Supporting Information for:

Exploring Synthetic Routes to 6-Functionalized 4-Azaspiro[2.3]hexanes

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List of Abbreviations

Calcd	Calculated
$CDCl_3$	Deuterated chloroform
DCM	Dichloromethane
ESI	Electrospray ionization
EtOAc	Ethyl acetate
HCl	Hydrochloric acid
H_2O	Water
HRMS	High-resolution mass spectrometry
LC-MS	Liquid chromatography-mass spectrometry
THF	Tetrahydrofuran
$KMnO_4$	Potassium permanganate
KOH	Potassium hydroxide
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
NaH	Sodium hydride
NaI	Sodium iodide
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
NBS	*N*-Bromosuccinimide
NEt_3	Triethylamine
TLC	Thin-layer chromatography
RT	Room temperature

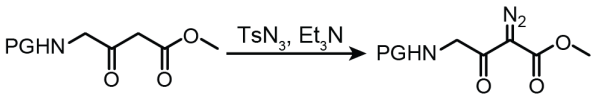
General materials and methods.

All chemical reagents were of analytical grade, obtained from commercial suppliers, and used without further purification unless otherwise specified. Reactions were monitored by thin-layer chromatography on pre-coated glass TLC plates (Analtech UNIPLATE™ silica gel HLF w/ organic binder, 250 µm thickness, with UV254 indicator) or by LC-MS (Agilent 6110 Single Quad, LC-MS, direct-injection mode, ESI). TLC plates were visualized by UV illumination or developed with potassium permanganate stain. NMR spectra (^{1}H and ^{13}C) were obtained using a 400, 500, or 700 MHz Bruker spectrometer and analyzed using TopSpin 4.2.0. ^{1}H, $^{19}F$and ^{13}C chemical shifts (δ) were referenced to residual solvent peaks. The following residual solvent peaks were chosen: (for ^{1}H NMR) $CDCl_3$, 7.26 ppm; - 66.10 ppm (for ^{19}F NMR) $TMSCF_3$[1]; (for ^{13}C NMR) $CDCl_3$, 77.16 ppm. The following abbreviations were used to define ^{1}H NMR peaks: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Low-resolution electrospray ionization (ESI) and high-resolution electrospray ionization (ESI) mass spectra were obtained at the CASDA Mass Spectrometry Center, Stony Brook University.

Synthetic details

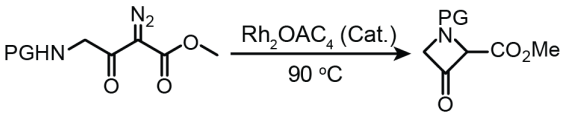
1. Construction of 3-substituted azetidin-2-ylmethanol

a. Rhodium catalysed carbenoid insertion into NH bonds



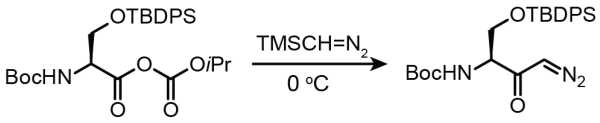
1a/1b

Methyl 4-((*tert*-butoxycarbonyl)amino)-2-diazo-3-oxobutanoate (**1a**): Into a solution of methyl 4-((*tert*-butoxycarbonyl)amino)-3-oxobutanoate (2.365 g, 10.23 mmol, 1 eq) in MeCN (40 mL), Tosyl azide (2.36 g, 11.96 mmol, 1.17 eq) and NEt_3 (4.25 mL, 30.69 mmol, 3 eq) were added slowly. The mixture was stirred at RT overnight and the completion of the reaction was confirmed by TLC. The resulting crude was first washed with DCM and then by 10% KOH. The aqueous layer was extracted with DCM twice. Then the combined organic layers were dried over Na_2SO_4. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (30% EtOAc/hexanes (v/v)) to obtain **1a** (1.2 g, 52%). Similar protocol was used for the preparation of **1b**. The characterization data agree with a previous report[2].



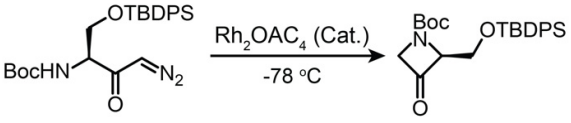
1a/1b **2a/2b**

1-(*tert*-butyl) 2-methyl 3-oxoazetidine-1,2-dicarboxylate (**2a**): Into a preheated solution of **1a** (402 mg, 1.56 mmol, 1 eq) in Toluene (15 mL), $Rh_2(OAc)_4$ (7 mg, 0.016 mmol, 0.01 eq) was added slowly. The mixture was stirred at 90 °C for 7 min and the completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo*, filtered through Celite and eluted with DCM to obtain **2a** (quantitative). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 5.37 (s, 1H), 4.89 – 4.86 (m, 1H), 4.79 – 4.77 (d, *J* = 14.0 Hz, 1H), 3.82 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 188.99, 164.37, 154.90, 82.65, 81.91, 71.44, 53.21, 28.31. MS (ESI): Calcd for $C_{10}H_{19}N_2O_5$ $[M+NH_4]^+$: 247.1, found: 247.1. Similar protocol was used for the preparation of **2b**. The characterization data agree with a previous report[2].



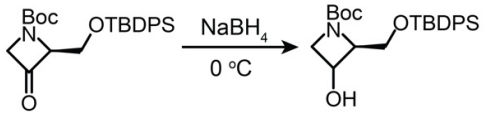
3a

***Tert*-butyl (*S*)-(1-((*tert*-butyldiphenylsilyl)oxy)-4-diazo-3-oxobutan-2-yl)carbamate** (**3a**): Into a solution of (*S*)-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)propanoic (isobutyl carbonic) anhydride (5.59 g, 10.3 mmol, 1 eq) in anhydrous MeCN (40 mL), $TMSCH=N_2$ (2M in hexane, 11 mL, 20.6 mmol, 2 eq) was added slowly under N_2. The mixture was stirred at 0 °C for 2 days, RT for 1 day, and the completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (10% EtOAc/hexanes (v/v)) to obtain **3a** (1.09 g, 21%). Similar yields were obtained starting from (*S*)-(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldiphenylsilyl)oxy)propanoic (ethyl carbonic) anhydride. The characterization data agree with a previous report[3].



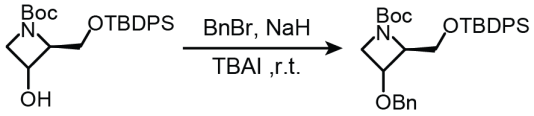
3a **3b**

***Tert*-butyl (*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-oxoazetidine-1-carboxylat**e (**3b**): Into a solution of **3a** (400 mg, 0.96 mmol, 1 eq) in dry DCM (9.6 mL), $Rh_2(OAc)_4$ (20 mg, 0.046 mmol, 0.048 eq) was added slowly. The mixture was stirred at -78 °C for 2 h and then at RT overnight. The completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (10% EtOAc/hexanes (v/v)) to obtain **3b** (120 mg, 32%). The characterization data agree with a previous report[3]. Relatively low yields (~23%) were obtained when reactions were performed at -95 °C (dry ice/methanol mixture).



3b **3c**

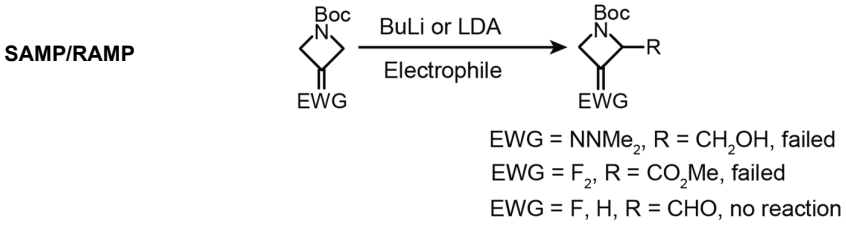
***Tert*-butyl (2*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-hydroxyazetidine-1-carboxylate** (**3c**): Into an ice-cold solution of **3b** (120 mg, 0.28 mmol, 1 eq) in methanol (4.5 mL), $NaBH_4$ (12.7 mg, 0.34 mmol, 1.2 eq) was slowly added. The resulting solution was stirred for another 0.5 h at the same temperature before addition of water. Extraction with DCM yielded **3c** (118 mg, 98%), which was used directly for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 – 7.67 (m, 4H), 7.45 – 7.39 (m, 6H), 4.69 (q, *J* = 6.7 Hz, 1H), 4.22 (dq, *J* = 19.6, 5.9 Hz, 4H), 4.00 (d, *J* = 10.3 Hz, 1H), 3.91 (dd, *J* = 9.5, 5.0 Hz, 1H), 1.43 – 1.32 (2s in total, 9H), 1.14 – 1.10 (2s in total, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.17, 137.09, 128.73, 128.35, 128.05, 73.46, 72.03, 30.38, 29.85, 29.46. MS (ESI): Calcd for $C_{25}H_{35}NaNO_4Si$ $[M+Na]^+$: 464.2, found: 464.2.



3c **3d**

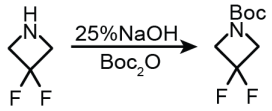
***Tert*-butyl (2*S*)-3-(benzyloxy)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)azetidine-1-carboxylate** (**3d**): Into an ice-cold solution of **3c** (118 mg, 0.27 mmol, 1 eq) in THF (5.3 mL), TBAI (29.5 mg, 0.08 mmol, 0.3 eq), BnBr (48 µL, 0.41 mmol, 1.5 eq) and NaH (12.8 mg, 0.32 mmol, 1.2 eq) were sequentially added. The resulting mixture was stirred at the same temperature for 10 min and overnight at room temperature. Flash chromatography was performed to obtain **3d** (36 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 – 7.68 (m, 4H), 7.42 – 7.29 (m, 11H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.46 – 4.40 (m, 2H), 4.21 (dd, *J* = 10.2, 7.8 Hz, 1H), 4.03 (m, *J* = 9.2, 6.7 Hz, 1H), 3.92 – 3.90 (m, 1H), 3.80 – 3.76 (m, 1H), 1.29 (s, 9H), 1.05 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.05, 137.94, 135.78, 133.57, 129.71, 128.54, 127.84, 127.77, 127.75, 79.65, 72.16, 69.18, 67.65, 60.09, 55.50, 28.47, 26.98, 19.35. MS (ESI): Calcd for $C_{32}H_{42}NO_4Si$ $[M+H]^+$: 532.2, found: 532.2.

b. Direct modification via α-lithiation and electrophile trapping



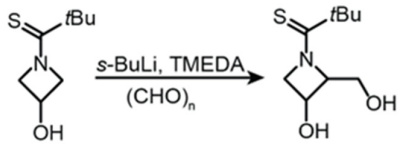
Scheme S1 Reaction scheme for the synthesis of 3-substituted azetidin-2-ylmethanol based on SAMP/RAMP[4].

***Tert*-butyl 3-(2,2-dimethylhydrazono)azetidine-1-carboxylate** was synthesized according to the previous report[4].



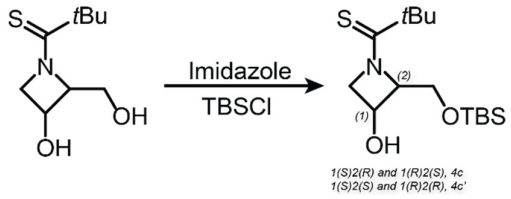
***Tert*-butyl 3,3-difluoroazetidine-1-carboxylate**: Into a solution of 3,3-difluoroazetidine hydrogen chloride (1 g, 7.72 mmol, 1 eq) in 25% NaOH (35 mL), $(Boc)_2O$ (20 mL) was added. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with H_2O followed by extraction with DCM and purified by flash chromatography to yield the product (1.042 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.17 (t, *J* = 12.2 Hz, 4H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.79, 115.45 (t, *J* = 274.7 Hz), 80.81, 61.10, 28.21. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -100.33 (p, *J* = 12.3 Hz).

***Tert*-butyl 3-fluoroazetidine-1-carboxylate**: Into an ice-cold solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (5.64 g, 32.58 mmol, 1 eq) in dry DCM (60 mL), DAST (6.46 mL, 48.87 mmol, 1.5 eq) was added slowly. The resulting mixture was stirred at 0 °C, then at room temperature overnight. Quenched by NaHCO3, followed by extraction with DCM. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (30% EtOAc/hexanes (v/v), TLC visualized with $KMnO_4$ stain) to obtain the product (1.79 g, 31%). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 5.30 (ddd, *J* = 9.5, 6.0, 3.5 Hz, 1H), 5.16 (ddd, *J* = 9.5, 6.0, 3.5 Hz, 1H), 4.17 (dddd, *J* = 20.1, 10.6, 6.0, 1.4 Hz, 2H), 4.04 (dddd, *J* = 24.4, 10.5, 3.5, 1.4 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = (155.79, 155.77), 82.75 (d, *J* = 205.0 Hz), 79.46, 56.70, 27.91. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -180.55 (d, *J* = 4.3 Hz), -180.59 – -180.63 (m), -180.64, -180.67 (d, *J* = 4.1 Hz), -180.70 (d, *J* = 4.2 Hz), -180.73, -180.74 – -180.78 (m), -180.82 (d, *J* = 4.1 Hz). MS (ESI): Calcd for $C_8H_{15}FNO_2$ $[M+H]^+$: 176.1, found 120.0 $[M-tBu+2H]^+$.



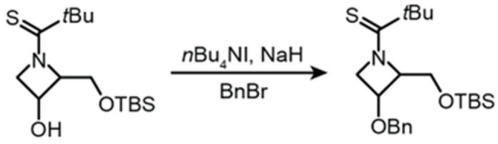
4a **4b**

1-(3-hydroxy-2-(hydroxymethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**4b**): Into a solution of **4a** (115.9 mg, 0.67 mmol, 1 eq) in dry THF (2.66 mL) at -78 °C, TMEDA (0.6 mL, 4 mmol, 6 eq) and *sec*-BuLi (1.3 M, 3.1 mL, 4 mmol, 6 eq) were added. The resulting mixture was stirred at -78 °C for 0.5 h. Then paraformaldehyde (121.6 mg, 4 mmol, 6 eq) was added and the resulting mixture was stirred at -78 °C for 0.5 h and stirred at room temperature for 0.5 h before quenched with 1 M HCl (5.3 mL), followed by extraction with DCM. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (50% EtOAc/hexanes (v/v)) to obtain **4b** (122 mg, 20%), which was used in next step directly. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 – 4.96 (m, 1H), 4.80 – 4.70 (m, 3H), 4.37 – 4.30 (m, 1H), 4.02 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.82 (s, 1H), 3.12 (s, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.17, 75.26, 67.52, 63.42, 59.25, 43.72, 29.69. Formation of product was confirmed by MS. MS (ESI): Calcd for $C_9H_{17}NNaO_2S$ $[M+Na]^+$: 226.1, found: 226.2.



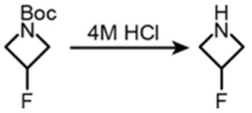
4b **4c** and **4c'**

1-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-hydroxyazetidin-1-yl)-2,2-dimethylpropane-1-thione (**4c**): Into an ice-cold solution of **4b** (26.7 mg, 0.13 mmol, 1 eq) in THF (1.3 mL), imidazole (9 mg, 0.13 mmol, 1 eq) and TBDMSCl (19.7 mg, 0.13 mmol, 1 eq) were sequentially added. The resulting reaction mixture was warmed to room temperature and stirred overnight. After that, H_2O was added and mixture was extracted with DCM. The reaction crude was concentrated *in vacuo*, purified by preparative TLC (20% EtOAc/hexanes (v/v)) to obtain **4c** (7 mg, 17%) and **4c'** (6 mg, 14%). **4c** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.66 – 4.59 (m, 2H), 4.27 – 4.13 (m, 3H), 3.82 – 3.71 (m, 2H), 1.36 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.52, 81.24, 65.52, 64.11, 63.05, 43.83, 29.88, 25.80, 18.05, -4.55, -4.81. **4c'** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 – 4.57 (m, 4H), 4.18 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.82 (dd, *J* = 10.9, 2.1 Hz, 1H), 1.34 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.61, 78.56, 66.06, 64.45, 58.88, 43.80, 29.94, 26.00, 18.29, -5.12, -5.38. MS (ESI): Calcd for $C_{15}H_{32}NO_2SSi$ $[M+H]^+$: 318.2, found: 318.2.

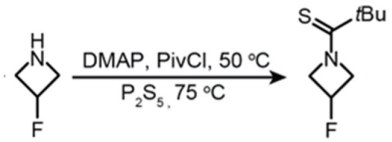


4c **4d**

1-(3-(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione (**4d**): Into an ice-cold solution of **4c** (31 mg, 0.1 mmol, 1 eq) in THF (2 mL), Bu_4NI (12 mg, 0.03 mmol, 0.3 eq), BnBr (18 µL, 0.15 mmol, 1.5 eq) and NaH (5 mg, 0.12 mmol, 1.2 eq) were sequentially added. The resulting reaction mixture was warmed to room temperature and stirred overnight. After that, H_2O was added and mixture was extracted with DCM. The reaction crude was concentrated in vacuo, purified by preparative TLC (10% EtOAc/hexanes (v/v)) to obtain **4d** (11.1 mg, 28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (tt, *J* = 8.2, 4.4 Hz, 5H), 4.75 – 4.74 (m, 1H), 4.59 – 4.54 (m, 2H), 4.48 (td, *J* = 6.8, 3.5 Hz, 2H), 4.32 (dt, *J* = 6.0, 2.8 Hz, 1H), 4.22 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.78 (dd, *J* = 10.8, 2.5 Hz, 1H), 1.33 (s, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.45, 137.30, 128.71, 128.25, 128.17, 71.37, 70.35, 63.71, 59.16, 43.75, 29.92, 26.01, 18.30, -5.13, -5.37. MS (ESI): Calcd for $C_{22}H_{38}NO_2SSi$ $[M+H]^+$: 408.2, found: 408.2.

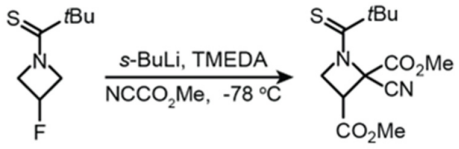


3-fluoroazetidine hydrogen chloride: Into a solution of 3F Boc azetidine (1.79 g, 10.23 mmol, 1 eq) in MeOH (18 mL), 4M HCl (18 mL) was slowly added. The resulting solution was stirred overnight and concentrated to obtain 3-fluoroazetidine hydrogen chloride, which was used directly without further purification. The presence of product was confirmed by MS. MS (ESI): Calcd for C_3H_6FN $[M+H]^+$: 76.1, found: 76.1.



4e

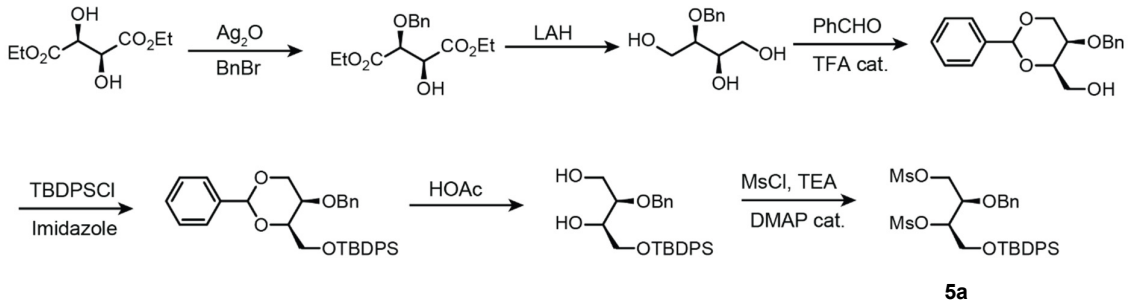
1-(3-fluoroazetidin-1-yl)-2,2-dimethylpropane-1-thione (**4e**): Into a solution of 3-fluoroazetidine hydrogen chloride (1.13 g, 10.2 mmol, 1 eq) in pyridine (22 mL), DMAP (262 mg, 2.14 mmol, 0.21 eq) and PivCl (2 mL, 16.8 mmol, 1.65 eq) were slowly added. The resulting mixture was stirred at 50 °C for 5 min, then at room temperature for 1 h. Into the resulting mixture was added P_2S_5 (5.27 g, 11.83 mmol, 1.16 eq). The resulting mixture was stirred at 75 °C for 1 h, and quenched with 2M HCl, followed by extraction with DCM. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (10% EtOAc/hexanes (v/v). TLC visualized with $KMnO_4$ stain) to obtain **4e** (455 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38 (tt, *J* = 6.1, 3.2 Hz, 0.5H), 5.24 (tt, *J* = 6.0, 3.3 Hz, 0.5H), 4.74 (dddd, *J* = 20.1, 11.9, 6.0, 2.4 Hz, 1H), 4.59 – 4.47 (m, 2H), 4.36 (ddt, *J* = 24.4, 14.4, 2.8 Hz, 1H), 1.35 (s, 9H). ^{13}C DEPT 135 (101 MHz, $CDCl_3$): δ = 81.75, 79.74, 63.84, 63.57, 63.26, 63.00, 30.33, 29.80. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -181.33, -181.39 (d, *J* = 3.7 Hz), -181.43 – -181.63 (m), -181.66 (d, *J* = 3.8 Hz), -181.72. MS (ESI): Calcd for $C_8H_{15}FNS$ $[M+H]^+$: 176.1, found: 176.1.



4e **4f**

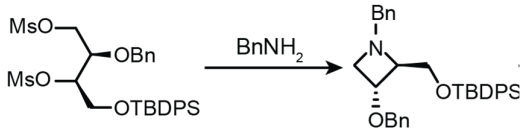
Dimethyl 2-cyano-1-(2,2-dimethylpropanethioyl)azetidine-2,3-dicarboxylate (**4f**): Into a solution of 1-(3-fluoroazetidin-1-yl)-2,2-dimethylpropane-1-thione (455 mg, 2.6 mmol, 1 eq) in dry THF (8 mL) at -78 °C, TMEDA (2.33 mL, 15.6 mmol, 6 eq) and *sec*-BuLi (1.3 M, 3 mL, 3.9 mmol, 1.5 eq) were sequentially added. The resulting mixture was stirred at the same temperature for an additional 0.5 h before the addition of $MeCO_2CN$ (0.33 mL, 4.2 mmol, 1.6 eq). The resulting solution was slowly warmed to room temperature and stirred overnight and quenched with addition of 1 M HCl. After extraction with EtOAc, the product was purified by flash chromatography and characterized to be **4f** (433 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (t, *J* = 9.2 Hz, 1H), 4.75 (dd, *J* = 9.2, 6.7 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.75 (dd, *J* = 8.9, 7.0 Hz, 1H), 1.35 (s, 9H). ^{13}C DEPT 135 (101 MHz, $CDCl_3$): δ = 57.53, 55.95, 53.51, 36.43, 29.31, 25.10. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 213.19, 164.48, 162.83, 115.55, 57.62, 56.05, 53.60, 43.57, 36.53, 29.41, 25.20. MS (ESI): Calcd for $C_{13}H_{19}N_2O_4S$ $[M+H]^+$: 299.1, found: 299.1.

c. Ring closure of 1,3-functionalized hydrocarbons/acyclic amines



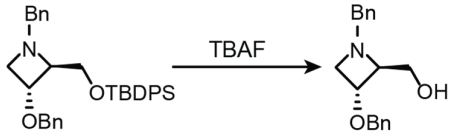
5a

Scheme S2 Reaction scheme for the synthesis of **5a** from reference[5].



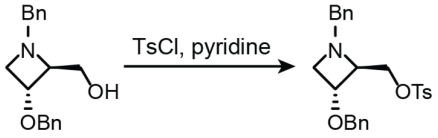
5a **5b**

(2*S*,3*R*)-1-benzyl-3-(benzyloxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)azetidine (**5b**) was prepared according to reference[5]. Yield, 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 – 7.64 (m, 4H), 7.47 – 7.18 (m, 16H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 3.98 (q, *J* = 6.1 Hz, 1H), 3.90 (d, *J* = 12.7 Hz, 1H), 3.68 (s, 2H), 3.64 – 3.57 (m, 1H), 3.53 (d, *J* = 12.7 Hz, 1H), 3.34 (q, *J* = 5.6 Hz, 1H), 2.81 (t, *J* = 6.9 Hz, 1H), 1.07 (s, 9H).



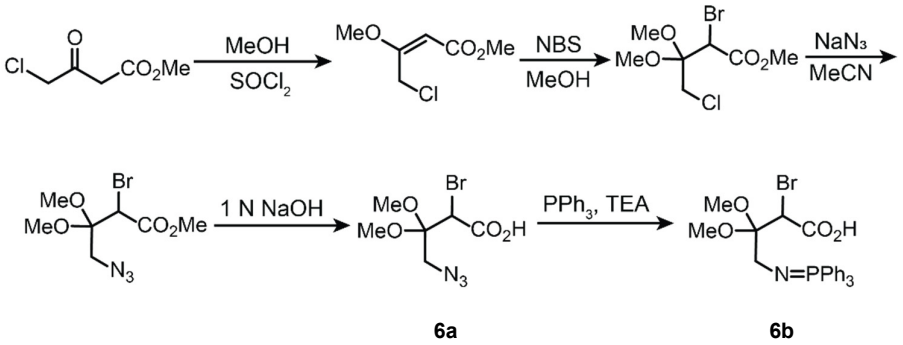
5b **5c**

((2*S*,3*R*)-1-benzyl-3-(benzyloxy)azetidin-2-yl)methanol (**5c**) was prepared according to reference[5]: Yield 48%. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.37 – 7.22 (m, 10H), 4.47 (s, 2H), 4.17 (q, *J* = 6.0 Hz, 1H), 3.72 (d, *J* = 12.6 Hz, 1H), 3.68 – 3.64 (m, 1H), 3.58 (t, *J* = 6.7 Hz, 1H), 3.36 (d, *J* = 11.5 Hz, 1H), 3.32 – 3.28 (m, 2H), 2.88 (t, *J* = 6.8 Hz, 1H), 2.75 (s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 156.43, 137.04, 128.57, 128.11, 127.75, 80.13, 71.96, 69.48, 67.41, 61.63, 55.91, 28.19.



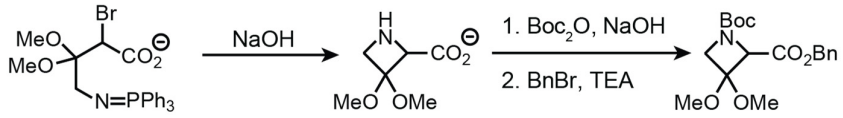
5c **5d**

((2*S*,3*R*)-1-benzyl-3-(benzyloxy)azetidin-2-yl)methyl 4-methylbenzenesulfonate (**5d**): Into a solution of **5c** (1.53 g, 5.4 mmol, 1 eq) in dry pyridine (24.5 mL) was added TsCl (5.2 g, 27.3 mmol, 5 eq). The resulting mixture was stirred at the same temperature overnight. The product was purified by flash chromatography (30% EtOAc/hexanes (v/v). TLC visualized with $KMnO_4$ stain) and characterized to be **5d** (0.83 g, 35%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.80 – 7.72 (m, 2H), 7.35 – 7.13 (m, 12H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 3.90 (q, *J* = 6.1 Hz, 1H), 3.83 – 3.78 (m, 2H), 3.69 (d, *J* = 12.6 Hz, 1H), 3.55 – 3.53 (m, 2H), 3.32 (q, *J* = 5.4 Hz, 1H), 2.79 (t, *J* = 6.9 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 144.89, 137.71, 137.62, 133.01, 130.02, 129.97, 128.85, 128.63, 128.50, 128.47, 128.08, 128.02, 127.41, 71.61, 71.11, 70.96, 70.63, 62.81, 59.35, 21.79.



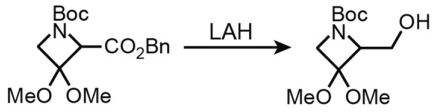
6a **6b**

Scheme S3 Reaction scheme for the synthesis of γ-halo amine precursor **6a** from reference[6].



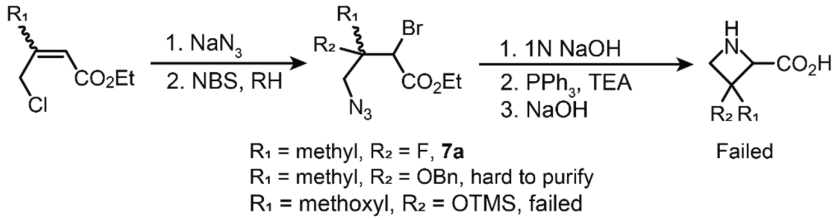
6b **6c** **6d**

2-benzyl 1-(*tert*-butyl) 3,3-dimethoxyazetidine-1,2-dicarboxylate (**6d**): Into a solution of crude **6b** (1.92 g, 3.82 mmol, 1 eq) in THF/H_2O (1:1 v/v, 15 mL) was added NaOH (323 mg, 8.03 mmol, 2.1 eq) and the resulting mixture was stirred for 4 h at 85 °C. The resulting solution was washed with DCM and concentrated *in vacuo* to obtain the azetidine amino acid intermediate **6c**, which was used in the next step without further purification. The formation of **6c** was confirmed by MS. MS (ESI): Calcd for $C_6H_{10}NNa_2O_4$ $[M+Na]^+$: 206.0, found 206.1. Into a solution of crude **6c** in 25% NaOH (25 mL), 30% Boc_2O (20 mL) was added, and the resulting mixture was stirred for 2 days at room temperature before being neutralized to pH 6–7. The aqueous layer was extracted with DCM twice and the combined organic layers were dried over Na_2SO_4. After concentration *in vacuo*, the crude Boc protected azetidine amino acid intermediate (900 mg) was obtained and used in the next step without further purification. The formation of the Boc protected azetidine amino acid intermediate was confirmed by MS. MS (ESI): Calcd for $C_{11}H_{23}N_2O_6$ $[M+NH_4]^+$: 279.2, found: 279.0. Into an ice-cold solution of crude Boc protected azetidine amino acid intermediate obtained (921 mg, 3.52 mmol, 1 eq) in THF(8.4 mL), benzyl bromide (0.46 mL, 3.87 mmol, 1 eq) and triethylamine (0.55 mL, 3.87 mmol, 1.1 eq) were added sequentially. The solution was warmed to room temperature overnight. After concentration *in vacuo*, the crude mixture was purified by flash chromatography (15–30% EtOAc/hexanes (v/v)) to obtain **6d** (720 mg, 32% over five steps starting from methyl 4-azido-2-bromo-3,3-dimethoxybutanoate). ^{1}H NMR (700 MHz, CDCl3): δ= 7.37 – 7.29 (m, 5H), 5.25 (s, 2H), 4.05 (d, *J* = 8.6 Hz, 1H), 3.81 – 3.79 (m, 1H), 3.31 (s, 3H), 3.16 (s, 3H), 1.47 – 1.36 (m, 9H). ^{13}C NMR (176 MHz, $CDCl_3$): δ= 167.02, 135.82, 128.54, 128.25, 98.27, 80.58, 66.89, 50.27, 49.90, 28.31. MS (ESI): Calcd for $C_{18}H_{26}NO_6$ $[M+H]^+$: 352.1755, found: 352.1743.



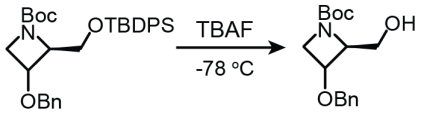
6d **6e**

***Tert*-butyl 2-(hydroxymethyl)-3,3-dimethoxyazetidine-1-carboxylate (6e)**: Into an ice-cold solution of **6d** (720 mg, 2.05 mmol, 1 eq) in THF (10 mL), LAH (86 mg, 2.26 mmol, 1.1 eq) was added. The reaction mixture was kept at this temperature for at least 1 h. The reaction was monitored by TLC or MS and additional LAH was added if necessary. After completion of the reaction, the crude was poured into ice-cold 1 M HCl and extracted with DCM twice. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to obtain crude **6e** (552 mg), which was used in the next step without further purification. The formation of **6e** was confirmed by MS. MS (ESI): Calcd for $C_{11}H_{22}NO_5$ $[M+H]^+$: 248.1, found: 248.1.



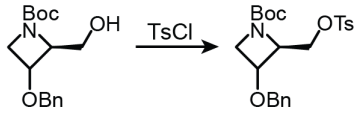
Scheme S4 Substrate scope extension trials starting from γ-halo amine analogues.

2. Synthesis of 6-substituted 4-azaspiro[2.3]hexanes



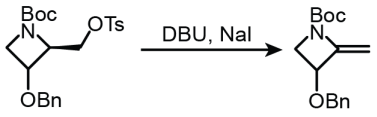
3d **3e**

***Tert*-butyl (2*S*)-3-(benzyloxy)-2-(hydroxymethyl)azetidine-1-carboxylate** (**3e**): Into a solution of **3d** (36 mg, 0.068 mmol, 1 eq) in anhydrous THF (520 µL) at -78 °C, TBAF (1M, 676 µL, 10 eq) was slowly added and the reaction mixture was stirred at RT overnight. The reaction was quenched with H_2O, followed by extraction with DCM. Flash chromatography was performed to obtain **3e** (12.6 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38 – 7.29 (m, 5H), 4.51 – 4.39 (m, 4H), 4.05 – 3.93 (m, 3H), 3.82 (dd, *J* = 9.4, 3.2 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.43, 137.04, 128.78, 128.35, 127.91, 80.42, 72.17, 69.68, 67.52, 62.02, 56.01, 53.57, 28.51. MS (ESI): Calcd for $C_{16}H_{24}NO_4$ $[M+H]^+$: 294.1, found: 294.1.



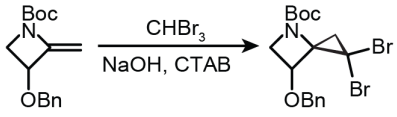
3e **3f**

***Tert*-butyl (2*S*)-3-(benzyloxy)-2-((tosyloxy)methyl)azetidine-1-carboxylate** (**3f**): Into an ice-cold solution of **3e** (12.6 mg, 0.043 mmol, 1 eq) in dry pyridine (196 µL), TsCl (41 mg, 0.22 mmol, 5 eq) was slowly added. The resulting mixture was stirred 0 °C for 5 min then warmed to room temperature and stirred overnight. The resulting mixture was quenched with 2M HCl and extracted with DCM. The reaction crude was concentrated *in vacuo* and purified by flash chromatography (50% EtOAc/hexanes (v/v)) to obtain **3f** (7 mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.28 (m, 4H), 4.51 – 4.25 (m, 5H), 4.00 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.69 (dd, *J* = 9.5, 4.3 Hz, 1H), 2.42 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.75, 144.90, 137.30, 132.95, 129.94, 128.63, 128.14, 128.11, 127.87, 80.47, 72.19, 68.47, 65.77, 64.20, 55.61, 28.40, 21.77. MS (ESI): Calcd for $C_{23}H_{30}NO_6S$ $[M+H]^+$: 448.2, found: 448.2.



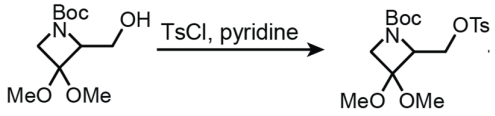
3f **3g**

***Tert*-butyl 3-(benzyloxy)-2-methyleneazetidine-1-carboxylate** (**3g**): Into a solution of **3f** (152 mg, 0.34 mmol, 1 eq) in glyme (5 mL), NaI (153 mg, 1.02 mmol, 3 eq), DBU (102 µL, 0.68 mmol, 2 eq) were added. The resulting mixture was heated to 105 °C for 4h before being quenched with the addition of H_2O. The mixture was extracted with ether. After concentration *in vacuo*, crude alkene **3g** (100 mg) was obtained, which was used directly for next step without any further purification. A relatively messy ^{1}H NMR spectrum was observed for the crude **3g**.



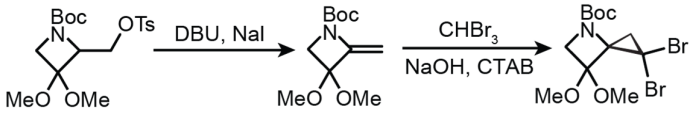
3g **3h**

***Tert*-butyl 6-(benzyloxy)-1,1-dibromo-4-azaspiro[2.3]hexane-4-carboxylate** (**3h**): Into a solution of **3g** (100 mg, 0.36 mmol, 1 eq), CTAB (2 mg, 0.0054 mmol, 0.015 eq), bromoform (200 µL, 2.2 mmol, 6 eq) and NaOH (50%, 200 µL) were sequentially added. The reaction mixture was stirred in the dark for 2 days and quenched with addition of H_2O, extracted with DCM. After concentration *in vacuo*, **3h** was obtained by preparative TLC (20 mg, 12%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.37 – 7.31 (m, 5H), 4.58 – 4.53 (m, 2H), 4.45 (dd, *J* = 5.8, 3.7 Hz, 1H), 4.09 (dd, *J* = 9.0, 5.9 Hz, 1H), 3.78 (dd, *J* = 9.0, 3.7 Hz, 1H), 2.86 (br, 1H), 1.99 (d, *J* = 9.3 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 155.17, 137.09, 128.73, 128.35, 128.05, 73.46, 72.03, 30.38, 29.85, 28.46. MS (ESI): Calcd for $C_{17}H_{22}Br_2NO_3$ $[M+H]^+$: 448.0, found 347.9 $[M-Boc+2H]^+$.



6e **6f**

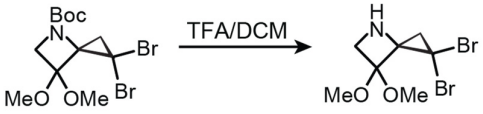
***Tert*-butyl 3,3-dimethoxy-2-((tosyloxy)methyl)azetidine-1-carboxylate (6f)**: The preparation of **6f** followed similar procedure for **3f** using the crude **6e** (552 mg, 2.23 mmol, 1 eq), TsCl (2.13 g, 11.15 mmol, 5 eq) in pyridine (10 mL). The reaction crude was purified by flash chromatography (20% - 25% EtOAc/hexanes (v/v)) to obtain **6f** (630 mg, 77% over two steps). ^{1}H NMR (700 MHz, $CDCl_3$): δ= 7.79 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.25 – 4.15 (m, 3H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.70 (d, *J* = 9.1 Hz, 1H), 3.16 (s, 3H), 3.10 (s, 3H), 2.44 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$): δ= 156.24, 144.91, 133.00, 129.84, 128.18, 97.94, 80.74, 66.22, 49.88, 49.54, 28.35, 21.76. MS (ESI): Calcd for $C_{18}H_{28}NO_7S$ $[M+H]^+$: 402.1581, found: 402.1581.



6f **6g**

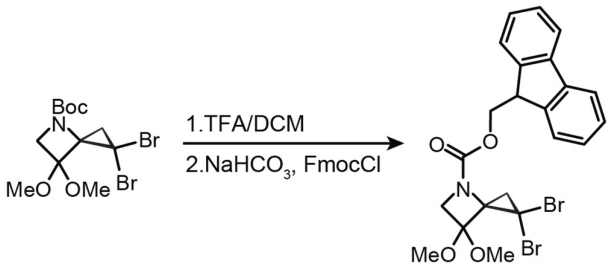
***Tert*-butyl 3,3-dimethoxy-2-methyleneazetidine-1-carboxylate**: The preparation of tert-butyl 3,3-dimethoxy-2-methyleneazetidine-1-carboxylate followed similar procedure for **3g** starting from **6f** (422 mg, 1.05 mmol, 1 eq), NaI (473 mg, 3.15 mmol, 3 eq), DBU (0.31 mL, 2.10 mmol, 2 eq) in glyme (10 mL). The reaction was quenched by adding H_2O, followed by extraction with ether. The organic layer was collected and washed with brine twice, dried over Na_2SO_4, concentrated *in vacuo*, the crude (216 mg) was obtained and used without further purification. ^{1}H NMR (500 MHz, CD_3CN): δ= 4.85 (br, 0.5H), 4.65 (br, 0.5H), 4.45 (d, J = 2.1 Hz, 1H), 3.79 (s, 2H), 3.29 (s, 6H), 1.46 (s, 9H).

***Tert*-butyl 1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexane-4-carboxylate** (**6g**): The preparation of **6g** followed similar procedure for **3h** using crude obtained above (216 mg, 1.03 mmol, 1 eq), CTAB (5.6 mg, 0.015 mmol, 0.015 eq), bromoform (0.37 mL, 4.12 mmol, 4 eq) and 50% NaOH (0.52 mL). The reaction crude was purified by flash chromatography (10 -15% EtOAc/hexanes (v/v)) to obtain **6g** (246 mg, 58% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 4.21 (d, J = 9.05 Hz, 1H), 3.96 (d, J = 9.05 Hz, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.03 – 3.02 (m, 1H), 2.13 (d, J = 9.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ= 155.01, 101.40, 62.97, 57.86, 51.29, 50.82, 28.48, 28.43, 27.16. HRMS (ESI): Calcd for $C_{12}H_{20}Br_2NO_4$ $[M+H]^+$: 401.9660, found: 313.8844 $[M\text{-}tBu\text{-}OCH_3+H]^+$.



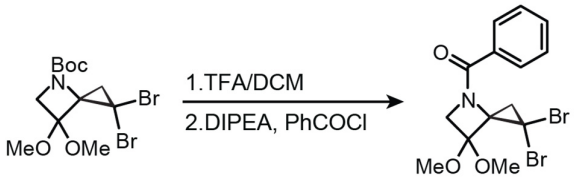
6g **6h**

1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexan-4-ium (**6h**): Into an ice-cold solution of *tert*-butyl 1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexane-4-carboxylate (40 mg, 0.1 mmol, 1 eq) in dry DCM (200 µl), TFA (80 µl, 1 mmol, 10 eq) was slowly added. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature. The completion of the reaction was confirmed by TLC. The reaction mixture was purified by HPLC (40% - 100%, MeOH + 0.1% TFA , 0.01min - 25min) to afford the pure product (11 mg, 37%). ^{1}H NMR (700 MHz, MeOD): δ = 4.22 (d, *J* = 10.9 Hz, 1H), 4.14 (d, *J* = 10.9 Hz, 1H), 3.47 (s, 3H), 3.40 (s, 3H), 2.66 (d, *J* = 10.6 Hz, 1H), 2.40 (d, *J* = 10.6 Hz, 1H). ^{13}C NMR (176 MHz, MeOD): δ = 103.20, 62.00, 52.82, 51.97, 51.45, 30.77. HRMS (ESI): Calcd for $C_7H_{12}Br_2NO_2$ $[M+H]^+$: 301.9229, found: 301.9211.



6g **6i**

(9*H*-fluoren-9-yl)methyl 1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexane-4-carboxylate (**6i**): Into an ice-cold solution of **6g** (40 mg, 0.1 mmol, 1 eq) in dry DCM (200 µL), TFA (80 µL, 1 mmol, 10 eq) was slowly added. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature. The completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and under high vacuum for 1.5 h. Into an ice-cold solution of the previously concentrated mixture in dry dioxane (200 µL) and 10% $NaHCO_3$ (400 µL), then FmocCl (57 mg, 0.22 mmol, 2.2 eq) was added dropwise sequentially. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature overnight. The reaction mixture was purified by preparative TLC (10% EtOAc/Hexane) to afford **6i** (13 mg, 24%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.78 (t, *J* = 8.2 Hz, 2H), 7.56 (dd, *J* = 17.7, 7.6 Hz, 2H), 7.41 (dt, *J* = 11.4, 7.4 Hz, 2H), 7.32 (dtd, *J* = 14.9, 7.5, 1.1 Hz, 2H), 4.54 (s, 1H), 4.43 (s, 1H), 4.24 (d, *J* = 9.0 Hz, 1H), 4.21 (t, *J* = 6.2 Hz, 1H), 3.96 (d, *J* = 8.9 Hz, 1H), 3.41 (s, 3H), 3.32 (s, 3H), 2.00 (s, 1H), 1.25 (s, 1H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 155.65, 143.82, 143.68, 141.55, 127.93, 127.25, 127.22, 124.95, 124.91, 120.23, 101.48, 67.08, 58.34, 51.21, 50.79, 47.21, 29.81, 26.31. HRMS (ESI): Calcd for $C_{22}H_{22}Br_2NO_4$ $[M+H]^+$: 523.9910, found: 523.9893.



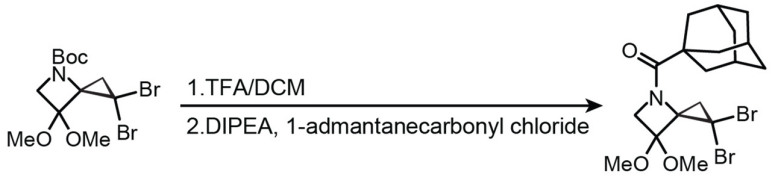
6g **6j**

(1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexan-4-yl)(phenyl)methanone (**6j**): Into an ice-cold solution of **6g** (40 mg, 0.1 mmol, 1 eq) in dry DCM (200 µL), TFA (80 µL, 1 mmol, 10 eq) was slowly added. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature. The completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and under high vacuum for 1.5h. Into an ice-cold solution of previously concentrated mixture in dry DCM (200 µL), DIPEA (41.7 µL, 0.24 mmol, 2.4 eq) was added dropwise, then benzoyl acid chloride (13.94 µL, 0.12 mmol, 1.2 eq) was added dropwise sequentially. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature overnight. The reaction mixture was purified by preparative TLC (10% EtOAc/Hexane) to afford **6j** (7 mg, 17%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.0 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 4.53 (d, *J* = 8.6 Hz, 1H), 3.92 (dd, *J* = 19.7, 9.0 Hz, 2H), 3.42 (s, 3H), 3.35 (s, 3H), 2.25 (d, *J* = 9.5 Hz, 1H).^{13}C NMR (176 MHz, $CDCl_3$): δ = 172.70, 134.28, 131.67, 128.66, 127.94, 101.12, 64.29, 62.23, 51.08, 50.88, 29.85, 26.61, 26.51. HRMS (ESI): Calcd for $C_{14}H_{16}Br_2NO_4$ $[M+H]^+$: 405.9491, found: 405.9472.

6g **6k**

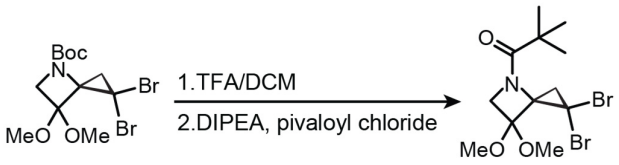
1-(1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexan-4-yl)prop-2-en-1-one (**6k**): Into an ice-cold solution of **6g** (40 mg, 0.1 mmol, 1 eq) in dry DCM (200 µL), TFA (80 µL, 1 mmol, 10 eq) was slowly added. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature. The completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and under high vacuum for 1.5h. Into an ice-cold solution of the previously concentrated mixture in dry DCM (200 µL), DIPEA (41.7 µL, 0.24 mmol, 2.4 eq) was added dropwise, then acryloyl chloride (9.5 µL, 0.12 mmol, 1.2 eq) was added dropwise sequentially. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature overnight. The reaction mixture was purified by preparative TLC (20% EtOAc/Hexane) to afford **6k** (4.1 mg, 12%).^{1}H NMR (700 MHz, $CDCl_3$): δ = 6.36 (dd, *J* = 16.9, 1.6 Hz, 1H), 6.17 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.73 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.46 (d, *J* = 8.1 Hz, 1H), 4.09 (d, *J* = 8.1 Hz, 1H), 3.69 (s, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 2.20 (d, *J* = 9.5 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 167.02, 128.93, 127.54,

100.98, 64.14, 59.18, 51.07, 50.89, 29.85, 26.26. HRMS (ESI): Calcd for $C_{10}H_{14}Br_2NO_3$ $[M+H]^+$: 355.9335, found: 355.9318.



6g **6l**

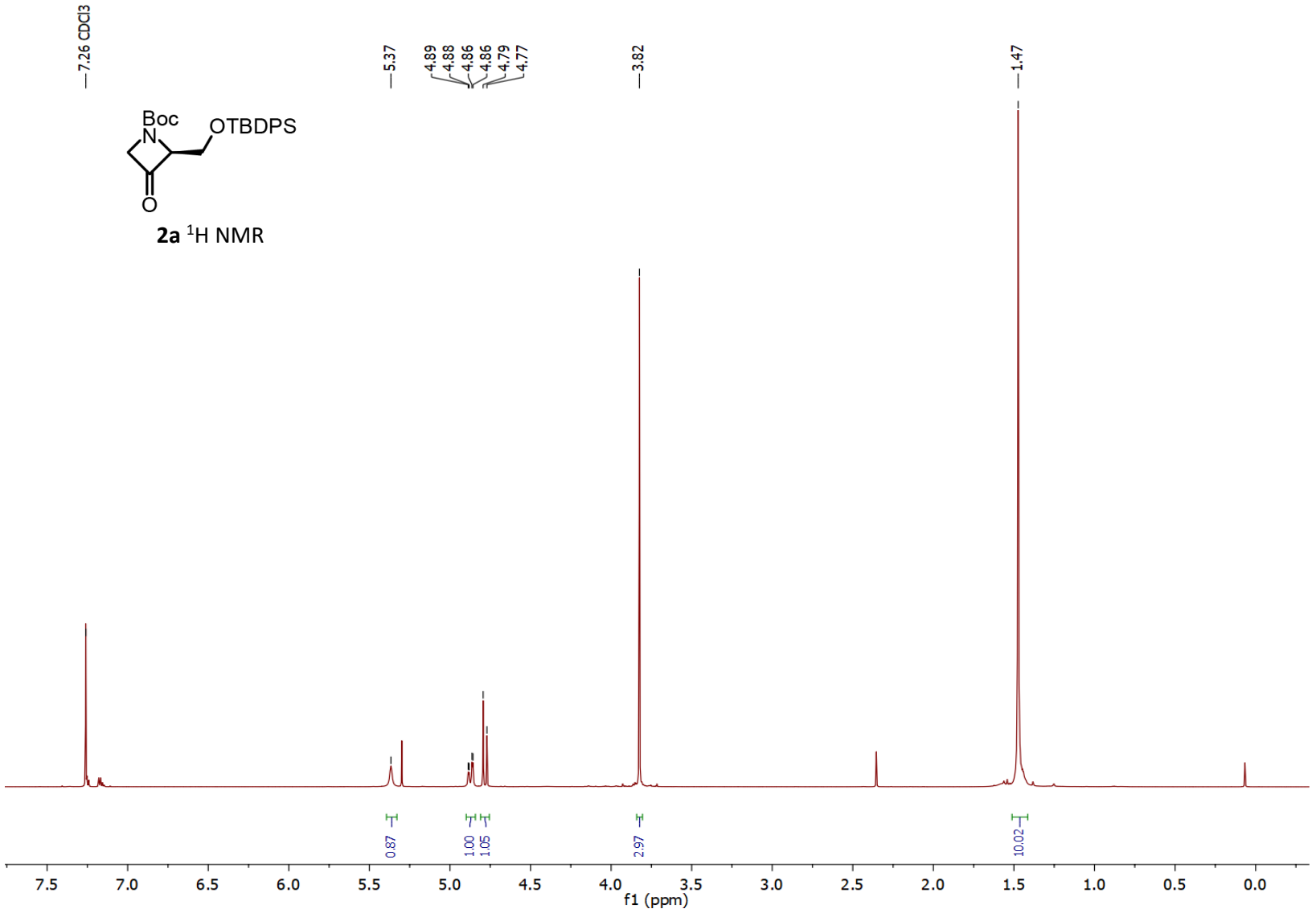
Adamantan-1-yl(1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexan-4-yl)methanone (**6l**): Into an ice-cold solution of **6g** (40 mg, 0.1 mmol, 1 eq) in dry DCM (200 µL), TFA (80 µL, 1 mmol, 10 eq) was slowly added. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature. The completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and under high vacuum for 1.5h. Into an ice-cold solution of the previously concentrated mixture was added DIPEA (41.7 µL, 0.24 mmol, 2.4 eq) dropwise, then a solution of 1-adamantanecarbonyl chloride (23.8 mg, 0.12 mmol, 1.2 eq) in dry DCM (200 µL) was added dropwise. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature overnight. The reaction mixture was purified by preparative TLC (20% EtOAc/Hexane) to afford **6l** (1.8 mg, 4%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 4.61 (d, *J* = 8.0 Hz, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 3.91 (d, *J* = 9.5 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.20 (d, *J* = 9.4 Hz, 1H), 2.05 (p, *J* = 3.3 Hz, 3H), 1.97 (dq, *J* = 12.6, 2.6 Hz, 3H), 1.89 (dq, *J* = 12.5, 2.6 Hz, 3H), 1.70 (dt, *J* = 14.9, 11.0 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 179.45, 101.12, 64.70, 61.95, 50.96, 50.85, 43.20, 38.53, 36.64, 29.85, 28.28, 26.78. HRMS (ESI): Calcd for $C_{18}H_{26}Br_2NO_3$ $[M+H]^+$: 464.0274, found: 464.0255.



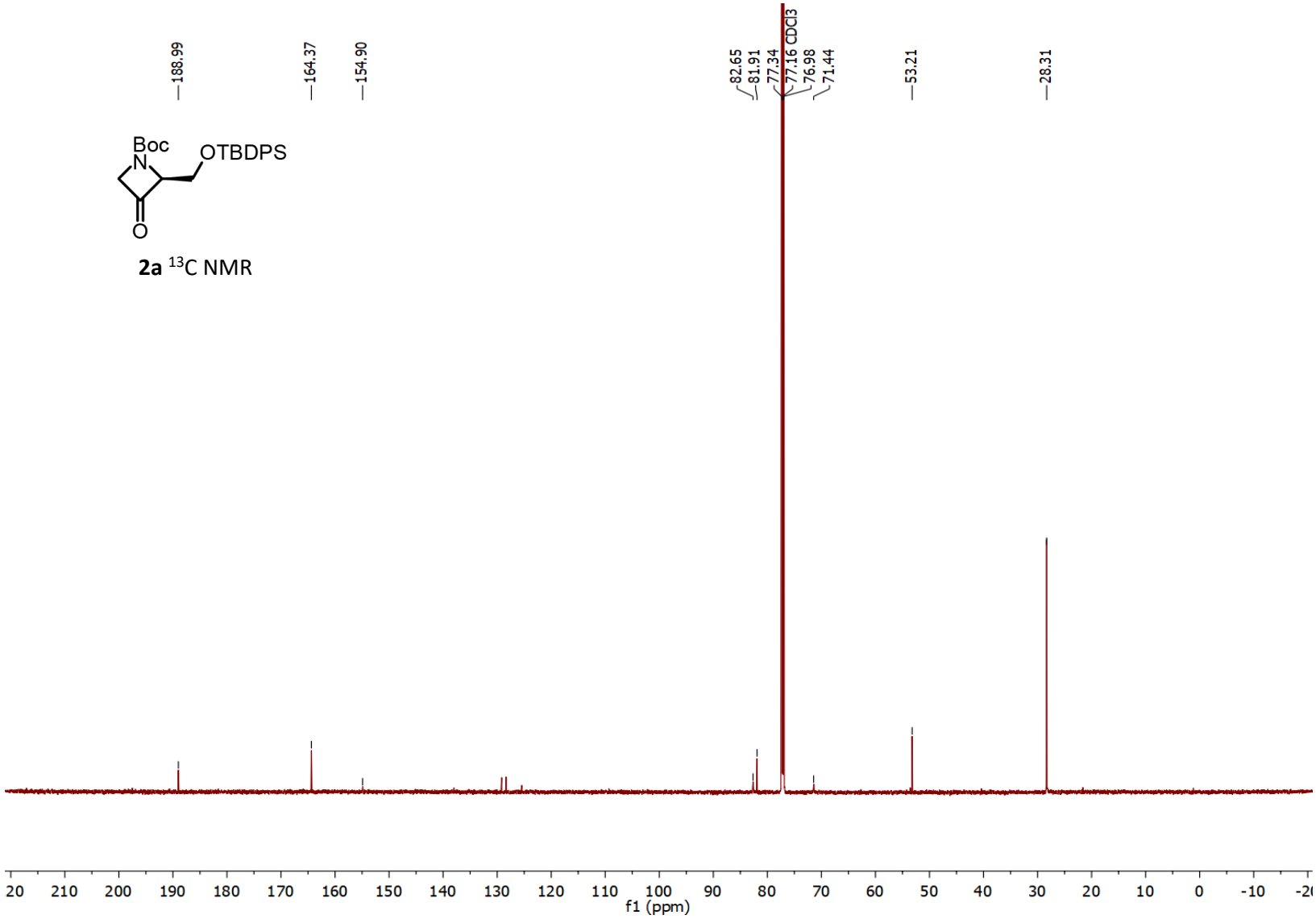
6g **6m**

1-(1,1-dibromo-6,6-dimethoxy-4-azaspiro[2.3]hexan-4-yl)-2,2-dimethylpropan-1-one (**6m**): Into an ice-cold solution of **6g** (40 mg, 0.1 mmol, 1 eq) in dry DCM (200 µL), TFA (80 µL, 1 mmol, 10 eq) was slowly added. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature. The completion of the reaction was confirmed by TLC. The reaction crude was concentrated *in vacuo* and under high vacuum for 1.5h to obtain crude **6h,** which was used for next step without further purification. Into an ice-cold solution of crude **6h** in dry DCM (200 µL), DIPEA (41.7 µL, 0.24 mmol, 2.4 eq) was added dropwise, then trimethylacetyl chloride (14.7 µL, 0.12 mmol, 1.2 eq) was added dropwise sequentially. The resulting mixture was stirred at the same temperature for 5 min and then at room temperature overnight. The reaction mixture was purified by preparative TLC (10% EtOAc/Hexane) to afford **6m** (13.4 mg, 35%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 4.51 (d, *J* = 8.1 Hz, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 3.85 (d, *J* = 9.4 Hz, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.16 (d, *J* = 9.5 Hz, 1H), 1.20 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 179.78, 100.91, 64.67, 61.87, 50.90, 50.81, 40.30, 27.33, 26.52, 26.44. HRMS (ESI): Calcd for $C_{12}H_{20}Br_2NO_3$ $[M+H]^+$: 385.9785, found: 385.9785.

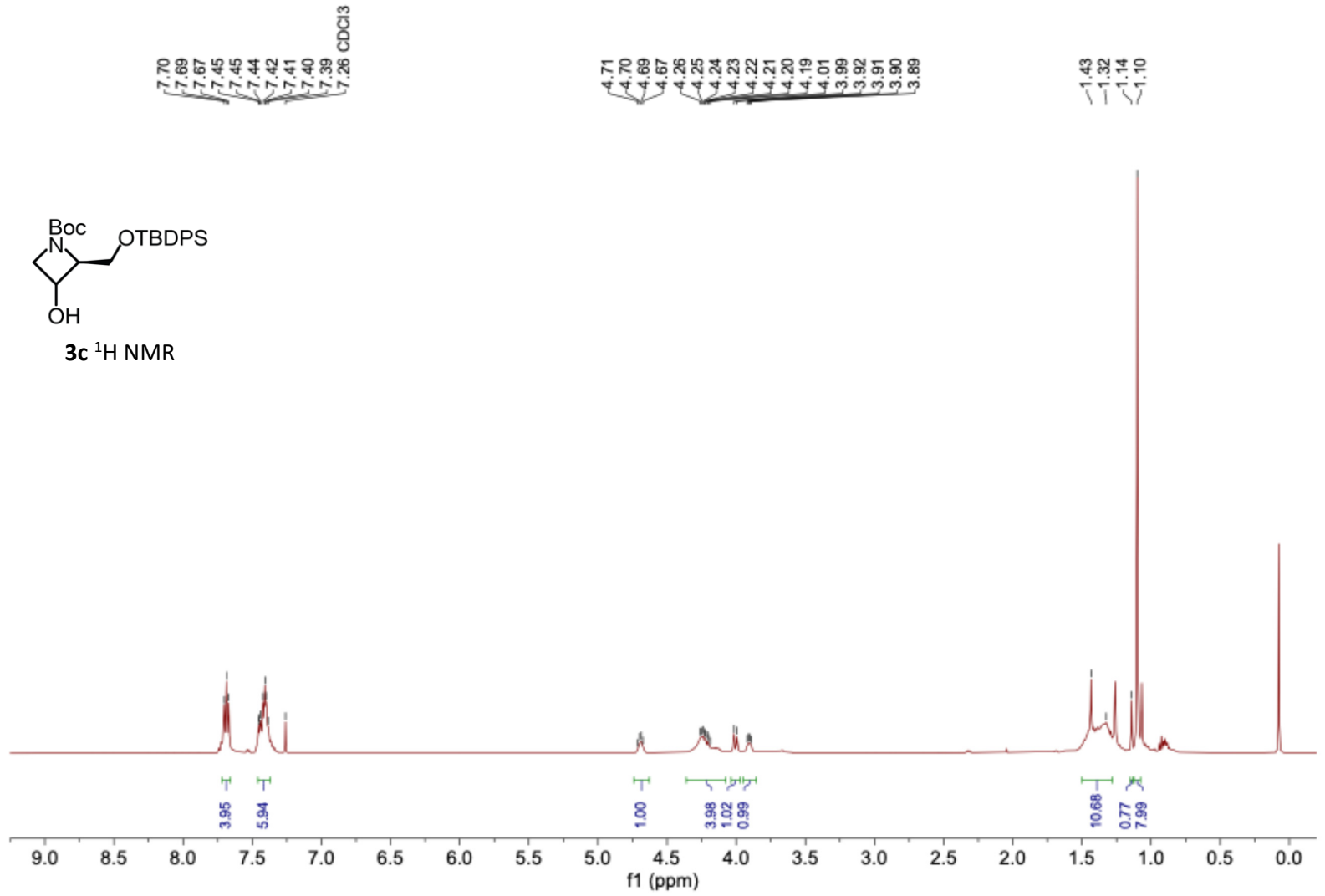
NMR spectra



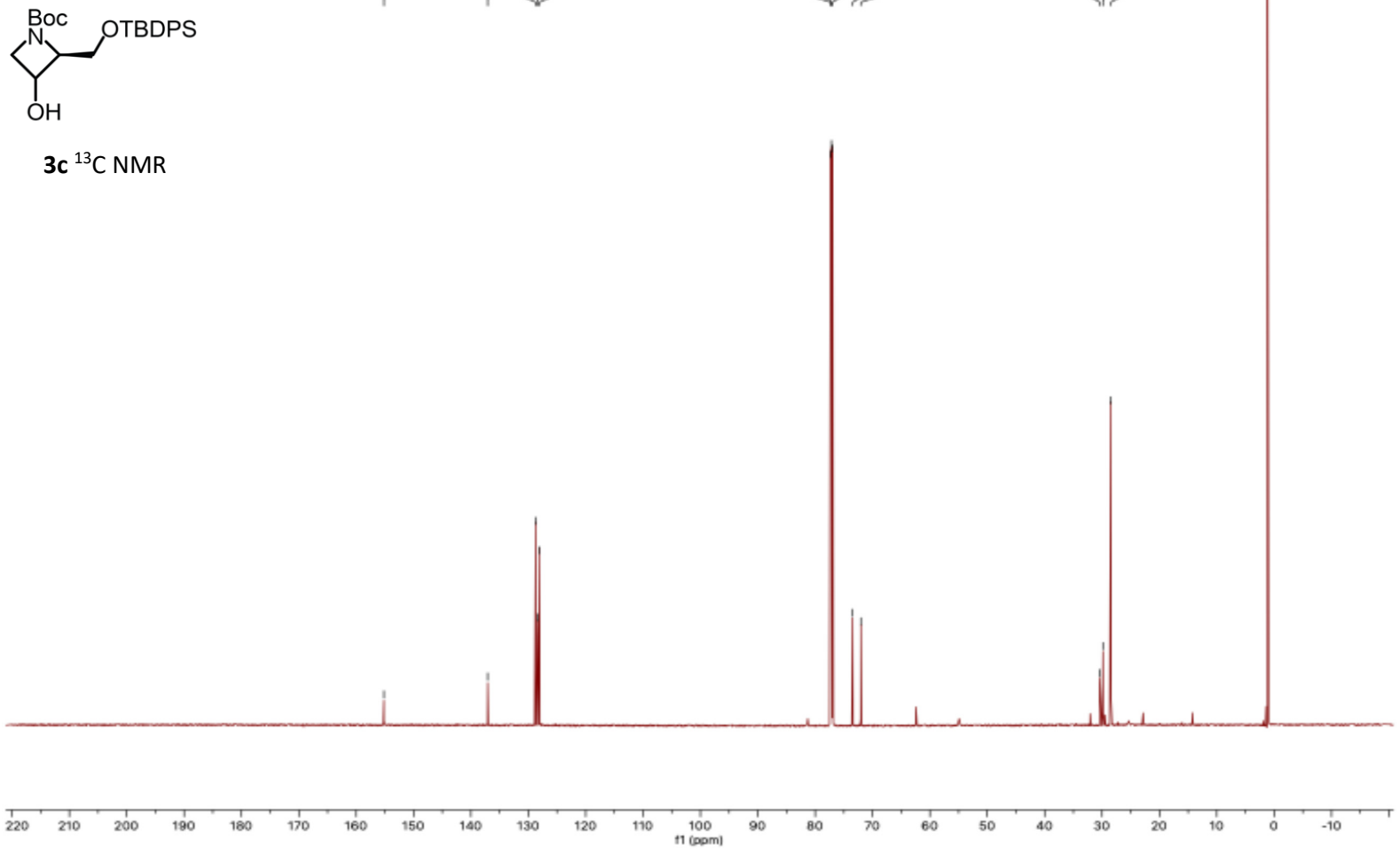
2a ^{1}H NMR


188.99
164.37
154.90
82.65
81.91
77.34
77.16 CDCl3
76.98
71.44
53.21
28.31
Boc
N
OTBDPS
O
f1 (ppm)

2a ^{13}C NMR


7.70
7.69
7.67
7.45
7.45
7.44
7.42
7.41
7.40
7.39
7.26 CDCl3
4.71
4.70
4.69
4.67
4.26
4.25
4.24
4.23
4.22
4.21
4.20
4.19
4.01
3.99
3.92
3.91
3.90
3.89
1.43
1.32
1.14
1.10
Boc
N
OTBDPS
OH
3.95
5.94
1.00
3.98
1.02
0.99
10.68
0.77
7.99
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)

3c ^{1}H NMR


Boc
N
OTBDPS
OH
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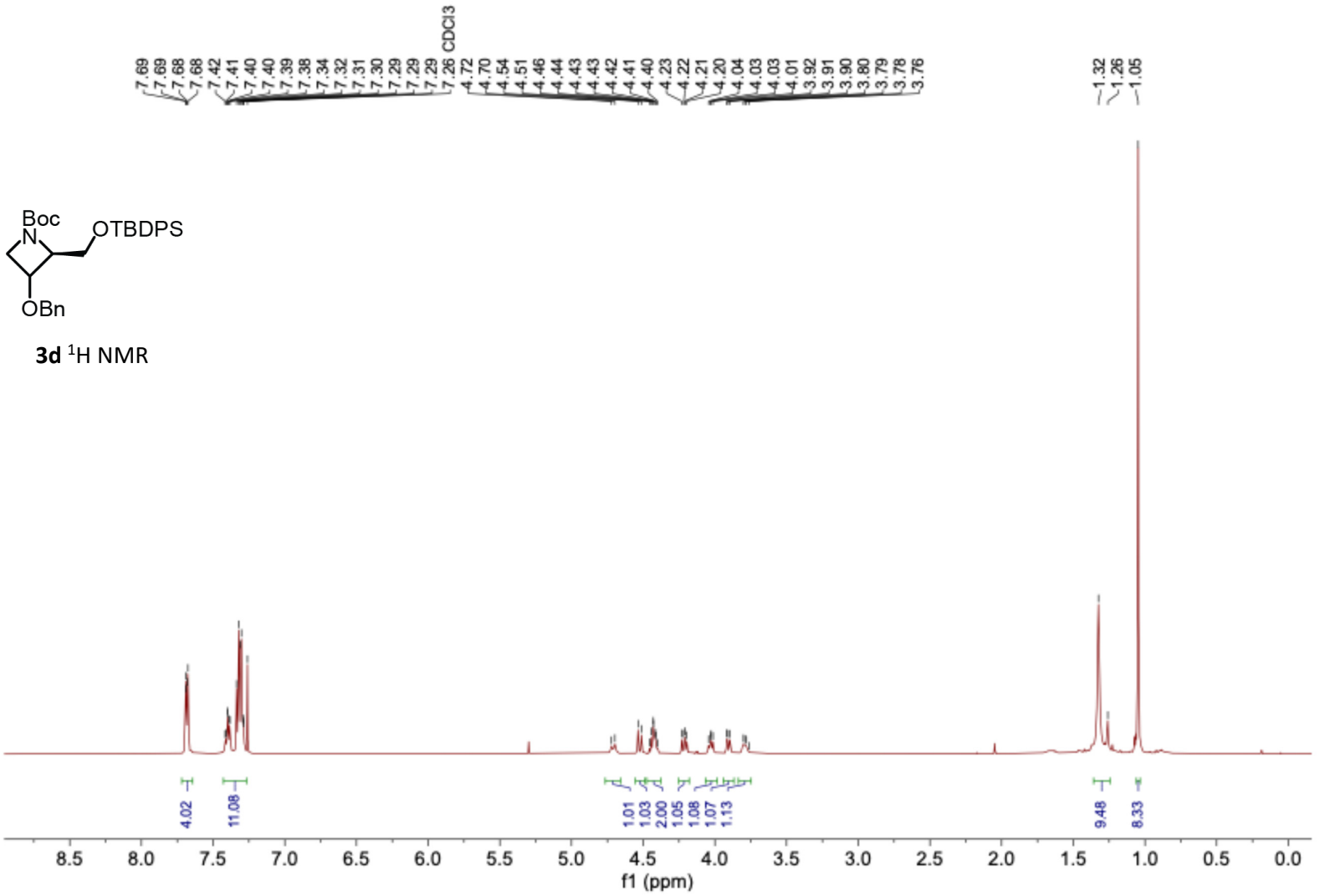
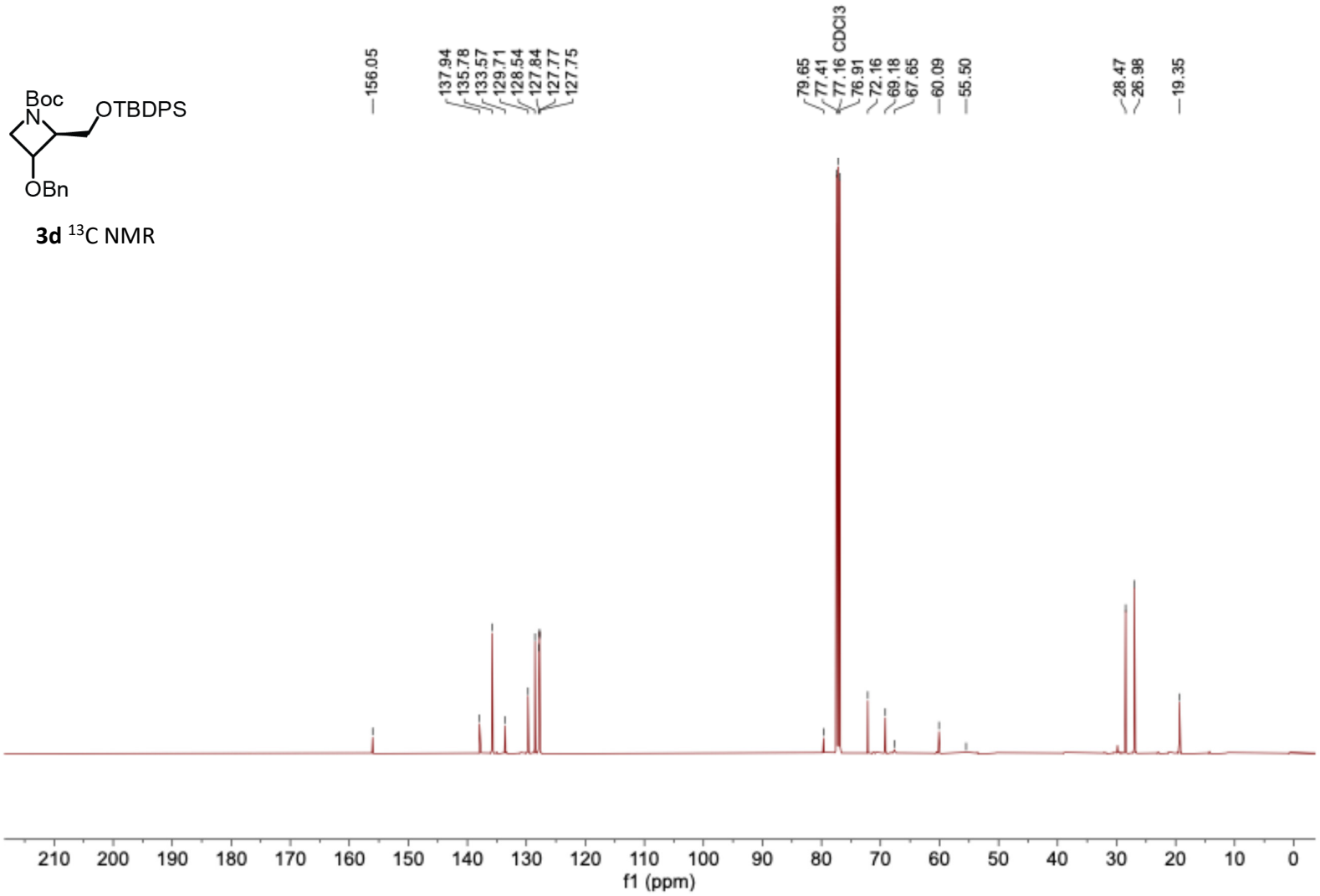
137.09
128.73
128.35
128.05
77.34
77.16 CDCl3
76.98
73.46
72.03
30.38
29.85
28.46
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

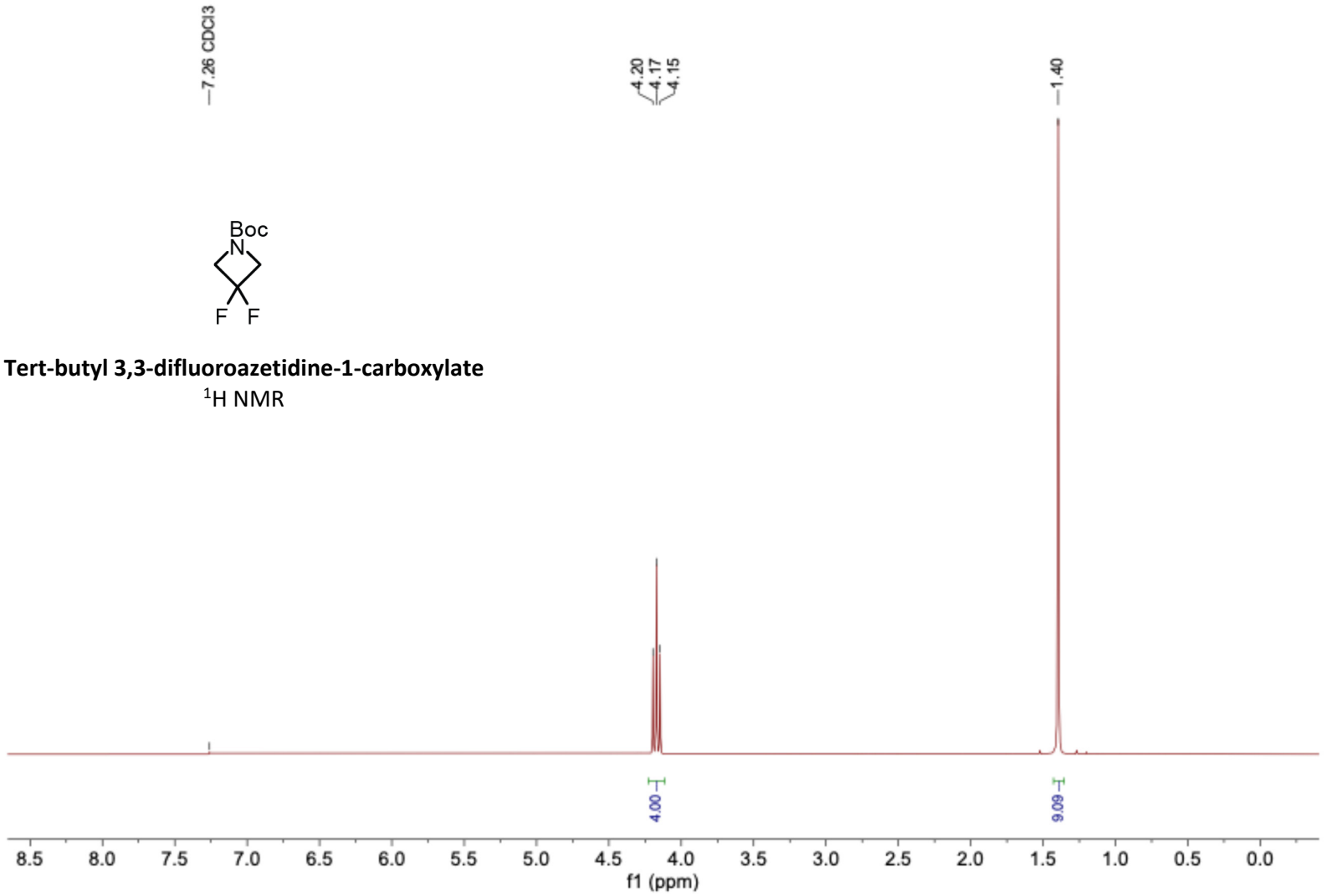
3c ^{13}C NMR


7.69
7.69
7.68
7.68
7.42
7.41
7.40
7.40
7.39
7.38
7.34
7.32
7.31
7.30
7.29
7.29
7.29
CDCl3
7.26
4.72
4.70
4.54
4.51
4.46
4.44
4.43
4.43
4.42
4.41
4.40
4.23
4.22
4.21
4.20
4.04
4.03
4.03
4.01
3.92
3.91
3.90
3.80
3.79
3.78
3.76
1.32
1.26
1.05
Boc
N
OTBDPS
OBn
4.02
11.08
1.01
1.03
2.00
1.05
1.08
1.07
1.13
9.48
8.33
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)

3d ^{1}H NMR

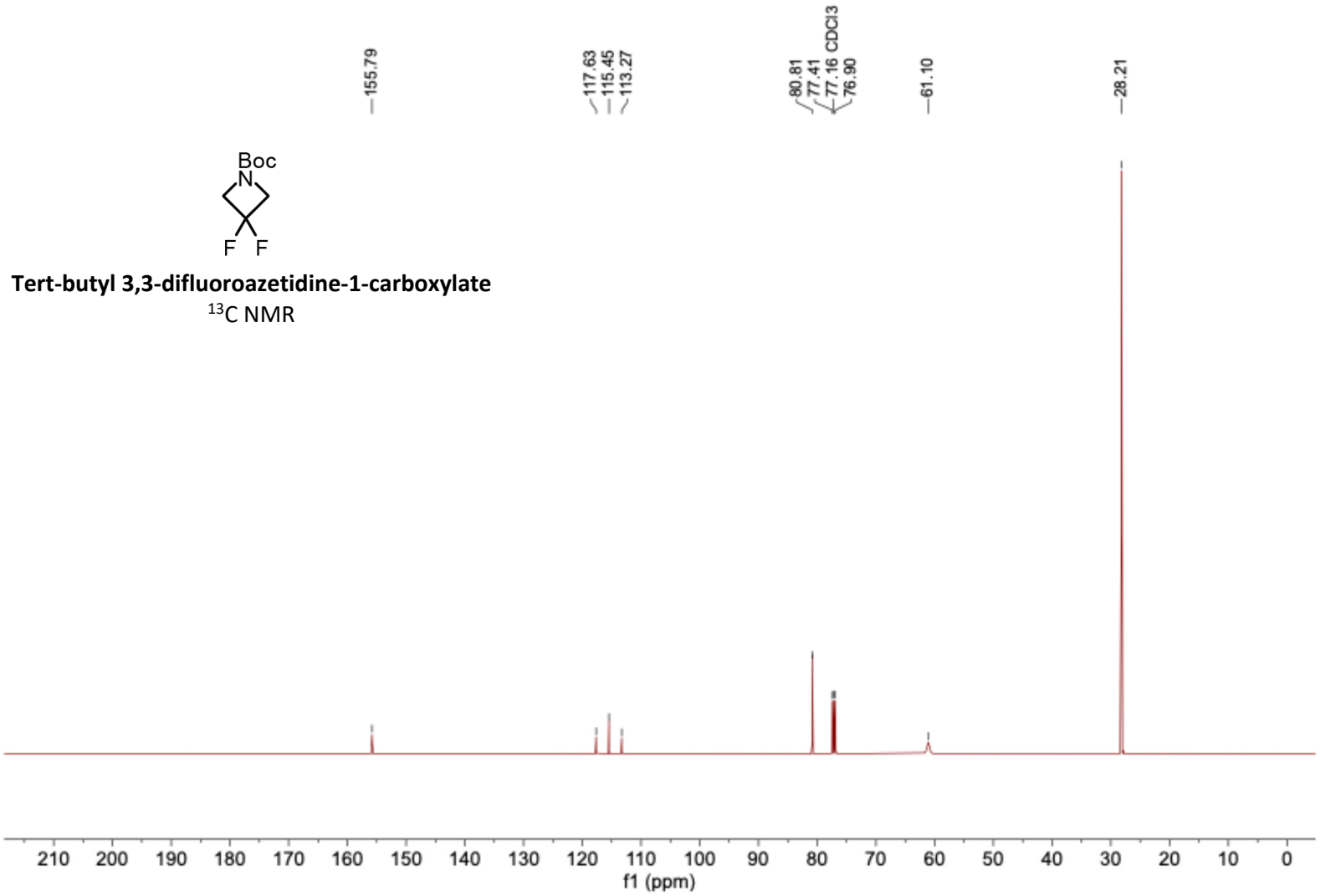

Boc
N
OTBDPS
OBn
156.05
137.94
135.78
133.57
129.71
128.54
127.84
127.77
127.75
79.65
77.41
77.16 CDCl3
76.91
72.16
69.18
67.65
60.09
55.50
28.47
26.98
19.35
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3d ^{13}C NMR



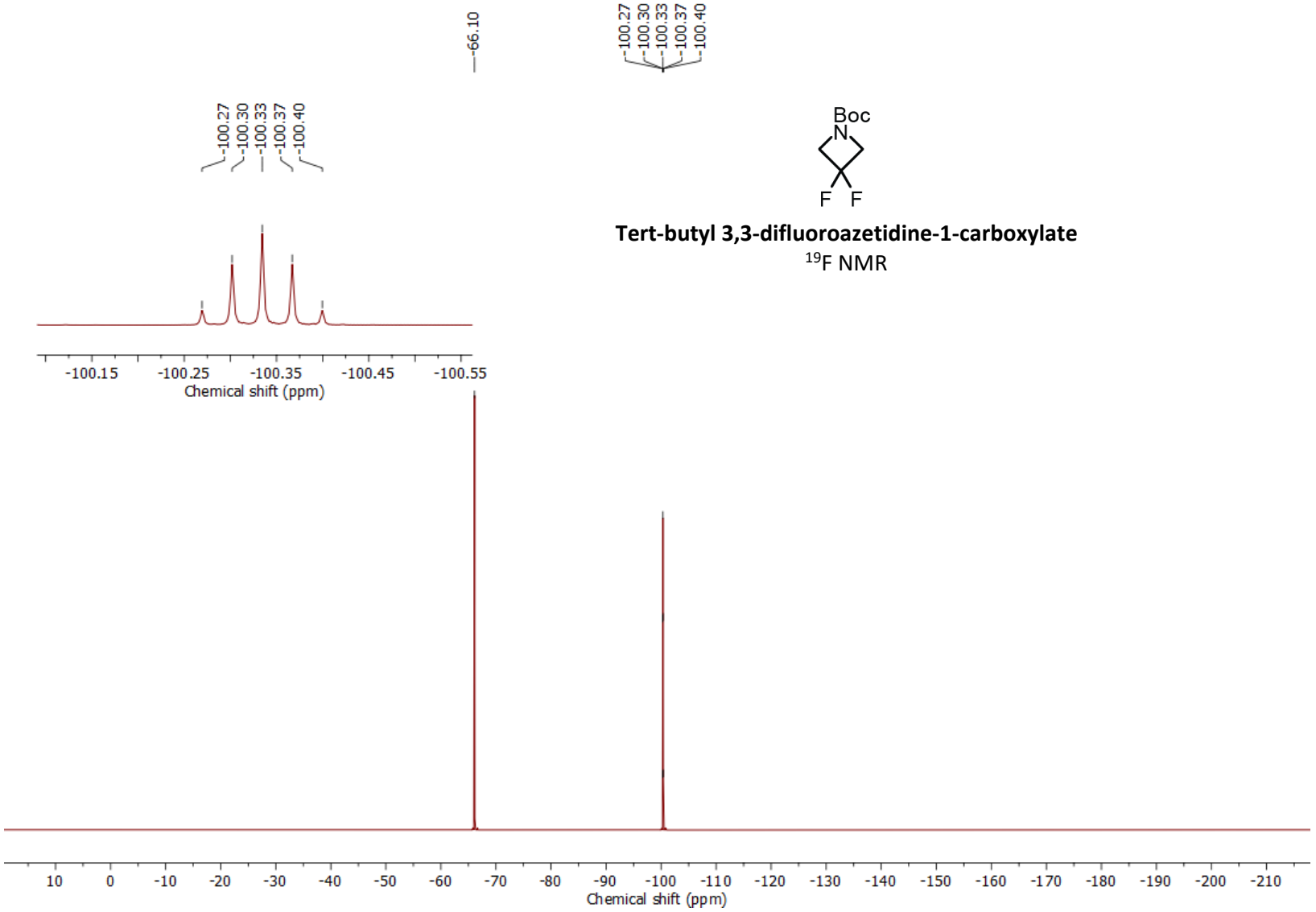
Tert-butyl 3,3-difluoroazetidine-1-carboxylate

^{1}H NMR



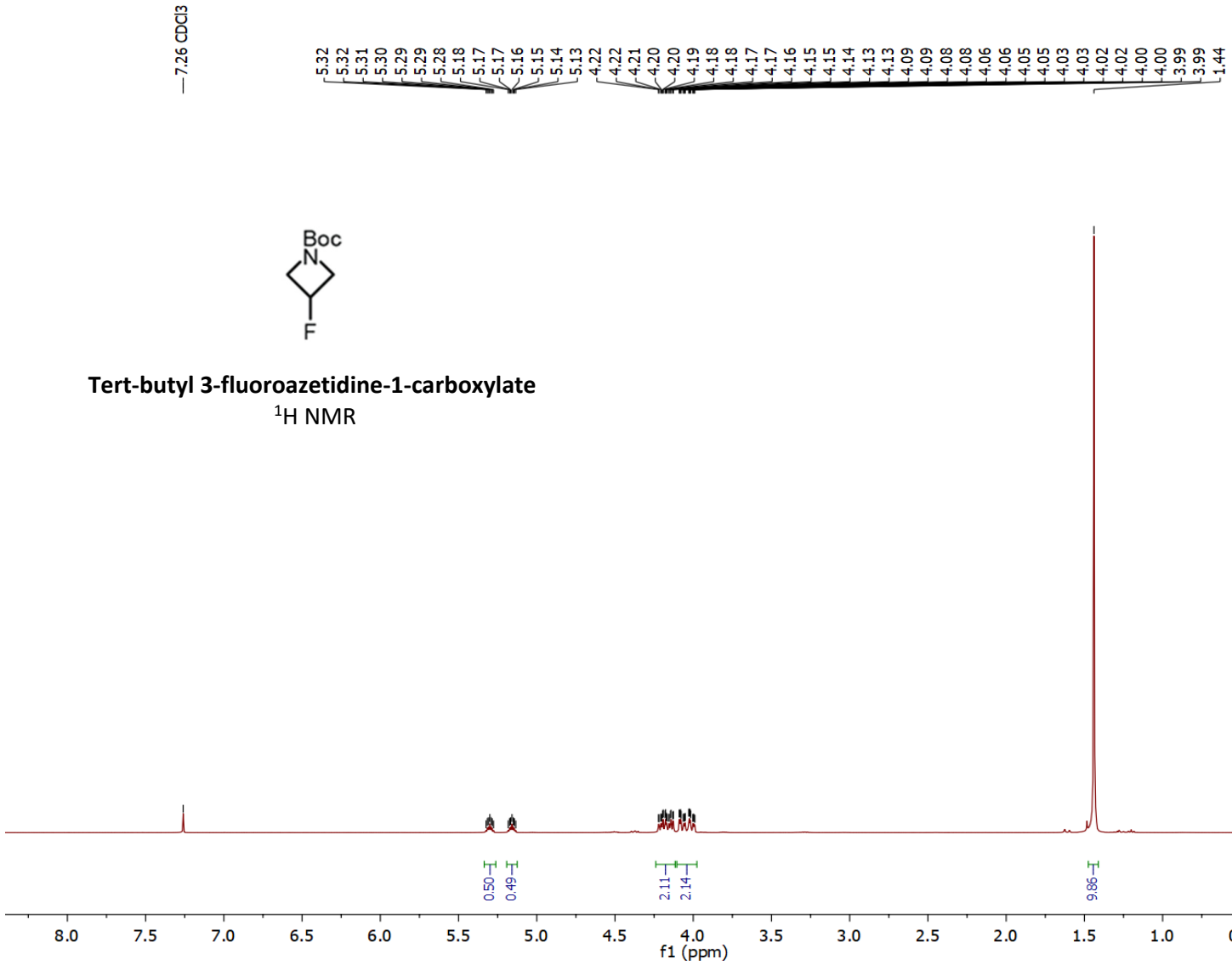
Tert-butyl 3,3-difluoroazetidine-1-carboxylate

^{13}C NMR



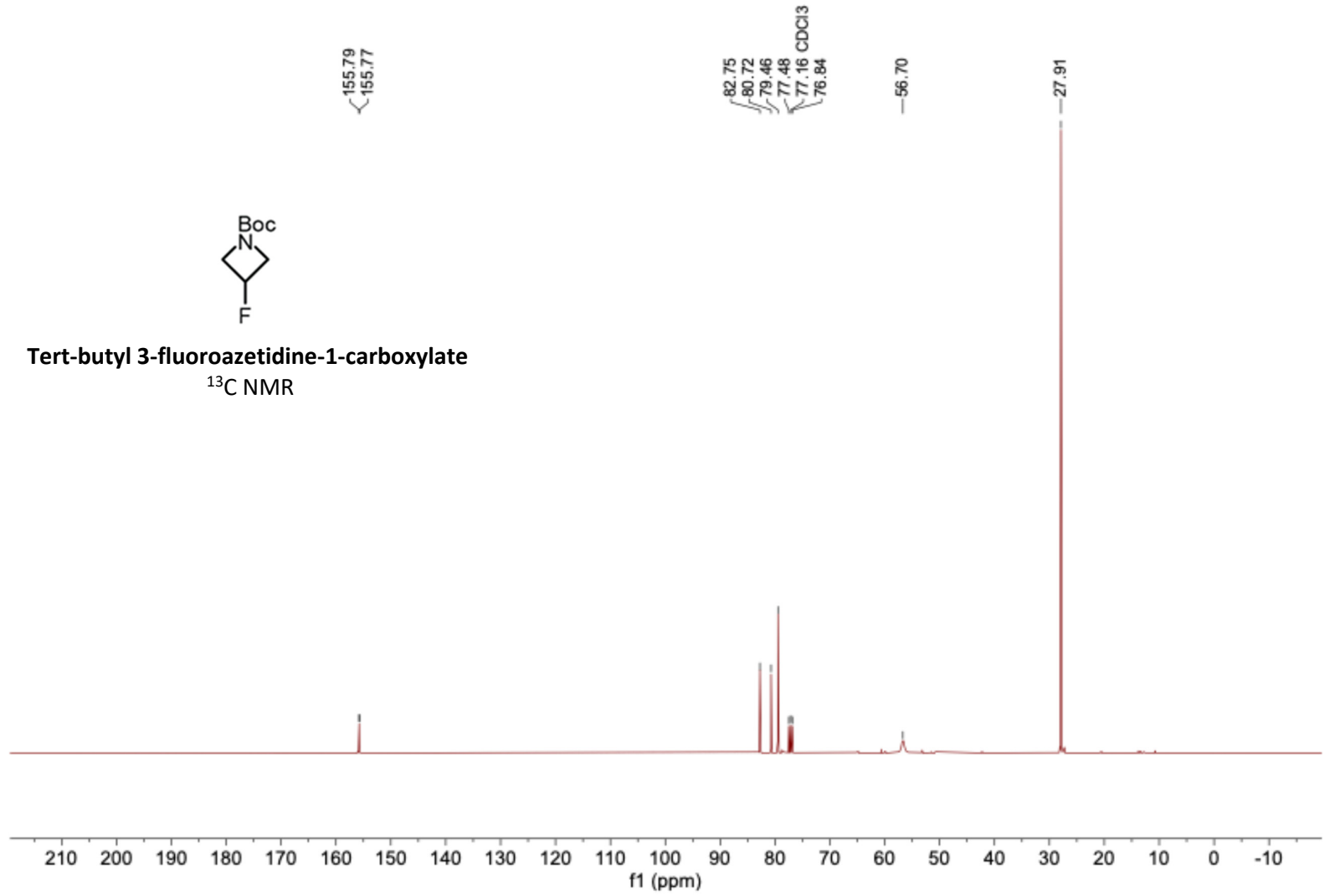
Tert-butyl 3,3-difluoroazetidine-1-carboxylate

^{19}F NMR



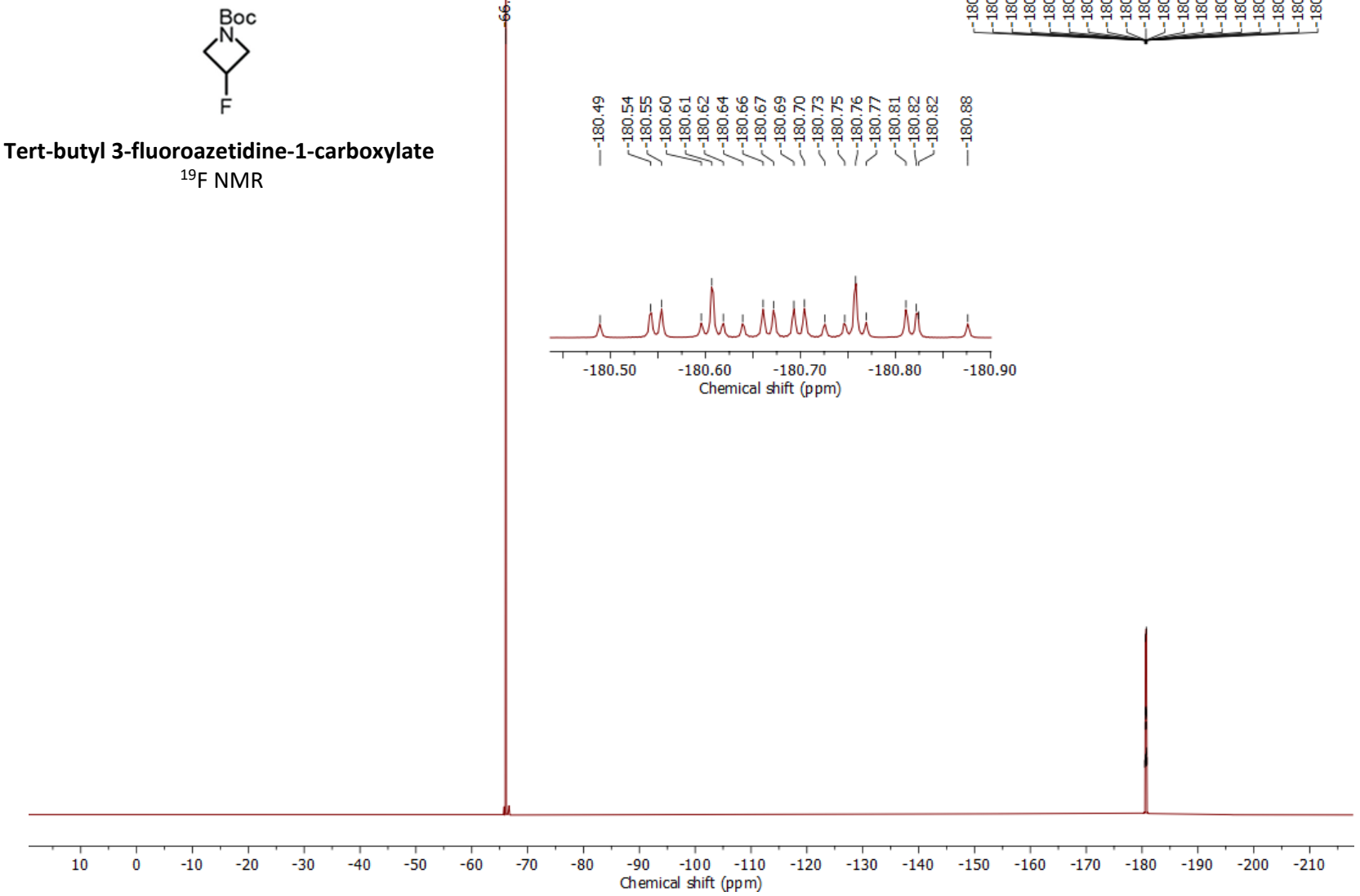
Tert-butyl 3-fluoroazetidine-1-carboxylate

^{1}H NMR



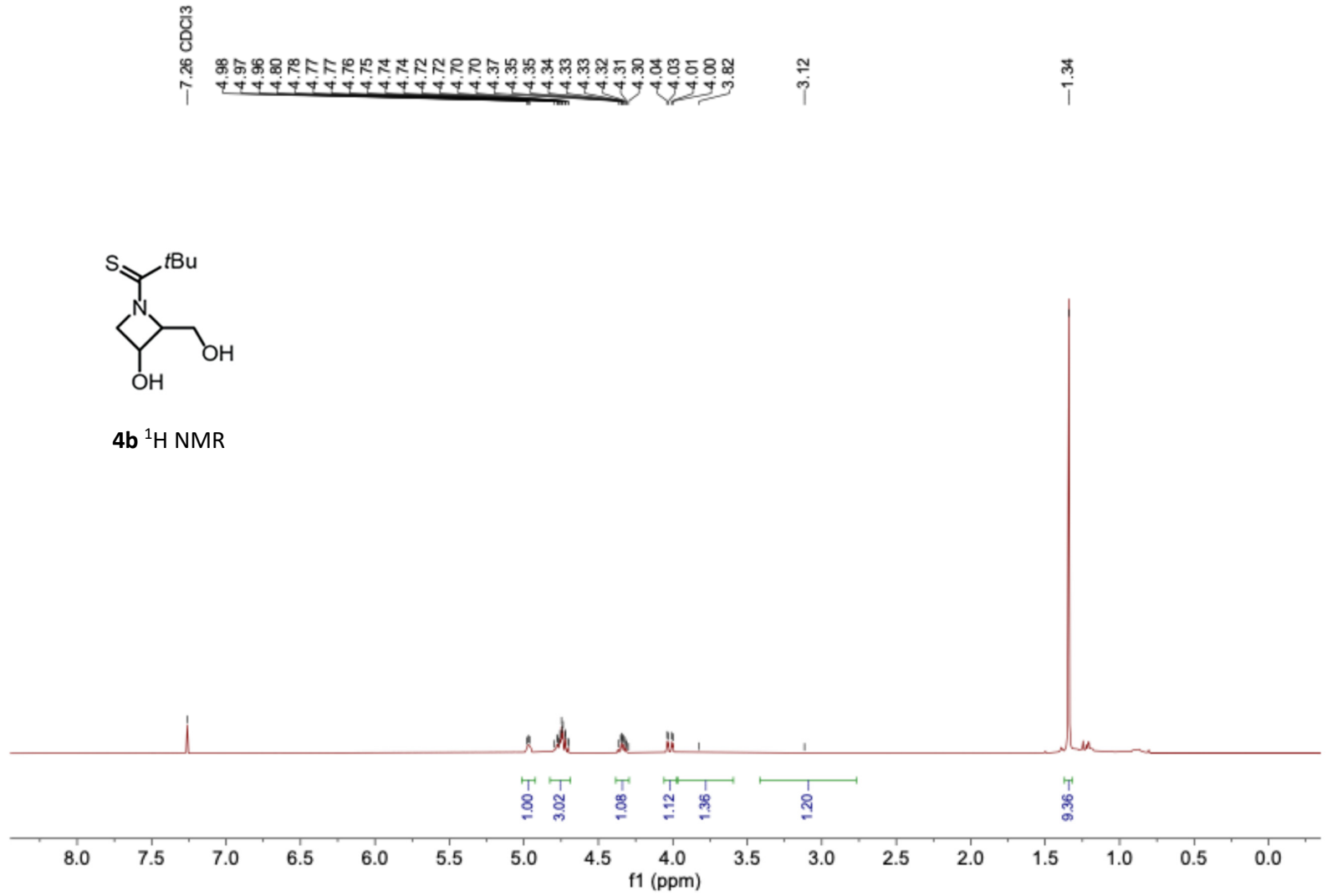
Tert-butyl 3-fluoroazetidine-1-carboxylate

^{13}C NMR



Tert-butyl 3-fluoroazetidine-1-carboxylate

^{19}F NMR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4.96
4.80
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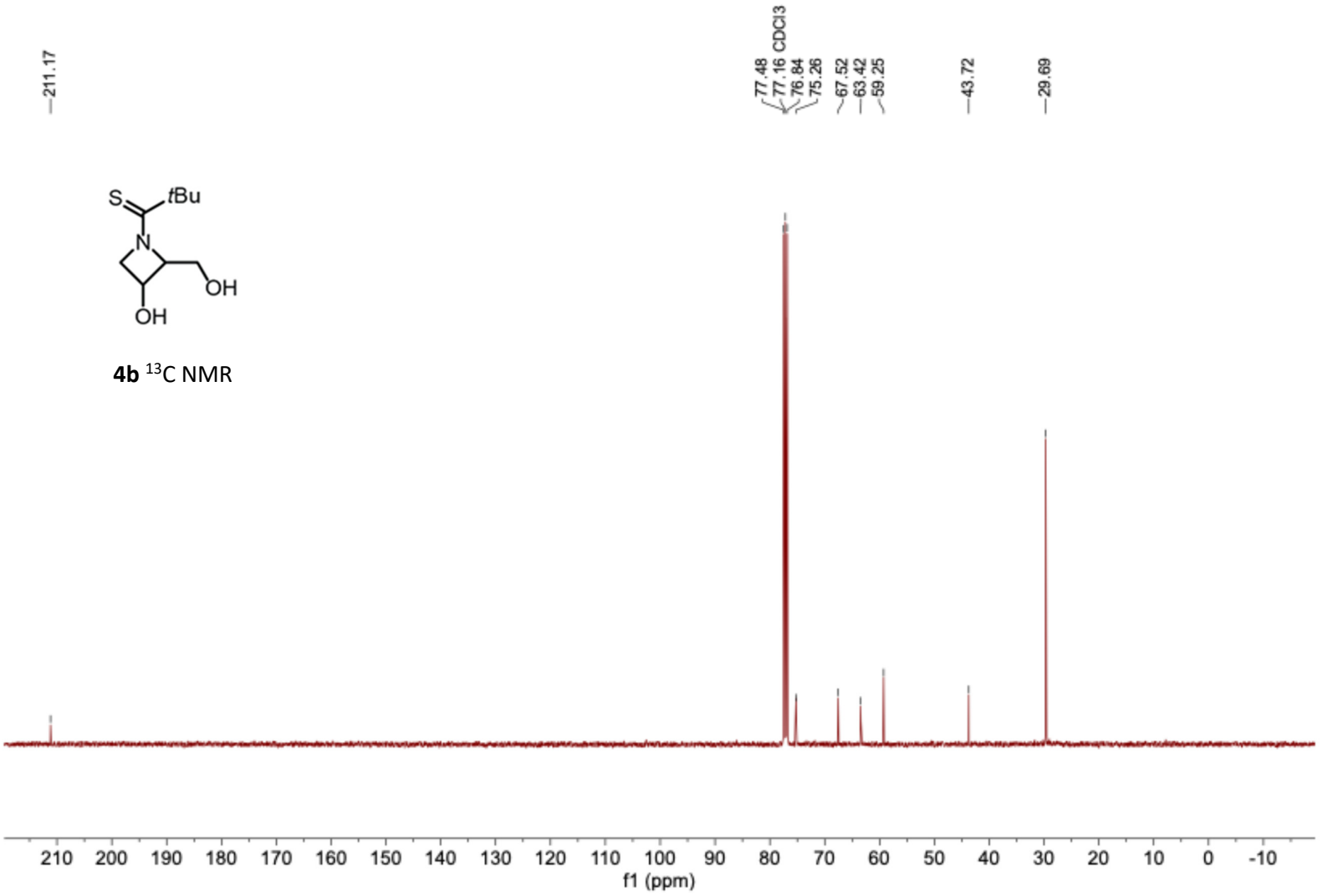
4.77
4.77
4.76
4.75
4.74
4.74
4.72
4.72
4.70
4.70
4.37
4.35
4.35
4.34
4.33
4.32
4.31
4.30
4.04
4.03
4.01
4.00
3.82
3.12
1.34
S
tBu
N
OH
OH
1.00
3.02
1.08
1.12
1.36
1.20
9.36
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

4b ^{1}H NMR


211.17
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75.26
67.52
63.42
59.25
43.72
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S
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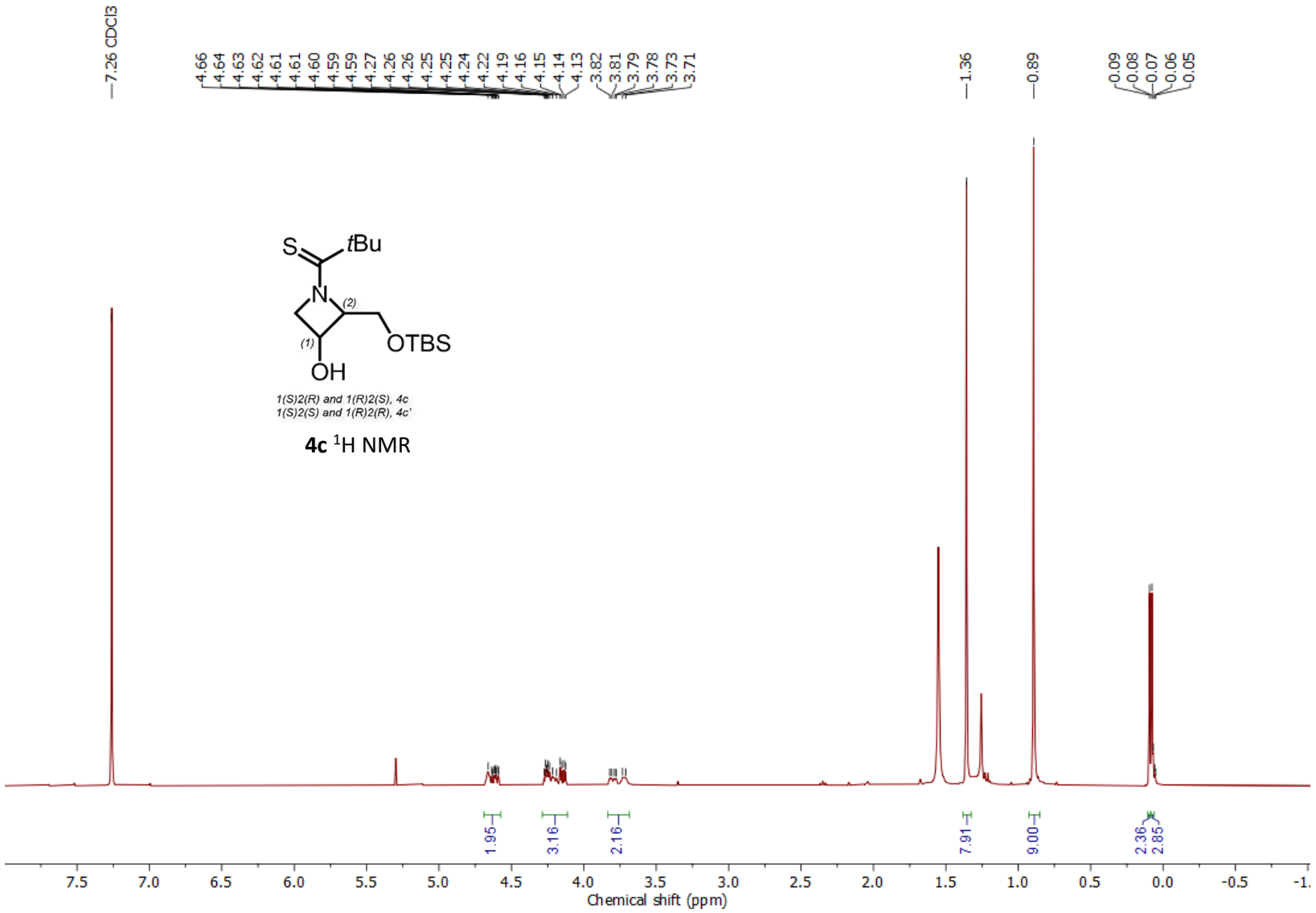
N
OH
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

4b ^{13}C NMR


7.26 CDCl3
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4.64
4.63
4.62
4.61
4.61
4.60
4.59
4.59
4.27
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4.26
4.25
4.25
4.24
4.22
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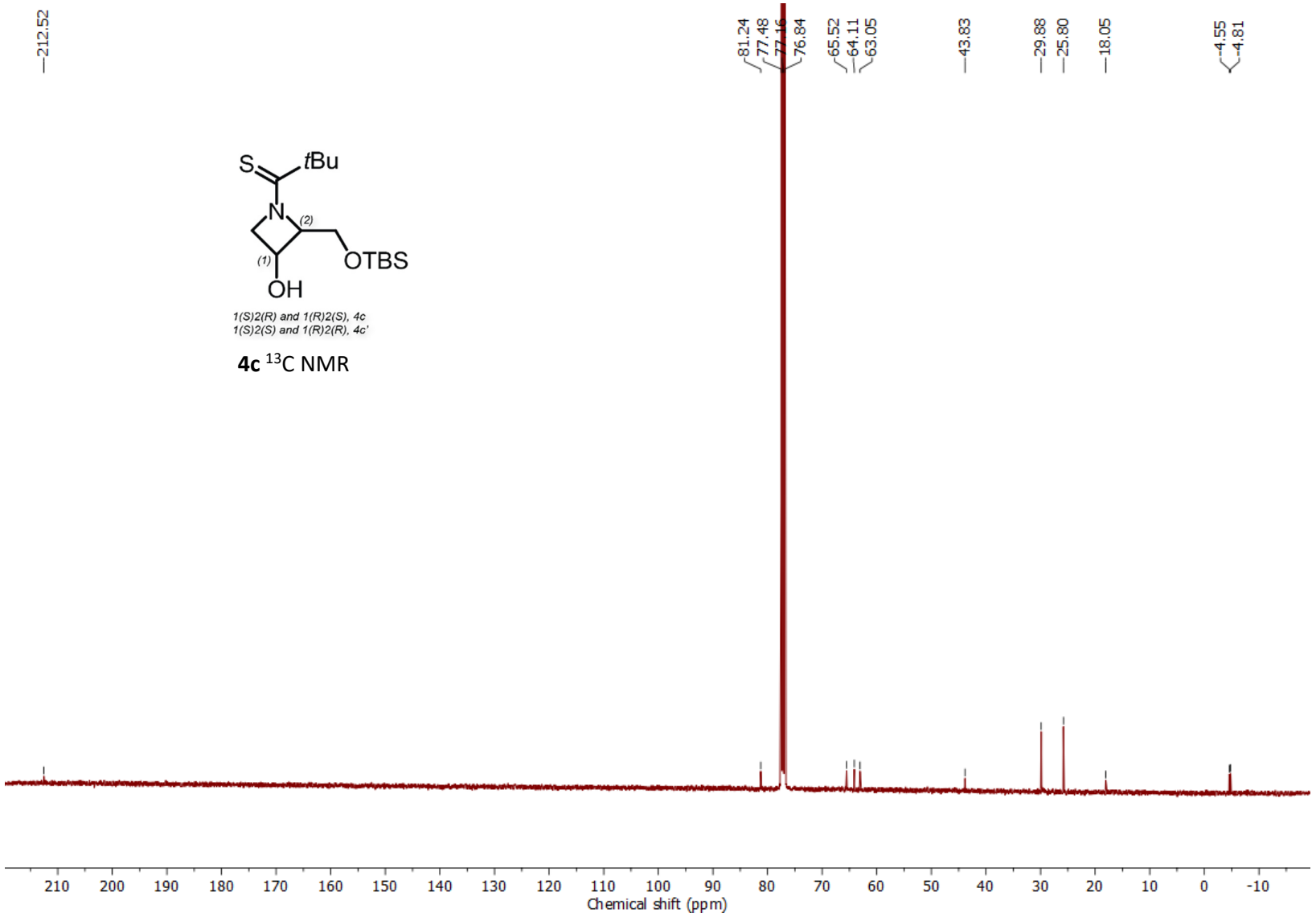
4.16
4.15
4.14
4.13
3.82
3.81
3.79
3.78
3.73
3.71
1.36
0.89
0.09
0.08
0.07
0.06
0.05
S
tBu
N
(2)
(1)
OTBS
OH
1(S)2(R) and 1(R)2(S), 4c
1(S)2(S) and 1(R)2(R), 4c'
1.95
3.16
2.16
7.91
9.00
2.36
2.85
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Chemical shift (ppm)

4c ^{1}H NMR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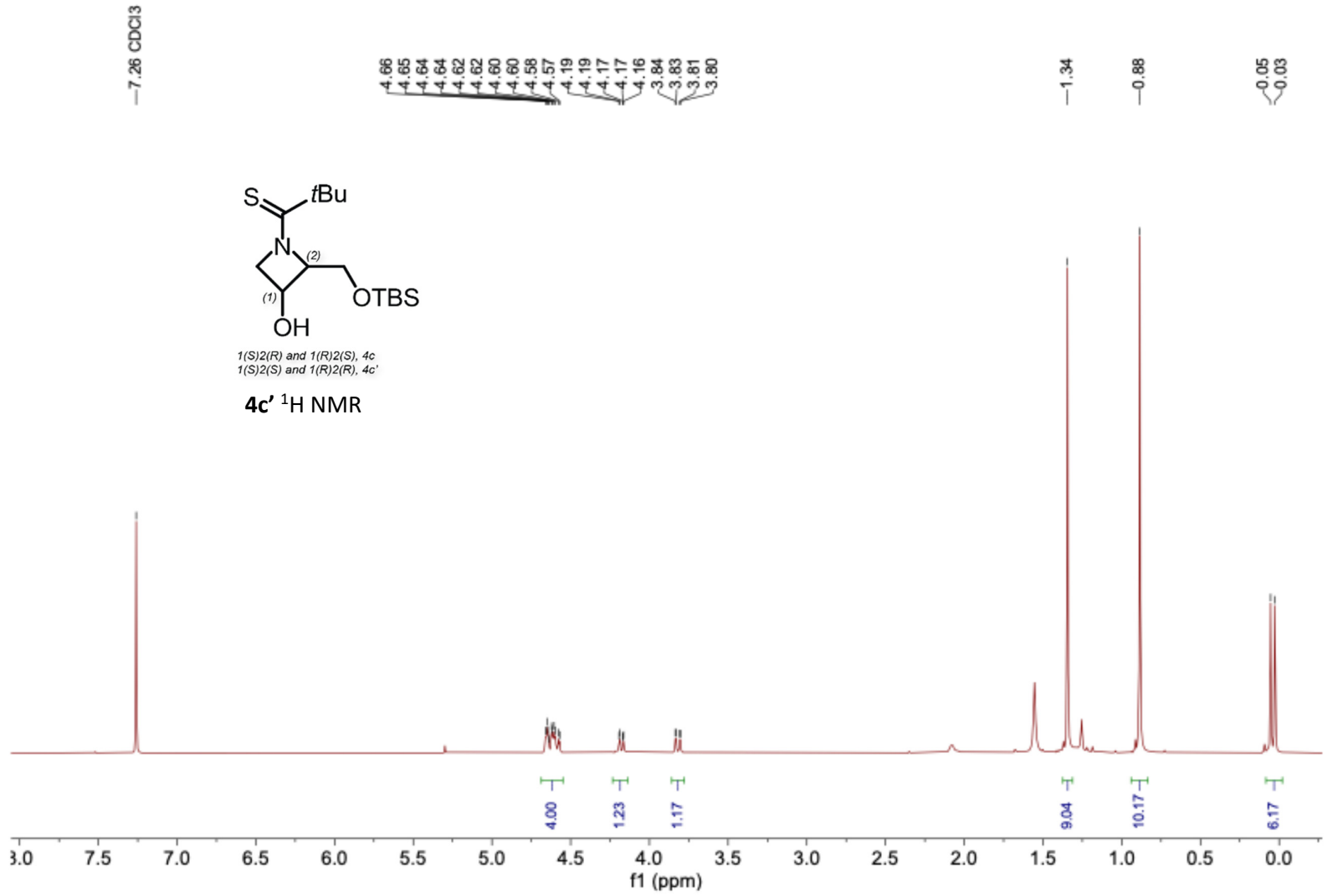
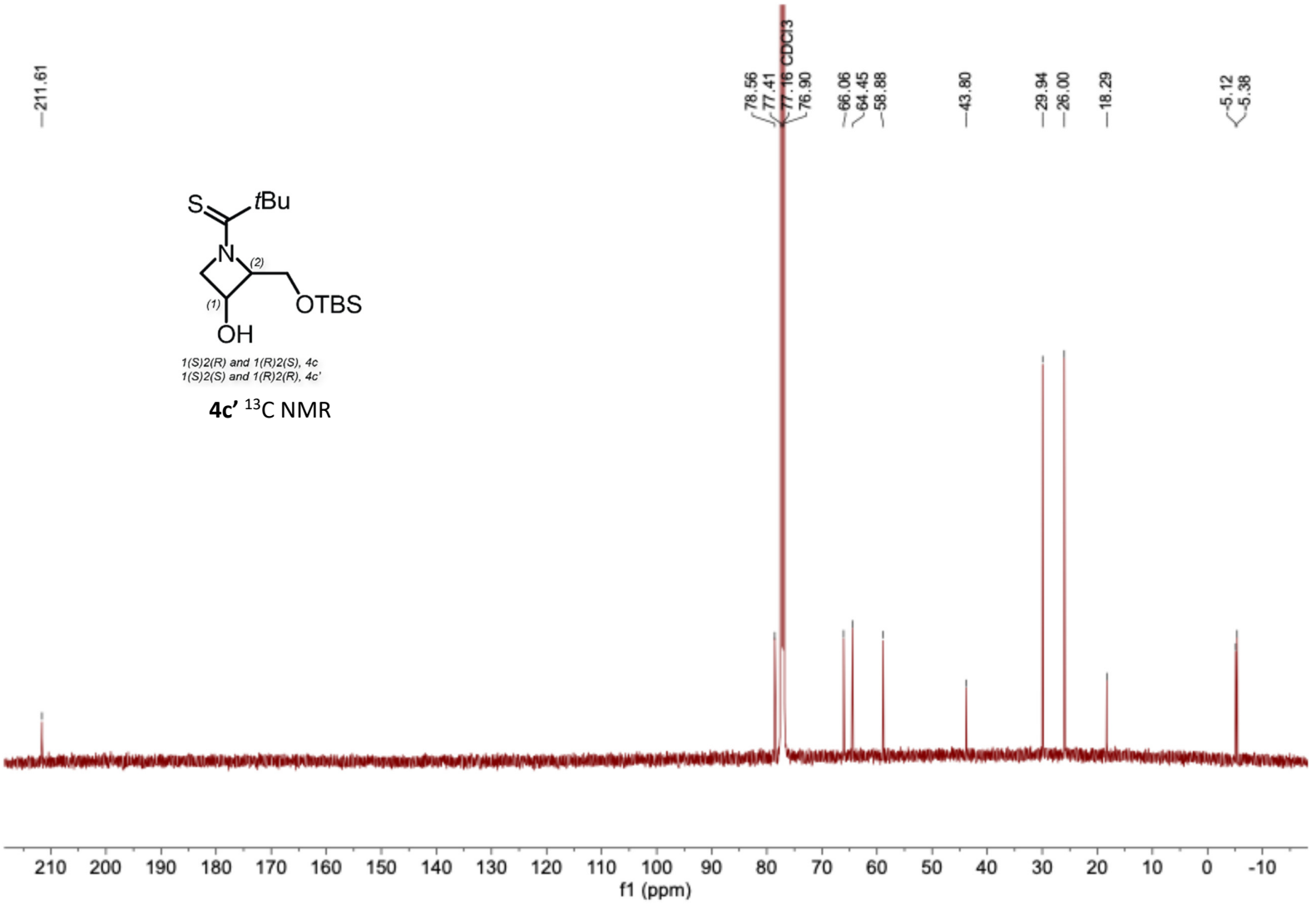
76.84
65.52
64.11
63.05
43.83
29.88
25.80
18.05
4.55
4.81
S
tBu
N
(2)
(1)
OTBS
OH
1(S)2(R) and 1(R)2(S), 4c
1(S)2(S) and 1(R)2(R), 4c'
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical shift (ppm)

4c ^{13}C NMR

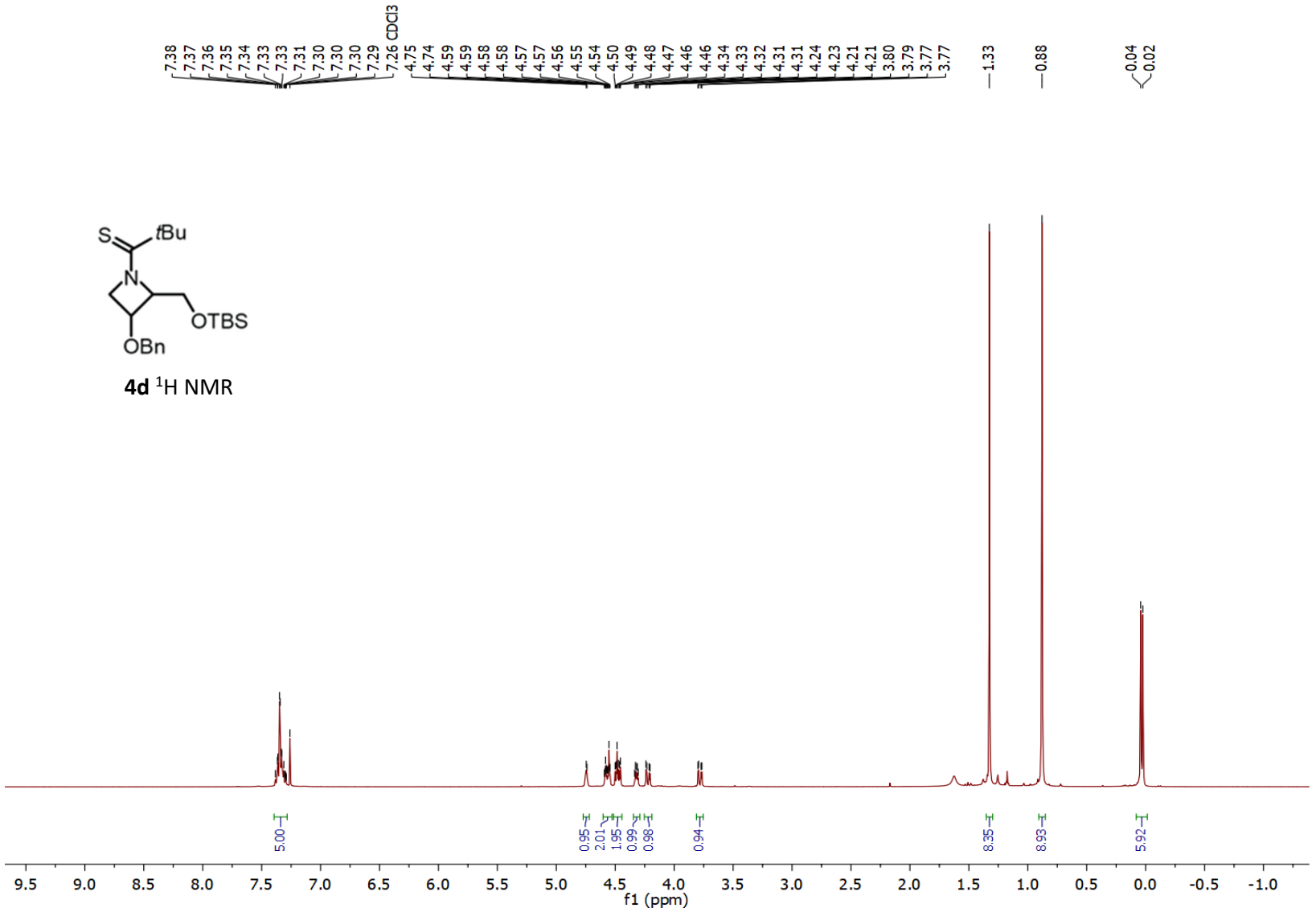


1(S)2(R) and 1(R)2(S), 4c
1(S)2(S) and 1(R)2(R), 4c'

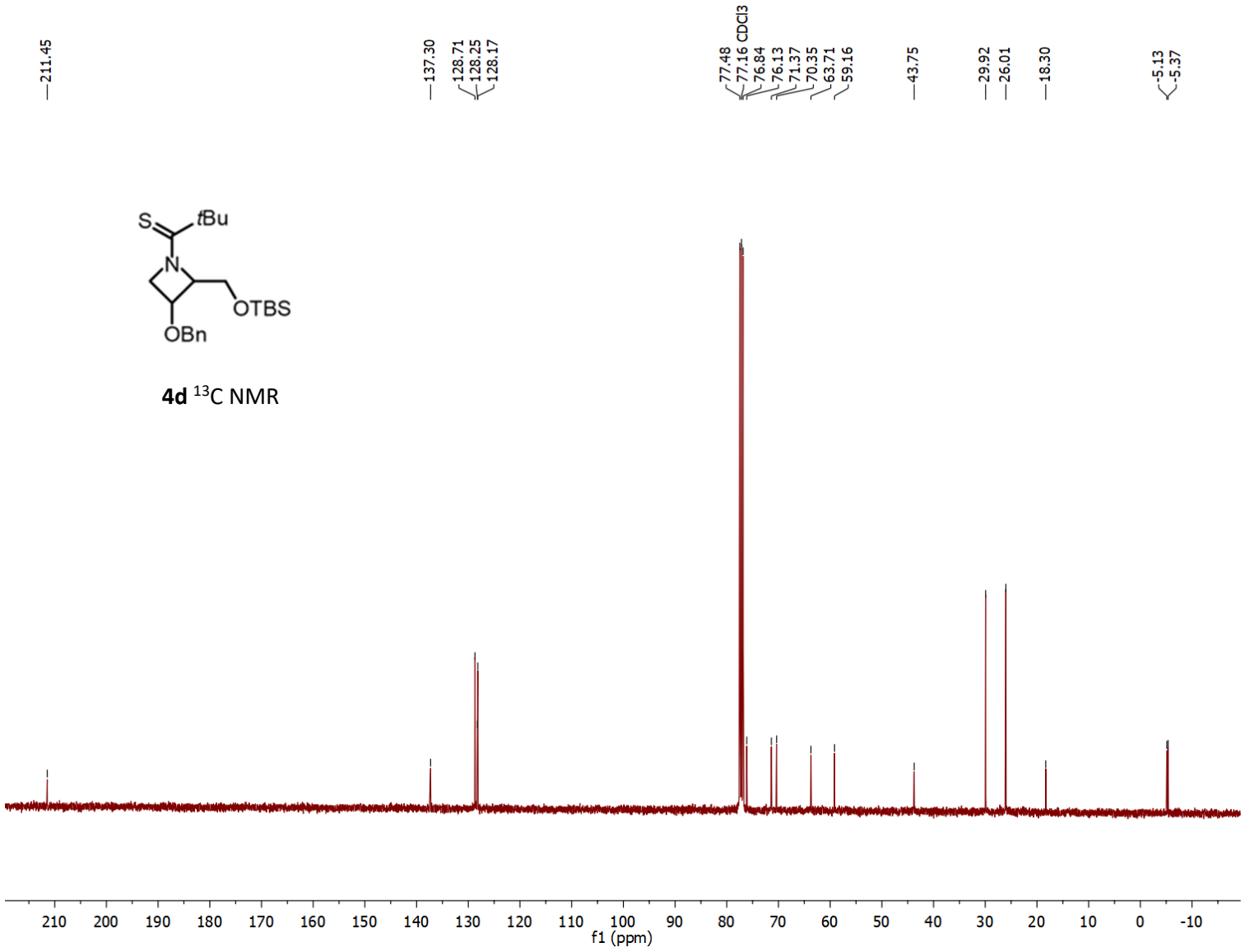
4c' ^{1}H NMR


211.61
78.56
77.41
77.16 CDCl3
76.90
66.06
64.45
58.88
43.80
29.94
26.00
18.29
5.12
-5.38
S
tBu
N
(2)
(1)
OTBS
OH
1(S)2(R) and 1(R)2(S), 4c
1(S)2(S) and 1(R)2(R), 4c'
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)

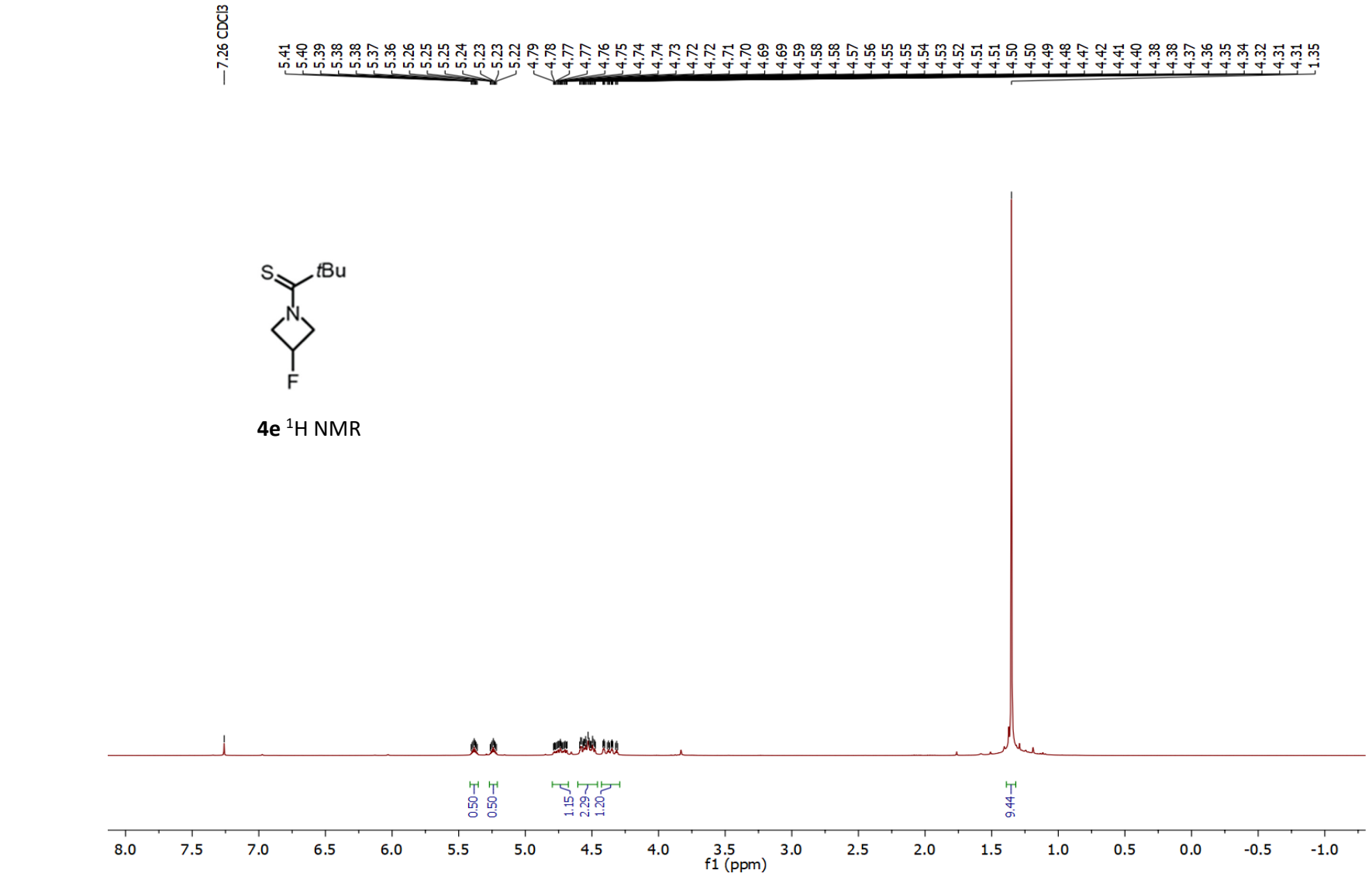
4c' ^{13}C NMR


7.38
7.37
7.36
7.35
7.34
7.33
7.33
7.31
7.30
7.30
7.30
7.29
7.26 CDCl3
4.75
4.74
4.59
4.59
4.58
4.58
4.57
4.57
4.56
4.55
4.54
4.50
4.49
4.48
4.47
4.46
4.46
4.34
4.33
4.32
4.31
4.31
4.24
4.23
4.21
4.21
3.80
3.79
3.77
3.77
1.33
0.88
0.04
0.02
S
tBu
N
OTBS
OBn
5.00
0.95
2.01
1.95
0.99
0.98
0.94
8.35
8.93
5.92
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
-1.0
f1 (ppm)

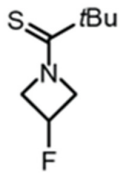
4d ^{1}H NMR


211.45
137.30
128.71
128.25
128.17
77.48
77.16 CDCl3
76.84
76.13
71.37
70.35
63.71
59.16
43.75
29.92
26.01
18.30
-5.13
-5.37
S
tBu
N
OTBS
OBn
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)

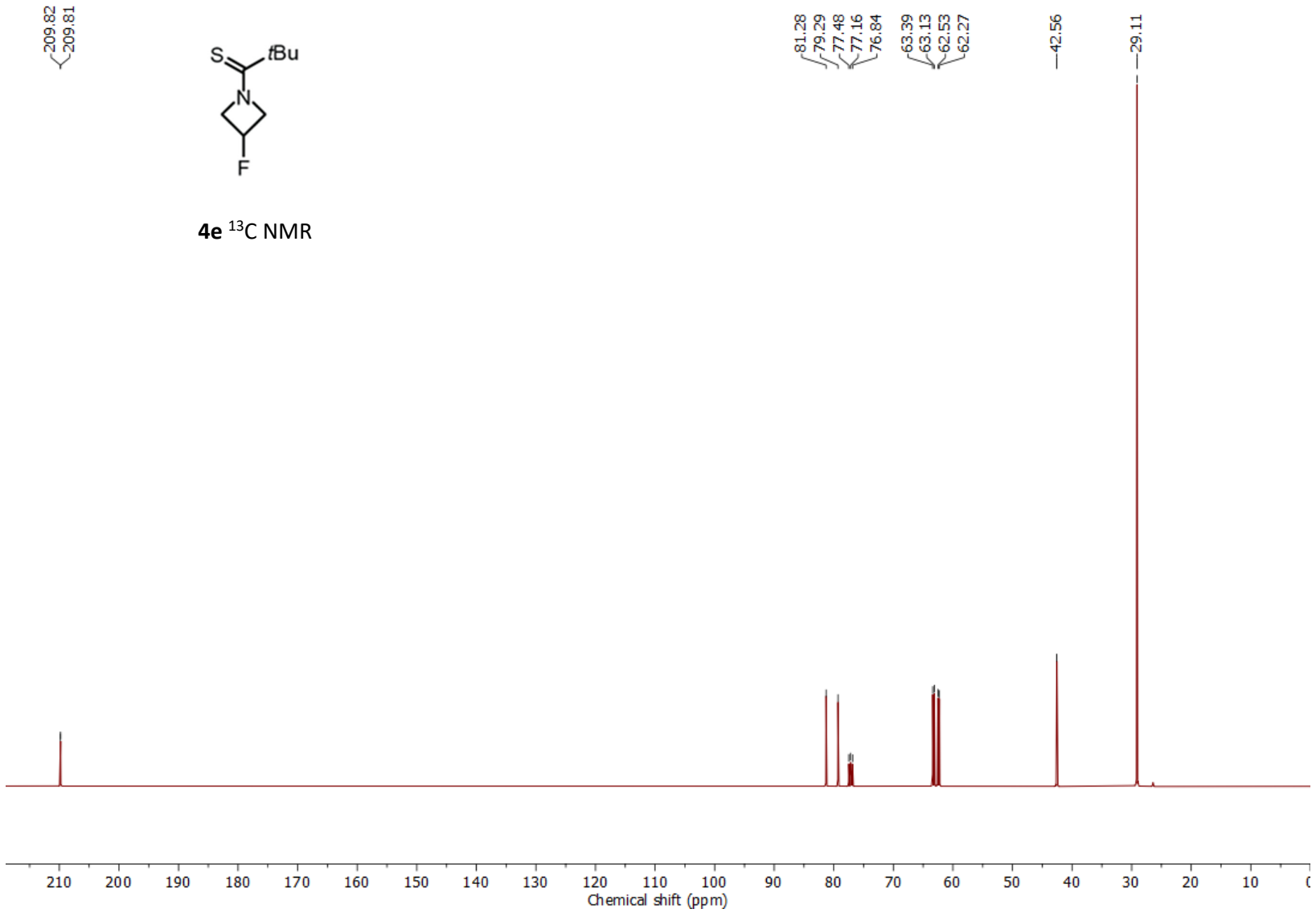
4d ^{13}C NMR


7.26 CDCl3
5.41
5.40
5.39
5.38
5.38
5.37
5.36
5.26
5.25
5.25
5.24
5.23
5.23
5.22
4.79
4.78
4.77
4.77
4.76
4.75
4.74
4.74
4.73
4.72
4.72
4.71
4.70
4.69
4.69
4.59
4.58
4.58
4.57
4.56
4.55
4.55
4.54
4.53
4.52
4.51
4.51
4.50
4.50
4.49
4.48
4.47
4.42
4.41
4.40
4.38
4.38
4.37
4.36
4.35
4.34
4.32
4.31
4.31
1.35
S
tBu
N
F
0.50
0.50
1.15
2.29
1.20
9.44
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
-1.0
f1 (ppm)

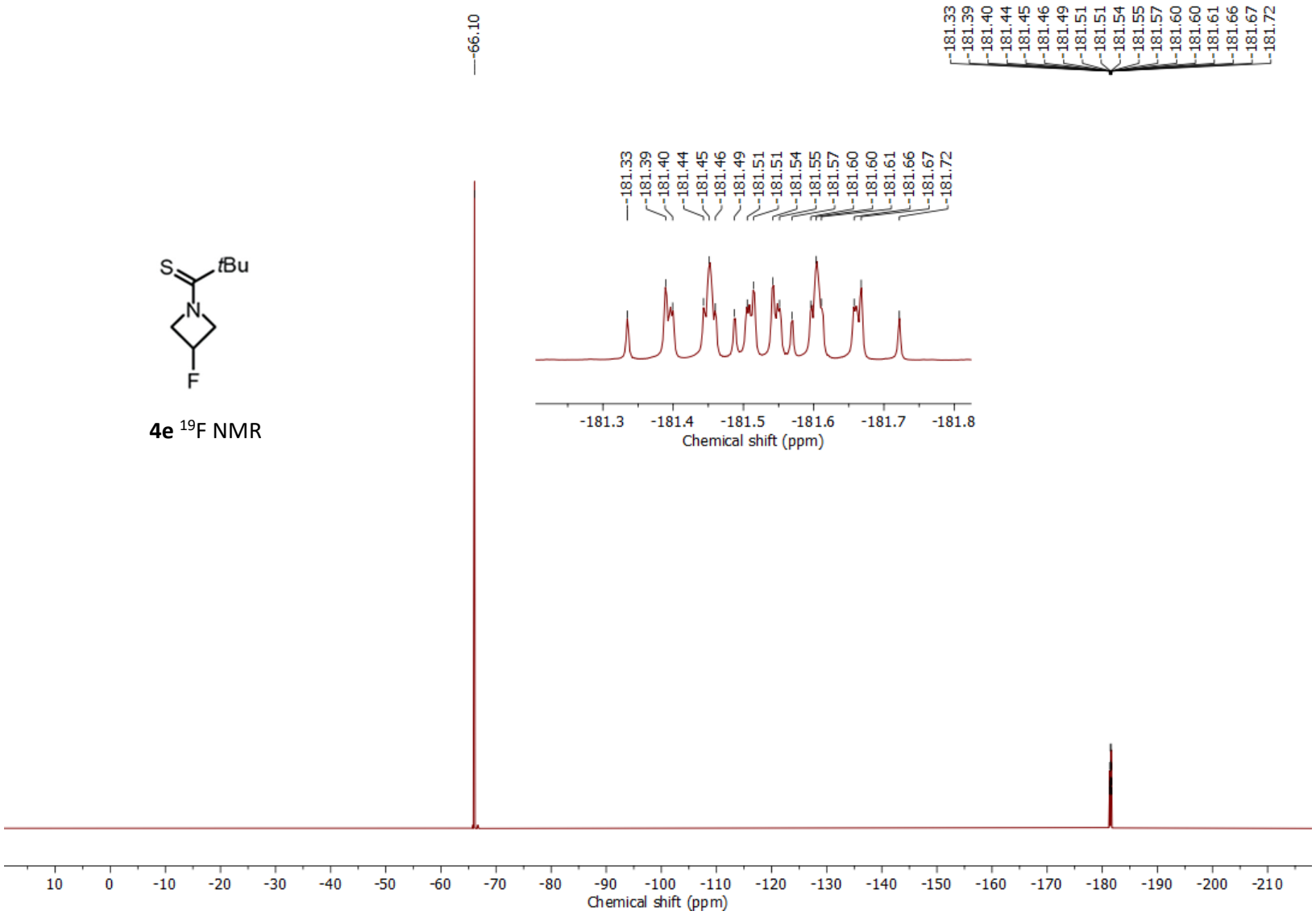
4e ^{1}H NMR



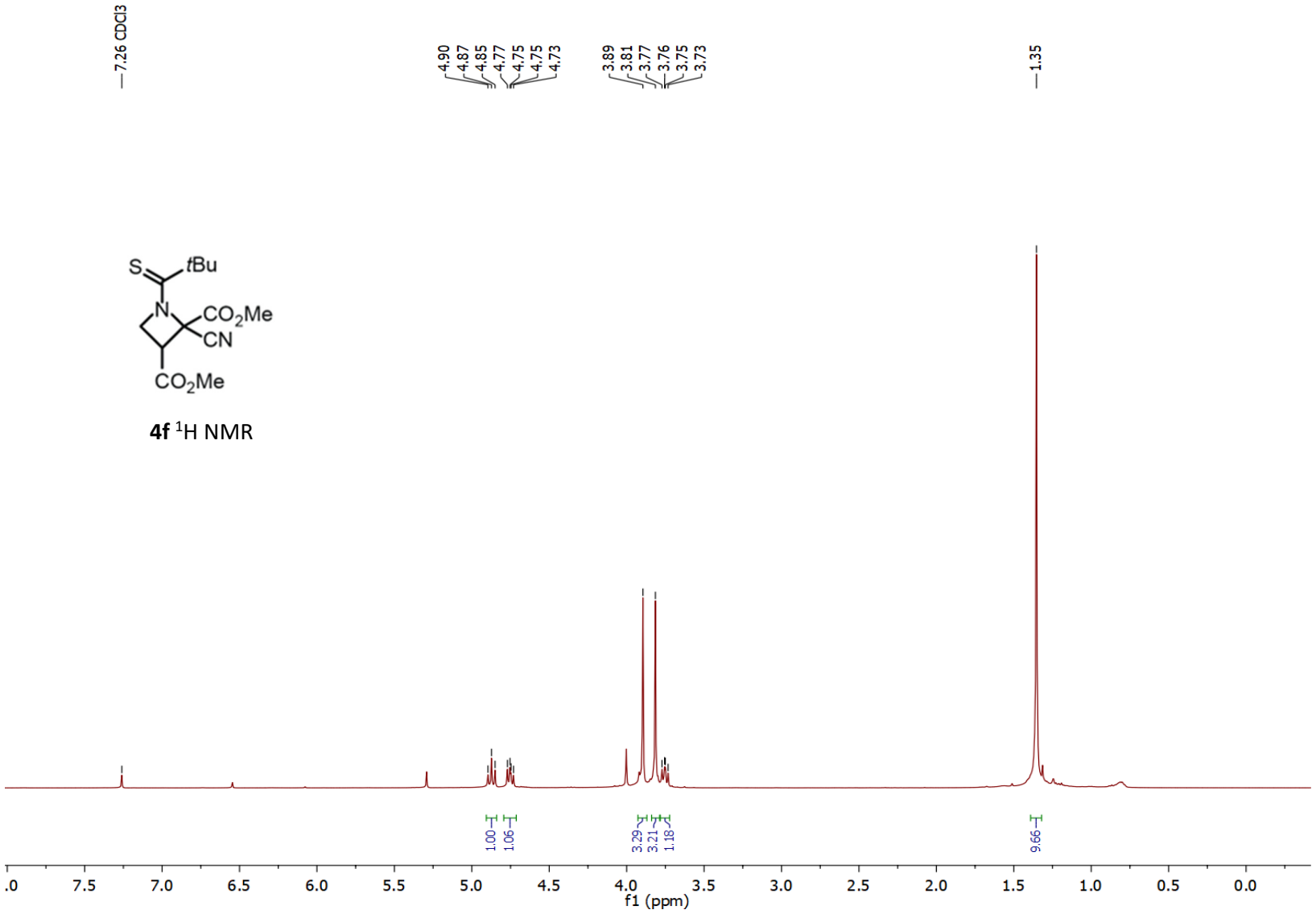
4e ^{13}C NMR (Dept135)


209.82
209.81
81.28
79.29
77.48
77.16
76.84
63.39
63.13
62.53
62.27
42.56
29.11
S
tBu
N
F
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical shift (ppm)

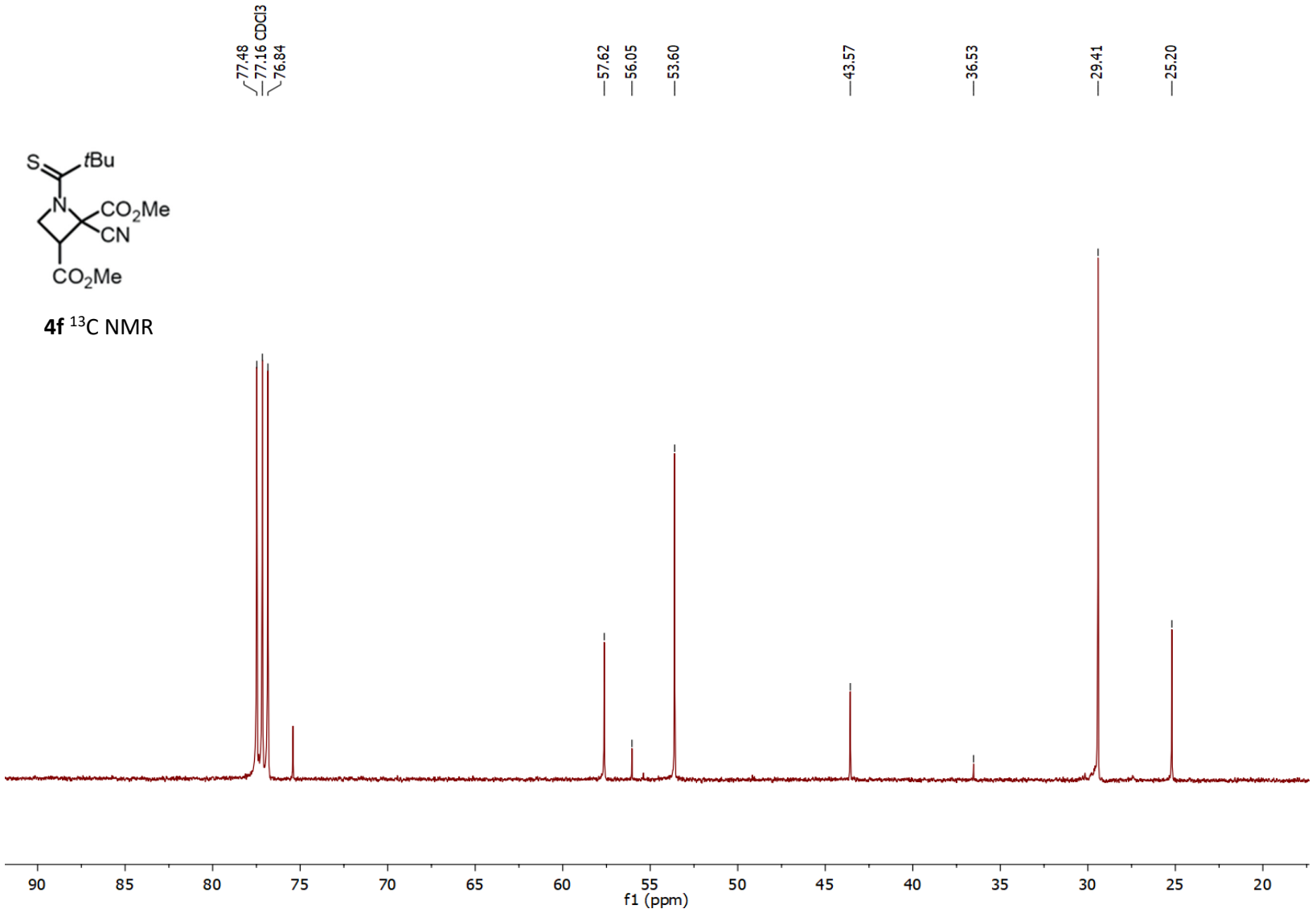
4e ^{13}C NMR


-66.10
-181.33
-181.39
-181.40
-181.44
-181.45
-181.46
-181.49
-181.51
-181.51
-181.54
-181.55
-181.57
-181.60
-181.60
-181.61
-181.66
-181.67
-181.72
S
tBu
N
F
-181.3
-181.4
-181.5
-181.6
-181.7
-181.8
Chemical shift (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
Chemical shift (ppm)

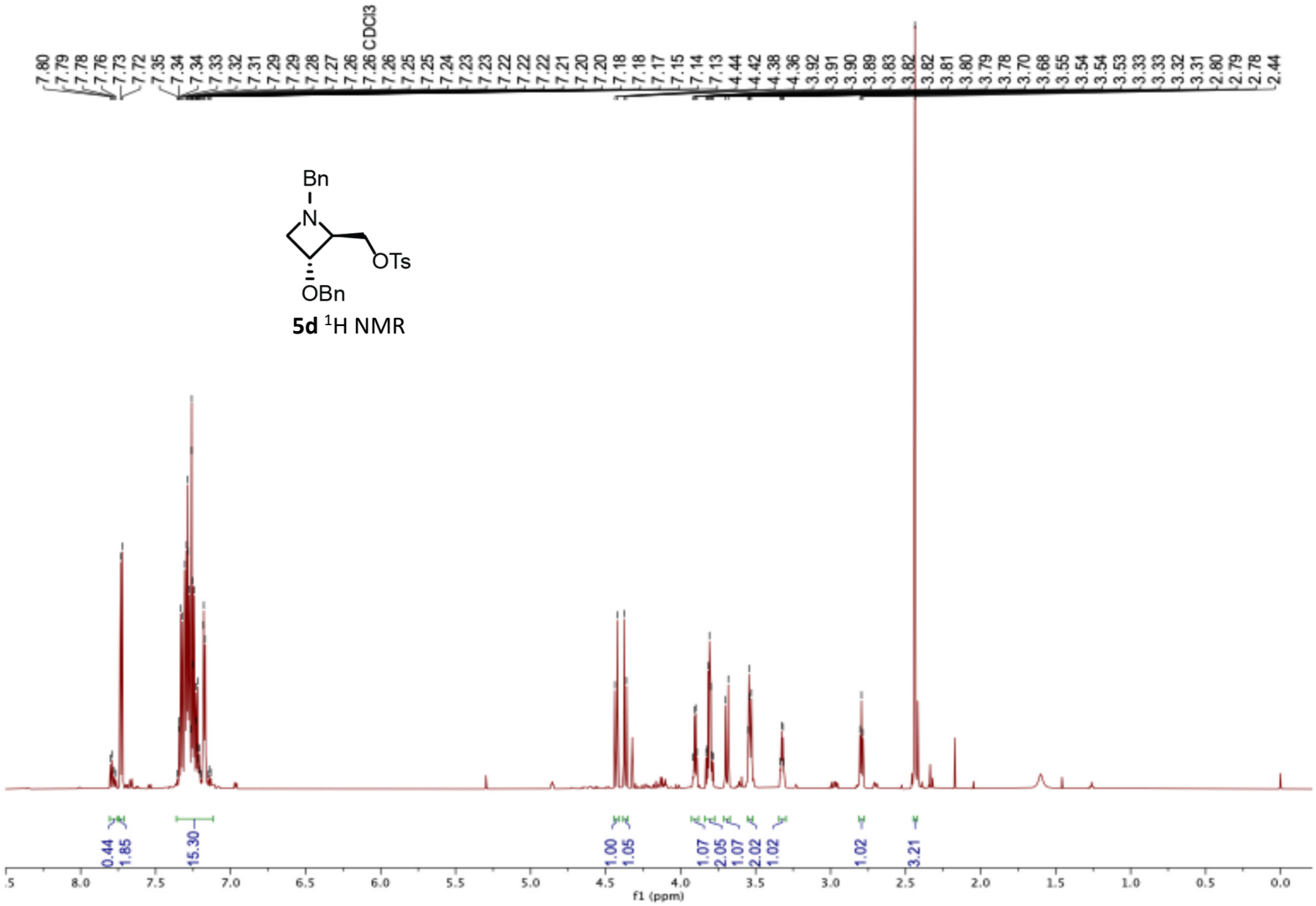
4e ^{19}F NMR


7.26 CDCl3
4.90
4.87
4.85
4.77
4.75
4.75
4.73
3.89
3.81
3.77
3.76
3.75
3.73
1.35
S
tBu
N
CO2Me
CN
CO2Me
1.00
1.06
3.29
3.21
1.18
9.66
f1 (ppm)

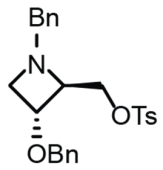
4f ^{1}H NMR


77.48
77.16 CDCl3
76.84
57.62
56.05
53.60
43.57
36.53
29.41
25.20
S
tBu
N
CO2Me
CN
CO2Me
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
f1 (ppm)

4f ^{13}C NMR

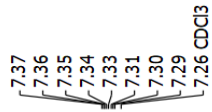

7.80 7.79 7.78 7.76 7.73 7.72 7.35 7.34 7.34 7.33 7.32 7.31 7.29 7.29 7.28 7.27 7.26 CDCl3 7.26 7.25 7.25 7.24 7.23 7.23 7.22 7.22 7.22 7.21 7.20 7.20 7.18 7.18 7.17 7.15 7.14 7.13 4.44 4.42 4.38 4.36 3.92 3.91 3.90 3.89 3.83 3.82 3.82 3.81 3.80 3.79 3.78 3.70 3.68 3.55 3.54 3.54 3.53 3.33 3.33 3.32 3.31 2.80 2.79 2.78 2.44
Bn
N
OTs
OBn
0.44 1.85 15.30 1.00 1.05 1.07 2.05 1.07 2.02 1.02 1.02 3.21
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)

5d ^{1}H NMR


Bn
N
OTs
OBn

5d ^{13}C NMR

144.89
137.71
137.62
133.01
130.02
129.97
128.85
128.63
128.50
128.47
128.08
128.02
127.41
77.34
77.16 CDCl3
76.98
71.61
71.11
70.96
70.63
62.81
59.35
21.79
f1 (ppm)

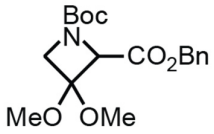

7.37
7.36
7.35
7.34
7.33
7.31
7.30
7.29
7.26 CDCl3


5.25

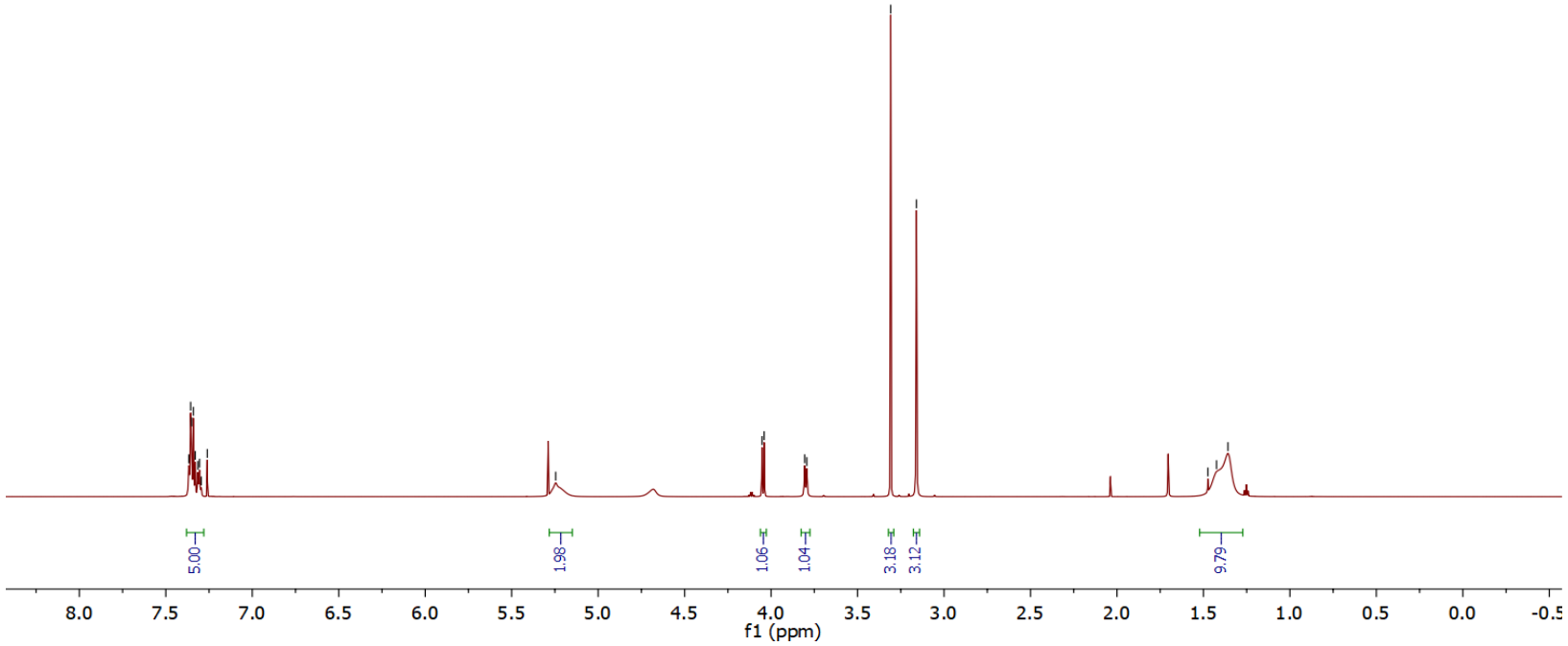

4.05
4.04
3.81
3.79

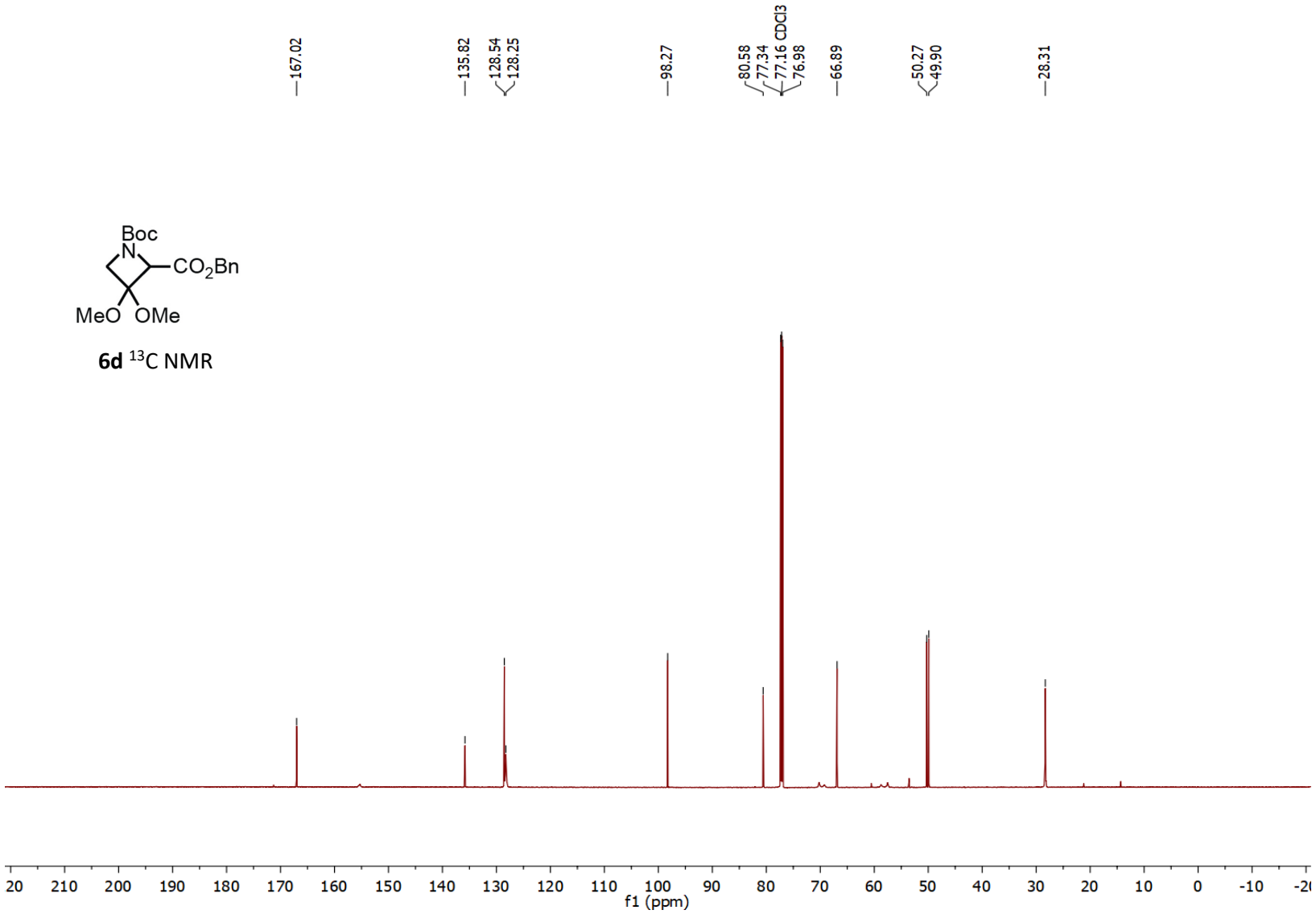

3.31
3.16

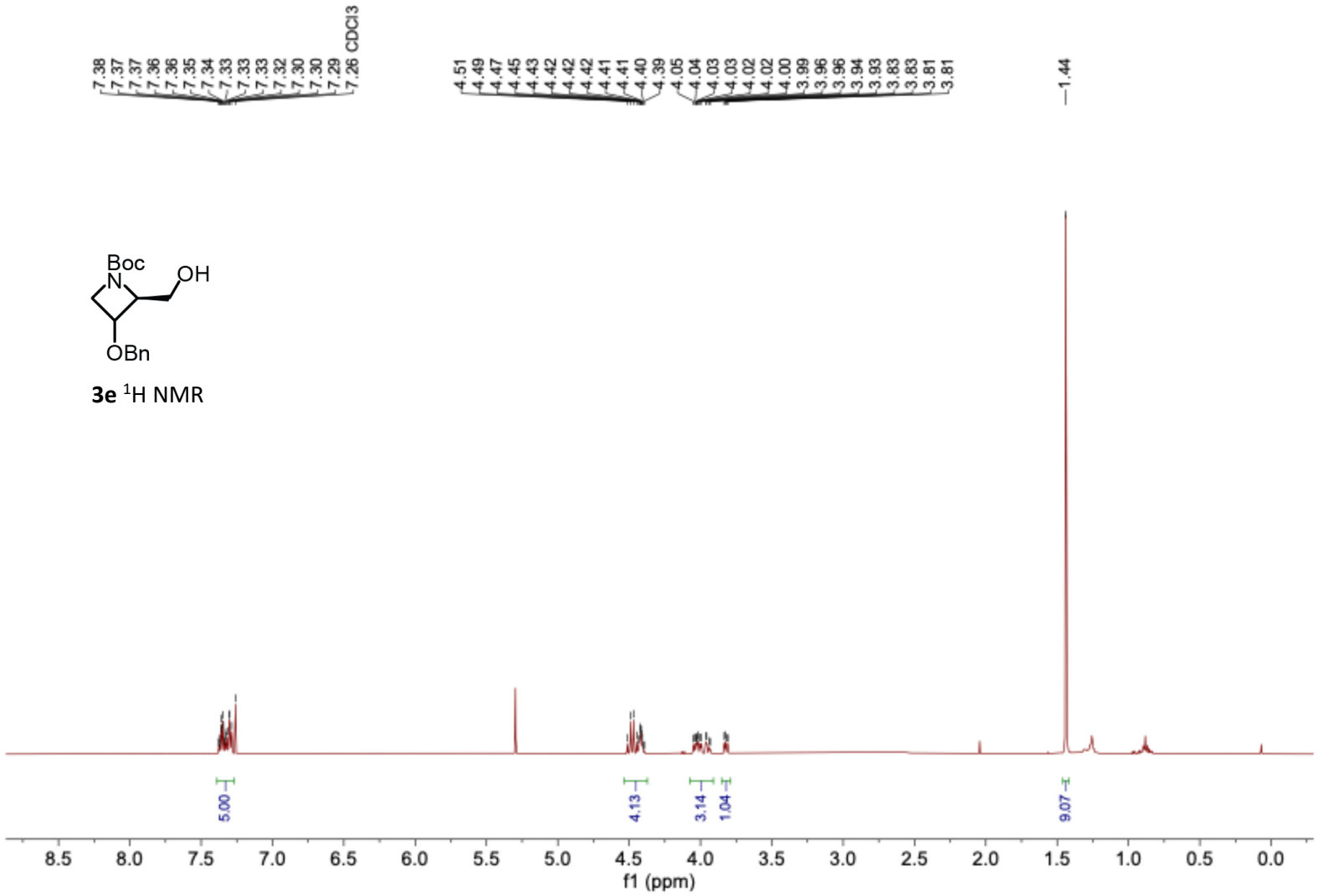

1.47
1.42
1.36


Boc
N
CO2Bn
MeO
OMe

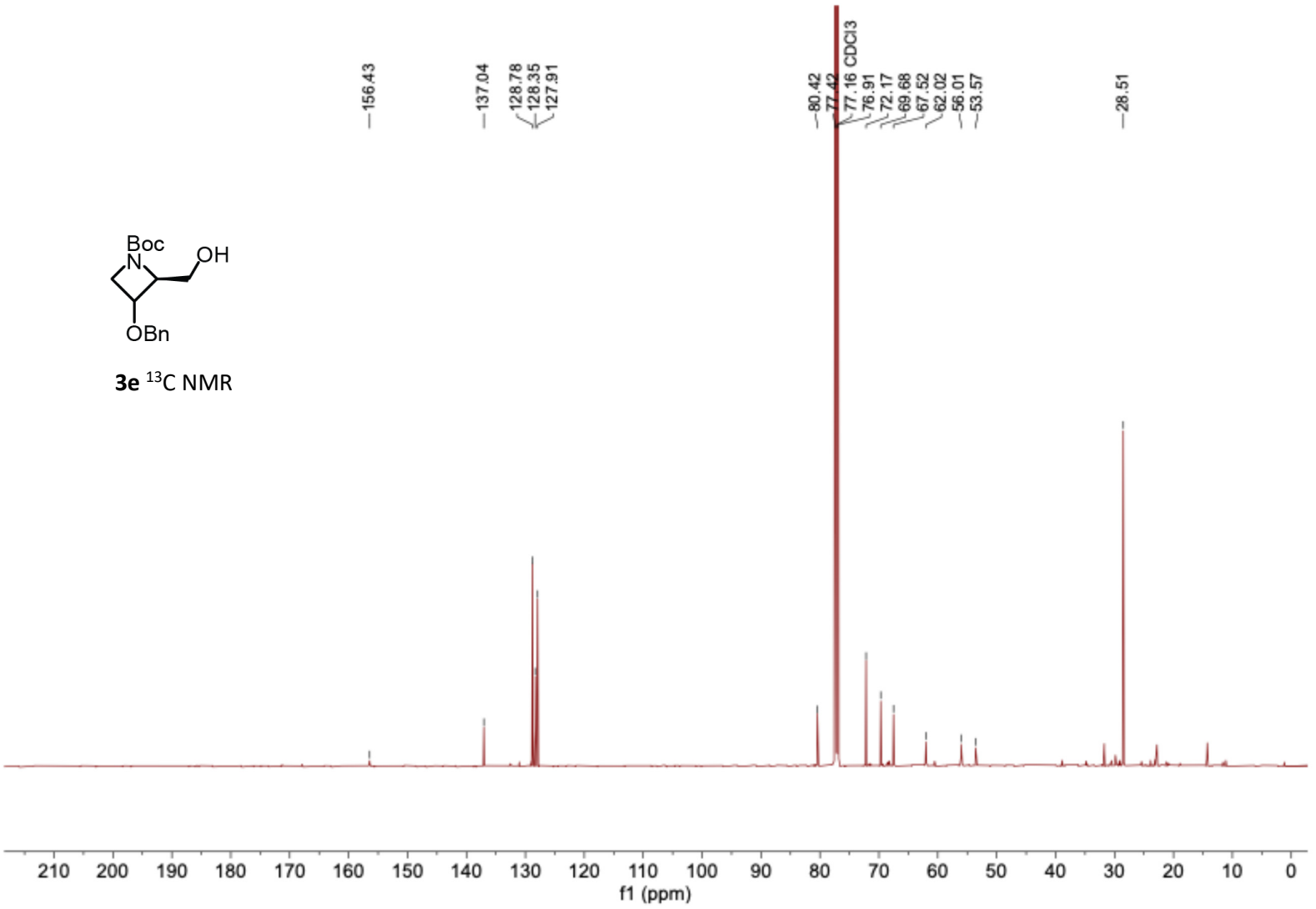
6d ^{1}H NMR


5.00
1.98
1.06
1.04
3.18
3.12
9.79
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)

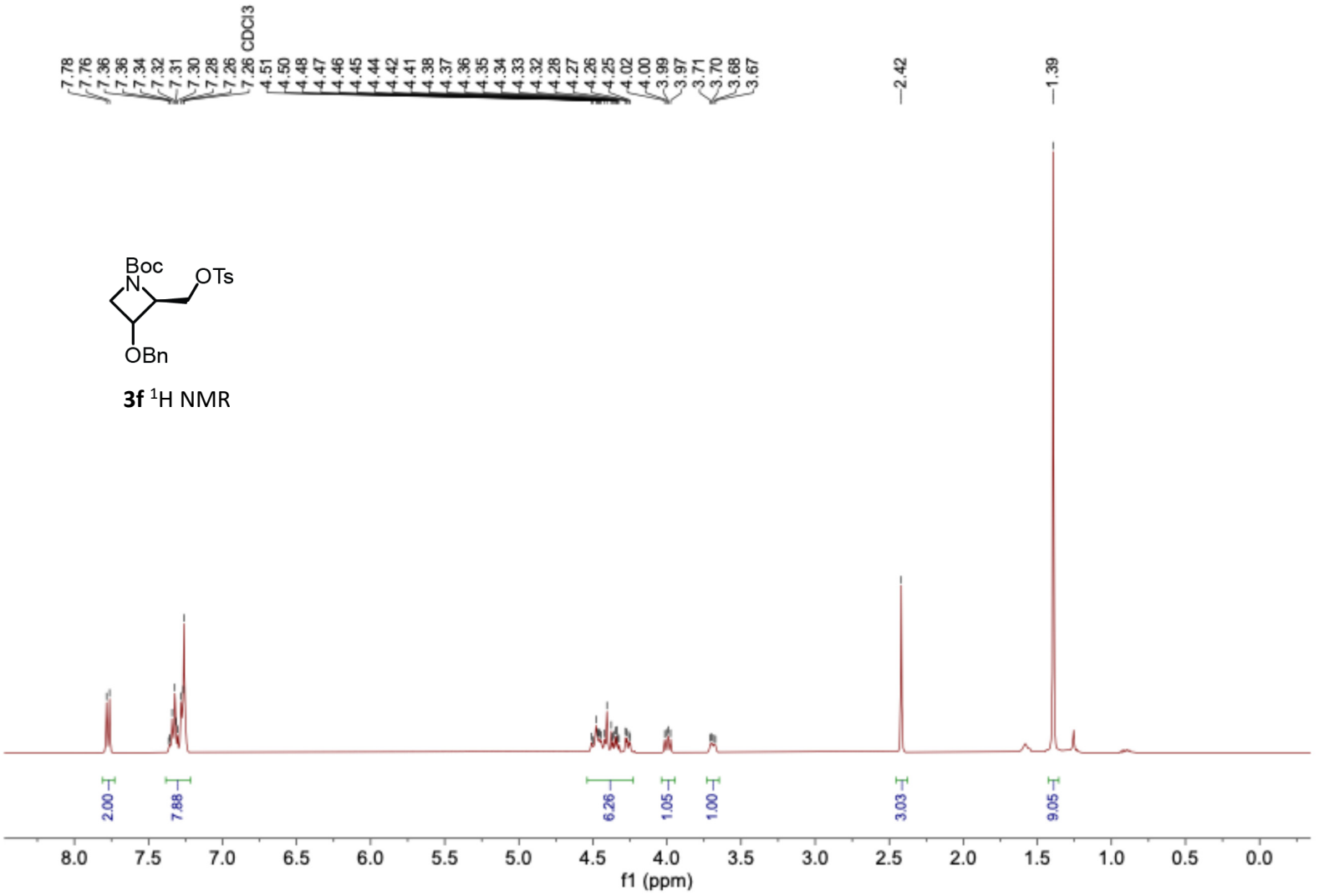

167.02
135.82
128.54
128.25
98.27
80.58
77.34
77.16 CDCl3
76.98
66.89
50.27
49.90
28.31
Boc
N
CO2Bn
MeO OMe
6d 13C NMR
f1 (ppm)


7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.33
7.33
7.33
7.32
7.30
7.30
7.29
7.26 CDCl3
4.51
4.49
4.47
4.45
4.43
4.42
4.42
4.42
4.41
4.41
4.40
4.39
4.05
4.04
4.03
4.03
4.02
4.02
4.00
3.99
3.96
3.96
3.94
3.93
3.83
3.83
3.81
3.81
1.44
Boc
N
OH
OBn
5.00
4.13
3.14
1.04
9.07
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)

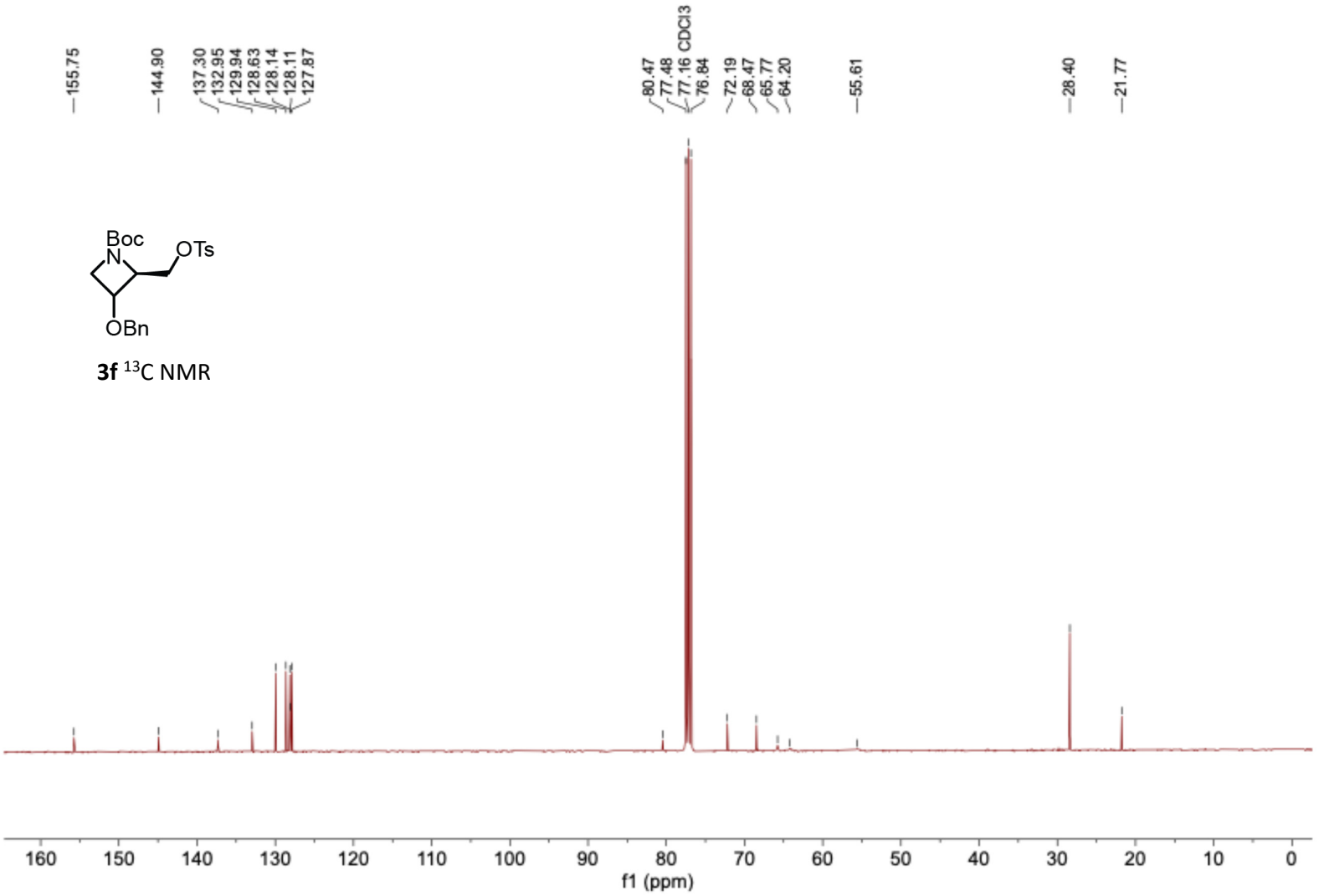
3e ^{1}H NMR


156.43
137.04
128.78
128.35
127.91
80.42
77.42
77.16 CDCl3
76.91
72.17
69.68
67.52
62.02
56.01
53.57
28.51
Boc
N
OH
OBn
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

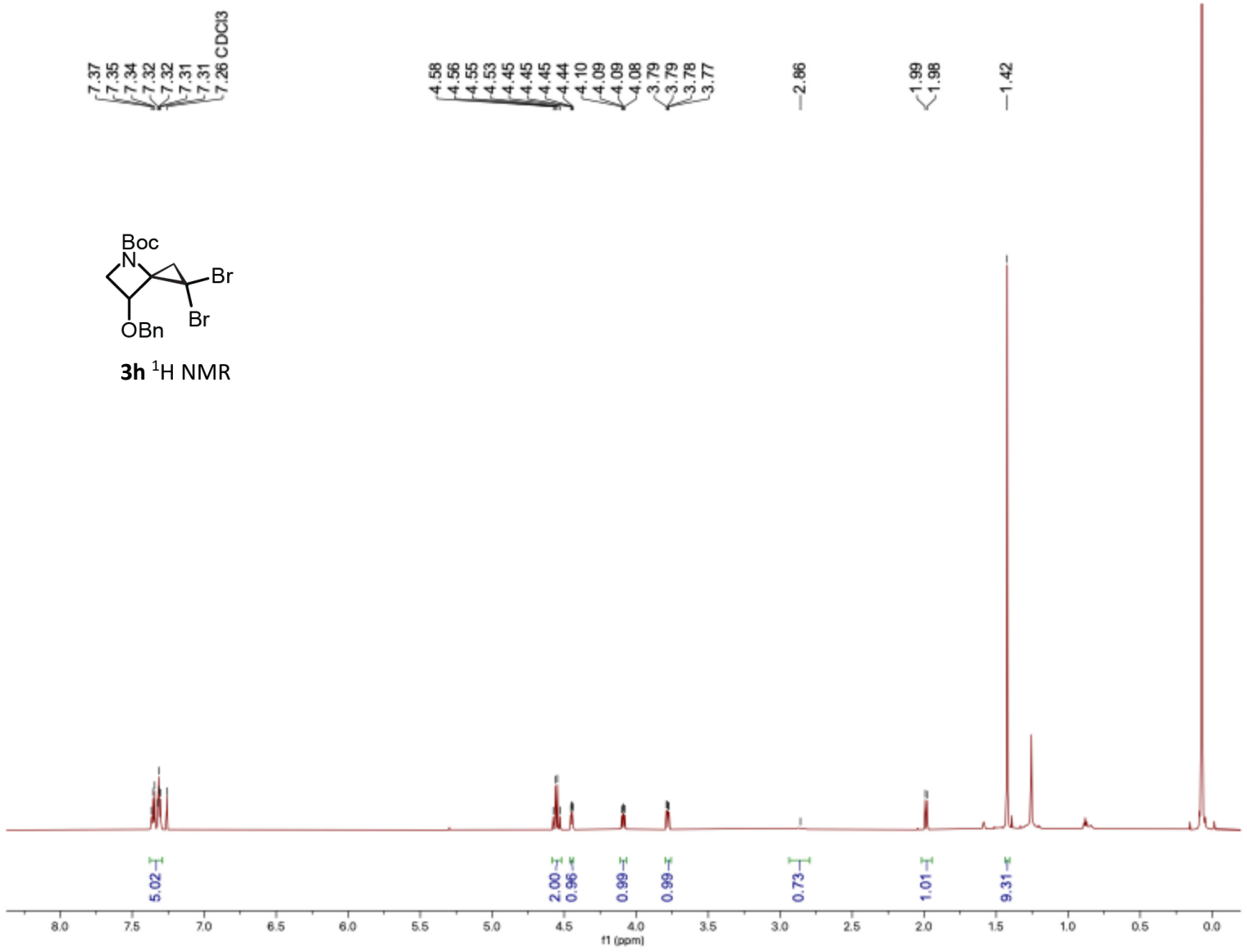
3e ^{13}C NMR


7.78
7.76
7.36
7.36
7.34
7.32
7.31
7.30
7.28
7.26
CDCl3
4.51
4.50
4.48
4.47
4.46
4.45
4.44
4.42
4.41
4.38
4.37
4.36
4.35
4.34
4.33
4.32
4.28
4.27
4.26
4.25
4.02
4.00
3.99
3.97
3.71
3.70
3.68
3.67
2.42
1.39
Boc
N
OTs
OBn
2.00
7.88
6.26
1.05
1.00
3.03
9.05
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)

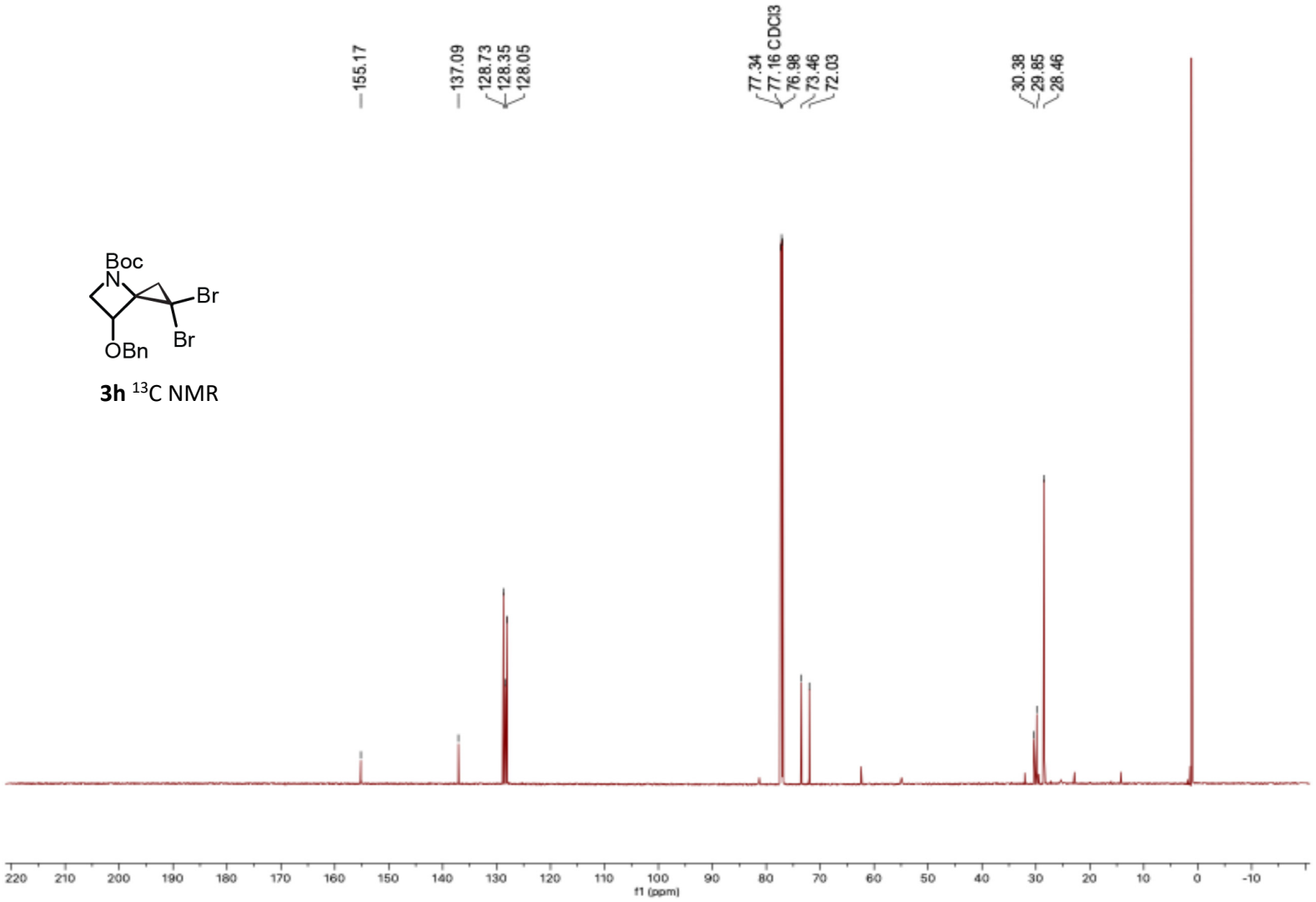
3f ^{1}H NMR


155.75
144.90
137.30
132.95
129.94
128.63
128.14
128.11
127.87
80.47
77.48
77.16 CDCl3
76.84
72.19
68.47
65.77
64.20
55.61
28.40
21.77
Boc
N
OTs
OBn
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

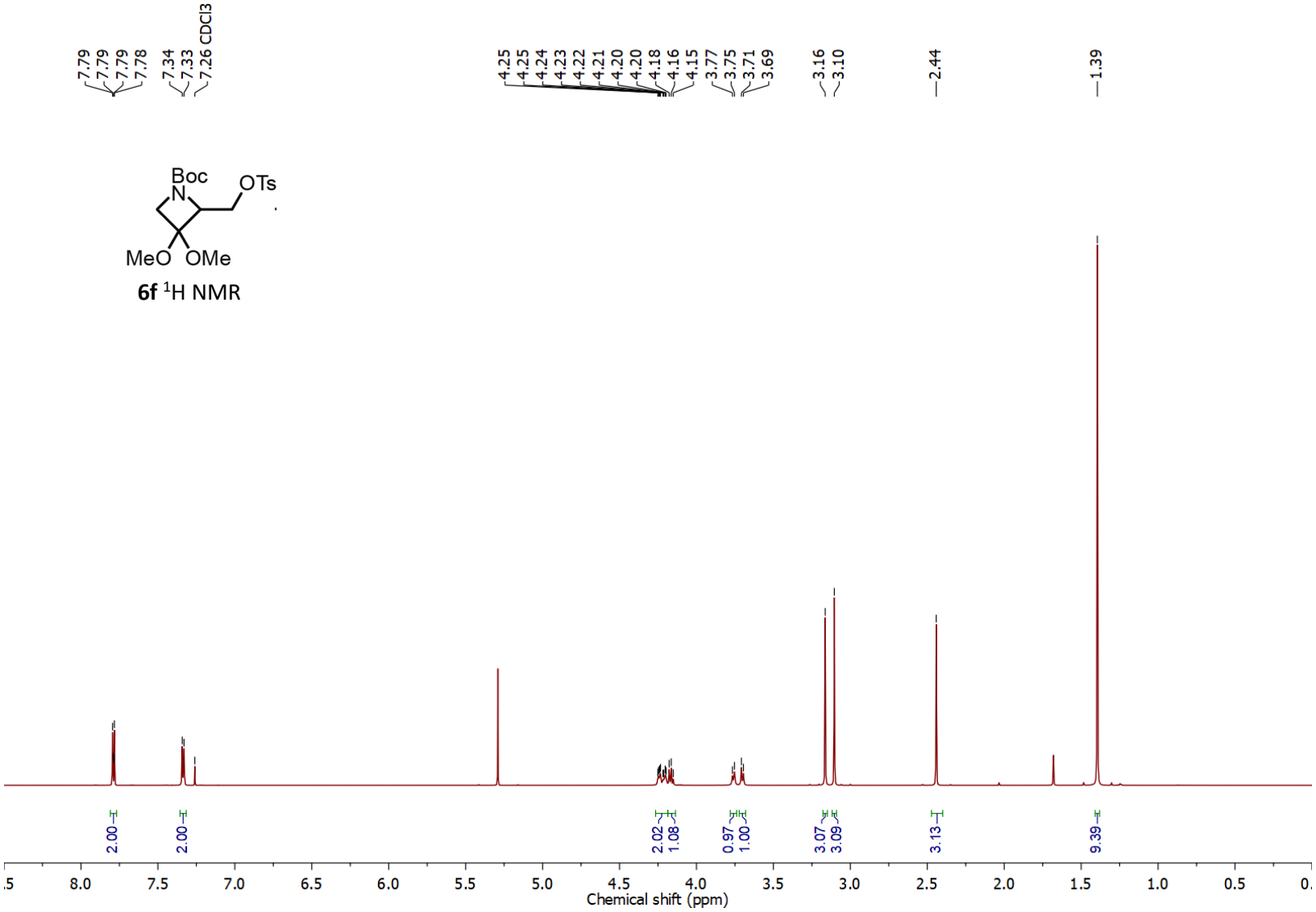
3f ^{13}C NMR


7.37
7.35
7.34
7.32
7.32
7.31
7.31
7.26 CDCl3
4.58
4.56
4.55
4.53
4.45
4.45
4.45
4.44
4.10
4.09
4.09
4.08
3.79
3.79
3.78
3.77
2.86
1.99
1.98
1.42
Boc
N
Br
Br
OBn
5.02
2.00
0.96
0.99
0.99
0.73
1.01
9.31
f1 (ppm)

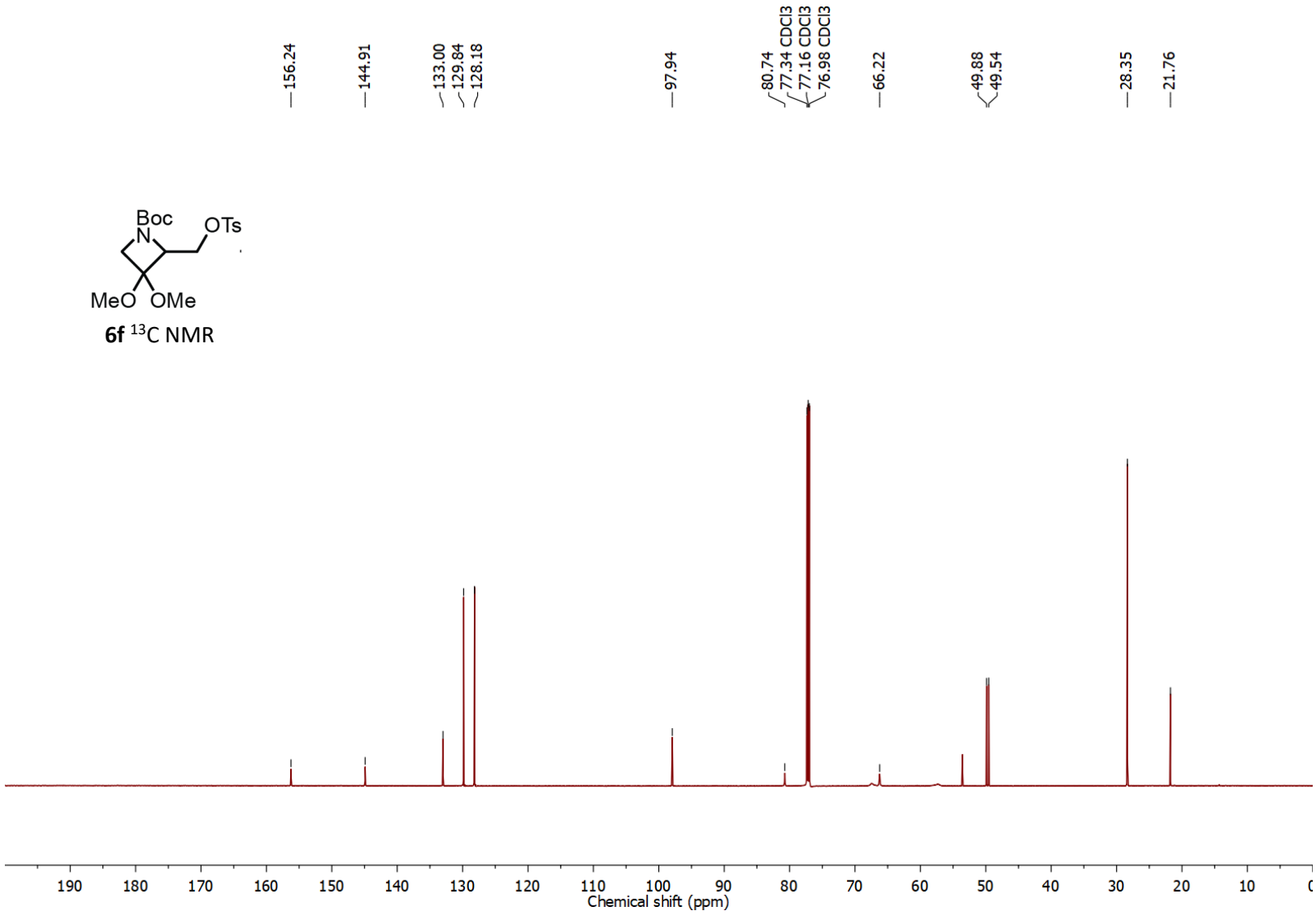
3h ^{1}H NMR


155.17
137.09
128.73
128.35
128.05
77.34
77.16 CDCl3
76.98
73.46
72.03
30.38
29.85
28.46
Boc
N
Br
Br
OBn
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)

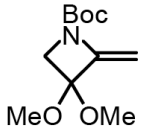
3h ^{13}C NMR


7.79
7.79
7.79
7.78
7.34
7.33
7.26 CDCl3
4.25
4.25
4.24
4.23
4.22
4.21
4.20
4.20
4.18
4.16
4.15
3.77
3.75
3.71
3.69
3.16
3.10
2.44
1.39
Boc
N
OTs
MeO
OMe
2.00
2.00
2.02
1.08
0.97
1.00
3.07
3.09
3.13
9.39
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
Chemical shift (ppm)

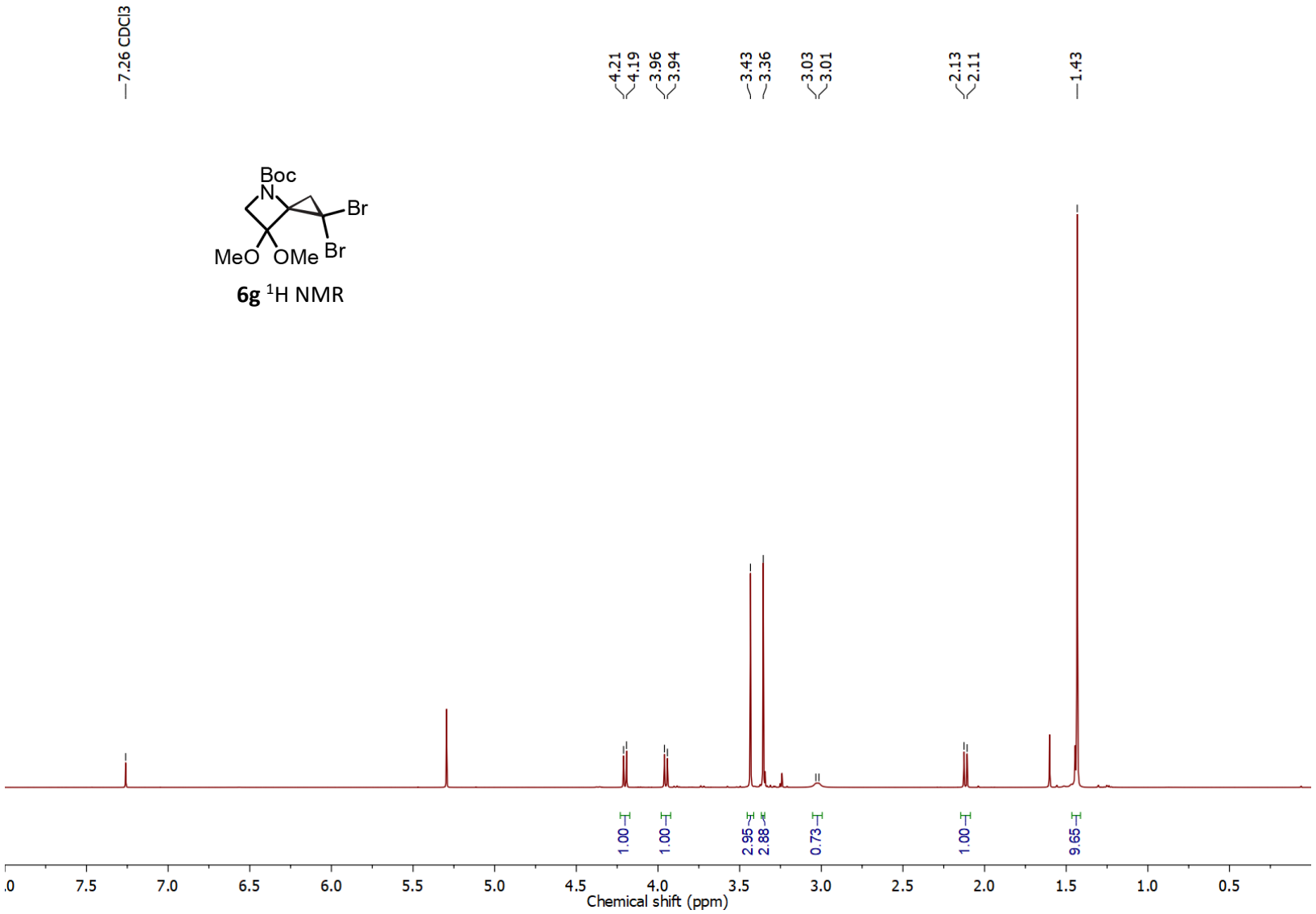
6f ^{1}H NMR


156.24
144.91
133.00
129.84
128.18
97.94
80.74
77.34 CDCl3
77.16 CDCl3
76.98 CDCl3
66.22
49.88
49.54
28.35
21.76
Boc
N
OTs
MeO
OMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical shift (ppm)

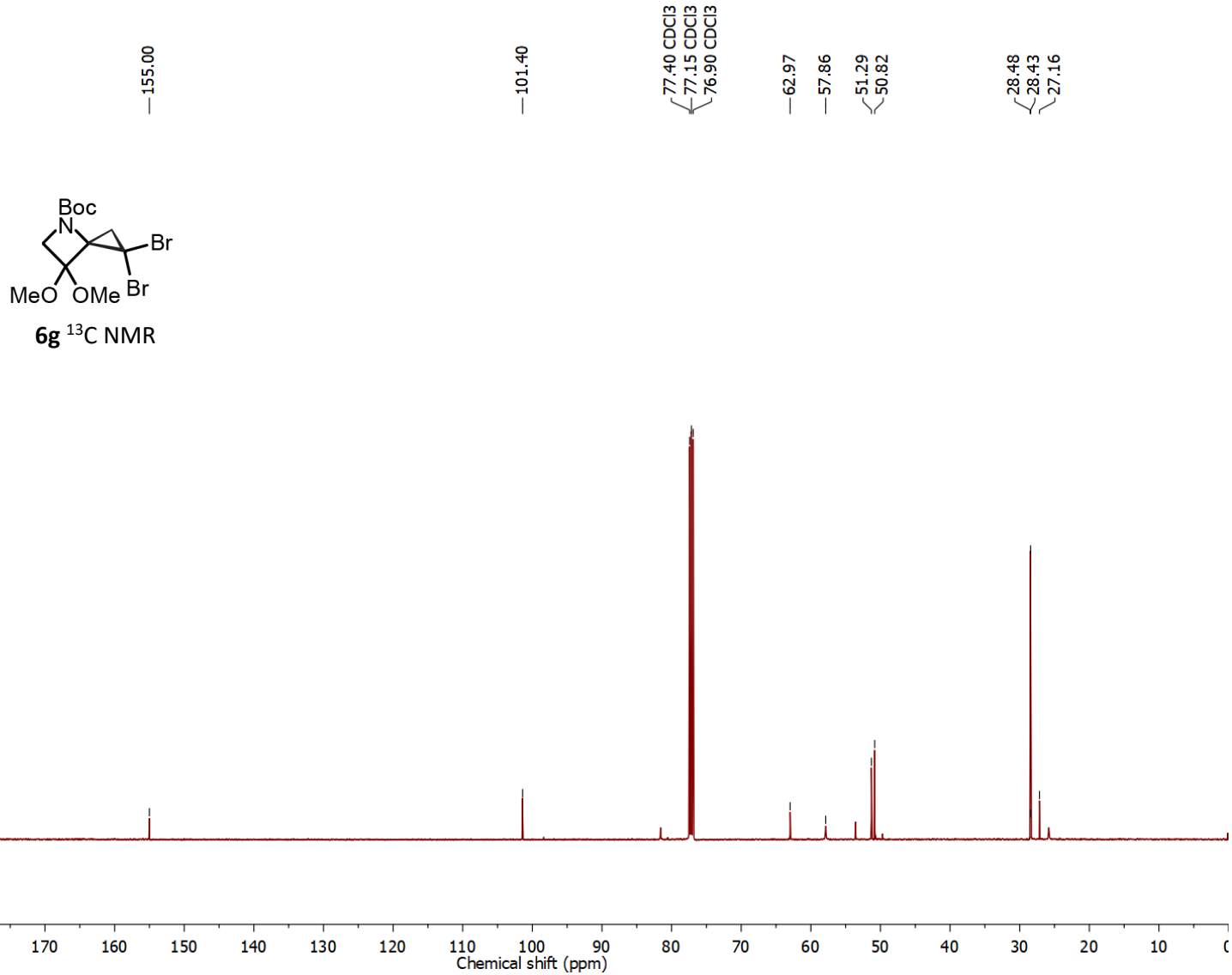
6f ^{13}C NMR



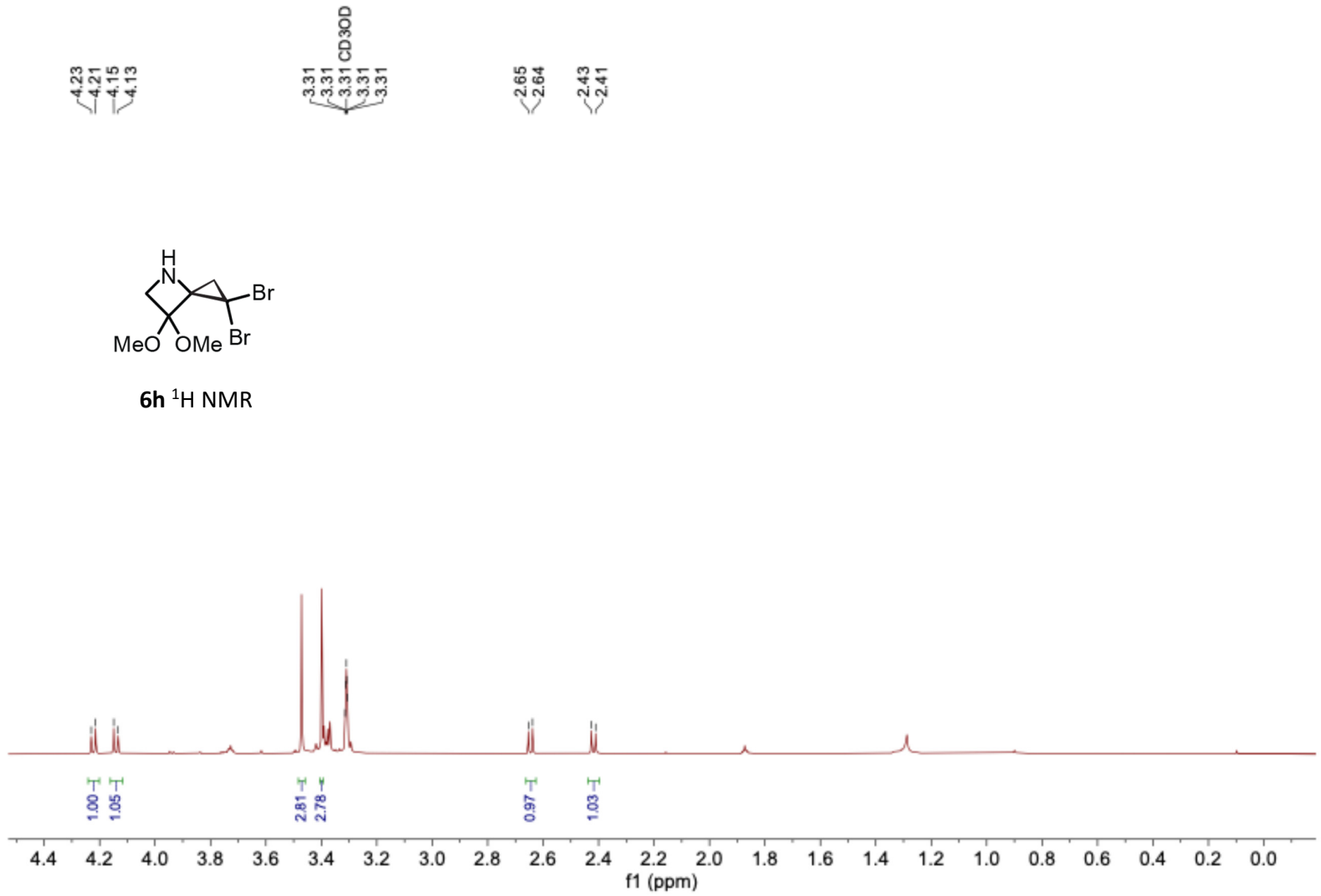
Alkene crude before 6g ^{1}H NMR


7.26 CDCl3
4.21
4.19
3.96
3.94
3.43
3.36
3.03
3.01
2.13
2.11
1.43
Boc
N
Br
Br
MeO
OMe
1.00
1.00
2.95
2.88
0.73
1.00
9.65
Chemical shift (ppm)

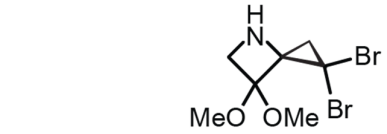
6g ^{1}H NMR


155.00
101.40
77.40 CDCl3
77.15 CDCl3
76.90 CDCl3
62.97
57.86
51.29
50.82
28.48
28.43
27.16
Boc
N
Br
Br
MeO
OMe
Chemical shift (ppm)

6g ^{13}C NMR

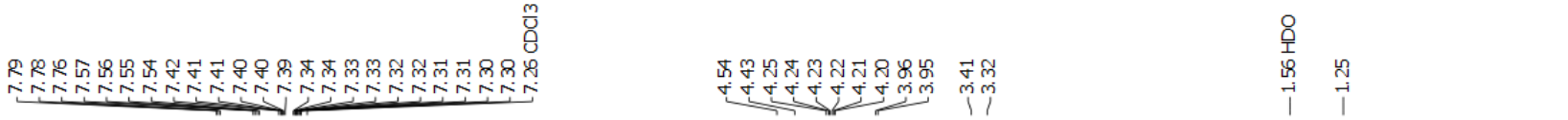

4.23
4.21
4.15
4.13
3.31
3.31
3.31 CD3OD
3.31
3.31
2.65
2.64
2.43
2.41
H
N
Br
Br
MeO
OMe
1.00
1.05
2.81
2.78
0.97
1.03
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
f1 (ppm)

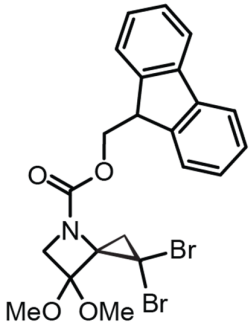
6h ^{1}H NMR


H
N
Br
MeO
OMe
Br

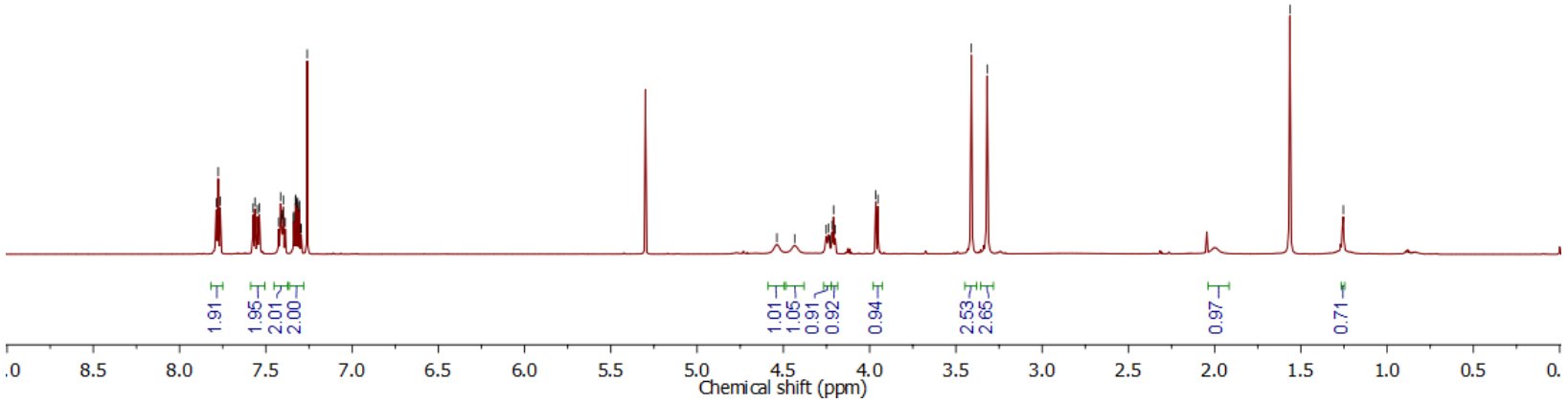
6h ^{13}C NMR

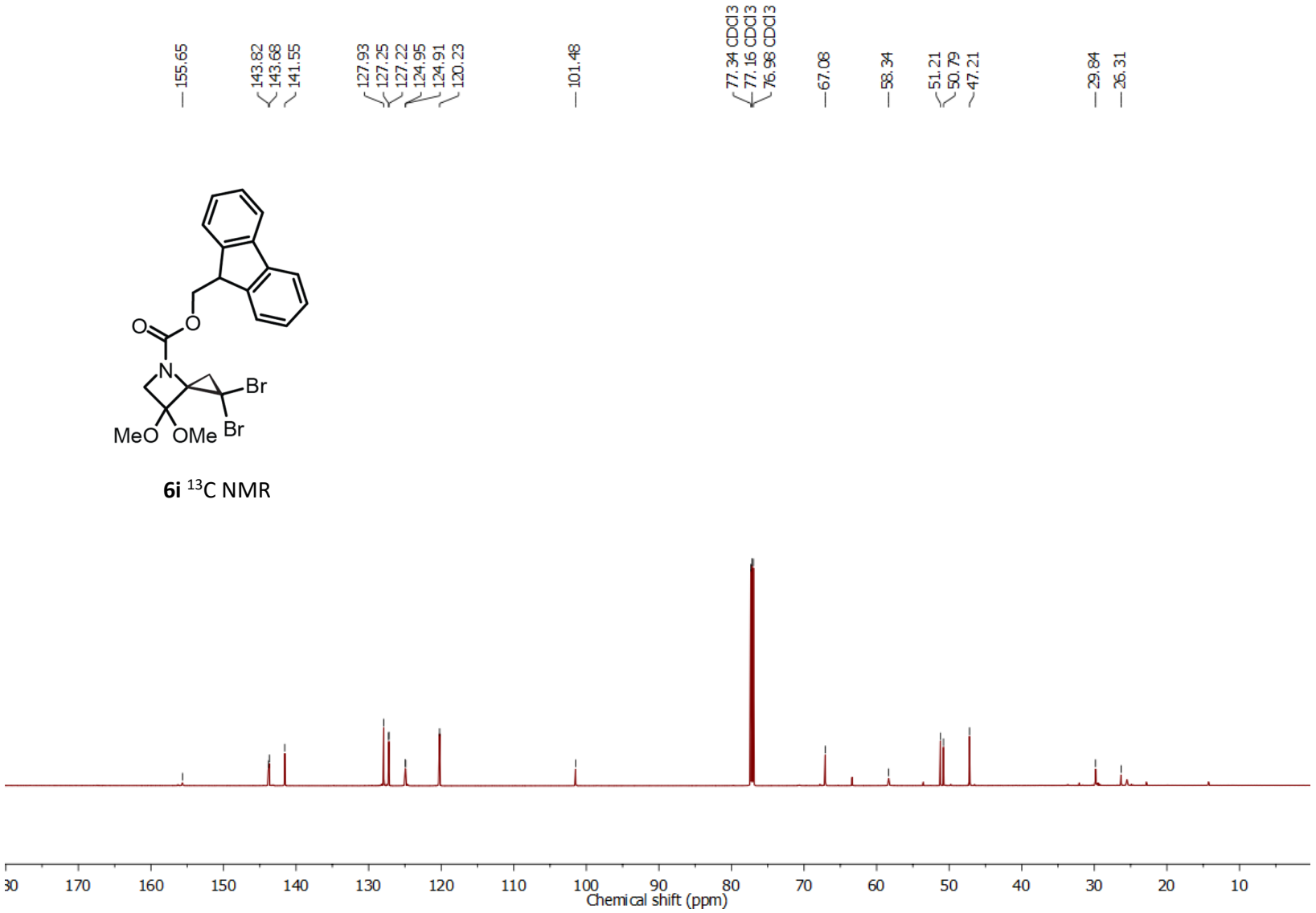
103.20
62.00
52.82
51.97
51.45
49.37
49.24
49.12
49.00 CD3OD
48.88
48.76
48.64
30.77
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.79
7.78
7.76
7.57
7.56
7.55
7.54
7.42
7.41
7.41
7.40
7.40
7.39
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.26 CDCl3
4.54
4.43
4.25
4.24
4.23
4.22
4.21
4.20
3.96
3.95
3.41
3.32
1.56 HDO
1.25

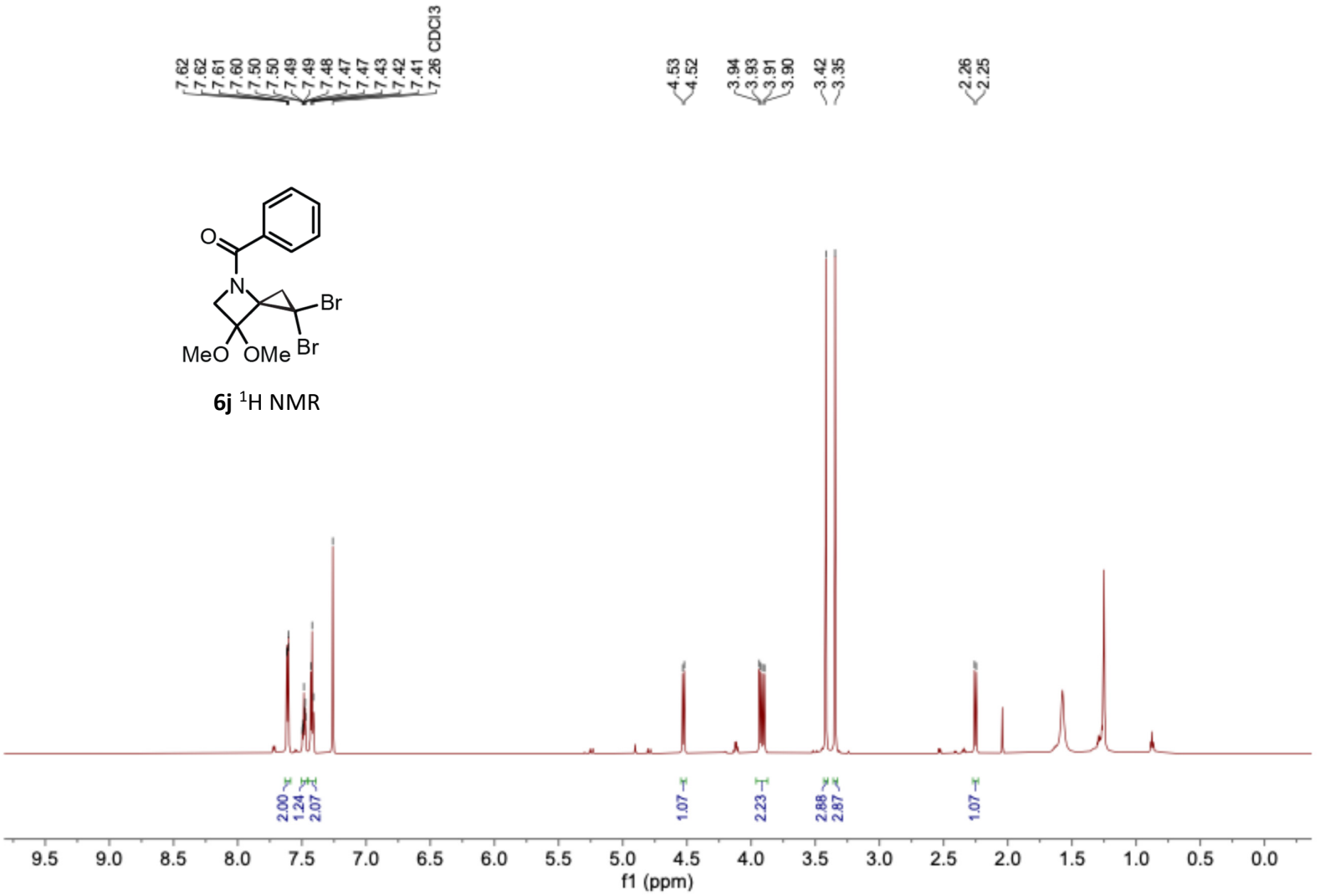

O
O
N
Br
Br
MeO
OMe

6i ^{1}H NMR

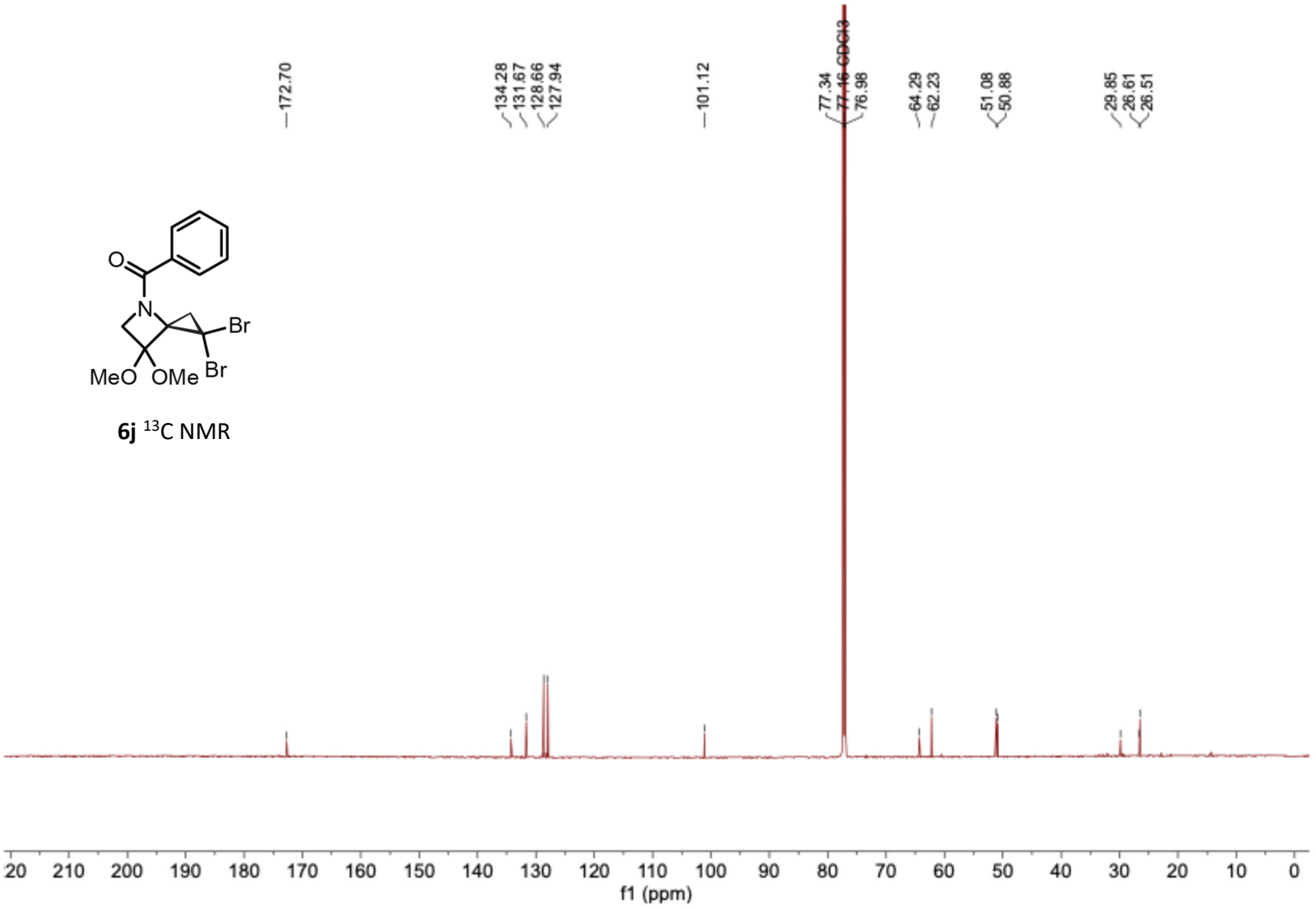

1.91
1.95
2.01
2.00
1.01
1.05
0.91
0.92
0.94
2.53
2.65
0.97
0.71
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical shift (ppm)


155.65
143.82
143.68
141.55
127.93
127.25
127.22
124.95
124.91
120.23
101.48
77.34 CDCl3
77.16 CDCl3
76.98 CDCl3
67.08
58.34
51.21
50.79
47.21
29.84
26.31
O
O
N
Br
Br
MeO
OMe
Chemical shift (ppm)

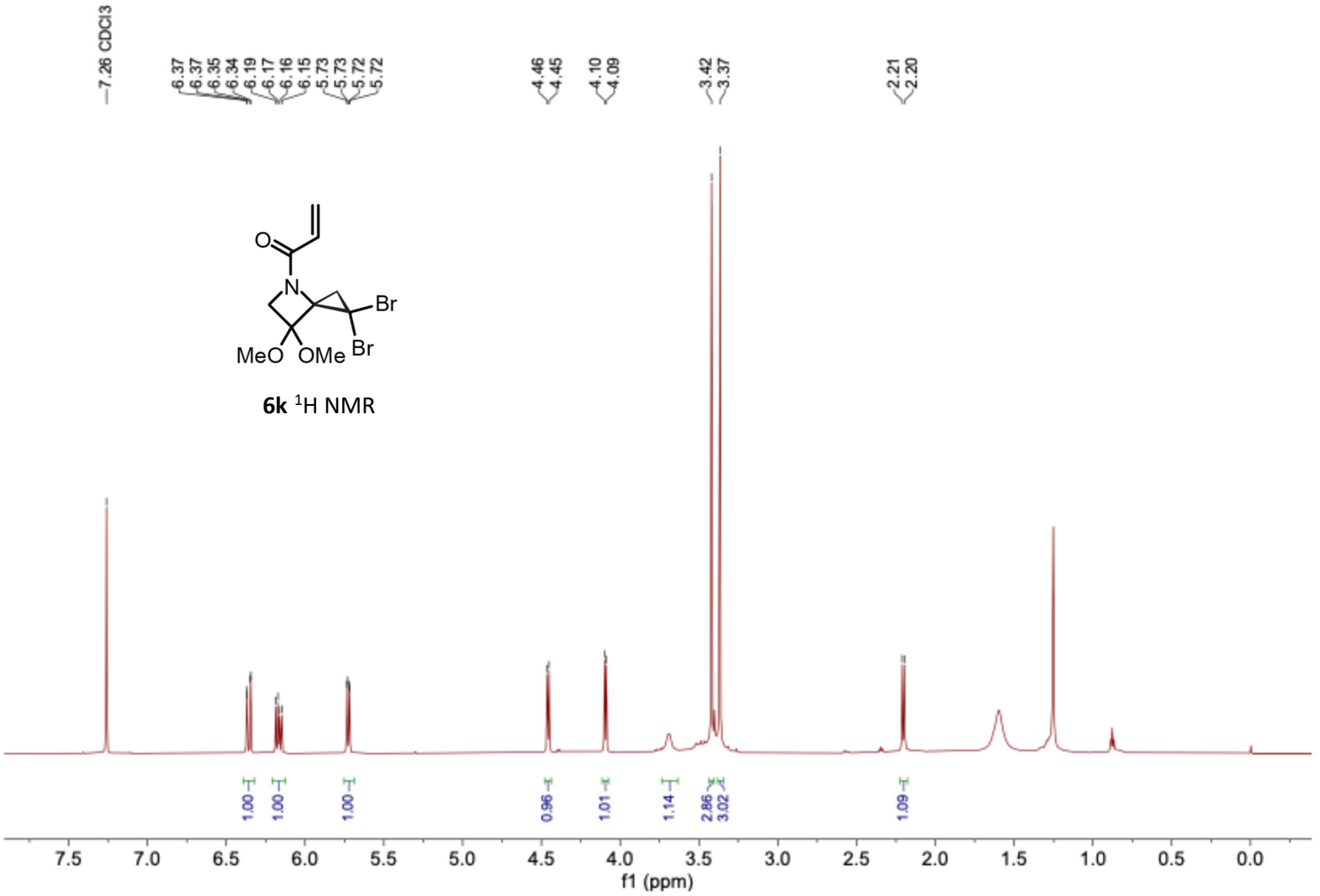
6i ^{13}C NMR


7.62
7.62
7.61
7.60
7.50
7.50
7.49
7.49
7.48
7.47
7.47
7.43
7.42
7.41
7.26 CDCl3
4.53
4.52
3.94
3.93
3.91
3.90
3.42
3.35
2.26
2.25
O
N
Br
Br
MeO
OMe
2.00
1.24
2.07
1.07
2.23
2.88
2.87
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
0.0
f1 (ppm)

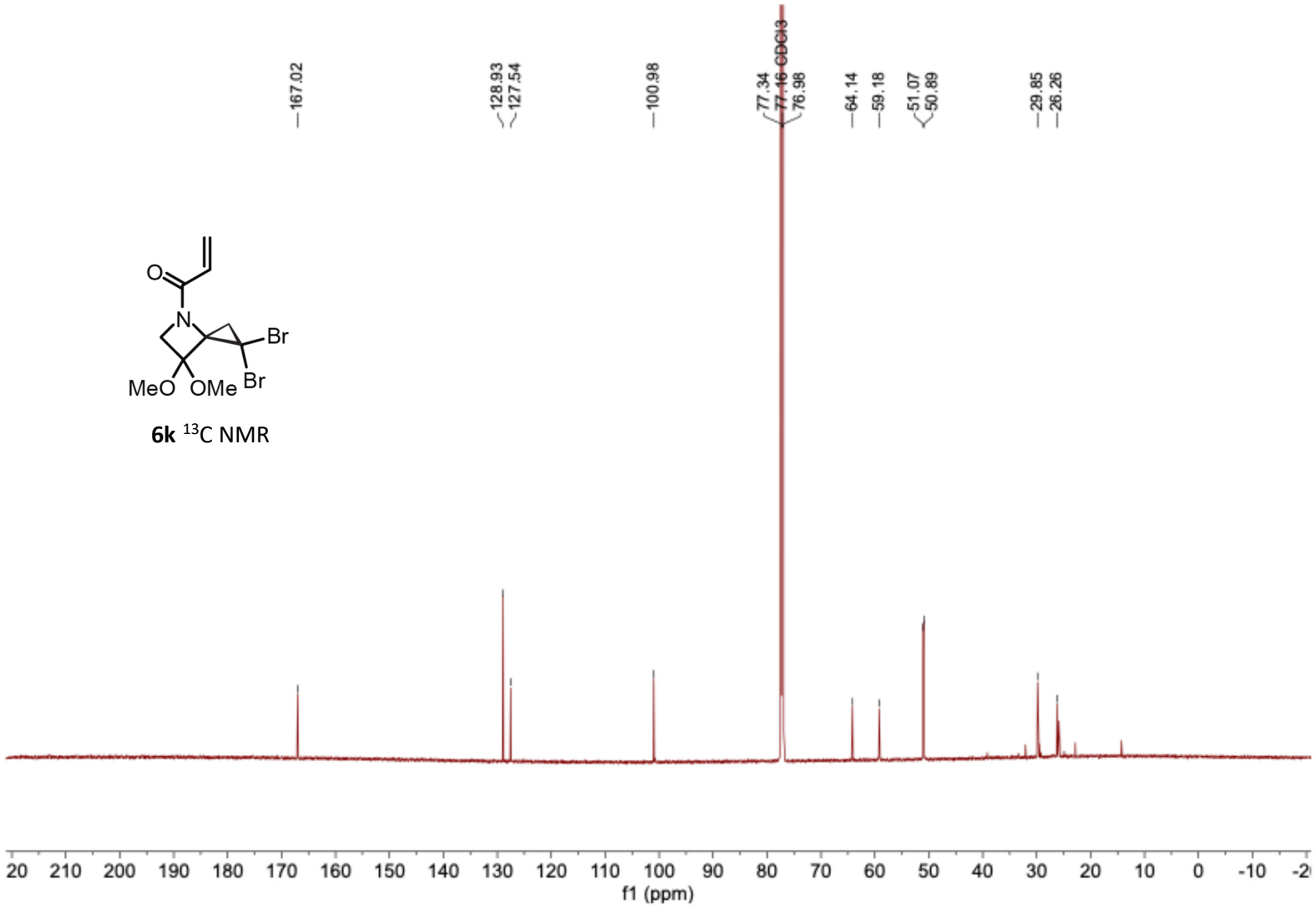
6j ^{1}H NMR


172.70
134.28
131.67
128.66
127.94
101.12
77.34
77.16 CDCl3
76.98
64.29
62.23
51.08
50.88
29.85
26.61
26.51
O
N
Br
Br
MeO
OMe
f1 (ppm)

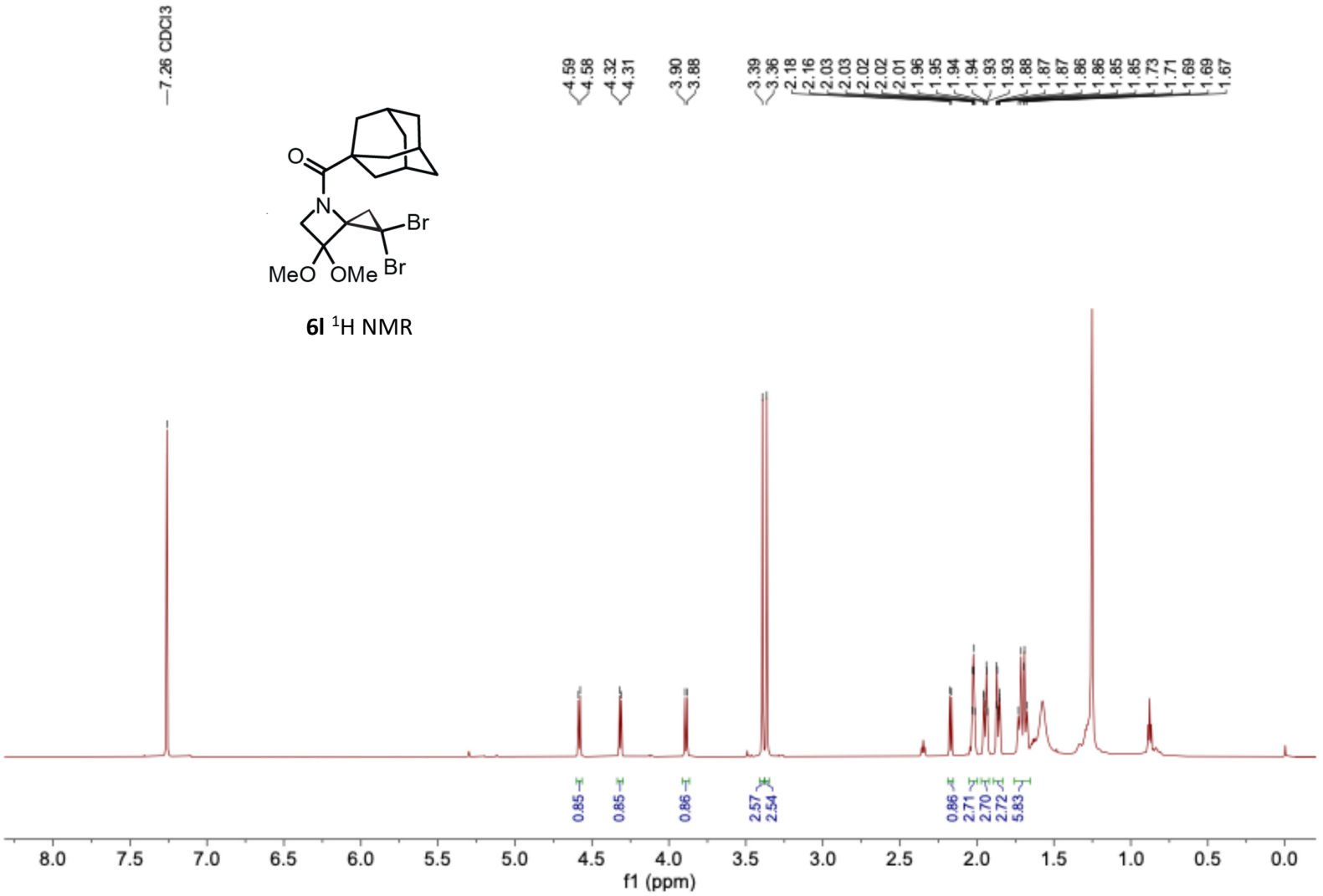
6j ^{13}C NMR


7.26 CDCl3
6.37
6.37
6.35
6.34
6.19
6.17
6.16
6.15
5.73
5.73
5.72
5.72
4.46
4.45
4.10
4.09
3.42
3.37
2.21
2.20
O
N
Br
Br
MeO
OMe
1.00
1.00
1.00
0.96
1.01
1.14
2.86
3.02
1.09
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)

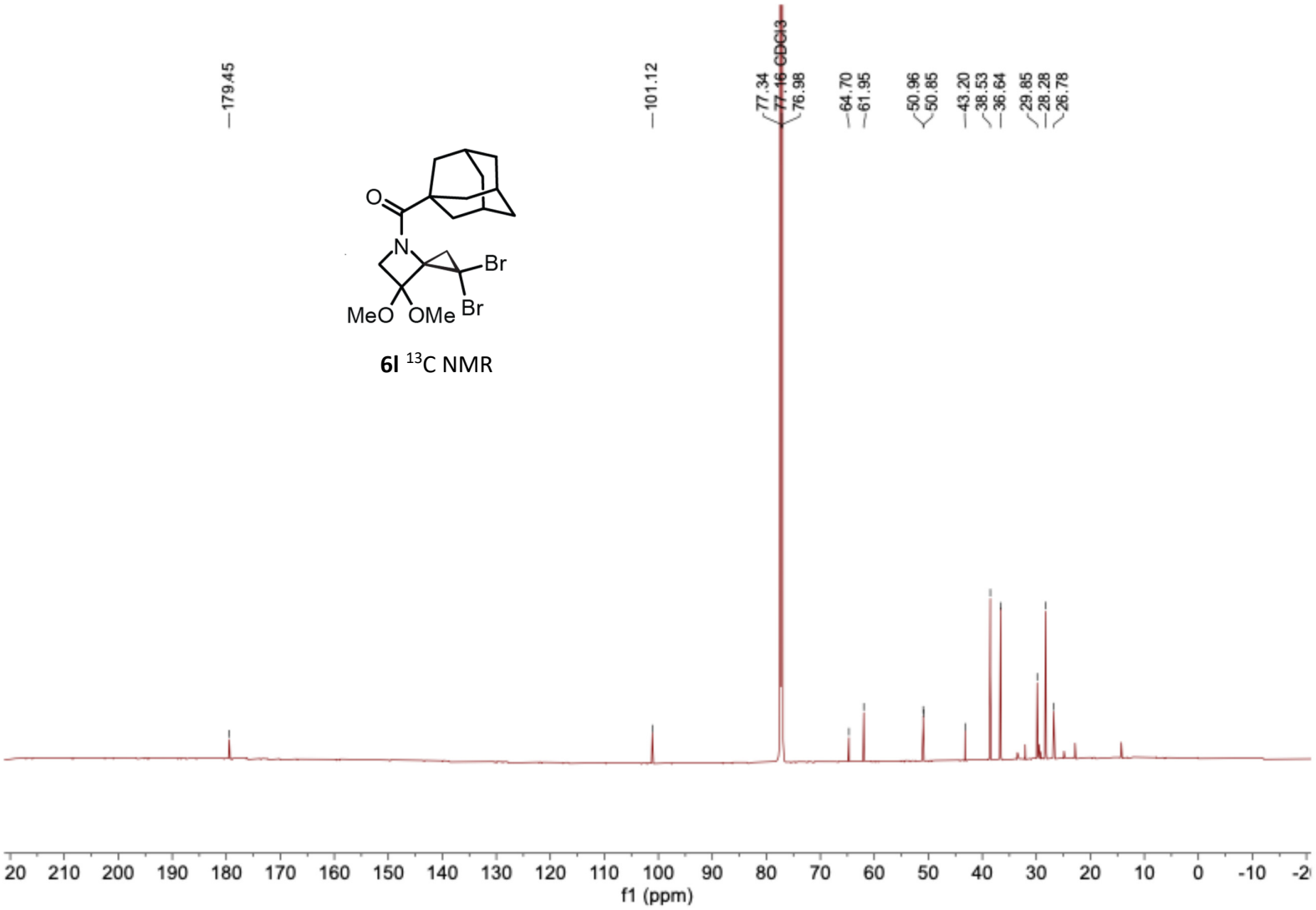
6k ^{1}H NMR


167.02
128.93
127.54
100.98
77.34
77.16 CDCl3
76.98
64.14
59.18
51.07
50.89
29.85
26.26
O
N
Br
Br
MeO
OMe
f1 (ppm)

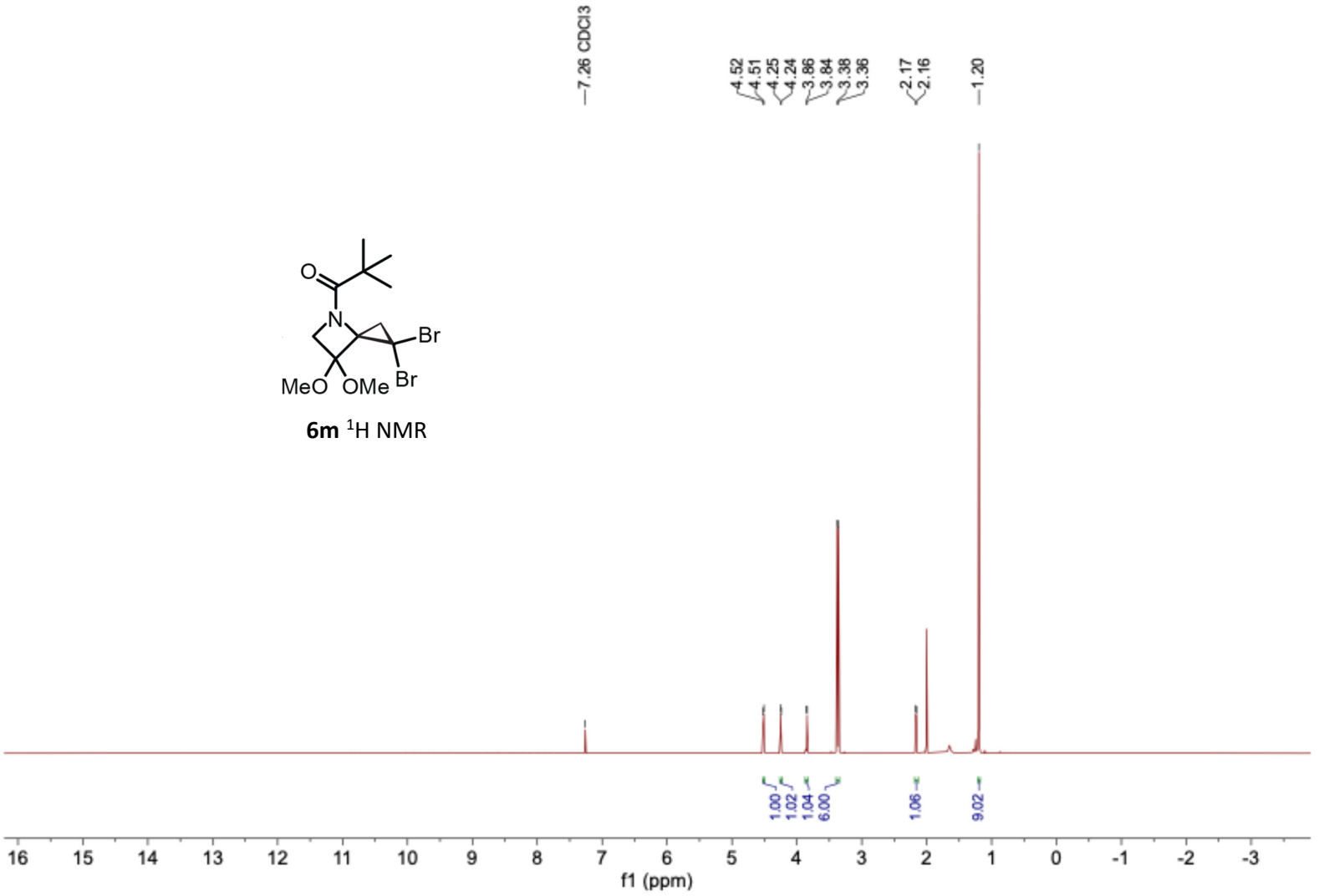
6k ^{13}C NMR


7.26 CDCl3
4.59
4.58
4.32
4.31
3.90
3.88
3.39
3.36
2.18
2.16
2.03
2.02
2.02
2.01
1.96
1.95
1.94
1.94
1.93
1.93
1.88
1.87
1.87
1.86
1.86
1.85
1.85
1.73
1.71
1.69
1.69
1.67
O
N
Br
Br
MeO
OMe
0.85
0.85
0.86
2.57
2.54
0.86
2.71
2.70
2.72
5.83
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)

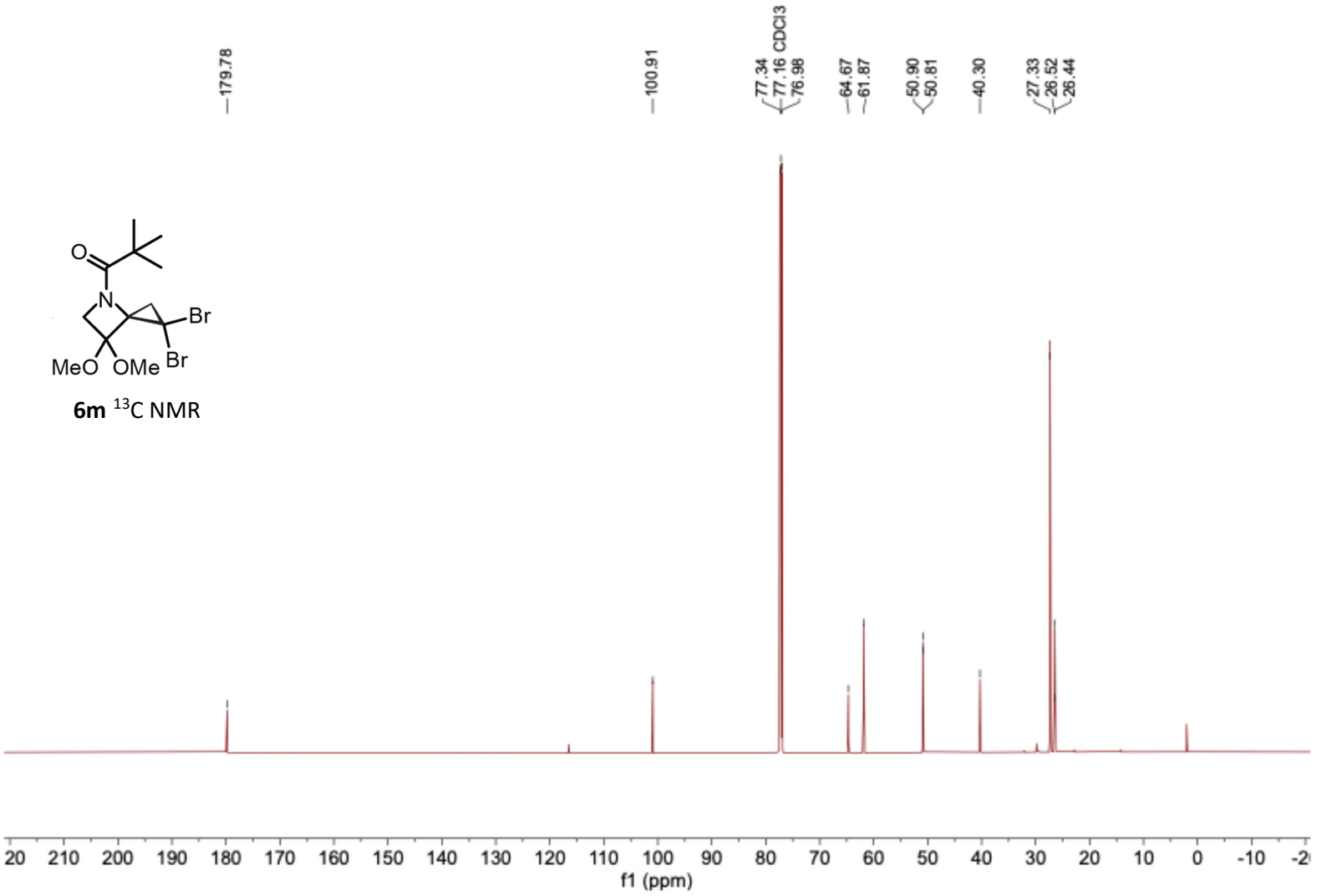
6l ^{1}H NMR


179.45
101.12
77.34
77.16 CDCl3
76.98
64.70
61.95
50.96
50.85
43.20
38.53
36.64
29.85
28.28
26.78
O
N
Br
Br
MeO
OMe
f1 (ppm)

6l ^{13}C NMR


7.26 CDCl3
4.52
4.51
4.25
4.24
3.86
3.84
3.38
3.36
2.17
2.16
1.20
O
N
Br
MeO
OMe
Br
1.00
1.02
1.04
6.00
1.06
9.02
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)

6m ^{1}H NMR


179.78
100.91
77.34
77.16 CDCl3
76.98
64.67
61.87
50.90
50.81
40.30
27.33
26.52
26.44
O
N
Br
Br
MeO
OMe
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

6m ^{13}C NMR

Reference

1 G. Pawelke, *J Fluor Chem*, 1989, 42, 429–433.
2 M. P. Moyer, P. L. Feldman and H. Rapoport, *J Org Chem*, 1985, 50, 5223–5230.
3 B. Bechi, D. Amantini, C. Tintori, M. Botta and R. di Fabio, *Beilstein Journal of Organic Chemistry*, 2014, 10, 1114–1120.
4 A. K. Pancholi, J. V Geden, G. J. Clarkson and M. Shipman, *J Org Chem*, 2016, 81, 7984–7992.
5 European Patent Application, PCT/JP2018/024476, 2020.
6 S. Mangelinckx, M. Boeykens, M. Vliegen, J. Van der Eycken and N. De Kimpe, *Tetrahedron Lett*, 2005, 46, 525–529.