The Formation of All-*cis*-(multi)fluorinated Piperidines by a Dearomatization-Hydrogenation Process

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Supplementary Information

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1. Materials and Methods

Unless otherwise noted, all reactions were carried out under an atmosphere of argon in oven-dried glassware. Reaction temperatures are reported as the temperature of the bath surrounding the vessel unless otherwise stated. The solvents used were purified by distillation over the drying agents indicated in parentheses and were transferred under argon: *n*-hexane (CaH_2), dichloromethane (CaH_2), diethylether (Na-benzophenone), THF (Na-benzophenone), MTBE (Na-benzophenone). Dichloroethane (4 Å), 1,4-dioxane (4 Å), 2-MeTHF (4 Å) and methanol (3 Å) were purchased as dry solvents from commercial suppliers and stored over molecular sieves.

All hydrogenation reactions were carried out in Berghof High Pressure Reactors using hydrogen gas. Commercially available chemicals were obtained from Acros Organics, Aldrich Chemical Co., Strem Chemicals, Alfa Aesar, ABCR, Combi-Blocks, Chempur and TCI Europe and used as received unless otherwise stated. 3-Fluoropyridine, 3,5-difluoropyridine, 3-fluoro-5-methylpyridine, 3-fluoro-2-methylpyridine, 3-fluoro-4-methylpyridine, 5-fluoro-2-methylpyridine, 5-fluoro-2-(trifluoromethyl)pyridine, 2,4-difluoropyridine, 4-fluoro-2-methylpyridine and 4-fluoro-3-methylpyridine were distilled over CaH_2 prior to use. Heterogeneous catalysts were obtained from Johnson Matthey (Rhodium/C, 5%, Ruthenium/C, 5%), Evonik Industries (Palladium/C, 10%), Acros Organics (PtO_2) or Alfa Aesar (Rhodium/Al_2O_3, 5%). The employed (CAAC)Rh(COD)Cl complex [**Rh-2**] was synthesized according to the literature. All analytical data was in agreement with the reported data.[1] A variety of rhodium complexes such as (CAArC)Rh(COD)Cl [**Rh-3**], (CAArC(NMe_2))Rh(COD)Cl [**Rh-4**], (ICy)Rh(COD)Cl [**Rh-5**], (IMes)Rh(COD)Cl [**Rh-6**], (SIMes)Rh(COD)Cl [**Rh-7**] and (SINpEt)Rh(COD)Cl [**Rh-8**] were prepared according to previously published procedures using $[Rh(COD)Cl]_2$ precursor.[2]

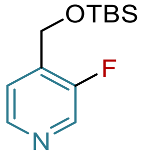
Analytical thin layer chromatography was performed on Polygram SIL G/UV_{254} plates. Visualization was accomplished with short wave UV light, and/or iodine, *p*-anisaldehyde, $KMnO_4$, phosphomolybdic acid (PMA), and Hanessian's (cerium ammonium molybdate) stains. Flash chromatography was performed on Merck silica gel (40–63 mesh) by standard technique eluting with solvents as indicated. GC-MS spectra were recorded on an Agilent Technologies 7890A GC-system with an Agilent 5975C VL MSD or an Agilent 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm x 30 m, film: 0.25 µm). The major signals are quoted in m/z with the relative intensity in parentheses. The method indicated as '50_40' starts with the injection temperature T0 (50°C); after holding this temperature for 3min, the column is heated by 40°C/min to temperature T1 (290°C or 320°C). ESI mass spectra were recorded on a Bruker Daltonics MicroTof spectrometer. Infrared spectra were recorded on a Shimadzu FTIR 8400S spectrometer as neat compound. The wave numbers (ν) of recorded IR-signals are quoted in cm^{-1}. GC-FID analysis was undertaken on an Agilent Technologies 6890A equipped with an HP-5 quartz column (0.32 mm x 30 m, film: 0.25 µm) using flame ionization detection. Method: Initial temperature 50 °C, hold 3 min, increment 40 °C/min, final temperature 280 °C, hold 3 min. ^{1}H and ^{13}C, ^{19}F, ^{31}P and ^{11}B NMR spectra were recorded on a Bruker Avance II 300 or Avance II 400, Agilent DD2 500 or Agilent DD2 600 in the indicated solvents. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm; C_6D_6: $\delta_H = 7.16$ ppm, $\delta_C = 128.06$ ppm, toluene-d_8: $\delta_H = 7.09$, 7.01, 6.97 and 2.08 ppm, $\delta_C = 137.48$, 128.87, 127.96, 125.13 and 20.43 ppm, CD_3OD: $\delta_H = 3.31$ ppm, $\delta_C = 49.00$ ppm, D_2O: $\delta_H = 4.79$ ppm). ^{19}F, ^{29}Si, ^{31}P and ^{11}B NMR spectra are referenced according to the proton resonance of TMS as the primary reference for the unified chemical shift scale (IUPAC recommendation 2001). Melting points were measured using a SMP 3 apparatus from Stuart Scientific. Optical specific rotations are measured with Schmidt Haensch Polartronic H (Na-vapor lamp, λ = 589 nm), calculated using the equation $[\alpha]_D^t = \frac{\alpha_{measured}}{l\cdot(c\cdot 10^{-3})}$, where $(l, dm; c, \frac{g}{dL})$, and reported as following: $[\alpha]_D^t$ value (*c* M, solvent). X-Ray diffraction data sets for compounds **23** and **58** were collected with a Bruker APEX II CCD diffractometer. Programs used: data collection: APEX3 V2016.1-0 (Bruker AXS Inc., **2016**);[3] cell refinement: SAINT V8.37A (Bruker AXS Inc., **2015**); data reduction: SAINT V8.37A (Bruker AXS Inc., **2015**);[4] absorption correction, SADABS V2014/7 (Bruker AXS Inc., **2014**);[5] structure solution SHELXT-2015 (Sheldrick, **2015**); structure refinement SHELXL-2015 (Sheldrick, **2015**)[6] and graphics, XP (Bruker AXS Inc., **1998**).[7] *R*-values are given for observed reflections, and wR^2 values are given for all reflections.

2. Preparation of Starting Materials

TBS-protection of alcohols

TBS-protection of (3-fluoropyridin-4-yl)methanol, (3-fluoropyridin-2-yl)methanol, (5-fluoropyridin-2-yl)methanol, (3,5-difluoropyridin-2-yl)methanol[8] and 2-(5-fluoropyridin-2-yl)ethan-1-ol[9] was carried out according to the literature.[10]

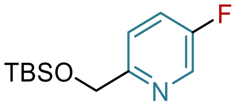
4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-fluoropyridine



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 1H), 8.33 (s, 1H), 7.47 (t, *J* = 5.6 Hz, 1H), 4.80 (s, 2H), 0.93 (d, *J* = 0.8 Hz, 9H), 0.10 (d, *J* = 0.8 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.64 (d, *J* = 254.3 Hz), 146.00 (d, *J* = 4.9 Hz), 137.58 (d, *J* = 11.9 Hz), 136.97 (d, *J* = 23.1 Hz), 122.06 (d, *J* = 1.8 Hz), 57.96 (d, *J* = 4.4 Hz), 25.90, 18.42, -5.39; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -134.2.

ESI-MS: calculated $[C_{12}H_{21}NOFSi]^+$: 242.1371, found 242.1381.

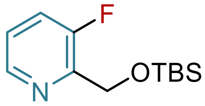
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-fluoropyridine



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.7 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.40 (td, *J* = 8.5, 2.8 Hz, 1H), 4.79 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.52 (d, *J* = 253.6 Hz), 157.32 (d, *J* = 3.7 Hz), 136.84 (d, *J* = 23.8 Hz), 123.43 (d, *J* = 18.2 Hz), 121.10 (d, *J* = 4.1 Hz), 65.72 (d, *J* = 1.5 Hz), 26.02, 18.47, -5.26; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -130.3.

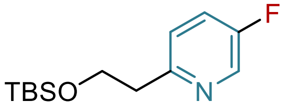
ESI-MS: calculated $[C_{12}H_{21}NOFSi]^+$: 242.1371, found 242.1375.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-fluoropyridine



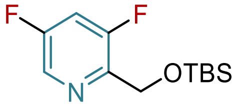
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 1H), 7.35 – 7.22 (m, 1H), 7.18 – 7.09 (m, 1H), 4.76 (d, *J* = 2.0 Hz, 2H), 0.80 (s, 9H), 0.00 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.07 (d, *J* = 259.0 Hz), 148.12 (d, *J* = 14.2 Hz), 144.97 (d, *J* = 5.4 Hz), 124.24 (d, *J* = 3.8 Hz), 123.27 (d, *J* = 18.9 Hz), 62.43 (d, *J* = 1.8 Hz), 26.02, 18.64, -5.13; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -125.3.
ESI-MS: calculated $[C_{12}H_{21}NOFSi]^+$: 242.1371, found 242.1372.

2-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-5-fluoropyridine



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.9 Hz, 1H), 7.35 (td, *J* = 8.3, 2.8 Hz, 1H), 7.25 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.02 (t, *J* = 6.4 Hz, 2H), 0.88 (s, 9H), 0.00 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.37 (d, *J* = 253.5 Hz), 155.73 (d, *J* = 4.0 Hz), 137.29 (d, *J* = 23.1 Hz), 124.87 (d, *J* = 3.9 Hz), 122.81 (d, *J* = 18.1 Hz), 62.84 (d, *J* = 0.9 Hz), 40.97, 25.95, 18.36, -5.38; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -131.3.
ESI-MS: calculated $[C_{13}H_{23}NOFSi]^+$: 256.1527, found: 256.1543.

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3,5-difluoropyridine

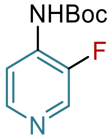


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.3 Hz, 1H), 7.18 (td, *J* = 9.2, 2.4 Hz, 1H), 4.83 (d, *J* = 2.0 Hz, 2H), 0.90 (s, 9H), 0.11 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.81 (dd, *J* = 261.3, 5.1 Hz), 157.39 (dd, *J* = 264.7, 5.9 Hz), 144.39 (dd, *J* = 14.2, 4.0 Hz), 133.14 (dd, *J* = 22.4, 4.8 Hz), 111.56 (t, *J* = 21.6 Hz), 61.88 (d, *J* = 1.8 Hz), 25.95, 18.56, -5.19; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -121.28 (d, *J* = 5.9 Hz), -124.61 (d, *J* = 5.9 Hz).
ESI-MS: calculated $[C_{12}H_{19}NOF_2Si +Na]^+$: 282.1102, found 282.1105.

Boc-protection of amines

Boc-protection of 3-fluoropyridin-4-amine and 5-fluoro-*1H*-pyrrolo[2,3-*b*]pyridine was carried out according to the literature.[11]

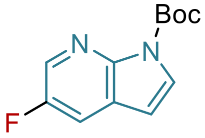
***tert*-Butyl (3-fluoropyridin-4-yl)carbamate**



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.6 Hz, 1H), 8.28 (d, *J* = 5.5 Hz, 1H), 8.10 (t, *J* = 6.3 Hz, 1H), 7.04 (bs, 1H), 1.53 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.11 (d, *J* = 70.1 Hz), 147.33, 146.87 (d, *J* = 5.4 Hz), 136.87 (d, *J* = 20.8 Hz), 134.22 (d, *J* = 8.0 Hz), 113.13, 82.43, 28.29; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -148.41.

ESI-MS: calculated $[C_{10}H_{14}N_2O_2F]^+$: 213.1034, found: 213.1036.

***tert*-Butyl 5-fluoro-*1H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate**



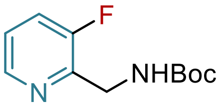
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 2.6, 1.1 Hz, 1H), 7.69 (d, *J* = 4.0 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.47 (d, *J* = 4.0 Hz, 1H), 1.65 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.71 (d, *J* = 247.0 Hz), 147.83, 144.70, 133.43 (d, *J* = 28.4 Hz), 128.70, 123.71 (d, *J* = 6.9 Hz), 115.11 (d, *J* = 20.9 Hz), 104.25 (d, *J* = 3.6 Hz), 84.47, 28.18; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -135.1.

ESI-MS: calculated $[C_{12}H_{13}N_2O_2F +Na]^+$: 259.0859, found: 259.0858.

Preparation of fluoropyridine methylcarbamate derivatives:

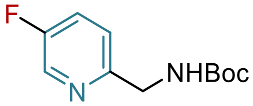
The preparation of the following starting materials was carried out according to the literature starting from 3-fluoropicolinonitrile, 5-fluoropicolinonitrile and 3,5-difluoropicolinonitrile respectively.[12]

tert-Butyl ((3-fluoropyridin-2-yl)methyl)carbamate



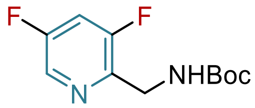
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 4.7 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.22 (dt, J = 8.6, 4.4 Hz, 1H), 5.75 (bs, 1H), 4.52 (d, J = 3.6 Hz, 2H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.04 (d, J = 257.8 Hz), 155.99, 145.27 (d, J = 15.6 Hz), 144.74 (d, J = 5.3 Hz), 123.61 (d, J = 3.6 Hz), 122.82 (d, J = 18.2 Hz), 79.63, 40.10, 28.52; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -126.2.
ESI-MS: calculated $[C_{11}H_{15}N_2O_2F +Na]^+$: 249.1010, found: 249.1017.

tert-Butyl ((5-fluoropyridin-2-yl)methyl)carbamate



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 2.8 Hz, 1H), 7.31 – 7.14 (m, 2H), 5.40 (bs, 1H), 4.30 (d, J = 5.6 Hz, 2H), 1.34 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.76 (d, J = 254.8 Hz), 156.07, 153.77 (d, J = 3.8 Hz), 137.32 (d, J = 23.8 Hz), 123.66 (d, J = 18.4 Hz), 122.69 (d, J = 3.6 Hz), 79.76, 45.33, 28.50; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -129.5.
ESI-MS: calculated $[C_{11}H_{15}N_2O_2F +Na]^+$: 249.1010, found: 249.1030.

tert-Butyl ((3,5-difluoropyridin-2-yl)methyl)carbamate

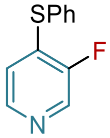


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.2 Hz, 1H), 7.18 (td, *J* = 9.1, 2.3 Hz, 1H), 5.64 (bs, 1H), 4.46 (s, 2H), 1.43 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.70 (dd, *J* = 225.2, 5.5 Hz), 156.10 (dd, *J* = 228.1, 5.5 Hz), 155.88, 141.64 (dd, *J* = 15.4, 3.7 Hz), 132.96 (dd, *J* = 23.0, 4.8 Hz), 111.44 (t, *J* = 21.5 Hz), 79.68, 39.88, 28.41; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -122.3, -125.6.

ESI-MS: calculated $[C_{11}H_{14}N_2O_2F_2 + Na]^+$: 267.0916, found: 267.0931.

Preparation of other fluoropyridine derivatives:

3-Fluoro-4-(phenylthio)pyridine

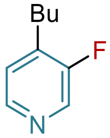


Following a modified literature procedure,[13] to a solution of LDA (1.12 g, 10.8 mmol, 1.05 equiv.) in THF (7.8 mL, 1.3 M) at -78 °C was added dropwise a solution of 3-fluoropyridine (0.88 mL, 10.3 mmol, 1.0 equiv.) in THF (2.5 mL, 5.3 M). After stirring for 30 min at -78 °C a white precipitate formed and a solution of diphenyl disulfide (2.42 g, 11.1 mmol, 1.08 equiv.) in THF (6.0 mL, 1.9 M) was added dropwise over a period of 30 min. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 15 h. After quenching the reaction by the addition of water (25 mL) and saturated aqueous $NaHCO_3$ solution (25 mL), the mixture was extracted with EtOAc (3×100 mL). The combined organic phases were washed with water and brine (2×) and dried over Na_2SO_4. Purification by column chromatography on silica (20% EtOAc in pentane) afforded 3-fluoro-4-(phenylthio)pyridine as a yellow oil (1.62 g, 7.88 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.7 Hz, 1H), 8.14 – 8.08 (m, 1H), 7.60 – 7.53 (m, 2H), 7.51 – 7.43 (m, 3H), 6.63 (dd, *J* = 6.4, 5.3 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.82 (d, *J* = 253.6 Hz), 145.64 (d, *J* = 5.0 Hz), 137.69 (d, *J* = 14.4 Hz), 136.89 (d, *J* = 23.3 Hz), 135.60, 130.25, 130.18, 128.00, 121.59; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -127.47.

ESI-MS: calculated $[C_{11}H_9FNS]^+$: 206.0434, found: 206.0436.

4-Butyl-3-fluoropyridine



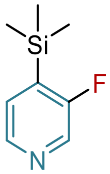
Following a modified literature procedure,[14] *n*BuLi (2.93 mL, 4.69 mmol, 1.1 equiv.) was added dropwise to a solution of 2-bromo-3-fluoropyridine (750 mg, 4.26 mmol, 1.0 equiv.) in THF (43 mL, 0.1 M) at -78 °C. After 15 min, 1-bromo butane (1.37 mL, 12.78 mmol, 3.0 equiv.) was added to the mixture at -78 °C. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 17 h. After quenching the reaction by the addition of water (100 mL), the mixture was extracted with Et_2O (3×100 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (0-20% Et_2O in pentane) to yield the title compound as a yellow oil (148 mg, 0.97 mmol, 23% - volatile).

NOTE: According to the literature,[14] direct lithiation of 2-bromo-3-fluoropyridine should generate 2-butyl-3-fluoropyridine, however in our case we observed the formation of 4-butyl-3-fluoropyridine instead.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 1.7 Hz, 1H), 8.30 (d, *J* = 4.8 Hz, 1H), 7.15 (t, *J* = 5.7 Hz, 1H), 2.67 (t, *J* = 7.8 Hz, 2H), 1.61 (p, *J* = 7.6 Hz, 2H), 1.38 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.67 (d, *J* = 253.8 Hz), 145.49 (d, *J* = 4.8 Hz), 138.66 (d, *J* = 13.6 Hz), 137.66 (d, *J* = 25.1 Hz), 125.23 (d, *J* = 2.5 Hz), 31.42 (d, *J* = 1.0 Hz), 28.14 (d, *J* = 2.0 Hz), 22.45, 13.90; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -133.50.

ESI-MS: calculated $[C_9H_{13}FN]^+$: 154.1027, found: 154.1012.

3-Fluoro-4-(trimethylsilyl)pyridine

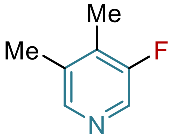


Following a modified literature procedure,[13] to a solution of LDA (1.12 g, 10.8 mmol, 1.05 equiv.) in THF (10 mL, 1.0 M) at -78 °C was added dropwise 3-fluoropyridine (0.86 mL, 10.0 mmol, 1.0 equiv.). After stirring for 30 min at -78 °C a white precipitate formed and chlorotrimethylsilane (1.40 mL, 11.0 mmol, 1.10 equiv.) was added dropwise. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 15 h. After quenching the reaction by the addition of water (25 mL) and saturated aqueous $NaHCO_3$ solution (25 mL), the mixture was extracted with EtOAc (3×25 mL). The combined organic phases were washed with water and brine (2×) and dried over Na_2SO_4. Purification by column chromatography on silica (0-10% EtOAc in pentane) afforded 3-fluoro-4-(trimethylsilyl)pyridine as a colorless oil (1.43 g, 8.4 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.13 (m, 2H), 7.14 – 7.08 (m, 1H), 0.15 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.93 (d, *J* = 250.3 Hz), 144.97 (d, *J* = 3.8 Hz), 137.17 (d, *J* = 28.6 Hz), 135.51 (d, *J* = 27.5 Hz), 128.87 (d, *J* = 7.3 Hz), -1.53(d, *J* = 1.0 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -115.3; **^{29}Si NMR** (79 MHz, $CDCl_3$) δ -3.37 (d, *J* = 5.2 Hz).

ESI-MS: calculated $[C_8H_{13}NFSi]^+$: 170.0796, found: 170.0798.

3-Fluoro-4,5-dimethylpyridine

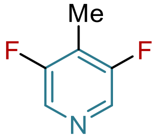


Following a modified literature procedure,[13] 3-fluoro-5-methylpyridine (0.5 g, 5.0 mmol, 1.0 equiv.) was added to a solution of LDA (0.59 g, 5.5 mmol, 1.1 equiv.) in THF (10 mL, 0.5 M) at -78 °C. After stirring for 30 min at -78 °C, iodomethane (0.34 mL, 5.5 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 15 h. After quenching the reaction by the addition of water (25 mL) and saturated aqueous $NaHCO_3$ solution (25 mL), the mixture was extracted with Et_2O (3×20 mL). The combined organic phases were washed with water and brine (2×) and dried over $MgSO_4$. Purification by column chromatography on silica (0-5% Et_2O in pentane) afforded 3-fluoro-4,5-dimethylpyridine as a colorless oil (292 mg, 2.33 mmol, 47% - volatile).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.14 (s, 1H), 2.25 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.56 (d, *J* = 252.4 Hz), 145.95 (d, *J* = 4.2 Hz), 135.21 (d, *J* = 25.5 Hz), 134.13 (d, *J* = 1.7 Hz), 132.46 (d, *J* = 13.6 Hz), 16.20 (d, *J* = 2.1 Hz), 10.57 (d, *J* = 4.8 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -133.7.

ESI-MS: calculated $[C_7H_9NF]^+$: 126.0714, found: 126.0713.

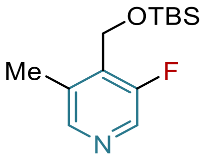
3,5-Difluoro-4-methylpyridine



Following a modified literature procedure,[13] 3,5-difluoropyridine (1.0 g, 8.68 mmol, 1.0 equiv.) was added to a solution of LDA (1.02 g, 9.54 mmol, 1.1 equiv.) in THF (20 mL, 0.43 M) at -78 °C. After stirring for 30 min at -78 °C, iodomethane (0.59 mL, 9.54 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 15 h. After quenching the reaction by the addition of water (25 mL) and saturated aqueous $NaHCO_3$ solution (25 mL), the mixture was extracted with Et_2O (3×20 mL). The combined organic phases were washed with water and brine (2×) and dried over $MgSO_4$. Purification by column chromatography on silica (0-10% Et_2O in pentane) afforded 3,5-difluoro-4-methylpyridine as a colorless oil (224 mg, 1.74 mmol, 20% - extremely volatile).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 2H), 2.28 (s, 3H); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$) δ 158.6, 133.3, 123.0, 7.1; **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$) δ -129.2.

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-fluoro-5-methylpyridine



Following a modified literature procedure,[15] 3-fluoro-5-methylpyridine (1.0 g, 9.0 mmol, 1.0 equiv.) was added to a solution of LDA (1.06 g, 9.9 mmol, 1.1 equiv.) in THF (13 mL, 0.7 M) at -78 °C. After stirring for 30 min at -78 °C, neat dimethylformamide (1.18 mL, 15.3 mmol, 1.7 equiv.) was added dropwise. The reaction mixture was allowed to slowly warm up to 0 °C then water (1.8 mL) was added, followed by the addition of $NaBH_4$ (0.51 g, 13.5 mmol, 1.5 equiv.). Upon the completion of the reaction, saturated aqueous $NaHCO_3$ solution (25 mL) was added. The mixture was extracted with EtOAc (3×20 mL) and the combined organic phases were washed with water and brine (2×) and dried over $MgSO_4$. Purification by column chromatography on silica (0-50% EtOAc in pentane) afforded (3-fluoro-5-methylpyridin-4-yl)methanol as a white solid (696 mg, 4.93 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.22 (s, 1H), 4.77 (d, *J* = 1.4 Hz, 2H), 2.69 (bs, 1H), 2.43 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.06 (d, *J* = 255.2 Hz), 146.93 (d, *J* = 4.4 Hz), 135.76 (d, *J* = 25.7 Hz), 134.66, 133.94 (d, *J* = 11.7 Hz), 54.97 (d, *J* = 5.1 Hz), 15.65 (d, *J* = 1.8 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -135.0.

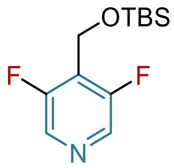
ESI-MS: calculated $[C_7H_9NOF]^+$: 142.0663, found: 142.0662.

TBS-protection of (3-fluoro-5-methylpyridin-4-yl)methanol (696 mg, 4.93 mmol) was carried out according to the literature[10] to afford 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluoro-5-methylpyridine as a colorless oil (1.16 g, 4.54 mmol, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.22 (s, 1H), 4.74 (d, *J* = 1.7 Hz, 2H), 2.41 (s, 3H), 0.88 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.46 (d, *J* = 254.8 Hz), 146.99 (d, *J* = 4.8 Hz), 135.81 (d, *J* = 25.8 Hz), 135.12, 133.89 (d, *J* = 11.8 Hz), 55.22 (d, *J* = 5.4 Hz), 25.88, 18.37, 15.76, -5.37; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -135.2.

ESI-MS: calculated $[C_{13}H_{23}NOFSi]^+$: 256.1527, found: 256.1527.

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3,5-difluoropyridine



Following a modified literature procedure,[8] to a suspension of 3,5-difluoroisonicotinic acid (1.0 g, 6.28 mmol, 1.0 equiv.) in ethanol (10 mL) at 0 °C was added thionyl chloride (4 mL). The solution was heated to 70 °C for 3 h. The reaction mixture was cooled to room temperature and excess of thionyl chloride was removed under reduced pressure to afford the ethyl ester hydrochloride salt. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 h.

To an ethanol solution of ethyl 3,5-difluoroisonicotinate hydrochloride salt from the previous step was added $NaBH_4$ (0.47 g, 12.5 mmol, 1.5 equiv.) at 0 °C. Upon the completion of the reaction, saturated aqueous $NaHCO_3$ solution (25 mL) was added. The mixture was extracted with EtOAc (3×20 mL) and the combined organic phases were washed with water and brine (2×) and dried over $MgSO_4$. Purification by column chromatography on silica (0-40% EtOAc in pentane) afforded (3,5-difluoropyridin-4-yl)methanol as a white solid (296 mg, 2.04 mmol, 32% overall yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 2H), 4.84 (s, 2H), 2.47 (bs, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.75 (dd, *J* = 261.3, 3.3 Hz), 134.49 (dd, *J* = 23.1, 5.6 Hz), 124.10, 52.64 (t, *J* = 3.5 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -130.6.

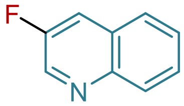
ESI-MS: calculated $[C_6H_6NOF_2]^+$: 146.0412, found: 146.0383.

TBS-protection of (3,5-difluoropyridin-4-yl)methanol (296 mg, 2.04 mmol) was carried out according to the literature[10] to afford 4-(((tert-butyldimethylsilyl)oxy)methyl)-3,5-difluoropyridine as a colorless oil (0.41 g, 1.6 mmol, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 2H), 4.79 (s, 2H), 0.89 (s, 9H), 0.11 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.85 (dd, *J* = 261.9, 3.4 Hz), 134.37 (d, *J* = 28.6 Hz), 124.48 (d, *J* = 16.3 Hz), 52.96 (t, *J* = 3.2 Hz), 25.84, 18.44, -5.40; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ -130.2.

ESI-MS: calculated $[C_{12}H_{20}NOF_2Si]^+$: 260.1277, found: 260.1268.

3-Fluoroquinoline



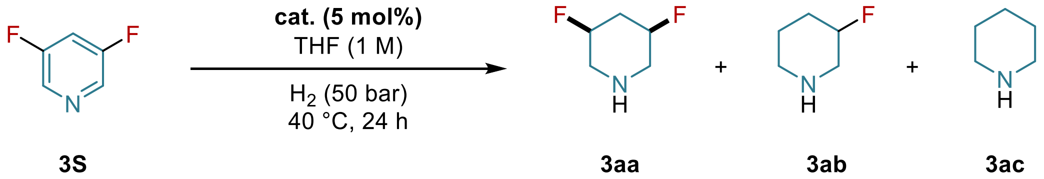
The title compound was prepared according to the literature. NMR spectra of the pure product were consistent with previously reported data.[16]

3. Reaction Optimization

General Procedure

An oven-dried reaction vessel (4 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then the indicated catalyst (and activated 4 Å MS (powdered, 50 mg)) was added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry solvent at the indicated concentration and liquid substrate (distilled over CaH_2, 1.0 equiv.). Then, if indicated, an additive was added at the indicated amount. The glass vial was then placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at the indicated temperature for the indicated time. After the autoclave was carefully depressurized, the reaction crude was filtrated over Whatman® filter. If indicated, trifluoroacetic anhydride (3.0 equiv.) and CH_2Cl_2 (0.5 mL) were added to the crude mixture and stirring was continued for 10 min at room temperature. After filtration over Whatman® filter, conversion and diastereomeric ratio (*d.r.*) were determined by ^{19}F NMR and GC analysis. NMR yield was calculated using hexafluorobenzene (20 µL, 0.173 mmol) as internal standard.

Evaluation of heterogeneous catalysts



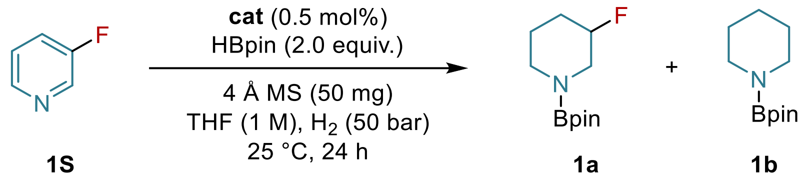
Supplementary Table 1. Screening of heterogeneous catalysts.

Entry	Catalyst	Conversion [%]	Yield **3aa** [%]	Yield **3ab** [%]
1	Rh/C	32	n.d.	5
2*	Rh/C	90	6	38
3	Rh/Al_2O_3	90	n.d.	18
4*	Rh/Al_2O_3	>99	32	53
5	Pd/C	<5	-	-
6	Ru/C	<5	-	-
7	PtO_2	<5	-	-

The reaction was carried out according to the general procedure on 0.25 mmol scale. NMR yields were determined using hexafluorobenzene (20 μL) as internal standard. n.d.: not detected. *HBpin (2 equiv.) was used as an additive.

Conclusion: Hydrogenation of fluoropyridine derivatives using heterogeneous catalysts is definitely possible, however the formation of fluorinated piperidine adducts in high chemoselective fashion is non-trivial due to the defluorination pathways.

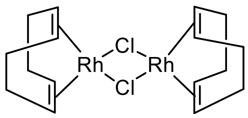
Evaluation of different rhodium catalysts



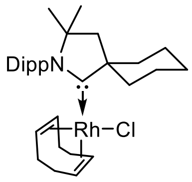
Supplementary Table 2. Screening of catalysts.

Entry	Catalyst	Conversion [%]	Yield **1a** [%]
1	[**Rh-1**]	>99	71
2*	[**Rh-2**]	<5	n.d.
3†	[**Rh-2**]	>99	<5
4‡	[**Rh-2**]	<5	n.d.
5	[**Rh-2**]	>99	92
6	[**Rh-3**]	87	77
7	[**Rh-4**]	82	71
8	[**Rh-5**]	95	80
9	[**Rh-6**]	25	17
10	[**Rh-7**]	<5	n.d.
11	[**Rh-8**]	<5	n.d.

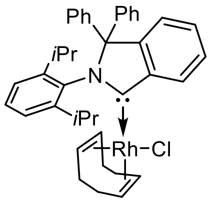
The reaction was carried out according to the general procedure on 1 mmol scale. NMR yields were determined using hexafluorobenzene (20 µL) as internal standard. n.d.: not detected. *The reaction was carried out in Hexane (1M) without the addition of HBpin. † The reaction was carried out in MeOH (1M) without the addition of HBpin. ‡ The reaction was carried out in THF (1M) without the addition of HBpin.



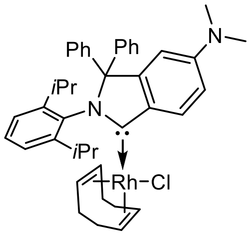
[RhCODCl]$_2$
[**Rh-1**]



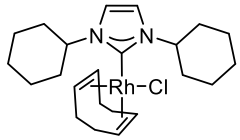
(CAAC)Rh(COD)Cl
[**Rh-2**]



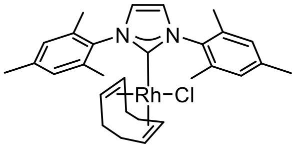
(CAArC)Rh(COD)Cl
[**Rh-3**]



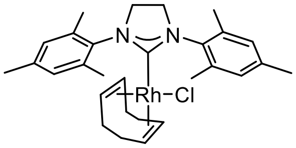
(CAArC(NMe$_2$))Rh(COD)Cl
[**Rh-4**]



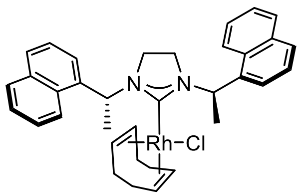
(ICy)Rh(COD)Cl
[**Rh-5**]



(IMes)Rh(COD)Cl
[**Rh-6**]



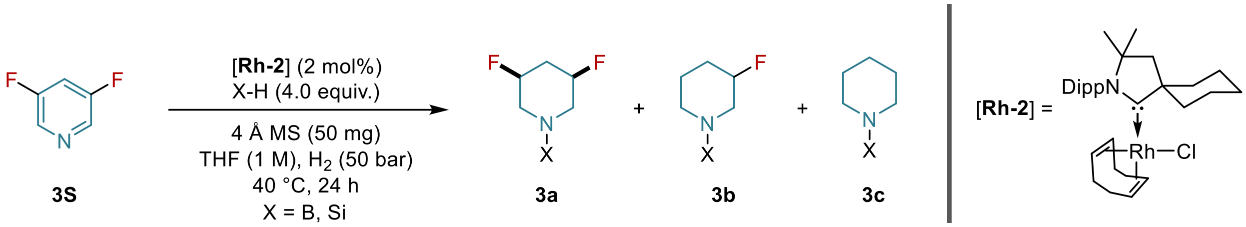
SIMesRh(COD)Cl
[**Rh-7**]



SINpEtRh(COD)Cl
[**Rh-8**]

Conclusion: Screening of different rhodium complexes for the dearomatization/hydrogenation of 3-fluoropyridine revealed that [**Rh-2**] complex afford the desired product with high efficiency and chemoselectivity. Other rhodium complexes such as [**Rh-3**] and [**Rh-5**] were found to be less compatible.

Evaluation of different hydride sources



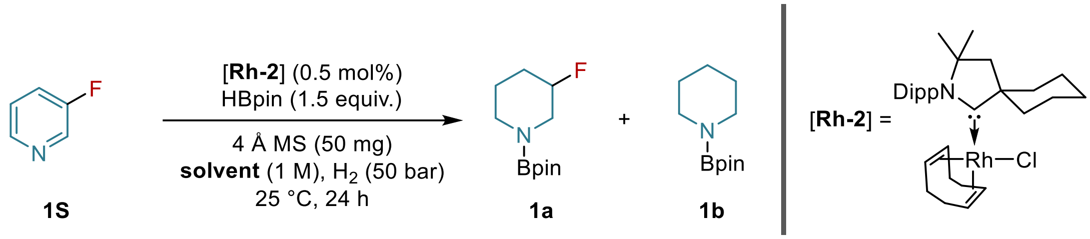
Supplementary Table 3. Screening of different hydride sources.

Entry	Hydride source	Conversion [%]	Yield **3a** [%]	Yield **3b** [%]
1*	HBpin	>99	95	<4
2	Catechol borane	59	10	n.d.
3†	9-Borabicyclo[3.3.1]nonane	90	34	n.d.
4	Dimethyl(phenyl)silane	<5	n.d.	n.d.
5	Methyl(phenyl)silane	20	5	n.d.
6	Phenylsilane	n.r	-	-
7	Triethoxysilane	n.r	-	-
8	Triethylsilane	n.r	-	-
9	Lithium aluminum hydride	n.r	-	-

The reaction was carried out according to the general procedure on 0.5 mmol scale. NMR yields were determined using hexafluorobenzene (20 µL) as internal standard. n.d.: not detected. *The reaction was carried out with 0.5 mol% catalyst and 2.0 equiv. of HBpin. †A solution of 9-borabicyclo[3.3.1]nonane in THF (0.5M) was used.

Conclusion: The **[Rh-2]** catalyzed dearomatization of 3,5-difluoropyridine and subsequent hydrogenation was highly efficient by employing HBpin as hydride source.

Evaluation of different solvents



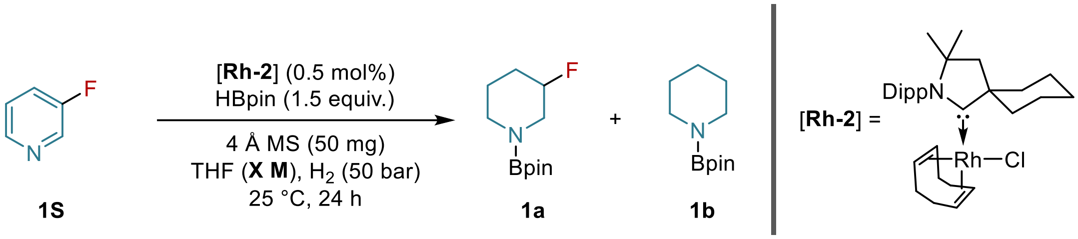
Supplementary Table 4. Screening of solvents.

Entry	Solvent	Conversion [%]	Yield **1a** [%]
1	MeOH	>99	n.d.
2	CH_2Cl_2	<5	n.d.
3	DCE	<5	n.d.
4	THF	92	86
5	2-MeTHF	81	69
6	1,4-Dioxane	50	36
7	MTBE	<5	n.d.
8	Et_2O	<5	n.d.
9	Et_2O:THF (1:1)	<5	n.d.
10	Hexane	<5	n.d.

The reaction was carried out according to the general procedure on 1 mmol scale. n.d.: not detected. NMR yields were determined using hexafluorobenzene (20 µL) as internal standard.

Conclusion: The desired product was obtained in high chemoselectivity when carrying out the reaction in THF. More polar solvents such as MeOH allowed, almost quantitatively, the formation of the undesired product **1b**.

Evaluation of different reaction concentration



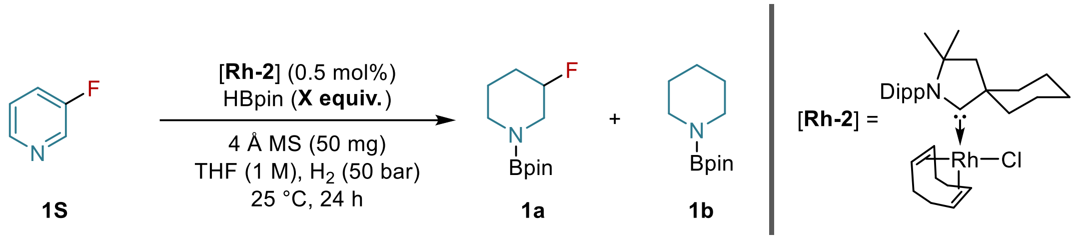
Supplementary Table 5. Screening of different concentration.

Entry	Concentration [M]	Conversion [%]	Yield **1a** [%]
1	0.25	>99	36
2	0.5	90	44
3	1.0	92	86

The reaction was carried out according to the general procedure on 1 mmol scale. NMR yields were determined using hexafluorobenzene (20 µL) as internal standard.

Conclusion: Carrying out the reaction in more concentrated media allows the formation of the desired product **1a** in a chemoselective fashion.

Evaluation of different amount of HBpin



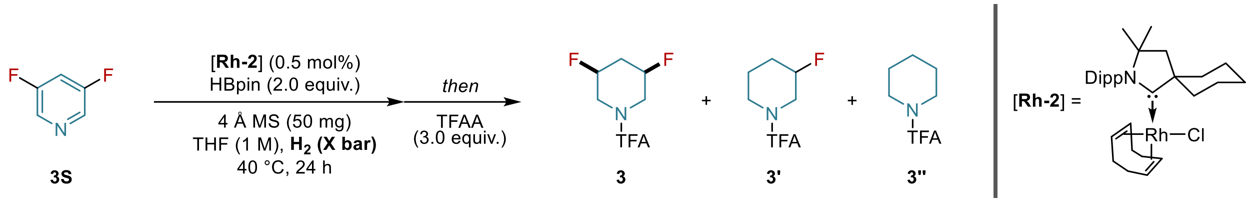
Supplementary Table 6. Screening of different amount of HBpin.

Entry	HBpin (equiv.)	Conversion [%]	Yield **1a** [%]
1	0.5	40	34
2	1.0	71	62
3	1.5	92	86
4	2.0	>99	92

The reaction was carried out according to the general procedure on 1 mmol scale. NMR yields were determined using hexafluorobenzene (20 µL) as internal standard.

Conclusion: Addition of high amount of HBpin improves the reaction efficiency. We also observed that high quantities of HBpin improve the diastereoselective ratio in the hydrogenation of substituted fluoropyridine derivatives (not shown).

Evaluation of different hydrogen pressure



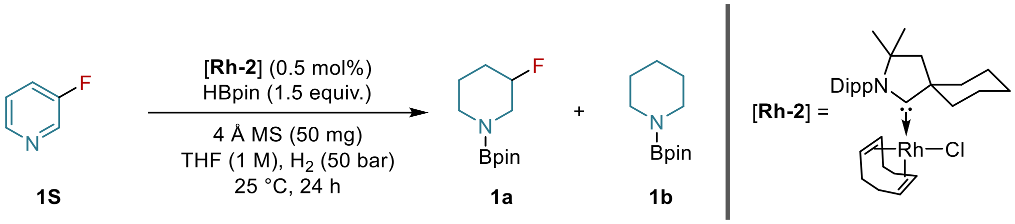
Supplementary Table 7. Screening of the hydrogen pressure.

Entry	Pressure	Conversion [%]	Yield **3** [%] (*d.r.*)*	Yield **3’** [%]
1†	10	53	31	3
2†	20	>99	84 (92:8)	12
3	50	>99	95 (>99:1)	<4

The reaction was carried out according to the general procedure on 0.5 mmol scale. NMR yields were determined using hexafluorobenzene (20 μL) as internal standard. TFAA: trifluoroacetic anhydride; TFA: trifluoroacetyl. *Diastereomeric ratio (*d.r.*) was determined by GC analysis of the TFA-protected piperidine. †A mixture of reaction intermediates was observed by ^{1}H and ^{19}F NMR.

Conclusion: A clean process was obtained with high pressure of molecular hydrogen. We also observed increase in diastereoselective ratios of the final product by increasing the reaction pressure.

Different suppliers of HBpin

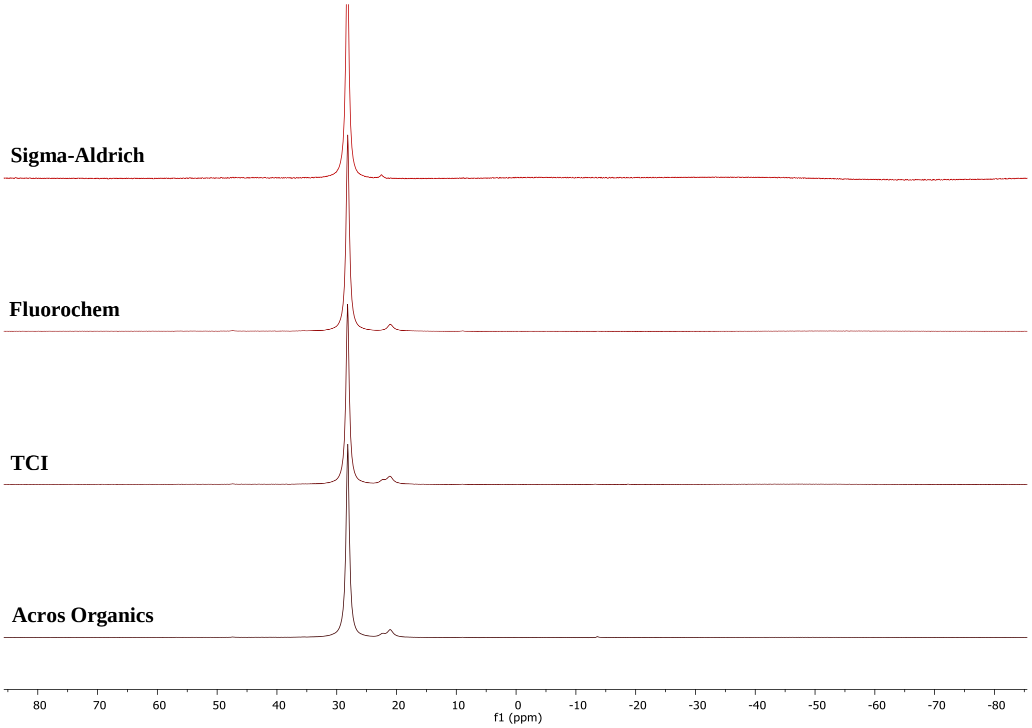


Supplementary Table 8. Screening of different suppliers of HBpin.

Entry	Supplier	Conversion [%]	Yield **1a** [%]
1	TCI	58	43
2	Acros Organics	30	19
3	Fluorochem	>99	68
4*	Fluorochem	>99	63
5†	Sigma-Aldrich	92	86

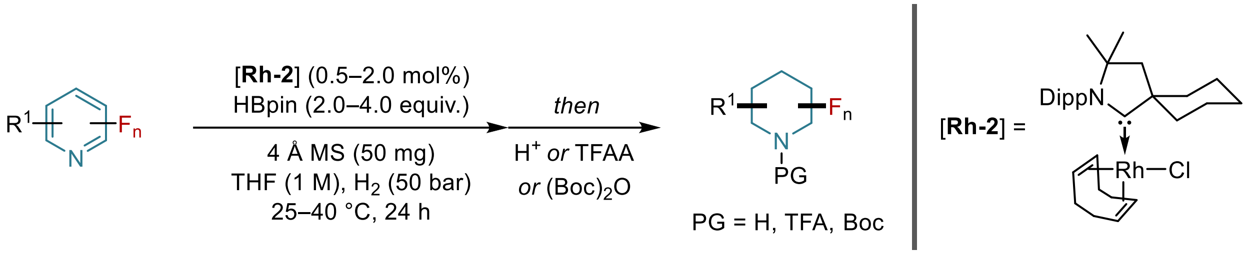
The reaction was carried out according to the general procedure on 1 mmol scale. NMR yields were determined using hexafluorobenzene (20 µL) as internal standard. *HBpin was distilled under argon atmosphere. †This batch was obtained sealed under argon.

Conclusion: HBpin from different chemical suppliers can dramatically affect the reactivity of the hydrogenation process. We believe that the presence of hydrolyzed HBpin can poison the catalyst which can lead to lower reactivity. ^{11}B NMR revealed that HBpin supplied from Sigma-Aldrich contain less than 1% of pinBOH while batches from other suppliers were found to contain at least 10% of the hydrolyzed species (Supplementary Fig. 1).



Supplementary Figure 1. ^{11}B NMR of HBpin from different suppliers. Different quantities of pinBOH (δ_B 22.2) were observed.

4. Synthesis of all-*cis*-(multi)fluorinated piperidines

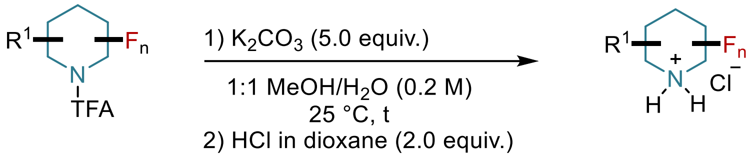


General procedure A

An oven-dried reaction vessel (4 or 9 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 50 mg), [**Rh-2**] (and solid substrates, 1.0 equiv.) were added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (1 M) (and liquid substrates – distilled over CaH_2, 1.0 equiv.). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 – 4.0 equiv. as indicated), the glass vial was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at the indicated temperature for 24 h. After the autoclave was carefully depressurized, trifluoroacetic anhydride (3.0 equiv.) and CH_2Cl_2 (0.5 mL) were added to the crude mixture and stirring was continued for 10 min at room temperature. Alternatively, di-*tert*-butyl dicarbonate (3.0 equiv.), triethyl amine (3.0 equiv.) and CH_2Cl_2 (0.5 mL) were added to the reaction mixture and stirring was continued for 2 h at room temperature. The crude was then filtered over fritted funnel and the remaining solid was washed with ethyl acetate (2×5 mL). The combined solution was concentrated under reduced pressure and submitted to column chromatography (pentane/ethyl acetate or pentane/dichloromethane) to obtain the final product. The indicated diastereoselectivities were determined by GC analysis or from the ^{19}F NMR spectrum immediately after the reaction. NMR yield was calculated using hexafluorobenzene (20 µL, 0.173 mmol) as internal standard.

General procedure B

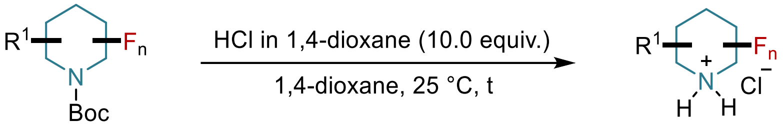
Deprotection of TFA-fluoropiperidine derivatives to the corresponding hydrochloride salts.



Following a literature procedure,[17] K_2CO_3 (5.0 equiv) was added in one portion to a solution of TFA-fluoropiperidine derivative (1.0 equiv.) in 1:1 methanol/water (0.2 M) at room temperature. After stirring the solution for the indicated time, the reaction mixture was acidified with 2 M aqueous solution of HCl. After removal of all volatiles, 2 M aqueous solution of NaOH and CH_2Cl_2 (5 mL) were added. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, dried over Mg_2SO_4 and filtrated. HCl (4 M in 1,4-dioxane, 2.0 equiv.) was added to the filtrate and all volatiles were removed to yield the corresponding fluoropiperidine hydrochloride as a white solid.

General procedure C

Deprotection of Boc-fluoropiperidine derivatives to the corresponding hydrochloride salts.



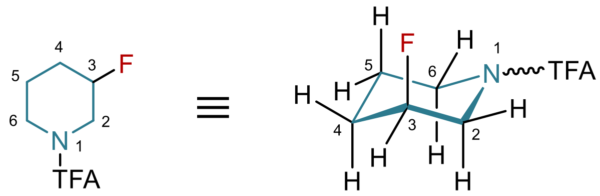
Following a literature procedure,[18] to a solution of the *N*-Boc-fluoropiperidine (1.0 equiv.) in 1,4-dioxane (0.85 M) was added HCl (4 M in 1,4-dioxane, 10.0 equiv.). The mixture was stirred at room temperature for the indicated time. Upon the completion of the reaction (followed by TLC), all volatiles were removed to yield the corresponding fluoropiperidine hydrochloride as a white solid.

Fluorinated piperidine conformational behavior

In order to determine whether the fluorine atoms adopt the axial or equatorial orientation on the piperidine ring, a series of NMR experiments were conducted. It should be noted that the vicinal ^{3}J(F,H) coupling constants are known to provide useful insight into the conformational structure, as large values of ^{3}J(F,H$_a$) indicate an axial orientation and small values of ^{3}J(F,H$_a$) indicate an equatorial orientation of the fluorine substituent due to a poorer orbital overlap (Karplus equation).[19] Considering this, we selected 18 relatively simple building blocks, which can cover a wide range of substitution patterns on the piperidine ring, from our scope (Fig. 2). Then, we conducted a complete NMR analysis for each example, including low and high temperature measurements, to first determine whether a single conformer or a mixture of conformers is obtained. Furthermore, we checked our assignment of the axial or equatorial orientation of the fluorine atoms as well as the rest of substituents on the ring through nuclear Overhauser effect (NOE) and heteronuclear NOE experiments for each example,. In all cases, the assigned orientations were in complete agreement with the obtained ^{3}J(F,H$_a$) values (Supplementary Table 9). Finally, the agreement of the assignments conducted via the ^{3}J(F,H$_a$) values and those conducted by NOE and Het-NOE experiments was further verified for a selected number of other scope entries (**33**, **38**). For the homonuclear NOE, the 1D-NOESY sequence with a mixing time of 0.5 seconds was employed. For the heteronuclear NOE, the 2D-HOESY sequence with ^{1}H- and ^{19}F-detection using a mixing time of 0.3 seconds was applied. For determining the ^{3}J(F,H$_a$) selective, multi-selective and band-selective decoupling schemes were used. This was done using the Pbox provided by Vnmrj of Agilent. If necessary, ^{19}F-decoupling was applied during the 1D-NOESY sequence.

Since the determination of the axial or equatorial orientation of the fluorine atoms is usually easier via ^{3}J(F,H$_a$) coupling by ^{1}H and ^{1}H{^{19}F} NMR than via NOE techniques, the former technique was employed for determining the fluorine orientation for the rest of the scope entries.

2,2,2-Trifluoro-1-(3-fluoropiperidin-1-yl)ethan-1-one (1)



Following general Procedure A on 1 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 25 °C, purification with 0-40% ethyl acetate in pentane. The product was isolated as a colorless oil (162 mg, 0.81 mmol, 81% (volatile compound, 92% NMR yield)). The product was present as a ~1:1 mixture of amide bond rotamers.

Rotamer A: **^{1}H NMR** (600 MHz, Toluene-d_8, 299 K) δ 3.94 (dtt, J = 47.0, 5.6, 2.2 Hz, 1H), 3.63 (ddd, J = 13.8, 8.9, 5.6 Hz, 1H), 3.01 (d, J = 14.3 Hz, 1H), 2.89 (dd, J = 26.0, 13.8 Hz, 1H), 2.65 – 2.59 (m, 1H), 1.39 – 1.28 (m, 2H), 1.14 – 0.95 (m, 1H), 0.86 – 0.77 (m, 1H); **^{1}H{^{19}F} NMR** (600 MHz, Toluene-d_8, 299 K) δ 3.94 (tt, J = 5.6, 2.2 Hz, 1H), 3.63 (dd, J = 13.8, 5.6 Hz, 1H), 3.01 (d, J = 14.3 Hz, 1H), 2.89 (dd, J = 13.8, 2.2 Hz, 1H), 2.61 (ddd, J = 14.3, 8.8, 3.1 Hz, 1H), 1.39 – 1.28 (m, 2H), 1.11 – 0.97 (m, 1H), 0.87 – 0.78 (m, 1H); **^{13}C NMR** (151 MHz, Toluene-d_8, 299 K) δ 155.90 – 155.49 (m), 117.18 (q, J = 288.2 Hz), 85.33 (d, J = 176.5 Hz), 46.73 (d, J = 25.4 Hz), 45.13 (q, J = 3.5 Hz), 29.26 (d, J = 21.1 Hz), 21.45 (d, J = 4.4 Hz); **^{13}C{sel-^{19}F at -185 ppm} NMR** (151 MHz, Toluene-d_8, 299 K) δ 155.96 – 155.39 (m), 117.18 (q, J = 288.2 Hz), 85.33, 46.73, 45.13 (q, J = 3.5 Hz), 29.26, 21.45; **^{19}F NMR** (564 MHz, Toluene-d_8, 299 K) δ -69.21, -184.91 – -185.20 (m); **^{19}F{^{1}H} NMR** (564 MHz, Toluene-d_8, 299 K) δ -69.21, -185.07.

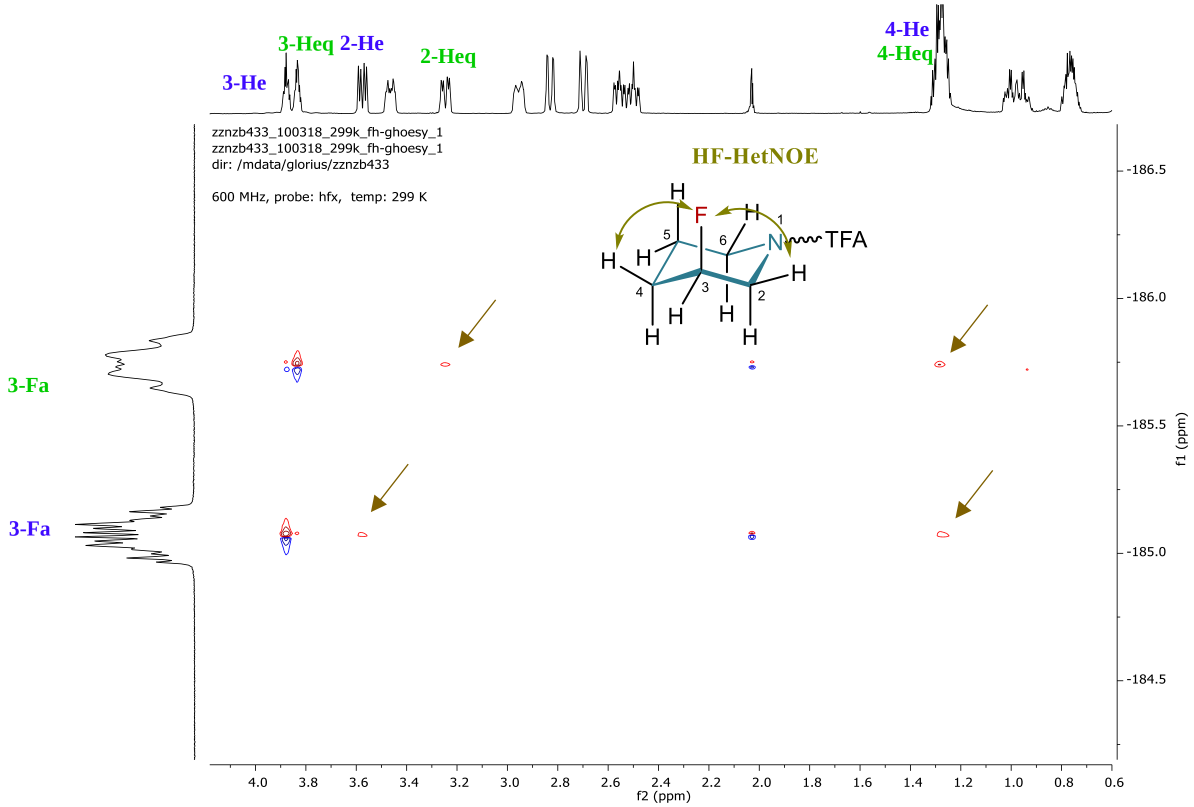
Rotamer B: **^{1}H NMR** (600 MHz, Toluene-d_8, 299 K) δ 3.89 (dtt, J = 47.0, 5.3, 2.0 Hz, 1H), 3.52 (dt, J = 13.4, 4.8 Hz, 1H), 3.30 (ddd, J = 14.3, 8.4, 5.3 Hz, 1H), 2.76 (ddd, J = 26.0, 14.3, 2.0 Hz, 1H), 2.59 – 2.53 (m, 1H), 1.39 – 1.27 (m, 2H), 1.13 – 0.94 (m, 1H), 0.86 – 0.78 (m, 1H); **^{1}H{^{19}F} NMR** (600 MHz, Toluene-d_8, 299 K) δ 3.89 (tt, J = 5.3, 2.0 Hz, 1H), 3.52 (dt, J = 13.4, 4.8 Hz, 1H), 3.30 (dd, J = 14.3, 5.3 Hz, 1H), 2.76 (dd, J = 14.3, 2.0 Hz, 1H), 2.56 (ddd, J = 13.4, 9.6, 3.2 Hz, 1H), 1.38 – 1.29 (m, 2H), 1.10 – 0.97 (m, 1H), 0.86 – 0.77 (m, 1H); **^{13}C NMR** (151 MHz, Toluene-d_8, 299 K) δ 156.16 – 155.39 (m), 117.15 (q, J = 288.6 Hz), 85.22 (d, J = 176.6 Hz), 48.85 (dq, J = 25.4, 3.5 Hz), 43.03, 29.11 (d, J = 20.9 Hz), 20.21 (d, J = 4.2 Hz); **^{13}C{sel-^{19}F at -185 ppm} NMR** (151 MHz, Toluene-d_8, 299 K) δ 155.98 – 155.44 (m), 117.16 (q, J = 288.6 Hz), 85.22, 48.85 (q, J = 3.5 Hz), 43.03, 29.11, 20.21; **^{19}F NMR** (564 MHz, Toluene-d_8, 299 K) δ -

68.46 (d, J = 2.8 Hz), -185.59 – -185.88 (m); **^{19}F{^{1}H} NMR** (564 MHz, Toluene-d_8, 299 K) δ -68.46 (d, J = 3.1 Hz), -185.74.

ESI-MS: calculated $[C_7H_9NOF_4 + Na]^+$: 222.0518, found: 222.0522.

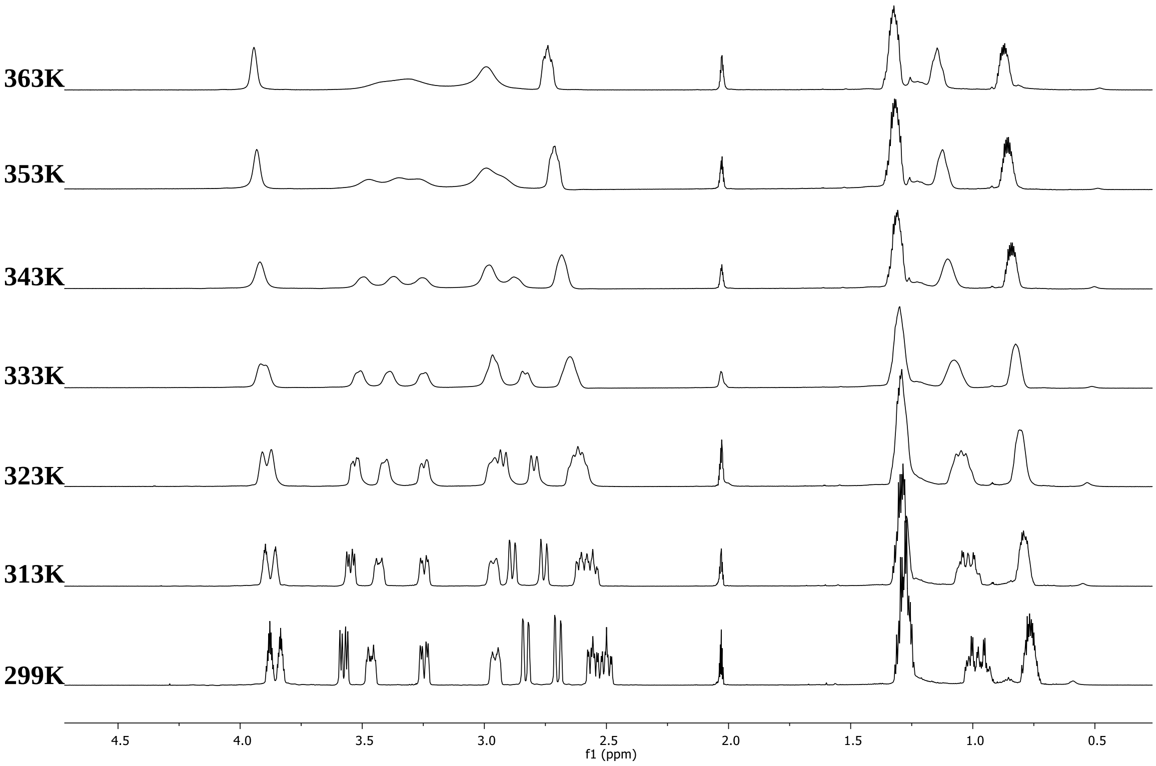
IR ν = 2955 (w), 1689.7 (s), 1465.9 (w), 1435.1 (w), 1373.3 (w), 1180.5 (s), 1141.9 (s), 1087.9 (m), 1003 (w), 972.1 (w), 910.4 (w), 756.1 (m), 748.4 (m), 732.9 (m), 648.1 (w).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. HF-HetNOE experiments showed unequivocally that the dominant orientation of the fluorine atom is axial (Supplementary Fig. 2).

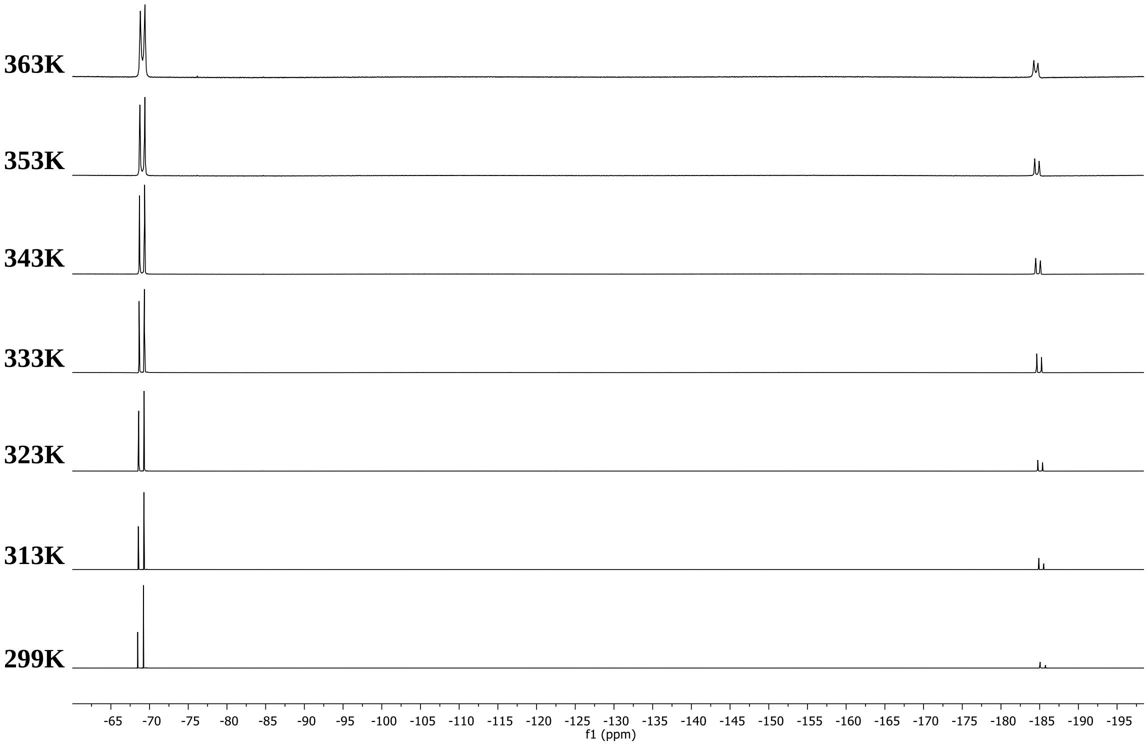


Supplementary Figure 2. 2D HF-Het-NOESY experiment for **1**.

The dynamics of conformational rotation of N–$COCF_3$ bond in **1** was monitored by ^{1}H{^{19}F} and ^{19}F{^{1}H} NMR experiments at different temperatures. At high temperature (363 K), the rotation was fast on the NMR time scale and single and/or broad merged peaks were observed (Supplementary Fig. 3–4).



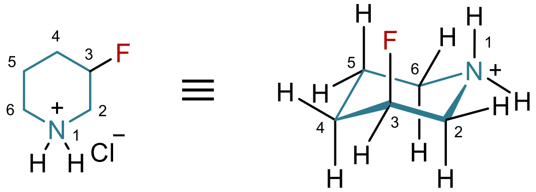
Supplementary Figure 3. $^{1}H\{^{19}F\}$ NMR experiments for **1** at different temperatures.



Supplementary Figure 4. $^{19}F\{^{1}H\}$ NMR experiments for **1** at different temperatures.

We also tried to verify whether this sample contain a mixture of conformers by measuring NMR at different low temperatures. However, we were unable to detect the equatorial conformer. Therefore we strongly believe that the dominant orientation of the fluorine atom is axial.

3-Fluoropiperidine hydrochloride (2)



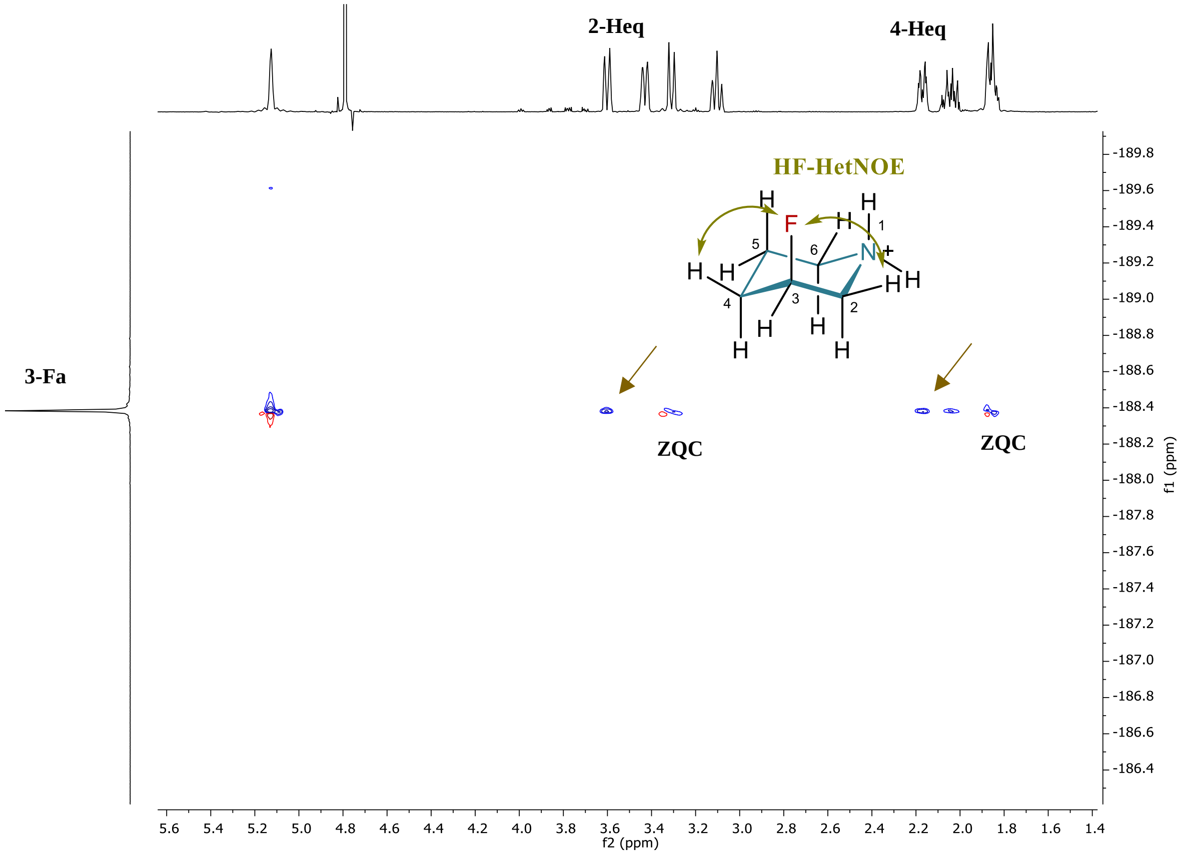
Compound **2** was prepared according to the general procedure B starting from 2,2,2-trifluoro-1-(3-fluoropiperidin-1-yl)ethan-1-one (**1**) (102 mg, 0.51 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for five minutes. Extraction and removal of all volatiles afforded the title compound as a white solid (50.0 mg, 0.36 mmol, 70%).

^{1}H NMR (599 MHz, D_2O, 299 K) δ 5.13 (d, *J* = 44.5 Hz, 1H), 3.60 (dddt, *J* = 14.0, 10.7, 3.2, 1.8 Hz, 1H), 3.43 (dm, *J* = 12.7 Hz, 1H), 3.31 (dd, *J* = 38.7, 14.1 Hz, 1H), 3.10 (t, *J* = 12.0 Hz, 1H), 2.21 – 2.14 (m, 1H), 2.09 – 2.00 (m, 1H), 1.93 – 1.77 (m, 2H); **^{1}H{^{19}F} NMR** (599 MHz, D_2O, 299 K) δ 5.13 (s, 1H), 3.60 (ddt, *J* = 14.0, 3.3, 1.8 Hz, 1H), 3.43 (dm, *J* = 12.7 Hz, 1H), 3.31 (d, *J* = 14.1 Hz, 1H), 3.10 (tm, *J* = 12.8 Hz, 1H), 2.21 – 2.15 (m, 1H), 2.09 – 1.99 (m, 1H), 1.90 – 1.82 (m, 2H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 85.08 (d, *J* = 168.5 Hz), 46.30 (d, *J* = 21.5 Hz), 43.44, 25.85 (d, *J* = 20.9 Hz), 16.56 (d, *J* = 2.3 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 85.1, 46.3, 43.4, 25.8, 16.6; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -188.20 – -188.55 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -188.4.

ESI-MS: calculated $[C_5H_{11}FN]^+$: 104.0870, found: 104.0866.

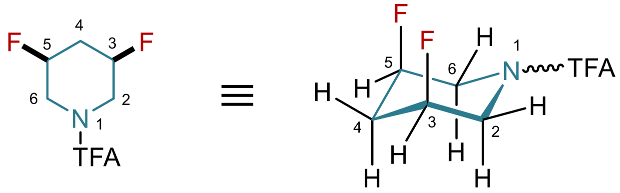
IR ν = 3341 (w), 2924 (m), 2785 (m), 2716 (m), 2616 (m), 2538 (m), 2340 (w), 1589 (m), 1443 (m), 1420 (m), 1358 (m), 1188 (w), 1142 (m), 1088 (m), 1034 (m), 949 (s), 895 (m), 841 (m), 802 (m), 694 (w), 579 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. HF-HetNOE experiment showed unequivocally that the fluorine atom adopts axial orientation (Supplementary Fig. 5).



Supplementary Figure 5. 2D HF-Het-NOESY experiment for **2**.

1-(*cis*-3,5-Difluoropiperidin-1-yl)-2,2,2-trifluoroethan-1-one (3)



Following general Procedure A on 1 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-100% CH_2Cl_2 in pentane. The product was isolated as a white solid (171 mg, 0.79 mmol, 79% (volatile compound, 95% NMR yield), *d.r.* >99:1).

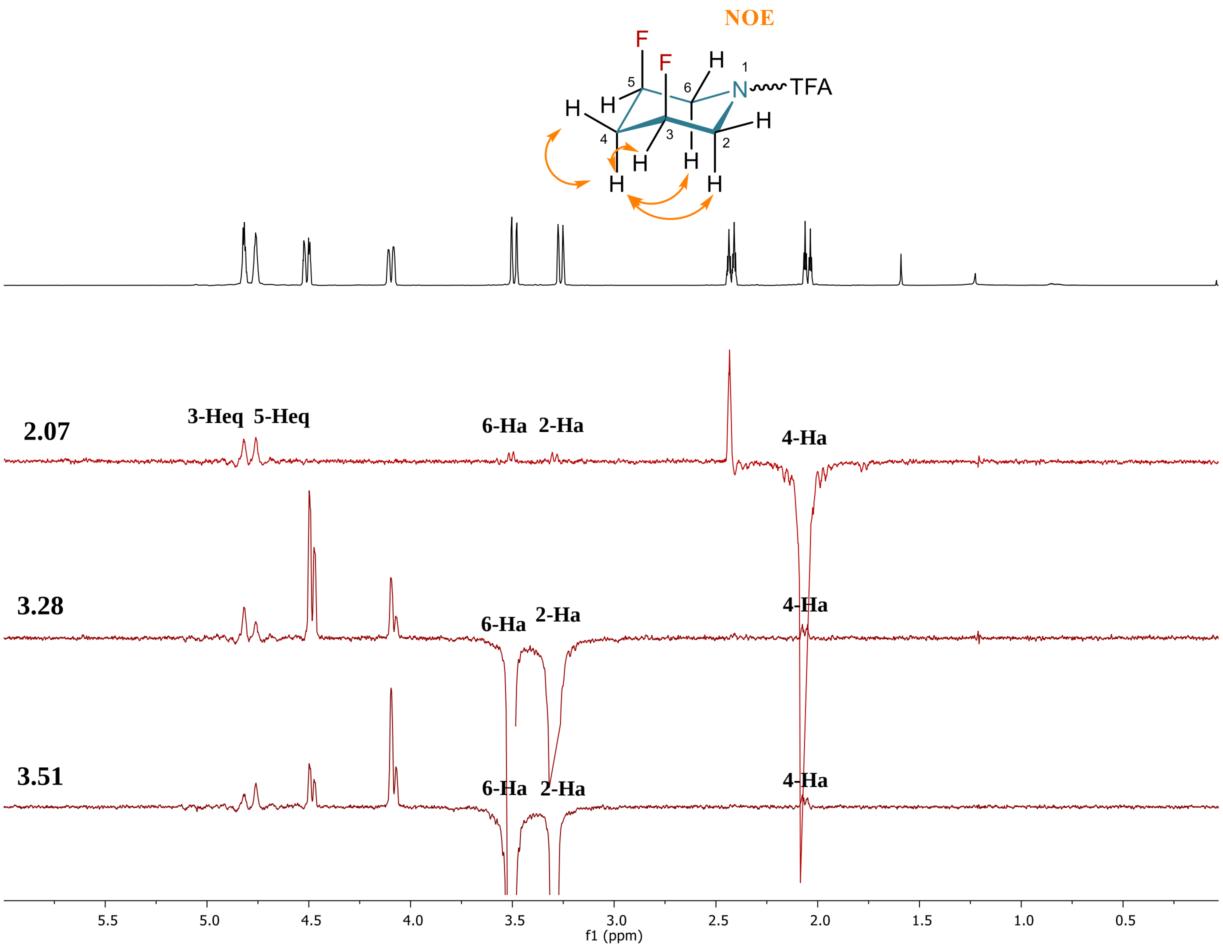
^{1}H NMR (600 MHz, $CDCl_3$, 299 K) δ 4.85 (dm, *J* = 34.3 Hz, 1H), 4.77 (dm, *J* = 34.5 Hz, 1H), 4.53 (ddm, *J* = 14.3, 10.8 Hz, 1H), 4.12 (ddm, *J* = 14.9, 9.2 Hz, 1H), 3.51 (ddd, *J* = 30.6, 14.9, 2.0 Hz, 1H), 3.29 (dd, *J* = 32.1, 14.3 Hz, 1H), 2.44 (ddddt, *J* = 15.5, 12.0, 12.0, 2.0, 2.0 Hz, 1H), 2.07 (tdt, *J* = 36.1, 15.5, 3.5 Hz, 1H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.84 (p, *J* = 3.5 Hz, 1H), 4.81 – 4.76 (m, 1H), 4.53 (ddd, *J* = 14.3, 3.9, 2.0 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.51 (dd, *J* = 14.9, 2.0 Hz, 1H), 3.28 (d, *J* = 14.3 Hz, 1H), 2.44 (dtt, *J* = 15.5, 4.0, 2.0 Hz, 1H), 2.07 (dt, *J* = 15.5, 3.5 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.12 (q, *J* = 36.4 Hz), 116.34 (q, *J* = 288.0 Hz), 83.53 (dd, *J* = 180.5, 1.3 Hz), 83.84 (dd, *J* = 180.9, 2.9 Hz), 48.67 (d, *J* = 23.6, 3.4 Hz), 46.47 (d, *J* = 23.7 Hz), 33.73 (t, *J* = 21.1 Hz); **^{13}C{sel-^{19}F at -68 and -183 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.0, 116.1, 83.7, 83.4, 48.5, 46.3, 33.6; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.27 (d, *J* = 4.0 Hz), -183.21 – -183.87 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.27 (d, *J* = 4.1 Hz), -183.51 (d, *J* = 12.4 Hz), -183.68 (dq, *J* = 12.4, 4.1 Hz).

ESI-MS: calculated $[C_7H_8NOF_5 +Na]^+$: 240.0424, found: 240.0427.

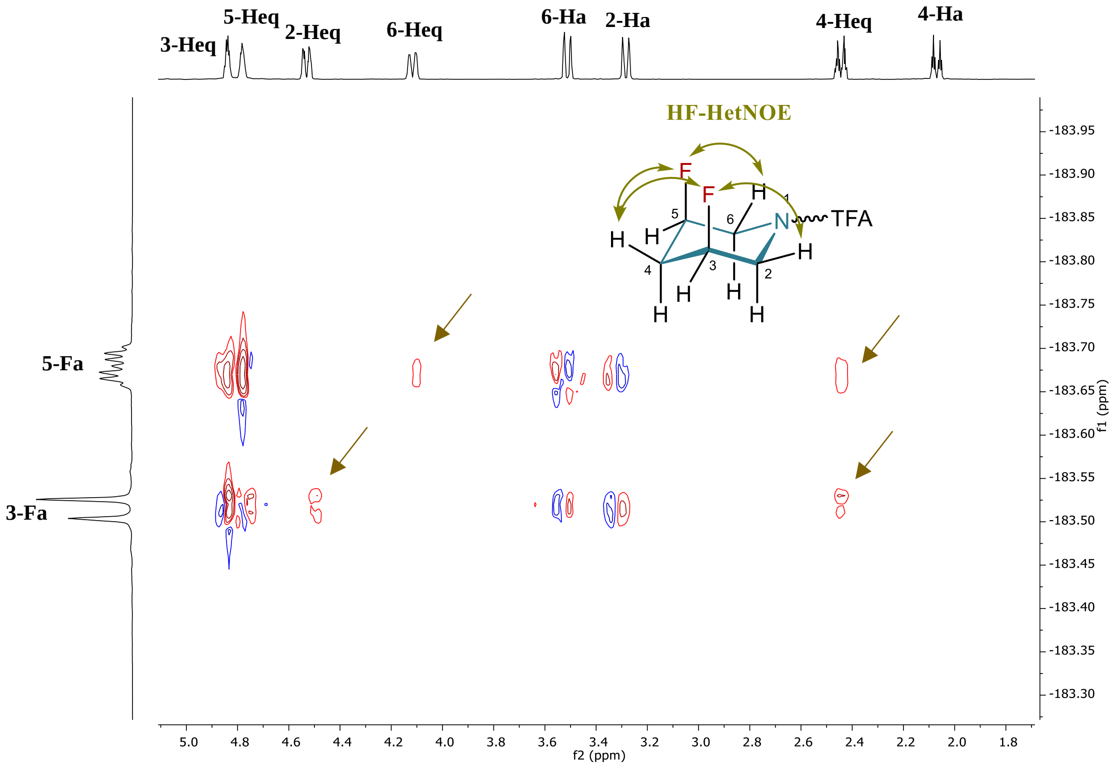
IR ν = 2916.5 (w), 2360.9 (w), 1689.7 (s), 1465.9 (m), 1419.6 (w), 1381.1 (w), 1303.9 (w), 1188.2 (s), 1134.2 (s), 1095.6 (s), 1064.7 (s), 972.2 (w), 918.1 (m), 879.6 (m), 848.7 (m), 771.5 (m), 748.4 (w), 671.2 (w), 624.9 (w).

M.p: 64-65 °C.

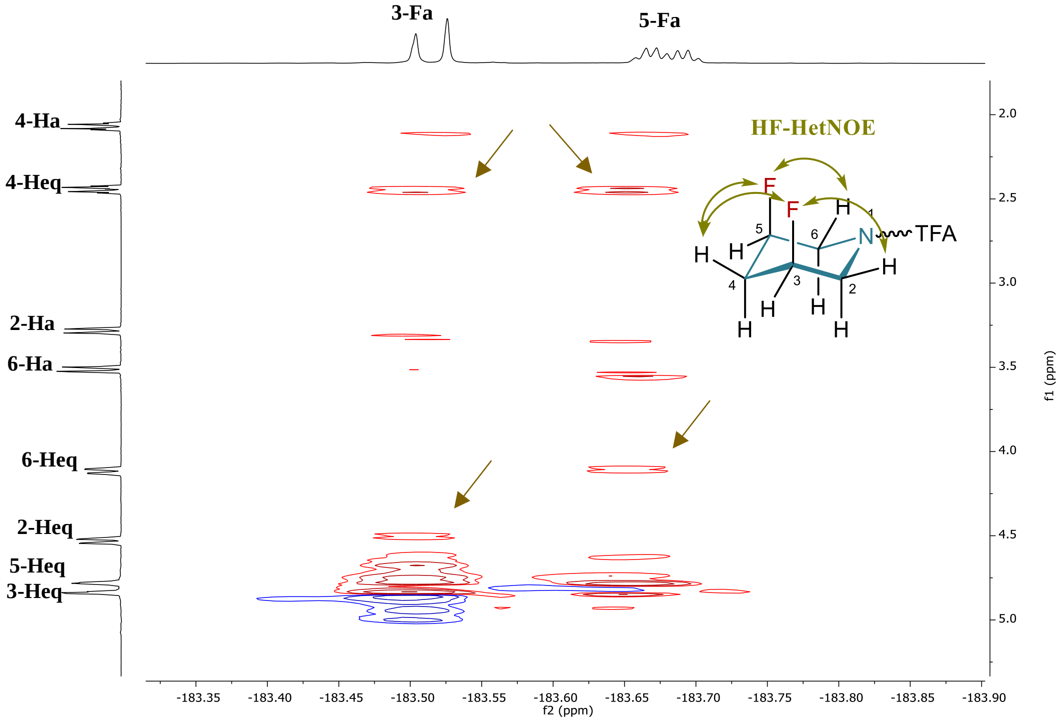
In order to prove whether the fluorine atoms are occupying axial or equatorial positions, we conducted a series of NMR studies that includes NOE and HF/FH-HetNOE experiments. All those experiments showed unequivocally that the dominant orientation of the fluorine atoms is axial (Supplementary Fig. 6–8).



Supplementary Figure 6. Selected 1D NOESY experiments for **3**. Irradiation at 3.51, 3.28, 2.07 ppm, respectively. Chemical exchange (2-H_a ↔ 6-H_a) was observed during the mixing time.

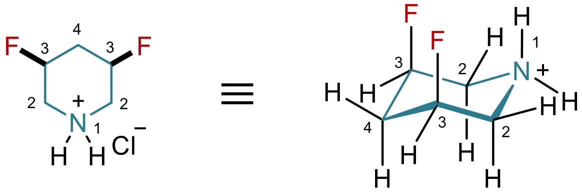


Supplementary Figure 7. 2D HF-Het-NOESY experiment for **3**.



Supplementary Figure 8. 2D FH-Het-NOESY experiment for **3**.

cis-3,5-Difluoropiperidine hydrochloride (4)



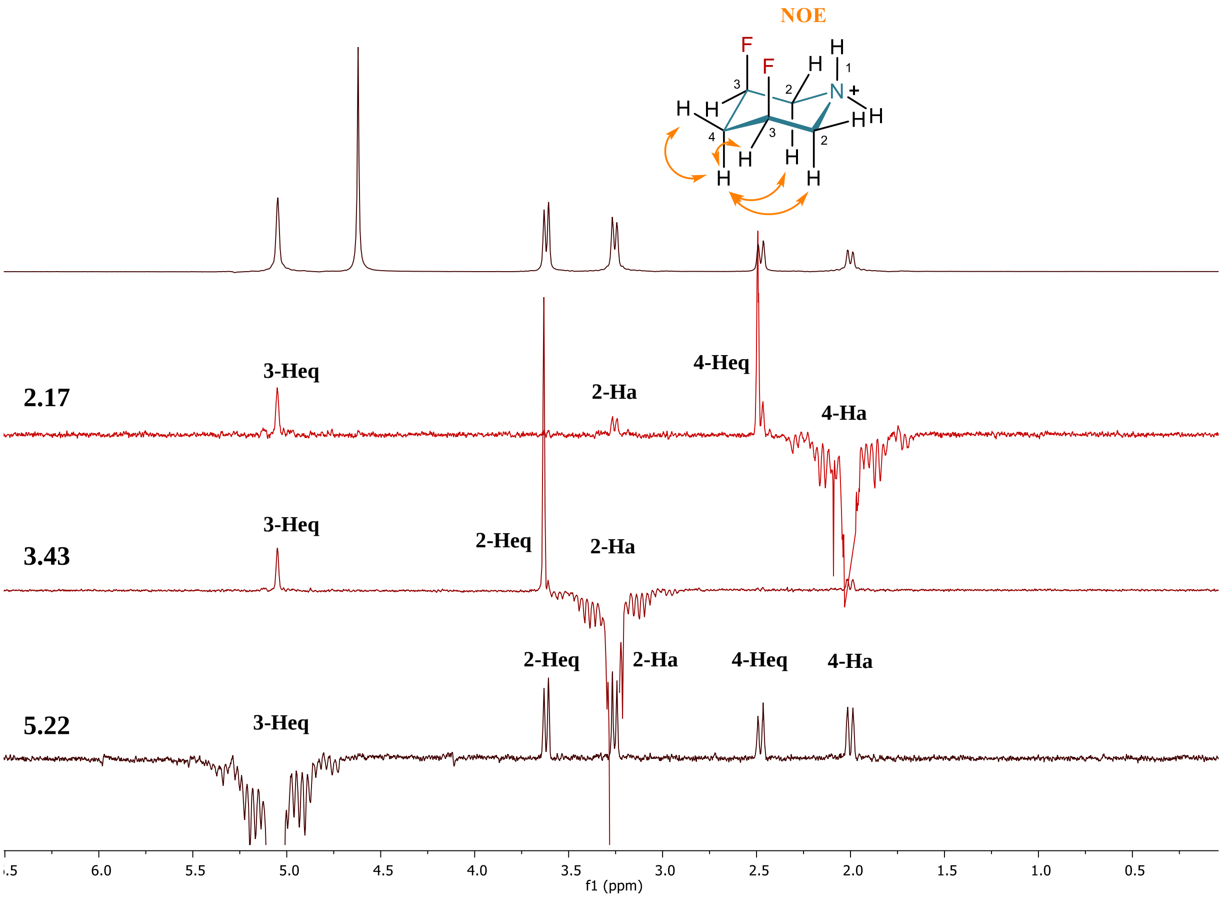
Compound **4** was prepared according to the general procedure B starting from 1-(*cis*-3,5-difluoropiperidin-1-yl)-2,2,2-trifluoroethan-1-one (**3**) (1.51 g, 6.96 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 1 h. Extraction and removal of all volatiles afforded the title compound as a white solid (1.04 g, 6.60 mmol, 95%, *d.r.* >99:1).

^{1}H NMR (600 MHz, D_2O, 299 K) δ 5.22 (d, *J* = 42.9 Hz, 2H), 3.79 (t, *J* = 12.3 Hz, 2H), 3.42 (dd, *J* = 39.5, 14.9 Hz, 2H), 2.65 (q, *J* = 14.9 Hz, 1H), 2.17 (td, *J* = 46.7, 17.1 Hz, 1H); **^{1}H{^{19}F} NMR** (600 MHz, D_2O, 299 K) δ 5.22 (s, 2H), 3.79 (d, *J* = 14.4 Hz, 2H), 3.43 (d, *J* = 14.4 Hz, 2H), 2.65 (d, *J* = 16.5 Hz, 1H), 2.17 (d, *J* = 16.5 Hz, 1H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 83.68 (dd, *J* = 174.8, 2.4 Hz), 45.84 (dd, *J* = 16.2, 5.3 Hz), 29.90 (t, *J* = 20.1 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 83.7, 45.8, 29.9; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -183.12 – -183.58 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -183.3.

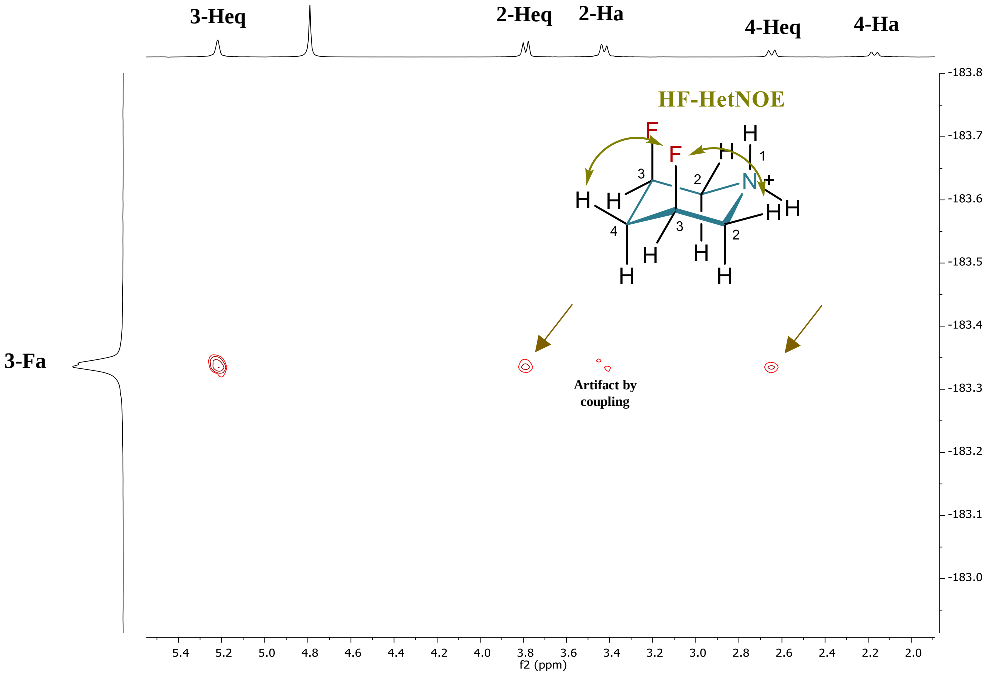
ESI-MS: calculated $[C_5H_{10}F_2N]^+$: 122.0776, found: 122.0783.

IR ν = 2176 (m), 2122 (m), 2068 (m), 1451 (w), 1389 (m), 1234 (w), 1111 (s), 1088 (m), 918 (s), 826 (m), 779 (w), 679 (w), 617 (m), 571 (s), 556 (s).

In order to prove whether the fluorine atoms are occupying axial or equatorial positions, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 9–10). All those experiments showed unequivocally that the fluorine atoms adopt axial orientation.

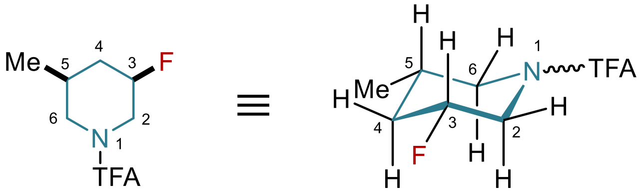


Supplementary Figure 9. Selected 1D NOESY experiments for **4**. Irradiation at 5.22, 3.43, 2.17 ppm, respectively.



Supplementary Figure 10. 2D HF-Het-NOESY experiment for **4**.

2,2,2-Trifluoro-1-(*cis*-3-fluoro-5-methylpiperidin-1-yl)ethan-1-one (5)



Following general procedure A on 1 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-3% EtOAc in pentane. The product was isolated as a colorless oil (172 mg, 0.806 mmol, 81% (volatile compound, 97% NMR yield), *d.r.* 90:10). The major diastereomer could be isolated by column chromatography. The product was present as a ~1:1 mixture of amide bond rotamers.

Rotamer A: **^{1}H NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.53 (dddt, *J* = 47.6, 14.4, 9.2, 4.5 Hz, 1H), 4.27 (ddq, *J* = 12.7, 3.9, 1.6 Hz, 1H), 4.13 (dddq, *J* = 13.3, 6.4, 3.1, 1.5 Hz, 1H), 3.13 (ddd, *J* = 13.3, 9.8, 4.4 Hz, 1H), 2.50 (dd, *J* = 12.7, 11.1 Hz, 1H), 2.31 – 2.24 (m, 1H), 1.81 – 1.73 (m, 1H), 1.46 – 1.37 (m, 1H), 1.05 (dd, *J* = 1.8, 0.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.53 (tq, *J* = 9.2, 4.5 Hz, 1H), 4.27 (ddd, *J* = 12.7, 4.1, 1.6 Hz, 1H), 4.13 (ddt, *J* = 13.3, 3.0, 1.5 Hz, 1H), 3.13 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.50 (dd, *J* = 12.7, 11.1 Hz, 1H), 2.27 (dq, *J* = 12.5, 4.0 Hz, 1H), 1.81 – 1.73 (m, 1H), 1.46 – 1.37 (m, 1H), 1.05 (d, *J* = 2.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.26 – 155.73 (m), 116.50 (d, *J* = 288.1 Hz), 86.48 (d, *J* = 177.9 Hz), 49.73, 49.23 (dq, *J* = 32.2, 3.5 Hz), 38.99 (d, *J* = 17.7 Hz), 28.97 (d, *J* = 8.6 Hz), 18.46; **^{13}C{sel-^{19}F at -180 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.92, 116.51 (d, *J* = 287.6 Hz), 86.48 (d, *J* = 5.1 Hz), 49.73, 49.23 (q, *J* = 3.3 Hz), 38.99, 28.97, 18.46; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.98, -179.83 – -180.12 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.98, -180.0.

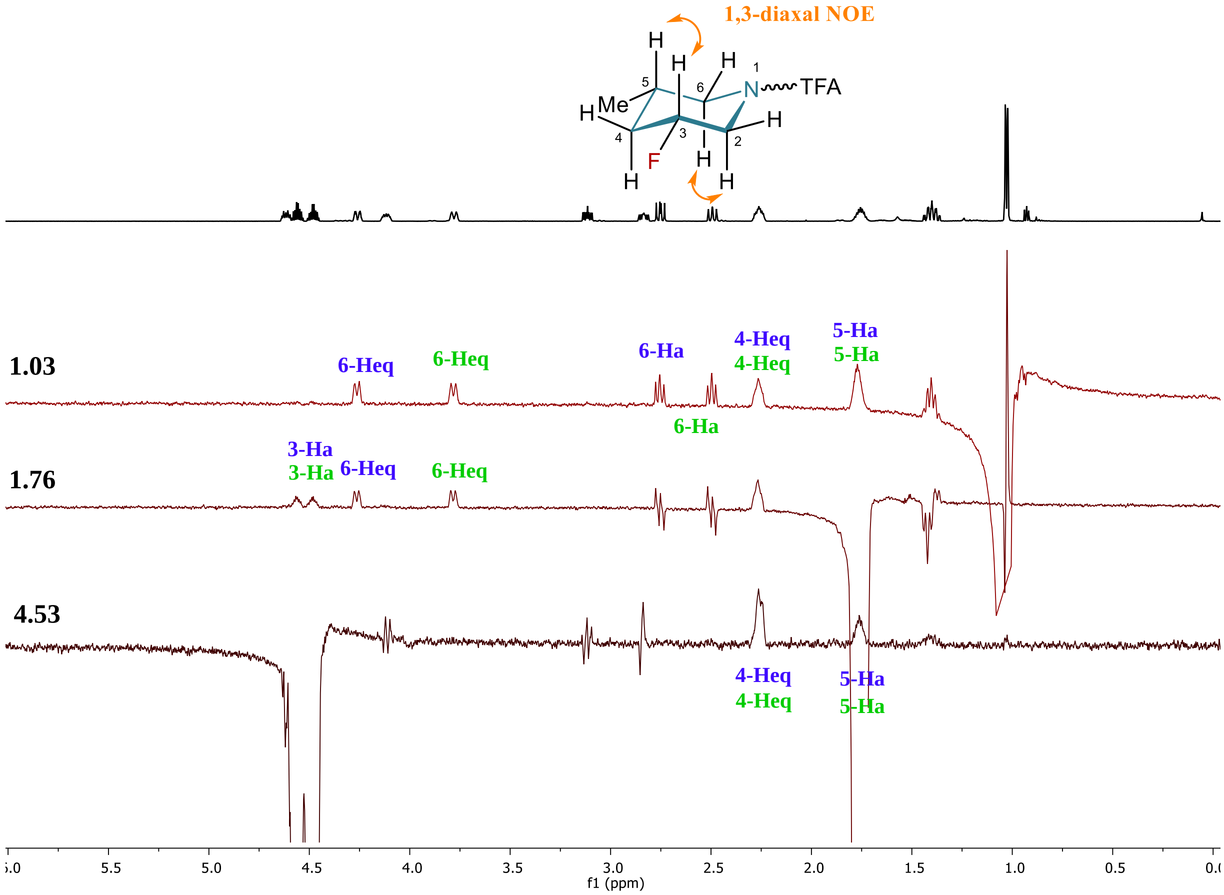
Rotamer B: **^{1}H NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.63 (dtq, *J* = 13.1, 4.8, 1.7 Hz, 1H), 4.53 (dddt, *J* = 47.6, 14.4, 9.2, 4.5 Hz, 1H), 3.79 (dddt, *J* = 13.8, 4.1, 2.7, 1.4 Hz, 1H), 2.85 (ddd, *J* = 12.6, 9.8, 5.1 Hz, 1H), 2.76 (dd, *J* = 13.8, 10.7 Hz, 1H), 2.31 – 2.24 (m, 1H), 1.80 – 1.72 (m, 1H), 1.46 – 1.36 (m, 1H), 1.03 (dd, *J* = 1.8, 0.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.63 (ddt, *J* = 12.6, 4.8, 1.7 Hz, 1H), 4.53 (tq, *J* = 9.2, 4.5 Hz, 1H), 3.79 (ddt, *J* = 13.8, 5.5, 1.5 Hz, 1H), 2.85 (dd, *J* = 12.6, 9.8 Hz, 1H), 2.76 (dd, *J* = 13.8, 10.7 Hz, 1H), 2.27 (dq, *J* = 12.5, 4.1 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.46 – 1.36 (m, 1H), 1.03 (d, *J* = 2.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.26 – 155.73 (m), 116.56 (d, *J* = 288.2 Hz), 85.72 (d, *J* = 177.9 Hz), 51.96 – 51.83 (m), 46.99 (d, *J* = 30.8 Hz), 39.09 (d, *J* = 17.9 Hz), 30.23 (d, *J* = 9.0 Hz), 18.31; **^{13}C{sel-^{19}F**

at -180 ppm } NMR (151 MHz, $CDCl_3$, 299 K) δ 155.85, 116.55 (d, *J* = 287.4 Hz), 85.71, 51.90 (q, *J* = 3.4 Hz), 46.99, 39.09, 30.23, 18.31; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.87, -179.83 – -180.12 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.87, -179.9.

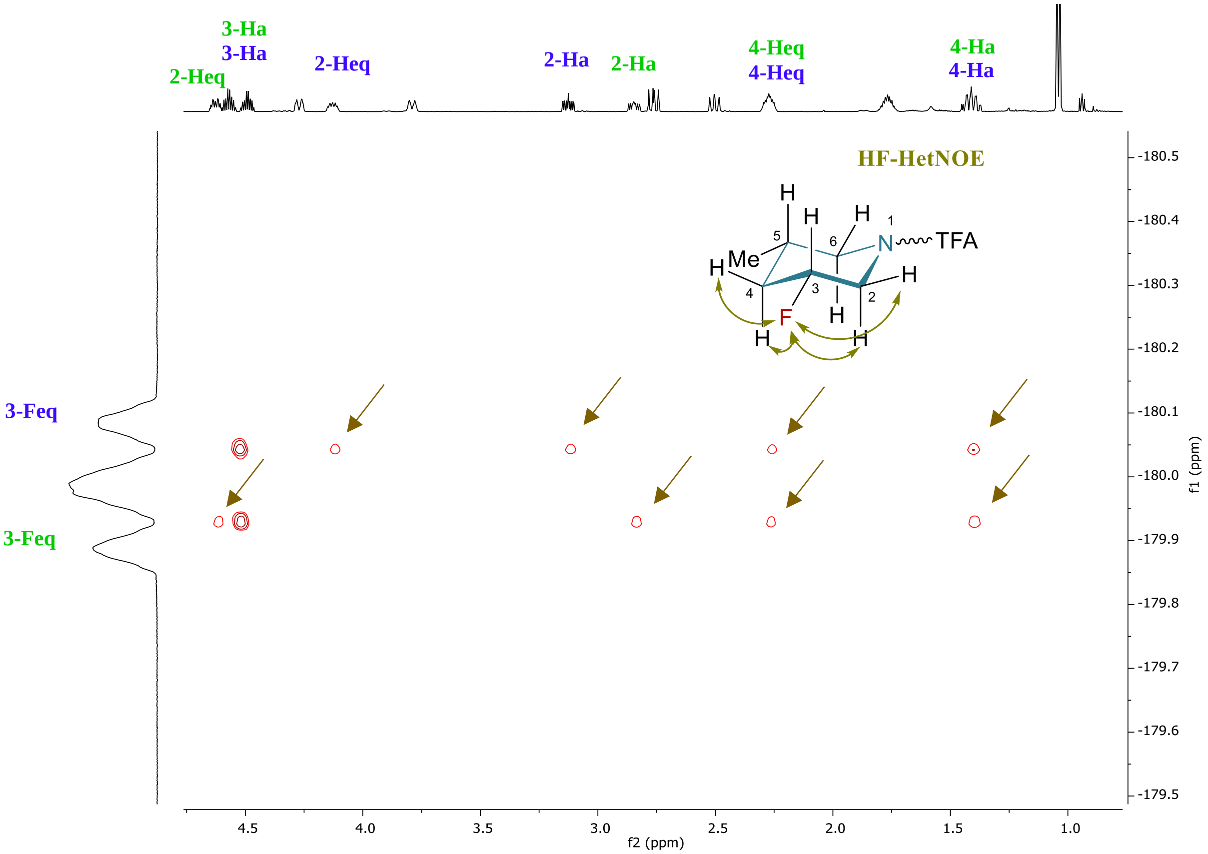
ESI-MS: calculated $[C_8H_{11}NOF_4 + Na]^+$: 236.0674, found: 236.0677.

IR ν = 2962.7 (w), 2939.6 (w), 1689.7 (s), 1458.2 (m), 1373.4 (w), 1296.2 (w), 1203.6 (s), 1188.2 (s), 1126.5 (s), 1087.9 (m), 1018.5 (m), 933.6 (w), 856.4 (w), 756.1 (m), 702.1 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 11–12). All those experiments showed unequivocally that the fluorine atom adopts equatorial orientation.

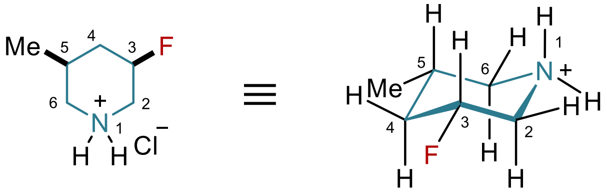


Supplementary Figure 11. Selected 1D NOESY experiments for **5**. Irradiation at 4.53, 1.76 and 1.03 ppm, respectively.



Supplementary Figure 12. 2D HF-Het-NOESY experiment for **5**.

cis-3-Fluoro-5-methylpiperidine hydrochloride (6)



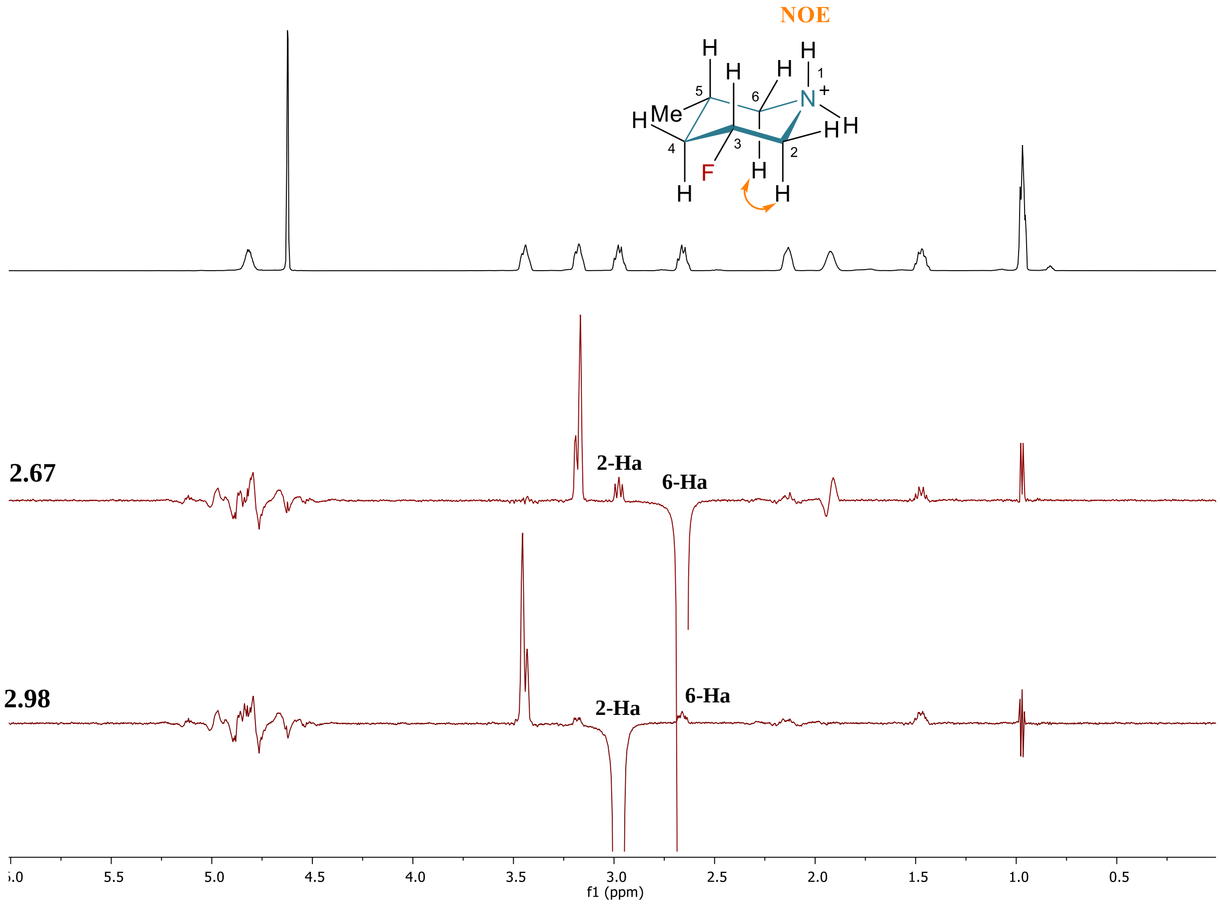
Compound **6** was prepared according to the general procedure B starting from 2,2,2-trifluoro-1-(*cis*-3-fluoro-5-methylpiperidin-1-yl)ethan-1-one (**5**) (100 mg, 0.47 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 2 h. Extraction and removal of all volatiles afforded the title compound as a white solid (64.5 mg, 0.42 mmol, 89%, *d.r.* >99:1).

^{1}H NMR (600 MHz, D_2O, 299 K) δ 4.98 (dm, *J* = 43.8 Hz, 1H), 3.66 – 3.56 (m, 1H), 3.39 – 3.30 (m, 1H), 3.19 – 3.08 (m, 1H), 2.87 – 2.77 (m, 1H), 2.36 – 2.24 (m, 1H), 2.13 – 2.04 (m, 1H), 1.69 – 1.57 (m, 1H), 1.18 – 1.10 (m, 3H); **^{1}H{^{19}F} NMR** (600 MHz, D_2O, 299 K) δ 5.05 – 4.94 (m, 1H), 3.65 – 3.55 (m, 1H), 3.37 – 3.31 (m, 1H), 3.21 – 3.10 (m, 1H), 2.87 – 2.77 (m, 1H), 2.34 – 2.25 (m, 1H), 2.13 – 2.04 (m, 1H), 1.69 – 1.59 (m, 1H), 1.16 – 1.10 (m, 3H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 85.26 (d, *J* = 171.5 Hz), 48.57, 45.42 (d, *J* = 30.10 Hz), 35.27 (d, *J* = 18.0 Hz), 25.68 (d, *J* = 9.3 Hz), 17.42; **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 85.3, 48.6, 45.4, 35.3, 25.7, 17.4; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -181.36 – -182.28 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -181.8.

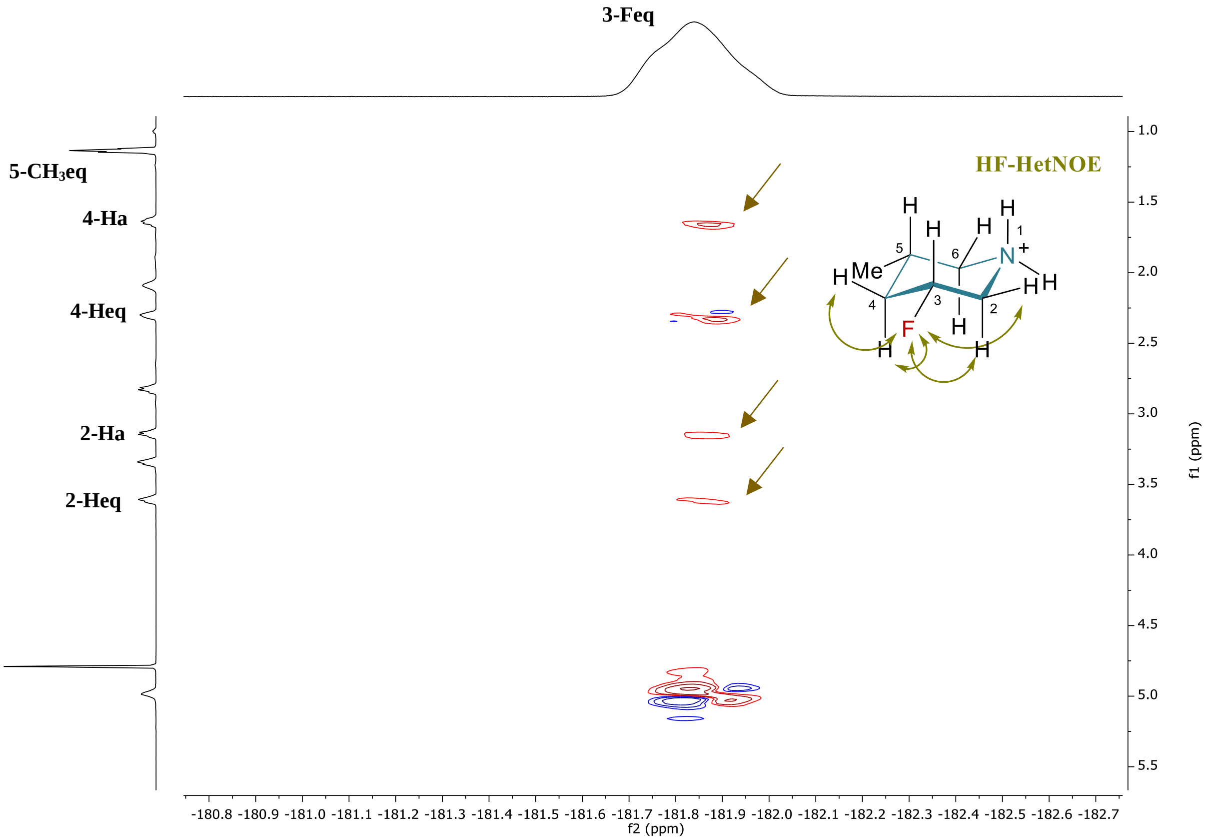
ESI-MS: calculated $[C_6H_{13}FN]^+$: 118.1027, found: 118.0994.

IR ν = 2955 (m), 2747 (m), 2685 (m), 2546 (m), 2415 (m), 1613 (w), 1589 (w), 1458 (m), 1427 (m), 1373 (w), 1265 (w), 1173 (w), 1103 (m), 1034 (w), 1011 (s), 926 (m), 864 (w), 571 (s).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and FH-HetNOE experiments (Supplementary Fig. 13–14). All those experiments showed unequivocally that the fluorine atom adopts equatorial orientation.

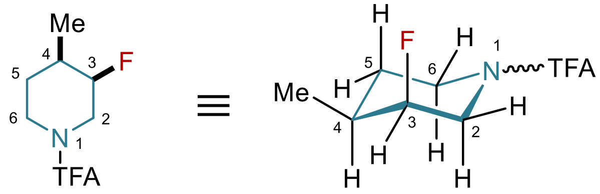


Supplementary Figure 13. Selected 1D NOESY experiments for **6**. Irradiation at 2.98 and 2.67 ppm, respectively.



Supplementary Figure 14. 2D FH-Het-NOESY experiment for **6**.

2,2,2-Trifluoro-1-(*cis*-3-fluoro-4-methylpiperidin-1-yl)ethan-1-one (7)



Following general procedure A on 2 mmol scale, 0.5 mol% catalyst, 4 mmol HBpin, 1 M THF at 40 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a colorless oil (383 mg, 1.79 mmol, 90%, *d.r.* 95:5). The major diastereomer could be isolated by column chromatography. The product was present as a ~1:1 mixture of amide bond rotamers.

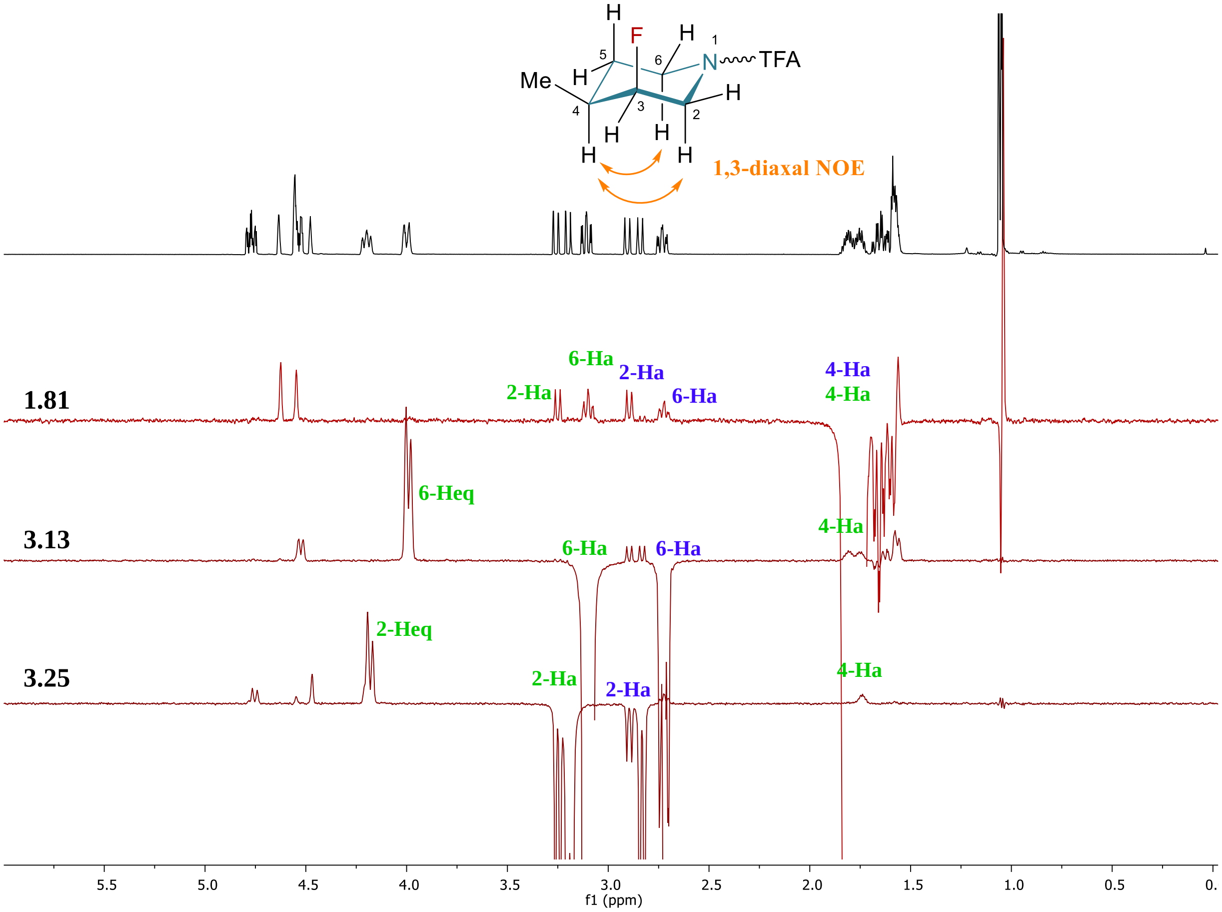
Rotamer A: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.79 (ddt, *J* = 14.2, 10.9, 2.8 Hz, 1H), 4.62 (d, *J* = 47.0 Hz, 1H), 4.57 – 4.53 (m, 1H), 2.89 (dd, *J* = 38.3, 14.8 Hz, 1H), 2.75 (td, *J* = 12.5, 4.0 Hz, 1H), 1.80 – 1.74 (m, 1H), 1.72 – 1.56 (m, 2H), 1.07 (d, *J* = 2.1 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.79 (dt, *J* = 14.5, 2.7 Hz, 1H), 4.63 – 4.61 (m, 1H), 4.58 – 4.52 (m, 1H), 2.89 (d, *J* = 14.8 Hz, 1H), 2.75 (td, *J* = 12.5, 4.2 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.71 – 1.56 (m, 2H), 1.07 (d, *J* = 2.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.45 (q, *J* = 35.6 Hz), 116.54 (q, *J* = 288.1 Hz), 88.45 (d, *J* = 180.6 Hz), 47.23 (d, *J* = 22.1 Hz), 43.47, 34.29 (d, *J* = 20.8 Hz), 27.28 (d, *J* = 1.0 Hz), 16.87 (d, *J* = 3.6 Hz); **^{13}C{sel-^{19}F at -69 and -203 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.5, 116.6, 88.5, 47.2, 43.5, 34.3, 27.3, 16.9; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.02, -203.54 – -204.00 (m); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.02, -203.69.

Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.54 (d, *J* = 47.0 Hz, 1H), 4.22 (dddt, *J* = 14.7, 9.6, 3.3, 1.7 Hz, 1H), 4.02 (ddd, *J* = 14.0, 4.0, 1.9 Hz, 1H), 3.25 (ddd, *J* = 36.6, 14.8, 1.1 Hz, 1H), 3.13 (td, *J* = 14.5, 13.8, 3.0 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.72 – 1.56 (m, 2H), 1.08 (d, J = 2.1 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.55 – 4.52 (m, 1H), 4.22 (dt, *J* = 14.7, 1.6 Hz, 1H), 4.02 (ddd, *J* = 14.0, 4.0, 1.9 Hz, 1H), 3.25 (dd, *J* = 14.8, 1.1 Hz, 1H), 3.13 (ddd, *J* = 14.0, 12.5, 3.0 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.71 – 1.56 (m, 2H), 1.08 (d, *J* = 2.1 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.48 (q, *J* = 35.9 Hz), 116.60 (q, *J* = 287.9 Hz), 88.99 (d, *J* = 179.7 Hz), 49.26 (dq, *J* = 21.7, 3.3 Hz), 45.61 (q, *J* = 3.6 Hz), 34.32 (d, *J* = 20.8 Hz), 28.20 (d, *J* = 1.5 Hz), 16.89 (d, *J* = 3.6 Hz); **^{13}C{sel-^{19}F at -68 and -203 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.5, 116.6, 89.0, 49.3, 45.6, 34.3, 28.2, 16.9; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -68.04 (d, *J* = 4.3 Hz), -203.54 – -204.00 (m); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -68.04 (d, *J* = 4.3 Hz), -203.69 (q, *J* = 4.3 Hz).

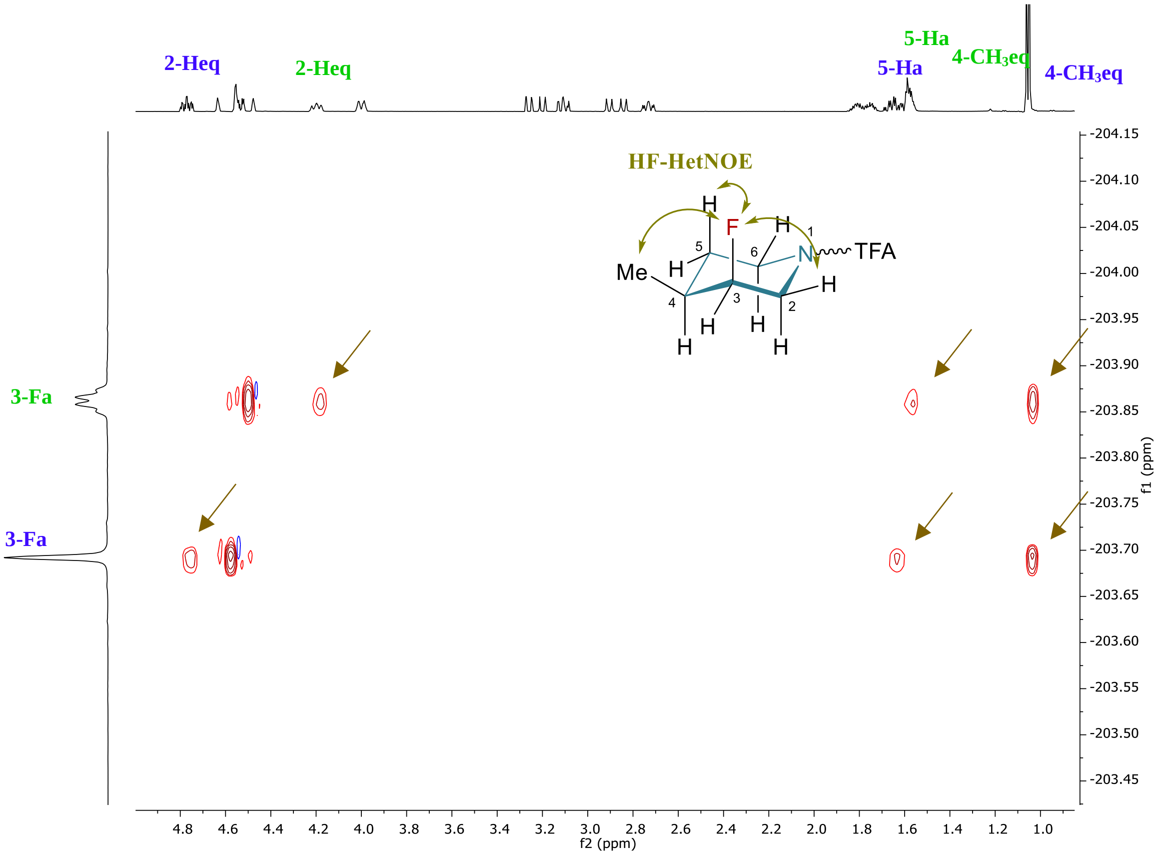
ESI-MS: calculated [$C_8H_{11}NOF_4$ +Na]$^+$: 236.0674, found: 236.0685.

IR ν = 2970.5 (w), 2939.6 (w), 2885.6 (w), 1689.7 (s), 1458.2 (m), 1273.1 (w), 1180.5 (s), 1134.2 (s), 1118.7 (s), 1049.3 (m), 995.3 (s), 964.4 (m), 856.4 (m), 756.1 (m), 648.1 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 15–16). All those experiments showed unequivocally that the dominant orientation of the fluorine atom is axial. Furthermore, the observed *cis*-selectivity is confirmed as well.

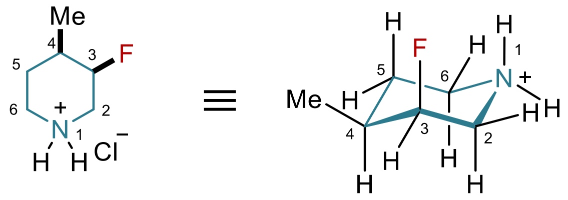


Supplementary Figure 15. Selected 1D NOESY experiments for **7**. Irradiation at 3.25, 3.13, 1.81 ppm, respectively. Chemical exchange (2-H_a ↔ 2-H_a and 6-H_a ↔ 6-H_a) was observed during the mixing time.



Supplementary Figure 16. 2D HF-Het-NOESY experiment for **7**.

***cis*-3-Fluoro-4-methylpiperidine hydrochloride (8)**



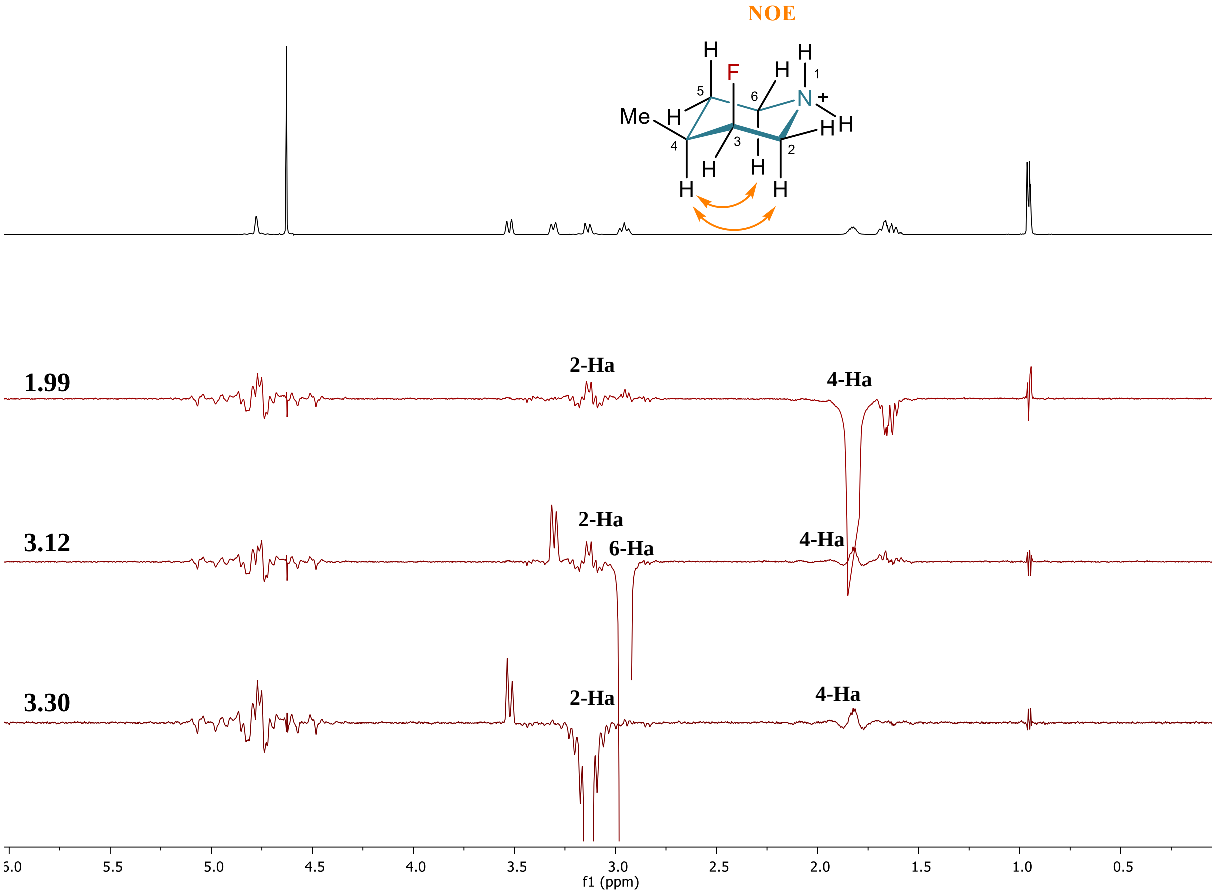
Compound **8** was prepared according to the general procedure B starting from 2,2,2-trifluoro-1-(*cis*-3-fluoro-4-methylpiperidin-1-yl)ethan-1-one (**7**) (100 mg, 0.47 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 1.5 h. Extraction and removal of all volatiles afforded the title compound as a white solid (72.6 mg, 0.47 mmol, 99%, *d.r.* >99:1).

^{1}H NMR (600 MHz, D_2O, 299 K) δ 4.94 (d, *J* = 45.6 Hz, 1H), 3.69 (dd, *J* = 14.7, 10.0 Hz, 1H), 3.47 (dm, *J* = 12.8 Hz, 1H), 3.30 (dd, *J* = 40.6, 14.7 Hz, 1H), 3.12 (t, *J* = 12.8 Hz, 1H), 1.99 (dm, *J* = 36.5 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.12 (dd, *J* = 6.8, 1.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, D_2O, 299 K) δ 4.94 (s, 1H), 3.69 (dd, *J* = 14.7, 1.7 Hz, 1H), 3.47 (dm, *J* = 12.8 Hz, 1H), 3.30 (d, *J* = 14.7 Hz, 1H), 3.12 (t, *J* = 12.8 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.87 – 1.75 (m, 2H), 1.12 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 88.62 (d, *J* = 171.9 Hz), 46.75 (d, *J* = 20.9 Hz), 43.55, 31.44 (d, *J* = 20.3 Hz), 24.03, 16.11; **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 88.6, 46.8, 43.5, 31.4, 24.0, 16.1; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -203.66 – -204.01 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -203.8.

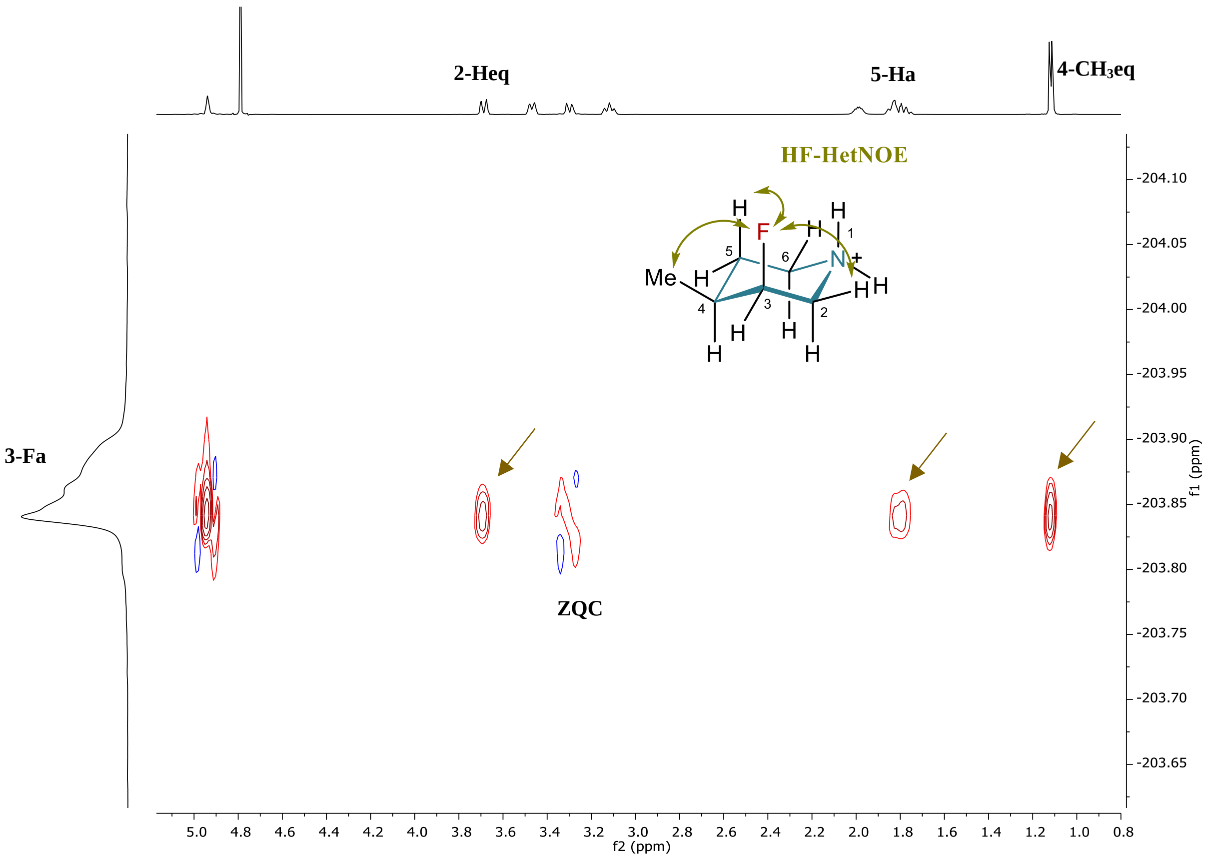
ESI-MS: calculated $[C_6H_{13}FN]^+$: 118.1027, found: 118.1036.

IR ν = 2947 (s), 2801 (s), 2724 (s), 1589 (s), 1451 (s), 1397 (m), 1234 (w), 1180 (w), 1150 (m), 1088 (m), 988 (s), 926 (s), 679 (w), 617 (w), 586 (s), 571 (s), 556 (s).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 17–18). All those experiments showed unequivocally that the fluorine atom adopts axial orientation.

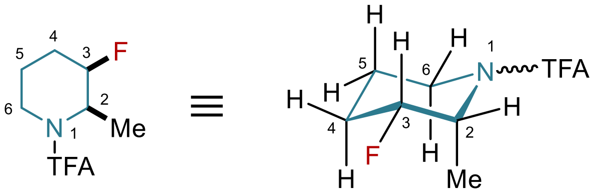


Supplementary Figure 17. Selected 1D NOESY experiments for **8**. Irradiation at 3.30, 3.12, 1.99 ppm, respectively.



Supplementary Figure 18. 2D FH-Het-NOESY experiment for **8**.

2,2,2-Trifluoro-1-(*cis*-3-fluoro-2-methylpiperidin-1-yl)ethan-1-one (9)



Following general procedure A on 1 mmol scale, 0.5 mol% catalyst, 4 mmol HBpin, 1 M THF at 40 °C, purification with 0-5% EtOAc in pentane. The product was isolated as a colorless oil (164 mg, 0.769 mmol, 77% (volatile compound, 89% NMR yield), *d.r.* 95:5). The major diastereomer could be isolated by column chromatography. The product was present as a ~1.5:1 mixture of amide bond rotamers. Traces of defluorinated side-product were inseparable from the product.

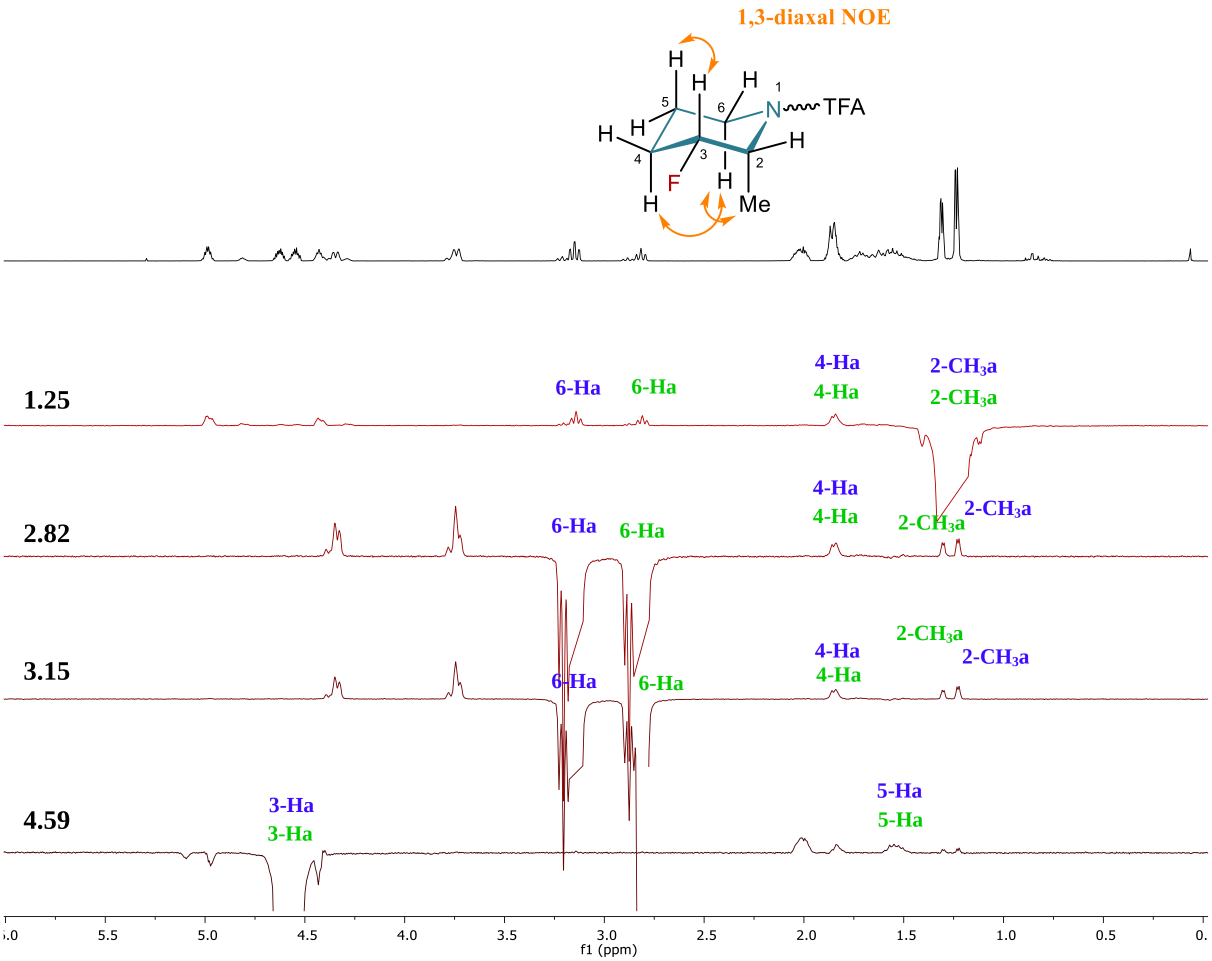
Rotamer A: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.99 (h, *J* = 6.6 Hz, 1H), 4.59 (dtd, *J* = 47.0, 10.3, 5.7 Hz, 1H), 3.74 (d, *J* = 14.5 Hz, 1H), 3.15 (td, *J* = 13.8, 2.9 Hz, 1H), 2.08 – 1.96 (m, 1H), 1.90 – 1.81 (m, 2H), 1.64 – 1.44 (m, 1H), 1.24 (dd, *J* = 7.0, 1.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.98 (p, *J* = 6.8 Hz, 1H), 4.58 (tt, *J* = 10.5, 5.7 Hz, 1H), 3.73 (d, *J* = 15.6 Hz, 1H), 3.14 (td, *J* = 13.8, 2.9 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.89 – 1.79 (m, 2H), 1.60 – 1.46 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.17 (d, *J* = 35.9 Hz), 116.57 (q, *J* = 288.4 Hz), 88.01 (d, *J* = 181.1 Hz), 48.80 (d, *J* = 26.6 Hz), 39.54 (q, *J* = 3.6 Hz), 24.75 (d, *J* = 19.2 Hz), 23.37 (d, *J* = 9.8 Hz), 9.70 (d, *J* = 2.6 Hz); **^{13}C{sel-^{19}F at -69 and -181 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.17, 116.57, 88.01, 48.80, 39.54, 24.76, 23.37, 9.70; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.05, -181.55 (d, *J* = 47.8 Hz); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.05, -181.5.

Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.59 (dtd, *J* = 47.0, 10.3, 5.8 Hz, 1H), 4.43 (t, *J* = 6.2 Hz, 1H), 4.35 (d, *J* = 13.6 Hz, 1H), 2.82 (t, *J* = 12.5 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.90 – 1.81 (m, 2H), 1.65 – 1.46 (m, 1H), 1.31 (dd, *J* = 6.7, 1.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.58 (tt, *J* = 10.3, 5.8 Hz, 1H), 4.42 (t, *J* = 6.2 Hz, 1H), 4.34 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.81 (t, *J* = 12.5 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.89 – 1.80 (m, 2H), 1.65 – 1.46 (m, 1H), 1.30 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.10 (d, *J* = 36.1 Hz), 116.73 (q, *J* = 287.9 Hz), 88.59 (d, *J* = 182.4 Hz), 51.54 (dd, *J* = 27.3, 3.5 Hz), 36.77, 24.80 (d, *J* = 19.2 Hz), 22.59 (d, *J* = 10.1 Hz), 10.91; **^{13}C{sel-^{19}F at -69 and -180 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.10, 116.73, 88.59, 51.54, 36.77, 24.80, 22.59, 10.91; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.14, -179.53 (d, *J* = 48.5 Hz); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.14, -179.5.

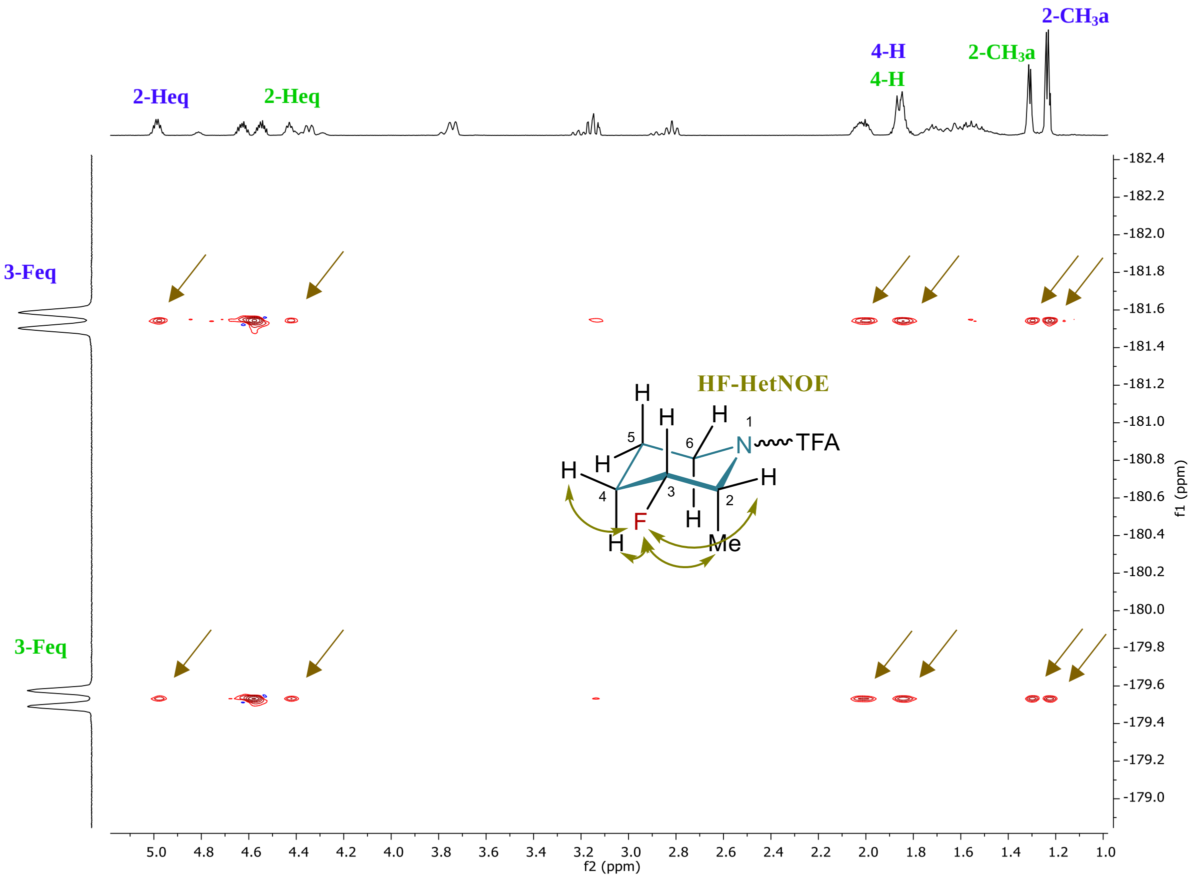
ESI-MS: calculated [$C_8H_{11}NOF_4$ +Na]$^+$: 236.0674, found: 236.0682.

IR ν = 2955 (w), 1681.9 (s), 1450.5 (m), 1381.1 (w), 1211.3 (s), 1188.2 (s), 1126.5 (s), 1057 (m), 1003 (m), 925.8 (m), 740.7 (m), 686.7 (m), 663.5 (m), 555.5 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 19–20). All those experiments showed unequivocally that the fluorine atom adopts equatorial orientation.

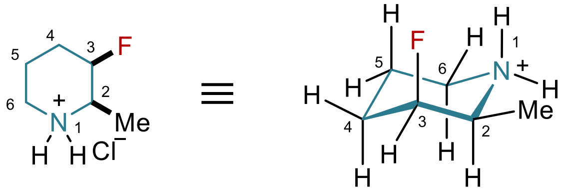


Supplementary Figure 19. Selected 1D NOESY experiments for **9**. Irradiation at 4.59, 3.15, 2.82 and 1.25 ppm, respectively. Chemical exchange (6-H$_a$ ↔ 6-H$_a$) was observed during the mixing time.



Supplementary Figure 20. 2D HF-Het-NOESY experiment for **9**. Chemical exchanges were observed during the mixing time.

cis-3-Fluoro-2-methylpiperidine hydrochloride (10)



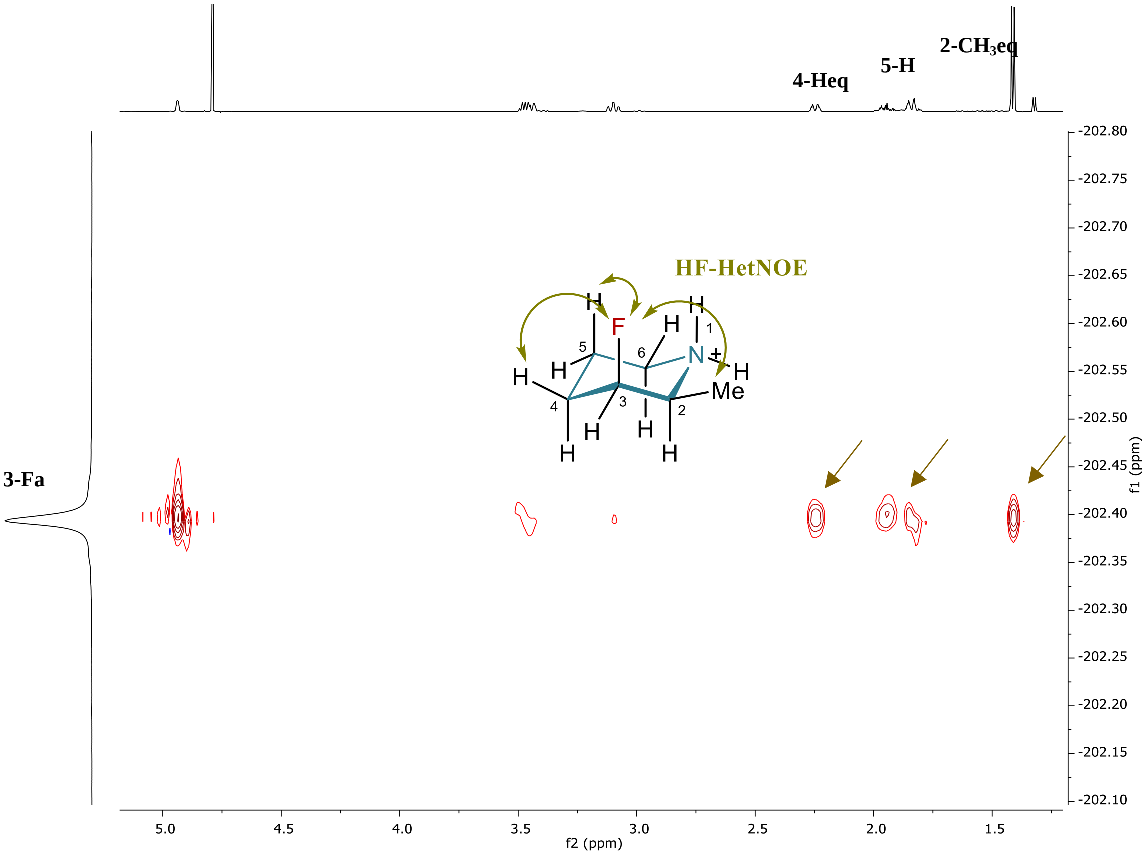
Compound **10** was prepared according to the general procedure B starting from 2,2,2-trifluoro-1-(*cis*-3-fluoro-2-methylpiperidin-1-yl)ethan-1-one (**9**) (105 mg, 0.49 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 18 h. Extraction and removal of all volatiles afforded the title compound as a white solid (74.3 mg, 0.48 mmol, 99%, *d.r.* >99:1). The NMR spectra contain traces of defluorinated piperidine hydrochloride salt that originated from the starting material **9**.

^{1}H NMR (600 MHz, D_2O, 299 K) δ 4.94 (dm, *J* = 47.0 Hz, 1H), 3.48 (dq, *J* = 31.5, 6.4 Hz, 1H) overlapping with 3.46 – 3.42 (m, 1H), 3.10 (td, *J* = 13.2, 3.1 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.01 – 1.75 (m, 3H), 1.41 (d, *J* = 6.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, D_2O, 299 K) δ 4.94 (s, 1H), 3.48 (q, *J* = 6.4 Hz, 1H), 3.46 – 3.43 (m, 1H), 3.10 (td, *J* = 13.2, 3.1 Hz, 1H), 2.25 (dm, *J* = 14.4 Hz, 1H), 2.00 – 1.90 (m, 1H), 1.88 – 1.80 (m, 2H), 1.41 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 88.36 (d, *J* = 172.6 Hz), 53.63 (d, *J* = 19.5 Hz), 43.76, 26.57 (d, *J* = 21.2 Hz), 15.87 (d, *J* = 1.8 Hz), 14.34 (d, *J* = 4.5 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 88.4, 53.6, 43.8, 26.6, 15.9, 14.3; **^{19}F NMR** (564 MHz, D_2O, 299 K) -202.19 – -202.61 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -202.4.

ESI-MS: calculated $[C_6H_{13}FN]^+$: 118.1027, found: 118.1027.

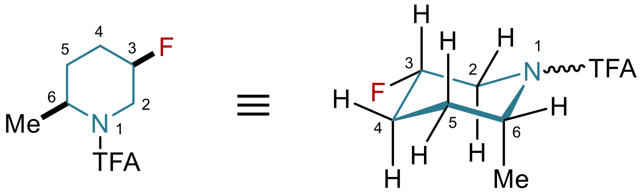
IR ν = 2940 (m), 2762 (m), 2708 (m), 2569 (m), 2500 (m), 2423 (w), 2361 (w), 1582 (m), 1458 (m), 1389 (w), 1350 (w), 1450 (w), 1088 (m), 1018 (m), 995 (m), 941 (m), 926 (m), 864 (w), 617 (w), 571 (s), 556 (s).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 21). HetNOE experiment showed unequivocally that the dominant orientation of the fluorine atom is axial. **Note** that the preferred conformation of the piperidine hydrochloride salt in this case is different than the TFA-analogue (**9**).



Supplementary Figure 21. 2D HF-Het-NOESY experiment for **10**.

2,2,2-Trifluoro-1-(*cis*-5-fluoro-2-methylpiperidin-1-yl)ethan-1-one (11)



Following general procedure A on 0.5 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-2% EtOAc in pentane. The product was isolated as a colorless oil (90 mg, 0.422 mmol, 84% (volatile compound, 95% NMR yield), *d.r.* 90:10). The major diastereomer could be isolated by column chromatography. The product was present as a ~1:1 mixture of amide bond rotamers.

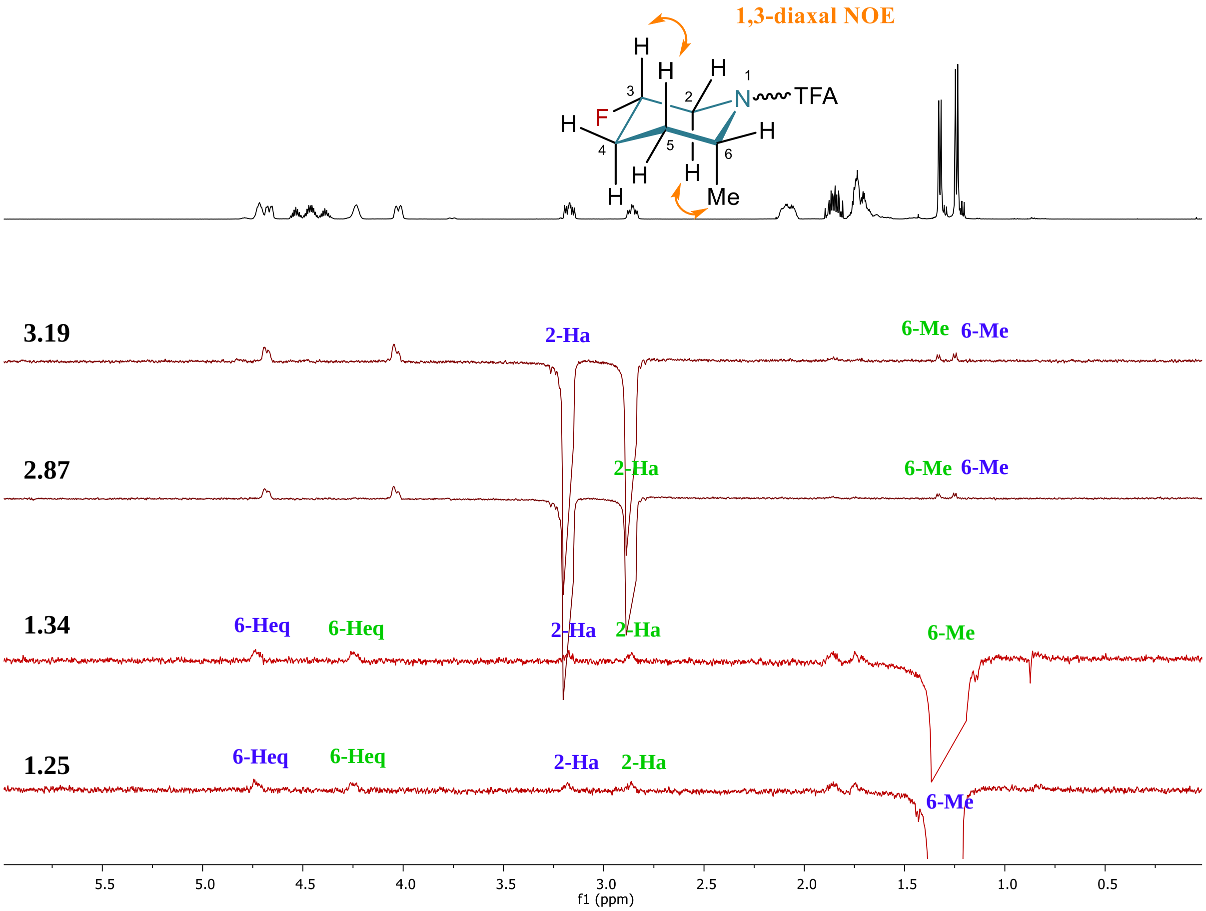
Rotamer A: **^{1}H NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.75 – 4.71 (m, 1H), 4.58 – 4.44 (m, 1H), 4.04 (d, *J* = 13.3 Hz, 1H), 3.18 (ddd, *J* = 13.3, 10.5, 5.8 Hz, 1H), 2.15 – 2.03 (m, 1H), 1.92 – 1.82 (m, 1H), 1.80 – 1.68 (m, 2H), 1.25 (d, *J* = 7.0 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.76 – 4.70 (m, 1H), 4.51 (tt, *J* = 10.3, 5.2 Hz, 1H), 4.04 (dd, *J* = 13.3, 4.2 Hz, 1H), 3.19 (dd, *J* = 13.3, 10.5 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.92 – 1.82 (m, 1H), 1.79 – 1.67 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.59 – 155.44 (m), 116.48 (q, *J* = 288.1 Hz), 87.12 (d, *J* = 177.3 Hz), 48.15 – 48.03 (m), 43.88 (dq, *J* = 32.6, 3.4, 2.7 Hz), 26.72 (d, *J* = 10.0 Hz), 25.95 (d, *J* = 19.0 Hz), 15.35; **^{13}C{sel-^{19}F at -179 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.51 – 155.59 (m), 116.48 (q, *J* = 288.1 Hz), 87.12, 48.09 (q, *J* = 3.3 Hz), 43.88 (q, *J* = 2.8 Hz), 26.72, 25.95, 15.35; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.24, -179.34 (d, *J* = 47.7 Hz); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.24, -179.4.

Rotamer B: **^{1}H NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.68 (dd, *J* = 12.6, 5.2 Hz, 1H), 4.51 – 4.36 (m, 1H), 4.25 (bs, 1H), 2.87 (td, *J* = 12.6, 5.8 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.92 – 1.82 (m, 1H), 1.79 – 1.64 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.68 (dd, *J* = 12.6, 4.7 Hz, 1H), 4.44 (tt, *J* = 10.6, 5.1 Hz, 1H), 4.25 (s, 1H), 2.87 (dd, *J* = 12.6, 10.6 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.91 – 1.82 (m, 1H), 1.79 – 1.68 (m, 2H), 1.34 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.59 – 155.44 (m), 116.76 (q, *J* = 288.1 Hz), 86.67 (d, *J* = 177.3 Hz), 45.61, 41.07 (d, *J* = 32.3 Hz), 28.34 (d, *J* = 11.0 Hz), 25.81 (d, *J* = 19.0 Hz), 16.61; **^{13}C{sel-^{19}F at -179 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.45 – 155.63 (m), 116.76 (q, *J* = 288.1 Hz), 86.67, 45.61, 41.07, 28.34, 25.81, 16.61; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.11, -179.03 (d, *J* = 47.7 Hz); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.11, -179.1.

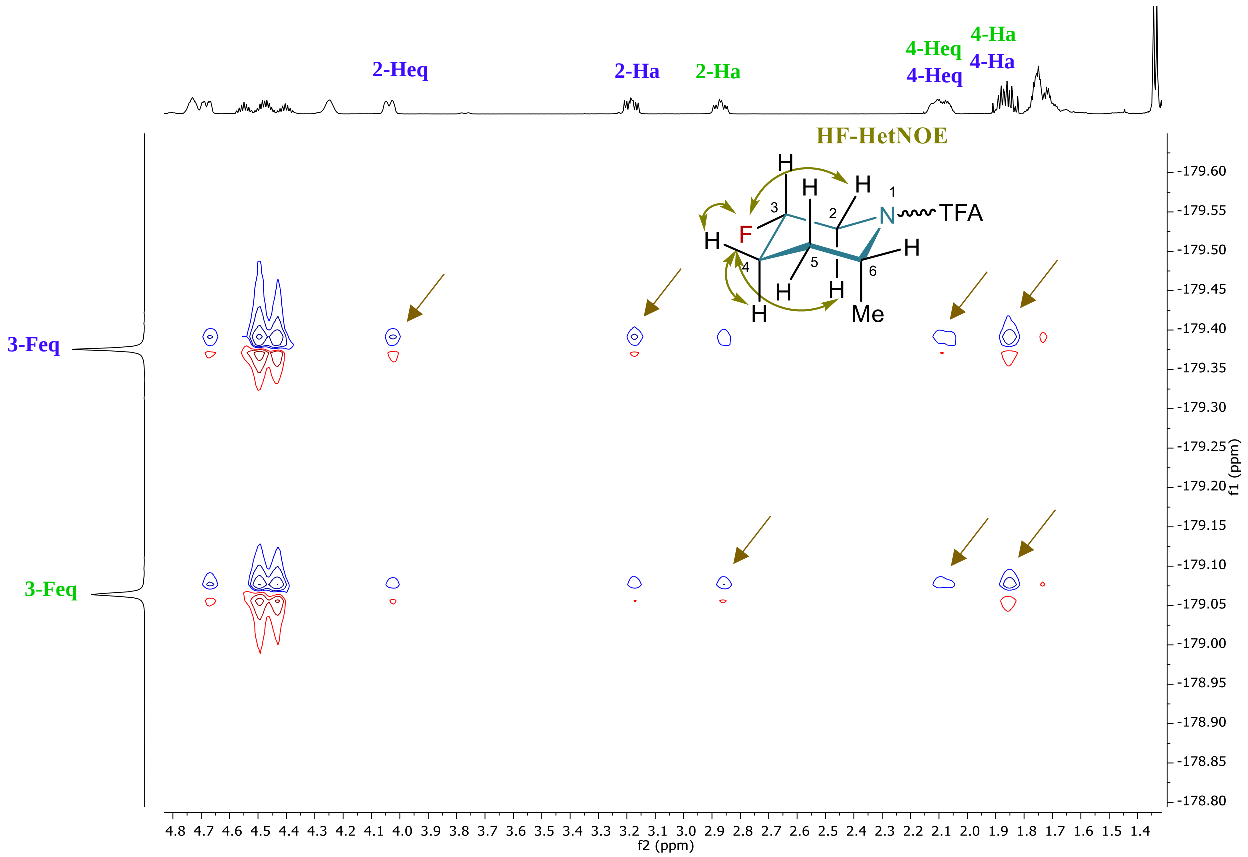
ESI-MS: calculated $[C_8H_{11}NOF_4 + Na]^+$: 236.0674, found: 236.0657.

IR ν = 2962.7 (w), 1681.9 (s), 1450.5 (m), 1381.1 (w), 1203.6 (m), 1188.2 (s), 1134.2 (s), 1049.3 (m), 995.3 (m), 949 (w), 756.1 (s), 709.8 (m), 686.7 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 22–23). All those experiments showed unequivocally that the fluorine atom adopts equatorial orientation.

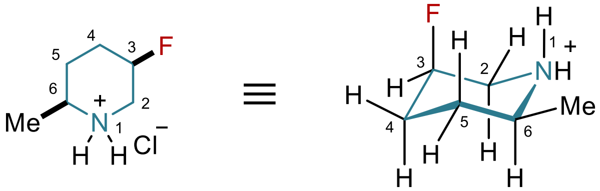


Supplementary Figure 22. Selected 1D NOESY experiments for **11**. Irradiation at 3.19, 2.87, 1.34 and 1.25 ppm, respectively. Chemical exchange (2-H_a ↔ 2-H_a) was observed during the mixing time.



Supplementary Figure 23. 2D HF-Het-NOESY experiment for **11**. Chemical exchanges were observed during the mixing time.

cis-5-Fluoro-2-methylpiperidine hydrochloride (12)



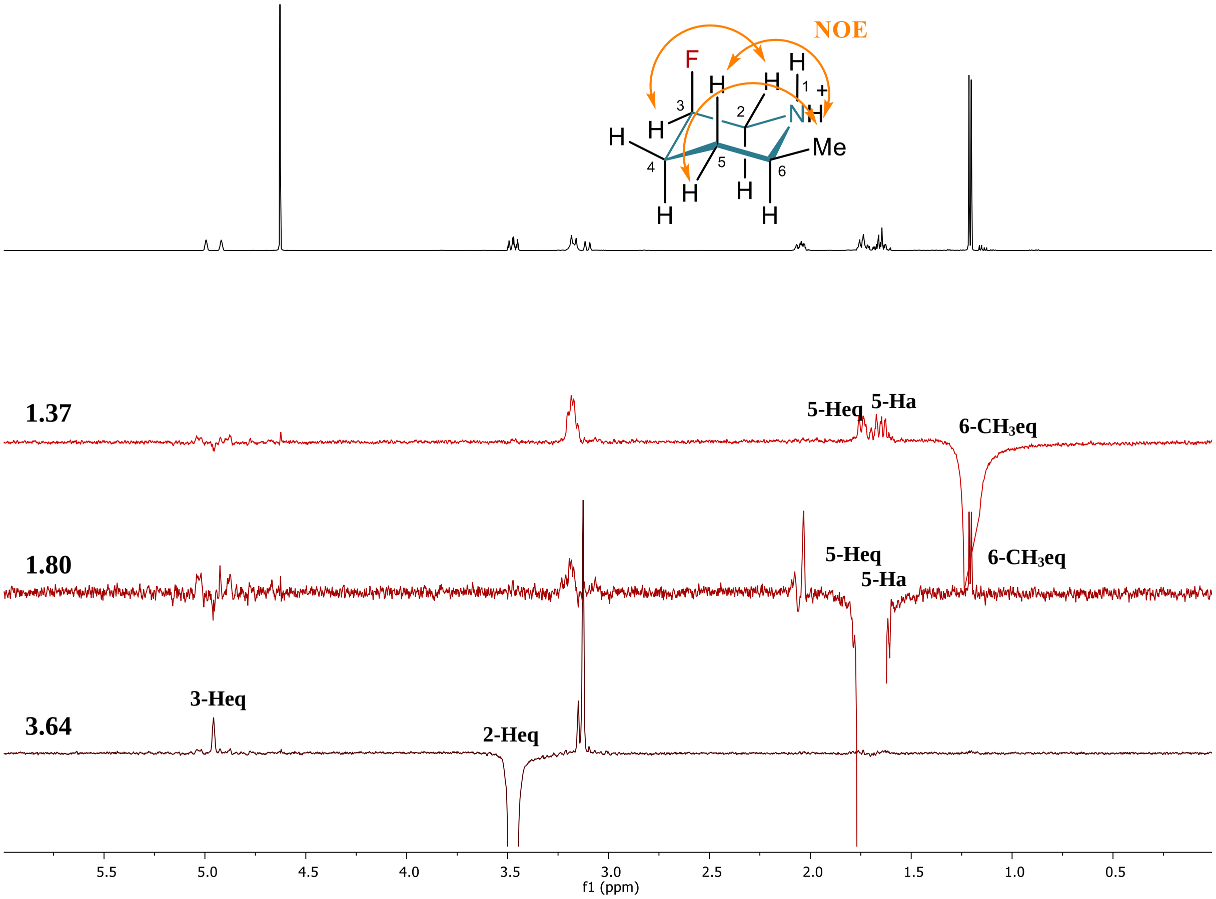
Compound **12** was prepared according to the general procedure B starting from 2,2,2-trifluoro-1-(*cis*-5-fluoro-2-methylpiperidin-1-yl)ethan-1-one (**11**) (32.7 mg, 0.15 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 3 h. Extraction and removal of all volatiles afforded the title compound as a white solid (22.8 mg, 0.15 mmol, 99%, *d.r.* >99:1).

^{1}H NMR (600 MHz, D_2O, 299 K) δ 5.12 (d, *J* = 45.2 Hz, 1H), 3.64 (ddt, *J* = 14.2, 10.8, 2.6 Hz, 1H), 3.37 – 3.31 (m, 1H), 3.30 (dd, *J* = 40.7, 14.2 Hz, 1H), 2.25 – 2.19 (m, 1H), 1.95 – 1.78 (m, 3H), 1.37 (d, *J* = 6.5 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, D_2O, 299 K) δ 5.12 (s, 1H), 3.64 (dt, *J* = 14.2, 2.6 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.30 (d, *J* = 14.2 Hz, 1H), 2.26 – 2.19 (m, 1H), 1.95 – 1.77 (m, 3H), 1.37 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 84.52 (d, *J* = 168.0 Hz), 52.37, 46.75 (d, *J* = 20.8 Hz), 26.26 (d, *J* = 21.0 Hz), 24.39, 18.28; **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 84.5, 52.4, 46.7, 26.3, 24.4, 18.3; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -188.10 – -188.56 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -188.3.

ESI-MS: calculated $[C_6H_{13}FN]^+$: 118.1027, found: 118.1039.

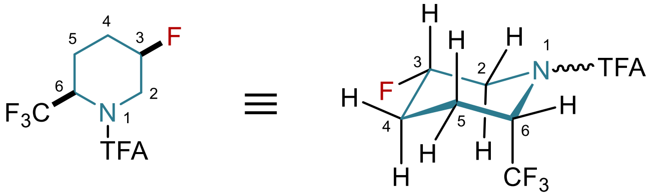
IR ν = 2934 (m), 2808 (m), 2716 (s). 2538 (m), 2392 (m), 1667 (w), 1582 (m), 1466 (m), 1435 (m), 1389 (w), 1358 (w), 1196 (w), 1142 (w), 1096 (m), 1042 (w), 1003 (s), 926 (s), 880 (w), 810 (w), 710 (w).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. 1D NOE experiments showed unequivocally that the fluorine atom adopts axial orientation (Supplementary Fig. 24). **Note** that the preferred conformation of the piperidine hydrochloride salt in this case is different than the TFA-analogue (**11**).



Supplementary Figure 24. Selected 1D NOESY experiments for **12**. Irradiation at 3.64, 1.80 and 1.37 ppm, respectively.

2,2,2-Trifluoro-1-(*cis*-5-fluoro-2-(trifluoromethyl)piperidin-1-yl)ethan-1-one (13)



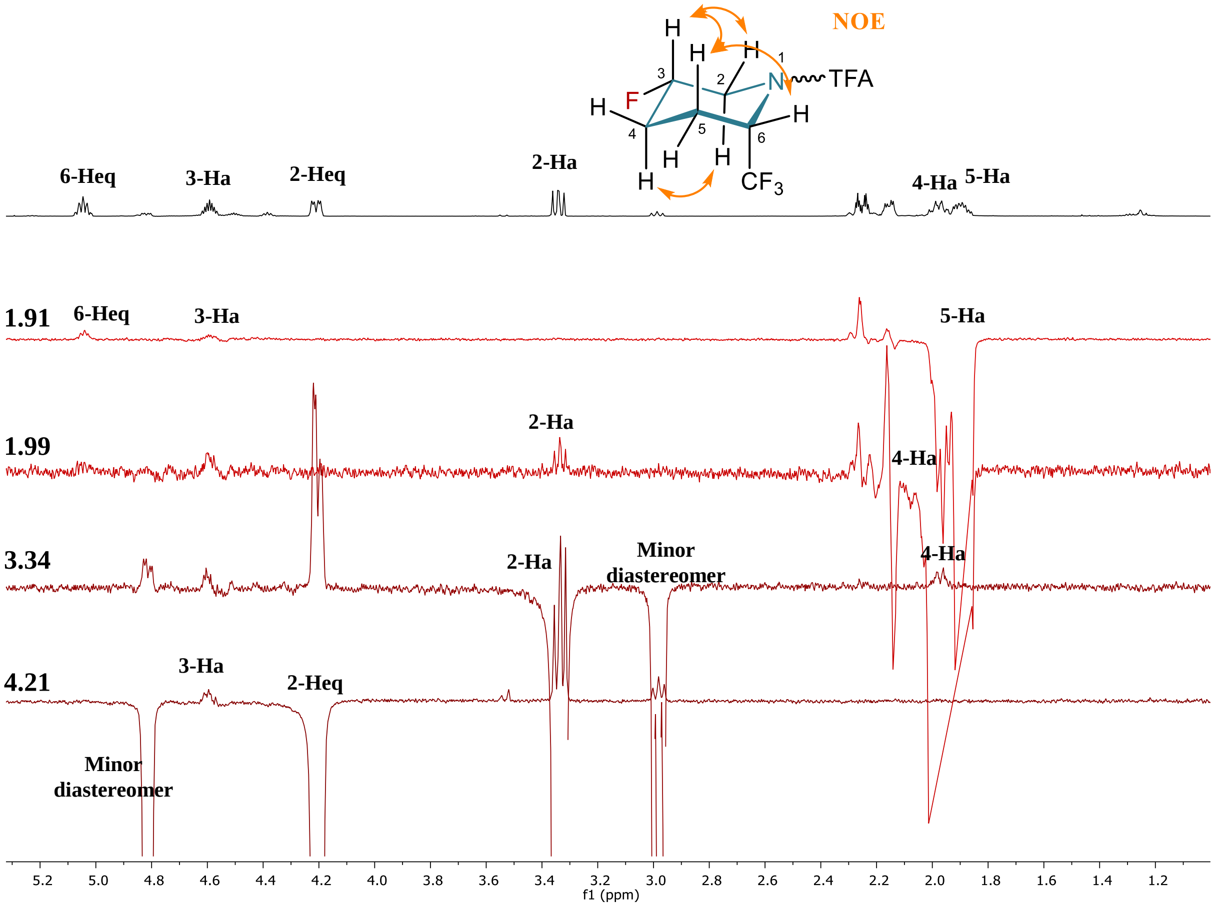
Following general procedure A on 0.5 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-5% Et_2O in pentane. The product was isolated as a colorless oil (105 mg, 0.395 mmol, 79% (volatile compound, 93% NMR yield), *d.r.* 93:7). Only the signals of the major diastereomer are listed. NMR spectra contain traces of pentane.

^{1}H NMR (599 MHz, $CDCl_3$, 299 K) δ 5.05 (p, *J* = 8.6 Hz, 1H), 4.60 (dtt, *J* = 47.7, 10.1, 5.2 Hz, 1H), 4.22 (d, *J* = 13.7 Hz, 1H), 3.34 (ddd, *J* = 14.1, 10.6, 5.8 Hz, 1H), 2.26 (dm, *J* = 15.0 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.03 – 1.95 (m, 1H), 1.95 – 1.85 (m, 1H); **^{1}H{^{19}F} NMR** (599 MHz, $CDCl_3$, 299 K) δ5.09 – 5.01 (m, 1H), 4.60 (tt, *J* = 10.1, 5.2 Hz, 1H), 4.21 (dd, *J* = 13.7, 5.2 Hz, 1H), 3.34 (dd, *J* = 13.7, 10.6 Hz, 1H), 2.26 (dm, *J* = 15.0 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.03 – 1.94 (m, 1H), 1.93 – 1.85 (m, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.35 (d, *J* = 36.8 Hz), 125.13 (q, *J* = 285.7 Hz), 116.12 (q, *J* = 287.5 Hz), 85.71 (d, *J* = 178.5 Hz), 49.61 (q, *J* = 33.6 Hz), 45.69 (d, *J* = 33.6 Hz), 26.33 (d, *J* = 20.2 Hz), 19.92 (d, *J* = 10.1 Hz); **^{13}C{sel-^{19}F at -181 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.35 (d, *J* = 37.0 Hz), 125.13 (q, *J* = 285.7 Hz), 116.12 (q, *J* = 287.5 Hz), 85.71, 49.61 (q, *J* = 31.3 Hz), 45.69, 26.33, 19.92; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.13 (d, *J* = 1.3 Hz), -70.09 (d, *J* = 8.7 Hz), -180.67 – -180.89 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.13, -70.09, -180.79.

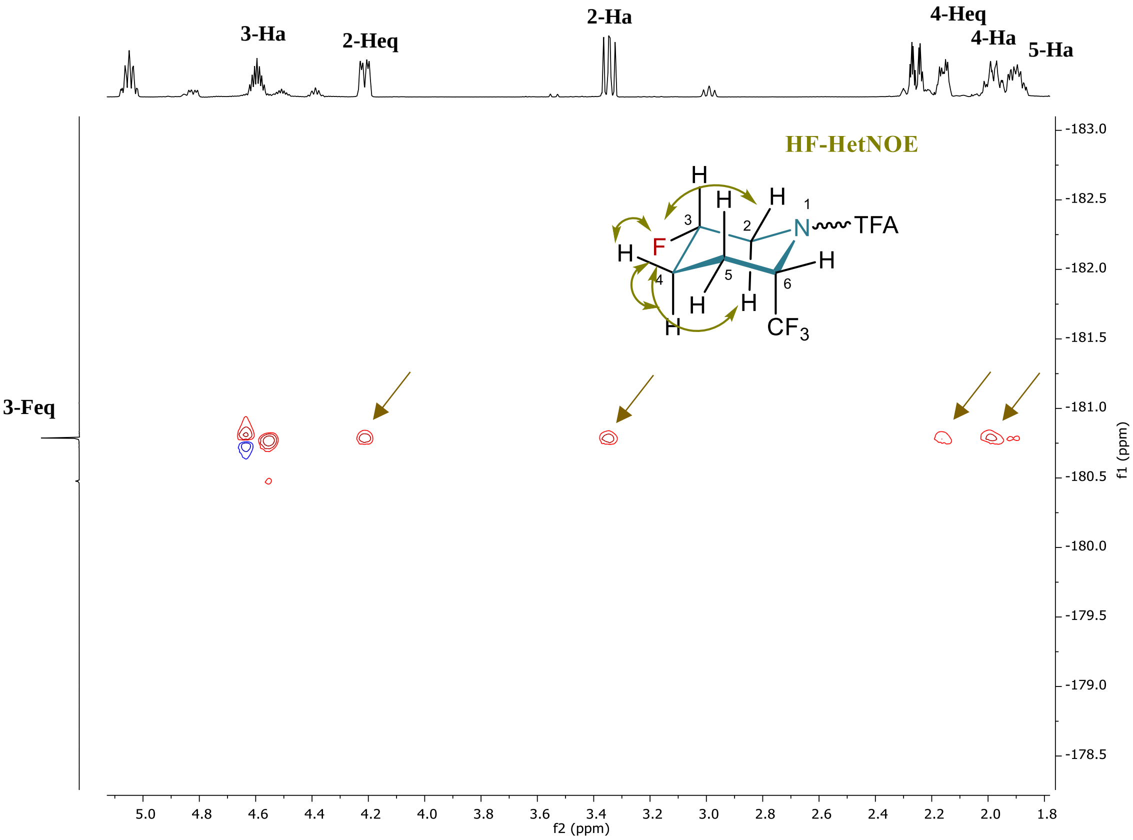
ESI-MS: calculated $[C_8H_8NOF_7 + Na]^+$: 290.0392, found: 290.0391.

IR ν = 1712.8 (m), 1450.5 (m), 1388.8 (w), 1288.5 (m), 1226.7 (m), 1195.9 (m), 1126.5 (s), 1072.5 (m), 1049.3 (m), 972.2 (m), 902.7 (w), 825.6 (w), 756.1 (m), 686.7 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. All those experiments showed unequivocally that the fluorine atom adopts equatorial orientation (Supplementary Fig. 25–26).

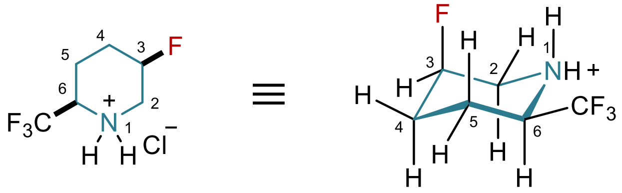


Supplementary Figure 25. Selected 1D NOESY experiments for **13**. Irradiation at 4.21, 3.34, 1.99 and 1.91 ppm, respectively. Chemical exchange with the minor diastereomer was observed during the mixing time.



Supplementary Figure 26. 2D HF-Het-NOESY experiment for **13**.

cis-5-Fluoro-2-(trifluoromethyl)piperidine hydrochloride (14)



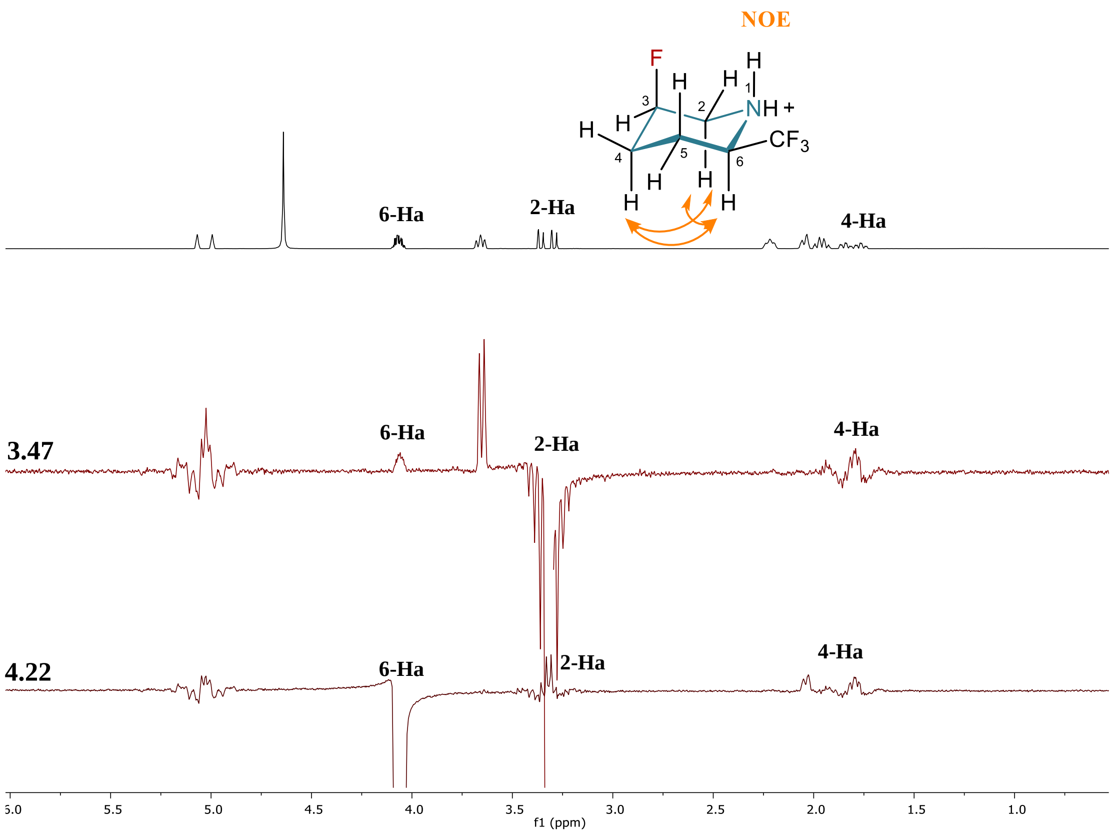
Compound **14** was prepared according to the general procedure B starting 2,2,2-trifluoro-1-(*cis*-5-fluoro-2-(trifluoromethyl)piperidin-1-yl)ethan-1-one (**13**) (93.8 mg, 0.35 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 21 h. The reaction mixture was stirred at room temperature for 21 h. Extraction and removal of all volatiles afforded the title compound as a white solid (58.2 mg, 0.28 mmol, 80%, *d.r.* >99:1).

^{1}H NMR (599 MHz, D_2O, 299 K) δ 5.18 (d, *J* = 44.6 Hz, 1H), 4.22 (dqd, *J* = 12.8, 6.6, 3.3 Hz, 1H), 3.81 (ddm, *J* = 14.2, 10.6 Hz, 1H), 3.48 (ddd, *J* = 39.7, 14.2, 1.3 Hz, 1H), 2.37 (ddm, *J* = 15.0, 9.9 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.11 (ddm, *J* = 14.2, 12.8 Hz, 1H), 1.95 (dtd, *J* = 45.0, 15.0, 4.4 Hz, 1H); **^{1}H{sel-^{19}F at -188 ppm} NMR** (599 MHz, D_2O, 299 K) δ 5.18 (s, 1H), 4.22 (dqd, *J* = 13.1, 6.6, 3.3 Hz, 1H), 3.81 (d, *J* = 14.2 Hz, 1H), 3.47 (d, *J* = 14.2 Hz, 1H), 2.37 (d, *J* = 15.0 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.11 (ddm, *J* = 14.3, 12.8 Hz, 1H), 1.95 (td, *J* = 15.0, 4.4 Hz, 1H); **^{1}H{sel-^{19}F at -75 ppm} NMR** (599 MHz, D_2O, 299 K) δ 5.18 (d, *J* = 44.6 Hz, 1H), 4.22 (dd, *J* = 12.8, 3.3 Hz, 1H), 3.81 (m, 1H), 3.47 (ddd, *J* = 39.7, 14.2, 1.3 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.23 – 2.17 (m, 1H), 2.11 (ddm, *J* = 14.3, 12.8 Hz, 1H), 1.95 (dtd, *J* = 45.0, 15.0, 4.4 Hz, 1H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 122.80 (q, *J* = 279.3 Hz), 83.62 (d, *J* = 170.0 Hz), 55.57 (q, *J* = 32.9 Hz), 47.15 (d, *J* = 20.7 Hz), 24.86 (d, *J* = 21.0 Hz), 16.16; **^{13}C{sel-^{19}F at -188 ppm} NMR** (151 MHz, D_2O, 299 K) δ 122.80 (q, *J* = 279.3 Hz), 83.62, 55.57 (q, *J* = 32.9 Hz), 47.15, 24.86, 16.16; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -74.84 – -75.06 (m), -188.34 – -188.71 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -74.99, -188.54.

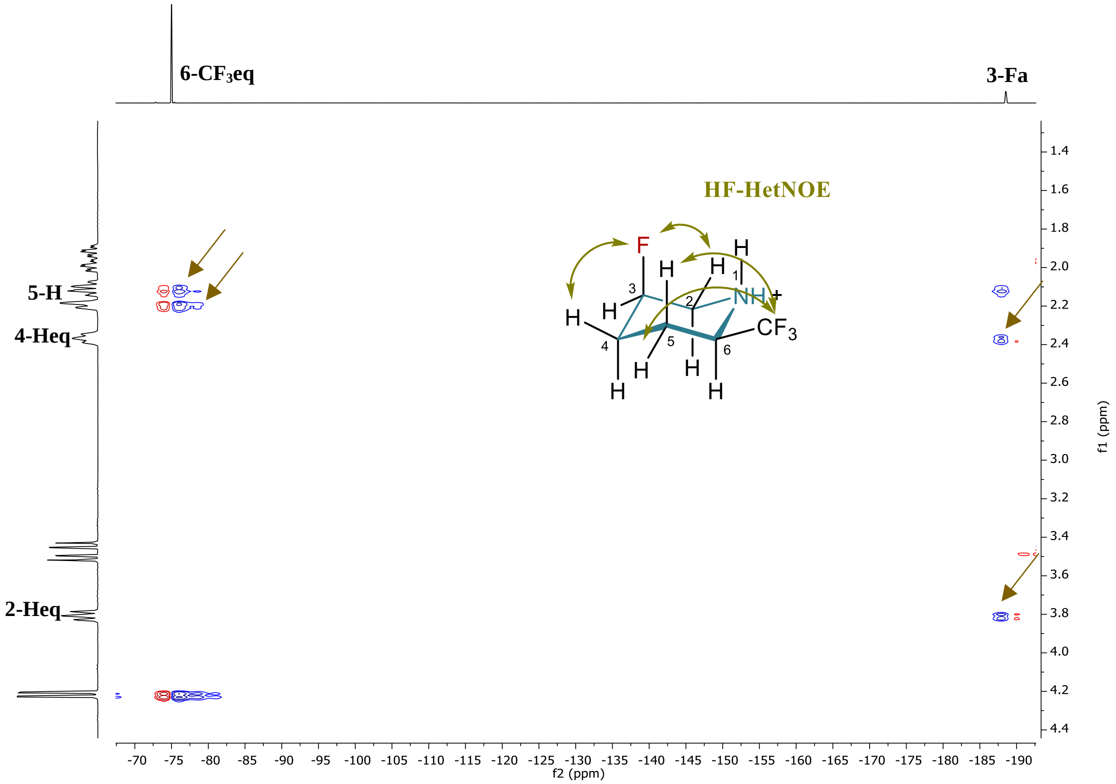
ESI-MS: calculated $[C_6H_{10}F_4N]^+$: 172.0744, found: 172.0739.

IR ν = 2934 (w), 2754 (w), 2585 (w), 2515 (m), 2376 (w), 1574 (m), 1458 (w), 1443 (w), 1389 (m), 1366 (w), 1265 (s), 1227 (s), 1211 (m), 1180 (s), 1157 (s), 1119 (m), 1034 (w), 1011 (w), 949 (s), 918 (m), 895 (m), 810 (w), 725 (w), 671 (m), 571 (s), 556 (s).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. All those experiments showed unequivocally that the fluorine atom adopts axial orientation (Supplementary Fig. 27–28). **Note** that the preferred conformation of the piperidine hydrochloride salt in this case is different than the TFA-analogue (**13**).

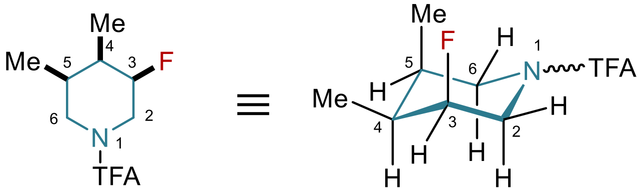


Supplementary Figure 27. Selected 1D NOESY experiments for **14**. Irradiation at 4.22 and 3.47 ppm, respectively.



Supplementary Figure 28. 2D FH-Het-NOESY experiment for **14**.

2,2,2-Trifluoro-1-(*cis*-3-fluoro-4,5-dimethylpiperidin-1-yl)ethan-1-one (15)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-4% EtOAc in pentane. The product was isolated as a colorless oil (79 mg, 0.35 mmol, 70%, *d.r.* 95:5:0). Only the signals of the major diastereomer are listed. The product was present as a ~1:1 mixture of amide bond rotamers.

Rotamer A: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.55 (ddt, *J* = 47.2, 5.6, 3.1 Hz, 1H), 3.93 (ddd, *J* = 14.2, 9.4, 5.6 Hz, 1H), 3.57 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.46 (ddd, *J* = 30.4, 14.2, 3.1 Hz, 1H), 3.37 (dd, *J* = 13.9, 3.7 Hz, 1H), 2.04 (dm, *J* = 27.0 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.06 (dd, *J* = 7.2, 2.1 Hz, 3H), 1.01 (dd, *J* = 7.2, 1.5 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.55 (dt, *J* = 5.6, 3.1 Hz, 1H), 3.93 (dd, *J* = 14.2, 5.6 Hz, 1H), 3.57 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.47 (dd, *J* = 14.2, 3.1 Hz, 1H), 3.37 (dd, *J* = 13.9, 3.7 Hz, 1H), 2.04 (ddp, *J* = 10.9, 7.3, 3.4 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.06 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.85 (d, *J* = 14.4 Hz), 116.60 (q, *J* = 287.5 Hz), 89.60 (d, *J* = 177.9 Hz), 49.69 (q, *J* = 3.1 Hz), 47.63 (dq, *J* = 25.3, 3.2 Hz), 36.64 (d, *J* = 18.6 Hz), 32.84 (d, *J* = 1.8 Hz), 13.75 (d, *J* = 3.4 Hz), 11.15 (d, *J* = 4.3 Hz); **^{13}C{sel-^{19}F at -191 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.85 (d, *J* = 14.1 Hz), 116.60 (q, *J* = 287.8 Hz), 89.60, 49.69 (q, *J* = 3.1 Hz), 47.63 (q, *J* = 3.4 Hz), 36.64, 32.83, 13.75, 11.15; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -68.29 (d, *J* = 2.5 Hz), -191.03 – -191.28 (m); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -68.29 (d, *J* = 2.5 Hz), -191.14 (d, *J* = 2.7 Hz).

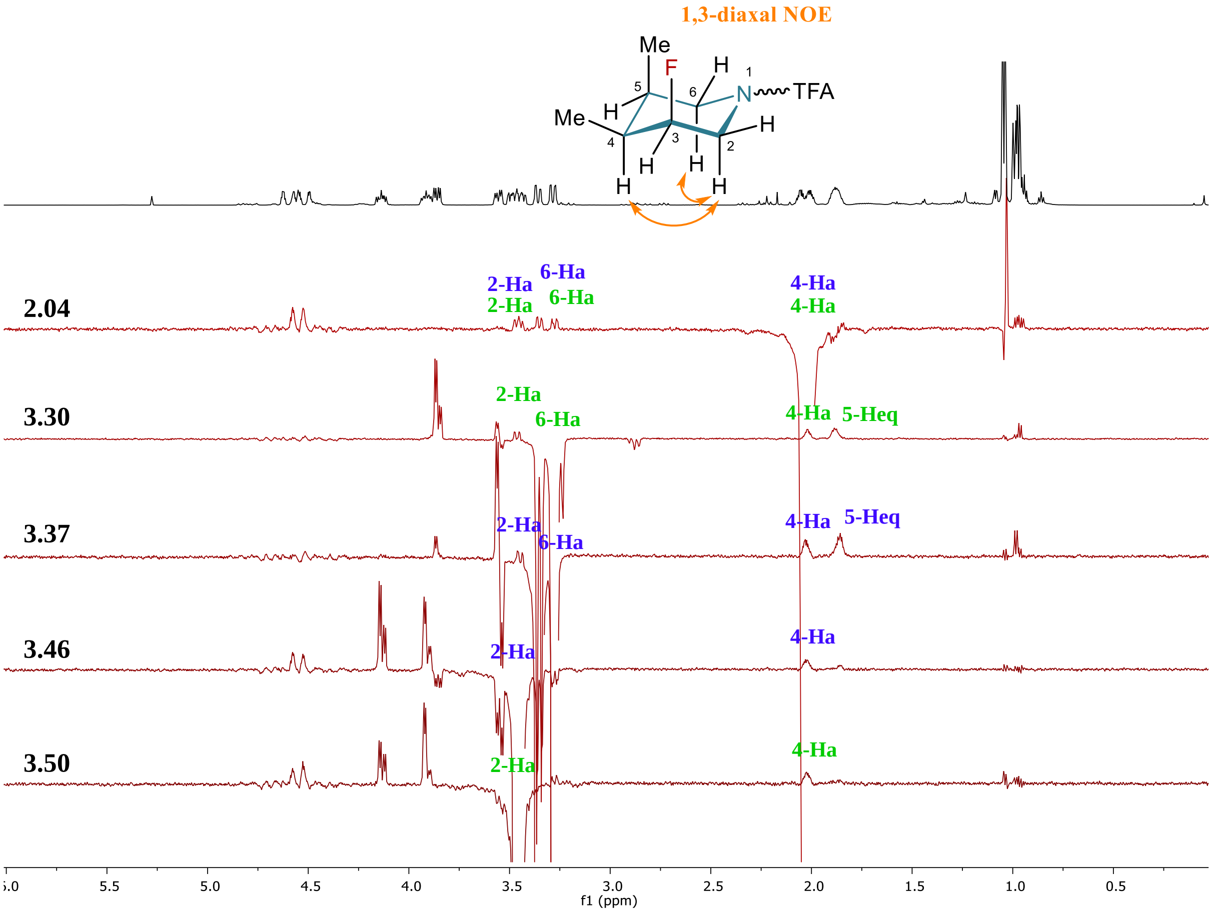
Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.60 (ddt, *J* = 47.2, 5.6, 3.1 Hz, 1H), 4.15 (ddd, *J* = 14.4, 10.0, 5.6 Hz, 1H), 3.87 (dd, *J* = 13.3, 5.6 Hz, 1H), 3.50 (ddd, *J* = 30.4, 14.4, 2.6 Hz, 1H), 3.30 (dd, *J* = 13.3, 3.7 Hz, 1H), 2.04 (dm, *J* = 27.0 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.06 (dd, *J* = 7.2, 2.1 Hz, 3H), 0.99 (dd, *J* = 7.2, 1.9 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.60 (dt, *J* = 5.6, 3.1 Hz, 1H), 4.15 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.87 (dd, *J* = 13.3, 5.6 Hz, 1H), 3.49 (dd, *J* = 14.4, 2.6 Hz, 1H), 3.30 (dd, *J* = 13.3, 3.7 Hz, 1H), 2.04 (ddp, *J* = 10.9, 7.3, 3.4 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.61 (d, *J* = 14.2 Hz), 116.58 (q, *J* = 288.1 Hz), 89.46 (d, *J* = 181.4 Hz), 47.89, 45.19 (d, *J*

= 25.9 Hz), 36.77 (d, *J* = 18.4 Hz), 32.53 (d, *J* = 1.4 Hz), 13.77 (d, *J* = 3.4 Hz), 11.28 (d, *J* = 4.5 Hz); **^{13}C{sel-^{19}F at -191 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.61 (d, *J* = 14.5 Hz), 116.58 (q, *J* = 287.9 Hz), 89.46, 47.88, 45.19, 36.77, 32.53, 13.77, 11.28; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.14, -190.54 (dtd, *J* = 47.0, 27.0, 9.7 Hz); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.14, -190.53.

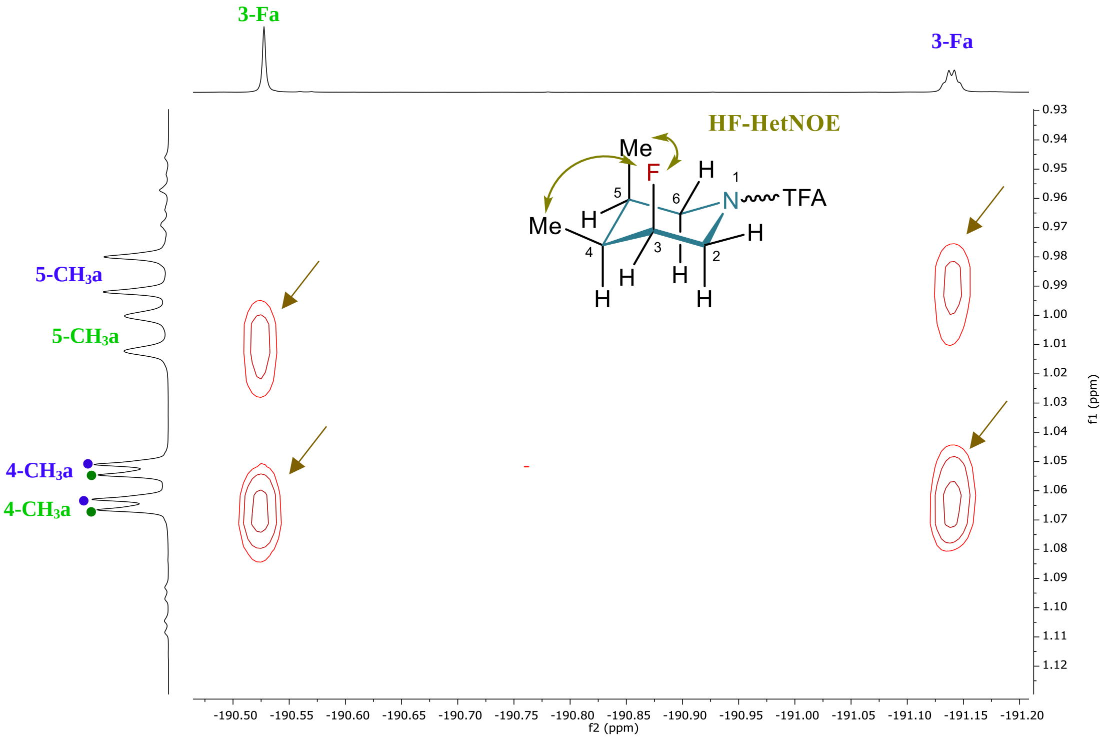
ESI-MS: calculated $[C_9H_{13}NOF_4 +Na]^+$: 250.0825, found: 250.0839.

IR ν = 2978.2 (w), 2939.6 (w), 2885.6 (w), 1689.7 (s), 1458.2 (m), 1303.9 (w), 1180.5 (s), 1141.9 (s), 1103.3 (m), 1041.6 (m), 979.8 (m), 879.6 (w), 802.4 (w), 756.1 (m), 663.5 (w).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments (Supplementary Fig. 29–30). All those experiments showed unequivocally that the dominant orientation of the fluorine atom is axial.

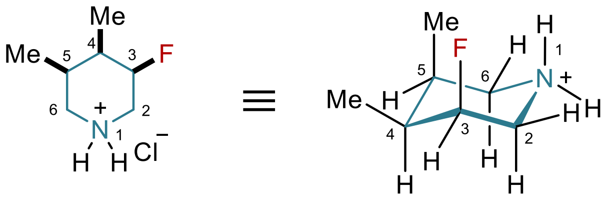


Supplementary Figure 29. Selected 1D NOESY experiments for **15**. Irradiation at 3.50, 3.46, 3.37, 3.30 and 2.04 ppm, respectively.



Supplementary Figure 30. 2D FH-Het-NOESY experiment for **15**.

cis-3-Fluoro-4,5-dimethylpiperidine hydrochloride (16)



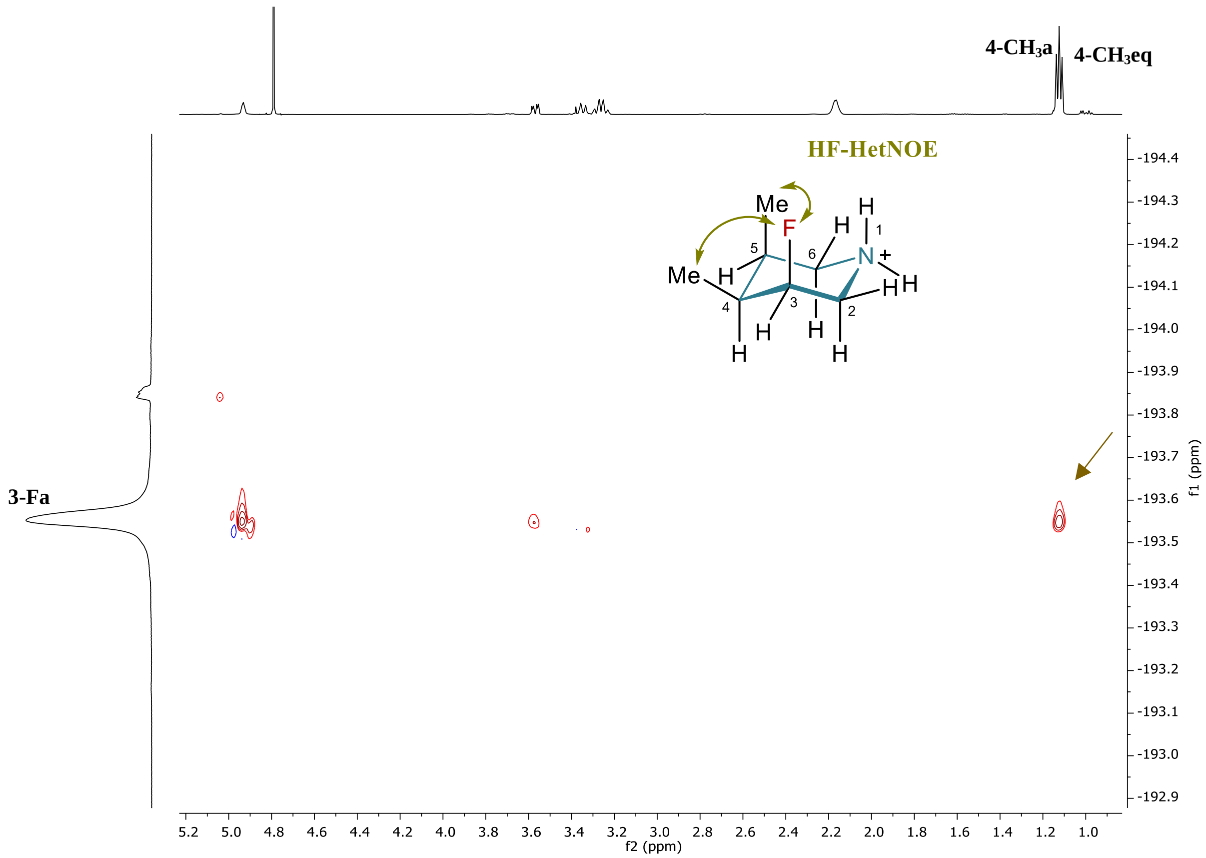
Compound **16** was prepared according to the general procedure B starting from 2,2,2-trifluoro-1-(*cis*-3-fluoro-4,5-dimethylpiperidin-1-yl)ethan-1-one (**15**) (73.7 mg, 0.32 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 3 h. Extraction and removal of all volatiles afforded the title compound as a white solid (53.0 mg, 0.32 mmol, 99%, *d.r.* 95:5:0). Only the signals of the major diastereomer are listed.

^{1}H NMR (599 MHz, D$_2$O, 299 K) δ 4.93 (d, *J* = 45.7 Hz, 1H), 3.57 (ddd, *J* = 13.8, 10.5, 4.5 Hz, 1H), 3.35 (dd, *J* = 34.3, 13.8 Hz, 1H), 3.30 – 3.22 (m, 2H), 2.23 – 2.12 (m, 2H), 1.15 – 1.10 (m, 6H); **^{1}H{^{19}F} NMR** (599 MHz, D$_2$O, 299 K) δ 4.93 (s, 1H), 3.57 (dd, *J* = 13.8, 4.5 Hz, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 3.31 – 3.21 (m, 2H), 2.21 – 2.13 (m, 2H), 1.16 – 1.10 (m, 6H); **^{13}C NMR** (151 MHz, D$_2$O, 299 K) δ 89.18 (d, *J* = 173.9 Hz), 48.23, 45.30 (d, *J* = 24.4 Hz), 33.83 (d, *J* = 18.3 Hz), 29.07 (d, *J* = 1.1 Hz), 12.90 (d, *J* = 4.2 Hz), 11.64 (d, *J* = 2.6 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D$_2$O, 299 K) δ 89.2, 48.2, 45.3, 33.8, 29.1, 12.9, 11.6; **^{19}F NMR** (564 MHz, D$_2$O, 299 K) δ -193.56 (q, *J* = 36.0, 35.3 Hz); **^{19}F{^{1}H} NMR** (564 MHz, D$_2$O, 299 K) δ -193.6.

ESI-MS: calculated [$C_7H_{15}FN$]$^+$: 132.1183, found: 132.1197.

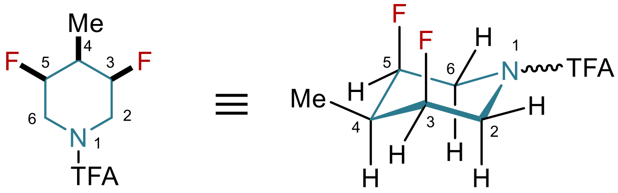
IR ν = 3380 (w), 2970 (s), 2932 (s), 2785 (s), 2739 (s), 2654 (s), 2577 (m), 1582 (s), 1458 (s), 1427 (m), 1381 (m), 1134 (m), 1088 (m), 1018 (m), 1003 (m), 949 8(s), 880 (m), 756 (m), 586 (m), 563 (m).

In order to prove whether the fluorine atom is occupying an axial or equatorial position, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. HF-HetNOE experiment showed unequivocally that the fluorine atom adopts axial orientation (Supplementary Fig. 31).



Supplementary Figure 31. 2D HF-Het-NOESY experiment for **16**.

1-(*cis*-3,5-Difluoro-4-methylpiperidin-1-yl)-2,2,2-trifluoroethan-1-one (17)



Following general procedure A on 0.25 mmol scale, 3 mol% catalyst, 1 mmol HBpin, 1 M THF at 40 °C, purification with 0-75% CH_2Cl_2 in pentane. The product was isolated as a white solid (42 mg, 0.181 mmol, 72%, *d.r.* 97:2:1). Only the signals of the major diastereomer are listed.

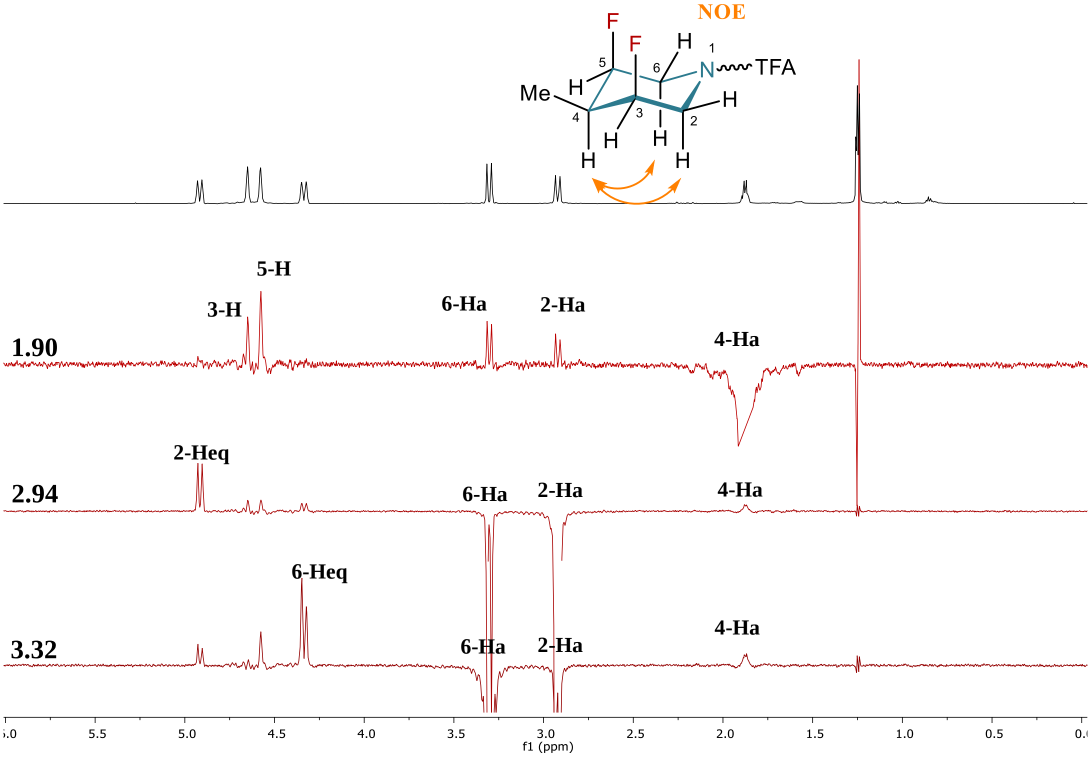
^{1}H NMR (600 MHz, $CDCl_3$, 299 K) δ 4.98 – 4.90 (m, 1H), 4.67 (d, *J* = 46.4 Hz, 1H), 4.60 (d, *J* = 46.4 Hz, 1H), 4.41 – 4.31 (m, 1H), 3.32 (dd, *J* = 35.6, 15.2 Hz, 1H), 2.94 (dd, *J* = 37.8, 14.8 Hz, 1H), 1.90 (tm, *J* = 34.9 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.94 (d, *J* = 14.8 Hz, 1H), 4.67 (s, 1H), 4.60 (s, 1H), 4.36 (d, *J* = 15.2 Hz, 1H), 3.32 (d, *J* = 15.2 Hz, 1H), 2.94 (d, *J* = 14.8 Hz, 1H), 1.93 – 1.87 (m, 1H), 1.26 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.21 (d, *J* = 36.3 Hz), 116.39 (q, *J* = 288.2 Hz), 87.65 (dd, *J* = 185.7, 2.1 Hz), 87.11 (d, *J* = 185.7 Hz), 48.89 (dq, *J* = 21.4, 3.4 Hz), 46.75 (d, *J* = 20.4 Hz), 36.86 (t, *J* = 20.1 Hz), 12.56 (t, *J* = 4.3 Hz); **^{13}C{sel-^{19}F at -197 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.21 (d, *J* = 36.3 Hz), 116.39 (q, *J* = 288.2 Hz), 87.65, 87.11, 48.89 (q, *J* = 3.4 Hz), 46.76, 36.86, 12.57; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -67.99 – -68.02 (m), -197.49 – -197.82 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -67.99 – -68.03 (m), -197.54 – -197.77 (m).

ESI-MS: calculated $[C_8H_{10}NOF_5 + Na]^+$: 254.0580, found: 254.0600.

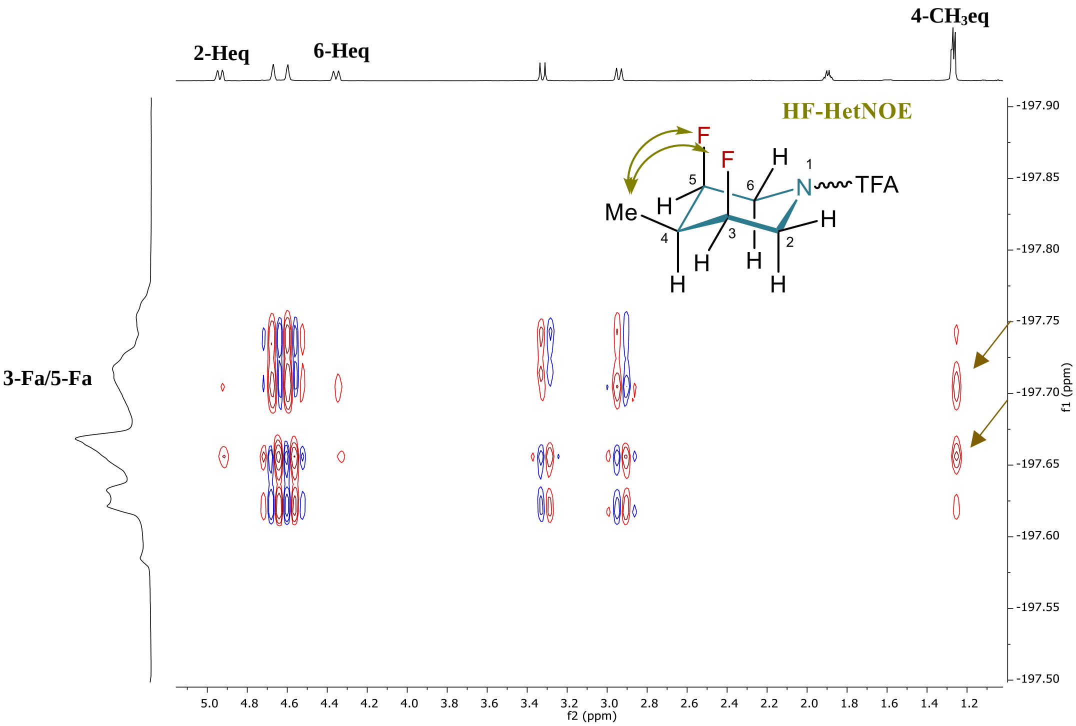
IR ν = 2924.2 (w), 1697.4 (s), 1458.2 (m), 1188.2 (s), 1141.9 (s), 1080.2 (m), 1049.3 (m), 987.6 (m), 856.4 (m), 748.4 (m), 717.5 (m), 624.9 (m).

M.p: 74-75 °C.

In order to prove whether the fluorine atoms are occupying axial or equatorial positions, we conducted a series of NMR studies that includes NOE and HF/FH-HetNOE experiments. All those experiments showed unequivocally that the fluorine atoms adopt axial orientation (Supplementary Fig. 32–33).

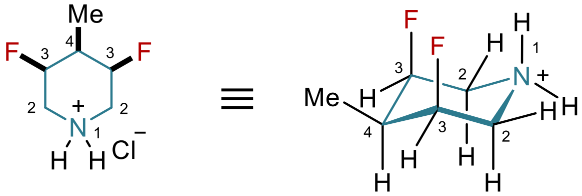


Supplementary Figure 32. Selected 1D NOESY experiments for **17**. Irradiation at 3.32, 2.94 and 1.90 ppm, respectively. Chemical exchange (2-H$_a$ ↔ 6-H$_a$) was observed during the mixing time.



Supplementary Figure 33. 2D HF-Het-NOESY experiment for **17**.

cis-3,5-Difluoro-4-methylpiperidine hydrochloride (18)



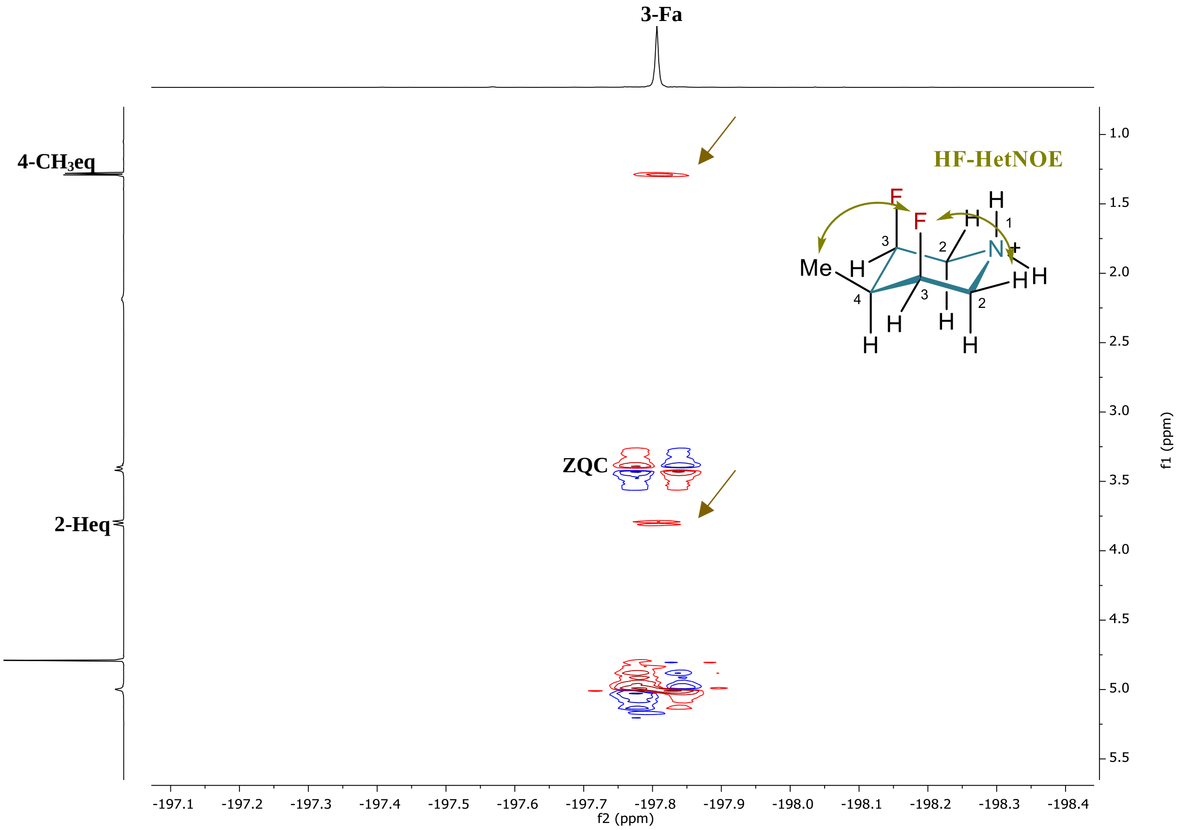
Compound **18** was prepared according to the general procedure B starting 1-(*cis*-3,5-difluoro-4-methylpiperidin-1-yl)-2,2,2-trifluoroethan-1-one (**17**) (31.5 mg, 0.14 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 21 h. Extraction and removal of all volatiles afforded the title compound as a white solid (23.3 mg, 0.135 mmol, 97%, *d.r.* 99:1:0).

^{1}H NMR (599 MHz, D_2O, 299 K) δ 5.00 (d, *J* = 45.5 Hz, 2H), 3.80 (ddm, *J* = 14.3, 11.0 Hz, 2H), 3.41 (dd, *J* = 40.9, 14.3 Hz, 2H), 2.18 (tm, *J* = 38.1 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); **^{1}H{^{19}F} NMR** (599 MHz, D_2O, 299 K) δ 5.00 (s, 2H), 3.80 (d, *J* = 14.3 Hz, 2H), 3.41 (d, *J* = 14.3 Hz, 2H), 2.28 – 2.13 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 87.33 (dd, *J* = 180.0, 4.7 Hz), 46.34 (dd, *J* = 15.2, 6.5 Hz), 34.04 (t, *J* = 19.4 Hz), 11.66 (t, *J* = 4.3 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 87.3, 46.3, 34.0, 11.7; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -197.61 – -197.95 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -197.8.

ESI-MS: calculated $[C_6H_{12}F_2N]^+$: 136.0932, found: 136.0931.

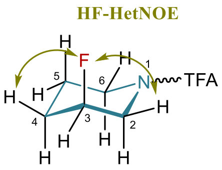
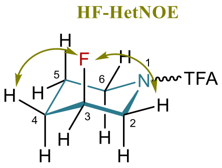
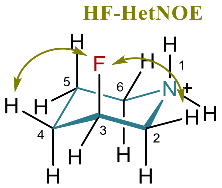
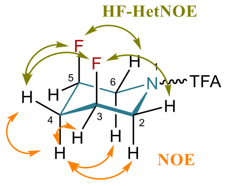
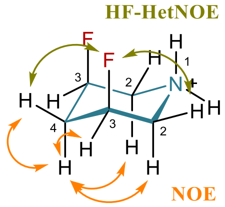
IR ν = 2986 (m), 2932 (m), 2801 (m), 2754 (m), 2662 (m), 2562 (m), 2508 (w), 2376 (w), 1582 (s), 1451 (m), 1319 (w), 1126 (m), 1065 (m), 995 (s), 926 (s), 864 (w), 802 (w), 710 (m), 633 (w), 571 (s), 556 (s).

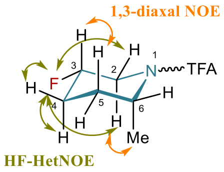
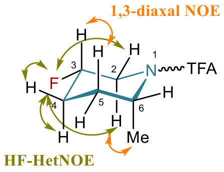
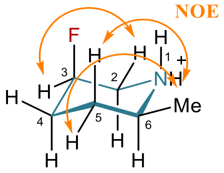
In order to prove whether the fluorine atoms are occupying axial or equatorial positions, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. HF-HetNOE experiment showed unequivocally that the fluorine atoms adopt axial orientation (Supplementary Fig. 34).

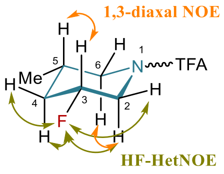
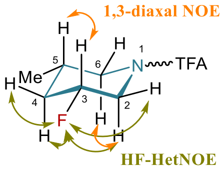
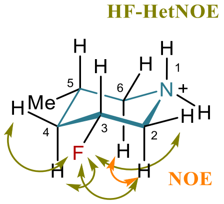


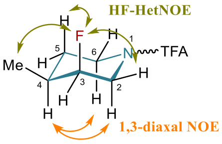
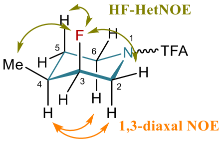
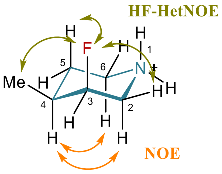
Supplementary Figure 34. 2D FH-Het-NOESY experiment for **18**.

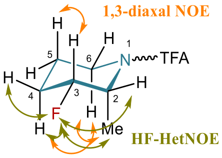
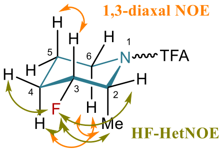
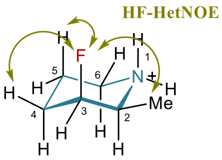
Supplementary Table 9. Summary of NMR data of Figure 2.

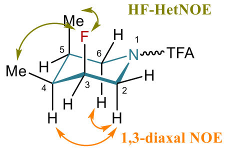
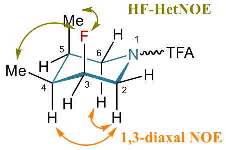
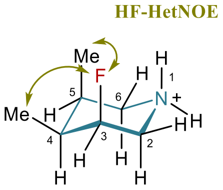
		position	δ(^{1}H) (eq/ax)	^{2}J(F,H) Hz	^{3}J(F,H) Hz	^{2}J(H,H) Hz	^{3}J(H,H) Hz
	**Rotamer A**	2	3.63/2.89		2He3Fa: 8.9	13.8	2He3He: 5.6
		3	3.94	47.0	**2Ha3Fa: 26**		2Ha3He:2.2
		4	1.35/1.10		4He3Fa: n.d		4He3He: n.d.
		5	1.35/0.85		4Ha3Fa: n.d		4Ha3He: n.d.
		6	3.01/2.63			14.3	
	**Rotamer B**	2	3.30/2.76		2He3Fa: 8.4	14.3	2He3He: 5.3
		3	3.89	47.0	**2Ha3Fa: 26**		2Ha3He:2.0
		4	1.35/1.10		4He3Fa: n.d		4He3He: n.d.
		5	1.35/0.85		4Ha3Fa: n.d		4Ha3He: n.d.
		6	3.52/2.54			14.3	
		2	3.60/3.31		2He3Fa: 10.7		
		3	5.13	44.5	**2Ha3Fa: 38.7**		
		4	2.17/1.80		4He3Fa: n.d		
		5	2.05/1.90		4Ha3Fa: n.d		
		6	3.43/3.10				
	**Only one rotamer**	2	4.53/3.29		2He3Fa: 10.8	14.3	2He3He: 2.0
		3	4.85	34.3	**2Ha3Fa: 32.1**		2Ha3He: 2.0
		4	2.44/2.07		4He3Fa: 12	15.5	4He3He: 2.0
		5	4.77	34.5	4He5Fa: 12		4He5He: 2.0
					4Ha3Fa: 36.1		4Ha3He: 3.5
		6	4.12/3.51		**4Ha5Fa: 36.1**	14.9	4Ha5He: 3.5
					6He5Fa: 9.2		6He5He: 2.0
					6Ha5Fa: 30.6		6Ha5He: 2.0
		2	3.79/3.42		2He3Fa: 12.3	14.9	2He3He <2.0
		3	5.22	42.9	**2Ha3Fa: 39.5**		2Ha3He< 2.0
		4	2.65/2.17		4He3Fa: 14.9	17.1	4He3He< 2.0
					4Ha3Fa: 46.7		4Ha3He: 3.5

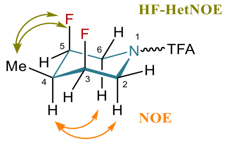
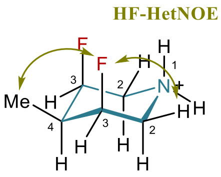
		position	**δ(^{1}H) (eq/ax)**	**^2J(F,H) Hz**	**^3J(F,H) Hz**	**^2J(H,H) Hz**	**^3J(H,H) Hz**
	**Rotamer A**	2	4.04/3.18		**2Ha3Fe: 5.8**	13.3	2Ha3Ha: 10.5
		3	4.50	47.7			3Ha4Ha: n.d.
		4	2.10/1.88		4Ha3Fe: n.d.		
		5	1.75				
		6	4.73				6He5Ha: n.d.
		6-Me	1.25				
	**Rotamer B**	2	4.68/2.87		**2Ha3Fe: 5.8**	12.6	2Ha3Ha: 10.6
		3	4.45	47.7			3Ha4Ha: n.d.
		4	2.10/1.88		4Ha3Fe: n.d.		
		5	1.75				
		6	4.25				6He5Ha: n.d.
		6-Me	1.34				
		2	3.64/3.30		**2Ha3Fa: 40.7**	14.2	2Ha3He< 2
		3	5.12	45.2			3He4Ha< 2
		4	2.23/1.90		4Ha3Fa: n.d.		
		5	1.85/1.70				
		6	3.35				6Ha5Ha: 12.4
		6-Me	1.37				

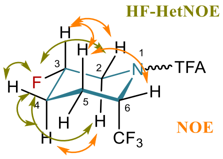
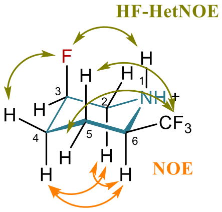
	**Rotamer A**	2	4.13/3.13		**2Ha3Fe: 4.4**	13.3	2Ha3Ha: 9.8
		3	4.53	47.6			3Ha4Ha: n.d.
		4	2.27/1.40		**4Ha3Fe: 12.0**		4Ha5Ha: n.d.
		5	1.77				
		5-Me	1.05				
		6	4.27/2.50			12.7	6Ha5Ha: 11.1
	**Rotamer B**	2	4.63/2.85		**2Ha3Fe: 5.1**	12.6	2Ha3Ha: 9.8
		3	4.53	47.6			3Ha4Ha: n.d.
		4	2.27/1.40		**4Ha3Fe: 12.0**		4Ha5Ha: n.d.
		5	1.77				
		5-Me	1.03				
		6	3.79/2.76			13.8	6Ha5Ha: 10.7
		2	3.60/3.12		2Ha3Fe: n.d.	n.d.	2Ha3Ha: n.d.
		3	4.98	43.8			3Ha4Ha: n.d.
		4	2.30/1.61		4Ha3Fe: n.d.		4Ha5Ha: n.d.
		5	2.09				
		5-Me	1.13				
		6	3.35/2.82			n.d.	6Ha5Ha: n.d.

		position	**δ(^{1}H) (eq/ax)**	**^2J(F,H) Hz**	**^3J(F,H) Hz**	**^2J(H,H) Hz**	**^3J(H,H) Hz**
	**Rotamer A**	2	4.79/2.89		**2Ha3Fa: 38.3**	14.8	2Ha3He: 3.0
		3	4.62	47.0			
		4	1.77		4Ha3Fa: n.d.		4Ha3He: n.d.
		4-Me	1.07				
		5	1.60				5Ha4Ha: n.d.
		6	4.55/2.75				
	**Rotamer B**	2	4.22/3.25		**2Ha3Fa: 36.6**	14.7	2Ha3He: n.d.
		3	4.54	47.0			
		4	1.77		4Ha3Fa: n.d.		4Ha3He: n.d.
		4-Me	1.08				
		5	1.60				5Ha4Ha: n.d.
		6	4.02/3.13				
		2	3.69/3.30		**2Ha3Fa: 36.6**	14.7	2Ha3He: n.d.
		3	4.94	45.6			
		4	1.99		**4Ha3Fa: 36.5**		4Ha3He: n.d.
		4-Me	1.12				
		5	1.80				5Ha4Ha: n.d.
		6	3.47/3.12				

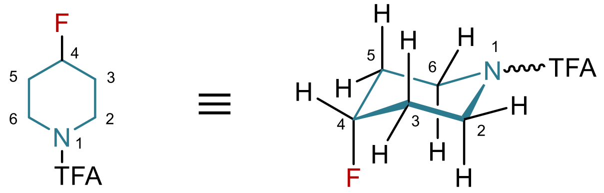
	**Rotamer A**	2-Me	1.24				
		2	4.99		2He3Fe: 3.3		2He3Ha: 5.7
		3	4.59	47.0			3Ha4Ha: n.d.
		4	2.04/1.85		4He3Fe: n.d.		
		5	1.85/1.50				
		6	3.74/3.15				
	**Rotamer B**	2-Me	1.30				
		2	4.43		2He3Fe: 3.3		2He3Ha: 5.8
		3	4.59	47.0			3Ha4Ha: n.d.
		4	2.04/1.85		4He3Fe: n.d.		
		5	1.85/1.50				
		6	4.35/2.82				
		2-Me	1.41				
		2	3.48		**2Ha3Fa: 31.5**		2He3He: n.d.
		3	4.94	47.0			3He4Ha: n.d.
		4	2.25/1.80		**4Ha3Fa: 46**		
		5	1.90/1.80				
		6	3.44/3.10				

		position	**δ(^{1}H) (eq/ax)**	**^2J(F,H) Hz**	**^3J(F,H) Hz**	**^2J(H,H) Hz**	**^3J(H,H) Hz**
	**Rotamer A**	2	3.93/3.46		**2Ha3Fa: 30.4**	14.2	2Ha3He: 3.1
		3	4.55	47.2			2He3He: 5.6
		4	2.04		**4Ha3Fa: 27.0**		4Ha3He: 3.1
		4-Me	1.01				
		5	1.90				
		5-Me	1.06				6He5He: 5.6
		6	3.57/3.37			13.9	6Ha5He: 3.7
	**Rotamer B**	2	4.15/3.50		**2Ha3Fa: 30.4**	14.4	2Ha3He: 2.6
		3	4.60	47.2			2He3He: 5.6
		4	2.04		**4Ha3Fa: 27.0**		4Ha3He: 3.1
		4-Me	1.06				
		5	1.89				
		5-Me	0.99				6He5He: 5.6
		6	3.87/3.30			13.3	6Ha5He: 3.7
		2	3.57/3.55		**2Ha3Fa: 34.3**		
		3	4.93	45.7			
		4	2.18		4Ha3Fa: n.d.		
		4-Me	1.13				
		5	2.18				
		5-Me	1.13				
		6	3.28				

		2	4.94/2.94			14.8	2Ha3He <3.0
		3	4.67	46.4	**2Ha3Fa: 37.8**		4Ha3He <3.0
		4	1.89		**4Ha3Fa: 34.9** **4Ha5Fa: 34.9**		4Ha5He <3.0
		4-Me	1.27				6Ha5He <3.0
		5	4.60	46.4			
		6	4.36/3.32		**6Ha5Fa: 35.6**	15.2	
		2	3.80/3.41		**2Ha3Fa: 40.9**	14.3	2Ha3He <3.0
		3	5.00	45.5			
		4	2.18		**4Ha3Fa: 38.1**		4Ha3He <3.0
		4-Me	1.29				

		position	**δ(^{1}H) (eq/ax)**	**^{2}*J*(F,H) Hz**	**^{3}*J*(F,H) Hz**	**^{2}*J*(H,H) Hz**	**^{3}*J*(H,H) Hz**
		2	4.22/3.34				
		3	4.60	47.7	**2Ha3Fe: 5.8**		2Ha3Ha: 10.6
		4	2.15/1.99		**4Ha3Fe: n.d.**		3Ha4Ha: 10.1
		5	2.26/1.91				
		6	5.05				6He5Ha: n.d
		6-CF$_3$					
		2	3.81/3.47		**2Ha3Fa: 39.7**	14.2	2Ha3He <3.0
		3	5.18	44.6			3He4Ha <3.0
		4	2.37/1.95		**4Ha3Fa: 45.0**	15.0	
		5	2.20/2.11				
		6	4.22				6Ha5Ha: 12.8
		6-CF$_3$	-				

2,2,2-Trifluoro-1-(4-fluoropiperidin-1-yl)ethan-1-one (19)



Following general procedure A on 1 mmol scale starting from 2,4-difluoropyridine, 1 mol% catalyst, 4 mmol HBpin, 1 M THF at 40 °C, purification with 0-5% Et_2O in pentane. The product was isolated as a colorless oil (40 mg, 0.20 mmol, 20%). Traces of defluorinated side-product were inseparable from the product. NMR spectra contain trances of pentane.

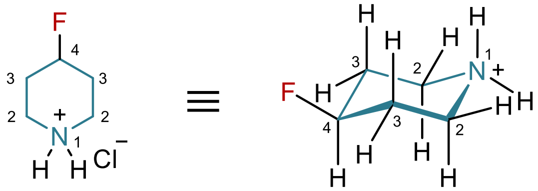
The orientation of the fluorine atom was assigned as axial due to the large values of ^3J(F,H_a). [**^3J(3-H_a,4-F) = ^3J(5-H_a,4-F) = 34.5 Hz**]

^{1}H NMR (599 MHz, $CDCl_3$, 299 K) δ 4.93 (dtt, *J* = 47.5, 5.2, 2.7 Hz, 1H), 4.06 (dt, *J* = 13.5, 4.4 Hz, 1H), 3.75 – 3.58 (m, 2H), 3.49 – 3.42 (m, 1H), 1.99 (dtd, *J* = 14.3, 7.3, 6.5, 3.9 Hz, 2H, 3-Heq overlaps with 5-Heq), 1.93 – 1.81 (dm, *J* = 34.5 Hz, 2H, 3-Ha overlaps with 5-Ha); **^{1}H{^{19}F} NMR** (599 MHz, $CDCl_3$, 299 K) δ 4.93 (dt, *J* = 5.0, 2.4 Hz, 1H), 4.06 (dt, *J* = 13.5, 4.5 Hz, 1H), 3.74 – 3.59 (m, 2H), 3.46 (td, *J* = 13.8, 12.4, 3.4 Hz, 1H), 2.02 – 1.95 (m, 2H), 1.92 – 1.83 (m, 2H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.62 (d, *J* = 35.6 Hz), 116.63 (q, *J* = 287.9 Hz), 86.59 (d, *J* = 171.6 Hz), 41.56 (p, *J* = 3.3, 2.9 Hz), 39.39 (d, *J* = 4.1 Hz), 31.65 (d, *J* = 20.7 Hz), 30.66 (d, *J* = 20.6 Hz); **^{13}C{sel-^{19}F at -69 and -185 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.62, 116.60, 86.59, 41.56, 39.39, 31.65, 30.66; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.12, -184.92 – -185.55 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.12, -185.21.

ESI-MS: calculated $[C_7H_9NOF_4 + Na]^+$: 222.0518, found: 222.0530.

IR ν = 2947 (w), 1790 (w), 1689 (s), 1458 (m), 1265 (w), 1195 (s), 1180 (s), 1134 (s), 1049 (m), 1003 (m), 933 (m), 756 (m), 655 (m).

4-Fluoropiperidine hydrochloride (20)



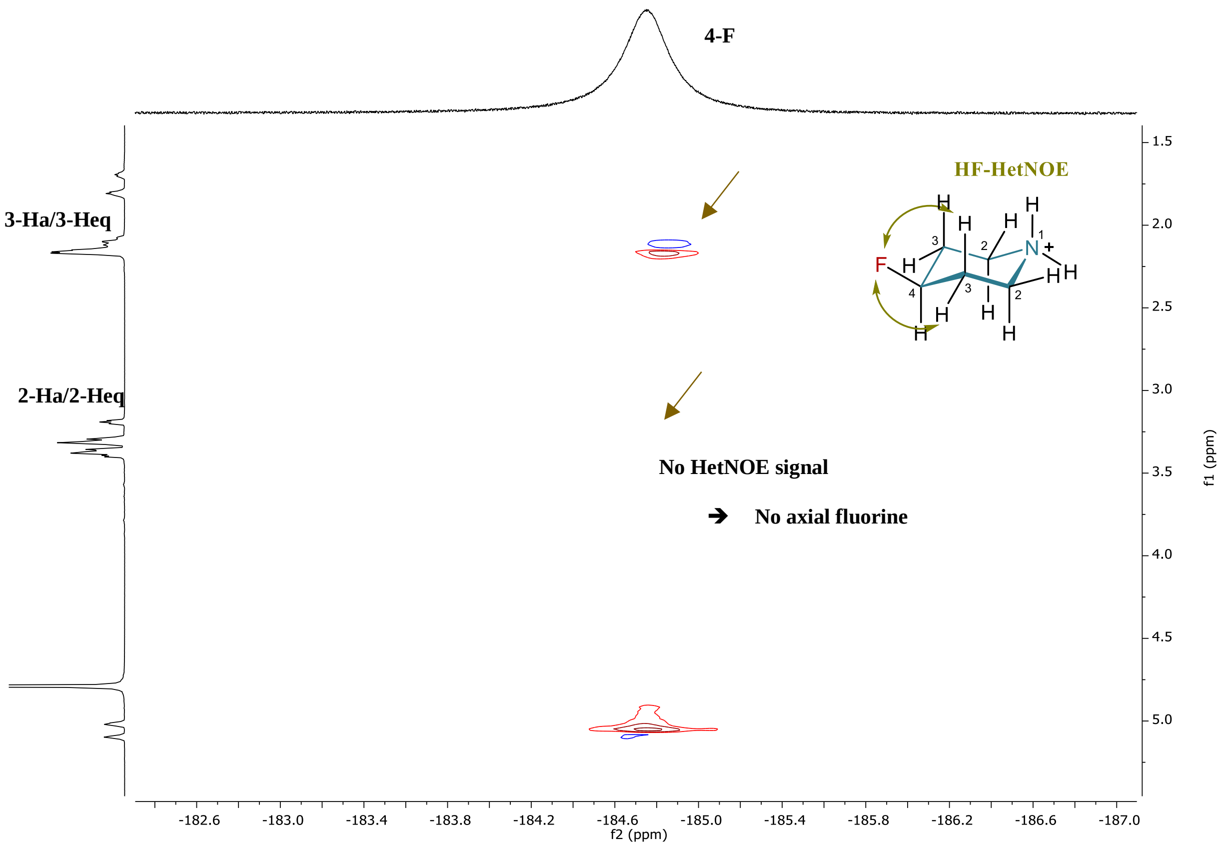
Compound **20** was prepared according to the general procedure B starting 2,2,2-trifluoro-1-(4-fluoropiperidin-1-yl)ethan-1-one (**19**) (40 mg, 0.2 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 1 h. Extraction and removal of all volatiles afforded the title compound as a white solid (26 mg, 0.186 mmol, 93%). Traces of defluorinated side-product were inseparable from the product.

Due to the broadening in NMR spectra we could not determine the orientation of the fluorine atom via ${}^{3}J$(F,H) values. We believe that in this case there is a dynamic behavior where the equilibrium favors equatorial fluorine orientation. FH-Het-NOESY experiment supports our claim (Supplementary Fig. 35).

^{1}H NMR (599 MHz, D_2O, 299 K) δ 5.14 – 4.99 (dm, *J* = 47.5 Hz, 1H), 3.43 – 3.26 (m, 4H), 2.22 – 2.08 (m, 4H); **^{1}H{^{19}F} NMR** (599 MHz, D_2O, 299 K) δ 5.06 (s, 1H), 3.44 – 3.26 (m, 4H), 2.23 – 2.10 (m, 4H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 85.24 (d, *J* = 168.8 Hz), 39.64 (d, *J* = 4.8 Hz), 27.07 (d, *J* = 21.2 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 85.24, 39.64, 27.07; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -184.75 (bs); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -184.76 (bs).

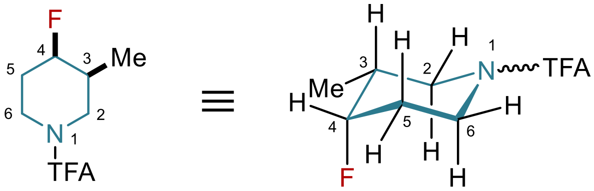
ESI-MS: calculated $[C_5H_{11}FN]^+$: 104.0870, found: 104.0866.

IR ν = 3379 (m), 2955 (s), 2808 (s), 2723 (s), 2630 (m), 2492 (m), 1620 (m), 1597 (m), 1458 (m), 1427 (m), 1381 (m), 1311 (m), 1141 (m), 1064 (m), 1026 (s), 972 (m), 954 (s), 910 (m), 840 (m).



Supplementary Figure 35. 2D FH-Het-NOESY experiment for **20**.

2,2,2-Trifluoro-1-(*cis*-4-fluoro-3-methylpiperidin-1-yl)ethan-1-one (21)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 4 mmol HBpin, 1 M THF at 40 °C, purification with 0-4% Et$_2$O in pentane. The product was isolated as a colorless oil (32.6 mg, 0.153 mmol, 31%, *d.r.* 97:3). Only the peaks of the major diastereomer are listed. The product was present as a ~1:1 mixture of amide bond rotamers.

The orientation of the fluorine atom was assigned as axial due to the large values of ^{3}J(F,H$_a$). [**^{3}J(3-H$_a$,4-F, Rot A) = 33.5 Hz, ^{3}J(5-H$_a$,4-F, Rot A) = 41.2 Hz, ^{3}J(3-H$_a$,4-F, Rot B) = 33.5 Hz, ^{3}J(5-H$_a$,4-F, Rot B) = 41.2 Hz**]

Rotamer A: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.75 (d, *J* = 48.2 Hz, 1H), 4.36 (dm, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 3.20 (dd, *J* = 13.5, 12.0 Hz, 1H), 3.10 (td, *J* = 13.2, 2.6 Hz, 1H), 2.11 (tm, *J* = 12.4 Hz, 1H), 1.84 (dm, *J* = 33.5 Hz, 1H overlaps with 5-H$_a$ and 5-H$_a$), 1.72 (dm, *J* = 41.2 Hz, 1H, overlaps with 3-H$_a$ and 3-H$_a$), 1.05 (d, *J* = 6.3 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.75 (s, 1H), 4.36 (dm, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 3.20 (dd, *J* = 13.7, 11.8 Hz, 1H), 3.10 (td, *J* = 13.2, 2.6 Hz, 1H), 2.11 (dm, *J* = 14.4 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.76 (tm, *J* = 13.8 Hz, 1H), 1.05 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.57 (d, *J* = 37.0 Hz), 116.68 (q, *J* = 288.0 Hz), 89.75 (d, *J* = 174.0 Hz), 46.89 (p, *J* = 3.4 Hz), 38.33 (d, *J* = 2.1 Hz), 35.93 (d, *J* = 19.7 Hz), 30.30 (d, *J* = 21.1 Hz), 14.12 (d, *J* = 4.5 Hz); **^{13}C{sel-^{19}F at -202 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.57 (d, *J* = 33.3 Hz), 116.69 (q, *J* = 287.5 Hz), 89.75, 46.89 (q, *J* = 3.5 Hz), 38.33, 35.93, 30.31, 14.12; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -68.94, -202.65 – -203.05 (m); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -68.94, -202.86 (bs).

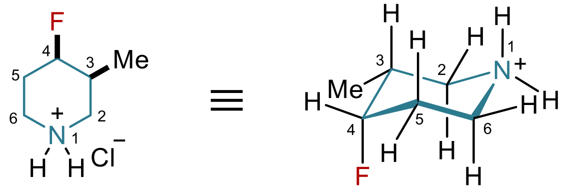
Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.75 (d, *J* = 48.2 Hz, 1H), 4.26 (dd, *J* = 13.1, 4.5 Hz, 1H), 3.82 (dm, *J* = 11.9 Hz, 1H), 3.44 (td, *J* = 13.6, 2.8 Hz, 1H), 2.85 (t, *J* = 12.5 Hz, 1H), 2.11 (tm, *J* = 12.4 Hz, 1H), 1.84 (dm, *J* = 33.5 Hz, 1H overlaps with 5-H$_a$ and 5-H$_a$), 1.72 (dm, *J* = 41.2 Hz, 1H, overlaps with 3-H$_a$ and 3-H$_a$), 1.06 (d, *J* = 6.5 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.75 (s, 1H), 4.26 (dd, *J* = 13.2, 4.5 Hz, 1H), 3.82 (dm, *J* = 12.0 Hz, 1H), 3.44 (td, *J* = 13.6, 2.8 Hz, 1H), 2.85 (t, *J* = 12.5 Hz, 1H), 2.11 (dp, *J* = 13.5, 3.4 Hz, 1H), 1.90 – 1.82

(m, 1H), 1.76 (tm, *J* = 13.8 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.57 (d, *J* = 35.5 Hz), 116.68 (q, *J* = 288.0 Hz), 89.72 (d, *J* = 173.9 Hz), 44.62 (d, *J* = 2.3 Hz), 40.53 (p, *J* = 3.7 Hz), 35.00 (d, *J* = 19.8 Hz), 31.47 (d, *J* = 21.1 Hz), 14.29 (d, *J* = 4.3 Hz); **^{13}C{sel-^{19}F at -202 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.58 (d, *J* = 36.0 Hz), 116.69 (q, *J* = 287.5 Hz), 89.72, 44.62, 40.53 (q, *J* = 3.5 Hz), 35.00, 31.47, 14.29; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.11, -202.65 – -203.05 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.11, -202.89 (bs).

ESI-MS: calculated $[C_8H_{11}NOF_4 + Na]^+$: 236.0674, found: 236.0676.

IR ν = 2939 (w), 1689 (s), 1465 (m), 1257 (m), 1195 (s), 1180 (s), 1134 (s), 979 (m), 933 (m), 756 (m).

cis-4-Fluoro-3-methylpiperidine hydrochloride (22)



Compound **22** was prepared according to the general procedure B starting 2,2,2-trifluoro-1-(*cis*-4-fluoro-3-methylpiperidin-1-yl)ethan-1-one (**21**) (33.5 mg, 0.157 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 1 h. Extraction and removal of all volatiles afforded the title compound as a white solid (24 mg, 0.156 mmol, 99%, *d.r.* 97:3). Only the signals of the major diastereomer are listed.

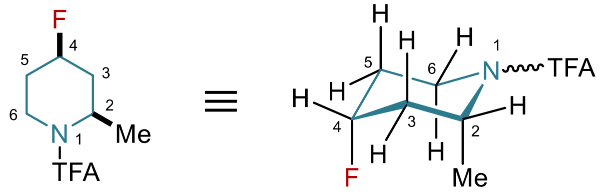
The orientation of the fluorine atom was assigned as axial due to the large values of ^{3}J(F,H$_a$). [**^{3}J(3-H$_a$,4-F) = 34.5 Hz, ^{3}J(5-H$_a$,4-F) = 43.3 Hz**]

^{1}H NMR (599 MHz, D$_2$O, 299 K) δ 4.90 (d, *J* = 47.8 Hz, 1H), 3.35 (dd, *J* = 13.0, 4.8 Hz, 1H), 3.29 – 3.19 (m, 2H), 3.01 (t, *J* = 12.7 Hz, 1H), 2.34 – 2.25 (m, 1H), 2.14 (dm, *J* = 34.5 Hz, 1H), 2.02 (dm, *J* = 43.3 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H); **^{1}H{^{19}F} NMR** (599 MHz, D$_2$O, 299 K) δ 4.90 (s, 1H), 3.35 (dd, *J* = 12.8, 4.7 Hz, 1H), 3.29 – 3.17 (m, 2H), 3.01 (t, *J* = 12.7 Hz, 1H), 2.29 (d, *J* = 14.5 Hz, 1H), 2.21 – 2.11 (m, 1H), 2.02 (t, *J* = 12.5 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, D$_2$O, 299 K) δ 88.43 (d, *J* = 171.0 Hz), 43.95 (d, *J* = 2.3 Hz), 38.17 (d, *J* = 1.9 Hz), 31.59 (d, *J* = 19.8 Hz), 26.89 (d, *J* = 21.1 Hz), 13.35 (d, *J* = 3.9 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D$_2$O, 299 K) δ 88.43, 43.95, 38.17, 31.59, 26.89, 13.35; **^{19}F NMR** (564 MHz, D$_2$O, 299 K) δ -203.02 – -203.35 (m); **^{19}F{^{1}H} NMR** (564 MHz, D$_2$O, 299 K) δ -203.17.

ESI-MS: calculated [$C_6H_{13}FN$]$^+$: 118.1027, found: 118.1020.

IR ν = 3379 (m), 2924 (s), 2769 (m), 2708 (m), 2530 (m), 1589 (w), 1465 (m), 1427 (m), 1357 (w), 1041 (m), 979 (m), 925 (s), 879 (m), 840 (m), 655 (m), 578 (m).

2,2,2-Trifluoro-1-(*cis*-4-fluoro-2-methylpiperidin-1-yl)ethan-1-one (23)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 4 mmol HBpin, 1 M THF at 40 °C, purification with 0-2% EtOAc in pentane. The product was isolated as a colorless oil (24 mg, 0.113 mmol, 23%, *d.r.* 92:8). Only the peaks of the major diastereomer are listed. The product was present as a ~1:1 mixture of amide bond rotamers. NMR spectra contain trances of pentane and EtOAc.

The orientation of the fluorine atom was assigned as axial due to the large values of ^{3}J(F,H$_a$). [**^{3}J(3-H$_a$,4-F, Rot A) = 47.0 Hz, ^{3}J(5-H$_a$,4-F, Rot A) = 44.0 Hz, ^{3}J(3-H$_a$,4-F, Rot B) = 47.0 Hz, ^{3}J(5-H$_a$,4-F, Rot B) = 44.0 Hz**]

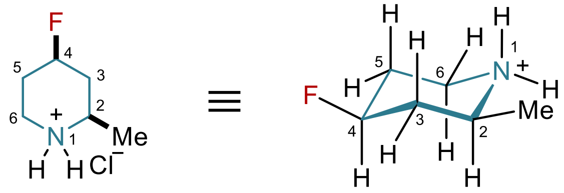
Rotamer A: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.99 (dm, *J* = 47.9 Hz, 1H), 4.83 (p, *J* = 7.0 Hz, 1H), 3.75 (dm, *J* = 14.3 Hz, 1H), 3.62 (td, *J* = 14.0, 2.5 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.88 (dm, *J* = 47.0 Hz, 1H), 1.75 (dm, *J* = 44.0 Hz, 1H), 1.37 (dd, *J* = 7.2, 1.4 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 5.01 – 4.97 (m, 1H), 4.83 (p, *J* = 7.0 Hz, 1H), 3.74 (dm, *J* = 12.9 Hz, 1H), 3.62 (td, *J* = 14.0, 2.5 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.88 (ddd, *J* = 15.2, 6.5, 2.7 Hz, 1H), 1.81 – 1.69 (m, 1H), 1.37 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.69 (q, *J* = 35.3 Hz), 116.69 (d, *J* = 288.0 Hz), 86.79 (d, *J* = 170.7 Hz), 44.74, 35.35 (q, *J* = 5.2, 4.2 Hz), 34.10 (d, *J* = 19.2 Hz), 30.87 (d, *J* = 21.2 Hz), 18.12 (d, *J* = 3.9 Hz); **^{13}C{sel-^{19}F at -180 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.69 (d, *J* = 35.3 Hz), 116.69 (d, *J* = 288.2 Hz), 86.76, 44.74, 35.35 (q, *J* = 3.8 Hz), 34.10, 30.87, 18.12; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.19, -180.20 (qt, *J* = 46.3, 11.7 Hz); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -69.19, -180.20.

Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.99 (dm, *J* = 47.9 Hz, 1H), 4.39 (dd, *J* = 13.7, 5.3 Hz, 1H), 4.30 (q, *J* = 6.6 Hz, 1H), 3.27 (t, *J* = 12.9 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.88 (dm, *J* = 47.0 Hz, 1H), 1.75 (dm, *J* = 44.0 Hz, 1H), 1.47 (d, *J* = 6.4 Hz, 3H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 5.01 – 4.98 (m, 1H), 4.39 (dd, *J* = 13.9, 5.5 Hz, 1H), 4.30 (q, *J* = 6.6 Hz, 1H), 3.27 (t, *J* = 12.8 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.88 (ddd, *J* = 15.2, 6.5, 2.7 Hz, 1H), 1.83 – 1.69 (m, 1H), 1.47 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.69 (q, *J* = 35.3 Hz), 116.89 (d, *J* = 287.8 Hz), 86.86 (d, *J* = 170.8 Hz), 47.84 (q, *J* = 4.0 Hz), 35.06 (d, *J* = 19.3 Hz), 32.52, 30.08 (d, *J* = 21.3 Hz), 19.65 (d, *J* = 4.3 Hz); **^{13}C{sel-^{19}F at -180 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.69 (d, *J* = 35.3 Hz), 116.89 (d, *J* = 289.4 Hz), 86.86, 47.84 (q, *J* = 4.0 Hz), 35.06, 32.52, 30.08, 19.65; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.03, -179.67 (qt, *J* = 46.0, 11.6 Hz); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -69.03, -179.67.

ESI-MS: calculated $[C_8H_{11}NOF_4 +Na]^+$: 236.0669, found: 236.0683.

IR ν = 2955 (w), 1681 (s), 1450 (m), 1195 (s), 1180 (s), 1134 (s), 1095 (m), 1041 (m), 1010 (w), 956 (m), 925 (m), 756 (m), 732 (m), 655 (m), 563 (w).

cis-4-Fluoro-2-methylpiperidine hydrochloride (24)



Compound **24** was prepared according to the general procedure B starting 2,2,2-trifluoro-1-(*cis*-4-fluoro-2-methylpiperidin-1-yl)ethan-1-one (**23**) (24 mg, 0.113 mmol, 1.0 equiv.). The reaction mixture was stirred at 50 °C for 3 h. Extraction and removal of all volatiles afforded the title compound as a white solid (17.2 mg, 0.112 mmol, 99%, *d.r.* 92:8). Only the signals of the major diastereomer are listed.

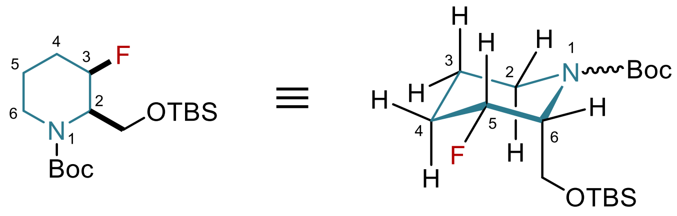
The orientation of the fluorine atom was assigned as equatorial due to the small values of $^{3}J(\mathrm{F,H_a})$. [$\boldsymbol{^{3}J(\mathrm{3\text{-}H_a,4\text{-}F}) = 10.5}$ **Hz,** $\boldsymbol{^{3}J(\mathrm{5\text{-}H_a,4\text{-}F}) = 10.0}$ **Hz**]

^{1}H NMR (599 MHz, D_2O, 299 K) δ 4.90 (ddt, *J* = 46.9, 10.7, 5.7 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.39 (bs, 1H), 3.08 (t, *J* = 12.9 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.40 – 2.33 (m, 1H), 1.92 – 1.81 (m, 1H), 1.73 (p, *J* = 12.0, 10.5 Hz, 1H), 1.40 (d, *J* = 6.5 Hz, 3H); **^{1}H{^{19}F} NMR** (599 MHz, D_2O, 299 K) δ 4.90 (dt, *J* = 10.9, 5.7 Hz, 1H), 3.55 (d, *J* = 13.3 Hz, 1H), 3.43 – 3.35 (m, 1H), 3.13 – 3.05 (m, 1H), 2.43 (d, *J* = 13.2 Hz, 1H), 2.37 (d, *J* = 12.9 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.73 (q, *J* = 12.0 Hz, 1H), 1.40 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 87.13 (d, *J* = 172.3 Hz), 50.96 (d, *J* = 12.3 Hz), 41.14 (d, *J* = 12.9 Hz), 36.01 (d, *J* = 20.9 Hz), 27.99 (d, *J* = 22.1 Hz), 17.97; **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 87.13, 50.96, 41.14, 36.01, 27.99, 17.97; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -174.04 (d, *J* = 48.8 Hz); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -174.05.

ESI-MS: calculated $[C_6H_{13}FN]^+$: 118.1027, found: 118.1033.

IR ν = 3379 (m), 2947 (m), 2808 (m), 2731 (s), 2708 (s), 2569 (m), 2492 (m), 1604 (w), 1589 (m), 1458 (m), 1388 (m), 1165 (w), 1087 (m), 1049 (m), 1018 (s), 1003 (m), 949 (m).

tert-Butyl *cis*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluoropiperidine-1-carboxylate (25)



Following general procedure A on 0.5 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-2% EtOAc in pentane. The product was isolated as a colorless oil (147 mg, 0.42 mmol, 84%, *d.r.* 99:1). Only the signals of the major diastereomer are listed. The defluorinated side-product was inseparable from the desired product.

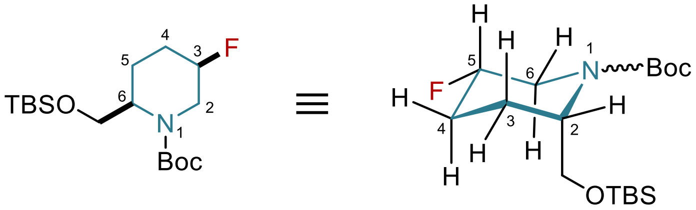
Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atom. However since we provided detailed NMR analysis on the simpler analogue (**9**), we therefore believe that the dominant orientation of the fluorine atom is equatorial.

^{1}H NMR (300 MHz, CDCl$_3$, 299 K) δ 4.67 (dm, *J* = 47.3 Hz, 1H), 4.52 – 4.40 (m, 1H), 3.99 – 3.87 (m, 2H), 3.85 – 3.77 (m, 1H), 2.93 (t, *J* = 11.6 Hz, 1H), 2.01 – 1.53 (m, 4H), 1.45 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (75 MHz, CDCl$_3$, 299 K) δ 155.20, 88.96 (d, *J* = 178.7 Hz), 79.85, 58.73 (d, *J* = 3.0 Hz), 54.99 (bs), 38.80 (bs), 28.53, 26.64 (d, *J* = 18.9 Hz), 26.03, 23.29 (d, *J* = 9.4 Hz), 18.34, -5.34, -5.40; **^{19}F{^{1}H} NMR** (282 MHz, CDCl$_3$, 299 K) δ -183.32; **^{29}Si NMR** (60 MHz, CDCl$_3$, 299 K) δ 20.28.

ESI-MS: calculated [$C_{17}H_{34}FNO_3Si$ +Na]$^+$: 370.2184, found: 370.2192.

IR ν = 2931.9 (m), 2854.7 (w), 1697.4 (s), 1458.2 (m), 1411.9 (m), 1365.6 (m), 1249.9 (s), 1141.9 (s), 1111.1 (m), 995.3 (m), 833.3 (s), 771.5 (s), 663.5 (w).

tert-Butyl *cis*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-fluoropiperidine-1-carboxylate (26)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 50-100% CH_2Cl_2 in pentane. The product was isolated as a colorless oil (163 mg, 0.47 mmol, 94%, *d.r.* 97:3). The major diastereomer could be isolated by column chromatography.

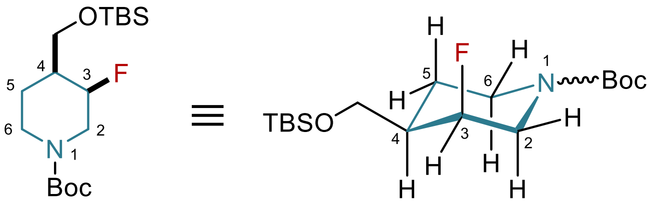
NMR at high temperature (363 K) was measured in order to eliminate to rotameric behavior of the Boc-group. The orientation of the fluorine atom was assigned as equatorial due to the small value of $^{3}J(F,H_a)$. [**$^{3}J(2\text{-}H_a,3\text{-}F)$ = 6.7 Hz, $^{3}J(4\text{-}H_a,3\text{-}F)$ = 12.8 Hz**]

^{1}H NMR (599 MHz, Toluene-*d*$_8$, 363 K) δ 4.35 (d, *J* = 12.7 Hz, 1H), 4.23 (dm, *J* = 49.2 Hz, 1H), 4.11 (s, 1H), 3.58 (m, 2H), 2.78 (ddd, *J* = 13.0, 10.7, 6.7 Hz, 1H), 1.74 (dm, *J* = 14.0 Hz, 1H), 1.69 – 1.61 (m, 1H), 1.57 (tm, *J* = 12.8 Hz, 1H), 1.39 (s, 9H), 1.34 – 1.26 (m, 1H), 0.89 (s, 9H), 0.01 (s, 6H); **^{1}H{^{19}F} NMR** (599 MHz, Toluene-*d*$_8$, 363 K) δ 4.35 (dd, *J* = 13.0, 5.3 Hz, 1H), 4.27 – 4.19 (m, 1H), 4.11 (s, 1H), 3.58 (m, 2H), 2.78 (dd, *J* = 13.0, 10.7 Hz, 1H), 1.78 – 1.71 (m, 1H), 1.69 – 1.63 (m, 1H), 1.61 – 1.53 (m, 1H), 1.39 (s, 9H), 1.34 – 1.26 (m, 1H), 0.89 (s, 9H), 0.01 (s, 6H); **^{13}C NMR** (151 MHz, Toluene-*d*$_8$, 363 K) δ 154.68, 87.34 (d, *J* = 176.2 Hz), 79.53, 61.91, 51.56, 44.59 (d, *J* = 30.9 Hz), 28.43, 27.01 (d, *J* = 19.3 Hz), 26.01, 22.53 (d, *J* = 9.1 Hz), 18.37, -5.35 (d, *J* = 8.4 Hz), -5.45 (d, *J* = 8.4 Hz); **^{13}C{^{19}F} NMR** (151 MHz, Toluene-*d*$_8$, 363 K) δ 154.68, 87.34, 79.53, 61.91, 51.57, 44.59, 28.43, 27.01, 26.02, 22.53, 18.37, -5.35 (d, *J* = 8.2 Hz), -5.45 (d, *J* = 8.7 Hz); **^{19}F NMR** (564 MHz, Toluene-*d*$_8$, 363 K) δ -178.79 (d, *J* = 49.2 Hz); **^{19}F{^{1}H} NMR** (564 MHz, Toluene-*d*$_8$, 363 K) δ -178.8; **^{29}Si NMR** (60 MHz, $CDCl_3$, 299 K) δ 20.2.

ESI-MS: calculated $[C_{17}H_{34}FNO_3Si + Na]^+$: 370.2184, found: 370.2186.

IR ν = 2955.1 (w), 2931.9 (w), 2862.5 (w), 2360.9 (w), 1697.4 (s), 1411.9 (m), 1365.6 (m), 1319.4 (w), 1249.9 (m), 1149.6 (s), 1111 (s), 1041.6 (m), 964.4 (w), 833.3 (s), 771.5 (s), 663.5 (w).

***tert*-Butyl *cis*-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluoropiperidine-1-carboxylate (27)**



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 1.5 mmol HBpin, 1 M THF at 40 °C, purification with 0-5% EtOAc in pentane. The product was isolated as a colorless oil (147 mg, 0.423 mmol, 85%, *d.r.* 95:5). The major diastereomer could be isolated by column chromatography.

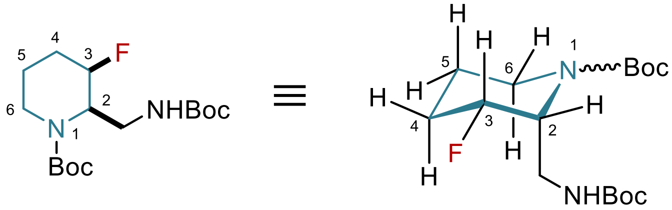
NMR at high temperature (363 K) was measured in order to eliminate to rotameric behavior of the Boc-group. The orientation of the fluorine atom was assigned as axial due to the large value of $^{3}J(\mathrm{F,H_a})$. [$\boldsymbol{^{3}J(2\text{-}H_a,3\text{-}F) = 38.4}$ **Hz**]

^{1}H NMR (599 MHz, Toluene-d_8, 363 K) δ 4.48 (d, J = 47.9 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.18 (d, J = 11.5 Hz, 1H), 3.57 – 3.52 (m, 1H), 3.37 – 3.32 (m, 1H), 2.46 (dd, J = 38.4, 14.5 Hz, 1H), 2.40 – 2.35 (m, 1H), 1.43 – 1.39 (m, 11H), 1.15 – 1.09 (m, 1H), 0.92 – 0.89 (m, 9H), 0.01 (s, 3H), 0.00 (s, 3H); **^{1}H{^{19}F} NMR** (599 MHz, Toluene-d_8, 363 K) δ 4.48 (s, 1H), 4.36 (d, J = 14.5 Hz, 1H), 4.19 (d, J = 11.5 Hz, 1H), 3.58 – 3.52 (m, 1H), 3.36 – 3.32 (m, 1H), 2.43 (d, J = 14.5 Hz, 1H), 2.38 (t, J = 10.8 Hz, 1H), 1.41 (s, 11H), 1.17 – 1.09 (m, 1H), 0.91 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.37, 85.54 (d, J = 176.4 Hz), 79.81, 63.32, 48.28 (bs), 42.86 (bs), 42.45 (d, J = 19.9 Hz), 28.51, 26.02, 22.53 (bs), 18.44, -5.34 (d, J = 4.4 Hz), -5.43 (d, J = 4.3 Hz); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.4, 85.5, 79.8, 63.3, 48.3 (bs), 42.8 (bs), 42.4, 28.5, 26.0, 22.5 (bs), 18.4, -5.3, -5.4; **^{19}F NMR** (564 MHz, Toluene-d_8, 363 K) δ -203.27 – -203.68 (m); **^{19}F{^{1}H} NMR** (564 MHz, Toluene-d_8, 363 K) δ -203.5; **^{29}Si NMR** (60 MHz, $CDCl_3$, 299 K) δ 19.8.

ESI-MS: calculated $[C_{17}H_{34}FNO_3Si + Na]^+$: 370.2184, found: 370.2185.

IR ν = 2955.1 (w), 2931.9 (w), 2854.7 (w), 1697.4 (s), 1419.6 (m), 1365.6 (m), 1257.6 (m), 1172.7 (m), 1103.3 (s), 1057 (m), 1003 (m), 925.8 (w), 833.3 (s), 779.3 (s), 663.5 (w).

tert-Butyl *cis*-2-(((*tert*-butoxycarbonyl)amino)methyl)-3-fluoropiperidine-1-carboxylate (28)



Following general procedure A on 0.5 mmol scale, 3 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a colorless solid (147 mg, 0.44 mmol, 88%, *d.r.* 99:1). The major diastereomer could be isolated by column chromatography. The product was present as a ~1:1 mixture of amide bond rotamers. Only the signals of one rotamer are listed.

Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atom. However since we provided detailed NMR analyses on the simpler analogue (**9**), we therefore believe that the dominant orientation of the fluorine atom is equatorial.

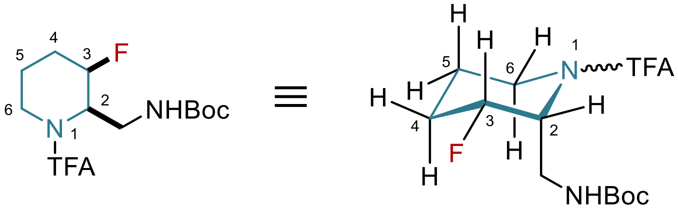
^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 4.81 – 4.22 (m, 3H), 4.10 – 3.46 (m, 2H), 3.32 – 3.01 (m, 1H), 2.90 – 2.73 (m, 1H), 2.05 – 1.90 (m, 1H), 1.77 – 1.65 (m, 1H), 1.63 – 1.54 (m, 2H), 1.47 – 1.43 (m, 9H), 1.40 (s, 9H); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.12, 155.67 (bs), 88.97, 80.48, 79.74, 50.16 (bs), 40.44, 37.71 (bs), 28.50, 28.48, 25.84, 23.29 (bs); **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -182.20 – -182.83 (m).

ESI-MS: calculated $[C_{16}H_{29}N_2O_4F+Na]^+$: 355.2004, found: 355.2009.

IR ν = 3348.5 (w), 2978.2 (w), 2931.9 (w), 1697.4 (s), 1674.3 (s), 1519.9 (m), 1419.6 (m), 1365.6 (s), 1249.9 (s), 1165.1 (s), 1141.9 (s), 1018.5 (m), 995.3 (m), 925.8 (m), 864.1 (m), 748.4 (m), 732.9 (s), 648.1 (m).

M.p.: 49-50 °C.

***tert*-Butyl ((*cis*-3-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-2-yl)methyl)carbamate (29)**



Following general procedure A on 0.5 mmol scale, 3 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-30% EtOAc in pentane. The product was isolated as a colorless solid (39 mg, 0.12 mmol, 24%, *d.r.* 99:1). The reason for the low yielding transformation originates from the deprotection of the Boc-group during the addition of trifluoroacetic anhydride. The major diastereomer could be isolated by column chromatography. The product was present as a ~4:1 mixture of amide bond rotamers. Only the signals of the major rotamer are listed.

Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atom. However since we provided detailed NMR analysis on the simpler analogue (**9**), we therefore believe that the dominant orientation of the fluorine atom is equatorial.

The equatorial orientation of the fluorine atom was confirmed by X-ray diffraction analysis. Single crystals of the title compound were obtained by crystallization at room temperature from a (1:1) mixture of *n*-hexane and ethyl acetate (slow evaporation of solvents). Detailed crystallographic data are reported in the corresponding section of the Supplementary Information.

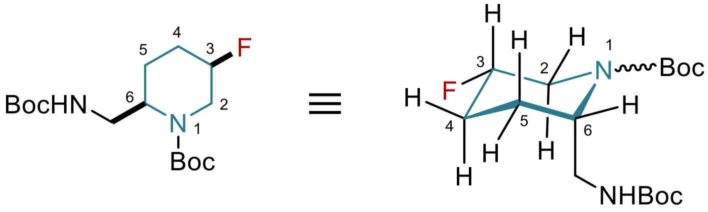
^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ 4.96 (s, 1H), 4.77 – 4.52 (m, 2H), 3.97 – 3.85 (m, 1H), 3.73 (d, *J* = 13.0 Hz, 1H), 3.55 – 3.46 (m, 1H), 3.24 (d, *J* = 12.8 Hz, 1H), 2.15 – 1.99 (m, 1H), 1.94 – 1.77 (m, 2H), 1.64 – 1.50 (m, 1H), 1.38 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$, 299 K) δ 157.34, 156.37, 116.53 (q, *J* = 287.7 Hz), 87.98 (d, *J* = 180.6 Hz), 79.96, 53.29 (d, *J* = 24.3 Hz), 40.43 (d, *J* = 3.5 Hz), 37.49, 35.25 (d, *J* = 3.7 Hz), 28.30, 23.24 (d, *J* = 9.9 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$, 299 K) δ -67.55 (minor rotamer), -68.91 (major rotamer), -181.06 (minor rotamer), -182.99 (major rotamer).

ESI-MS: calculated $[C_{13}H_{20}N_2O_3F_4 + Na]^+$: 351.1302, found: 351.1304.

IR ν = 3379.4 (m), 2970.4 (w), 2924.1 (w), 1705.1 (m), 1681.9 (s), 1527.6 (m), 1435.1 (w), 1365.6 (w), 1280.7 (m), 1249.9 (m), 1203.6 (s), 1141.9 (s), 1126.5 (s), 1041.6 (m), 1018.5 (m), 964.4 (m), 864.1 (m), 748.4 (m), 663.5 (m), 617.2 (m).

M.p.: 88-89 °C.

tert-Butyl *cis*-2-(((*tert*-butoxycarbonyl)amino)methyl)-5-fluoropiperidine-1-carboxylate (30)



Following general procedure A on 0.5 mmol scale, 3 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a white solid (125 mg, 0.376 mmol, 75%, *d.r.* 97:3). The major diastereomer could be isolated by column chromatography. The product was present as a ~5.5:1 mixture of amide bond rotamers. Only the signals of the major rotamer are listed.

Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atom. However since we provided detailed NMR analysis on the simpler analogue (**11**, **13**), we therefore believe that the dominant orientation of the fluorine atom is equatorial.

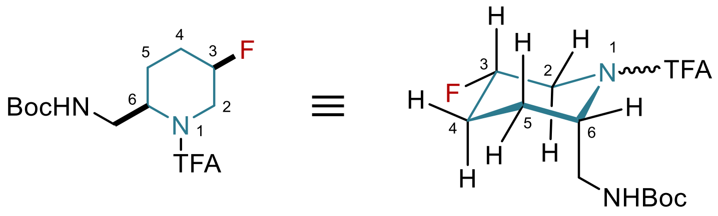
^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 4.75 (bs, 1H), 4.56 – 4.06 (m, 3H), 3.64 – 3.39 (m, 1H), 3.09 (dt, *J* = 13.5, 5.2 Hz, 1H), 2.86 – 2.71 (m, 1H), 2.00 (bs, 1H), 1.77 – 1.58 (m, 2H), 1.44 (s, 10H), 1.39 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 156.02, 155.26 (bs), 87.35 (d, *J* = 175.4 Hz), 80.54, 79.42, 49.28 (bs), 42.75 (bs), 39.86, 28.45, 28.42, 26.56 (d, *J* = 18.8 Hz), 23.97 (bs); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -179.94 (bs, major rotamer), -187.69 (bs, minor rotamer).

ESI-MS: calculated $[C_{16}H_{29}N_2O_4F + Na]^+$: 355.2004, found: 355.2010.

IR ν = 3356.2 (w), 2978.2 (w), 2931.9 (w), 1697.4 (s), 1674.3 (s), 1535.4 (m), 1419.6 (m), 1365.6 (m), 1273.1 (m), 1249.9 (m), 1172.7 (s), 1141.9 (s), 1041.6 (m), 1018.4 (m), 918.1 (w), 864.1 (m), 748.4 (m), 732.9 (m), 648.1 (m).

M.p.: 68-69 °C.

***tert*-Butyl (*cis*-5-fluoro-1-(2,2,2-trifluoroacetyl)piperidin-2-yl)methyl)carbamate (31)**



Following general procedure A on 0.25 mmol scale, 3 mol% catalyst, 1 mmol HBpin, 1 M THF at 40 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a colorless oil (50 mg, 0.153 mmol, 61% (95% NMR yield), *d.r.* 97:3). Only the peaks of the major diastereomer are listed. The product was present as a ~2.5:1 mixture of amide bond rotamers. Only the signals of the major rotamer are listed.

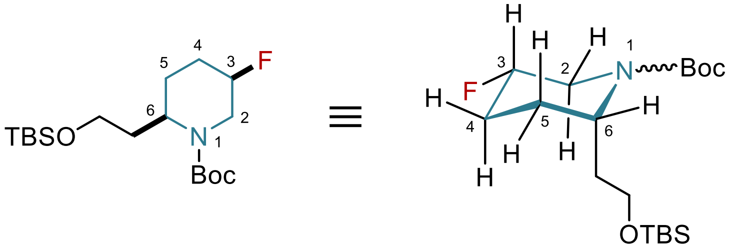
The orientation of the fluorine atom was assigned as equatorial due to the small value of $^{3}J(\mathrm{F},\mathrm{H_a})$. **[$^{3}J(2\text{-}\mathrm{H_a},3\text{-F})$ = 5.2 Hz]**

^{1}H NMR (599 MHz, $CDCl_3$, 299 K) δ 4.77 – 4.70 (m, 1H), 4.64 – 4.59 (m, 1H), 4.50 (dm, *J* = 48.1 Hz, 1H), 4.09 – 4.00 (m, 1H), 3.82 – 3.72 (m, 1H), 3.45 (ddd, *J* = 13.7, 11.3, 5.2 Hz, 1H), 3.10 (dt, *J* = 14.0, 4.5 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.89 – 1.80 (m, 1H), 1.76 – 1.70 (m, 1H), 1.52 – 1.44 (m, 1H), 1.40 (s, 9H); **^{1}H{^{19}F} NMR** (599 MHz, $CDCl_3$, 299 K) δ 4.77 – 4.68 (m, 1H), 4.64 – 4.59 (m, 1H), 4.55 – 4.47 (m, 1H), 4.08 – 4.00 (m, 1H), 3.82 – 3.75 (m, 1H), 3.45 (dd, *J* = 13.7, 11.3 Hz, 1H), 3.10 (dt, *J* = 14.0, 4.5 Hz, 1H), 2.10 (d, *J* = 12.7 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.73 (dt, *J* = 13.4, 4.9 Hz, 1H), 1.54 – 1.45 (m, 1H), 1.39 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.36 (d, *J* = 36.0 Hz), 156.16, 116.45 (q, *J* = 287.6 Hz), 86.72 (d, *J* = 177.9 Hz), 80.02, 50.13, 44.71 (d, *J* = 35.9 Hz), 39.58, 28.32, 26.45 (d, *J* = 19.2 Hz), 23.19 (d, *J* = 10.0 Hz); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 157.36 (d, *J* = 36.0 Hz), 156.16, 116.45 (q, *J* = 287.6 Hz), 86.71, 80.02, 50.13, 44.72, 39.58, 28.32, 26.45, 23.19; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.02 (minor rotamer), -68.96 (major rotamer), -178.93 (d, *J* = 48.2 Hz, minor rotamer), -179.92 – -180.08 (m, major rotamer); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.0 (minor rotamer), -69.0 (major rotamer), -178.93 (minor rotamer), -180.00 (major rotamer).

ESI-MS: calculated $[C_{13}H_{20}N_2O_3F_4 + Na]^+$: 351.1302, found: 351.1313.

IR ν = 3379.4 (w), 2978.2 (w), 1681.9 (s), 1512.2 (m), 1458.2 (m), 1365.6 (m), 1219.1 (m), 1180.5 (s), 1141.9 (s), 1049.3 (m), 756.1 (m), 732.9 (m), 709.8 (m).

tert-Butyl _cis_-2-(2-((_tert_-butyldimethylsilyl)oxy)ethyl)-5-fluoropiperidine-1-carboxylate (32)



Following General procedure A on 0.5 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-4% EtOAc in pentane. The product was isolated as a colorless oil (167 mg, 0.46 mmol, 92%, *d.r.* 95:5). The major diastereomer could be isolated by column chromatography. Traces of the defluorinated side-product were inseparable from the desired product.

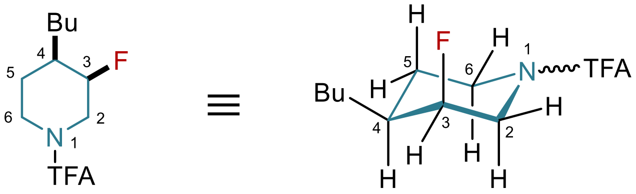
Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atom. However since we provided detailed NMR analysis on the simpler analogue (**11**, **13**), we therefore believe that the dominant orientation of the fluorine atom is equatorial.

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 4.61 – 4.14 (m, 3H), 3.70 – 3.50 (m, 2H), 2.87 – 2.68 (m, 1H), 2.11 – 1.82 (m, 2H), 1.76 – 1.60 (m, 4H), 1.44 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$, 299 K) δ 154.82, 87.74 (d, *J* = 175.3 Hz), 80.09, 60.90, 47.38, 42.62, 32.87, 28.52, 26.55 (d, *J* = 4.9 Hz), 26.40 (d, *J* = 3.2 Hz), 26.08, 18.44, -5.21, -5.24; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -179.05; **^{29}Si NMR** (60 MHz, $CDCl_3$, 299 K) δ 19.29.

ESI-MS: calculated $[C_{18}H_{36}FNO_3Si + Na]^+$: 384.2341, found: 384.2357.

IR ν = 2955.1 (m), 2931.9 (m), 2862.5 (m), 1697.4 (s), 1473.6 (m), 1411.9 (m), 1365.6 (m), 1249.9 (m), 1172.7 (m), 1149.6 (s), 1095.6 (s), 972.2 (w), 833.3 (s), 771.5 (s), 663.5 (w).

1-(*cis*-4-Butyl-3-fluoropiperidin-1-yl)-2,2,2-trifluoroethan-1-one (33)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-10% Et_2O in pentane. The product was isolated as a colorless oil (102 mg, 0.399 mmol, 80%, *d.r.* 99:1). The product was present as a ~1:1 mixture of amide bond rotamers.

The orientation of the fluorine atom was assigned as axial due to the large values of ^3J(F,H_a). [**^3J(2-H_a,3-F, Rot A) = 37.1 Hz, ^3J(2-H_a,3-F, Rot B) = 38.8 Hz**]

Rotamer A: **^{1}H NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.64 (d, *J* = 47.3 Hz, 1H), 4.62 – 4.57 (m, 1H), 4.28 – 4.22 (m, 1H), 3.23 (ddd, *J* = 37.1, 14.6, 0.9 Hz, 1H), 2.76 – 2.70 (m, 1H), 1.68 – 1.55 (m, 3H), 1.53 – 1.46 (m, 2H), 1.40 – 1.27 (m, 4H), 0.92 – 0.89 (m, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.64 (s, 1H), 4.60 (dm, *J* = 13.3 Hz, 1H), 4.25 (d, *J* = 14.6 Hz, 1H), 3.23 (dd, *J* = 14.6, 0.9 Hz, 1H), 2.76 – 2.70 (m, 1H), 1.69 – 1.56 (m, 3H), 1.54 – 1.46 (m, 2H), 1.39 – 1.28 (m, 4H), 0.92 – 0.89 (m, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.45 (q, *J* = 35.8 Hz), 116.62 (q, *J* = 287.9 Hz), 87.59 (d, *J* = 179.3 Hz), 49.44 (d, *J* = 21.2 Hz), 43.60, 39.41 (d, *J* = 20.7 Hz), 31.01 (d, *J* = 3.0 Hz), 28.73, 25.82 (d, *J* = 0.9 Hz), 22.78, 14.05; **^{13}C{sel-^{19}F at -69 and -203 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.47, 116.61, 87.58, 49.44, 43.59, 39.41, 31.01, 28.73, 25.82, 22.78, 14.06; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.98, -202.97 – -203.42 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.98, -203.12.

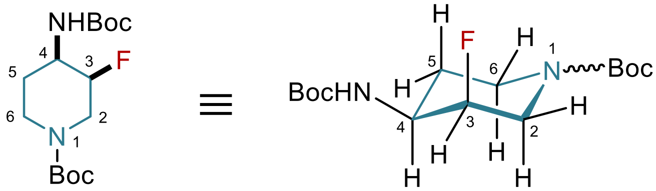
Rotamer B: **^{1}H NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.83 (ddt, *J* = 14.3, 11.0, 2.7 Hz, 1H), 4.72 (d, *J* = 47.3 Hz, 1H), 4.05 (dm, *J* = 13.6 Hz, 1H), 3.11 (dt, *J* = 14.9, 7.5 Hz, 1H), 2.86 (dd, *J* = 38.8, 14.6 Hz, 1H), 1.68 – 1.54 (m, 3H), 1.53 – 1.46 (m, 2H), 1.39 – 1.27 (m, 4H), 0.92 – 0.88 (m, 3H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.83 (dt, *J* = 14.3, 2.7 Hz, 1H), 4.72 (s, 1H), 4.05 (dm, *J* = 14.0 Hz, 1H), 3.16 – 3.08 (m, 1H), 2.86 (d, *J* = 14.6 Hz, 1H), 1.69 – 1.56 (m, 3H), 1.54 – 1.45 (m, 2H), 1.39 – 1.27 (m, 4H), 0.92 – 0.88 (m, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.47 (q, *J* = 35.8 Hz), 116.56 (q, *J* = 288.1 Hz), 87.10 (d, *J* = 179.3 Hz), 47.41 (d, *J* = 21.5 Hz), 45.75 (q, *J* = 3.6 Hz), 39.39 (d, *J* = 20.7 Hz), 30.98 (d, *J* = 3.0 Hz), 28.73, 26.77 (d, *J* = 1.3 Hz), 22.78, 14.05; **^{13}C{sel-^{19}F at -68 and -203 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.45, 116.56 (q, *J*

= 4.4 Hz), 87.09, 47.41, 45.75, 39.38, 30.98, 28.73, 26.77, 22.78, 14.06; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.00 (d, *J* = 4.4 Hz), -202.97 – -203.42 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -68.00 (d, *J* = 4.4 Hz), -203.27 (q, *J* = 4.4 Hz).

ESI-MS: calculated $[C_{11}H_{17}NOF_4 +Na]^+$: 278.1144, found: 278.1142.

IR ν = 2931.9 (w), 2862.5 (w), 1689.7 (s), 1458.2 (m), 1203.6 (s), 1172.7 (s), 1141.9 (s), 995.3 (m), 856.4 (m), 756.1 (m), 709.8 (w), 648.1 (m).

***tert*-Butyl *cis*-4-((*tert*-butoxycarbonyl)amino)-3-fluoropiperidine-1-carboxylate (34)**



Following general procedure A on 0.25 mmol scale, 3 mol% catalyst, 1 mmol HBpin, 0.25 M THF (for better solubility) at 40 °C, purification with 0-30% EtOAc in pentane. The product was isolated as a white solid (75 mg, 0.235 mmol, 94%, *d.r.* 97:3). Only the peaks of the major diastereomer are listed. The product was present as a ~2.5:1 mixture of amide bond rotamers. Only the signals of the major rotamer are listed.

NMR at high temperature (363 K) was measured in order to eliminate to rotameric behavior of the Boc-group. The orientation of the fluorine atom was assigned as axial due to the large value of ^{3}J(F,H$_a$). [**^{3}J(4-H$_a$,3-F) = 38.8 Hz**]

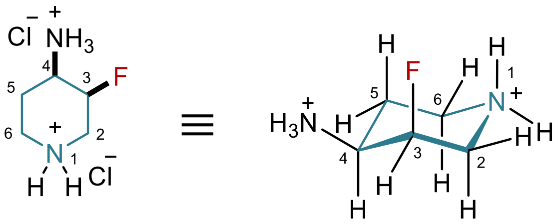
^{1}H NMR (599 MHz, Toluene-d_8, 363 K) δ 4.40 (bs, 1H), 4.29 – 4.14 (m, 1H), 4.06 – 3.98 (m, 2H), 3.91 – 3.77 (m, 1H), 3.51 – 3.33 (m, 1H), 2.36 (ddd, J = 38.8, 14.8, 4.7 Hz, 1H), 2.31 – 2.24 (m, 1H), 1.40 – 1.36 (m, 18H); **^{1}H{^{19}F} NMR** (600 MHz, Toluene-d_8, 363 K) δ 4.40 (bs, 1H), 4.25 – 4.14 (m, 2H), 4.07 – 3.95 (m, 1H), 3.92 – 3.78 (m, 1H), 3.51 – 3.39 (m, 1H), 2.37 (dd, J = 14.8, 4.7 Hz, 1H), 2.33 – 2.26 (m, 1H), 1.41 – 1.34 (m, 18H); **^{13}C NMR** (151 MHz, Toluene-d_8, 363 K) δ 155.14, 154.98, 88.12 (d, J = 177.7 Hz), 79.58, 79.39, 50.83 (d, J = 18.2 Hz), 47.33 (d, J = 20.6 Hz), 42.88, 28.64, 28.60, 26.99; **^{13}C{^{19}F} NMR** (151 MHz, Toluene-d_8, 363 K) δ 155.15, 154.99, 88.12, 79.58, 79.39, 50.83, 47.31, 42.88, 28.64, 28.60, 26.99; **^{19}F NMR** (564 MHz, Toluene-d_8, 363 K) δ -204.37 – -204.72 (m); **^{19}F{^{1}H} NMR** (564 MHz, Toluene-d_8, 363 K) δ -204.57.

ESI-MS: calculated [$C_{15}H_{27}N_2O_4F$ +Na]$^+$: 341.1847, found: 341.1828.

IR ν = 3348.5 (w), 2978.2 (w), 2931.9 (w), 1674.3 (s), 1519.9 (m), 1427.4 (m), 1365.6 (m) 1303.9 (m), 1242.2 (m), 1149.6 (s), 1126.5 (s), 1041.6 (m), 1026.2 (m), 1003 (m), 910.4 (m), 864.1 (m), 756.1 (s), 732.9 (s).

M.p.: 123-124 °C.

cis-4-Ammonio-3-fluoropiperidine hydrochloride (35)



Compound **35** was prepared according to the general procedure C starting from *tert*-butyl *cis*-4-((*tert*-butoxycarbonyl)amino)-3-fluoropiperidine-1-carboxylate (**34**) (106 mg, 0.33 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 5 h. Removal of all volatiles afforded the title compound as a white solid (62.9 mg, 0.33 mmol, 99%, *d.r.* 97:3). Only the peaks of the major diastereomer are listed.

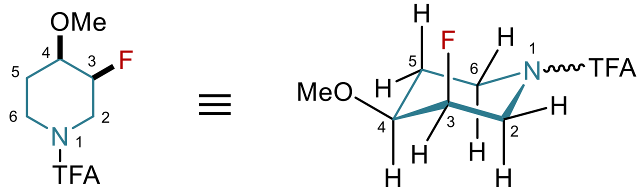
The orientation of the fluorine atom was assigned as axial due to the large value of $^{3}J(\mathrm{F},\mathrm{H_a})$. [$\mathbf{^{3}J(2\text{-}H_a,3\text{-}F) = 40.2\ Hz}$]

^{1}H NMR (599 MHz, D_2O, 299 K) δ 5.37 (d, *J* = 47.2 Hz, 1H), 3.96 – 3.84 (m, 2H), 3.68 – 3.59 (m, 1H), 3.51 (dd, *J* = 40.2, 14.8 Hz, 1H), 3.27 (td, *J* = 13.3, 3.5 Hz, 1H), 2.41 – 2.21 (m, 2H); **^{1}H{^{19}F} NMR** (599 MHz, D_2O, 299 K) δ 5.37 (s, 1H), 3.95 – 3.86 (m, 2H), 3.68 – 3.60 (m, 1H), 3.53 – 3.48 (m, 1H), 3.27 (td, *J* = 13.3, 3.4 Hz, 1H), 2.39 – 2.20 (m, 2H); **^{13}C NMR** (151 MHz, D_2O, 299 K) δ 84.15 (d, *J* = 177.4 Hz), 47.43 (d, *J* = 19.7 Hz), 45.19 (d, *J* = 19.4 Hz), 41.65, 21.10 (d, *J* = 1.9 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D_2O, 299 K) δ 84.15, 47.43, 45.19, 41.65, 21.10; **^{19}F NMR** (564 MHz, D_2O, 299 K) δ -205.62 – -205.92 (m); **^{19}F{^{1}H} NMR** (564 MHz, D_2O, 299 K) δ -205.77 – -205.81 (m).

ESI-MS: calculated $[C_5H_{12}FN_2]^+$: 119.0979, found: 119.0992.

IR ν = 2924 (s), 2785 (s), 2724 (s), 2616 (s), 2546 (s), 2060 (m), 1597 (m), 1528 (m), 1458 (m), 1443 (m), 1404 (m), 1165 (m), 1088 (m), 1049 (m), 988 (s), 957 (s), 856 (m), 841 (m).

2,2,2-Trifluoro-1-(*cis*-3-fluoro-4-methoxypiperidin-1-yl)ethan-1-one (36)



Following general procedure A on 0.5 mmol scale, 3 mol% catalyst, 2 mmol HBpin, 0.5 M THF at 40 °C, purification with 0-100% CH_2Cl_2 in pentane. The product was isolated as a colorless oil (80 mg, 0.35 mmol, 70%, *d.r.* 99:1). The major diastereomer could be isolated by column chromatography. The product was present as a ~1:1 mixture of amide bond rotamers. Traces of the defluorinated side-product were inseparable from the desired product.

Due to the broadening in NMR spectra and peaks overlapping, we could not verify the orientation of the fluorine atoms. However detailed NMR analysis of the similar analogues (**33**–**35**, **37** and **38**) showed that the fluorine atom is occupying axial positions therefore we believe that the dominant orientation of the fluorine atom in this case is axial as well.

Rotamer A: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.75 (ddt, *J* = 47.4, 6.1, 2.6 Hz, 1H), 4.18 (dt, *J* = 13.7, 6.9 Hz, 1H), 3.98 – 3.94 (m, 1H overlaps with 2-H$_{eq}$), 3.65 – 3.59 (m, 1H overlaps with 4-H and 4-H), 3.59 – 3.54 (m, 1H overlaps with 4-H), 3.46 – 3.44 (m, 3H overlaps with 4-OCH$_3$), 3.41 – 3.33 (m, 1H overlaps with 6-H), 2.02 – 1.89 (m, 1H overlaps with 5-H), 1.84 – 1.78 (m, 1H overlaps with 5-H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.77 – 4.73 (m, 1H), 4.18 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.99 – 3.94 (m, 1H overlaps with 2-H$_{eq}$), 3.63 – 3.59 (m, 1H overlaps with 4-H and 4-H), 3.59 – 3.55 (m, 1H overlaps with 4-H), 3.46 – 3.44 (m, 3H overlaps with 4-OCH$_3$), 3.41 – 3.34 (m, 1H overlaps with 6-H), 2.02 – 1.89 (m, 1H overlaps with 5-H), 1.84 – 1.77 (m, 1H overlaps with 5-H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.32 (q, *J* = 36.0 Hz), 116.43 (q, *J* = 288.0 Hz), 86.11 (d, *J* = 184.6 Hz), 76.07 (d, *J* = 17.4 Hz), 57.26, 44.07 (d, *J* = 26.0 Hz), 42.22 (q, *J* = 3.6 Hz), 27.16 (d, *J* = 4.1 Hz); **^{13}C{sel-^{19}F at -200 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.32 (q, *J* = 35.8 Hz), 116.43 (q, *J* = 287.7 Hz), 86.11, 76.07, 57.26, 44.07, 42.22 (q, *J* = 3.6 Hz), 27.16; **^{19}F NMR** (600 MHz, CDCl$_3$, 299 K) δ -68.44 (d, *J* = 2.3 Hz), -200.30; **^{19}F{^{1}H} NMR** (282 MHz, CDCl$_3$, 299 K) δ -68.44 (d, *J* = 2.6 Hz), -200.26.

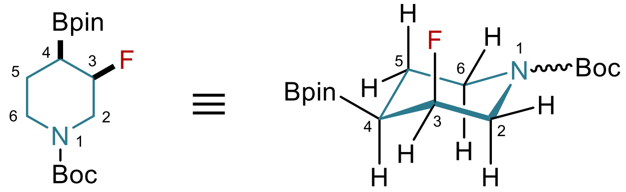
Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.72 (ddt, *J* = 47.6, 5.9, 2.4 Hz, 1H), 4.04 – 3.98 (m, 1H overlaps with 6-H), 3.80 – 3.75 (m, 1H), 3.60 – 3.55 (m, 1H overlaps with 4-H), 3.54 – 3.49 (m, 1H), 3.46 – 3.44 (m, 3H overlaps with 4-OCH$_3$), 3.41 – 3.34 (m, 1H overlaps with 6-

H), 2.03 – 1.88 (m, 1H overlaps with 5-H), 1.84 – 1.78 (m, 1H overlaps with 5-H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.73 – 4.70 (m, 1H), 4.03 – 3.99 (m, 1H overlaps with 6-H), 3.82 – 3.74 (m, 1H), 3.59 – 3.55 (m, 1H overlaps with 4-H), 3.55 – 3.51 (m, 1H), 3.46 – 3.44 (m, 3H overlaps with 4-OCH$_3$), 3.41 – 3.34 (m, 1H overlaps with 6-H), 2.03 – 1.90 (m, 1H overlaps with 5-H), 1.85 – 1.78 (m, 1H overlaps with 5-H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.32 (q, *J* = 36.0 Hz), 116.49 (q, *J* = 287.6 Hz), 85.98 (d, *J* = 185.4 Hz), 76.16 (d, *J* = 17.3 Hz), 57.17, 46.17 (dq, *J* = 25.3, 3.3 Hz), 40.22, 26.00 (d, *J* = 3.9 Hz); **^{13}C{sel-^{19}F at -200 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.32 (q, *J* = 36.2 Hz), 116.49 (q, *J* = 287.4 Hz), 85.98, 76.16, 57.17, 46.17 (q, *J* = 3.5 Hz), 40.22, 26.00; **^{19}F NMR** (600 MHz, CDCl$_3$, 299 K) δ -69.06 – -69.10 (m), -200.69; **^{19}F{^{1}H} NMR** (282 MHz, CDCl$_3$, 299 K) δ -69.07 – -69.09 (m), -200.65.

ESI-MS: calculated [$C_8H_{11}NO_2F_4$ +Na]$^+$: 252.0624, found: 252.0632.

IR ν = 2939.6 (w), 1689.7 (s), 1458.2 (m), 1373.3 (w), 1203.6 (s), 1165.1 (s), 1141.9 (s), 1087.8 (s), 1003.1 (m), 864.1 (w), 756.1 (w), 709.8 (w), 624.9 (w).

tert-Butyl *cis*-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (37)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 0.5 M THF (for better solubility) at 40 °C, purification with 0-10% EtOAc in pentane. The product was isolated as a white solid (120 mg, 0.364 mmol, 73%, *d.r.* 96:4). The major diastereomer could be isolated by column chromatography. The title compound is not stable over silica column therefore traces of the decomposition product *tert*-butyl 3,6-dihydropyridine-1(*2H*)-carboxylate were observed in NMR spectra.

The orientation of the fluorine atom was assigned as axial due to the large value of $^{3}J(\mathrm{F,H_a})$. [$\boldsymbol{^{3}J(2\text{-}H_a,3\text{-}F) = 39.2}$ **Hz**]

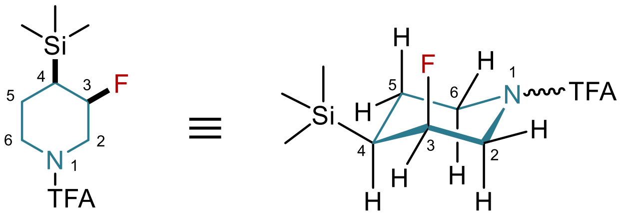
^{1}H NMR (599 MHz, $CDCl_3$, 299 K) δ 4.83 (d, *J* = 45.8 Hz, 1H), 4.24 (bs, 1H), 4.11 (bs, 1H), 2.92 (bs, 1H), 2.74 (bs, 1H), 1.85 (qd, *J* = 12.3, 4.2 Hz, 1H), 1.58 (dm, *J* = 13.6 Hz, 1H), 1.44 (s, 9H), 1.33 – 1.27 (m, 1H), 1.25 (s, 6H), 1.24 (s, 6H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.83 (s, 1H), 4.24 (bs, 1H), 4.11 (bs, 1H), 2.94 (bs, 1H), 2.74 (bs, 1H), 1.85 (qd, *J* = 12.2, 4.2 Hz, 1H), (dm, *J* = 13.6 Hz, 1H), 1.44 (s, 9H), 1.30 – 1.26 (m, 1H), 1.25 (s, 6H), 1.24 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.30, 87.98 (d, *J* = 172.9 Hz), 83.80, 79.68, 48.73 (bs), 43.55 (bs), 28.55, 25.29 (bs), 24.95, 24.76, 21.50 (bs); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 155.30, 87.98, 83.80, 79.68, 48.84 (bs), 43.53 (bs), 28.55, 25.30 (bs), 24.95, 24.76, 21.53 (bs); **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -186.46 (q, *J* = 39.2 Hz); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -186.50; **^{11}B NMR** (192 MHz, $CDCl_3$, 299 K) δ 33.07.

ESI-MS: calculated $[C_{16}H_{29}NO_4BF + Na]^+$: 352.2071, found: 352.2073.

IR ν = 2978.2 (w), 2847 (w), 1681.9 (s), 1404.2 (m), 1388.8 (s), 1365.6 (m), 1334.8 (s), 1249.9 (m), 1165.1 (s), 1141.9 (s), 1111 (s), 1057 (m), 995.3 (m), 856.4 (m), 779.3 (m), 671.2 (w).

M.p.: 86-88 °C.

2,2,2-Trifluoro-1-(*cis*-3-fluoro-4-(trimethylsilyl)piperidin-1-yl)ethan-1-one (38)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-10% EtOAc in pentane. The product was isolated as a yellow oil (96 mg, 0.355 mmol, 71% (83% NMR yield), *d.r.* >99:1). The product was present as a ~1:1 mixture of amide bond rotamers.

The orientation of the fluorine atom was assigned as axial due to the large values of ^3J(F,H$_a$). [**^3J(2-H$_a$,3-F, Rot A) = 37.5 Hz, ^3J(4-H$_a$,3-F, Rot A) = 48.2 Hz, ^3J(2-H$_a$,3-F, Rot B) = 39.3 Hz, ^3J(4-H$_a$,3-F, Rot A) = 48.2 Hz**]

Rotamer A: ^{1}H NMR (600 MHz, CDCl$_3$, 299 K) δ 4.81 (d, *J* = 47.3 Hz, 1H overlaps with 2-H$_{eq}$), 4.64 (dm, *J* = 13.0 Hz, 1H), 4.28 – 4.20 (m, 1H), 3.23 (ddd, *J* = 37.5, 14.7, 1.3 Hz, 1H), 2.71 (td, *J* = 12.9, 2.5 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.67 – 1.60 (m, 1H), 0.97 (dm, *J* = 48.2 Hz 1H), 0.07 – 0.05 (m, 9H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.80 (s, 1H overlaps with 2-H$_{eq}$), 4.64 (dm, *J* = 13.0 Hz, 1H), 4.23 (d, *J* = 14.7 Hz, 1H), 3.23 (dd, *J* = 14.7, 1.3 Hz, 1H), 2.71 (td, *J* = 12.9, 2.5 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.67 – 1.61 (m, 1H), 0.99 – 0.94 (m, 1H), 0.09 – 0.03 (m, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.34 (q, *J* = 35.7 Hz), 116.58 (q, *J* = 288.1 Hz), 87.31 (d, *J* = 174.5 Hz), 50.78 (dq, *J* = 23.2, 3.2 Hz), 44.84, 29.07 (d, *J* = 14.6 Hz), 20.93, -2.51 – -2.95 (m); **^{13}C{sel-^{19}F at -188 ppm} NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.34 (q, *J* = 35.7 Hz), 116.58 (q, *J* = 287.9 Hz), 87.31, 50.78 (q, *J* = 3.2 Hz), 44.84, 29.11, 20.93, -2.57 – -2.91 (m); **^{19}F{^{1}H} NMR** (282 MHz, CDCl$_3$, 299 K) δ -67.98 (d, *J* = 4.6 Hz), -188.03 (q, *J* = 4.6 Hz).

Rotamer B: **^{1}H NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.89 (d, *J* = 47.3 Hz, 1H), 4.84 – 4.78 (m, 1H overlaps with 3-H$_{eq}$), 4.10 (dm, *J* = 13.7 Hz, 1H), 3.10 (td, *J* = 13.2, 2.7 Hz, 1H), 2.85 (dd, *J* = 39.3, 14.4 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.67 – 1.60 (m, 1H), 0.97 (dm, *J* = 48.2 Hz 1H), 0.08 – 0.04 (m, 9H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.89 (s, 1H), 4.84 – 4.79 (m, 1H overlaps with 3-H$_{eq}$), 4.10 (dd, *J* = 13.7, 1.8 Hz, 1H), 3.10 (td, *J* = 13.2, 2.8 Hz, 1H), 2.85 (d, *J* = 14.4 Hz, 1H), 1.92 – 1.76 (m, 1H), 1.67 – 1.59 (m, 1H), 0.99 – 0.94 (m, 1H), 0.06 (t, *J* = 1.6 Hz, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 156.37 (q, *J* = 35.7 Hz), 116.64 (q, *J* = 287.9 Hz), 87.78 (d, *J* = 173.3 Hz), 48.56 (d, *J* = 23.7 Hz), 47.15 (q, *J* = 3.5 Hz), 29.25 (d, *J* = 14.7 Hz), 21.95, -2.57 – -

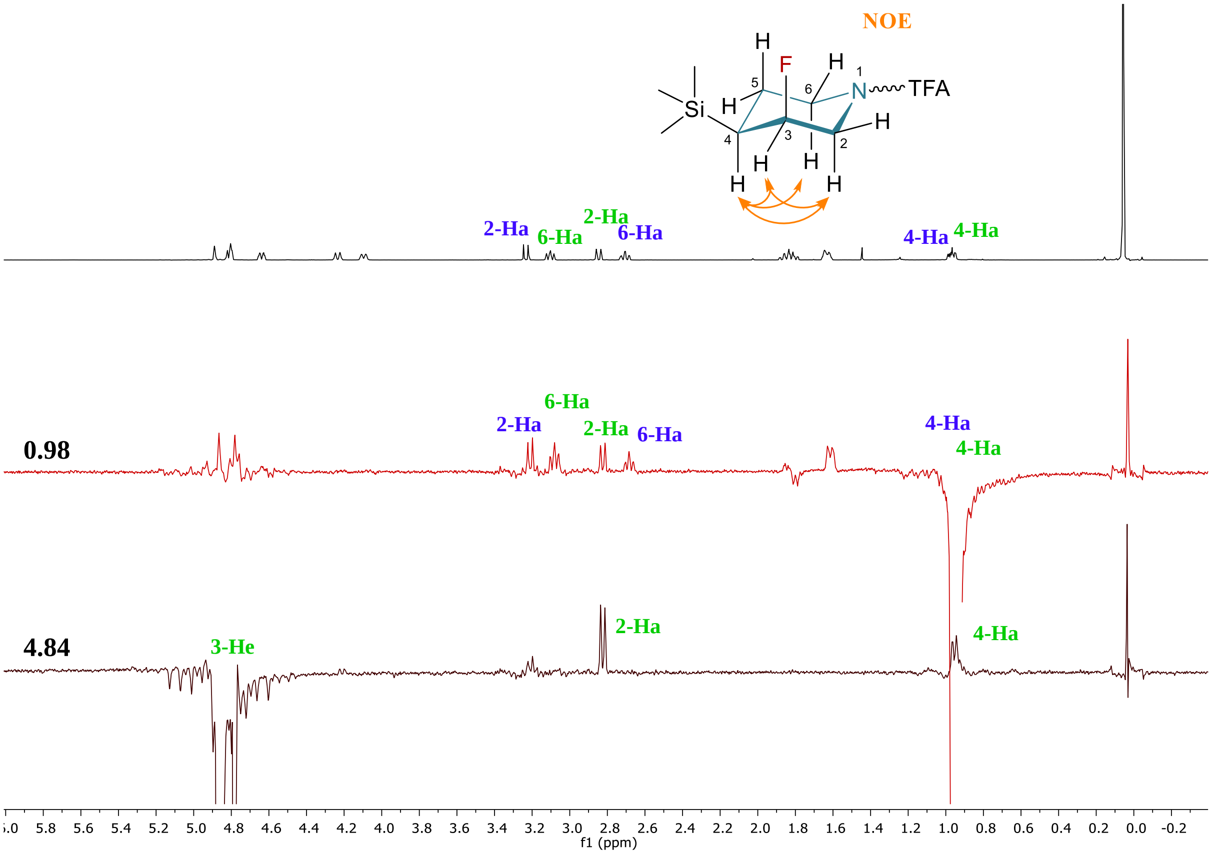
2.95 (m); **^{13}C{sel-^{19}F at -188 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.37 (q, *J* = 35.6 Hz), 116.64 (q, *J* = 287.6 Hz), 87.78, 48.56, 47.15 (q, *J* = 3.4 Hz), 29.21, 21.95, -2.57 – -2.89 (m); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -68.88, -187.60.

^{29}Si NMR (60 MHz, $CDCl_3$, 299 K) δ 3.43, 3.34 (both rotamers).

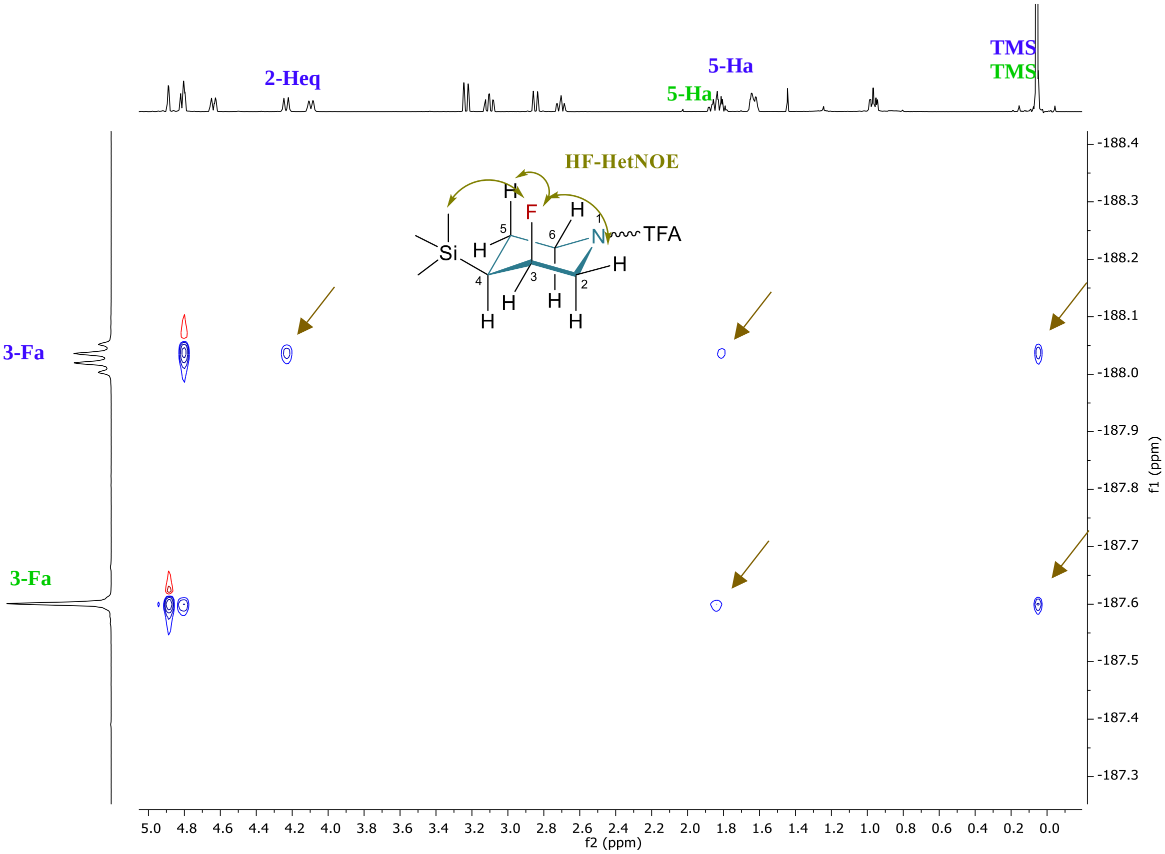
ESI-MS: calculated $[C_{10}H_{17}NOSiF_4 + Na]^+$: 294.0913, found: 294.0913.

IR ν = 2955.1 (w), 1689.7 (s), 1458.2 (w), 1249.9 (m), 1195.9 (s), 1141.9 (s), 1095.6 (m), 1049.3 (m), 1003 (m), 864.1 (s), 833.3 (s), 748.4 (m), 694.4 (w), 663.5 (w).

For this scope entry, we also measured NOE and HF-HetNOE NMR experiments in order to prove that the fluorine atom is occupying an axial position (Supplementary Fig. 36–37).

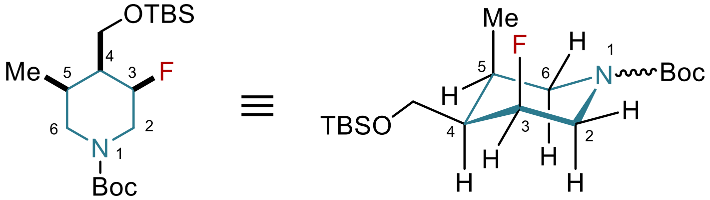


Supplementary Figure 36. Selected 1D NOESY experiments for **38**. Irradiation at 4.84 and 0.98 ppm, respectively.



Supplementary Figure 37. 2D HF-Het-NOESY experiment for **38**.

tert-Butyl *cis*-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-fluoro-5-methylpiperidine-1-carboxylate (39)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-4% EtOAc in pentane. The product was isolated as a colorless oil (115 mg, 0.32 mmol, 64% (91% NMR yield), *d.r.* 93:7:0). Only the peaks of the major diastereomer are listed. The product was present as a ~1:1 mixture of amide bond rotamers. The peaks of both rotamers are listed.

The orientation of the fluorine atom was assigned as axial due to the large value of ${}^{3}J(\mathrm{F,H_a})$. [**${}^{3}J$(4-H$_a$,3-F) = 37.2 Hz**]

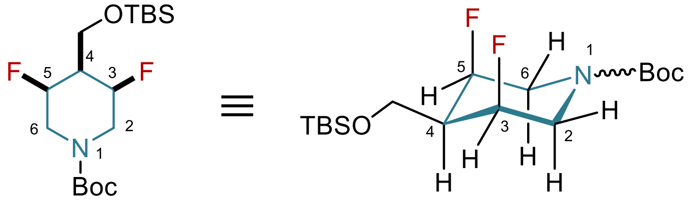
^{1}H NMR (600 MHz, CDCl$_3$, 299 K) δ 4.70 (dd, *J* = 47.7, 12.9 Hz, 2H), 4.49 (t, *J* = 13.0 Hz, 1H), 4.34 (t, *J* = 12.5 Hz, 1H), 4.05 (d, *J* = 11.4 Hz, 1H), 3.94 (d, *J* = 12.3 Hz, 1H), 3.73 (t, *J* = 9.1 Hz, 2H), 3.56 (dd, *J* = 9.5, 6.4 Hz, 2H), 2.99 – 2.72 (m, 4H), 1.88 (bs, 2H), 1.77 (dm, *J* = 37.2 Hz, 2H), 1.45 – 1.40 (m, 18H), 0.94 (d, *J* = 7.1 Hz, 6H), 0.86 – 0.84 (m, 18H), 0.03 (s, 12H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.71 (d, *J* = 14.2 Hz, 2H), 4.48 (d, *J* = 13.2 Hz, 1H), 4.34 (d, *J* = 13.4 Hz, 1H), 4.05 (d, *J* = 11.9 Hz, 1H), 3.94 (d, *J* = 11.6 Hz, 1H), 3.75 (t, *J* = 9.1 Hz, 2H), 3.58 (dd, *J* = 9.6, 6.3 Hz, 2H), 2.87 (d, *J* = 46.6 Hz, 4H), 1.90 (bs, 2H), 1.79 – 1.74 (m, 2H), 1.47 – 1.41 (m, 18H), 0.95 (d, *J* = 7.2 Hz, 6H), 0.90 – 0.85 (m, 18H), 0.04 (s, 12H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.66, 87.31 (d, *J* = 177.5 Hz), 79.65, 61.65 (d, *J* = 4.1 Hz), 50.70 (bs), 49.43 (bs), 48.58 (d, *J* = 22.8 Hz), 47.48 (d, *J* = 24.1 Hz), 44.78 (d, *J* = 18.6 Hz), 29.61, 28.48, 25.99, 18.36, 14.13 – 13.78 (m), -5.41 (m); **^{13}C{^{19}F} NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.65, 87.30, 79.65, 61.65, 50.67, 49.42, 48.57, 47.48, 44.78, 29.60, 28.48, 25.98, 18.36, 13.90, -5.41 (m); **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -191.95 – -192.59 (m); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -192.14, -192.43; **^{29}Si NMR** (119 MHz, CDCl$_3$, 299 K) δ 19.66.

We also measured NMR spectra in toluene-*d*$_8$ at 363 K to eliminate the rotameric behavior of the product. The same value of ${}^{3}J(\mathrm{F,H_a})$ was obtained.

ESI-MS: calculated $[\mathrm{C_{18}H_{36}FNO_3Si + Na}]^+$: 384.2346, found: 384.2340.

IR ν = 2955 (w), 2931.9 (w), 2854.7 (w), 1697.4 (s), 1458.2 (w), 1427.4 (m), 1365.6 (m), 1257.6 (m), 1242.2 (m), 1172.7 (m), 1141.9 (m), 1103.3 (s), 1080.2 (m), 833.3 (s), 771.5 (s), 663.5 (w).

***tert*-Butyl *cis*-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,5-difluoropiperidine-1-carboxylate (40)**



Following general procedure A on 0.25 mmol scale, 3 mol% catalyst, 1 mmol HBpin, 0.5 M THF (for better solubility) at 40 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a white solid (73 mg, 0.199 mmol, 80%, *d.r.* 90:10:0). The major diastereomer could be isolated by column chromatography. Broadened peaks in NMR spectra were observed due to the rotameric behavior of the product.

The orientation of the fluorine atoms was assigned as axial due to the large values of ^3J(F,H$_a$). [**^3J(4-H$_a$,3-F) = ^3J(4-H$_a$,5-F) = 36.0 Hz**]

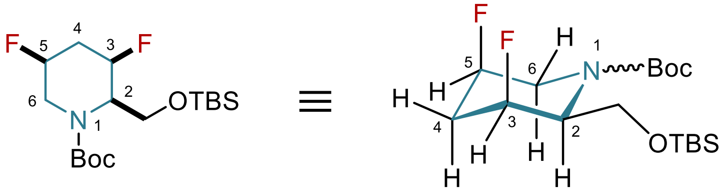
^{1}H NMR (599 MHz, CDCl$_3$, 299 K) δ 4.76 (d, *J* = 47.1 Hz, 2H), 4.66 (bs, 1H), 4.51 (bs, 1H), 3.86 (d, *J* = 6.4 Hz, 2H), 3.06 – 2.75 (m, 2H), 1.80 (tm, *J* = 36.0 Hz, 1H), 1.47 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H); **^{1}H{^{19}F} NMR** (600 MHz, CDCl$_3$, 299 K) δ 4.76 (s, 2H), 4.65 (bs, 1H), 4.52 (bs, 1H), 3.86 (d, *J* = 6.0 Hz, 2H), 2.99 – 2.77 (m, 2H), 1.80 (td, *J* = 7.3, 3.6 Hz, 1H), 1.47 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.50, 85.06 (dm, *J* = 170.2 Hz, ×2), 80.46, 60.23 (t, *J* = 4.2 Hz), 47.89 (bs), 46.80 (bs), 44.91 (t, *J* = 19.2 Hz), 28.47, 26.00, 18.43, -5.39, -5.48; **^{13}C{^{19}F} NMR** (151 MHz, CDCl$_3$, 299 K) δ 155.50, 85.17 (bs), 85.06 (bs), 80.46, 60.23, 47.94 (bs), 46.76 (bs), 44.91, 28.47, 26.00, 18.43, -5.39, -5.48; **^{19}F NMR** (564 MHz, CDCl$_3$, 299 K) δ -196.91 – -197.37 (m); **^{19}F{^{1}H} NMR** (564 MHz, CDCl$_3$, 299 K) δ -197.15 (d, *J* = 34.6 Hz); **^{29}Si NMR** (119 MHz, CDCl$_3$, 299 K) δ 20.89.

ESI-MS: calculated [$C_{17}H_{33}NO_3F_2Si$ +Na]$^+$: 388.2095, found: 388.2098.

IR ν = 2924.2 (m), 2854.7 (m), 1689.7 (s), 1450.5 (m), 1435.1 (s), 1365.6 (m), 1249.9 (m), 1172.7 (m), 1118.7 (s), 1080.2 (s), 1064.7 (s), 1003.1 (m), 856.4 (m), 833.3 (s), 779.3 (s), 732.9 (m).

M.p.: 58-59 °C.

tert-Butyl-_cis_-2-(((_tert_-butyldimethylsilyl)oxy)methyl)-3,5-difluoropiperidine-1-carboxylate (41)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 25-100% CH_2Cl_2 in pentane. The product was isolated as a white solid (146 mg, 0.40 mmol, 80%, *d.r.* 99:1:0). The product was present as a ~1:1 mixture of amide bond rotamers. The peaks of both rotamers are listed.

Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atoms. However detailed NMR analysis of the crossponding free amine analogue (**42**) and hydrochloride salt (**43**) showed that the fluorine atoms are occupying axial positions therefore we believe that the dominant orientation of the fluorine atoms is axial as well.

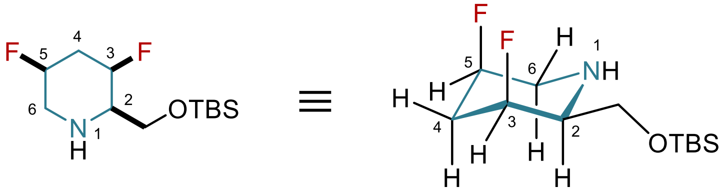
^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 4.74 (dm, *J* = 47.02 Hz, 1H), 4.56 (d, *J* = 47.5 Hz, 1H), 4.34 (bs, 2H), 4.01 – 3.74 (m, 2H), 3.05 (bs, 1H), 2.52 – 2.30 (m, 1H), 2.28 – 2.05 (m, 1H), 1.45 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 154.88, 85.81 (d, *J* = 181.8 Hz), 85.66 (d, *J* = 181.8 Hz), 84.89 (d, *J* = 177.5 Hz), 84.75 (d, *J* = 177.8 Hz), 80.79, 58.87 (d, *J* = 3.8 Hz), 53.97, 42.60, 34.06 (t, *J* = 20.3 Hz), 28.42, 25.97, 18.29, -5.42, -5.46; **^{19}F{H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -181.90 (bs), -187.94 (bs); **^{29}Si NMR** (60 MHz, $CDCl_3$, 299 K) δ 21.00.

ESI-MS: calculated $[C_{17}H_{33}NO_3F_2Si +Na]^+$: 388.2095, found: 388.2089.

IR ν = 2931.9 (w), 2854.7 (w), 2360.9 (w), 1681.9 (s), 1458.2 (w), 1411.9 (m), 1365.6 (m), 1319.4 (w), 1257.6 (m), 1172.7 (w), 1149.6 (s), 1089.9 (s), 1064.7 (s), 1018.5 (m), 995.3 (m), 979.8 (s), 910.4 (w), 871.8 (s), 840.9 (m), 771.5 (s), 717.5 (w), 678.9 (w), 563.2 (w).

M.p.: 45-46 °C.

cis-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3,5-difluoropiperidine (42)



Following general procedure A on 0.5 mmol scale, 2 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C. The crude was quenched with MeOH (2 mL) and purified over silica column with 30-50% EtOAc in pentane. The product was isolated as a colorless oil (61.1 mg, 0.23 mmol, 46%, *d.r.* 99:1:0).

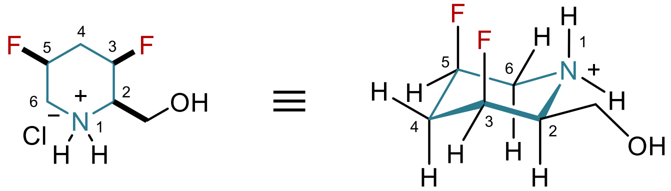
The orientation of the fluorine atoms was assigned as axial due to the large values of ${}^{3}J(\mathrm{F,H_a})$. [**${}^{3}J(\mathrm{2\text{-}H_a,3\text{-}F})$ = 30.0 Hz, ${}^{3}J(\mathrm{4\text{-}H_a,3\text{-}F})$ = 44.8 Hz, ${}^{3}J(\mathrm{4\text{-}H_a,5\text{-}F})$ = 44.8 Hz, ${}^{3}J(\mathrm{6\text{-}H_a,5\text{-}F})$ = 40.0 Hz**]

^{1}H NMR (600 MHz, $CDCl_3$, 299 K) δ 4.76 (d, *J* = 46.4 Hz, 1H), 4.64 (d, *J* = 47.2 Hz, 1H), 3.71 – 3.58 (m, 2H), 3.35 (t, *J* = 14.2 Hz, 1H), 2.84 (dd, *J* = 40.0, 14.7 Hz, 1H), 2.75 (dt, *J* = 30.0, 7.2 Hz, 1H), 2.60 – 2.51 (m, 1H), 1.86 (bs, 1H overlaps with 4-Ha), 1.81 (tdt, *J* = 44.8, 16.1, 3.0 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); **^{1}H{^{19}F} NMR** (600 MHz, $CDCl_3$, 299 K) δ 4.76 (s, 1H), 4.64 (s, 1H), 3.71 – 3.58 (m, 2H), 3.35 (d, *J* = 14.7 Hz, 1H), 2.84 (d, *J* = 14.7 Hz, 1H), 2.77 – 2.73 (m, 1H), 2.55 (dt, *J* = 16.1, 2.7 Hz, 1H), 1.86 (s, 1H), 1.81 (dt, *J* = 16.1, 3.0 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 85.31 (d, *J* = 172.6 Hz), 84.21 (d, *J* = 175.2 Hz), 62.52 (d, *J* = 5.6 Hz), 59.54 (d, *J* = 19.7 Hz), 49.69 (d, *J* = 21.9 Hz), 33.52 (t, *J* = 20.9 Hz), 26.01, 18.43, -5.38 (m); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 85.31, 84.21, 62.52, 59.54, 49.69, 33.52, 26.01, 18.43, -5.38 (m); **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -182.17 – -182.68 (m), -200.47 – -201.01 (m); **^{19}F{^{1}H} NMR** (564 MHz, $CDCl_3$, 299 K) δ -182.43 (d, *J* = 14.6 Hz), -200.77 (d, *J* = 14.6 Hz).

ESI-MS: calculated $[C_{12}H_{26}NOF_2Si]^+$: 266.1752, found: 266.1757.

IR ν = 2955.1 (m), 2931.9 (m), 2854.7 (w), 1458.2 (m), 1357.9 (w), 1257.6 (m), 1118.7 (m), 1095.6 (s), 941.3 (w), 833.3 (s), 779.3 (s), 717.5 (m), 655.8 (w).

***cis*-3,5-Difluoro-2-(hydroxymethyl) piperidine hydrochloride (43)**



Compound **43** was prepared according to the general procedure C starting from *tert*-butyl-*cis*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,5-difluoropiperidine-1-carboxylate (**41**) (36.8 mg, 0.10 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 16 h. Removal of all volatiles afforded the title compound as a white solid (18.7 mg, 0.10 mmol, 99%, *d.r.* 99:1:0). Only the peaks of the major diastereomer are listed.

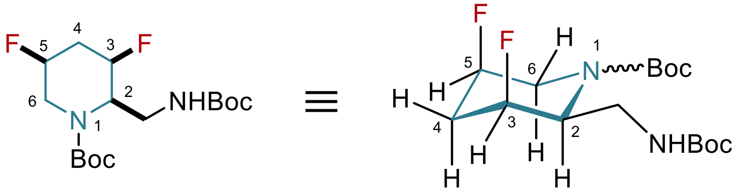
The orientation of the fluorine atoms was assigned as axial due to the large values of ^{3}J(F,H$_a$). [**^{3}J(2-H$_a$,3-F) = 31.5 Hz, ^{3}J(4-H$_a$,3-F) = 46.5 Hz, ^{3}J(4-H$_a$,5-F) = 46.6 Hz, ^{3}J(6-H$_a$,5-F) = 40.4 Hz**]

^{1}H NMR (600 MHz, D$_2$O, 299 K) δ 5.23 (d, *J* = 44.3 Hz, 1H), 5.19 (d, *J* = 45.5 Hz, 1H), 4.02 (dd, *J* = 12.3, 5.1 Hz, 1H), 3.91 (dd, *J* = 12.2, 8.9 Hz, 1H), 3.83 (ddm, *J* = 14.5, 13.2 Hz, 1H), 3.62 (dm, *J* = 31.5 Hz, 1H), 3.46 (dd, *J* = 40.4, 14.5 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.18 (td, *J* = 46.6, 46.5, 16.6 Hz, 1H); **^{1}H{^{19}F} NMR** (600 MHz, D$_2$O, 299 K) δ 5.23 (s, 1H), 5.19 (s, 1H), 4.02 (dd, *J* = 12.3, 5.1 Hz, 1H), 3.91 (dd, *J* = 12.3, 8.8 Hz, 1H), 3.83 (dt, *J* = 14.5, 2.4 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.46 (d, *J* = 14.5 Hz, 1H), 2.71 (dq, *J* = 16.9, 2.7 Hz, 1H), 2.18 (d, *J* = 16.6 Hz, 1H); **^{13}C NMR** (151 MHz, D$_2$O, 299 K) δ 84.37 (d, *J* = 174.2 H), 83.60 (d, *J* = 171.4 Hz), 58.44 (d, *J* = 5.6 Hz), 58.28 (d, *J* = 19.1 Hz), 46.39 (d, *J* = 21.5 Hz), 30.66 (t, *J* = 19.7 Hz); **^{13}C{^{19}F} NMR** (151 MHz, D$_2$O, 299 K) δ 84.37, 83.60, 58.44, 58.28, 46.39, 30.66; **^{19}F NMR** (564 MHz, D$_2$O, 299 K) δ -182.65 – -183.21 (m), -195.73 – -196.17 (m); **^{19}F{^{1}H} NMR** (564 MHz, D$_2$O, 299 K) δ -182.87 (dd, *J* = 18.1, 5.0 Hz), -195.91 – -195.98 (m).

ESI-MS: calculated [$C_6H_{12}F_2NO$]$^+$: 152.0881, found: 152.0853.

IR ν = 3356 (m), 2924 (m), 2808 (m), 2646 (m), 2538 (w), 1589 (w), 1559 (m), 1451 (m), 1427 (m), 1350 (w), 1258 (w), 1219 (w), 1126 (m), 1111 (s), 1096 (s), 1065 (s), 1003 (s), 988 (s), 949 (m), 826 (s), 818 (m), 756 (w), 741 (w), 579 (s), 563 (s), 548 (s).

***tert*-Butyl *cis*-2-(((*tert*-butoxycarbonyl)amino)methyl)-3,5-difluoropiperidine-1-carboxylate (44)**



Following general procedure A on 0.25 mmol scale, 3 mol% catalyst, 1 mmol HBpin, 1 M THF at 50 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a colorless oil (52.6 mg, 0.15 mmol, 60%, *d.r.* 99:1:0).

Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atoms. However since we provided detailed NMR analyses on the similar analogues (**41**–**43**), we therefore believe that the dominant orientation of the fluorine atoms is axial as well.

^{1}H NMR (599 MHz, $CDCl_3$, 299 K) δ 4.85 – 4.13 (m, 5H), 3.87 – 3.47 (m, 1H), 3.31 (bs, 1H), 3.07 – 2.75 (m, 1H), 2.46 (dh, *J* = 17.4, 5.5 Hz, 1H), 1.96 (q, *J* = 11.1 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.03 (bs, ×2), 85.89 (bs), 84.37 (bs), 81.38, 79.68 (bs), 51.93 (bs), 42.41 (bs), 35.61, 33.40, 28.50, 28.39; **^{19}F NMR** (564 MHz, $CDCl_3$, 299 K) δ -182.92 (bs), -183.21 (bs), -187.08 (bs), -187.23 (bs) [multiple peaks due to the rotameric behavior of Boc-groups].

ESI-MS: calculated $[C_{16}H_{28}N_2O_4F_2 + Na]^+$: 373.1915, found: 373.1915.

IR ν = 3363.9 (w), 2978.2 (w), 2931.9 (w), 1697.4 (s), 1512.2 (m), 1411.9 (m), 1365.6 (m), 1249.9 (m), 1149.6 (s), 1080.2 (m), 1003 (m), 864.1 (m), 756.1 (m), 732.9 (m).

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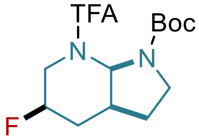
tert-Butyl _cis_-5-fluoro-7-(2,2,2-trifluoroacetyl)octahydro-_1H_-pyrrolo[2,3-_b_]pyridine-1-carboxylate (45)



Following general procedure A on 0.5 mmol scale, 3 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-20% EtOAc in pentane. The product was isolated as a colorless oil (75 mg, 0.22 mmol, 44% (91% NMR yield), *d.r.* 86:14:0). The major diastereomer could be isolated by column chromatography. The product was present as a ~4:1 mixture of amide bond rotamers. The peaks of both rotamers are listed.

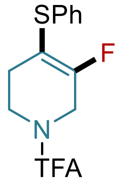
Due to the broadening in NMR spectra we could not verify the orientation of the fluorine atom.

^{1}H NMR (599 MHz, $CDCl_3$, 299 K) δ 6.03 (bs, 1H), 4.55 (d, *J* = 48.6 Hz, 1H), 3.98 (bs, 1H), 3.77 – 3.52 (m, 2H), 3.18 (bs, 1H), 2.50 (bs, 1H), 2.20 – 2.13 (m, 1H), 2.06 – 1.97 (m, 1H), 1.76 – 1.57 (m, 2H), 1.38 (s, 9H); **^{1}H{^{19}F} NMR** (599 MHz, $CDCl_3$, 299 K) δ 6.03 (bs, 1H), 4.55 (bs, 1H), 3.98 (bs, 1H), 3.69 – 3.55 (m, 2H), 3.17 (bs, 1H), 2.50 (bs, 1H), 2.20 – 2.14 (m, 1H), 2.06 – 1.96 (m, 1H), 1.74 – 1.58 (m, 2H), 1.38 (s, 9H); **^{13}C{sel-^{19}F at -179 ppm} NMR** (151 MHz, $CDCl_3$, 299 K) δ 156.05, 154.83, 116.26 (d, *J* = 289.8 Hz), 85.73, 81.22, 65.97, 45.18, 42.90, 36.06, 31.73, 28.36, 27.72; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -66.41 (minor rotamer), -69.51 (major rotamer), -178.50, (major rotamer) -179.73 (minor rotamer).

ESI-MS: calculated $[C_{14}H_{20}F_4N_2O_3 + Na]^+$: 363.1308, found: 363.1317.

IR ν = 2978.2 (w), 1697.4 (s), 1458.2 (m), 1396.5 (m), 1365.6 (m), 1219.1 (m), 1188.2 (m), 1172.7 (s), 1134.2 (s), 1111 (s), 1064.7 (m), 1010.7 (m), 887.3 (w), 756.1 (m), 694.4 (m).

2,2,2-Trifluoro-1-(5-fluoro-4-(phenylthio)-3,6-dihydropyridin-1(*2H*)-yl)ethan-1-one (46)



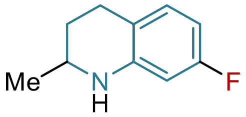
Following general procedure A on 0.25 mmol scale, 3 mol% catalyst, 1 mmol HBpin, 1 M THF at 40 °C, purification with 0-10% Et_2O in pentane. The product was isolated as a colorless oil (31 mg, 0.102 mmol, 41%, 60% conversion). The product was present as a ~3:1 mixture of amide bond rotamers. Only the peaks of the major rotamer are listed.

^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ 7.31 – 7.18 (m, 5H), 4.26 (s, 2H), 3.59 (t, *J* = 5.5 Hz, 2H), 2.27 – 2.15 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$, 299 K) δ 155.97 (d, *J* = 36.3 Hz), 152.88 (d, *J* = 256.9 Hz), 131.94, 131.68, 129.40, 127.82, 116.30 (dd, *J* = 576.0, 288.0 Hz), 107.69 (d, *J* = 11.8 Hz), 44.55 (dq, *J* = 41.6, 4.2 Hz), 43.45, 28.84; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$, 299 K) δ -69.25, -104.10.

ESI-MS: calculated $[C_{13}H_{11}NOSF_4 + Na]^+$: 328.0395, found: 328.0393.

IR ν = 1697.4 (s), 1681.9 (s), 1581.7 (w), 1458.2 (m), 1442.8 (m), 1288.5 (m), 1211.3 (s), 1172.7 (s), 1141.9 (s), 1049.3 (m), 1018.4 (m), 864.1 (m), 740.7 (s), 686.7 (s).

7-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (47)



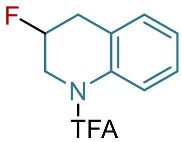
Following general procedure A on 0.5 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-2% EtOAc in pentane. The product was isolated as a yellow oil (75 mg, 0.454 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ 6.91 – 6.82 (m, 1H), 6.29 (td, *J* = 8.5, 2.5 Hz, 1H), 6.17 (dd, *J* = 10.8, 2.5 Hz, 1H), 3.85 (bs, 1H), 3.40 (dqd, *J* = 9.3, 6.3, 2.9 Hz, 1H), 2.72 (tdd, *J* = 20.4, 10.0, 5.4 Hz, 2H), 1.99 – 1.87 (m, 1H), 1.56 (dddd, *J* = 12.9, 11.2, 9.9, 5.5 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$, 299 K) δ 162.25 (d, *J* = 240.6 Hz), 145.89 (d, *J* = 10.6 Hz), 130.17 (d, *J* = 9.8 Hz), 116.66 (d, *J* = 2.5 Hz), 103.46 (d, *J* = 21.5 Hz), 100.30 (d, *J* = 24.4 Hz), 47.14, 30.08, 26.07, 22.56; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -117.11.

ESI-MS: calculated $[C_{10}H_{13}NF]^+$: 166.1032, found: 166.1025.

IR ν = 3402.5 (w), 2962.7 (w), 2924.2 (w), 2847 (w), 1612.5 (m), 1597.1 (m), 1504.5 (m), 1489.1 (m), 1450.5 (m), 1311.6 (m), 1249.9 (m), 1165.1 (s), 1111 (m), 995.3 (m), 833.3 (s), 779.3 (m), 756.1 (m), 732.9 (m).

2,2,2-Trifluoro-1-(3-fluoro-3,4-dihydroquinolin-1(*2H*)-yl)ethan-1-one (48)



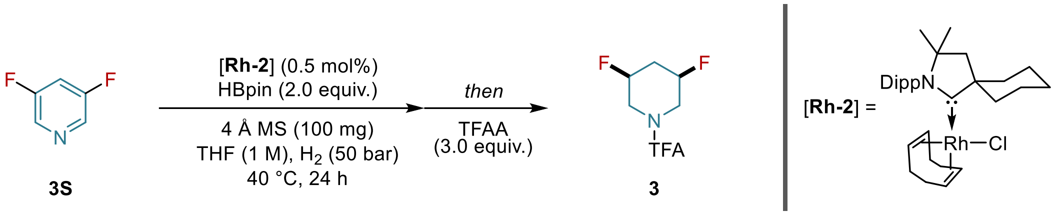
Following general procedure A on 0.5 mmol scale, 0.5 mol% catalyst, 2 mmol HBpin, 1 M THF at 40 °C, purification with 0-4% EtOAc in pentane. The product was isolated as a colorless oil (97 mg, 0.39 mmol, 78%). The product was present as a ~1.5:1 mixture of amide bond rotamers. Broadened peaks in NMR spectra were observed due to the rotameric behavior of the product.

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 7.87 – 7.09 (m, 4H), 5.28 (d, *J* = 50.1 Hz, 1H), 4.35 – 3.60 (m, 2H), 3.33 – 2.96 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 156.39 (bs), 136.37 (bs), 129.53, 127.05 (bs), 124.57 (bs), 116.57 (q, *J* = 288.1 Hz), 85.27 (d, *J* = 181.4 Hz), 49.94 (bs), 48.46 (bs), 32.92 (bs); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -66.17, -67.91, -171.65, -178.20.

ESI-MS: calculated $[C_{11}H_9NOF_4 + Na]^+$: 270.0518, found: 270.0516.

IR ν = 1697.4 (s), 1496.8 (m), 1427.4 (m), 1203.6 (s), 1180.5 (s), 1141.9 (s), 1087.9 (s), 1049.3 (m), 949 (w), 918.1 (w), 763.8 (s), 717.5 (m), 655.8 (m).

5. Scale-up experiment

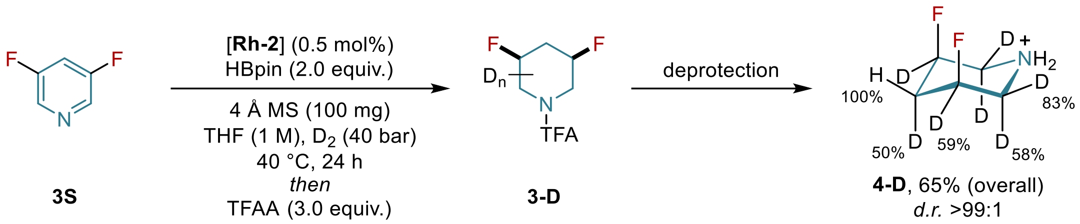


An oven-dried 50 mL glass cylinder equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 100 mg), [**Rh-2**] (28.6 mg, 0.05 mmol, 0.5 mol%) were added under air. The cylinder was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (10 mL, 1 M) and 3,5-difluoropyridine (**3S**) (1.15 g, 10.0 mmol, 0.916 mL). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.56 g, 20.0 mmol, 2.9 mL), the glass cylinder was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 °C for 24 h. After the autoclave was carefully depressurized, trifluoroacetic anhydride (6.3 g, 30.0 mmol, 4.17 mL) and CH_2Cl_2 (3 mL) were added to the crude mixture and stirring was continued for 20 min at room temperature. The crude was then filtered over fritted funnel and the remaining solid was washed with ethyl acetate (2×10 mL). The combined solution was concentrated under reduced pressure and submitted to column chromatography (0-100% CH_2Cl_2 in pentane) to obtain the final product (**3**) as a white solid (1.57 g, 7.23 mmol, 72% - volatile compound, *d.r.* >99:1).

The title compound can now be obtained from Sigma-Aldrich (product #903817).

6. Mechanistic studies

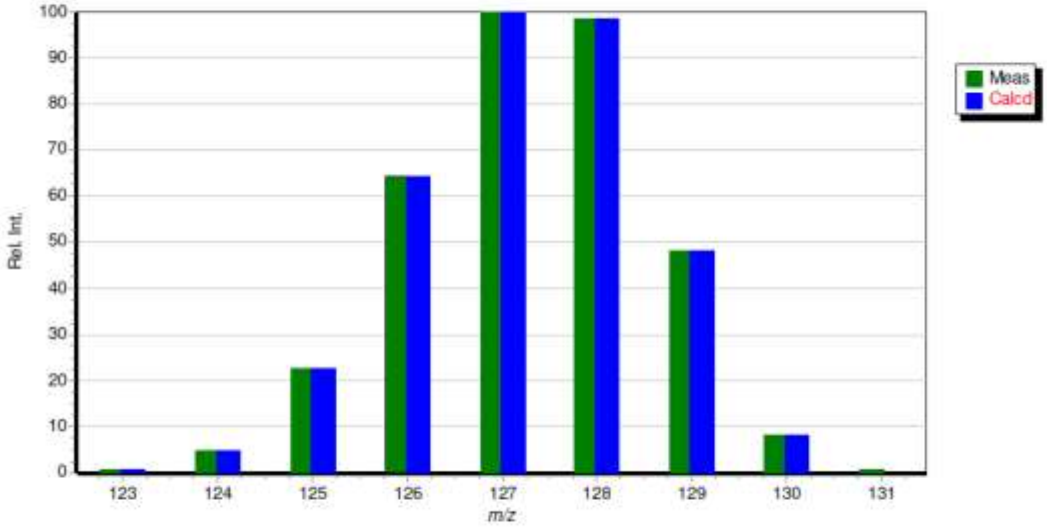
A. Deuterium labeling experiment



An oven-dried reaction vessel (9 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 100 mg), [**Rh-2**] (5.7 mg, 0.01 mmol, 0.5 mol%) were added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (2 mL, 1 M) and 3,5-difluoropyridine (**3S**) (230.16 mg, 2.0 mmol, 183 µL). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (511.9 mg, 4.0 mmol, 0.58 mL), the glass vial was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with deuterium gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 ºC for 24 h. After the autoclave was carefully depressurized, trifluoroacetic anhydride (1.26 g, 6.0 mmol, 0.83 mL) and CH_2Cl_2 (1 mL) were added to the crude mixture and stirring was continued for 20 min at room temperature. The crude was then filtered over fritted funnel and the remaining solid was washed with ethyl acetate (2×10 mL). The combined solution was concentrated under reduced pressure and submitted to column chromatography (0-100% CH_2Cl_2 in pentane) to obtain **3-D** as a white solid.

Compound **4-D** was prepared according to the general procedure B starting from **3-D.** The reaction mixture was stirred at room temperature for 1 h. Extraction and removal of all volatiles afforded the title compound as a white solid (211.6 mg, 1.30 mmol, 65%-overall, *d.r.* >99:1).

NMR analysis of the final product showed that the isotopologues of the 3,5-difluoropiperidine hydrochloride (**4-D**) were formed with isotopologues-d_5 and -d_6 as the most dominant species according to ESI-MS (Supplementary Fig. 38). Deuterium scrambling at the α-position can be rationalized due to the formation of imine-enamine intermediates.



```
Deuterium: 0-fold (%): 0,00  0,00
Deuterium: 1-fold (%): 0,65  0,19
Deuterium: 2-fold (%): 4,94  1,45
Deuterium: 3-fold (%): 23,39  6,86
Deuterium: 4-fold (%): 65,35  19,17
Deuterium: 5-fold (%): 100,00  29,33
Deuterium: 6-fold (%): 96,52  28,31
Deuterium: 7-fold (%): 44,17  12,96
Deuterium: 8-fold (%): 5,92  1,74
Deuterium: 9-fold (%): 0,00  0,00
Label Atom Sum: 5,21 (52,14%)
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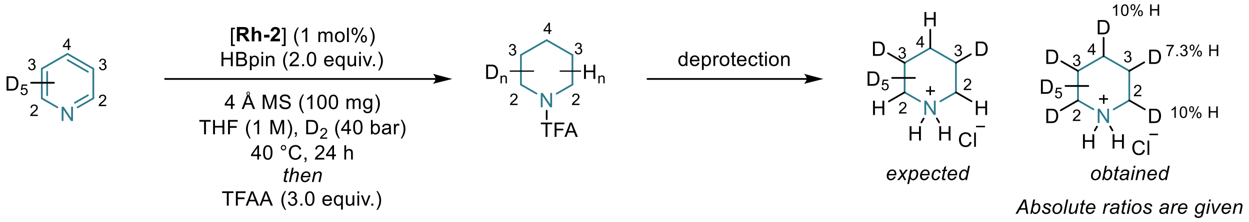
Supplementary Figure 38. Label-checker results of **4-D** incorporated with ESI-MS.

B. Hydrogen labeling experiment

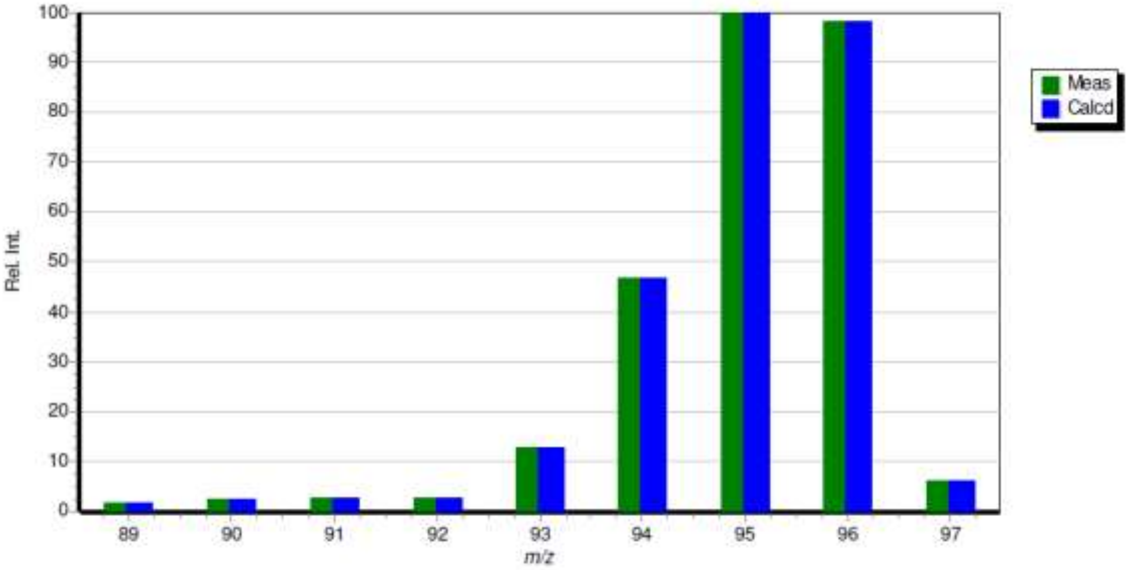


An oven-dried reaction vessel (9 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 100 mg), [**Rh-2**] (11.46 mg, 0.02 mmol, 1.0 mol%) were added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (2 mL, 1 M) and pyridine-*d*5 (168.26 mg, 2.0 mmol, 160 µL). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (511.9 mg, 4.0 mmol, 0.58 mL), the glass vial was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with deuterium gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 ºC for 24 h. After the autoclave was carefully depressurized, trifluoroacetic anhydride (1.26 g, 6.0 mmol, 0.83 mL) and CH_2Cl_2 (1 mL) were added to the crude mixture and stirring was continued for 20 min at room temperature. The crude was then filtered over fritted funnel and the remaining solid was washed with ethyl acetate (2×10 mL). The combined solution was concentrated under reduced pressure and submitted to column chromatography (0-5% ethyl acetate in pentane) to obtain the deuterated TFA-protected piperidine as a colorless oil.

The deuterated piperidine hydrochloride was prepared according to the general procedure B starting from the TFA-analogue**.** The reaction mixture was stirred at room temperature for 1 h. Extraction and removal of all volatiles afforded the final product as a white solid (180 mg, 1.38 mmol, 69%-overall).

NMR analysis of the final product showed that the isotopologues of the piperidine hydrochloride were formed with isotopologues-d_9 and –d_{10} as the most dominant species according to ESI-MS (Supplementary Fig. 39). Deuterium scrambling at the α-position can be rationalized due to the formation of imine-enamine intermediates.

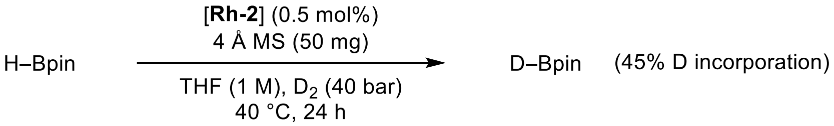
According to the proposed mechanism we would expect ^{1}H-labeling at two positions on the ring, C2 and C4 as described in the literature. However, while the obtained result showed ^{1}H-labeling at C2 and C4 positions as expected, we also observed ^{1}H-labeling at C3 position. This puzzling result can by rationalized due to the fact that HBpin can undergoes H/D exchange under the reaction conditions as shown in a separate experiment (see below).



```
Deuterium:  0-fold (%): 0.00   0.00
Deuterium:  1-fold (%): 0.00   0.00
Deuterium:  2-fold (%): 0.00   0.00
Deuterium:  3-fold (%): 1.83   0.69
Deuterium:  4-fold (%): 2.23   0.84
Deuterium:  5-fold (%): 2.77   1.04
Deuterium:  6-fold (%): 2.57   0.97
Deuterium:  7-fold (%): 12.87   4.85
Deuterium:  8-fold (%): 47.40   17.86
Deuterium:  9-fold (%): 100.00   37.69
Deuterium:  10-fold (%): 95.02   35.81
Deuterium:  11-fold (%): 0.67   0.25
Label Atom Sum: 8.93 (74.45%)
```

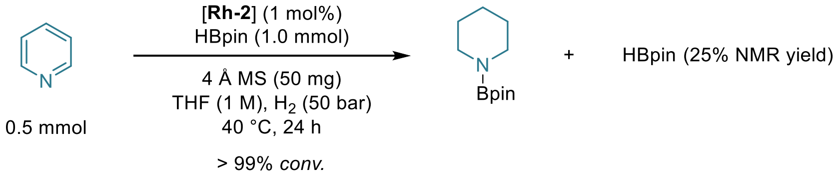
Supplementary Figure 39. Label-checker results of deuterated piperidine hydrochloride incorporated with ESI-MS.

C. D-incorporation into HBpin



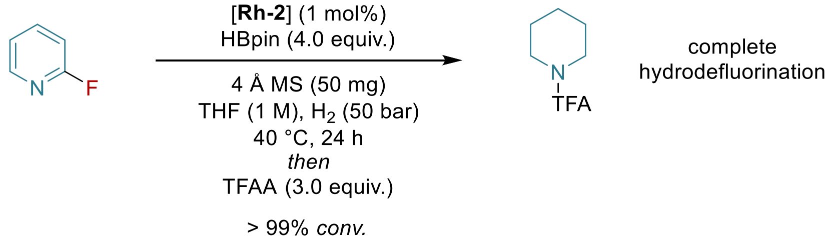
An oven-dried reaction vessel (9 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 50 mg), [**Rh-2**] (2.9 mg, 0.005 mmol, 0.5 mol%) were added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (1 mL, 1 M). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (127.9 mg, 1.0 mmol, 145 μL), the glass vial was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with deuterium gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 ºC for 24 h. After the autoclave was carefully depressurized, benzene-d_6 (20 μL, 0.225 mmol) was added to the reaction mixture as internal standard. The amount of D-incorporation was determined to be 45% by integration of the ^{2}H resonances of DBpin and C_6D_6.

D. Consumption of HBpin



An oven-dried reaction vessel (9 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 50 mg), [**Rh-2**] (2.9 mg, 0.005 mmol, 1.0 mol%) were added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (0.5 mL, 1 M) and pyridine (39.5 mg, 0.5 mmol, 40.3 µL). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (127.9 mg, 1.0 mmol, 145 µL), the glass vial was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 ^{o}C for 24 h. After the autoclave was carefully depressurized, benzene (20 µL, 0.224 mmol) was added to the reaction mixture as internal standard. The amount of unreacted HBpin was determined to be 25% by integration of the ^{1}H resonances of HBpin and C_6H_6.

E. Hydrogenation of 2-fluoropyridine

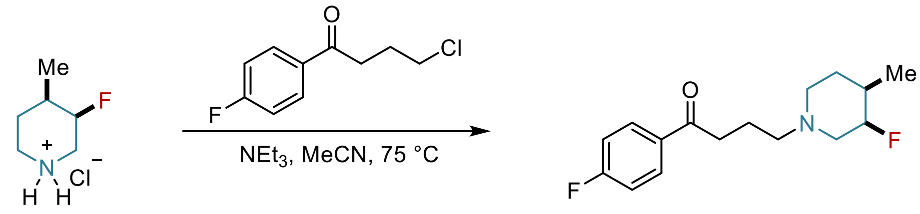


An oven-dried reaction vessel (9 mL screw-cap vial) equipped with a stirring bar was allowed to cool to room temperature under vacuum. Then activated 4 Å MS (crushed, 50 mg), [**Rh-2**] (5.7 mg, 0.01 mmol, 1 mol%) were added under air. The vial was then depressurized and pressurized with argon gas three times prior the addition of dry tetrahydrofuran (1 mL, 1 M) and 2-fluoropyridine (97.09 mg, 1.0 mmol, 86 µL). Upon the addition of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (511.9 mg, 4.0 mmol, 0.58 mL), the glass vial was placed in a 150 mL stainless steel autoclave under argon atmosphere. The autoclave was pressurized and depressurized with deuterium gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 ºC for 24 h. After the autoclave was carefully depressurized, trifluoroacetic anhydride (1.26 g, 6.0 mmol, 0.83 mL) and CH_2Cl_2 (1 mL) were added to the crude mixture and stirring was continued for 20 min at room temperature. Only the formation of the hydrodefluorinated side product was detected by NMR and GC-MS analysis of the crude reaction.

7. Applications

A. Drugs analogues

Synthesis of the fluorinated **Melperone** analogue



8, *d.r.* >99:1

49, **F-Melperone** analogue

4-Chloro-1-(4-fluorophenyl)butan-1-one (49.5 µL, 0.30 mmol, 1.0 equiv.), *cis*-3-fluoro-4-methylpiperidine hydrochloride (**8**) (92.0 mg, 0.60 mmol, 2.0 equiv.), triethylamine (125.5 µL, 0.90 mmol, 3.0 equiv.) and acetonitrile (0.6 mL, 0.5 M) were stirred in a sealed tube at 75 °C overnight. The mixture was partitioned between $NaHCO_3$ (sat. aq.) and CH_2Cl_2, extracted with CH_2Cl_2 (3×20 mL), dried over $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, 0-50% EtOAc in pentane) to yield the title compound as a white solid (71.1 mg, 0.25 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 8.01 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.11 (t, *J* = 8.7 Hz, 2H), 4.50 (d, *J* = 48.2 Hz, 1H), 3.20 – 3.07 (m, 1H), 2.98 (td, *J* = 7.1, 1.9 Hz, 2H), 2.86 (dm, *J* = 9.6 Hz, 1H), 2.48 – 2.36 (m, 2H), 2.22 – 1.86 (m, 4H), 1.71 – 1.43 (m, 3H), 1.03 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 198.96, 165.76 (d, *J* = 254.3 Hz), 133.61 (d, *J* = 3.0 Hz), 130.90 (d, *J* = 9.3 Hz), 115.70 (d, *J* = 21.8 Hz), 90.80 (d, *J* = 176.0 Hz), 57.42, 56.84 (d, *J* = 19.6 Hz), 52.84, 36.18, 34.02 (d, *J* = 20.3 Hz), 28.58 (d, *J* = 1.0 Hz), 21.55, 16.81 (d, *J* = 4.0 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -105.7, -198.8.

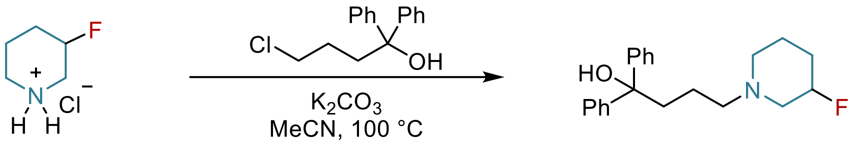
ESI-MS: calculated $[C_{16}H_{22}F_2NO]^+$: 282.1664, found: 282.1661.

IR ν = 2947 (m), 2816 (w), 2785 (w), 1682 (s), 1597 (s), 1505 (m), 1485 (m), 1412 (m), 1366 (m), 1343 (m), 1265 (m), 1250 (m), 1227 (s), 1204 (s), 1165 (m), 1150 (m), 1103 (m), 1026 (m), 1003 (m), 988 (m), 880 (w), 856 (s). 826 (s), 748 (m), 702 (w), 594 (m), 563 (s).

M.p: 92-93 °C.

Synthesis of the fluorinated **Diphenidol** analogues

F-Diphenidol:



2

50, **F-Diphenidol** analogue

A solution of 4-chloro-1,1-diphenylbutan-1-ol[20] (78 mg, 0.3 mmol, 1.5 equiv.), 3-fluoropiperidine hydrochloride (**2**) (27.9 mg, 0.2 mmol, 1.0 equiv.) and potassium carbonate (83 mg, 0.6 mmol, 3.0 equiv.) in acetonitrile (0.4 mL, 0.5 M) was stirred at 100 °C for 3 h. After addition of water (10 mL) and CH_2Cl_2 (10 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried over Mg_2SO_4 and purified by column chromatography on silica gel (0-30% EtOAc in pentane). The title compound was obtained as a white solid (24.7 mg, 0.075 mmol, 38%).

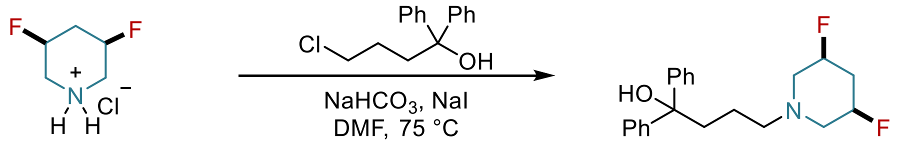
^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 7.57 – 7.49 (m, 4H), 7.38 – 7.27 (m, 4H), 7.25 – 7.16 (m, 2H), 4.70 (dm, *J* = 47.5 Hz, 1H), 2.82 – 2.66 (m, 1H), 2.62 – 2.34 (m, 5H), 2.32 – 2.19 (m, 1H), 2.15 – 1.88 (m, 2H), 1.88 – 1.79 (m, 1H), 1.72 – 1.54 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 148.44, 148.18, 128.11, 128.03, 126.43, 126.33, 126.31, 126.27, 87.58 (d, *J* = 172.4 Hz), 76.74, 59.28, 57.62 (d, *J* = 24.3 Hz), 52.69, 42.50, 30.24 (d, *J* = 19.2 Hz), 21.85, 21.49 (d, *J* = 8.7 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -180.8.

ESI-MS: calculated $[C_{21}H_{27}FNO]^+$: 328.2071, found: 328.2076.

IR ν = 3024.5 (m), 2947.3 (m), 2808.4 (m), 2769.8 (m), 1697.4 (w), 1597.1 (w), 1489.1 (m), 1442.8 (m), 1265.3 (w), 1111.1 (w), 1057.1 (m), 1018.5 (m), 964.4 (m), 864.1 (w), 748.4 (m), 702.1 (s).

M.p.: 81-82 °C.

F_2-Diphenidol:



4, *d.r.* >99:1

51, F_2-Diphenidol analogue

A solution of 4-chloro-1,1-diphenylbutan-1-ol[20] (52 mg, 0.2 mmol, 1.0 equiv.), *cis*-3,5-difluoropiperidine hydrochloride (**4**) (47 mg, 0.3 mmol, 1.5 equiv.), sodium bicarbonate (59 mg, 0.7 mmol, 3.5 equiv.) and sodium iodide (6 mg, 0.04 mmol, 0.2 equiv.) in DMF (0.66 mL, 0.3 M) was stirred at 75 °C for 25 h. After addition of EtOAc (10 mL), the organic phase was washed twice with aqueous LiCl solution (5 wt%) and brine. The organic phase was dried over Na_2SO_4 and purified by column chromatography on silica gel (0-30% EtOAc in pentane). The title compound was obtained as a white solid (40.7 mg, 0.12 mmol, 59%).

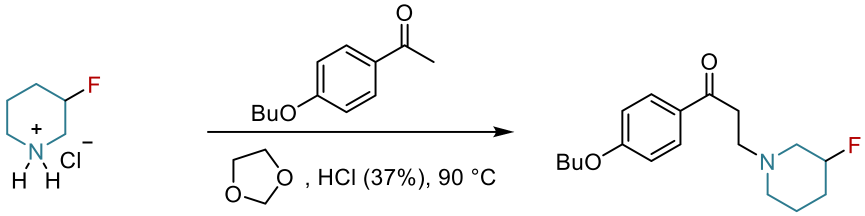
^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 7.38 (d, *J* = 7.5 Hz, 4H), 7.29 – 7.18 (m, 4H), 7.17 – 7.09 (m, 2H), 5.99 (s, 1H), 4.57 (dm, *J* = 46.4 Hz, 2H), 2.83 – 2.67 (m, 2H), 2.41 (dt, *J* = 20.4, 6.0 Hz, 5H), 2.15 – 2.02 (m, 2H), 1.82 – 1.49 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 147.78, 128.23, 126.67, 126.15, 85.27 (d, *J* = 175.3 Hz), 85.10 (d, *J* = 175.4 Hz), 77.09, 58.57, 56.60 (d, *J* = 1.5 Hz), 56.26 (d, *J* = 1.4 Hz), 41.68, 36.96 (t, *J* = 20.1 Hz), 21.71; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -184.7.

ESI-MS: calculated $[C_{21}H_{26}F_2NO]^+$: 346.1977, found: 346.1984.

IR ν = 3148 (w), 2924 (w), 2816 (w), 1489 (w), 1389 (w), 1265 (w), 1219 (m), 1103 (m), 1049 (m), 995 (s), 910 (m), 779 (m), 748 (m), 694 (s), 617 (m).

M.p.: 110-111 °C.

Synthesis of the fluorinated **Dyclonine** analogue



2

52, **F-Dyclonine** analogue

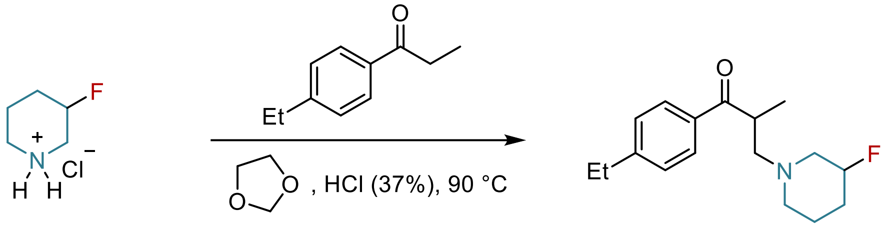
Following a literature procedure,[21] a mixture of 4′-butoxyacetophenone (134.6 mg, 0.7 mmol, 1.0 equiv.), 1,3-dioxolane (196 µL, 2.8 mmol, 4.0 equiv.), 3-fluoropiperidine hydrochloride (**2**) (111.7 mg, 0.8 mmol, 1.15 equiv.) and HCl (37%, 6 µL, 0.07 mmol, 0.1 equiv.) was heated at 90 °C for 8 h. The reaction mixture was cooled to room temperature, diluted with water and basified with a solution of NaOH (1M). The aqueous solution was extracted with EtOAc (3×20 mL) and the combined organic phase was washed with water, dried over $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, 0-50% EtOAc in pentane) to yield the title compound as a colorless oil (158.8 mg, 0.52 mmol, 74%).

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 7.92 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.65 (dm, *J* = 47.9, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.17 – 3.10 (m, 2H), 2.90 – 2.70 (m, 3H), 2.60 – 2.36 (m, 3H), 1.93 – 1.74 (m, 4H), 1.70 – 1.45 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 197.78, 163.30, 130.43, 129.86, 114.33, 88.18 (d, *J* = 171.6 Hz), 68.08, 57.84 (d, *J* = 22.8 Hz), 53.51, 53.27 (d, *J* = 0.8 Hz), 35.94, 31.26, 30.06 (d, *J* = 19.5 Hz), 22.06 (d, *J* = 6.9 Hz), 19.31, 13.94; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -180.9.

ESI-MS: calculated $[C_{18}H_{27}FNO_2]^+$: 308.2020, found: 308.2026.

IR ν = 2947 (m), 2870 (w), 2778 (w), 1674 (m), 1597 (s), 1574 (m), 1512 (w); 1466 (w), 1358 (w), 1312 (m), 1258 (s), 1211 (s), 1173 (s), 1111 (m), 1026 (m), 964 (m), 841 (m), 633 (w), 563 (w).

Synthesis of the fluorinated **Eperisone** analogue



2

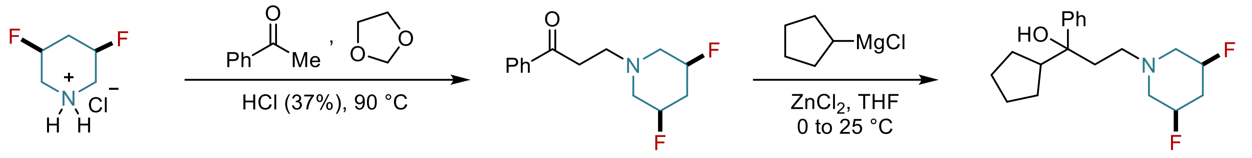
53, **F-Eperisone** analogue

Following a literature procedure,[21] a mixture of 4'-ethylpropiophenone (116 µL, 0.7 mmol, 1.0 equiv.), 1,3-dioxolane (196 µL, 2.8 mmol, 4.0 equiv.), 3-fluoropiperidine hydrochloride (**2**) (111.7 mg, 0.8 mmol, 1.15 equiv.) and HCl (37%, 6 µL, 0.07 mmol, 0.1 equiv.) was heated at 90 °C for 8 h. The reaction mixture was cooled to room temperature, diluted with water and basified with a solution of NaOH (1M). The aqueous solution was extracted with EtOAc (3×20 mL) and the combined organic phase was washed with water, dried over $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, 0-50% EtOAc in pentane) to yield the title compound as a colorless oil (157.7 mg, 0.57 mmol, 81%, *d.r.* 1:1). The signals of both diastereomer are reported. **^{1}H NMR** (300 MHz, $CDCl_3$, 299 K) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.51 (dm, *J* = 48.3 Hz, 1H), 3.70 (q, *J* = 7.3, 6.5 Hz, 1H), 2.96 – 2.77 (m, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.45 (m, 2H), 2.39 – 2.29 (m, 1H), 2.21 (td, *J* = 10.0, 2.8 Hz, 1H), 1.95 – 1.61 (m, 2H), 1.59 – 1.37 (m, 2H), 1.26 (t, *J* = 7.6 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 203.51, 203.49, 150.04, 134.61, 134.57, 128.66, 128.62, 128.29, 128.28, 88.39 (d, *J* = 171.5 Hz), 88.29 (d, *J* = 171.4 Hz), 61.51, 61.48, 58.41 (d, *J* = 11.5 Hz), 58.10 (d, *J* = 11.4 Hz), 53.61 (*J* = 16.0 Hz), 53.60 (d, *J* = 16.3 Hz), 38.88, 38.85, 30.42 (d, *J* = 1.3 Hz), 30.17 (d, *J* = 1.5 Hz), 29.06, 22.41 (d, *J* = 4.6 Hz), 22.30 (d, *J* = 4.6 Hz), 16.87, 16.84, 15.33; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -180.4, -180.5.

ESI-MS: calculated $[C_{17}H_{25}FNO]^+$: 278.1915, found: 278.1922.

IR ν = 2947 (m), 2870 (w), 2801 (w), 2778 (w), 1682 (s), 1605 (m), 1566 (w), 1458 (m), 1412 (w), 1373 (m), 1296 (w), 1227 (s), 1165 (m), 1111 (m), 1018 (m), 972 (s), 849 (m), 702 (w), 602 (w).

Synthesis of the fluorinated **Cycrimine** analogue



4, *d.r.* >99:1 **54** **55**, F$_2$-**Cycrimine** analogue

Following a literature procedure,[21] a mixture of acetophenone (93.5 µL, 0.8 mmol, 1.0 equiv.), 1,3-dioxolane (224 µL, 3.2 mmol, 4.0 equiv.), *cis*-3,5-difluoropiperidine hydrochloride (**4**) (151 mg, 0.96 mmol, 1.2 equiv.) and HCl (37%, 7 µL, 0.08 mmol, 0.1 equiv.) was heated at 90 °C for 8 h. The reaction mixture was cooled to room temperature, diluted with water and basified with a solution of NaOH (1M). The aqueous solution was extracted with EtOAc (3×20 mL) and the combined organic phase was washed with water, dried over $MgSO_4$, concentrated and purified by flash column chromatography (silica gel, 0-50% EtOAc in pentane) to yield 3-(*cis*-3,5-difluoropiperidin-1-yl)-1-phenylpropan-1-one (**54**) as a colorless oil (107 mg, 0.42 mmol, 53%).
^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ 7.99 – 7.91 (m, 2H), 7.61 – 7.55 (m, 1H), 7.50 – 7.44 (m, 2H), 4.64 (dm, *J* = 47.1 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.88 – 2.77 (m, 2H), 2.59 (dt, *J* = 11.3, 7.4 Hz, 2H), 2.38 – 2.20 (m, 1H), 2.03 – 1.87 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$, 299 K) δ 198.91, 136.91, 133.40, 128.82, 128.15, 85.79 (d, *J* = 175.3 Hz), 85.69 (d, *J* = 175,3f Hz), 56.83 (d, *J* = 2.6 Hz), 56.58 (d, *J* = 2.6 Hz), 52.56, 36.13, 35.97 (t, *J* = 20.3 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -182.9.
ESI-MS: calculated $[C_{14}H_{18}F_2NO]^+$: 254.1351, found: 254.1356;

Following a literature procedure,[22] to a Schlenk tube, $ZnCl_2$ (37.3 mg, 0.274 mmol, 1.1 equiv.) was added and melt-dried (>300 °C) by a heat gun under reduced pressure for 5 min. Cyclopentyl-MgCl (2 M in THF, 411 µL, 0.82 mmol, 3.3 equiv.) and THF (150 µL) were added to keep the concentration at ca. 1.5 M, and the solution was stirred at that temperature for 5 min. The solution was then cooled at 0 °C and 3-(*cis*-3,5-difluoropiperidin-1-yl)-1-phenylpropan-1-one (**54**) (62 mg, 0.25 mmol, 1.0 equiv.) was added and stirring was continued at 0 °C for 2 h. The resulting mixture was quenched with saturated aqueous solution of NH_4Cl (20 mL), extracted with EtOAc (3×30 mL), and washed with brine (30 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (0-10% EtOAc in pentane) to yield F_2-Cycrimine (**55**) as a white solid (21.2 mg, 0.066 mmol, 26%). NMR spectra contain traces of pentane.

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 7.46 – 7.39 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.16 (m, 1H), 5.96 (bs, 1H), 4.64 (dm, *J* = 46.8 Hz, 2H), 2.89 – 2.75 (m, 1H), 2.69 (dt, *J* = 14.8, 7.6 Hz, 1H), 2.45 – 2.14 (m, 7H), 2.10 – 1.90 (m, 1H), 1.80 – 1.69 (m, 3H), 1.68 – 1.58 (m, 1H), 1.57 – 1.44 (m, 2H), 1.41 – 1.23 (m, 2H), 1.13 – 0.99 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 147.73, 128.05, 126.03, 125.81, 85.31 (d, *J* = 173.4 Hz), 85.22 (d, *J* = 176.2 Hz), 78.73, 56.65 (d, *J* = 23.1 Hz), 56.41 (d, *J* = 23.4 Hz), 54.50, 51.53, 35.61, 35.50 (t, *J* = 20.3 Hz), 26.79, 26.62, 26.10, 25.56; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -182.8, -183.1.

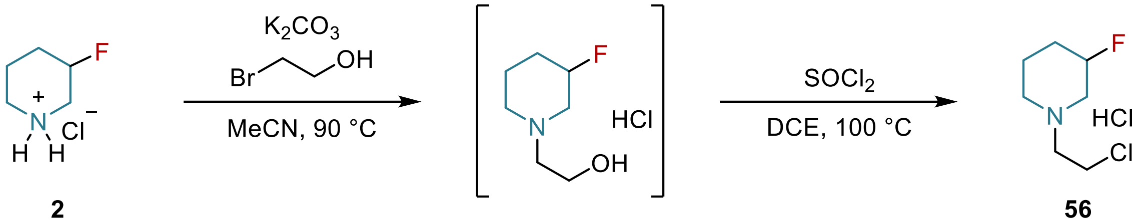
ESI-MS: calculated $[C_{19}H_{28}F_2NO]^+$: 324.2133, found: 324.2137.

IR ν = 3241 (m), 2940 (s), 2824 (m), 1443 (m), 1304 (m), 1219 (m), 1173 (m), 1142 (m), 1103 (s), 926 (s), 880 (w), 856 (m), 779 (m), 756 (s), 702 (s).

M.p.: 104-105 °C.

Synthesis of the fluorinated **Cloperastine** analogues

F-Cloperastine:



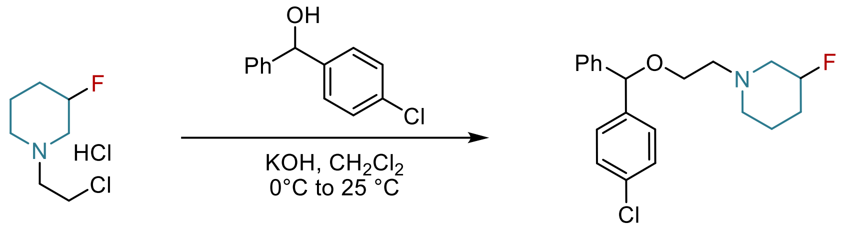
2 **56**

Following a literature procedure,[23] a suspension of 3-fluoropiperidine hydrochloride (**2**) (140 mg, 1.0 mmol, 1.0 equiv.), 2-bromo-1-ethanol (143 µL, 2.0 mmol, 2.0 equiv.), and K_2CO_3 (829 mg, 6.0 mmol, 6.0 equiv.) in dry acetonitrile (7 mL, 0.14 M) was heated at 90 °C for 20 h. The reaction mixture was evaporated to dryness, diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 2-(3-fluoropiperidin-1-yl)ethan-1-ol hydrochloride (122.4 mg, 0.83 mmol, 83%).

The alcohol (122.4 mg, 0.83 mmol, 1.0 equiv.), used without further purification, was dissolved in dry 1,2-DCE (2.5 mL, 0.33 M) and thionyl chloride (174 µL, 2.5 mmol, 3.0 equiv.) was added. The solution was heated at 100 °C for 3 h before being cooled with an ice bath. The reaction was quenched with solution of $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. HCl (4M in dioxane) was added to the reaction crude and the resulting precipitate was collected by filtration and washed with EtOAc to afford 1-(2-chloroethyl)-3-fluoropiperidine hydrochloride (**56**) as a white solid (61.2 mg, 0.3 mmol, 38%).

^{1}H NMR (300 MHz, CD_3OD, 299 K) δ 5.11 (d, *J* = 45.1 Hz, 1H), 4.02 (t, *J* = 6.2 Hz, 2H), 3.93 – 3.38 (m, 5H), 3.35 – 3.18 (m, 1H), 2.31 – 1.75 (m, 4H); **^{13}C NMR** (75 MHz, CD_3OD, 299 K) δ 86.37 (d, *J* = 171.6 Hz), 58.67, 55.22 (d, *J* = 21.0 Hz), 54.04, 37.69, 27.04, 18.72 (d, *J* = 2.6 Hz); **^{19}F{^{1}H} NMR** (282 MHz, CD_3OD, 299 K) δ -182.89.

ESI-MS: calculated $[C_7H_{14}ClFN]^+$: 166.0793, found: 166.0777.



56

57, **F-Cloperastine** analogue

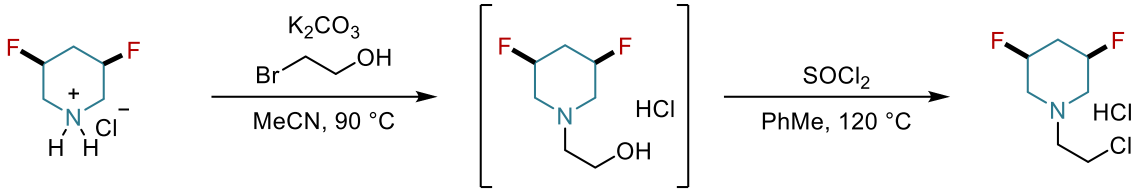
Following a modified literature procedure,[24] to a solution containing 4-chlorobenzhydrol (43.7 mg, 0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL, 0.1 M) was added 1-(2-chloroethyl)-3-fluoropiperidine hydrochloride (**56**) (61 mg, 0.3 mmol, 1.5 equiv.). The resulting solution was cooled to 0 °C followed by the addition of KOH (24 mg, 0.6 mmol, 3.0 equiv.). After the mixture had been stirred for 30 min at 0 °C and then overnight at room temperature, it was quenched with water and extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica (0-30% EtOAc in pentane) to give F-Cloperastine (**57**) as a colorless oil (24.9 mg, 0.07 mmol, 36%).

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 7.26 – 7.16 (m, 9H), 5.27 (s, 1H), 4.55 (dm, *J* = 48.0 Hz, 1H), 3.50 (t, *J* = 5.9 Hz, 2H), 2.81 – 2.59 (m, 3H), 2.52 – 2.38 (m, 2H), 2.34 – 2.25 (m, 1H), 1.90 – 1.65 (m, 2H), 1.64 – 1.37 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 141.83, 140.97, 133.26, 128.64, 128.62, 128.42, 127.81, 127.06, 88.21 (d, *J* = 171.4 Hz), 83.37, 67.05 (d, *J* = 1.3 Hz), 58.17 (d, *J* = 22.8 Hz), 57.96, 53.55, 30.04 (d, *J* = 19.5 Hz), 22.14 (d, *J* = 7.2 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -180.86.

ESI-MS: calculated $[C_{20}H_{24}ClFNO]^+$: 348.1525, found: 348.1518.

IR ν = 3295 (m), 2932 (w), 2693 (m), 2600 (m), 1659 (m), 1597 (w), 1489 (m), 1451 (m), 1273 (m), 1234 (w), 1134 (w), 1088 (s), 1049 (m), 1018 (m), 980 (s), 910 (m), 841 (m), 826 (m), 748 (m), 733 (m), 694 (s), 602 (m), 586 (m).

F_2-Cloperastine:



4, *d.r.* >99:1

58, *d.r.* >99:1

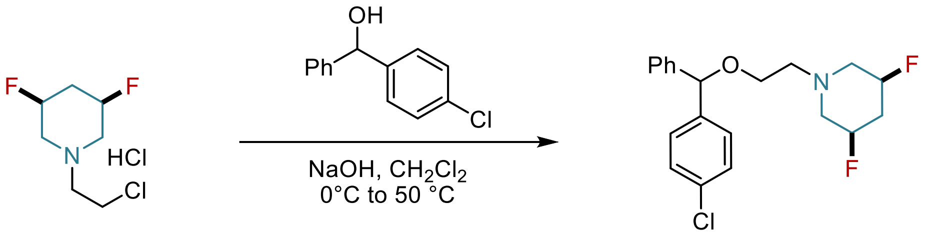
Following a literature procedure,[23] a suspension of 3,5-difluoropiperidine hydrochloride (**4**) (157 mg, 1.0 mmol, 1.0 equiv.), 2-bromo-1-ethanol (143 µL, 2.0 mmol, 2.0 equiv.), and K_2CO_3 (690 mg, 5.0 mmol, 5.0 equiv.) in dry acetonitrile (2.86 mL, 0.35 M) was heated at 90 °C for 20 h. The reaction mixture was evaporated to dryness, diluted with water (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give 2-(3,5-difluoropiperidin-1-yl)ethan-1-ol (152 mg, 0.92 mmol, 92%).

The alcohol (182 mg, 1.10 mmol, 1.0 equiv.), used without further purification, was dissolved in dry toluene (1.7 mL, 0.66 M) and thionyl chloride (240 µL, 3.30 mmol, 3.0 equiv.) was added. The solution was heated at 120 °C for 13 h before being cooled with an ice bath. The resulting precipitate was collected by filtration and washed with diethyl ether and pentane to give 1-(2-chloroethyl)-3,5-difluoropiperidine hydrochloride (**58**) as a brown solid (183 mg, 0.83 mmol, 76%, *d.r.* >99:1).

^{1}H NMR (400 MHz, CD_3OD, 299 K) δ 5.17 (d, *J* = 44.6 Hz, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 3.99 – 3.90 (m, 2H), 3.77 – 3.48 (m, 4H), 2.65 – 2.47 (m, 1H), 2.18 (td, *J* = 44.3, 16.5 Hz, 1H); **^{13}C NMR** (101 MHz, CD_3OD, 299 K) δ 85.10 (d, *J* = 175.4 Hz), 58.83, 55.40, 37.22, 31.15 (t, *J* = 20.1 Hz); **^{19}F{^{1}H} NMR** (376 MHz, CD_3OD, 299 K) δ -182.89.

ESI-MS: calculated $[C_7H_{13}ClF_2N]^+$: 184.0699, found: 184.0700.

IR ν = 2569 (w), 2508 (w), 1451 (m), 1427 (m), 1343 (w), 1304 (w), 1211 (w), 1126 (s), 1088 (m), 972 (w), 918 (m), 903 (m), 787 (m), 664 (m), 571 (s), 556 (s).



58, *d.r.* >99:1

59, **F$_2$-Cloperastine** analogue

Following a modified literature procedure,[24] to a solution containing 4-chlorobenzhydrol (43.7 mg, 0.2 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (2.0 mL, 0.1 M) was added 1-(2-chloroethyl)-3,5-difluoropiperidine hydrochloride (**58**) (53 mg, 0.24 mmol, 1.2 equiv.). The resulting solution was cooled at 0 °C followed by the addition of NaOH powder (24 mg, 0.6 mmol, 3.0 equiv.). After the mixture had been stirred for 30 min at 0 °C and then for 72 h at 50 °C, it was quenched with water and extracted with CH$_2$Cl$_2$ (3×20 mL). The organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica (0-30% EtOAc in pentane) to give F$_2$-Cloperastine (**59**) as a colorless oil (16.7 mg, 0.046 mmol, 23%).

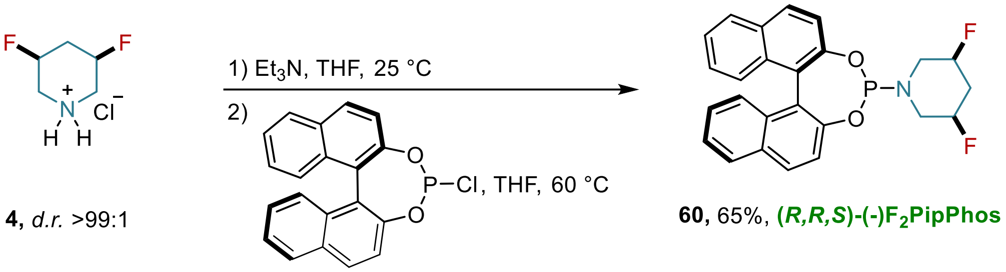
^{1}H NMR (300 MHz, CDCl$_3$, 299 K) δ 7.37 – 7.24 (m, 9H), 5.34 (s, 1H), 4.62 (dm, *J* = 47.1 Hz, 2H), 3.58 (t, *J* = 5.6 Hz, 2H), 2.97 – 2.83 (m, 2H), 2.80 (t, *J* = 5.6 Hz, 2H), 2.65 – 2.51 (m, 2H), 2.42 – 2.17 (m, 1H), 2.01 – 1.78 (m, 1H); **^{13}C NMR** (75 MHz, CDCl$_3$, 299 K) δ 141.71, 140.86, 133.35, 128.69, 128.67, 128.37, 127.90, 127.03, 86,90 (d, *J* = 175.1 Hz), 85.77 (d, *J* = 175.2 Hz), 83.50, 66.91, 57.26, 57.11 (t, *J* = 2.0 Hz), 56.77 (t, *J* = 2.2 Hz), 36.12 (t, *J* = 20.2 Hz); **^{19}F{^{1}H} NMR** (282 MHz, CDCl$_3$, 299 K) δ -183.14.

ESI-MS: calculated [$C_{20}H_{22}ClF_2NO$ +Na]$^+$: 388.1250, found: 388.1246.

IR ν = 2947 (w), 2801 (w), 1597 (w), 1489 (m), 1451 (w), 1358 (w), 1265 (w), 1188 (w), 1088 (s), 995 (s), 918 (m), 795 (m), 756 (m), 717 (m), 702 (s), 625 (m).

B. Fluorinated ligand analogue:

Synthesis of the fluorinated **PipPhos** analogue



4, *d.r.* >99:1

60, 65%, **(*R,R,S*)-(-)F$_2$PipPhos**

Following a modified literature procedure,[25] a 25 mL Schlenk flask was charged with (*R*)-(+)-1,1'-bi(2-naphthol) (78.7 mg, 0.275 mmol, 1.1 equiv.), phosphorus trichloride (0.24 mL, 2.75 mmol, 11 equiv.), dimethylformamide (1.5 µL, 0.02 mmol, 0.08 equiv.) under argon. The reaction mixture was heated to 50 °C for 15 min and all volatiles were removed under reduced pressure. CH_2Cl_2 (3×2 mL) was used to remove the traces of phosphorus trichloride. The resulting oil was kept under vacuum for 1 h and was used directly in next step.

In a separate 25 mL Schlenk flask, a mixture of *cis*-3,5-difluoropiperidine hydrochloride (**4**) (39.4 mg, 0.25 mmol, 1.0 equiv.), triethylamine (0.1 mL, 0.75 mmol, 3.0 equiv.) and THF (1 mL, 0.25M) was stirred at room temperature for 1 h. Then, the above made chlorophosphite was dissolved in THF (3×2 mL) and was transferred to the reaction flask. The reaction mixture was warmed to 60 °C and stirring was continued for 18 h. The resulting precipitate was removed by filtration and washed with EtOAc. The filtrate was concentrated and purified by flash column chromatography (0-10% EtOAc in pentane) to yield the desired ligand as a white solid (70.5 mg, 0.162 mmol, 65%).

Single crystals of the title compound suitable for X-ray diffraction analysis were obtained by crystallization at room temperature from (1:1) a mixture of *n*-hexane and ethyl acetate (slow evaporation of solvents). Detailed crystallographic data are reported in the corresponding section of the Supplementary Information.

^{1}H NMR (600 MHz, C_6D_6, 299 K) δ 7.66 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.15 – 7.11 (m, 2H), 6.95 – 6.91 (m, 2H), 3.89 (dm, *J* = 47.4 Hz, 1H), 3.79 (dm, *J* = 47.4 Hz, 1H), 3.16 – 3.02 (m, 2H), 2.69 (dq, *J* = 13.3, 6.2 Hz, 1H), 2.53 (dq, *J* = 13.1, 6.5 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.52 (h, *J* = 11.6 Hz, 1H); **^{1}H{^{19}F} NMR** (600 MHz, C_6D_6, 299 K) δ

7.66 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.15 – 7.11 (m, 2H), 6.93 (tdd, J = 8.2, 4.6, 2.6 Hz, 2H), 3.87 (tt, J = 7.8, 4.1 Hz, 1H), 3.81 (tt, J = 8.6, 4.1 Hz, 1H), 3.11 (dt, J = 12.8, 4.6 Hz, 1H), 3.07 (ddd, J = 13.4, 7.9, 4.3 Hz, 1H), 2.69 (ddd, J = 13.4, 7.8, 5.5 Hz, 1H), 2.53 (ddd, J = 12.8, 7.8, 5.5 Hz, 1H), 1.78 (dt, J = 12.7, 4.1 Hz, 1H), 1.52 (dt, J = 12.7, 8.6 Hz, 1H); **^{1}H{^{31}P} NMR** (600 MHz, C_6D_6, 299 K) δ 7.66 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.13 (t, J = 7.4 Hz, 2H), 6.95 – 6.91 (m, 2H), 3.89 (d, J = 47.4 Hz, 1H), 3.80 (d, J = 47.4 Hz, 1H), 3.09 (dt, J = 28.5, 12.7 Hz, 2H), 2.69 (dt, J = 13.6, 6.7 Hz, 1H), 2.53 (dt, J = 13.6, 7.1 Hz, 1H), 1.78 (td, J = 16.5, 12.4 Hz, 1H), 1.59 – 1.48 (m, 1H); **^{1}H{^{19}F, ^{31}P} NMR** (600 MHz, C_6D_6, 299 K) δ 7.66 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.13 (t, J = 7.4 Hz, 2H), 6.95 – 6.91 (m, 2H), 3.87 (tt, J = 7.8, 4.1 Hz, 1H), 3.81 (tt, J = 8.6, 4.1 Hz, 1H), 3.11 (dd, J = 12.8, 4.1 Hz, 1H), 3.07 (dd, J = 13.4, 4.3 Hz, 1H), 2.69 (dd, J = 13.4, 7.8 Hz, 1H), 2.53 (dd, J = 12.8, 7.8 Hz, 1H), 1.78 (dt, J = 12.7, 4.1 Hz, 1H), 1.52 (dt, J = 12.7, 8.6 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$, 299 K) δ 149.04 (×2), 149.00, 132.87 (d, J = 1.6 Hz), 132.70 (d, J = 1.1 Hz), 131.63 (d, J = 0.6 Hz), 131.05, 130.61, 130.40, 128.52 (d, J = 1.8 Hz), 127.09, 127.07, 126.47, 126.37, 125.14, 125.05, 123.96 (d, J = 5.0 Hz), 122.95 (d, J = 2.3 Hz), 121.89 (d, J = 1.7 Hz), 121.60, 84,95 (ddd, J = 180.7, 8.2, 5.3 Hz), 84.70 (ddd, J = 181.4, 8.8, 3.5 Hz), 47.91 (t, J = 25.0 Hz), 47.48 (dd, J = 26.2, 14.8 Hz), 37.12 (t, J = 20.3 Hz); **^{13}C{^{19}F} NMR** (151 MHz, $CDCl_3$, 299 K) δ 149.04 (×2), 149.00, 132.87 (d, J = 1.5 Hz), 132.70 (d, J = 1.1 Hz), 131.63, 131.05, 130.61, 130.40, 128.52 (d, J = 1.8 Hz), 127.09, 127.07, 126.47, 126.37, 125.14, 125.05, 123.96 (d, J = 5.0 Hz), 122.95 (d, J = 2.2 Hz), 121.89 (d, J = 1.7 Hz), 121.60, 84.95 (d, J = 5.4 Hz), 84.70 (d, J = 3.3 Hz), 47.91 (d, J = 24.9 Hz), 47.48 (d, J = 14.6 Hz), 37.12; **^{19}F NMR** (564 MHz, C_6D_6, 299 K) δ -180.67 – -180.91 (m), -181.68 – -181.94 (m); **^{19}F{^{1}H} NMR** (564 MHz, C_6D_6, 299 K) δ -180.80 (d, J = 6.2 Hz), -181.80 (d, J = 6.2 Hz); **^{19}F{^{31}P, ^{1}H} NMR** (564 MHz, C_6D_6, 299 K) δ -180.80 (d, J = 6.2 Hz), -181.80 (d, J = 6.2 Hz); **^{19}F{^{31}P} NMR** (564 MHz, C_6D_6, 299 K) δ -180.80 (dm, J = 47.4 Hz), -181.80 (dm, J = 47.4 Hz); **^{31}P NMR** (243 MHz, C_6D_6, 299 K) δ 144.8; **^{31}P{^{1}H} NMR** (243 MHz, C_6D_6, 299 K) δ 144.8.

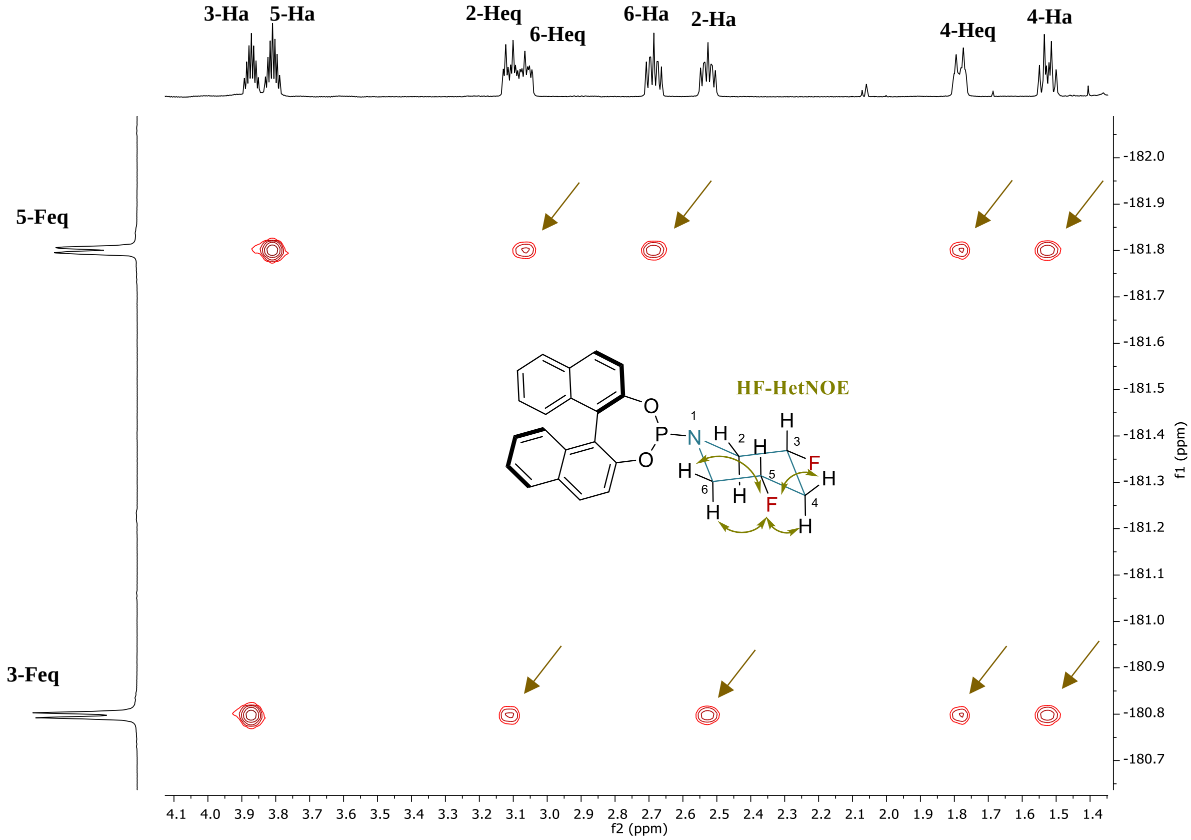
ESI-MS: calculated $[C_{25}H_{20}F_2NO_2P + Na]^+$: 458.1097, found: 458.1094.

IR ν = 3055.3 (w), 2939.6 (w), 1735.9 (w), 1589.4 (w), 1504.5 (w), 1465.9 (w), 1327.1 (m), 1226.7 (m), 1195.9 (m), 1141.9 (m), 1072.5 (m), 1010.7 (m), 941.3 (s), 902.7 (m), 825.6 (s), 802.4 (m), 748.4 (s), 686.7 (m), 632.7 (m), 594.1 (m), 555.5 (s).

M.p.: 154-156 °C.

$[\alpha]_D^{25}$ = -446.4 (0.011 M in CH_3Cl).

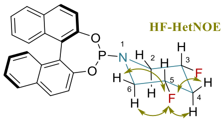
In order to prove whether the fluorine atoms are occupying axial or equatorial positions, we conducted a series of NMR studies that includes NOE and HF-HetNOE experiments. HF-HetNOE experiment showed unequivocally that the fluorine atoms are occupying equatorial positions (Supplementary Fig. 40).



Supplementary Figure 40. 2D HF-Het-NOESY experiment for **60**.

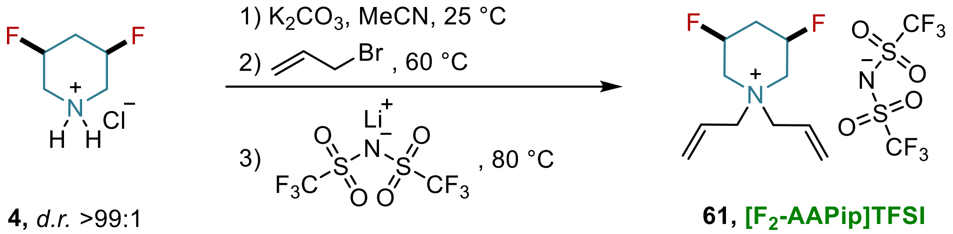
Note: In the solid state of the title compound we observed that the fluorine atoms are occupying axial positions (See X-Ray structure), while in solution, we observed only the equatorial conformer. We measured NMR spectra in C_6D_6 and $CDCl_3$ as well and in both cases the equatorial conformer was observed (^{3}J(F,H_a) < 15 Hz → F_{eq}).

Supplementary Table 10. Summary of NMR data for **60**.

	position	**δ(^{1}H) (eq/ax)**	**^2J(F,H) Hz**	**^3J(F,H) Hz**	**^2J(H,H) Hz**	**^3J(H,H) Hz**
	2	3.11/2.53		**2Ha3Fe: 6.8** 2He3Fe: 12.8	12.8	3Ha2Ha: 7.8 3Ha2He:4.1
	3	3.89	47.4			3Ha4Ha: 8.6 3Ha4He:4.1
	4	1.78/1.52		**4Ha3Fe: 11.7** **4Ha5Fe: 11.7** 4He3Fe: 16.5 4He5Fe: 16.5	12.7	
	5	3.79	47.4			5Ha6Ha: 7.8 5Ha4Ha: 8.6 5Ha4He: 4.1
	6	3.07/2.69		**6Ha5Fe: 6.4** 6He5Fe: 12.8	13.4	5Ha6He: 4.3

C. Fluorinated ionic liquids analogue:

Synthesis of the fluorinated **[AAPip]TFSI** analogue



4, *d.r.* >99:1

61, [F_2-AAPip]TFSI

Following a modified literature procedure,[26] a mixture of *cis*-3,5-difluoropiperidine hydrochloride (**4**) (78.8 mg, 0.5 mmol, 1.0 equiv.), K_2CO_3 (276.4 mg, 2.0 mmol, 4.0 equiv.) and MeCN (2 mL, 0.25 M) was stirred at room temperature for 30 min. Then, allyl bromide (0.17 mL, 2.0 mmol, 4.0 equiv.) was added and the reaction mixture was heated to 60 °C for 18 h. The resulting precipitate was filtrated and washed with EtOAc (10 mL). The crude was then concentrated under reduced pressure and used in next step without further purification.

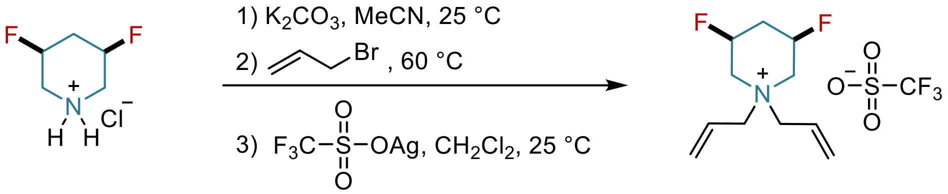
To a solution of piperidinium bromide in distilled water (10 mL) was added lithium bis(trifluoromethanesulfonyl)imide (215.3 mg, 0.75 mmol, 1.5 equiv.). The reaction mixture was stirred for 18 h at 80 °C. After the reaction mixture was cooled to room temperature, distilled water (10 mL) was added and the mixture was extracted with EtOAc (3×20 mL). The separated organic layer was washed with distilled water (2×20 mL), dried with $MgSO_4$ and purified by flash column chromatography (0-10% MeOH in CH_2Cl_2) to yield *cis*-1,1-diallyl-3,5-difluoropiperidinium bis((trifluoromethyl)sulfonyl)amide [F_2-AAPip]TFSI (**61**) as a yellow oil (121 mg, 0.251 mmol, 50% overall).

^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ 5.94 (dt, J = 16.0, 7.2 Hz, 2H), 5.87 – 5.68 (m, 4H), 5.17 (dm, J = 46.1 Hz, 2H), 4.26 (d, J = 7.1 Hz, 2H), 3.98 – 3.83 (m, 4H), 3.72 (d, J = 37.0 Hz, 2H), 2.66 (d, J = 14.2 Hz, 1H), 2.36 (td, J = 43.1, 42.2, 14.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$, 299 K) δ 131.74, 131.50, 123.51, 122.16, 119.86 (q, J = 320.9 Hz, ×2), 84.03 (d, J = 178.5 Hz, ×2), 67.05, 62.88 (t, J = 8.7 Hz), 58.49 (d, J = 19.7 Hz, ×2), 29.97 (t, J = 20.2 Hz); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$, 299 K) δ -78.8, -177.0.

ESI-MS: calculated $[C_{11}H_{18}NF_2]^+$: 202.1402, found: 202.1409; **ESI-MS:** calculated $[C_2F_6NO_4S_2]^-$: 279.9178, found: 279.9199.

IR ν = 1465.9 (w), 1427.4 (w), 1350.2 (m), 1327.1 (m), 1180.5 (s), 1134.2 (s), 1049.3 (s), 956.7 (m), 786.9 (w), 740.7 (w), 617.2 (s), 601.8 (s), 570.9 (s).

Synthesis of the fluorinated **[AAPip]OTf** analogue



4, *d.r.* >99:1

62, **[F$_2$-AAPip]OTf**

Following a modified literature procedure,[26] a mixture of *cis*-3,5-difluoropiperidine hydrochloride (**4**) (78.8 mg, 0.5 mmol, 1.0 equiv.), K_2CO_3 (276.4 mg, 2.0 mmol, 4.0 equiv.) and MeCN (2 mL, 0.25 M) was stirred at room temperature for 30 min. Then, allyl bromide (0.17 mL, 2.0 mmol, 4.0 equiv.) was added and the reaction mixture was heated to 60 °C for 18 h. The resulting precipitate was filtrated and washed with EtOAc (10 mL). The residue was concentrated under reduced pressure and used in next step without further purification.

To a solution of piperidinium bromide in dry CH_2Cl_2 (5 mL) was added silver trifluoromethanesulfonate (192.7 mg, 0.75 mmol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography (0-10% MeOH in CH_2Cl_2) to yield *cis*-1,1-diallyl-3,5-difluoropiperidinium trifluoromethanesulfonate [F$_2$-AAPip]OTf (**62**) as a yellow solid (71.1 mg, 0.202 mmol, 40% overall).

^{1}H NMR (300 MHz, $CDCl_3$, 299 K) δ 6.11 – 5.67 (m, 6H), 5.17 (d, *J* = 46.3 Hz, 2H), 4.23 (d, *J* = 7.1 Hz, 2H), 4.16 – 3.76 (m, 6H), 2.81 – 2.29 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$, 299 K) δ 131.51, 131.11, 123.72, 122.46, 120.6 (q, *J* = 319.5 Hz), 84.34 (d, *J* = 177.9 Hz, ×2), 66.63, 62.51 (t, *J* = 9.2 Hz), 58.46 (d, *J* = 18.8 Hz, ×2), 30.00 (t, *J* = 20.0 Hz); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$, 299 K) δ -78.6, -176.7.

ESI-MS: calculated $[C_{11}H_{18}NF_2]^+$: 202.1402, found: 202.1418; **ESI-MS:** calculated $[CF_3O_3S]^-$: 148.9526, found: 148.9519.

IR ν = 1458.2 (w), 1427.4 (w), 1280.8 (m), 1249.9 (s), 1226.7 (m), 1157.3 (s), 1126.5 (m), 1026.1 (s), 949.1 (m), 879.6 (m), 632.7 (s), 570.9 (m).

8. References:

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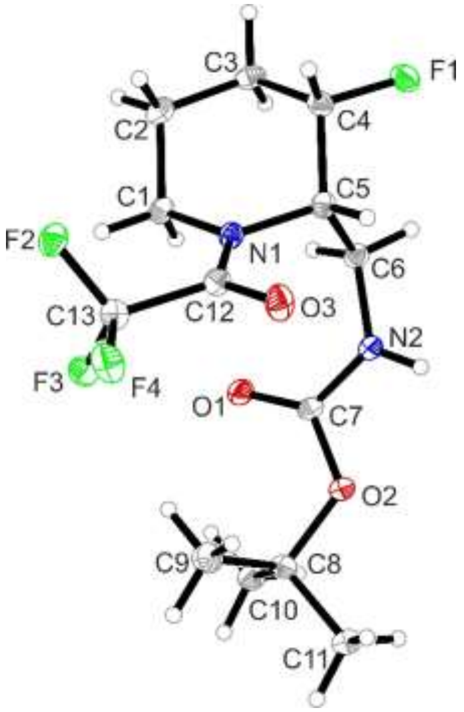
9. X-ray crystal structure analysis

X-ray crystal structure analysis of **29 (glo9085)**:

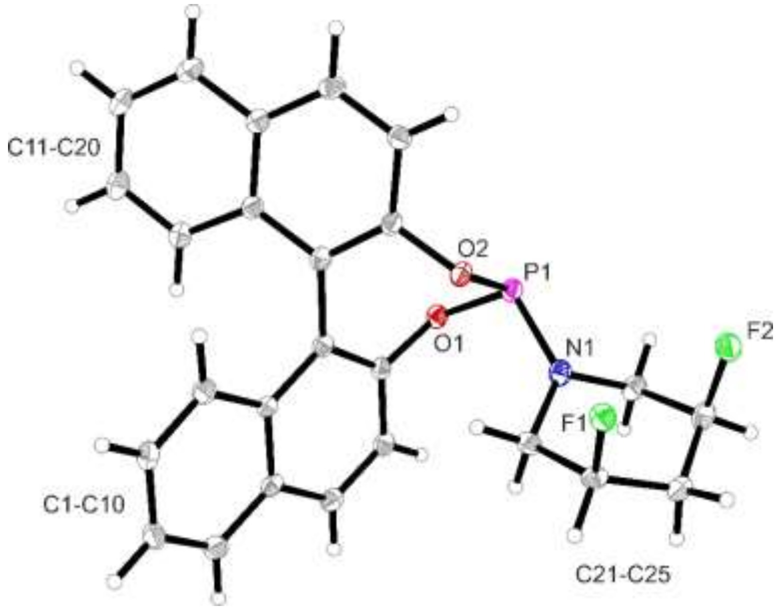
A colorless plate-like specimen of $C_{13}H_{20}F_4N_2O_3$, approximate dimensions 0.030 mm x 0.120 mm x 0.220 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1859 frames were collected. The total exposure time was 26.82 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 27488 reflections to a maximum θ angle of 66.67° (0.84 Å resolution), of which 2727 were independent (average redundancy 10.080, completeness = 99.9%, R_{int} = 12.14%, R_{sig} = 5.29%) and 1924 (70.55%) were greater than $2\sigma(F^2)$. The final cell constants of a = 11.5651(5) Å, b = 12.1973(5) Å, c = 11.5976(5) Å, β = 109.315(3)°, volume = 1543.91(12) $Å^3$, are based upon the refinement of the XYZ-centroids of 2671 reflections above 20 σ(I) with $9.361° < 2\theta < 124.2°$. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.807. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7860 and 0.9660. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1/n$, with Z = 4 for the formula unit, $C_{13}H_{20}F_4N_2O_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 206 variables converged at R1 = 4.54%, for the observed data and wR2 = 11.67% for all data. The goodness-of-fit was 0.998. The largest peak in the final difference electron density synthesis was 0.210 $e^-/Å^3$ and the largest hole was -0.247 $e^-/Å^3$ with an RMS deviation of 0.055 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.412 g/cm^3 and F(000), 688 e^-. CCDC number: 1845054.



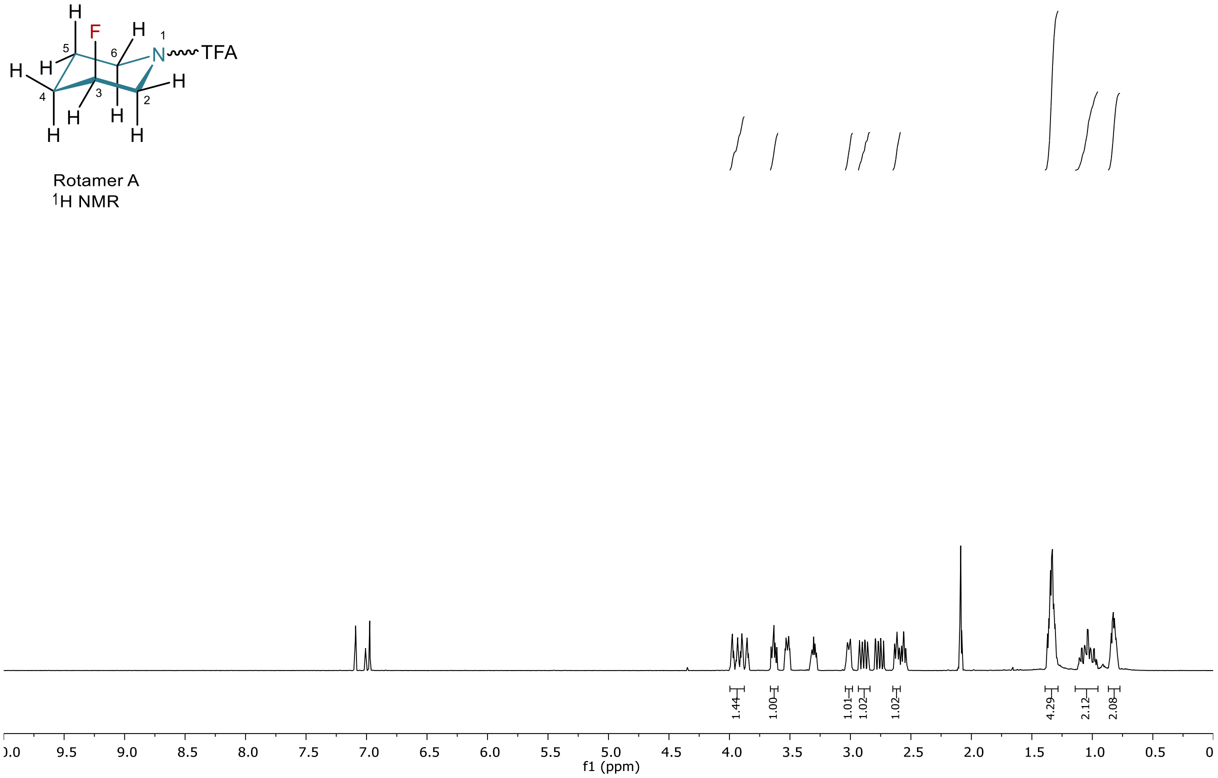
Supplementary Figure 41. Crystal structure of compound **29** (Thermals ellipsoids are shown with 30% probability).

X-ray crystal structure analysis of **60 (glo9114)**:

A colorless plate-like specimen of $C_{25}H_{20}F_2NO_2P$, approximate dimensions 0.050 mm x 0.090 mm x 0.220 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1586 frames were collected. The total exposure time was 24.37 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 16007 reflections to a maximum θ angle of 66.66° (0.84 Å resolution), of which 3588 were independent (average redundancy 4.461, completeness = 99.8%, R_{int} = 7.46%, R_{sig} = 6.23%) and 3049 (84.98%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 9.5933(3) Å, $\underline{b}$ = 7.7083(3) Å, $\underline{c}$ = 13.8260(5) Å, β = 90.061(2)°, volume = 1022.40(6) $Å^3$, are based upon the refinement of the XYZ-centroids of 5803 reflections above 20 $\sigma(I)$ with $11.22° < 2\theta < 133.1°$. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.803. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7270 and 0.9270. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1$, with Z = 2 for the formula unit, $C_{25}H_{20}F_2NO_2P$. The final anisotropic full-matrix least-squares refinement on F^2 with 280 variables converged at R1 = 4.52%, for the observed data and wR2 = 11.36% for all data. The goodness-of-fit was 1.058. The largest peak in the final difference electron density synthesis was 0.250 $e^-/Å^3$ and the largest hole was -0.231 $e^-/Å^3$ with an RMS deviation of 0.053 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.414 g/cm^3 and F(000), 452 e^-. Flack parameter was refined to -0.01(3). CCDC number: 1845055.



Supplementary Figure 42. Crystal structure of compound **60** (Thermals ellipsoids are shown with 30% probability).



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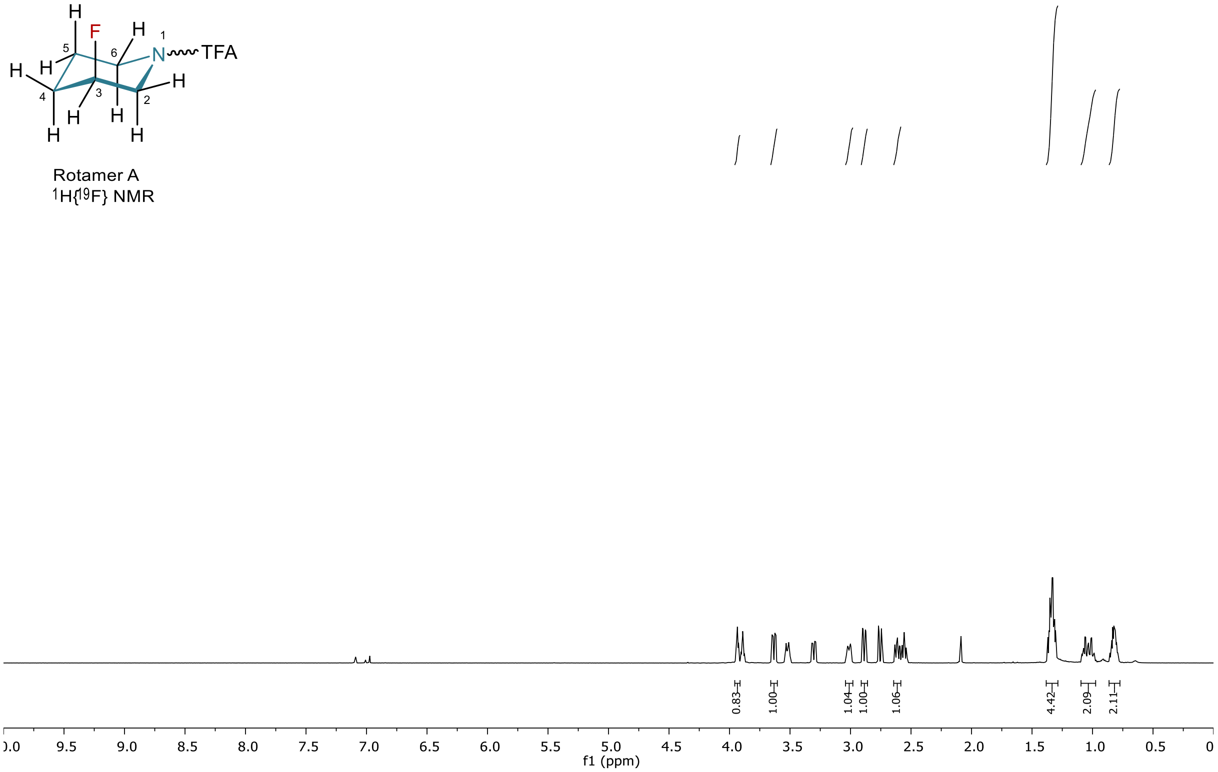
^{1}H NMR



Rotamer A
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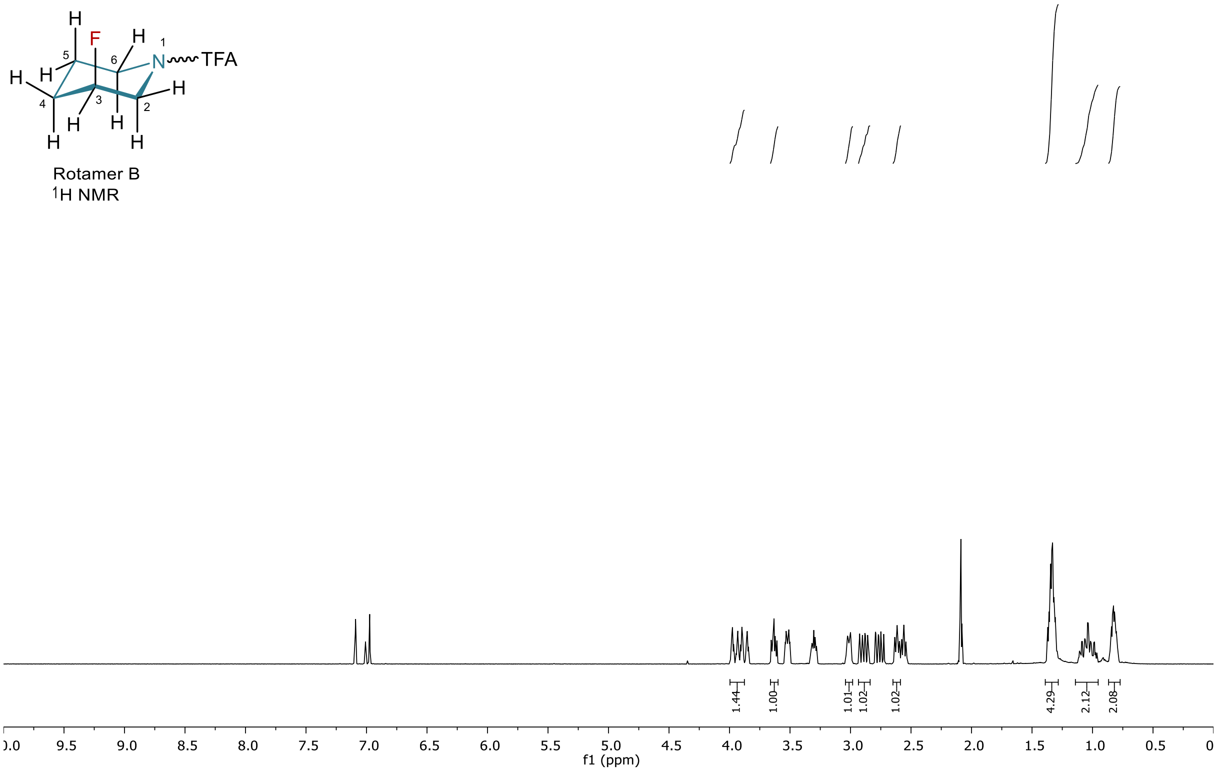

Rotamer B
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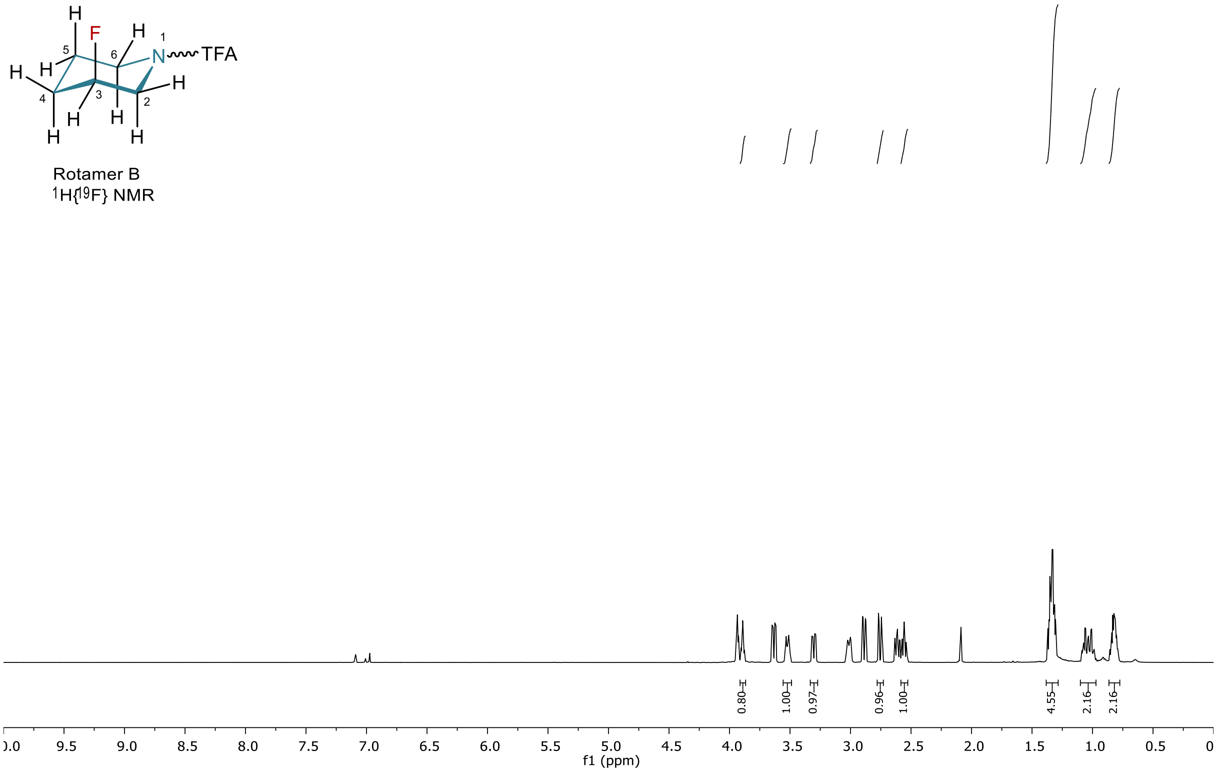

Rotamer B
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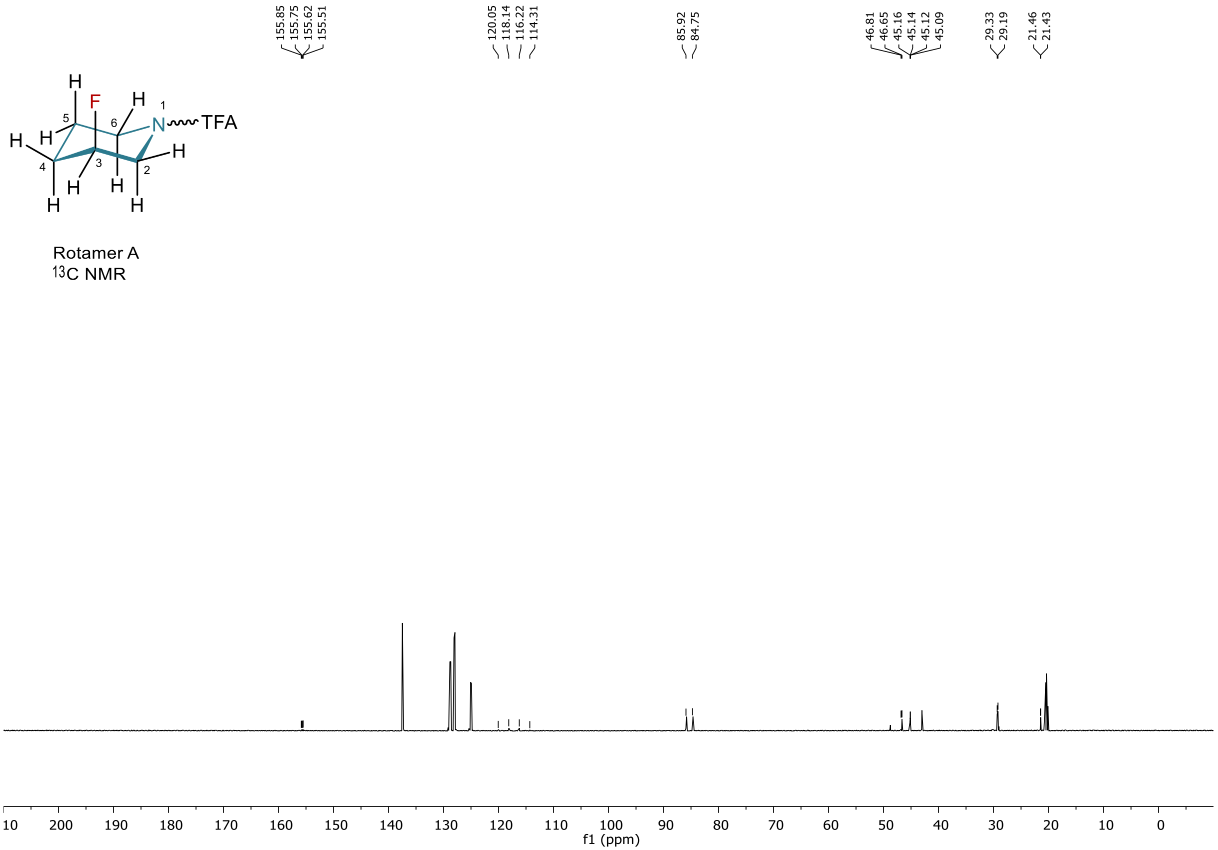

Rotamer A
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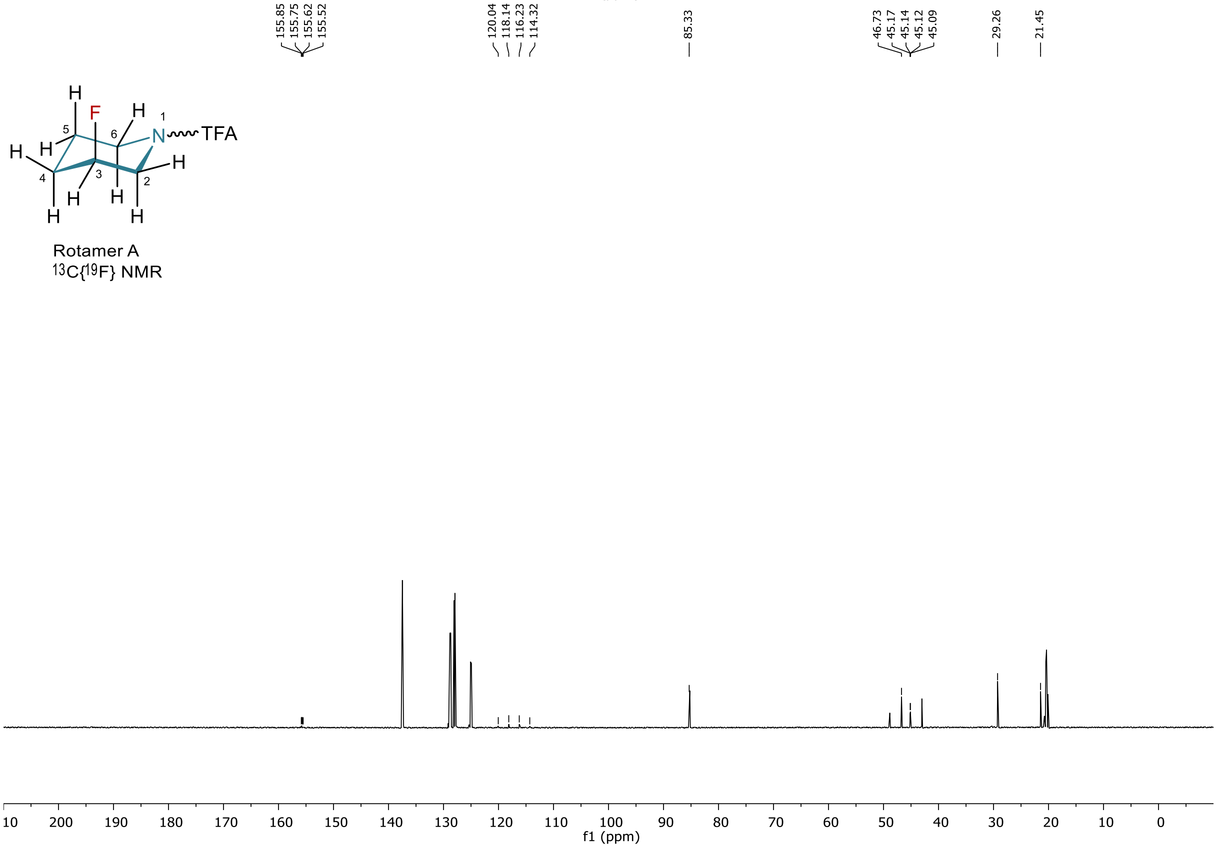

Rotamer A
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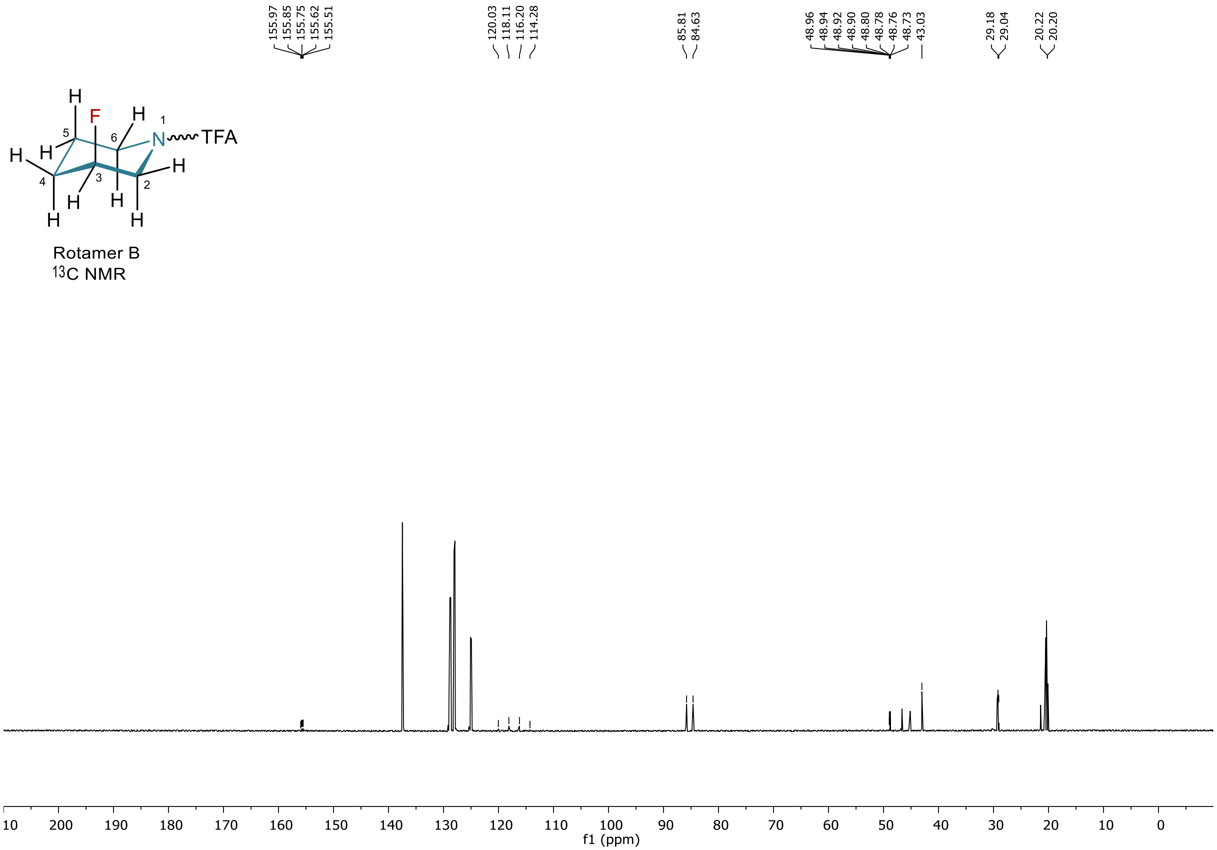
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Rotamer B
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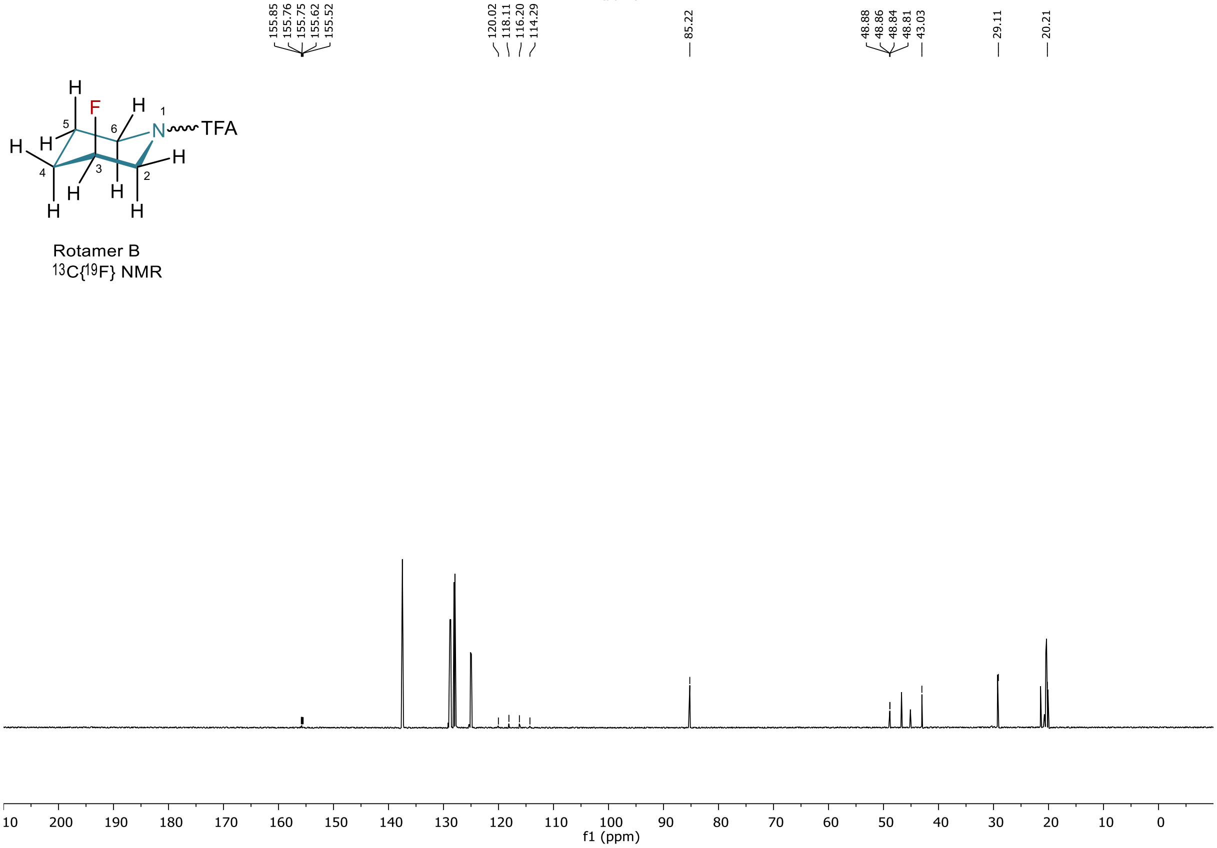
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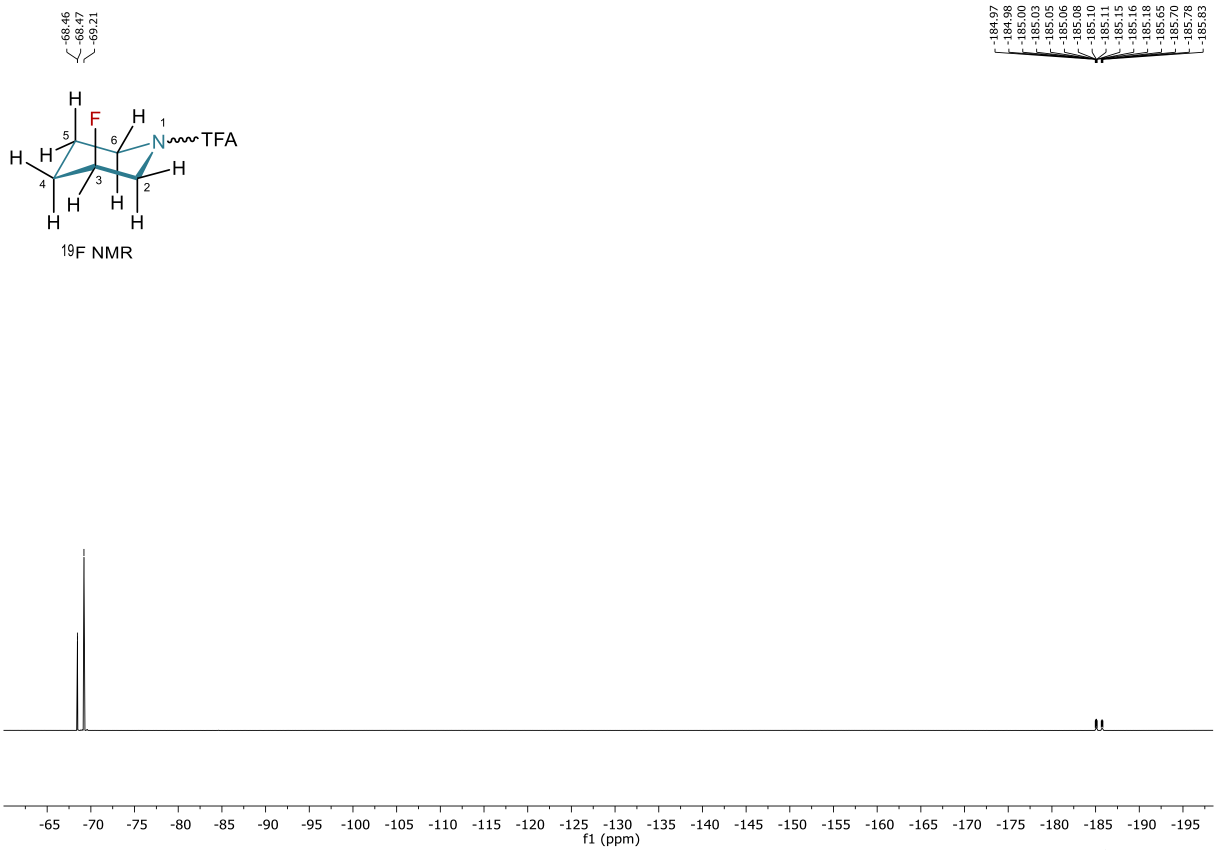
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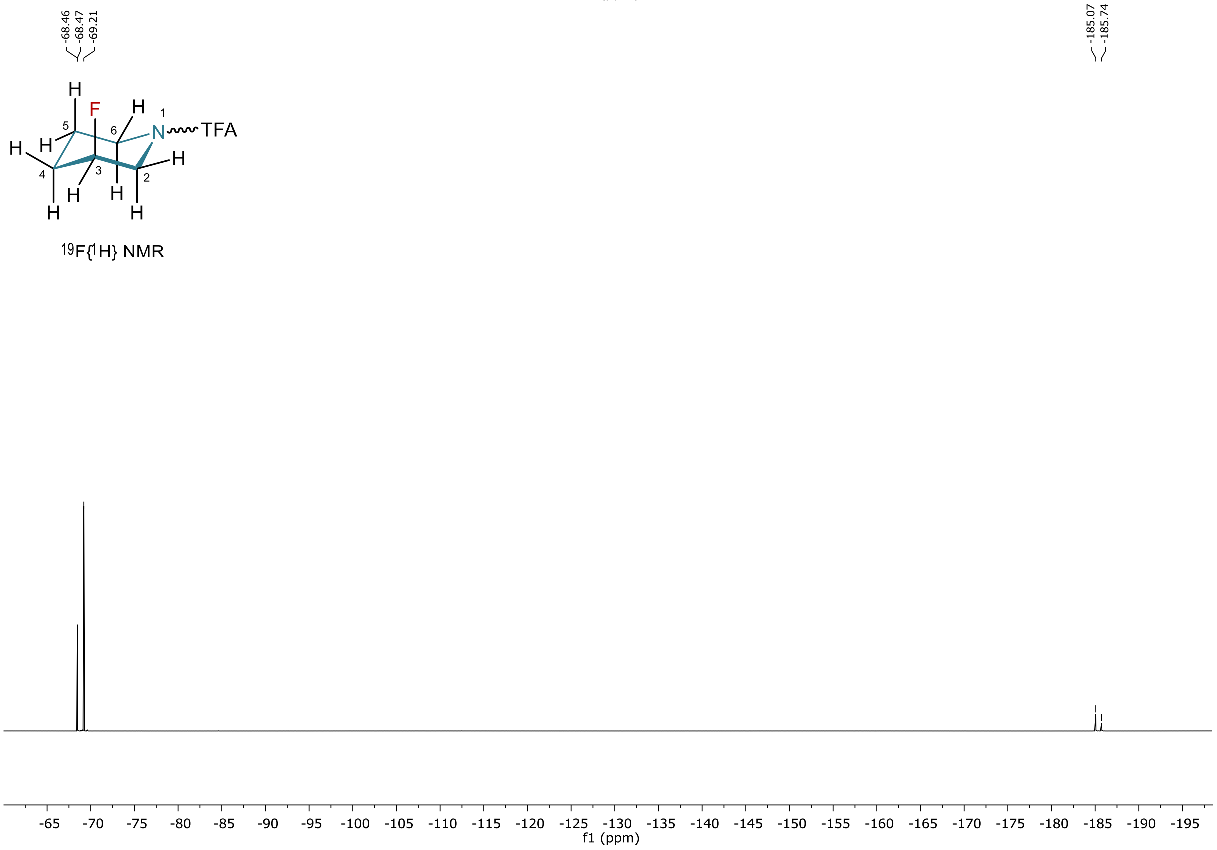
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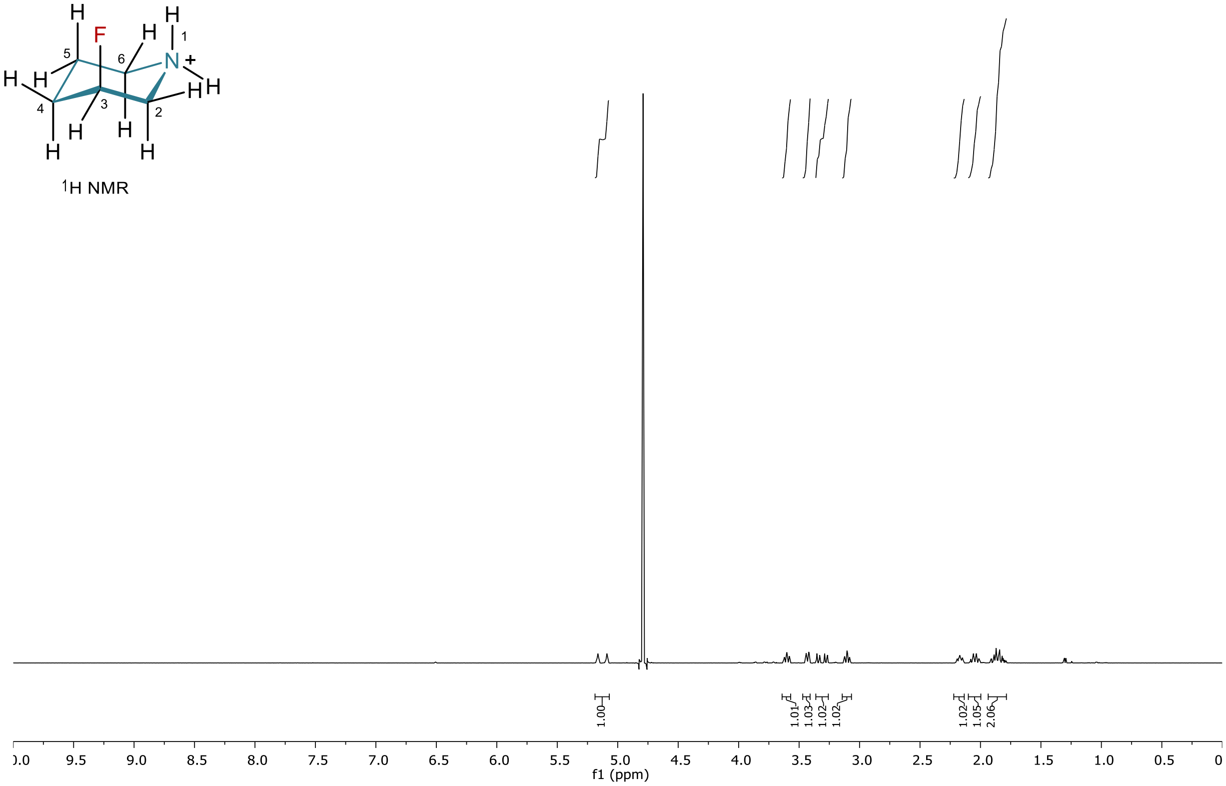

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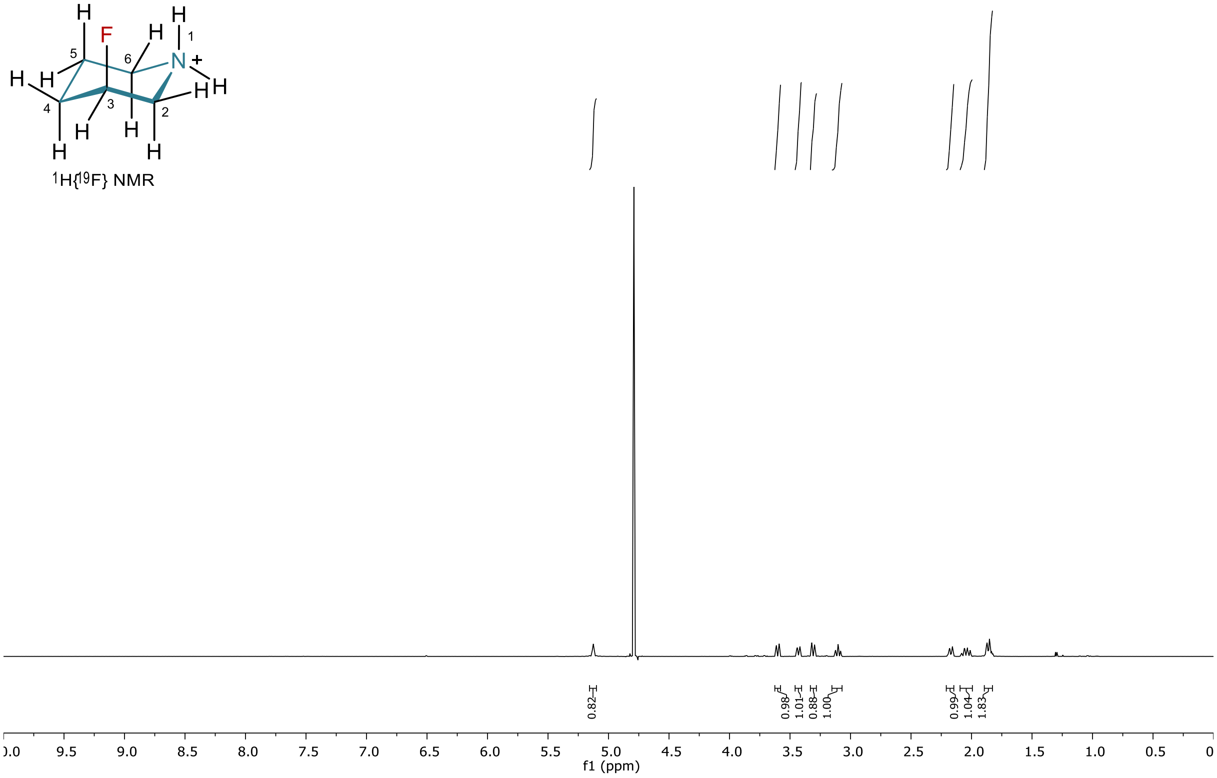

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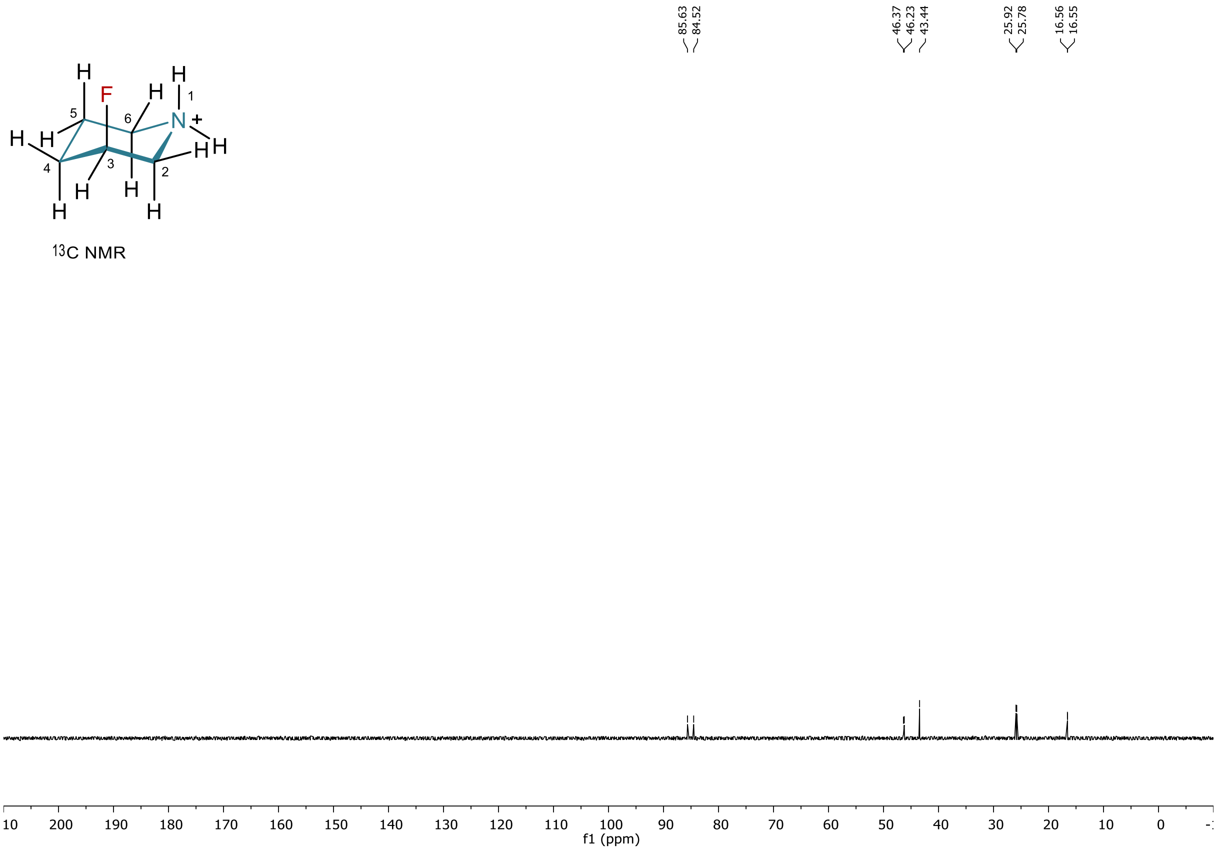
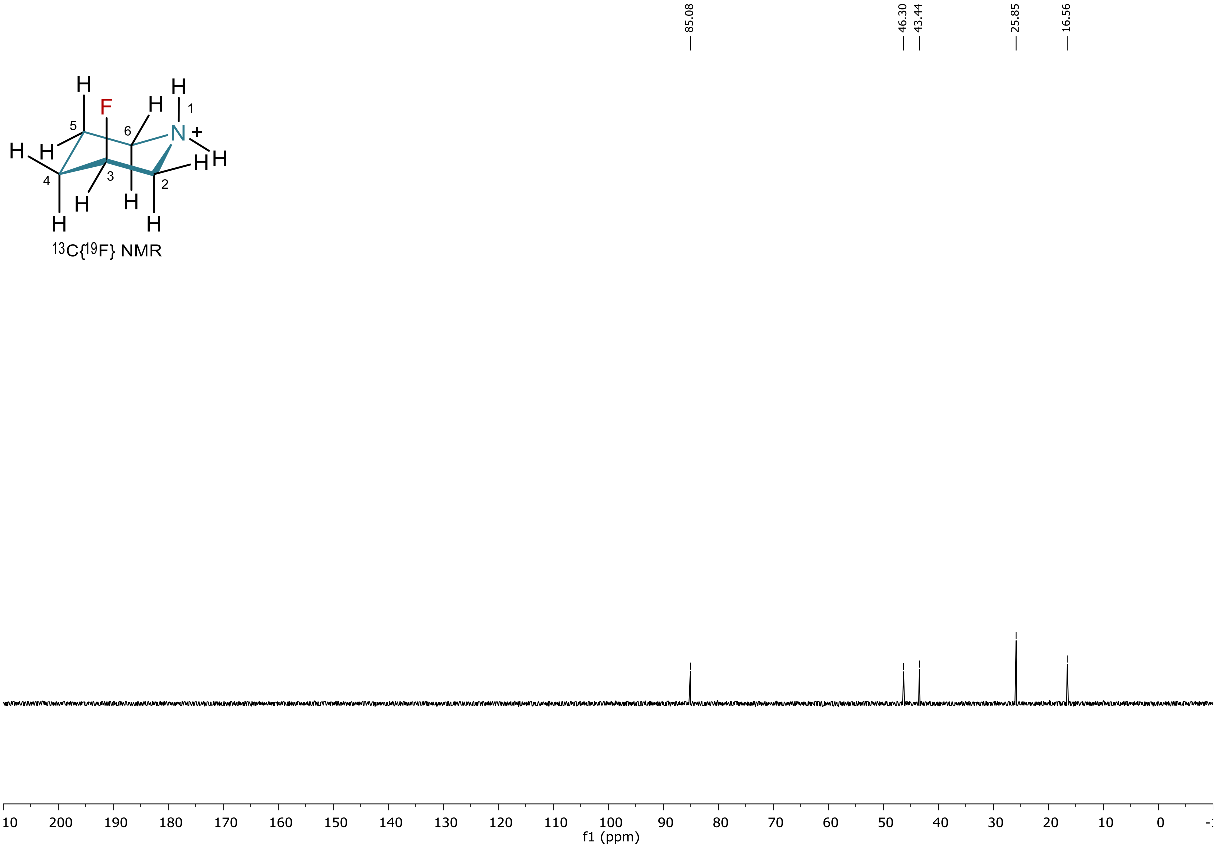
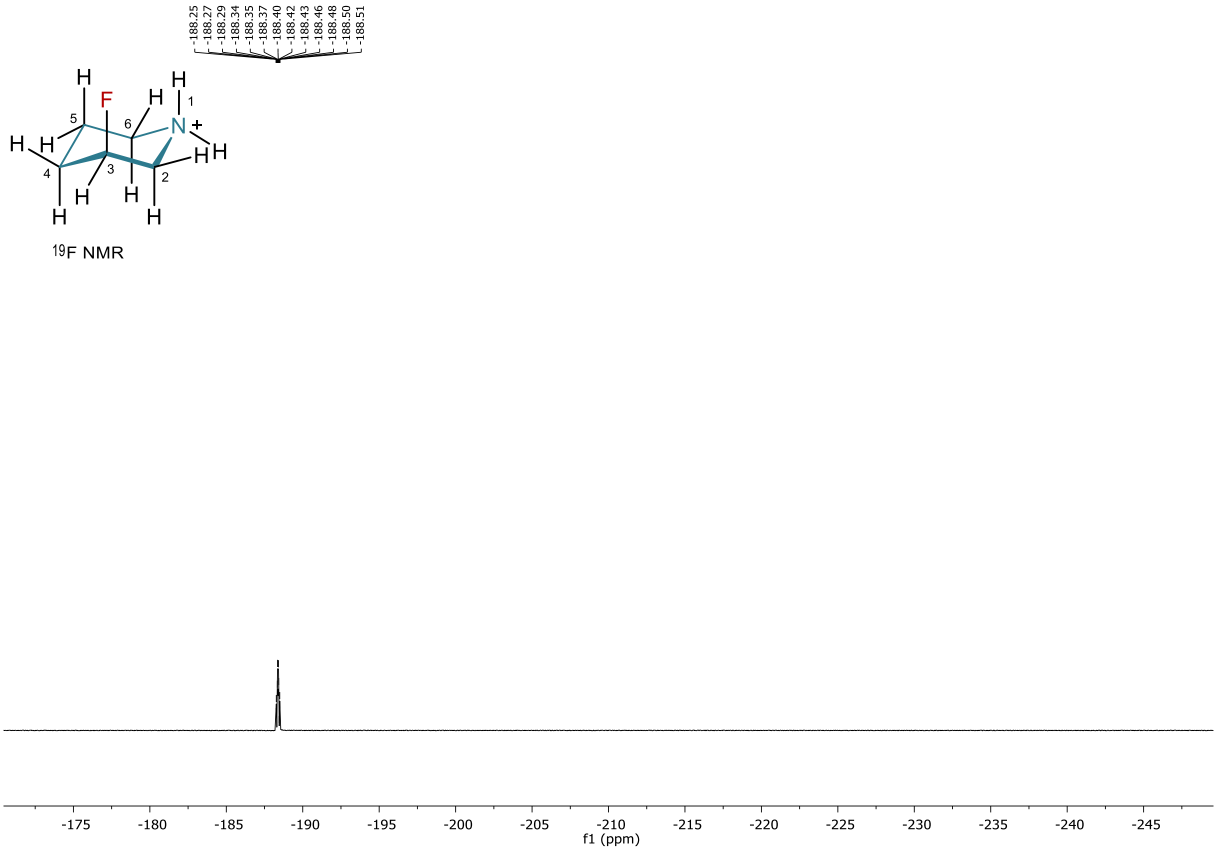


^{13}C NMR



^{13}C{^{19}F} NMR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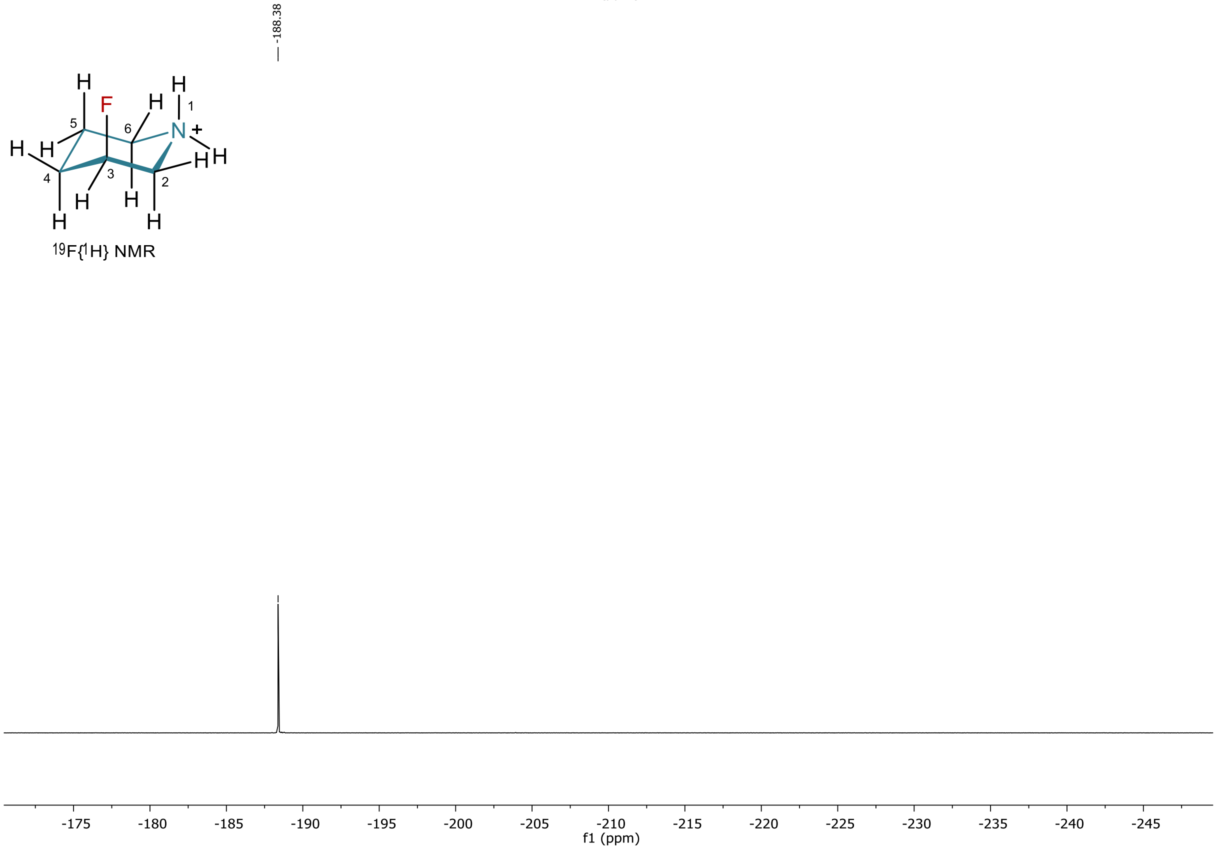
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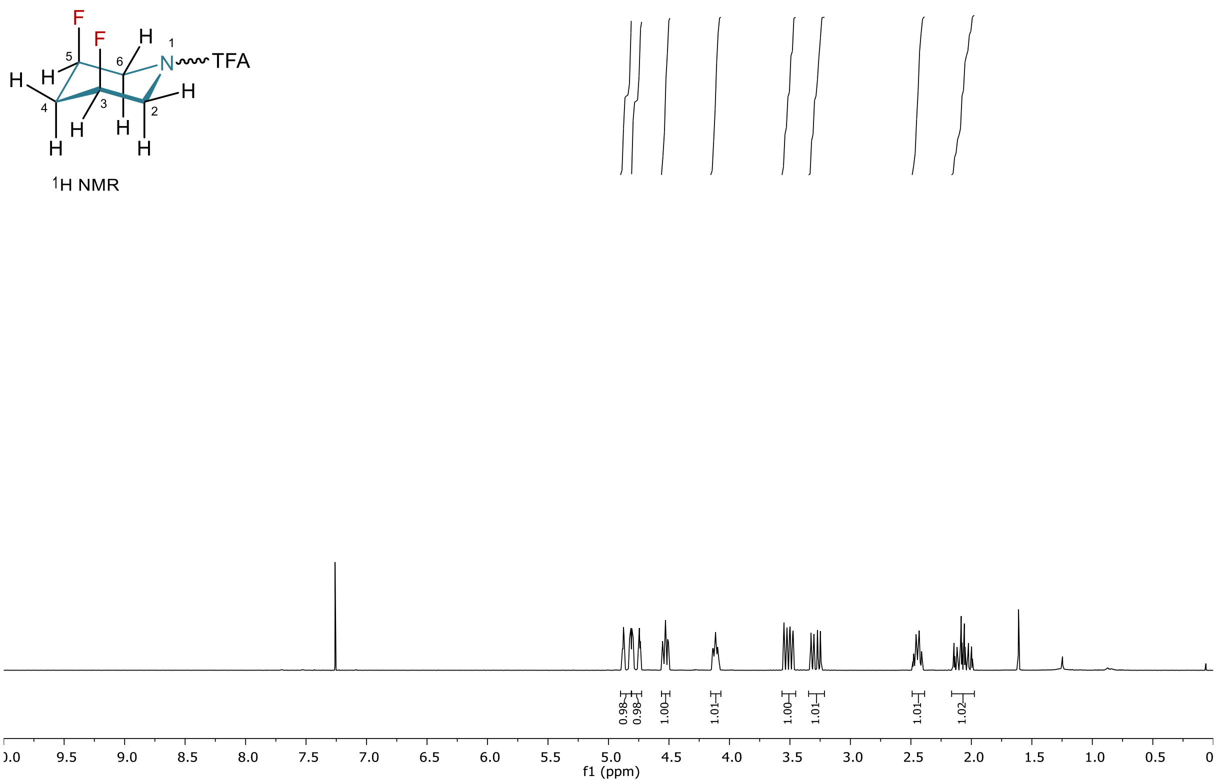
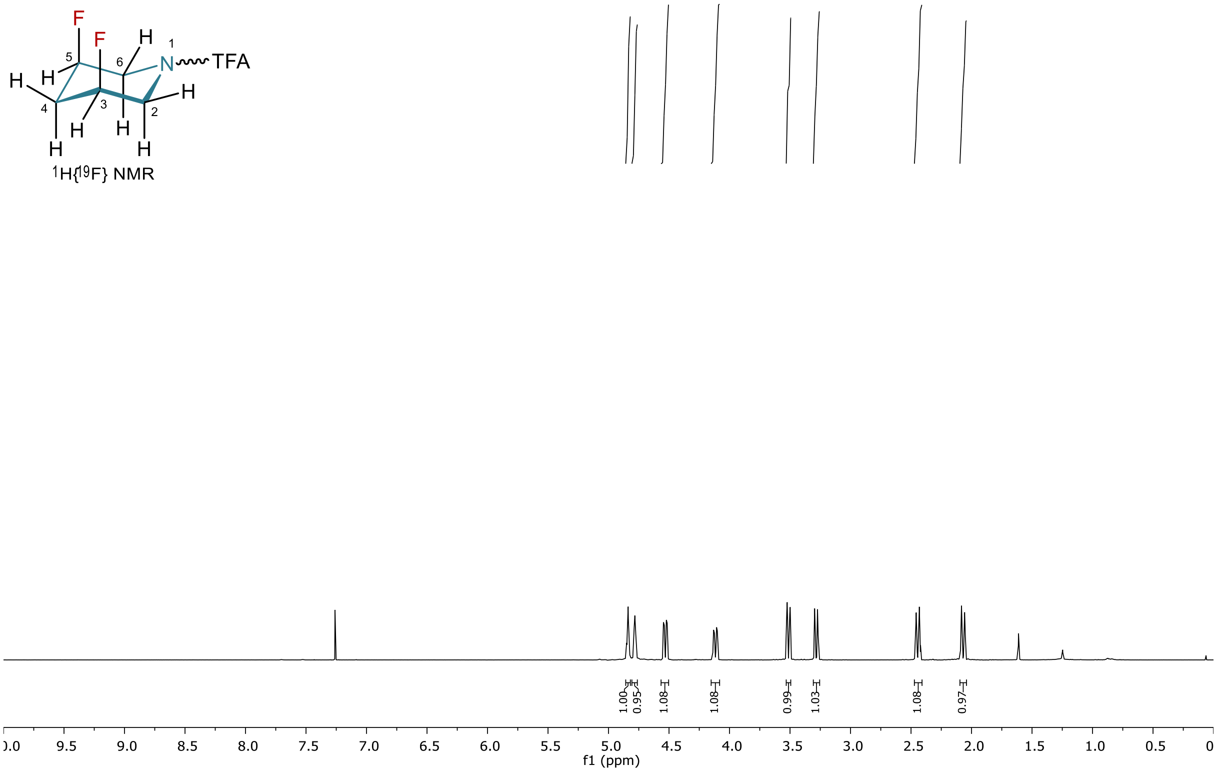
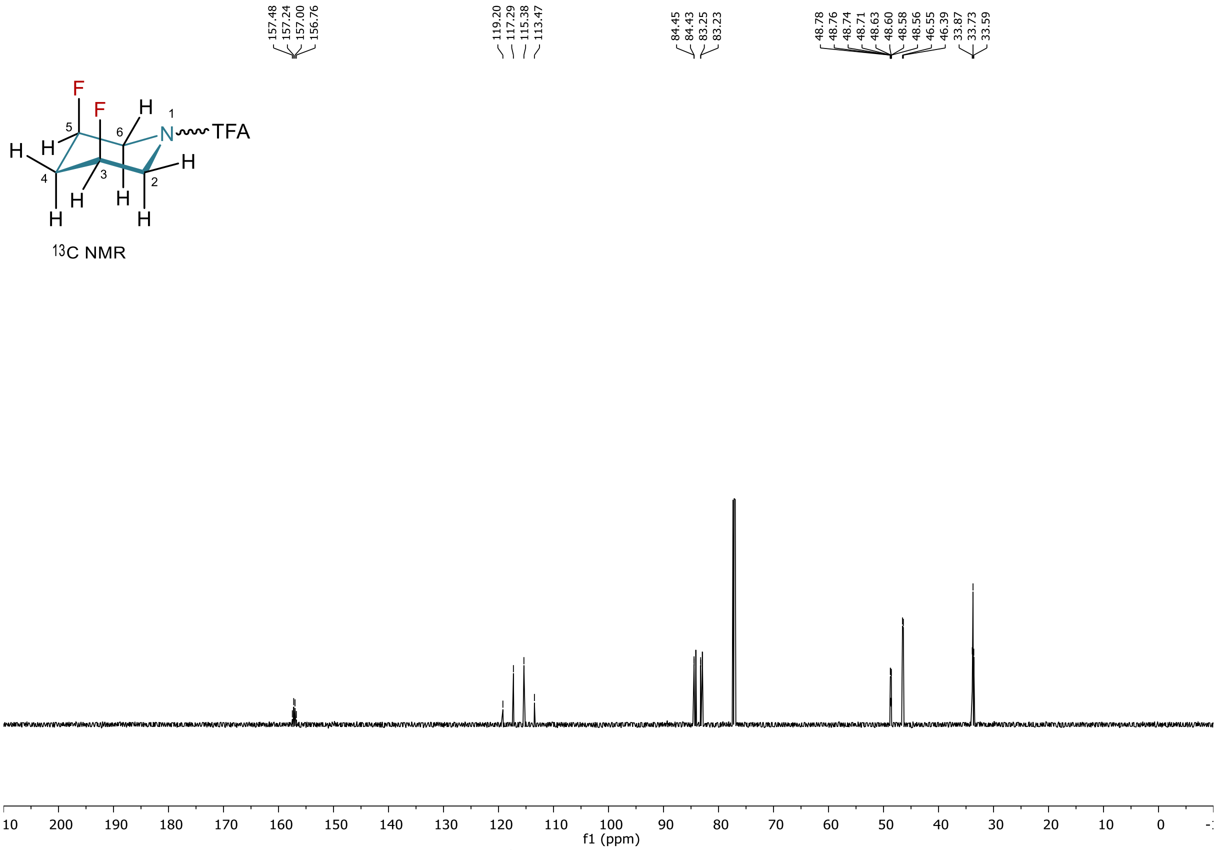
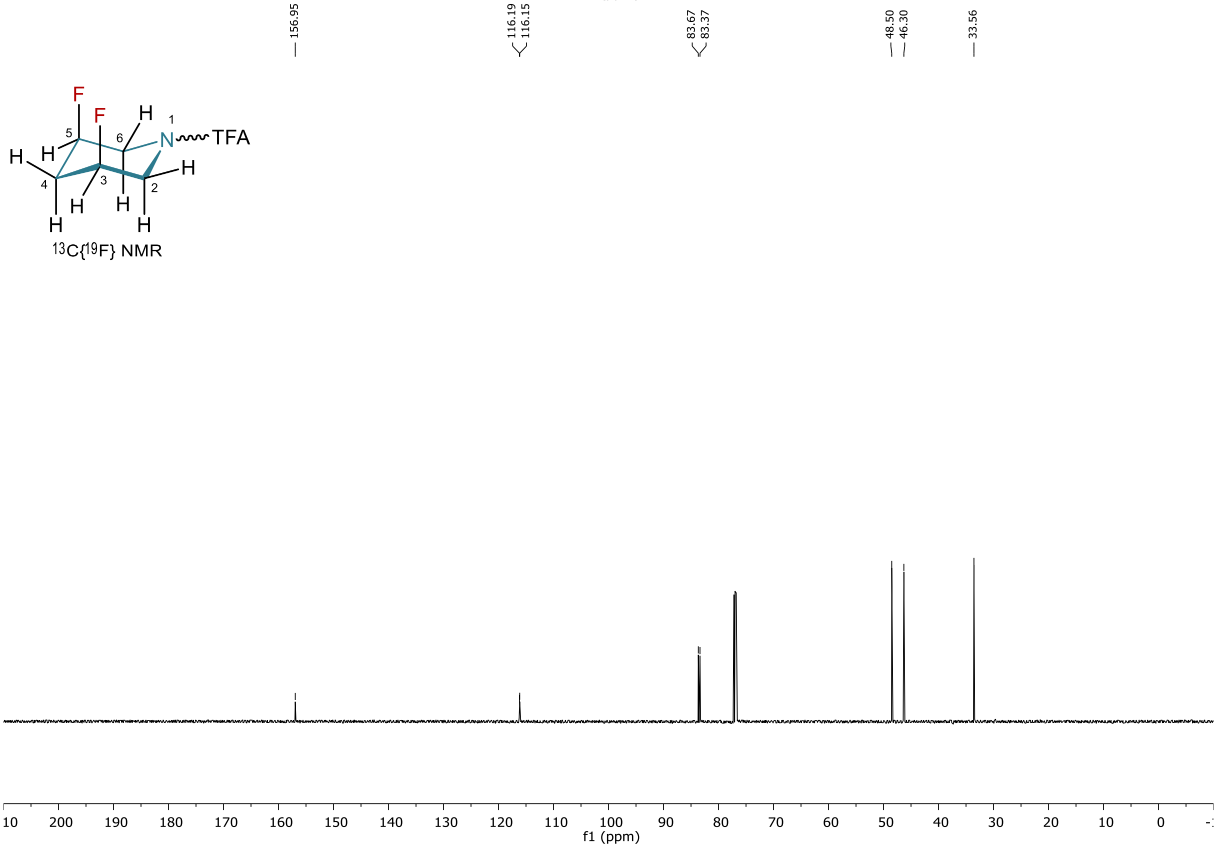
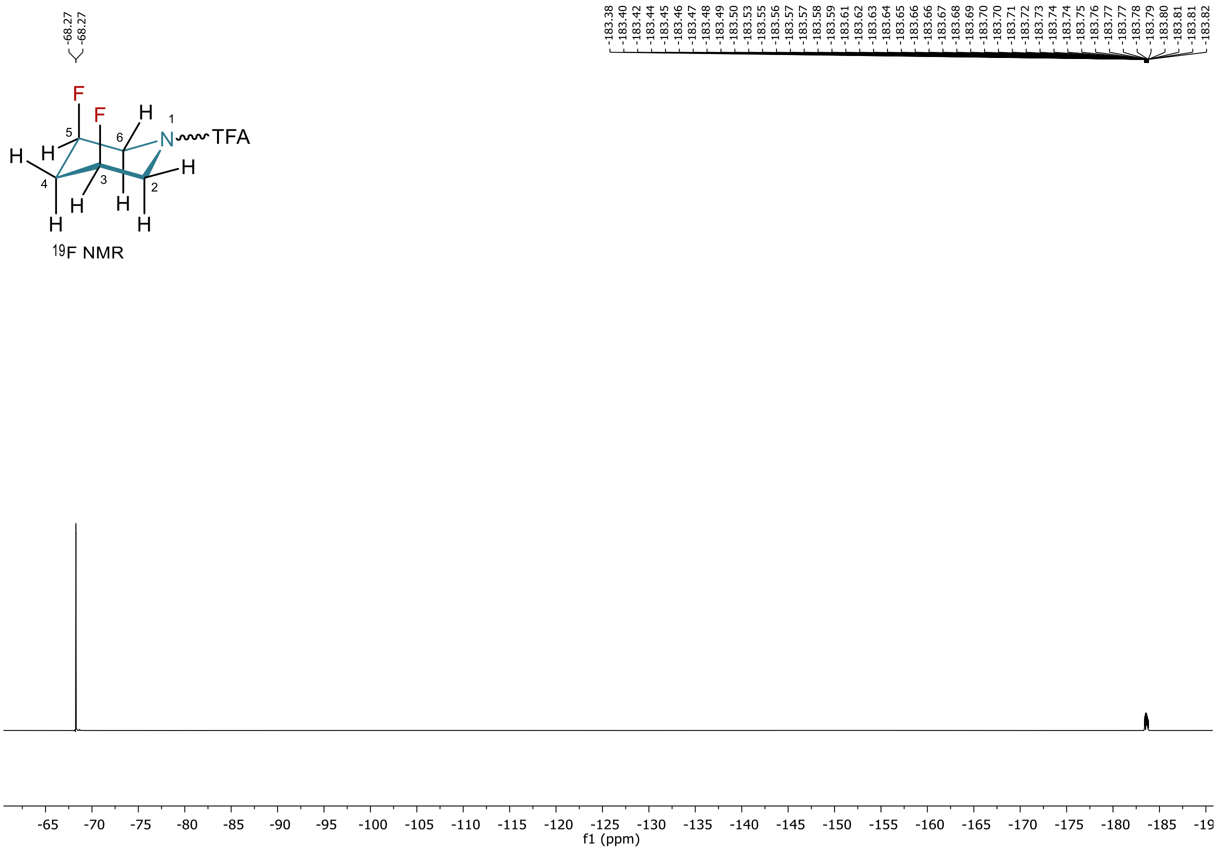
-245
f1 (ppm)


F
F
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
H
H
^{1}H NMR
0.98
0.98
1.00
1.01
1.00
1.01
1.01
1.02
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


F
F
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
H
H
^{1}H{^{19}F} NMR
1.00
0.95
1.08
1.08
0.99
1.03
1.08
0.97
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


157.48
157.24
157.00
156.76
119.20
117.29
115.38
113.47
84.45
84.43
83.25
83.23
48.78
48.76
48.74
48.71
48.63
48.60
48.58
48.56
46.55
46.39
33.87
33.73
33.59
F
F
H
1
N
TFA
5
6
H
H
H
4
3
2
H
H
H
H
13C NMR
f1 (ppm)


156.95
116.19
116.15
83.67
83.37
48.50
46.30
33.56
F
F
H
1
N
TFA
5
6
H
H
H
4
3
2
H
H
H
H
13C{19F} NMR
f1 (ppm)


-68.27
-68.27
-183.38
-183.40
-183.42
-183.44
-183.45
-183.46
-183.47
-183.48
-183.49
-183.50
-183.53
-183.55
-183.56
-183.57
-183.57
-183.58
-183.59
-183.61
-183.62
-183.63
-183.64
-183.65
-183.66
-183.66
-183.67
-183.68
-183.69
-183.70
-183.70
-183.71
-183.72
-183.73
-183.74
-183.74
-183.75
-183.76
-183.77
-183.77
-183.78
-183.79
-183.80
-183.81
-183.81
-183.82
F
F
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
H
H
19F NMR
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
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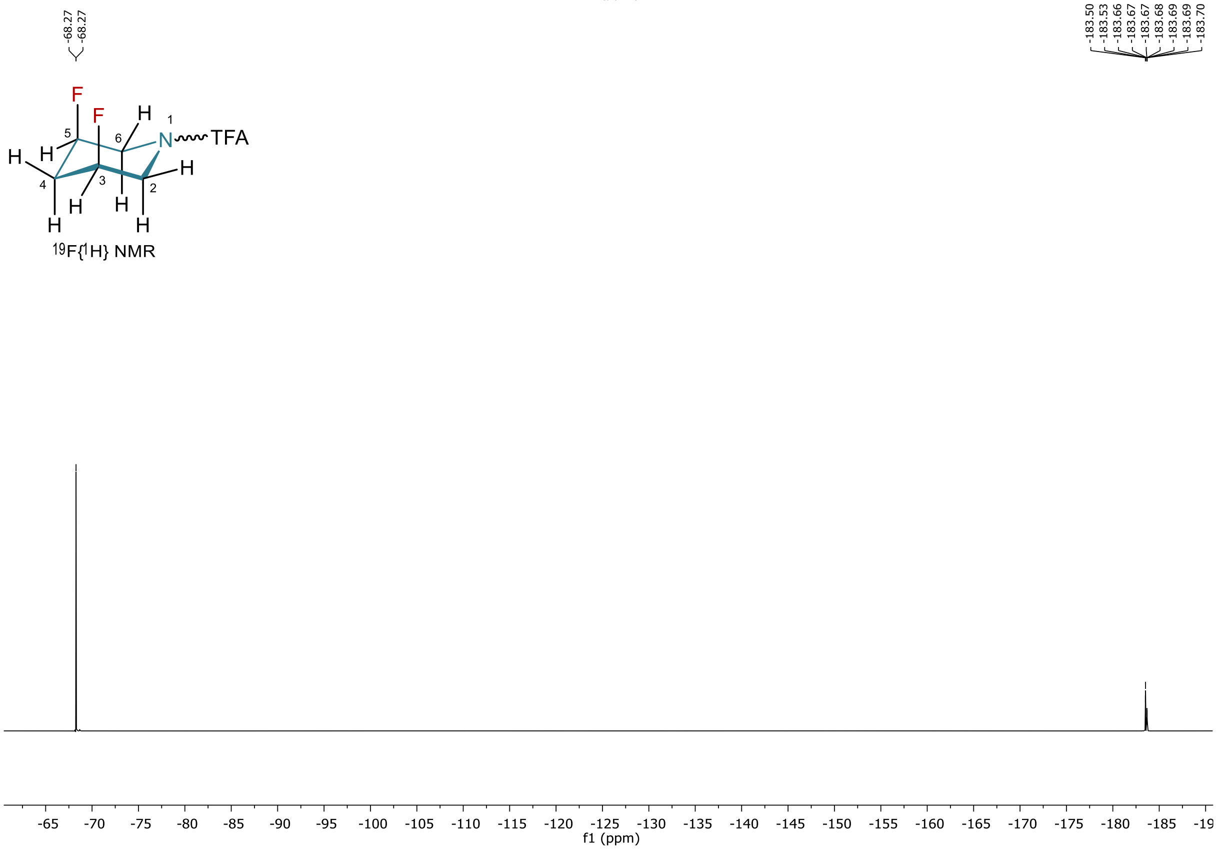
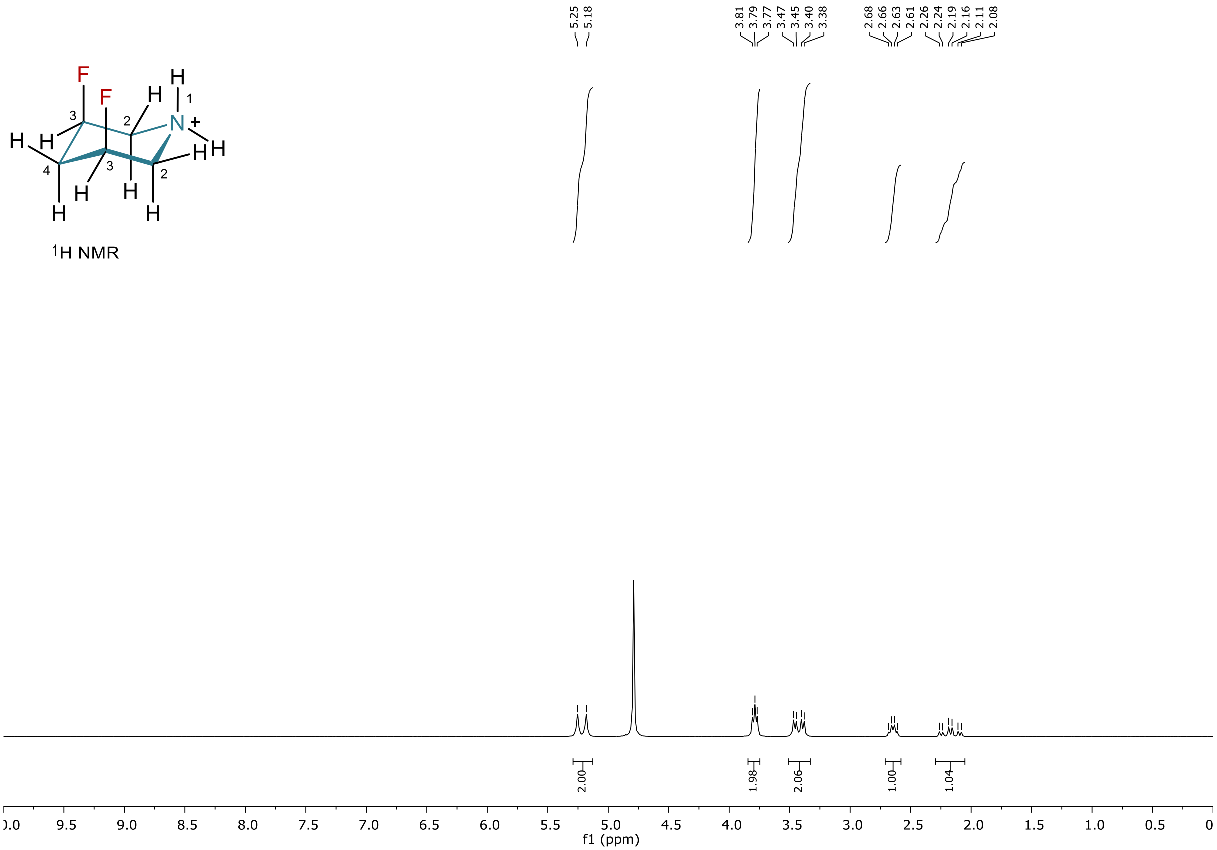
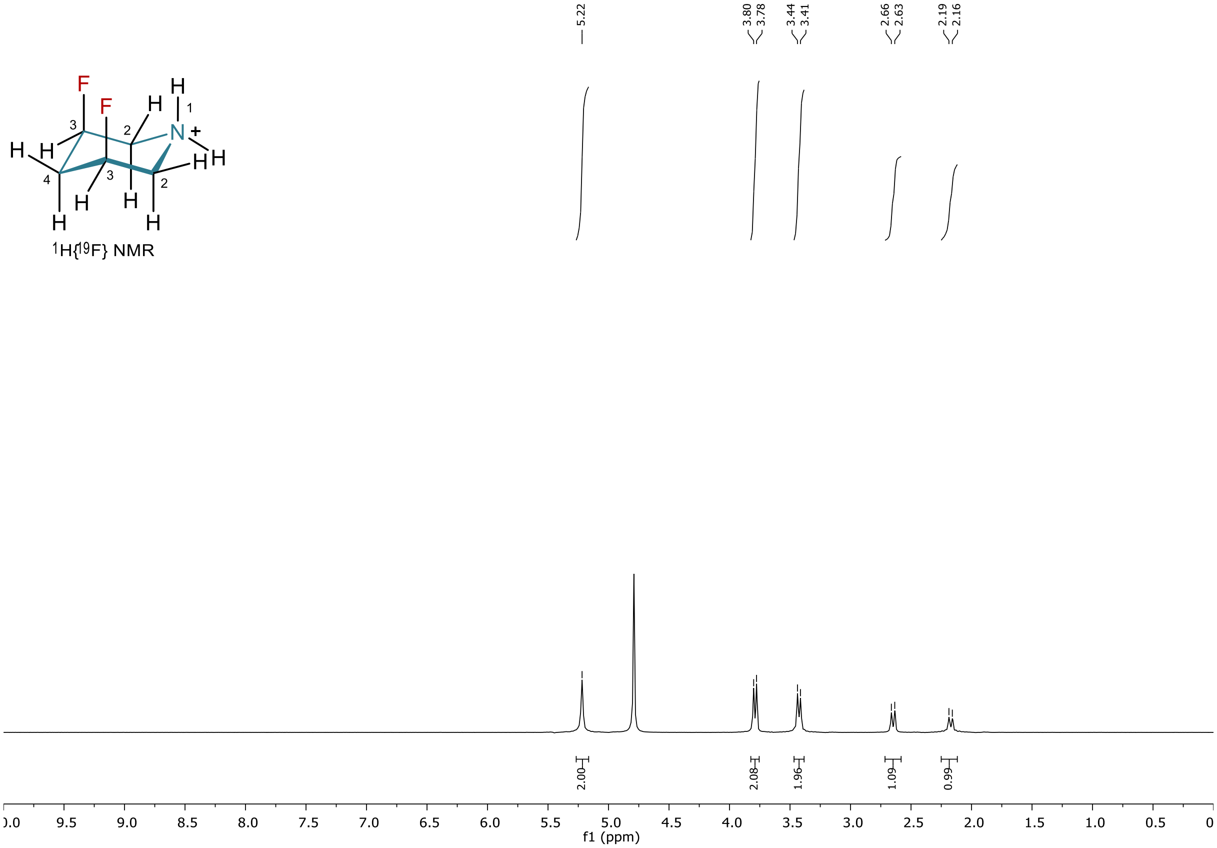
-160
-165
-170
-175
-180
-185
-19
f1 (ppm)

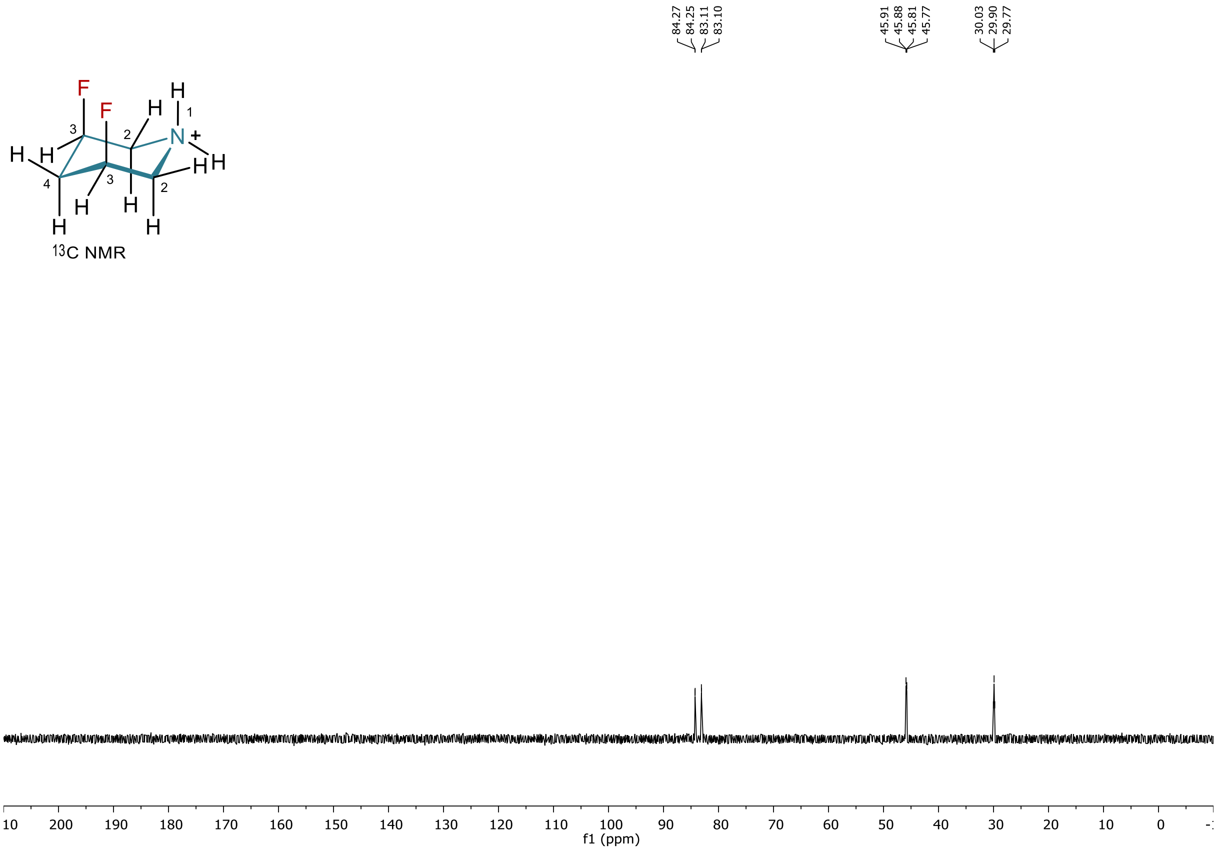

-68.27
-68.27
-183.50
-183.53
-183.66
-183.67
-183.67
-183.68
-183.69
-183.69
-183.70
F
F
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
H
H
19F{1H} NMR
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-19
f1 (ppm)



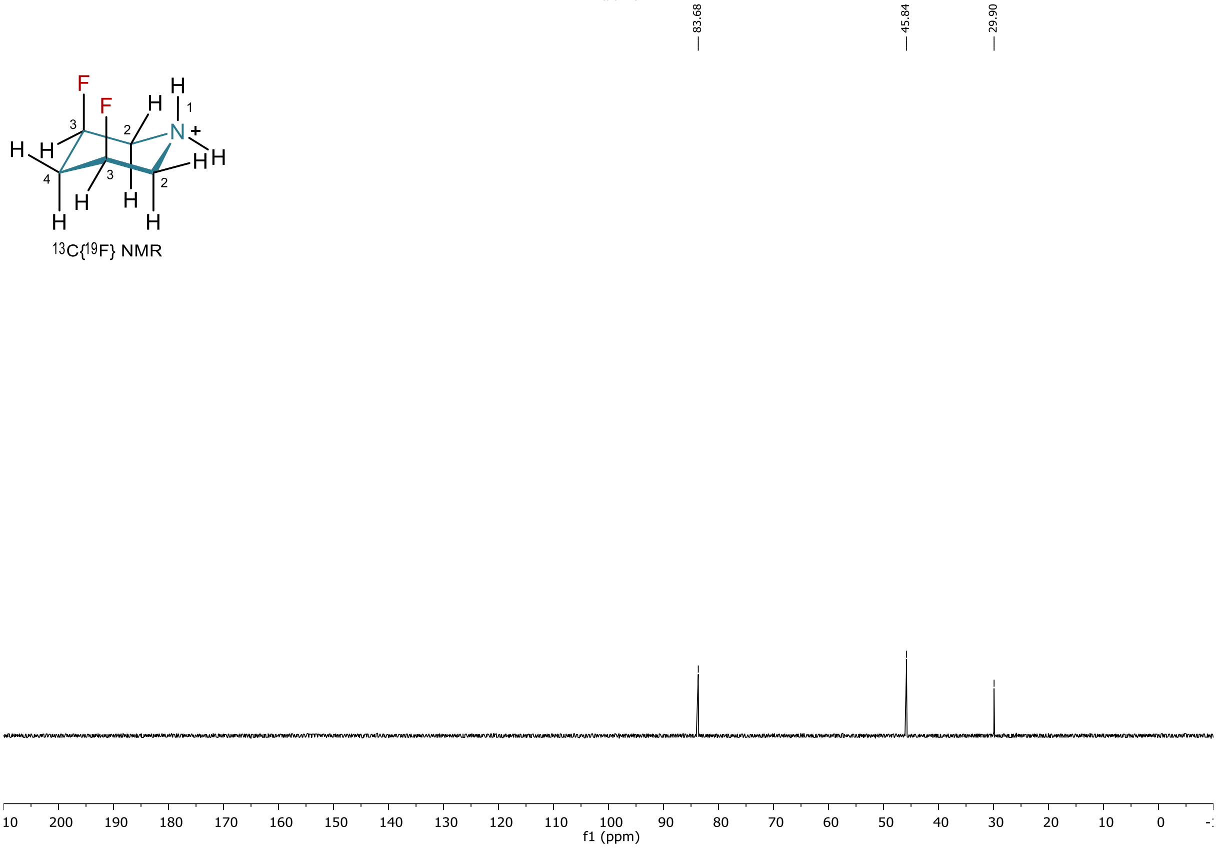
^{1}H NMR



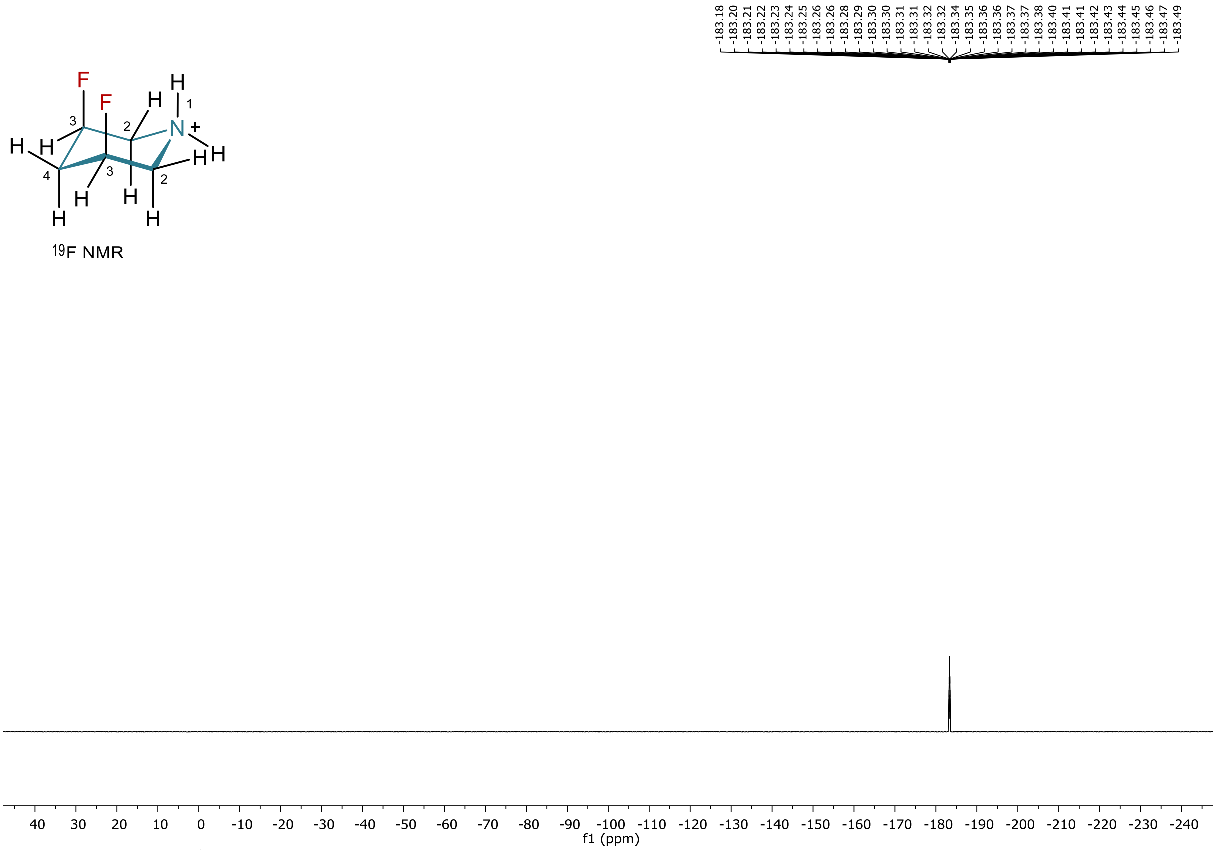
^{1}H{^{19}F} NMR

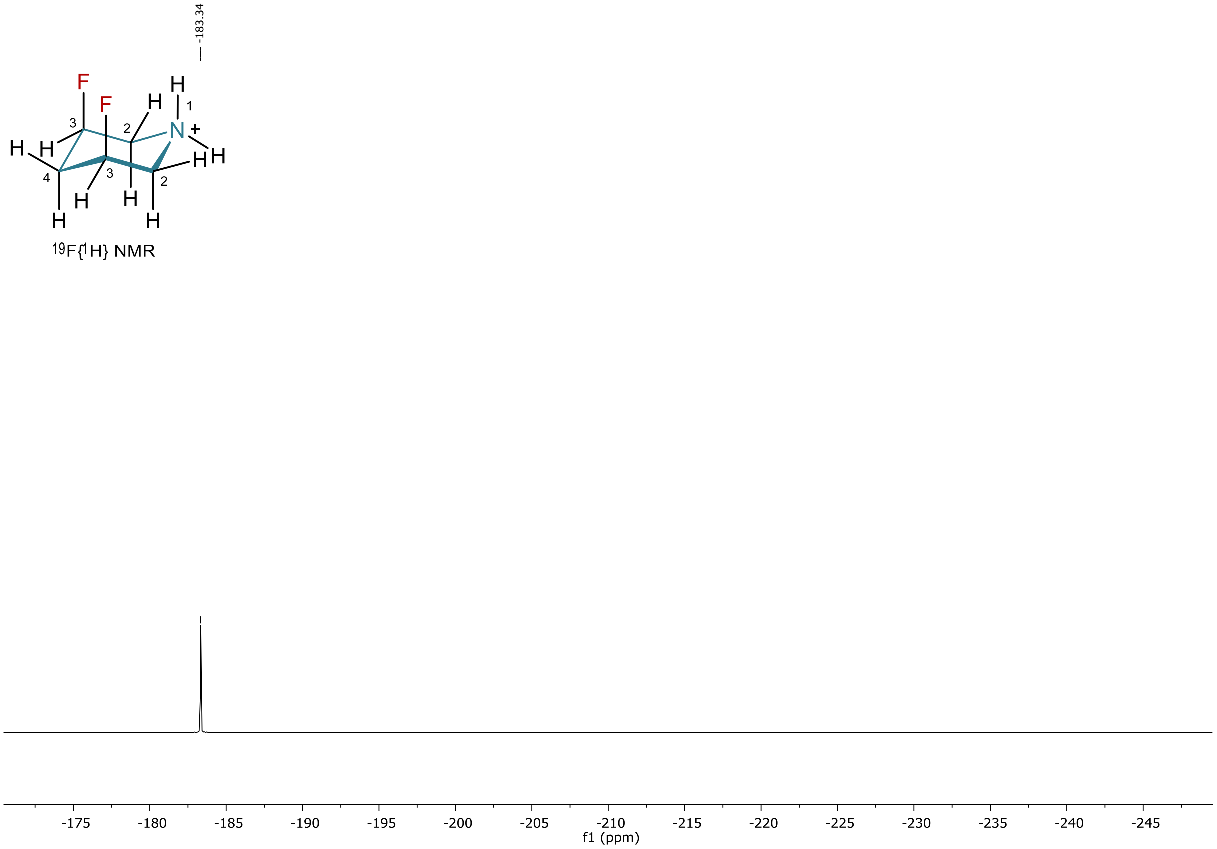


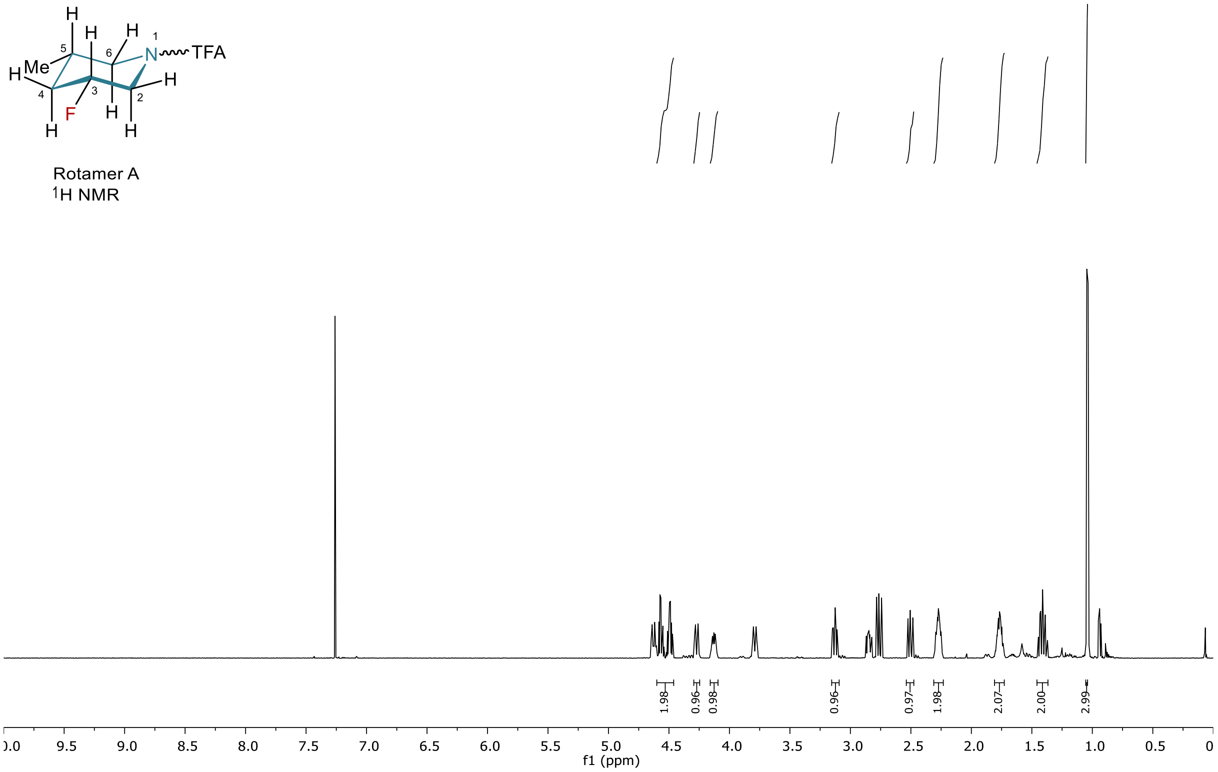
^{13}C NMR



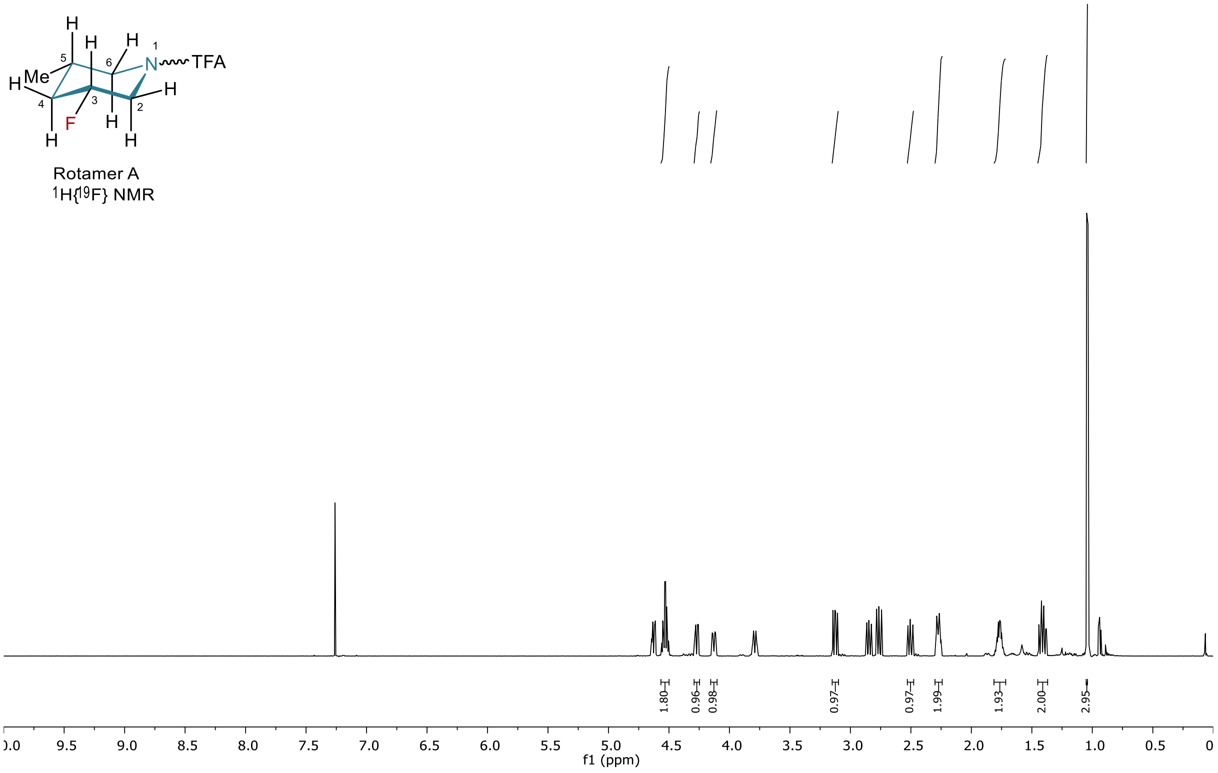
^{13}C{^{19}F} NMR


-183.18
-183.20
-183.21
-183.22
-183.23
-183.24
-183.25
-183.26
-183.26
-183.28
-183.29
-183.30
-183.30
-183.31
-183.31
-183.32
-183.32
-183.34
-183.35
-183.36
-183.36
-183.37
-183.37
-183.38
-183.40
-183.41
-183.41
-183.42
-183.43
-183.44
-183.45
-183.46
-183.47
-183.49
F
F
H
H
1
N+
H
H
H
H
3
2
4
3
2
H
H
H
H
^{19}F NMR
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)

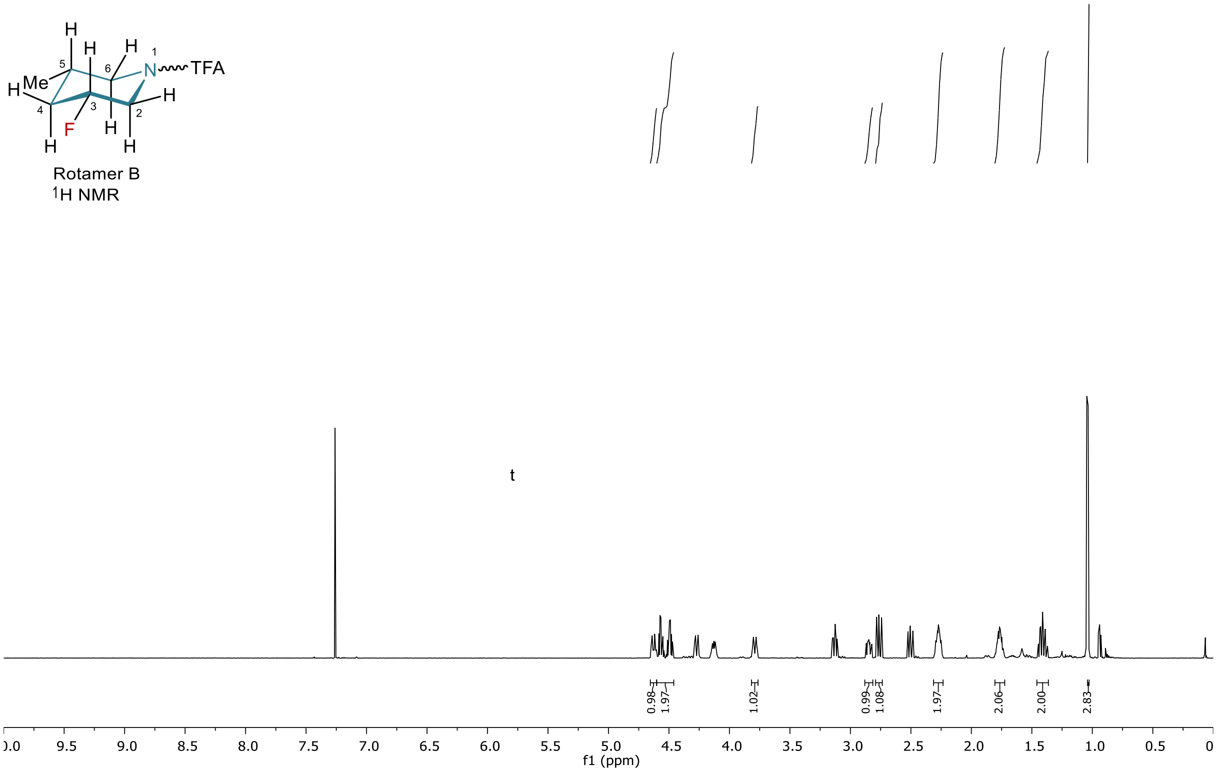

-183.34
F
F
H
H
1
N+
H
H
H
H
3
2
4
3
2
H
H
H
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

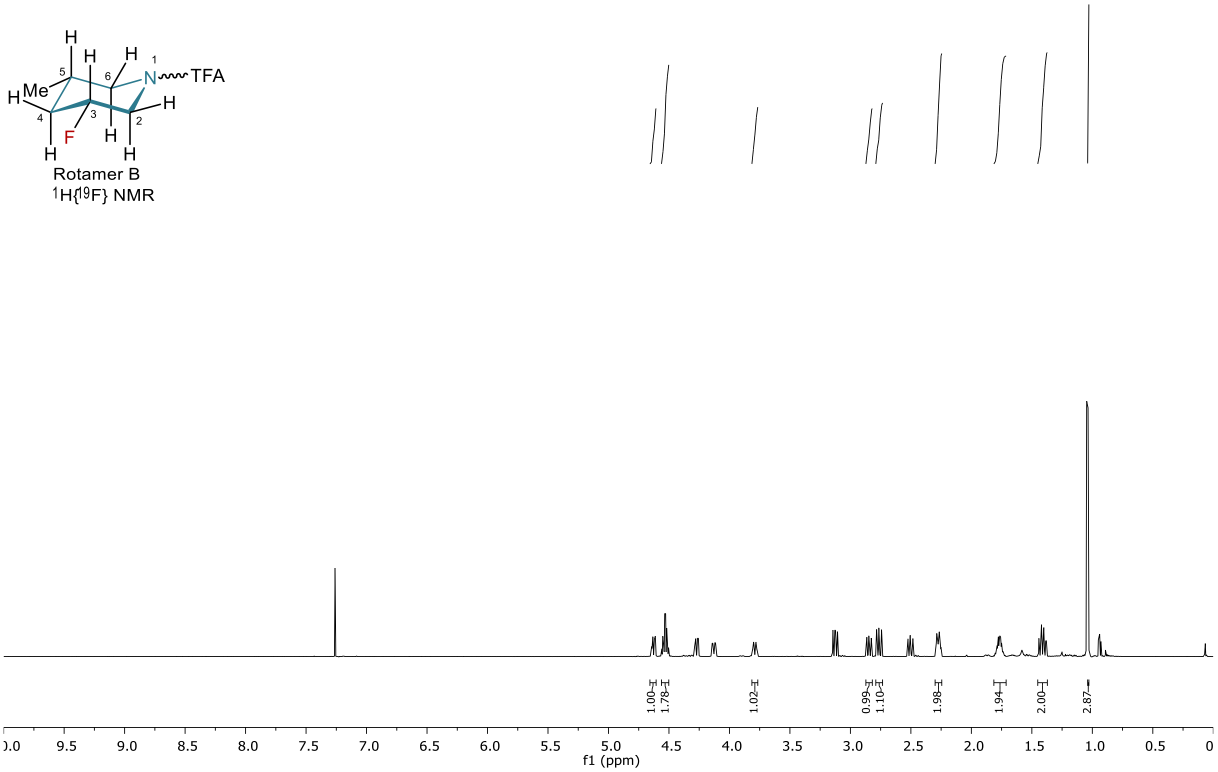


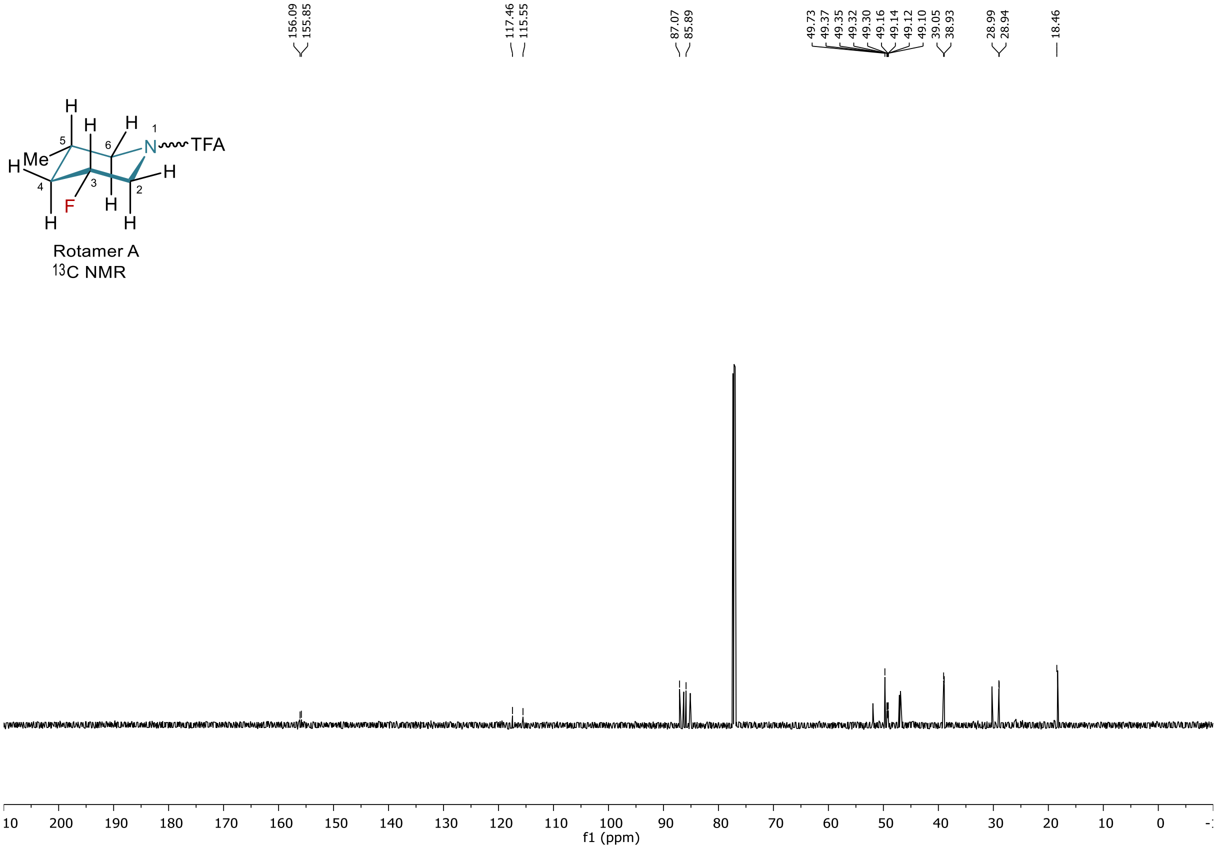
Rotamer A
^{1}H NMR

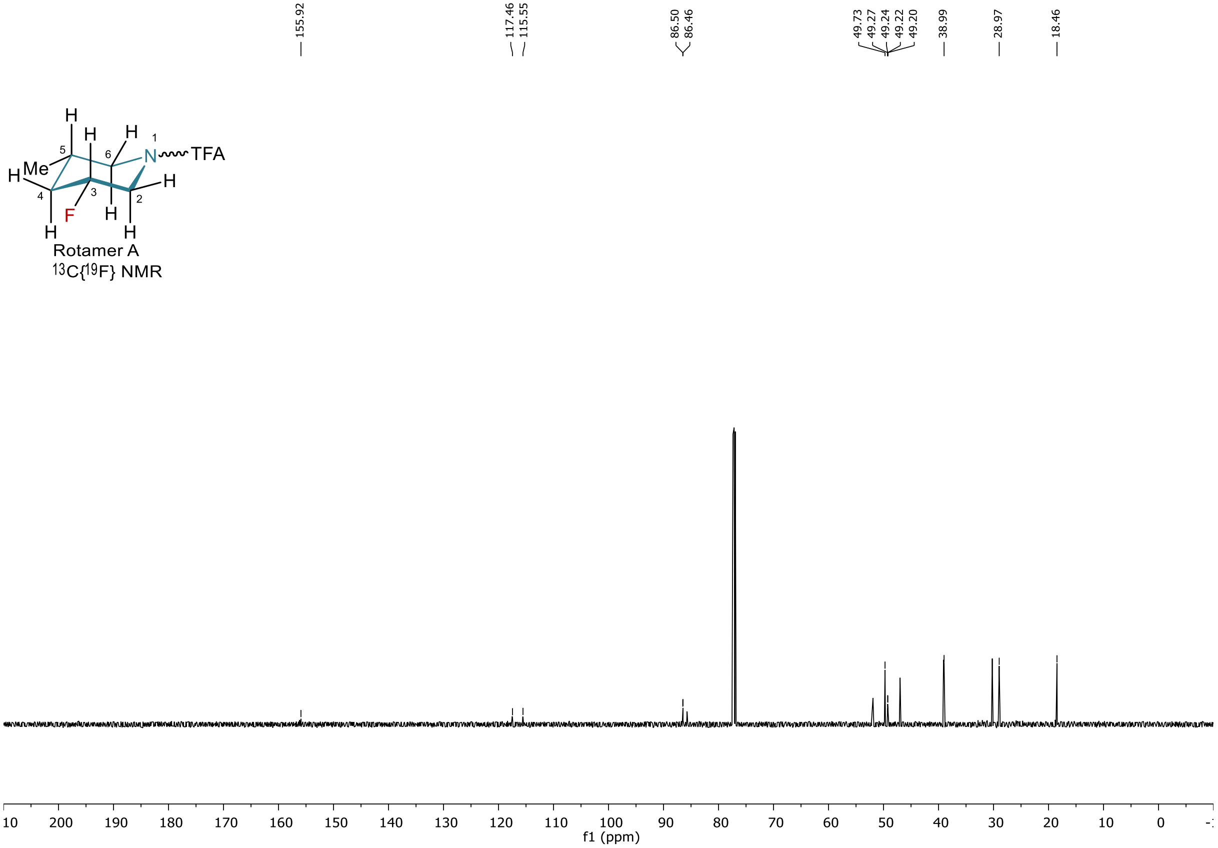


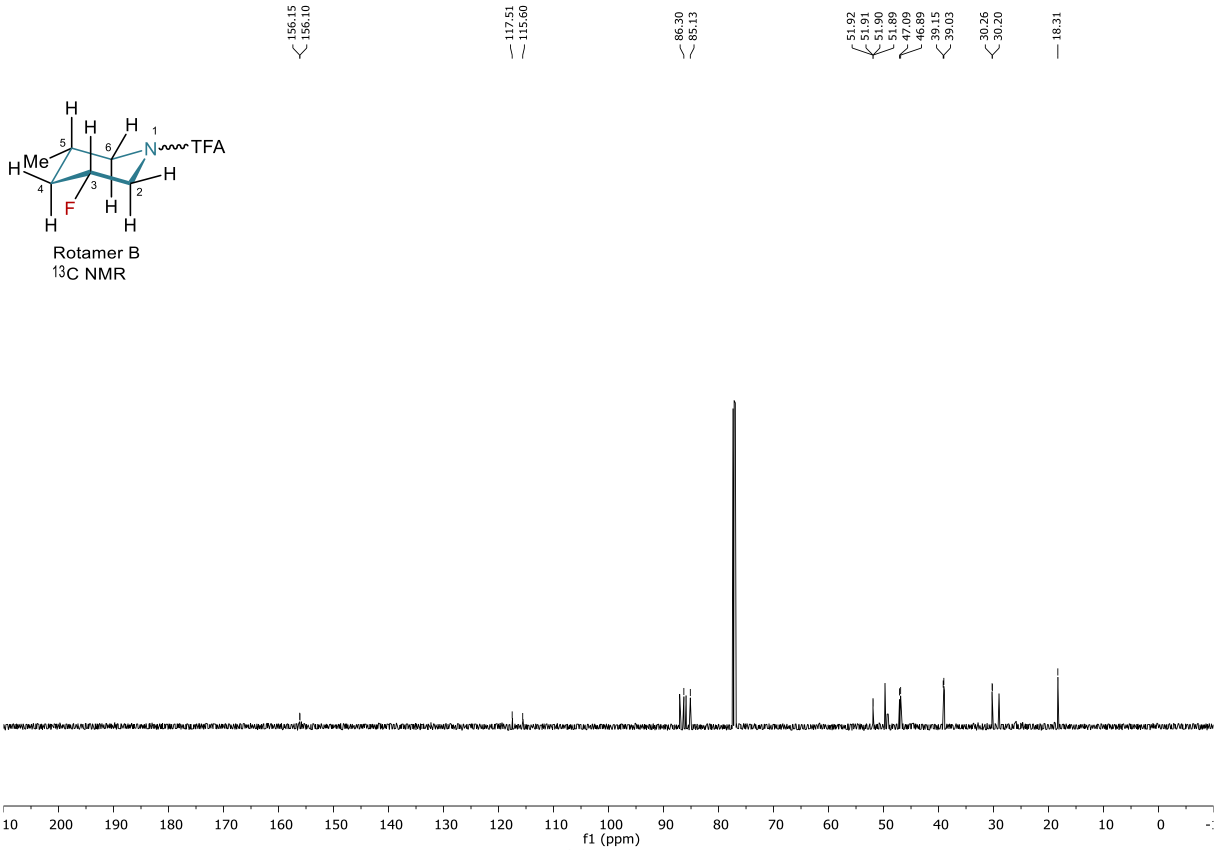
Rotamer A
^{1}H{^{19}F} NMR

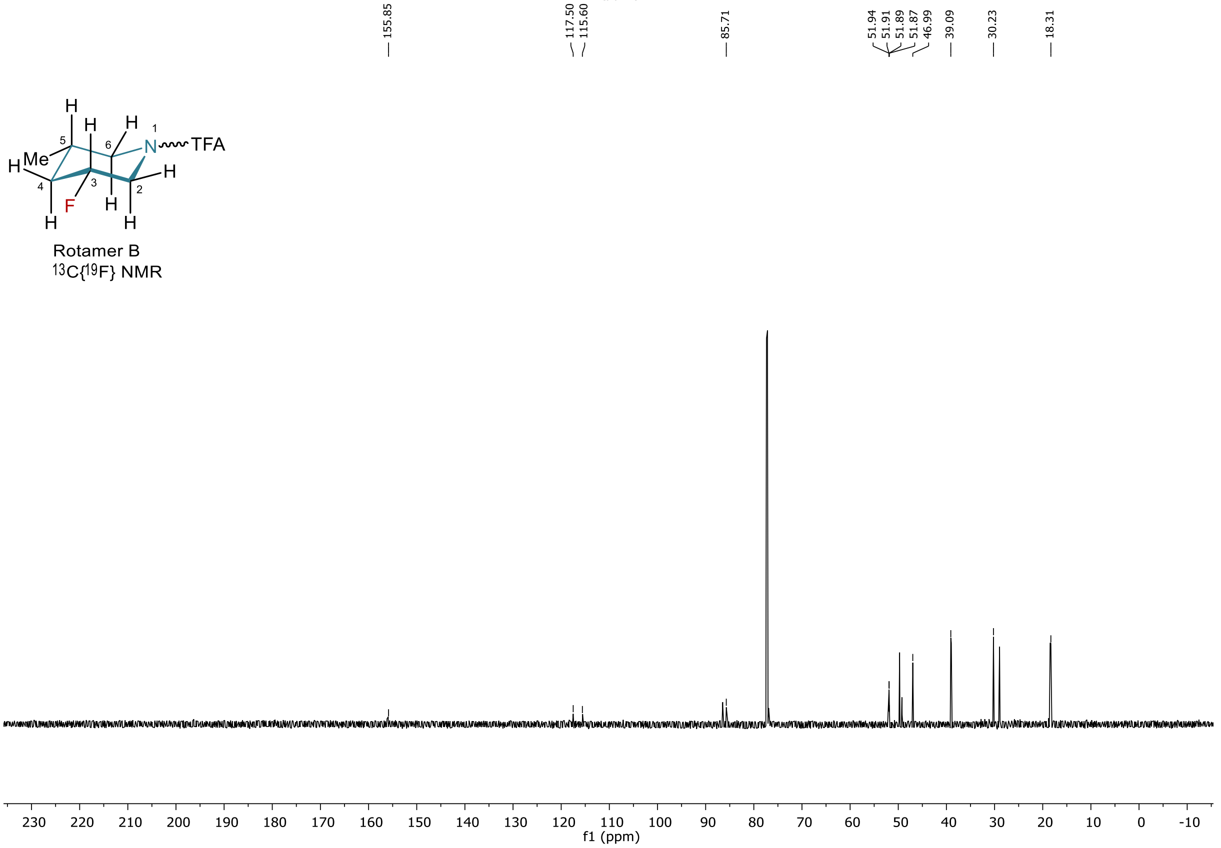

H
H
H
Me
H
5
6
1
N
TFA
H
4
3
2
F
H
H
H
Rotamer B
^{1}H NMR
t
0.98
1.97
1.02
0.99
1.08
1.97
2.06
2.00
2.83
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

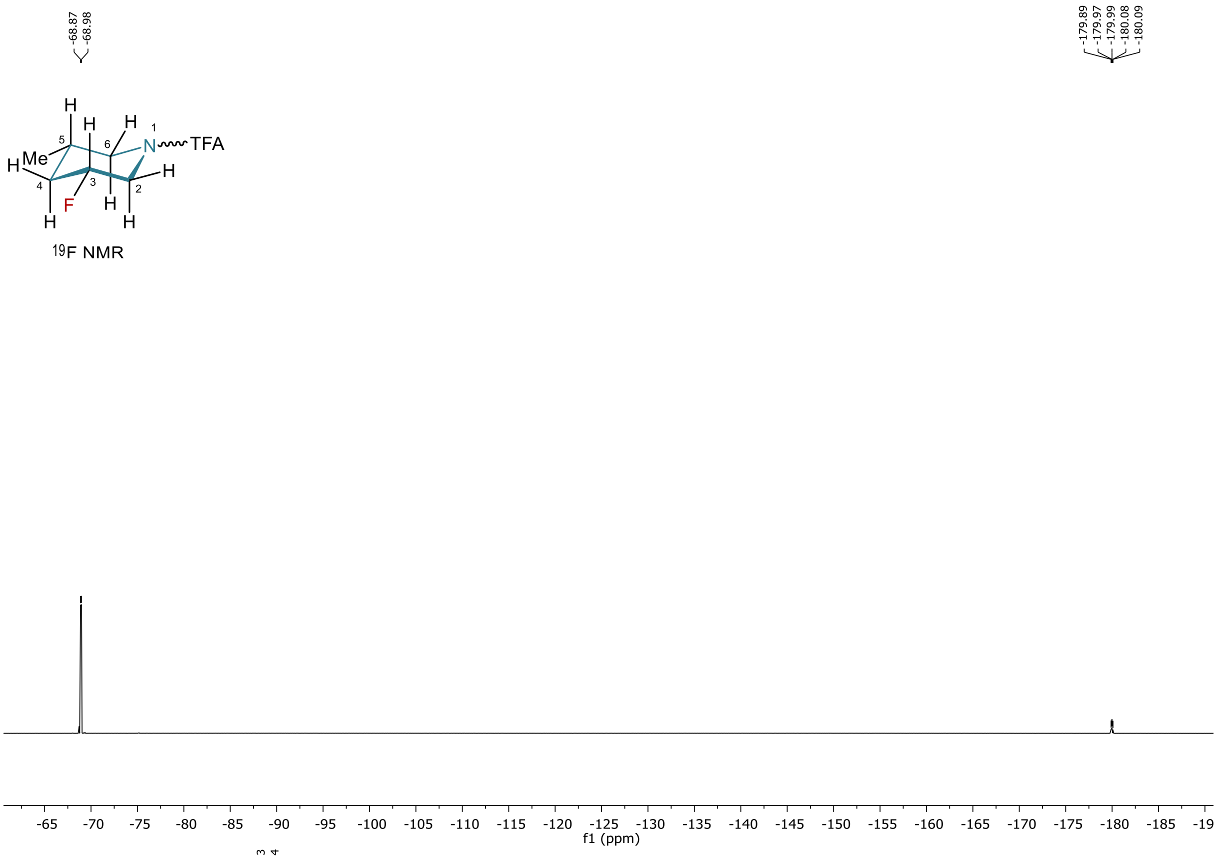

H
H
H
Me
H
5
6
1
N
TFA
H
4
3
2
F
H
H
H
Rotamer B
^{1}H{^{19}F} NMR
1.00
1.78
1.02
0.99
1.10
1.98
1.94
2.00
2.87
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

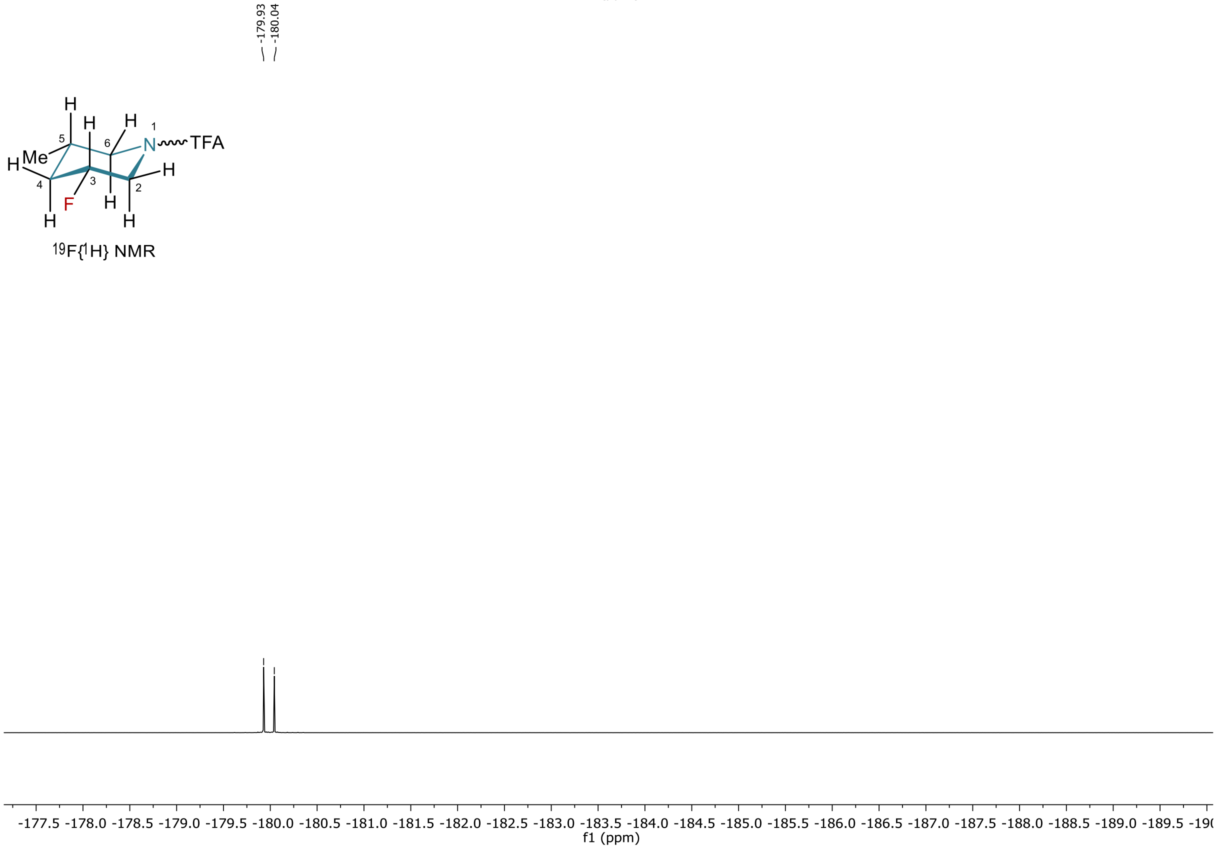

156.09
155.85
117.46
115.55
87.07
85.89
49.73
49.37
49.35
49.32
49.30
49.16
49.14
49.12
49.10
39.05
38.93
28.99
28.94
18.46
H
H
H
1
5
6
N
TFA
Me
H
H
4
3
2
F
H
H
H
Rotamer A
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

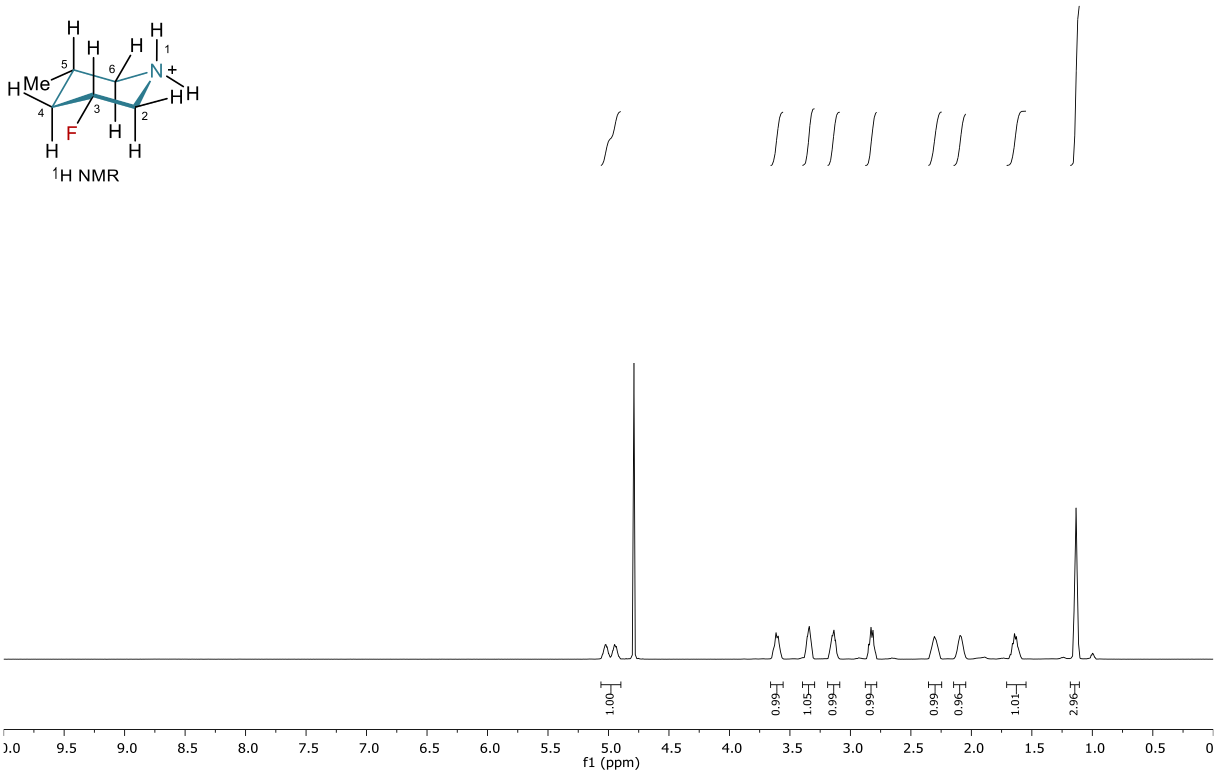

155.92
117.46
115.55
86.50
86.46
49.73
49.27
49.24
49.22
49.20
38.99
28.97
18.46
H
H
H
1
5
6
N
TFA
Me
H
H
4
3
2
F
H
H
H
Rotamer A
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


156.15
156.10
117.51
115.60
86.30
85.13
51.92
51.91
51.90
51.89
47.09
46.89
39.15
39.03
30.26
30.20
18.31
H
H
H
1
5
6
N
TFA
Me
H
H
4
3
2
F
H
H
H
Rotamer B
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

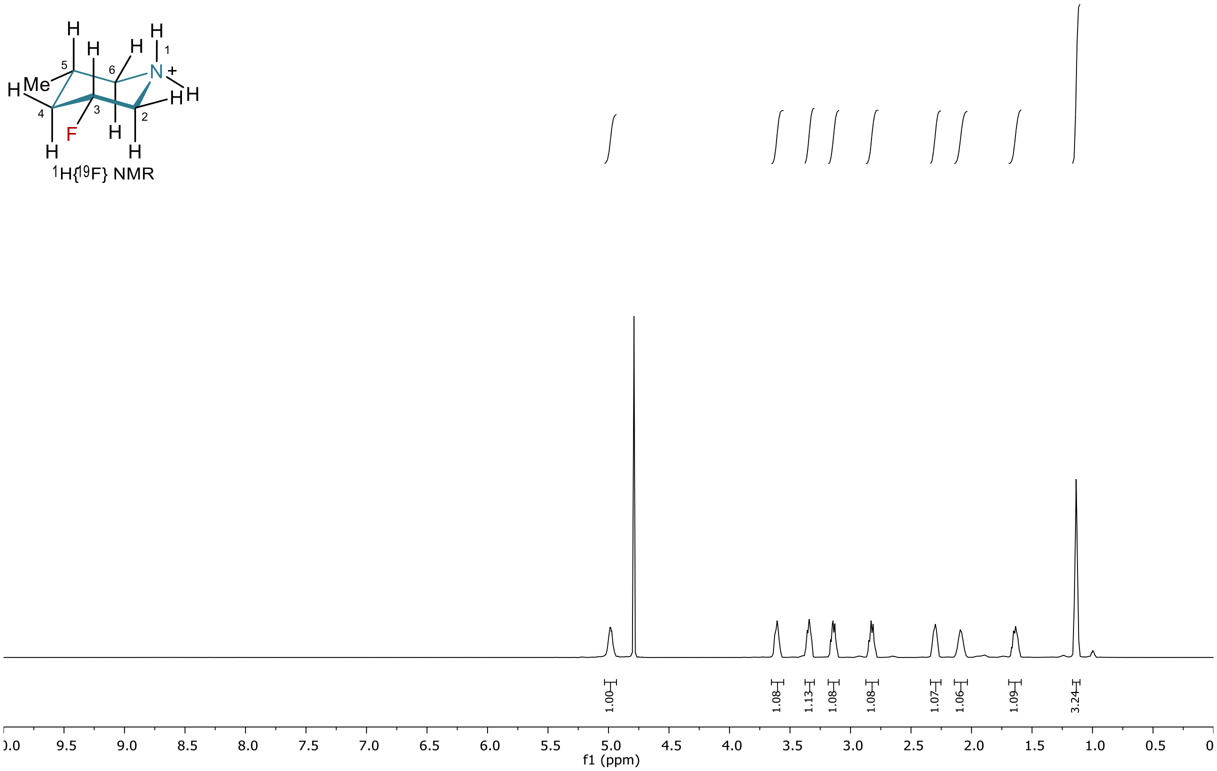

155.85
117.50
115.60
85.71
51.94
51.91
51.89
51.87
46.99
39.09
30.23
18.31
H
H
H
1
5
6
N
TFA
Me
H
H
4
3
2
F
H
H
H
Rotamer B
13C{19F} NMR
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-68.87
-68.98
-179.89
-179.97
-179.99
-180.08
-180.09
H
H
H
1
Me
5
6
N
TFA
H
H
4
3
2
F
H
H
H
19F NMR
-65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -19
f1 (ppm)

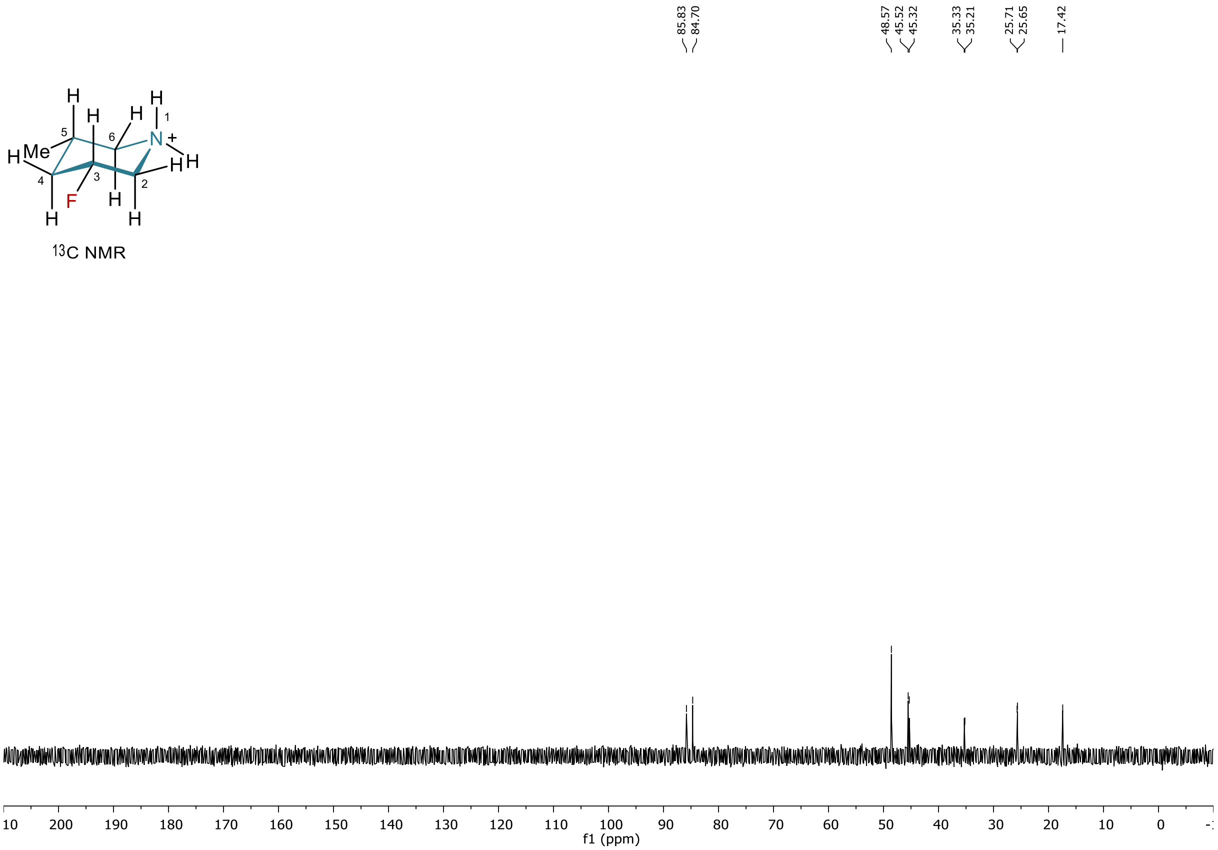

-179.93
-180.04
H
H
H
1
Me
5
6
N
TFA
H
H
4
3
2
F
H
H
H
19F{1H} NMR
-177.5 -178.0 -178.5 -179.0 -179.5 -180.0 -180.5 -181.0 -181.5 -182.0 -182.5 -183.0 -183.5 -184.0 -184.5 -185.0 -185.5 -186.0 -186.5 -187.0 -187.5 -188.0 -188.5 -189.0 -189.5 -190
f1 (ppm)

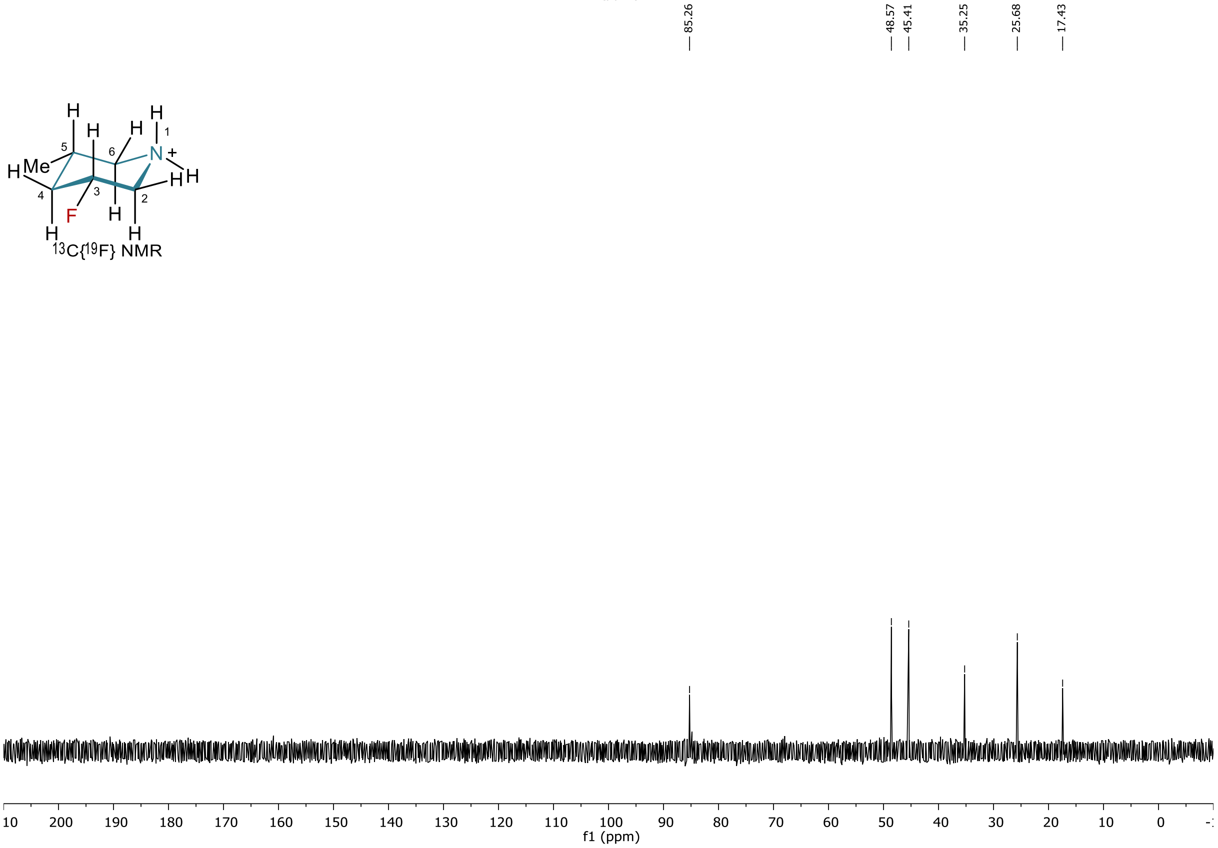


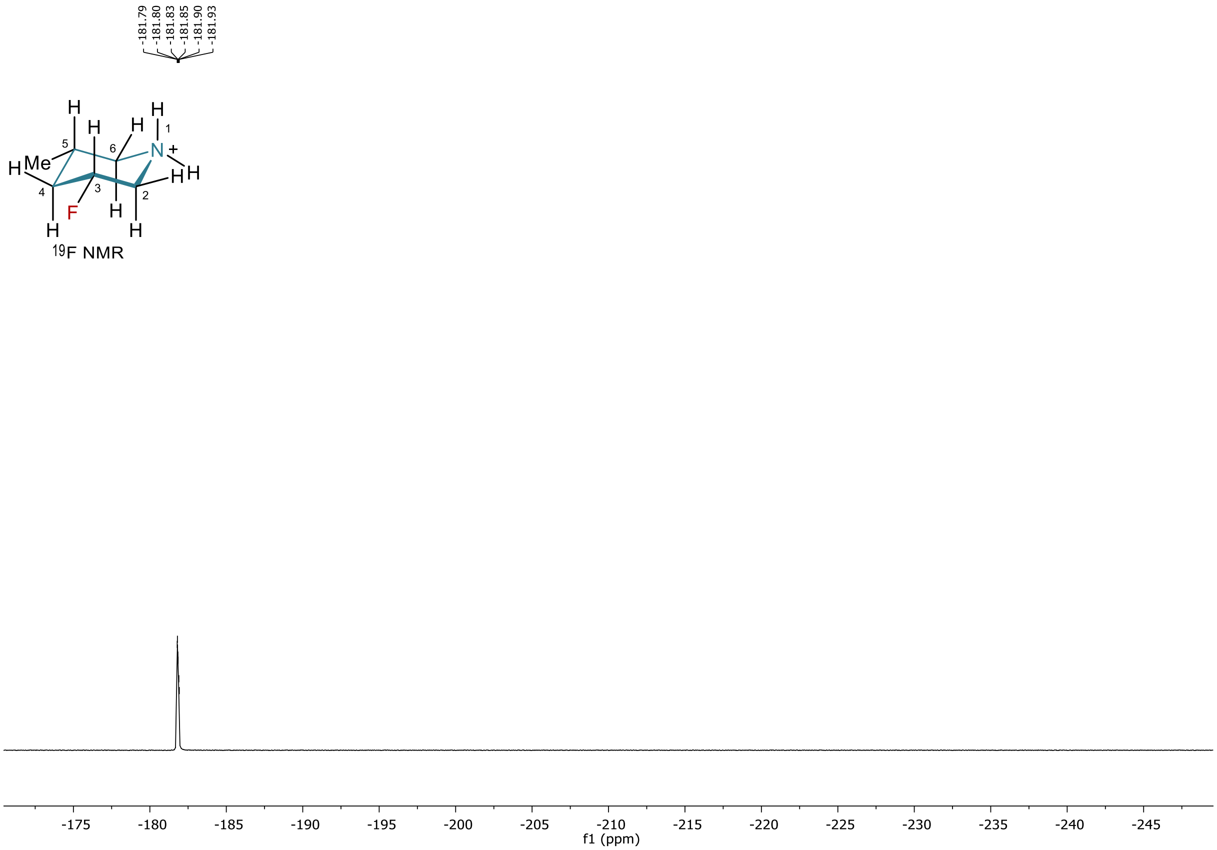
1H NMR
Me
F
N+
1
2
3
4
5
6
1.00
0.99
1.05
0.99
0.99
0.99
0.96
1.01
2.96
f1 (ppm)

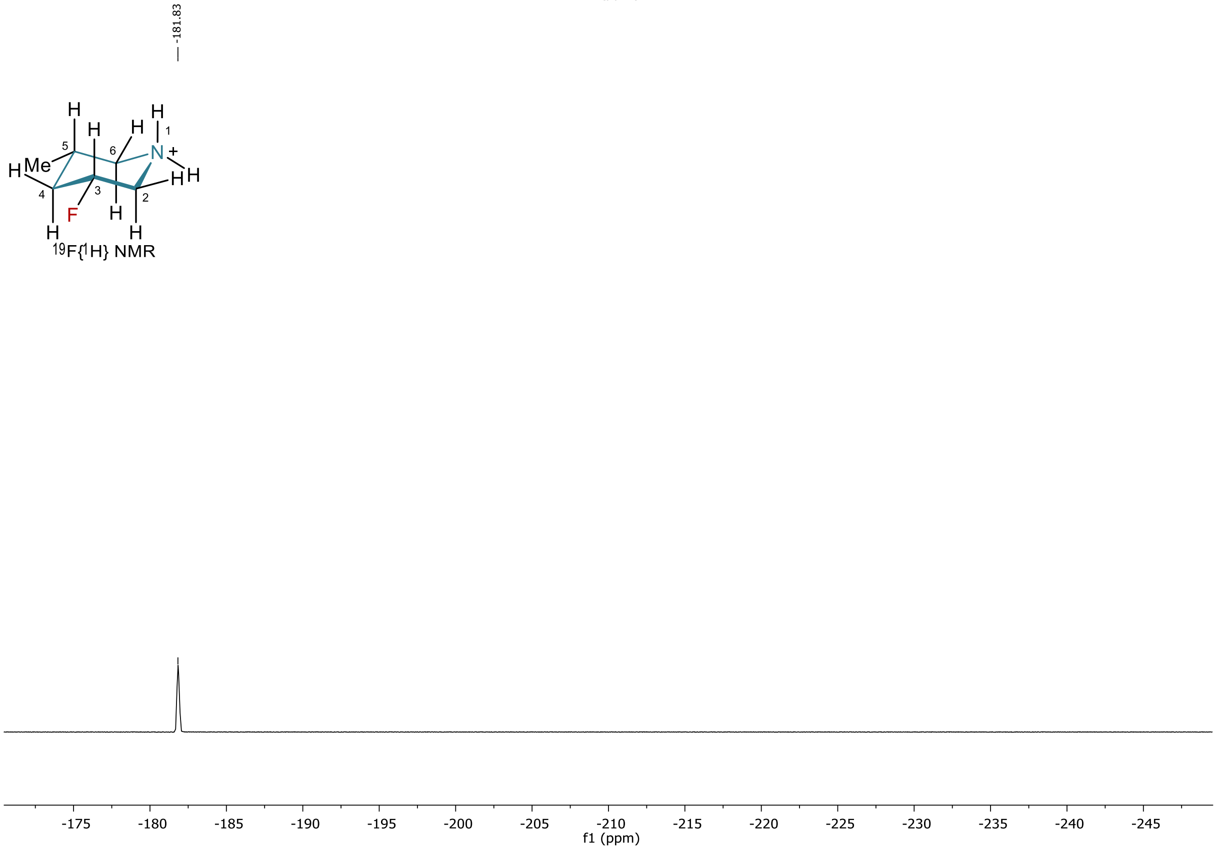


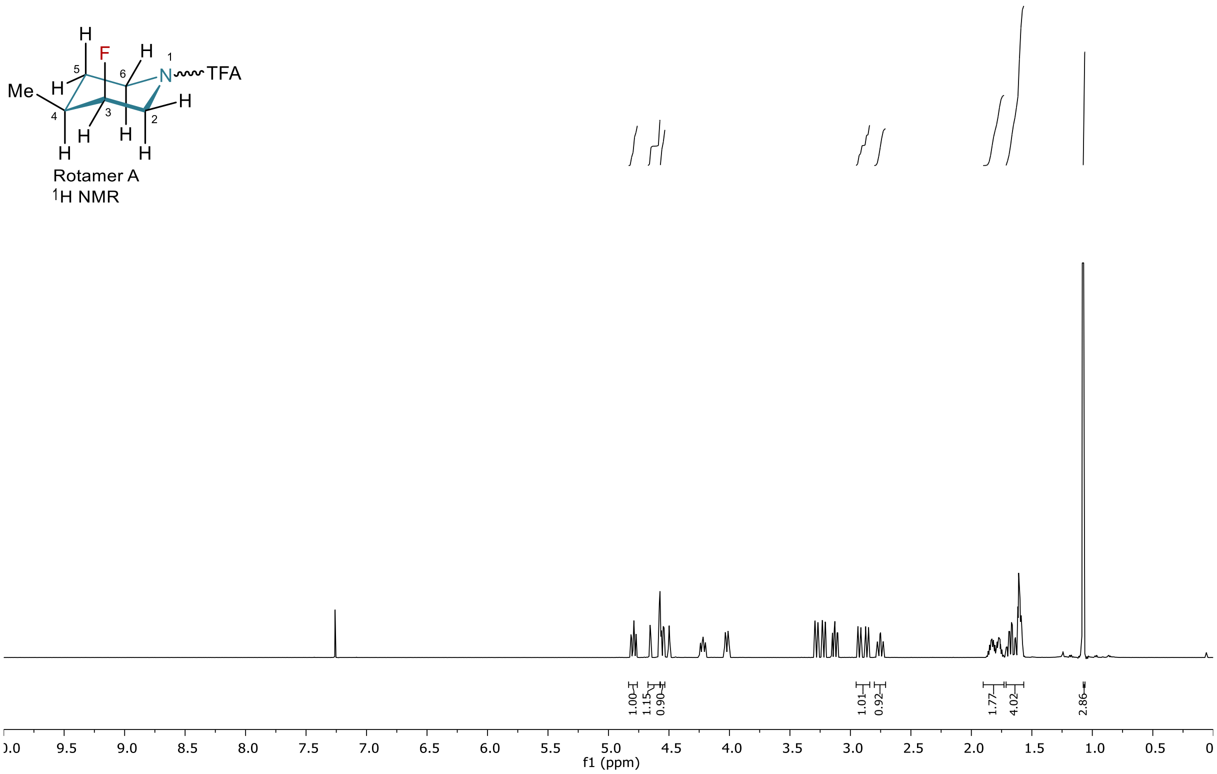
1H{19F} NMR
Me
F
N+
1
2
3
4
5
6
1.00
1.08
1.13
1.08
1.08
1.07
1.06
1.09
3.24
f1 (ppm)

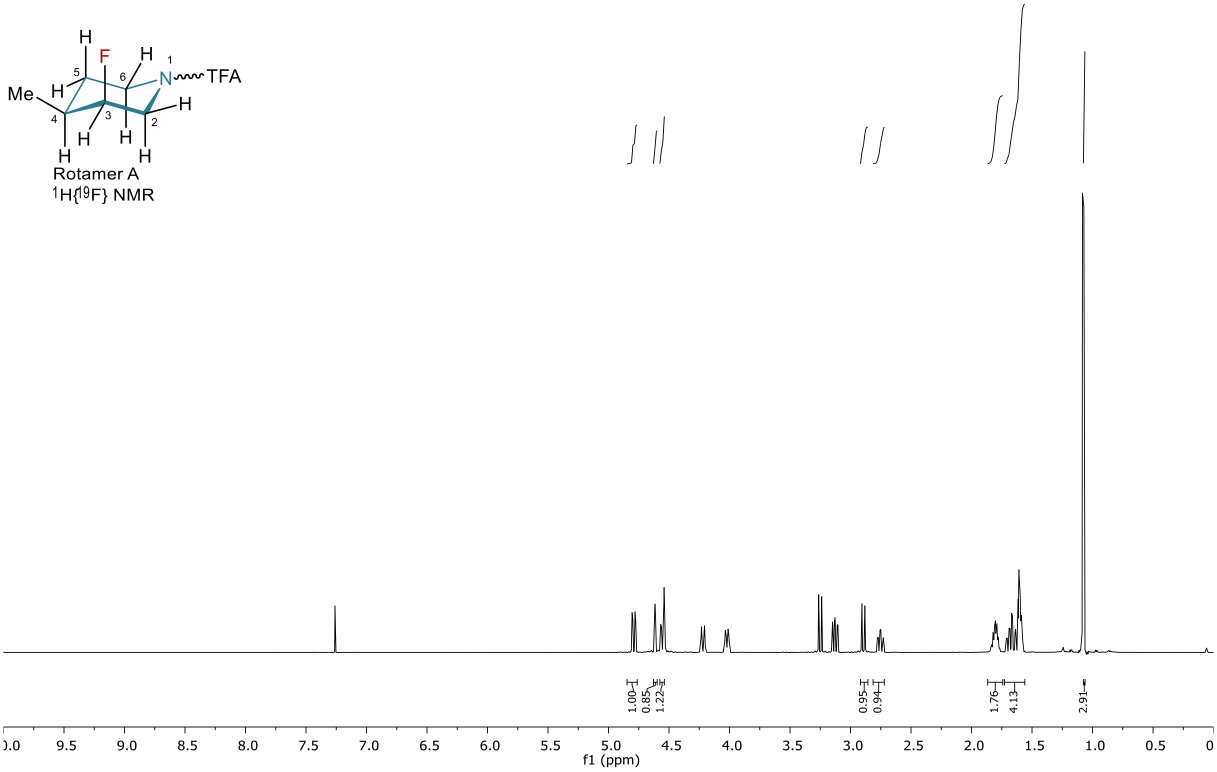

85.83
84.70
48.57
45.52
45.32
35.33
35.21
25.71
25.65
17.42
H
H
H
H
5
6
1
Me
N+
H
H
H
4
3
2
F
H
H
H
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

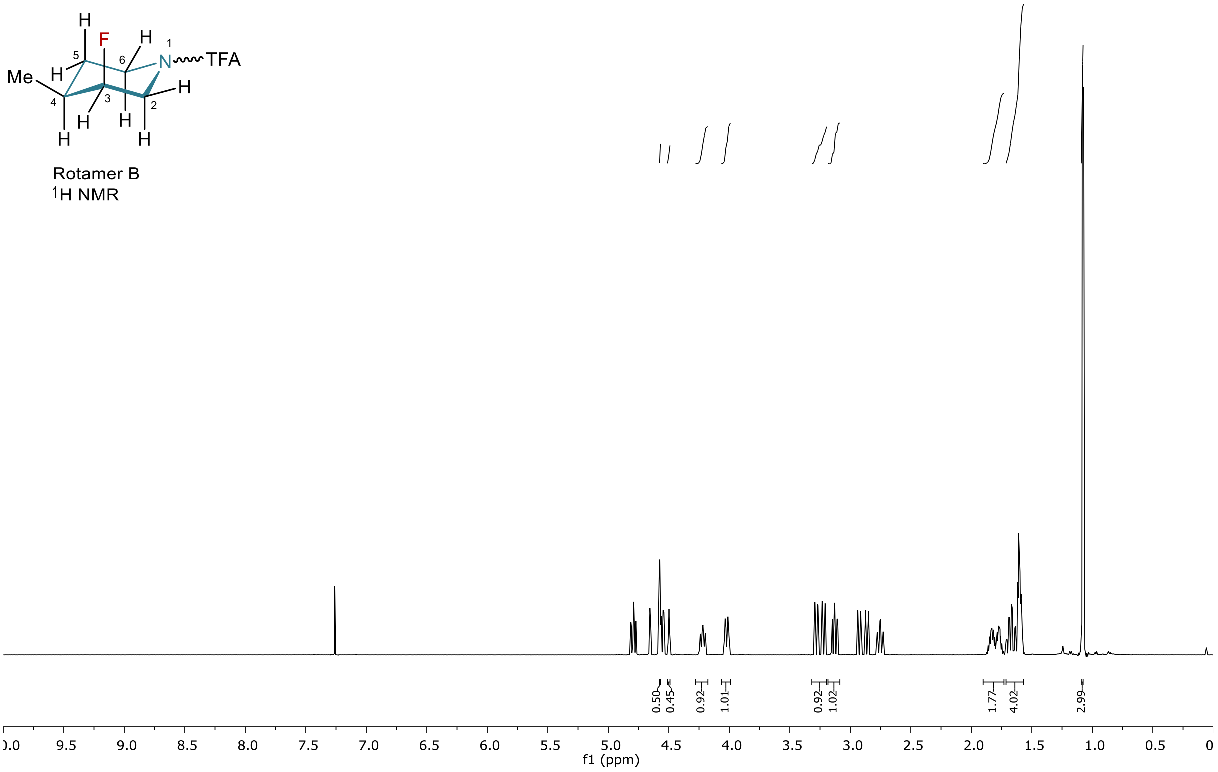

85.26
48.57
45.41
35.25
25.68
17.43
H
H
H
H
5
6
1
Me
N+
H
H
H
4
3
2
F
H
H
H
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-181.79
-181.80
-181.83
-181.85
-181.90
-181.93
H
H
H
H
1
5
6
N+
H
Me
H
H
4
3
2
F
H
H
H
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

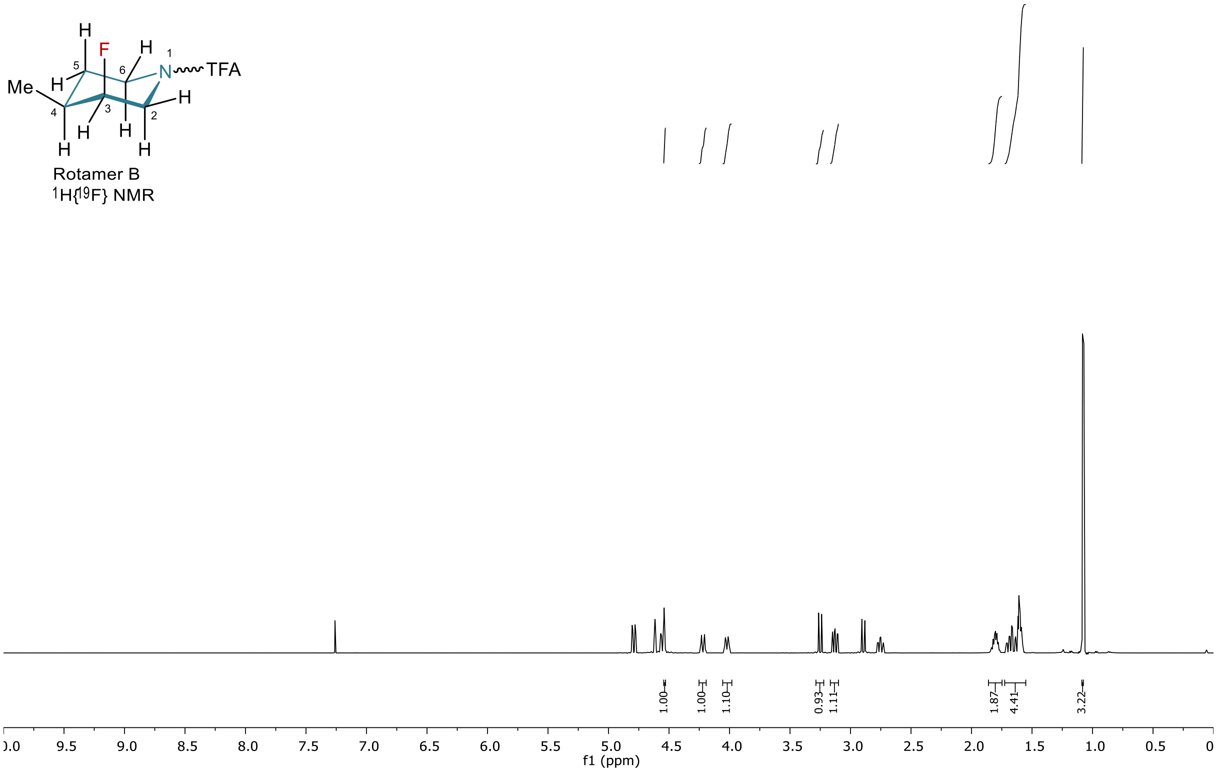

-181.83
H
H
H
H
1
5
6
N+
H
Me
H
H
4
3
2
F
H
H
H
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


H
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer A
^{1}H NMR
1.00
1.15
0.90
1.01
0.92
1.77
4.02
2.86
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

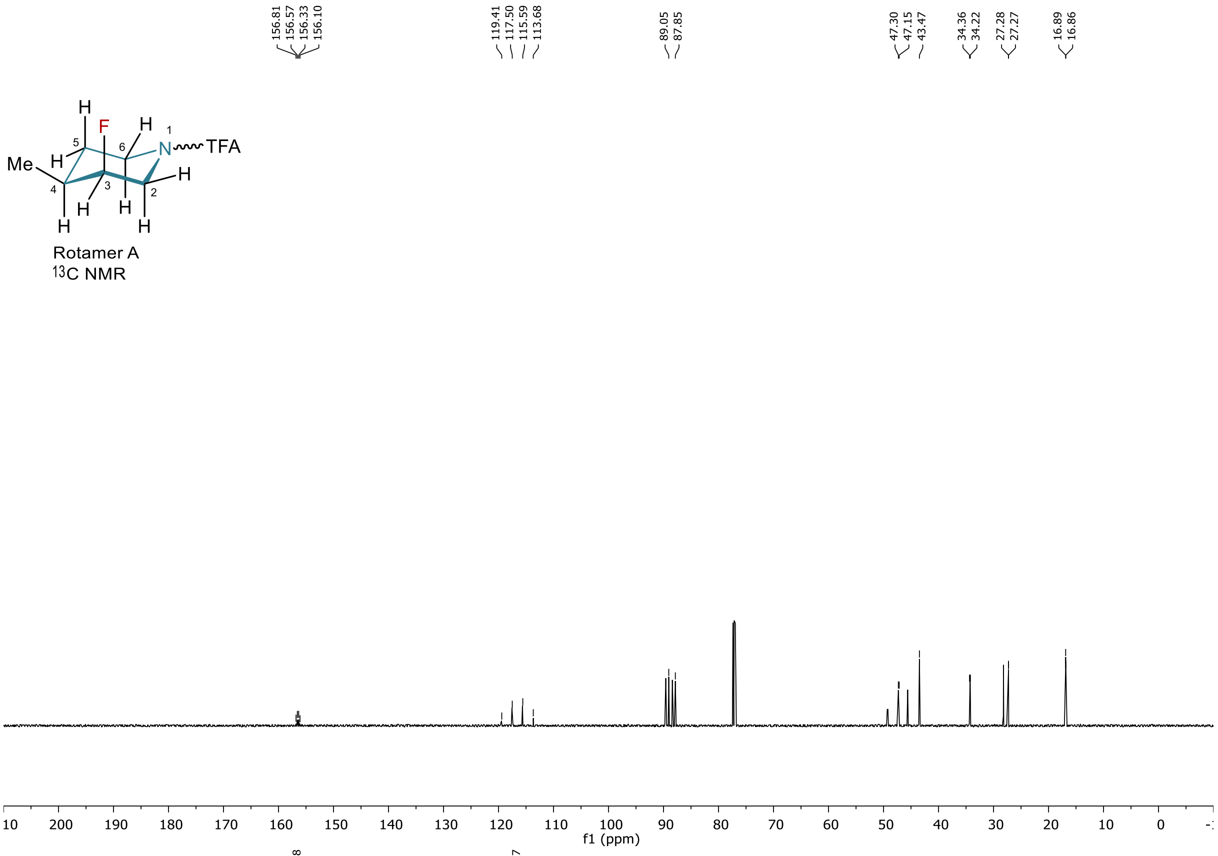

H
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer A
^{1}H{^{19}F} NMR
1.00
0.85
1.22
0.95
0.94
1.76
4.13
2.91
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)



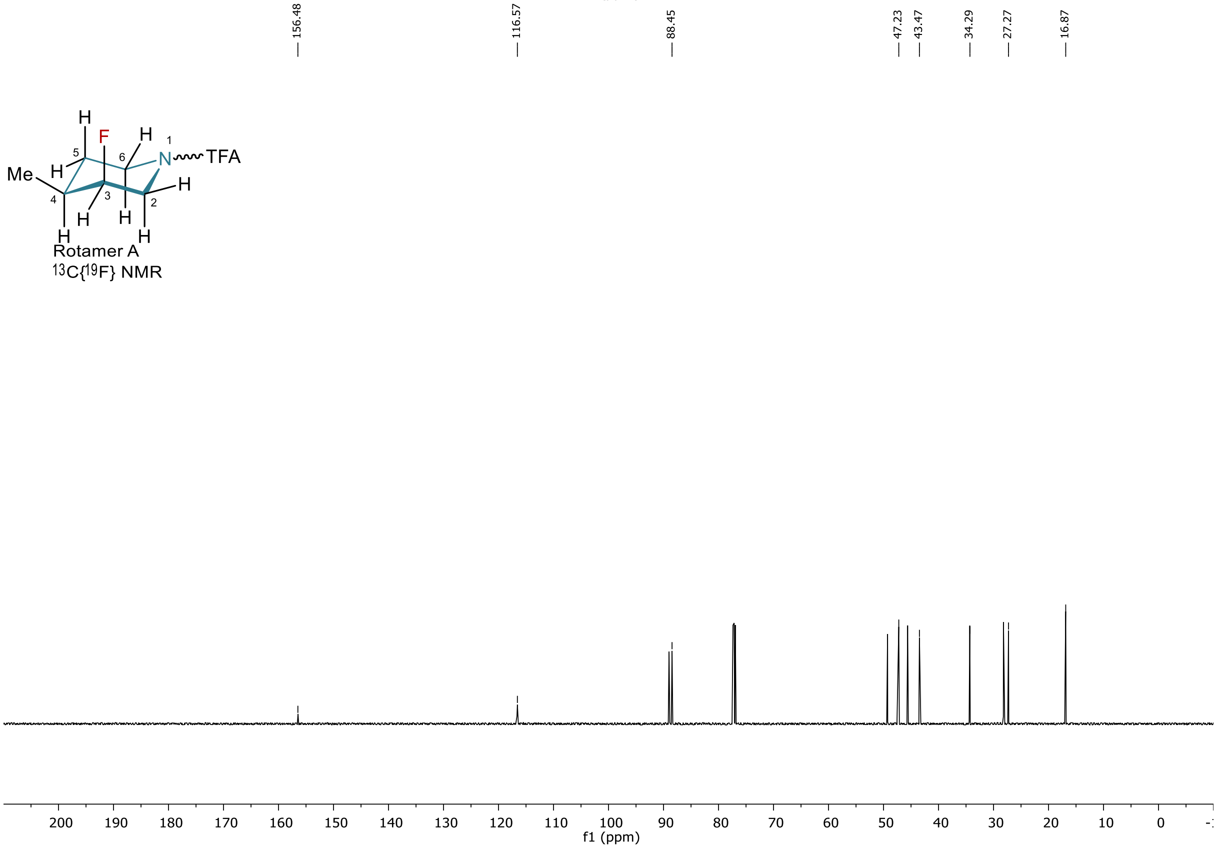
Rotamer B
^{1}H NMR



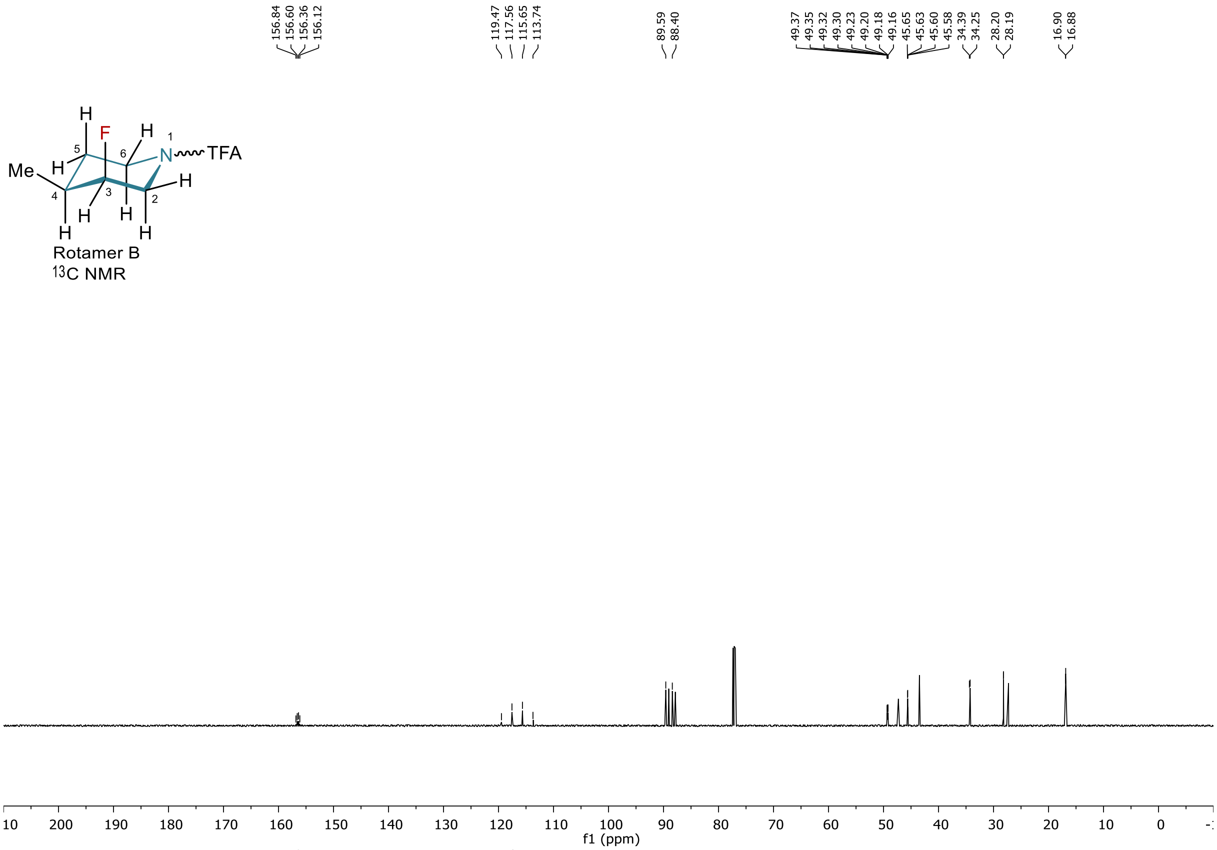
Rotamer B
^{1}H{^{19}F} NMR

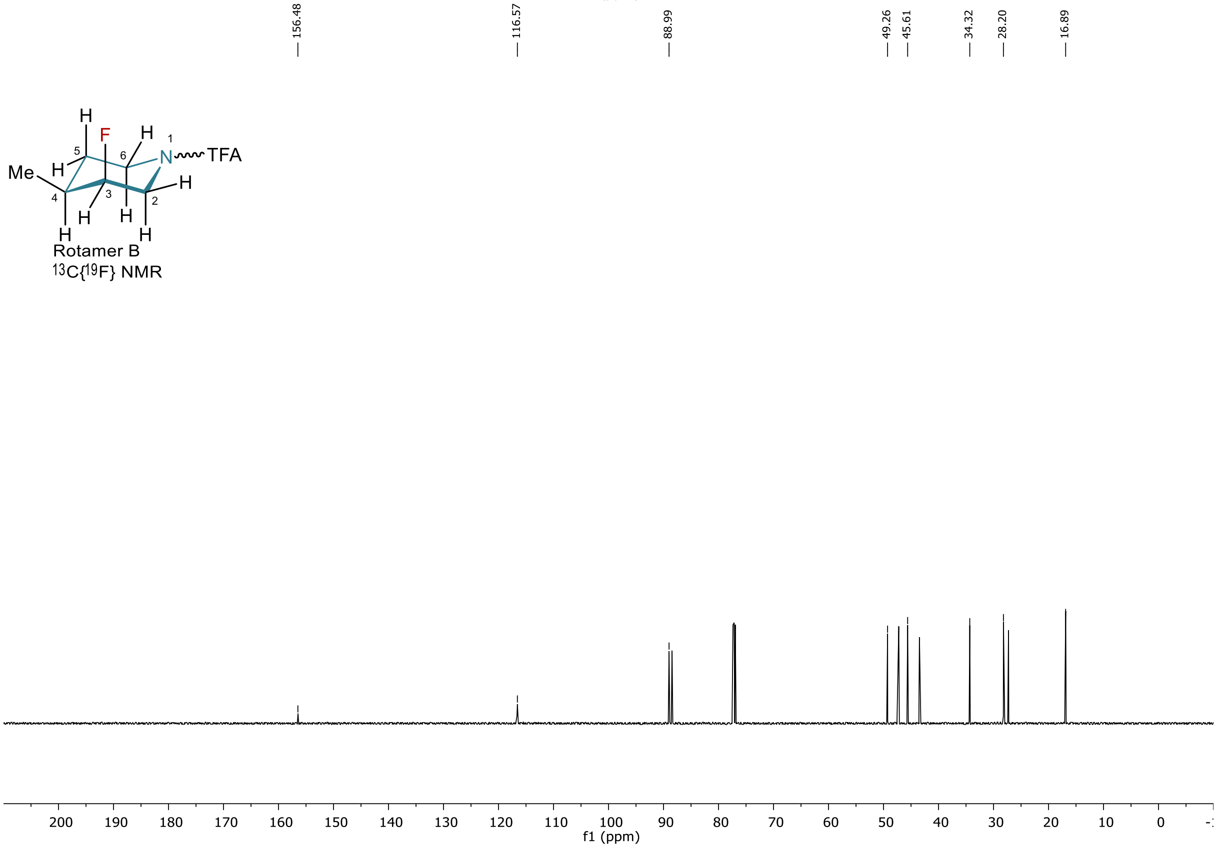


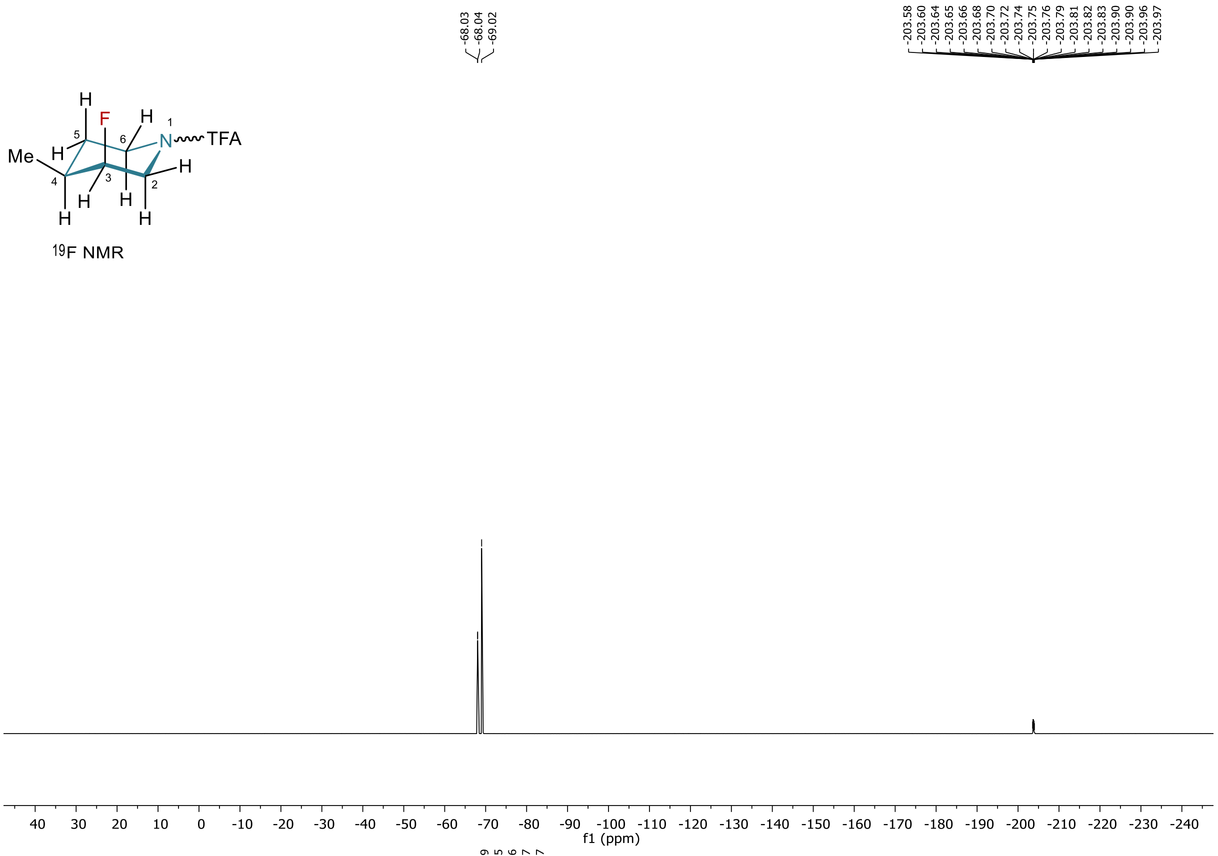
Rotamer A
^{13}C NMR



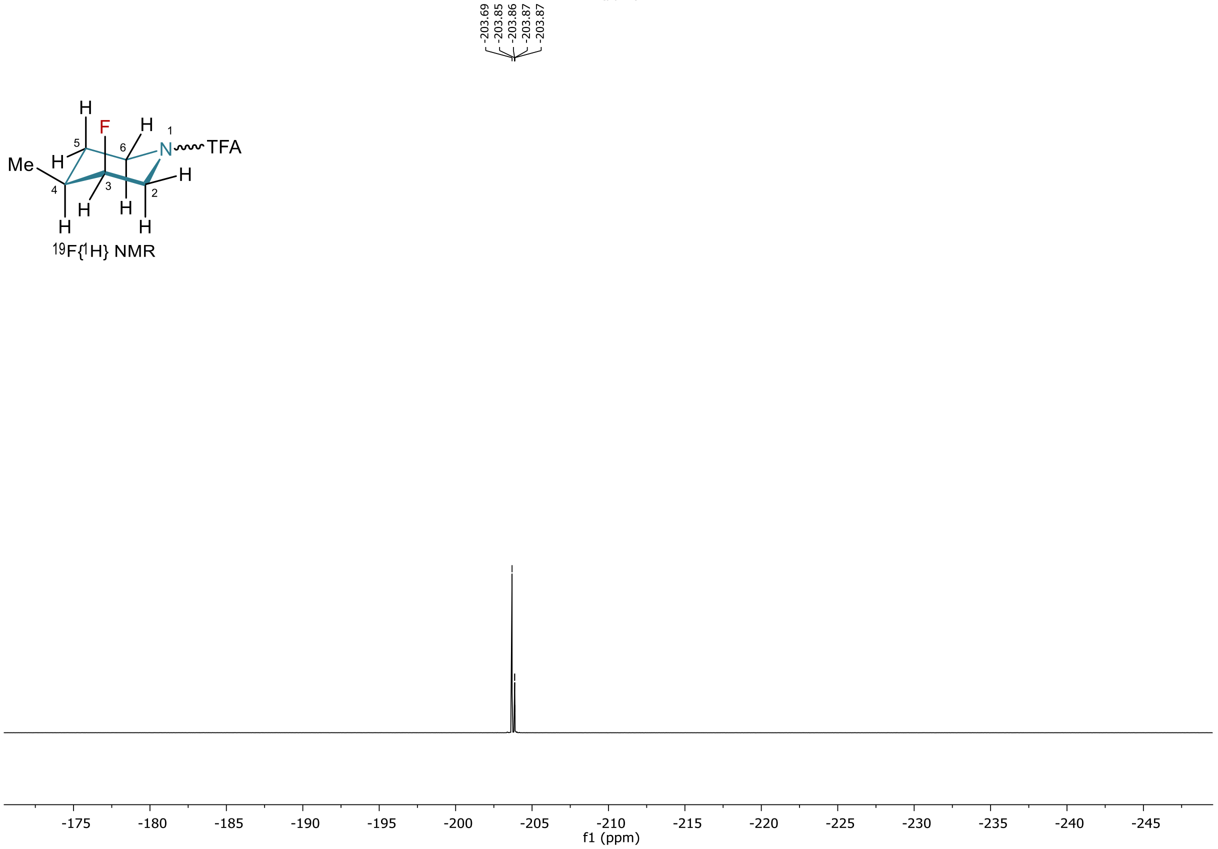
Rotamer A
^{13}C{^{19}F} NMR


156.84
156.60
156.36
156.12
119.47
117.56
115.65
113.74
89.59
88.40
49.37
49.35
49.32
49.30
49.23
49.20
49.18
49.16
45.65
45.63
45.60
45.58
34.39
34.25
28.20
28.19
16.90
16.88
H
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer B
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-:
f1 (ppm)

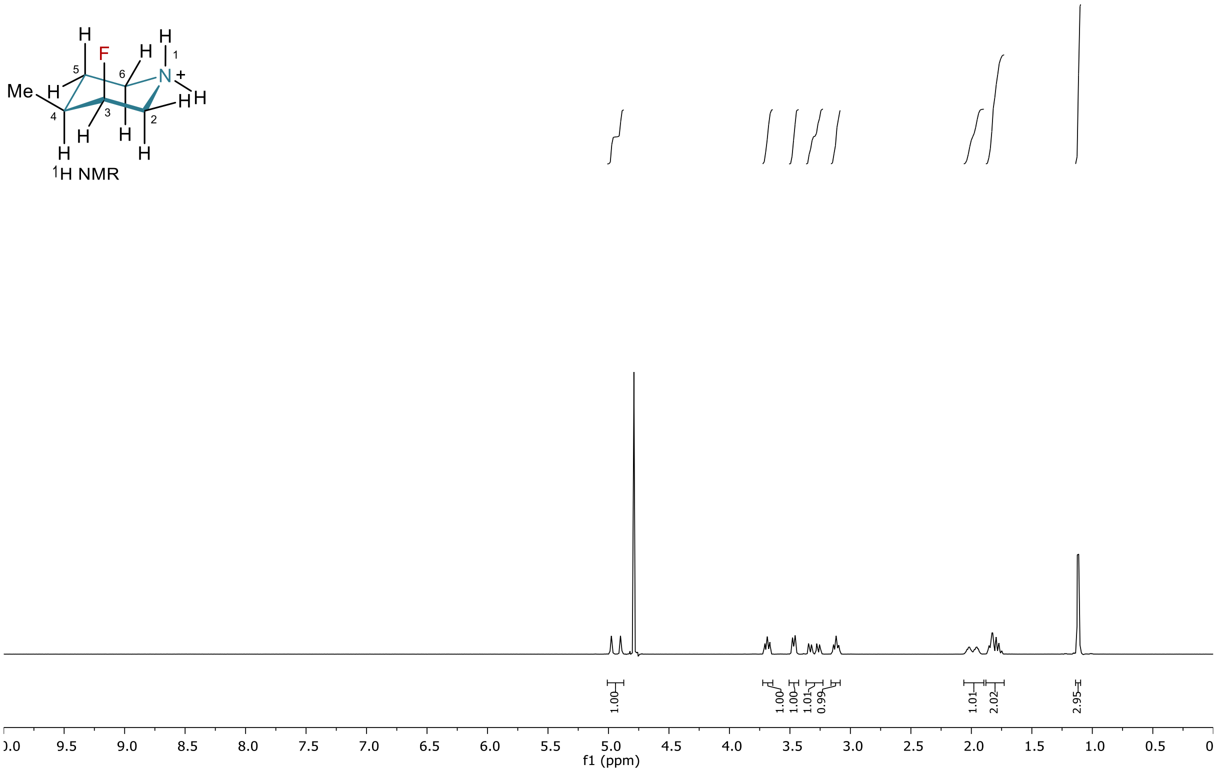

156.48
116.57
88.99
49.26
45.61
34.32
28.20
16.89
H
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer B
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-:
f1 (ppm)

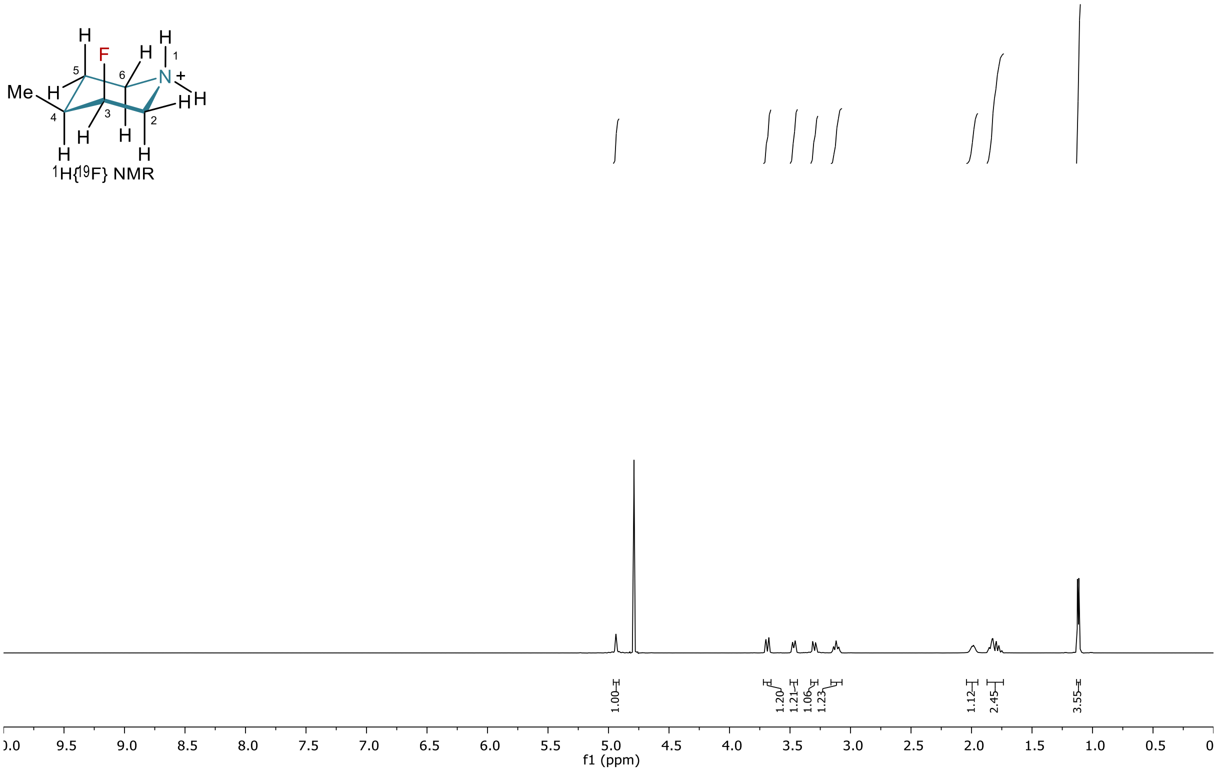


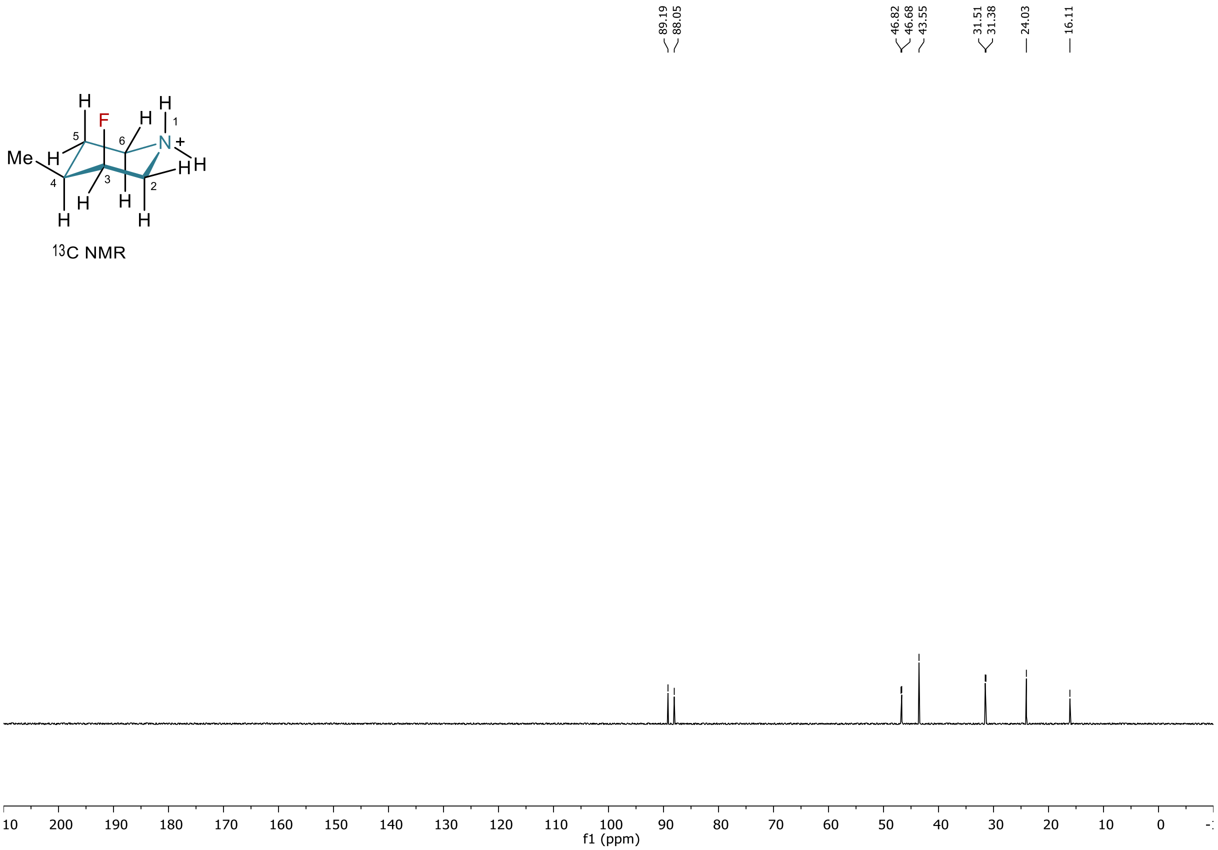
-68.03
-68.04
-69.02
-203.58
-203.60
-203.64
-203.65
-203.66
-203.68
-203.70
-203.72
-203.74
-203.75
-203.76
-203.79
-203.81
-203.82
-203.83
-203.90
-203.90
-203.96
-203.97
H
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
19F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)



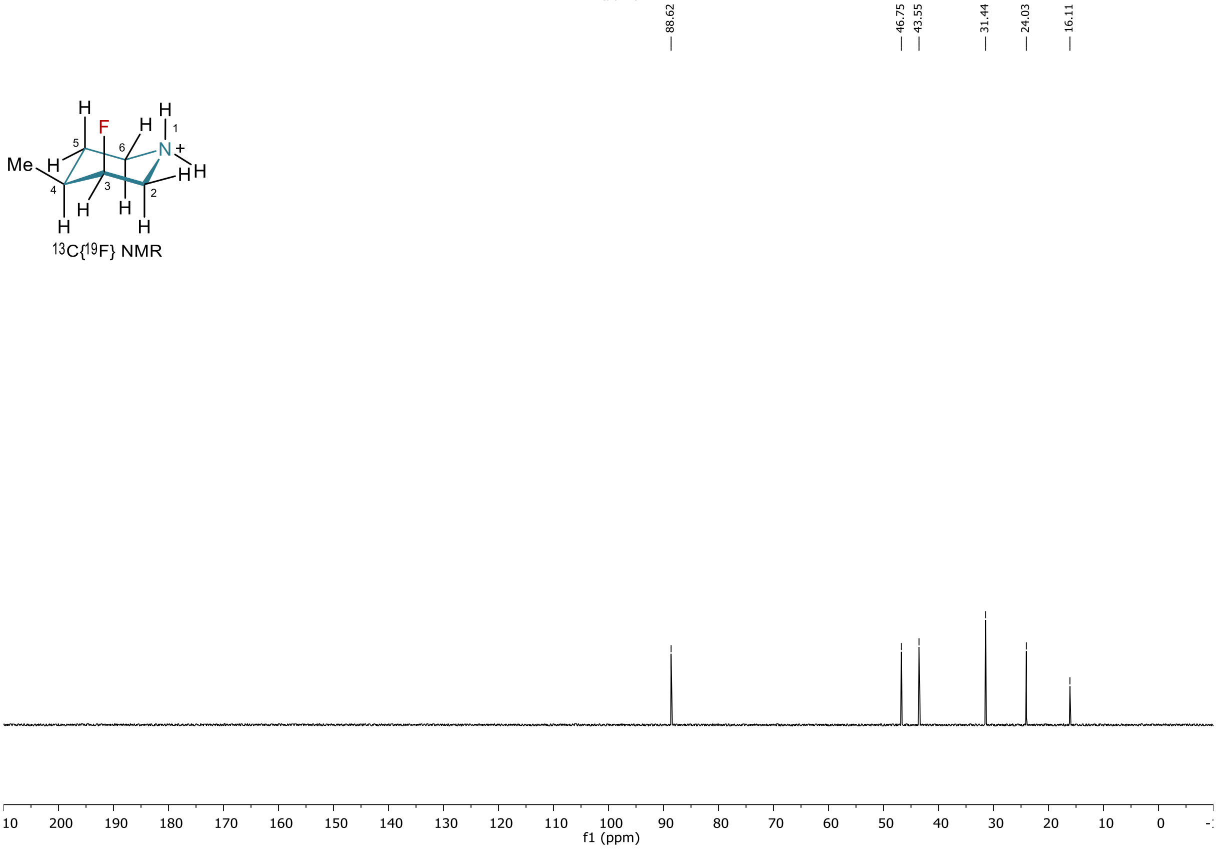
-203.69
-203.85
-203.86
-203.87
-203.87
H
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
19F{1H} NMR
-175 -180 -185 -190 -195 -200 -205 -210 -215 -220 -225 -230 -235 -240 -245
f1 (ppm)


Me
H
F
H
H
N
+
H
H
H
H
H
H
1
2
3
4
5
6
1H NMR
1.00
1.00
1.00
1.01
0.99
1.01
2.02
2.95
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

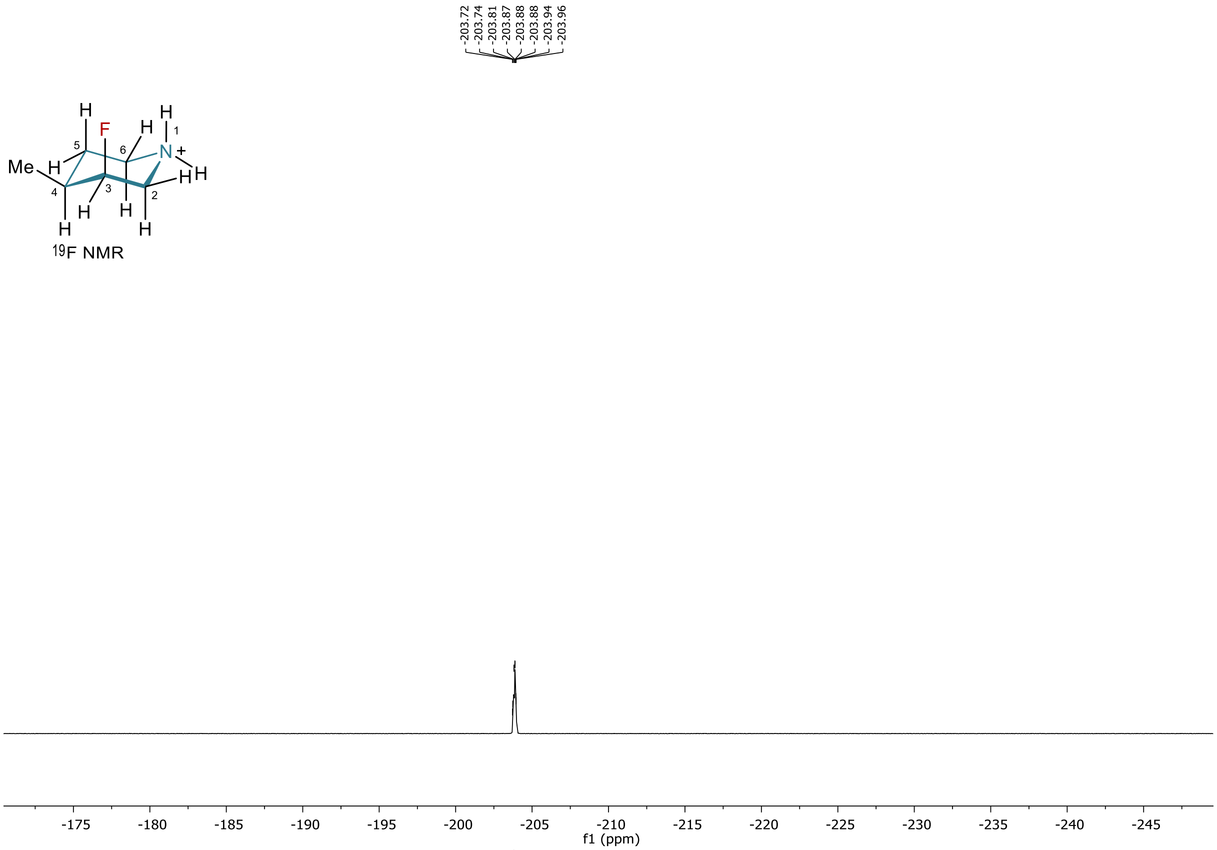

Me
H
F
H
H
N
+
H
H
H
H
H
H
1
2
3
4
5
6
1H{19F} NMR
1.00
1.20
1.21
1.06
1.23
1.12
2.45
3.55
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)



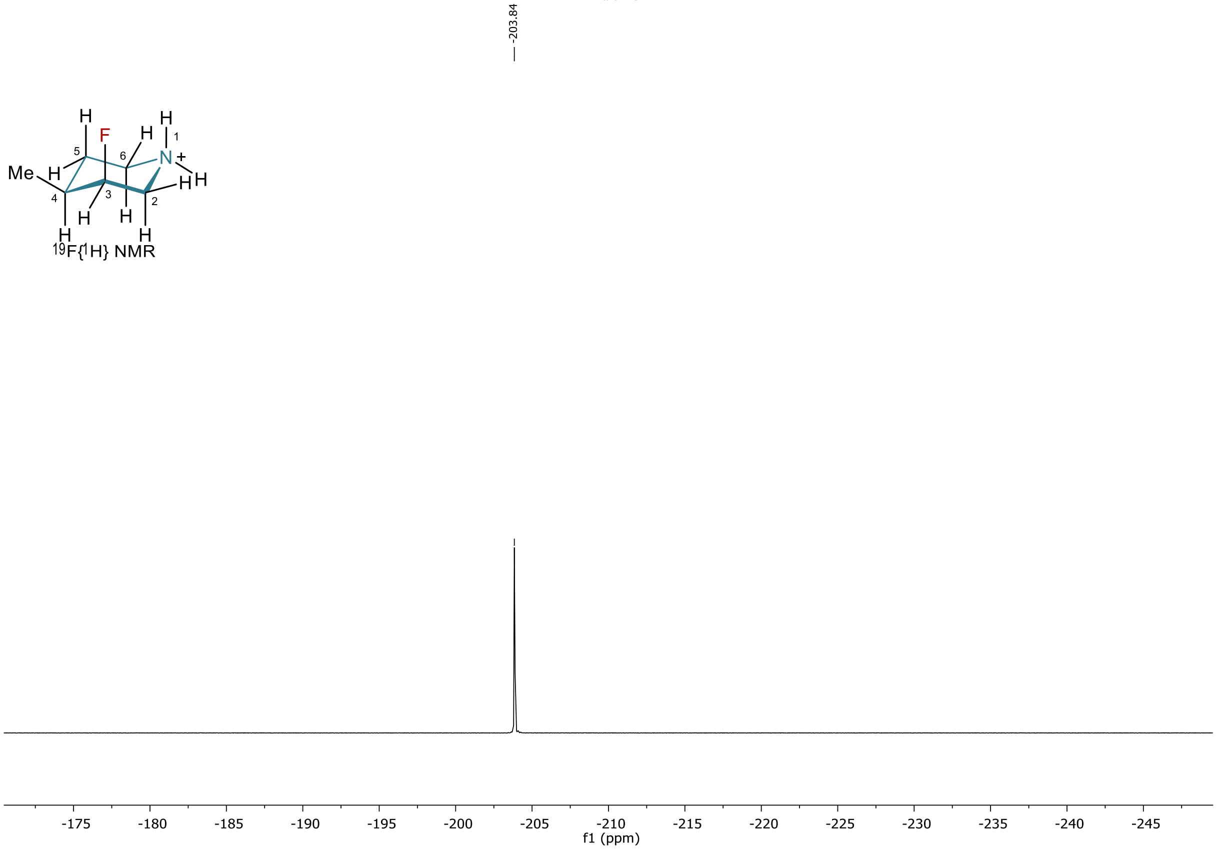
89.19
88.05
46.82
46.68
43.55
31.51
31.38
24.03
16.11
Me
F
N+
H
1
2
3
4
5
6
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



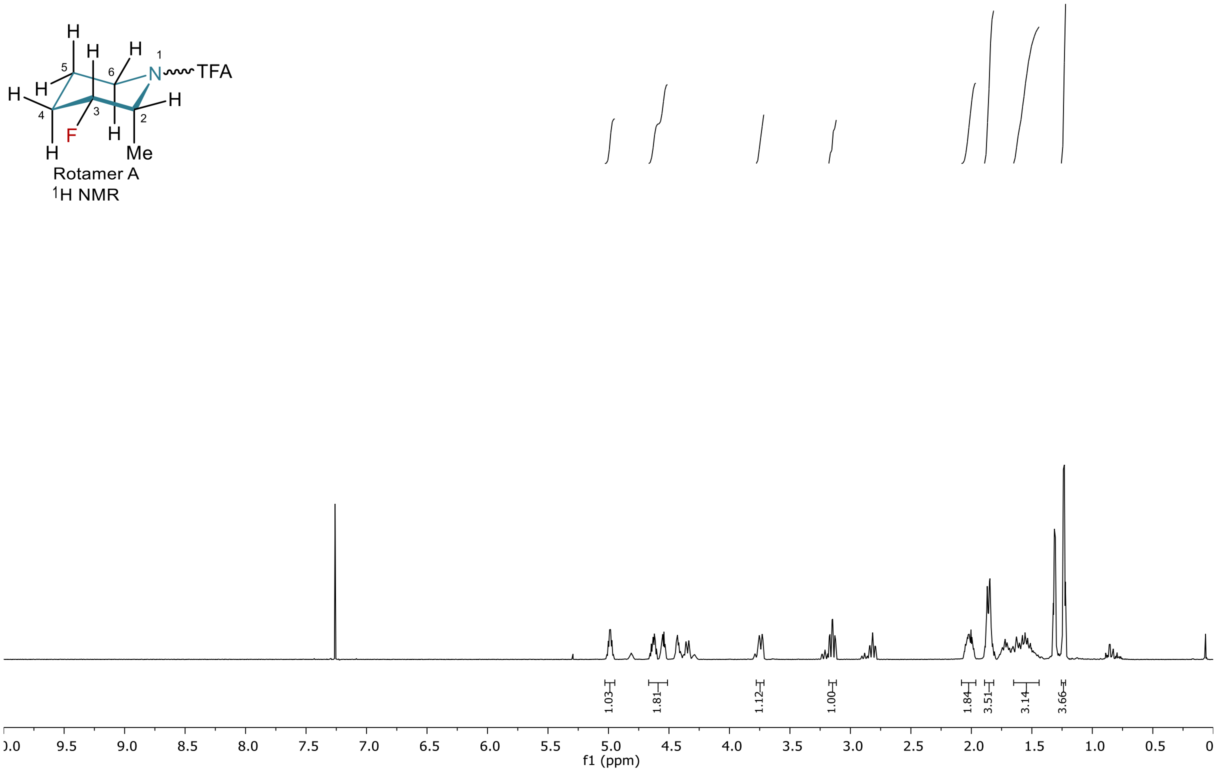
88.62
46.75
43.55
31.44
24.03
16.11
Me
F
N+
H
1
2
3
4
5
6
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

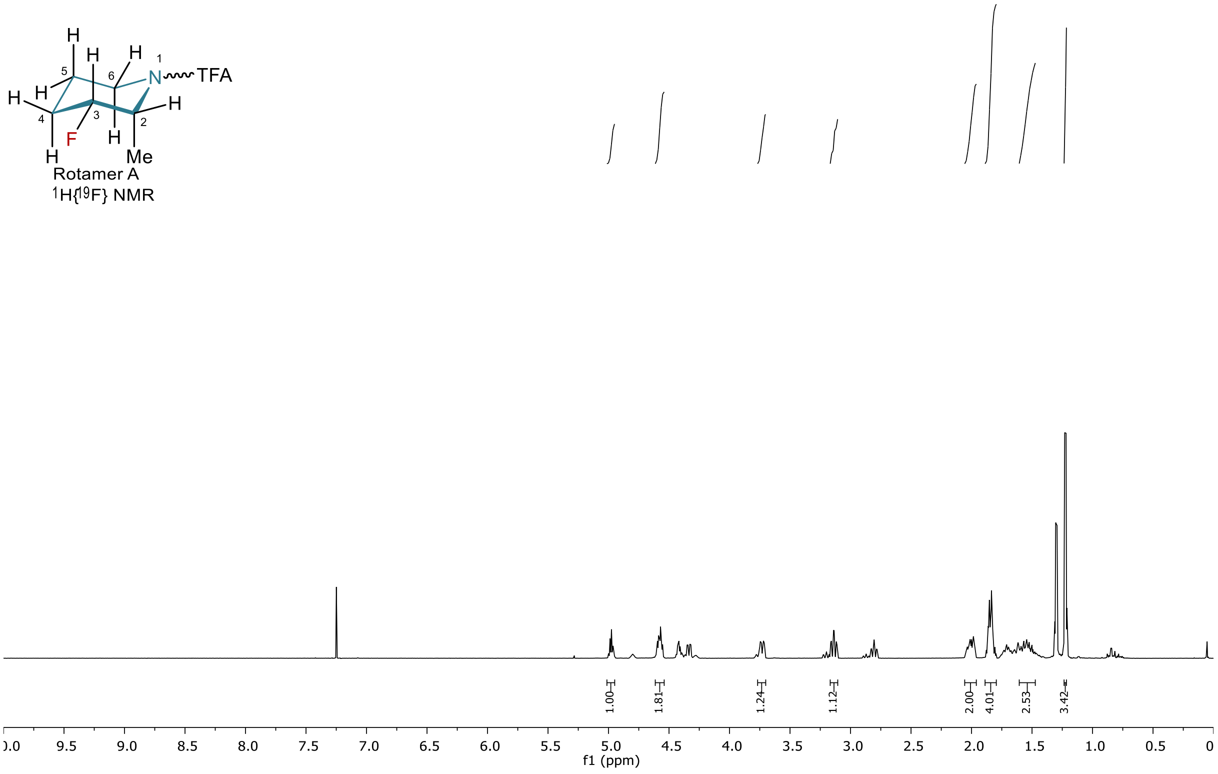


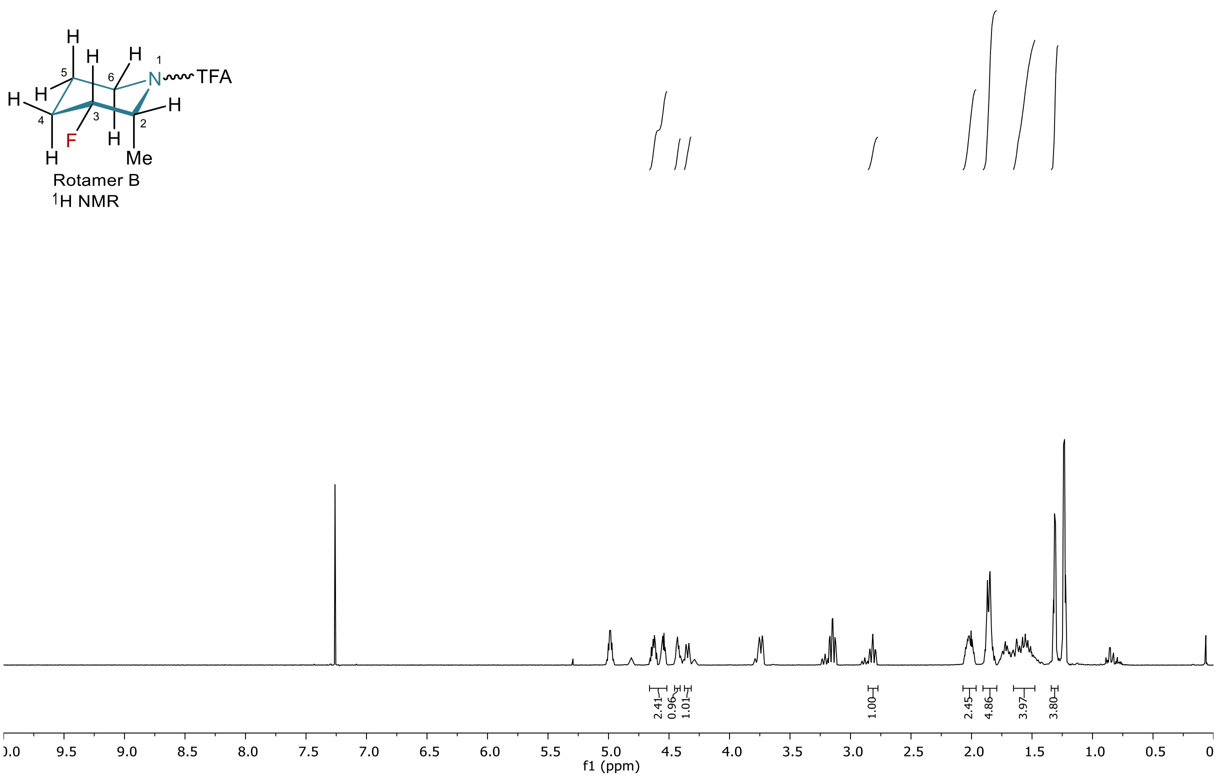
^{19}F NMR



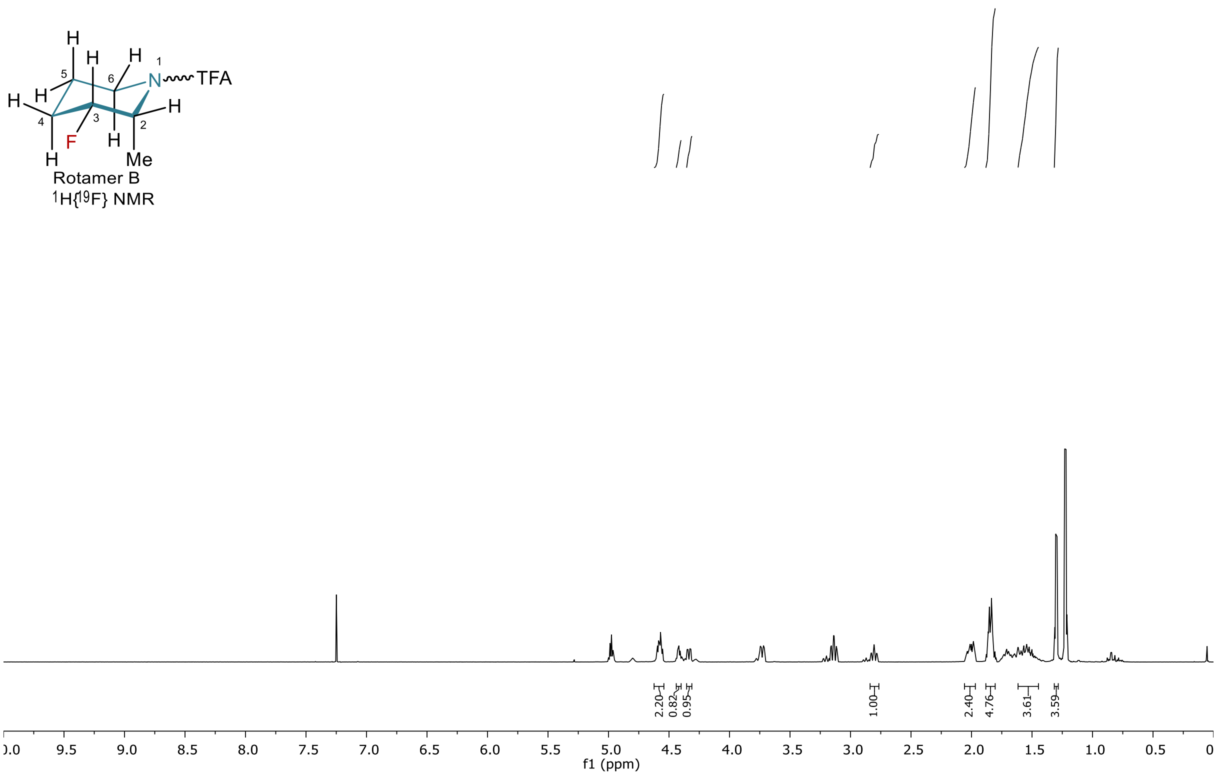
^{19}F{^{1}H} NMR


H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
F
H
H
Me
Rotamer A
^{1}H NMR
1.03
1.81
1.12
1.00
1.84
3.51
3.14
3.66
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

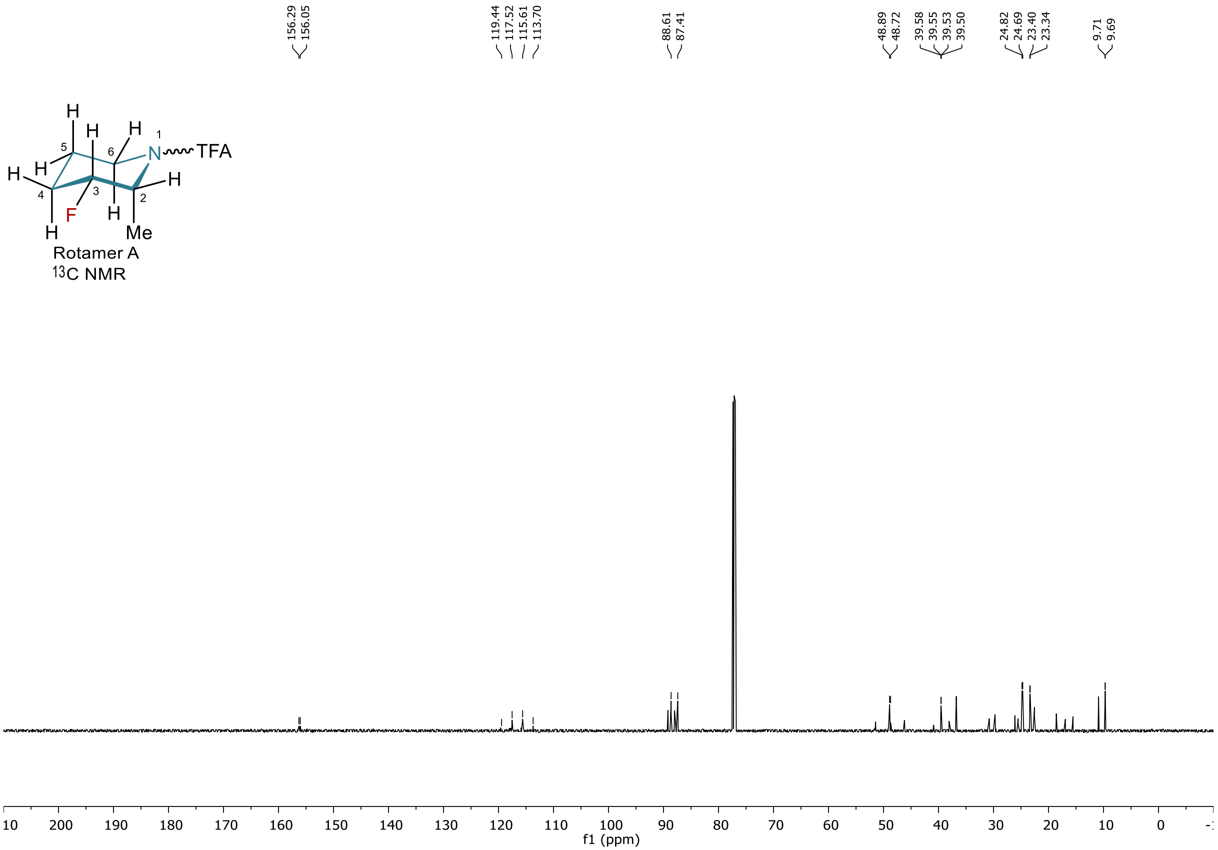

H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
F
H
H
Me
Rotamer A
^{1}H{^{19}F} NMR
1.00
1.81
1.24
1.12
2.00
4.01
2.53
3.42
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

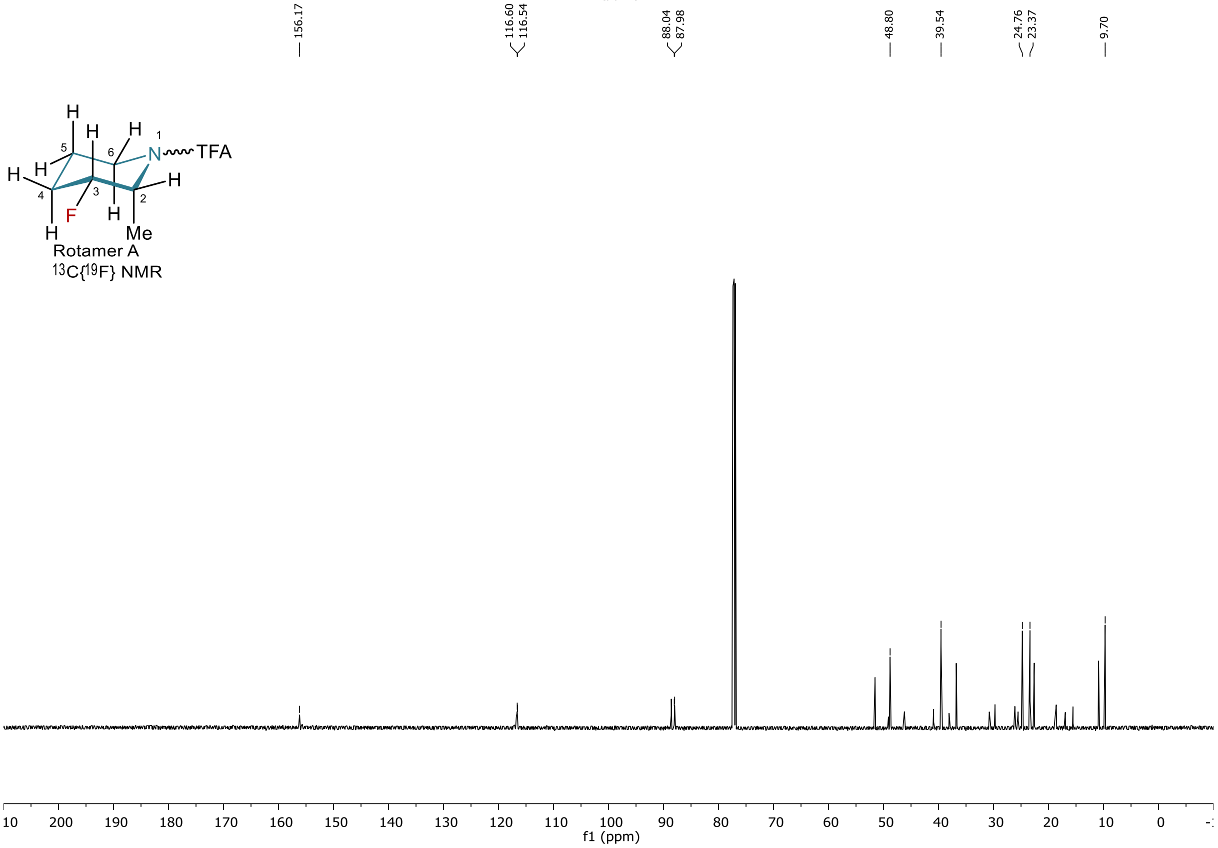


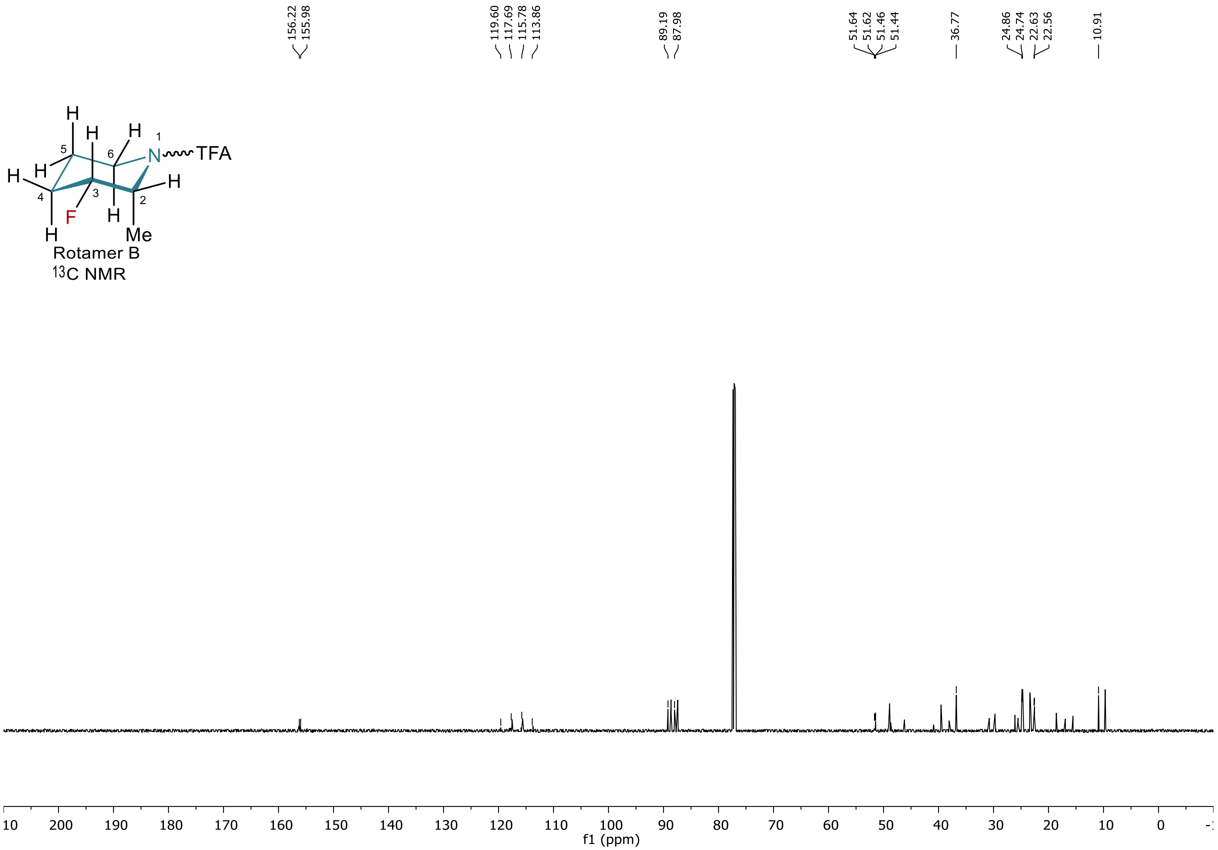
H
H
H
1
N
TFA
5
6
H
H
H
4
3
2
F
H
H
Me
Rotamer B
^{1}H NMR
2.41
0.96
1.01
1.00
2.45
4.86
3.97
3.80
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

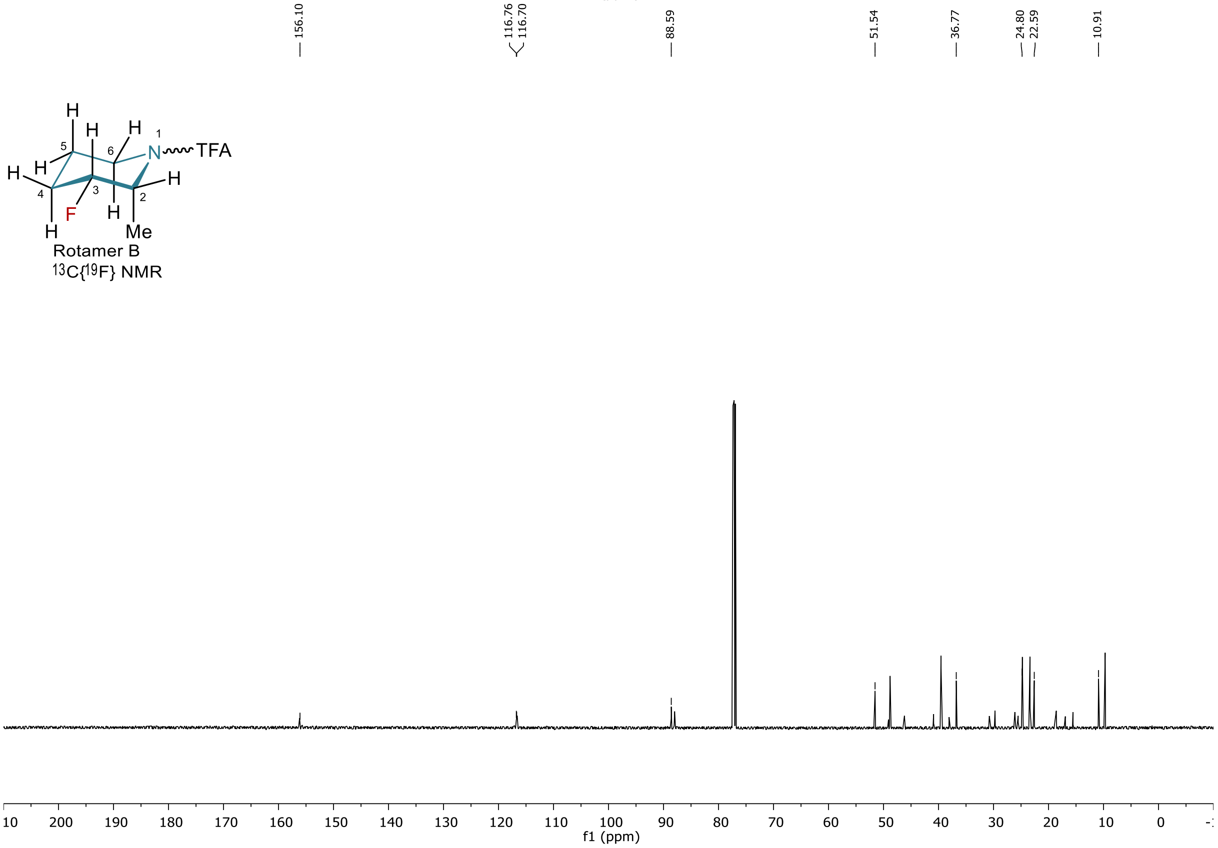


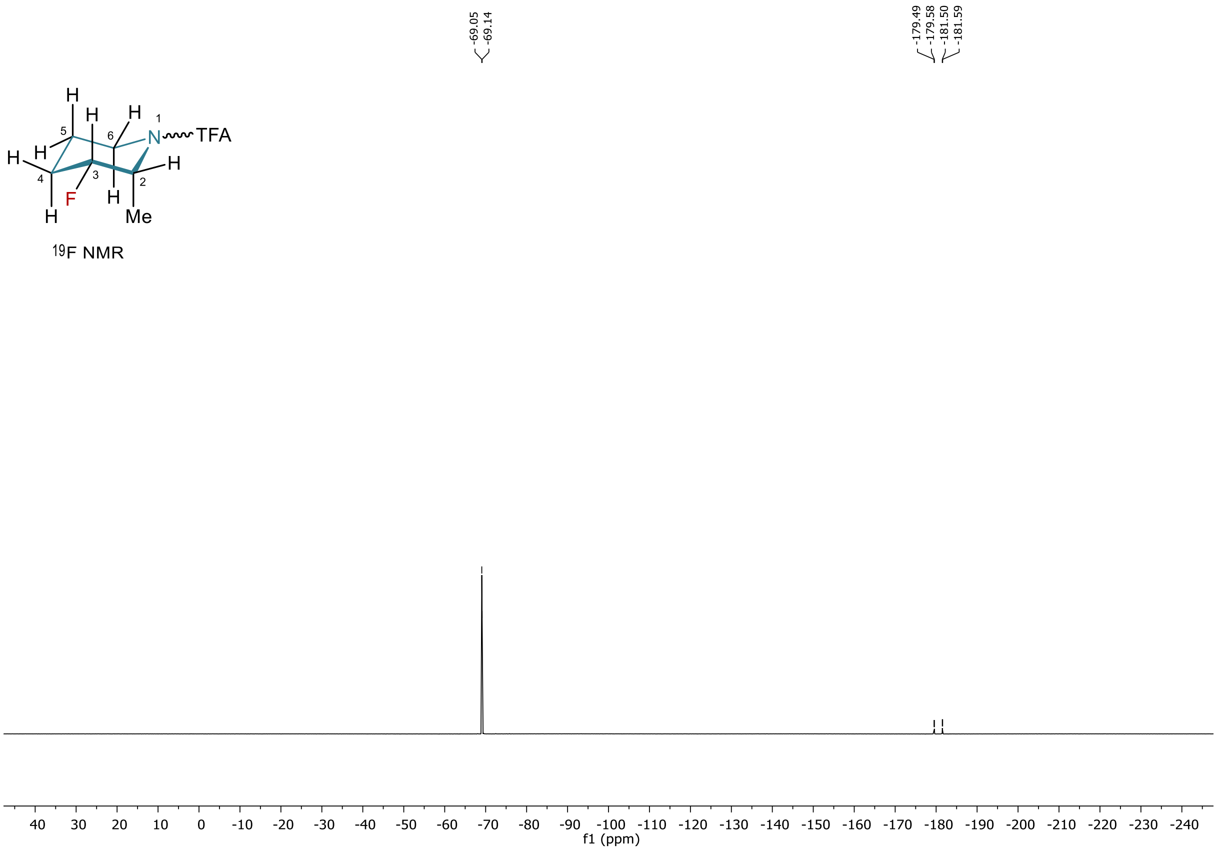
H
H
H
1
N
TFA
5
6
H
H
H
4
3
2
F
H
H
Me
Rotamer B
^{1}H{^{19}F} NMR
2.20
0.82
0.95
1.00
2.40
4.76
3.61
3.59
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


156.29
156.05
119.44
117.52
115.61
113.70
88.61
87.41
48.89
48.72
39.58
39.55
39.53
39.50
24.82
24.69
23.40
23.34
9.71
9.69
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
F
H
H
Me
Rotamer A
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

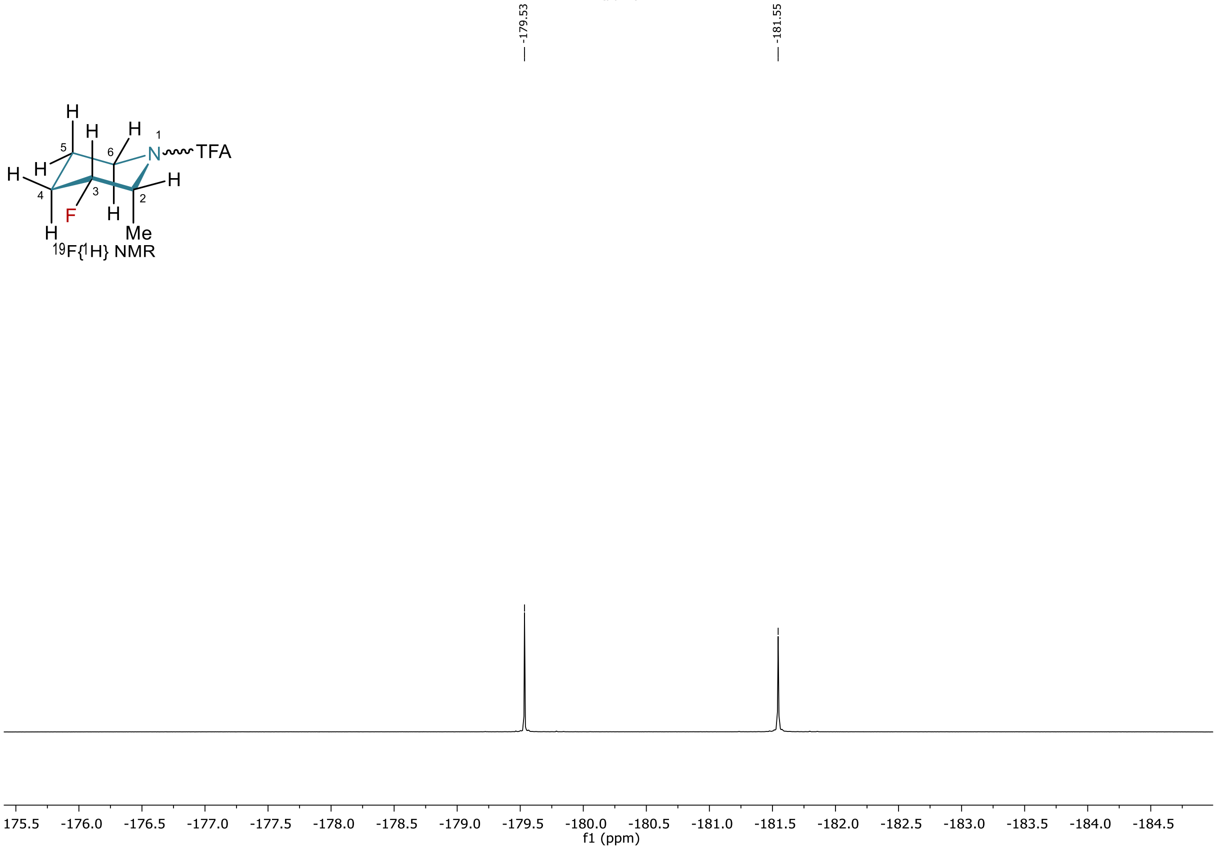

156.17
116.60
116.54
88.04
87.98
48.80
39.54
24.76
23.37
9.70
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
F
H
H
Me
Rotamer A
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


156.22
155.98
119.60
117.69
115.78
113.86
89.19
87.98
51.64
51.62
51.46
51.44
36.77
24.86
24.74
22.63
22.56
10.91
H
H
H
1
N
TFA
5
6
H
H
H
4
3
2
F
H
H
Me
Rotamer B
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

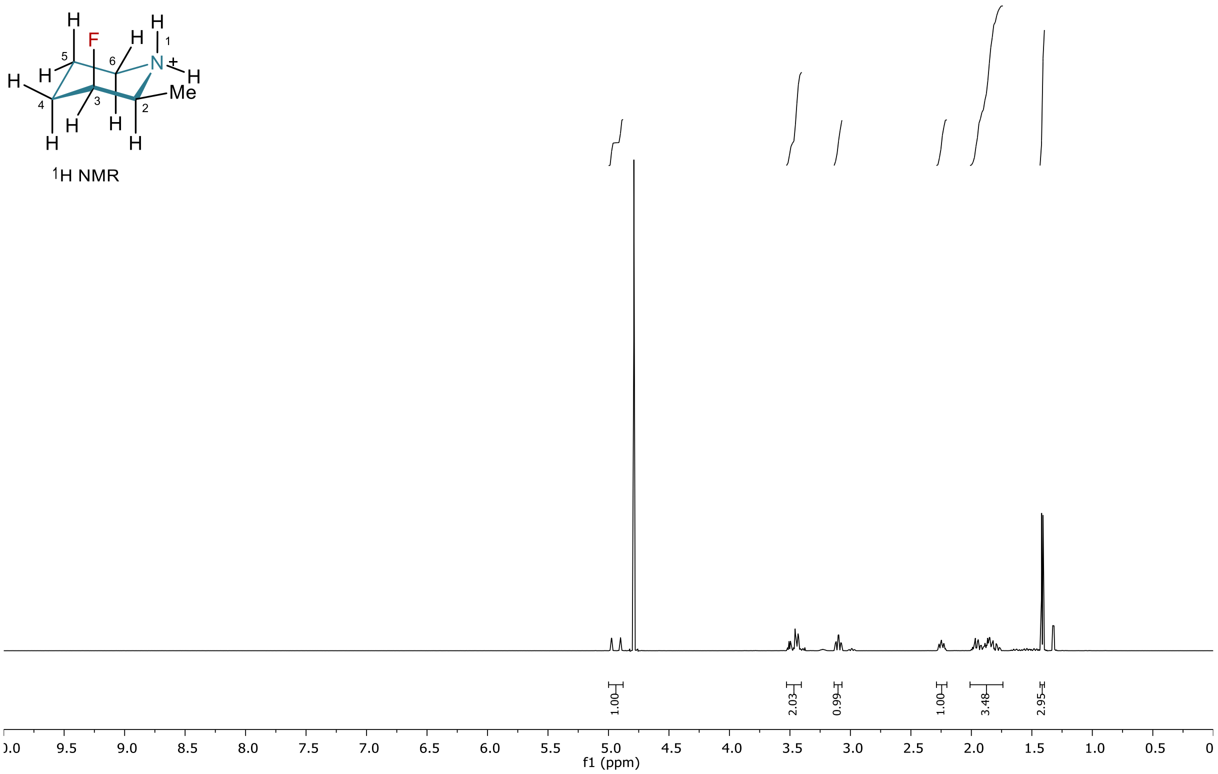

156.10
116.76
116.70
88.59
51.54
36.77
24.80
22.59
10.91
H
H
H
1
N
TFA
5
6
H
H
H
4
3
2
F
H
H
Me
Rotamer B
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

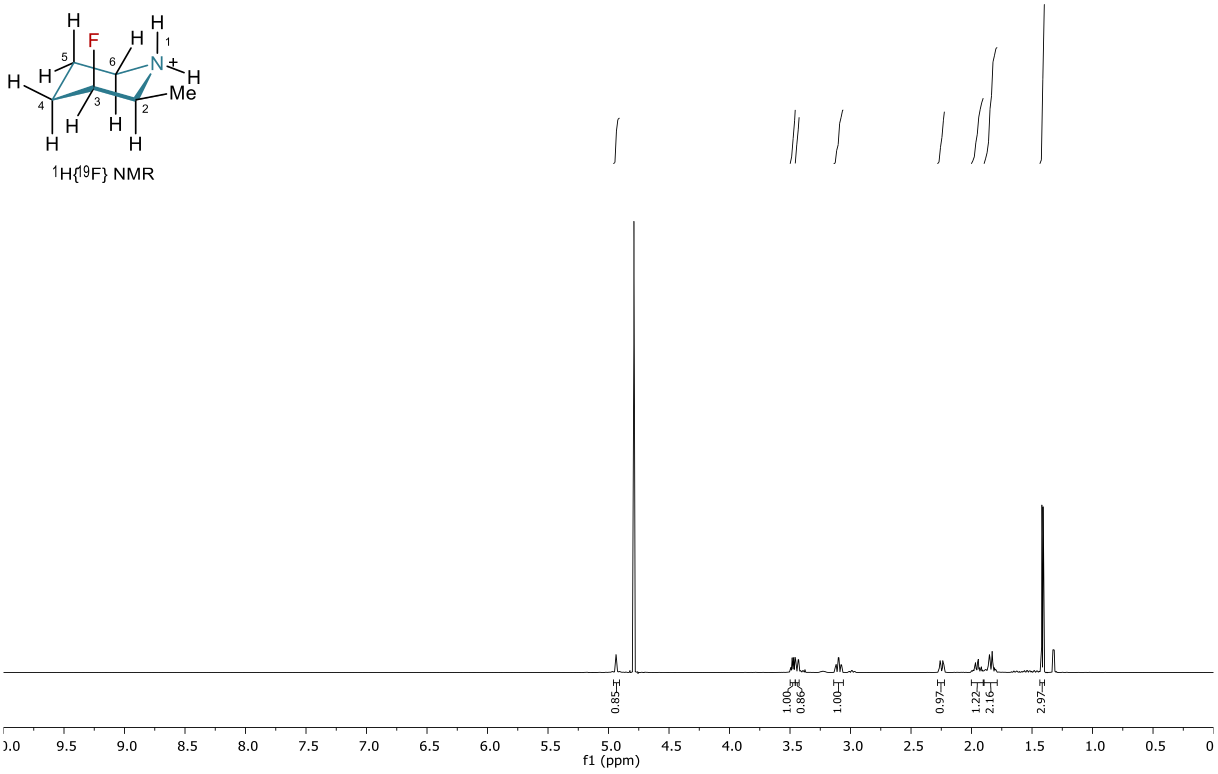


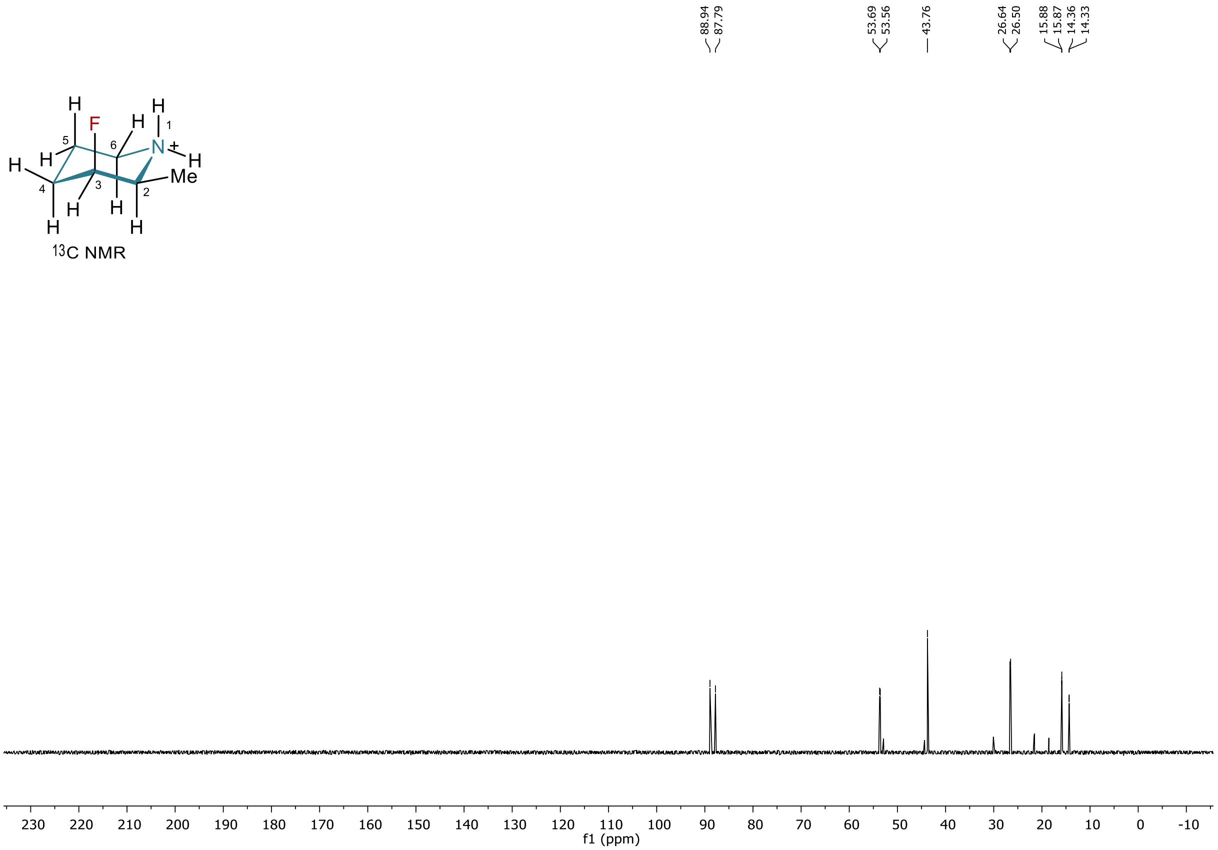
-69.05
-69.14
-179.49
-179.58
-181.50
-181.59
H
H
H
5
6
N
1
TFA
H
H
4
3
2
H
F
H
H
Me
19F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

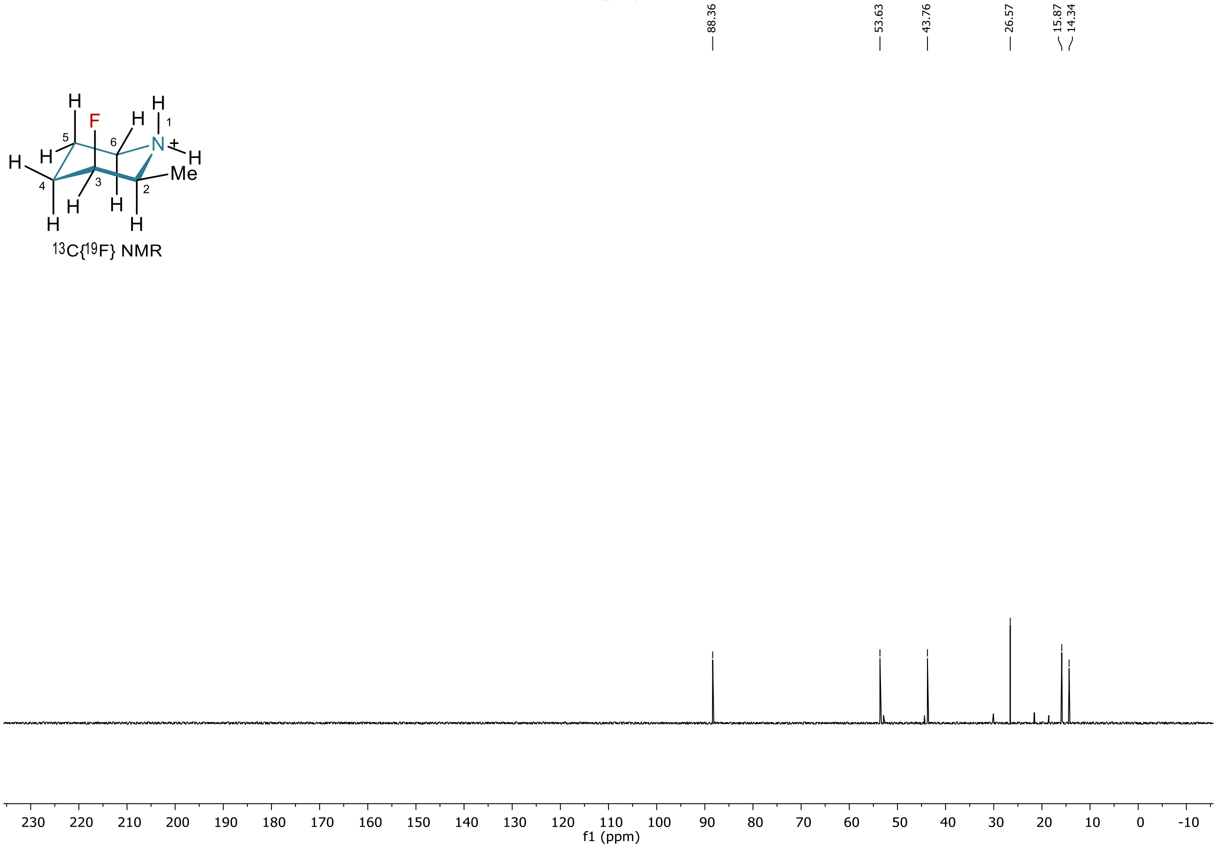


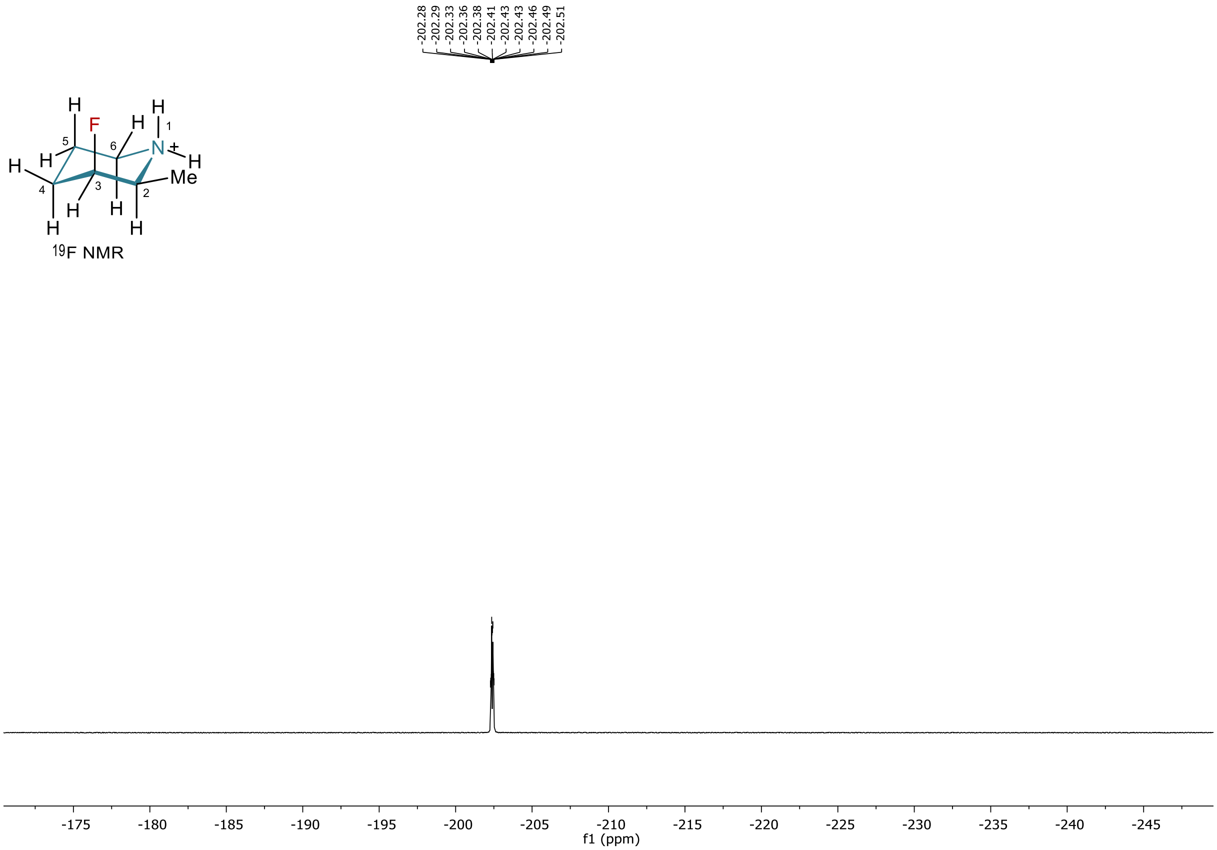
-179.53
-181.55
H
H
H
5
6
N
1
TFA
H
H
4
3
2
H
F
H
H
Me
19F{1H} NMR
175.5 -176.0 -176.5 -177.0 -177.5 -178.0 -178.5 -179.0 -179.5 -180.0 -180.5 -181.0 -181.5 -182.0 -182.5 -183.0 -183.5 -184.0 -184.5
f1 (ppm)

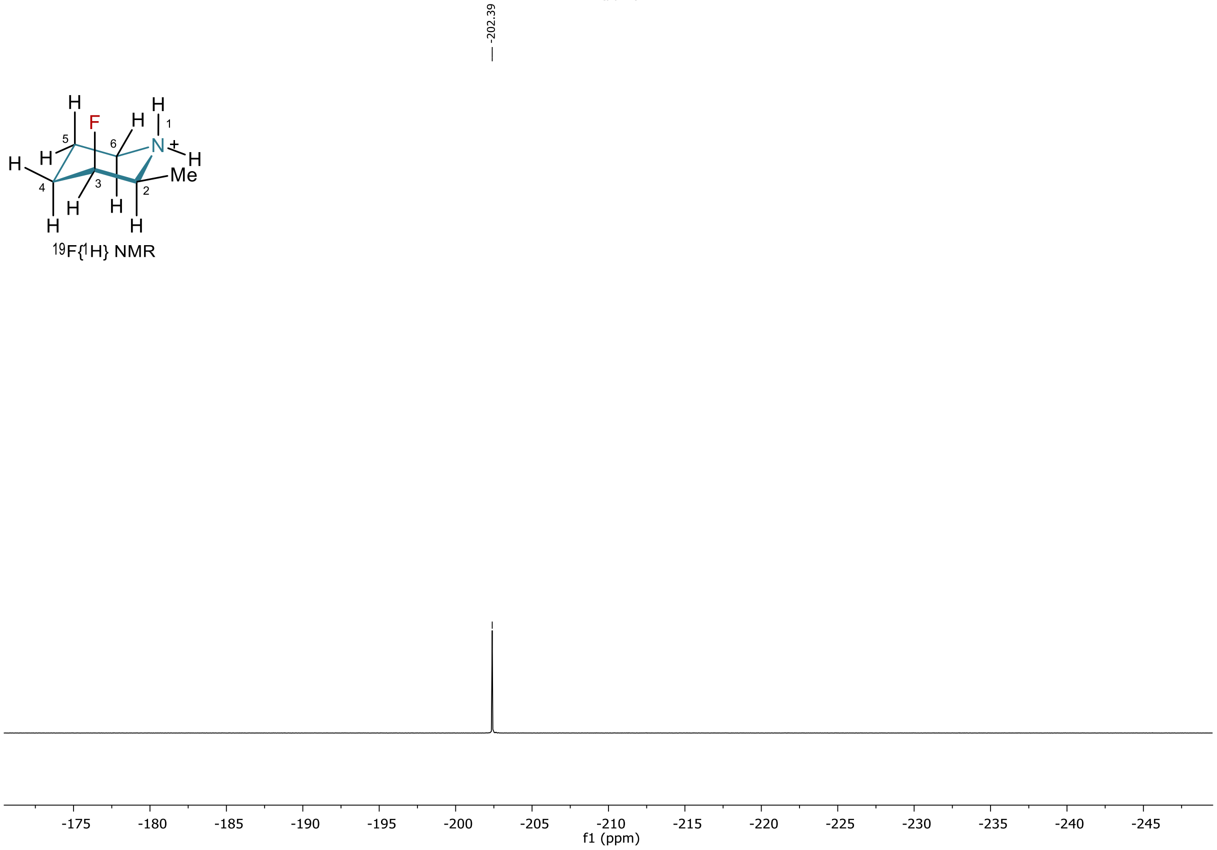

H
F
H
H
1
5
6
N+
H
H
Me
4
3
2
H
H
H
H
H
¹H NMR
1.00
2.03
0.99
1.00
3.48
2.95
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

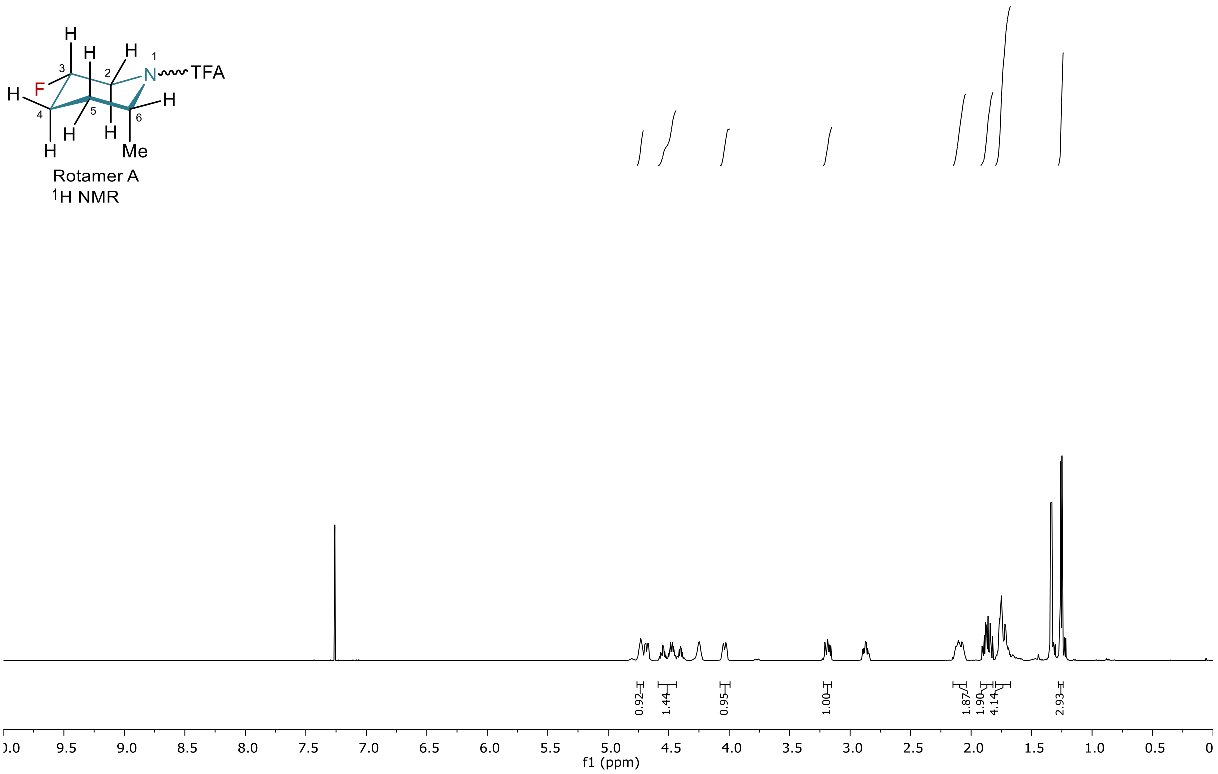

H
F
H
H
1
5
6
N+
H
H
Me
4
3
2
H
H
H
H
H
¹H{¹⁹F} NMR
0.85
1.00
0.86
1.00
0.97
1.22
2.16
2.97
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

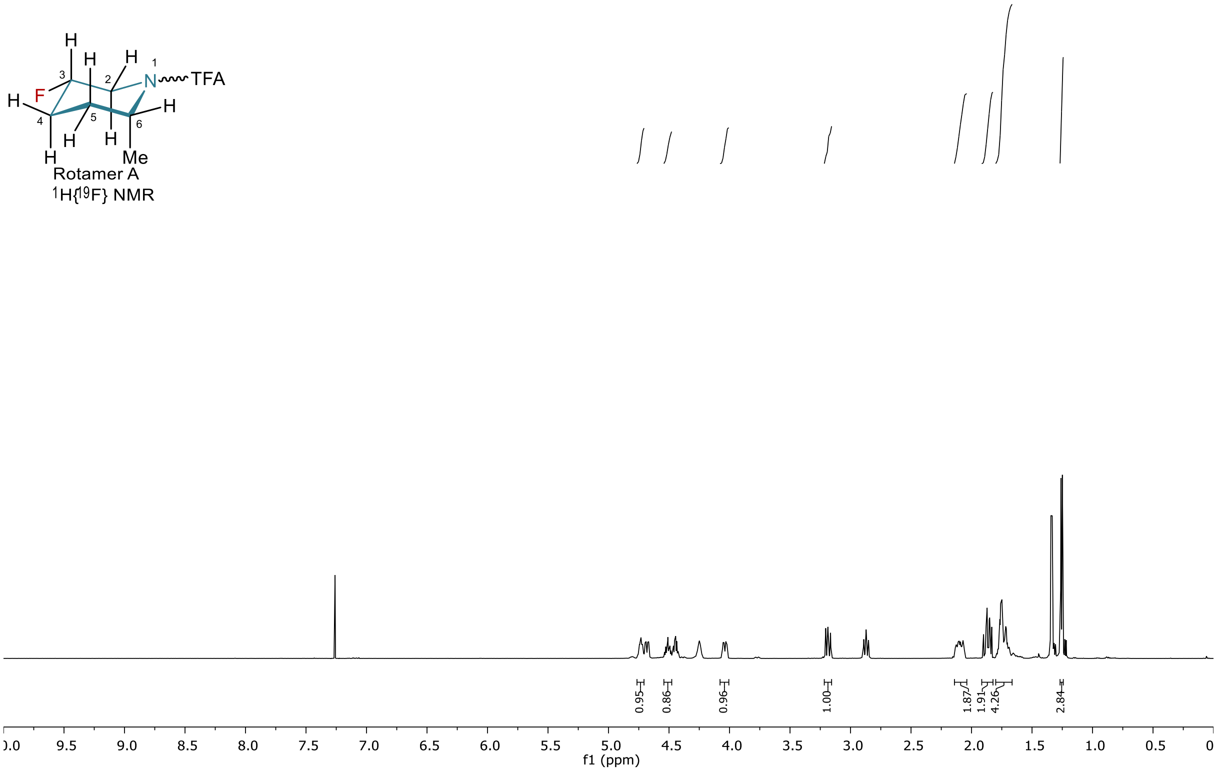

88.94
87.79
53.69
53.56
43.76
26.64
26.50
15.88
15.87
14.36
14.33
H
F
H
H
1
5
6
N+
H
H
H
Me
4
3
2
H
H
H
H
13C NMR
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

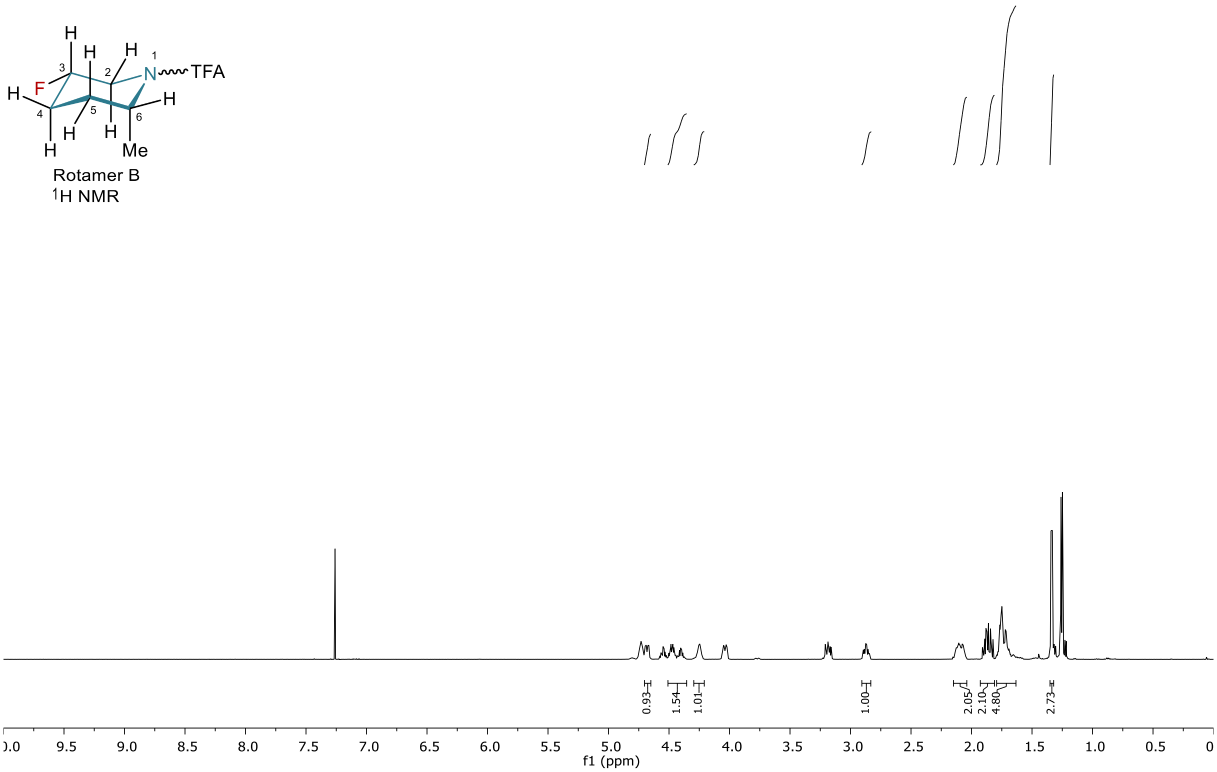

88.36
53.63
43.76
26.57
15.87
14.34
H
F
H
H
1
5
6
N+
H
H
H
Me
4
3
2
H
H
H
H
13C{19F} NMR
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

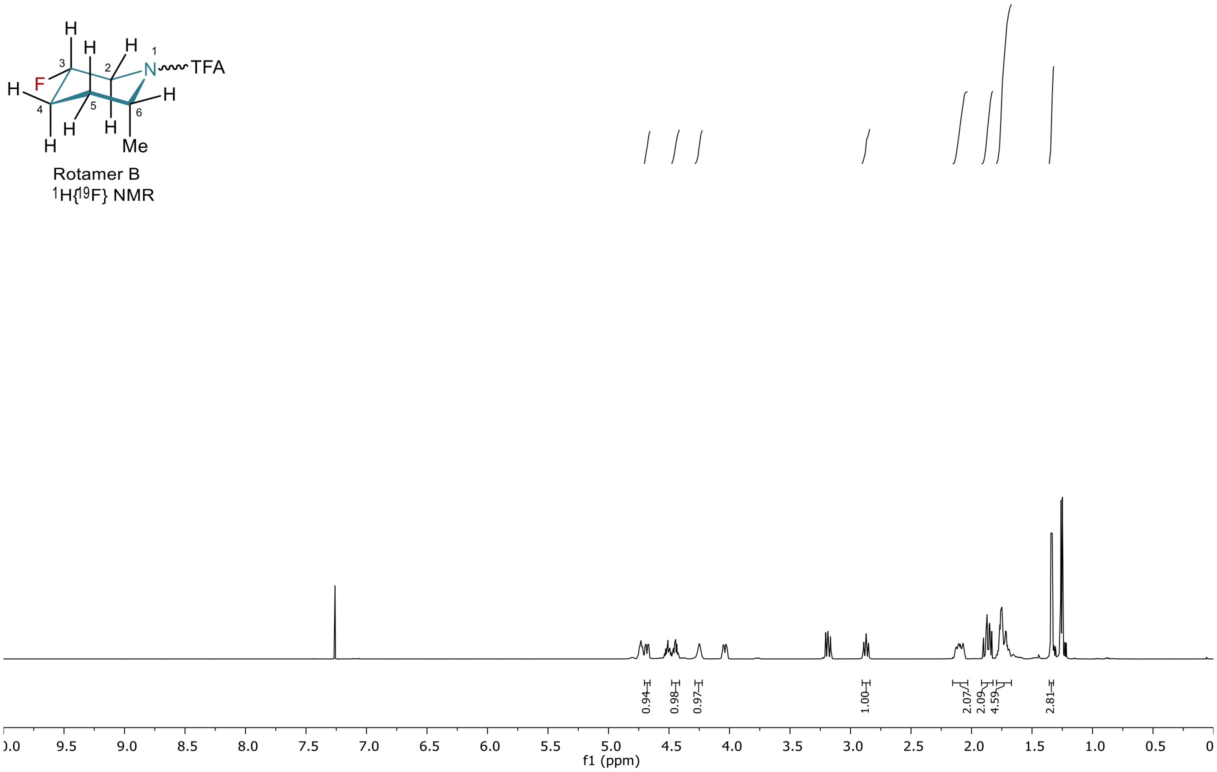

-202.28
-202.29
-202.33
-202.36
-202.38
-202.41
-202.43
-202.43
-202.46
-202.49
-202.51
H
F
H
H
1
5
6
N+
H
H
H
Me
4
3
2
H
H
H
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

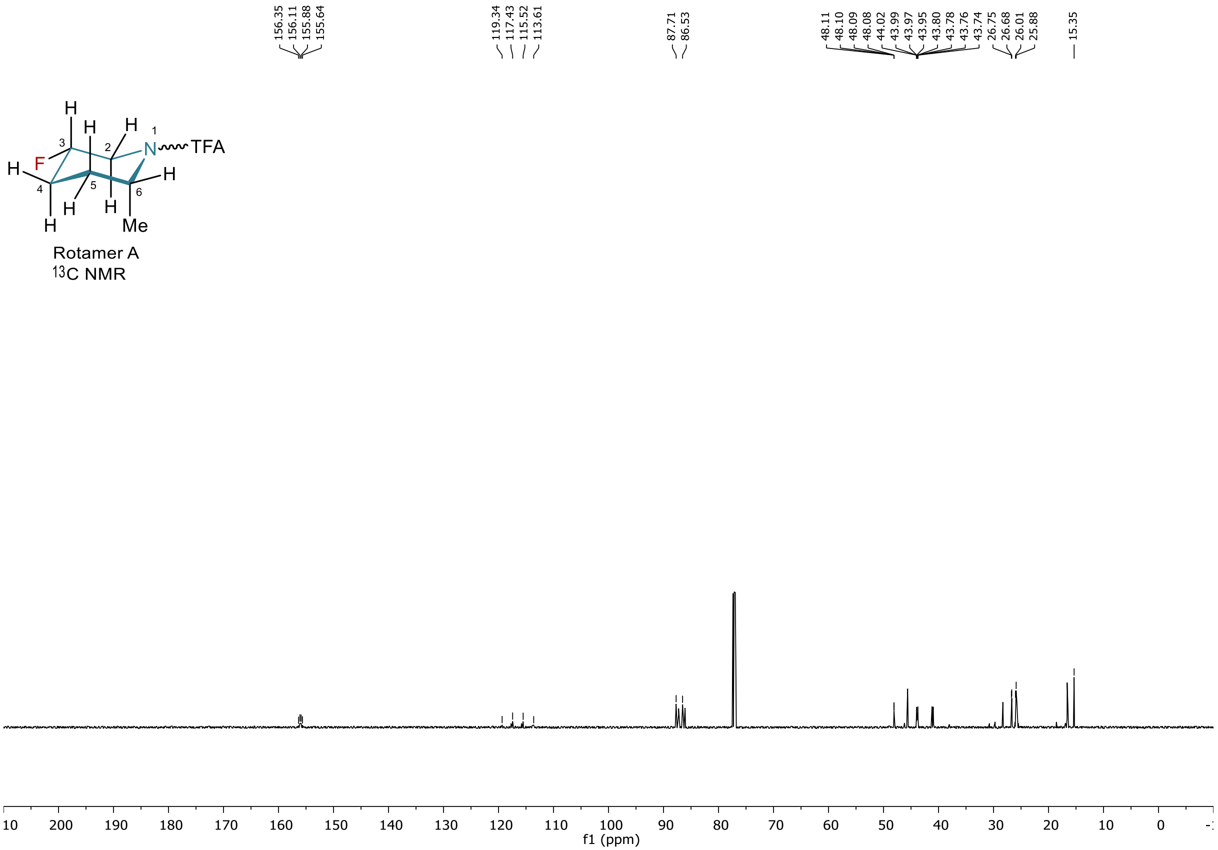

-202.39
H
F
H
H
1
5
6
N+
H
H
H
Me
4
3
2
H
H
H
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


Rotamer A
^{1}H NMR


Rotamer A
^{1}H{^{19}F} NMR


H
H
H
1
F
3
2
N
TFA
H
4
5
6
H
H
H
H
Me
Rotamer B
¹H NMR
0.93
1.54
1.01
1.00
2.05
2.10
4.80
2.73
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


H
H
H
1
F
3
2
N
TFA
H
4
5
6
H
H
H
H
Me
Rotamer B
¹H{¹⁹F} NMR
0.94
0.98
0.97
1.00
2.07
2.09
4.59
2.81
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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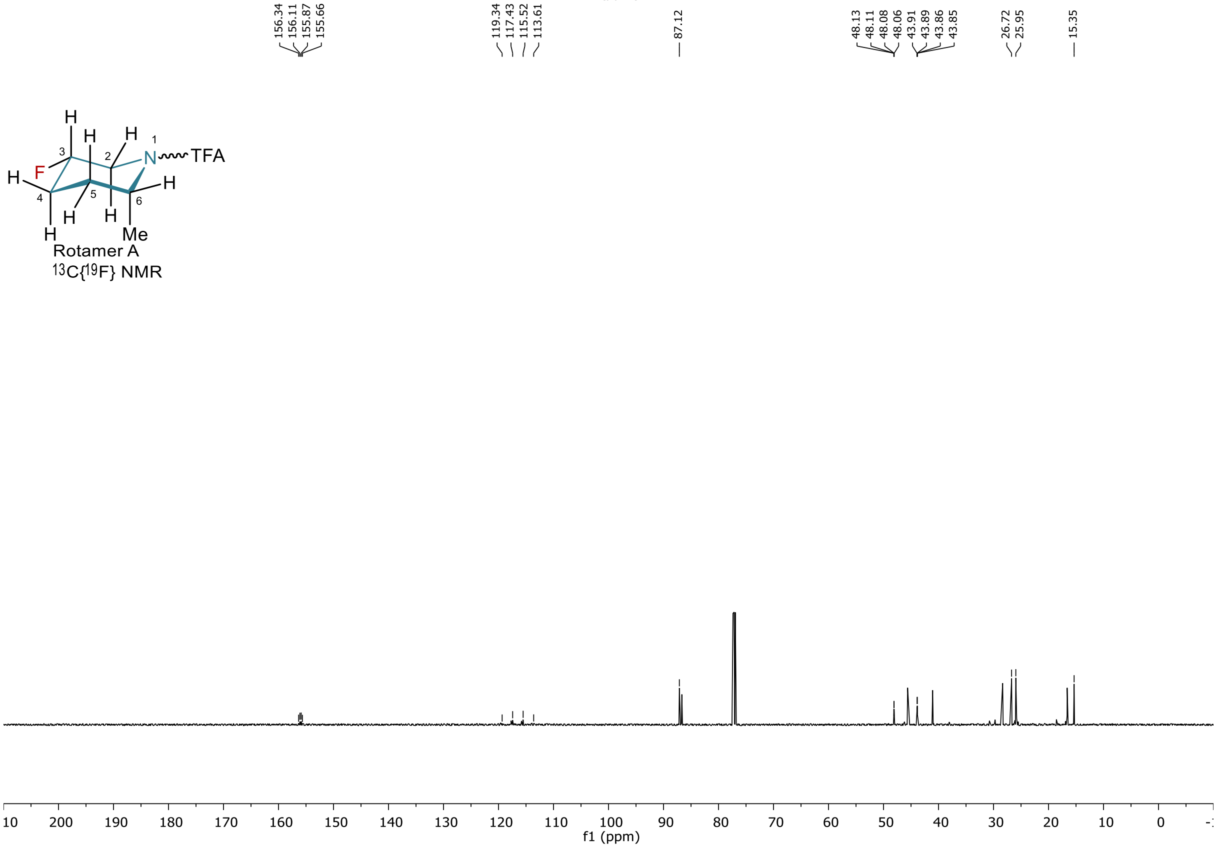
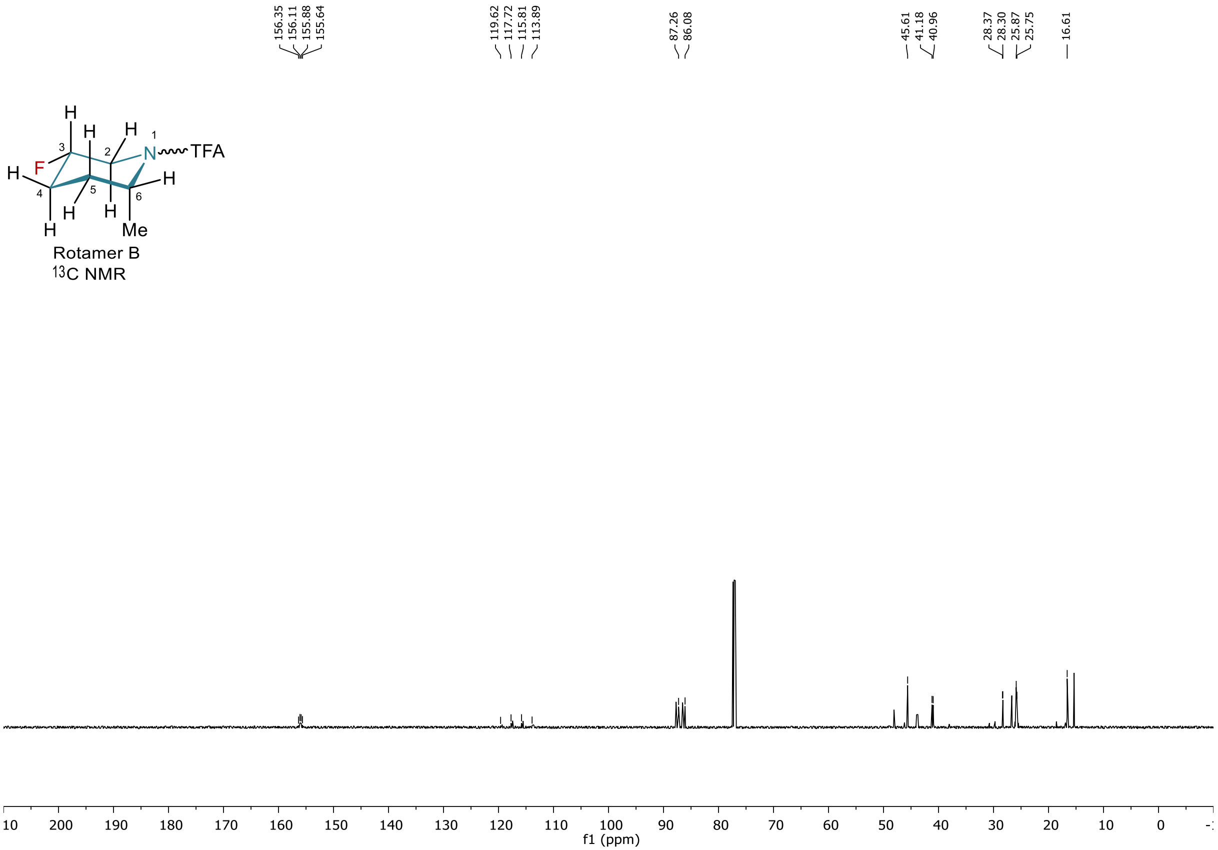
156.11
155.88
155.64
119.34
117.43
115.52
113.61
87.71
86.53
48.11
48.10
48.09
48.08
44.02
43.99
43.97
43.95
43.80
43.78
43.76
43.74
26.75
26.68
26.01
25.88
15.35
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
Me
Rotamer A
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


156.34
156.11
155.87
155.66
119.34
117.43
115.52
113.61
87.12
48.13
48.11
48.08
48.06
43.91
43.89
43.86
43.85
26.72
25.95
15.35
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
Me
Rotamer A
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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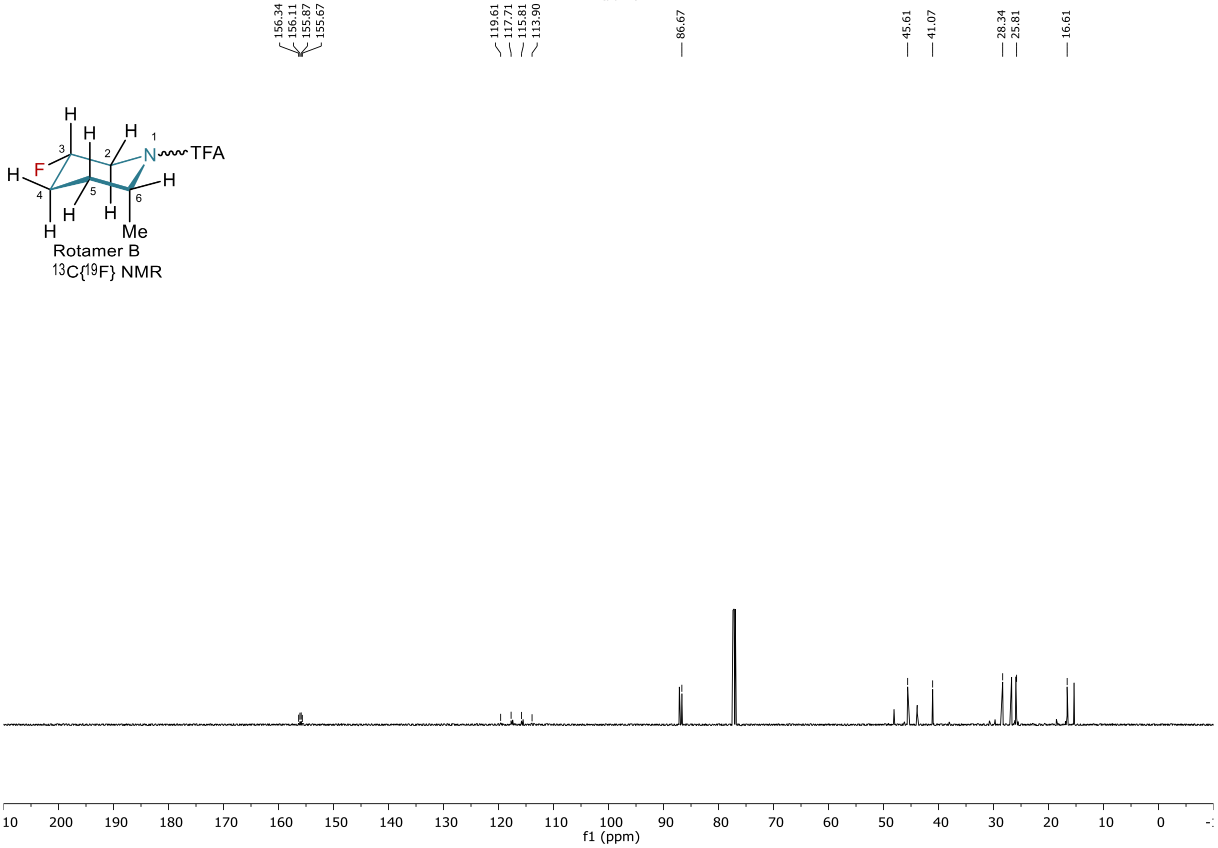
156.11
155.88
155.64
119.62
117.72
115.81
113.89
87.26
86.08
45.61
41.18
40.96
28.37
28.30
25.87
25.75
16.61
H
H
H
1
3
2
N
TFA
H
F
H
4
5
6
H
H
H
Me
Rotamer B
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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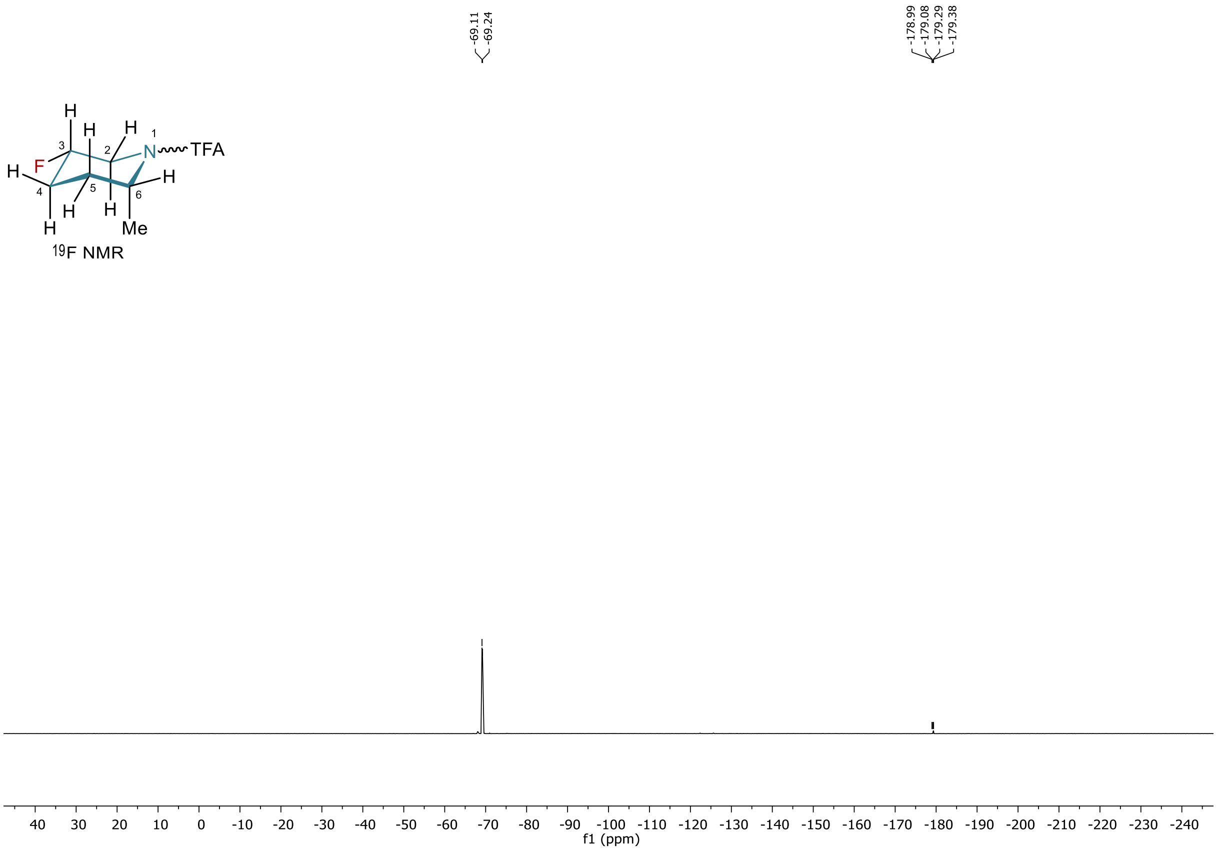
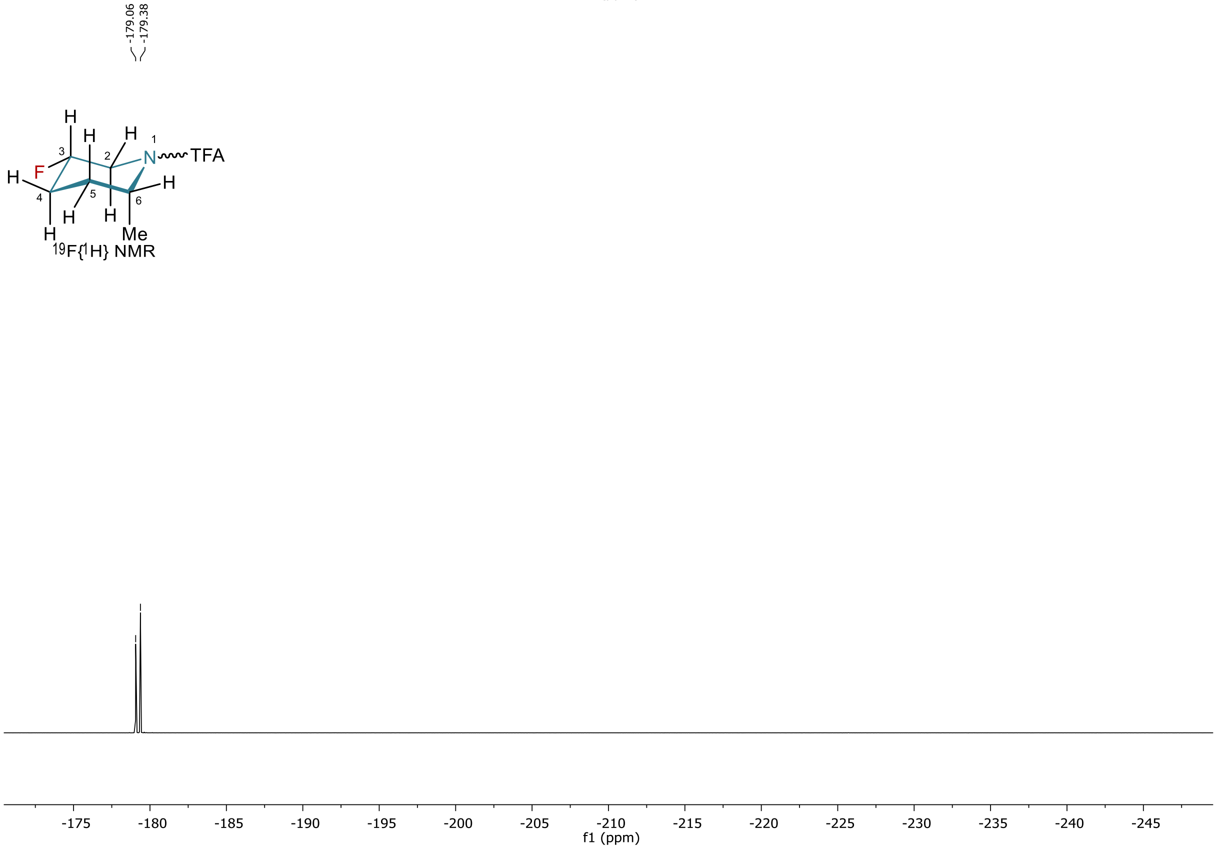
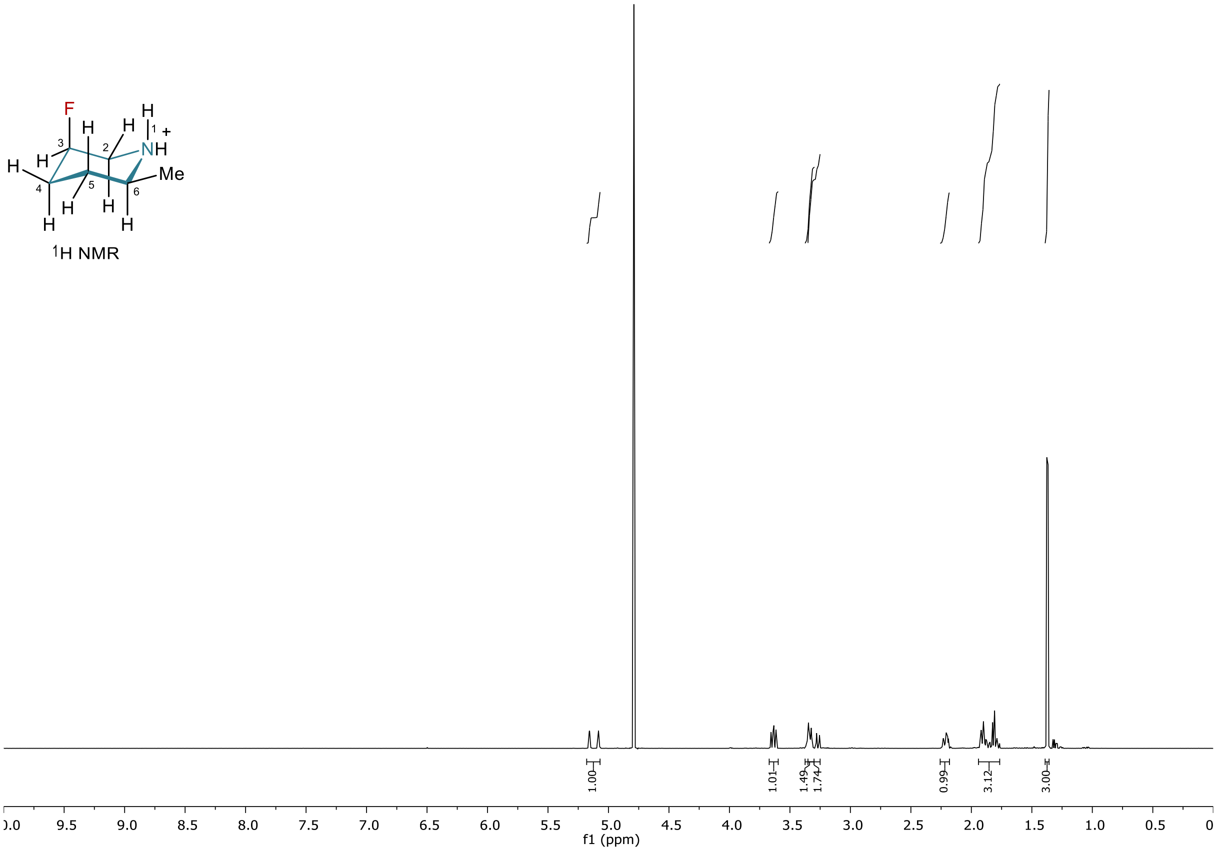
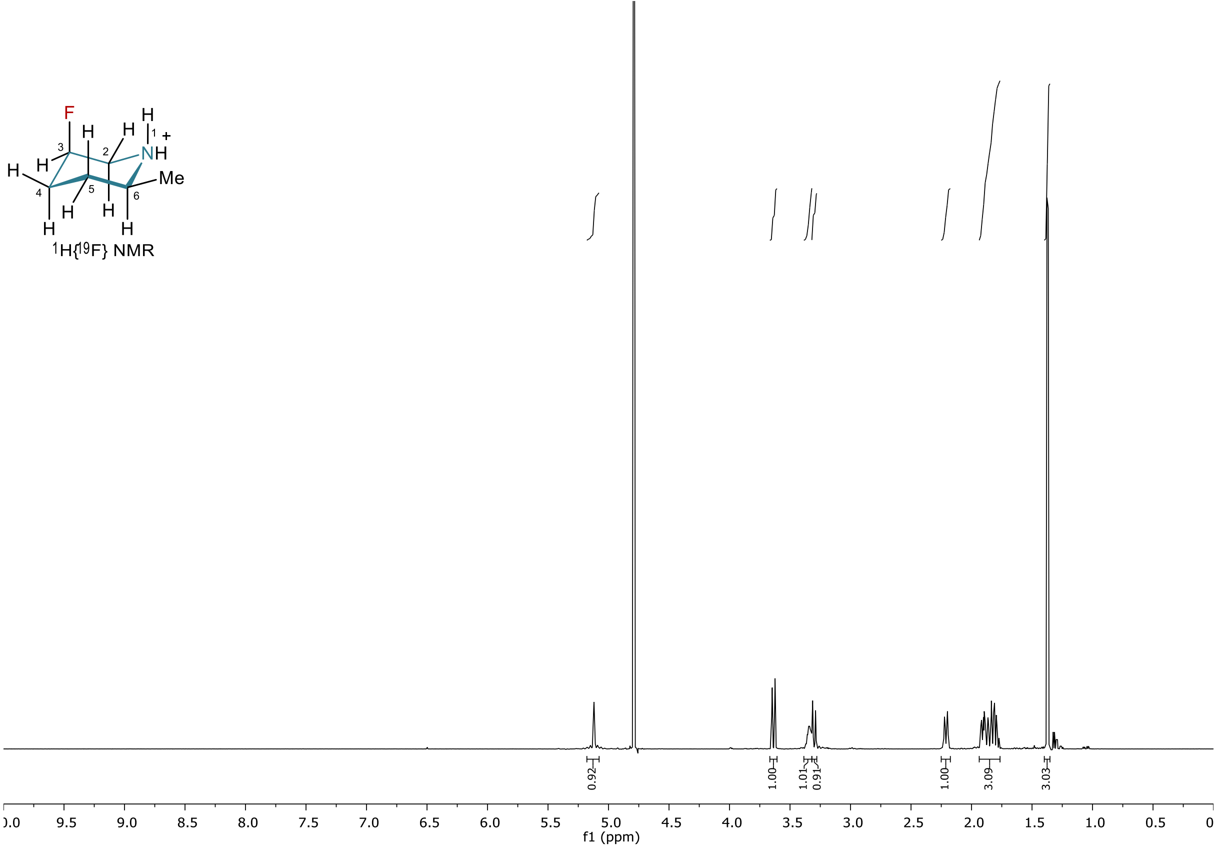
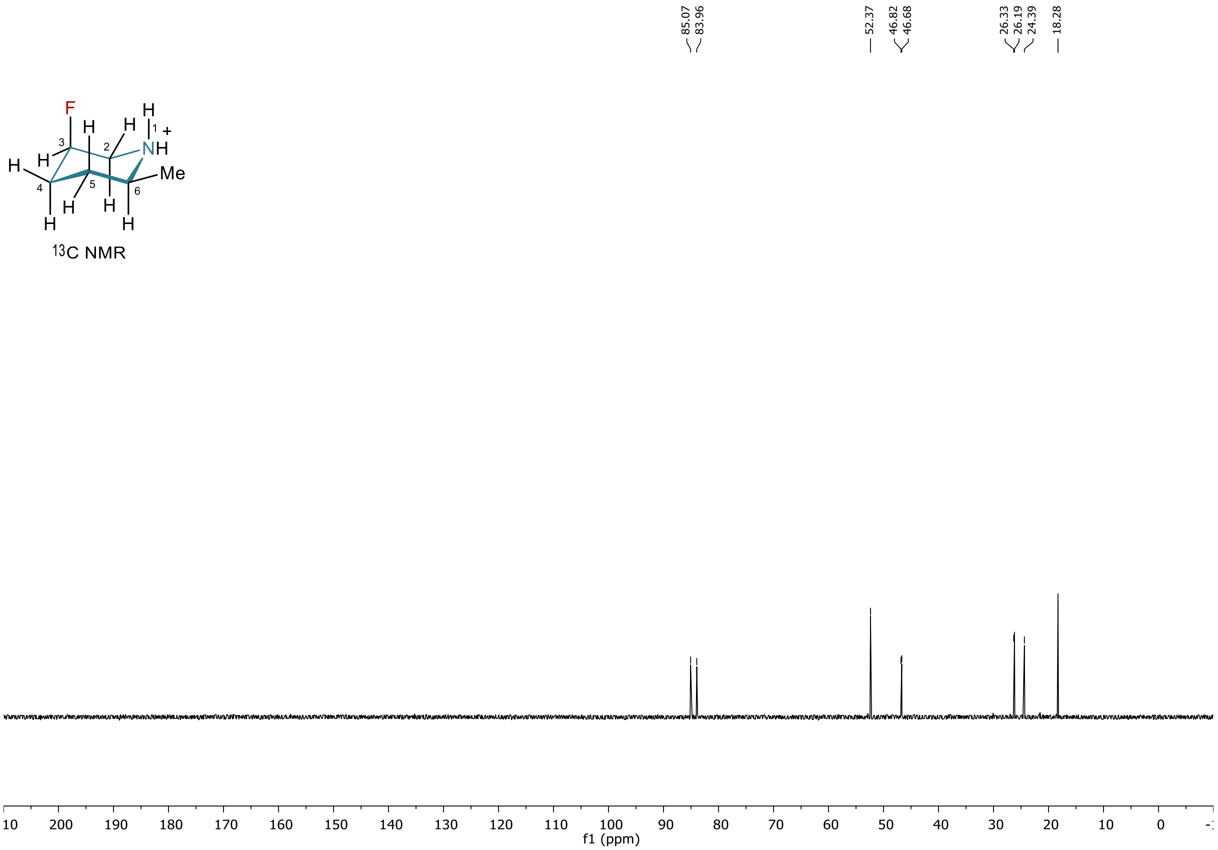
155.87
155.67
119.61
117.71
115.81
113.90
86.67
45.61
41.07
28.34
25.81
16.61
H
H
H
1
3
2
N
TFA
H
F
H
4
5
6
H
H
H
Me
Rotamer B
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

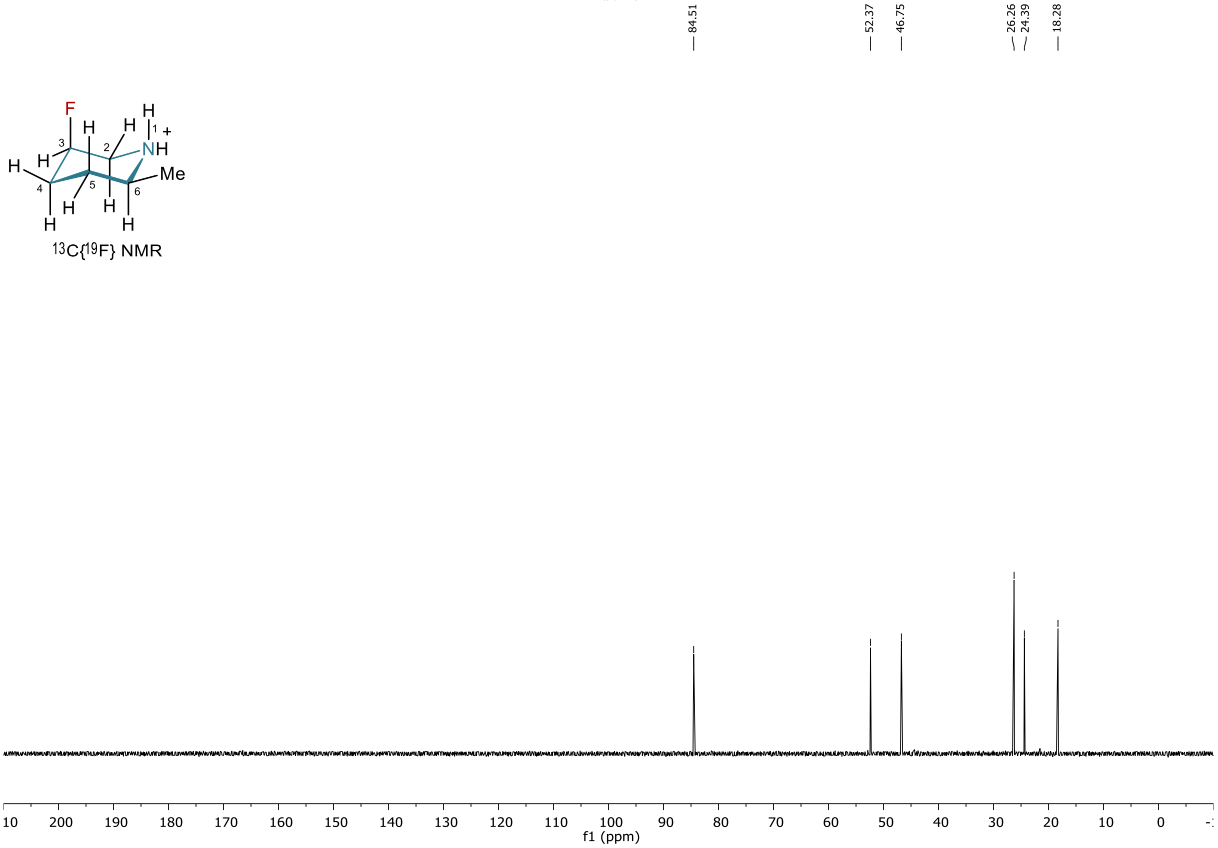

-69.11
-69.24
-178.99
-179.08
-179.29
-179.38
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
Me
19F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

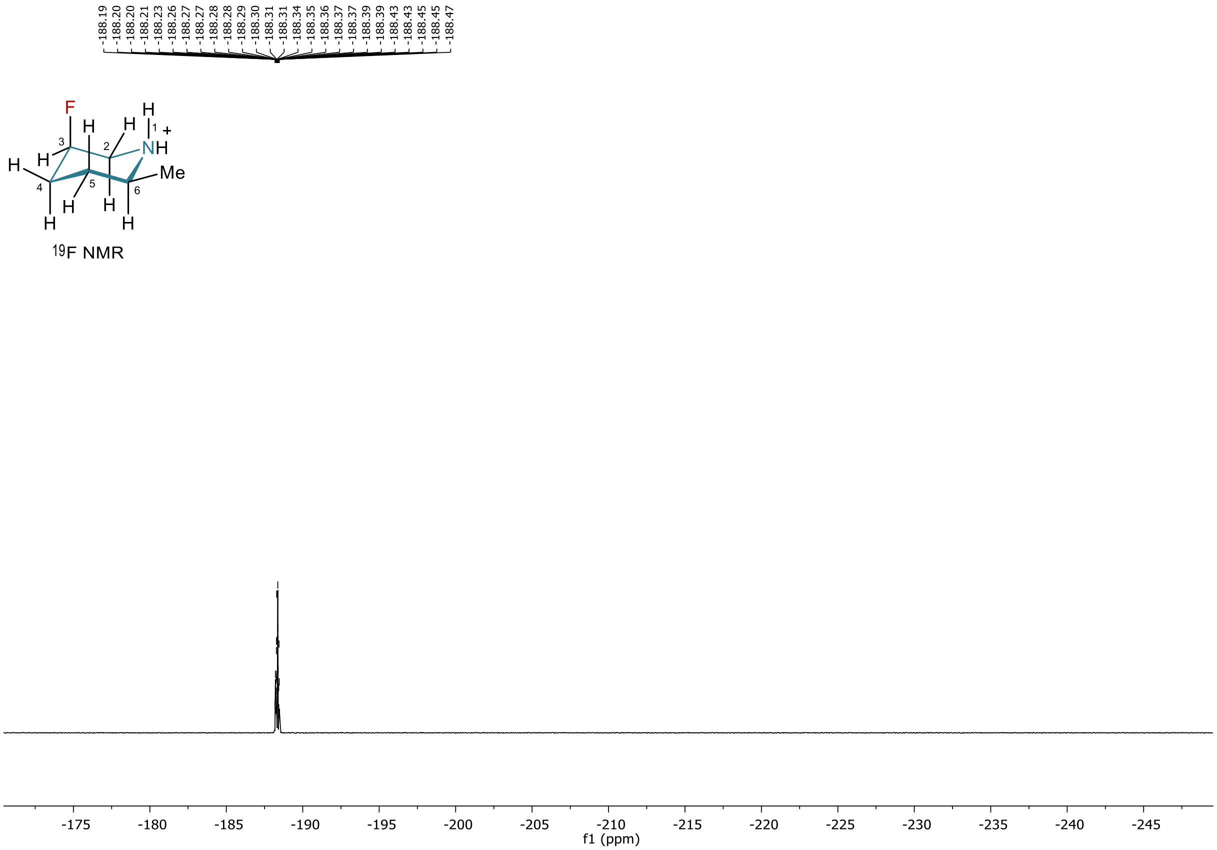

-179.06
-179.38
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
Me
19F{1H} NMR
-175 -180 -185 -190 -195 -200 -205 -210 -215 -220 -225 -230 -235 -240 -245
f1 (ppm)


F
H
N
+
Me
1
2
3
4
5
6
1H NMR
1.00
1.01
1.49
1.74
0.99
3.12
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

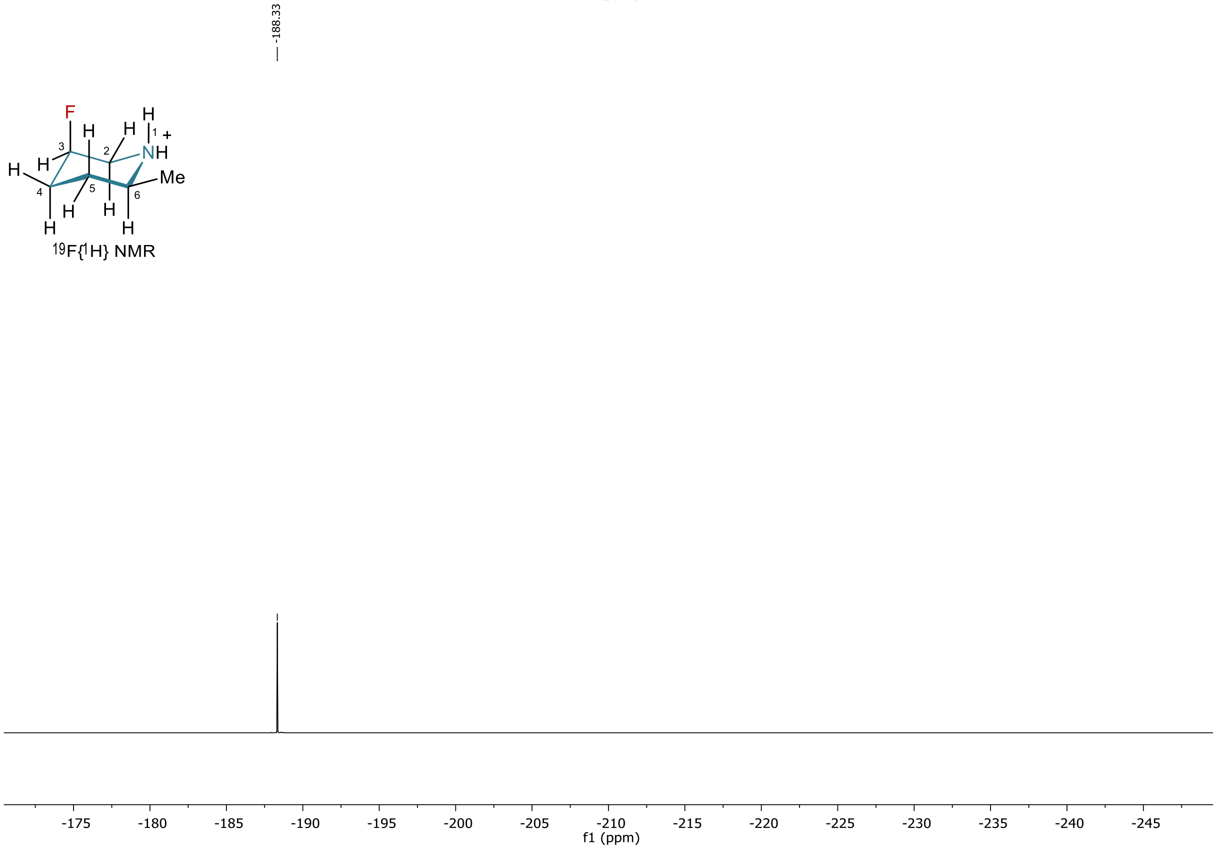

F
H
N
+
Me
1
2
3
4
5
6
1H{19F} NMR
0.92
1.00
1.01
0.91
1.00
3.09
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


85.07
83.96
52.37
46.82
46.68
26.33
26.19
24.39
18.28
F
H
H
H
1
+
NH
H
3
2
H
4
5
6
Me
H
H
H
H
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

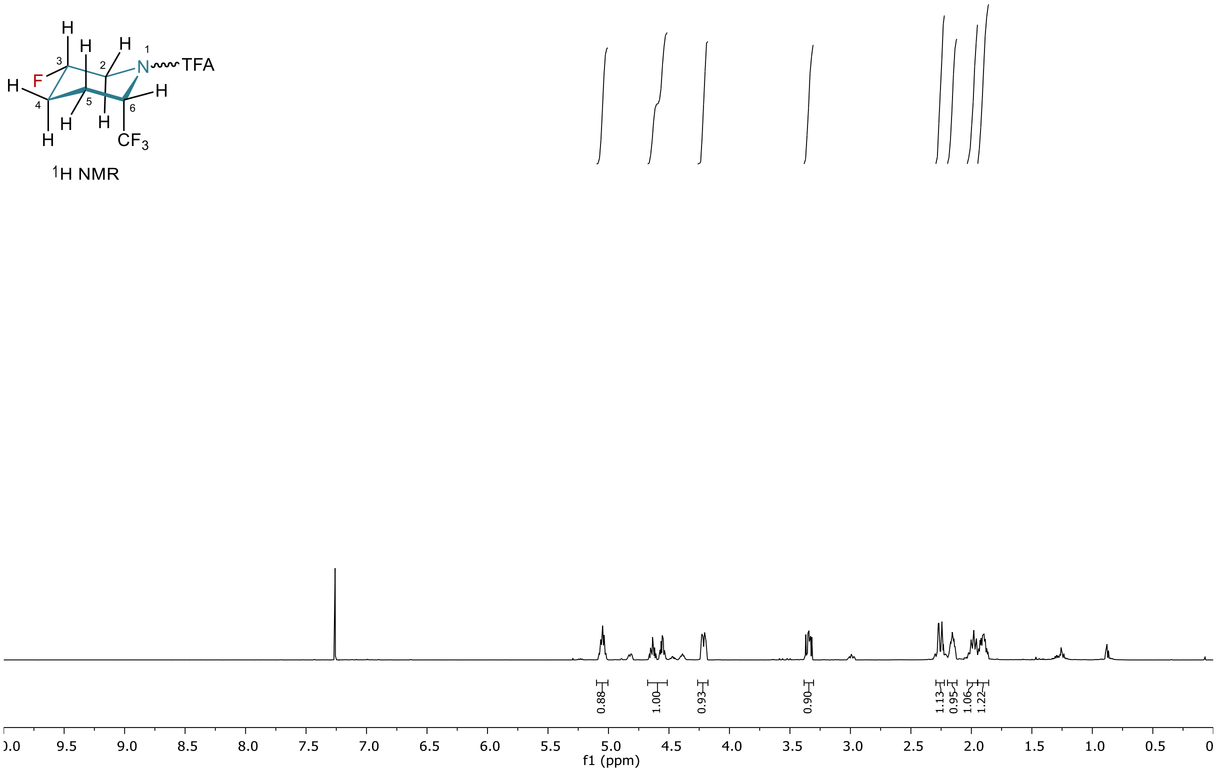

84.51
52.37
46.75
26.26
24.39
18.28
F
H
H
H
1
+
NH
H
3
2
H
4
5
6
Me
H
H
H
H
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



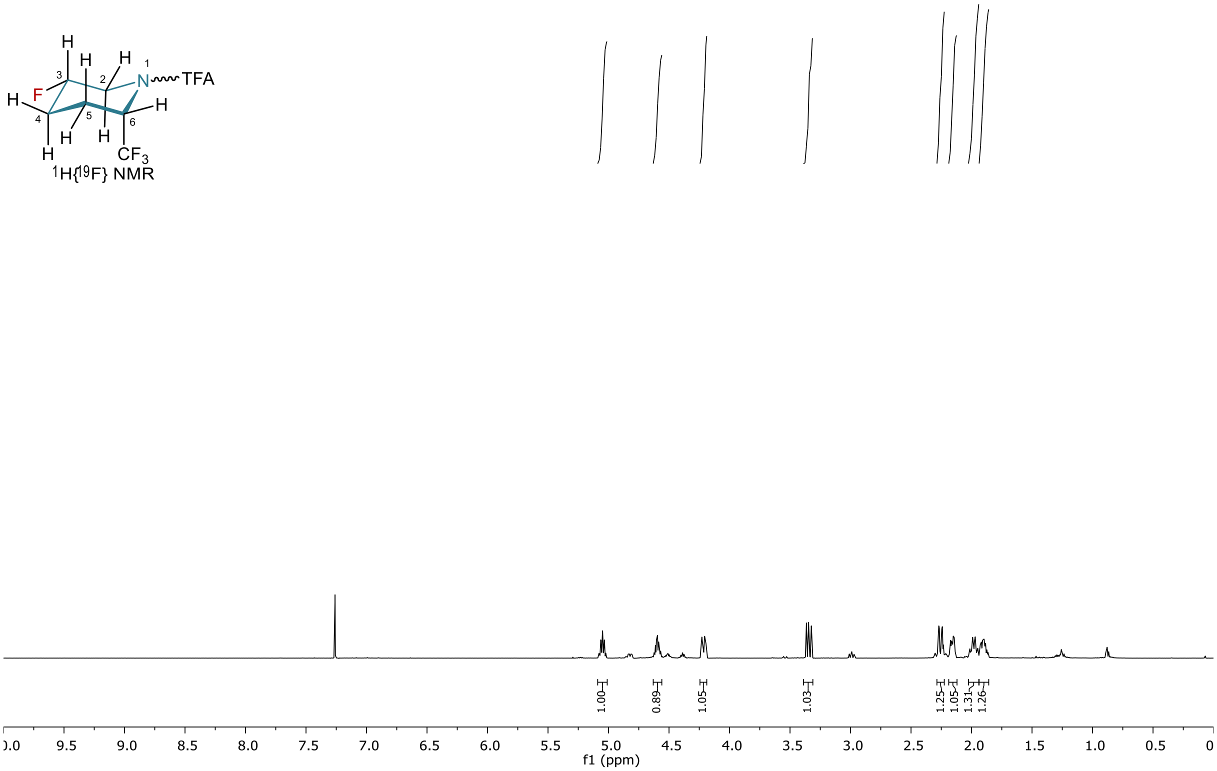
-188.19
-188.20
-188.20
-188.21
-188.23
-188.26
-188.27
-188.27
-188.28
-188.28
-188.29
-188.30
-188.31
-188.31
-188.34
-188.35
-188.36
-188.37
-188.37
-188.39
-188.39
-188.43
-188.43
-188.45
-188.45
-188.47
F
H
H
H
1
+
NH
Me
3
2
4
5
6
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)



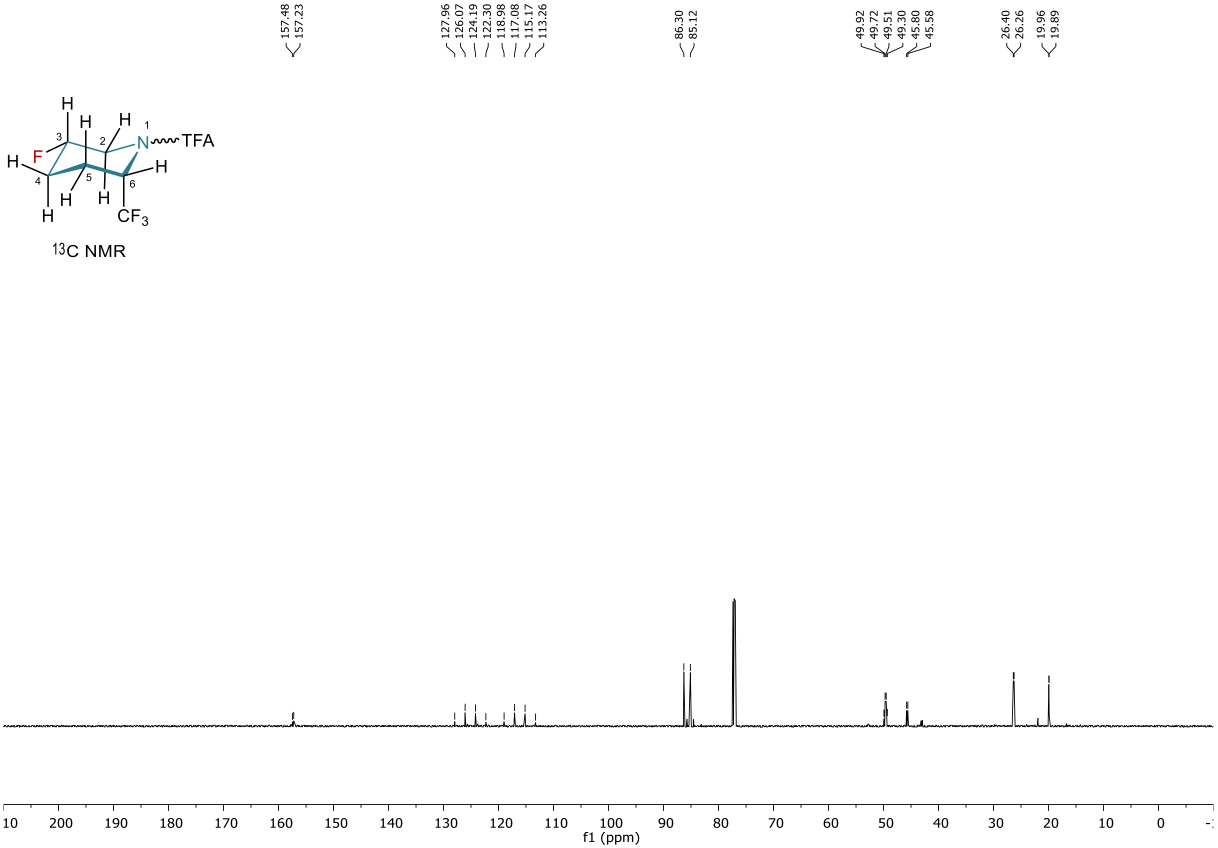
-188.33
F
H
H
H
1
+
NH
Me
3
2
4
5
6
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)



H
H
H
1
F
3
2
N
TFA
H
4
5
6
H
H
H
H
CF3
1H NMR
0.88
1.00
0.93
0.90
1.13
0.95
1.06
1.22
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)



H
H
H
1
F
3
2
N
TFA
H
4
5
6
H
H
H
H
CF3
1H{19F} NMR
1.00
0.89
1.05
1.03
1.25
1.05
1.31
1.26
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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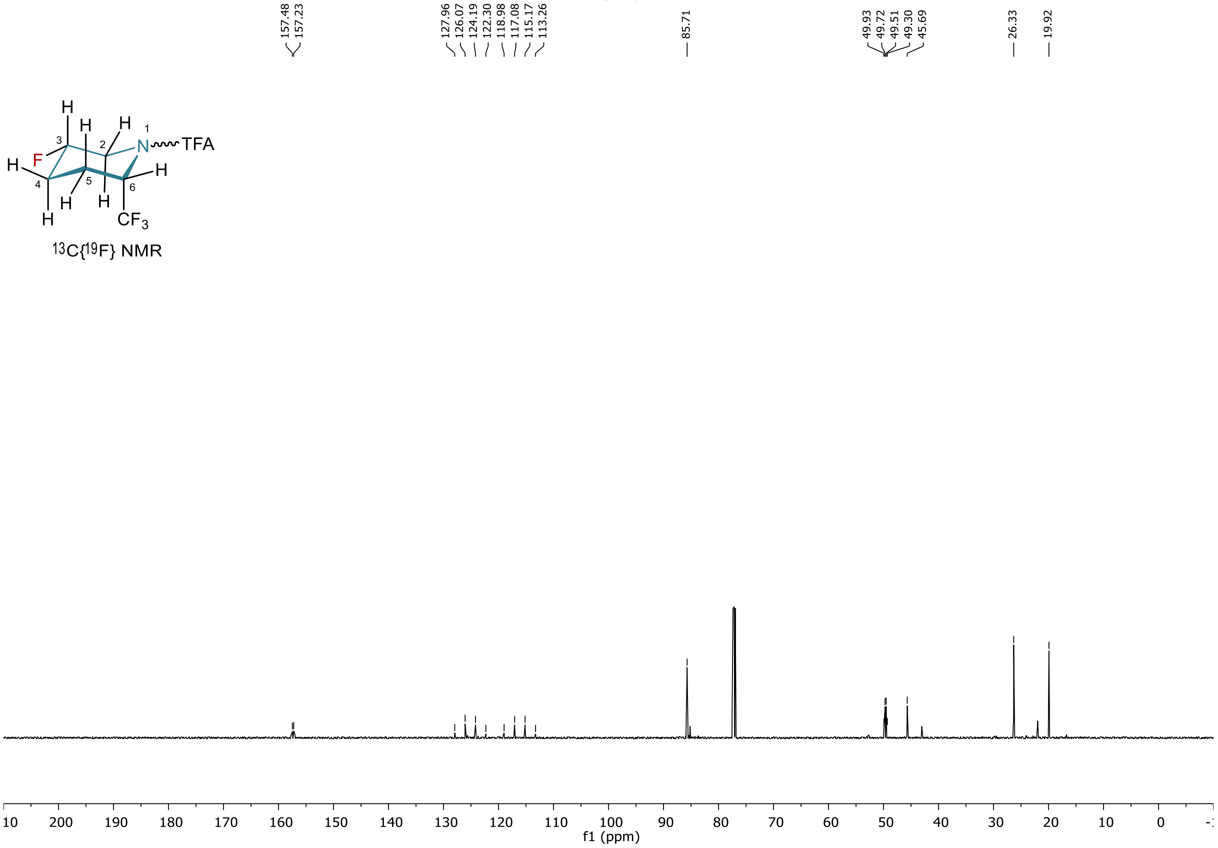
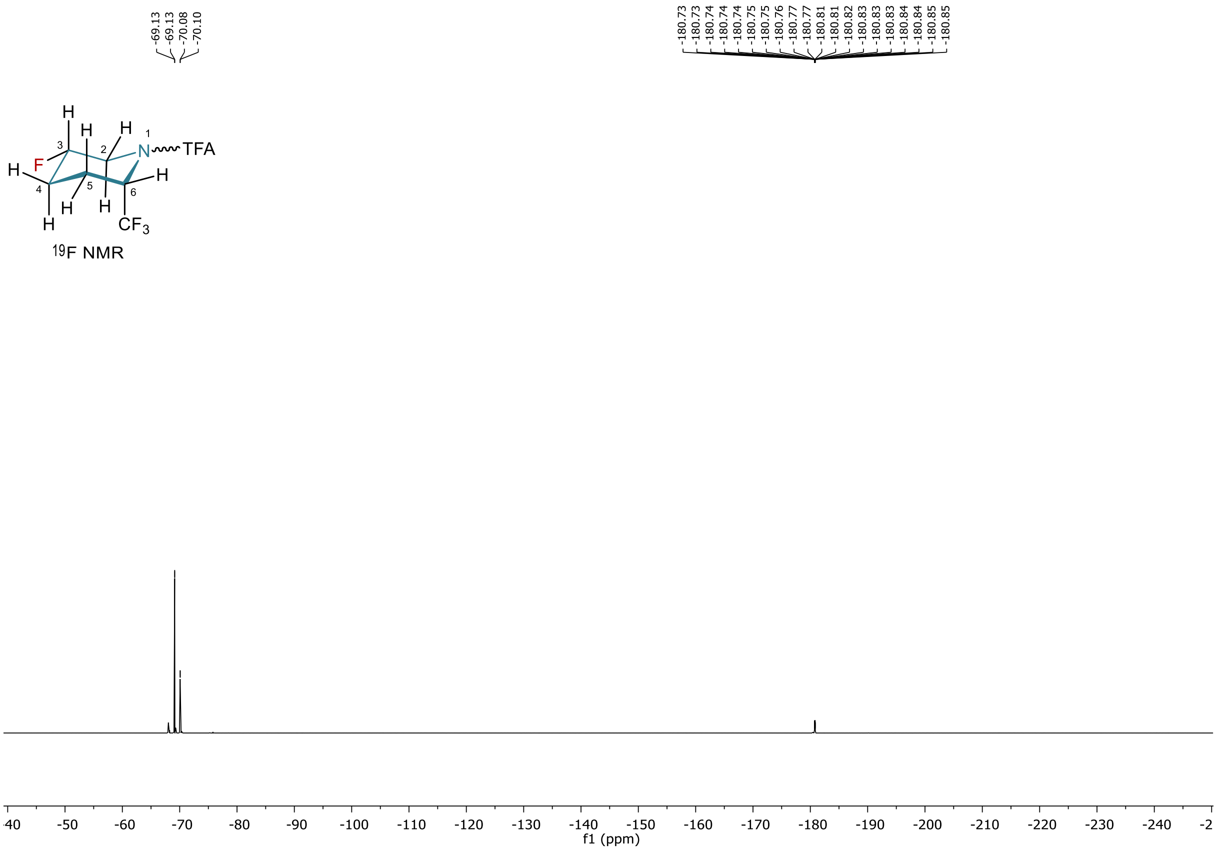
157.23
127.96
126.07
124.19
122.30
118.98
117.08
115.17
113.26
86.30
85.12
49.92
49.72
49.51
49.30
45.80
45.58
26.40
26.26
19.96
19.89
H
H
H
1
3
2
F
N
TFA
H
4
5
6
H
H
H
H
CF3
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


157.48
157.23
127.96
126.07
124.19
122.30
118.98
117.08
115.17
113.26
85.71
49.93
49.72
49.51
49.30
45.69
26.33
19.92
H
H
H
1
3
2
F
N
TFA
H
4
5
6
H
H
H
H
CF3
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-69.13
-69.13
-70.08
-70.10
-180.73
-180.73
-180.74
-180.74
-180.74
-180.75
-180.75
-180.76
-180.77
-180.77
-180.81
-180.81
-180.82
-180.83
-180.83
-180.83
-180.84
-180.84
-180.85
-180.85
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
CF3
19F NMR
40
-50
-60
-70
-80
-90
-100
-110
-120
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-200
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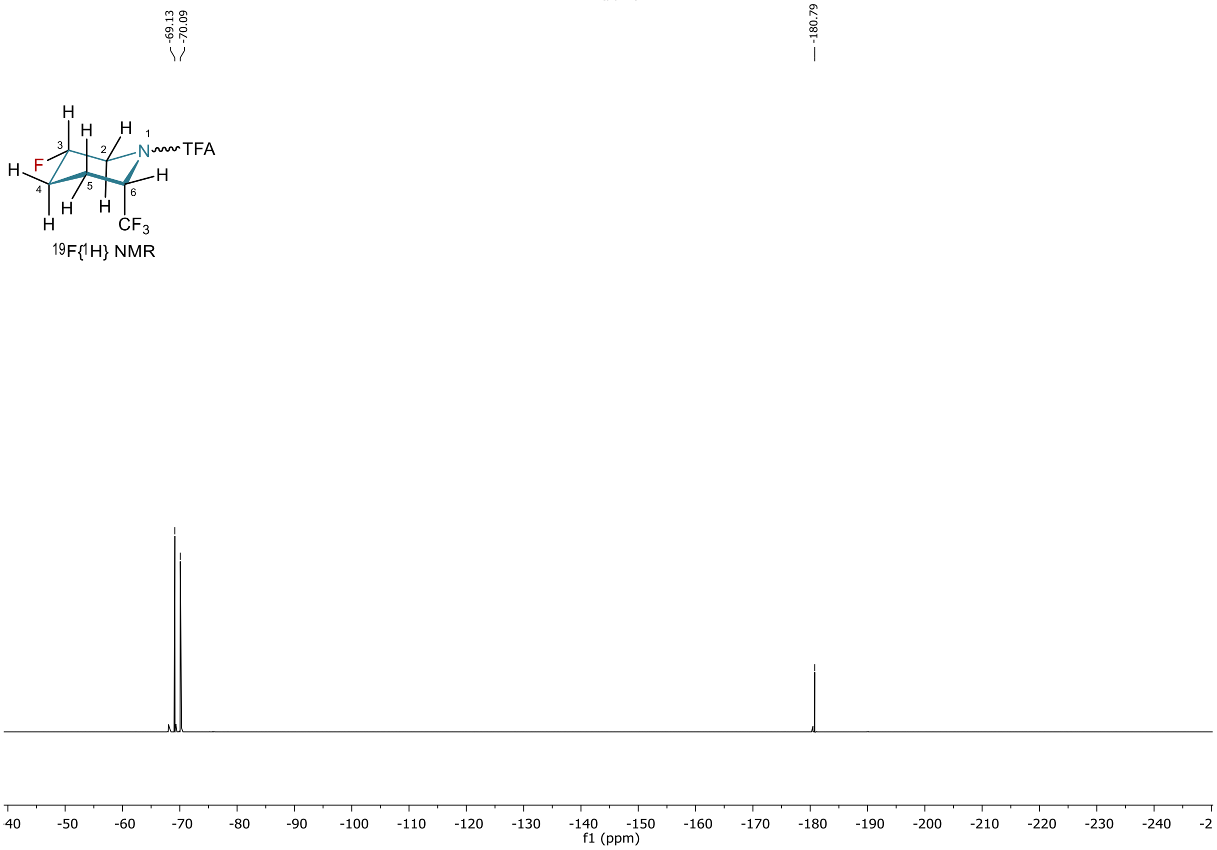
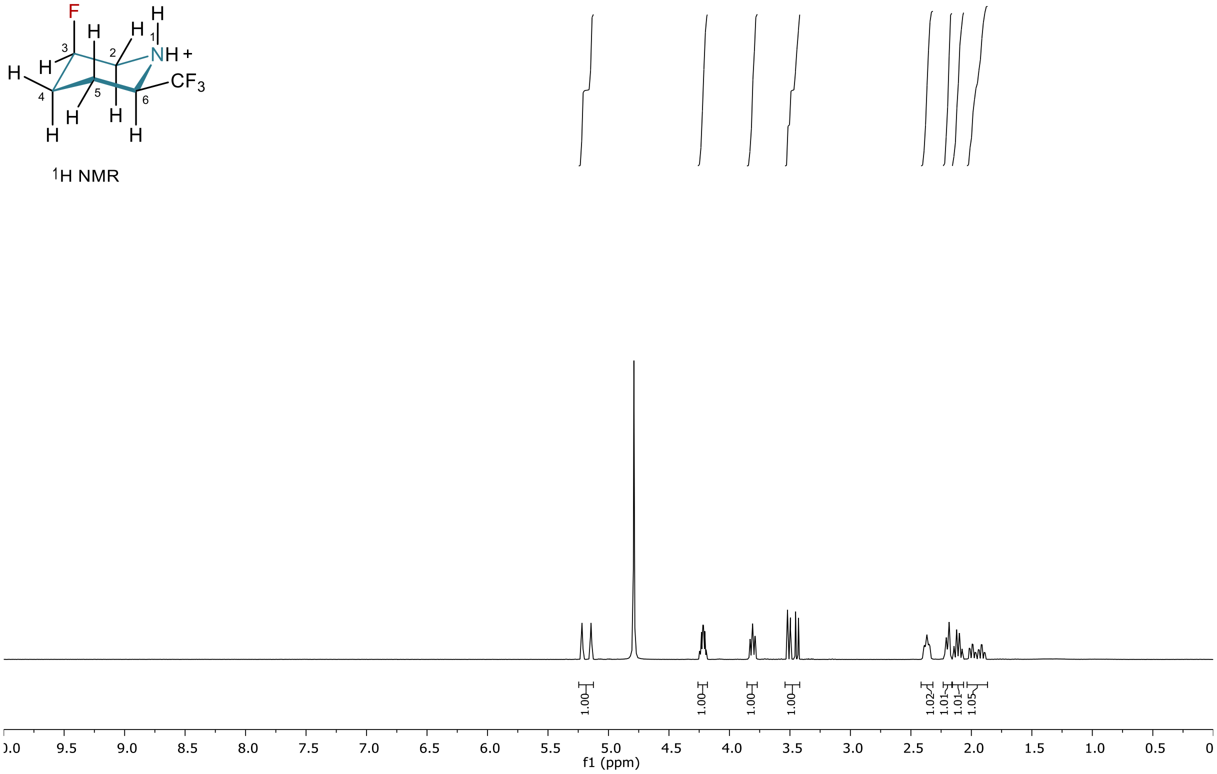
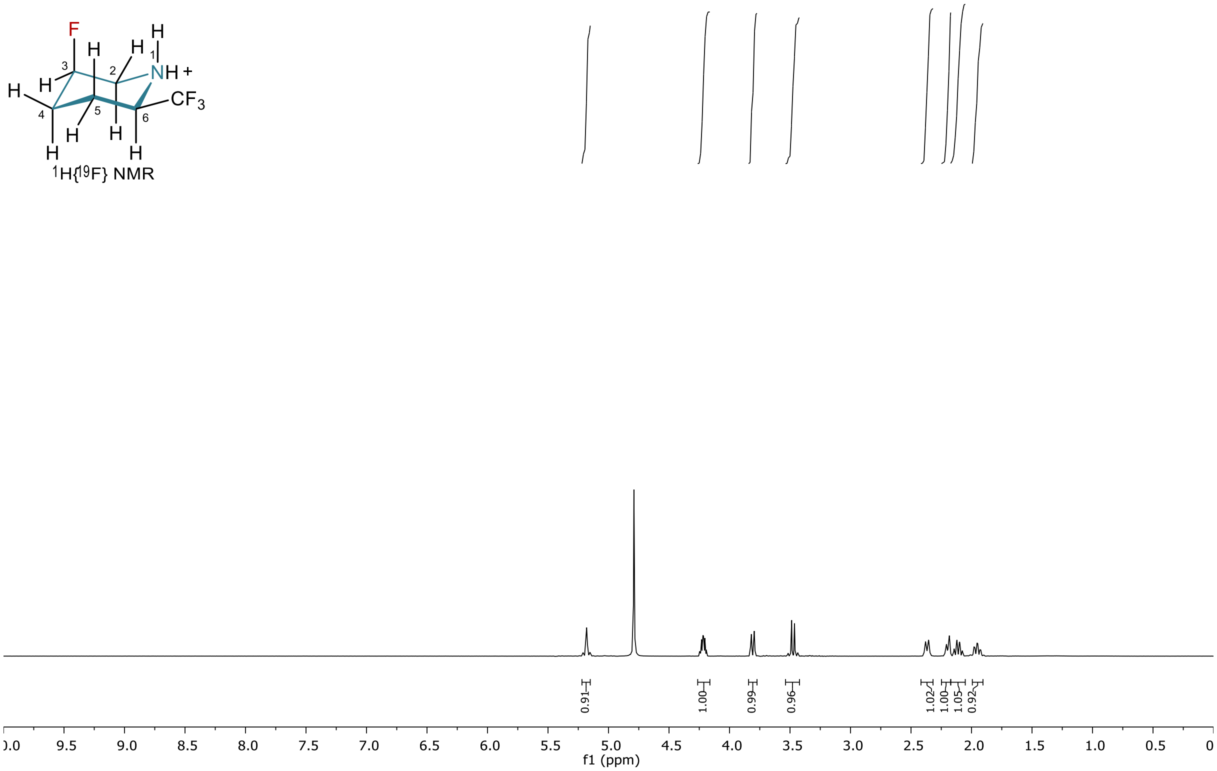
-220
-230
-240
-2
f1 (ppm)

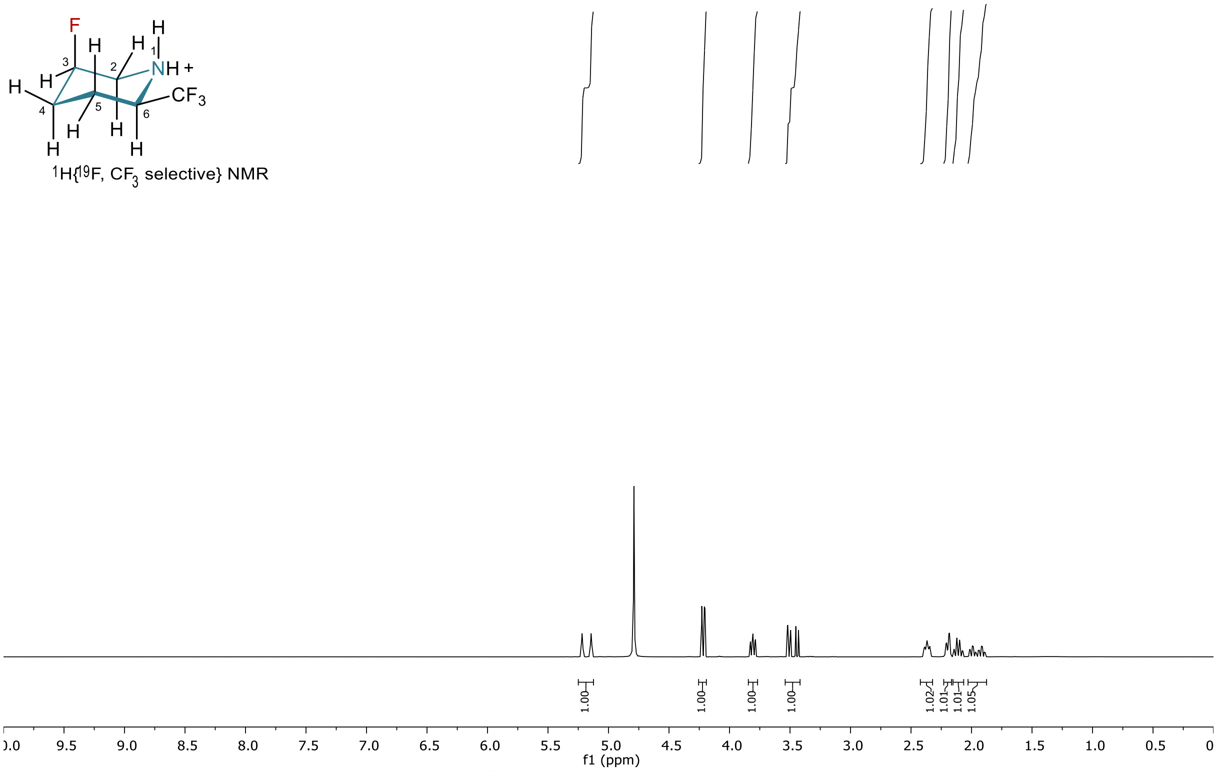

-69.13
-70.09
-180.79
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
CF3
19F{1H} NMR
40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
-2
f1 (ppm)

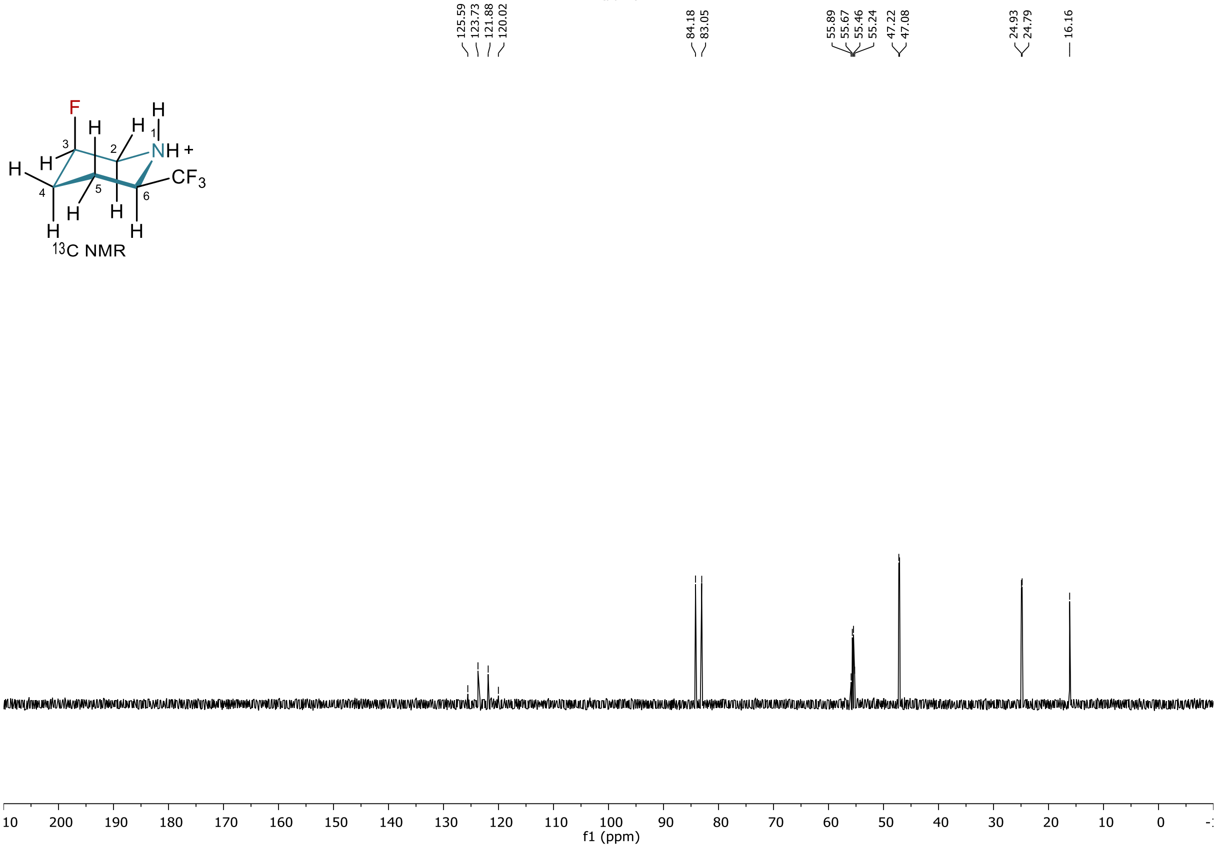


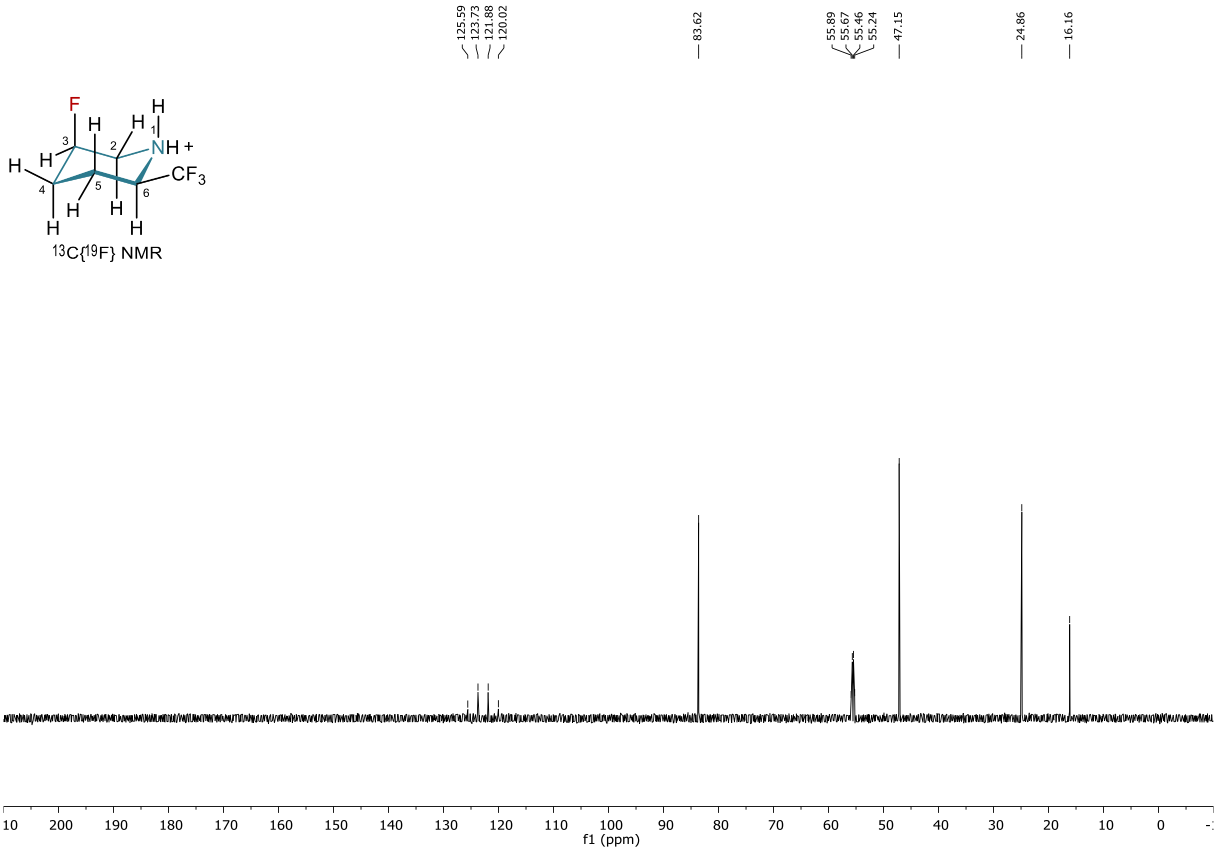
^{1}H NMR



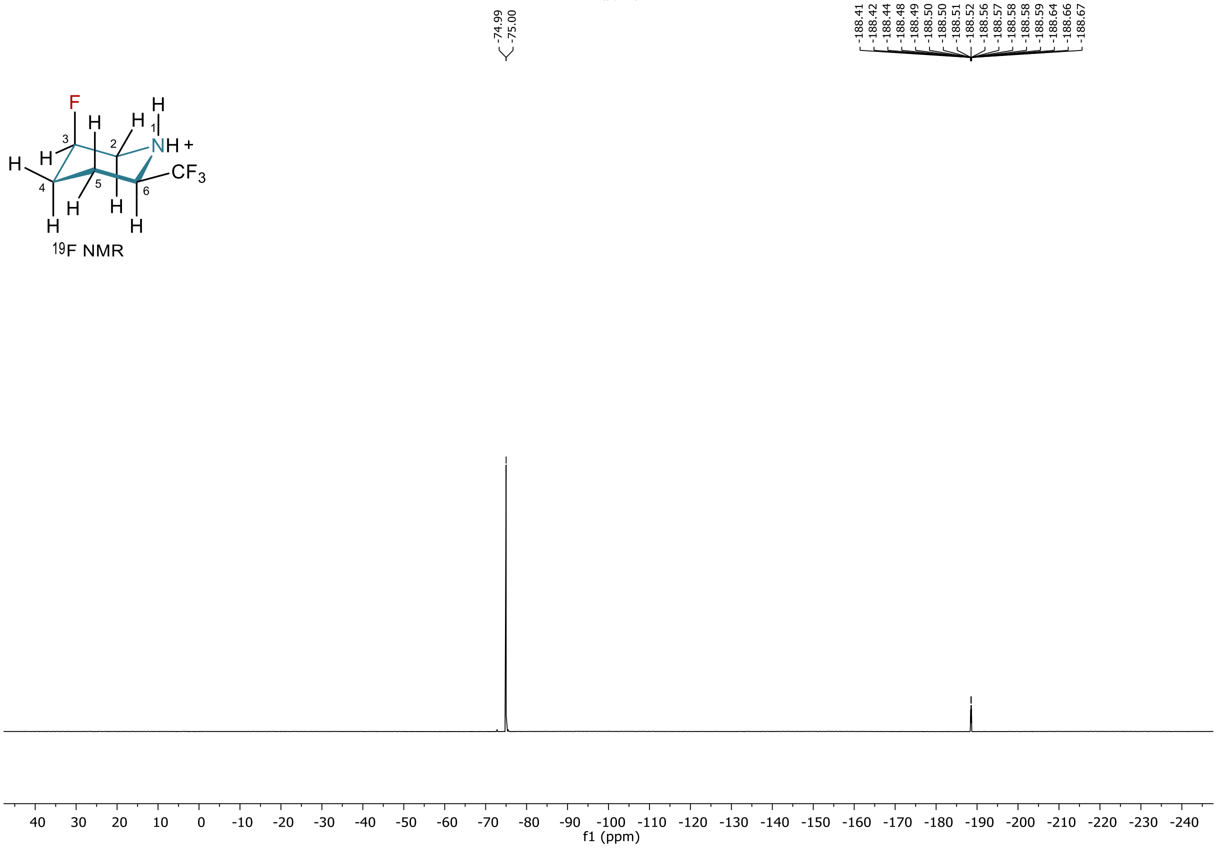
^{1}H{^{19}F} NMR


F
H
H
H
H
1
NH +
CF3
2
3
4
5
6
H
H
H
H
^{1}H{^{19}F, CF$_3$ selective} NMR
1.00
1.00
1.00
1.00
1.02
1.01
1.01
1.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

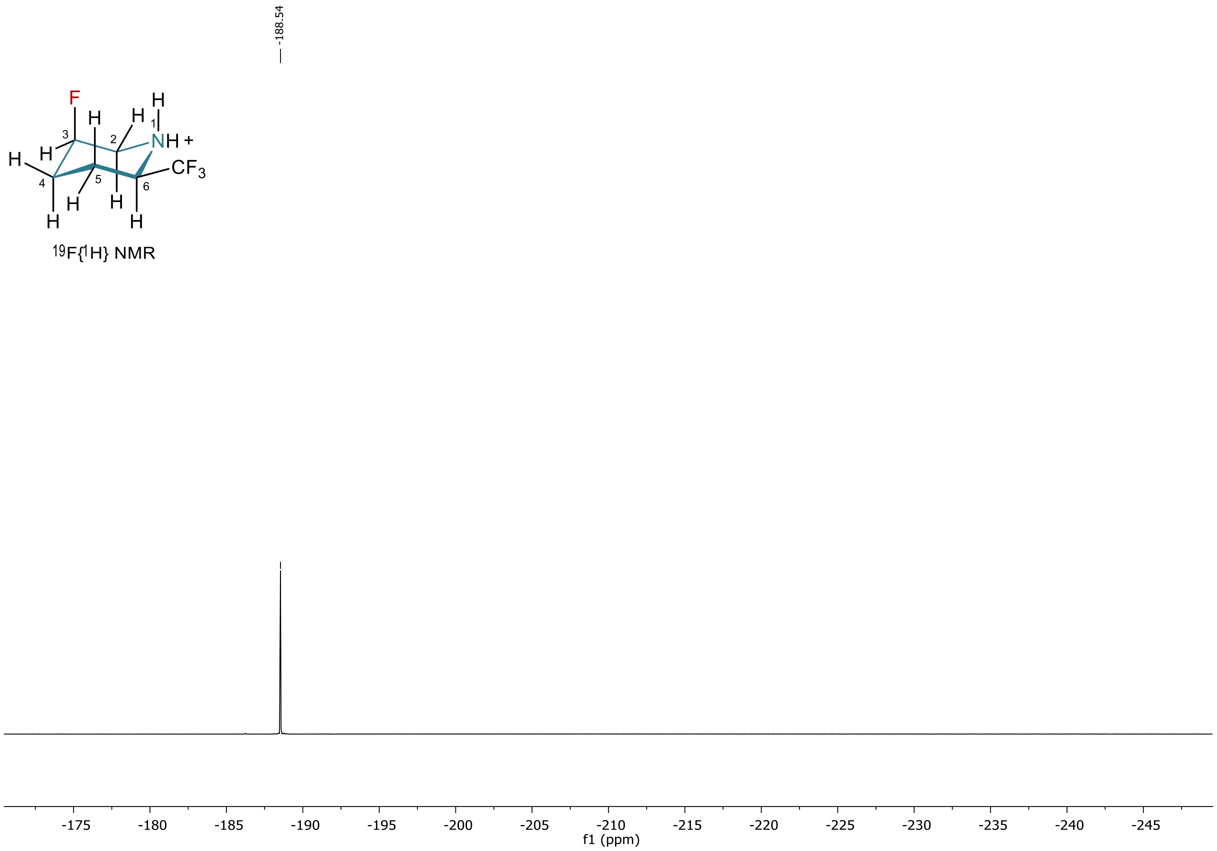

125.59
123.73
121.88
120.02
84.18
83.05
55.89
55.67
55.46
55.24
47.22
47.08
24.93
24.79
16.16
F
H
H
H
H
1
NH +
CF3
2
3
4
5
6
H
H
H
H
^{13}C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

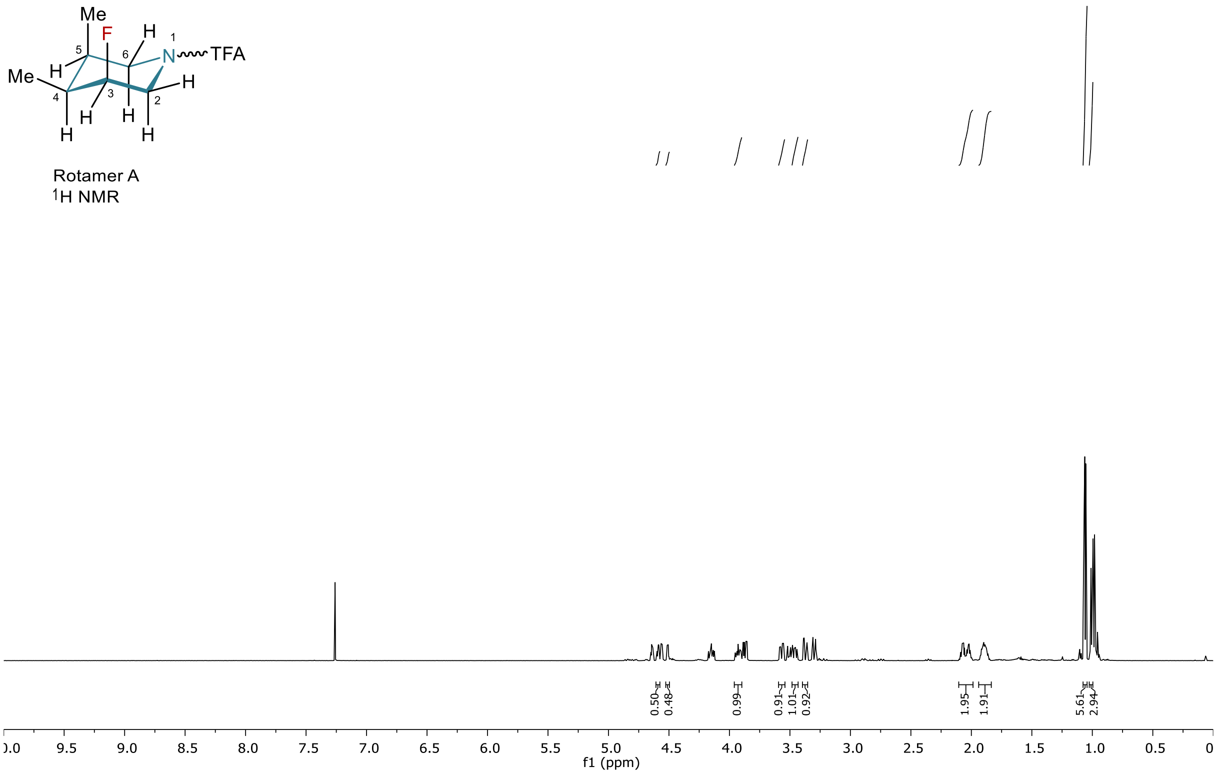


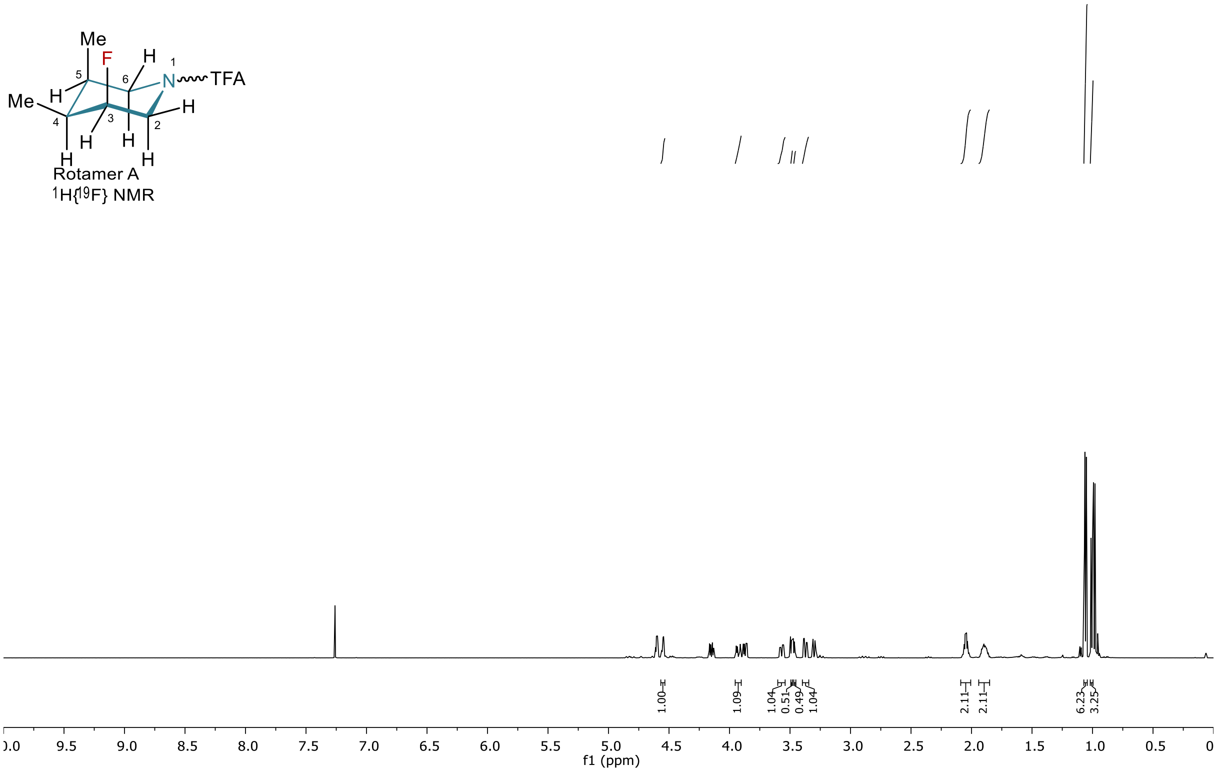
125.59
123.73
121.88
120.02
83.62
55.89
55.67
55.46
55.24
47.15
24.86
16.16
F
H
H
H
1
NH +
CF3
3
2
4
5
6
H
H
H
H
H
H
13C{19F} NMR
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

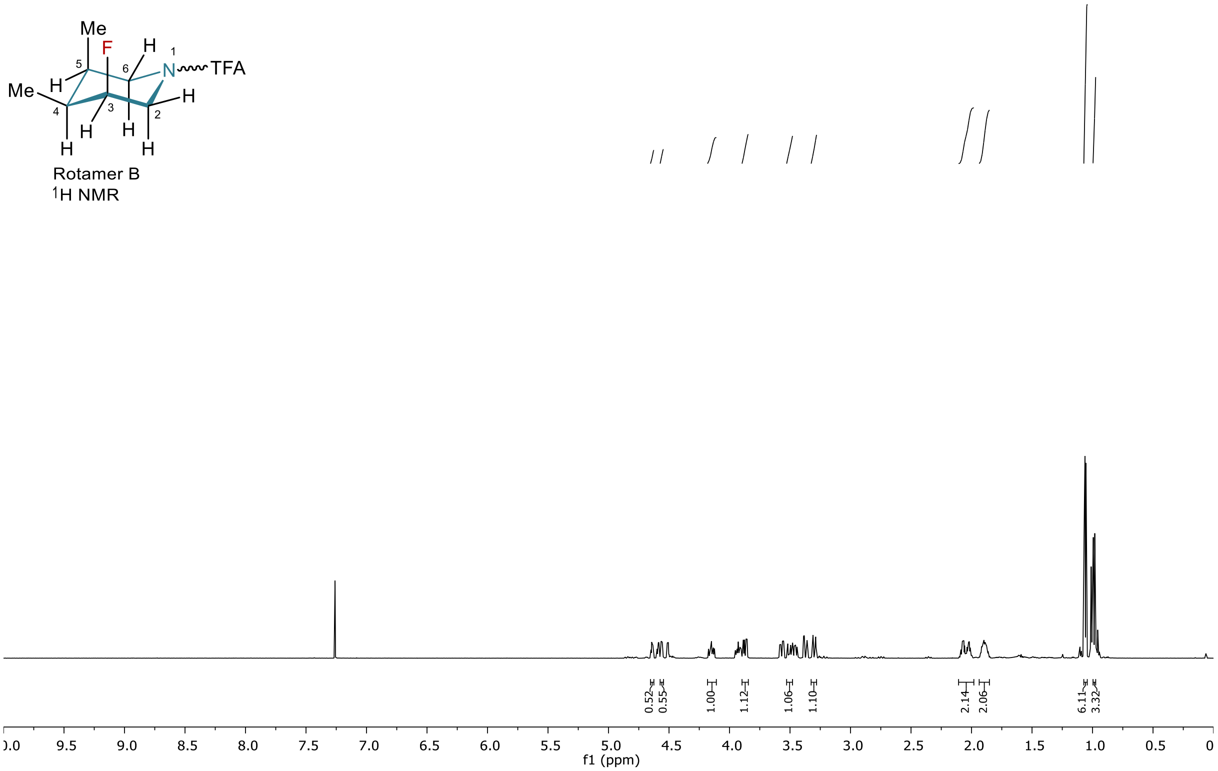


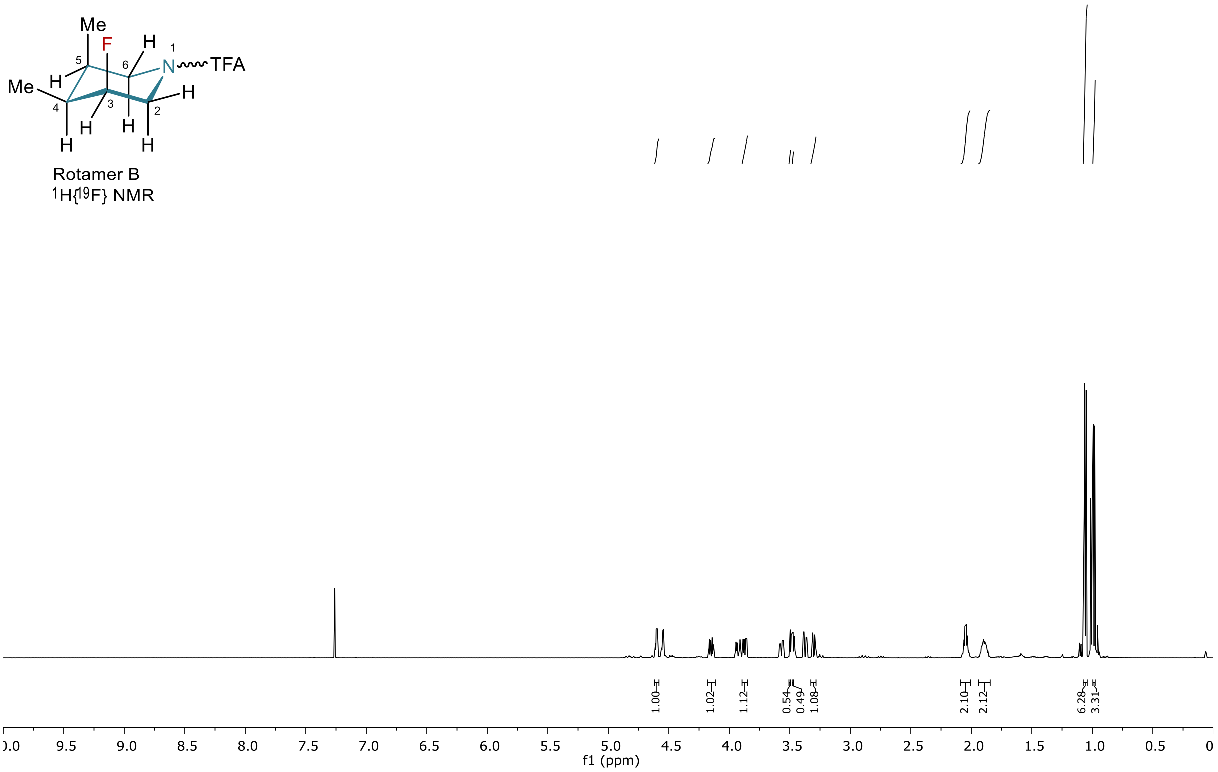
-74.99
-75.00
-188.41
-188.42
-188.44
-188.48
-188.49
-188.50
-188.50
-188.51
-188.52
-188.56
-188.57
-188.58
-188.58
-188.59
-188.64
-188.66
-188.67
F
H
H
H
1
NH +
CF3
3
2
4
5
6
H
H
H
H
H
H
19F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

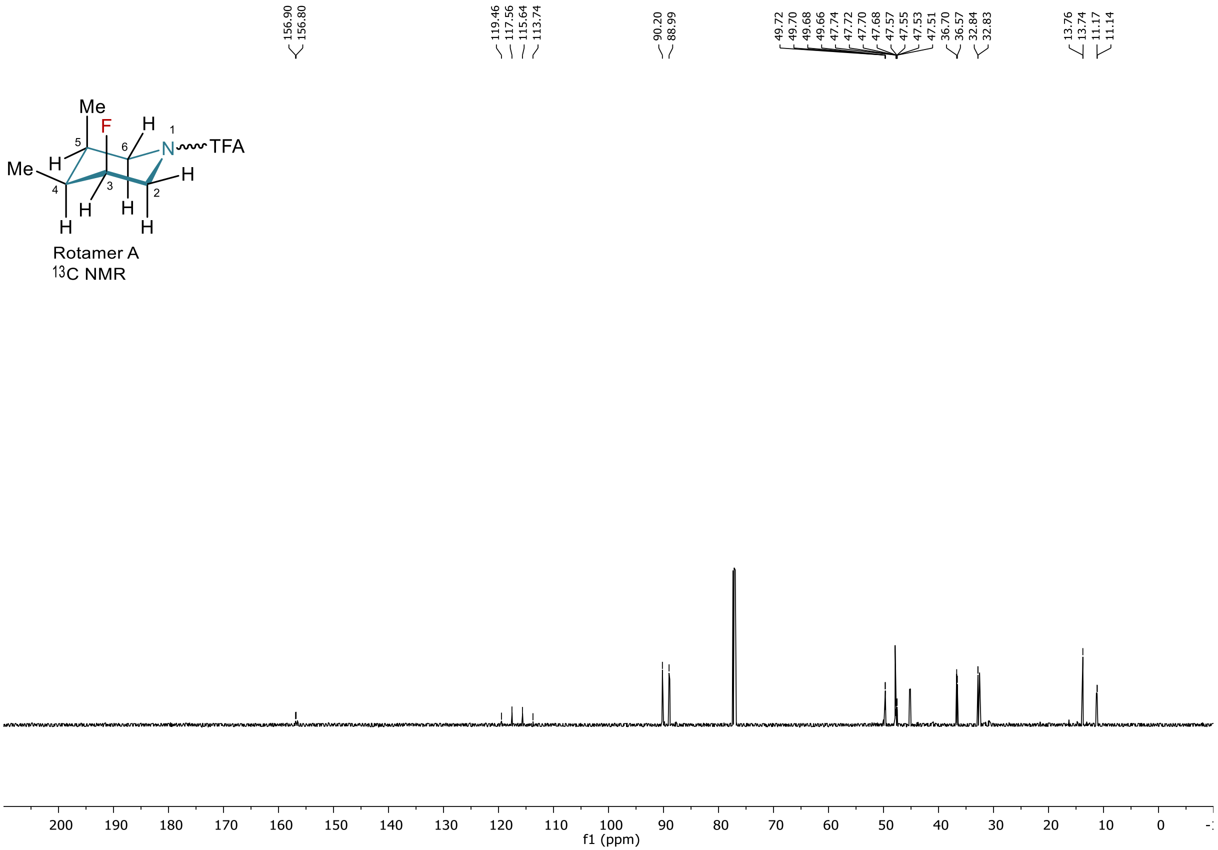

-188.54
F
H
H
H
H
H
N
H +
CF3
H
H
H
H
1
2
3
4
5
6
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


Me
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer A
^{1}H NMR
0.50
0.48
0.99
0.91
1.01
0.92
1.95
1.91
5.61
2.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


Me
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer A
^{1}H{^{19}F} NMR
1.00
1.09
1.04
0.51
0.49
1.04
2.11
2.11
6.23
3.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


Me
F
H
1
N
TFA
5
6
H
Me
H
4
3
2
H
H
H
H
Rotamer B
¹H NMR
0.52
0.55
1.00
1.12
1.06
1.10
2.14
2.06
6.11
3.32
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


Me
F
H
1
N
TFA
5
6
H
Me
H
4
3
2
H
H
H
H
Rotamer B
¹H{¹⁹F} NMR
1.00
1.02
1.12
0.54
0.49
1.08
2.10
2.12
6.28
3.31
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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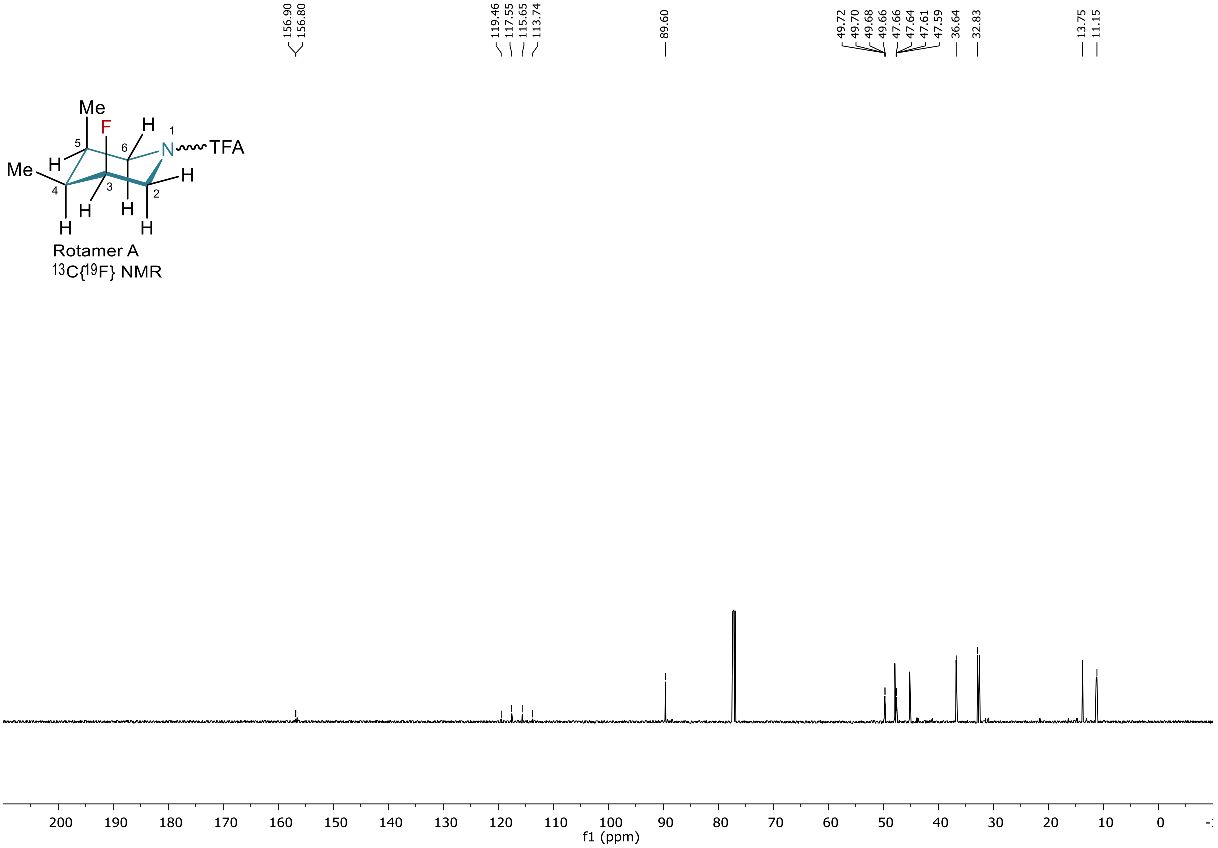
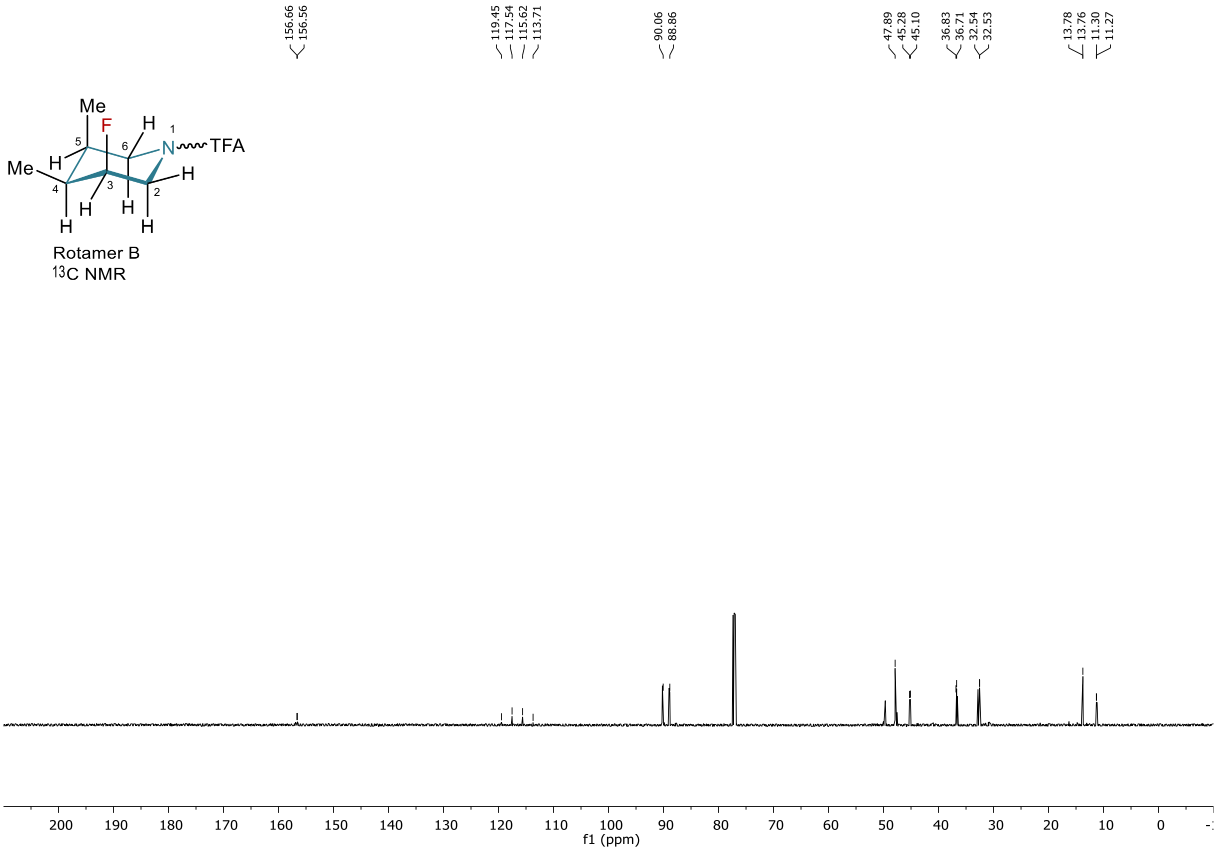
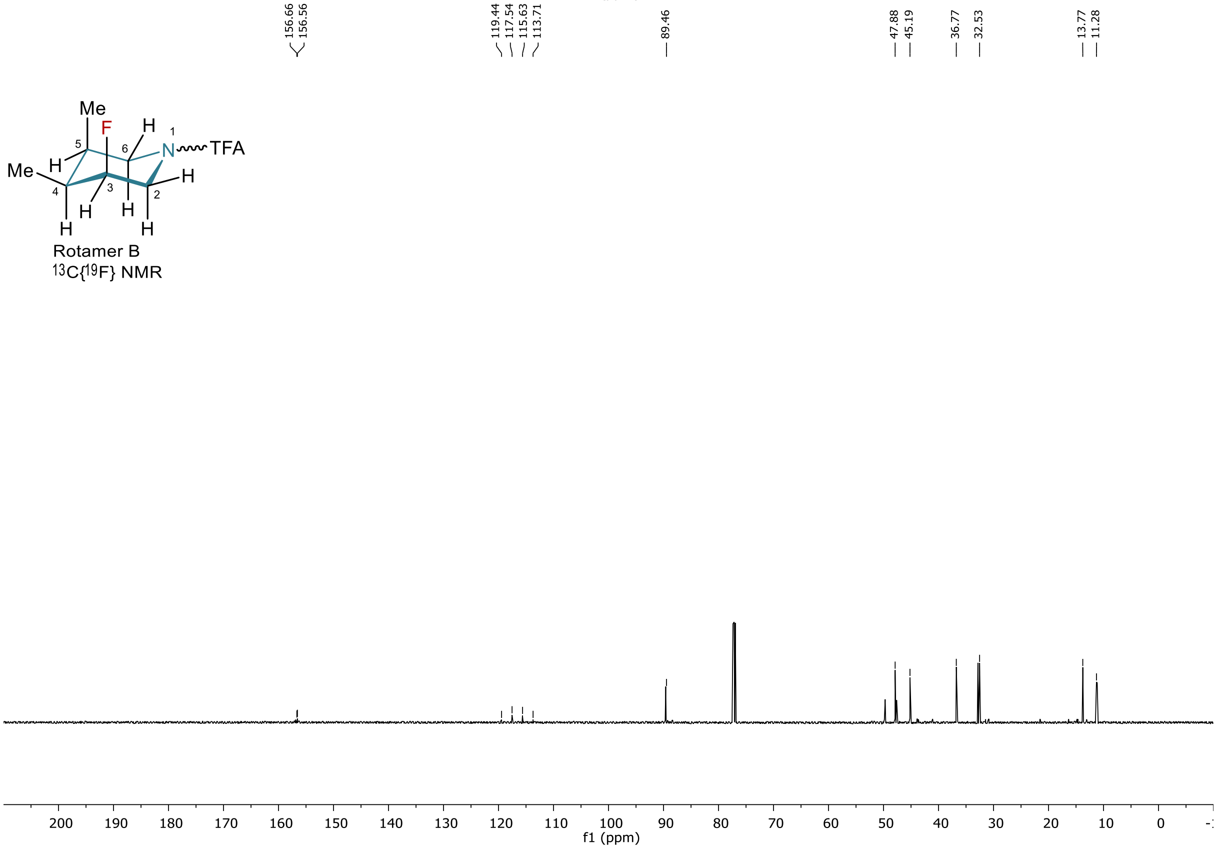
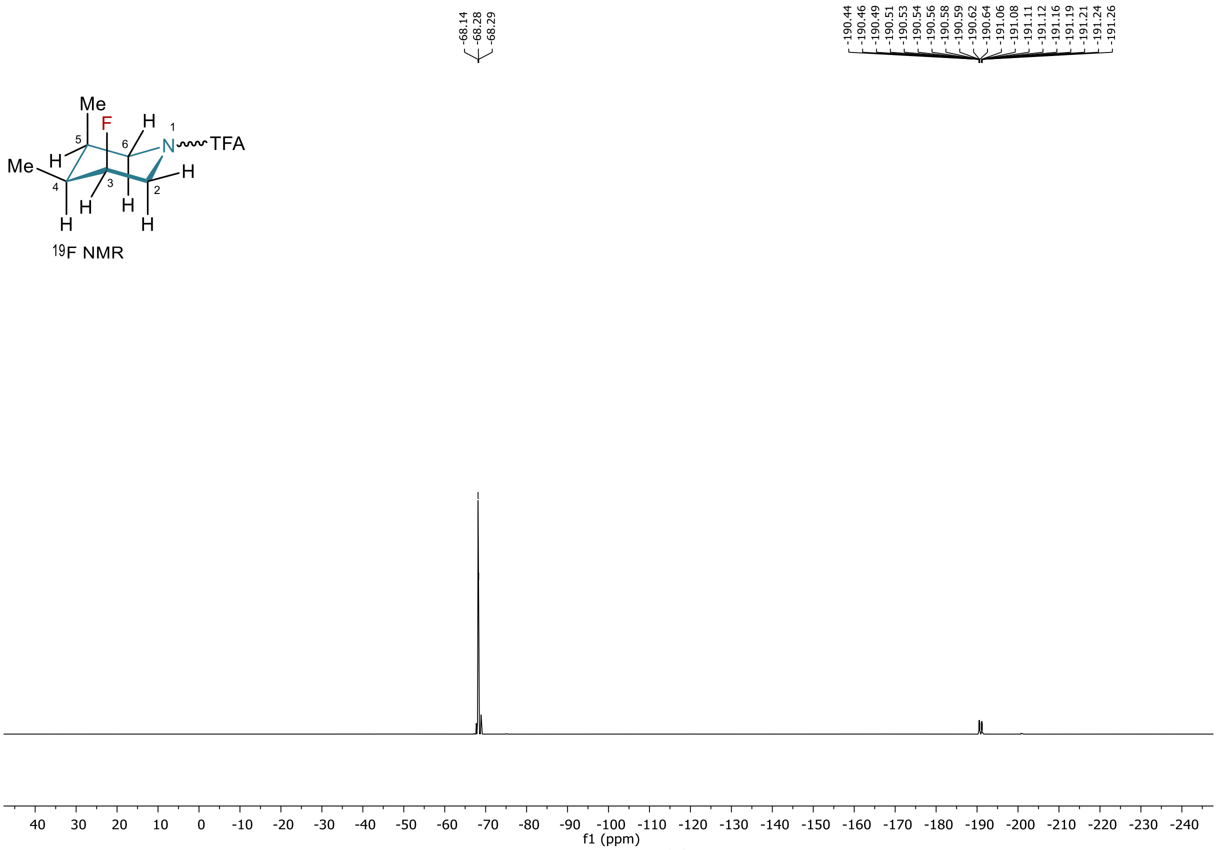
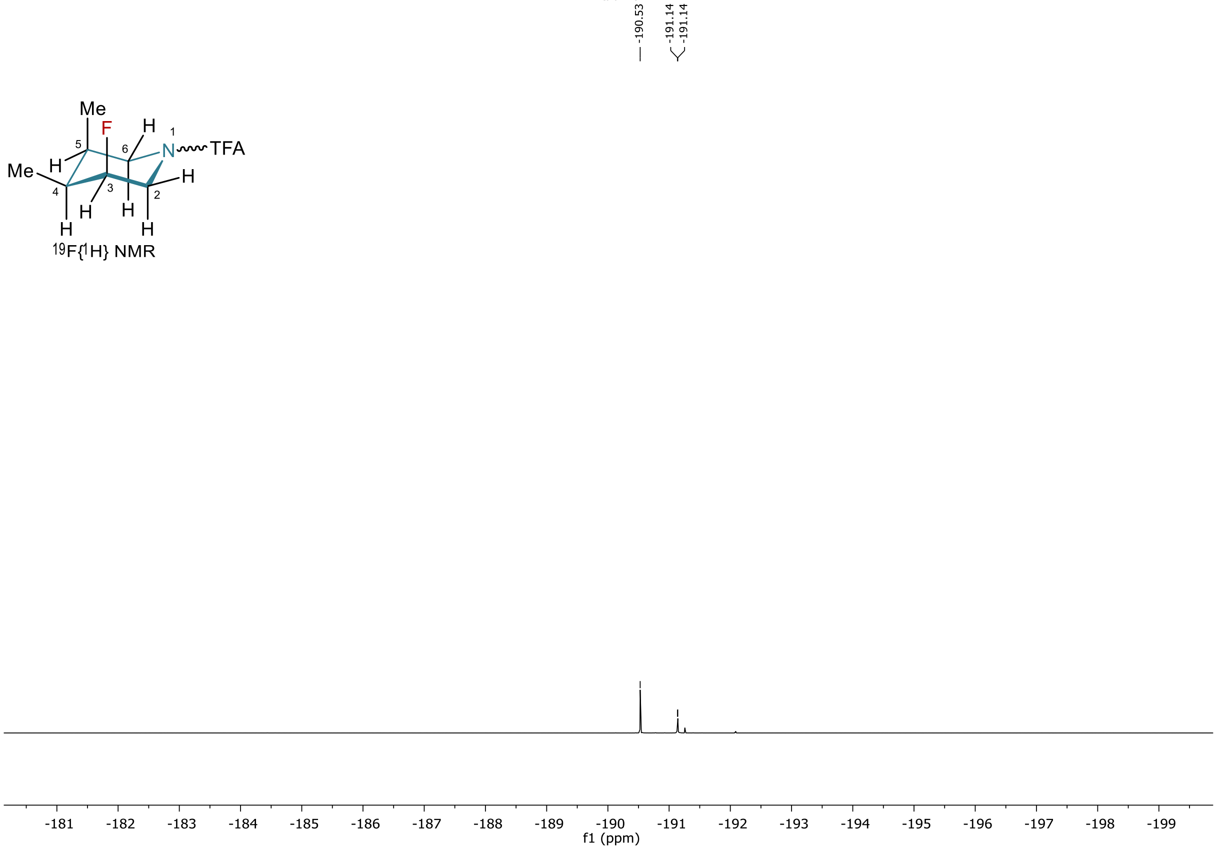
156.80
119.46
117.56
115.64
113.74
90.20
88.99
49.72
49.70
49.68
49.66
47.74
47.72
47.70
47.68
47.57
47.55
47.53
47.51
36.70
36.57
32.84
32.83
13.76
13.74
11.17
11.14
Me
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

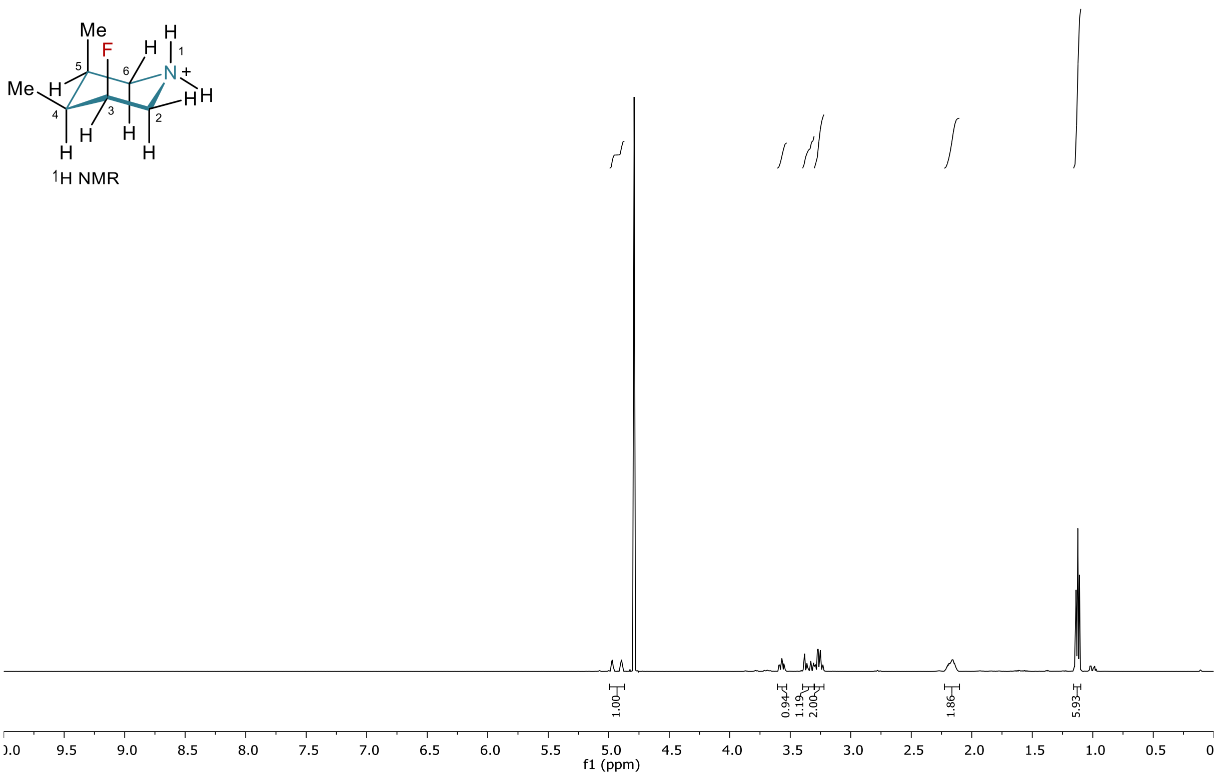

156.90
156.80
119.46
117.55
115.65
113.74
89.60
49.72
49.70
49.68
49.66
47.66
47.64
47.61
47.59
36.64
32.83
13.75
11.15
Me
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

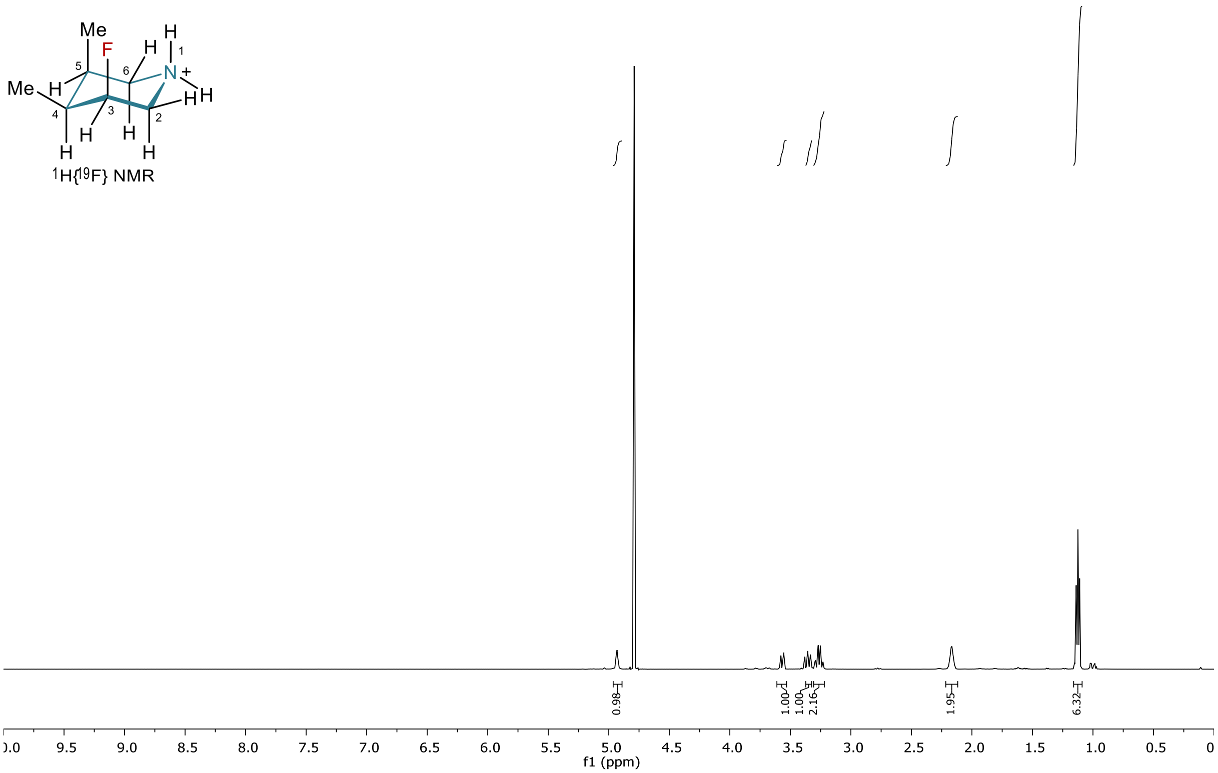

156.66
156.56
119.45
117.54
115.62
113.71
90.06
88.86
47.89
45.28
45.10
36.83
36.71
32.54
32.53
13.78
13.76
11.30
11.27
Me
F
H
1
N
TFA
5
6
Me
H
H
4
3
2
H
H
H
H
Rotamer B
^{13}C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

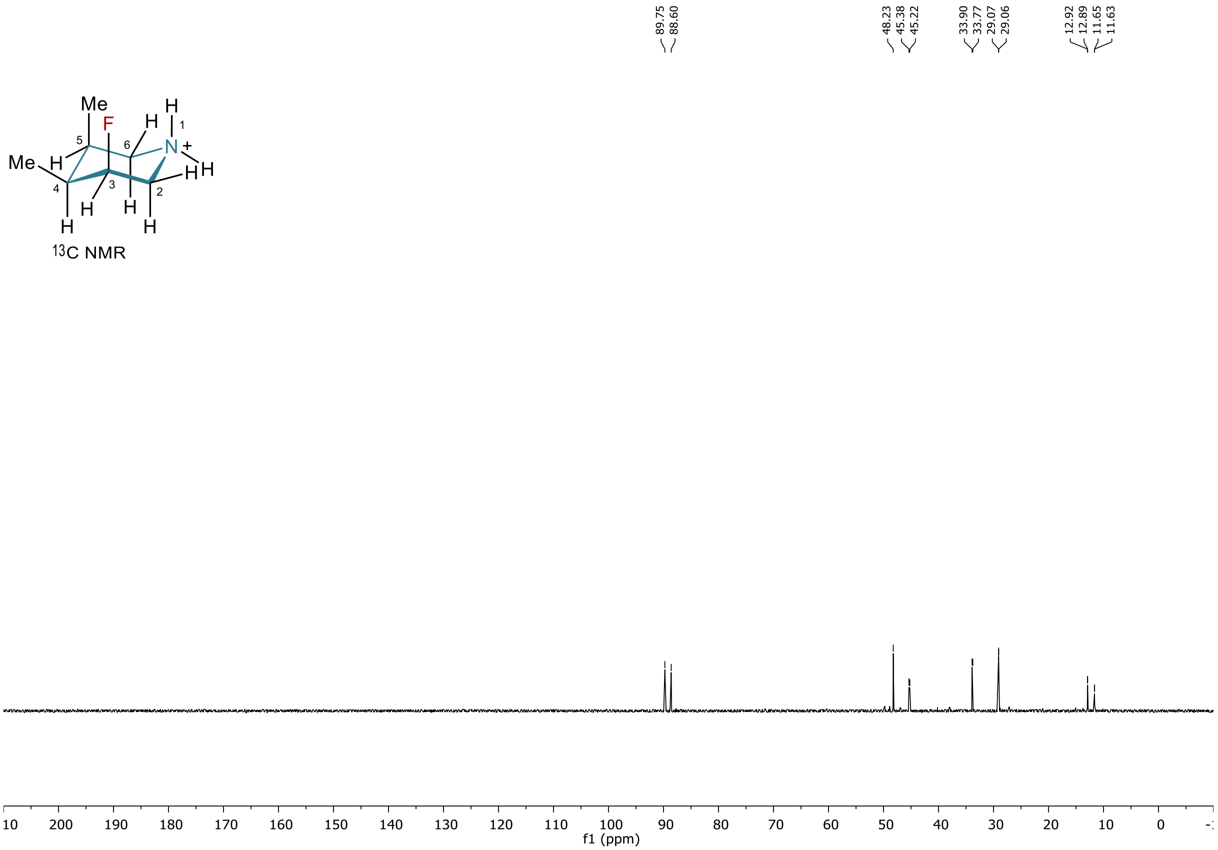

156.66
156.56
119.44
117.54
115.63
113.71
89.46
47.88
45.19
36.77
32.53
13.77
11.28
Me
F
H
1
N
TFA
5
6
Me
H
H
4
3
2
H
H
H
H
Rotamer B
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

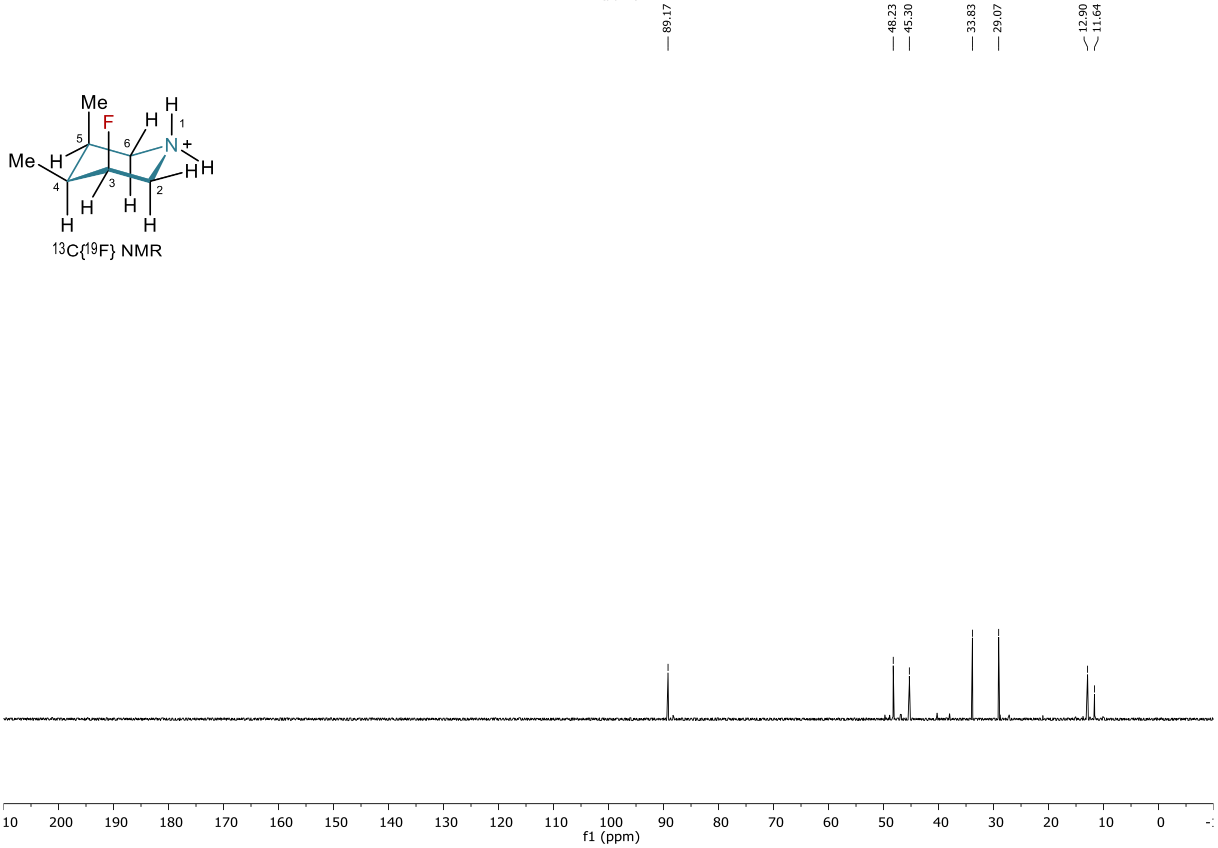

-68.14
-68.28
-68.29
-190.44
-190.46
-190.49
-190.51
-190.53
-190.54
-190.56
-190.58
-190.59
-190.62
-190.64
-191.06
-191.08
-191.11
-191.12
-191.16
-191.19
-191.21
-191.24
-191.26
Me
F
H
1
5
6
N
TFA
H
Me
H
4
3
2
H
H
H
H
19F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

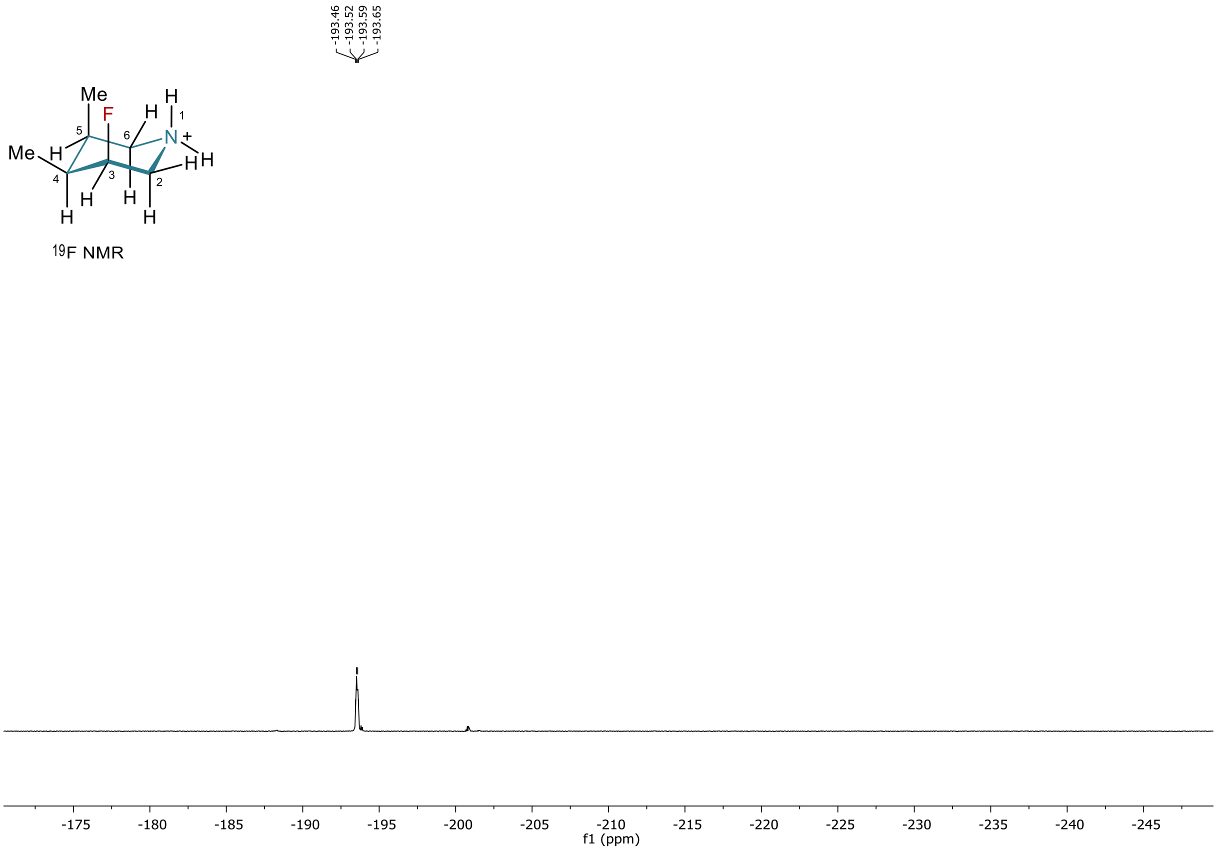

-190.53
-191.14
-191.14
Me
F
H
1
5
6
N
TFA
H
Me
H
4
3
2
H
H
H
H
19F{1H} NMR
-181 -182 -183 -184 -185 -186 -187 -188 -189 -190 -191 -192 -193 -194 -195 -196 -197 -198 -199
f1 (ppm)

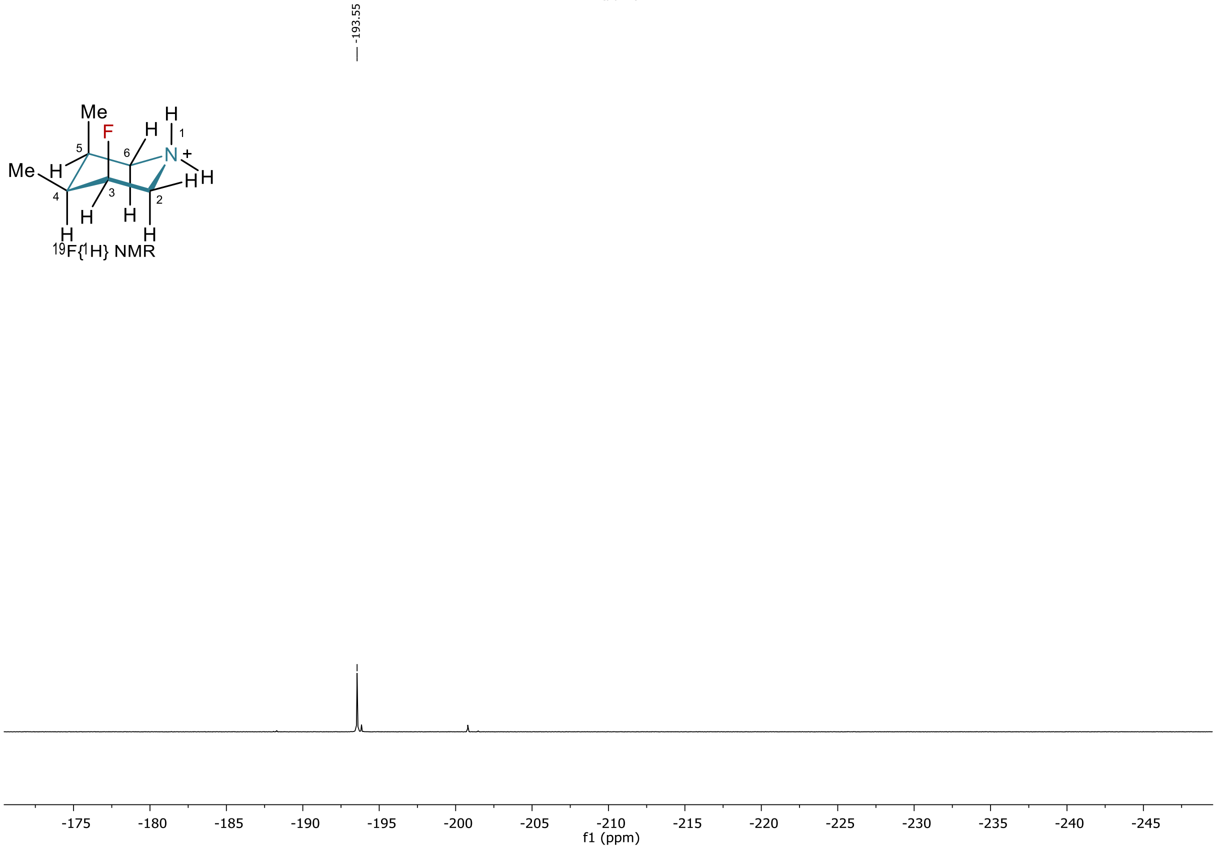

Me
F
H
H
1
N+
Me
H
5
6
H
H
4
3
2
H
H
H
H
1H NMR
1.00
0.94
1.19
2.00
1.86
5.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

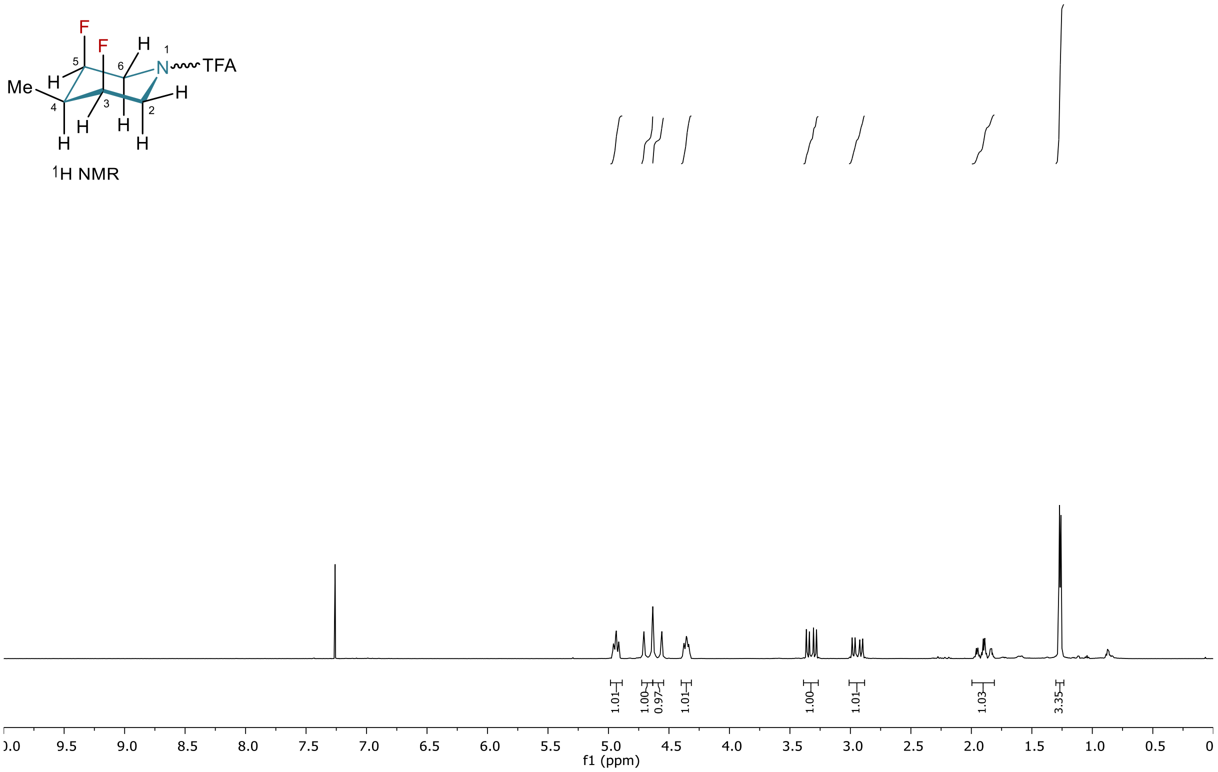

Me
F
H
H
1
N+
Me
H
5
6
H
H
4
3
2
H
H
H
H
1H{19F} NMR
0.98
1.00
1.00
2.16
1.95
6.32
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

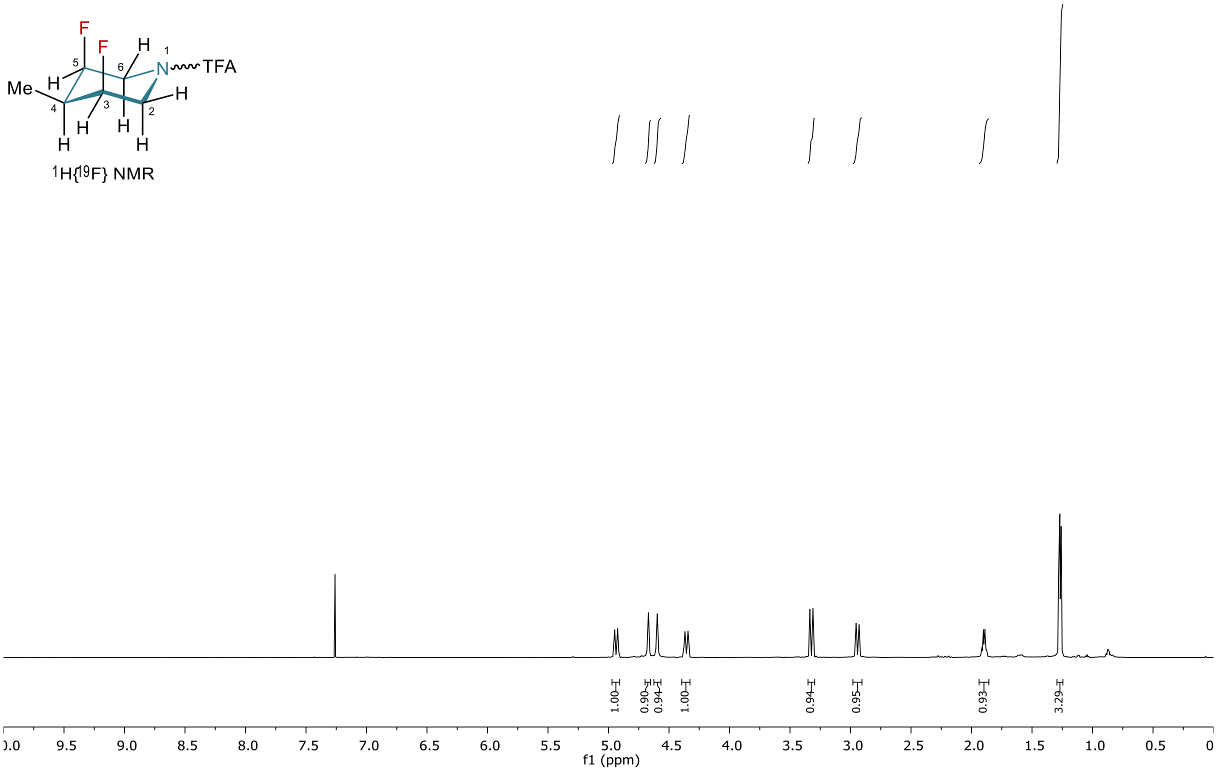

89.75
88.60
48.23
45.38
45.22
33.90
33.77
29.07
29.06
12.92
12.89
11.65
11.63
Me
F
H
H
1
5
6
N+
Me
H
H
H
4
3
2
H
H
H
H
^{13}C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

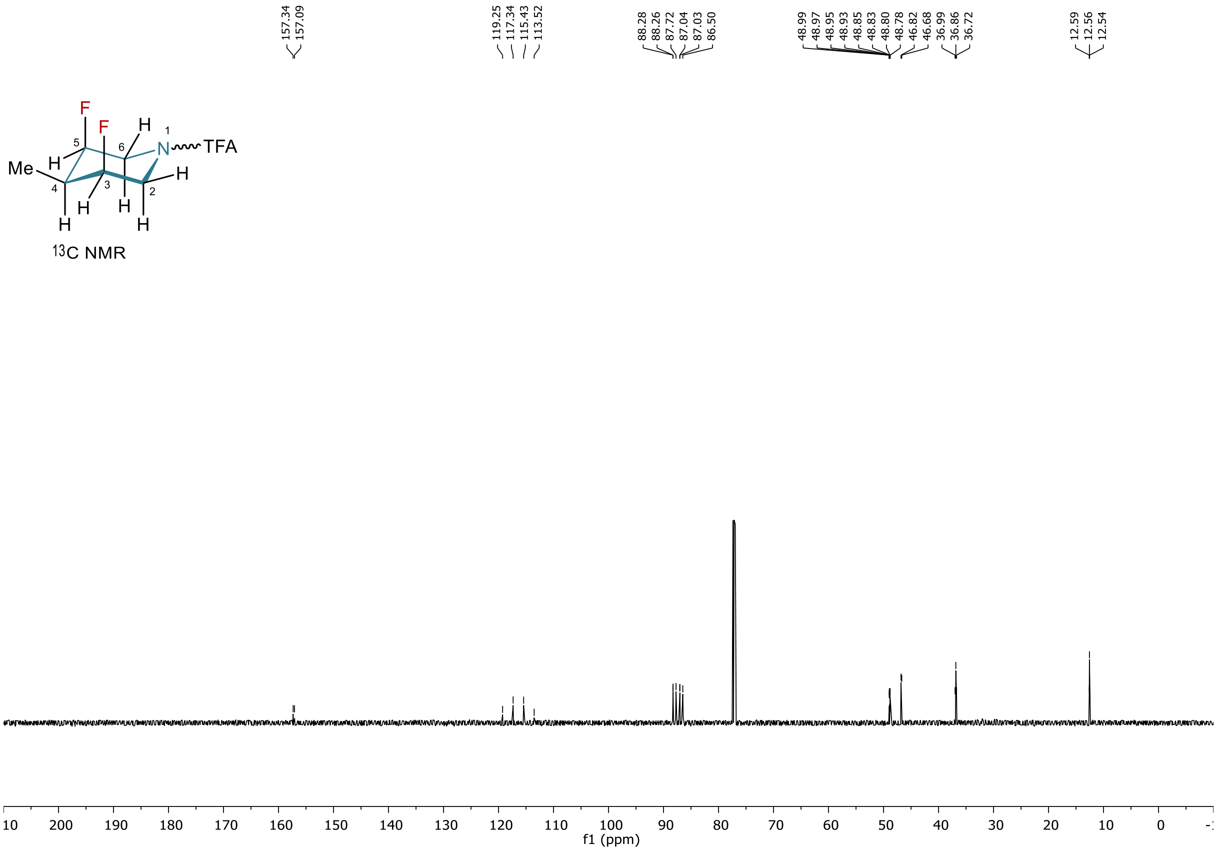

89.17
48.23
45.30
33.83
29.07
12.90
11.64
Me
F
H
H
1
5
6
N+
Me
H
H
H
4
3
2
H
H
H
H
^{13}C{^{19}F} NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

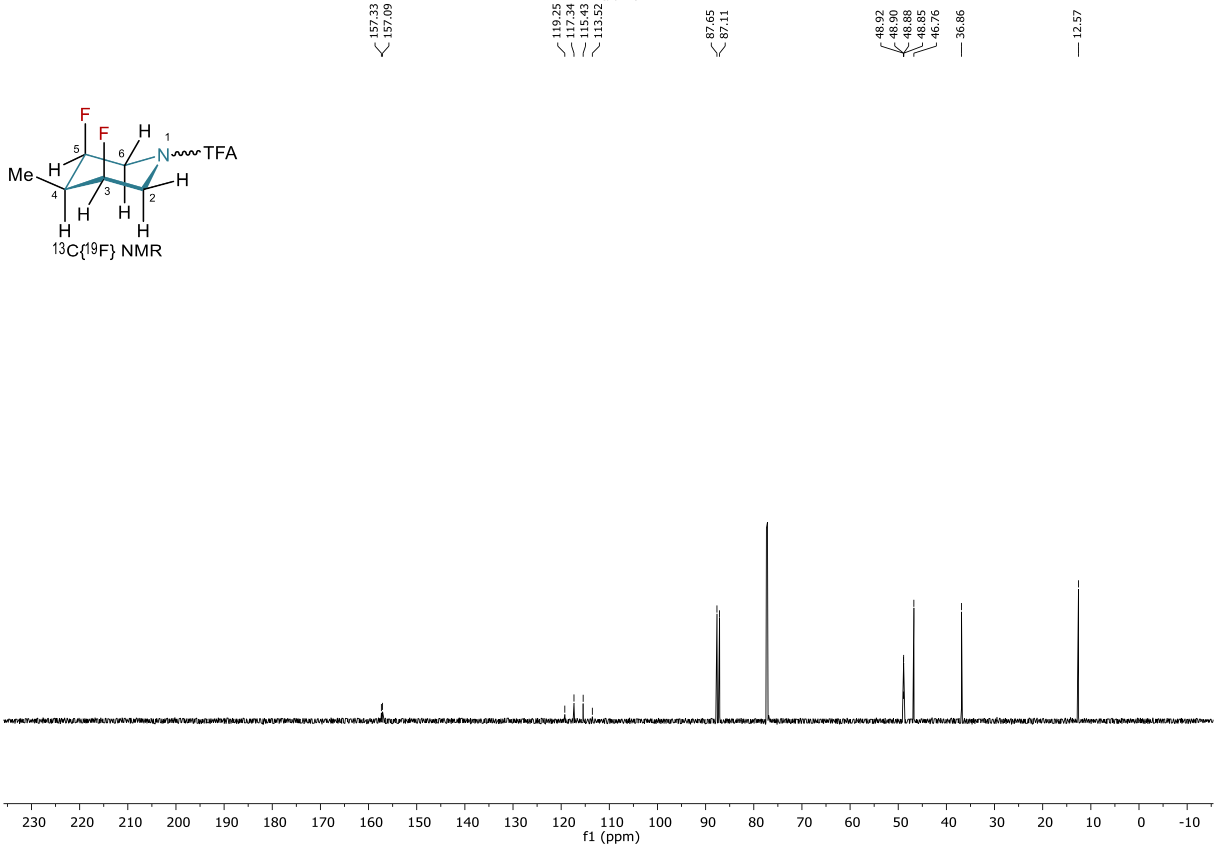

-193.46
-193.52
-193.59
-193.65
Me
F
H
H
1
5
6
N+
Me
H
H
H
4
3
2
H
H
H
H
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

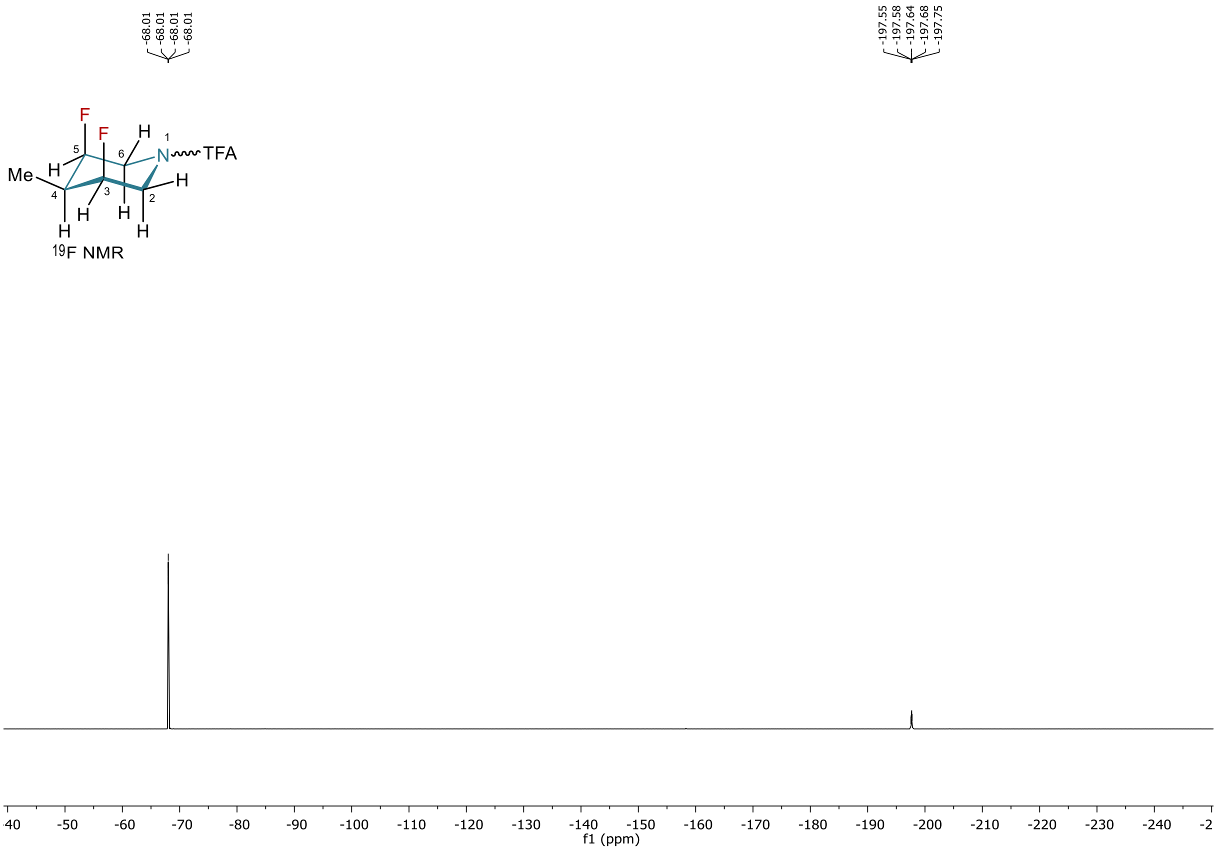

-193.55
Me
F
H
H
1
5
6
N+
Me
H
H
H
4
3
2
H
H
H
H
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

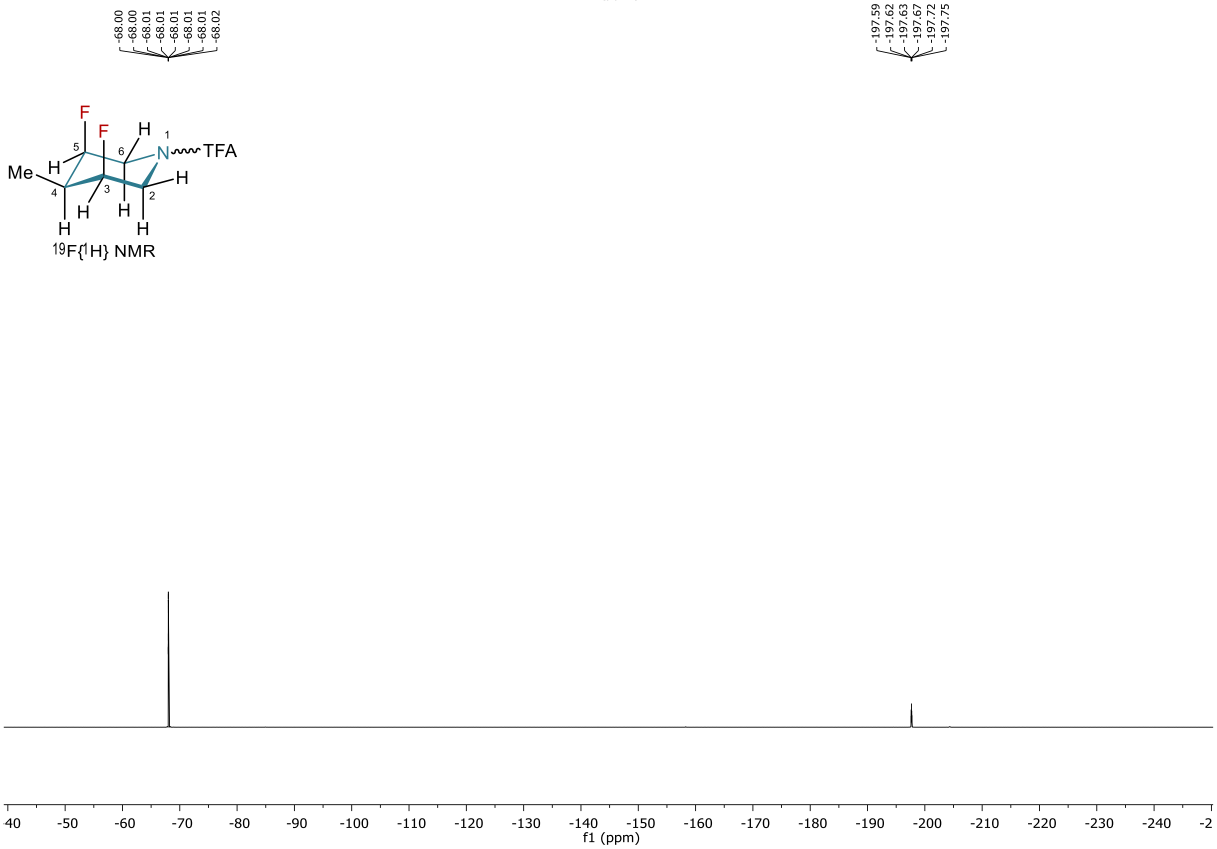

F
F
H
1
N
TFA
5
6
H
Me
H
4
3
2
H
H
H
H
^{1}H NMR
1.01
1.00
0.97
1.01
1.00
1.01
1.03
3.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

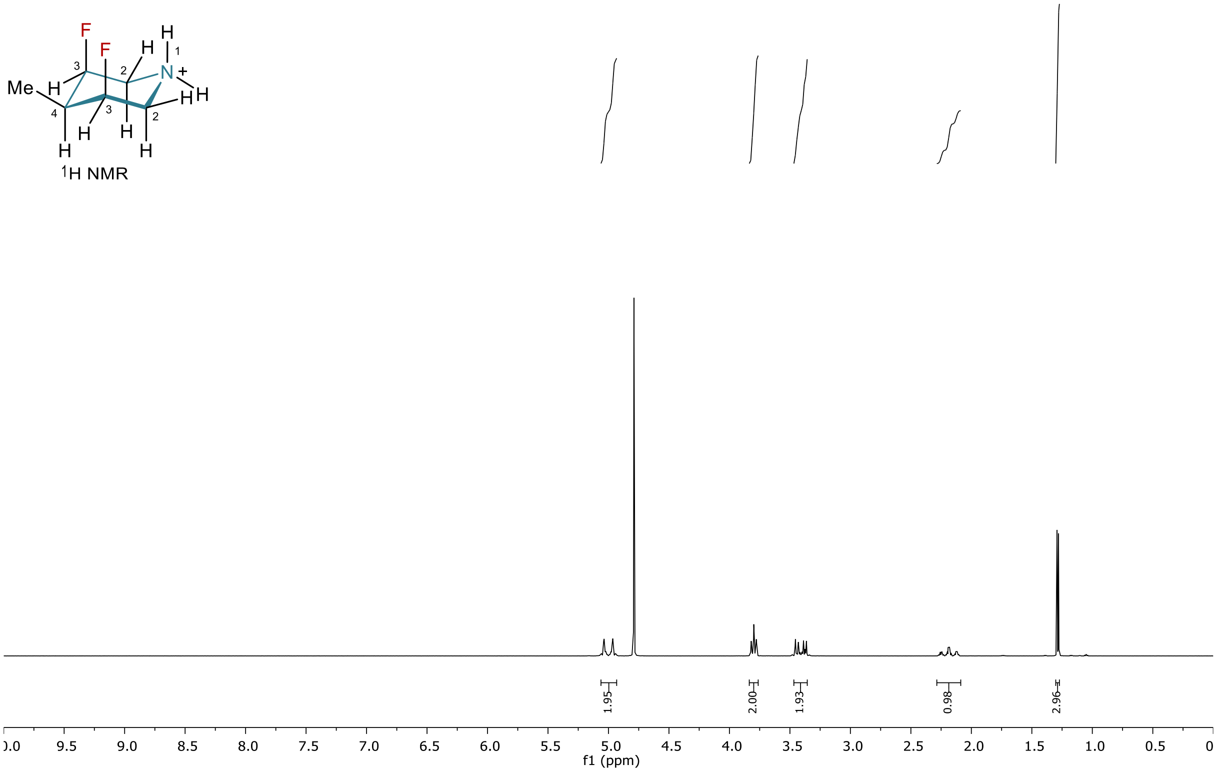

F
F
H
1
N
TFA
5
6
H
Me
H
4
3
2
H
H
H
H
^{1}H{^{19}F} NMR
1.00
0.90
0.94
1.00
0.94
0.95
0.93
3.29
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

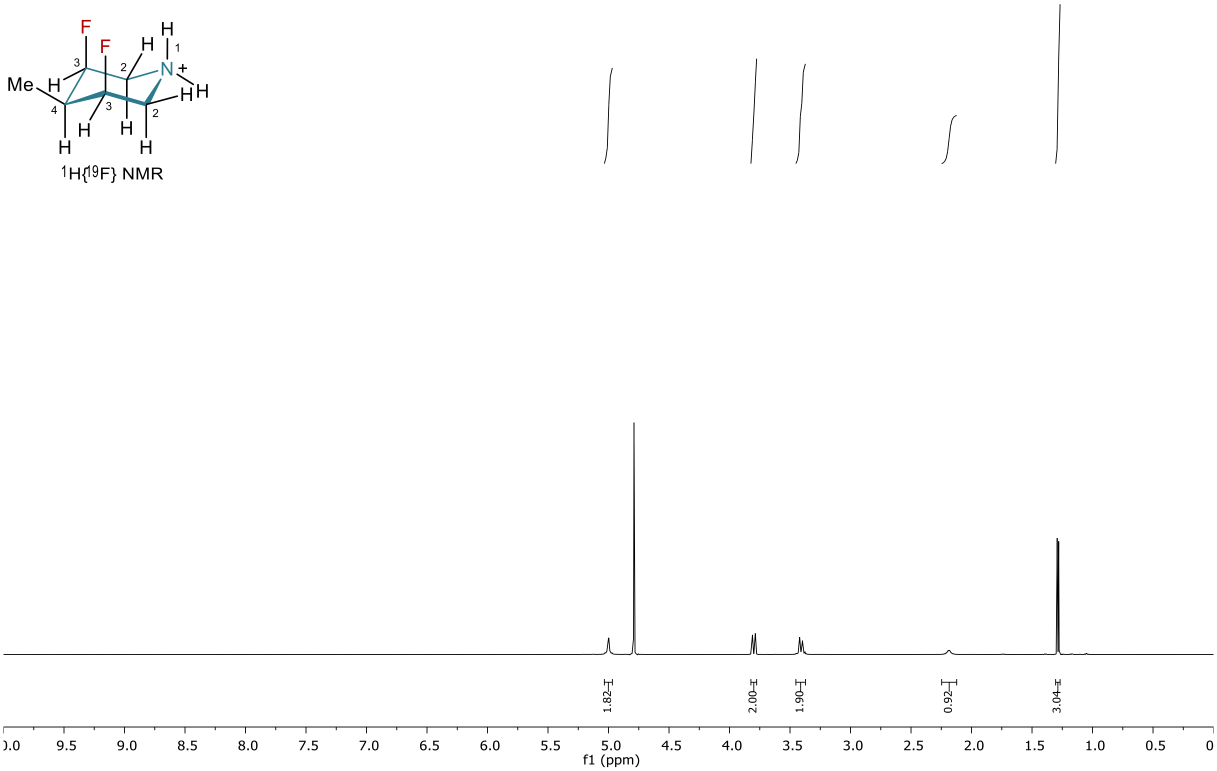

157.34
157.09
119.25
117.34
115.43
113.52
88.28
88.26
87.72
87.04
87.03
86.50
48.99
48.97
48.95
48.93
48.85
48.83
48.80
48.78
46.82
46.68
36.99
36.86
36.72
12.59
12.56
12.54
F
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

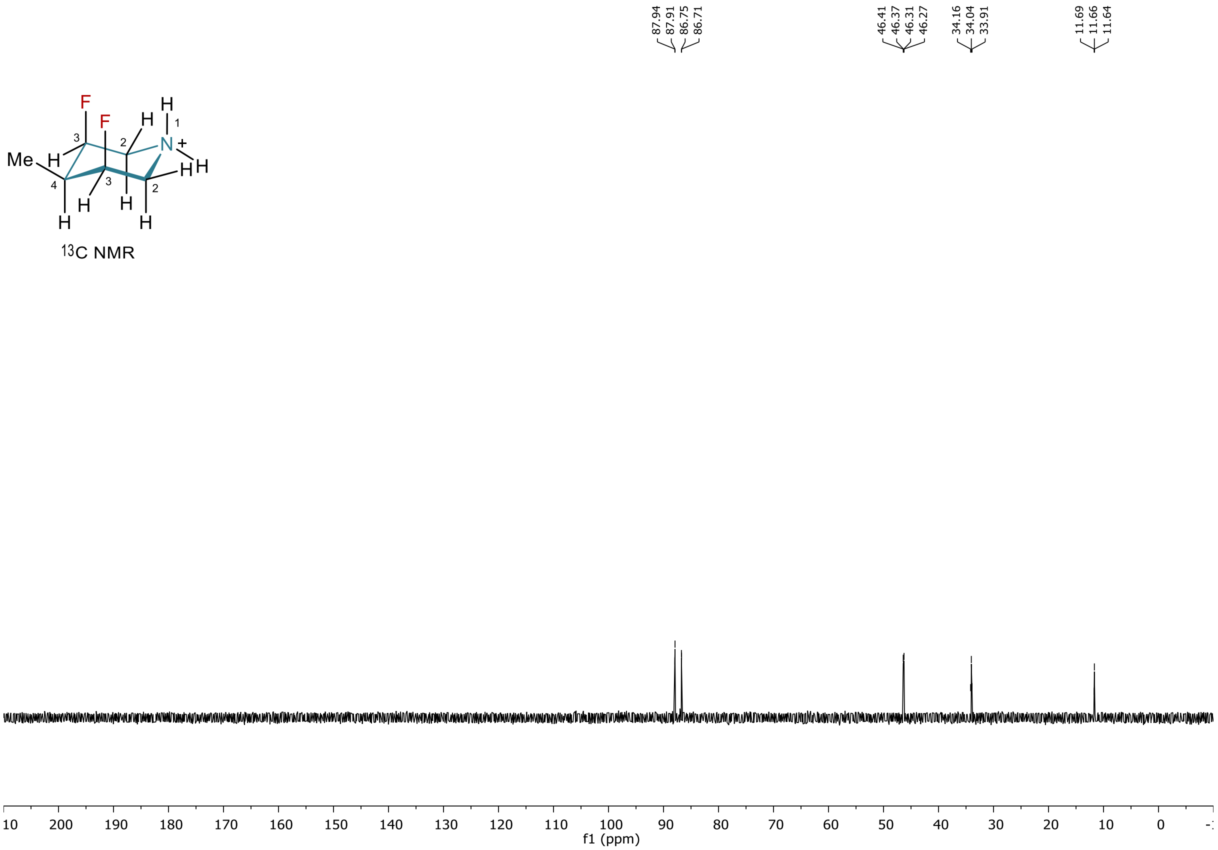

157.33
157.09
119.25
117.34
115.43
113.52
87.65
87.11
48.92
48.90
48.88
48.85
46.76
36.86
12.57
F
F
H
1
5
6
N
TFA
Me
H
H
4
3
2
H
H
H
H
13C{19F} NMR
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-68.01
-68.01
-68.01
-68.01
-197.55
-197.58
-197.64
-197.68
-197.75
F
F
H
1
5
6
N
TFA
H
H
Me
4
3
2
H
H
H
H
19F NMR
40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
-2
f1 (ppm)

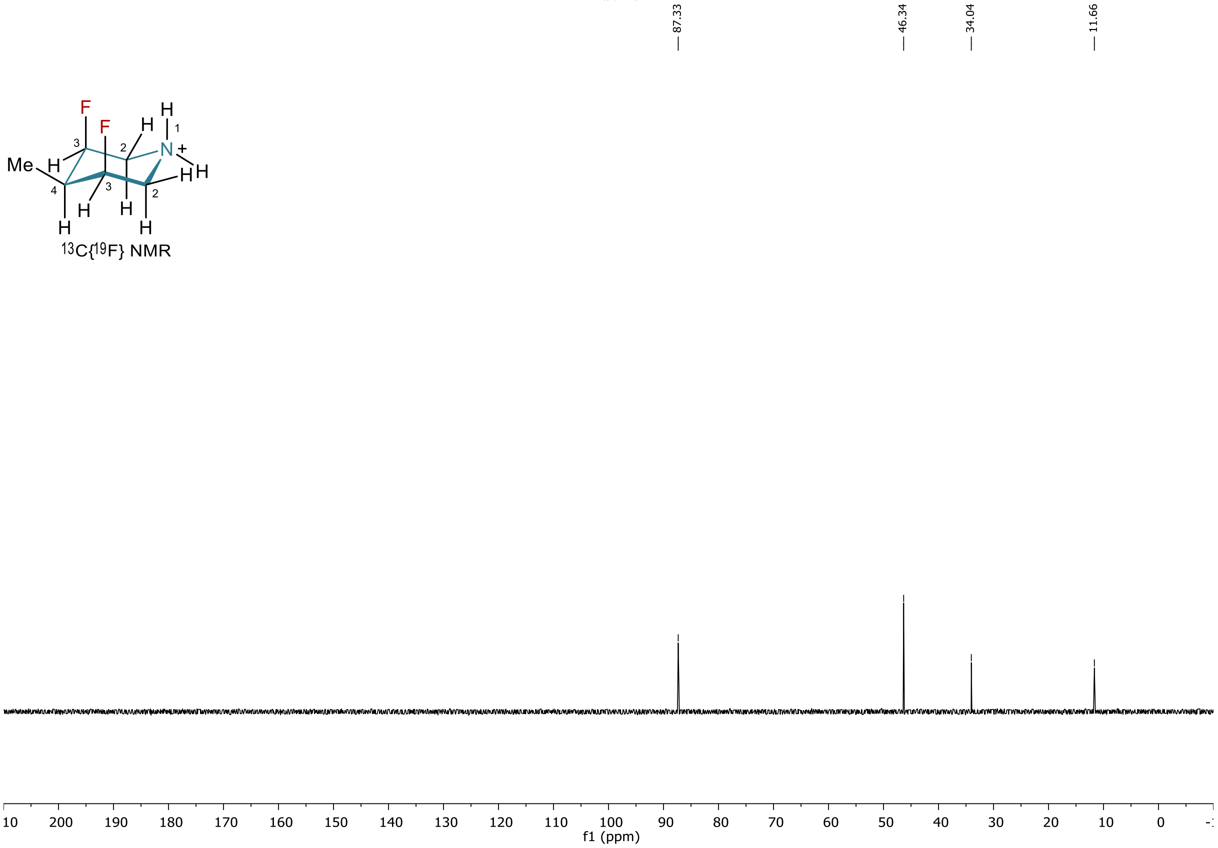

-68.00
-68.00
-68.01
-68.01
-68.01
-68.01
-68.01
-68.02
-197.59
-197.62
-197.63
-197.67
-197.72
-197.75
F
F
H
1
5
6
N
TFA
H
H
Me
4
3
2
H
H
H
H
19F{1H} NMR
40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
-2
f1 (ppm)


F
F
H
H
1
3
2
N+
Me
H
H
4
3
2
H
H
H
H
1H NMR
1.95
2.00
1.93
0.98
2.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

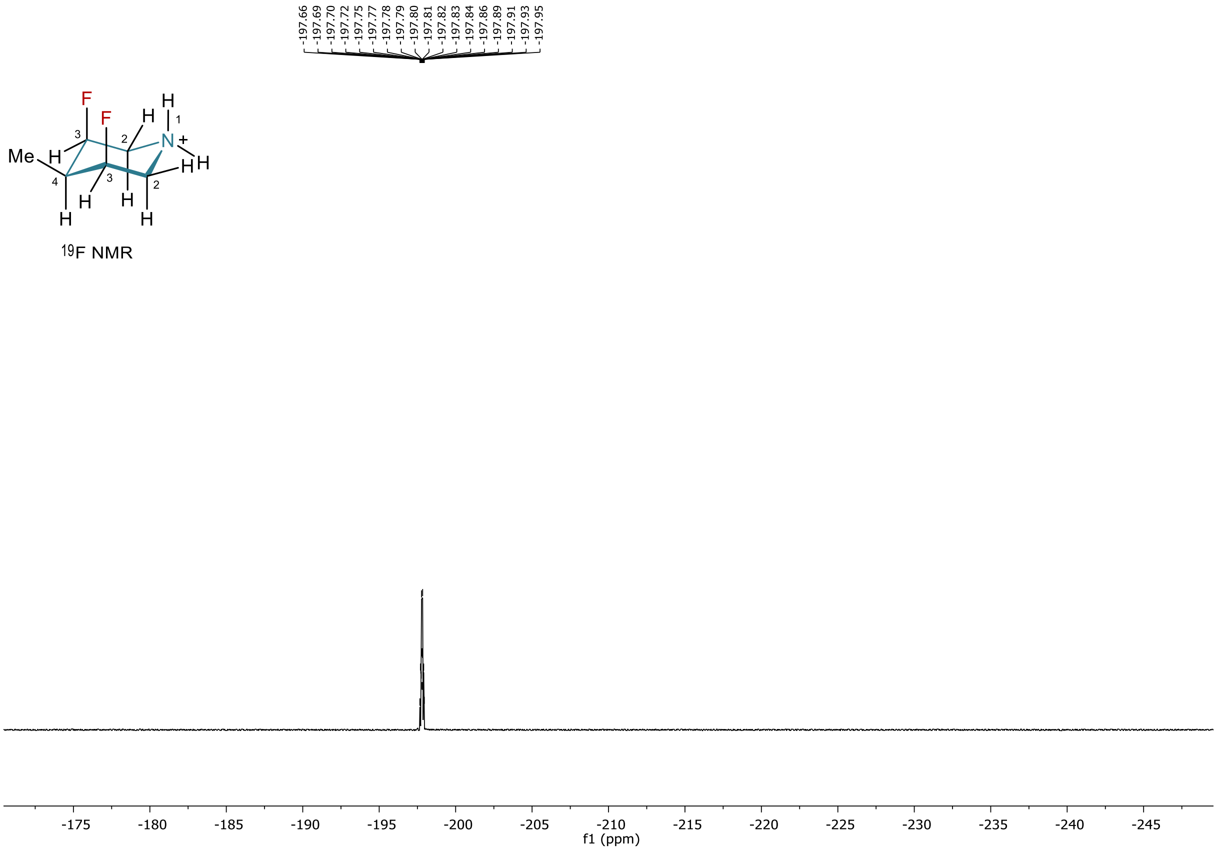

F
F
H
H
1
3
2
N+
Me
H
H
4
3
2
H
H
H
H
1H{19F} NMR
1.82
2.00
1.90
0.92
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

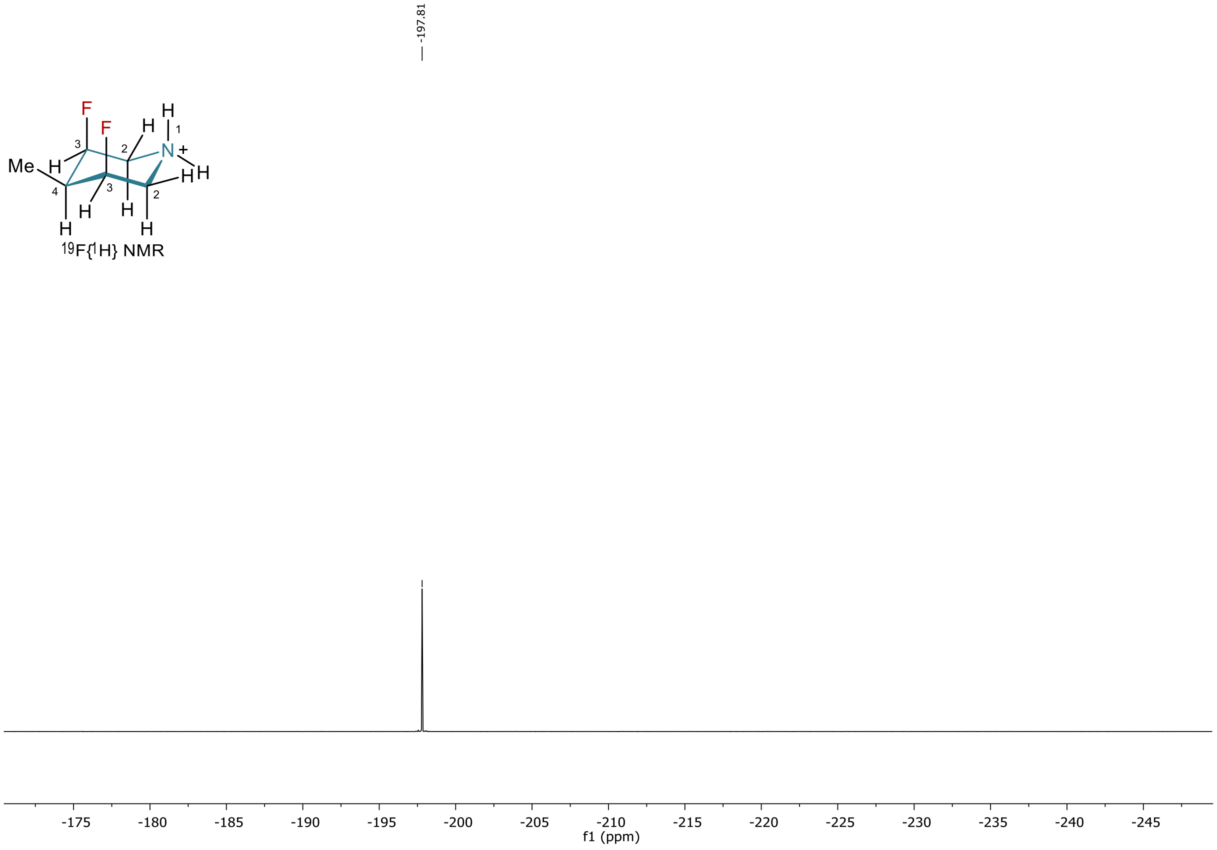


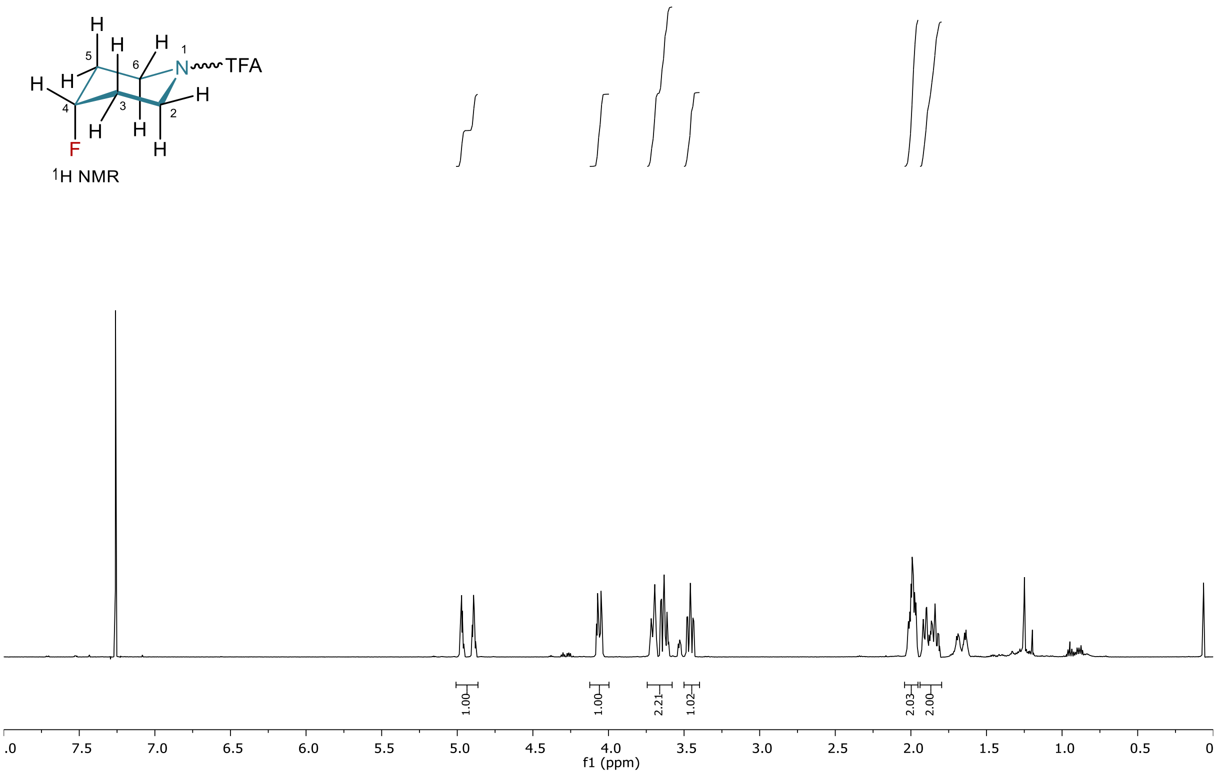
87.94
87.91
86.75
86.71
46.41
46.37
46.31
46.27
34.16
34.04
33.91
11.69
11.66
11.64
F
F
H
H
1
3
2
N+
Me
H
H
H
4
3
2
H
H
H
H
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



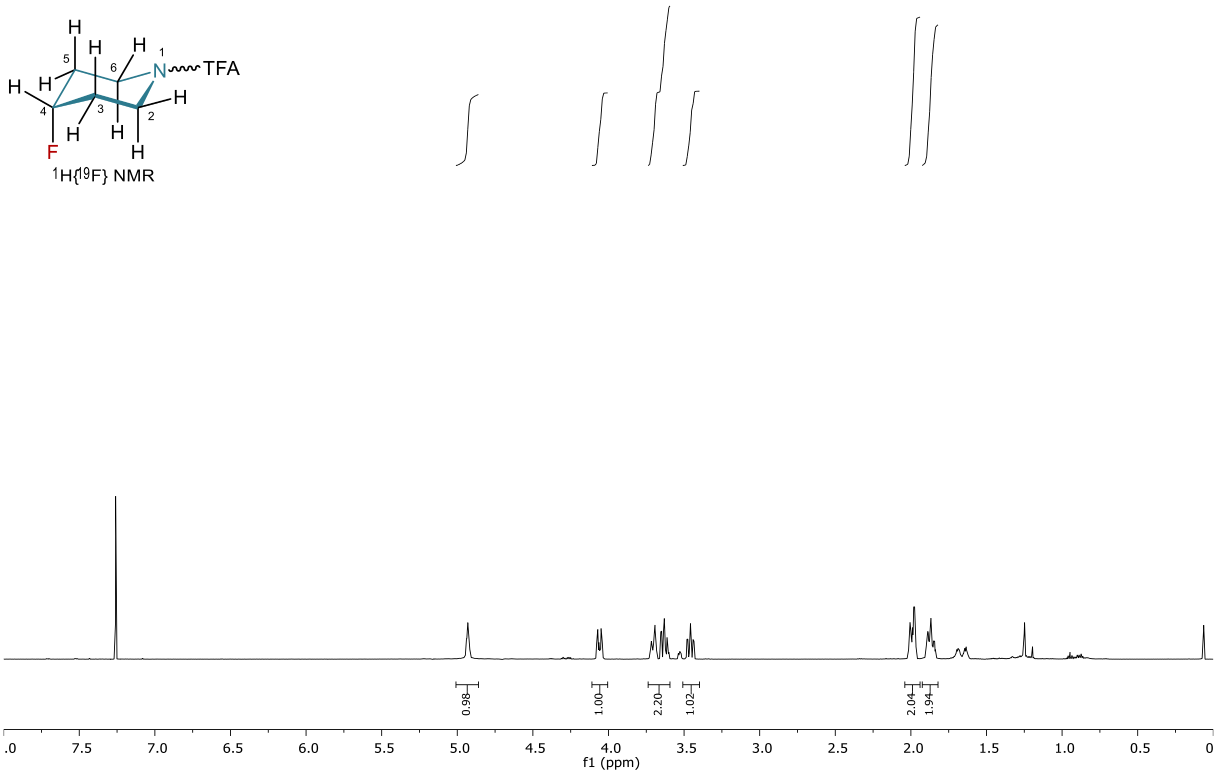
87.33
46.34
34.04
11.66
F
F
H
H
1
3
2
N+
Me
H
H
H
4
3
2
H
H
H
H
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

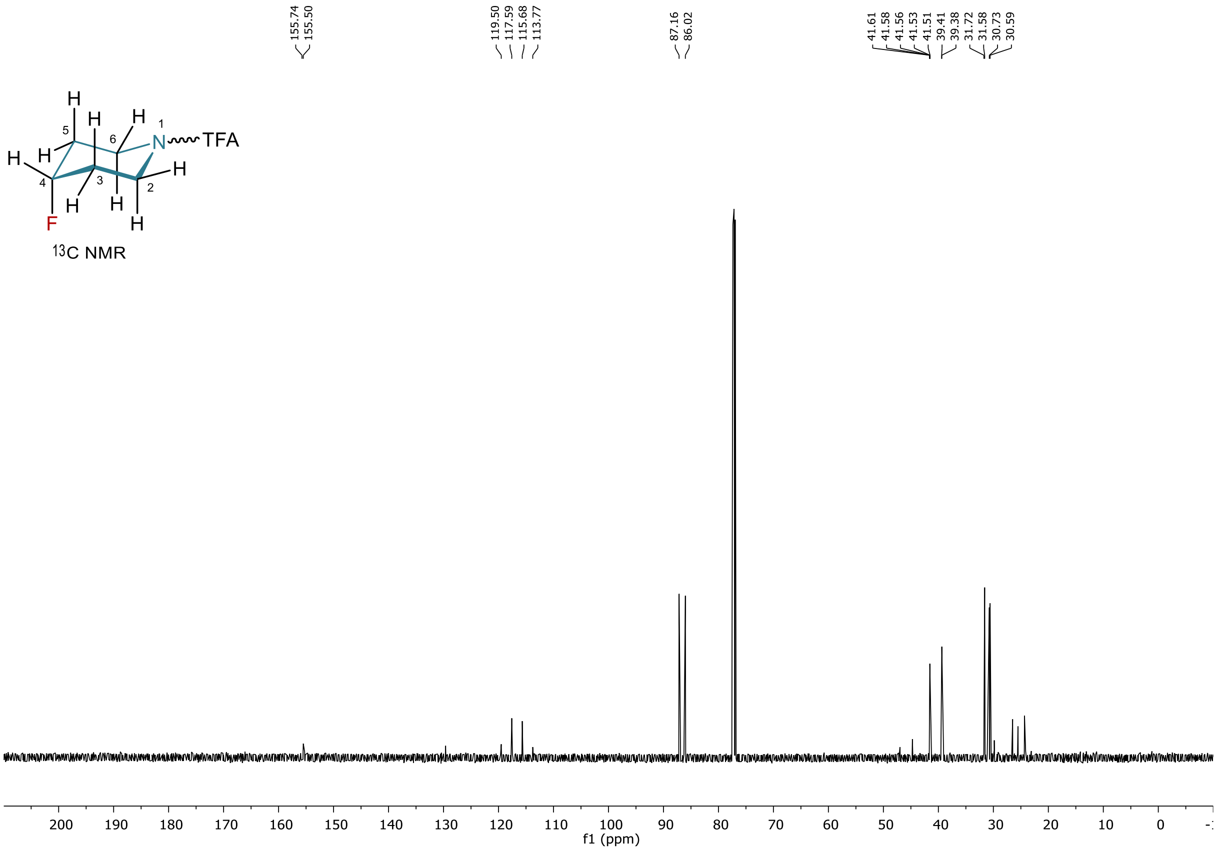

-197.66
-197.69
-197.70
-197.72
-197.75
-197.77
-197.78
-197.79
-197.80
-197.81
-197.82
-197.83
-197.84
-197.86
-197.89
-197.91
-197.93
-197.95
F
F
H
H
1
N+
H
H
Me
H
3
2
4
3
2
H
H
H
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

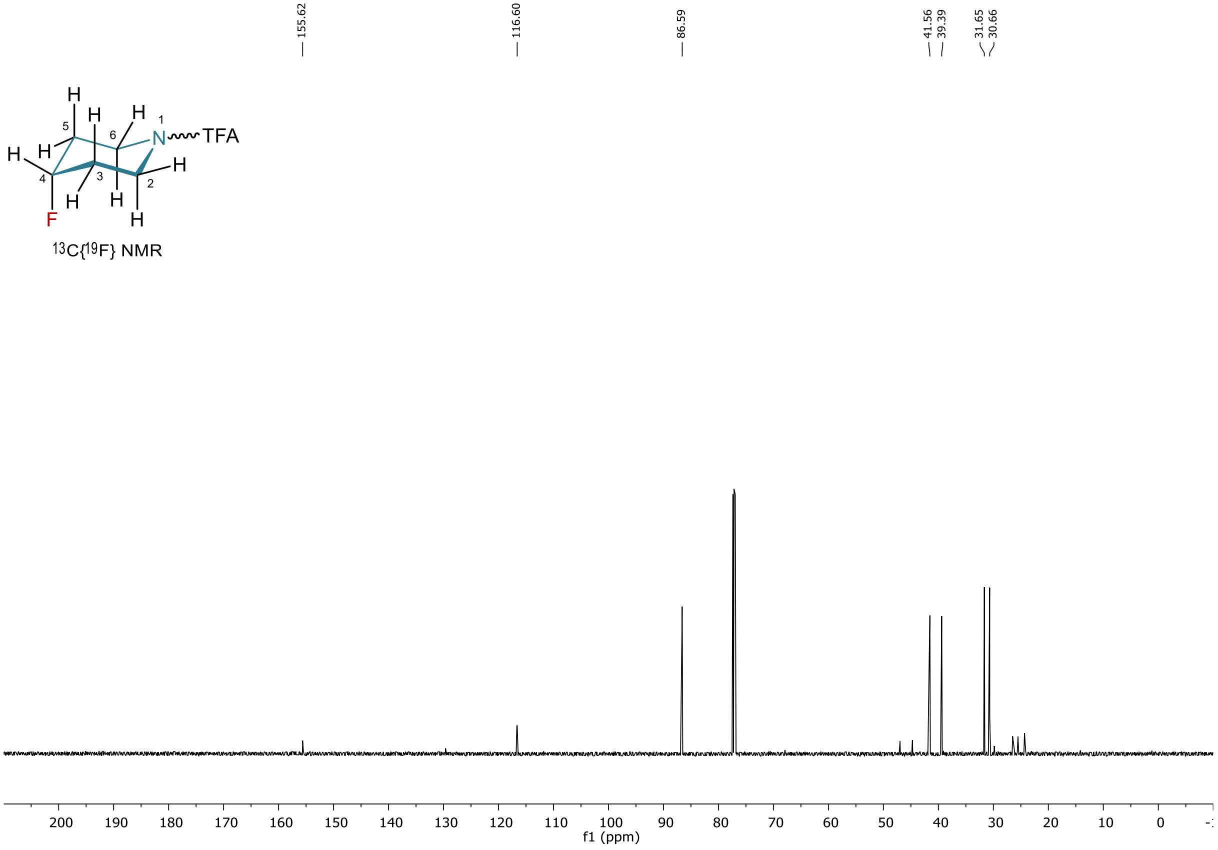

-197.81
F
F
H
H
1
N+
H
H
Me
H
3
2
4
3
2
H
H
H
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

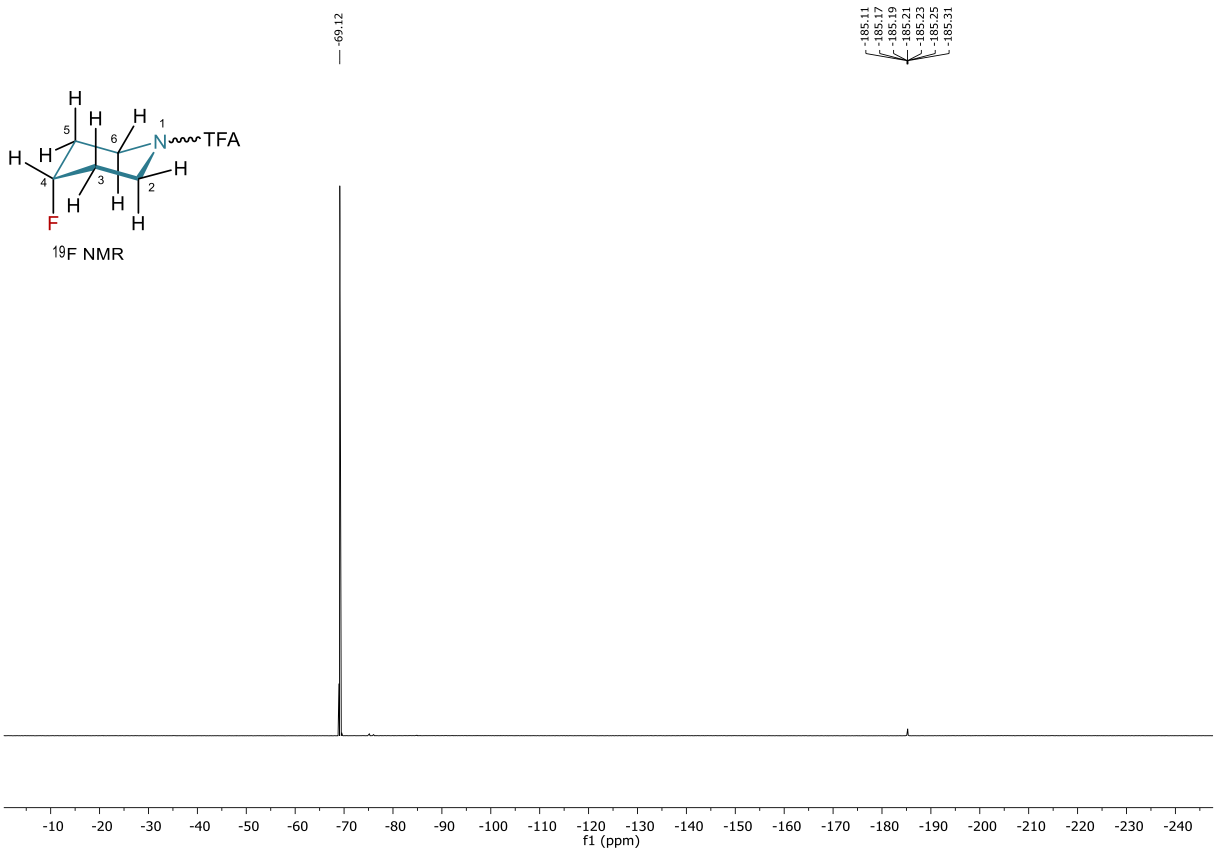


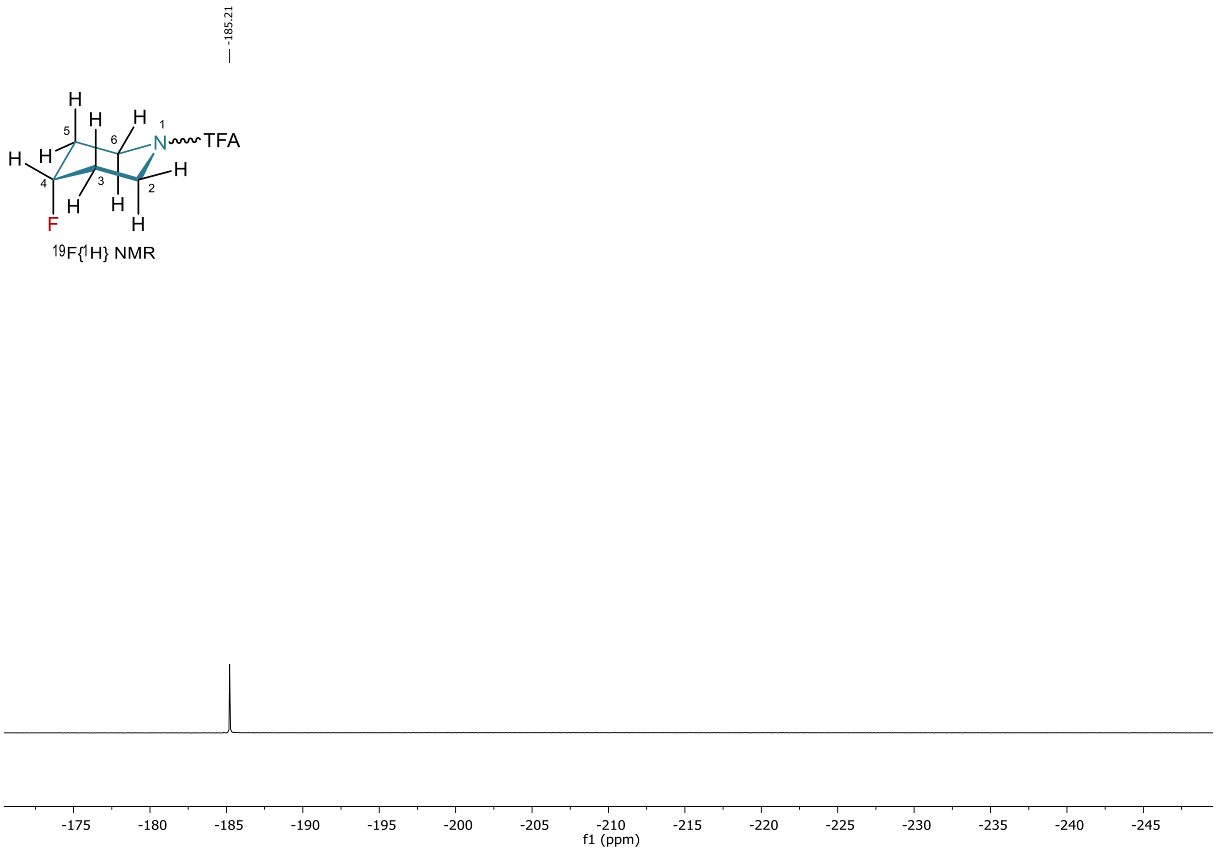
1
N
TFA
2
3
4
5
6
F
^{1}H NMR
1.00
1.00
2.21
1.02
2.03
2.00
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

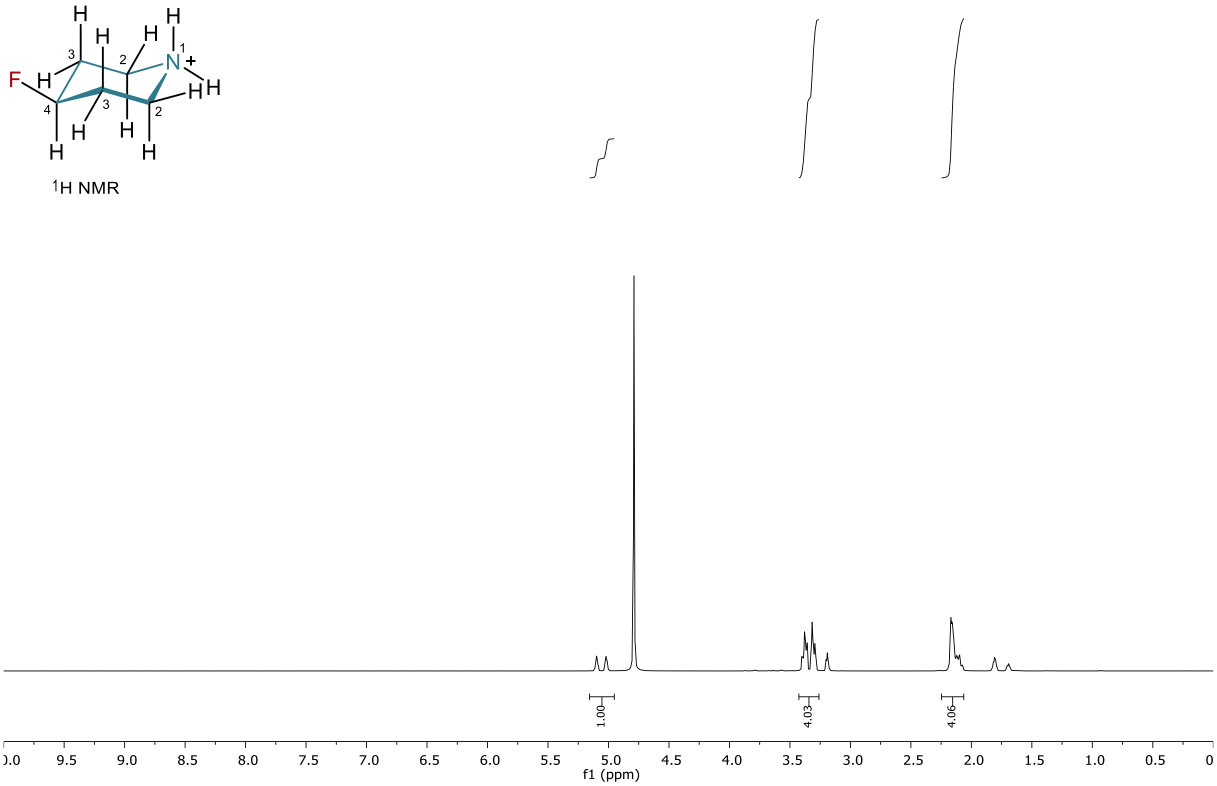
H
H
H
H
5
6
1
N
TFA
H
H
4
3
2
H
H
H
F
H
^{1}H{^{19}F} NMR
0.98
1.00
2.20
1.02
2.04
1.94
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

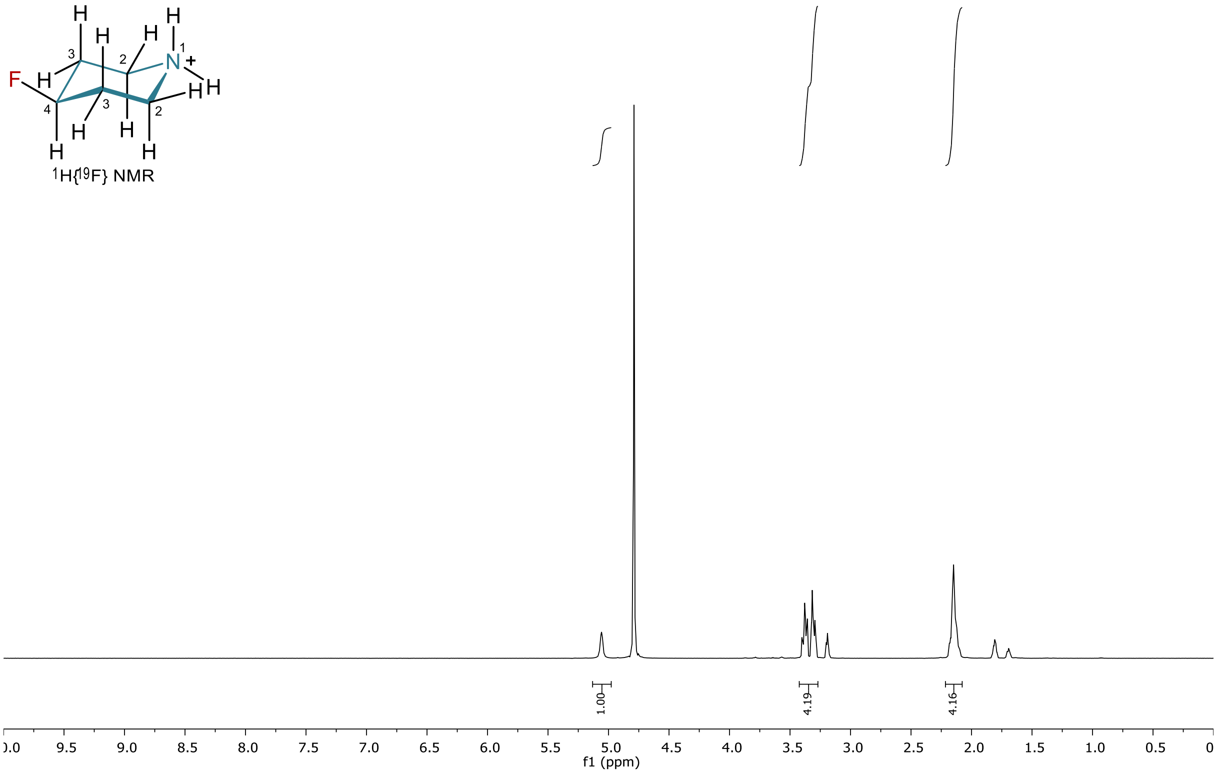

155.74
155.50
119.50
117.59
115.68
113.77
87.16
86.02
41.61
41.58
41.56
41.53
41.51
39.41
39.38
31.72
31.58
30.73
30.59
H
H
H
5
6
1
N
TFA
H
H
4
3
2
H
H
H
F
H
^{13}C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

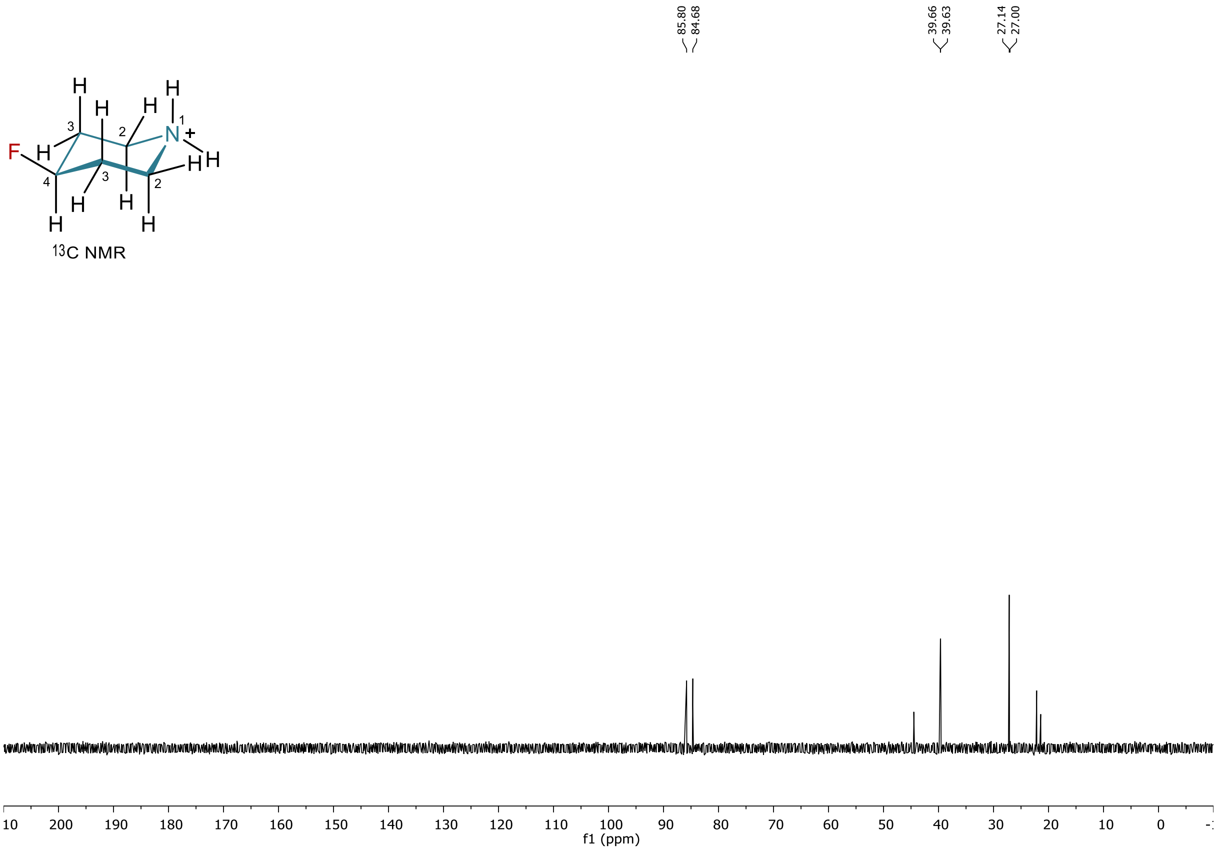

155.62
116.60
86.59
41.56
39.39
31.65
30.66
H
H
H
5
6
1
N
TFA
H
H
4
3
2
H
H
H
F
H
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

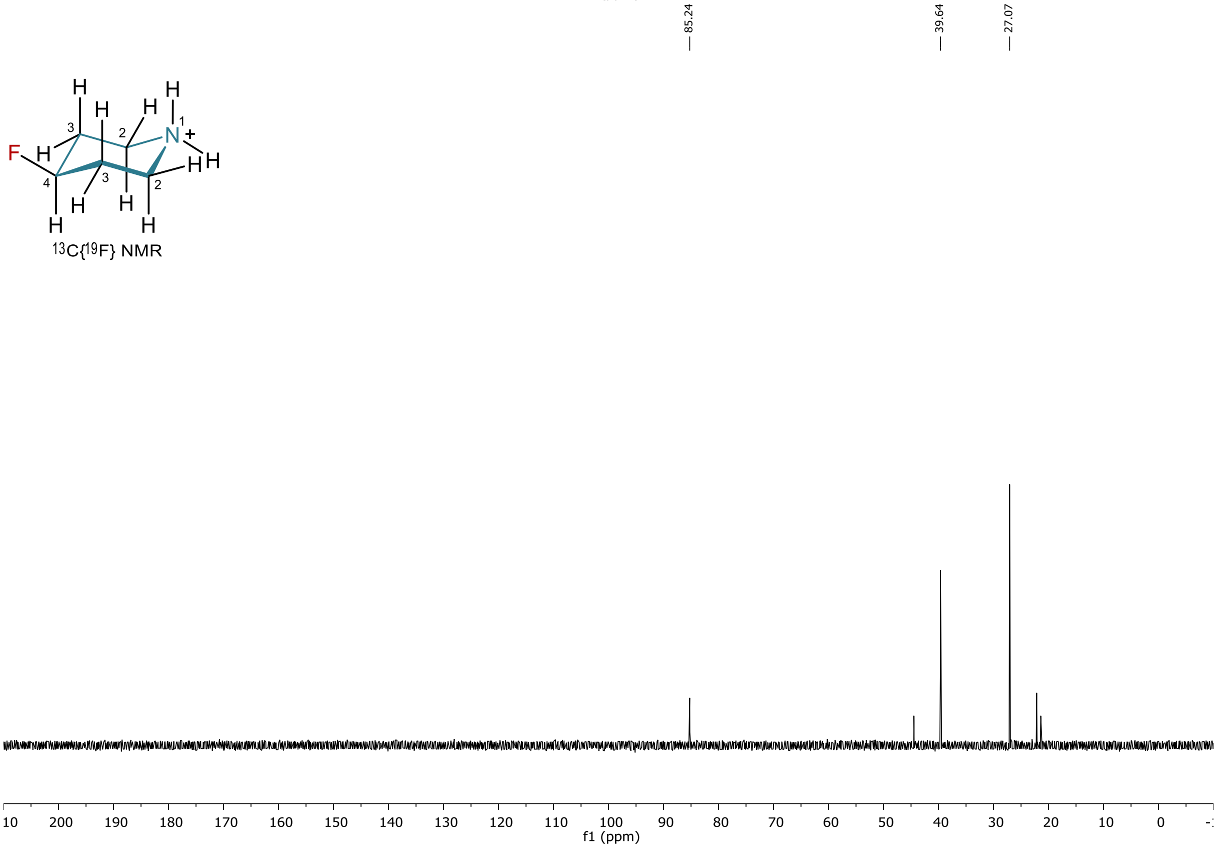

-69.12
-185.11
-185.17
-185.19
-185.21
-185.23
-185.25
-185.31
H
H
H
H
H
5
6
1
N
TFA
H
4
3
2
H
H
H
F
19F NMR
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)

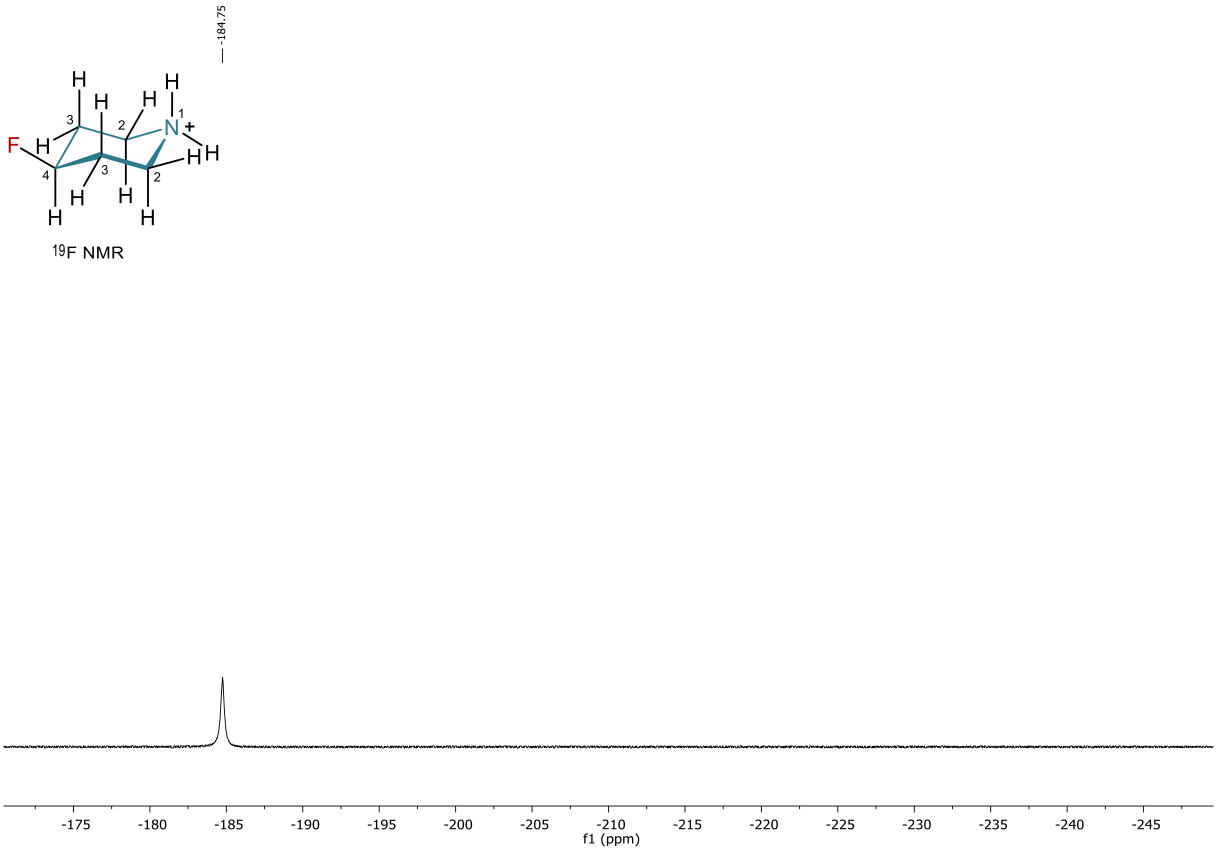

-185.21
H
H
H
H
H
H
H
H
H
F
5
6
1
4
3
2
N
TFA
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

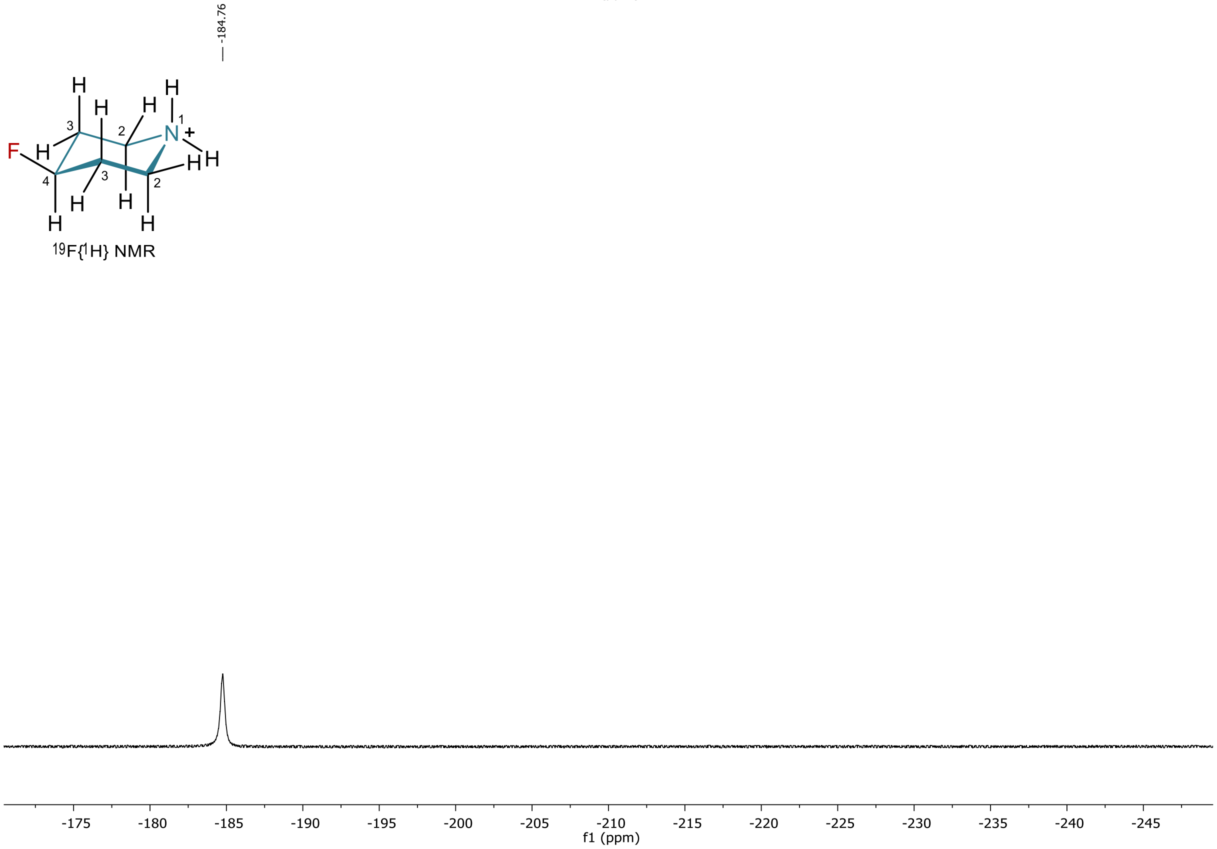

F
N
+
1H NMR
1.00
4.03
4.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

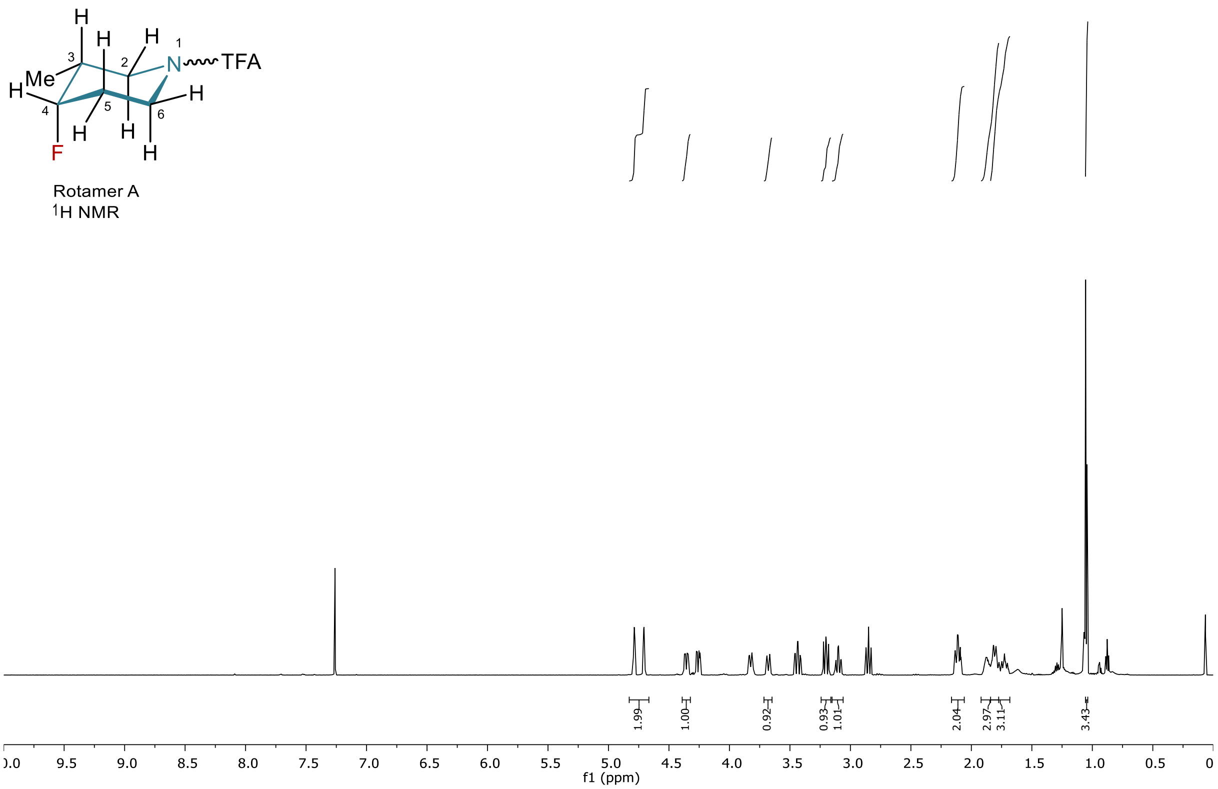

F
N
+
1H{19F} NMR
1.00
4.19
4.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

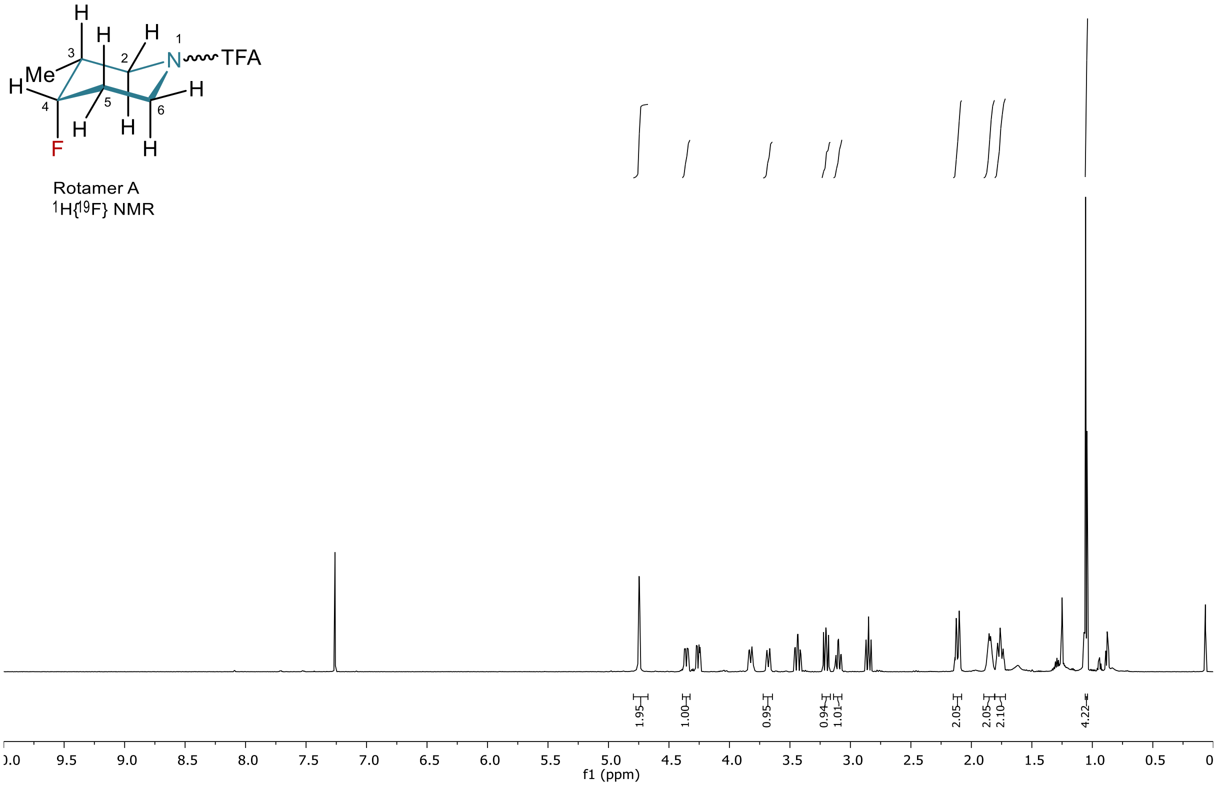

85.80
84.68
39.66
39.63
27.14
27.00
F
H
N
+
1
2
3
4
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


85.24
39.64
27.07
F
H
N
+
1
2
3
4
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

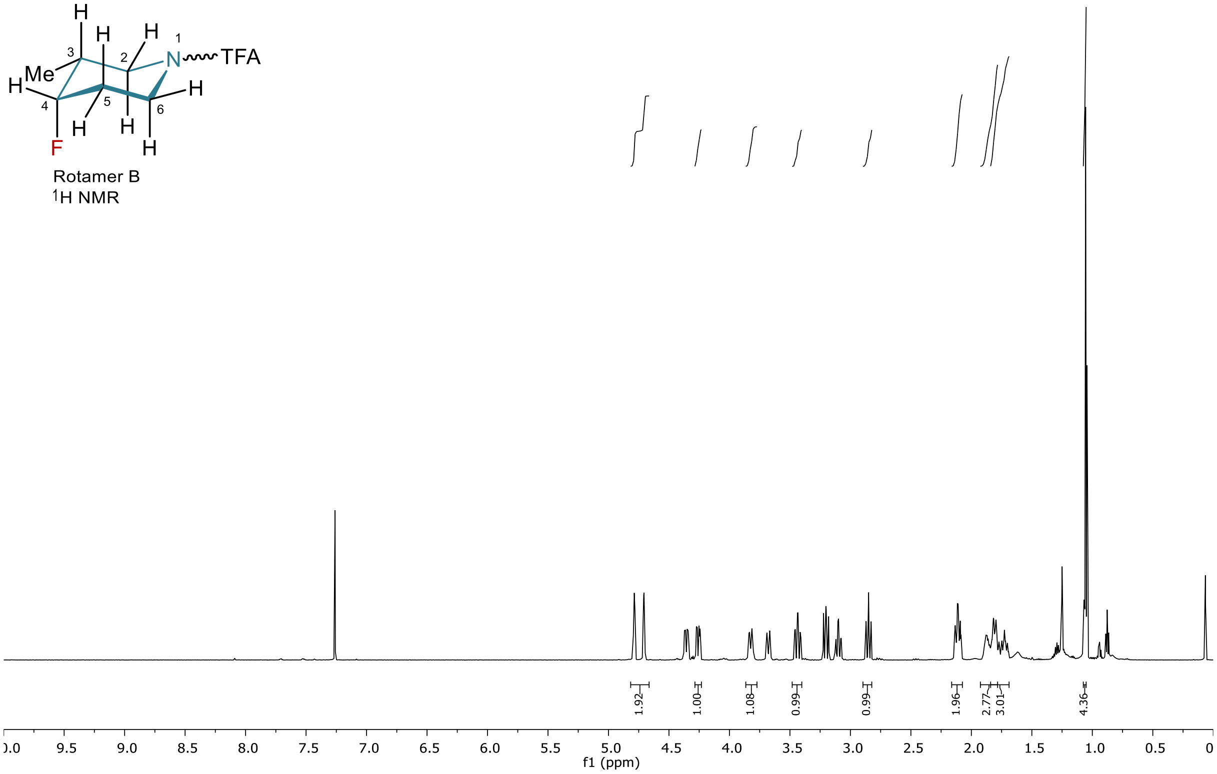

-184.75
F
H
1
N+
2
3
4
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


-184.76
F
H
1
N+
2
3
4
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

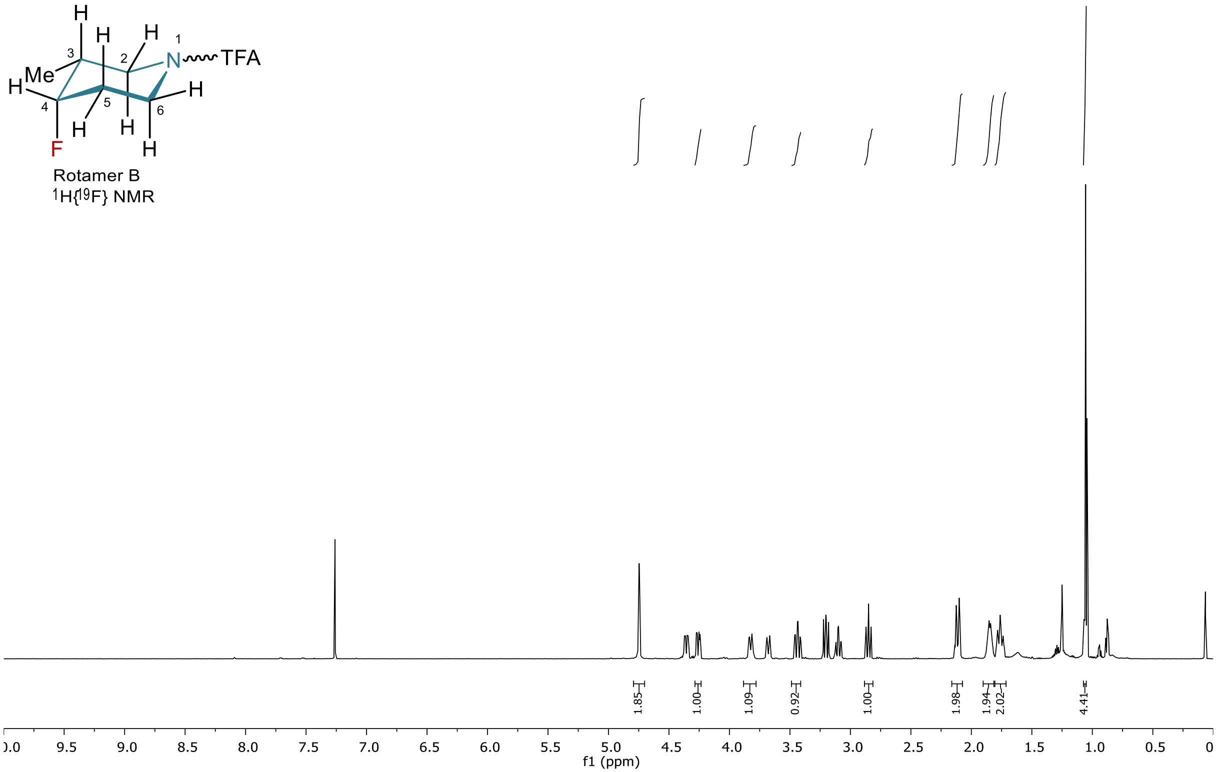

H
H
H
1
3
2
Me
N
TFA
H
H
5
4
6
H
H
H
F
H
Rotamer A
^{1}H NMR
1.99
1.00
0.92
0.93
1.01
2.04
2.97
3.11
3.43
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

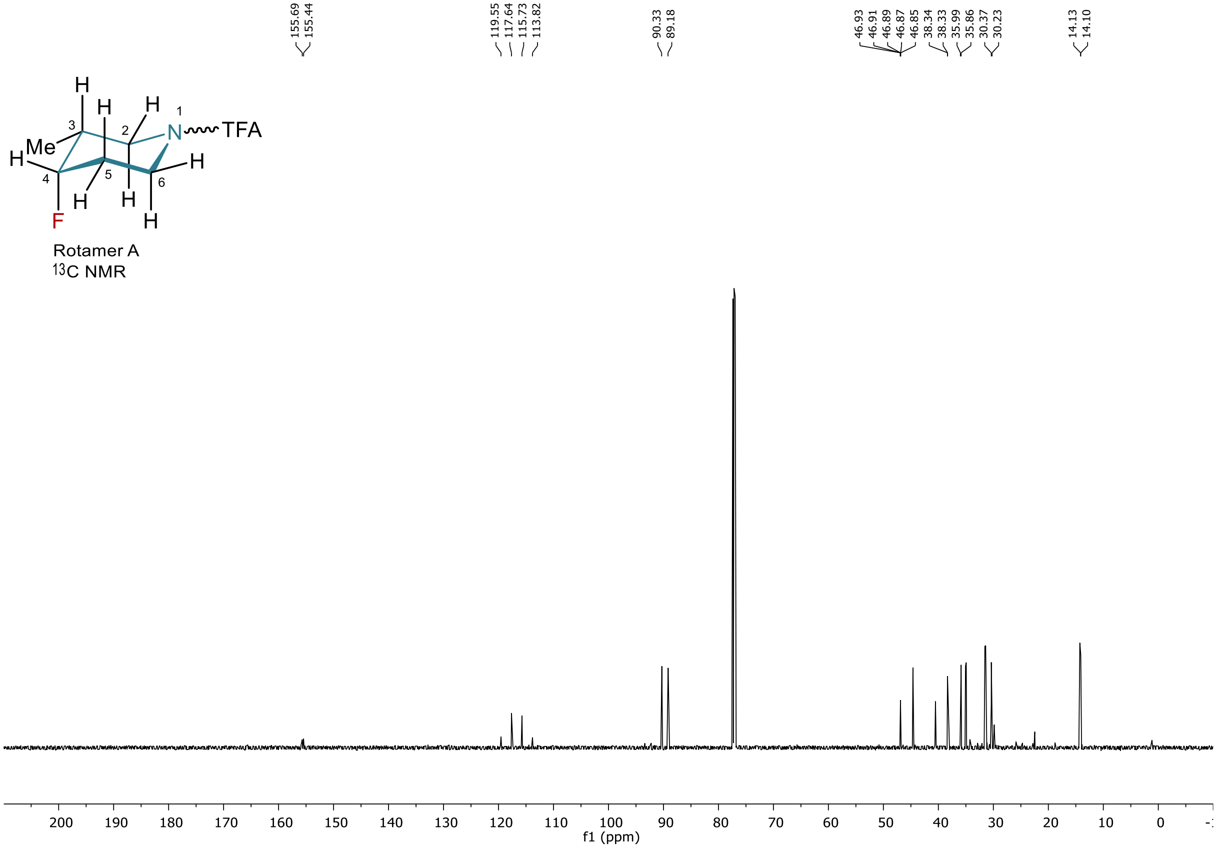


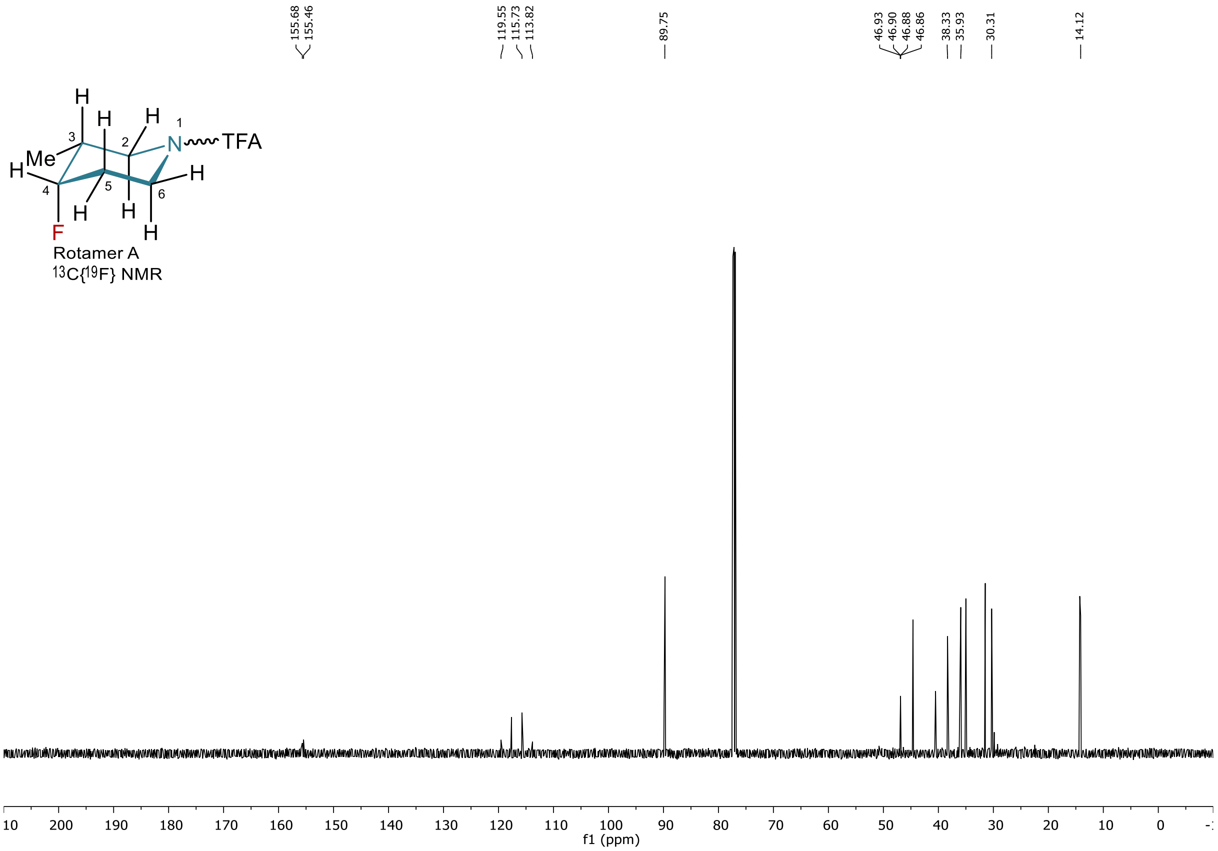
Rotamer A
$^1H\{^{19}F\}$ NMR

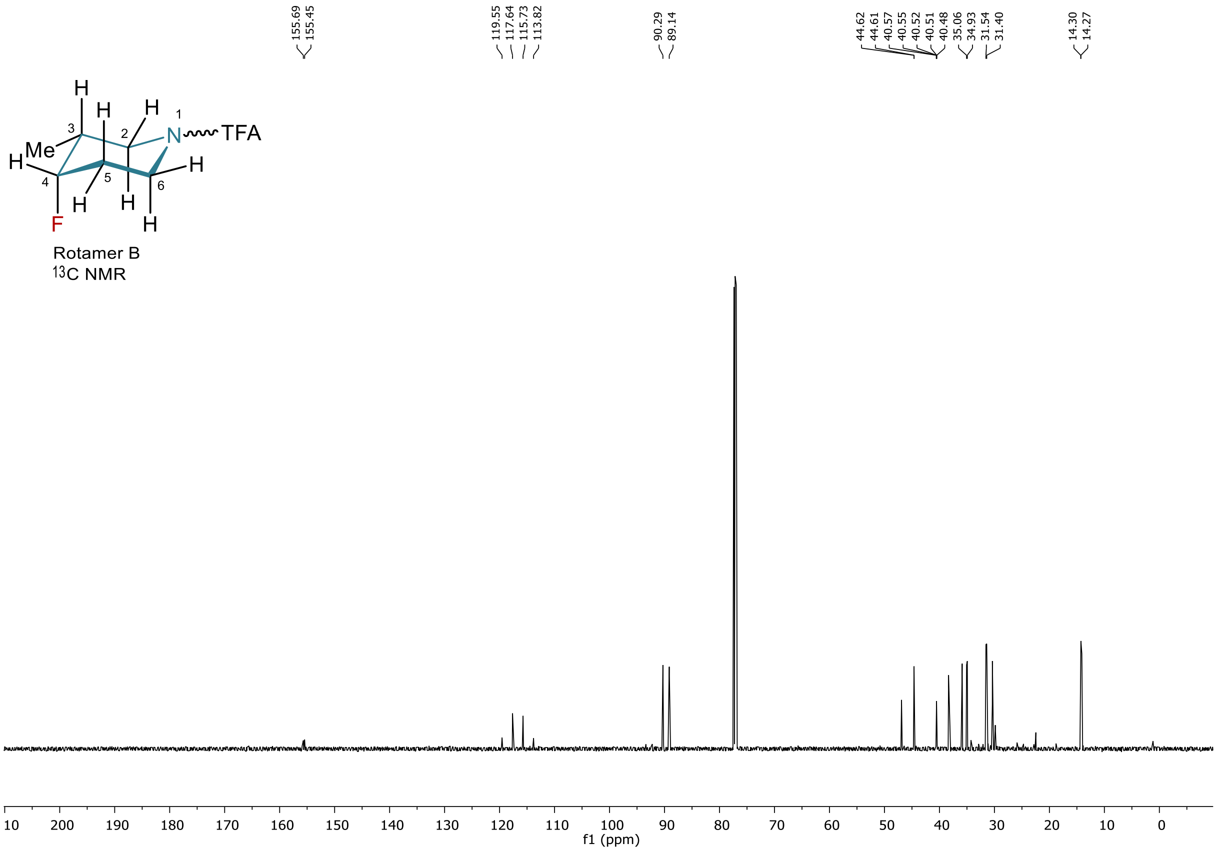


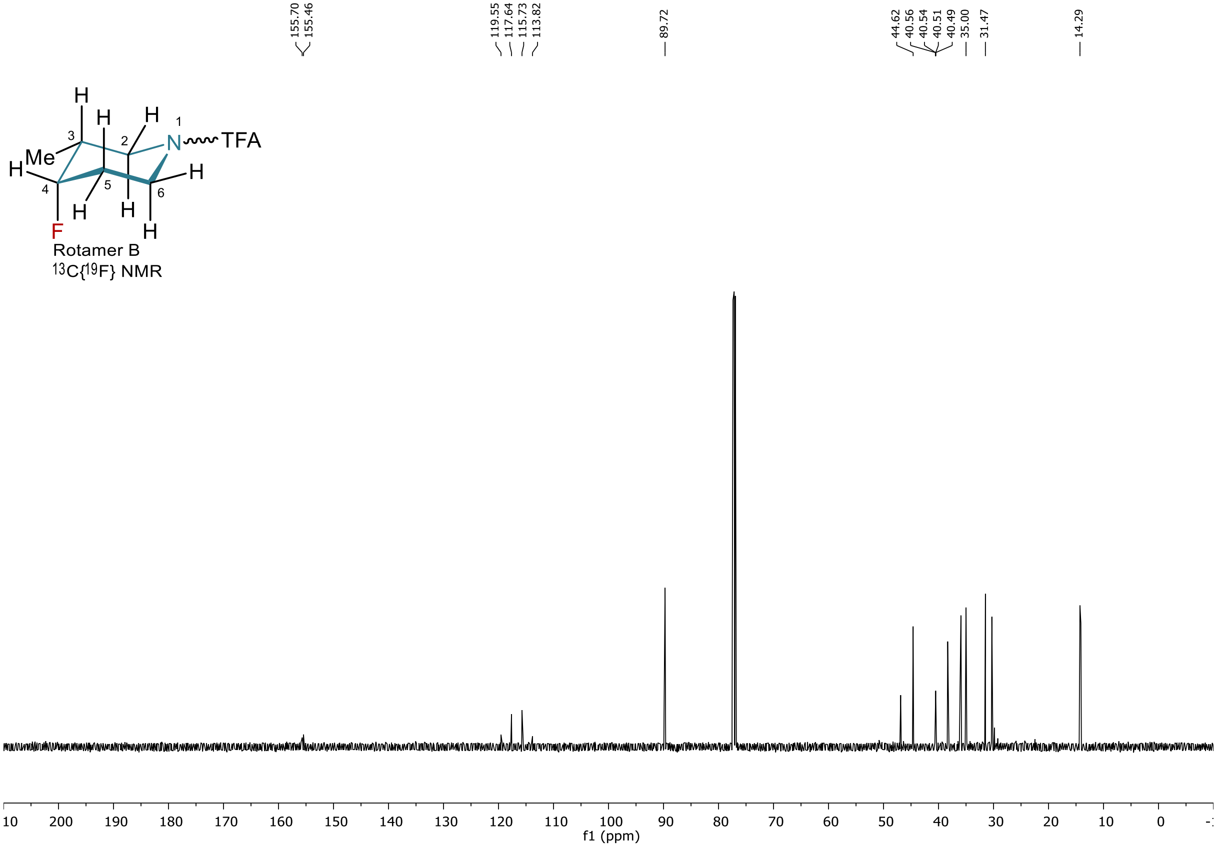
Rotamer B
^1H NMR

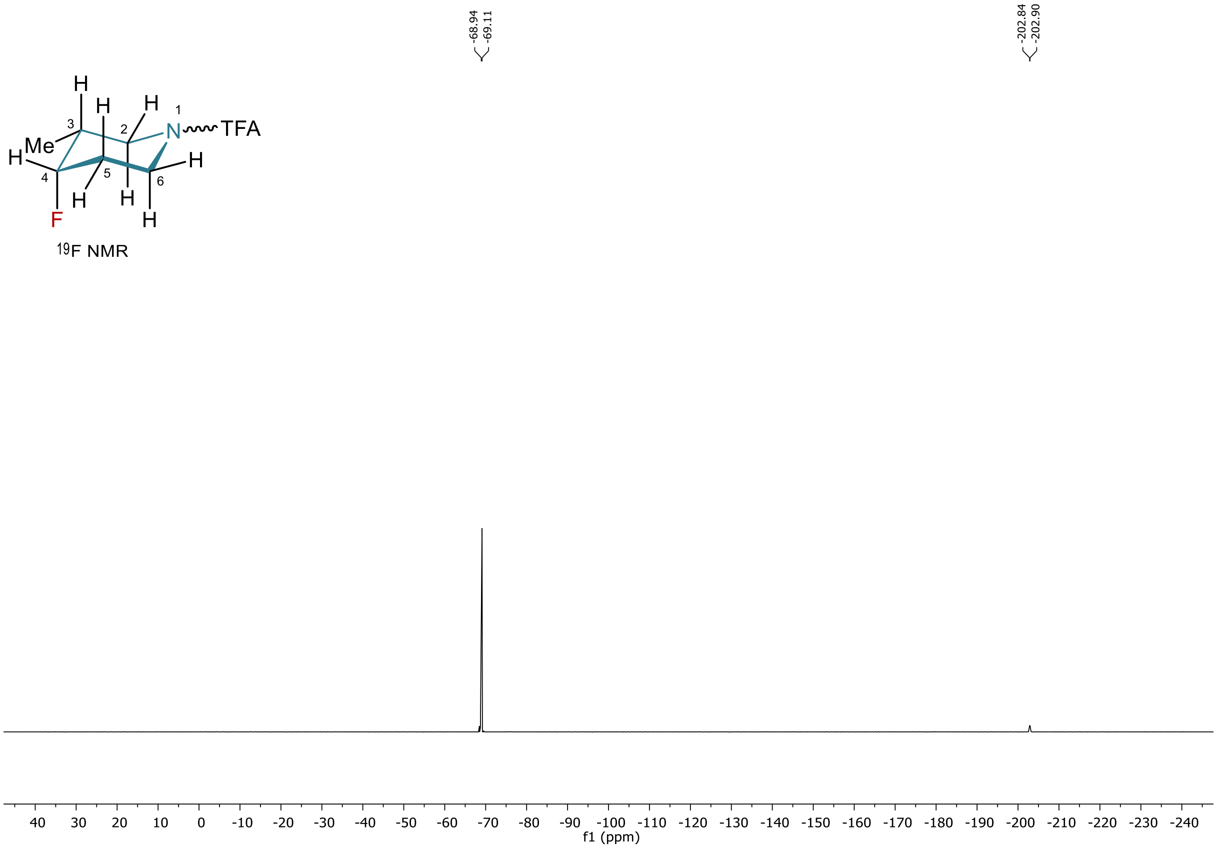

Rotamer B
$^1H\{^{19}F\}$ NMR

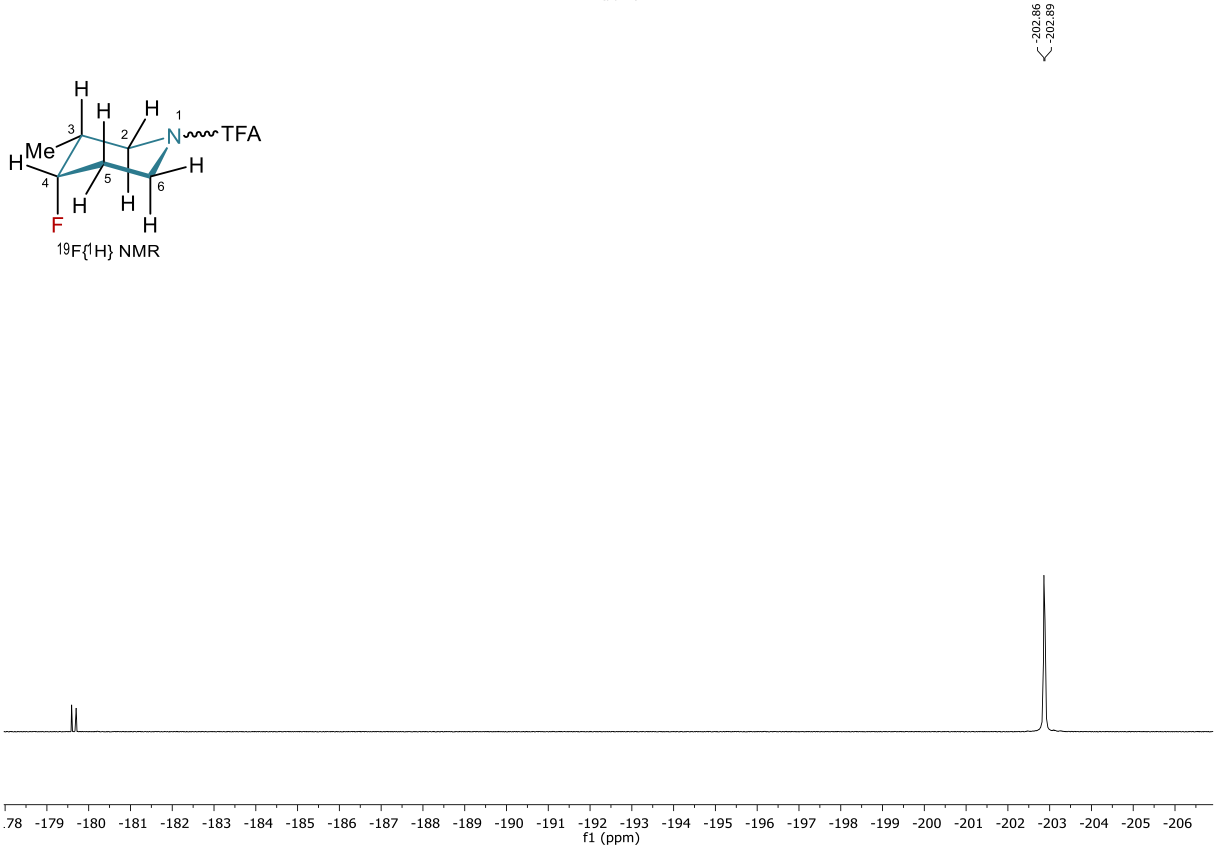

Rotamer A
^{13}C NMR

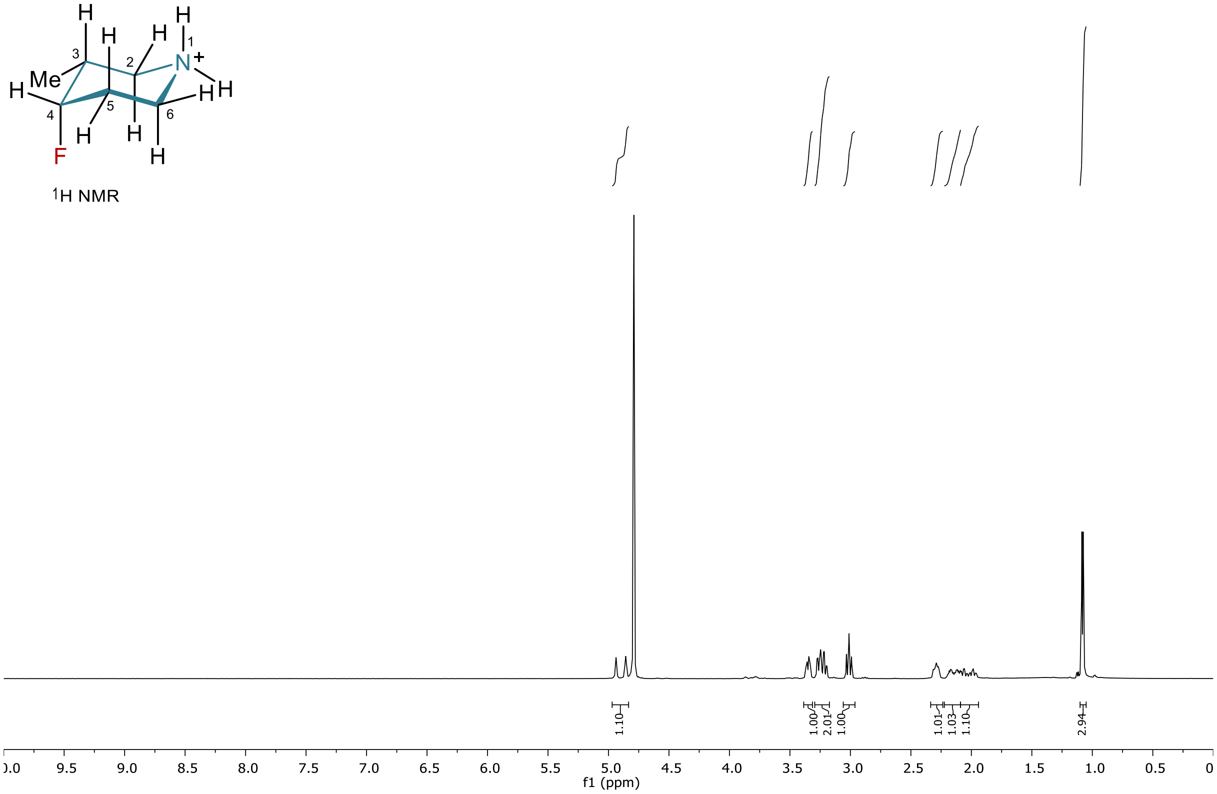

155.68
155.46
119.55
115.73
113.82
89.75
46.93
46.90
46.88
46.86
38.33
35.93
30.31
14.12
H
H
H
1
3
2
N
TFA
Me
H
H
4
5
6
H
H
F
H
Rotamer A
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


155.69
155.45
119.55
117.64
115.73
113.82
90.29
89.14
44.62
44.61
40.57
40.55
40.52
40.51
40.48
35.06
34.93
31.54
31.40
14.30
14.27
H
H
H
1
3
2
N
TFA
Me
H
H
4
5
6
H
H
H
F
H
Rotamer B
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

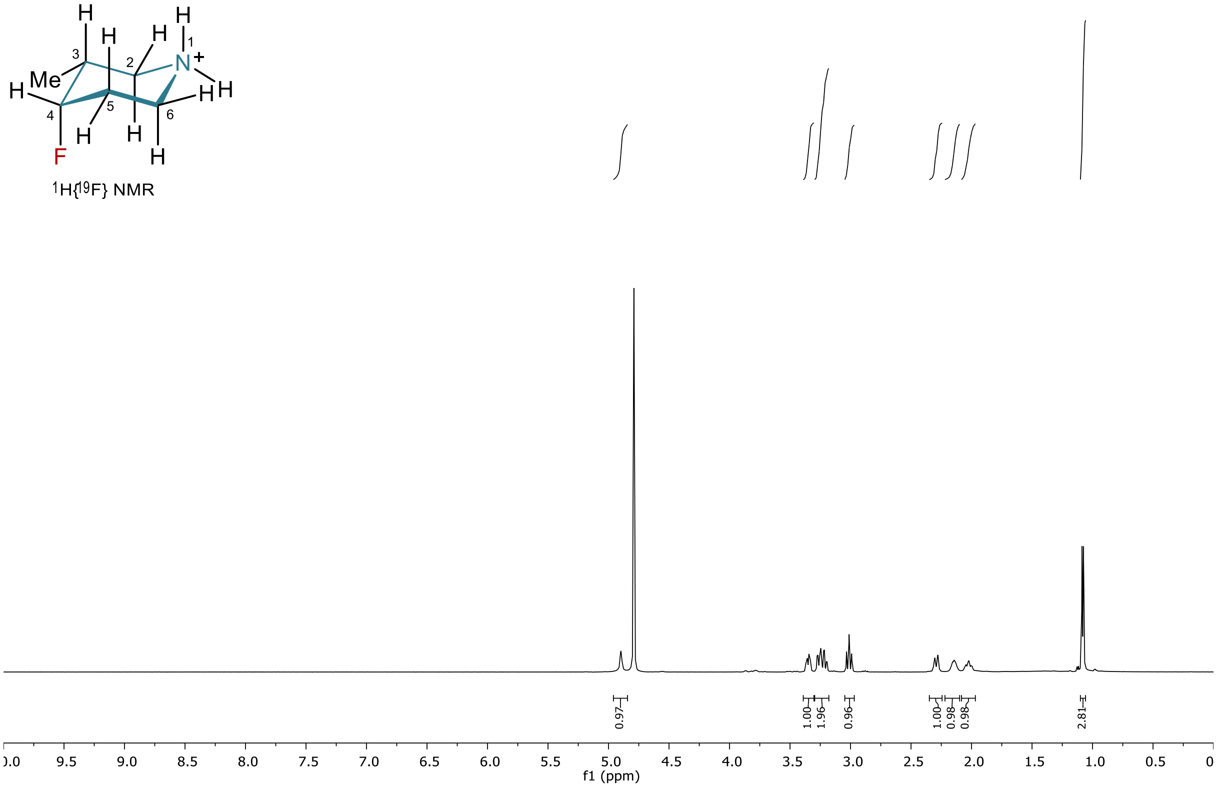

155.70
155.46
119.55
117.64
115.73
113.82
89.72
44.62
40.56
40.54
40.51
40.49
35.00
31.47
14.29
H
H
H
1
3
2
N
TFA
Me
H
H
4
5
6
H
H
H
F
H
Rotamer B
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-68.94
-69.11
-202.84
-202.90
H
H
H
1
3
2
N
TFA
Me
H
H
4
5
6
H
H
F
H
^{19}F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

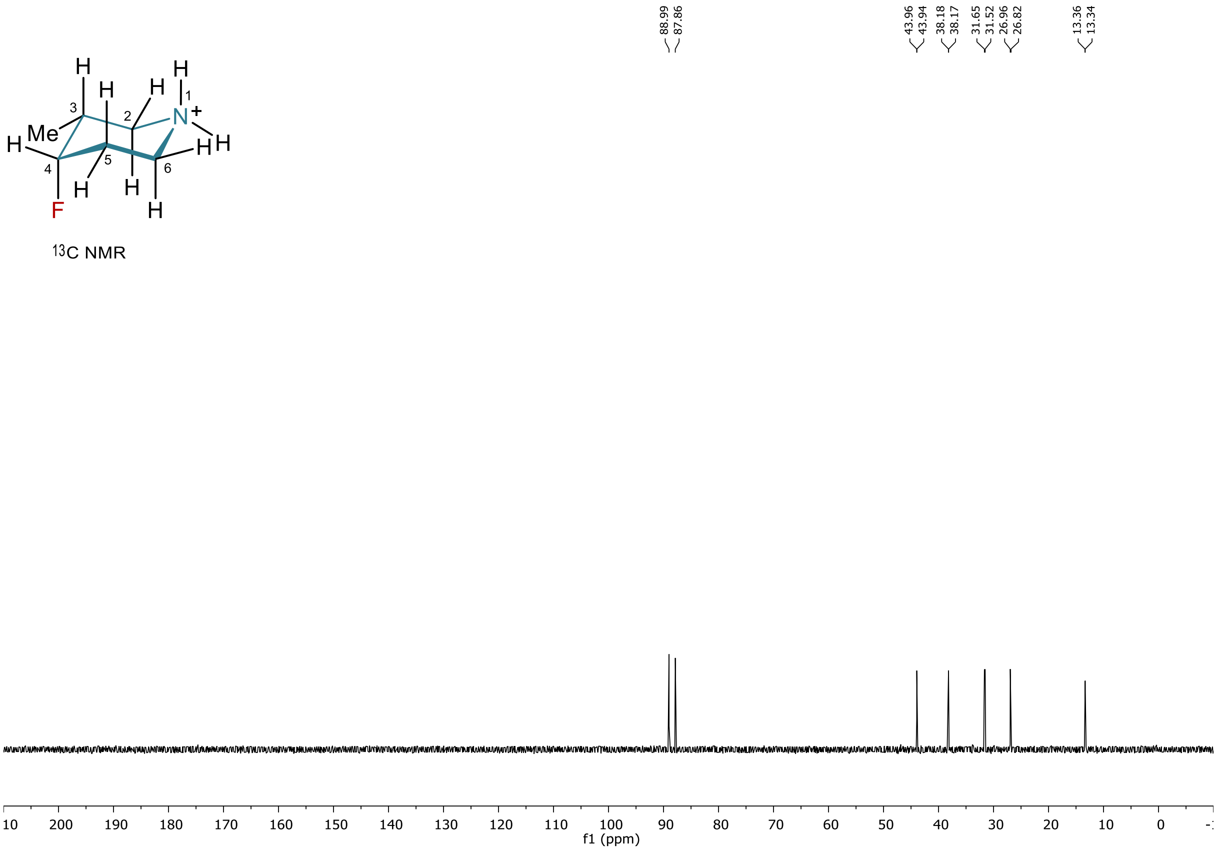

-202.86
-202.89
H
H
H
1
3
2
N
TFA
Me
H
H
4
5
6
H
H
F
H
^{19}F{^{1}H} NMR
.78 -179 -180 -181 -182 -183 -184 -185 -186 -187 -188 -189 -190 -191 -192 -193 -194 -195 -196 -197 -198 -199 -200 -201 -202 -203 -204 -205 -206
f1 (ppm)



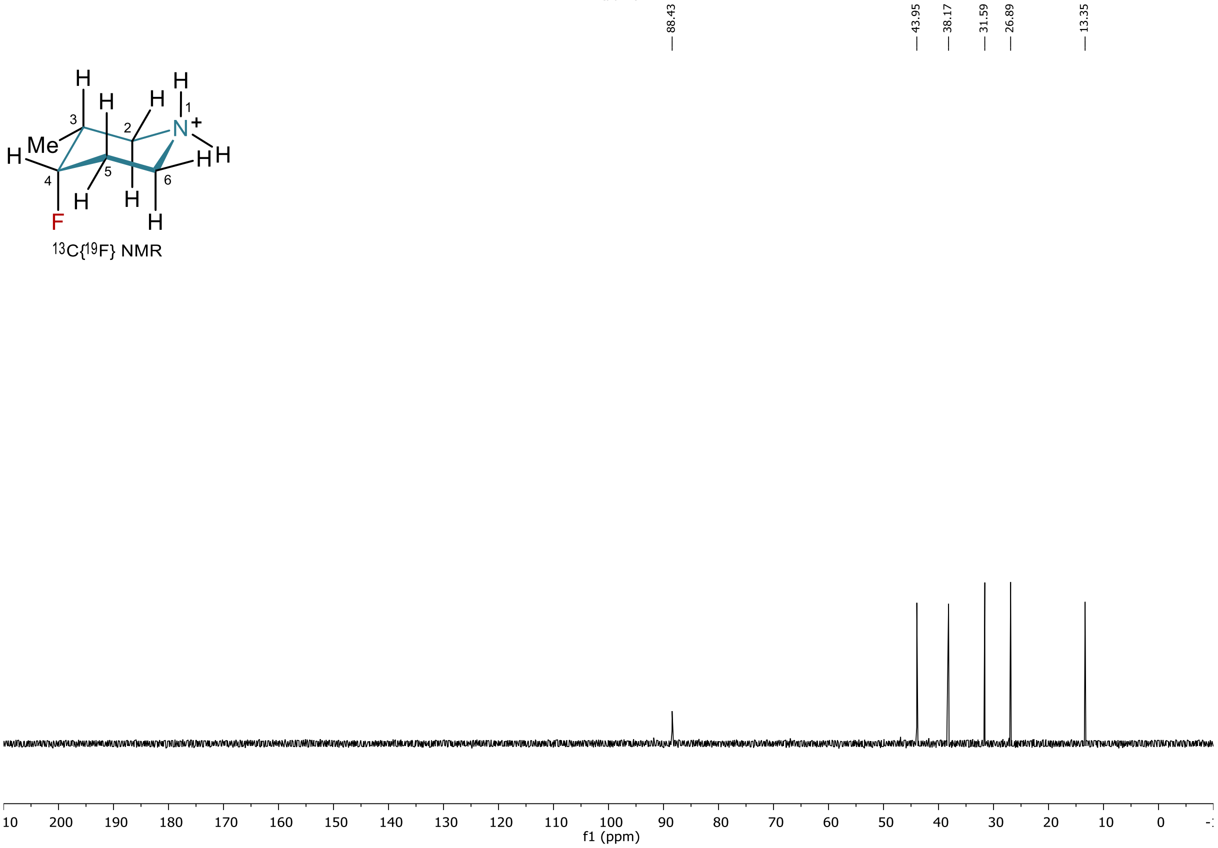
H
H
H
H
3
2
1
Me
N+
H
H
H
5
6
4
H
H
H
F
1H NMR
1.10
1.00
2.01
1.00
1.01
1.03
1.10
2.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)



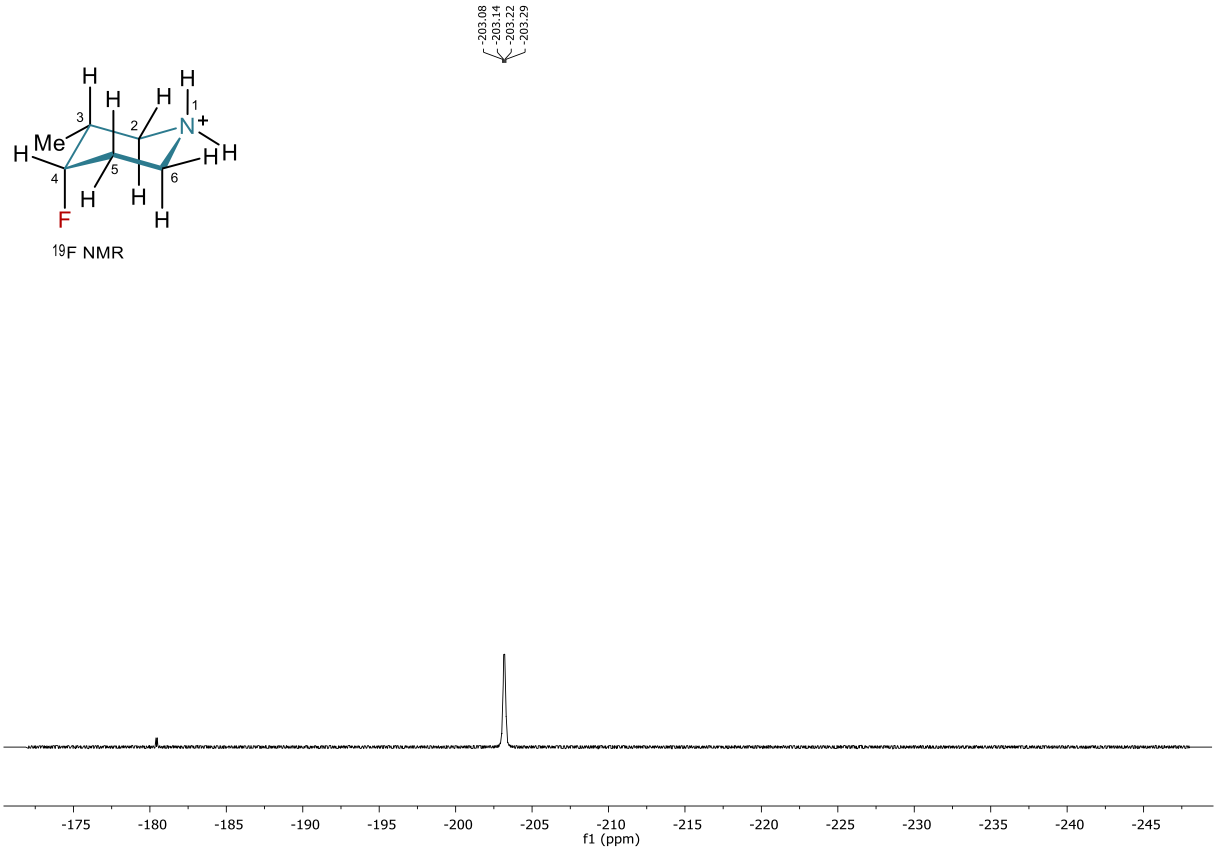
H
H
H
H
3
2
1
Me
N+
H
H
H
5
6
4
H
H
H
F
1H{19F} NMR
0.97
1.00
1.96
0.96
1.00
0.98
0.98
2.81
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

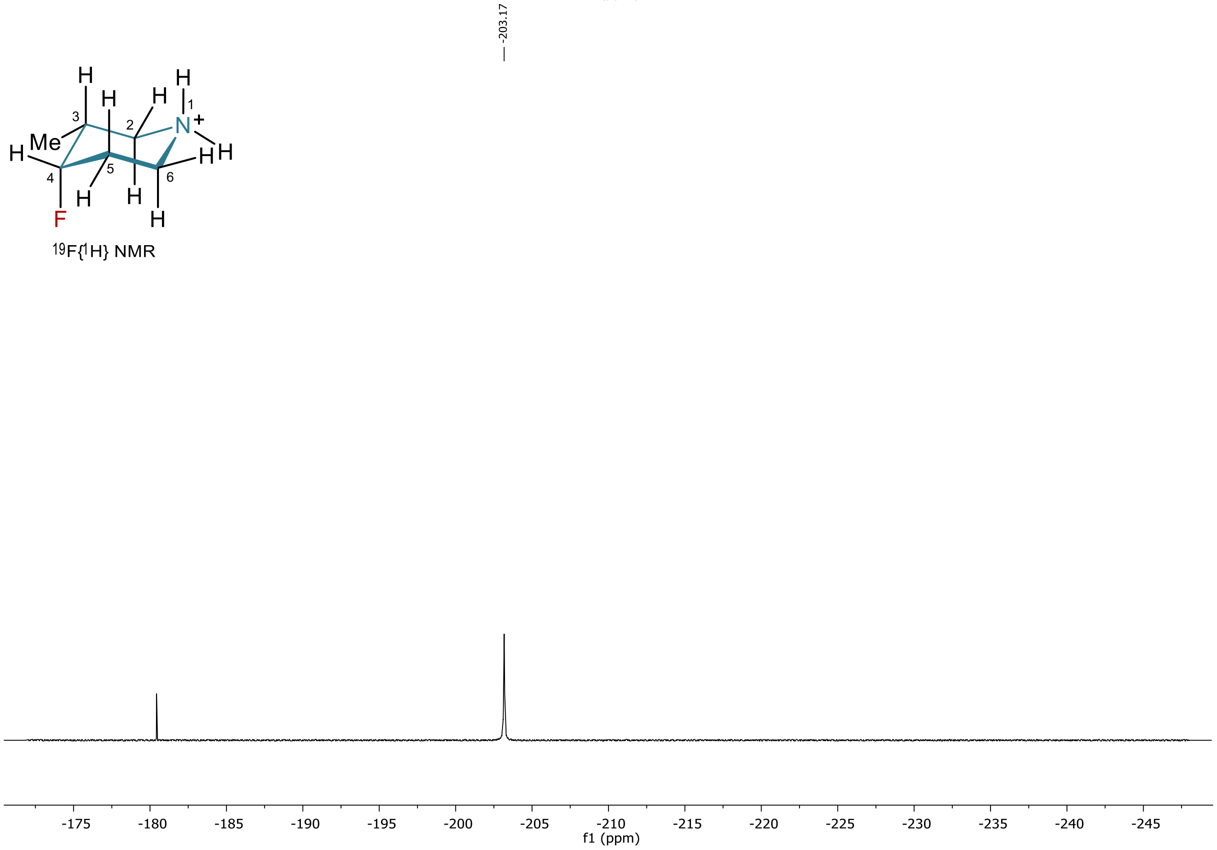


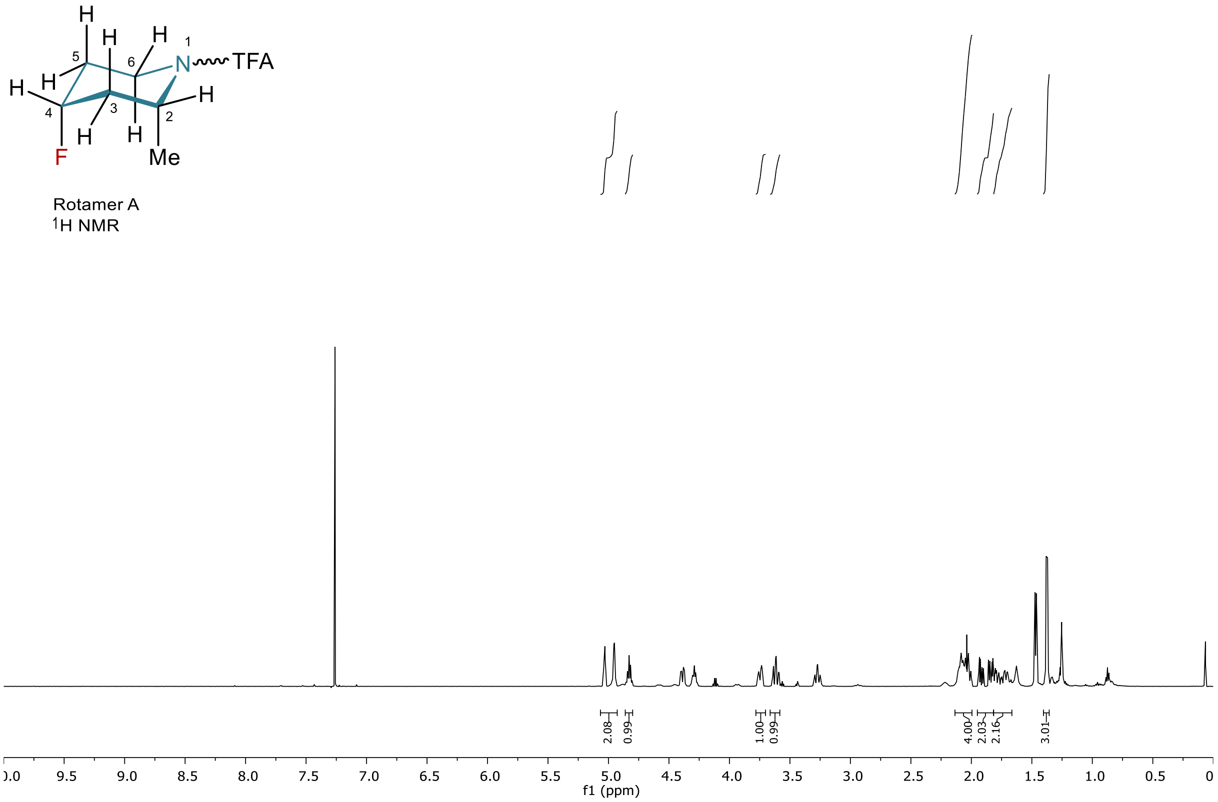
^{13}C NMR



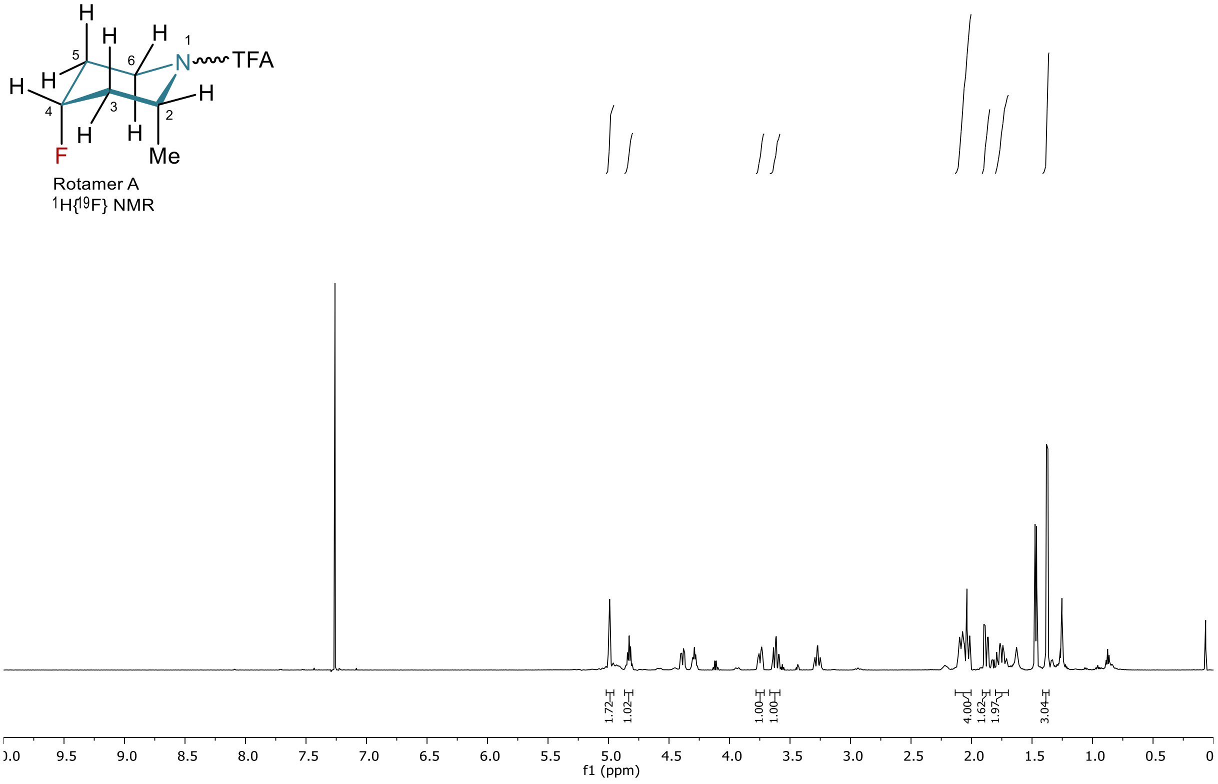
^{13}C{^{19}F} NMR


-203.08
-203.14
-203.22
-203.29
H
H
H
H
1
3
2
N+
Me
H
H
H
4
5
6
H
H
F
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

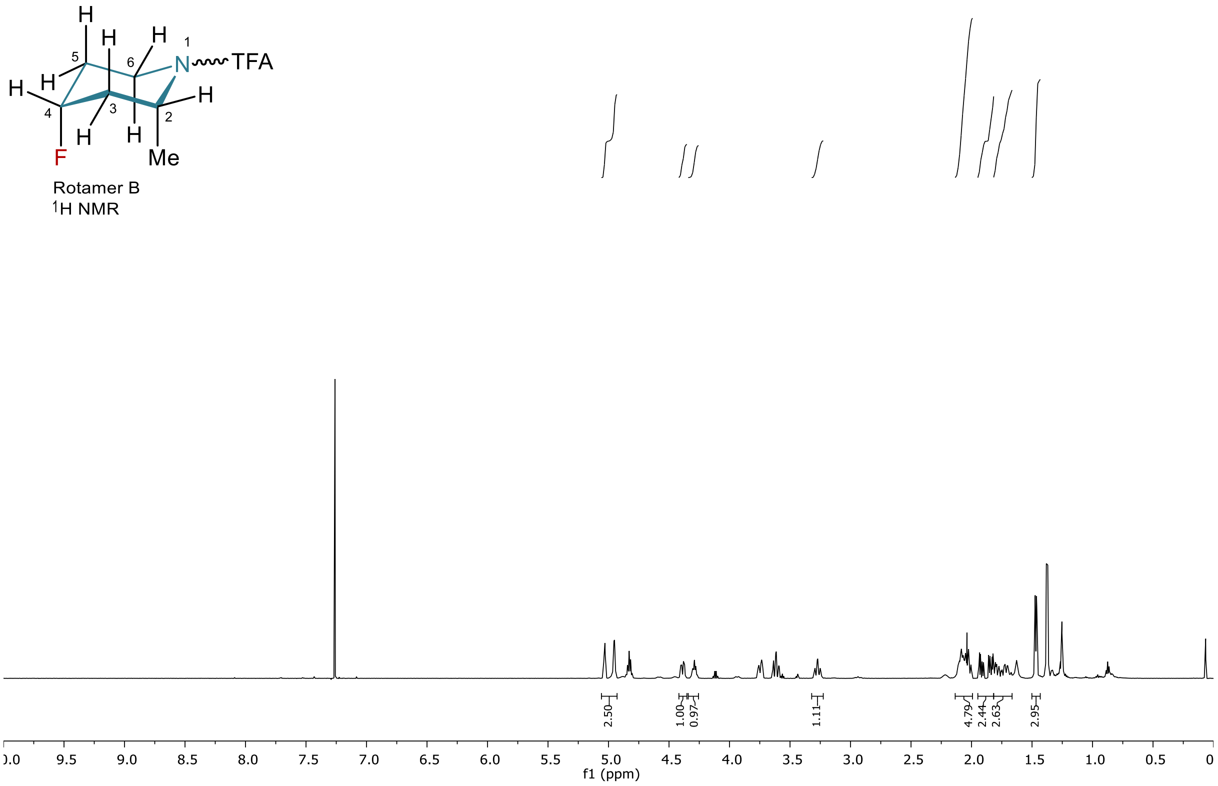

-203.17
H
H
H
H
1
3
2
N+
Me
H
H
H
4
5
6
H
H
F
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)



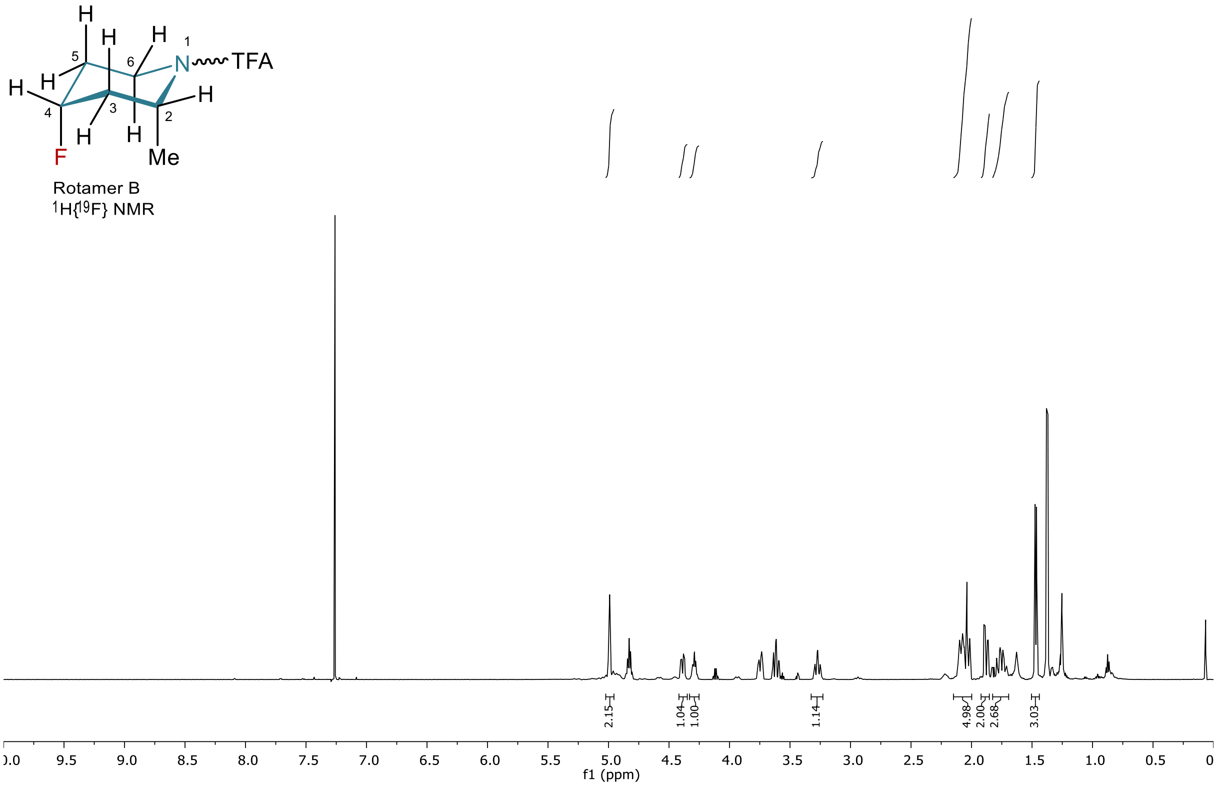
Rotamer A
^{1}H NMR



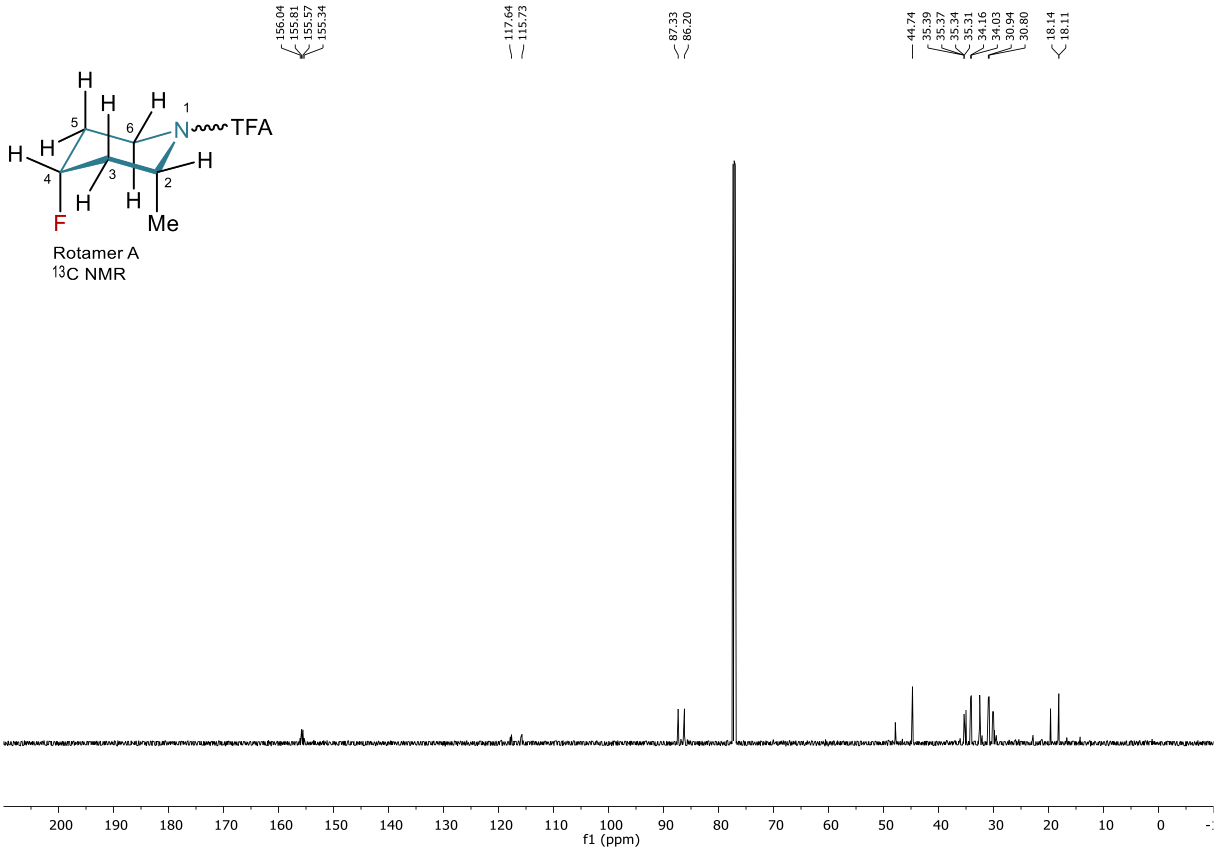
Rotamer A
^{1}H{^{19}F} NMR



Rotamer B
^{1}H NMR



Rotamer B
^{1}H{^{19}F} NMR


156.04
155.81
155.57
155.34
117.64
115.73
87.33
86.20
44.74
35.39
35.37
35.34
35.31
34.16
34.03
30.94
30.80
18.14
18.11
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
F
Me
Rotamer A
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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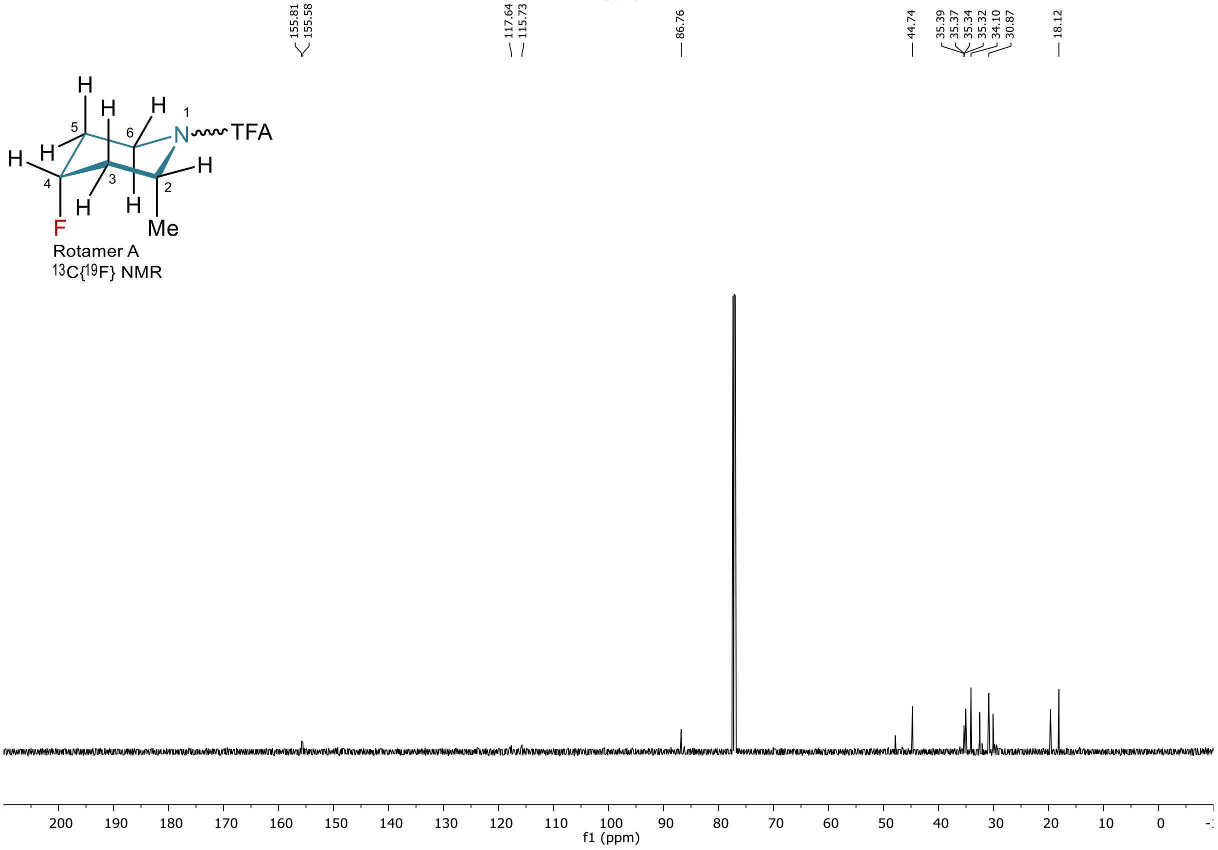
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155.58
117.64
115.73
86.76
44.74
35.39
35.37
35.34
35.32
34.10
30.87
18.12
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
F
Me
Rotamer A
13C{19F} NMR
200
190
180
170
160
150
140
130
120
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90
80
70
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50
40
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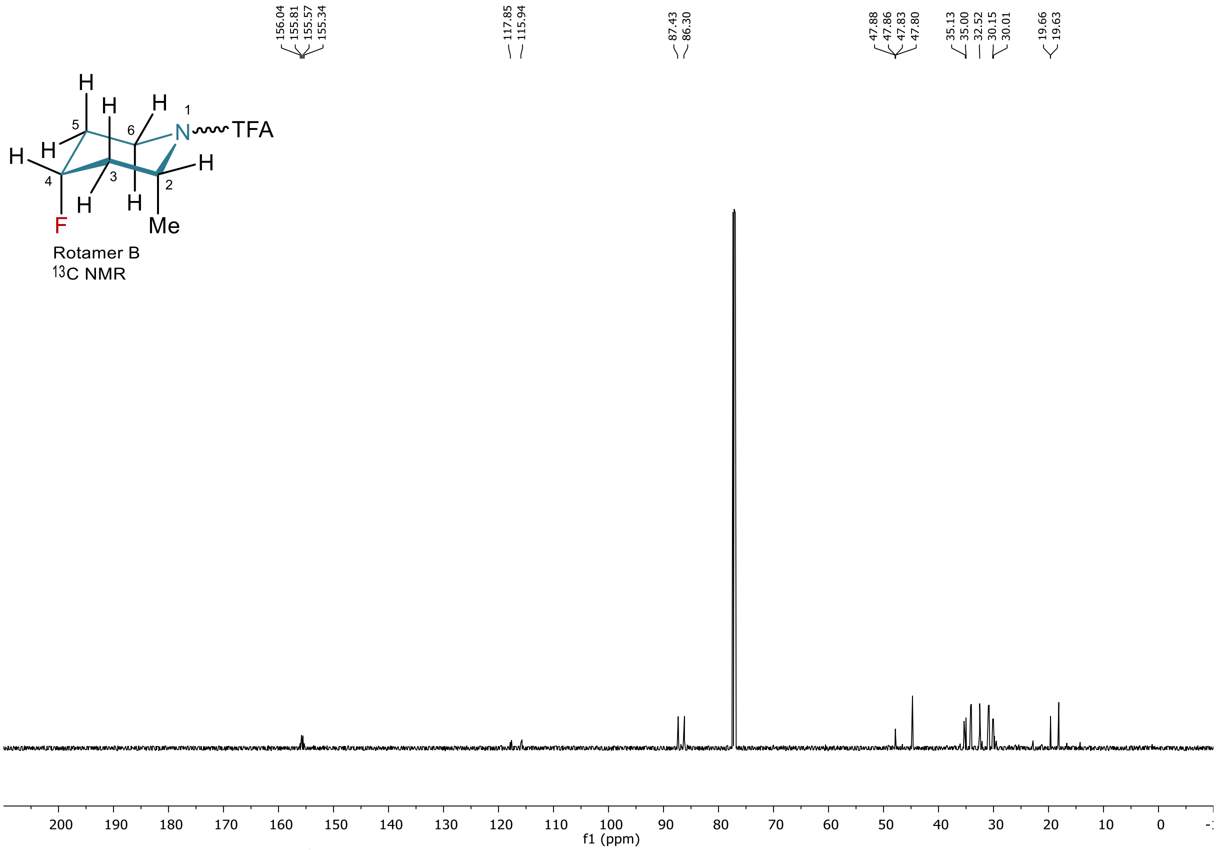
f1 (ppm)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86.30
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47.86
47.83
47.80
35.13
35.00
32.52
30.15
30.01
19.66
19.63
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
F
Me
Rotamer B
^{13}C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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50
40
30
20
10
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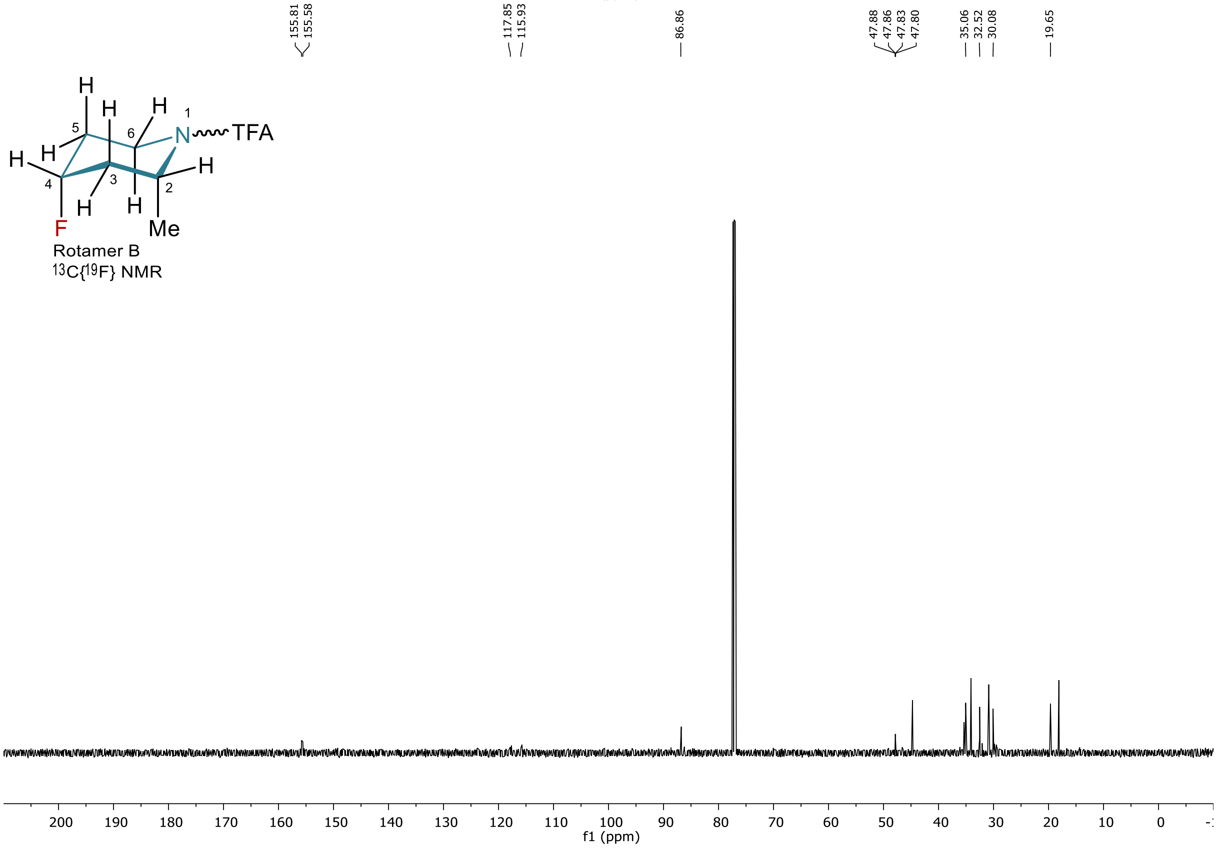
f1 (ppm)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155.58
117.85
115.93
86.86
47.88
47.86
47.83
47.80
35.06
32.52
30.08
19.65
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
F
Me
Rotamer B
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
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50
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30
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10
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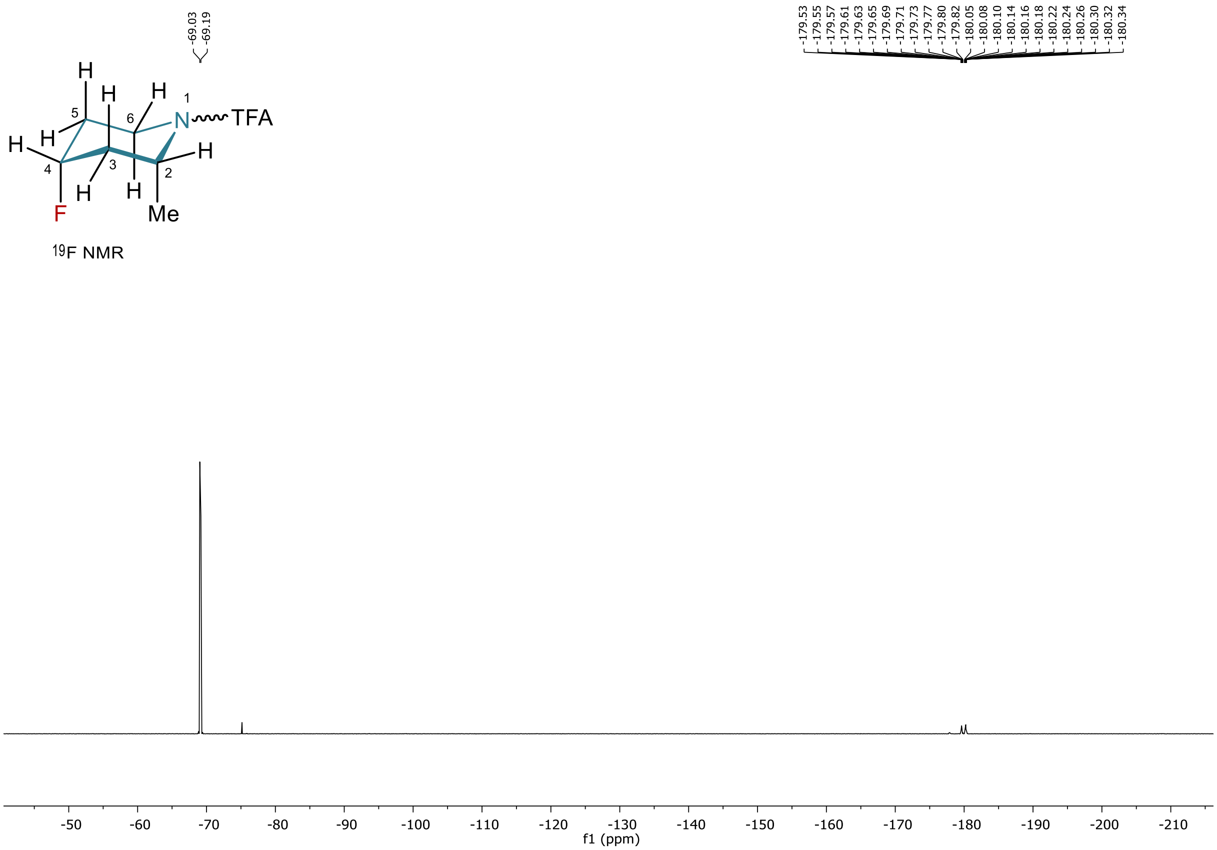
f1 (ppm)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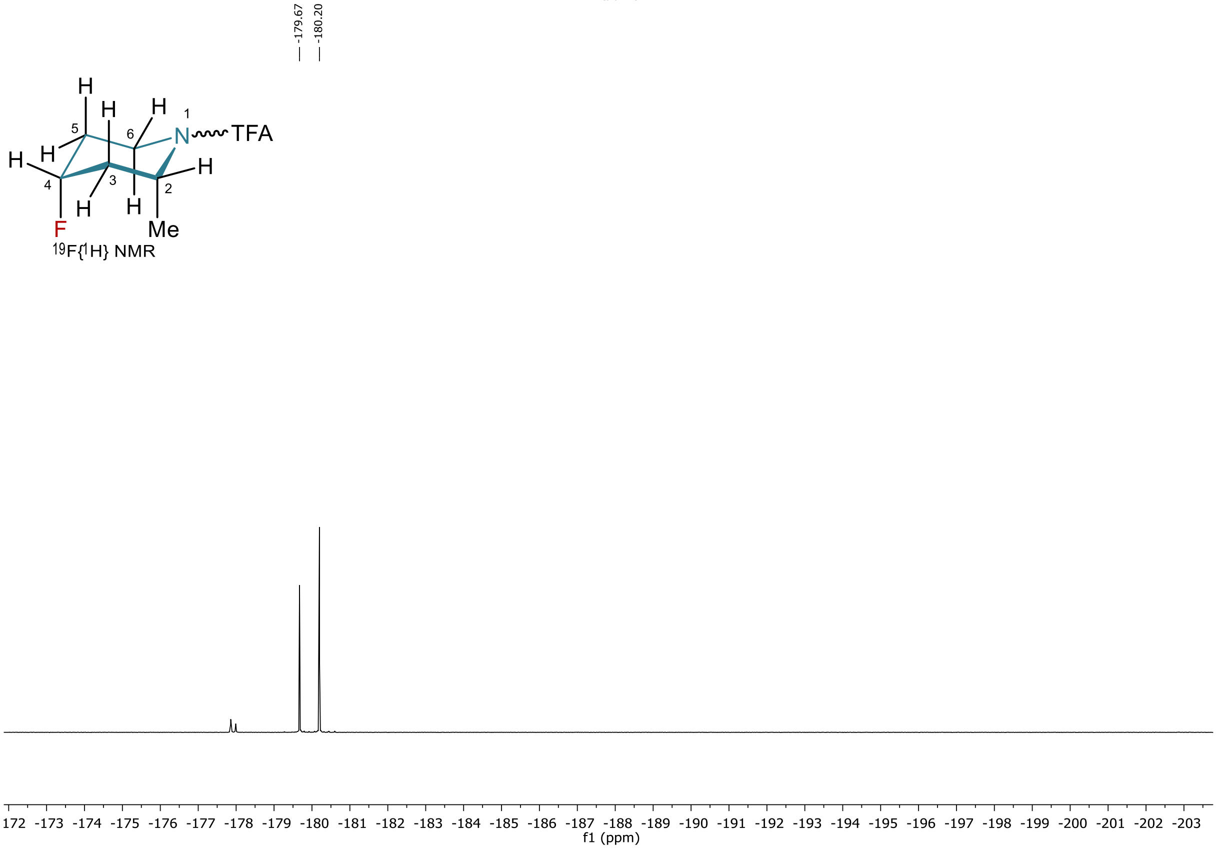
-69.19
-179.53
-179.55
-179.57
-179.61
-179.63
-179.65
-179.69
-179.71
-179.73
-179.77
-179.80
-179.82
-180.05
-180.08
-180.10
-180.14
-180.16
-180.18
-180.22
-180.24
-180.26
-180.30
-180.32
-180.34
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
F
Me
19F NMR
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


-179.67
-180.20
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
H
H
F
Me
19F{1H} NMR
172
-173
-174
-175
-176
-177
-178
-179
-180
-181
-182
-183
-184
-185
-186
-187
-188
-189
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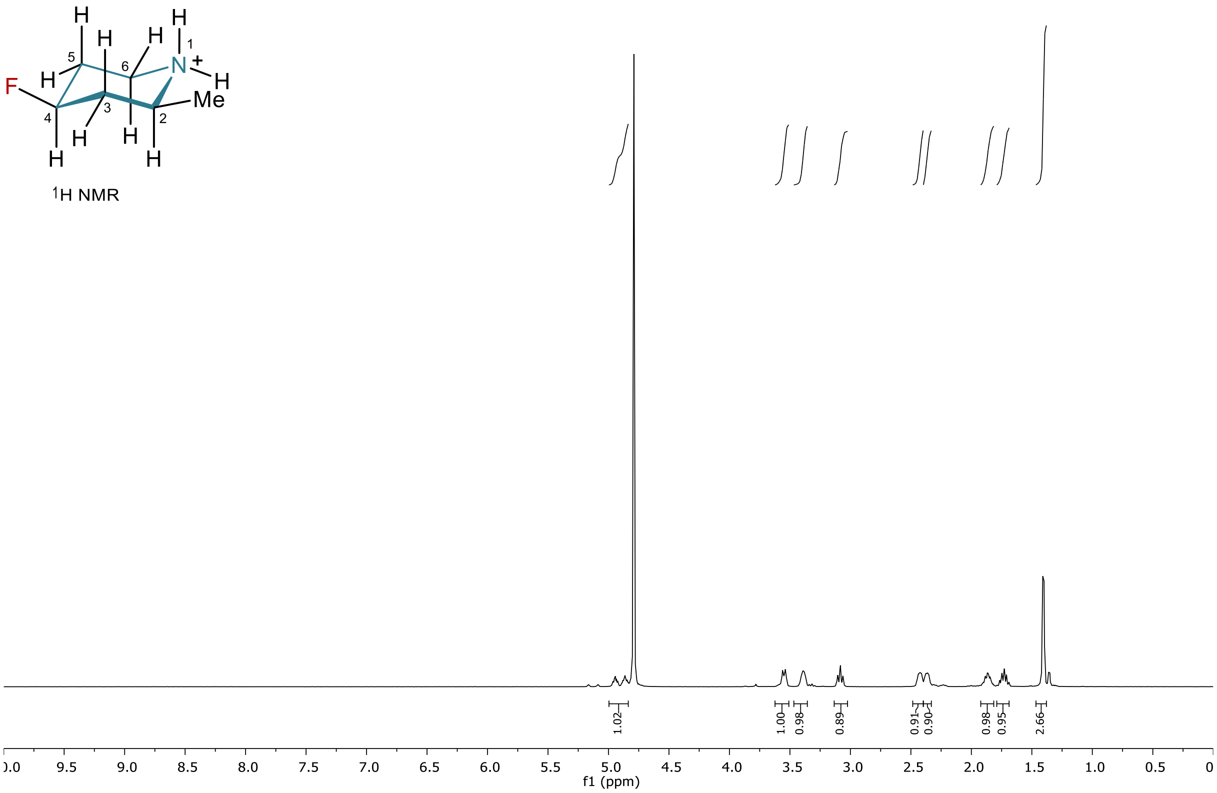
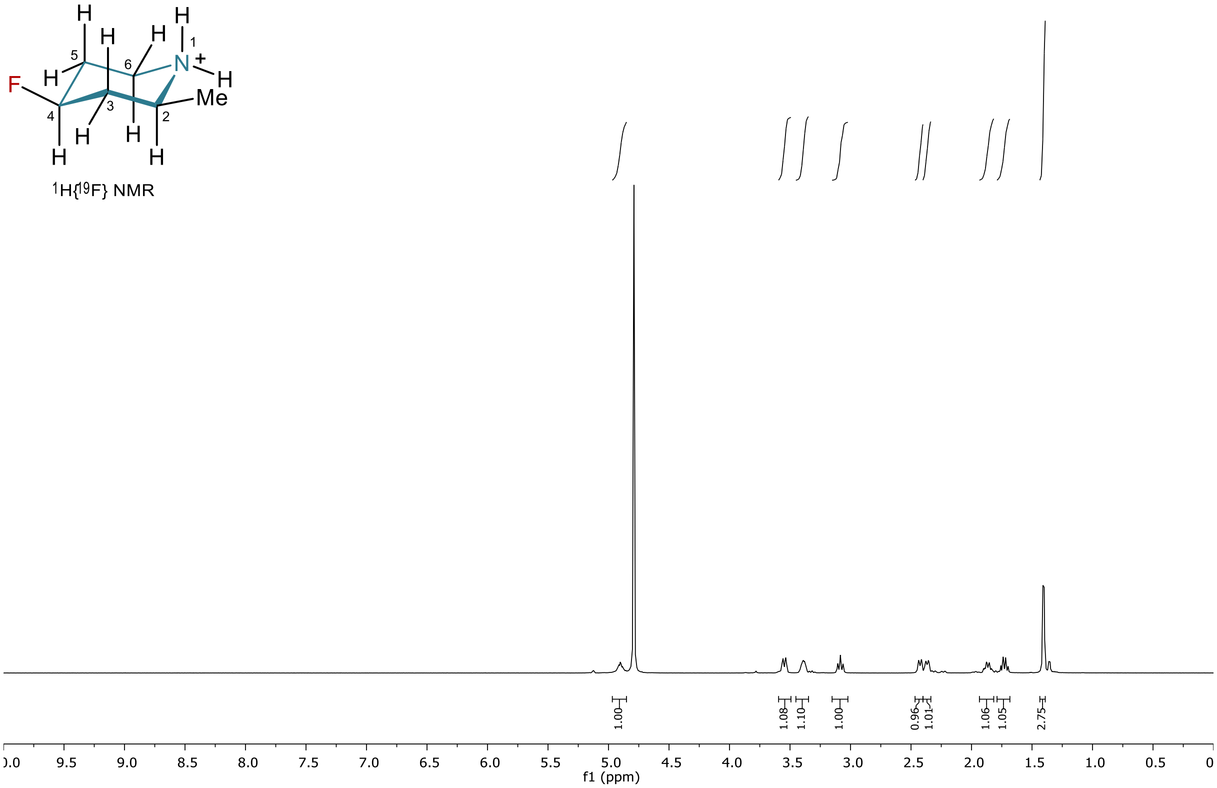
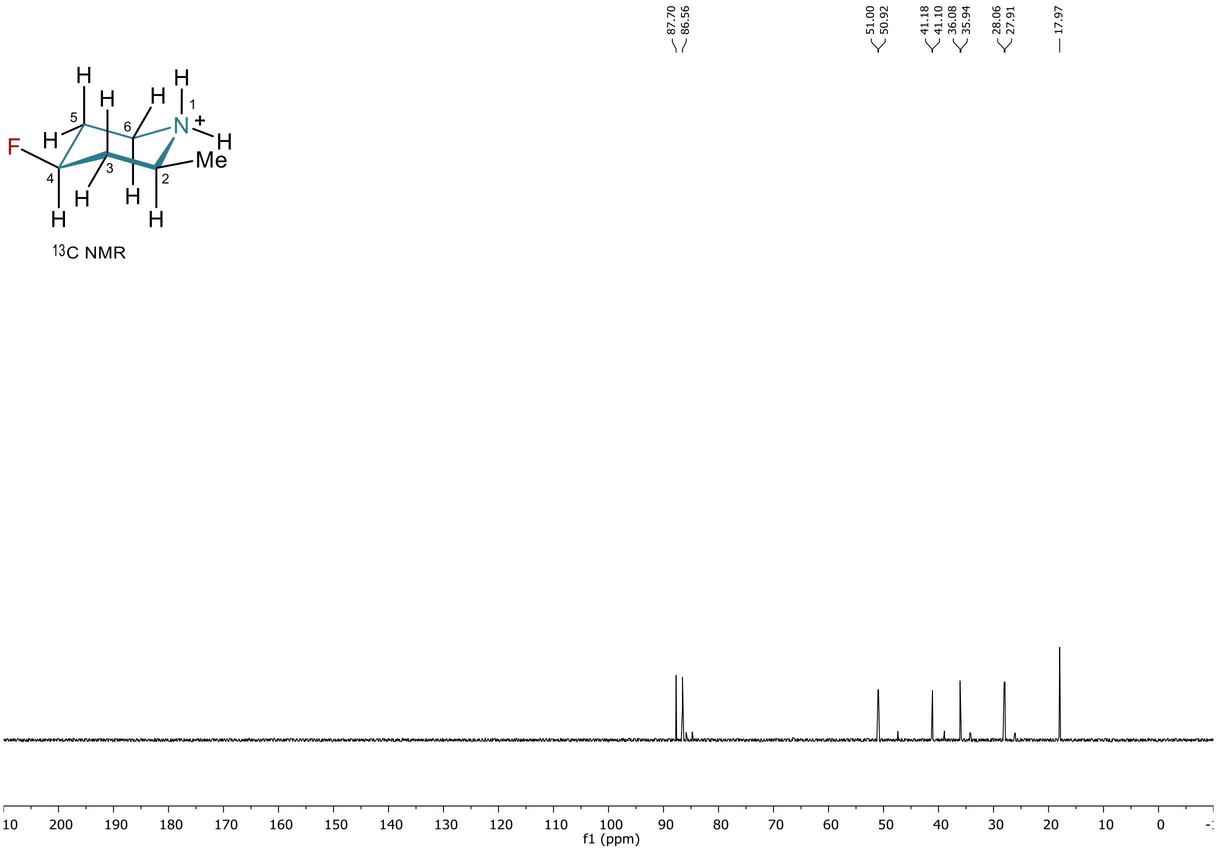
-201
-202
-203
f1 (ppm)



F
N+
Me
H
1
2
3
4
5
6
1H NMR
1.02
1.00
0.98
0.89
0.91
0.90
0.98
0.95
2.66
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)



F
N+
Me
H
1
2
3
4
5
6
1H{19F} NMR
1.00
1.08
1.10
1.00
0.96
1.01
1.06
1.05
2.75
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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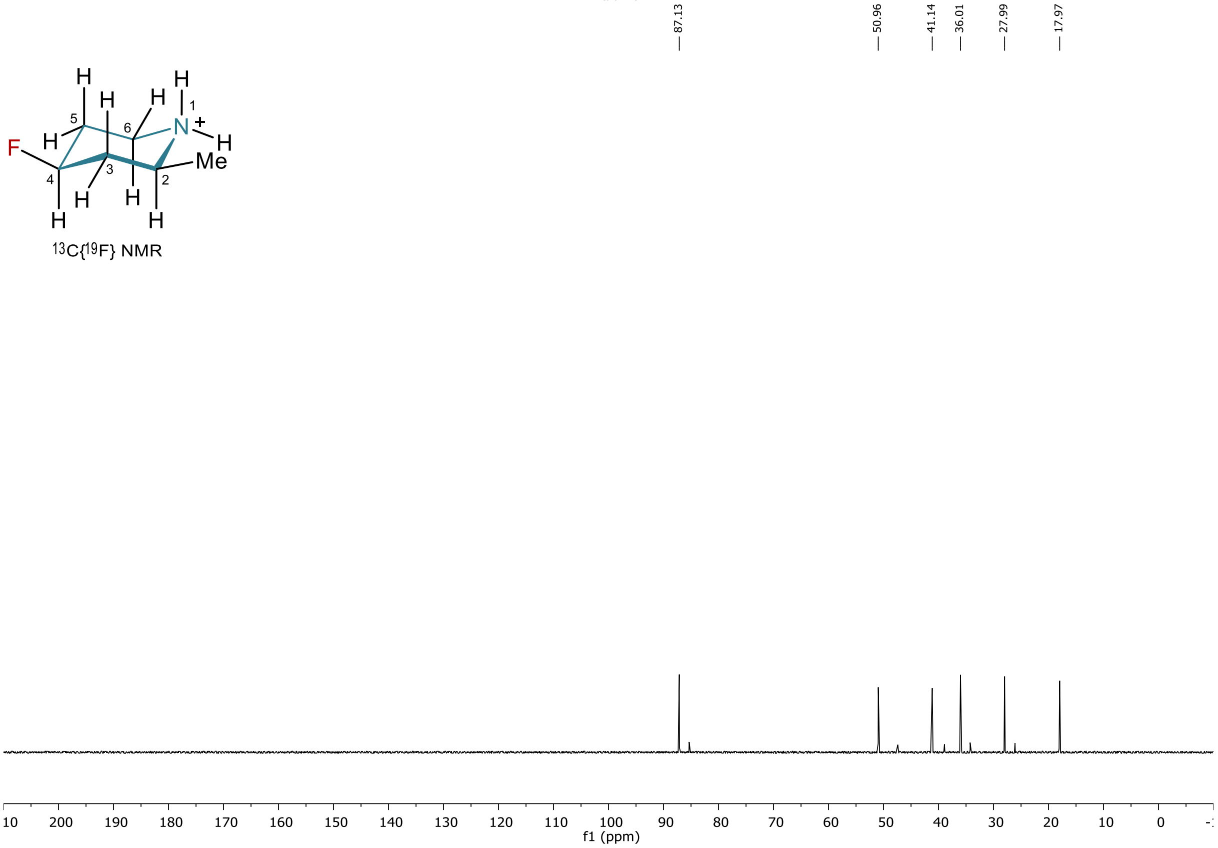
86.56
51.00
50.92
41.18
41.10
36.08
35.94
28.06
27.91
17.97
F
H
N
+
Me
1
2
3
4
5
6
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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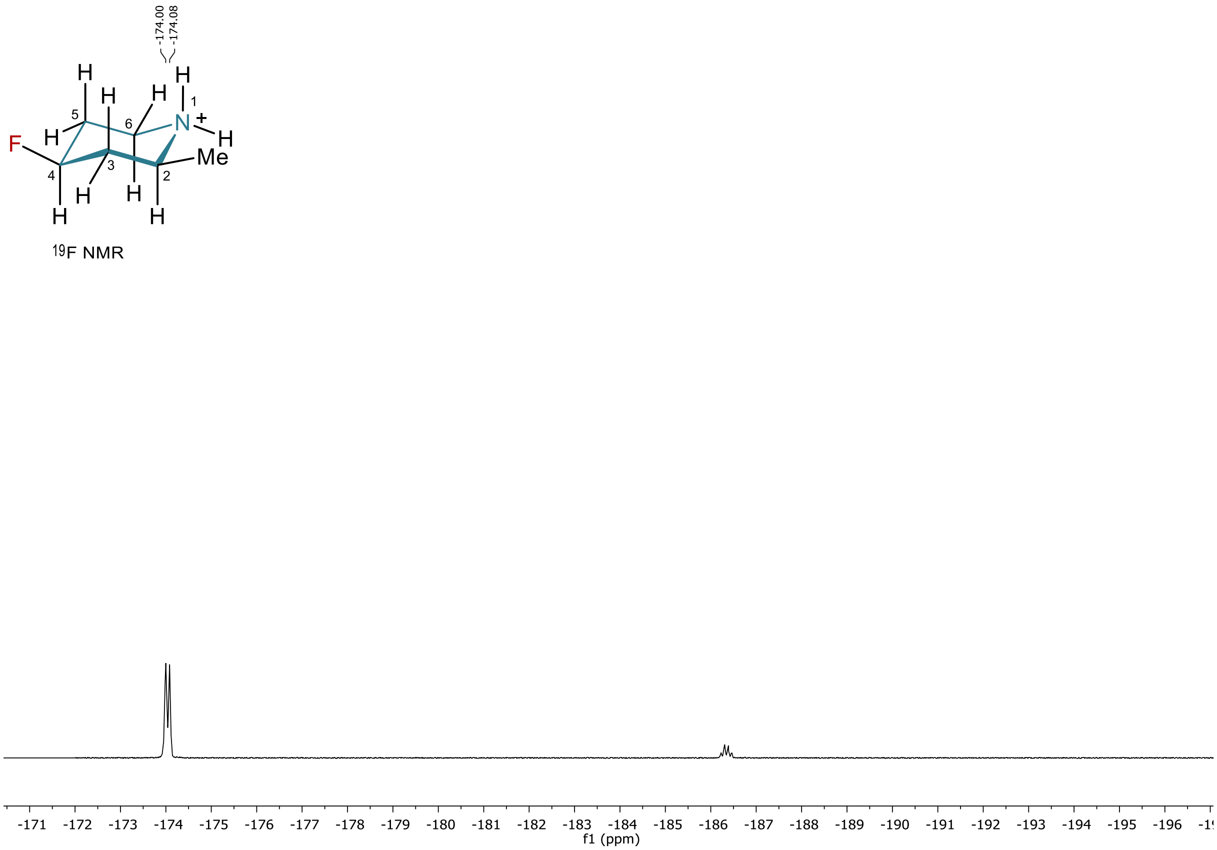
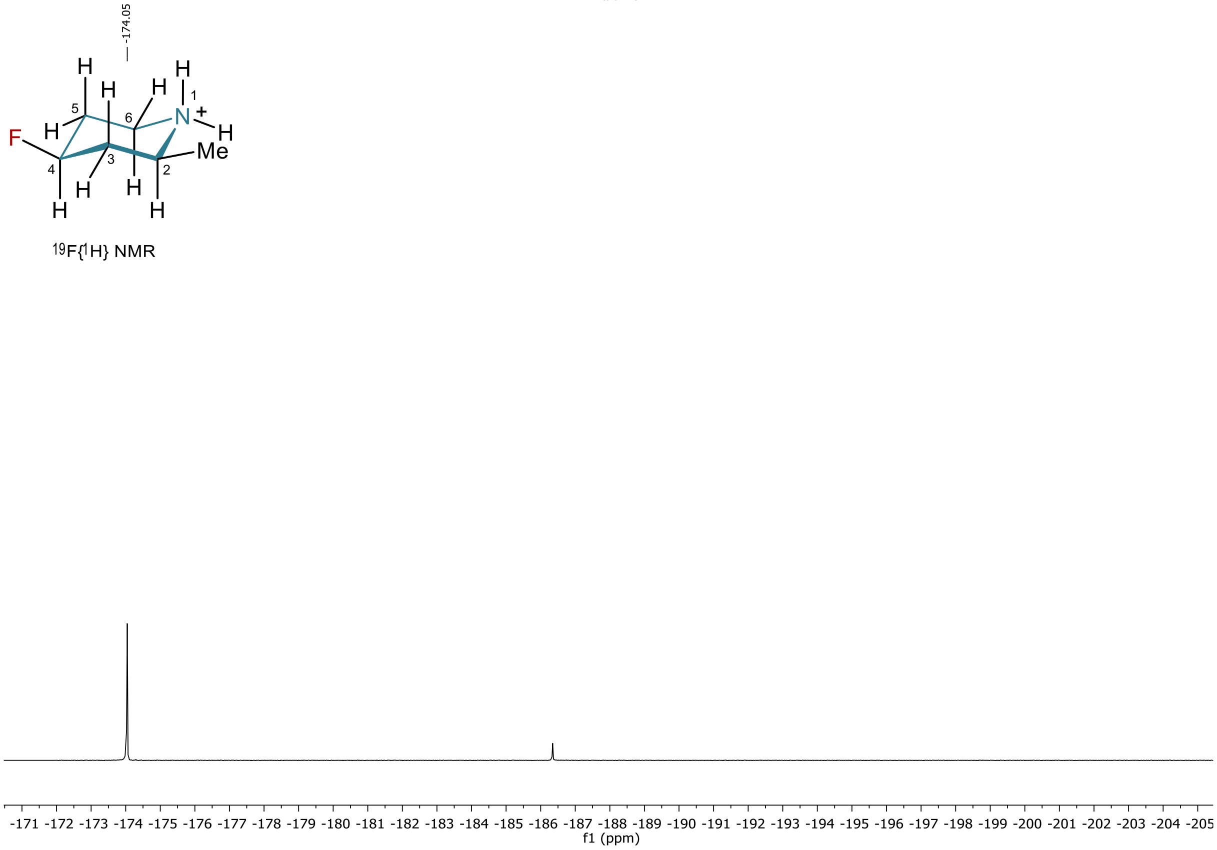
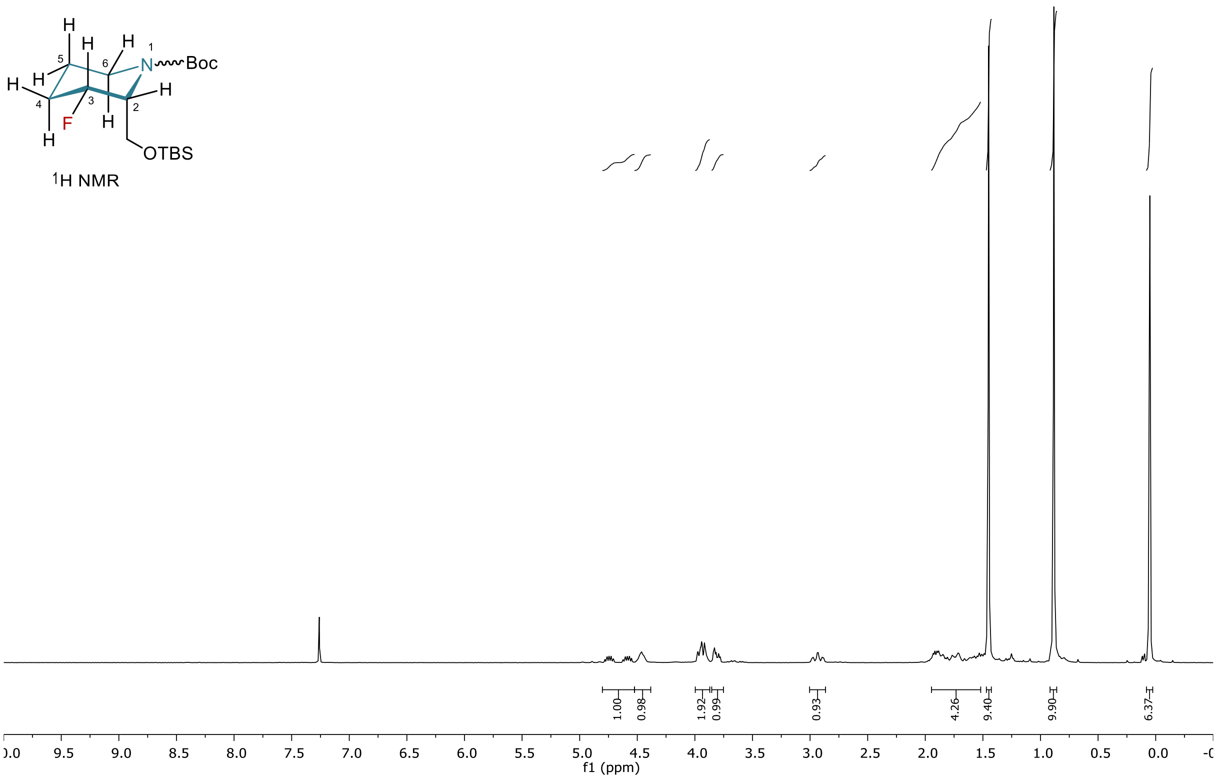
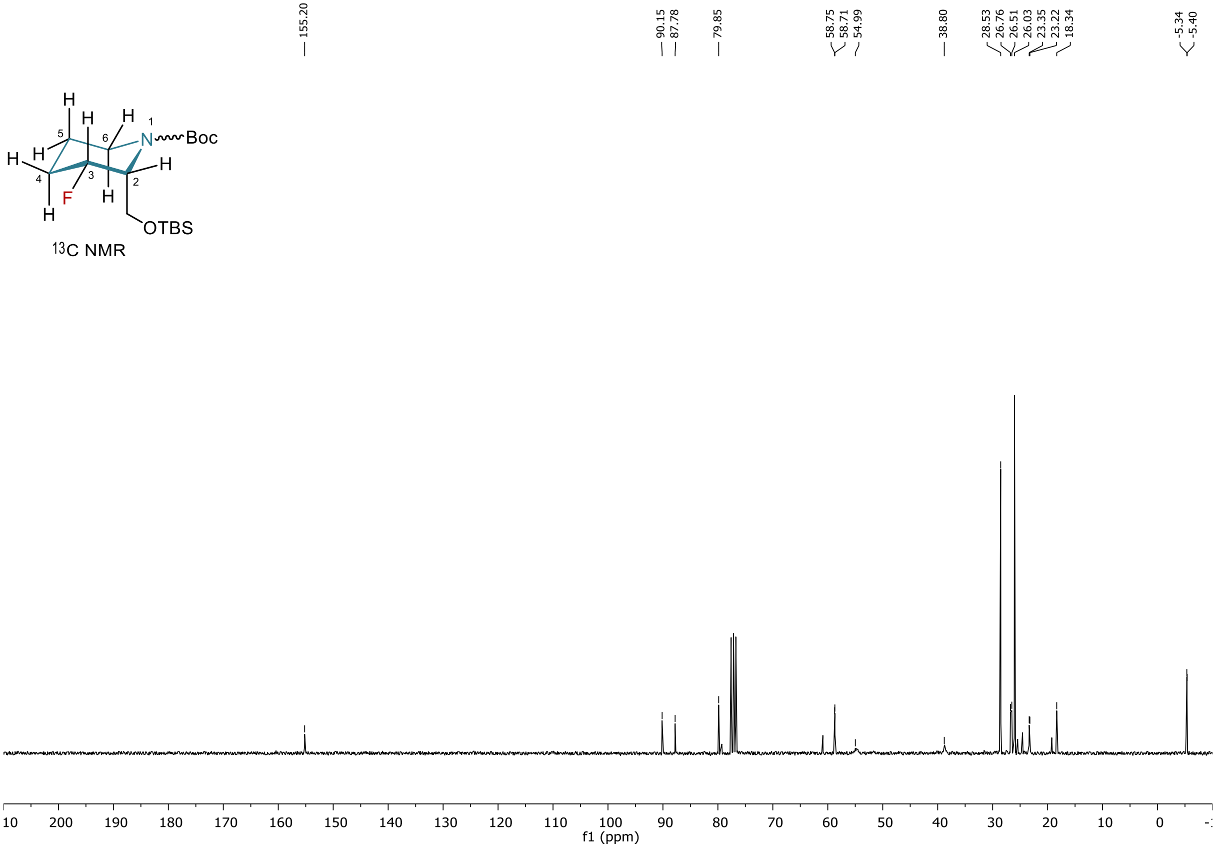
50.96
41.14
36.01
27.99
17.97
F
H
N
+
Me
1
2
3
4
5
6
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-174.00
-174.08
F
H
N+
Me
1
2
3
4
5
6
19F NMR
-171 -172 -173 -174 -175 -176 -177 -178 -179 -180 -181 -182 -183 -184 -185 -186 -187 -188 -189 -190 -191 -192 -193 -194 -195 -196
f1 (ppm)


-174.05
F
H
N+
Me
1
2
3
4
5
6
19F{1H} NMR
-171 -172 -173 -174 -175 -176 -177 -178 -179 -180 -181 -182 -183 -184 -185 -186 -187 -188 -189 -190 -191 -192 -193 -194 -195 -196 -197 -198 -199 -200 -201 -202 -203 -204 -205
f1 (ppm)



H
H
H
1
N
Boc
5
6
H
H
4
3
2
F
H
H
OTBS
1H NMR
1.00
0.98
1.92
0.99
0.93
4.26
9.40
9.90
6.37
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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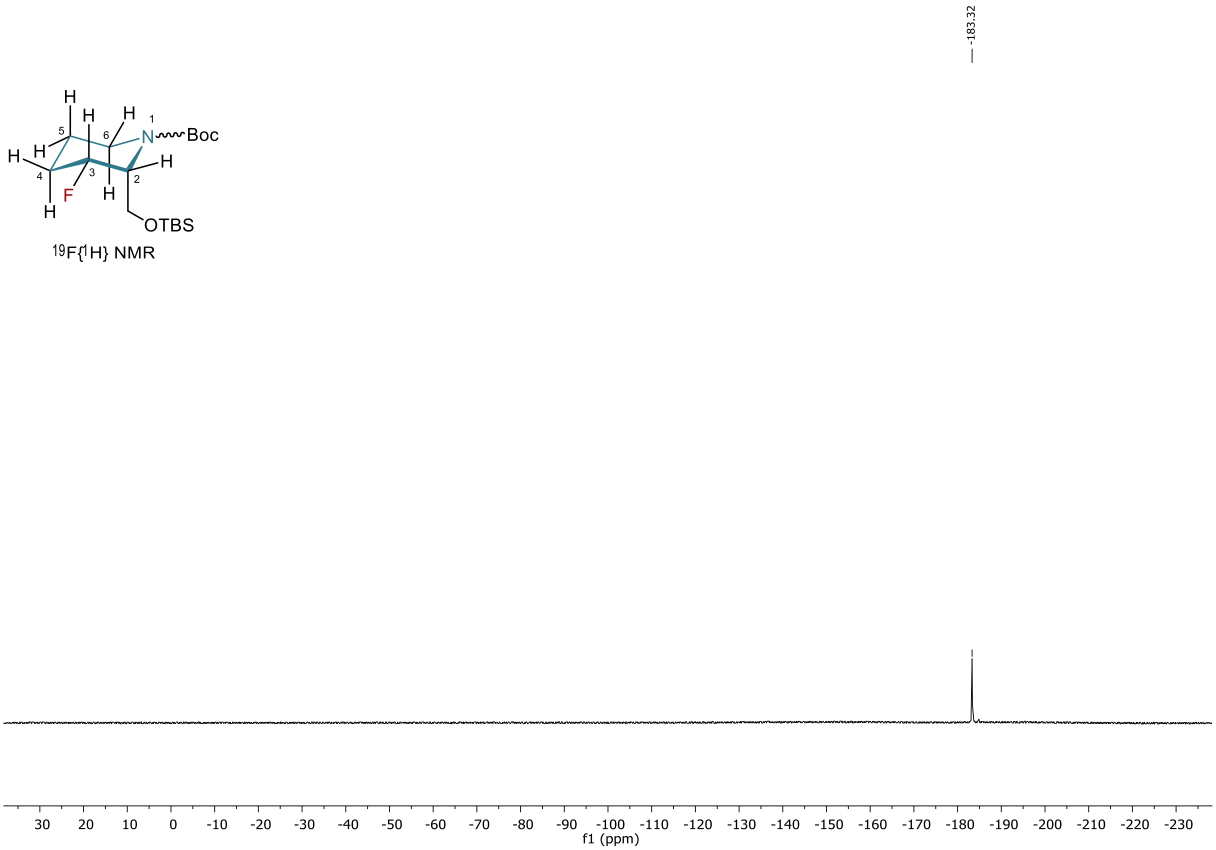
90.15
87.78
79.85
58.75
58.71
54.99
38.80
28.53
26.76
26.51
26.03
23.35
23.22
18.34
-5.34
-5.40
H
H
H
1
N
Boc
5
6
H
H
4
3
2
F
H
H
OTBS
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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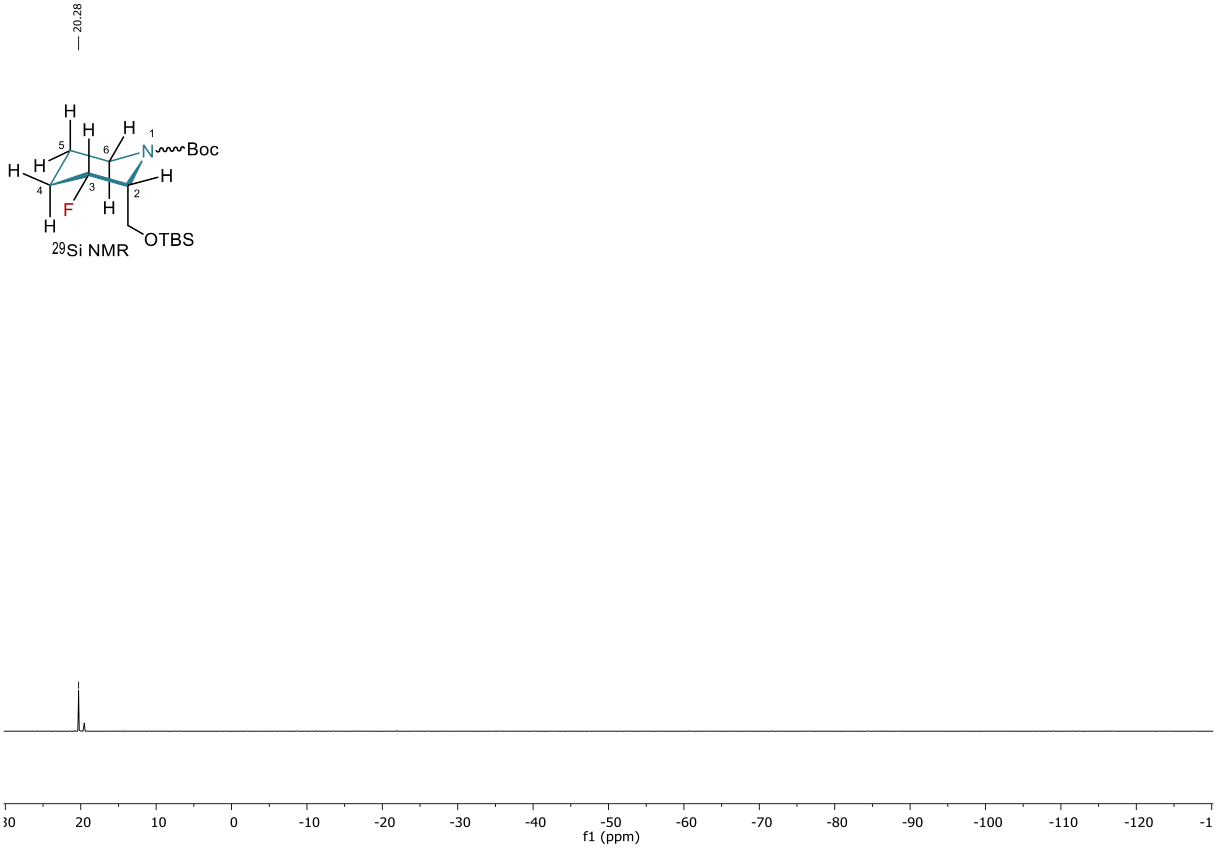
H
H
H
N
1
Boc
5
6
H
H
H
4
3
2
F
H
H
OTBS
19F{1H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)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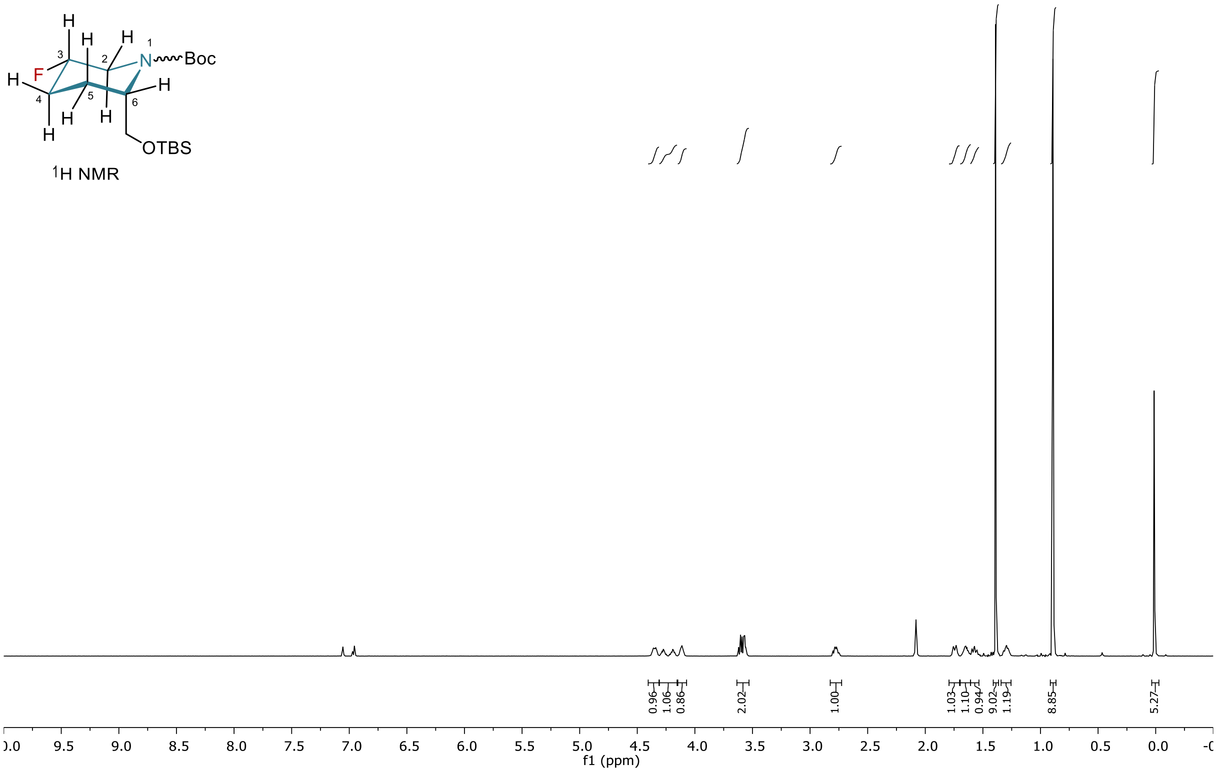
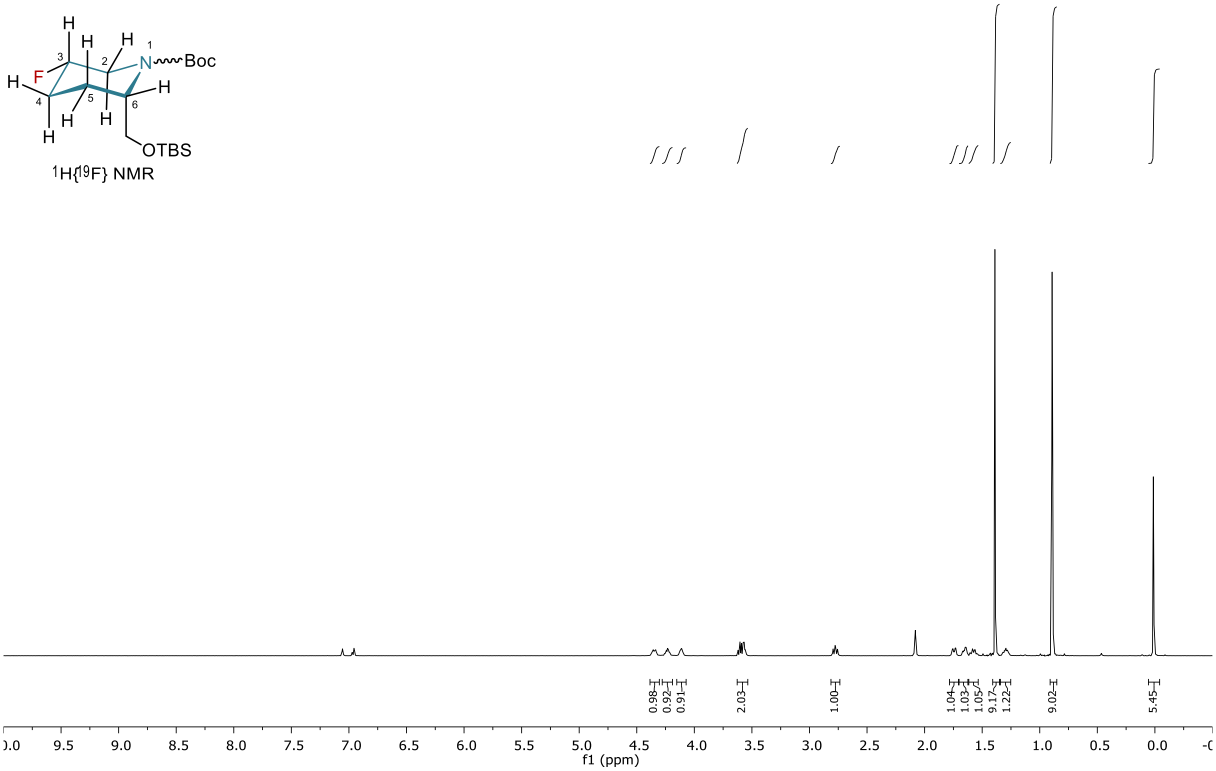
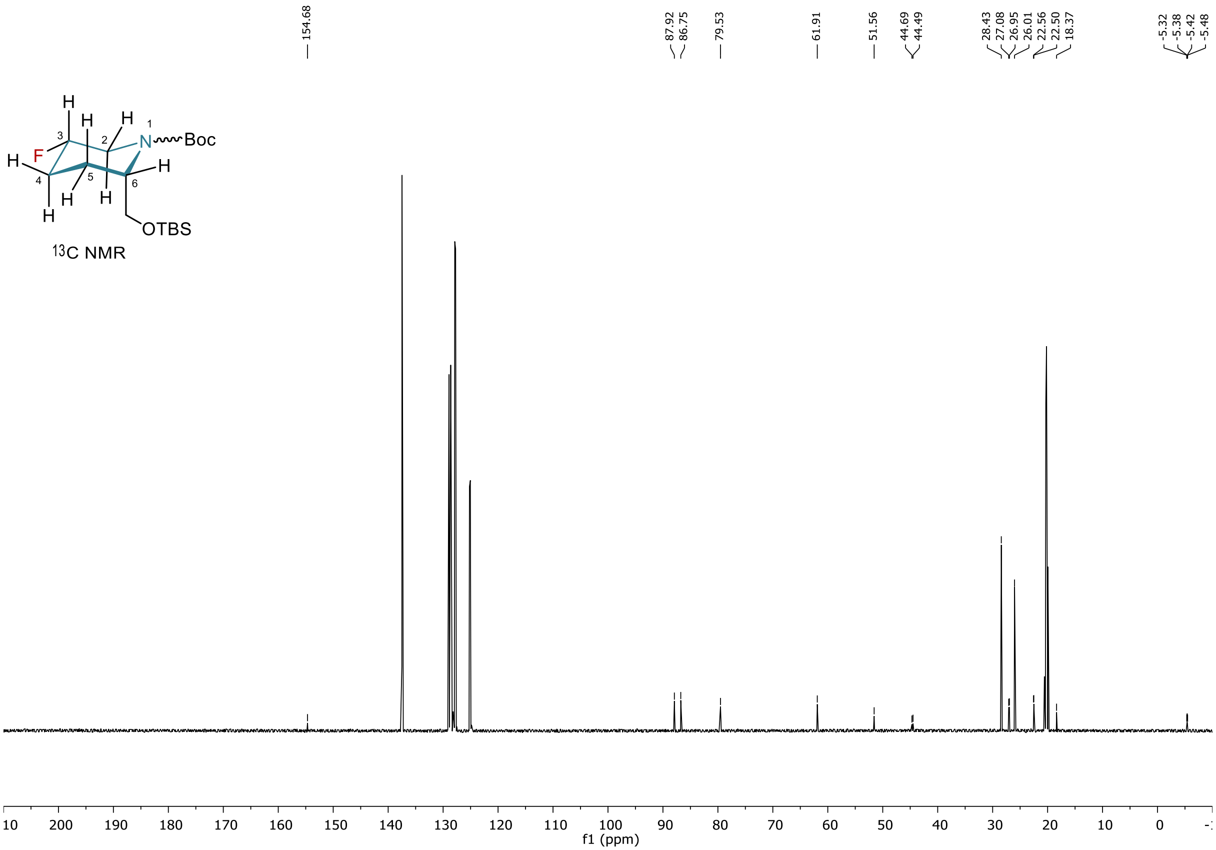
H
H
H
N
1
Boc
5
6
H
H
H
4
3
2
F
H
H
OTBS
29Si NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -1
f1 (ppm)


H
H
H
1
3
2
N
Boc
H
F
H
4
5
6
H
H
H
OTBS
1H NMR
0.96
1.06
0.86
2.02
1.00
1.03
1.10
0.94
9.02
1.19
8.85
5.27
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


H
H
H
1
3
2
N
Boc
H
F
H
4
5
6
H
H
H
OTBS
1H{19F} NMR
0.98
0.92
0.91
2.03
1.00
1.04
1.03
1.05
9.17
1.22
9.02
5.45
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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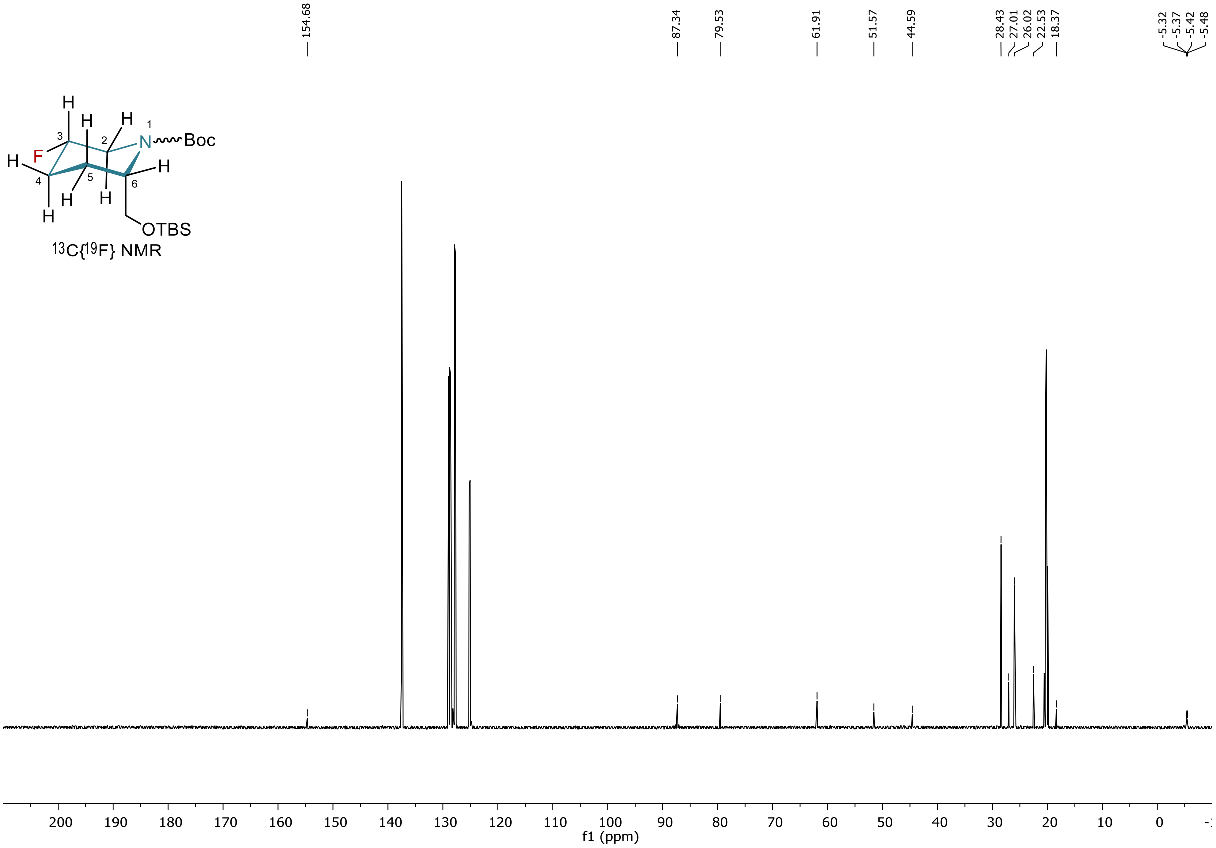
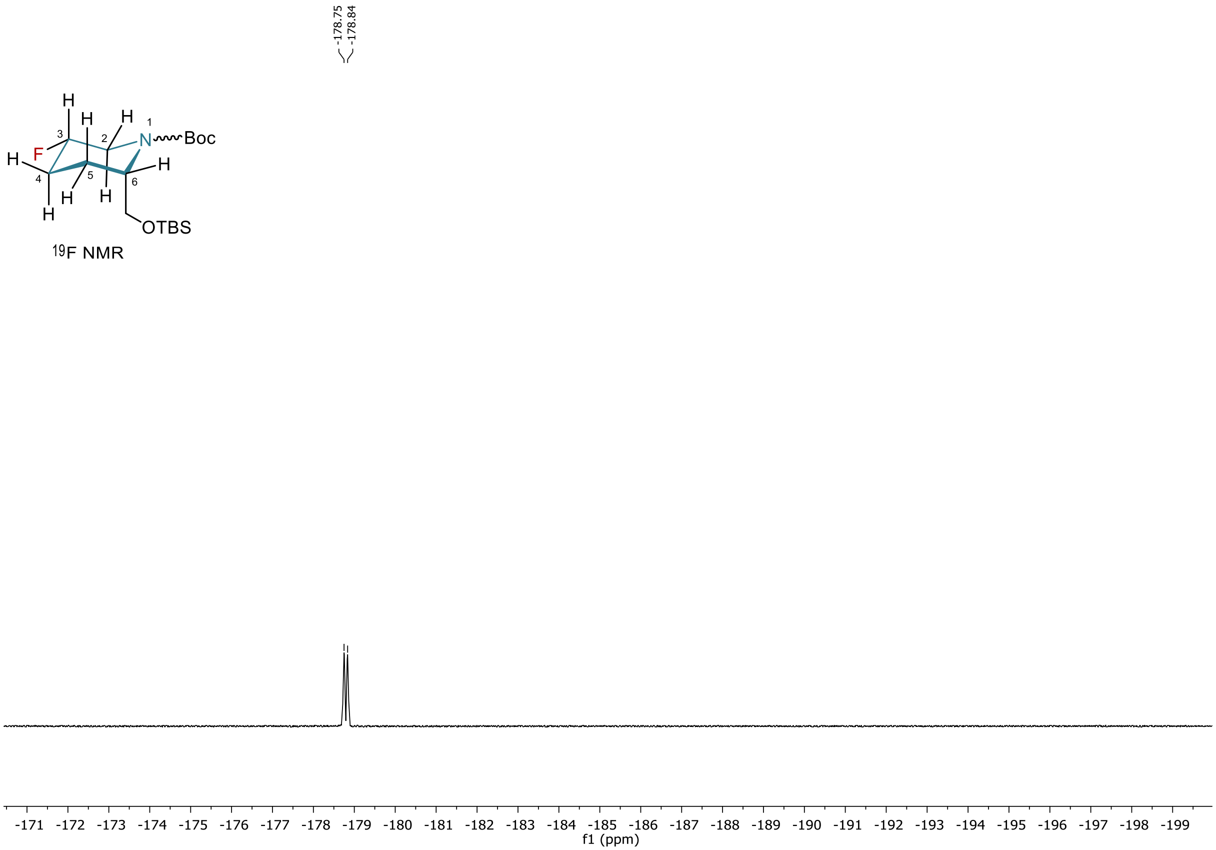
86.75
79.53
61.91
51.56
44.69
44.49
28.43
27.08
26.95
26.01
22.56
22.50
18.37
-5.32
-5.38
-5.42
-5.48
H
H
H
1
3
2
N
Boc
F
H
4
5
6
H
H
H
H
OTBS
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


154.68
87.34
79.53
61.91
51.57
44.59
28.43
27.01
26.02
22.53
18.37
-5.32
-5.37
-5.42
-5.48
H
H
H
1
3
2
N
Boc
F
H
4
5
6
H
H
H
H
OTBS
13C{19F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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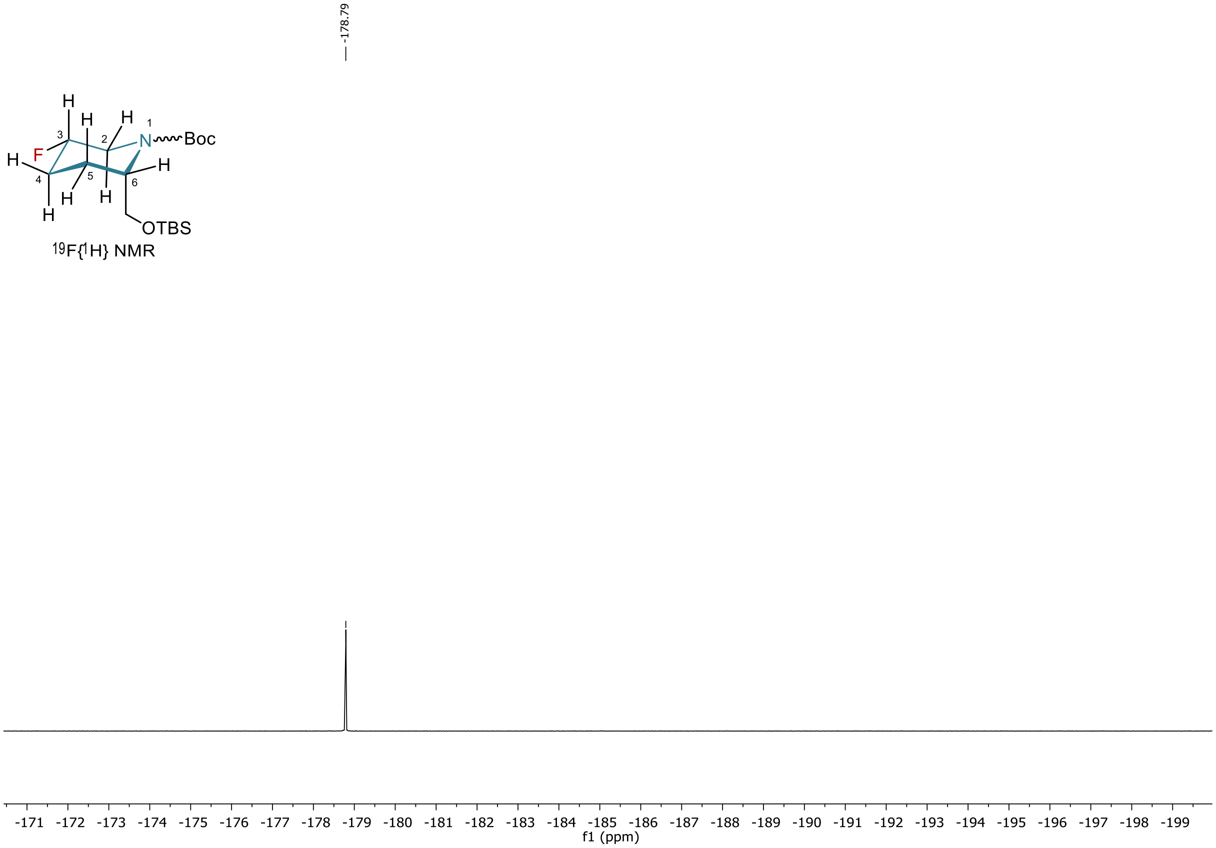
-178.84
H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
OTBS
19F NMR
-171 -172 -173 -174 -175 -176 -177 -178 -179 -180 -181 -182 -183 -184 -185 -186 -187 -188 -189 -190 -191 -192 -193 -194 -195 -196 -197 -198 -199
f1 (ppm)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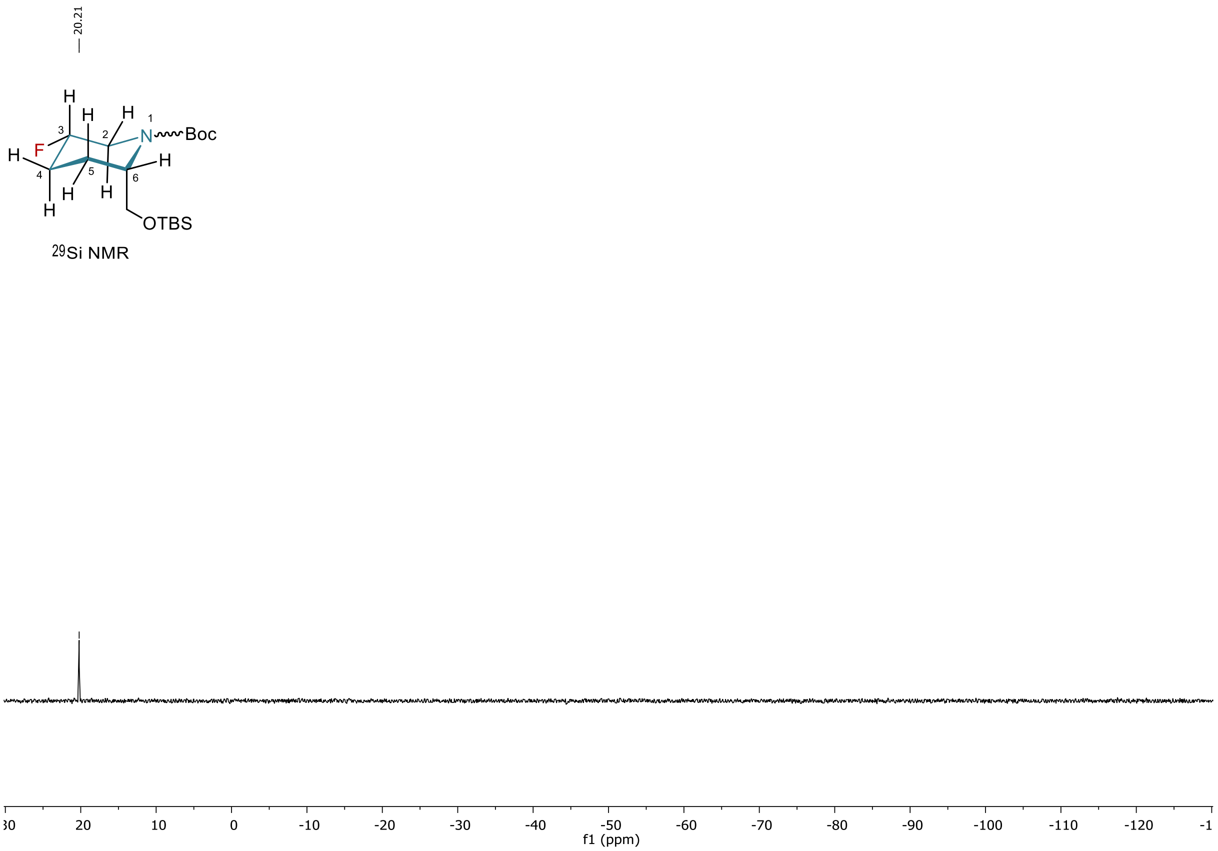
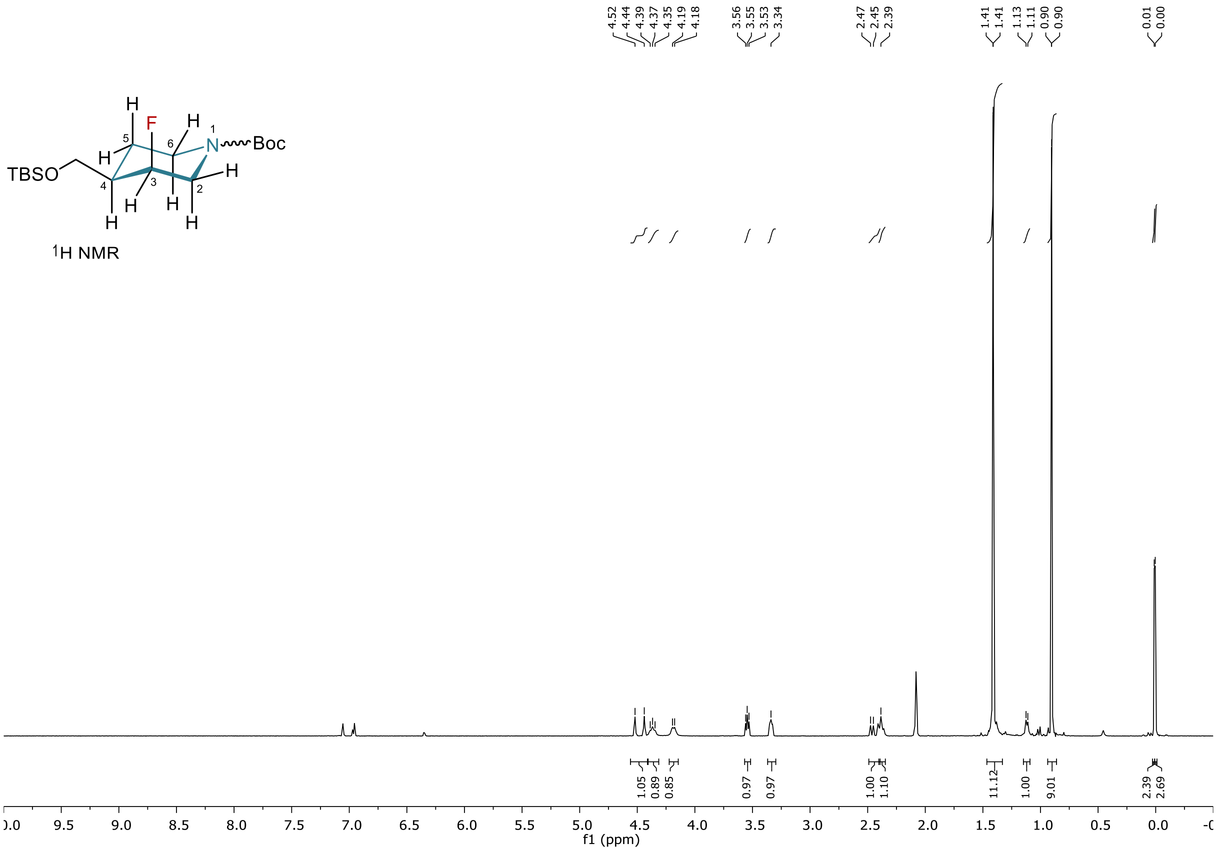
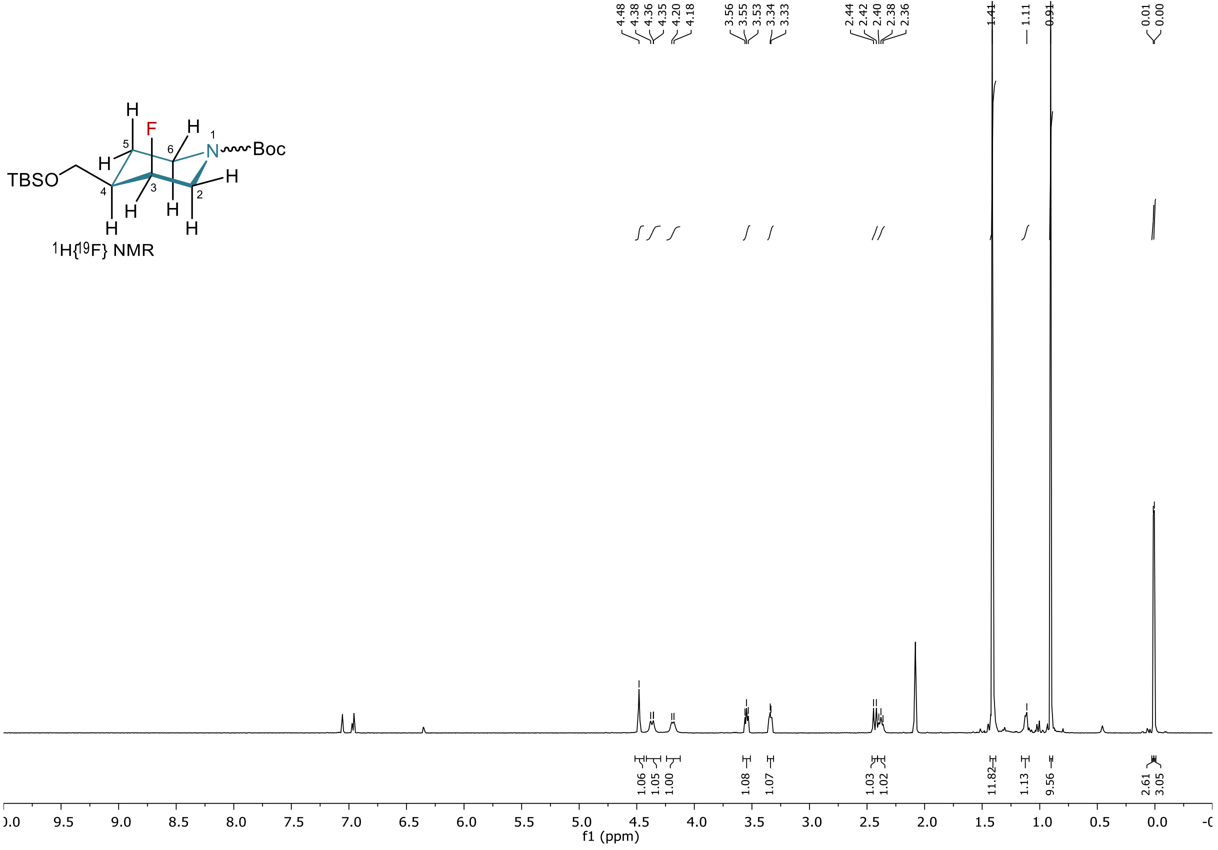
H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
OTBS
19F{1H} NMR
-171 -172 -173 -174 -175 -176 -177 -178 -179 -180 -181 -182 -183 -184 -185 -186 -187 -188 -189 -190 -191 -192 -193 -194 -195 -196 -197 -198 -199
f1 (ppm)

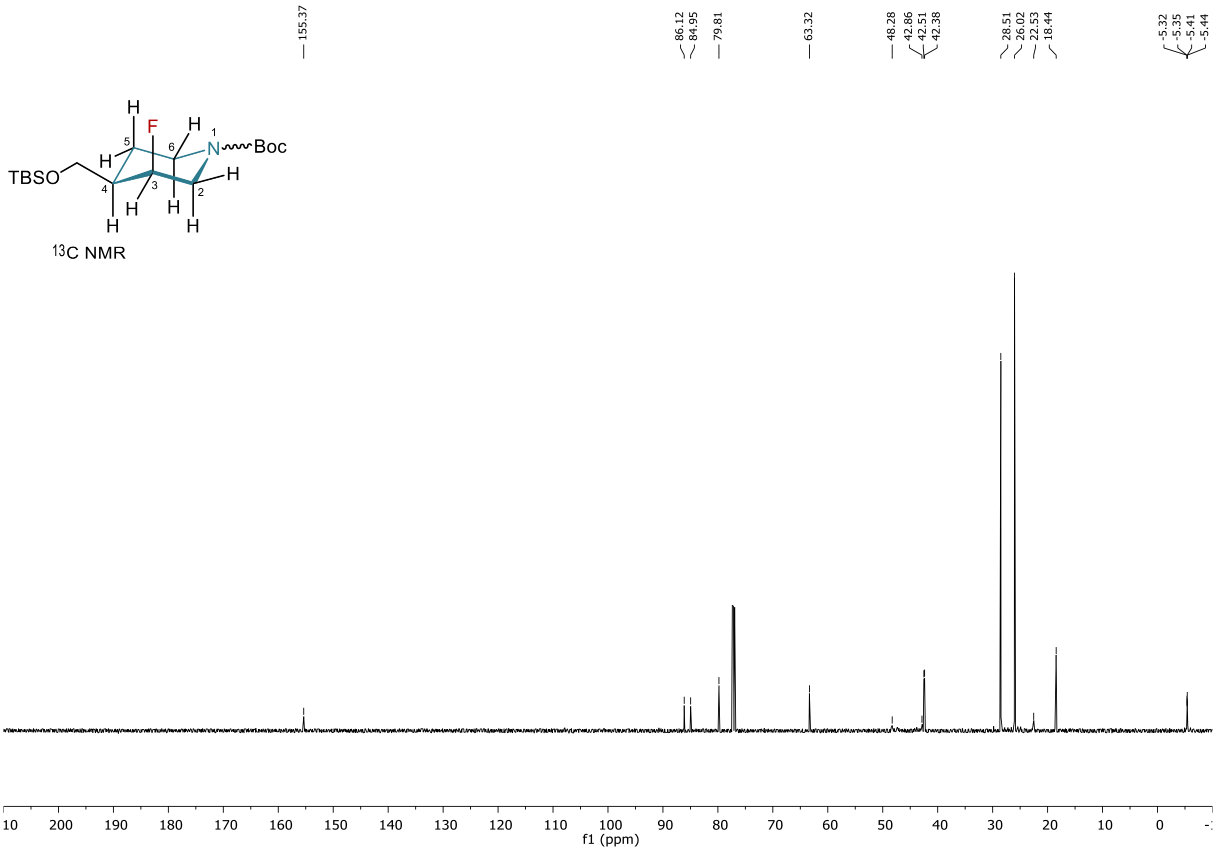

20.21
H
H
H
1
3
2
N
Boc
F
H
4
5
6
H
H
H
H
OTBS
^{29}Si NMR
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-1
f1 (ppm)



TBSO
F
N
Boc
H
1
2
3
4
5
6
1H NMR
4.52
4.44
4.39
4.37
4.35
4.19
4.18
3.56
3.55
3.53
3.34
2.47
2.45
2.39
1.41
1.41
1.13
1.11
0.90
0.90
0.01
0.00
1.05
0.89
0.85
0.97
0.97
1.00
1.10
11.12
1.00
9.01
2.39
2.69
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)



TBSO
F
N
Boc
H
1
2
3
4
5
6
1H{19F} NMR
4.48
4.38
4.36
4.35
4.20
4.18
3.56
3.55
3.53
3.34
3.33
2.44
2.42
2.40
2.38
2.36
1.41
1.11
0.91
0.01
0.00
1.06
1.05
1.00
1.08
1.07
1.03
1.02
11.82
1.13
9.56
2.61
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)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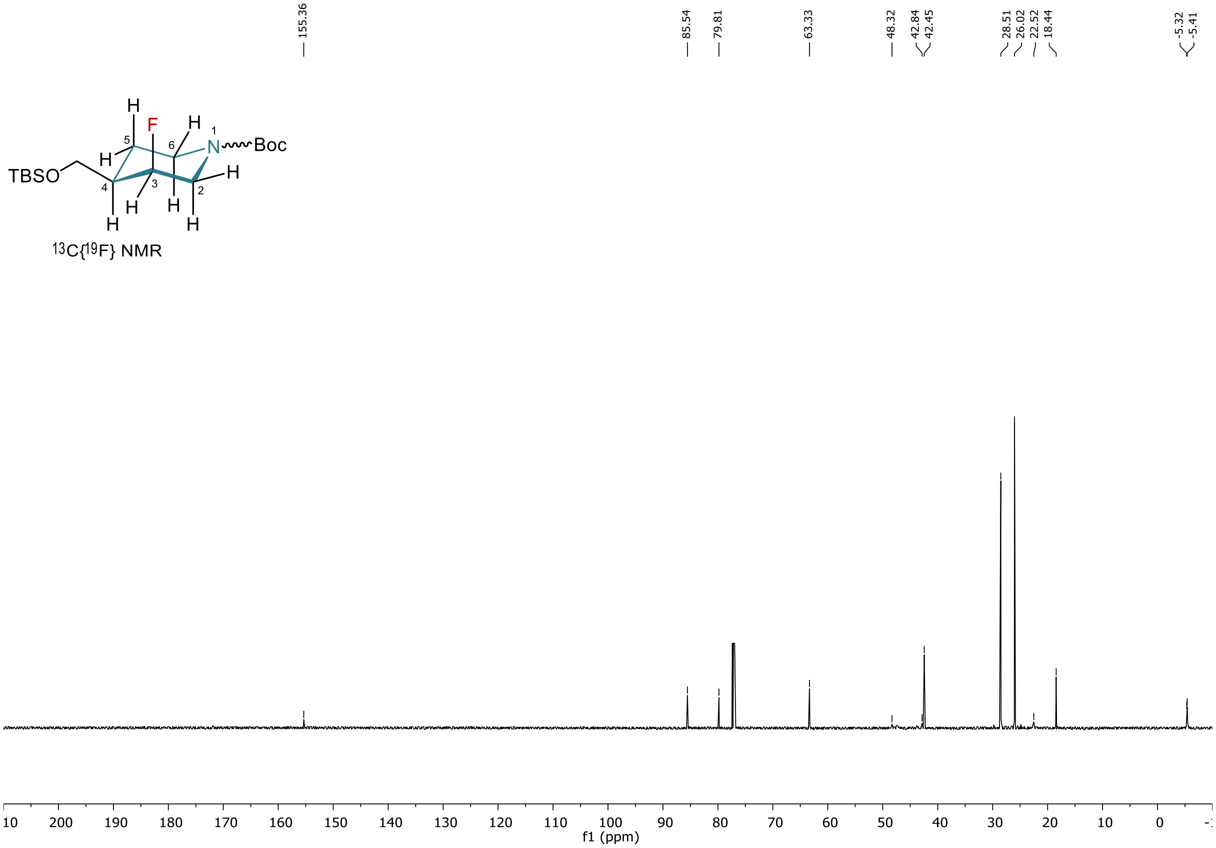
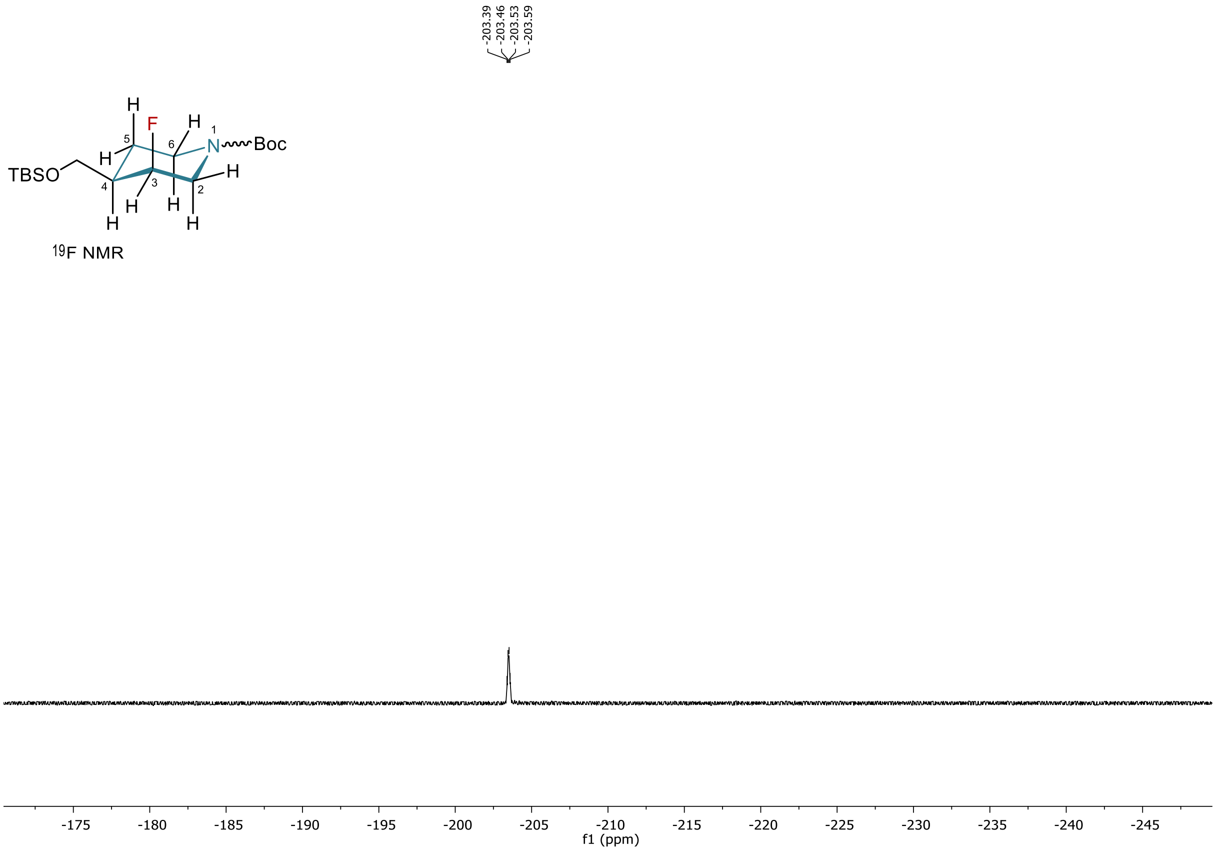
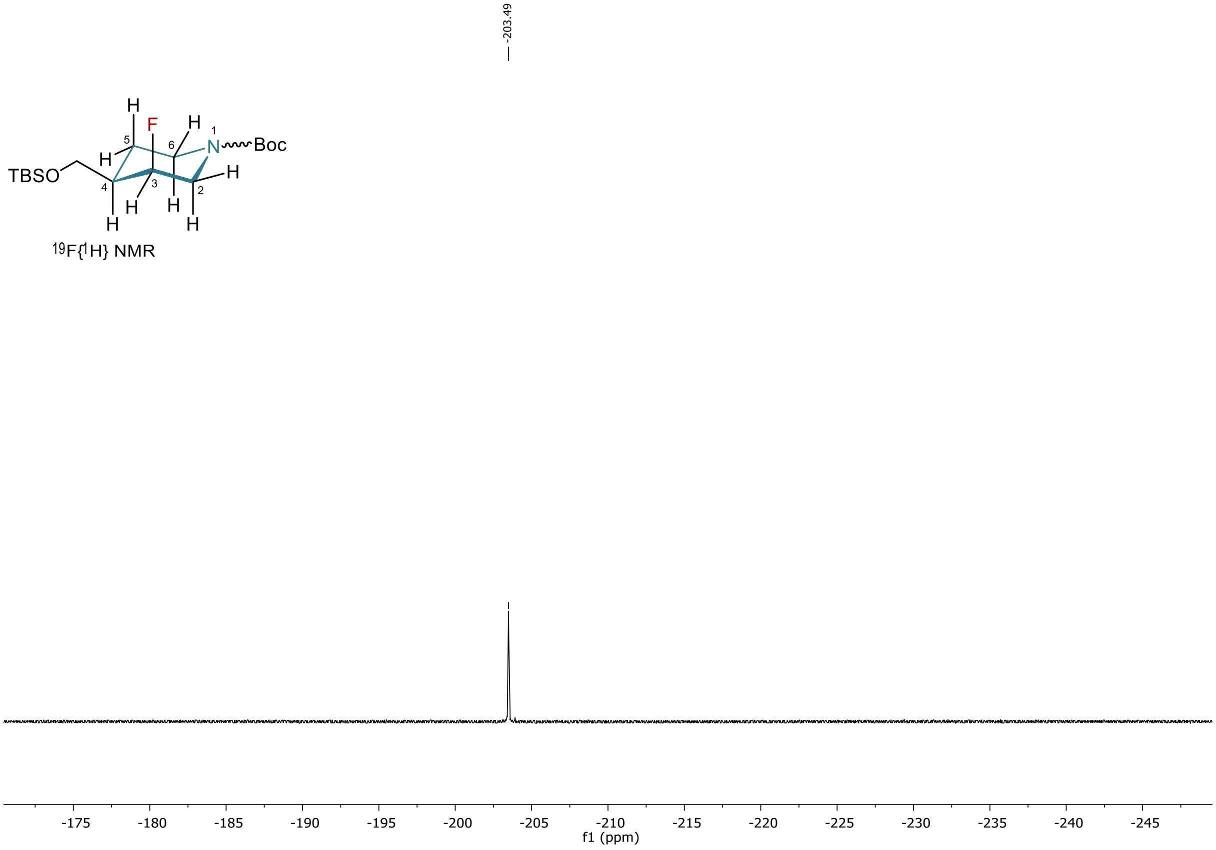
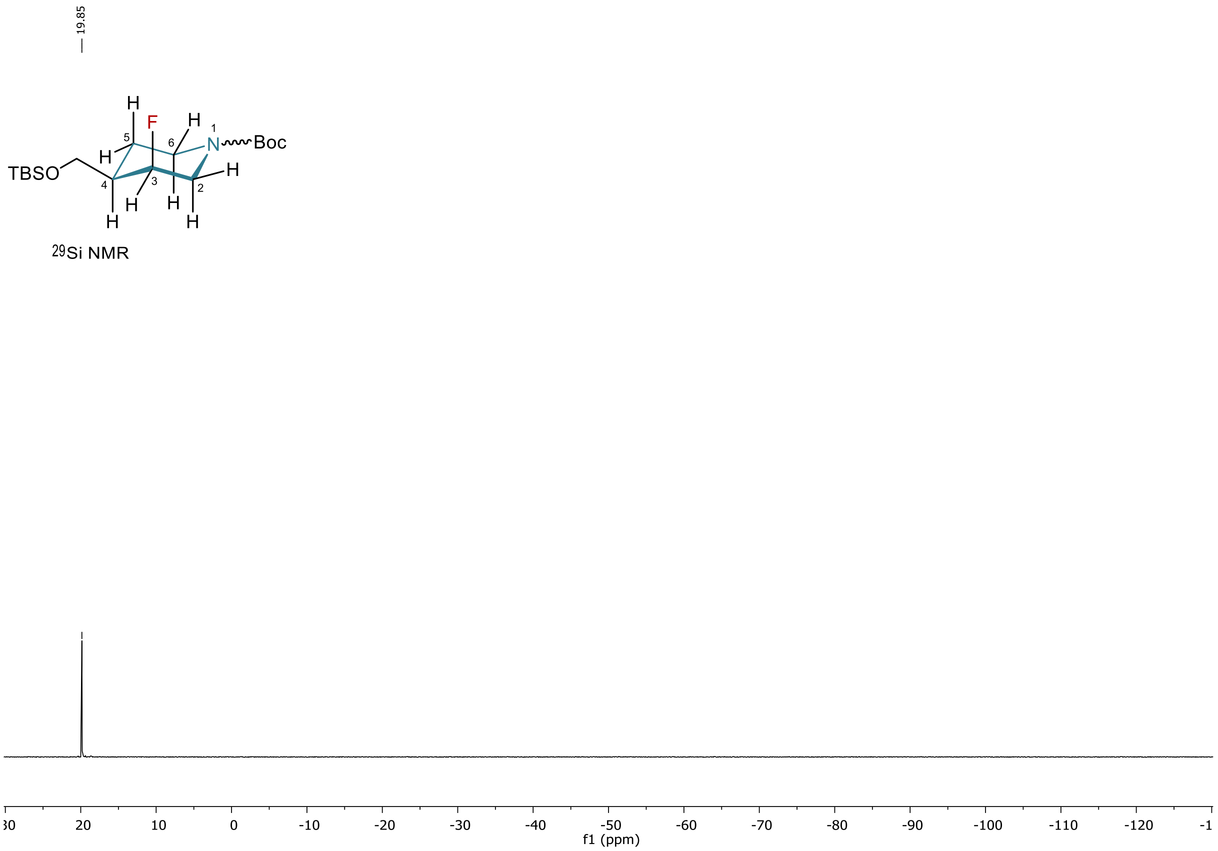
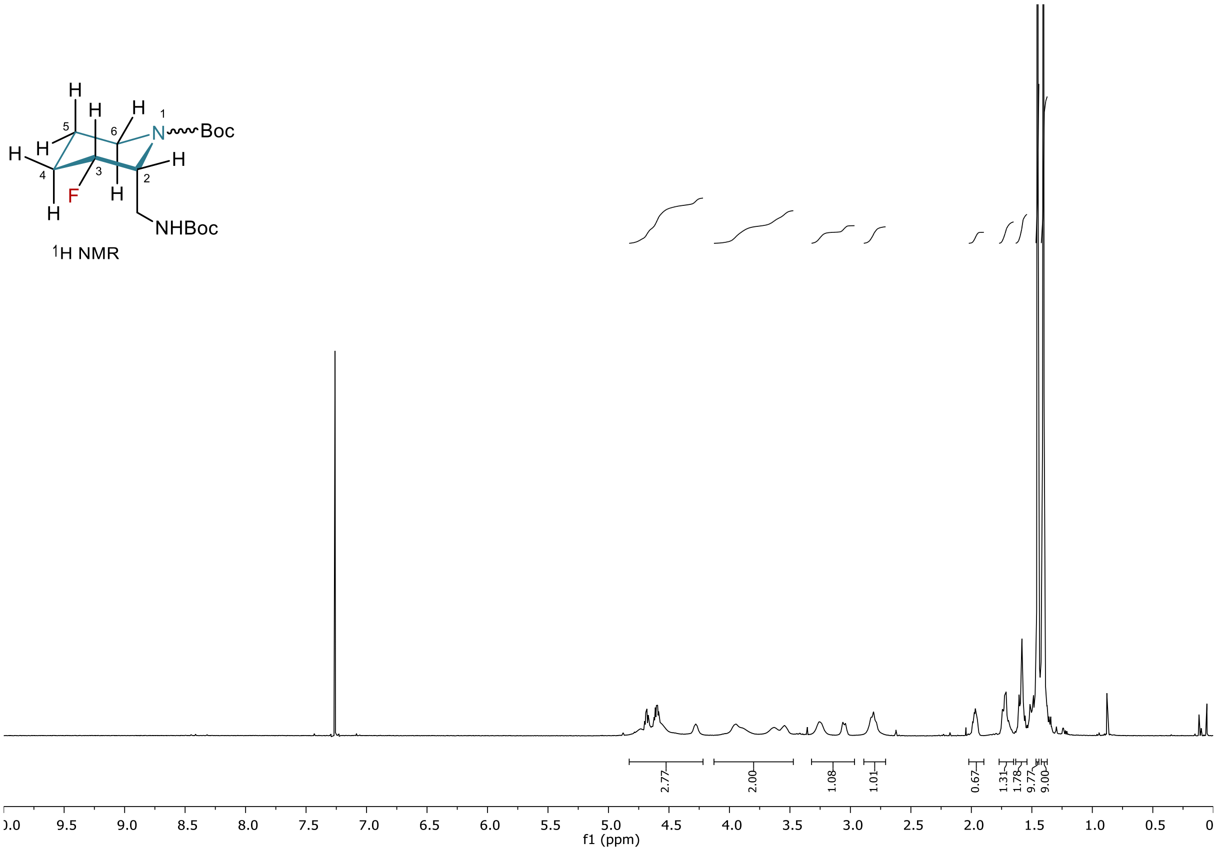
86.12
84.95
79.81
63.32
48.28
42.86
42.51
42.38
28.51
26.02
22.53
18.44
-5.32
-5.35
-5.41
-5.44
H
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

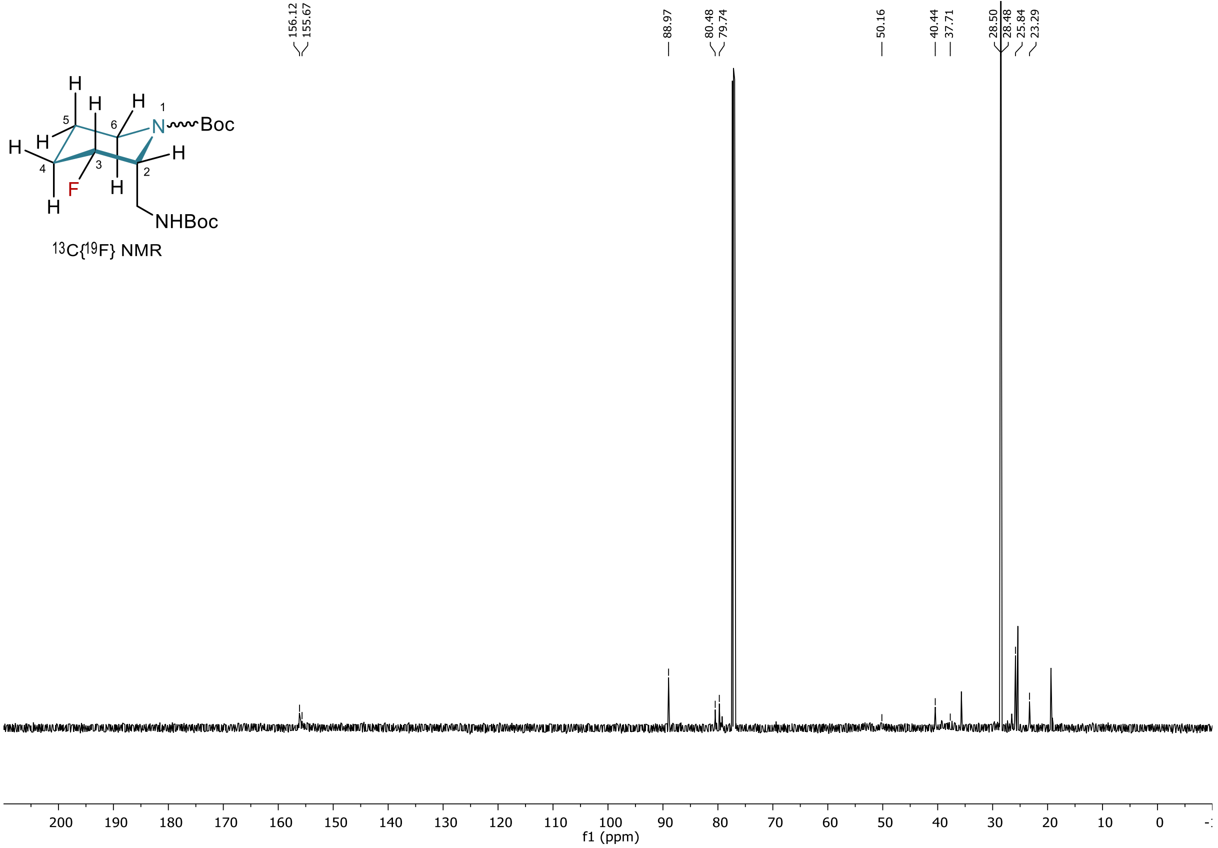

155.36
85.54
79.81
63.33
48.32
42.84
42.45
28.51
26.02
22.52
18.44
-5.32
-5.41
H
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

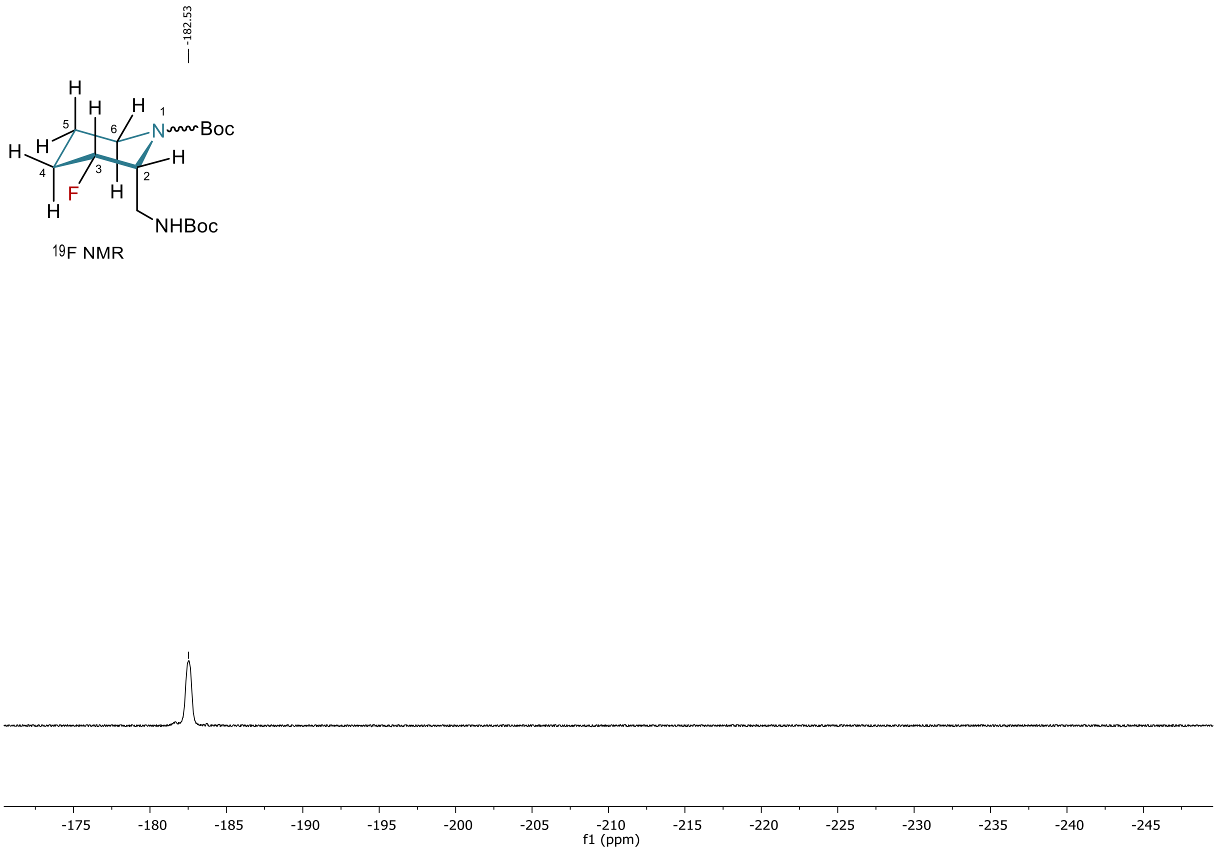

-203.39
-203.46
-203.53
-203.59
TBSO
F
H
N
Boc
1
2
3
4
5
6
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

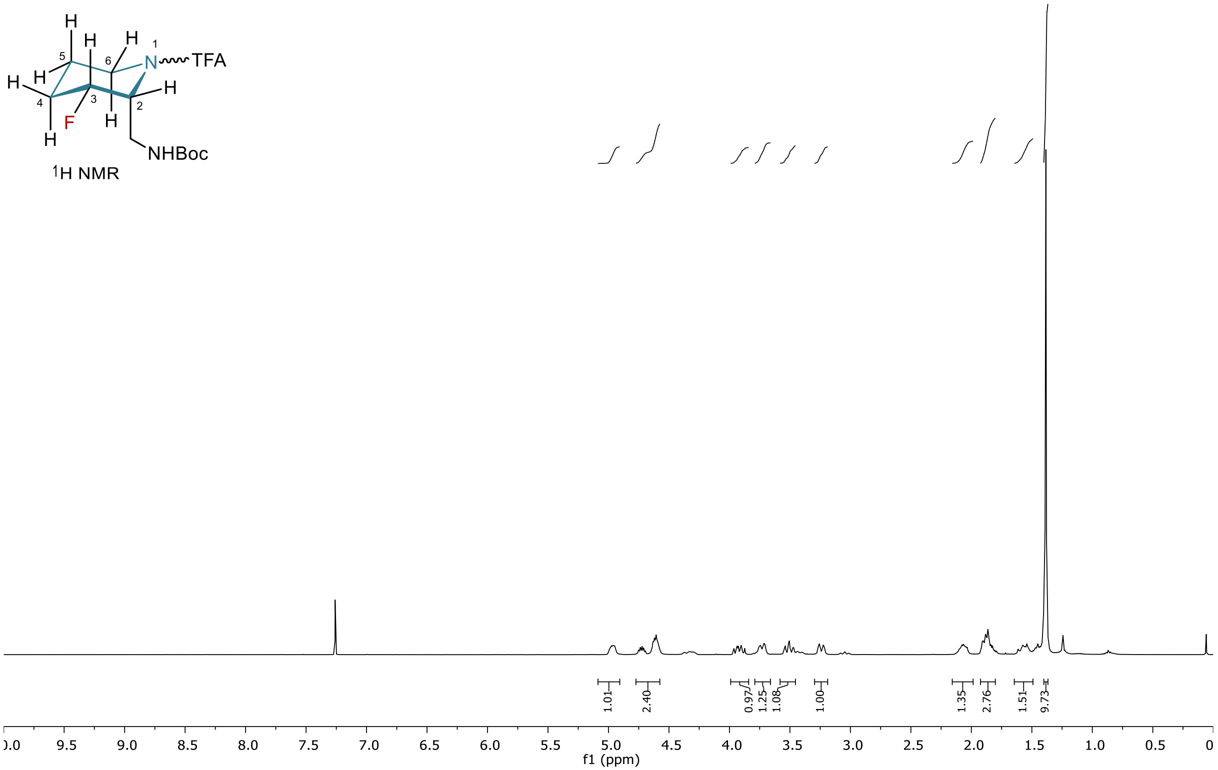

-203.49
TBSO
F
H
N
Boc
1
2
3
4
5
6
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

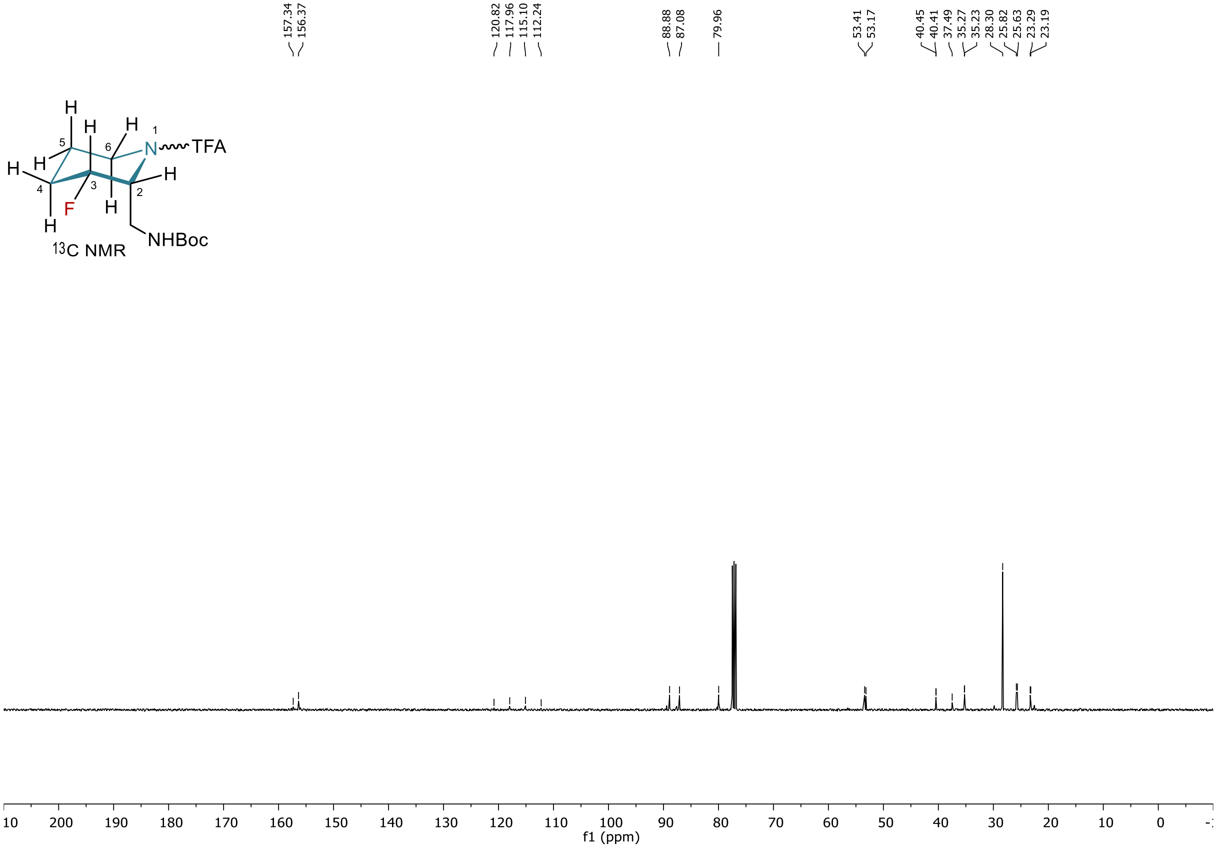

19.85
H
F
H
1
5
6
H
N
Boc
TBSO
H
4
3
2
H
H
H
H
^{29}Si NMR
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
f1 (ppm)

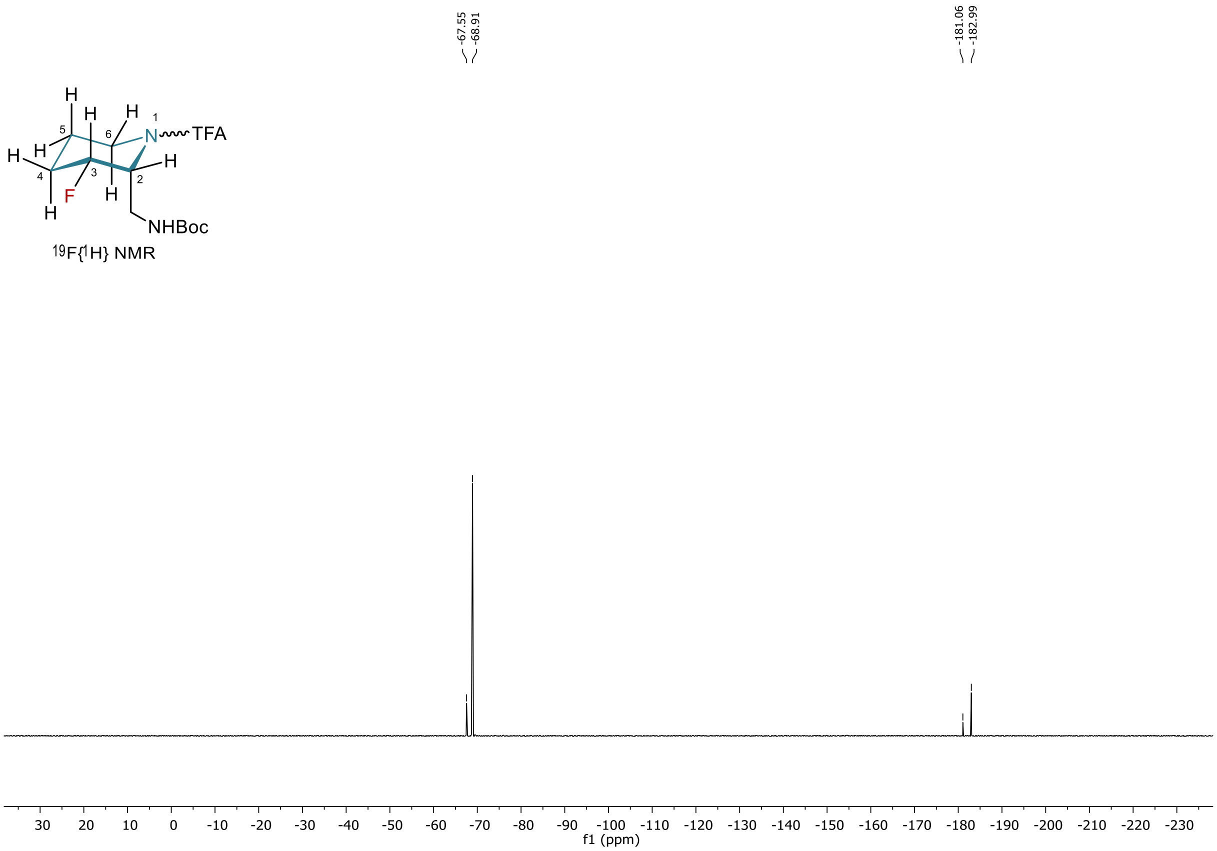

H
H
H
5
6
1
N
Boc
H
H
4
3
2
H
F
H
H
NHBoc
1H NMR
2.77
2.00
1.08
1.01
0.67
1.31
1.78
9.77
9.00
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

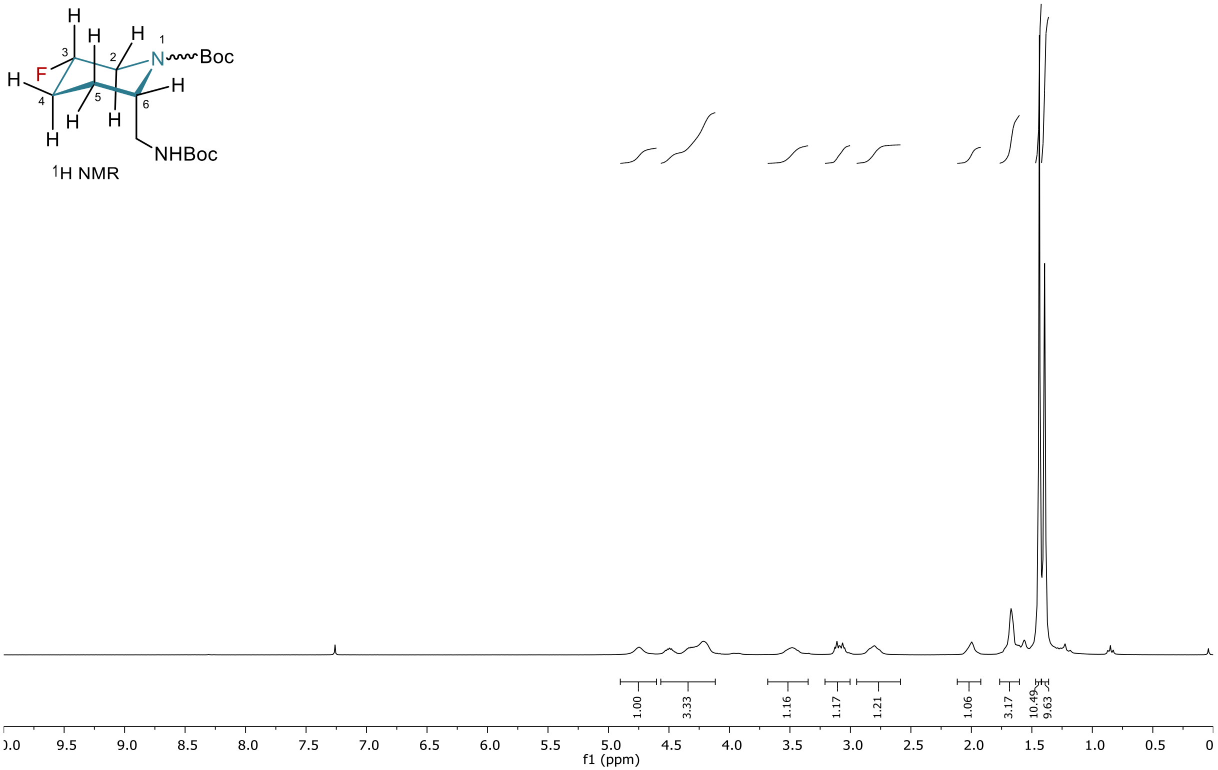

156.12
155.67
88.97
80.48
79.74
50.16
40.44
37.71
28.50
28.48
25.84
23.29
H
H
H
5
6
1
N
Boc
H
H
4
3
2
H
F
H
H
NHBoc
13C{19F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-182.53
H
H
H
1
5
6
N
Boc
H
H
H
4
3
2
F
H
H
NHBoc
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

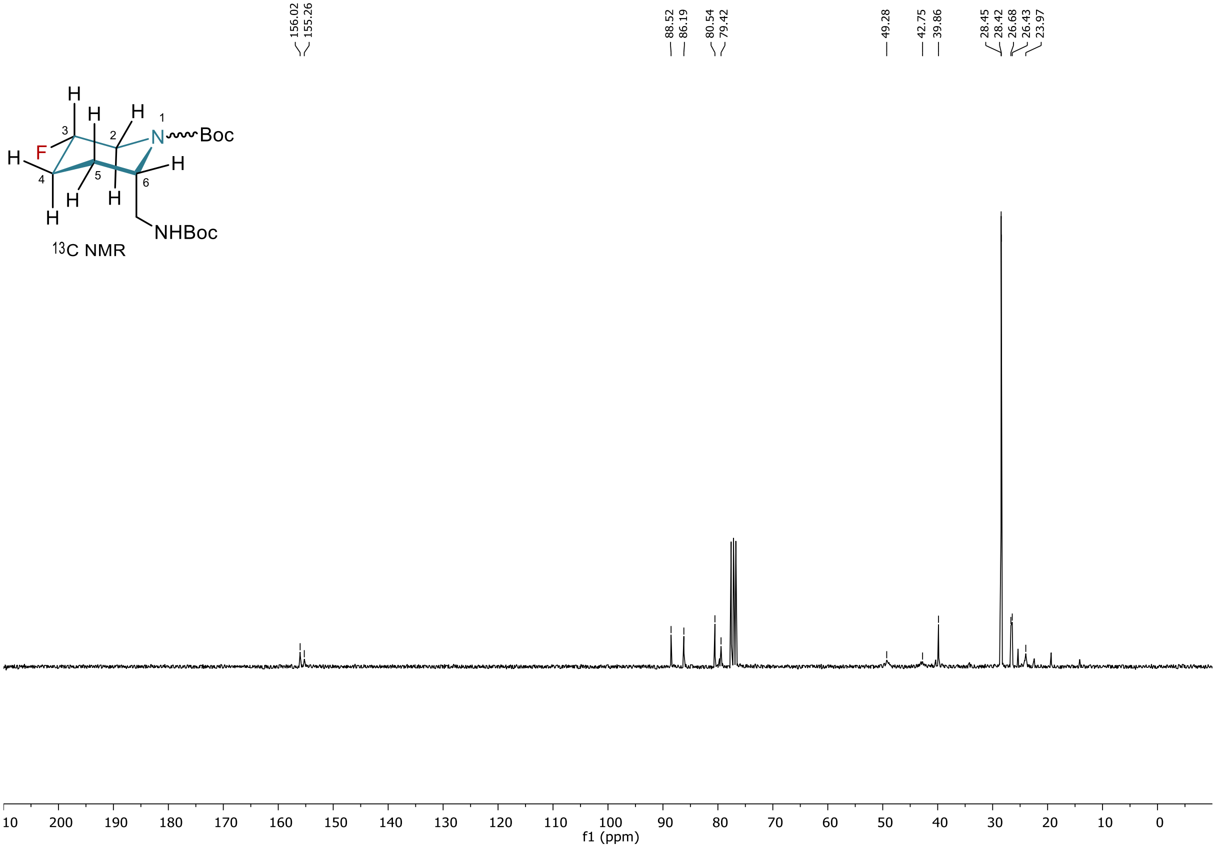

H
H
H
H
H
H
H
H
1
6
5
4
3
2
N
TFA
F
NHBoc
1H NMR
1.01
2.40
0.97
1.25
1.08
1.00
1.35
2.76
1.51
9.73
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


157.34
156.37
120.82
117.96
115.10
112.24
88.88
87.08
79.96
53.41
53.17
40.45
40.41
37.49
35.27
35.23
28.30
25.82
25.63
23.29
23.19
H
H
H
H
H
H
H
H
1
6
5
4
3
2
N
TFA
F
NHBoc
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

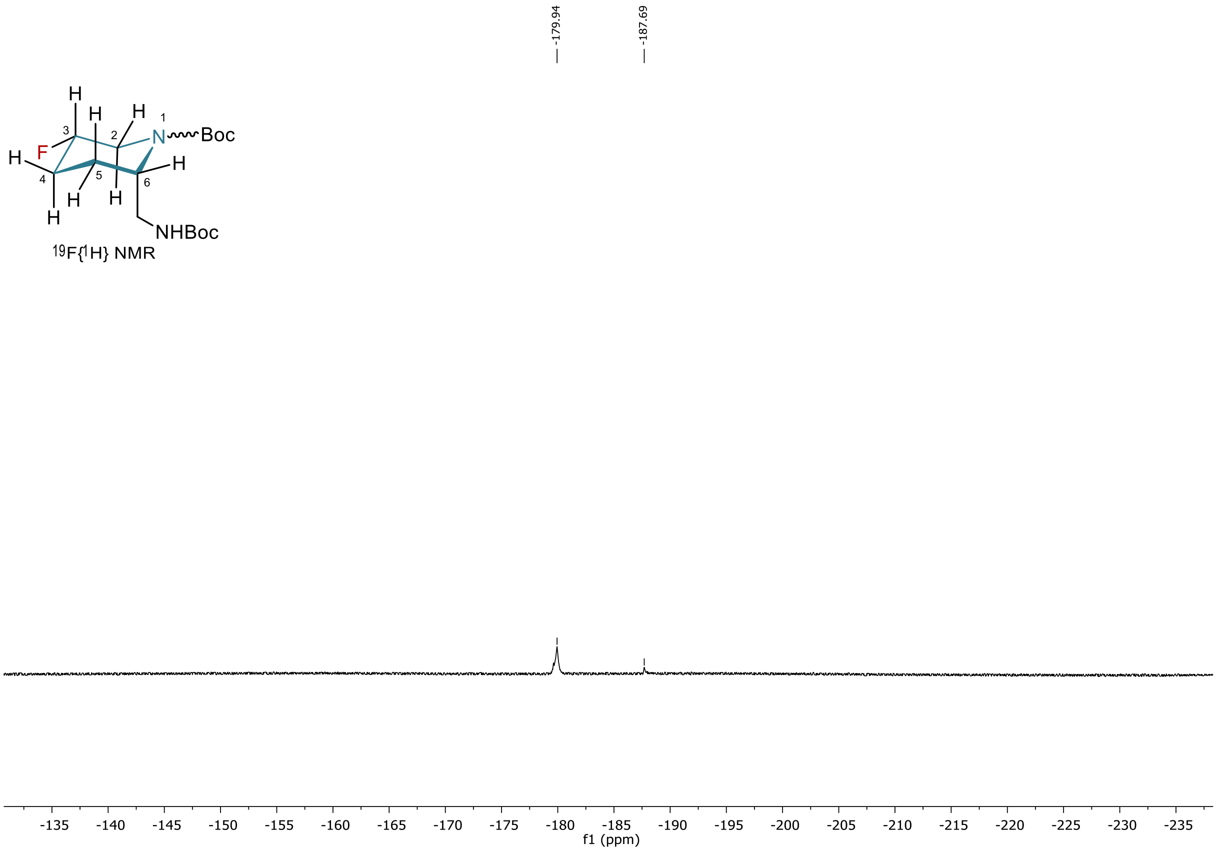

-67.55
-68.91
-181.06
-182.99
H
H
H
1
5
6
N
TFA
H
H
H
4
3
2
F
H
H
NHBoc
^{19}F{^{1}H} NMR
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)

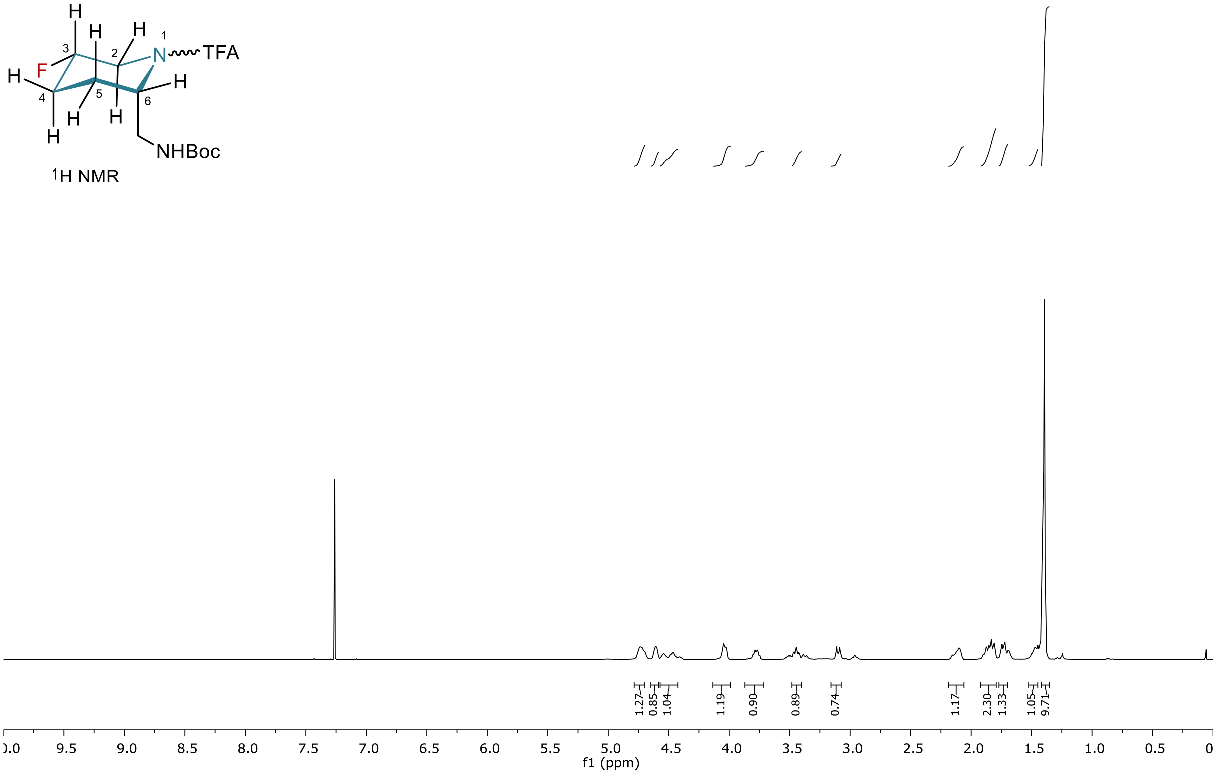


H
H
H
1
3
2
N
Boc
H
F
H
4
5
6
H
H
H
NHBoc
^{1}H NMR
1.00
3.33
1.16
1.17
1.21
1.06
3.17
10.49
9.63
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

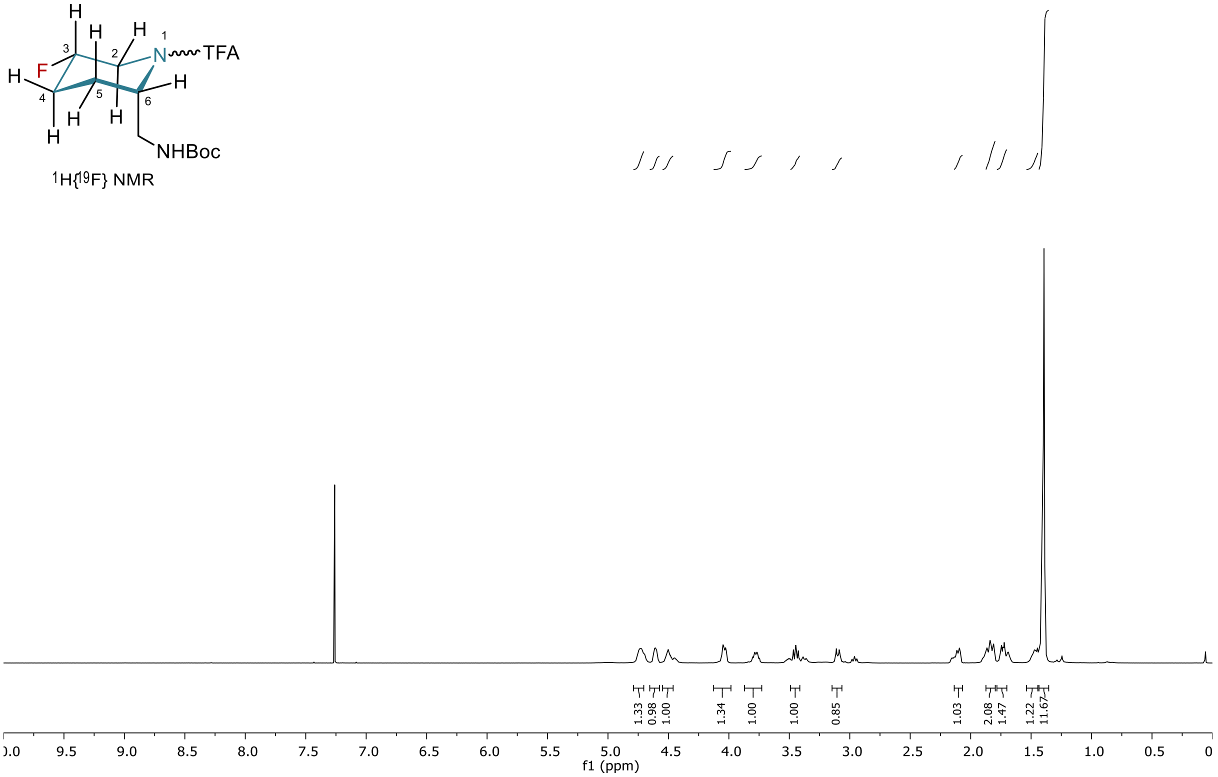


156.02
155.26
88.52
86.19
80.54
79.42
49.28
42.75
39.86
28.45
28.42
26.68
26.43
23.97
H
H
H
1
3
2
N
Boc
H
F
H
4
5
6
H
H
H
NHBoc
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

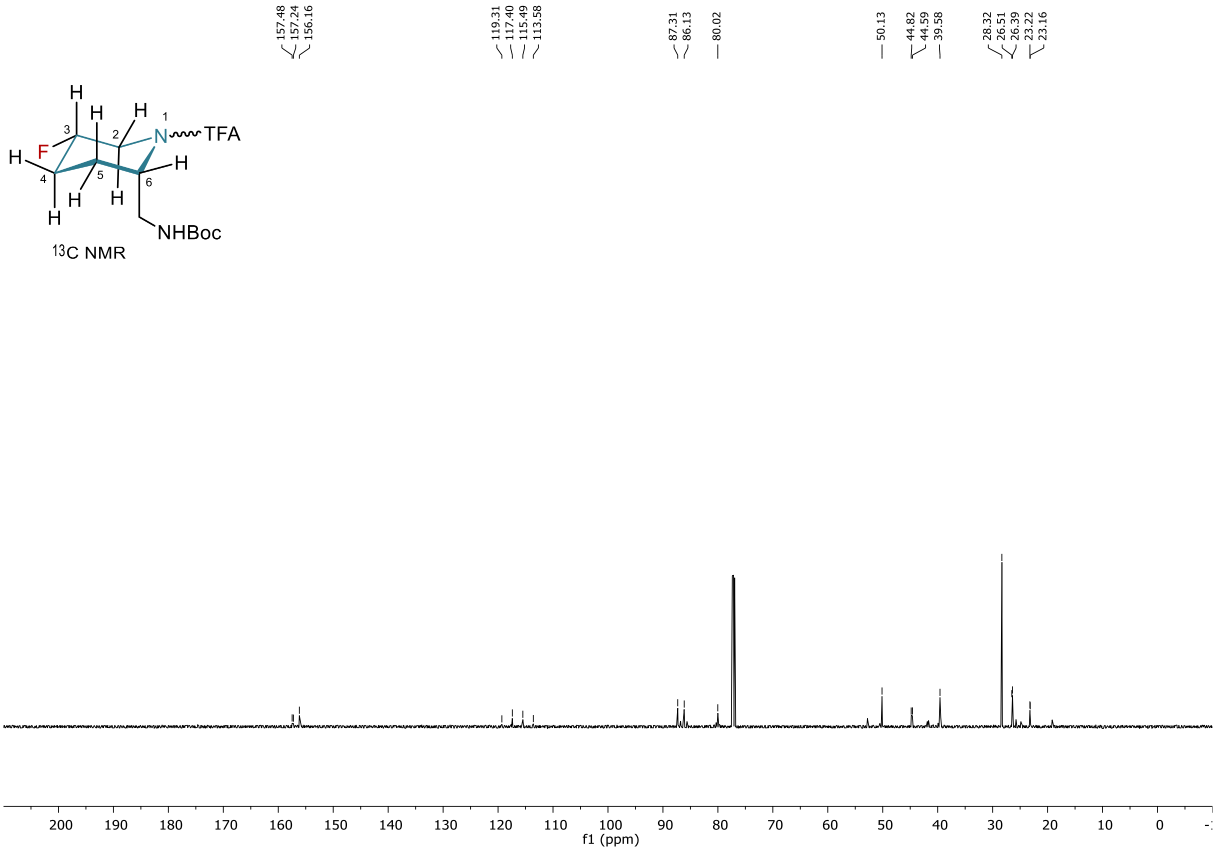

-179.94
-187.69
H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
NHBoc
^{19}F{^{1}H} NMR
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
f1 (ppm)

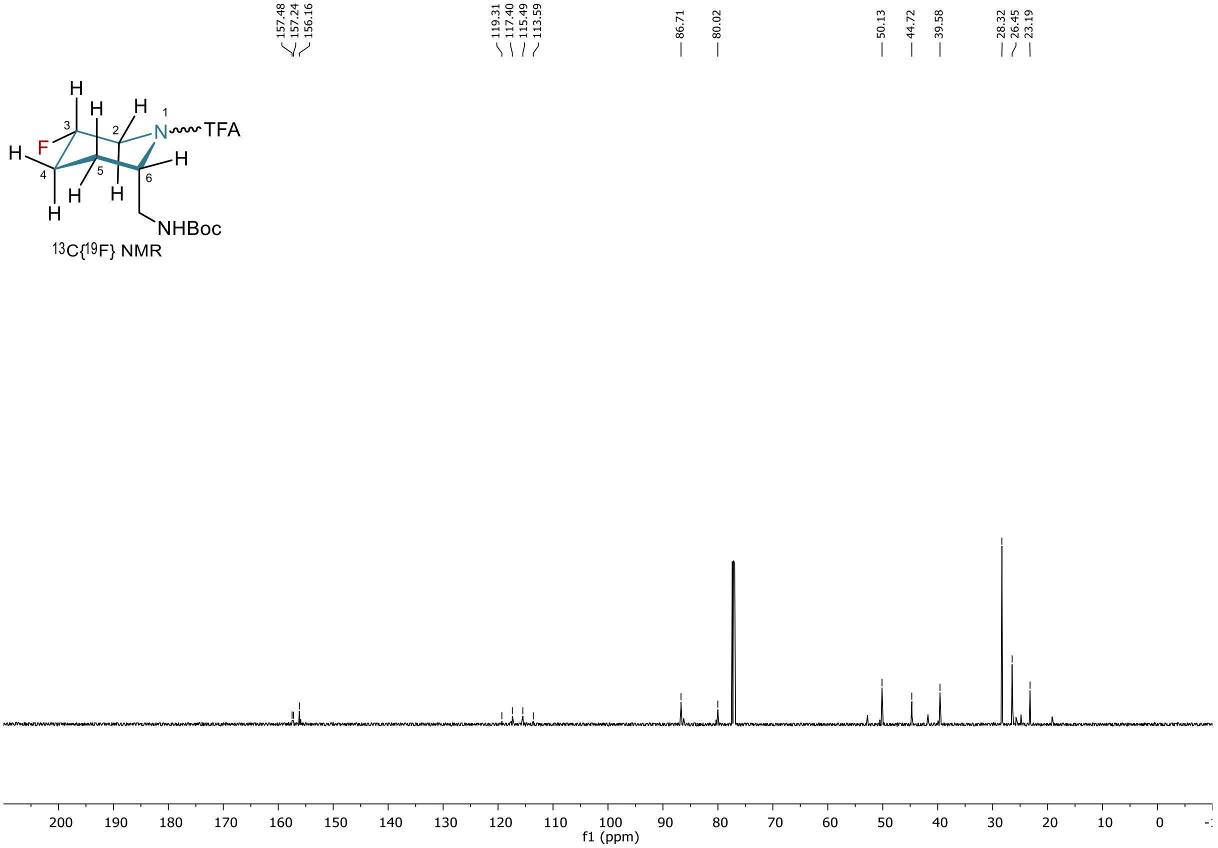


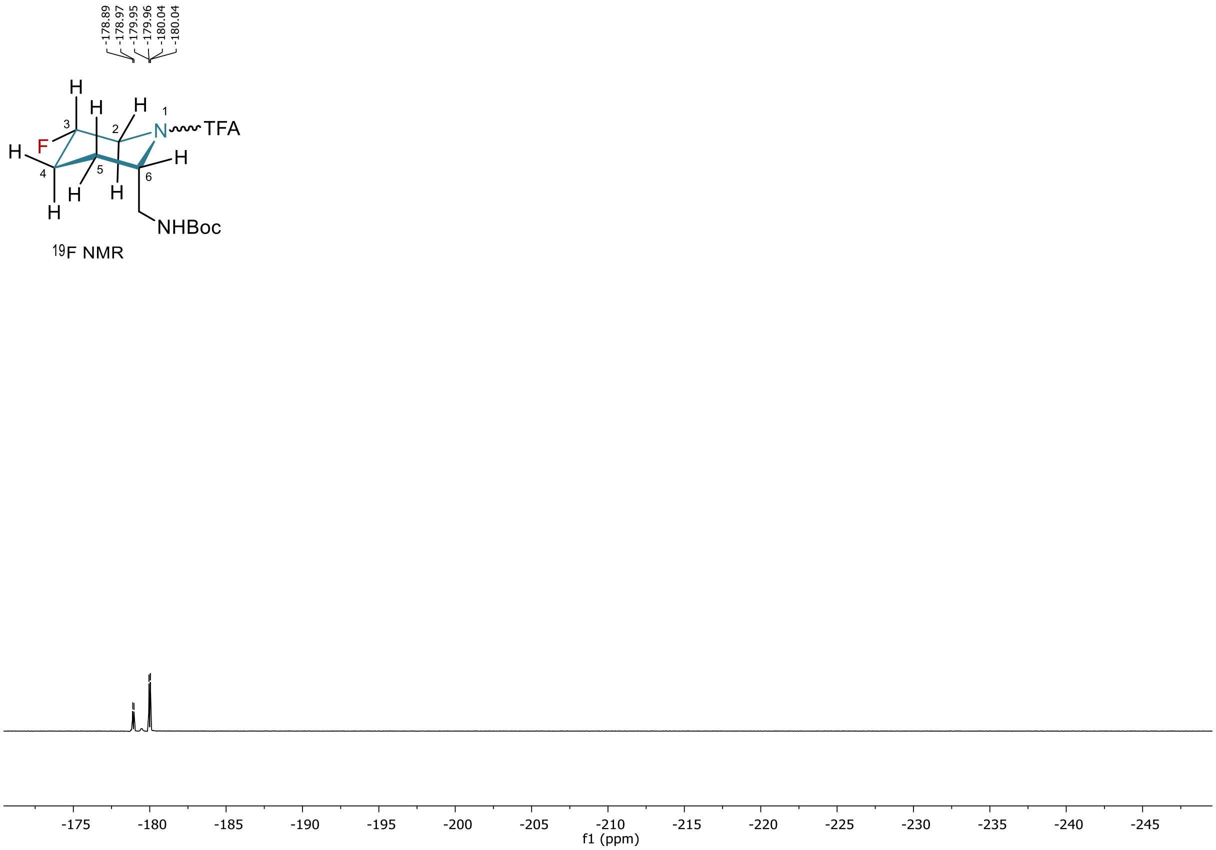
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
NHBoc
¹H NMR
1.27
0.85
1.04
1.19
0.90
0.89
0.74
1.17
2.30
1.33
1.05
9.71
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

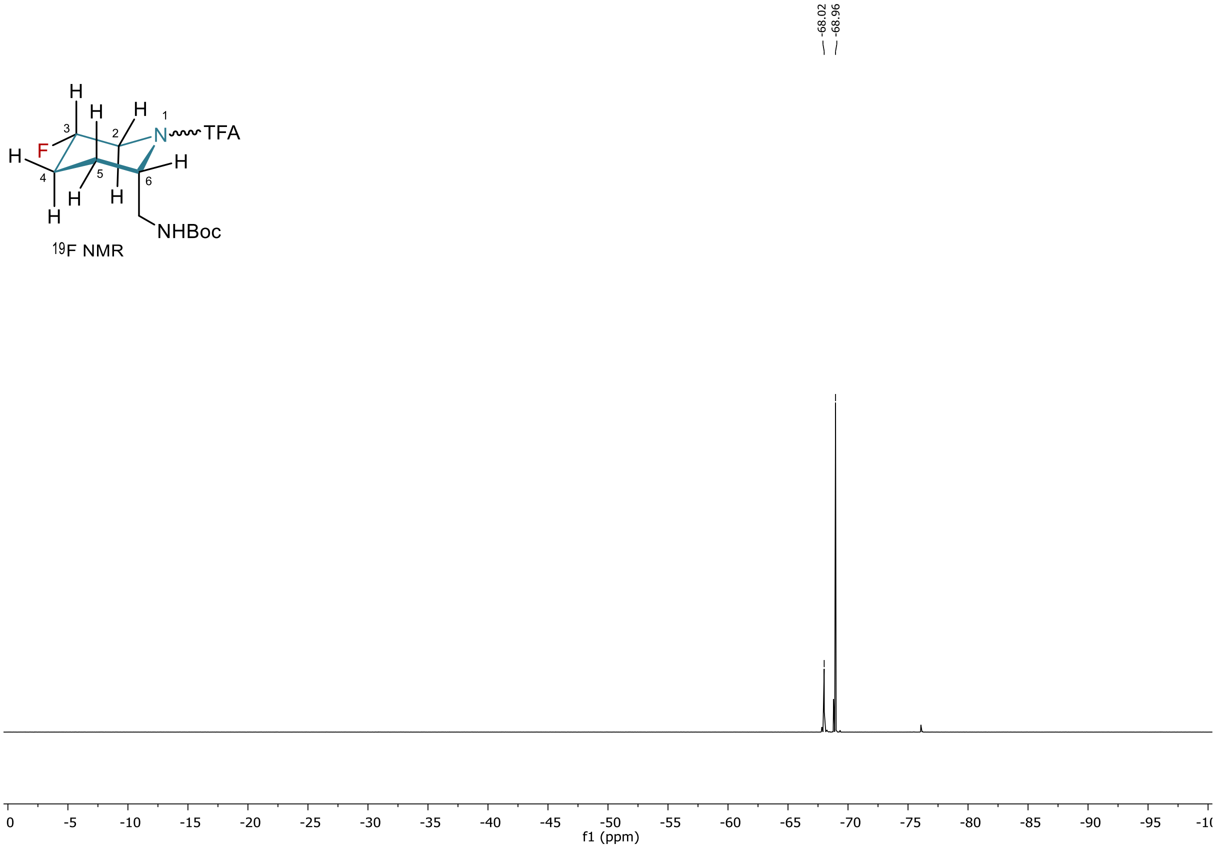


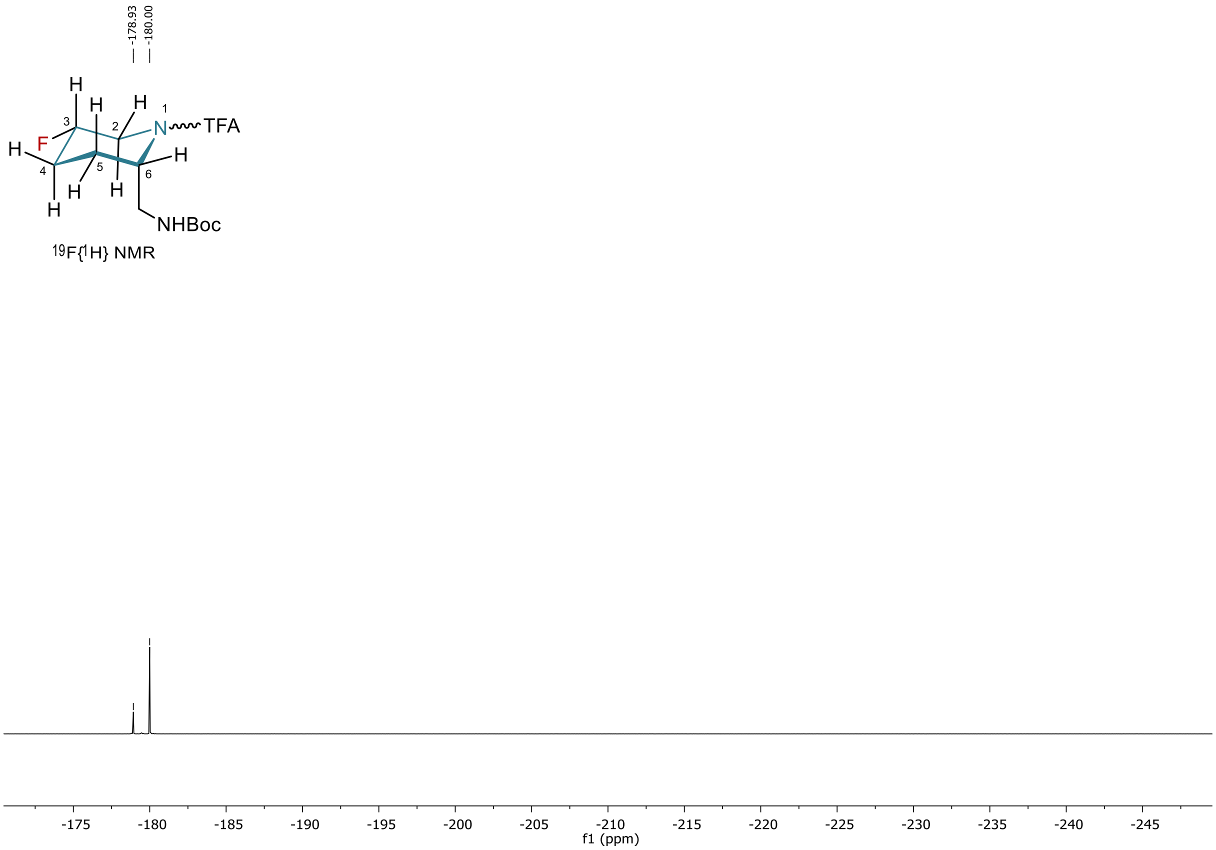
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
NHBoc
¹H{¹⁹F} NMR
1.33
0.98
1.00
1.34
1.00
1.00
0.85
1.03
2.08
1.47
1.22
11.67
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

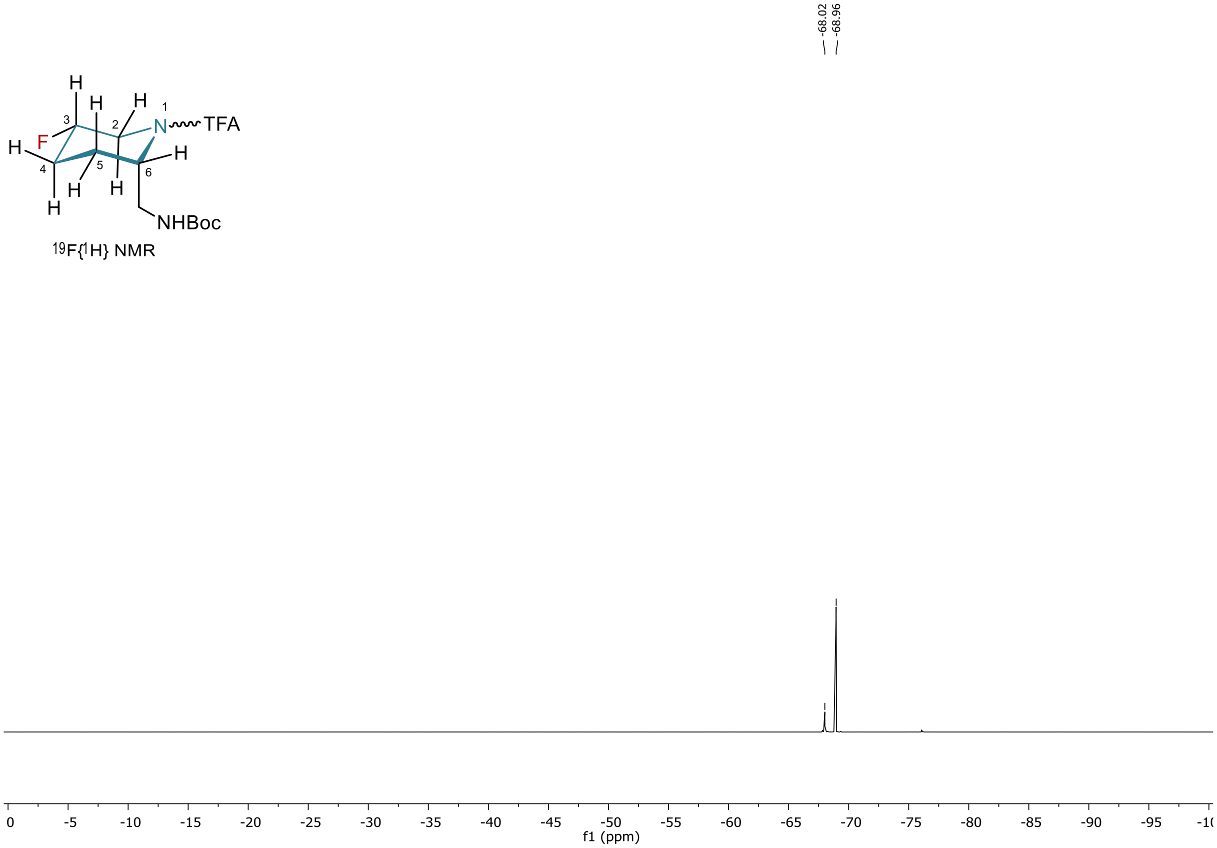

157.48
157.24
156.16
119.31
117.40
115.49
113.58
87.31
86.13
80.02
50.13
44.82
44.59
39.58
28.32
26.51
26.39
23.22
23.16
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
NHBoc
^{13}C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

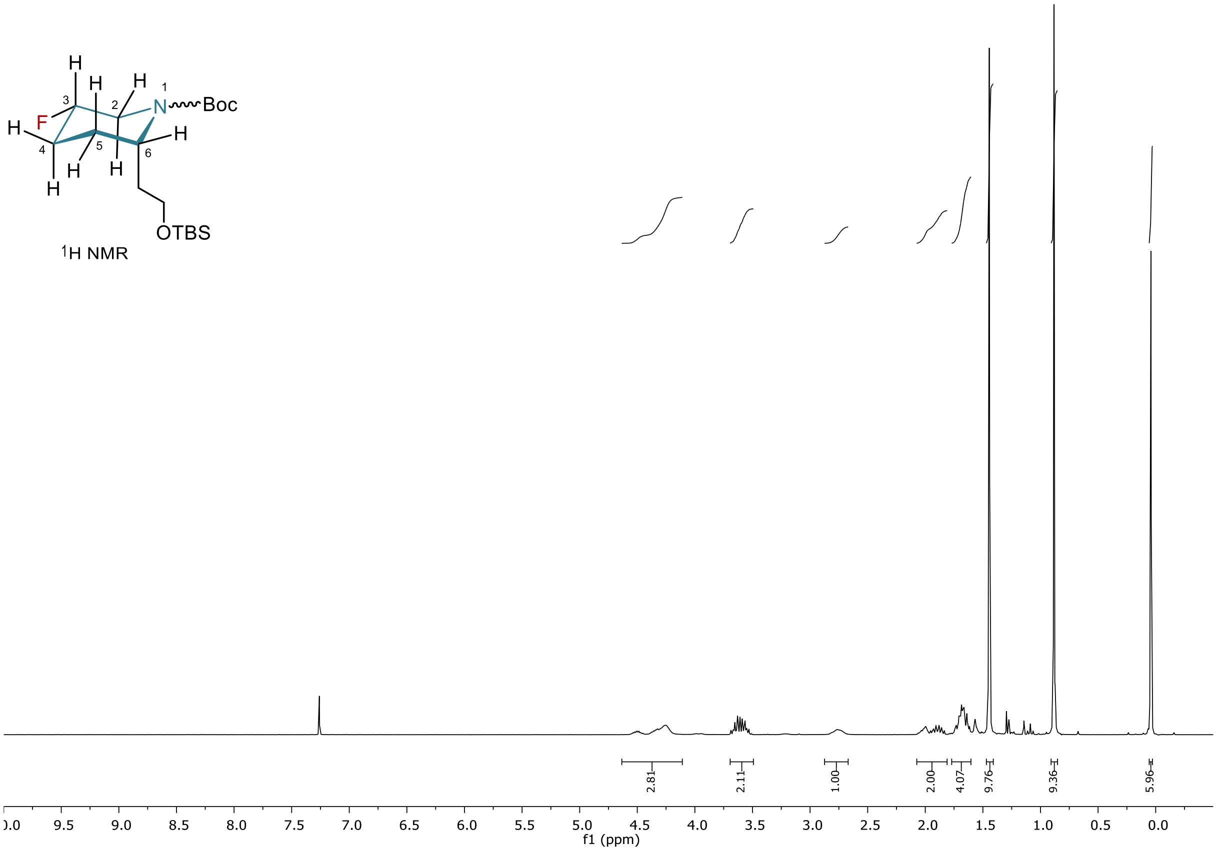

157.48
157.24
156.16
119.31
117.40
115.49
113.59
86.71
80.02
50.13
44.72
39.58
28.32
26.45
23.19
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
NHBoc
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

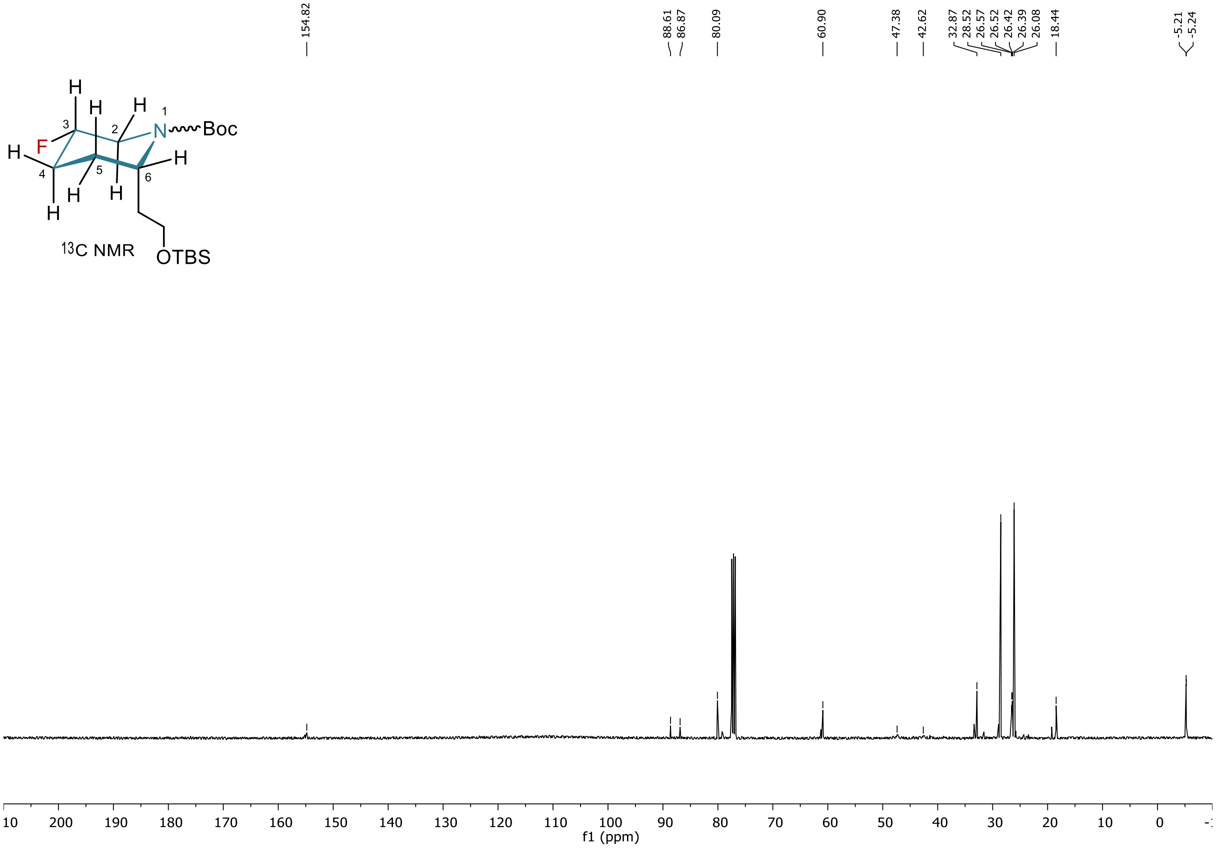

-178.89
-178.97
-179.95
-179.96
-180.04
-180.04
H
H
H
F
H
N
TFA
H
H
H
H
1
2
3
4
5
6
NHBoc
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

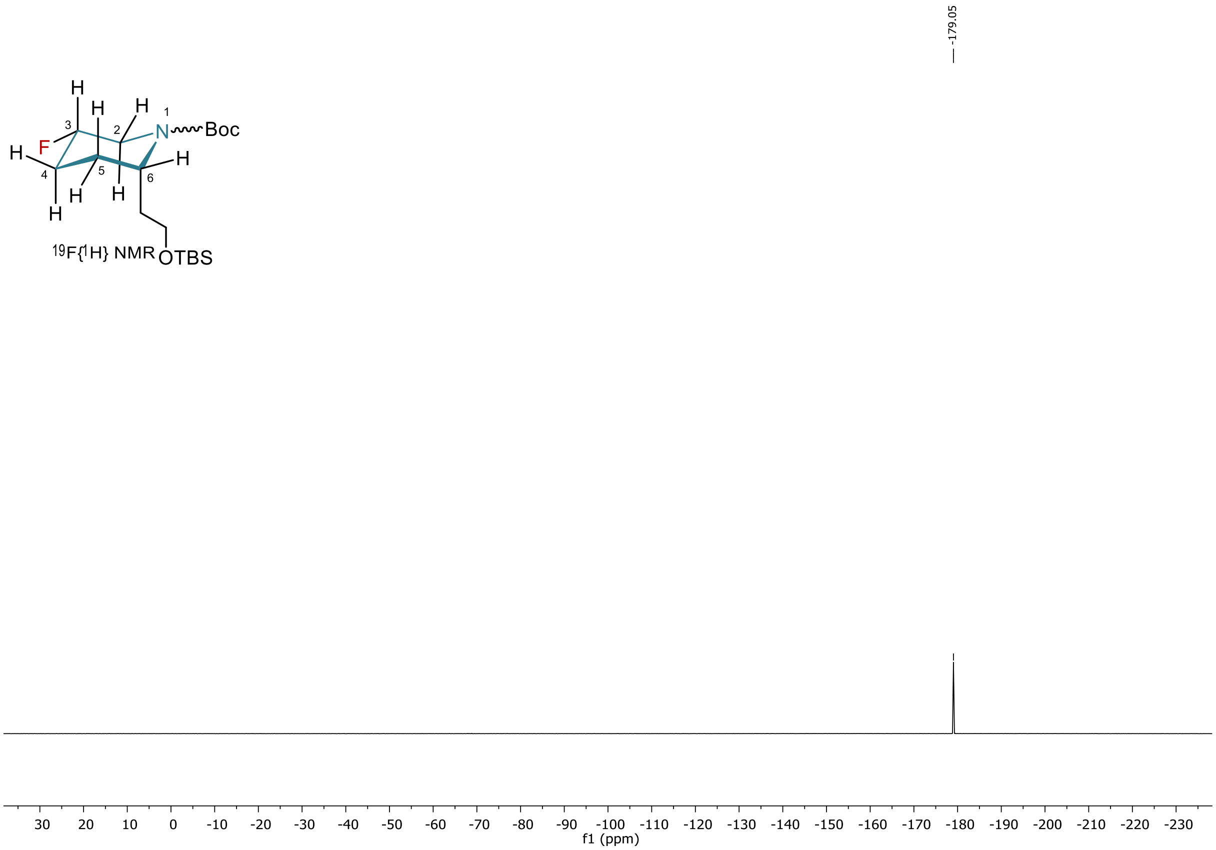

-68.02
-68.96
H
H
H
F
H
N
TFA
H
H
H
H
1
2
3
4
5
6
NHBoc
19F NMR
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
f1 (ppm)

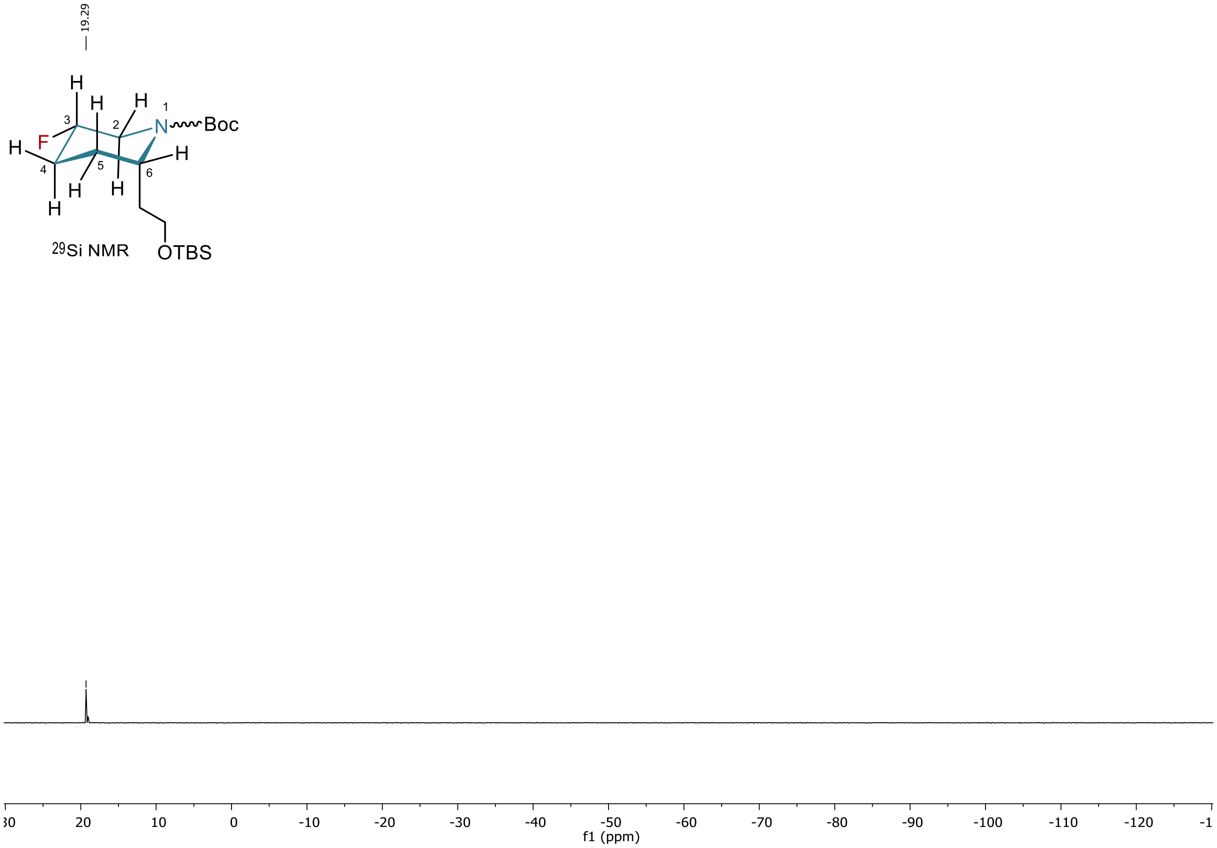

-178.93
-180.00
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
NHBoc
$^{19}F\{^1H\}$ NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

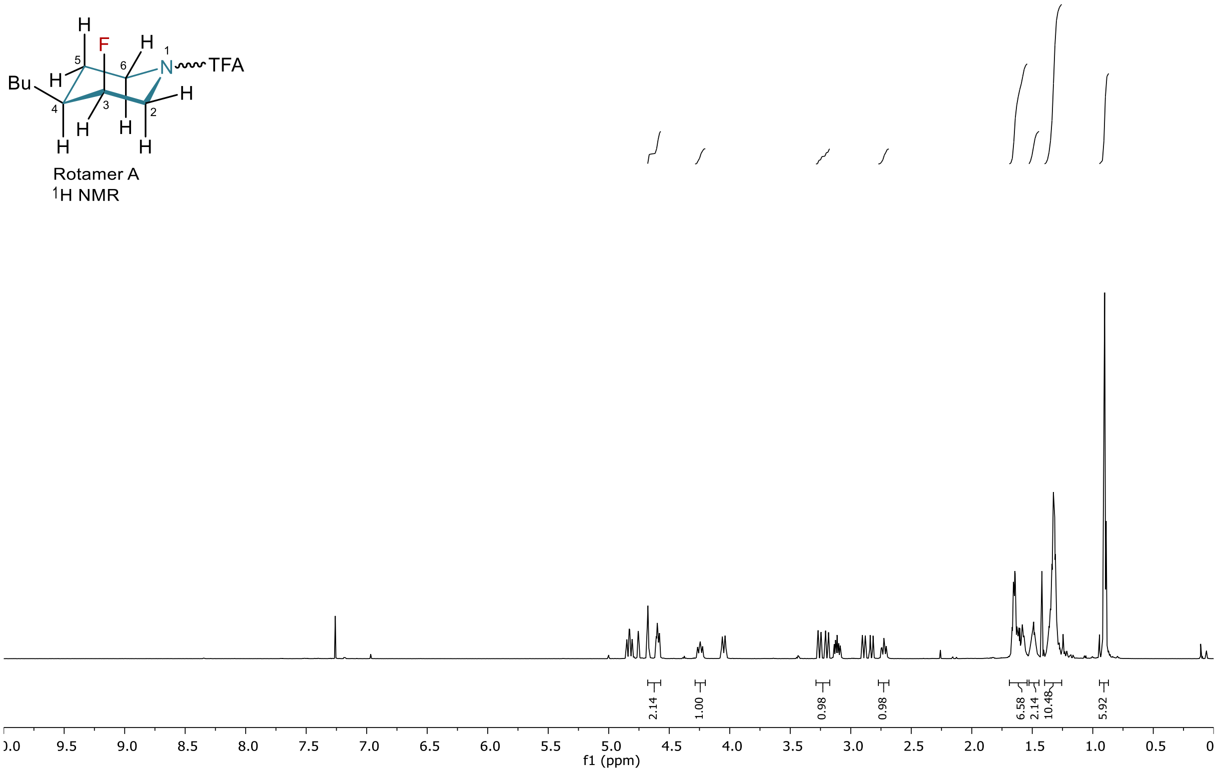

-68.02
-68.96
H
H
H
1
3
2
N
TFA
F
H
H
4
5
6
H
H
H
NHBoc
$^{19}F\{^1H\}$ NMR
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-10
f1 (ppm)


H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
OTBS
1H NMR
2.81
2.11
1.00
2.00
4.07
9.76
9.36
5.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

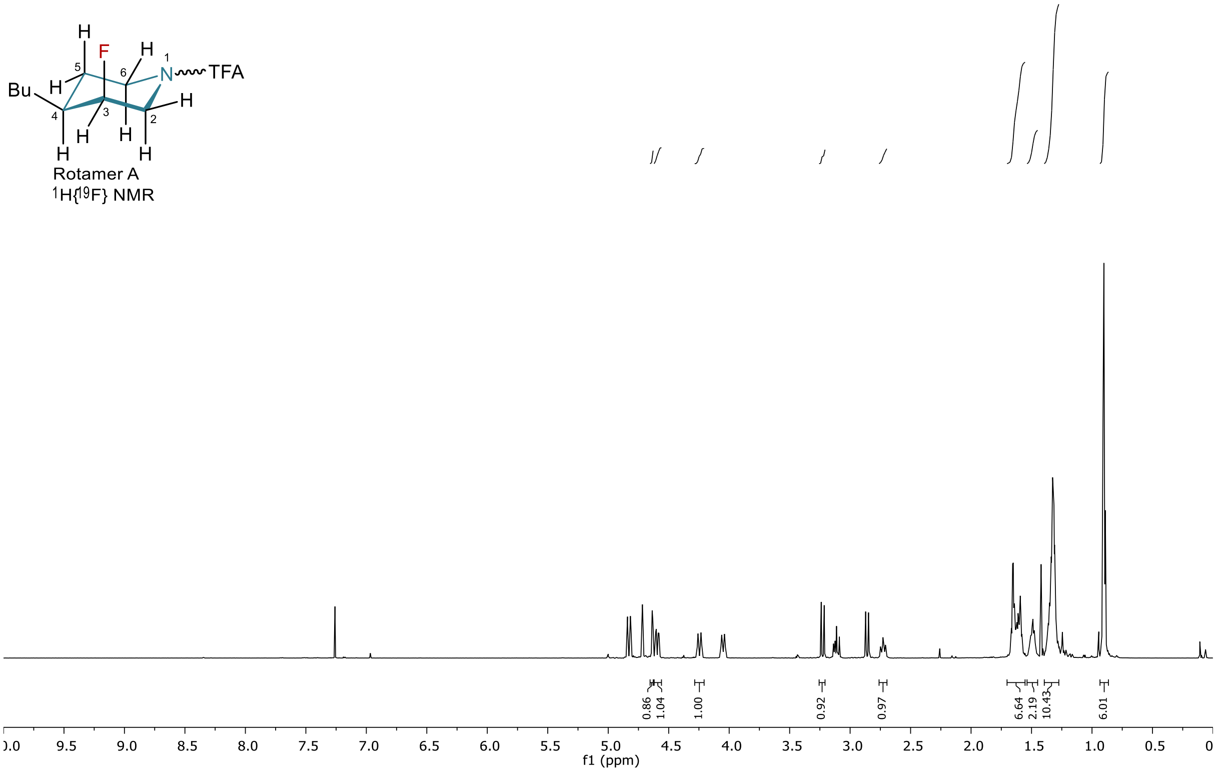

154.82
88.61
86.87
80.09
60.90
47.38
42.62
32.87
28.52
26.57
26.52
26.42
26.39
26.08
18.44
-5.21
-5.24
H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
13C NMR
OTBS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-179.05
H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
19F{1H} NMR
OTBS
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)

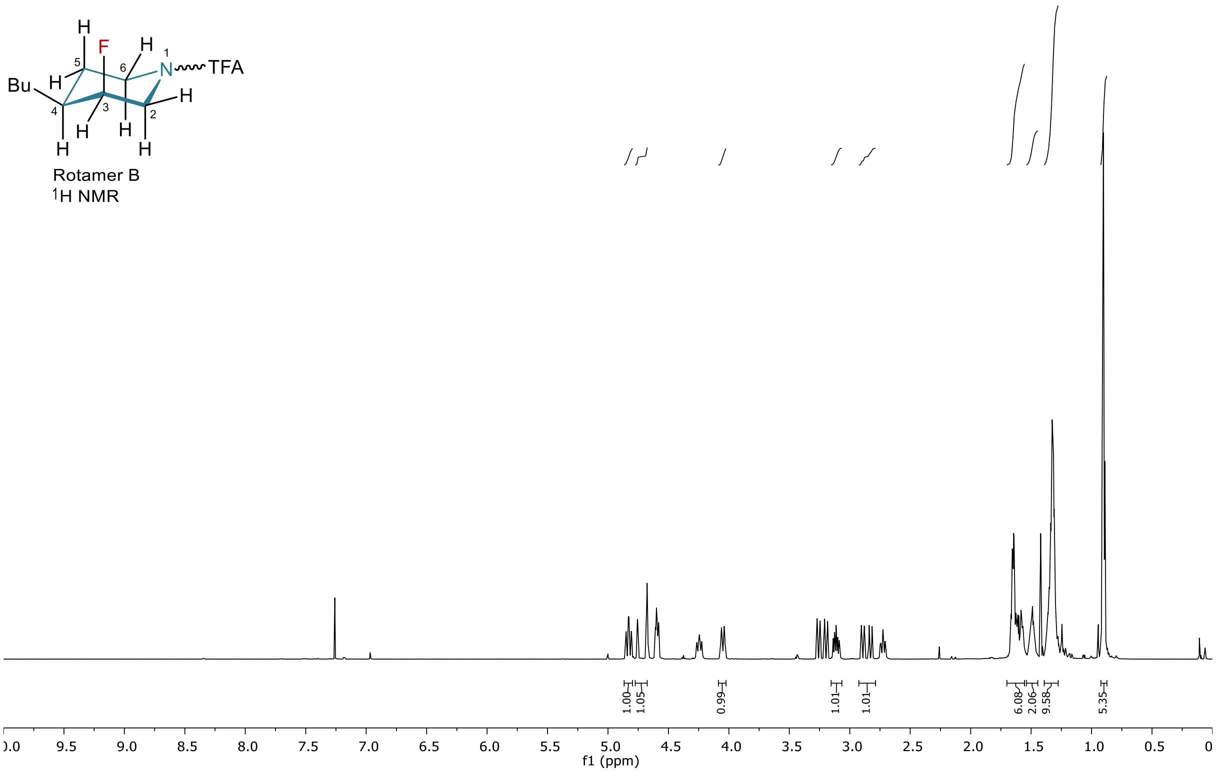

19.29
H
H
H
1
3
2
N
Boc
F
H
H
4
5
6
H
H
H
29Si NMR
OTBS
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
f1 (ppm)

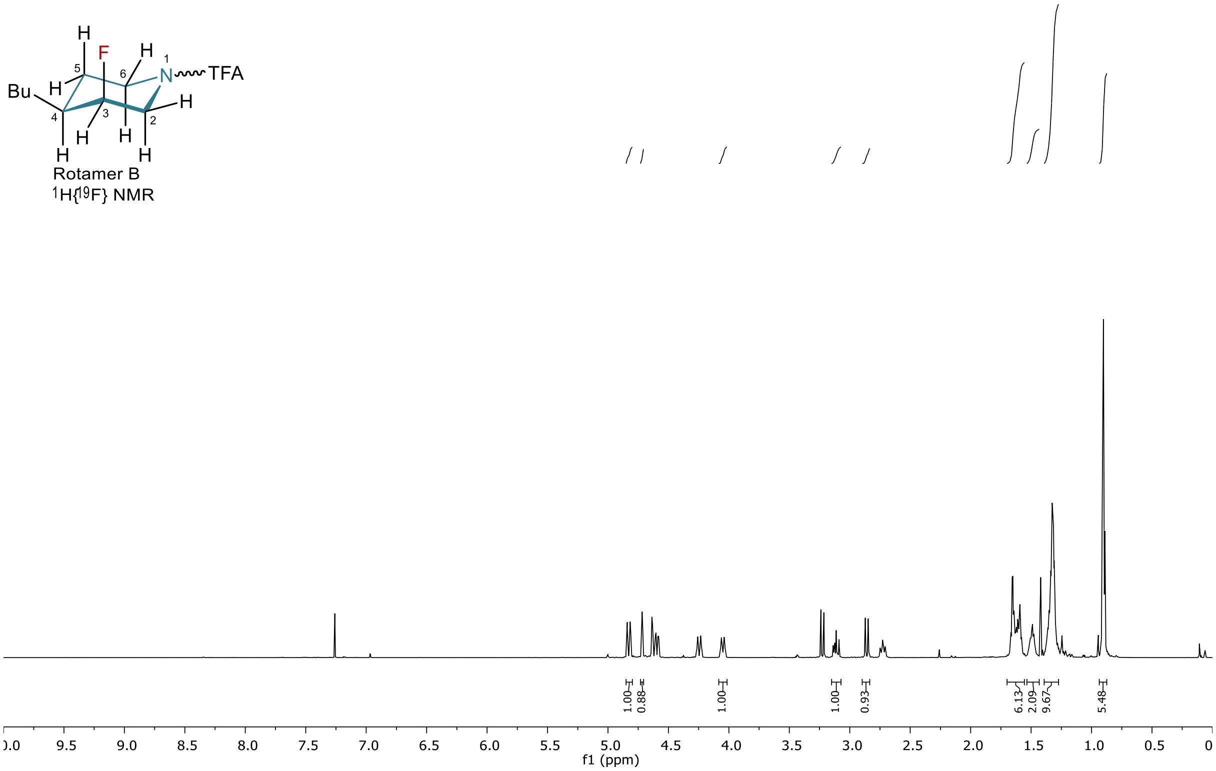


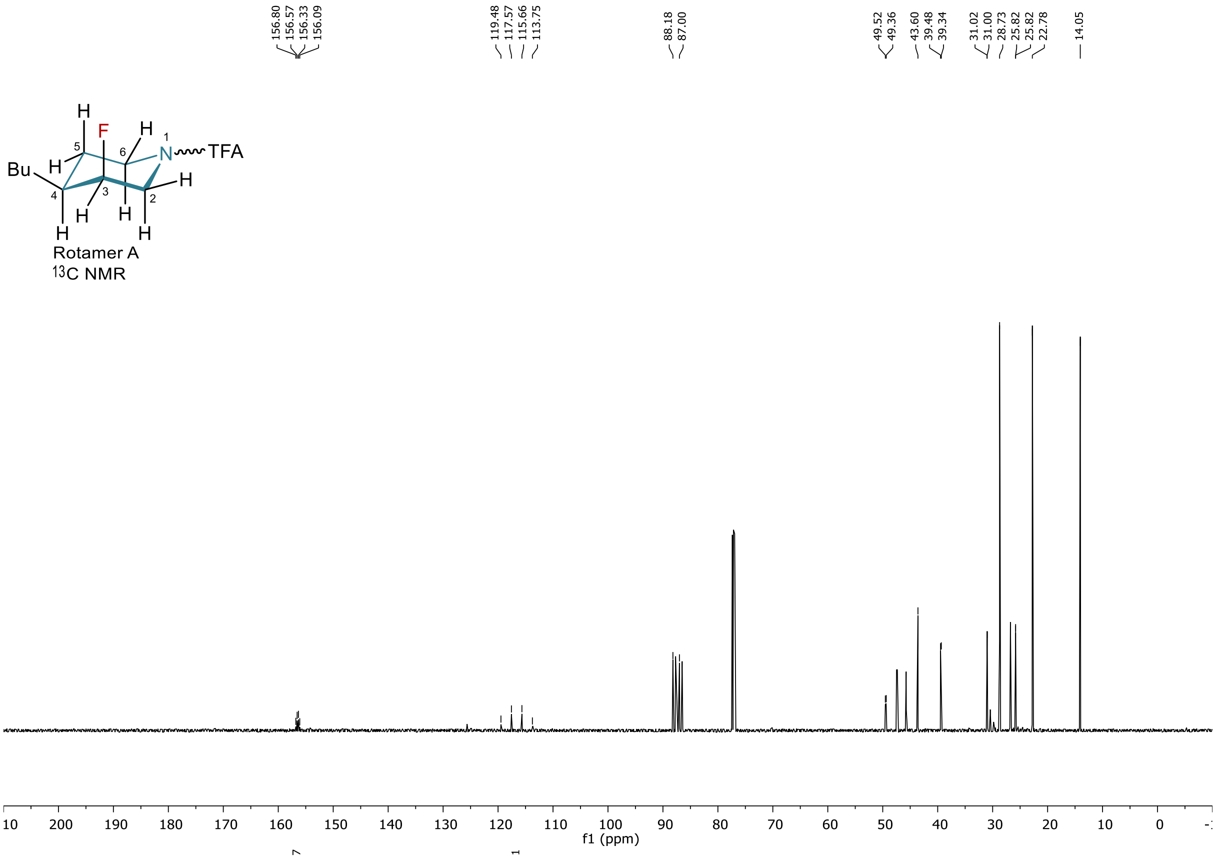
Bu
H
F
H
1
N
TFA
H
5
6
4
3
2
Rotamer A
^{1}H NMR
2.14
1.00
0.98
0.98
6.58
2.14
10.48
5.92
f1 (ppm)



Bu
H
F
H
1
N
TFA
H
5
6
4
3
2
Rotamer A
^{1}H{^{19}F} NMR
0.86
1.04
1.00
0.92
0.97
6.64
2.19
10.43
6.01
f1 (ppm)


H
F
H
1
5
6
N
TFA
Bu
H
H
4
3
2
H
H
H
H
Rotamer B
^{1}H NMR
1.00
1.05
0.99
1.01
1.01
6.08
2.06
9.58
5.35
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


H
F
H
1
5
6
N
TFA
Bu
H
H
4
3
2
H
H
H
H
Rotamer B
^{1}H{^{19}F} NMR
1.00
0.88
1.00
1.00
0.93
6.13
2.09
9.67
5.48
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


156.80
156.57
156.33
156.09
119.48
117.57
115.66
113.75
88.18
87.00
49.52
49.36
43.60
39.48
39.34
31.02
31.00
28.73
25.82
25.82
22.78
14.05
H
F
H
1
5
6
N
TFA
Bu
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C NMR
10
200
190
180
170
160
150
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130
120
110
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90
80
70
60
50
40
30
20
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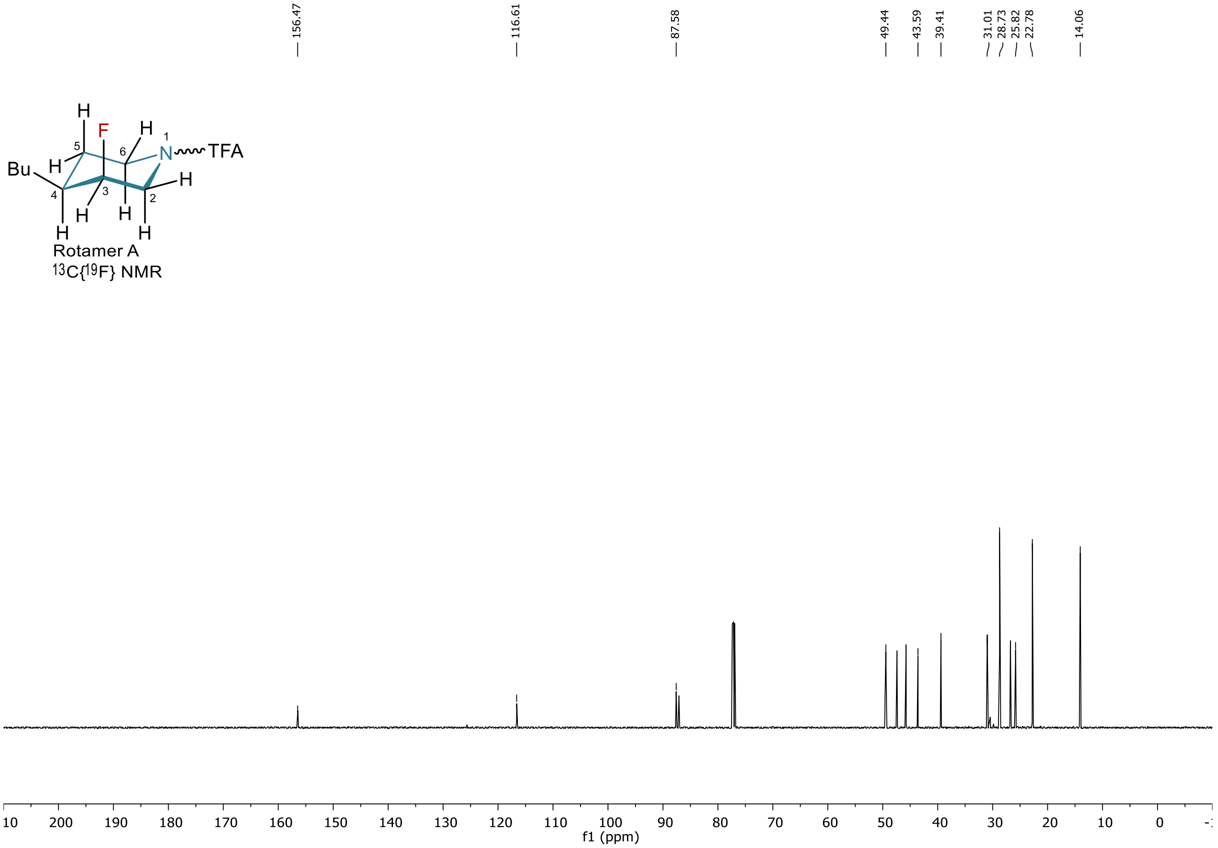
f1 (ppm)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87.58
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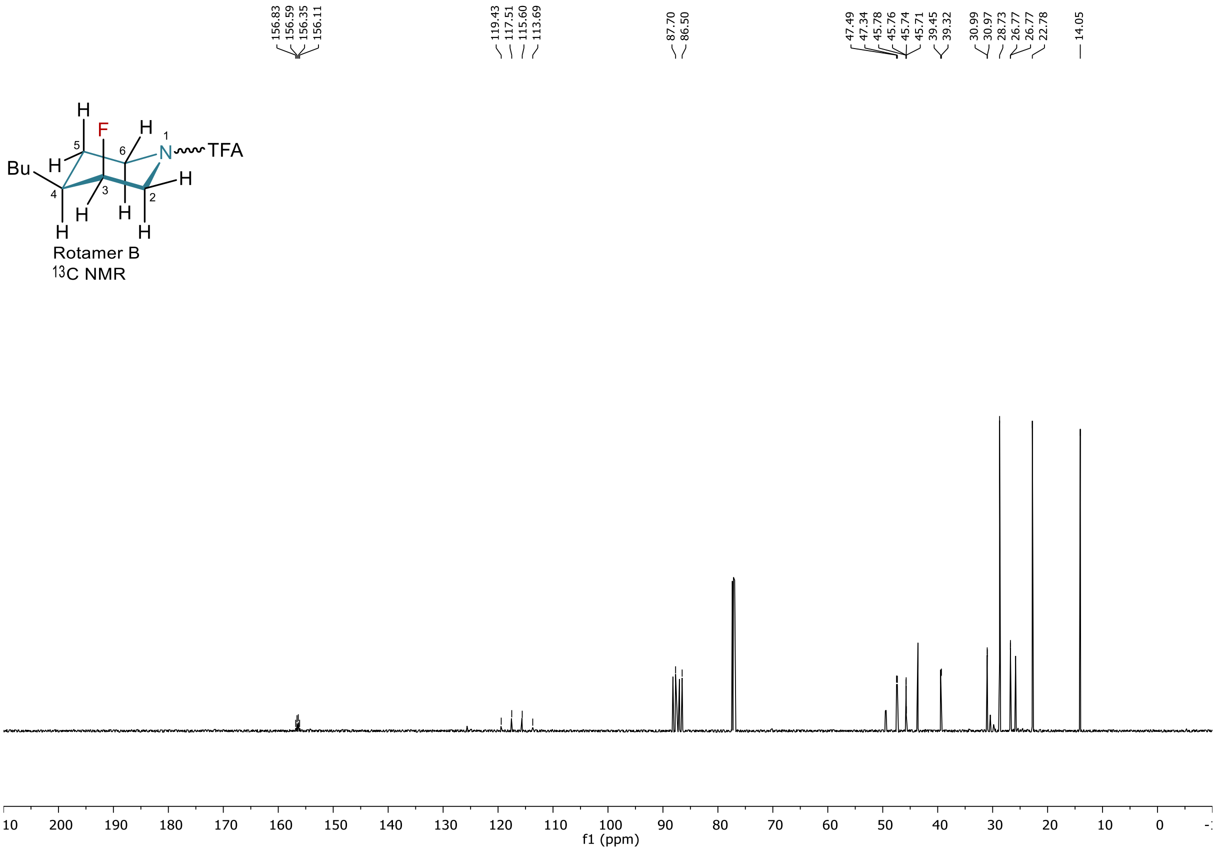
43.59
39.41
31.01
28.73
25.82
22.78
14.06
H
F
H
1
5
6
N
TFA
Bu
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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156.35
156.11
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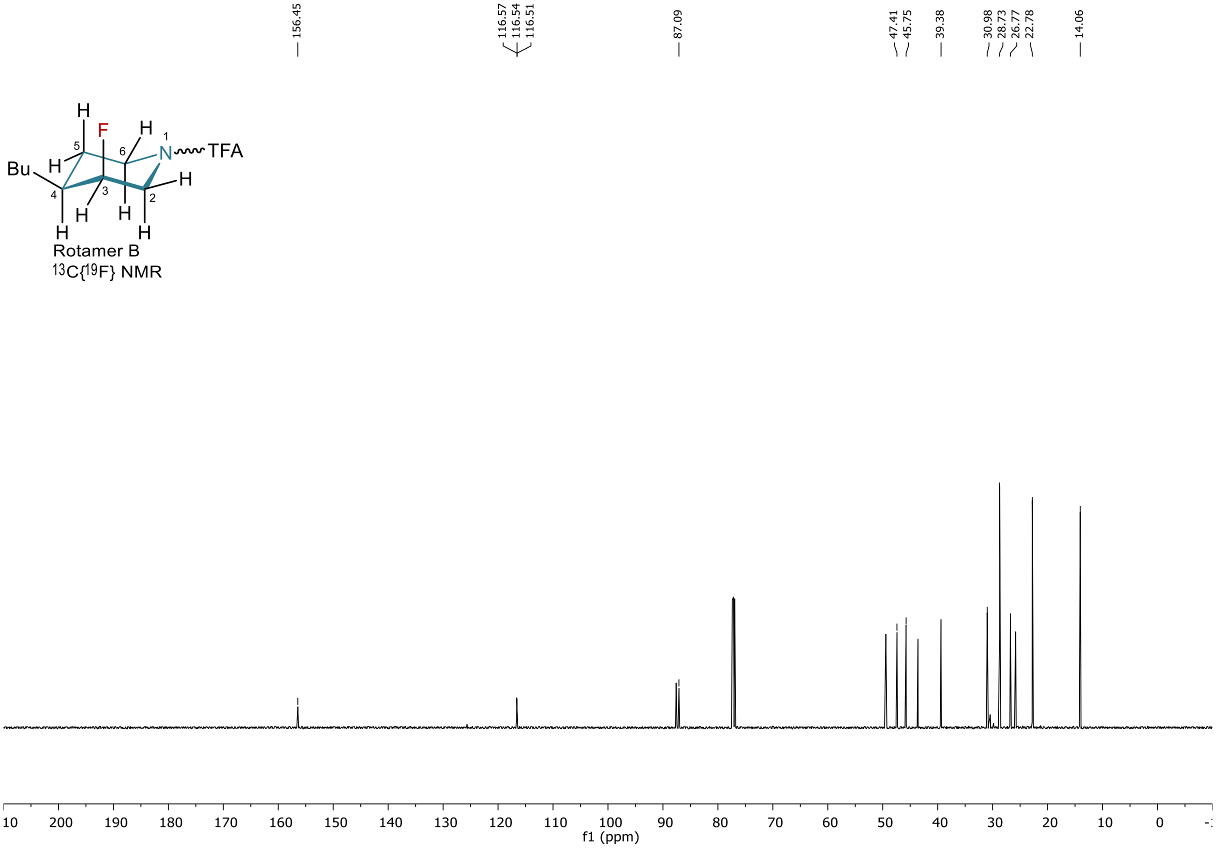
117.51
115.60
113.69
87.70
86.50
47.49
47.34
45.78
45.76
45.74
45.71
39.45
39.32
30.99
30.97
28.73
26.77
26.77
22.78
14.05
H
F
H
1
N
TFA
5
6
Bu
H
H
4
3
2
H
H
H
H
Rotamer B
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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39.38
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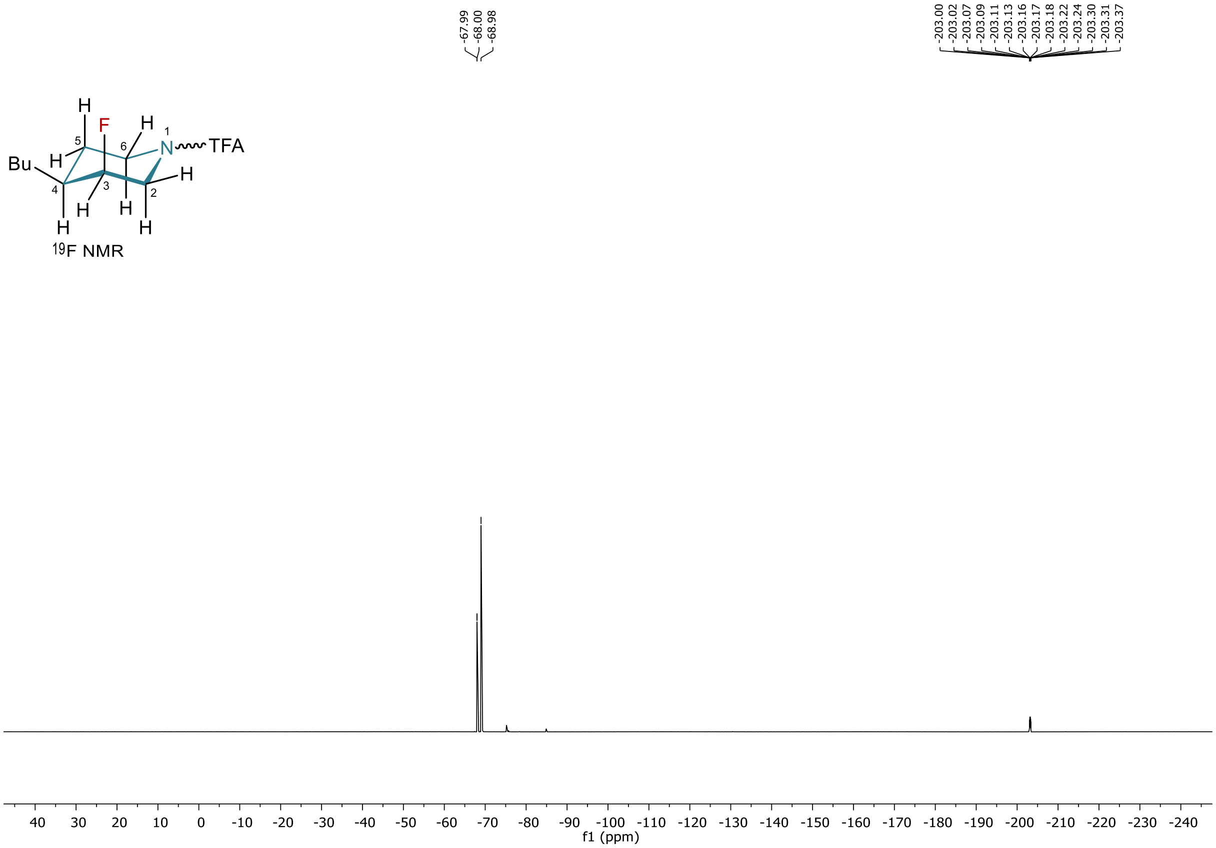
28.73
26.77
22.78
14.06
H
F
H
1
N
TFA
5
6
Bu
H
H
4
3
2
H
H
H
H
Rotamer B
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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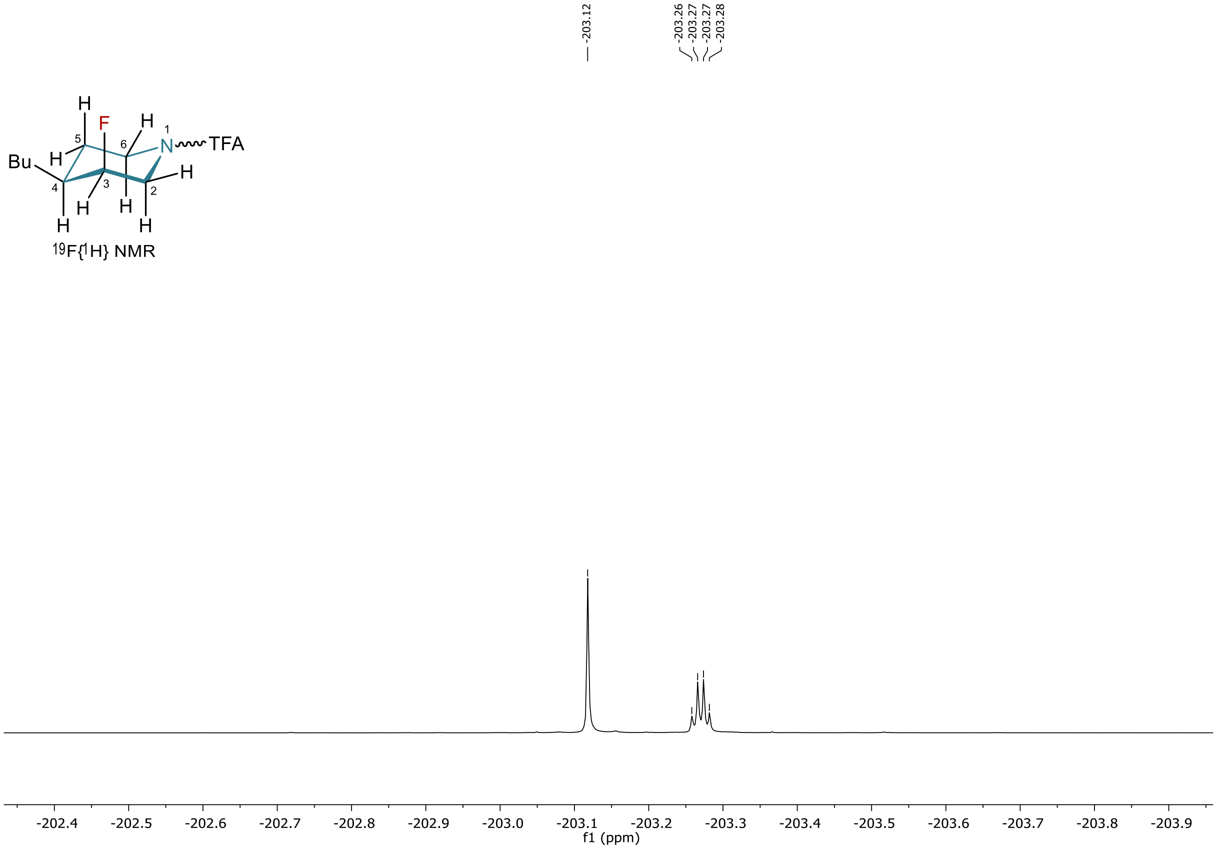
-68.00
-68.98
-203.00
-203.02
-203.07
-203.09
-203.11
-203.13
-203.16
-203.17
-203.18
-203.22
-203.24
-203.30
-203.31
-203.37
H
F
H
1
5
6
N
TFA
H
Bu
H
3
4
2
H
H
H
H
19F NMR
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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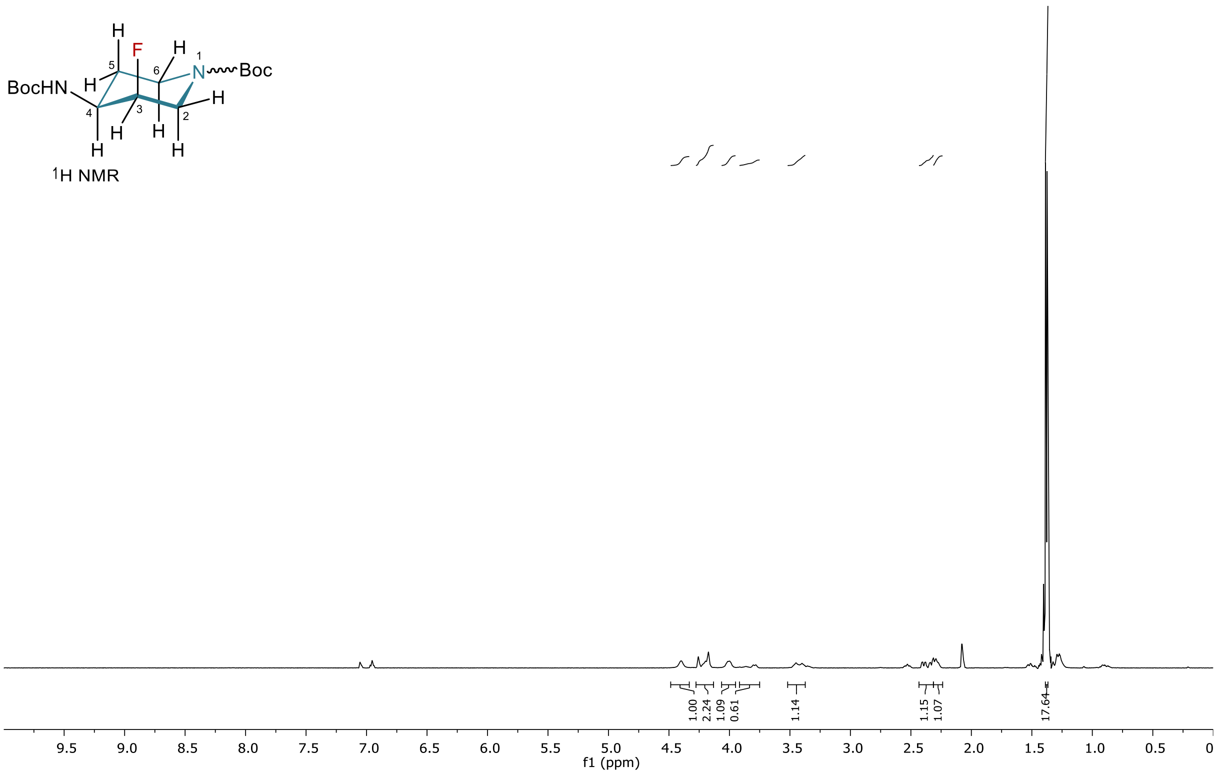
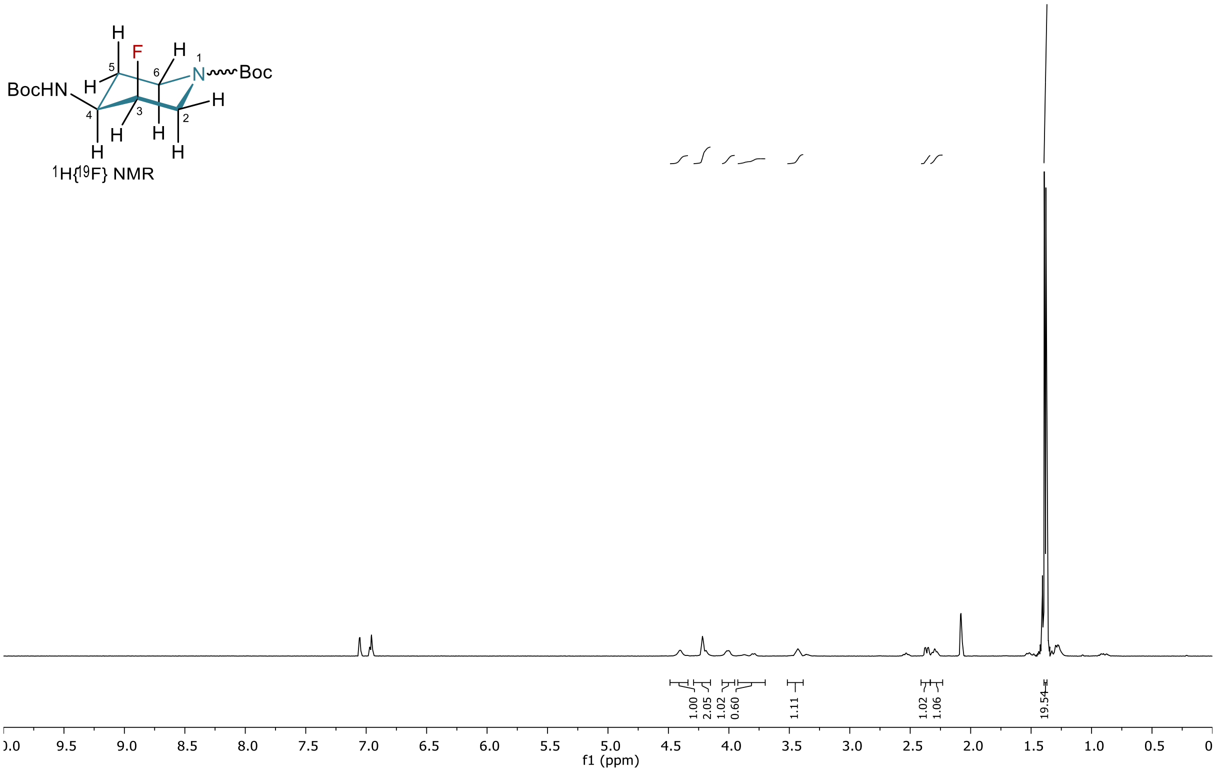
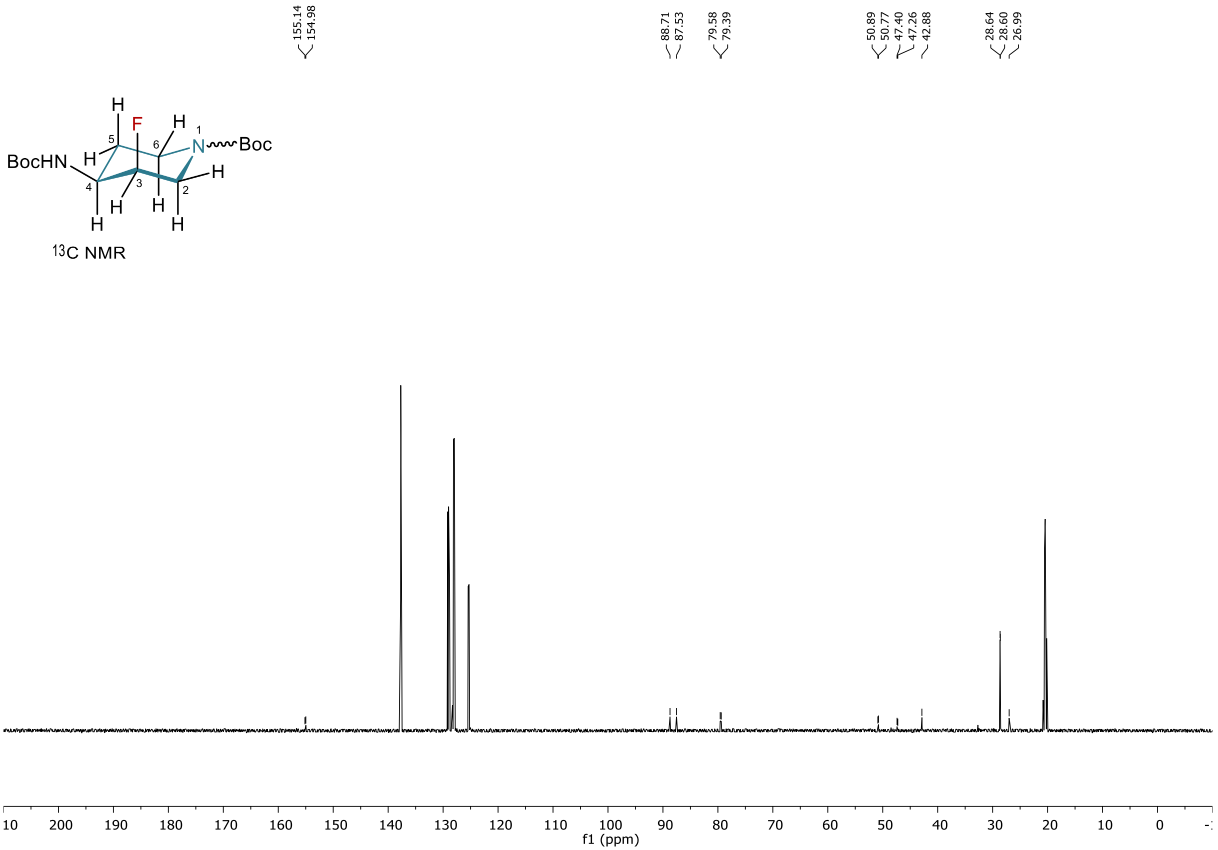
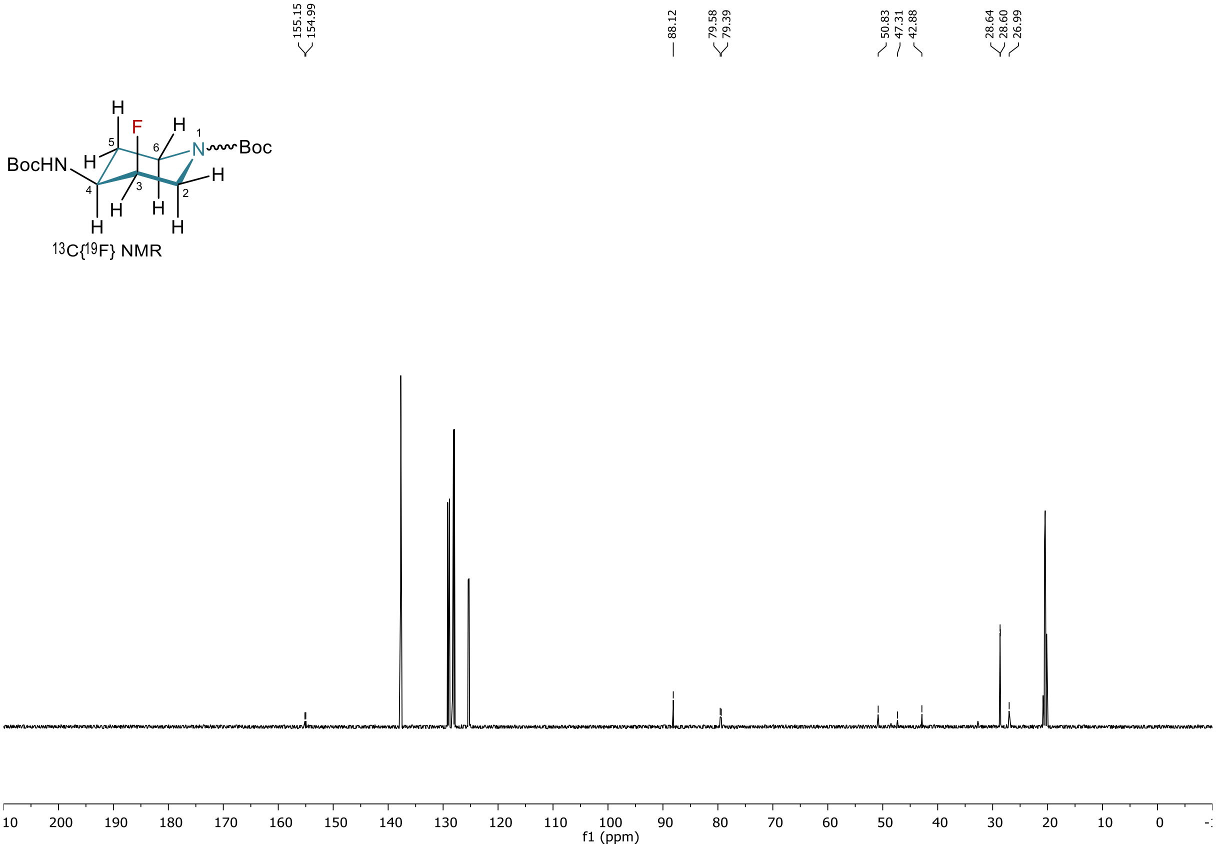
-203.26
-203.27
-203.27
-203.28
H
F
H
1
5
6
N
TFA
H
Bu
H
3
4
2
H
H
H
H
19F{1H} NMR
-202.4 -202.5 -202.6 -202.7 -202.8 -202.9 -203.0 -203.1 -203.2 -203.3 -203.4 -203.5 -203.6 -203.7 -203.8 -203.9
f1 (ppm)


BocHN
F
N
Boc
H
1
2
3
4
5
6
¹H NMR
1.00
2.24
1.09
0.61
1.14
1.15
1.07
17.64
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


BocHN
F
N
Boc
H
1
2
3
4
5
6
¹H{¹⁹F} NMR
1.00
2.05
1.02
0.60
1.11
1.02
1.06
19.54
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


155.14
154.98
88.71
87.53
79.58
79.39
50.89
50.77
47.40
47.26
42.88
28.64
28.60
26.99
BocHN
F
H
H
H
H
H
H
H
H
1
2
3
4
5
6
N
Boc
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-
f1 (ppm)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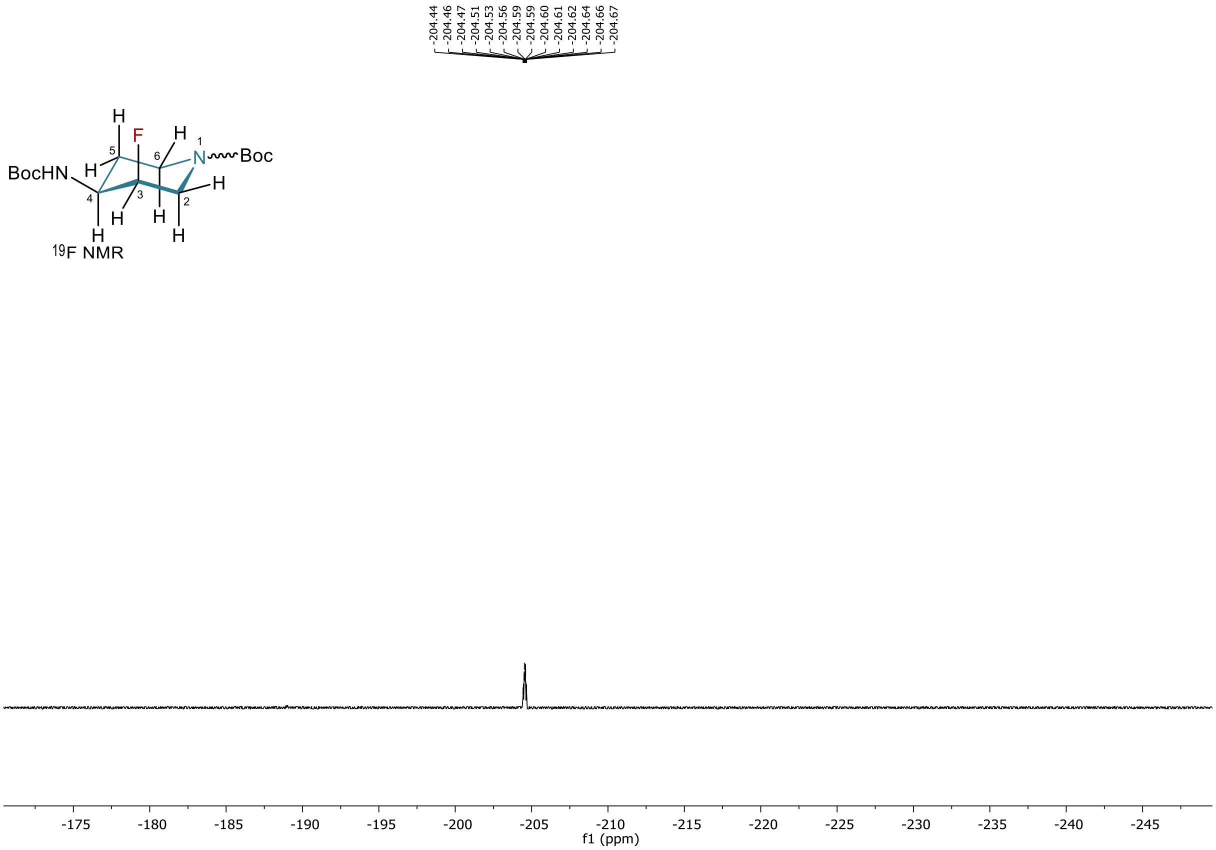
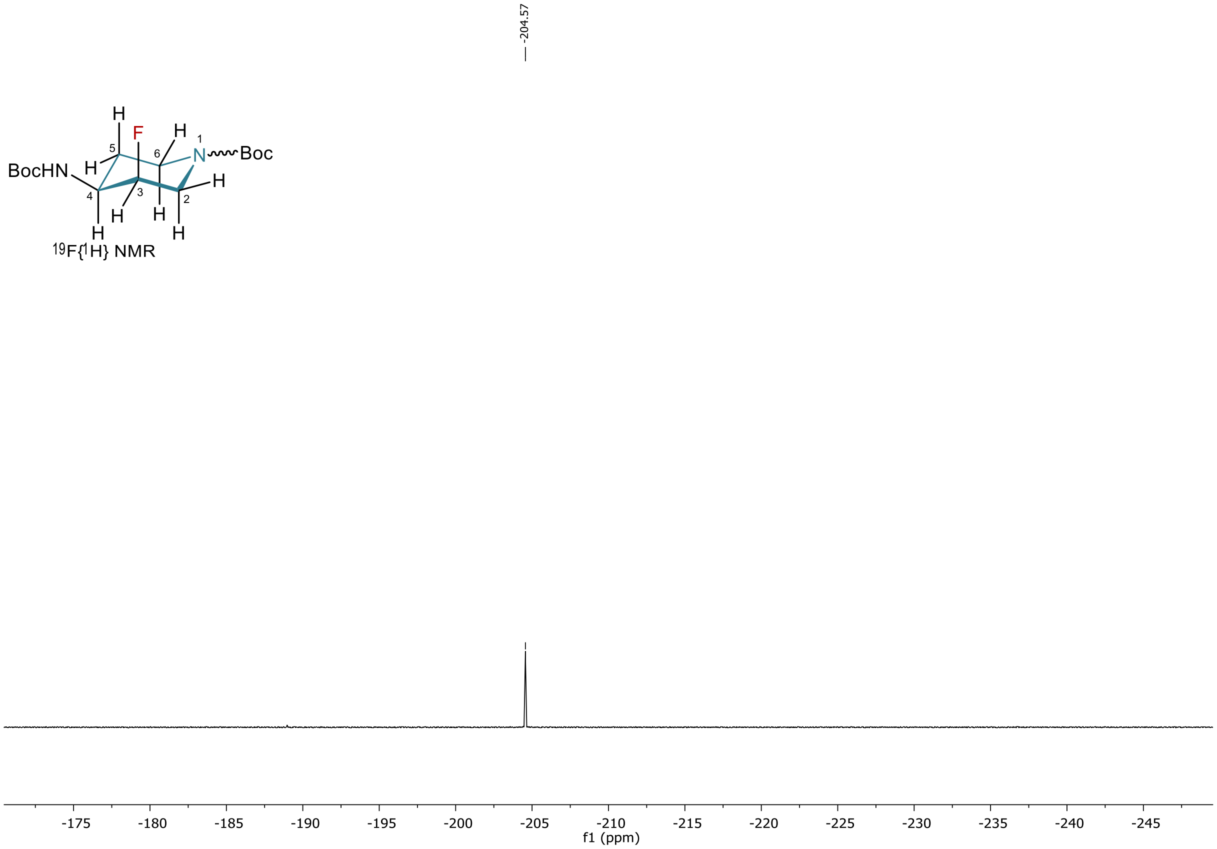
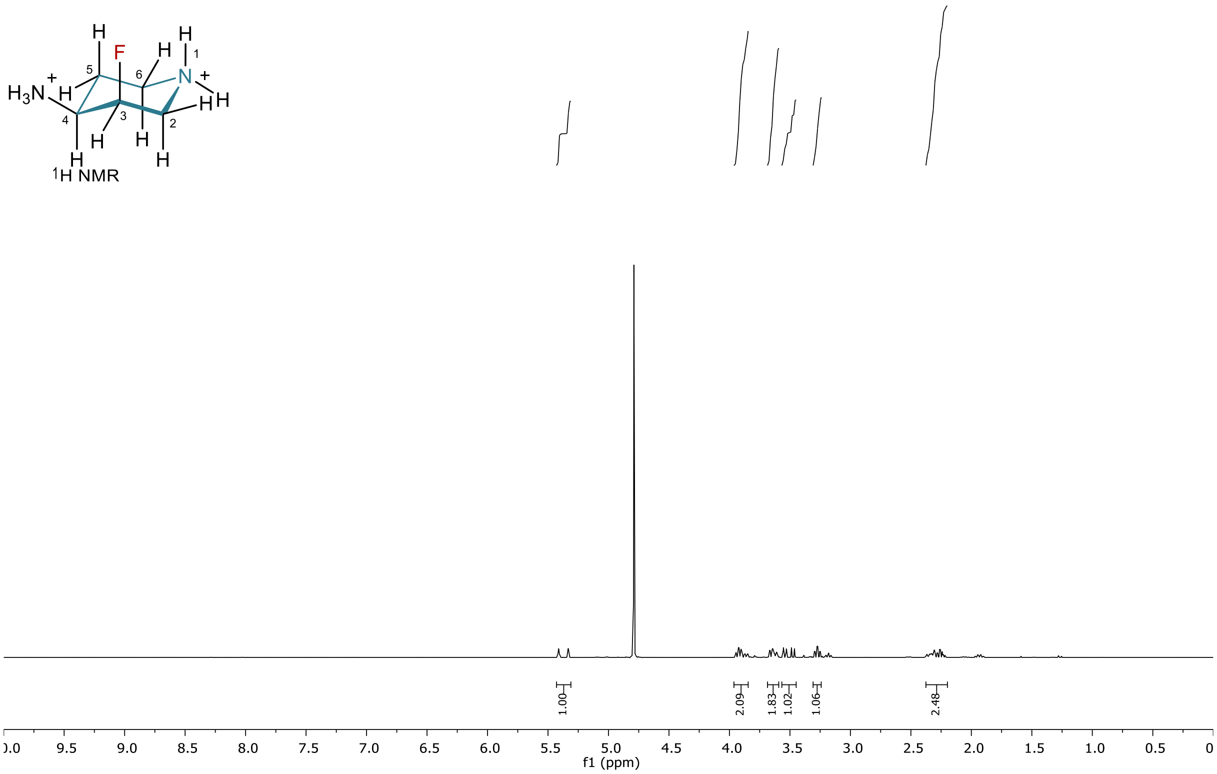
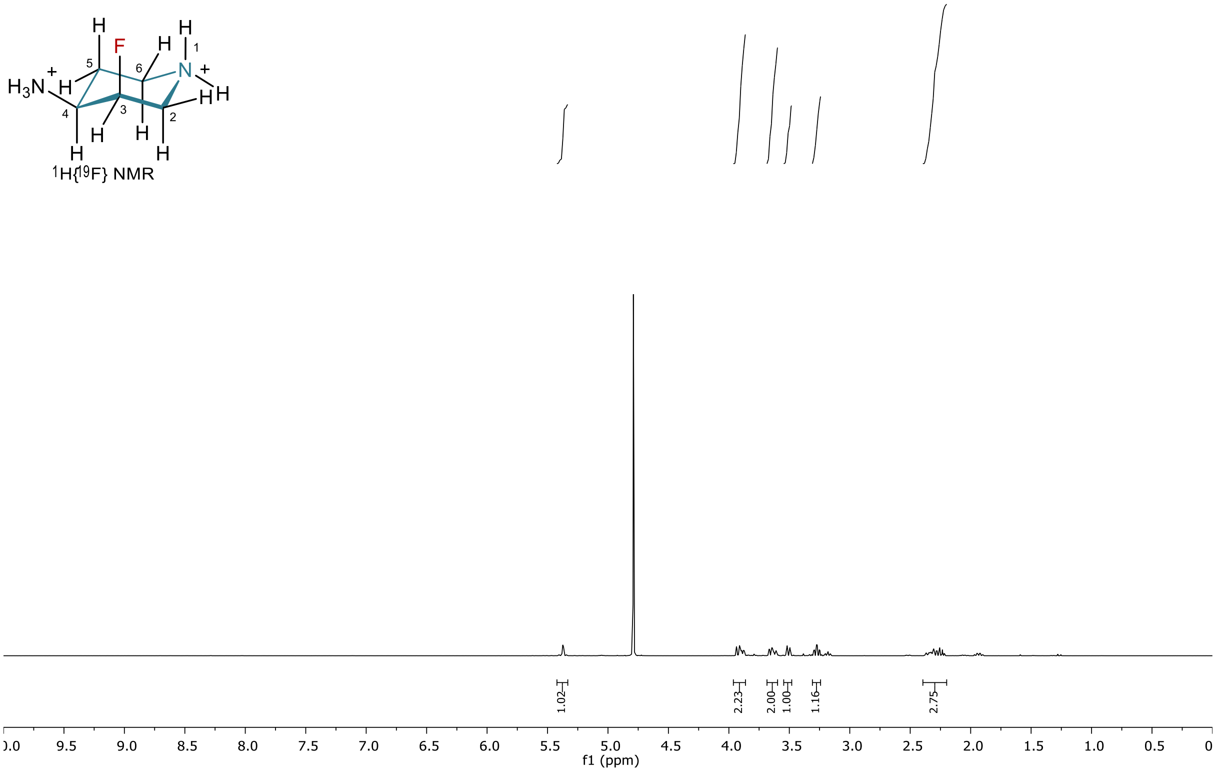
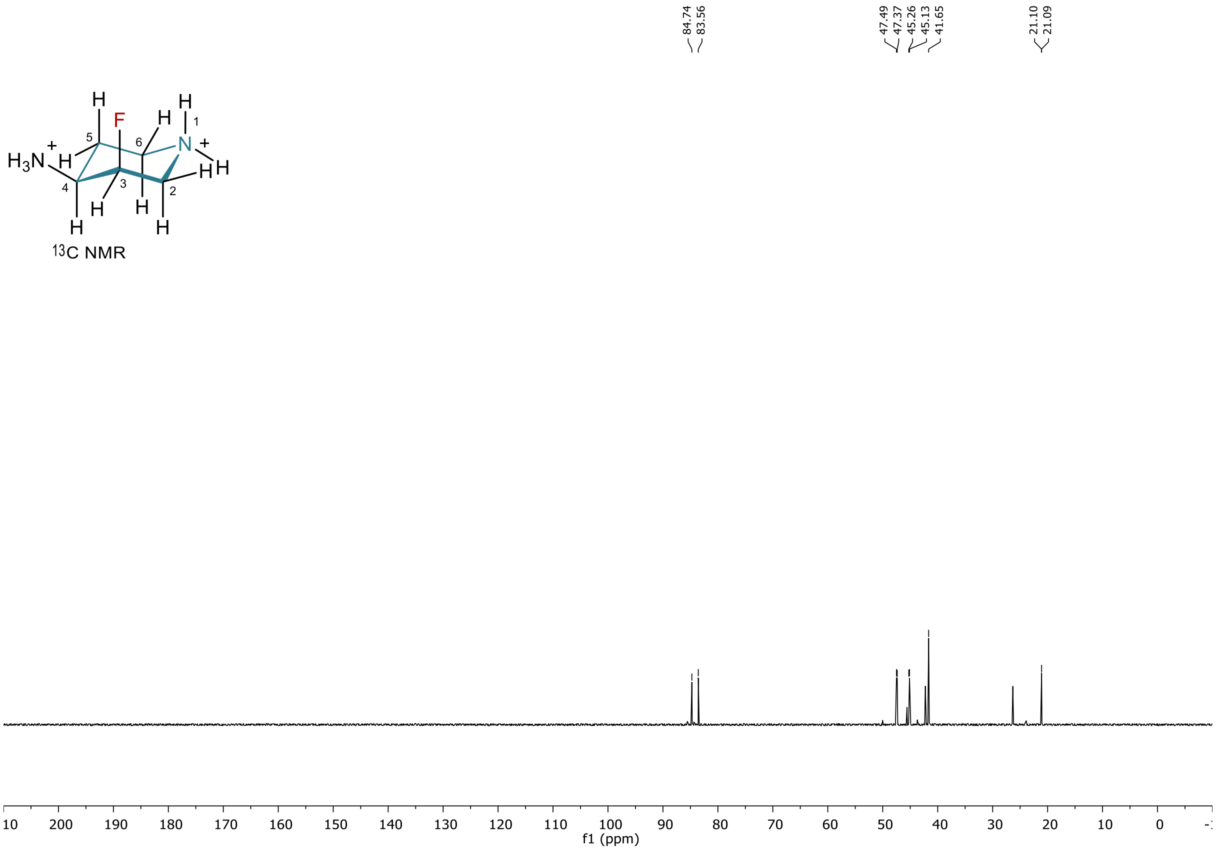
154.99
88.12
79.58
79.39
50.83
47.31
42.88
28.64
28.60
26.99
BocHN
F
H
H
H
H
H
H
H
H
1
2
3
4
5
6
N
Boc
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-
f1 (ppm)

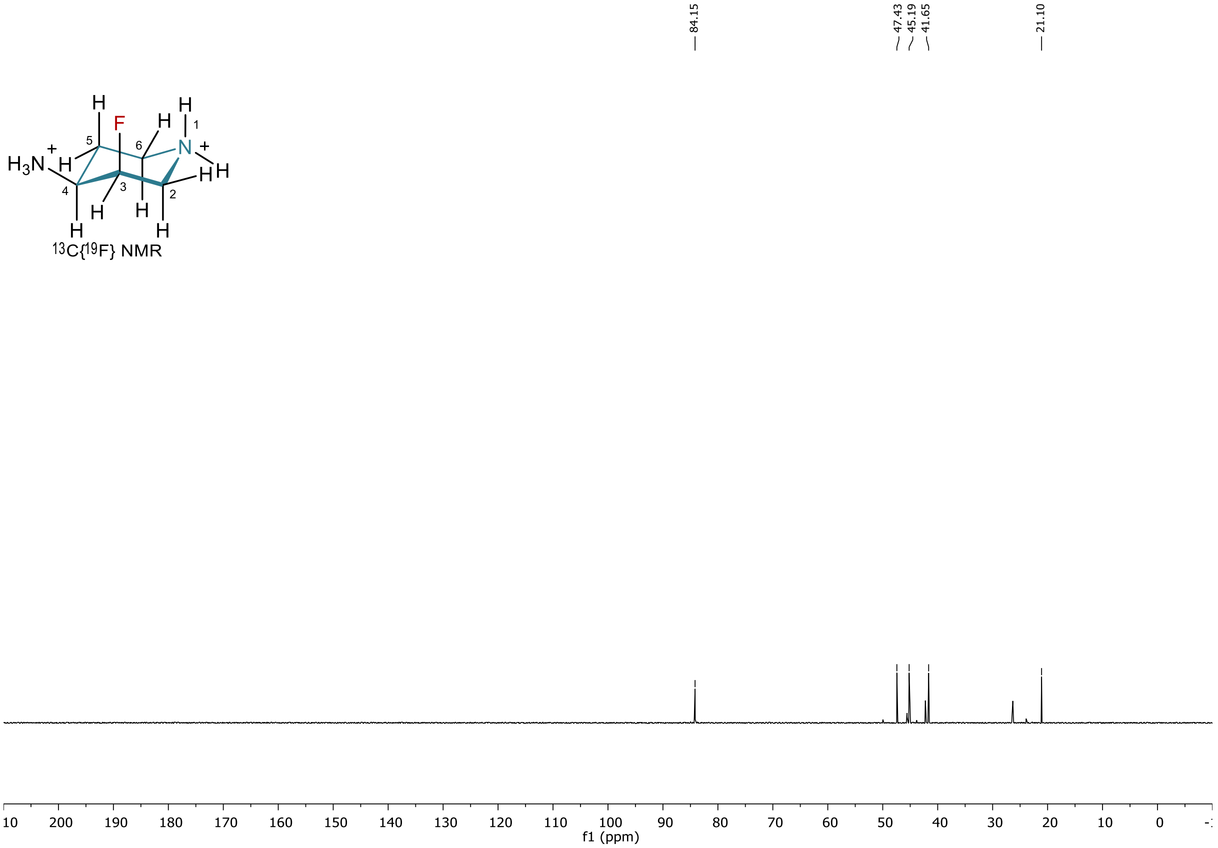

-204.44
-204.46
-204.47
-204.51
-204.53
-204.56
-204.59
-204.59
-204.60
-204.61
-204.62
-204.64
-204.66
-204.67
BocHN
F
Boc
N
1
2
3
4
5
6
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

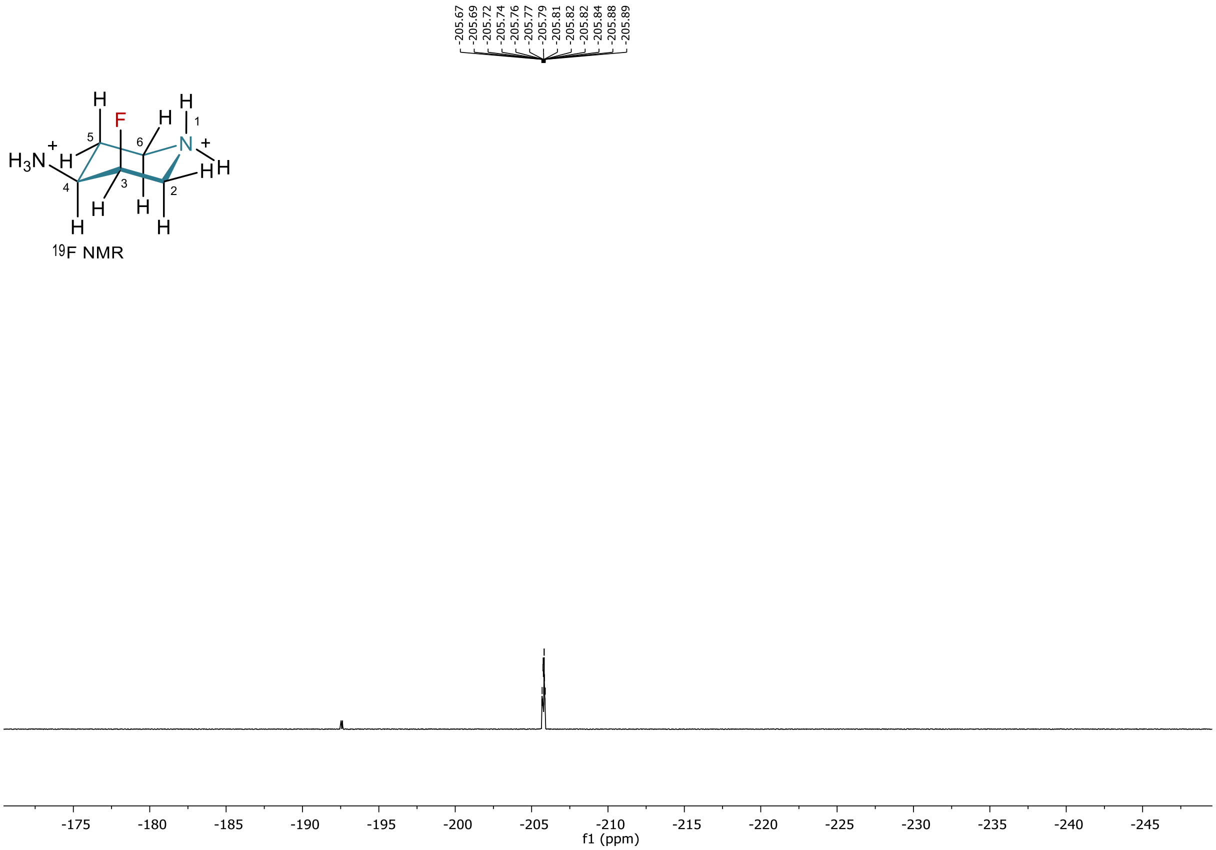

-204.57
BocHN
F
Boc
N
1
2
3
4
5
6
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


H
F
H
H
1
5
6
N+
H3N+
H
H
H
4
3
2
H
H
H
H
1H NMR
1.00
2.09
1.83
1.02
1.06
2.48
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


H
F
H
H
1
5
6
N+
H3N+
H
H
H
4
3
2
H
H
H
H
1H{19F} NMR
1.02
2.23
2.00
1.00
1.16
2.75
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


84.74
83.56
47.49
47.37
45.26
45.13
41.65
21.10
21.09
H
F
H
H
1
5
6
N
+
H_3N^+
H
H
H
4
3
2
H
H
H
H
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


84.15
47.43
45.19
41.65
21.10
H
F
H
H
1
5
6
N
+
H_3N^+
H
H
H
4
3
2
H
H
H
H
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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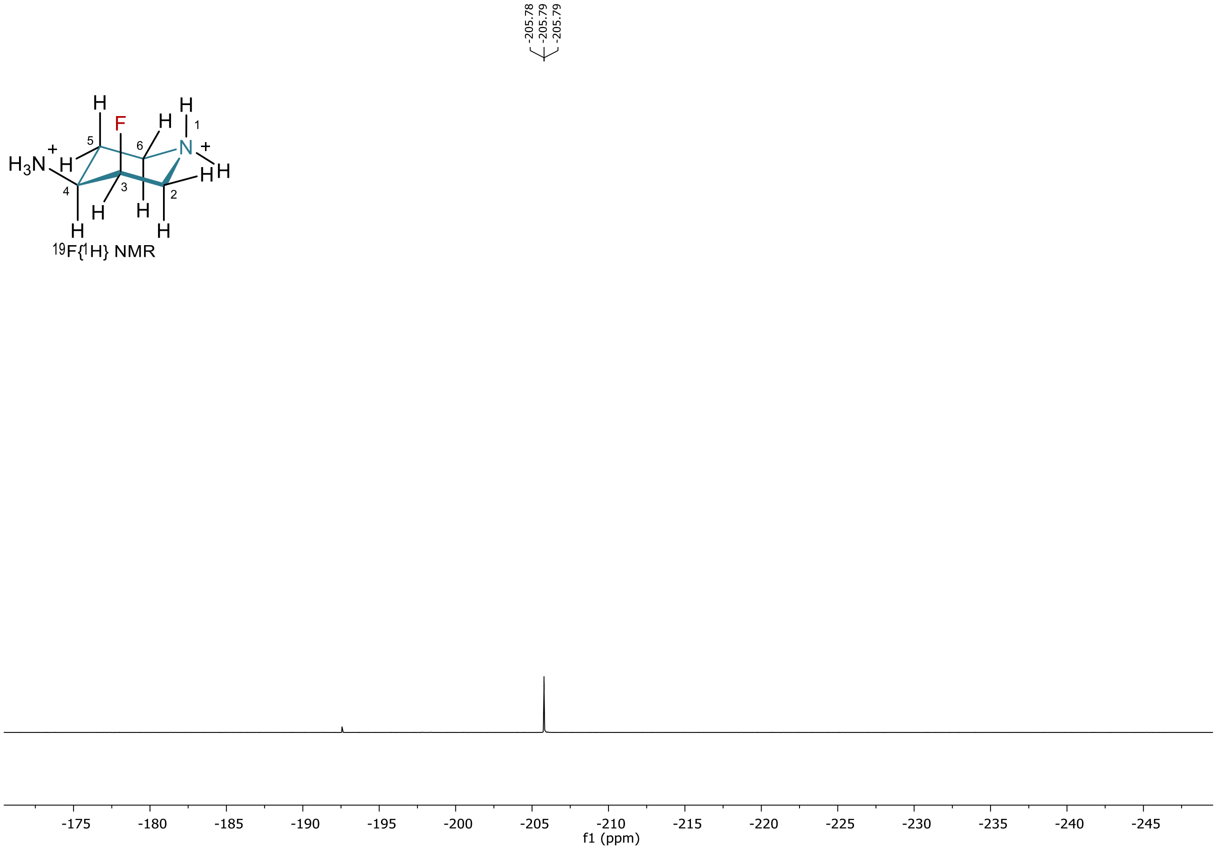
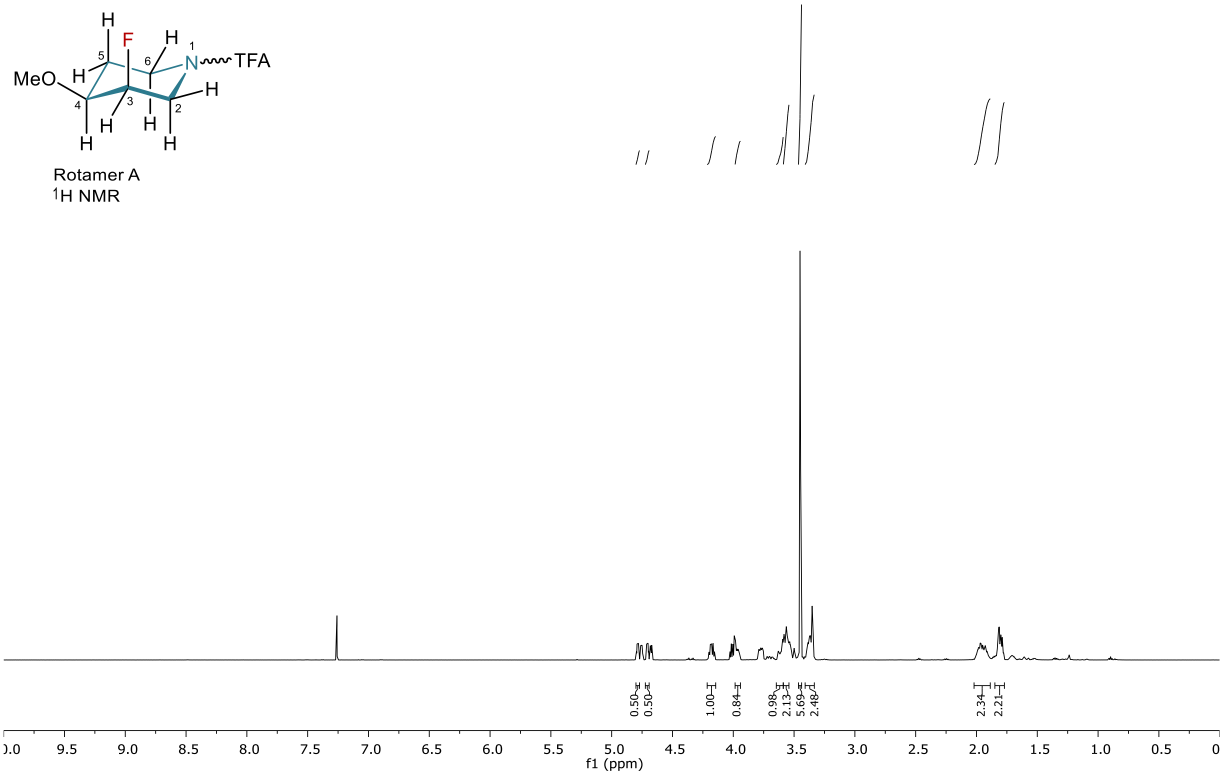
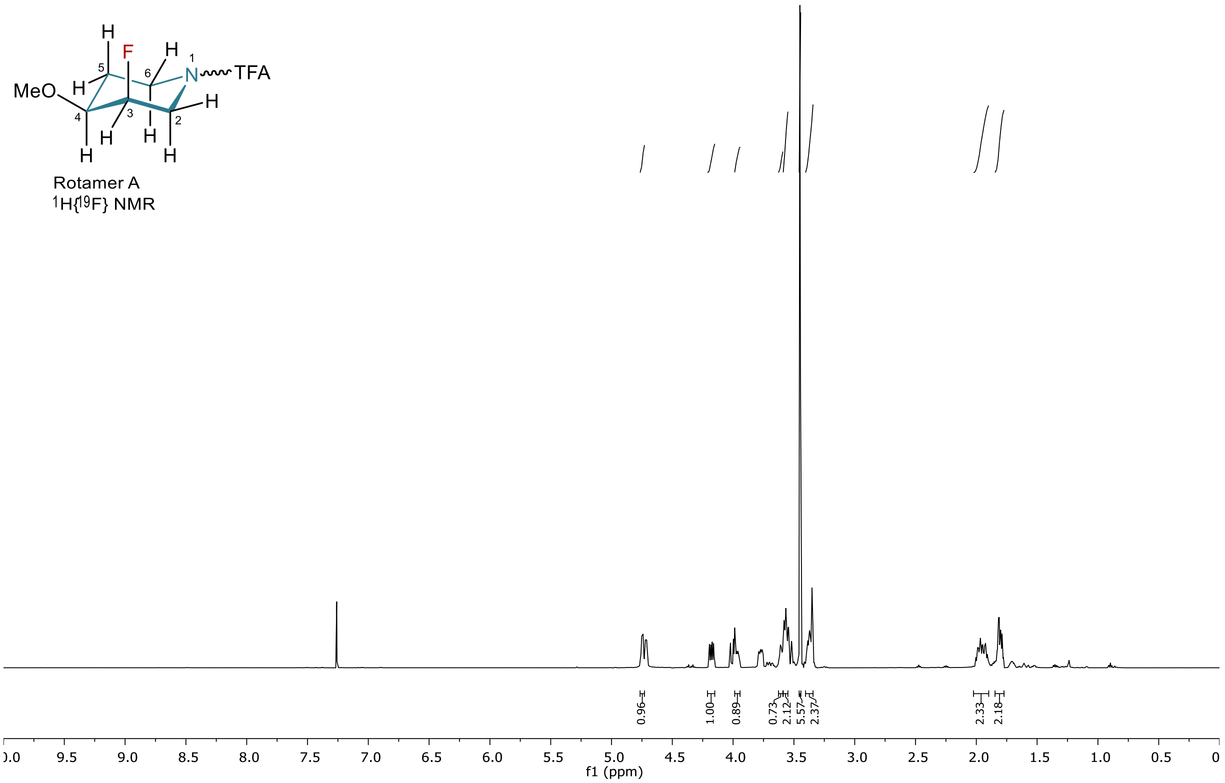
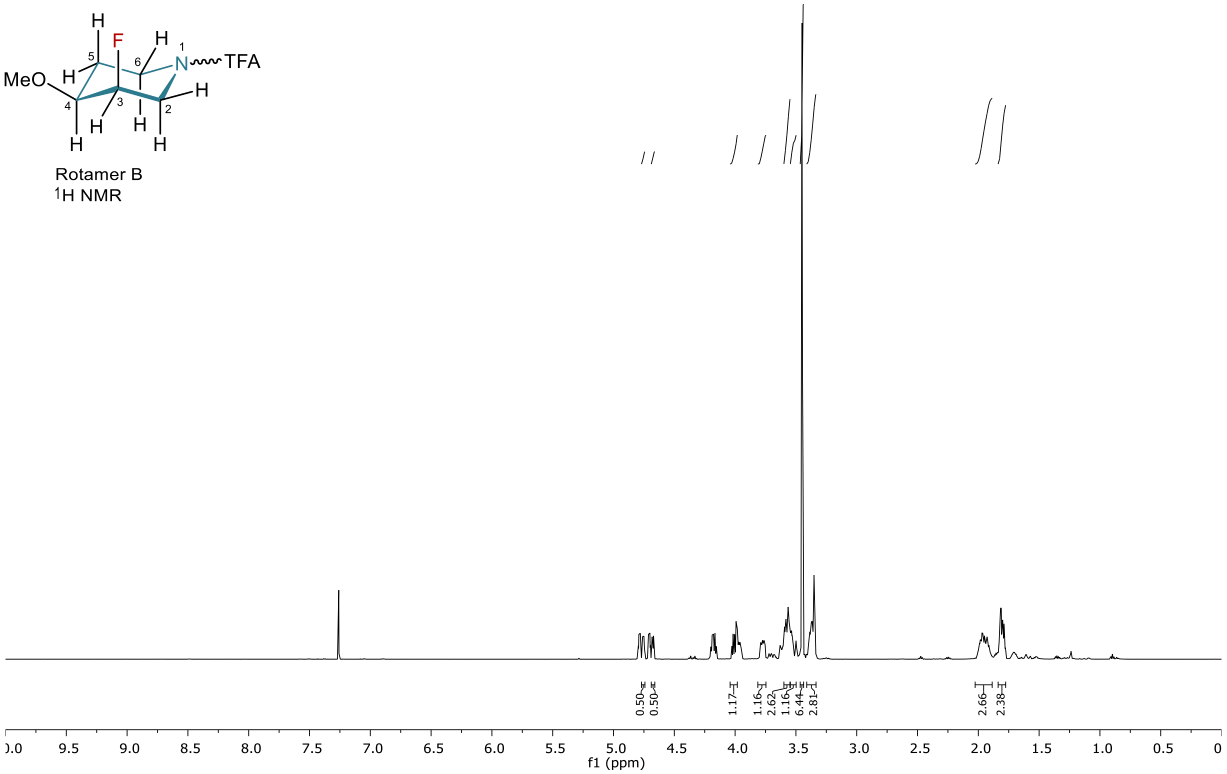
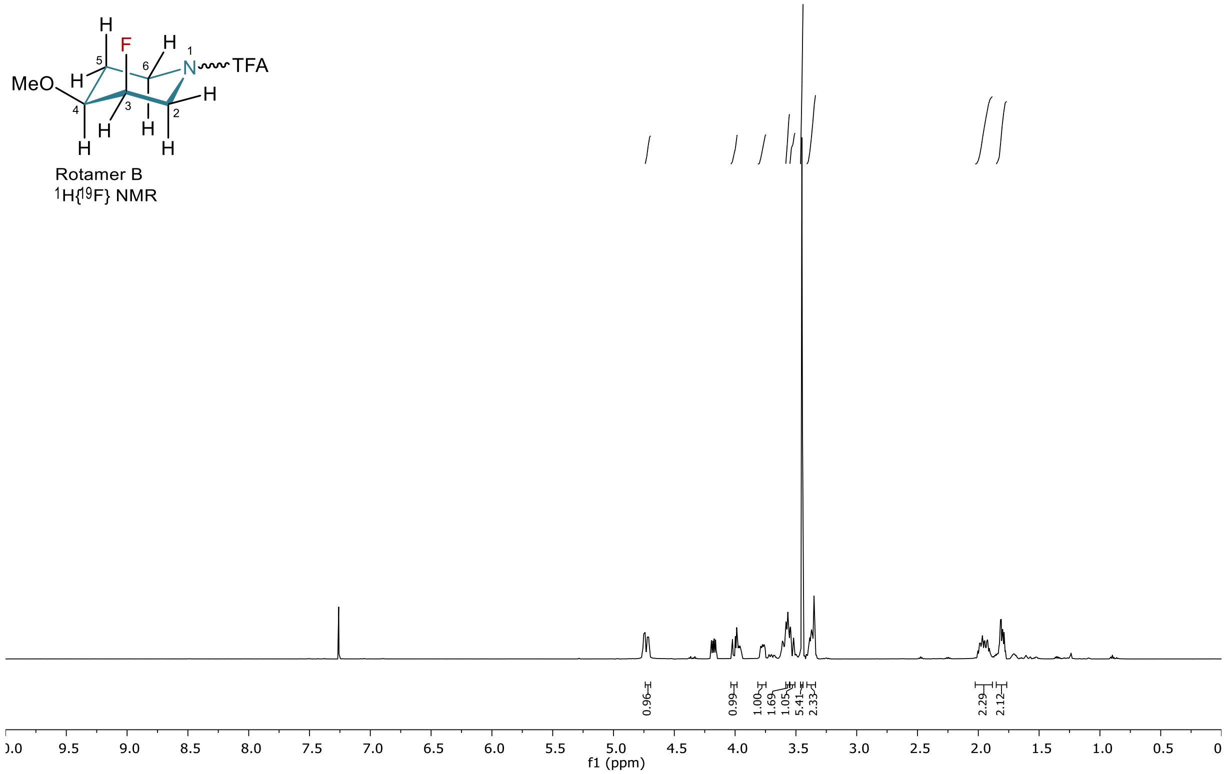
-205.69
-205.72
-205.74
-205.76
-205.77
-205.79
-205.81
-205.82
-205.82
-205.84
-205.88
-205.89
H
F
H
H
1
5
6
N
+
H_3N^+
H
H
H
4
3
2
H
H
H
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

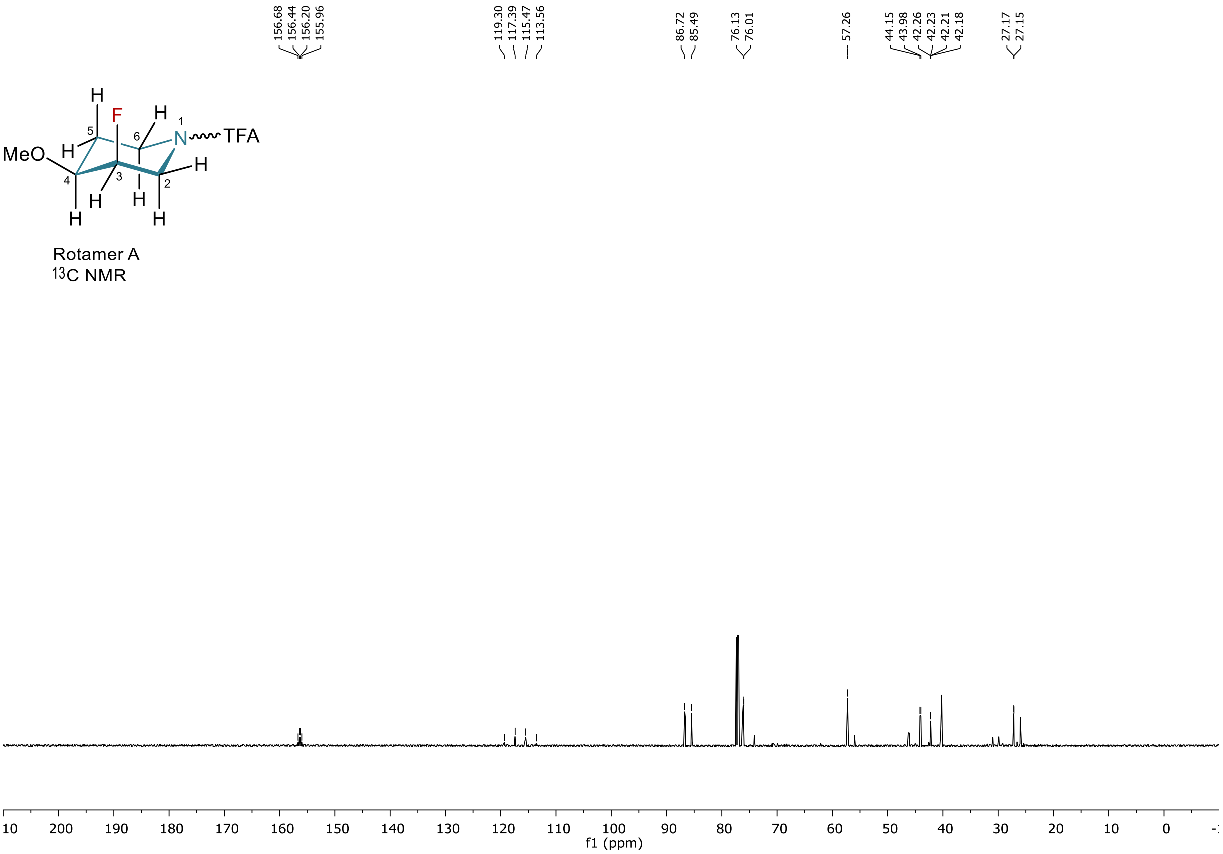

-205.78
-205.79
-205.79
H
F
H
H
1
5
6
N
+
H_3N^+
H
H
H
4
3
2
H
H
H
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

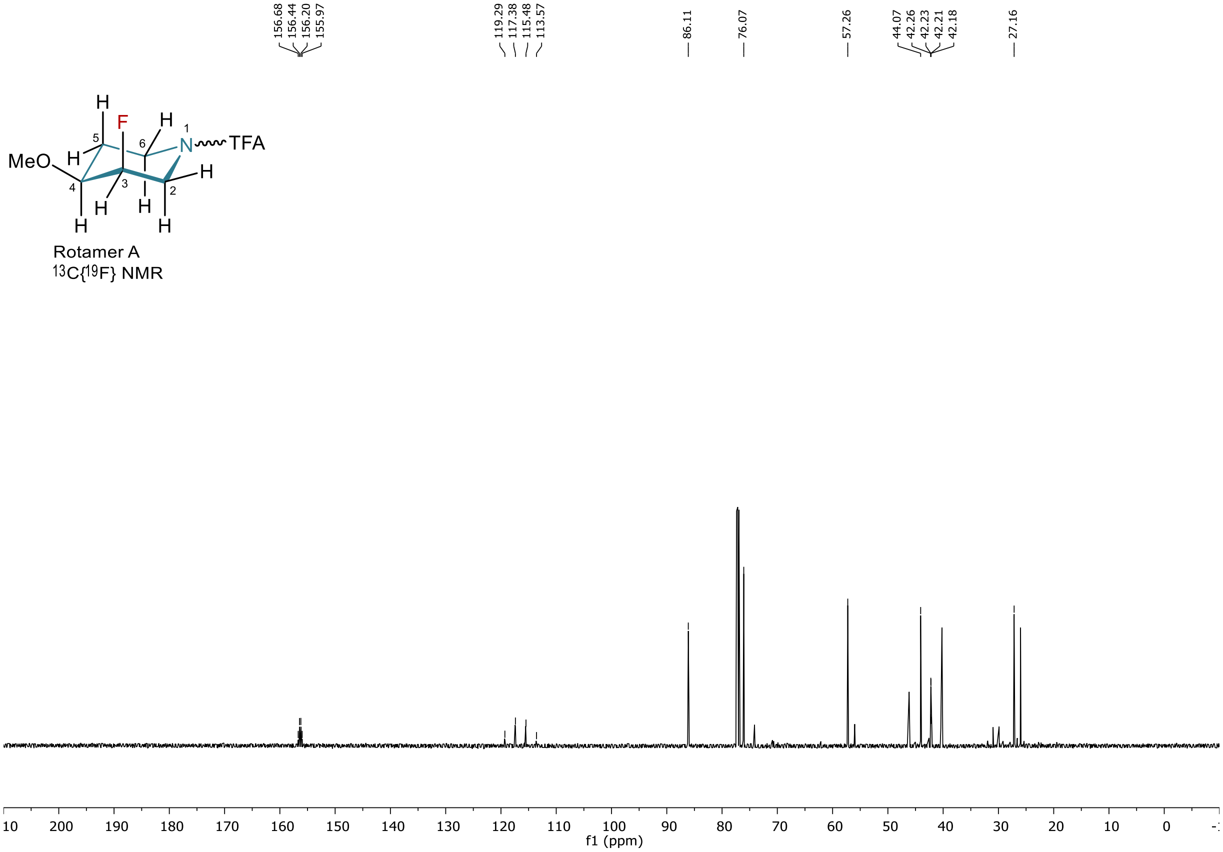

H
F
H
1
5
6
N
TFA
H
MeO
H
4
3
2
H
H
H
H
Rotamer A
1H NMR
0.50
0.50
1.00
0.84
0.98
2.13
5.69
2.48
2.34
2.21
).0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

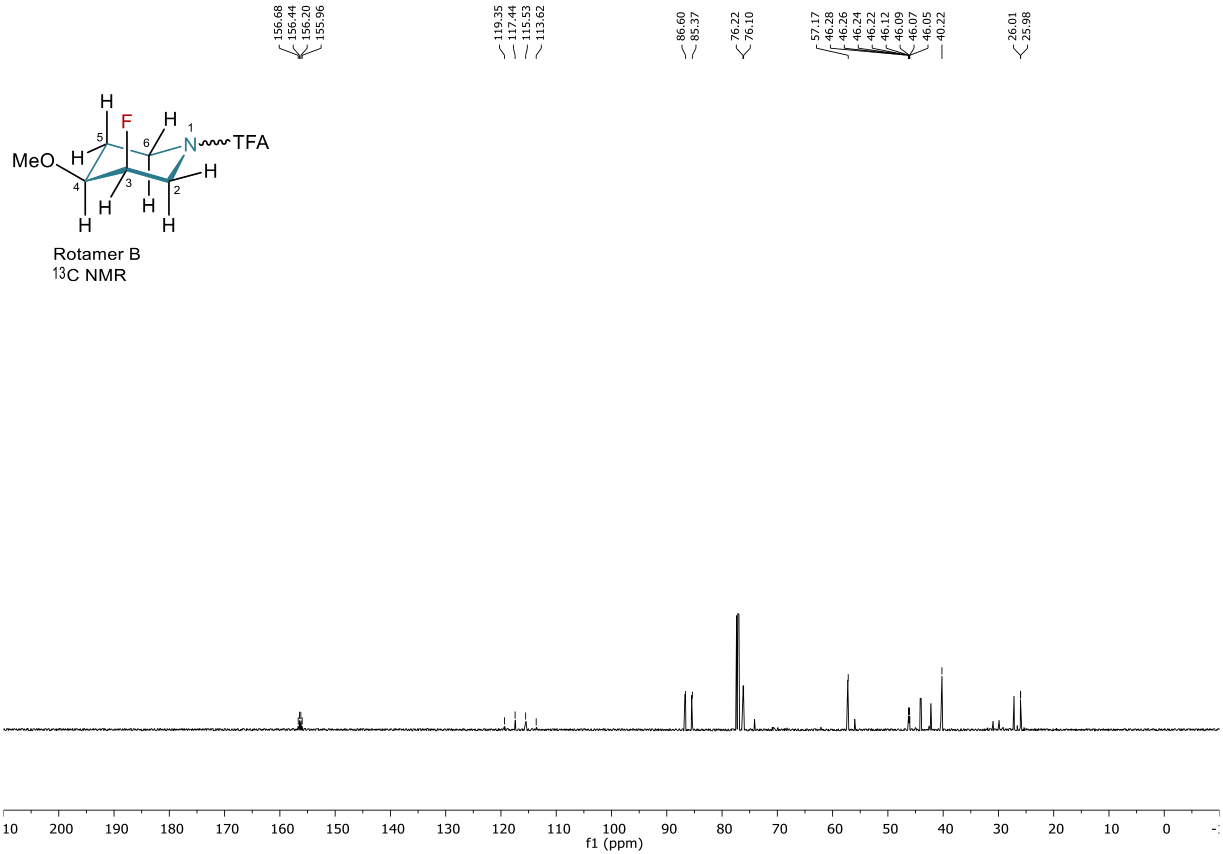

H
F
H
1
5
6
N
TFA
H
MeO
H
4
3
2
H
H
H
H
Rotamer A
1H{19F} NMR
0.96
1.00
0.89
0.73
2.12
5.57
2.37
2.33
2.18
).0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

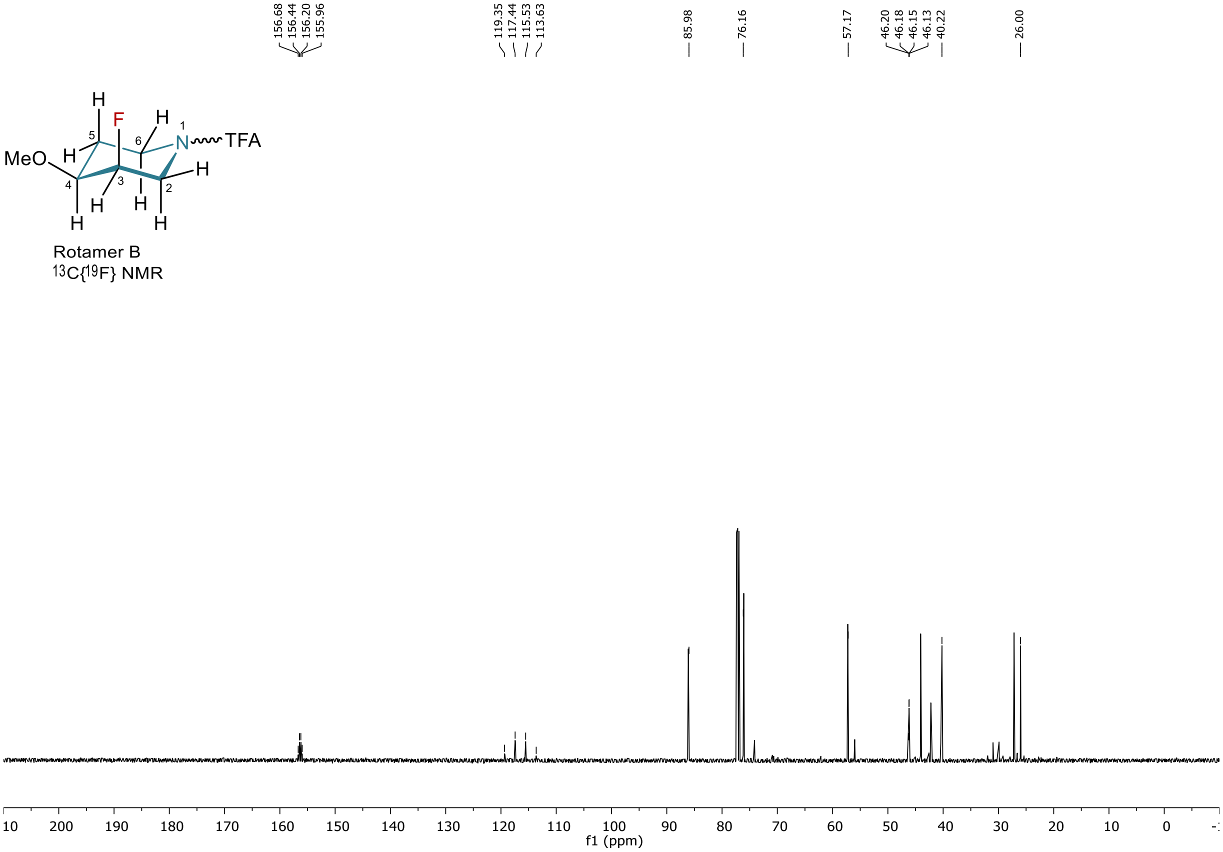

MeO
F
N
TFA
H
1
2
3
4
5
6
Rotamer B
^{1}H NMR
0.50
0.50
1.17
1.16
2.62
1.16
6.44
2.81
2.66
2.38
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

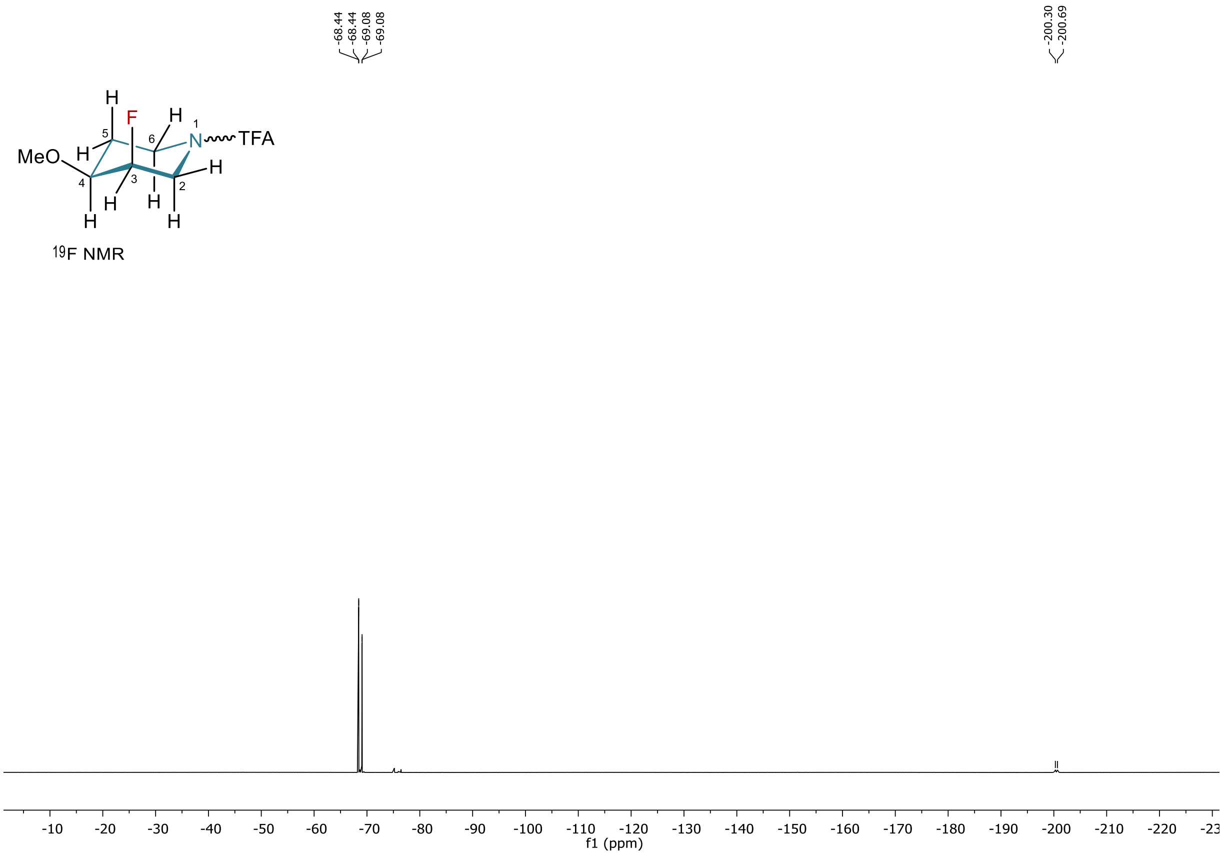

MeO
F
N
TFA
H
1
2
3
4
5
6
Rotamer B
^{1}H{^{19}F} NMR
0.96
0.99
1.00
1.69
1.05
5.41
2.33
2.29
2.12
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

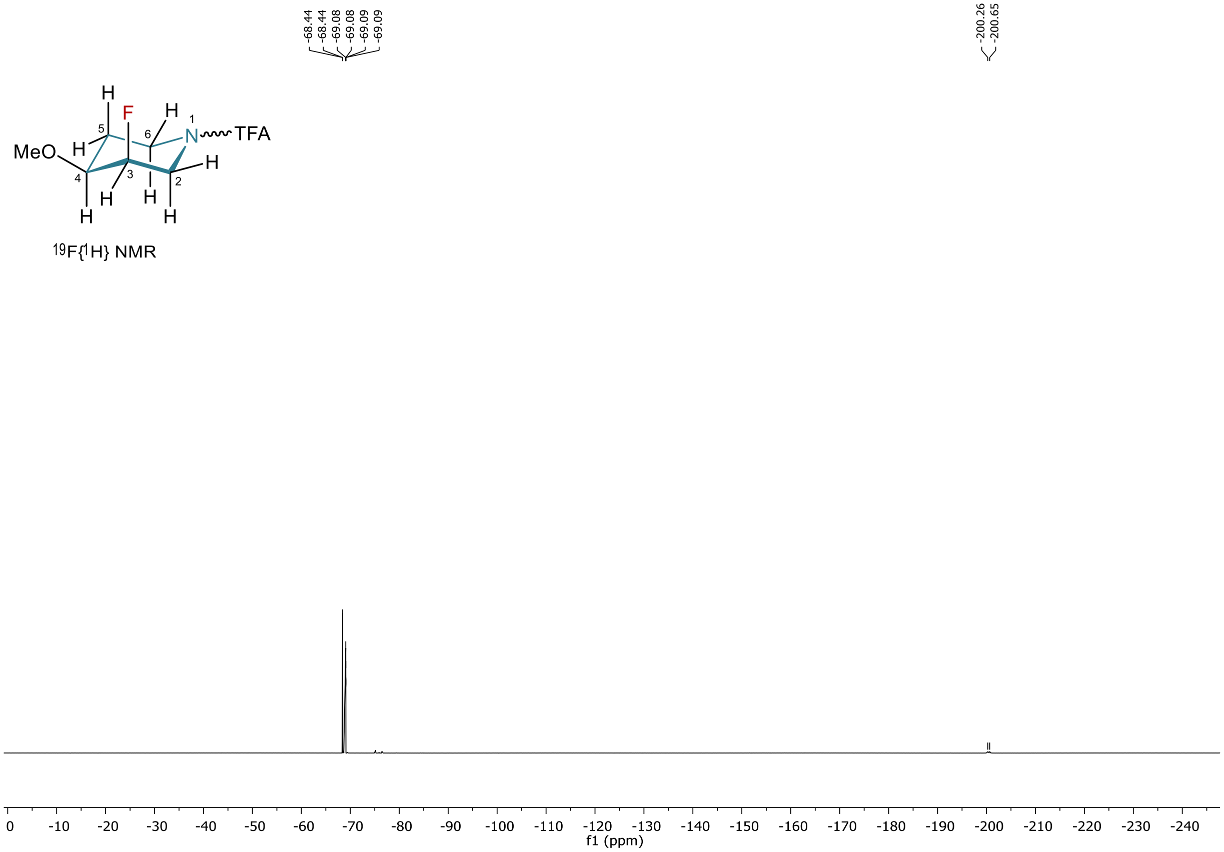

156.68
156.44
156.20
155.96
119.30
117.39
115.47
113.56
86.72
85.49
76.13
76.01
57.26
44.15
43.98
42.26
42.23
42.21
42.18
27.17
27.15
H
F
H
1
5
6
N
TFA
MeO
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

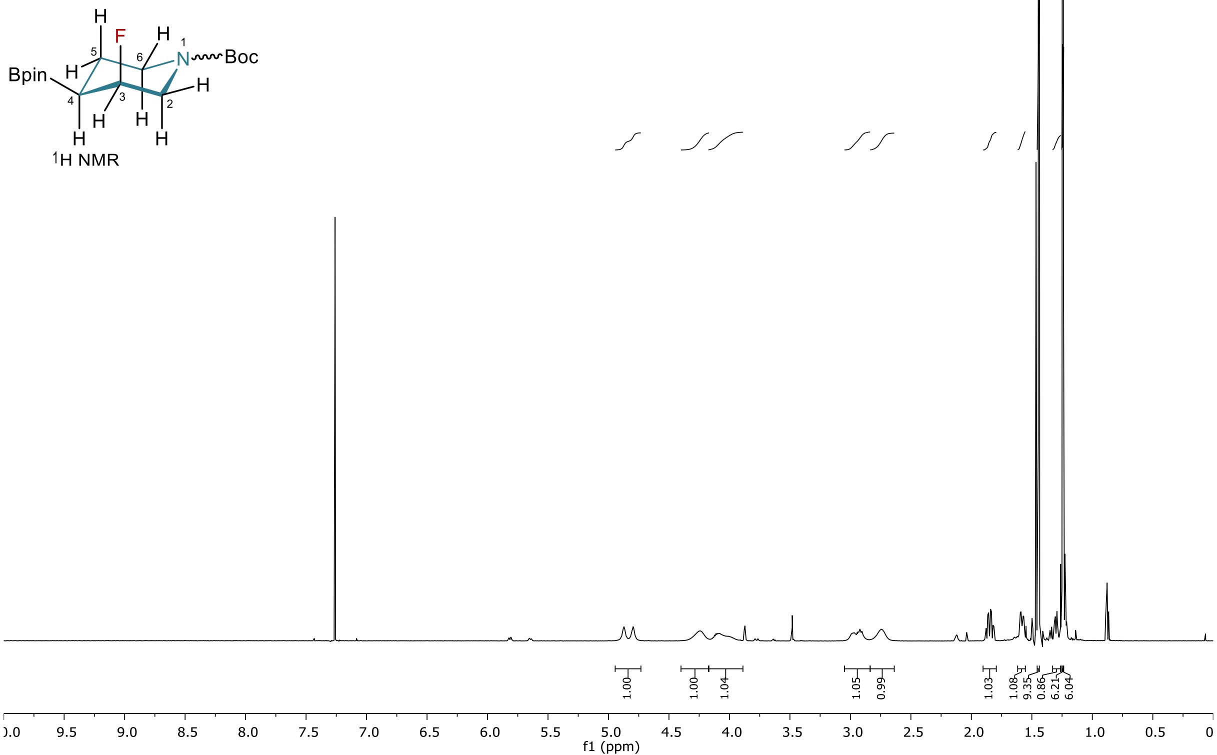

156.68
156.44
156.20
155.97
119.29
117.38
115.48
113.57
86.11
76.07
57.26
44.07
42.26
42.23
42.21
42.18
27.16
H
F
H
1
5
6
N
TFA
MeO
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


156.68
156.44
156.20
155.96
119.35
117.44
115.53
113.62
86.60
85.37
76.22
76.10
57.17
46.28
46.26
46.24
46.22
46.12
46.09
46.07
46.05
40.22
26.01
25.98
H
F
H
1
5
6
N
TFA
MeO
H
H
4
3
2
H
H
H
H
Rotamer B
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

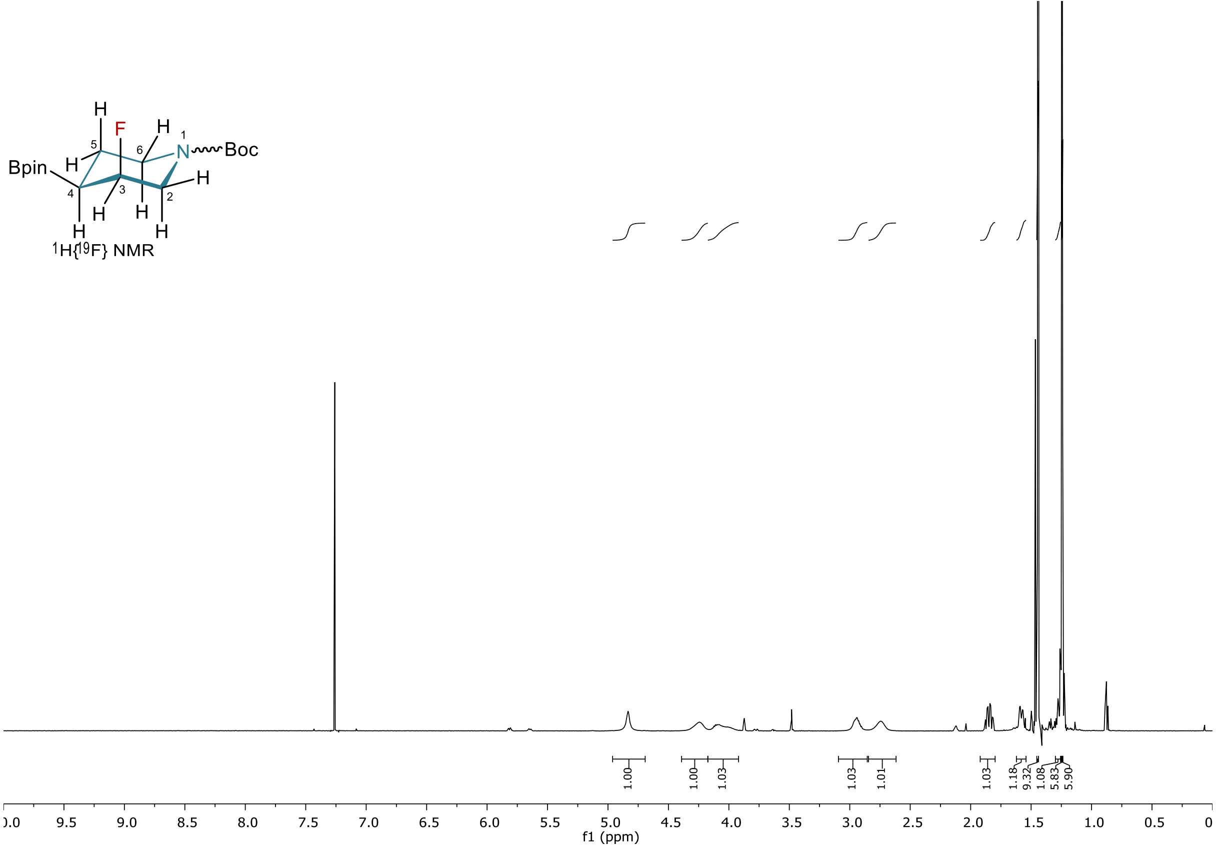

156.68
156.44
156.20
155.96
119.35
117.44
115.53
113.63
85.98
76.16
57.17
46.20
46.18
46.15
46.13
40.22
26.00
H
F
H
1
5
6
N
TFA
MeO
H
H
4
3
2
H
H
H
H
Rotamer B
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-68.44
-68.44
-69.08
-69.08
-200.30
-200.69
MeO
F
N
TFA
H
1
2
3
4
5
6
19F NMR
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-23
f1 (ppm)

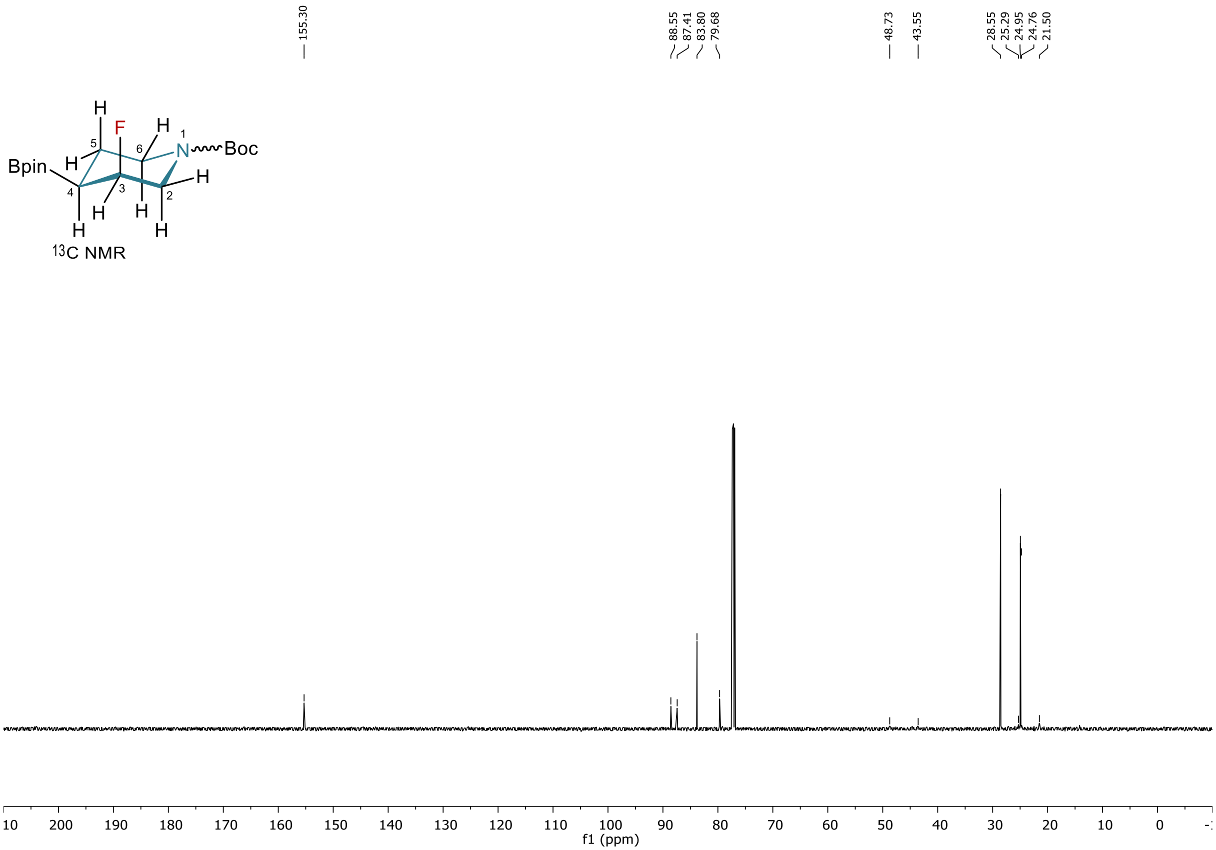

-68.44
-68.44
-69.08
-69.08
-69.09
-69.09
-200.26
-200.65
MeO
F
N
TFA
H
1
2
3
4
5
6
19F{1H} NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)

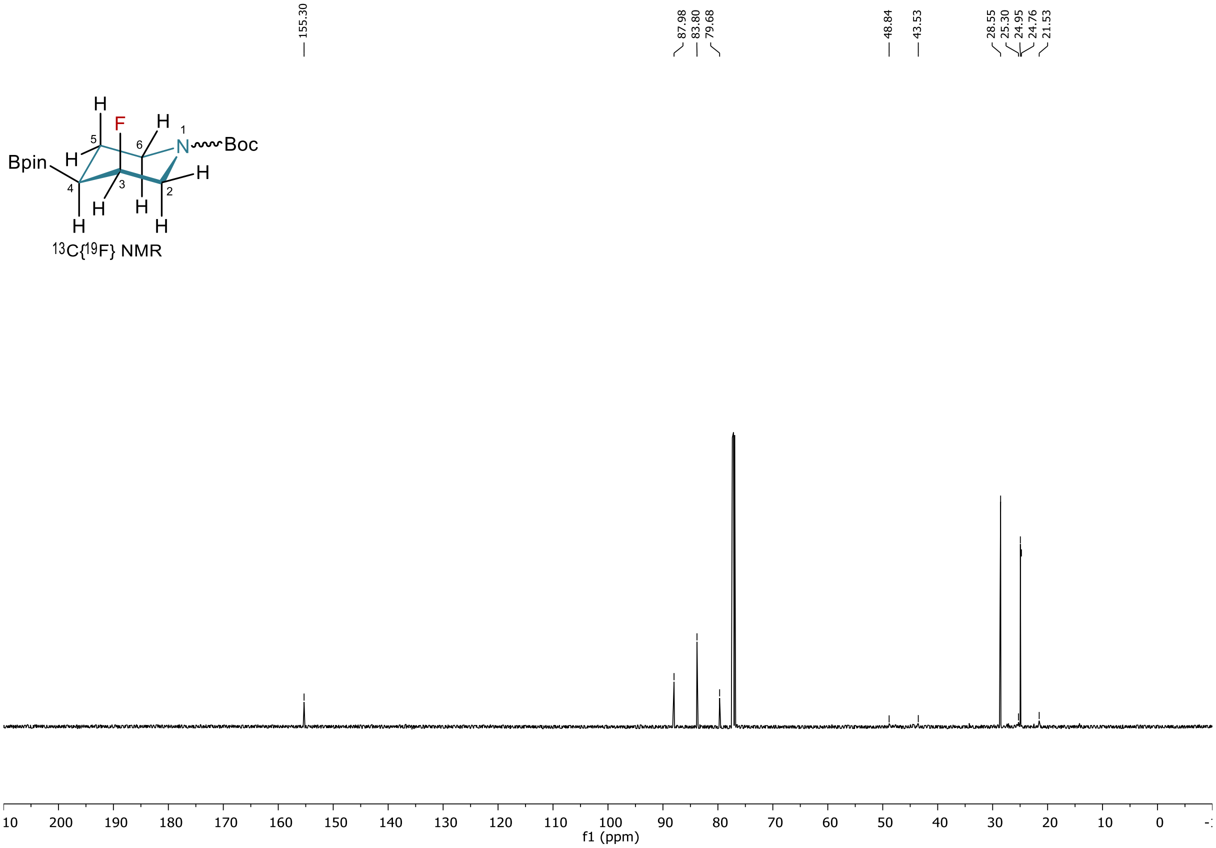


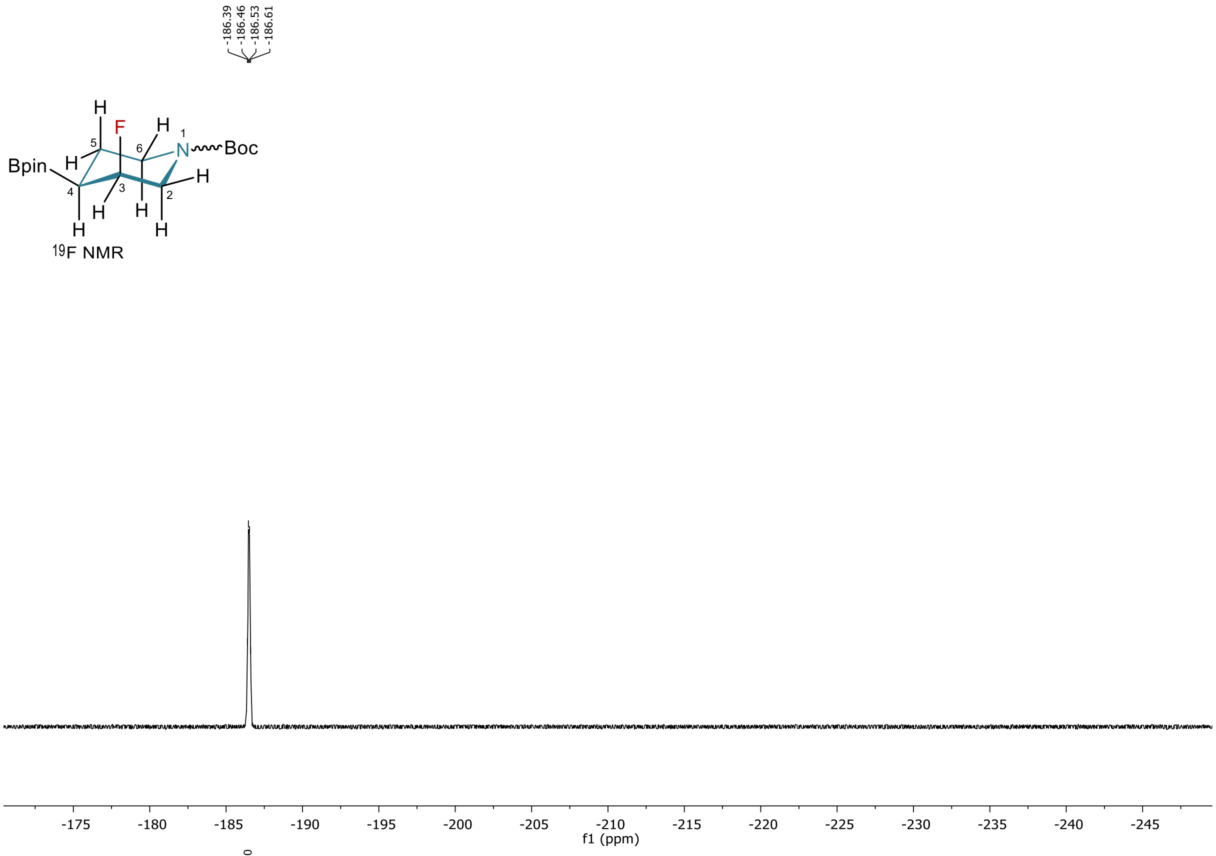
H
F
H
1
5
6
N
Boc
Bpin
H
H
4
3
2
H
H
H
H
1H NMR
1.00
1.00
1.04
1.05
0.99
1.03
1.08
9.35
0.86
6.21
6.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

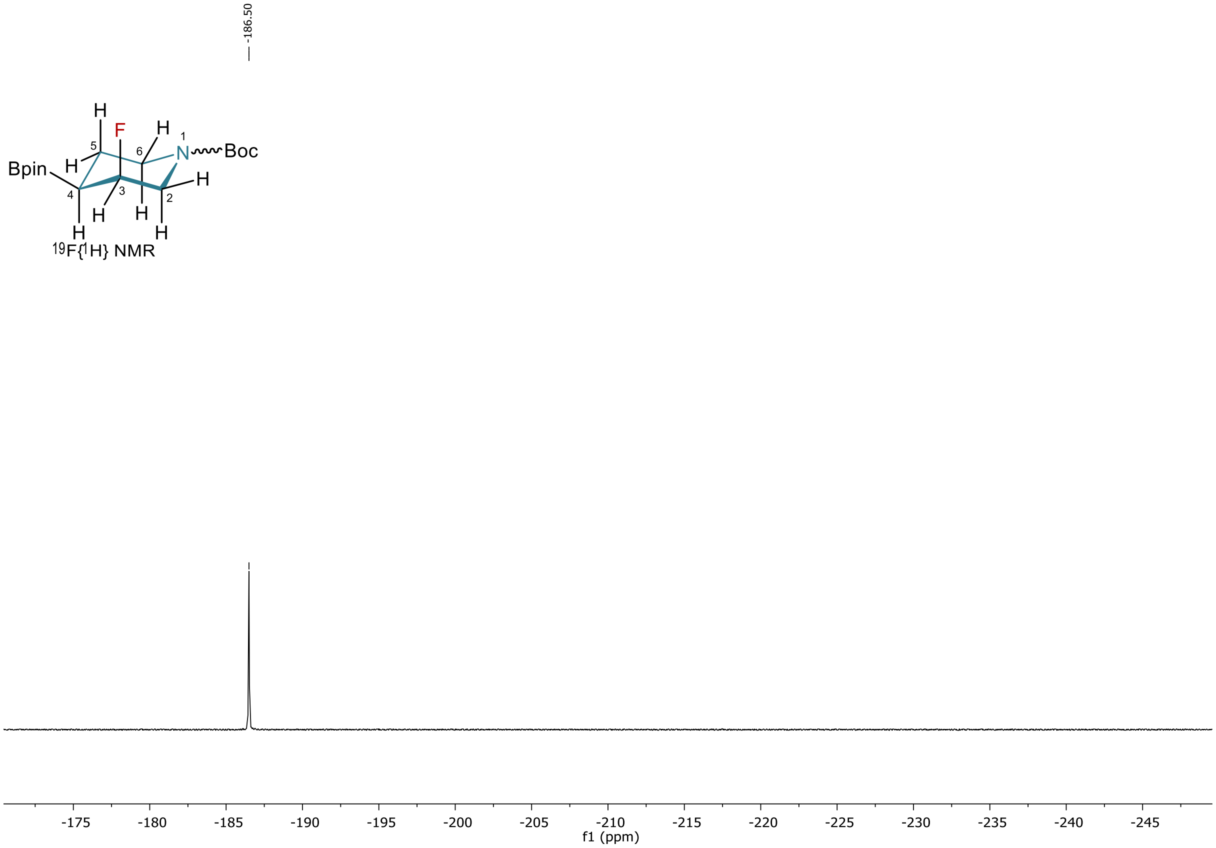


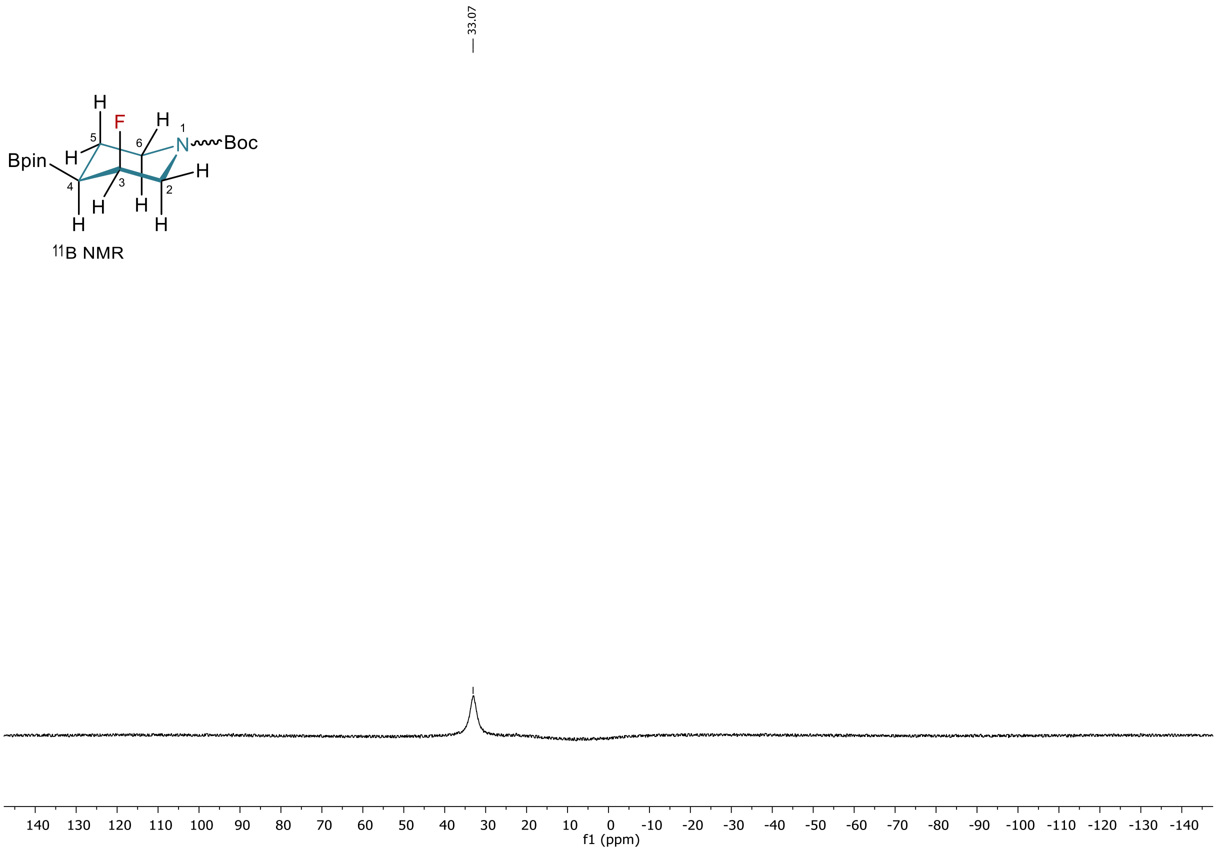
H
F
H
1
5
6
N
Boc
Bpin
H
H
4
3
2
H
H
H
H
1H{19F} NMR
1.00
1.00
1.03
1.03
1.01
1.03
1.18
9.32
1.08
5.83
5.90
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

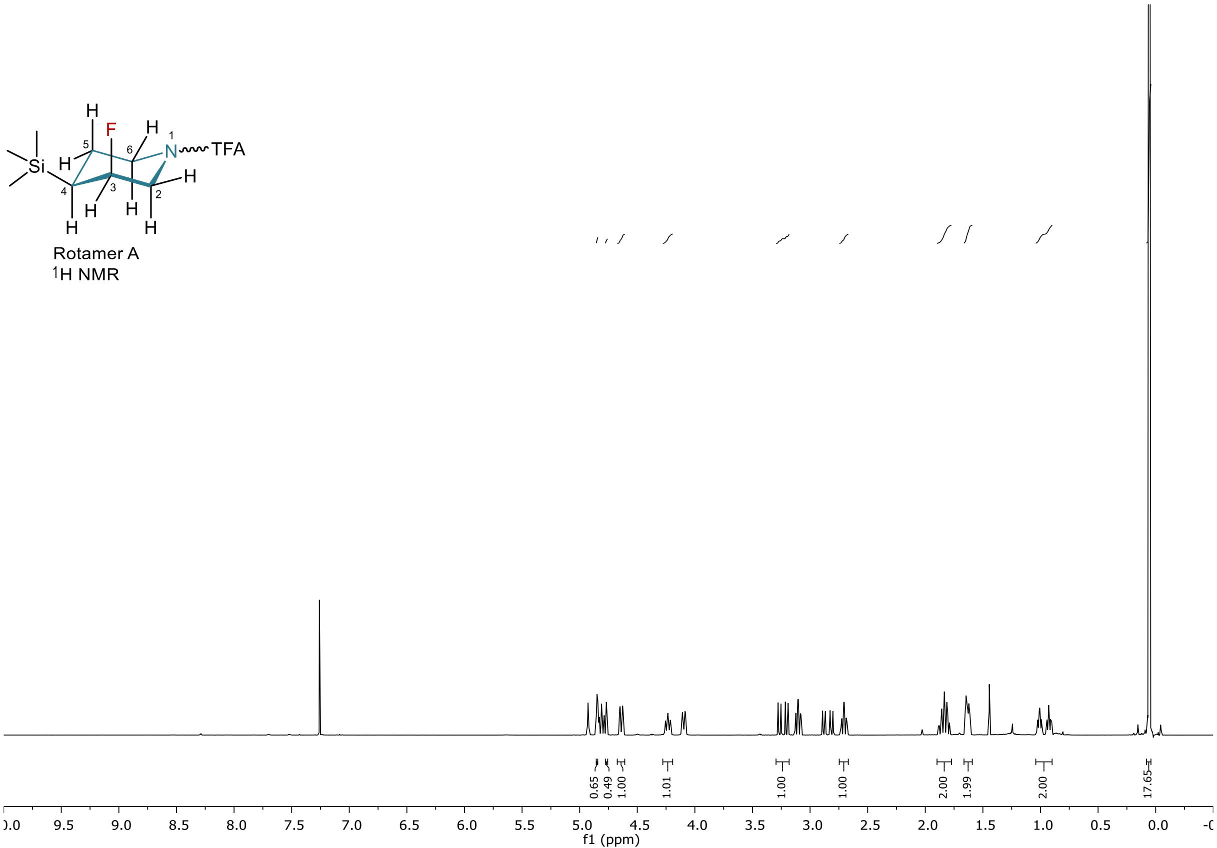

155.30
88.55
87.41
83.80
79.68
48.73
43.55
28.55
25.29
24.95
24.76
21.50
H
F
H
1
5
6
N
Boc
Bpin
H
H
4
3
2
H
H
H
H
^{13}C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

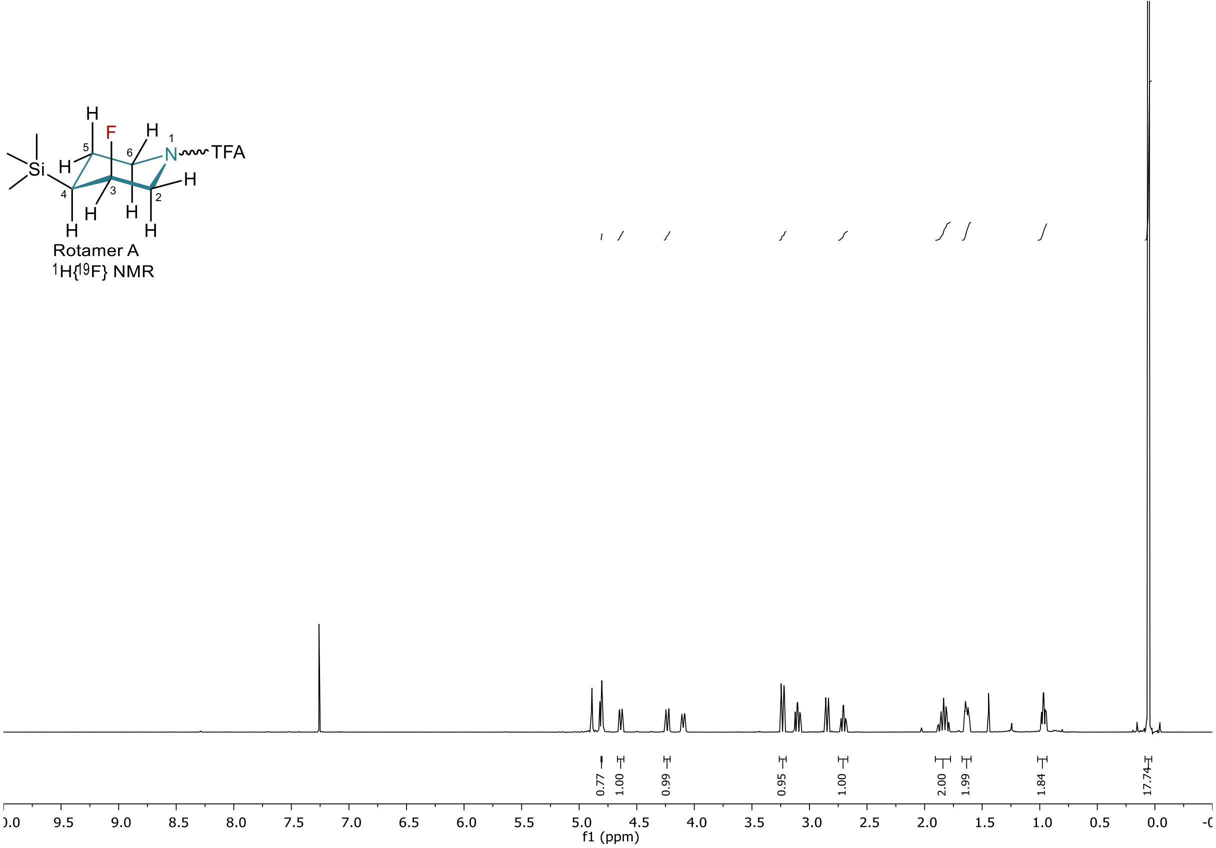

155.30
87.98
83.80
79.68
48.84
43.53
28.55
25.30
24.95
24.76
21.53
H
F
H
1
5
6
N
Boc
Bpin
H
H
4
3
2
H
H
H
H
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

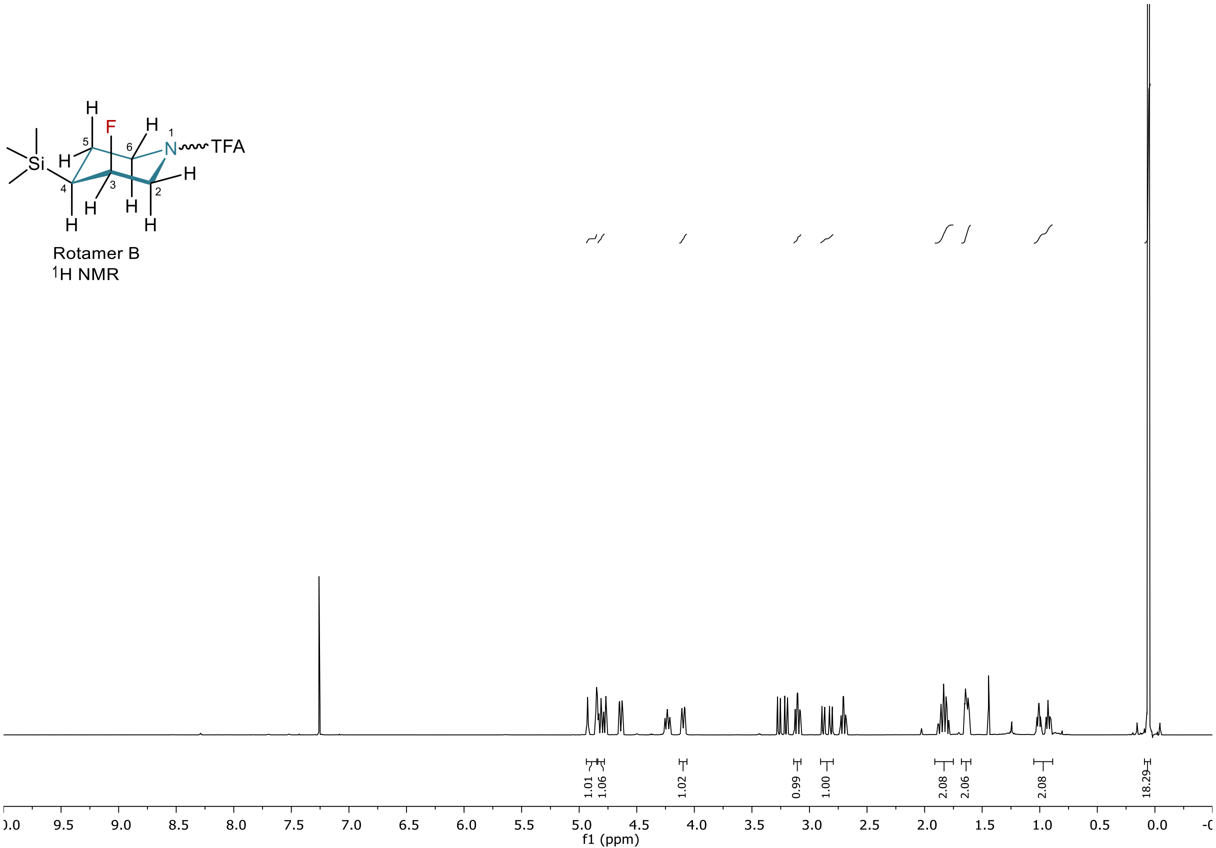

-186.39
-186.46
-186.53
-186.61
Bpin
F
N
Boc
H
1
2
3
4
5
6
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


-186.50
Bpin
F
N
Boc
H
1
2
3
4
5
6
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

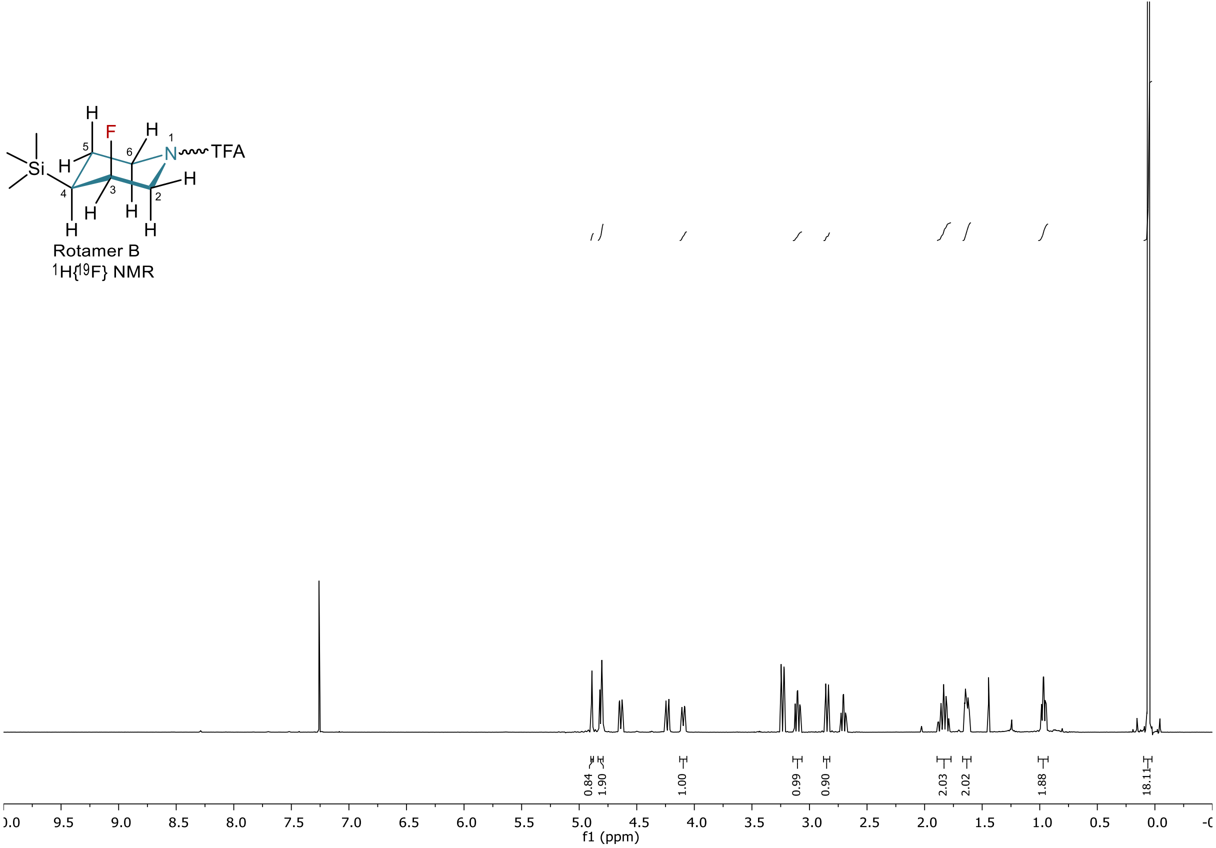

33.07
H
F
H
1
5
6
N
Boc
Bpin
H
H
4
3
2
H
H
H
H
¹¹B NMR
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140
f1 (ppm)


Si
H
F
H
1
N
TFA
5
6
H
H
4
3
2
H
H
H
H
Rotamer A
^{1}H NMR
0.65
0.49
1.00
1.01
1.00
1.00
2.00
1.99
2.00
17.65
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

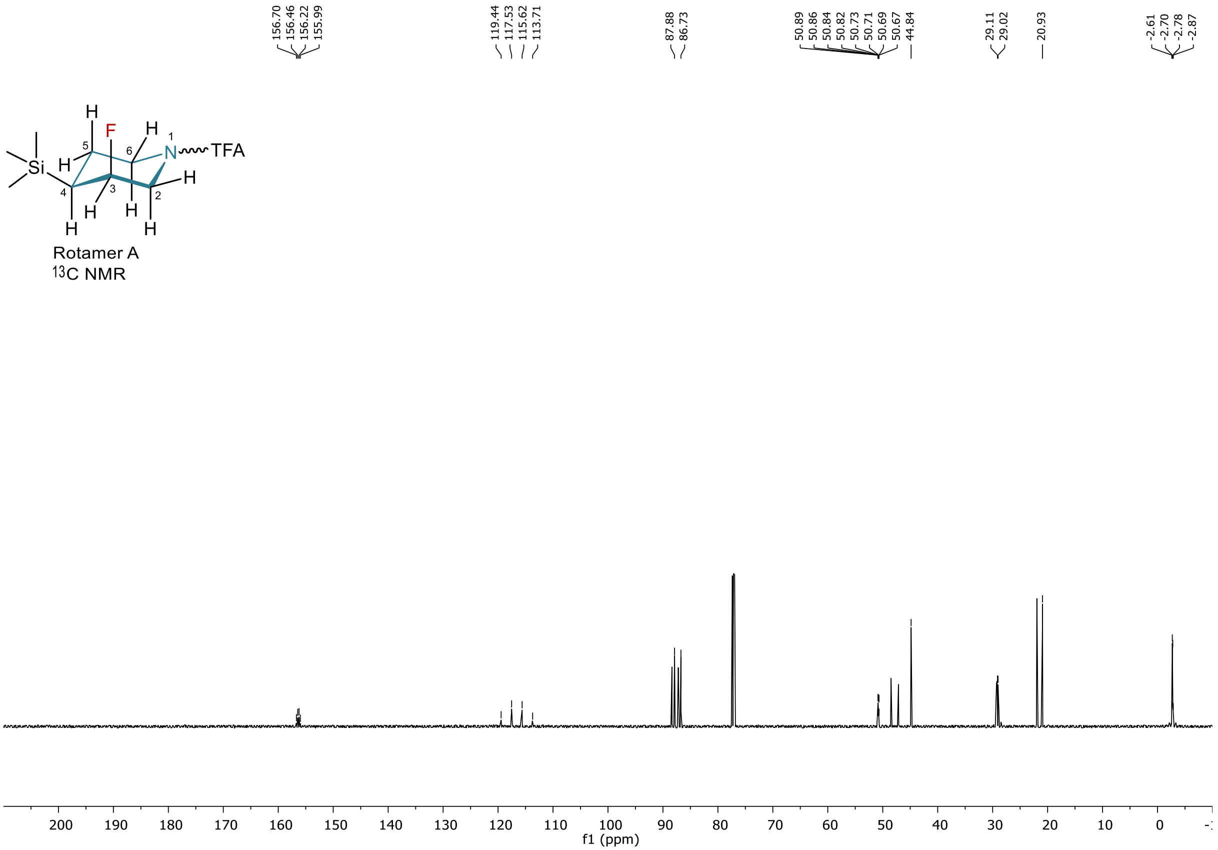

Si
H
F
H
1
N
TFA
5
6
H
H
4
3
2
H
H
H
H
Rotamer A
^{1}H{^{19}F} NMR
0.77
1.00
0.99
0.95
1.00
2.00
1.99
1.84
17.74
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

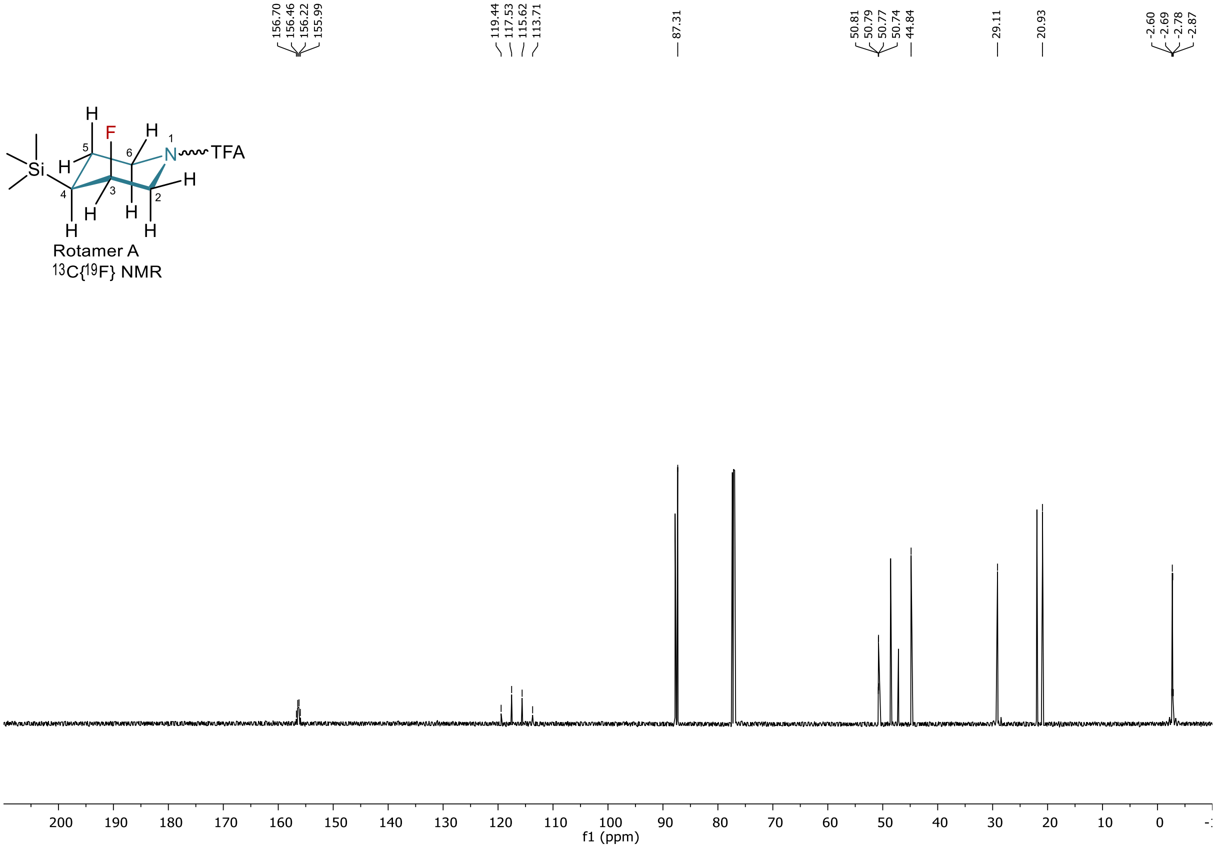


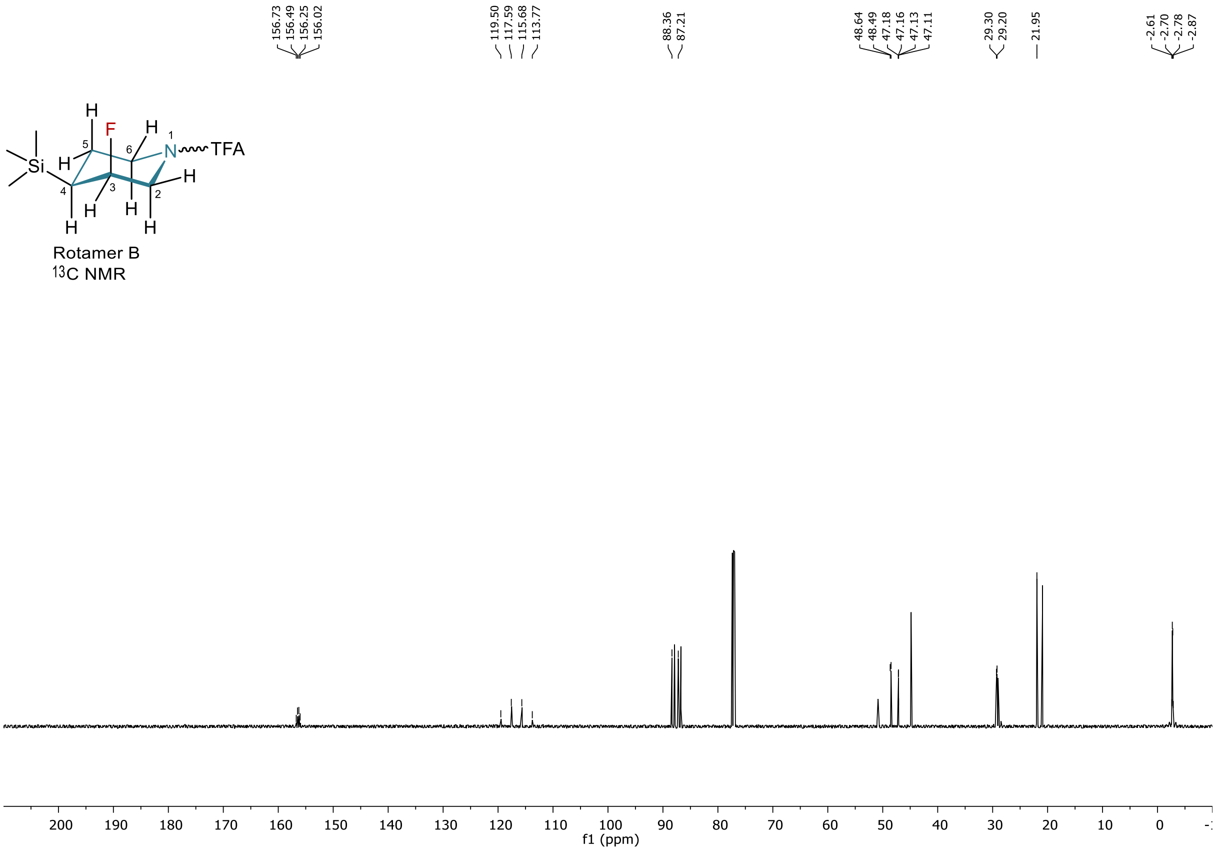
Rotamer B
^{1}H NMR

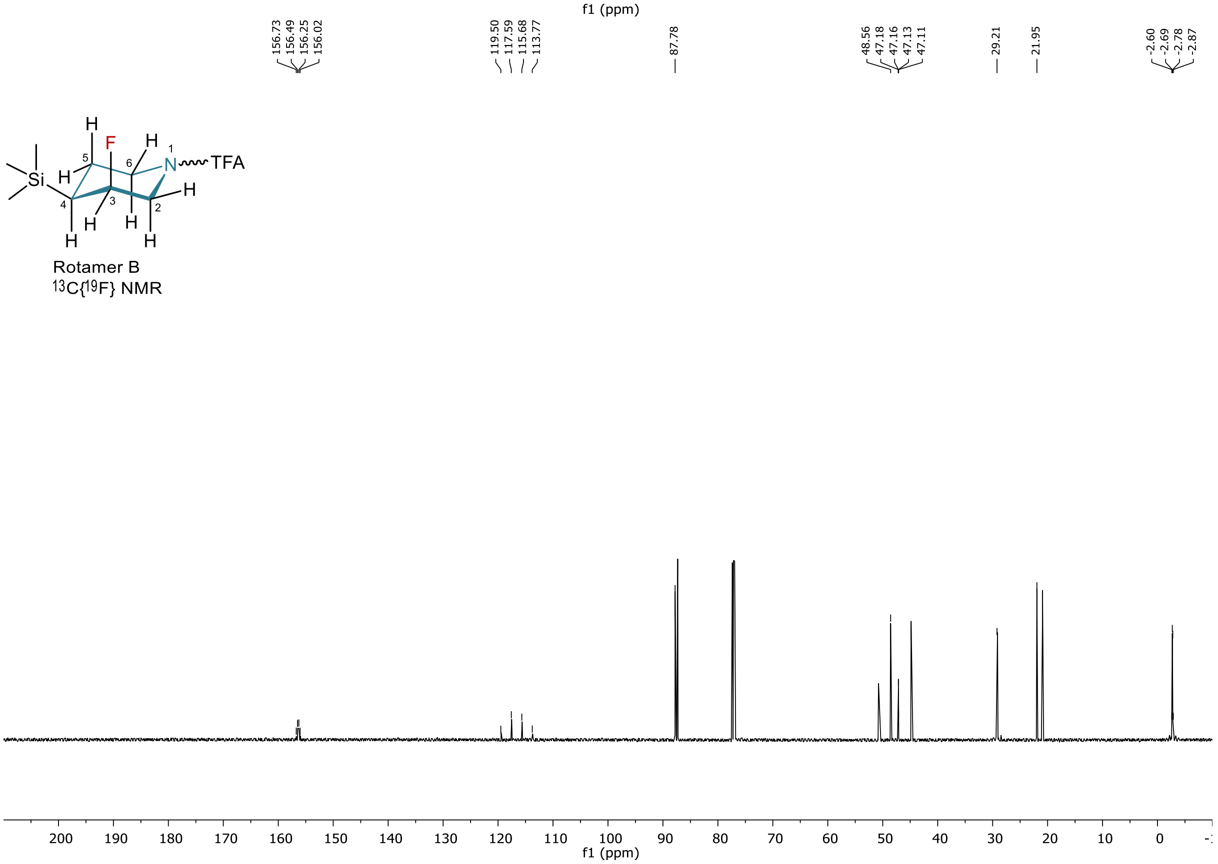


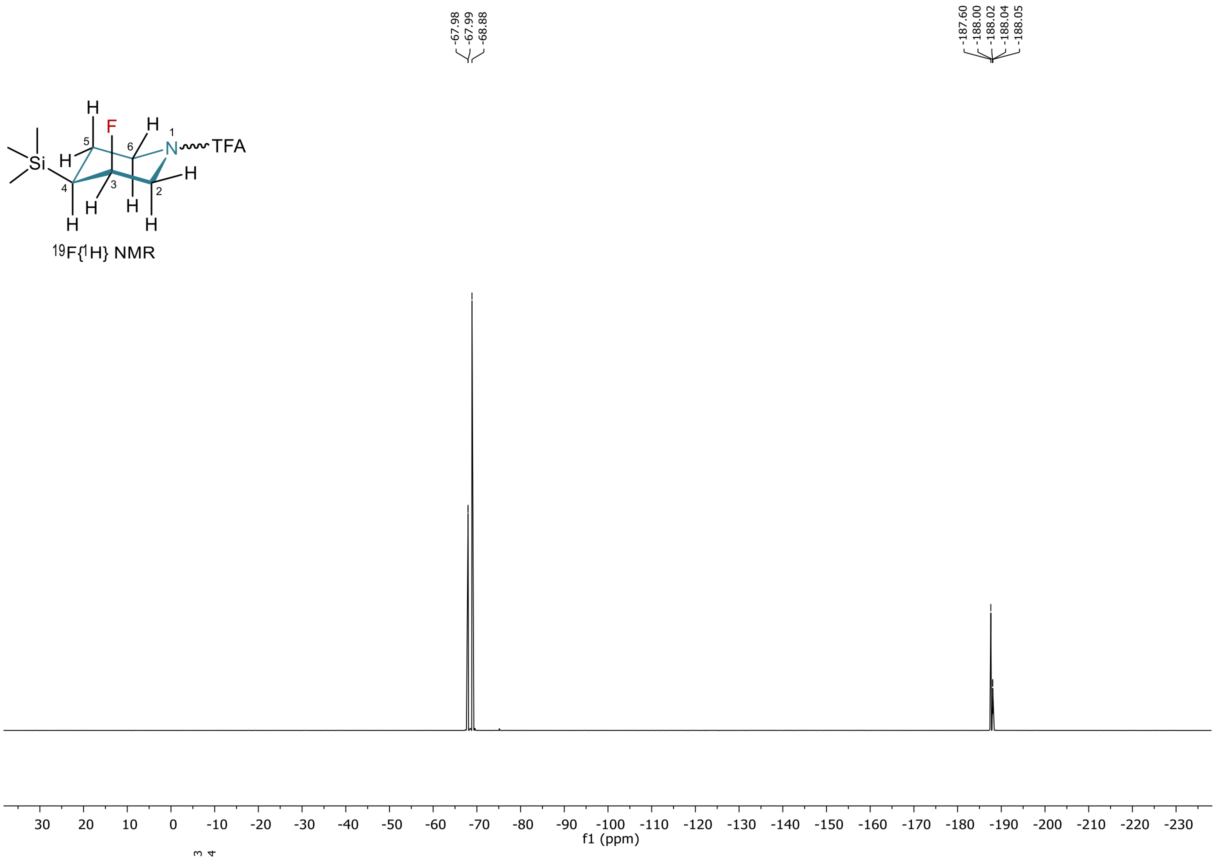
Rotamer B
^{1}H{^{19}F} NMR

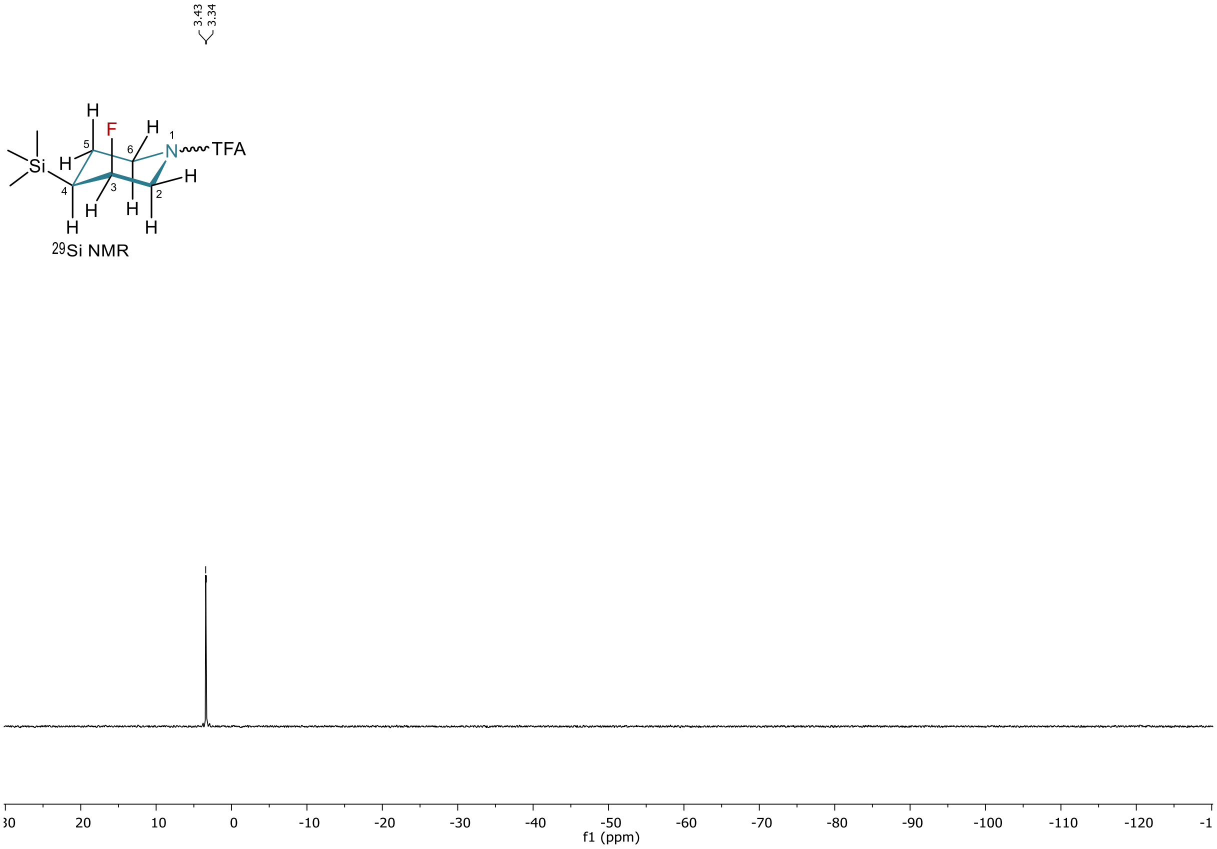

156.70
156.46
156.22
155.99
119.44
117.53
115.62
113.71
87.88
86.73
50.89
50.86
50.84
50.82
50.73
50.71
50.69
50.67
44.84
29.11
29.02
20.93
-2.61
-2.70
-2.78
-2.87
Si
H
F
H
1
N
TFA
5
6
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

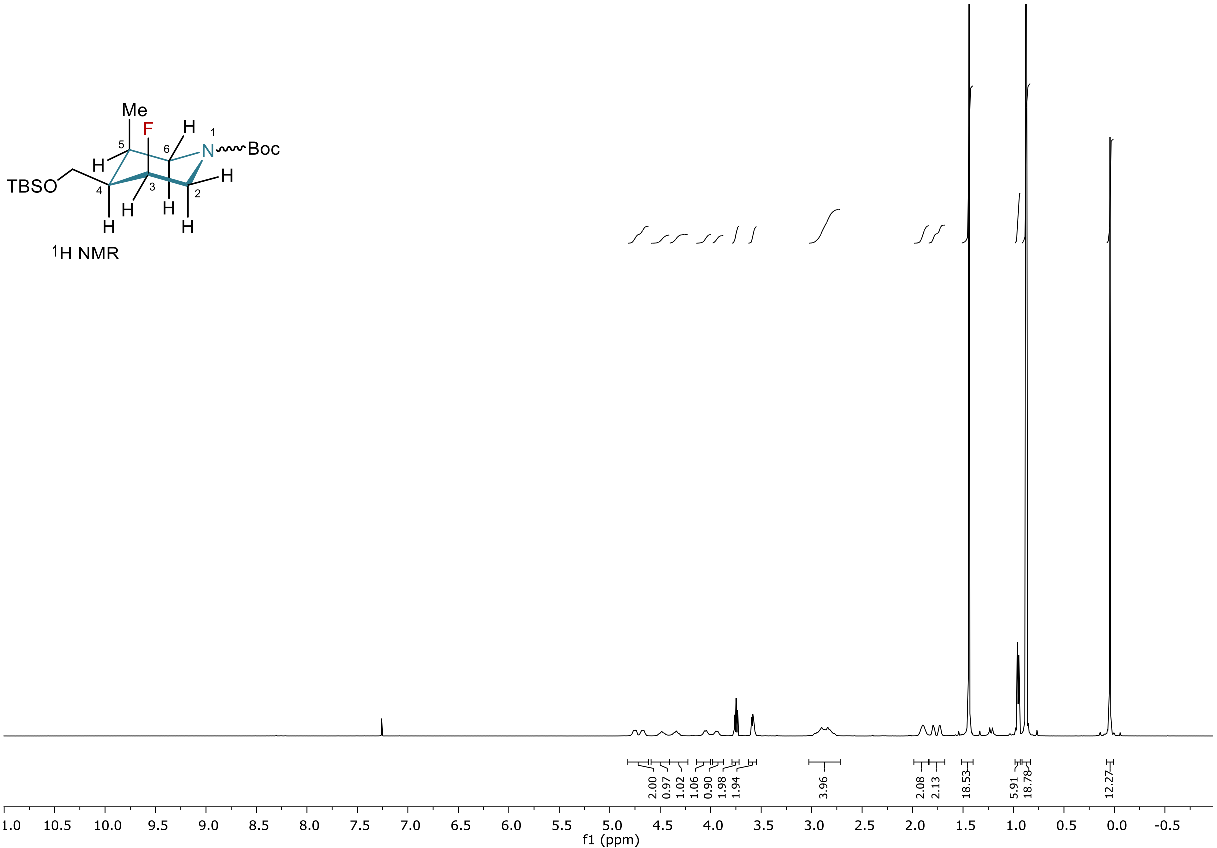

156.70
156.46
156.22
155.99
119.44
117.53
115.62
113.71
87.31
50.81
50.79
50.77
50.74
44.84
29.11
20.93
-2.60
-2.69
-2.78
-2.87
Si
H
F
H
1
N
TFA
5
6
H
H
4
3
2
H
H
H
H
Rotamer A
^{13}C{^{19}F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

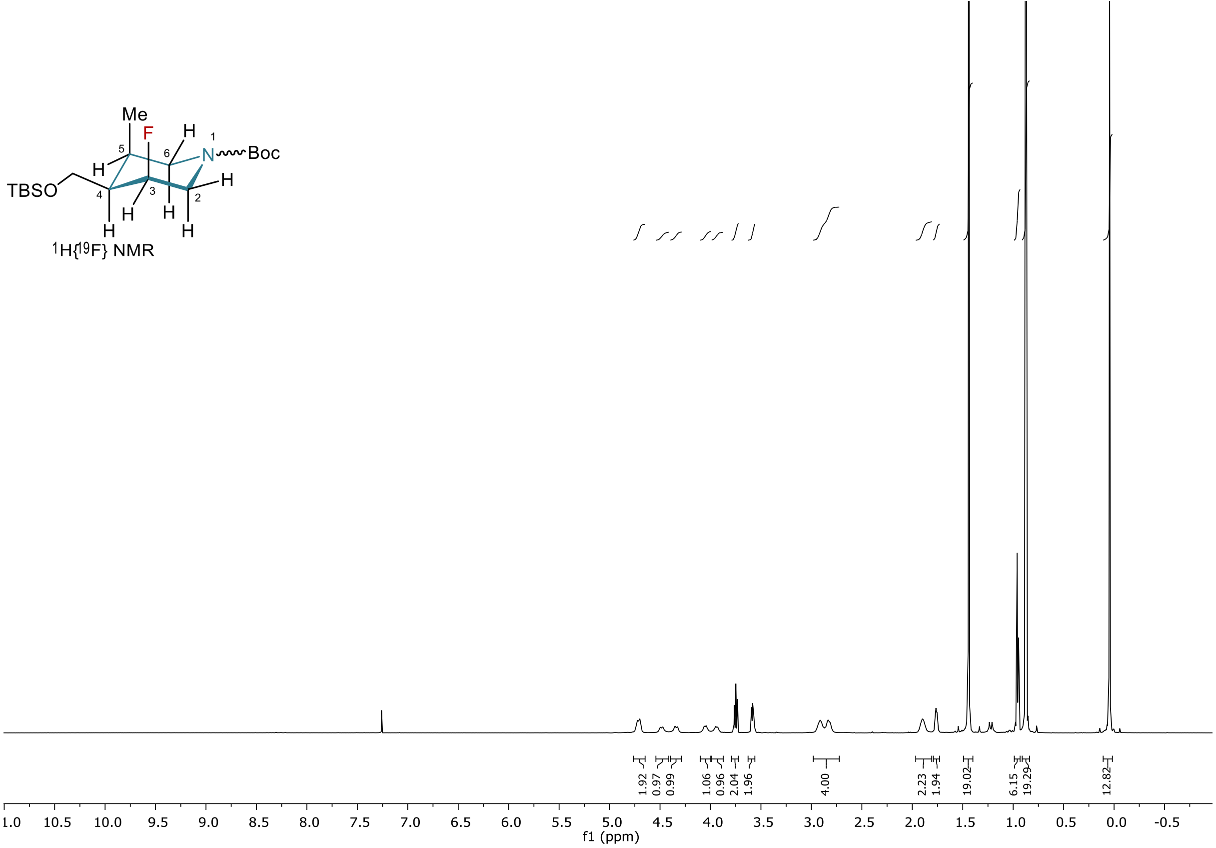

156.73
156.49
156.25
156.02
119.50
117.59
115.68
113.77
88.36
87.21
48.64
48.49
47.18
47.16
47.13
47.11
29.30
29.20
21.95
-2.61
-2.70
-2.78
-2.87
Si
H
F
H
1
N
TFA
5
6
H
4
3
2
H
H
H
H
H
Rotamer B
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

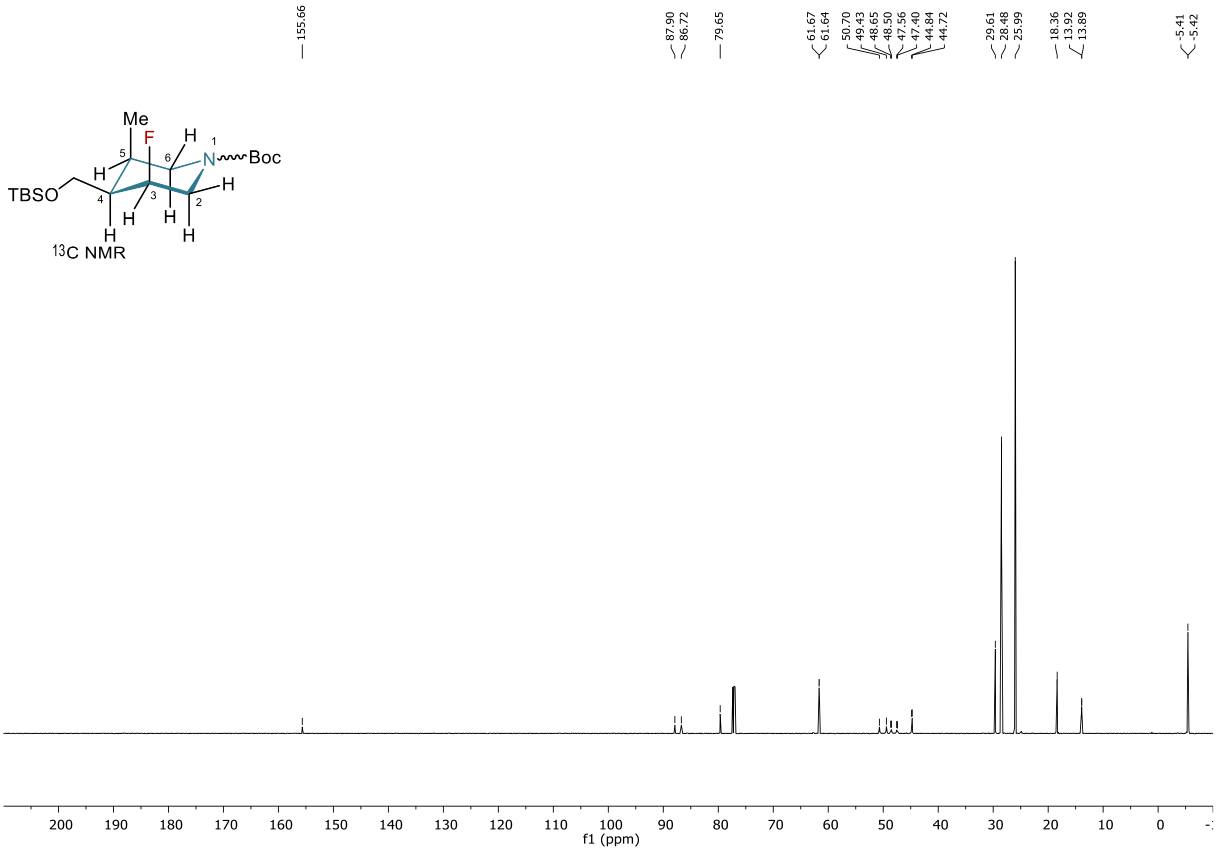

156.73
156.49
156.25
156.02
119.50
117.59
115.68
113.77
87.78
48.56
47.18
47.16
47.13
47.11
29.21
21.95
-2.60
-2.69
-2.78
-2.87
Si
H
F
H
1
N
TFA
5
6
H
4
3
2
H
H
H
H
H
Rotamer B
13C{19F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

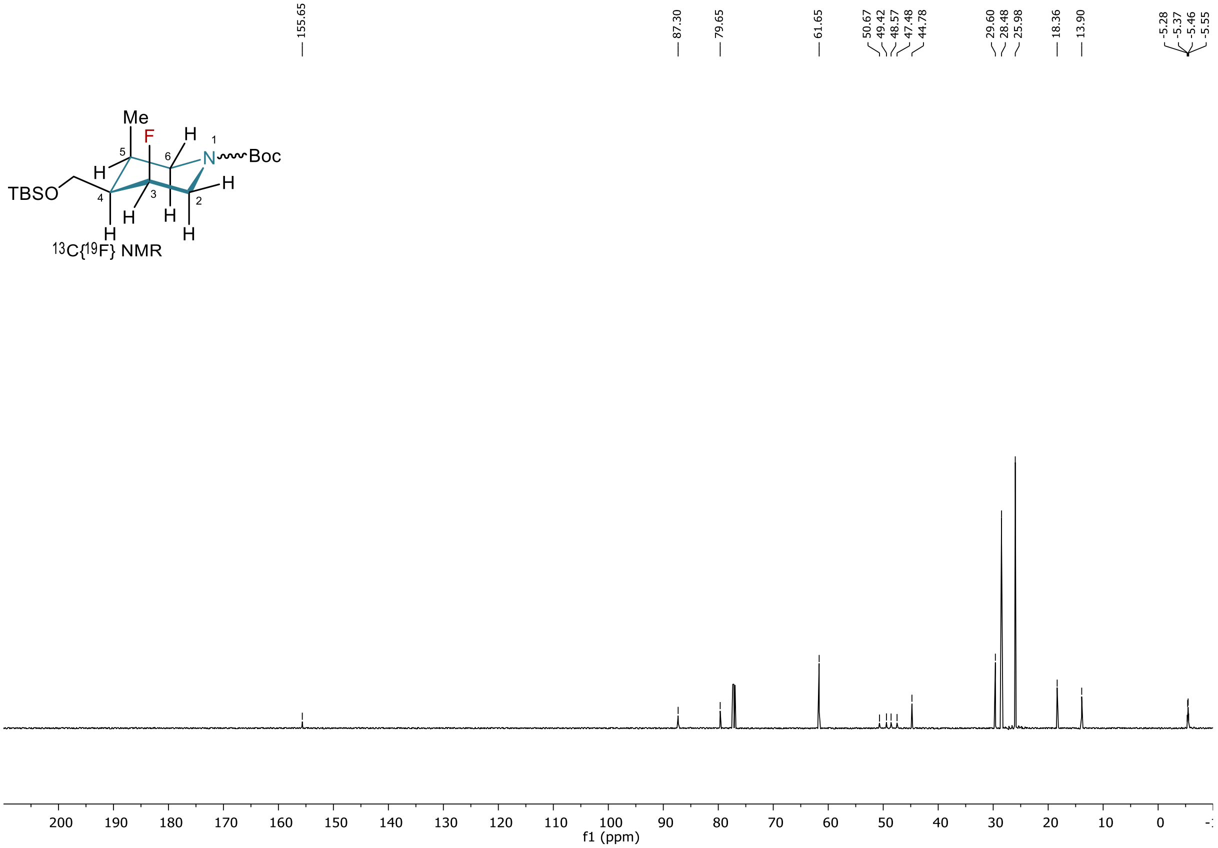

-67.98
-67.99
-68.88
-187.60
-188.00
-188.02
-188.04
-188.05
Si
F
H
N
TFA
1
2
3
4
5
6
^{19}F{^{1}H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

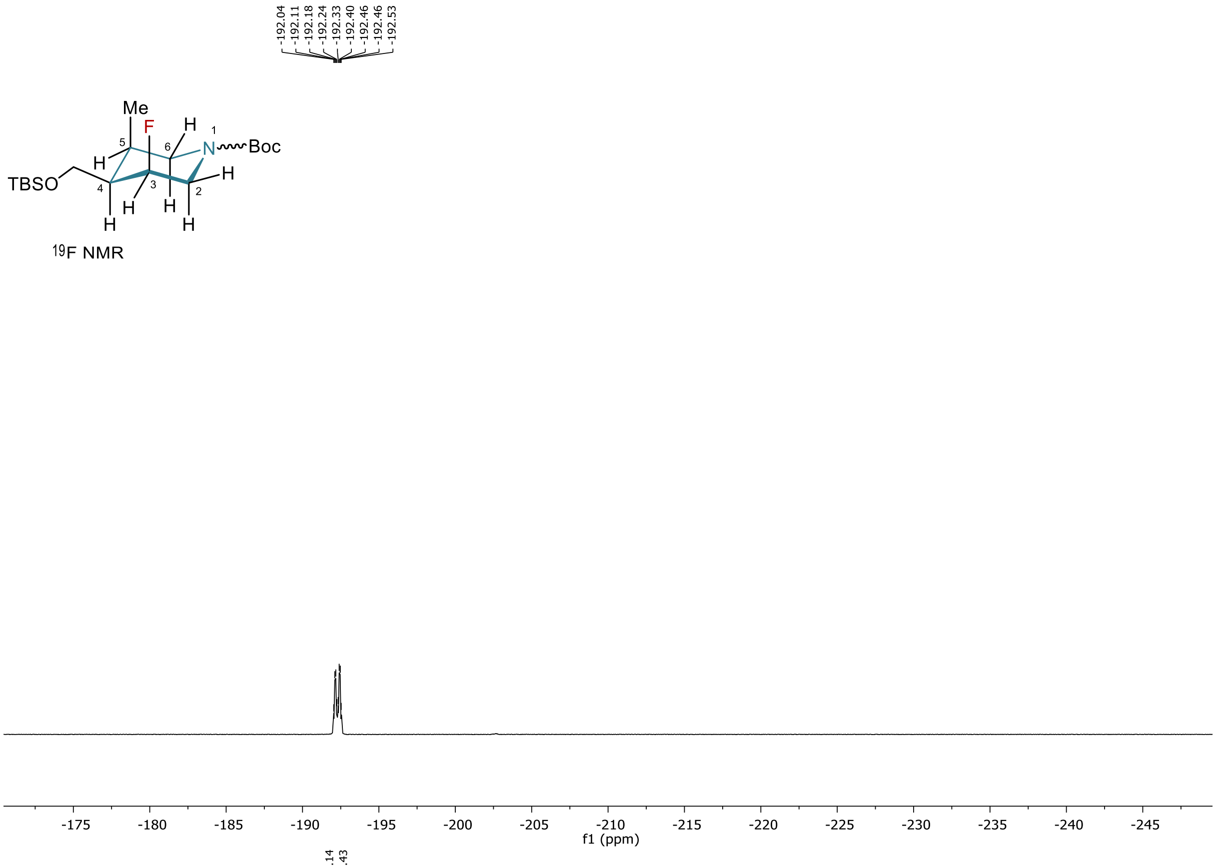

3.43
3.34
Si
F
H
N
TFA
1
2
3
4
5
6
^{29}Si NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -1
f1 (ppm)

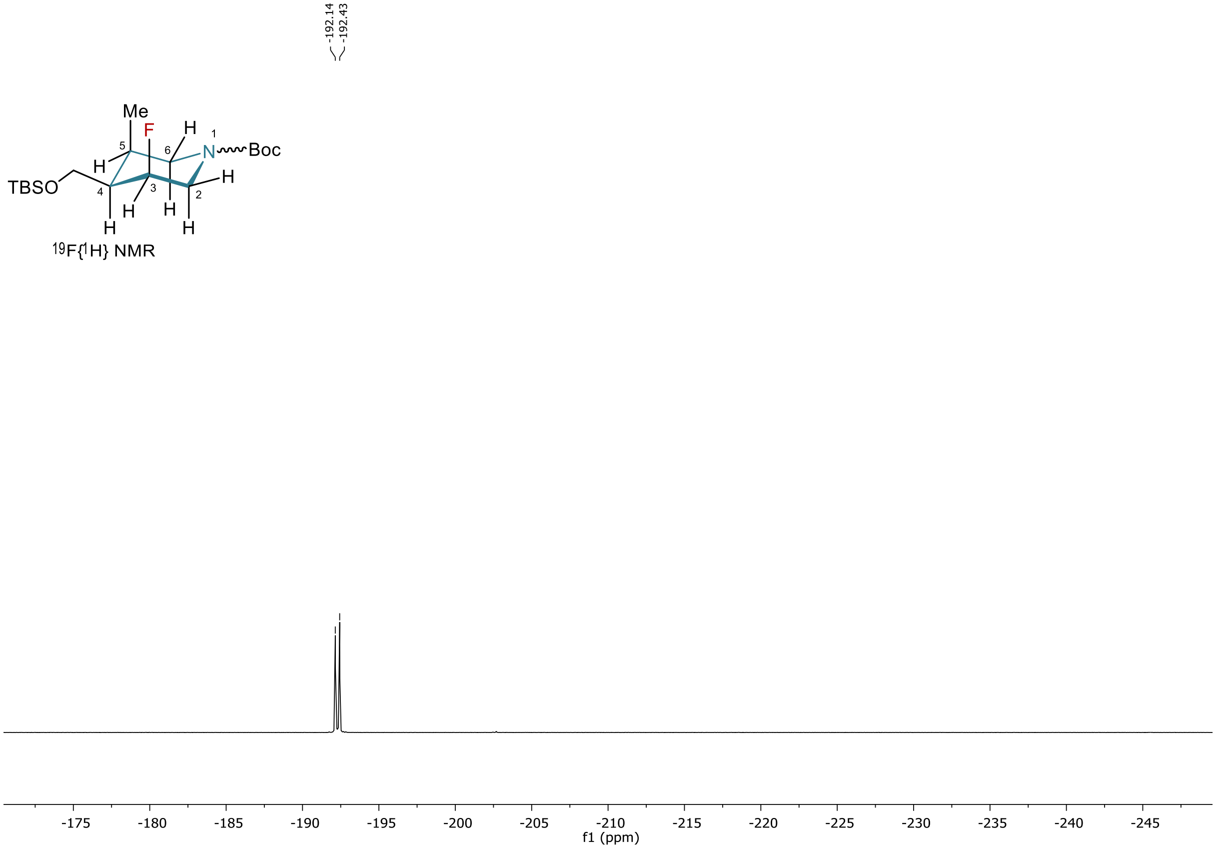

Me
F
H
1
N
Boc
5
6
H
H
TBSO
4
3
2
H
H
H
H
1H NMR
2.00
0.97
1.02
1.06
0.90
1.98
1.94
3.96
2.08
2.13
18.53
5.91
18.78
12.27
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

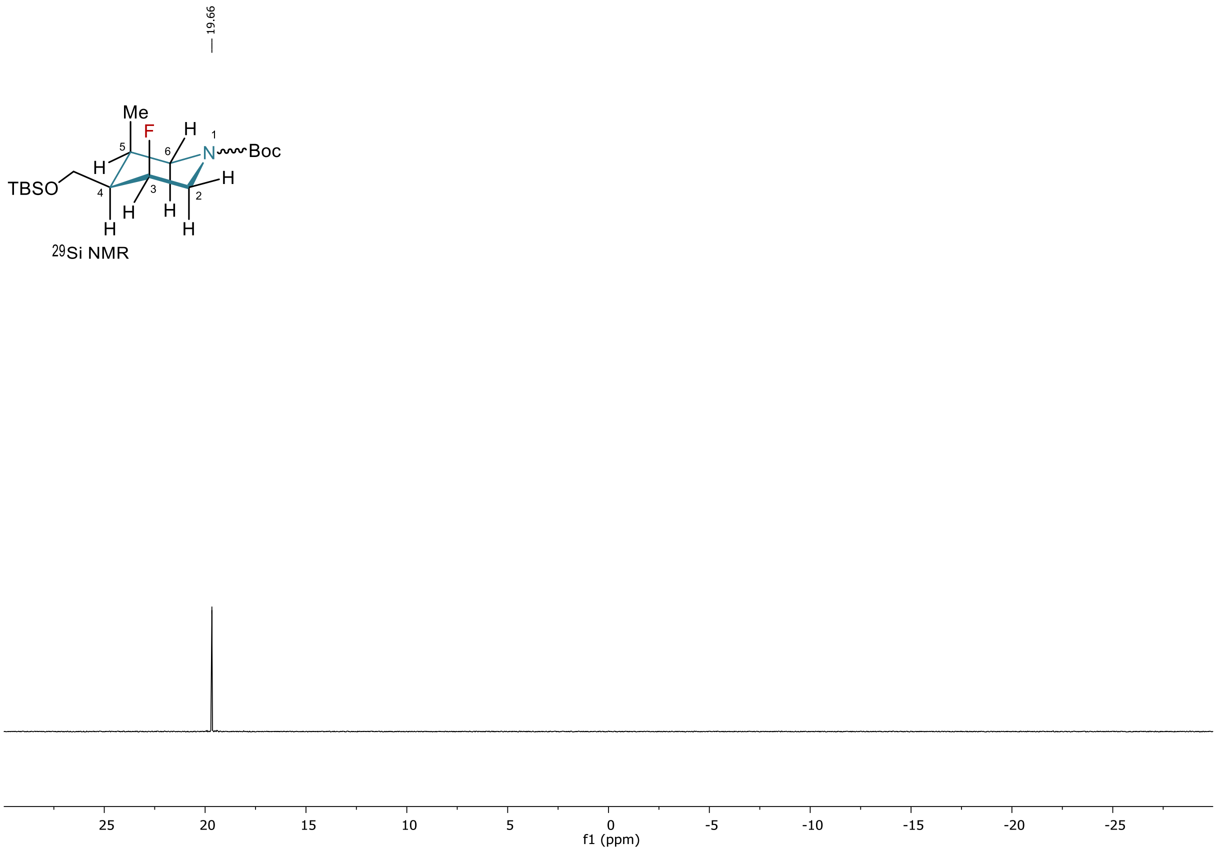

Me
F
H
1
N
Boc
5
6
H
H
TBSO
4
3
2
H
H
H
H
1H{19F} NMR
1.92
0.97
0.99
1.06
0.96
2.04
1.96
4.00
2.23
1.94
19.02
6.15
19.29
12.82
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


155.66
87.90
86.72
79.65
61.67
61.64
50.70
49.43
48.65
48.50
47.56
47.40
44.84
44.72
29.61
28.48
25.99
18.36
13.92
13.89
-5.41
-5.42
Me
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

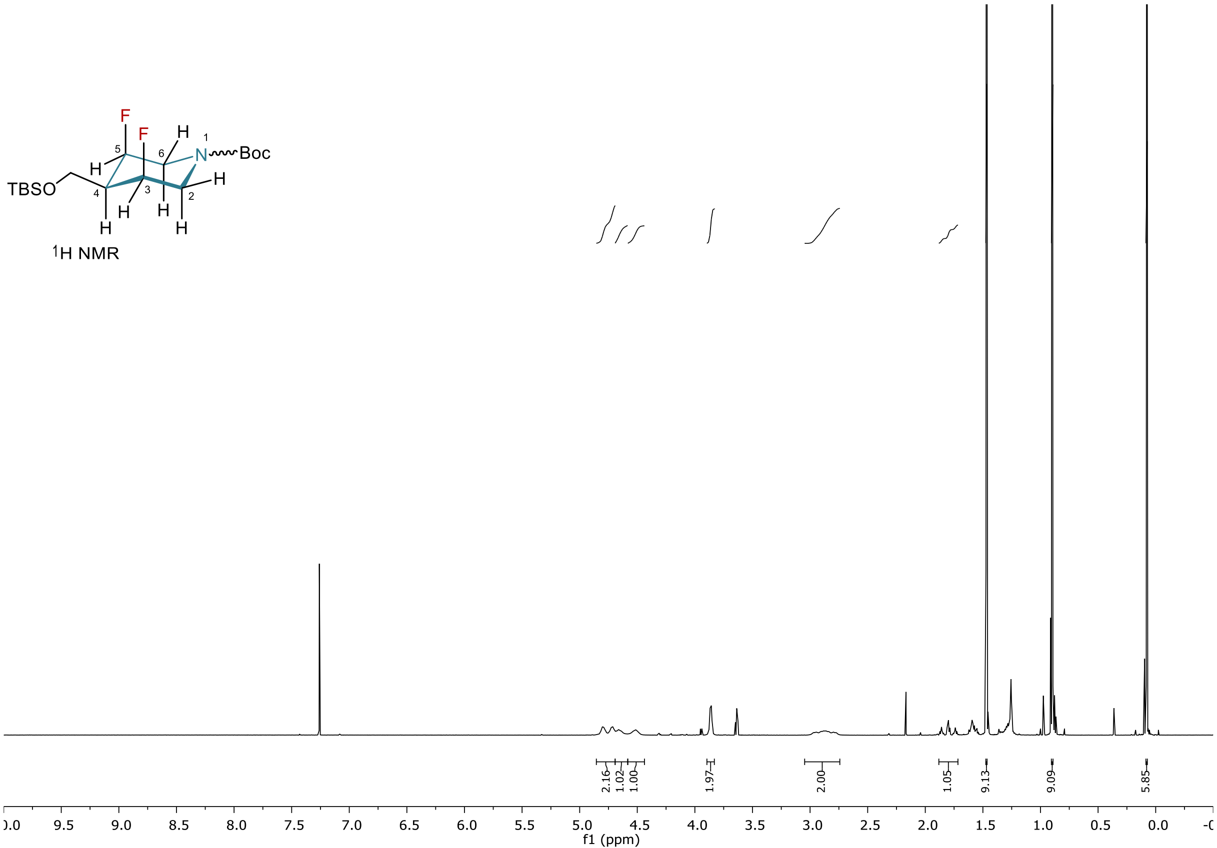

155.65
87.30
79.65
61.65
50.67
49.42
48.57
47.48
44.78
29.60
28.48
25.98
18.36
13.90
-5.28
-5.37
-5.46
-5.55
Me
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
13C{19F} NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

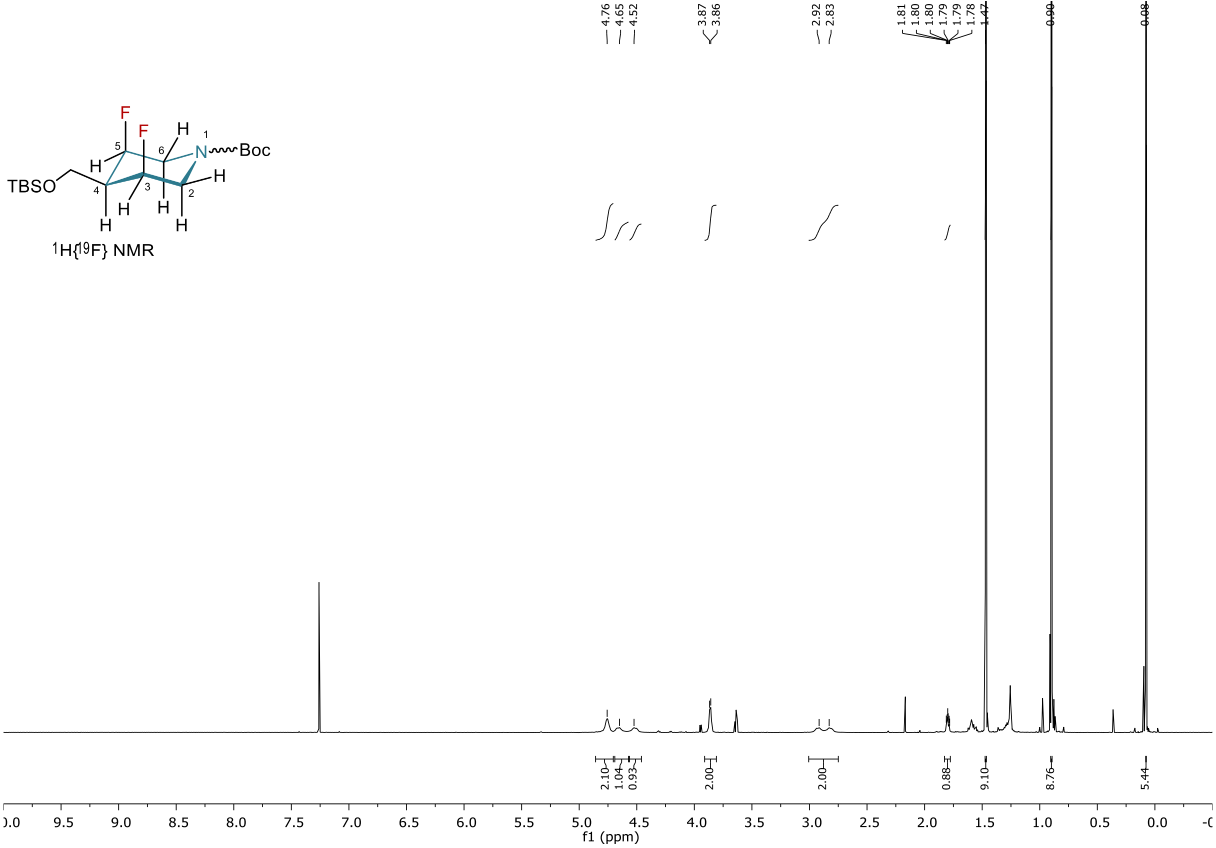

-192.04
-192.11
-192.18
-192.24
-192.33
-192.40
-192.46
-192.46
-192.53
Me
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

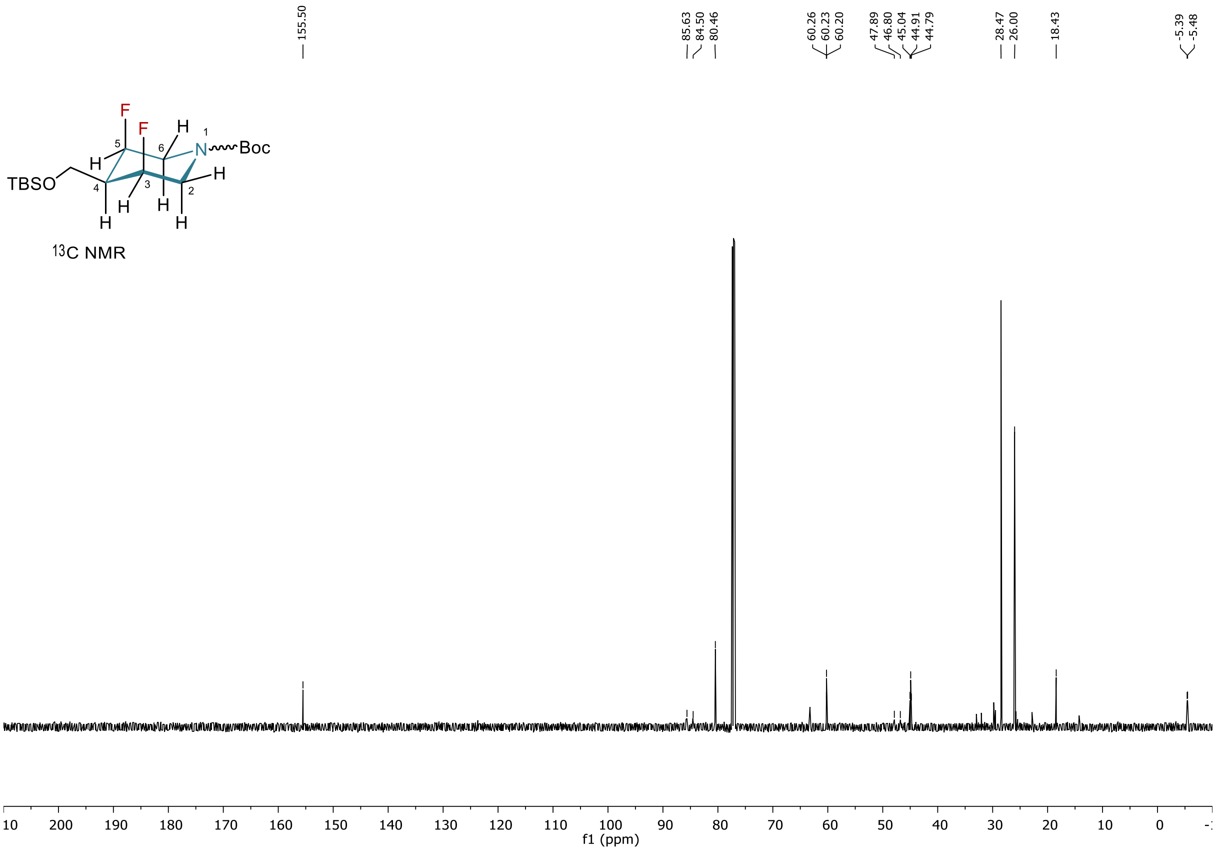

-192.14
-192.43
Me
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)


19.66
Me
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
25
20
15
10
5
0
-5
-10
-15
-20
-25
f1 (ppm)

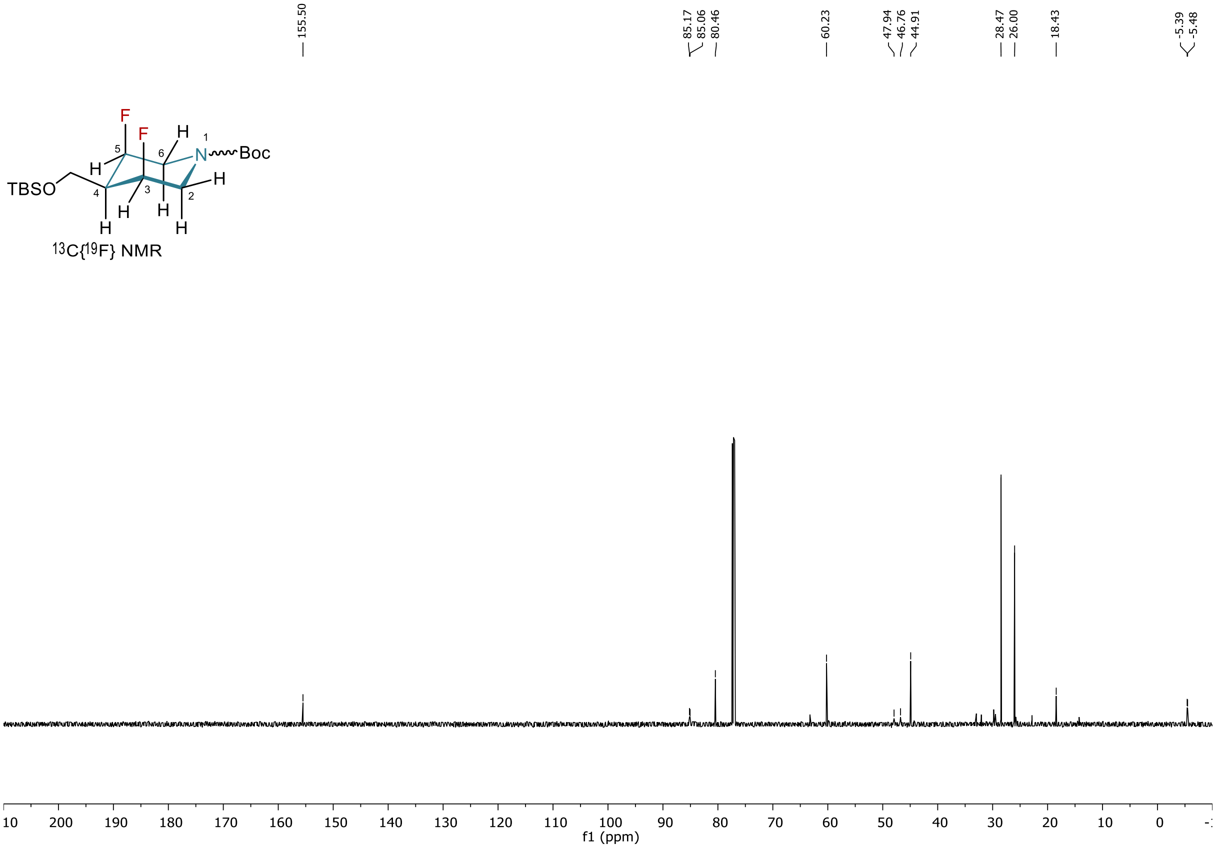
^{29}Si NMR


F
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
¹H NMR
2.16
1.02
1.00
1.97
2.00
1.05
9.13
9.09
5.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

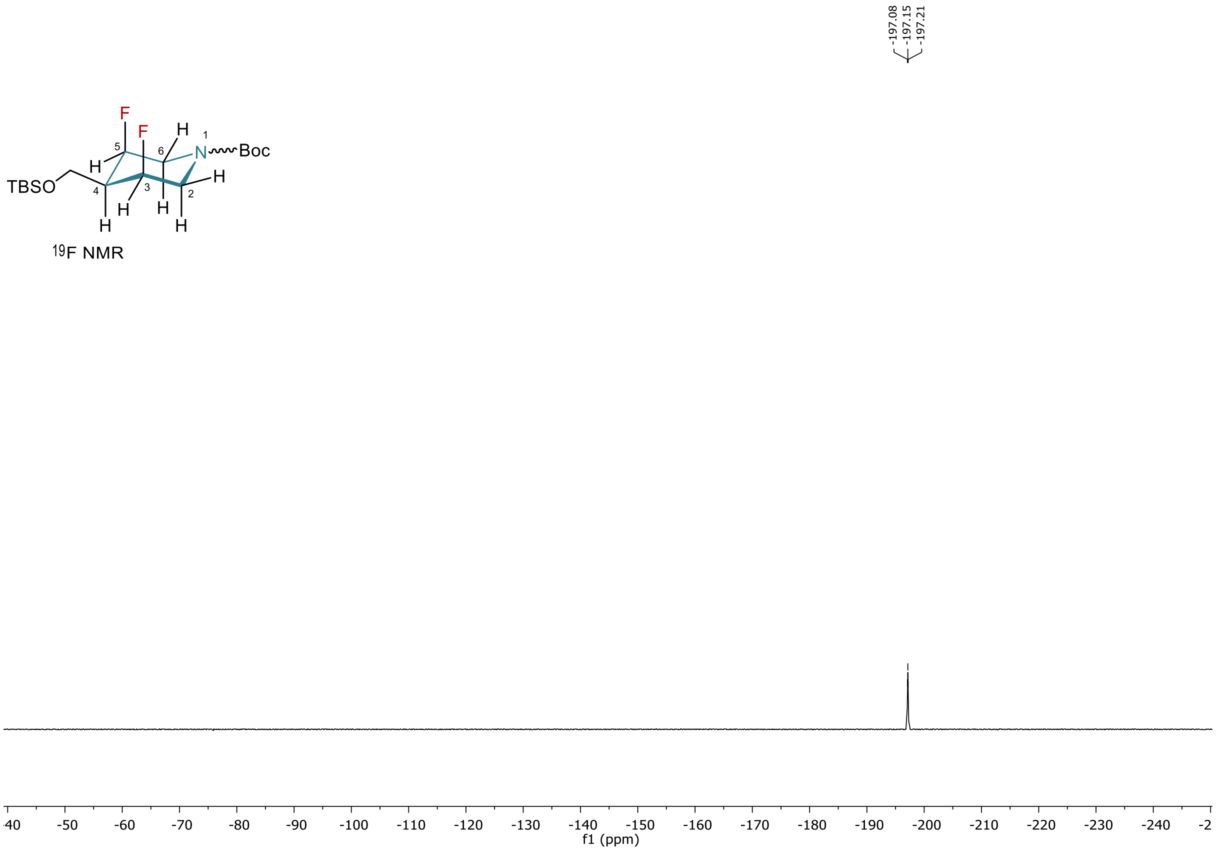

4.76
4.65
4.52
3.87
3.86
2.92
2.83
1.81
1.80
1.80
1.79
1.79
1.78
1.47
0.90
0.08
F
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
¹H{¹⁹F} NMR
2.10
1.04
0.93
2.00
2.00
0.88
9.10
8.76
5.44
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



155.50
85.63
84.50
80.46
60.26
60.23
60.20
47.89
46.80
45.04
44.91
44.79
28.47
26.00
18.43
-5.39
-5.48
F
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



155.50
85.17
85.06
80.46
60.23
47.94
46.76
44.91
28.47
26.00
18.43
-5.39
-5.48
F
F
H
1
5
6
N
Boc
H
H
TBSO
4
3
2
H
H
H
H
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-197.08
-197.15
-197.21
F
F
H
1
N
Boc
5
6
H
H
TBSO
4
3
2
H
H
H
H
^{19}F NMR
40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
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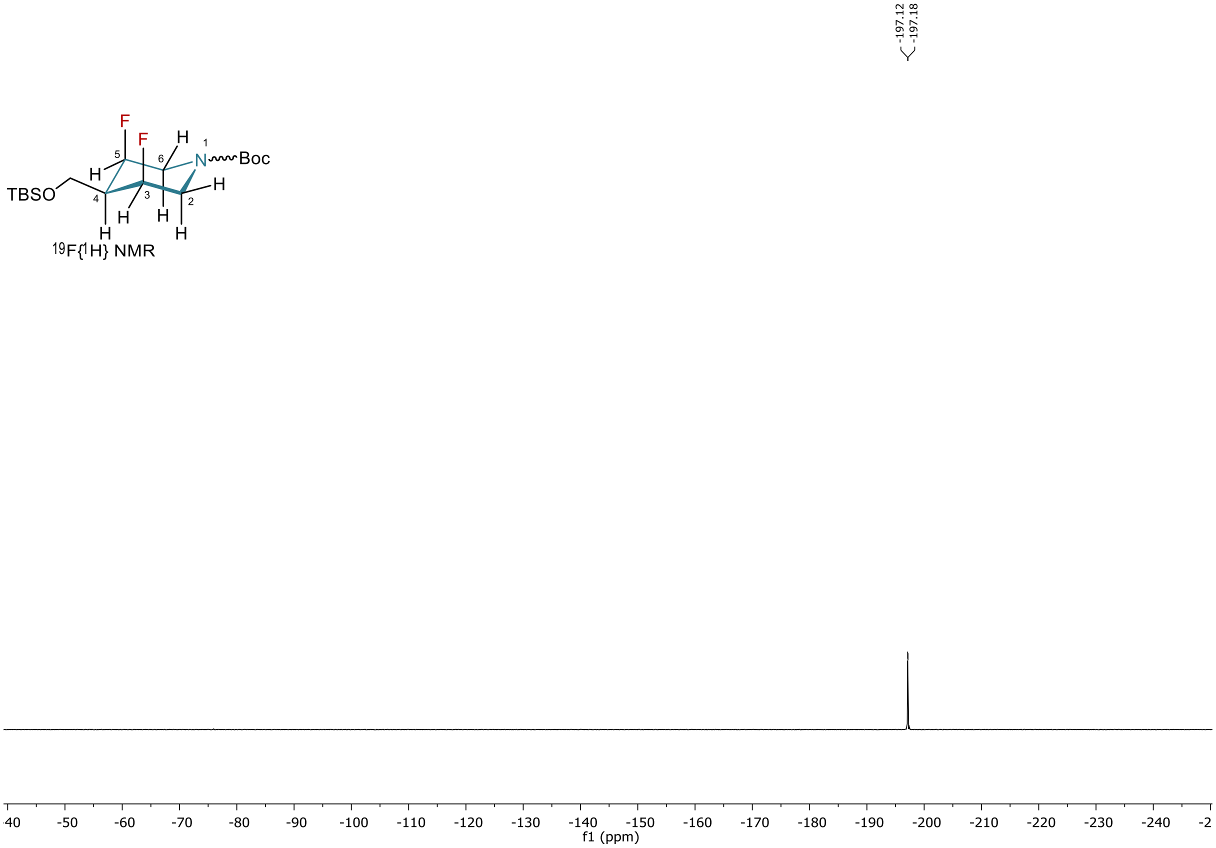
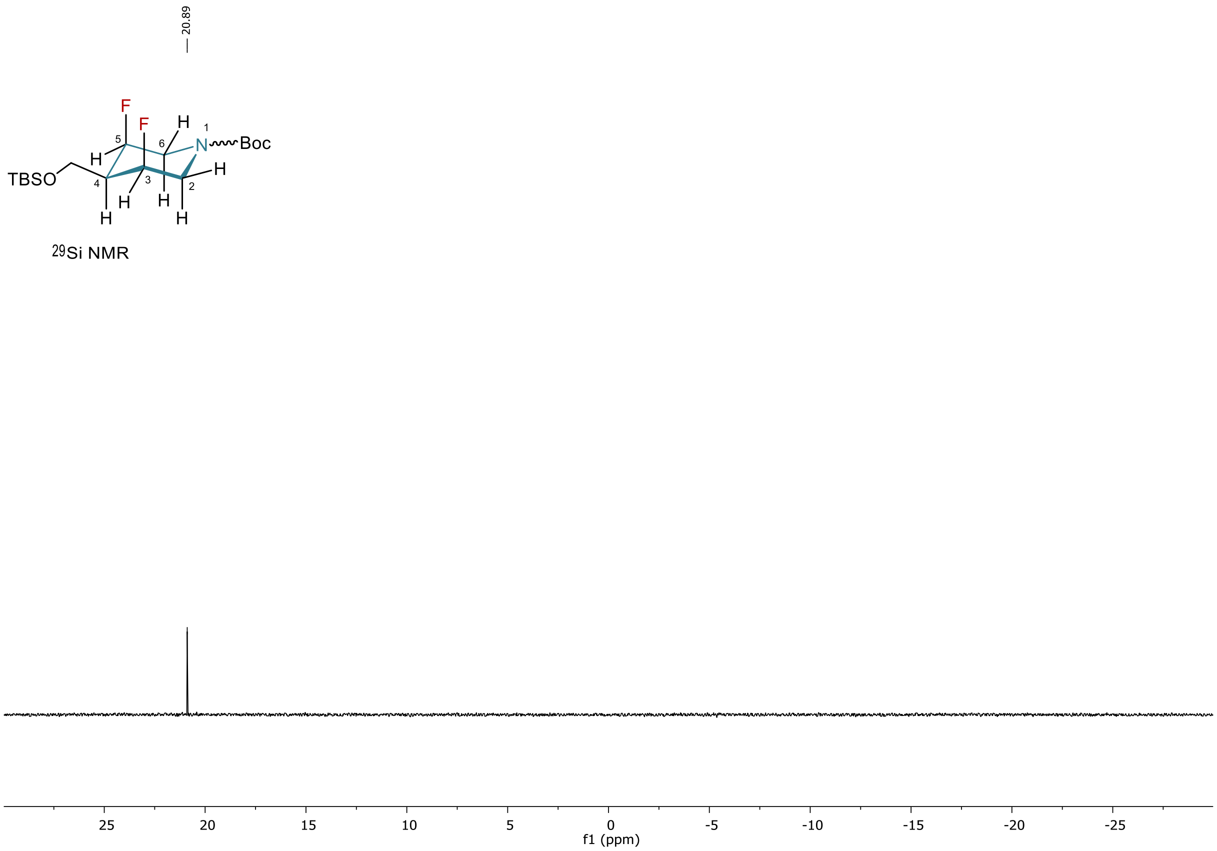
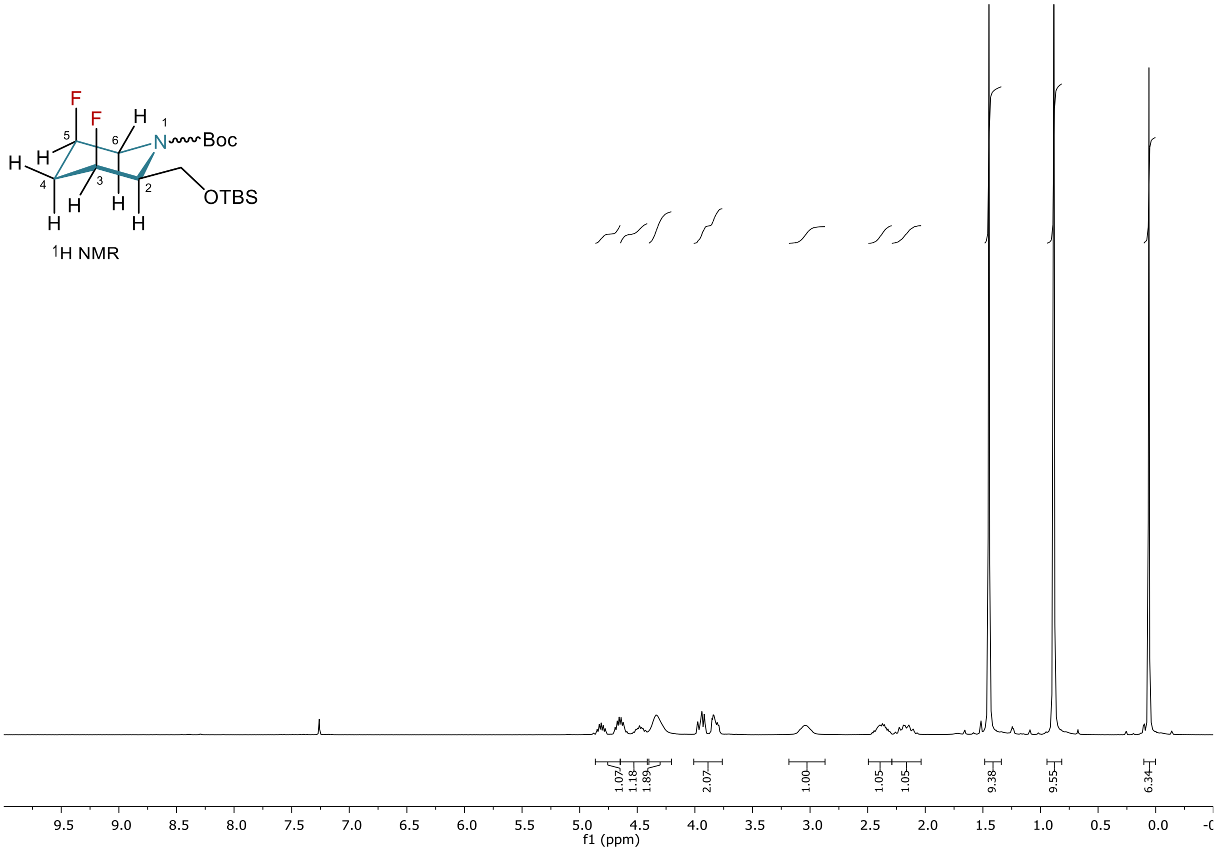
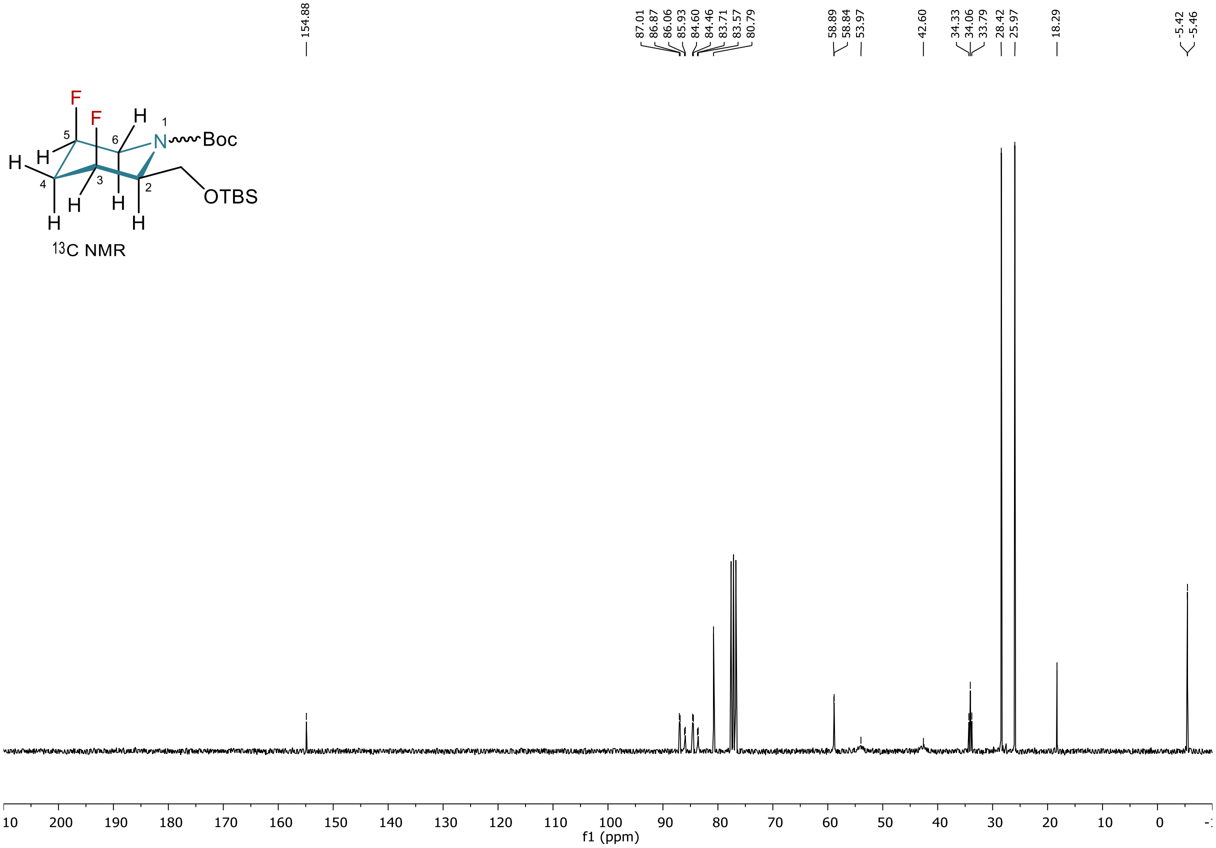
-220
-230
-240
-2
f1 (ppm)


-197.12
-197.18
F
F
H
1
N
Boc
5
6
H
H
TBSO
4
3
2
H
H
H
H
^{19}F{^{1}H} NMR
40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
-2
f1 (ppm)


20.89
F
F
H
1
5
6
N
Boc
H
TBSO
4
3
2
H
H
H
H
H
29Si NMR
25
20
15
10
5
0
-5
-10
-15
-20
-25
f1 (ppm)


F
F
H
1
N
Boc
5
6
H
H
4
3
2
OTBS
H
H
H
H

1H NMR
1.07
1.18
1.89
2.07
1.00
1.05
1.05
9.38
9.55
6.34
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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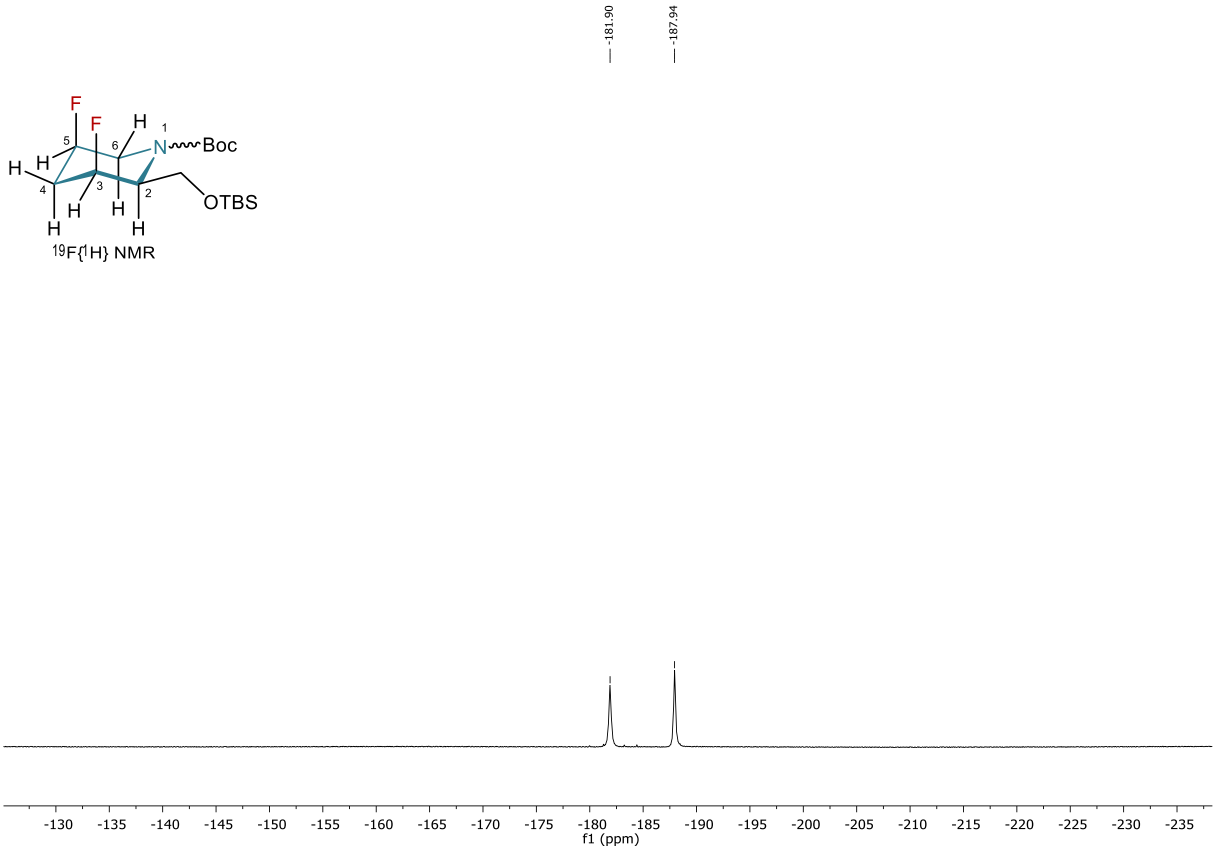
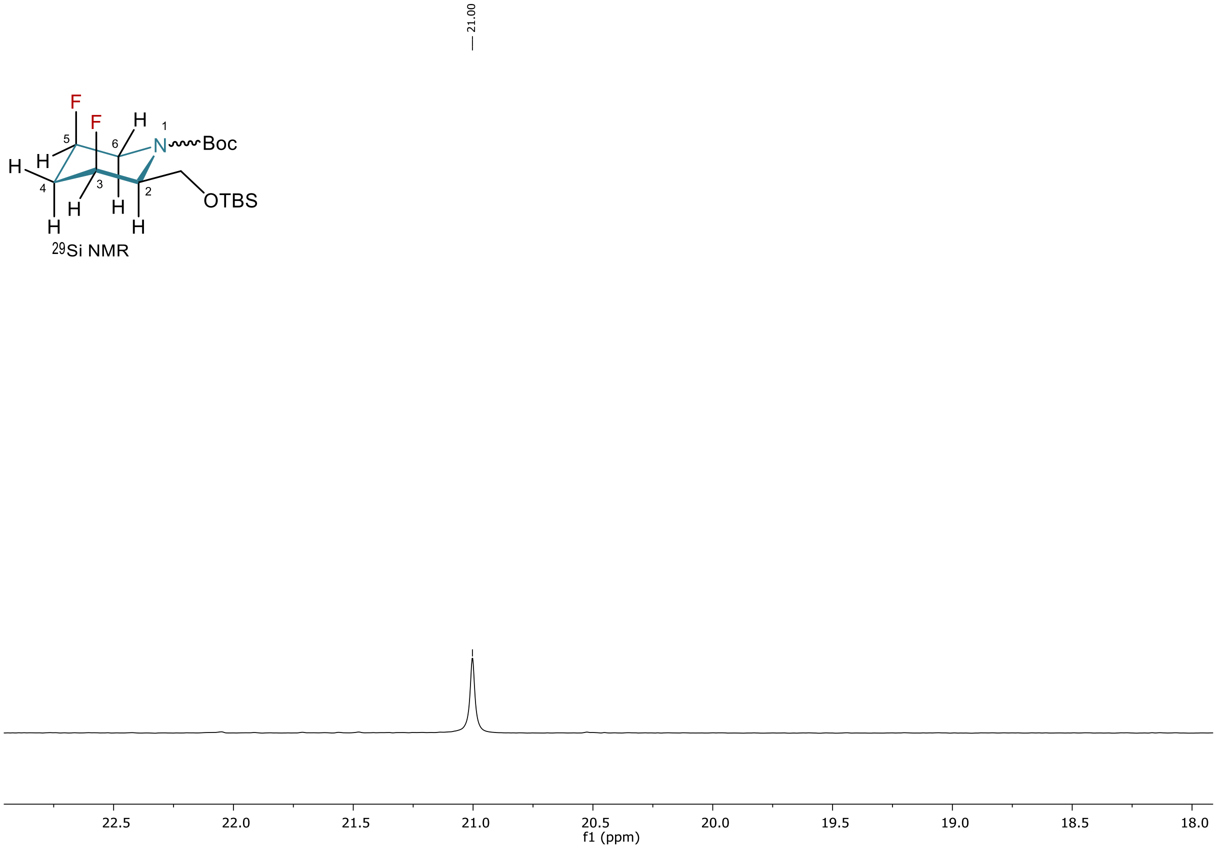
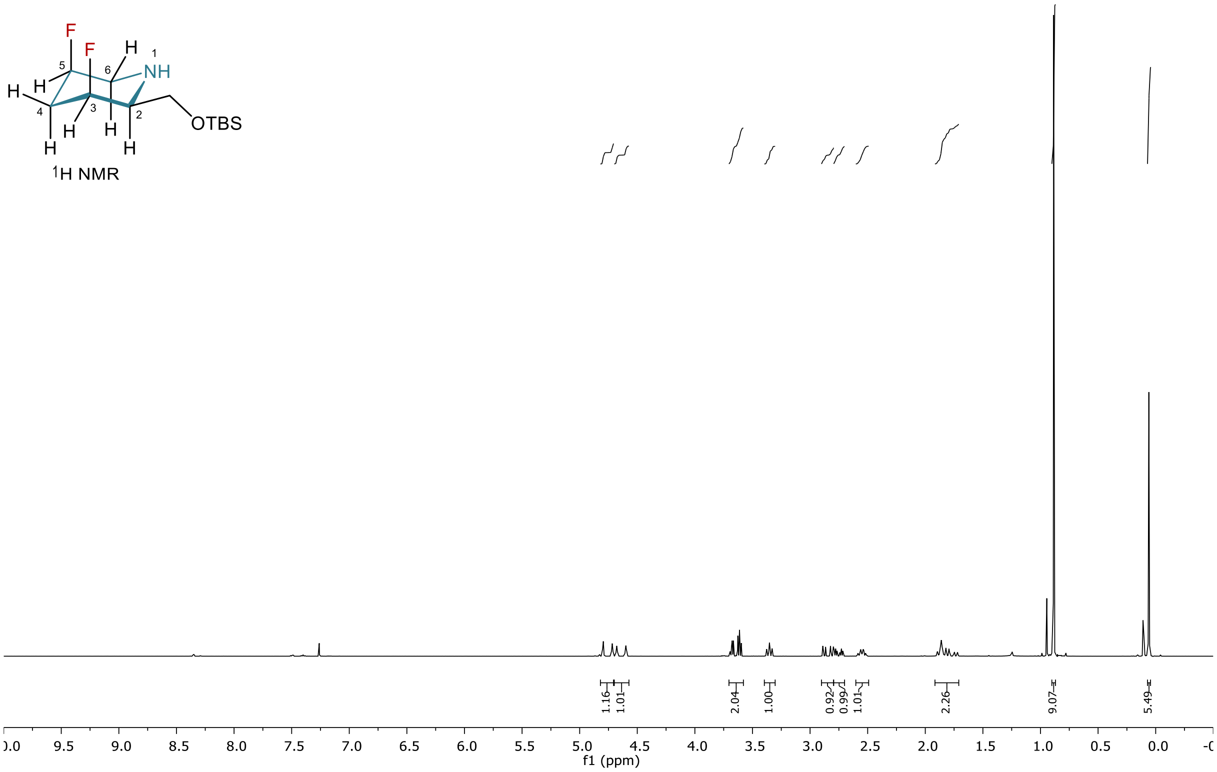
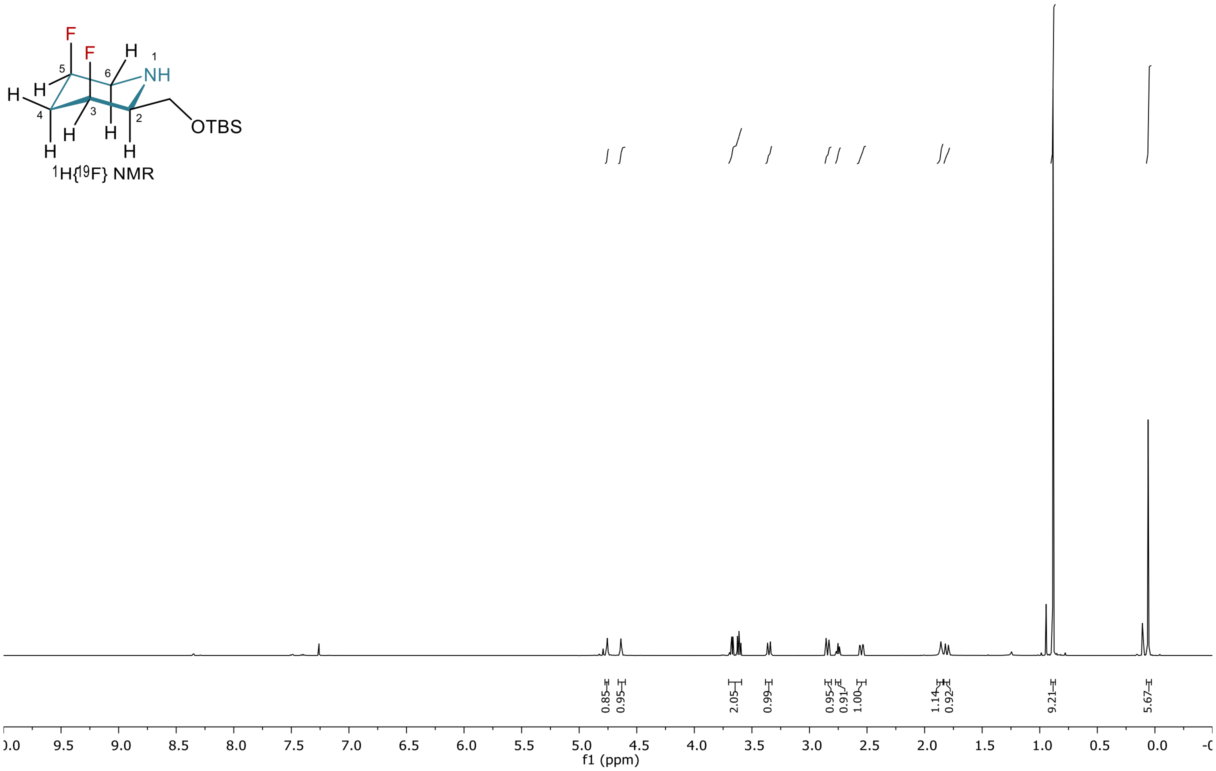
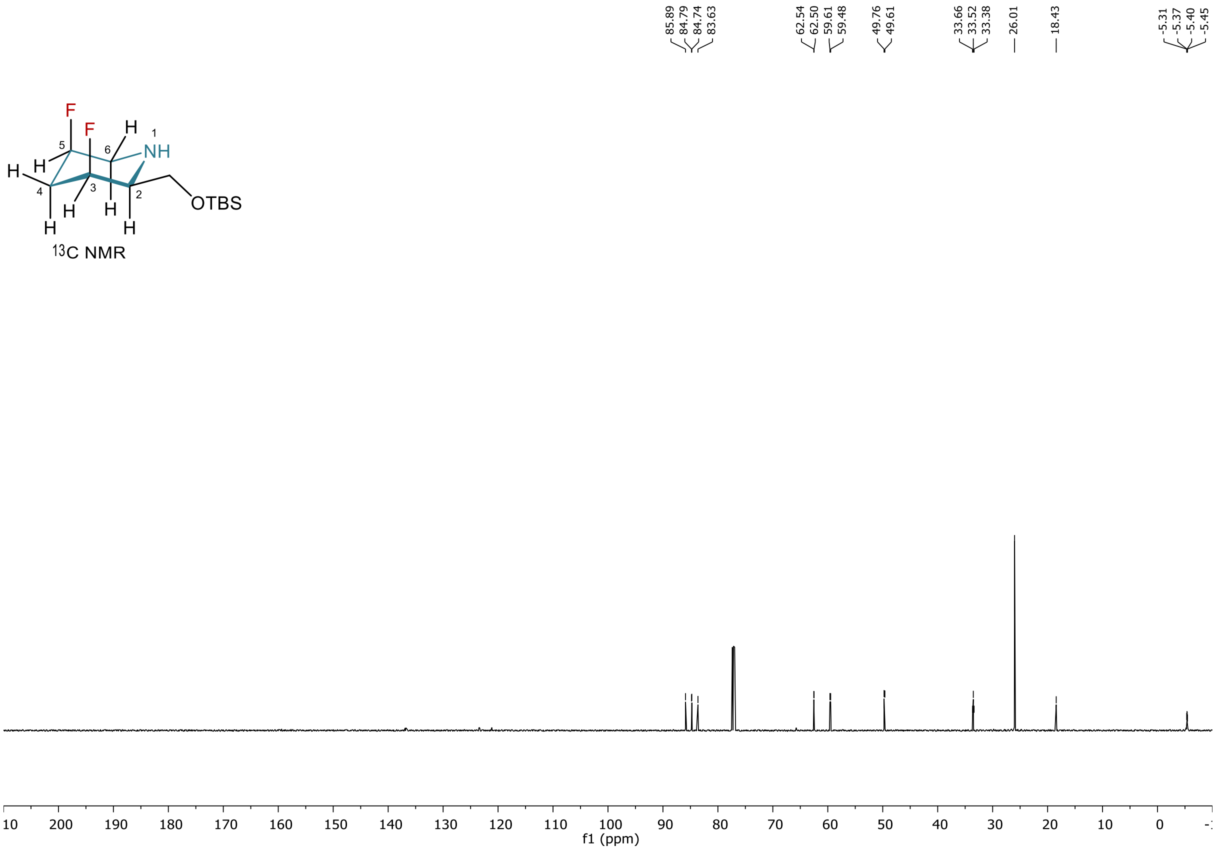
87.01
86.87
86.06
85.93
84.60
84.46
83.71
83.57
80.79
58.89
58.84
53.97
42.60
34.33
34.06
33.79
28.42
25.97
18.29
-5.42
-5.46
F
F
H
1
N
Boc
5
6
H
H
4
3
2
OTBS
H
H
H
H
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

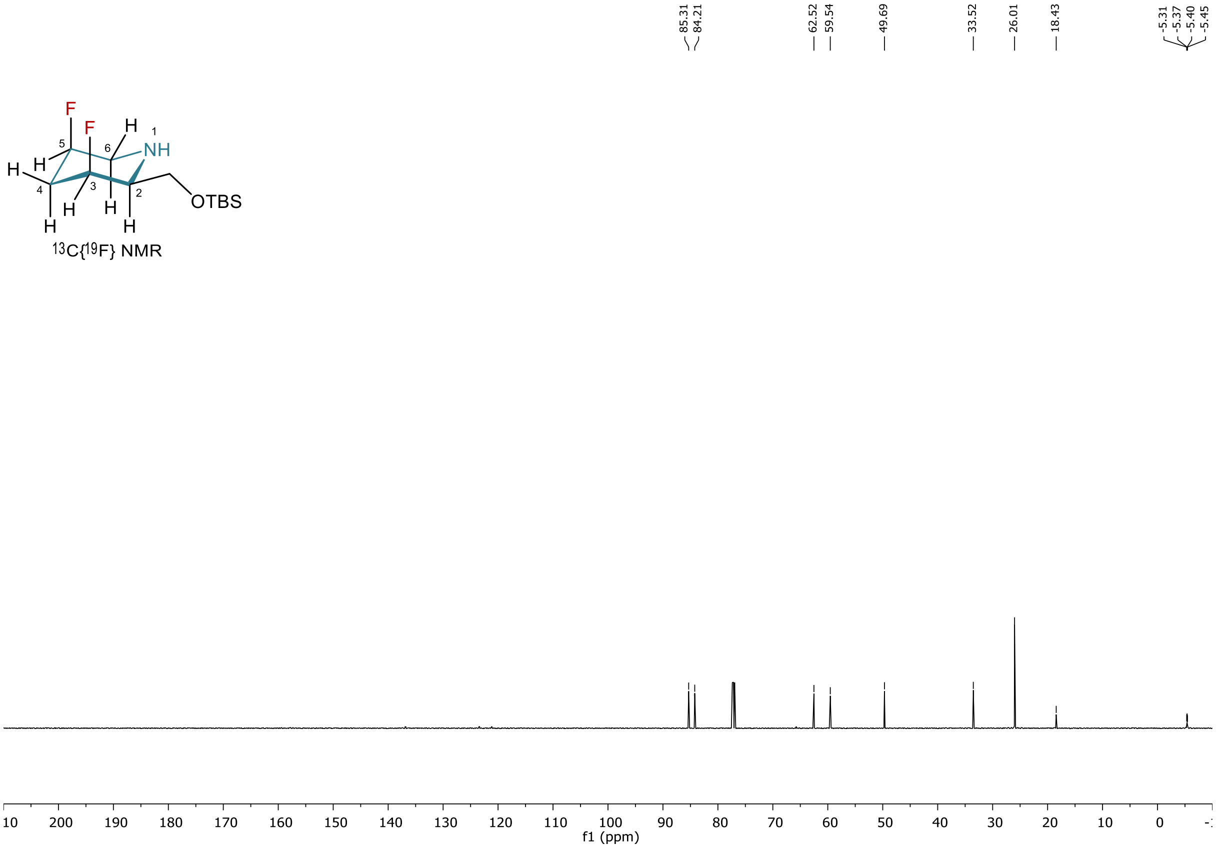

-181.90
-187.94
F
F
H
1
5
6
N
Boc
H
H
4
3
2
OTBS
H
H
H
H
19F{1H} NMR
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
f1 (ppm)

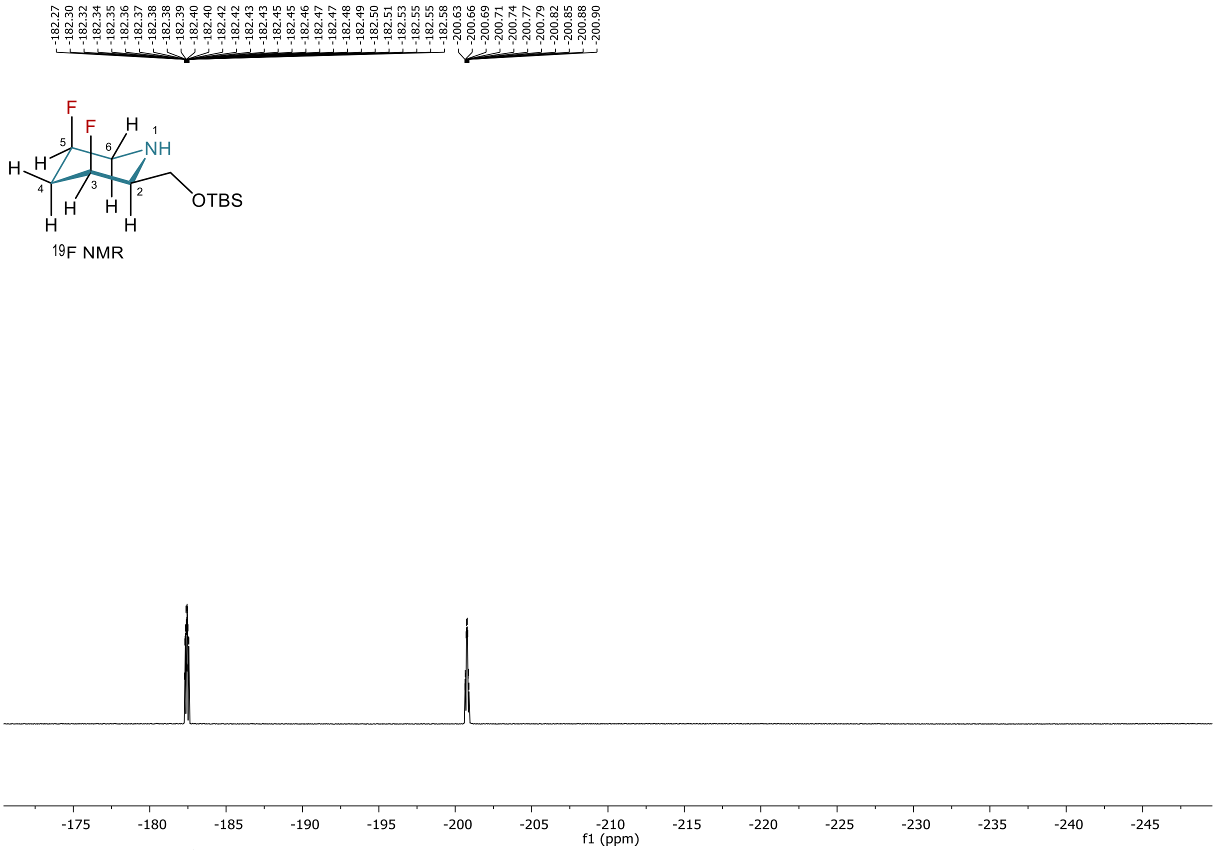

21.00
F
F
H
1
5
6
N
Boc
H
H
4
3
2
OTBS
H
H
H
H
29Si NMR
22.5
22.0
21.5
21.0
20.5
20.0
19.5
19.0
18.5
18.0
f1 (ppm)

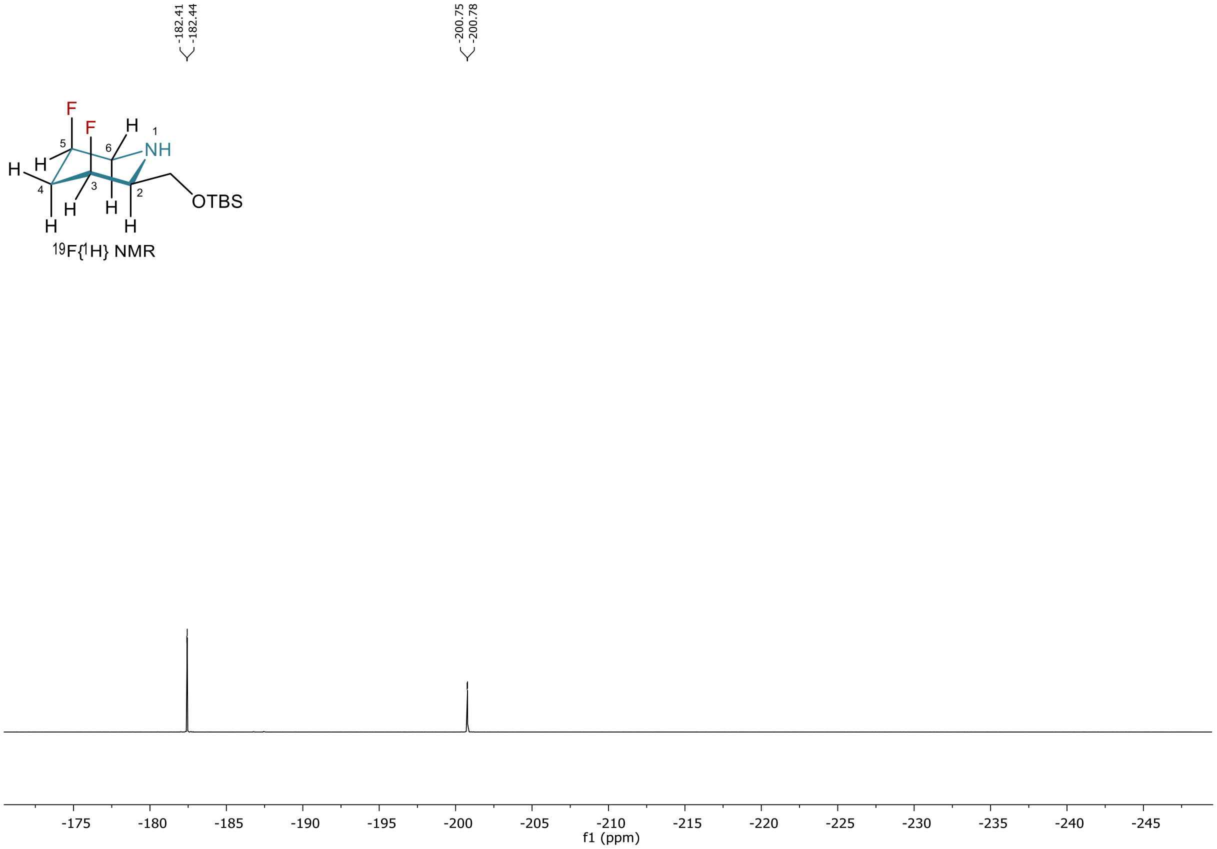

F
F
H
1
NH
5
6
H
H
4
3
2
OTBS
H
H
H
H
1H NMR
1.16
1.01
2.04
1.00
0.92
0.99
1.01
2.26
9.07
5.49
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

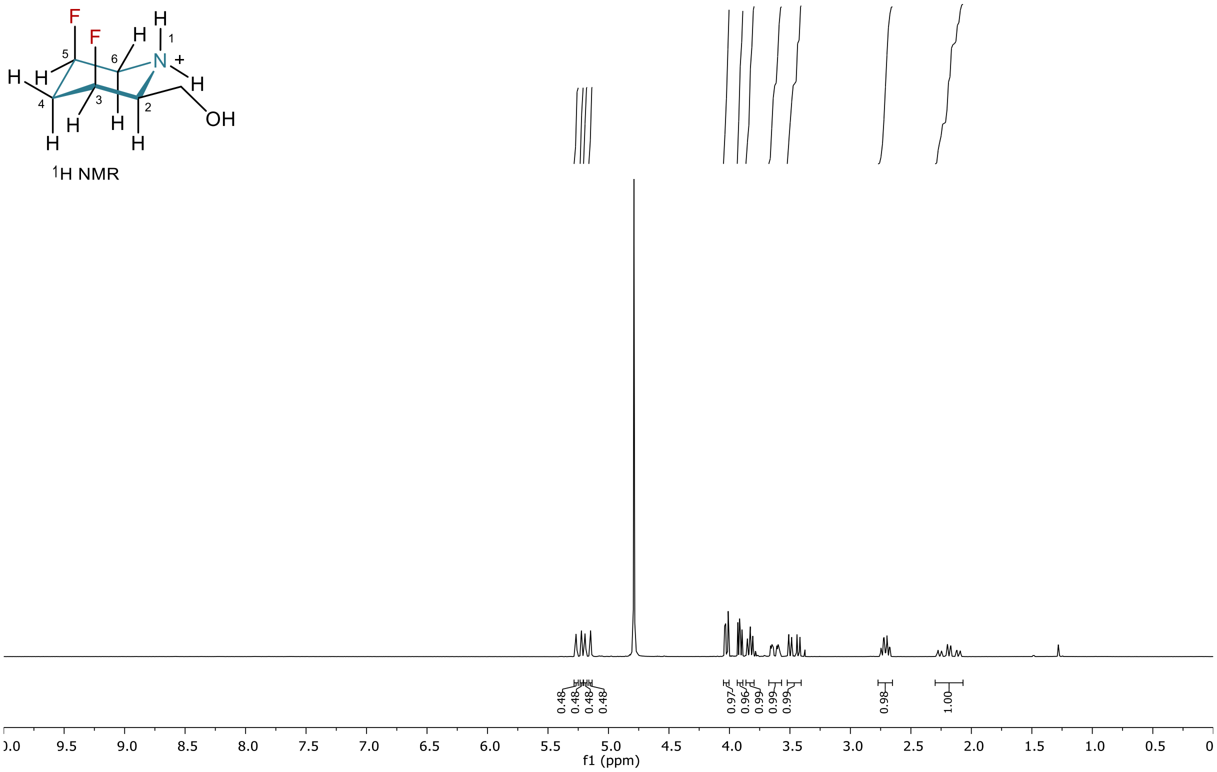

F
F
H
1
NH
5
6
H
H
4
3
2
OTBS
H
H
H
H
1H{19F} NMR
0.85
0.95
2.05
0.99
0.95
0.91
1.00
1.14
0.92
9.21
5.67
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

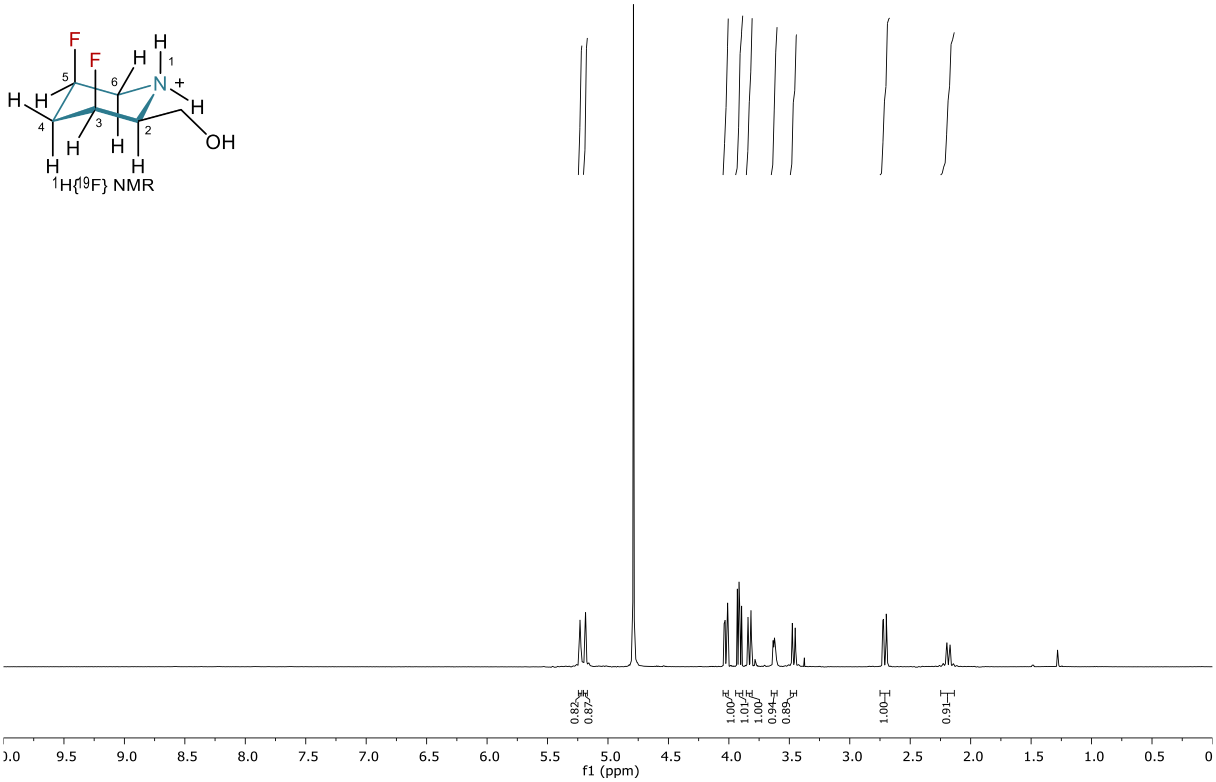

85.89
84.79
84.74
83.63
62.54
62.50
59.61
59.48
49.76
49.61
33.66
33.52
33.38
26.01
18.43
-5.31
-5.37
-5.40
-5.45
F
F
H
1
NH
5
6
H
H
4
3
2
OTBS
H
H
H
H
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

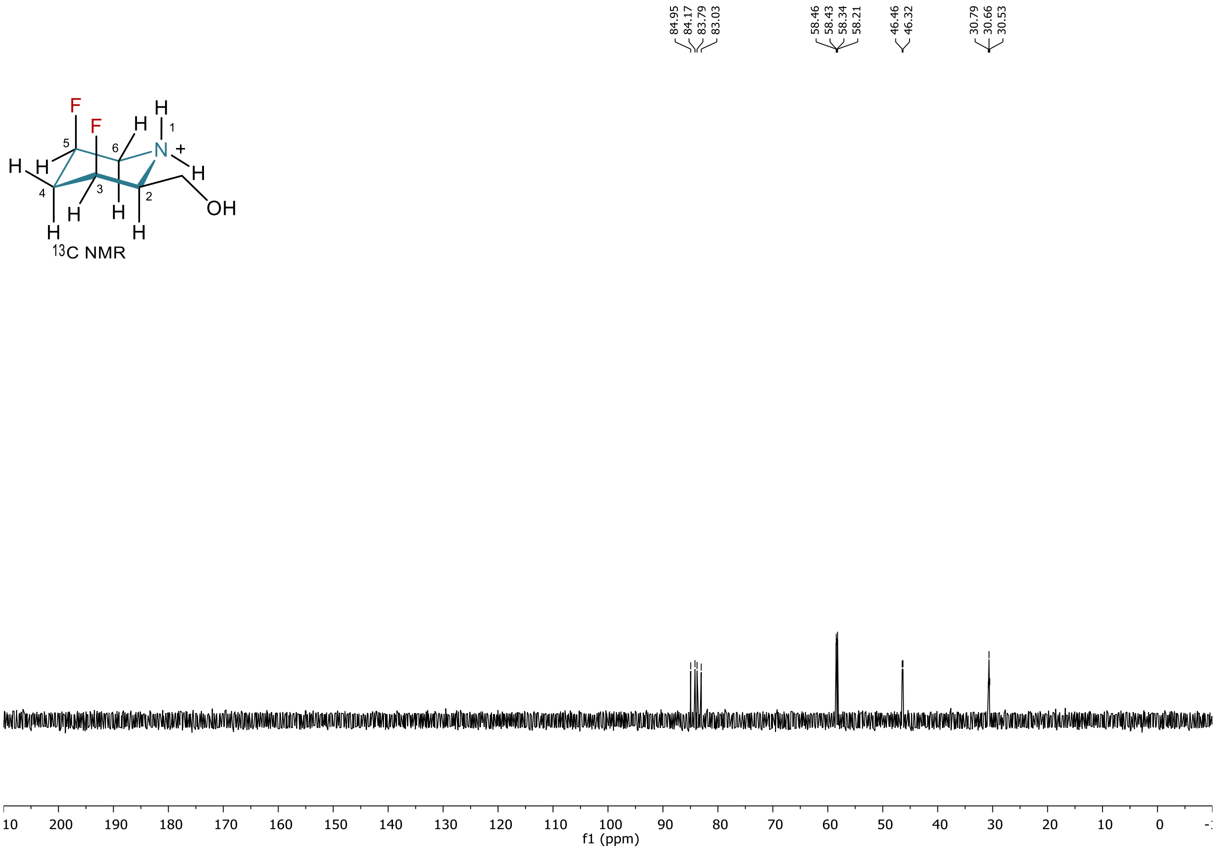

85.31
84.21
62.52
59.54
49.69
33.52
26.01
18.43
-5.31
-5.37
-5.40
-5.45
F
F
H
1
NH
5
6
H
H
4
3
2
OTBS
H
H
H
H
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

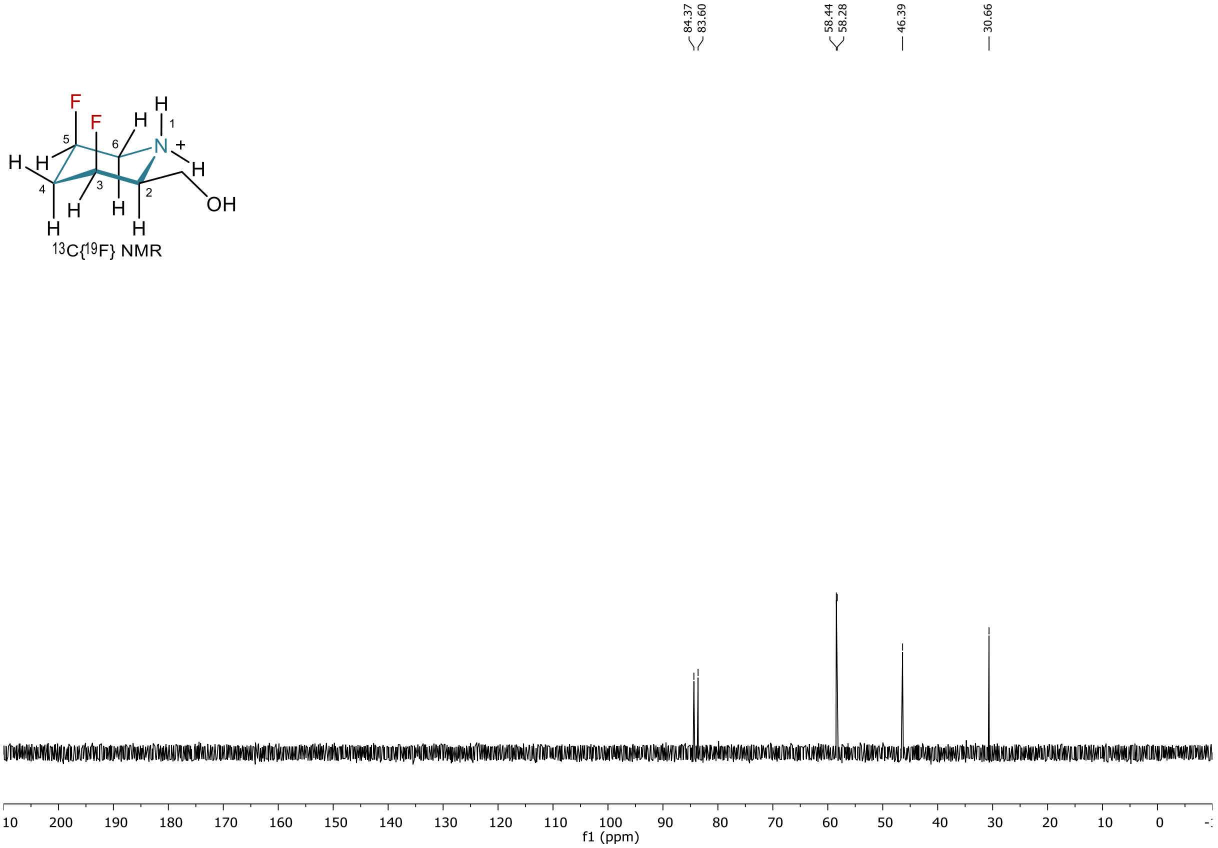

-182.27
-182.30
-182.32
-182.34
-182.35
-182.36
-182.37
-182.38
-182.38
-182.39
-182.40
-182.40
-182.42
-182.42
-182.43
-182.43
-182.45
-182.45
-182.46
-182.47
-182.47
-182.48
-182.49
-182.50
-182.51
-182.53
-182.55
-182.55
-182.58
-200.63
-200.66
-200.69
-200.71
-200.74
-200.77
-200.79
-200.82
-200.85
-200.88
-200.90
F
F
H
1
NH
5
6
H
H
4
3
2
OTBS
H
H
H
H
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

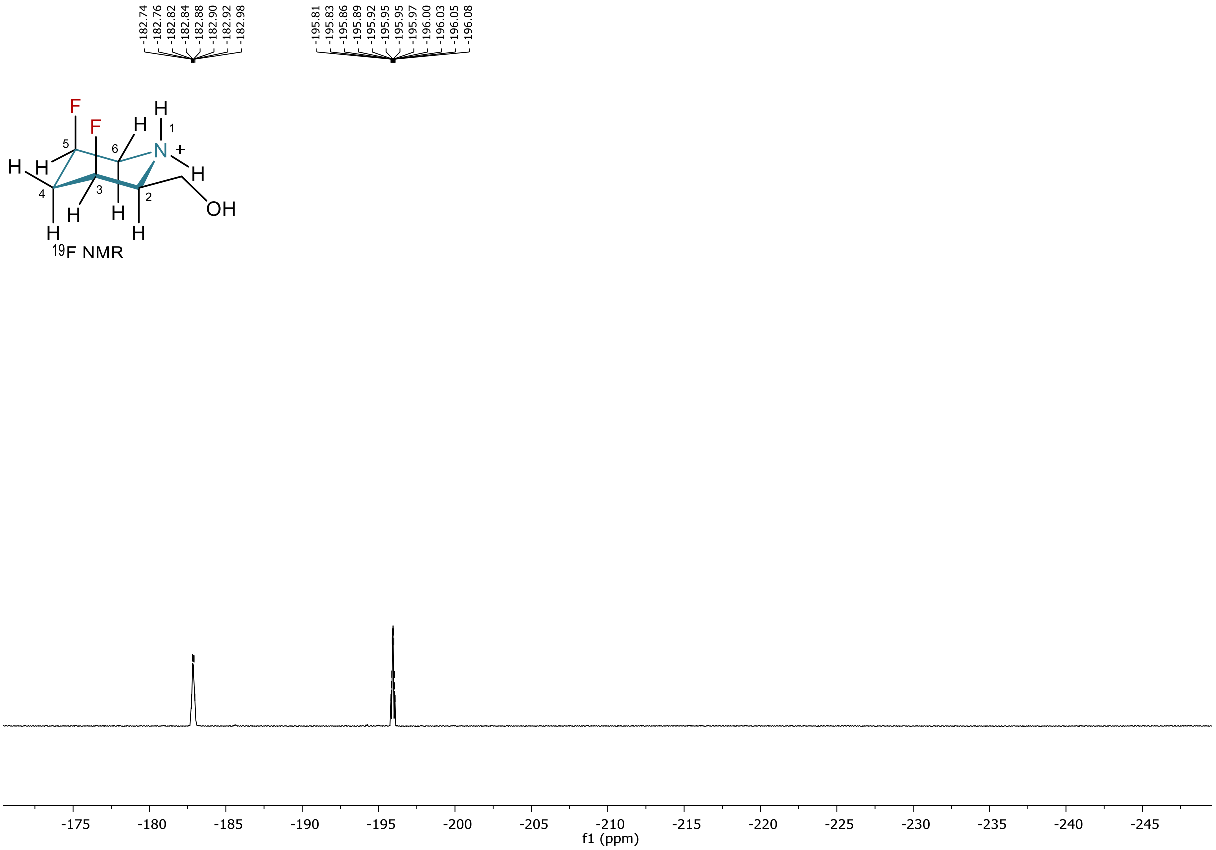

-182.41
-182.44
-200.75
-200.78
F
F
H
1
NH
5
6
H
H
4
3
2
OTBS
H
H
H
H
19F{1H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

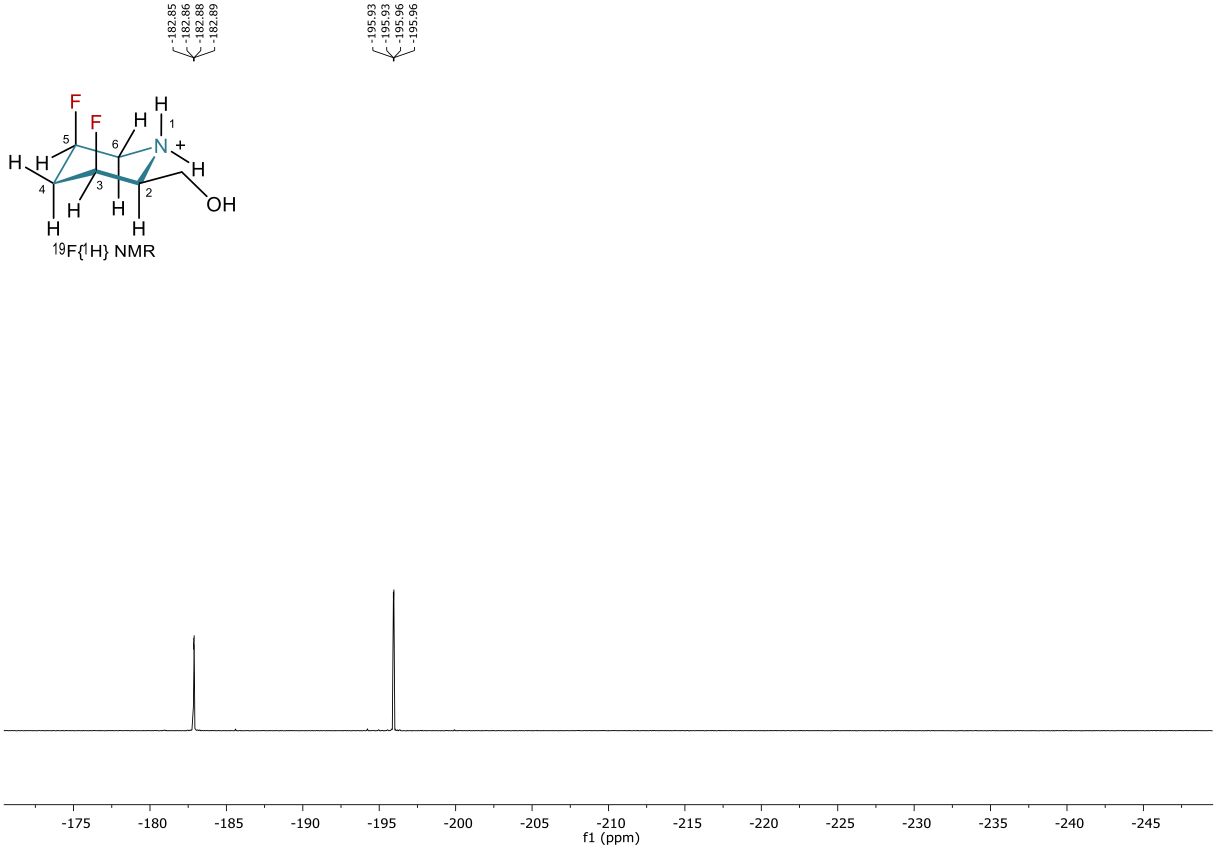

F
F
H
H
1
5
6
N
+
H
H
H
4
3
2
H
H
OH
H
H
¹H NMR
0.48
0.48
0.48
0.48
0.97
0.96
0.99
0.99
0.99
0.98
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

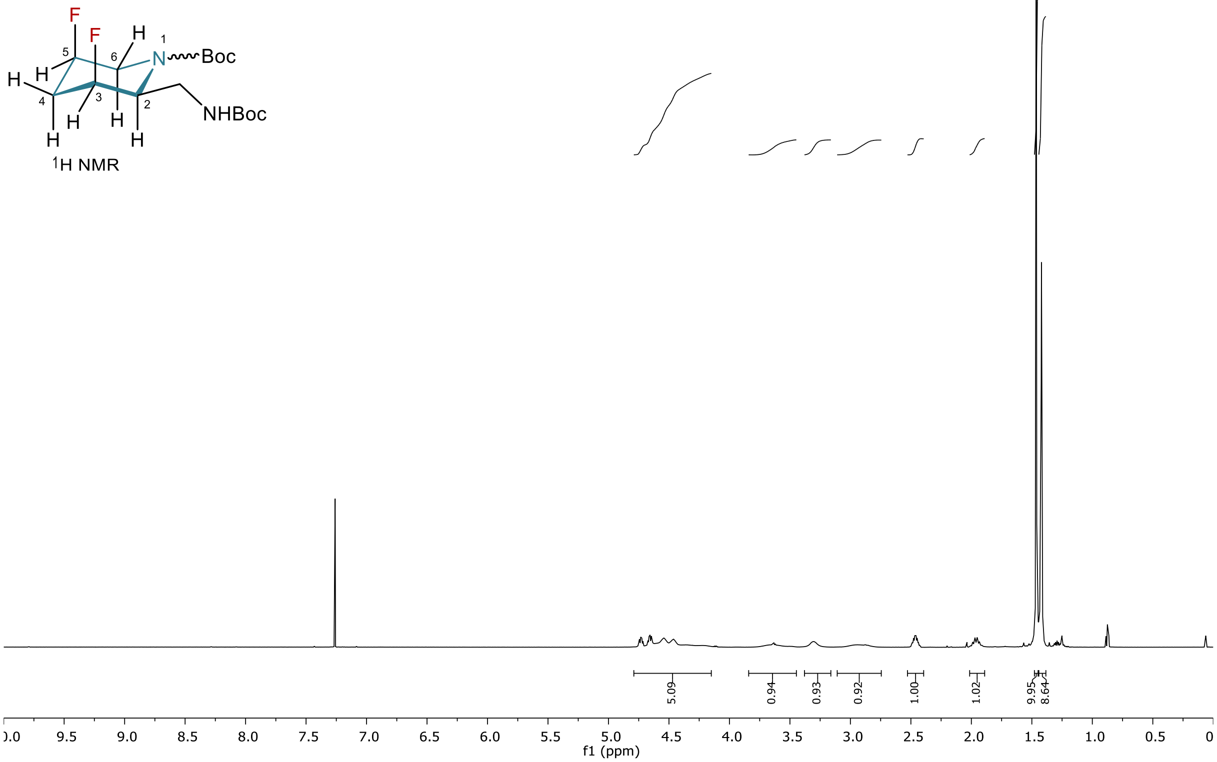

F
F
H
H
1
5
6
N
+
H
H
H
4
3
2
H
H
OH
H
H
¹H{¹⁹F} NMR
0.82
0.87
1.00
1.01
1.00
0.94
0.89
1.00
0.91
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


84.95
84.17
83.79
83.03
58.46
58.43
58.34
58.21
46.46
46.32
30.79
30.66
30.53
F
F
H
H
1
5
6
N
+
H
H
H
4
3
2
H
H
H
OH
H
H
13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

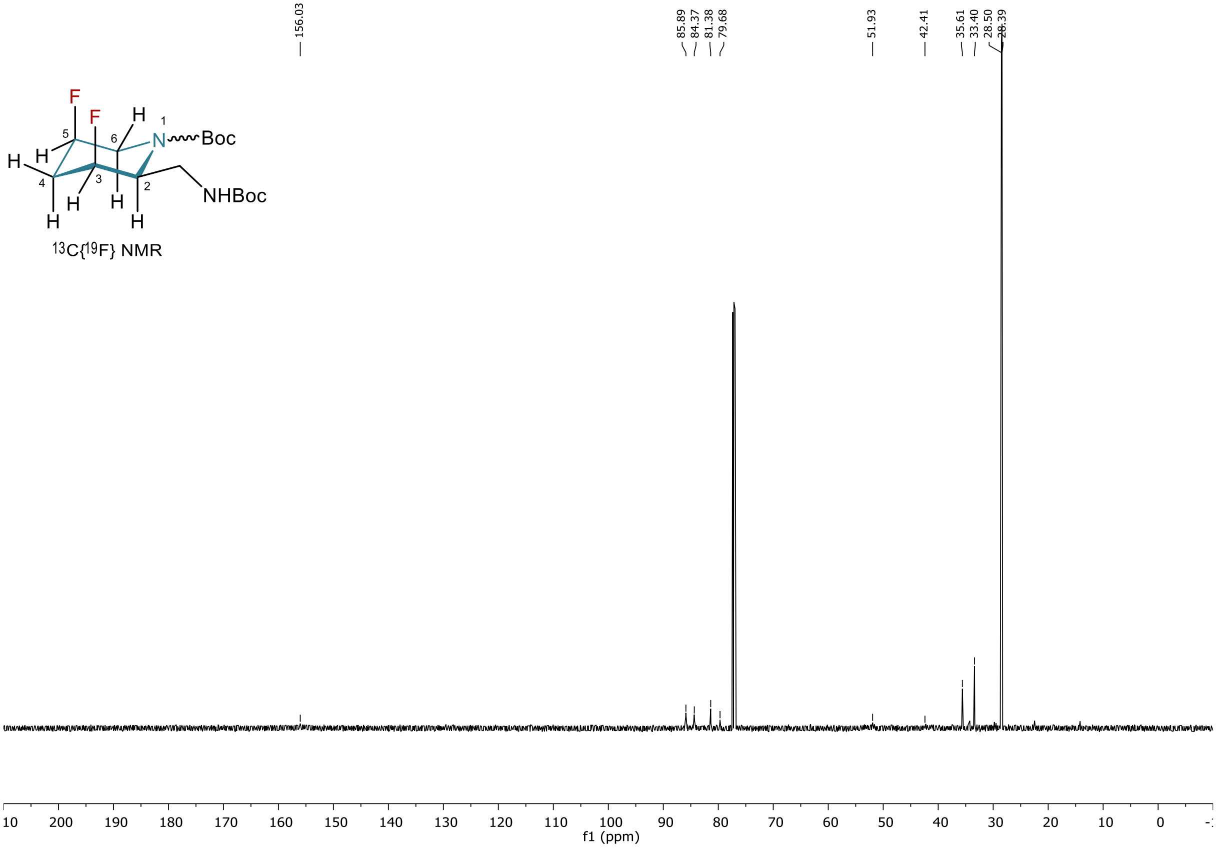

84.37
83.60
58.44
58.28
46.39
30.66
F
F
H
H
1
5
6
N
+
H
H
H
4
3
2
H
H
H
OH
H
H
13C{19F} NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-182.74
-182.76
-182.82
-182.84
-182.88
-182.90
-182.92
-182.98
-195.81
-195.83
-195.86
-195.89
-195.92
-195.95
-195.95
-195.97
-196.00
-196.03
-196.05
-196.08
F
F
H
H
1
5
6
N
+
H
H
H
4
3
2
OH
H
H
H
H
^{19}F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

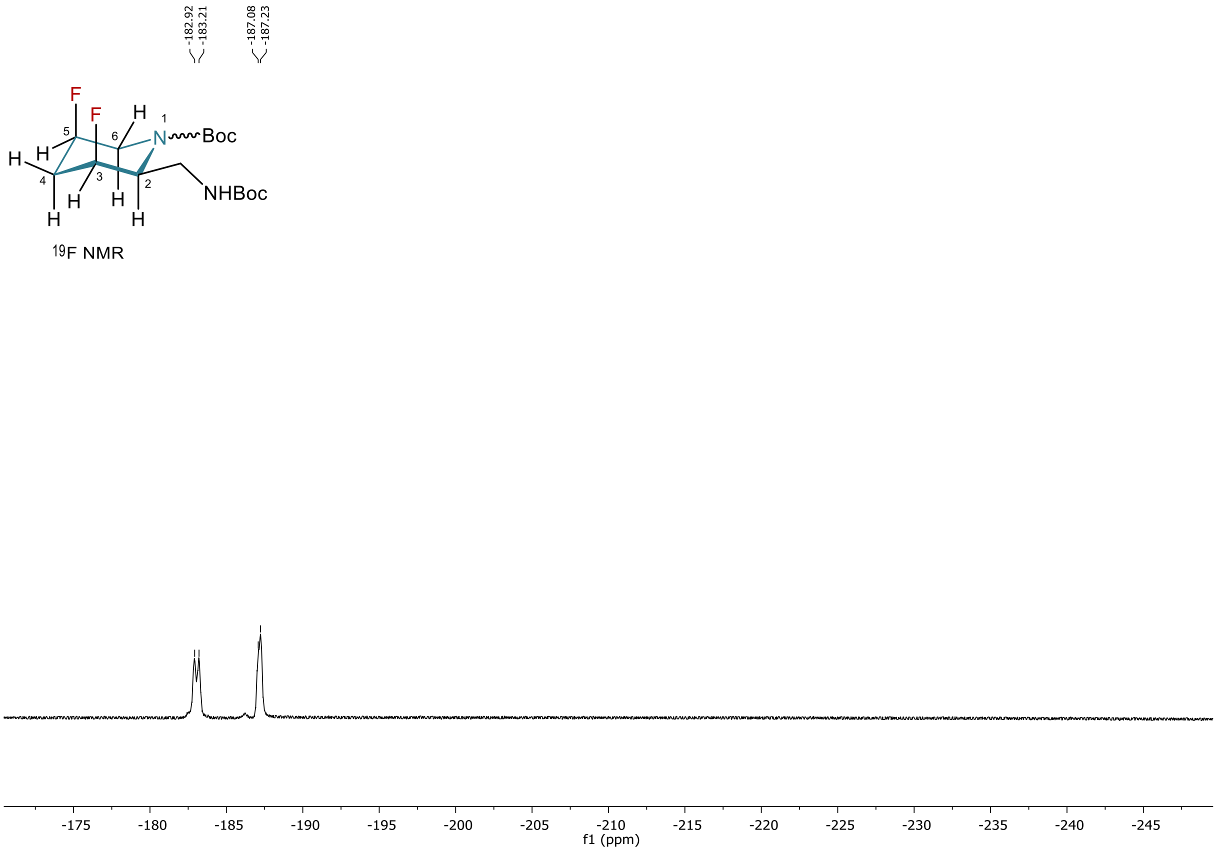

-182.85
-182.86
-182.88
-182.89
-195.93
-195.93
-195.96
-195.96
F
F
H
H
1
5
6
N
+
H
H
H
4
3
2
OH
H
H
H
H
^{19}F{^{1}H} NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

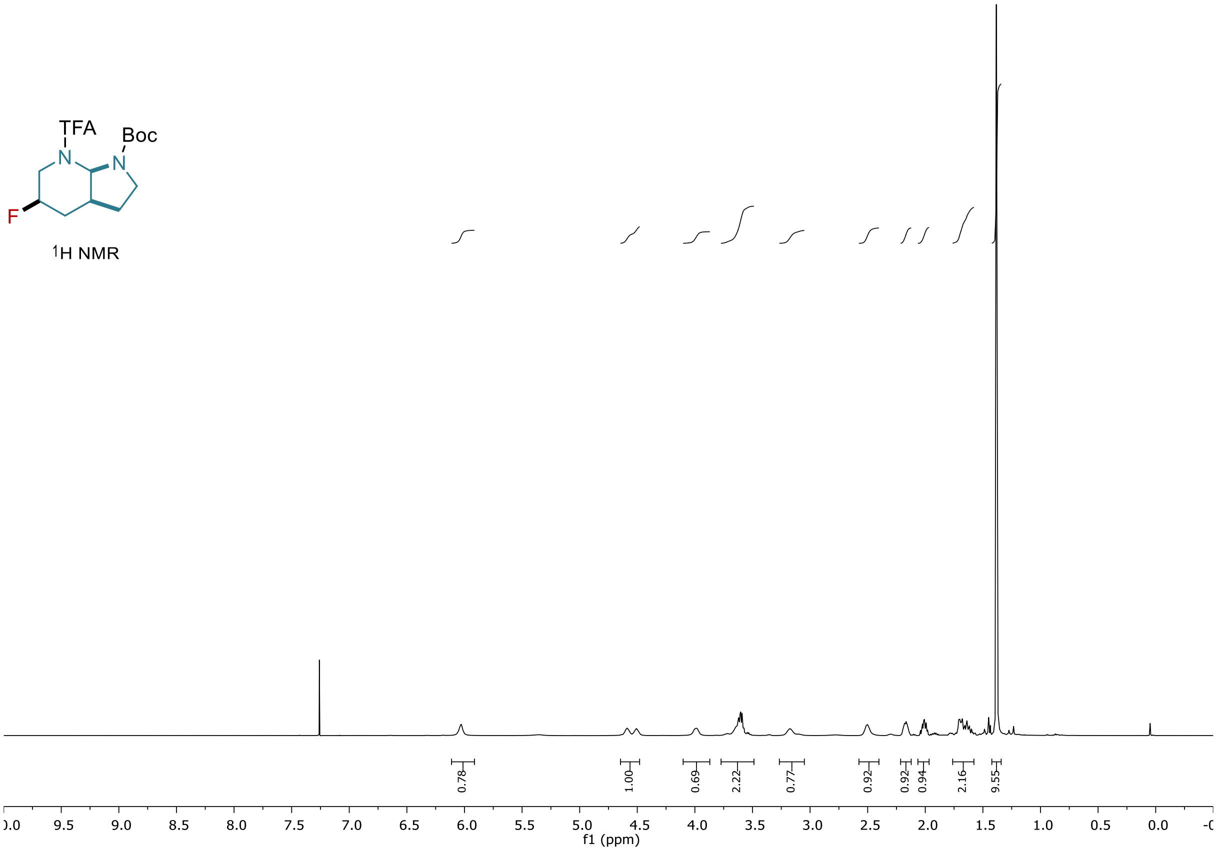


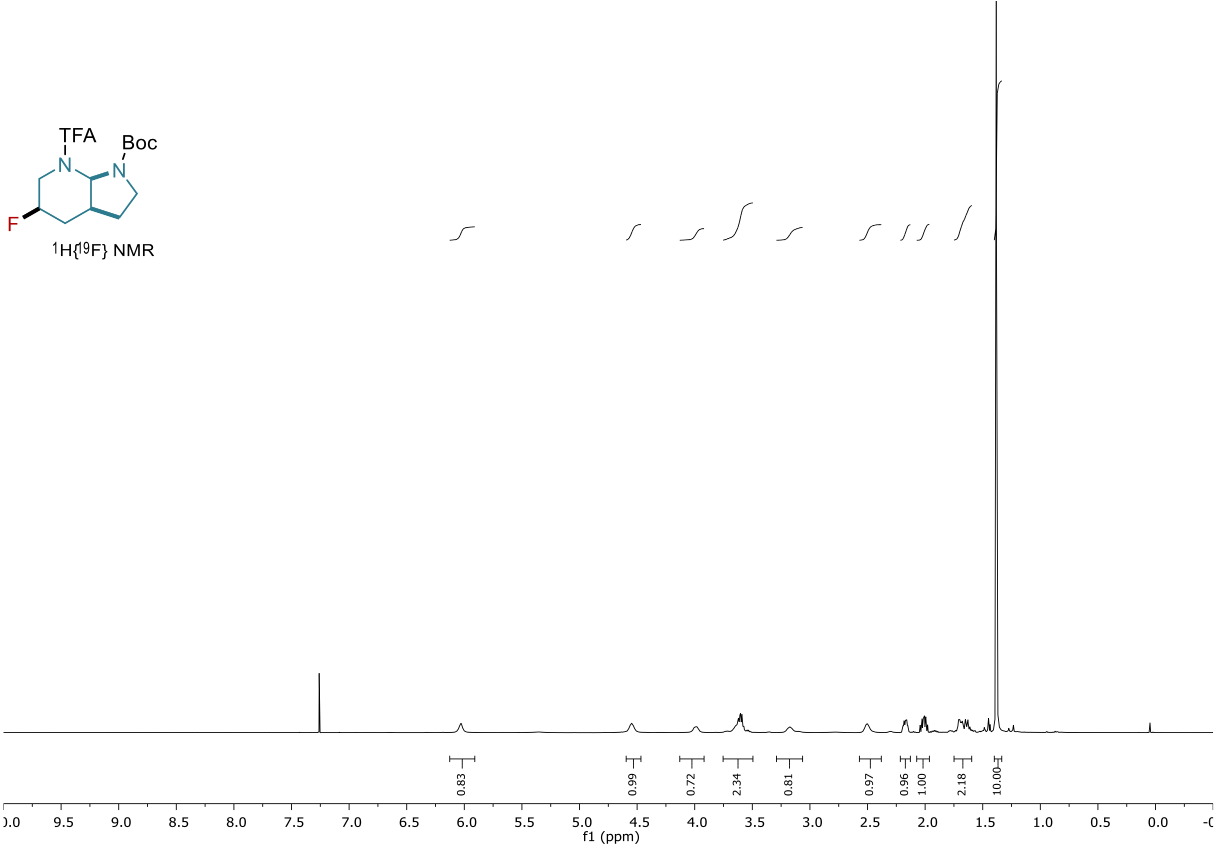
F
F
H
1
N
Boc
5
6
H
H
4
3
2
NHBoc
H
H
H
H
^{1}H NMR
5.09
0.94
0.93
0.92
1.00
1.02
9.95
8.64
.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

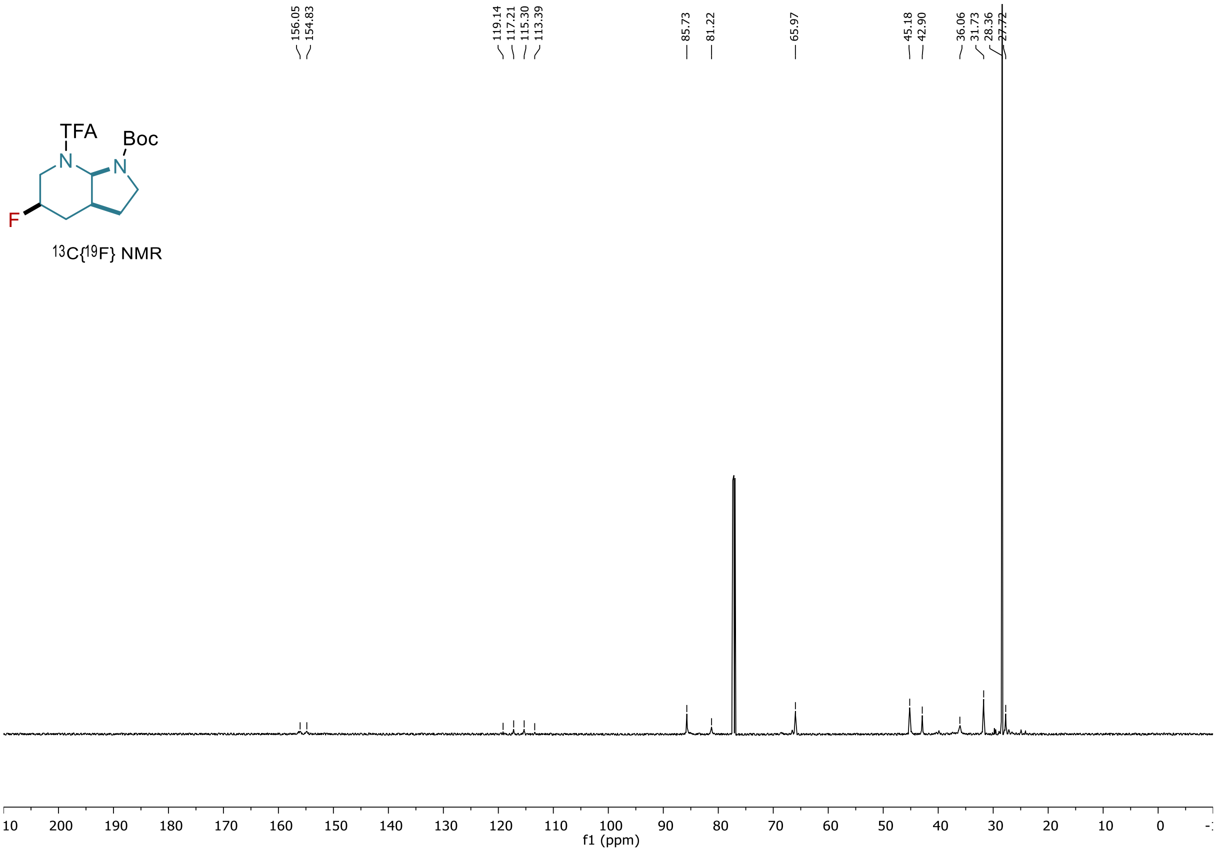


156.03
85.89
84.37
81.38
79.68
51.93
42.41
35.61
33.40
28.50
28.39
F
F
H
1
N
Boc
5
6
H
H
4
3
2
NHBoc
H
H
H
H
^{13}C{^{19}F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

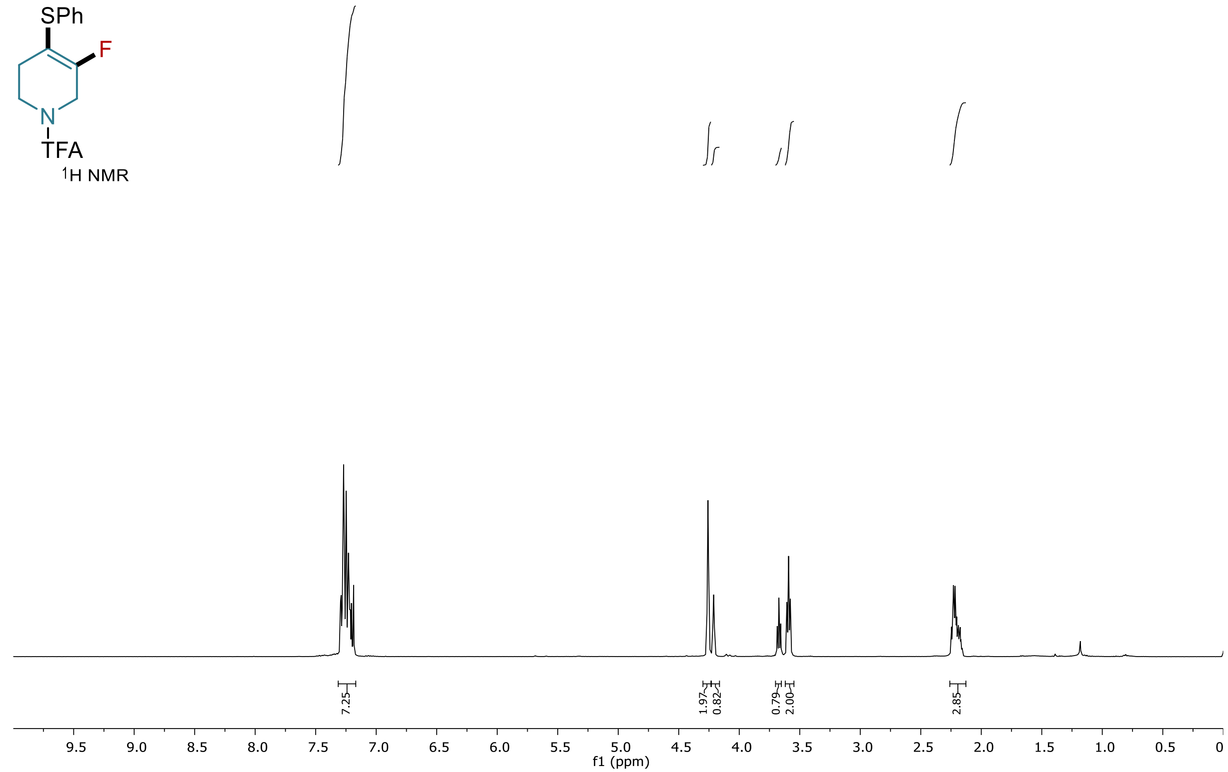

-182.92
-183.21
-187.08
-187.23
F
F
H
1
5
6
N
Boc
H
H
4
3
2
NHBoc
H
H
H
H
19F NMR
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
f1 (ppm)

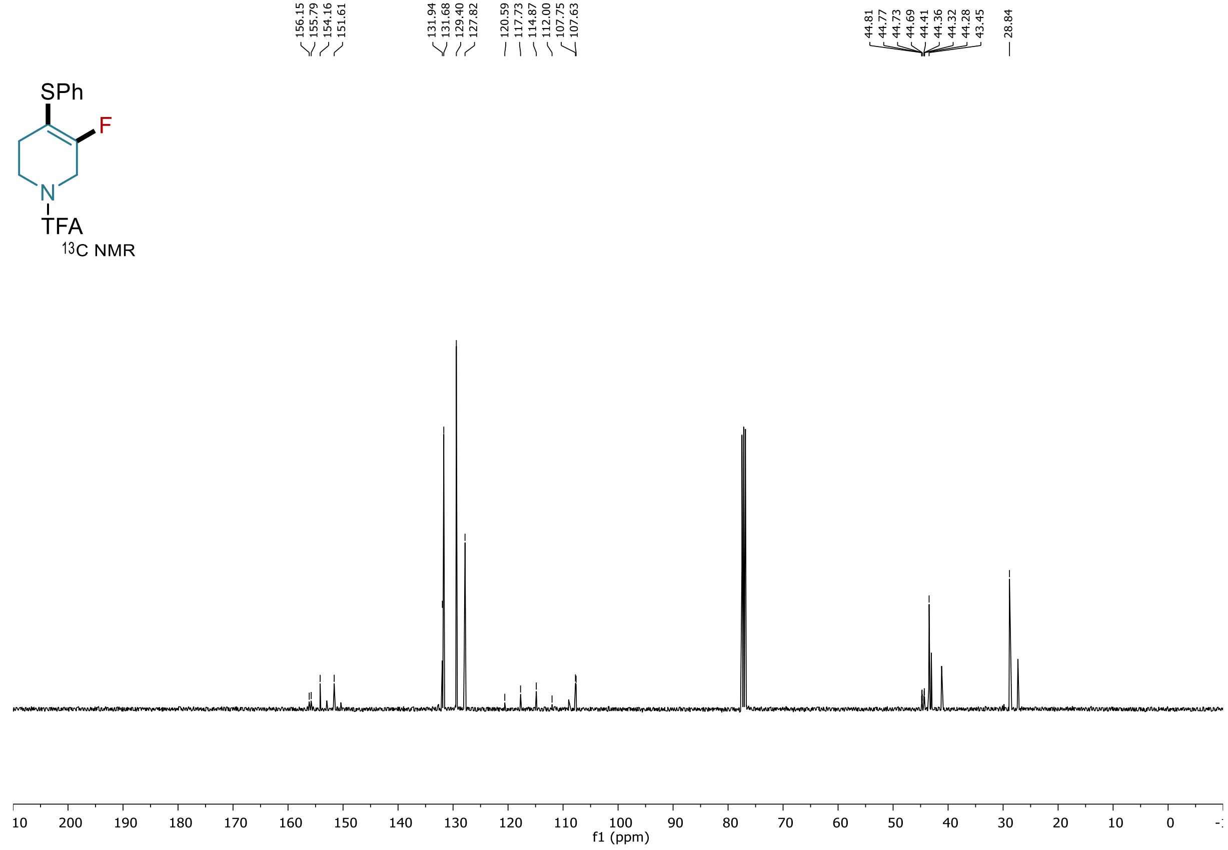

TFA
Boc
N
N
F
1H NMR
0.78
1.00
0.69
2.22
0.77
0.92
0.92
0.94
2.16
9.55
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

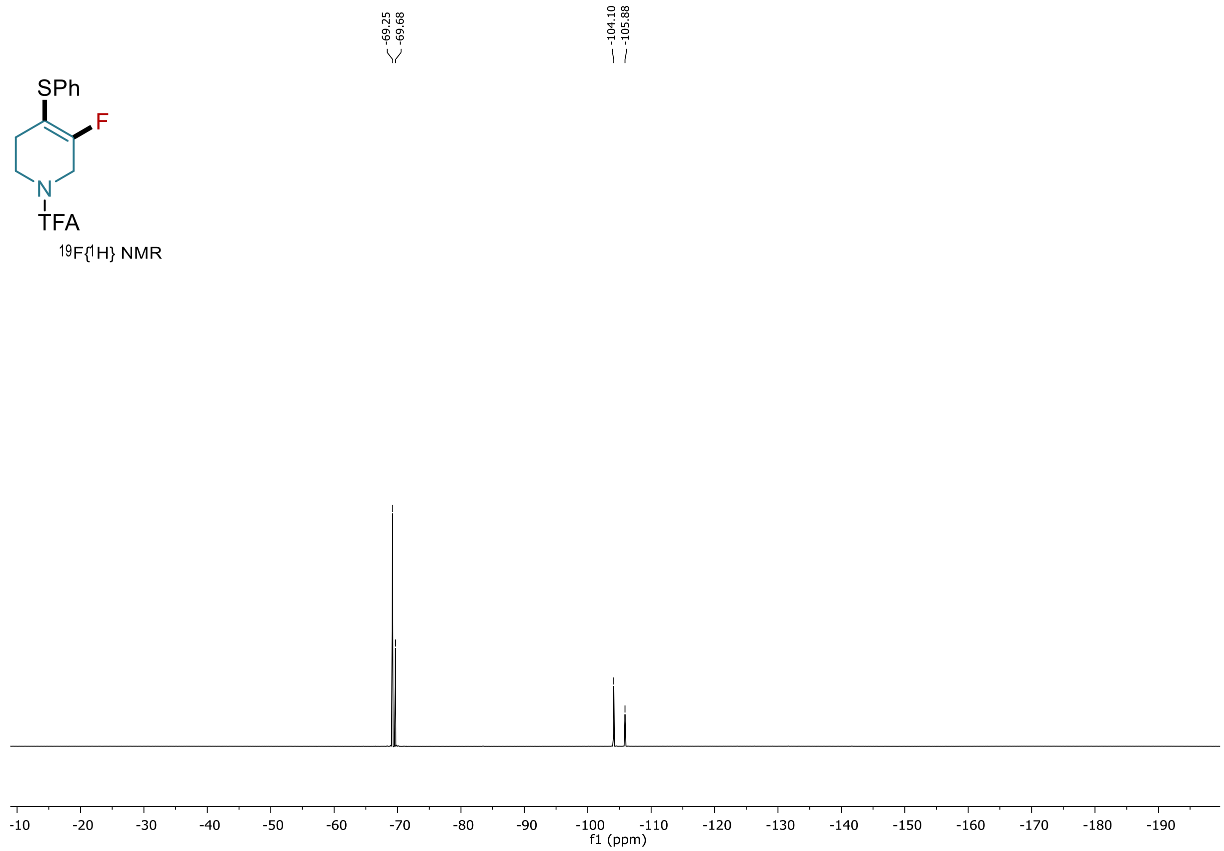

TFA
Boc
N
N
F
1H{19F} NMR
0.83
0.99
0.72
2.34
0.81
0.97
0.96
1.00
2.18
10.00
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

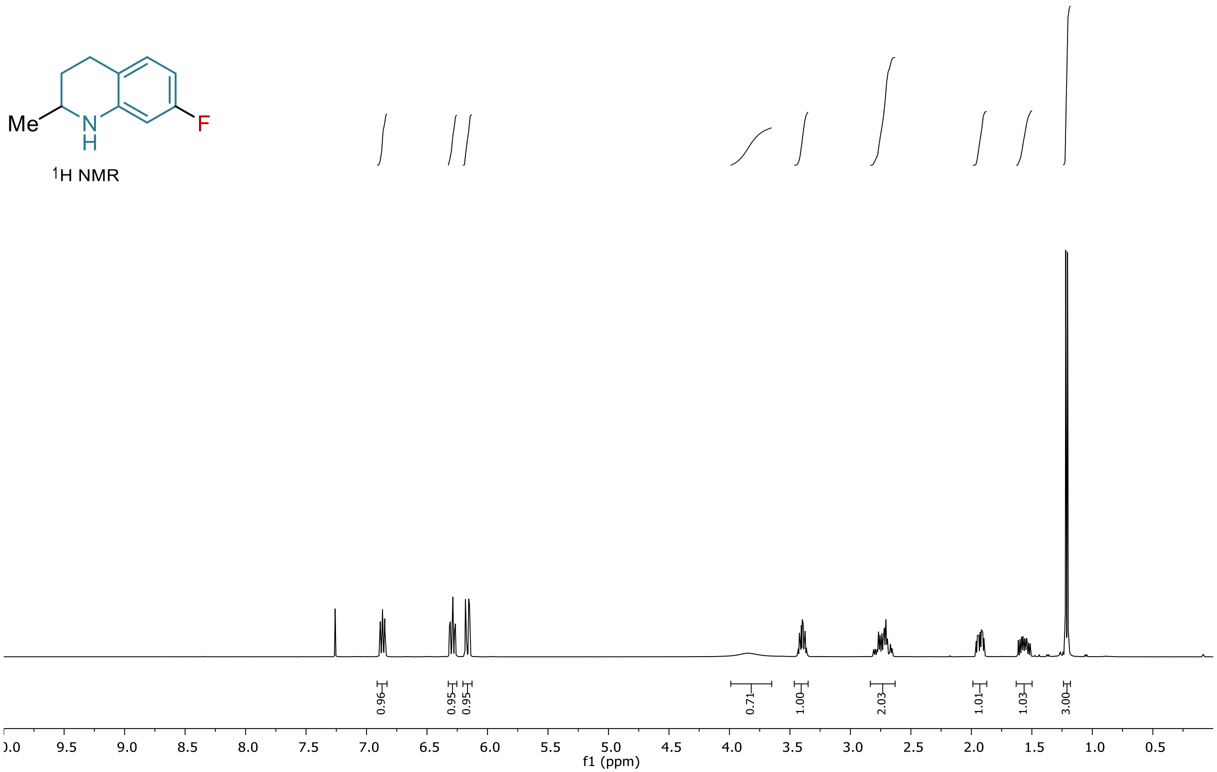

156.05
154.83
119.14
117.21
115.30
113.39
85.73
81.22
65.97
45.18
42.90
36.06
31.73
28.36
27.72
TFA
N
Boc
N
F
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-66.41
-69.51
-178.50
-179.73
TFA
N
Boc
N
F
19F{1H} NMR
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
f1 (ppm)

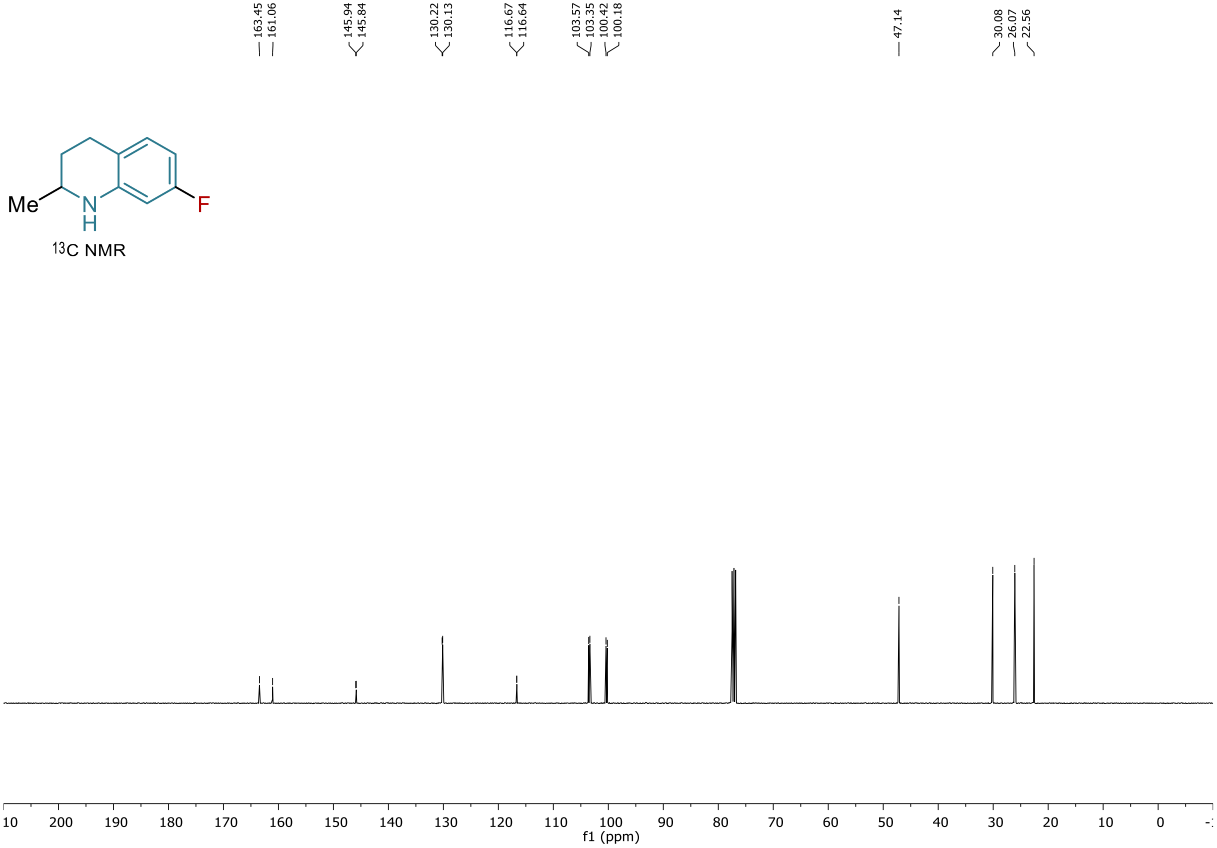

SPh
F
N
TFA
1H NMR
7.25
1.97
0.82
0.79
2.00
2.85
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


156.15
155.79
154.16
151.61
131.94
131.68
129.40
127.82
120.59
117.73
114.87
112.00
107.75
107.63
44.81
44.77
44.73
44.69
44.41
44.36
44.32
44.28
43.45
28.84
SPh
F
N
TFA
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

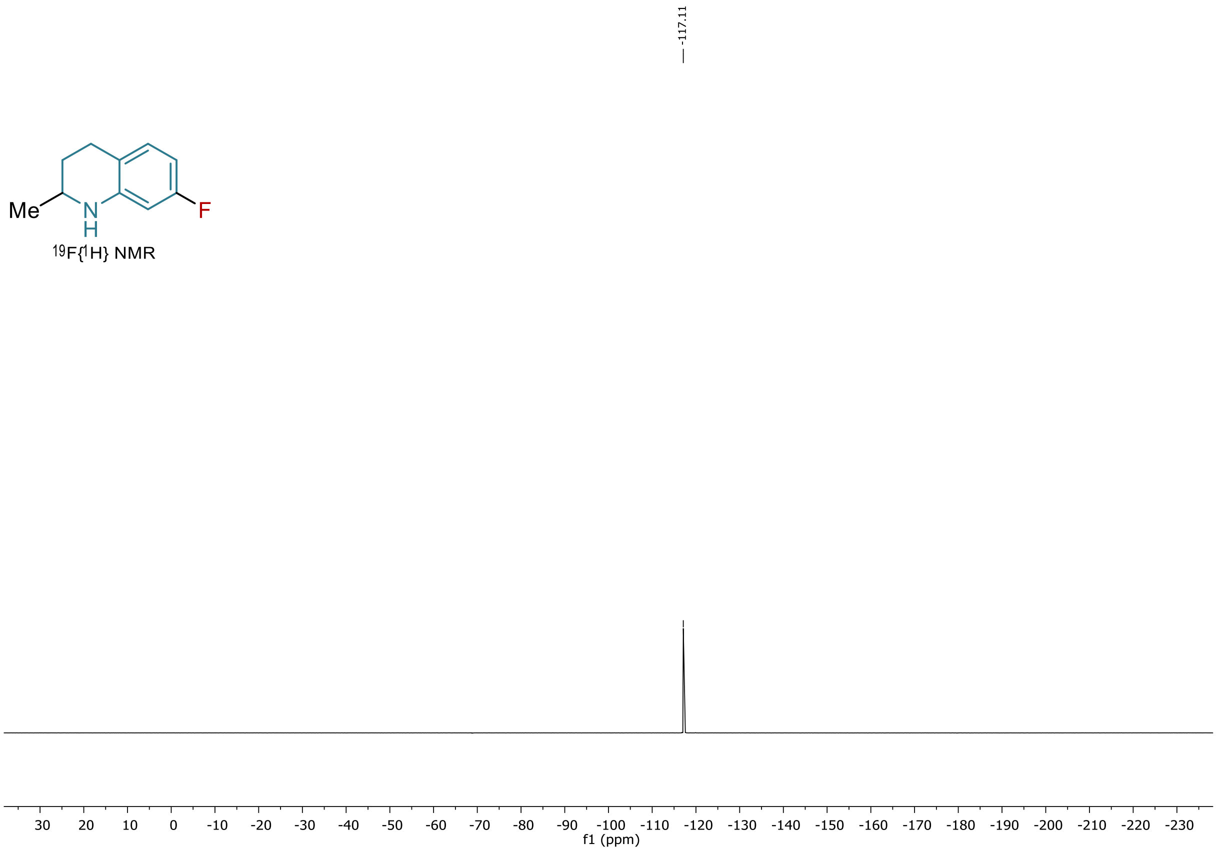

-69.25
-69.68
-104.10
-105.88
SPh
F
N
TFA
^{19}F{^{1}H} NMR
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

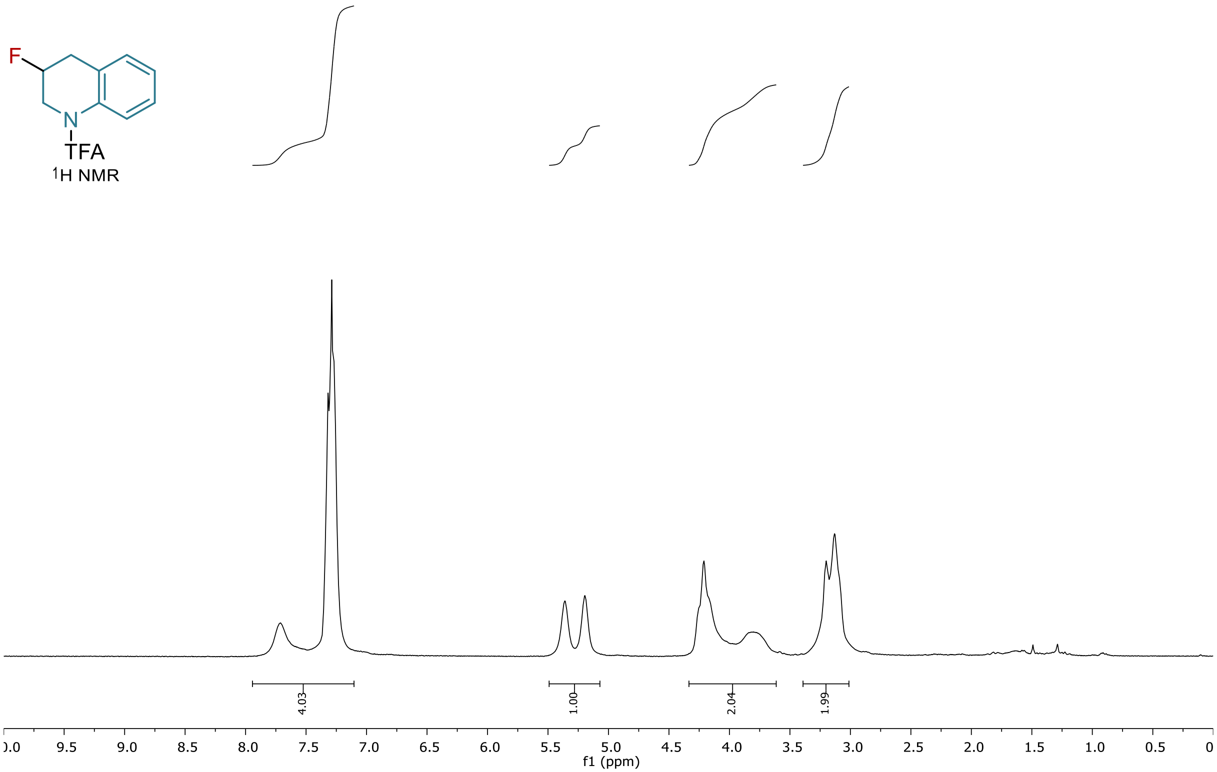


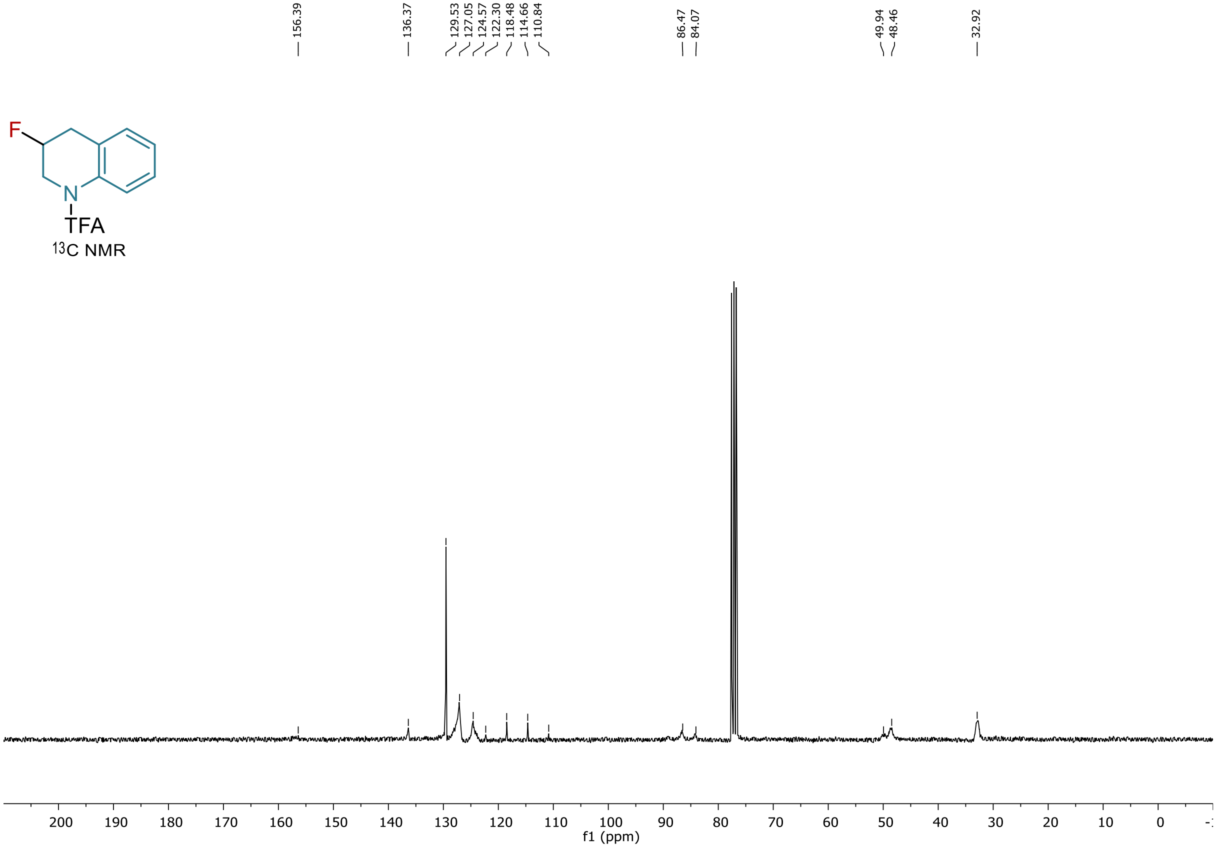
^{1}H NMR

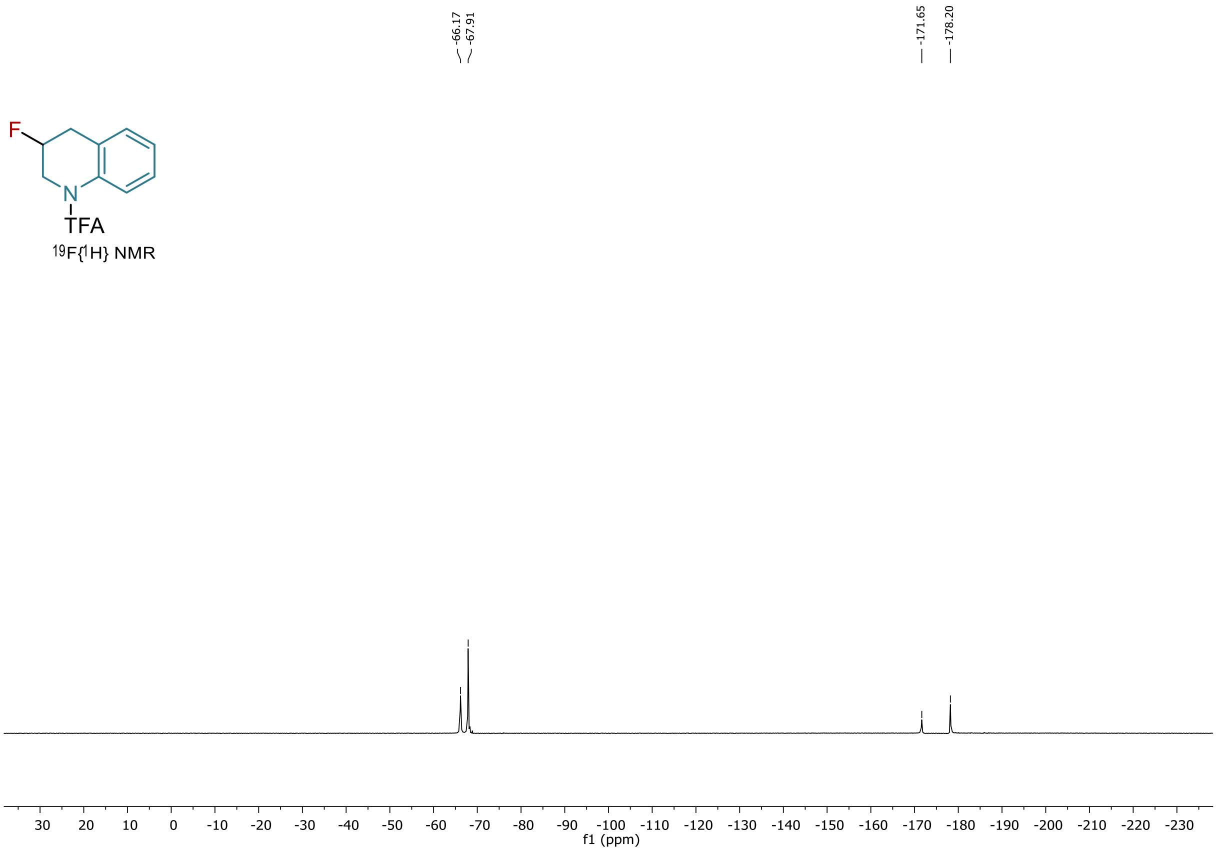


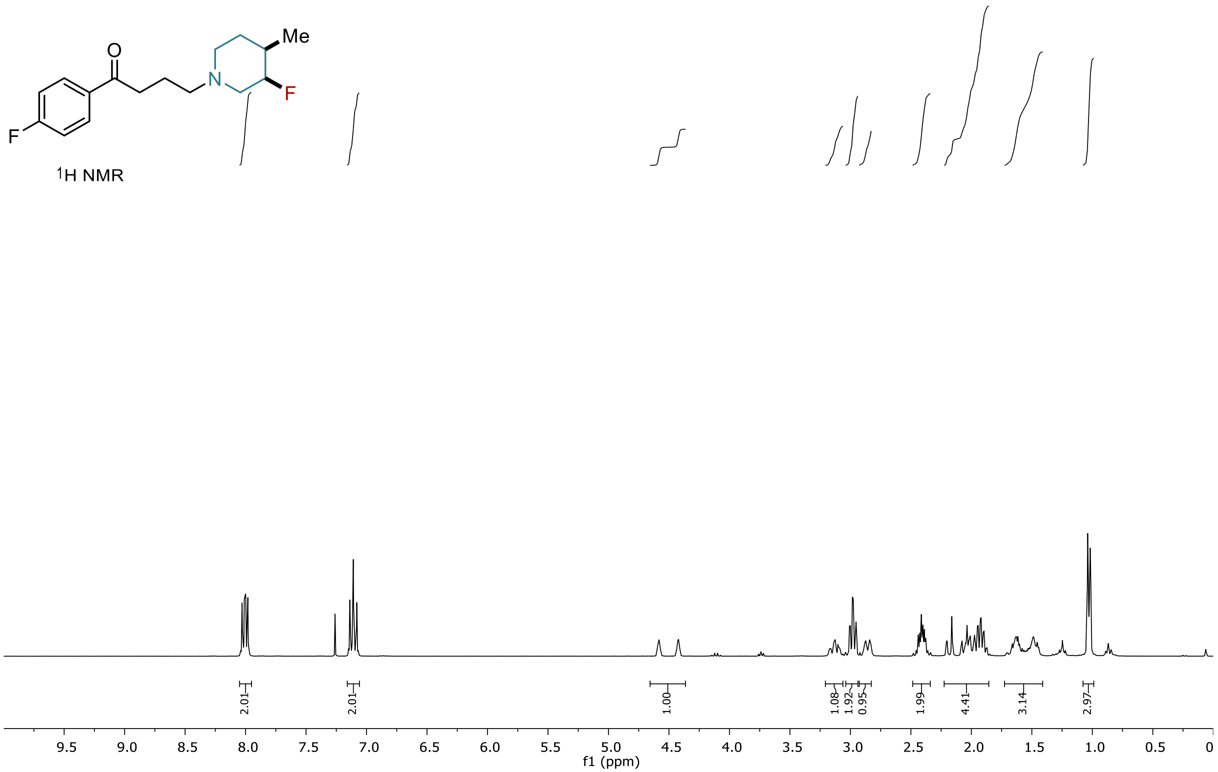
^{13}C NMR


-117.11
Me
N
H
F
$^{19}F\{^1H\}$ NMR
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)

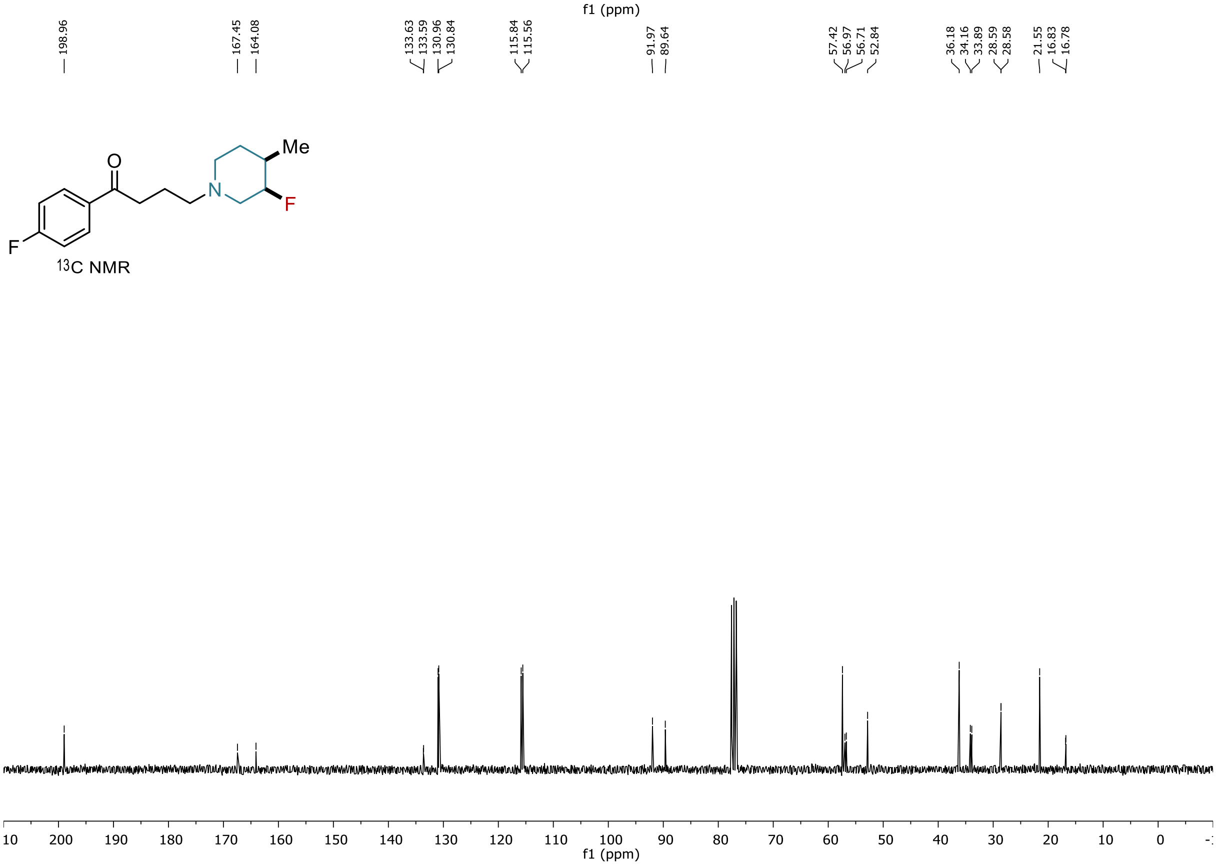

F
N
TFA
1H NMR
4.03
1.00
2.04
1.99
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


156.39
136.37
129.53
127.05
124.57
122.30
118.48
114.66
110.84
86.47
84.07
49.94
48.46
32.92
F
N
TFA
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

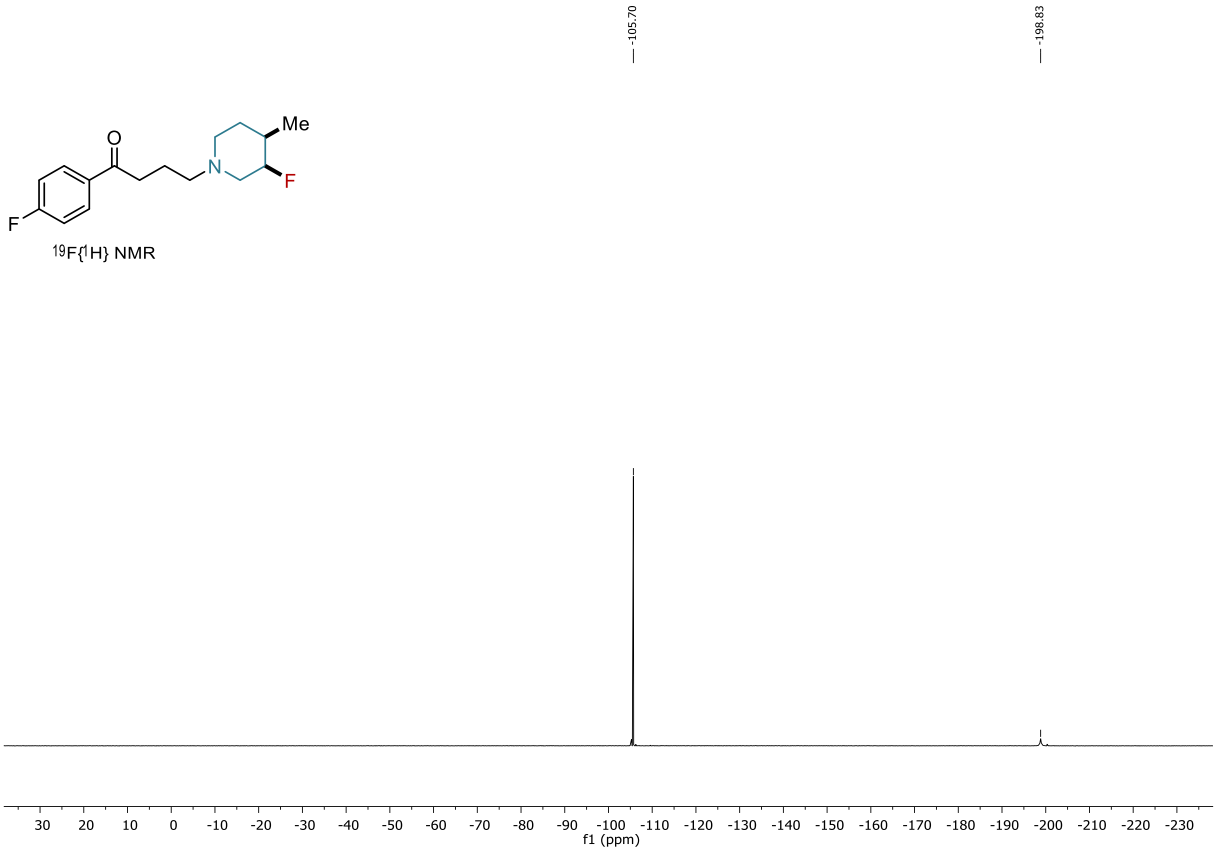

-66.17
-67.91
-171.65
-178.20
F
N
TFA
19F{1H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

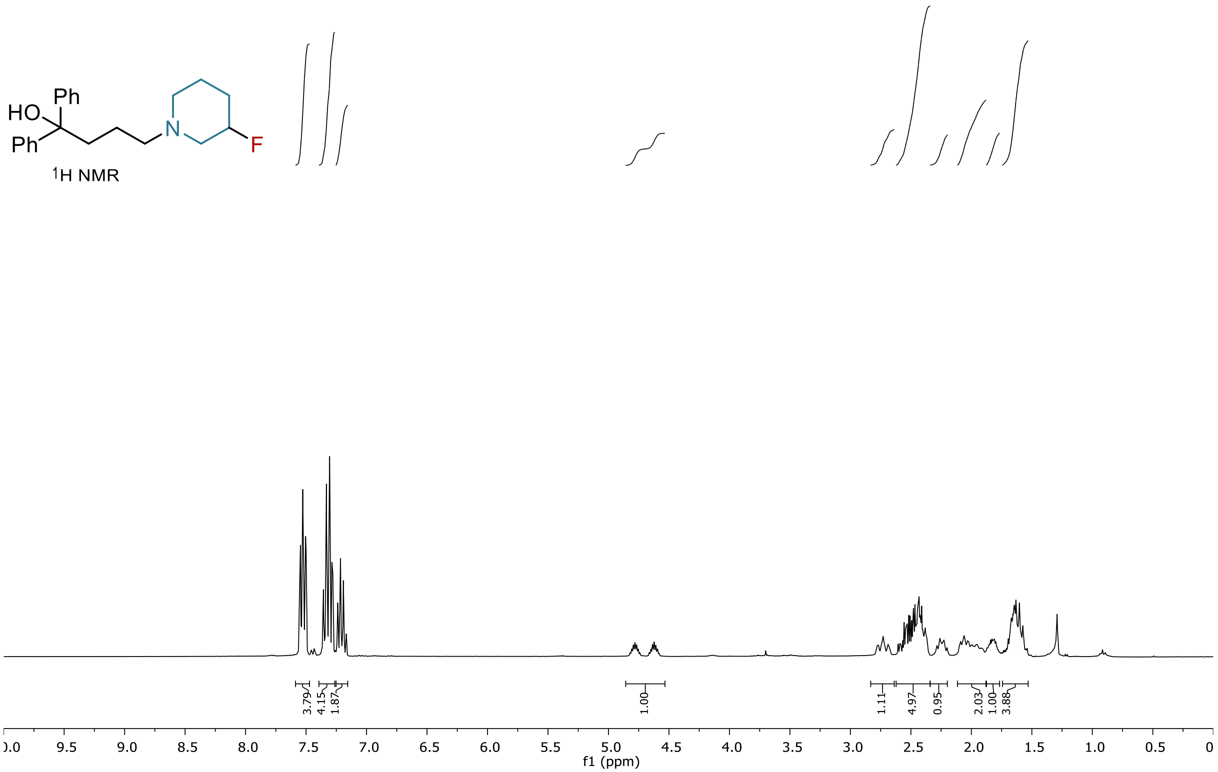


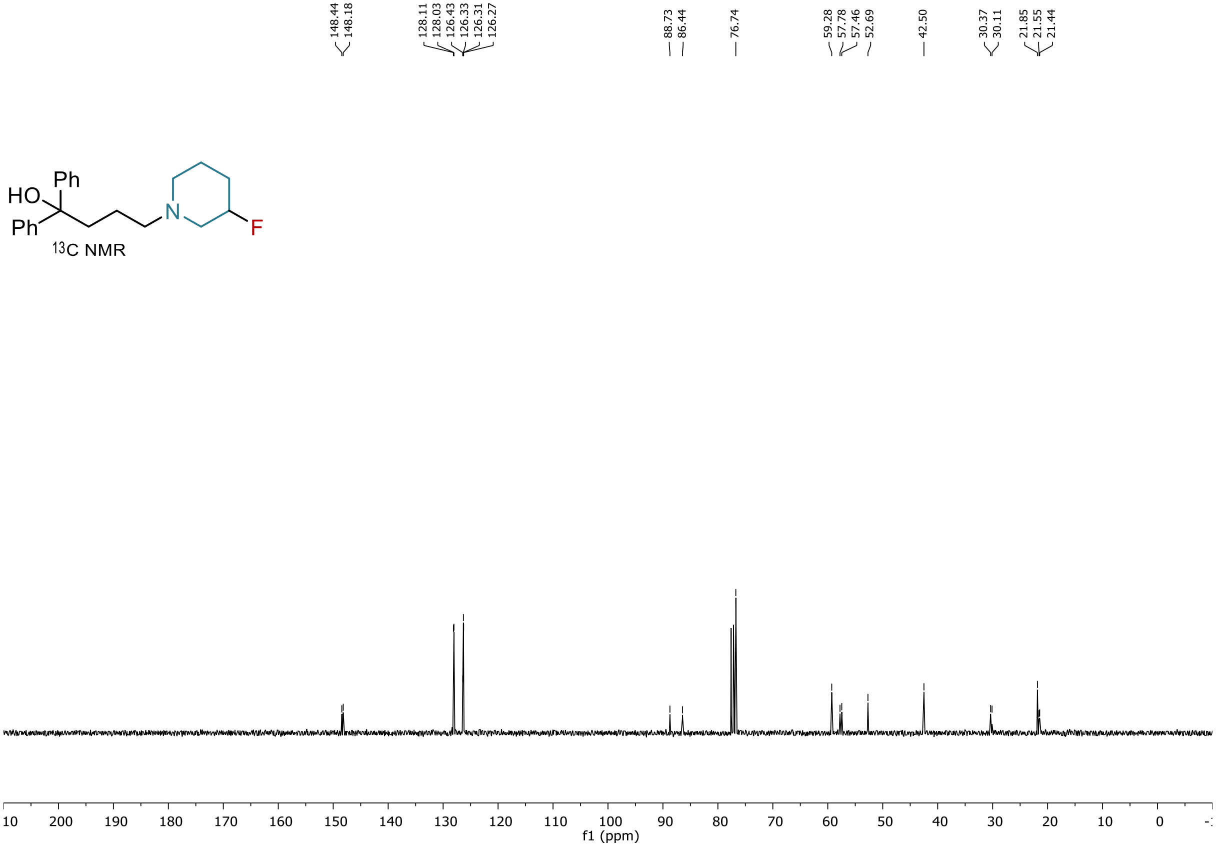
^{1}H NMR

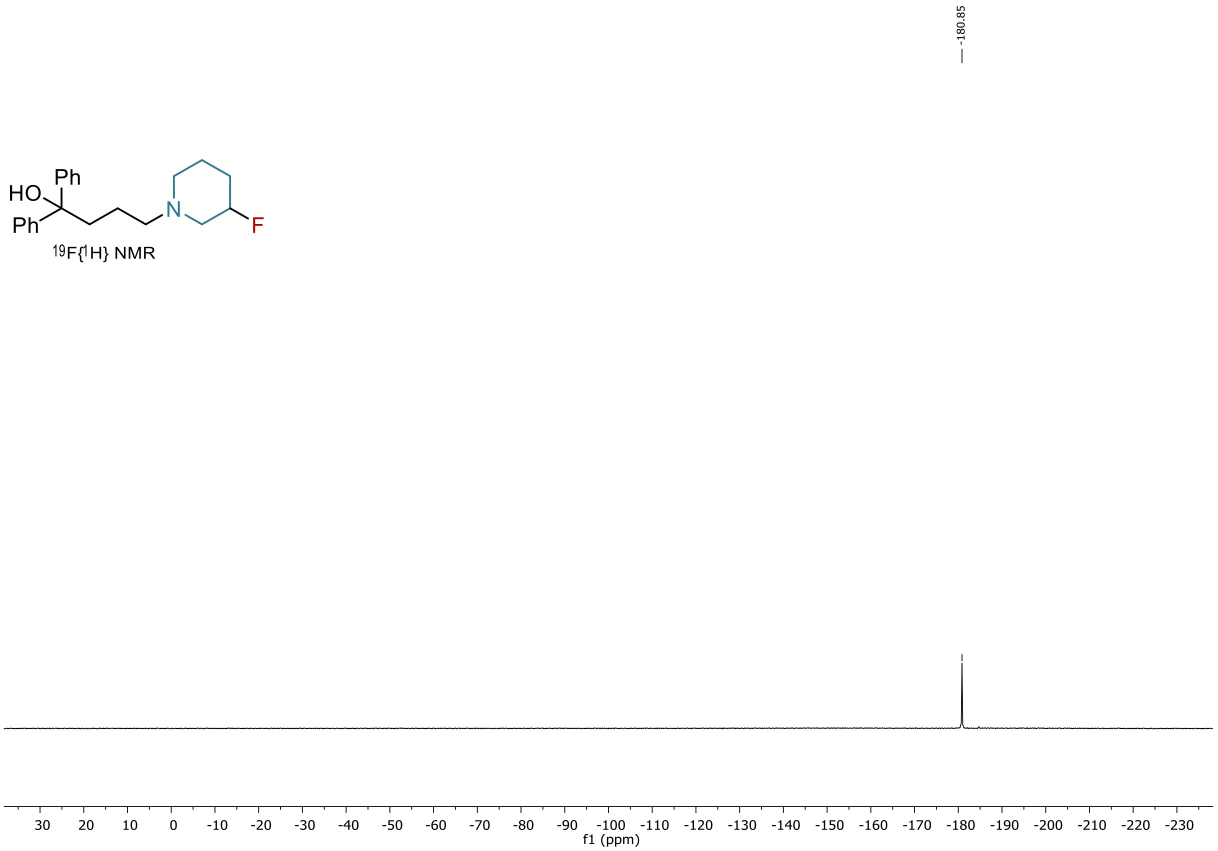


^{13}C NMR

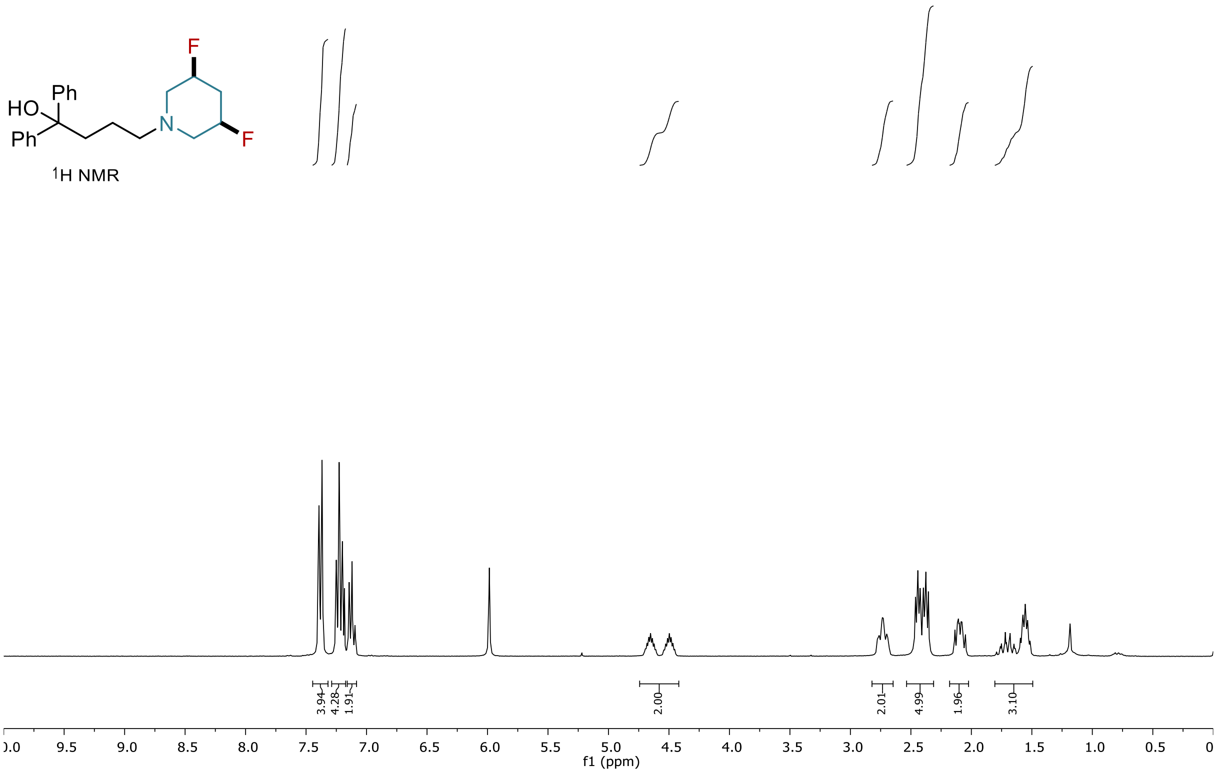

-105.70
-198.83
O
Me
N
F
F
19F{1H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

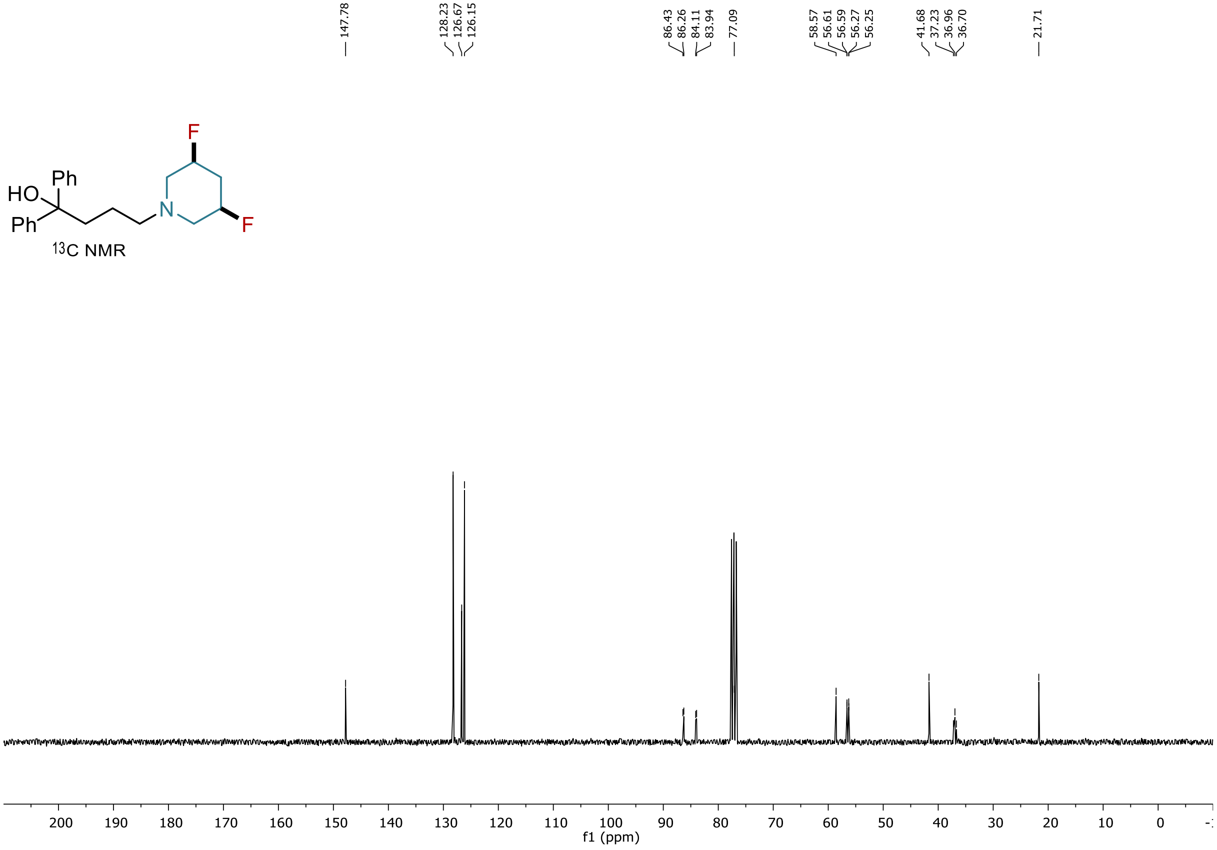

HO
Ph
Ph
N
F
1H NMR
3.79
4.15
1.87
1.00
1.11
4.97
0.95
2.03
1.00
3.88
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

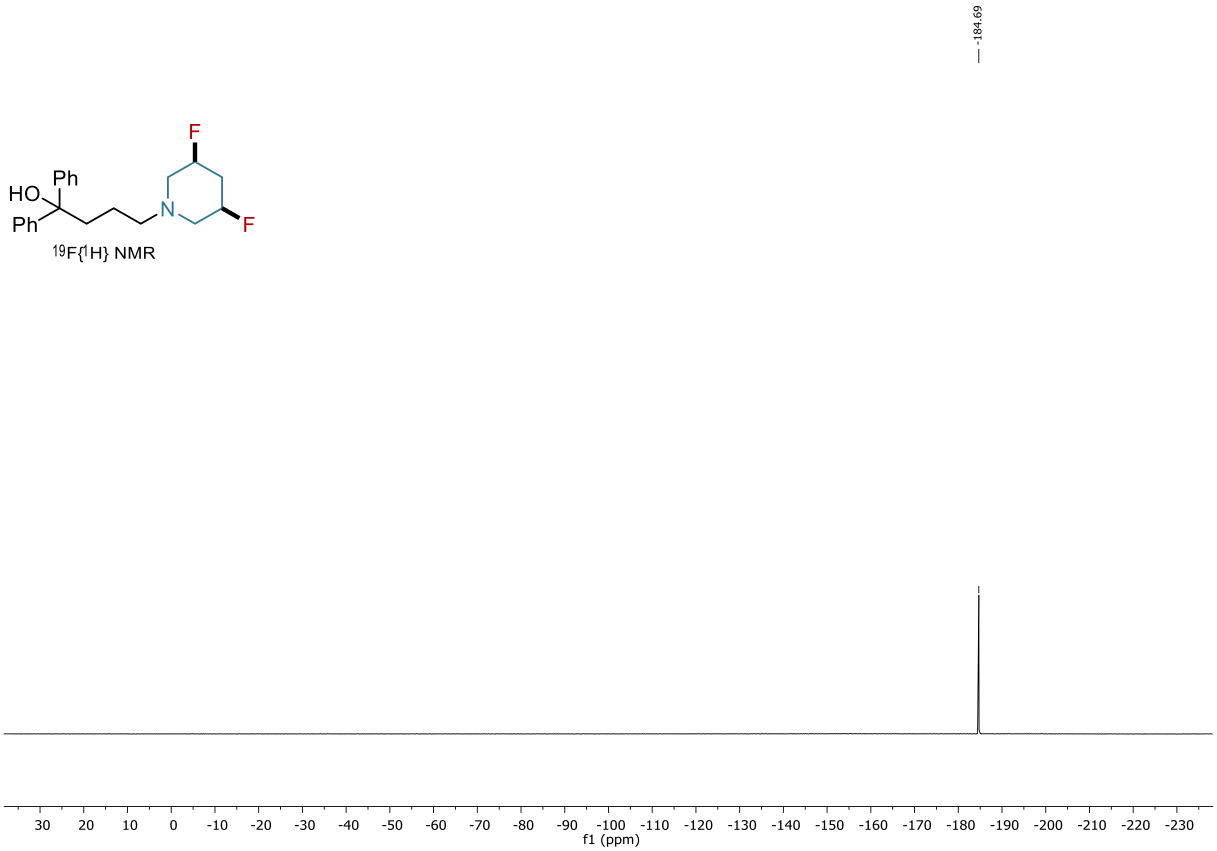

148.44
148.18
128.11
128.03
126.43
126.33
126.31
126.27
88.73
86.44
76.74
59.28
57.78
57.46
52.69
42.50
30.37
30.11
21.85
21.55
21.44
HO
Ph
Ph
N
F
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

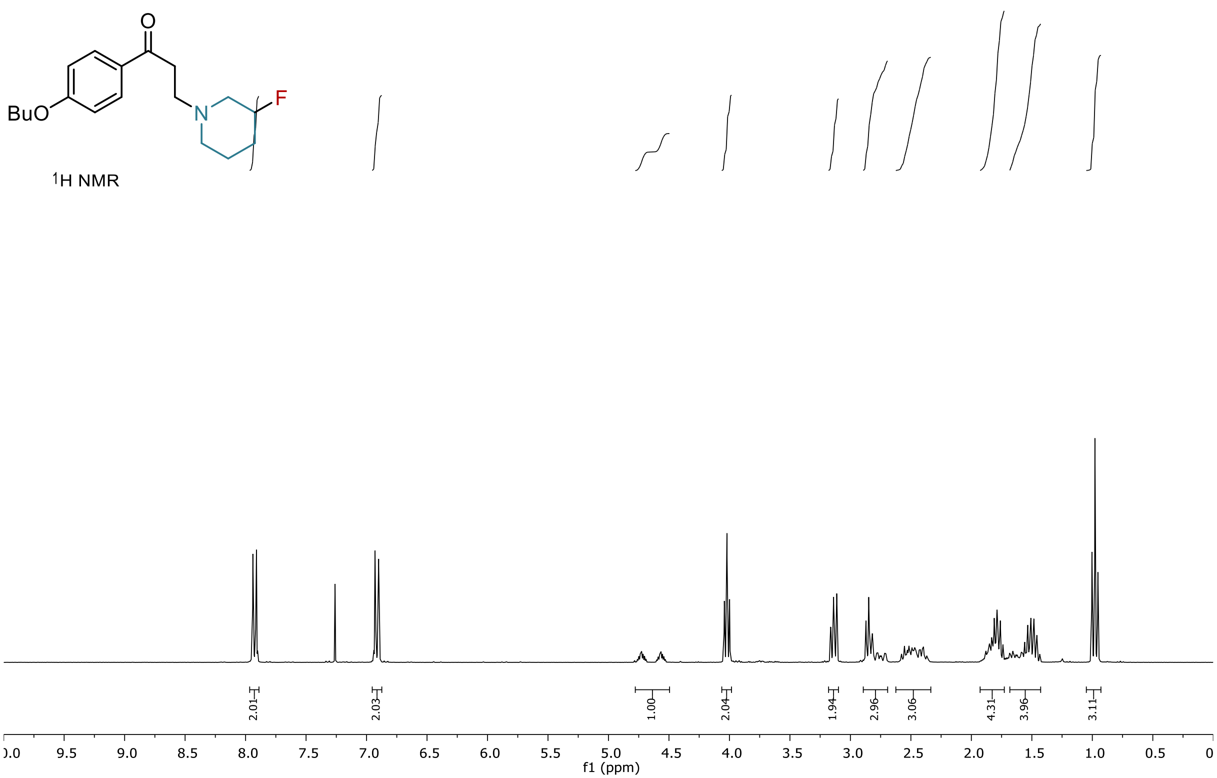


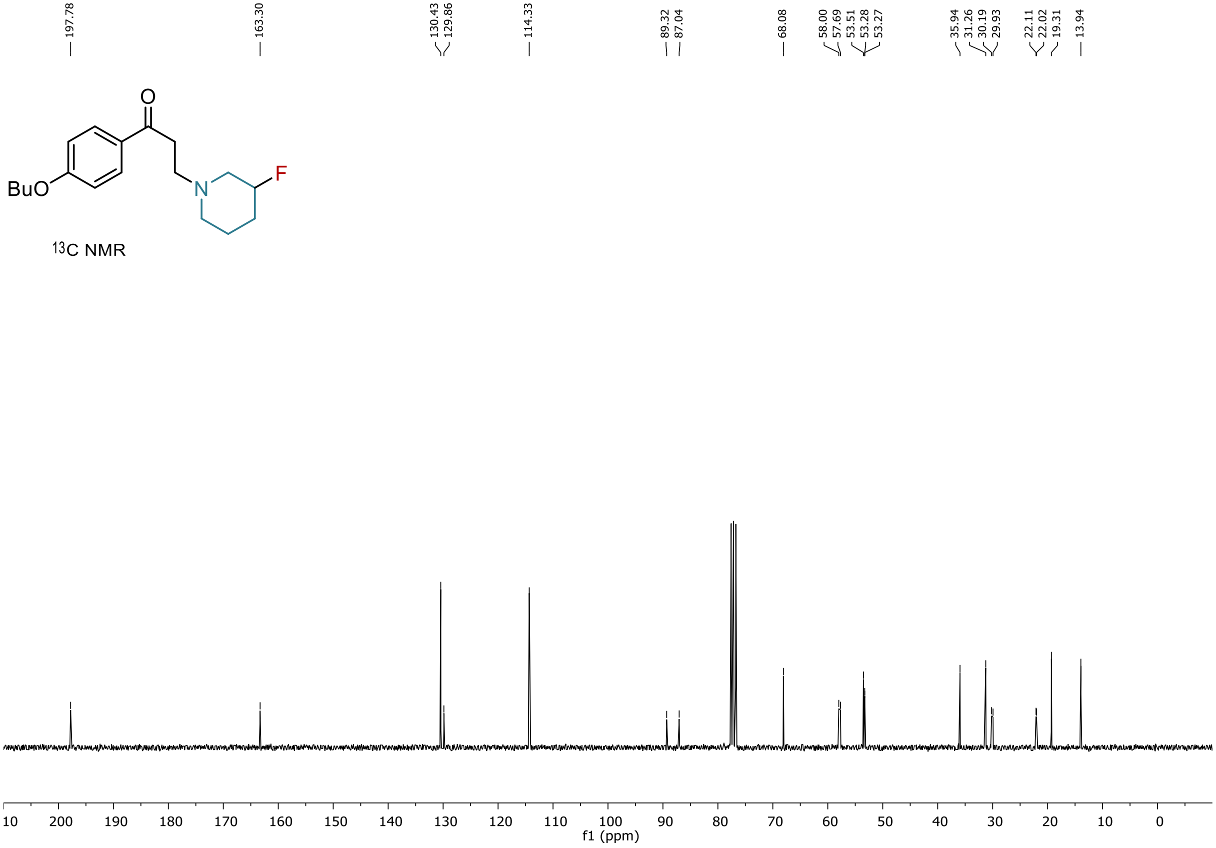
-180.85
HO
Ph
Ph
N
F
^{19}F{^{1}H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

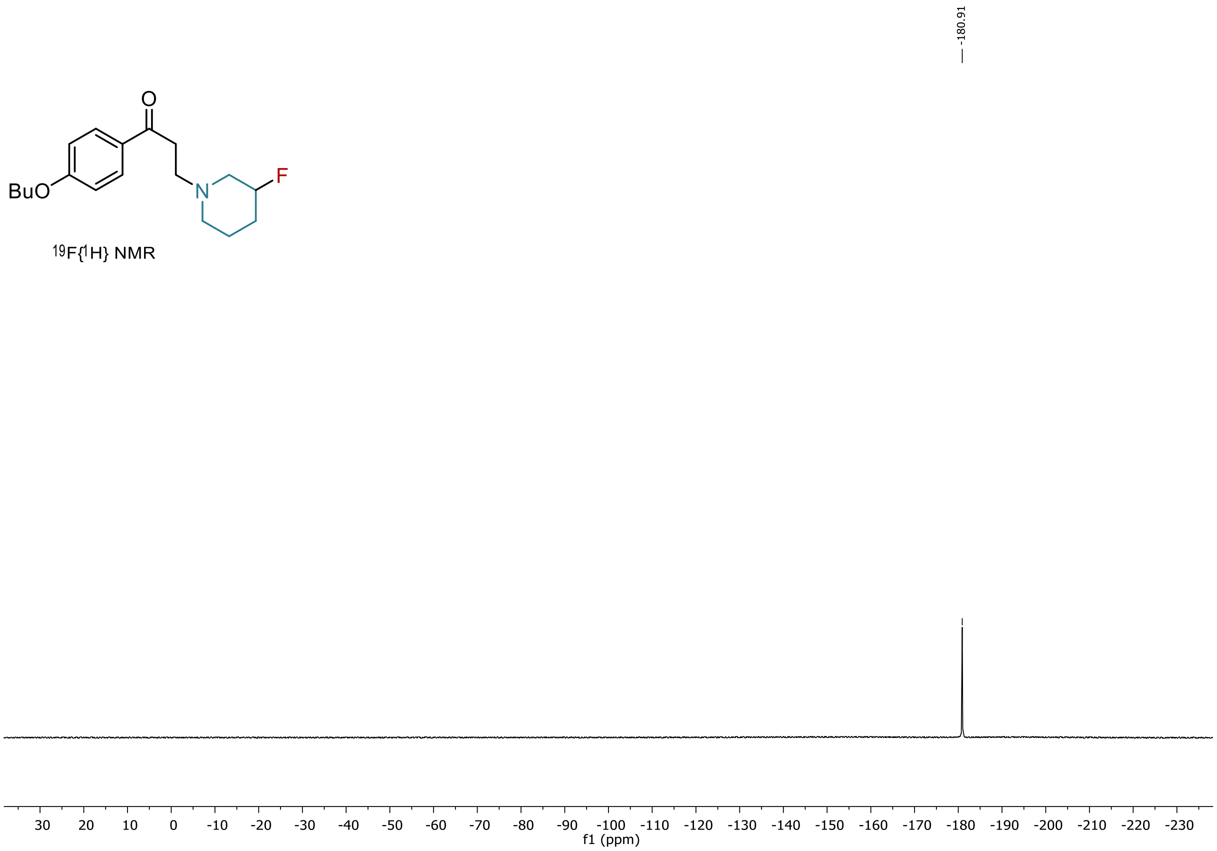

F
Ph
HO
N
Ph
F
1H NMR
3.94
4.28
1.91
2.00
2.01
4.99
1.96
3.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

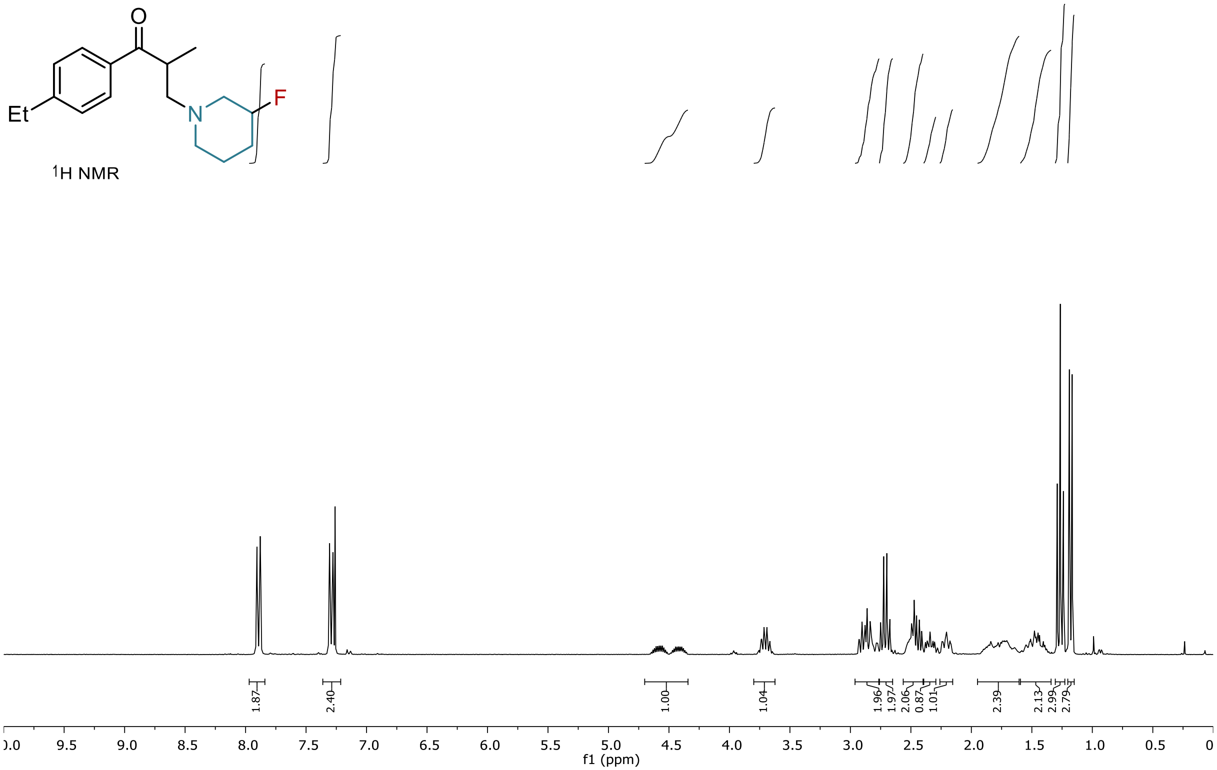

147.78
128.23
126.67
126.15
86.43
86.26
84.11
83.94
77.09
58.57
56.61
56.59
56.27
56.25
41.68
37.23
36.96
36.70
21.71
F
Ph
HO
N
Ph
F
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-184.69
F
Ph
HO
Ph
N
F
^{19}F{^{1}H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

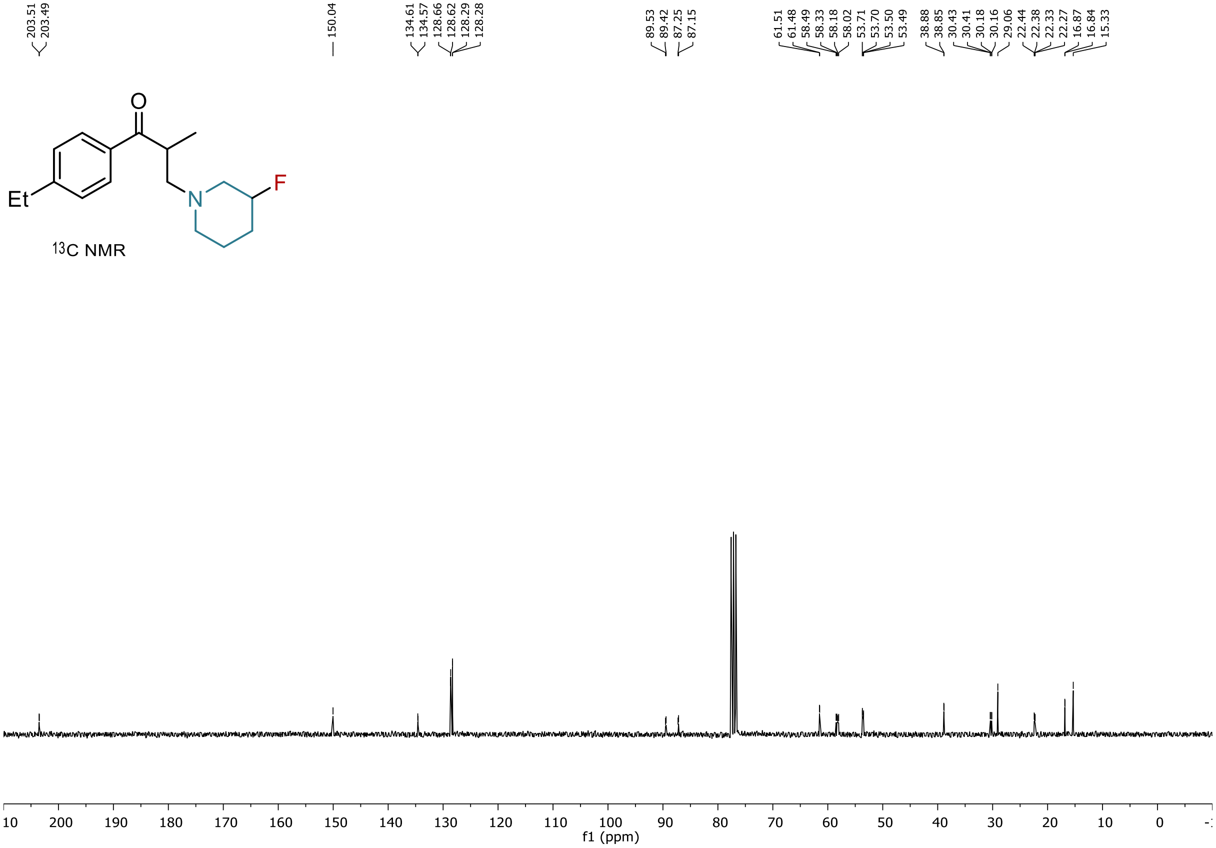

BuO
O
N
F
1H NMR
2.01
2.03
1.00
2.04
1.94
2.96
3.06
4.31
3.96
3.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


197.78
163.30
130.43
129.86
114.33
89.32
87.04
68.08
58.00
57.69
53.51
53.28
53.27
35.94
31.26
30.19
29.93
22.11
22.02
19.31
13.94
BuO
O
N
F
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

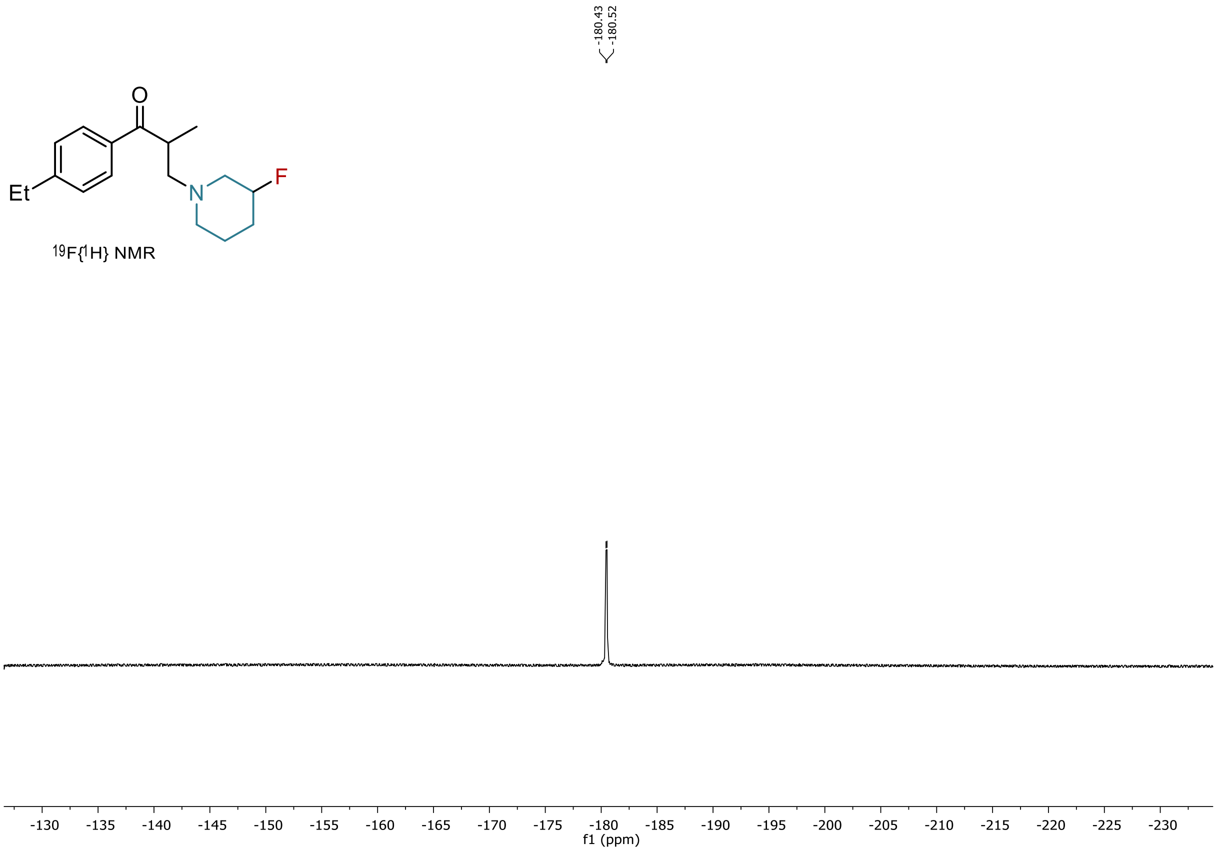

-180.91
O
BuO
N
F
^{19}F{^{1}H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

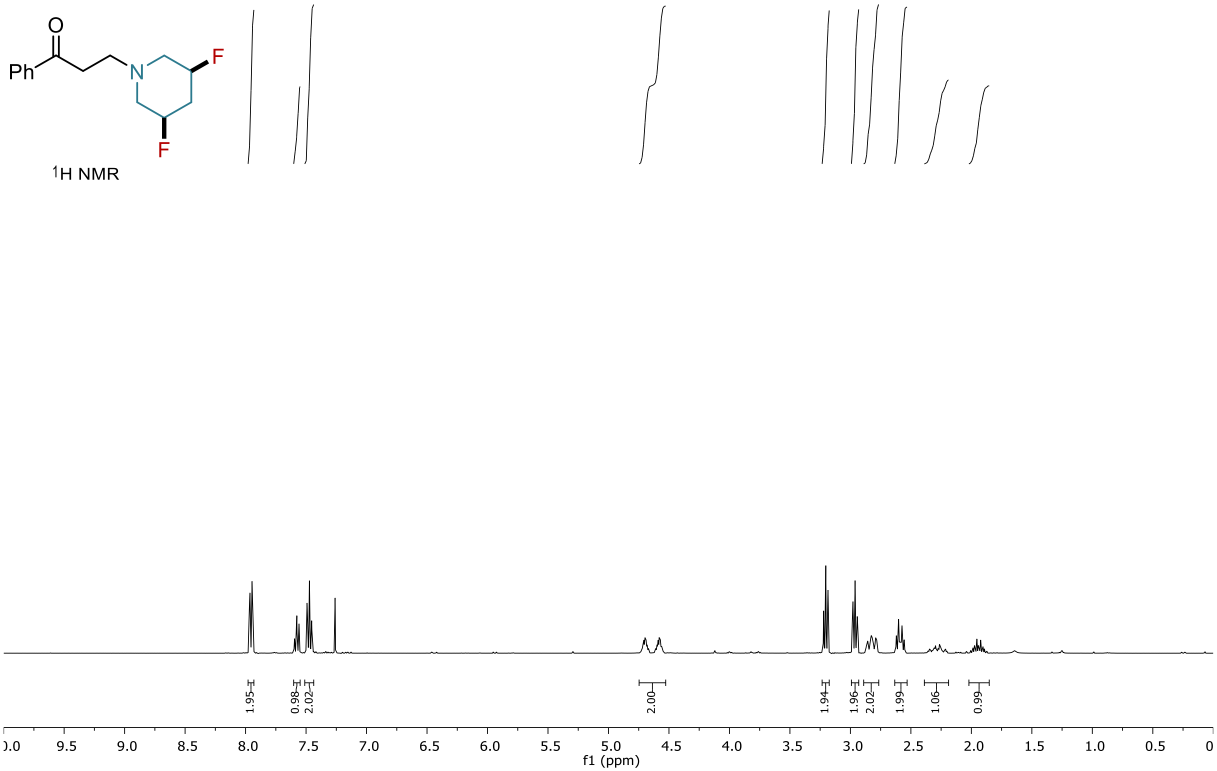


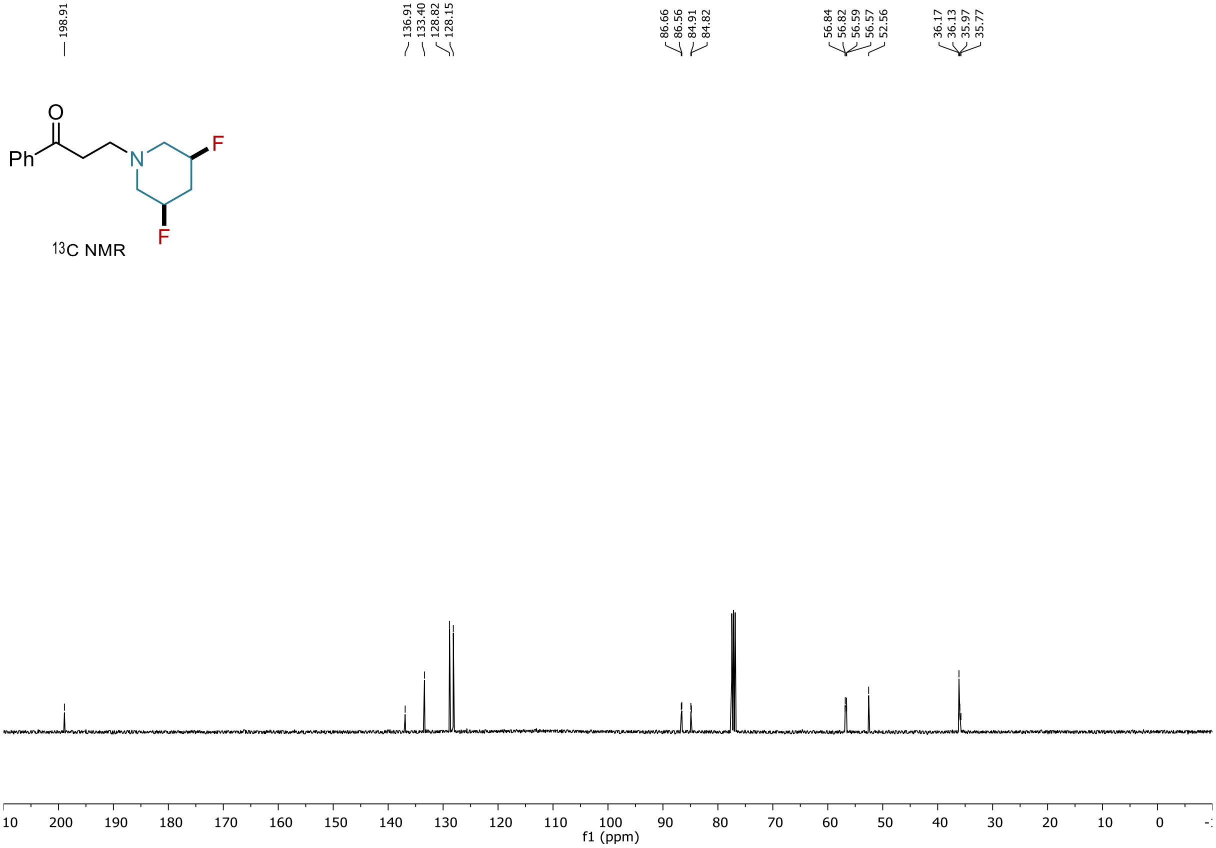
O
Et
N
F
¹H NMR
1.87
2.40
1.00
1.04
1.96
1.97
2.06
0.87
1.01
2.39
2.13
2.99
2.79
).0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

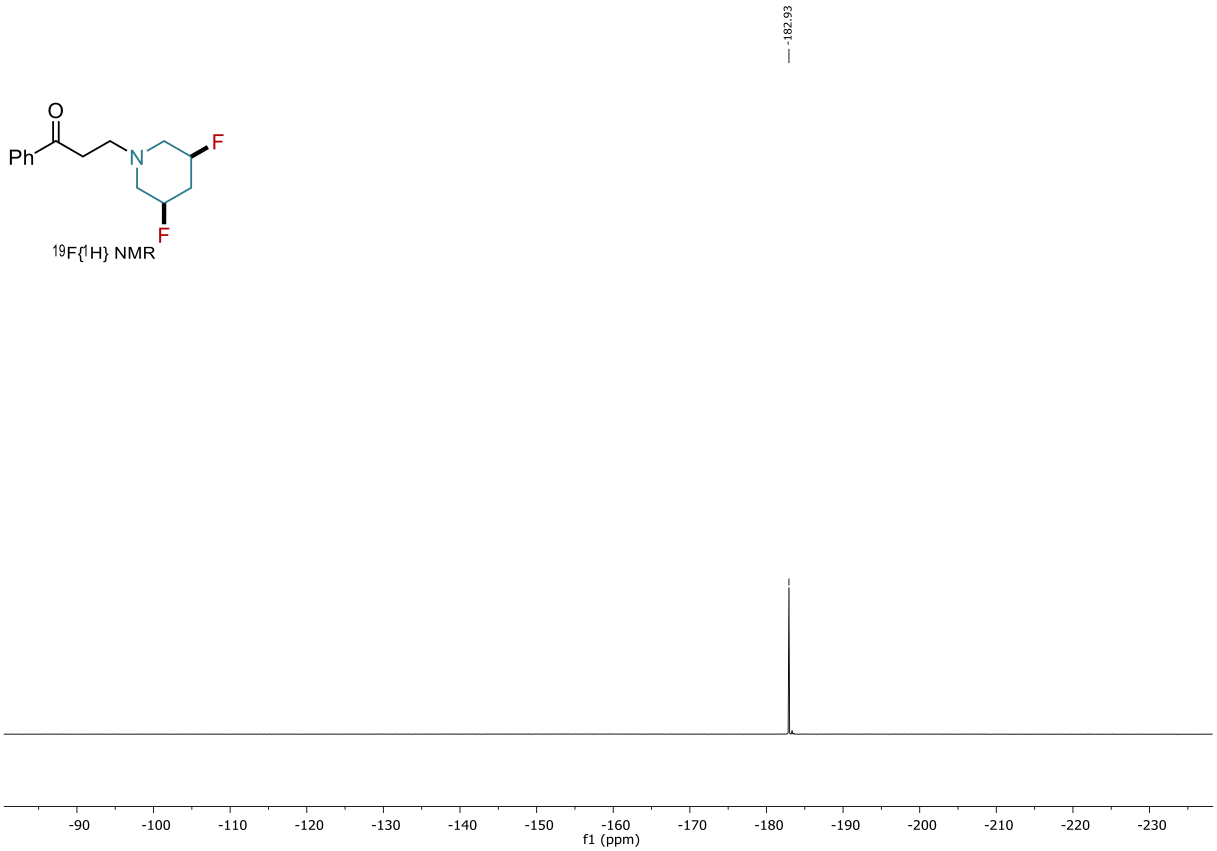


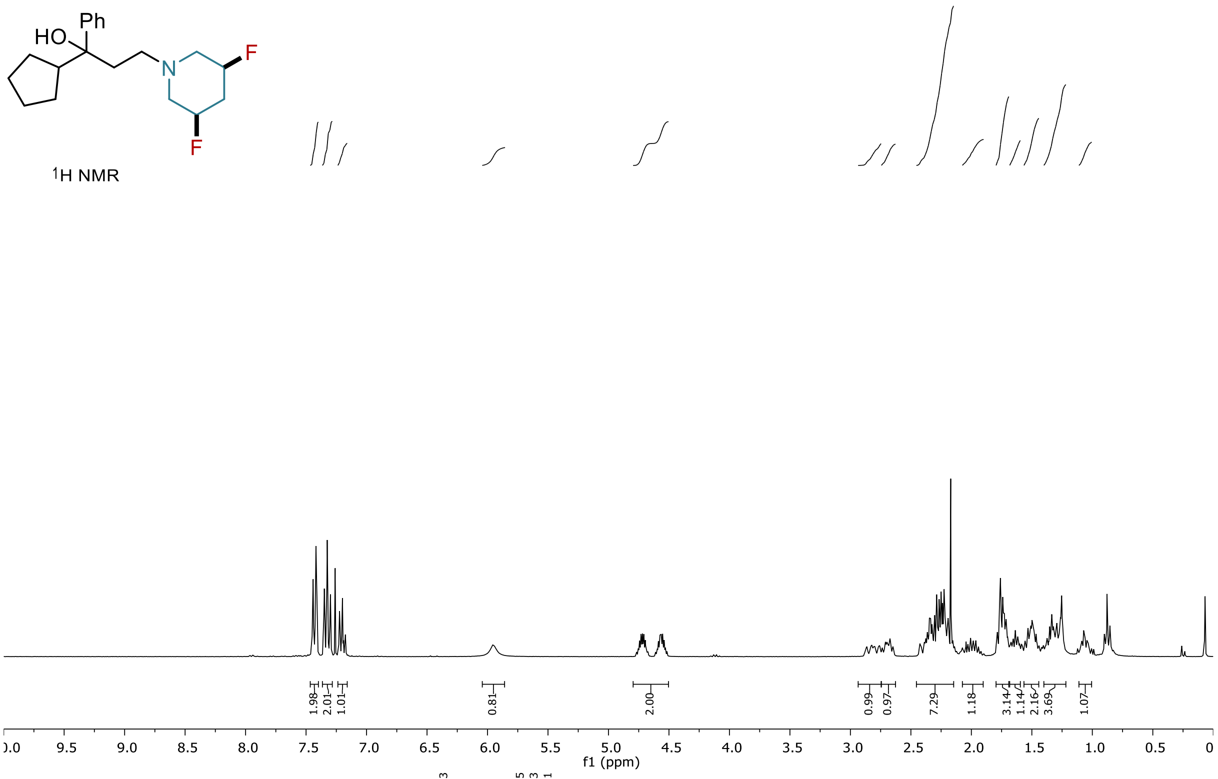
203.51
203.49
150.04
134.61
134.57
128.66
128.62
128.29
128.28
89.53
89.42
87.25
87.15
61.51
61.48
58.49
58.33
58.18
58.02
53.71
53.70
53.50
53.49
38.88
38.85
30.43
30.41
30.18
30.16
29.06
22.44
22.38
22.33
22.27
16.87
16.84
15.33
O
Et
N
F
¹³C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-:
f1 (ppm)


-180.43
-180.52
Et
O
N
F
^{19}F{^{1}H} NMR
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
f1 (ppm)

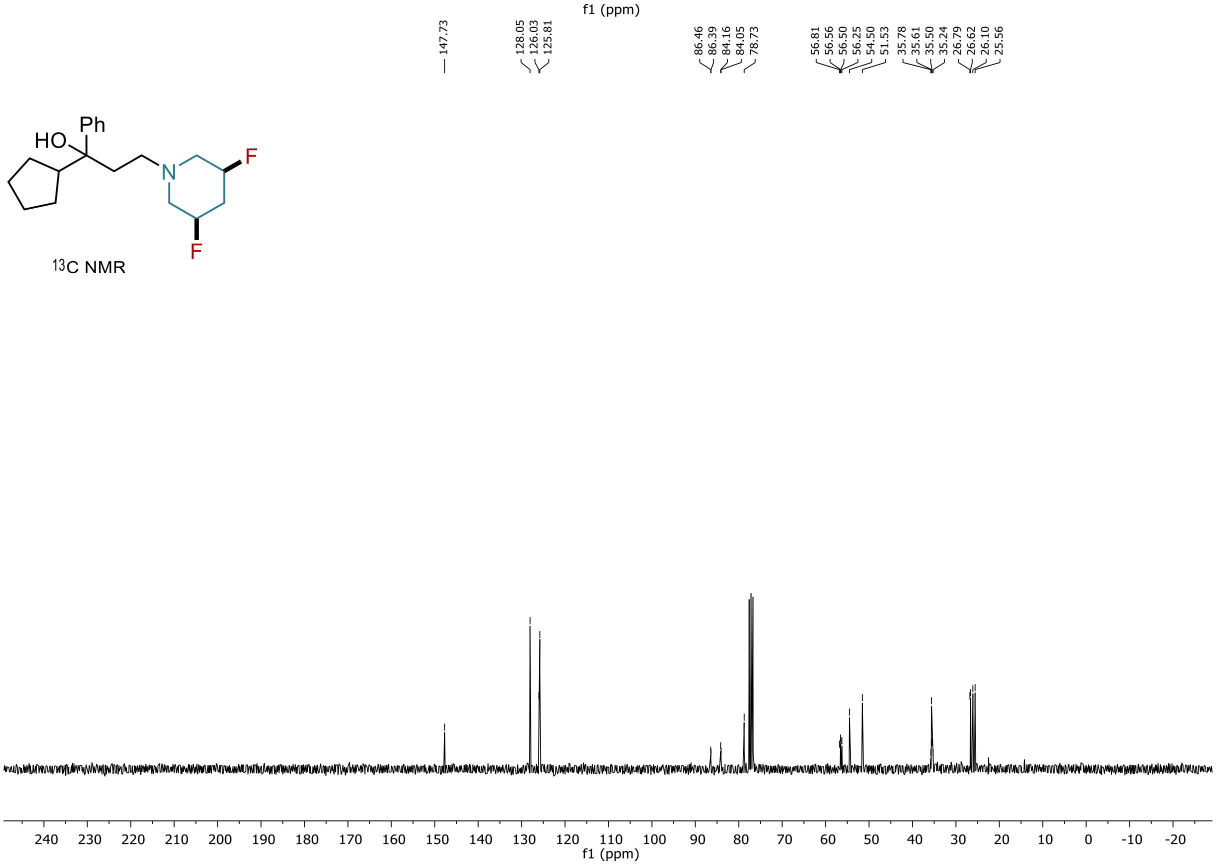

O
Ph
N
F
F
1H NMR
1.95
0.98
2.02
2.00
1.94
1.96
2.02
1.99
1.06
0.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


198.91
136.91
133.40
128.82
128.15
86.66
86.56
84.91
84.82
56.84
56.82
56.59
56.57
52.56
36.17
36.13
35.97
35.77
O
Ph
N
F
F
13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

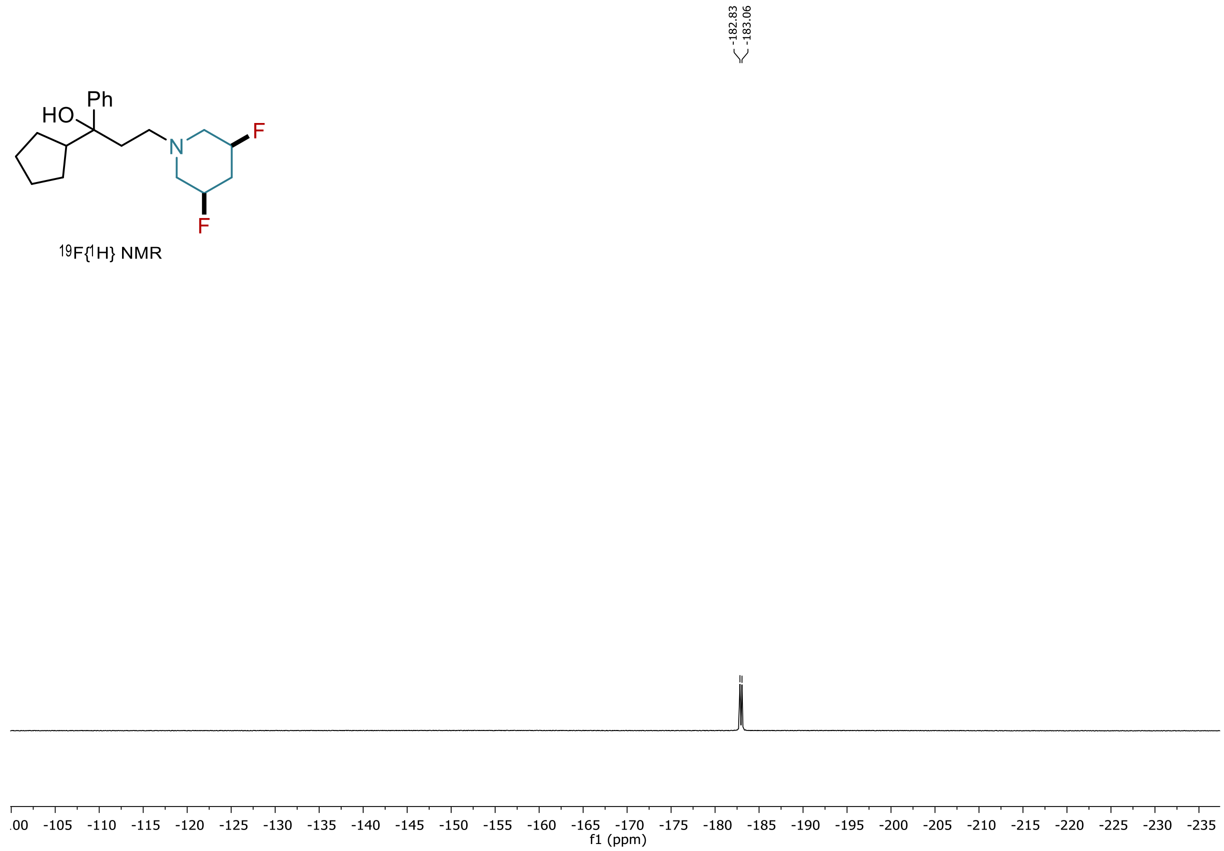

-182.93
O
Ph
N
F
F
$^{19}F\{^1H\}$ NMR
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)

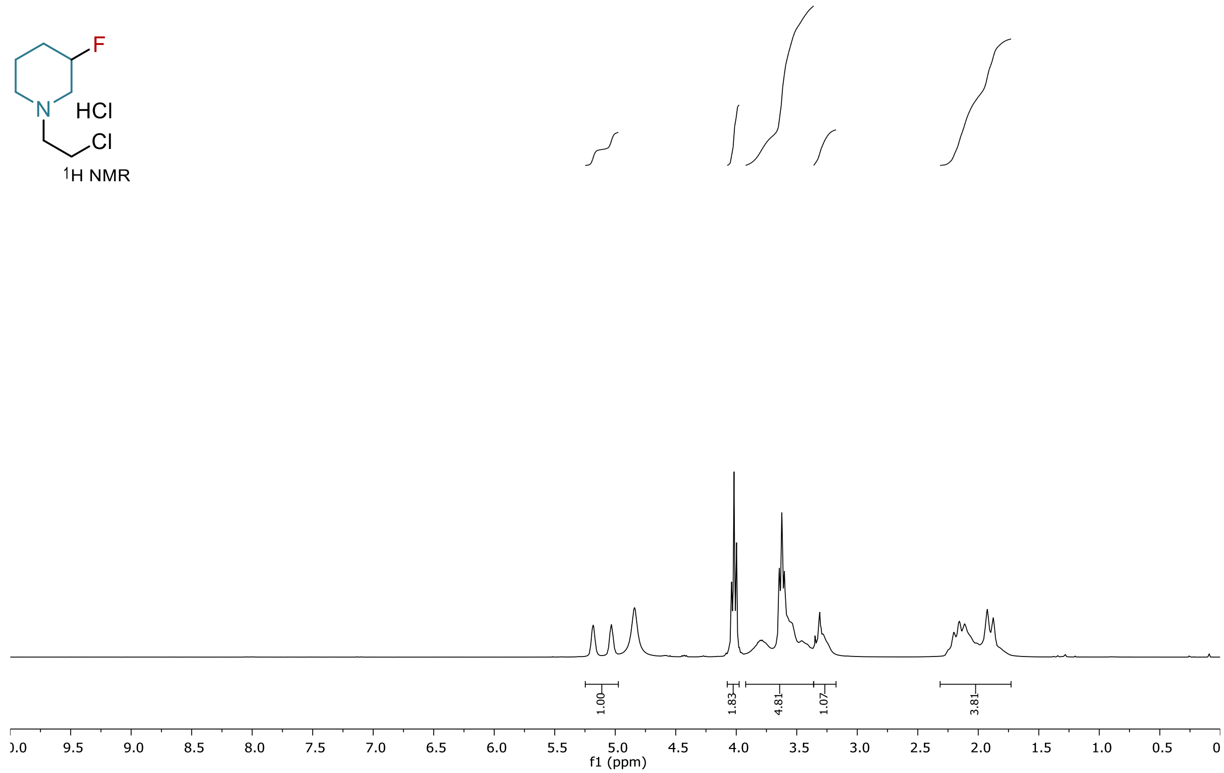


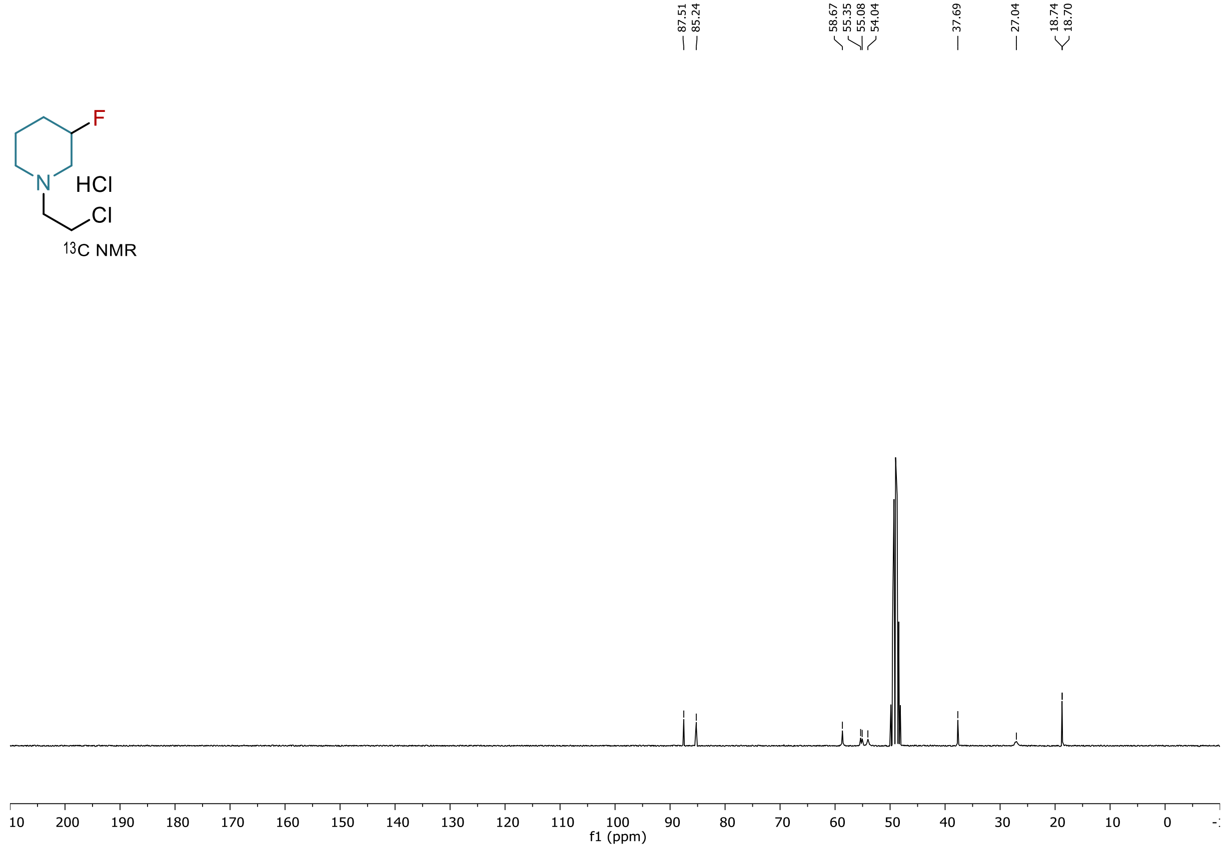
¹H NMR

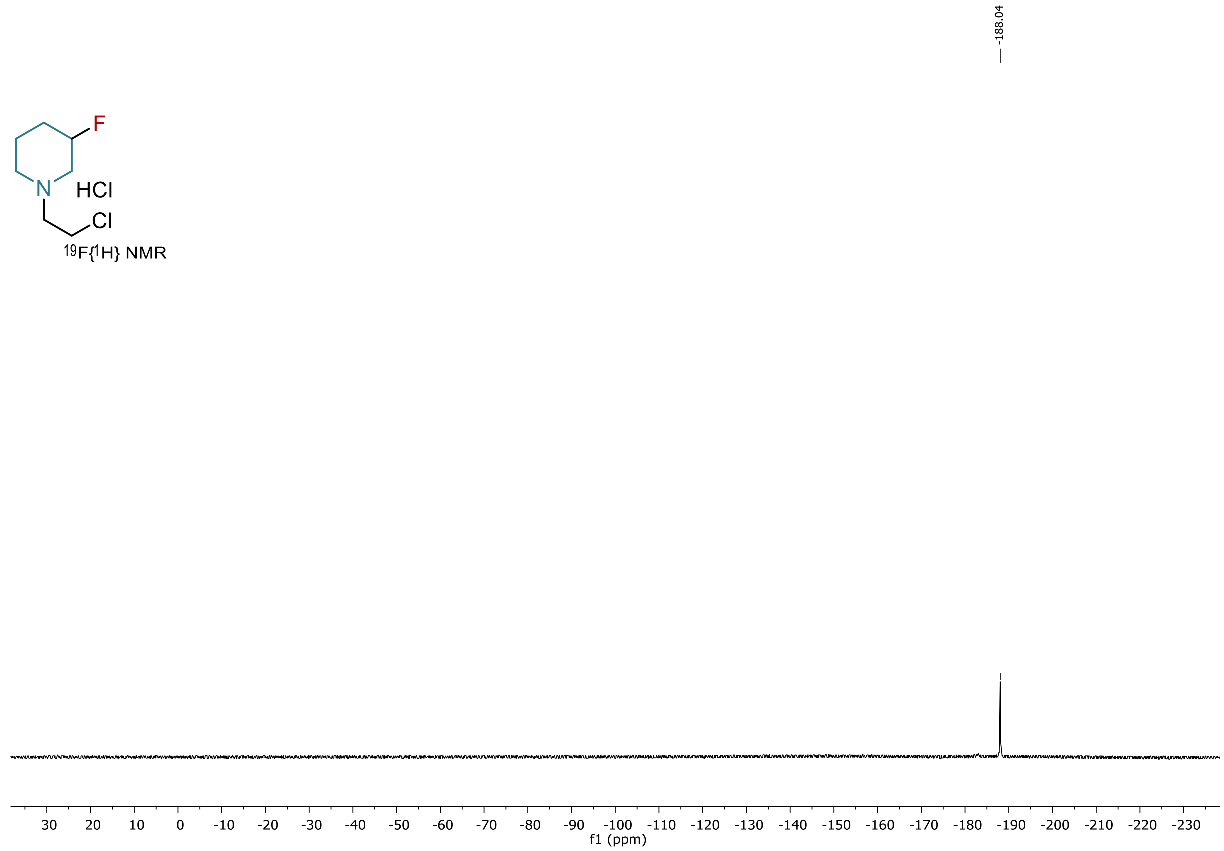


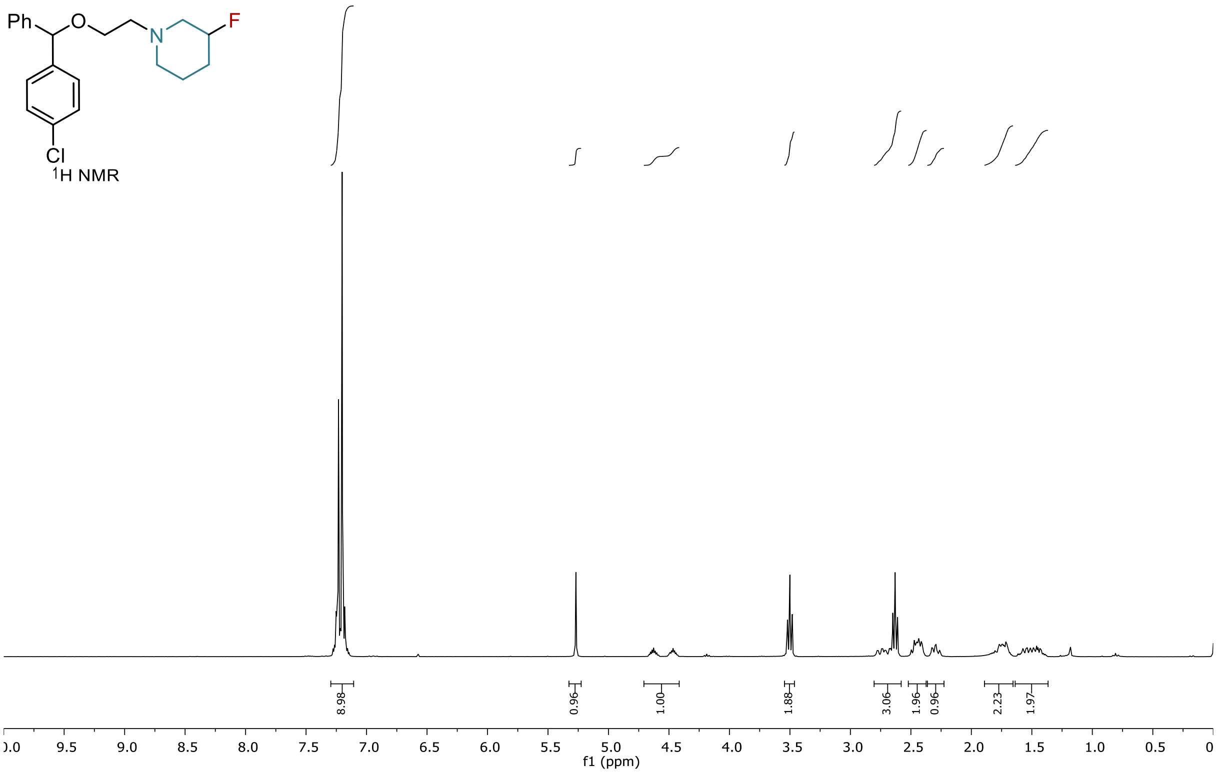
¹³C NMR

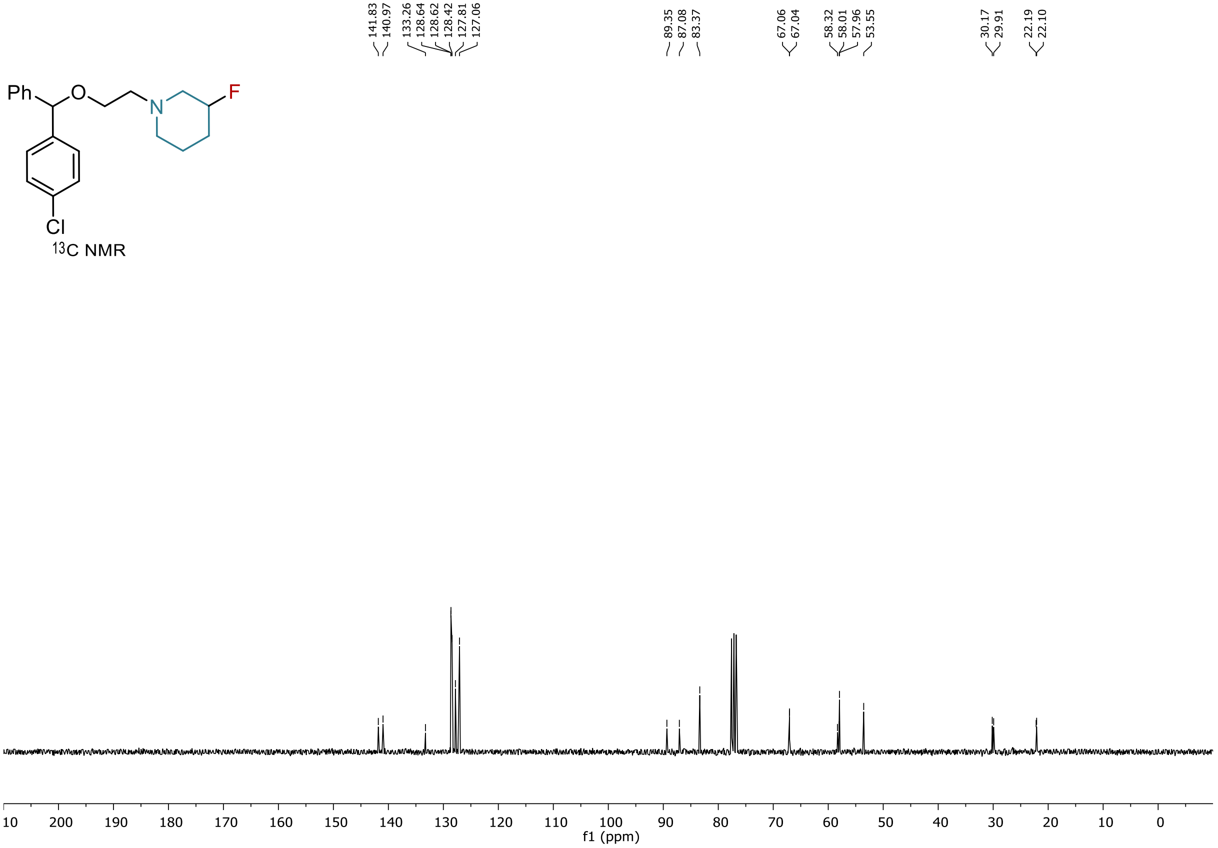

-182.83
-183.06
Ph
HO
N
F
F
19F{1H} NMR
.00 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 -210 -215 -220 -225 -230 -235
f1 (ppm)

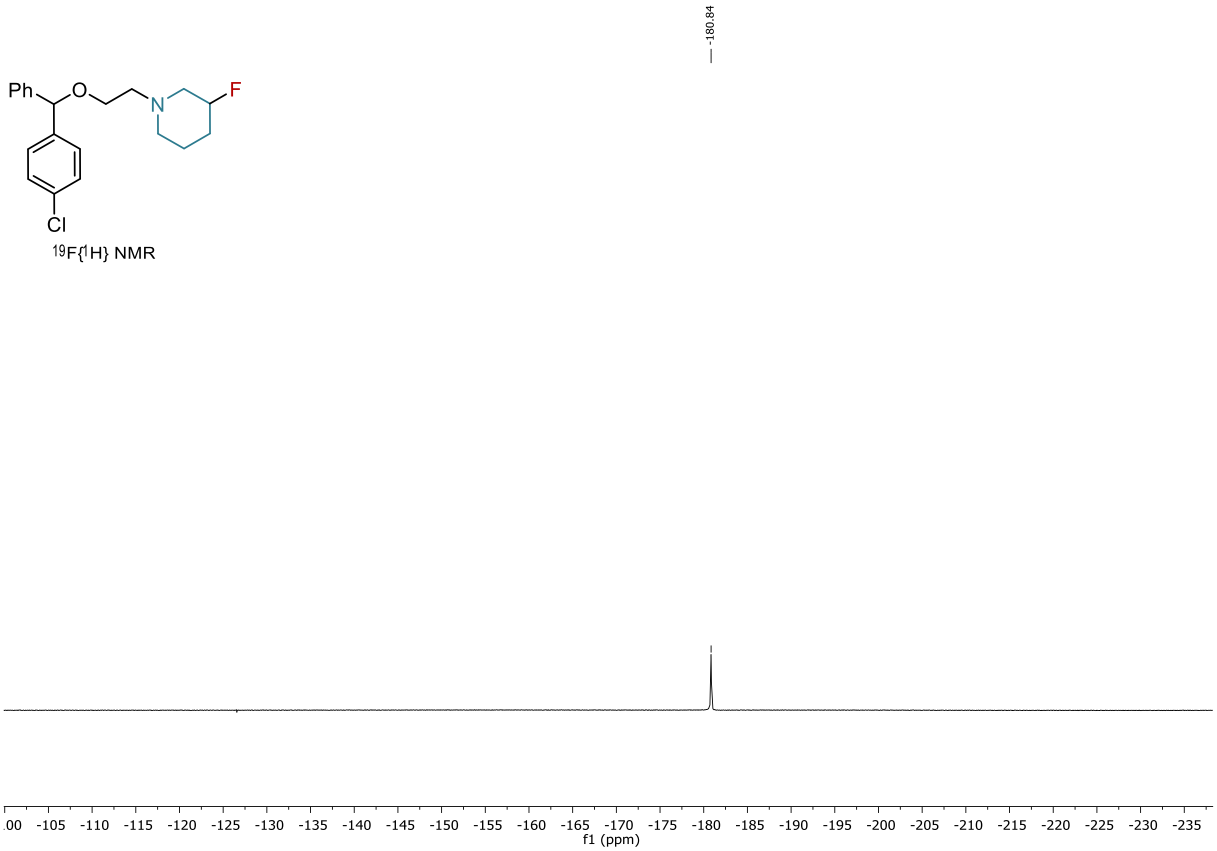

F
N
HCl
Cl
1H NMR
1.00
1.83
4.81
1.07
3.81
).0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

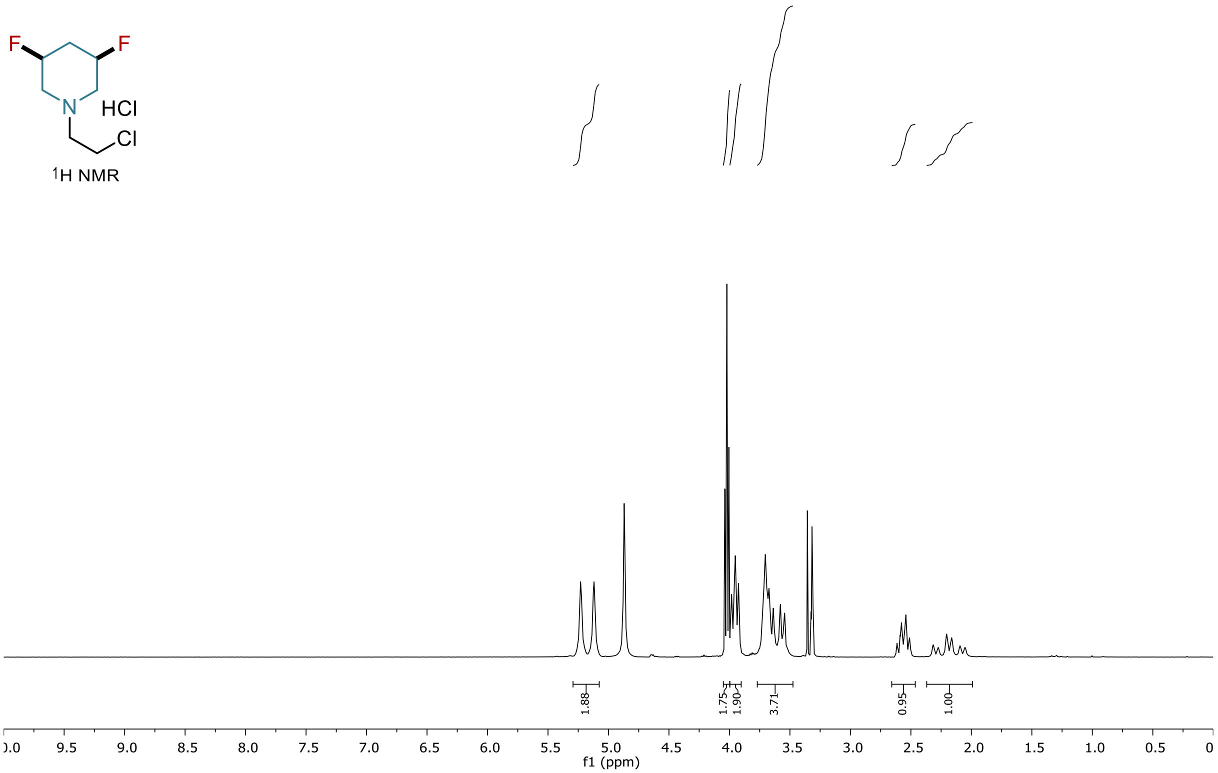

87.51
85.24
58.67
55.35
55.08
54.04
37.69
27.04
18.74
18.70
F
N
HCl
Cl
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-:
f1 (ppm)

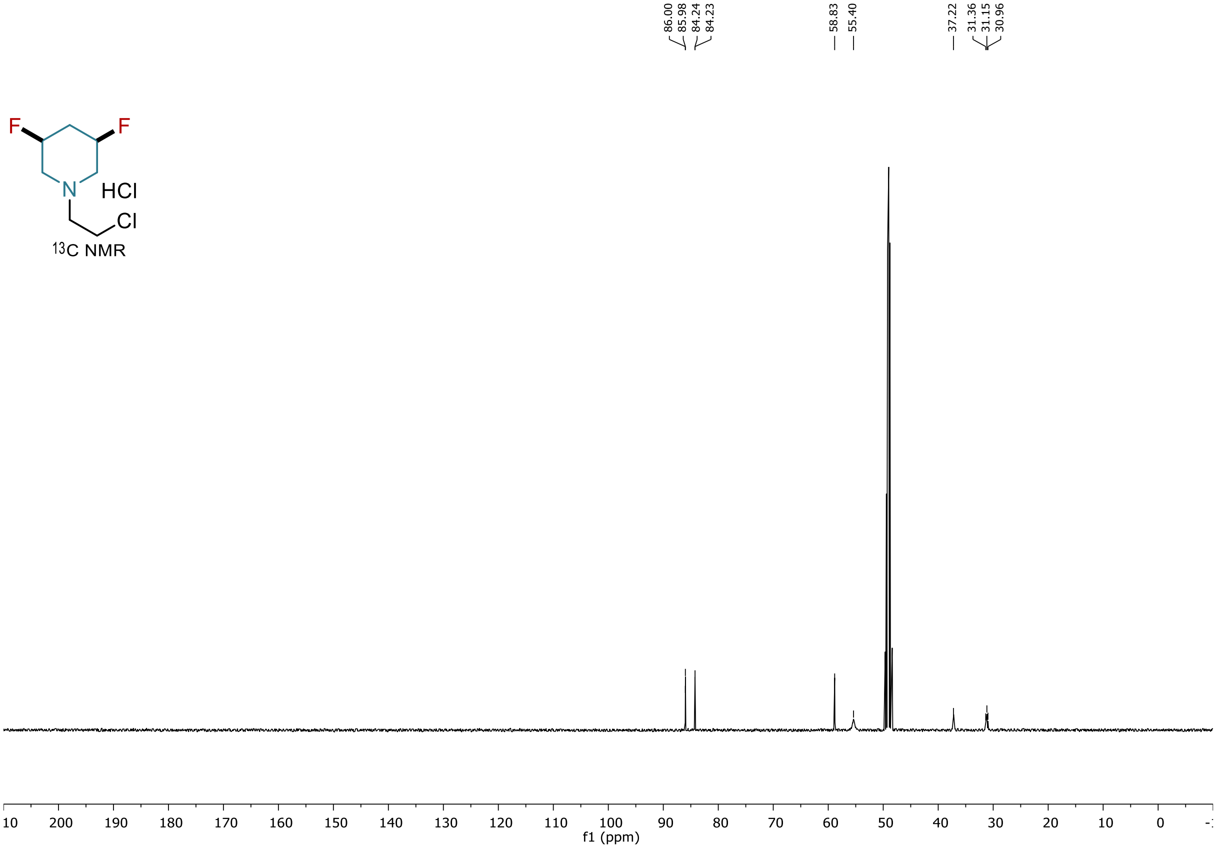

-188.04
F
N
HCl
Cl
19F{1H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

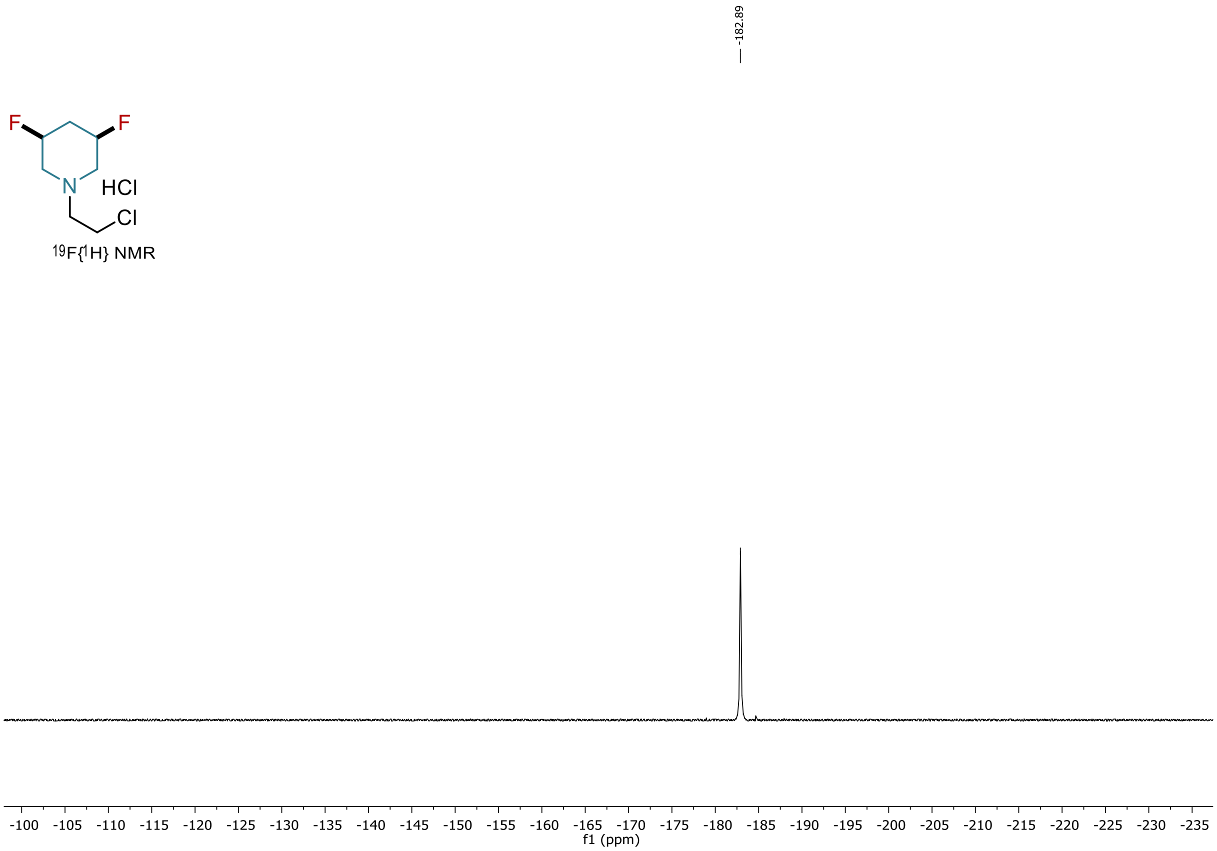

Ph
O
N
F
Cl
1H NMR
8.98
0.96
1.00
1.88
3.06
1.96
0.96
2.23
1.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

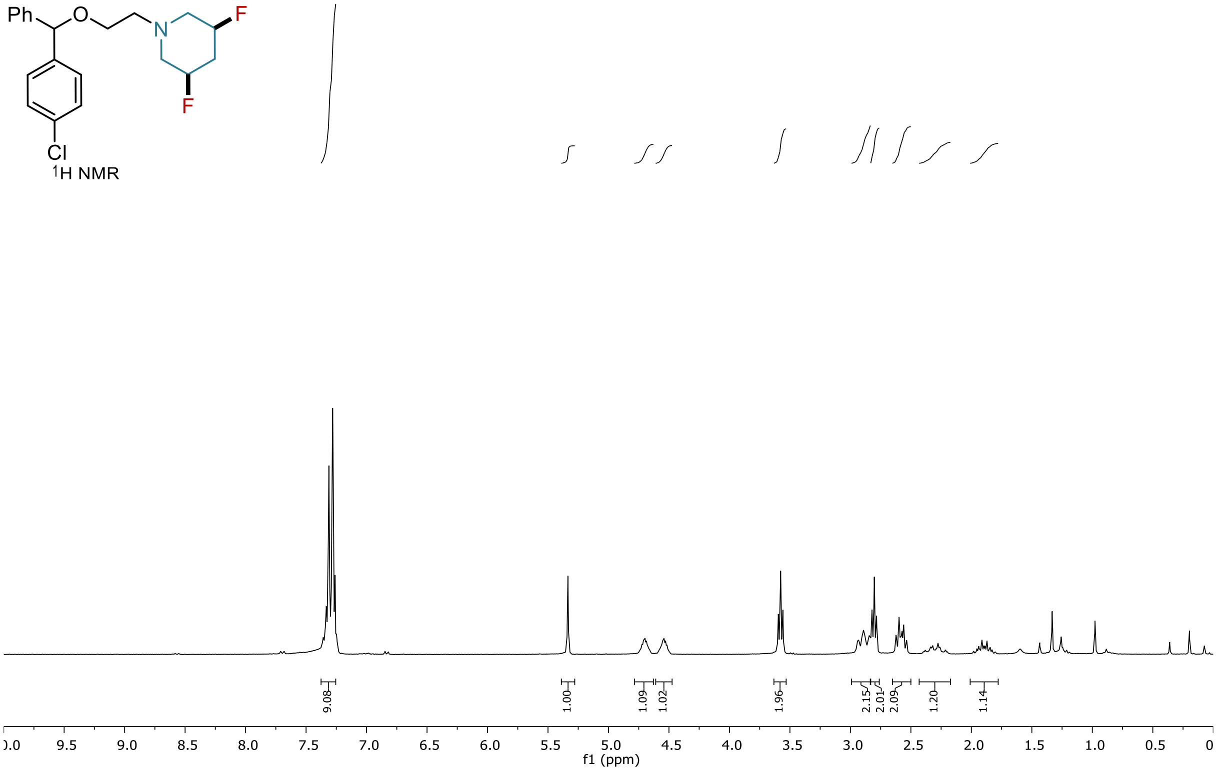

141.83
140.97
133.26
128.64
128.62
128.42
127.81
127.06
89.35
87.08
83.37
67.06
67.04
58.32
58.01
57.96
53.55
30.17
29.91
22.19
22.10
Ph
O
N
F
Cl
13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

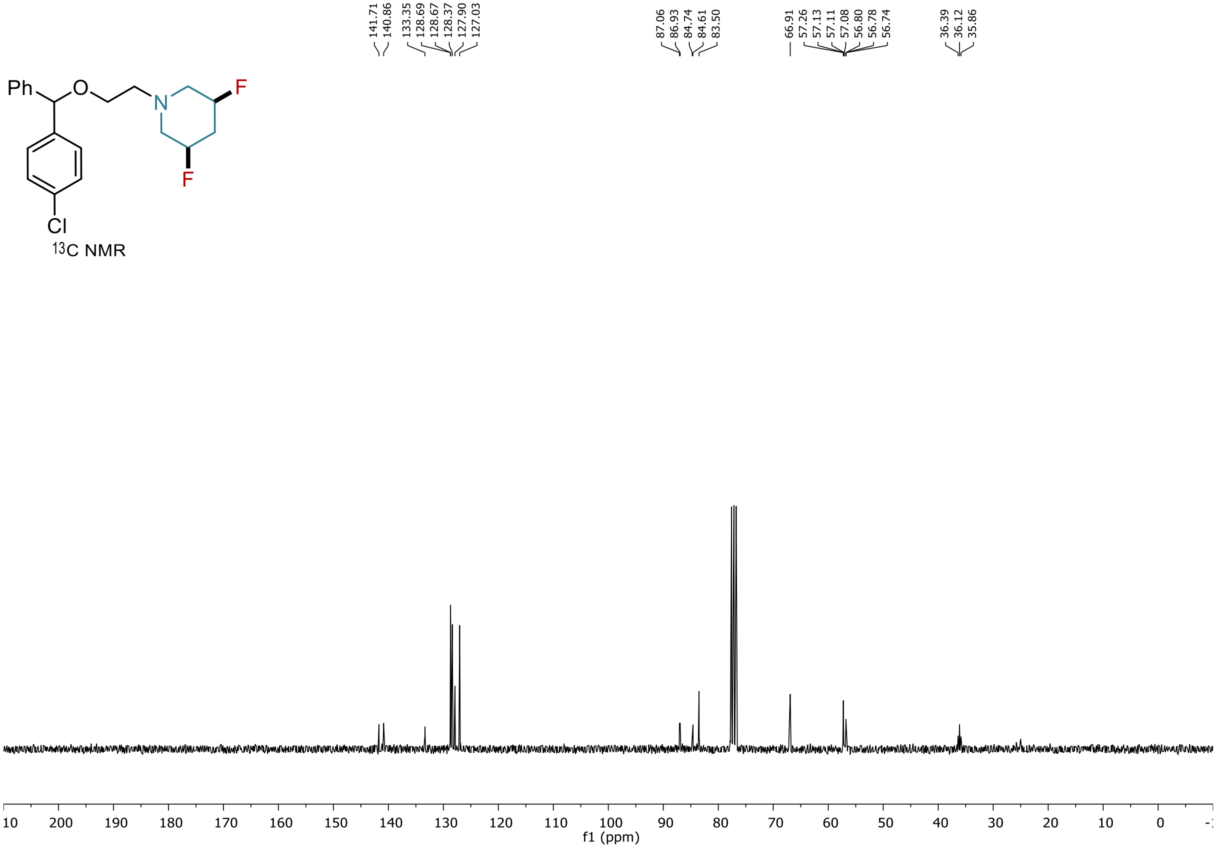

Ph
O
N
F
Cl
^{19}F{^{1}H} NMR
-180.84
.00
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
f1 (ppm)

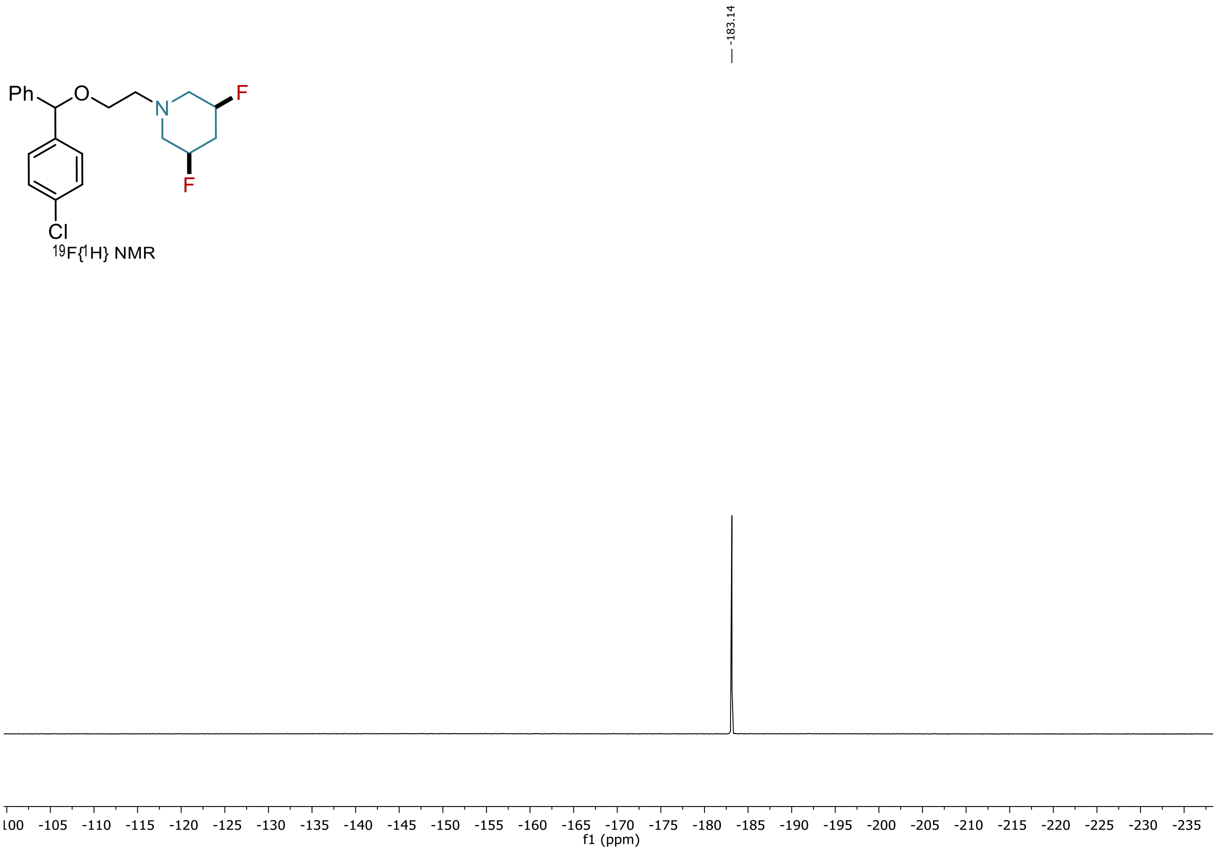

F
F
N
HCl
Cl
1H NMR
1.88
1.75
1.90
3.71
0.95
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


86.00
85.98
84.24
84.23
58.83
55.40
37.22
31.36
31.15
30.96
F
F
N
HCl
Cl
13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-182.89
F
F
N
HCl
Cl
^{19}F{^{1}H} NMR
-100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 -210 -215 -220 -225 -230 -235
f1 (ppm)

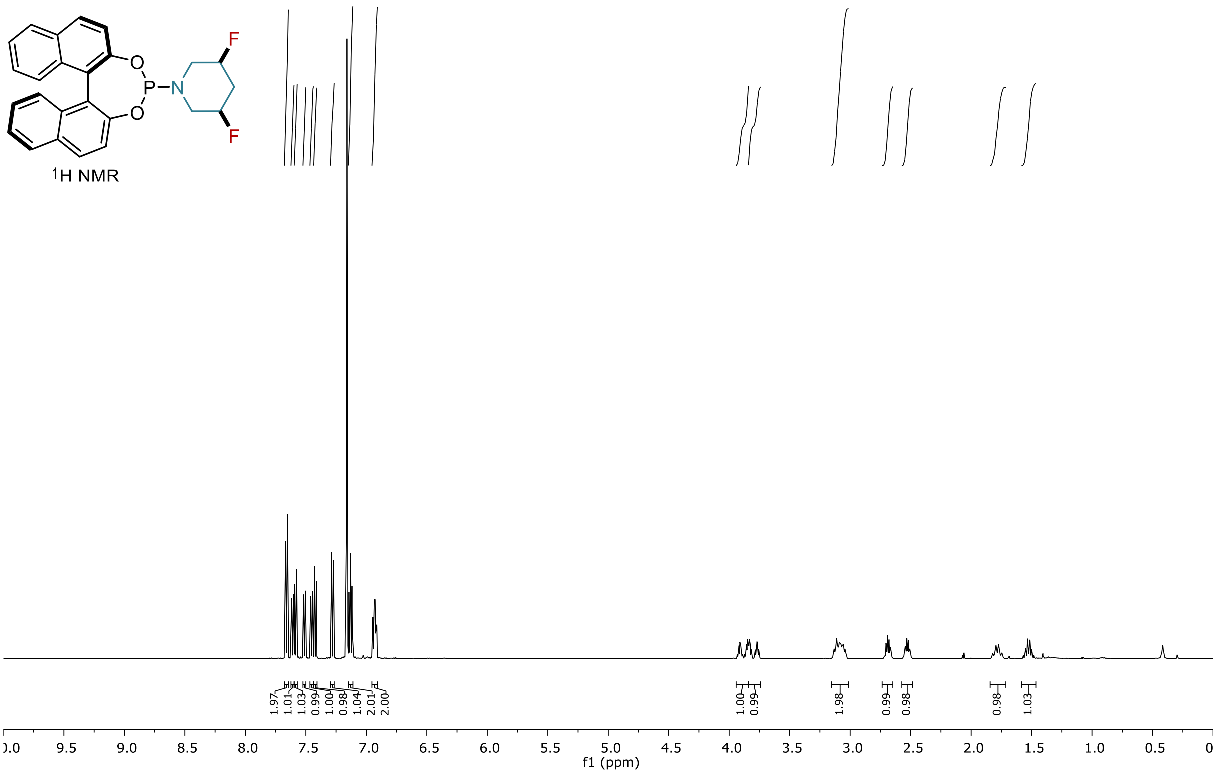

Ph
O
N
F
F
Cl
1H NMR
9.08
1.00
1.09
1.02
1.96
2.15
2.01
2.09
1.20
1.14
).0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


141.71
140.86
133.35
128.69
128.67
128.37
127.90
127.03
87.06
86.93
84.74
84.61
83.50
66.91
57.26
57.13
57.11
57.08
56.80
56.78
56.74
36.39
36.12
35.86
Ph
O
N
F
F
Cl
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-:
f1 (ppm)

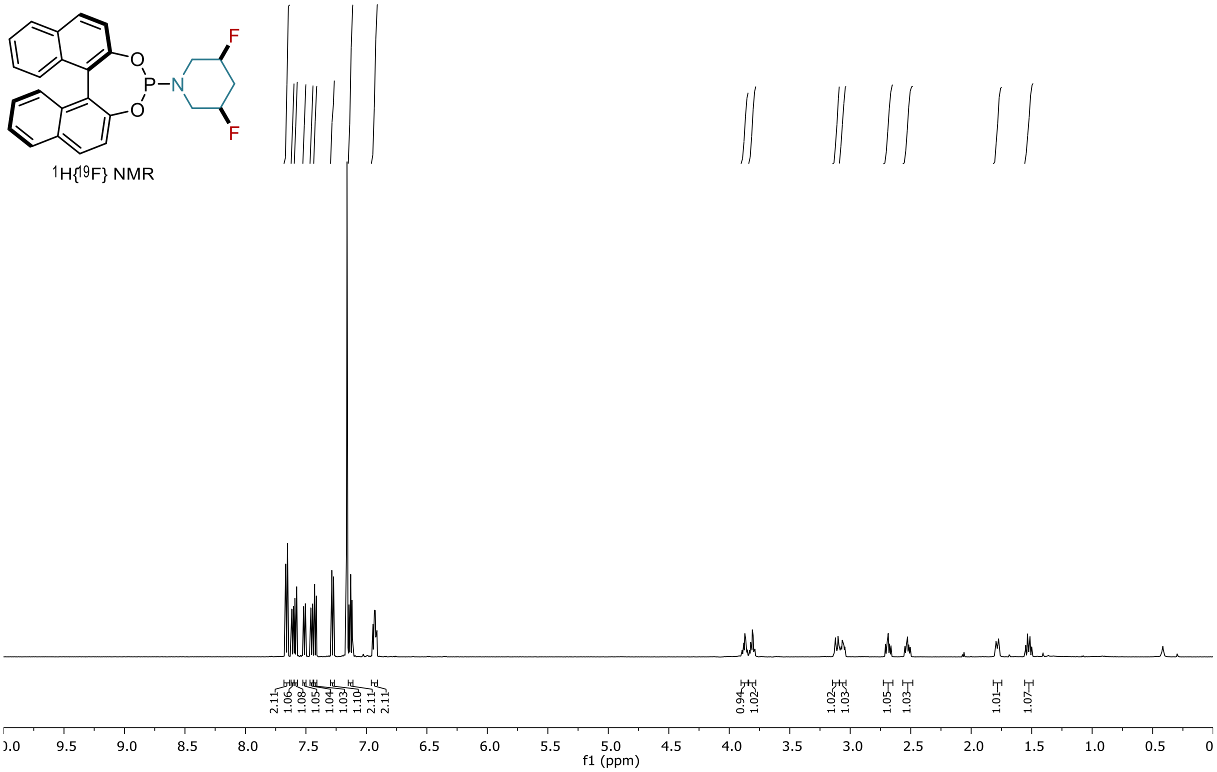


Ph
O
N
F
F
Cl
-183.14
100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
f1 (ppm)

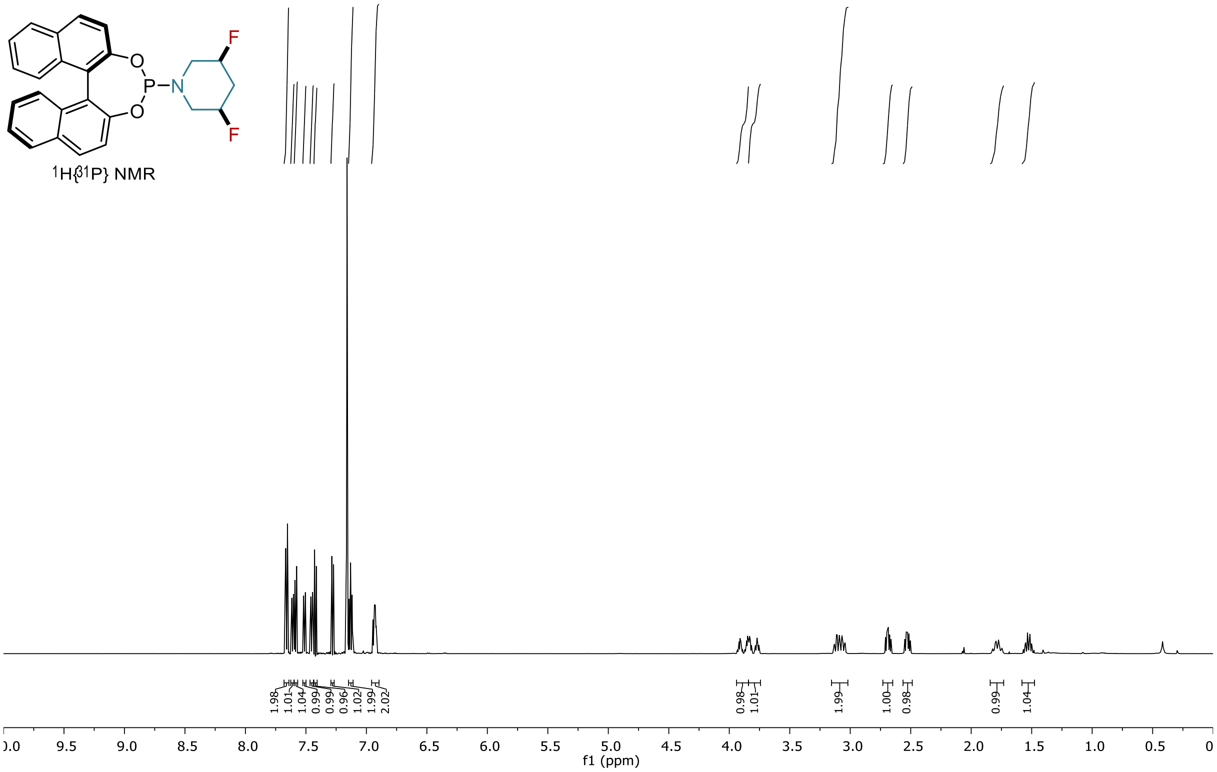
$^{19}F\{^{1}H\}$ NMR

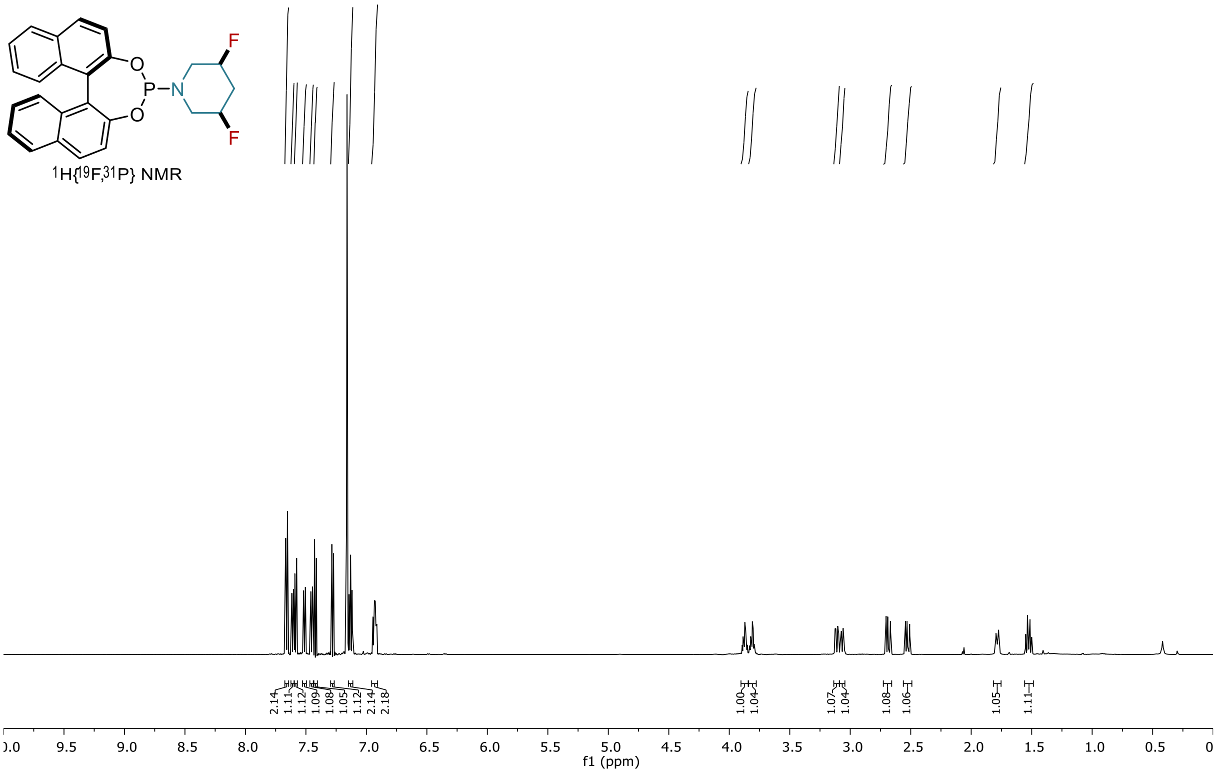


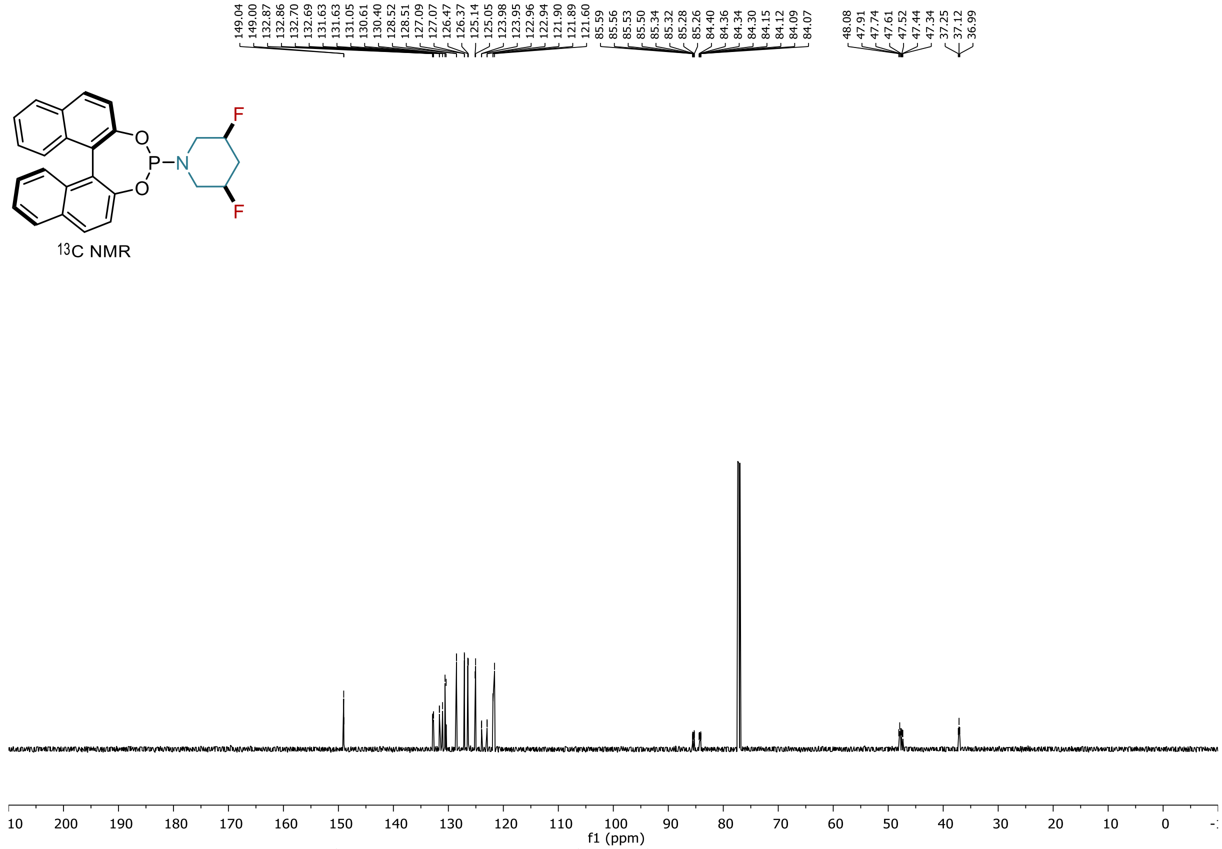
O
P
N
O
F
F
^{1}H NMR
1.97
1.01
1.03
0.99
1.00
0.98
1.04
2.01
2.00
1.00
0.99
1.98
0.99
0.98
0.98
1.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

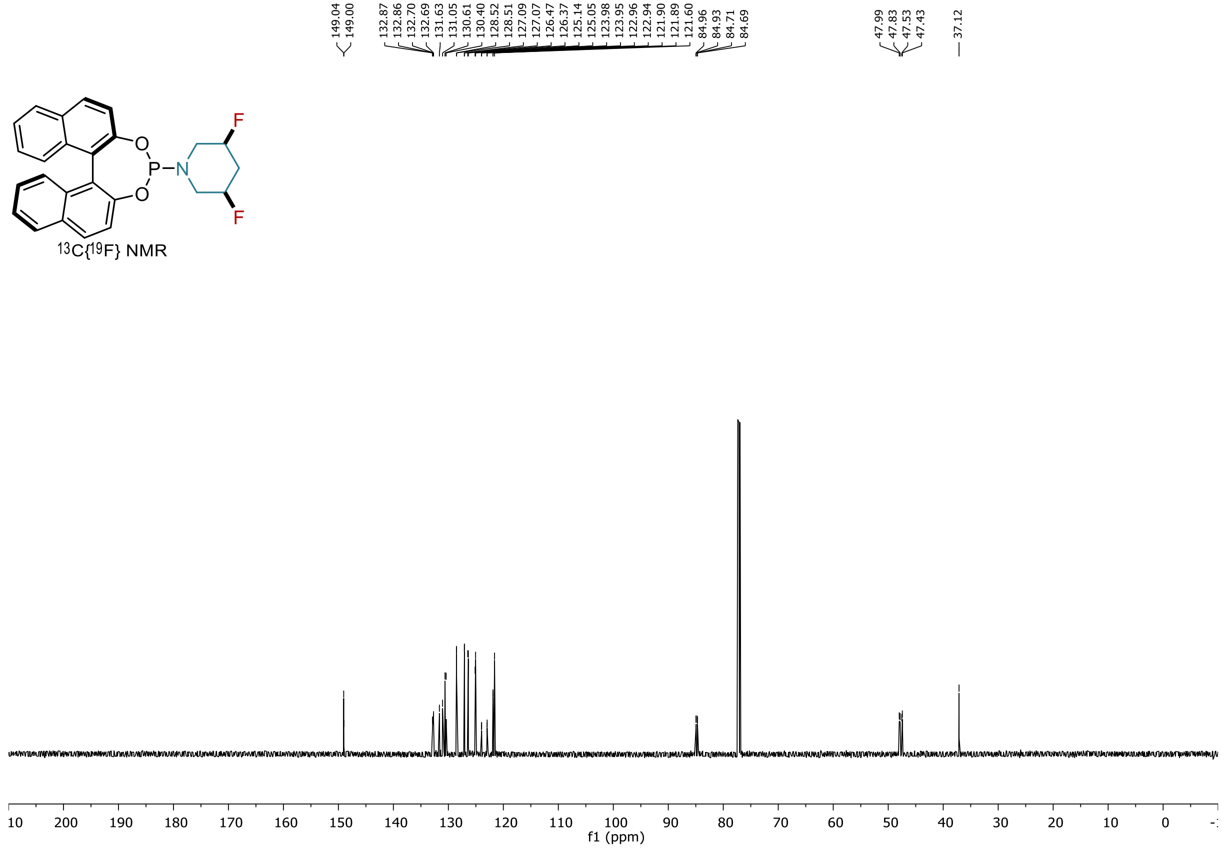


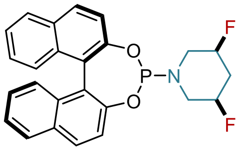
O
P
N
O
F
F
^{1}H{^{19}F} NMR
2.11
1.06
1.08
1.05
1.04
1.03
1.10
2.11
2.11
0.94
1.02
1.02
1.03
1.05
1.03
1.01
1.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


O
P
N
O
F
F
^{1}H{^{31}P} NMR
1.98
1.01
1.04
0.99
0.99
0.96
1.02
1.99
2.02
0.98
1.01
1.99
1.00
0.98
0.99
1.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

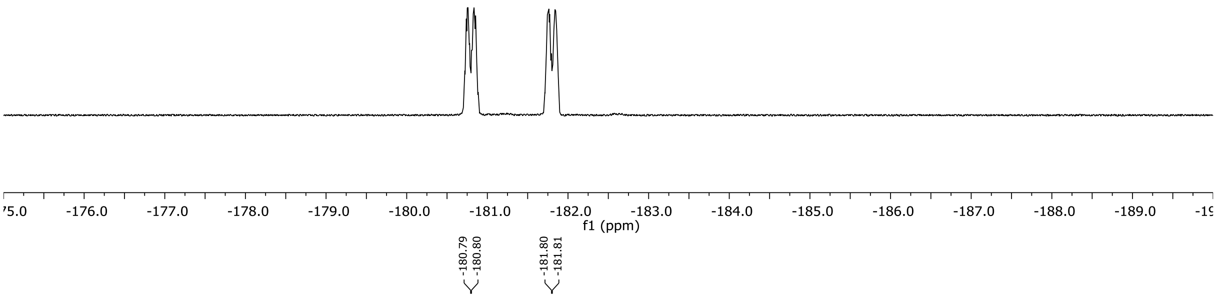

O
P
N
O
F
F
^{1}H{^{19}F,^{31}P} NMR
2.14
1.11
1.12
1.09
1.08
1.05
1.12
2.14
2.18
1.00
1.04
1.07
1.04
1.08
1.06
1.05
1.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

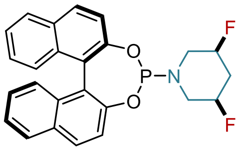

149.04
149.00
132.87
132.86
132.70
132.69
131.63
131.63
131.05
130.61
130.40
128.52
128.51
127.09
127.07
126.47
126.37
125.14
125.05
123.98
123.95
122.96
122.94
121.90
121.89
121.60
85.59
85.56
85.53
85.50
85.34
85.32
85.28
85.26
84.40
84.36
84.34
84.30
84.15
84.12
84.09
84.07
48.08
47.91
47.74
47.61
47.52
47.44
47.34
37.25
37.12
36.99
O
P
N
O
F
F
13C NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-
f1 (ppm)


149.04
149.00
132.87
132.86
132.70
132.69
131.63
131.05
130.61
130.40
128.52
128.51
127.09
127.07
126.47
126.37
125.14
125.05
123.98
123.95
122.96
122.94
121.90
121.89
121.60
84.96
84.93
84.71
84.69
47.99
47.83
47.53
47.43
37.12
O
P
N
O
F
F
13C{19F} NMR
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-
f1 (ppm)

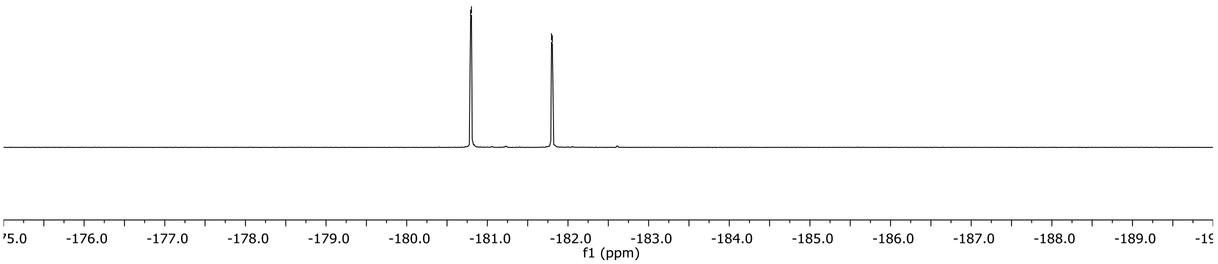


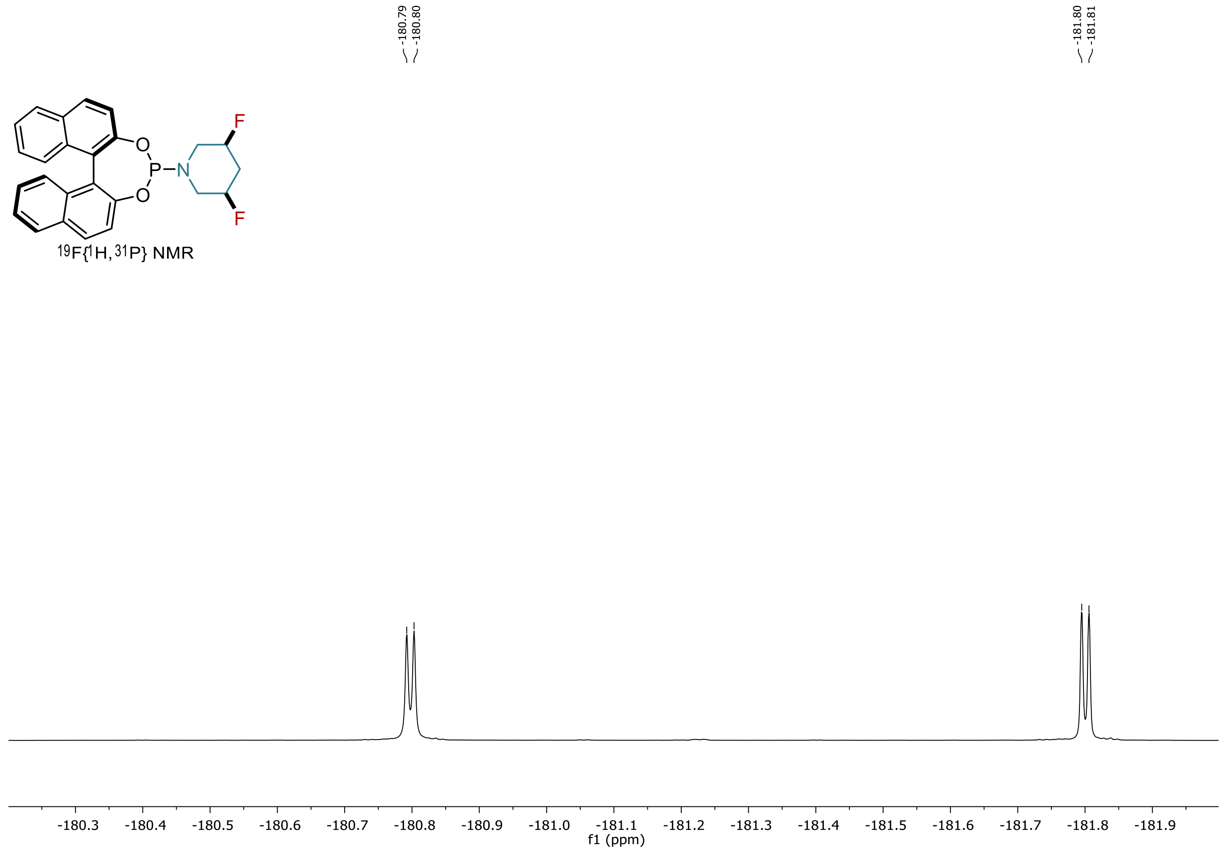
^{19}F NMR

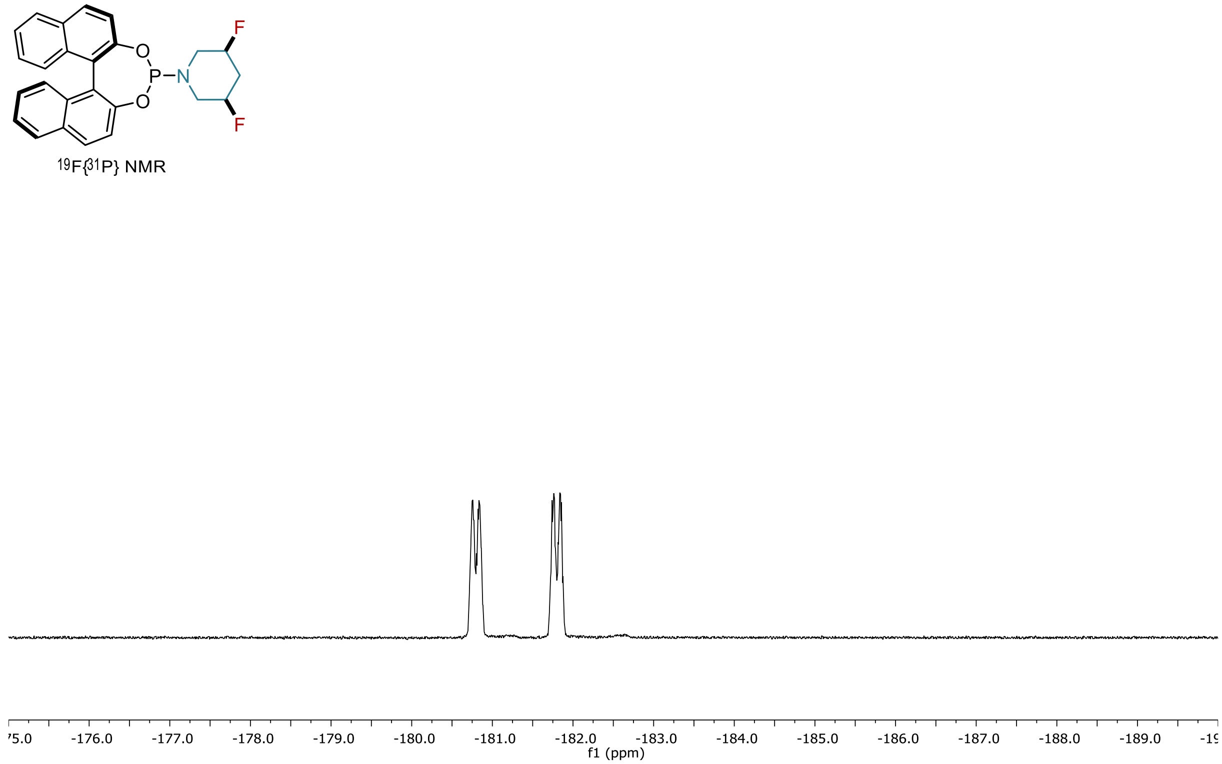


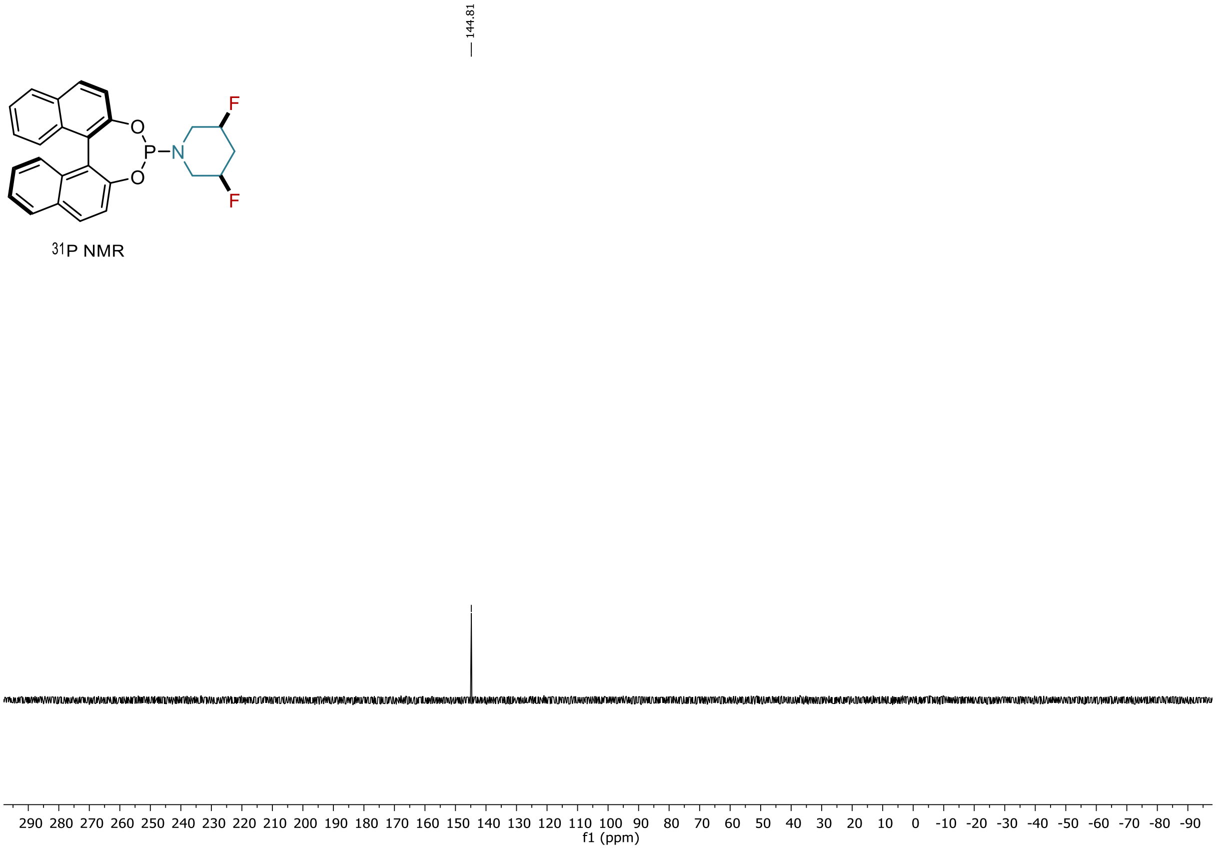


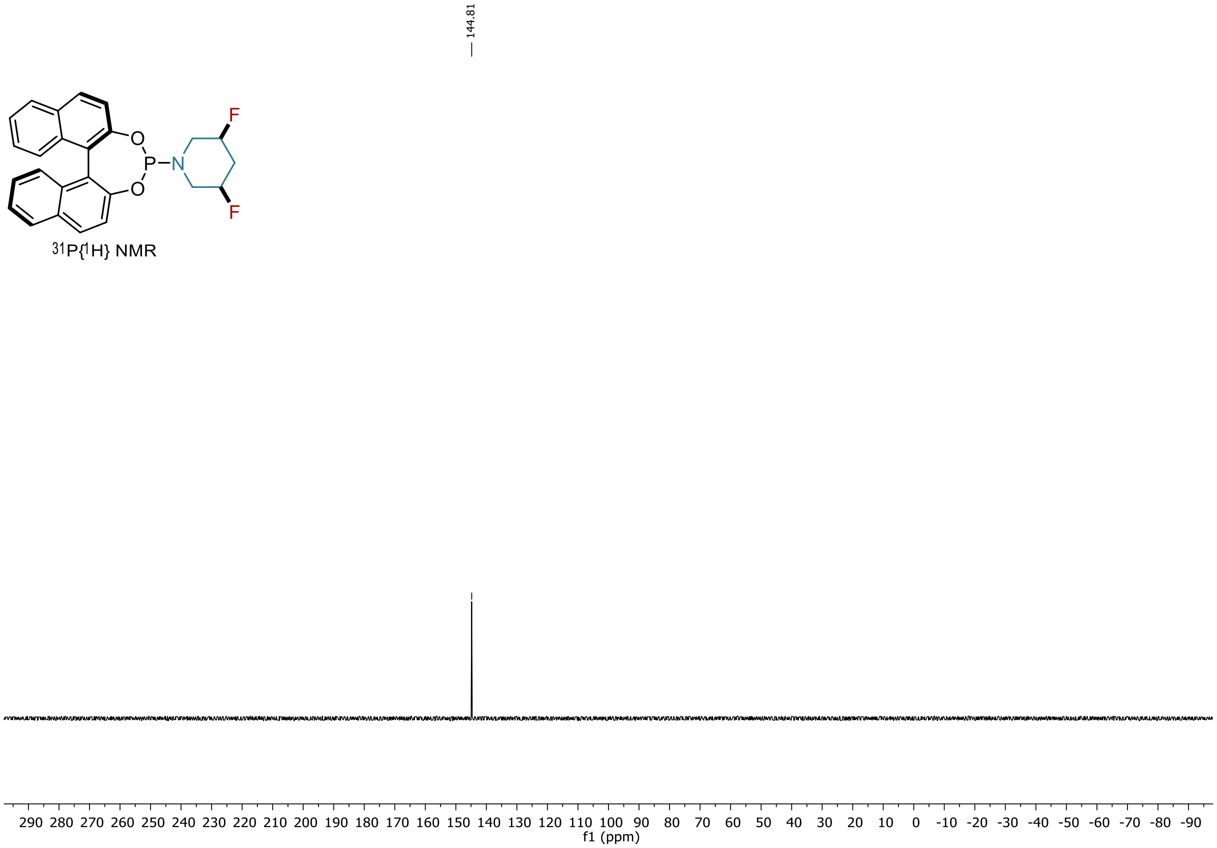
^{19}F{^{1}H} NMR

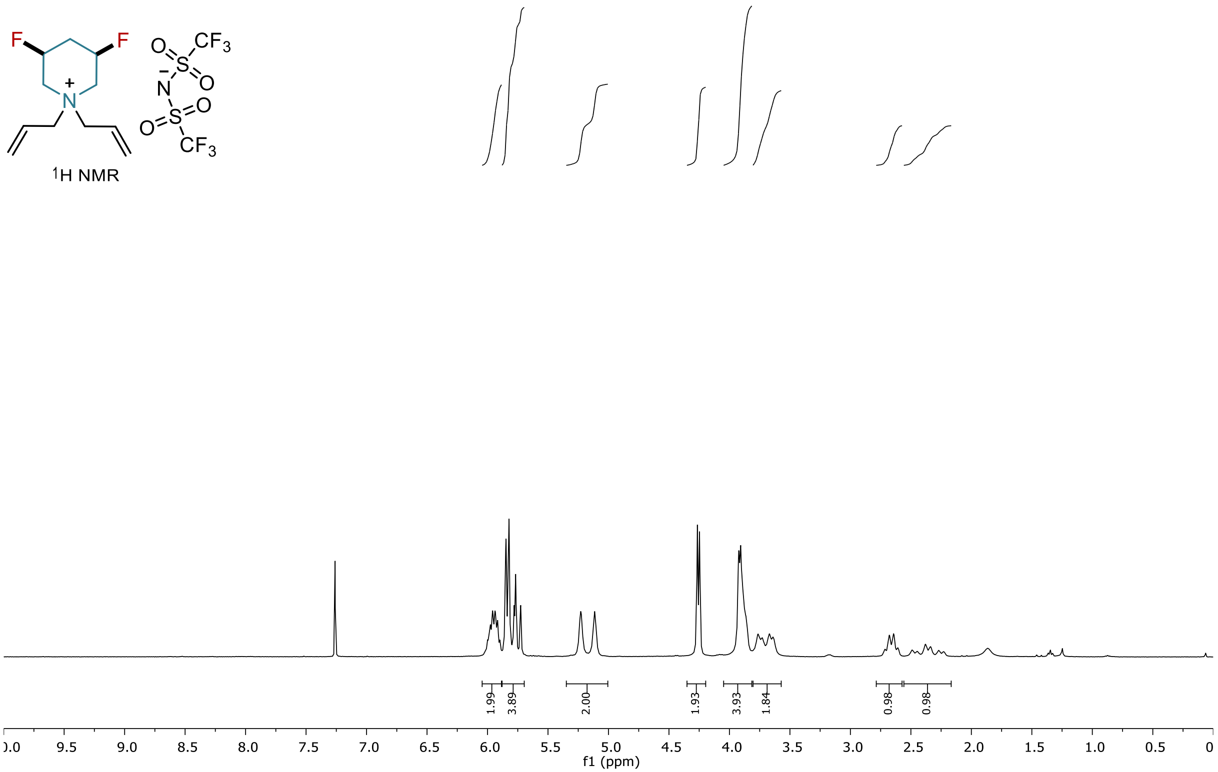


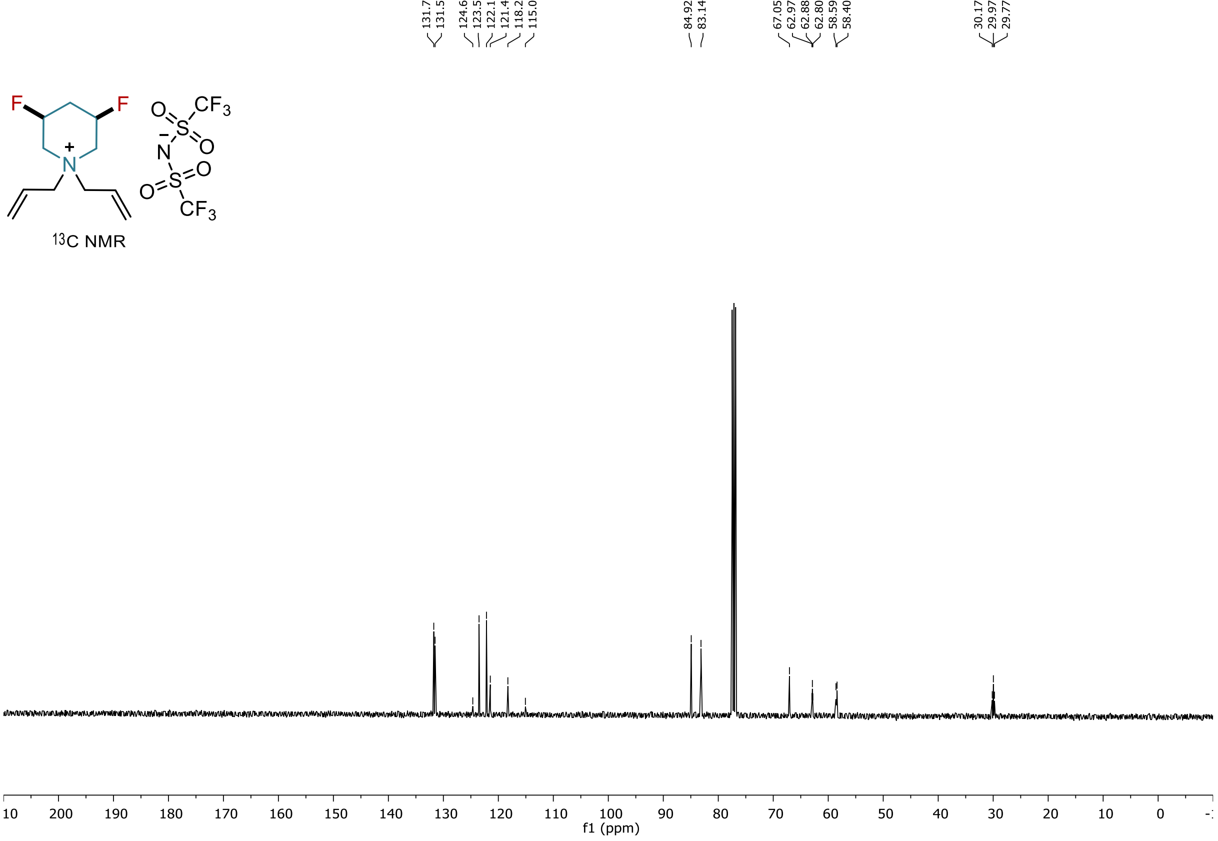

-180.79
-180.80
-181.80
-181.81
^{19}F{^{1}H,^{31}P} NMR
-180.3
-180.4
-180.5
-180.6
-180.7
-180.8
-180.9
-181.0
-181.1
-181.2
-181.3
-181.4
-181.5
-181.6
-181.7
-181.8
-181.9
f1 (ppm)

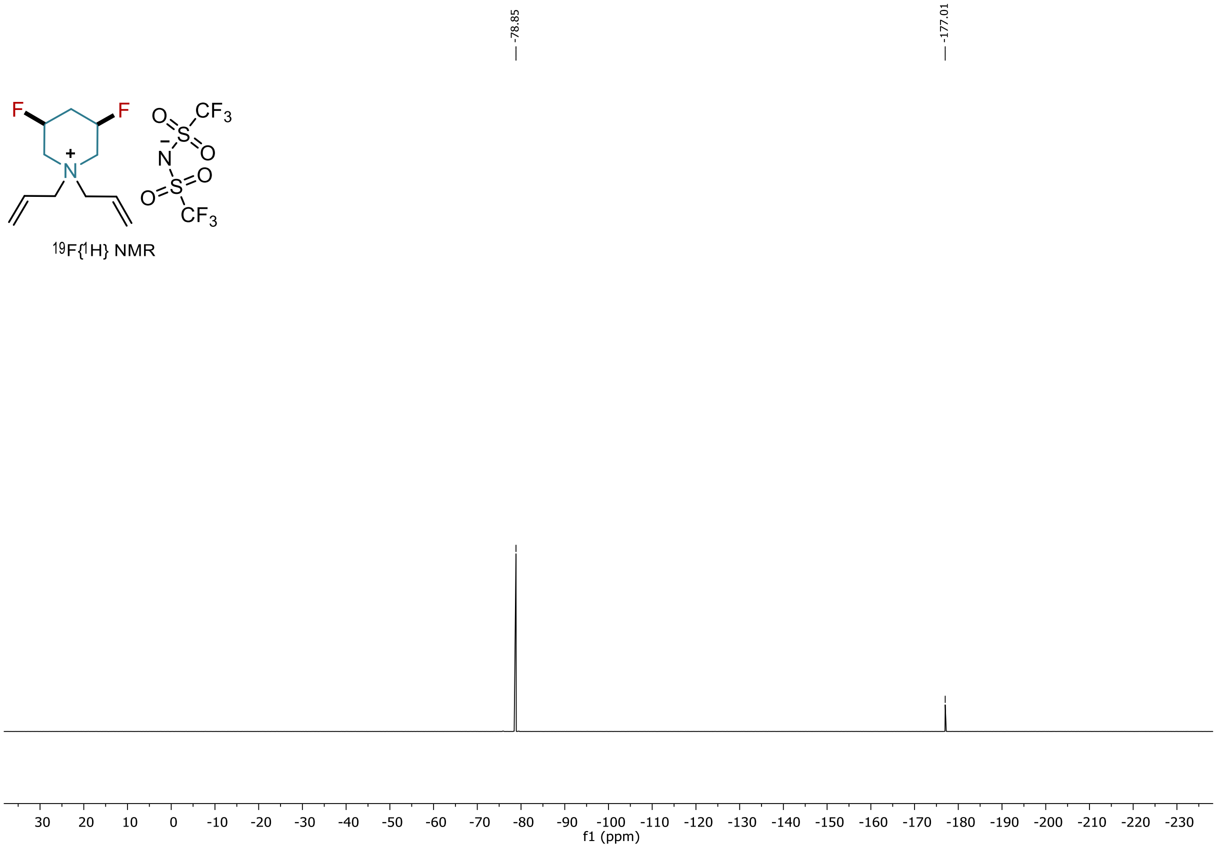

^{19}F{^{31}P} NMR
75.0
-176.0
-177.0
-178.0
-179.0
-180.0
-181.0
-182.0
-183.0
-184.0
-185.0
-186.0
-187.0
-188.0
-189.0
-19
f1 (ppm)

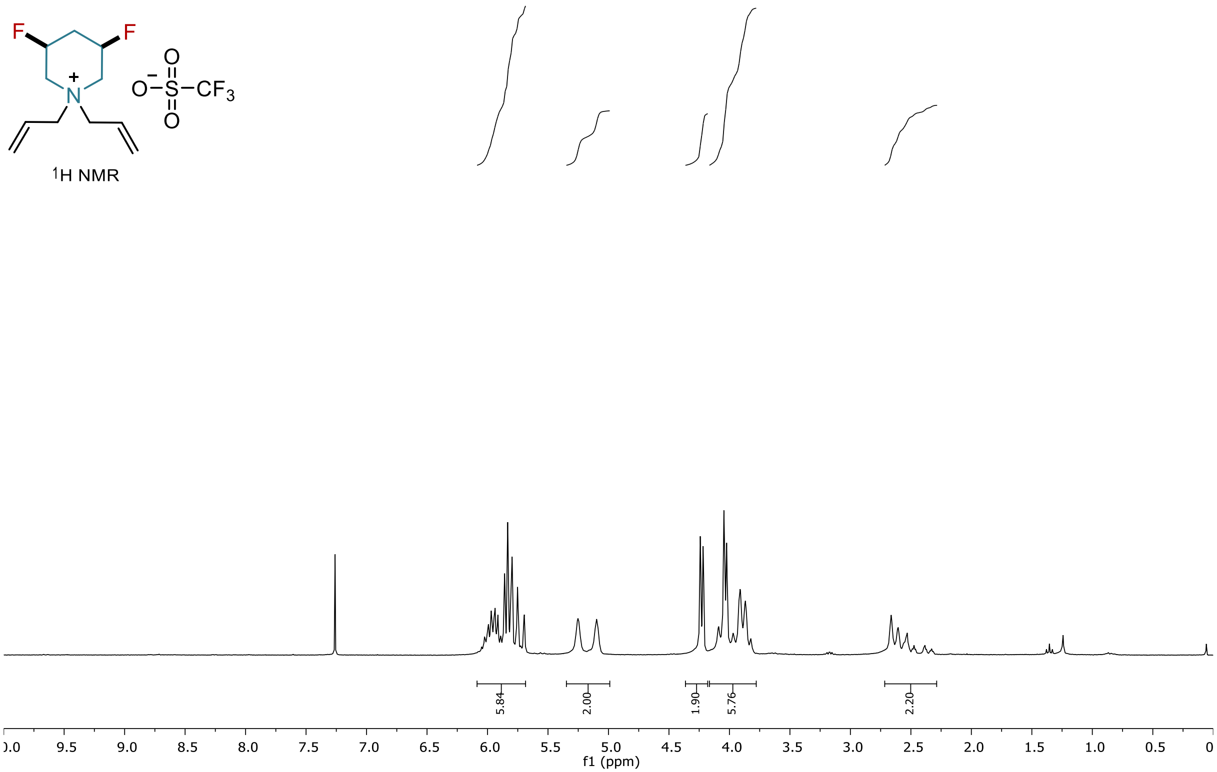

144.81
O
P
N
O
F
F
31P NMR
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)


144.81
O
P
N
O
F
F
31P{1H} NMR
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

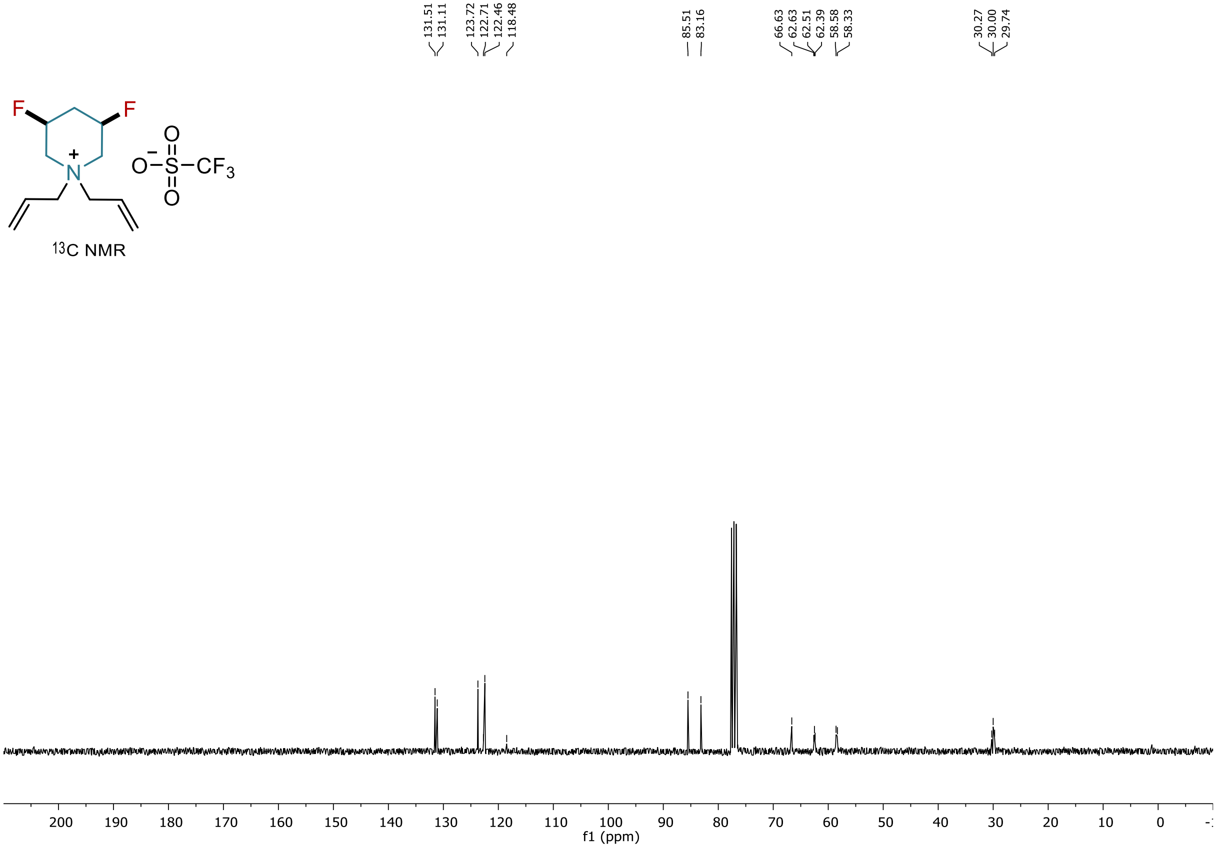

F
F
N
+
O
S
CF3
O
N
S
O
O
CF3
1H NMR
1.99
3.89
2.00
1.93
3.93
1.84
0.98
0.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


131.74
131.50
124.65
123.51
122.16
121.46
118.27
115.08
84.92
83.14
67.05
62.97
62.88
62.80
58.59
58.40
30.17
29.97
29.77
F
F
N
+
O
S
CF3
O
N
S
O
O
CF3
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

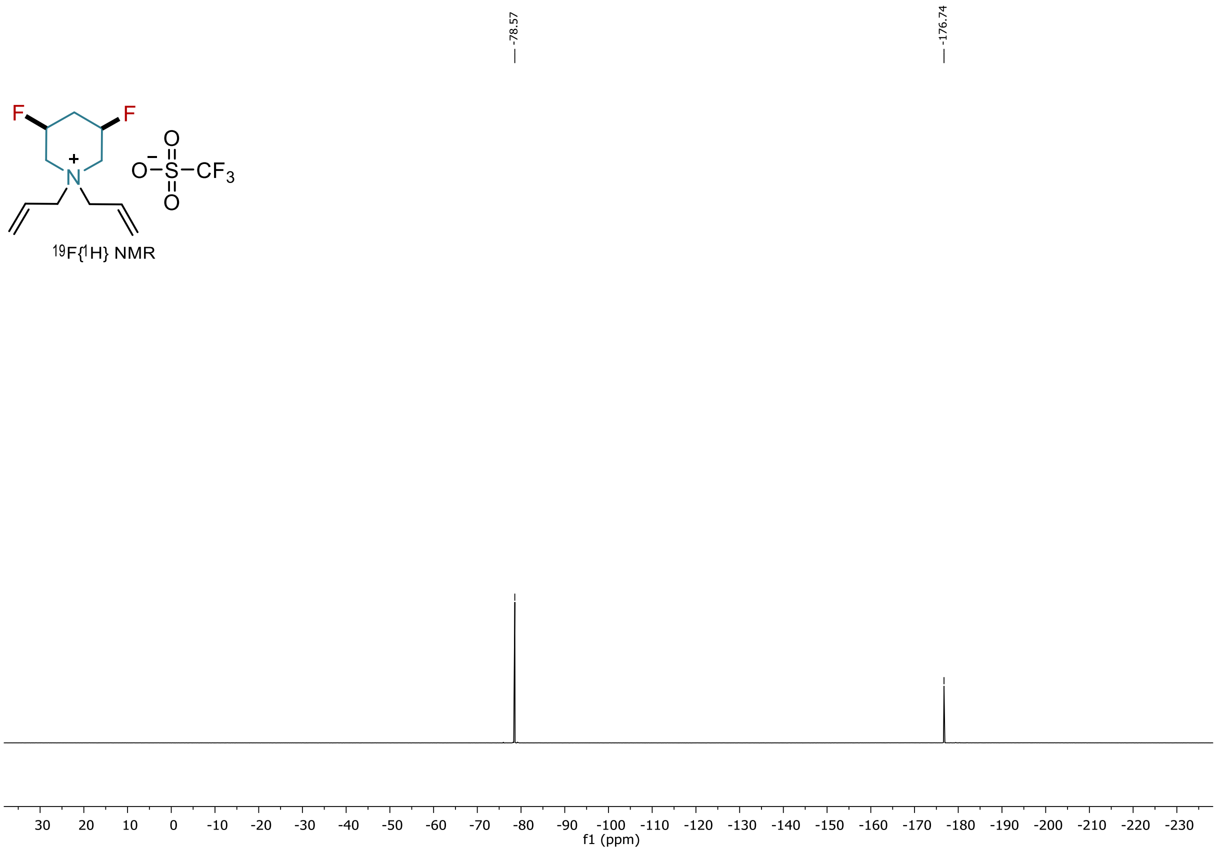

-78.85
-177.01
F
F
CF3
O
S
O
N
S
O
O
CF3
N
+
−
19F{1H} NMR
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)



^{1}H NMR



^{13}C NMR


-78.57
-176.74
F
F
N
+
O
O
S
CF3
O
−
19F{1H} NMR
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)