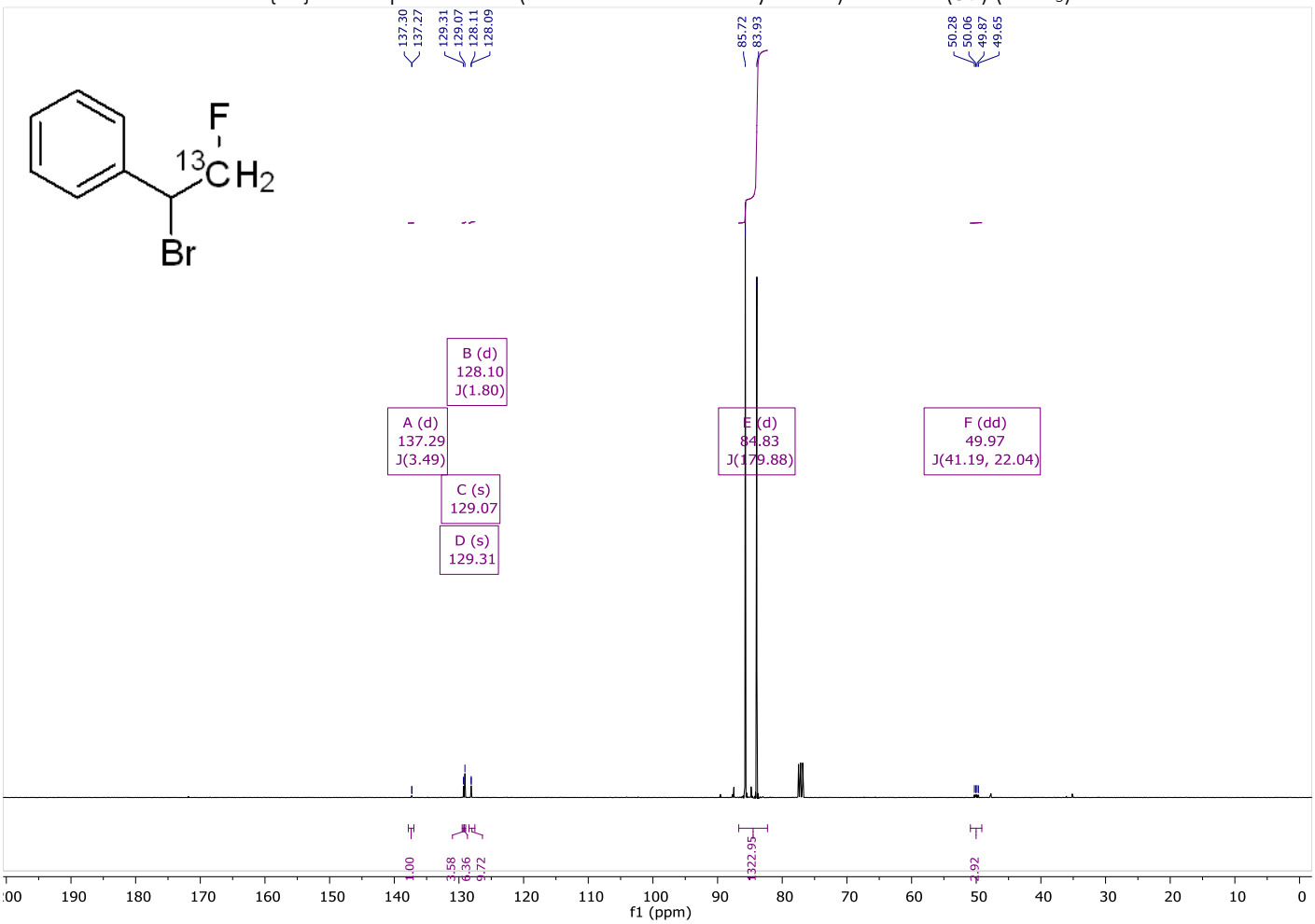
^{1}H NMR spectrum of (1-bromo-2-fluoroethyl-2-^{13}C)benzene (**57**) ($CDCl_3$)



^{19}F NMR spectrum of (1-bromo-2-fluoroethyl-2-^{13}C)benzene (**57**) ($CDCl_3$)



$^{13}C\{^{1}H\}$ NMR spectrum of (1-bromo-2-fluoroethyl-2-^{13}C)benzene (**57**) ($CDCl_3$)



GC-MS of (1-bromo-2-fluoroethyl-2-^{13}C)benzene (**57**)

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File        :D:\DATA_2021\01-Jan-2021\28_14988.D
Operator    : E
Acquired    : 28 Jan 2021  15:59      using AcqMethod LAURA.M
Instrument :     GCMS
Sample Name: Maleckis OSM6-AM-F701
Misc Info  :
Vial Number: 29
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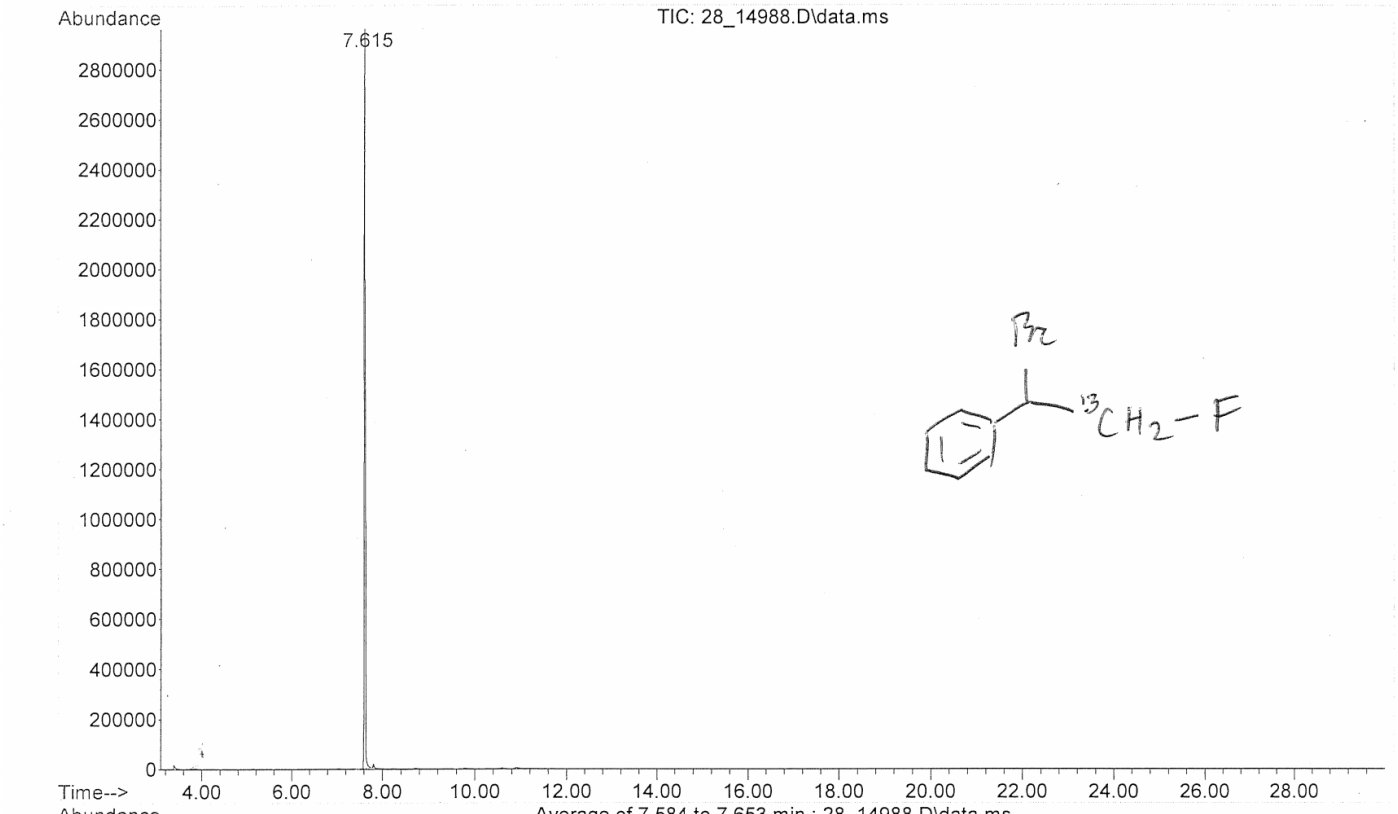
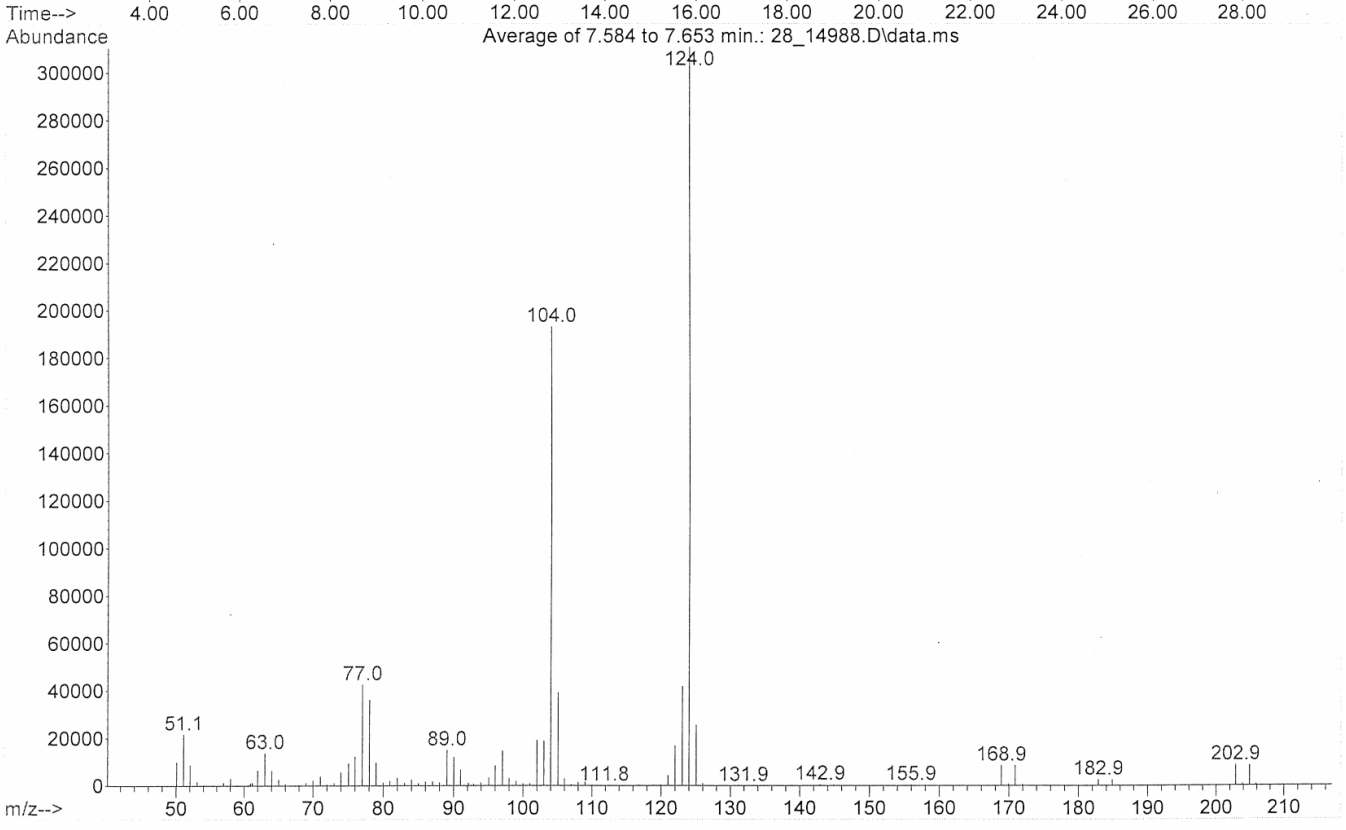
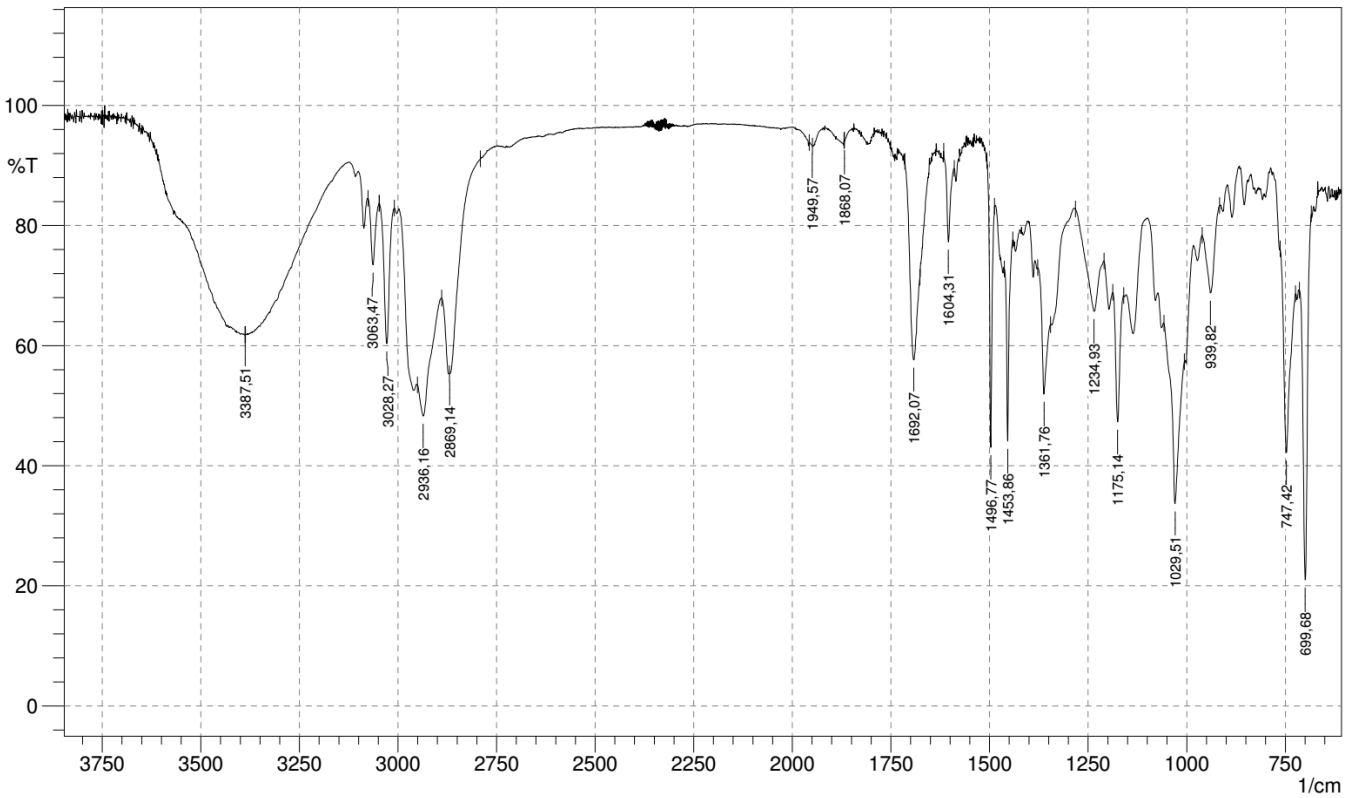
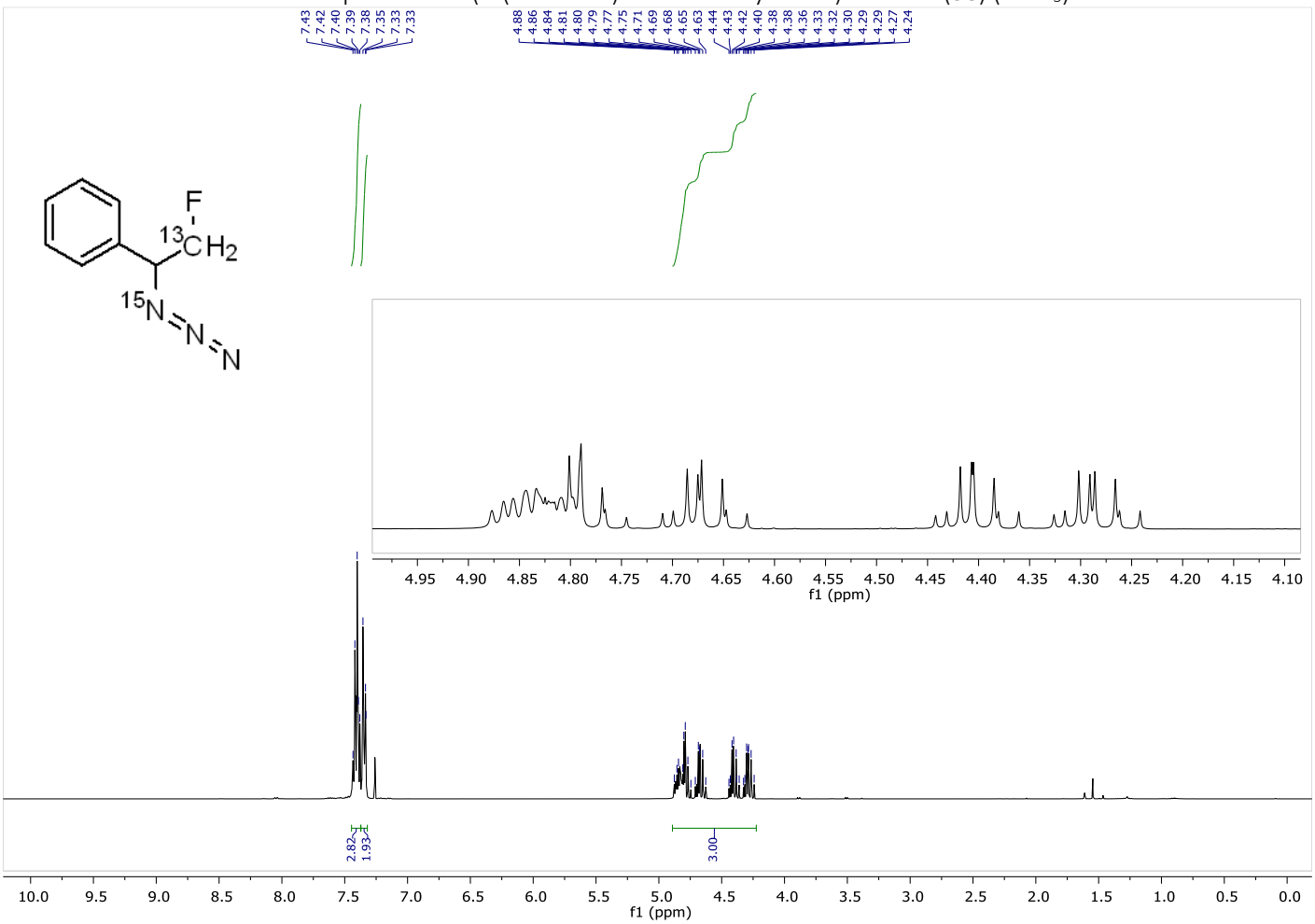




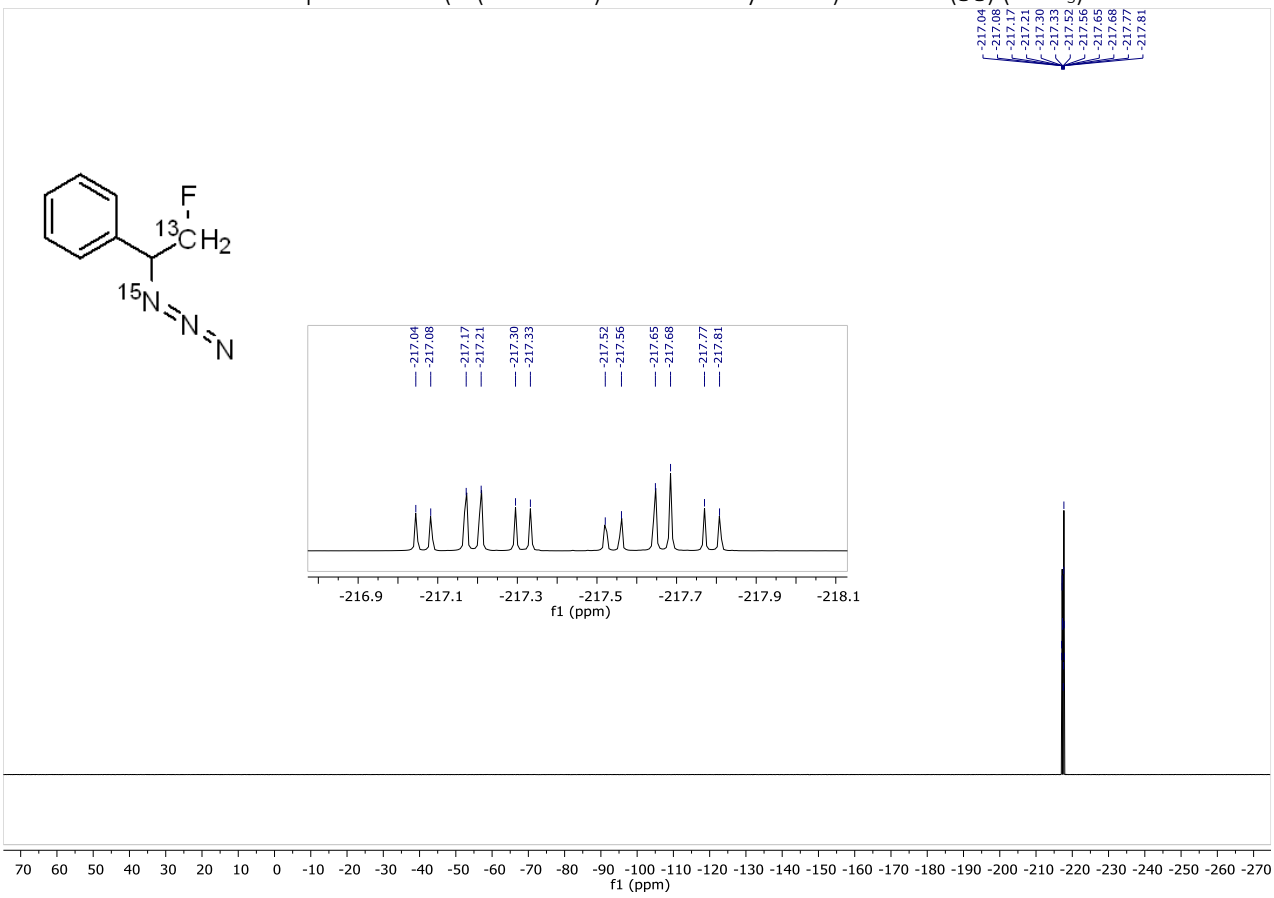
IR(ATR) spectrum of (1-bromo-2-fluoroethyl-2-^{13}C)benzene (**57**)



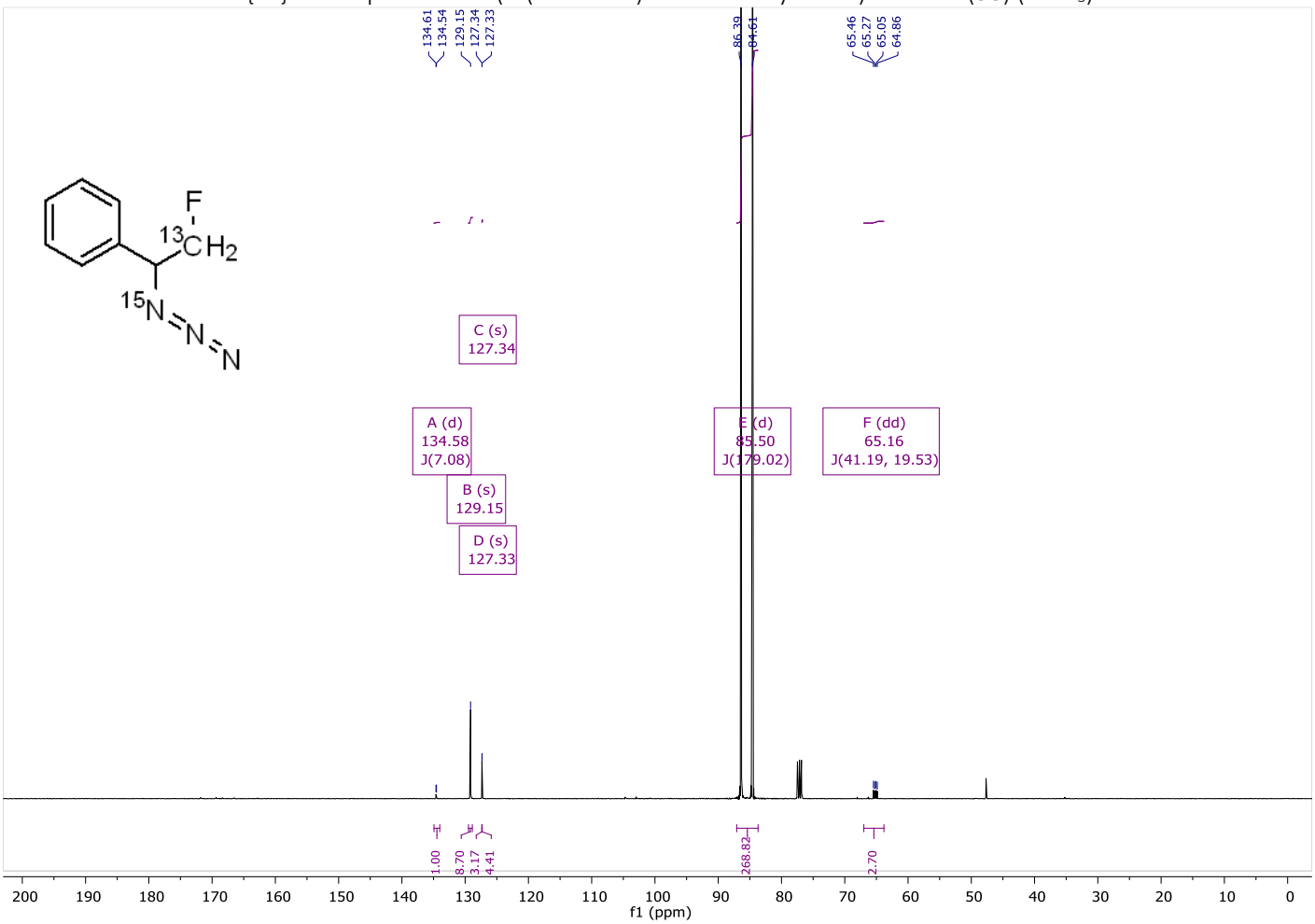
^{1}H NMR spectrum of (1-(azido-^{15}*N*)-2-fluoroethyl-2-^{13}*C*)benzene (**58**) ($CDCl_3$)



^{19}F NMR spectrum of (1-(azido-^{15}*N*)-2-fluoroethyl-2-^{13}*C*)benzene (**58**) ($CDCl_3$)

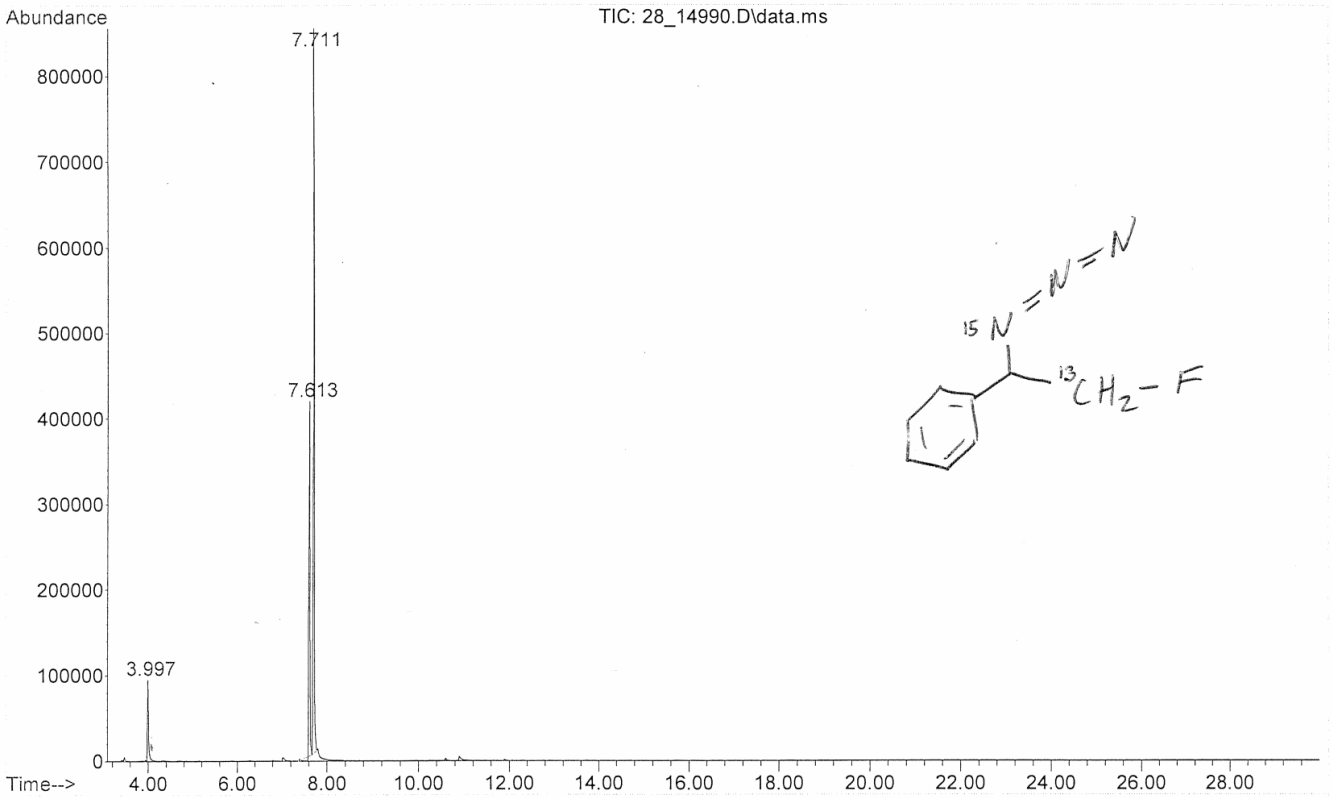


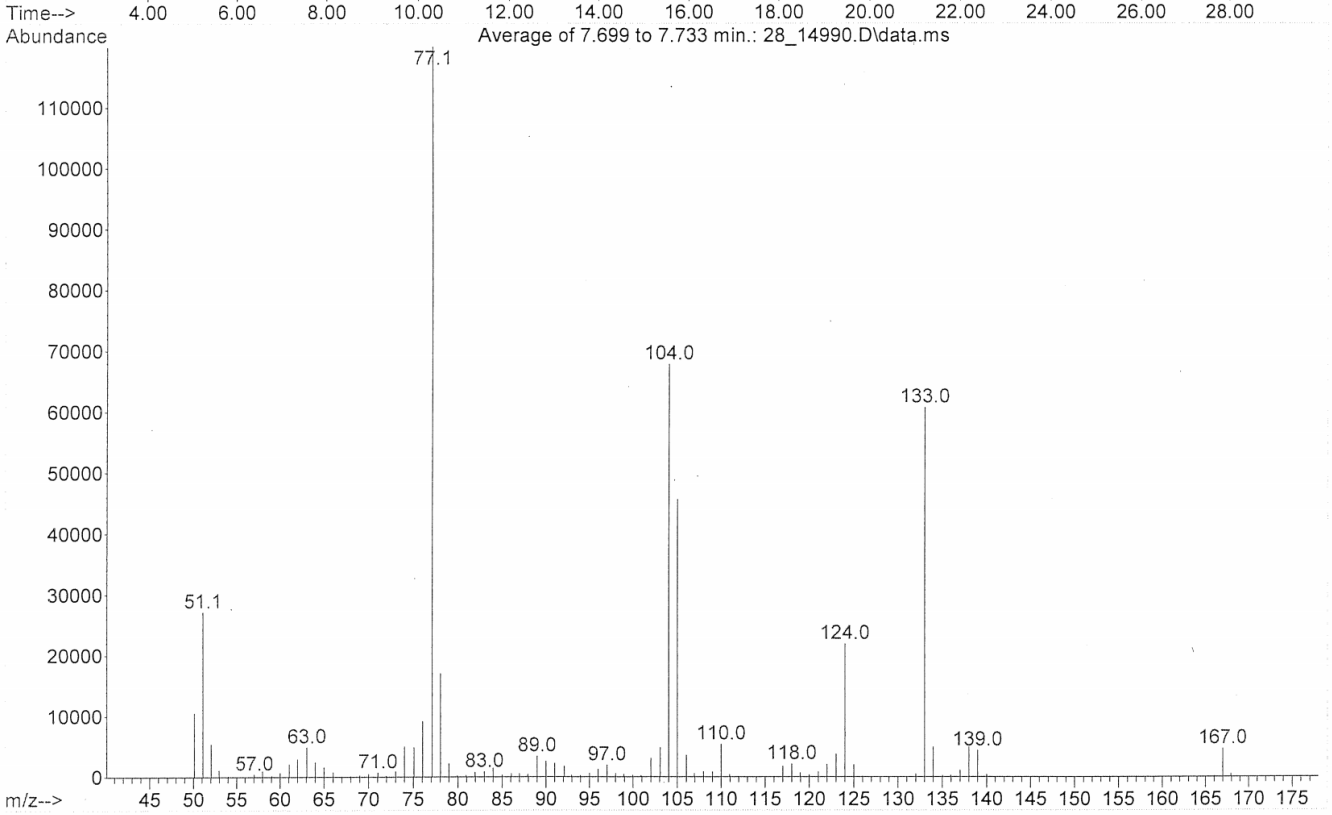
$^{13}C\{^{1}H\}$ NMR spectrum of (1-(azido-^{15}N)-2-fluoroethyl-2-^{13}C)benzene (**58**) ($CDCl_3$)



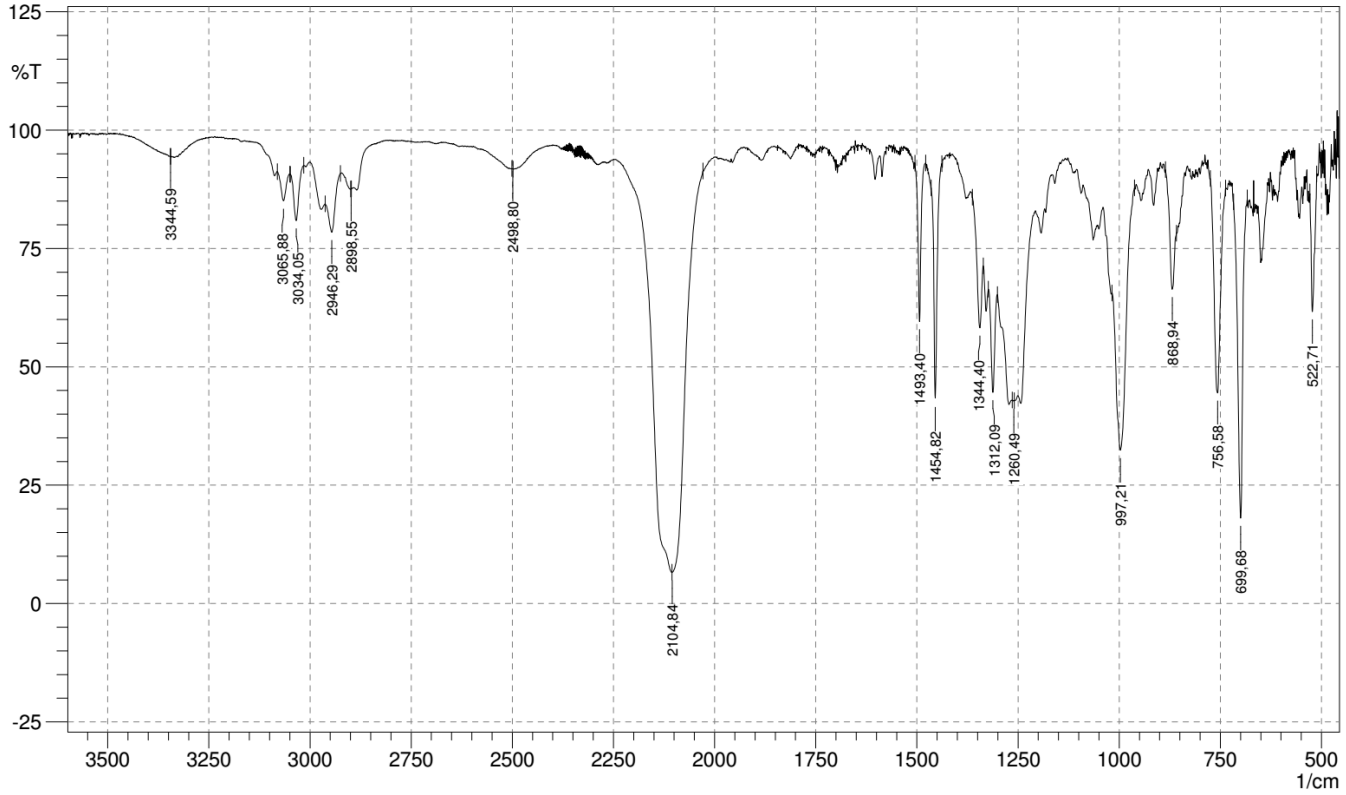
GC-MS of (1-(azido-^{15}N)-2-fluoroethyl-2-^{13}C)benzene (**58**)

```
File        :D:\DATA_2021\01-Jan-2021\28_14990.D
Operator    : E
Acquired    : 28 Jan 2021   17:06      using AcqMethod LAURA.M
Instrument :     GCMS
Sample Name: Maleckis OSM6-AM-F702
Misc Info   :
Vial Number: 31
```

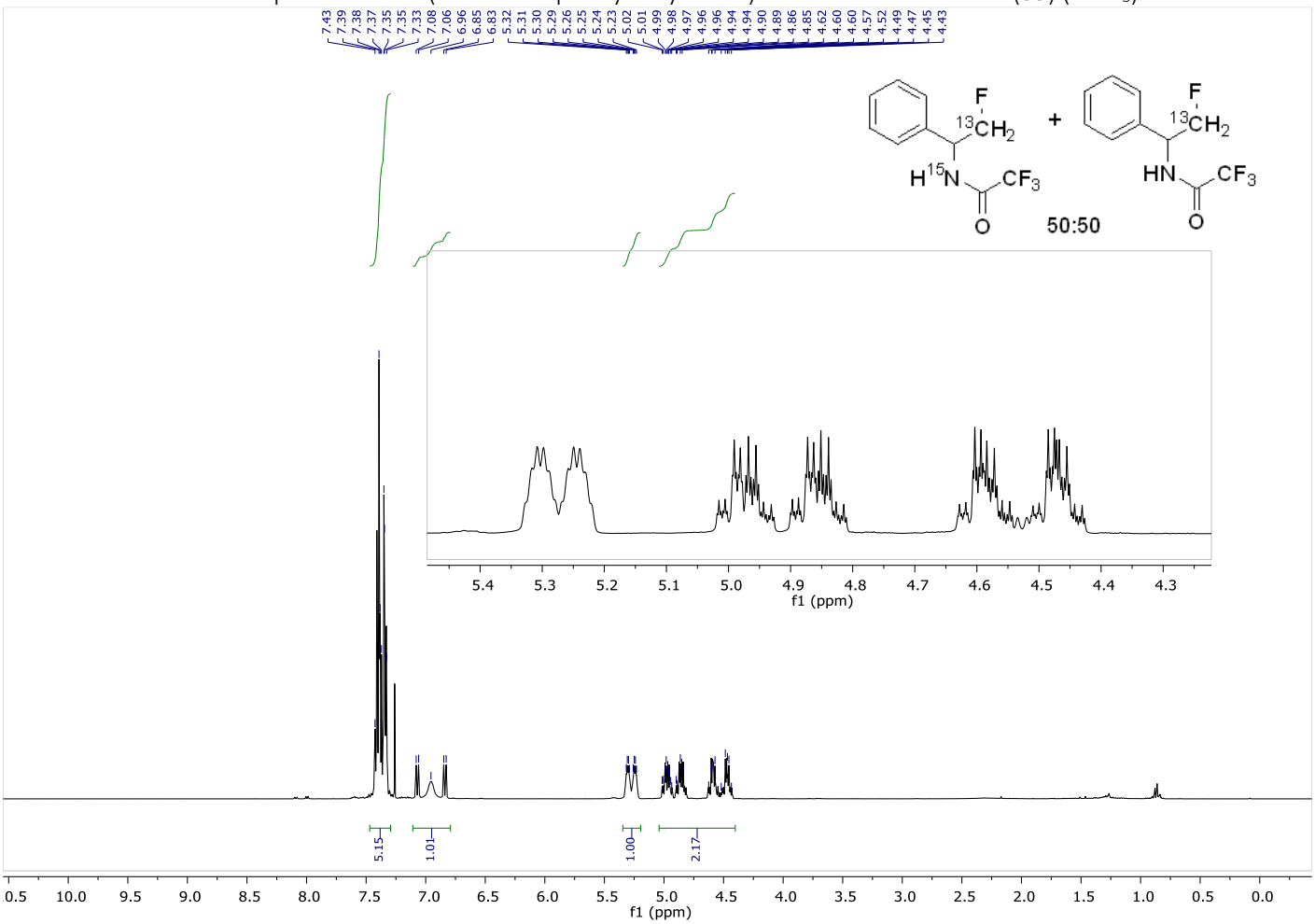




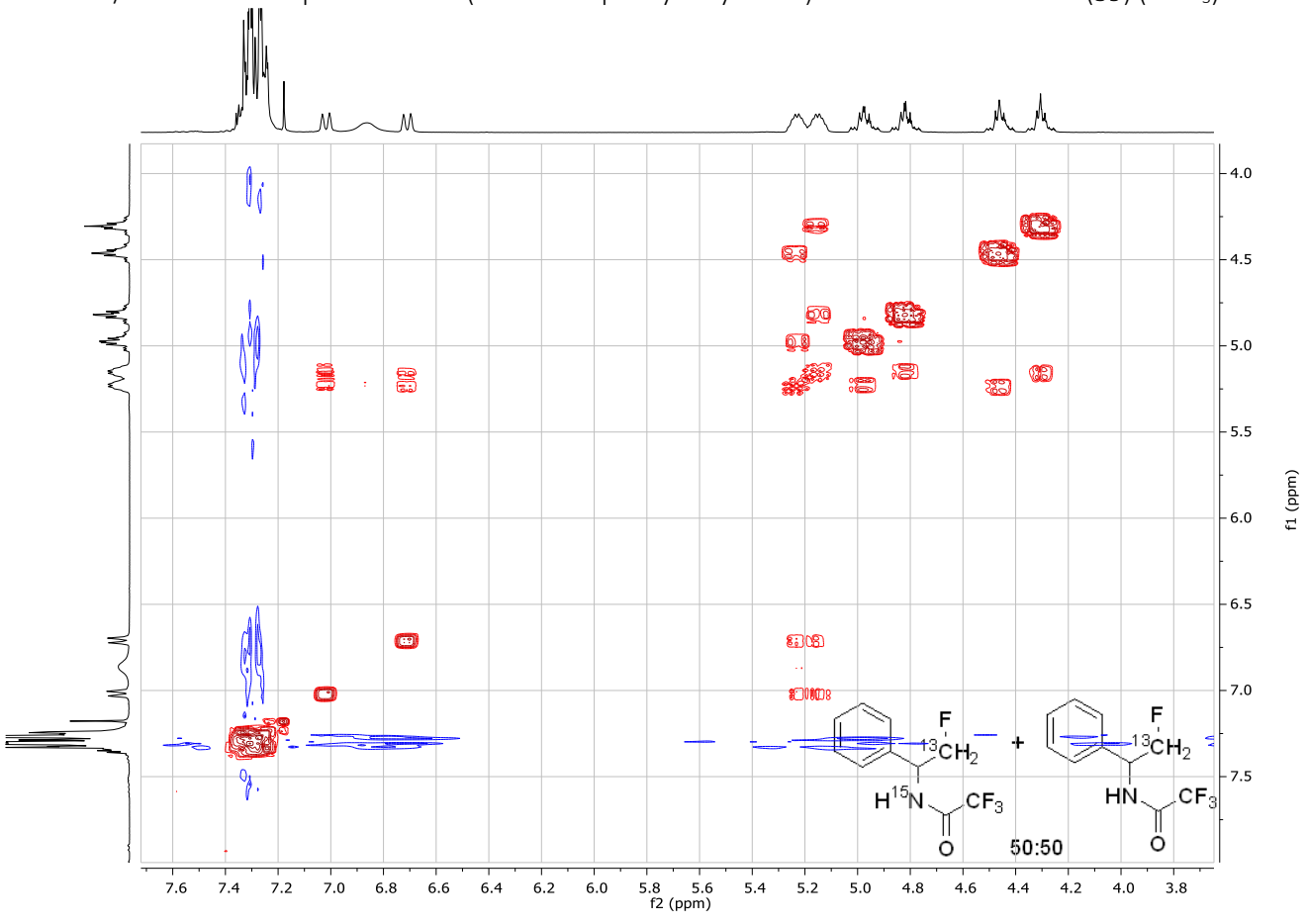
IR(ATR) spectrum of (1-(azido-^{15}N)-2-fluoroethyl-2-^{13}C)benzene (**58**)



^{1}H NMR spectrum of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (**59**) ($CDCl_3$)

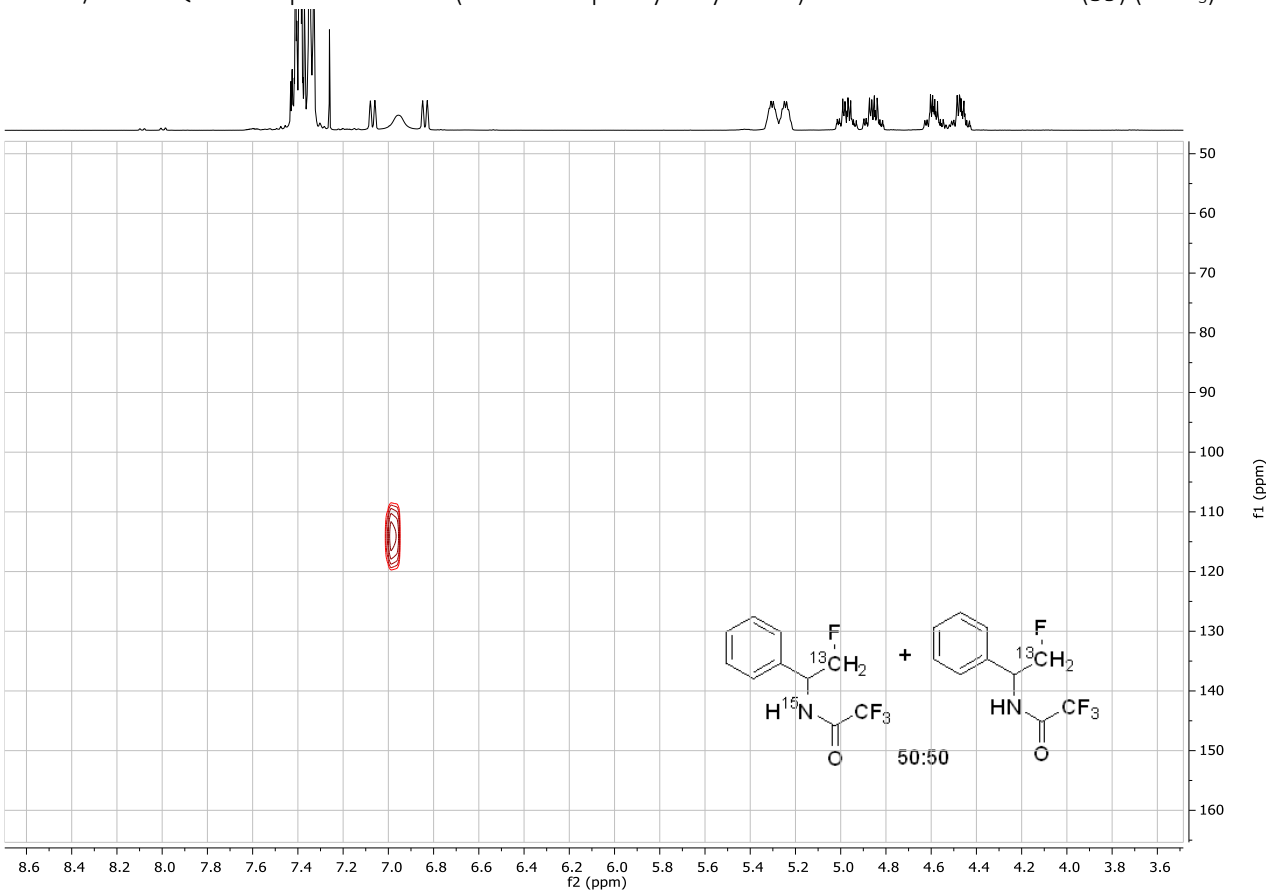


^{1}H/^{1}H COSY NMR spectrum of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (**59**) ($CDCl_3$)

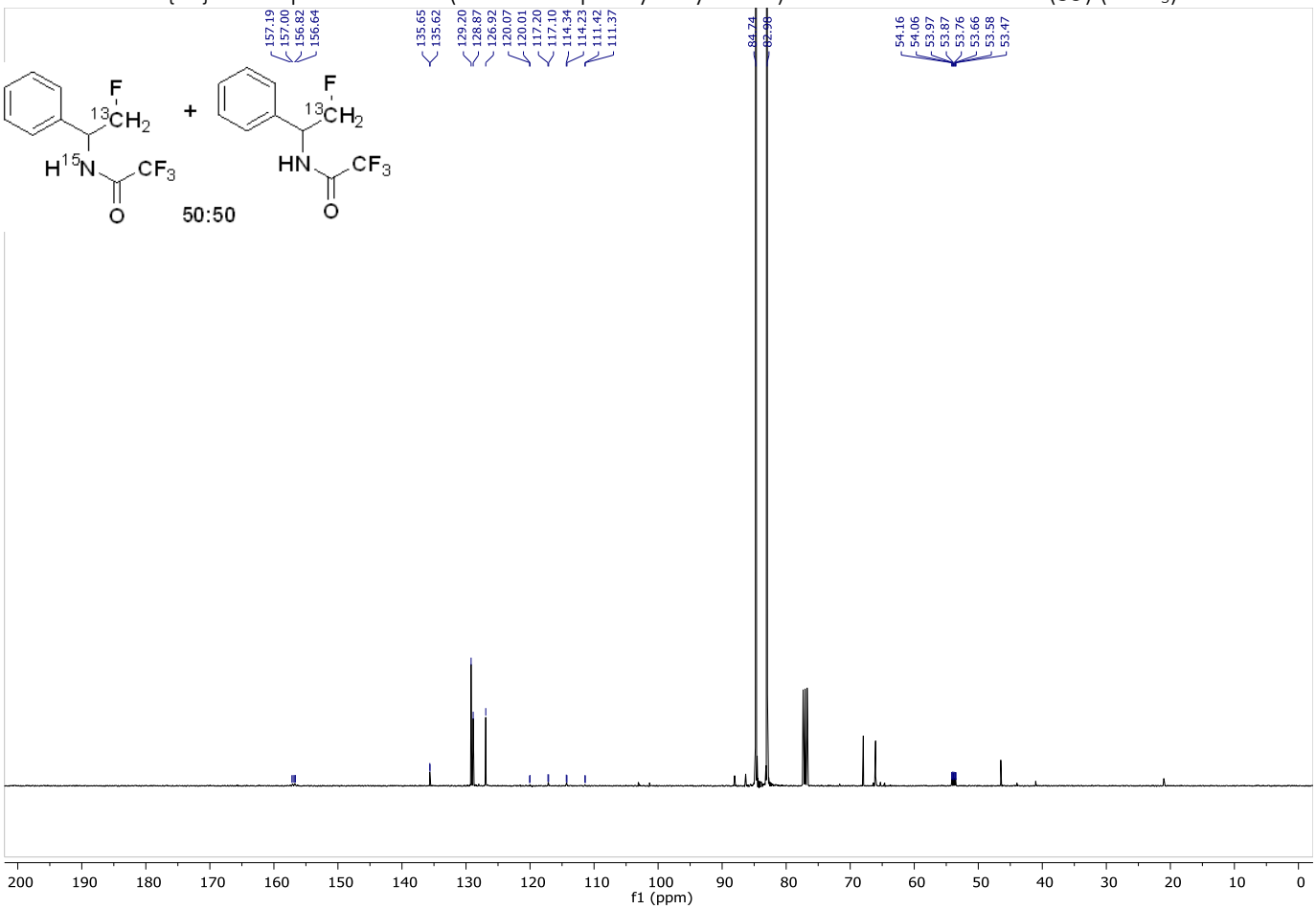


^{19}F NMR spectrum of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (**59**) ($CDCl_3$)

^{1}H/^{15}N HSQC NMR spectrum of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (**59**) ($CDCl_3$)



^{13}C{^{1}H} NMR spectrum of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (**59**) ($CDCl_3$)



HRMS of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (59)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2021_02_046 165 Maleckis OSM6-AM-F704
MS_NEG_RES_4min ACN_Form_5-98_040_4min 1:C,1 5.000000 MS_Tune Col#66

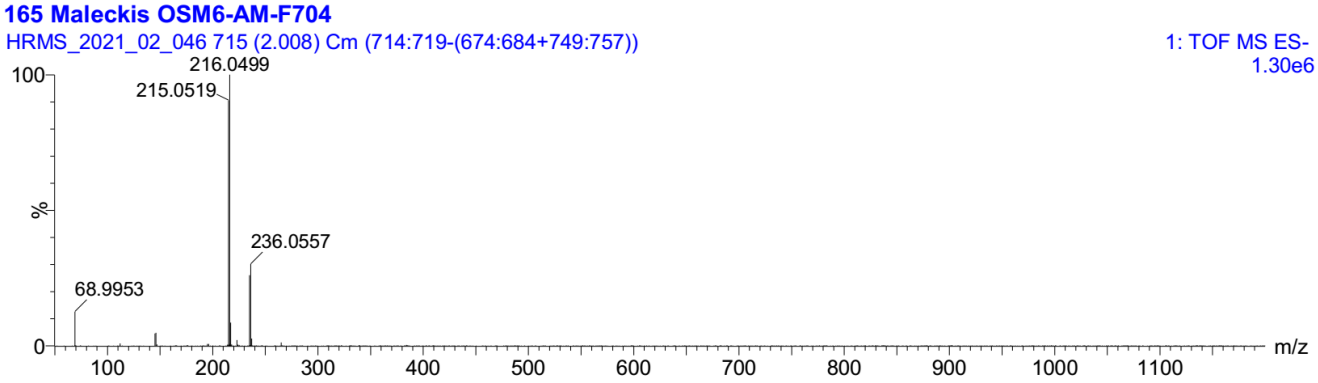
Elemental Composition Report:

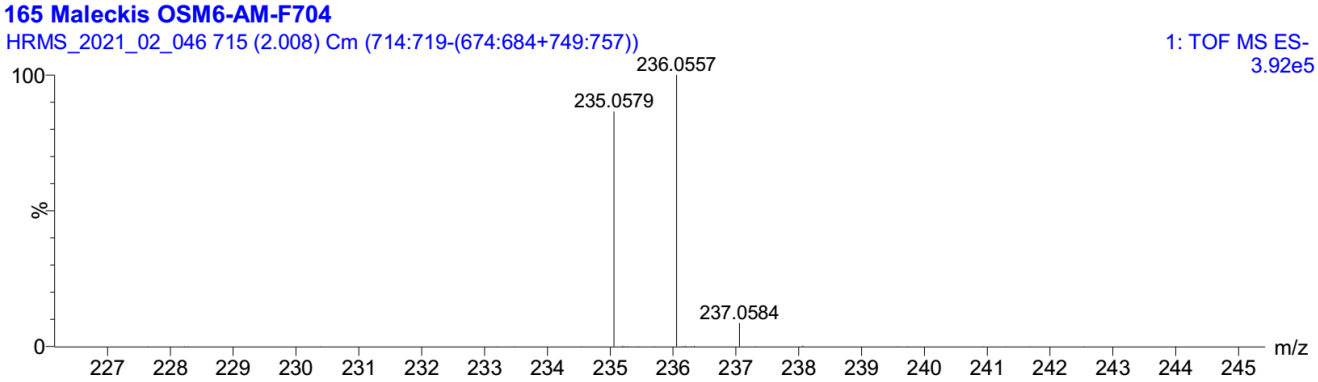
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
1593 formula(e) evaluated with 3 results within limits (up to 5 closest results for each mass)
Elements Used:
12C: 1-50 13C: 0-2 H: 0-100 14N: 0-10 15N: 0-2 O: 0-15 F: 4-4

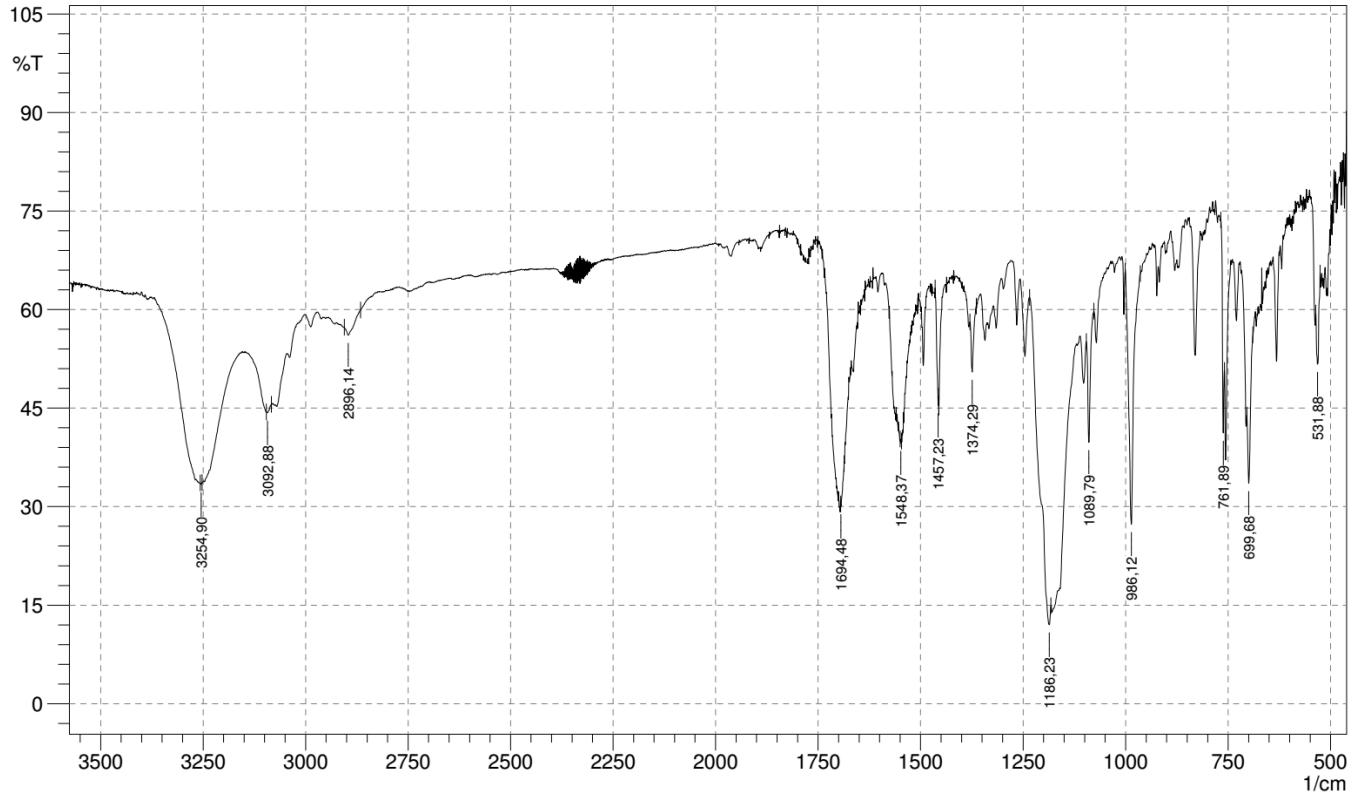
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
235.0579	235.0576	0.3	1.3	5.5	149.7	0.780	45.86	12C9 13C H8 14N O F4
	235.0575	0.4	1.7	2.5	152.5	3.574	2.81	12C H5 14N8 15N2 F4
	235.0584	-0.5	-2.1	1.5	149.6	0.667	51.33	12C4 H8 14N4 15N O2 F4

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
236.0557	236.0555	0.2	0.8	1.5	109.7	1.392	24.85	12C4 H8 14N3 15N2 O2 F4
	236.0559	-0.2	-0.8	5.5	109.4	1.082	33.90	12C7 H6 14N5 F4
	236.0546	1.1	4.7	0.5	109.8	1.518	21.91	12C6 H10 14N O4 F4
	236.0546	1.1	4.7	5.5	110.0	1.643	19.33	12C9 13C H8 15N O F4

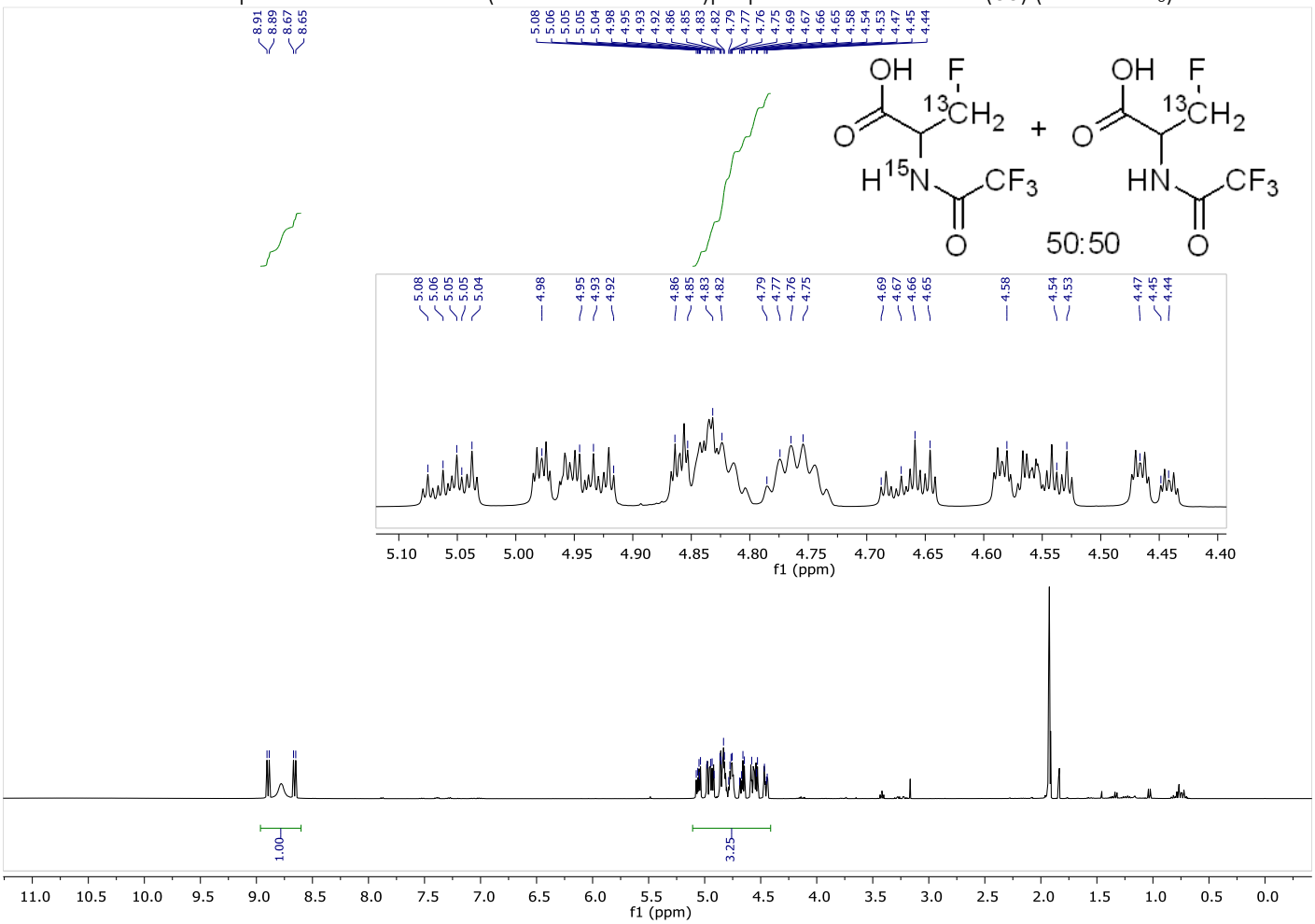




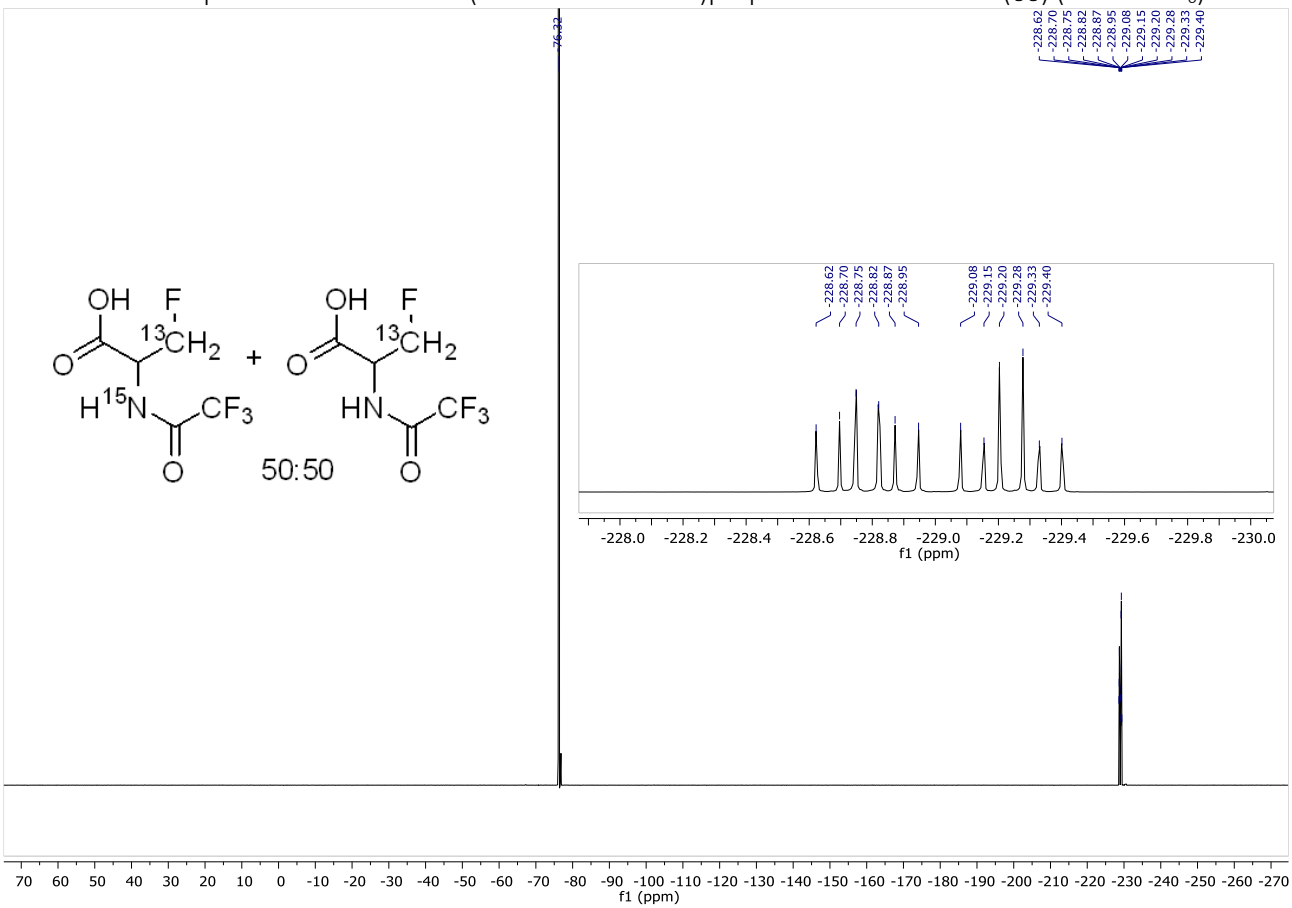
IR(ATR) spectrum of *N*-(2-fluoro-1-phenylethyl-2-^{13}C)trifluoroacetamide-^{15}*N* (**59**)



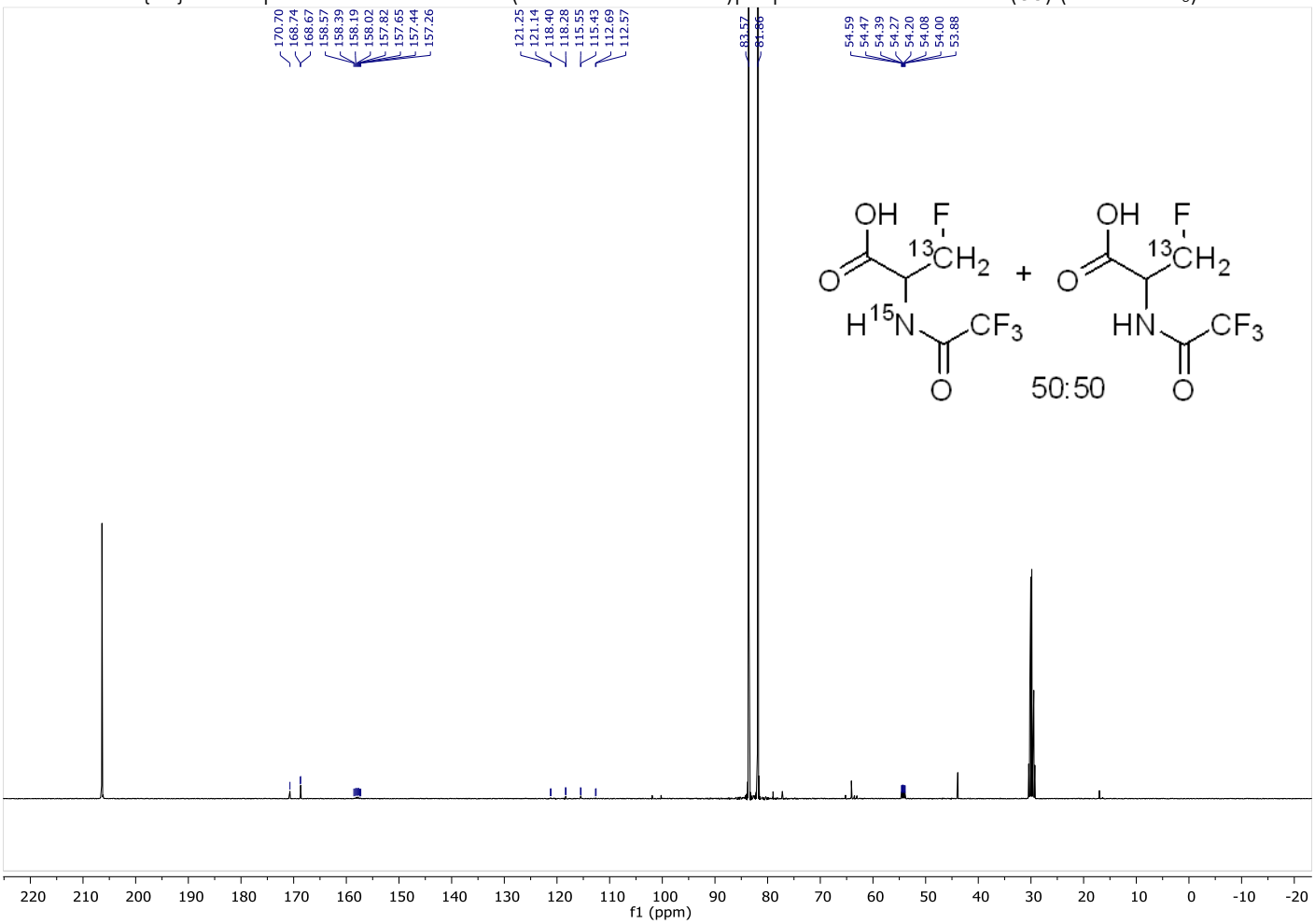
^{1}H NMR spectrum of 3-fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**) (Acetone-d_6)



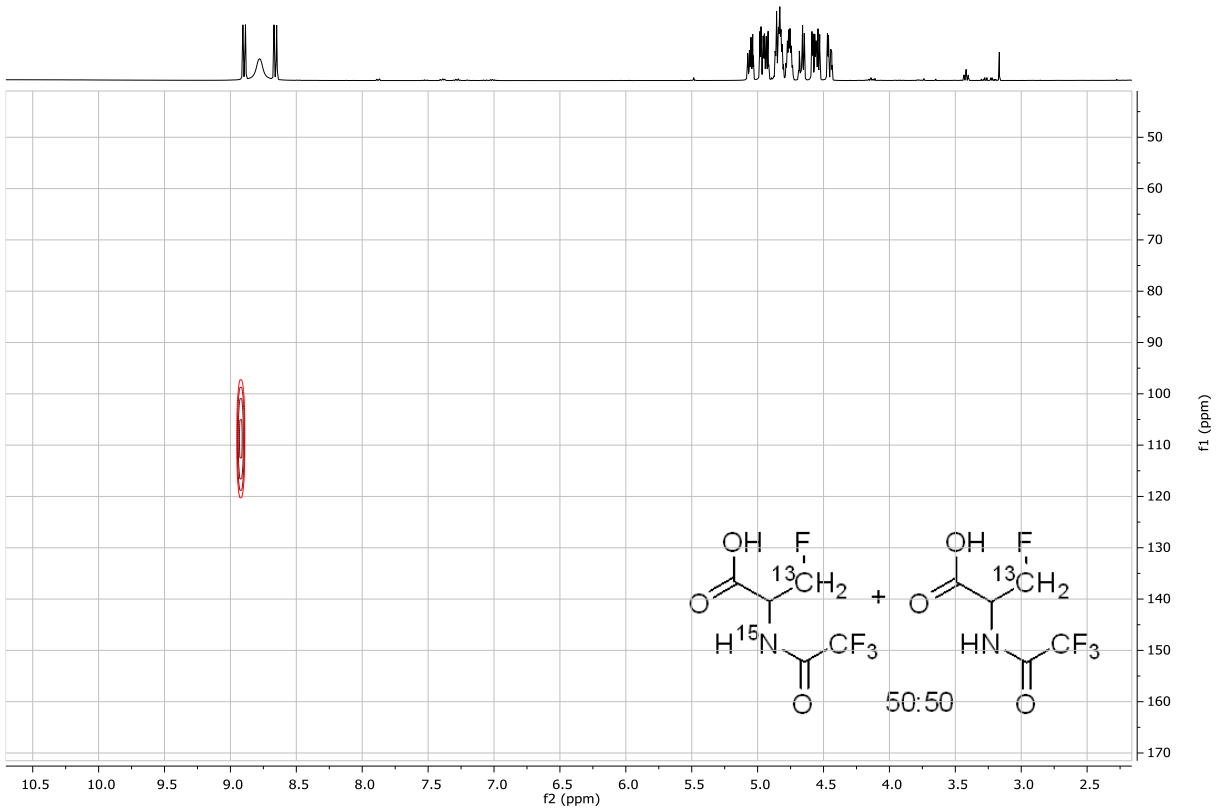
^{19}F NMR spectrum of 3-fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**) (Acetone-d_6)



$^{13}C\{^{1}H\}$ NMR spectrum of 3-fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**) (Acetone-d_6)



$^{1}H/^{15}N$ HSQC NMR spectrum of 3-fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**) (Acetone-d_6)



HRMS of 3-fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**)

MS: Waters Synapt G2-*Si*	Capillary, kV:	2.5	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18
ESI-	Cone, V:	40			2.1x50mm, 1.7µm

Sample:

HRMS_2021_02_048 166 Maleckis OSM6-AM-F707
MS_NEG_RES_4min ACN_Form_5-98_040_4min 1:C,2 5.000000 MS_Tune Col#66

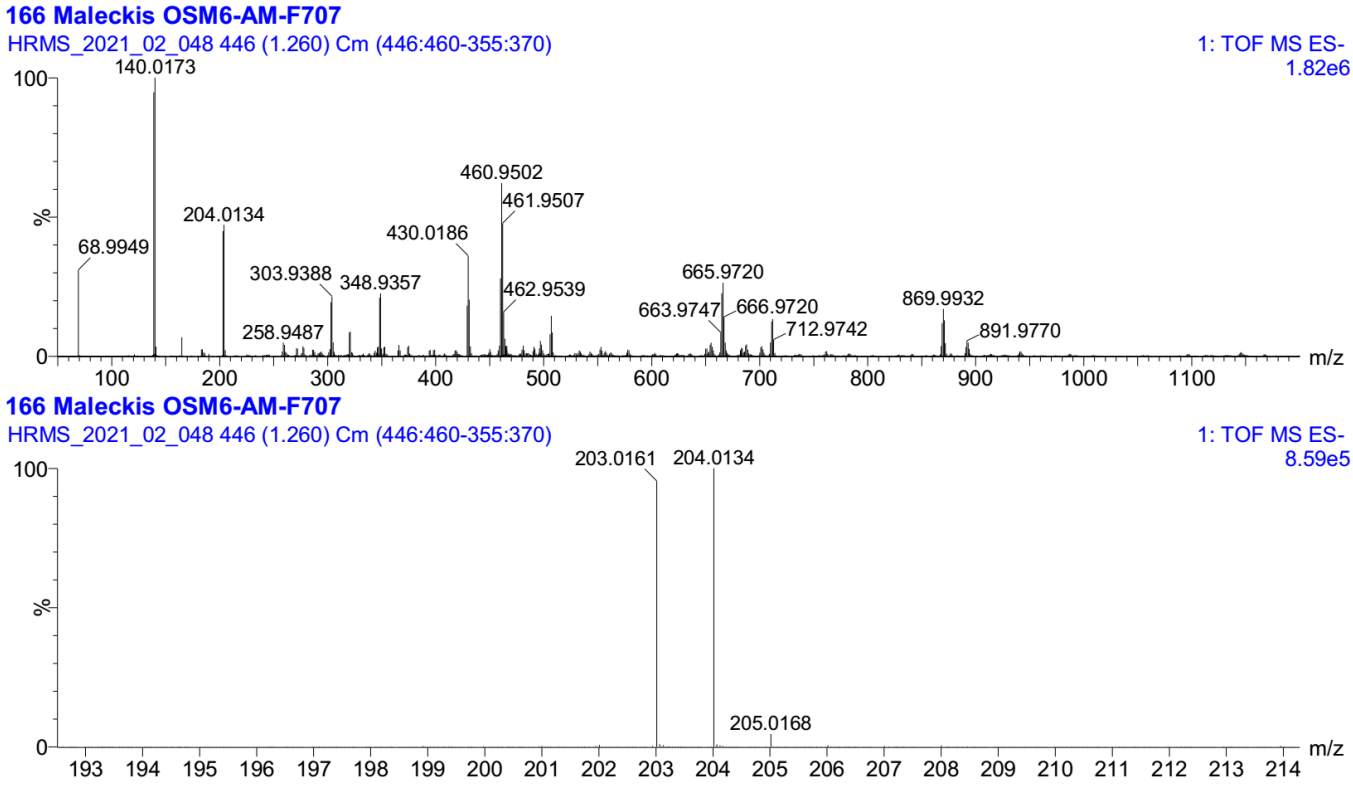
Elemental Composition Report:

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

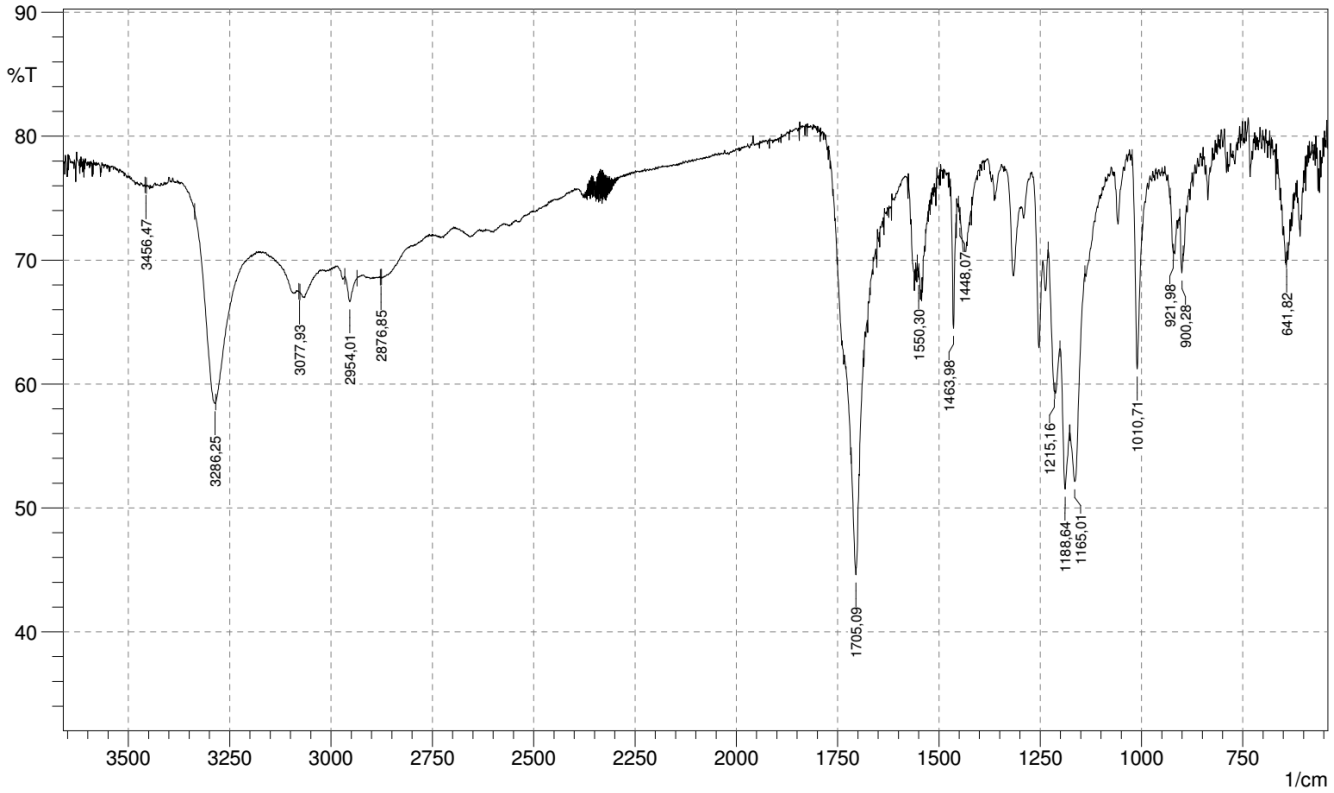
Monoisotopic Mass, Even Electron Ions
752 formula(e) evaluated with 4 results within limits (up to 5 closest results for each mass)
Elements Used:
12C: 1-50 13C: 0-2 H: 0-100 14N: 0-10 15N: 0-2 O: 0-15 F: 4-4

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
203.0161	203.0161	0.0	0.0	7.5	1130.3	29.436	0.00	12C7 13C2 H2 15N F4
	203.0161	0.0	0.0	2.5	1100.9	0.071	93.12	12C4 13C H4 14N O3 F4
	203.0152	0.9	4.4	3.5	1116.7	15.905	0.00	12C 13C H 14N5 15N O F4
	203.0170	-0.9	-4.4	3.5	1103.5	2.677	6.88	12C2 13C H2 14N3 15N2 O F4

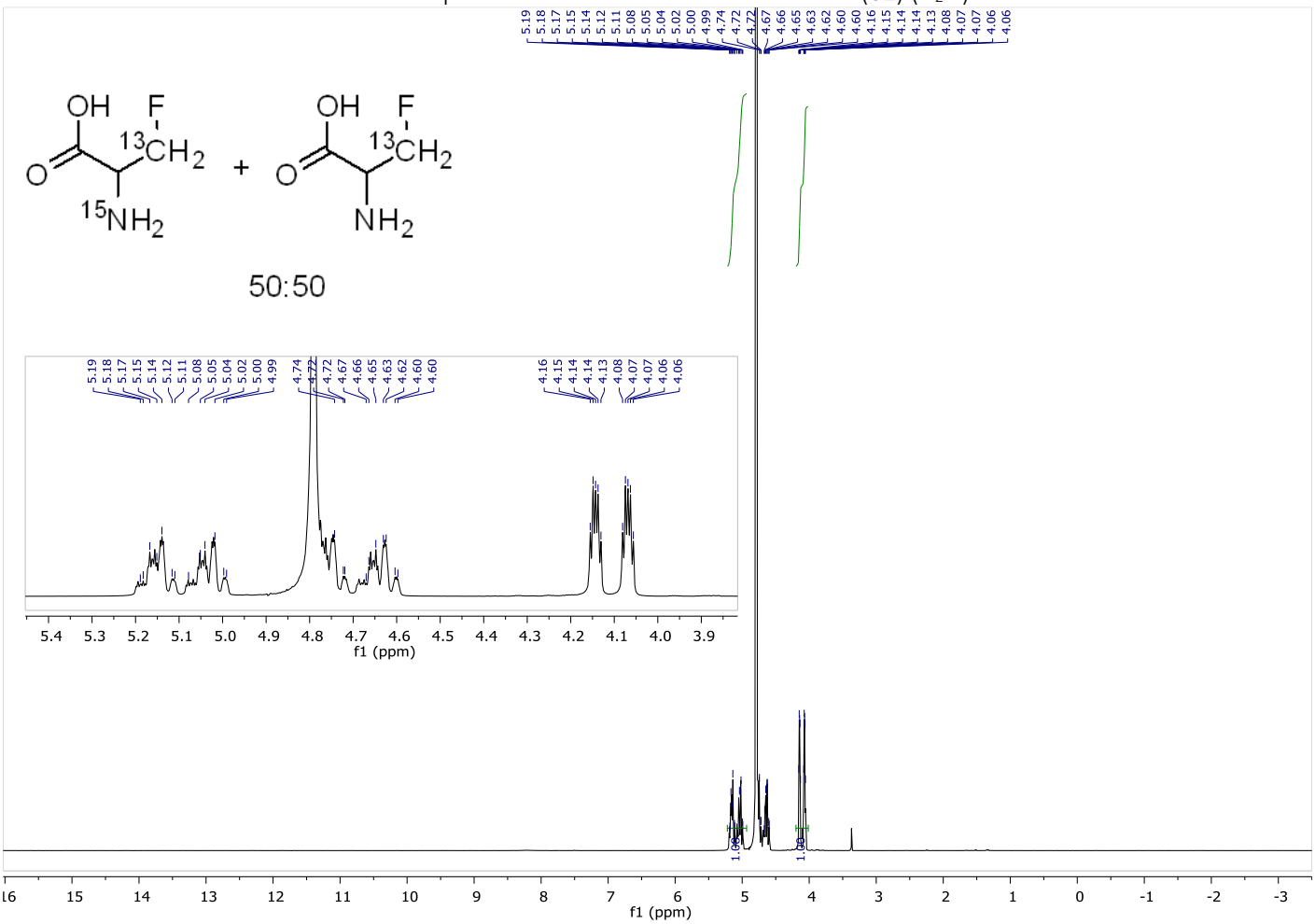
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
204.0134	204.0131	0.3	1.5	2.5	991.8	n/a	n/a	12C4 13C H4 15N O3 F4



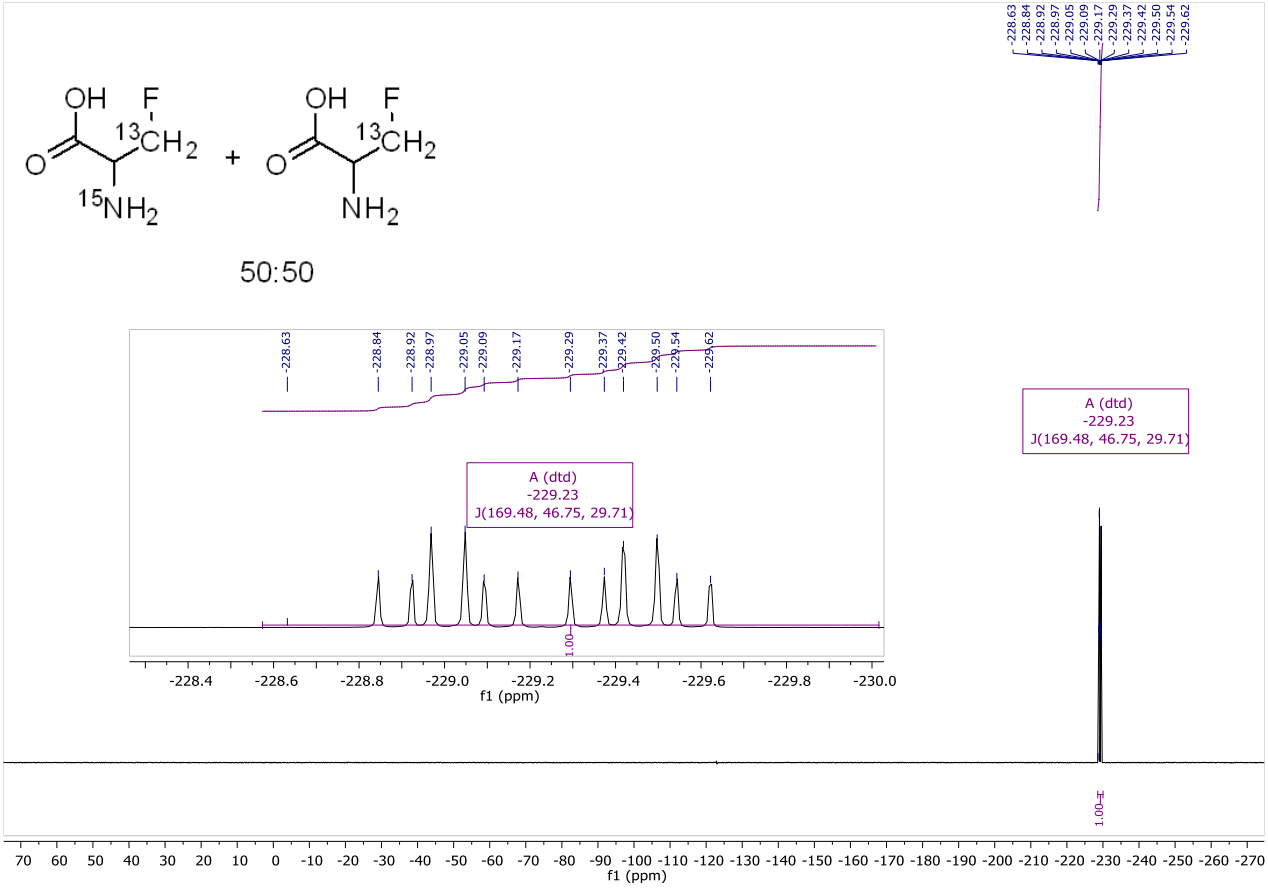
IR(ATR) spectrum of 3-fluoro-2-(trifluoroacetamido)propanoic-3-^{13}C-^{15}N acid (**60**)



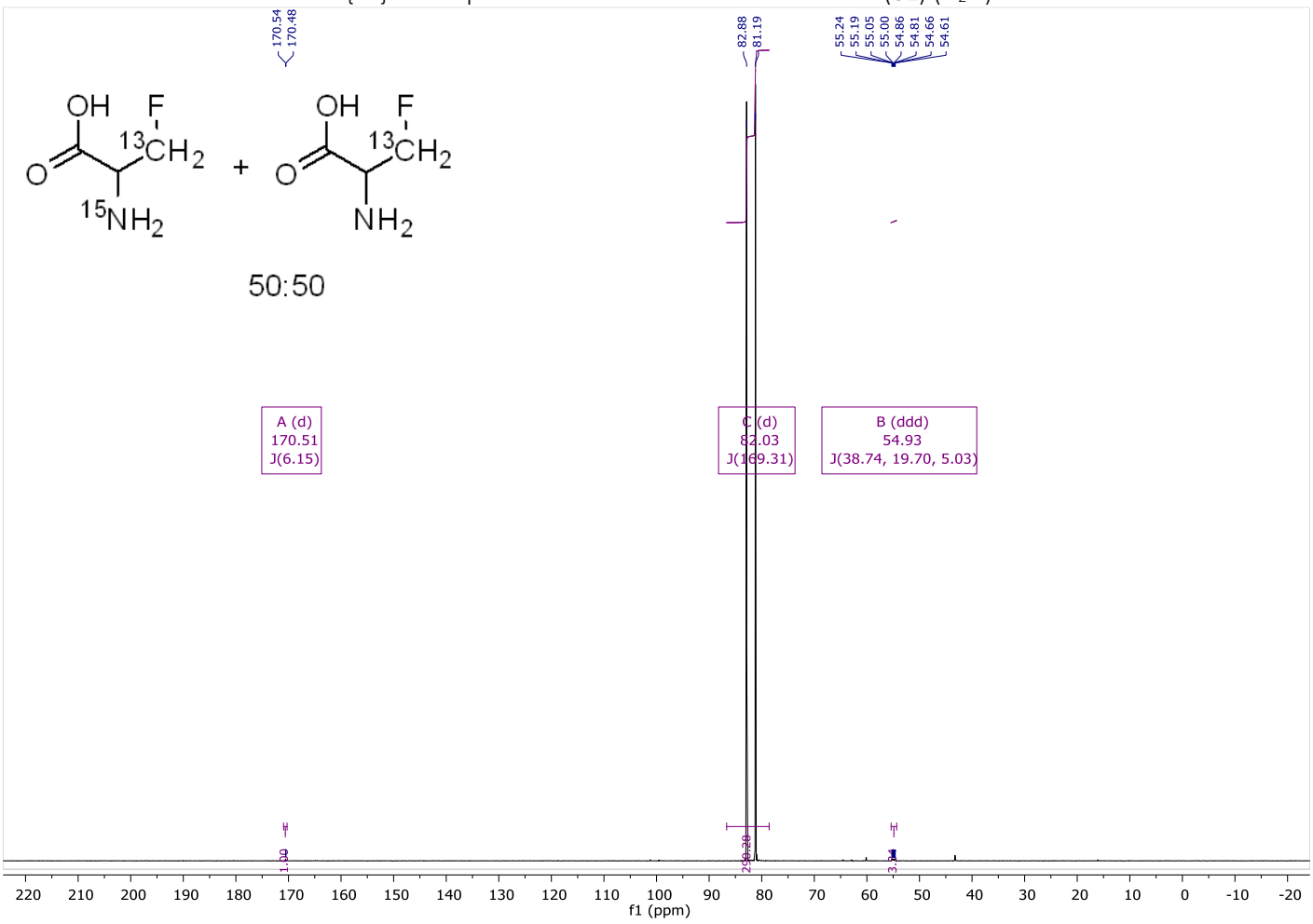
^{1}H NMR spectrum of 3-fluoro-alanine-3-^{13}C-^{15}N (**61**) (D_2O)



^{19}F NMR spectrum of 3-fluoro-alanine-3-^{13}C-^{15}N (**61**) (D_2O)



$^{13}C\{^{1}H\}$ NMR spectrum of 3-fluoro-alanine-3-^{13}C-^{15}N (**61**) (D_2O)



MS: Waters Synapt G2-*Si* **ESI-**	Capillary, kV: Cone, V:	2.5 40	**LC: Acquity UPLC H-Class**	Column:	Acquity UPLC BEH C18 2.1x50mm, 1.7µm

Sample:

HRMS_2021_02_050 167 Maleckis OSM6-AM-F711
MS_NEG_RES_4min ACN_Form_5-98_040_4min 1:C,3 5.000000 MS_Tune Col#66

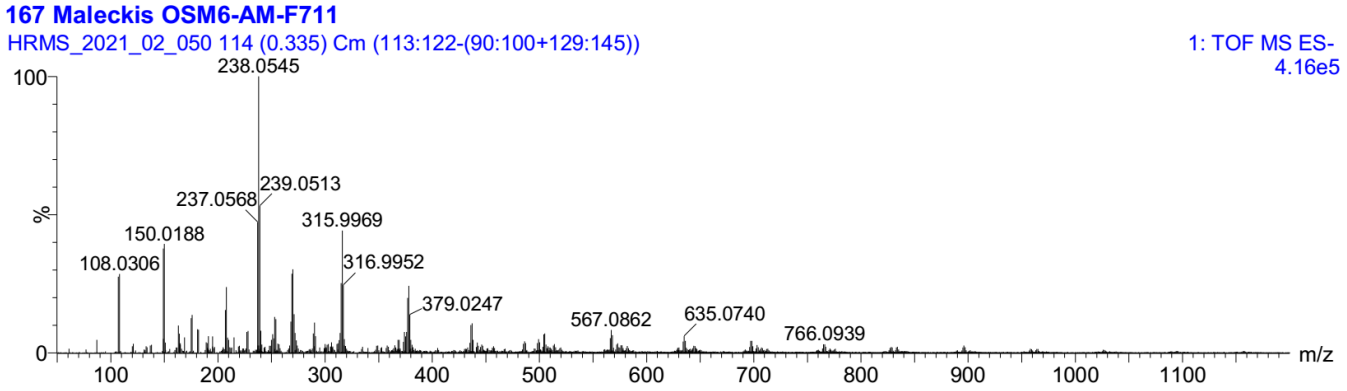
Elemental Composition Report:

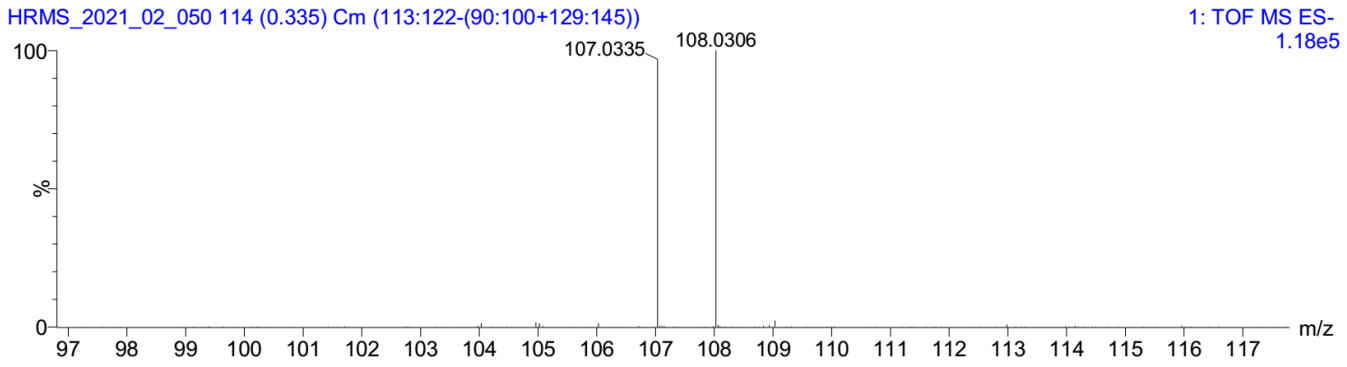
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

Monoisotopic Mass, Even Electron Ions
214 formula(e) evaluated with 1 results within limits (up to 5 closest results for each mass)
Elements Used:
12C: 1-50 13C: 0-2 H: 0-100 14N: 0-10 15N: 0-2 O: 0-15 F: 1-1

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
107.0335	107.0338	-0.3	-2.8	1.5	357.6	n/a	n/a	12C2 13C H5 14N O2 F

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
108.0306	108.0308	-0.2	-1.9	1.5	316.0	n/a	n/a	12C2 13C H5 15N O2 F





IR(ATR) spectrum of 3-fluoro-alanine-3-^{13}C-^{15}N (**61**)