Supporting Information for

Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity

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General Methods

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Dry tetrahydrofuran (THF) was obtained by passing the previously degassed solvent through an activated alumina column. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by LC-MS or thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using shortwave UV light as the visualizing agent and iodine (mixed with silica gel) or $KMnO_4$ and heat as developing agents. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.043 – 0.063 mm). NMR spectra were recorded on Bruker AVIII-600, DRX-500, AV-400, and DPX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm ^{1}H NMR, 77.2 ppm ^{13}C NMR; MeOH-d_4: 3.31 ppm ^{1}H NMR, 29.8 ppm ^{13}C NMR; acetone-d_6: 2.05 ppm ^{1}H NMR, 29.8 ppm ^{13}C NMR; C_6D_6: 7.16 ppm ^{1}H NMR, 128.1 ppm ^{13}C NMR; DMSO-d_6: 2.50 ppm 1 H NMR, 39.5 ppm ^{13}C NMR, CD_3CN: 1.94 ppm ^{1}H NMR, 118.3 ppm ^{13}C NMR). For ^{19}F NMR, CF_3Cl was referenced at 0 ppm. The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. High–resolution mass spectra (HRMS) were recorded on an Agilent LCMS TOF mass spectrometer using electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and were uncorrected.

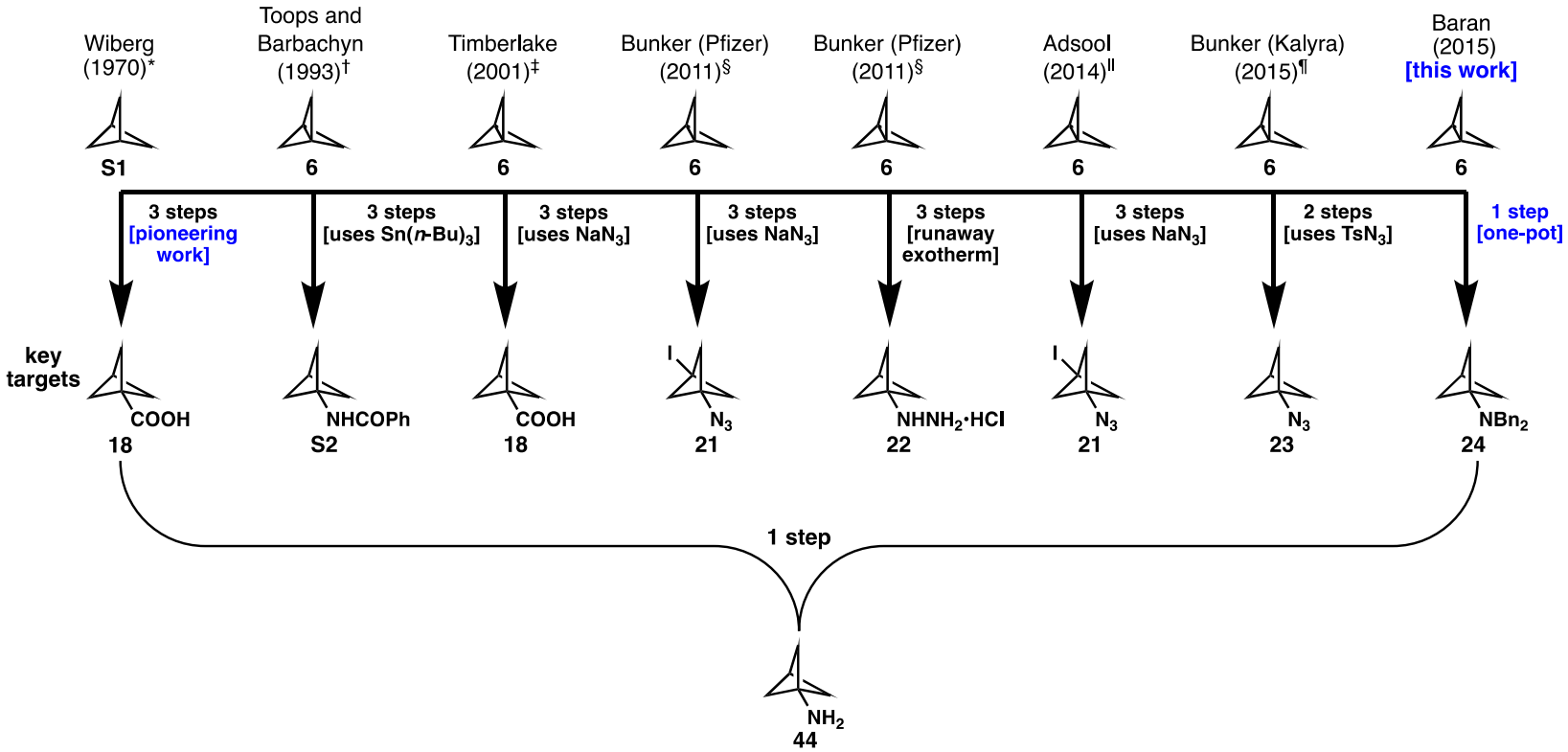
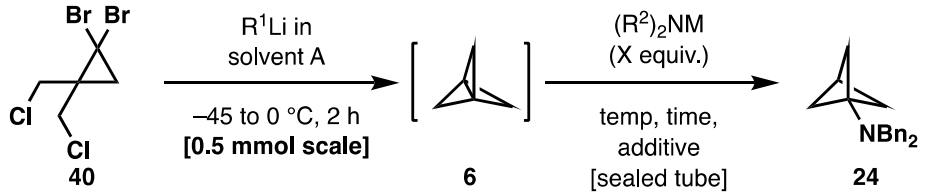


Fig. S1. Timeline of the synthetic approaches toward bicyclo[1.1.1]pentan-1-amine **(44)**. *See reference[7]. †See reference[39]. ‡See reference[40]. §See reference[10]. ‖See reference[41]. ¶See reference[42].

Table S1. Selected optimization reactions in the development of $Bn_2NMgCl•LiCl$

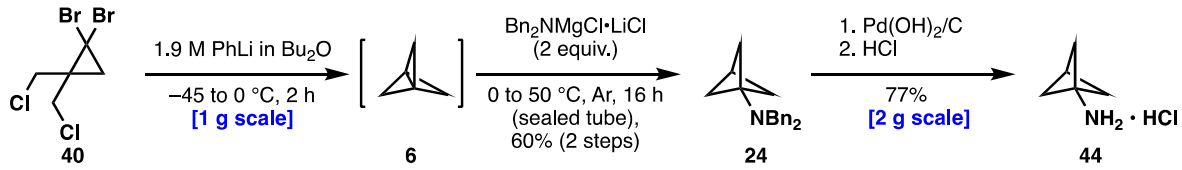


Entry	R^1	Solvent	R^2	Metal	Equiv. Amide	Temp	Time	Additives	Yield %
1	**Me**	**pentane/Et_2O**	**Boc**	**Li**	**1.5**	**–78 °C to r.t.**	**36h**	**–**	**0**
2	**Me**	**pentane/Et_2O**	**TMS**	**Li**	**1.5**	**–78 °C to r.t.**	**36h**	**–**	**0**
3	**Me**	**pentane/Et_2O**	**H**	**Li**	**1.5**	**–78 °C to r.t.**	**36h**	**–**	**0**
4	**Me**	**pentane/Et_2O**	**Bn**	**Li**	**1.5**	**–78 °C to r.t.**	**36h**	**–**	**0**
5	**Ph**	**pentane/Et_2O**	**Boc**	**Li**	**2**	**–78 °C to r.t.**	**36h**	**–**	**0**
6	**Ph**	**pentane/Et_2O**	**TMS**	**Li**	**2**	**–78 °C to r.t.**	**36h**	**–**	**0**
7	**Ph**	**pentane/Et_2O**	**H**	**Li**	**2**	**–78 °C to r.t.**	**36h**	**–**	**0**
8	**Ph**	**pentane/Et_2O**	**Bn**	**Li**	**2**	**–78 °C to r.t.**	**36h**	**–**	**trace**
9	**Ph**	**pentane/Et_2O**	**Bn**	**none**	**3**	**r.t.**	**36h**	**[control]**	**0**
10	**Ph**	**pentane/Et_2O**	**Bn**	**none**	**3**	**r.t. to 120 °C**	**36h**	**[control]**	**trace***
11	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**2**	**–78 °C to r.t.**	**72h**	**–**	**18**
12	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**3**	**–78 to 0 °C**	**>72h**	**–**	**< 5**
13	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**3**	**–78 to 50 °C**	**9h**	**–**	**26**
14	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**5**	**–78 to 50 °C**	**72h**	**HMPA**	**15**
15	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**5**	**–78 to 50 °C**	**72h**	**TMEDA**	**20**
16	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**5**	**–78 to 50 °C**	**72h**	**–**	**trace†**
17	**Ph**	**heptane/MTBE**	**Bn**	**Li**	**5**	**–78 to 50 °C**	**72h**	**CuI**	**trace**
18	**Me**	**heptane/MTBE**	**Bn**	**Li**	**5**	**–78 to 50 °C**	**72h**	**TEA**	**41**

19	**Ph**	**THF**	**Bn**	**Na**	**4**	**–78 to 50 °C**	**16h**	**–**	**20**
20	**Ph**	**THF**	**Bn**	**K**	**4**	**–78 to 50 °C**	**16h**	**–**	**trace**
21	**Ph**	**THF**	**Bn**	**Zn**	**4**	**–78 to 50 °C**	**16h**	**–**	**10**
22	**Ph**	**THF**	**Bn**	**Mg**	**4**	**–78 to 50 °C**	**16h**	**–**	**0**
23	**Me**	**heptane/MTBE**	**Bn**	**MgCl•LiCl**	**5**	**–78 to 50 °C**	**72h**	**–**	**73**
24	**Me**	**heptane/MTBE**	**Bn**	**MgCl•LiCl**	**5**	**–78 to 50 °C**	**72h**	**TEA**	**71**
25	**Me/DEM**[‡]	**heptane/MTBE**	**Bn**	**MgCl•LiCl**	**5**	**–78 to 50 °C**	**72h**	**–**	**86**
26	**Me**	**heptane/MTBE**	**Bn**	**MgCl•LiCl**	**5**	**–78 °C to r.t.**	**72h**	**–**	**55**
27	**Ph**	**Bu_2O**	**Bn**	**MgCl•LiCl**	**1.5**	**–78 to 50 °C**	**16h**	**–**	**46**
28	**Ph**	**Bu_2O**	**Bn**	**MgCl•LiCl**	**2**	**–78 to 50 °C**	**16h**	**–**	**60**[§]
29	**Ph**	**Bu_2O**	**Bn**	**MgCl•LiCl**	**5**	**–78 to 50 °C**	**16h**	**–**	**61**

[*]Entry 10 was adapted from Butov's work on dehydroadamantane.[68] [†]Dioxane used as solvent for amination step; [‡]Diethoxymethane was used as the solvent for [1.1.1]propellane formation; [§]Equivalents of "turbo amide" and number of different solvents reduced for economics on process scale.

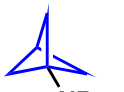
Gram-Scale Preparation of 44



Preparation of "turbo amide" $Bn_2NMgCl•LiCl$: To a flame dried round bottom flask under argon was added dibenzylamine (5.7 mL, 30 mmol) and dibutyl ether (7.2 mL). To this was added *i*PrMgCl•LiCl (27 mL, 1.11M in THF) via syringe at room temp (Caution: vigorous gas evolution!) and stirred at room temp for another 2 hours. Mixture turned a progressively darker red over that period of time. Used directly in reaction below. Note: 1.3M solution of *i*PrMgCl•LiCl can be used to prepare the turbo amide.

Formation of [1.1.1]propellane: A 110 mL flame-dried pressure tube fitted with a septa and under argon (balloon) was charged with **40** (1 g, 3.41 mmol) and dry dibutyl ether (1 mL). The reaction was cooled to –45 °C in a dry ice/isopropanol bath. PhLi (3.79 mL, 6.82 mmol, 1.8M in dibutyl ether) was added slowly *via* syringe and stirred at the same temperature for *ca.* 5 min. The reaction temperature was allowed to warm to 0 °C and stirred for 2h in an ice bath (or in cold room) to form **6**.

Amination of [1.1.1]propellane: The reaction was removed from the cold room and the reaction temperature was allowed to become ambient. $Bn_2NMgCl•LiCl$ (9 mL, 2 equiv., 0.75M) was added slowly *via* syringe, the septum was removed and the reaction was quickly capped with a Teflon pressure tube cap. The reaction was transferred to an oil bath that was pre-heated to 50 °C and the reaction was stirred at this temperature for 16 h. The reaction was removed from the oil bath and cooled in an ice bath for *ca.* 10 min and quenched slowly with sat. aq. NH_4Cl. The reaction was then diluted with EtOAc and transferred into a separatory funnel. The layers were separated and the organics were washed with H_2O (2 X 20 mL). The organics were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residual solvent was removed by hi-vacuum and the crude material was passed over a silica pad (20 g) while eluting with EtOAc/hexanes (0 to 3%) to a yield of *ca.* 98% of yellow oil **24** which solidified upon cooling to –20 °C (yields range from 50 – 60%). The material could be further purified by recrystallization from EtOH with cooling to –20 °C overnight.



24

***N*,*N*-dibenzylbicyclo[1.1.1]pentan-1-amine (24)**

Physical State: white solid (m.p. = 46-48 °C);

R_f = 0.52 (1:20 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (ddt, *J* = 7.7, 1.5, 0.7 Hz, 4H), 7.32 – 7.28 (m, 4H), 7.24 – 7.20 (m, 2H), 3.66 (s, 4H), 2.31 (s, 1H), 1.71 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 140.8 (2C), 128.5 (4C), 128.1 (4C), 126.7 (2C), 61.3, 55.1 (2C), 49.7 (3C), 22.9;

HRMS (ESI-TOF): calc'd for $C_{19}H_{22}N$ [M+H$^+$] 264.1752; found 264.1756.

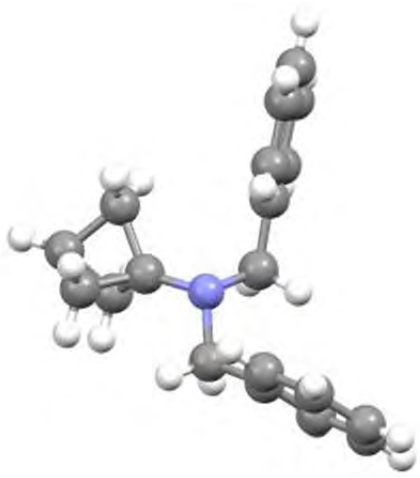


Fig. S2. Crystal structure of *N*,*N*-dibenzylbicyclo[1.1.1]pentan-1-amine (**24**)

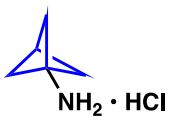
Table S2. Crystal data and structure refinement for **24**

Identification code	CCDC 1431179
Empirical formula	$C_{19}H_{21}N$
Formula weight	263.37

Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.8460(4) Å	α= 90°.
	b = 14.9613(9) Å	β= 90°.
	c = 16.7311(12) Å	γ = 90°.
Volume	1463.37(17) $Å^3$	
Z	4	
Density (calculated)	1.195 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	568	
Crystal size	0.290 x 0.260 x 0.200 mm^3	
Theta range for data collection	1.826 to 28.274°.	
Index ranges	-7<=h<=7, -19<=k<=19, -22<=l<=17	
Reflections collected	8634	
Independent reflections	3633 [R(int) = 0.0407]	
Completeness to theta = 25.000°	99.9 %	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3633 / 0 / 181	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.1020	
R indices (all data)	R1 = 0.0455, wR2 = 0.1051	
Absolute structure parameter	-0.1(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.201 and -0.233 e.$Å^{-3}$	

Deprotection of 24 to bicyclo[1.1.1]pentan-1-amine hydrochloride (44): To a mixture of *N,N*-dibenzylbicyclo[1.1.1]pent-1-yl-amine (2.1 g, 8.0 mmol) in methanol (20 mL) was added 20% palladium hydroxide on carbon (45 mg, 50% water) in one portion at 25 °C under nitrogen. The stainless steel vessel was attached to a pressure apparatus, stirring was initiated (900 rpm) and after three 1.5 to 4 bar purges of nitrogen the reaction was pressurized under 4 bar of hydrogen and left at 50 °C. After 72 h, the chamber was de-pressurized and purged with three 1.5 to 4 bar purges of nitrogen. LC/MS gave only product. The crude product was filtered through a glass fiber filter and 3.8 mL of 4M HCl-dioxane (2 eq) was added to the filtrate. The solvent was removed under reduced pressure

and a beige solid was isolated from EtOAc (819 mg). The beige solid was triturated with EtOAc and filtered. A fluffy off-white solid was collected (702 mg, 74% yield). All spectroscopic data matched that which was previously reported in the literature.[10]



44

Bicyclo[1.1.1]pentan-1-amine hydrochloride (44)

Physical State: off-white solid (m.p. = 241-243 °C; lit: 247-251 °C);

R_f = 0.70 (10% MeOH in EtOAc + 0.1% NH_4OH, vis. I_2);

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 3H), 2.58 (s, 1H), 1.98 (s, 6H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 51.0 (3C), 45.5, 23.6;

HRMS (ESI-TOF): calc'd for C_5H_9N [M^+] 83.0735; found 83.0734.

Graphical Gram-Scale Preparation of 24.

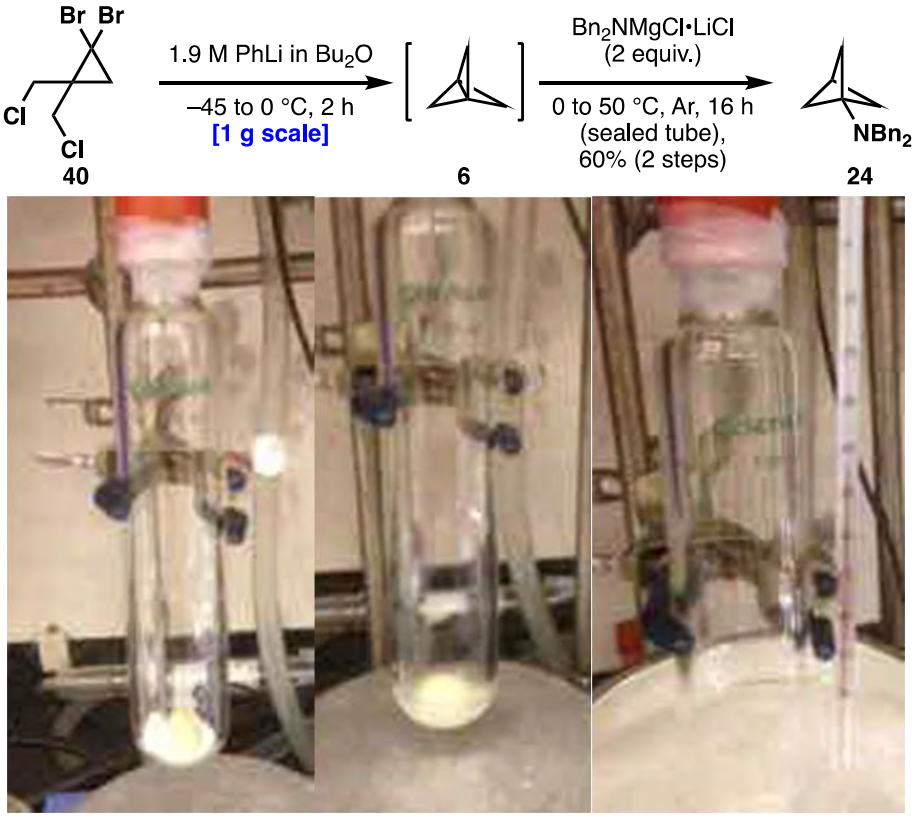


Fig. S3. Left. Tetrahalide **40** is added to a thick walled pressure tube equipped with a stir bar. **Center.** Bu_2O is added under an argon balloon sealed with a septum. **Right.** The mixture is cooled to –45 °C with a dry ice/isopropanol bath.

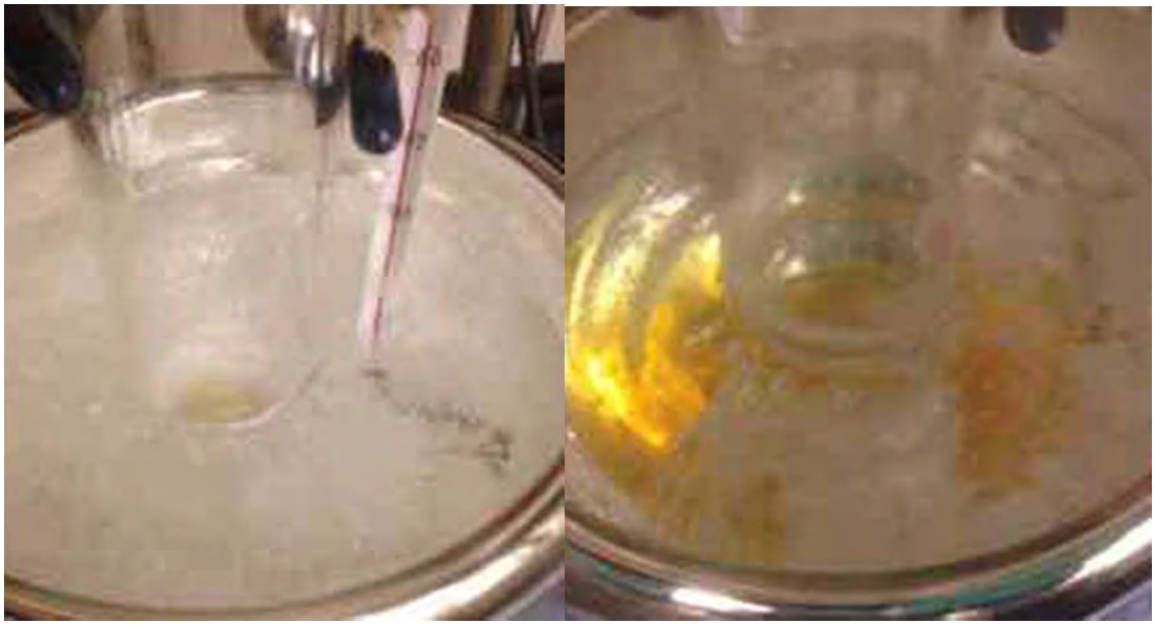


Fig. S4. Left. To consistently maintain –45 °C for *ca.* 20 minutes, the dry ice should be dissolved in isopropanol. The bath should appear homogeneous and not contain any solid pieces of dry ice. **Right.** After addition of the PhLi, the solution will change from a clear colorless/white to clear yellow.

Fig. S5. Left. The reaction was moved to a cold room (*ca.* 5 °C) and stirred for 2 h under argon. **Right.** Close up view of reaction mixture in cold room.

Fig. S6. Left. Flask of the "turbo amide" solution (ready to be used). **Center.** Upon addition of the "turbo amide" the color of the reaction mixture changes from yellow to orange/red. **Right.** Close up of the reaction mixture after the addition of the "turbo amide."

Fig. S7. Left. The reaction is heated to 50 °C for *ca.* 16h. **Right.** Close up view of the heated reaction mixture.

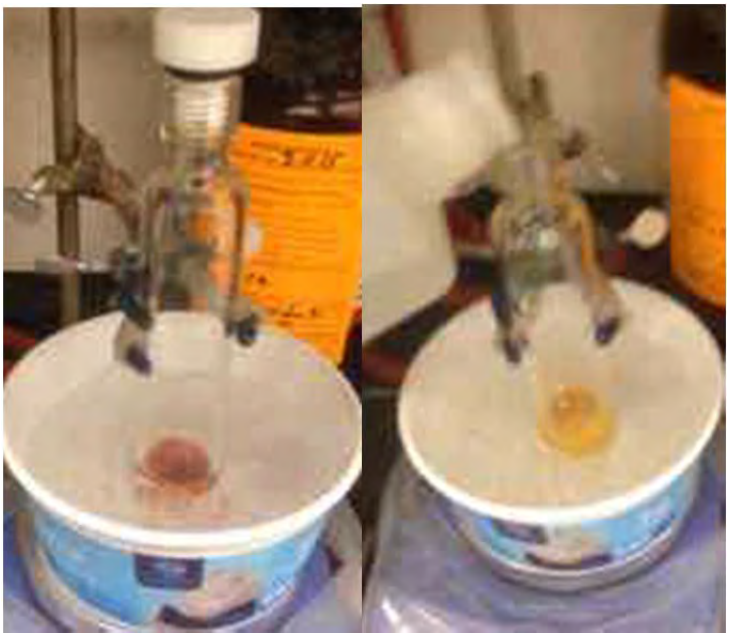


Fig. S8. Left. After completion, the mixture is cooled to 0 °C in an ice bath. **Right.** The color changes from red to yellow after slowly quenching with sat. aq. NH_4Cl.

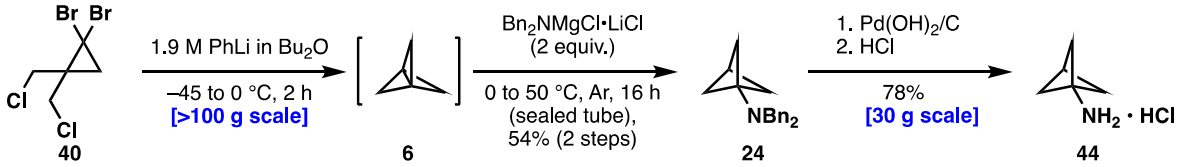
Fig. S9. Left. The quenched reaction mixture is diluted with EtOAc. **Right.** The solution is transferred to a separatory funnel and the organics washed with H_2O.

Fig. S10. Left. The combined organics are dried over Na_2SO_4. **Right.** The combined organics are filtered through cotton and concentrated *in vacuo*.

Fig. S11. Left. The crude material is wet loaded onto silica (ca. 20 g) and eluted in a single flask (no fractions) with 0 to 3% EtOAc in hexanes. **Right.** Alternatively, the crude material was dry loaded onto a silica pad in a sintered glass funnel and eluted in a single flask (no fractions) with 0 to 3% EtOAc in hexanes. Note: this picture is from a 10 g scale run.

Fig. S12. Left. The crude material is obtained as yellow oil that solidified upon cooling in a –20 °C freezer. **Right.** The material can be further purified by recrystallization from EtOH at –20 °C followed by collection by filtration, washing with ice cold EtOH, and drying under vacuum.

Multi-decagram Scale Prep of 24 and 44 (conducted at WuXi)



Preparation of "turbo amide" $Bn_2NMgCl•LiCl$: To a stirred colorless solution of dibenzylamine (150.0 g, 0.76 mol) in dibutyl ether (150 mL) was added dropwise *i*PrMgCl•LiCl (450 mL, 0.76 mol, 1.3 M in THF) between 5-10 °C over a period of 50 min. The mixture turned dark red during this time. After the addition, it was slowly warmed to 25 °C and stirred for two hours. This solution was used for the next step directly without further workup.

Amination of [1.1.1]propellane: The reaction was carried out in two parallel batches. To a stirred suspension of compound **40** (112.7 g, 0.38 mol) in dibutyl ether (120 mL) was added dropwise PhLi (400 mL, 0.76 mol, 1.9 M in dibutyl ether) between –40 to –45 °C over a period of 1h. After the addition was complete, the dark reaction solution was stirred at 0 °C for two hours. The solution of $Bn_2NMgCl•LiCl$ (0.76 mol) was added dropwise to the above mixture between 5-10 °C over a period of 30 min. After addition, the orange mixture was heated to 60 °C (the oil bath was preheated to 60 °C) and stirred at that temperature for 16 hours. The reaction mixture was cooled to 0 °C and sat. aq. NH_4Cl (200 mL) was added dropwise to the above mixture between 5-15 °C. The combined mixtures from two batches were filtered and the filtrate was extracted with EtOAc (2 x 1.5 L). The combined organic layers were washed with brine (1 L), dried over Na_2SO_4, filtered, and concentrated to give the crude product. The crude product was purified by column chromatography on silica gel eluted with petroleum ether (100%) to give the desired product as a liquid. The product was triturated with heptane (400 mL) with stirring between –20 to –30 °C for 1h. Many solids were formed and the mixture was filtered immediately. The solid was collected to give compound **24** (91 g, 45.5%) as an off-white solid. The filtrate was evaporated under reduced pressure to give a second batch of crude product that was purified by column chromatography on silica gel eluted with petroleum ether (100%) to give the desired product as a liquid. The product was triturated with heptane (100 mL) with stirring between –20 to –30 °C for 1h. The mixture was filtered as soon as possible and the solid was collected (41 g). Both batches of solid were combined together to give compound **24** as a white solid. 132 g of compound **24** was prepared from 275.4 g of compound **40**; the overall yield was 54%. The spectroscopic data were identical to that reported above.

Deprotection step: Synthesis of bicyclo[1.1.1]pentan-1-amine hydrochloride (44): The reaction was carried out in three parallel batches. To a mixture of compound **24** (30.0 g, 0.114 mol) in MeOH (600 mL) was added $Pd(OH)_2/C$ (2.0 g, 20% $Pd(OH)_2$, 50% H_2O) in one portion at 25 °C under argon. After addition, it was degassed with argon two times and purged with H_2 two times. The reaction mixture was stirred at 30 °C under 50 psi of H_2 for 12 hours. The mixture was allowed to stand for 24 hours before workup. TLC (petroleum ether/EtOAc = 20/1, EtOAc /MeOH = 20/1, UV, I_2) showed that the starting material was consumed completely and the desired product was detected. The mixtures from three batches were filtered through a pad of Celite and the filter cake was washed with MeOH (2 x 600 mL). HCl-dioxane (4.0 M, 200 mL) was added dropwise to the above filtrate between 0-3 °C. After addition, it was stirred at 25 °C for 30 min. The mixture was evaporated under reduced pressure to give a crude product, which was triturated with EtOAc (100 mL) with stirring for 30 min. The mixture was filtered and the solid was collected to give **44** (32.0 g, 78.3%) as a light-brown solid. The spectroscopic data were identical to that reported above.

Preparation of [1.1.1]propellane stock solution[10,43]

A 250 mL flame dried flask under argon was charged with **40** (9.51 g, 32.45 mmol) and dry diethyl ether (20 mL). The reaction was cooled to –40 °C in a dry ice/isopropanol bath. PhLi (36 mL, 64.9 mmol, 31.8M in dibutyl ether) was added slowly via syringe and stirred at the same temperature for *ca.* 5 min. The reaction temperature was allowed to warm to 0 °C and stirred for 2h in an ice bath (or in cold room). Upon completion of the reaction, the solvent was removed *via* rotovap (pump pressure of *ca.* 4 Torr) in a room temperature rotovap bath and the catch flask of the rotovap was immersed in a –78 °C bath. The product (**6**) was collected as a clear, colorless solution in diethyl ether in the catch flask and the approximate concentration of the solution was calculated using quantitative NMR.

Quantitative NMR Experiment:

A sample of the solution containing **6** (200 μL) in diethyl ether was diluted with dichloroethane (DCE) (50 μL) and $CDCl_3$ was added (*ca.* 0.5 mL). The ratio of the DCE:propellane was determined and used for the calculation of the concentration of the propellane solution. This is run in duplicate and the average of the two runs is used as the final approximated concentration.

Determination of the Concentration of Dichloroethane:

50µl DCE X 1.253g/mL = 62.65mg DCE ÷ 98.96mg/mmol = **0.63mmol** DCE

0.63 was then divided by the ratio of DCE:propellane NMR peaks. We obtained ratios of 3.03:1 and 2.74:1.

$$\textbf{[propellane stock]} = \left(\mathbf{0.63} \div \textbf{nmr peak ratio}\,\frac{\textbf{DCE}}{\textbf{stock}}\right) \div \mathbf{0.2mL}$$

Sample 1: 0.63mmol ÷ 3.03 ÷ 0.2mL = 1.035M
Sample 2: 0.63mmol ÷ 2.74 ÷ 0.2mL = 1.145M

Average = 1.09 M.

Overall Yield Calculation:

Theoretical yield of 10 g solution: (10 g ÷ 293 (MW of tetrahalide **40**) = 34.13 mmol) X 66 (mw of propellane **6**) = 2.252 g

Calculated concentration X mL of propellane solution X 66 (Propellane MW) = g propellane in solution.

1.09 M X 25 mL X 66 = 1.798 g (~ 80% yield)

Note: We have obtained yields that range from 78% (6 g scale) to 95% (9.51 g scale) depending on the scale.

Graphical Preparation of [1.1.1]Propellane Stock Solution in Et_2O

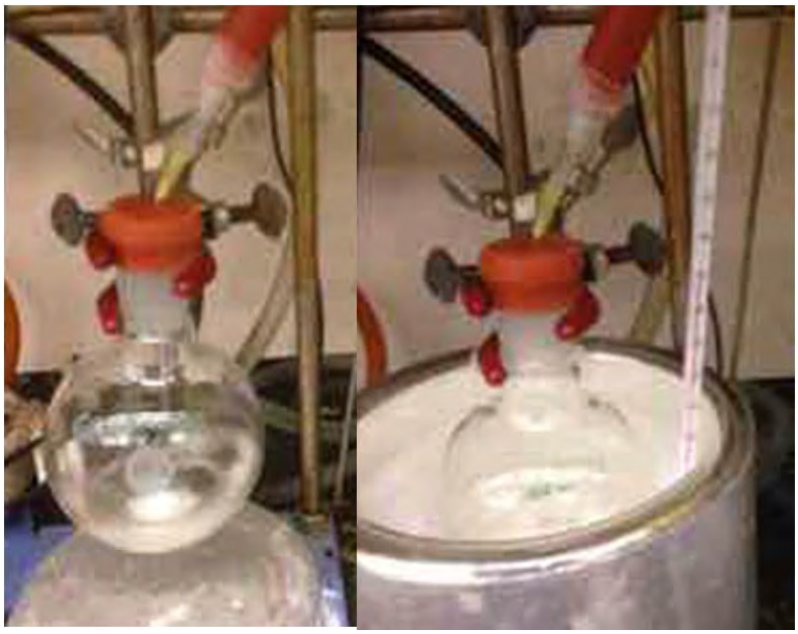


Fig. S13. Left. Tetrahalide **40** is dissolved in Bu_2O under argon and sealed with a septum. **Right.** The reaction is cooled to –45 °C in a dry ice/isopropanol bath.

Fig. S14. Left. To consistently maintain –45 °C for *ca.* 20 minutes, the dry ice should be dissolved in isopropanol. The bath should appear homogeneous and not contain any solid pieces of dry ice. **Right.** Addition of PhLi at –45 °C.

Fig. S15. Left. After addition of the PhLi, the solution will change from a clear colorless/white to clear yellow. **Right.** Close up view of yellow solution after PhLi addition.

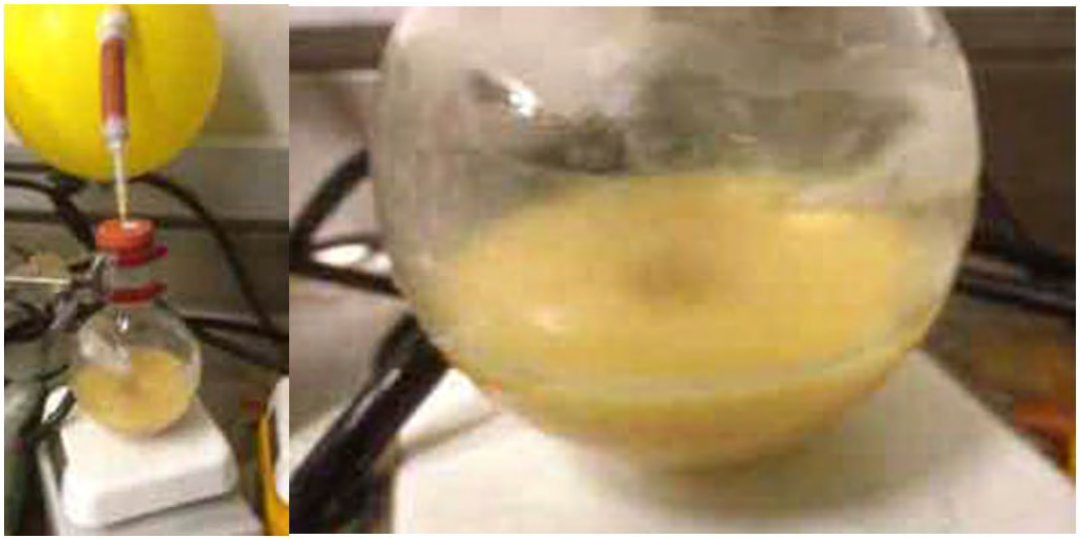


Fig. S16. Left. Reaction is transferred to a cold room (*ca.* 5 ºC) and stirred for 2h under argon. The clear yellow solution becomes an opaque yellow suspension once warmed to *ca.* 5 ºC. **Right.** Close up view of the suspension.

Fig. S17. Left. After stirring for 2h, the suspension turns a dark brown color. **Right.** Close up view of the suspension.

Fig. S18. Left. The suspension is distilled directly on the rotovap. **Right.** The water bath is maintained at *ca.* 20 °C during the course of the distillation.

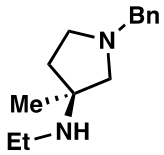
Fig. S19. Left. The receiving flash is immersed in a dry ice/acetone bath at –78 °C. **Right.** The pressure of the distillation is carefully controlled beginning at *ca.* 10 Torr.

Fig. S20. Left. View of the distillation in progress. **Right.** The pressure is reduced to *ca.* 4 Torr to complete the distillation.

Fig. S21. Left. View of the reaction flask at the end of distillation. **Do not distill to dryness**; the flask should contain a suspension of salts in Bu_2O. **Right.** Stock solution of [1.1.1]propellane in diethyl ether.

Starting Amines for Strain Release Amination

Aniline, *N*-methylaniline, benzylamine, dibenzylamine, diallylamine, morpholine, piperidine, 4-phenylpiperidine, *N*-benzylmethylamine, *N*-benzylethylamine, *N*-benzyl-(cyclobutylmethyl)amine, nornicotine, perhydroisoquinoline, 1,2,3,4-tetrahydroisoquinoline, 1-(3-methoxyphenyl)-2,2-dimethylpiperazine, maprotiline hydrochloride, nortriptyline, sertraline, paroxetine, fluoxetine, lorcaserin, quipazine, and amoxapine were purchased from commercial sources and were used as received. All others are referenced in the appropriate sections.



S3

(*S*)-1-benzyl-*N*-ethyl-3-methylpyrrolidin-3-amine (S3)

In a 100 mL RB flask, *(S)-N*-(1-benzyl-3-methylpyrrolidin-3-yl)acetamide[44] (683 mg, 2.94 mmol) was diluted with THF (5.00 mL, c=0.588 M) under nitrogen and cooled to 0 °C. Lithium aluminum hydride (2.0 M in THF) (411 mg, 10.3 mmol , 5.14 mL, 2.0 M) was then added drop-wise (bubbling noted at beginning of addition) and the vessel warmed to ambient temperature followed by fitting with a reflux condenser and heating to reflux temperature overnight (mantle set to 75 °C). After ~21 hours, the reaction was cooled to ambient temperature. LC/MS indicated complete reduction. The reaction was cooled to 0 °C, diluted with diethyl ether and treated sequentially with 0.4 mL water, 0.4 mL 15% KOH and 1.2 mL water) then warmed to ambient temperature. After 10 minutes, magnesium sulfate was added, the mixture stirred for 5 minutes, and then filtered (solids washed with diethyl ether). The filtrate was concentrated to give **S3** (466.4 mg, 73% yield).

Physical State: colorless oil;

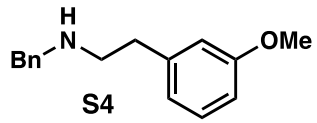
$\boldsymbol{R_f}$ = 0.31 (10:1 CH_2Cl_2:MeOH);

$[\alpha]_D^{22}$ = –2.6 (c = 1.3, MeOH);

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 – 7.27 (m, 4H), 7.26 – 7.18 (m, 1H), 3.60 – 3.50 (m, 2H), 2.63 – 2.44 (m, 5H), 2.28 (d, *J* = 8.9 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.60 – 1.51 (m 1H), 1.25 (br s, 1H), 1.16 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 139.3, 128.2 (2C), 128.0 (2C), 126.6, 65.9, 60.1, 59.7, 53.0, 37.7, 36.9, 26.6, 16.0;

HRMS (ESI-TOF): calc'd for $C_{14}H_{23}N_2$ [M+H$^+$] 219.1856; found 219.1859.



S4

***N*-benzyl-2-(3-methoxyphenyl)ethan-1-amine (S4)**

To a solution of 2-(4-methoxyphenyl)ethan-1-amine (1.48 g, 9.80 mmol, 1.0 equiv.) in dry trifluoroethanol (50 mL) was added benzaldehyde (998 μL, 9.80 mmol, 1.2 equiv.) and the mixture stirred at 40 °C for 5 min. The reaction was cooled to 0 °C and $NaBH_4$ (435 mg, 1.2 equiv.) was added in 3 equal portions and the reaction stirred at room temperature until TLC indicated complete conversion (*ca.* 60 min.) Water was added and the mixture extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0% to 40% EtOAc:hexanes) to give 1.23 g of **S4** (52%).

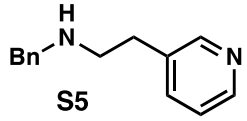
Physical State: colorless oil;

R_f = 0.60 (100% EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 4H), 7.28 – 7.20 (m, 2H), 6.83 – 6.80 (m, 1H), 6.77 (dd, *J* = 6.6, 1.1 Hz, 2H), 3.82 (s, 2H), 3.80 (s, 3H), 2.92 (td, *J* = 7.1, 0.8 Hz, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), no N–H peak observed;

^{13}C NMR (151 MHz, $CDCl_3$): δ 159.8, 141.8, 140.4, 129.5, 128.5 (2C), 128.2 (2C), 127.0, 121.2, 114.5, 111.6, 55.2, 54.0, 50.5, 36.5;

HRMS (ESI-TOF): calc'd for $C_{16}H_{20}NO$ [M+H$^+$] 242.1545; found 242.1542.



S5

***N*-benzyl-2-(pyridin-3-yl)ethan-1-amine (S5)**

To a solution of 3-(2-aminoethyl)pyridine in dry MeOH (4 mL) was added benzaldehyde (200 μL, 2 mmol, 1.0 equiv.) and the mixture stirred at 40 ºC for 12h. The reaction was cooled to 0 °C and $NaBH_4$ (100 mg, 1.2 equiv.) was added in 3 equal portions and the reaction stirred at room temperature until TLC indicated complete conversion (*ca.* 60 min.). Water was added and the mixture extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 0% to 20% MeOH in EtOAc) to

give 356 mg of **S5** (84%).

Physical State: yellow oil;

R_f = 0.29 (3:7 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.49 – 8.45 (m, 2H), 7.54 – 7.50 (m, 1H), 7.34 – 7.28 (m, 4H), 7.26 – 7.23 (m, 1H), 7.21 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 3.83 (s, 2H), 2.92 (td, *J* = 7.2, 1.0 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), no N–H peak observed;

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.3, 147.9, 136.3, 135.3, 128.6 (2C), 128.5, 128.4 (2C), 127.3, 123.5, 53.8, 50.1, 33.5;

HRMS (ESI-TOF): calc'd for $C_{14}H_{17}N_2$ [M+H$^+$] 213.1392; found 213.1387.

General medicinal chemistry procedure for the propellerization of amines using the propellane stock solution (prepared above)

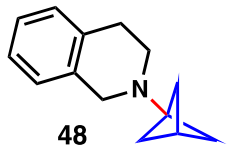
***N,N*-dibenzylbicyclo[1.1.1]pentylamine (24):** To a flame-dried vessel under argon was added dibenzylamine (198 μL, 1.0 mmol) and dry THF (1 mL). To this was added *i*PrMgCl•LiCl (0.90 mL, 1.0 mmol, 1.11M in THF) via syringe at room temp (CAUTION: gas evolution) and stirred at room temp for 2h. To this solution was added a stock solution of propellane (0.57 mL, 0.50 mmol, 0.875M in diethyl ether). The vial was sealed and heated to 90 °C overnight. The reaction was cooled to 0 °C and quenched with sat. aq. NH_4Cl (2 mL) and H_2O (2 mL) and extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residual oil was purified by flash chromatography (SiO_2, 0% hexanes → 20% EtOAc/hexanes) to give the desired product (**24**, 62%). All spectroscopic data matched previously prepared samples.

Note: Dibenzylamine dihydrochloride can also be used in the above preparation in place of dibenzylamine. Two equivalents of *i*PrMgCl•LiCl (1.80 mL, 2.0 mmol, 1.11M in THF) are needed and **24** is obtained in 54% yield. The spectroscopic data were identical to that reported above.

Notes, Troubleshooting, and Limitations for the "Propellerization" of Amines:

1. If the "turbo amide" as prepared above is insoluble, add additional THF to give a homogeneous solution. The solution or suspension may also become homogeneous upon heating to 90 °C.
2. In some cases, the hydrochloride salt of the starting amine may be used, but the resulting yields may be lower. It is recommended to use the free base wherever possible.
3. Higher yields of products are obtained with increasing equivalents of turbo amide. For precious amines, a stoichiometry of 1:1 amine:propellane should still give product.
4. Adding excess propellane to the reaction mixture results in no product formation.
5. Excessive dilution of the reaction mixture results in lower yields.
6. **Limitations:**
    a. Primary amines cannot be used as the source of "turbo amide." Instead, a benzyl group can be added to the primary amine and removed after "propellerization."
    b. Turbo amides of 2-pyridyl-substituted amines are generally unreactive with propellane under the above conditions. This is presumed to be due to chelation of the magnesium between the amide nitrogen and pyridine nitrogen.
    c. Functional groups such as ketones, amides, carbamates, and free alcohols or thiols are incompatible with "turbo amides."

Substrates for the "Propellerization" of Amines



48

2-(bicyclo[1.1.1]pentan-1-yl)-1,2,3,4-tetrahydroisoquinoline (48)
For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 1,2,3,4-tetrahydroisoquinoline to **48** in 57% yield.

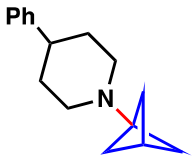
Physical State: pale yellow oil;

R_f = 0.50 (20% EtOAc in hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 – 7.01 (m, 4H), 3.67 (s, 2H), 2.92 (t, *J* = 6.0 Hz, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.49 (s, 1H), 1.87 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 134.5, 129.1, 127.1, 126.5, 126.0, 60.8, 51.1, 48.3 (3C), 46.1, 29.5, 22.8;

HRMS (ESI-TOF): calc'd for $C_{14}H_{18}N$ [$M+H^+$] 200.1439; found 200.1440.



52

1-(bicyclo[1.1.1]pentan-1-yl)-4-phenylpiperidine (52)
For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 4-phenylpiperidine to **52** in 50% yield.

Physical State: white solid (m.p. = 47-48 °C);

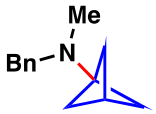
R_f = 0.55 (1:4 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.16 (m, 5H), 3.06 (dt, *J* = 12.5, 3.0 Hz, 2H), 2.47 (d, *J* = 5.1 Hz, 2H), 2.14 (td, *J* = 11.5, 3.1 Hz, 2H), 1.95 – 1.74 (m, 10H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.6, 128.5 (2C), 127.0 (2C), 126.2, 60.9, 49.0 (3C),

47.9 (2C), 42.7, 33.2 (2C), 22.3;

HRMS (ESI-TOF): calc'd for $C_{16}H_{22}N$ [M+H$^+$] 228.1752; found 228.1755.



53

***N*-benzyl-*N*-methylbicyclo[1.1.1]pentan-1-amine (53)**

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzylmethylamine to **53** in 48% yield.

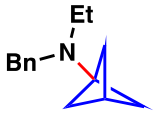
Physical State: colorless oil;

R_f = 0.68 (20% EtOAc in hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.38 (m, 4H), 7.34 – 7.32 (m, 1H), 3.59 (s, 2H), 2.52 (s, 1H), 2.21 (s, 3H), 1.90 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 129.1 (2C), 128.3 (2C), 127.0, 61.7, 57.5, 48.4 (3C), 37.1, 22.3;

HRMS (ESI-TOF): calc'd for $C_{13}H_{18}N$ [M+H$^+$] 188.1439; found 188.1441.



54

***N*-benzyl-*N*-ethylbicyclo[1.1.1]pentan-1-amine (54)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzylethylamine to **54** in 64% yield.

Physical State: colorless oil;

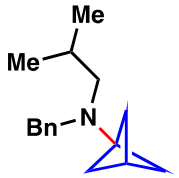
R_f = 0.50 (3% MTBE/heptane, vis. $KMnO_4$);

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35 – 7.25 (m, 4H), 7.23 – 7.15 (m, 1H), 3.58 (s, 2H), 2.53 (q, J = 7.5 Hz, 2H), 2.33 (s, 1H), 1.72 (s, 6H), 0.93 (t, J = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 141.1, 128.5 (2C), 128.4 (2C), 126.9, 61.2, 53.4, 49.9

(3C), 44.1, 22.8, 13.6;

HRMS (ESI-TOF): calc'd for $C_{14}H_{20}N$ [M+H$^+$] 202.1596; found 202.1597.



55

***N*-benzyl-*N*-isobutylbicyclo[1.1.1]pentan-1-amine (55)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzylisobutylamine[45] to **55** in 72% yield.

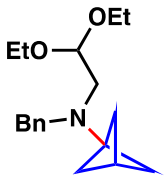
Physical State: colorless oil;

***R*$_f$** = 0.60 (5% EtOAc/heptane, vis. I_2);

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.35 – 7.24 (m, 4H), 7.23 – 7.14 (m, 1H), 3.57 (s, 2H), 2.30 (s, 1H), 2.20 (d, *J* = 7.1 Hz, 2H), 1.67 (s, 6H), 1.56 (dt, *J* = 13.5, 6.7 Hz, 1H), 0.77 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 140.9, 128.0 (2C), 127.8 (2C), 126.4, 61.0, 58.7, 55.2, 49.0 (3C), 26.9, 22.2, 20.5 (2C);

HRMS (ESI-TOF): calc'd for $C_{16}H_{24}N$ [M+H$^+$] 230.1909; found 230.1908.



56

***N*-benzyl-*N*-(2,2-diethoxyethyl)bicyclo[1.1.1]pentan-1-amine (56)**

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(2,2-diethoxyethyl)amine[46] to **56** in 12% yield.

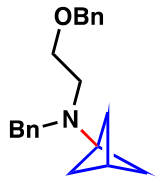
Physical State: colorless oil;

***R*$_f$** = 0.63 (19% EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.0 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.42 (t, *J* = 5.2 Hz, 1H), 3.74 (s, 2H), 3.55 (dq, *J* = 9.3, 7.1 Hz, 2H), 3.43 (dq, *J* = 9.3, 7.0 Hz, 2H), 2.70 (d, *J* = 5.3 Hz, 2H), 2.33 (s, 1H), 1.75 (s, 6H), 1.15 (t, *J* = 7.1 Hz, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.1, 128.7 (2C), 128.1 (2C), 126.7, 102.6, 62.1 (2C), 61.3, 55.7, 53.5, 49.9 (3C), 22.8, 15.5 (2C);

HRMS (ESI-TOF): calc'd for $C_{18}H_{28}NO_2$ [M+H$^+$] 290.2120; found 290.2116.



57

***N*-benzyl-*N*-(2-(benzyloxy)ethyl)bicyclo[1.1.1]pentan-1-amine (57)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(2-(benzyloxy)ethyl)amine[47] to **57** in 51% yield.

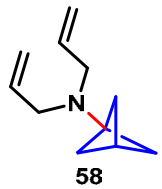
Physical State: colorless oil;

***R*$_f$** = 0.81 (3:1 heptane/EtOAc, vis. $KMnO_4$);

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.36 – 7.24 (m, 9H), 7.23 – 7.17 (m, 1H), 4.39 (s, 2H), 3.65 (s, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H), 2.32 (s, 1H), 1.70 (s, 6H);

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 140.4, 138.5, 128.1 (2C), 128.0 (2C), 127.9 (2C), 127.3 (2C), 127.2, 126.5, 71.9, 68.6, 60.6, 54.3, 49.3, 49.2 (3C), 22.1;

HRMS (ESI-TOF): calc'd for $C_{21}H_{26}NO$ [M+H$^+$] 308.2009; found 308.2017.



58

***N*,*N*-diallylbicyclo[1.1.1]pentan-1-amine (58)**

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*,*N*-diallylamine to **58** in 46% yield.

Note: compound **58** is volatile.

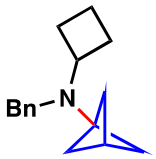
Physical State: colorless liquid;

R_f = 0.84 (10% EtOAc in hexanes; vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.86 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 2H), 5.17 – 5.05 (m, 4H), 3.17 (dt, *J* = 6.6, 1.4 Hz, 4H), 2.38 (s, 1H), 1.82 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 136.4, 117.1, 60.9, 52.8, 50.2, 23.1;

HRMS (ESI-TOF): calc'd for $C_{11}H_{17}N$ [M+H^+] 164.1439; found 164.1438.



59

***N*-benzyl-*N*-cyclobutylbicyclo[1.1.1]pentan-1-amine (59)**

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzylcyclobutylamine[48] to **59** in 42% yield.

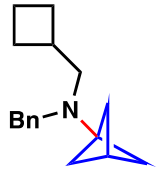
Physical State: colorless oil;

R_f = 0.80 (3:7 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.6 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 3.57 (s, 2H), 3.37 – 3.28 (m, 1H), 2.24 (s, 1H), 2.03 – 1.89 (m, 4H), 1.67 (s, 8H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.8, 128.4 (2C), 128.0 (2C), 126.5, 60.1, 56.5, 51.6, 50.5 (3C), 29.6 (2C), 23.6, 15.3;

HRMS (ESI-TOF): calc'd for $C_{16}H_{22}N$ [M+H^+] 228.1752; found 228.1753.



60

***N*-benzyl-*N*-(cyclobutylmethyl)bicyclo[1.1.1]pentan-1-amine (60)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl(cyclobutylmethyl)amine to **60** in 46% yield.

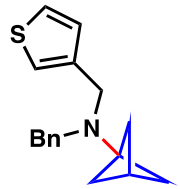
Physical State: colorless oil;

R_f = 0.70 (3% MTBE/heptane, vis. $KMnO_4$);

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 – 7.24 (m, 4H), 7.22 – 7.15 (m, 1H), 3.55 (s, 2H), 2.47 (d, *J* = 7.3 Hz, 2H), 2.40 – 2.32 (m, 1H), 2.32 (s, 1H), 1.94 – 1.83 (m, 2H), 1.81 – 1.61 (m, 8H), 1.53 – 1.40 (m, 2H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 141.5, 128.5 (2C), 128.3 (2C), 126.9, 61.4, 56.9, 54.7, 49.6 (3C), 34.5, 26.9 (2C), 22.6, 18.4;

HRMS (ESI-TOF): calc'd for $C_{17}H_{24}N$ [M+H$^+$] 242.1909; found 242.1907.



61

***N*-benzyl-*N*-(thiophen-3-ylmethyl)bicyclo[1.1.1]pentan-1-amine (61)**

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(thiophen-3-ylmethyl)amine[49] to **61** in 74% yield.

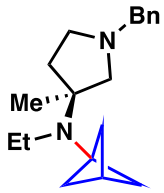
Physical State: colorless oil;

R_f = 0.30 (1:40 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.1 Hz, 2H), 7.30 – 7.24 (m, 2H), 7.23 – 7.17 (m, 2H), 7.11 – 7.04 (m, 2H), 3.65 (s, 2H), 3.63 (s, 2H), 2.30 (s, 1H), 1.69 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.1, 140.2, 127.8 (2C), 127.7, 127.5 (2C), 126.1, 124.5, 121.2, 60.6, 54.2, 49.5, 49.1 (3C), 22.3;

HRMS (ESI-TOF): calc'd for $C_{17}H_{20}NS$ [M+H$^+$] 270.1316; found 270.1312.



62

1-benzyl-*N*-(bicyclo[1.1.1]pentan-1-yl)-*N*-ethyl-3-methylpyrrolidin-3-amine (62)

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert (*S*)-1-benzyl-*N*-ethyl-3-methylpyrrolidin-3-amine **S3** to **62** in 54% yield.

Physical State: light yellow oil;

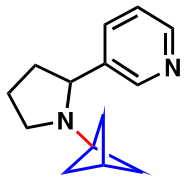
R_f = 0.29 (3:1 heptane:EtOAc, vis. $KMnO_4$);

$[\alpha]_D^{22}$ = – 19.0 (c = 0.60, MeOH);

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 3.62 (d, *J* = 13.3 Hz, 1H), 3.53 (d, *J* = 13.3 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.65 – 2.38 (m, 5H), 2.25 (s, 1H), 1.94 – 1.85 (m, 7H), 1.66 – 1.58 (m, 1H), 1.19 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-d_6): δ 139.2, 128.2 (2C), 128.1 (2C), 126.6, 67.0, 65.2, 59.7, 59.5, 52.5 (3C), 52.3, 41.2, 23.6, 23.5, 18.0 (1 sp^3 signal missing due to solvent overlap);

HRMS (ESI-TOF): calc'd for $C_{19}H_{29}N_2$ [M+H$^+$] 285.2331; found 285.2325.



63

(±)-3-(1-(bicyclo[1.1.1]pentan-1-yl)pyrrolidin-2-yl)pyridine (63)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *rac*-nornicotine to **63** in 54% yield.

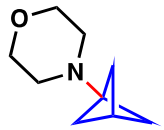
Physical State: yellow oil;

R_f = 0.42 (3:7 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53 (d, *J* = 2.2 Hz, 1H), 8.48 – 8.40 (m, 1H), 7.71 (dt, *J* = 7.8, 2.1 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 3.15 – 3.02 (m, 1H), 2.59 (q, *J* = 8.8 Hz, 1H), 2.28 – 2.13 (m, 2H), 1.96 – 1.85 (m, 1H), 1.80 – 1.72 (m, 1H), 1.70 – 1.63 (m, 1H), 1.62 – 1.47 (m, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.3, 148.3, 140.9, 134.8, 123.3, 62.9, 58.7, 50.4, 49.3 (3C), 36.3, 23.3, 23.1;

HRMS (ESI-TOF): calc'd for $C_{14}H_{19}N_2$ [M+H$^+$] 215.1548; found 215.1544.



64

4-(bicyclo[1.1.1]pentan-1-yl)morpholine (64)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert morpholine to **64** in 42% yield.

Note: compound **64** is volatile.

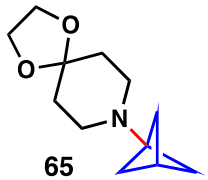
Physical State: colorless liquid;

R_f = 0.62 (20% EtOAc in hexanes; vis. I_2);

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 – 3.70 (m, 4H), 2.47 – 2.43 (m, 5H), 1.76 (s, 6H);

^{13}C NMR (126 MHz, DMSO-*d6*): δ 66.7, 60.4, 48.3, 47.6, 22.4;

HRMS (ESI-TOF): calc'd for $C_9H_{16}NO$ [M+H$^+$] 154.1232; found 154.1234.



65

8-(bicyclo[1.1.1]pentan-1-yl)-1,4-dioxa-8-azaspiro[4.5]decane (65)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 1,4-dioxa-8-azaspiro[4.5]decane[50] to **65** in 52% yield.

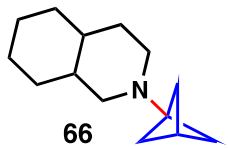
Physical State: yellow oil;

R_f = 0.32 (3:7 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.93 (s, 4H), 2.54 (s, 4H), 2.38 (s, 1H), 1.76 (s, 6H), 1.73 (t, *J* = 5.8 Hz, 4H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 107.3, 64.3 (2C), 60.5, 48.1 (3C), 46.4 (2C), 34.6 (2C), 22.1;

HRMS (ESI-TOF): calc'd for $C_{12}H_{20}NO_2$ [M+H$^+$] 210.1494; found 210.1494.



66

2-(bicyclo[1.1.1]pentan-1-yl)decahydroisoquinoline (66)

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert perhydroisoquinoline to **66** in 32% yield.

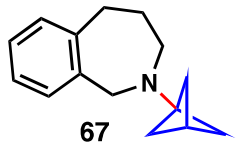
Physical State: yellow oil;

R_f = 0.64 (3:7 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.88 (d, *J* = 9.6 Hz, 1H), 2.72 (d, *J* = 10.9 Hz, 1H), 2.38 (s, 1H), 2.00 – 1.92 (m, 1H), 1.74 (s, 6H), 1.70 (d, *J* = 9.7 Hz, 2H), 1.64 – 1.57 (m, 2H), 1.57 – 1.49 (m, 2H), 1.35 – 1.14 (m, 4H), 1.04 – 0.86 (m, 2H), 0.87 – 0.76 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 60.9, 55.0, 49.0, 47.8 (3C), 41.8, 41.7, 33.2, 32.8, 30.9, 26.7, 26.3, 22.3;

HRMS (ESI-TOF): calc'd for $C_{14}H_{24}N$ [M+H$^+$] 206.1909; found 206.1912.



67

2-(bicyclo[1.1.1]pentan-1-yl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (67)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine[51] to **67** in 53% yield.

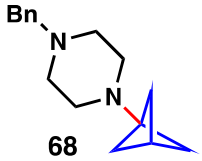
Physical State: yellow oil;

***R*$_f$** = 0.53 (1:4 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 – 7.06 (m, 4H), 3.83 (s, 2H), 3.06 (t, *J* = 5.4 Hz, 2H), 2.96 – 2.82 (m, 2H), 2.37 (s, 1H), 1.81 – 1.77 (s, 8H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 140.3, 129.5, 129.0, 127.2, 126.1, 60.9, 56.3, 54.9, 49.8 (3C), 35.8, 27.8, 22.8;

HRMS (ESI-TOF): calc'd for $C_{15}H_{20}N$ [M+H$^+$] 214.1596; found 214.1599.



68

1-benzyl-4-(bicyclo[1.1.1]pentan-1-yl)piperazine (68)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzylpiperazine[52] to **68** in 67% yield.

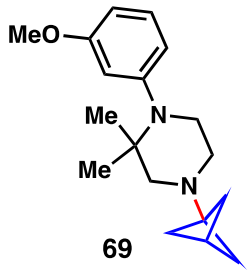
Physical State: pale yellow oil;

***R*$_f$** = 0.53 (3:7 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 4H), 7.24 (td, *J* = 5.7, 2.8 Hz, 1H), 3.52 (s, 2H), 2.50 (s, 8H), 2.41 (s, 1H), 1.76 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.2, 129.3 (2C), 128.3 (2C), 127.1, 63.3, 60.5, 52.8 (2C), 48.0 (2C), 47.8 (3C), 22.3;

HRMS (ESI-TOF): calc'd for $C_{16}H_{23}N_2$ [M+H$^+$] 243.1861; found 243.1859.



69

4-(bicyclo[1.1.1]pentan-1-yl)-1-(3-methoxyphenyl)-2,2-dimethylpiperazine (69)
For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert 1-(3-methoxyphenyl)-2,2-dimethylpiperazine to **69** in 69% yield.

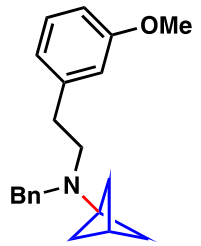
Physical State: colorless oil;

***R**$_f$* = 0.65 (1:4 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.70 – 6.63 (m, 2H), 3.77 (s, 3H), 3.13 (t, *J* = 5.0 Hz, 2H), 2.56 (t, *J* = 5.0 Hz, 2H), 2.42 (s, 1H), 2.33 (s, 2H), 1.77 (s, 6H), 1.08 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 151.0, 128.5, 120.1, 113.8, 109.6, 61.5, 60.8, 55.3, 54.6, 49.3, 47.7 (3C), 47.6, 23.3 (br s, 2C), 22.3;

HRMS (ESI-TOF): calc'd for $C_{18}H_{27}N_2O$ [M+H$^+$] 287.2123; found 287.2126.



70

***N*-benzyl-*N*-(3-methoxyphenethyl)bicyclo[1.1.1]pentan-1-amine (70)**
For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(3-methoxyphenethyl)amine **S4** to **70** in 54% yield.

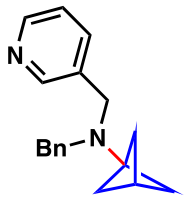
Physical State: yellow oil;

***R*$_f$** = 0.79 (3:7 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.32 (m, 2H), 7.31 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.16 (dd, *J* = 8.2, 7.5 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.63 (dd, *J* = 2.6, 1.7 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 2H), 2.78 – 2.74 (m, 2H), 2.71 – 2.66 (m, 2H), 2.39 (s, 1H), 1.82 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 159.7, 142.5, 140.6, 129.3, 128.6 (2C), 128.2 (2C), 126.8, 121.2, 114.6, 111.2, 61.2, 55.2, 54.5, 52.4, 50.1 (3C), 35.1, 23.0;

HRMS (ESI-TOF): calc'd for $C_{21}H_{26}NO$ [M+H$^+$] 308.2014; found 308.2018.



71

***N*-benzyl-*N*-(pyridin-3-ylmethyl)bicyclo[1.1.1]pentan-1-amine (71)**

For 0.25 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(pyridin-3-ylmethyl)amine to **71** in 60% yield.

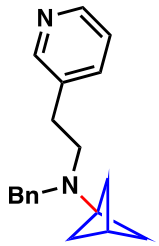
Physical State: colorless oil;

***R*$_f$** = 0.43 (3:1 heptane/EtOAc; vis. $KMnO_4$);

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.51 (d, *J* = 1.6 Hz, 1H), 8.40 (dd, *J* = 4.6, 1.2 Hz, 1H), 7.71 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.37 – 7.26 (m, 5H), 7.23 – 7.17 (m, 1H), 3.62 (s, 4H), 2.30 (s, 1H), 1.65 (s, 6H);

^{13}C NMR (101 MHz, DMSO-*d*$_6$): δ 149.3, 147.9, 139.9, 135.7, 135.6, 128.1 (2C), 128.0 (2C), 126.7, 123.1, 60.6, 54.5, 51.6, 49.1 (3C), 22.2;

HRMS (ESI-TOF): calc'd for $C_{18}H_{21}N_2$ [M+H$^+$] 265.1699; found 265.1700.



72

***N*-benzyl-*N*-(2-(pyridin-3-yl)ethyl)bicyclo[1.1.1]pentan-1-amine (72)**

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(2-(pyridin-3-yl)ethyl)amine **S5** to **72** in 39% yield.

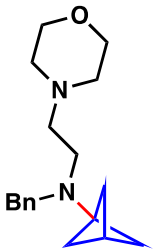
Physical State: colorless oil;

R_f = 0.65 (1:1 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, *J* = 4.7 Hz, 1H), 8.42 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.26 (m, 5H), 7.21 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.76 (s, 2H), 2.82 (dd, *J* = 9.0, 5.6 Hz, 2H), 2.73 (dd, *J* = 9.0, 6.0 Hz, 2H), 2.47 (s, 1H), 1.89 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 147.3, 140.1, 136.2, 136.1, 128.6 (2C), 128.2 (2C), 126.9, 123.2, 61.0, 54.8, 51.7, 49.9 (3C), 32.3, 22.9;

HRMS (ESI-TOF): calc'd for $C_{19}H_{23}N_2$ [M+H$^+$] 279.1861; found 279.1863.



73

***N*-benzyl-*N*-(2-morpholinoethyl)bicyclo[1.1.1]pentan-1-amine (73)**

For 0.5 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert *N*-benzyl-(2-morpholinoethyl)amine[53] to **73** in 48% yield.

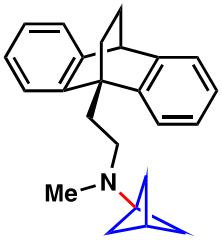
Physical State: pale yellow oil;

R_f = 0.37 (50% EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 6.9 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 3.73-3.72 (m, 6H), 2.75-2.72 (m, 2H), 2.47-2.42 (m, 7H), 1.85 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 128.5 (2C), 128.1 (2C), 126.8, 66.9 (2C), 61.2, 58.0, 55.2, 54.1 (2C), 49.7 (3C), 47.3, 22.8;

HRMS (ESI-TOF): calc'd for $C_{18}H_{27}N_2O$ [M+H$^+$] 287.2123; found 287.2133.



74

***N*-(3-((9*R*,10*R*)-9,10-ethanoanthracen-9(10*H*)-yl)propyl)-*N*-methylbicyclo[1.1.1]pentan-1-amine, "propellerized" maprotiline (74)**

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert maprotiline hydrochloride to **74** in 80% yield.

Note 1: Two equivalents of *i*PrMgCl•LiCl (1.80 mL, 2.0 mmol, 1.11M in THF) were used.

Note 2: Unreacted maprotiline (170 mg, 86%) was recovered from the reaction.

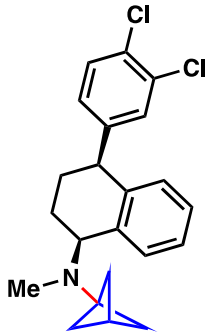
Physical State: colorless oil;

***R*$_f$** = 0.53 (1:4 EtOAc:hexanes; vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (ddd, *J* = 7.3, 6.3, 1.4 Hz, 4H), 7.14 (dtd, *J* = 23.9, 7.4, 1.4 Hz, 4H), 4.32 (s, 1H), 2.76 – 2.68 (m, 2H), 2.54 – 2.45 (m, 3H), 2.35 (s, 3H), 2.06 – 1.96 (m, 2H), 1.95 – 1.83 (m, 8H), 1.67 – 1.59 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.6 (2C), 145.1 (2C), 125.3 (2C), 125.3 (2C), 123.4 (2C), 121.4 (2C), 61.5, 53.8, 48.5 (3C), 44.9, 44.6, 37.2, 29.8, 29.1, 27.8, 23.6, 22.4;

HRMS (ESI-TOF): calc'd for $C_{25}H_{30}N$ [M+H$^+$] 344.2378; found 344.2381.



75

***N*-((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylbicyclo[1.1.1]pentan-1-amine, "propellerized" sertraline (75)**

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert Sertraline to **75** in 62% yield.

Note: Unreacted Sertraline (239 mg, 93%) was recovered from the reaction.

Physical State: colorless oil;

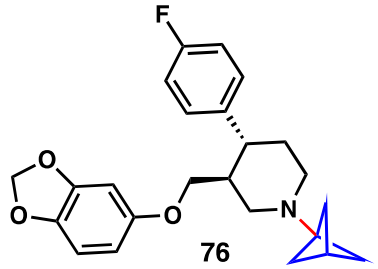
R_f = 0.65 (1:1 EtOAc:hexanes; vis. UV);

$[\alpha]_D^{20}$ = + 94.1 (c = 1.00, $CDCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.16 – 7.09 (m, 2H), 6.85 (ddd, *J* = 32.4, 8.0, 1.7 Hz, 2H), 4.11 (dq, *J* = 9.9, 5.6, 4.4 Hz, 2H), 2.41 (s, 1H), 2.18 (dddd, *J* = 13.4, 12.4, 5.7, 2.9 Hz, 1H), 2.13 (s, 3H), 1.98 (dd, *J* = 5.9, 3.3 Hz, 1H), 1.90 (dd, *J* = 9.4, 1.6 Hz, 3H), 1.80 (dd, *J* = 9.4, 1.6 Hz, 3H), 1.73 (tdd, *J* = 12.9, 10.3, 2.8 Hz, 1H), 1.65 (ddt, *J* = 10.5, 8.1, 2.9 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 147.7, 139.7, 138.2, 132.2, 130.9, 130.2, 130.0, 129.9, 128.7, 128.3, 127.0, 126.8, 61.1, 57.7, 50.5 (3C), 43.6, 30.9, 30.5, 22.4, 18.7;

HRMS (ESI-TOF): calc'd for $C_{22}H_{24}Cl_2N$ [M+H$^+$] 372.1286; found 372.1280.



76

(3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)piperidine, "propellerized" paroxetine (76)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert Paroxetine to **76** in 67% yield.

Note: Unreacted Paroxetine (240 mg, 91%) was recovered from the reaction.

Physical State: colorless oil;

R_f = 0.30 (1:5 EtOAc:hexanes; vis. UV);

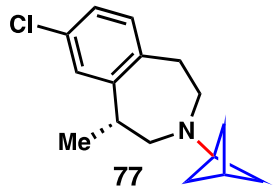
$[\alpha]_D^{20}$ = – 59.6 (c = 1.00, $CDCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.87 (s, 2H), 3.58 (dd, *J* = 9.4, 2.8 Hz, 1H), 3.45 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.23 (ddd, *J* = 11.4, 3.7, 1.6 Hz, 1H), 3.04 (d, *J* = 11.4 Hz, 1H), 2.50 – 2.41 (m, 2H), 2.25 – 2.06 (m, 3H), 1.83 (s, 8H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 161.6 (d, $^1J_{C\text{-}F}$ = 244 Hz), 154.5, 148.3, 141.7, 139.8, 129.0 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 2C), 115.5 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, 2C), 108.0, 105.7, 101.2, 98.1, 69.7, 60.7, 52.3, 48.9, 48.0 (3C), 44.0, 41.9, 34.0, 22.3;

^{19}F NMR (376 MHz, $CDCl_3$): δ –116.8;

HRMS (ESI-TOF): calc'd for $C_{24}H_{27}FNO_3$ [M+H$^+$] 396.1975; found 396.1972.



77

(*R*)-3-(bicyclo[1.1.1]pentan-1-yl)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, "propellerized lorcaserin" (77)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert Lorcaserin to **77** in 84% yield.

Note: Unreacted Lorcaserin (136 mg, 90%) was recovered from the reaction.

Physical State: colorless oil;

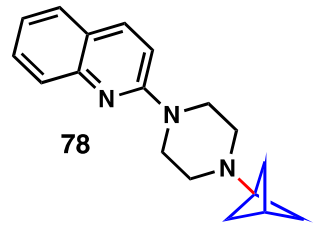
R_f = 0.60 (1:5 EtOAc:hexanes; vis. UV);

$[\alpha]_D^{20}$ = +7.9 (c = 1.00, $CDCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (d, *J* = 2.2 Hz, 1H), 7.08 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 3.15 (p, *J* = 7.5 Hz, 1H), 3.09 – 3.00 (m, 1H), 3.00 – 2.92 (m, 1H), 2.85 – 2.78 (m, 2H), 2.41 (s, 1H), 2.25 (t, *J* = 11.3 Hz, 1H), 2.17 (dd, *J* = 12.3, 8.5 Hz, 1H), 1.78 (s, 6H), 1.34 (d, *J* = 7.2 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 147.0, 139.6, 131.5, 129.9, 125.3, 125.0, 60.9, 56.5, 49.3, 47.9 (3C), 37.2, 35.2, 21.6, 17.9;

HRMS (ESI-TOF): calc'd for $C_{16}H_{21}ClN$ [M+H$^+$] 262.1363; found 262.1364.



78

2-(4-(bicyclo[1.1.1]pentan-1-yl)piperazin-1-yl)quinoline, "propellerized" quipazine (78)

For 0.50 mmol scale of [1.1.1]propellane, the standard procedure was followed to convert Quipazine to **78** in 81% yield.

Note: Unreacted Quipazine (160 mg, 96%) was recovered from the reaction.

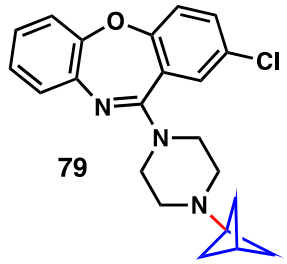
Physical State: white solid (m.p. = 143-144 °C);

R_f = 0.34 (1:2 EtOAc:hexanes; vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 1H), 3.83 – 3.76 (m, 4H), 2.63 – 2.58 (m, 4H), 2.46 (s, 1H), 1.81 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.5, 148.0, 137.6, 129.6, 127.3, 126.8, 123.2, 122.5, 109.7, 60.5, 48.0 (2C), 47.8 (3C), 44.9 (2C), 22.4;

HRMS (ESI-TOF): calc'd for $C_{18}H_{22}N_3$ [M+H$^+$] 280.1814; found 280.1811.



79

11-(4-(bicyclo[1.1.1]pentan-1-yl)piperazin-1-yl)-2-chlorodibenzo[*b*,*f*][1,4]oxazepine, "propellerized" amoxapine (79)

For 0.50 mmol scale of [1.1.1.]propellane, the standard procedure was followed to convert amoxapine to **79** in 31% yield.

Note: Unreacted amoxapine (286 mg, 89%) was recovered from the reaction.

Physical State: colorless oil;

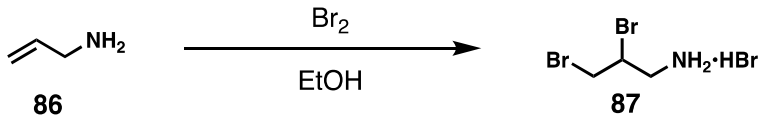
R_f = 0.35 (1:4 EtOAc:hexanes; vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.11 – 7.06 (m, 2H), 6.98 (td, *J* = 7.7, 1.7 Hz, 1H), 3.58 (s, 4H), 2.59 (s, 4H), 2.47 (s, 1H), 1.82 (s, 6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 159.4, 158.9, 151.9, 140.3, 132.6, 130.3, 129.2, 127.2, 125.9, 125.2, 124.6, 122.8, 120.2, 60.4, 47.9 (2C), 47.9 (3C), 47.2 (2C), 22.4;

HRMS (ESI-TOF): calc'd for $C_{22}H_{23}ClN_3O$ [M+H$^+$] 380.1530; found 380.1529.

Synthesis of Azetidine Hydrobromide Precursor on Decagram Scale (87)



86 87

1-Amino-2,3-dibromopropane hydrobromide (87): Following the literature method of Nagao, (*54*) a solution of Br_2 (40 mL, 0.785 mol, 2.1 equiv.) was added ***very slowly dropwise*** under vigorous stirring to a solution of ethanol (100 mL) in a 1L round bottom flask at 0 °C (***Caution: exothermic, fuming***). After the addition was complete, allylamine (28 mL, 0.374 mol, 1.0 equiv.) was added ***very slowly dropwise*** under vigorous stirring at 0 °C (***Caution: Fuming!***). The mixture was allowed to warm to room temperature and stirred at this temperature overnight (16-18 hours). The precipitate was collected via suction filtration and washed with small portions of ice-cold Et_2O. The crude material was recrystallized from MeOH to give **87** as colorless prisms (55.5 g, 50% first crop, 30.6 g 28%, second crop → 86.1 g, 78% overall). The spectroscopic data were identical to that reported in the literature.[54]

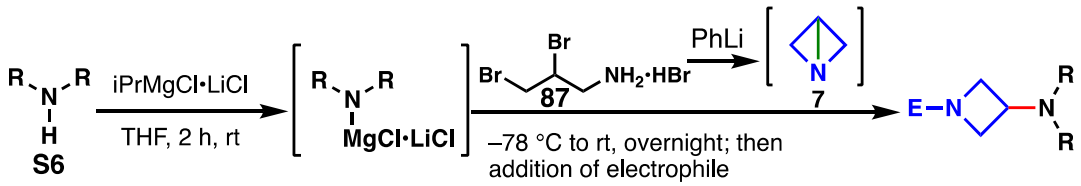
Sigma-Aldrich Catalog Number: MKE151704;

Physical State: white solid (m.p. = 173-174 °C);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 – 4.46 (m, 1H), 4.01 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.86 (dd, *J* = 11.0, 8.7 Hz, 1H), 3.70 (dd, *J* = 14.0, 3.2 Hz, 1H), 3.38 – 3.31 (m, 1H).

Fig. S22. 1-Amino-2,3-dibromopropane hydrobromide **(87)**

General Medicinal Chemistry Procedure For The One-pot "Azetidinylation" of Amines Using 87 (prepared above)



Turbo amide formation: To a flame-dried round bottom flask containing the starting amine **S6** (1 eq.) was added *i*PrMgCl•LiCl (1.04M in THF, 1.0 eq) slowly dropwise (*Caution: gas evolution*) at room temperature. The mixture was stirred for 2 h at room temperature and used as directed below.

Azabicyclobutane (ABB) formation and reaction: To a flame-dried 25 or 50 mL round bottom flask was added amine salt **87** (298 mg, 1.0 mmol, 1.0 eq.) and dry THF (3 mL) with an argon balloon. The resulting suspension was cooled to –78 °C (dry ice/acetone). A solution of PhLi (1.67 mL, 3.0 mmol, 1.8M solution in Bu_2O, 3.0 eq.) was added **slowly dropwise** and the resulting mixture stirred at –78 °C for 2h. A pre-made solution of turbo amide (1.0 equiv., *see above*) was then added dropwise at –78 °C. The flask was removed from the dry ice bath and allowed to warm to room temperature overnight (~16h). The reaction was cooled to 0 °C and treated **slowly dropwise** with a solution of electrophilic trapping agent (e.g. Boc_2O, $ClCO_2Et$, TsCl) (2.0 eq.) in dry THF (5 mL). The reaction was removed from the bath and stirred at room temperature for 3 hours. The resulting mixture was poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give the desired product.

Notes, Troubleshooting, and Limitations For The "Azetidinylation" of Amines:

1. Use of a 25 or 50 mL round bottom flask for azabicyclobutane (ABB) formation is preferred to maintain consistent stirring of the suspension.
2. Initial dilution of 3 mL THF per 1 mmol of **87** is optimal.
3. Slow addition of PhLi (during ABB formation) and of the electrophilic solution (during quench) is required for optimal yields.
4. Regarding time:
    a. 2 hours for ABB formation appears optimal for maximum yield (more than 2 hours will result in degradation of the ring system; less time may not give full conversion from **87** to ABB).
    b. 16 hours for the amination reaction and 3 hours for the electrophilic quench are general and meant to cover a full range of substrates; reaction time for individual substrates may be further optimized if desired.
7. **Limitations:**
    a. Primary amines cannot be used as the source of "turbo amide." Instead, a benzyl group can be added to the primary amine and removed after "azetidinylation."
    b. Turbo amides of 2-pyridyl-substituted amines are generally unreactive with ABB under the above conditions. This is presumed to be due to chelation of the magnesium between the amide nitrogen and pyridine nitrogen.
    c. Functional groups such as ketones, amides, carbamates, and free alcohols or thiols are incompatible with "turbo amides."

Graphical Procedure For The One-pot "Azetidinylation" of Amines

Fig. S23. Left. Suspension of **87** in dry THF is cooled to –78 °C. **Right.** After addition of PhLi, the color changes from colorless/white to pale yellow.

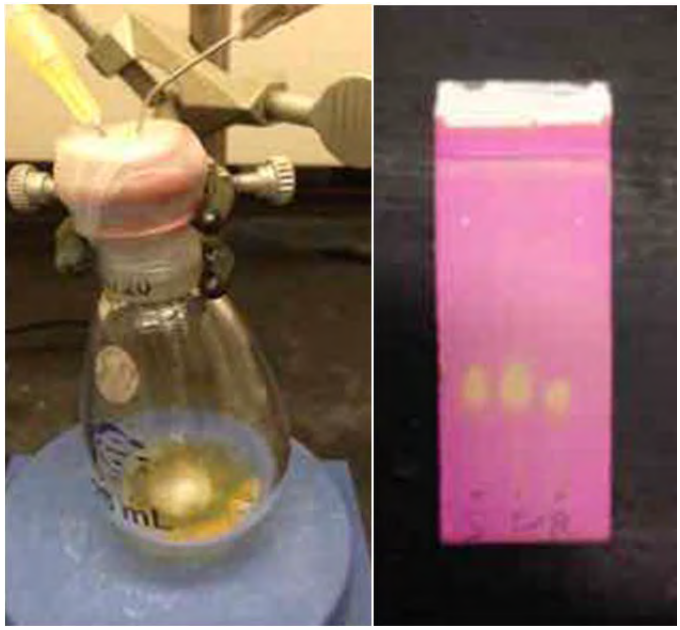
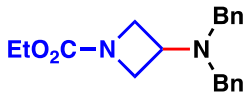


Fig. S24. Left. Solution of the "turbo amide " of morpholine. This is added to the solution in Figure S23 (right) at –78 °C then removed from the dry ice bath and stirred at room temperature overnight. **Right.** TLC of reaction after quench with Boc_2O in THF. From left to right: authentic sample of **103**, co-spot, crude reaction mixture.

Substrates for the "Azetidinylation" of Amines

Note on ^{13}C NMR of protected azetidines: When protected with Boc or CO_2Et, C2 and C4 on the azetidine ring typically appear as broad singlets or doublets at 50-55 ppm. These peaks sometimes overlap with other signals and do not resolve well from the baseline. Expanded insets are included where possible in the NMR spectra section. An X-ray crystal structure is provided for **103** and HSQC is included for **96** and **99**. Similar observations for these compounds have been reported previously in the literature.[55, 56]



89

Ethyl 3-(dibenzylamino)azetidine-1-carboxylate (89)

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to **89** in 82% yield.

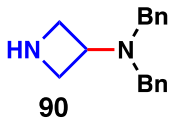
Physical State: pale yellow oil;

***R*$_f$** = 0.70 (1:2 EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (dt, *J* = 13.1, 7.1 Hz, 8H), 7.29 – 7.25 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.96 – 3.89 (m, 2H), 3.85 (dd, *J* = 9.0, 5.8 Hz, 2H), 3.66 – 3.59 (m, 1H), 3.56 (s, 4H), 1.23 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.9, 138.1 (2C), 129.1 (4C), 128.5 (4C), 127.4 (2C), 61.1, 54.6 (2C), 53.7 (br s, 2C), 52.0, 14.9;

HRMS (ESI-TOF): calc'd for $C_{20}H_{25}N_2O_2$ [M+H$^+$] 325.1916; found 325.1919.



90

***N*,*N*-dibenzylazetidin-3-amine (90)**

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to **90** in 53% yield. For ^{1}H, ^{13}C, and ^{19}F NMR **90** was analyzed as the bis-TFA salt. [57]

Physical State: yellow solid (m.p. = 138-139 °C);

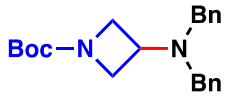
***R*$_f$** = 0.43 (20:2:1 $CHCl_3$:MeOH:acetone);

^{1}H NMR (600 MHz, MeOD): δ 7.47 – 7.28 (m, 10H), 4.02 (q, *J* = 7.7 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.85 – 3.78 (m, 2H), 3.76 (s, 4H), NH proton not observed;

^{13}C NMR (151 MHz, $CDCl_3$): δ 161.8 (q, $^2J_{C\text{-}F}$ = 37.1 Hz, from TFA), 130.2 (2 signals overlapping, 6C), 129.3 (4C), 127.9 (2C), 115.6 (q, $^1J_{C\text{-}F}$ = 290 Hz, from TFA), 56.9 (2C), 54.6, 48.1 (2C);

^{19}F NMR (376 MHz, $CDCl_3$): δ –77.0 (t, *J* = 38.5 Hz), –77.1 (t, *J* = 37.9 Hz) [from TFA];

HRMS (ESI-TOF): calc'd for $C_{17}H_{21}N_2$ [M+H$^+$] 253.1705; found 253.1701.



91

***tert*-butyl 3-(dibenzylamino)azetidine-1-carboxylate (91)**

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to **91** in 93% yield.

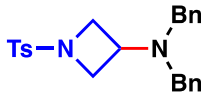
Physical State: pale yellow oil;

***R*$_f$** = 0.62 (1:4 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 8H), 7.28 – 7.24 (m, 2H), 3.88 (t, *J* = 8.3 Hz, 2H), 3.80 (dd, *J* = 9.0, 5.7 Hz, 2H), 3.62 – 3.53 (m, 5H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 138.1 (2C), 129.2 (4C), 128.4 (4C), 127.4 (2C), 79.5, 54.5 (2C), 53.6 (br d, *J* = 97.9 Hz, 2C), 51.6, 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{22}H_{29}N_2O_2$ [M+H$^+$] 353.2229; found 353.2229.



92

***N*,*N*-dibenzyl-1-tosylazetidin-3-amine (92)**

For 1.0 mmol scale, the standard procedure was followed to convert dibenzylamine to **92** in 78% yield.

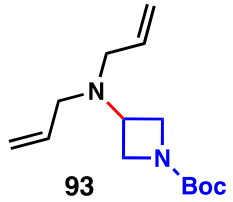
Physical State: pale yellow oil;

R_f = 0.63 (1:2 EtOAc/hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.22 (m, 6H), 7.12 (d, *J* = 6.8 Hz, 4H), 3.69 (q, *J* = 6.0 Hz, 2H), 3.53 – 3.44 (m, 3H), 3.35 (s, 4H), 2.49 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.1, 138.1 (2C), 131.4, 129.8 (2C), 128.9 (4C), 128.6 (2C), 128.4 (4C), 127.5 (2C), 55.5 (2C), 54.9 (2C), 51.3, 21.8;

HRMS (ESI-TOF): calc'd for $C_{24}H_{27}N_2O_2S$ [M+H$^+$] 407.1793; found 407.1795.



93

***tert*-butyl 3-(diallylamino)azetidine-1-carboxylate (93)**

For 1.0 mmol scale, the standard procedure was followed to convert diallylamine to **93** in 52% yield.

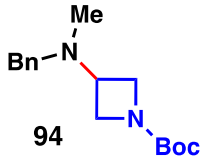
Physical State: pale yellow oil;

R_f = 0.30 (1:3 EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, MeOD): δ 5.89 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 2H), 5.30 – 5.16 (m, 4H), 3.93 (d, *J* = 7.5 Hz, 2H), 3.83 (d, *J* = 5.7 Hz, 2H), 3.56 (ddd, *J* = 13.1, 7.3, 5.8 Hz, 1H), 3.13 (d, *J* = 6.7 Hz, 4H), 1.45 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 134.6 (2C), 118.4 (2C), 79.5, 54.5 (br s, 2C), 53.6 (2C), 51.6, 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{14}H_{25}N_2O_2$ [M+H$^+$] 253.1916; found 253.1916.



***tert*-butyl 3-(benzyl(methyl)amino)azetidine-1-carboxylate (94)**

For 1.0 mmol scale, the standard procedure was followed to convert *N*-benzylmethylamine to **94** in 46% yield.[58]

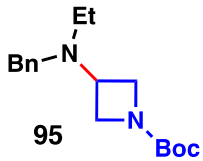
Physical State: yellow oil;

R_f = 0.30 (1:5 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 5H), 3.95 (dd, *J* = 8.7, 7.1 Hz, 2H), 3.85 (dd, *J* = 8.8, 5.5 Hz, 2H), 3.41 (s, 2H), 3.27 (tt, *J* = 7.2, 5.5 Hz, 1H), 2.08 (s, 3H), 1.46 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 137.7, 129.2 (2C), 128.4 (2C), 127.4, 79.5, 58.9, 53.9, 53.1 (br s, 2C) 38.0, 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{16}H_{25}N_2O_2$ [M+H$^+$] 277.1916; found 277.1914



***tert*-butyl 3-(benzyl(ethyl)amino)azetidine-1-carboxylate (95)**

For 1.0 mmol scale, the standard procedure was followed to *N*-benzylethylamine to **95** in 44% yield.

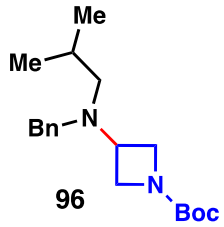
Physical State: light yellow oil;

R_f = 0.45 (3:1 heptanes:EtOAc, vis. $KMnO_4$);

^{1}H NMR (400 MHz, MeCN-d_3): δ 7.35 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 3.84 (t, *J* = 7.9 Hz, 2H), 3.72 – 3.66 (m, 2H), 3.59 – 3.48 (m, 3H), 2.46 (q, *J* = 7.1 Hz, 2H), 1.40 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 138.5, 129.1 (2C), 128.4 (2C), 127.3, 79.5, 54.1, 53.7 (br s, 2C), 51.7, 44.3, 28.5 (3C), 11.6;

HRMS (ESI-TOF): calc'd for $C_{17}H_{27}N_2O_2$ [M+H$^+$] 291.2067; found 291.2077.



96

***tert*-butyl 3-(benzyl(isobutyl)amino)azetidine-1-carboxylate (96)**

For 1.0 mmol scale, the standard procedure was followed to convert *N*-benzylisobutylamine[46] to **96** in 42% yield.

Physical State: colorless oil;

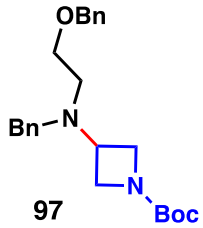
***R*$_f$** = 0.66 (3:1 heptanes:EtOAc, vis. $KMnO_4$);

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.36 – 7.21 (m, 5H), 3.79 (br s, 2H), 3.58 (br s, 2H), 3.53, (s, 2H), 3.49 – 3.40 (m, 1H), 2.08 (d, *J* = 7.1 Hz, 2H), 1.69 (dt, *J* = 13.4, 6.6 Hz, 1H), 1.35 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 156.0, 139.0, 129.4 (2C), 128.6 (2C), 127.4, 79.0, 58.8, 55.8, 53.9 (br d, *J* = 95.7 Hz, 2C), 52.2, 28.5 (3C), 26.0, 21.2 (2C);

HSQC: See pages S510-S511;

HRMS (ESI-TOF): calc'd for $C_{19}H_{30}N_2NaO_2$ [M+Na$^+$] 341.2205; found 341.2202.



97

***tert*-butyl 3-(benzyl(2-(benzyloxy)ethyl)amino)azetidine-1-carboxylate (97)**

For 1.0 mmol scale, the standard procedure was followed to convert *N*-benzyl-(2-(benzyloxy)ethyl)amine[47] to **97** in 45% yield.

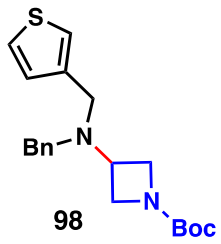
Physical State: colorless oil;

R_f = 0.40 (25% EtOAc in heptanes, vis. $KMnO_4$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 10H), 4.45 (s, 2H), 3.94 – 3.88 (m, 2H), 3.84 – 3.77 (m, 2H), 3.68 – 3.62 (m, 3H), 3.48 (t, *J* = 5.8 Hz, 2H), 2.72 (t, *J* = 5.8 Hz, 2H), 1.43 (s, 9H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.4, 138.5, 138.3, 129.1 (2C), 128.5 (2C), 128.4 (2C), 127.8 (2C), 127.7, 127.3, 79.4, 73.4, 68.3, 55.4, 54.0 (br s, 2C), 52.3, 49.9, 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{24}H_{33}N_2O_3$ [M+H$^+$] 397.2486; found 397.2493.



98

***tert*-butyl 3-(benzyl(thiophen-3-ylmethyl)amino)azetidine-1-carboxylate (98)**

For 1.0 mmol scale, the standard procedure was followed to convert *N*-benzyl-(thiophen-3-ylmethyl)amine[49] to **98** in 42% yield.

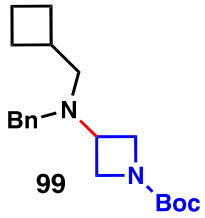
Physical State: colorless oil;

R_f = 0.50 (1:10 EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 – 7.22 (m, 6H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.01 – 6.98 (m, 1H), 3.89 (t, *J* = 8.2 Hz, 2H), 3.80 (dd, *J* = 8.9, 5.7 Hz, 2H), 3.62 – 3.51 (m, 5H), 1.43 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 138.6, 138.2, 129.1 (2C), 128.6, 128.5 (2C), 127.4, 125.8, 123.1, 79.6, 54.2, 53.6 (br s, 2C), 51.5, 49.0, 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{20}H_{27}N_2O_2S$ [M+H$^+$] 359.1793; found 359.1789.



99

***tert*-butyl 3-(benzyl(cyclobutylmethyl)amino)azetidine-1-carboxylate (99)**

For 1.0 mmol scale, the standard procedure was followed to convert *N*-benzyl-(cyclobutylmethyl)amine to **99** in 50% yield.

Physical State: colorless oil;

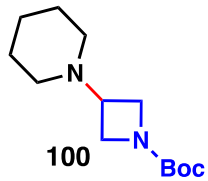
R_f = 0.58 (3:1 heptanes:EtOAc, vis. $KMnO_4$);

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 – 7.20 (m, 5H), 3.82 (br s, 2H), 3.60 (br s, 2H), 3.50 (s, 2H), 3.48 – 3.42 (m, 1H), 2.48 – 2.39 (m, 1H), 2.37 – 2.31 (m, 2H), 1.97 – 1.87 (m, 2H), 1.85 – 1.75 (m, 1H), 1.75 – 1.65 (m, 1H), 1.59 – 1.47 (m, 2H), 1.41 – 1.30 (m, 9H);

^{13}C NMR (151 MHz, DMSO-d_6): δ 156.0, 139.4, 129.1 (2C), 128.6 (2C), 127.3, 79.0, 56.7, 54.8, 54.0 (br d, J = 103 Hz, 2C), 52.1, 33.0, 28.5 (3C), 27.1 (2C), 18.5;

HSQC: See pages S518-S519;

HRMS (ESI-TOF): calc'd for $C_{20}H_{30}N_2NaO_2$ [M+Na$^+$] 353.2205; found 353.2199.



100

***tert*-butyl 3-(piperidin-1-yl)azetidine-1-carboxylate (100)**

For 1.0 mmol scale, the standard procedure was followed to convert piperidine to **100** in 56% yield.

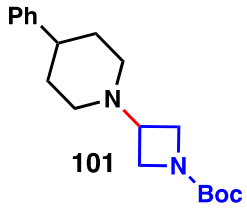
Physical State: yellow oil;

R_f = 0.50 (50% EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.93 – 3.86 (m, 2H), 3.80 (dd, *J* = 8.8, 5.6 Hz, 2H), 2.99 (p, *J* = 6.9, 6.4 Hz, 1H), 2.25 (s, 4H), 1.60 (p, *J* = 5.6 Hz, 4H), 1.51 – 1.43 (m, 2H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 79.4, 54.5, 53.6 (br d, *J* = 186 Hz, 2C), 51.0 (2C), 28.5 (3C), 25.6 (2C), 24.3;

HRMS (ESI-TOF): calc'd for $C_{13}H_{25}N_2O_2$ [M+H$^+$] 241.1916; found 241.1915.



***tert*-butyl 3-(4-phenylpiperidin-1-yl)azetidine-1-carboxylate (101)**

For 1.0 mmol scale, the standard procedure was followed to convert 4-phenylpiperidine to **101** in 65% yield.

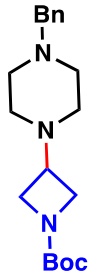
Physical State: white solid (m.p. = 72-73 °C);

R_f = 0.55 (50% EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (dd, *J* = 10.4, 7.3 Hz, 3H), 3.98 – 3.91 (m, 2H), 3.85 (dd, *J* = 8.8, 5.6 Hz, 2H), 3.08 (p, *J* = 7.0, 6.3 Hz, 1H), 2.94 (d, *J* = 10.2 Hz, 2H), 2.52 (ddt, *J* = 12.0, 7.7, 3.9 Hz, 1H), 1.99 – 1.91 (m, 2H), 1.87 (d, *J* = 12.4 Hz, 2H), 1.80 (qd, *J* = 12.6, 3.6 Hz, 2H), 1.43 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 146.1, 128.6 (2C), 126.9 (2C), 126.4, 79.5, 54.3, 52.9 (br s, 2C), 50.9, 42.6 (2C), 33.0 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{19}H_{29}N_2O_2$ [M+H$^+$] 317.2229; found 317.2230.



102

***tert*-butyl 3-(4-benzylpiperazin-1-yl)azetidine-1-carboxylate (102)**

For 1.0 mmol scale, the standard procedure was followed to convert *N*-benzylpiperazine[52] to **102** in 47% yield.

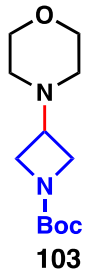
Physical State: colorless oil.

R_f = 0.40 (50% EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 – 7.15 (m, 5H), 3.94 – 3.86 (m, 2H), 3.79 (dd, *J* = 8.8, 5.4 Hz, 2H), 3.52 (s, 2H), 3.07 (p, *J* = 7.0, 6.2 Hz, 1H), 2.44 (d, *J* = 69.7 Hz, 8H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 137.7, 129.4 (2C), 128.4 (2C), 127.4, 79.5, 63.0, 54.0, 53.8 (br s, 2C), 52.6 (2C), 49.6 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{19}H_{30}N_3O_2$ [M+H$^+$] 332.2338; found 332.2337.



103

***tert*-butyl 3-morpholinoazetidine-1-carboxylate (103)**

For 1.0 mmol scale, the standard procedure was followed to convert morpholine to **103** in 58% yield.[59]

Physical State: white solid (m.p. = 73-74 °C);

R_f = 0.40 (4:1 EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.93 – 3.89 (m, 2H), 3.79 (dd, *J* = 8.8, 5.3 Hz, 2H), 3.72 (t, *J* = 4.6 Hz, 4H), 3.06 (ddd, *J* = 12.4, 7.0, 5.4 Hz, 1H), 2.35 (s, 4H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 79.6, 66.7 (2C), 54.1, 52.9 (br d, *J* = 167 Hz, 2C), 50.2 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{12}H_{23}N_2O_3$ [M+H$^+$] 243.1709; found 243.1703.

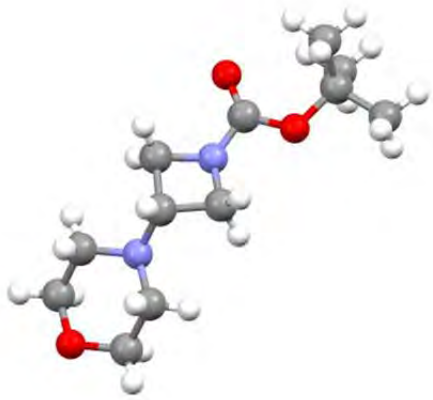
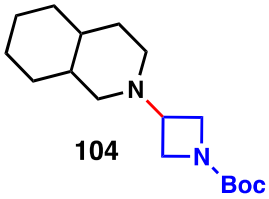


Fig. S25. Crystal structure of *tert*-butyl 3-morpholinoazetidine-1-carboxylate (**103**).

Table S3. Crystal data and structure refinement for **103**.

Identification code	CCDC 1431180	
Empirical formula	$C_{12}H_{22}N_2O_3$	
Formula weight	242.31	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 13.4547(10) Å	α = 90°.
	b = 8.8610(7) Å	β = 93.662(3)°.
	c = 11.0710(10) Å	γ = 90°.
Volume	1317.21(19) Å^3	
Z	4	
Density (calculated)	1.222 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	528	
Crystal size	0.32 x 0.3 x 0.25 mm^3	

Theta range for data collection	2.754 to 25.345°.
Index ranges	-16<=h<=16, -10<=k<=10, -13<=l<=13
Reflections collected	7814
Independent reflections	2406 [R(int) = 0.0371]
Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.0916 and 0.0669
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2406 / 0 / 242
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.0872
R indices (all data)	R1 = 0.0544, wR2 = 0.0951
Extinction coefficient	n/a
Largest diff. peak and hole	0.152 and -0.244 e.Å^{-3}



104

***tert*-butyl 3-(octahydroisoquinolin-2(1*H*)-yl)azetidine-1-carboxylate (104)**

For 1.0 mmol scale, the standard procedure was followed to convert perhydroisoquinoline to **104** in 60% yield.

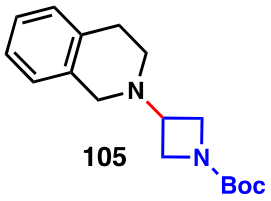
Physical State: yellow oil;

R_f = 0.56 (1:2 EtOAc:hexanes vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.93 – 3.85 (m, 2H), 3.85 – 3.76 (m, 2H), 2.99 (p, *J* = 6.5 Hz, 1H), 2.80 (d, *J* = 9.9 Hz, 1H), 2.63 (d, *J* = 10.0 Hz, 1H), 1.79 (s, 1H), 1.71 (d, *J* = 9.7 Hz, 3H), 1.61 (s, 1H), 1.59 – 1.50 (m, 2H), 1.46 (d, *J* = 11.0 Hz, 1H), 1.41 (s, 9H), 1.32 – 1.18 (m, 4H), 0.91 (dd, *J* = 11.9, 8.8 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 79.4, 56.9, 54.2, 52.9 (br s, 2C), 50.9, 41.9, 41.6, 33.0, 32.6, 30.8, 28.5 (3C), 26.6, 26.2;

HRMS (ESI-TOF): calc'd for $C_{17}H_{31}N_2O_2$ [M+H$^+$] 295.2386; found 295.2382.



***tert*-butyl 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)azetidine-1-carboxylate (105)**

For 1.0 mmol scale, the standard procedure was followed to convert 1,2,3,4-tetrahydroisoquinoline to **105** in 55% yield.

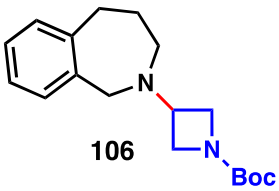
Physical State: colorless oil;

R_f = 0.57 (1:2 EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (dq, *J* = 13.1, 8.0, 6.6 Hz, 3H), 7.02 (d, *J* = 6.7 Hz, 1H), 4.05 – 3.98 (m, 2H), 3.92 (dd, *J* = 8.7, 5.4 Hz, 2H), 3.54 (s, 2H), 3.26 (p, *J* = 6.9 Hz, 1H), 2.92 (t, *J* = 5.9 Hz, 2H), 2.64 (s, 2H), 1.43 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 134.0, 133.8, 128.1, 126.8, 126.6, 126.0, 79.6, 53.8, 53.6 (br d, J = 182 Hz, 2C), 52.9, 47.4, 28.9, 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{17}H_{25}N_2O_2$ [$M+H^+$] 289.1916; found 289.1917.



***tert*-butyl 3-(1,3,4,5-tetrahydro-2*H*-benzo[*c*]azepin-2-yl)azetidine-1-carboxylate (106)**

For 1.0 mmol scale, the standard procedure was followed to convert 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine[51] to **106** in 43% yield.

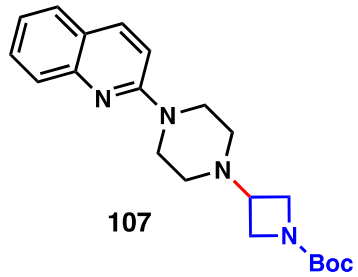
Physical State: yellow oil;

R_f = 0.40 (3:4 EtOAc/hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 – 7.09 (m, 3H), 7.09 – 7.02 (m, 1H), 3.91 – 3.84 (m, 2H), 3.81 (dd, *J* = 8.4, 5.7 Hz, 2H), 3.71 (s, 2H), 3.28 (p, *J* = 6.8, 6.3 Hz, 1H), 2.91 (br s, 4H), 1.78 – 1.70 (m, 2H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.5, 142.8, 138.5, 129.4, 129.1, 127.7, 126.5, 79.5, 57.2, 55.9, 53.9 (br d, *J* = 187 Hz, 2C), 50.8, 35.8, 28.5 (3C), 26.1;

HRMS (ESI-TOF): calc'd for $C_{18}H_{27}N_2O_2$ [M+H$^+$] 303.2073; found 303.2072.



107

***tert*-butyl 3-(4-(quinolin-2-yl)piperazin-1-yl)azetidine-1-carboxylate, "azetidinylated" quipazine (107)**

For 1.0 mmol scale, the standard procedure was followed to convert quipazine to **107** in 51% yield.

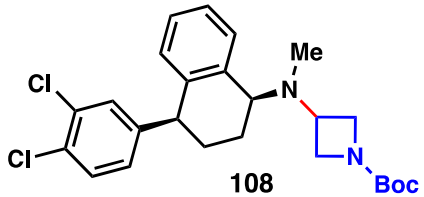
Physical State: white solid (m.p. = 138 °C, decomposition);

***R*$_f$** = 0.50 (20:1:1 $CHCl_3$:MeOH:acetone, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.25 – 7.20 (m, 1H), 6.97 (d, *J* = 9.1 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.87 (dd, *J* = 8.7, 5.4 Hz, 2H), 3.78 (s, 4H), 3.11 (ddd, *J* = 12.4, 7.0, 5.4 Hz, 1H), 2.53 – 2.44 (m, 4H), 1.44 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.4, 156.4, 147.9, 137.7, 129.7, 127.3, 126.8, 123.3, 122.7, 109.6, 79.6, 54.0, 53.2 (br d, *J* = 161 Hz, 2C), 49.7 (2C), 44.9 (2C), 28.5 (3C);

HRMS (ESI-TOF): calc'd for $C_{21}H_{29}N_4O_2$ [M+H$^+$] 369.2291; found 369.2292.



108

***tert*-butyl 3-(((1*S*,4*S*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl) amino)azetidine-1-carboxylate, "azetidinylated" sertraline (108)**

For 1.0 mmol scale, the standard procedure was followed to convert sertraline to **108** in 45% yield.

Physical State: colorless oil;

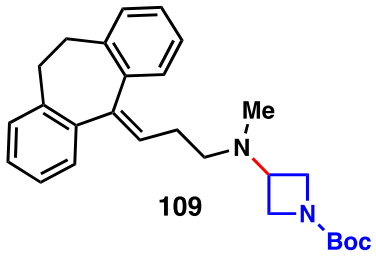
R_f = 0.45 (1:2 EtOAc/hexanes, vis. UV);

$[\alpha]_D^{20}$ = +57.1 (c = 1.00, $CDCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.27 (d, *J* = 6.3 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.14 (d, *J* = 3.1 Hz, 1H), 3.90 (dq, *J* = 10.6, 5.9, 4.3 Hz, 4H), 3.85 (t, *J* = 8.0 Hz, 1H), 3.68 (p, *J* = 6.5 Hz, 1H), 2.16 (s, 3H), 2.12 (dd, *J* = 15.3, 5.6 Hz, 1H), 2.02 – 1.94 (m, 1H), 1.59 – 1.52 (m, 2H), 1.45 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.6, 147.4, 138.6, 138.2, 132.3, 130.8, 130.4, 130.1, 130.1, 128.4, 128.2, 127.3, 127.2, 79.5, 59.5, 53.5 (br s, 2C), 50.8, 43.5, 31.8, 30.2, 28.6 (3C), 16.5;

HRMS (ESI-TOF): calc'd for $C_{25}H_{31}Cl_2N_2O_2$ [M+H$^+$] 461.1763; found 461.1761.



109

***tert*-butyl 3-((3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)(methyl)amino) azetidine-1-carboxylate, "azetidinylated" nortriptyline (109)**

For 1.0 mmol scale, the standard procedure was followed to convert nortriptyline to **109** in 45% yield.

Physical State: pale yellow oil;

R_f = 0.65 (1:1 EtOAc:hexanes, vis. $KMnO_4$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.27 (m, 1H), 7.24 – 7.11 (m, 6H), 7.06 – 7.02 (m, 1H), 5.84 (t, *J* = 7.2 Hz, 1H), 3.85 (d, *J* = 7.9 Hz, 2H), 3.75 (dd, *J* = 8.7, 5.5 Hz, 2H), 3.36 (d, *J* = 63.7 Hz, 2H), 3.17 – 3.09 (m, 1H), 2.98 (d, *J* = 15.8 Hz, 1H), 2.77 (d, *J* = 14.7 Hz, 1H), 2.40 – 2.24 (m, 4H), 2.04 (s, 3H), 1.44 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 144.2, 141.1, 140.0, 139.4, 137.1, 130.1 (2C), 128.6, 128.1 (2C), 127.6, 127.2, 126.1, 125.8, 79.4, 54.0, 53.9, 52.9 (br s, 2C), 37.7, 33.8, 32.1, 28.5 (3C), 27.0;

HRMS (ESI-TOF): calc'd for $C_{27}H_{35}N_2O_2$ [M+H^+] 419.2699; found 419.2702.

Synthesis of 1-((3,5-Difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (8g)

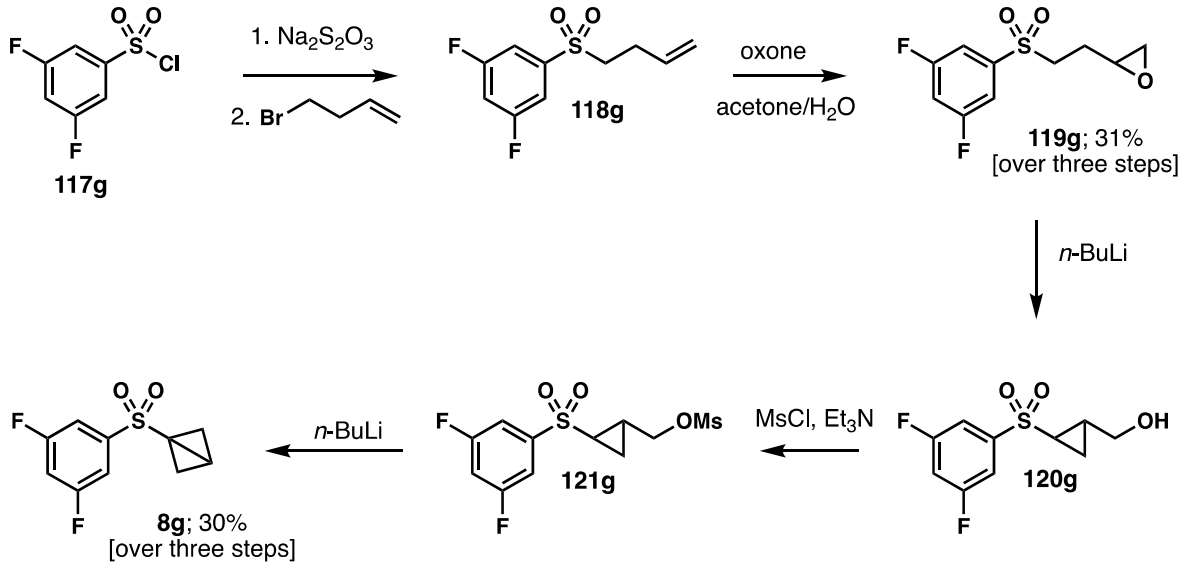
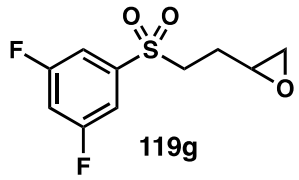


Fig. S26. Overall scheme for the synthesis of **8g**



2-(2-((3,5-difluorophenyl)sulfonyl)ethyl)oxirane (119g)

A 500 mL round bottom flask was charged with 3,5-difluorobenzenesulfonyl chloride (10 g, 47 mmol, 1 equiv.), H_2O (100 mL), Na_2SO_3 (12 g, 95.2 mmol, 2 equiv.), and heated to 80 °C. $NaHCO_3$ (8 g, 95.2 mmol, 2 equiv.) was added portionwise over 30 minutes (*watch for vigorous bubbling*) and the flask was fitted with a reflux condenser. The reaction was stirred for 16 h at 80 °C and was then removed from the heating bath and allowed to reach ambient temperature. The reaction was concentrated under reduced pressure and the residual water was azeotroped with toluene (*ca.* 100 mL). The residual solvent was removed under hi-vacuum to obtain a yellowish solid. Hot MeOH (50 mL) was added to flask and the suspension was filtered to leave behind a yellow cake. The filtrate was concentrated under reduced pressure to give a white solid and used directly in the next reaction without further purification.

The sulfinate salt was dissolved in DMF (100 mL) at room temperature and 4-bromobut-1-ene (5.72 mL, 56.4 mmol, 1.2 equiv.) was added. A septum was placed on the round bottom flask and the reaction was warmed to 60 °C for 2 h. The reaction was removed from the heating bath and the reaction was diluted with EtOAc and H_2O was

added. The layers were separated and the aqueous layer was extracted with EtOAc. The organics were combined and washed with LiCl (5% aqueous solution), dried with Na_2SO_4 and passed over a pad of silica while eluting with EtOAc. The organics were concentrated under reduced pressure and used directly in the next reaction without further purification.

The crude alkene was diluted in acetone (100 mL) and H_2O (100 mL) and the flask was charged with oxone (9.3 g, 61.1 mmol, 1.3 eq) and $NaHCO_3$ (19.7 g, 235 mmol, 5 eq). The solution was stirred at room temperature for 20 h and monitored by TLC (Note: a second portion of oxone (1.3 eq.) and $NaHCO_3$ (5 eq.) along with acetone (100 mL) and H_2O (100mL) was added and stirred for another 3h until TLC indicated the reaction reached completion. The recharge step was added on large scale for safety purposes). The reaction was filtered through a fritted funnel, EtOAc was added, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered over a pad of silica and concentrated under reduced pressure. The crude material was purified (silica gel) with the following gradient of EtOAc:hexanes (0%→30%) to afford **119g** as a white solid (3.61 g, 31%).

Physical State: pale yellow solid (m.p. = 44-45 °C);

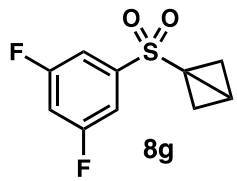
$\boldsymbol{R_f}$ = 0.38 (3:7 EtOAc: hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.43 (m, 2H), 7.12 (tt, *J* = 8.3, 2.3 Hz, 1H), 3.30 – 3.20 (m, 2H), 3.02 (dtd, *J* = 6.6, 3.9, 2.5 Hz, 1H), 2.80 (dd, *J* = 4.7, 3.9 Hz, 1H), 2.52 (dd, *J* = 4.8, 2.6 Hz, 1H), 2.21 (dddd, *J* = 14.3, 8.5, 7.1, 4.0 Hz, 1H), 1.81 (ddt, *J* = 13.9, 9.0, 6.9 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.1 (dd, $^1J_{C\text{-}F}$ = 245, 11.4 Hz, 2C), 142.3 (t, $^3J_{C\text{-}F}$ = 7.8 Hz), 111.8 (q, $^2J_{C\text{-}F}$ = 6.7 Hz, 2C), 109.8 (t, $^2J_{C\text{-}F}$ = 25.2 Hz), 52.8, 50.0, 47.2, 25.8;

^{19}F NMR (376 MHz, $CDCl_3$): δ –104.7;

HRMS (ESI-TOF): calc'd for $C_{10}H_{11}F_2O_3S$ [M+H$^+$] 249.0397; found 249.0391.



8g

1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (8g)

Epoxide **119g** (3.61 g, 14.55 mmol, 1 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. *n*-BuLi (10.2 mL, 14.3 mmol, 1.40 M, 1 eq.) was added slowly and the solution turned from colorless to orange to red. After stirring for 5 minutes, TLC (7:3 hexanes:EtOAc) indicated that the reaction was complete. Sat. aq. NH_4Cl was added and the solution was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and passed over a pad of silica while eluting with EtOAc. The material obtained was used directly in the next reaction without further purification.

The crude alcohol was diluted in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (2.43 mL, 17.46 mmol, 1.2 eq.) was added followed by methanesulfonyl chloride (1.351 mL, 17.46 mmol, 1.2 eq). The reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was diluted with CH_2Cl_2, H_2O was added, and the layers were separated. The combined organic layers were dried over Na_2SO_4 and passed over a pad of silica to obtain a solid that contained minor impurities. This material was used directly in the next step without further purification.

The mesylate was dissolved in THF (100 mL) and cooled to 0 °C. *n*-BuLi (5.65 mL, 7.91 mmol, 1.40M, 1 eq.) was added slowly and the reaction monitored by TLC (EtOAc/hexanes 4:1). The reaction was quenched after 5 minutes by addition of sat. aq. NH_4Cl. CH_2Cl_2 and H_2O were added and the layers were separated (a thick emulsion appears in the aqueous layer). The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and filtered over a pad of silica. The crude material was purified by silica gel chromatography (0→20% EtOAc in hexanes) to obtain the final product (1 g, 30% from **119g**). *(Alternative purification: The reaction was quenched with sat. aq. NH_4Cl (ca. 2 mL), passed over a pad of silica and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (EtOAc/hexanes 0→20%) to obtain the final product).*

Sigma-Aldrich Catalog Number: MKE151703;

Physical State: white solid (m.p. = 60-62 °C);

$\boldsymbol{R_f}$ = 0.93 (30% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 2H), 7.06 (tt, *J* = 8.4, 2.3 Hz, 1H), 2.69 (tt, *J* = 3.7, 2.9 Hz, 1H), 2.55 (dt, *J* = 3.7, 1.1 Hz, 2H), 1.45 (dt, *J* = 2.9, 1.0 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 243, 11.3 Hz, 2C), 145.5 (t, $^3J_{C\text{-}F}$ = 7.9 Hz), 110.8 (q, $^2J_{C\text{-}F}$ = 7.3 Hz, 2C), 108.8 (t, $^2J_{C\text{-}F}$ = 25.3 Hz), 38.9 (2C), 22.6, 13.7;

^{19}F NMR (376 MHz, $CDCl_3$): δ −105.7;

HRMS (ESI-TOF): calc'd for $C_{10}H_9F_2O_2S$ [$M+H^+$] 231.0286; found 231.0283.

Graphical Preparation of Designer Sulfone 8g

Fig. S27. Left. Conversion of 3,5-difluorobenzenesulfonyl chloride to sodium 3,5-difluorobenzenesulfinate after heating at 80 ºC for 16 h. **Right.** The crude product was azeotroped with toluene to remove residual H_2O.

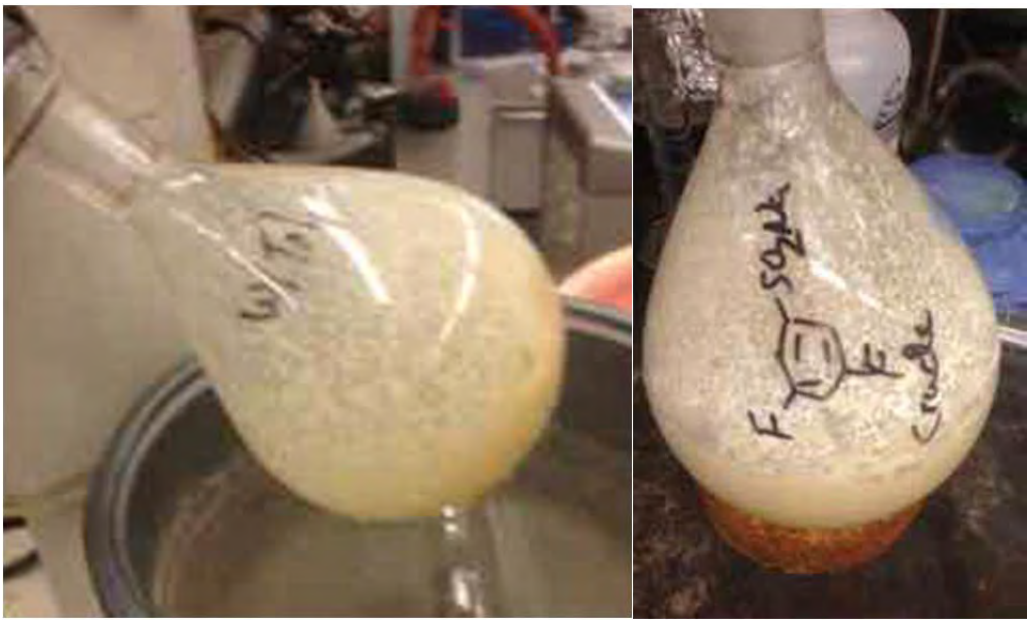


Fig. S28. Left. Crude sodium 3,5-difluorobenzenesulfinate after azeotrope. **Right.** Crude sodium 3,5-difluorobenzenesulfinate after hi-vacuum.

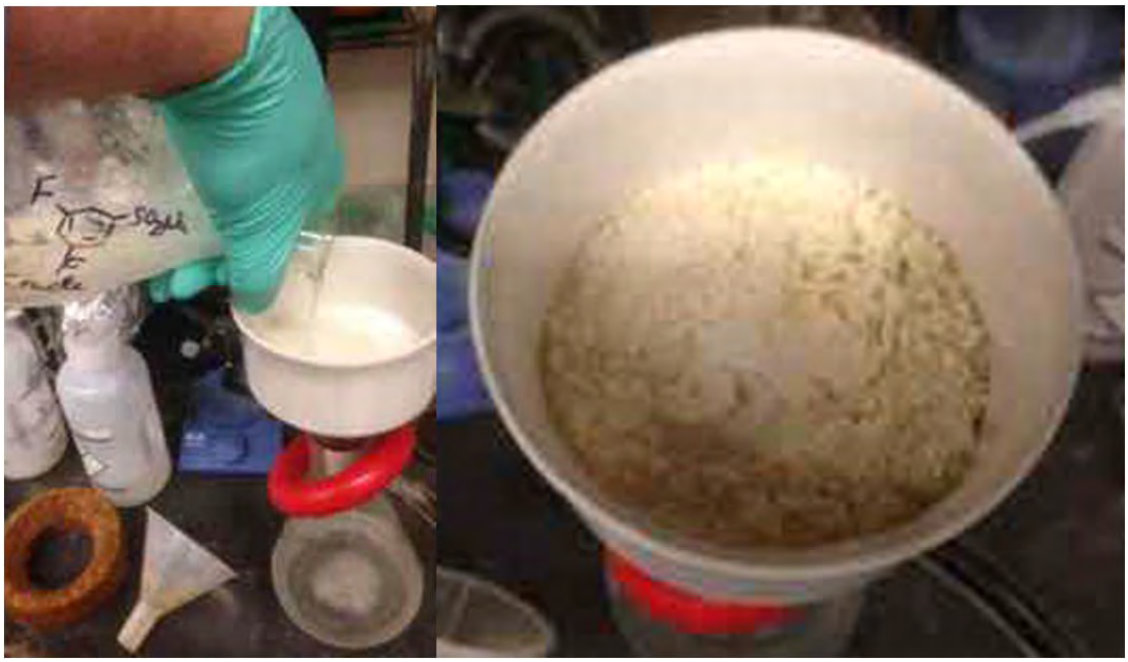


Fig. S29. Left. Hot MeOH was added to the crude sodium 3,5-difluorobenzenesulfinate and the suspension filtered. **Right.** Pure sodium 3,5-difluorobenzenesulfinate collected by filtration.

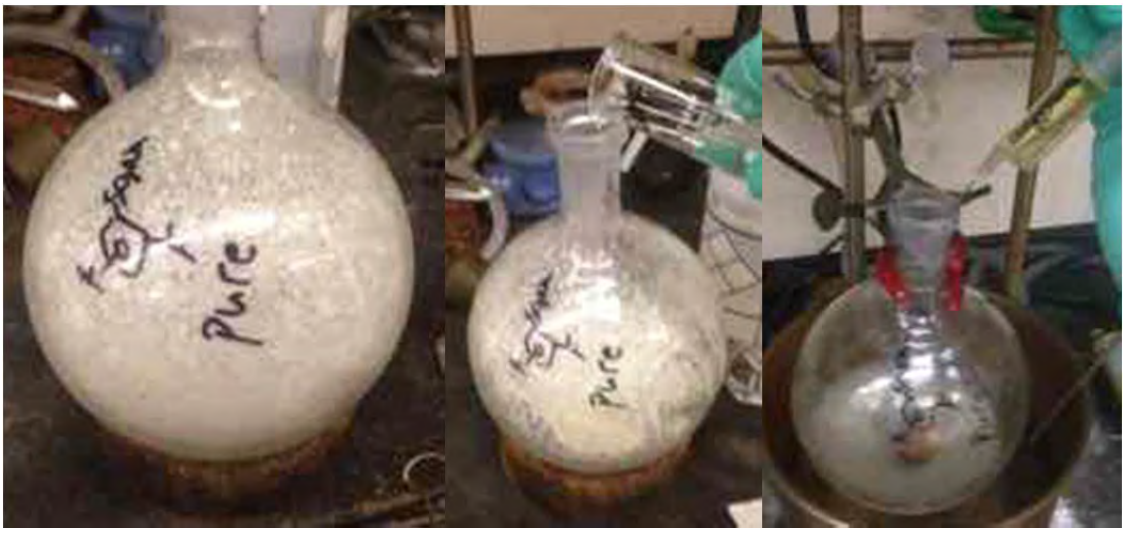


Fig. S30. Left. Purified sodium 3,5-difluorobenzenesulfinate was transferred to a round bottom flask. **Center.** DMF was added. **Right.** 4-Bromobut-1-ene was added.

Fig. S31. Left. The reaction was heated at 60 ºC for 2h. **Center.** The reaction was diluted with EtOAc and H_2O. The organic layers were combined and washed with 5% aqueous LiCl. **Right.** The combined organics were dried over Na_2SO_4.

Fig. S32. Left. The combined organics were passed over sílica. **Right.** The crude material was collected in a single flask and used in the next reaction without further purification.

Fig. S33. Left. The crude alkene was dissolved in 1:1 acetone and H_2O. Oxone was added. **Center.** $NaHCO_3$ was added. **Right.** The mixture was stirred at room temperature for 20 h.

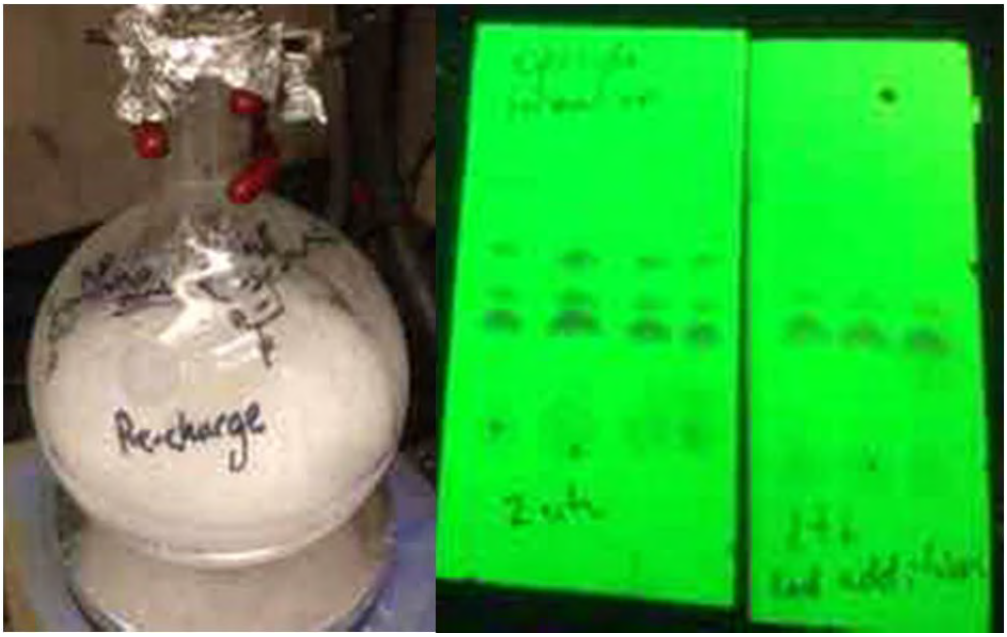


Fig. S34. Left. The reaction was recharged with acetone, H_2O, oxone, and $NaHCO_3$. **Right.** TLC (on left) indicates reaction after 20 h and before recharge. All lanes are crude reaction mixture. Top most spot is starting olefin. Bottom spot is product **119g**. TLC (on right) indicated completion of the reaction after recharge and stirring for another 3 h. All lanes are crude reaction mixture. Starting material consumed. Bottom spot is product **119g** (1:1 EtOAc:hexanes).

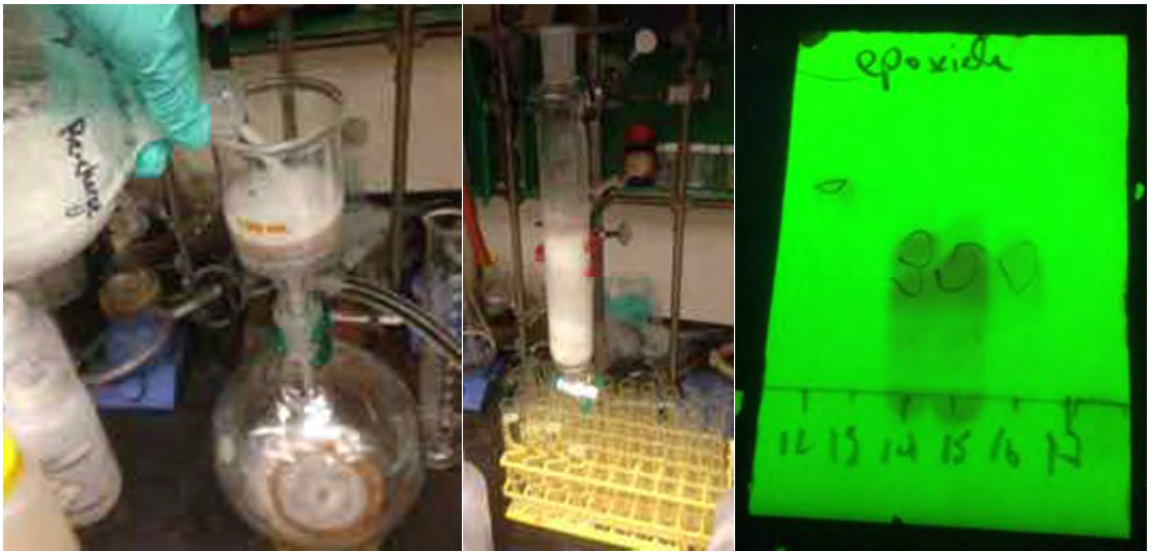


Fig. S35. Left. The mixture was directly filtered through a fritted funnel. **Center.** The crude product was purified by column chromatography (0%→20%→30% EtOAc in hexanes). **Right.** TLC of purified fractions; 30% EtOAc in hexanes; 14-16 = **119g**.

Fig. S36. Left. Pure epoxide (white solid). **Center.** The epoxide was dissolved in THF and cooled to 0 °C. **Right.** *n*-BuLi was slowly added to the reaction mixture.

Fig. S37. Left. During the addition of *n*-BuLi, the reaction turns orange. **Center.** By the end of the *n*-BuLi addition, the mixture turns red. **Right.** After 5 minutes, TLC shows complete consumption of the starting material. Lanes: Left = Starting epoxide; Center = Co-spot; Right = Crude reaction mixture (solvent system = 7:3 EtOAc:hexanes).

Fig. S38. Left. The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc. **Right.** The dried, combined organic layer was passed over silica gel

Fig. S39. Left. The crude alcohol was dissolved in CH_2Cl_2 and cooled to 0 °C. **Center.** Et_3N was added. **Right.** Methanesulfonyl chloride was added.

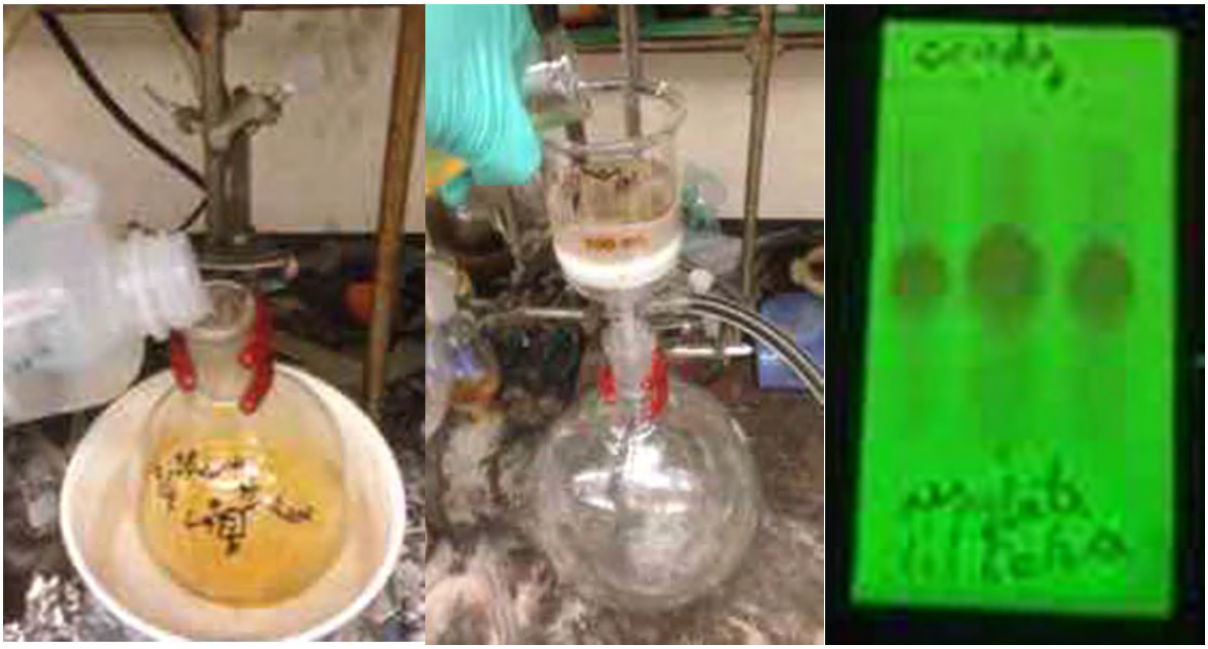


Fig. S40. Left. After stirring for 16 h at room temperature, the reaction was diluted with CH_2Cl_2 and washed with H_2O. **Center.** The combined organics were dried over Na_2SO_4, concentrated, and passed over silica gel to obtain the mesylated product. **Right.** TLC of mesylate (all lanes); solvent system – 1:1 EtOAc:hexanes.

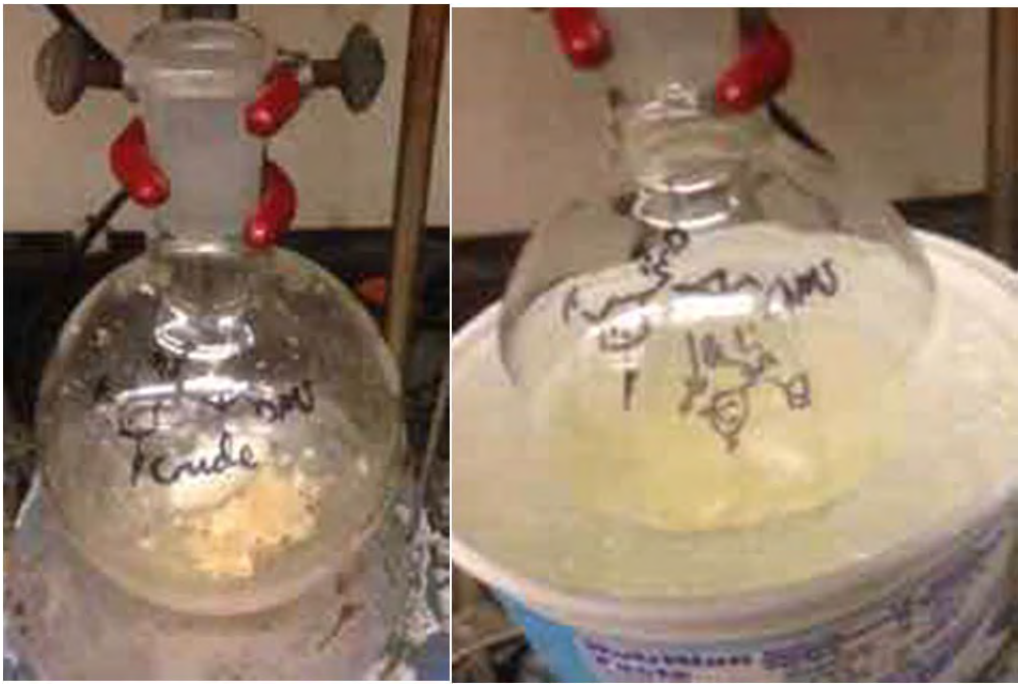


Fig. S41. Left. Crude mesylated product obtained as a pale yellow solid. **Center.** The mesylate was dissolved in THF and cooled to 0 °C.

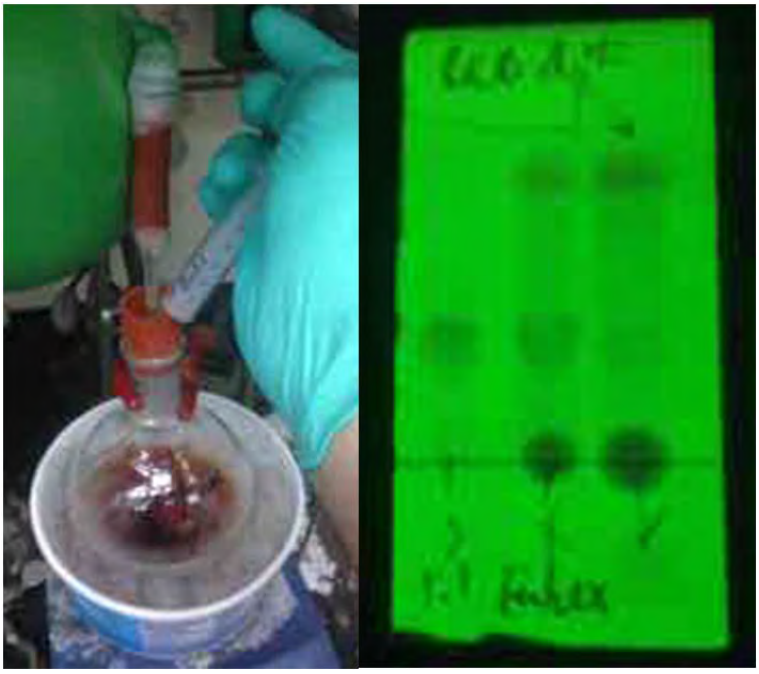


Fig. S42. Left. *n*-BuLi was added slowly and the reaction darkened. **Right.** After 5 minutes, TLC indicated complete consumption of the starting material. Lanes: Left = Starting mesylate; Center = Co-spot; Right = Crude reaction mixture (solvent system = 4:1 EtOAc:hexanes).

Fig. S43. Left. The reaction was quenched with sat. aq. NH_4Cl and extracted with CH_2Cl_2. **Right.** The aqueous layer was extracted with CH_2Cl_2 (note: thick emulsion in aqueous layer).

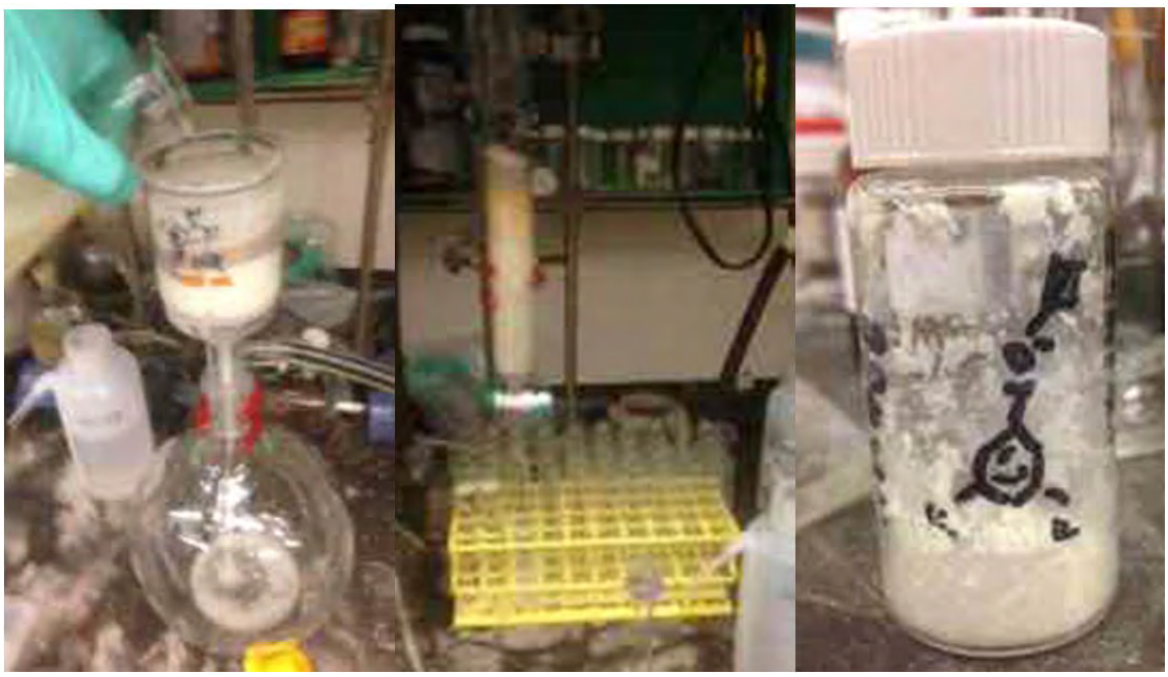


Fig. S44. Left. The combined organics were dried over Na_2SO_4 and filtered through a pad of silica gel. **Center.** The crude bicycle was purified by column chromatography (0%→20% EtOAc in hexanes). **Right.** 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (**8g**) was obtained as a white solid.

Synthesis of Other Substituted Phenylsulfonylcyclobutanes: General Scheme for the Synthesis of Designer Sulfones 8c – 8f:

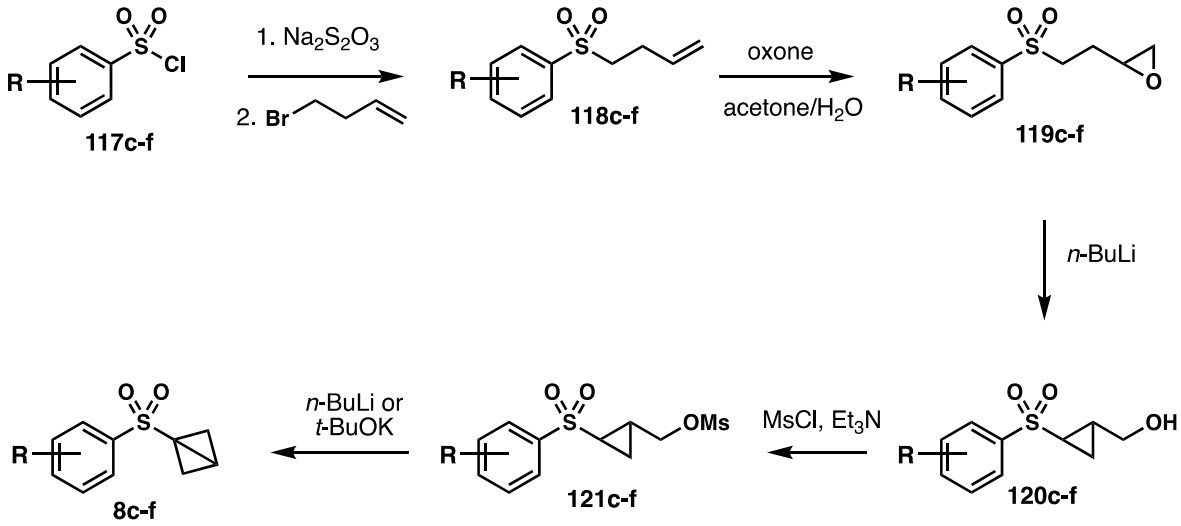
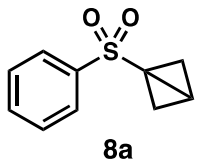


Fig. S45. Overall scheme for the synthesis of sulfones **8c-8f**

Note: The reaction sequence from the starting sulfonyl chloride to the final bicycles (**8a**-**8g**) can be telescoped in a variety of ways. Our optimal approach to **8g** is described above (both in text and graphics). The sulfone bicycles described below and in the literature demonstrate other ways these reactions can be run either stepwise or telescoped. [60,61]



8a

1-(phenylsulfonyl)bicyclo[1.1.0]butane (8a) (see reference[60])

Physical State: white solid (m.p. = 75 °C);

$\boldsymbol{R_f}$ = 0.80 (1:1 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H), 7.64 – 7.60 (m, 1H), 7.59 – 7.53 (m, 2H), 2.56 (tt, *J* = 3.9, 2.7 Hz, 1H), 2.51 (dt, *J* = 3.7, 0.9 Hz, 2H), 1.38 (dt, *J* = 2.7, 0.9 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.0, 133.1, 129.2 (2C), 127.2 (2C), 38.3 (2C), 23.1, 12.7;

HRMS (ESI-TOF): calc'd for $C_{10}H_{11}O_2S$ [M+H$^+$] 195.0474; found 195.0475.

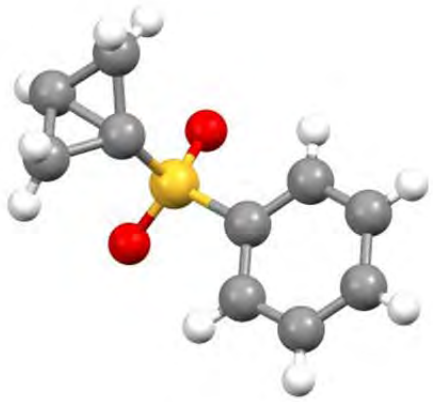
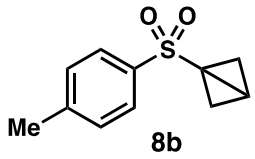


Fig. S46. Crystal structure of 1-(phenylsulfonyl)bicyclo[1.1.0]butane **(8a)**

Table S4. Crystal data and structure refinement for **8a**

Identification code	CCDC 1431182	
Empirical formula	$C_{10}H_{10}O_2S$	
Formula weight	194.24	
Temperature	100 K	
Wavelength	0.71073 ≈	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 5.9300(3) ≈	α = 90°.
	b = 7.2867(5) ≈	β = 90.331(3)°.
	c = 20.9055(13) ≈	γ = 90°.
Volume	903.31(10) ≈^{3}	
Z	4	
Density (calculated)	1.428 Mg/m^3	
Absorption coefficient	0.318 mm^{-1}	
F(000)	408	
Crystal size	0.34 x 0.28 x 0.25 mm^3	
Theta range for data collection	2.960 to 26.404∞.	
Index ranges	-7<=h<=5, -9<=k<=7, -25<=l<=26	

Reflections collected	6607
Independent reflections	1856 [R(int) = 0.0435]
Completeness to theta = 25.242∞	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.2602 and 0.2007
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1856 / 0 / 118
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0817
R indices (all data)	R1 = 0.0435, wR2 = 0.0871
Extinction coefficient	n/a
Largest diff. peak and hole	0.316 and -0.390 e.Å^{-3}



8b

1-tosylbicyclo[1.1.0]butane (8b) (see (*61*))

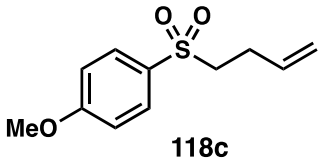
Physical State: white solid (m.p. = 82-84 °C);

R_f = 0.58 (3:7 EtOAc:hexanes, vis. UV);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 – 7.79 (m, 2H), 7.35 (dt, *J* = 7.1, 0.9 Hz, 2H), 2.53 – 2.47 (m, 3H), 2.44 (s, 3H), 1.38 – 1.34 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0, 139.1, 129.9 (2C), 127.3 (2C), 38.2 (2C), 23.4, 21.7, 12.6;

HRMS (ESI-TOF): calc'd for $C_{11}H_{13}O_2S$ [M+H$^+$] 209.0631; found 209.0631.



118c

1-(but-3-en-1-ylsulfonyl)-4-methoxybenzene (118c)

4-Methoxybenzenesulfonyl chloride (10.0 g, 4.8 mmol) was added to a solution of Na_2SO_3 (15.5 g, 2.0 equiv) and $NaHCO_3$ (8.0 g, 2.0 equiv) in H_2O (50 mL) portionwise at room temperature. The mixture was heated at 80 ºC for 5 h, cooled to room temperature, and extracted with EtOH (3 x 50 mL). The combined solutions were evaporated, dissolved in DMF (100 mL) and allowed to react with 4-bromo-1-butene (5.8 mL, 1.2 equiv) at 50 ^oC overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with brine (3 x 25 mL), dried with Na_2SO_4, and evaporated *in vacuo* to give alkene **118c** (6.46 g, 60%).

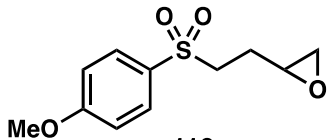
Physical State: colorless oil;

R_f = 0.46 (3:7 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 – 7.73 (m, 2H), 7.05 – 6.93 (m, 2H), 5.70 (ddtd, *J* = 16.7, 10.2, 6.5, 0.9 Hz, 1H), 5.09 – 4.94 (m, 2H), 3.85 (s, 3H), 3.17 – 3.06 (m, 2H), 2.48 – 2.36 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.8, 133.9, 130.4, 130.2 (2C), 117.0, 114.5 (2C), 55.7, 55.6, 27.0;

HRMS (ESI-TOF): calc'd for $C_{11}H_{15}O_3S$ [M+H^+] 227.0736; found 227.0736.



119c

2-(2-((4-methoxyphenyl)sulfonyl)ethyl)oxirane (119c)

Alkene **118c** (6.3 g, 27.7 mmol) and $NaHCO_3$ (11.6 g, 5.0 equiv) were dissolved in acetone (90 mL) and H_2O (90 mL). Oxone (22.1 g, 2.6 equiv) was added portionwise during a period of 4 hours at room temperature. After stirring for another 6 h, the mixture was evaporated *in vacuo* to remove the acetone, the residue diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, and evaporated *in vacuo* to give epoxide **119c** (6.7 g, quant.).

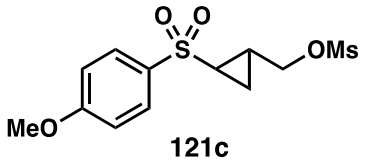
Physical State: colorless oil;

R_f = 0.14 (3:7 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 – 7.72 (m, 2H), 6.99 – 6.92 (m, 2H), 3.80 (s, 3H), 3.13 (ddd, *J* = 8.3, 6.6, 1.2 Hz, 2H), 2.92 (dtd, *J* = 6.7, 4.1, 2.6 Hz, 1H), 2.68 (dd, *J* = 4.8, 3.9 Hz, 1H), 2.41 (dd, *J* = 4.8, 2.6 Hz, 1H), 2.03 (dddd, *J* = 14.3, 8.6, 7.0, 4.3 Hz, 1H), 1.77 – 1.70 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.8, 130.2, 130.1 (2C), 114.5 (2C), 55.7, 52.8, 50.0, 47.0, 26.0;

HRMS (ESI-TOF): calc'd for $C_{11}H_{15}O_4S$ [$M+H^+$] 243.0691; found 243.0687.



121c

(2-((4-methoxyphenyl)sulfonyl)cyclopropyl)methyl methanesulfonate (121c)

Epoxide **119c** (6.3 g, 26 mmol) was dissolved in THF (130 mL) and *n*-BuLi (1.97 M in hexane, 13.2 mL, 1.0 equiv) was added dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 45 min before being quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give intermediate alcohol **120c** (5.1 g, 81%) which was used directly in the next step. To a solution of the intermediate alcohol (4.9 g, 20.2 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (3.1 mL, 1.1 equiv) and methanesulfonyl chloride (1.7 mL, 1.1 equiv) successively at room temperature. After stirring for 2h, the reaction mixture was washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (3:2 hexanes:EtOAc) to give mesylate **121c** (6.26 g, 97%).

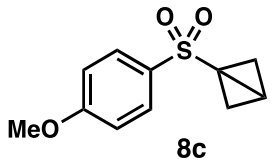
Physical State: colorless oil;

R_f = 0.42 (1:1 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 – 7.78 (m, 2H), 7.02 – 6.99 (m, 2H), 4.24 (dd, *J* = 11.3, 6.1 Hz, 1H), 3.98 (dd, *J* = 11.3, 7.6 Hz, 1H), 3.86 (s, 3H), 2.95 (s, 3H), 2.54 (ddd, *J* = 8.5, 5.2, 4.3 Hz, 1H), 2.12 (ddtd, *J* = 9.4, 7.5, 6.1, 4.3 Hz, 1H), 1.58 (dt, *J* = 9.4, 5.5 Hz, 1H), 1.12 (dt, *J* = 8.5, 6.0 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.9, 131.6, 129.9 (2C), 114.6 (2C), 69.3, 55.8, 38.2, 38.1, 18.5, 10.9;

HRMS (ESI-TOF): calc'd for $C_{12}H_{16}NaO_6S_2$ [M+Na^+] 343.0286; found 343.0285.



8c

1-((4-methoxyphenyl)sulfonyl)bicyclo[1.1.0]butane (8c)

To mesylate **121c** (5.9 g, 18.4 mmol) in THF (100 mL) was added *n*-BuLi (1.97 M in hexane, 8.9 mL, 0.95 equiv) dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (15:1 hexanes:EtOAc) to give bicyclobutane sulfone **8c** (2.63 g, 64%).

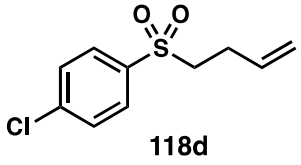
Physical State: white solid (m.p. = 63 °C);

R_f = 0.73 (1:1 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 2H), 7.03 – 7.00 (m, 2H), 3.88 (s, 3H), 2.51 – 2.45 (m, 3H), 1.37 – 1.32 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.3, 133.6, 129.5 (2C), 114.4 (2C), 55.8, 38.1 (2C), 23.7, 12.5;

HRMS (ESI-TOF): calc'd for $C_{11}H_{13}O_3S$ [M+H^+] 225.0585; found 225.0581.



118d

1-(but-3-en-1-ylsulfonyl)-4-chlorobenzene (118d)

4-Chlorobenzenesulfonyl chloride (10.0 g, 46 mmol) was added to a solution of Na_2SO_3 (11.6 g, 2.0 equiv) and $NaHCO_3$ (7.7 g, 2.0 equiv) in H_2O (50 mL) portionwise at room temperature. The mixture was heated at 80 ºC for 6h, cooled to room temperature, and extracted with EtOH (3 x 50 mL). The combined solutions were evaporated, dissolved in DMF (63 mL) and allowed to react with 4-bromo-1-butene (3.9 mL, 1.2 equiv) at 50 °C for 2h. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL),

washed with brine (3 x 25 mL), dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (8:1 hexanes:EtOAc) to give alkene **118d** (4.9 g, 46%).

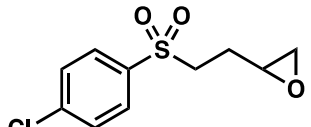
Physical State: colorless oil;

R_f = 0.58 (3:7 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 – 8.40 (m, 2H), 8.15 – 8.11 (m, 2H), 5.71 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.12 – 5.04 (m, 2H), 3.27 – 3.18 (m, 2H), 2.54 – 2.44 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 151.1, 144.8, 133.2, 129.8 (2C), 124.7 (2C), 117.9, 55.4, 26.8;

HRMS (ESI-TOF): calc'd for $C_{10}H_{12}ClO_2S$ [M+H$^+$] 231.0247; found 231.0249.



119d

2-(2-((4-chlorophenyl)sulfonyl)ethyl)oxirane (119d)

Alkene **118d** (4.9 g, 21.2 mmol) and $NaHCO_3$ (8.9 g, 5.0 equiv) were dissolved in acetone (70 mL) and H_2O (70 mL). Oxone (16.9 g, 2.6 equiv) was added portionwise during a period of 4 h at room temperature. After stirring for another 1 h, the mixture was evaporated *in vacuo* to remove the acetone, the residue diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give epoxide **119d** (4.71 g, 90%).

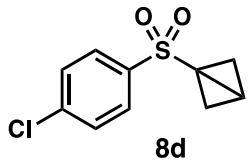
Physical State: colorless oil;

R_f = 0.75 (1:1 EtOAc:hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.47 – 8.39 (m, 2H), 8.19 – 8.09 (m, 2H), 3.29 (dd, *J* = 8.7, 7.0 Hz, 2H), 3.03 (dtd, *J* = 6.7, 3.9, 2.6 Hz, 1H), 2.81 (dd, *J* = 4.7, 3.9 Hz, 1H), 2.52 (dd, *J* = 4.7, 2.5 Hz, 1H), 2.26 (dddd, *J* = 14.3, 8.3, 7.2, 3.9 Hz, 1H), 1.87 – 1.76 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 151.2, 144.6, 129.8 (2C), 124.8 (2C), 52.9, 50.0, 47.3, 25.8;

HRMS (ESI-TOF): calc'd for $C_{10}H_{12}ClO_3S$ [M+H$^+$] 247.0196; found 247.0194.



8d

1-((4-chlorophenyl)sulfonyl)bicyclo[1.1.0]butane (8d)

Epoxide **119d** (4.71 g, 19.1 mmol) was dissolved in THF (100 mL) and *n*-BuLi (1.97 M in hexane, 9.7 mL, 1.05 equiv) was added dropwise at 0 ^{o}C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na_2SO_4, evaporated *in vacuo*, and filtered through a pad of silica gel. This material was used directly in the next reaction. To a solution of the sulfone alcohol **120d** (2.85 g, 11.5 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (1.8 mL, 1.1 equiv) and methanesulfonyl chloride (1.0 mL, 1.1 equiv) successively at room temperature. After stirring for 1 h, the reaction mixture was washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and filtered through a pad of silica gel. This material was used directly in the next reaction. To the sulfone mesylate **121d** (3.70 g, 11.4 mmol) in THF (60 mL) was added *n*-BuLi (1.97 M in hexane, 5.5 mL, 0.95 equiv) dropwise at 0 ^{o}C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (15:1 hexanes:EtOAc) to give bicyclobutane sulfone **8d** (1.23 g, 28% over three steps).

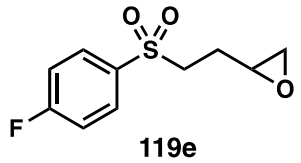
Physical State: white powder (m.p. = 83-84 °C);

$\boldsymbol{R_f}$ = 0.53 (3:7 EtOAc:hexanes, vis. UV);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 – 7.84 (m, 2H), 7.55 – 7.49 (m, 2H), 2.60 (ddd, *J* = 6.4, 3.7, 2.8 Hz, 1H), 2.51 (dt, *J* = 3.7, 1.0 Hz, 2H), 1.39 (dt, *J* = 2.8, 1.0 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 140.6, 139.7, 129.6 (2C), 128.7 (2C), 38.5 (2C), 23.1, 13.1;

HRMS (ESI-TOF): calc'd for $C_{10}H_{10}ClO_2S$ [M+H^{+}] 229.0085; found 229.0084.



119e

2-(2-((4-fluorophenyl)sulfonyl)ethyl)oxirane (119e)

A 500 mL round bottom flask was charged with 4-fluorobenzenesulfonyl chloride (10 g, 51.55 mmol, 1 equiv.), H_2O (100 mL), Na_2SO_3 (13 g, 103.1 mmol, 2 equiv.), and heated to 80 °C. $NaHCO_3$ (8.66 g, 103.1 mmol, 2 equiv.) was added portionwise over 30 minutes (*watch for vigorous bubbling*) and the flask was fitted with a reflux condenser. The reaction was stirred for 16 h at 80 °C and was then removed from the heating bath and allowed to reach ambient temperature. The reaction was concentrated under reduced pressure and the residual water was azeotroped with toluene (*ca.* 100 mL). The residual traces of solvent were removed under hi-vacuum to obtain a yellowish solid. Hot MeOH (50 mL) was added to flask and the suspension was filtered to leave behind a yellow cake. The filtrate was concentrated under reduced pressure to give a white solid and used directly in the next reaction without further purification.

The sulfinate salt was dissolved in DMF (100 mL) at room temperature and 4-bromobut-1-ene (6.3 mL, 61.7 mmol, 1.2 equiv.) was added. A septum was placed on the round bottom flask and the reaction was warmed to 60 °C for 2 h. The reaction was removed from the heating bath and the reaction was diluted with EtOAc and H_2O was added. The layers were separated and the aqueous layer was extracted with EtOAc. The organics were combined and washed with LiCl (5% aqueous solution), dried with Na_2SO_4 and passed over a pad of silica while eluting with EtOAc. The organics were concentrated under reduced pressure and used directly in the next reaction without further purification.

The crude alkene **118e** was diluted in acetone (200 mL) and H_2O (200 mL) and the flask was charged with oxone (47.5 g, 155 mmol, 3 eq) and $NaHCO_3$ (21.6 g, 257 mmol, 5 eq). The solution was stirred at room temperature for 20h and monitored by TLC. The reaction was filtered through a fritted funnel, EtOAc was added, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered over a pad of silica and concentrated under reduced pressure. The crude material was purified (silica gel) with the following gradient of EtOAc:hexanes (0%→40%) to afford the **119e** as a white solid (6.48 g, 56%).

Physical State: colorless oil;

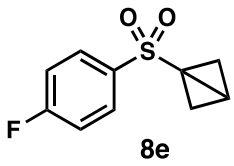
$\boldsymbol{R_f}$ = 0.55 (1:1 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.91 (m, 2H), 7.28 – 7.23 (m, 2H), 3.28 – 3.18 (m, 2H), 3.01 (dtd, *J* = 6.7, 4.0, 2.6 Hz, 1H), 2.78 (dd, *J* = 4.8, 3.9 Hz, 1H), 2.50 (dd, *J* = 4.8, 2.6 Hz, 1H), 2.18 (dddd, *J* = 14.3, 8.7, 6.9, 4.2 Hz, 1H), 1.86 – 1.77 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.0 (d, $^1J_{C\text{-}F}$ = 257 Hz), 135.0 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 131.1 (d, $^3J_{C\text{-}F}$ = 9.7 Hz, 2C), 116.9 (d, $^2J_{C\text{-}F}$ = 22.8 Hz, 2C), 53.0, 50.1, 47.2, 26.0;

^{19}F NMR (376 MHz, $CDCl_3$): δ –103.3;

HRMS (ESI-TOF): calc'd for $C_{10}H_{12}FO_3S$ [$M+H^+$] 231.0491; found 231.0486.



8e

1-((4-fluorophenyl)sulfonyl)bicyclo[1.1.0]butane (8e)

The epoxide **119e** (6.0 g, 26 mmol, 1 equiv.) was dissolved in THF (100 mL) and cooled to 0 °C. *n*-BuLi (3.32 mL, 26 mmol, 1.97M, 1.0 eq.) was added slowly and the solution turned from colorless to orange to red. After stirring for 5 minutes, TLC (7:3 hexanes:EtOAc) indicated that the reaction was complete. Sat. aq. NH_4Cl was added and the solution was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and passed over a pad of silica while eluting with EtOAc. The material obtained was used directly in the next reaction without further purification.

The crude alcohol **120e** was diluted in CH_2Cl_2 (150 mL) and cooled to 0 °C. Et_3N (5.1 mL, 36.8 mmol, 1.2 eq.) was added followed by methanesulfonyl chloride (2.85 mL, 36.8 mmol, 1.2 eq). The reaction was allowed to warm to ambient temperature and stirred for 16 h. The reaction was diluted with CH_2Cl_2, H_2O was added, and the layers were separated. The combined organic layers were dried over Na_2SO_4 and passed over a pad of silica to obtain a solid that contained minor impurities. This material was used directly in the next step without further purification.

The mesylate **121e** was dissolved in THF (150 mL) and cooled to 0 °C. *n*-BuLi (8.23 mL, 16.23 mmol, 1.97 M, 1.0 eq) was added slowly and the reaction monitored by TLC (EtOAc/hexanes 4:1). The reaction was quenched after 5 minutes by addition of sat. aq. NH_4Cl. CH_2Cl_2 and H_2O were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and filtered over a pad of silica. The crude material was purified by silica gel chromatography (0→20%→40% EtOAc in hexanes) to obtain **8e** (1.0 g, 12% from **119e**).

Physical State: white solid (m.p. = 71-72 °C);

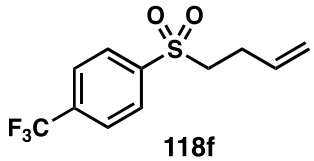
R_f = 0.48 (3:7 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 – 7.93 (m, 2H), 7.26 – 7.20 (m, 2H), 2.58 (p, *J* = 3.2 Hz, 1H), 2.51 (dd, *J* = 3.7, 0.9 Hz, 2H), 1.39 (dd, *J* = 2.7, 0.9 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.5 (d, $^1J_{C\text{-}F}$ = 255 Hz), 138.2 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 130.0 (d, $^3J_{C\text{-}F}$ = 9.7 Hz, 2C), 116.5 (d, $^2J_{C\text{-}F}$ = 22.8 Hz, 2C), 38.4 (2C), 23.2, 13.0;

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.0;

HRMS (ESI-TOF): calc'd for $C_{10}H_{10}FO_2S$ [M+H$^+$] 213.0386; found 213.0382.



118f

1-(but-3-en-1-ylsulfonyl)-4-(trifluoromethyl)benzene (118f)

4-(Trifluoromethyl)benzenesulfonyl chloride (4.89 g, 20 mmol) was added to a solution of Na_2SO_3 (5.04 g, 2.0 equiv) and $NaHCO_3$ (3.36 g, 2.0 equiv) in H_2O (20 mL) portionwise at room temperature. The mixture was heated at 50 ºC for 2h, cooled to room temperature, and extracted with EtOH (3 x 50 mL). The combined solutions were evaporated, dissolved in DMF (30 mL) and allowed to react with 4-bromo-1-butene (4.06 mL, 2.0 equiv) at 50 °C overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with brine (3 x 25 mL), dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (8:1 hexanes:EtOAc) to give alkene **118f** (3.88 g, 73%).

Physical State: colorless oil;

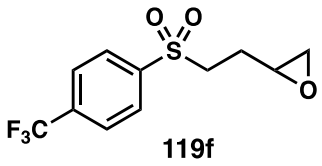
R_f = 0.70 (1:3 EtOAc:hexanes, vis. UV);

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 – 8.02 (m, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 5.72 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.12 – 5.01 (m, 2H), 3.23 – 3.16 (m, 2H), 2.52 – 2.45 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 135.7 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 133.4, 129.0 (2C), 126.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2C), 123.2 (q, $^1J_{C\text{-}F}$ = 273 Hz), 117.6, 55.4, 26.8;

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.5;

HRMS (ESI-TOF): calc'd for $C_{11}H_{12}F_3O_2S$ [M+H$^+$] 265.0505; found 265.0507.



119f

2-(2-((4-(trifluoromethyl)phenyl)sulfonyl)ethyl)oxirane (119f)

Alkene **118f** (3.88 g, 14.6 mmol) and $NaHCO_3$ (6.18 g, 5.0 equiv) were dissolved in acetone (37 mL) and H_2O (37 mL). Oxone (11.75 g, 2.6 equiv) was added portionwise during a period of 4 hours at room temperature. After stirring for another 1h, the mixture was evaporated *in vacuo* to remove the acetone, the residue diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give epoxide **119f** (3.96 g, 96%).

Physical State: white solid (m.p. = 60-63 °C);

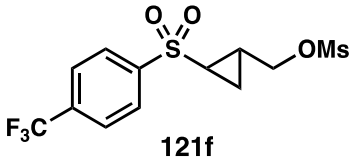
R_f = 0.20 (1:3 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 3.25 (ddd, *J* = 8.5, 6.6, 1.4 Hz, 2H), 3.02 (dtd, *J* = 6.7, 4.0, 2.6 Hz, 1H), 2.79 (dd, *J* = 4.7, 3.9 Hz, 1H), 2.51 (dd, *J* = 4.7, 2.5 Hz, 1H), 2.21 (dddd, *J* = 14.4, 8.7, 6.9, 4.0 Hz, 1H), 1.81 (ddt, *J* = 13.7, 9.1, 6.8 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.5, 135.8 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 128.9 (2C), 126.7 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, 2C), 123.2 (q, $^1J_{C\text{-}F}$ = 273 Hz), 52.8, 50.1, 47.2, 25.8;

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.5;

HRMS (ESI-TOF): calc'd for $C_{11}H_{12}F_3O_3S$ [M+H$^+$] 281.0459; found 281.0454.



121f

(2-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopropyl)methyl methanesulfonate (121f)

Epoxide **119f** (2.56 g, 9.1 mmol) was dissolved in THF (60 mL) and *n*-BuLi (1.97 M in hexane, 4.85 mL, 1.05 equiv) was added dropwise at 0 °C. After the addition was complete,

the mixture was stirred a further 5 min before being quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer extracted with EtOAc twice. The combined organic layers were dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (1:1 hexanes:EtOAc) to give the desired alcohol **120f** (2.30 g, 90%). To a solution of the alcohol **120f** (2.30 g, 8.2 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (2.27 mL, 2.0 equiv) and methanesulfonyl chloride (0.95 mL, 1.5 equiv) successively at room temperature. After stirring for 1h, the reaction mixture was washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (3:2 hexanes:EtOAc) to give mesylate **121f** (2.80 g, 95%).

Physical State: colorless oil;

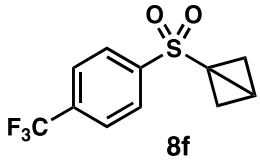
R_f = 0.30 (1:1 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 4.32 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.95 (dd, *J* = 11.4, 7.8 Hz, 1H), 2.93 (s, 3H), 2.66 – 2.58 (m, 1H), 2.18 (ddtd, *J* = 10.0, 7.8, 6.0, 4.4 Hz, 1H), 1.67 (dt, *J* = 9.5, 5.6 Hz, 1H), 1.21 (dt, *J* = 8.4, 6.1 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.5, 135.5 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 128.5 (2C), 126.6 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, 2C), 123.2 (q, $^1J_{C\text{-}F}$ = 273 Hz), 68.8, 38.1, 37.7, 19.0, 11.0;

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.5;

HRMS (ESI-TOF): calc'd for $C_{12}H_{13}F_3NaO_5S_2$ [M+Na^+] 381.0054; found 381.0055.



8f

1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[1.1.0]butane (8f)

To mesylate **121f** (2.69 g, 7.5 mmol) in THF (75 mL) was added *n*-BuLi (1.97 M in hexane, 3.8 mL, 1.0 equiv) dropwise at 0 °C. After the addition was complete, the mixture was stirred a further 5 min before being quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography (15:1 hexanes:EtOAc) to give bicyclobutane sulfone **8f** (0.81 g, 41%, 68% brsm).

Physical State: white solid (m.p. = 68-72 °C);

$\boldsymbol{R_f}$ = 0.75 (2:3 EtOAc:hexanes, vis. UV);

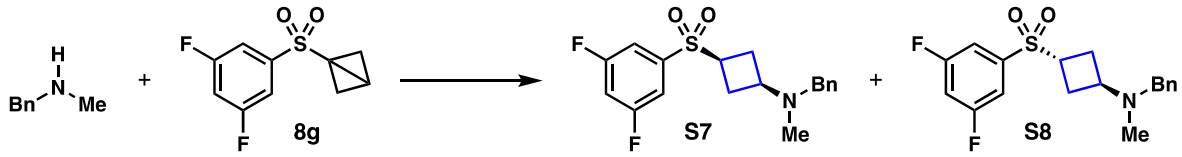
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 2.69 (ddd, *J* = 6.5, 3.7, 2.9 Hz, 1H), 2.56 (dt, *J* = 3.8, 1.0 Hz, 2H), 1.44 (dd, *J* = 2.6, 1.3 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.7, 134.8 (q, $^{2}J_{C\text{-}F}$ = 33.0 Hz), 127.8 (2C), 126.5 (q, $^{3}J_{C\text{-}F}$ = 4.3 Hz, 2C), 123.4 (q, $^{1}J_{C\text{-}F}$ = 273 Hz), 38.8 (2C), 22.8, 13.5;

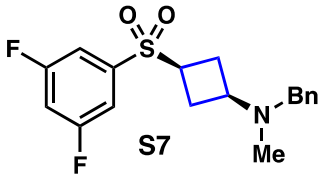
^{19}F NMR (376 MHz, $CDCl_3$): δ –63.4;

HRMS (ESI-TOF): calc'd for $C_{11}H_{10}F_3O_2S$ [M+H^+] 263.0348; found 263.0348.

Characterization of Aminated Sulfone Intermediates (*cis*- and *trans*-isomers)



N-Methylbenzylamine (61 mg, 0.5 mmol), sulfone **8g** (121 mg, 1.05 equiv) and LiCl (64 mg, 3.0 equiv) were dissolved in DMSO (1.25 mL) and stirred at room temperature for 12h. After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel chromatography (8:1 to 3:1 hexanes:EtOAc) to give *cis*-isomer **S7** (88 mg, 50% yield) and *trans*-isomer **S8** (76 mg, 43% yield).



***cis*-*N*-benzyl-3-((3,5-difluorophenyl)sulfonyl)-*N*-methylcyclobutan-1-amine (S7)**

Physical State: white solid (m.p. = 81-83 °C);

R_f = 0.55 (1:2 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.40 (m, 2H), 7.37 – 7.23 (m, 5H), 7.11 (tt, *J* = 8.4, 2.4 Hz, 1H), 3.53 – 3.44 (m, 1H), 3.42 (s, 2H), 2.95 (tt, *J* = 8.8, 7.0 Hz, 1H), 2.49 (qd, *J* = 9.3, 2.7 Hz, 2H), 2.37 – 2.26 (m, 2H), 2.08 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 244, 11.4 Hz, 2C), 141.8 (t, $^3J_{C\text{-}F}$ = 8.0 Hz), 138.1, 129.1 (2C), 128.4 (2C), 127.3, 111.9 (q, $^2J_{C\text{-}F}$ = 8.2 Hz, 2C), 109.5 (t, $^2J_{C\text{-}F}$ = 25.0 Hz), 58.4, 54.1, 50.5, 37.6, 28.9 (2C);

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.2;

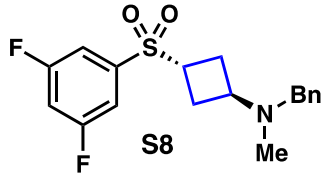
HRMS (ESI-TOF): calc'd for $C_{18}H_{20}F_2NO_2S$ [M+H$^+$] 352.1183; found 352.1184.

Fig. S47. Crystal structure of *cis*-*N*-benzyl-3-((3,5-difluorophenyl)sulfonyl)-*N*-methylcyclobutan-1-amine **(S7)**

Table S5. Crystal data and structure refinement for **S7**

Identification code	CCDC 1431183	
Empirical formula	$C_{18}H_{19}F_2NO_2S$	
Formula weight	351.40	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.5183(10) Å	α = 81.396(8)°.
	b = 12.654(3) Å	β = 81.489(7)°.
	c = 12.840(2) Å	γ = 77.545(7)°.
Volume	859.4(3) $Å^3$	
Z	2	
Density (calculated)	1.358 Mg/m^3	
Absorption coefficient	0.218 mm^{-1}	
F(000)	368	
Crystal size	0.33 x 0.3 x 0.25 mm^3	
Theta range for data collection	1.616 to 25.345°.	
Index ranges	-6<=h<=6, -15<=k<=15, -10<=l<=15	
Reflections collected	9662	
Independent reflections	3132 [R(int) = 0.0362]	
Completeness to theta = 25.242°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.0916 and 0.0638	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3132 / 0 / 218
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.0945
R indices (all data)	R1 = 0.0532, wR2 = 0.1008
Extinction coefficient	n/a
Largest diff. peak and hole	0.338 and -0.373 e.Å^{-3}



***trans*-*N*-benzyl-3-((3,5-difluorophenyl)sulfonyl)-*N*-methylcyclobutan-1-amine (S8)**

Physical State: white solid (m.p. = 47-50 °C);

R_f = 0.45 (1:2 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 – 7.43 (m, 2H), 7.37 – 7.23 (m, 5H), 7.12 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.74 (tt, *J* = 9.2, 4.2 Hz, 1H), 3.38 (s, 2H), 3.28 (p, *J* = 7.4 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.41 – 2.30 (m, 2H), 2.03 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 244, 11.4 Hz, 2C), 141.5 (t, $^3J_{C\text{-}F}$ = 8.0 Hz), 138.1, 129.2 (2C), 128.4 (2C), 127.3, 112.0 (q, $^2J_{C\text{-}F}$ = 8.3 Hz, 2C), 109.5 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 58.6, 56.9, 53.2, 37.9, 28.5 (2C);

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.2;

HRMS (ESI-TOF): calc'd for $C_{18}H_{20}F_2NO_2S$ [$M+H^+$] 352.1183; found 252.1185.

General Medicinal Chemistry Preparations for the "Cyclobutylation" of Amines using 8g (prepared above)

General procedure A: (Compounds 124, 125, 126, 129, 130, 131, 132)
The free amine (1.0 equiv), sulfone **8g** (1.05 equiv) and LiCl (3.0 equiv) were dissolved in DMSO (0.4 M) stirred at room temperature for 12h (36 hours for **124** and **126**). After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in MeOH (0.04 M) and refluxed with freshly activated Mg turnings (40 equiv).[62] After completion of the reaction (typically < 2 h), the mixture was cooled to room temperature, diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography to give the desired products.

General procedure B: (Compounds 123, 127, 128)
The free amine (1.0 equiv), sulfone **8g** (1.05 equiv) and LiCl (3.0 equiv) were dissolved in DMSO (0.4 M) stirred at room temperature for 12h. After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by silica gel flash chromatography to give the intermediate aminated cyclobutylsulfones. The product above was dissolved in MeOH (0.04 M) and refluxed with freshly activated Mg turnings (40 equiv).[62] After completion of the reaction (typically < 2 h), the mixture was cooled to room temperature, diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography to give the desired products.

General procedure C: (Compounds 133, 134, 135, 136, 137)
The free amine (1.0 equiv), sulfone **8g** (1.05 equiv) and LiCl (3.0 equiv) were dissolved in DMSO (0.4 M) stirred at room temperature for 12h. After completion, the reaction was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in MeOH (0.04 M) and freshly activated Mg turnings (40 equiv) were added.[62] After sonication for 5 min, the reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography to give the desired products.

Notes, Troubleshooting, and Limitations for the "Cyclobutylation" of Amines:

1. The desulfonylation reaction must be initiated by 1 of 3 methods (after initial activation of the Mg turnings)[62]:
    a. Reflux at 80 ºC until the mixture turns opaque or muddy.
    b. Sonication until bubbling is observed.
    c. Washing the Mg turnings again with dilute HCl.
2. Limitations for the amination of primary amines:
    a. Benzylamine: low isolated yield (40%) due to bis-addition of **8g**.
    b. 4-Aminopyridine: mostly bis-addition of **8g** observed.
    c. 2-Aminopyridine: low conversion (mixture of mono- and bis-addition of **8g**).
3. Limitations for the reduction:
    a. Amoxapine: The amination proceeds well, but a mixture of reduction products is observed.
    b. Quipazine: The amination proceeds well, but a mixture of reduction products is observed.
    c. Preliminary studies have been conducted which suggest SmI_2 or Raney nickel can serve as alternative reduction procedures.

Graphical Preparation for the “Cyclobutylation” of Amines

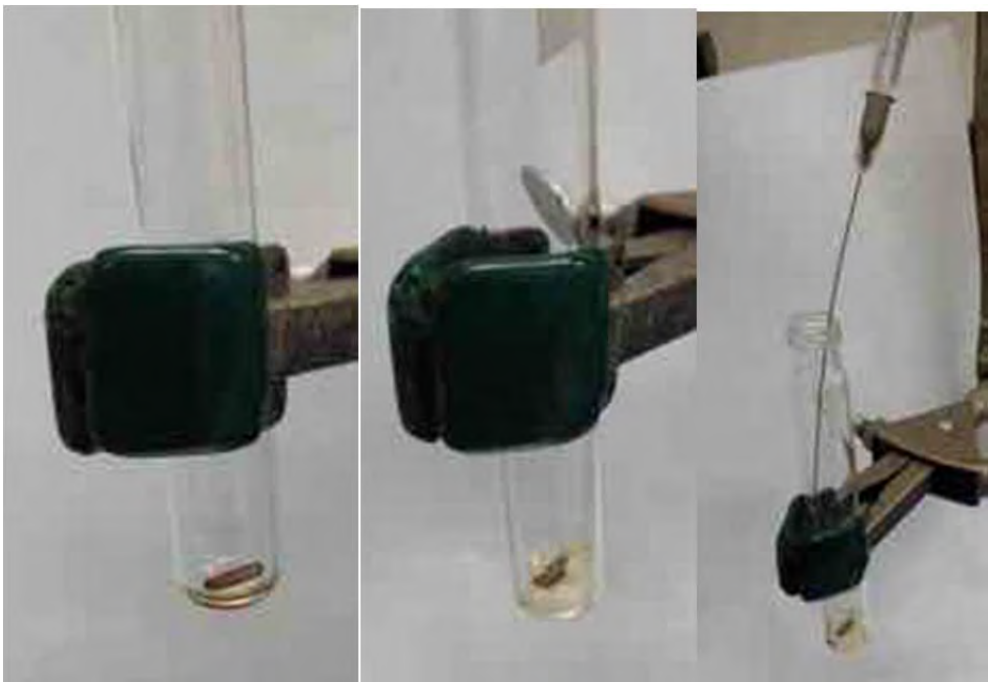


Fig. S48. Left. Addition of stir bar and dibenzylamine to a reaction tube. **Center.** Addition of sulfone **8g** and LiCl to reaction tube. **Right.** Addition of DMSO to reaction tube.

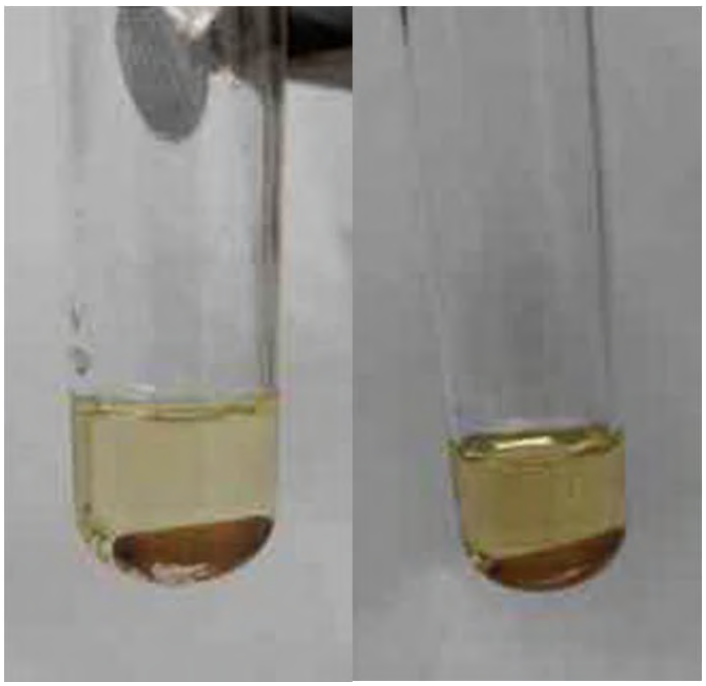


Fig. S49. Left. Reaction after stirring for 2 min. **Right.** Reaction after stirring for 12 h.

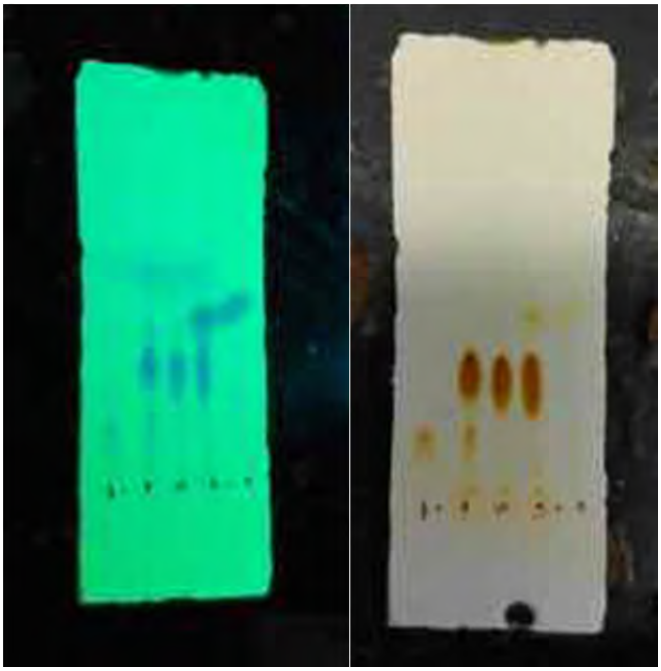


Fig. S50. Left. TLC under UV visualization (1:6 EtOAc:hexanes). Lane 1 = Bn_2NH; Lane 2 = co-spot of Bn_2NH and crude reaction mixture; Lane 3 = crude reaction mixture; Lane 4 = co-spot of crude reaction mixture and sulfone **8g**; Lane 5 = pure sulfone **8g**. **Right.** Same TLC plate with I_2 development.

Fig. S51. Left. The reaction was dissolved in EtOAc and washed with brine. **Right.** The organic layers were dried over Na_2SO_4 and concentrated on the rotovap.

Fig. S52. Left. The crude product (same flask as rotovap) was dissolved in MeOH and activated Mg turnings added. **Right.** The Mg/MeOH reduction after heating at 80 °C for 2 h.

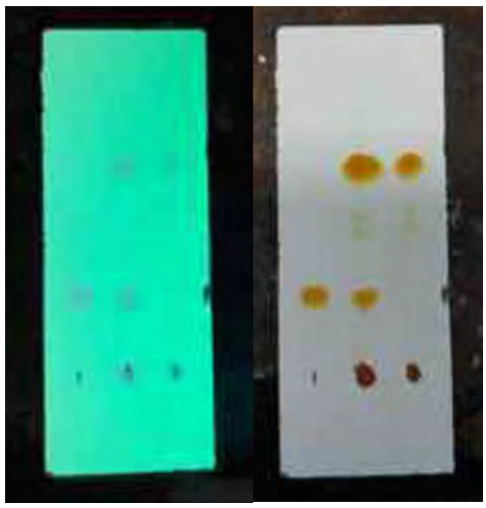
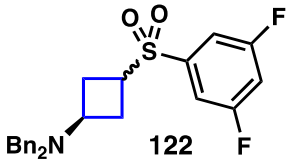


Fig. S53. Left. TLC under UV visualization (1:10 EtOAc:hexanes). Lane 1 = Bn_2N cyclobutylsulfone **122**; Lane 2 = co-spot of **122** and crude reaction mixture; Lane 3 = crude reaction mixture. **Right.** Same TLC plate with I_2 development.

Graphical Preparation for Reduction Step of Complex Example 134

Fig. S54. Left. Aminated sulfone intermediate of **134** dissolved in MeOH with activated Mg turnings added. **Left-Center.** Sonication of reaction for 5 min. **Right-Center.** Reaction after stirring with MeOH/Mg until completion. **Right.** TLC with I_2 development (1:6 MeOH:CH_2Cl_2). Lane 1 = nortriptyline cyclobutylsulfone; Lane 2 = co-spot of nortriptyline cyclobutylsulfone and crude reaction mixture; Lane 3 = crude reaction mixture.

Substrates for the "Cyclobutylation" of Amines



[inseparable mixture of cis/trans isomers]

***(cis/trans)*-*N*,*N*-dibenzyl-3-((3,5-difluorophenyl)sulfonyl)cyclobutan-1-amine (122)**
dibenzyl-amine (0.5 mmol), sulfone **8g** (121 mg, 1.05 equiv) and LiCl (64 mg, 3.0 equiv) were dissolved in DMSO (1.25 mL) and stirred at room temperature for 12 h. The reaction was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel chromatography (15:1 hexanes:EtOAc) to give **122** (207 mg, 97% yield, ~1:1 ratio of diastereoisomers).

Physical State: white solid (mixture of cis/trans isomers);

R_f = 0.35 (1:6 EtOAc/hexanes, vis. UV);

Major isomer (*trans*):

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (ddd, *J* = 5.0, 2.3, 1.1 Hz, 2H), 7.38 – 7.25 (m, 10H), 7.15 – 7.07 (m, 1H), 3.66 (ttd, *J* = 9.7, 4.0, 1.1 Hz, 1H), 3.52 (s, 4H), 3.39 (tt, *J* = 9.6, 7.7 Hz, 1H), 2.55 (dddd, *J* = 11.8, 8.0, 4.0, 2.7 Hz, 2H), 2.37 – 2.28 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 255, 11.1 Hz, 2C), 141.5 (t, $^3J_{C\text{-}F}$ = 7.8 Hz), 138.5 (2C), 129.1 (4C), 128.4 (4C), 127.2 (2C), 112.0 (q, $^2J_{C\text{-}F}$ = 6.6 Hz, 2C), 109.5 (t, $^2J_{C\text{-}F}$ = 24.6 Hz), 54.6 (2C), 54.4, 51.9, 29.0 (2C);

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.2;

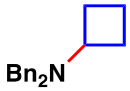
Minor isomer (*cis*):

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 – 7.38 (m, 2H), 7.38 – 7.25 (m, 10H), 7.15 – 7.07 (m, 1H), 3.61 (qd, *J* = 7.9, 1.2 Hz, 1H), 3.58 (s, 4H), 3.23 (tt, *J* = 9.1, 7.1 Hz, 1H), 2.49 (qd, *J* = 9.4, 2.7 Hz, 2H), 2.23 (dtq, *J* = 11.4, 6.8, 2.0 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 255, 11.5 Hz, 2C), 141.8 (t, $^3J_{C\text{-}F}$ = 7.7 Hz), 138.6 (2C), 129.0 (4C), 128.4 (4C), 127.2 (2C), 111.9 (q, $^2J_{C\text{-}F}$ = 6.5 Hz, 2C), 109.4 (t, $^2J_{C\text{-}F}$ = 25.2 Hz), 55.2 (2C), 53.6, 50.9, 29.1 (2C);

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.2;

HRMS (ESI-TOF): calc'd for $C_{24}H_{24}F_2NO_2S$ [M+H$^+$] 428.1496; found 428.1496.



123

***N*,*N*-dibenzylcyclobutanamine (123)**

On 0.5 mmol scale, general procedure B was followed to convert dibenzylamine to **123** in 97% and 72% yield (for the amination and reduction, respectively).

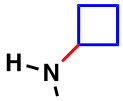
Physical State: colorless oil;

***R*$_f$** = 0.70 (1:10 EtOAc:hexanes, vis. I_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 8H), 7.30 – 7.23 (m, 2H), 3.53 (s, 4H), 3.26 – 3.14 (m, 1H), 2.06 – 1.86 (m, 4H), 1.74 – 1.54 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.5 (2C), 129.3 (4C), 128.1 (4C), 126.8 (2C), 58.2, 54.3 (2C), 28.3 (2C), 14.6;

HRMS (ESI-TOF): calc'd for $C_{18}H_{22}N$ [M+H$^+$] 252.1752; found 252.1753.



124

***N*-cyclobutylaniline (124)**

On 0.5 mmol scale, general procedure A was followed to convert aniline to **124** in 61% yield (over two steps).[63]

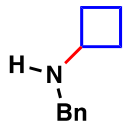
Physical State: light yellow oil;

***R*$_f$** = 0.75 (1:5 EtOAc:hexanes, vis. I_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.14 (m, 2H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.61 – 6.55 (m, 2H), 4.00 – 3.89 (m, 1H), 3.83 (br s, 1H), 2.52 – 2.37 (m, 2H), 1.93 – 1.74 (m, 4H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.3, 129.3 (2C), 117.4, 113.1 (2C), 49.1, 31.4 (2C), 15.4;

HRMS (ESI-TOF): calc'd for $C_{10}H_{14}N$ [M+H$^+$] 148.1126; found 148.1126.



125

***N*-benzylcyclobutanamine (125)**

For 0.5 mmol scale, general procedure A was followed to convert benzylamine to **125** in 40% yield (over two steps).[48]

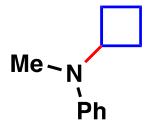
Physical State: colorless oil;

***R*$_f$** = 0.40 (1:6 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 3.71 (s, 2H), 3.36 – 3.25 (m, 1H), 2.27 – 2.17 (m, 2H), 2.01 (s, 1H), 1.80 – 1.59 (m, 4H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.1, 128.5 (2C), 128.4 (2C), 127.1, 53.6, 51.1, 31.1 (2C), 15.0;

HRMS (ESI-TOF): calc'd for $C_{11}H_{16}N$ [M+H$^+$] 162.1283; found 162.1279.



126

***N*-cyclobutyl-*N*-methylaniline (126)**

For 0.5 mmol scale, general procedure A was followed to convert *N*-methylaniline to **126** in 73% yield (over two steps).[64]

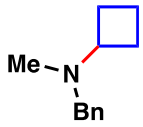
Physical State: colorless oil;

***R*$_f$** = 0.75 (1:6 EtOAc:hexanes, vis. I_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.25 (m, 2H), 6.89 – 6.78 (m, 3H), 4.07 – 3.97 (m, 1H), 2.89 (s, 3H), 2.37 – 2.25 (m, 2H), 2.23 – 2.09 (m, 2H), 1.83 – 1.70 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4, 129.0 (2C), 117.9, 115.2 (2C), 55.3, 34.8, 29.0 (2C), 14.6;

HRMS (ESI-TOF): calc'd for $C_{11}H_{16}N$ [M+H$^+$] 162.1283; found 162.1278.



127

***N*-benzyl-*N*-methylcyclobutanamine (127)**

For 0.5 mmol scale (step 1) and 0.2 mmol scale (step 2), general procedure B was followed to convert *N*-benzylmethylamine to **127** in 93% and 71% yield (for the amination and reduction, respectively).

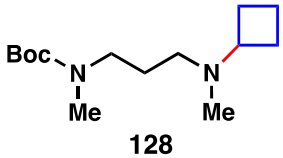
Physical State: colorless oil;

***R*$_f$** = 0.50 (1:10 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 4H), 7.27 – 7.22 (m, 1H), 3.36 (s, 2H), 2.89 – 2.81 (m, 1H), 2.09 – 2.02 (m, 2H), 2.00 (s, 3H), 1.97 – 1.88 (m, 2H), 1.76 – 1.60 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.8, 129.5 (2C), 128.3 (2C), 127.0, 60.5, 58.6, 37.9, 28.0 (2C), 14.1;

HRMS (ESI-TOF): calc'd for $C_{12}H_{18}N$ [M+H$^+$] 176.1439; found 176.1433.



128

***tert*-butyl (3-(cyclobutyl(methyl)amino)propyl)(methyl)carbamate (128)**

For 0.5 mmol scale, general procedure B was followed to convert *tert*-butyl methyl(3-(methylamino)propyl)carbamate to **128** in 95% and 82% yield (for the amination and reduction, respectively).[65]

Physical State: colorless oil;

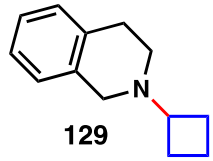
R_f = 0.40 (1:8 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$ + NH_4OH): δ 3.20 (s, 2H), 2.82 (s, 3H), 2.75 – 2.67 (m, 1H), 2.22 – 2.14 (m, 2H), 2.06 (s, 3H), 2.04 – 1.95 (m, 2H), 1.87 – 1.77 (m, 2H), 1.72 – 1.56 (m, 4H), 1.43 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.9, 79.3, 60.8, 51.6, 47.2, 37.9, 34.3, 28.6 (3C), 28.0 (2C), 25.6, 14.1;

HSQC: See page S580 for correlations of doubled peaks;

HRMS (ESI-TOF): calc'd for $C_{14}H_{29}N_2O_2$ [M+H$^+$] 257.2229; found 257.2231.



129

2-cyclobutyl-1,2,3,4-tetrahydroisoquinoline (129)

For 0.5 mmol scale, general procedure A was followed to convert 1,2,3,4-tetrahydroisoquinoline to **129** in 68% yield (over two steps).

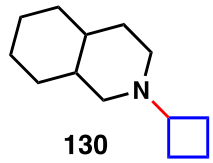
Physical State: light yellow oil;

R_f = 0.40 (1:1 EtOAc:hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 – 7.06 (m, 3H), 7.01 (dd, *J* = 6.6, 2.0 Hz, 1H), 3.50 (s, 2H), 2.89 (q, *J* = 7.5, 6.7 Hz, 3H), 2.60 (t, *J* = 6.0 Hz, 2H), 2.17 – 2.10 (m, 2H), 2.03 – 1.94 (m, 2H), 1.80 – 1.71 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 134.6, 134.4, 128.8, 126.8, 126.2, 125.7, 60.1, 52.6, 47.0, 28.9, 27.6 (2C), 14.6;

HRMS (ESI-TOF): calc'd for $C_{13}H_{18}N$ [M+H$^+$] 188.1439; found 188.1436.



130

2-cyclobutyldecahydroisoquinoline (130)

For 0.5 mmol scale, general procedure A was followed to convert perhydroisoquinoline to **130** in 71% yield (over two steps).

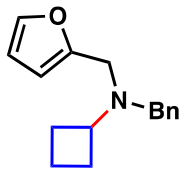
Physical State: colorless oil;

R_f = 0.40 (1:6 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (d, *J* = 11.1 Hz, 1H), 2.80 – 2.62 (m, 2H), 2.07 – 1.87 (m, 4H), 1.78 – 1.47 (m, 8H), 1.43 – 1.16 (m, 5H), 1.03 – 0.80 (m, 3H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 60.6, 56.5, 50.5, 41.8, 41.2, 33.0, 32.3, 30.8, 27.4, 27.3, 26.6, 26.2, 14.4;

HRMS (ESI-TOF): calc'd for $C_{13}H_{24}N$ [M+H$^+$] 194.1909; found 194.1912.



131

***N*-benzyl-*N*-(furan-2-ylmethyl)cyclobutanamine (131)**

For 0.2 mmol scale, general procedure A was followed to convert *N*-benzyl-*N*-(furan-2-ylmethyl)amine to **131** in 60% yield (over two steps).[66]

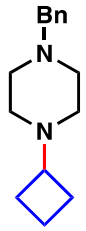
Physical State: colorless oil;

R_f = 0.75 (1:4 EtOAc:hexanes, vis. I_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.31 (m, 5H), 7.31 – 7.23 (m, 1H), 6.34 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.14 (d, *J* = 3.1 Hz, 1H), 3.55 (s, 2H), 3.50 (s, 2H), 3.19 – 3.08 (m, 1H), 2.15 – 2.02 (m, 2H), 2.02 – 1.86 (m, 2H), 1.78 – 1.60 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.6, 141.9, 139.1, 129.5 (2C), 128.2 (2C), 126.9, 110.1, 108.8, 57.6, 53.5, 45.0, 28.4 (2C), 14.3;

HRMS (ESI-TOF): calc'd for $C_{16}H_{20}NO$ [M+H$^+$] 242.1545; found 242.1546.



132

1-benzyl-4-cyclobutylpiperazine (132)

For 0.5 mmol scale, general procedure A was followed to convert *N*-benzylpiperazine to **132** in 76% yield (over two steps).[52]

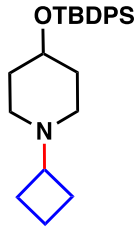
Physical State: colorless oil;

***R*$_f$** = 0.60 (1:10 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 4H), 7.23 (tt, *J* = 5.1, 3.3 Hz, 1H), 3.52 (s, 2H), 2.79 – 2.71 (m, 1H), 2.49 (s, 8H), 2.05 – 1.97 (m, 2H), 1.95 – 1.84 (m, 2H), 1.75 – 1.61 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.1, 129.3 (2C), 128.3 (2C), 127.1, 63.2, 60.4 (2C), 52.7, 49.5 (2C), 27.1 (2C), 14.4;

HRMS (ESI-TOF): calc'd for $C_{15}H_{23}N_2$ [M+H$^+$] 231.1861; found 231.1864.



133

4-((*tert*-butyldiphenylsilyl)oxy)-1-cyclobutylpiperidine (133)

For 0.2 mmol scale, general procedure C was followed to convert 4-((*tert*-butyldiphenylsilyl)oxy)piperidine to **133** in 75% yield (over two steps).[67]

Physical State: colorless oil;

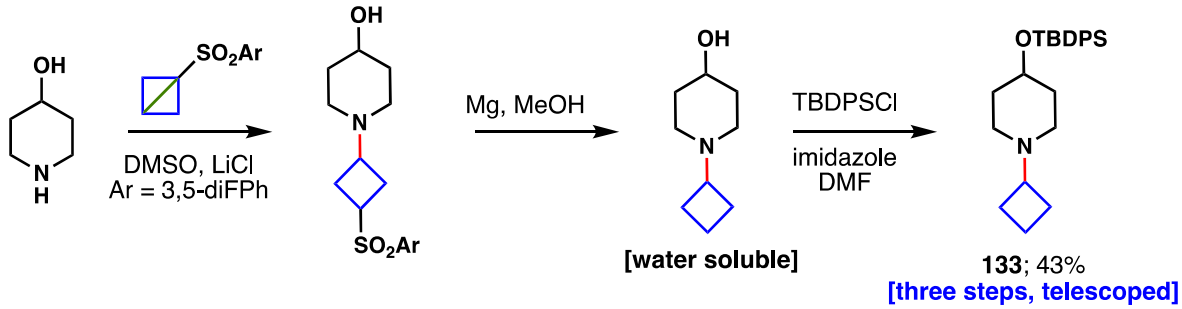
R_f = 0.60 (1:1 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (dt, *J* = 6.7, 1.5 Hz, 4H), 7.43 – 7.39 (m, 2H), 7.39 – 7.34 (m, 4H), 3.78 (s, 1H), 2.65 (p, *J* = 7.9 Hz, 1H), 2.54 (s, 2H), 1.99 (dddt, *J* = 11.4, 9.4, 4.3, 2.1 Hz, 3H), 1.92 – 1.78 (m, 3H), 1.73 – 1.58 (m, 6H), 1.06 (s, 9H);

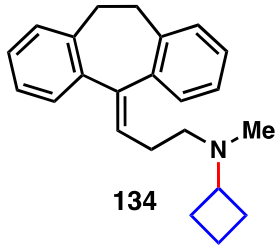
^{13}C NMR (151 MHz, $CDCl_3$): δ 135.9 (4C), 134.7 (2C), 129.6 (2C), 127.6 (4C), 68.7, 60.6, 46.8 (2C), 34.0 (2C), 27.6 (2C), 27.1 (3C), 19.4, 14.3;

HRMS (ESI-TOF): calc'd for $C_{25}H_{36}NOSi$ [M+H$^+$] 394.2561; found 394.2556.

Alternatively, **133** can be prepared from 4-hydroxypiperidine:



4-Hydroxypiperidine (51 mg, 0.5 mmol), sulfone **8g** (121 mg, 1.05 equiv) and LiCl (64 mg, 3.0 equiv) were dissolved in DMSO (1.25 mL) and stirred at room temperature for 12 h. The reaction was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and concentrated under reduced pressure. The crude aminated product was dissolved in MeOH (12.5 mL) and activated Mg turnings[62] (40 equiv) were added. After sonication for 5 min, the reaction mixture was stirred at room temperature until completion. To the mixture was added sat. aq. NH_4Cl and solid NaCl until saturation. To remove the water-soluble product, the mixture was extracted with CH_2Cl_2 (10 times), dried with Na_2SO_4, and concentrated under reduced pressure. To the crude cyclobutylated product was added DMF (3 mL), imidazole (68 mg) and TBDPSCl (0.19 mL) sequentially and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, concentrated under reduced pressure, and purified by silica gel chromatography (1:1 hexanes:EtOAc) to give **133** (85 mg, 43% yield). The spectroscopic data matched that from **133** as prepared above.



134

***N*-(3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl)-*N*-methylcyclobutanamine, "cyclobutylated" nortriptyline (134)**

For 0.2 mmol scale (step 1) and 0.08 mmol scale (step 2), general procedure C was followed to convert nortriptyline to **134** in 83% and 72% yield (for the amination and reduction, respectively).

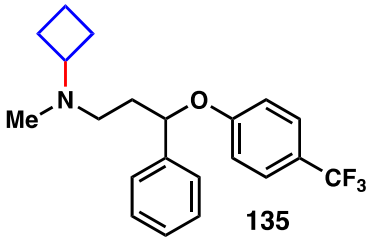
Physical State: colorless oil;

R_f = 0.40 (1:6 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.24 (m, 2H), 7.21 – 7.10 (m, 5H), 7.05 – 7.01 (m, 1H), 5.84 (t, *J* = 7.2 Hz, 1H), 3.36 (br d, *J* = 57.1 Hz, 2H), 2.96 (br s, 1H), 2.82 – 2.67 (m, 2H), 2.39 – 2.21 (m, 3H), 2.00 (s, 3H), 1.96 (d, *J* = 8.4 Hz, 1H), 1.80 (p, *J* = 10.6, 9.9 Hz, 2H), 1.69 – 1.52 (m, 4H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.6, 141.5, 140.2, 139.4, 137.2, 130.1, 129.6, 128.7, 128.3, 128.1, 127.5, 127.1, 126.1, 125.9, 60.4, 53.8, 37.8, 33.9, 32.2, 28.0 (2C), 27.3, 14.1;

HRMS (ESI-TOF): calc'd for $C_{23}H_{28}N$ [M+H$^+$] 318.2222; found 318.2223.



135

***(rac)*-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)cyclobutanamine, "cyclobutylated" fluoxetine (135)**

For 0.1 mmol scale, general procedure C was followed to convert fluoxetine to **135** in 61% yield (over two steps).

Physical State: colorless oil;

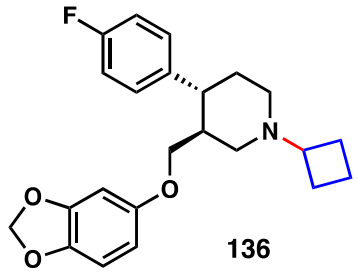
R_f = 0.25 (1:15 MeOH:CH_2Cl_2, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.27 (dd, *J* = 8.4, 4.6 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.44 (ddd, *J* = 12.4, 8.4, 6.6 Hz, 1H), 2.35 (ddd, *J* = 12.4, 8.5, 5.2 Hz, 1H), 2.15 (dtd, *J* = 13.7, 8.4, 5.2 Hz, 1H), 2.10 (s, 3H), 2.02 – 1.93 (m, 3H), 1.89 – 1.72 (m, 2H), 1.68 – 1.54 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 160.8, 141.4, 128.9 (2C), 127.9, 126.8 (q, $^3J_{C\text{-}F}$ = 4.2 Hz, 2C), 126.0, (2C) 124.5 (q, $^1J_{C\text{-}F}$ = 271 Hz), 122.8 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 115.9 (2C), 78.8, 60.8, 50.2, 38.0, 36.4, 28.0 (2C), 14.1;

^{19}F NMR (376 MHz, $CDCl_3$): δ –61.8;

HRMS (ESI-TOF): calc'd for $C_{21}H_{25}F_3NO$ [M+H$^+$] 364.1888; found 364.1892.



136

(3*S*,4*R*)-3-((benzo[*d*][1,3]dioxol-5-yloxy)methyl)-1-cyclobutyl-4-(4-fluorophenyl)piperidine, "cyclobutylated" paroxetine (136)

For 0.1 mmol scale, general procedure C was followed to convert paroxetine to **136** in 70% yield (over two steps).

Physical State: colorless oil;

R_f = 0.25 (1:15 MeOH:CH_2Cl_2, vis. I_2);

$[\alpha]_D^{20}$ = –70.1 (c = 0.76, $CHCl_3$);

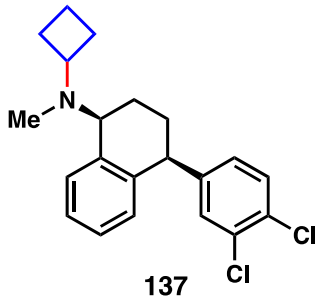
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 8.4, 5.5 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 2.6 Hz, 1H), 6.12 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.87 (s, 2H), 3.57 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.44 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.21 (ddd, *J* = 11.4, 3.8, 1.7 Hz, 1H), 3.07 – 2.97 (m, 1H), 2.79 (p, *J* = 8.0 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.24 – 2.13

(m, 1H), 2.13 – 2.03 (m, 2H), 2.03 – 1.90 (m, 2H), 1.91 – 1.79 (m, 4H), 1.79 – 1.65 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 161.6 (d, $^{1}J_{C\text{-}F}$ = 244 Hz), 154.5, 148.2, 141.7, 139.8 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 129.0 (d, $^{3}J_{C\text{-}F}$ = 7.6 Hz, 2C), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz, 2C), 108.0, 105.7, 101.2, 98.1, 69.7, 60.7, 53.8, 50.4, 44.2, 41.8, 34.0, 27.5, 27.5, 14.4;

^{19}F NMR (376 MHz, $CDCl_3$): δ –117.0;

HRMS (ESI-TOF): calc'd for $C_{23}H_{27}FNO_3$ [M+H$^+$] 384.1975; found 384.1974.



137

(1*S*,4*S*)-*N*-cyclobutyl-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine, "cyclobutylated" sertraline (137)

For 0.1 mmol scale, general procedure C was followed to convert sertraline to **137** in 67% yield (over two steps).

Physical State: colorless oil;

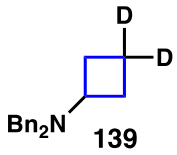
R_f = 0.50 (1:10 EtOAc:hexanes, vis. I_2);

$[\alpha]_D^{20}$ = + 97.8 (c = 1.22, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.13 (tt, *J* = 7.5, 1.1 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.88 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.2 Hz, 1H), 4.12 (td, *J* = 4.7, 4.0, 2.5 Hz, 1H), 3.90 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.30 – 3.21 (m, 1H), 2.18 – 2.08 (m, 1H), 2.08 – 1.87 (m, 8H), 1.74 – 1.53 (m, 4H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 147.8, 139.9, 138.2, 132.2, 130.9, 130.2, 130.0, 129.9, 128.6, 128.4, 127.1, 126.7, 57.5, 57.1, 43.7, 31.8, 30.4, 28.8, 28.1, 15.7, 14.4;

HRMS (ESI-TOF): calc'd for $C_{21}H_{24}Cl_2N$ [M+H$^+$] 360.1286; found 360.1288.



139

***N*,*N*-dibenzylcyclobutan-1-amine-3,3-d_2 (139)**

Amine **122** (40 mg, 0.094 mmol) was dissolved in CD_3OD (5 mL) and added to CD_3ONa in CD_3OD (freshly prepared from Na (s) and CD_3OD) and stirred at 60 ^oC for 5 h. The reaction was cooled to room temperature, Na/Hg (4-5%, 240 mg, 5 equiv) was added and the suspension stirred at room temperature for another 1h. The reaction was diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo* and purified by silica gel flash chromatography to give **139** (13 mg, 55%).

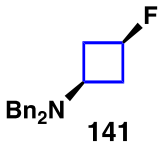
Physical State: colorless oil;

***R*$_f$** = 0.60 (1:15 EtOAc/hexanes, vis. I_2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 8H), 7.25 – 7.20 (m, 2H), 3.49 (s, 4H), 3.15 (tt, *J* = 9.0, 7.0 Hz, 1H), 1.94 (ddd, *J* = 9.5, 7.0, 2.8 Hz, 2H), 1.86 (t, *J* = 9.9 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.5 (2C), 129.3 (4C), 128.1 (4C), 126.8 (2C), 58.1, 54.3 (2C), 28.1 (2C) [CD_2 peak at ~14 ppm almost imperceptible];

HRMS (ESI-TOF): calc'd for $C_{18}H_{20}D_2N$ [M+H$^+$] 254.1878; found 254.1872.



141

***(cis)*-*N*,*N*-dibenzyl-3-fluorocyclobutan-1-amine (141)**

To a solution of amine **122** (47 mg, 0.11 mmol) in THF (2 mL) was added LHMDS (1.0 M in THF, 0.13 mL, 1.2 equiv) at –40 ^oC. The reaction was stirred for 10 min before *N*-fluorobenzenesulfonimide (NFSI) (32 mg, 1.0 equiv) in THF (0.5 mL) was added. The resulting mixture was stirred at –40 ^oC for 2h before being quenched by sat. aq. NH_4Cl. The mixture was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in MeOH (2 mL) and Na/Hg (4-5%, 310 mg, 6 equiv) was added and the suspension stirred at room temperature for 1h. The mixture was diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel flash chromatography to give

141 (15 mg, 51% for 2 steps). Note: the reaction gave a 7:1 mixture of cis:trans diastereomers. After purification with prep TLC, the cis isomer (the major product) was shown in the spectra.

Physical State: white solid (m.p. = 67-69 °C);

R_f = 0.70 (1:6 EtOAc/hexanes, vis. I_2);

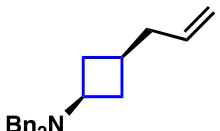
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 8H), 7.24 (ddt, *J* = 8.6, 5.6, 2.8 Hz, 2H), 4.69 (dp, *J* = 56.1, 7.0 Hz, 1H), 3.51 (s, 4H), 2.67 (ttd, *J* = 8.5, 6.6, 1.6 Hz, 1H), 2.51 – 2.40 (m, 2H), 2.17 – 2.03 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.9 (2C), 129.2 (4C), 128.3 (4C), 127.1 (2C), 81.8 (d, $^1J_{C\text{-}F}$ = 211 Hz), 54.9 (2C), 47.7 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, 2C), 19.7 (d, $^3J_{C\text{-}F}$ = 19.7 Hz);

2D NOESY: See page S606;

^{19}F NMR (376 MHz, $CDCl_3$): δ –168.3;

HRMS (ESI-TOF): calc'd for $C_{18}H_{21}FN$ [M+H$^+$] 270.1658; found 270.1659.



143

***(cis)*-3-allyl-*N*,*N*-dibenzylcyclobutan-1-amine (143)**

To a solution of amine **122** (40 mg, 0.094 mmol) in THF (1 mL) was added LHMDS (1.0 M in THF, 0.14 mL, 1.5 equiv) at –78 °C. The mixture was stirred for 30 min before allyl bromide (24 μL, 3 equiv) was added. The resulting mixture was stirred at –78 °C for 2h before being quenched by sat. aq. NH_4Cl. The mixture was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4, evaporated *in vacuo* and purified by silica gel flash chromatography to give the allylated product (38 mg, 87%). This allylated product **142** was dissolved in MeOH (2 mL) and treated with activated Mg turnings (78 mg, 40 equiv).[62] After sonication for 5 min, the reaction mixture was stirred at room temperature until completion. The mixture was diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo* and purified by silica gel flash chromatography to give **143** (19 mg, 80%). Note: The reaction gave a 2.7:1 mixture of cis:trans diastereomers. After purification with prep TLC, a ratio of 3.8:1 mixture of cis:trans diastereomers was shown in the spectra.

Physical State: colorless oil;

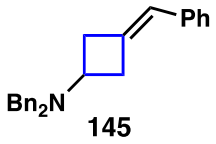
R_f = 0.60 (1:15 EtOAc:hexanes, vis. I_2);

^{1}H NMR for cis isomer (600 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 8H), 7.23 (ddd, *J* = 8.6, 5.5, 2.5 Hz, 2H), 5.73 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.03 – 4.91 (m, 2H), 3.49 (s, 4H), 3.00 (tt, *J* = 9.0, 6.9 Hz, 1H), 2.22 – 2.10 (m, 4H), 1.90 (tp, *J* = 9.6, 7.3 Hz, 1H), 1.51 (qd, *J* = 9.0, 2.7 Hz, 2H);

^{13}C NMR for cis isomer (151 MHz, $CDCl_3$): δ 139.3 (2C), 136.9, 129.3 (4C), 128.1 (4C), 126.8 (2C), 115.0, 54.6, 54.3 (2C), 41.2, 34.3 (2C), 27.6;

2D NOESY: See page S609;

HRMS (ESI-TOF): calc'd for $C_{21}H_{26}N$ [M+H$^+$] 292.2065; found 292.2062.



145

***N*,*N*-dibenzyl-3-benzylidenecyclobutan-1-amine (145)**

To a solution of amine **122** (76 mg, 0.18 mmol) and benzaldehyde (36 μL, 2.0 equiv) in THF (5 mL) was added a solution of *t*BuOK (0.75 M in THF, 0.48 mL, 2.0 equiv) dropwise at 0 °C. The reaction was stirred for 1h at 0 °C before being quenched by sat. aq. NH_4Cl. The mixture was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (5 mL), and then DMAP (2 mg), Et_3N (74 μL, 3 equiv) and Ac_2O (33 μL, 2 equiv) were added successively. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with brine twice, dried with Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in MeOH (5 mL) and Na/Hg (4-5%, 546 mg, 6 equiv) was added and the suspension stirred at room temperature for 1h. The mixture was diluted with EtOAc, washed successively with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated *in vacuo* and purified by silica gel flash chromatography to give **145** (38 mg, 63% for 3 steps).

Physical State: colorless oil;

R_f = 0.50 (1:20 EtOAc:hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 12H), 7.26 – 7.22 (m, 2H), 7.20 (td, *J* = 7.3, 1.4 Hz, 1H), 6.21 (t, *J* = 2.4 Hz, 1H), 3.62 (q, *J* = 14.0 Hz, 4H), 3.40 (p, *J* = 7.3 Hz, 1H), 3.13 – 3.01 (m, 2H), 2.87 (dt, *J* = 7.4, 2.1 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.9 (2C), 138.0, 137.4, 129.3 (4C), 128.5 (2C), 128.3 (4C), 127.2 (2C), 127.0 (2C), 126.1, 121.7, 54.8, 54.3 (2C), 38.7, 38.4;

HRMS (ESI-TOF): calc'd for $C_{25}H_{26}N$ [M+H$^+$] 340.2065; found 340.2067.

Comparison of Two-step, One-pot (with DMSO/MeOH), and One-pot (MeOH only) Prep. for the "Cyclobutylation" of *N*-Benzylmethylamine (to give 127)

Two step protocol: For 0.5 mmol scale (step 1) and 0.2 mmol scale (step 2), general procedure B was followed to convert *N*-benzylmethylamine to **127** in 93% and 71% yield (for the amination and reduction, respectively). Overall yield was 66%.

One-pot with DMSO and MeOH: *N*-Methylbenzylamine (24 mg, 0.2 mmol), sulfone **8g** (48 mg, 1.05 equiv) and LiCl (25 mg, 3.0 equiv) were dissolved in DMSO (0.5 mL) stirred at room temperature for 12 h. Activated Mg turnings[62] (480 mg, 100 equiv) were added, the suspension diluted with MeOH (5 mL), and then heated to reflux. After TLC indicated completion of the reaction, the mixture was diluted with EtOAc, washed with sat. aq. NH_4Cl and brine successively, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel chromatography (30:1 CH_2Cl_2:MeOH) to give **127** (19 mg, 59% yield).

One-pot with MeOH only: *N*-Methylbenzylamine (24 mg, 0.2 mmol), sulfone **8g** (48 mg, 1.05 equiv) and LiCl (25 mg, 3.0 equiv) were added to MeOH (0.5 mL) and the mixture stirred at room temperature for 60h. Activated Mg turnings[62] (192 mg, 40 equiv) were added, the suspension diluted with MeOH (5 mL), and then heated to reflux. After TLC indicated completion of the reaction, the mixture was diluted with EtOAc, washed with sat. aq. NH_4Cl and brine successively, dried with Na_2SO_4, evaporated *in vacuo*, and purified by silica gel chromatography (30:1 CH_2Cl_2:MeOH) to give **127** (24 mg, 74% yield).

Methods for Peptide Synthesis and Cysteine Labeling:

Analytical reverse-phase HPLC was performed on a Hitachi D-7000 separations module equipped with a L-4500A photodiode array detector. Peptides were analyzed using a Venusil ASB C18 column (5 μm, 4.6 x 150 mm, Bonna-Agela Technologies) at a flow rate of 1.5 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B). Results were analyzed using Hitachi Model D-7000 Chromatography Data Station Software.

Preparative reverse-phase HPLC was performed using a Hitachi system comprised of an L-7150 pump and L-4000 programmable UV detector operating at a wavelength of 230 nm coupled to a Hitachi D-2500 Chromato-Integrator. Peptides were purified on a Thermo Scientific Bio-basic C18 10 μm preparative column operating at a flow rate of 12 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B) and a linear gradient as specified. Peptides were isolated as the corresponding TFA salts and as white solids (unless otherwise noted) following lyophilization.

Preparation of Peptides 153 and 146:

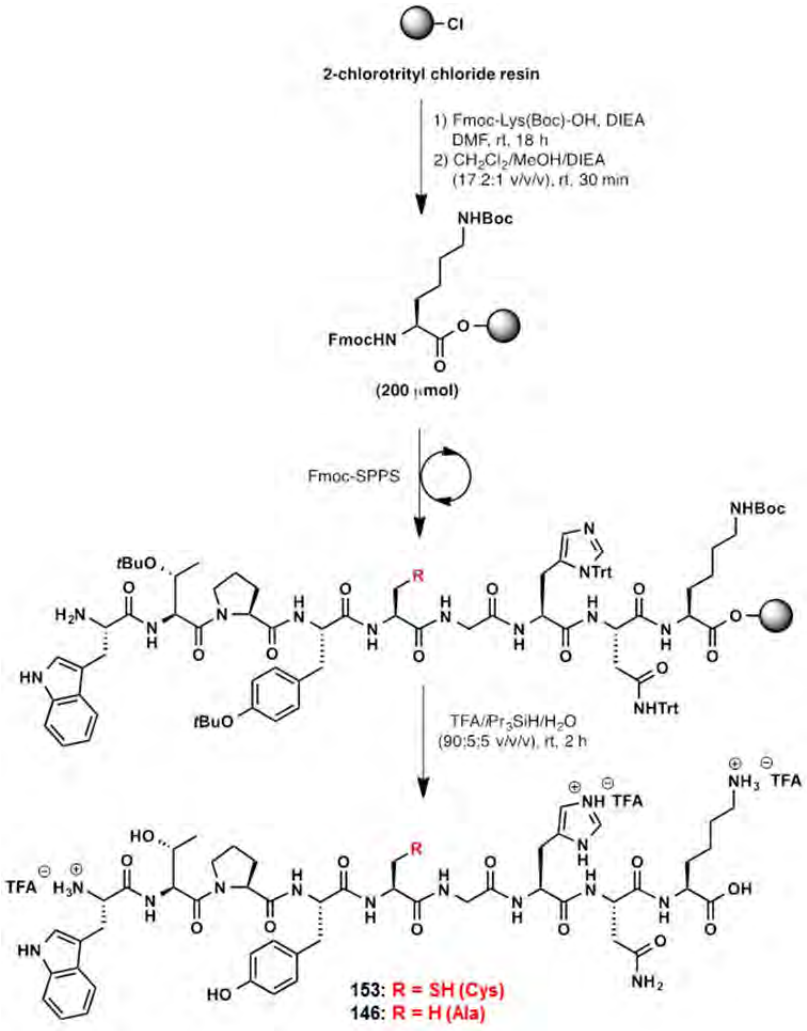


Fig. S55. Preparation of peptides **153** and **146** using Fmoc-SPPS on 2-chlorotrityl chloride resin.

Solid-phase Peptide Synthesis

Preloading 2-chloro-trityl chloride resin

2-chloro-trityl chloride resin (265 mg, 1.51 mmol/g loading) was swollen in dry DCM for 30 min then washed with CH_2Cl_2 (5 x 3 mL) and DMF (5 x 3 mL). A solution of Fmoc-Lys(Boc)-OH (210 μmol) and *N*,*N*-diisopropylethylamine (DIEA) (420 μmol) in DMF (2

mL) was added and the resin agitated on an orbital shaker at rt for 18 h. The resin was washed with DMF (5 x 3 mL) and CH_2Cl_2 (5 x 3 mL) and treated with a solution of CH_2Cl_2/CH_3OH/DIEA (17:2:1 v/v/v, 3 mL) for 0.5 h. The resin washed with DMF (5 x 3 mL), CH_2Cl_2 (5 x 3 mL), and DMF (5 x 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS).

The loading efficiency was evaluated through treatment of the resin with 20% piperidine/DMF (3 mL, 2 × 3 min) to deprotect the Fmoc group. The combined deprotection solutions were diluted to 10 mL with 20% piperidine/DMF. An aliquot of this mixture (50 μL) was diluted 200-fold with 20% piperidine/DMF and the UV absorbance of the piperidine-fulvene adduct was measured (λ = 301 nm, ε = 7800 M^{-1} cm^{-1}) to quantify the amount of amino acid loaded onto the resin.

General Iterative Peptide Assembly (Fmoc-SPPS)

Peptides were elongated using iterative Fmoc-solid-phase peptide synthesis (Fmoc-SPPS), according to the following general protocols:

Deprotection: The resin was treated with 20% piperidine/DMF (3 mL, 2 x 3 min) and washed with DMF (5 x 3 mL), CH_2Cl_2 (5 x 3 mL) and DMF (5 x 3 mL).

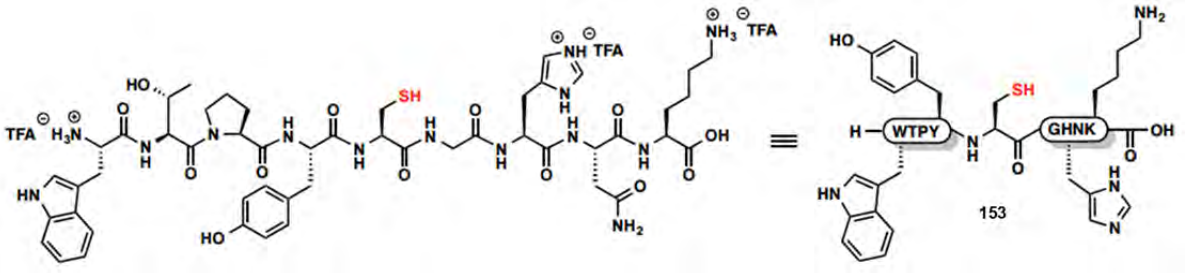
General amino acid coupling: A preactivated solution of protected amino acid (4 eq.), PyAOP (4 eq.) and *N*-methylmorpholine (8 eq.) in DMF (final concentration 0.1 M) was added to the resin. After 1 h, the resin was washed with DMF (5 x 3 mL), CH_2Cl_2 (5 x 3 mL) and DMF (5 x 3 mL).

Capping: Acetic anhydride/pyridine (1:9 v/v) was added to the resin (3 mL). After 3 min the resin was washed with DMF (5 x 3 mL), CH_2Cl_2 (5 x 3 mL) and DMF (5 x 3 mL).

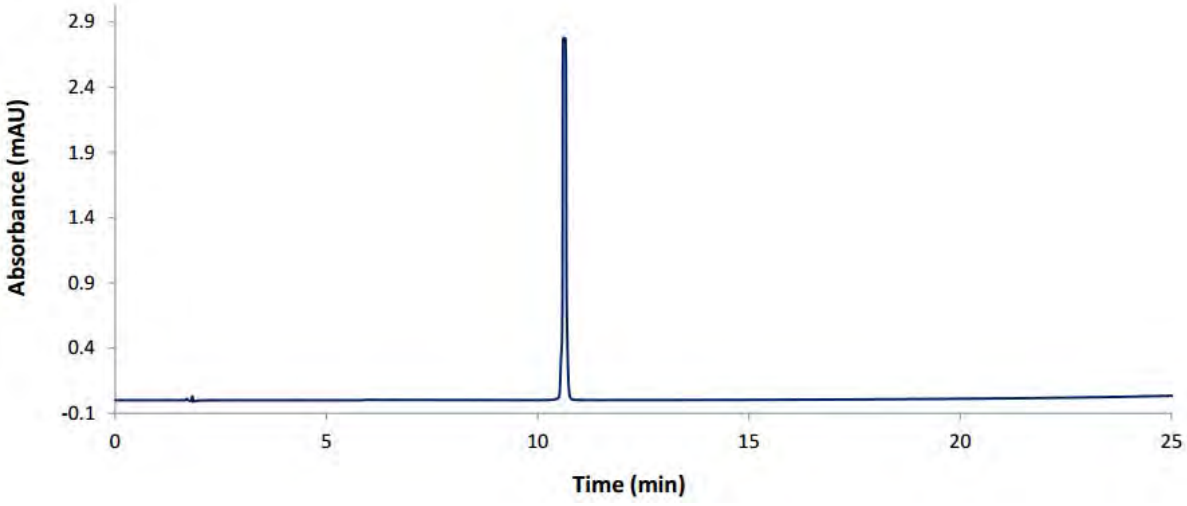
Cleavage: A mixture of TFA, triisopropylsilane (TIS) and water (90:5:5 v/v/v) was added to the resin. After 2 h, the resin was washed with TFA (3 x 2 mL).

Work-up: The combined cleavage solution and TFA washes were concentrated under a stream of nitrogen. The residue was treated with cold Et_2O to precipitate the crude peptide, which was subsequently dissolved in water containing 0.1% TFA, filtered and purified by reverse-phase HPLC.

Peptide **153**: H-WTPYCGHNK-OH

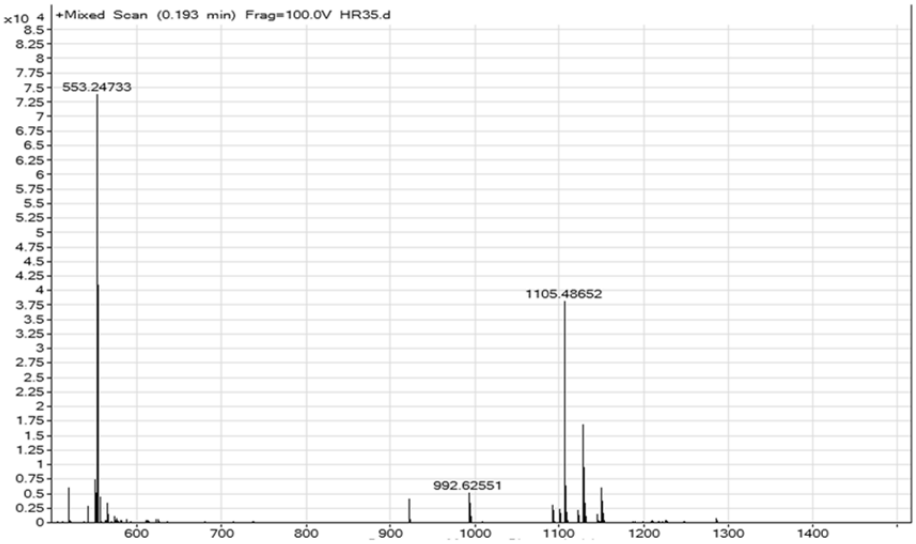


Peptide **153** was prepared using iterative Fmoc-SPPS (50 μmol scale) and purified by reverse-phase HPLC (gradient: 10% B for 5 min, 10% to 40% B over 35 min) to afford the target compound as a white solid following lyophilization (3 x TFA salt). Note: for clarity, TFA salts have been omitted from the condensed structure.



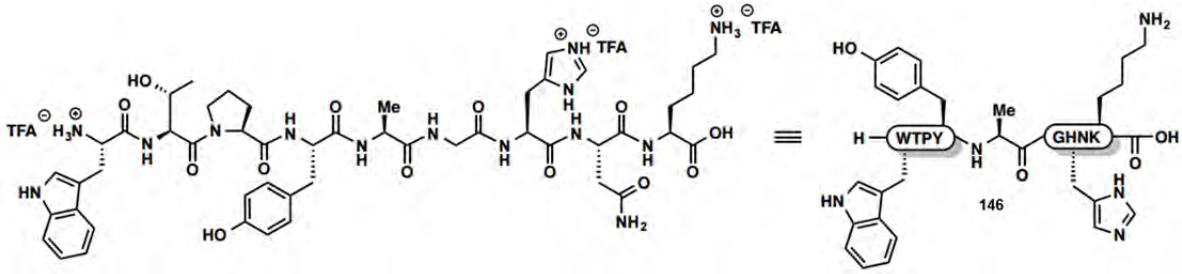
Analytical HPLC (0 to 100% B over 25 min, λ = 230 nm, R_t = 10.6 min) of purified peptide **153**.

Peptide **153**: HRMS

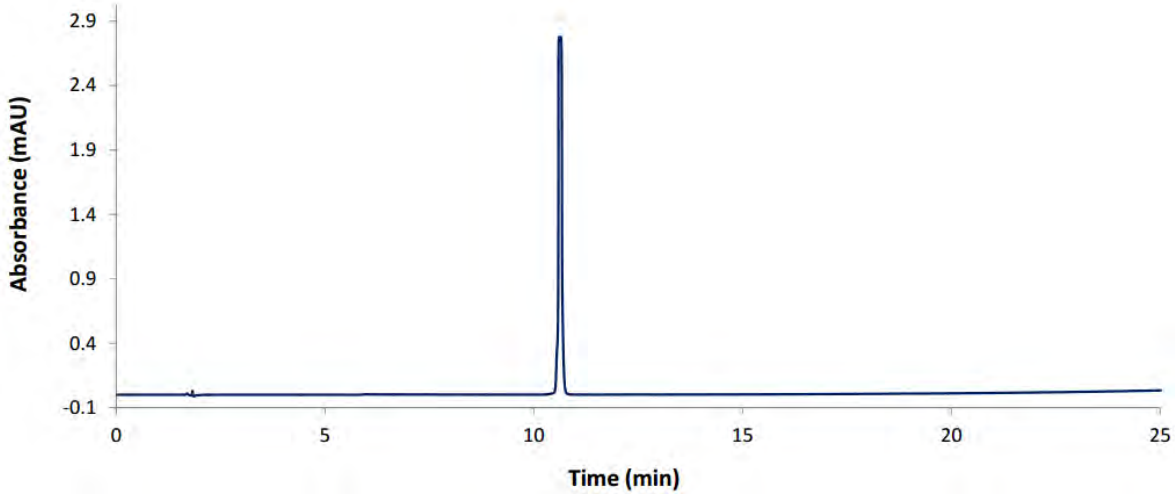


HRMS (ESI-TOF): calc'd for $C_{50}H_{69}N_{14}O_{13}S$ $[M+H]^+$ 1105.4884, found 1105.4865 $[M+H]^+$, 553.2473 $[M+2H]^{2+}$

Peptide **146**: H-WTPY**A**GHNK-OH

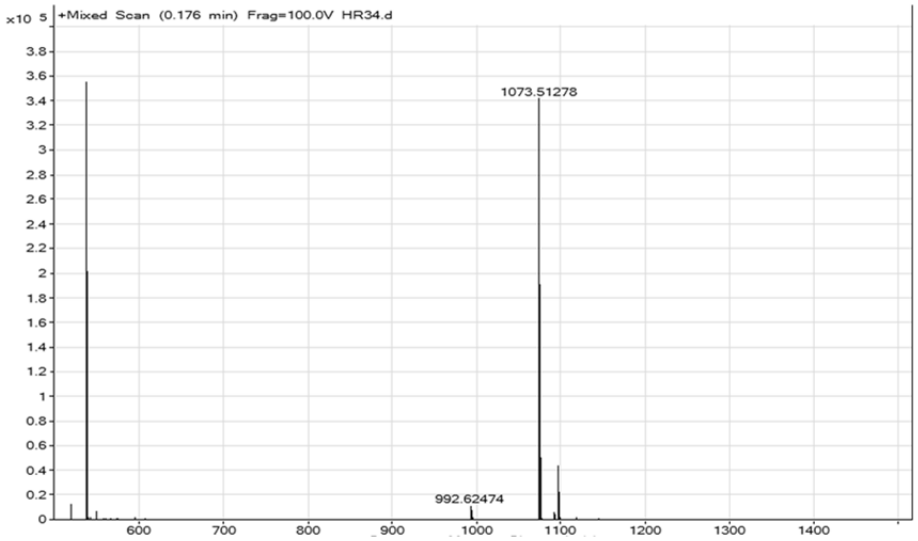


Peptide **146** was prepared using iterative Fmoc-SPPS (50 μmol scale) and purified by reverse-phase HPLC (gradient: 15% B for 5 min, 15% to 45% B over 25 min) to afford the target compound as a white solid following lyophilization (3 x TFA salt). **Note**: for clarity, TFA salts have been omitted from the condensed structure.



Analytical HPLC (0 to 100% B over 25 min, λ = 230 nm, R_t = 10.3 min) of purified peptide **146**.

Peptide **146**: HRMS



HRMS (ESI-TOF): calc'd for $C_{50}H_{69}N_{14}O_{13}$ $[M+H]^+$ 1073.5163, found 1073.5128 $[M+H]^+$, 537.2605 $[M+2H]^{2+}$

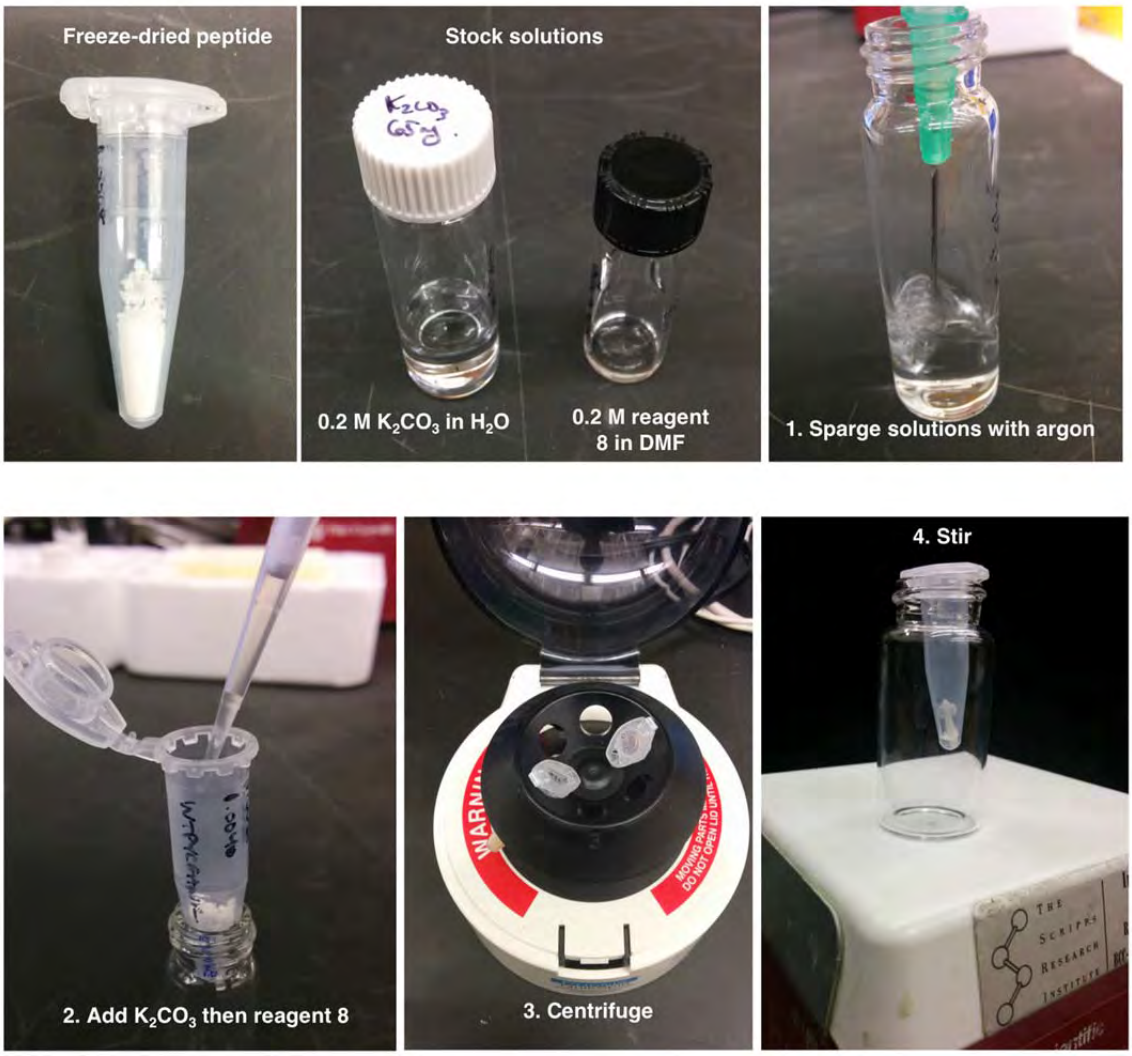


Fig. S56. General protocol for the reaction of cysteine-containing peptides with bicyclobutane sulfone reagents **8**.

Note: Stock solutions of K_2CO_3 may also be prepared in aqueous denaturing buffer (6 M guanidine hydrochloride/0.2 M phosphate, pH = 7.0).

General procedure:

To a solution of thiol-containing peptide (1.0 equiv.) in degassed 0.2 M K_2CO_3 (2.6 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8** in DMF (1.3 equiv. reagent **8**) to give a final concentration of 0.05 M with respect to the peptide. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC, and the reaction quenched by the addition of water containing 0.1% TFA upon

consumption of the starting peptide. The crude mixture was immediately purified by reverse-phase HPLC and lyophilized to afford the cysteine-labeled peptide as a white solid.

Notes, Troubleshooting, and Limitations for Cysteine Tagging:

1. Solvent and concentration:

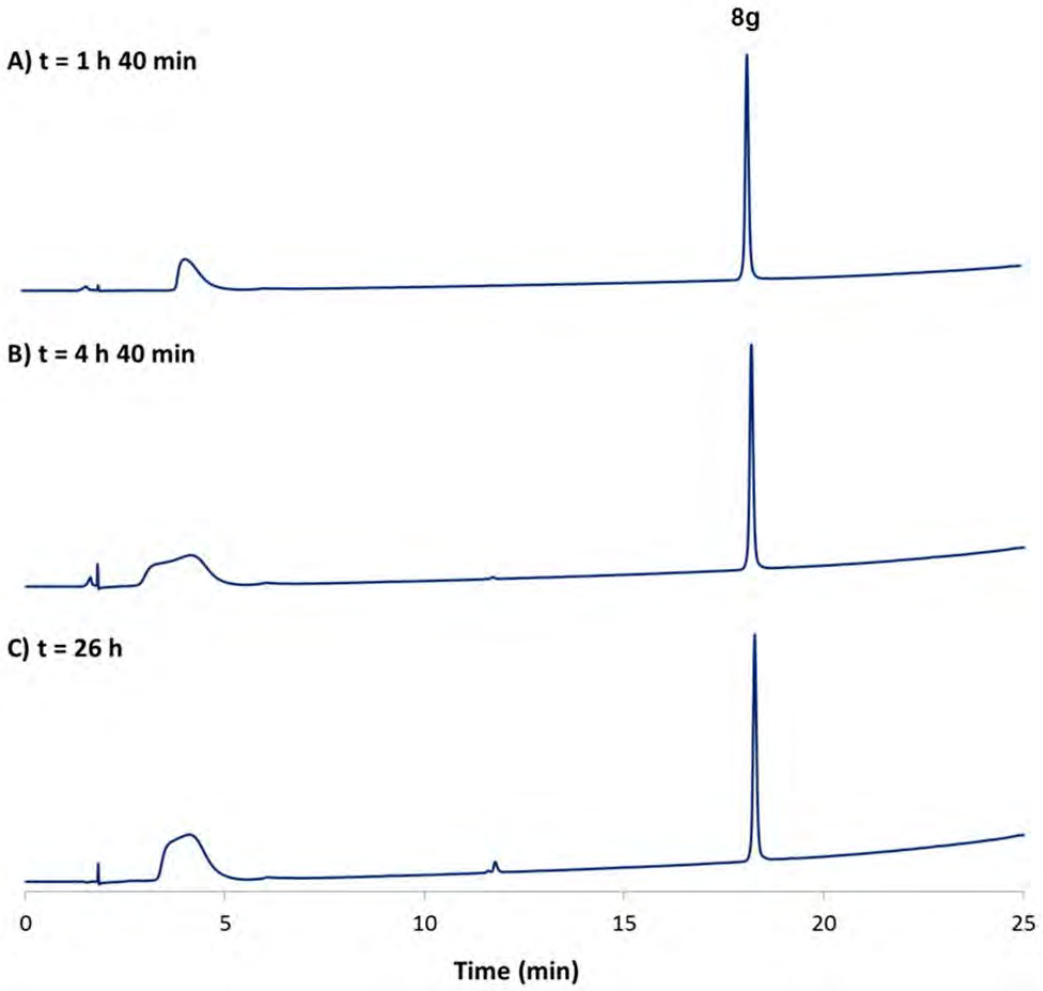
a. Aqueous denaturing buffer (6 M guanidine hydrochloride, 0.2 M phosphate) may be readily employed in place of H_2O as a suitable reaction medium.
b. The reaction may also be performed at higher dilution. Suitable tagging was observed in aqueous denaturing buffer (6 M guanidine hydrochloride, 0.2 M phosphate) at a concentration of 10 mM with respect to the cysteine-containing peptide – see Fig. S58.

2. Addition of base and pH considerations:

a. Varying equivalents of K_2CO_3 were employed based on the relative number of basic side-chains (e.g. lysine, arginine, and histidine, which are protonated in TFA buffer upon HPLC purification) in the starting amino acid or peptide. Reaction of cysteine methyl ester hydrochloride and **8a** in the absence of base did not proceed. The addition of 1.0 equiv. of K_2CO_3 facilitated rapid and efficient tagging. The tagging of glutathione also proceeded efficiently in the presence of 1.0 equiv. of K_2CO_3. In the case of peptide **153** (a tri TFA salt), the addition of 2.6 equiv. of K_2CO_3 facilitated efficient cysteine tagging.
b. The pH of the reaction mixture following addition of an appropriate amount of K_2CO_3 was measured to be between approximately 9-10, allowing for deprotonation of the cysteine thiol (pKa = 8.14). It is anticipated that reactions may be run with similar efficiency in the absence of K_2CO_3 in aqueous buffer maintained at a pH of approximately 8 or above.

3. Degassing:

a. Solvents were degassed prior to use by bubbling argon through the solutions (~3 min of sparging per solution). The exclusion of oxygen is important to keep thiols in reduced form.
b. Alternatively, tris(carboxyethyl)phosphine (TCEP) may be employed as a water-soluble reductant. Sulfone reagent **8g** (1.0 equiv.) is stable to the presence of TCEP (2.0 equiv.) in 2:1 (v/v) 0.2 M aqueous K_2CO_3/DMF:



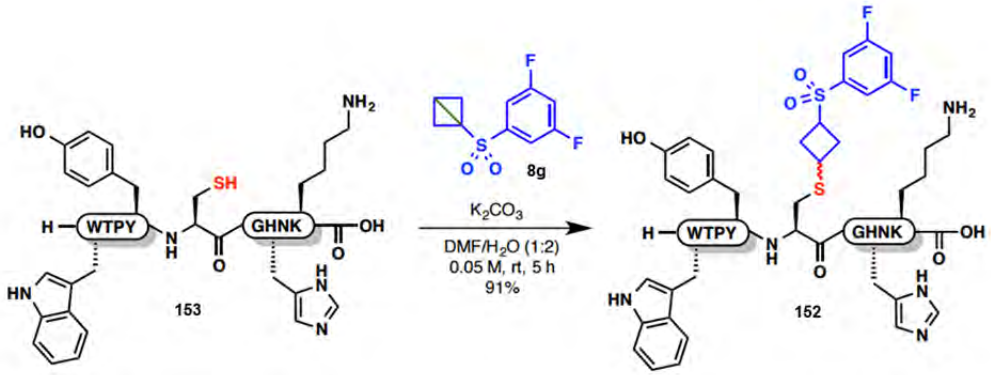
Stability of reagent **8g** to TCEP: Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of **8g** after treatment with TCEP. A) t = 1 h 40 min; B) t = 4h 40 min; C) t = 26 h.

4. Limitations:

a. Designer sulfone reagents **8a-8g** are not water-soluble. The reaction must therefore be performed with a suitable organic cosolvent (e.g. DMF) to solubilize the strain release reagent. THF may also be employed as an organic cosolvent, although rates of cysteine tagging in the presence of THF were observed to be substantially slower than with DMF.

b. Thiol reductants (e.g. dithiothreitol, β-mercaptoethanol) should be avoided to prevent competitive tagging of the reductants.

Peptide **152**:



To a solution of peptide **153** (3.25 mg, 2.25 µmol) in degassed 0.2 M K_2CO_3 (29.4 µL, 2.6 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8g** in DMF (14.6 µL, 2.94 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide 1**53**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC, and then quenched at t = 5 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 55% B over 30 min) and lyophilized to afford peptide **152** as a white solid (3 x TFA salt, 3.3 mg, 91% yield).

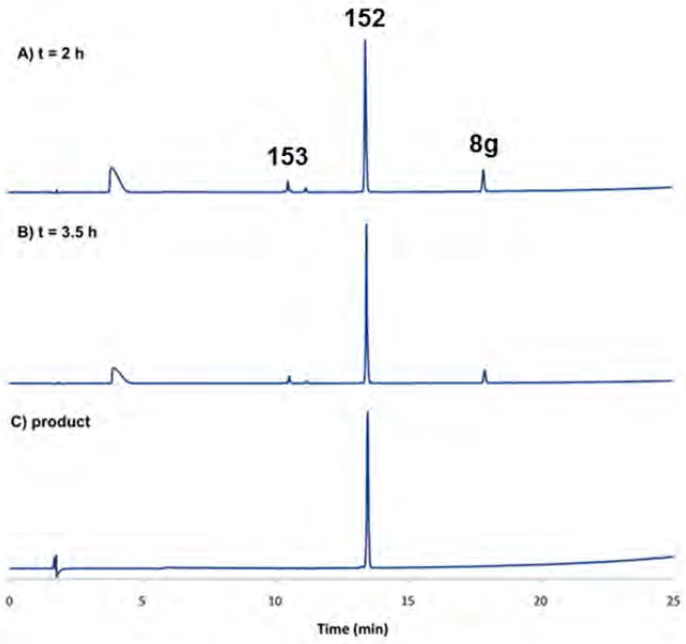
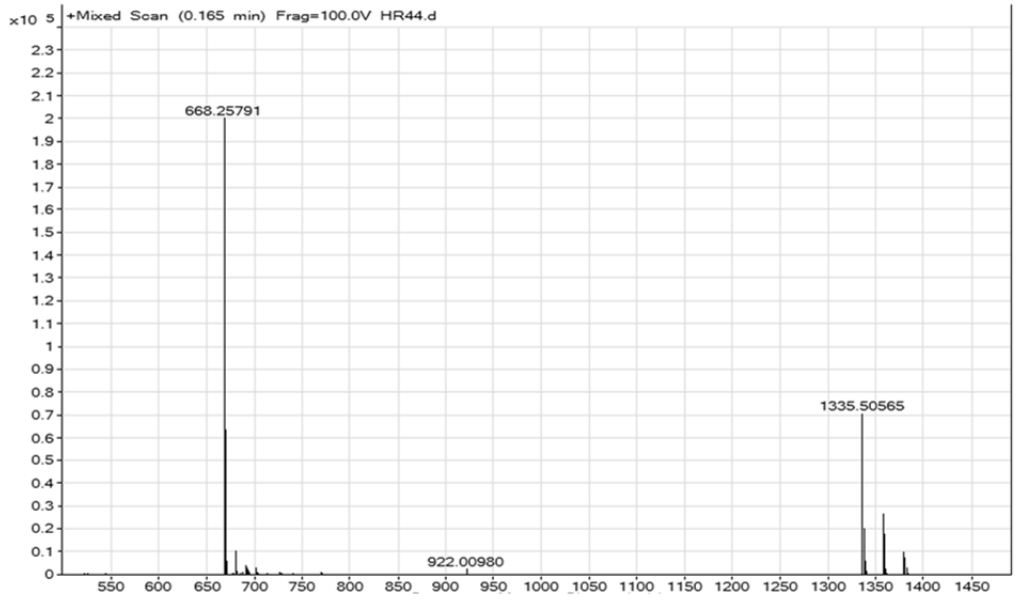


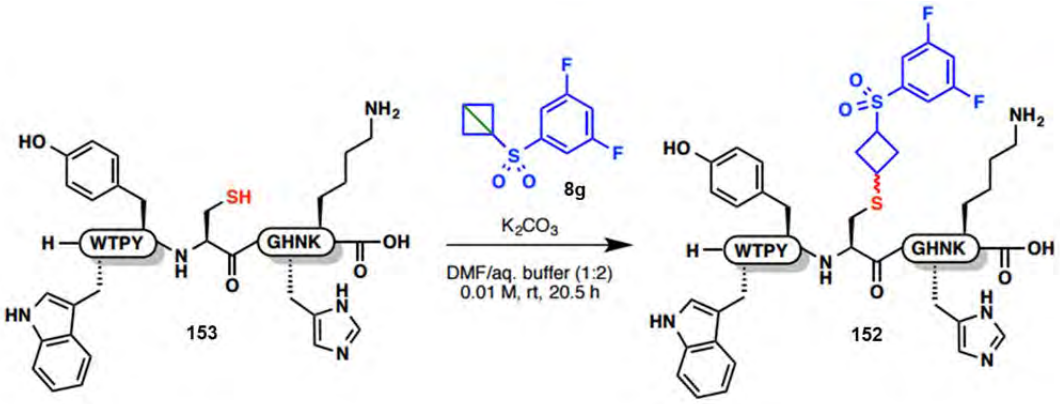
Fig. S57. A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **153** with sulfone **8g** at t = 2 h and B) t = 3.5 h; C) Purified peptide product **152** (R_t = 13.5 min).

Peptide **152**: HRMS



HRMS (ESI-TOF): calc'd for $C_{60}H_{77}F_2N_{14}O_{15}S_2$ $[M+H]^+$ 1335.5097, found 1335.5056 $[M+H]^+$, 668.2579 $[M+2H]^{2+}$

Preparation of **152** in denaturing buffer (0.01 M concentration):



The reaction of peptide **153** and reagent **8g** could also be performed in aqueous denaturing buffer. Peptide **153** (2.1 mg, 1.45 µmol) was dissolved in a degassed solution of 0.039 M K_2CO_3 prepared in aqueous 6 M guanidine hydrochloride/0.2 M Na_2HPO_4 (97 µL, 2.6 equiv. K_2CO_3). A 0.039 M solution of sulfone **8g** in DMF (48 µL, 1.89 µmol, 1.3 equiv.) was added to the peptide to give a final concentration of 0.01 M with respect to peptide **153**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

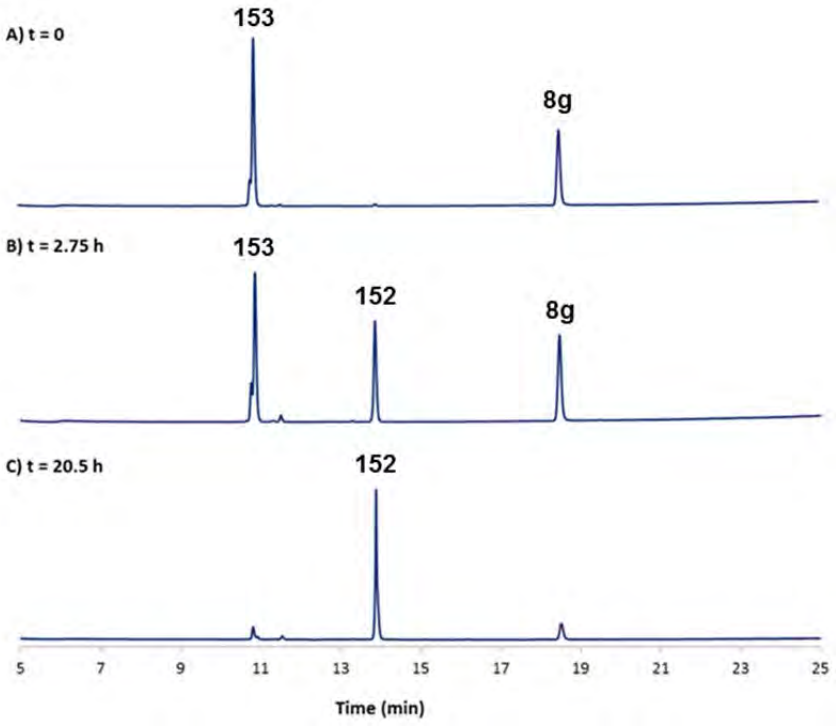
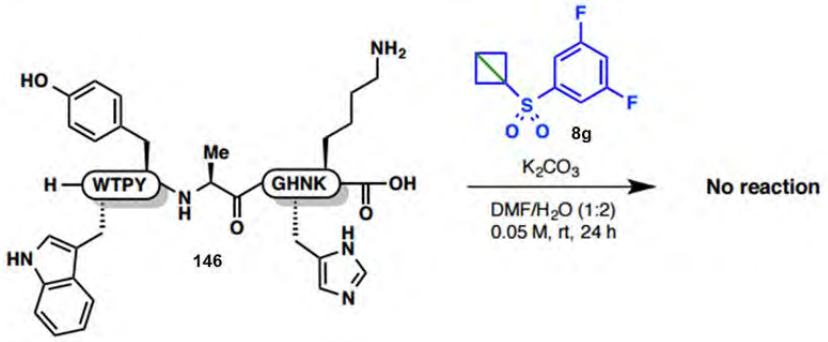


Fig. S58. A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **153** with sulfone **8g** at t = 0 h, B) t = 2.75 h, and C) t = 20.5 h.

Peptide Control Studies:



To a solution of peptide **146** (3.59 mg, 2.54 μmol) in degassed 0.2 M K_2CO_3 (33.3 μL, 2.6 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8g** in DMF (16.7 μL, 3.35 μmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide **146**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

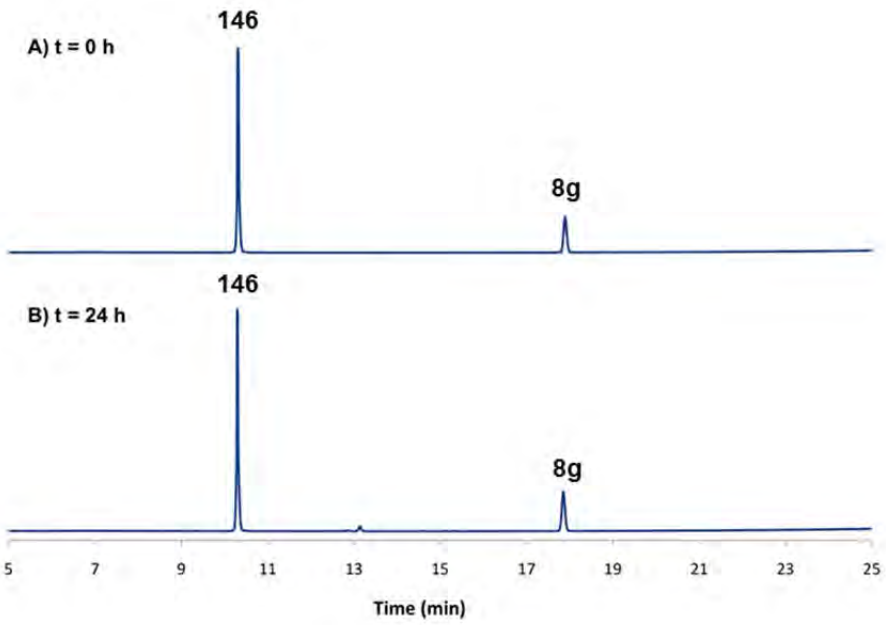
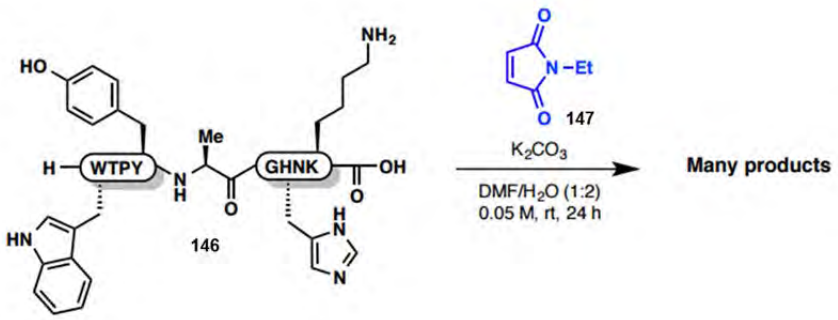


Fig. S59. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **146** with sulfone **8g** at A) t = 0 h and B) t = 24 h.



To a solution of peptide **146** (1.98 mg, 1.40 μmol) in degassed 0.2 M K_2CO_3 (18.4 μL, 2.6 equiv. K_2CO_3) was added a 0.2 M solution of *N*-ethylmaleimide **147** in DMF (9.2 μL, 1.84 μmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide **146**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

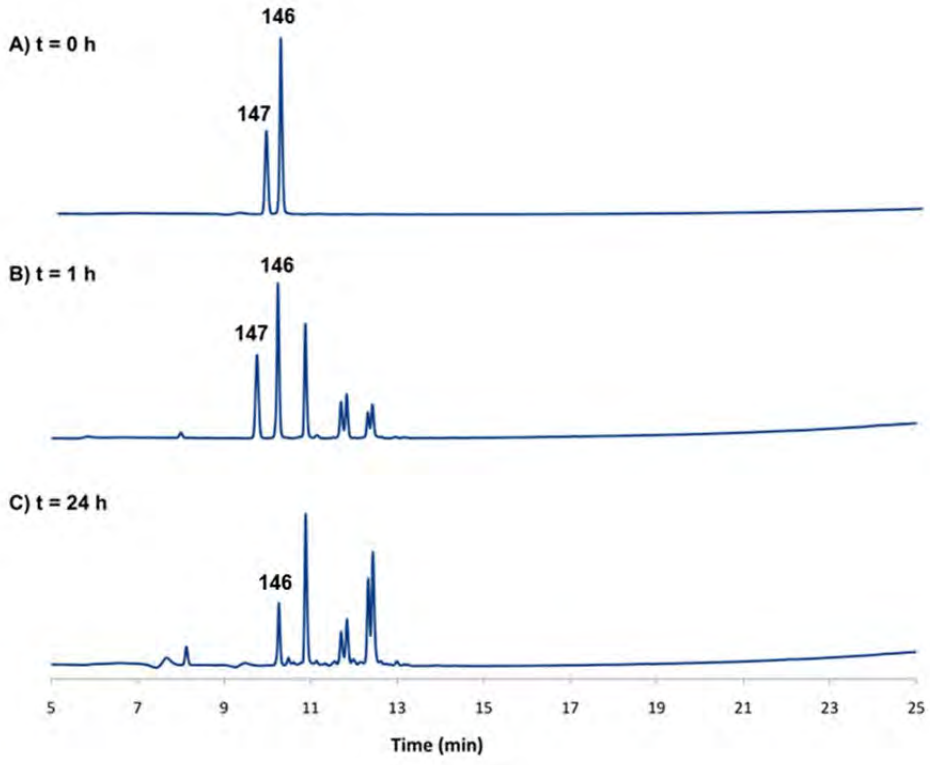
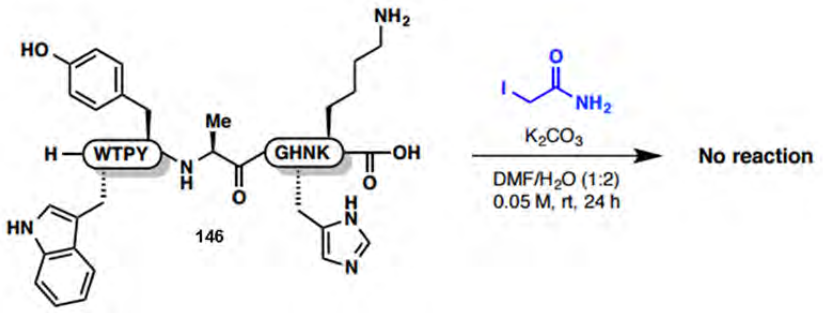


Fig. S60. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **146** with *N*-ethylmaleimide **147** at A) t = 0 h, B) t = 1 h, and C) t = 24 h.



To a solution of peptide **146** (3.27 mg, 2.31 μmol) in degassed 0.2 M K_2CO_3 (30.0 μL, 2.6 equiv. K_2CO_3) was added a 0.2 M solution of iodoacetamide in DMF (15.0 μL, 3.04 μmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide **146**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

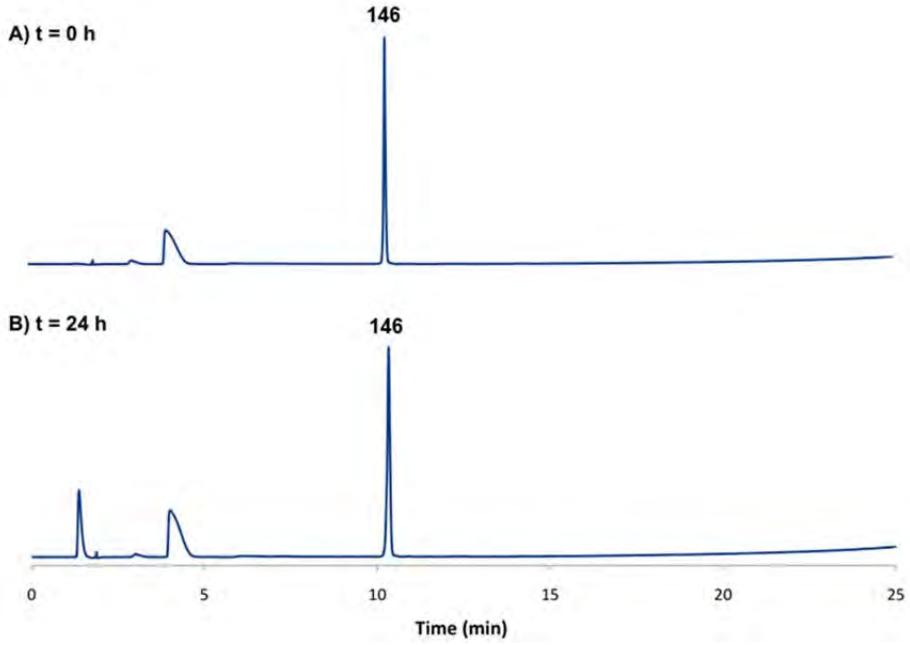
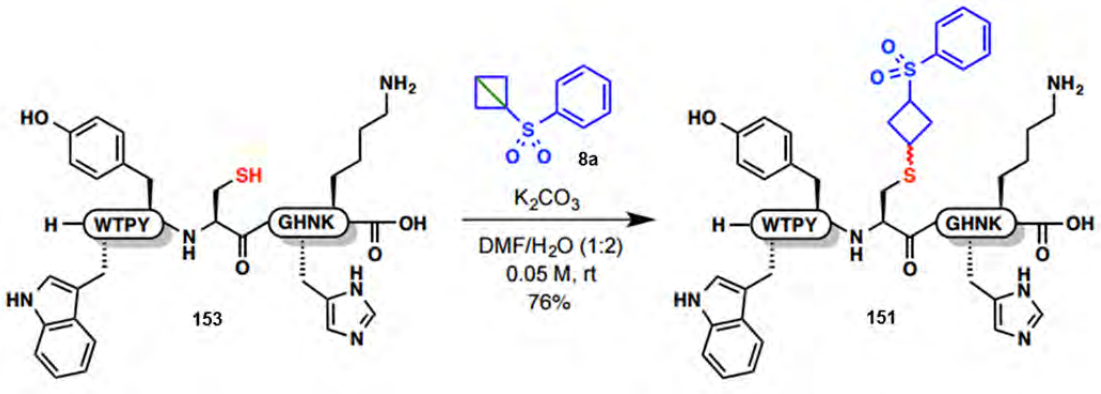


Fig. S61. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **146** with iodoacetamide at A) t = 0 h and B) t = 24 h.

Peptide **151**:



To a solution of peptide **153** (4.29 mg, 2.96 µmol) in degassed 0.2 M K_2CO_3 (39.0 µL, 2.6 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8a** in DMF (19.0 µL, 3.88 µmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide **153**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC, and then quenched at t = 24 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 50% B over 30 min) and lyophilized to afford peptide **151** as a white solid (3 x TFA salt, 3.7 mg, 76% yield).

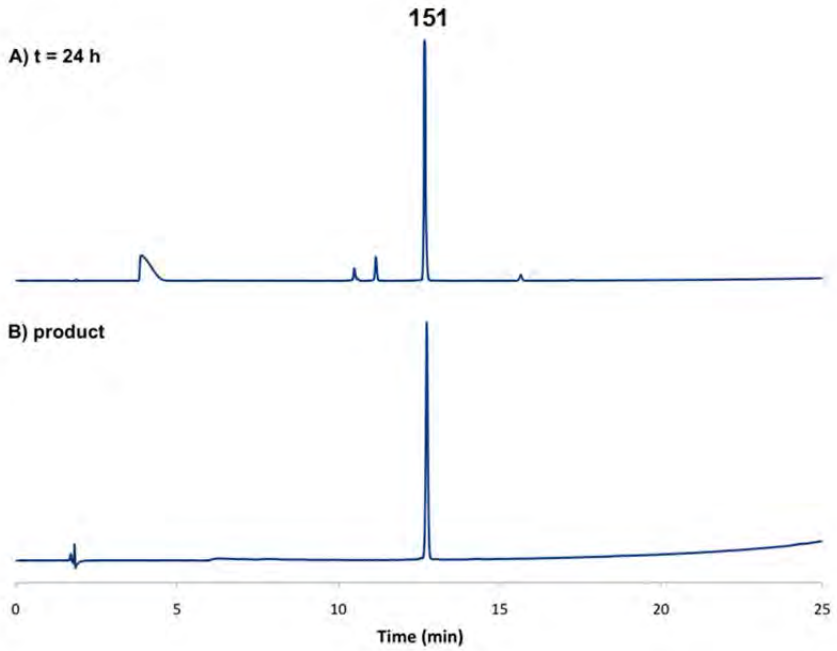
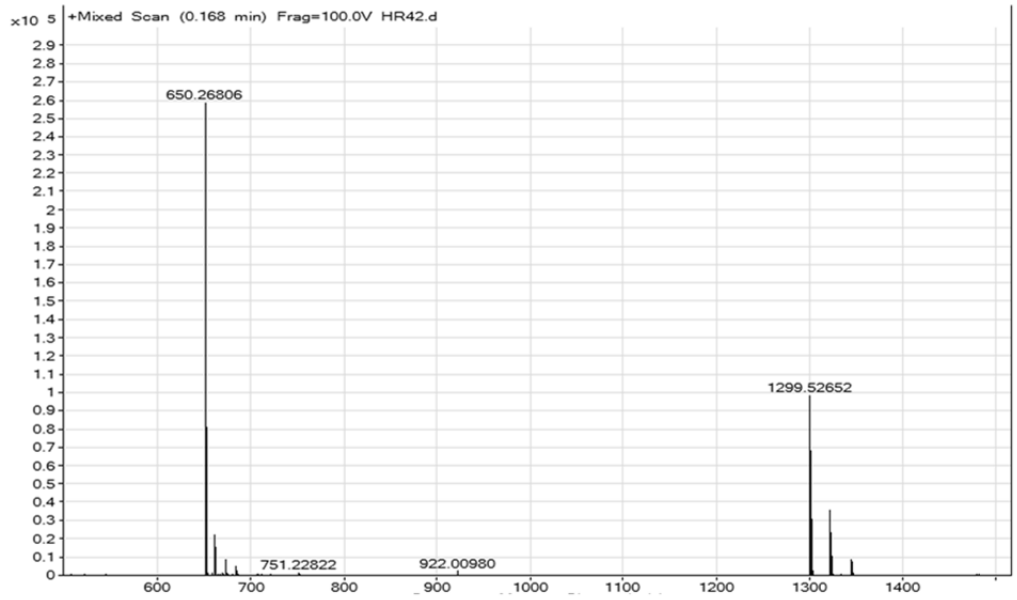
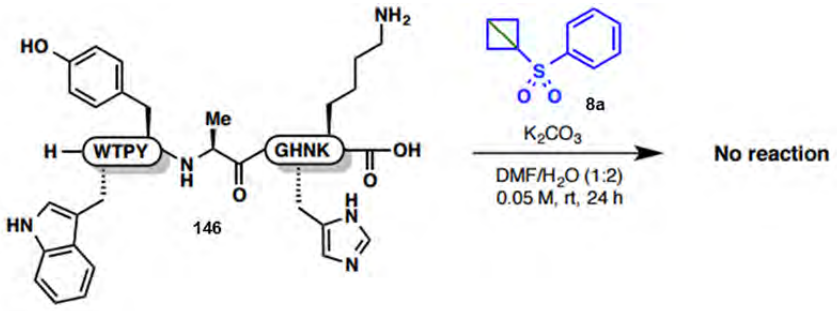


Fig. S62. A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **153** with sulfone **8a** at t = 24 h; and B) purified peptide product **151** (R_t = 12.7 min)

Peptide **151**: HRMS



HRMS (ESI-TOF): calc'd for $C_{60}H_{79}N_{14}O_{15}S_2$ $[M+H]^+$ 1299.5285, found 1299.5265 $[M+H]^+$, 650.2681 $[M+2H]^{2+}$



To a solution of peptide **146** (3.47 mg, 2.45 μmol) in degassed 0.2 M K_2CO_3 (32.0 μL, 2.6 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8a** in DMF (16.0 μL, 3.23 μmol, 1.3 equiv.) to give a final concentration of 0.051 M with respect to peptide **146**. The reaction vial was flushed with Ar(g) and stirred at rt. The progress of the reaction was monitored by analytical HPLC.

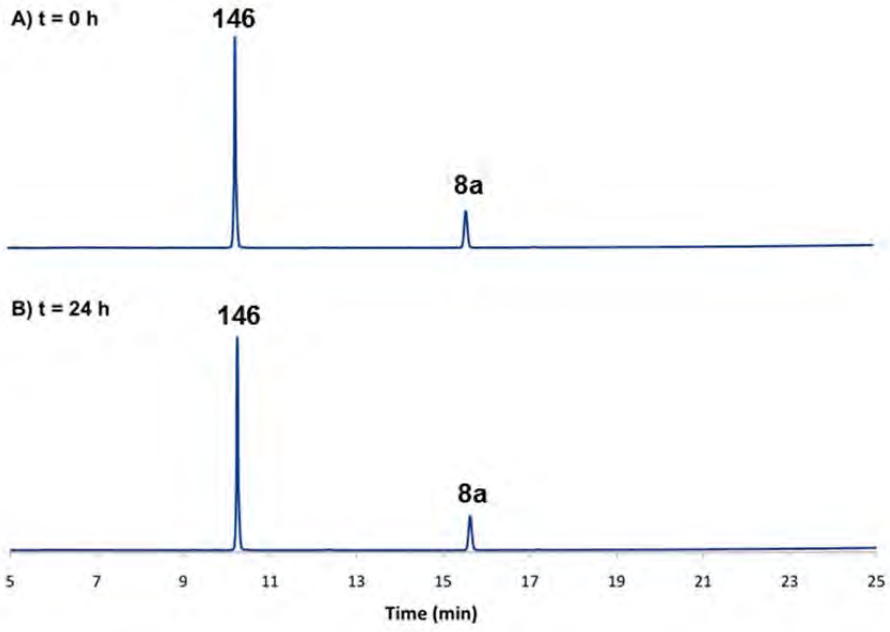


Fig. S63. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of peptide **146** with sulfone **8a** at A) t = 0 h and B) t = 24 h.

Reaction Kinetics:

The rates of reaction between peptide **153** and bicyclobutane arylsulfones (reagent **8**) were evaluated by peak integration of analytical HPLC chromatograms (0 to 100% B over 25 min, λ = 280 nm). Reactions were performed under the conditions previously described. Aliquots (0.8 μL) were removed at various time points and quenched by dilution with water containing 0.1% TFA (360 μL) and immediately frozen. Prior to analysis, the samples were thawed and treated with a 10 mg/mL solution of TCEP in water containing 0.1% TFA (120 μL) to reduce any peptide disulfides. Chromatograms were integrated at λ = 280 nm (corresponding to the λ_{max} of the phenolic tyrosine side-chain). At this wavelength, bicyclobutane arylsulfones **8** exhibited minimal absorbance (<10%) relative to the peptide starting material. The peak area of the bicyclobutane labeled product relative to the unfunctionalized peptide starting material was used to approximate relative percent conversion at each time point.

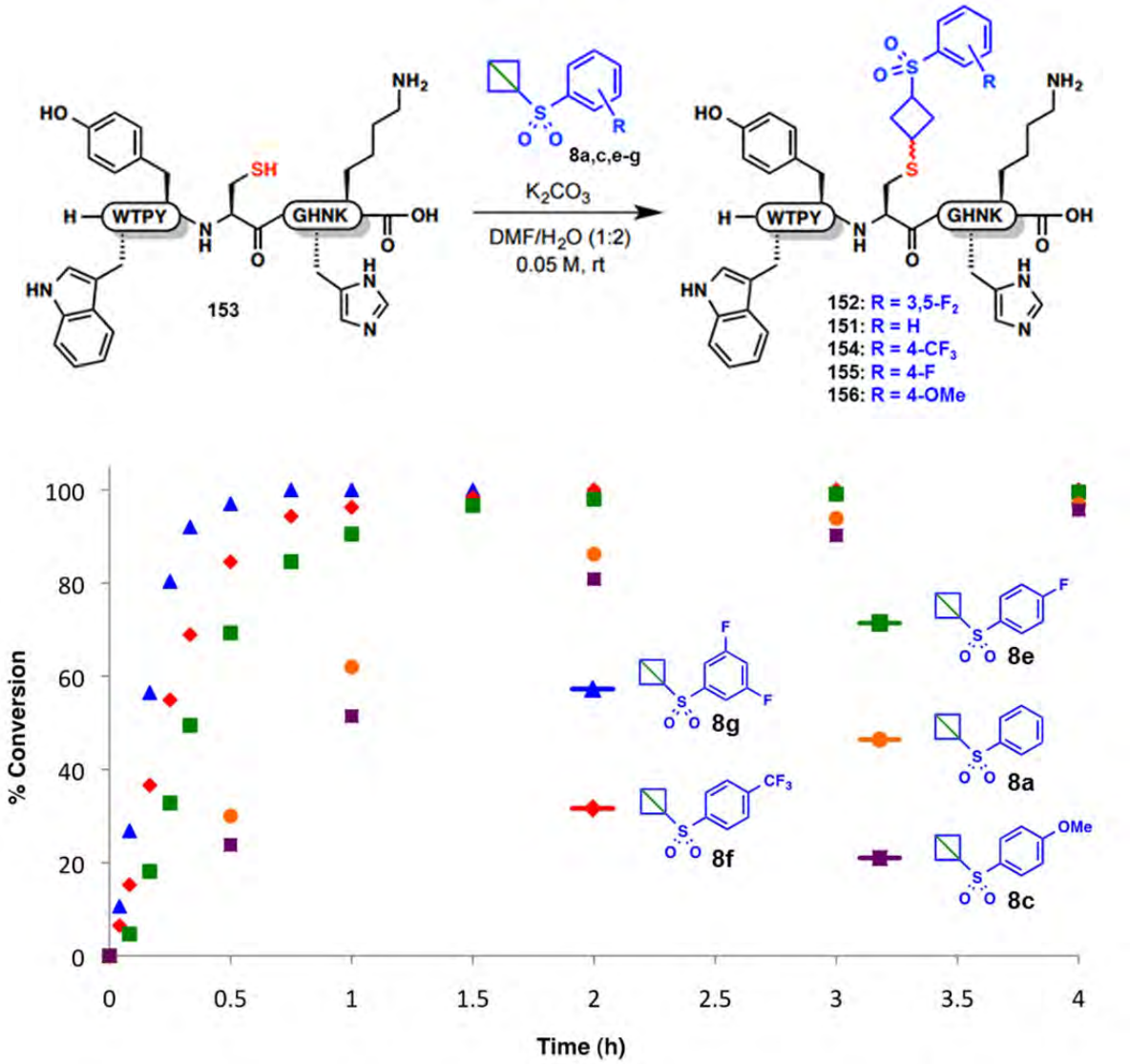


Fig. S64. Kinetic plot depicting the relative rate of reaction between peptide **153** and sulfone reagents **8a**, **8c**, and **8e-g**.

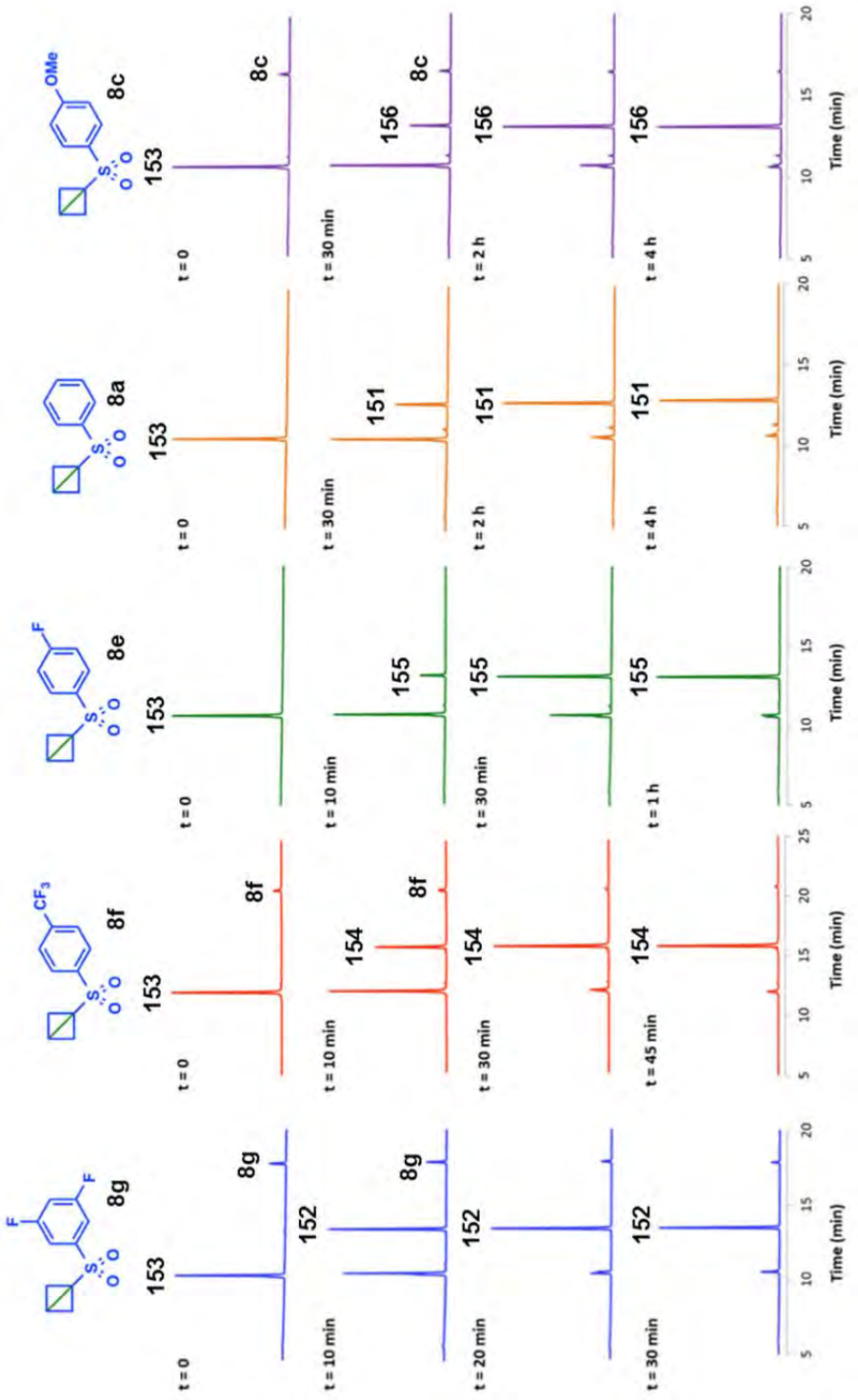
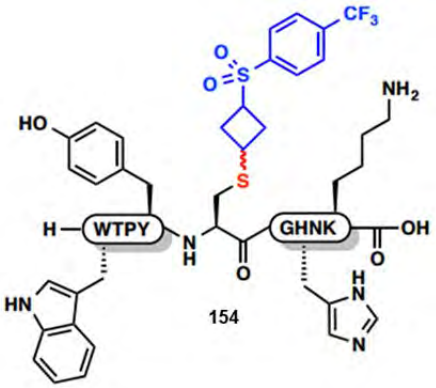
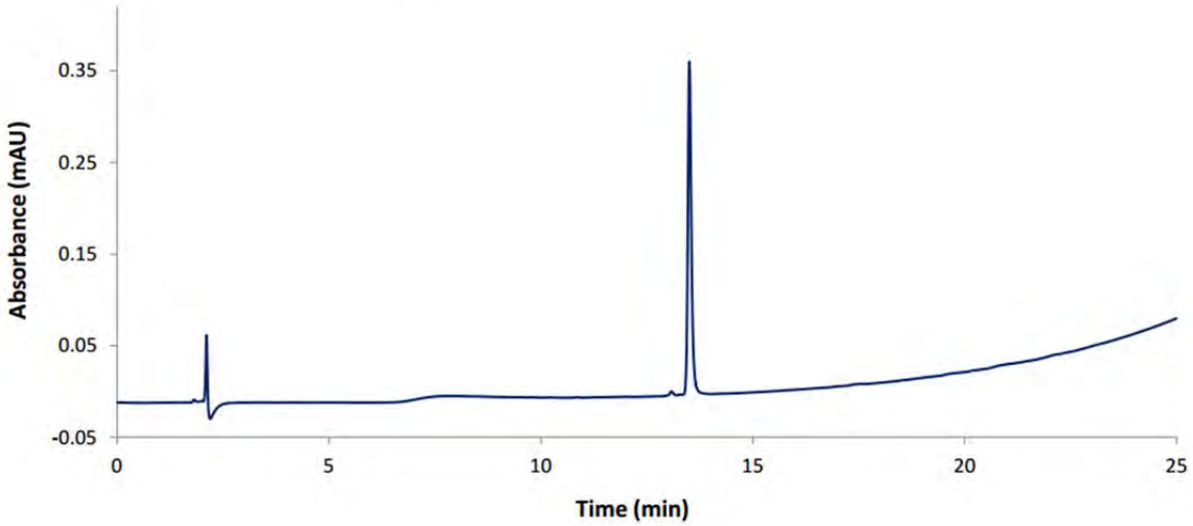


Fig. S65. Crude analytical HPLC traces (0 to 100% B over 25 min, λ = 280 nm) depicting the reaction of peptide **153** with sulfone reagents **8a, 8c**, and **8e-g** at various time points.

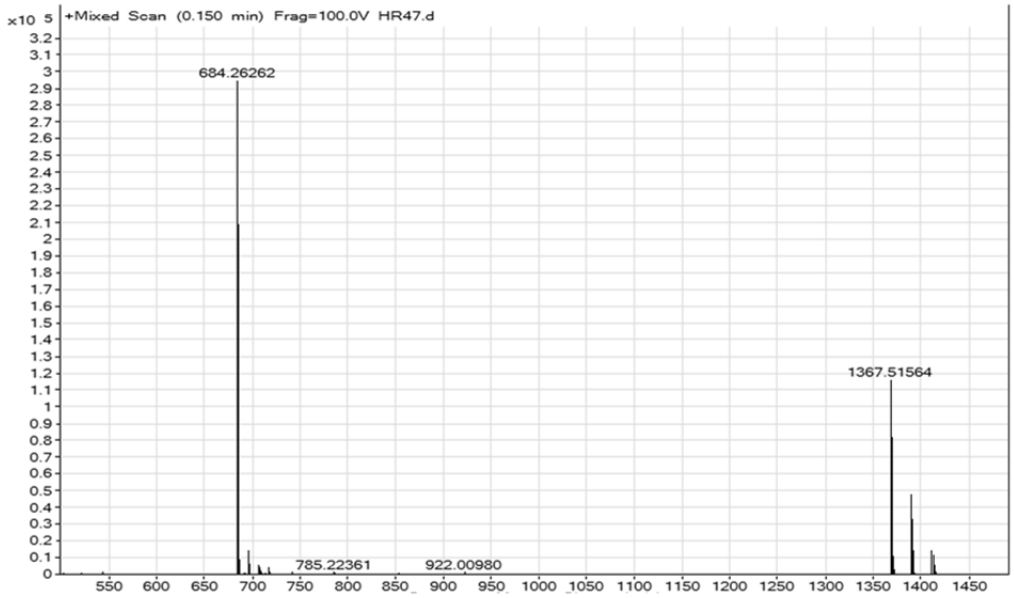
Peptide **154**:





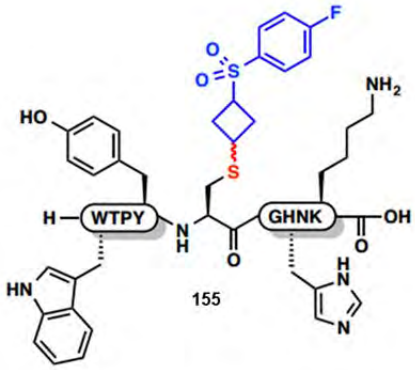
Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm, R_t = 13.5 min) of peptide **154**.

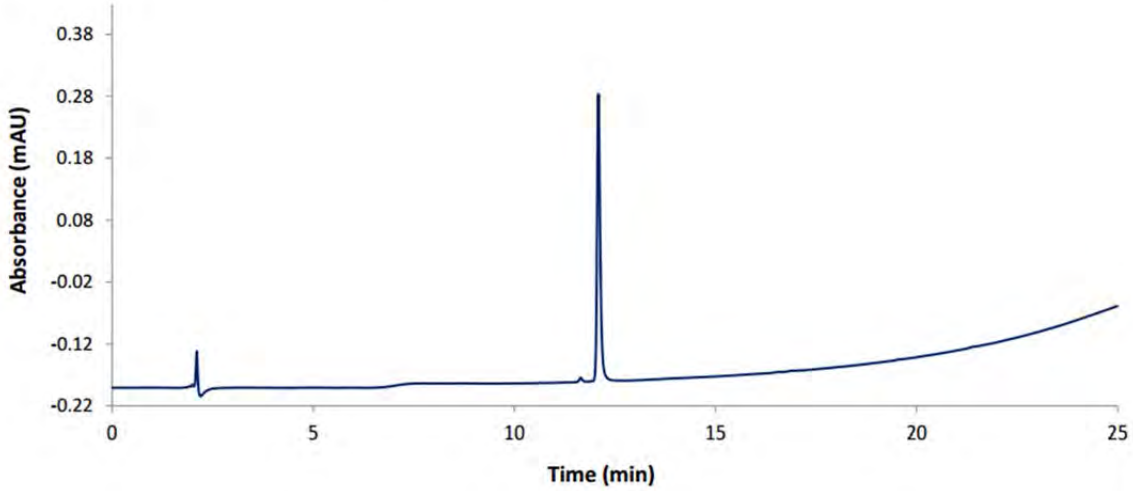
Peptide **154**: HRMS



HRMS (ESI-TOF): calc'd for $C_{61}H_{78}F_3N_{14}O_{15}S_2$ $[M+H]^+$ 1367.5159, found 1367.5156 $[M+H^+]$, 684.2626 $[M+2H]^{2+}$

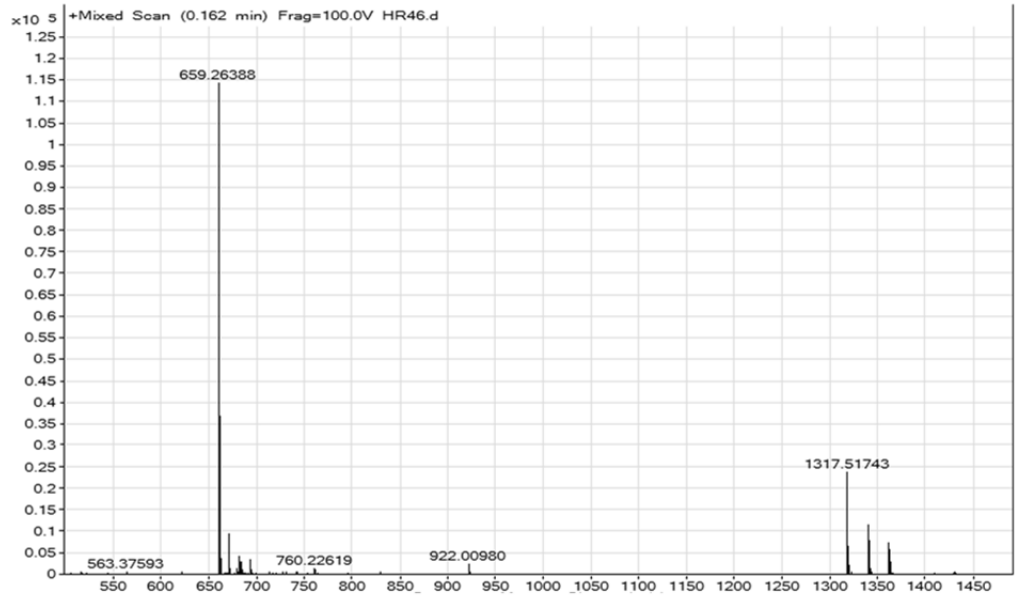
Peptide **155**:





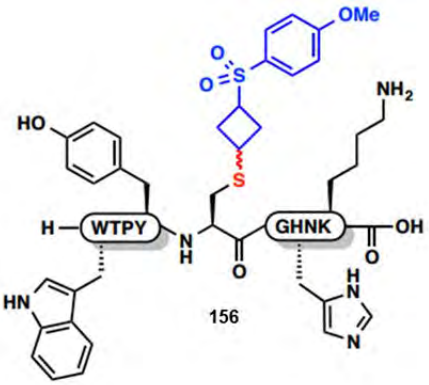
Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm, R_t = 12.1 min) of peptide **155**.

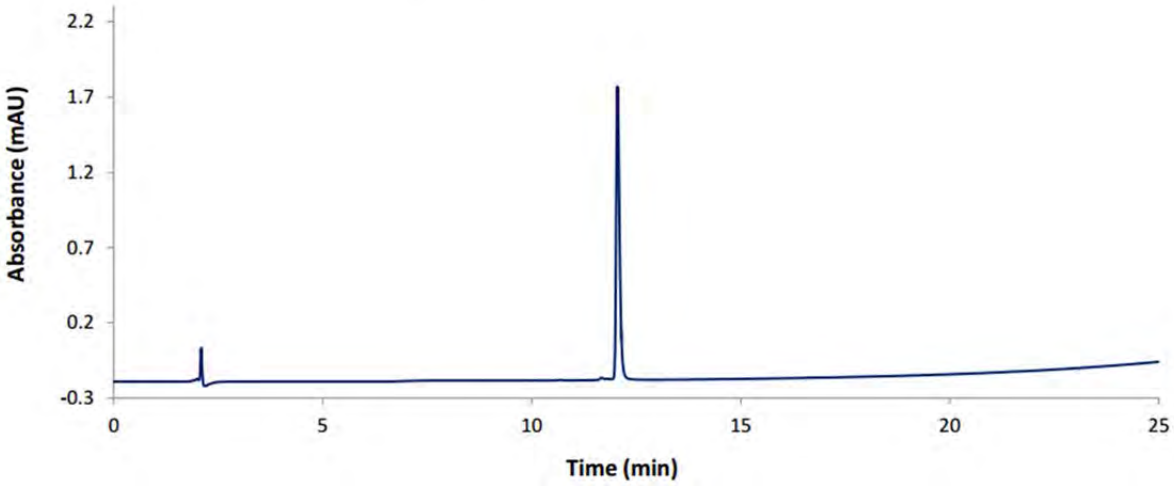
Peptide **155**: HRMS



HRMS (ESI-TOF): calc'd for $C_{60}H_{78}FN_{14}O_{15}S_2$ $[M+H]^+$ 1317.5191, found 1317.5174 $[M+H]^+$, 659.2639 $[M+2H]^{2+}$

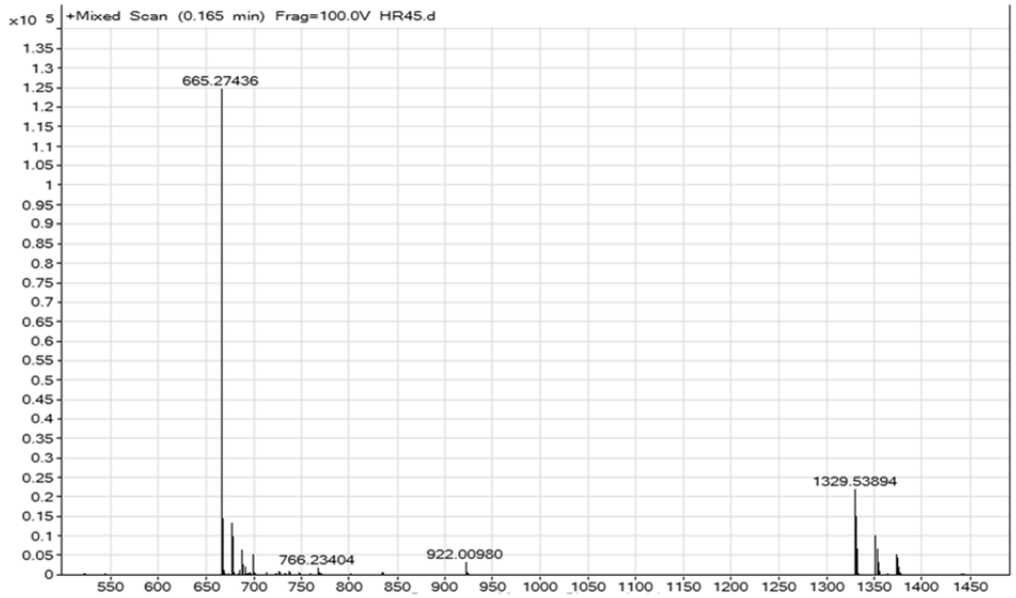
Peptide **156**:





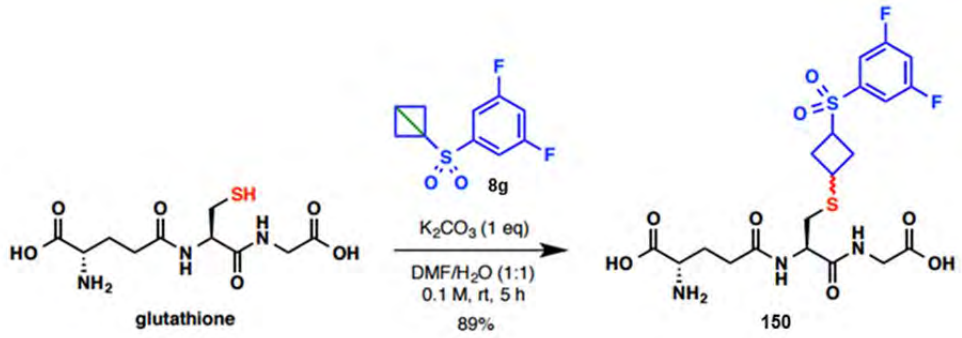
Analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm, R_t = 12.1 min) of peptide **156**.

Peptide **156**: HRMS



HRMS (ESI-TOF): calc'd for $C_{61}H_{81}N_{14}O_{16}S_2$ $[M+H]^+$ 1329.5391, found 1329.5389 $[M+H]^+$, 665.2744 $[M+2H]^{2+}$

Compound **150**:



To a solution of glutathione (10.0 mg, 32.5 μmol) in degassed 0.2 M K_2CO_3 (162 μL, 1.0 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8g** in DMF (162 μL, 1.0 equiv.) to give a final concentration of 0.1 M with respect to glutathione. The reaction vial was flushed with Ar(g) and stirred at rt. The reaction was monitored by analytical HPLC, and then quenched at t = 5 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 60% B over 30 min) and lyophilized to afford **150** as a white solid (1 x TFA salt, 18.5 mg, 89% yield).

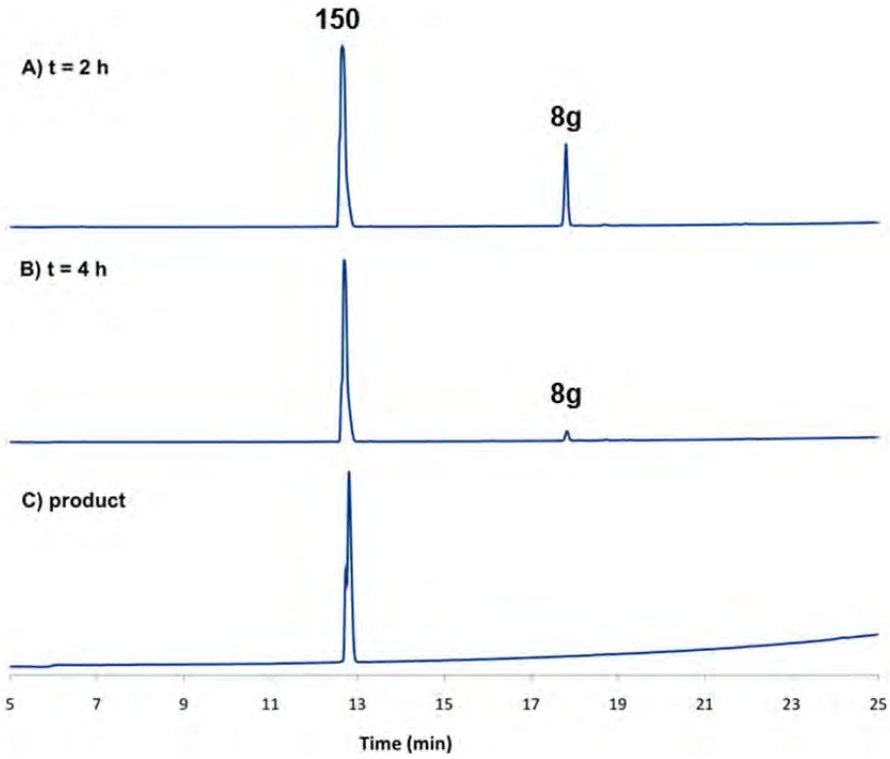
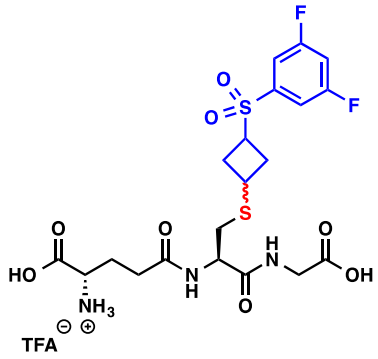


Fig. S66. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of glutathione with sulfone **8g** at A) t = 2 h and B) t = 4 h; C) purified product **150**.

150 (TFA salt):



3.7:1 dr;

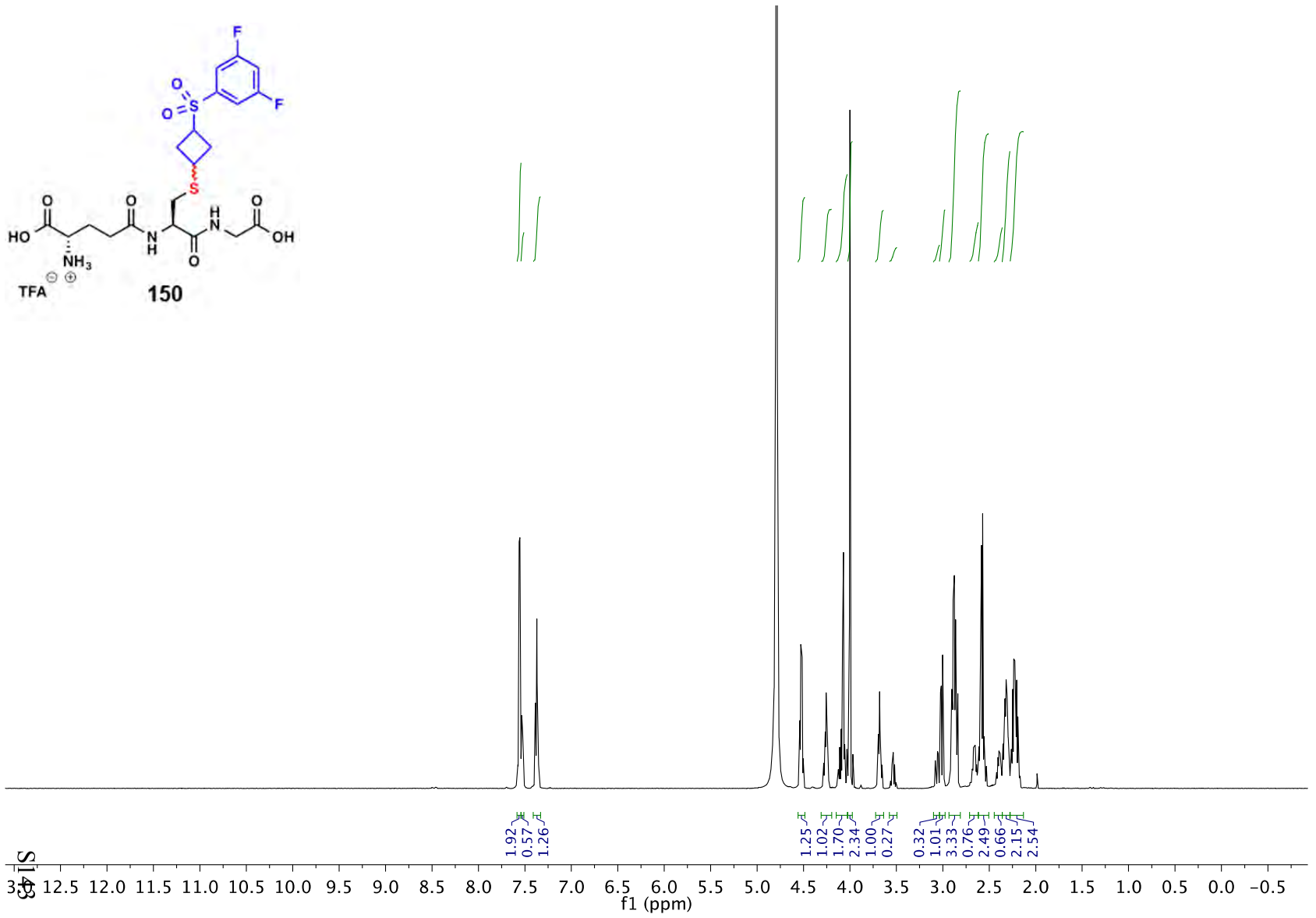
Physical state: fluffy white solid (following lyophilization);

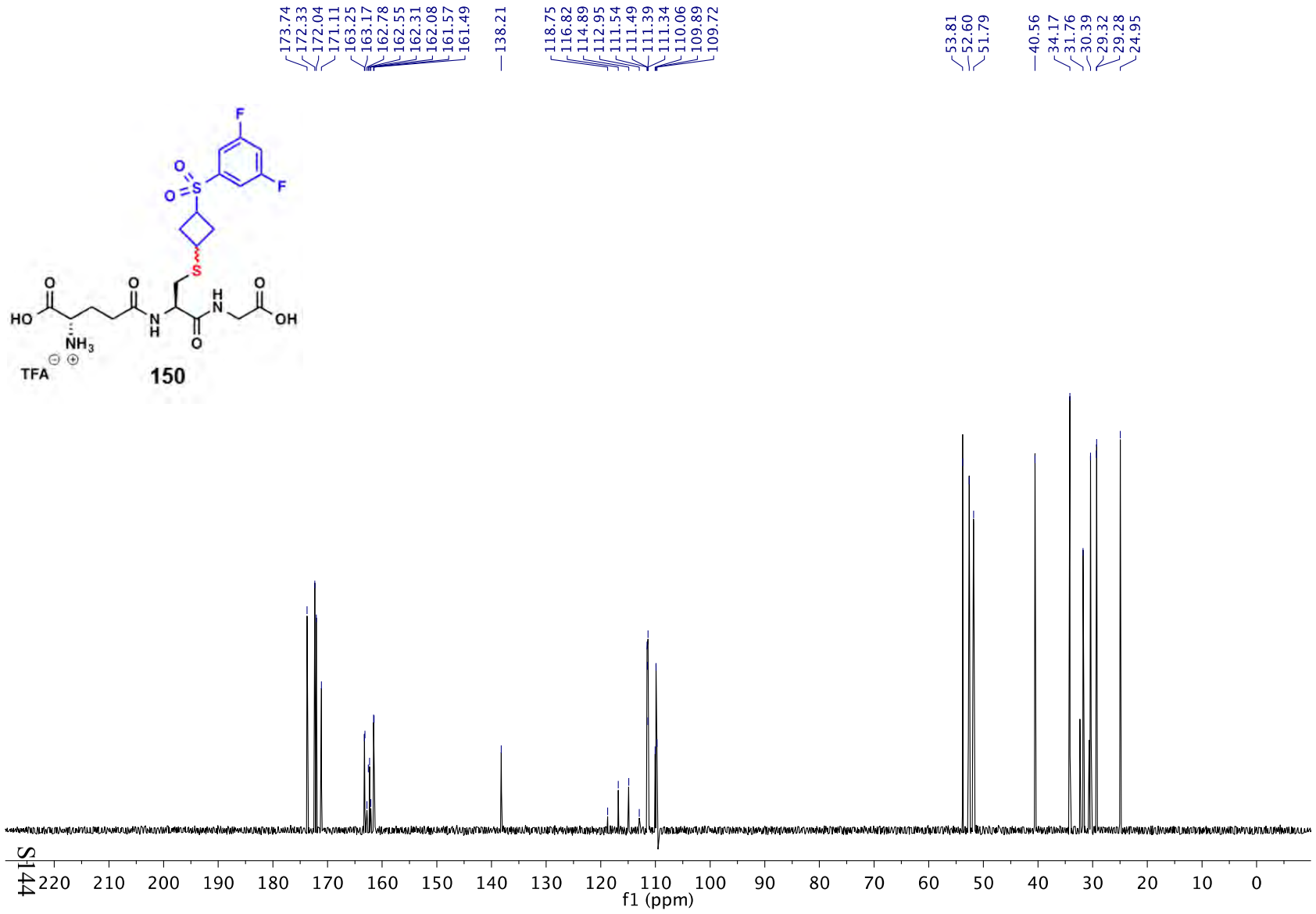
^{1}H NMR (600 MHz, D_2O) *major diastereomer*: δ 7.58 – 7.54 (m, 2H), 7.37 (tt, $^{3}J_{H\text{-}F}$ = 8.8, $^{4}J_{H\text{-}H}$ = 2.3 Hz, 1H), 4.58 – 4.47 (m, 1H), 4.26 (m, 1H), 4.07 (t, *J* = 6.6 Hz, 1H), 4.00 (d, *J* = 1.9 Hz, 2H), 3.73 – 3.63 (m, 1H), 3.01 (dd, *J* = 14.1, 5.3 Hz, 1H), 2.93 – 2.81 (m, 3H), 2.58 (m, *J* = 8.2 Hz, 2H), 2.32 (m, 2H), 2.23 (m, 2H) ppm;

minor diastereomer: δ 7.55 – 7.51 (m, 2H), 7.37 (tt, $^{3}J_{H\text{-}F}$ = 8.8, $^{4}J_{H\text{-}H}$ = 2.3 Hz, 1H), 4.58 – 4.47 (m, 1H), 4.15 – 4.08 (m, 2H), 4.00 (d, *J* = 1.9 Hz, 2H), 3.58 – 3.49 (m, 1H), 3.06 (dd, *J* = 14.1, 5.3 Hz, 1H), 2.92 – 2.80 (m, 1H), 2.71 – 2.63 (m, 2H), 2.62 – 2.52 (m, 2H), 2.44 – 2.36 (m, 2H), 2.27 – 2.15 (m, 2H) ppm;

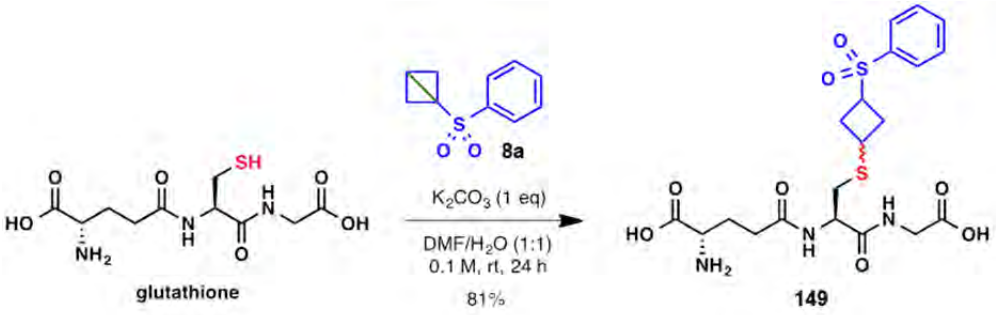
^{13}C NMR (151 MHz, D_2O) *major diastereomer*: δ 173.7, 172.3, 172.0, 171.1, 162.4 (dd, $^{1}J_{C\text{-}F}$ = 253.7 Hz, $^{3}J_{F\text{-}C}$ = 12.0 Hz, 2C), 162.4 (q, $^{2}J_{C\text{-}F}$ = 35.4 Hz), 138.2 (t, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 115.8 (q, $^{1}J_{C\text{-}F}$ = 291.4 Hz), 111.4 (dd, $^{2}J_{C\text{-}F}$ = 22.0 Hz, $^{4}J_{C\text{-}F}$ = 7.4 Hz, 2C), 109.9 (t, *J* = 25.6 Hz), 53.8, 52.6, 51.8, 40.6, 34.2, 31.8, 30.4, 29.3, 29.3, 24.9 ppm;

HRMS (ESI-TOF): calc'd for $C_{20}H_{26}F_2N_3O_8S_2$ $[M+H]^+$ 538.1124, found 538.1120.


F
F
O
O
S
S
HO
O
O
N
H
H
N
O
OH
NH3
TFA
150
1.92
0.57
1.26
1.25
1.02
1.70
2.34
1.00
0.27
0.32
1.01
3.33
0.76
2.49
0.66
2.15
2.54
f1 (ppm)


173.74
172.33
172.04
171.11
163.25
163.17
162.78
162.55
162.31
162.08
161.57
161.49
138.21
118.75
116.82
114.89
112.95
111.54
111.49
111.39
111.34
110.06
109.89
109.72
53.81
52.60
51.79
40.56
34.17
31.76
30.39
29.32
29.28
24.95
F
F
O
O
S
S
HO
O
O
N
H
H
N
O
O
OH
NH3
TFA
150
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)

Compound **149**:



To a solution of glutathione (10.1 mg, 32.9 μmol) in degassed 0.2 M K_2CO_3 (162 μL, 1.0 equiv. K_2CO_3) was added a 0.2 M solution of sulfone **8a** in DMF (162 μL, 1.0 equiv.) to give a final concentration of 0.1 M with respect to glutathione. The reaction vial was flushed with Ar(g) and stirred at rt. The reaction was monitored by analytical HPLC, and then quenched at t = 24 h by the addition of water containing 0.1% TFA. The crude mixture was immediately purified by reverse-phase HPLC (0% B for 10 min, 0% to 60% B over 40 min) and lyophilized to afford **149** as a white solid (1 x TFA salt, 16.2 mg, 81% yield).

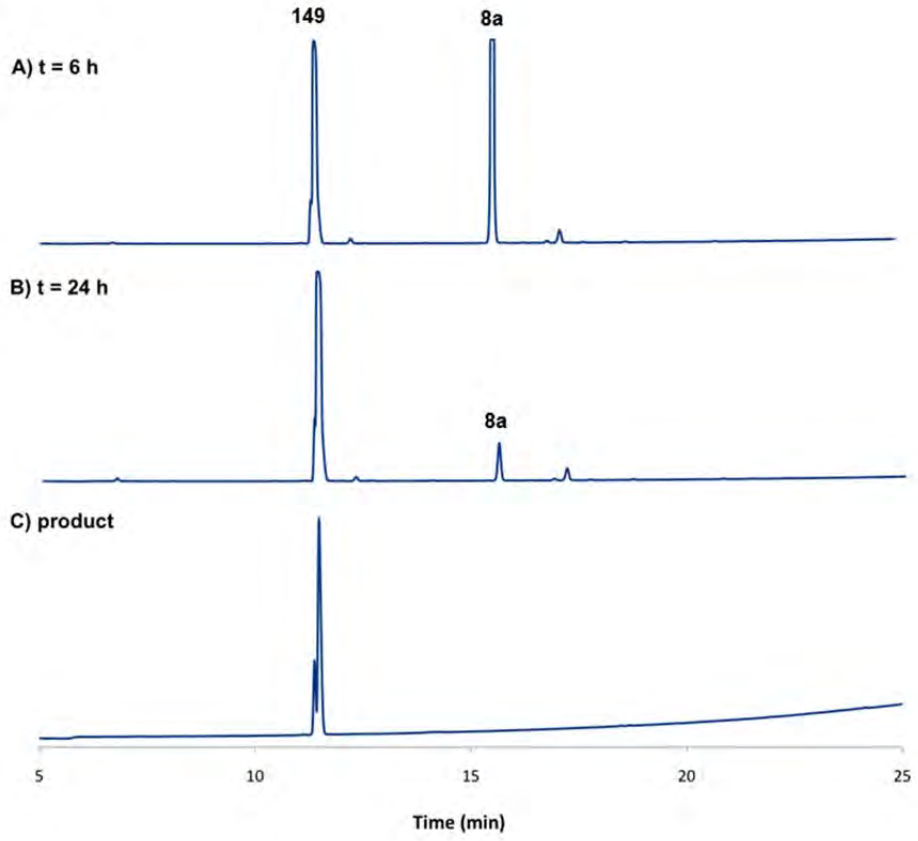
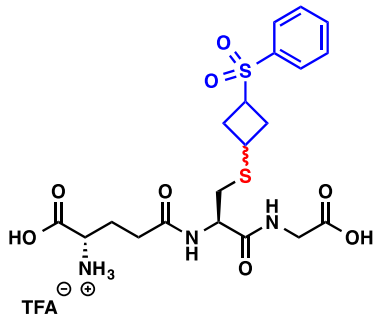


Fig. S67. Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the reaction of glutathione with sulfone **8a** at A) t = 6 h and B) t = 24 h; C) purified peptide product **149**.

149 (TFA salt):



4.8:1 dr;

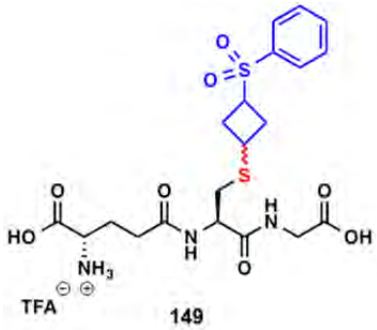
Physical state: fluffy white solid (following lyophilization);

^{1}**H NMR** (600 MHz, D_2O) *major diastereomer*: δ 7.93 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.87 – 7.77 (m, 1H), 7.75 – 7.65 (m, 2H), 4.63 – 4.45 (m, 1H), 4.35 – 4.15 (m, 1H), 4.16 – 4.02 (m, 1H), 4.02 (s, 2H), 3.74 – 3.59 (m, 1H), 3.02 (dd, *J* = 14.2, 5.4 Hz, 1H), 2.93 – 2.80 (m, 3H), 2.66 – 2.53 (m, 2H), 2.35 – 2.27 (m, 2H), 2.27 – 2.15 (m, 2H) ppm;

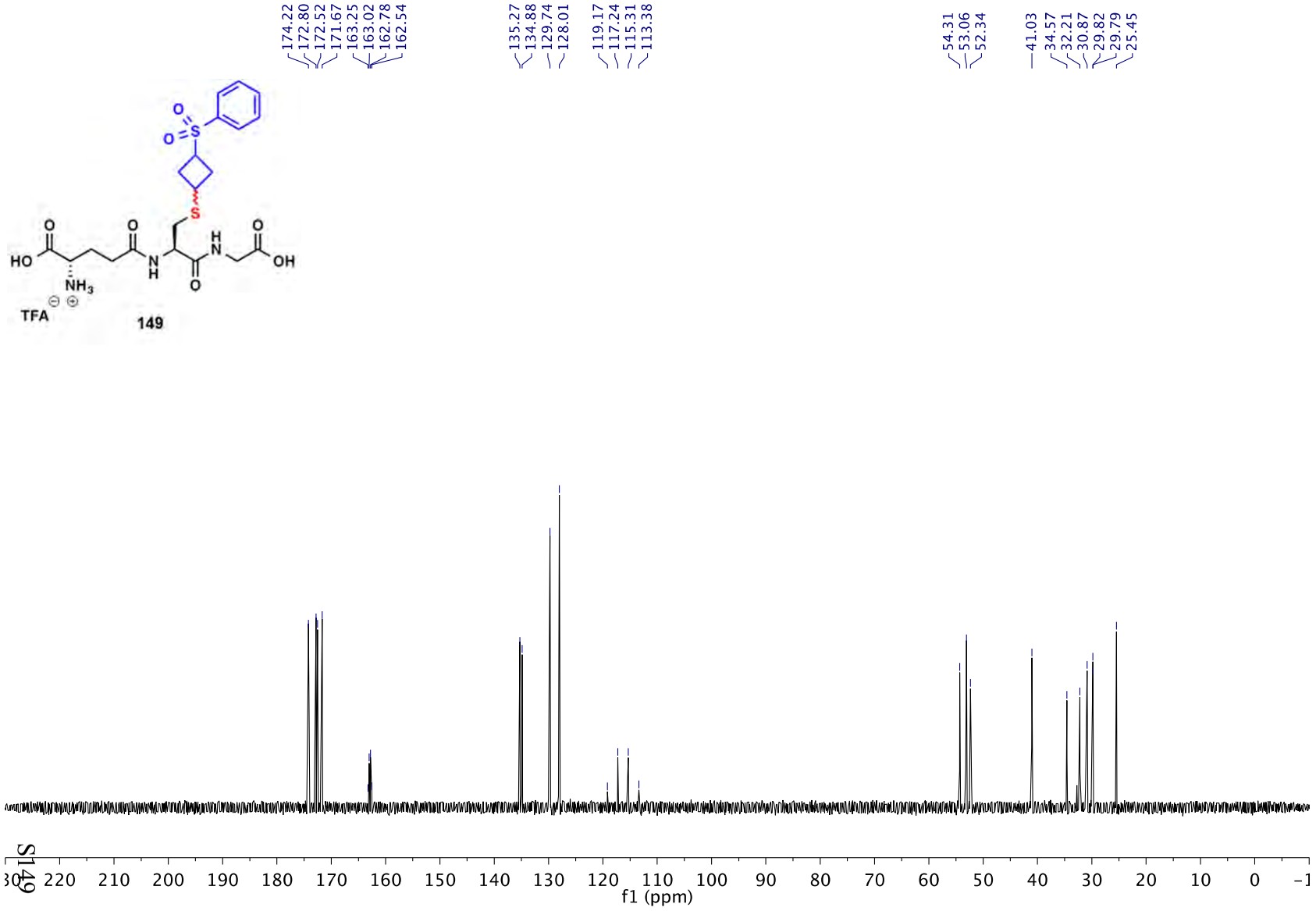
minor diastereomer: δ 7.90 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.87 – 7.77 (m, 1H), 7.75 – 7.65 (m, 2H), 4.63 – 4.45 (m, 1H), 4.16 – 4.02 (m, 2H), 4.02 (s, 2H), 3.59 – 3.44 (m, 1H), 3.09 – 3.03 (m, 1H), 2.93 – 2.86 (m, 1H), 2.70 – 2.62 (m, 2H), 2.62 – 2.52 (m, 2H), 2.43 – 2.36 (m, 2H), 2.27 – 2.15 (m, 2H) ppm;

^{13}**C NMR** (151 MHz, D_2O) *major diastereomer*: δ 174.2, 172.8, 172.5, 171.7, 162.9 (q, *J* = 35.5 Hz), 135.3, 134.9, 129.7 (2C), 128.0 (2C), 116.3 (q, *J* = 291.5 Hz), 54.3, 53.1, 52.3, 41.0, 34.6, 32.2, 30.9, 29.8, 29.8, 25.4 ppm;

HRMS (ESI-TOF): calc'd for $C_{20}H_{28}N_3O_8S_2$ $[M+H]^+$ 502.1312, found 502.1301.


HO
O
O
O
S
S
N
H
H
N
O
OH
NH3
TFA
149

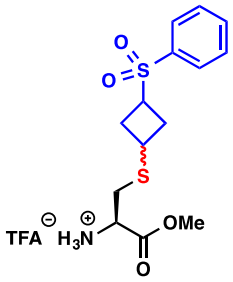
1.96
0.40
1.17
2.35
1.18
1.01
1.55
2.27
1.00
0.21
0.24
0.97
3.21
2.82
0.45
4.44
f1 (ppm)


174.22
172.80
172.52
171.67
163.25
163.02
162.78
162.54
135.27
134.88
129.74
128.01
119.17
117.24
115.31
113.38
54.31
53.06
52.34
41.03
34.57
32.21
30.87
29.82
29.79
25.45
HO
O
O
NH3
TFA
N
H
O
O
S
O
O
S
H
N
O
OH
149
f1 (ppm)

Compound **148**:

Cysteine methyl ester hydrochloride (30 mg, 0.17 mmol) was dissolved in degassed 0.2 M K_2CO_3 (0.87 mL, 1.0 equiv. K_2CO_3). A solution of **8a** (34 mg, 0.17 mmol) in DMF (0.87 mL) was prepared and added to the reaction mixture to give a final concentration of 0.1 M with respect to cysteine methyl ester. The reaction vial was flushed with Ar(g) and stirred at rt for 8 h. The DMF was removed under a stream of N_2 and the resultant solution diluted in water containing 0.1% TFA and purified by reverse-phase HPLC (0% B for 10 min, 0% to 60% B over 30 min) and lyophilized to afford **148** as a clear oil (TFA salt, 68 mg, 88% yield).

148 (TFA salt):



5.3:1 dr;

Physical state: clear oil;

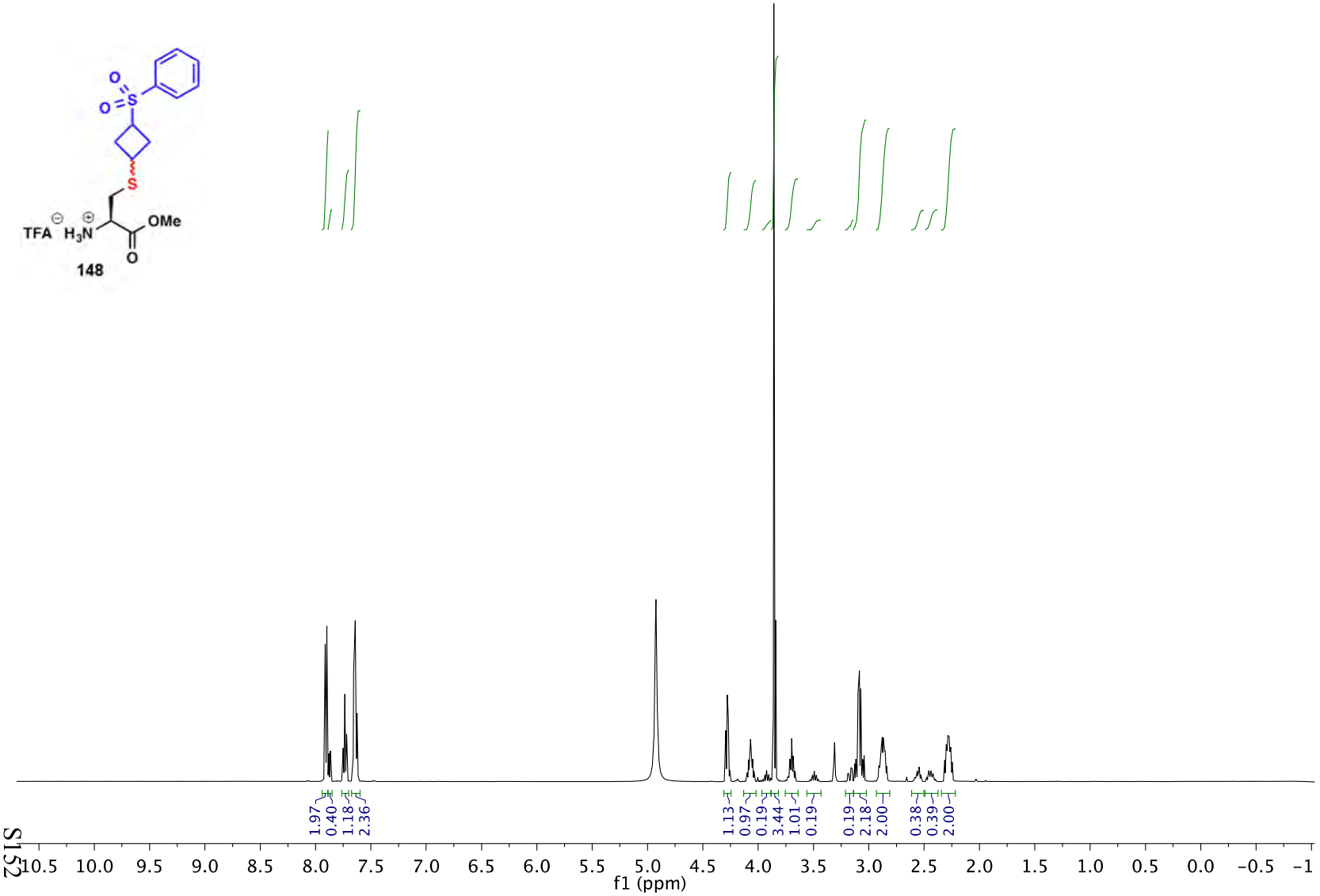
^{1}**H NMR** (500 MHz, CD_3OD) *major diastereomer*: δ 7.94 – 7.89 (m, 2H), 7.73 (td, *J* = 7.3, 1.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 4.28 (dd, *J* = 6.4, 5.0 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.86 (s, 3H), 3.76 – 3.64 (m, 1H), 3.11 – 3.04 (m, 2H), 2.93 – 2.81 (m, 2H), 2.34 – 2.22 (m, 2H) ppm;

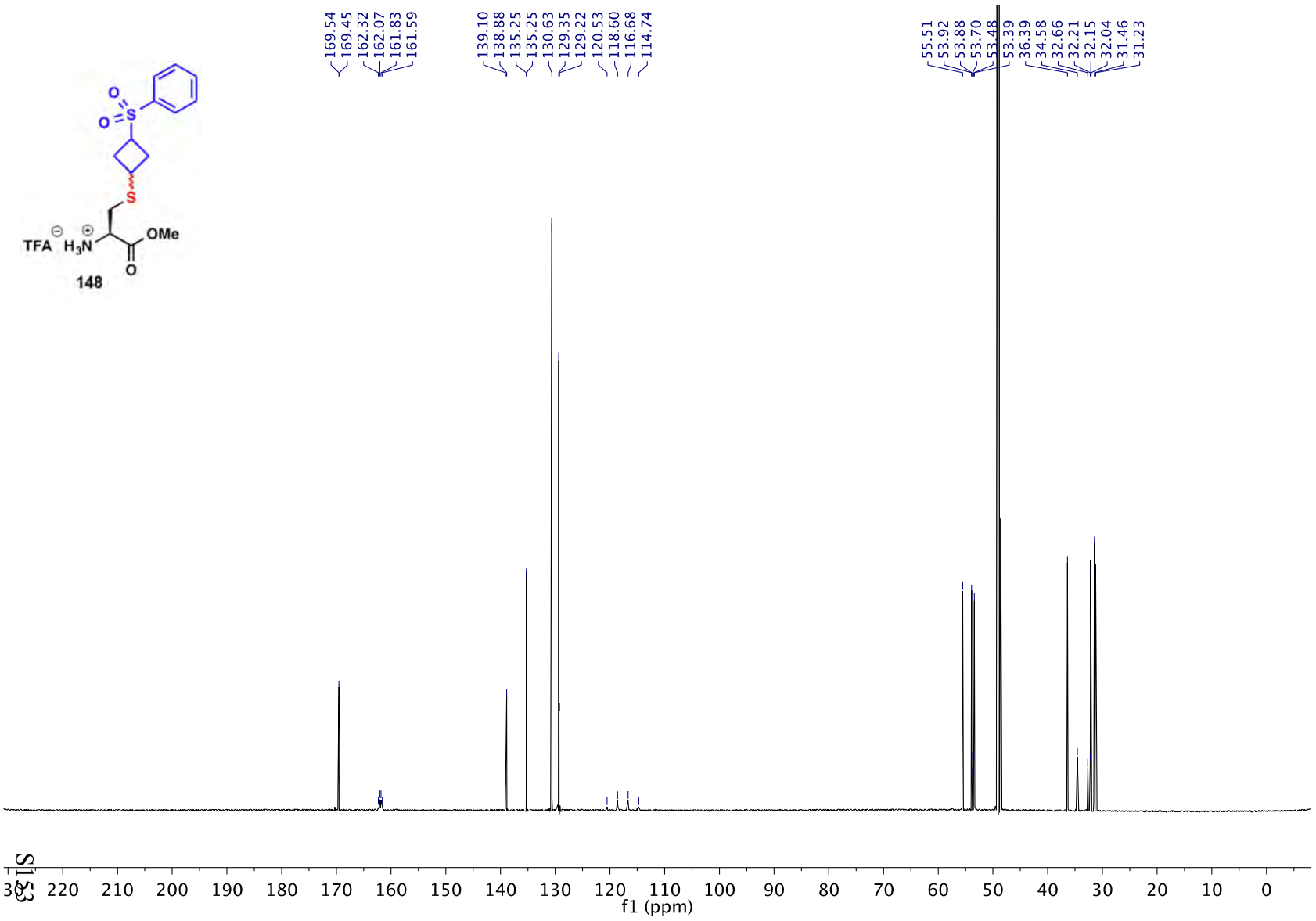
minor diastereomer: δ 7.89 – 7.86 (m, 2H), 7.73 (td, *J* = 7.3, 1.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 4.34 – 4.23 (m, 1H), 3.96 – 3.88 (m, 1H), 3.84 (s, 3H), 3.56 – 3.43 (m, 1H), 3.17 (dd, *J* = 14.7, 4.8 Hz, 1H), 3.13 – 3.04 (m, 1H), 2.60 – 2.51 (m, 2H), 2.48 – 2.38 (m, 2H) ppm;

^{13}C NMR (151 MHz, CD_3OD) *major diastereomer*: δ 169.5, 162.0 (q, $^2J_{C\text{-}F}$ = 36.9 Hz), 138.9, 135.2, 130.6 (2C), 129.3 (2C), 117.6 (q, $^1J_{C\text{-}F}$ = 291 Hz), 55.5, 53.9, 53.4, 36.4, 32.1, 31.5, 31.2 ppm;

minor diastereomer: δ 169.4, 162.0 (q, $^2J_{C\text{-}F}$ = 36.9 Hz), 139.1, 135.2, 130.6 (2C), 129.2 (2C), 117.6 (q, $^1J_{C\text{-}F}$ = 291 Hz), 53.9, 53.7, 53.5, 34.6, 32.7, 32.2, 32.0 ppm;

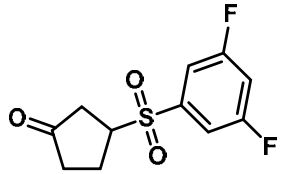
HRMS (ESI-TOF): calc'd for $C_{14}H_{20}NO_4S_2$ [$M+H^+$] 330.0828, found 330.0822.


TFA
H3N
OMe
148
1.97
0.40
1.18
2.36
1.13
0.97
0.19
3.44
1.01
0.19
0.19
2.18
2.00
0.38
0.39
2.00
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 -1
f1 (ppm)


169.54
169.45
162.32
162.07
161.83
161.59
139.10
138.88
135.25
135.25
130.63
129.35
129.22
120.53
118.60
116.68
114.74
55.51
53.92
53.88
53.70
53.48
53.39
36.39
34.58
32.66
32.21
32.15
32.04
31.46
31.23
TFA
H3N
OMe
148
f1 (ppm)

Synthesis of Racemic Housane Strain-release Reagents

3,5-Difluorophenylsulfone Reagent (9)



163

3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-one (163)

To a stirred solution of **162** (16.7 mL, 199.9 mmol, 1.0 equiv.) and 3,5-difluorobenzenesulfinate (50.00 g, 249.8 mmol, 1.25 equiv.) in H_2O (300 mL) was slowly added aq. HCl (300 mL, 1M). A white precipitate appeared and the mixture was stirred for 16 h at room temperature. The precipitate was collected by filtration, triturated with H_2O and subsequently azeotroped with toluene to remove residual H_2O. Further removal of solvent under reduced pressure yielded the desired product **163** (50.5 g, 199.9 mmol, 97% yield).

Physical State: crystalline white solid (m.p. = 133-136 °C);

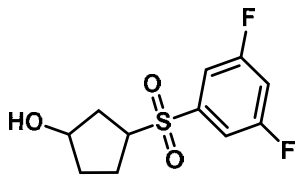
R_f = 0.45 (40% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.42 (m, 2H), 7.14 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.82 – 3.76 (m, 1H), 2.67 – 2.61 (m, 1H), 2.58 – 2.45 (m, 2H), 2.45 – 2.38 (m, 1H), 2.32 – 2.23 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 211.9, 163.1 (dd, $^1J_{C–F}$ = 256.5, 11.9 Hz), 140.9 (t, $^3J_{C–F}$ = 7.7 Hz), 112.3 (dd, $^2J_{C–F}$ = 22.0, 6.3 Hz), 110.1 (t, $^2J_{C–F}$ = 24.6 Hz), 60.7, 38.4, 36.9, 23.1;

^{19}F NMR (376 MHz, $CDCl_3$): δ –104.5;

HRMS (ESI-TOF): calc'd for $C_{11}H_{10}F_2NaO_3S$ [M+Na^+] 283.0211; found 283.0222.



167

3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-ol (167)

To a solution of **163** (40.00 g, 153.7 mmol) in MeOH (500 mL) at 0 °C was slowly added $NaBH_4$ (5.81 g, 153.7 mmol, 1.0 equiv.) and stirring was continued for 1 h. Subsequently, half sat. aq. NH_4Cl (ca. 120 mL) was added followed by CH_2Cl_2 and a separation of phases. The aqueous phase was extracted using CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, passed through a pad of silica gel and concentrated *in vacuo* to yield **167** in quantitative yield.

Physical State: white solid (m.p. = 83-85 °C);

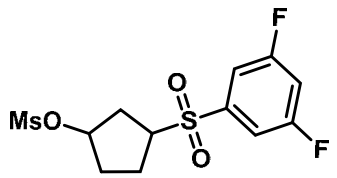
R_f = 0.61 (75% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 – 7.45 (m, 2H), 7.12 (tt, *J* = 8.3, 2.3 Hz, 1H), 4.36 (dtt, *J* = 8.1, 5.3, 3.0 Hz, 1H), 3.61 (dddd, *J* = 9.5, 8.7, 7.3, 5.4 Hz, 1H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.26 – 2.16 (m, 2H), 1.98 – 1.91 (m, 2H), 1.84 – 1.77 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.1 (dd, $^1J_{C–F}$ = 256.3, 11.9 Hz), 141.7 (t, $^3J_{C–F}$ = 8.2 Hz), 112.3 (dd, $^2J_{C–F}$ = 21.9, 6.6 Hz), 109.7 (t, $^2J_{C–F}$ = 24.8 Hz), 72.6, 63.2, 36.3, 35.6, 24.9;

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.0;

HRMS (ESI-TOF): calc'd for $C_{11}H_{12}F_2NaO_3S$ [M+Na^+] 285.0367; found 285.0353.



165

3-((3,5-difluorophenyl)sulfonyl)cyclopentyl methanesulfonate (165)

To a stirred solution of **167** (40.31 g, 153.70 mmol) in CH_2Cl_2 (550 mL) was added Et_3N (27.9 mL, 199.8 mmol) followed by the dropwise addition of MsCl (15.46 mL, 199.8 mmol). The reaction mixture was stirred for 16 h from 0 °C to ambient temperature while precipitation occurred. Subsequently, H_2O was added and the layers were separated, the organic layer was dried over $MgSO_4$, passed through a pad of silica gel and concentrated *in vacuo* to afford **165** (45.6 g, 134.0 mmol, 87% yield).

Physical State: white solid (m.p. = 99-100 °C);

R_f = 0.31 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 – 7.42 (m, 2H), 7.13 (tt, *J* = 8.3, 2.3 Hz, 1H), 5.16 – 5.11 (m, 1H), 3.55 (dq, *J* = 9.2, 8.2 Hz, 1H), 3.04 (s, 3H), 2.44 – 2.39 (m, 2H), 2.33 – 2.24 (m, 1H), 2.21 – 2.15 (m, 1H), 2.02 – 1.93 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.1 (dd, $^{1}J_{C\text{-}F}$ = 256, 11.7 Hz, 2C), 141.7 (t, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 112.3 (q, $^{2}J_{C\text{-}F}$ = 6.6 Hz, 2C), 109.8 (t, $^{2}J_{C\text{-}F}$ = 25.1 Hz), 80.0, 62.1, 38.8, 33.7, 33.1, 24.9;

^{19}F NMR (376 MHz, $CDCl_3$): δ –104.8;

HRMS (ESI-TOF): calc'd for $C_{12}H_{14}F_2NaO_5S_2$ [M+Na^+] 363.0148; found 363.0149.

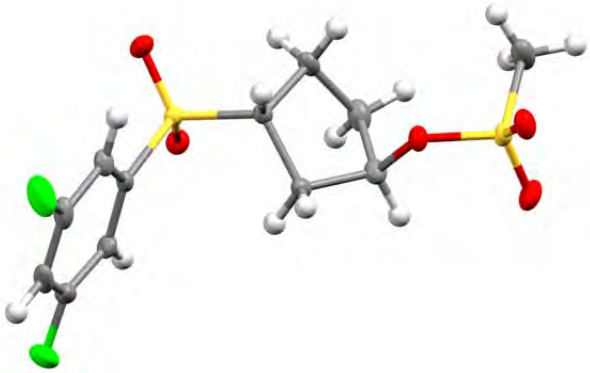
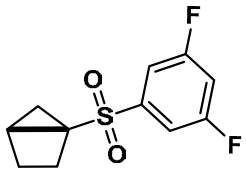


Fig. S68. Crystal structure of (1*R*,3*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl methanesulfonate (**165**).

Identification code	110685-2309-3	
Empirical formula	$C_{12}H_{14}F_2O_5S_2$	
Formula weight	340.35	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 2_1 1	
Unit cell dimensions	a = 9.6649(15) Å	α = 90°.
	b = 5.7972(9) Å	β = 99.212(4)°.
	c = 25.224(4)	γ = 90°.
Volume	1395.0(4) $Å^3$	
Z	4	

Density (calculated)	1.621 Mg/m^3
Absorption coefficient	0.423 mm^{-1}
F(000)	704
Crystal size	0.278 x 0.215 x 0.164 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	2.135 to 26.428 °.
Index ranges	$-11 \leq h \leq 12$, $-7 \leq k \leq 7$, $-31 \leq l \leq 31$
Reflections collected	16199
Independent reflections	5569 [R(int) = 0.0389, R(sigma) = 0.0466]
Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.2602 and 0.2329
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5569/ 1 /381
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R_1 = 0. 0334, wR_2 = 0. 0731
R indices (all data)	R_1 = 0.0389, wR_2 = 0.0762
Absolute structure parameter	–0.006(36)
Extinction coefficient	n/a
Largest diff. peak and hole	0.305 and –0.315 $e.Å^{-3}$



9

1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane (9)

Compound **165** (10.2 g, 29.97 mmol) was dissolved in THF (150 mL, 0.2M) and cooled to -20 °C on a NaCl ice-bath. Subsequently, *n*-BuLi (15.2 mL, 1.97M) was added over the course of 2 min and the reaction mixture was further stirred for 5 min followed by the addition of half sat. aq. NH_4Cl. CH_2Cl_2 (300 mL) was added and the layers were separated followed by extraction from the aqueous phase using CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified using silica gel chromatography (SiO_2 plug, 20% Et_2O in hexanes, isocratic) to provide **9** in 78% yield.

Physical State: crystalline white solid (m.p. = 59-60 °C);

Sigma-Aldrich Catalog Number: MKE151701;

R_f = 0.25 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 – 7.35 (m, 2H), 7.07 (tt, *J* = 8.5, 2.3 Hz, 1H), 2.69 (ddd, *J* = 6.6, 4.2, 1.9 Hz, 1H), 2.55 (tdd, *J* = 11.0, 4.1, 1.9 Hz, 1H), 2.24 (ttd, *J* = 11.0, 4.7, 1.4 Hz, 1H), 1.80 (td, *J* = 6.5, 5.7, 2.4 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.43 (ddd, *J* = 10.9, 6.3, 4.1 Hz, 1H), 1.31 (dd, *J* = 4.8, 2.4 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 255, 11.6 Hz, 2C), 143.4 (t, $^3J_{C\text{-}F}$ = 7.9 Hz), 111.3 (q, $^2J_{C\text{-}F}$ = 6.7 Hz, 2C), 109.0 (t, $^2J_{C\text{-}F}$ = 25.3 Hz), 40.0, 26.1, 22.5, 22.4, 20.4;

^{19}F NMR (376 MHz, $CDCl_3$): δ –105.7;

HRMS (ESI-TOF): calc'd for $C_{11}H_{11}F_2O_2S$ [M+H$^+$] 245.0448; found 245.0442;

Note: The racemic reagent **9** was separated using chiral SFC to provide a set of enantiomers that were further characterized by X-ray crystallography and optical rotation (*vide infra*).

$[\alpha]_D^{22}$ = –50.0 (c =0.6, MeOH) for **(–)-9**.

$[\alpha]_D^{22}$ = +43.0 (c =1.4, $CHCl_3$) for (+)-**9**.

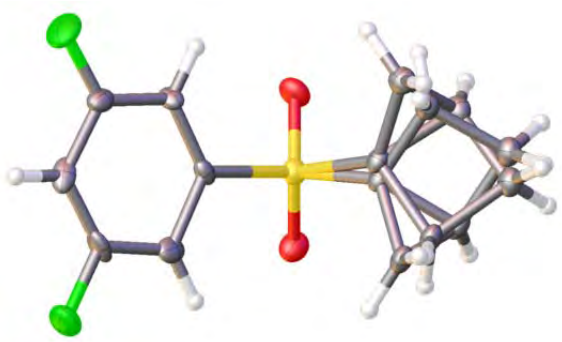


Fig. S69. Crystal structure of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane **9**.

Identification code	baran566	
Empirical formula	$C_{11}H_{10}F_2O_2S$	
Formula weight	244.25	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pna2_1$	
Unit cell dimensions	a = 6.7725(7) Å	α = 90°.
	b = 13.8233(13) Å	β = 90°.
	c = 11.1737(18)	γ = 90°.
Volume	1046.1(2) $Å^3$	
Z	4	
Density (calculated)	1.551 Mg/m^3	
Absorption coefficient	0.318 mm^{-1}	
F(000)	504	
Crystal size	0.3 x 0.3 x 0.3 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	4.688 to 52.732 °.	
Index ranges	$-8 \le h \le 7, -17 \le k \le 16, -10 \le l \le 13$	
Reflections collected	5198	
Independent reflections	1792 [R(int) = 0.0312]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.2363 and 0.1946
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1792/ 61 /174
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R_1 = 0. 0308, wR_2 = 0. 0770
R indices (all data)	R_1 = 0.0401, wR_2 = 0.0978
Absolute structure parameter	0.2(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.41 and –0.32 e.Å^{-3}

Fig. S70. Crystal structure of (1*S*,4*S*)-1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane (**(+)-9**).

Identification code	4-JML-043-POS	
Empirical formula	$C_{11}H_{10}F_2O_2S$	
Formula weight	244.25	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.7986(6) Å	α= 90°.
	b = 11.0791(9) Å	β= 90°.
	c = 13.9050(11) Å	γ = 90°.
Volume	1047.36(15) Å^3	
Z	4	
Density (calculated)	1.549 Mg/m^3	

Absorption coefficient	0.318 mm^{-1}
F(000)	504
Crystal size	0.253 x 0.249 x 0.221 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	2.350 to 25.376°.
Index ranges	$-8 \leq h \leq 8$, $-13 \leq k \leq 13$, $-16 \leq l \leq 16$
Reflections collected	18098
Independent reflections	1925 [R(int) = 0.0827]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.2363 and 0.1946
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1925 / 0 / 145
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	$R_1 = 0.0376$, $wR_2 = 0.0953$
R indices (all data)	$R_1 = 0.0401$, $wR_2 = 0.0978$
Absolute structure parameter	-0.06(8)
Extinction coefficient	n/a
Largest diff. peak and hole	0.269 and -0.410 $e.Å^{-3}$

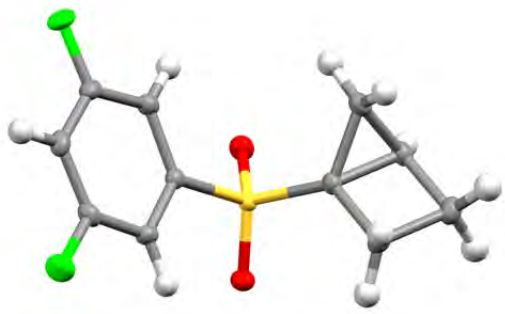
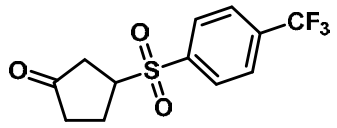


Fig. S71. Crystal structure of (1*R*,4*R*)-1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane (**(–)-9)**.

Identification code	4-JML-043-NEG
Empirical formula	$C_{11}H_{10}F_2O_2S$

Formula weight	244.25	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.7965(3) Å	α = 90°.
	b = 11.0812(5) Å	β = 90°.
	c = 13.9075(5) Å	γ = 90°.
Volume	1047.42(8) $Å^3$	
Z	4	
Density (calculated)	1.549 Mg/m^3	
Absorption coefficient	0.318 mm^{-1}	
F(000)	504	
Crystal size	0.353 x 0.278 x 0.211 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	2.350 to 25.314°.	
Index ranges	$-8 \le h \le 7$, $-11 \le k \le 13$, $-16 \le l \le 15$	
Reflections collected	10937	
Independent reflections	1916 [R(int) = 0.0550]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2439 and 0.2101	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1916 / 0 / 145	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R_1 = 0.0307, wR_2 = 0.0797	
R indices (all data)	R_1 = 0.0319, wR_2 = 0.0814	
Absolute structure parameter	-0.04(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.312 and -0.319 $e.Å^{-3}$	

4-(Trifluoromethyl)phenylsulfone Reagent (10)



164

3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentan-1-one (164)

To a stirred solution of **162** (24.34 mL, 290.50 mmol, 1.0 equiv.) and 4-(trifluoromethyl)benzenesulfinate (84.30 g, 363.12 mmol, 1.25 equiv.) in H_2O (436 mL) was slowly added aq. HCl (436 mL, 1M) while precipitation occurred over the course of 24 h. Subsequently, the precipitate was collected by filtration, triturated with H_2O and azeotroped with toluene to remove residual H_2O. The material was then dissolved in CH_2Cl_2 and passed through a plug of silica gel followed by evaporation of volatiles *in vacuo* to provide the desired product **164** (81.72 g, 279.6 mmol, 96% yield).

Physical State: crystalline white solid (m.p. = 103-105 °C);

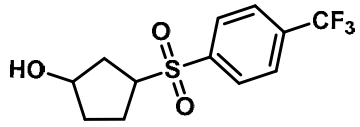
R_f = 0.57 (45% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H), 3.81 – 3.76 (m, 1H), 2.72 – 2.66 (m, 1H), 2.62 – 2.55 (m, 1H), 2.53 – 2.43 (m, 2H), 2.34 – 2.24 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 212.0, 141.3, 136.1 (q, $^2J_{C–F}$ = 33.2 Hz), 129.4, 126.9 (q, $^3J_{C–F}$ = 4.2 Hz), 123.1 (q, $^1J_{C–F}$ = 273.2 Hz), 60.8, 38.5, 37.0, 23.2;

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.6;

HRMS (ESI-TOF): calc'd for $C_{12}H_{11}F_3NaO_3S$ [M+Na^+] 315.0273; found 315.0278.



168

3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentan-1-ol (168)

To a solution of **164** (30.00 g, 102.64 mmol) in MeOH (350 mL) at 0 °C was slowly added $NaBH_4$ (3.88 g, 102.64 mmol, 1.0 equiv.) and stirring was continued for 1 h. Subsequently, half sat. aq. NH_4Cl (ca. 60 mL) was added followed by CH_2Cl_2 and a separation of phases.

The aqueous phase was extracted using CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, passed through a pad of silica gel and concentrated *in vacuo* to yield **168** (29.47 g, 100.14 mmol, 98% yield).

Physical State: colorless crystals (m.p. = 122-124 °C);

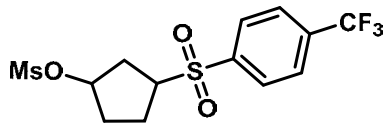
R_f = 0.45 (60% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 2H), 4.35 – 4.29 (m, 1H), 3.64 – 3.57 (m, 1H), 2.70 (d, *J* = 7.5 Hz, 1H), 2.30 – 2.23 (m, 1H), 2.21 – 2.13 (m, 2H), 1.94 – 1.87 (m, 2H), 1.82 – 1.75 (m, 1H). [for major diastereomer];

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.8, 135.6 (q, $^2J_{C–F}$ = 33.3 Hz), 129.3, 126.6 (q, $^3J_{C–F}$ = 3.4 Hz), 123.2 (q, $^1J_{C–F}$ = 273.1 Hz), 72.5, 63.1, 63.1, 36.1, 35.4, 24.8;

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.5;

HRMS (ESI-TOF): $C_{12}H_{14}F_3O_3S$ [M+H$^+$] 295.0610; found 295.0608.



166

3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl methanesulfonate (166)

To a stirred solution of **168** (29.45 g, 100.1 mmol) in CH_2Cl_2 (350 mL) was added Et_3N (16.7 mL, 120.1 mmol) followed by the dropwise addition of MsCl (9.3 mL, 120.1 mmol). The reaction mixture was stirred for 16 h from 0 °C to ambient temperature followed by the addition of extra MsCl (4.65 mL, 60.1 mmol). After 1 h, Et_3N (8.35 mL, 60.1 mmol) was added and the mixture stirred for 1 h while precipitation occurred. The reaction was quenched by the addition of H_2O, the layers were separated, the organic layer was dried over $MgSO_4$, passed through a pad of silica gel and concentrated *in vacuo* to afford **166** (33.36 g, 100.07 mmol, 90% yield).

Physical State: crystalline white solid (m.p. = 93-94 °C);

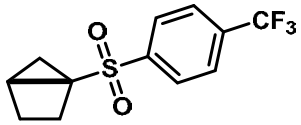
R_f = 0.28 (1% MeOH in CH_2Cl_2, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 – 8.04 (m, 2H), 7.87 – 7.85 (m, 2H), 5.15 – 5.11 (m, 1H), 3.59 – 3.52 (m, 1H), 3.03 (s, 3H), 2.47 – 2.37 (m, 2H), 2.34 – 2.27 (m, 1H), 2.22 – 2.16 (m, 1H), 2.01 – 1.93 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.9, 135.8 (q, $^{2}J_{C–F}$ = 33.3 Hz), 129.4, 126.7 (q, $^{3}J_{C–F}$ = 3.8 Hz), 123.2 (q, $^{1}J_{C–F}$ = 273.1 Hz), 80.0, 62.2, 38.9, 33.7, 33.1, 24.8;

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.5;

HRMS (ESI-TOF): calc'd $C_{13}H_{16}F_3O_5S_2$ [M+H^+] 373.0386; found 373.0395.



10

1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[2.1.0]pentane (10)

A stirred solution of **166** (33.36 g, 89.59 mmol) in THF (480 mL) was cooled to -20 °C on a NaCl ice-bath. Subsequently, *n*-BuLi was added over the course of 10 min and the reaction mixture was further stirred for 5 min followed by the addition of half sat. aq. NH_4Cl. CH_2Cl_2 (500 mL) was added and the layers were separated followed by extraction from the aqueous phase using CH_2Cl_2 (3 x 400 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified using silica gel chromatography (SiO_2 plug, 20% Et_2O in hexanes, isocratic) to provide **10** (17.60 g, 63.71 mmol, 71% yield).

Physical State: colorless crystals (m.p. = 44-45 °C);

R_f = 0.47 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 2.70 – 2.66 (m, 1H), 2.54 (tdd, *J* = 11.1, 4.2, 1.9 Hz, 1H), 2.25 – 2.19 (m, 1H), 1.81 (td, *J* = 6.4, 5.6, 2.2 Hz, 1H), 1.67 – 1.61 (m, 1H), 1.44 – 1.39 (m, 1H), 1.28 (dd, *J* = 4.8, 2.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.6, 134.9 (q, $^{2}J_{C–F}$ = 33.2 Hz), 128.3, 126.5 (q, $^{3}J_{C–F}$ = 3.9 Hz), 123.3 (q, $^{1}J_{C–F}$ = 272.9 Hz), 40.1, 26.0, 22.4, 22.3, 20.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.4;

HRMS (ESI-TOF): calc'd for $C_{12}H_{12}F_3O_2S$ [M+H^+] 277.0505; found 277.0508.

Note: Racemic **10** was separated using chiral SFC to provide a set of enantiomers that were further characterized by X-ray crystallography and optical rotation (*vide infra*).

$[\alpha]_D^{22}$ = –43.0 (c =1.4, $CHCl_3$) for **(–)-10**.

$[\alpha]_D^{22}$ = +38.8 (c =0.8, $CHCl_3$) for **(+)-10**.

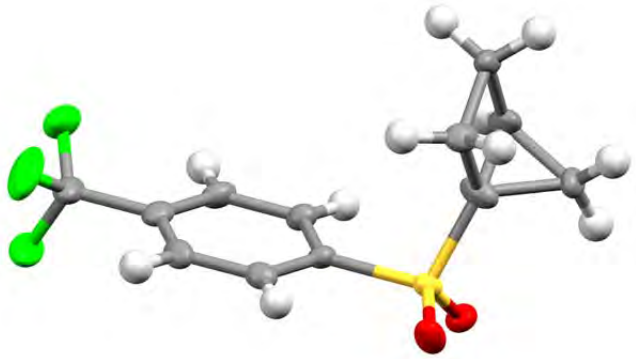


Fig. S72. Crystal structure of (1*S*,4*S*)-1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[2.1.0]pentane (**(+)-10**).

Identification code	KF10-C4-plus	
Empirical formula	$C_{12}H_{11}F_3O_2S$	
Formula weight	276.27	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 7.9193(11) Å	α = 104.903(4)°.
	b = 8.1426(12) Å	β = 109.324(3)°.
	c = 10.5945(18) Å	γ = 99.177(3)°.
Volume	600.17(16) Å3	
Z, Z’	2, 2	
Density (calculated)	1.529 Mg/m3	
Absorption coefficient	0.299 mm-1	
F(000)	284	
Crystal size	0.3 x 0.26 x 0.23 mm^3	

Theta range for data collection	2.687 to 26.442°.
Index ranges	$-9 \leq h \leq 9$, $-10 \leq k \leq 10$, $-13 \leq l \leq 13$
Reflections collected	8224
Independent reflections	4709 [R(int) = 0.0224]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.4908 and 0.4544
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4709 / 3 / 344
Goodness-of-fit on F2	1.025
Final R indices [I>2sigma(I)]	$R_1 = 0.0335$, $wR_2 = 0.0794$
R indices (all data)	$R_1 = 0.0390$, $wR_2 = 0.0829$
Absolute structure parameter	0.00(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.309 and -0.325 e.Å^{-3}

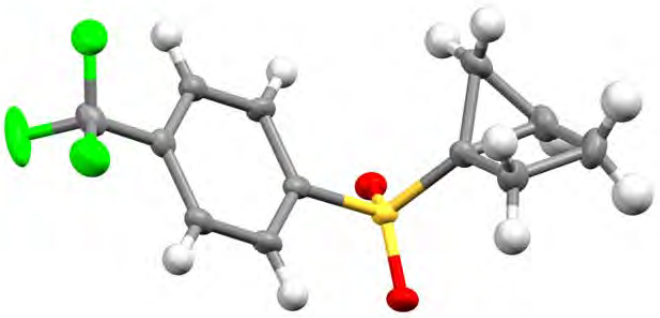


Fig. S73. Crystal structure of (1*R*,4*R*)-1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[2.1.0]pentane ((–)-**10**).

Identification code	KF10-C2-minus	
Empirical formula	$C_{12}H_{11}F_3O_2S$	
Formula weight	276.27	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 7.925(3) Å	α = 104.921(9)°.

	b = 8.141(3) Å	β = 109.227(7)°.
	c = 10.592(3) Å	γ = 99.411(16)°.
Volume	599.9(3) Å3	
Z	2	
Density (calculated)	1.529 Mg/m3	
Absorption coefficient	0.299 mm-1	
F(000)	284	
Crystal size	0.29 x 0.26 x 0.22 mm3	
Theta range for data collection	2.161 to 26.425°.	
Index ranges	$-9 \leq h \leq 9$, $-10 \leq k \leq 10$, $-13 \leq l \leq 13$	
Reflections collected	19332	
Independent reflections	4796 [R(int) = 0.0398]	
Completeness to theta = 25.242°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2886 and 0.2354	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	4796 / 297 / 325	
Goodness-of-fit on F2	1.045	
Final R indices [I>2sigma(I)]	$R_1 = 0.0494$, $wR_2 = 0.1332$	
R indices (all data)	$R_1 = 0.0520$, $wR_2 = 0.1360$	
Absolute structure parameter	0.06(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.379 and -0.362 e.Å^{-3}	

Graphical SI for The Preparation of Housane 9

Fig. S74. Left. The sulfonyl chloride was suspended in H_2O. **Center.** Sodium sulfite was added. **Right.** The suspension was heated to 80 ºC and became a clear solution.

Fig. S75. Left. Sodium bicarbonate was added slowly portionwise. **Center.** Vigorous bubbling was observed with each addition. **Right.** The flask was fitted with a reflux condenser and heated at 80 ºC overnight.

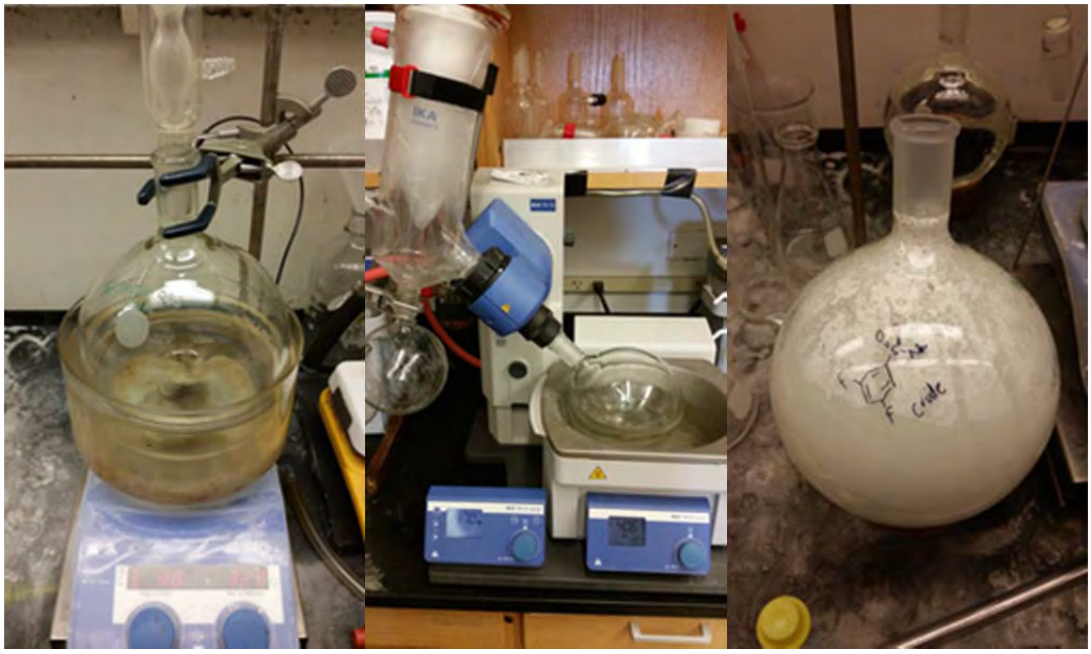


Fig. S76. Left. View of the reaction after completion. **Center.** The mixture was cooled to room temperature and concentrated on the rotary evaporator. **Right.** Product after concentration and azeotrope with toluene.

Fig. S77. Left. The crude sulfinate was treated with 500 mL of hot MeOH (twice) and filtered. **Center.** Cake of inorganic salts removed from sulfinate. **Right.** Purified sulfinate as a flowing white solid after concentration, azeotrope with toluene, and high vac.

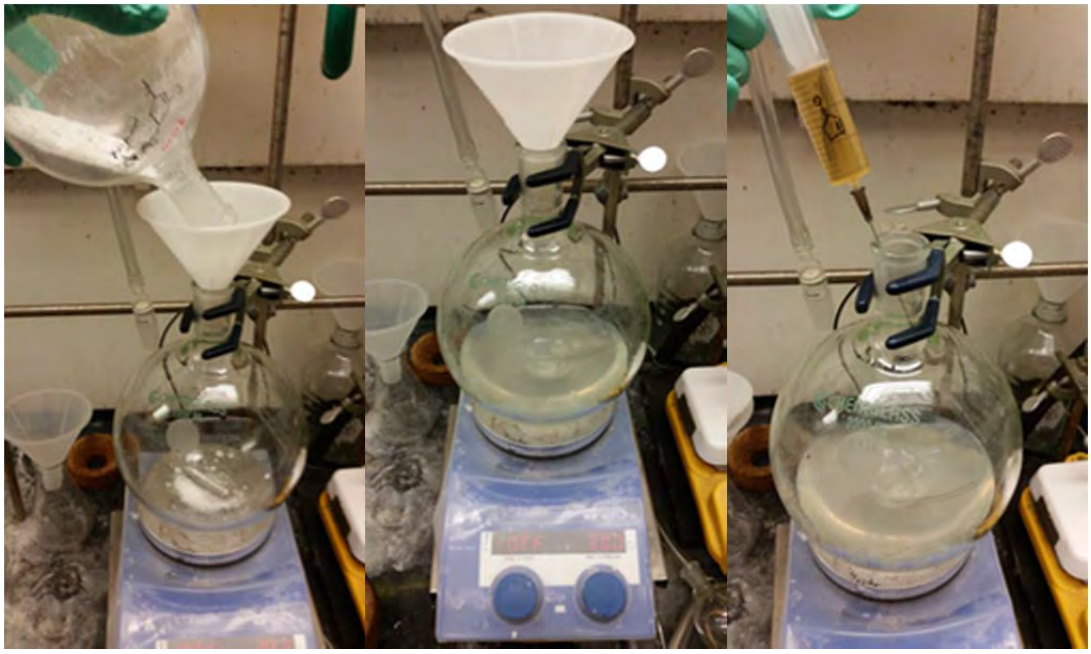


Fig. S78. Left. The purified sulfinate was added to a 2L round bottom flask. **Center.** H_2O (500 mL) was added to dissolve the sulfinate. **Right.** Enone **162** was added at room temperature.

Fig. S79. Left. The reaction became yellow with the addition of **162**. **Center.** The flask was fitted with an addition funnel containing 1M HCl. **Right.** During the initial addition of the HCl, the reaction turned from yellow to colorless.

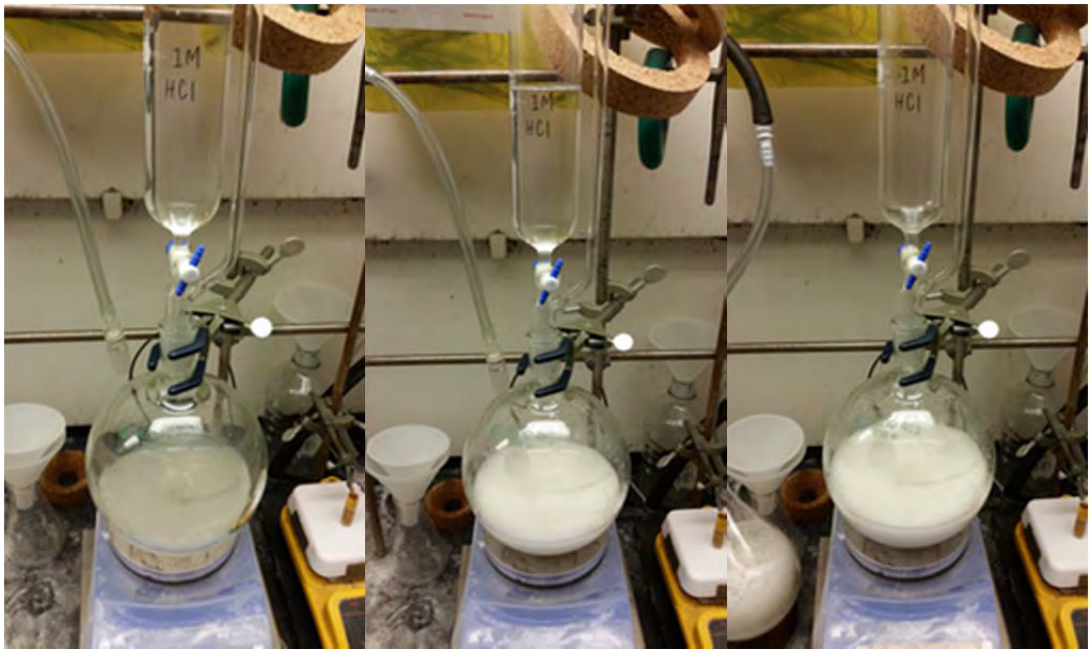


Fig. S80. Left to Right. Over the course of the addition of the HCl, copious amounts of white precipitate formed.

Fig. S81. Left. Reaction after stirring overnight. **Center.** The suspension was filtered with water. **Right.** The ketone was collected as a white solid.

Fig. S82. Left. The ketone was azeotroped with toluene and could be used in the next reaction without further purification. **Center.** If desired, the ketone could be recrystallized from CH_2Cl_2. **Right.** Crystals form after slow cooling to –20 ºC.

Fig. S83. Left. The crystals were collected by filtration. **Center.** The crystals were washed with a small portion of ice cold CH_2Cl_2. **Right.** Recrystallized ketone.

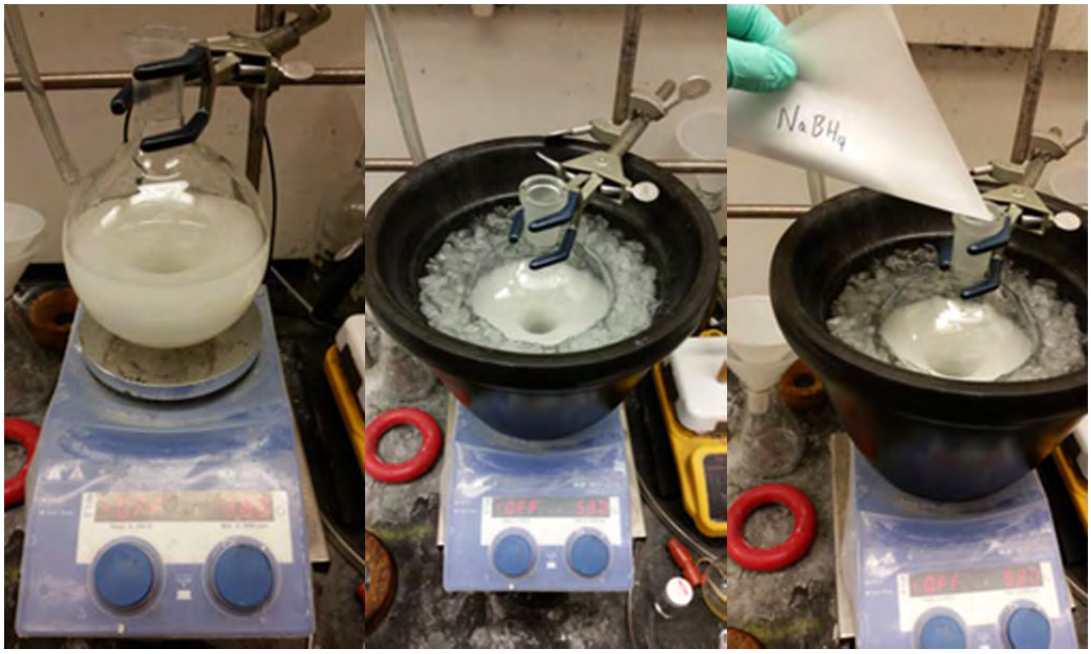


Fig. S84. Left. The ketone was dissolved in MeOH at room temperature. **Center.** The reaction was cooled to 0 ºC in an ice-water bath. **Right.** Sodium borohydride was added portion-wise to the reaction.

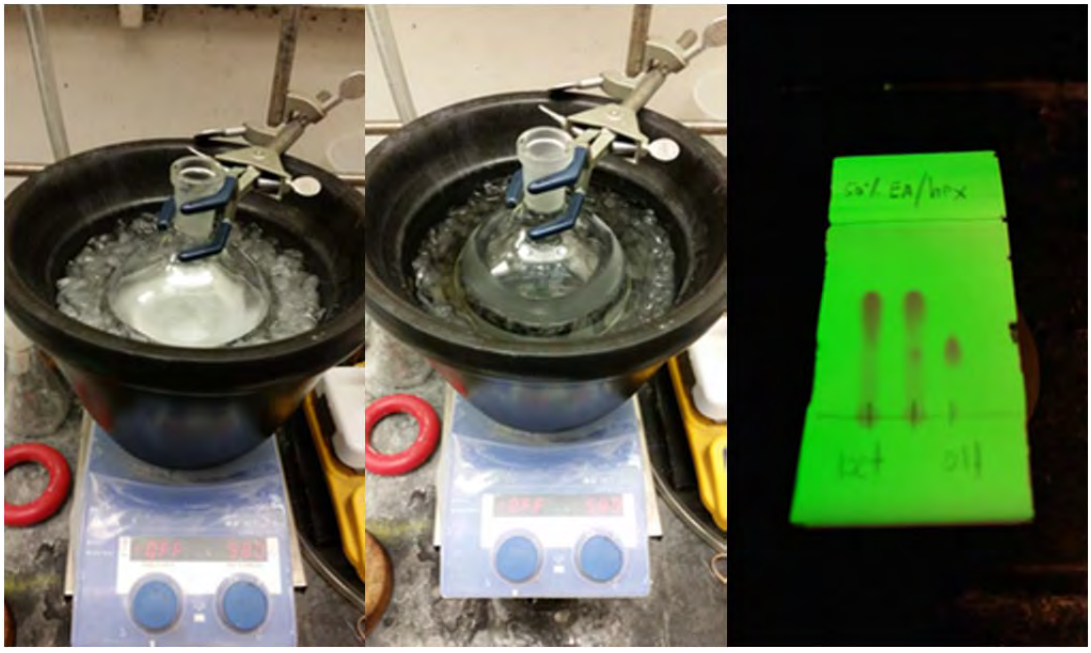


Fig. S85. Left. Vigorous bubbling was observed with each addition. **Center.** The reaction was stirred at 0 ºC for 60 minutes until TLC indicated full consumption of the starting material. **Right.** TLC conditions – 50% EtOAc in hexanes; left lane – crude ketone; center lane – co-spot; right – reaction mixture.

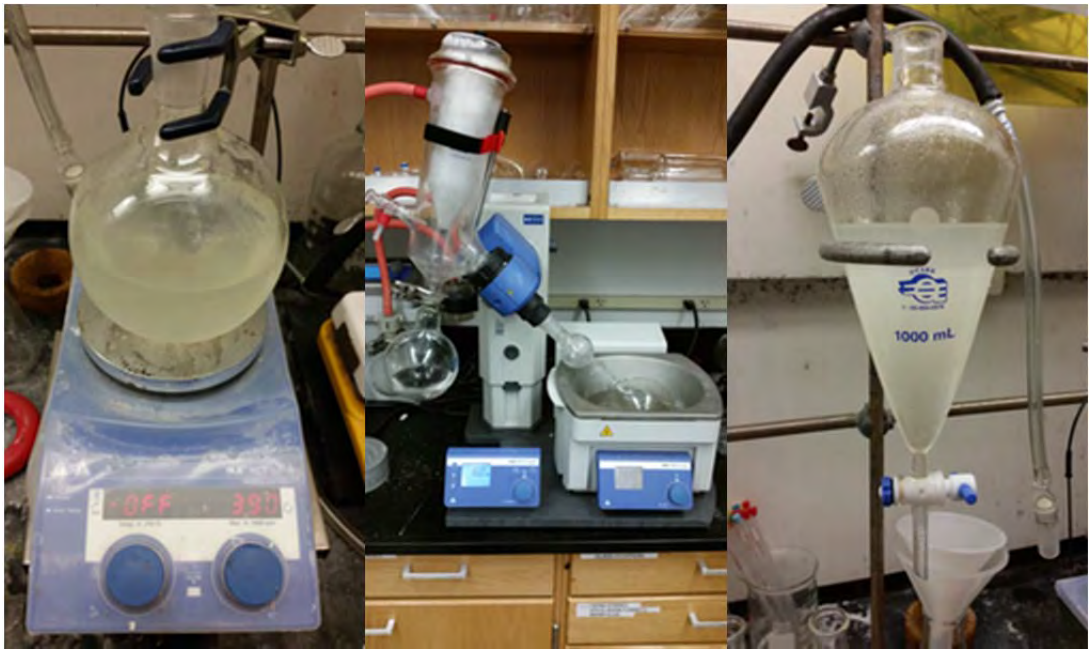


Fig. S86. Left. The reaction was quenched with sat. aq. NH_4Cl and warmed to room temperature. **Center.** The mixture was concentrated to half its volume on the rotovap. **Right.** Added CH_2Cl_2 (500 mL) and brine (100 mL), and the layers were separated.

Fig. S87. Left. The combined organic layers were dried over Na_2SO_4. **Center.** The dried, combined organic layers were passed over a short pad of silica gel. **Right.** The solvent was removed *in vacuo* to give the crude alcohol as a white solid.

Fig. S88. Left. The crude alcohol was dissolved in CH_2Cl_2. **Center.** The solution was cooled to 0 ºC in an ice-water bath. **Right.** Triethylamine was added via syringe (slow stream for addition, not dropwise).

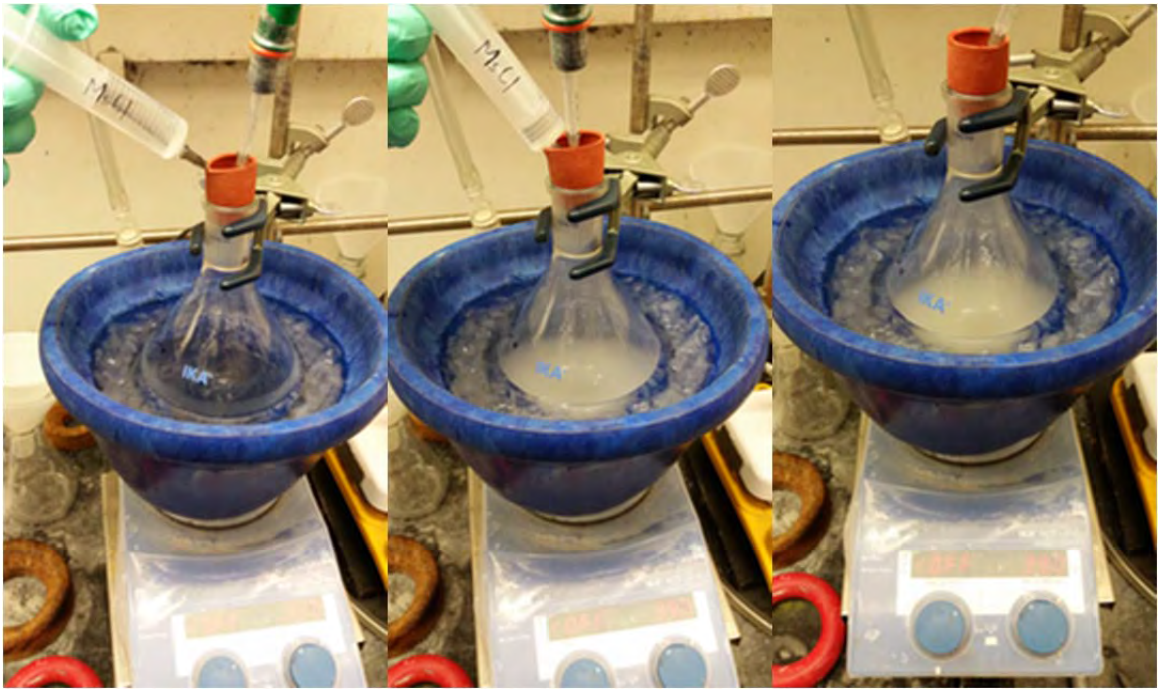


Fig. S89. Left to Right. MsCl was added slowly via syringe. The reaction became increasingly turbid over the course of the addition.

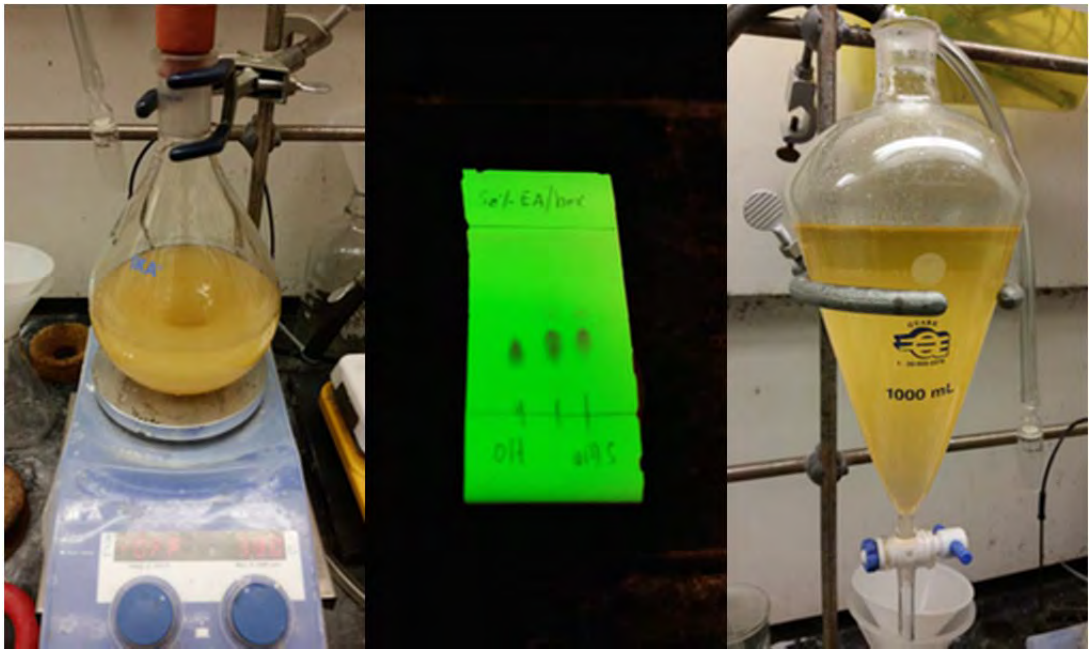


Fig. S90. Left. The reaction was allowed to warm to room temperature overnight (solution became yellow). **Center.** TLC conditions – 50% EtOAc in hexanes; left lane – crude alcohol; center lane – co-spot; right – reaction mixture. **Right.** H_2O was added to the reaction mixture, the layers separated and the organic layer dried over Na_2SO_4.

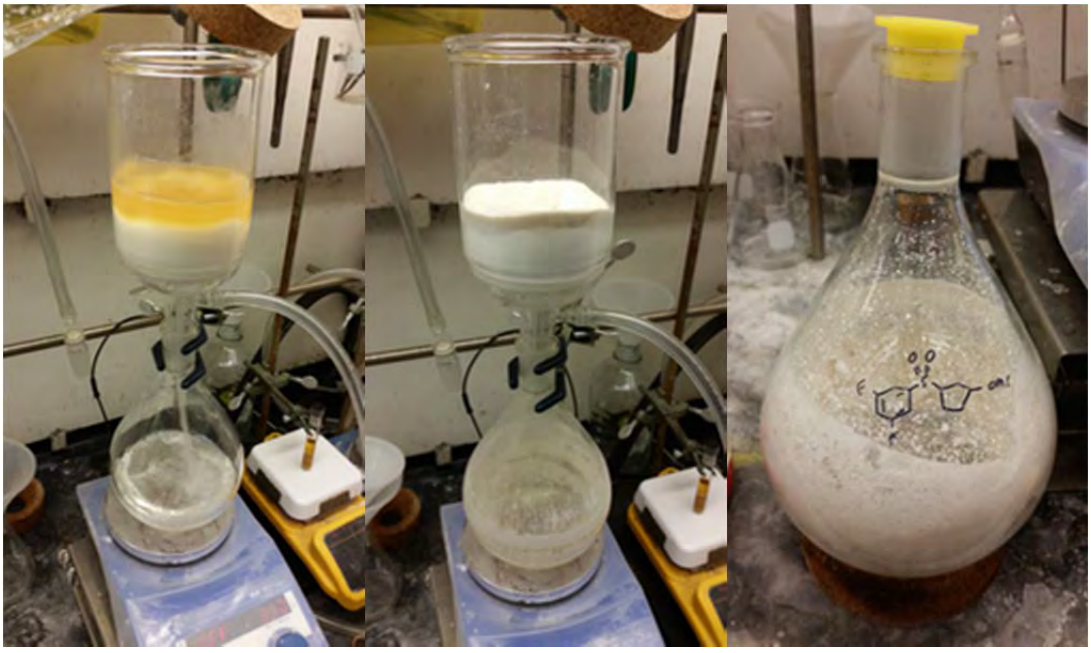


Fig. S91. Left. The dried, combined organic layers were passed over a short pad of silica gel. **Center.** The pad was washed with 15% EtOAc in CH_2Cl_2 (200 mL). **Right.** The extracts were concentrated to a white solid.

Fig. S92. Left. The crude mesylate was added to a flame-dried round bottom flask under Argon. **Center.** An ice-NaCl bath was prepared at a temperature of –20 ºC. **Right.** THF (30 mL) was added and the reaction cooled to –20 ºC.

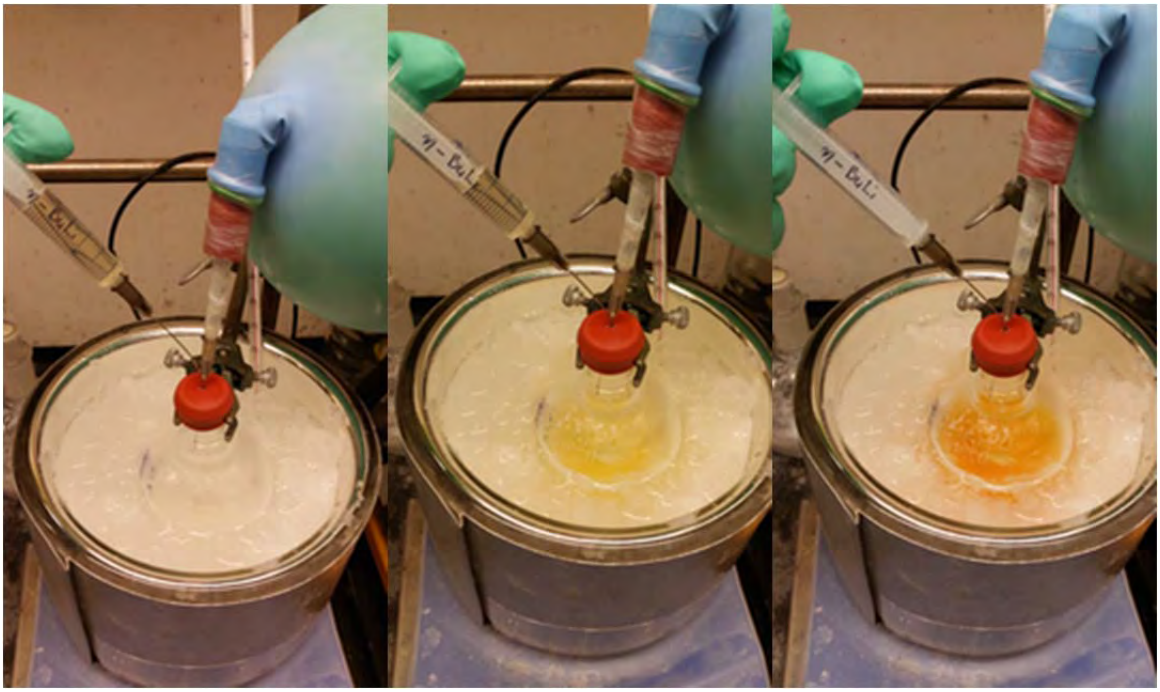


Fig. S93. Left to Right. *n*-BuLi was added quickly via syringe. The color changed from colorless to orange over the course of the addition.

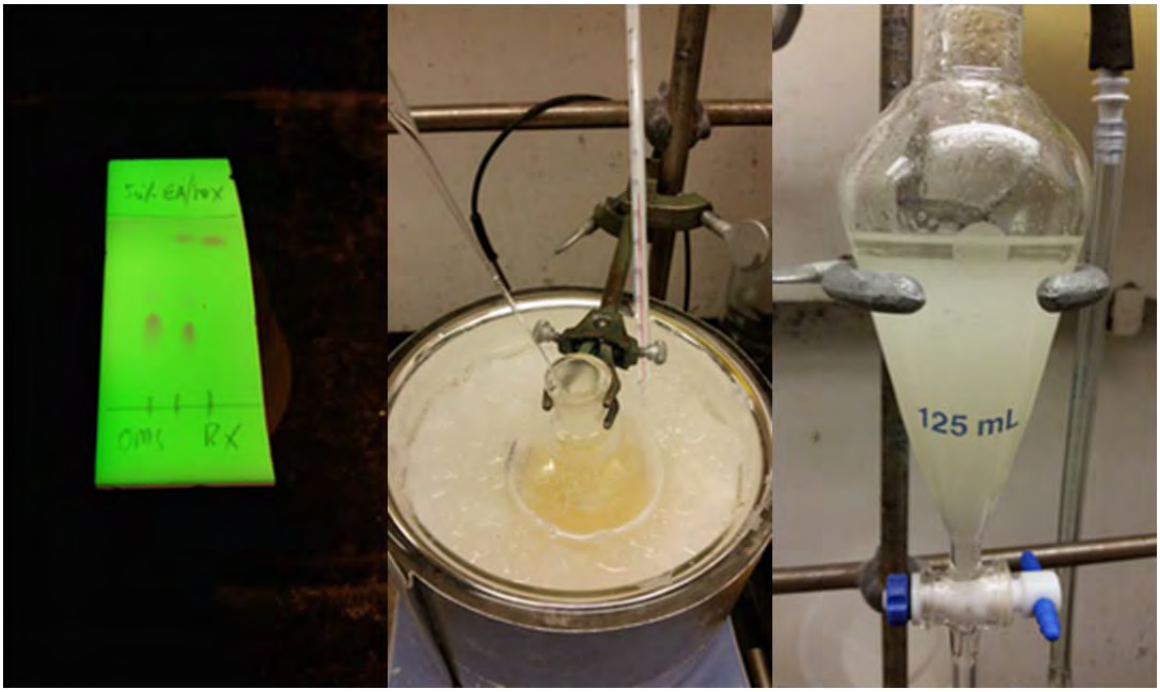


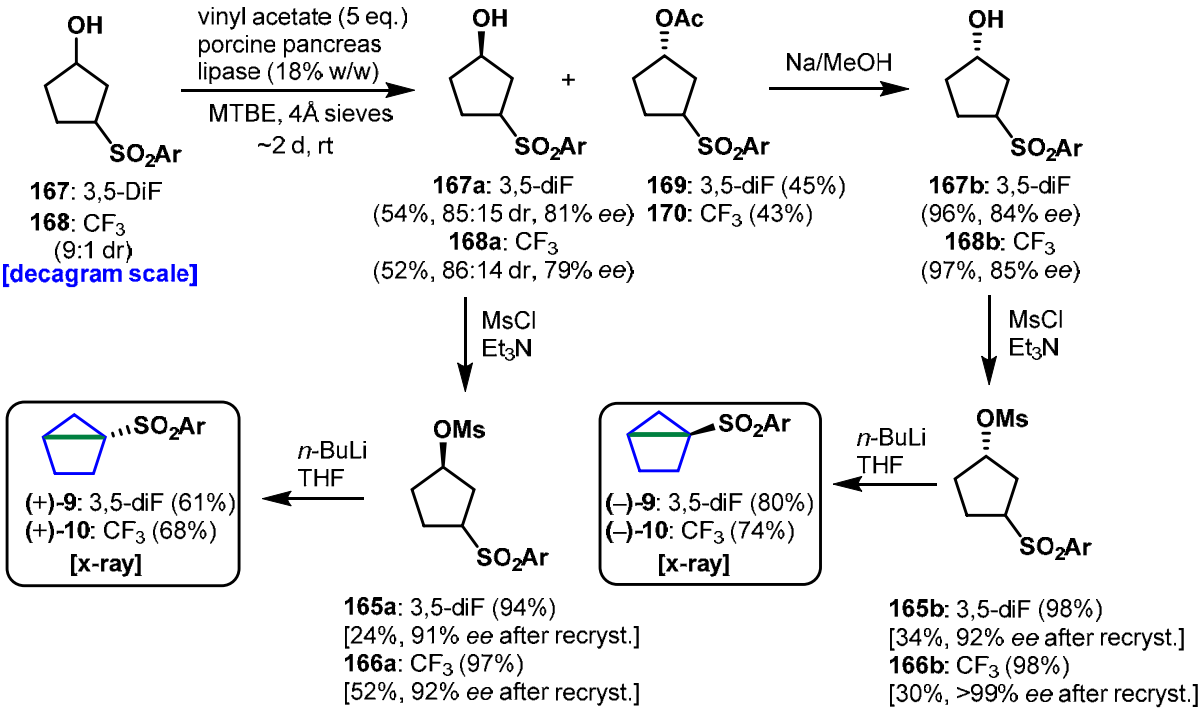
Fig. S94. Left. The reaction was complete within 5 minutes. TLC conditions – 50% EtOAc in hexanes; left lane – crude mesylate; center lane – co-spot; right – reaction mixture. **Center.** After a total of 6 minutes, the reaction was quenched with sat. aq. NH_4Cl (4 mL in one portion). **Right.** The mixture was transferred to a separatory funnel with H_2O (30 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted twice more with CH_2Cl_2 (2 x 50 mL).

Fig. S95. Left. The dried, combined organic layers were filtered and concentrated. **Center.** Crude strain-release reagent **9** as a pale yellow solid. **Right.** Purification by flash chromatography (0 to 20% EtOAc in hexanes) gave **9** as a white crystalline solid.

Asymmetric Synthesis of Strain-release Reagents 9 and 10

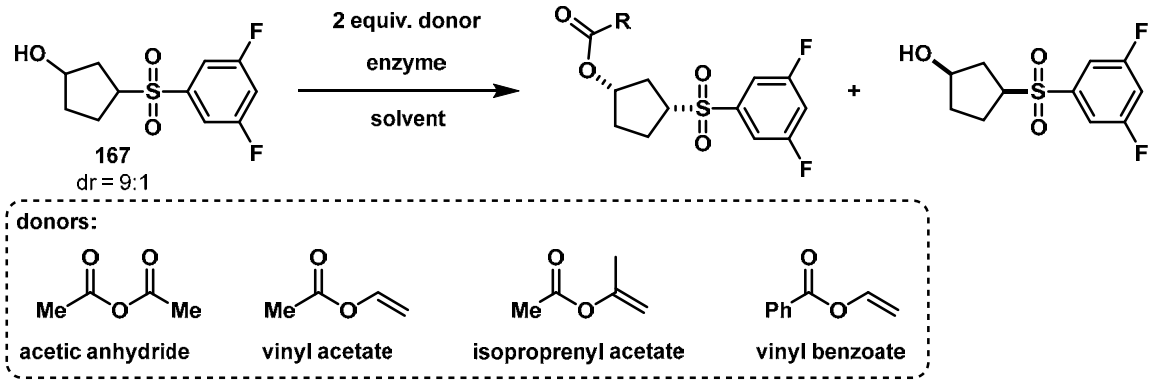
Kinetic Resolution using Lipase

The general route is outlined below:



Screening of Lipase Conditions

Initial screening and hit identification



For the initial screening, 4 different acylating agents were examined in MTBE (**1**), heptane (**2**), and toluene (**3**) using 4 different enzymes: Lipase from Porcine Pancreas (**A**), Amano Lipase from Burkholderia cepacia (**B**), Lipase from Candida rugosa (**C**) and Lipase B Candida Antarctica (**D**) at 40 °C on 0.1 mmol scale (26 mg material).

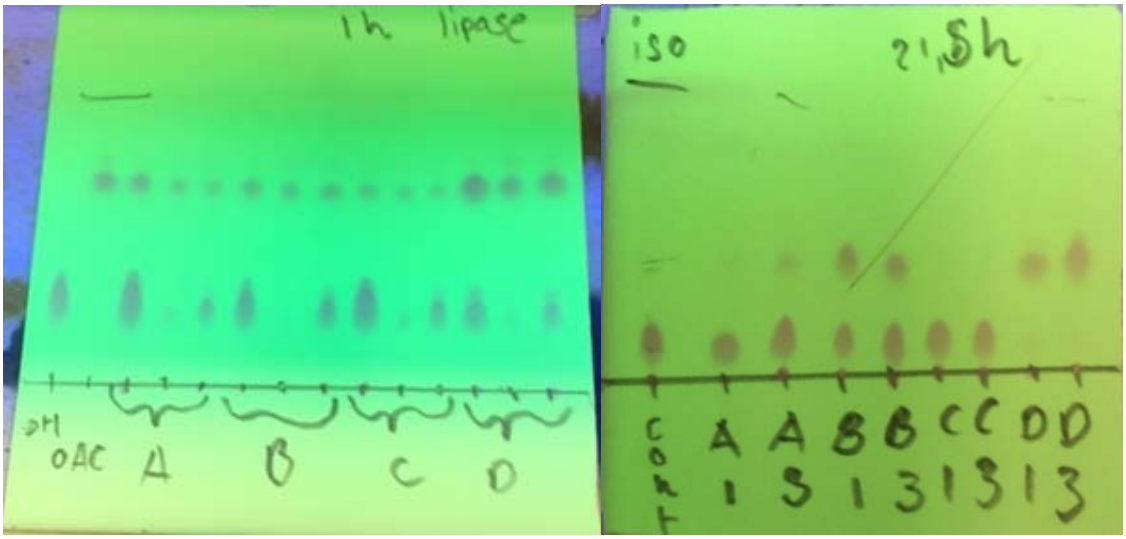


Fig. S96. Left. TLC of reactions with acetic anhydride donor after 1 h showing high conversions (eluent = 50% EtOAc in hexanes). Lanes: 1st = alcohol starting material; 2nd = acetate product; 3rd-5th = enzyme **A** in solvents **1**, **2** and **3**; 6th-8th = enzyme **B** in solvents **1**, **2** and **3**; 9th-11th = enzyme **C** in solvents **1**,**2** and **3**. 12th-14th = enzyme **D** in solvents **1**,**2** and **3**. **Right**. TLC of reactions with isoproprenyl acetate after 21.5 h (eluent = 30% EtOAc in hexanes). Lanes: 1st = control with no enzyme showing no conversion; 2nd-9th = enzymes **A**-**D** in solvent **1** or **3**.

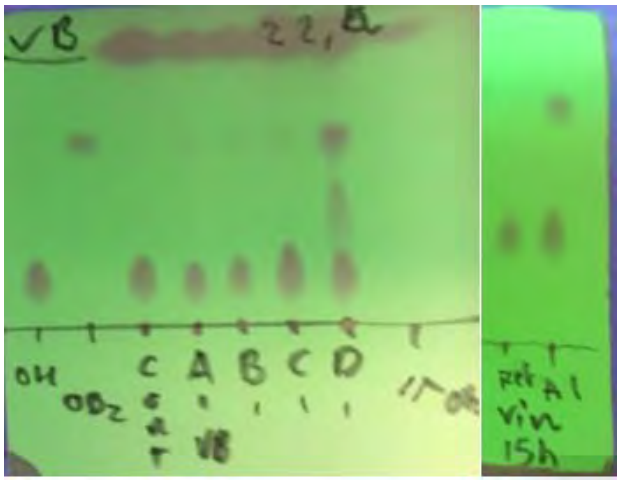


Fig. S97. Left. TLC of reactions with vinyl benzoate in solvent **1** (eluent = 30% EtOAc in hexanes). Lanes: 1st = alcohol starting material; 2nd = benzoate product; 3rd = control with no enzyme showing no conversion; 4th-7th = enzymes **A-D** in solvent **1**; 8th = vinyl benzoate reference. **Center.** TLC of reactions with vinyl acetate after 15 h: without enzyme (left lane) illustrating no background reaction at this point, and with enzyme **A** in solvent **1** – initial hit (right lane).

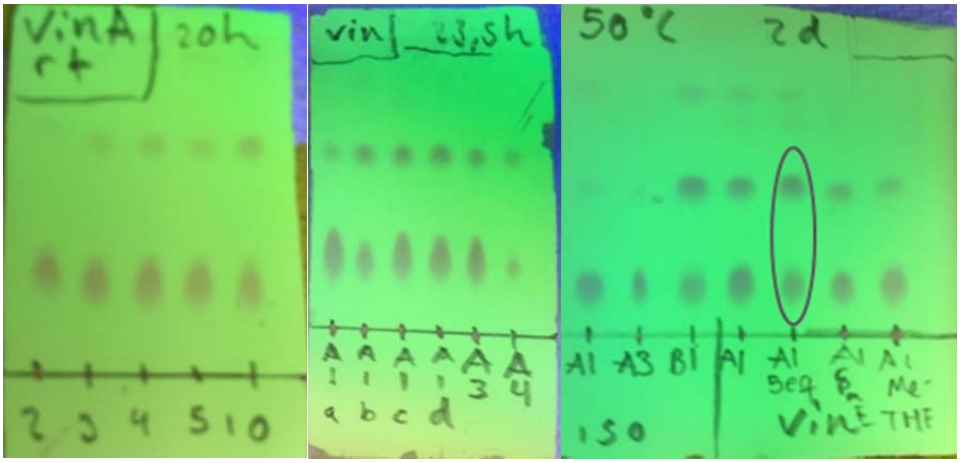


Fig. S98. Left. TLC (eluent = 50% EtOAc in hexanes) after 20 h using enzyme **A** at rt with 2, 3, 4, 5 and 10 equivalents of vinyl acetate, respectively (*left to right*). **Center.** TLC (eluent = 50% EtOAc in hexanes) after 23.5 h at 40 °C using enzyme **A**. Lanes: 1st = no mol. sieves; 2nd = 3 x amount of sieves (30 mol. sieves/0.1 mmol SM); 3rd = 2 x amount of enzyme (extra equiv. after 19 h); 4th = 2 x amount of donor (extra equiv. after 19 h); 5th = toluene as solvent; 6th = 40% MTBE in heptane (solubility issues). **Right.** Reactions after 2 d at 50 °C using isoproprenyl acetate donor (lane 1-3) or vinyl acetate (lane 4-7). Lanes: 1st = enzyme **A** in MTBE; 2nd = enzyme **A** in toluene; 3rd = enzyme **B** in MTBE; 4th = enzyme **A** in MTBE; 5th = 5 equiv. donor in MTBE with enzyme **A** (first lead); 6th = enzyme **A**, cyclopentyl methyl ether; 7th = Enzyme **A**, 2-MeTHF.

Optimization of conditions

The conversion of the lipase-mediated kinetic resolutions can be precisely monitored using ^{1}H NMR analysis of aliquots (~0.2-0.4 mL) from the crude reaction mixture. The optimization of reaction conditions was performed on 0.38 mmol scale (100 mg material).

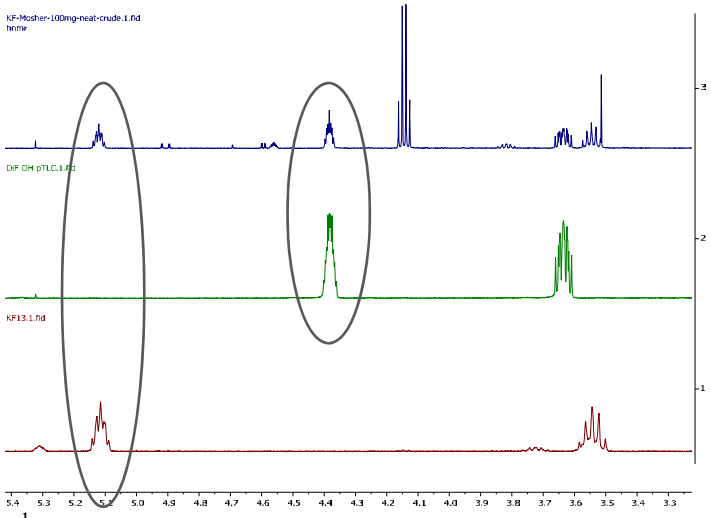


Fig. S99. Stacked ^{1}H NMR spectra (5.4 to 3.3 ppm section) of crude reaction mixture (**top**), reference starting material **167** (**middle**) and reference product **169** (**bottom**) exemplifying how the conversion can be measured.

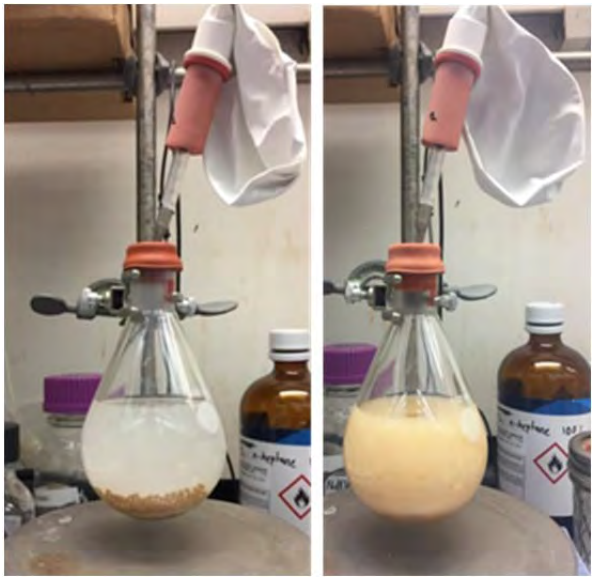


Fig. S100. Graphical presentation of kinetic resolution of 100 mg **167**.
Left. 0 h; **Right.** 48 h. The empty balloon is attached in order to accommodate potential build-up of gas.

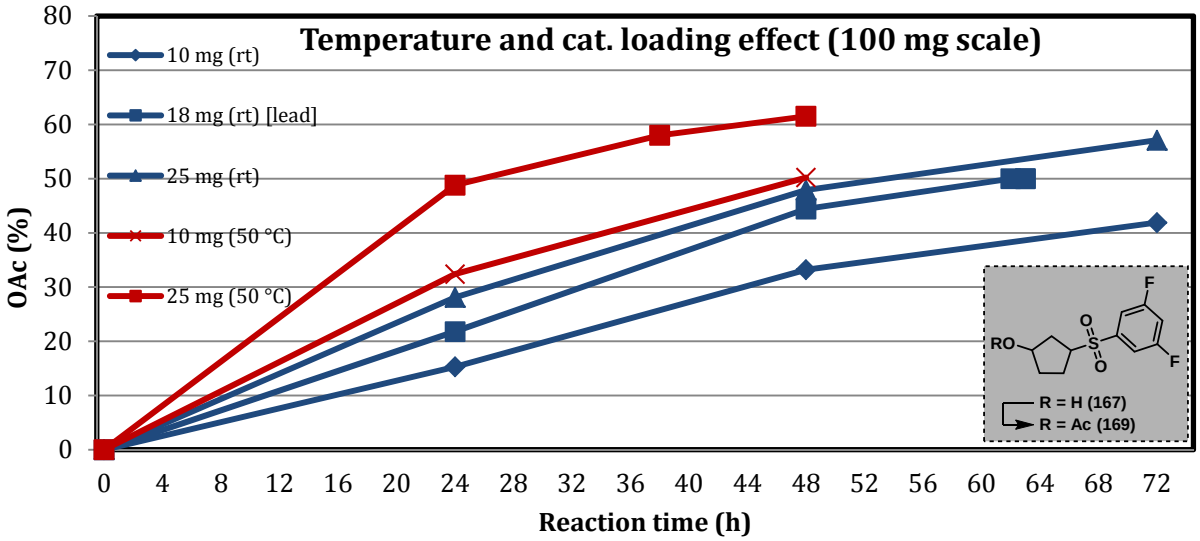


Fig. S101. Conversion plot illustrating the effect of different lipase loadings and temperatures. The conversions were determined by ^{1}H NMR analysis of the crude reaction mixtures. Enzyme loadings = 10, 18 or 25 mg at rt (blue) or 50 °C (red curve).

The most practical time and cost-efficient conditions were found with 18% w/w lipase loading, molecular sieves and 5 equiv. of vinyl acetate in MTBE at rt.

Determination of Enantiomeric Excess (*ee*)

The enantiomeric excess of resolved starting materials and acetate products were determined by chiral derivatization and subsequent ^{19}F NMR analysis.

Flow chart illustrating the process of *ee* determination:

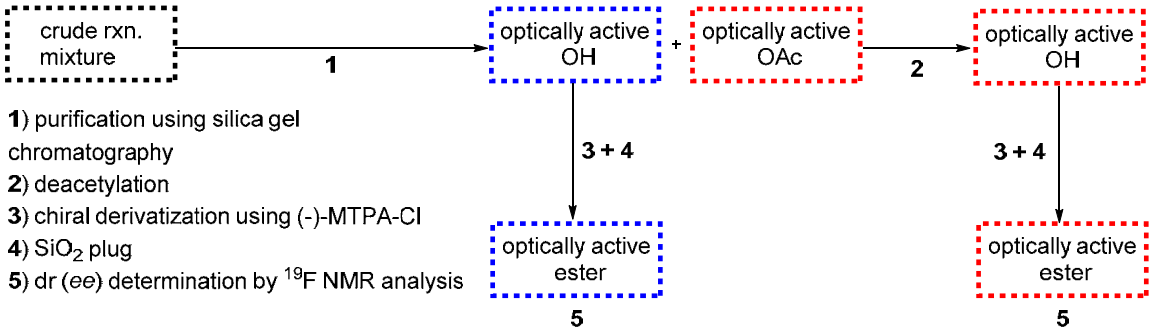


Fig. S102. Flow chart illustrating the process of *ee* determination during the screening.

^{19}F NMR Analysis of Optically Active chiral derivatives

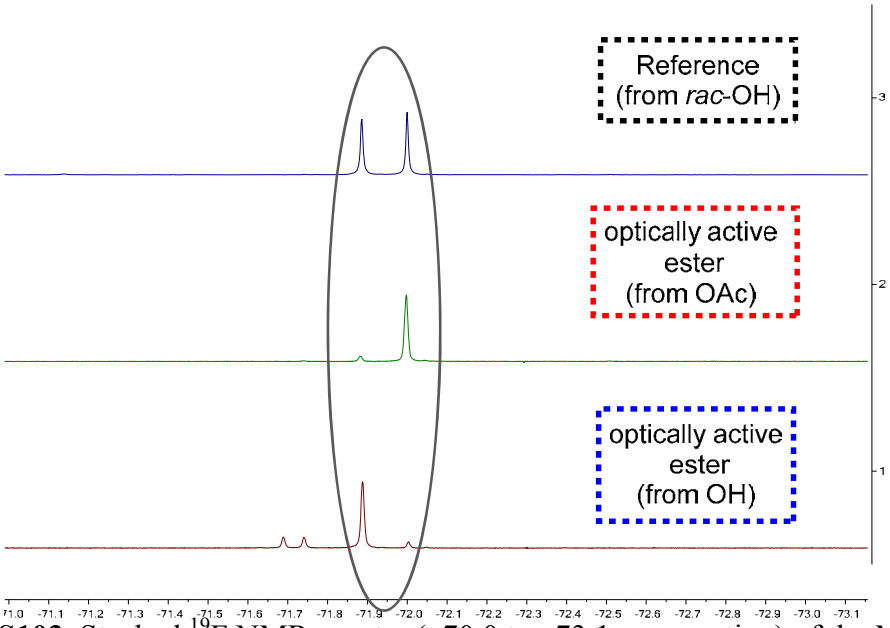


Fig. S103. Stacked ^{19}F NMR spectra (–70.0 to –73.1 ppm section) of the Mosher's derivative of **167** as reference (**top**), Mosher's derivative from **169** (**middle**) and Mosher's derivative of resolved **167a** (**bottom**) exemplifying how the *ee*'s were determined throughout the screening. The two peaks (*bottom left*) are the Mosher products of the unreacted minor diastereoisomer *trans*-**167**.

Kinetic Resolution Profiles

The final kinetic resolutions on decagram scale monitored for **167** and **168**, respectively:

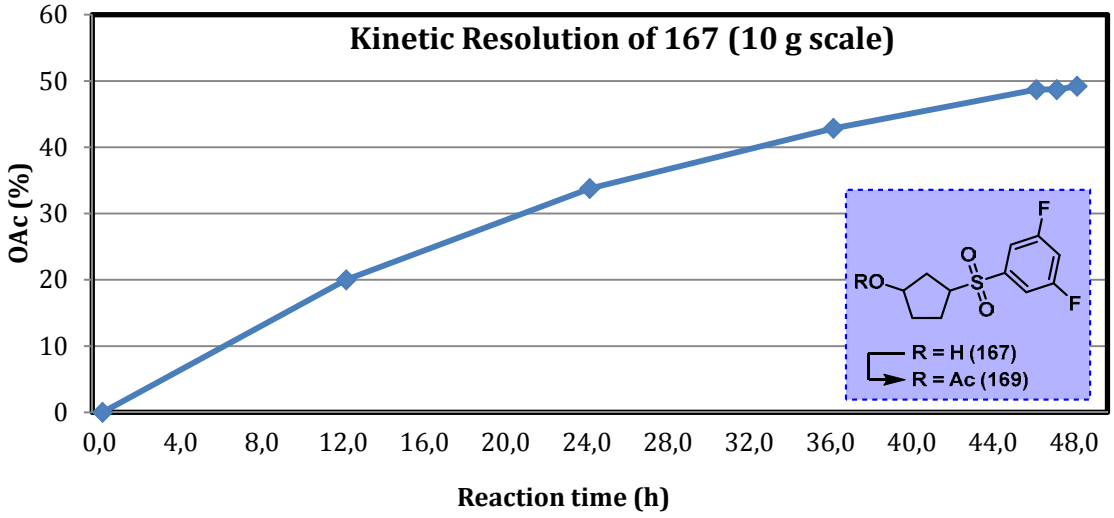


Fig. S104. Kinetic resolution plot of **167** on a 10 g scale. The conversion was measured every 12 h until around 50%.

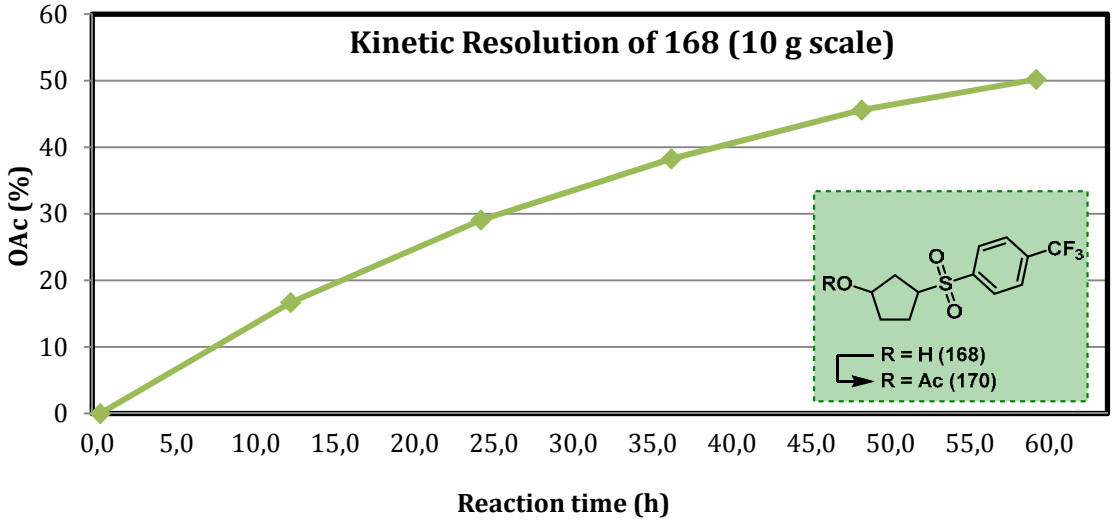
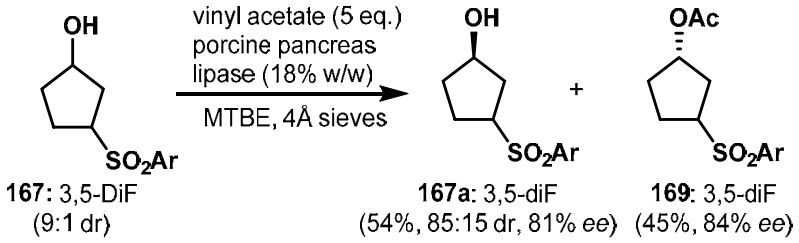


Fig. S105. Kinetic resolution plot of **168** on a 10 g scale. The conversion was measured every 12 h until around 50%.

Kinetic Resolution Procedures

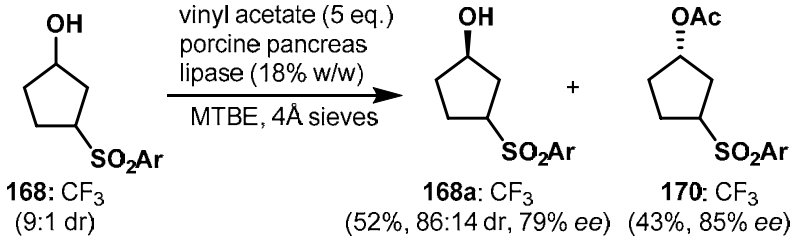
Kinetic Resolution [***Decagram scale***]**:**



LPP enzyme = Lipase from porcine pancreas *(Sigma #L3126, Lot#SLBL2143V)*

A flame-dried round-bottom flask was charged with molecular sieves (47.5 g, 4Å), **167** (10 g, 38.1 mmol) and LPP enzyme (1.80 g) after which anhydrous MTBE (800 mL) was added and the contents were stirred for 1 min followed by the addition of vinyl acetate (16.4 g, 191 mmol, 5 equiv.) by syringe. The resulting suspension was stirred at 200 rpm using a mechanical stirrer. Throughout the course of the reaction, aliquots were taken out (~0.3 mL by syringe), passed through SiO_2, dried *in vacuo* and examined by ^1H NMR to determine the conversion. After 49 h, the reaction mixture was transferred to a frit-funnel with a short plug of SiO_2 and the resolved materials passed through using EtOAc and subsequently concentrated *in vacuo* to provide a crystalizing white oil that was further purified using silica gel chromatography (30% EtOAc/hexanes, isocratic) to provide **169** (5.22 g, 17.55 mmol, 45% yield) as a colorless oil and **167a** (5.39 g, 20.55 mmol, 54% recovery, 85:15 dr, 81% *ee*) as a white solid.

Note: Characterization data for **167** and **169** can be found *vide infra*.



A flame-dried round-bottom flask was charged with molecular sieves (47.5 g, 4Å), **168** (10.0 g, 33.98 mmol) and LPP enzyme (1.80 g) after which anhydrous MTBE (800 mL) was added and the contents were stirred for 1 min followed by the addition of vinyl acetate (14.63 g, 169.9 mmol, 5 equiv.) by syringe. The resulting suspension was stirred at 200 rpm using a mechanical stirrer. Throughout the course of the reaction, aliquots were taken

out (~0.3 mL by syringe), passed through SiO_2, dried *in vacuo* and examined by ^1H NMR to determine the conversion. After 60 h, the reaction mixture was transferred to a frit-funnel with a short plug of SiO_2 and the resolved materials passed through using EtOAc and subsequently concentrated *in vacuo* to provide a crystalizing white oil that was further purified using silica gel chromatography (30% EtOAc/hexanes, isocratic) to provide **170** (4.93 g, 14.66 mmol, 43% yield) as a colorless oil and **168a** (5.23 g, 17.77 mmol, 52% recovery, 86:14 dr, 79% *ee*) as a white solid.

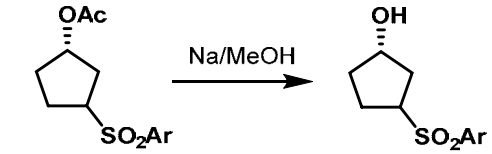
Note: Characterization data for **168** and **170** can be found *vide infra*.

Kinetic Resolution of 167 (1 g scale):

A flame-dried glass container was charged with molecular sieves (4.75 g, 4Å), **167** (1.00 g, 3.81 mmol), LPP enzyme (180 mg) and a stir bar after which anhydrous MTBE (80 mL) was added and the glass-container sealed. The contents were stirred for 1 min followed by the addition of vinyl acetate (1.64 g, 19.1 mmol, 5 equiv.) by syringe and the resulting suspension was stirred at 1200 rpm. Throughout the course of the reaction, aliquots were taken out (~0.3 mL by syringe), passed through SiO_2, dried *in vacuo* and examined by ^1H NMR to determine the conversion. After 53.5 h, the reaction mixture was transferred to a frit-funnel with a short plug of SiO_2 and the resolved materials passed through using EtOAc and subsequently concentrated *in vacuo* to provide a crystalizing white oil that was further purified using silica gel chromatography (30% EtOAc/hexanes, isocratic) to provide **169** (545 mg, 1.79 mmol, 47% yield) as a colorless oil and **167a** (483 mg, 1.84 mmol, 48% yield) as a white solid.

Note: characterization data for **167** and **169** can be found *vide infra*.

Deacetylation of 169:



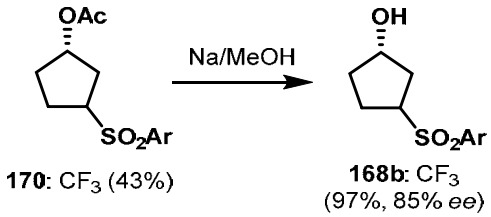
169: 3,5-diF (45%)

167b: 3,5-diF (96%, 84% *ee*)

To a flask containing **169** (5.22 g, 17.55 mmol) was added dry MeOH (60 mL) and a piece of Na (s) (~120 mg, 0.3 equiv.). The contents were stirred for 30 min after which half sat. aq. NH_4Cl and CH_2Cl_2 were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 three times and the combined organic extracts were dried over

Na_2SO_4, decanted and concentrated *in vacuo* to provide **167b** (4.3 g, 16.40 mmol, 96% yield, >99:1 dr, 84% *ee*)

Deacetylation of 170:

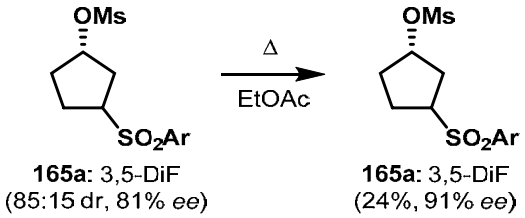


To a flask containing **170** (4.93 g, 14.66 mmol) was added dry MeOH (60 mL) and a piece of Na (s) (~100 mg, 0.3 equiv.). The contents were stirred for 30 min after which half sat. aq. NH_4Cl and CH_2Cl_2 were added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 three times and the combined organic extracts were dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide **168b** (4.2 g, 14.27 mmol, 97% yield, >99:1 dr, 85% *ee*)

Chiral Derivatization using Mosher's Acid Chloride:

To a flame-dried vial containing the alcohol (~5 mg of **167** or **168**) was added MTPA-Cl (0.1 mmol, 1 mL, 0.1M in $CDCl_3$) from a freshly prepared stock solution[69] followed by a drop of triethylamine and a small crystal of DMAP. The reaction mixture was stirred for 1 h at rt until TLC indicated full conversion of the alcohol after which the crude reaction mixture was passed through a plug of SiO_2, concentrated *in vacuo* and directly analyzed using ^{19}F NMR.

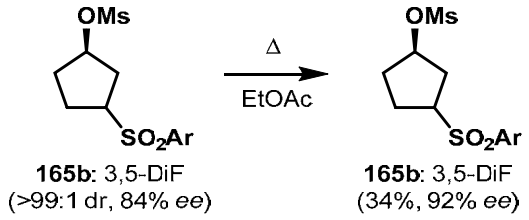
Enantioenrichment of 165a by Recrystallization [*Mother Liquor*]:



To a round-bottom flask containing **165a** (13.3 g, 33.22 mmol, 85:15 dr, 81% *ee*) was added EtOAc (~130 mL) and the stirred suspension was heated with a heat gun until the solution became clear and all material was dissolved. The flask was sealed with a rubber

septum and placed at rt for 1 h during which no crystallization occurred. The sealed flask still containing the stirbar (**important**) was then placed at -20 °C overnight after which the crystals were collected by filtration (**has to be done cold!)** and kept for further recrystallization. The remaining crystals were then suspended in EtOAc (10 mL/1 g of **165a**), the suspension brought to the boiling point using a heat gun, cooled to rt and placed at –20°C overnight while crystallization occurred. The mother liquor was combined with the mother liquor from the first recrystallization and the solvent subsequently removed *in vacuo* to provide a white powder that was purified using silica gel chromatography to provide **165a** (2.72 g, 24% yield, 91% *ee*) as a white powder.

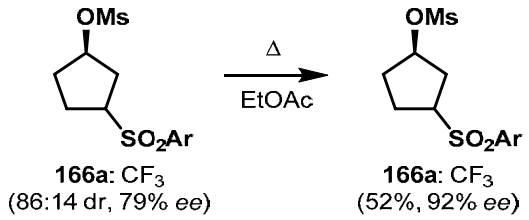
Enantioenrichment of 165b by Recrystallization [*Mother Liquor*]:



165b: 3,5-DiF (>99:1 dr, 84% *ee*) → **165b**: 3,5-DiF (34%, 92% *ee*)

To a round-bottom flask containing **165b** (10.4 g, 30.56 mmol 84% *ee*) was added EtOAc (~100 mL) and the stirred suspension was heated with a heat gun until the solution became clear and all material was dissolved. The flask was sealed with a rubber septum and placed at rt for 1 h during which no crystallization occurred. The sealed flask still containing the stirbar (**important**) was then placed at -20 °C overnight after which the crystals were collected by filtration (**has to be done cold!)** and kept for further recrystallization. The remaining crystals were then suspended in EtOAc (10 mL/1 g of **165b**), the suspension brought to the boiling point using a heat gun, cooled to rt and placed at –20°C overnight while crystallization occurred (the recrystallization was done a total of 3 times). The 3 mother liquors were analyzed using chiral HPLC and combined. Subsequent removal of volatiles provided **165b** (3.56 g, 34% yield, 92% *ee*) as a white powder.

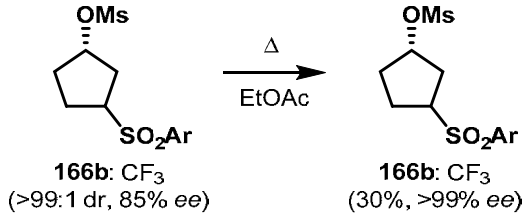
Enantioenrichment of 166a by Recrystallization [*Crystals*]:



166a: CF_3 (86:14 dr, 79% *ee*) → **166a**: CF_3 (52%, 92% *ee*)

To a round-bottom flask containing **166a** (6.3 g, 16.92 mmol, 86:14 dr, 79% *ee*) was added EtOAc (~40 mL) and the stirred suspension was heated with a heat gun until the solution became clear and all material was dissolved. The flask was sealed with a rubber septum and placed at rt for 1 h during which no crystallization occurred. The sealed flask still containing the stirbar (**important**) was placed at -20 °C overnight after which the crystals were collected by filtration and gently triturated with MTBE. The mother liquor was concentrated *in vacuo* and suspended in EtOAc (6 mL/1 g of **166a**), the suspension brought to the boiling point using a heat gun, cooled to rt and placed at –20°C overnight while crystallization occurred. The crystals were collected by filtration, triturated with MTBE and analyzed using chiral HPLC (the recrystallization was done a total of 3 times). The 3 crops were combined to provide **166a** (3.26g, 52% yield, 92% *ee*).

Enantioenrichment of 166b by Recrystallization [*Crystals*]:



166b: CF_3 (>99:1 dr, 85% *ee*) → **166b**: CF_3 (30%, >99% *ee*)

To a round-bottom flask containing **166b** (4.17 g, 14.17 mmol, 85% *ee*) was added EtOAc (~25 mL) and the stirred suspension was heated with a heat gun until the solution became clear and all material was dissolved. The flask was sealed with a rubber septum and placed at rt for 1 h during which no crystallization occurred. The sealed flask still containing the stirbar (**important**) was placed at -20 °C overnight after which the crystals were collected by filtration and gently triturated with MTBE. The mother liquor was concentrated *in vacuo* and suspended in EtOAc (6 mL/1 g of **166b**), the suspension brought to the boiling point using a heat gun, cooled to rt and placed at –20°C overnight while crystallization occurred. The crystals were collected by filtration, triturated with MTBE and analyzed using chiral HPLC (the recrystallization was done a total of 3 times). The 3 crops were combined to provide **166b** (1.56g, 30% yield, >99% *ee*).

Graphical Preparation of Kinetically Resolved Strain-Release Intermediates

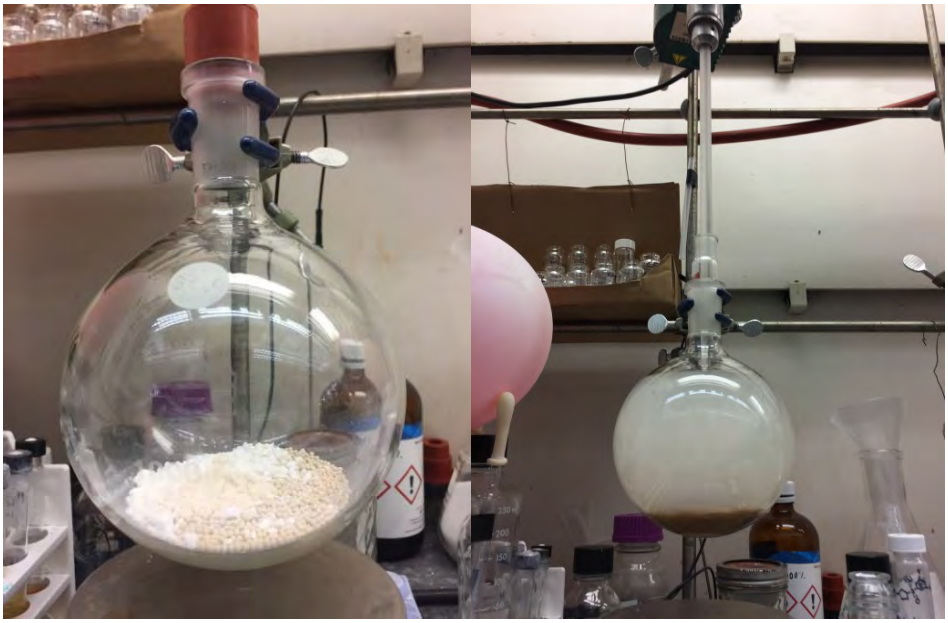


Fig. S106. Left. Addition of **167** (10 g), lipase, and molecular sieves in an oven-dried round-bottom flask. **Right.** Addition of MTBE (800 mL) and attachment of mechanical stirrer

Fig. S107. Left. Addition of vinyl acetate by syringe. Teflon tape is wrapped around the flask's neck to suppress solvent evaporation. **Right.** The reaction mixture after 12 h stirring.

Fig. S108. Left. The reaction is stopped by passing the reaction mixture through a short plug of SiO_2 on a frit funnel. Additional EtOAc is added to pull material through the plug. Subsequently, all volatiles including excess vinyl acetate are removed on a rotary evaporator. **Right.** Concentrated reaction mixture after filtration.

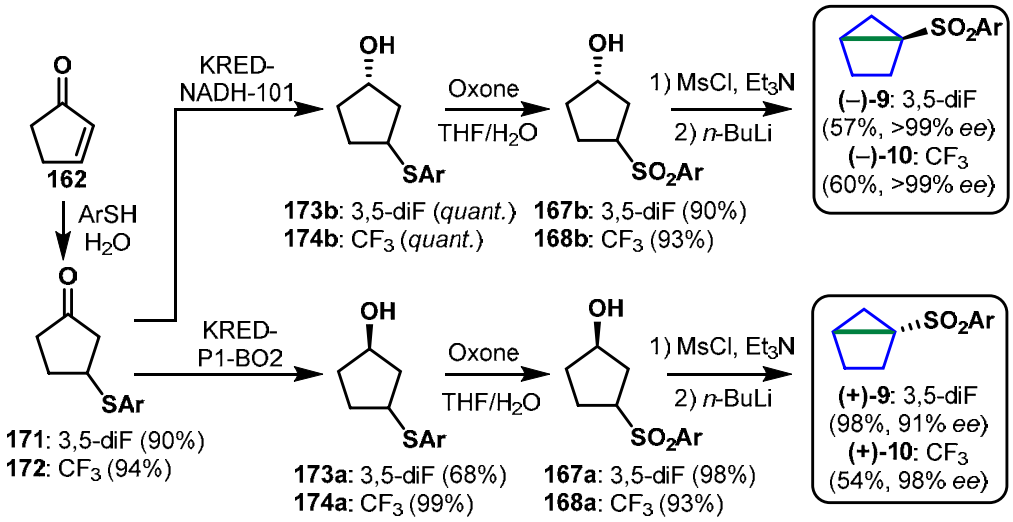
Fig. S109. Left. The alcohol **167a** and acetate **169** were readily separated using silica gel chromatography. The acetate is then directly dissolved in MeOH and deacetylated using Na(s). **Right.** The resolved alcohol starting material (*left vial*) and deacetylated product after aqueous work-up (*right vial*).

Fig. S110. Left. After mesylation, **165b** is boiled in EtOAc and allowed to reach ambient temperature followed by -20 °C. **Right.** Crystallization happened at -20 °C leading to enantioenrichment in the mother liquor.

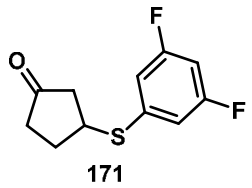
Fig. S111. Left. The cold (-20 °C) reaction mixture is filtered. **Center.** Crystals isolated by filtration, which can be recrystallized again. **Right**. Concentrated enantioenriched mother liquor (92% *ee*).

Enantiodivergent Synthesis using Ketoreductases

An overview of the ketoreductase-mediated asymmetric synthesis of housane **9** and **10** is presented below.



Procedures Toward the 3,5-Difluorophenylsulfone Reagents (+)-9 and (–)-9:



171

3-((3,5-difluorophenyl)thio)cyclopentan-1-one (171)

To a stirred solution of 3,5-difluorobenzenethiol (8.77 g, 60.0 mmol) in H_2O (120 mL) was added cyclopent-2-en-1-one (7.39 g, 90.0 mmol) at rt and the resulting biphasic mixture was stirred overnight. The mixture was diluted with brine (200 mL), the phases separated and the aqueous phase extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a clear oil that was purified using silica gel chromatography affording **171** in 90% yield.

Physical State: clear oil;

$\boldsymbol{R_f}$ = 0.4 (20% EtOAc in hexanes, vis. UV);

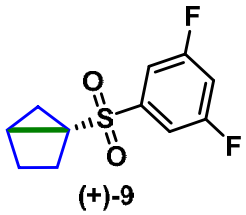
^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.19 - 7.00 (m, 3H), 4.22 (q, *J* = 6.5 Hz, 1H), 2.77 (dd, *J* = 18.2, 7.2 Hz, 1H), 2.45 - 2.36 (m, 1H), 2.34 - 2.19 (m, 2H), 2.13 (dd, *J* = 18.2, 6.4 Hz, 1H), 1.95 - 1.83 (m, 1H);

^{13}C NMR (101 MHz, DMSO-*d6*): δ 215.0 163.0 (dd, *J* = 248, 14.0 Hz), 140.6 (t, *J* = 10.3 Hz), 111.6 (q, *J* = 9.0 Hz), 102.0 (t, *J* = 26.0 Hz), 45.02, 41.5, 36.9, 29.1;

^{19}F NMR (376 MHz, DMSO-*d6*): δ -109.1;

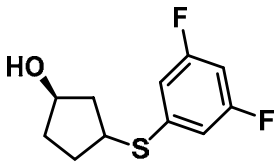
HRMS (ESI-TOF): calc'd for $C_{11}H_{10}F_2OS$ [M^+] 228.0414; found 228.0420.

Synthesis of (+)-9:



(+)-9

(1*S*,4*S*)-1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane ((+)-9)
Synthesized in **37%** overall yield and **91%** ***ee*** from 3,5-difluorobenzenethiol and **162**.



173a

(1*R*)-3-((3,5-difluorophenyl)thio)cyclopentan-1-ol (173a)
In a 100 mL glass vessel with overhead stirring was added **171** (11.4 g, 50 mmol) followed by KRED Recycle Mix N from Codexis (sodium phosphate (250 mM), magnesium sulfate (2 mM), NADP+ (1.1 mM), NAD+ (1.1 mM), *D*-glucose (80 mM), glucose dehydrogenase (10 U/mL, pH 7.0)) and sodium phosphate tribasic (2.05 g, 12.5 mmol) in H_2O (100 mL). To this mixture was then added *D*-glucose (22.5 g, 125 mmol) and KRED-P1-BO2 (200 mg, 0.768 mmol) followed by NAD+ (250.0 mg, 0.377 mmol) and stirring was initiated. The pH automation controller (NaOH (1M)) was set to 7, the vessel sealed and the temperature brought to 38 °C. Stirring was continued for 18 h after which an aliquot (0.1 mL) was taken and diluted with MeCN (0.4 mL) + MeOH (0.2 mL) for SFC/MS analysis which indicated complete conversion of the starting material to product. The aqueous mixture was extracted with EtOAc (500 mL). The layers were separated and the organic layer was diluted with brine (500 mL) and split into four portions. Each portion was diluted with EtOAc (500 mL) and the emulsions were allowed to separate into two phases and all of the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated which gave **173a** in 68% yield.

Physical State: colorless oil;

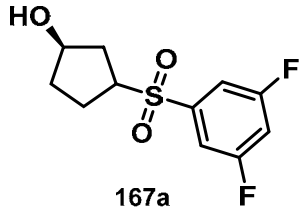
^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.07 - 6.94 (m, 3 H), 4.66 (d, *J* = 4.0 Hz, 1H, distinct diastereoisomer), 4.62 (d, *J* = 3.8 Hz, 1H, distinct diastereoisomer), 4.25 - 4.21 (m, 1H, distinct diastereoisomer), 4.17 - 4.11 (m, 1H, distinct diastereoisomer), 3.99 - 3.89 (m, distinct diastereoisomer), 3.76 - 3.69 (m, 1H, distinct diastereoisomer), 2.46 - 2.36 (m, 1H,

distinct diastereoisomer), 2.34 - 2.21 (m, 1H, distinct diastereoisomer), 2.14 - 2.00 (m, 1H), 1.94 - 1.81 (m, 1H, distinct diastereoisomer), 1.77 - 1.44 (m, 3H), 1.43 - 1.34 (m, 1H, distinct diastereoisomer), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (101 MHz, DMSO-*d6*) δ 162.5 (dd, *J* = 247.5, 13.9 Hz), 142.2 (2 x t, *J* = 10.1 Hz, diastereoisomers), 110.5 – 109.7 (m, mixture of diastereoisomers) 100.7 (2 x t, *J* = 25.0 Hz, diastereoisomers), 70.9, 70.8, 42.2, 42.0, 41.8, 41.2, 34.4, 34.0, 31.0, 30.7;

^{19}F NMR (376 MHz, DMSO-*d6*): δ -109.5, -109.3;

HRMS (ESI-TOF): calc'd for $C_{11}H_{12}F_2OS$ 230.0573; found 230.0577.



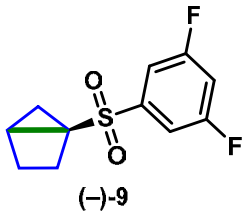
167a

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-ol (167a):
To a solution of **173a** (8.7 g, 37.8 mmol) in a 1:1 mixture of THF and water (126 mL) was added Oxone (32.5 g, 52.9 mmol) and the reaction mixture was stirred at rt for 1 h. Subsequently, the reaction mixture was concentrated *in vacuo* followed by the addition of H_2O (180 mL) and EtOAc (220 mL). The phases were separated, the aqueous phase extracted with EtOAc (2 x 220 mL), the organic phases combined and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* followed by silica gel chromatography to provide **167a** in 98% yield.

Note: The characterization data for the title compound can be found *vide supra*.

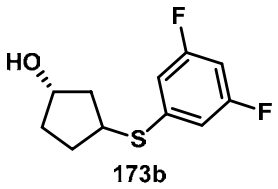
The alcohol (**167a**) subsequently underwent mesylation and ring-closure using the procedures described for the synthesis of racemic reagent **9** (*vide supra*).

Synthesis of (–)-9:



(–)-9

(1*R*,4*R*)-1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane ((–)-9)
Synthesized in **46%** overall yield in **>99.5%** ***ee*** from 3,5-difluorobenzenethiol and **162**.

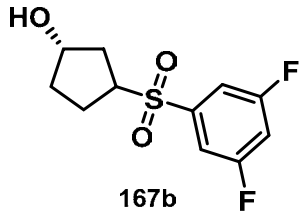


173b

(1*S*)-3-((3,5-difluorophenyl)thio)cyclopentan-1-ol (173b):
In a 100 mL glass vessel with overhead stirring was added **171** (1.14 g, 5 mmol) followed by KRED Recycle Mix N from Codexis (sodium phosphate (250 mM), magnesium sulfate (2 mM), NADP+ (1.1 mM), NAD+ (1.1 mM), *D*-glucose (80 mM), glucose dehydrogenase (10 U/mL, pH 7.0)) and sodium phosphate tribasic (1 g, 6.2 mmol) in H_2O (50 mL). To this mixture was then added *D*-glucose (2.25 g, 12.5 mmol) and KRED-NADH-101 (104 mg, 0.400 mmol) followed by NAD+ (49.8 mg, 0.075 mmol) and stirring was initiated. The pH automation controller (NaOH (1M)) was set to 7, the vessel sealed and the temperature brought to 38 °C. Stirring was continued for 18 h after which an aliquot (0.1 mL) was taken and diluted with MeCN (0.4 mL) + MeOH (0.2 mL) for SFC/MS analysis which indicated complete conversion of the starting material to product. The aqueous mixture was then extracted with EtOAc (2 x 75 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **173b** in quantitative yield.

Note: The characterization data for the title compound matches that provided for **173a**.

Physical State: clear oil;



167b

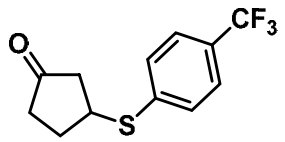
(1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-ol (167b)

To a solution of **173b** (885 mg, 3.84 mmol) in a 1:1 mixture of THF and water (12.8 mL) was added Oxone (2.84 g, 4.61 mmol) and the reaction mixture was stirred at rt for 2 h. Subsequently, the reaction mixture was concentrated *in vacuo* followed by the addition of H_2O (60 mL) and EtOAc (50 mL). The phases were separated, the aqueous phase extracted with EtOAc (2 x 50 mL), the organic phases combined and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* followed by silica gel chromatography to provide **167b** in 90% yield.

Note: The characterization data for the title compound matches that provided for **167**.

The alcohol (**167b**) subsequently underwent mesylation and ring-closure using the procedures described for the synthesis of racemic reagent **9** (*vide supra*).

Procedures Toward the (4-Trifluoromethyl)phenylsulfone Reagents (+)-10 and (–)-10:



172

3-((4-(trifluoromethyl)phenyl)thio)cyclopentan-1-one (172)

To a stirred solution of 4-(trifluoromethyl)benzenethiol (5.00 g, 28.06 mmol) in H_2O (56 mL) was added **162** (3.46 g, 42.1 mmol) at rt and the resulting biphasic mixture was stirred for 18.5 h followed by the addition of additional cyclo-pent-2-en-1-one (0.5 mL). Stirring was continued for 23 h after which the mixture was diluted with brine (50 mL), the phases separated and the aqueous phase extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a clear oil that was purified using silica gel chromatography affording **172** in 94% yield.

Note: the above reaction was also performed on decagram scale affording **172** in 82% yield (12 g).

Physical State: clear oil;

R_f = 0.4 (20% EtOAc in hexanes, vis. UV);

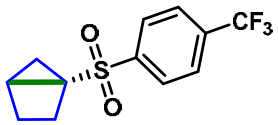
^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 4.20 - 4.26 (m, 1H), 2.79 (dd, *J* = 18.2, 7.3 Hz, 1H), 2.39 - 2.48 (m, 1H), 2.21 - 2.38 (m, 2H), 2.15 (dd, *J* = 18.2, 6.5 Hz, 1H), 1.84 - 1.99 (m, 1H).

^{13}C NMR (101 MHz, DMSO-*d6*): δ 253.0, 179.2, 165.9, 163.5 (q, *J* = 32.7 Hz), 163.4 (q, *J* = 3.8 Hz), 160.5, 82.2, 78.3, 74.0, 66.3.

^{19}F NMR (376 MHz, DMSO-*d6*): δ -60.9.

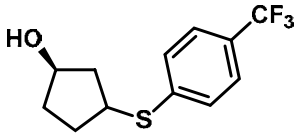
HRMS (ESI-TOF): calc'd for $C_{12}H_{11}F_3OS$ 260.0483; found 260.0483.

Synthesis of (+)-10:



(+)-10

(1*S*,4*S*)-1-((4-(trifluoromethyl)phenyl)sulfonyl)bicyclo[2.1.0]pentanepentane ((+)-10)
Synthesized in **47%** overall yield with **98%** ***ee*** from 4-(trifluoromethyl)benzenethiol and **162**.



174a

(1*R*)-3-((4-(trifluoromethyl)phenyl)thio)cyclopentan-1-ol (174a)
In a 100 mL glass vessel with overhead stirring was added **172** (1.3 g, 5 mmol) followed by KRED Recycle Mix N from Codexis (sodium phosphate (250 mM), magnesium sulfate (2 mM), NADP+ (1.1 mM), NAD+ (1.1 mM), *D*-glucose (80 mM), glucose dehydrogenase (10 U/mL, pH 7.0)) and sodium phosphate tribasic (1.0 g, 6.2 mmol) in H_2O (100 mL). To this mixture was then added *D*-glucose (2.25 g, 12.5 mmol) and KRED-P1-BO2 (50 mg, 0.19 mmol) followed by NAD+ (50.0 mg) and stirring was initiated. The pH automation controller (NaOH (1M)) was set to 7, the vessel sealed and the temperature brought to 38 °C. Stirring was continued for 18 h after which an aliquot (0.1 mL) was taken and diluted with MeCN (0.4 mL) + MeOH (0.2 mL) for SFC/MS analysis which indicated complete conversion of the starting material to product. The aqueous mixture was filtered. The semi-solid from the filter paper could not be removed. The filter paper was washed with EtOAc and the aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic extracts and the filter paper were washed with brine, dried over $MgSO_4$, filtered and concentrated to give **174a** in 99% yield.

Physical State: clear oil;

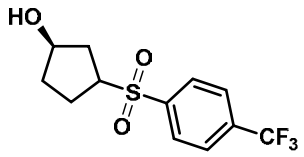
1H NMR (400 MHz, DMSO-*d6*): δ 7.64 - 7.60 (m, 2H), 7.48 - 7.46 (m, 2H), 4.67 (d, *J* = 4.0 Hz, 1H, distinct diastereoisomer), 4.63 (d, *J* = 3.7 Hz, 1H, distinct diastereoisomer), 4.28 - 4.19 (m, 1H, distinct diastereoisomer), 4.19 - 4.08 (m, 1H, distinct diastereoisomer), 3.99 - 3.91 (m, 1H, distinct diastereoisomer), 3.76 - 3.69 (m, 1H, distinct diastereoisomer), 2.47 - 2.38 (m, 1H, distinct diastereoisomer), 2.37 - 2.23 (m, 1H, distinct diastereoisomer), 2.17 - 2.0 (m, 1 H), 1.82 - 1.95 (m, 1H, distinct diastereoisomer), 1.79 - 1.34 (m, 4H, 1H

from distinct diastereoisomer), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (101 MHz, DMSO-*d6*): δ 143.6 (2 x q, *J* = 1.4 Hz, diastereoisomers), 127.4, 127.1, 125.7 – 124.6 (m, 2 x 2C, diastereoisomers), 123.1 – 122.8 (m, 2C, diastereoisomers) 70.9 (2C), 42.4, 42.1, 41.4, 41.0, 34.4, 34.0, 31.1, 30.9.

^{19}F NMR (376 MHz, DMSO-*d6*): δ -60.7, -60.8;

HRMS (ESI-TOF): calc'd for $C_{12}H_{13}F_3OS$ [M+] 262.0629; found 262.0639.



168a

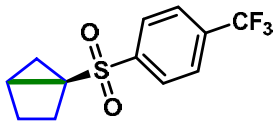
(1*R*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentan-1-ol (168a)

To a solution of **174a** (1.26 g, 4.80 mmol) in a 1:1 mixture of THF and water (16 mL) was added Oxone (3.54 g, 5.76 mmol) and the reaction mixture was stirred at rt for 1 h. Subsequently, the reaction mixture was concentrated *in vacuo* followed by the addition of H_2O (350 mL) and EtOAc (350 mL). The phases were separated, the aqueous phase extracted with EtOAc (2 x 350 mL), the organic phases combined and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* followed by silica gel chromatography to provide **168a** in 93% yield.

Note: The characterization data for the title compound can be found *vide supra*.

The alcohol (**168a**) subsequently underwent mesylation and ring-closure using the procedures described for the synthesis of racemic reagent **10** (*vide supra*).

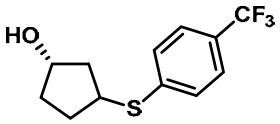
Synthesis of (–)-10:



(–)-10

(1*R*)-1-((3,5-difluorophenyl)sulfonyl)bicyclo[2.1.0]pentane ((–)-10)

Synthesized in **52%** overall yield with **>99%** ***ee*** from 4-(trifluoromethyl)benzenethiol and **162**.

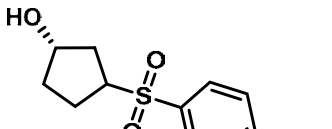


174b

(1*S*)-3-((4-(trifluoromethyl)phenyl)thio)cyclopentan-1-ol (174b)

In a 100 mL glass vessel with overhead stirring was added **172** (12.00 g, 46 mmol) followed by KRED Recycle Mix N from Codexis (sodium phosphate (250 mM), magnesium sulfate (2 mM), NADP+ (1.1 mM), NAD+ (1.1 mM), *D*-glucose (80 mM), glucose dehydrogenase (10 U/mL, pH 7.0)) and sodium phosphate tribasic (2.05 g, 12.5 mmol) in H_2O (100 mL). To this mixture was then added *D*-glucose (20.7 g, 46 mmol) and KRED-NADH-101 (250 mg, 0.961 mmol) followed by NAD+ (250 mg, 0.377 mmol) and stirring was initiated. The pH automation controller (NaOH (1M)) was set to 7, the vessel sealed and the temperature brought to 38 °C. Stirring was continued for 18 h after which an aliquot (0.1 mL) was taken and diluted with MeCN (0.4 mL) + MeOH (0.2 mL) for SFC/MS analysis which indicated complete conversion of the starting material to product. The crude reaction mixture from was extracted with EtOAc and the organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in* vacuo to give **174b** in quantitative yield.

Note: The characterization data for the title compound matches that provided for **174a**.



168b

(1*S*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentan-1-ol (168b)

To a solution of **174b** (10.10 g, 38.51 mmol) in a 1:1 mixture of THF and water (128 mL) was added Oxone (33.1 g, 53.9 mmol) and the reaction mixture was stirred at rt for 1 h.

Subsequently, the reaction mixture was concentrated *in vacuo* followed by the addition of H_2O (350 mL) and EtOAc (350 mL). The phases were separated, the aqueous phase extracted with EtOAc (2 x 350 mL), the organic phases combined and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* followed by silica gel chromatography to provide **168b** in 93% yield.

Note: The characterization data for the title compound can be found *vide supra*.

The alcohol (**168b**) subsequently underwent mesylation and ring-closure using the procedures described for the synthesis of racemic reagent **10** (*vide supra*).

Fig. S112. Reaction vessel with ketoreductase, buffer and ketone.

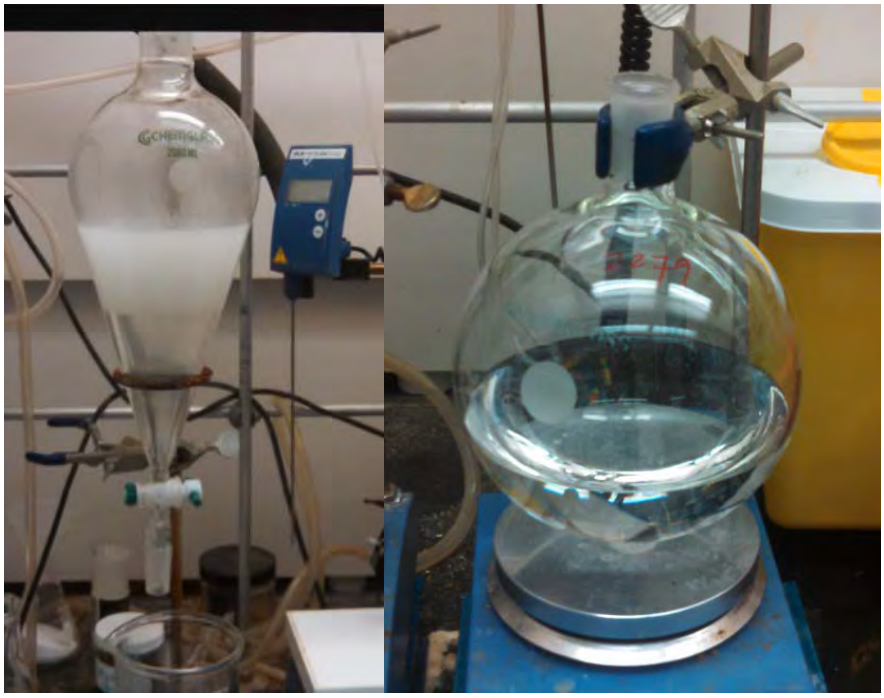


Fig. S113. Left. Reaction mixture being extracted. **Right**. Combined organic extracts prior to evaporation *in vacuo*.

Stereospecific X–H Functionalization

General Procedure: Simple Amines

To a test tube were added (–)-**9** or (+)-**9** (0.1 mmol, 24.4 mg), amine (0.12 mmol, 10.5 mg) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and subsequently purified using silica gel chromatography to afford the desired product.

General Procedure: Amino Acids

To a test tube were added (+)-**9** (0.1 mmol, 24.4 mg), amino acid (0.20 mmol), K_2CO_3 (0.15 mmol, 20.7 mg), DMF (0.3 mL) and H_2O (0.2 mL). The mixture was heated to 90 °C overnight. The resulting solution was acidified with TFA (0.4 mmol, 30 uL), diluted with brine and extracted with solvents ($CHCl_3$/iPrOH = 7/3). The combined organic layer was dried over Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (0.5 mL) after which $SOCl_2$ (0.6 mmol, 43 uL) was added. After stirring overnight at 80 °C, the reaction was carefully quenched with 1N NaOH and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to afford the desired product.

General Procedure: Carboxylic Acids

To a test tube were added (+)-**9** (0.1 mmol, 24.4 mg), carboxylic acid (0.2 mmol), iPr_2NEt (0.2 mmol, 34 uL) and DMF (0.1 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/AcOEt = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to afford the desired product.

General Procedure: Amides, Imides and Sulfonamides

To a solution of amide (0.12 mmol) in DMF (0.3 mL) was added LHMDS (0.12 mmol) at ambient temperature under argon atmosphere. After stirring for 10 min, (+)-**9** (0.1 mmol, 24.4 mg) was added and the mixture was heated to 90 °C. After 2 h, the reaction was quenched with 1 N HCl and the aqueous phase was extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography to provide the desired product.

General procedure A for S-H functionalization (organic solvent):

The following procedure was employed for substrates that are soluble in organic solvent:

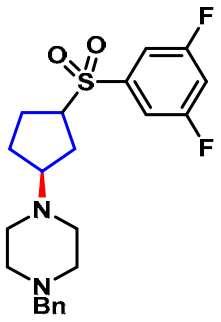
K_2CO_3 (1.0 equiv.) was added to a flame-dried reaction tube under an argon atmosphere. Dry DMF (0.1 M concentration) was added and the vessel was purged twice with alternating vacuum/argon fills. The thiol (1.0 equiv.) was added to the reaction mixture followed by strain-release reagent **9** (1.05 equiv.). The reaction vessel was flushed with argon and stirred at rt. The progress of the reaction was monitored by TLC. Upon completion (30 min – 16 h), the reaction was diluted with EtOAc (25 mL) and poured into a solution of 1 M HCl (20 mL). The organic layer was separated and washed with brine (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the target compound.

General procedure B for S-H functionalization (aqueous co-solvent):

The following procedure was employed for polar substrates (e.g. peptides, unprotected amino acids) that are sparingly soluble in organic solvent:

To a solution of thiol-containing substrate (1.0 equiv.) in degassed 0.2 M K_2CO_3 (2.0 equiv. K_2CO_3) was added a solution of **9** (1.05 quiv.) in an equal volume of DMF to give a 1:1 v/v solution of 0.2 M K_2CO_3/DMF at a final concentration of 0.1 M (unless otherwise noted) with respect to the thiol-containing substrate. The reaction mixture was heated at 40 ^oC and monitored by LC-MS and analytical HPLC. Upon completion of the reaction, the crude mixture was diluted with water and acetonitrile and purified by preparative reverse-phase HPLC using a linear gradient as specified.

Amines & Anilines



158

1-benzyl-4-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)piperazine (158)
To a test tube were added (–)-**9** (0.1 mmol, 24.4 mg), *N*-benzylpiperazine (0.12 mmol, 21.1 mg) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (EtOAc/MeOH = 10/1) to give **158** as a mixture of diastereoisomers in 68% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 61% yield.

Physical State: white solid; (m.p. = 128 °C);

R_f = 0.6 (10% MeOH in EtOAc, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.32 – 7.28 (m, 4H), 7.26 – 7.22 (m, 1H), 7.11 – 7.07 (m, 1H), 3.64 – 3.56 (m, 1H, distinct diastereoisomer), 3.53 – 3.46 (m, 3H), 2.76 (dtd, *J* = 9.8, 8.0, 5.9 Hz, 1H, distinct diastereoisomer), 2.62 (tt, *J* = 10.3, 6.5 Hz, 1H), 2.55 – 2.39 (m, 7H), 2.33 (ddd, *J* = 13.6, 7.6, 5.3 Hz, 1H, distinct diastereoisomer), 2.22 – 2.16 (m, 1H, distinct diastereoisomer), 2.14 – 1.96 (m, 2H), 1.95 – 1.80 (m, 3H), 1.71 – 1.64 (m, 1H, distinct diastereoisomer), 1.57 – 1.48 (m, 1H, distinct diastereoisomer), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (2 x dd, *J* = 255.0, 11.7 Hz), 142.3 – 141.9 (m, overlapping diastereoisomers), 138.0 (2C), 129.4, 129.3, 128.3, 127.2, 112.2 (2 x dd, *J* = 37.4, 6.4 Hz), 109.5 (t, *J* = 25.2 Hz), 66.2, 65.5, 63.1 (2C), 62.8, 62.5, 53.0, 51.9, 51.8, 31.5, 30.8, 30.6, 29.0, 25.8, 24.5;

^{19}F NMR (376 MHz, $CDCl_3$) δ -102.26 (minor diastereoisomer), -102.34 (major diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{22}H_{27}F_2N_2O_2S$ [M+H$^+$] 421.1761; found 421.1769.

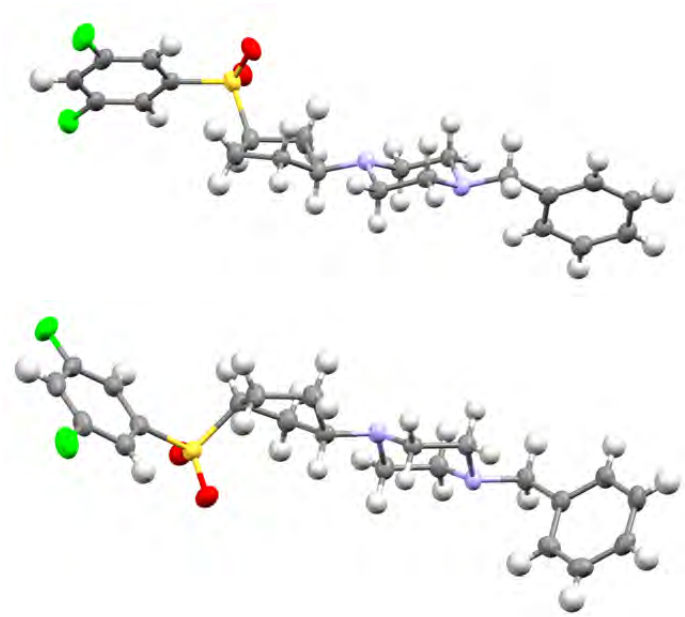


Fig. S114. Crystal structure of diastereomeric pair (**top**) *cis*- and (**bottom**) *trans-1*-benzyl-4-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)piperazine (**158**).

Identification code	60706C Needles	
Empirical formula	$C_{22}H_{26}F_2N_2O_2S$	
Formula weight	420.51	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.5529(3) Å	α = 90°.
	b = 5.9734(2) Å	β = 90.348(2)°.
	c = 35.8785(11) Å	γ = 90°.
Volume	2047.31(11) Å^3	
Z	4	
Density (calculated)	1.364 Mg/m^3	
Absorption coefficient	1.742 mm^{-1}	

F(000)	888
Crystal size	0.153 x 0.066 x 0.049 mm^3
Crystal color, habit	Colorless Needle
Theta range for data collection	1.231 to 68.451°.
Index ranges	$-10 \leq h \leq 10$, $-7 \leq k \leq 7$, $-43 \leq l \leq 42$
Reflections collected	28436
Independent reflections	6924 [R(int) = 0.0731, R(sigma) = 0.0741]
Completeness to theta = 67.500°	96.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.3180 and 0.2060
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6924 / 1 / 523
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	$R_1 = 0.0460$, $wR_2 = 0.1033$
R indices (all data)	$R_1 = 0.0579$, $wR_2 = 0.1088$
Absolute structure parameter	0.019(16)
Extinction coefficient	n/a
Largest diff. peak and hole	0.276 and -0.268 $e.Å^{-3}$

The above reaction was also run with (+)-**9** and the product (***ent*-158**) characterized using X-ray crystallography.

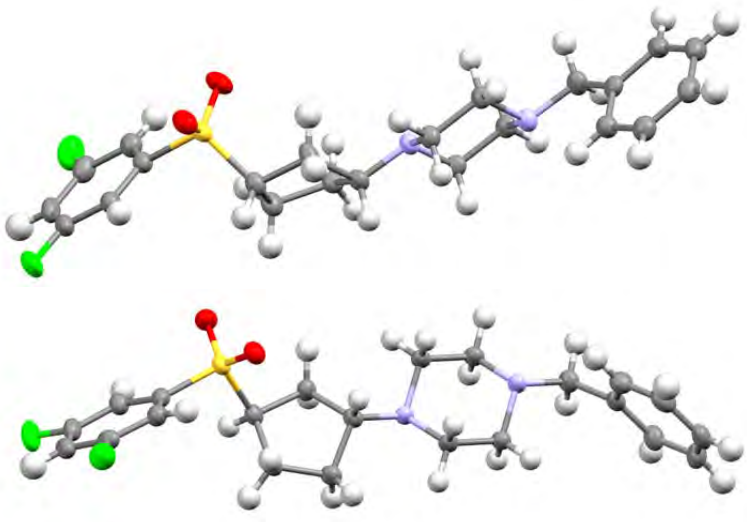
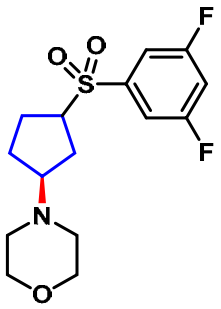


Fig. S115. Crystal structure of diastereomeric pair (**top**) *cis*- and (**bottom**) *trans*-*1*-benzyl-4-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)piperazine (***ent*-158**).

Identification code	60629C	
Empirical formula	$C_{22}H_{26}F_2N_2O_2S$	
Formula weight	420.51	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 9.5438(2) Å	α = 90°.
	b = 5.97810(10) Å	β = 90.3490(10)°.
	c = 35.8879(7) Å	γ = 90°.
Volume	2047.50(7) $Å^3$	
Z	4	
Density (calculated)	1.364 Mg/m^3	
Absorption coefficient	1.742 mm^{-1}	
F(000)	888	
Crystal size	0.261 x 0.149 x 0.138 mm^3	
Crystal color, habit	Colorless Needle	
Theta range for data collection	2.462 to 68.230°.	
Index ranges	$-11 \le h \le 11$, $-6 \le k \le 6$, $-43 \le l \le 43$	
Reflections collected	37179	
Independent reflections	6948 [R(int) = 0.0396]	
Completeness to theta = 67.500°	96.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3200 and 0.2232	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6948 / 1 / 523	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R_1 = 0.0335, wR_2 = 0.0871	
R indices (all data)	R_1 = 0.0364, wR_2 = 0.0895	
Absolute structure parameter	0.006(11)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.236 and -0.250 $e.Å^{-3}$	



175

4-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)morpholine (175)

To a test tube were added (–)-**9** (0.1 mmol, 24.4 mg), morpholine (0.12 mmol, 10.5 mg) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (EtOAc) to give **175** in 82% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 79% yield.

Major Diastereoisomer:

Physical State: colorless oil;

R_f = 0.4 (EtOAc, vis. UV);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.11 (tt, *J* = 8.3, 2.3 Hz, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 3.66 – 3.57 (m, 1H), 2.76 (dtd, *J* = 10.0, 8.1, 5.2 Hz, 1H), 2.46 (t, *J* = 4.7 Hz, 4H), 2.35 (ddd, *J* = 13.4, 7.7, 5.2 Hz, 1H), 2.11 – 1.97 (m, 3H), 1.84 (ddd, *J* = 14.1, 10.3, 8.2 Hz, 1H), 1.58 – 1.47 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.3, 11.1 Hz), 142.1 (t, *J* = 7.7 Hz), 112.2 (dd, *J* = 21.6, 6.5 Hz), 109.5 (t, *J* = 24.8 Hz), 67.0, 65.8, 62.6, 52.5, 30.7, 30.3, 25.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.13;

HRMS (ESI-TOF): calc'd for $C_{15}H_{20}F_2NO_3S$ [M+H$^+$] 332.1132; found 332.1129;

$[\alpha]_D^{20}$ = –0.8 (c = 0.67, $CHCl_3$).

Minor Diastereoisomer:

Physical State: white solid;

R_f = 0.3 (EtOAc, vis. UV);

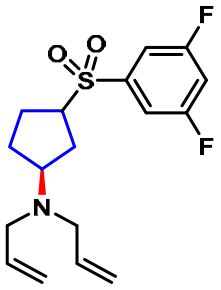
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.10 (tt, *J* = 8.3, 2.3 Hz, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 3.55 – 3.46 (m, 1H), 2.61 (tt, *J* = 10.2, 6.5 Hz, 1H), 2.49 – 2.41 (m, 4H), 2.23 – 2.17 (m, 1H), 2.13 (dt, *J* = 13.4, 6.9 Hz, 1H), 1.95 – 1.84 (m, 3H), 1.71 – 1.64 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 256.2, 11.3 Hz), 142.1 (t, *J* = 7.8 Hz), 112.2 (dd, *J* = 21.8, 6.5 Hz), 109.5 (t, *J* = 24.8 Hz), 66.9, 66.5, 62.3, 52.4, 31.3, 28.8, 24.5;

^{19}F NMR (376 MHz, $CDCl_3$) δ -102.20;

HRMS (ESI-TOF): calc'd for $C_{15}H_{20}F_2NO_3S$ [M+H$^+$] 332.1132; found 332.1123;

$[\alpha]_D^{20}$ = –2.1 (c = 1.0, $CHCl_3$).



176

(1*S*)-*N*,*N*-diallyl-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-amine (176)

To a test tube were added **(–)-9** (0.1 mmol, 24.4 mg), diallylamine (0.12 mmol, 11.7 mg) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 1/1) to give **176** as a mixture of diastereoisomers in 77% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 67% yield.

Major Diastereoisomer:

Physical state: colorless liquid;

R_f = 0.6 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.12 – 7.08 (m, 1H), 5.86 – 5.77 (m, 2H), 5.19 – 5.11 (m, 4H), 3.59 (dtd, *J* = 10.2, 8.2, 5.4 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.13 (d, *J* = 6.5 Hz, 4H), 2.32 – 2.26 (m, 1H), 2.06 – 1.96 (m, 3H), 1.87 – 1.80 (m, 1H), 1.59 – 1.51 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 256.3, 11.1 Hz), 142.2 (t, *J* = 7.7 Hz), 135.0, 117.9, 112.2 (dd, *J* = 21.9, 6.4 Hz), 109.5 (t, *J* = 25.2 Hz), 109.3, 62.8, 61.6, 54.1, 30.7, 30.3, 25.5;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.29;

HRMS (ESI-TOF): calc'd $C_{17}H_{22}F_2NO_2S$ [M+H$^+$] 342.1339; found 342.1340;

$[\alpha]_D^{20}$ = –10.0 (c = 1.0, $CHCl_3$).

Minor Diastereoisomer:

Physical state: colorless liquid;

R_f = 0.7 (50% EtOAc in hexanes, vis. UV);

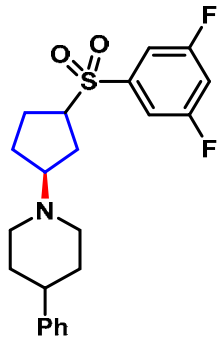
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.10 (tt, *J* = 8.4, 2.3 Hz, 1H), 5.82 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 2H), 5.18 – 5.10 (m, 4H), 3.49 – 3.42 (m, 1H), 3.16 – 3.12 (m, 5H), 2.16 (dtd, *J* = 13.5, 6.4, 3.6 Hz, 1H), 2.07 (dt, *J* = 13.5, 7.1 Hz, 1H), 1.95 – 1.79 (m, 3H), 1.73 – 1.67 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.6, 11.2 Hz), 142.2 (t, *J* = 7.9 Hz), 135.6, 117.6, 112.2 (dd, *J* = 22.0, 6.6 Hz), 109.5 (t, *J* = 25.2 Hz), 62.2, 62.1, 54.1, 30.3, 28.3, 24.5;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.30;

HRMS (ESI-TOF): calc'd $C_{17}H_{22}F_2NO_2S$ [M+H$^+$] 342.1339; found 342.1335;

$[\alpha]_D^{20}$ = –3.5 (c = 0.9, $CHCl_3$).



177

1-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-4-phenylpiperidine (177)

To a test tube were added **(–)-9** (0.1 mmol, 24.4 mg), 4-phenylpiperidine (0.12 mmol, 19.3 mg) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 1/1) to give **177** in 80% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 74% yield.

Major Diastereoisomer:

Physical State: colorless oil.

R_f = 0.3 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.31 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 7.10 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.56 – 3.49 (m, 1H), 3.11 – 3.02 (m, 2H), 2.75 – 2.68 (m, 1H), 2.49 (tt, *J* = 11.9, 4.1 Hz, 1H), 2.25 – 2.04 (m, 4H), 2.02 – 1.71 (m, 8H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.7, 11.4 Hz), 146.2, 142.1 (t, *J* = 7.7 Hz), 128.6, 127.0, 126.4, 112.3 (dd, *J* = 21.2, 7.3 Hz), 109.5 (t, *J* = 24.8 Hz), 66.4, 62.6, 52.8, 52.7, 42.7, 33.4, 31.3, 28.9, 24.6, 24.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.26.

HRMS (ESI-TOF): calc'd for $C_{22}H_{26}F_2NO_2S$ [M+H$^+$] 406.1652; found 406.1651;

$[\alpha]_D^{20}$ = +3.7 (c = 1.0, $CHCl_3$).

Minor Diastereoisomer:

Physical State: white solid.

R_f = 0.2 (50% EtOAc in hexanes, vis. UV);

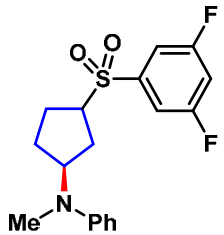
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 7.11 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.08 (t, *J* = 14.0 Hz, 2H), 2.85 – 2.78 (m, 1H), 2.50 (tt, *J* = 12.1, 3.9 Hz, 1H), 2.44 – 2.38 (m, 1H), 2.16 – 2.01 (m, 6H), 1.93 – 1.83 (m, 3H), 1.80 – 1.72 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.2, 11.2 Hz), 146.2, 142.2 (t, *J* = 7.7 Hz), 128.6, 127.0, 126.4, 112.2 (dd, *J* = 21.4, 6.5 Hz), 109.5 (t, *J* = 24.8 Hz), 65.8, 62.8, 53.3, 52.9, 42.6, 33.5, 33.4, 31.1, 30.8, 25.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.19.

HRMS (ESI-TOF): calc'd for $C_{22}H_{26}F_2NO_2S$ [M+H$^+$] 406.1652; found 406.1649;

$[\alpha]_D^{20}$ = –1.3 (c = 0.74, $CHCl_3$).



178

***N*-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-*N*-methylaniline (178)**

To a test tube were added (–)**-9** (0.1 mmol, 24.4 mg), *N*-methylaniline (0.20 mmol, 24 uL) and DMSO (0.3 mL). The mixture was heated to 80 °C for 3 days. The resulting solution

was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 4/1) to give **178** in 72% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 70% yield.

Major Diastereoisomer:

Physical State: colorless liquid.

R_f = 0.4 (20% EtOAc in hexanes, vis. UV);

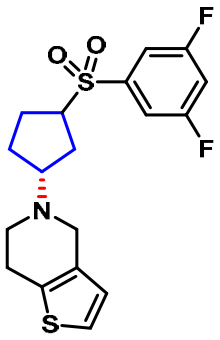
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.27 – 7.23 (m, 2H), 7.11 (tt, *J* = 8.4, 2.3 Hz, 1H), 6.86 – 6.83 (m, 2H), 6.82 – 6.79 (m, 1H), 4.37 – 4.30 (m, 1H), 3.67 – 3.60 (m, 1H), 2.75 (s, 3H), 2.35 (ddd, *J* = 13.9, 8.1, 5.4 Hz, 1H), 2.15 – 2.03 (m, 3H), 1.89 (ddd, *J* = 14.5, 10.0, 8.2 Hz, 1H), 1.83 – 1.72 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.4, 11.0 Hz), 142.1 (t, *J* = 7.7 Hz), 112.4 – 112.0 (m), 109.6 (t, *J* = 24.8 Hz);

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.06;

HRMS (ESI-TOF): calc'd for $C_{18}H_{20}F_2NO_2S$ [$M+H^+$] 352.1183; found 352.1190;

$[\alpha]_D^{20}$ = +39.9 (c = 1.0, $CHCl_3$).



179

5-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (179)

To a Teflon-capped screw top vial with stirbar was added **(+)-9** (67 mg, 0.27 mmol, 1.0 equiv) and 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (57.8 mg, 0.329 mmol, 1.2 equiv). The solids were dissolved in DMSO (0.669 mL) and the atmosphere was sparged with argon. The resulting solution was stirred at 80 °C overnight whereby analysis by TLC and LCMS confirmed the consumption of starting material and presence of the desired product. Purification by silica gel chromatography (0-30% MeOH/DCM) furnished **179** in 65% yield as an inseparable mixture of diastereomers.

Note: The reaction was performed under argon to avoid the formation of oxidation by-products.

Physical State: colorless oil;

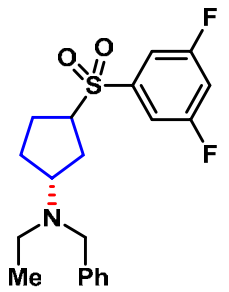
$\mathbf{R_f}$ = 0.35 (20% MeOH in CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 3H), 7.15 – 7.05 (m, 2H), 6.71 (d, *J* = 5.1 Hz, 1H, major diastereoisomer), 4.60 – 4.54 (m, 1H, major diastereoisomer), 4.21 (p, *J* = 6.4 Hz, 1H, minor diastereoisomer), 3.91 – 3.81 (m, 1H, major diastereoisomer), 3.65 – 3.50 (m, 2H), 3.08 – 2.77 (m, 3H), 2.56 – 2.19 (m, 5H), 2.18 – 1.87 (m, 3H), 1.86 – 1.74 (m, 1H, major diastereoisomer), overlapping diastereoisomer signals;

^{13}C NMR (100 MHz, $CDCl_3$): 163.0 (2 x dd, *J* = 255.9, 11.4), 142.0 (t, *J* = 7.9 Hz), 141.6 (t, *J* = 8.0 Hz), 133.2, 132.8, 125.2, 123.2, 112.6 – 111.9 (m), 109.7 (t, *J* = 25.0 Hz), 109.6 (t, *J* = 24.8 Hz), 65.1, 62.7, 62.3, 62.2, 60.7, 57.0, 51.6, 49.1, 38.2, 37.4, 36.5, 36.3, 31.3, 29.0, 25.4, 24.4, mixture of diastereoisomers.

^{19}F NMR (376 MHz, $CDCl_3$): -104.89

HRMS (ESI-TOF): calc'd for $C_{18}H_{19}F_2NO_2S_2$ [M+H$^+$] 384.0898; found 384.0901.



180

(1*R*)-*N*-benzyl-3-((3,5-difluorophenyl)sulfonyl)-*N*-ethylcyclopentan-1-amine (180)

To a reaction vial equipped with a stir bar was added *N*-benzyl-*N*-ethylamine (111 mg, 0.819 mmol), DMSO (1 mL) and **(+)-9** (100 mg, 0.409 mmol). The clear solution was stirred at 80 °C for 18 h after which it was cooled to room temperature, and poured into H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated to give an amber oil. The crude product was purified using silica gel chromatography to provide **180** as a set of diastereoisomers in 71% yield.

Fast-eluting Diastereoisomer (EtOAc/hexanes):

Physical State: beige solid (m.p. = 72.2 °C);

R_f = 0.5 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.80 – 7.70 (m, 1H), 7.65 – 7.57 (m, 2H), 7.30 (s, 2H), 7.29 – 7.26 (m, 2H), 4.03 – 3.81 (m, 1H), 3.56 (s, 2H), 3.20 - 3.05 (m, 1H), 2.49 – 2.43 (m, 2H), 2.02 – 1.96 (m, 1H), 1.96 – 1.89 (m, 1H), 1.86 – 1.78 (m, 1H), 1.78 – 1.73 (m, 1H), 1.72 – 1.64 (m, 1H), 1.57 – 1.43 (m, 1H), 0.91 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-*d6*) δ 162.8 (dd, *J* = 11.7, 252 Hz, 2C), 142.3 (t, *J* = 8.4 Hz, 1C), 141.0, 128.6 (s, 2C), 128.5 (s, 2C), 127.0, 112.8 - 112.1 (m, 2C), 110.2 (t, *J* = 25.7 Hz, 1C), 62.3, 60.8, 54.7, 45.0, 30.1, 28.7, 24.2, 12.0;

^{19}F NMR (376 MHz, DMSO-*d6*) δ -105.9;

HRMS (ESI-TOF): calc'd for $C_{20}H_{23}F_2NO_2S$ [M+H$^+$] 379.1418; found 379.1424.

Slow-eluting Diastereoisomer (EtOAc/hexanes):

Physical State: beige solid (m.p. = 68.4 °C);

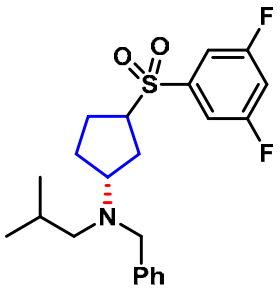
R_f = 0.3 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.78 – 7.70. (m, 1H), 7.68 – 7.60 (m, 2H), 7.30 (s, 2H), 7.29 (s, 2H), 7.23 – 7.17 (m, 1H), 4.13 – 3.95 (m, 1H), 3.55 (s, 2H), 3.26 – 3.08 (m, 1H), 2.49 – 2.41 (m, 2H), 2.12 – 2.04 (m, 1H), 1.93 – 1.88 (m, 1H), 1.87 – 1.82 (m, 1H), 1.82 – 1.77 (m, 1H), 1.77 – 1.69 (m, 1H), 1.58 - 1.43 (m, 1H), 0.91 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (101 MHz, DMSO-*d6*) δ 162.8 (dd, *J* = 11.7, 252 Hz, 2C), 142.3 (t, *J* = 8.1 Hz, 1C), 141.0, 128.6 (s, 2C), 128.5 (s, 2C), 127.0, 112.8 - 112.1 (m, 2C), 110.2 (t, *J* = 25.7 Hz, 1C), 61.8, 61.4, 54.6, 44.9, 29.7, 29.6, 25.1, 11.7;

^{19}F NMR (376 MHz, DMSO-*d6*) δ -105.9;

HRMS (ESI-TOF): calc'd for $C_{20}H_{23}F_2NO_2S$ [M+H+] 379.1418; found 379.1424.



181

(1*R*)-*N*-benzyl-3-((3,5-difluorophenyl)sulfonyl)-*N*-isobutylcyclopentan-1-amine (181)
To a reaction vial equipped with a stir bar was added 2-methyl-*N*-phenethylpropan-1-amine (80.2 mg, 0.491 mmol), DMSO (1 mL) and **(+)-9** (100 mg, 0.409 mmol). The clear solution was stirred at 80 °C for 28 h after which 2-methyl-*N*-phenethylpropan-1-amine (53.5 mg, 0.328 mmol) was added and stirring was continued for 16 h. Subsequently, the mixture was cooled to room temperature, and poured into H_2O (20 mL). The aqueous layer was extracted with MTBE (2 x 20 mL), the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated to give an amber oil. The crude product was purified using silica gel chromatography to provide **181** in 71% yield.

Physical State: colorless oil;

R_f = 0.6 (25% EtOAc in hexanes, vis. UV);

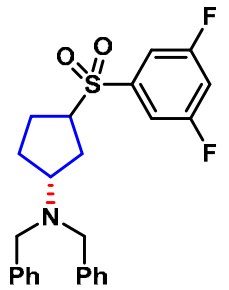
^{1}H NMR (600 MHz, DMSO-*d6*): δ 7.77 – 7.68 (m, 1H), 7.65 – 7.57 (m, 2H), 7.32 – 7.32 (m, 4H), 7.24 – 7.16 (m, 1H), 4.07 – 3.91 (m, 1H), 4.58 – 3.49 (m, 2H), 3.24 – 3.06 (m, 1H), 2.20 – 2.10 (m, 2H), 1.99 (ddd, *J* =14.0, 8.2, 5.6 Hz, 1H), 1.85 – 1.56 (m, 5H), 1.56 – 1.42 (m, 1H), 0.82 - 0.74 (m, 6H);

^{13}C NMR (101 MHz, DMSO): δ 162.2 (2 x dd, *J* = 252.3, 12.2 Hz, diastereoisomers), 141.7 (2 x t, *J* = 8.2 Hz, diastereoisomers), 140.5 (2C), 128.2 – 127.9 (m, diastereoisomers), 126.5, 112.1 – 111.6 (m, diastereoisomers), 109.7 (2 x t, *J* = 25.6 Hz,

diastereoisomers), 61.9, 61.5, 60.9, 60.0, 58.9, 58.7, 56.1, 56.0, 27.8, 27.7, 27.2, 26.6, 26.3, 26.2, 24.6, 23.6, 20.6;

^{19}F NMR (376 MHz, DMSO-*d6*): δ -105.88 (minor diastereoisomer), -105.90 (major diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{22}H_{27}F_2NO_2S$ [M+H$^+$] 407.1731; found 407.1733.



182

(1*R*)-*N*,*N*-dibenzyl-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-amine (182)
To a test tube were added **(+)-9** (0.1 mmol, 24.4 mg), dibenzylamine (0.12 mmol, 23 uL) and DMSO (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 10/1) to give **182** in 69% yield.

Note: The above reaction was run with racemic **9** on 8.2 mmol scale to give the desired product in 73% yield.

Physical State: colorless oil;

***R*$_f$** = 0.4 (10% EtOAc in hexanes, vis. UV);

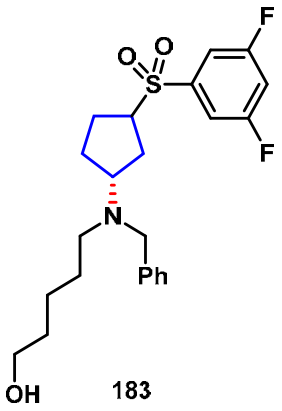
^{1}H NMR (600 MHz, CDCl$_3$) δ 7.39 – 7.35 (m, 2H), 7.35 – 7.32 (m, 2H), 7.31 – 7.27 (m, 6H), 7.24 – 7.19 (m, 2H), 7.10 – 7.05 (m, 1H), 3.68 – 3.54 (m, 4H), 3.52 – 3.45 (m, 1H, distinct diastereoisomer), 3.42 – 3.34 (m, 1H), 3.26 – 3.19 (m, 1H, distinct diastereoisomer), 2.19 – 2.11 (m, 1H), 2.02 – 1.93 (m, 2H), 1.92 – 1.74 (m, 2H), 1.70 – 1.63 (m, 1H), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, CDCl$_3$) δ 163.0 (2 x dd, *J* = 255.8, 11.0 Hz, diastereoisomers), 162.2, 162.2, 162.1, 162.1, 142.3 – 142.0 (m, overlapping diastereoisomers), 140.0, 139.8,

128.6, 128.5, 128.4, 127.1, 127.1, 112.1 (dd, J = 22.2, 6.6 Hz), 109.4 (t, J = 24.7 Hz), 63.0, 62.1, 62.1, 61.7, 55.8, 55.4, 29.4, 29.3, 28.9, 26.9, 25.5, 24.3;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.21 (distinct diastereoisomer), -105.29 (distinct diastereoisomer), -105.61 (trace impurity);

HRMS (ESI-TOF): calc'd for $C_{25}H_{26}F_2NO_2S$ [M+H$^+$] 442.1652; found 442.1659.



183

5-(benzyl((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)amino)pentan-1-ol (183)
To a 1 dram vial were added **(+)-9** (105 mg, 0.43 mmol), 5-(benzylamino)pentan-1-ol (79.0 mg, 0.41 mmol) and DMSO (1 mL). The mixture was heated to 80 °C for 17 h after which water and EtOAc were added and the phases separated. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product that was purified using silica gel chromatography to afford **183** in 70% yield.

Trans-Diastereomer:

Physical State: liquid;

R_f = 0.4 (10% MeOH in CH_2Cl_2, UV/$KMnO_4$ visualization);

^{1}H NMR (400 MHz, CD_3CN) δ 7.51 – 7.45 (m, 2H), 7.33 – 7.25 (m, 5H), 7.25 – 7.18 (m, 1H), 3.77 – 3.67 (m, 1H), 3.59 (br s, 2H), 3.43 (t, J= 6.5 Hz, 2H), 3.29 – 3.20 (m, 1H), 2.43 (t, J= 7.4 Hz, 2H), 2.16 – 2.05 (m, 3H, partially obscured by residual water), 1.91 – 1.75 (m, 3H), 1.61 – 1.52 (m, 1H), 1.45 – 1.35 (m, 4H), 1.28 – 1.19 (m, 2H);

^{13}C NMR (101MHz, DMSO-*d6*) δ = 162.3 (dd, J=12.1, 252.7 Hz, 2C), 141.7 (t,

J = 8.8 Hz, 1C), 140.5, 128.1 (2C), 128.0 (2C), 126.5, 111.9 (dd, *J* = 9.5, 19.8 Hz, 2C), 109.7 (t, *J* = 26.0 Hz, 1C), 61.6, 60.9, 60.6, 54.9, 50.7, 32.3, 28.7, 28.6, 26.2, 24.6, 23.2;

^{19}F NMR (376 MHz, CD_3CN) δ -107.52.

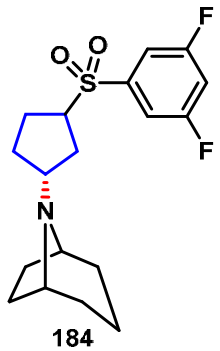
HRMS (ESI-TOF): calc'd for $C_{23}H_{30}F_2NO_3S$ [M+H$^+$] 438.1909; found 438.1913.

Cis-Diastereomer:

Physical State: liquid;

^{1}H NMR (400 MHz, MeCN-*d3*): δ 7.51 – 7.45 (m, 2H), 7.36 – 7.26 (m, 5H), 7.25 – 7.19 (m, 1H), 3.65 – 3.57 (m, 3H), 3.43 (t, *J*= 6.5 Hz, 2H), 3.22-3.12 (m, 1H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.07 – 1.96 (m, 3H), 1.87 – 1.74 (m, 3H), 1.66 – 1.55 (m, 1H), 1.46 – 1.35 (m, 4H), 1.29 – 1.20 (m, 2H);

^{13}C NMR (101 MHz, DMSO-*d6*): δ = 162.3 (dd, *J* = 12.1, 252.0 Hz, 2C), 141.8 (t, *J* = 8.8 Hz, 1C), 140.6, 128.1 (s, 2C), 128.0 (s, 2C), 126.5, 111.9 (dd, *J* = 8.1, 19.8 Hz, 1C), 109.7 (t, *J* = 25.7 Hz, 1C), 62.0, 60.6, 60.2, 55.1, 50.7, 32.3, 28.9, 27.6, 26.5, 23.7, 23.2.



184

(1*R*,5*S*)-8-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-8-azabicyclo[3.2.1]octane (184)

To a Teflon-capped screw top vial with stirbar was added (+)-**9** (69 mg, 0.28 mmol, 1.0 equiv) and amine (37.7 mg, 0.339 mmol, 1.2 equiv). The solids were dissolved in DMSO (0.706 m, 0.41 M) and the atmosphere was sparged with argon. The resulting solution was stirred at 80 °C overnight. Purification by silica gel chromatography (0-30% MeOH in CH_2Cl_2) furnished **184** in 53% yield as an inseparable mixture of diastereomers.

Note: The reaction was performed under argon to avoid the formation of oxidation by-products.

Physical State: colorless oil;

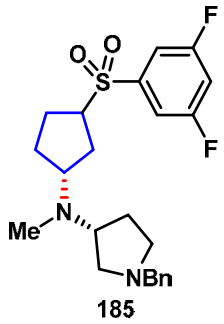
$\mathbf{R_f}$ = 0.45 (20% MeOH in CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.39 (m, 2H), 7.14 – 7.04 (m, 1H), 4.61 – 4.52 (m, 1H, major diastereoisomer), 4.21 (p, *J* = 6.4 Hz, 1H, minor diastereoisomer), 3.91 – 3.79 (m, 1H, major diastereoisomer), 3.78 – 3.68 (m, 1H, minor diastereoisomer), 3.60 – 3.46 (m, 1H, major diastereoisomer), 3.38 – 3.30 (m, 2H, minor diastereoisomer), 3.24 – 3.12 (m, 2H, major diastereoisomer), 2.94 – 2.84 (m, 1H, major diastereoisomer), 2.56 – 1.77 (m, 9H), 1.77 – 1.20 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): 163.1 (2 x dd, *J* = 255.9, 11.4 Hz), 142.1 (2 x t, *J* = 7.8 Hz), 112.7 – 111.9 (m), 110.1 – 109.1 (m), 62.9 (2C), 62.7, 62.2, 60.7, 58.2 (2C), 58.1, 57.0, 38.2, 37.4, 36.5, 36.3, 33.6, 30.6, 29.3 (2C), 27.0 (2C), 25.8, 25.4, 24.6, 24.4, 16.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.34, -104.98;

HRMS (ESI-TOF): calc'd for $C_{18}H_{23}F_2NO_2S$ [M+H$^+$] 356.149; found 356.1488.



185

(3*R*)-1-benzyl-*N*-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-N-methylpyrrolidin-3-amine (185)

In a 1 dram vial, (*R*)-1-benzyl-*N*-methylpyrrolidin-3-amine (75 mg, 0.39 mmol) was diluted with DMSO (1 mL) and **(+)-9** (101 mg, 0.414 mmol) was added. The mixture was stirred at 80 °C for 17 h after which the temperature was lowered to rt. Water and EtOAc were added, the layers were separated and the aqueous phase extracted using EtOAc. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered and concentrated to provide the crude product that was further purified using silica gel chromatography to provide **185** in 75% yield.

Physical State: light orange oil;

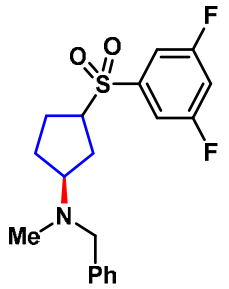
R_f = 0.43 (1% MeOH in CH_2Cl_2, vis. UV);

^{1}H NMR (400 MHz, CD_3CN) δ 7.53 - 7.46 (m, 2H), 7.34 - 7.21 (m, 6H), 3.76 - 3.55 (m, 2H), 3.49 (s, 1H, major diastereomer), 3.46 (s, 1H, minor diastereoisomer), 3.38 - 3.29 (m, 1H), 3.06 - 2.94 (m, 1H), 2.60 - 2.51 (m, 1H), 2.47 - 2.34 (m, 3H), 2.12 - 1.97 (m, 4H), 1.91 - 1.65 (m, 6H), 1.48 - 1.44 (m, 1H);

^{13}C NMR (101 MHz, CD_3CN) δ 163.9 (dd, *J* = 253.0, 11.8 Hz), 143.3 (2 x t, *J* = 7.6 Hz), 140.7, 129.5, 129.2, 127.8, 113.3 – 112.8 (m), 110.2 (t, *J* = 25.6 Hz), 64.3, 63.9, 63.8, 63.0, 62.5, 62.4, 62.3, 62.2, 62.1 (3C), 57.4 (3C), 57.3, 54.3, 33.7 (3C), 30.5 (2C), 30.0, 29.9, 29.0 (2C), 27.9, 27.8, 27.7, 27.6, 26.0, 24.9, 24.8, mixture of diastereoisomers;

^{19}F NMR (376 MHz, CD_3CN) δ -107.50, -107.51, -107.52, diastereoisomers;

HRMS (ESI-TOF): calc'd for $C_{23}H_{29}F_2N_2O_2S$ [M+H$^+$] 435.1912; found 435.1920.



186

(1*S*)-*N*-benzyl-3-((3,5-difluorophenyl)sulfonyl)-*N*-methylcyclopentan-1-amine (186)
To a test tube were added **(–)-9** (0.1 mmol, 24.4 mg), *N*-benzyl-*N*-methylamine (0.12 mmol, 14.5 mg) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 1/1) to give **186** in 90% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 85% yield.

Major Diastereoisomer:

Physical State: colorless liquid;

R_f = 0.4 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.33 – 7.27 (m, 4H), 7.26 – 7.22 (m, 1H), 7.10 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.56 – 3.46 (m, 3H), 2.91 (tt, *J* = 10.1, 6.6 Hz, 1H), 2.24 – 2.18 (m, 1H), 2.15 (s, 3H), 2.14 – 2.09 (m, 1H), 2.04 – 1.97 (m, 1H), 1.96 – 1.90 (m, 1H), 1.90 – 1.84 (m, 1H), 1.82 – 1.75 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.5, 11.2 Hz), 142.2 (t, *J* = 7.8 Hz), 139.0, 129.0, 128.4, 127.2, 112.2 (dd, *J* = 21.2, 6.7 Hz), 109.5 (t, *J* = 25.2 Hz), 65.3, 62.5, 60.4, 39.5, 30.7, 28.7, 24.6;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.25 (major diastereoisomer), -109.32 (trace impurity);

HRMS (ESI-TOF): calc'd for $C_{19}H_{22}F_2NO_2S$: $[M+H^+]$ 366.1339; found 366.1342;

$[\alpha]_D^{20}$ = –2.5 (c = 1.0, $CHCl_3$).

Minor Diastereoisomer:

Physical State: colorless liquid;

R_f = 0.5 (50% EtOAc in hexanes, vis. UV);

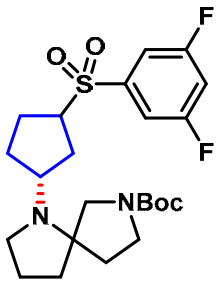
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.32 – 7.26 (m, 4H), 7.26 – 7.22 (m, 1H), 7.10 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.63 (dtd, *J* = 10.2, 8.3, 5.7 Hz, 1H), 3.49 (s, 2H), 3.05 – 2.98 (m, 1H), 2.37 – 2.31 (m, 1H), 2.11 (s, 3H), 2.09 – 2.01 (m, 3H), 1.94 (ddd, *J* = 14.1, 10.1, 7.7 Hz, 1H), 1.69 – 1.63 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.6, 11.3 Hz), 142.2 (t, *J* = 7.8 Hz), 138.9, 129.0, 128.4, 127.2, 112.2 (dd, *J* = 20.7, 6.4 Hz), 109.5 (t, *J* = 25.2 Hz), 65.2, 62.9, 60.5, 39.9, 30.9, 30.6, 25.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.23;

HRMS (ESI-TOF): calc'd for $C_{19}H_{22}F_2NO_2S$: $[M+H^+]$ 366.1339; found 366.1337;

$[\alpha]_D^{20}$ = +1.7 (c = 1.0, $CHCl_3$).



187

***tert*-butyl 1-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-1,7-diazaspiro[4.4]nonane-7-carboxylate (187)**

In a 1 dram vial, *tert*-butyl 1,7-diazaspiro[4.4]nonane-7-carboxylate (70 mg, 0.31 mmol) was diluted with DMSO (0.77 mL) and **(+)-9** (79.3 mg, 0.325 mmol) was added. The mixture was stirred at ambient temperature overnight followed by 27 h at 80 °C. The temperature was subsequently lowered to rt, water and EtOAc were added, the layers separated and the aqueous phase extracted using EtOAc. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered and concentrated to provide the crude product that was further purified using silica gel chromatography to provide **187** in 70% yield.

Physical State: orange foam;

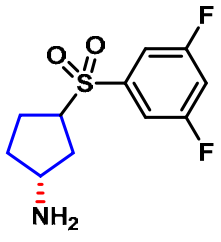
R_f = 0.53 (10% MeOH in CH_2Cl_2, vis. UV);

^{1}H NMR (400 HMz, CD_3CN) δ 7.54 - 7.46 (m, 2H), 7.30 (tt, *J*= 8.9, 2.5 Hz, 1H), 3.77 - 3.56 (m, 1H), 3.47 - 3.27 (m, 2H), 3.21 - 3.10 (m, 1H), 3.09 - 2.95 (m, 2H), 2.89 - 2.64 (m, 2H), 2.09 -1.97 (m, 1H), 1.94 - 1.78 (m, 5H, partially obscured by residual solvent), 1.78 - 1.56 (m, 5H), 1.57 - 1.46 (m, 1H), 1.45 - 1.34 (m, 9H);

^{13}C NMR (101 MHz, CD_3CN) δ 163.9 (dd, *J* = 252.8, 11.7 Hz), 155.4, 143.4 (q, *J* = 8.2 Hz), 113.0 (dd, *J* = 28.2, 4.1 Hz), 110.2 (t, *J* = 25.6 Hz), 79.4, 69.8, 69.2, 63.3, 63.1, 62.5, 62.4, 57.9, 57.8, 57.5, 57.3, 54.7, 54.3, 54.1, 47.1, 46.8, 46.6, 45.5, 45.1, 39.6, 39.5, 34.6, 34.0, 31.9, 31.6, 31.4, 31.3, 30.9, 30.8, 30.3, 30.1, 29.5, 26.1, 25.1, 25.0, 24.9, 22.7, mixture of conformers;

^{18}F NMR (376 MHz, CD_3CN) δ -107.57;

HRMS (ESI-TOF): calc'd for $C_{23}H_{33}F_2N_2O_4S$ [M+H$^+$] 471.2124; found 471.2125.



188

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-amine (188)

To a test tube were added **(+)-9** (0.1 mmol, 24.4 mg), concentrated NH_3 (0.1 mL) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with brine and extracted with solvents (hexane/AcOEt = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography ($CHCl_3$/MeOH/NH_3 = 100/10/1) to give **188** in 92% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 88% yield.

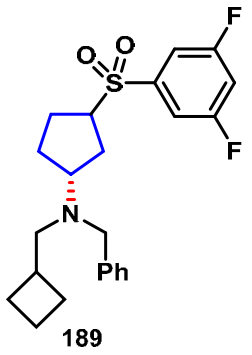
Physical State: colorless liquid;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.15 – 7.09 (m, 1H), 3.80 (p, *J* = 8.0 Hz, 1H, minor diastereoisomer), 3.71 – 3.65 (m, 1H, minor diastereoisomer), 3.59 – 3.52 (m, 1H, major diastereoisomer), 3.42 (p, *J* = 6.8 Hz, 1H, major diastereoisomer), 2.32 – 2.18 (m, 2H), 2.15 – 2.01 (m, 1H), 1.98 – 1.82 (m, 2H), 1.74 – 1.68 (m, 1H, distinct diastereoisomer), 1.51 – 1.45 (m, 1H, distinct diastereoisomer), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.0, 11.4 Hz), 142.2 (t, *J* = 8.1 Hz), 112.2 (2 x dd, *J* = 21.7, 6.9 Hz), 109.5 (2 x t, *J* = 24.9 and 14.6 Hz, diastereoisomers), 63.0 (2C) 53.3, 52.5, 36.8, 36.5, 35.7, 35.1, 25.1 (2C);

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.25 (major diastereoisomer), -105.36 (minor diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{11}H_{14}F_2NO_2S$ [M+H$^+$] 262.0713; found 262.0718.



189

(1*R*)-*N*-benzyl-*N*-(cyclobutylmethyl)-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-amine (189)

To a reaction vial equipped with a stir bar was added *N*-benzyl-1-cyclobutylmethanamine (144 mg, 0.819 mmol), DMSO (1 mL) and **(+)-9** (100 mg, 0.409 mmol). The clear solution was stirred at 80 °C for 15 h after which it was cooled to room temperature, and poured into H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated to give an amber oil. The crude product was purified using silica gel chromatography to provide a set of separately isolated diastereoisomers in 67% yield.

Fast-eluting Diastereoisomer (EtOAc/hexanes) [cis]:

Physical State: beige solid (m.p. = 77.8 °C);

R_f = 0.4 (10% EtOAc in hexanes, vis. UV);

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.69 - 7.80 (m, 1H), 7.55 - 7.66 (m, 2H), 7.12 - 7.34 (m, 5H), 3.80 - 4.00 (m, 1H), 3.53 (s, 2H), 3.03 - 3.18 (m, 1H), 2.32 - 2.46 (m, 3H), 1.86 - 1.98 (m, 4H), 1.62 - 1.83 (m, 5H), 1.41 - 1.60 (m, 3H);

^{13}C NMR (101 MHz, DMSO-*d6*) δ 162.8 (dd, *J* = 11.7, 252 Hz, 2C), 142.3 (t, *J* = 8.1 Hz, 1C), 141.2, 128.5 (s, 2C), 128.5 - 128.4 (m, 2C), 127.0, 112.4 (dd, *J* = 8.8, 19.1 Hz, 2C), 110.2 (br t, *J* = 25.3 Hz, 1C), 62.7, 60.7, 57.4, 55.8, 34.0, 29.0, 27.8, 26.9 (s, 2C), 24.2, 18.6;

^{19}F NMR (376MHz, DMSO-*d6*) δ -105.9;

HRMS (ESI-TOF): calc'd for $C_{23}H_{27}F_2NO_2S$ [M+H$^+$] 419.1731; found 419.1728.

Slow-eluting Diastereoisomer (EtOAc/hexanes) [trans]:

Physical State: beige solid (m.p. = 67.8 °C);

R_f = 0.3 (10% EtOAc in hexanes, vis. UV);

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.73 (t, *J* = 9.2 Hz, 1H), 7.60 - 7.65 (m, 2H), 7.13 - 7.32 (m, 5H), 3.90 - 4.07 (m, 1H), 3.51 (s, 2H), 2.31 - 2.45 (m, 3H), 3.09 - 3.23 (m, 1H), 1.96 - 2.07 (m, 1H), 1.62 - 1.96 (m, 8H), 1.37 - 1.60 (m, 3H);

^{13}C NMR (101 MHz, DMSO-*d6*) δ 162.8 (dd, *J* = 12, 252 Hz, 2C), 142.3 (t, *J* = 8.1 Hz, 1C), 141.2, 128.5 (s, 2C), 128.5 (s, 2C), 127.0, 112.4 (dd, *J* = 8.1, 19.8 Hz, 2C), 110.2 (t, *J* = 25.7 Hz, 1C), 62.3, 61.4, 57.6, 55.6, 33.9, 28.9, 28.6, 27.0 (s, 2C), 25.1, 18.6;

^{19}F NMR (376 MHz, DMSO-*d6*) δ -105.9;

HRMS (ESI-TOF): calc'd for $C_{23}H_{27}F_2NO_2S$ [M+H$^+$] 419.1731; found 419.1727.

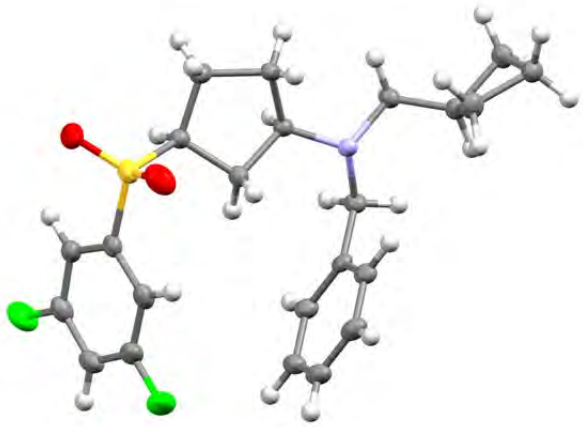
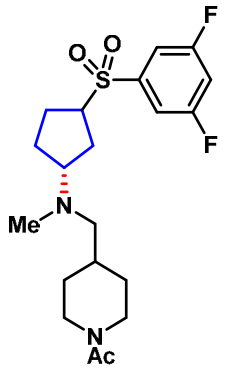


Fig. S116. Crystal structure of the minor diastereoisomer (1*R*,3*S*)-*N*-benzyl-*N*-(cyclobutylmethyl)-3-((3,5-difluorophenyl)sulfonyl)cyclopentan-1-amine (**189**).

Identification code	110685-2174-003
Empirical formula	$C_{23}H_{27}F_2NO_2S$
Formula weight	419.51
Temperature	100.0 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 1 21 1

Unit cell dimensions	a = 5.4305(5) Å	α= 90°.
	b = 14.9364(14) Å	β= 91.931(2)°.
	c = 12.9201(12) Å	γ = 90°.
Volume	1047.38(17) $Å^3$	
Z	2	
Density (calculated)	1.330 Mg/m^3	
Absorption coefficient	0.191 mm^{-1}	
F(000)	444	
Crystal size	0.374 x 0.106 x 0.087 mm^3	
Crystal color, habit	Colorless Rod	
Theta range for data collection	1.577 to 25.357°.≤	
Index ranges	$-4 \leq h \leq 6$, $-17 \leq k \leq 18$, $-15 \leq l \leq 15$	
Reflections collected	14017	
Independent reflections	3834 [R(int) = 0.0463, R(sigma) = 0.0479]	
Completeness to theta = 68.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2590 and 0.2269	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3834 / 1 / 262	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R_1 = 0.0354, wR_2 = 0.0751	
R indices (all data)	R_1 = 0.0440, wR_2 = 0.0794	
Absolute structure parameter	0.00(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.152 and -0.213 $e.Å^{-3}$	



190

1-(4-((((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)(methyl)amino)methyl)piperidin-1-yl)ethan-1-one (190)

In a 1 dram vial, 1-(4-((methylamino)methyl)piperidin-1-yl)ethan-1-one (83 mg, 0.49 mmol) was diluted with DMSO (1.2 mL) and **(+)-9** (125 mg, 0.512 mmol) was added. The mixture was stirred at 80 °C for 17 h after which the temperature was lowered to rt. Water and EtOAc were added, the layers were separated and the aqueous phase extracted several times using EtOAc and then CH_2Cl_2. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered and concentrated to provide the crude product that was further purified using silica gel chromatography to provide **190** in 67% yield.

Physical State: viscous oil;

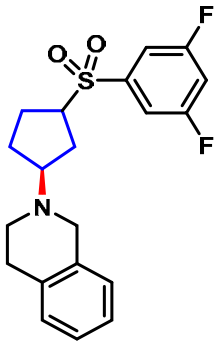
R_f = 0.45 (10% MeOH in CH_2Cl_2, vis. UV);

^{1}H NMR (400 MHz, CD_3CN) δ 7.54 - 7.47 (m, 2H), 7.31 (tt, *J* = 9.0, 2.4 Hz, 1H), 4.45 - 4.36 (m 1H), 3.82 - 3.59 (m, 2H), 3.05 - 2.90 (m, 1H), 2.87 - 2.72 (m, 1H), 2.17 - 2.09 (m, 6H), 2.09 - 2.00 (m, 1H), 1.99 - 1.96 (m, 3H), 1.92 - 1.59 (m 7H), 1.53 - 1.40 (m, 1H), 1.07 - 1.82 (m, 2H);

^{13}C NMR (101 MHz, CD_3CN) δ 169.2, 163.9 (dd, *J* = 252.7, 11.9 Hz), 143.3 (2 x t, *J* = 8.2 Hz, diastereoisomers), 113.0 (2 x dd, *J* = 17.4, 8.5 Hz, diastereoisomers), 110.22 (2 x t, *J* = 25.7 Hz, diastereoisomers) 66.9, 66.5, 63.1, 62.7, 62.1 (2C), 62.0, 47.2, 42.1, 40.5, 40.4, 35.2, 32.0, 31.9, 31.4, 31.3, 31.2 (2C), 30.9, 30.6, 29.8, 29.7, 26.0, 25.1, 21.7, mixture of diastereoisomers.

^{19}F NMR (376 MHz, CD_3CN) δ -107.59;

HRMS (ESI-TOF): calc'd for $C_{20}H_{29}N_2O_3S$ [M+H$^+$] 415.1861; found 415.1872.



191

2-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-1,2,3,4-tetrahydroisoquinoline (191)

To a test tube were added (–)-**9** (0.1 mmol, 24.4 mg), tetrahydroisoquinoline (0.12 mmol, 16 uL) and DMSO (0.3 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (CH_2Cl_2/EtOAc = 2/1) to give **191** in 72% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 75% yield.

***Major Diastereoisomer*:**

Physical State: colorless liquid;

R_f = 0.5 (33% EtOAc in CH_2Cl_2, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.14 – 7.07 (m, 4H), 7.01 – 6.98 (m, 1H), 3.68 (s, 2H), 3.60 – 3.51 (m, 1H), 2.91 – 2.83 (m, 3H), 2.82 – 2.73 (m, 2H), 2.28 – 2.21 (m, 2H), 2.08 – 1.99 (m, 2H), 1.97 – 1.89 (m, 1H), 1.81 (dq, *J* = 12.3, 9.6 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.9, 11.5 Hz), 142.0 (t, *J* = 7.7 Hz), 134.3, 134.2, 128.8, 126.8, 126.4, 125.9, 112.3 (dd, *J* = 21.5, 6.4 Hz), 109.5 (t, *J* = 25.2 Hz), 65.6, 62.5, 54.8, 49.1, 31.5, 29.1, 29.1, 29.0, 24.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.22;

HRMS (ESI-TOF): calc'd for $C_{20}H_{22}F_2NO_2S$ [M+H$^+$] 378.1339; found 378.1339;

$[\alpha]_D^{20}$ = +1.1 (c = 1.0, $CHCl_3$).

***Minor Diastereoisomer*:**

Physical State: white solid, (m.p. = 91 °C);

R_f = 0.4 (33% EtOAc in CH_2Cl_2, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.13 – 7.07 (m, 4H), 7.02 – 6.99 (m, 1H), 3.71 – 3.62 (m, 3H), 3.01 – 2.94 (m, 1H), 2.90 – 2.86 (m, 2H), 2.80 – 2.73 (m, 2H), 2.47 (dddd, *J* = 14.1, 7.7, 5.5, 1.1 Hz, 1H), 2.22 – 2.16 (m, 1H), 2.12 – 2.02 (m, 2H), 1.98 (ddd, *J* = 13.9, 10.2, 8.1 Hz, 1H), 1.68 – 1.62 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 255.9, 11.5 Hz), 142.2 (t, *J* = 7.7 Hz), 134.3, 134.1, 128.8, 126.8, 126.5, 125.9, 112.2 (dd, *J* = 21.9, 6.6 Hz), 109.5 (t, *J* = 25.3 Hz), 65.1, 62.8, 55.0, 49.5, 31.3, 30.9, 29.1, 25.8;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.16;

HRMS (ESI-TOF): calc'd for $C_{20}H_{22}F_2NO_2S$ [$M+H^+$] 378.1339; found 378.1338;

$[\alpha]_D^{20}$ = –1.4 (c = 0.4, $CHCl_3$).

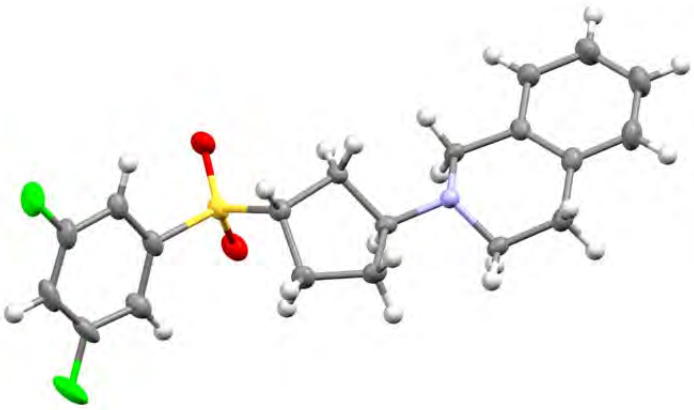


Fig. S117. Crystal structure of the minor diastereoisomer 2-((1*S*,3*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-1,2,3,4-tetrahydroisoquinoline (**191**).

Empirical formula	$C_{20}H_{21}F_2NO_2S$	
Formula weight	377.44	
Temperature	125 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C 1 2 1	
Unit cell dimensions	a = 63.0604(12) Å	α= 90°.
	b = 6.02030(10) Å	β= 98.1230(10)°.
	c = 9.4894(2) Å	γ = 90°.
Volume	3566.43(12) $Å^3$	
Z	8	
Density (calculated)	1.406 Mg/m^3	
Absorption coefficient	1.920 mm^{-1}	
F(000)	1584	
Crystal size	0.131 x 0.125 x 0.087 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	2.831 to 68.324°.	
Index ranges	$-75 \leq h \leq 75$, $-7 \leq k \leq 7$, $-11 \leq l \leq 10$	
Reflections collected	21244	
Independent reflections	6431 [R(int) = 0.0516, R(sigma) = 0.0517]	
Completeness to theta = 68.000°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3201 and 0.2033	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6431 / 1 / 469	
Goodness-of-fit on F^2	1.076	
Final R indices [I>2sigma(I)]	R_1 = 0.0338, wR_2 = 0.0790	
R indices (all data)	R_1 = 0.0372, wR_2 = 0.0809	
Absolute structure parameter	0.027(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.202 and -0.240 $e.Å^{-3}$	

The above reaction was also run with (+)-**9** and the minor diastereoisomer was characterized by X-ray crystallography.

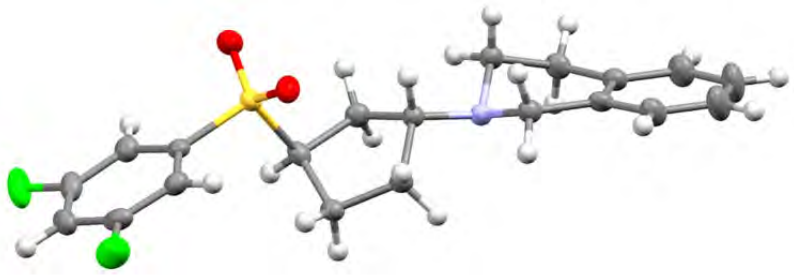
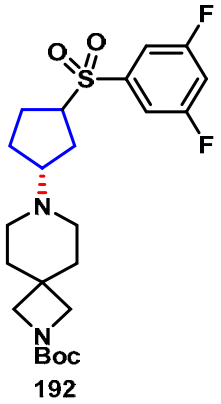


Fig. S118. Crystal structure of the minor diastereoisomer 2-((1*R*,3*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-1,2,3,4-tetrahydroisoquinoline (***ent*-191**).

Identification code	60711B	
Empirical formula	$C_{20}H_{21}F_2NO_2S$	
Formula weight	377.44	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C 1 2 1	
Unit cell dimensions	a = 63.0115(19) Å	α= 90°.
	b = 6.0061(2) Å	β= 98.1860(10)°.
	c = 9.4791(3) Å	γ = 90°.
Volume	3550.8(2) $Å^3$	
Z	8	
Density (calculated)	1.412 Mg/m^3	
Absorption coefficient	1.928 mm^{-1}	
F(000)	1584	
Crystal size	0.134 x 0.122 x 0.095 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	1.417 to 68.328°.	
Index ranges	$-75 \leq h \leq 73$, $-6 \leq k \leq 7$, $-11 \leq l \leq 11$	
Reflections collected	29665	
Independent reflections	6267 [R(int) = 0.0678, R(sigma) = 0.0541]	
Completeness to theta = 68.000°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3200 and 0.1518	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	6267 / 1 / 469
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	$R_1 = 0.0380$, $wR_2 = 0.0984$
R indices (all data)	$R_1 = 0.0401$, $wR_2 = 0.1003$
Absolute structure parameter	0.042(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.250 and -0.442 e.Å^{-3}



192

***tert*-butyl 7-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate (192)**

To a Teflon-capped screw top vial with stirbar was added **(+)-9** (120 mg, 0.491 mmol, 1.0 equiv) and tert-butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate (133 mg, 0.590 mmol, 1.2 equiv). The solids were dissolved in DMSO (4.91 mL, 0.1 M) and the atmosphere was sparged with argon. The resulting solution was stirred at room temperature overnight. The mixture was quenched with water and extracted with MTBE (x4). The combined organic layer was dried over $MgSO_4$, filtered and concentrated to give crude product. The crude product was purified using silica gel chromatography to provide **192** in 78% yield.

Physical State: colorless oil;

R_f = 0.59 (10% MeOH in CH_2Cl_2);

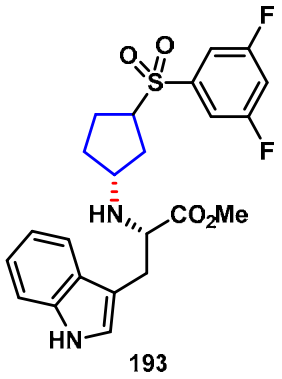
^{1}H NMR (400MHz, $CDCl_3$): δ = 7.47 - 7.38 (m, 2H), 7.15 - 7.05 (m, 1H), 3.58 (s, 4H), 3.54 - 3.44 (m, 1H), 2.65 - 2.54 (m, 1H), 2.46 - 2.25 (m, 4H), 2.21 - 2.05 (m, 2H), 1.95 - 1.80 (m, 3H), 1.74 (t, *J*=5.1 Hz, 4H), 1.70 - 1.63 (m, 1H), 1.43 (s, 9H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0 (dd, $^1J_{C\text{-}F}$ = 257.5, 12.1 Hz, 2C), 156.4 (2C), 141.9 (t, $^3J_{C\text{-}F}$ = 8.0 Hz), 112.2, 112.1, 109.2 (2 x t, $^2J_{C\text{-}F}$ = 25 Hz), 79.31 (minor

diastereoisomer), 79.2 (major diastereoisomer), 66.0, 65.3 (minor diastereoisomer), 62.4 (minor diastereoisomer), 62.24 (major diastereoisomer), 49.0 (minor diastereoisomer), 48.77 (major diastereoisomer), 35.3, 33.1, 33.0 (minor diastereoisomer), 31.1, 28.8 (minor diastereoisomer), 28.3 (major diastereoisomer), 25.5 (minor diastereoisomer), 24.3 (major diastereoisomer);

^{19}F NMR (376 MHz, $CDCl_3$): major: δ –104.97; minor: δ –104.85;

HRMS (ESI-TOF): calc'd for $C_{23}H_{33}F_2N_2O_4S$ [M+H] 471.2124; found 471.2139.



193

methyl ((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-*L*-tryptophanate (193)
Synthesized using the "General Procedure: Amino Acids" on 0.1 mmol scale to provide **193** in 58% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give **193** in 49% yield.

Physical State: colorless liquid;

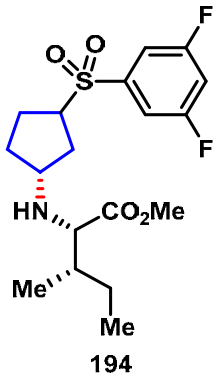
R_f = 0.5 (60% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 1H), 7.60 – 7.58 (m, 1H, major diastereoisomer), 7.56 – 7.54 (m, 1H, minor diastereoisomer), 7.41 – 7.33 (m, 3H), 7.21 – 7.16 (m, 1H), 7.14 – 7.05 (m, 3H), 3.64 (s, 3H, major diastereoisomer), 3.63 (s, 3H, minor diastereoisomer), 3.56 – 3.53 (m, 1H, minor diastereoisomer), 3.44 – 3.37 (m, 1H, major diastereoisomer), 3.28 – 3.25 (m, 1H, minor diastereoisomer), 3.19 – 3.15 (m, 1H, major diastereoisomer), 3.13 – 2.99 (m, 2H), 2.16 – 1.93 (m, 2H), 1.87 – 1.64 (m, 5H), 1.47 – 1.38 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.6, 175.4, 163.0 (dd, *J* = 255.4, 11.1 Hz), 142.4 (t, *J* = 7.6 Hz, minor diastereoisomer), 142.2 (t, *J* = 7.7 Hz, major diastereoisomer), 136.4, 136.3, 127.6, 127.4, 123.3, 122.7, 122.3, 119.6, 119.6, 118.8, 118.8, 112.2 (2 x dd, *J* = 21.6, 6.4 Hz), 111.5, 111.4, 111.3, 111.1, 109.4 (2 x t, *J* = 24.8 Hz), 62.8, 62.6, 60.4, 60.2, 57.6, 57.3, 52.0, 34.8, 34.5, 31.7, 31.6, 29.7, 24.6, 24.4;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.32 (major diastereoisomer), -105.36 (minor diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{23}H_{25}F_2N_2O_4S$ [M+H$^+$] 463.1503; found 463.1505.



194

methyl ((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-*L*-isoleucinate (194)
Synthesized using the "General Procedure: Amino Acids" on 0.1 mmol scale to provide **194** in 41% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 43% yield.

Physical State: colorless liquid;

***R*$_f$** = 0.5 (66% EtOAc in hexanes, vis. UV);

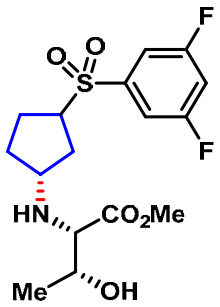
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.09 (tt, *J* = 8.3, 2.3 Hz, 1H), 3.69 (s, 3H), 3.51 – 3.44 (m, 1H), 3.03 – 2.97 (m, 2H), 2.26 – 2.17 (m, 1H), 2.12 – 2.03 (m, 1H), 1.89 – 1.75 (m, 3H), 1.60 – 1.45 (m, 4H), 1.17 – 1.07 (m, 1H), 0.90 – 0.82 (m, 6H), mixture of diastereoisomers;

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.9, 163.2 (2 x dd, *J* = 255.6, 11.4 Hz), 142.2 (t, *J* = 7.7 Hz), 112.5 – 111.9 (m, overlapping diastereoisomers), 109.4 (2 x t, *J* = 24.8 Hz), 64.9,

63.9, 63.0, 62.8, 57.9, 57.4, 51.7 (2C), 38.5, 38.4, 35.2, 34.7, 31.9, 31.4, 29.8, 25.4, 24.8, 24.6, 15.8 (2C), 11.4, mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.36 (minor diastereoisomer), -105.39 (major diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{18}H_{26}F_2NO_4S$ [$M+H^+$] 390.1551; found 390.1556.



195

methyl ((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-*L*-threoninate (195)
Synthesized using the "General Procedure: Amino Acids" on 0.1 mmol scale to provide **195** in 57% yield as a mixture of diastereoisomers.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 57% yield.

Physical State: colorless liquid;

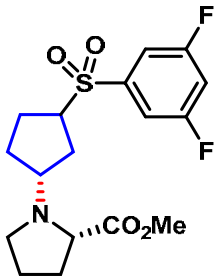
R_f = 0.5 (75% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.13 – 7.08 (m, 1H), 3.75 (s, 3H, major diastereoisomer), 3.74 (s, 3H, minor diastereoisomer), 3.74 – 3.69 (m, 1H, major diastereoisomer), 3.66 – 3.59 (m, 1H), 3.53 – 3.47 (m, 1H, minor diastereoisomer), 3.33 – 3.28 (m, 1H, major diastereoisomer), 3.16 – 3.11 (m, 1H, minor diastereoisomer), 2.98 – 2.95 (m, 1H), 2.31 – 2.20 (m, 1H), 2.16 – 2.00 (m, 2H), 1.97 – 1.82 (m, 2H), 1.74 – 1.68 (m, 1H), 1.59 – 1.52 (m, 1H), 1.18 (2 x d, J = 6.2 Hz, 3H, overlapping diastereoisomers);

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4 (major diastereoisomer), 174.3 (minor diastereoisomer), 163.3 (2 x dd, J = 255.7, 11.4 Hz), 142.3 (2 x t, J = 7.8 Hz), 112.37 – 111.98 (m, mixture of diastereoisomers), 109.5 (2 x t, J = 24.9 Hz), 68.1 (2C), 66.9, 65.9, 62.8, 57.9, 57.7, 52.4, 52.3, 34.8, 34.5, 31.7, 24.8, 24.7, 19.3, mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.13 (major diastereoisomer), -105.15 (minor diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{16}H_{22}F_2NO_5S$ [M+H$^+$] 378.1187; found 378.1190.



196

methyl ((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-*L*-prolinate (196)
Synthesized using the "General Procedure: Amino Acids" on 0.1 mmol scale to provide **196** in 60% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 53% yield.

Physical State: colorless liquid;

R_f = 0.5 (60% EtOAc in hexanes, vis. UV);

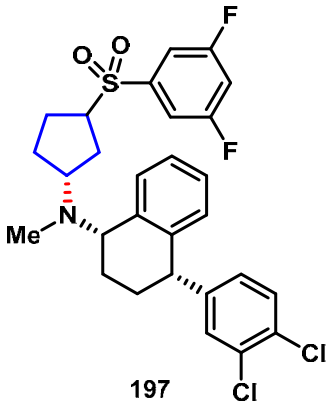
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.11 – 7.07 (m, 1H), 3.68 (s, 3H), 3.52 – 3.45 (m, 1H), 3.35 (dd, *J* = 9.1, 4.0 Hz, 1H), 3.15 – 3.06 (m, 1H), 2.98 – 2.91 (m, 1H), 2.61 – 2.55 (m, 1H), 2.25 – 2.07 (m, 2H), 2.06 – 1.99 (m, 1H), 1.98 – 1.69 (m, 7H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.1, 163.0 (dd, *J* = 256.1, 11.3 Hz), 142.0 (t, *J* = 7.8 Hz), 112.5 – 112.0 (m), 109.5 (t, *J* = 25.2 Hz), 64.5, 63.5, 62.4, 52.0, 51.8, 33.0, 30.1, 29.6, 24.2, 23.6;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.32;

HRMS (ESI-TOF): calc'd for $C_{17}H_{22}F_2NO_4S$ [M+H$^+$] 374.1238; found 374.1237;

$[\alpha]_D^{20}$ = –19.8 (c = 1.0, $CHCl_3$).



197

(1*S*,4*S*)-4-(3,4-dichlorophenyl)-*N*-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (197)

To a test tube were added (+)-**9** (0.1 mmol, 24.4 mg), Sertraline hydrochloride (0.10 mmol, 34.2 mg), K_2CO_3 (0.15 mmol, 20.7 mg) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 4/1) to give **197** in 57% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 53% yield.

Physical State: colorless amorphous solid;

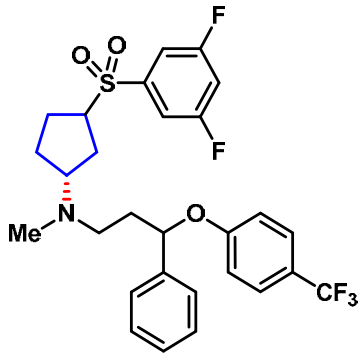
R_f = 0.5 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (t, *J* = 8.1 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.33 – 7.30 (m, 1H), 7.26 – 7.22 (m, 1H), 7.16 – 7.08 (m, 3H), 6.91 – 6.88 (m, 1H), 6.81 – 6.78 (m, 1H), 4.16 – 4.11 (m, 1H), 4.02 – 3.92 (m, 1H), 3.70 – 3.63 (m, 1H), 3.32 – 3.25 (m, 1H), 2.39 – 2.27 (m, 1H), 2.18 – 2.10 (m, 1H), 2.10 – 2.07 (m, 3H), 2.07 – 1.92 (m, 5H), 1.70 – 1.60 (m, 3H), mixture of diastereoisomers;

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 255.8, 11.5 Hz), 147.6, 147.5, 142.2 (q, *J* = 8.1, 7.3 Hz), 139.6, 138.1, 132.3, 130.8, 130.5, 130.5, 130.1, 130.0, 128.3, 128.1, 128.0, 127.2, 127.0, 112.2 (dd, *J* = 22.3, 5.7 Hz), 109.5 (t, *J* = 24.5 Hz), 62.8, 62.8, 61.9, 61.5, 60.2, 59.9, 43.5, 34.1, 33.8, 32.0, 31.7, 31.4, 31.0, 30.3 (2C), 25.7, 25.5, 15.9, 15.6, mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.21, -105.23, pair of diastereoisomers;

HRMS (ESI-TOF): calc'd for $C_{28}H_{28}Cl_2F_2NO_2S$ [M+H^+] 550.1186; found 550.1163.



198

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)-*N*-methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)cyclopentan-1-amine (198)

To a test tube were added **(+)-9** (0.1 mmol, 24.4 mg), Fluoxetine hydrochloride (0.10 mmol, 34.6 mg), K_2CO_3 (0.15 mmol, 20.7 mg) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (CH_2Cl_2/EtOAc = 4/1) to give the desired product in 84% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 85% yield.

Physical State: colorless liquid;

***R*$_f$** = 0.5 (60% EtOAc in hexanes, vis. UV);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 4H), 7.34 – 7.31 (m, 4H), 7.30 – 7.25 (m, 1H), 7.10 (tt, *J* = 8.3, 2.6 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.32 – 5.22 (m, 1H), 3.50 – 3.40 (m, 1H), 2.87 – 2.74 (m, 1H), 2.67 – 2.55 (m, 1H), 2.55 – 2.39 (m, 1H), 2.24 (s, 3H), 2.20 – 2.08 (m, 2H), 2.07 – 1.56 (m, 6H), [major pair of diastereoisomers];

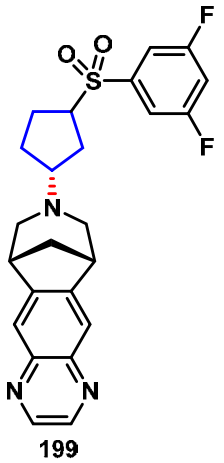
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.8, 11.5 Hz), 160.7, 142.2 (t, *J* = 7.7 Hz), 141.2, 128.9, 128.0, 127.02 – 126.78 (m), 124.8 (q, *J* = 271.3 Hz), 126.0 (2C), 123.3 – 122.5 (m), 115.9, 112.2 (dd, *J* = 22.4, 6.9 Hz), 109.5 (t, *J* = 24.9 Hz), 78.3, 78.2, 65.9 (2C),

62.4, 62.3, 51.6, 51.5, 39.5, 36.4, 30.7, 30.3, 28.7, 24.6, 24.5, [major pair of diastereoisomers];

^{19}F NMR (376 MHz, $CDCl_3$) δ -61.83, -61.84, -105.24, [major pair of diastereoisomers];

HRMS (ESI-TOF): calc'd for $C_{28}H_{29}F_5NO_3S$ [M+H$^+$] 554.1783; found 554.1799;

$[\alpha]_D^{20}$ = –2.9 (c = 1.0, $CHCl_3$).



199

(6*R*,10*S*)-8-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxaline (199)

To a Teflon-capped screw top vial with stirbar was added **(+)-9** (120 mg, 0.491 mmol, 1.0 equiv) and amine (195 mg, 0.540 mmol, 1.1 equiv). The solids were dissolved in DMSO (4.91 mL, 0.1 M) and the atmosphere was sparged with argon. The resulting solution was stirred at room temperature overnight. The mixture was quenched with water and extracted with methyl *tert*-butyl ether (x4). The combined organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude product. The crude product was subsequently purified using silica gel chromatography to furnish **199** in 89% yield as two separable diastereoisomers.

Cis-Diastereoisomer:

Physical State: yellow foam;

$\mathbf{R_f}$ = 0.54 (10% MeOH in CH_2Cl_2);

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.79 - 8.71 (m, 2H), 7.83 - 7.72 (m, 2H), 7.40 - 7.31 (m, 2H), 7.11 - 7.02 (m, 1H), 3.45 - 3.28 (m, 3H), 3.12 - 2.97 (m, 2H), 2.71 (br. s., 1H), 2.62 - 2.48 (m, 2H), 2.38 - 2.29 (m, 1H), 2.23 - 2.11 (m, 1H), 2.08 - 1.98 (m, 1H), 1.98 - 1.88 (m, 1H), 1.85 (d, *J*=10.5 Hz, 1H), 1.81 - 1.65 (m, 2H), 1.50 - 1.37 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0 (dd, $^{1}J_{C\text{-}F}$ = 258, 11.1 Hz, 2C), 150.1, 143.4 (dd, $J_{C\text{-}F}$ = 6.1, 2.0 Hz) 143.3 (t, $J_{C\text{-}F}$ = 2.0 Hz), 142.0 (t, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 120.7, 120.6, 112.0 (q, $^{2}J_{C\text{-}F}$ = 9.0 Hz, 2C), 109.3 (t, $^{2}J_{C\text{-}F}$ = 25.3 Hz), 65.6, 62.2, 62.1, 56.5, (d, *J* = 36.3 Hz), 55.9 (d, *J* = 27.3 Hz), 43.0, 41.0, 40.9, 30.4, 30.1, 28.2, 25.1, 24.1;

^{19}F NMR (376 MHz, $CDCl_3$): δ –104.9;

HRMS (ESI-TOF): calc'd for $C_{24}H_{24}F_2N_3O_2S$ [M+H] 456.1552; found 456.1550.

Trans-Diastereoisomer:

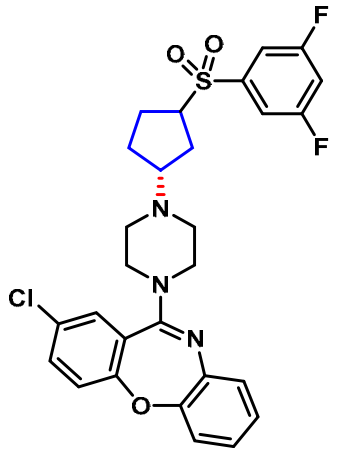
Physical State: yellow foam;

R_f = 0.49 (10% MeOH in CH_2Cl_2);

^{1}H NMR (400MHz, $CDCl_3$): δ = 8.78 - 8.69 (m, 2H), 7.81 - 7.71 (m, 2H), 7.39 - 7.30 (m, 2H), 7.10 - 7.00 (m, 1H), 3.36 (br. s., 3H), 3.02 (br. s., 2H), 2.70 (d, *J*=6.2 Hz, 1H), 2.56 (dd, *J*=3.7, 9.6 Hz, 2H), 2.36 - 2.26 (m, 1H), 2.21 - 2.10 (m, 1H), 2.06 - 1.99 (m, 1H), 1.99 - 1.90 (m, 1H), 1.84 (d, *J*=10.9 Hz, 1H), 1.80 - 1.64 (m, 2H), 1.47 - 1.35 (m, 1H), 1.47 - 1.35 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0 (dd, $^{1}J_{C\text{-}F}$ = 258, 11.1 Hz, 2C), 150.2, 143.4 (dd, $J_{C\text{-}F}$ = 7.0, 2.0 Hz), 143.3 (t, $J_{C\text{-}F}$ = 2.0 Hz), 142.0 (t, $^{3}J_{C\text{-}F}$ = 7.0 Hz), 120.7, 120.6, 112.0 (q, $^{2}J_{C\text{-}F}$ = 9.0 Hz, 2C), 109.3 (t, $^{2}J_{C\text{-}F}$ = 25.3 Hz), 65.6, 62.2, 62.1, 56.4, (d, *J* = 35.4 Hz), 55.9 (d, *J* = 27.3 Hz), 43.0, 41.0, 40.9, 30.4, 30.1, 28.2, 25.1, 24.1;

^{19}F NMR (376 MHz, $CDCl_3$): δ –104.9.



200

2-chloro-11-(4-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)piperazin-1-yl)dibenzo[b,f][1,4]oxazepine (200)

To a test tube were added (+)**-9** (0.1 mmol, 24.4 mg), Amoxapine (0.10 mmol, 31.4 mg) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (Hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 1/3) to give **200** in 92% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 86% yield.

Major Diastereoisomer:

Physical State: colorless liquid;

R_f = 0.4 (75% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.38 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.14 – 7.06 (m, 4H), 7.00 – 6.97 (m, 1H), 3.67 – 3.61 (m, 1H), 3.51 (br, 4H), 2.88 (t, *J* = 7.9 Hz, 1H), 2.60 (br, 4H), 2.39 (ddd, *J* = 13.4, 7.6, 5.1 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.91 (d, *J* = 12.3 Hz, 1H), 1.74 – 1.54 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.0, 11.4 Hz), 159.5, 158.9, 151.9, 142.1 (t, *J* = 7.7 Hz), 140.2, 132.7, 130.4, 129.2, 127.2, 125.9, 125.0, 124.8, 122.9, 120.2, 112.2 (dd, *J* = 21.8, 6.2 Hz), 109.6 (t, *J* = 24.9 Hz), 65.5, 62.7, 51.7, 47.3, 30.9, 30.4, 25.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.07;

HRMS (ESI-TOF): calc'd for $C_{28}H_{28}F_2N_3O_3S$ [M+H$^+$] 558.1430; found 558.1421;

$[\alpha]_D^{20}$ = +11.6 (c = 1.0, $CHCl_3$).

Minor Diastereoisomer:

Physical State: colorless liquid;

R_f = 0.5 (75% EtOAc in hexanes, vis. UV);

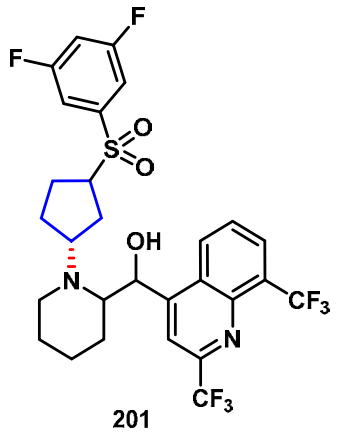
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.14 – 7.06 (m, 4H), 7.00 – 6.97 (m, 1H), 3.61 – 3.49 (m, 4H), 2.75 (s, 1H), 2.61 (s, 4H), 2.27 – 2.16 (m, 2H), 2.03 – 1.94 (m, 1H), 1.93 – 1.86 (m, 1H), 1.81 – 1.73 (m, 1H), 1.62 (br, 4H, 2H overlapping with residual H_2O signal);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.2, 11.2 Hz), 159.5, 158.8, 151.9, 142.0 (t, *J* = 6.4 Hz), 140.2, 132.7, 130.4, 129.2, 127.2, 126.0, 125.0, 124.7, 122.9, 120.2, 112.3 (dd, *J* = 21.5, 6.5 Hz), 109.6 (t, *J* = 24.9 Hz), 66.2, 62.4, 51.5, 47.2, 31.2, 28.8, 24.6;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.10;

HRMS (ESI-TOF): calc'd for $C_{28}H_{28}F_2N_3O_3S$ [M+H$^+$] 558.1430; found 558.1419;

$[\alpha]_D^{20}$ = +2.3 (c = 0.77, $CHCl_3$).



201

(2,8-bis(trifluoromethyl)quinolin-4-yl)(1-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)piperidin-2-yl)methanol (201)

To a test tube were added (+)-**9** (0.1 mmol, 24.4 mg), Mefloquine hydrochloride (0.10 mmol, 41.4 mg) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/EtOAc = 1/1) to give **201** in 32% yield (85% brsm).

Notes: 0.053 mmol of starting material was recovered after purification. The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 35% yield.

Physical State: colorless liquid;

R_f = 0.4 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.15 (m, 2H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 5.83 (d, *J* = 3.8 Hz, 1H), 4.05 (p, *J* = 7.9 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.10 – 3.05 (m, 1H), 2.95 (dt, *J* = 11.1, 3.7 Hz, 1H), 2.50 – 2.42 (m, 2H), 2.24 – 2.17 (m, 1H), 2.14 – 2.04 (m, 2H), 1.95 – 1.85 (m, 2H), 1.73 – 1.67 (m, 1H), 1.63 – 1.58 (m, 1H), 1.46 – 1.36 (m, 1H), 1.34 – 1.26 (m, 2H), 1.05 – 0.96 (m, 1H), 0.61 – 0.56 (m, 1H), [major diastereoisomer];

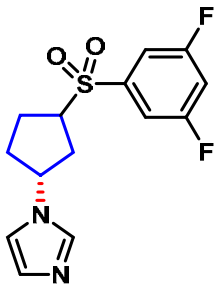
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 256.2, 11.6 Hz), 150.3, 148.6 (q, *J* = 35.2 Hz), 143.8, 142.1 (t, *J* = 8.1 Hz), 130.1, 129.9, 128.8 (q, *J* = 5.5 Hz), 127.3, 126.5, 126.4, 124.5, 124.2, 122.7, 122.3, 120.5, 116.1 (q, *J* = 2.5 Hz), 112.2 (dd, *J* = 21.7, 7.5 Hz), 109.8 (t, *J* = 24.8 Hz), 67.6, 62.9, 61.3, 58.7, 44.6, 28.8, 25.6, 25.3, 25.1, 23.4, 23.3, [major diastereoisomer];

^{19}F NMR (376 MHz, $CDCl_3$) δ -60.65, -68.23, -104.78;

HRMS (ESI-TOF): calc'd for $C_{28}H_{27}F_8N_2O_3S$ [M+H^+] 623.1615; found 623.1621;

$[\alpha]_D^{20}$ = +1.2 (c = 0.82, $CHCl_3$).

NH-Heterocycles



202

1-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-1*H*-imidazole (202)
To a test tube were added (+)-**9** (0.1 mmol, 24.4 mg), imidazole (0.20 mmol, 13.2 mg) and DMSO (0.3 mL). The mixture was heated to 90 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (EtOAc/MeOH = 10/1) to give **202** in 81% yield.

Note: The above reaction was run with racemic **9** to give the desired product in 80% yield.

***Major Diastereoisomer*:**

Physical State: colorless liquid;

R_f = 0.5 (10% MeOH in EtOAc, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (br, 1H), 7.48 – 7.44 (m, 2H), 7.14 (tt, *J* = 8.3, 2.3 Hz, 1H), 7.10 (br, 1H), 7.06 (br, 1H), 4.54 (tt, *J* = 9.5, 7.4 Hz, 1H), 3.68 – 3.61 (m, 1H), 2.55 (dt, *J* = 13.3, 8.0 Hz, 1H), 2.44 (dddd, *J* = 14.2, 9.1, 5.4, 4.0 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.32 – 2.26 (m, 1H), 2.23 – 2.16 (m, 1H), 2.03 (dtd, *J* = 14.3, 9.4, 7.4 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.5 (dd, *J* = 256.2, 11.4 Hz), 141.6 (t, *J* = 7.9 Hz), 136.3, 130.3, 117.0, 112.2 (dd, *J* = 21.3, 6.2 Hz), 110.0 (t, *J* = 24.2 Hz), 61.9, 57.2, 34.2, 32.9, 25.1;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.49;

HRMS (ESI-TOF): calc'd for $C_{14}H_{15}F_2N_2O_2S$ [M+H$^+$] 313.0822; found 313.0801;

$[\alpha]_D^{20}$ = –7.5 (c = 0.8, $CHCl_3$).

***Minor Diastereoisomer*:**

Physical State: colorless liquid;

R_f = 0.6 (10% MeOH in EtOAc, vis. UV);

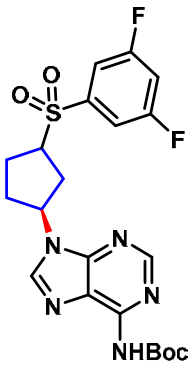
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (br, 1H), 7.49 – 7.44 (m, 2H), 7.14 (tt, *J* = 8.3, 2.3 Hz, 1H), 7.08 (br, 1H), 6.91 (s, 1H), 4.76 (p, *J* = 7.4 Hz, 1H), 3.78 – 3.72 (m, 1H), 2.76 – 2.70 (m, 1H), 2.50 – 2.43 (m, 1H), 2.30 (dtd, *J* = 14.9, 8.4, 6.7 Hz, 1H), 2.19 (dtd, *J* = 14.2, 8.6, 4.5 Hz, 2H), 2.08 – 2.00 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 256.7, 11.4 Hz), 141.5 (t, *J* = 7.9 Hz), 135.9, 130.1, 117.2, 112.2 (dd, *J* = 21.6, 6.5 Hz), 110.0 (t, *J* = 24.9 Hz), 62.1, 57.1, 34.4, 33.0, 25.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.49;

HRMS (ESI-TOF): calc'd for $C_{14}H_{15}F_2N_2O_2S$ [M+H$^+$] 313.0822; found 313.0805;

$[\alpha]_D^{20}$ = +0.8 (c = 0.46, $CHCl_3$).



203

***tert*-butyl (9-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-9*H*-purin-6-yl) carbamate (203)**

To a stirred solution of Boc_2Adenine (40.2 mg, 0.120 mmol, 1.20 equiv.) in THF (0.1 mL) was added LHMDS (0.12 mL, 0.120 mmol, 1.2 equiv.) at rt and stirring was continued for 10 min followed by the addition of DMF (0.3 mL) and (–)**-9** (24.4 mg, 0.100 mmol, 1

equiv.). The resulting mixture was subsequently heated to 80 °C and stirring was continued for 2.5 h followed by the addition of half sat. aq. NH_4Cl and EtOAc. The phases were separated and the aqueous phase was extracted using EtOAc (3 x 4 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to provide **203** in 58% yield.

Note: The above reaction was run with racemic **9** to give the desired product in 61% yield.

Physical State: off-white film;

$\boldsymbol{R_f}$ = 0.57 (EtOAc, vis. UV);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 7.51 – 7.43 (m, 2H), 7.19 – 7.09 (m, 1H), 5.06 (p, *J* = 8.4 Hz, 1H), 3.78 – 3.68 (m, 1H), 2.76 – 2.67 (m, 1H), 2.57 – 2.47 (m, 2H), 2.42 – 2.33 (m, 2H), 2.18 – 2.07 (m, 1H), 1.56 (s, 9H);

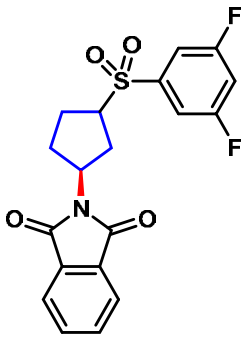
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2 (dd, *J* = 256.7, 11.3 Hz), 153.0, 151.2, 150.1, 149.8, 141.3 (t, *J* = 8.0 Hz), 140.2, 122.0, 112.3 (dd, *J* = 21.9, 6.5 Hz), 110.0 (dd, *J* = 39.4, 10.5 Hz), 82.5, 62.1, 54.6, 33.3, 31.8, 28.3, 25.3;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.45;

HRMS (ESI-TOF): calc'd for $C_{21}H_{24}F_2N_5O_4S$ [M+H^+] 480.1512; found 480.1516;

$\boldsymbol{[\alpha]_D^{20}}$ = +7.4 (c = 0.95, $CHCl_3$).

Amides, Imides and Sulfonamides



204

2-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)isoindoline-1,3-dione (204)
To a stirred solution of phthalimide (18 mg, 0.122 mmol, 1.22 equiv.) in THF (0.1 mL) was added LHMDS (0.12 mL, 0.120 mmol, 1.2 equiv.) at rt and stirring was continued for 10 min followed by the addition of DMF (0.3 mL) and **(–)-9** (24.4 mg, 0.100 mmol, 1 equiv.). The resulting mixture was subsequently heated to 90 °C and stirring was continued for 2.5 h followed by the addition of half sat. aq. NH_4Cl and EtOAc. The phases were separated and the aqueous phase was extracted using EtOAc (3 x 4 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to provide **204** in 53% yield as a mixture of diastereoisomers.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 49% yield.

Physical state: white film;

R_f = 0.23 (50% Et_2O in hexanes, vis. UV);

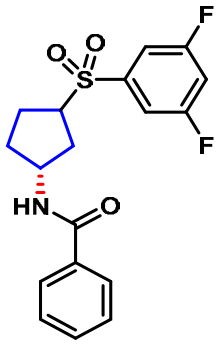
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.5, 3.1 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.78 – 7.74 (m, 1H), 7.73 – 7.70 (m, 1H), 7.50 – 7.46 (m, 2H), 7.14 – 7.08 (m, 1H), 4.95 – 4.88 (m, 1H, major diastereoisomer), 4.67 – 4.60 (m, 1H, minor diastereoisomer), 4.09 – 4.02 (m, 1H, major diastereoisomer), 3.61 – 3.55 (m, 1H, minor diastereoisomer), 2.74 (dt, *J* = 12.6, 10.8 Hz, 1H, minor diastereoisomer), 2.54 – 2.47 (m, 1H), 2.39 (dddd, *J* = 23.2, 14.4, 9.2, 5.6 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.21 – 2.11 (m, 2H), 2.07 – 1.98 (m, 1H, major diastereoisomer);

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.1, 168.0, 167.9, 163.07 (2 x dd, *J* = 256.6, 11.6 Hz, mixture of diastereoisomers), 142.18 (t, *J* = 7.9 Hz, distinct diastereoisomer), 141.73 (t, *J* =

7.9 Hz, distinct diastereoisomer), 134.5, 134.3, 134.3, 132.8, 131.9, 131.9, 123.8, 123.5, 123.4, 112.48 (dd, J = 21.8, 6.5 Hz, distinct diastereoisomer), 112.19 (dd, J = 21.4, 6.8 Hz, distinct diastereoisomer), 109.62 (2 x t, J = 25.6, 24.8 Hz, mixture of diastereoisomers), 63.7, 62.7, 49.9, 49.4, 30.8, 30.4, 30.3, 28.1, 26.9, 25.0 (mixture of diastereoisomers);

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.08 (major diastereoisomer), -105.20 (minor diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{19}H_{16}F_2NO_4S$ [M+H$^+$] 392.0763; found 392.0769.



205

***N*-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)benzamide (205)**
Synthesized using the "General Procedure: Amides, Imides and Sulfonamides" on 0.1 mmol scale to provide **205** in 61% yield.

Note: The above reaction was run with racemic **9** to give the desired product in 55% yield.

Physical State: white solid;

***R*$_f$** = 0.4 (50% EtOAc in hexanes, vis. UV);

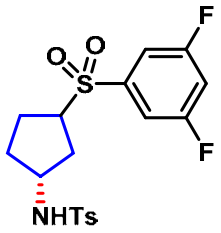
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 1H), 7.71 – 7.68 (m, 1H), 7.52 – 7.41 (m, 4H), 7.40 – 7.36 (m, 1H), 7.21 (d, J = 7.9 Hz, 1H, minor diastereoisomer), 7.15 – 7.08 (m, 1H), 6.29 (d, J = 6.4 Hz, 1H, major diastereoisomer), 4.69 – 4.63 (m, 1H, minor diastereoisomer), 4.53 – 4.46 (m, 1H, major diastereoisomer), 3.75 – 3.68 (m, 1H), 2.49 (dt, J = 14.6, 7.5 Hz, 1H, major diastereoisomer), 2.39 – 2.32 (m, 1H, minor diastereoisomer), 2.31 – 2.25 (m, 1H, major diastereoisomer), 2.24 – 2.09 (m, 1H), 2.05 – 1.98 (m, 1H), 1.96 – 1.90 (m, 1H, minor diastereoisomer), 1.79 – 1.71 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 166.7, 163.1 (2 x dd, J = 251.1, 16.0 Hz, overlapping diastereoisomers), 141.9 (t, J = 7.8 Hz, distinct diastereoisomer), 141.5 (t, J =

7.7 Hz, distinct diastereoisomer), 134.3, 134.1, 131.8 (2C), 128.7 (2C), 127.0 (2C), 127.0, 112.3 (t, J = 6.6 Hz, distinct diastereoisomer), 112.1 (t, J = 6.7 Hz, distinct diastereoisomer), 109.9 (t, J = 24.9 Hz, distinct diastereoisomer), 109.6 (t, J = 24.8 Hz, distinct diastereoisomer) 63.1, 62.7, 51.5, 50.7, 33.8, 33.5, 33.4, 32.3, 25.4, 25.3, **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.58 (minor diastereoisomer), -104.96 (major diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{18}H_{18}F_2NO_3S$ [M+H$^+$] 366.0975; found 366.0956.



206

***N*-((1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)-4-methylbenzenesulfonamide (206)**

Synthesized using the "General Procedure: Amides, Imides and Sulfonamides" on 0.1 mmol scale to provide the desired product in 71% yield.

Note: The above reaction was run with racemic **9** to give the desired product in 74% yield.

***Major Diastereoisomer*:**

Physical State: white amorphous solid;

R_f = 0.6 (10% EtOAc in CH_2Cl_2, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 – 7.75 (m, 2H), 7.37 – 7.34 (m, 2H), 7.33 – 7.31 (m, 2H), 7.11 (tt, J = 8.3, 2.3 Hz, 1H), 5.21 (d, J = 9.0 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.51 – 3.45 (m, 1H), 2.43 (s, 3H), 2.20 – 2.12 (m, 1H), 2.08 – 2.02 (m, 1H), 1.91 – 1.78 (m, 4H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, J = 256.4, 11.2 Hz), 143.8, 141.4 (t, J = 7.9 Hz), 138.1, 130.0, 127.1, 112.2 (dd, J = 21.9, 7.1 Hz), 109.9 (t, J = 25.0 Hz), 62.5, 54.3, 33.9, 33.5, 24.8, 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.68;

HRMS (ESI-TOF): calc'd for $C_{18}H_{20}F_2NO_4S_2$ [M+H^+] 416.0802; found 416.0781;

$[\alpha]_D^{20}$ = +3.5 (c = 1.0, $CHCl_3$).

***Minor Diastereoisomer*:**

Physical State: colorless oil;

R_f = 0.8 (10% EtOAc in CH_2Cl_2, vis. UV);

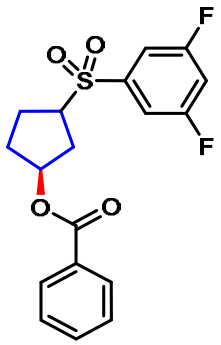
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.13 – 7.08 (m, 1H), 4.57 (s, 1H), 3.76 – 3.71 (m, 1H), 3.62 – 3.56 (m, 1H), 2.45 (s, 3H), 2.23 – 2.18 (m, 1H), 2.14 – 2.06 (m, 1H), 2.06 – 1.98 (m, 2H), 1.87 – 1.81 (m, 1H), 1.56 – 1.52 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 256.7, 11.8 Hz), 144.2, 141.8 (t, *J* = 7.7 Hz), 136.8, 130.1, 127.3, 112.1 (dd, *J* = 21.2, 6.7 Hz), 109.7 (t, *J* = 25.2 Hz), 62.0, 54.4, 34.3, 33.1, 24.4, 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.86;

$[\alpha]_D^{20}$ = +0.54 (c = 1.0, $CHCl_3$).

Carboxylic Acids



207

(1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl benzoate (207)

A screw-cap vial was charged with **(–)-9** (24.4 mg, 0.100 mmol), benzoic acid (14.7 mg, 0.120 mmol, 1.2 equiv), diisopropylamine (0.023 mL, 0.130 mmol, 1.3 equiv) and DMF (0.3 mL) after which the contents were stirred at 90 °C for 23 h. Subsequently, half sat. aq. NaCl was added followed by EtOAc and the phases were separated. The aqueous layer was extracted using EtOAc (3 x 5 mL) , the organic phases combined, washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to provide **207** in 82% yield.

Note: The above reaction was also run with both racemic **9** and (+)**-9** separately on 0.1 mmol scale to give the desired products in 60% yield and 74% yield, respectively.

Major Diastereoisomer:

Physical state: colorless oil;

R_f = 0.29 (50% Et_2O/hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 2H), 7.59 – 7.56 (m, 1H), 7.48 – 7.43 (m, 4H), 7.04 (tt, *J* = 8.4, 2.3 Hz, 1H), 5.39 (tt, *J* = 5.9, 3.9 Hz, 1H), 3.66 – 3.59 (m, 1H), 2.47 (ddd, *J* = 15.6, 9.7, 6.3 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.17 – 2.11 (m, 1H), 2.10 – 1.96 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.2, 163.1 (dd, *J* = 256.1, 11.4 Hz), 142.0 (t, *J* = 7.9 Hz), 133.3, 130.0, 129.8, 128.5, 112.3 (dd, *J* = 21.6, 6.6 Hz), 109.6 (t, *J* = 24.9 Hz), 75.0, 62.8, 33.3, 32.5, 25.4;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.05;

HRMS (ESI-TOF): calc'd for $C_{18}H_{17}F_2O_4S$ [M+H^+] 367.0810; found 367.0814;

$[\alpha]_D^{20}$ = +19.6 (c = 1.05, $CHCl_3$) [product obtained from **(–)-9**].

$[\alpha]_D^{20}$ = –16.6 (c = 0.65, $CHCl_3$) [product obtained from **(+)-9**].

Minor Diastereoisomer:

Physical state: colorless oil;

$\mathbf{R_f}$ = 0.52 (50% Et_2O/hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.56 (ddt, *J* = 8.7, 7.1, 1.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.44 – 7.41 (m, 2H), 7.12 (tt, *J* = 8.3, 2.3 Hz, 1H), 5.57 – 5.54 (m, 1H), 3.81 – 3.75 (m, 1H), 2.43 (ddd, *J* = 14.5, 9.0, 5.4 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.26 – 2.17 (m, 3H), 2.08 – 2.02 (m, 1H);

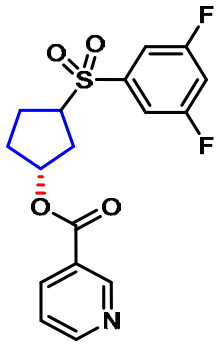
^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 163.1 (dd, *J* = 256.1, 11.3 Hz), 142.1 (t, *J* = 7.8 Hz), 133.4, 130.1, 129.7, 128.6, 112.2 (dd, *J* = 21.6, 6.5 Hz), 109.7 (t, *J* = 24.9 Hz), 76.5, 62.7, 34.4, 32.1, 25.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.91;

HRMS (ESI-TOF): calc'd for $C_{18}H_{17}F_2O_4S$ [M+H^+] 367.0810; found 367.0813;

$[\alpha]_D^{20}$ = +8.0 (c = 0.45, $CHCl_3$) [product obtained from **(–)-9**].

$[\alpha]_D^{20}$ = –6.2 (c = 0.33, $CHCl_3$) [product obtained from **(+)-9**].



208

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl nicotinate (208)
Synthesized using the "General Procedure: Carboxylic Acids" on 0.1 mmol scale to provide **208** in 79% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 84% yield.

Physical State: white solid;

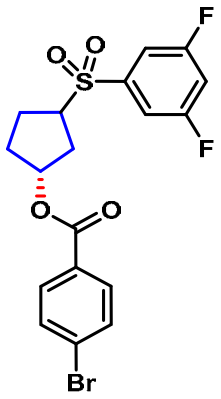
R_f = 0.5 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 – 9.12 (m, 1H), 8.82 – 8.76 (m, 1H), 8.32 (d, *J* = 8.0 Hz, 1H, major diastereoisomer), 8.23 (d, *J* = 8.1 Hz, 1H, minor diastereoisomer), 7.48 – 7.44 (m, 2H), 7.43 – 7.38 (m, 1H), 7.12 (tt, *J* = 8.2, 2.4 Hz, 1H, minor diastereoisomer), 7.08 (tt, *J* = 8.3, 2.3 Hz, 1H, major diastereoisomer), 5.60 – 5.56 (m, 1H, minor diastereoisomer), 5.45 – 5.41 (m, 1H, major diastereoisomer), 3.82 – 3.75 (m, 1H, minor diastereoisomer), 3.67 – 3.60 (m, 1H, major diastereoisomer), 2.50 – 2.44 (m, 1H), 2.41 – 2.14 (m, 3H), 2.09 – 1.97 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 164.6, 163.1 (2 x dd, *J* = 256.3, 11.9 Hz), 153.8, 153.7, 151.1, 150.8, 142.0 (2 x t, *J* = 7.6 Hz), 137.4, 137.2, 126.0, 123.5, 112.3 (2 x dd, *J* = 21.9, 6.5 Hz), 109.7 (2 x t, *J* = 25.1 Hz) 75.6, 62.6, 34.2, 33.3, 32.5, 32.1, 25.4, 25.0, mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.79 (minor diastereoisomer), -104.90 (major diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{17}H_{16}F_2NO_4S$ [$M+H^+$] 368.0768; found 368.0772.



209

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl 4-bromobenzoate (209)
Synthesized using the "General Procedure: Carboxylic Acids" on 0.1 mmol scale to provide **209** in 82% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 72% yield.

Physical State: colorless solid (m.p. = 110 °C);

R_f = 0.2 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.62 – 7.57 (m, 2H), 7.46 (ddd, *J* = 5.0, 2.3, 1.1 Hz, 2H), 7.07 (tt, *J* = 8.3, 2.3 Hz, 1H), 5.38 (tt, *J* = 5.8, 3.8 Hz, 1H), 3.62 (dtd, *J* = 9.6, 8.3, 7.2 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.39 – 2.32 (m, 2H), 2.14 (ddtd, *J* = 13.0, 7.6, 3.6, 1.4 Hz, 1H), 2.09 – 1.94 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.5, 163.1 (dd, *J* = 256.1, 11.5 Hz), 142.1 (t, *J* = 7.9 Hz), 131.9, 131.4, 128.9, 128.5, 112.3 (dd, *J* = 22.2, 6.7 Hz), 109.7 (t, *J* = 24.9 Hz), 75.3, 62.7, 33.3, 32.5, 25.4;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.95;

HRMS (ESI-TOF): calc'd for $C_{18}H_{16}BrF_2O_4S$ [M+H$^+$] 444.9915; found 444.9921;

$[\alpha]_D^{20}$ = –12.4 (c = 1.0, $CHCl_3$).

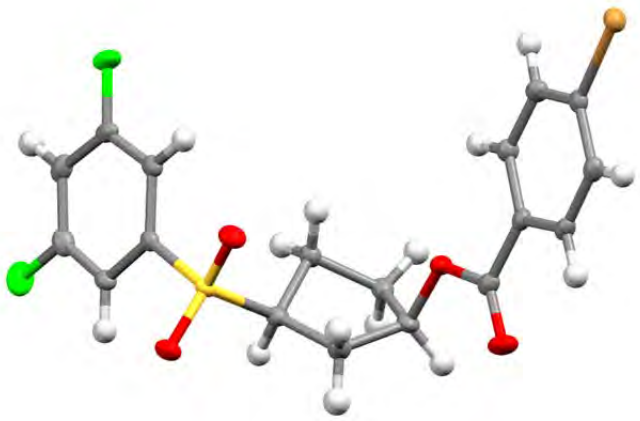
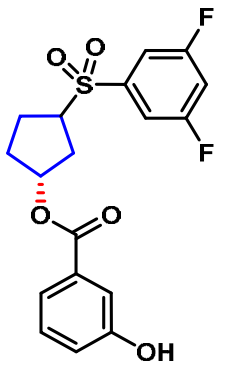


Fig. S119. Crystal structure of (1*R*,3*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl 4-bromobenzoate (**209**).

Identification code	baran590	
Empirical formula	$C_{18}H_{15}BrF_2O_4S$	
Formula weight	445.27	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.4069(3) Å	α= 90°.
	b = 12.6398(4) Å	β= 90°.
	c = 13.3704(4) Å	γ = 90°.
Volume	1758.76(9) $Å^3$	
Z	4	
Density (calculated)	1.682 Mg/m^3	
Absorption coefficient	2.498 mm^{-1}	
F(000)	896	
Crystal size	0.225 x 0.2 x 0.2 mm^3	
Crystal color, habit	colorless block	
Theta range for data collection	2.217 to 27.920°.	
Index ranges	$-13 \leq h \leq 13$, $-16 \leq k \leq 16$, $-17 \leq l \leq 17$	
Reflections collected	27368	
Independent reflections	4207 [R(int) = 0.0872]	
Completeness to theta = 26.000°	100.0 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.4339 and 0.3576
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4207 / 0 / 235
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	$R_1 = 0.0315$, $wR_2 = 0.0775$
R indices (all data)	$R_1 = 0.0355$, $wR_2 = 0.0797$
Absolute structure parameter	0.001(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.283 and -0.410 e.Å^{-3}



210

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl 3-hydroxybenzoate (210)
Synthesized using the "General Procedure: Carboxylic Acids" on 0.1 mmol scale to provide **210** in 56% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 56% yield.

Physical State: colorless liquid;

R_f = 0.6 (50% EtOAc in hexanes, vis. UV);

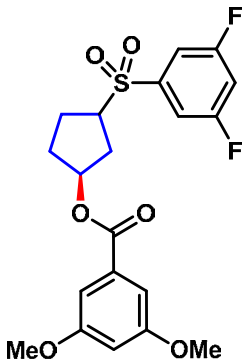
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.53 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.46 (ddd, *J* = 4.9, 2.3, 1.1 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.30 (s, 1H), 5.40 (tt, *J* = 5.6, 3.4 Hz, 1H), 3.64 (dtd, *J* = 9.9, 8.5, 7.0 Hz, 1H), 2.44 (ddd, *J* = 15.8, 10.0, 6.1 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.14 (ddtd, *J* = 12.6, 7.4, 3.5, 1.5 Hz, 1H), 2.05 (dtd, *J* = 13.1, 7.7, 3.5 Hz, 1H), 1.99 – 1.92 (m, 1H) [major diastereoisomer];

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0, 163.1 (dd, *J* = 256.1, 11.7 Hz), 156.1, 141.9 (t, *J* = 7.9 Hz), 131.3, 129.9, 122.1, 120.7, 116.4, 112.3 (dd, *J* = 21.3, 6.6 Hz), 109.7 (t, *J* = 24.8 Hz), 75.2, 62.8, 33.3, 32.7, 25.5 [major diastereoisomer];

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.04 [major diastereoisomer];

HRMS (ESI-TOF): calc'd for $C_{18}H_{17}F_2O_5S$ [$M+H^+$] 383.0765; found 383.0764;

$[\alpha]_D^{20}$ = –9.5 (c = 1.0, $CHCl_3$).



211

(1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl 3,5-dimethoxybenzoate (211)

A screw-cap vial was charged with **(–)-9** (24.4 mg, 0.100 mmol), 3,5-dimethoxybenzoic acid (21.9 mg, 0.120 mmol, 1.2 equiv), diisopropylamine (0.023 mL, 0.130 mmol, 1.3 equiv) and DMF (0.3 mL) after which the contents were stirred at 100 °C for 18 h. Subsequently, half sat. aq. NaCl was added followed by EtOAc and the phases were separated. The aqueous layer was extracted using EtOAc (3 x 5 mL), the organic phases combined, washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to provide **211** in 50% yield.

Note: The above reaction was run with racemic **9** on 0.41 mmol scale to give the desired product in 67% yield.

***Major Diastereoisomer*:**

Physical State: white solid (m.p. = 128-129 °C);

R_f = 0.57 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.20 (d, *J* = 2.3 Hz, 2H), 7.07 – 7.03 (m, 1H), 6.67 – 6.65 (m, 1H), 5.39 – 5.36 (m, 1H), 3.84 (s, 6H), 3.66 – 3.60 (m, 1H), 2.44 (ddd, *J* = 15.6, 9.8, 6.1 Hz, 1H), 2.39 – 2.32 (m, 2H), 2.16 – 2.11 (m, 1H), 2.08 – 2.02 (m, 1H), 1.97 (dddd, *J* = 13.1, 9.9, 7.3, 5.4 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 163.1 (dd, *J* = 256.0, 11.3 Hz), 160.8, 142.0 (t, *J* = 7.9 Hz), 131.9, 112.3 (dd, *J* = 21.5, 6.1 Hz), 109.6 (t, *J* = 24.9 Hz), 107.4, 106.2, 75.2, 62.7, 55.8, 33.3, 32.5, 25.3;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.05;

HRMS (ESI-TOF): calc'd for $C_{20}H_{21}F_2O_6S$ [M+H^+] 427.1021; found 427.1027;

$[\alpha]_D^{20}$ = –27.5 (c = 0.65, $CHCl_3$).

***Minor Diastereoisomer*:**

Physical State: white film;

R_f = 0.66 (50% EtOAc in hexanes, vis. UV);

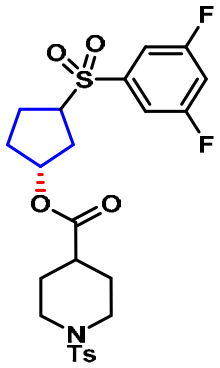
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.14 – 7.10 (m, 1H), 7.08 (d, *J* = 2.3 Hz, 2H), 6.64 – 6.63 (m, 1H), 5.54 – 5.50 (m, 1H), 3.81 (s, 6H), 3.80 – 3.74 (m, 1H), 2.42 (ddd, *J* = 14.5, 9.0, 5.5 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.24 – 2.15 (m, 3H), 2.05 – 1.99 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7, 163.1 (dd, *J* = 256.0, 11.4 Hz), 160.8, 142.1 (t, *J* = 7.9 Hz), 131.9, 112.2 (dd, *J* = 22.0, 6.4 Hz), 109.7 (t, *J* = 25.0 Hz), 107.5, 105.5, 76.7, 62.7, 55.7, 34.3, 32.0, 25.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.92;

HRMS (ESI-TOF): calc'd for $C_{20}H_{21}F_2O_6S$ [M+H^+] 427.1021; found 427.1028;

$[\alpha]_D^{20}$ = –25.0 (c = 0.10, $CHCl_3$).



212

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl 1-tosylpiperidine-4-carboxylate (212) Synthesized using the "General Procedure: Carboxylic Acids" on 0.1 mmol scale to provide **212** in 55% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 62% yield.

***Major Diastereoisomer*:**

Physical State: white amorphous solid;

R_f = 0.4 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 2H), 7.46 – 7.41 (m, 2H), 7.33 – 7.30 (m, 2H), 7.12 (tt, *J* = 8.3, 2.3 Hz, 1H), 5.29 – 5.24 (m, 1H), 3.67 – 3.60 (m, 3H), 2.43 (s, 3H), 2.42 – 2.38 (m, 2H), 2.31 (ddd, *J* = 14.4, 8.8, 5.5 Hz, 1H), 2.22 – 2.14 (m, 2H), 2.10 (dtd, *J* = 13.6, 8.4, 4.9 Hz, 1H), 2.05 – 1.96 (m, 2H), 1.93 – 1.87 (m, 2H), 1.81 – 1.70 (m, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 163.1 (dd, *J* = 256.5, 11.2 Hz), 143.8, 141.9 (t, *J* = 8.0 Hz), 133.2, 129.8, 127.8, 112.2 (dd, *J* = 22.1, 6.6 Hz), 109.8 (t, *J* = 25.3 Hz), 76.1, 62.6, 45.4, 40.3, 34.0, 32.0, 27.6, 27.5, 24.9, 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -101.85;

HRMS (ESI-TOF): calc'd for $C_{24}H_{28}F_2NO_6S_2$ [M+H$^+$] 528.1326; found 528.1322;

$[\alpha]_D^{20}$ = +3.0 (c = 1.0, $CHCl_3$).

***Minor Diastereoisomer*:**

Physical State: white amorphous solid;

R_f = 0.5 (50% EtOAc in hexanes, vis. UV);

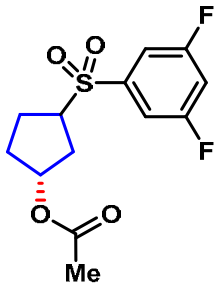
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 – 7.62 (m, 2H), 7.43 – 7.39 (m, 2H), 7.34 – 7.30 (m, 2H), 7.11 (tt, *J* = 8.3, 2.3 Hz, 1H), 5.10 (tt, *J* = 6.0, 3.7 Hz, 1H), 3.68 – 3.63 (m, 2H), 3.55 – 3.49 (m, 1H), 2.46 – 2.41 (m, 2H), 2.43 (s, 3H), 2.33 – 2.27 (m, 1H), 2.27 – 2.18 (m, 2H), 2.17 – 2.12 (m, 1H), 2.01 – 1.90 (m, 4H), 1.87 – 1.75 (m, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 163.4 (dd, *J* = 257.7, 11.3 Hz), 143.7, 142.2 (t, *J* = 7.7 Hz), 133.2, 129.8, 127.8, 112.1 (dd, *J* = 21.8, 6.5 Hz), 109.7 (t, *J* = 24.8 Hz), 74.8, 62.5, 45.6, 45.5, 40.2, 33.1, 32.3 (2C) 27.5, 27.4, 25.4, 21.7;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.81;

HRMS (ESI-TOF): calc'd for $C_{24}H_{28}F_2NO_6S_2$ [M+H$^+$] 528.1326; found 528.1329;

$[\alpha]_D^{20}$ = –0.3 (c = 0.50, $CHCl_3$).



213

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl acetate (213)
Synthesized using the "General Procedure: Carboxylic Acids" on 0.1 mmol scale to provide the desired product in 55% yield.

Note: The above reaction was run with racemic **9** on 0.1 mmol scale to give the desired product in 60% yield.

***Major Diastereoisomer*:**

Physical State: colorless liquid;

R_f = 0.5 (33% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.11 (tt, *J* = 8.4, 2.3 Hz, 1H), 5.12 – 5.07 (m, 1H), 3.55 – 3.49 (m, 1H), 2.35 (ddd, *J* = 14.8, 9.4, 6.4 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.19 – 2.13 (m, 1H), 2.03 (s, 3H), 2.00 – 1.87 (m, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 163.1 (dd, *J* = 255.6, 11.6 Hz), 142.1 (t, *J* = 8.2 Hz), 112.3 (dd, *J* = 21.5, 6.6 Hz), 109.6 (t, *J* = 24.9 Hz), 74.4, 62.6, 33.2, 32.0, 25.1, 21.2;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.06;

HRMS (ESI-TOF): calc'd for $C_{13}H_{15}F_2O_4S$ [M+H^+] 305.0654; found 305.0642;

$[\alpha]_D^{20}$ = +7.0 (c = 1.0, $CHCl_3$).

Minor Diastereoisomer:

Physical State: colorless liquid;

R_f = 0.6 (33% EtOAc in hexanes, vis. UV);

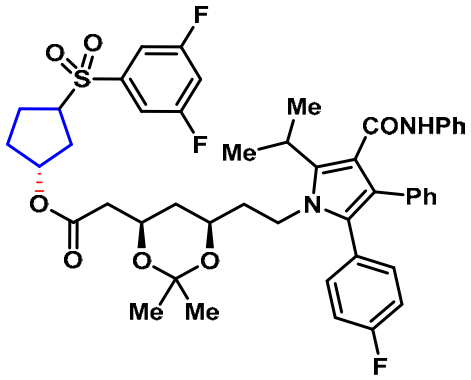
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.12 (tt, *J* = 8.3, 2.3 Hz, 1H), 5.31 – 5.28 (m, 1H), 3.73 – 3.67 (m, 1H), 2.30 (ddd, *J* = 14.5, 9.0, 5.5 Hz, 1H), 2.24 – 2.18 (m, 1H), 2.15 – 2.02 (m, 3H), 1.99 (s, 3H), 1.90 – 1.84 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 163.1 (dd, *J* = 256.0, 11.5 Hz), 142.1 (t, *J* = 7.7 Hz), 112.2 (dd, *J* = 21.3, 6.0 Hz), 109.7 (t, *J* = 24.8 Hz), 75.9, 62.6, 34.2, 31.9, 24.8, 21.3;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.97;

HRMS (ESI-TOF): calc'd for $C_{13}H_{14}F_2NaO_4S$ [M+Na^+] 327.0473; found 327.0473;

$[\alpha]_D^{20}$ = +2.9 (c = 0.26, $CHCl_3$).



214

(1*R*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (214)

To a test tube were added (+)-**9** (0.03 mmol, 7.3 mg), Atorvastatin (0.06 mmol, 35.9 mg), iPr_2NEt (0.1 mmol, 17 uL) and DMSO (0.2 mL). The mixture was heated to 80 °C for 2 days. The resulting solution was diluted with water and extracted with solvents (hexane/CH_2Cl_2 = 1/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (CH_2Cl_2/AcOEt = 20/1) to give **214** in 85% yield.

Note: 0.018 mmol of unreacted Atorvastatin was recovered after purification. The above reaction was run with racemic **9** to give the desired product in 86% yield.

Physical State: colorless amorphous solid;

R_f = 0.5 (5% EtOAc in CH_2Cl_2, vis. UV);

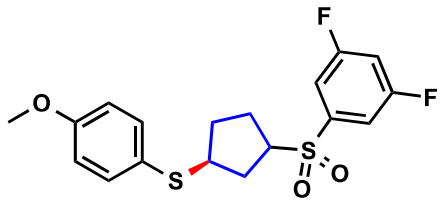
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.21 – 7.14 (m, 9H), 7.11 (tt, *J* = 8.3, 2.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.00 – 6.96 (m, 3H), 6.86 (s, 1H), 5.15 – 5.12 (m, 1H), 4.24 – 4.19 (m, 1H), 4.10 – 4.04 (m, 1H), 3.86 – 3.79 (m, 1H), 3.74 – 3.69 (m, 1H), 3.60 – 3.48 (m, 2H), 2.50 – 2.46 (m, 1H), 2.37 – 2.29 (m, 2H), 2.28 – 2.20 (m, 1H), 2.19 – 2.14 (m, 1H), 1.99 – 1.85 (m, 3H), 1.71 – 1.66 (m, 4H), 1.53 (s, 3H), 1.52 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.5, 164.9, 163.1 (dd, *J* = 256.4, 11.5 Hz), 162.5 (d, *J* = 248.4 Hz), 142.2 (t, *J* = 7.8 Hz), 141.6, 138.5, 134.8, 133.3 (d, *J* = 7.9 Hz), 130.6, 128.9, 128.8, 128.5, 128.4 (d, *J* = 3.0 Hz), 126.7, 123.6, 121.9, 119.7, 115.6, 115.5, 115.4, 112.2 (dd, *J* = 21.5, 6.8 Hz), 109.7 (t, *J* = 24.9 Hz), 98.9, 74.6, 66.5, 65.7, 62.6, 41.6, 41.0, 38.2, 36.1, 33.1, 32.2, 30.0, 26.2, 25.3, 21.9, 21.7, 19.9;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.93, -114.05;

HRMS (ESI-TOF): calc'd for $C_{47}H_{49}F_3N_2NaO_7S$ [$M+H^+$] 865.3110; found 865.3105.

Thiols & Selenols



215

((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)(4-methoxyphenyl)sulfane (215)
Compound **215** was prepared from 4-methoxythiophenol (0.085 mmol) and strain-release reagent **(–)-9** using general procedure A. The crude mixture was purified using flash column chromatography (silica gel, 1:6 EtOAc/Hex to 1:4 EtOAc/Hex) to afford **215** as a separable mixture of diastereomers (21.9 mg combined yield, 69%).

The reaction was also carried out with racemic reagent **9** to afford compound **215** as a mixture of four diastereomers (93% isolated yield).

Physical State: clear oil

Major diastereomer:

R_f = 0.47 (4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.10 (tt, *J* = 8.4, 2.3 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.77 – 3.70 (m, 1H), 3.66 – 3.61 (m, 1H), 2.43 – 2.35 (m, 1H), 2.19 – 2.07 (m, 3H), 1.97 – 1.88 (m, 1H), 1.73 – 1.65 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 255.9, 11.5 Hz, 2C), 159.8, 142.2 (t, *J* = 7.8 Hz), 135.2 (2C), 124.6, 114.8 (2C), 113.0 – 111.4 (m, 2C), 109.5 (t, *J* = 24.9 Hz), 63.0, 55.5, 47.9, 33.9, 32.4, 25.9;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.1;

HRMS (ESI-TOF): calc'd for $C_{18}H_{19}F_2O_3S_2$ [M+H$^+$] 385.0738; found 385.0740.

Minor diastereomer:

Rf = 0.37 (4:1 hexanes:EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.09 (tt, *J* = 8.4, 2.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.59 – 3.42 (m, 1H), 3.36 – 3.24 (m, 1H), 2.31 – 2.20 (m, 2H), 2.07 – 1.85 (m, 3H), 1.80 – 1.69 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (dd, *J* = 256.2, 11.5 Hz), 159.9, 142.0 (t, *J* = 7.7 Hz), 135.7, 124.4, 114.7, 113.8 – 111.6 (m), 109.6 (t, *J* = 24.9 Hz), 63.4, 55.5, 47.4, 34.4, 32.6, 26.1;

^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.2;

HRMS (ESI-TOF): calc'd for $C_{18}H_{19}F_2O_3S_2$ [M+H$^+$] 385.0738; found 385.0743.

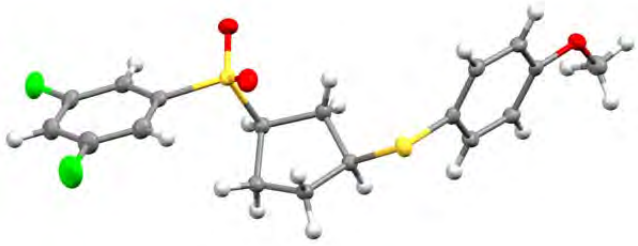
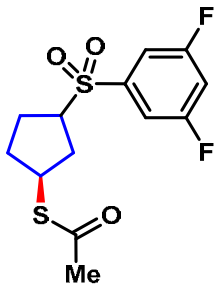


Fig. S120. Crystal structure of ((1*R*,3*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)(4-methoxyphenyl)sulfane (**215**).

Identification code	LRM-43-1	
Empirical formula	$C_{18}H_{18}F_2O_3S_2$	
Formula weight	384.44	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.8306(11) Å	α = 90°.
	b = 5.4318(7) Å	β = 98.442(6)°.
	c = 20.139(3) Å	γ = 90°.
Volume	847.33(19) Å^3	
Z	2	
Density (calculated)	1.507 Mg/m^3	
Absorption coefficient	3.181 mm^{-1}	
F(000)	400	

Crystal size	0.16 x 0.12 x 0.06 mm^3
Theta range for data collection	2.218 to 68.505°.
Index ranges	$-9 \leq h \leq 9, -6 \leq k \leq 6, -21 \leq l \leq 24$
Reflections collected	7769
Independent reflections	2963 [R(int) = 0.0352]
Completeness to theta = 68.000°	98.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.3200 and 0.1783
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2963 / 1 / 227
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	$R_1 = 0.0269$, $wR_2 = 0.0673$
R indices (all data)	$R_1 = 0.0272$, $wR_2 = 0.0675$
Absolute structure parameter	0.048(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.267 and -0.243 $e.Å^{-3}$



216

***S*-((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl) ethanethioate (216)**

A screw-cap vial was charged with **(–)-9** (24.4 mg, 0.100 mmol), thioacetic acid (0.014 mL, 0.200 mmol, 2 equiv.), diisopropylamine (0.035 mL, 0.200 mmol, 2 equiv.) and DMF (0.3 mL) after which the contents were stirred at rt for 22 h. Subsequently, half sat. aq. NaCl was added followed by EtOAc and the phases were separated. The aqueous layer was extracted using EtOAc (3 x 5 mL) , the organic phases combined, washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified using silica gel chromatography to provide **216** in 93% yield.

Note: The above reaction was run with racemic **9** to provide the desired product in 90% yield.

Major Diastereoisomer:

Physical State: white solid (m.p. = 96-97 °C);

R_f = 0.25 (40% Et_2O in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.13 – 7.09 (m, 1H), 3.69 (tt, *J* = 9.6, 7.2 Hz, 1H), 3.60 – 3.54 (m, 1H), 2.44 – 2.39 (m, 1H), 2.31 (s, 3H), 2.30 – 2.25 (m, 1H), 2.17 – 2.11 (m, 1H), 2.01 – 1.94 (m, 2H), 1.81 – 1.73 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 195.8 (2C), 163.1 (dd, *J* = 256.0, 11.5 Hz), 142.0 (t, *J* = 7.9 Hz), 112.2 (dd, *J* = 21.7, 6.4 Hz), 109.7 (t, *J* = 24.9 Hz), 63.1, 41.3, 34.1, 32.0, 30.7, 26.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.99;

HRMS (ESI-TOF): calc'd for $C_{13}H_{15}F_2O_3S_2$ [M+H^+] 321.0425; found 321.0424;

$[\alpha]_D^{20}$ = –20.6 (c = 1.49, $CHCl_3$).

Minor Diastereoisomer:

Physical State: white film;

R_f = 0.35 (40% Et_2O in hexanes, vis. UV);

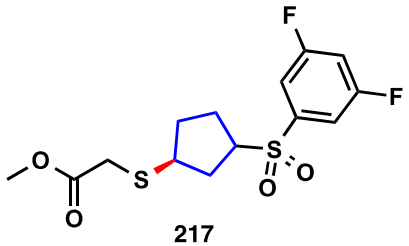
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.13 – 7.09 (m, 1H), 3.94 – 3.89 (m, 1H), 3.65 (tt, *J* = 8.9, 7.1 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.33 – 2.27 (m, 1H), 2.29 (s, 3H), 2.23 – 2.16 (m, 1H), 2.11 – 2.04 (m, 1H), 1.95 – 1.89 (m, 1H), 1.74 – 1.67 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 195.2, 163.1 (dd, *J* = 255.7, 10.9 Hz), 142.0 (t, *J* = 7.6 Hz), 112.3 (dd, *J* = 21.7, 6.2 Hz), 109.7 (t, *J* = 25.2 Hz), 63.1, 42.5, 34.4, 32.3, 30.8 (2C), 26.3;

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.98;

HRMS (ESI-TOF): calc'd for $C_{13}H_{15}F_2O_3S_2$ [M+H^+] 321.0425; found 321.0427;

$[\alpha]_D^{20}$ = –16.7 (c = 0.45, $CHCl_3$).



217

methyl 2-(((1*S*)-3-((3,5-difluorophenyl)sulfonyl)cyclopentyl)thio)acetate (217)

Compound **217** was prepared from methyl thioglycolate (0.12 mmol) and strain-release reagent **(–)-9** using general procedure A. The crude mixture was purified using flash column chromatography (silica gel, 1:6 EtOAc/Hex to 1:4 EtOAc/Hex) to afford **217** as a separable mixture of diastereomers (36.2 mg combined yield, 86%).

The reaction was also carried out with racemic reagent **9** to afford compound **217** as a mixture of four diastereomers (79% isolated yield).

Physical State: oily solid

Major diastereomer:

Rf = 0.22 (4:1 hexanes:EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 2H), 7.10 (tt, *J* = 8.4, 2.3 Hz, 1H), 3.71 (s, 3H), 3.60 – 3.48 (m, 1H), 3.27 – 3.19 (m, 1H), 3.24 (s, 2H), 2.42 – 2.33 (m, 1H), 2.32 – 2.24 (m, 1H), 2.15 – 2.07 (m, 1H), 2.00 – 1.89 (m, 1H), 1.79 – 1.68 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 163.0 (dd, *J* = 256.0, 11.5 Hz, 2C), 142.0 (t, *J* = 8.0 Hz), 112.6 – 111.8 (m, 2C), 109.6 (t, *J* = 25.0 Hz), 63.3, 52.6, 43.5, 34.6, 33.4, 32.6, 26.1;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.0;

HRMS (ESI-TOF): calc'd for $C_{14}H_{17}F_2O_4S_2$ [M+H$^+$] 351.0531; found 351.0536.

Minor diastereomer:

Rf = 0.28 (4:1 hexanes:EtOAc);

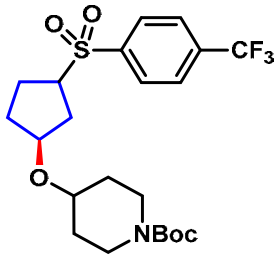
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 2H), 7.11 (tt, *J* = 8.3, 2.5 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.73 (s, 3H), 3.58 – 3.44 (m, 1H), 3.24 (s, 2H), 2.66 – 2.40 (m, 1H), 2.37 – 2.19 (m, 1H), 2.20 – 2.04 (m, 1H), 2.03 – 1.88 (m, 1H), 1.76 – 1.61 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 163.1 (dd, *J* = 255.7, 11.4 Hz, 2C), 142.2 (t, *J* = 7.7 Hz), 112.7 – 111.8 (m, 2C), 109.6 (t, *J* = 25.0 Hz), 63.0, 52.7, 44.3, 34.2, 33.7, 32.8, 26.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.0;

HRMS (ESI-TOF): calc'd for $C_{14}H_{17}F_2O_4S_2$ [M+H^+] 351.0531; found 351.0543.

Alcohols & Phenols



225

***tert*-butyl 4-(((1*S*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)oxy)piperidine -1-carboxylate (225)**

To a solution of *N*-Boc-piperidine-4-ol (0.12 mmol, 24 mg) in THF/toluene (1/1, 0.6 mL) was added LHMDS (0.12 mmol) at ambient temperature under argon atmosphere. After stirring for 10 min, **(–)-10** (0.1 mmol, 27.8 mg) was added and the mixture was stirred at 90 °C for 3 days. The reaction was quenched with sat. aq. NH_4Cl, the phases were separated and the aqueous phase was extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography (hexane/AcOEt = 1/1) to give **225** in 35% yield.

Note: The above reaction was run with racemic **10** to give the desired product in 40% yield.

Physical State: colorless oil;

R_f = 0.3 (25% EtOAc in hexanes, vis. UV);

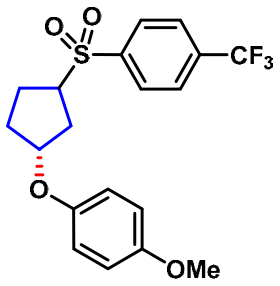
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H), 4.19 (br, 1H), 3.78 – 3.66 (m, 3H), 3.48 – 3.38 (m, 1H), 3.04 (t, *J* = 11.3 Hz, 2H), 2.23 – 1.89 (m, 6H), 1.82 – 1.69 (m, 4H), 1.46 – 1.42 (m, 9H) [major diastereoisomer];

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.9, 142.6, 135.5 (q, *J* = 33.3 Hz), 129.2, 126.6 (q, *J* = 3.9 Hz), 123.2 (q, *J* = 272.9 Hz), 79.7, 72.9, 62.7, 41.6 (br), 34.2, 32.3, 31.7, 31.6, 28.6, 24.6 [major diastereoisomer];

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.48 [major diastereoisomer];

HRMS (ESI-TOF): calc'd for $C_{22}H_{30}F_3NNaO_5S$ [M+Na^+] 500.1694; found 500.1690;

$[\alpha]_D^{20}$ = –2.1 (c = 0.52, $CHCl_3$).



226

1-methoxy-4-(((1*R*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)oxy)benzene (226)

To a test tube were added **(+)-10** (0.1 mmol, 27.8 mg), 4-methoxyphenol (0.20 mmol, 24.8 mg), K_2CO_3 (0.2 mmol, 27.6 mg) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. Water was added to the reaction mixture and the aqueous layer was extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography (hexane/CH_2Cl_2 = 1/10) to provide **226** in 80% yield.

Note: The above reaction was run with racemic **10** to give the desired product in 87% yield.

Physical State: colorless oil;

R_f = 0.5 (10% hexanes in CH_2Cl_2, vis. UV);

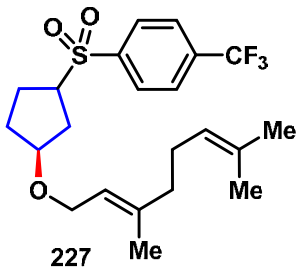
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 6.80 – 6.77 (m, 2H), 6.69 – 6.65 (m, 2H), 4.67 – 4.64 (m, 1H), 3.76 (s, 3H), 3.59 (tt, *J* = 9.5, 7.9 Hz, 1H), 2.36 (ddd, *J* = 15.3, 9.6, 6.0 Hz, 1H), 2.30 – 2.22 (m, 2H), 2.10 – 2.04 (m, 1H), 2.00 (dtd, *J* = 12.9, 7.4, 3.5 Hz, 1H), 1.85 (dddd, *J* = 12.9, 10.3, 7.0, 5.6 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.3, 151.1, 141.8, 135.5 (q, *J* = 33.0 Hz), 129.7, 126.5 (q, *J* = 3.4 Hz), 123.3 (q, *J* = 273.5 Hz), 116.9, 114.8, 77.9, 63.3, 55.8, 33.3, 32.5, 25.6;

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.47;

HRMS (ESI-TOF): calc'd for $C_{19}H_{20}F_3O_4S$ [M+H$^+$] 401.1034; found 401.1045;

$[\alpha]_D^{20}$ = –0.8 (c = 1.0, $CHCl_3$).



1-(((3*S*)-3-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)cyclopentyl)sulfonyl)-4-(trifluoromethyl)benzene (227)

To a solution of geraniol (0.12 mmol, 21 uL) in THF/toluene (1/1, 0.6 mL) was added LHMDS (0.12 mmol) at ambient temperature under argon atmosphere. After stirring for 10 min, **(–)-10** (0.1 mmol, 27.8 mg) was added and the mixture was stirred at 90 °C for 3 days. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography (hexane/EtOAc = 1/1) to give **227** in 50% yield.

Note: The above reaction was run with racemic **10** to give the desired product in 49% yield.

Physical State: colorless oil;

R_f = 0.5 (16% EtOAc in hexanes, vis. UV);

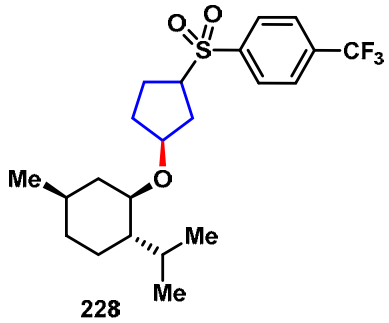
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 5.29 – 5.22 (m, 1H), 5.10 – 5.03 (m, 1H), 4.12 – 4.05 (m, 1H), 3.95 – 3.84 (m, 2H), 3.77 – 3.67 (m, 1H), 2.20 – 1.81 (m, 10H), 1.67 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.7, 140.6, 135.5 (q, *J* = 32.8 Hz), 131.9, 129.1, 126.5 (q, *J* = 3.4 Hz), 124.1 (q, *J* = 273.4 Hz), 124.0, 120.6, 79.4, 65.4, 62.8, 39.7, 33.7, 31.6, 26.5, 25.8, 24.6, 17.8, 16.6;

^{19}F NMR (376 MHz, $CDCl_3$) δ -60.50;

HRMS (ESI-TOF): calc'd for $C_{22}H_{29}F_3NaO_3S$ [M+Na^+] 453.1687; found 453.1684;

$[\alpha]_D^{20}$ = –1.8 (c = 1.0, $CHCl_3$).



228

1-(((3*S*)-3-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)cyclopentyl)sulfonyl)-4-(trifluoromethyl)benzene (228)

To a solution of menthol (0.12 mmol, 18.7 mg) in DMF (0.3 mL) was added LHMDS (1.0 M in THF, 0.12 mmol, 0.12 mL) at ambient temperature under argon atmosphere. After stirring for 10 min, **(–)-10** (0.1 mmol, 27.8 mg) was added and the mixture was stirred at 90 °C for 20 h. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase was extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography (hexane/EtOAc = 5/1) to give **228** in 12% yield as a mixture of diastereoisomers.

Physical State: colorless oil;

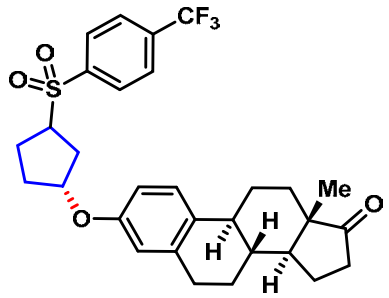
R_f = 0.5 (16% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 2H), 7.85 – 7.82 (m, 2H), 4.20 – 4.15 (m, 1H), 3.77 – 3.62 (m, 1H), 3.05 – 2.96 (m, 1H), 2.21 – 1.75 (m, 8H), 1.65 – 1.58 (m, 3H), 1.13 – 1.07 (m, 1H), 0.96 – 0.91 (m, 1H), 0.90 (d, *J* = 1.0 Hz, 3H, distinct diastereoisomer), 0.89 (d, *J* = 1.0 Hz, 3H, distinct diastereoisomer), 0.86 (d, *J* = 4.2 Hz, 3H, distinct diastereoisomer), 0.85 (d, *J* = 4.2 Hz, 3H, distinct diastereoisomer), 0.84 – 0.74 (m, 2H), 0.72 (d, *J* = 6.9 Hz, 3H, distinct diastereoisomer), 0.64 (d, *J* = 7.0 Hz, 3H, distinct diastereoisomer), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.7, 135.5 (2 x q, *J* = 33.5 Hz), 129.2, 129.1, 126.5 (q, *J* = 3.9 Hz), 123.3 (q, *J* = 272.9 Hz), 62.9, 62.7, 48.6, 48.5, 41.5, 41.2, 35.3, 34.6, 34.5, 33.7, 33.1, 31.7 (2C), 31.6, 25.4 (2C), 24.4, 24.2, 23.2 (2C), 22.4, 21.3, 16.1, 16.0, mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.48 (br);

HRMS (ESI-TOF): calc'd for $C_{22}H32F_3O_3S$ [M+H$^+$] 433.2019; found 433.2022.



229

(8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(((1*R*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one (229)

To a test tube were added **(+)-10** reagent (0.1 mmol, 27.8 mg), Estrone (0.10 mmol, 27.0 mg), K_2CO_3 (0.2 mmol, 27.6 mg) and DMF (0.3 mL). The mixture was heated to 90 °C overnight. Water was added to the reaction and the aqueous layer was extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography (hexane/EtOAc = 2/1) to give **229** in 72% yield.

Note: The above reaction was run with racemic **10** to give the desired product in 66% yield.

Physical State: white needle (m.p. = 102 °C);

R_f = 0.4 (33% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.55 – 6.51 (m, 1H), 6.47 (s, 1H), 4.74 – 4.68 (m, 1H), 3.60 (p, *J* = 8.7 Hz, 1H), 2.85 (d, *J* = 6.9 Hz, 2H), 2.50 (dd, *J* = 19.1, 8.8 Hz, 1H), 2.45 – 2.35 (m, 2H), 2.31 – 2.20 (m, 3H), 2.14 (dt, *J* = 18.6, 8.9 Hz, 1H), 2.09 – 1.84 (m, 6H), 1.66 – 1.38 (m, 6H), 0.91 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 221.0, 155.2, 141.8, 138.0, 135.5 (q, *J* = 33.1 Hz), 132.6, 129.7, 126.5 – 126.4 (m, 2C), 123.3 (q, *J* = 273.3 Hz), 115.9, 115.8, 113.0, 112.9, 77.0, 63.3, 50.5, 48.1, 44.1, 38.4, 36.0, 33.5 (2C), 32.4, 31.7, 29.7, 26.6, 26.0, 25.6, 21.7, 14.0;

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.42;

HRMS (ESI-TOF): calc'd for $C_{30}H_{34}F_3O_4S$ [$M+H^+$] 547.2130; found 547.2132;

$[\alpha]_D^{20}$ = –64.0 (c = 1.0, $CHCl_3$).

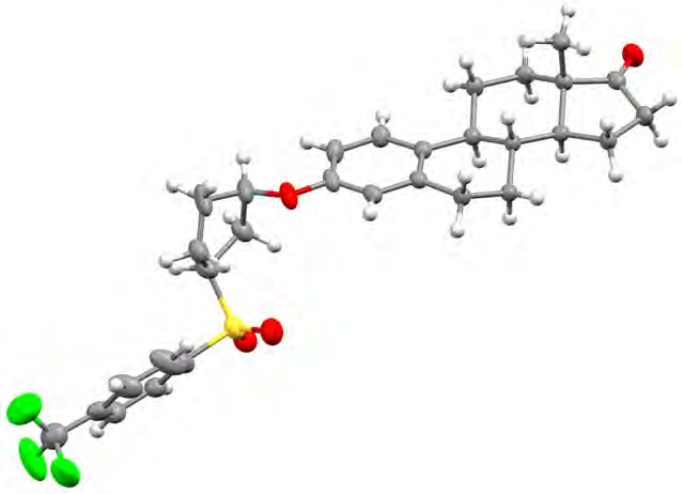
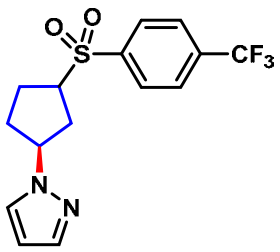


Fig. S121. Crystal structure of (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(((1*R*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (**229**).

Identification code	60629H	
Empirical formula	$C_{30}H_{33}F_3O_4S$	
Formula weight	546.62	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.6458(2) Å	α= 90°.
	b = 8.1522(3) Å	β= 90°.
	c = 48.2280(15) Å	γ = 90°.
Volume	2612.89(15) Å^3	
Z	4	
Density (calculated)	1.390 Mg/m^3	
Absorption coefficient	1.592 mm^{-1}	

F(000)	1152
Crystal size	0.177 x 0.153 x 0.116 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	1.832 to 68.217°.
Index ranges	$-7 \leq h \leq 8$, $-9 \leq k \leq 9$, $-55 \leq l \leq 58$
Reflections collected	15810
Independent reflections	4723 [R(int) = 0.0317, R(sigma) = 0.0404]
Completeness to theta = 68.000°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.3201 and 0.2155
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4723 / 0 / 385
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	$R_1 = 0.0391$, $wR_2 = 0.0953$
R indices (all data)	$R_1 = 0.0414$, $wR_2 = 0.0968$
Absolute structure parameter	0.048(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.184 and -0.285 $e.Å^{-3}$

Other Substrates: Avoiding Significant Formation of S_NAr Products



230

1-((1*S*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-1*H*-pyrazole (230)
To a solution of pyrazole (0.12 mmol, 8.1 mg) in DMF (0.3 mL) was added LHMDS (0.12 mmol) at ambient temperature under argon atmosphere. After stirring for 10 min, **(–)-10** (0.1 mmol, 27.8 mg) was added and the mixture was stirred at 90 °C for 2 h. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography (hexane/EtOAc = 1/1) to give **230** in 80% yield.

Note: The above reaction was run with racemic **10** to give the desired product in 87% yield. The crystal structure provided below was obtained from the reaction between pyrazole and **(+)-10**.

***Major Diastereoisomer*:**

Physical State: colorless oil;

R_f = 0.7 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 2.3, 0.7 Hz, 1H), 6.21 (t, *J* = 2.1 Hz, 1H), 4.91 – 4.86 (m, 1H), 3.99 – 3.93 (m, 1H), 2.62 – 2.56 (m, 1H), 2.46 – 2.40 (m, 1H), 2.39 – 2.33 (m, 1H), 2.31 – 2.16 (m, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.3, 139.7, 135.7 (q, *J* = 33.1 Hz), 129.2, 128.6, 126.6 (q, *J* = 3.3 Hz), 123.2 (q, *J* = 273.1 Hz), 105.6, 63.1, 61.6, 34.0, 32.9, 25.5;

^{19}F NMR (376 MHz, $CDCl_3$) δ -60.55;

HRMS (ESI-TOF): calc'd for $C_{15}H_{16}F_3N_2O_2S$ [M+H$^+$] 345.0885; found 345.0859;

$[\alpha]_D^{20}$ = –0.3 (c = 1.0, $CDCl_3$).

***Minor Diastereoisomer*:**

Physical State: white solid (m.p. = 146 °C)

R_f = 0.4 (50% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.49 – 7.48 (m, 2H), 6.26 – 6.25 (m, 1H), 4.71 (p, *J* = 8.1 Hz, 1H), 3.68 – 3.61 (m, 1H), 2.53 – 2.48 (m, 2H), 2.48 – 2.42 (m, 1H), 2.29 – 2.24 (m, 2H), 2.05 (ddd, *J* = 16.9, 13.9, 7.9 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.9, 139.5, 135.8 (q, *J* = 33.4 Hz), 129.4, 127.4, 126.7 (q, *J* = 3.8, 3.4 Hz), 123.2 (q, *J* = 273.4 Hz), 105.9, 62.3, 61.6, 33.9, 32.0, 24.9;

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.52;

HRMS (ESI-TOF): calc'd for $C_{15}H_{16}F_3N_2O_2S$ [M+H$^+$] 345.0885; found 345.0802;

$[\alpha]_D^{20}$ = –5.7 (c = 0.8, $CDCl_3$).

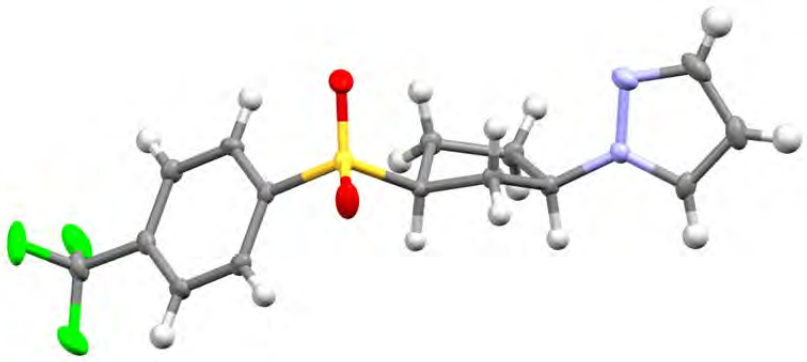
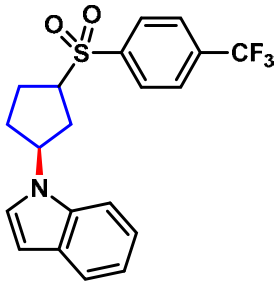


Fig. S122. Crystal structure of the minor isomer 1-((1*S*,3*R*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-1*H*-pyrazole (***ent*-230**).

Identification code baran591

Empirical formula	$C_{15}H_{15}F_3N_2O_2S$	
Formula weight	344.35	
Temperature	296.15 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 10.9261(7) Å	α= 90°.
	b = 5.0669(3) Å	β= 107.161(2)°.
	c = 14.3346(9) Å	γ = 90°.
Volume	758.25(8) $Å^3$	
Z	2	
Density (calculated)	1.508 Mg/m^3	
Absorption coefficient	0.257 mm^{-1}	
F(000)	356	
Crystal size	0.32 x 0.2 x 0.08 mm^3	
Crystal color, habit	colorless plank	
Theta range for data collection	2.780 to 26.022°.	
Index ranges	$-11 \leq h \leq 13$, $-6 \leq k \leq 6$, $-17 \leq l \leq 17$	
Reflections collected	15847	
Independent reflections	2988 [R(int) = 0.0337]	
Completeness to theta = 26.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6465 and 0.5916	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2988 / 1 / 208	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R_1 = 0.0278, wR_2 = 0.0649	
R indices (all data)	R_1 = 0.0302, wR_2 = 0.0664	
Absolute structure parameter	-0.02(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.316 and -0.237 $e.Å^{-3}$	



231

1-((1*S*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)-1*H*-indole (231)

To a solution of indole (0.12 mmol, 14.1 mg) in DMF (0.3 mL) was added LHMDS (0.12 mmol) at ambient temperature under argon atmosphere. After stirring for 10 min, (–)-**10** (0.1 mmol, 27.8 mg) was added and the mixture was stirred overnight at ambient temperature. The reaction was quenched with sat. aq. NH_4Cl and the aqueous phase was extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified using silica gel chromatography (hexane/CH_2Cl_2 = 1/2) to give **231** in 58% yield.

Note: The above reaction was run with racemic **10** to give the desired product in 64% yield.

Physical State: colorless oil;

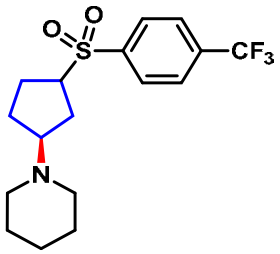
R_f = 0.4 (66% CH_2Cl_2 in hexanes, vis. UV);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (t, *J* = 7.2 Hz, 2H), 7.85 (t, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 6.7 Hz, 1H), 7.28 (tdd, *J* = 24.7, 16.2, 7.3 Hz, 3H), 7.15 – 7.05 (m, 1H), 6.53 (d, *J* = 17.7 Hz, 1H), 5.12 – 5.02 (m, 1H, distinct diastereoisomer), 4.89 – 4.78 (m, 1H, distinct diastereoisomer), 3.83 – 3.64 (m, 1H), 2.77 – 2.04 (m, 6H), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.0 (2C), 136.1 (2C), 135.8 (2 x q, *J* = 33.0 Hz), 129.3, 128.9 (2C), 126.7 (2 x q, *J* = 3.3 Hz), 124.3, 123.6, 122.7 (q, *J* = 273.3 Hz), 122.0, 121.8, 121.4, 121.3, 120.0, 119.9, 109.7, 109.3, 102.5, 102.3, 62.5, 62.1, 56.2, 55.9, 33.5, 33.3, 31.8, 31.5, 25.1, 24.8, mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.53;

HRMS (ESI-TOF): calc'd for $C_{20}H_{19}F_3NO_2S$ [$M+H^+$] 394.1089; found 394.1069.



232

1-((1*S*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)piperidine (232)

To a test tube were added **(–)-10** (27.6 mg, 0.10 mmol), piperidine (0.011 mL, 0.12 mmol) and DMF (0.3 mL) and the mixture was stirred for 22 h at 80 °C followed by the addition of half sat. brine (0.3 mL), EtOAc (2 mL) and a separation of the phases. The aqueous phase was extracted using EtOAc and the organic phases combined, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide an oil that was purified using silica gel chromatography to provide **232** in 86% yield.

Note: The above reaction was run with racemic **10** on 0.91 mmol scale to give the desired product in 89% yield.

Physical State: orange amorphous solid;

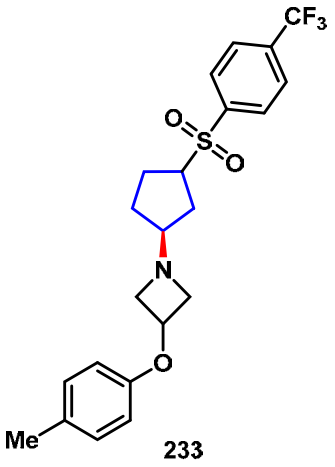
$\mathbf{R_f}$ = 0.33 (10% MeOH/CH_2Cl_2, vis. UV);

^{1}H NMR (600 MHz, DMSO-*d6*) δ 8.08 (d, *J* = 8.1 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 3.96 – 3.90 (m, 1H, distinct diastereoisomer), 3.86 (tdd, *J* = 9.5, 7.9, 5.5 Hz, 1H, distinct diastereoisomer), 2.57 – 2.50 (m, 1H), 2.46 (p, *J* = 1.8 Hz, 1H), 2.26 (br, 3H), 2.06 (ddd, *J* = 13.2, 7.8, 4.8 Hz, 1H, distinct diastereoisomer), 1.99 – 1.93 (m, 1H, distinct diastereoisomer), 1.93 – 1.84 (m, 1H), 1.84 – 1.70 (m, 2H), 1.69 – 1.58 (m, 1H), 1.44 – 1.27 (m, 7H), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, DMSO-*d6*) δ 142.3 (2C), 133.4 (q, *J* = 32.5 Hz), 126.7 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 273.1 Hz), 66.0, 65.6, 60.9, 60.6, 52.2 (2C), 40.4, 30.5, 29.9, 29.5, 28.7, 25.5, 24.9, 24.1, 23.8, mixture of diastereoisomers;

^{19}F NMR (376 MHz, DMSO-*d6*) δ -61.39 (2 peaks);

HRMS (ESI-TOF): calc'd for $C_{17}H_{23}F_3NO_2S$ [M+H^+] 362.1396; found 362.1395.



233

3-(*p*-tolyloxy)-1-((1*S*)-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentyl)azetidine (233)

To a test tube were added (–)-**10** (50 mg, 0.18 mmol), 3-(*p*-tolyloxy)azetidine hydrochloride (43.4, 0.217 mmol), DMSO (0.82 mL) and triethyl amine (0.06 mL, 0.45 mmol). The mixture was heated to 60 °C overnight. The resulting solution was diluted with water and extracted with EtOAc twice. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude material was purified using silica gel chromatography to provide **233** in 59% yield.

Physical State: amorphous white solid;

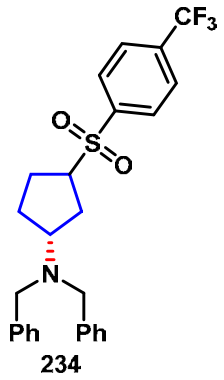
R_f = 0.22 (10% EtOAc in heptanes, vis. UV);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 2H), 7.86 – 7.81 (m, 2H), 7.07 – 7.03 (m, 2H), 6.67 – 6.61 (m, 2H), 4.73 – 4.62 (m, 1H), 3.78 – 3.65 (m, 3H, 1H from minor diastereoisomer), 3.58 – 3.47 (m, 1H, major diastereoisomer), 3.08 – 2.98 (m, 3H, 1H from minor diastereoisomer), 2.83 (p, *J* = 6.6 Hz, 1H, major diastereoisomer), 2.27 (2 x s, 3H, diastereoisomers), 2.23 – 1.51 (m, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 142.7 (q, *J* = 1.0 Hz), 142.4 (q, *J* = 1.3 Hz), 135.4 (2 x q, *J* = 33.2 Hz), 130.7, 130.6, 130.1, 129.4 (3C), 129.1, 126.6 – 126.4 (m), 123.3 (q, *J* = 273.0 Hz), 114.6 (2C), 68.9, 68.0, 66.2, 65.8, 63.4, 63.1, 62.7, 60.3, 60.1, 59.9, 57.0, 37.4, 36.5, 31.4, 31.2, 29.7, 29.5, 25.5, 25.3 (2C), 20.6, mixture of diastereoisomers;

^{19}F NMR (376 MHz, CD_3CN) δ -107.52;

HRMS (ESI-TOF): calc'd for $C_{22}H_{25}F_3NO_3S$ [M+H$^+$] 440.1505; found 440.1526.



234

(1*R*)-*N*,*N*-dibenzyl-3-((4-(trifluoromethyl)phenyl)sulfonyl)cyclopentan-1-amine (234)
To a test tube were added **(+)-10** (500 mg, 1.81 mmol), dibenzylamine (0.696 mL, 3.62 mmol) and DMSO (3.2 mL). The mixture was heated to 80 °C overnight. The resulting solution was diluted with water and extracted with solvents (hexane/EtOAc = 3/1) three times. The combined organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and subsequently purified using silica gel chromatography to afford **234** in 53% yield.

Physical State: white amorphous solid;

$\mathbf{R_f}$ = 0.17 (60% CH_2Cl_2 in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 2H), 7.82 – 7.78 (m, 2H), 7.35 – 7.32 (m, 1H), 7.31 – 7.26 (m, 7H), 7.24 – 7.20 (m, 2H), 3.67 – 3.55 (m, 4H), 3.54 – 3.48 (m, 1H, major diastereoisomer), 3.43 – 3.35 (m, 1H), 3.25 – 3.19 (m, 1H, minor diastereoisomer), 2.24 – 2.15 (m, 1H), 2.03 – 1.74 (m, 4H), 1.69 – 1.61 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.4, 142.3, 140.0, 139.8, 135.4 (q, *J* = 33.2 Hz), 129.2, 129.2, 128.6, 128.5, 128.4, 127.1, 127.0, 126.5 (q, *J* = 3.6 Hz), (q, *J* = 273.2 Hz), 63.1, 62.1, 62.0, 61.8, 55.8, 55.4, 29.3, 29.2, 29.0, 26.9, 25.5, 24.3. Mixture of diastereoisomers;

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.44 (major diastereoisomer), -63.45 (minor diastereoisomer);

HRMS (ESI-TOF): calc'd for $C_{26}H_{27}F_3NO_2S$ [M+H$^+$] 474.1709; found 474.1726.

Graphical Procedure for Stereospecific Strain-Release Amination

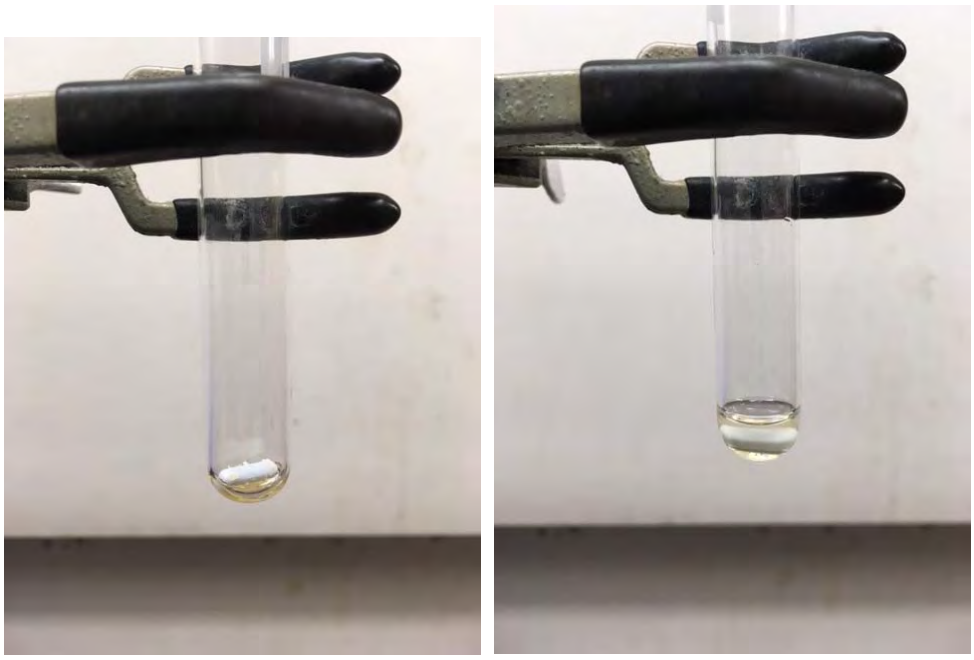


Fig. S123. Left. A mixture of strain-release reagent and diallylamine. **Right.** DMF (0.3 mL) is added and the reaction is stirred overnight.

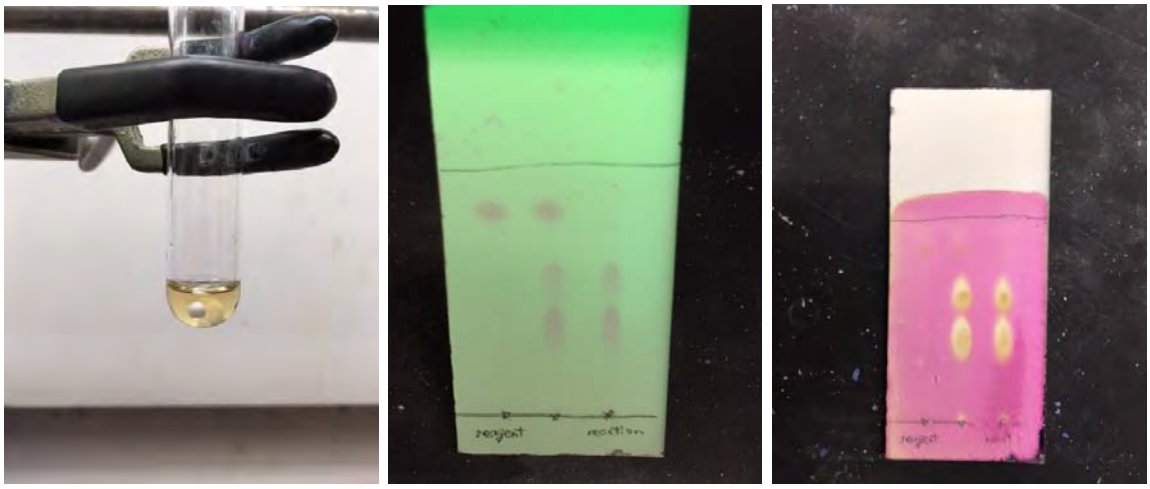
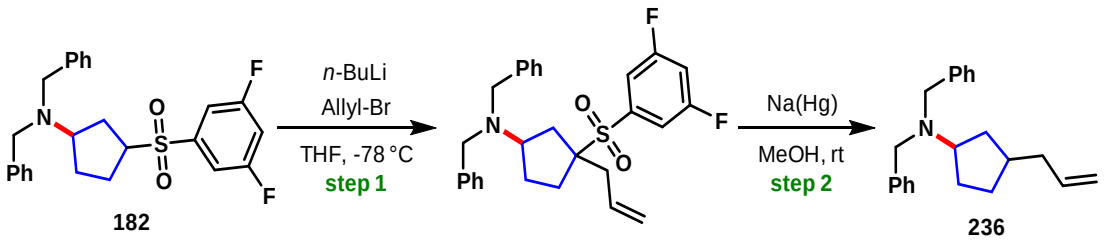


Fig. S124. Left. After the reaction has run overnight. **Center**. TLC plate under UV (eluent = 25% EtOAc in hexanes). 1st lane = strain-release reagent; 2nd lane = co-spot; 3rd lane = reaction mixture illustrating full conversion and the formation of products as a pair of diastereoisomers. **Right.** Same TLC plate after KMnO4 stain.

Diversification of Strain-release Intermediates

Notes and Considerations:
To suppress formation of side-products, it is recommended to add the electrophile rapidly after the organolithium species is formed.



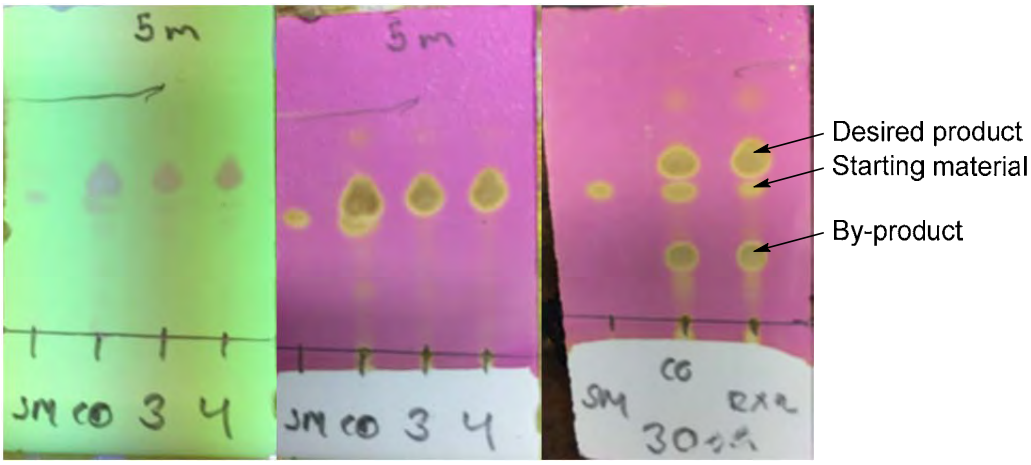
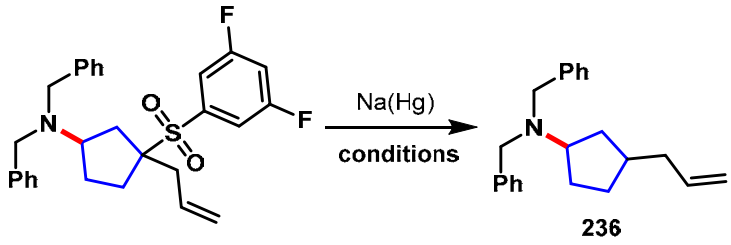


Fig. S125. Left. TLC plate of reaction mixture at -78 °C 5 min after the addition of allyl bromide – allyl bromide was added 45 s after *n*-BuLi. Lanes = 1st: starting material; 2nd: co-spot; 3rd–4th : reaction mixture at different concentrations. **Center.** Same TLC plate after $KMnO_4$ stain. **Right**. TLC plate of reaction mixture at -78 °C 5 min after the addition of allyl bromide – allyl bromide was added 5 min after *n*-BuLi. A significant by-product spot has appeared.

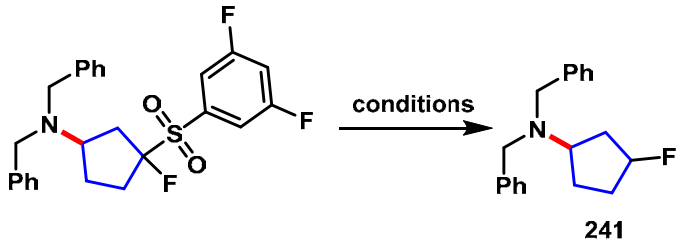
Screening of Desulfonylation Conditions

A range of conditions were tested in order to examine if the diastereoselectivity could be improved upon desulfonylation:



236

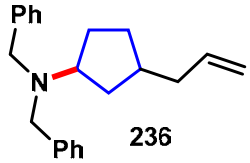
Conditions	dr
MeOH, rt.	47:53
MeOH, -78 °C to -20 °C.	52:48
EtOH, rt.	49:51
MeOH/benzene 1:1, rt.	50:50
MeOH/benzene 1:1, rt. K_2HPO_4	52:48
MeOH, -78 °C, K_2HPO_4	53:47
MeOH, -78 °C, TMS_3SiH	50:50
THF, -78 °C, TMS_3SiH	50:50
Li-naphthalenide, THF, -78 °C, then sat. aq. NH_4Cl	50:50
Li-naphthalenide, THF, -78 °C, then quinine	50:50



241

Conditions	dr
Mg (40 eq.), MeOH, 80 °C	1.7:1
Mg (40 eq.), MeOH, rt	1.3:1
Mg (40 eq.), MeOH/THF (1/1), rt.	1.1:1
Mg (40 eq.), MeOH/benzene (1/1), rt.	1.4:1
Mg (40 eq.), *i*PrOH, 80 °C	poor conversion
Na(Hg), MeOH, rt.	1:1

Note. As the dr was little influenced by the varied conditions, Na(Hg) in MeOH was chosen as the preferred desulfonylation method requiring only short reaction times at rt. (~15 min).



236

3-allyl-*N*,*N*-dibenzylcyclopentan-1-amine (236)

To a stirred solution of **182** (44 mg, 0.1 mmol) in THF (0.5 mL, 0.2M) at -78 °C was added *n*-BuLi (42 µL, 1.05 mmol, 2.5M) and after 45 s was subsequently added allyl bromide (26 µL, 0.3 mmol, 3 equiv.) and the mixture was stirred for 10 min followed by the addition of sat. aq. NH_4Cl (0.5 mL) and EtOAc (2 mL). The phases were separated, the organic phase washed with brine, dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide a colorless oil that dissolved in MeOH (2 mL) after which Na(Hg) 4-5% (300 mg, 6 equiv.) was added. This mixture was stirred at rt for 15 min followed by the addition of EtOAc. The remaining mercury was removed by decantation using a pipette and to the resulting mixture was added sat. aq. NH_4Cl. The organic phase was dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide a colorless oil that was purified using silica gel chromatography to yield **236** in 56% yield over two steps.

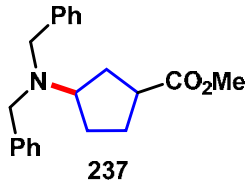
Physical State: yellow oil;

R_f = 0.85 (3% MeOH in CH_2Cl_2, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.30 – 7.27 (m, 4H), 7.22 – 7.18 (m, 2H), 5.85 – 5.72 (m, 1H), 5.05 – 4.92 (m, 2H), 3.67 – 3.55 (m, 4H), 3.23 – 3.14 (m, 1H), 2.33 – 2.14 (m, 2H), 2.10 – 1.41 (m, 7H), mixture of diastereoisomers.

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.1, 139.9, 137.5, 135.6, 128.2, 128.1, 127.7, 127.6, 126.2, 126.1, 115.2, 114.5, 61.1, 60.3, 58.2, 54.6 (2C), 53.8, 40.2, 40.0, 38.0, 37.3, 36.6, 35.6, 34.5, 34.2, 33.3, 31.1, 29.9, 28.1, 26.7, mixture of diastereoisomers.

HRMS (ESI-TOF): calc'd for $C_{22}H_{28}N$ [M+H$^+$] 306.2216; found 306.2203.



237

methyl 3-(dibenzylamino)cyclopentane-1-carboxylate (237)

To a stirred solution of **182** (44 mg, 0.1 mmol) in THF (0.5 mL, 0.2M) at -78 °C was added *n*-BuLi (48 µL, 0.13 mmol, 2.5M) and after 45 s was added Mander's Reagent (16 µL, 0.2

mmol, 2 equiv.) and the mixture was stirred for 45 min followed by the addition of sat. aq. NH_4Cl (0.5 mL) and EtOAc (2 mL). The phases were separated, the organic phase was washed with brine, dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide a yellow oil that was dissolved in MeOH (2 mL), after which Na(Hg) 4-5% (300 mg, 6 equiv.) was added. This mixture was stirred at rt for 15 min followed by the addition of EtOAc. The remaining mercury was removed by decantation using a pipette and to the resulting mixture was added sat. aq. NH_4Cl and the phases were separated. The organic phase was dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide a colorless oil that was purified using silica gel chromatography (7% EtOAc in hexanes) to yield **237** (18.9 mg, 0.58 mmol, 58% yield, two steps) as a 1:1 mixture of diastereoisomers.

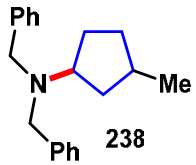
Physical State: colorless oil;

R_f = 0.12 (60% CH_2Cl_2 in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 4H), 7.33 – 7.29 (m, 4H), 7.25 – 7.21 (m, 2H), 3.69 (s, 3H, distinct diastereoisomer), 3.67 (s, 3H, distinct diastereoisomer), 3.66 – 3.59 (m, 4H), 3.41 – 3.35 (m, 1H, distinct diastereoisomer), 3.29 – 3.23 (m, 1H, distinct diastereoisomer), 2.88 – 2.82 (m, 1H, distinct diastereoisomer), 2.71 – 2.65 (m, 1H, distinct diastereoisomer), 2.13 – 1.97 (m, 2H), 1.95 – 1.55 (m, 4H), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.18, 176.15, 139.82, 139.71, 128.11, 128.06, 127.67, 126.24, 61.10, 60.96, 54.82, 54.53, 51.23, 51.20, 42.05, 41.37, 31.17, 31.02, 28.59, 28.22, 27.12, 26.41, mixture of diastereoisomers;

HRMS (ESI-TOF): calc'd for $C_{21}H_{26}NO_2$ [M+H$^+$] 324.1958; found 324.1944.



238

***N*,*N*-dibenzyl-3-methylcyclopentan-1-amine (238)**

To a stirred solution of **182** (44 mg, 0.1 mmol) in THF (0.5 mL, 0.2M) at -78 °C was added *n*-BuLi (48 µL, 0.13 mmol, 2.5M) and after 45 s was added MeI (37.8 mg, 0.12 mmol, 1.2 equiv.) and the mixture was stirred for 2 min followed by the addition of sat. aq. NH_4Cl (0.5 mL) and EtOAc (2 mL). The phases were separated, the organic phase was washed with brine, dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide a yellow oil that was dissolved in MeOH (2 mL), after which Na(Hg) 4-5% (300 mg, 6 equiv.) was

added. This mixture was stirred at rt for 15 min followed by the addition of EtOAc. The remaining mercury was removed by decantation using a pipette and to the resulting mixture was added sat. aq. NH_4Cl and the phases were separated. The aqueous phase was extracted using EtOAc and the organic layers combined, dried over Na_2SO_4, decanted and concentrated *in vacuo*. The resulting crude material was subsequently purified using silica gel chromatography to yield **238** in 51% yield.

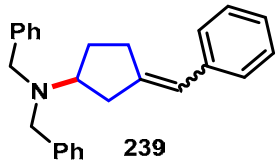
Physical State: yellow oil;

R_f = 0.84 (25% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.31 – 7.27 (m, 4H), 7.23 – 7.19 (m, 2H), 3.70 – 3.54 (m, 4H), 3.37 – 3.19 (m, 1H), 2.42 – 2.28 (m, 2H), 2.03 – 1.64 (m, 4H), 1.20 – 1.09 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H, distinct diastereoisomer), 0.94 (d, *J* = 6.7 Hz, 3H, distinct diastereoisomer), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.8, 140.6, 140.5, 128.8, 128.7 (2C), 128.2 (3C), 126.8 (2C), 126.7, 62.1, 62.0, 55.4, 55.2, 54.4, 39.2, 37.5, 36.1, 34.9, 33.2, 33.1, 31.3, 28.9, 27.7, 20.9, 16.9, mixture of diastereoisomers.

HRMS (ESI-TOF): calc'd for $C_{20}H_{26}N$ [M+H$^+$] 280.2060; found 280.2053.



239

(*E*)-*N*,*N*-dibenzyl-3-benzylidenecyclopentan-1-amine (239)

To a solution of **182** (44.2 mg, 0.1 mmol) in THF (0.5 mL) was added *n*-BuLi (0.044 mL, 0.11 mmol, 2.5M) at once at –78 °C. The mixture was stirred for 30 s followed by the addition of benzaldehyde (21.2 mg, 0.2 mmol) and stirring was continued at -78 °C for 30 min after which sat. aq. NH_4Cl was added. The mixture was subsequently diluted with EtOAc, the phases separated and the aqueous phase extracted twice with EtOAc. The combined organic phases were washed with brine, dried Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (2 mL) followed by the addition of DMAP (2 mg), Et_3N (0.041 mL, 0.3 mmol) and Ac_2O (0.018 mL, 0.2 mmol) after which the mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide an oil that was dissolved in MeOH (2 mL) and subjected to Na/Hg pellets (4-5%, 303 mg, 0.6

mmol) at rt. Stirring was continued for 45 min followed by the addition of EtOAc after which the mixture was decanted and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* followed by purification using silica gel chromatography to provide **239** as a 44:56 mixture of *E*- and *Z*-isomers (19 mg, 0.054 mmol, 54% yield over 3 steps).

Note: By several rounds of preparatory TLC it was possible to separate the *E*- and *Z*-isomers for characterization.

Major Diastereoisomer:

Physical State: colorless film;

R_f = 0.48 tailing (40% CH_2Cl_2 in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 4H), 7.32 – 7.28 (m, 6H), 7.24 – 7.20 (m, 4H), 7.18 – 7.15 (m, 1H), 6.29 – 6.24 (m, 1H), 3.70 (d, *J* = 14.1 Hz, 2H), 3.64 (d, *J* = 14.1 Hz, 2H), 3.30 (dddd, *J* = 10.4, 9.6, 7.6, 6.2 Hz, 1H), 2.79 (dd, *J* = 17.0, 7.7 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.53 – 2.45 (m, 1H), 2.45 – 2.37 (m, 1H), 1.94 – 1.89 (m, 1H), 1.71 – 1.60 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 144.2, 140.5, 138.6, 128.7, 128.3, 128.3, 128.1, 126.8, 125.9, 122.0, 63.1, 55.6, 34.7, 33.8, 27.9;

HRMS (ESI-TOF): calc'd for $C_{26}H_{28}N$ [M+H^+] 354.2216; found 474.2211.

Minor Diastereoisomer:

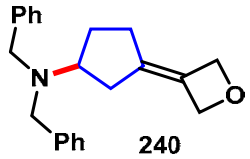
Physical State: colorless film;

R_f = 0.36 tailing (40% CH_2Cl_2 in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 4H), 7.31 – 7.28 (m, 6H), 7.25 – 7.20 (m, 4H), 7.16 – 7.13 (m, 1H), 6.33 – 6.28 (m, 1H), 3.71 – 3.63 (m, 4H), 3.28 – 3.19 (m, 1H), 2.74 – 2.63 (m, 2H), 2.60 – 2.53 (m, 1H), 2.49 – 2.41 (m, 1H), 2.02 – 1.97 (m, 1H), 1.80 – 1.72 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 144.5, 140.5, 138.6, 128.7, 128.3, 128.3, 128.1, 126.8, 125.9, 121.9, 61.2, 55.6, 39.1, 29.7, 29.5;

HRMS (ESI-TOF): calc'd for $C_{26}H_{28}N$ [M+H$^+$] 354.2216; found 474.2217.



240

***N*,*N*-dibenzyl-3-(oxetan-3-ylidene)cyclopentan-1-amine (240)**

To a solution of **182** (44.2 mg, 0.1 mmol) in THF (0.5 mL) was added *n*-BuLi (0.044 mL, 0.11 mmol, 2.5M) at once at –78 °C. The mixture was stirred for 30 s followed by the addition 3-oxetanone (7.6 µL, 0.13 mmol) and stirring was continued at -78 °C for 2.5 h after which sat. aq. NH_4Cl was added. The mixture was subsequently diluted with EtOAc, the phases separated and the aqueous phase extracted twice with EtOAc. The combined organic phases were washed with brine, dried Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (2 mL) followed by the addition of DMAP (2 mg), Et_3N (0.041 mL, 0.3 mmol) and Ac_2O (0.018 mL, 0.2 mmol) after which the mixture was stirred at room temperature for 15 h. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide an oil that was dissolved in MeOH (2 mL) and subjected to Na/Hg pellets (4-5%, 303 mg, 0.6 mmol) at rt. Stirring was continued for 25 min followed by the addition of EtOAc after which the mixture was decanted and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* followed by purification using silica gel chromatography to provide **240** in 41% yield over three steps.

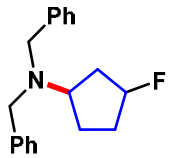
Physical State: white amorphous solid;

R_f = 0.50 (20% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 4H), 7.31 – 7.28 (m, 4H), 7.24 – 7.20 (m, 2H), 5.15 – 5.07 (m, 4H), 3.67 – 3.60 (m, 4H), 3.27 – 3.20 (m, 1H), 2.28 – 2.23 (m, 1H), 2.17 – 2.08 (m, 2H), 2.01 – 1.93 (m, 1H), 1.92 – 1.86 (m, 1H), 1.70 – 1.62 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.2, 130.0, 128.7, 128.3, 126.9, 124.6, 79.3, 79.2, 62.2, 55.4, 31.9, 28.5, 27.4.

HRMS (ESI-TOF): calc'd for $C_{22}H_{26}NO$ [M+H$^+$] 320.2009; found 320.2005.



241

***N*,*N*-dibenzyl-3-fluorocyclopentan-1-amine (241)**

To a stirred solution of **182** (44 mg, 0.1 mmol) in THF (0.5 mL, 0.2M) at -78 °C was added *n*-BuLi (48 µL, 0.13 mmol, 2.5M) and after 45 s was added *N*-fluorobenzenesulfonimide (37.8 mg, 0.12 mmol, 1.2 equiv.) and the mixture was stirred for 2 h followed by the addition of sat. aq. NH_4Cl (0.5 mL) and EtOAc (2 mL). The phases were separated, the organic phase was washed with brine, dried over Na_2SO_4, decanted and concentrated *in vacuo* to provide a yellow oil that was dissolved in MeOH (2 mL), after which Na(Hg) 4-5% (300 mg, 6 equiv.) was added. This mixture was stirred at rt for 15 min followed by the addition of EtOAc. The remaining mercury was removed by decantation using a pipette and to the resulting mixture was added sat. aq. NH_4Cl and the phases were separated. The aqueous phase was extracted using EtOAc and the organic layers combined, dried over Na_2SO_4, decanted and concentrated *in vacuo*. The resulting crude material was subsequently purified using silica gel chromatography to yield **241** (14.8 mg, 0.52 mmol, 52% yield, two steps) as a ~1:1 mixture of diastereoisomers.

Physical State: colorless oil;

R_f = 0.68 (25% EtOAc in hexanes, vis. UV);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.31 – 7.28 (m, 4H), 7.23 – 7.20 (m, 2H), 5.17 – 4.97 (m, 1H), 3.63 (s, 2H), 3.59 (s, 2H), 3.57 – 3.51 (m, 1H, distinct diastereoisomer), 3.34 – 3.27 (m, 1H, distinct diastereoisomer), 2.14 – 1.60 (m, 6H), **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{13}C NMR (151 MHz, $CDCl_3$) δ 128.7, 128.7, 128.3, 126.9, 126.9, 95.8 – 95.5 (2 x d, J = 171 Hz, diastereoisomers) 60.3, 60.2, 55.5, 55.1, 36.6 (d, J = 20.9 Hz, distinct diastereoisomer), 34.9 (d, J = 20.7 Hz, distinct diastereoisomer), 32.6 (d, J = 22.0 Hz, distinct diastereoisomer), 32.1 (d, J = 22.0 Hz, distinct diastereoisomer) 26.2, 25.2, **note**: distinct diastereoisomer: spectrally isolated diastereoisomer signal;

^{19}F NMR (376 MHz, $CDCl_3$) δ -167.83, -169.14, diastereoisomers.

HRMS (ESI-TOF): calc'd for $C_{19}H_{23}FN$ [M+H$^+$] 284.1809; found 284.1807.

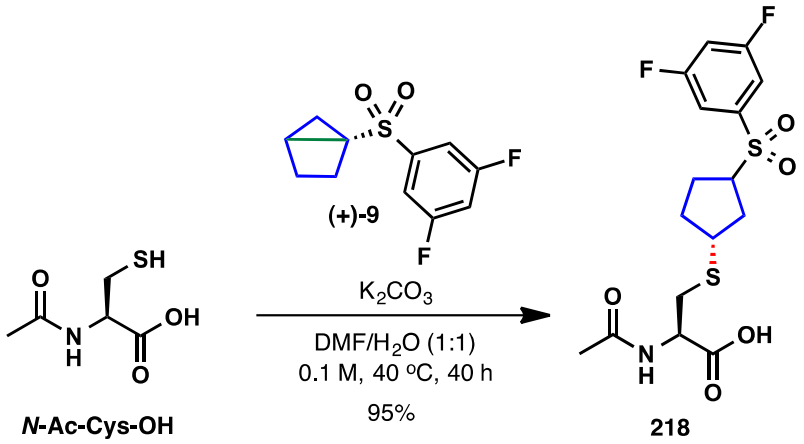
Housane-based Strain-Release on Amino Acids and Peptides

General Methods for HPLC Purification and Analysis

Analytical reverse-phase HPLC was performed on a Hitachi D-7000 separations module equipped with a L-4500A photodiode array detector. Amino acids and peptides were analyzed using a Vydac 218TP54 Protein & Peptide C18 column (5 μm, 4.6 mm x 250 mm) at a flow rate of 1.5 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B). Results were analyzed using Hitachi Model D-7000 Chromatography Data Station Software.

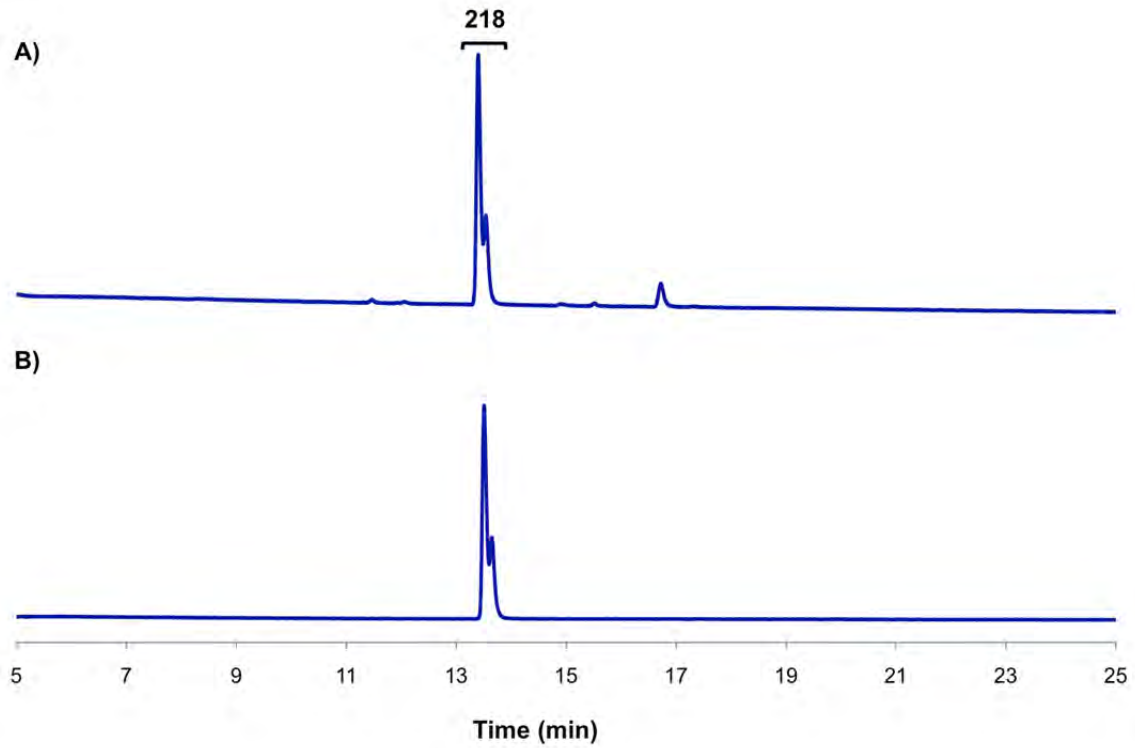
Preparative reverse-phase HPLC was performed using a Hitachi system comprised of an L-7150 pump and L-4000 programmable UV detector operating at a wavelength of 230 nm coupled to a Hitachi D-2500 Chromato-Integrator. Amino acids and peptides were purified on a Thermo Scientific Bio-basic C18 10 μm preparative column operating at a flow rate of 12 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B) and a linear gradient as specified. Compounds were isolated as white solids (unless otherwise noted) following lyophilization.

Compound **218**

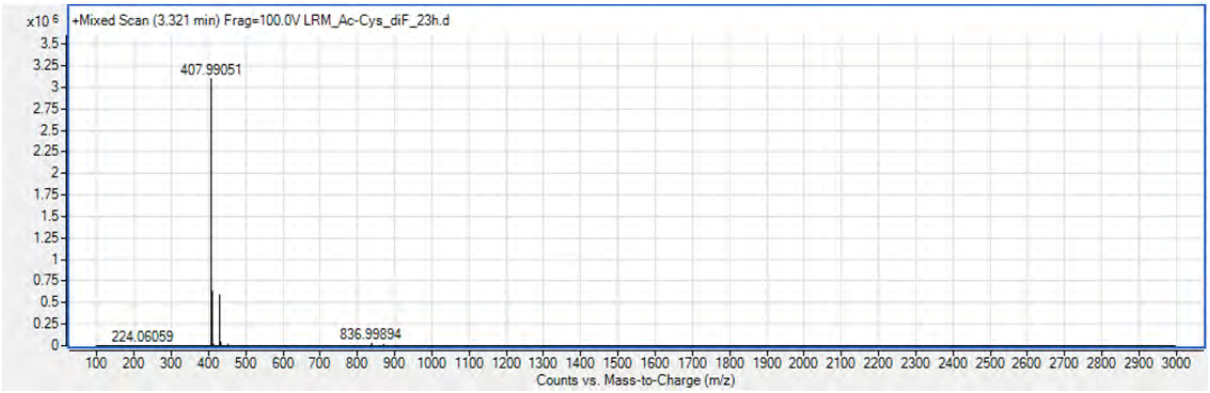


Compound **218** was prepared from *N*-Ac-Cys-OH (0.090 mmol) and strain-release reagent **(+)-9** using general procedure B for S-H functionalization. Purification of the crude reaction mixture by preparative reverse-phase HPLC (30% B for 5 min, then 30% to 65% B over 25 min) afforded compound **218** as a mixture of diastereomers and as a white solid following lyophilization (35.0 mg, 95% yield).

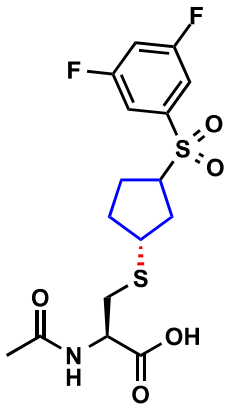
The reaction was also carried out with racemic reagent **9** to afford compound **218** as a mixture of four diastereomers (92% isolated yield).



A) Crude analytical HPLC trace (t = 40 h) of the reaction of **(+)-9** with *N*-Ac-Cys-OH (5 to 100% B over 25 min, λ = 280 nm); B) Purified product **218** (5 to 100% B over 25 min, λ = 280 nm, Rt (major diastereomer = 13.5 min), Rt (minor diastereomer) = 13.6 min).



LRMS (ESI-TOF): calc'd for $C_{16}H_{20}F_2NO_5S_2$ $[M+H]^+$ 408.07; found 407.99.



218

Physical State: fluffy white solid (following lyophilization)

Major diastereomer

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.58 – 7.54 (m, 2H), 7.45 – 7.36 (m, 1H), 4.63 – 4.53 (m, 1H), 3.90 – 3.79 (m, 1H), 3.27 – 3.15 (m, 1H), 3.06 (dd, J = 13.8, 4.9 Hz, 1H), 2.86 (dd, J = 13.9, 7.9 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.25 – 2.15 (m, 1H), 2.15 – 2.05 (m, 1H), 1.99 (s, 3H), 1.97 – 1.89 (m, 1H), 1.88 – 1.79 (m, 1H), 1.71 – 1.59 (m, 1H).

^{13}C NMR (126 MHz, Methanol-d_4) δ 173.6, 173.3, 164.5 (dd, J = 254.1, 11.6 Hz, 2C), 143.6 (t, J = 8.2 Hz), 113.4 – 112.9 (m, 2C), 110.5 (t, J = 25.8 Hz), 63.9, 53.7, 44.5, 35.7, 34.3, 34.2, 26.9, 22.4.

^{19}F NMR (376 MHz, Methanol-d_4) δ -107.5 (+ residual TFA from HPLC) [NMR data from racemic sample].

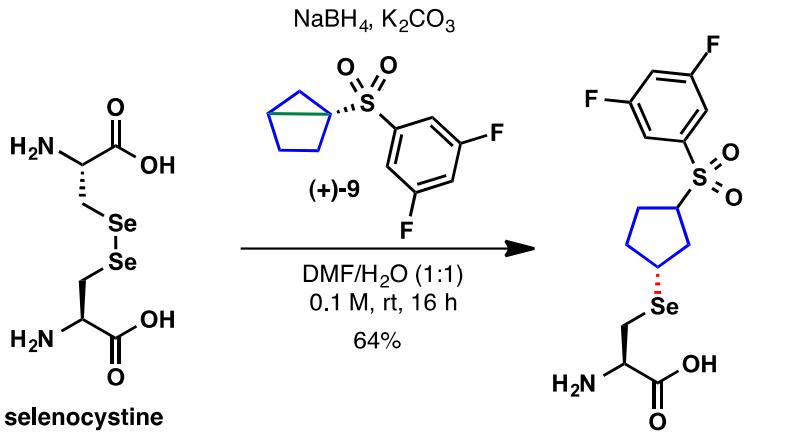
Minor diastereomer

^{1}H NMR (500 MHz, Methanol-d_4) δ 7.61 – 7.57 (m, 2H), 7.45 – 7.36 (m, 1H), 4.63 – 4.53 (m, 1H), 4.02 – 3.93 (m, 1H), 3.46 – 3.37 (m, 1H), 3.06 – 3.01 (m, 1H), 2.91 – 2.83 (m, 1H), 2.49 – 2.41 (m, 1H), 2.24 – 2.15 (m, 1H), 2.15 – 2.05 (m, 1H), 1.99 (s, 3H), 1.97 – 1.89 (m, 1H), 1.88 – 1.79 (m, 1H), 1.71 – 1.59 (m, 1H).

^{13}C NMR (126 MHz, Methanol-d_4) δ 173.5, 173.3, 164.5 (dd, J = 254.1, 11.6 Hz, 2C), 143.6 (t, J = 8.2 Hz), 113.4 – 112.9 (m, 2C), 110.5 (t, J = 25.8 Hz), 63.7, 53.8, 45.1, 35.3, 34.2, 34.2, 26.8, 22.4.

^{19}F NMR (376 MHz, Methanol-d_4) δ -107.4 (+ residual TFA from HPLC) [NMR data from racemic sample].

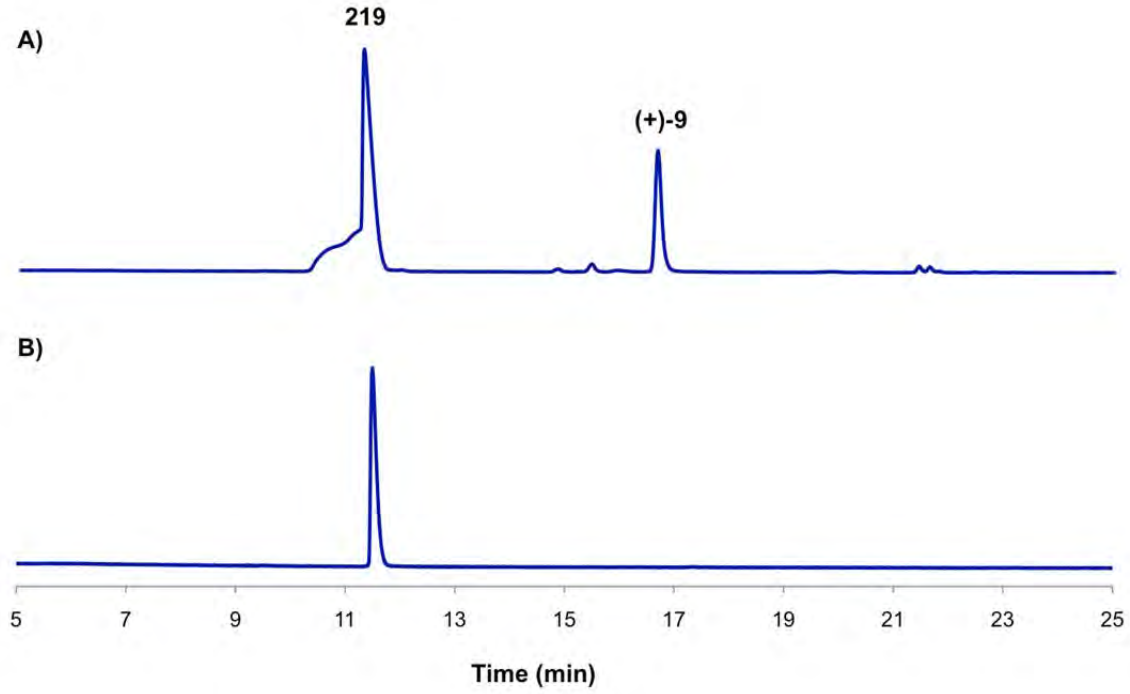
Compound **219**



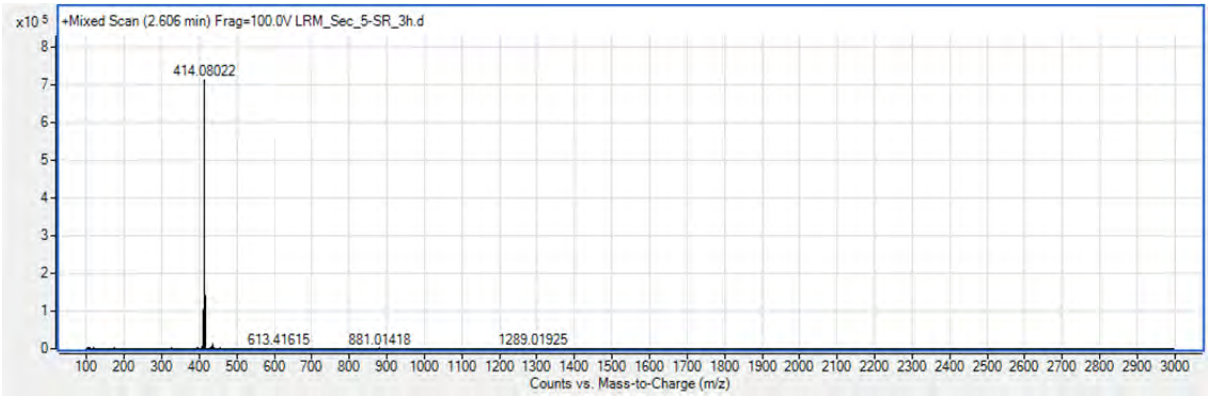
(isolated as a TFA salt following HPLC purification)

Compound **219** was prepared from selenocystine dimer (0.045 mmol) and strain-release reagent **(+)-9** using a modification of general procedure B. Selenocystine was dissolved in 0.2 M K_2CO_3 (0.45 mL) and treated with a solution of **(+)-9** (0.095 mmol) in DMF (0.45 mL). The resulting reaction mixture was treated with $NaBH_4$ (2 equiv.) and stirred at rt. Following the addition of $NaBH_4$, a yellow color emerged accompanied by effervescence. After stirring at rt for 30 min, an additional dose (2 equiv.) of $NaBH_4$ was added and the reaction was stirred at rt for an additional 15 h. The crude reaction mixture was purified immediately by preparative reverse-phase HPLC (20% B for 5 min, then 20% to 55% B over 25 min) to afford compound **219** as a mixture of diastereomers and as a white solid following lyophilization (30.1 mg, 64% yield).

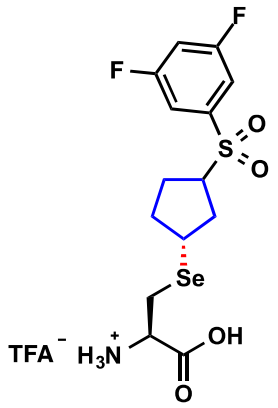
The reaction was also carried out with racemic reagent **9** to afford compound **219** as a mixture of four diastereomers (83% isolated yield).



A) Crude analytical HPLC trace (t = 16 h) of the reaction of **(+)-9** with selenocystine (5 to 100% B over 25 min, λ = 280 nm); B) Purified product **219** (5 to 100% B over 25 min, λ = 280 nm, Rt = 11.5 min).



LRMS (ESI-TOF): calc'd for $C_{14}H_{18}F_2NO_4SSe$ $[M+H]^+$ 414.01; found 414.08.



219

Physical State: fluffy white solid (following lyophilization)

Major diastereomer:

^{1}H NMR (600 MHz, Methanol-d_4 + 5 µL TFA) δ 7.58 – 7.55 (m, 2H), 7.41 (tt, J = 8.9, 2.3 Hz, 1H), 4.31 – 4.23 (m, 1H), 3.89 – 3.82 (m, 1H), 3.44 – 3.34 (m, 1H), 3.20 (dd, J = 13.9, 4.6 Hz, 1H), 3.09 (dd, J = 13.9, 7.0 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.25 – 2.14 (m, 2H), 2.12 – 1.89 (m, 2H), 1.85 – 1.70 (m, 1H).

^{13}C NMR (151 MHz, Methanol-d_4 + 5 µL TFA) δ 170.4, 164.5 (dd, J = 253.8, 11.7 Hz, 2C), 160.4 (q, J = 38.9 Hz), 143.6 (t, J = 8.0 Hz), 116.9 (q, J = 287.2, 286.4 Hz), 113.8 – 112.3 (m, 2C), 110.5 (t, J = 25.8 Hz), 64.1, 54.1, 37.9, 36.0, 34.9, 27.4, 23.5.

^{19}F NMR (376 MHz, $CDCl_3$/MeOD, 3:2 v/v) δ -76.1, -104.7.

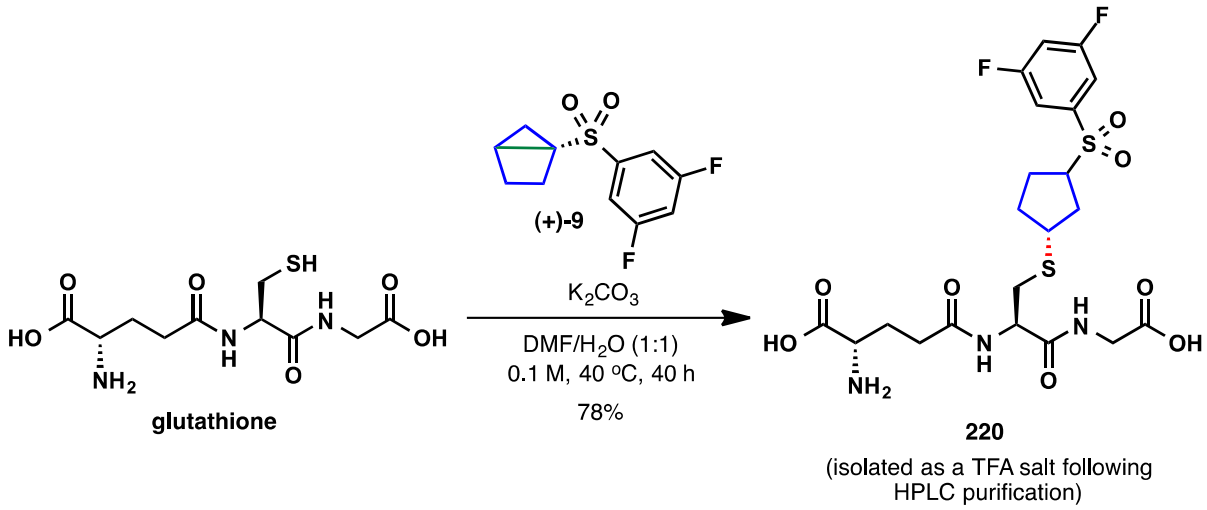
Minor diastereomer:

^{1}H NMR (600 MHz, Methanol-d_4 + 5 µL TFA) δ 7.60 – 7.55 (m, 2H), 7.41 (tt, J = 8.9, 2.3 Hz, 1H), 4.31 – 4.23 (m, 1H), 4.03 – 3.96 (m, 1H), 3.64 – 3.54 (m, 1H), 3.19 – 3.13 (m, 1H), 3.12 – 3.06 (m, 1H), 2.61 – 2.54 (m, 1H), 2.33 – 2.25 (m, 1H), 2.12 – 1.97 (m, 3H), 1.85 – 1.70 (m, 1H).

^{13}C NMR (151 MHz, Methanol-d_4 + 5 µL TFA) δ 170.4, 164.5 (dd, J = 253.8, 11.7 Hz, 2C), 160.4 (q, J = 38.9 Hz), 143.6 (t, J = 8.0 Hz), 116.9 (q, J = 287.2, 286.4 Hz), 113.8 – 112.3 (m, 2C), 110.5 (t, J = 25.8 Hz), 63.8, 54.0, 38.6, 35.8, 34.9, 27.3, 23.5.

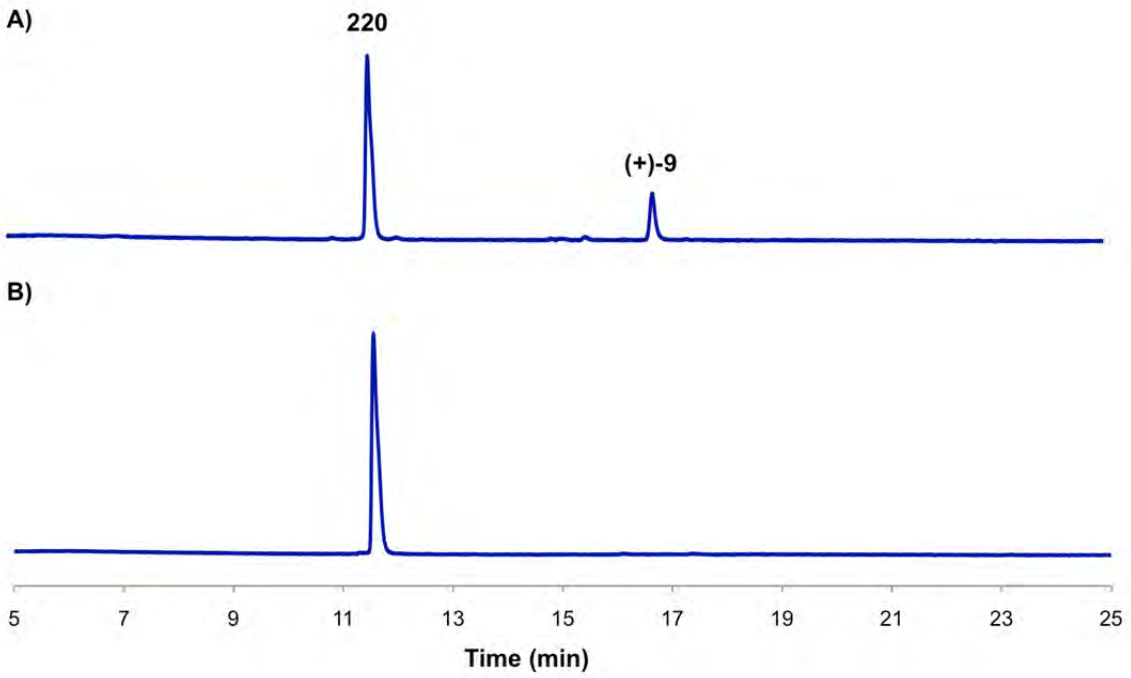
^{19}F NMR (376 MHz, $CDCl_3$/MeOD, 3:2 v/v) δ -76.1, -104.6.

Compound **220**

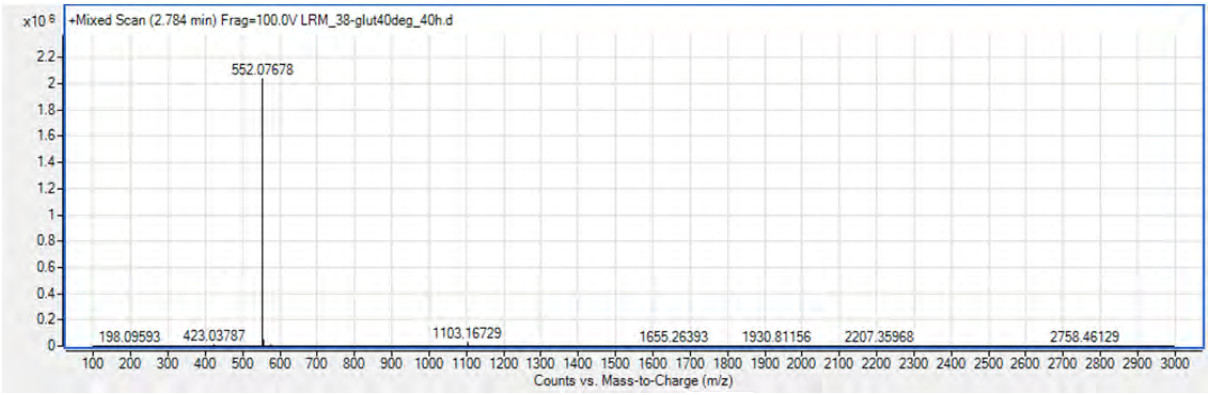


Compound **220** was prepared from glutathione (31 μmol) and strain-release reagent **(+)-9** using general procedure B for S-H functionalization. Purification of the crude reaction mixture by preparative reverse-phase HPLC (20% B for 5 min, then 20% to 55% B over 25 min) afforded compound **220** as a mixture of diastereomers and as a white solid following lyophilization (15.8 mg, 78% yield).

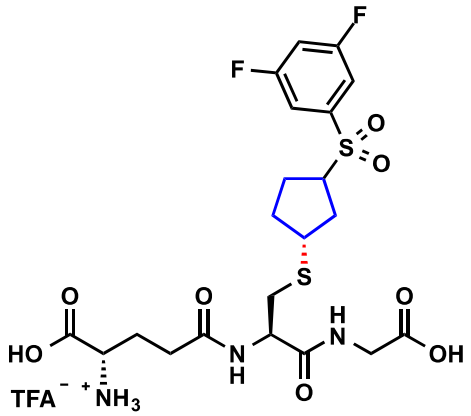
The reaction was also carried out with racemic reagent **9** to afford compound **220** as a mixture of four diastereomers (96% isolated yield).



A) Crude analytical HPLC trace (t = 40 h) of the reaction of **(+)-9** with glutathione (5 to 100% B over 25 min, λ = 280 nm); B) Purified product **220** (5 to 100% B over 25 min, λ = 280 nm, Rt = 11.5 min).



LRMS (ESI-TOF): calc'd for $C_{21}H_{28}F_2N_3O_8S_2$ $[M+H]^+$ 552.13; found 552.08.



220

Physical State: fluffy white solid (following lyophilization)

Major diastereomer

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.63 – 7.53 (m, 2H), 7.44 – 7.39 (m, 1H), 4.61 – 4.53 (m, 1H), 4.09 – 4.01 (m, 1H), 4.00 – 3.89 (m, 2H), 3.90 – 3.80 (m, 1H), 3.29 – 3.18 (m, 1H), 3.05 (dd, J = 13.9, 5.3 Hz, 1H), 2.82 (dd, J = 13.9, 8.7 Hz, 1H), 2.58 (t, J = 7.2 Hz, 2H), 2.42 – 2.34 (m, 1H), 2.30 – 2.02 (m, 4H), 2.00 – 1.80 (m, 2H), 1.71 – 1.59 (m, 1H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 174.4, 173.0, 172.6, 171.5, 164.5 (dd, J = 253.8, 11.7 Hz, 2C), 162.2 (q, J = 35.6 Hz), 143.6 (t, J = 8.2 Hz), 117.8 (q, J = 290.7 Hz), 114.0 – 112.0 (m, 2C), 110.5 (t, J = 25.7 Hz), 64.0, 54.4, 53.6, 44.5, 41.8, 35.7, 34.5, 34.2, 32.4, 27.1, 27.0.

^{19}F NMR (376 MHz, Methanol-d_4) δ -77.2, -107.5.

Minor diastereomer

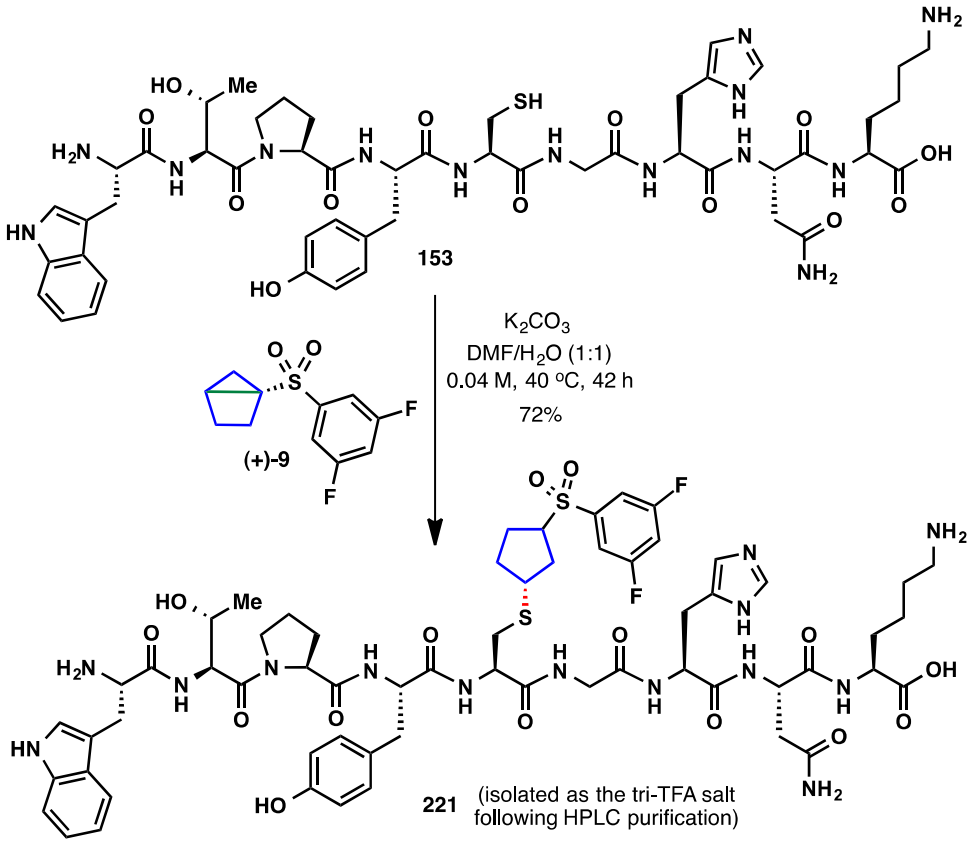
^{1}H NMR (600 MHz, Methanol-d_4) δ 7.63 – 7.53 (m, 2H), 7.44 – 7.39 (m, 1H), 4.61 – 4.53 (m, 1H), 4.09 – 4.01 (m, 1H), 3.99 – 3.92 (m, 3H), 3.45 – 3.38 (m, 1H), 3.03 (dd, J = 14.0, 5.5 Hz, 1H), 2.84 – 2.79 (m, 1H), 2.58 (t, J = 7.2 Hz, 2H), 2.51 – 2.45 (m, 1H), 2.30 – 2.02 (m, 4H), 2.00 – 1.80 (m, 2H), 1.71 – 1.59 (m, 1H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 174.4, 173.0, 172.6, 171.5, 164.5 (dd, J = 253.8, 11.7 Hz, 2C), 162.2 (q, J = 35.6 Hz), 143.6 (t, J = 8.2 Hz), 117.8 (q, J = 290.7 Hz), 114.0 –

112.0 (m, 2C), 110.5 (t, J = 25.7 Hz), 63.7, 54.4, 53.6, 44.8, 41.8, 35.2, 34.3, 34.2, 32.4, 27.0, 27.0.

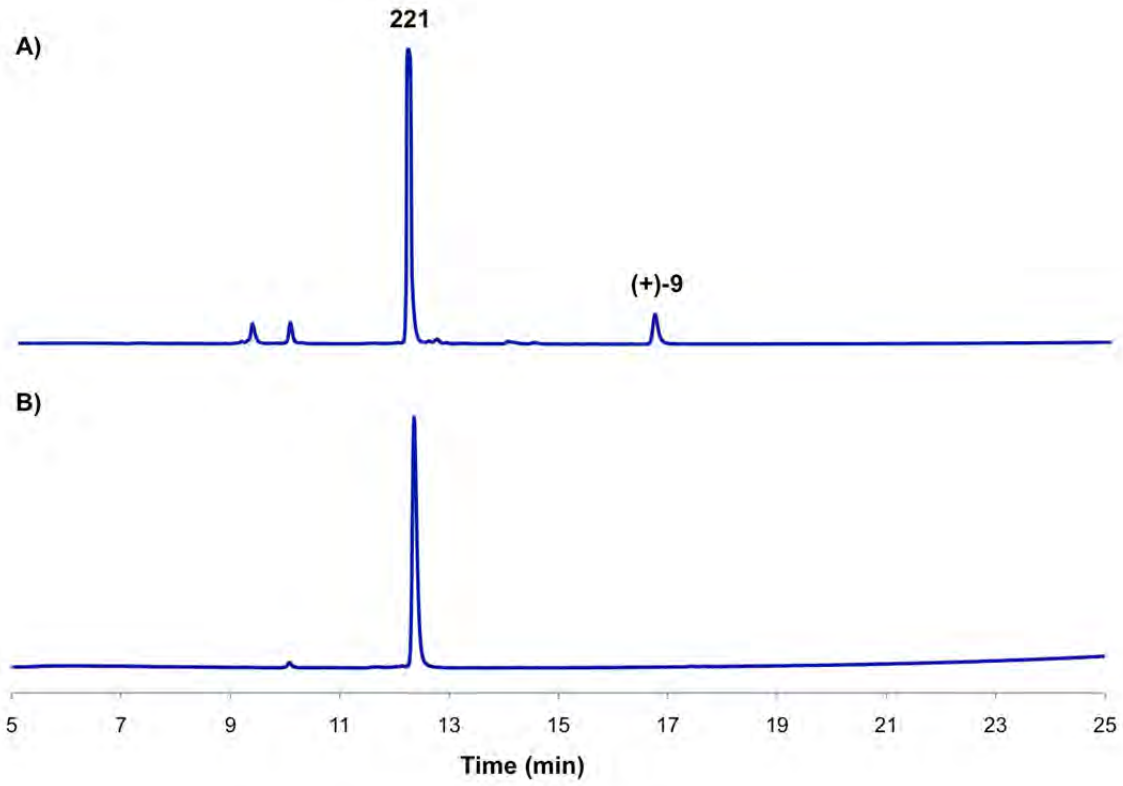
^{19}F NMR (376 MHz, MeOD) δ -77.2, -107.4.

Compound 221

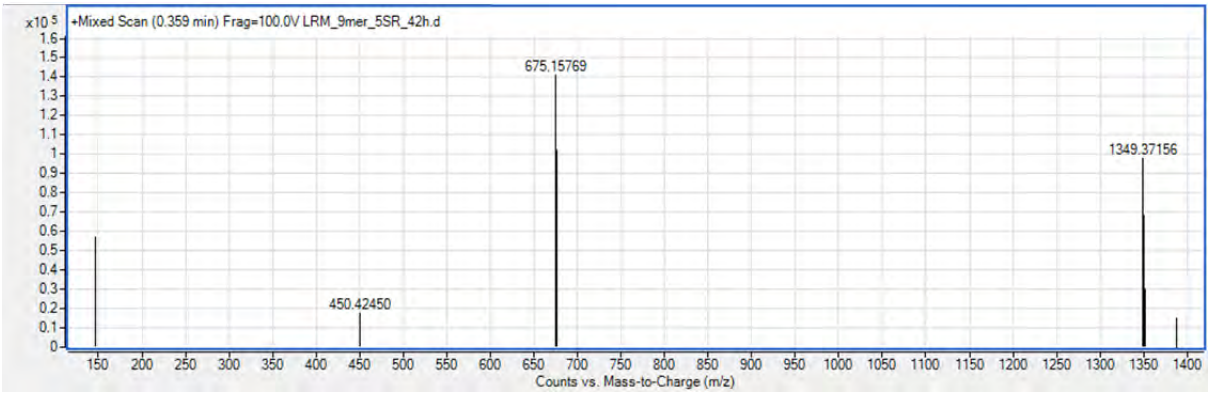


Compound **221** was prepared from peptide **153** (3.1 mg, 2.1 µmol, 3 x TFA salt) and strain-release reagent **(+)-9** using general procedure B for S-H functionalization at a final concentration of 0.04 M with respect to **153**. Purification of the crude reaction mixture by preparative reverse-phase HPLC (20% B for 5 min, then 20% to 55% B over 25 min) afforded compound **221** as a mixture of diastereomers and as a white solid following lyophilization (2.6 mg, 72% yield, 3 x TFA salt).

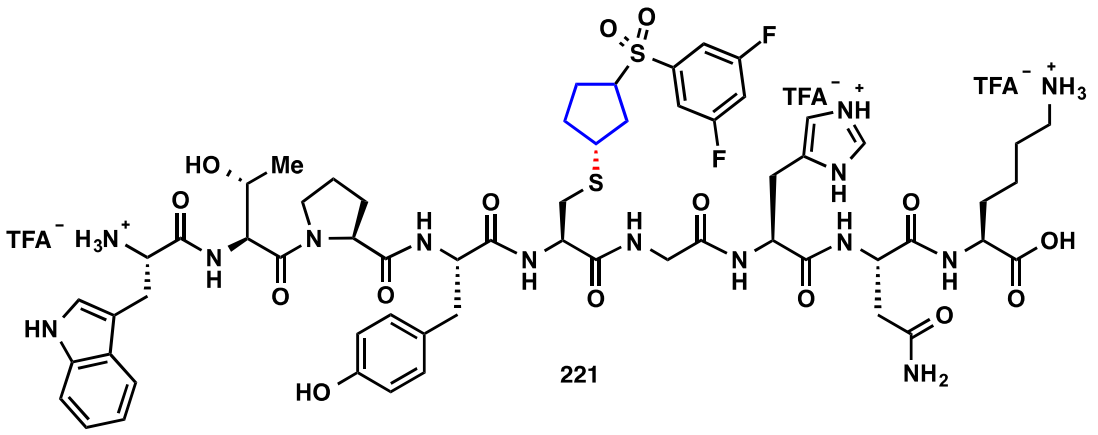
Note: Peptide H-WTPYCGHNK-OH **153** was prepared as the tri-TFA salt as previously described.[70]



A) Crude analytical HPLC trace (t = 42 h) of the reaction of **(+)-9** with **153** (5 to 100% B over 25 min, λ = 230 nm); B) Purified product **221** (5 to 100% B over 25 min, λ = 230 nm, Rt = 12.4 min).



LRMS (ESI-TOF): calc'd for $C_{61}H_{79}F_2N_{14}O_{15}S_2$ $[M+H]^+$ 1349.53; found 1349.37; $[M+2H]^{2+}$ 675.27; found 675.16.



Physical State: fluffy white solid (following lyophilization)

^{1}H NMR (600 MHz, 20:1 v/v DMSO-d_6/D_2O, diastereomers) δ 8.93 (d, *J* = 1.5 Hz, 1H), 8.73 (d, *J* = 7.6 Hz, 1H, N*H*), 8.28 (d, *J* = 7.0 Hz, 1H, N*H*), 8.23 (d, *J* = 7.4 Hz, 1H, N*H*), 8.19 (t, *J* = 5.8 Hz, 1H, N*H*), 8.12 (d, *J* = 8.3 Hz, 1H, N*H*), 8.06 (d, *J* = 7.8 Hz, 1H, N*H*), 7.81 (d, *J* = 7.9 Hz, 1H, N*H*), 7.76 – 7.68 (m, 1H), 7.69 – 7.62 (m, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.35 (s, 1H), 7.35 – 7.31 (m, 1H), 7.18 (s, 1H), 7.08 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.97 (apparent t, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 4.65 – 4.53 (m, 2H), 4.48 (d, *J* = 6.5 Hz, 1H), 4.46 – 4.36 (m, 2H), 4.32 (dd, *J* = 8.4, 4.0 Hz, 1H), 4.20 – 4.10 (m, 2H), 4.11 – 4.03 (m, 0.24H, minor diastereomer), 4.01 – 3.92 (m, 0.76H, major diastereomer), 3.93 – 3.86 (m, 1H), 3.77 – 3.68 (m, 2H), 3.63 – 3.56 (m, 2H), 3.51 – 3.41 (m, 0.76H, major diastereomer, partially obscured by H_2O peak), 3.40 – 3.30 (m, 0.24H, minor diastereomer), 3.23 – 3.14 (m, 2H), 3.12 – 3.01 (m, 2H), 3.00 – 2.79 (m, 3H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.71 – 2.58 (m, 3H), 2.59 – 2.41 (m, 2H), 2.37 – 2.26 (m, 1H), 2.04 – 1.87 (m, 3H), 1.87 – 1.78 (m, 1H), 1.77 – 1.39 (m, 7H), 1.38 – 1.28 (m, 2H), 1.16 – 1.05 (m, 3H). (Note: some N*H* peaks exhibit slow exchange with D_2O).

^{19}F NMR (376 MHz, DMSO) δ -73.5, -105.2.

On-resin peptide cyclopentylation

An Innova 2000 portable platform shaker (operating at 145-170 rpm) was used for the general mixing and agitation of solid-phase reactions (including SPPS and on-resin 1,4-addition reactions).

Analytical HPLC and LC-MS analysis of crude reaction mixtures was carried out as described in the general methods. Preparative reverse-phase HPLC for the purification of peptide products was performed as described in the general methods.

Materials

Commercial materials were used as received unless otherwise noted. Amino acids and coupling reagents were obtained from Novabiochem or Combi-blocks. 2-Chlorotrityl chloride resin (1.51 mmol/g) was purchased from Novabiochem. Solid-phase reaction vessels and pressure caps were purchased from Torviq. Reagents that were not commercially available were synthesized following literature procedures.

(Left) Solid-phase reaction vessels purchased from Torviq. **(Right)** Orbital shaker for solid-phase peptide synthesis (SPPS).

Solid-phase peptide synthesis

Preloading 2-chlorotrityl chloride resin

2-chlorotrityl chloride resin (1.0 equiv., substitution = 1.51 mmol/g) was swollen in dry DCM for 30 min then washed with DCM (5 x 3 mL) and DMF (5 x 3 mL). A solution of Fmoc-AA-OH (4.0 equiv.) and *N*,*N*-diisopropylethylamine (DIEA) (8.0 equiv.) in DMF

(final concentration of 0.1 M with respect to the resin) was added and the resin agitated on an orbital shaker at rt for 16 h. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and capped with a solution of DCM/MeOH/DIEA (17:2:1 v/v/v, 3 mL) for 30 min. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS).

Estimation of amino acid loading

The loading efficiency was evaluated through treatment of the resin with 20% piperidine/DMF (3 mL, 2 × 3 min) to deprotect the Fmoc group. The combined deprotection solutions were diluted to 10 mL with 20% piperidine/DMF. An aliquot of this mixture (50 μL) was diluted 200-fold with 20% piperidine/DMF and the UV absorbance of the piperidine-fulvene adduct was measured (λ = 301 nm, ε = 7800 M^{-1} cm^{-1}) to quantify the amount of amino acid loaded onto the resin. The theoretical maximum for the reported yields of all isolated peptides is based on the numerical value obtained from the resin loading.

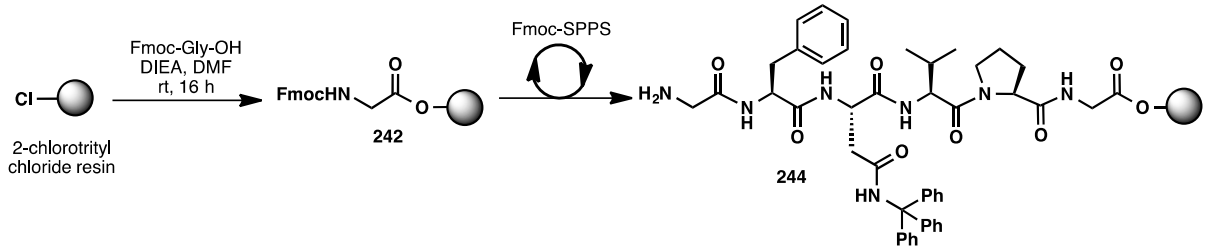
General iterative peptide assembly (Fmoc-SPPS)

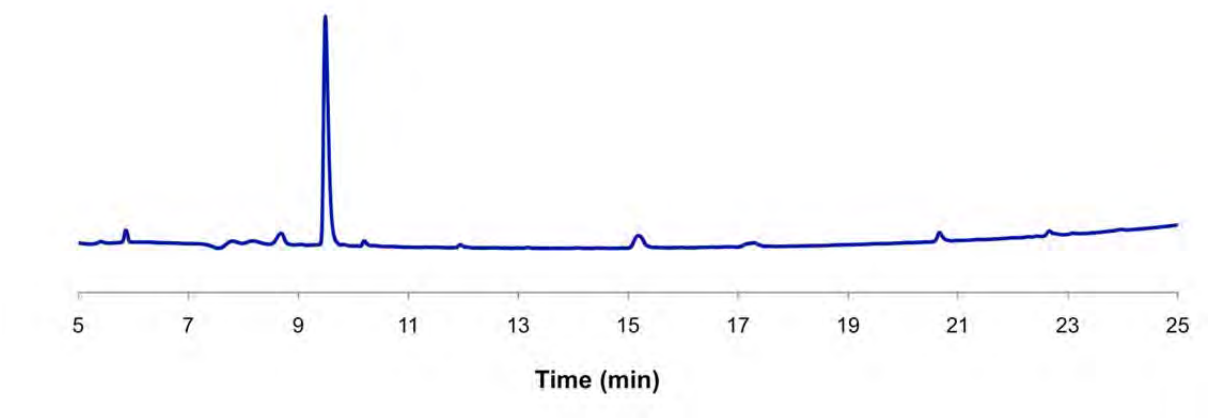
Peptides were elongated using iterative Fmoc-solid-phase peptide synthesis (Fmoc-SPPS), according to the following general protocols:

Deprotection: The resin was treated with 20% piperidine/DMF (3 mL, 2 x 3 min) and washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

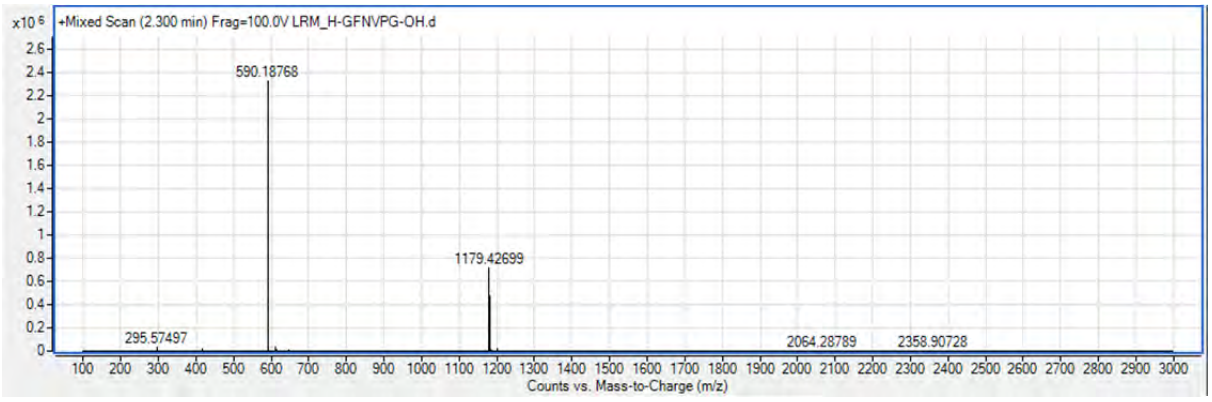
General amino acid coupling: A preactivated solution of protected amino acid (4 equiv.), PyBOP (4 equiv.) and *N*-methylmorpholine (NMM) (8 equiv.) in DMF (final concentration 0.1 M) was added to the resin. After 1 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

Capping: Acetic anhydride/pyridine (1:9 v/v) was added to the resin (3 mL). After 3 min the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).





Crude analytical HPLC trace of the solid-phase synthesis of hexapeptide **244** beginning with 2-chlorotrityl chloride resin (5 to 100% B over 25 min, λ = 230 nm). Note: the HPLC chromatogram depicts peptide **244'** following cleavage from the resin and loss of side-chain protecting groups.



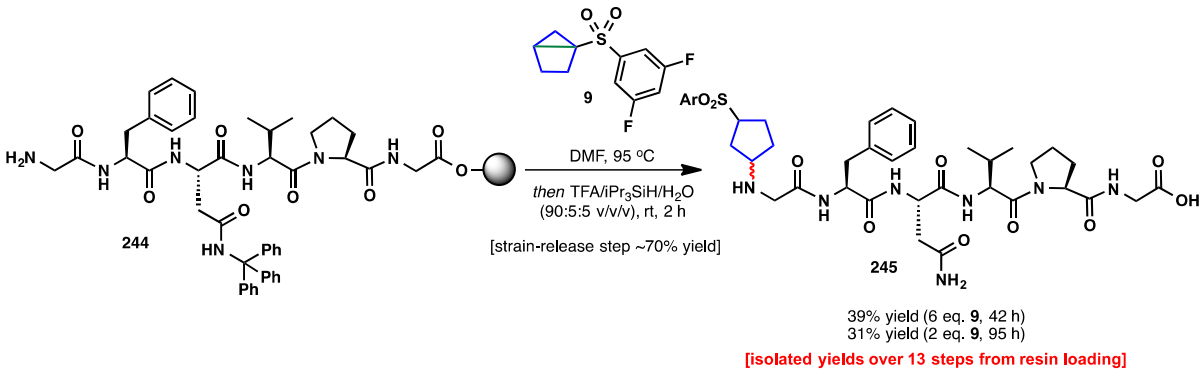
LRMS (ESI-TOF): calc'd for $C_{27}H_{40}N_7O_8$ $[M+H]^+$ 590.29; found 590.19.

On-resin strain-release reaction: Resin-bound peptide **244** (15 μmol) was placed into a glass reaction tube equipped with a stir bar. To the vial was added the appropriate strain-release reagent **9** or **(–)-9** (2 equiv. or 6 equiv.) and dry DMF (0.2 mL). The reaction tube was sealed and heated at 95 °C with stirring. The reaction was monitored by removal of a small number of resin beads, cleavage from the resin (see general cleavage procedure below), and LC-MS analysis of the crude cleavage solution. Following completion of the reaction, the resin was transferred to a fritted syringe and washed thoroughly with DMF (5 x 3 mL) and DCM (10 x 3 mL). The peptide was then cleaved and purified as described below.

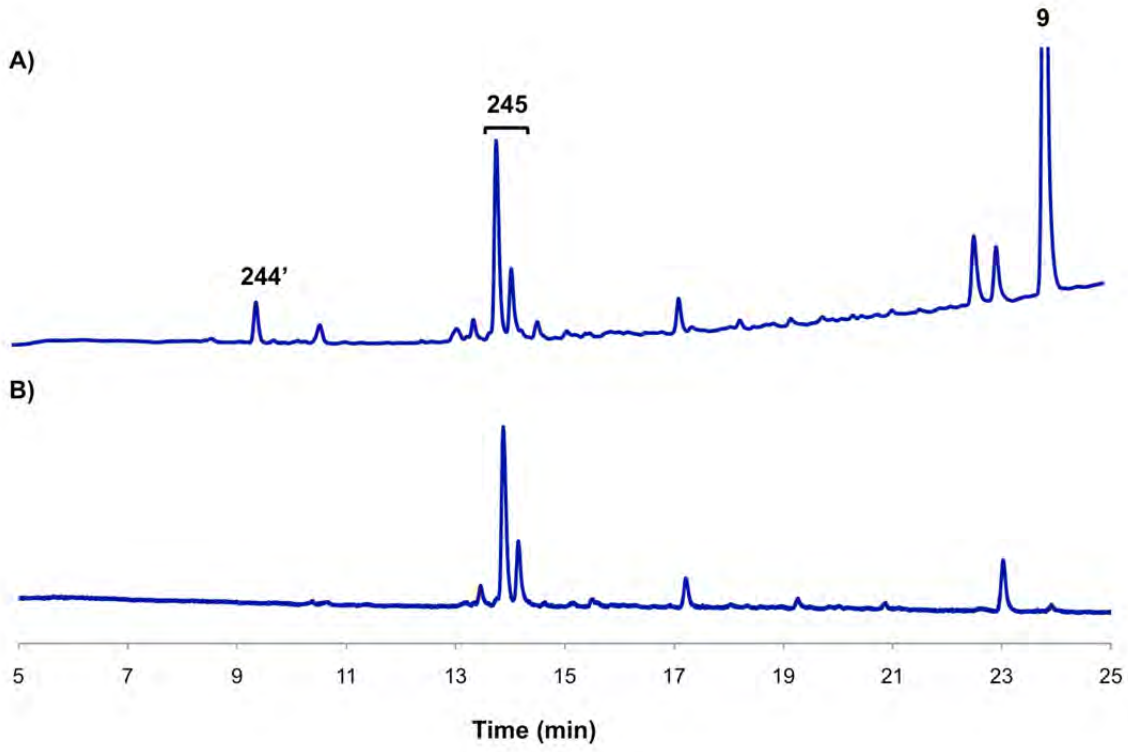
Cleavage: A mixture of TFA/*i*Pr$_3$SiH/water (90:5:5 v/v/v) was added to the resin. After 2 h, the resin was washed with TFA (3 x 2 mL) and DCM (3 x 2 mL).

Work-up: The combined cleavage solution and TFA and DCM washes were concentrated under a stream of nitrogen. The residue was treated with cold Et_2O to precipitate the crude peptide. The peptide was collected by centrifugation and the crude residue was purified by reverse-phase HPLC.

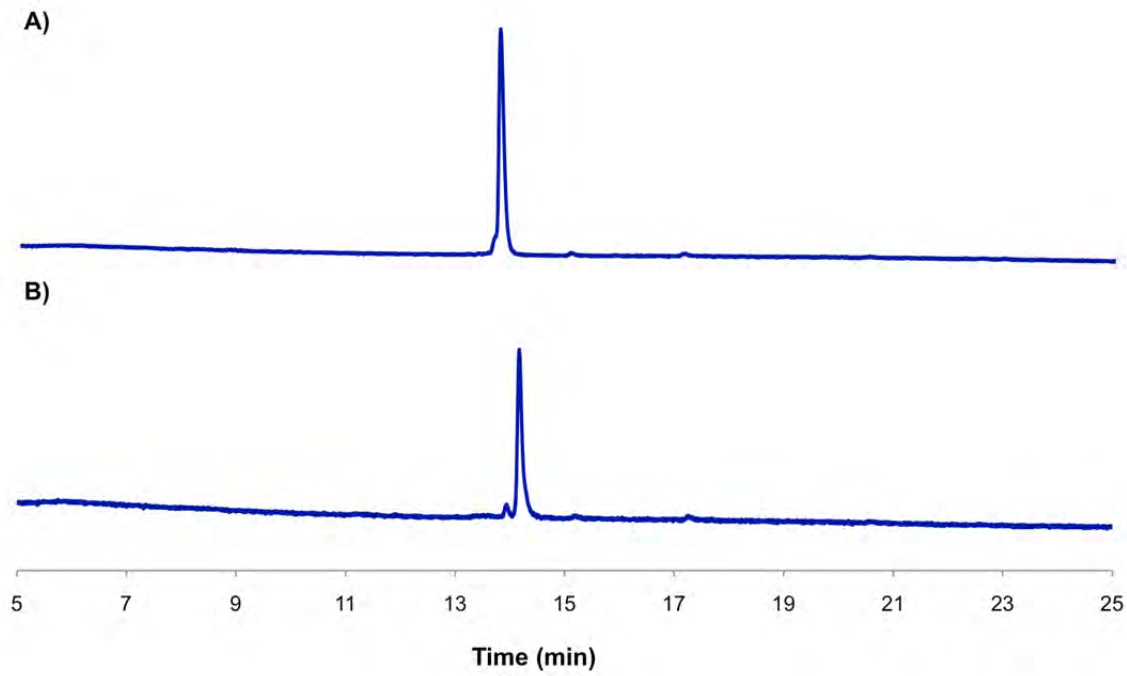
On-resin reaction with 9 (racemic)



Compound **245** was prepared from resin-bound peptide **244** and strain-release reagent **9** using the general procedure for on-resin strain-release described above. The reaction was carried out with 2 equiv. of **9** (95 h at 95 °C with 15 µmol of resin) and with 6 equiv. of **9** (42 h at 95 °C with 13.5 µmol of resin). Following completion of the reaction, the peptide was cleaved from the resin and purified by preparative reverse-phase HPLC (25% B for 5 min, then 25% to 60% B over 30 min) to afford compound **245** (TFA salt) as a separable mixture of diastereomers (combined yield: 4.4 mg, 31% yield for 2 equiv.; combined yield: 5.0 mg, 39% yield for 6 equiv.).

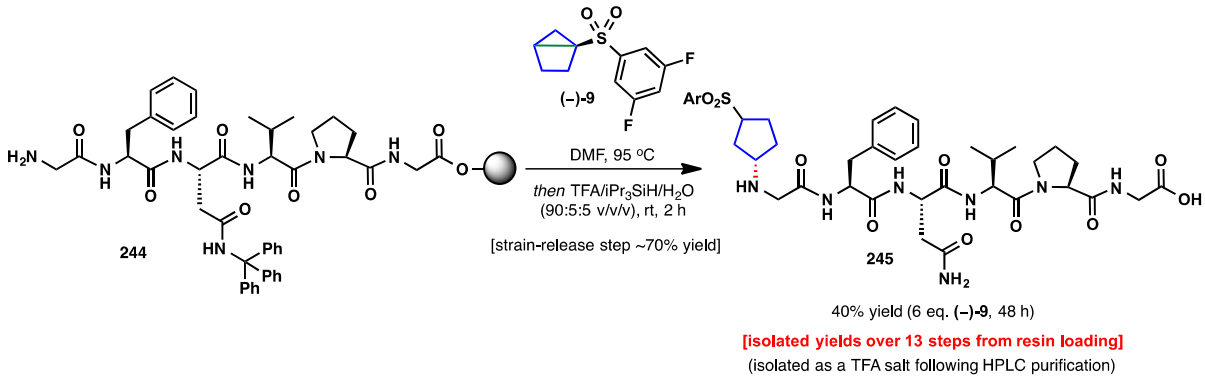


A) Crude analytical HPLC trace (t = 40 h) of the reaction of **9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 230 nm). Note: the HPLC chromatogram depicts peptide **244'** following cleavage from the resin and loss of side-chain protecting groups. B) Crude analytical HPLC trace of the reaction of **9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 280 nm).

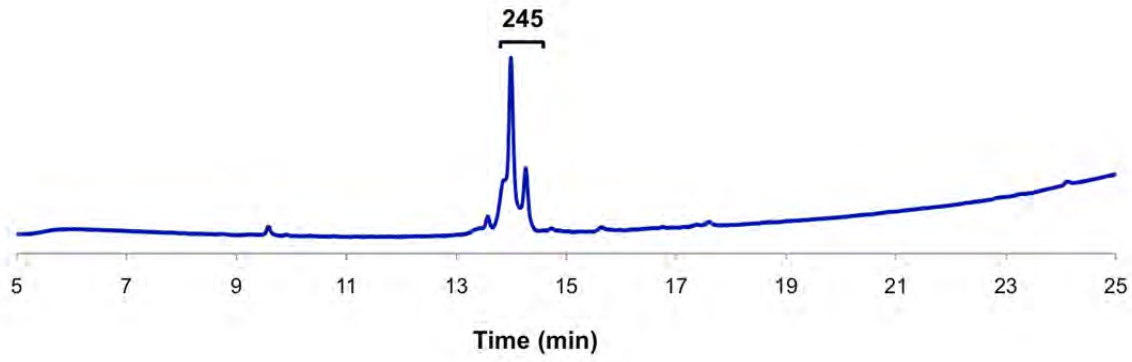


A) Purified major diastereomer of the reaction of **9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 280 nm); B) Purified minor diastereomer of the reaction of **9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 280 nm).

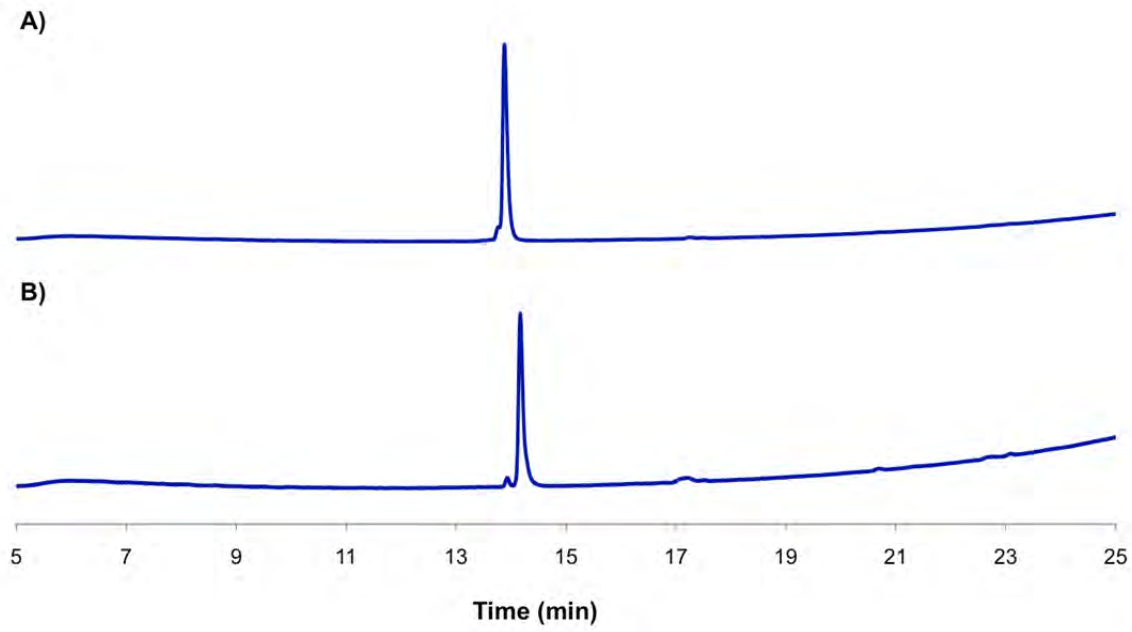
On-resin reaction with (–)-9 (chiral)



Compound **245** was prepared from resin-bound peptide **244** (13.5 μmol) and strain-release reagent **(–)-9** using the general procedure for on-resin strain-release described above. The reaction was carried out with 6 equiv. of **(–)-9** (48 h at 95 °C). Following completion of the reaction, the peptide was cleaved from the resin and purified by preparative reverse-phase HPLC (30% B for 5 min, then 30% to 60% B over 30 min) to afford compound **245** (TFA salt) as a separable mixture of diastereomers (combined yield: 5.1 mg, 40% yield).



Crude analytical HPLC trace (t = 47 h) of the reaction of **(–)-9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 230 nm).



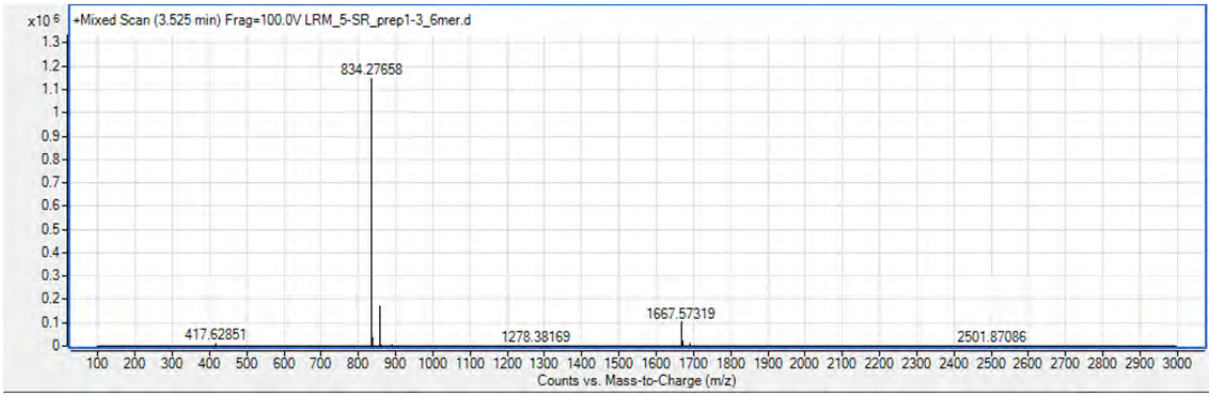
A) Purified major diastereomer of the reaction of **(–)-9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 230 nm, Rt = 13.9 min); B) Purified minor diastereomer of the reaction of **(–)-9** with resin-bound peptide **244** (5 to 100% B over 25 min, λ = 280 nm, Rt = 14.2 min).

Major diastereomer

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.71 (d, *J* = 8.5 Hz, 1H), 8.60 (d, *J* = 7.6 Hz, 1H), 8.32 – 8.21 (m, 1H), 7.95 – 7.86 (m, 2H), 7.78 (tt, *J* = 9.2, 2.3 Hz, 1H), 7.74 – 7.64 (m, 2H),

7.44 – 7.35 (m, 1H), 7.30 – 7.15 (m, 5H), 7.13 (s, 1H), 7.05 (s, 1H), 6.94 – 6.89 (m, 1H), 5.14 – 4.96 (m, 1H), 4.80 – 4.65 (m, 1H), 4.65 – 4.52 (m, 1H), 4.47 – 4.29 (m, 2H), 4.12 – 3.95 (m, 1H), 3.85 (dd, *J* = 17.4, 6.1 Hz, 1H), 3.76 – 3.46 (m, 4H), 3.43 – 3.33 (m, 1H), 3.05 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.70 (dd, *J* = 14.0, 10.3 Hz, 1H), 2.55 (dd, *J* = 15.8, 5.4 Hz, 1H), 2.39 (dd, *J* = 15.7, 8.0 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.13 – 2.04 (m, 1H), 2.04 – 1.71 (m, 9H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H).

^{19}F NMR (376 MHz, DMSO-d_6): δ -73.4, -105.4.



LRMS (ESI-TOF): calc'd for $C_{38}H_{50}F_2N_7O_{10}S$ $[M+H]^+$ 834.33; found 834.28.

Minor diastereomer

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.70 (d, *J* = 8.6 Hz, 1H), 8.59 (d, *J* = 7.7 Hz, 1H), 8.21 (t, *J* = 5.9 Hz, 1H), 7.94 – 7.85 (m, 2H), 7.77 (tt, *J* = 9.0, 2.3 Hz, 1H), 7.72 – 7.65 (m, 3H), 7.37 (d, *J* = 2.6 Hz, 1H), 7.29 – 7.24 (m, 5H), 7.23 – 7.17 (m, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 5.20 – 5.13 (m, 1H), 4.68 (ddd, *J* = 10.4, 8.7, 3.6 Hz, 1H), 4.66 – 4.58 (m, 1H), 4.40 – 4.35 (m, 1H), 4.33 (dd, *J* = 8.5, 4.4 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.81 (dd, *J* = 17.4, 6.0 Hz, 1H), 3.71 (dd, *J* = 17.4, 5.7 Hz, 1H), 3.68 – 3.62 (m, 1H), 3.61 – 3.54 (m, 1H), 3.53 – 3.32 (m, 2H, partially obscured by H_2O peak), 3.04 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.69 (dd, *J* = 13.9, 10.4 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.43 – 2.34 (m, 1H), 2.24 – 2.17 (m, 1H), 2.09 – 2.02 (m, 1H), 2.02 – 1.70 (m, 9H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{19}F NMR (376 MHz, DMSO-d_6): δ -73.6, -105.4.

LRMS (ESI-TOF): calc'd for $C_{38}H_{50}F_2N_7O_{10}S$ $[M+H]^+$ 834.33; found 834.26.

Glutathione Assay for the Evaluation of Covalent Reactive Groups (Table 2)

The procedure was followed as reported in the literature.[71]

250 μL of a 10.0 mM solution of electrophile (**8b**-**8g**) in DMA was manually transferred to a reaction vial. 250 μL of a 2.0 mM solution of indoprofen (used as internal standard in MS analysis) in DMA was automatically transferred to the vial using the liquid handler system of ReactArray. 4.50 mL of a 11.1 mM solution of glutathione in 100 mM potassium phosphate buffer (pH 7.4) was automatically transferred to the vial using ReactArray's liquid handler system. The reactions were initiated upon addition of GSH and run at 37 ºC. After the above operations were performed, each reaction vessel contained 1 mM electrophile, 0.10 mM indoprofen, and 10 mM GSH in 100 mM potassium phosphate buffer:DMA, 90:10, in a total volume of 5 mL. The liquid handler system automatically sampled each reaction mixture every 60 minutes (for a total of 7 h) by taking out 100 μL of the reaction mixture and diluting with 900 μL of deionized (DI) water. Half-life was determined with MS by degradation of electrophiles **8b**-**8g**.

References

(1) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529-2591.
(2) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, ***115***, 765-825.
(3) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012,** *492*, 95-99.
(4) Westphal, M. V.; Wolfstadter, B. T.; Plancher, J. M.; Gatfield, J.; Carreira, E. M. *ChemMedChem* **2015**, *10*, 461-469.
(5) Michaudel, Q.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2015**, *48*, 712-721.
(6) Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; DiRico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.; O'Donnell, C. J. *J. Med. Chem*. **2012**, ***55***, 3414-3424.
(7) Wiberg, K. B.; Williams, V. Z. *J. Org. Chem.* **1970**, *35*, 369-373.
(8) M. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev.* **2000**, *100*, 169-234.
(9) Wiberg, K. B. *Chem. Rev.* **1989**, *89*, 975-983.
(10) Bunker, K. D.; Sach, N. W.; Huang, Q. H.; Richardson, P. F. *Org. Lett.* **2011**, *13*, 4746-4748.
(11) Zehnder, L.; Bennett, M.; Meng, J.; Huang, B.; Ninkovic, S.; Wang, F.; Braganza, J.; Tatlock, J.; Jewell, T.; Zhou, J. Z.; Burke, B.; Wang, J.; Maegley, K.; Mehta, P. P.; Yin, M.; Ketan S. Gajiwala, Michael J. Hickey, Shinji Yamazaki, Evan Smith, Ping Kang, Anand Sistla, Elena Dovalsantos, Michael R. Gehring, Robert Kania, Martin Wythes, and Pei-Pei Kung *J. Med. Chem.* **2011**, *54*, 3368-3385.
(12) Bennett, B. L.; Elsner, J.; Erdman, P.; Hilgraf, R.; Lebrun, L. A.; McCarrick, M.; Moghaddam, M. F.; Nagy, M. A.; Norris, S.; Paisner, D. A.; Sloss, M.; Romanow, W. J.; Satoh, Y.; Tikhe, J.; Yoon, W. H.; Delgado, M. PCT Int. Appl. **2012**, WO 2012145569.
(13) Hayashi, K.; Watanabe, T.; Toyama, K.; Kamon, J.; Minami, M.; Uni, M.; Nasu, M. PCT Int. Appl. **2013**, WO 2013024895.
(14) Wiberg, K. B.; Walker, F. H. *J. Am. Chem. Soc*. **1982**, *104*, 5239-5240.
(15) Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312-322.
(16) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
(17) Della, E. W.; Taylor, D. K.; Tsanaktsidis, J. *Tetrahedron Lett.* **1990**, *31*, 5219-5220.
(18) Messner, M.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 1137-1155.
(19) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron Asymmetry* **2012**, *23*, 1111-1153.
(20) Han, Y.; Han, M.; Shin, D.; Song, C.; Hahn, H. G. *J. Med. Chem.* **2012**, *55*, 8188-8192.
(21) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev*. **2008**, *108*, 3988-4035.
(22) Ikee, Y.; Hashimoto, K.; Kamino, M.; Nakashima, M.; Hayashi, K.; Sano, S.; Shiro, M.; Nagao, Y., *Chem. Pharm. Bull.* **2008**, *56*, 346-356.

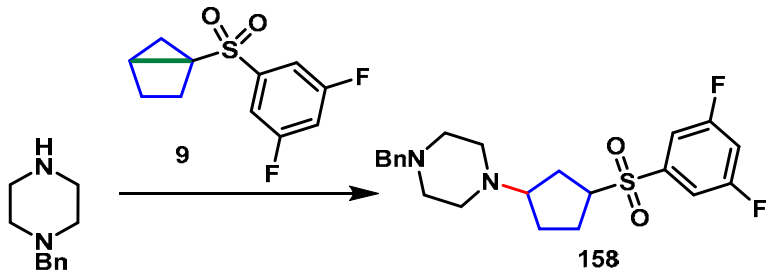
(23) Wrobleski, M. L.; Reichard, G. A.; Paliwal, S.; Shah, S.; Tsui, H.-C.; Duffy, R. A.; Lachowicz, J. E.; Morgan, C. A.; Varty, G. B.; Shih N.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3859-3863.
(24) Wiberg, K. B.; Ciula, R. P. *J. Am. Chem. Soc*. **1959**, *81*, 5261-5262.
(25) Wiberg, K. B. *Advances in Alicyclic Chemistry* **1968**, *2*, 185-254 (Academic Press).
(26) Walczak, M. A. A.; Krainz, T.; Wipf, P *Acc. Chem. Res*. **2015**, *48*, 1149-1158.
(27) Lampman, G. M.; Aumiller, J. C. *Org. Synth*. **1971**, *51*, 55-59.
(28) Gaoni, Y. *Tetrahedron Lett.* **1988**, *29*, 1591-1594.
(29) Gaoni, Y. *Org. Prep. Proc Intl.* **1995**, *27*, 185-212.
(30) Jeffery, S. M.; Stirling, C. J. M. *J. Chem. Soc. Perkin Trans.* **1993**, *2*, 1617-1624.
(31) Boutureira, O.; Bernardes, G. J. L. *Chem. Rev.* **2015**, *115*, 2174-2195.
(32) McKay, C. S.; Finn, M. G. *Chemistry & Biology* **2014**, *21*, 1075-1101.
(33) Stephanopoulos, N.; Francis, M. B. *Nat. Chem. Biol.* **2011**, *7*, 876-884.
(34) Kalia, J.; Raines, R. T. *Curr. Org. Chem.* **2010**, *14*, 138-147.
(35) Lau, Y. H.; de Andrade, P.; Y.; Wu, D. R. Spring, *Chem. Soc. Rev.* **2015**, *44*, 91-102.
(36) Spokoyny, A. M.; Zou, Y.; Ling, J. J.; Yu, H.; Lin, Y.-S.; Pentelute, B. L *J. Am. Chem. Soc.* **2013**, *135*, 5946-5949.
(37) Wang, Y.; Chou, D. H.-C. *Angew. Chem. Int. Ed*. **2015**, 54, 10931-10934.
(38) Brown, S. P.; Smith III, A. B. *J. Am. Chem. Soc.* **2015**, *137*, 4034-4037.
(39) Toops, D. S.; Barbachyn, M. R. *J. Org. Chem*. **1993**, *58*, 6505-6508.
(40) Hossain, M. T.; Timberlake, J. W. *J. Org. Chem*. **2001**, *66*, 6282-6285.
(41) Goh, Y. L.; Tam, E. K. W.; Bernardo, P. H.; Cheong, C. B.; Johannes, C. W.; William, A. D.; Adsool, V. A. Org. Lett. **2014**, *16*, 1884-1887.
(42) Bunker, K. D. PCT Int. Appl. **2015**, WO 201589170.
(43) Shtarev, A. B.; Pinkhassik, E.; Levin, M. D.; Stibor, I.; Michl, J. *J. Am. Chem. Soc*. **2001**, *123*, 3484-3492.
(44) Eli Lilly and Company, PCT Int. Appl. WO, **2006**, 2006044454.
(45) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem*. **1995**, *60*, 5995-5996.
(46) Yang Ji Chemical Company Ltd., US Pat. Appl., **2005**, 20050075345.
(47) Chen, Z.; Chen, Z.; Jiang, Y.; Hu, W. *Tetrahedron* **2005**, *61*, 1579-1586.
(48) Bumgardner, C. L.; Lawton, E. L.; Carver, J. G. *J. Org. Chem*. **1972**, *37*, 407-409.
(49) Satake, K.; Imai, T.; Kimura, M.; Morosawa S. *Heterocycles* **1981**, *16*, 1271-1274.
(50) Prokopcová, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, Wouter.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J*. **2010**, *16*, 13063-13067.
(51) Meyers, A. I.; Hutchings, R. H. *Tetrahedron* **1993**, *49*, 1807-1820.
(52) Bergbreiter, D. E.; Osburn, P. L.; Li, C. *Org. Lett.* **2002**, *4*, 737-740.
(53) Largeron, M.; Fleury, M.-B. *Org. Lett.* **2009**, *11*, 883-886.
(54) Hayashi, K.; Kumagai, T.; Nagao, Y. *Heterocycles* **2000**, *53*, 447-452.
(55) Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. *Org. Lett*. **2014**, *16*, 6160-6163.
(56) Hodgson, D. M.; Mortimer, C. L.; McKenna, J. M. *Org. Lett.* **2015**, *17*, 330-333.
(57) Han, M.; Song, C.; Jeong, N.; Hahn, H.-G. *ACS Med. Chem. Lett*. **2014**, *5*, 999-1004.

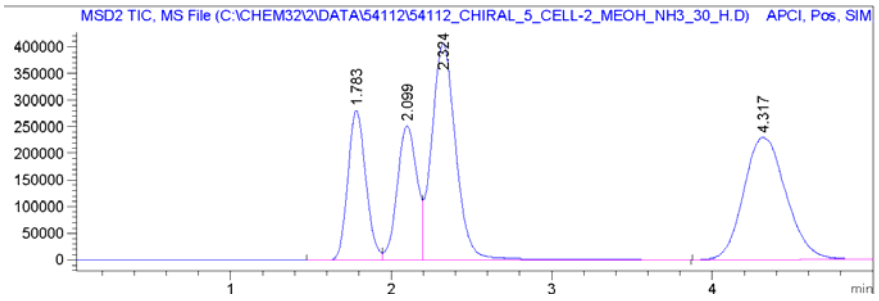
(58) Salituro, F. G.; Saunders, J. O.; Yan, S. PCT Int. Appl. **2012**, WO 201283246.
(59) Pauls, H. W. *et al.*, PCT Int. Appl. **2013**, WO 201353051.
(60) Gaoni, Y. *J. Org. Chem.***1982**, *47*, 2564-2571.
(61) Gaoni, Y.; Tomazic, A. *J. Org. Chem*. **1985**, *50*, 2948-2957.
(62) Brown, A. C.; Carpino, L. A. *J. Org. Chem*. **1985**, *50*, 1749-1750.
(63) Oh, H. K.; Kwon, Y. B.; Cho, I. H.; Lee, I. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 1697-1701.
(64) Satoh, T.; Kasuya, T.; Ishigaki, M.; Inumaru, M.; Miyagawa, T.; Nakaya, N.; Sugiyama, S. *Synthesis* **2011**, 397-408.
(65) Marugan, J. J.; Zheng, W.; Motabar, O.; Southall, N.; Goldin, E.; Westbroek, W.; Stubblefield, B. K.; Sidransky, E.; Aungst, R. A.; Lea, W. A.; Simeonov, A.; Leister, W.; Austin, C. P. *J. Med. Chem*. **2011**, *54*, 1033-1058.
(66) Cheng, C.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 11304-11307.
(67) Härter, M.; Beck, H.; Thierauch, K.-H.; Ellinghaus, P.; Greschat, S.; Schuhmacher, J. US Pat. Appl. **2013**, US 2013150325.
(68) Butov, G. M.; Mokhov, V. M. *Russ. J. Org. Chem.* **2014**, 50, 447-448.
(69) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166.
(70) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *Science* **2016**, *351*, 241-246.
(71) Flanagan, M. E.; Abramite, J. A.; Anderson, D. P.; Aulabaugh, A.; Dahal, U. P.; Gilbert, A. M.; Li, C.; Montgomery, J.; Oppenheimer, S. R.; Ryder, T.; Schuff, B. P.; Uccello, D. P.; Walker, G. S.; Wu, Y.; Brown, M. F.; Chen, J. M.; Hayward, M. M.; Noe, M. C.; Obach, R. S.; Philippe, L.; Shanmugasundaram, V.; Shapiro, M. J.; Starr, J.; Stroh, J.; Che, Y. *J. Med. Chem*. **2014**, ***57***, 10072-10079.

SFC Analysis of Strain-release Products

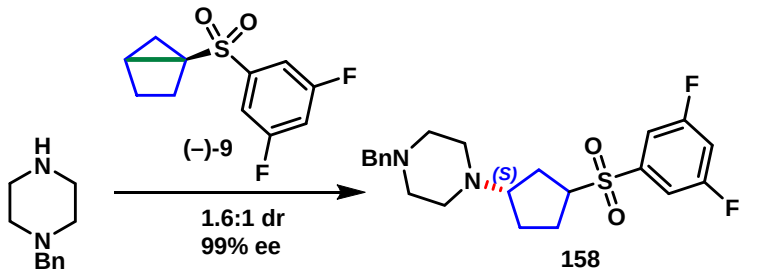
SFC analysis of compound 158

The analysis was performed on a Lux Cellulose-2 4.6 x 100 mm 3µ column using 30% MeOH + 10mM NH_3, 120 bar, 4 mL/min

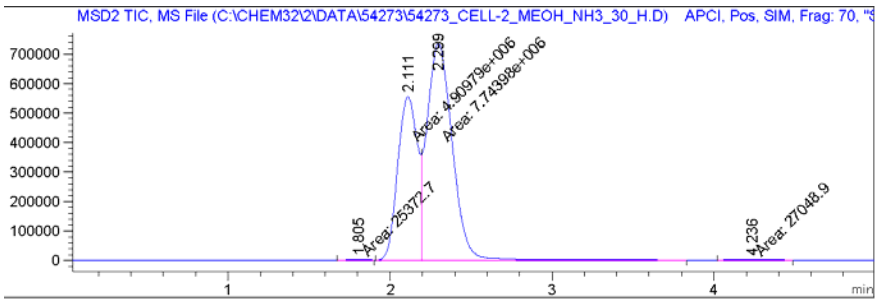




Retention Time (MS)	MS Area	Mol. Weight or Ion
1.780	613581	422.15 I
		421.20 I
		155.15 I
		87.10 I
		72.20 I
2.083	561559	422.15 I
		421.10 I
		155.20 I
		98.10 I
		87.15 I
		73.15 I
		72.10 I
2.324	1068233	422.10 I
		421.10 I
		155.20 I
		87.15 I
		72.20 I
4.307	1104921	422.10 I
		421.10 I
		155.15 I
		98.15 I
		87.10 I
		73.10 I
		72.20 I

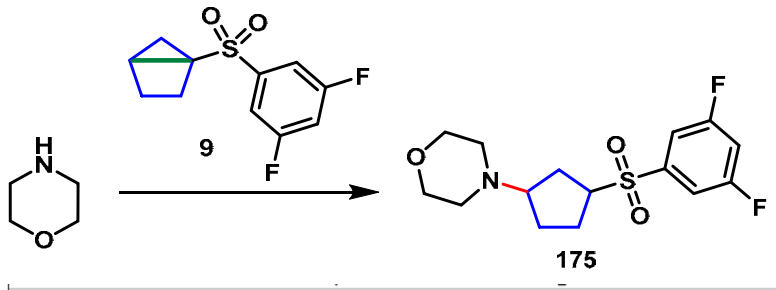


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.805	25373	421.00 I
2.111	4909790	421.00 I
2.299	7743984	421.00 I
4.236	27049	421.00 I

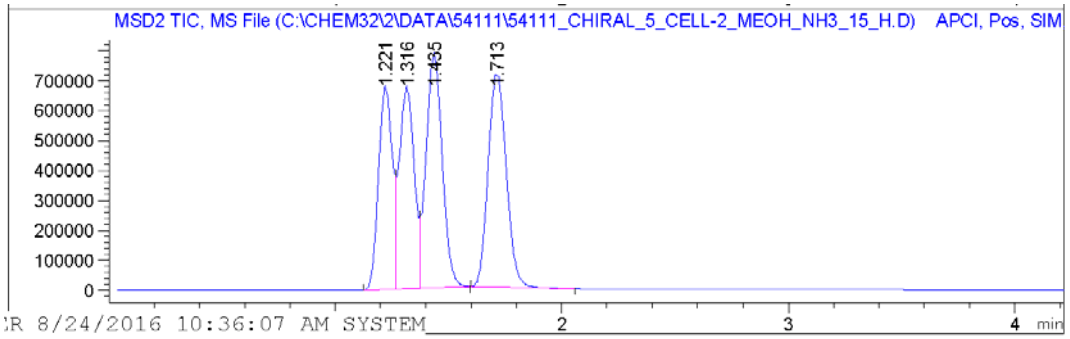


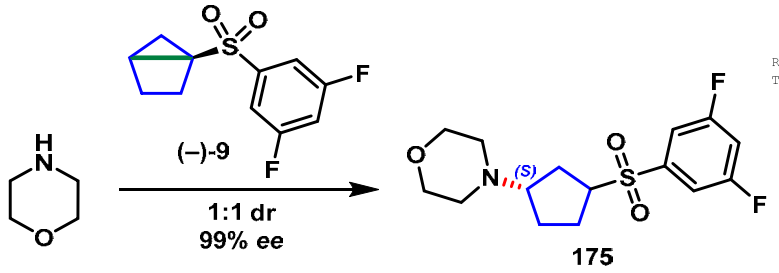
SFC analysis of compound 175

The analysis was performed on a Lux Cellulose-2 4.6 x 100 mm 3µ column using 15% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

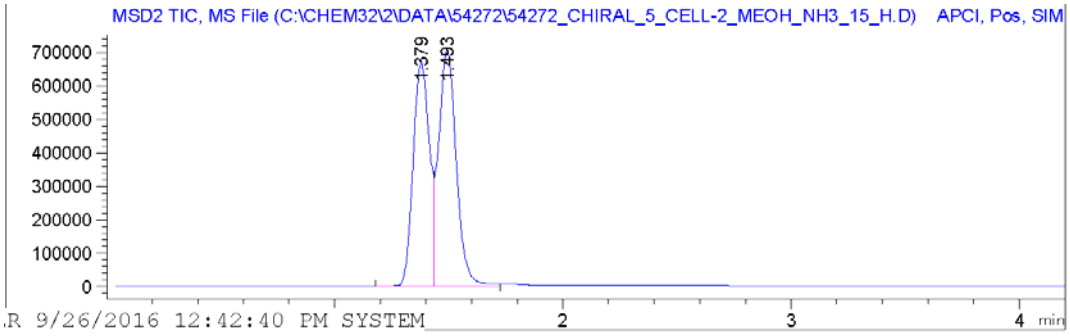


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.671	816912	157.05 I 79.10 I
1.220	657168	333.10 I 332.10 I
1.315	713941	333.10 I 332.00 I
1.434	911297	333.10 I 332.10 I
1.715	853151	333.05 I 332.10 I



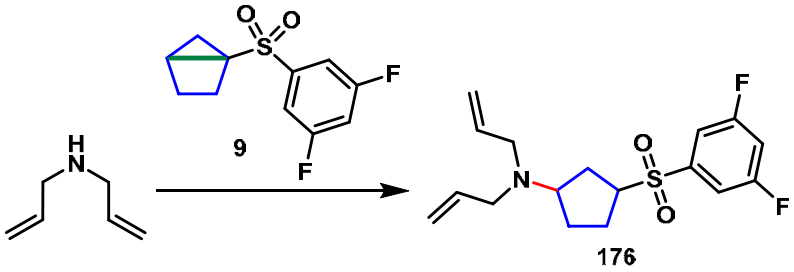


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.649	149516	155.15 I 87.15 I 74.10 I
1.383	784218	333.10 I 332.00 I
1.493	803643	333.00 I 332.00 I

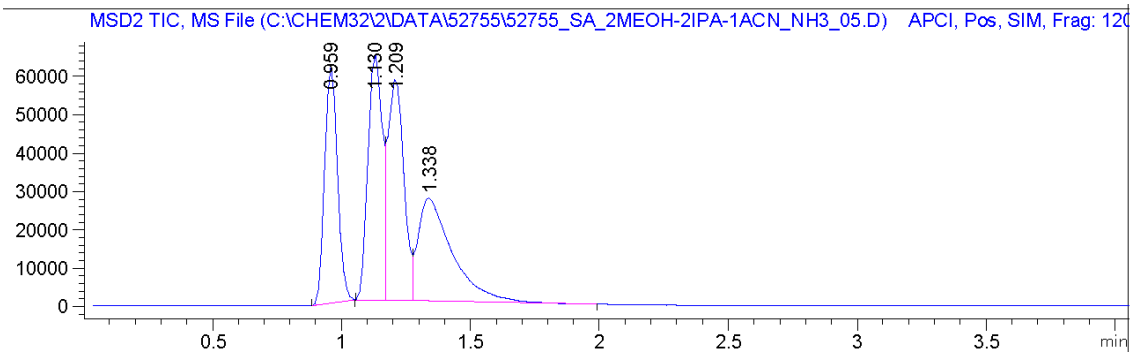


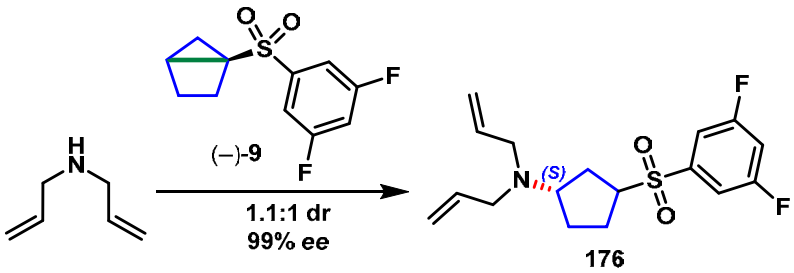
SFC analysis of compound 176

The analysis was performed on a YMC Amylose-SA 4.6 x 100 mm 3µ column using 5% (2:2:1 MeOH:IPA:MeCN) with 10mM NH_3, 120 bar, 4 mL/min.

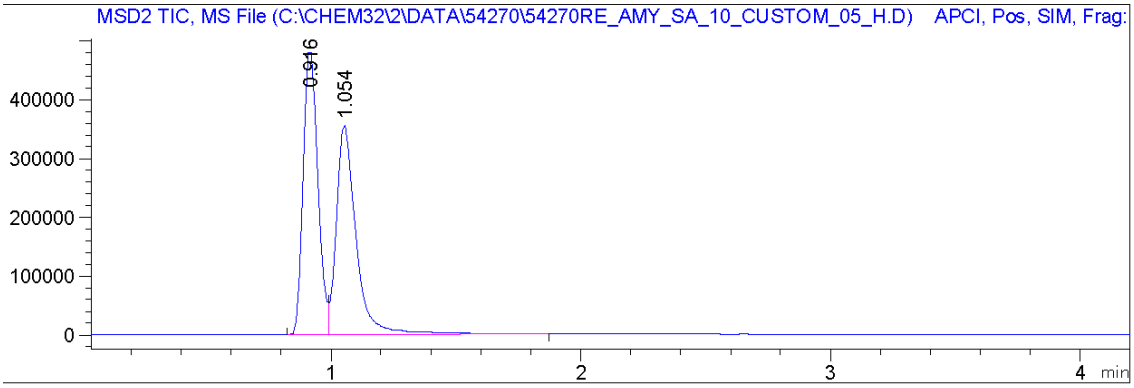


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.959	211730	342.00 I
1.130	246160	342.00 I
1.209	247531	342.00 I
1.338	246850	342.00 I



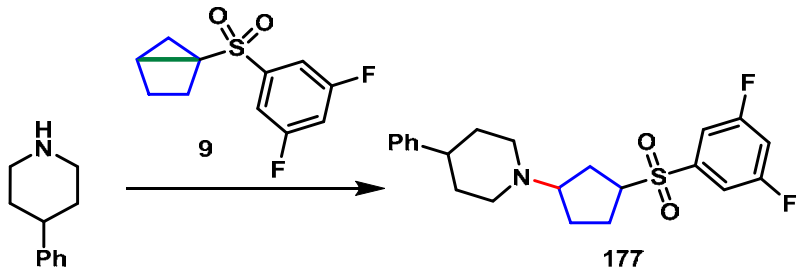


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.417	336078	142.10 I
0.510	84079	142.20 I 114.20 I
0.913	546778	343.10 I 342.10 I 142.10 I
1.053	612671	343.10 I 342.10 I 142.20 I

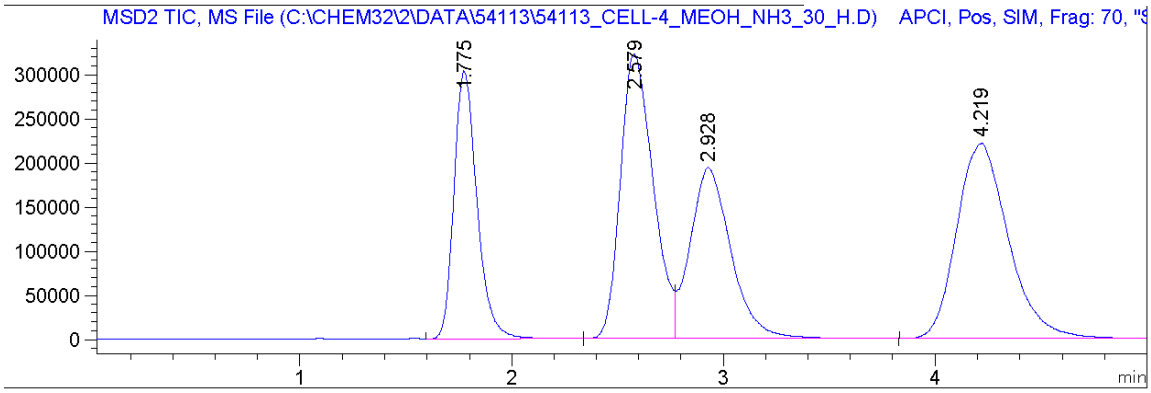


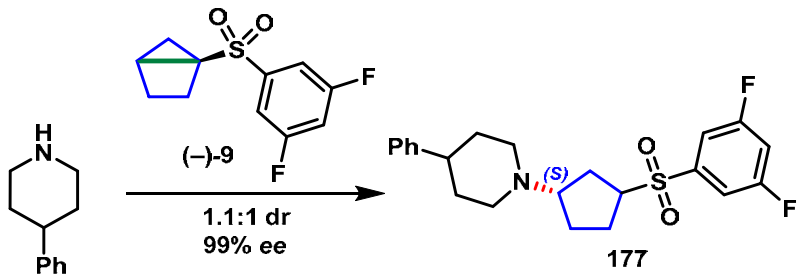
SFC analysis of compound 177

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 30% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

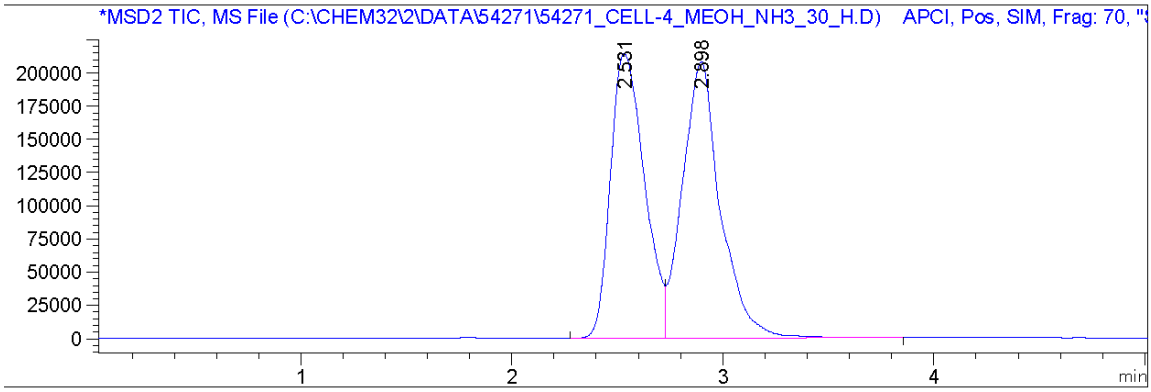


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.502	436361	157.10 I
1.767	628140	407.10 I
2.594	922812	407.10 I
2.908	715002	407.10 I
4.246	944659	407.10 I



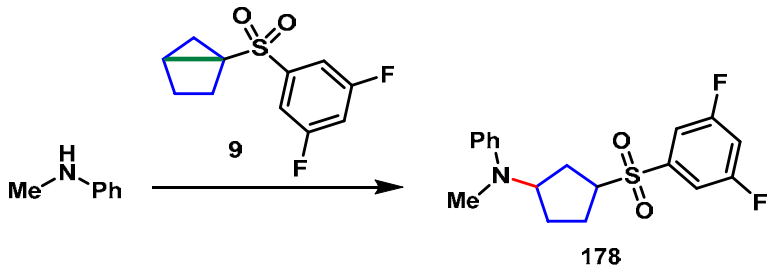


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.531	2398217	406.00 I
2.898	2588203	406.00 I

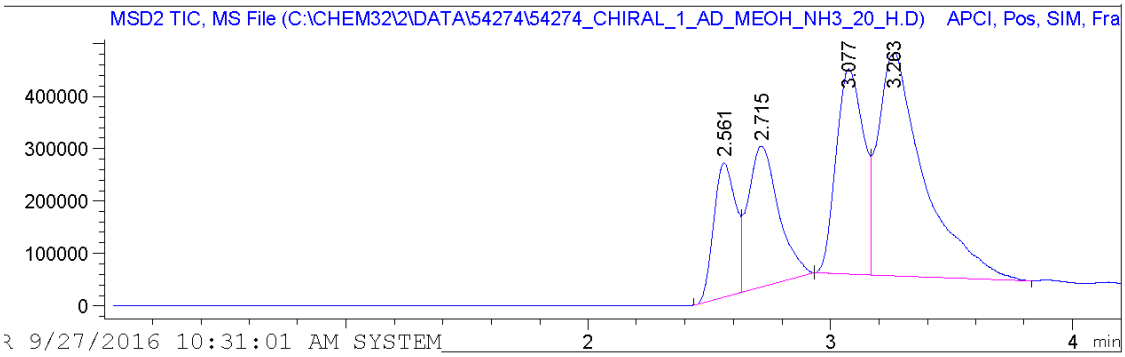


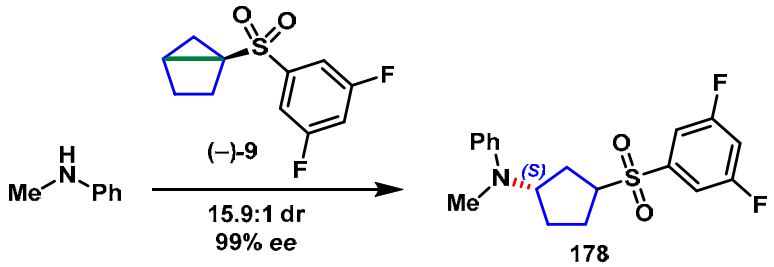
SFC analysis of compound 178

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 20% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

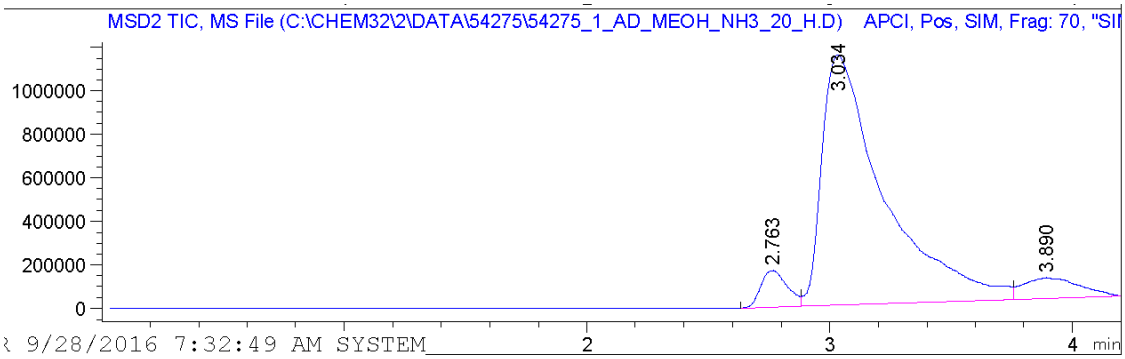


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.561	1626054	352.00 I
2.715	2352524	352.00 I
3.077	3068653	352.00 I
3.263	5596978	352.00 I

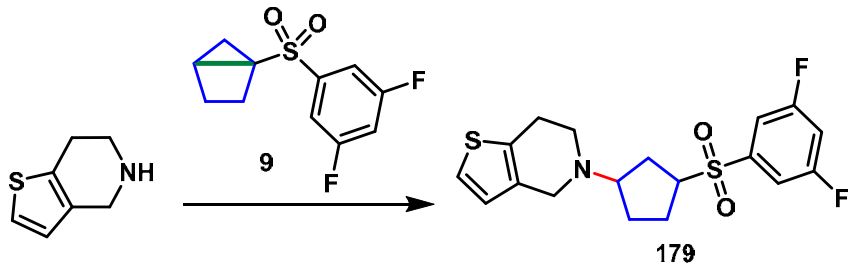




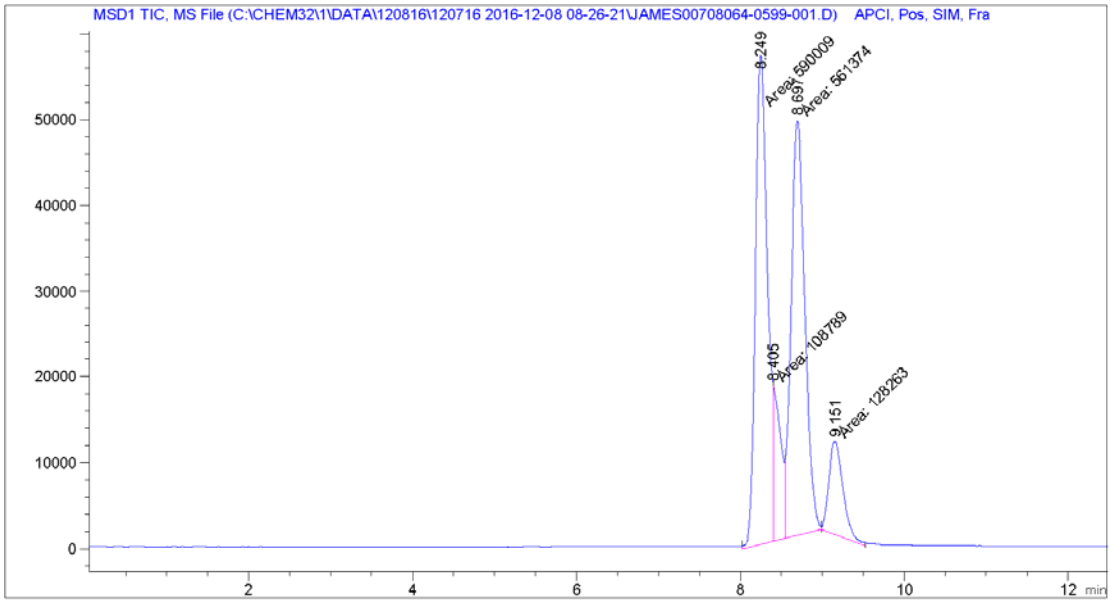
Retention Time (MS)	MS Area	Mol. Weight or Ion
2.763	1285722	352.00 I
3.034	20426322	352.00 I
3.890	1505571	352.00 I



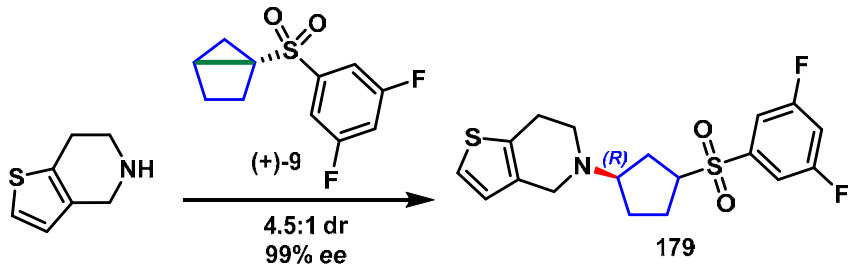
SFC analysis of compound 179

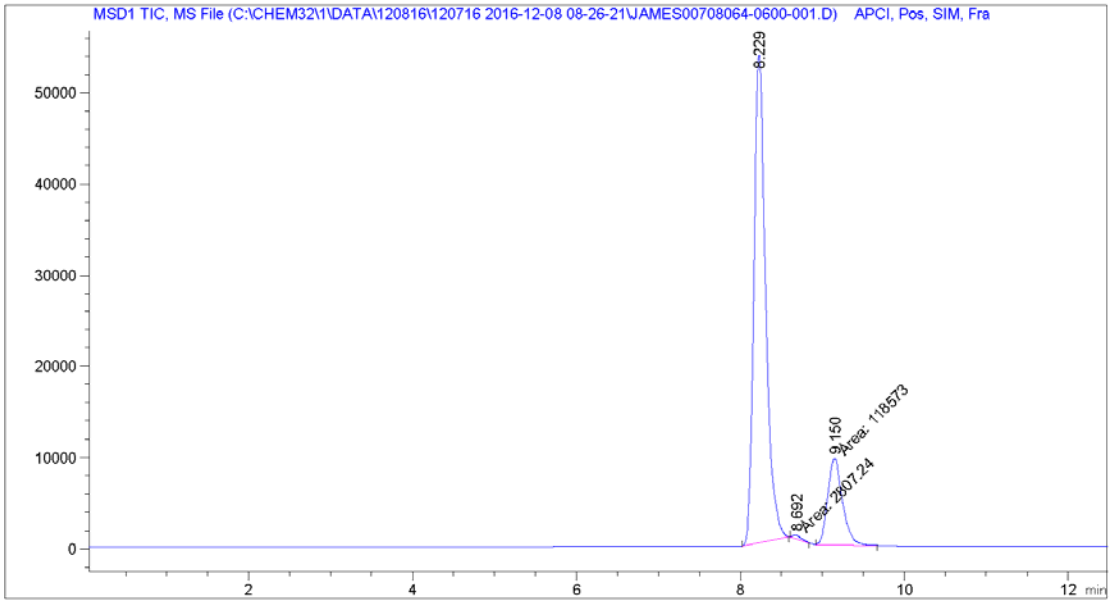


179



Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	8.249	MF	0.1722	5.90008e5	5.71111e4	42.4945
2	8.405	FM	0.1003	1.08789e5	1.80756e4	7.8354
3	8.697	FM	0.1932	5.61374e5	4.84203e4	40.4321
4	9.151	MM	0.1984	1.28263e5	1.07737e4	9.2380

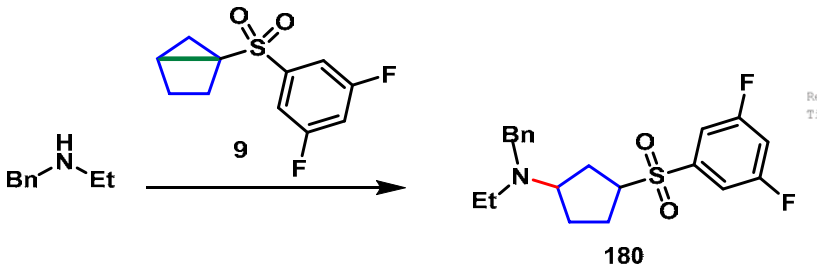




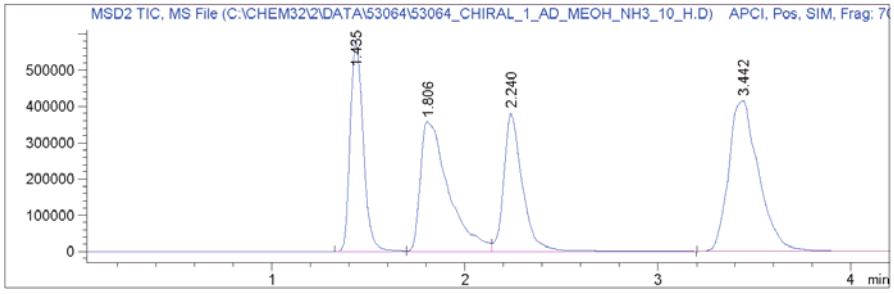
Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	8.229	BB	0.1510	5.31876e5	5.35657e4	81.4192
2	8.692	MM	0.1161	2807.24341	402.99368	0.4297
3	9.150	MM	0.2092	1.18573e5	9444.82617	18.1511

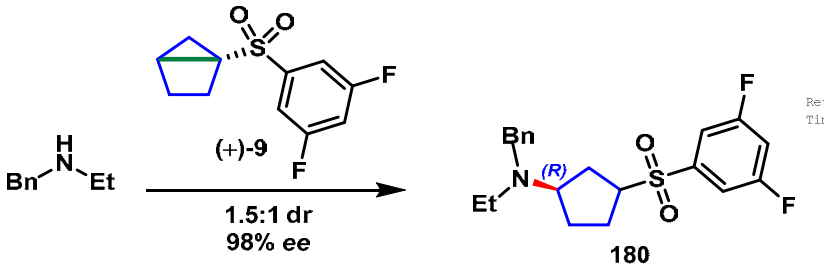
SFC analysis of compound 180

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 10% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

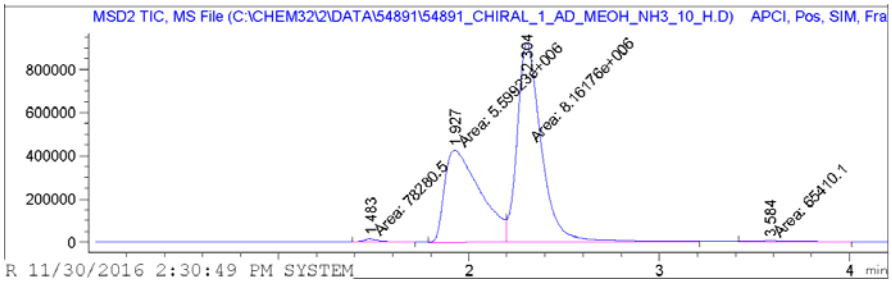


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.435	2707859	380.00 I
1.806	3607287	380.00 I
2.240	2545277	380.00 I
3.442	4464623	380.00 I





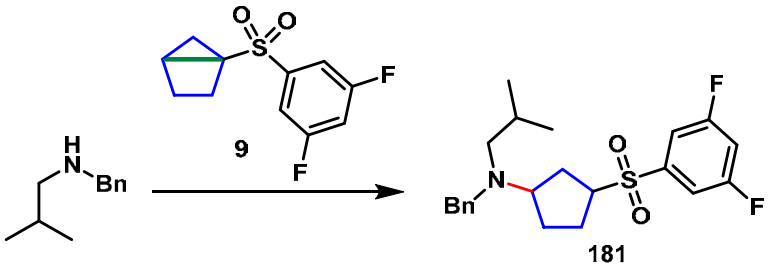
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.483	78280	380.00 I
1.927	5599234	380.00 I
2.304	8161763	380.00 I
3.584	65410	380.00 I



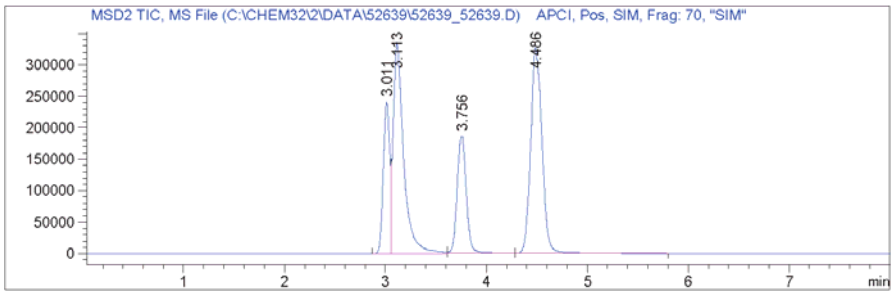
Note: the above reaction was run with 98% *ee* (+)-**9**.

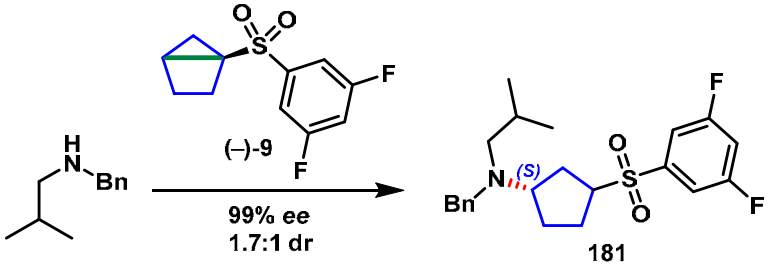
SFC analysis of compound 181

The analysis was performed on a Chiralpak AD-H 4.6 x 250 mm 5µ column using 5-30% MeOH + 10mM NH_3 in 5.0 minutes, 120 bar, 4 mL/min.

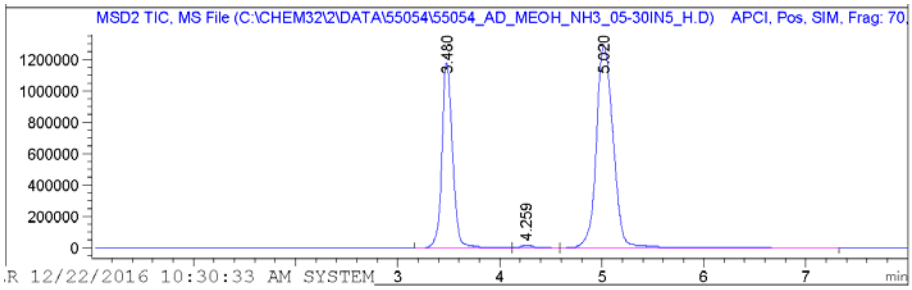


Retention Time (MS)	MS Area	Mol. Weight or Ion
3.011	1042659	408.00 I
3.113	2397703	408.00 I
3.756	1161672	408.00 I
4.486	2520488	408.00 I



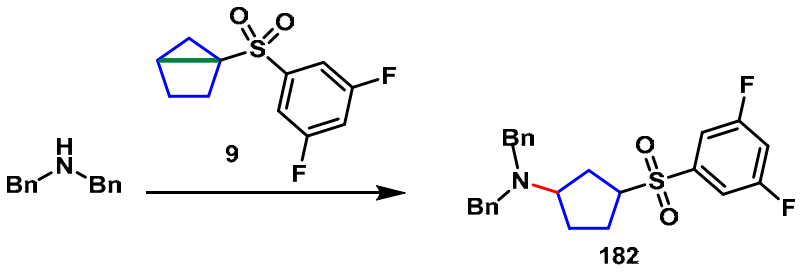


Retention Time (MS)	MS Area	Mol. Weight or Ion
3.480	8562436	408.00 I
4.259	156102	408.00 I
5.020	14861728	408.00 I

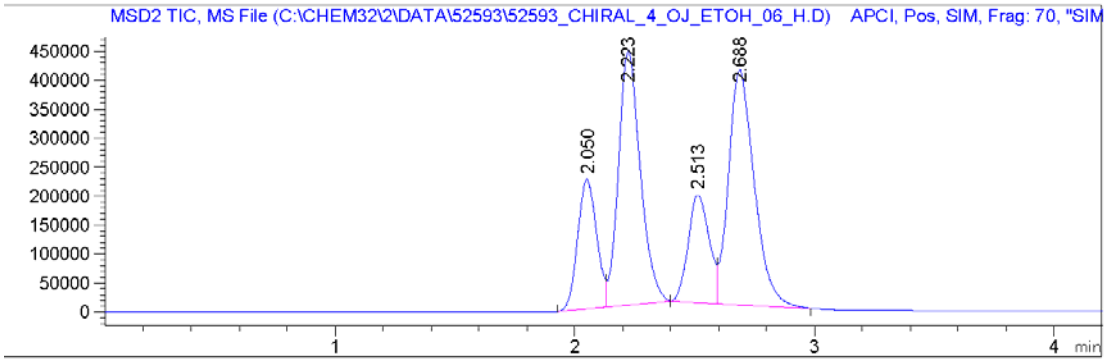


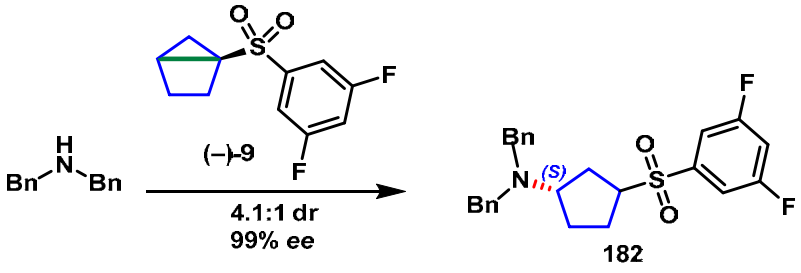
SFC analysis of compound 182

The analysis was performed on a Chiralcel OJ-3 4.6 x 100 mm 3µ column using 6% EtOH, 120 bar, 4 mL/min.

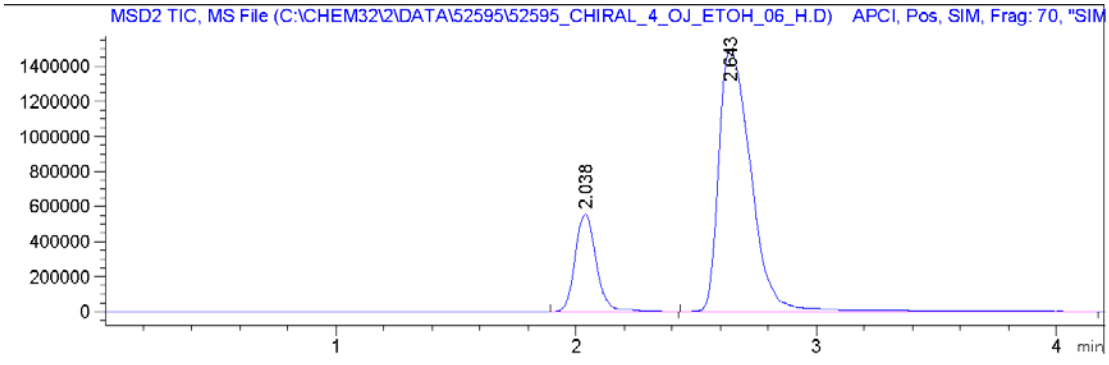


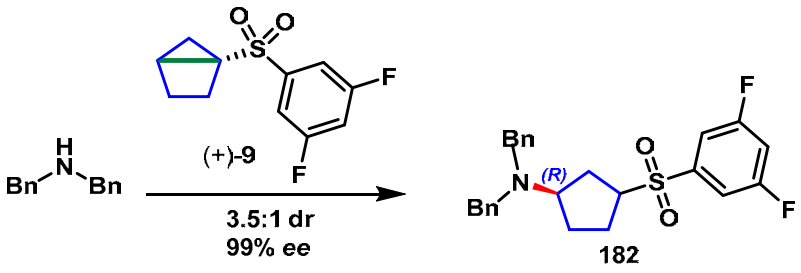
Retention Time (MS)	MS Area	Mol. Weight or Ion
2.050	1229169	442.00 I
2.223	2769774	442.00 I
2.513	1128732	442.00 I
2.688	3011820	442.00 I



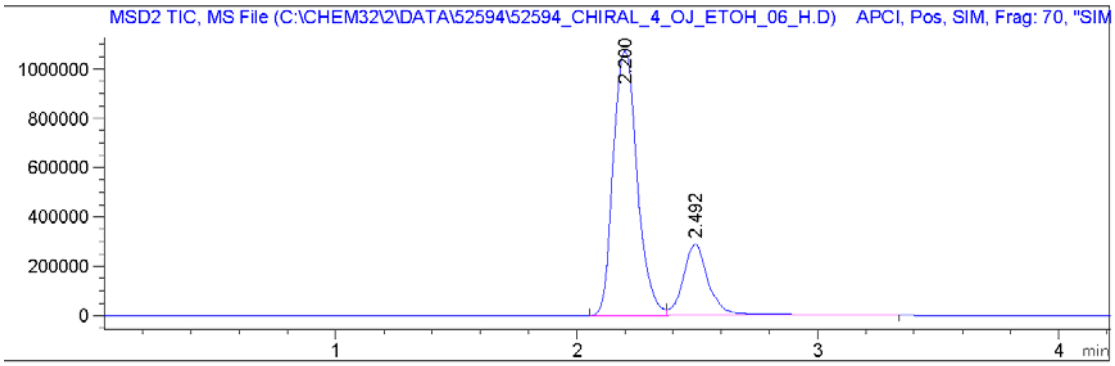


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.038	3336016	442.00 I
2.643	13744646	442.00 I



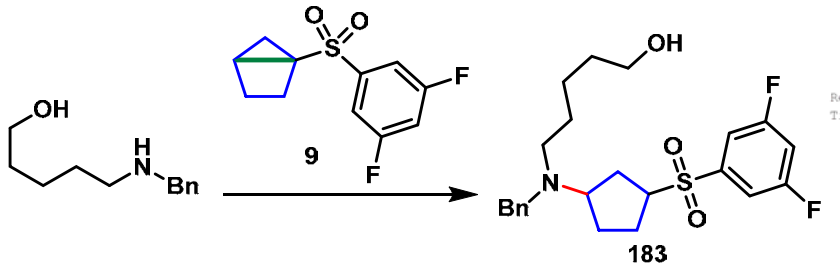


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.200	7376105	442.00 I
2.492	2084467	442.00 I

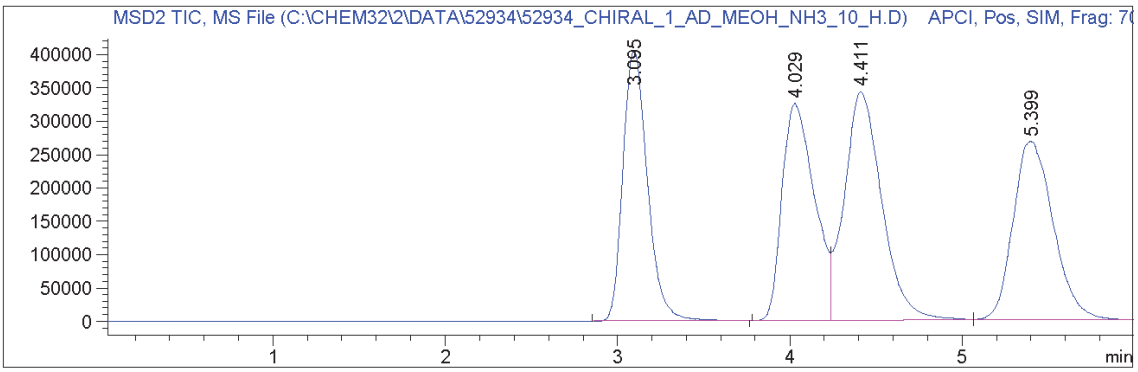


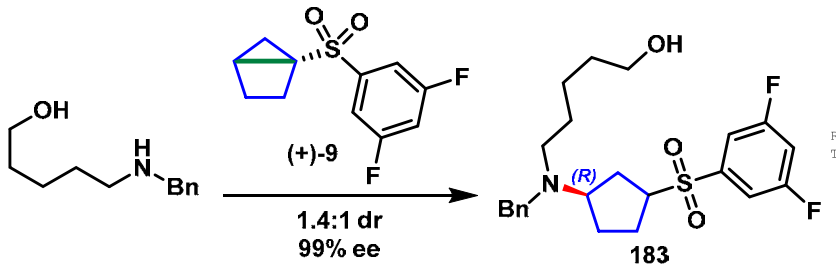
SFC analysis of compound 183

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 10% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

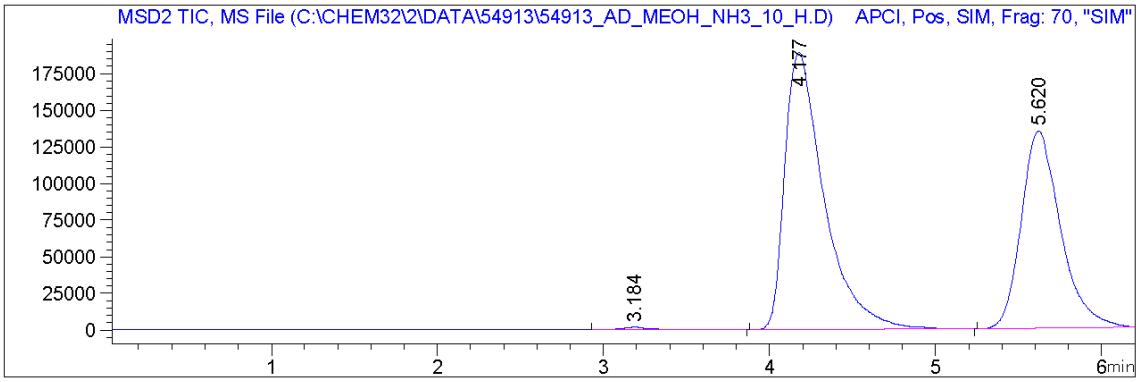


Retention Time (MS)	MS Area	Mol. Weight or Ion
3.095	3982370	438.00 I
4.029	4227525	438.00 I
4.411	5184959	438.00 I
5.399	4321936	438.00 I



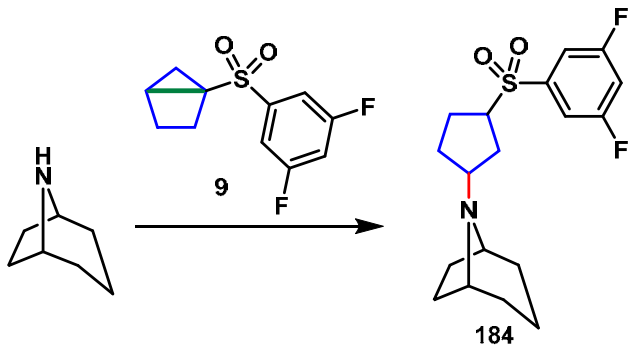


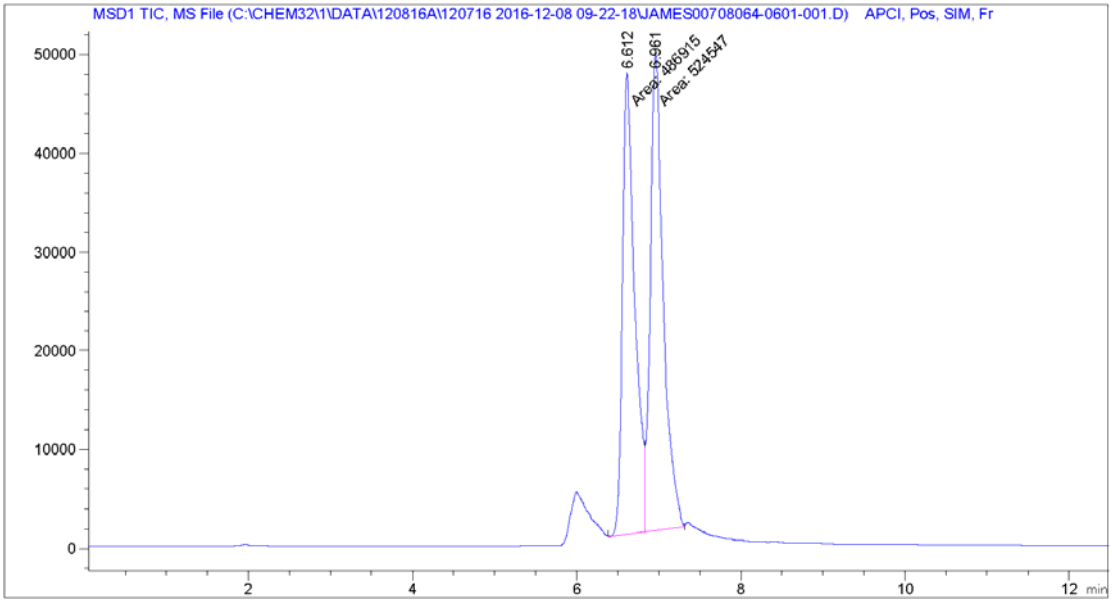
Retention Time (MS)	MS Area	Mol. Weight or Ion
3.184	16767	438.00 I
4.177	3100098	438.00 I
5.620	2195046	438.00 I



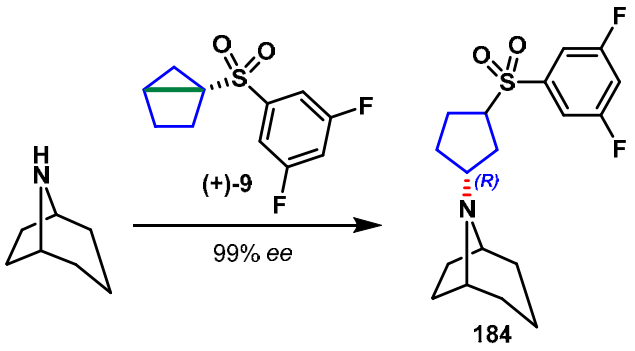
SFC analysis of compound 184

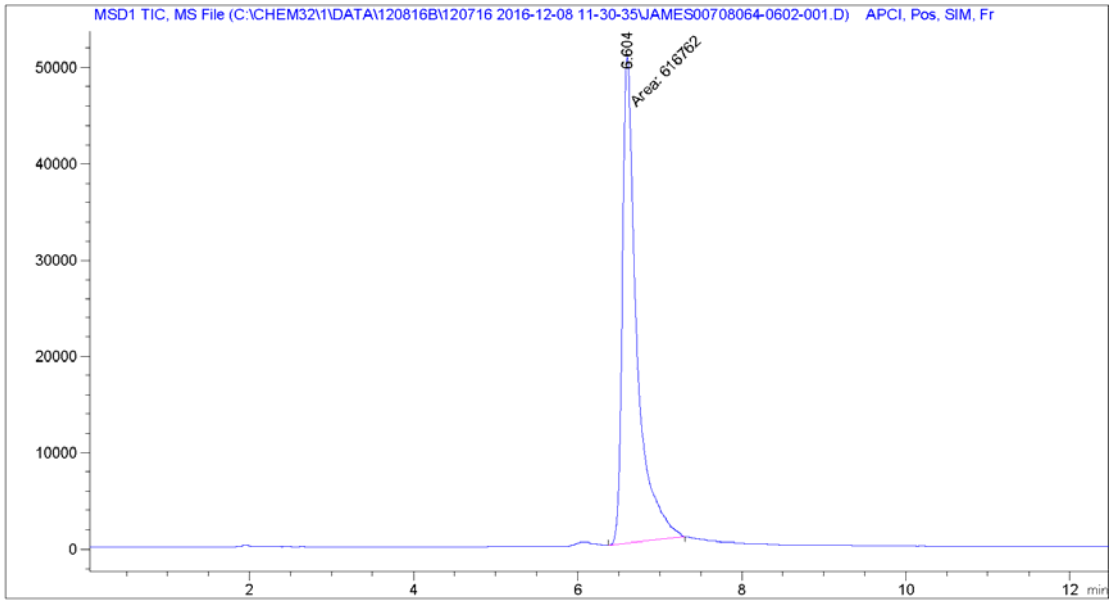
The analysis was performed using Chiral Normal Phase LC-MS with a Lux Cellulose-4 250mm x 4.6mm 5µ column eluting with EtOH in heptanes (5-100% gradient) at 1.5 mL/min.





Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	6.612	MF	0.1734	4.86915e5	4.68021e4	48.1397
2	6.961	FM	0.1814	5.24547e5	4.81991e4	51.8603

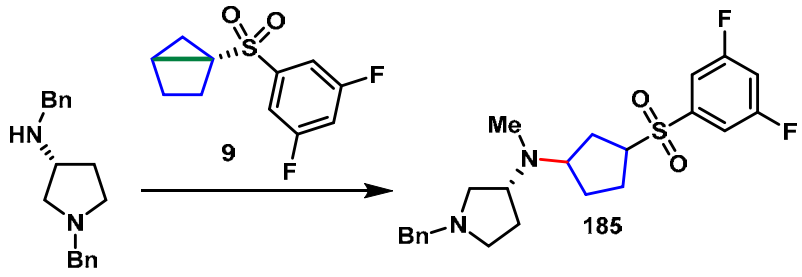




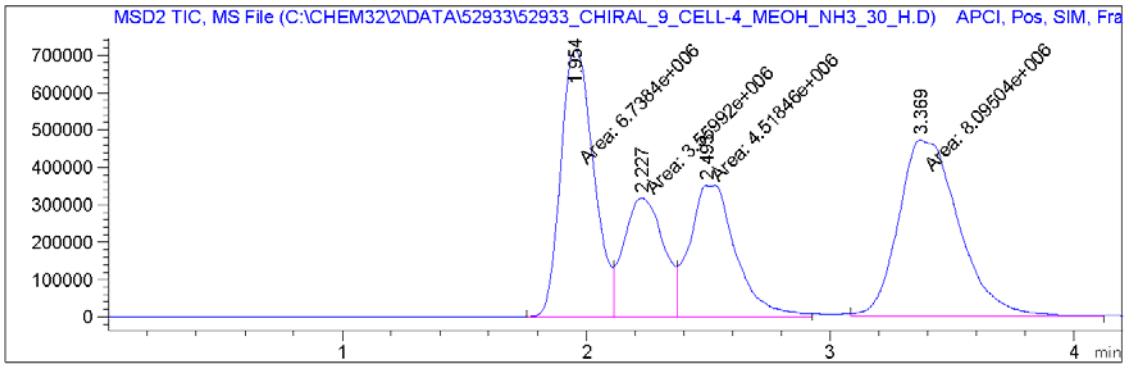
Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	6.604	MM	0.2028	6.16762e5	5.06938e4	100.0000

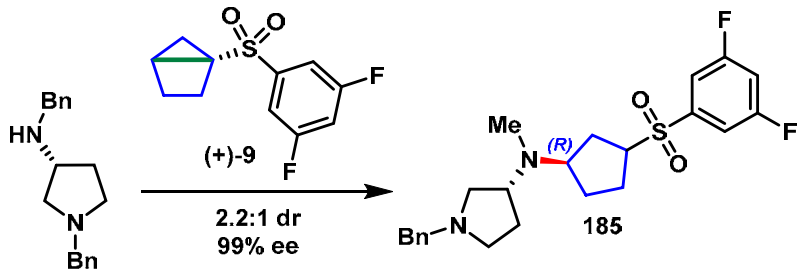
SFC analysis of compound 185

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 30% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

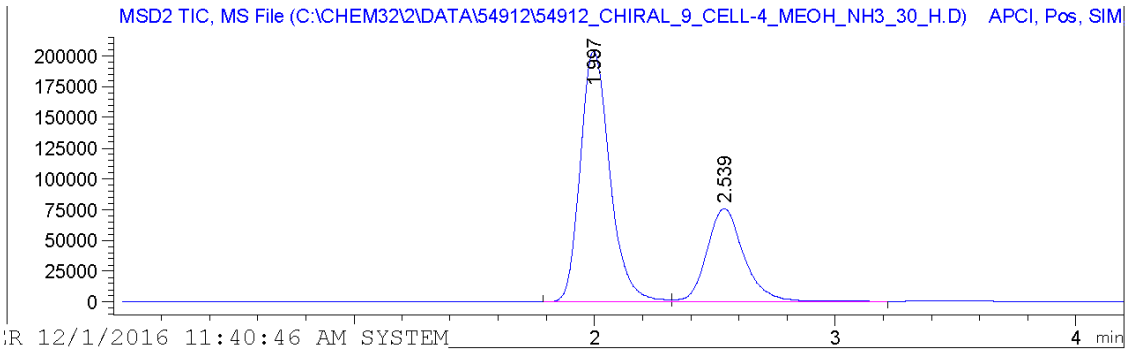


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.954	6738395	435.00 I
2.227	3559917	435.00 I
2.493	4518461	435.00 I
3.369	8095037	435.00 I



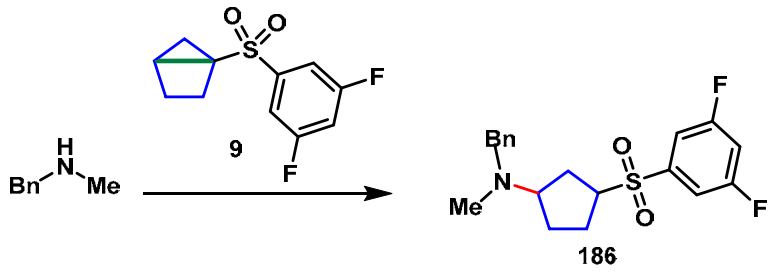


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.997	1735920	435.00 I
2.539	800213	435.00 I

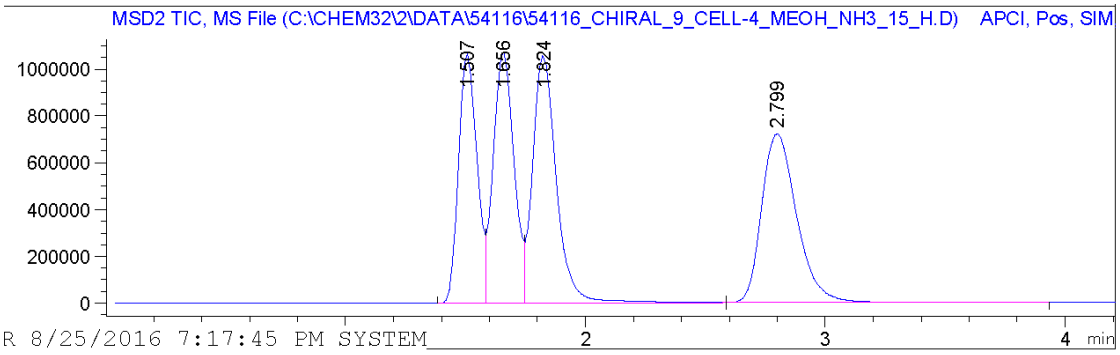


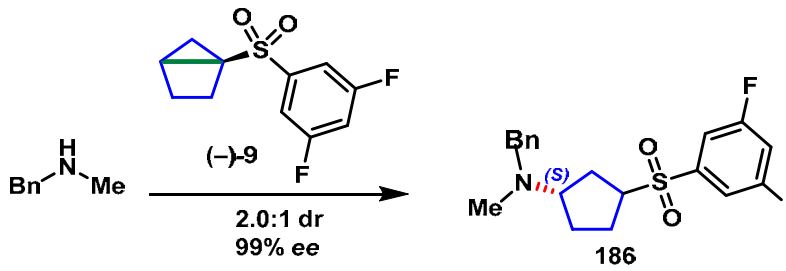
SFC analysis of compound 186

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 15% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

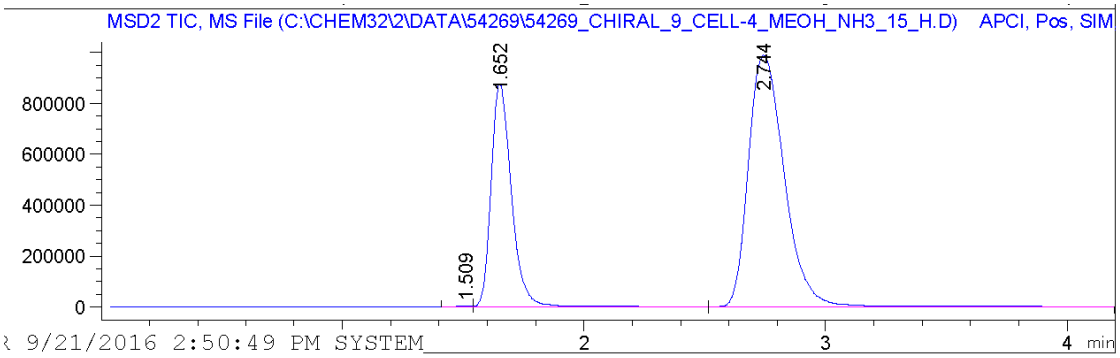


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.507	5649518	366.00 I
1.656	6430955	366.00 I
1.824	7232560	366.00 I
2.799	7297609	366.00 I



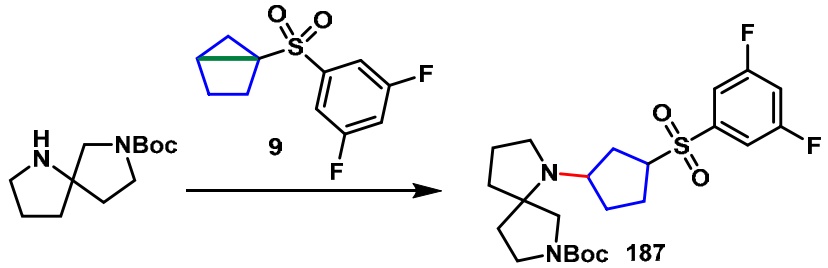


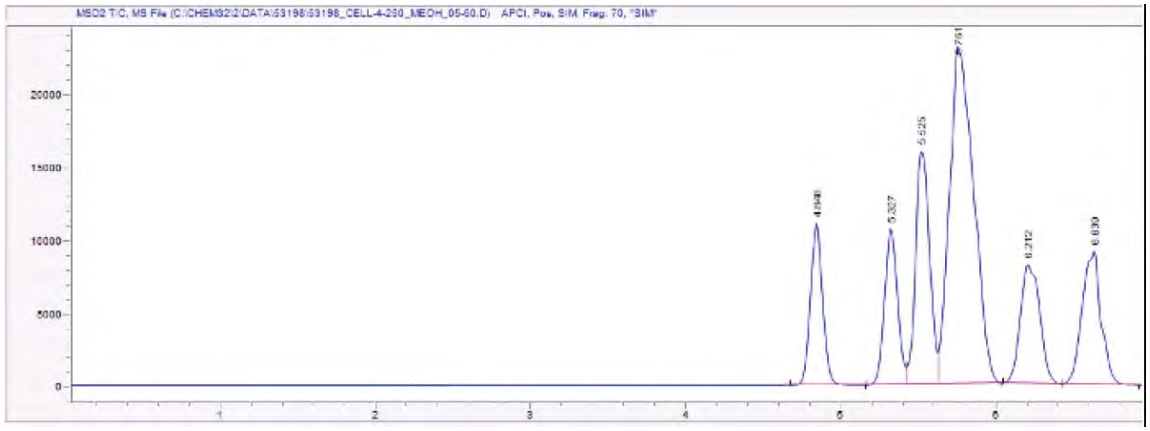
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.650	1227148	367.10 I 366.10 I
2.745	2403119	367.10 I 366.10 I

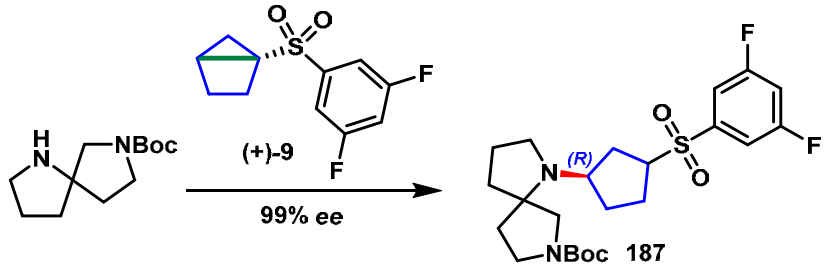


SFC analysis of compound 187

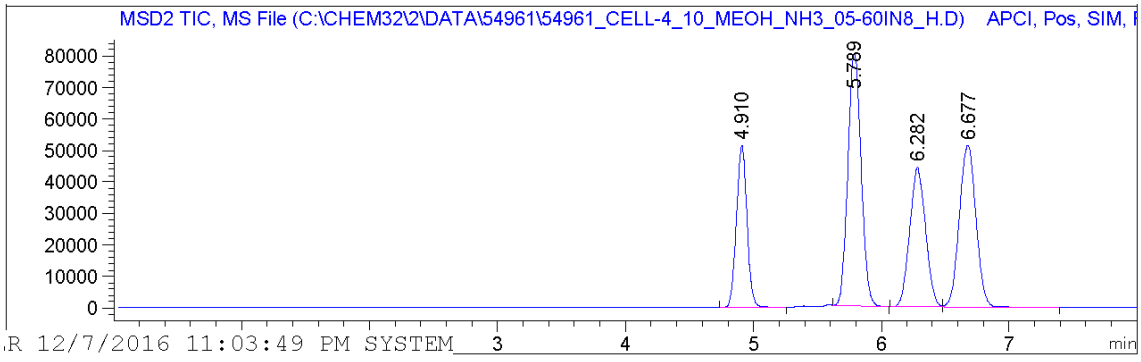
The analysis was performed on Lux Cellulose-2 4.6 x 250 mm 5µ column using 5-60% MeOH + 10mM NH_3 in 7.0 minutes, 120 bar, 4 mL/min





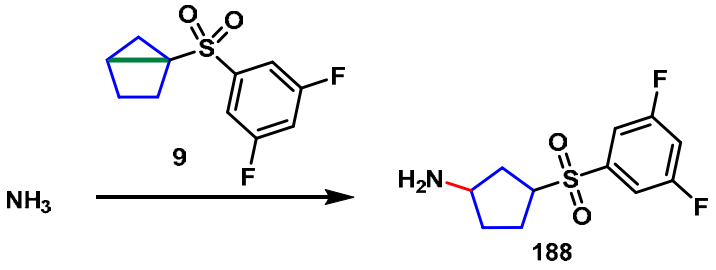


Retention Time (MS)	MS Area	Mol. Weight or Ion
4.910	290909	471.00 I
5.789	579036	471.00 I
6.282	380109	471.00 I
6.677	464216	471.00 I

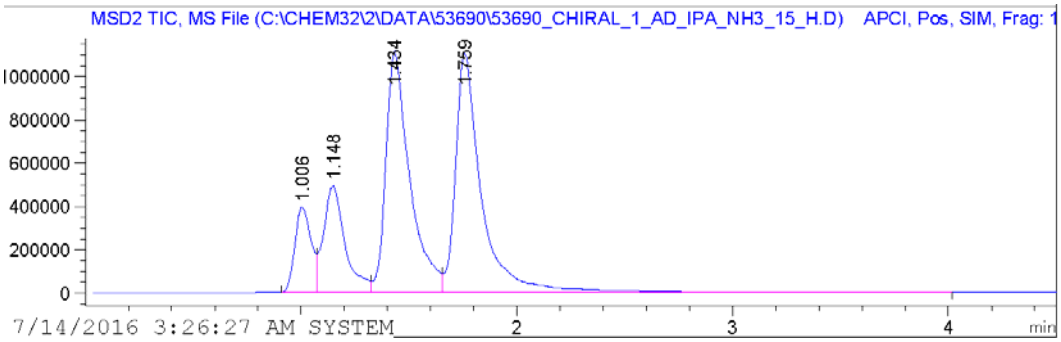


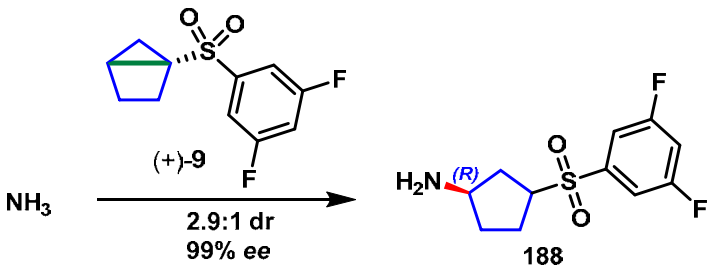
SFC analysis of compound 188

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 15% IPA + 10mM NH_3, 120 bar, 4 mL/min.

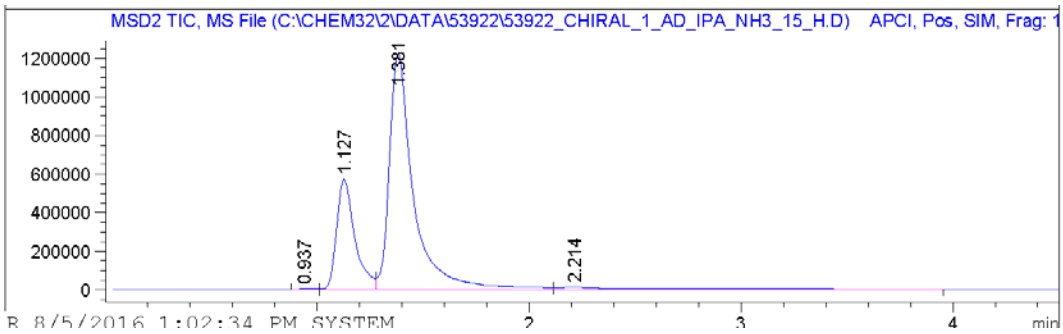


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.006	2038644	262.00 I
1.148	3398251	262.00 I
1.434	8544140	262.00 I
1.759	9360669	262.00 I



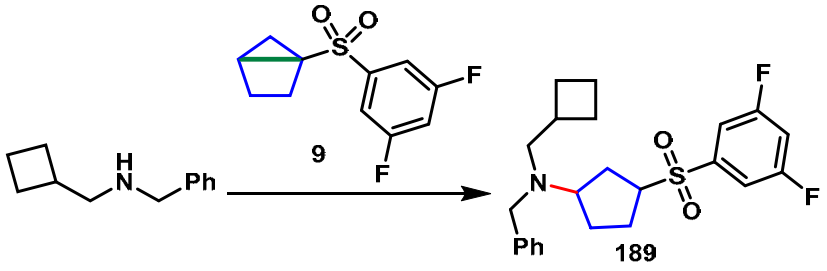


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.937	18401	262.00 I
1.127	3403154	262.00 I
1.381	9730784	262.00 I
2.214	293105	262.00 I

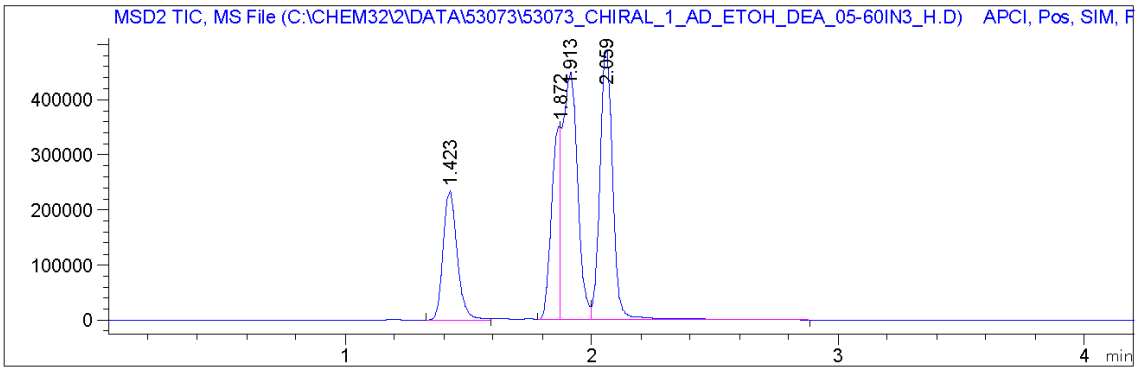


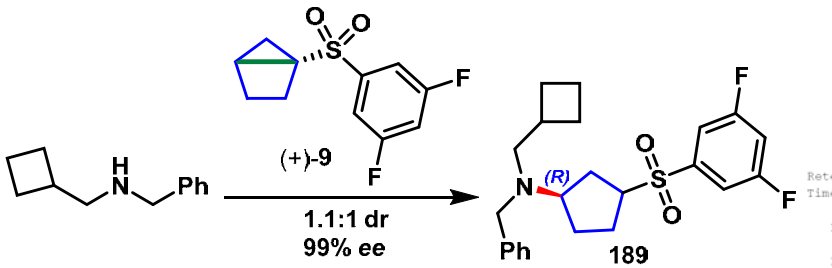
SFC analysis of compound 189

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 5% EtOH for 1 min followed by 5-60%EtOH + 0.05% DEA in 3 minutes, 120 bar, 4 mL/min.

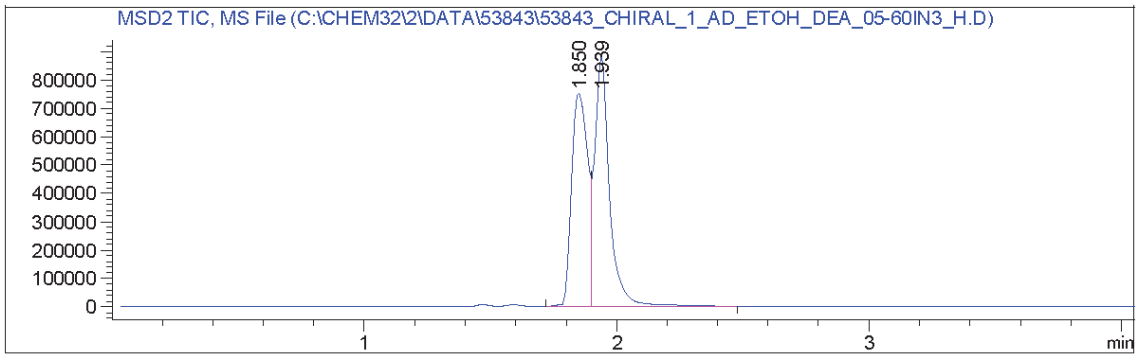


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.423	926086	420.00 I
1.872	864367	420.00 I
1.913	1859740	420.00 I
2.059	1775214	420.00 I



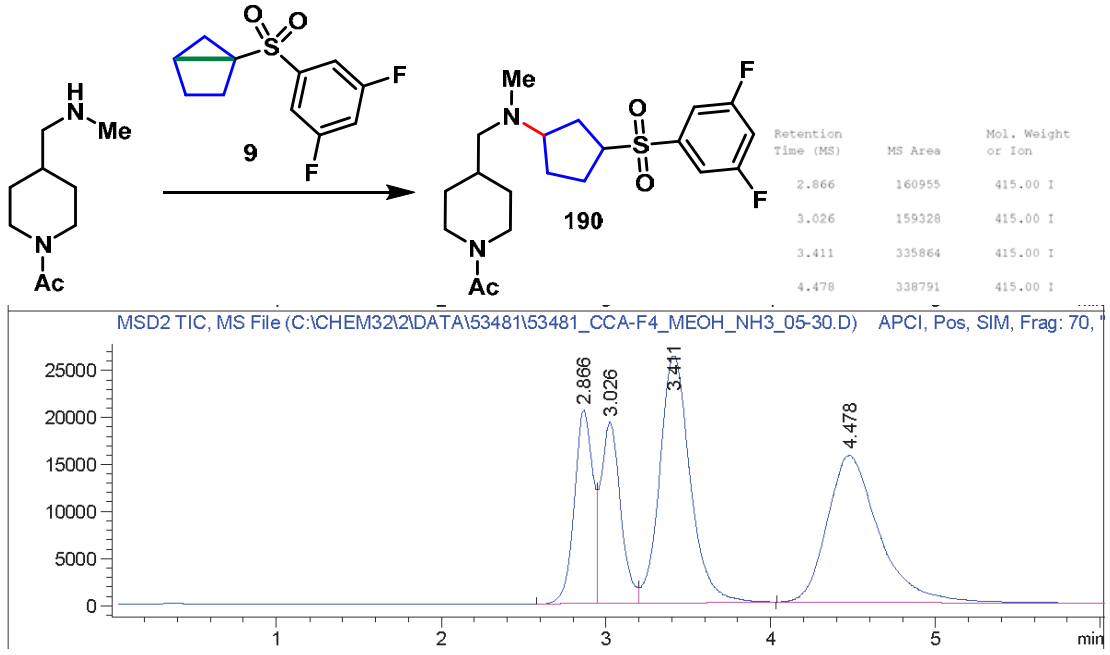


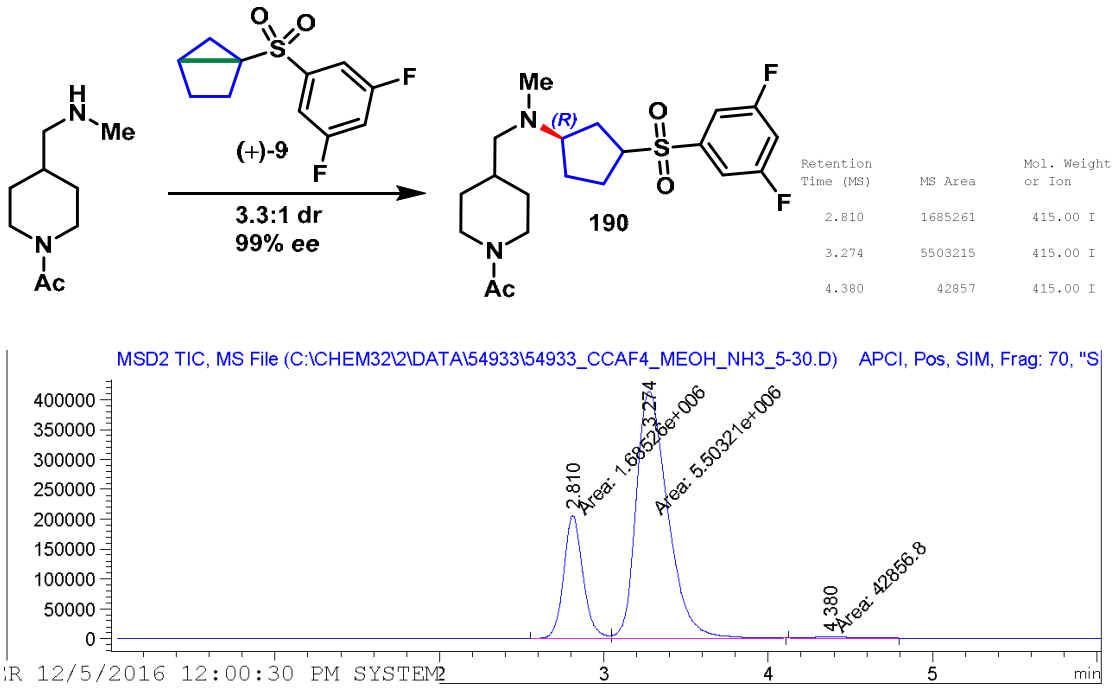
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.850	3233631	420.00 I
1.939	3639011	420.00 I



SFC analysis of compound 190

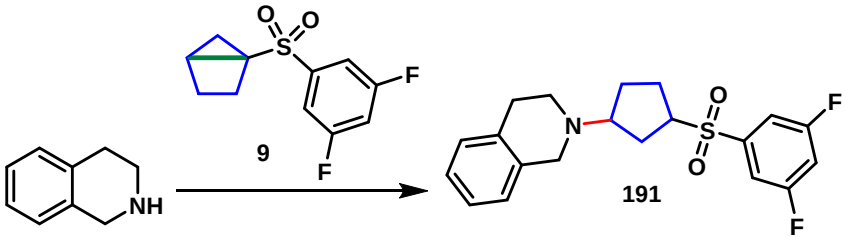
The analysis was performed on a ES Industries CCA F4 3.0 x 150 mm 5µ column using 5-30% MeOH + 10mM NH_3 in 5.0 min, 120 bar, 3 mL/min.



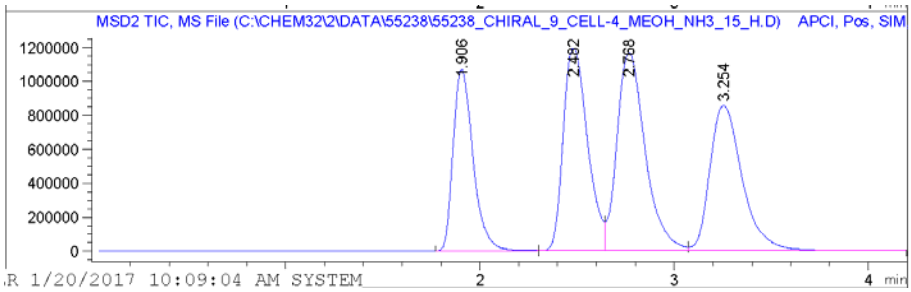


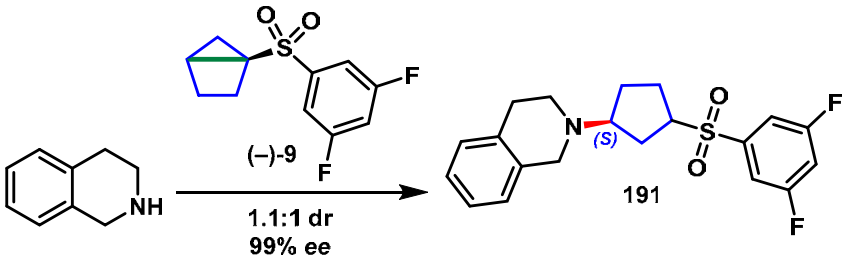
SFC analysis of compound 191

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 15% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

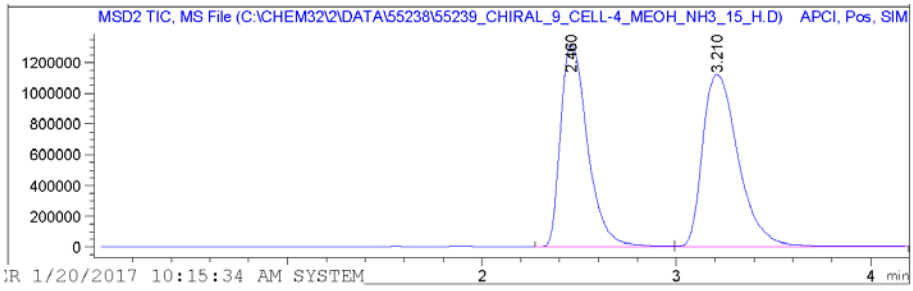


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.906	7557528	378.00 I
2.482	10344922	378.00 I
2.768	11746544	378.00 I
3.254	9828949	378.00 I



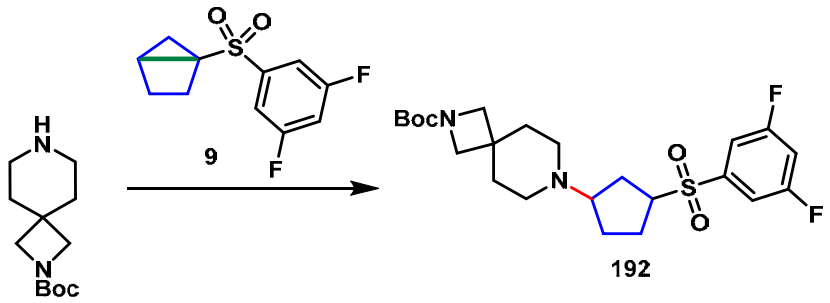


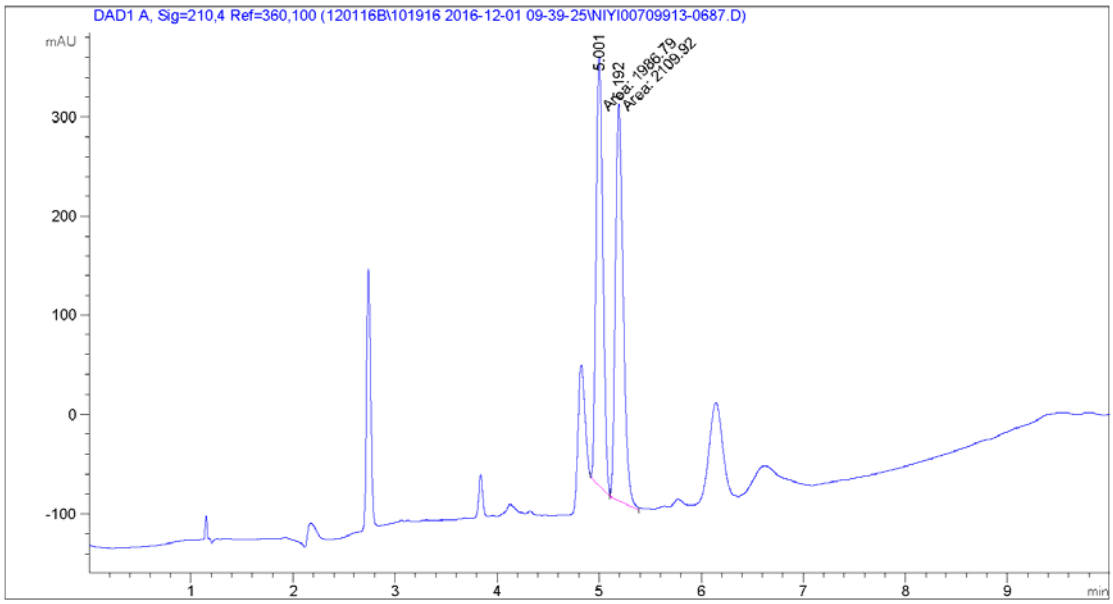
Retention Time (MS)	MS Area	Mol. Weight or Ion
2.460	12748778	378.00 I
3.210	14307706	378.00 I



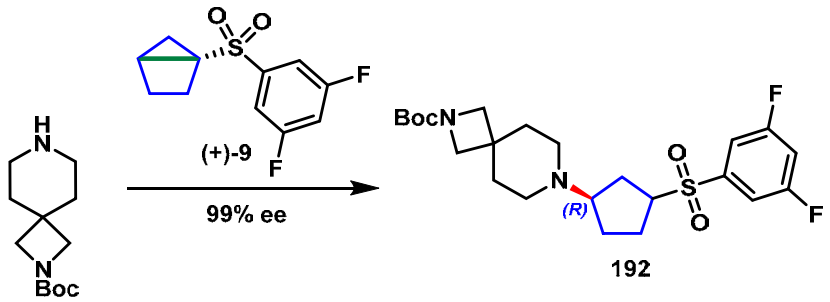
SFC analysis of compound 192

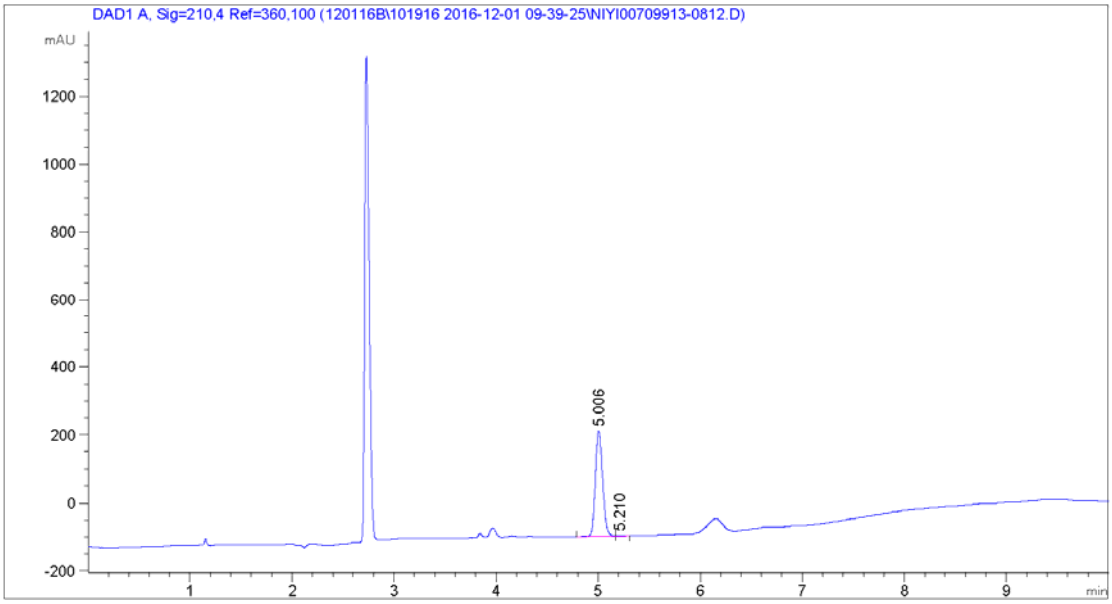
The analysis was performed on a Lux Amylose-1 250mm x 4.6mm 5µ column eluting with 40% MeOH + 0.2% (7N Ammonia in MeOH) at 120 bar, 3.0 mL/min.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.001	MM	0.0767	1986.79211	431.56891	48.4972
2	5.192	MM	0.0880	2109.92261	399.47623	51.5028

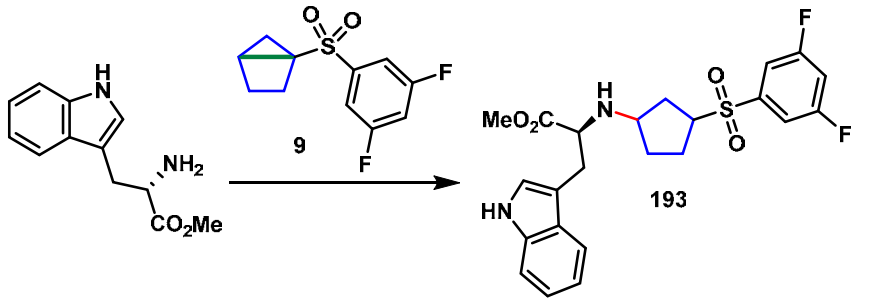




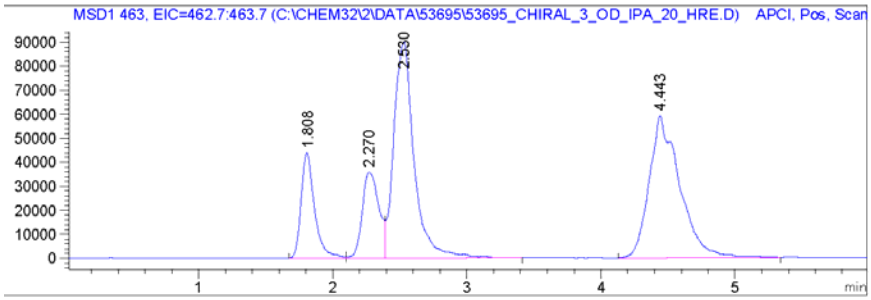
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.006	BV	0.0762	1520.97620	310.01352	99.2911
2	5.210	VB	0.0658	10.85865	2.15459	0.7089

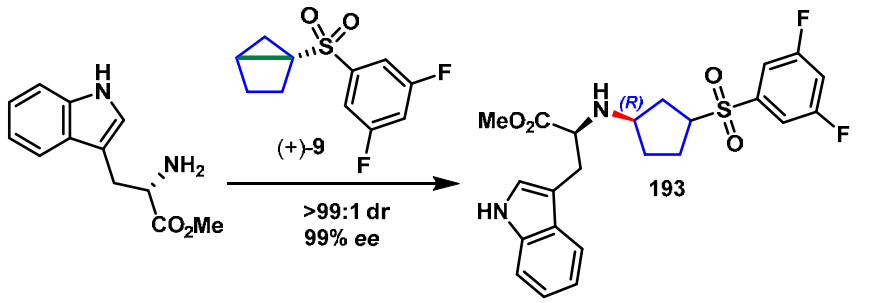
SFC analysis of compound 193

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column using 20% isopropanol, 120 bar, 4 mL/min.

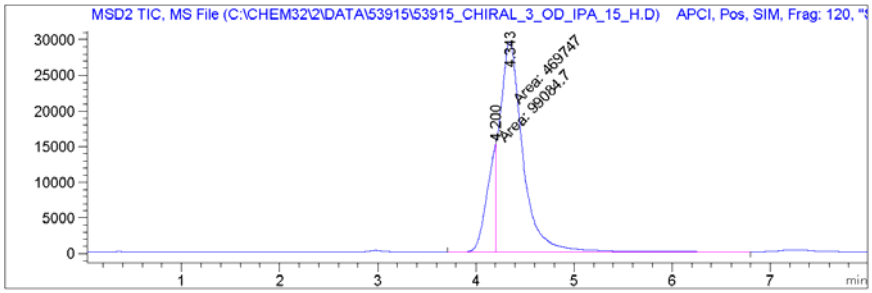


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.348	124376	520.05 I
		519.10 I
		447.00 I
		446.05 I
		445.05 I
		371.10 I
		237.05 I
		219.10 I
		121.15 I
1.808	563944	464.10 I
		463.10 I
2.275	510841	464.10 I
		463.10 I
		332.05 I
2.525	1579554	464.10 I
		463.10 I
4.442	1657417	464.10 I
		463.10 I
		332.00 I



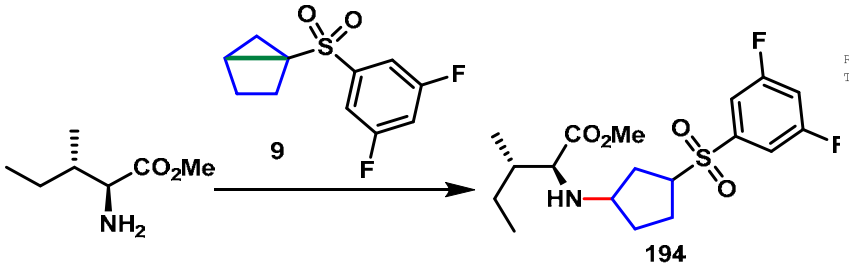


Retention Time (MS)	MS Area	Mol. Weight or Ion
4.200	99085	463.00 I
4.343	469747	463.00 I

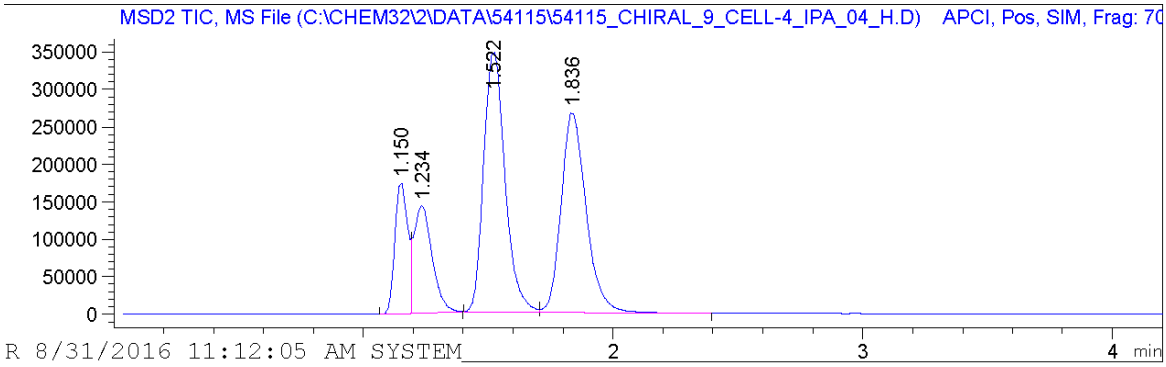


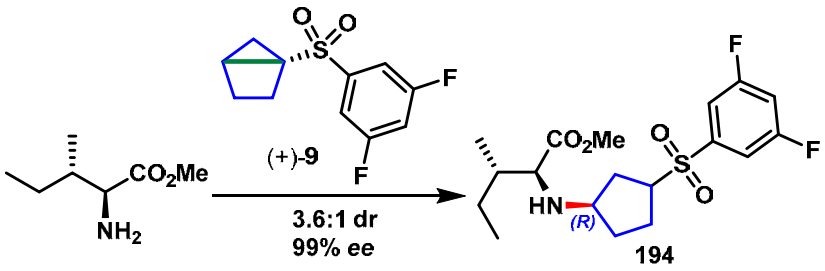
SFC analysis of compound 194

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 4% IPA, 120 bar, 4 mL/min.

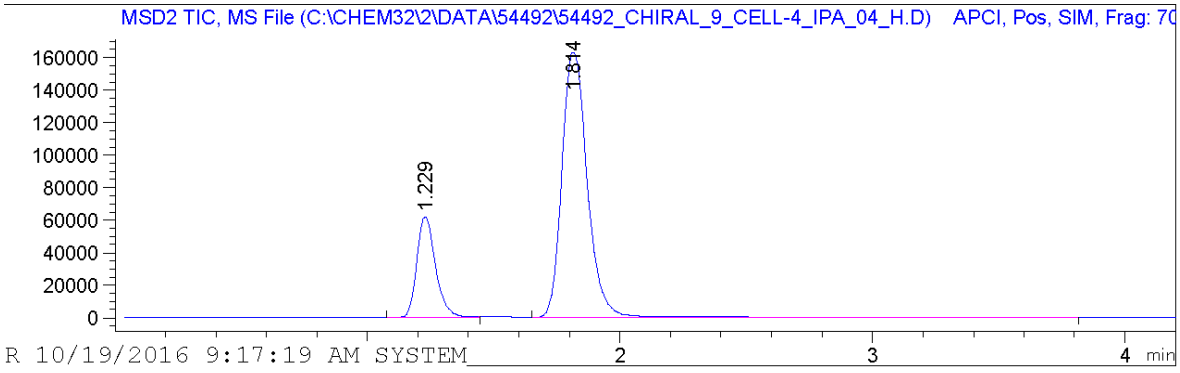


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.150	624355	390.00 I
1.234	720343	390.00 I
1.522	2060093	390.00 I
1.836	1848775	390.00 I



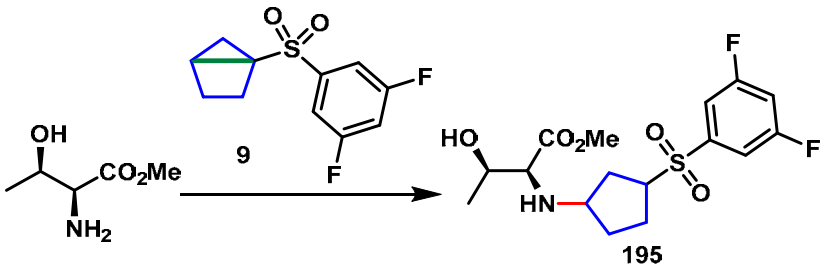


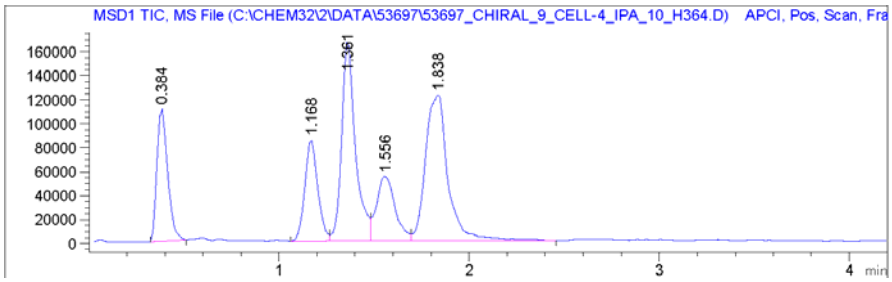
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.229	315776	390.00 I
1.814	1136695	390.00 I



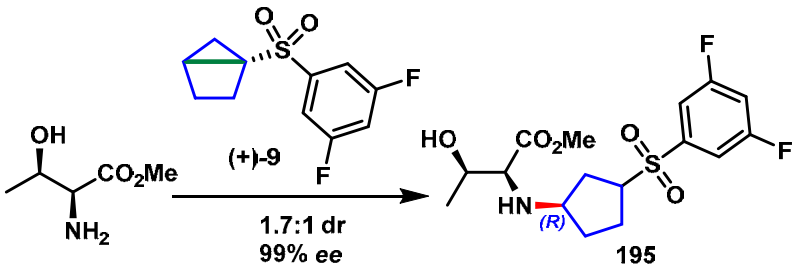
SFC analysis of compound 195

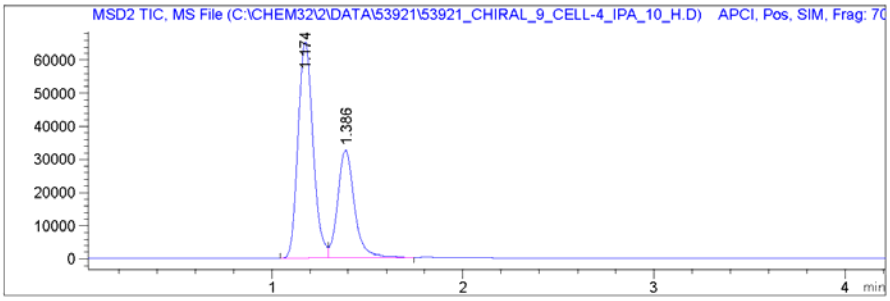
The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 10% IPA, 120 bar, 4 mL/min.





Retention Time (MS)	MS Area	Mol. Weight or Ion
0.384	428686	521.10 I 520.10 I 519.10 I 448.10 I 447.10 I 446.10 I 445.10 I 429.00 I 373.00 I 372.05 I 371.10 I 355.00 I
1.168	400997	379.10 I 378.10 I 334.05 I
1.361	841405	379.10 I 378.05 I 334.10 I 332.00 I
1.556	365732	379.05 I 378.10 I 334.10 I 332.05 I
1.838	1010182	379.10 I 378.10 I 334.10 I 332.05 I

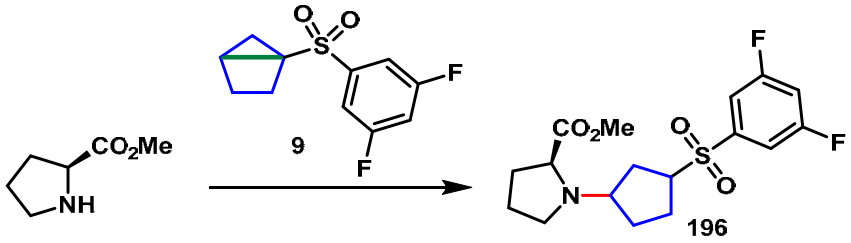


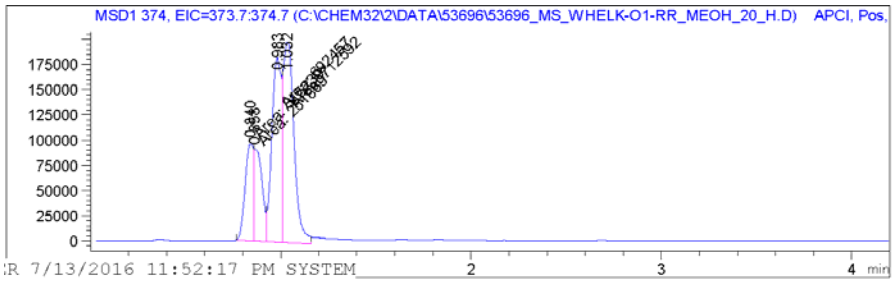


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.166	213767	379.10 I 378.10 I 334.05 I 332.05 I
1.376	128509	379.05 I 378.10 I 334.05 I 332.00 I

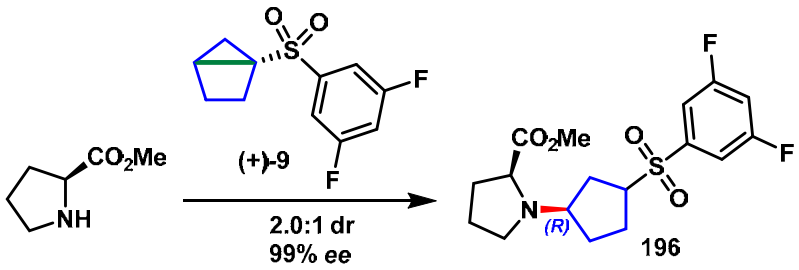
SFC analysis of compound 196

The analysis was performed on a Regis Whelk-O1 (*R*,*R*) 4.6 x 100 mm 5µ column using 20% MeOH, 120 bar, 4.0 mL/min.

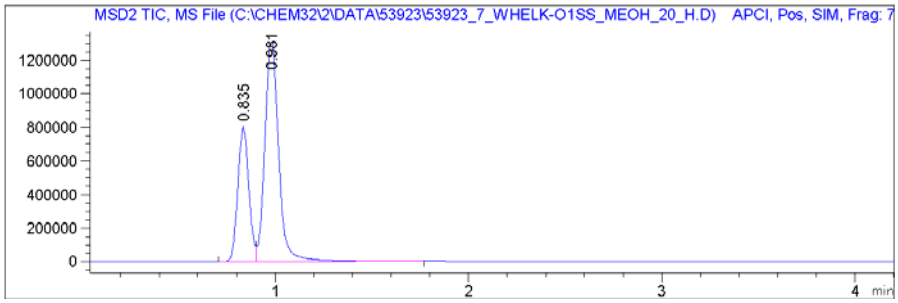




Retention Time (MS)	MS Area	Mol. Weight or Ion
0.365	547374	519.10 I
		447.10 I
		446.10 I
		445.10 I
		373.10 I
		372.05 I
		371.10 I
		238.10 I
		237.10 I
		87.15 I
0.662	110643	285.10 I
		87.15 I
		74.20 I
0.840	677038	375.10 I
		374.10 I
0.983	736785	375.10 I
		374.10 I
1.037	976644	375.10 I
		374.10 I
1.252	51843	374.10 I
		355.10 I
		354.10 I
		87.15 I
1.831	96816	373.10 I
		372.10 I
		87.20 I

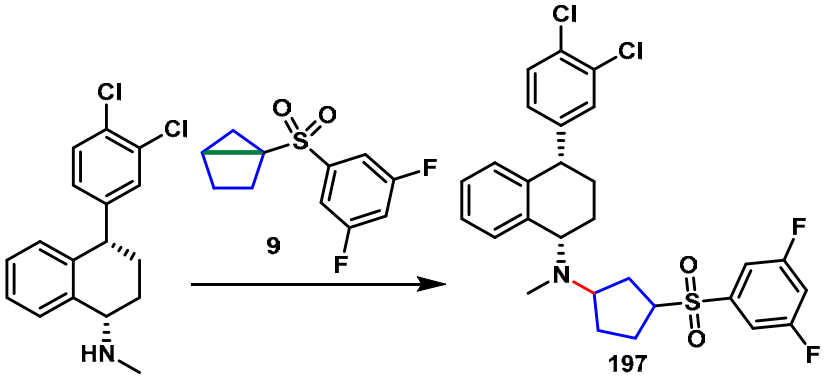


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.835	3173450	374.00 I
0.981	6480040	374.00 I

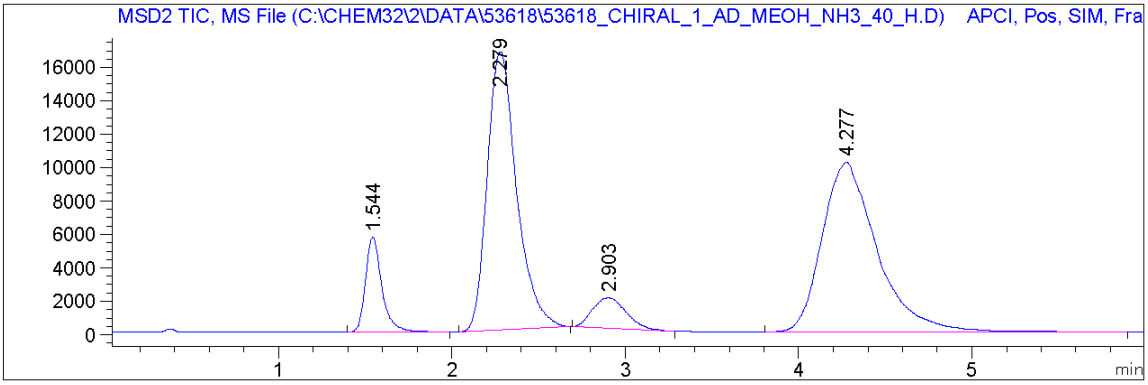


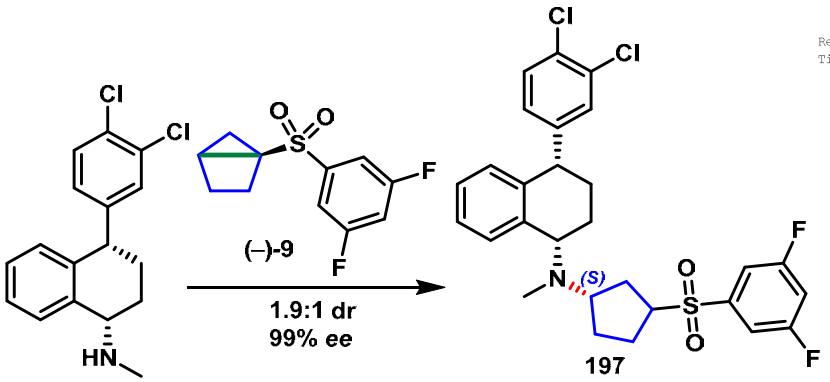
SFC analysis of compound 197

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 40% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

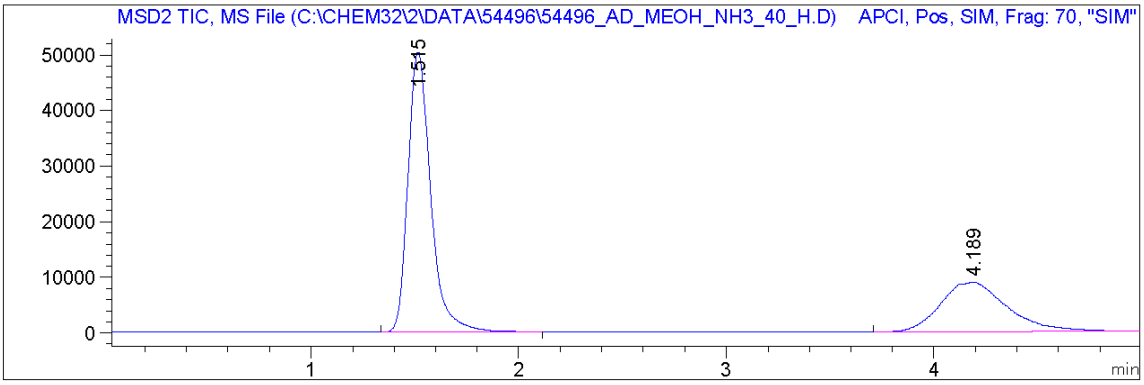


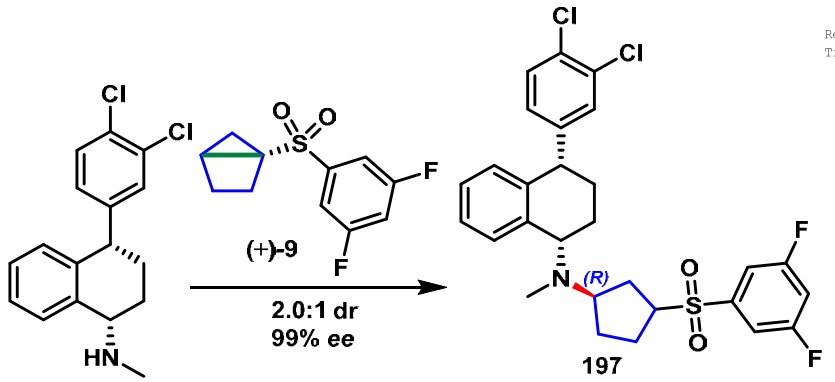
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.544	36732	551.00 I
2.279	195515	551.00 I
2.903	24254	551.00 I
4.277	221746	551.00 I



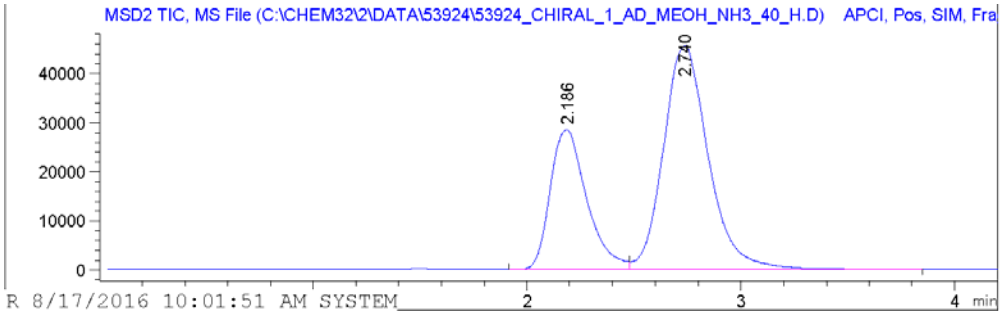


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.515	381389	551.00 I
4.189	198187	551.00 I



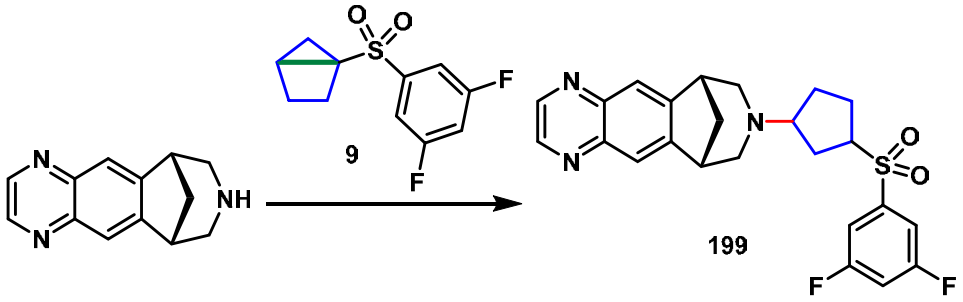


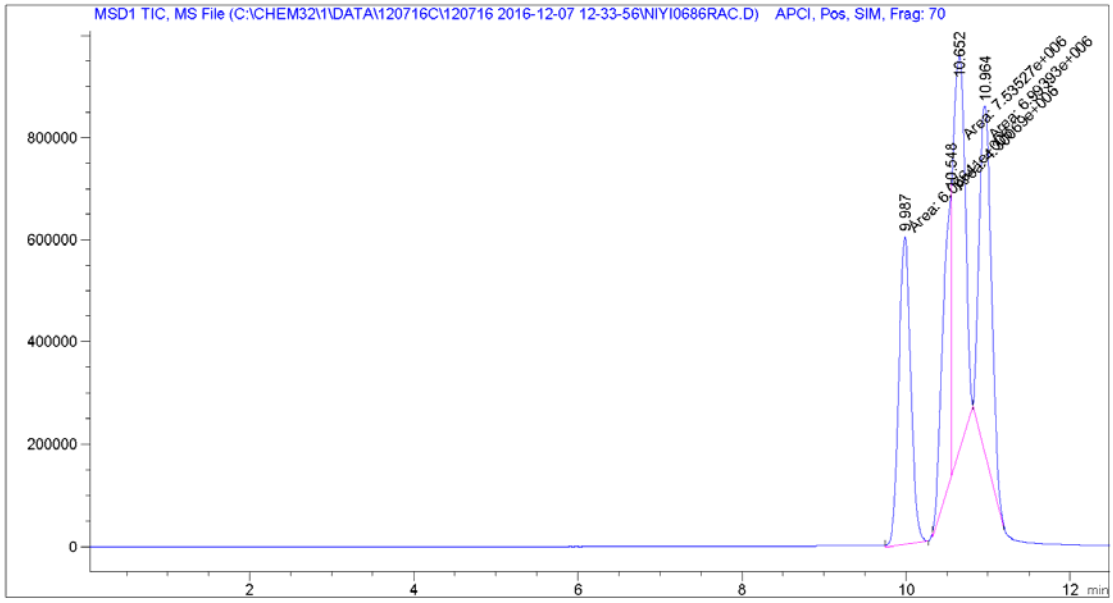
Retention Time (MS)	MS Area	Mol. Weight or Ion
2.186	335469	551.00 I
2.740	661419	551.00 I



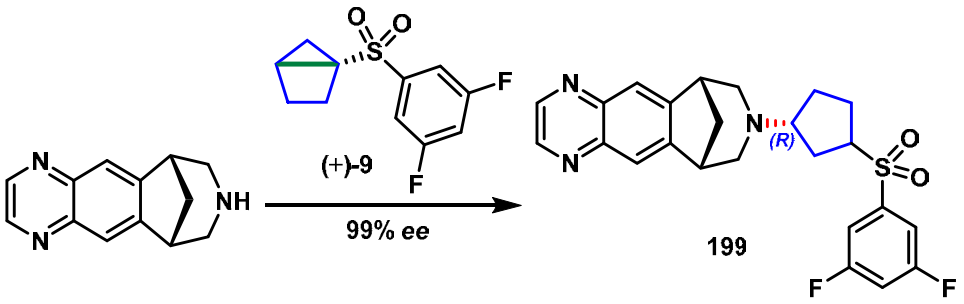
SFC analysis of compound 199

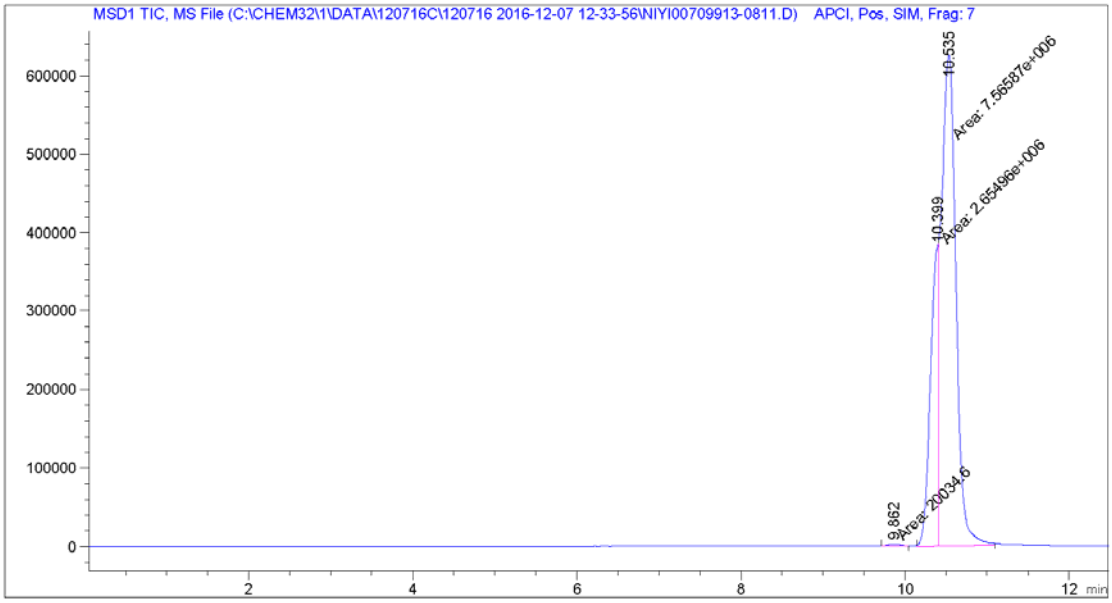
The analysis was performed on Chiral Normal Phase LC-MS using a Lux Cellulose-4 250mm x 4.6mm 5µ column eluting with 5%-100% EtOH in heptanes at 1.5 mL/min.





Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	9.987	MM	0.1676	6.06641e6	6.03329e5	24.3667
2	10.548	MF	0.1288	4.30069e6	5.56318e5	17.2744
3	10.652	FM	0.1624	7.53527e6	7.73262e5	30.2666
4	10.964	MM	0.1714	6.99393e6	6.80240e5	28.0922

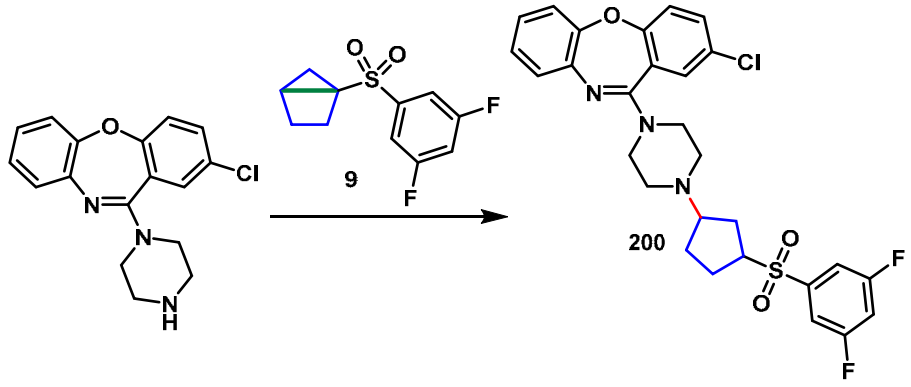




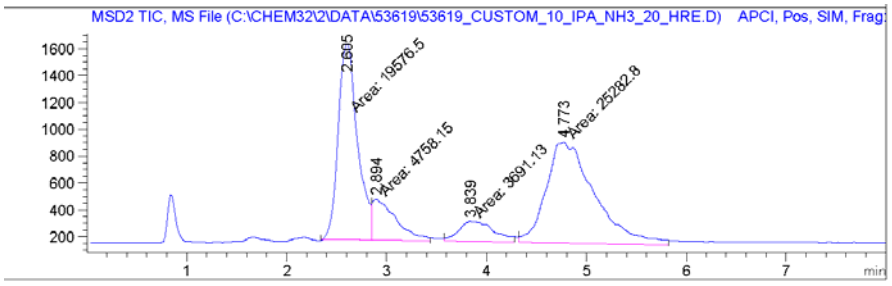
Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	9.862	MM	0.1511	2.00346e4	2210.15308	0.1956
2	10.399	MF	0.1161	2.65496e6	3.81167e5	25.9251
3	10.535	FM	0.2017	7.56587e6	6.25247e5	73.8792

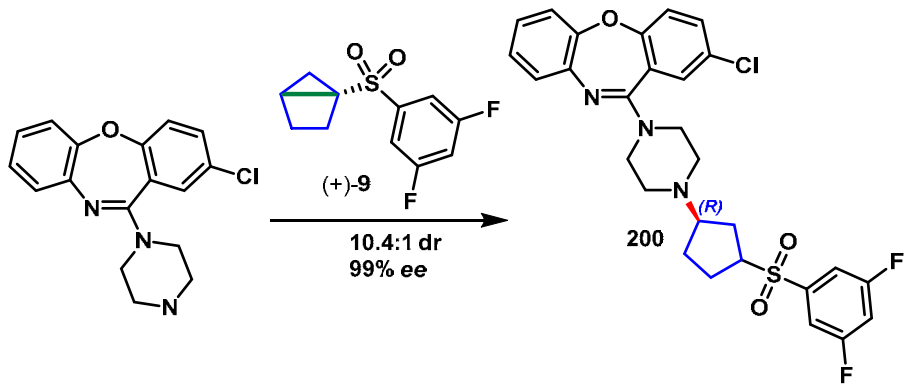
SFC analysis of compound 200

The analysis was performed on an ES Ind. CCO F4 4.6 x 250 mm 5µ column using 20% IPA + 10mM NH_3, 120 bar, 4 mL/min.

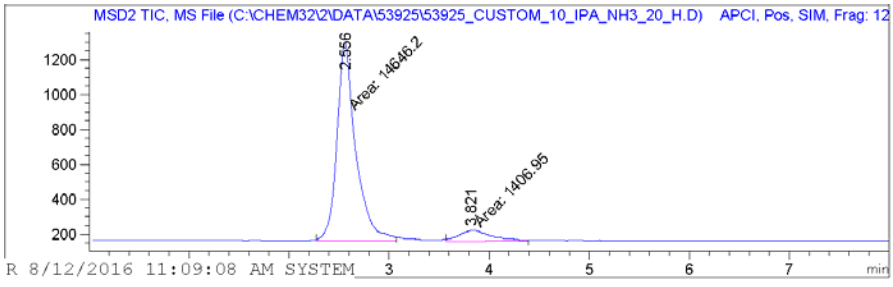


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.234	787939	74.15 I
2.586	311097	380.10 I 288.10 I 271.00 I 235.10 I 212.10 I 196.10 I 74.20 I
3.003	352241	316.10 I 314.10 I 88.10 I 74.10 I
3.775	174308	88.15 I 74.15 I 70.20 I
4.232	269826	344.10 I 343.15 I 342.10 I 88.10 I 74.15 I
4.794	432619	212.05 I 88.15 I 74.15 I



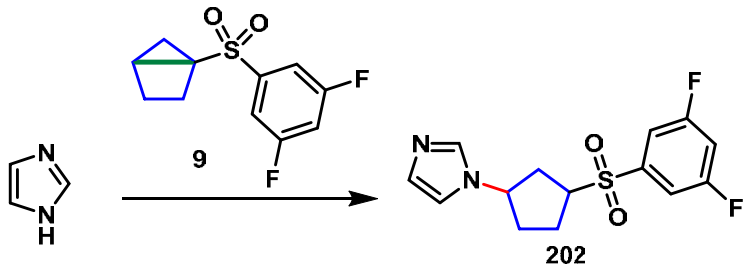


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.556	14646	524.00 I
3.821	1407	

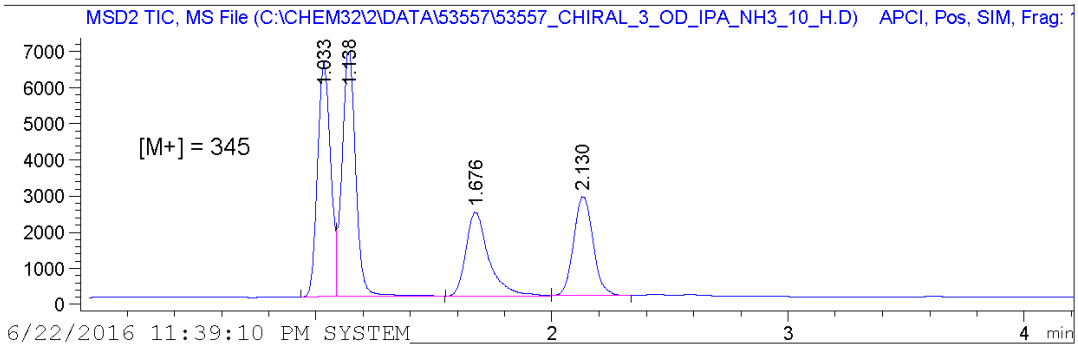


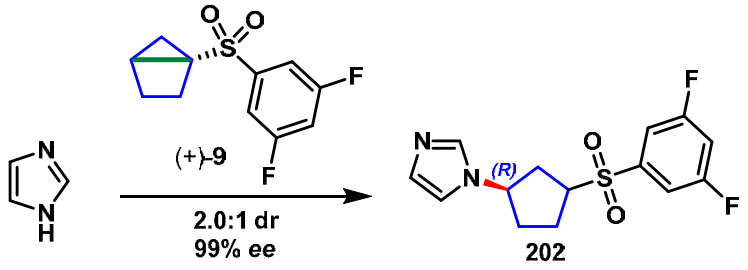
SFC analysis of compound 202

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column using 10% iPrOH with 10mM NH_3, 120 bar, 4 mL/min.

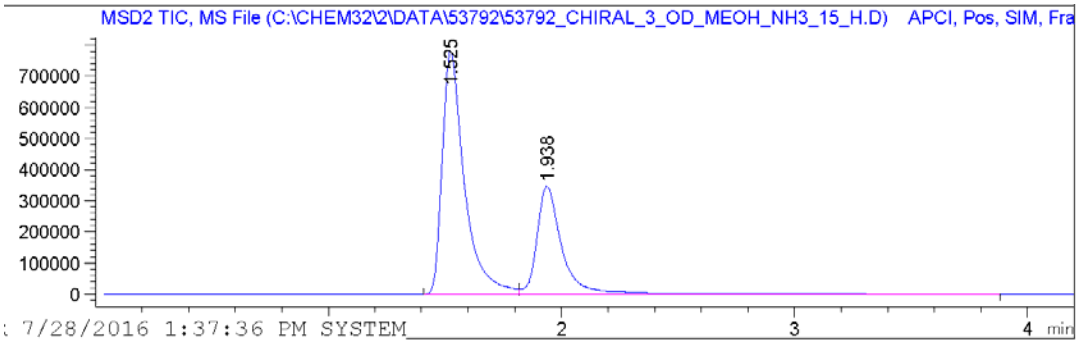


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.033	24915	345.00 I
1.138	27211	345.00 I
1.676	15605	345.00 I
2.130	15709	345.00 I



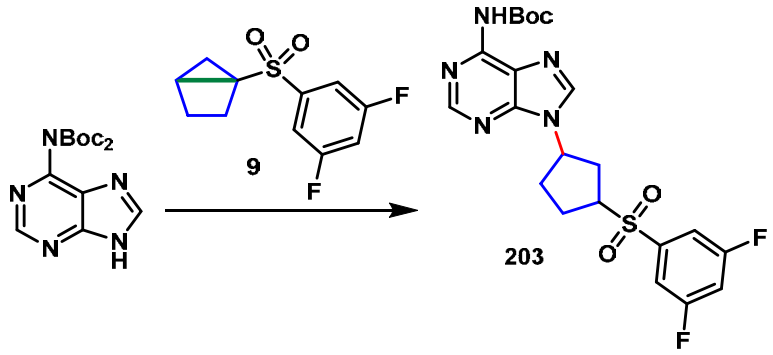


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.525	5143120	313.00 I
1.938	2596606	313.00 I

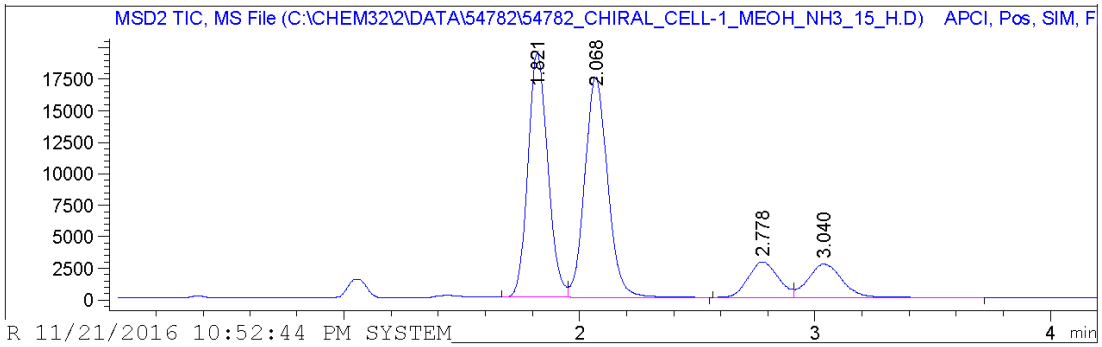


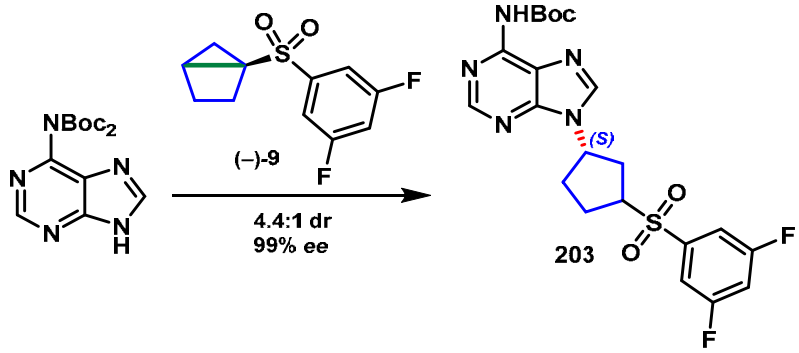
SFC analysis of compound 203

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column using 15% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

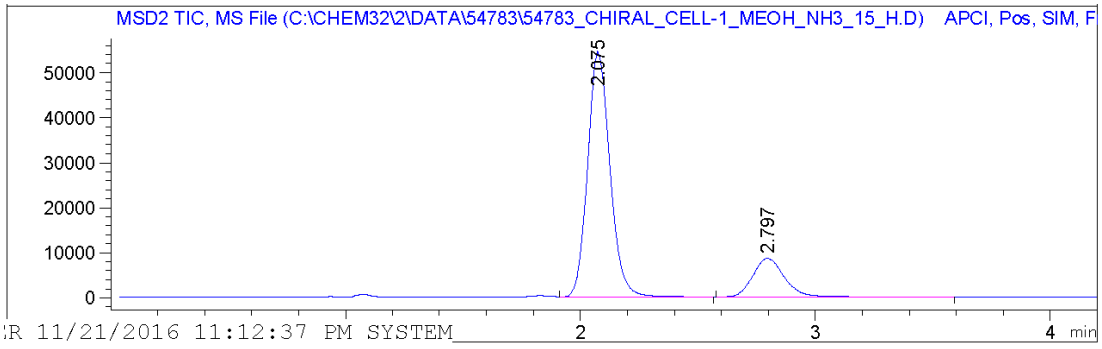


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.821	114283	480.00 I
2.068	117837	480.00 I
2.778	24881	480.00 I
3.040	26980	480.00 I



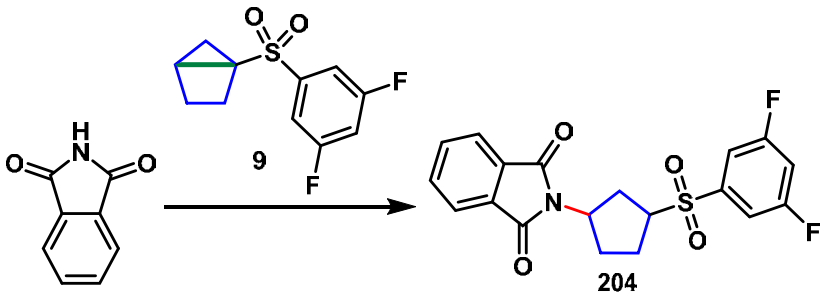


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.075	356509	480.00 I
2.797	80171	480.00 I

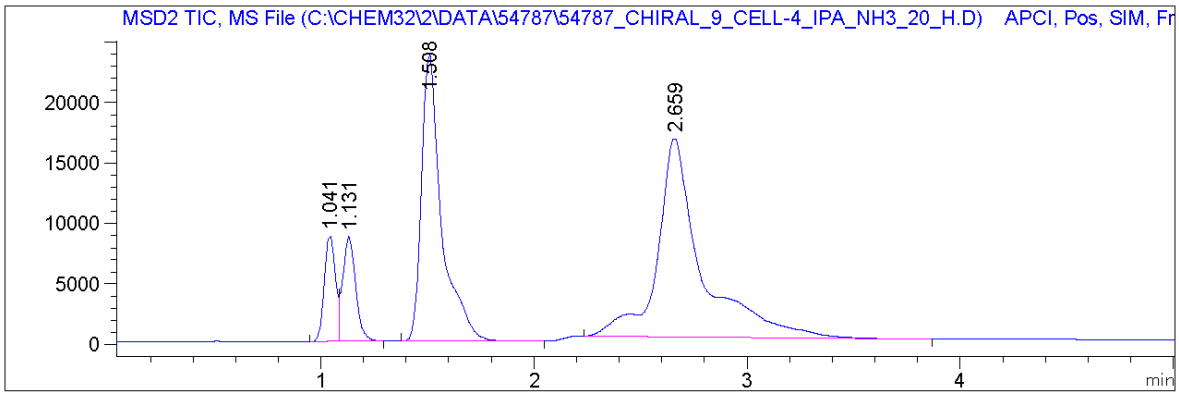


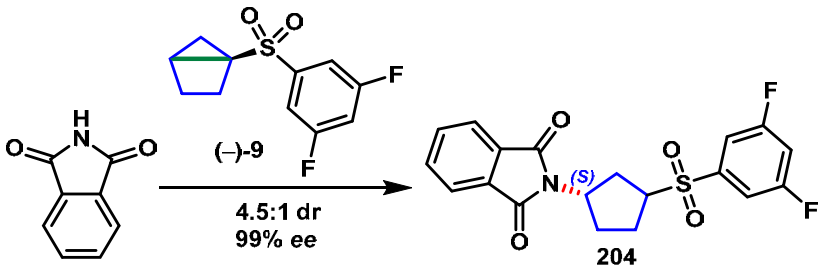
SFC analysis of compound 204

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 20% iPrOH + 10mM NH_3, 120 bar, 4 mL/min.

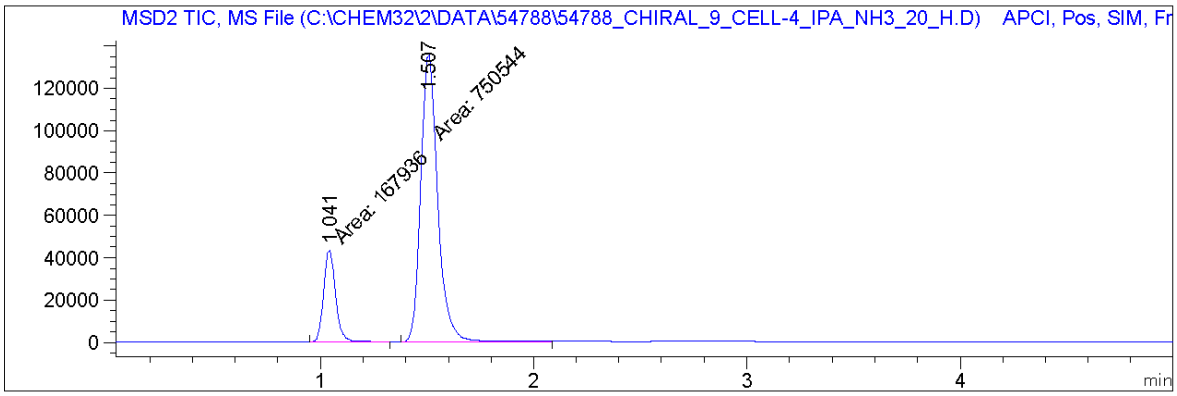


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.041	31556	392.00 I
1.131	36119	392.00 I
1.508	153779	392.00 I
2.659	236562	392.00 I



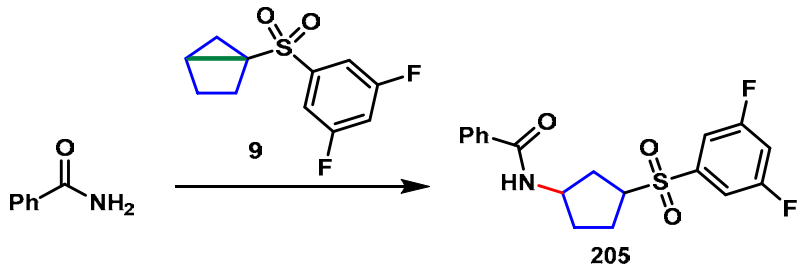


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.041	167936	392.00 I
1.507	750544	392.00 I

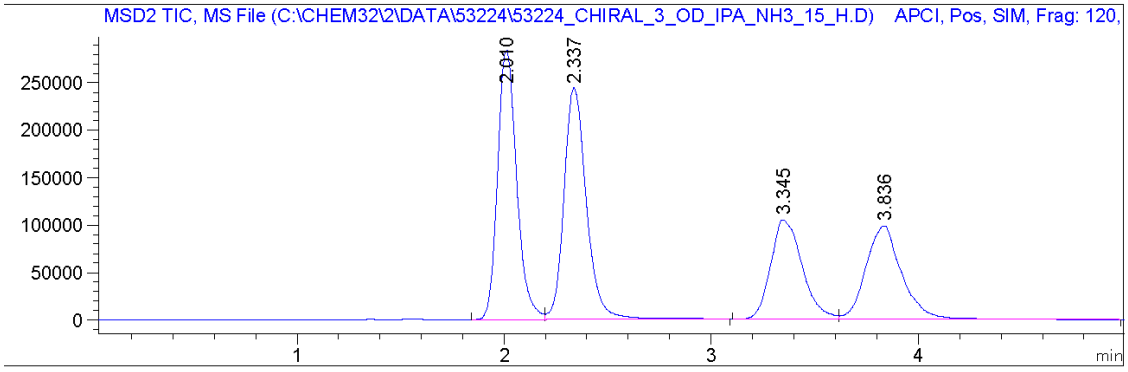


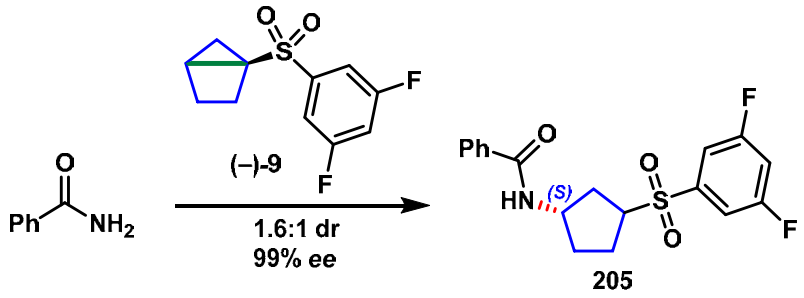
SFC analysis of compound 205

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column
15% IPA + 10mM NH_3, 120 bar, 4 mL/min.

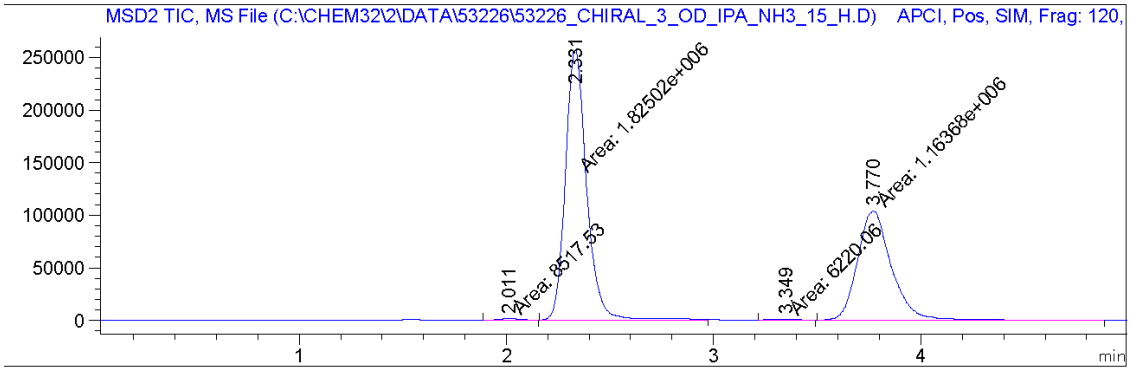


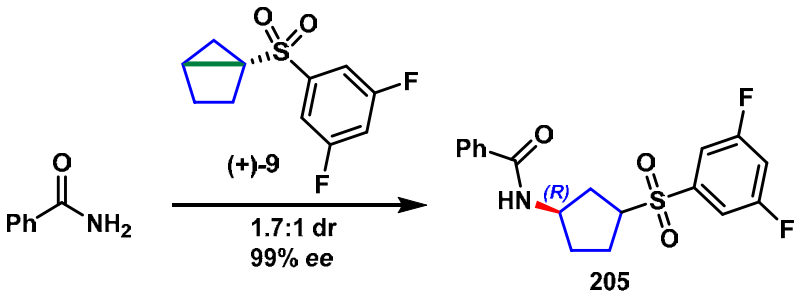
Retention Time (MS)	MS Area	Mol. Weight or Ion
2.010	1812940	366.00 I
2.337	1840456	366.00 I
3.345	1096120	366.00 I
3.836	1168892	366.00 I



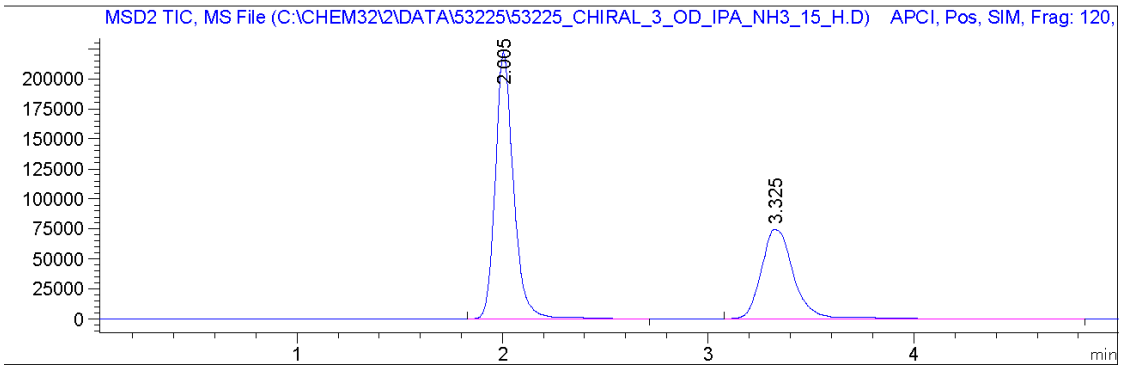


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.011	8518	366.00 I
2.331	1825020	366.00 I
3.349	6220	
3.770	1163680	366.00 I



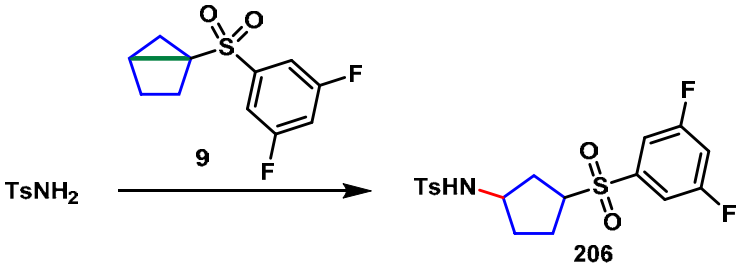


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.005	1355925	366.00 I
3.325	798834	366.00 I

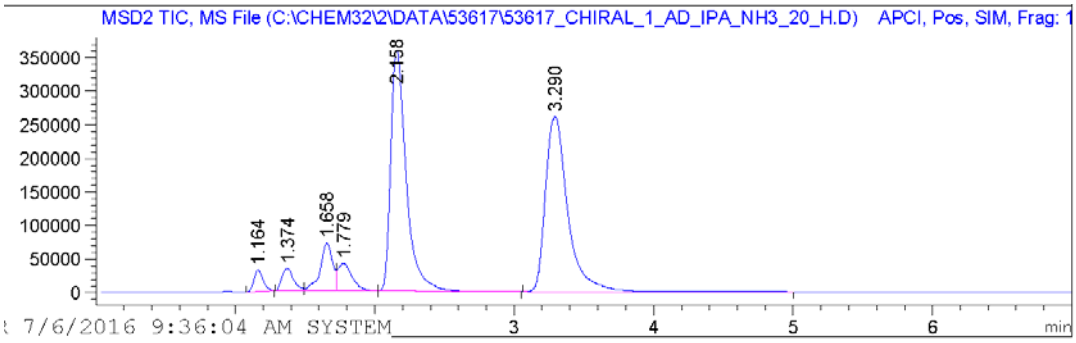


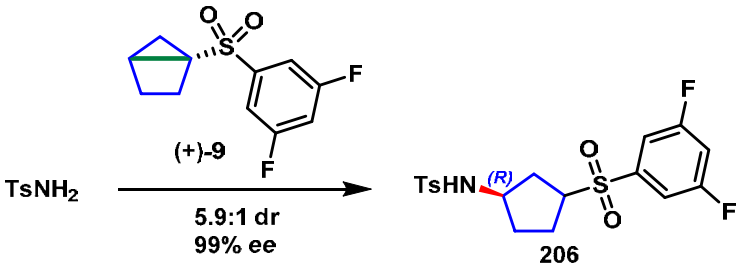
SFC analysis of compound 206

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 20% IPA + 10mM NH_3, 120 bar, 4 mL/min.

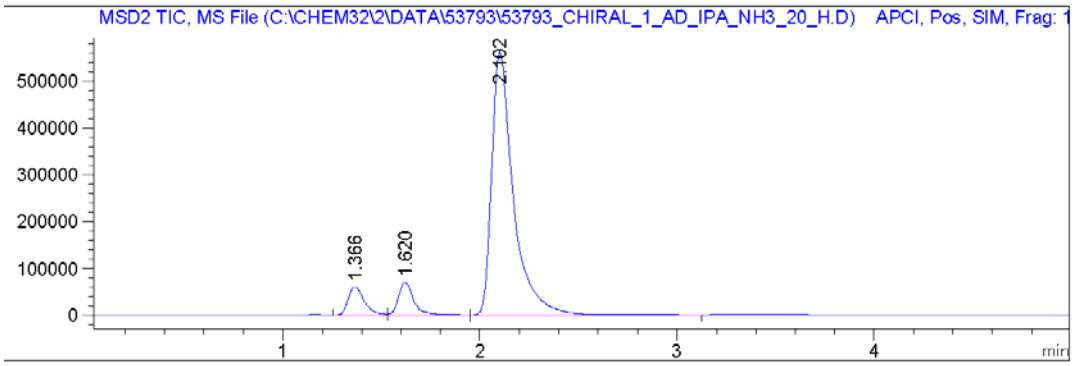


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.164	142127	416.00 I
1.374	188336	416.00 I
1.658	444402	416.00 I
1.779	286516	416.00 I
2.158	2706475	416.00 I
3.290	2909726	416.00 I



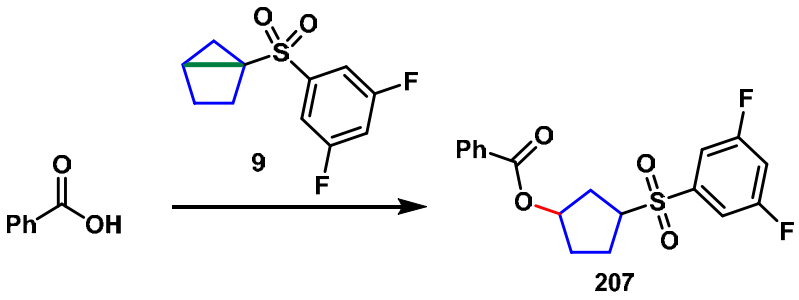


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.366	345695	416.00 I
1.620	380510	416.00 I
2.102	4284411	416.00 I

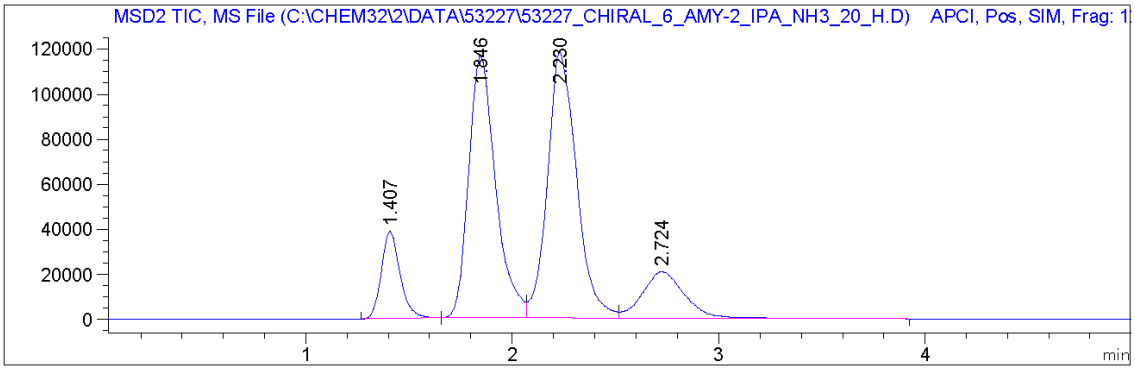


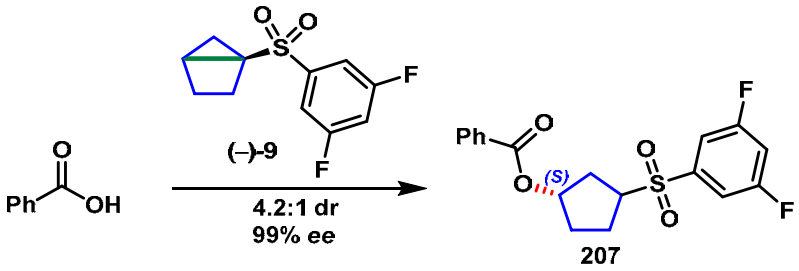
SFC analysis of compound 207

The analysis was performed on a Lux Amylose-2 4.6 x 100 mm 3µ column using 20% IPA + 0.1% DEA, 120 bar, 4 mL/min.

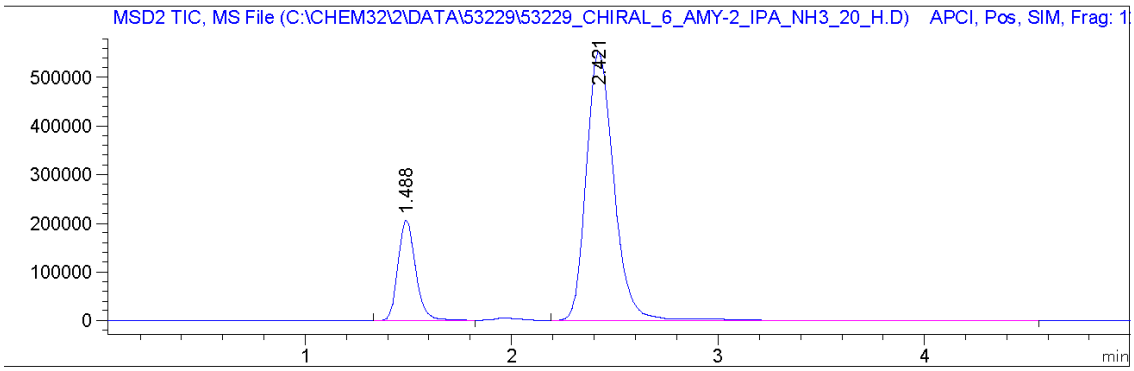


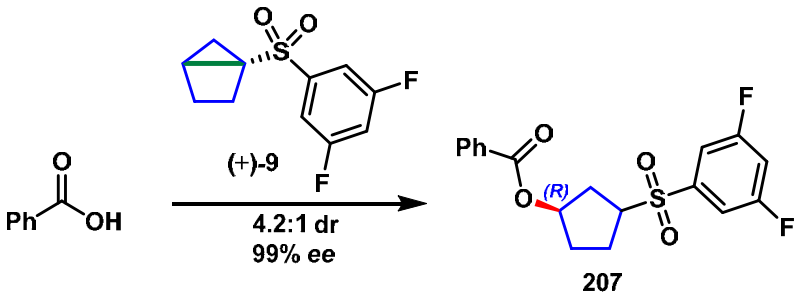
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.407	240892	368.00 I
1.846	1053271	368.00 I
2.230	1152847	368.00 I
2.724	289135	368.00 I



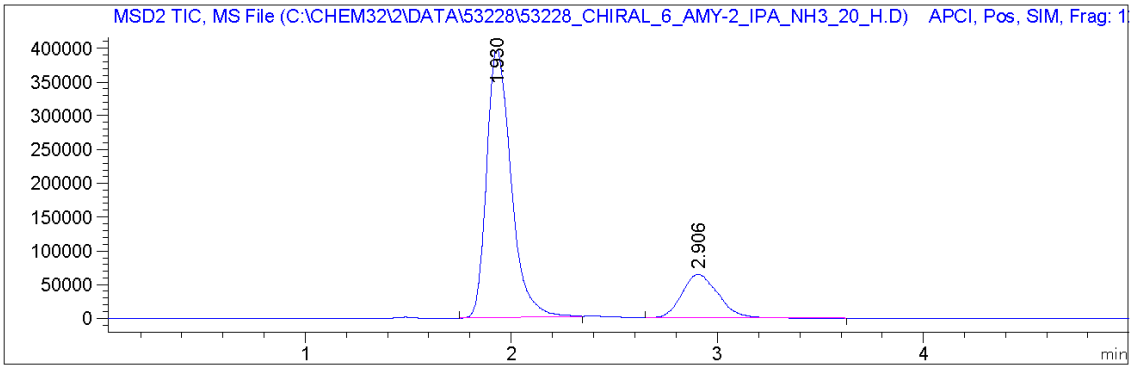


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.488	1207046	368.00 I
2.421	5120314	368.00 I



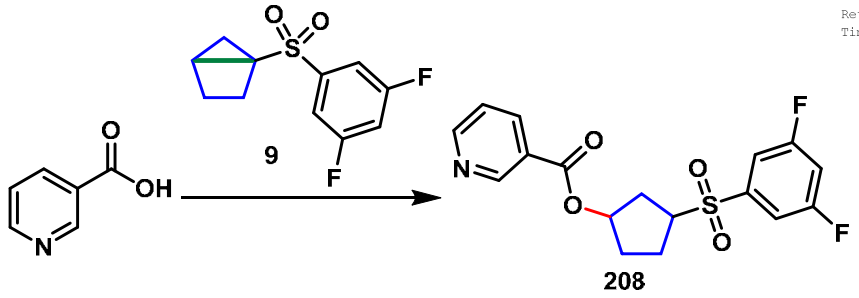


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.930	3264455	368.00 I
2.906	769093	368.00 I

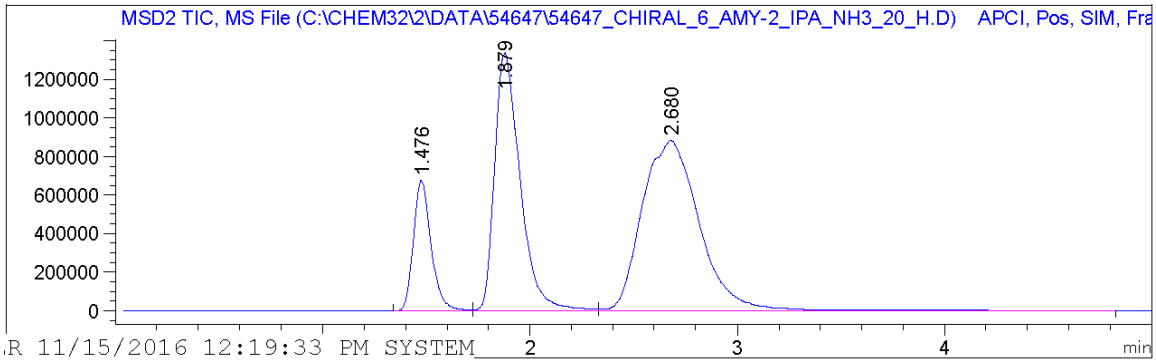


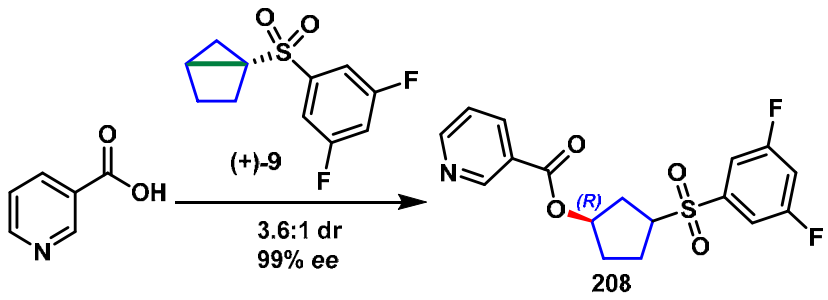
SFC analysis of compound 208

The analysis was performed on a Lux Amylose-2 4.6 x 100 mm 3µ column using 20% IPA + 10 mM NH_3, 120 bar, 4 mL/min.

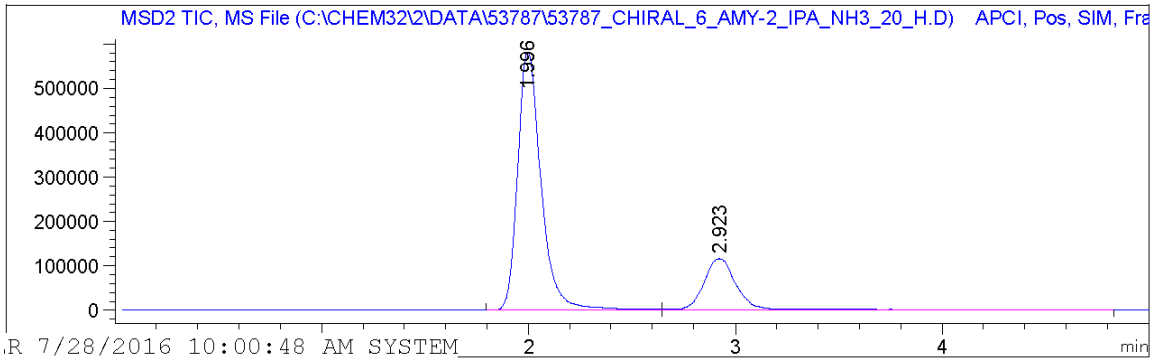


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.476	3992781	368.00 I
1.879	11396410	368.00 I
2.680	16860338	368.00 I



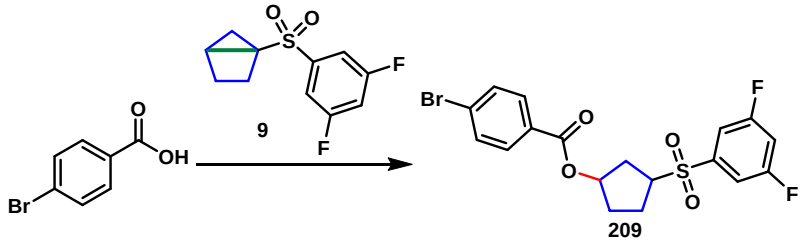


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.996	4574216	368.00 I
2.923	1267392	368.00 I

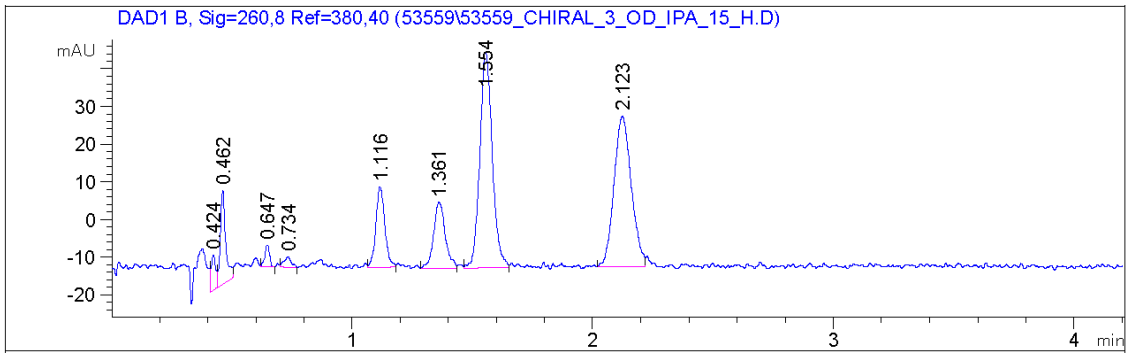


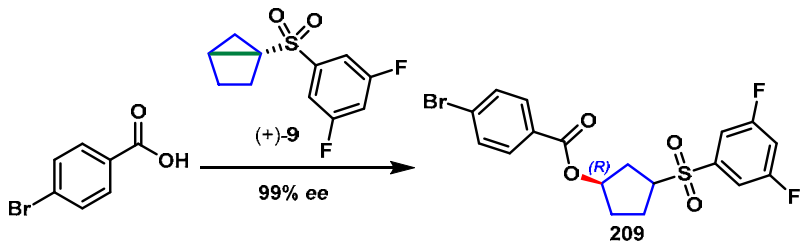
SFC analysis of compound 209

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column using 15% isopropanol, 120 bar, 4 mL/min.

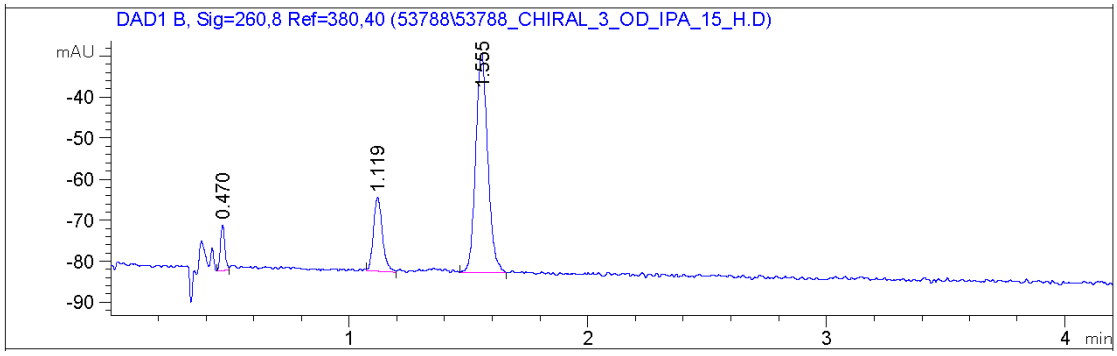


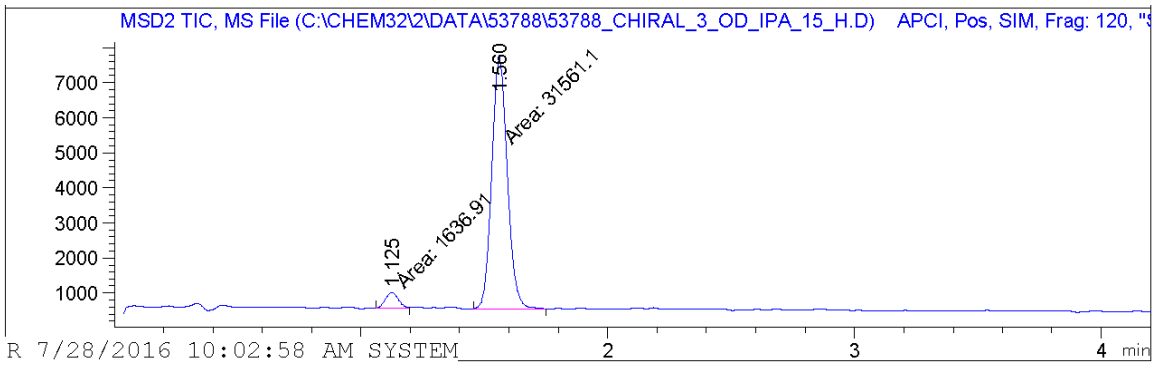
Retention Time (MS)	MS Area	Mol. Weight or Ion
0.354	54675	519.00 I 445.10 I
1.124	11940	245.00 I
1.361	14951	245.00 I
1.566	35423	367.05 I
2.131	40229	





Retention Time (MS)	MS Area	Mol. Weight or Ion
1.125	1637	
1.560	31561	445.00 I

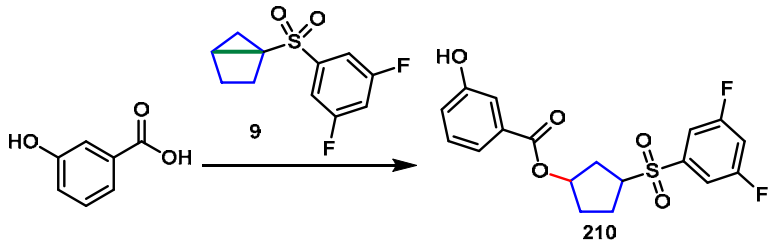




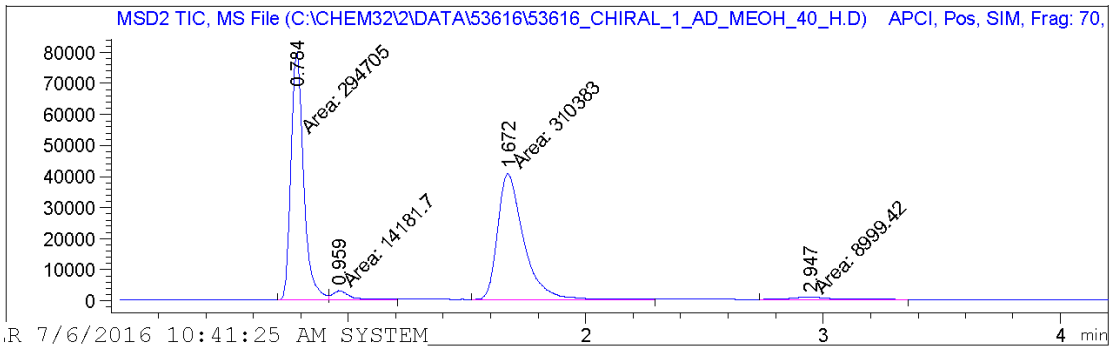
Note: the compound did not ionize very well. The UV chromatograms are included instead. dr not determined.

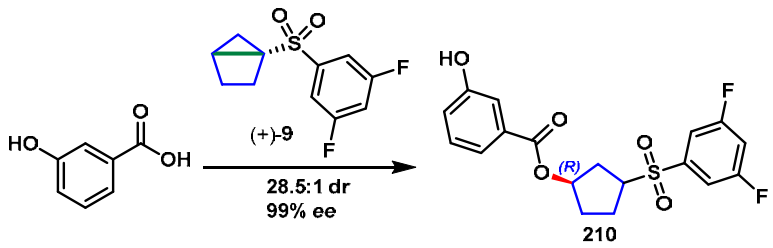
SFC analysis of compound 210

The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 40% MeOH, 120 bar, 4 mL/min.

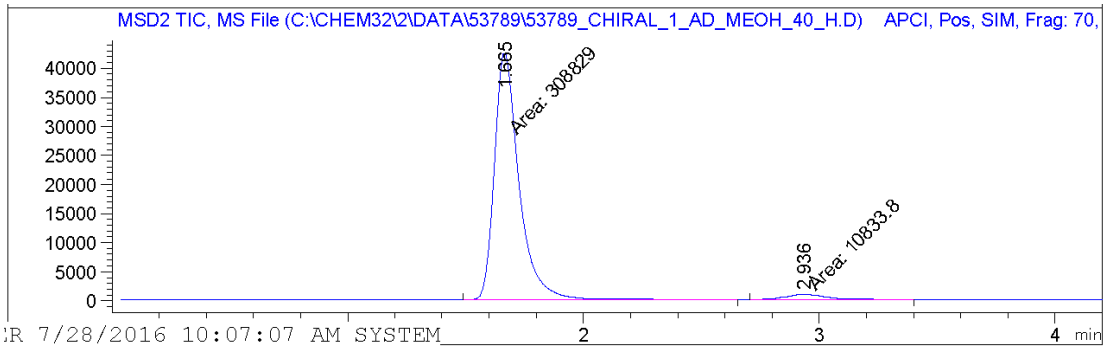


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.784	294705	383.00 I
0.959	14182	383.00 I
1.672	310383	383.00 I
2.947	8999	



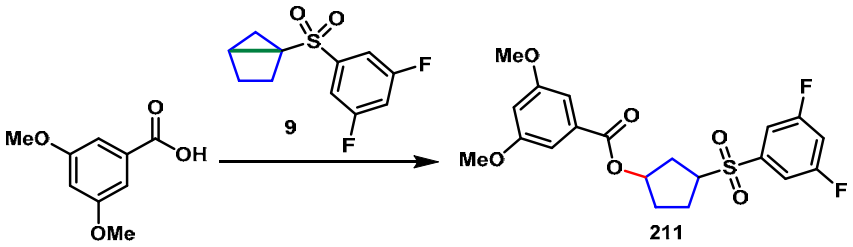


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.665	308829	383.00 I
2.936	10834	

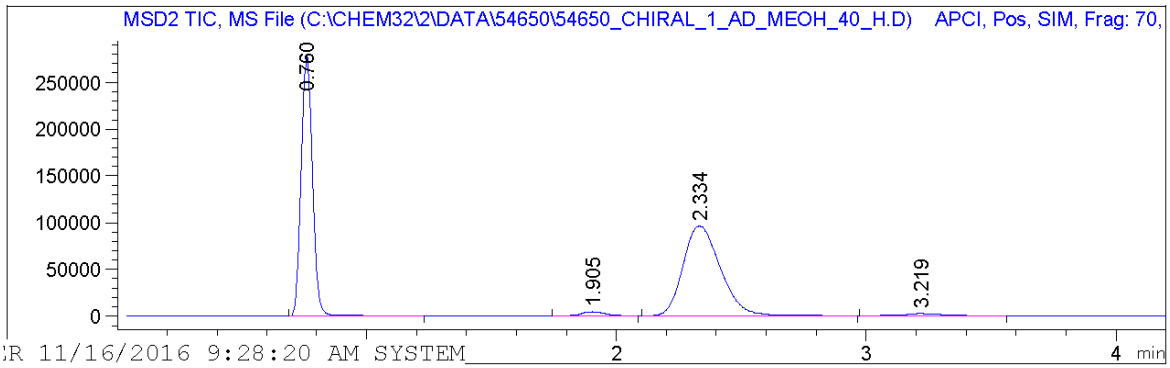


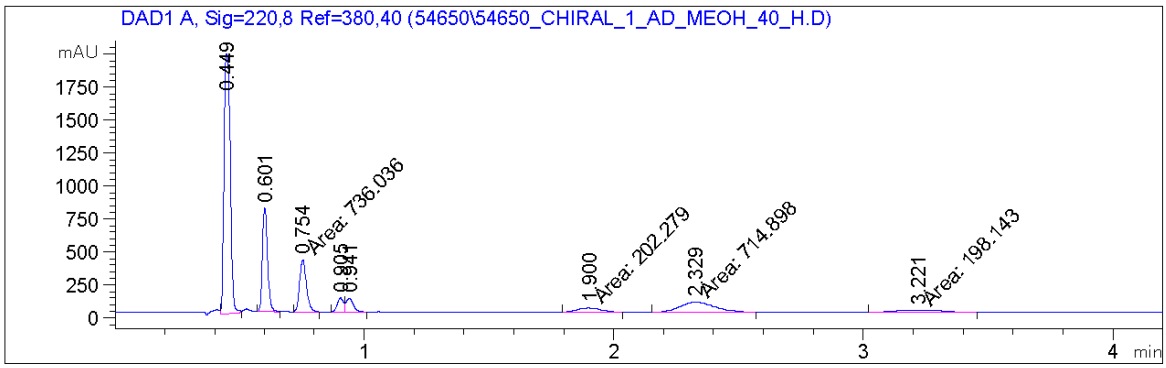
SFC analysis of compound 211

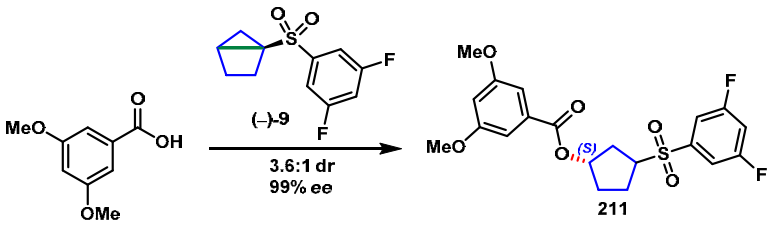
The analysis was performed on a Chiralpak AD-3 4.6 x 100 mm 3µ column using 40% MeOH, 120 bar, 4 mL/min.



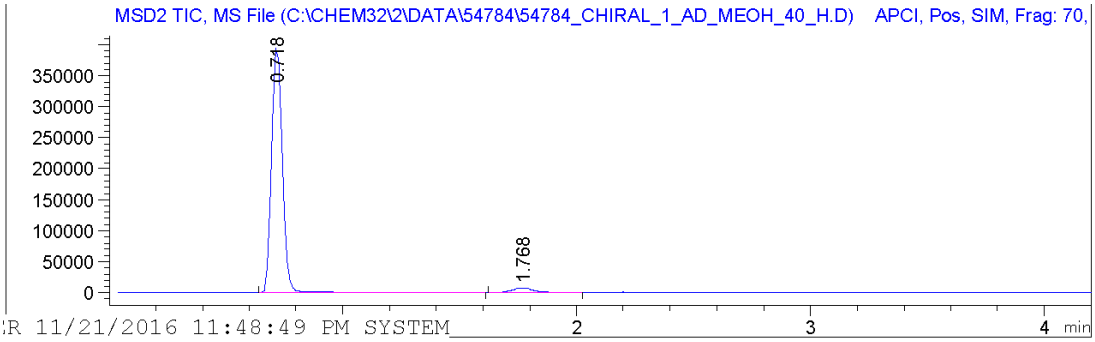
Retention Time (MS)	MS Area	Mol. Weight or Ion
0.760	880270	427.00 I
1.905	29009	427.00 I
2.334	988325	427.00 I
3.219	27502	427.00 I

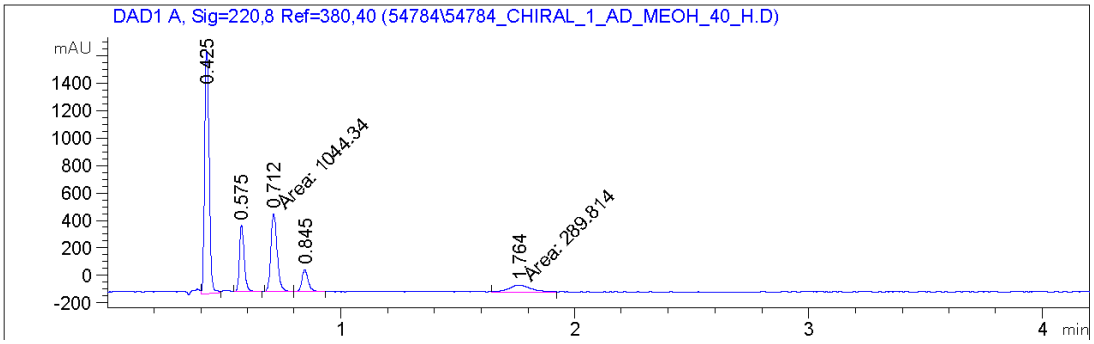






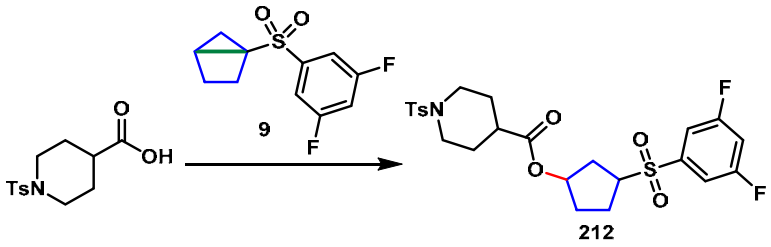
Retention Time (MS)	MS Area	Mol. Weight or Ion
0.718	1283148	427.00 I
1.768	47588	427.00 I



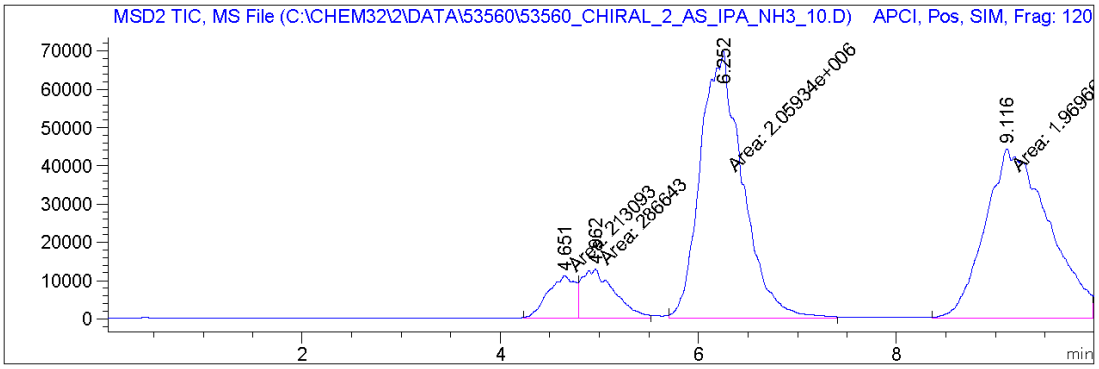


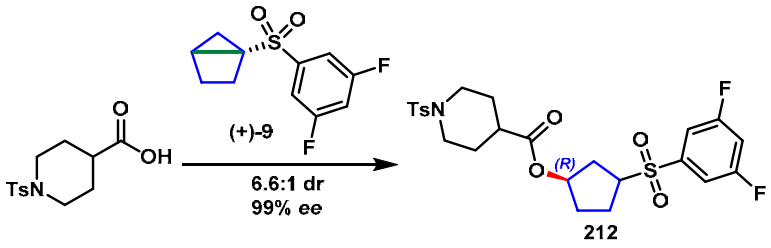
SFC analysis of compound 212

The analysis was performed on a Chiralpak AS-3 4.6 x 100 mm 3µ column using 10% iPrOH with 10mM NH_3, 120 bar, 4 mL/min.

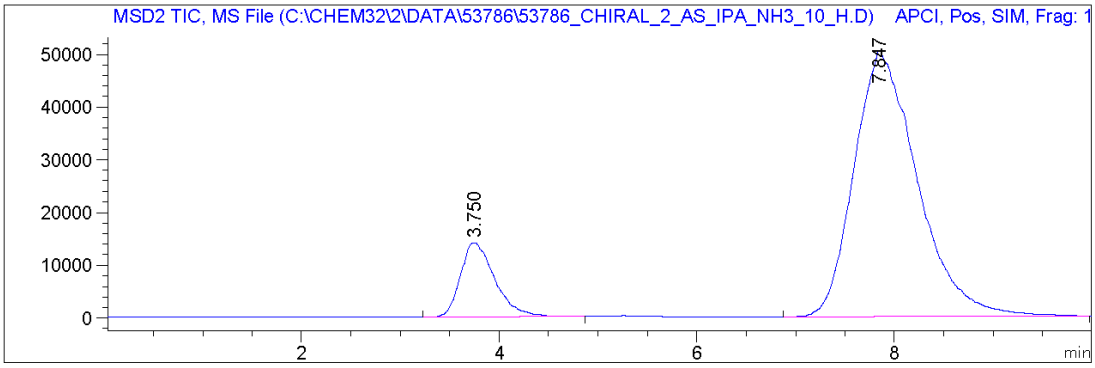


Retention Time (MS)	MS Area	Mol. Weight or Ion
4.651	213093	528.00 I
4.962	286643	528.00 I
6.252	2059339	528.00 I
9.116	1969658	528.00 I



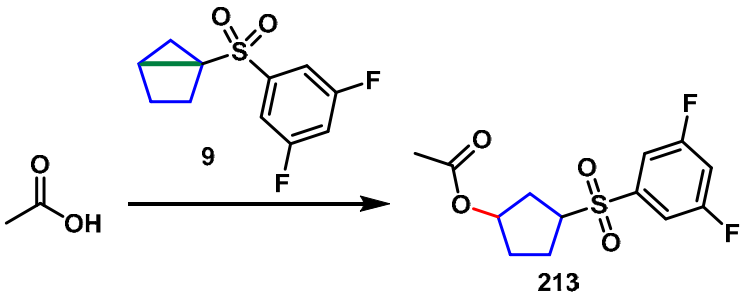


Retention Time (MS)	MS Area	Mol. Weight or Ion
3.750	337355	528.00 I
7.847	2227564	528.00 I

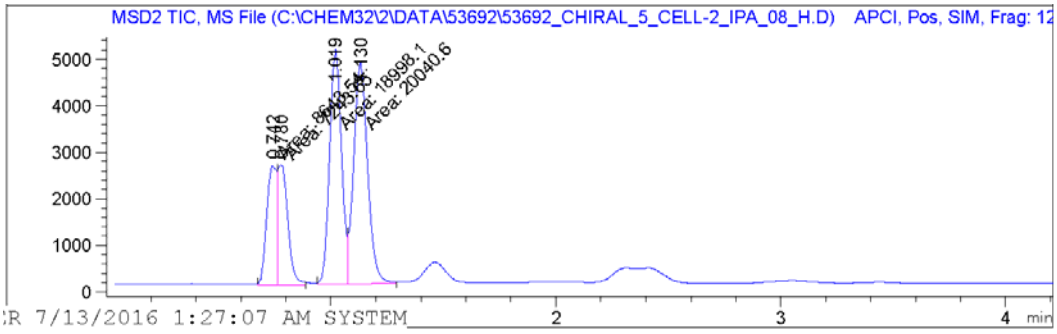


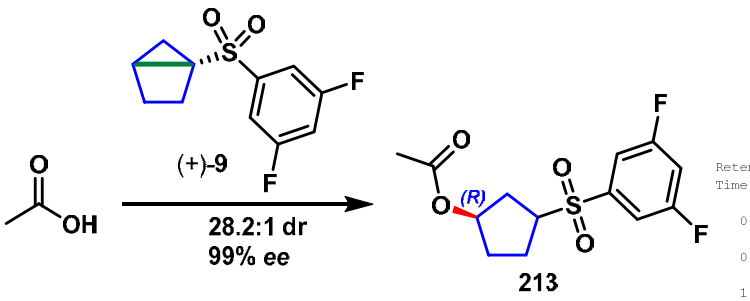
SFC analysis of compound 213

The analysis was performed on a Lux Cellulose-2 4.6 x 100 mm 5µ column using 8% iPrOH, 120 bar, 4 mL/min.

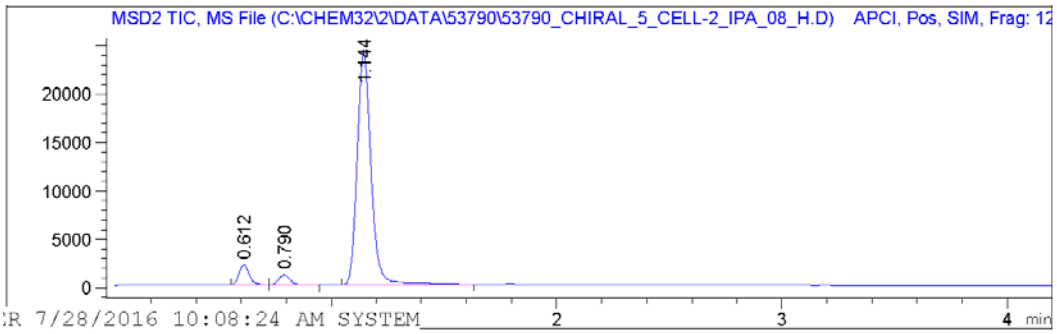


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.742	8644	322.00 I
0.780	7244	322.00 I
1.019	18998	322.00 I
1.130	20041	322.00 I



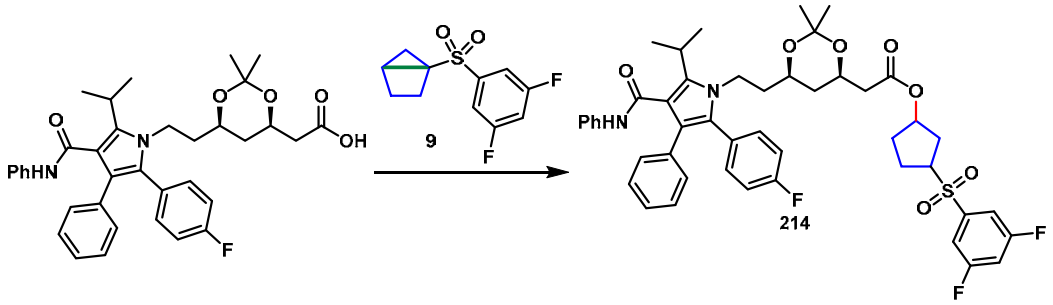


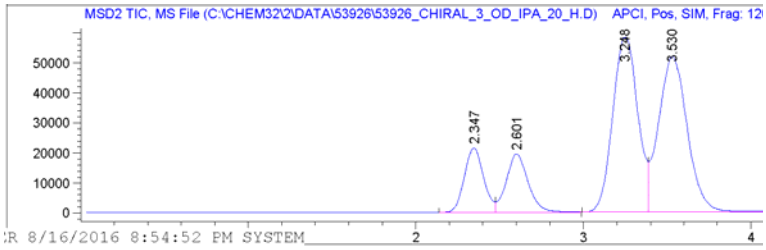
Retention Time (MS)	MS Area	Mol. Weight or Ion
0.612	6544	305.00 I
0.790	3666	305.00 I
1.144	103374	305.00 I



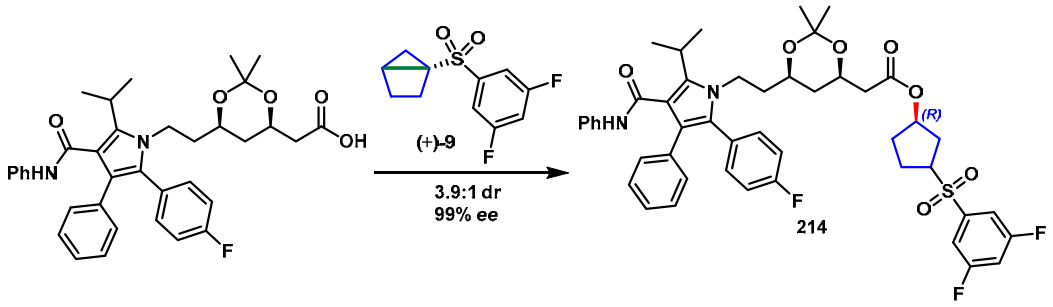
SFC analysis of compound 214

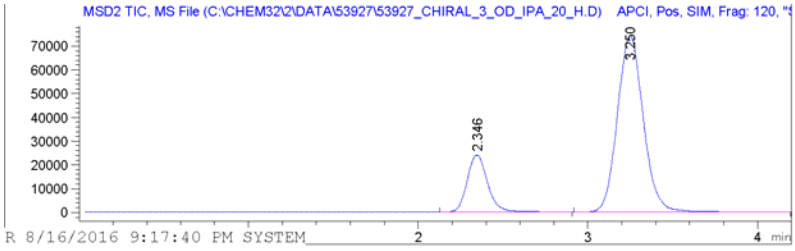
The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column using 20% isopropanol, 120 bar, 4 mL/min.





Retention Time (MS)	MS Area	Mol. Weight or Ion
2.347	170160	843.00 I
2.601	174446	843.00 I
3.248	606464	843.00 I
3.530	617788	843.00 I

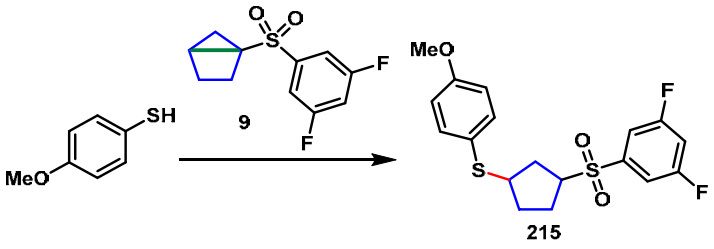




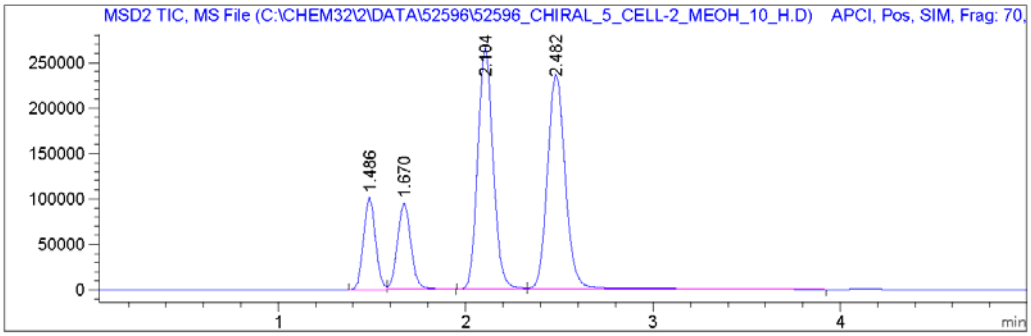
Retention Time (MS)	MS Area	Mol. Weight or Ion
2.346	199022	843.00 I
3.250	783306	843.00 I

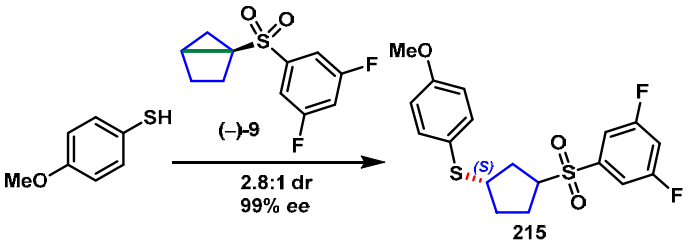
SFC analysis of compound 215

The analysis was performed on a Lux Cellulose-2 4.6 x 100 mm 3µ column using 10% MeOH, 120 bar, 4 mL/min.

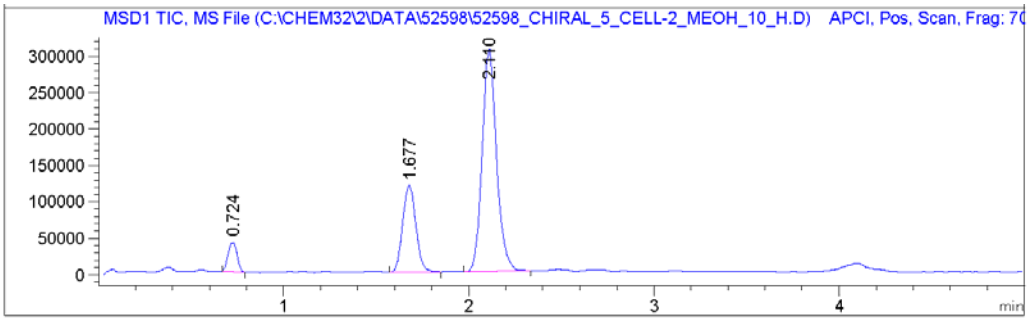


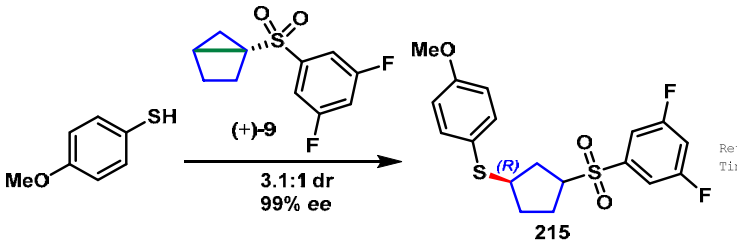
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.486	446974	385.00 I
1.670	468041	385.00 I
2.104	1507033	385.00 I
2.482	1571897	385.00 I



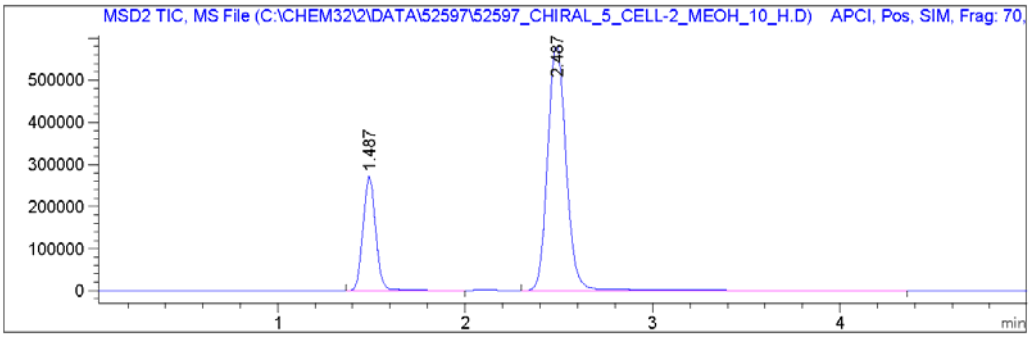


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.724	134930	147.00 I
1.677	587639	386.80 I 385.85 I 384.80 I
2.110	1639907	386.80 I 385.85 I 384.90 I



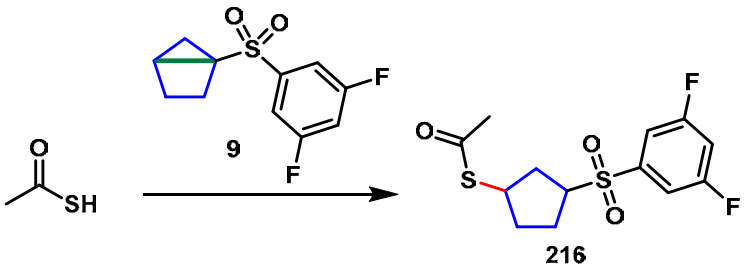


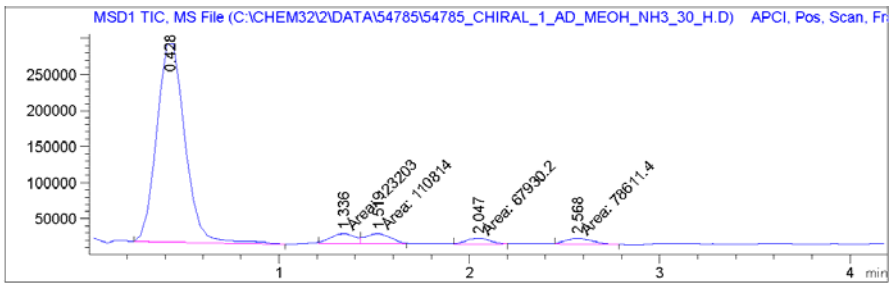
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.487	1273725	385.00 I
2.487	4001142	385.00 I



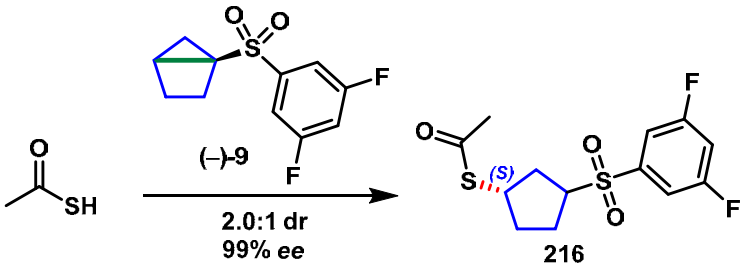
SFC analysis of compound 216

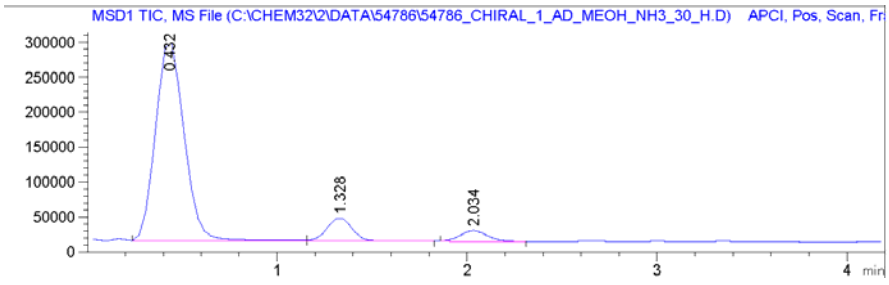
The analysis was performed on a Chiralpak AD-3 4.6x100mm column, 30% MeOH+NH_3, 120bar, 4mL/min.





Retention Time (MS)	MS Area	Mol. Weight or Ion
0.428	2840464	147.10 I 130.20 I 74.10 I
1.336	123203	339.10 I 338.10 I 87.10 I 74.10 I 73.10 I
1.519	110814	339.10 I 338.10 I 87.10 I 74.10 I 73.10 I
2.047	67930	338.10 I 87.10 I 74.10 I 73.15 I
2.568	78611	338.10 I 87.10 I 74.10 I 73.10 I

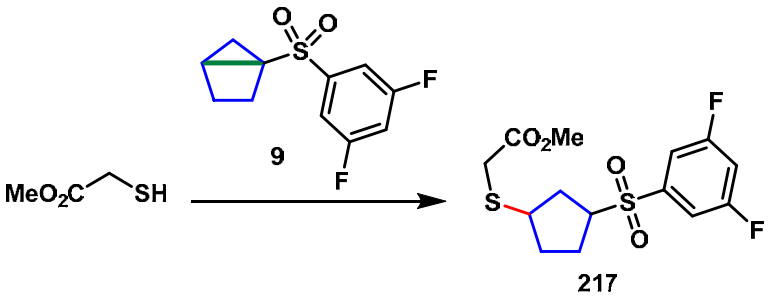




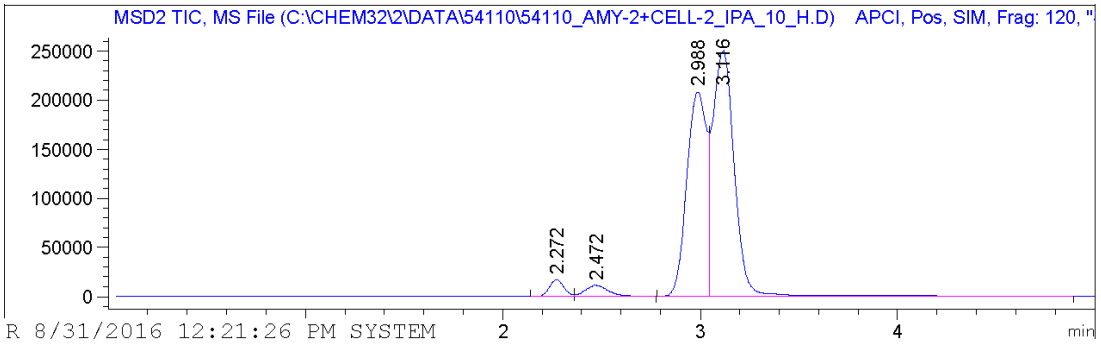
Retention Time (MS)	MS Area	Mol. Weight or Ion
0.432	2983497	147.10 I 130.20 I 102.10 I 74.10 I
1.328	307409	340.10 I 339.10 I 338.10 I 87.10 I
2.034	152127	340.05 I 339.00 I 338.10 I 87.10 I 74.10 I 73.10 I

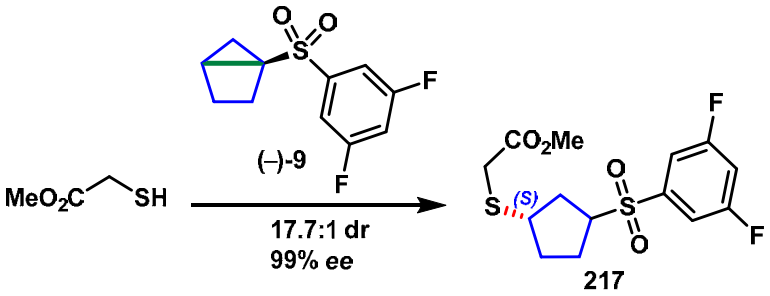
SFC analysis of compound 217

The analysis was performed on Lux Amylose-2 and Cellulose-2 4.6 x 100 mm 3µ columns using 10% IPA, 120 bar, 4 mL/min.

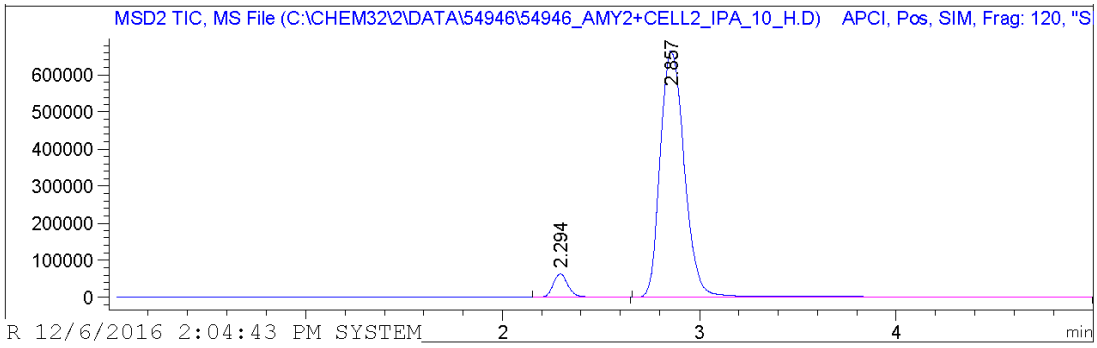


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.272	85026	351.00 I
2.472	89876	351.00 I
2.988	1429999	351.00 I
3.116	1918129	351.00 I



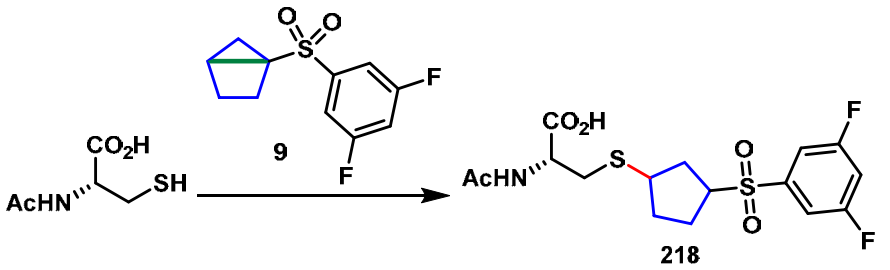


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.294	322910	351.00 I
2.857	5709633	351.00 I

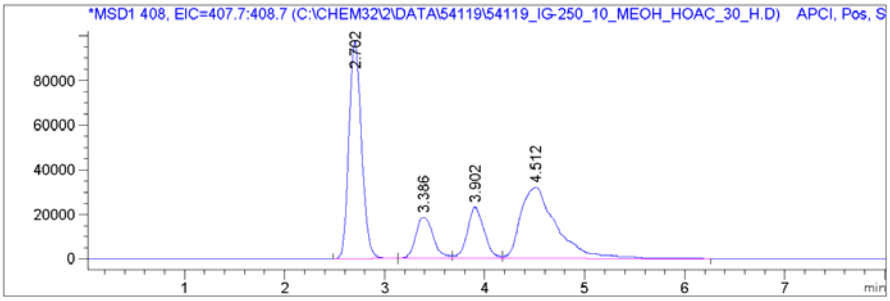


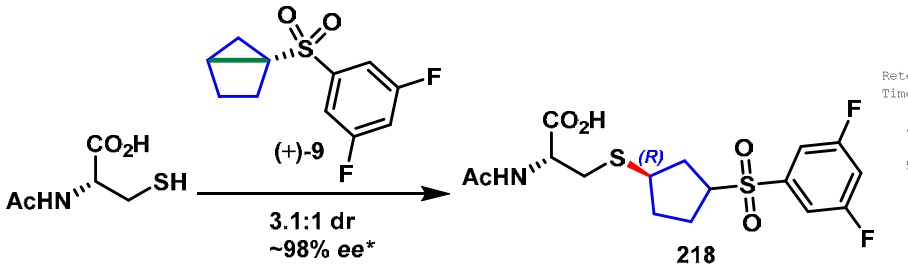
SFC analysis of compound 218

The analysis was performed on a Chiralpak IG-H 4.6 x 250 mm 5µ column using 30% MeOH + 0.05% HOAc, 120 bar, 4 mL/min.

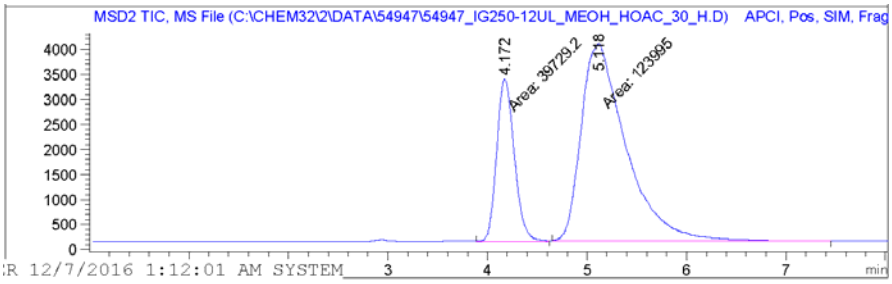


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.897	223941	519.05 I
		447.10 I
		446.10 I
		445.10 I
		373.00 I
		372.10 I
		371.05 I
		239.05 I
		238.10 I
		237.10 I
		195.10 I
1.245	1528083	147.10 I
2.704	1280442	410.00 I
		409.05 I
		408.05 I
3.380	334963	410.05 I
		409.00 I
		408.10 I
3.903	368516	410.00 I
		409.10 I
		408.05 I
4.517	1132010	410.00 I
		409.05 I
		408.10 I





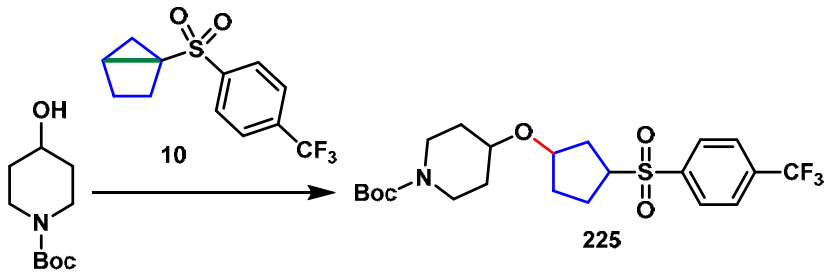
Retention Time (MS)	MS Area	Mol. Weight or Ion
4.172	39729	408.00 I
5.118	123995	408.00 I



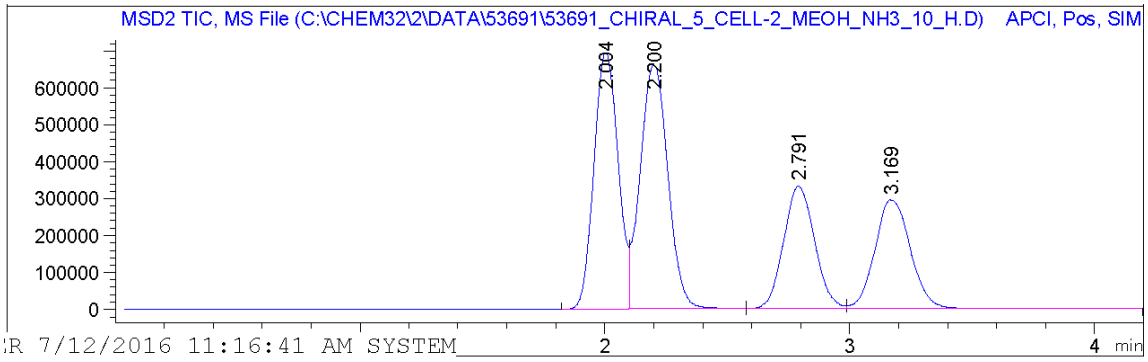
Note. For the reaction above, the enantiopurity of **(+)-9** was 98% *ee* (*).

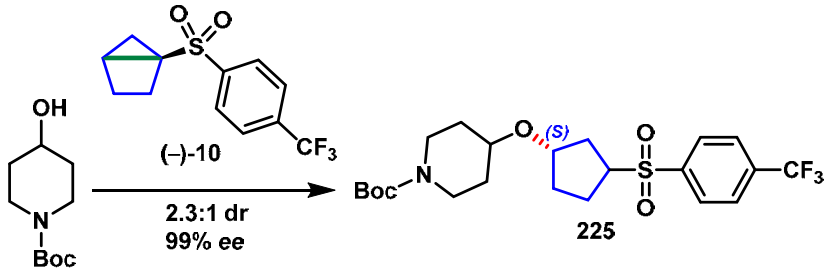
SFC analysis of compound 225

The analysis was performed on a Lux Cellulose-2 4.6 x 100 mm 3µ column
10% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

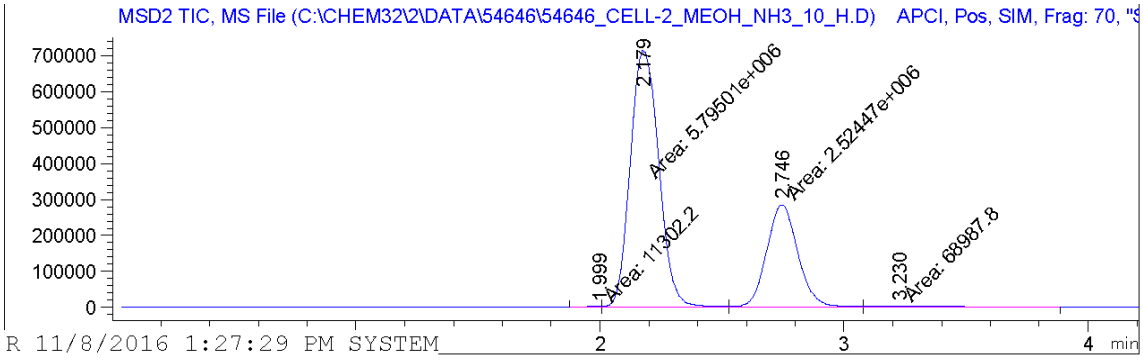


Retention Time (MS)	MS Area	Mol. Weight or Ion
2.004	4754527	378.00 I
2.200	5190905	378.00 I
2.791	2885570	378.00 I
3.169	2949849	378.00 I



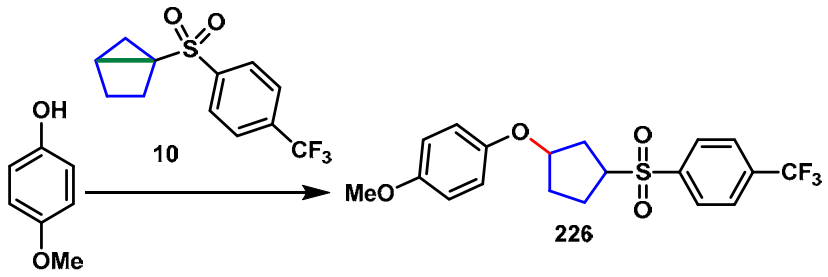


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.999	11302	378.00 I
2.179	5795006	378.00 I
2.746	2524472	378.00 I
3.230	68988	378.00 I

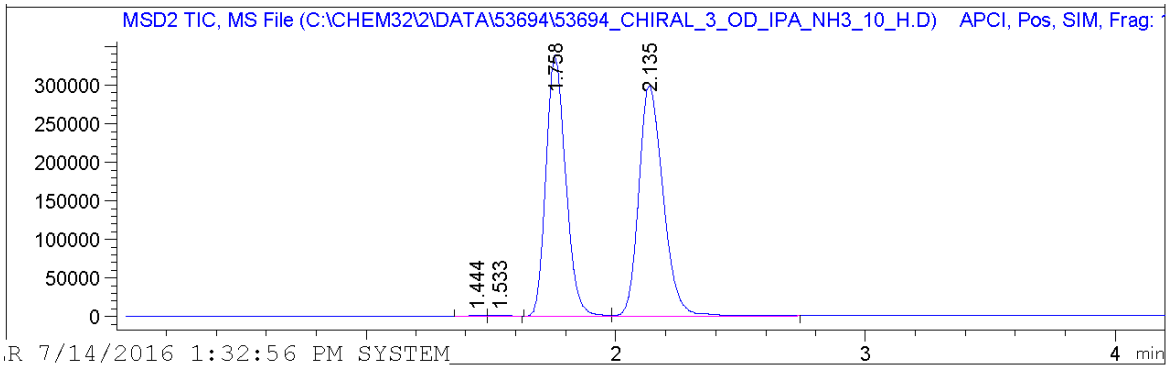


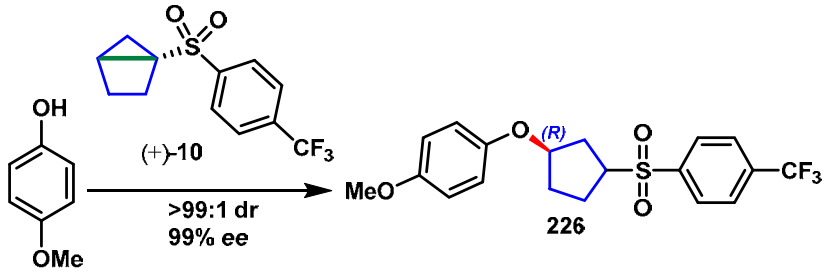
SFC analysis of compound 226

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column
10% *i*PrOH with 10mM NH_3, 120 bar, 4 mL/min.

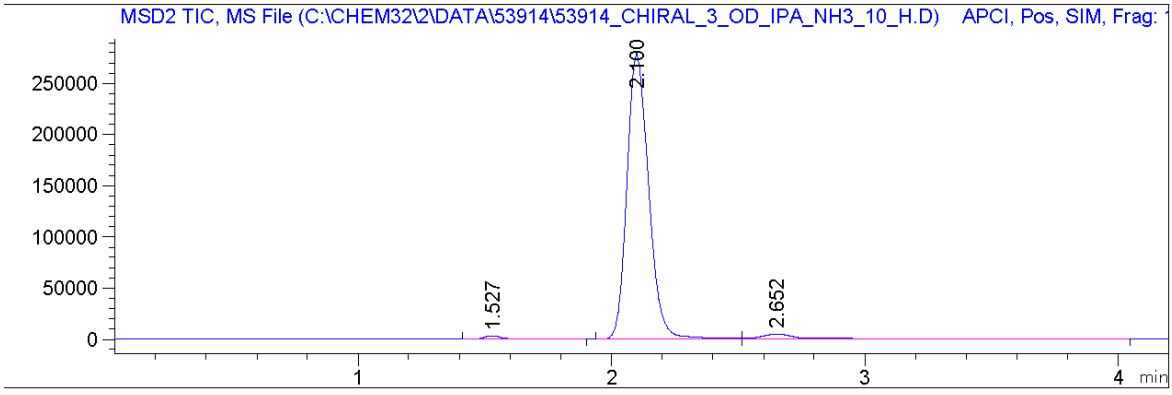


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.444	5914	401.00 I
1.533	8297	401.00 I
1.758	1831402	401.00 I
2.135	2023897	401.00 I



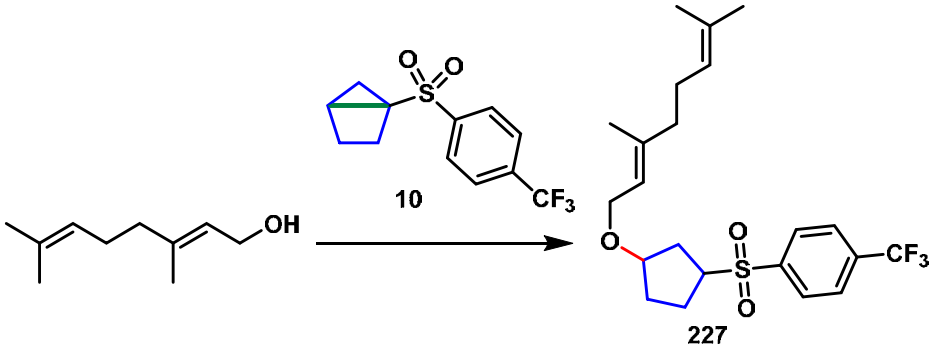


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.527	14170	401.00 I
2.100	1642508	401.00 I
2.652	52397	401.00 I

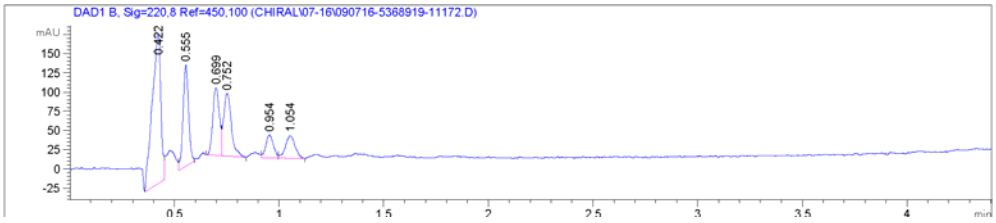


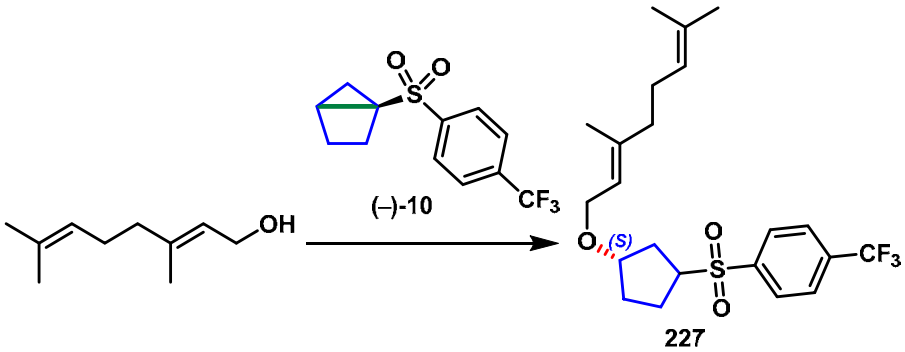
SFC analysis of compound 227

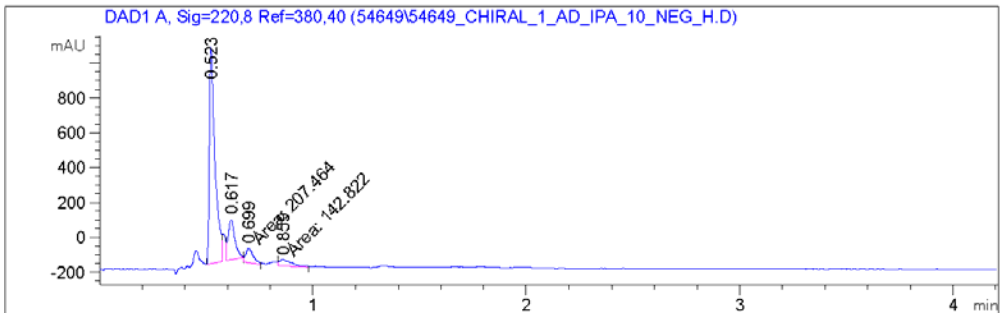
The analysis was performed on a Lux Amylose-2 3µ 4.6 x 100mm column using 10-60% isopropanol at 120 bar, 4.0 mL/min.



Note: the compound did not ionize very well. The UV chromatograms are included instead. dr not determined.

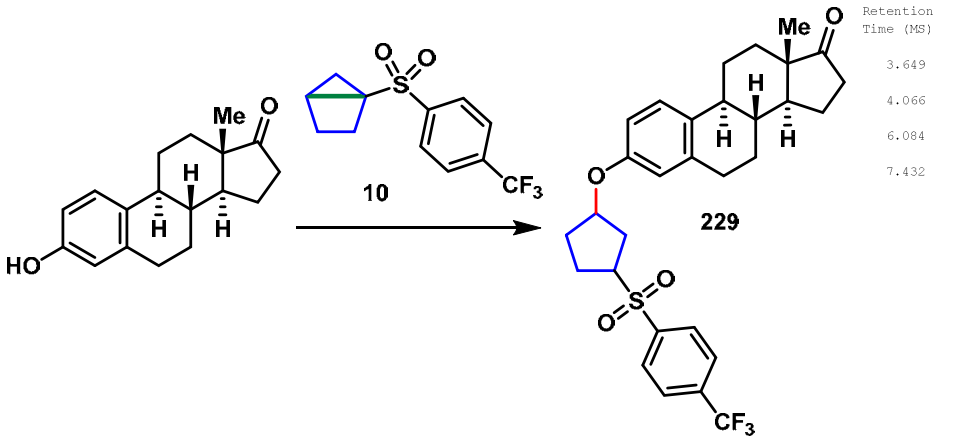




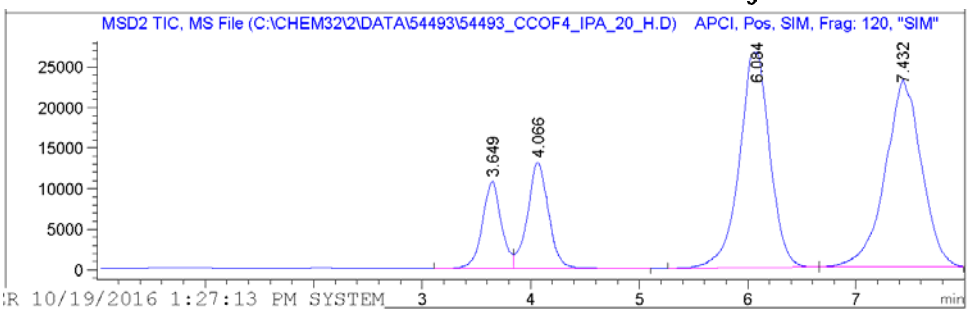


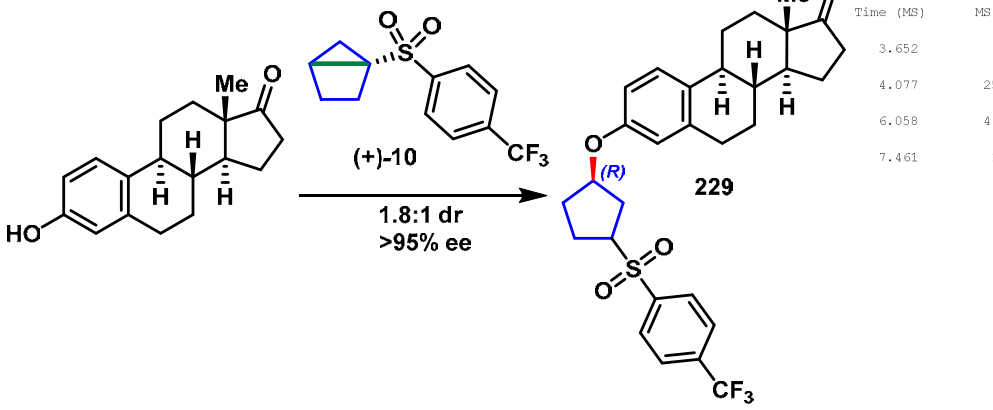
SFC analysis of compound 229

The analysis was performed on Chiralpak AD-H 4.6 x 250 mm 5µ column using 20% IPA, 120 bar, 4 mL/min.

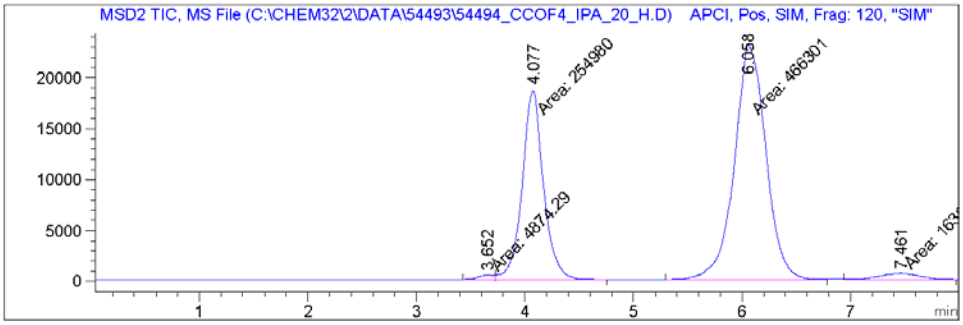


Retention Time (MS)	MS Area	Mol. Weight or Ion
3.649	129915	547.00 I
4.066	173770	547.00 I
6.084	519324	547.00 I
7.432	535463	547.00 I



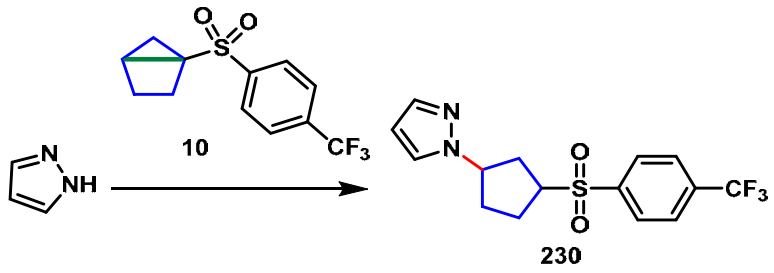


Retention Time (MS)	MS Area	Mol. Weight or Ion
3.652	4874	
4.077	254980	547.00 I
6.058	466301	547.00 I
7.461	16368	

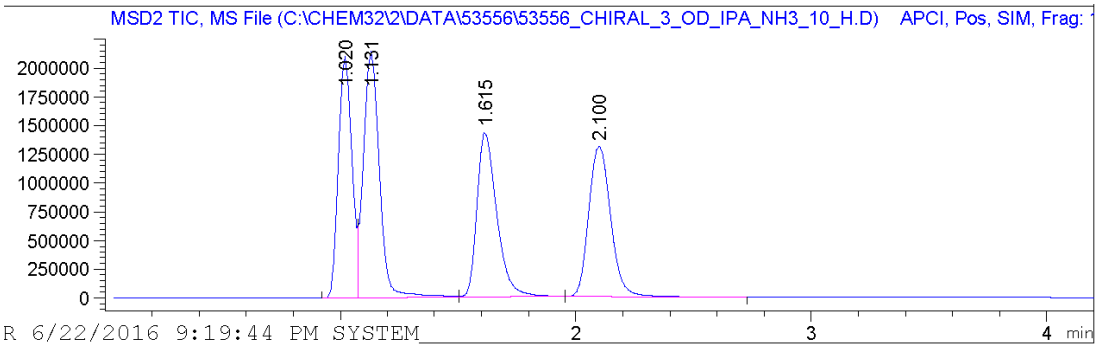

MSD2 TIC, MS File (C:\CHEM32\2\DATA\54493\54494_CCOF4_IPA_20_H.D) APCI, Pos, SIM, Frag: 120, "SIM"
20000
15000
10000
5000
0
1
2
3
4
5
6
7
min
3.652
Area: 4874.29
4.077
Area: 254980
6.058
Area: 466301
7.461

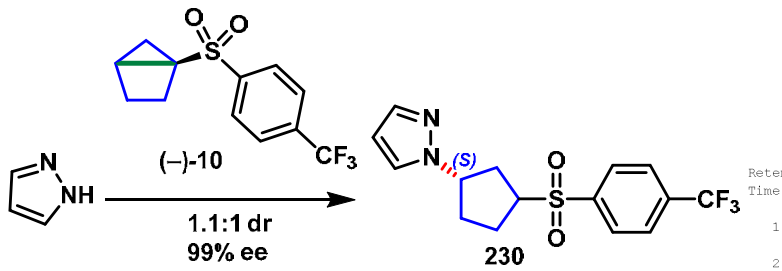
SFC analysis of compound 230

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column
10% *i*PrOH with 10mM NH_3, 120 bar, 4 mL/min.

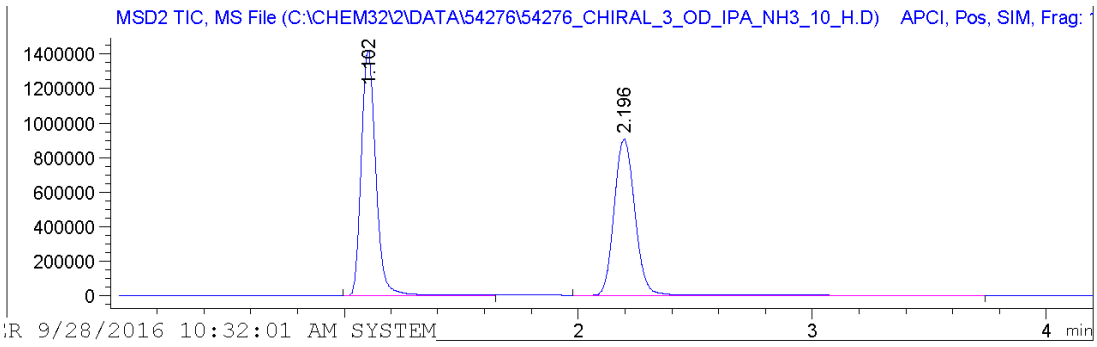


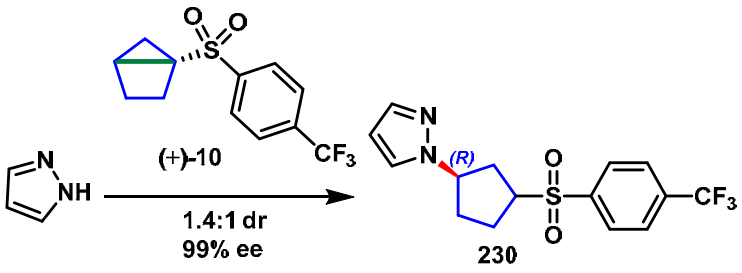
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.020	8337801	345.00 I
1.131	10176622	345.00 I
1.615	8335638	345.00 I
2.100	8435295	345.00 I



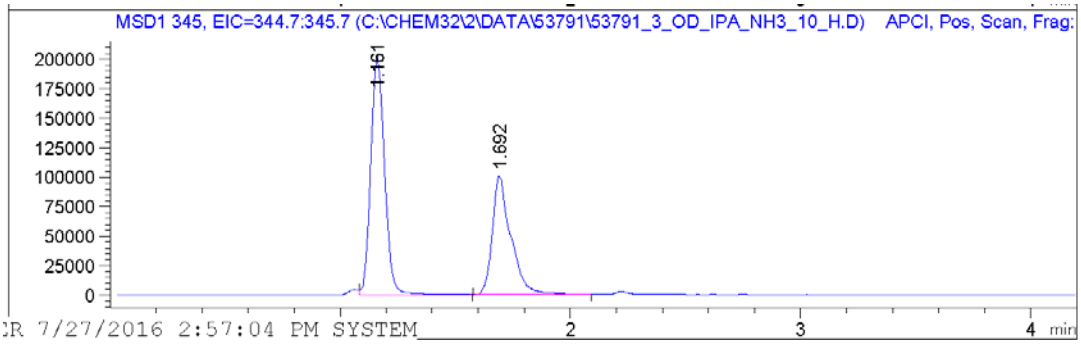


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.102	6188478	345.00 I
2.196	5702225	345.00 I



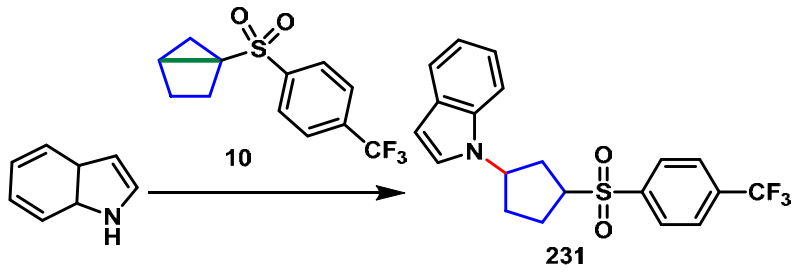


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.161	1041526	346.00 I 345.05 I
1.692	748407	346.05 I 345.00 I

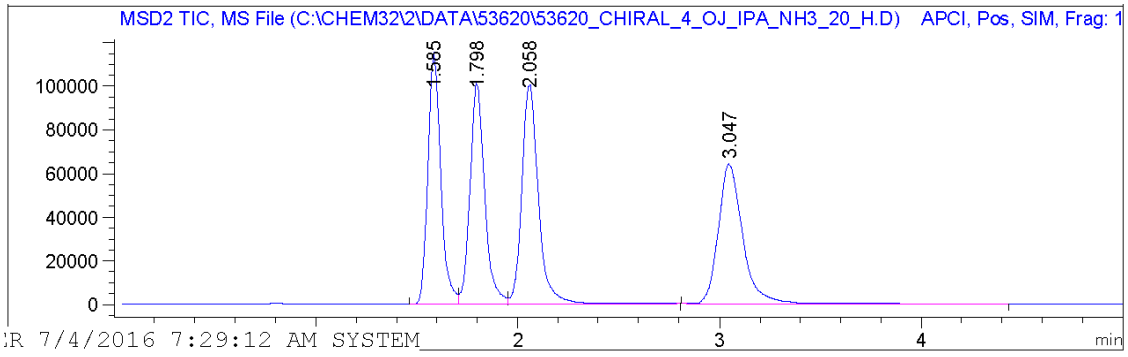


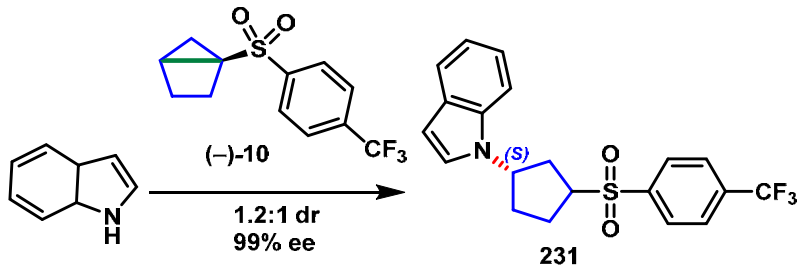
SFC analysis of compound 231

The analysis was performed on a Chiralcel OJ-3 4.6 x 100 mm 3µ column using 20% IPA + 10mM NH_3, 120 bar, 4 mL/min.

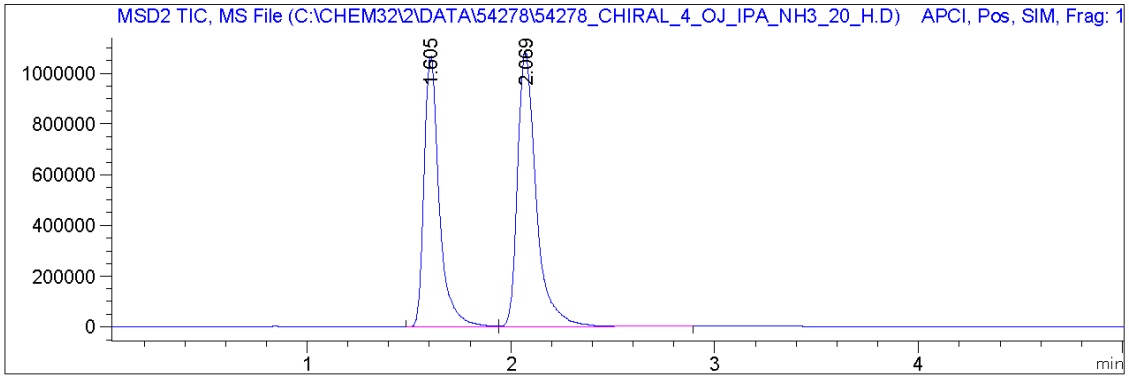


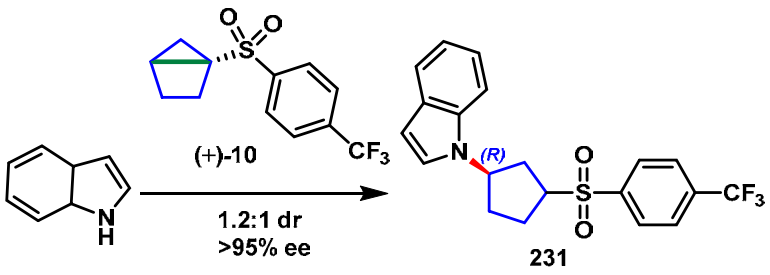
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.585	509615	394.00 I
1.798	511441	394.00 I
2.058	568902	394.00 I
3.047	533545	394.00 I



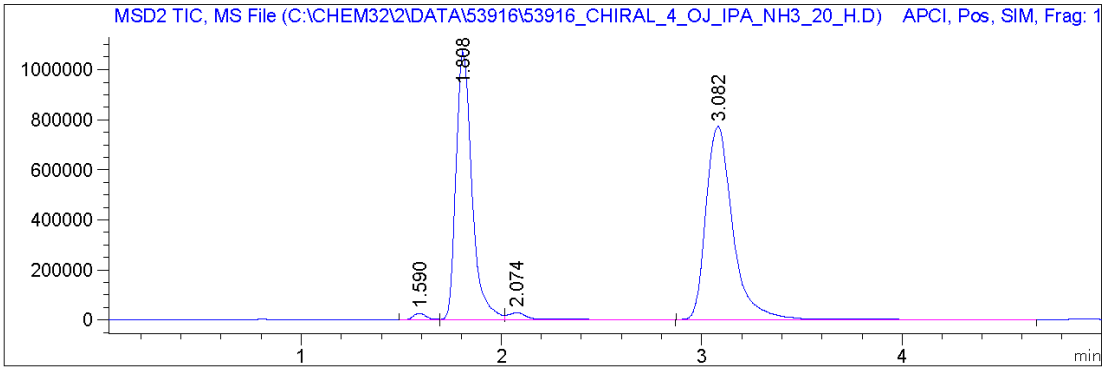


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.605	5548294	394.00 I
2.069	6910095	394.00 I



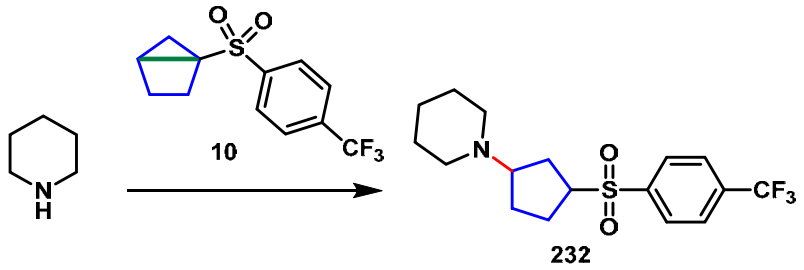


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.590	114540	394.00 I
1.808	5894771	394.00 I
2.074	210959	394.00 I
3.082	7172063	394.00 I

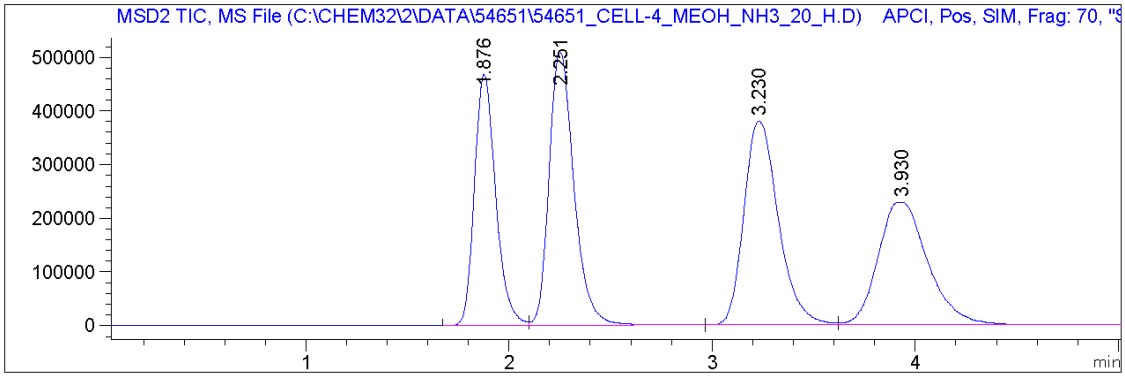


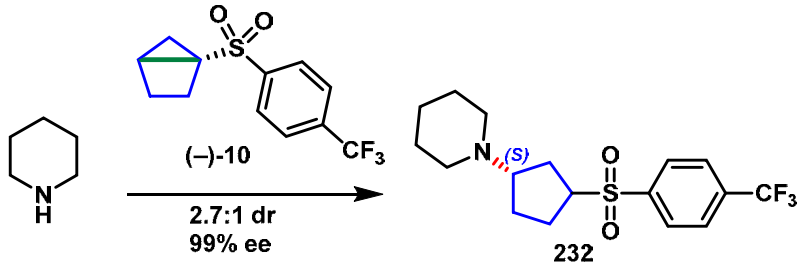
SFC analysis of compound 232

The analysis was performed on a Lux Cellulose-4 4.6 x 100 mm 3µ column using 20% MeOH + 10mM NH_3, 120 bar, 4 mL/min.

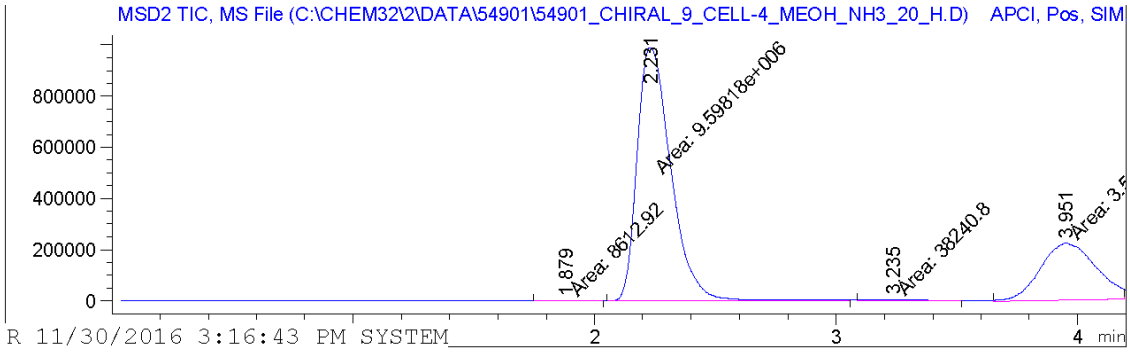


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.876	3393212	362.00 I
2.251	4320458	362.00 I
3.230	4452393	362.00 I
3.930	3875122	362.00 I



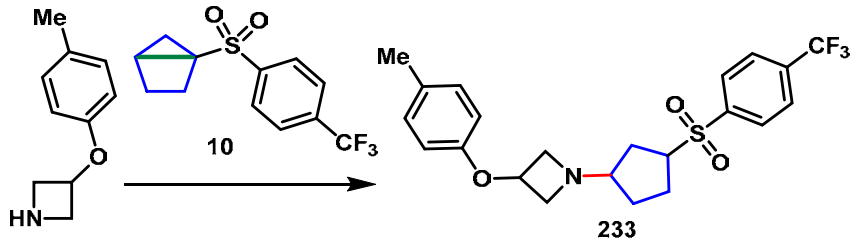


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.879	8613	362.00 I
2.231	9598176	362.00 I
3.235	38241	362.00 I
3.951	3533795	362.00 I

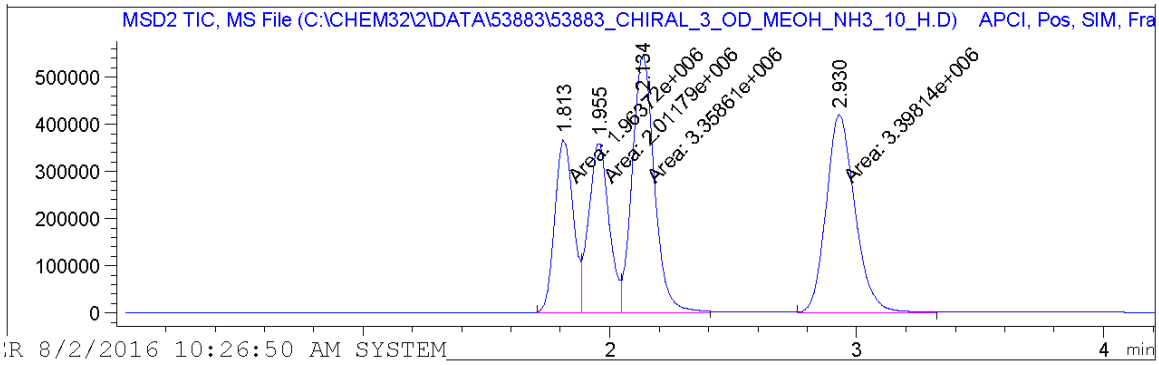


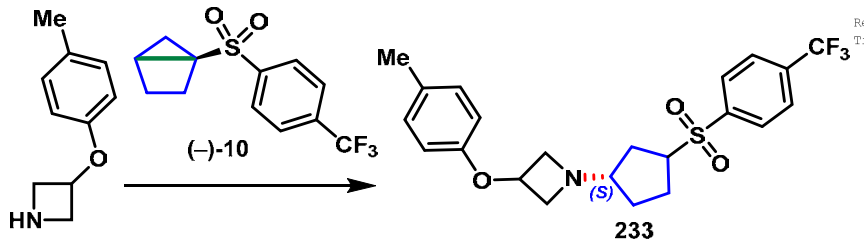
SFC analysis of compound 233

The analysis was performed on a Lux Cellulose-1 4.6 x 100 mm 3µ column using 10% MeOH + 10mM NH_3, 120 bar, 4 mL/min

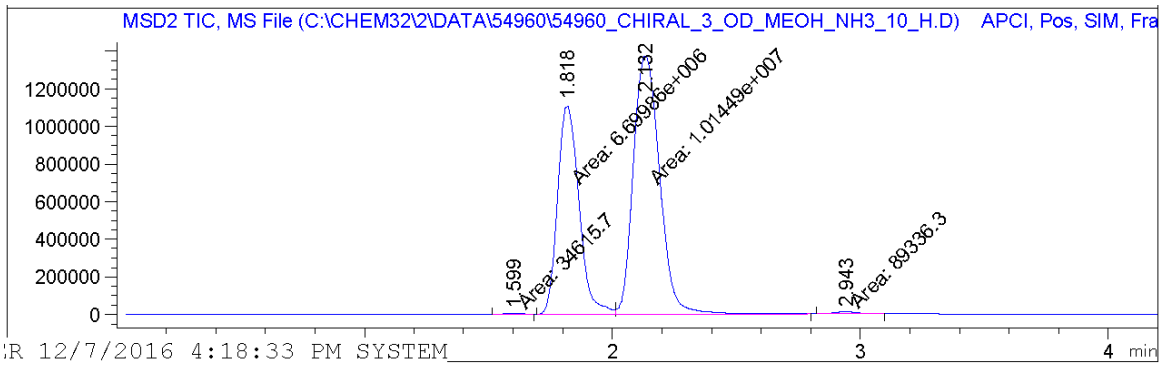


Retention Time (MS)	MS Area	Mol. Weight or Ion
1.813	1963719	440.00 I
1.955	2011791	440.00 I
2.134	3358611	440.00 I
2.930	3398143	440.00 I





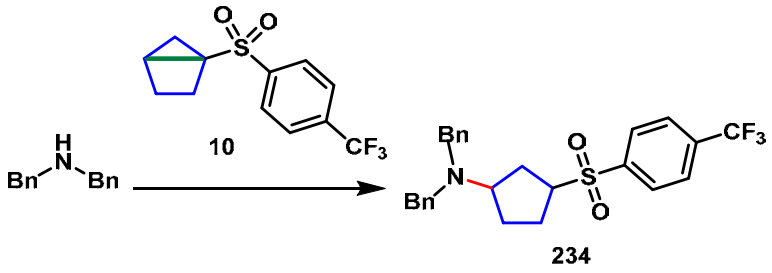
Retention Time (MS)	MS Area	Mol. Weight or Ion
1.599	34616	440.00 I
1.818	6699856	440.00 I
2.132	10144890	440.00 I
2.943	89336	440.00 I



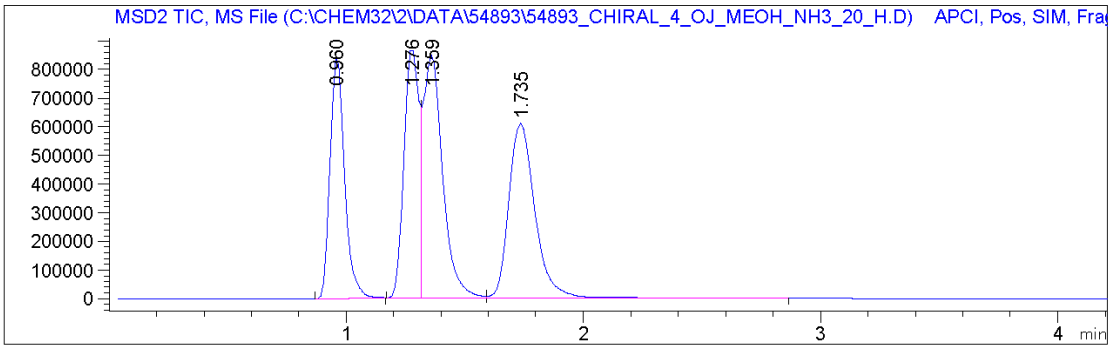
Note: the above reaction was run with 98% *ee* (–)-**10**.

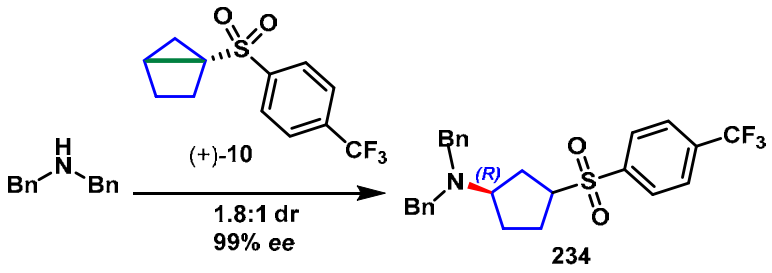
SFC analysis of compound 234

The analysis was performed on a Chiralcel OJ-3 4.6x100mm column using 20% MeOH+NH_3, 120bar, 4mL/min.

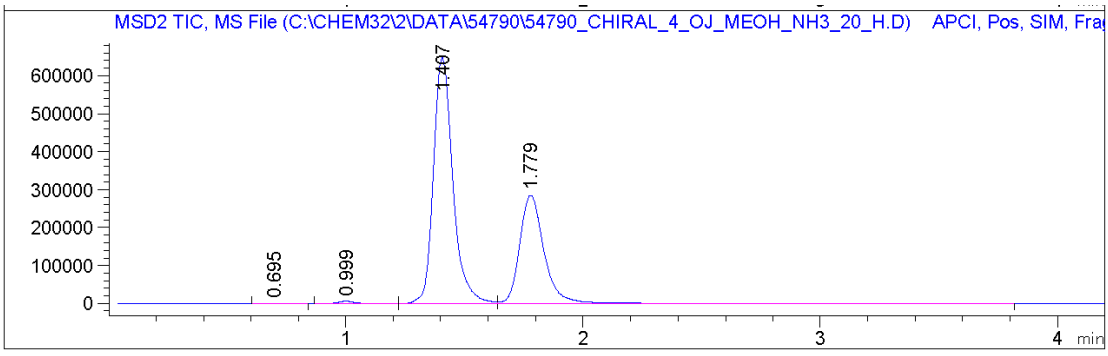


Retention Time (MS)	MS Area	Mol. Weight or Ion
0.960	3565748	474.00 I
1.276	3858430	474.00 I
1.359	4769592	474.00 I
1.735	4628967	474.00 I





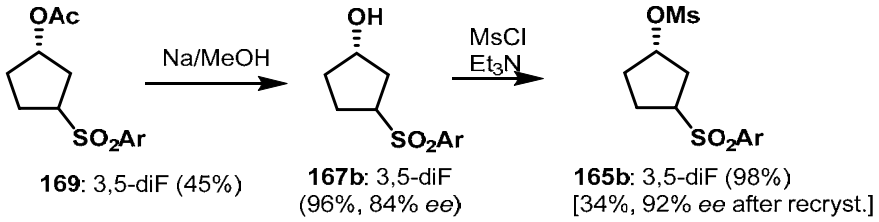
Retention Time (MS)	MS Area	Mol. Weight or Ion
0.695	2074	
0.999	27442	474.00 I
1.407	3665734	474.00 I
1.779	2033836	474.00 I



Determination of *ee* of Key Intermediates

Recrystallization of Mesylate 165b

The *ee* of the acetate **169** was determined on the corresponding mesylate **165b** after deacetylation and mesylation. The HPLC analysis was performed on a ChiralPak® AD-H column (4.6 mm x 250 mmL) using 30% IPA in hexanes as eluent.

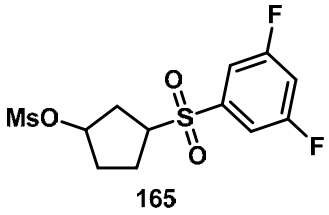


169: 3,5-diF (45%)

167b: 3,5-diF (96%, 84% *ee*)

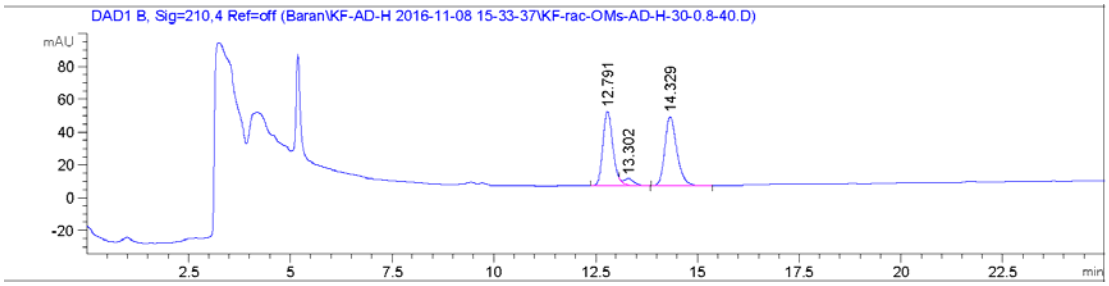
165b: 3,5-diF (98%) [34%, 92% *ee* after recryst.]

HPLC analysis of *rac*-165:



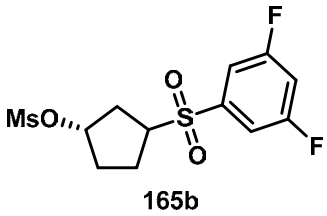
165

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.791	BV R	0.2620	779.41608	45.45605	45.4571
2	13.302	VB E	0.2502	65.71028	3.94726	3.8324
3	14.329	BB	0.3115	869.49414	42.35877	50.7106



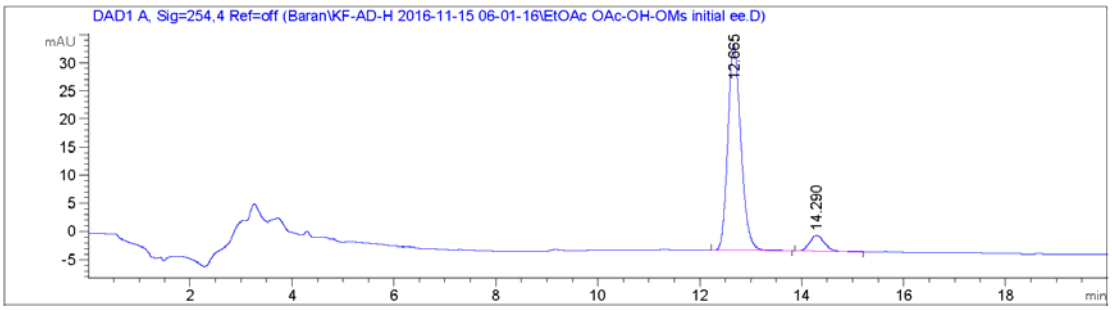
Note. The peak at 13.30 min corresponds to residual minor diastereoisomer.

Initial *ee* before recrystallization:



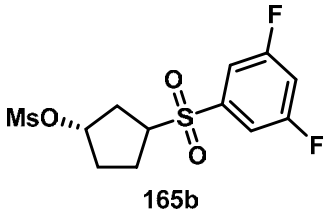
165b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.665	BB	0.2729	7828.49805	441.37332	92.2411
2	14.291	BB	0.3043	658.49725	33.35473	7.7589



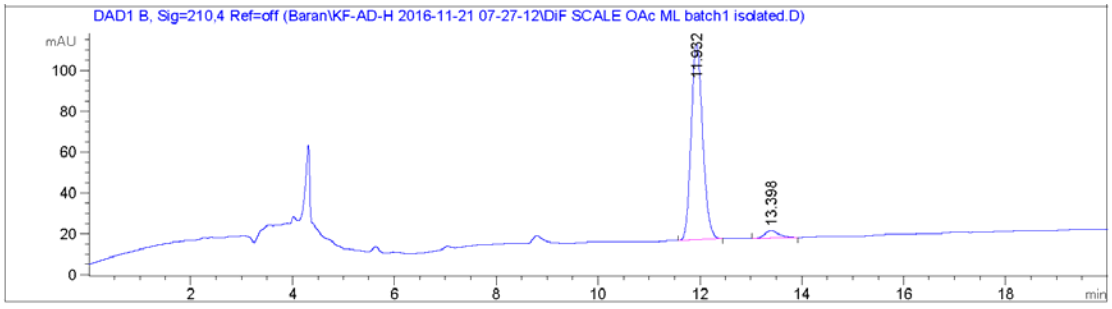
Enantiopurity = 84% *ee*

1st crop (*mother liquor*) after recrystallization at -20 °C:



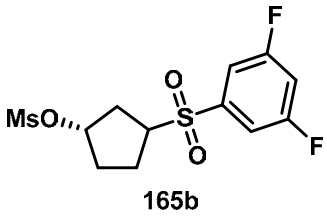
165b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.932	BB	0.2401	1497.18628	95.94070	95.5929
2	13.398	BB	0.2837	69.02518	3.59920	4.4071



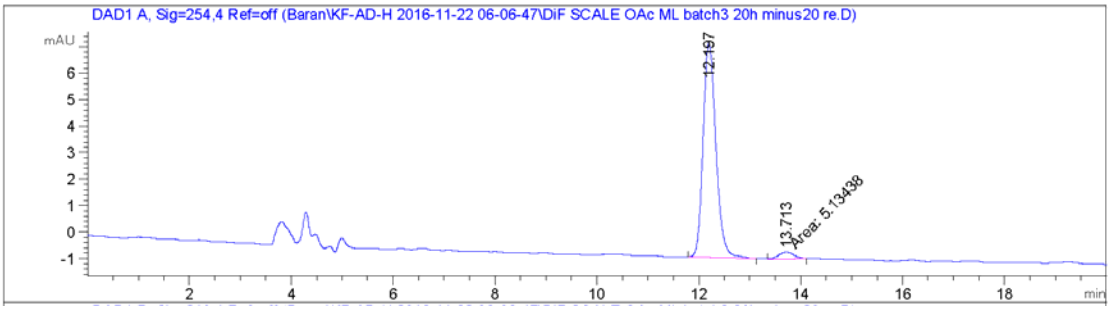
Enantiopurity = 91% *ee*

2nd crop (*mother liquor*) after recrystallization at -20 °C:



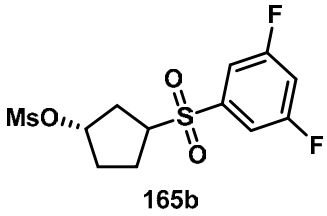
165b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.197	BB	0.2671	141.27025	8.11683	96.4930
2	13.713	MM	0.3338	5.13438	2.56398e-1	3.5070



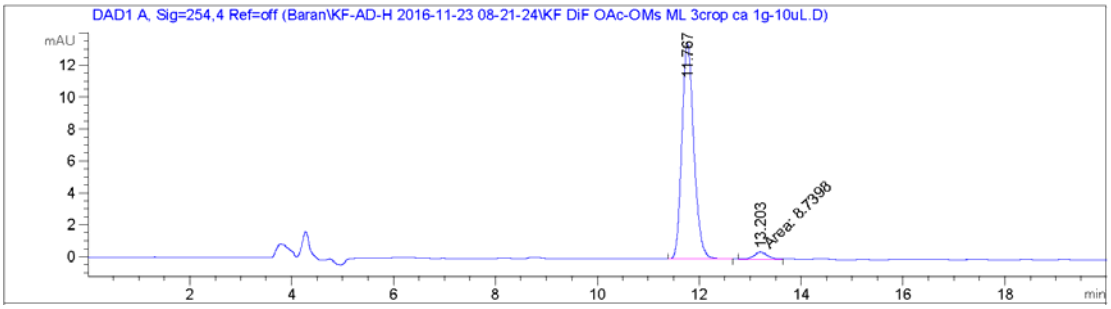
Enantiopurity = 93% *ee*

3rd crop (*mother liquor*) after recrystallization at -20 °C:



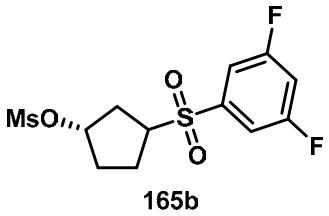
165b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.767	BB	0.2528	221.47522	13.54123	96.2036
2	13.203	MM	0.3251	8.73980	4.48056e-1	3.7964



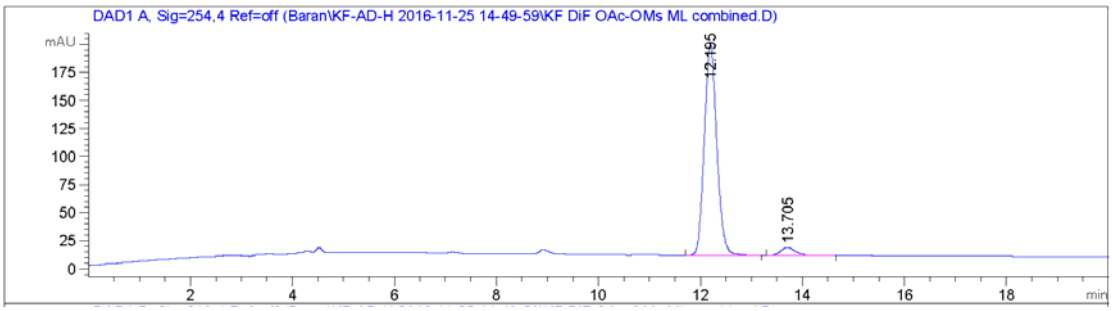
Enantiopurity = 92% *ee*

Combined crops (*mother liquor*) after 3 x recrystallizations at -20 °C:



165b

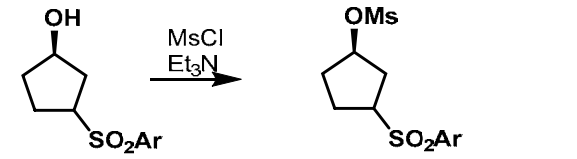
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.195	BB	0.2613	3181.03613	188.11156	95.8055
2	13.705	BB	0.3006	139.27174	7.10901	4.1945



Enantiopurity = 92% *ee*

Recrystallization of Mesylate 165a

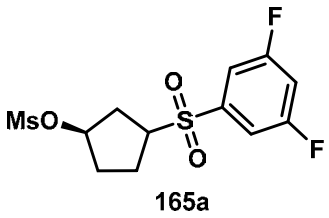
The *ee* of the resolved alcohol **167a** was determined on the corresponding mesylate **165a** after mesylation. The HPLC analysis was performed on a ChiralPak® AD-H column (4.6 mm x 250 mmL) using 30% IPA in hexanes as eluent.



167a: 3,5-diF (81% *ee*)

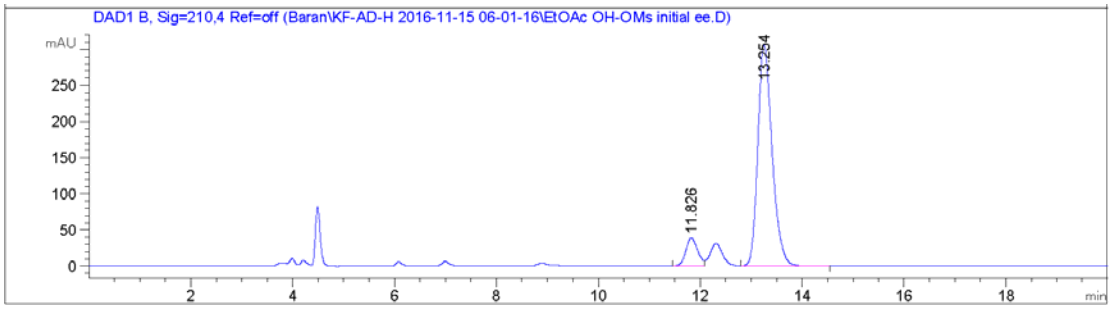
165a: 3,5-diF (94%) [24%, 91% *ee* after recryst.]

Initial *ee* before recrystallization:



165a

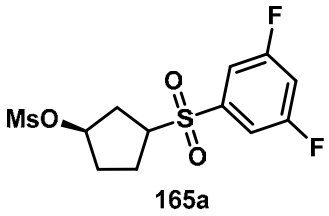
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.826	BV	0.2451	613.49005	38.66628	9.3623
2	13.254	BB	0.2949	5939.25537	305.32437	90.6377



Note: the peak in between 11.83 and 13.25 min corresponds to residual minor diastereoisomer. It can be removed by silica gel chromatography.

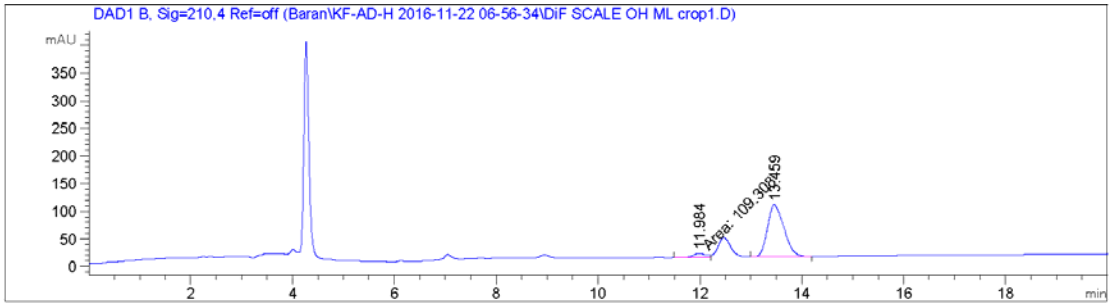
Enantiopurity = 81% *ee*

1st crop (*mother liquor*) after recrystallization at -20 °C:



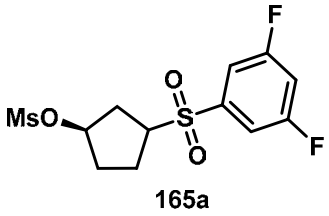
165a

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.984	MF	0.2864	109.30762	6.36016	5.0145
2	13.459	BB	0.3492	2070.52686	93.20806	94.9855



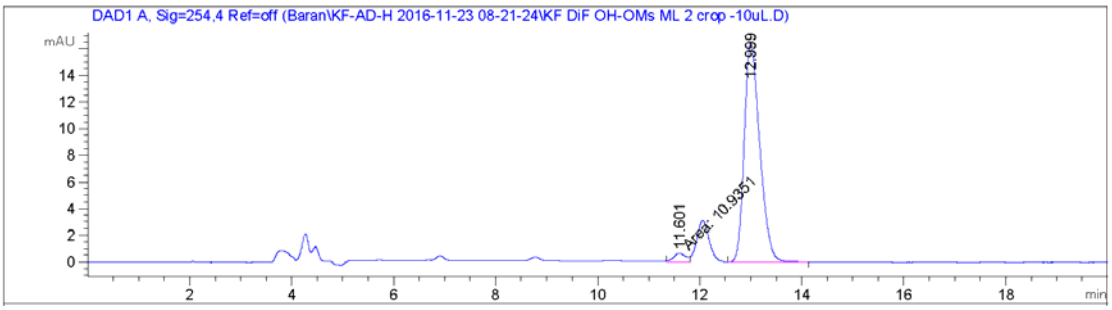
Enantiopurity = 90% *ee*

2nd crop (*mother liquor*) after recrystallization at -20 °C:



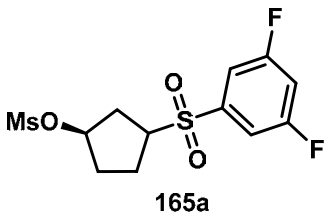
165a

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.601	MF	0.2838	10.93510	6.42295e-1	3.0640
2	12.999	BB	0.3183	345.95108	16.38821	96.9360



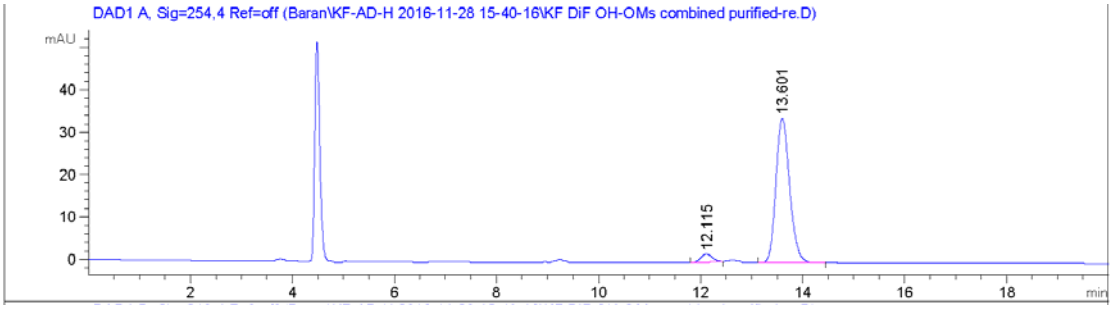
Enantiopurity = 94% *ee*

Combined crops (*mother liquor*) after 2 x recrystallizations at -20 °C and silica gel chromatography:



165a

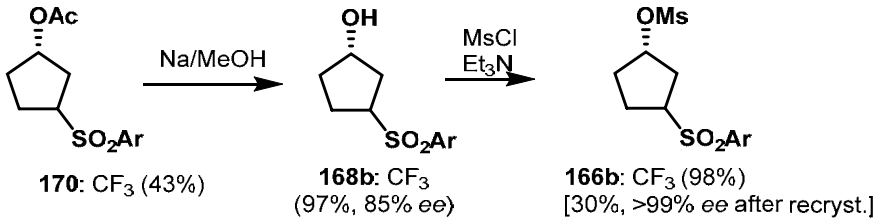
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.115	BB	0.2367	29.05006	1.89683	4.3847
2	13.601	BB	0.2870	633.48187	34.06521	95.6153



Enantiopurity = 91% *ee*

Recrystallization of Mesylate 166b

The *ee* of the acetate **170** was determined on the corresponding mesylate **166b** after deacetylation and mesylation. The HPLC analysis was performed on a ChiralCel® OD-H column (4.6 mm x 250 mmL) using either 30% IPA or 20% IPA in hexanes as eluent.

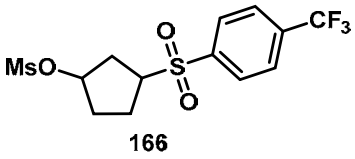


170: CF_3 (43%)

168b: CF_3 (97%, 85% *ee*)

166b: CF_3 (98%) [30%, >99% *ee* after recryst.]

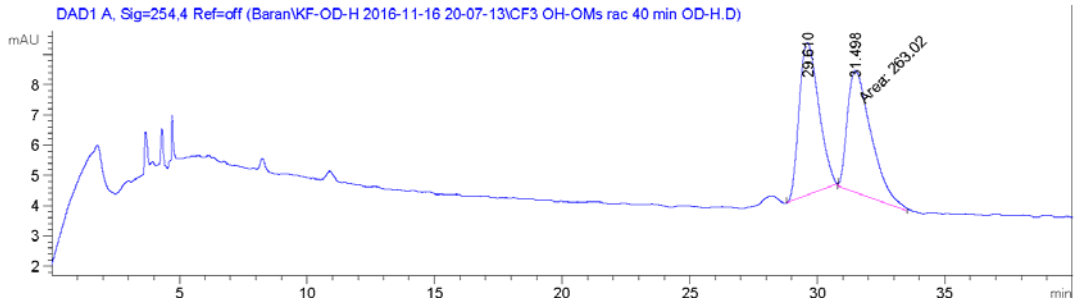
HPLC analysis of *rac*-166:

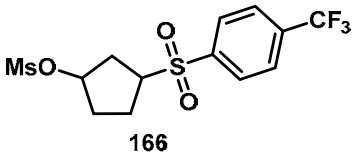


166

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.610	BB	0.7670	269.83298	5.05283	50.6393
2	31.498	MM	1.0884	263.01981	4.02747	49.3607

Eluent: 20% IPA in hexanes

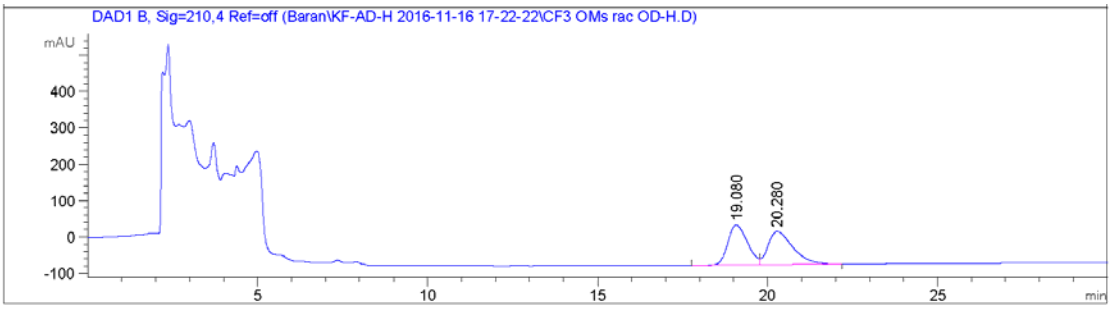




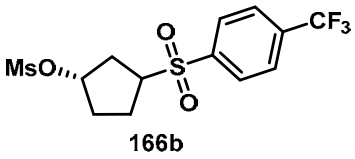
166

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.073	BB	0.5408	217.59219	6.00450	50.3929
2	20.272	BB	0.6404	214.19925	4.69392	49.6071

Eluent: 30% IPA in hexanes



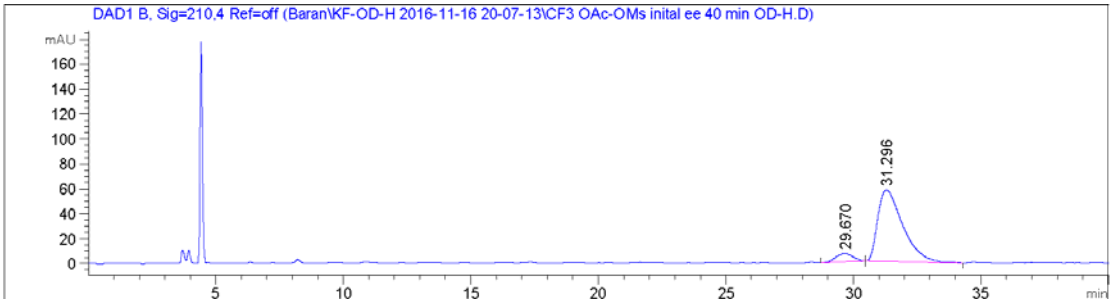
Initial *ee* before recrystallization:



166b

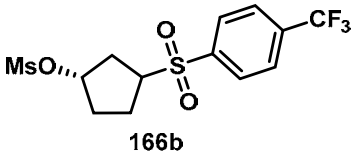
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.670	BB	0.6831	311.84338	6.55436	7.4148
2	31.296	BB	1.0213	3893.82422	57.40979	92.5852

Eluent: 20% IPA in hexanes



Enantiopurity: 85%

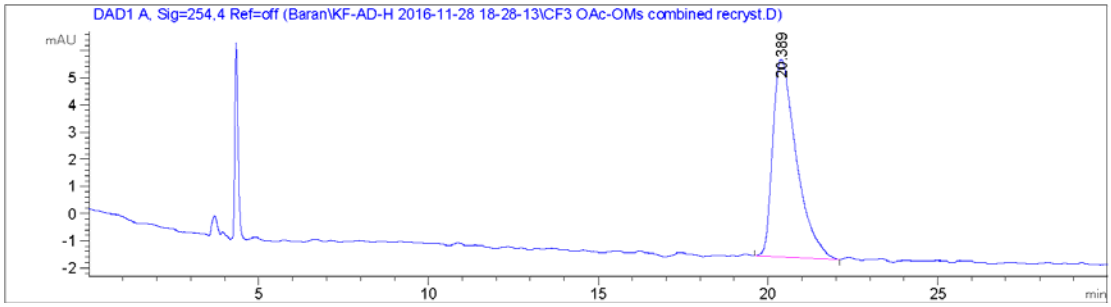
Combined crops (*crystals*) after 3 x recrystallizations at -20 °C:



166b

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.389	BB	0.7047	352.08551	7.27383	100.0000

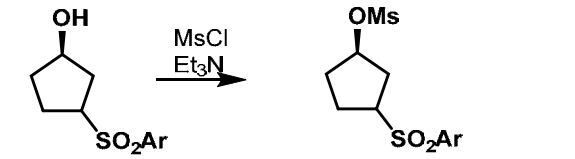
Eluent: 30% IPA in hexanes



Enantiopurity: >99%

Recrystallization of Mesylate 166a

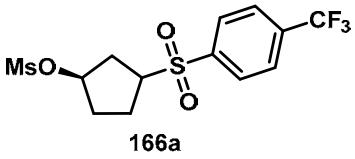
The *ee* of the resolved alcohol **168a** was determined on the corresponding mesylate **166a** after mesylation. The HPLC analysis was performed on a ChiralCel® OD-H column (4.6 mm x 250 mmL) using either 30% IPA or 20% IPA in hexanes as eluent.



168a: CF_3 (52%, 79% *ee*)

166a: CF_3 (97%) [52%, 92% *ee* after recryst.]

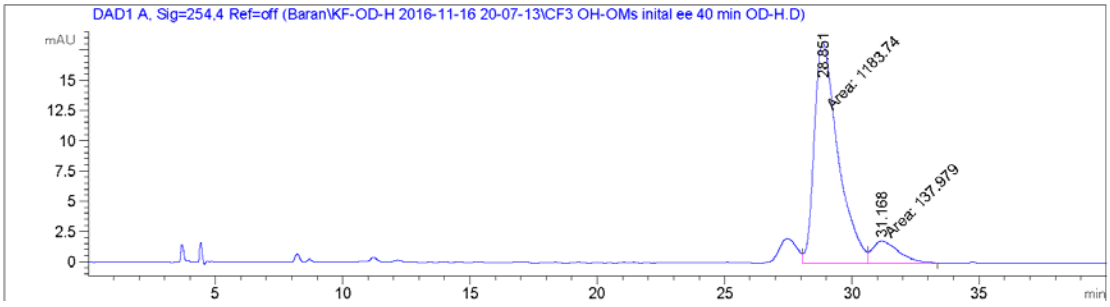
Initial *ee* before recrystallization:



166a

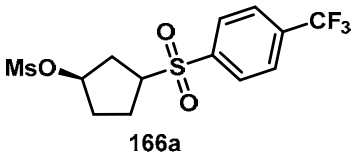
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.851	MF	1.0814	1183.74475	18.24439	89.5607
2	31.168	FM	1.2513	137.97890	1.83778	10.4393

Eluent: 20% IPA in hexanes



Enantiopurity: 79%

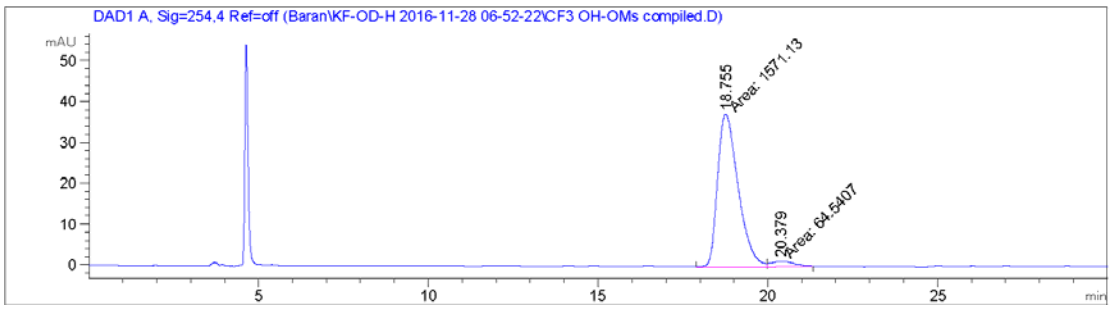
Combined crops (*crystals*) after 3 x recrystallizations at -20 °C:



166a

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.755	MF	0.7018	1571.12622	37.31288	96.0542
2	20.379	FM	0.8231	64.54067	1.30693	3.9458

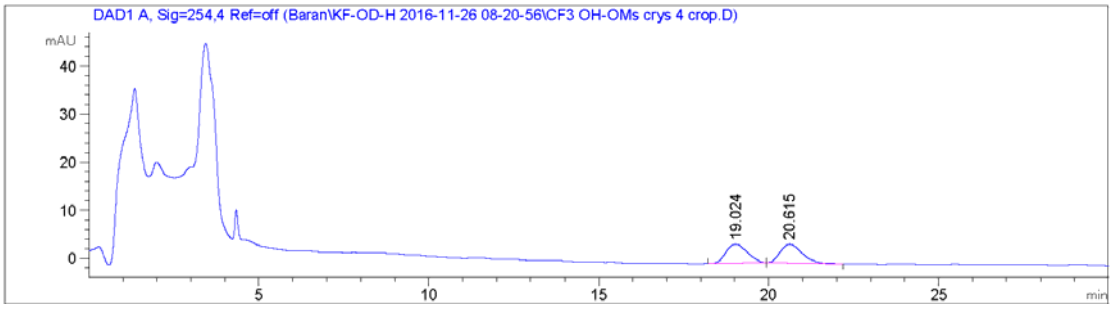
Eluent: 30% IPA in hexanes



Enantiopurity: 92%

Note: A further attempt to increase the yield by recrystallization of combined mother liquors after the third recrystallization resulted in racemic crystals.

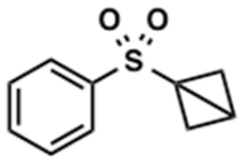
Eluent: 30% IPA in hexanes



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.024	BB	0.6581	174.08884	3.98146	49.4937
2	20.615	BB	0.6639	177.65074	3.95636	50.5063

Enantiopurity: 0%

Spectra


O
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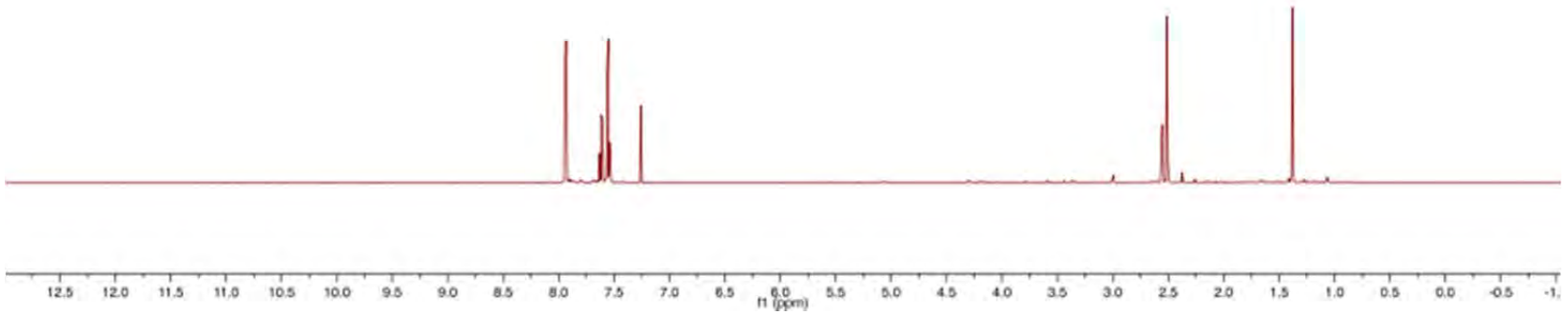
S

8a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f1 (ppm)
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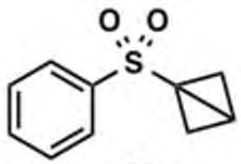
O
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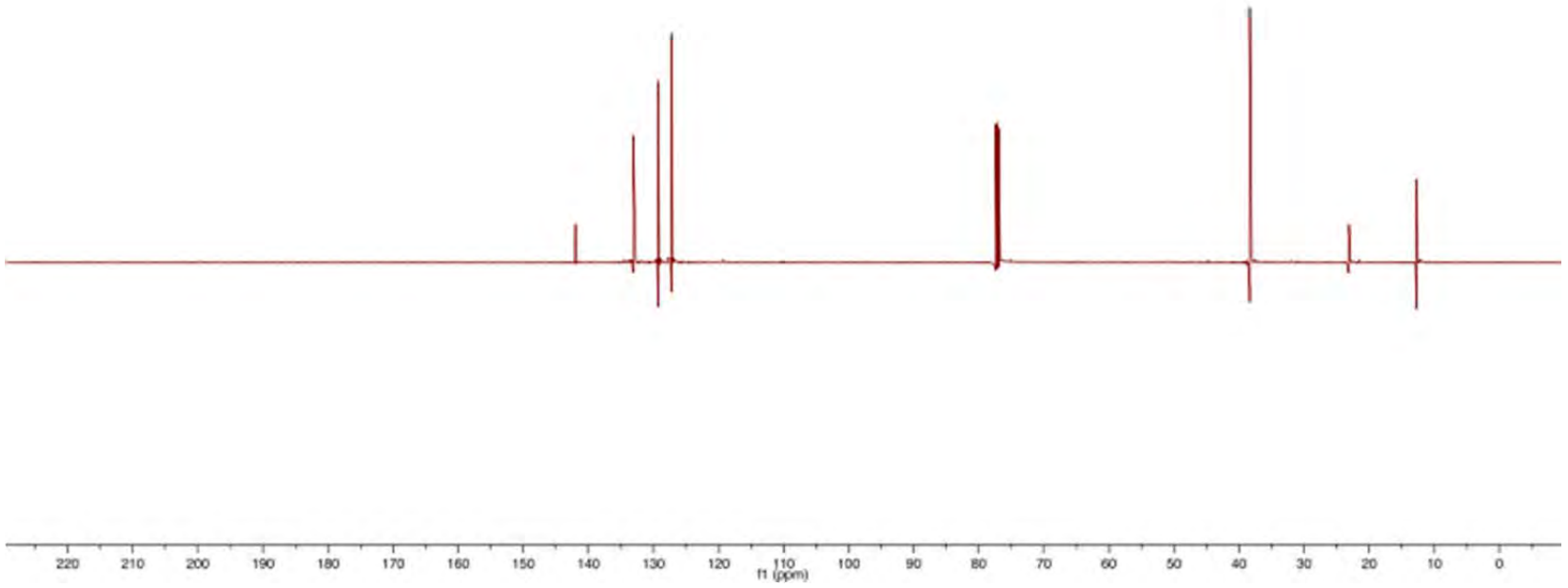
8a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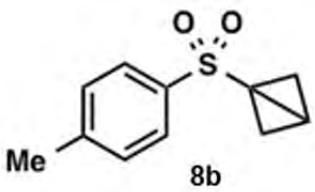
O
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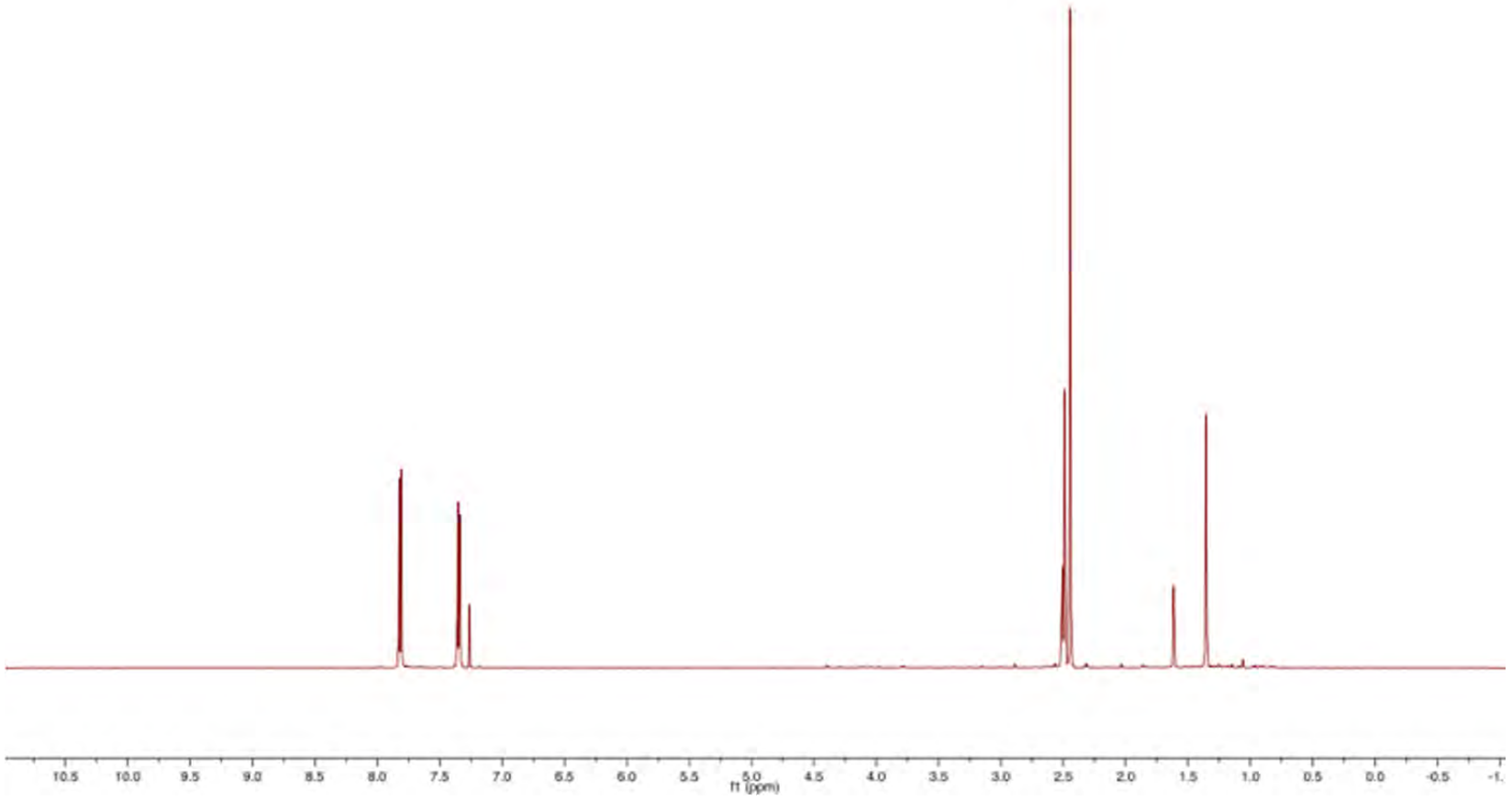
8b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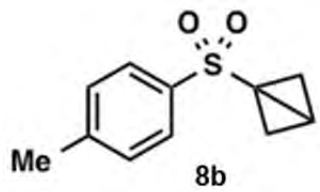
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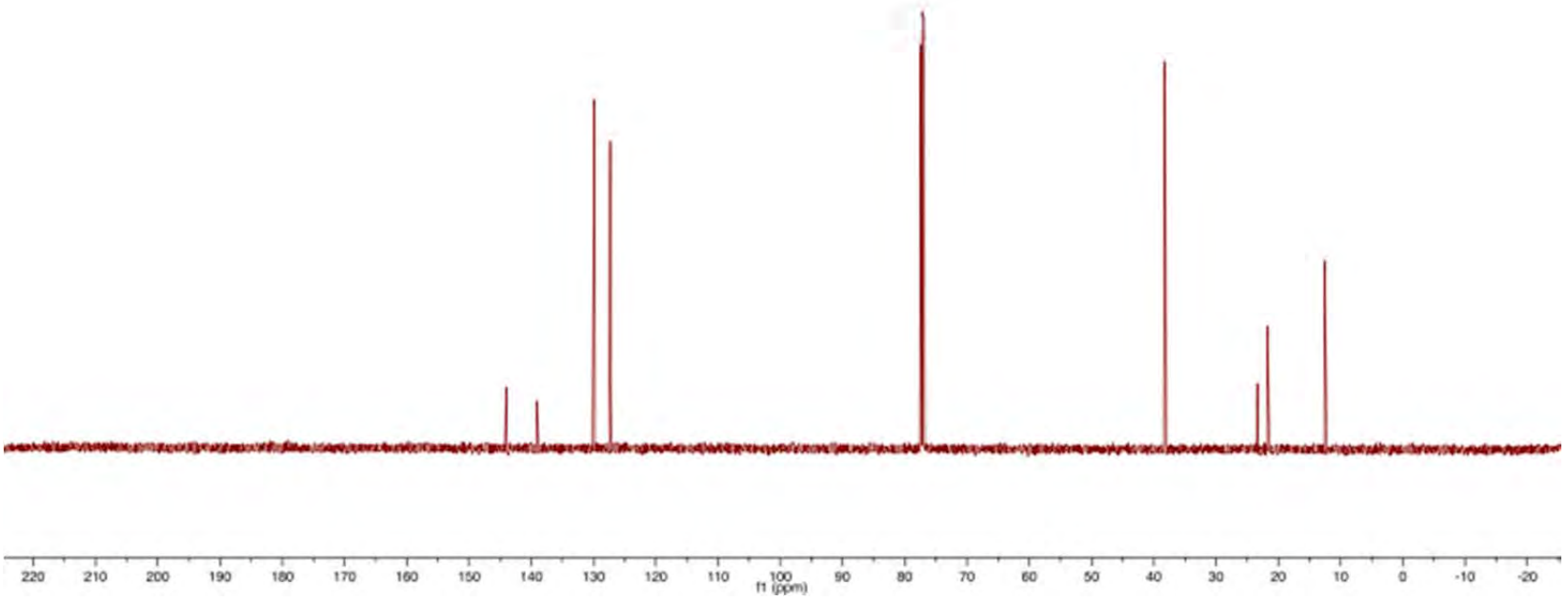
8b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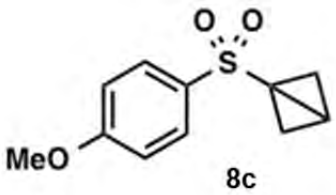
O
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MeO

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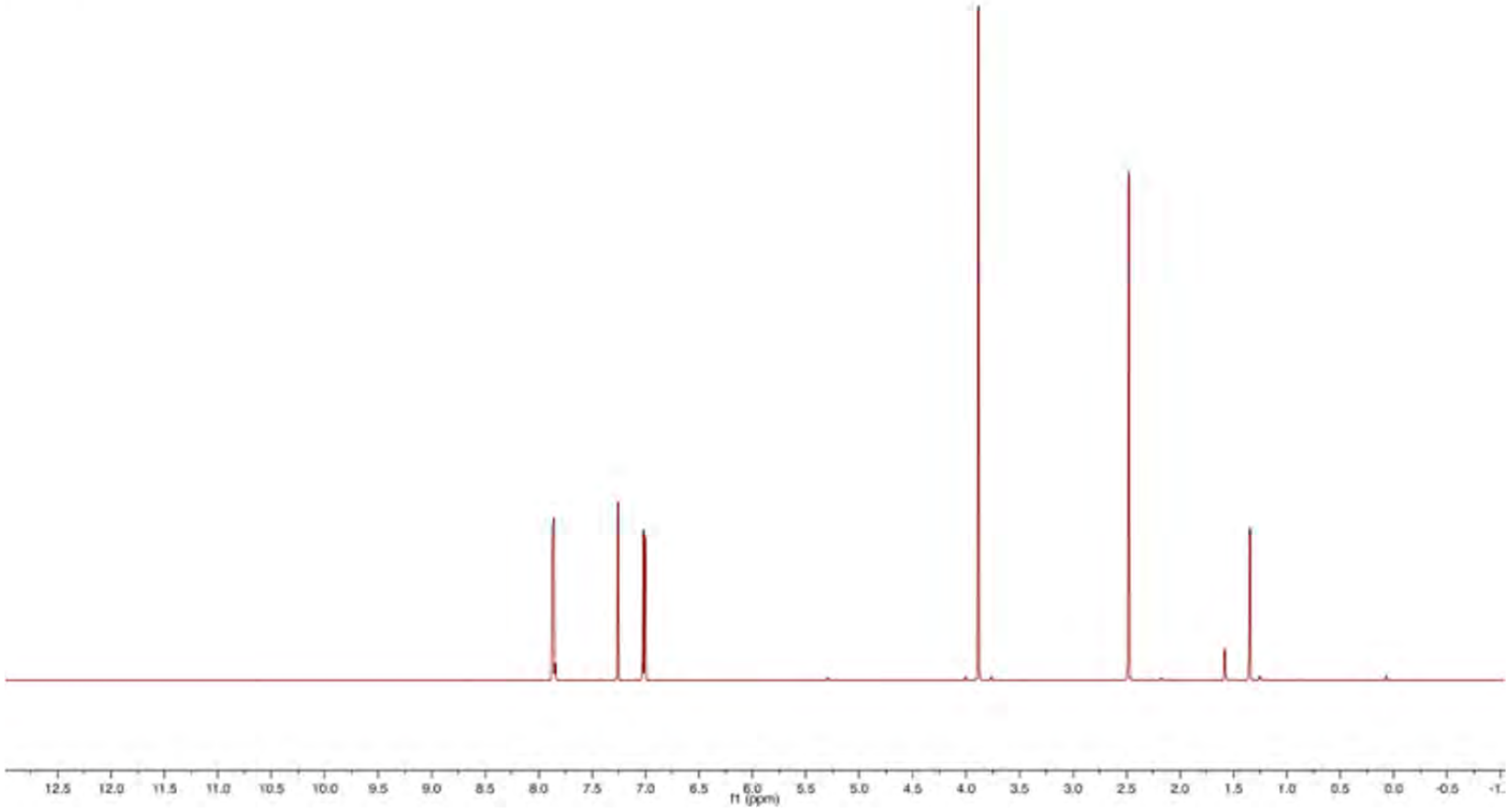
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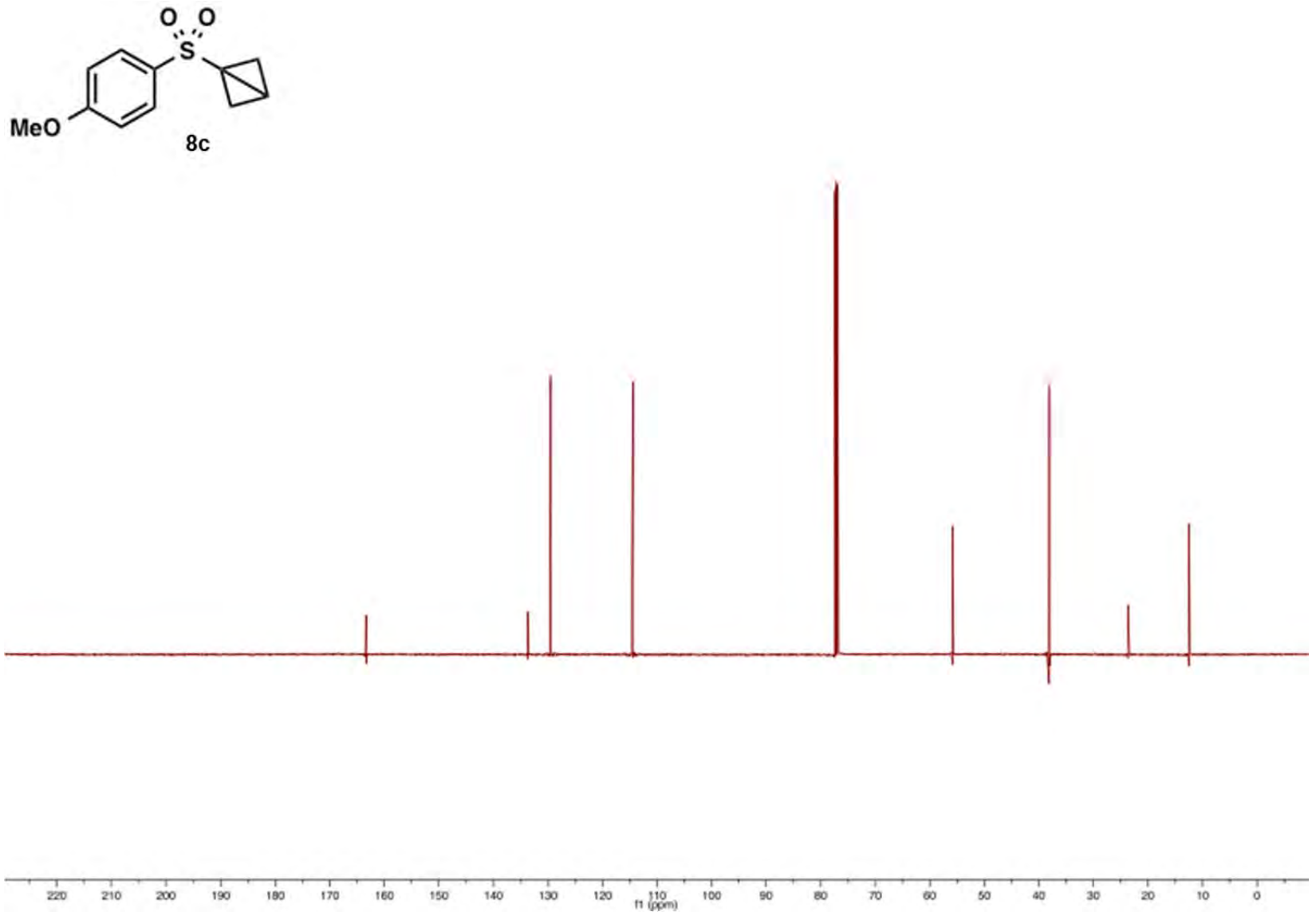
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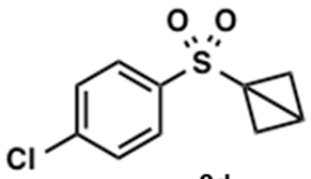
f1 (ppm)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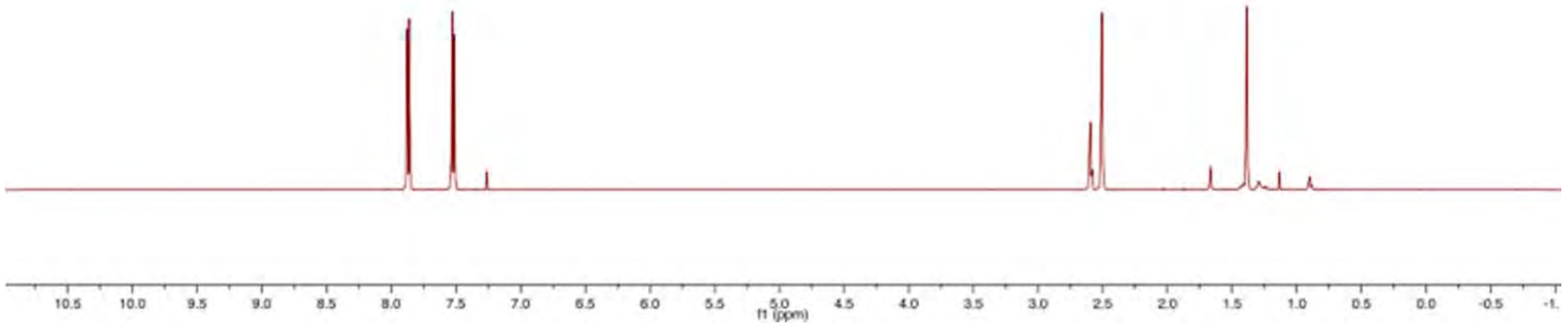
Cl

8d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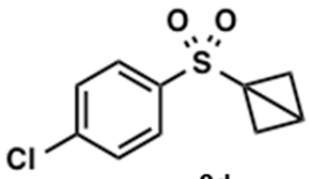
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Cl

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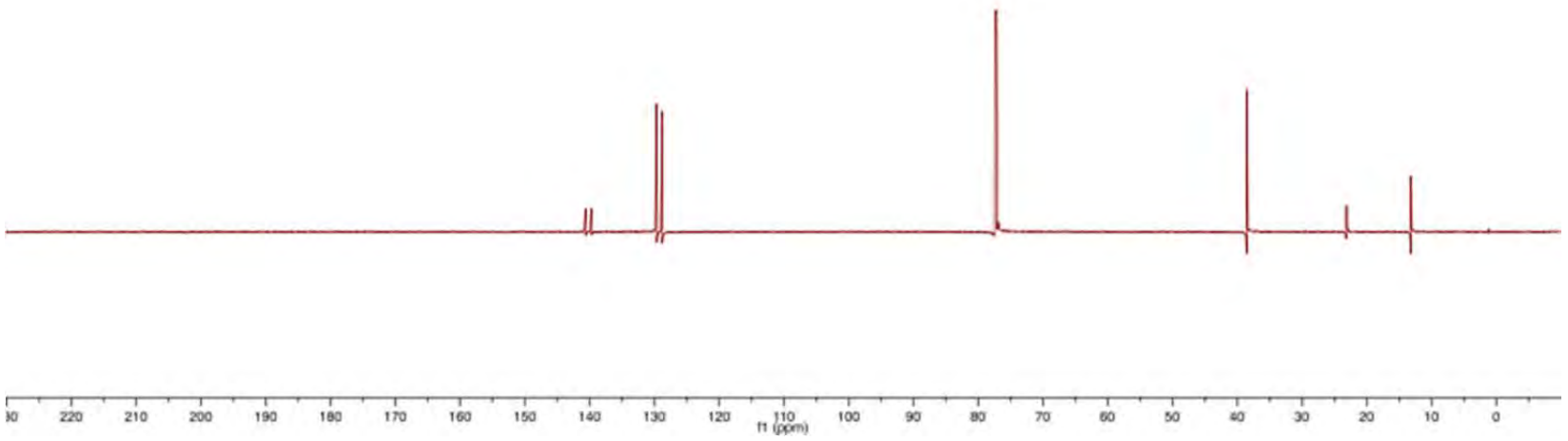
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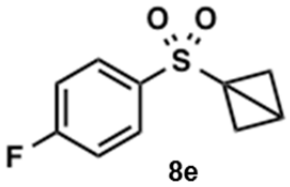
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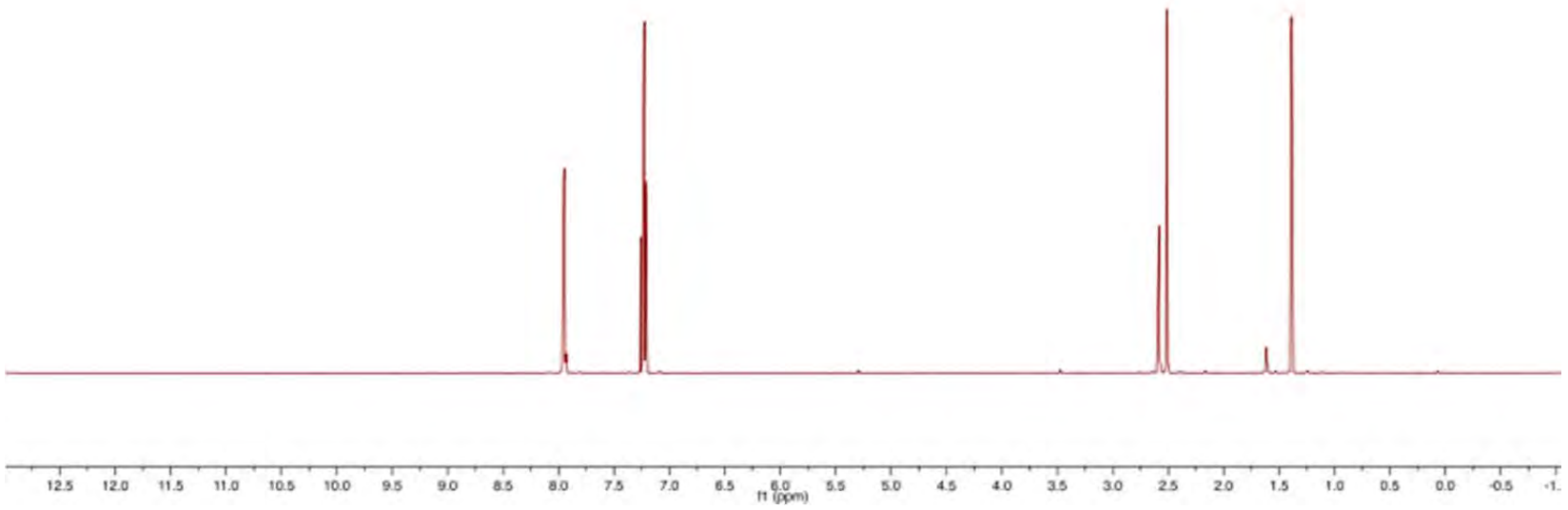
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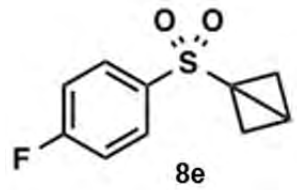
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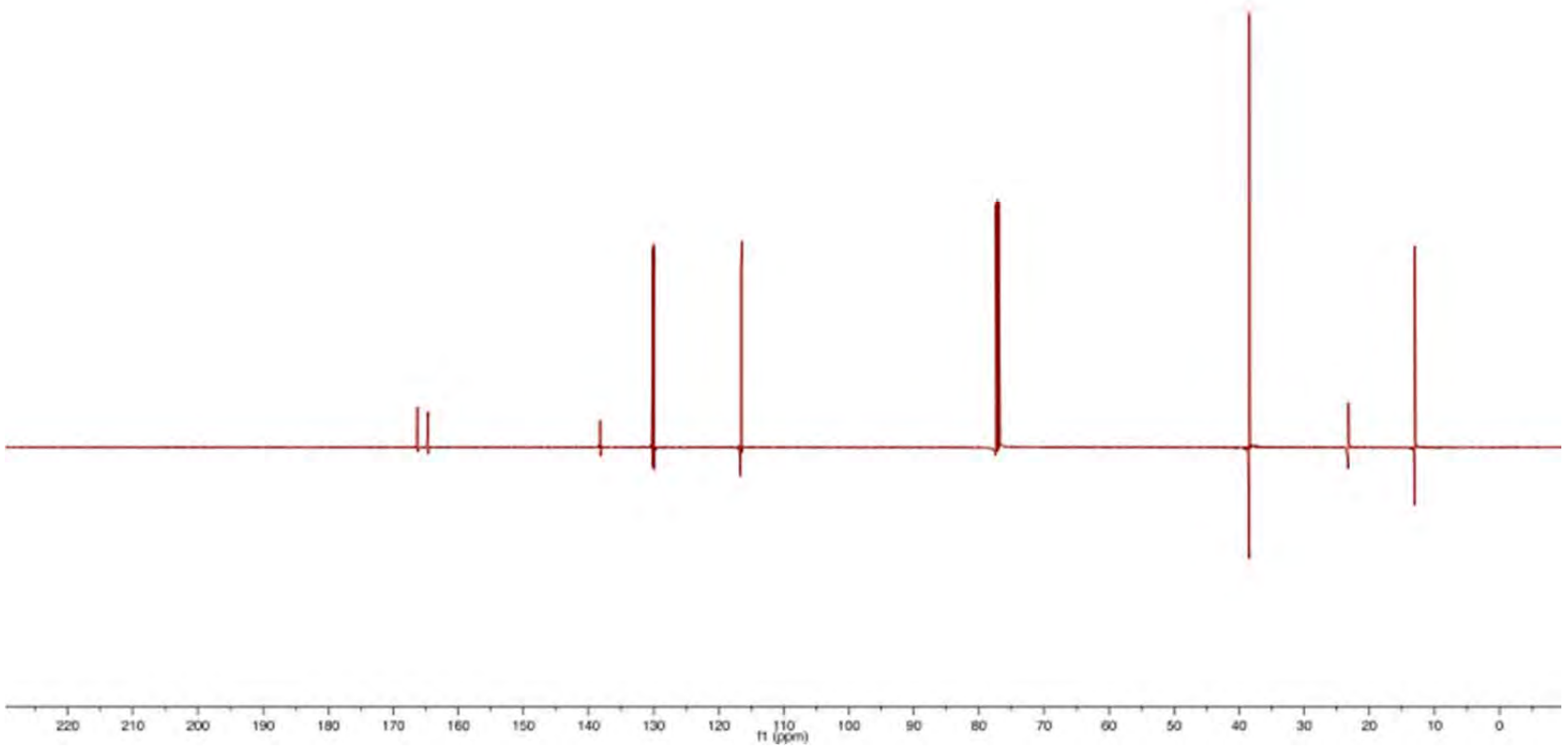
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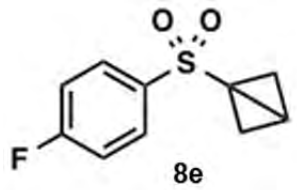
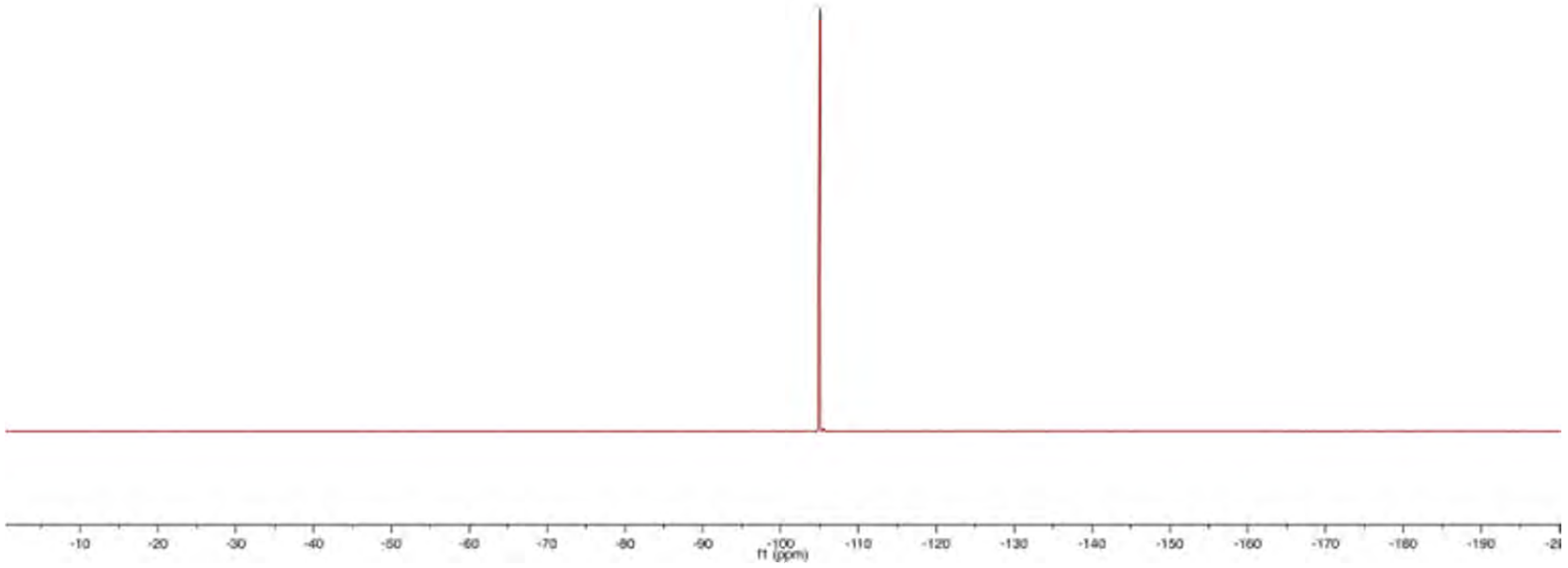

O
O
S
F

8e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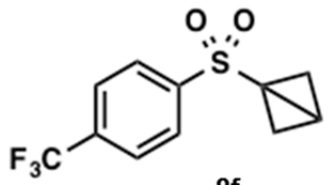
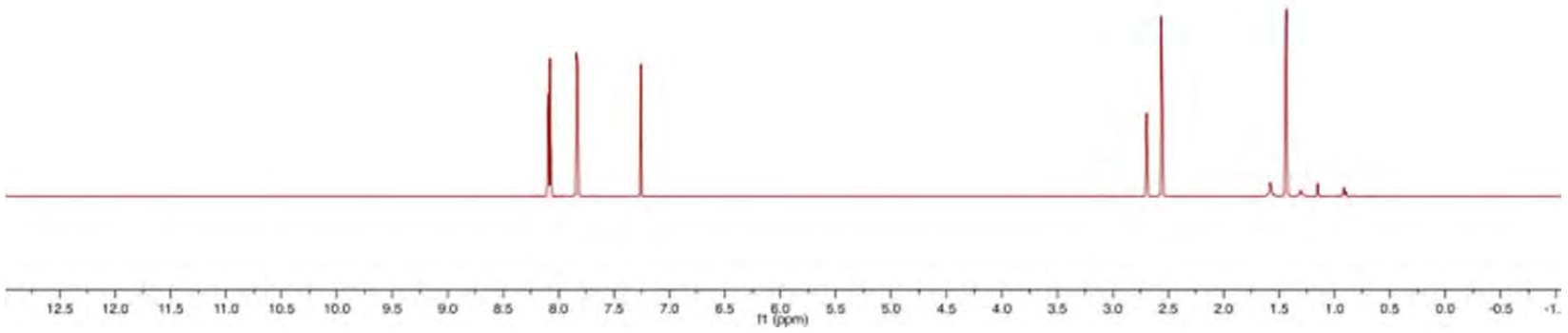

O
O
S
F3C

8f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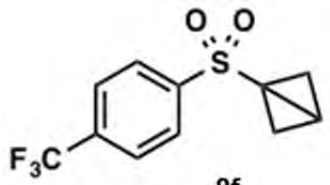
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O
S
F3C

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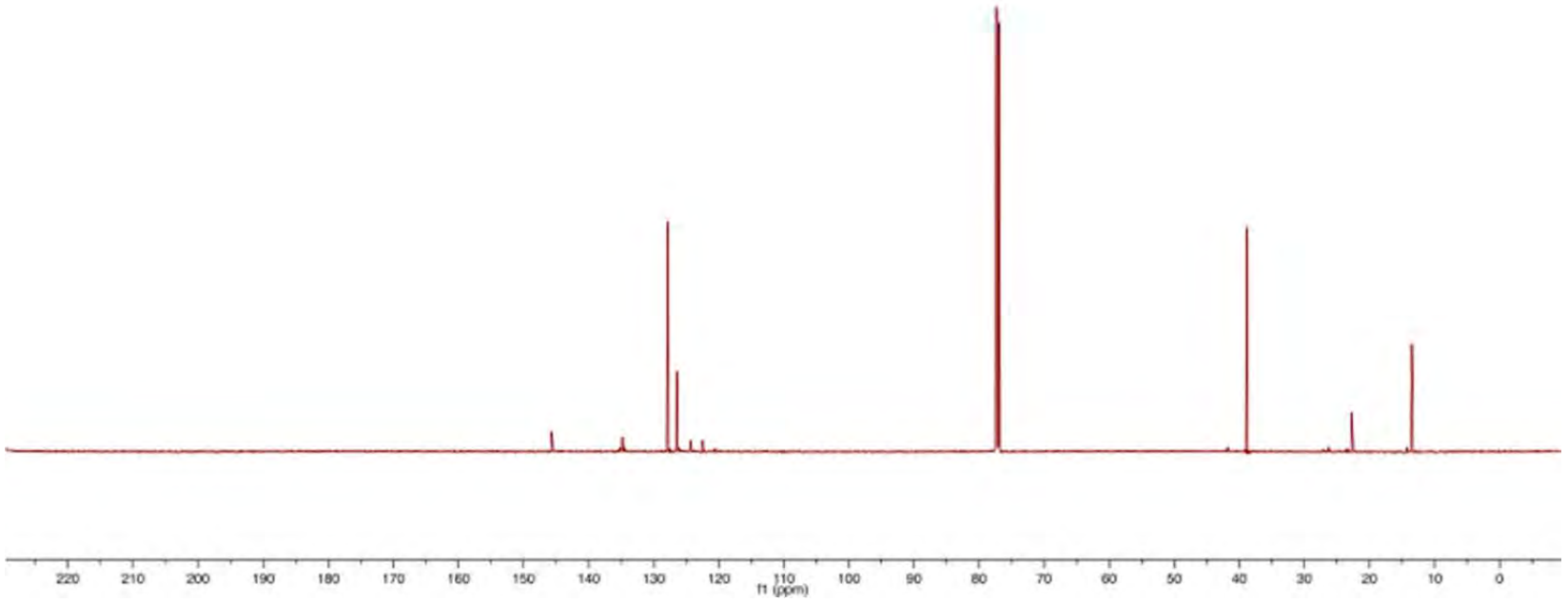
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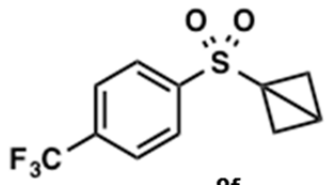
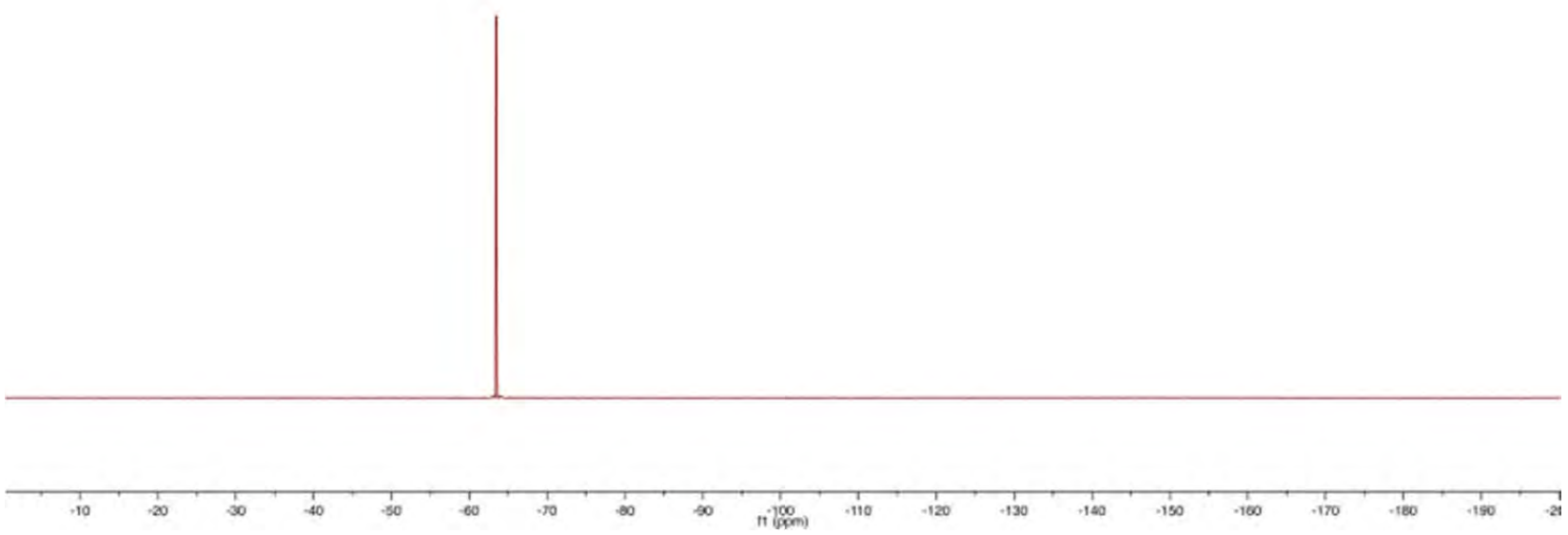
f1 (ppm)


O
O
S
F3C

8f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-100
f1 (ppm)
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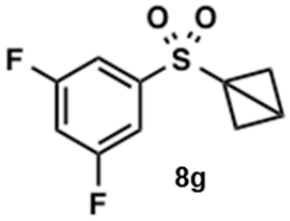
-140
-150
-160
-170
-180
-190


O
O
S
F
F

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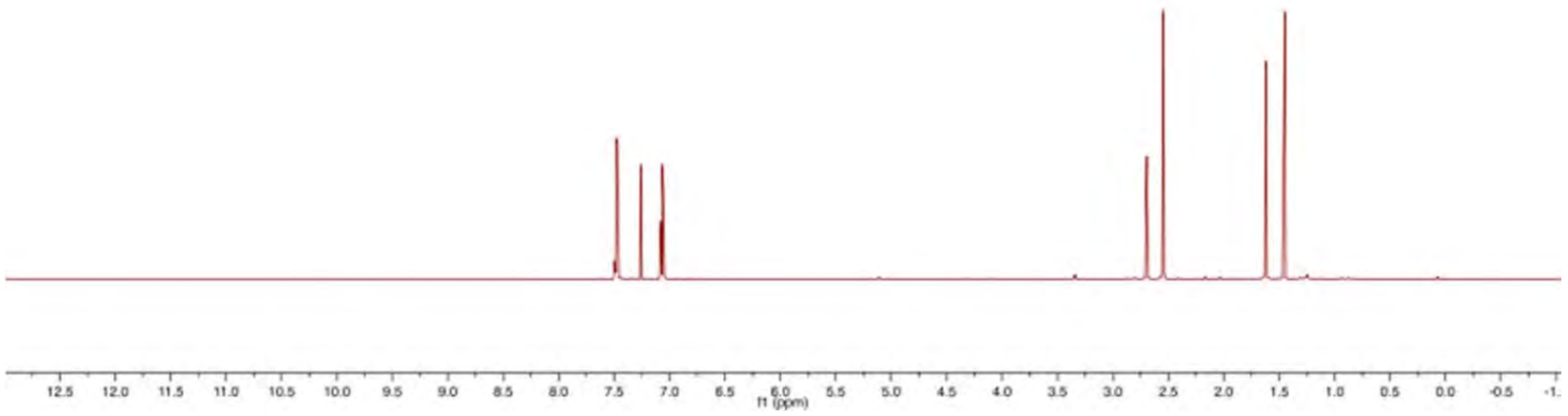
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6.5
6.0
f1 (ppm)
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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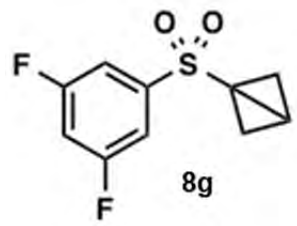
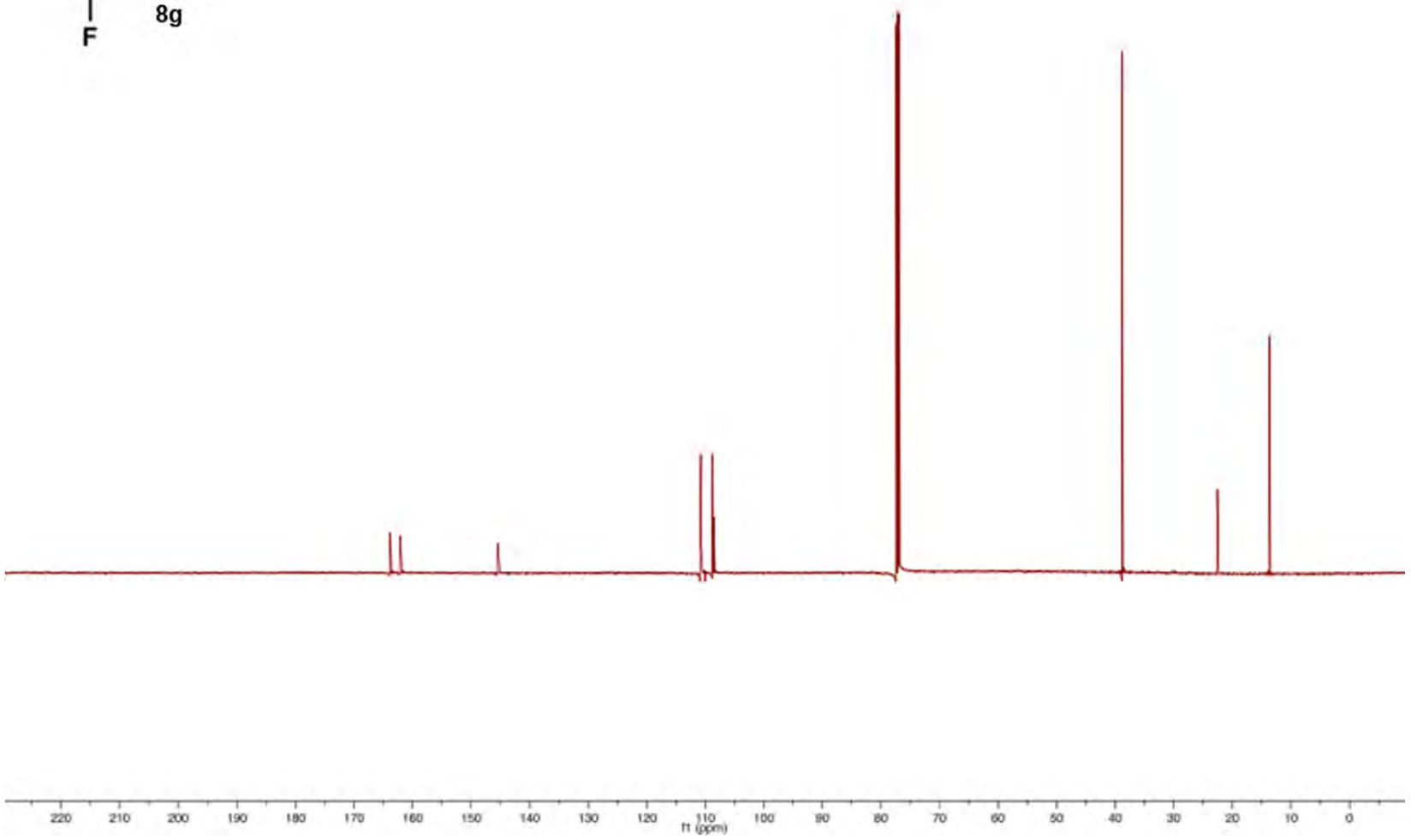
0.0
-0.5


O
O
S
F
F

8g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100
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40
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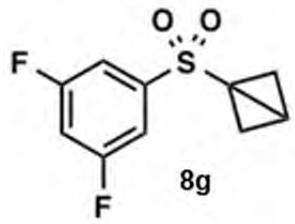
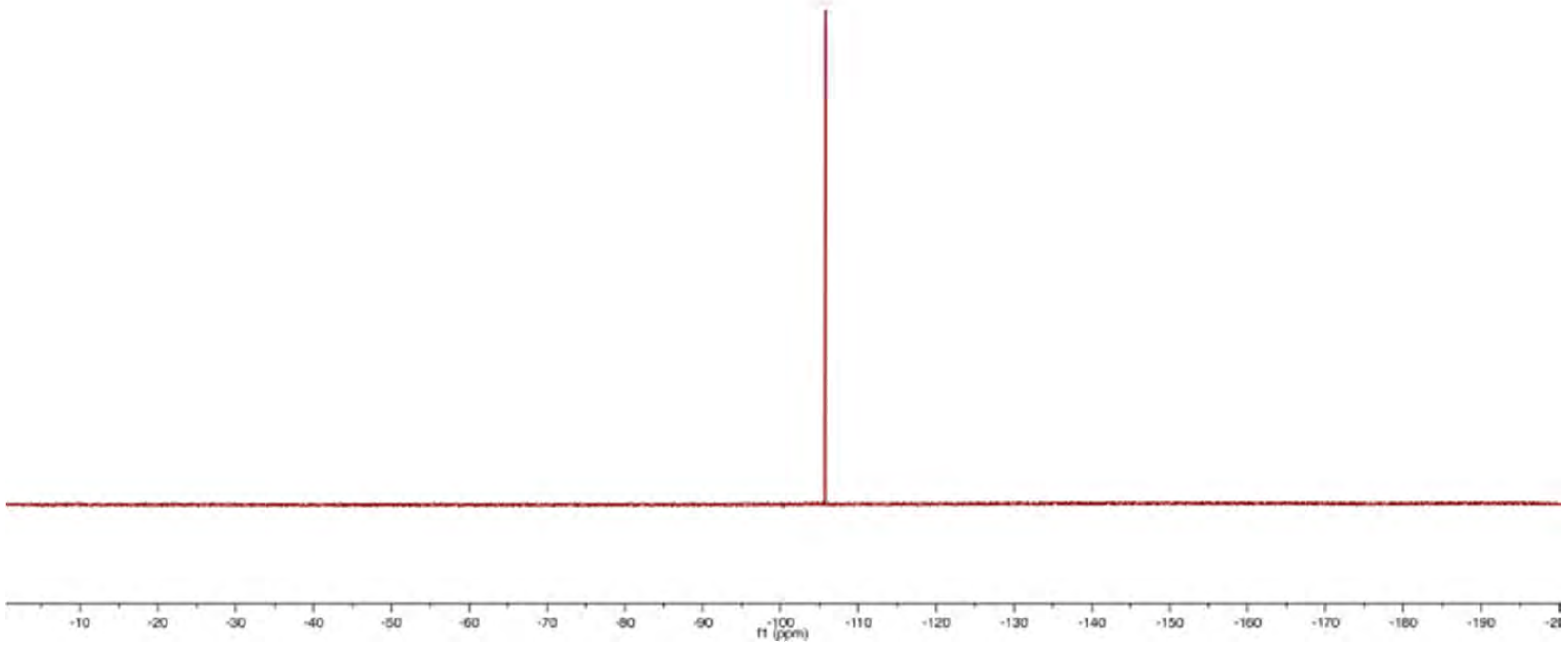
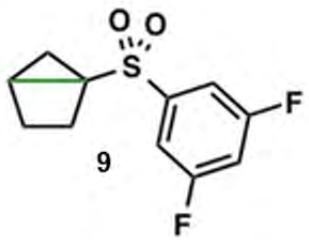
10
0
f1 (ppm)

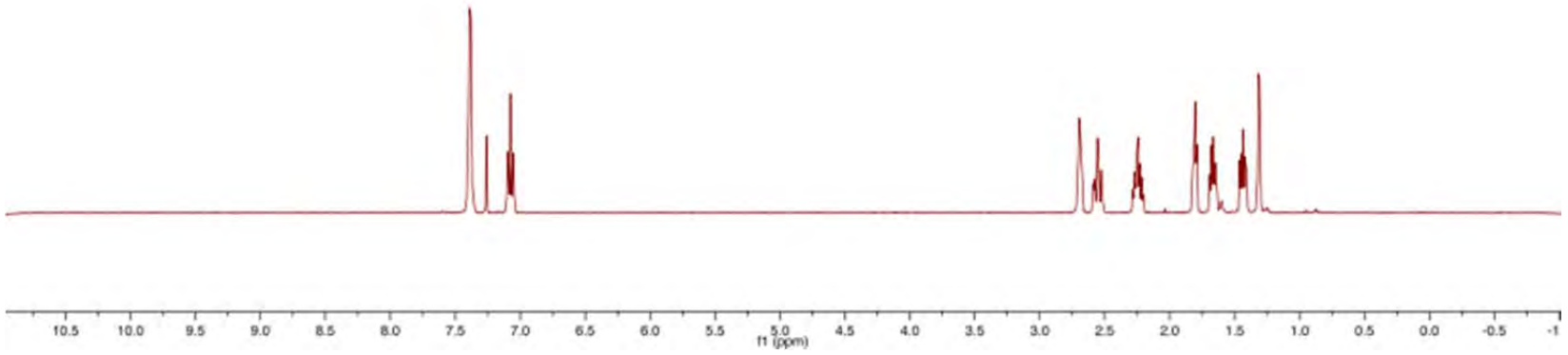

O
O
S
F
F

8g


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190


O
O
S
F
F

9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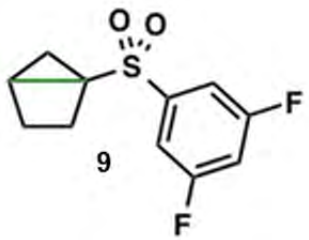
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


O
O
S
F
F

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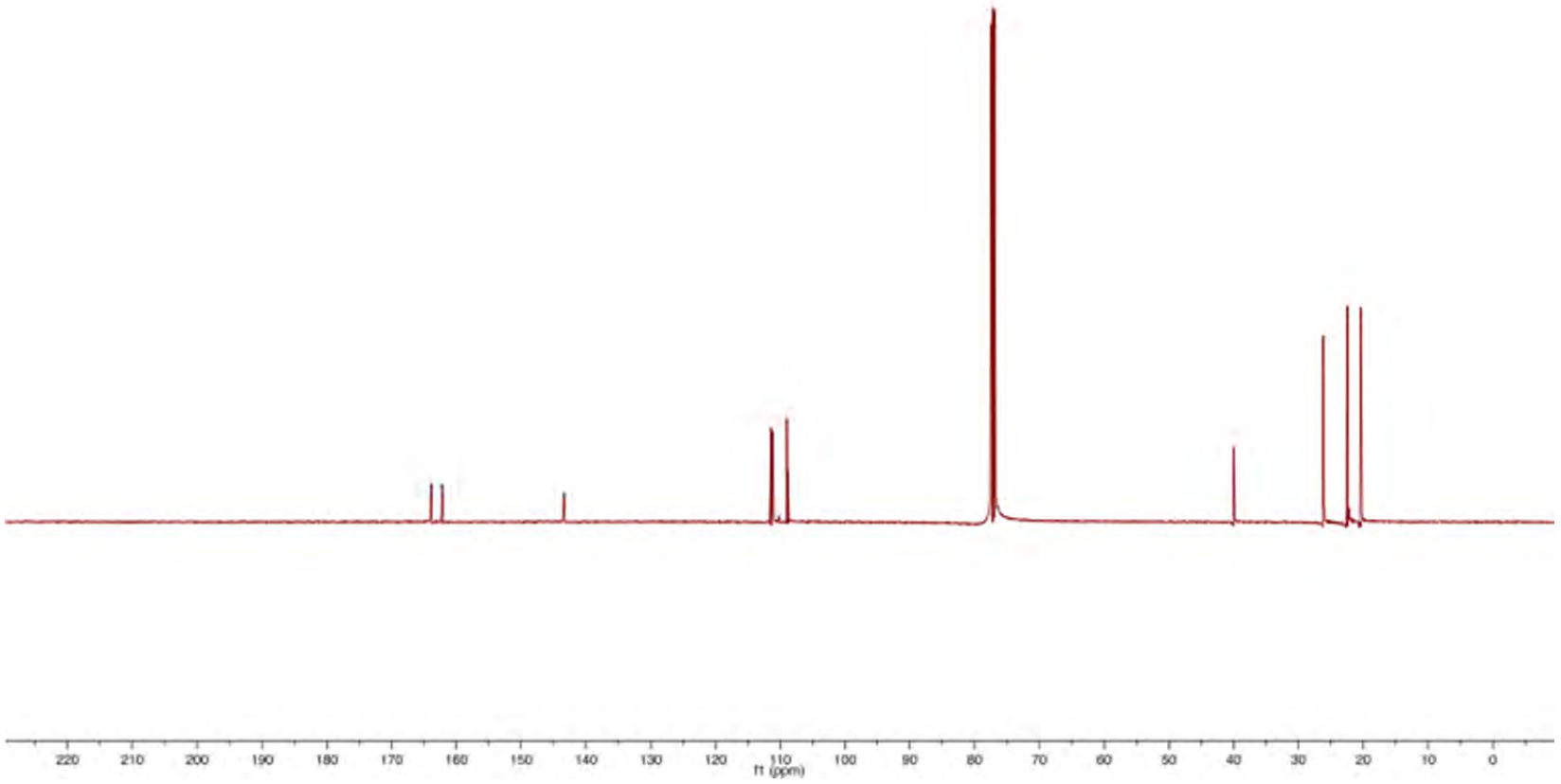
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180
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100
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80
70
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40
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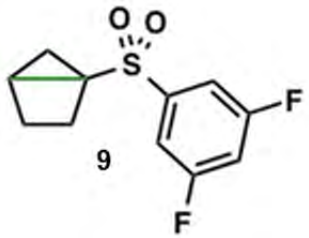
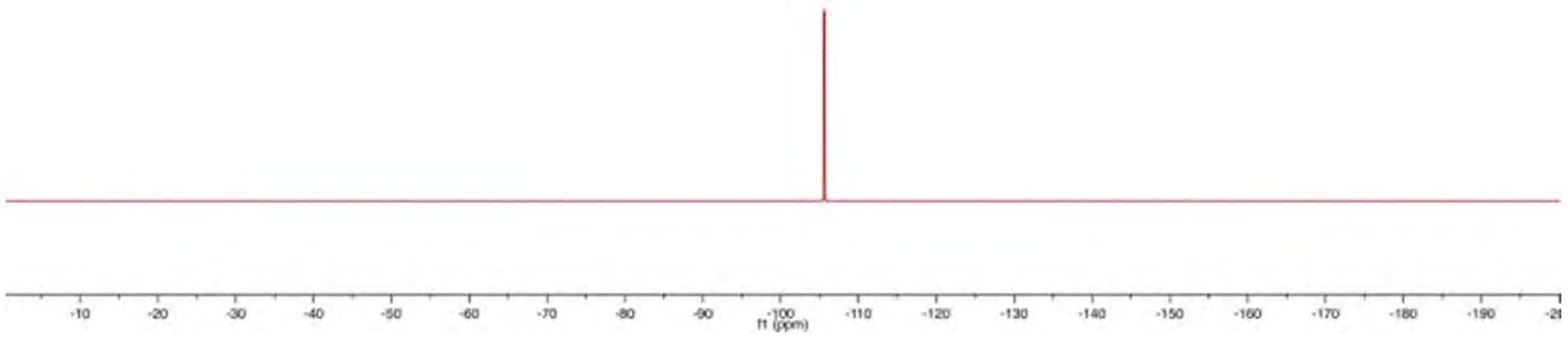
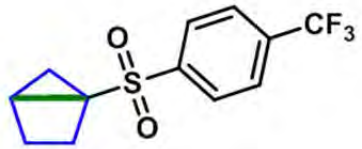
20
10
0
f1 (ppm)

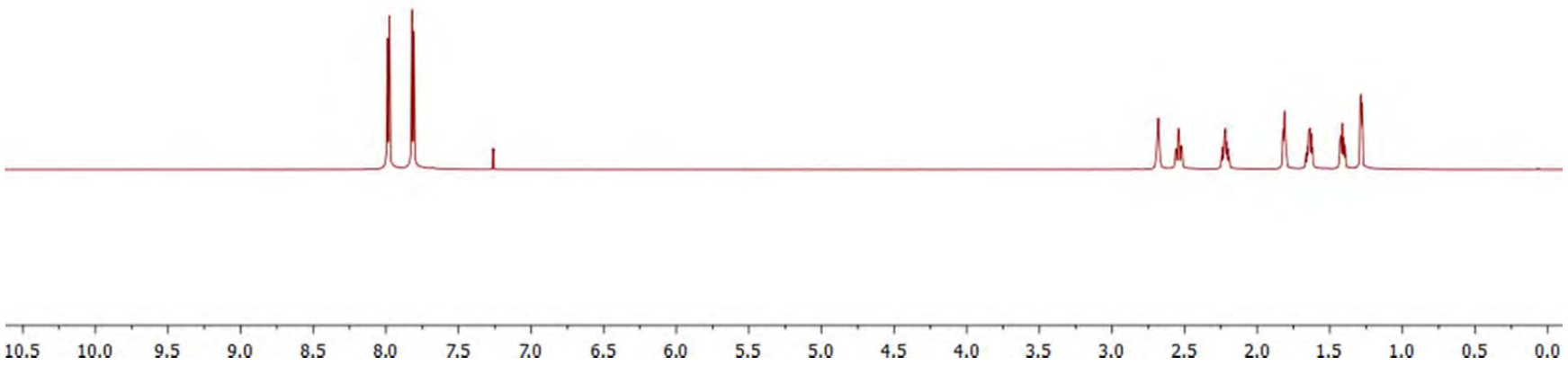

O
O
S
F
F

9


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190


O
S
O
CF3

10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9.5
9.0
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8.0
7.5
7.0
6.5
6.0
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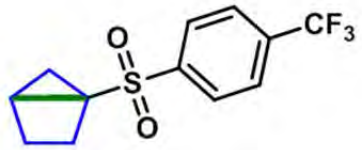
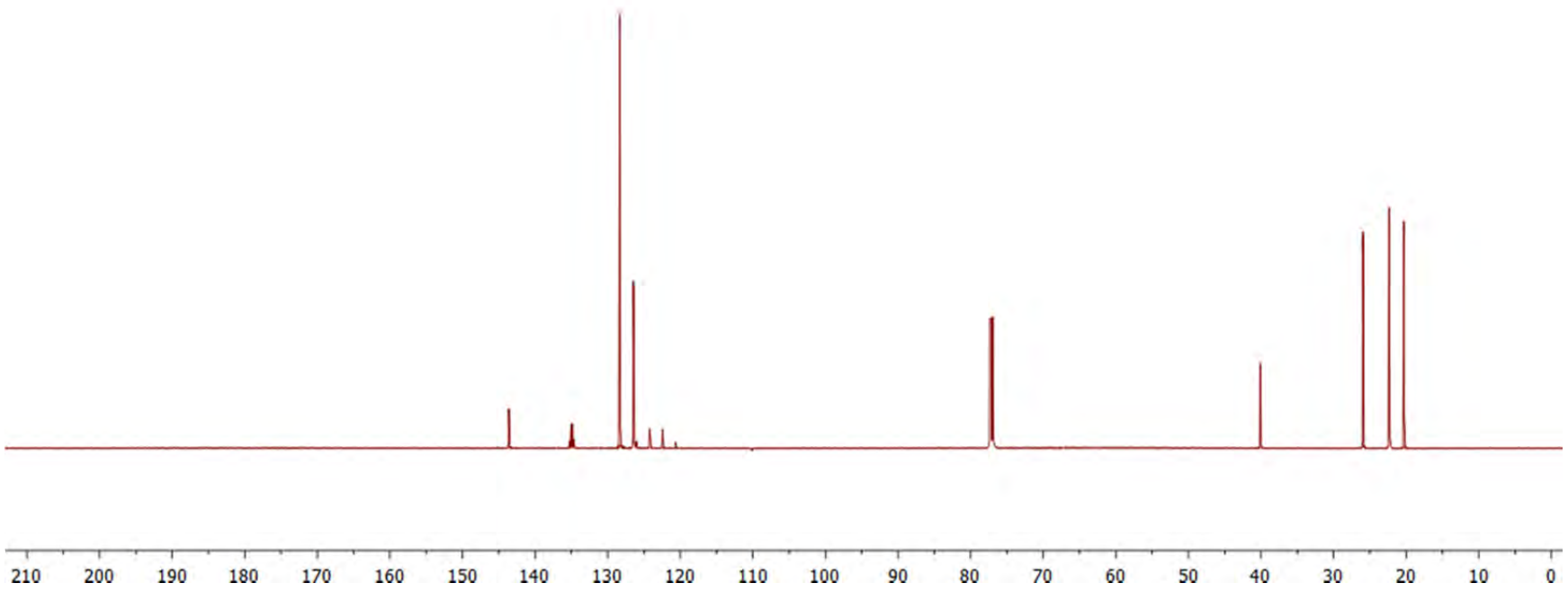
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


O
S
O
CF3

10


210
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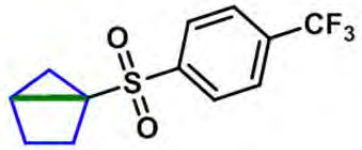
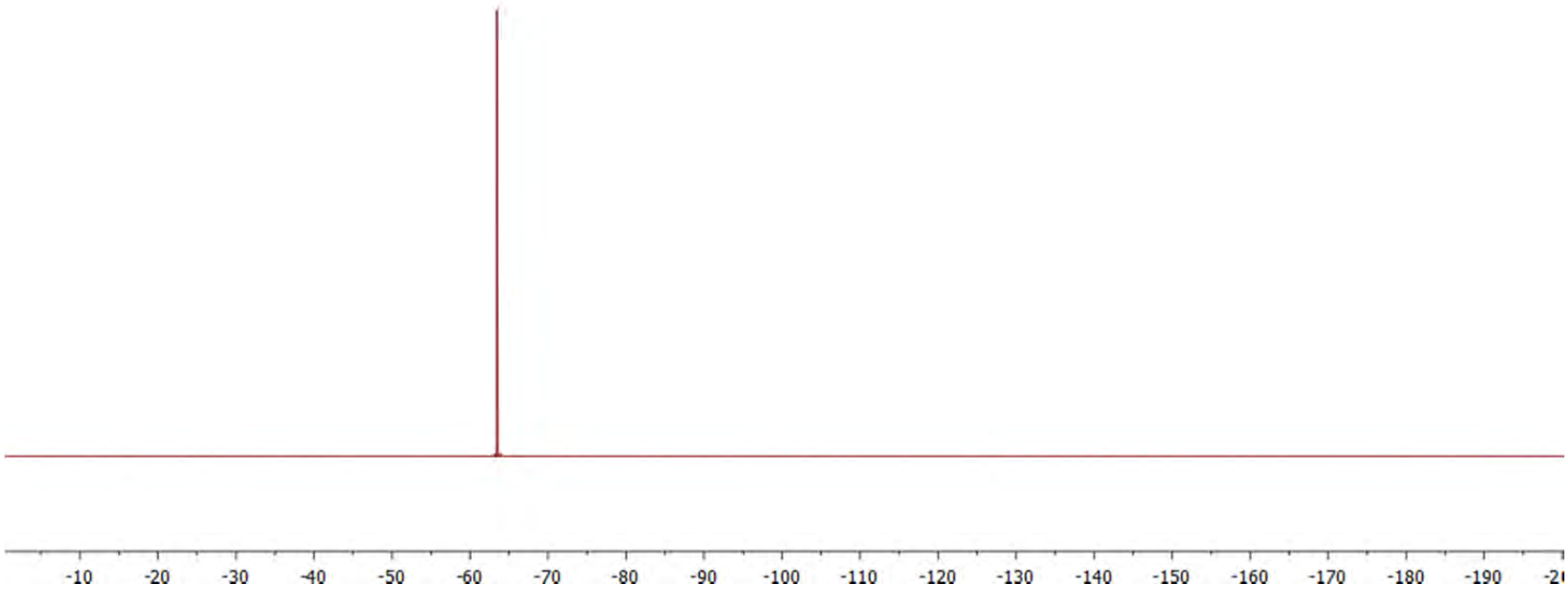
10
0


O
S
O
CF3

10


-10
-20
-30
-40
-50
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-80
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-100
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-120
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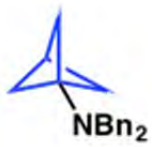
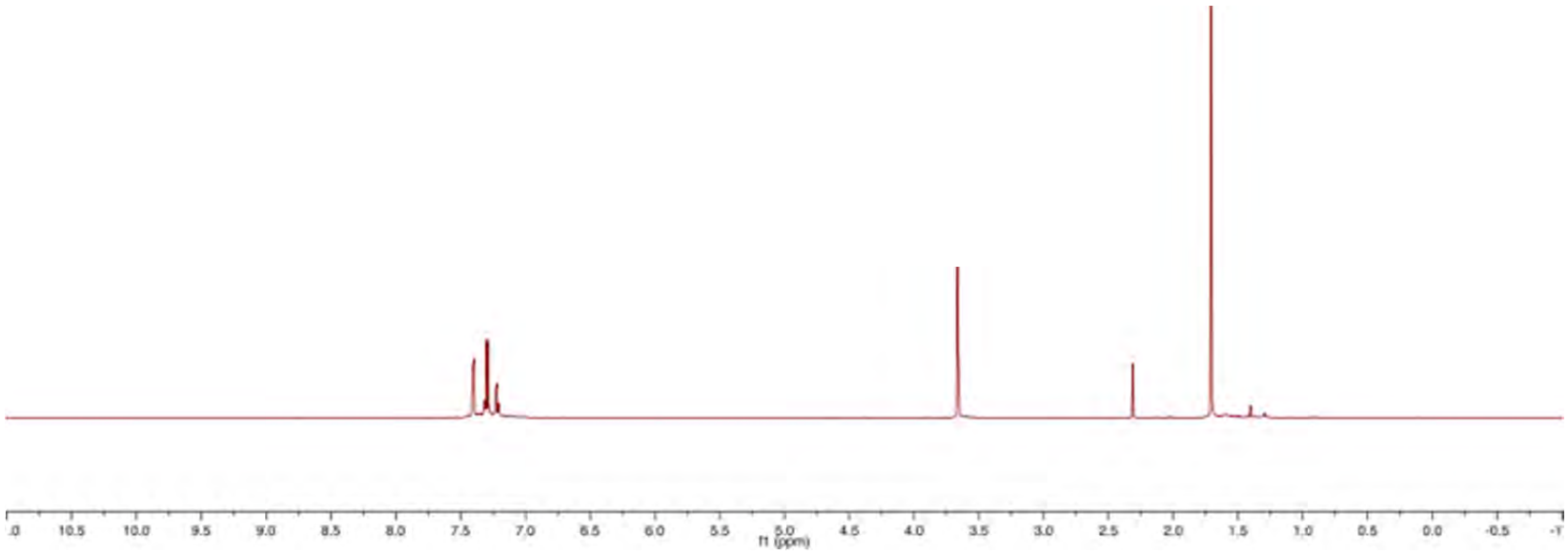
-140
-150
-160
-170
-180
-190

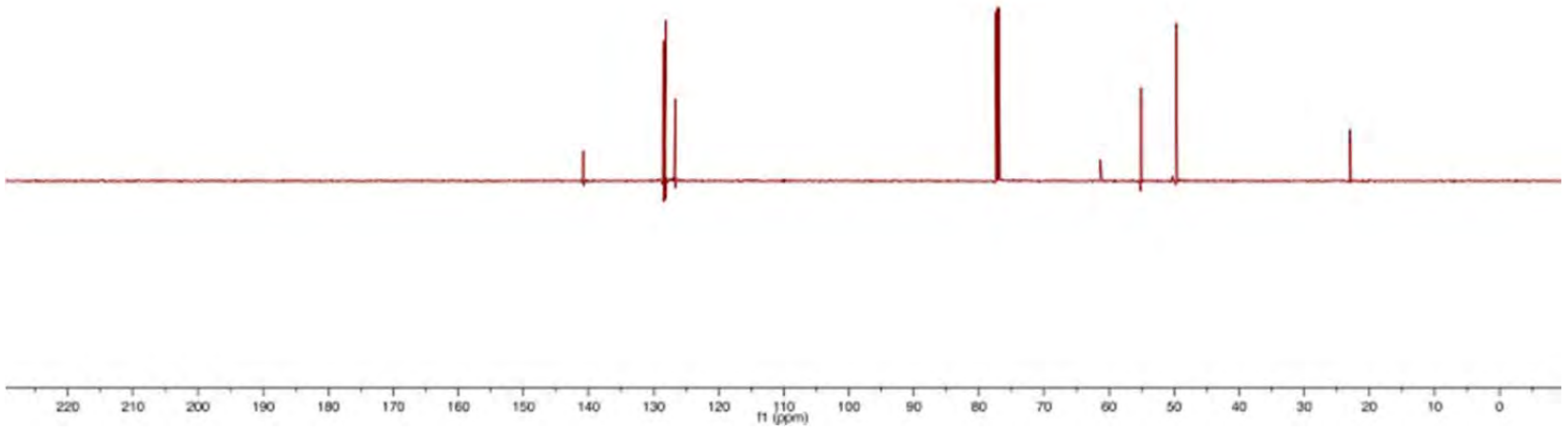


24




NBn2

24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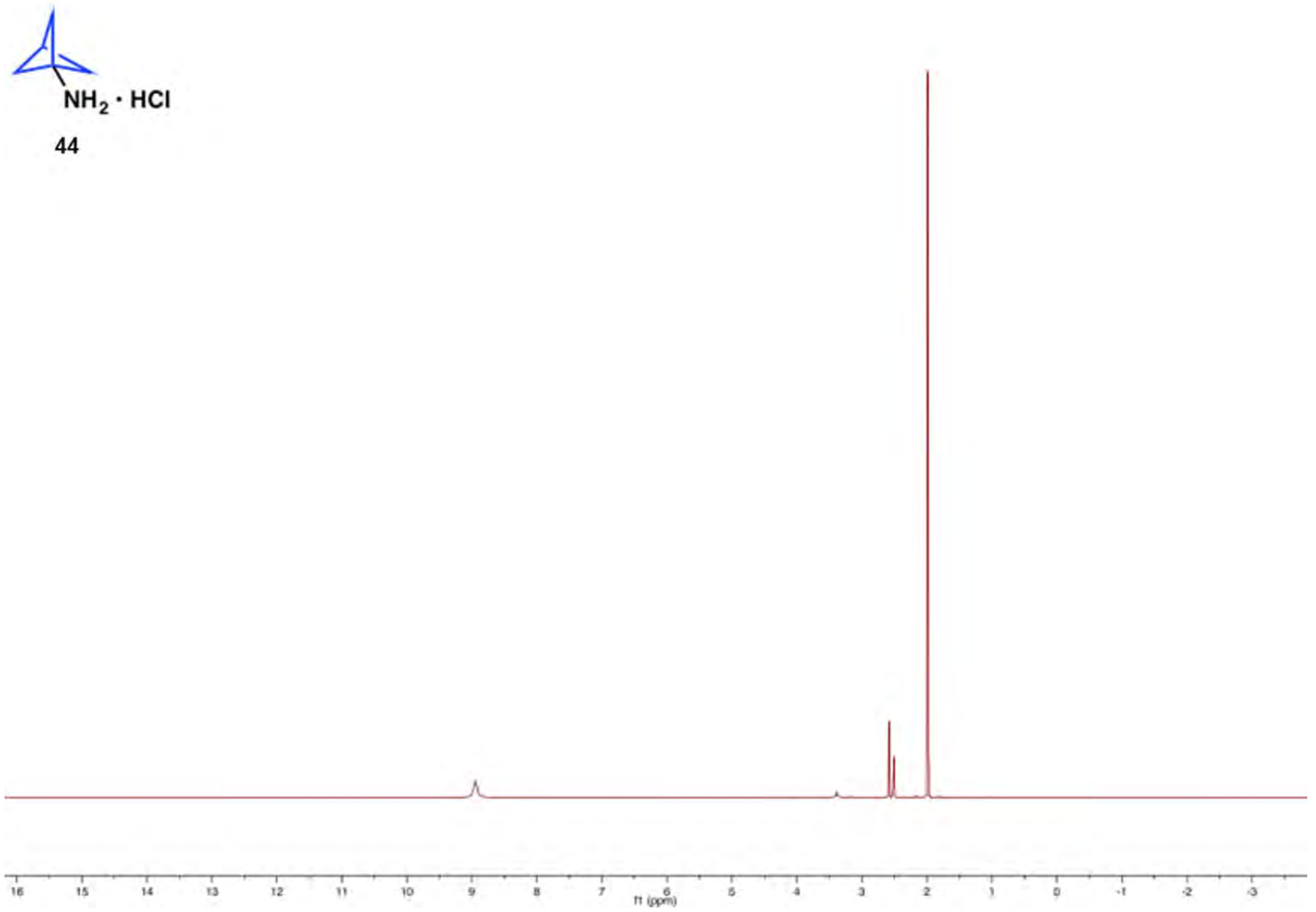
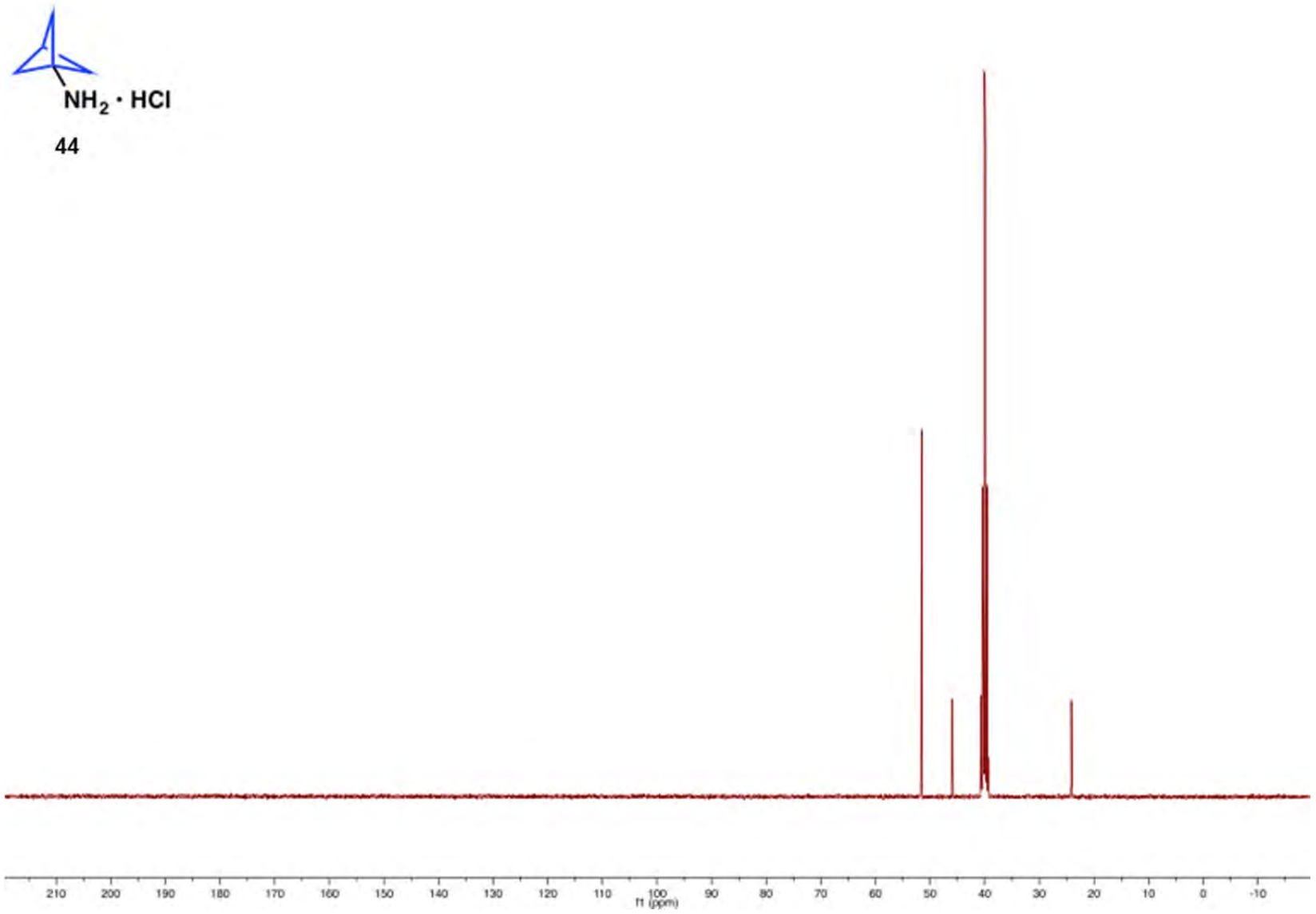
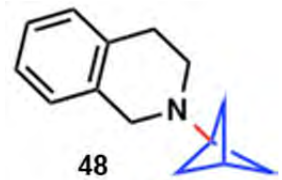
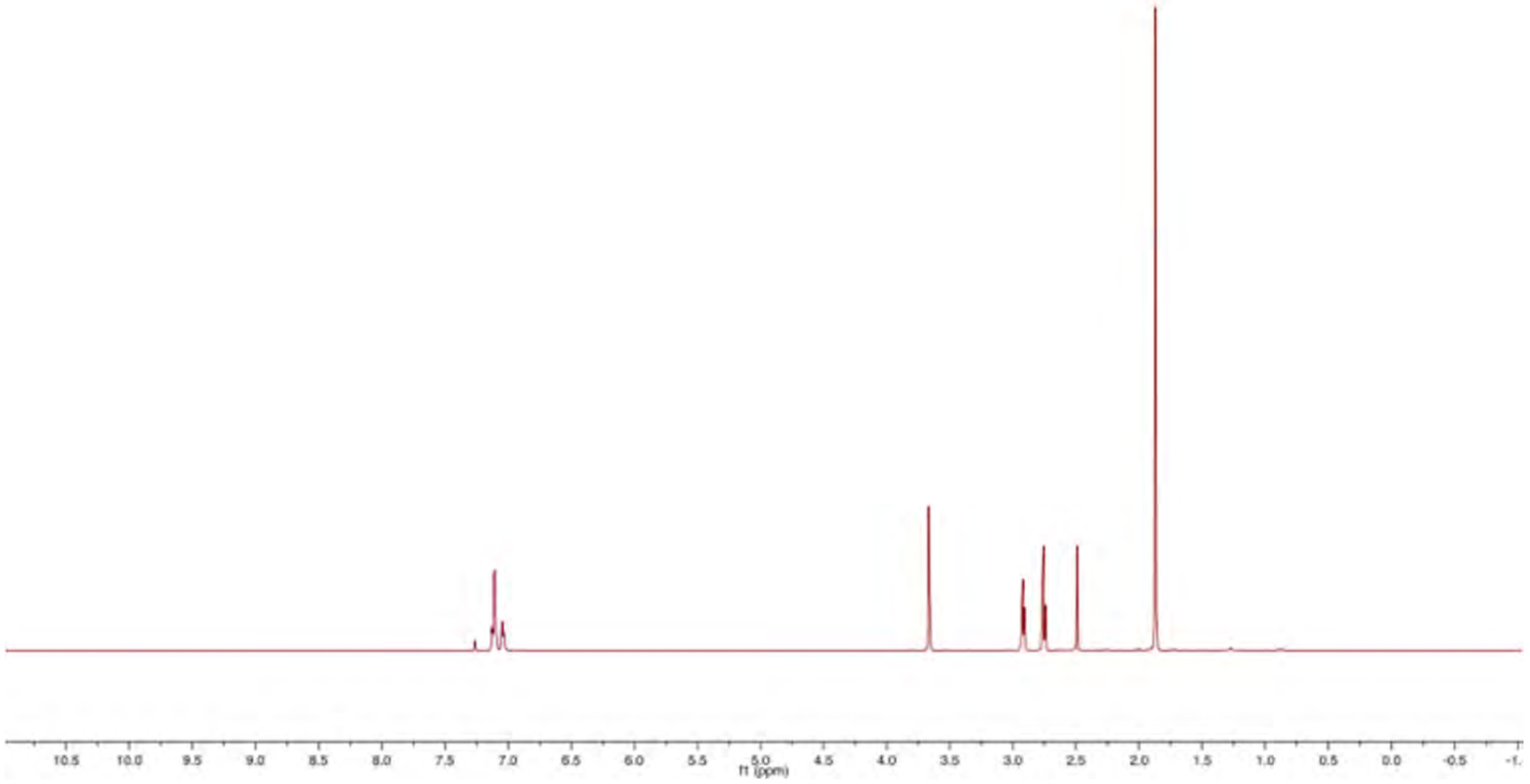
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NH2 · HCl
44
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)


NH2 · HCl
44
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)


N

48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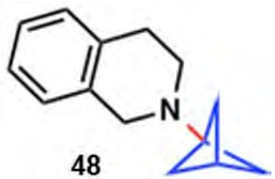
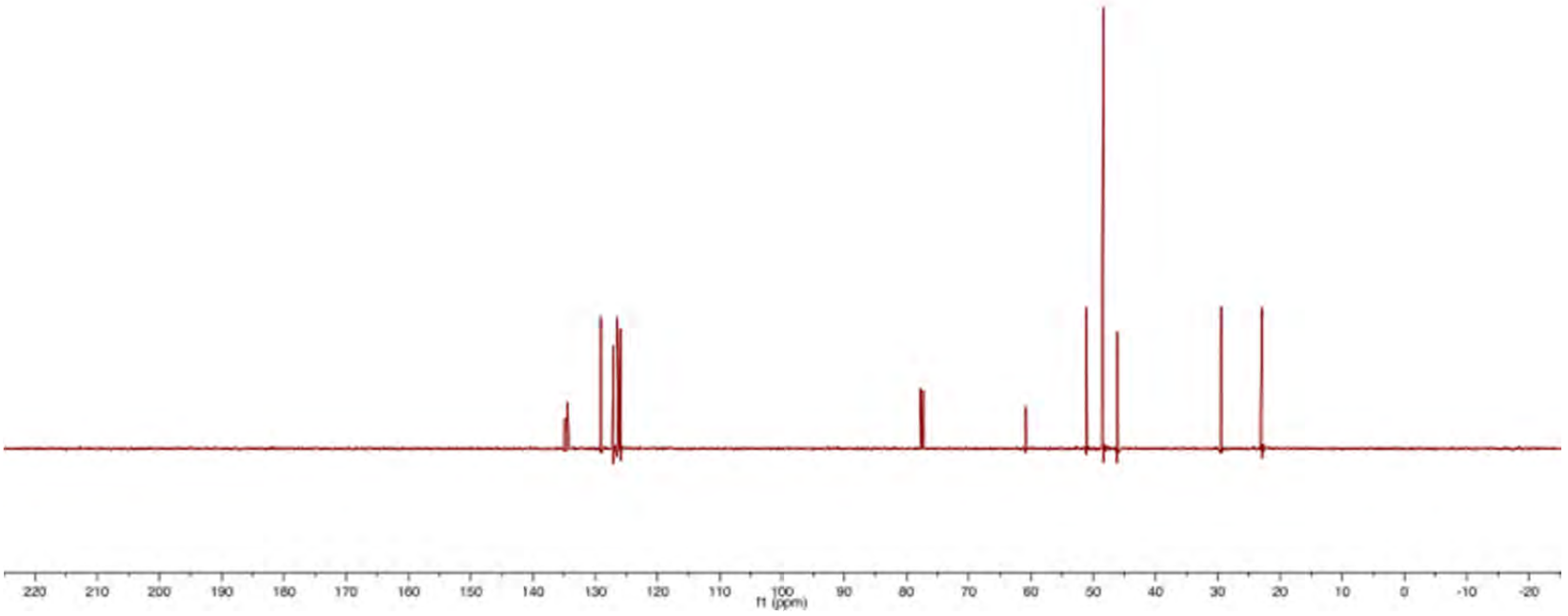
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


N

48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210
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180
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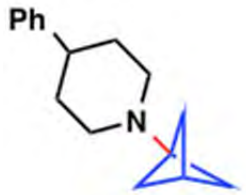
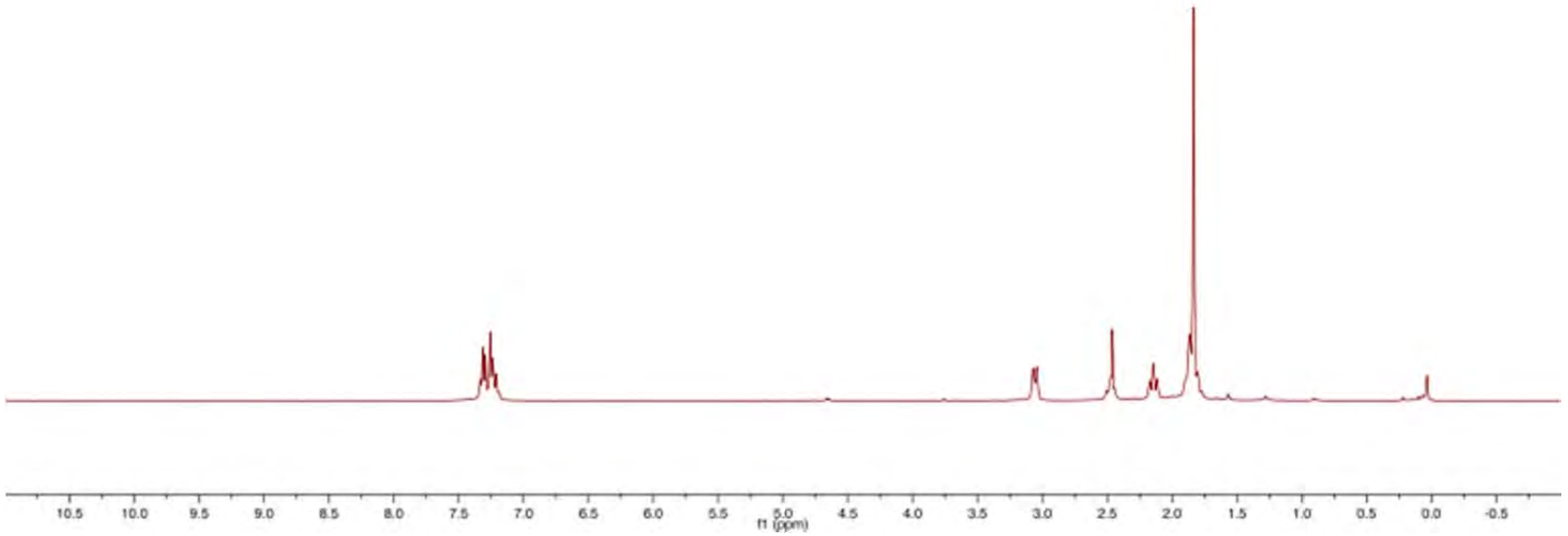
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


Ph
N

52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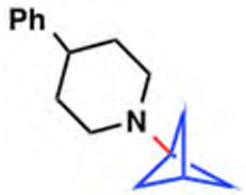
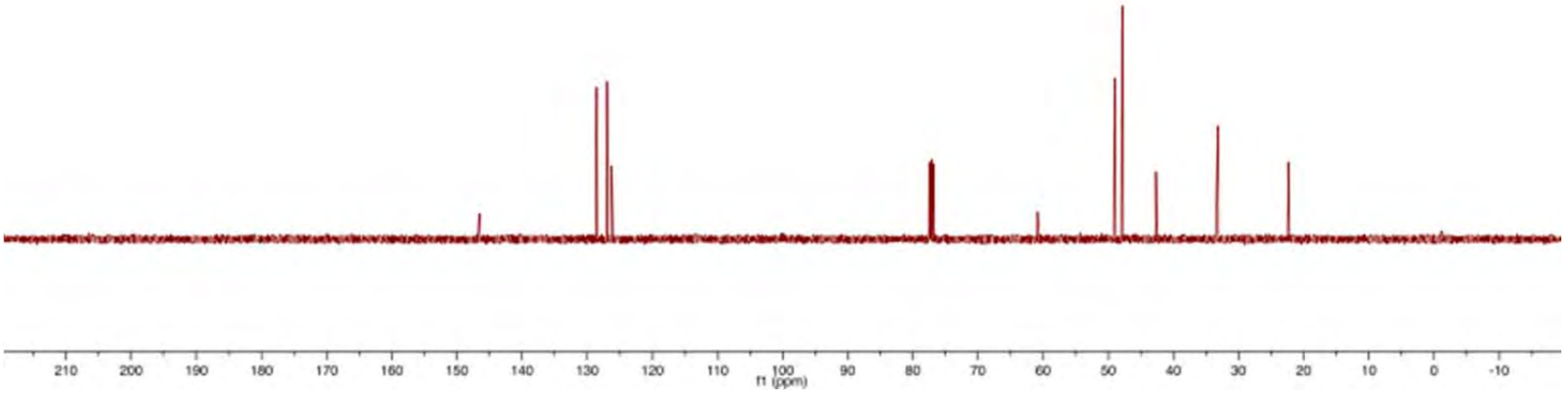
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Ph
N

52


210
200
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180
170
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140
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120
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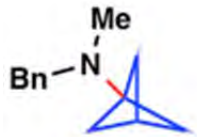
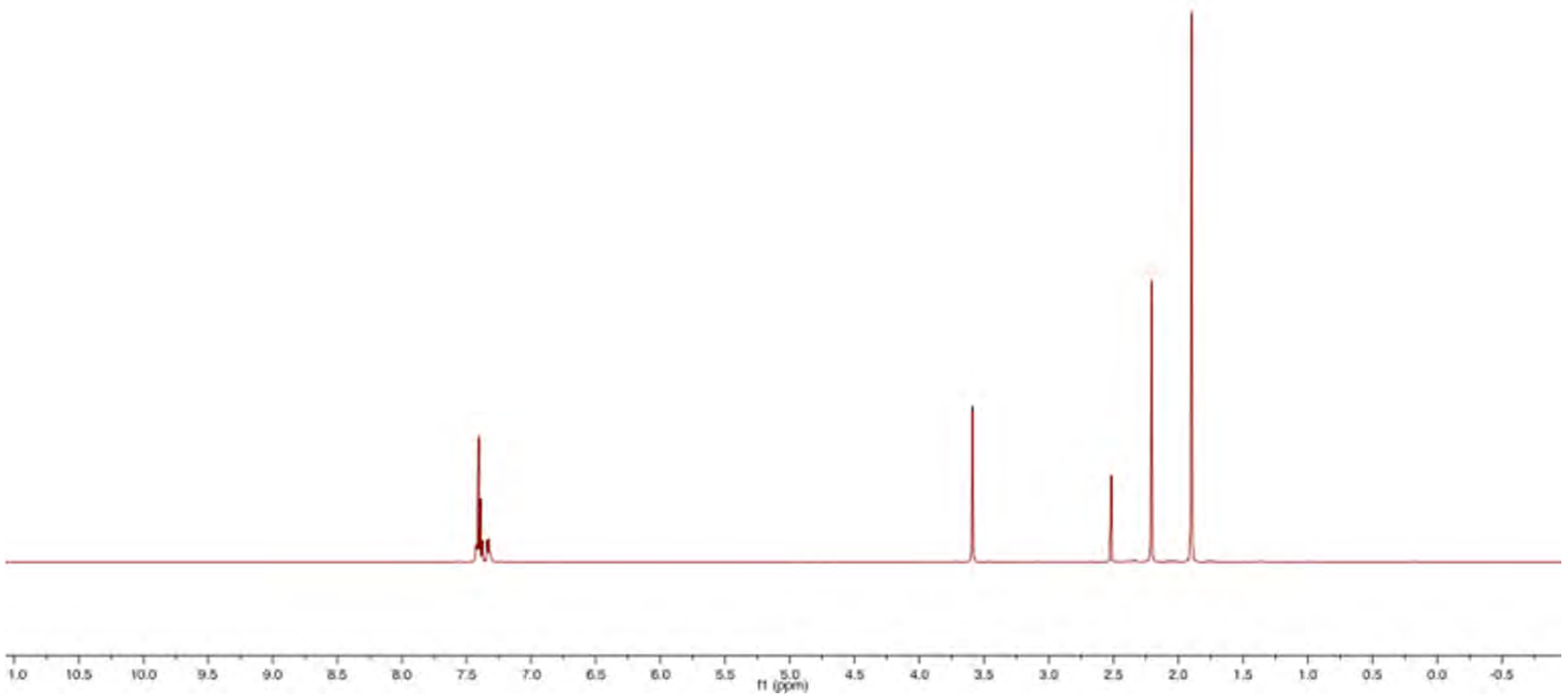
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Me
N
Bn

53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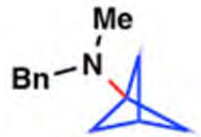
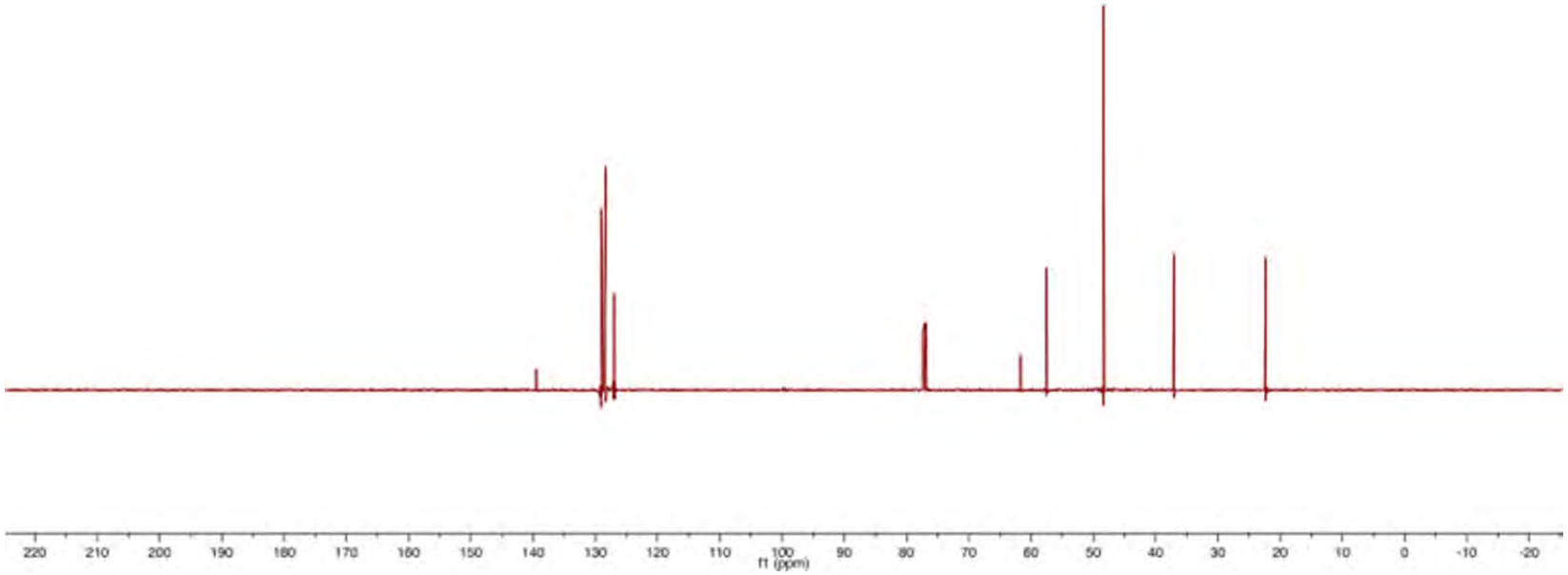
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Me
N
Bn

53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100
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60
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40
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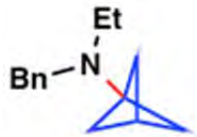
20
10
0
-10
-20
f1 (ppm)



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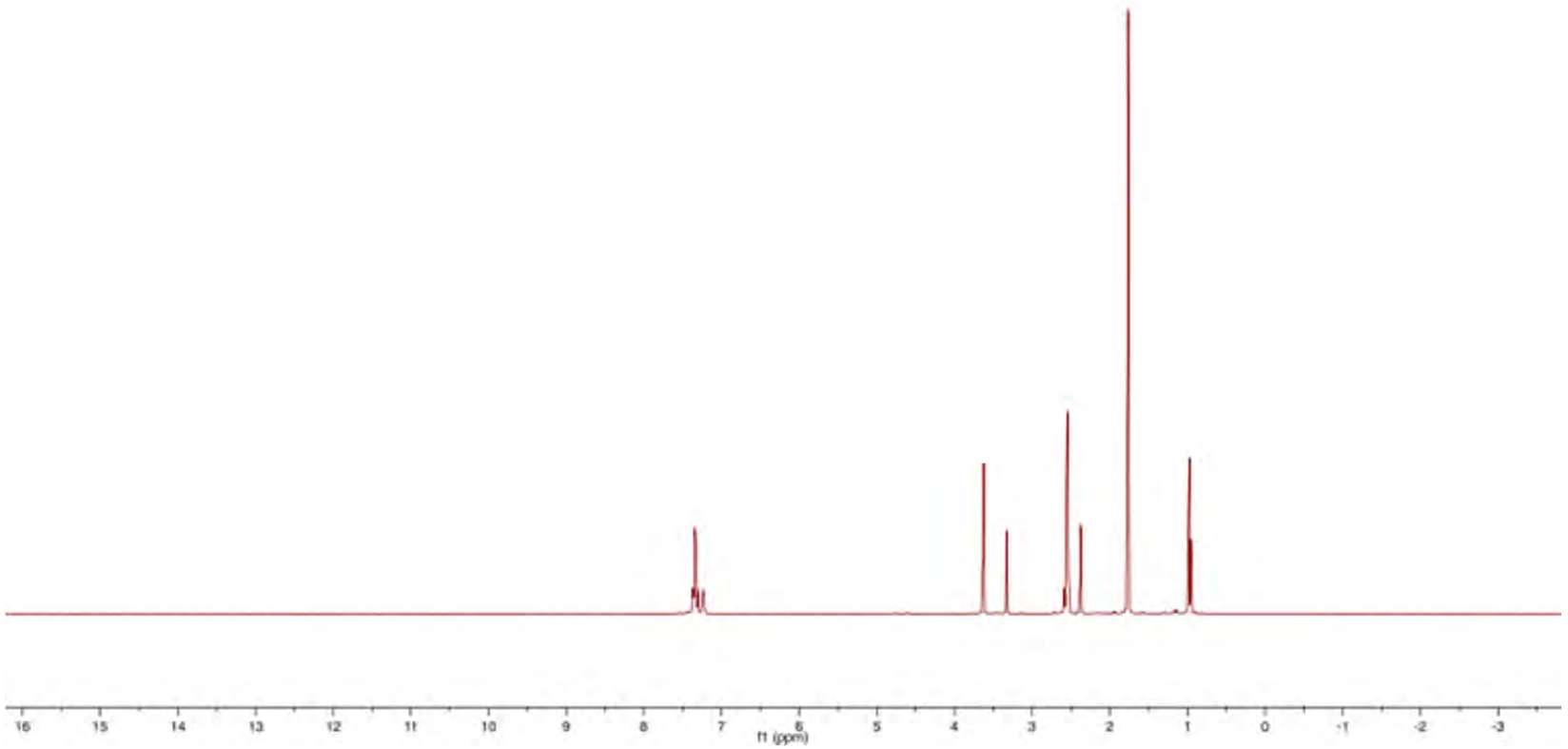

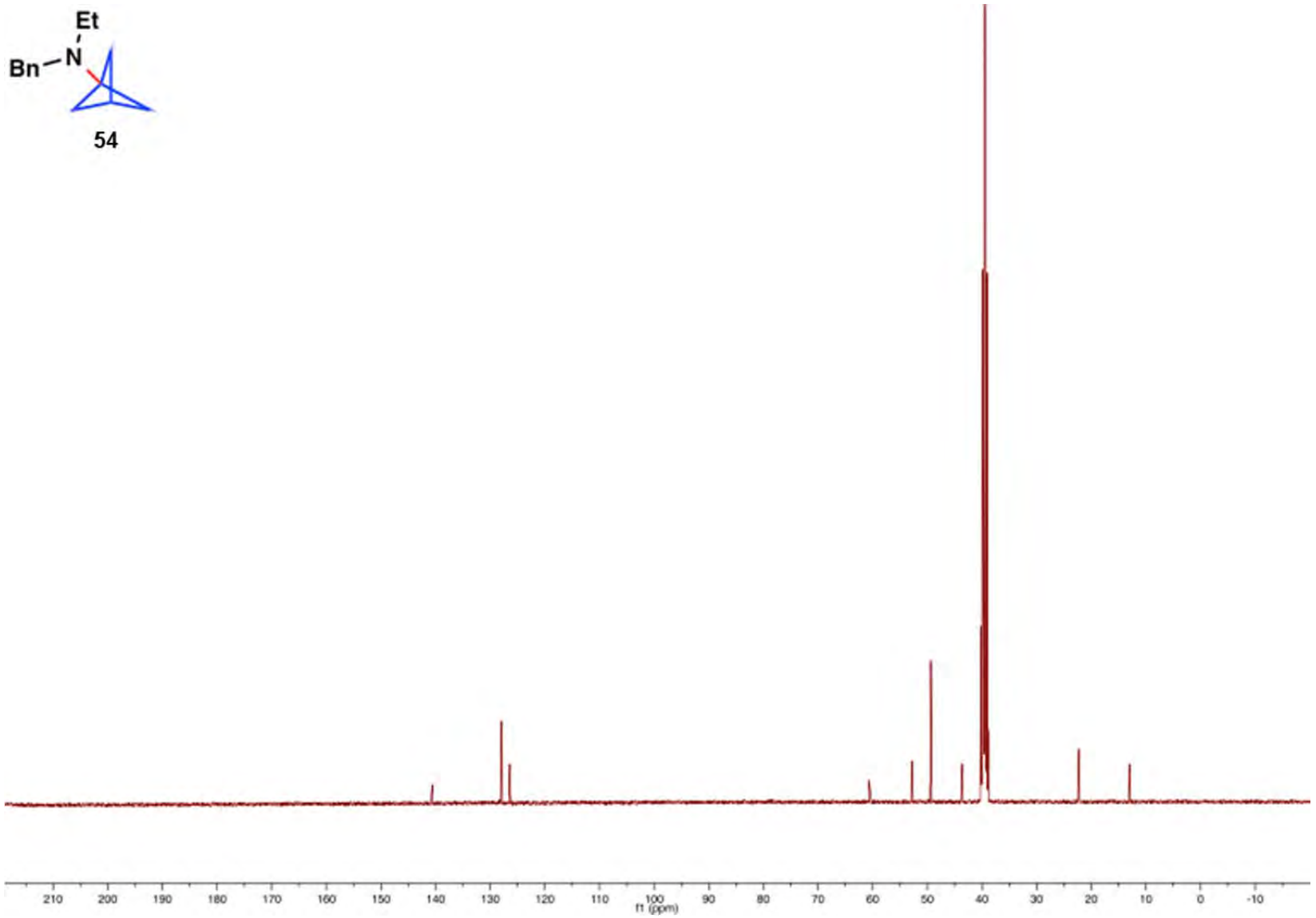
Et
N
Bn
54
210
200
190
180
170
160
150
140
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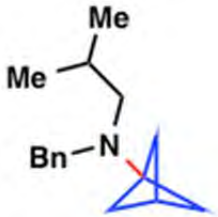
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



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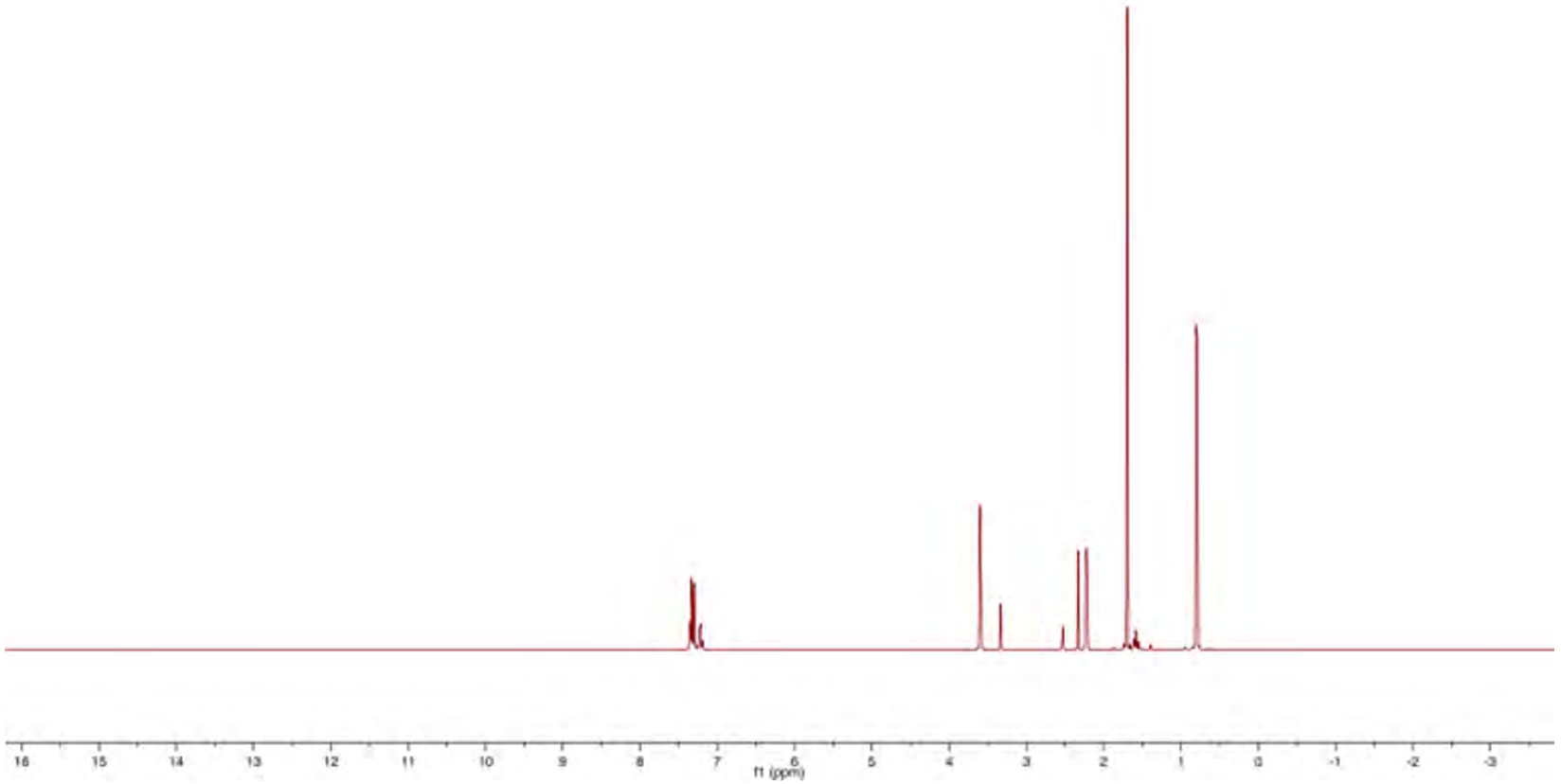
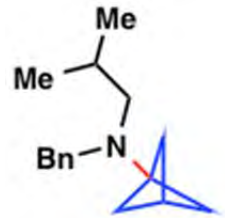
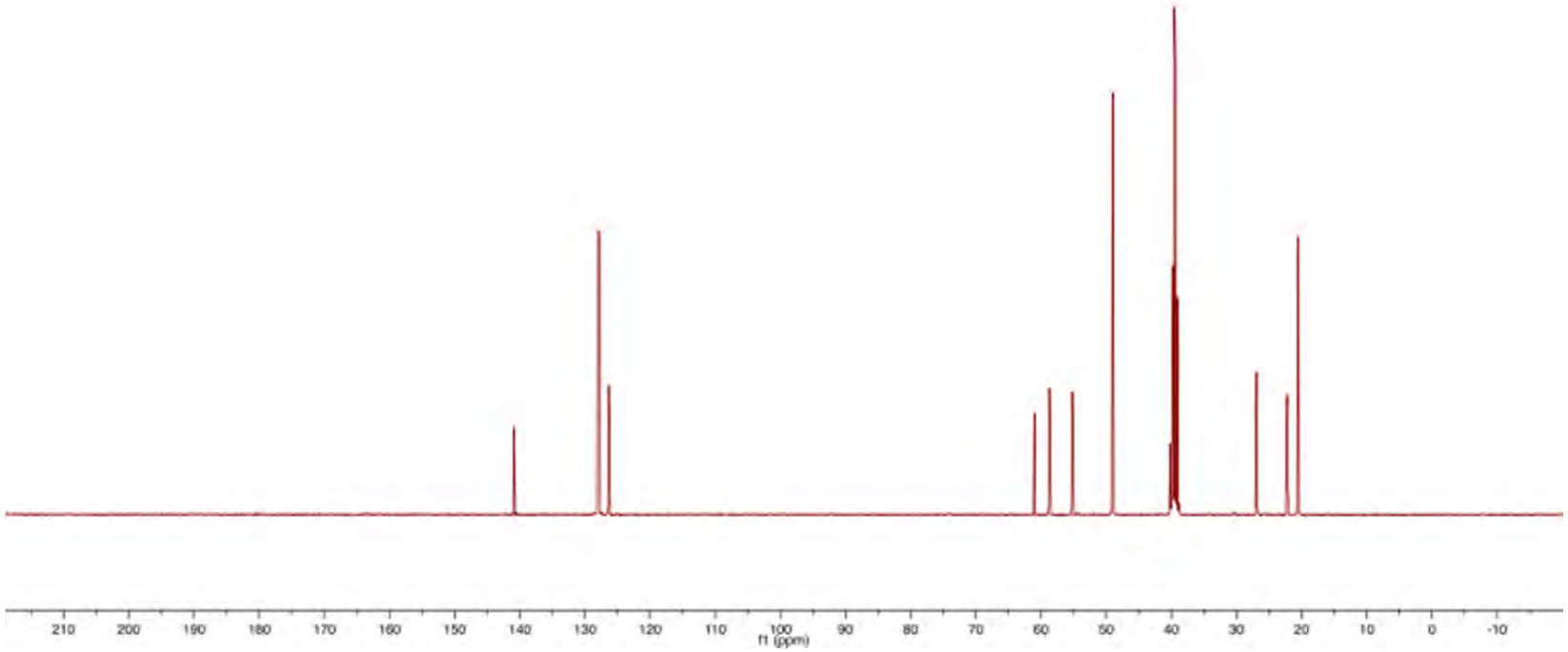



Me
Me
Bn
N

55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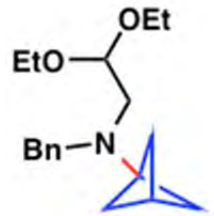
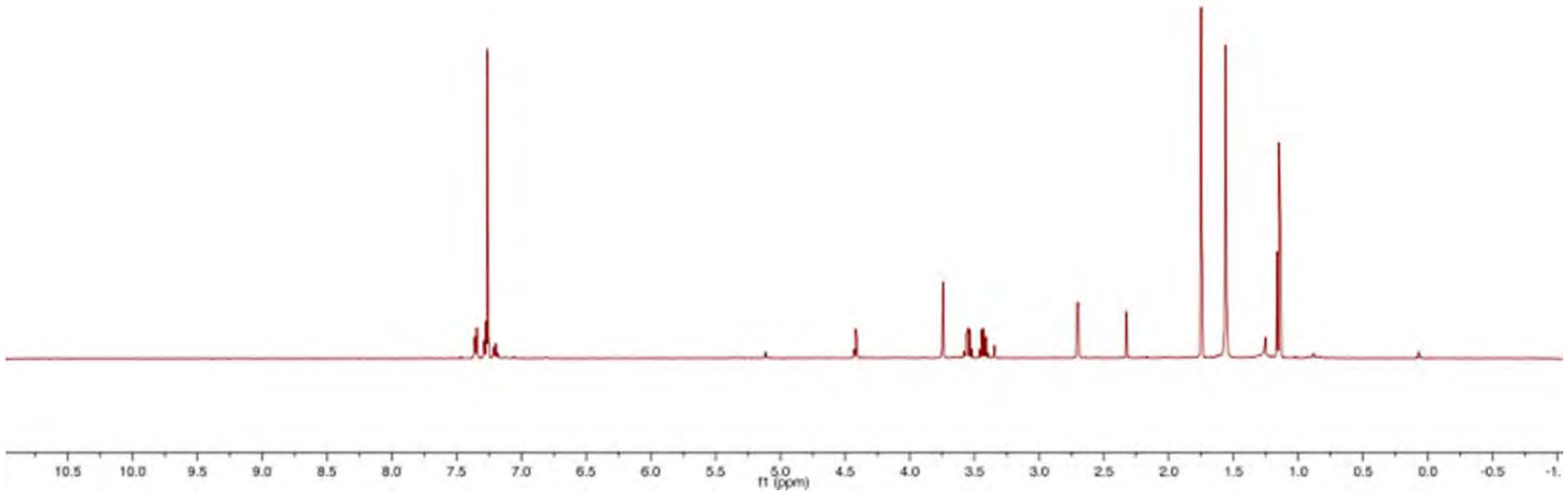
f1 (ppm)


OEt
EtO
Bn
N

56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5.0
f1 (ppm)
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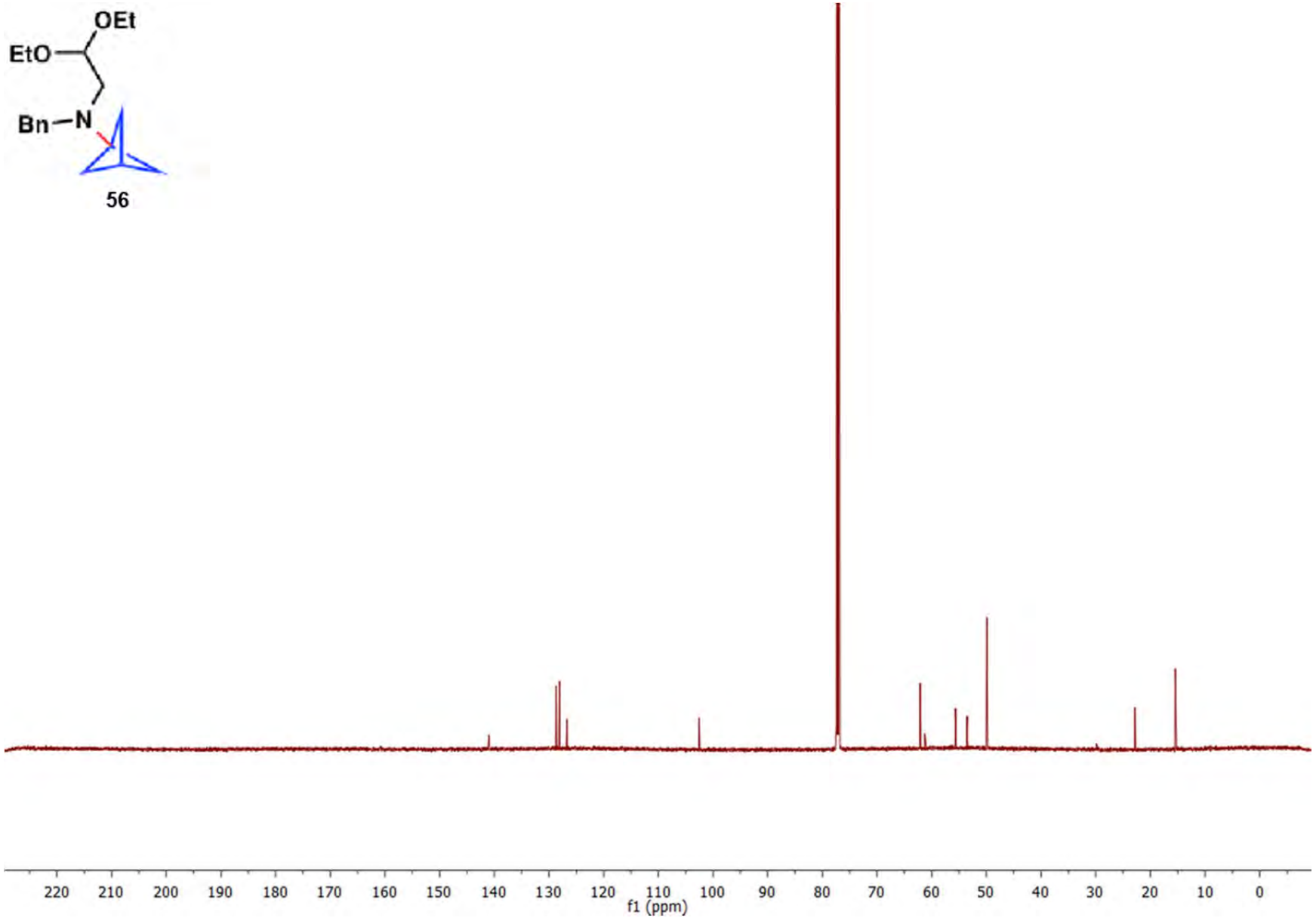
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EtO
Bn–N
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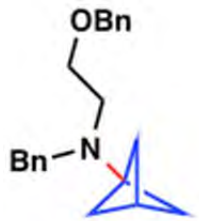

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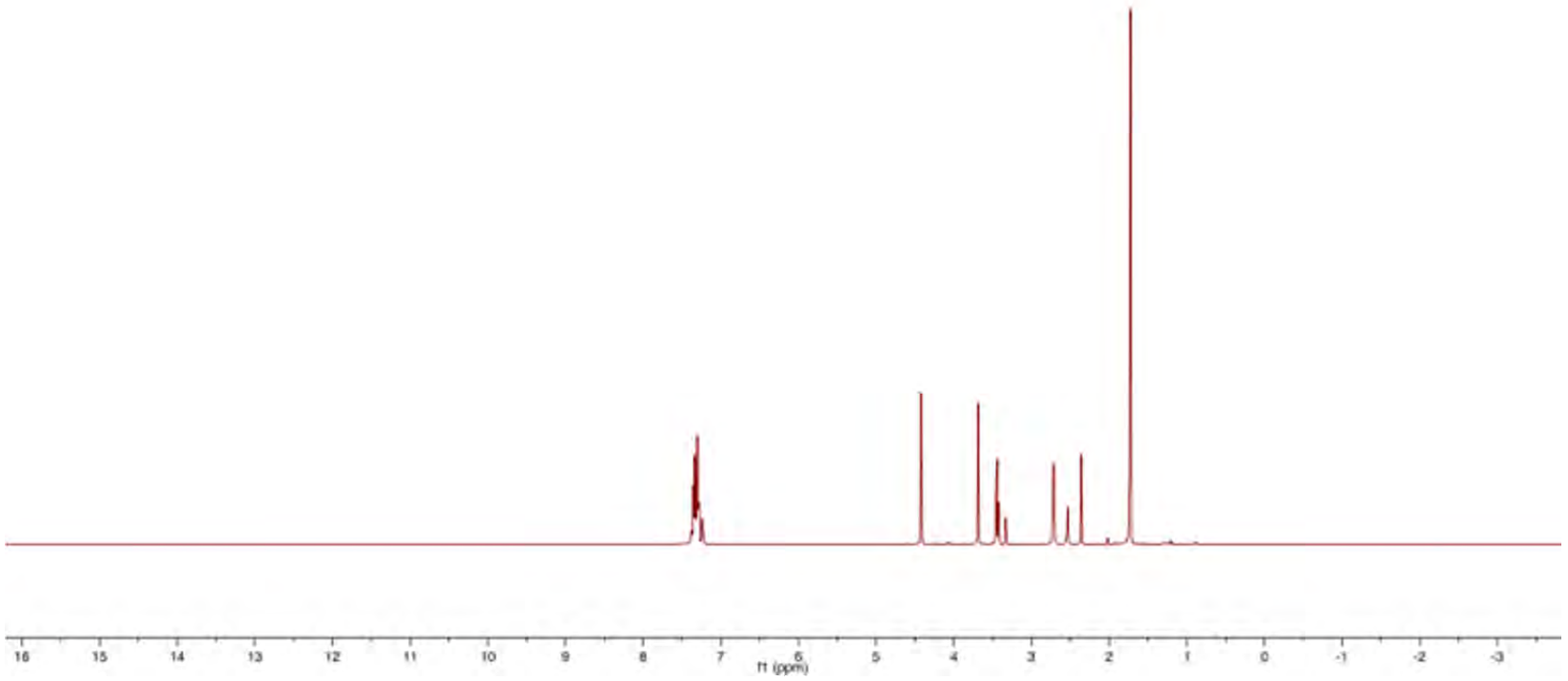

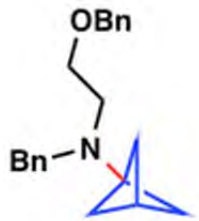
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Bn
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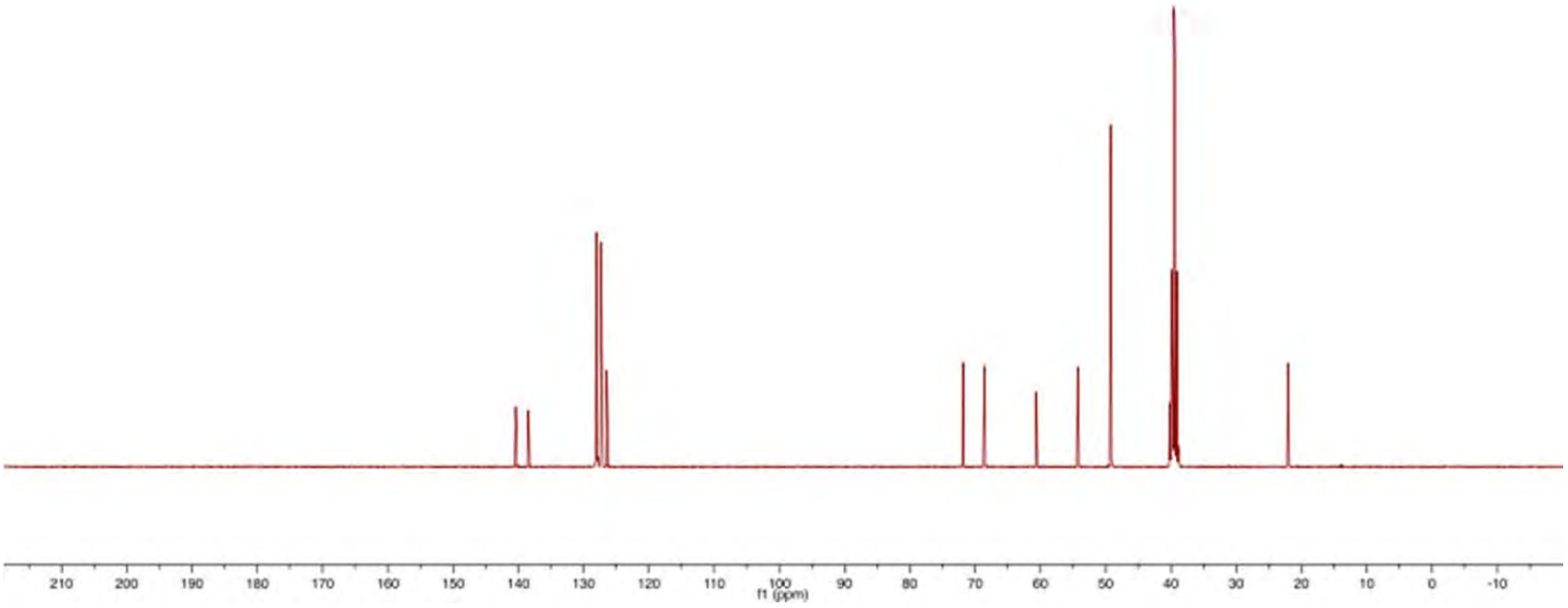
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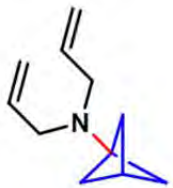
f1 (ppm)



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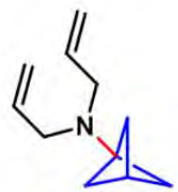
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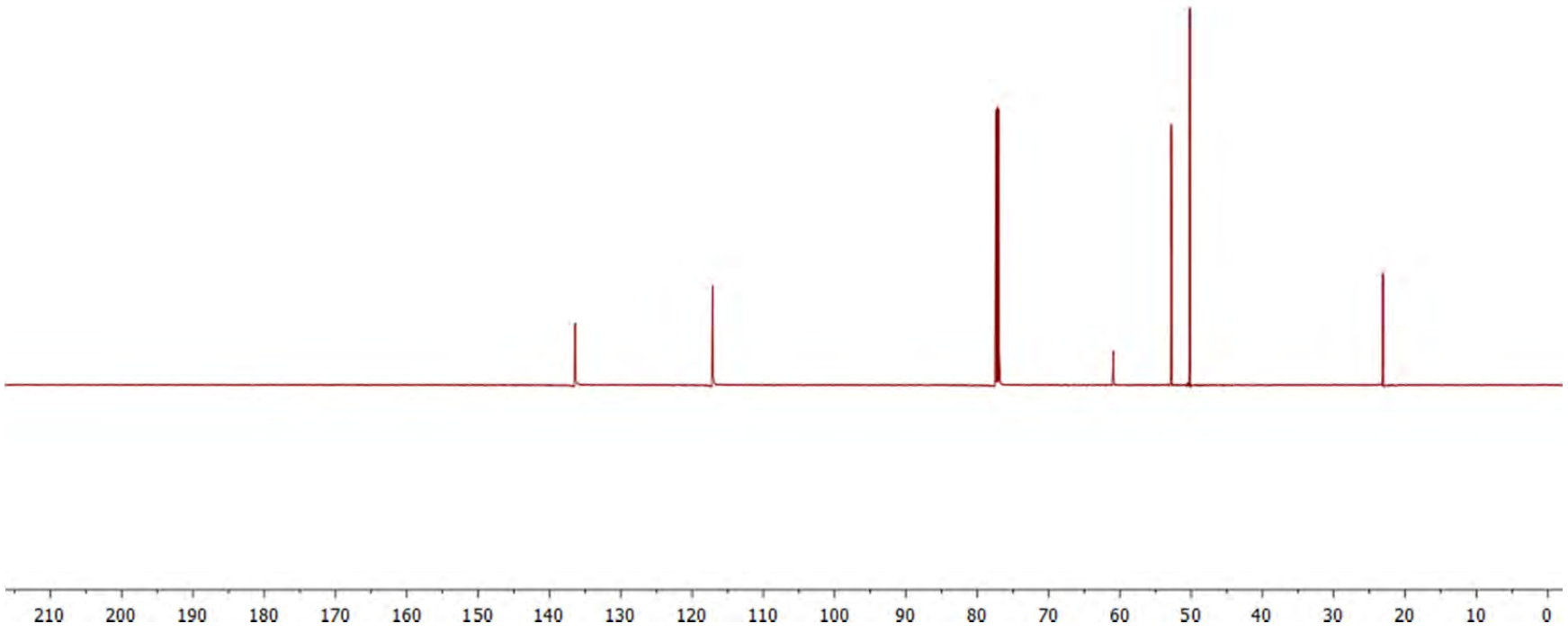
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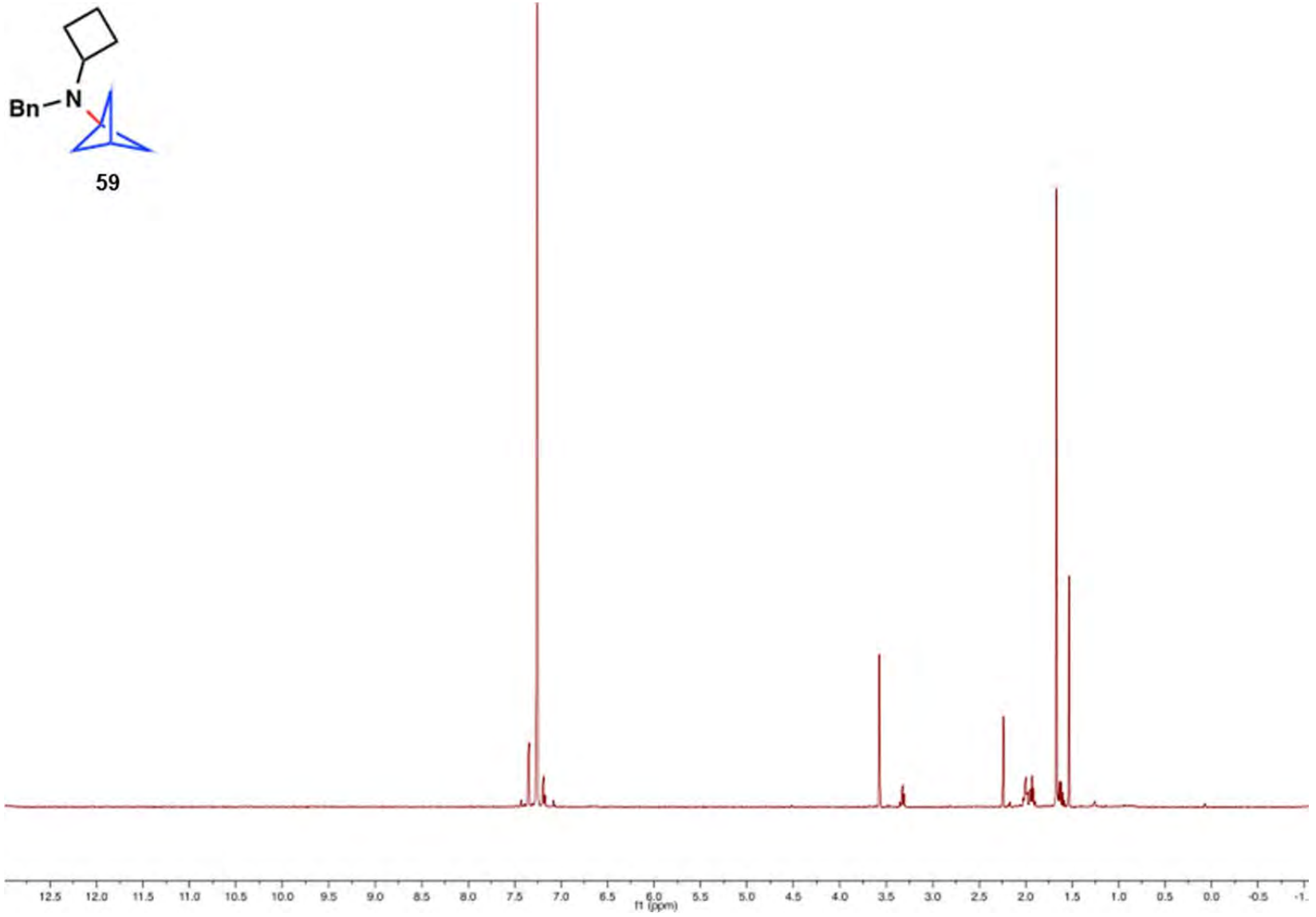
Bn
N
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7.5
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4.0
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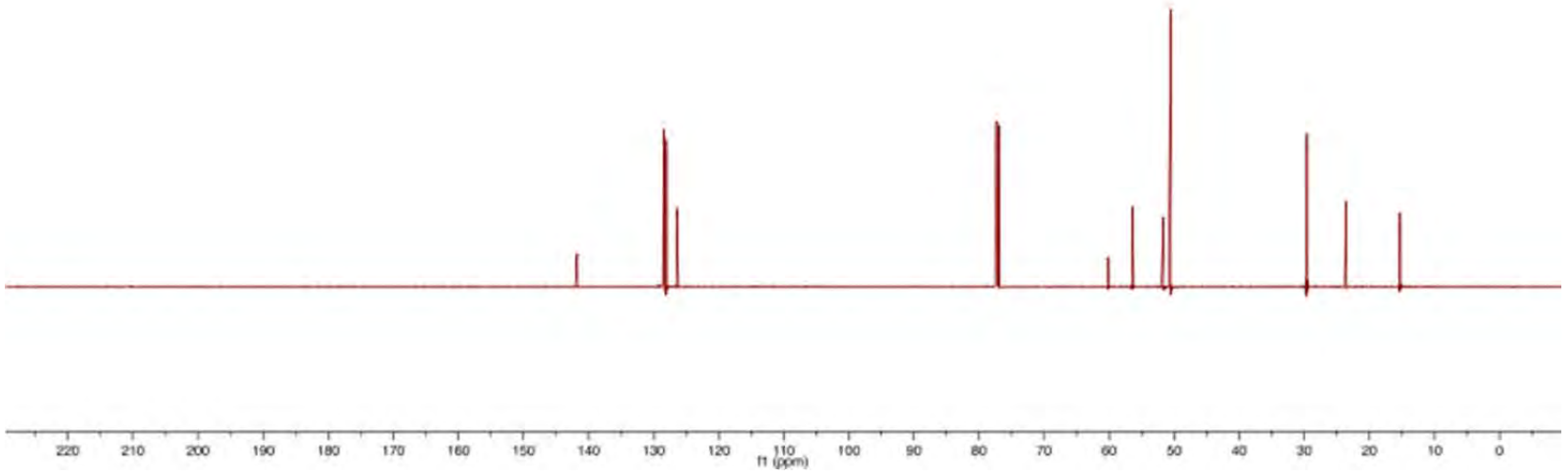
-0.5
f1 (ppm)


Bn
N

59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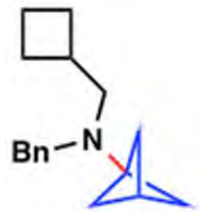
f1 (ppm)



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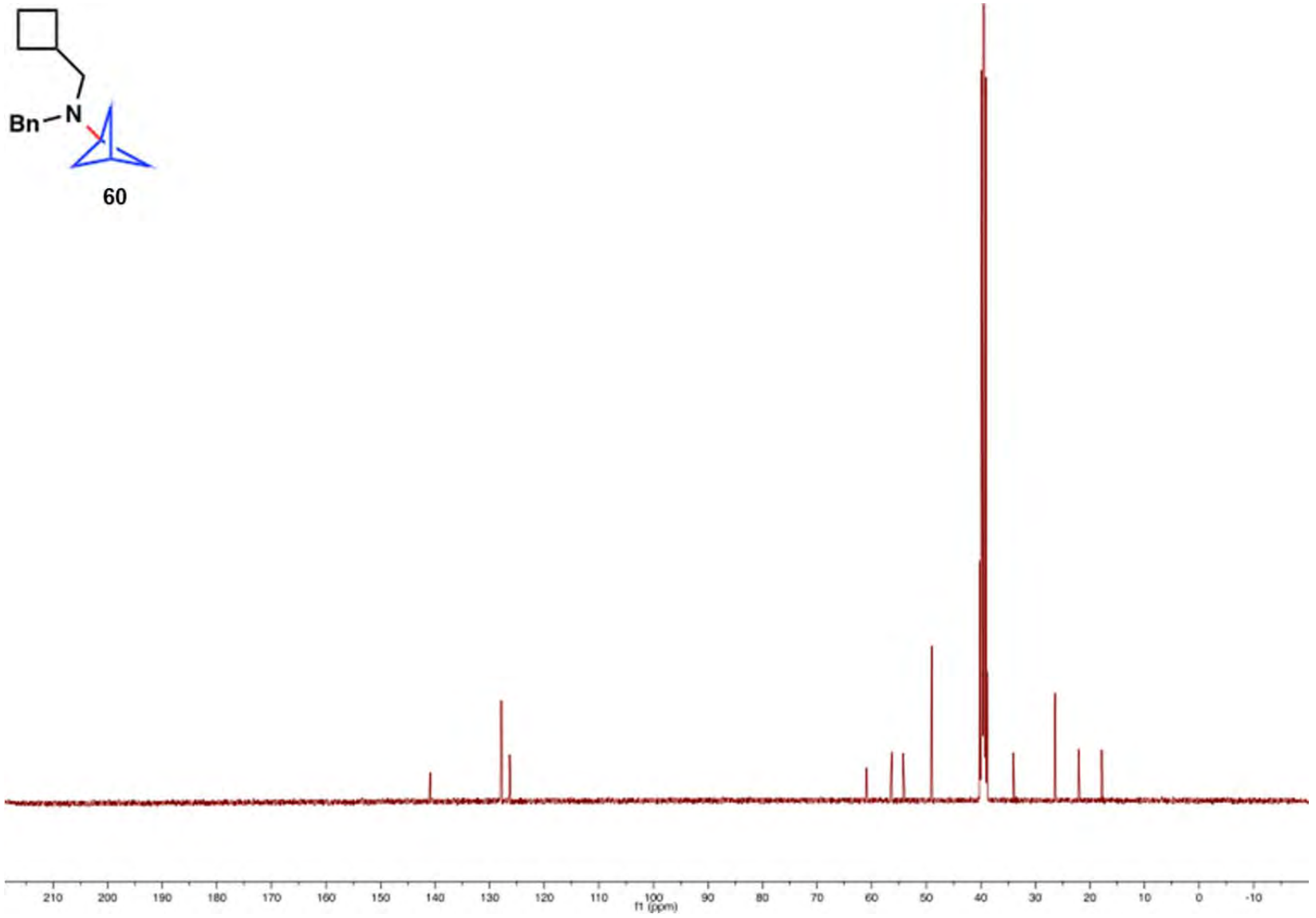
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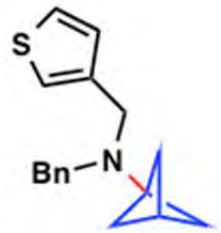
-10
f1 (ppm)


S
Bn
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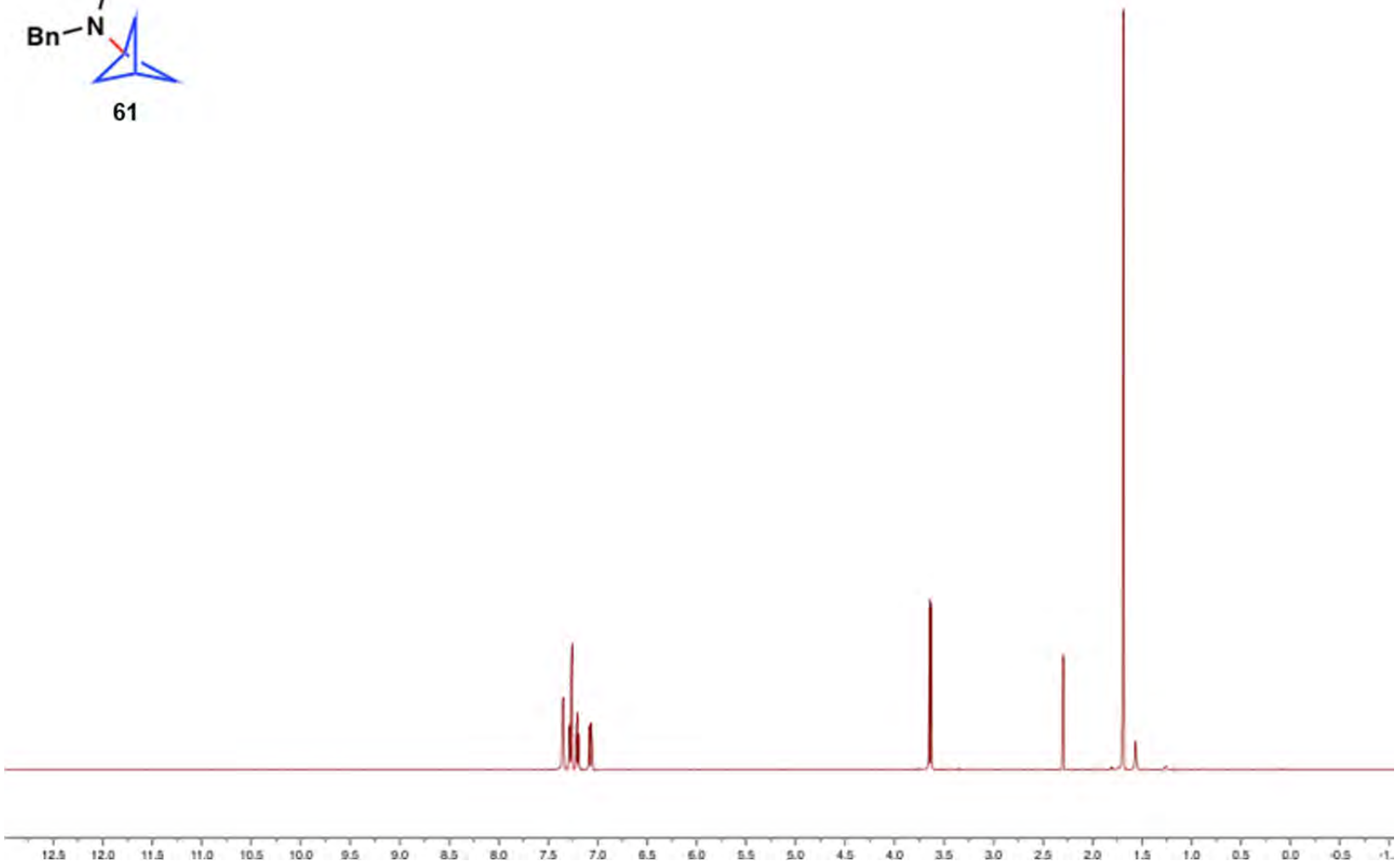
61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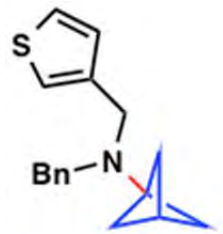
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Bn
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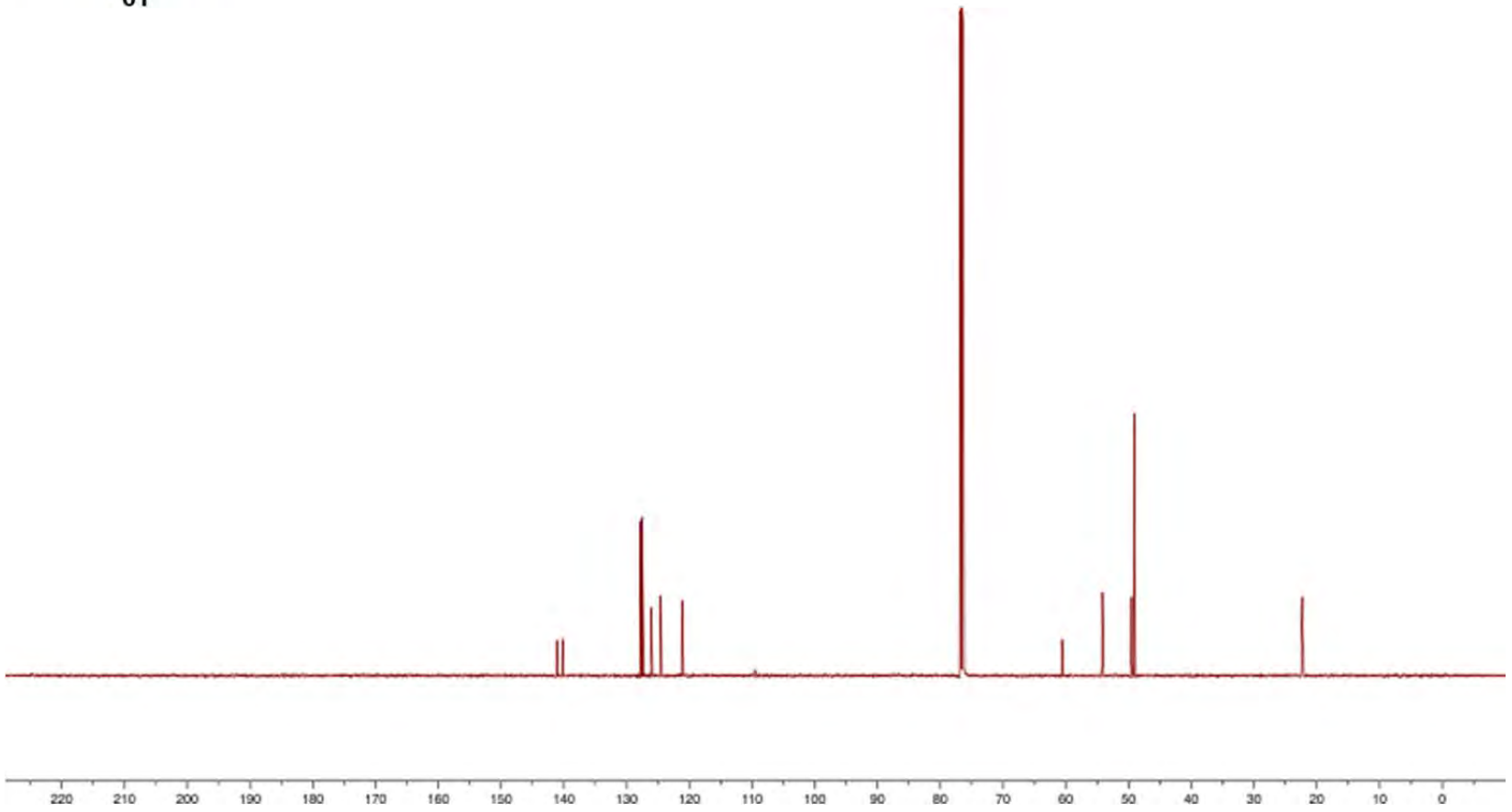
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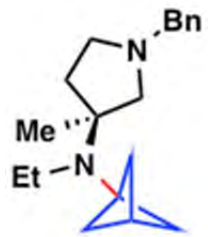

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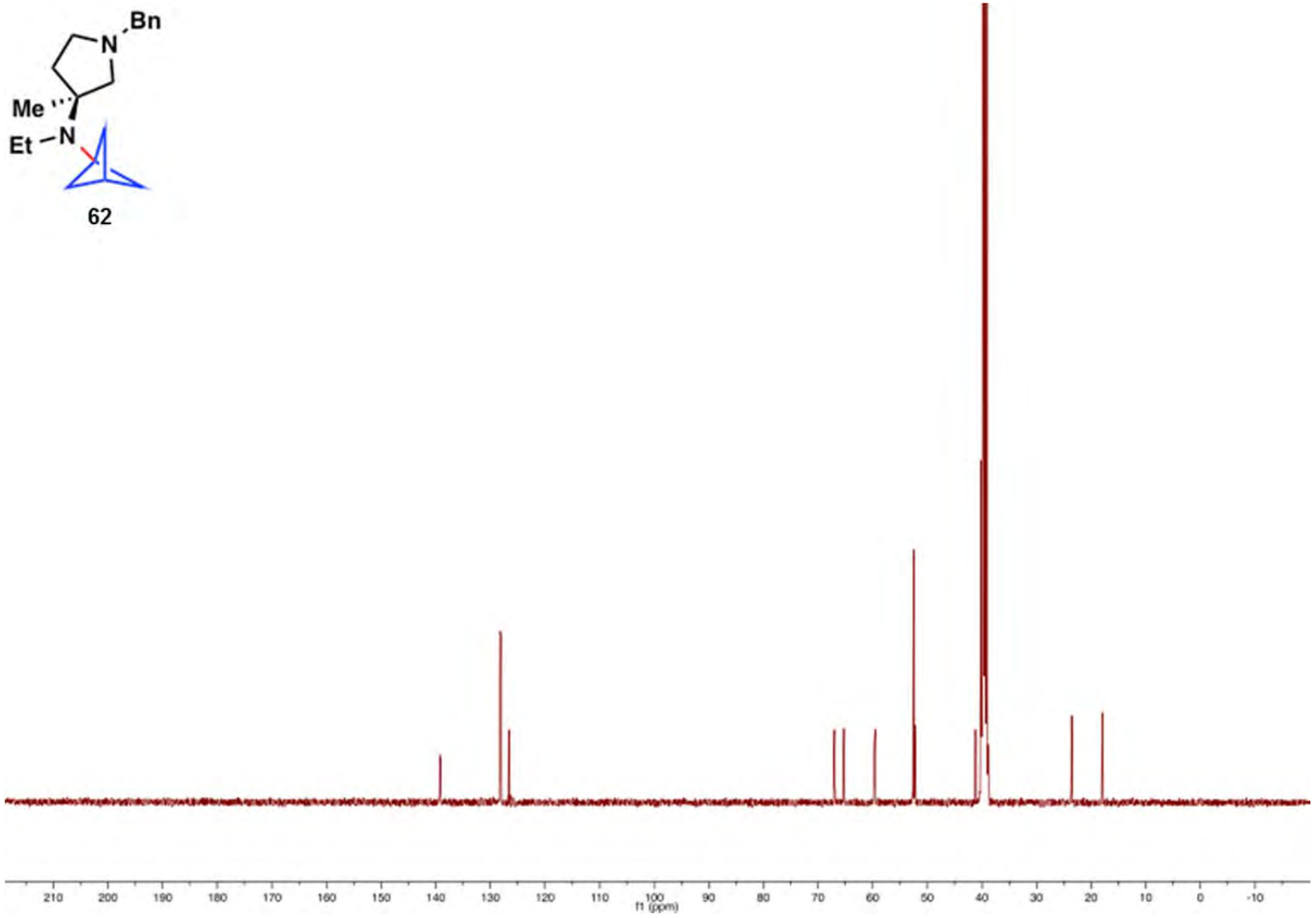
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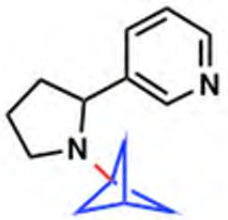
0
-10
f1 (ppm)



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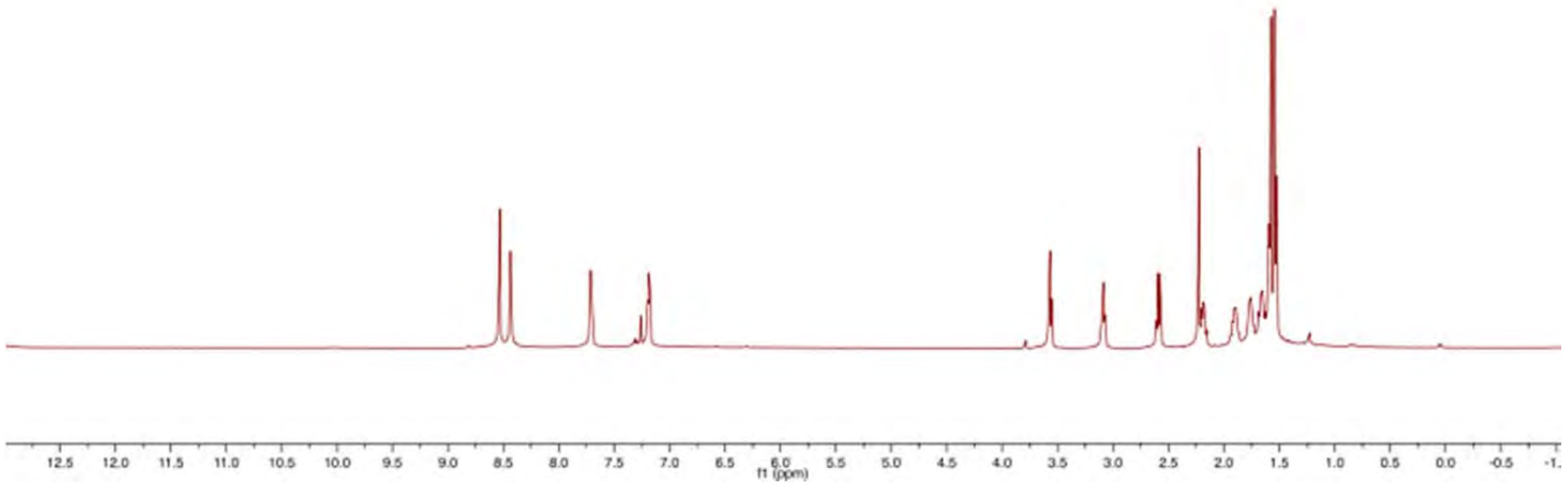
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9.0
8.5
8.0
7.5
7.0
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6.0
f1 (ppm)
5.5
5.0
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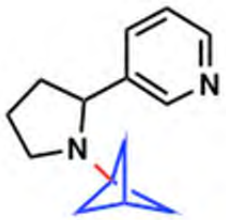
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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N

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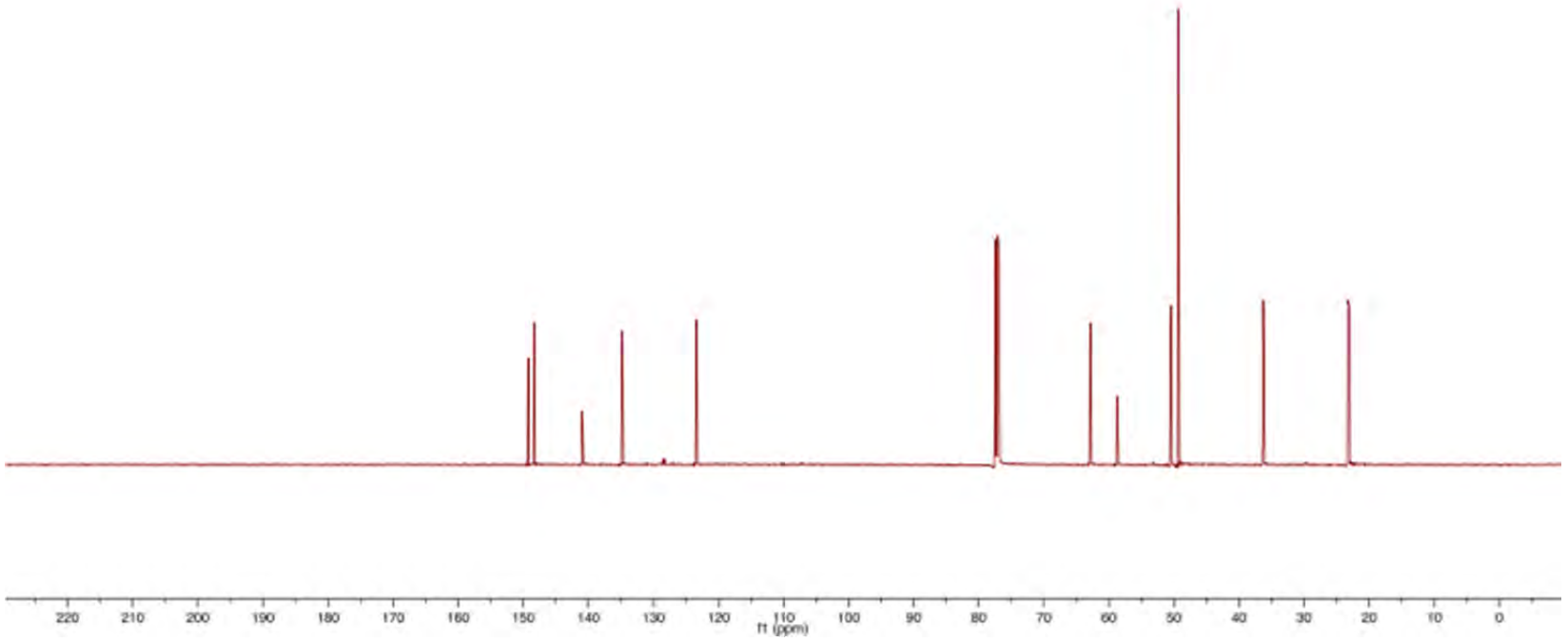
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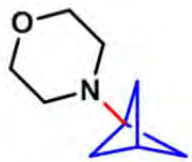
0
f1 (ppm)



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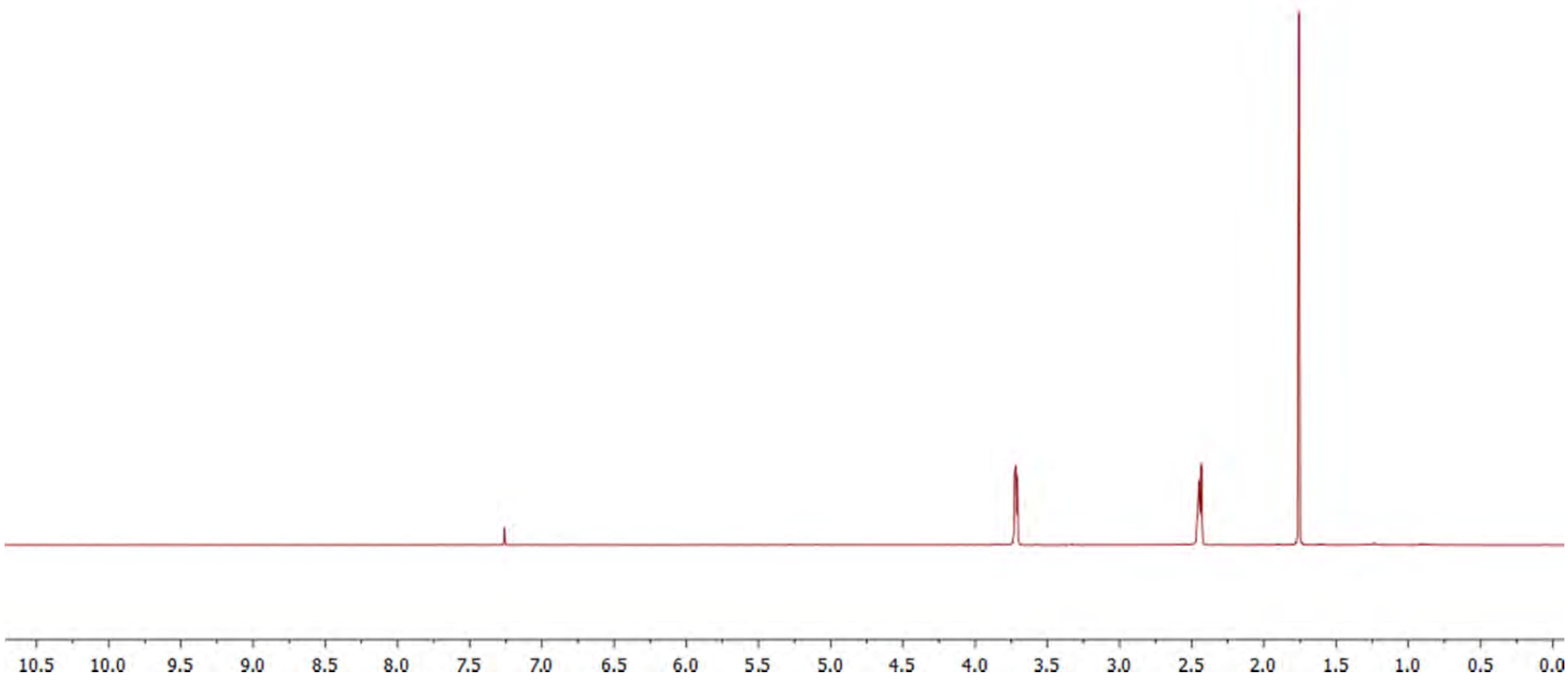

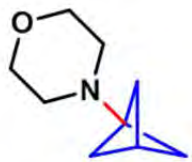
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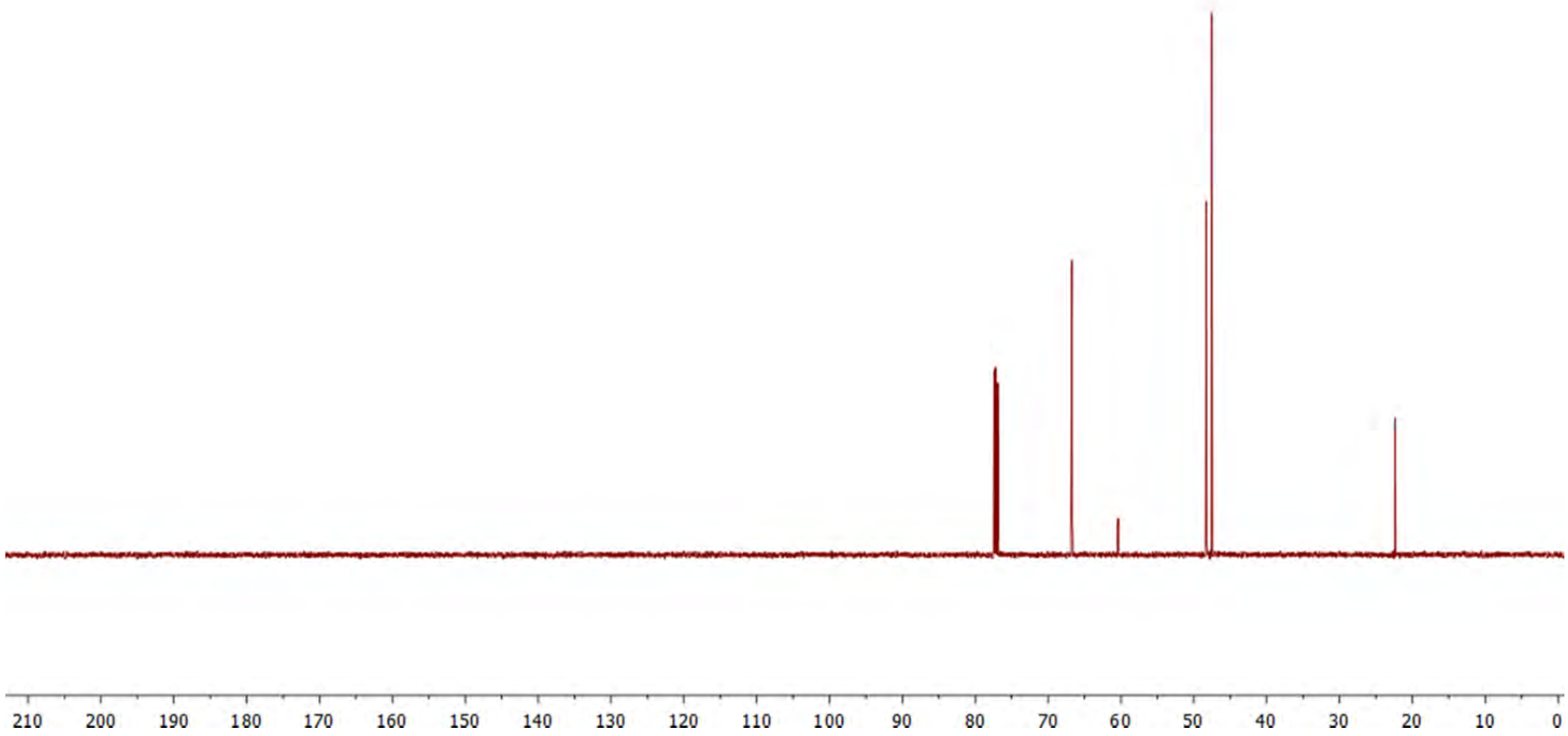
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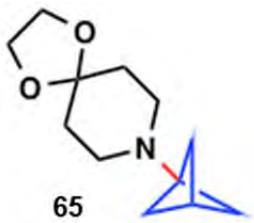
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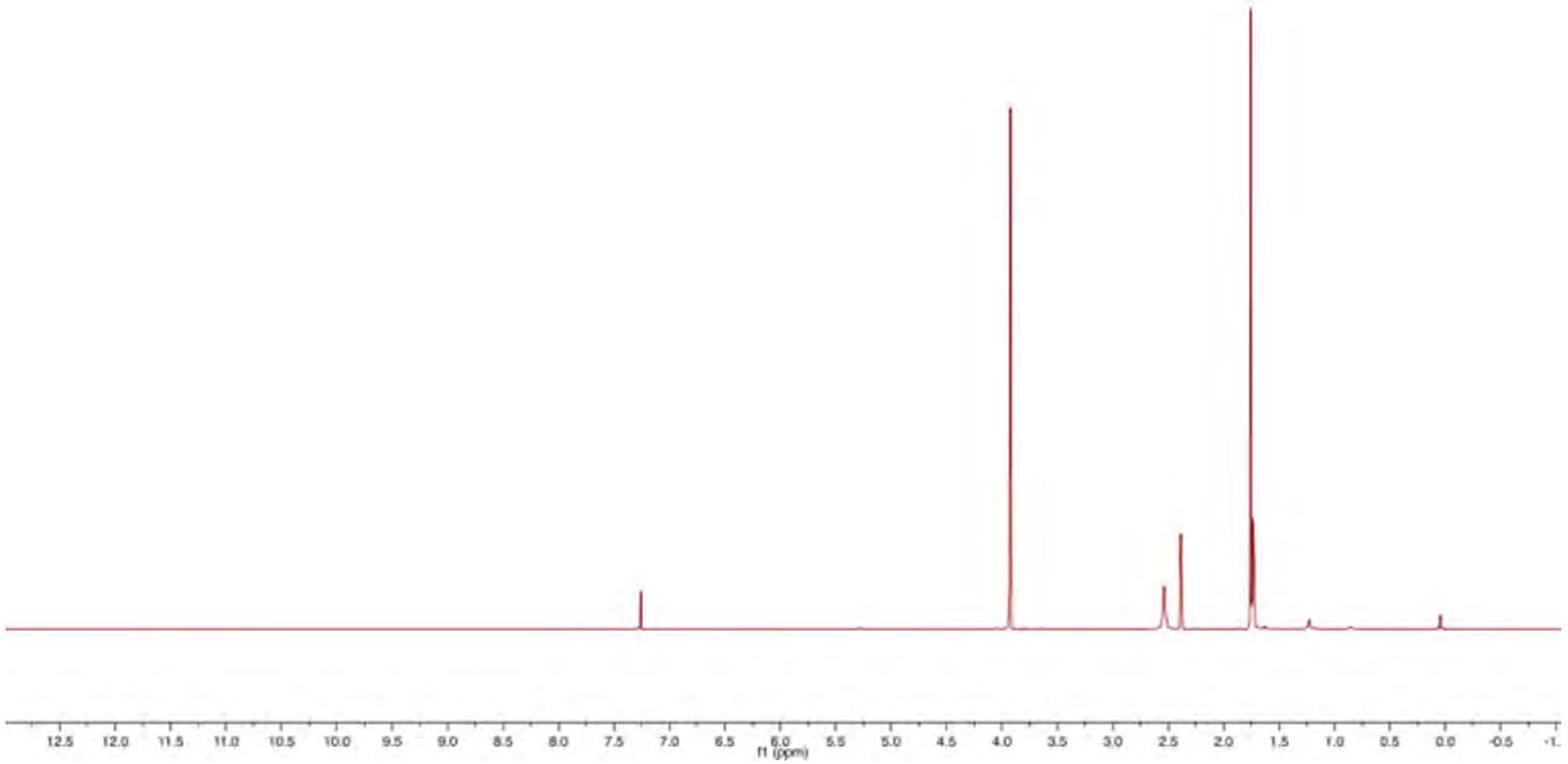
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8.0
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7.0
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6.0
f1 (ppm)
5.5
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2.5
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1.0
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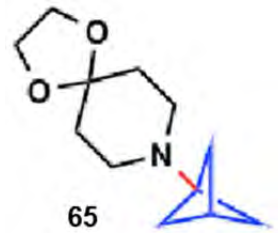
-0.5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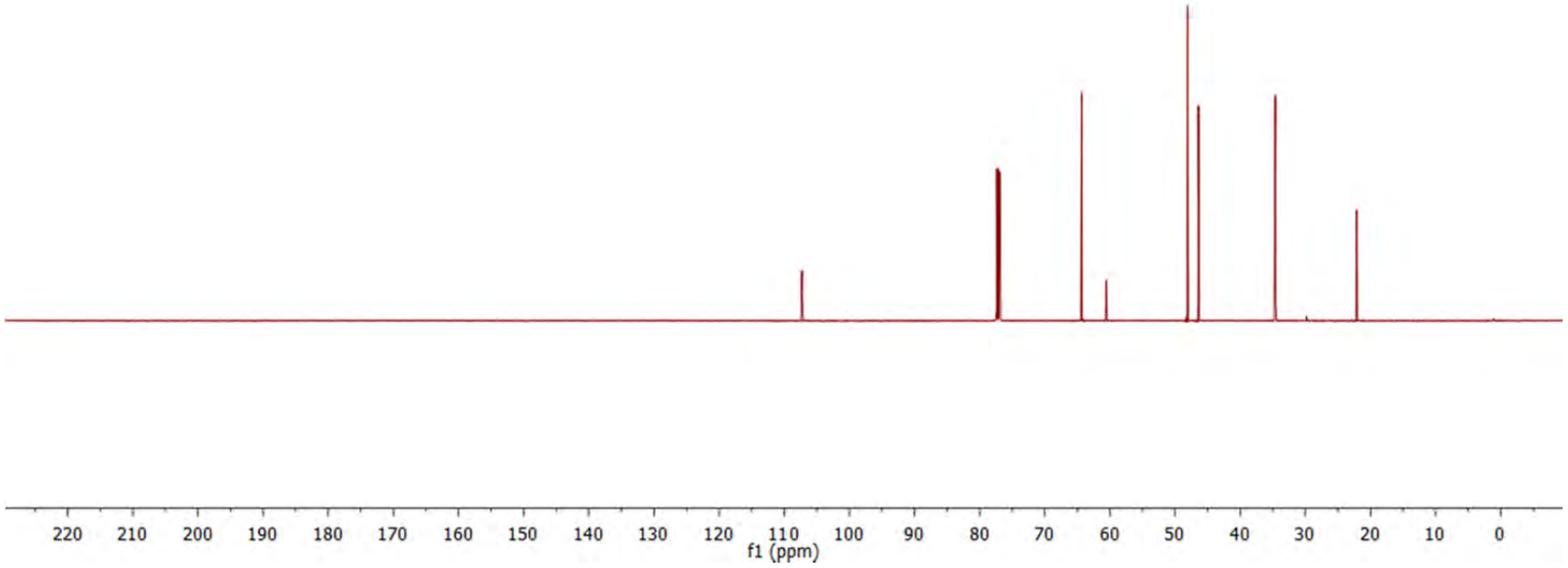
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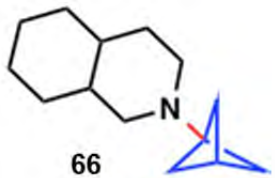
0
f1 (ppm)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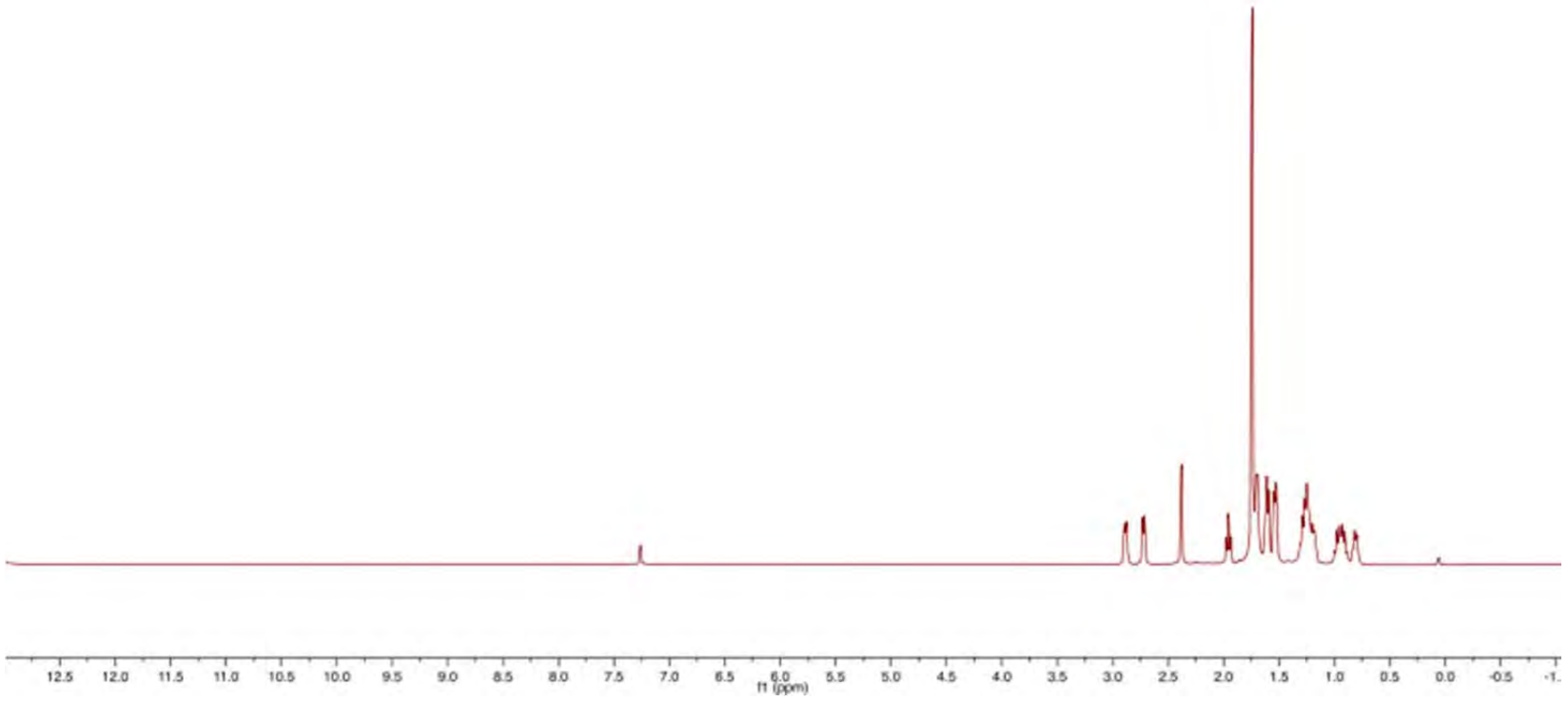
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
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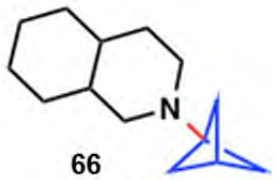
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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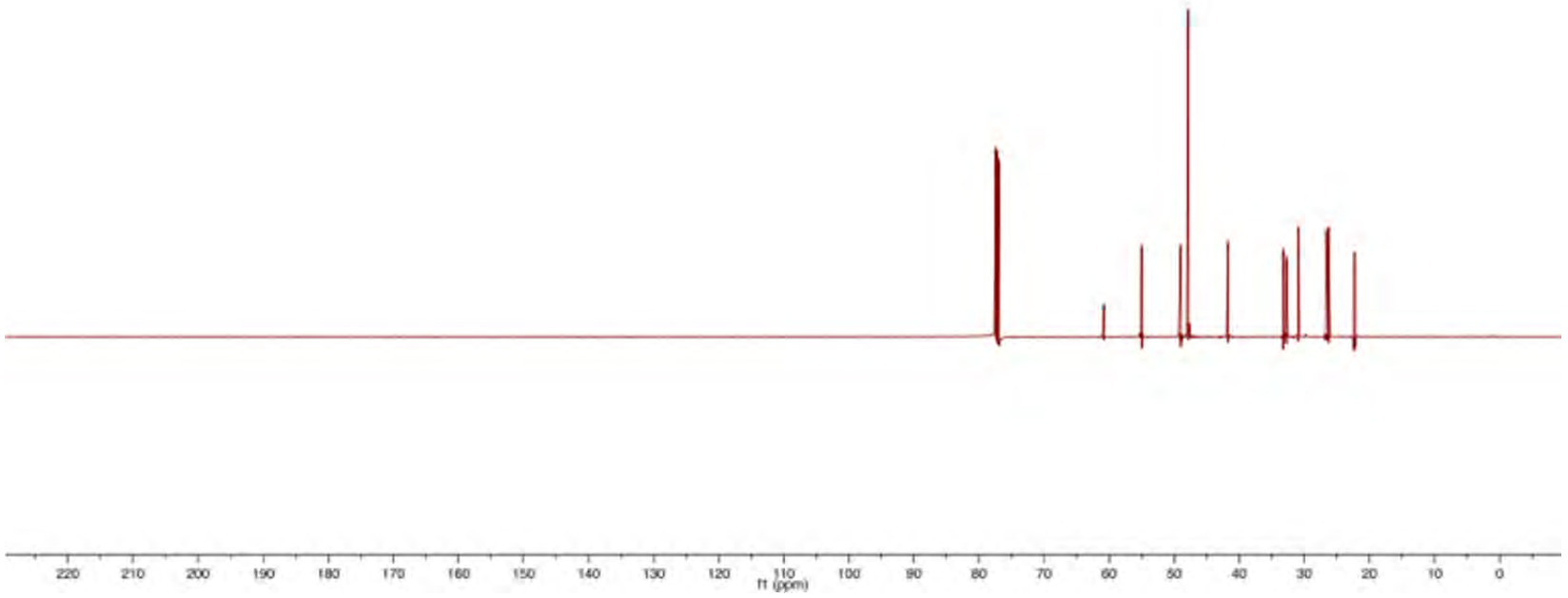
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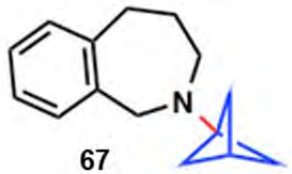
10
0
f1 (ppm)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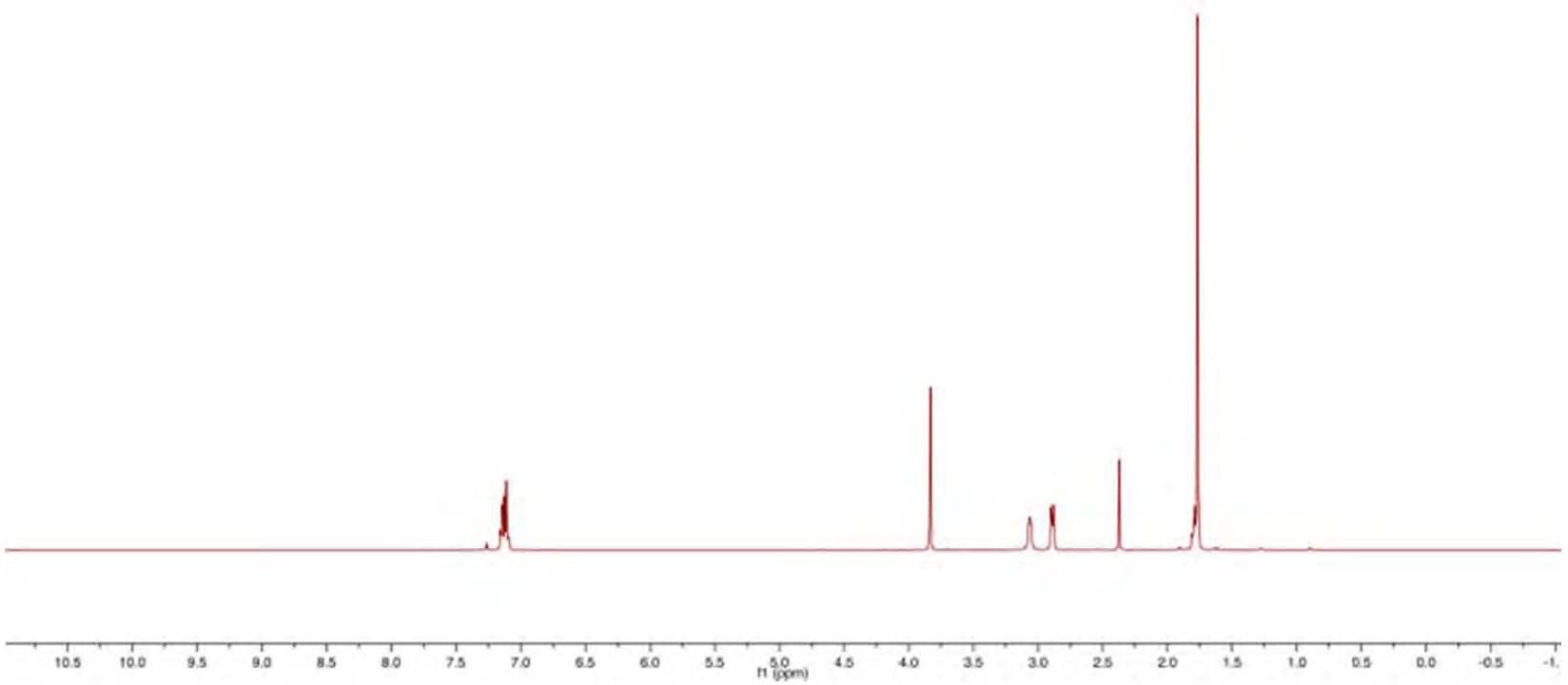
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9.0
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8.0
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7.0
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6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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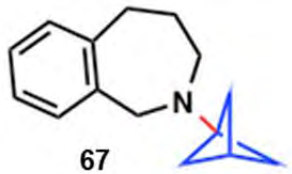
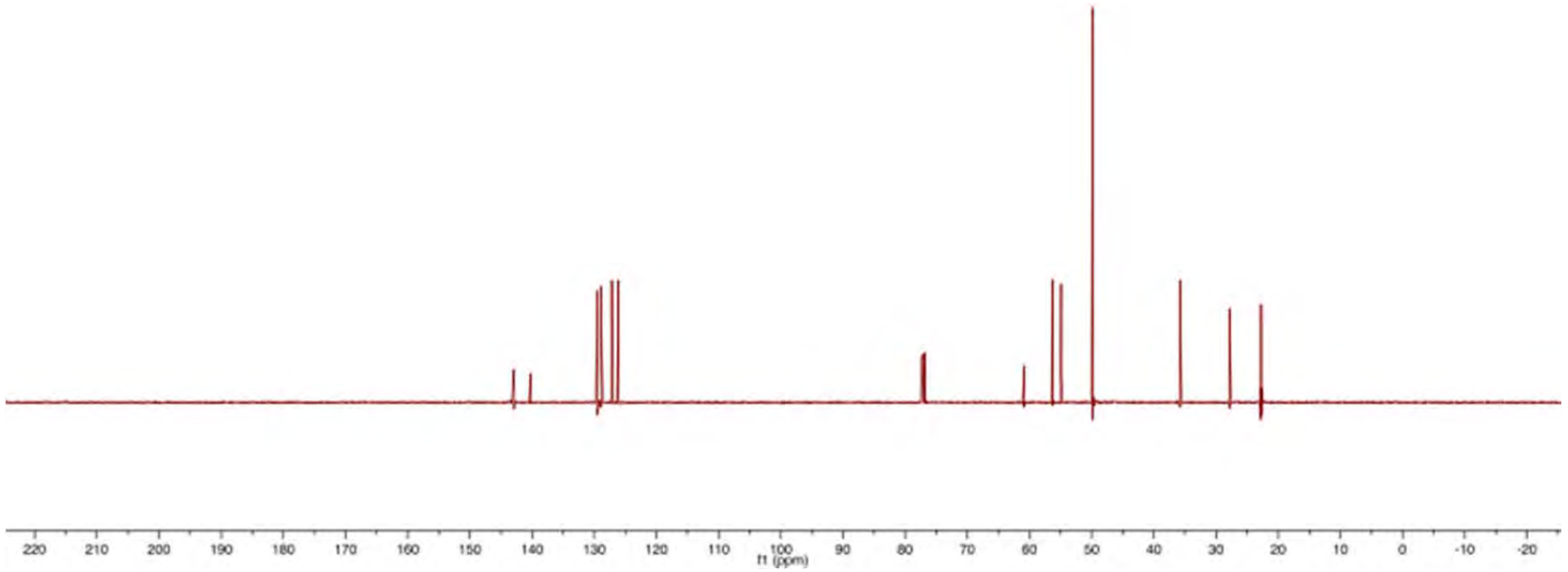
-0.5


N

67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160
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60
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20
10
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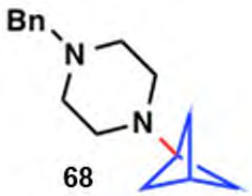
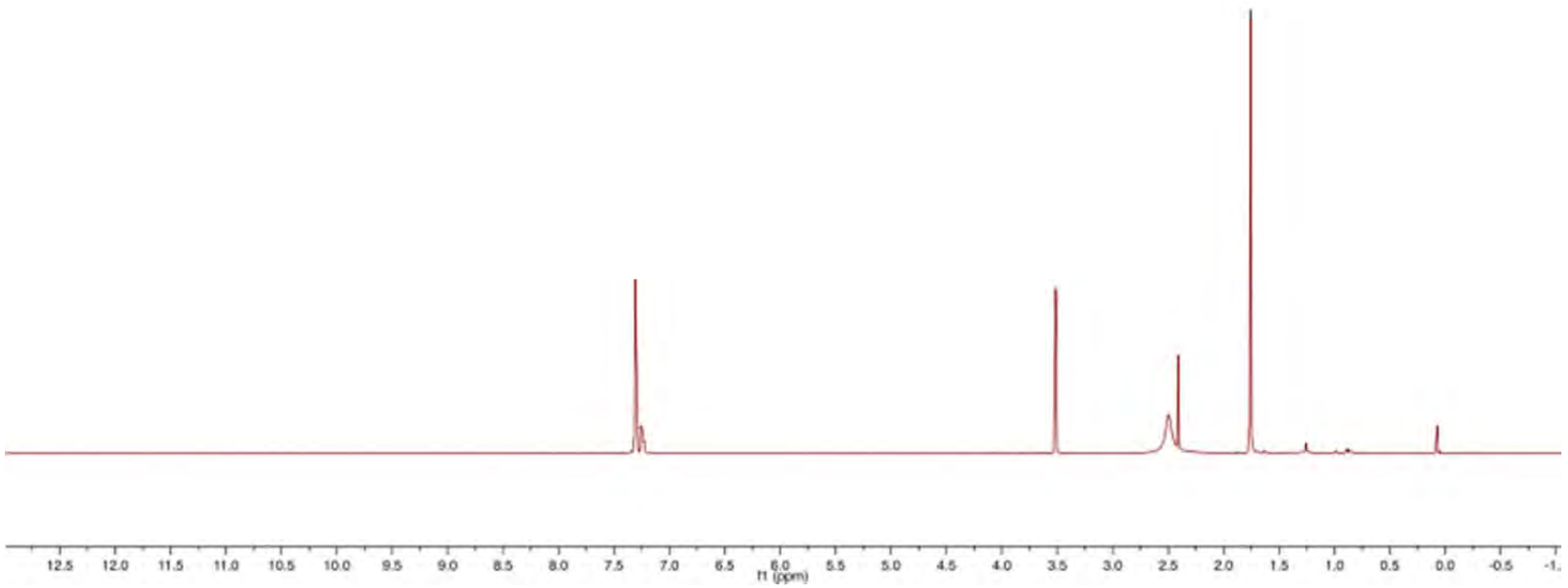
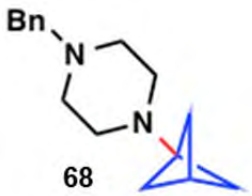
-10
-20
f1 (ppm)

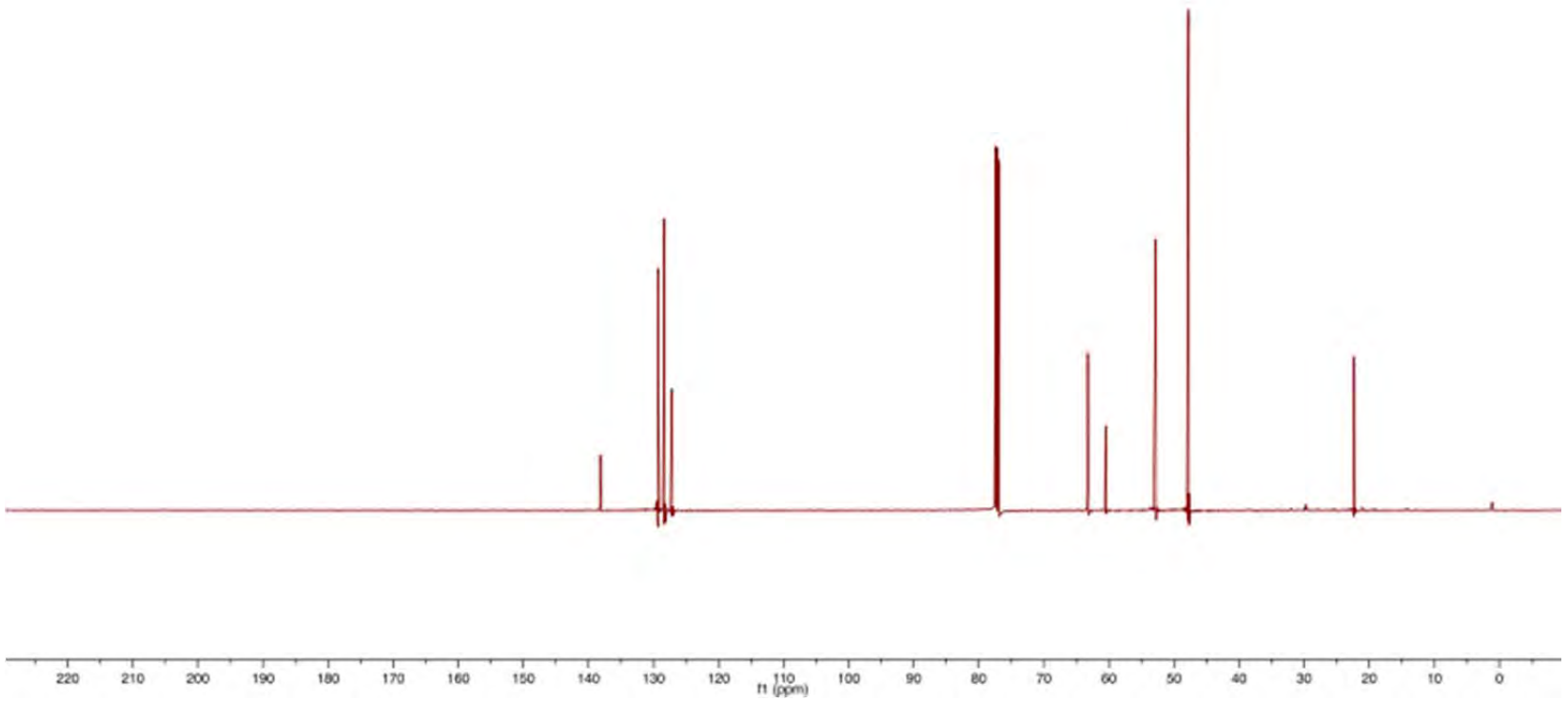

Bn
N
N

68


12.5 12.0 11.5 11.0 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)


Bn
N
N

68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20
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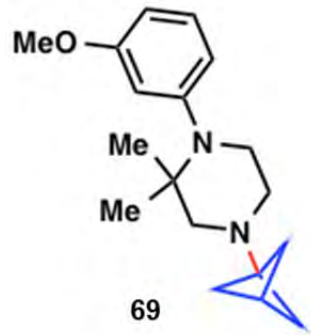
0
f1 (ppm)


MeO
Me
N
Me
N

69

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10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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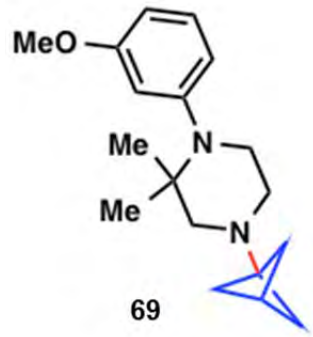
0.0
-0.5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Me
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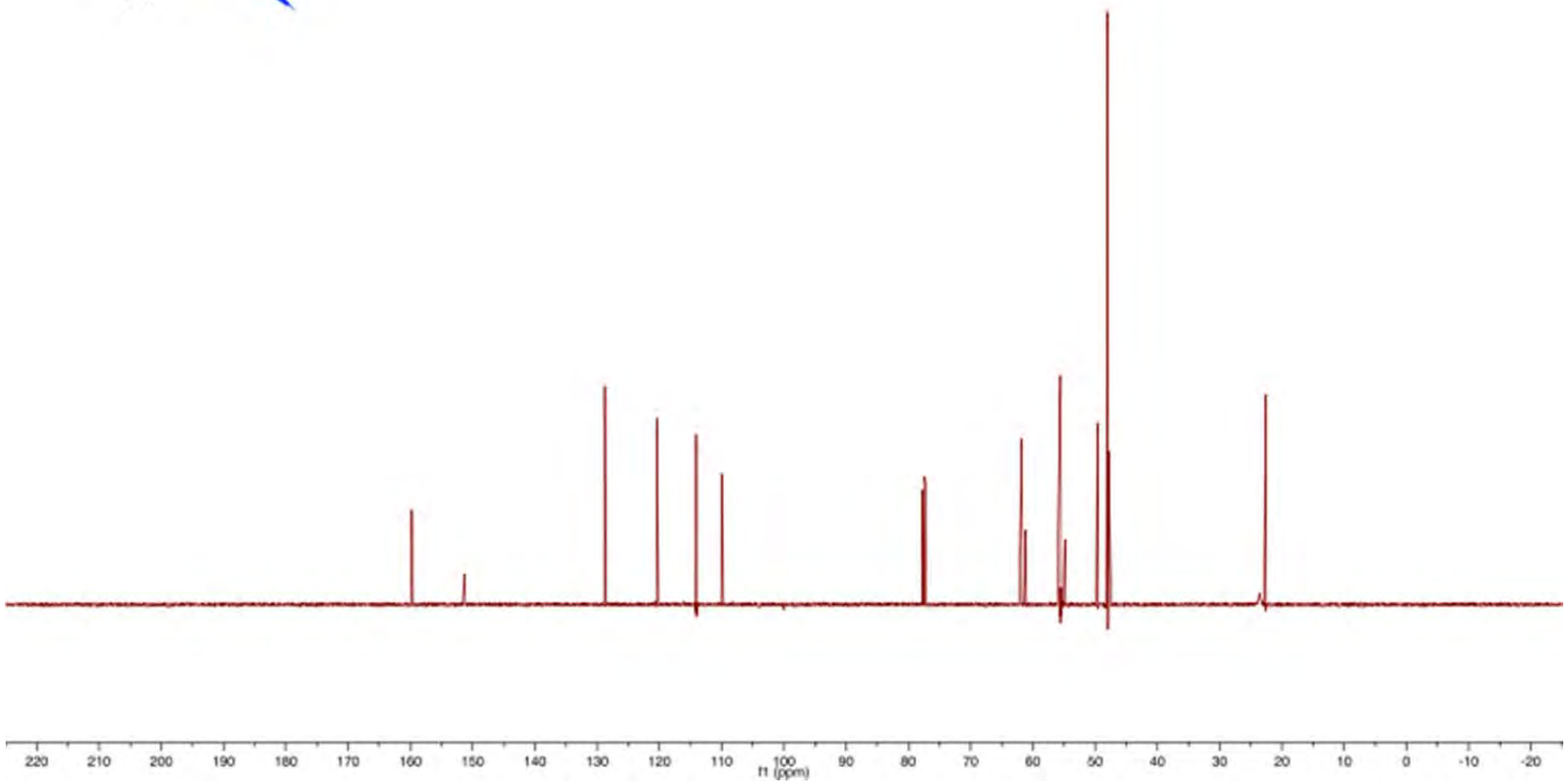
Me
N

69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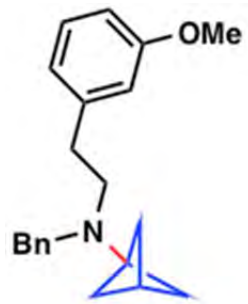
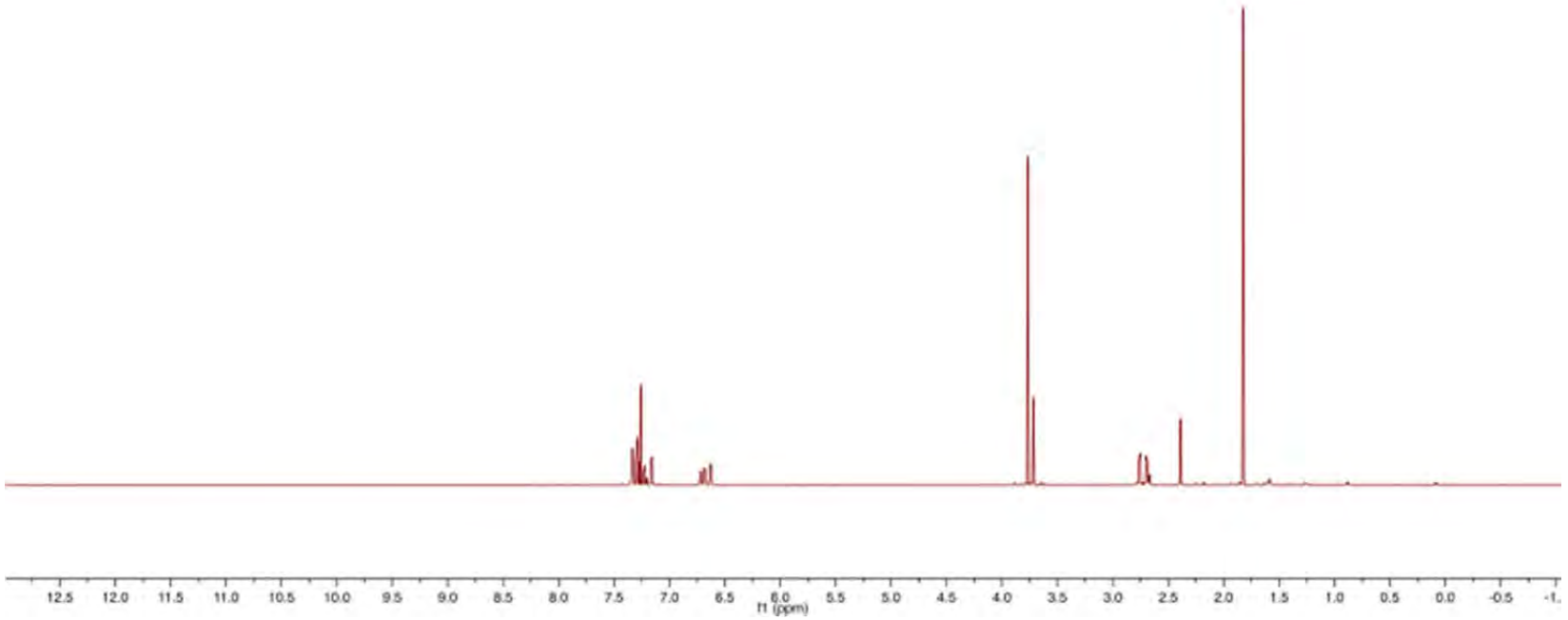
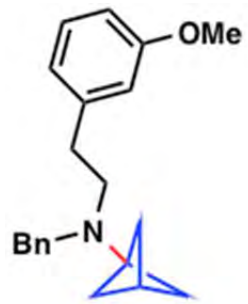
-20
f1 (ppm)

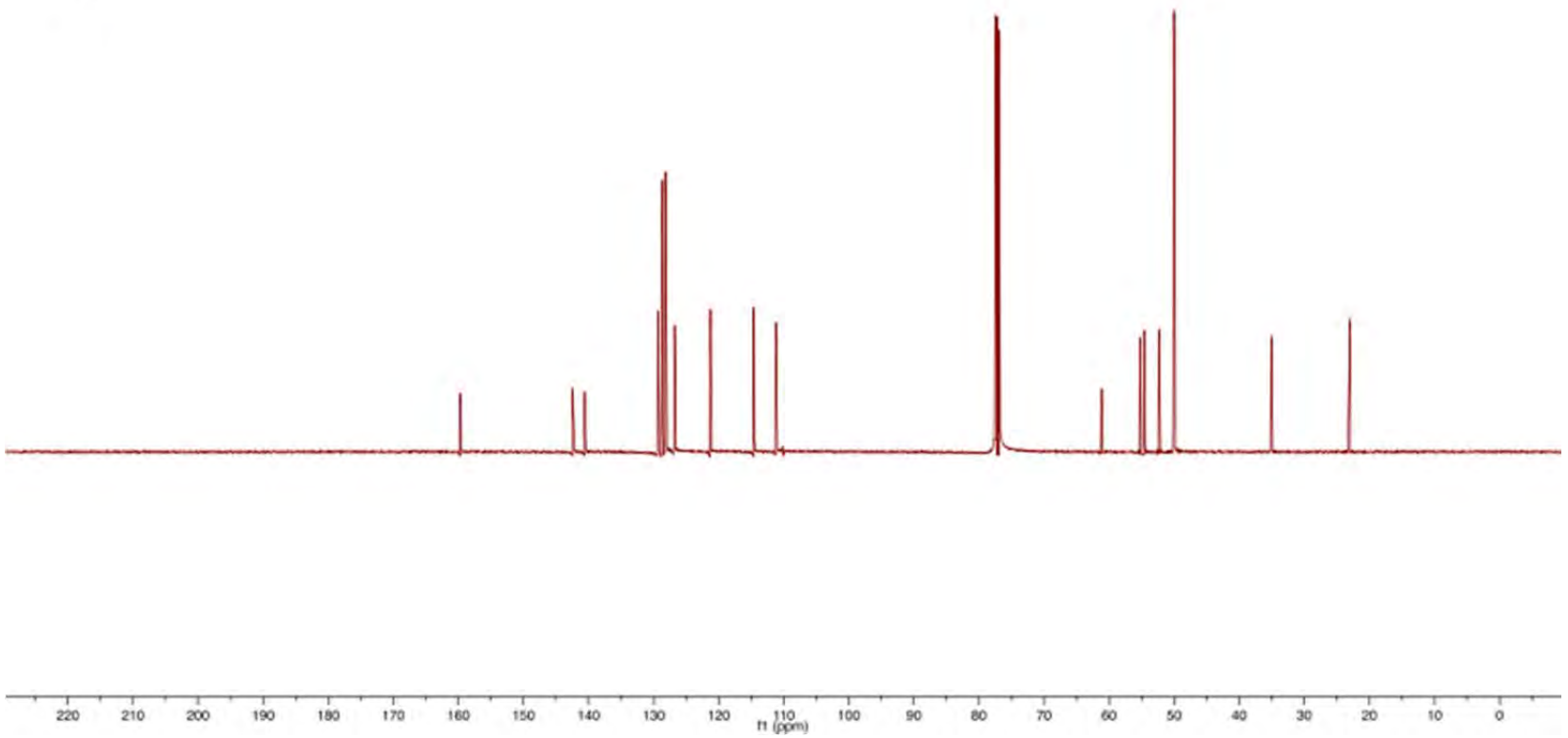

OMe
Bn
N

70


12.5 12.0 11.5 11.0 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)


OMe
Bn
N

70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100
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80
70
60
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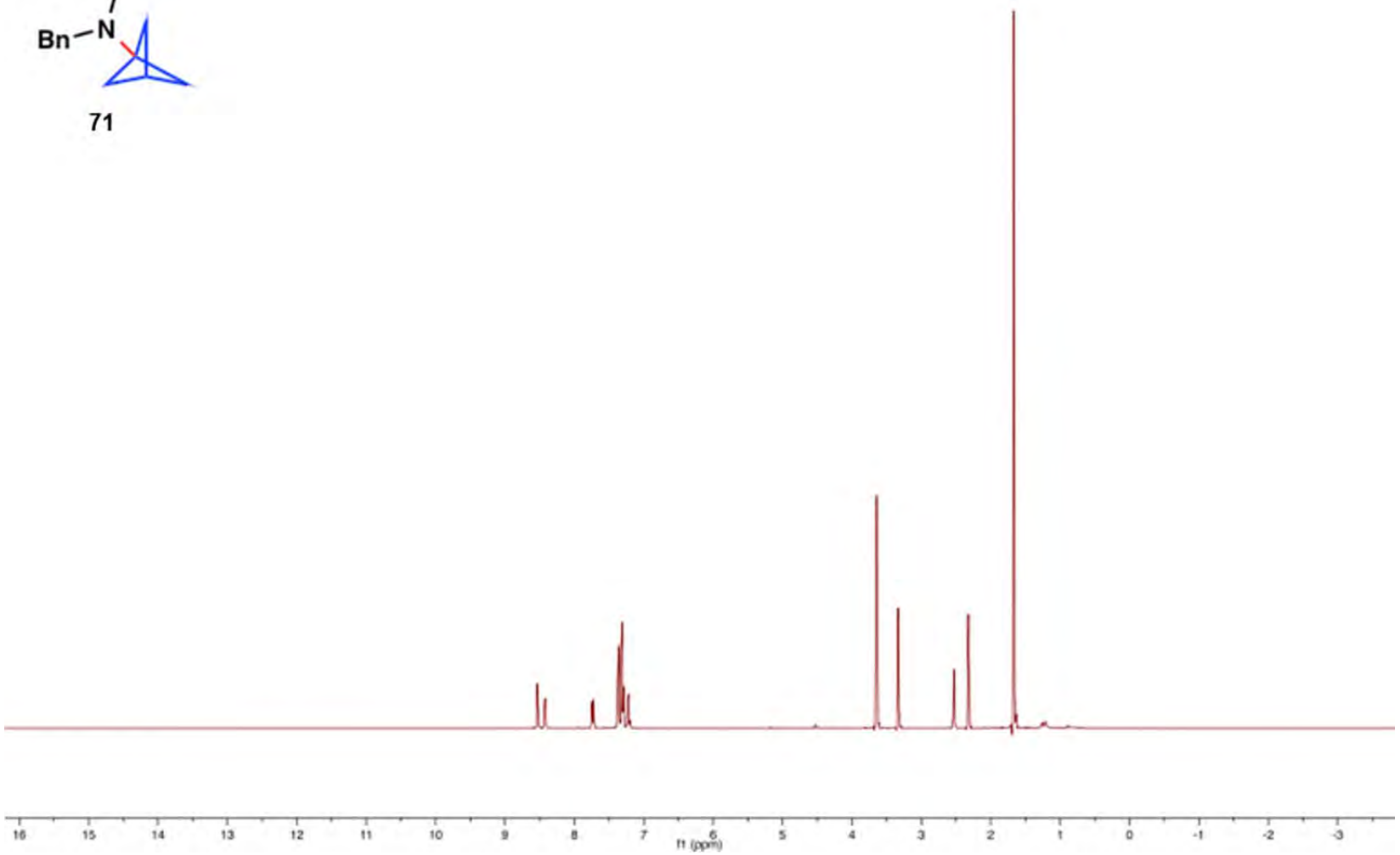
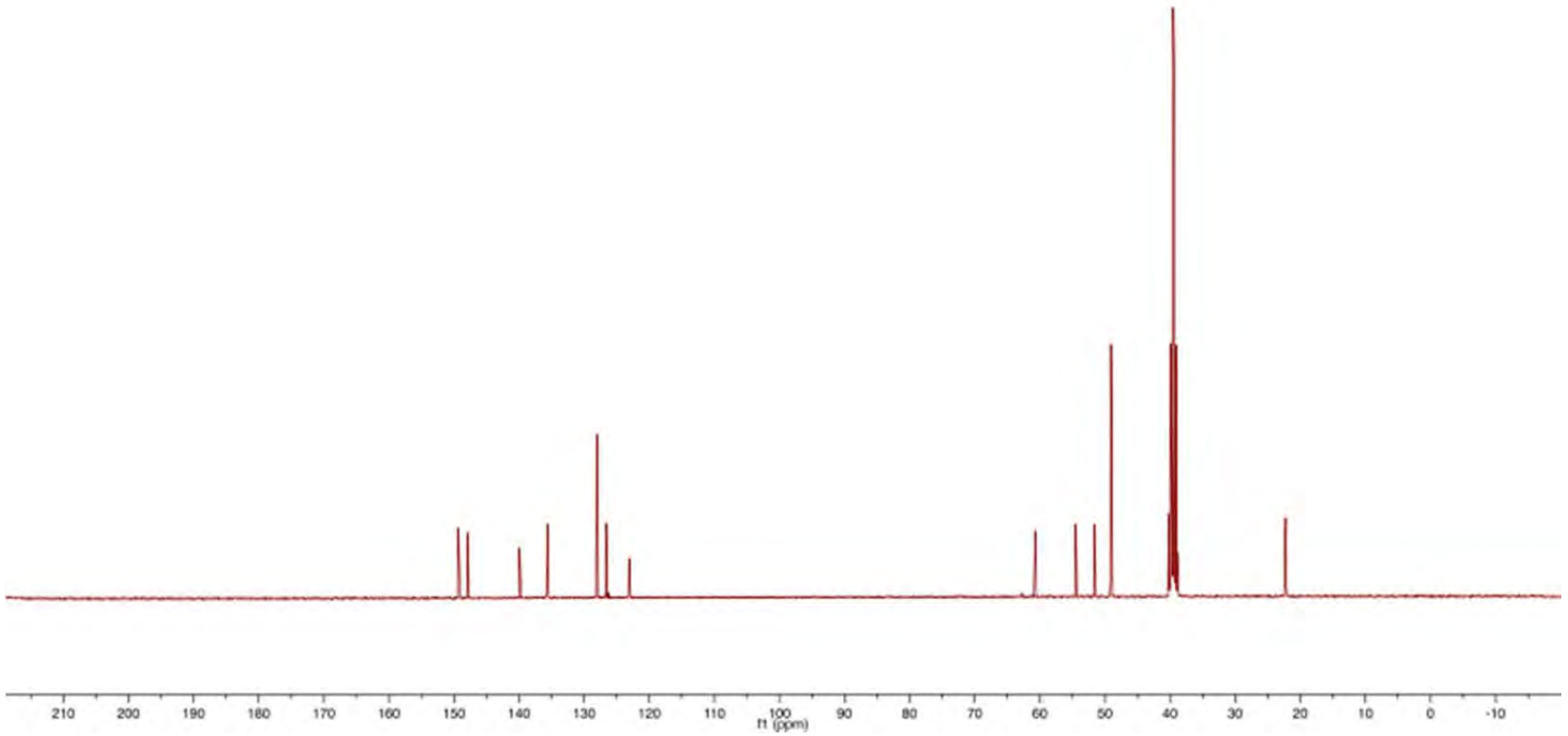
40
30
20
10
0
f1 (ppm)

71




N
Bn
N

71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30
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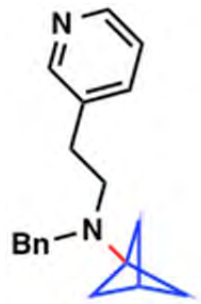
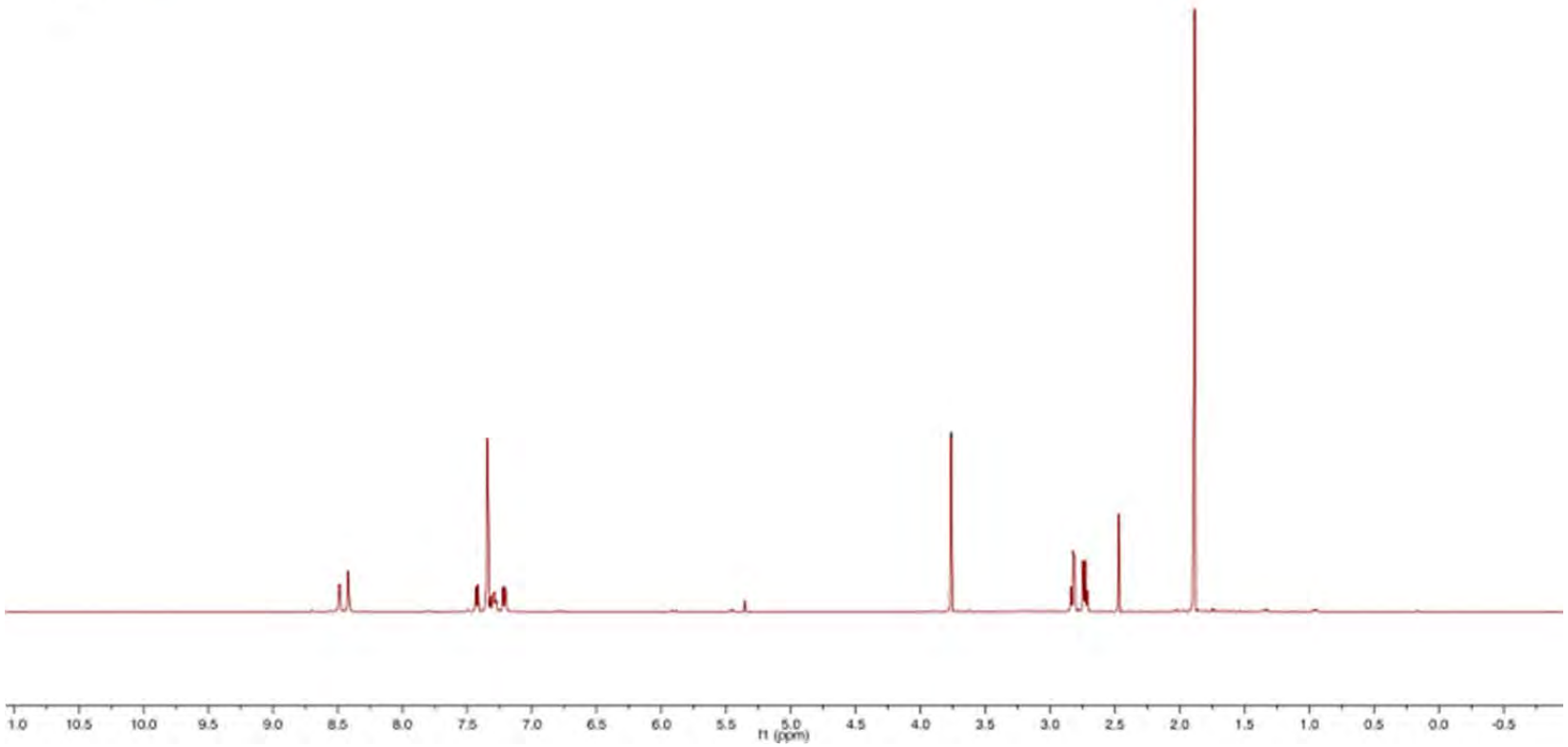
10
0
-10
f1 (ppm)


N
Bn
N

72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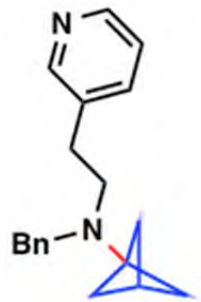
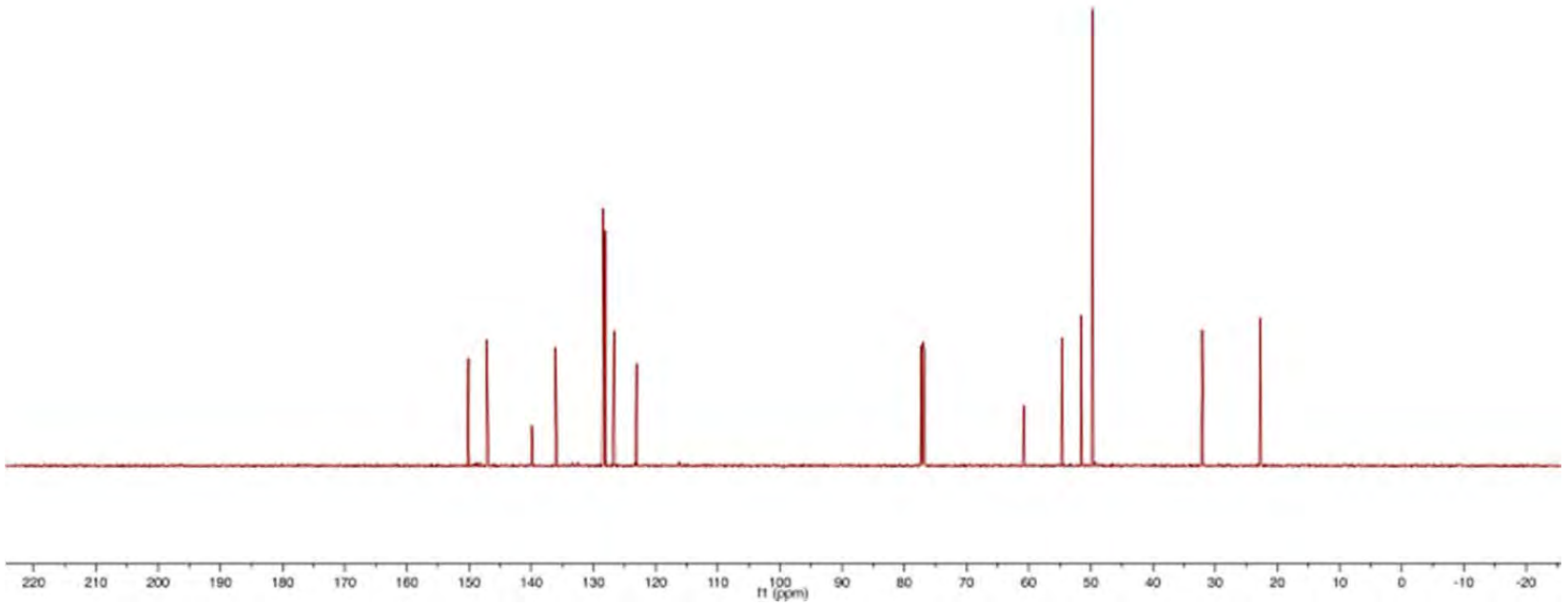
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


N
Bn
N

72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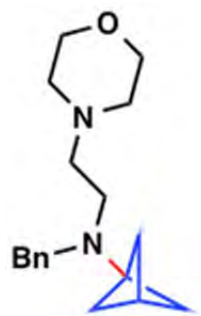
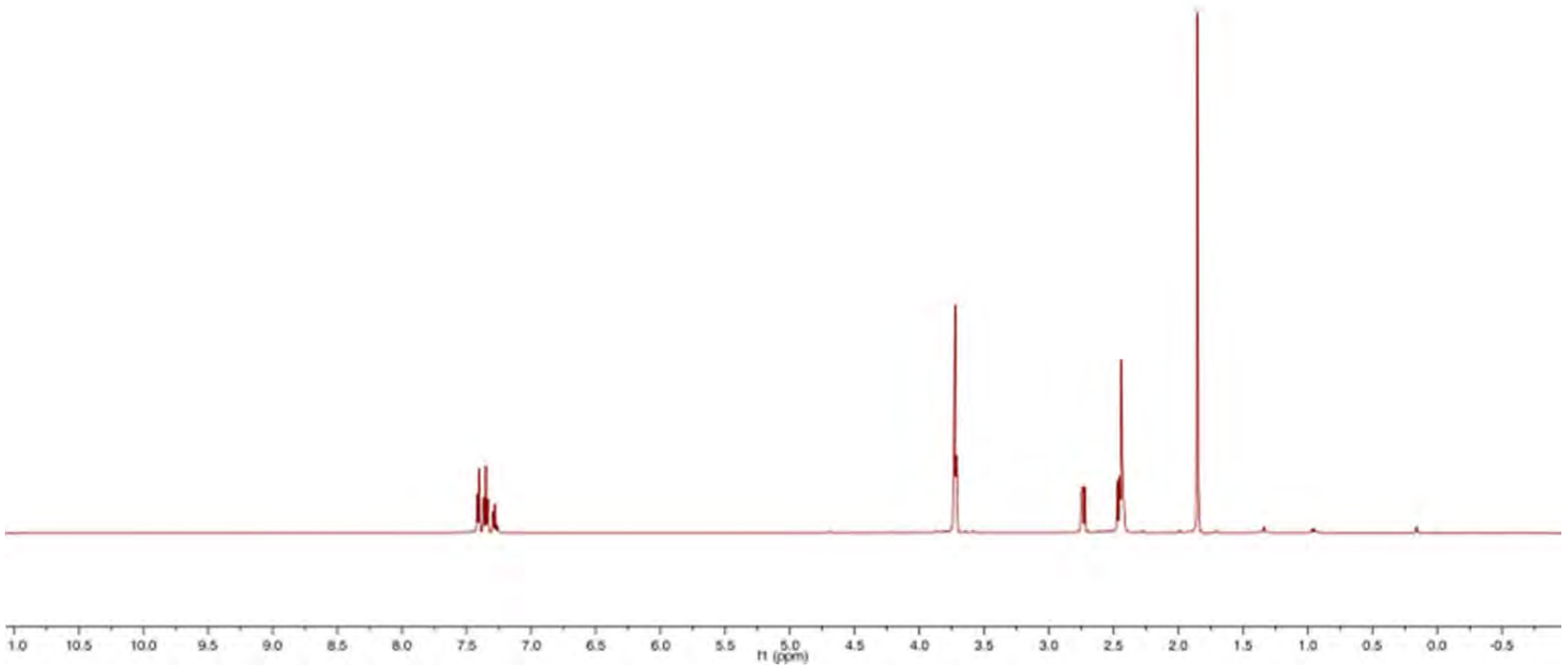
-20
f1 (ppm)


O
N
Bn
N

73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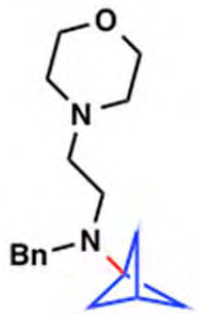
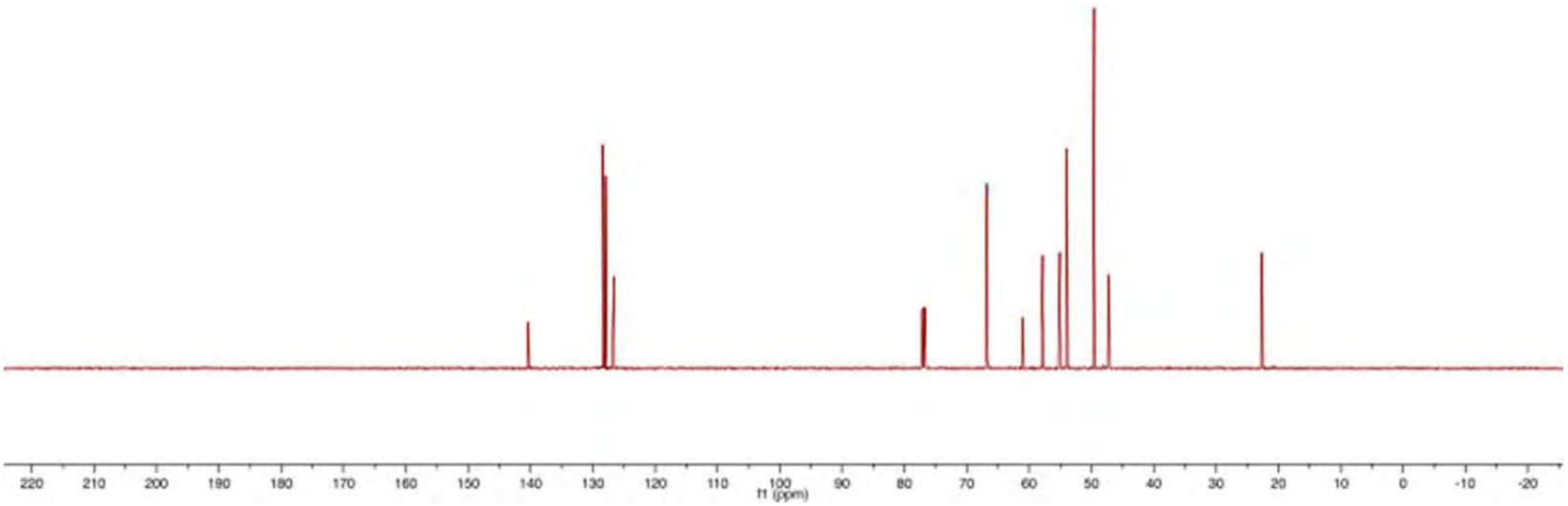
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


O
N
Bn
N

73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20
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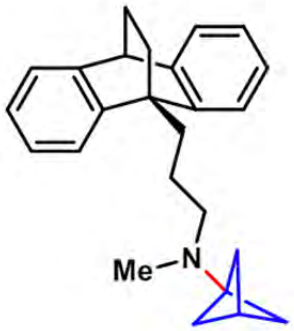
-10
-20
f1 (ppm)


Me
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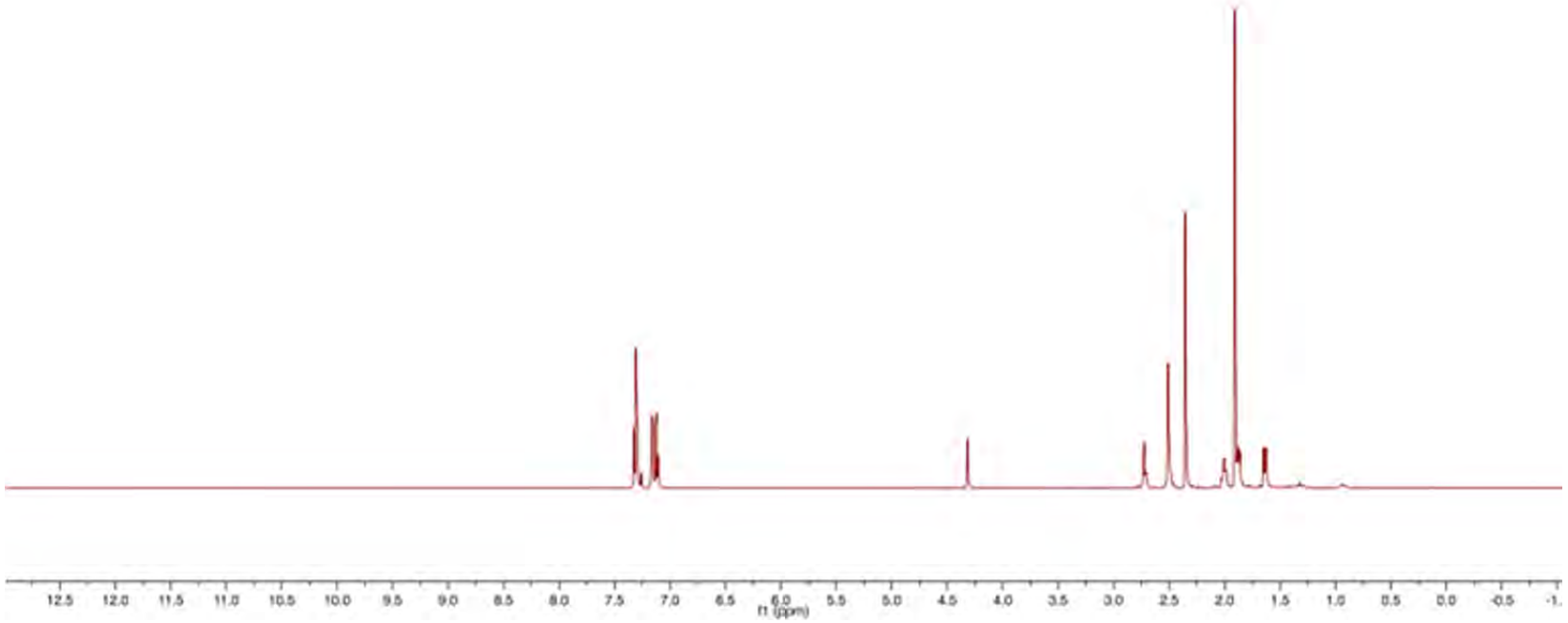
74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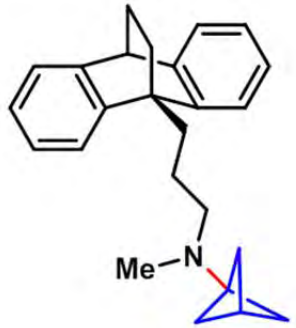
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Me
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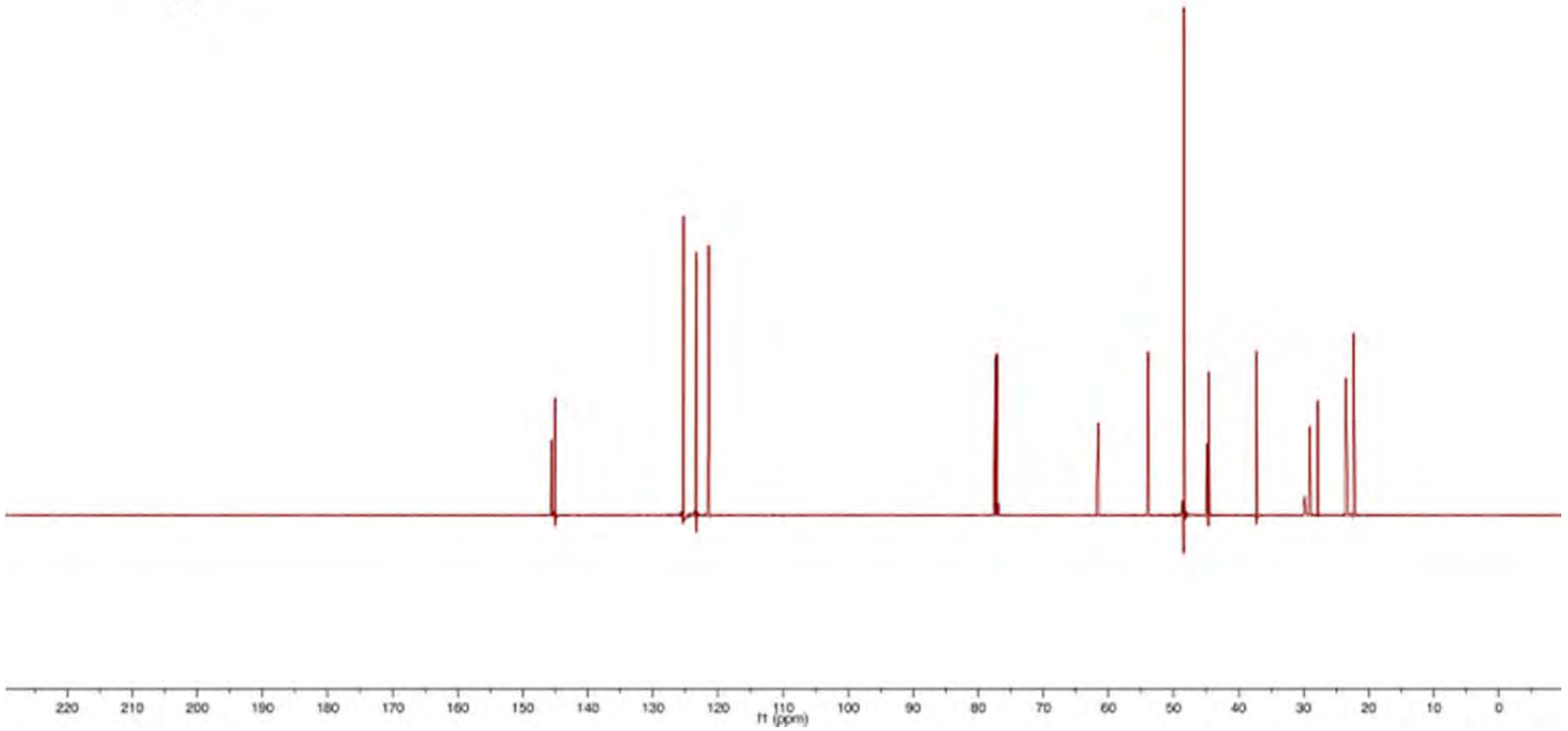
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180
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100
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80
70
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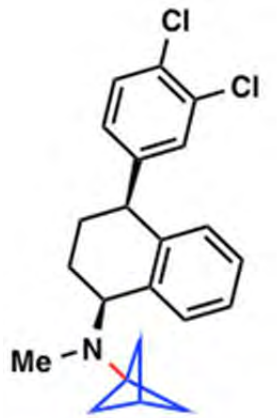
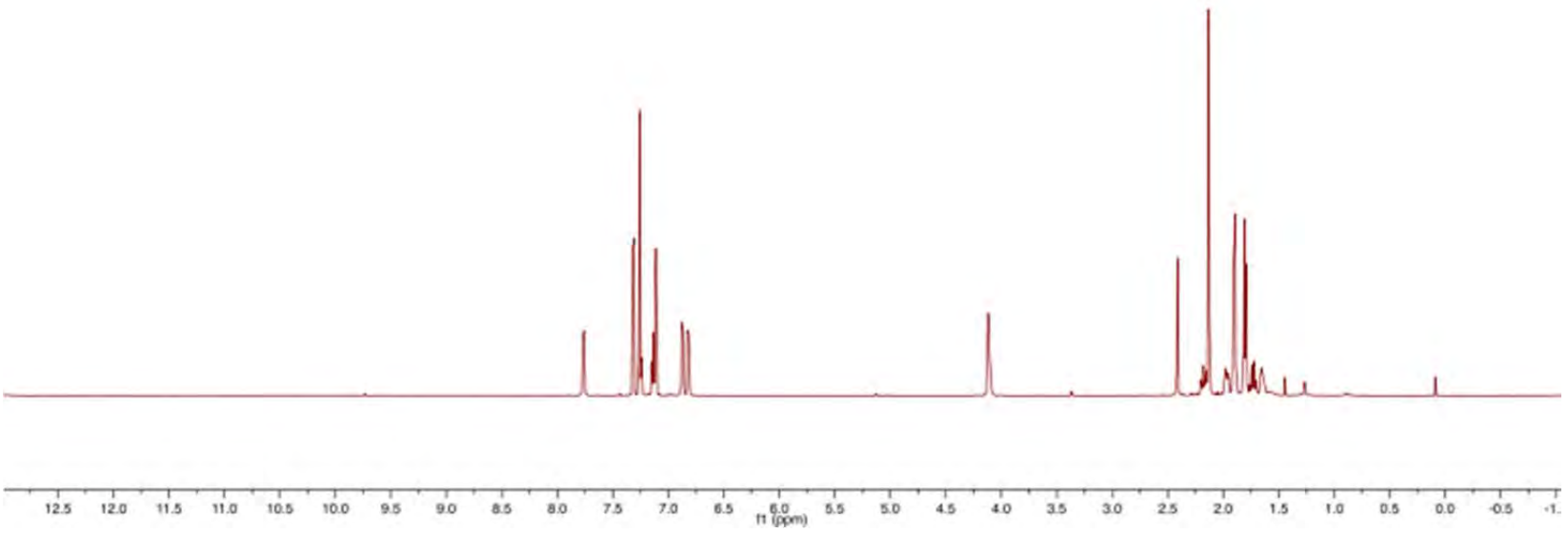
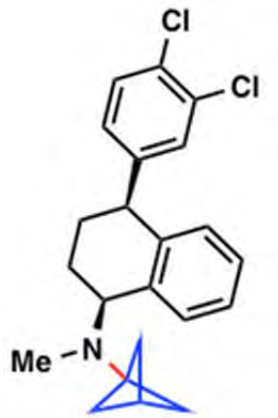
40
30
20
10
0
f1 (ppm)

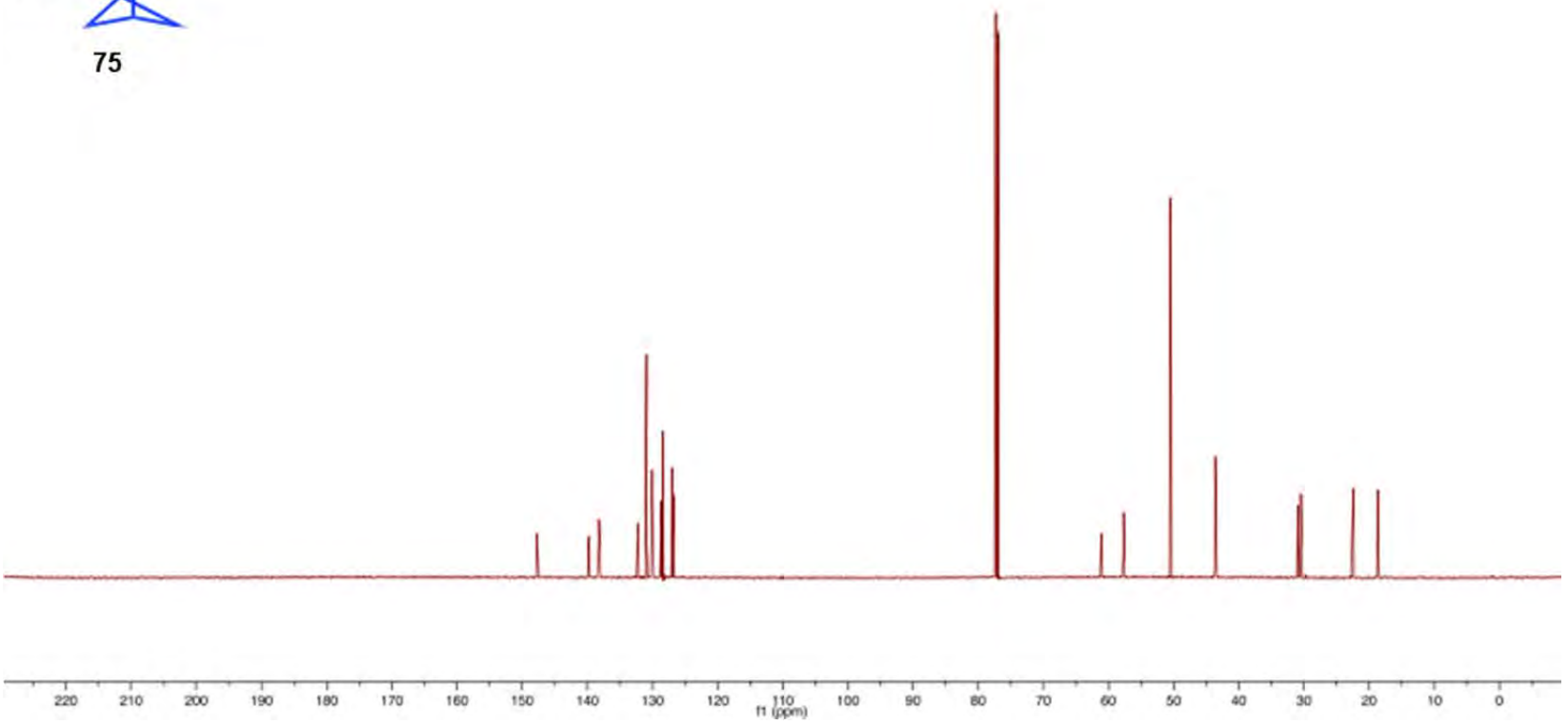

Cl
Cl
Me
N

75


12.5 12.0 11.5 11.0 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)


Cl
Cl
Me
N

75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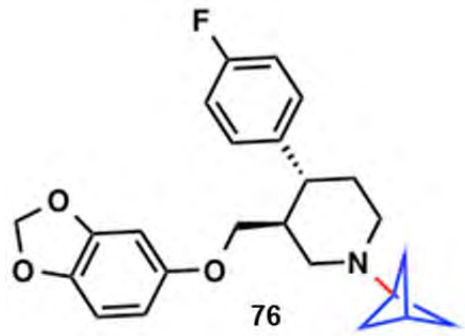
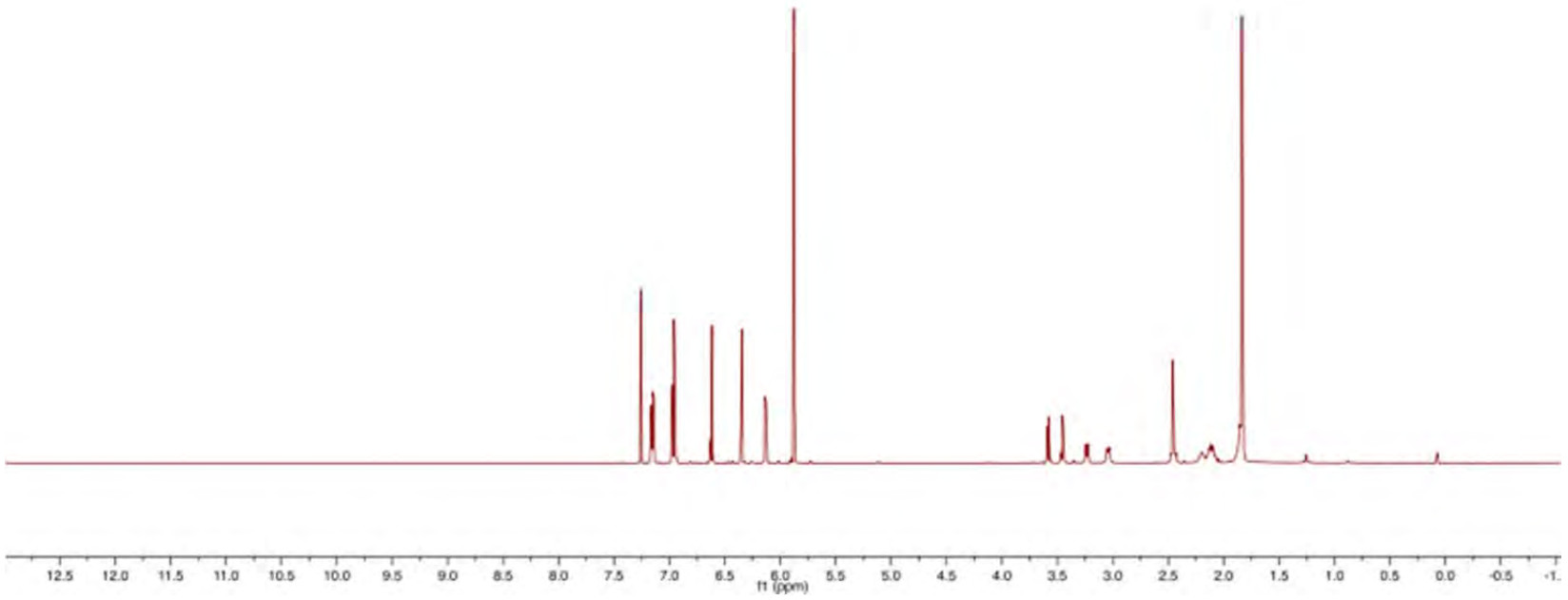
10
0
f1 (ppm)


F
O
O
O
N

76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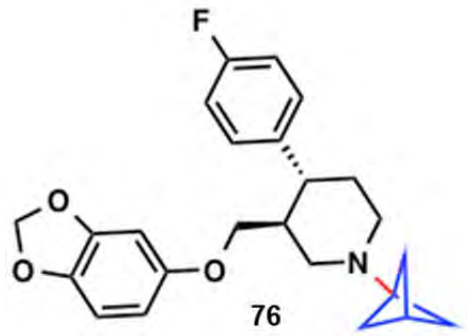
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


F
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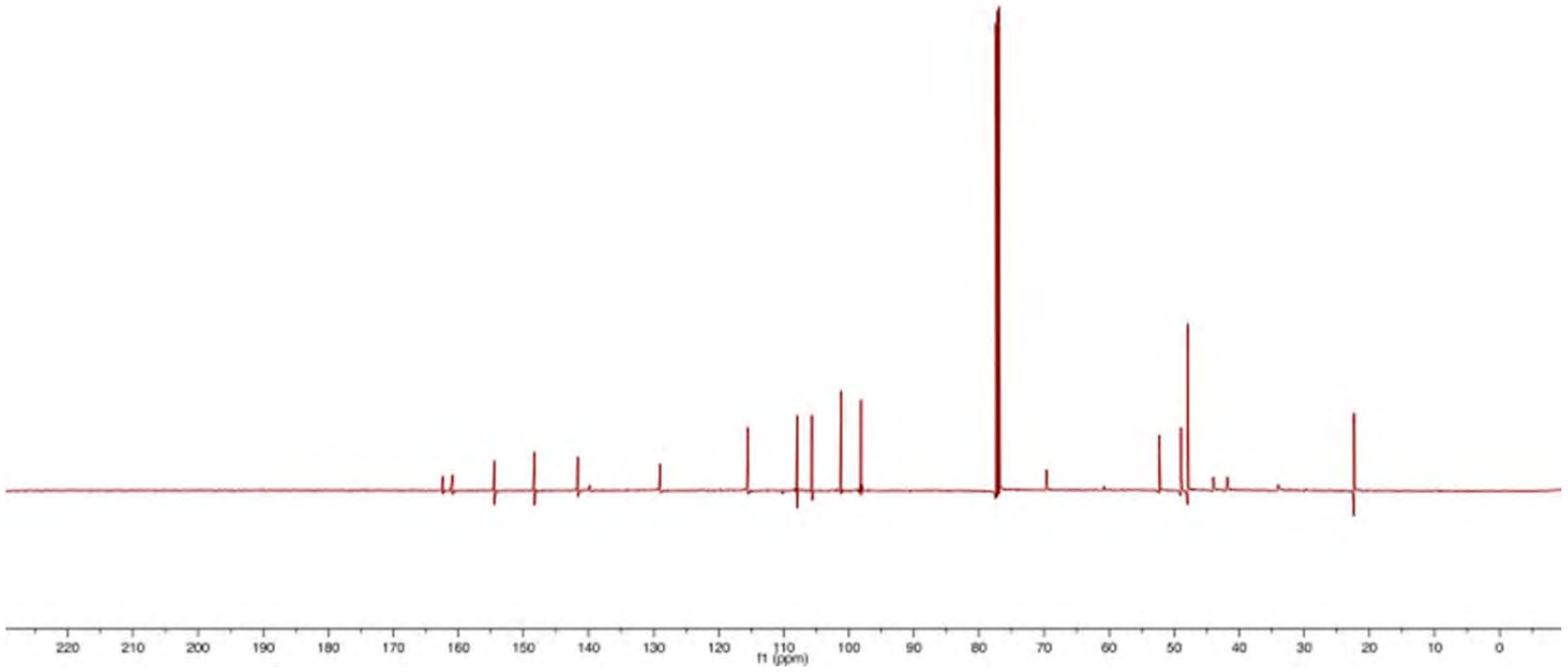
O
O
N

76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180
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100
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40
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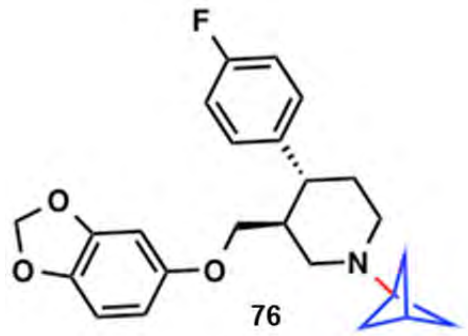
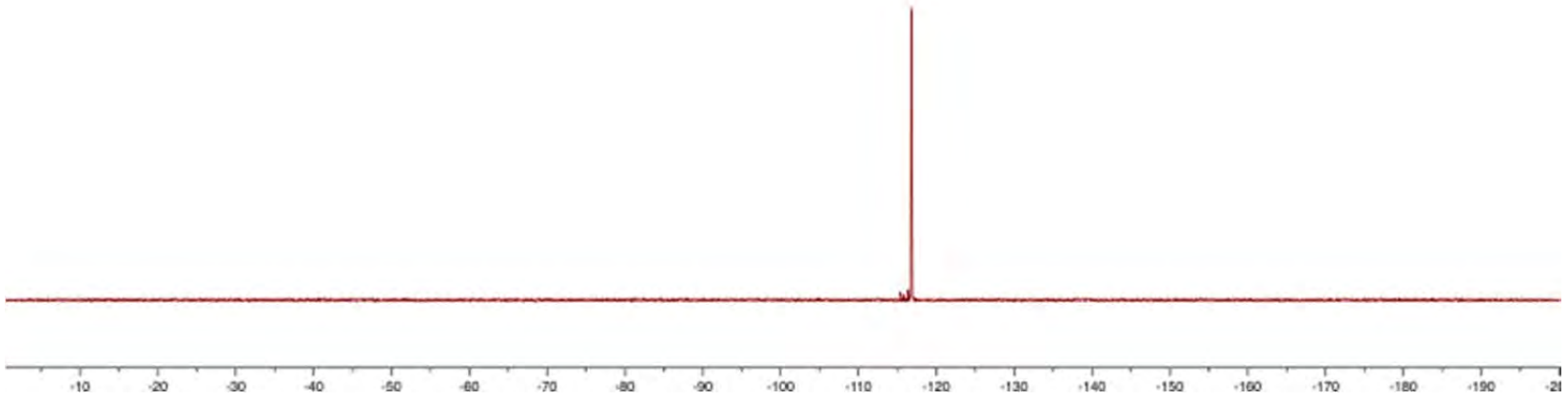
20
10
0
f1 (ppm)


F
O
O
O
N

76


-10
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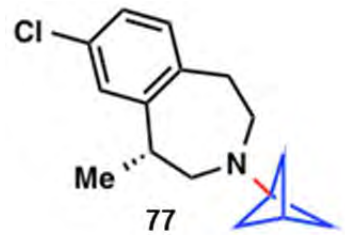
-160
-170
-180
-190

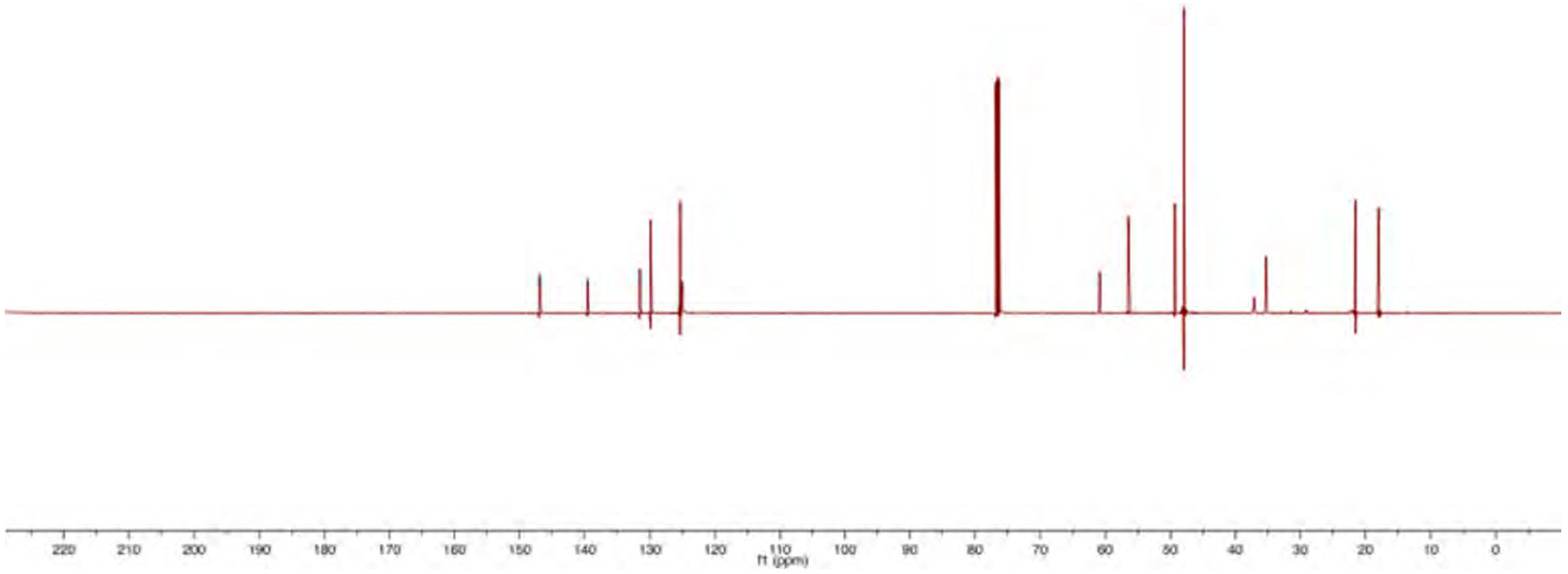

Cl
Me
N

77

12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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


Cl
Me
N

77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210
200
190
180
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20
10
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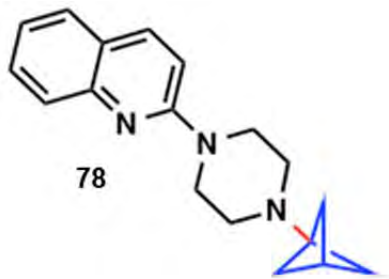
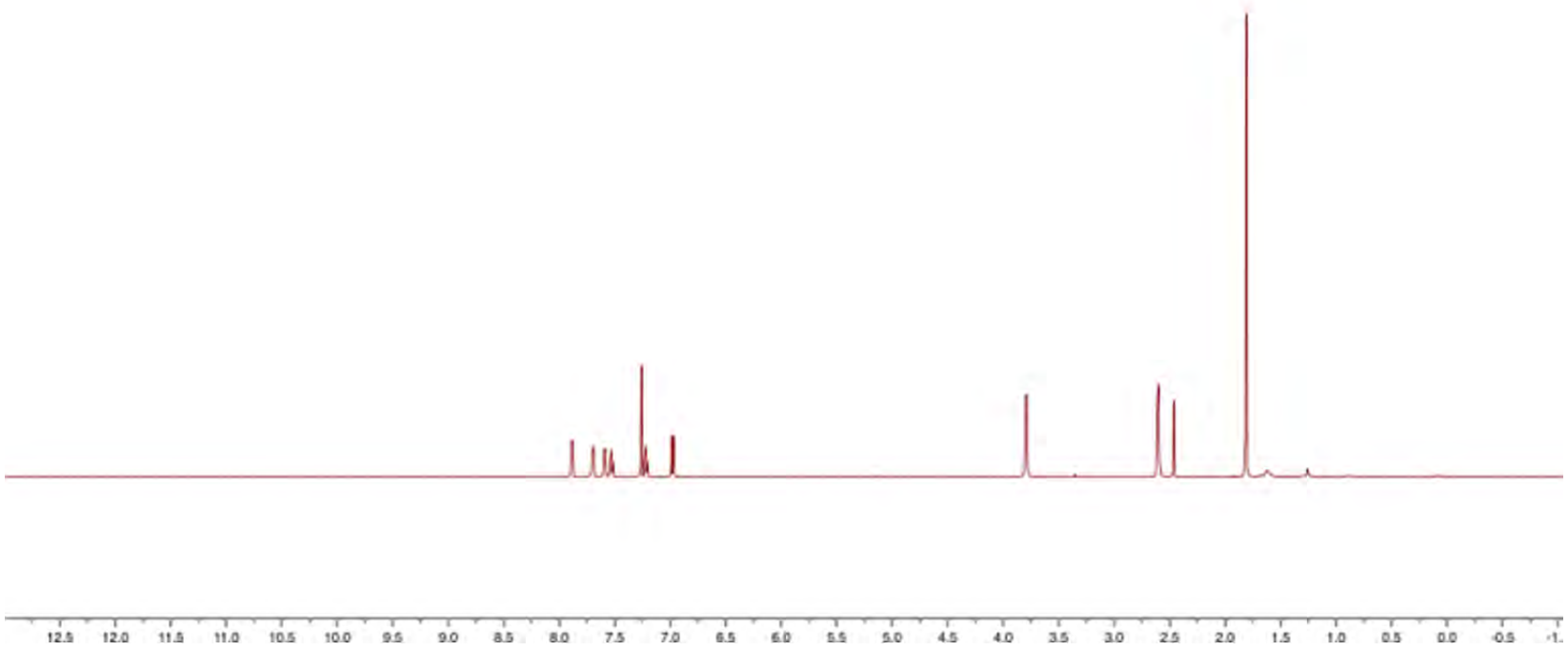
f1 (ppm)


N
N
N

78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9.0
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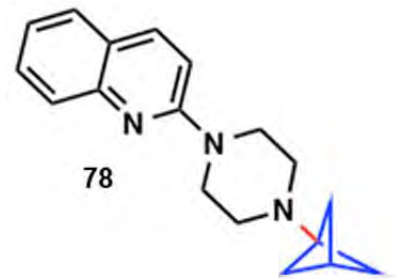
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


N
N
N

78

220
210
200
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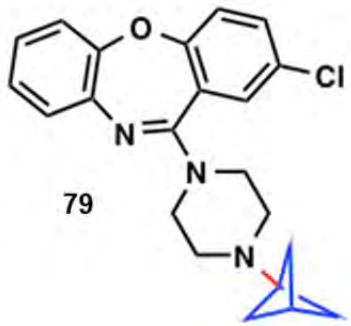
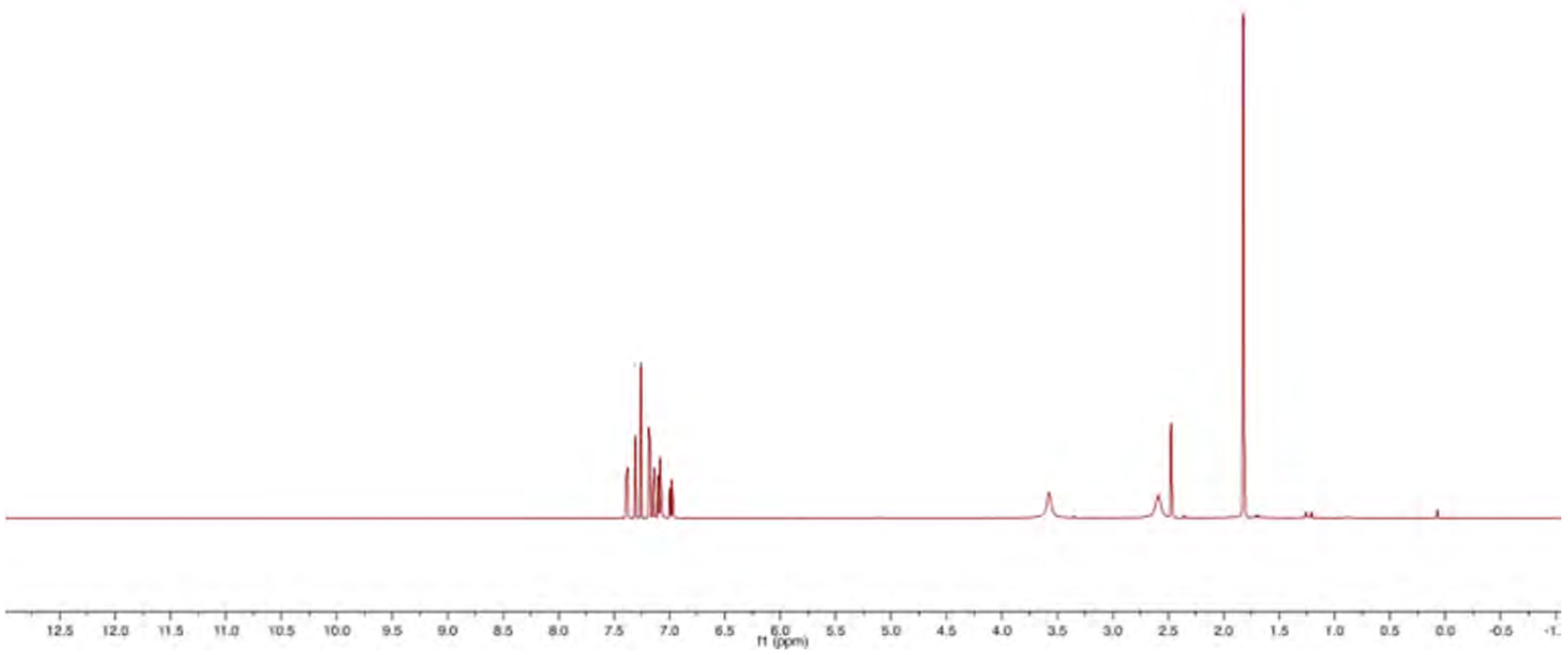
10
0


O
Cl
N
N
N

79


12.5
12.0
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11.0
10.5
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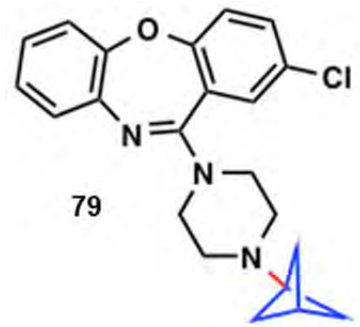
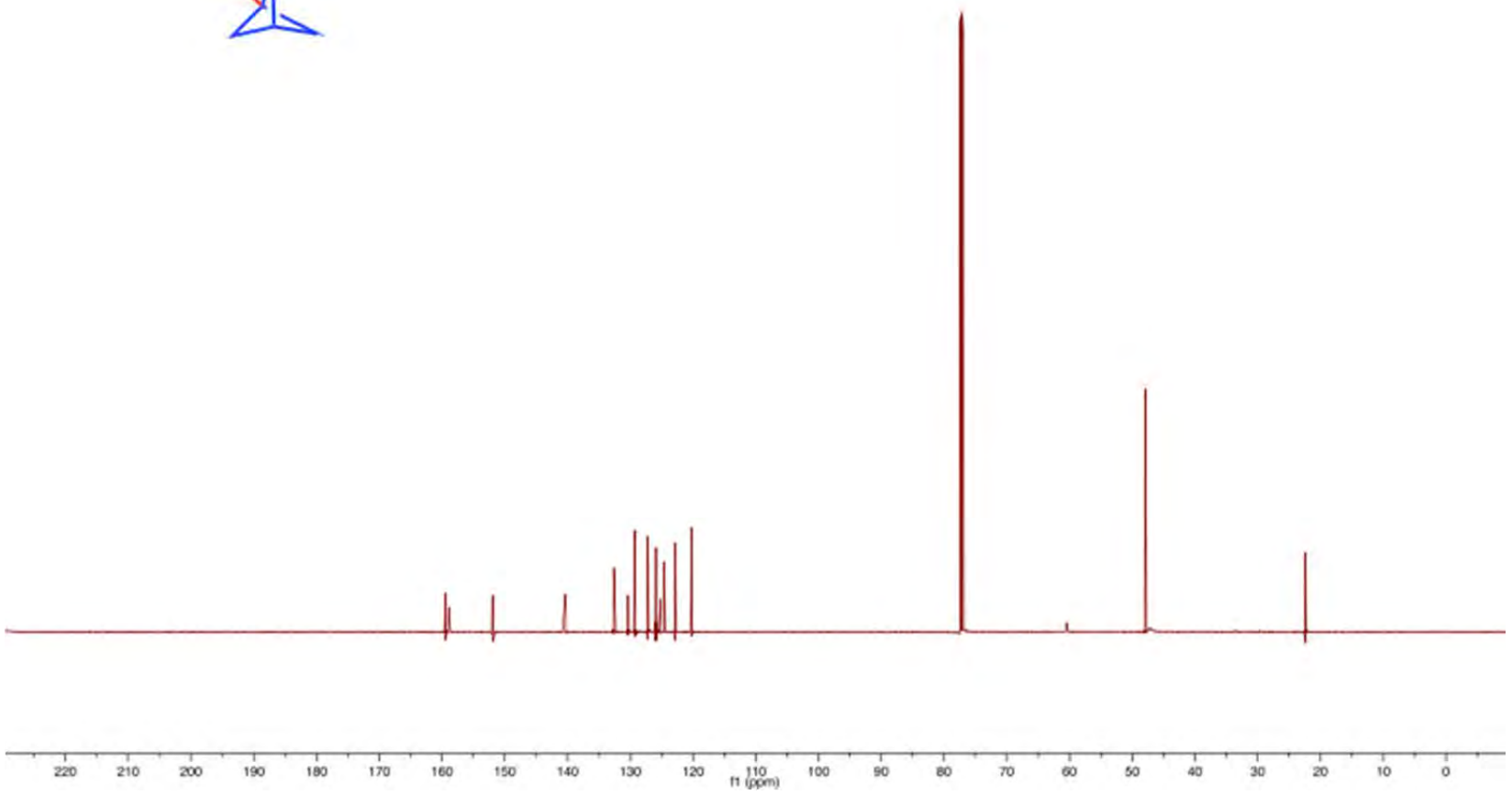
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


O
Cl
N
N
N

79


220
210
200
190
180
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160
150
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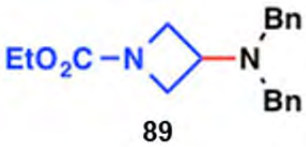
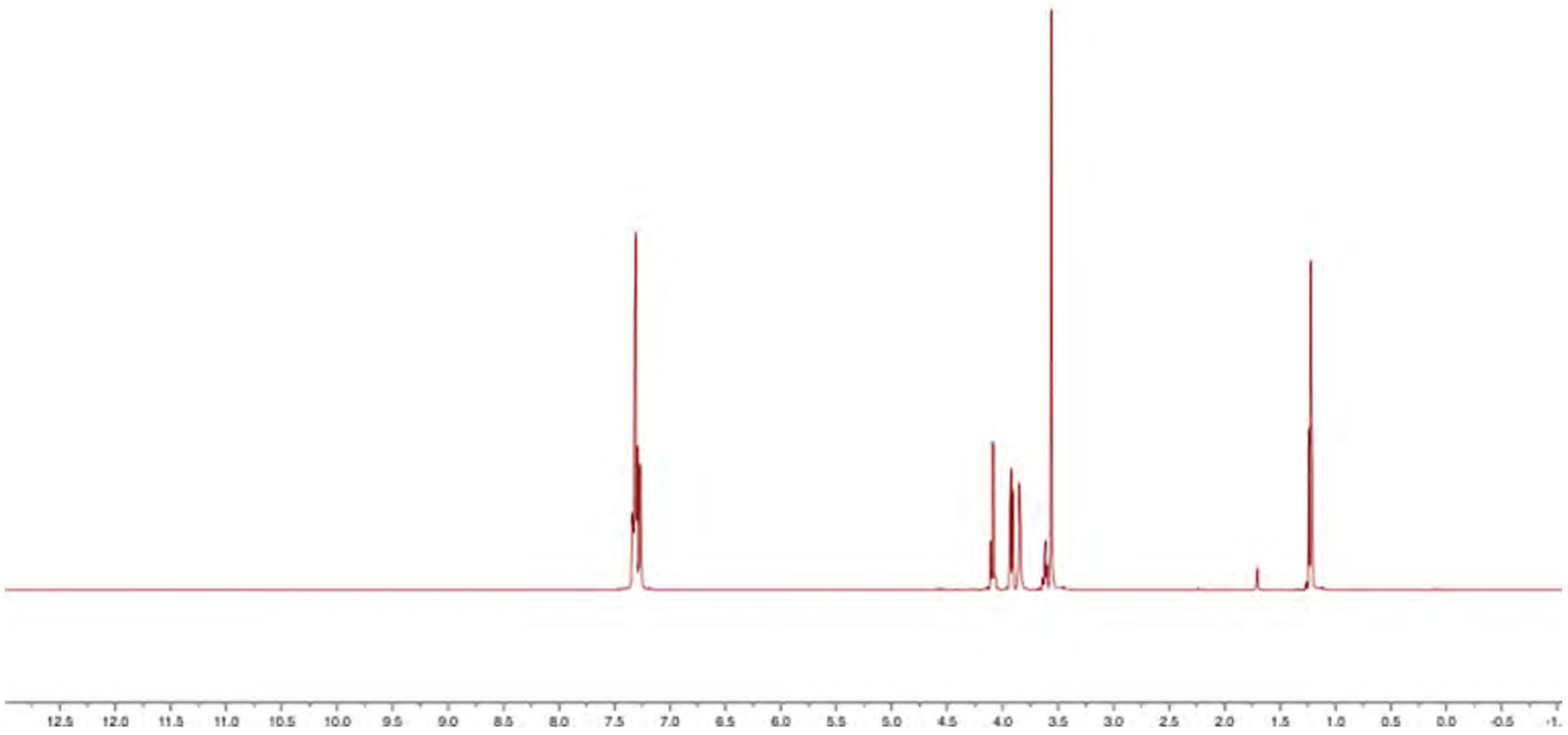
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


EtO2C–N
N
Bn
Bn

89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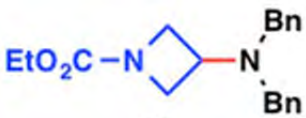
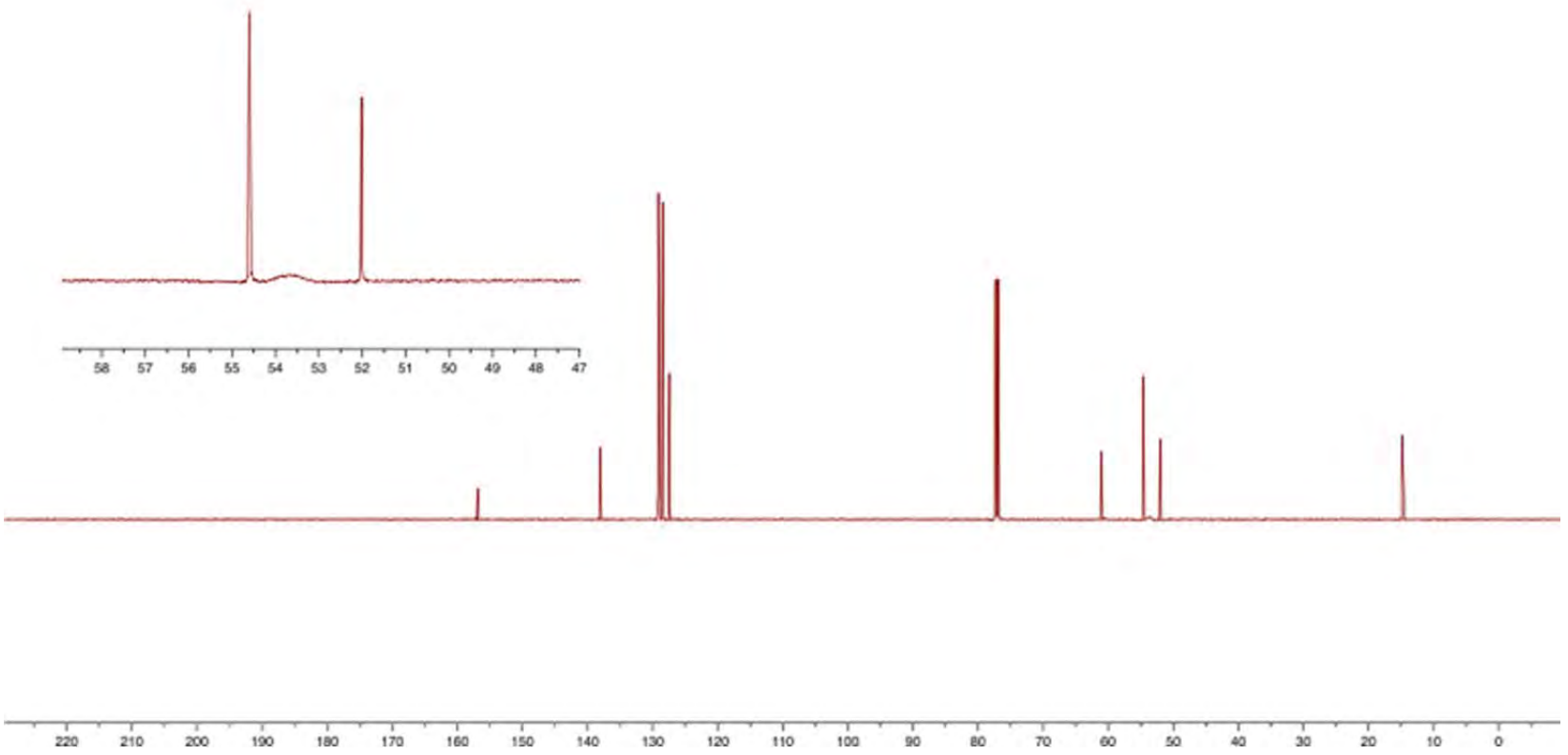
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

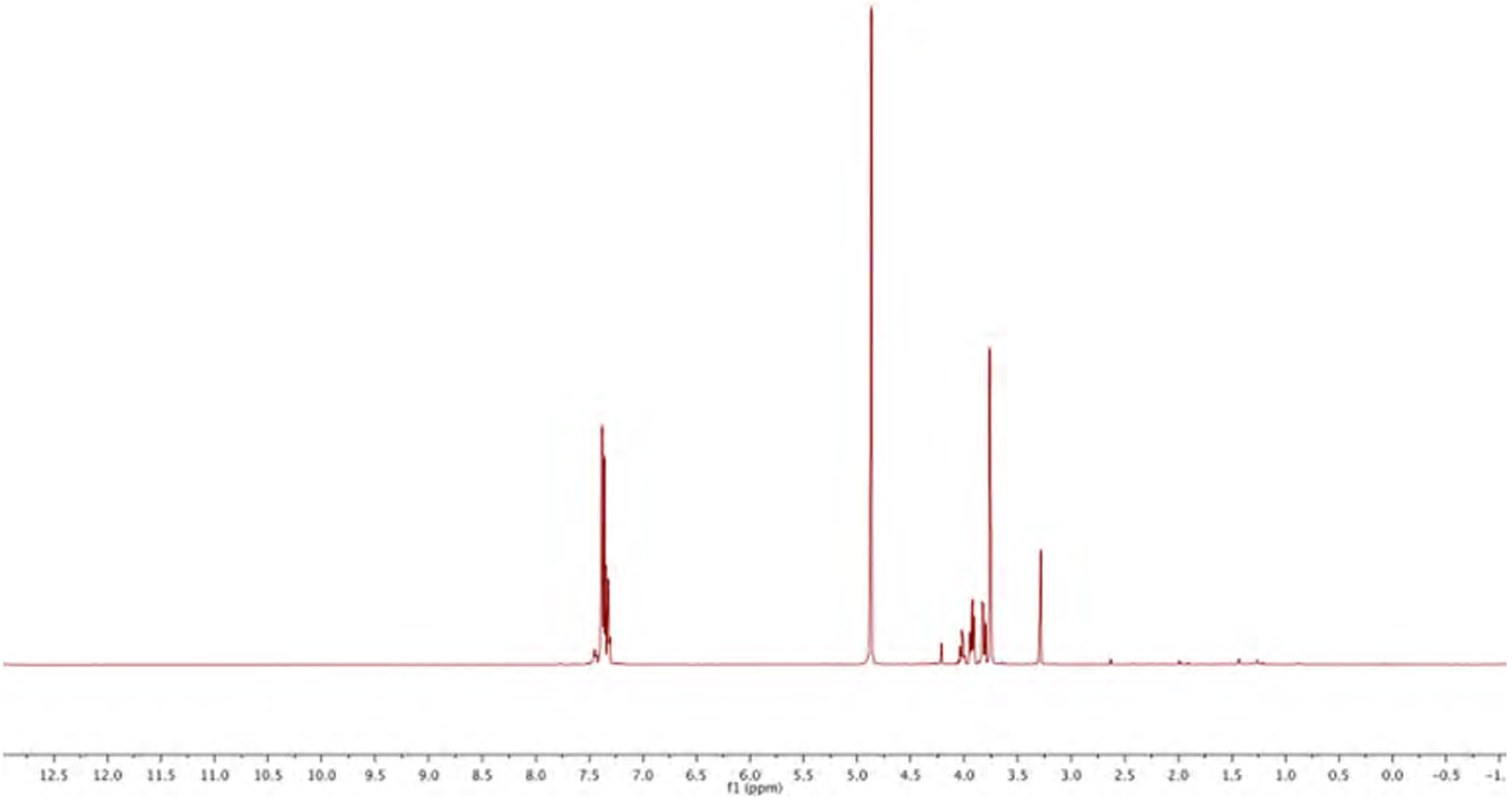

EtO2C–N
N
Bn
Bn

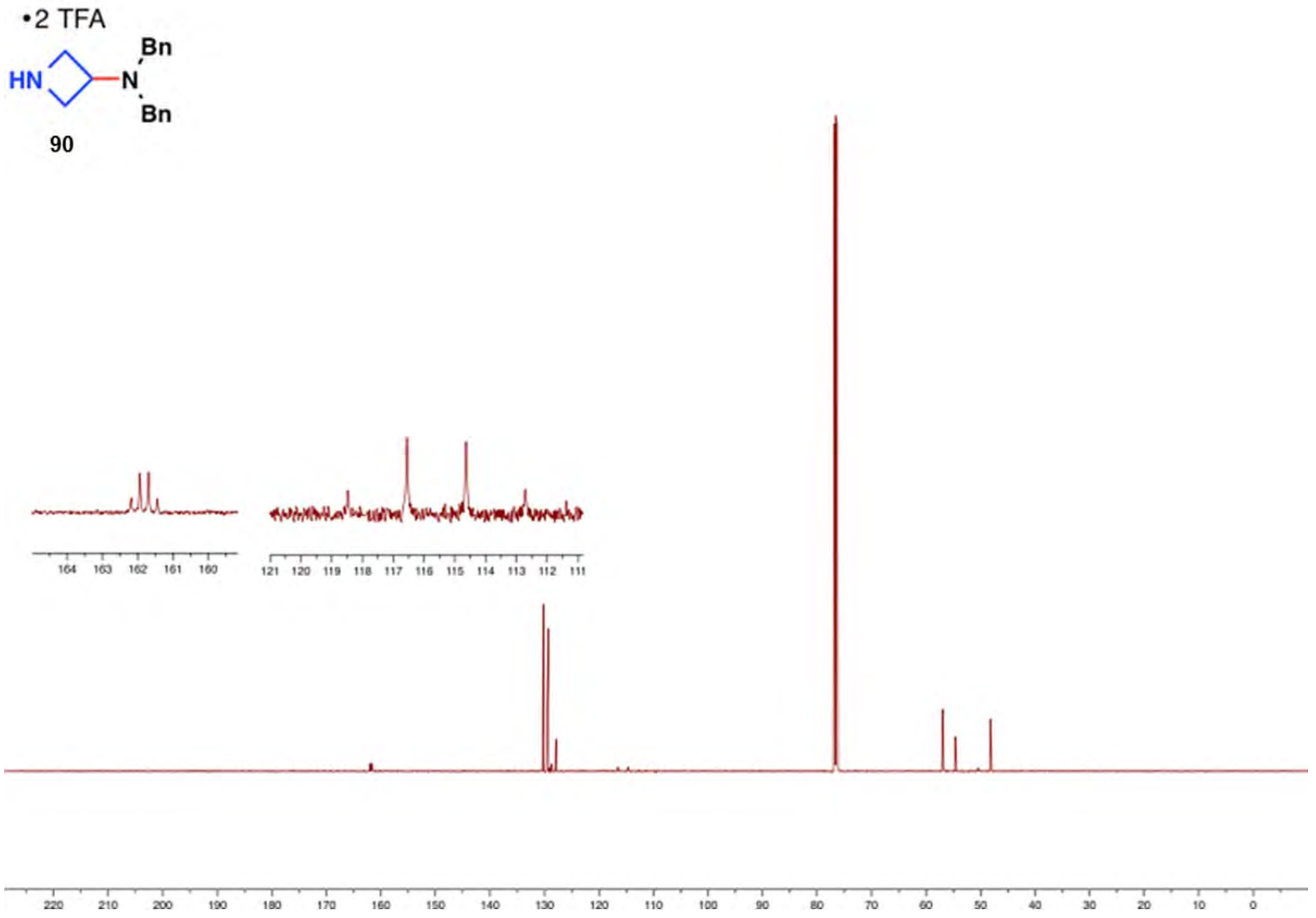
89

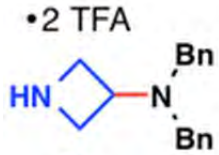

58 57 56 55 54 53 52 51 50 49 48 47
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


•2 TFA
HN
N
Bn
Bn

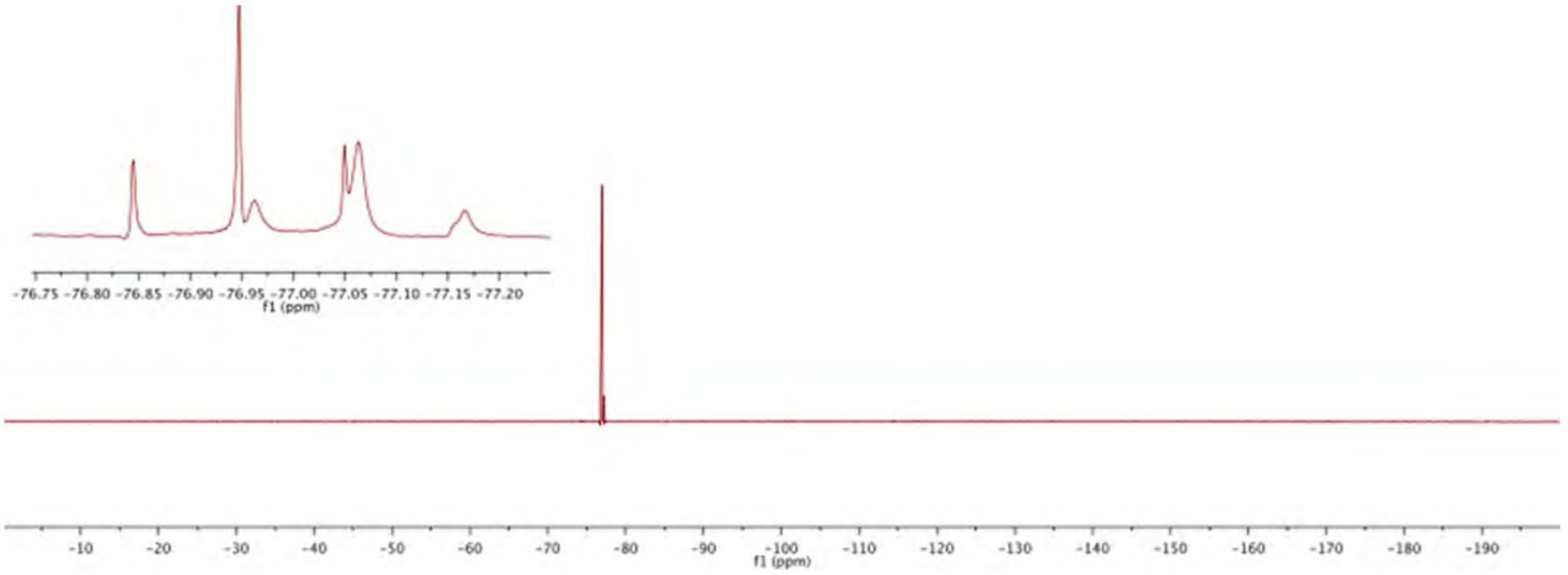
90

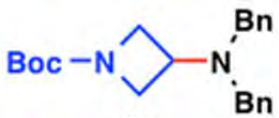

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)


•2 TFA
HN
N
Bn
Bn
90
164 163 162 161 160
121 120 119 118 117 116 115 114 113 112 111
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

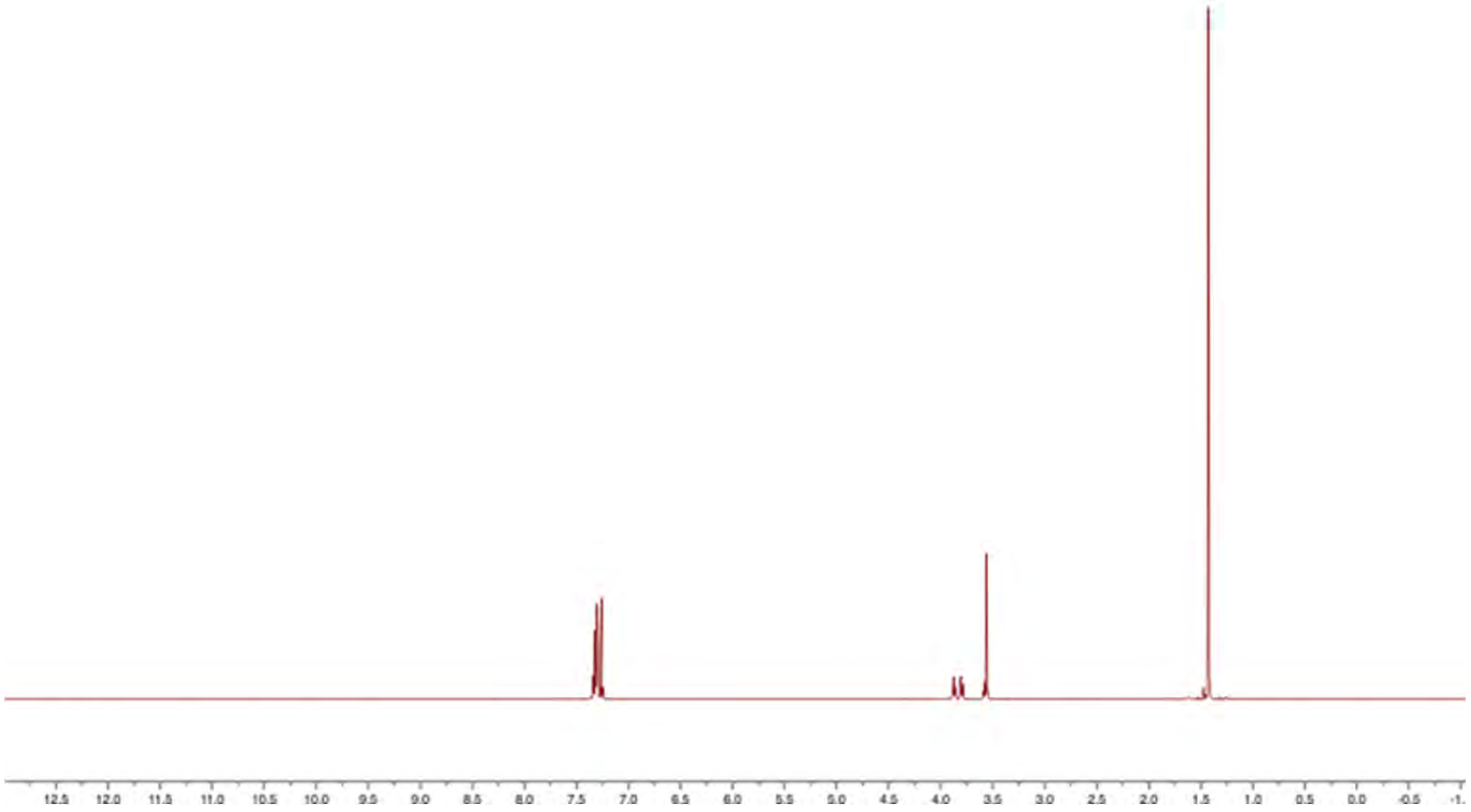

•2 TFA
HN
N
Bn
Bn

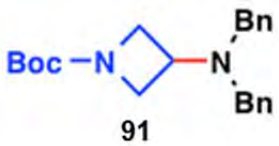
90


-76.75 -76.80 -76.85 -76.90 -76.95 -77.00 -77.05 -77.10 -77.15 -77.20
f1 (ppm)
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

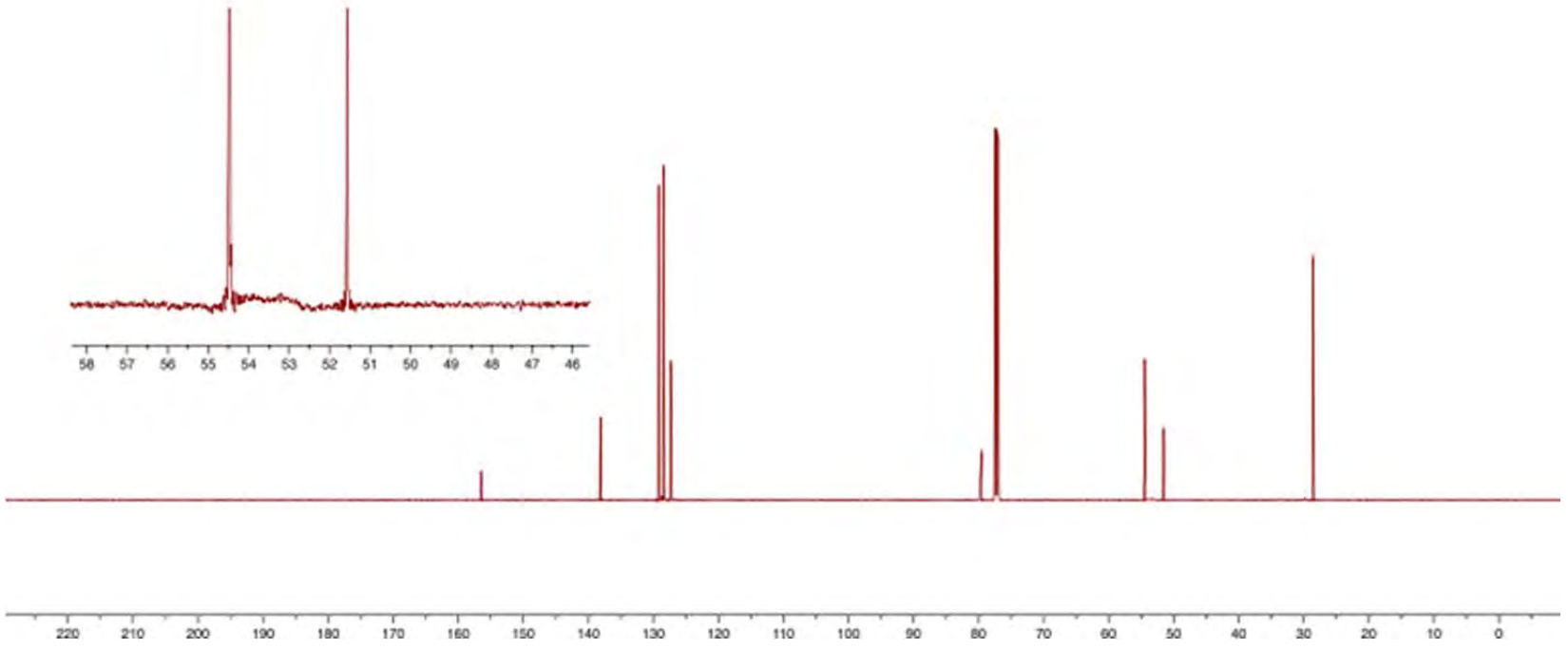

Boc
N
N
Bn
Bn

91


12.5
12.0
11.5
11.0
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


Boc
N
N
Bn
Bn

91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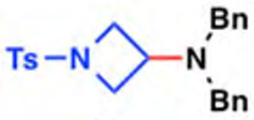
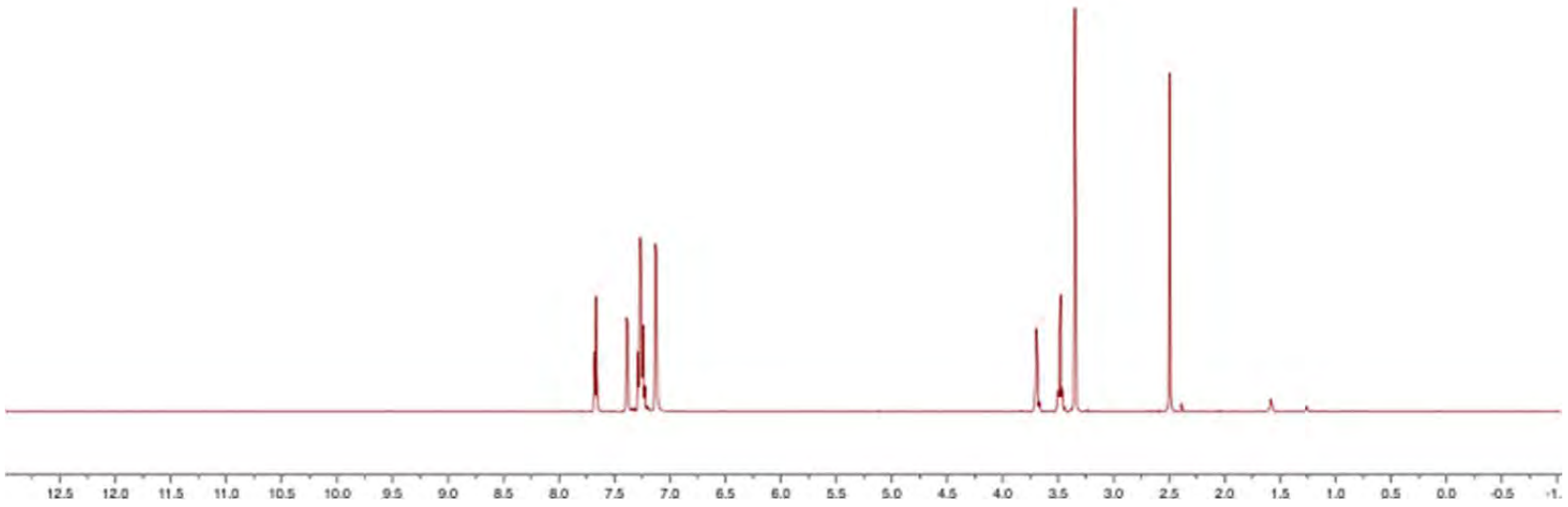
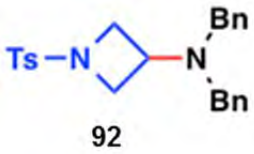
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

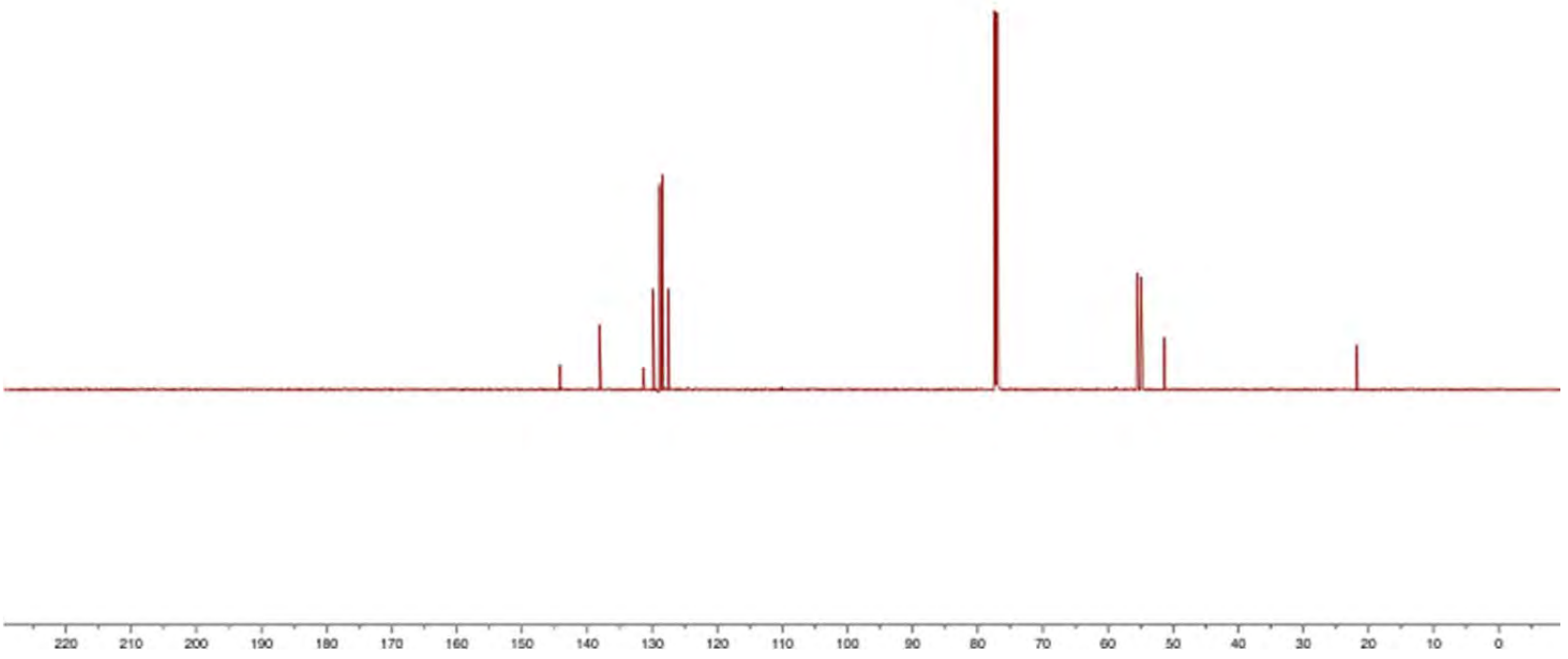

Ts
N
N
Bn
Bn

92


12.5
12.0
11.5
11.0
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


Ts
N
N
Bn
Bn

92


220
210
200
190
180
170
160
150
140
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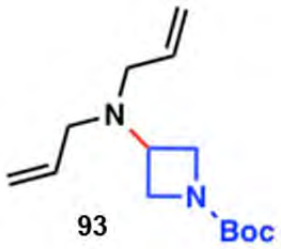
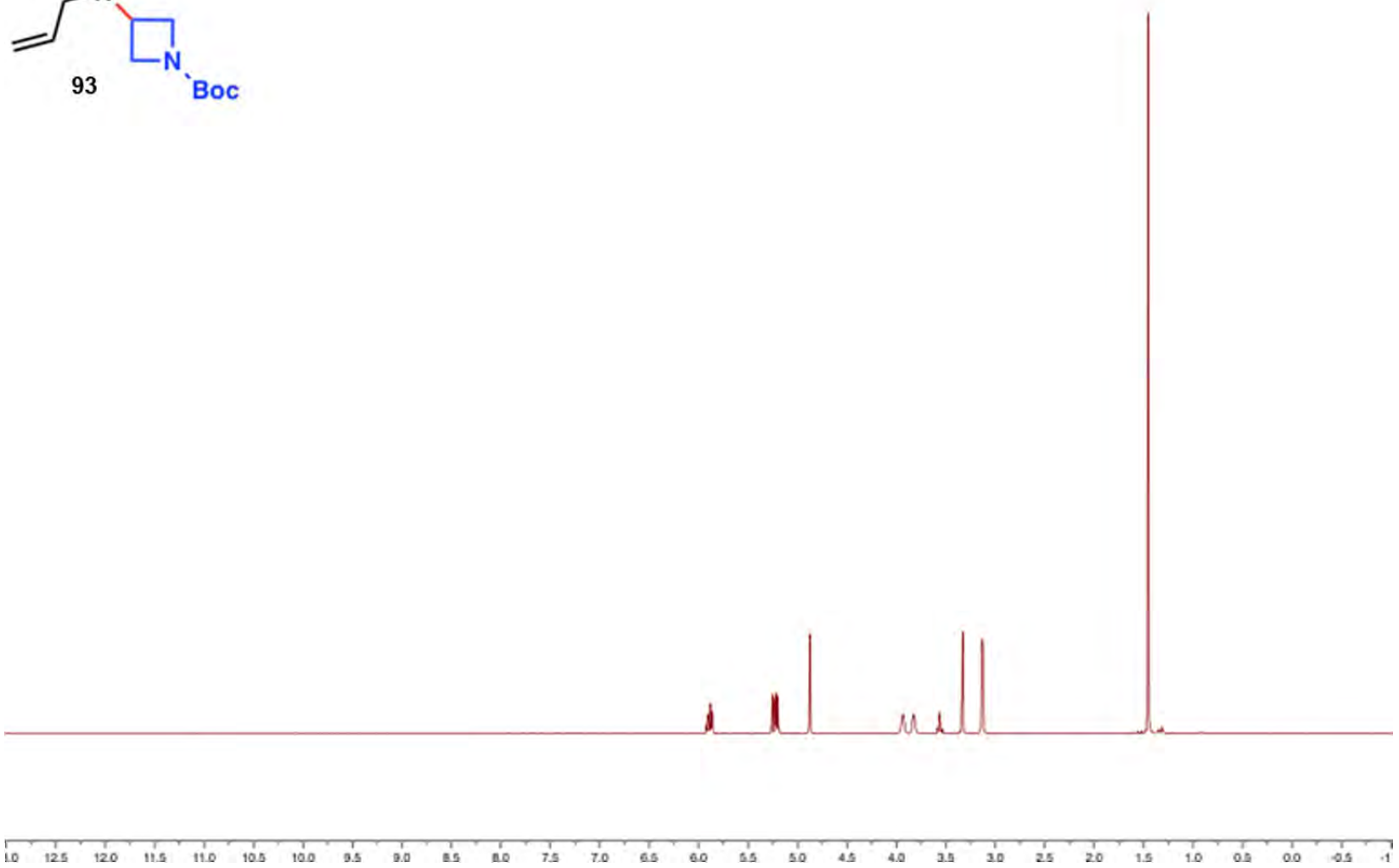
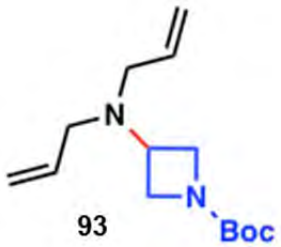
120
110
100
90
80
70
60
50
40
30
20
10
0

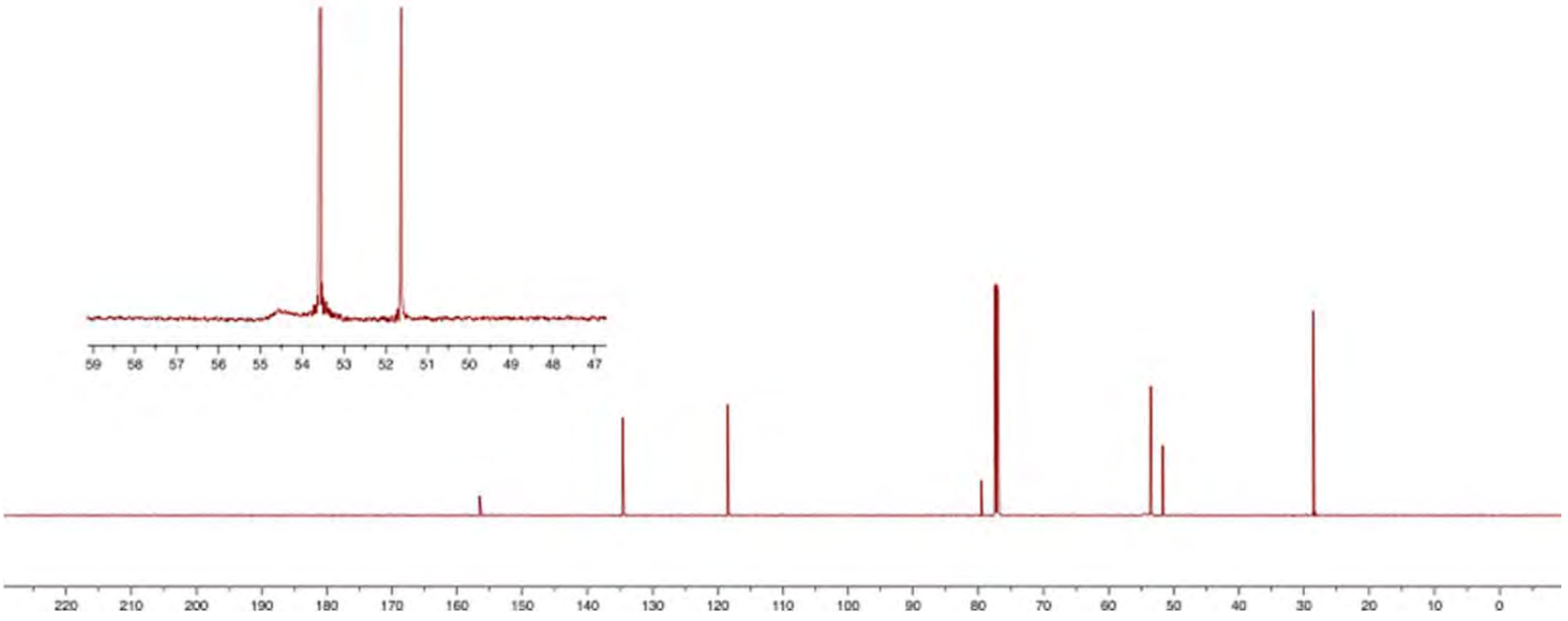

N
N
Boc

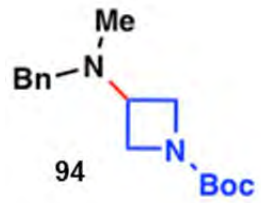
93


13.0
12.5
12.0
11.5
11.0
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
-1


N
N
Boc

93


59 58 57 56 55 54 53 52 51 50 49 48 47
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



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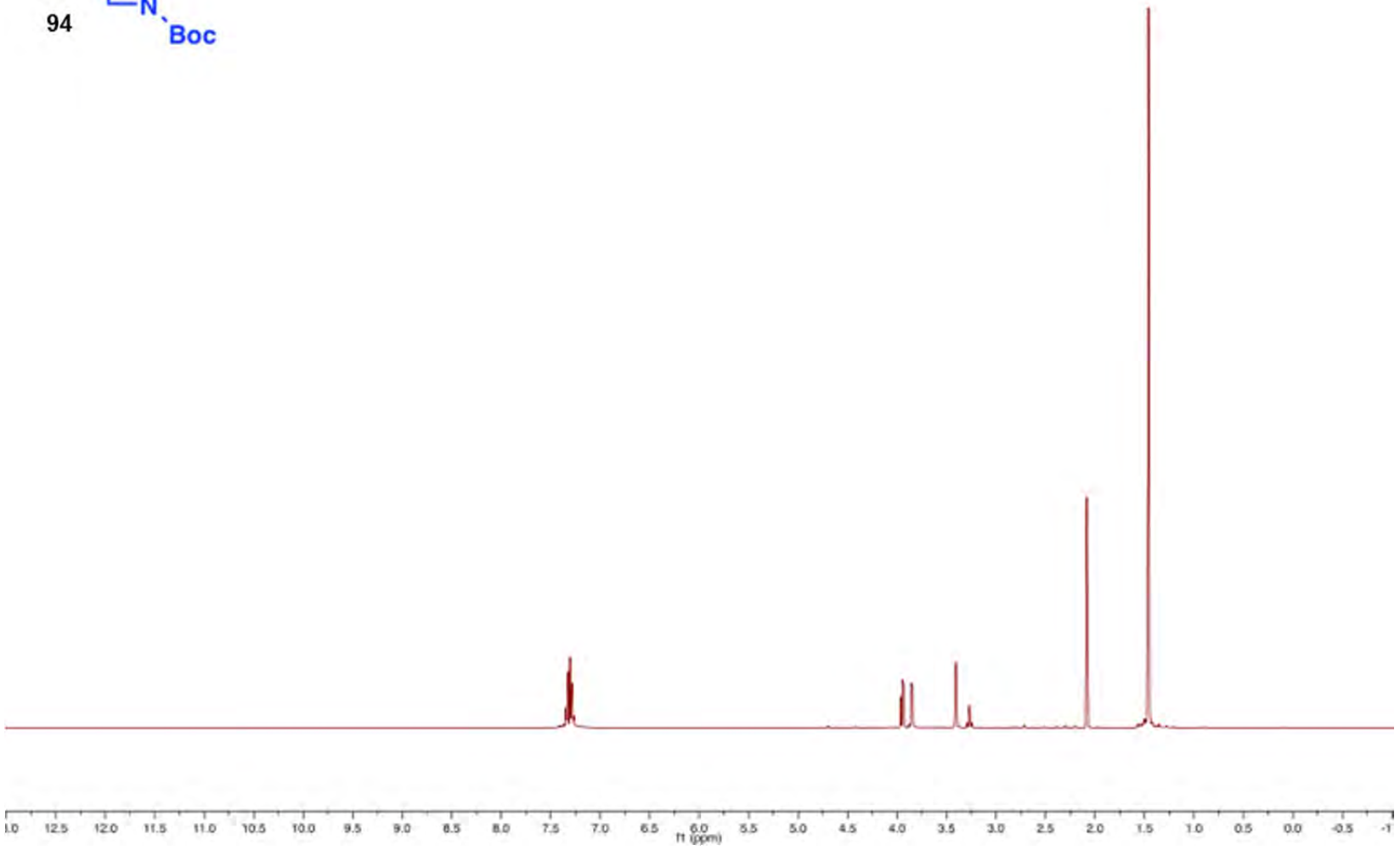
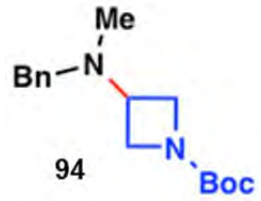
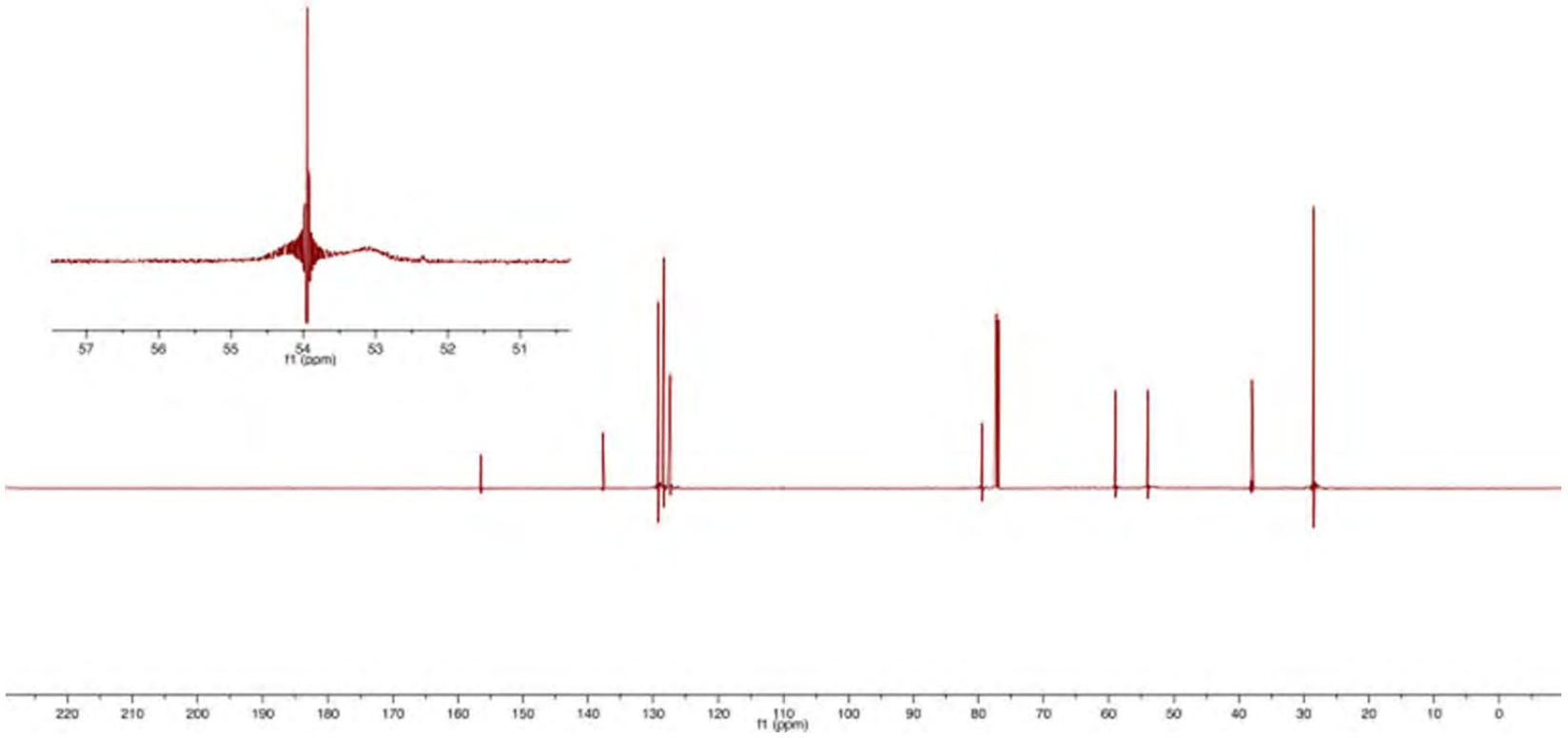
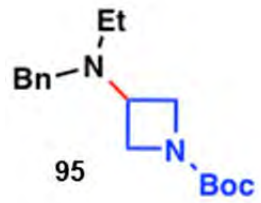


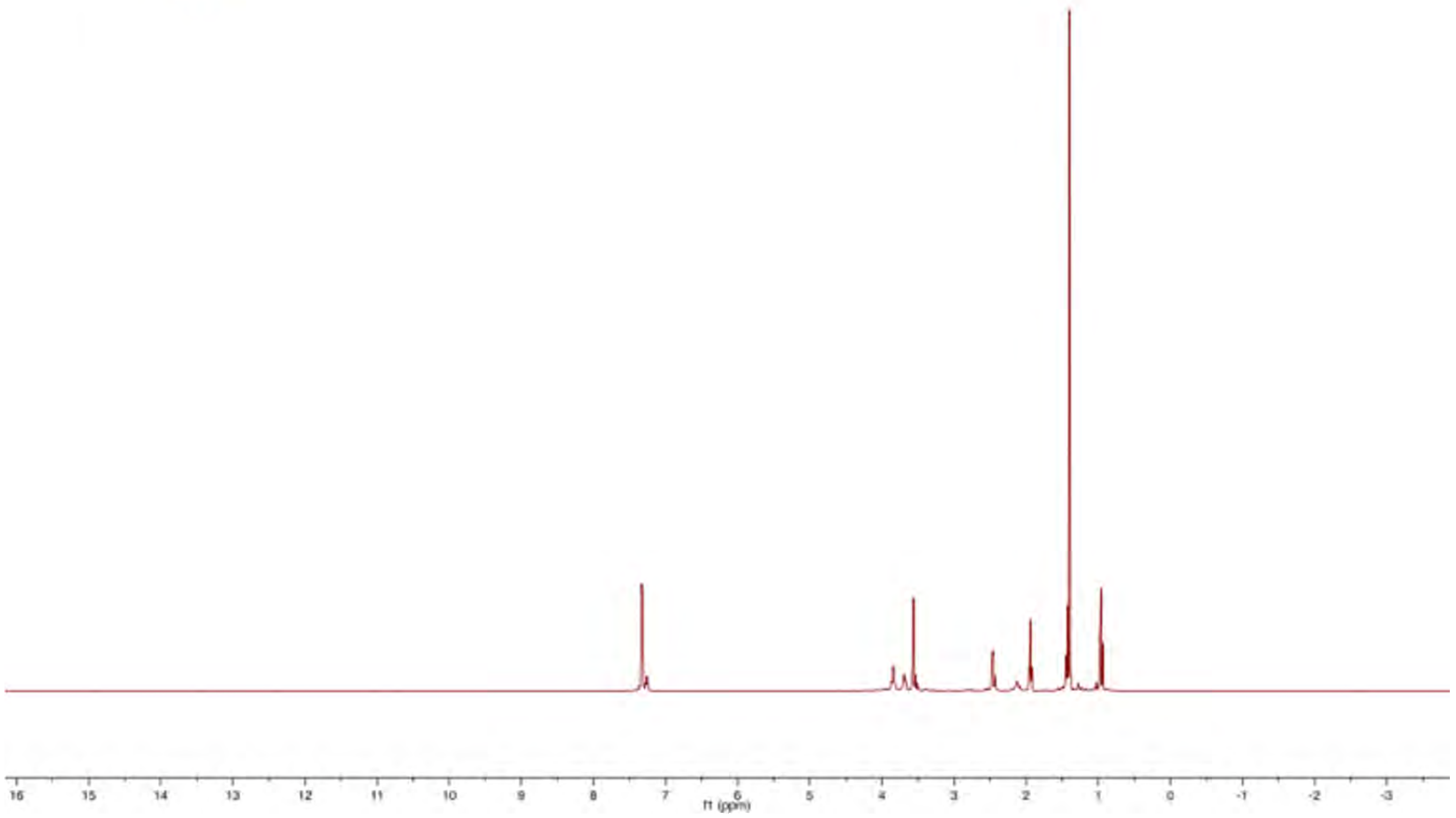

Me
Bn
N
N
Boc

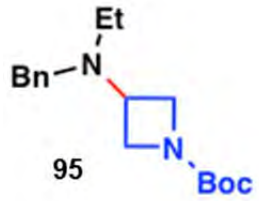
94


57
56
55
54
53
52
51
f1 (ppm)
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)

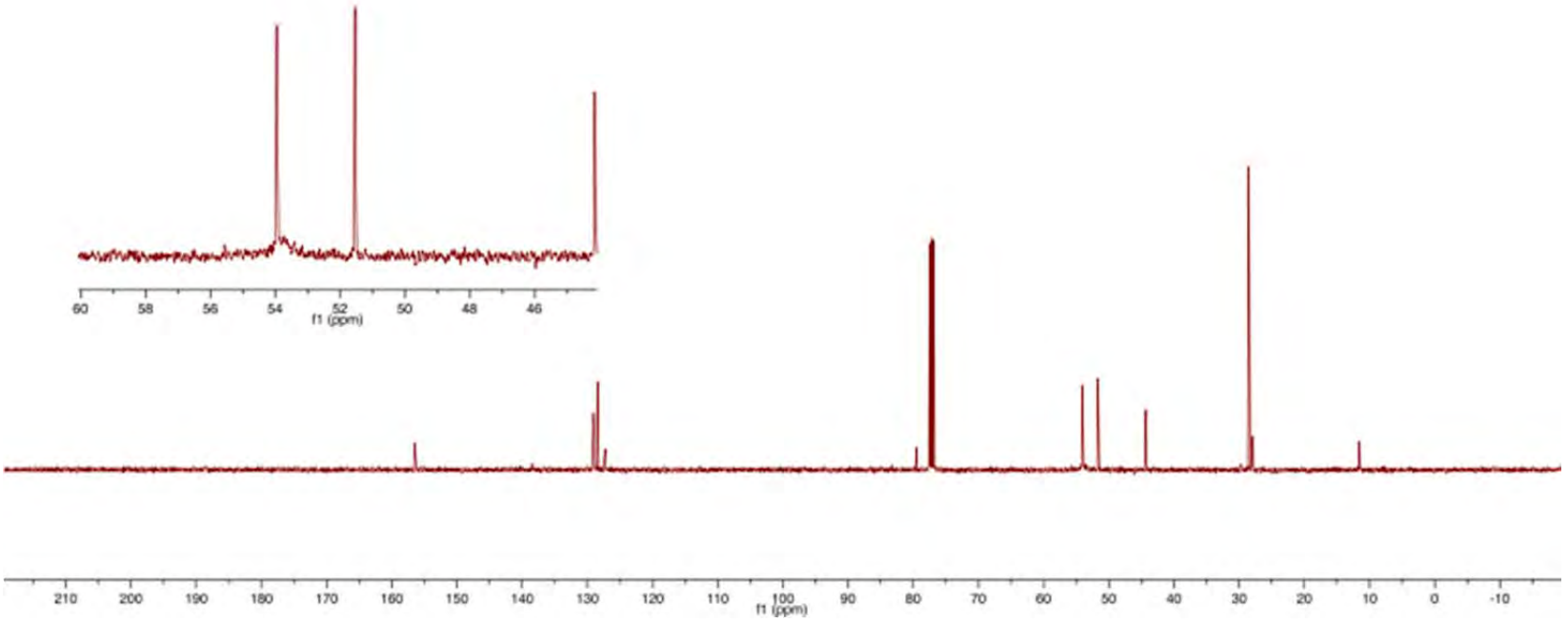


95

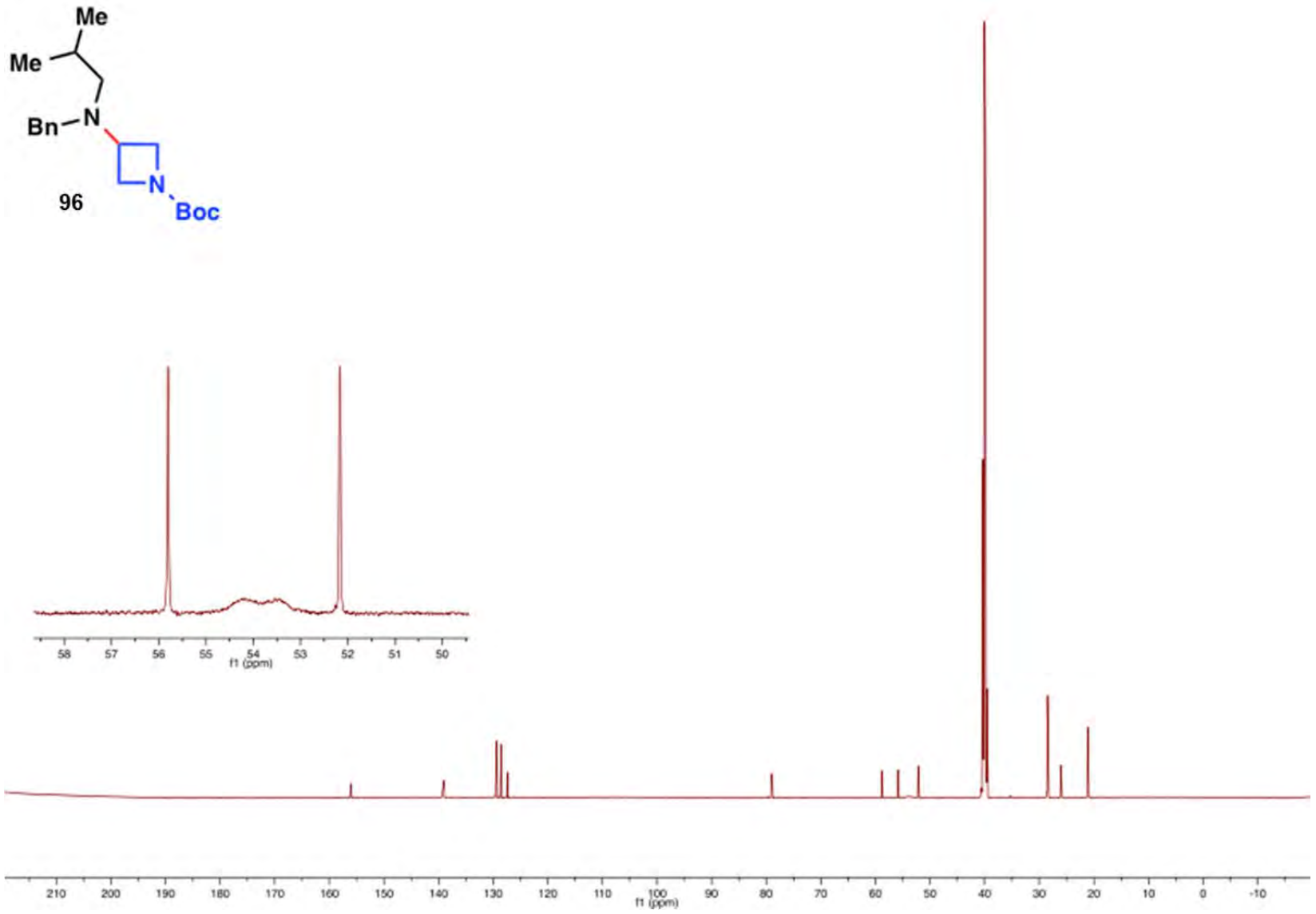



Et
Bn
N
N
Boc

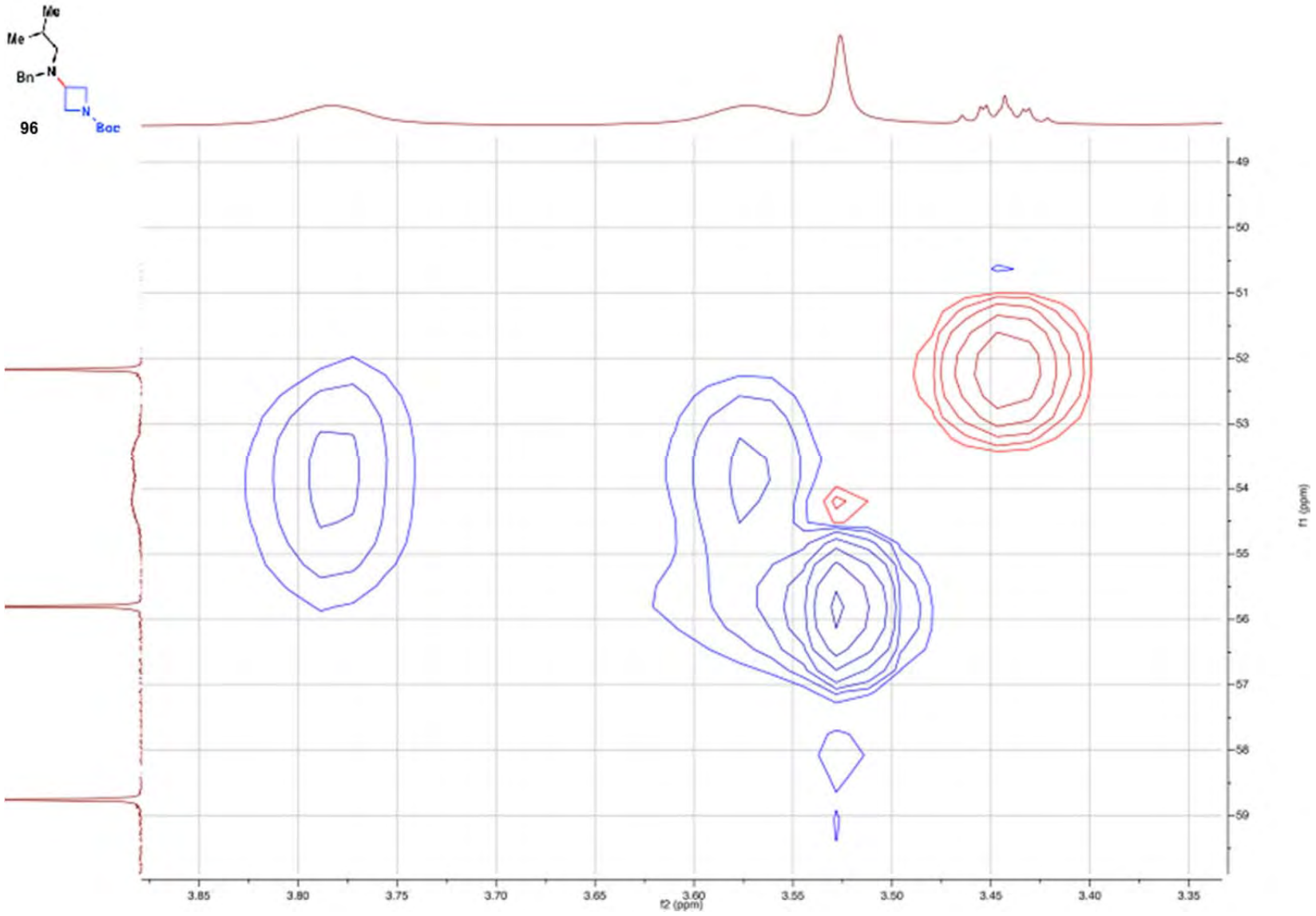
95

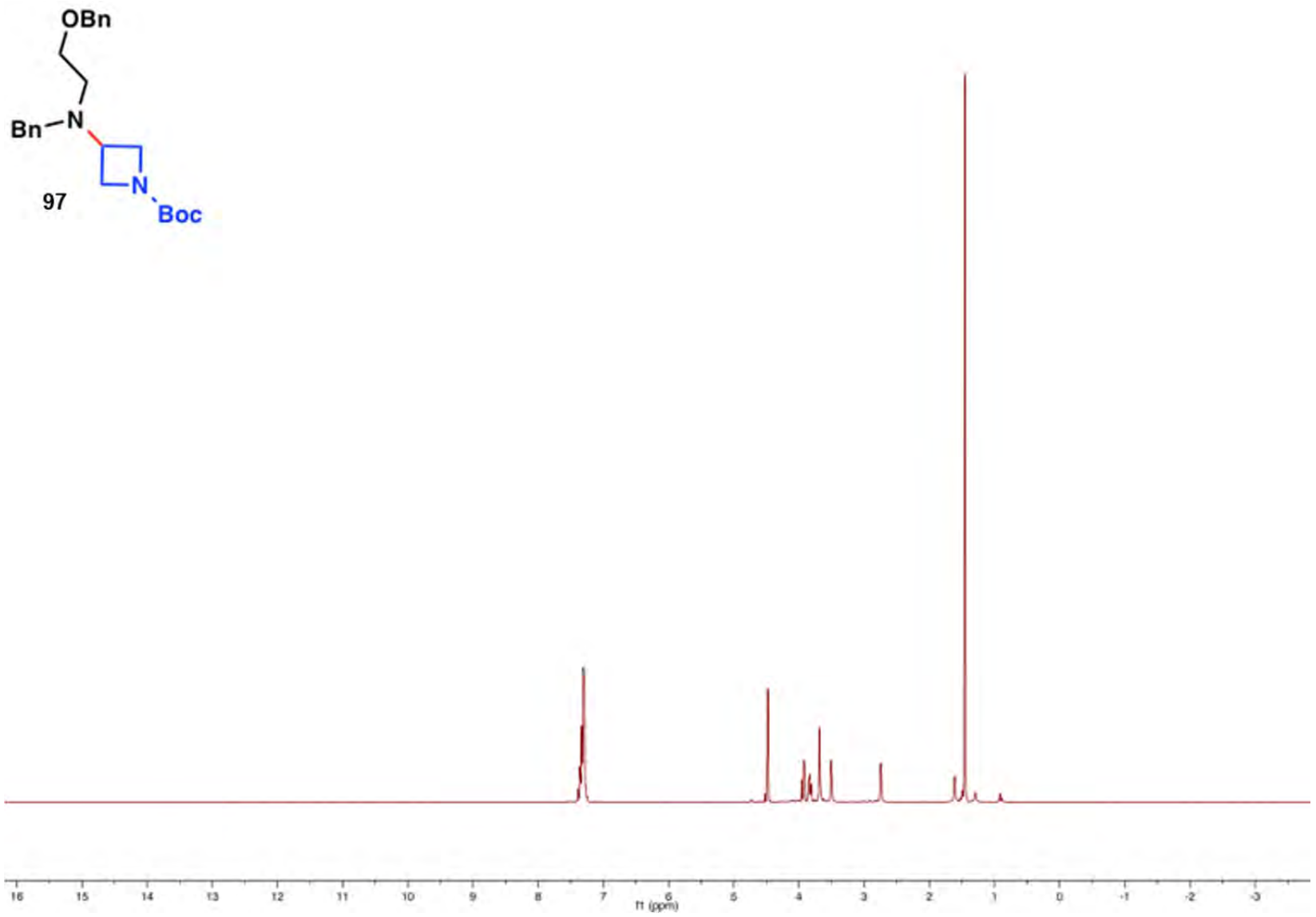

60
58
56
54
52
50
48
46
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

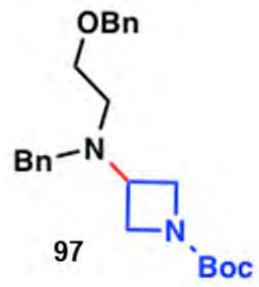
96


Me
Me
Bn
N
N
Boc
96
58
57
56
55
54
53
52
51
50
f1 (ppm)
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)

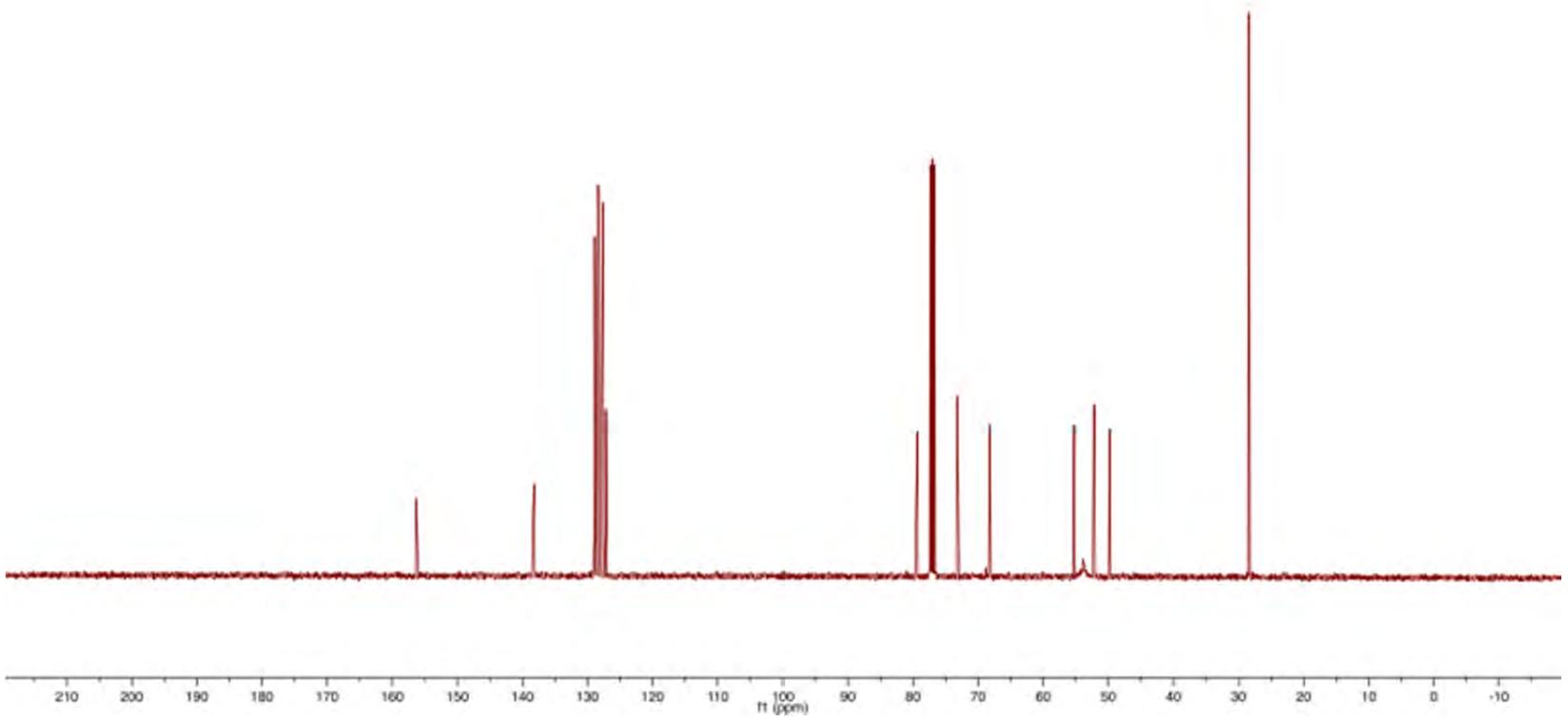

Me
Me
Bn
N
N
Boc
96
f2 (ppm)
f1 (ppm)


Me
Me
Bn
N
N
Boc
96
49
50
51
52
53
54
55
56
57
58
59
f1 (ppm)
3.85
3.80
3.75
3.70
3.65
3.60
3.55
3.50
3.45
3.40
3.35
f2 (ppm)


OBn
Bn
N
N
Boc
97
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f1 (ppm)

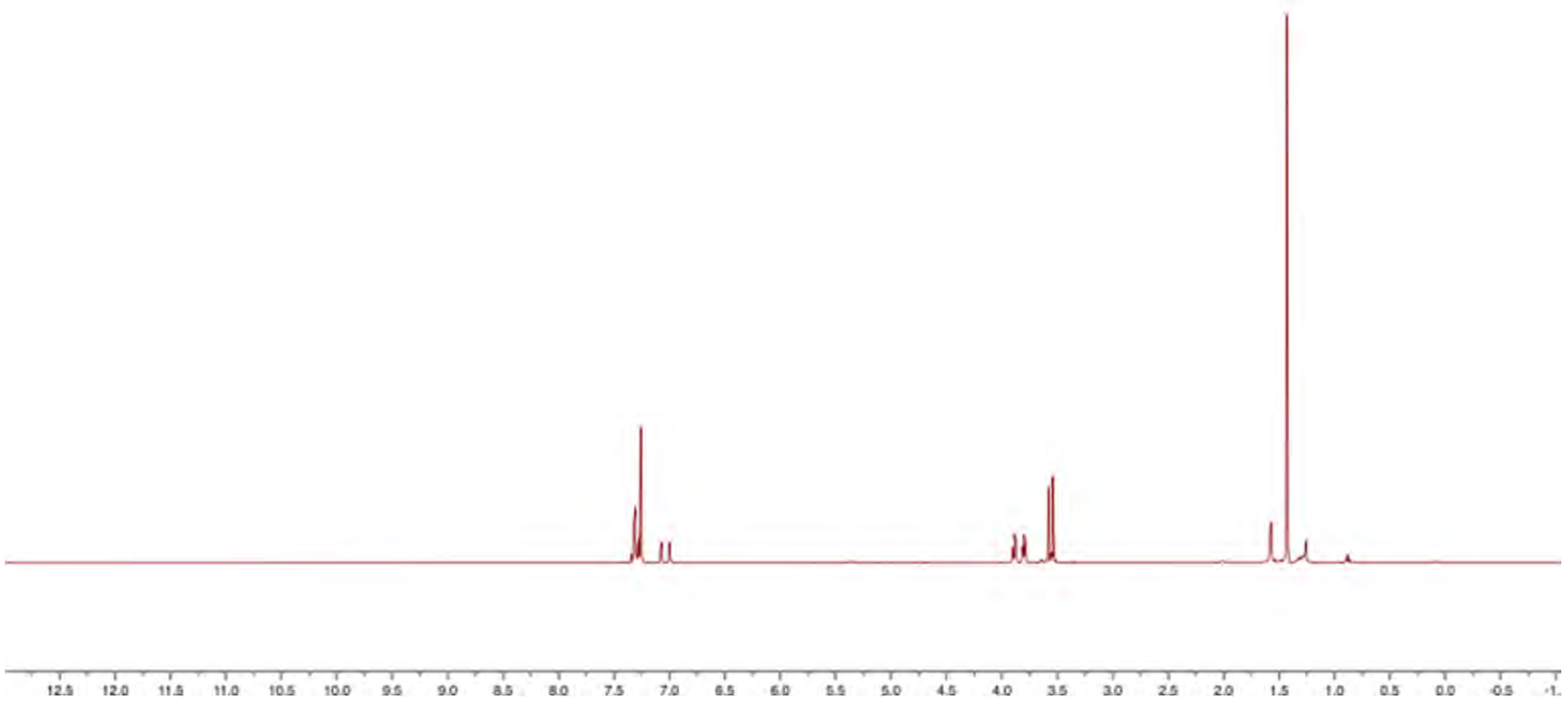

OBn
Bn
N
N
Boc

97


210
200
190
180
170
160
150
140
130
120
110
100
f1 (ppm)
90
80
70
60
50
40
30
20
10
0
-10

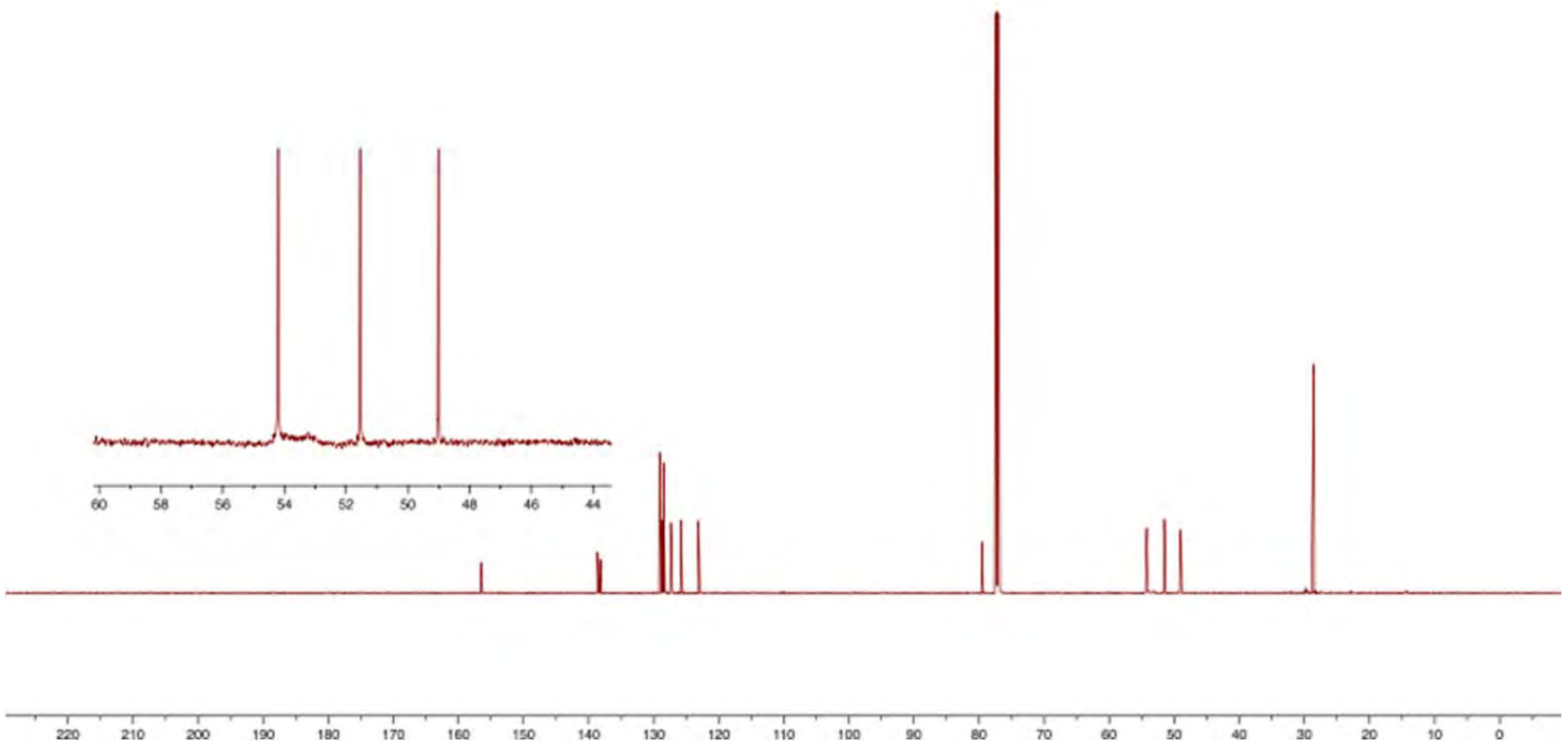

S
Bn
N
N
Boc

98


12.5 12.0 11.5 11.0 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


S
Bn
N
N
Boc

98


60
58
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52
50
48
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44
220
210
200
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180
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120
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100
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70
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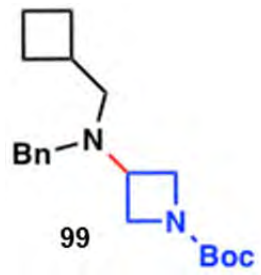
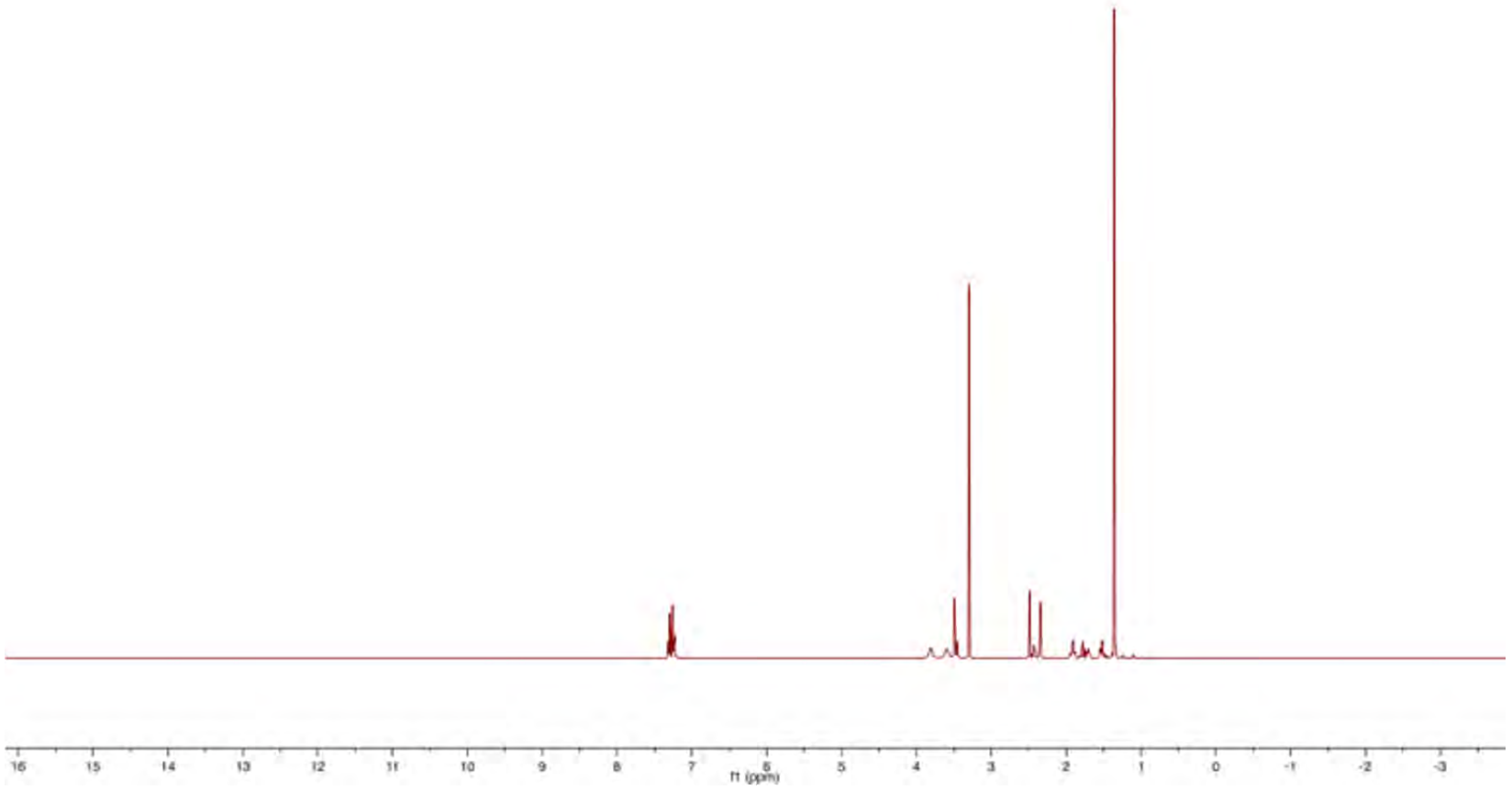
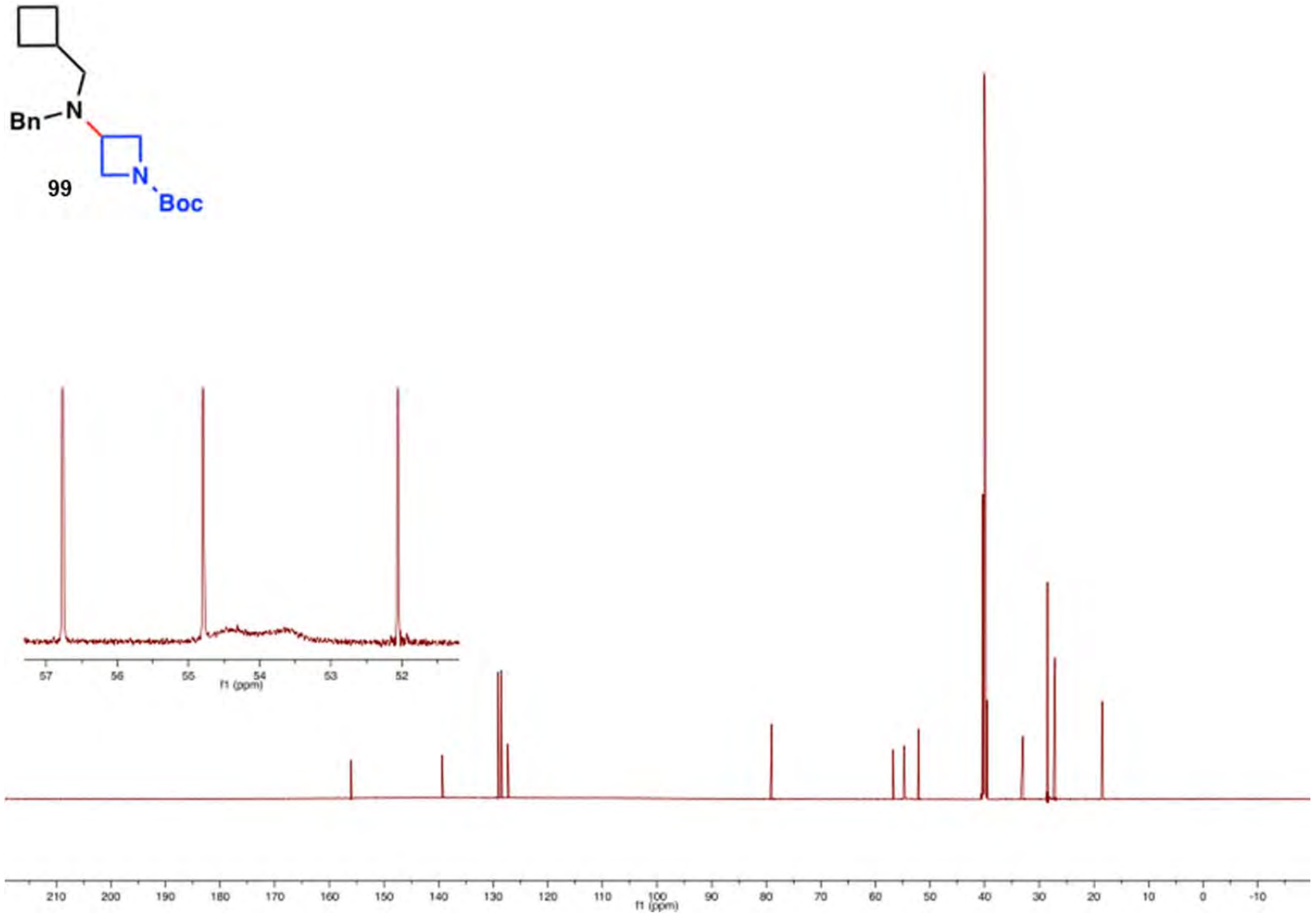
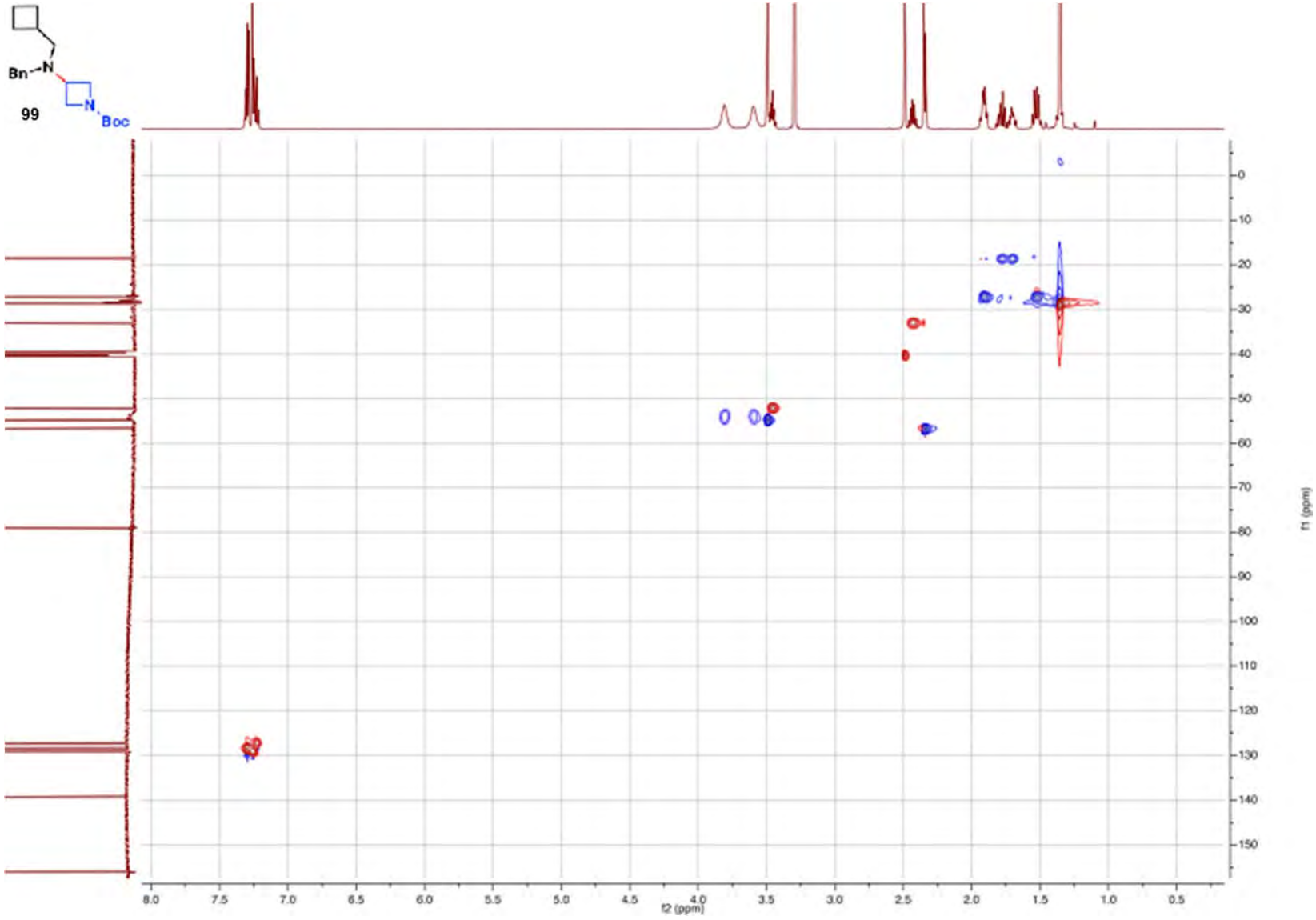
30
20
10
0

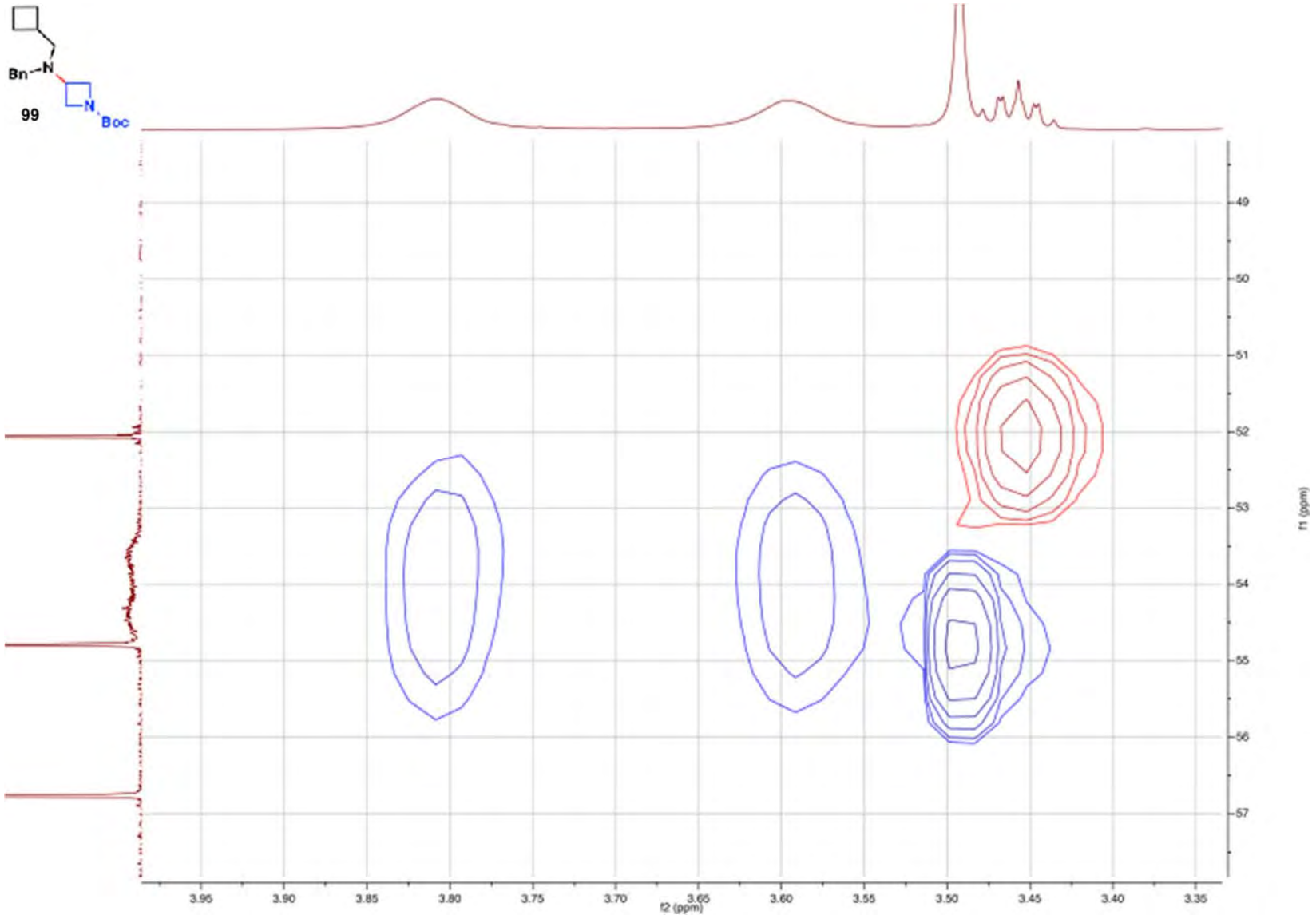


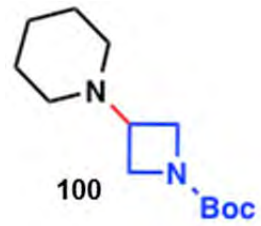
99




Bn
N
N
Boc
99
57
56
55
54
53
52
f1 (ppm)
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)

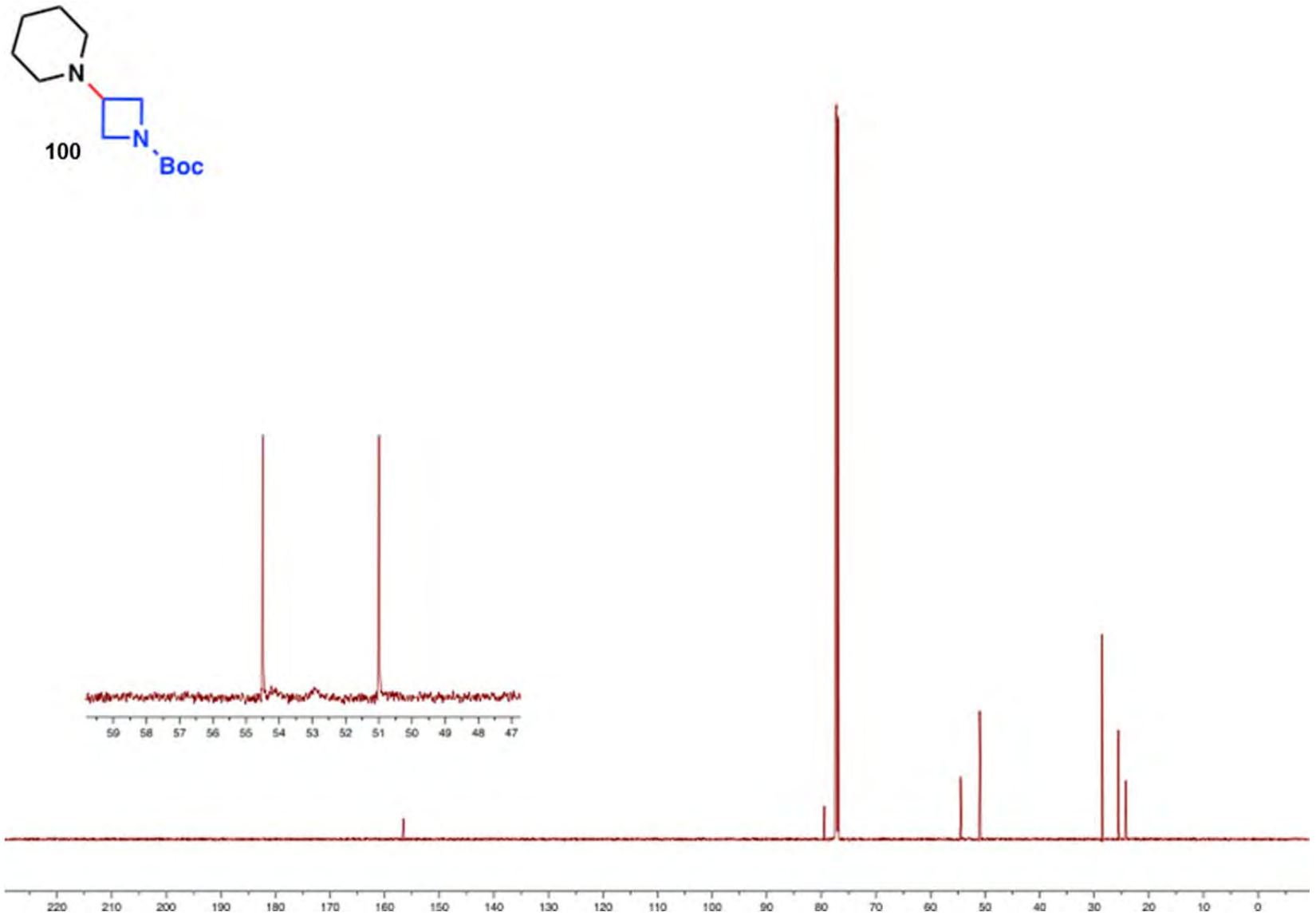

Bn
N
N
Boc
99
f2 (ppm)
f1 (ppm)

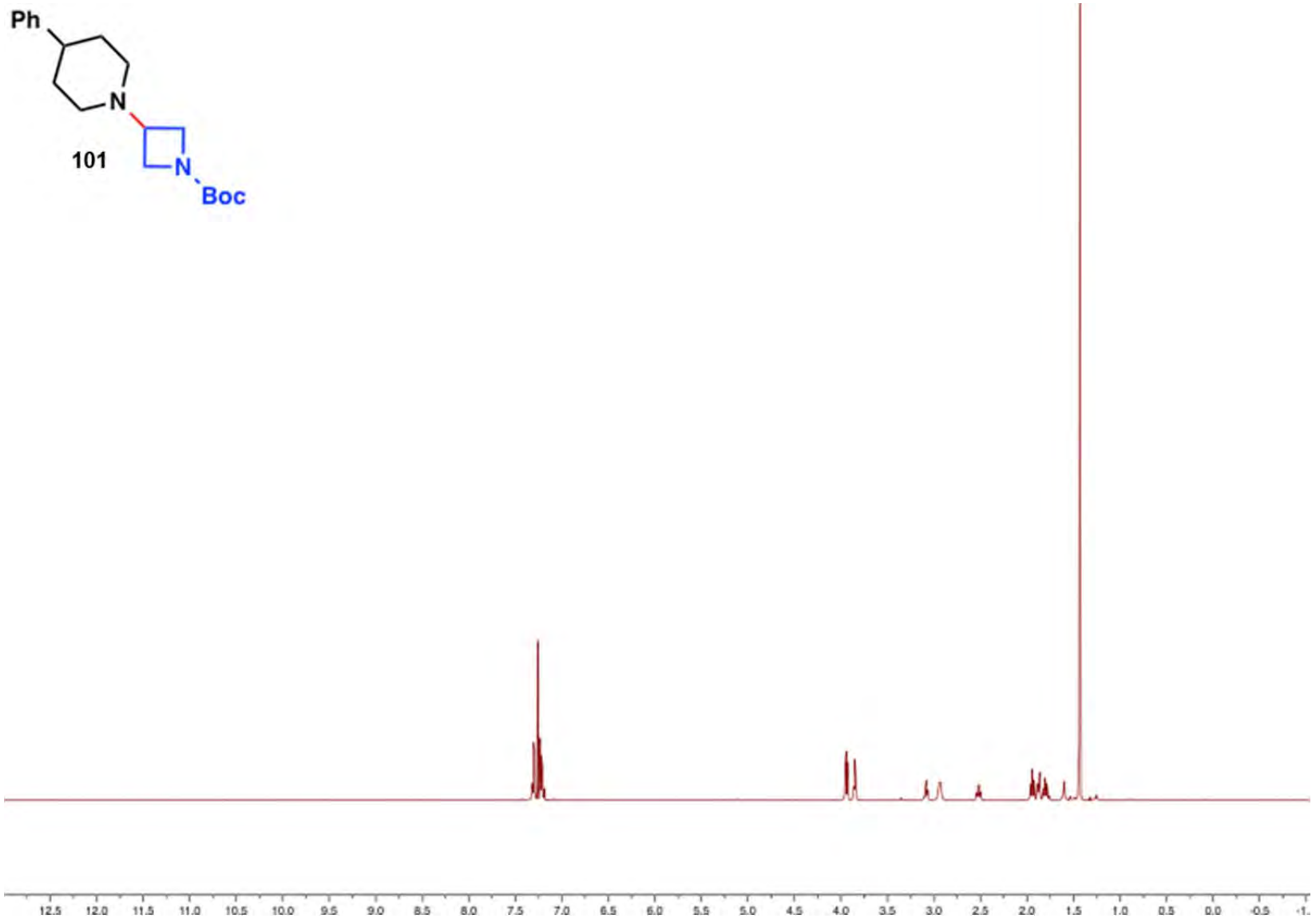

Bn
N
N
Boc
99
49
50
51
52
53
54
55
56
57
f1 (ppm)
3.95
3.90
3.85
3.80
3.75
3.70
3.65
3.60
3.55
3.50
3.45
3.40
3.35
f2 (ppm)


N
N
Boc

100

12.5 12.0 11.5 11.0 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


N
N
Boc
100
59 58 57 56 55 54 53 52 51 50 49 48 47
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Ph
N
101
N
Boc
12.5
12.0
11.5
11.0
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
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3.5
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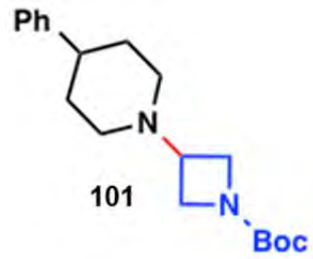
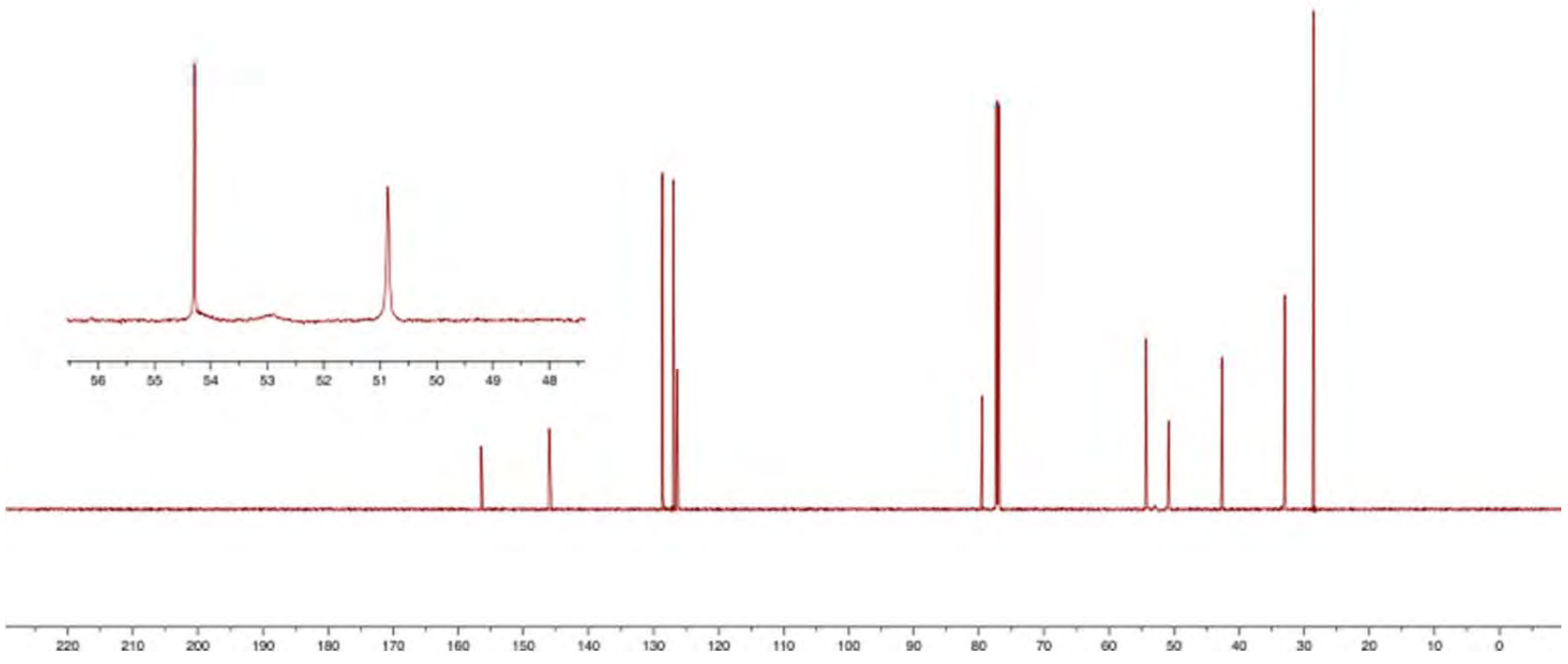
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Ph
N
N
Boc

101


56
55
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52
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210
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110
100
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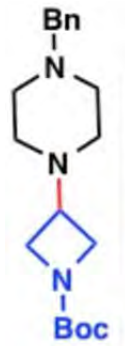
30
20
10
0


Bn
N
N
N
Boc

102

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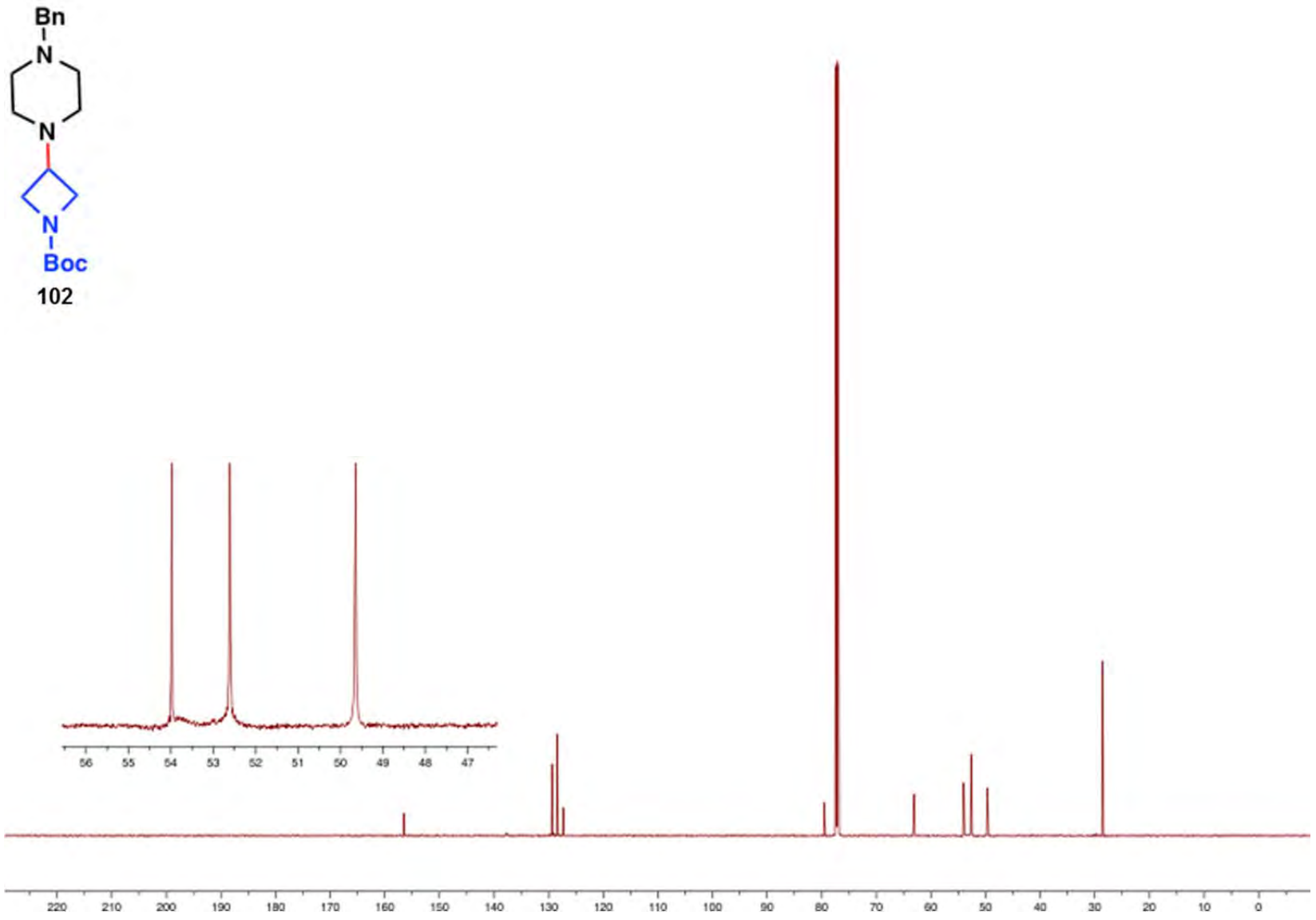
Bn
N
N
N
Boc
102
56
55
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220
210
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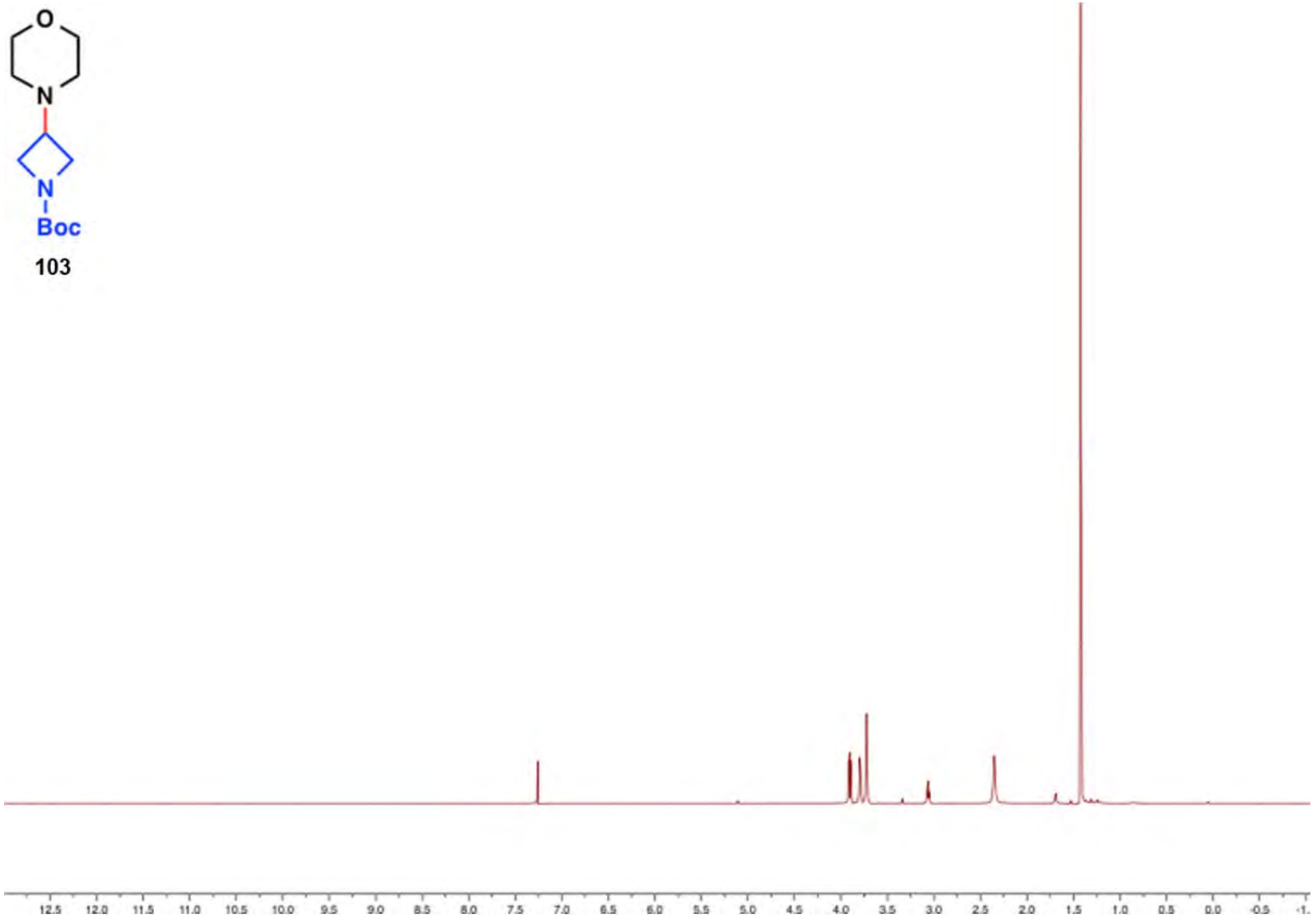
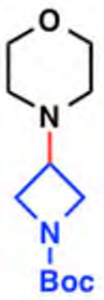
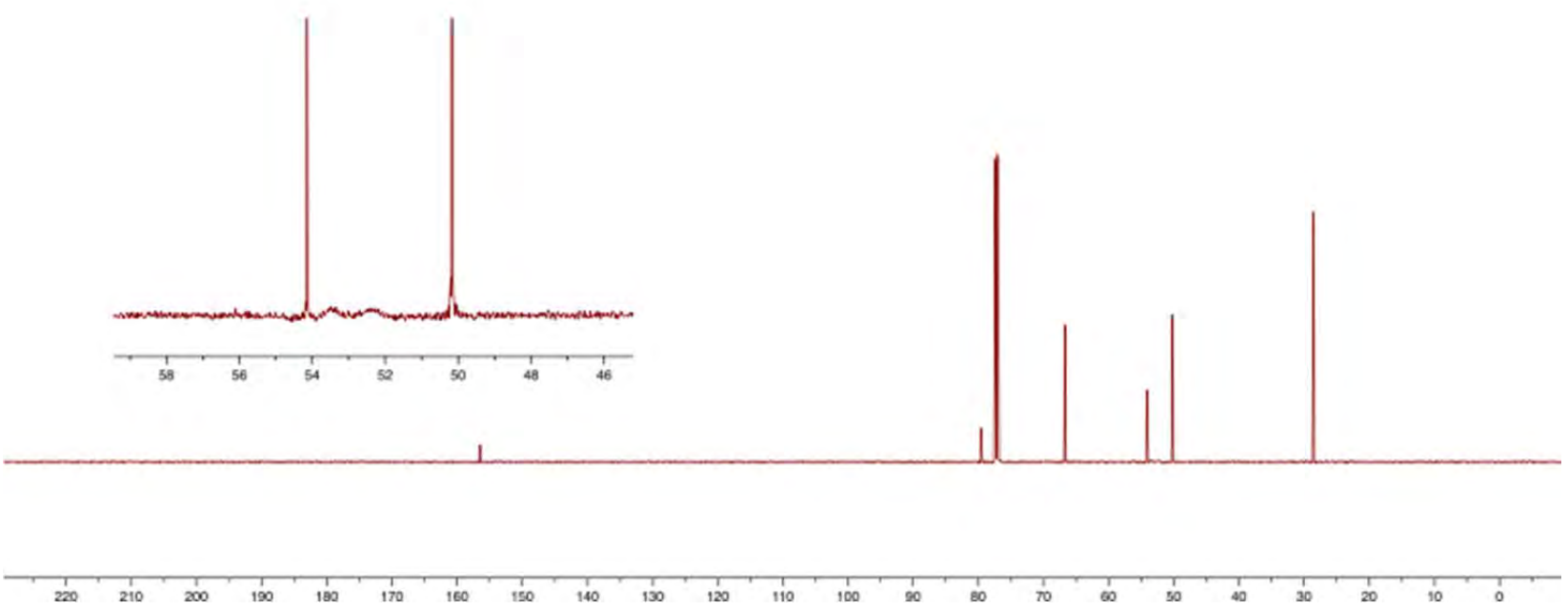

O
N
N
Boc
103
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


O
N
N
Boc

103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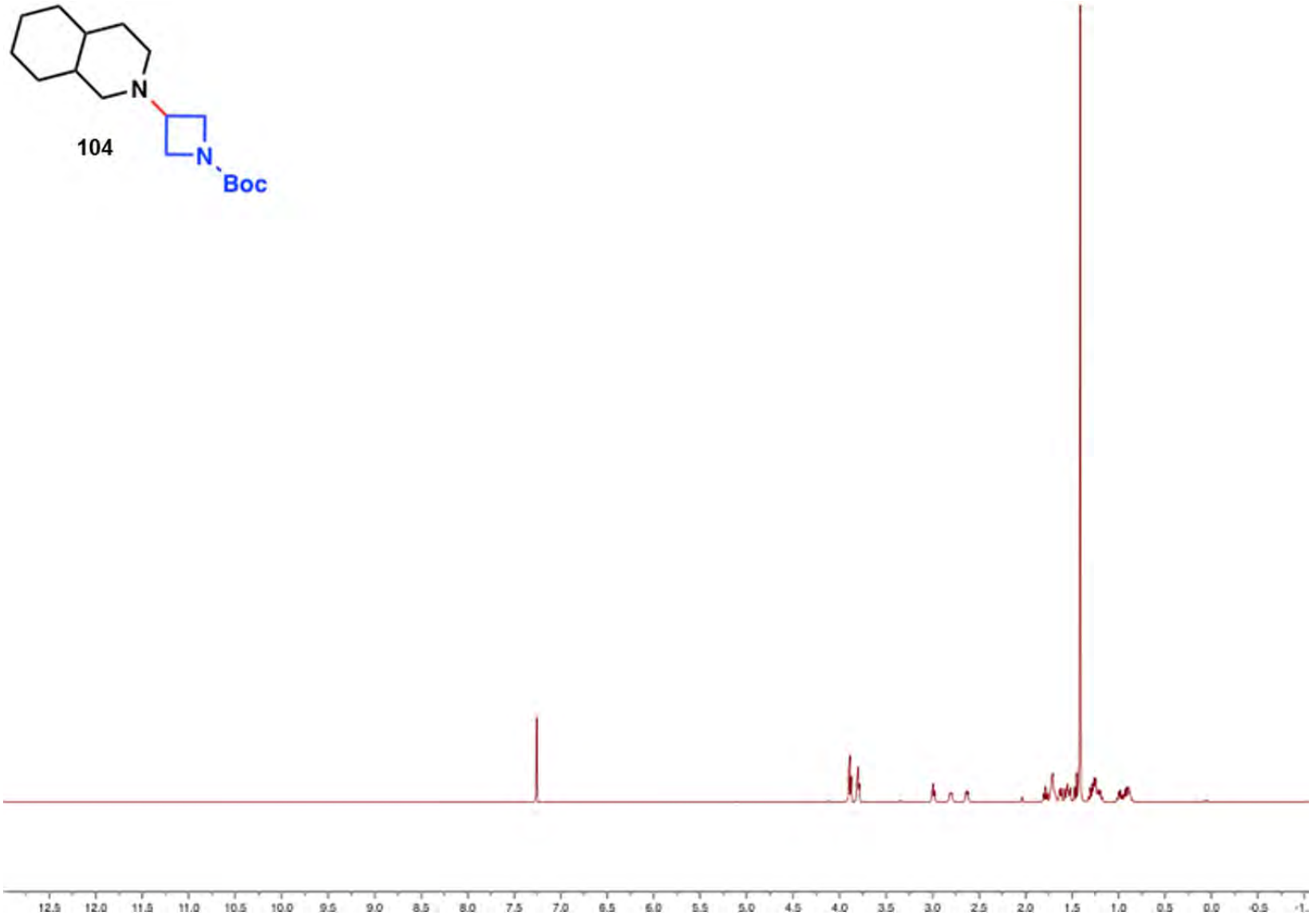
10
0


N
104
N
Boc
12.5
12.0
11.5
11.0
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
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3.5
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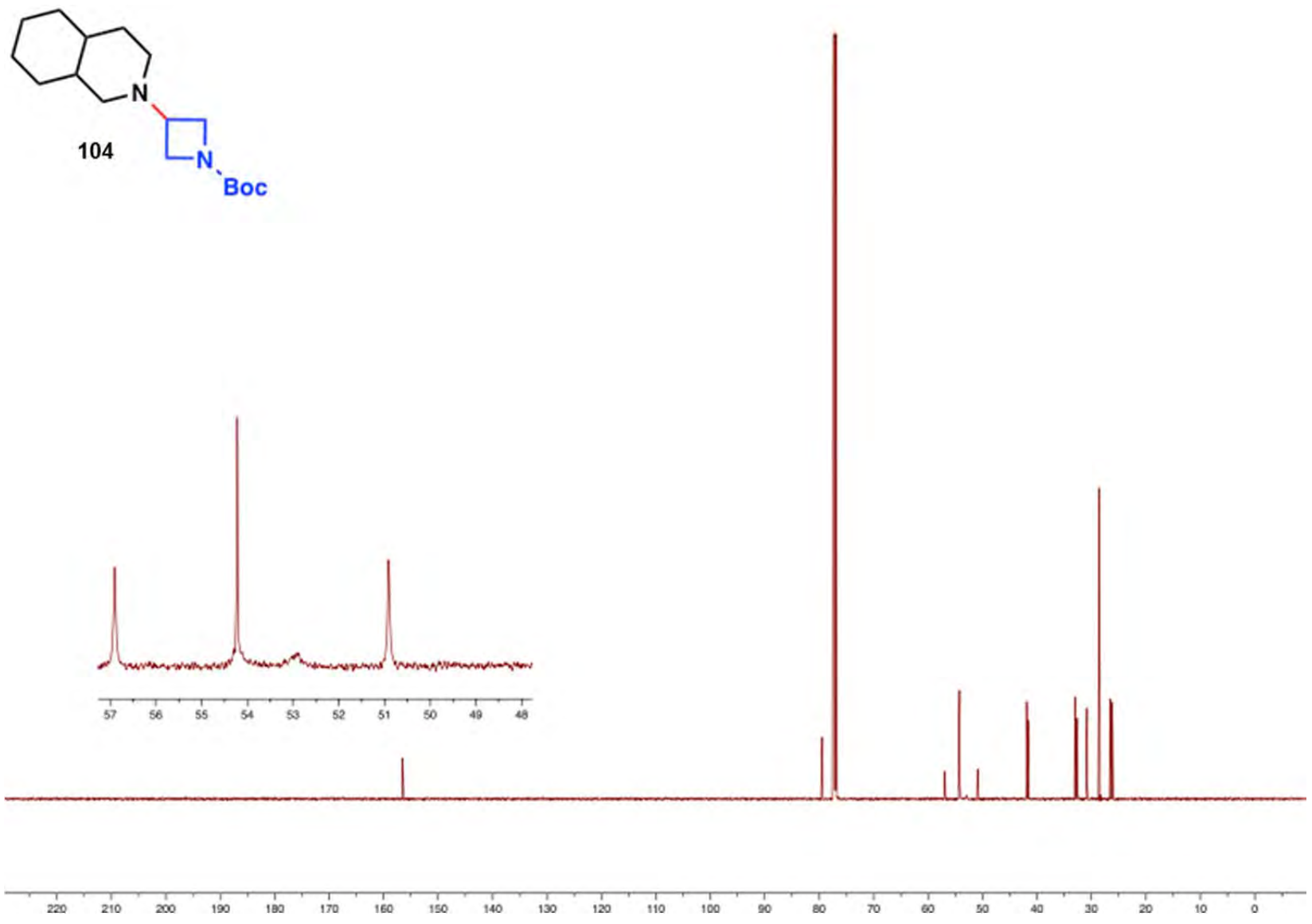
2.0
1.5
1.0
0.5
0.0
-0.5


N
104
N
Boc
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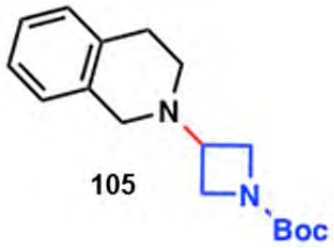
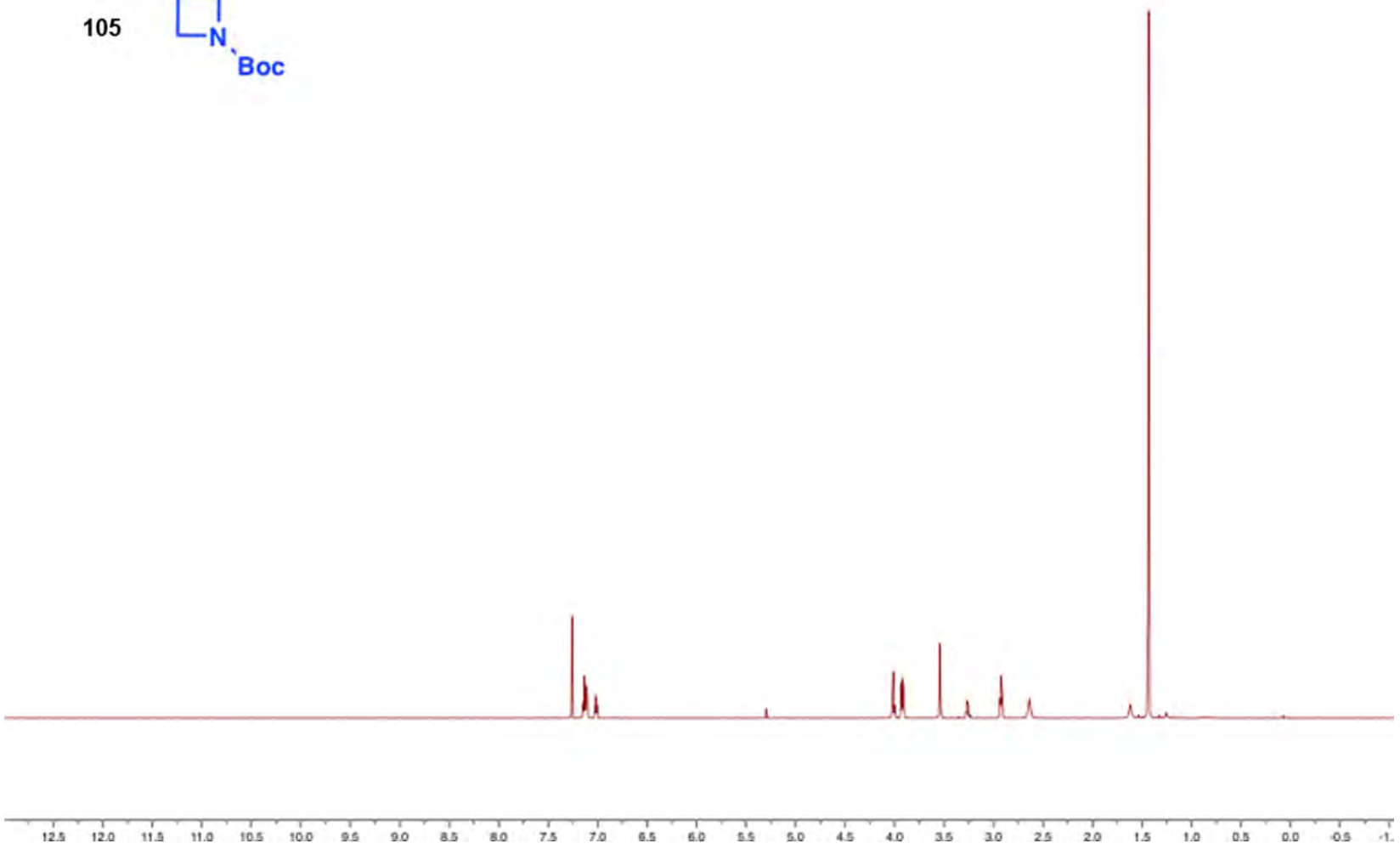
10
0


N
N
Boc

105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11.0
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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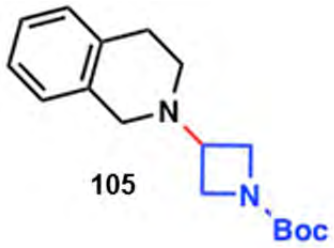
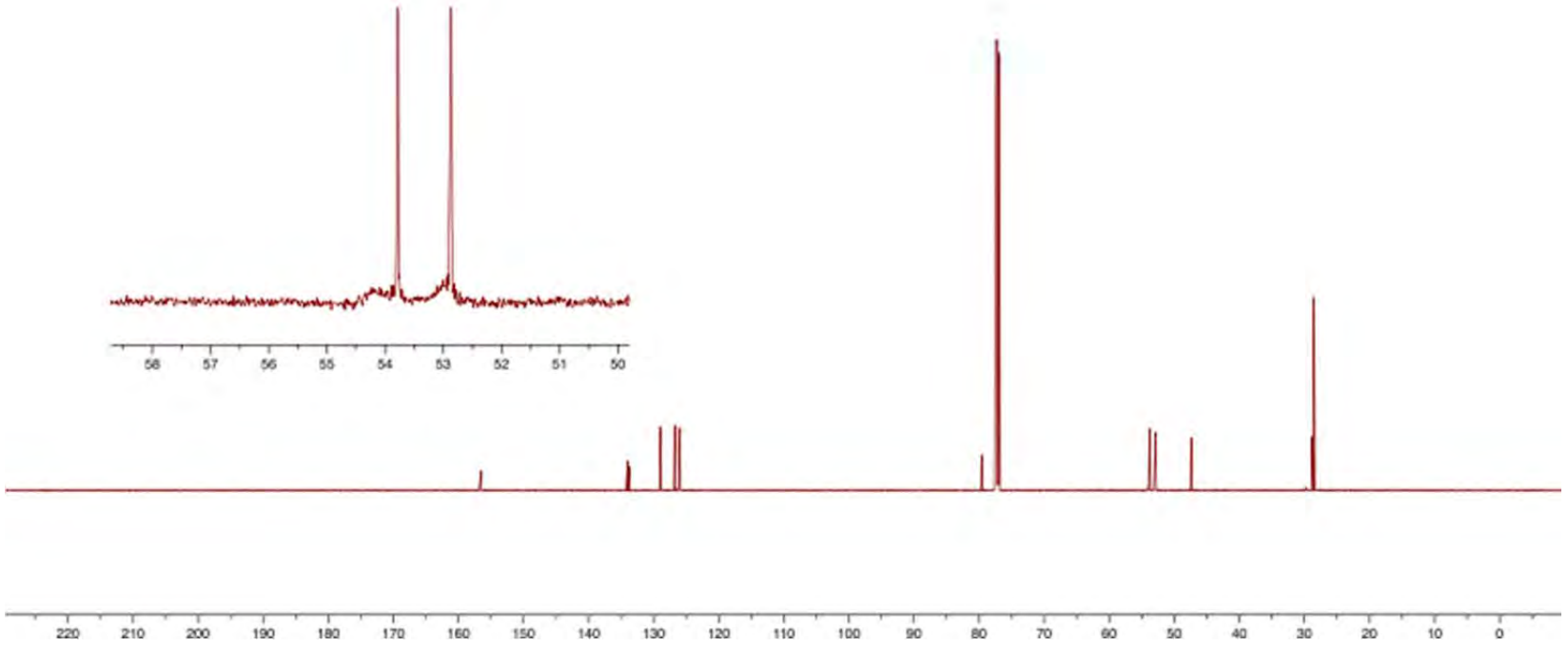
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


N
N
Boc

105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30
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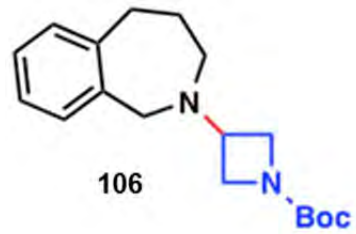
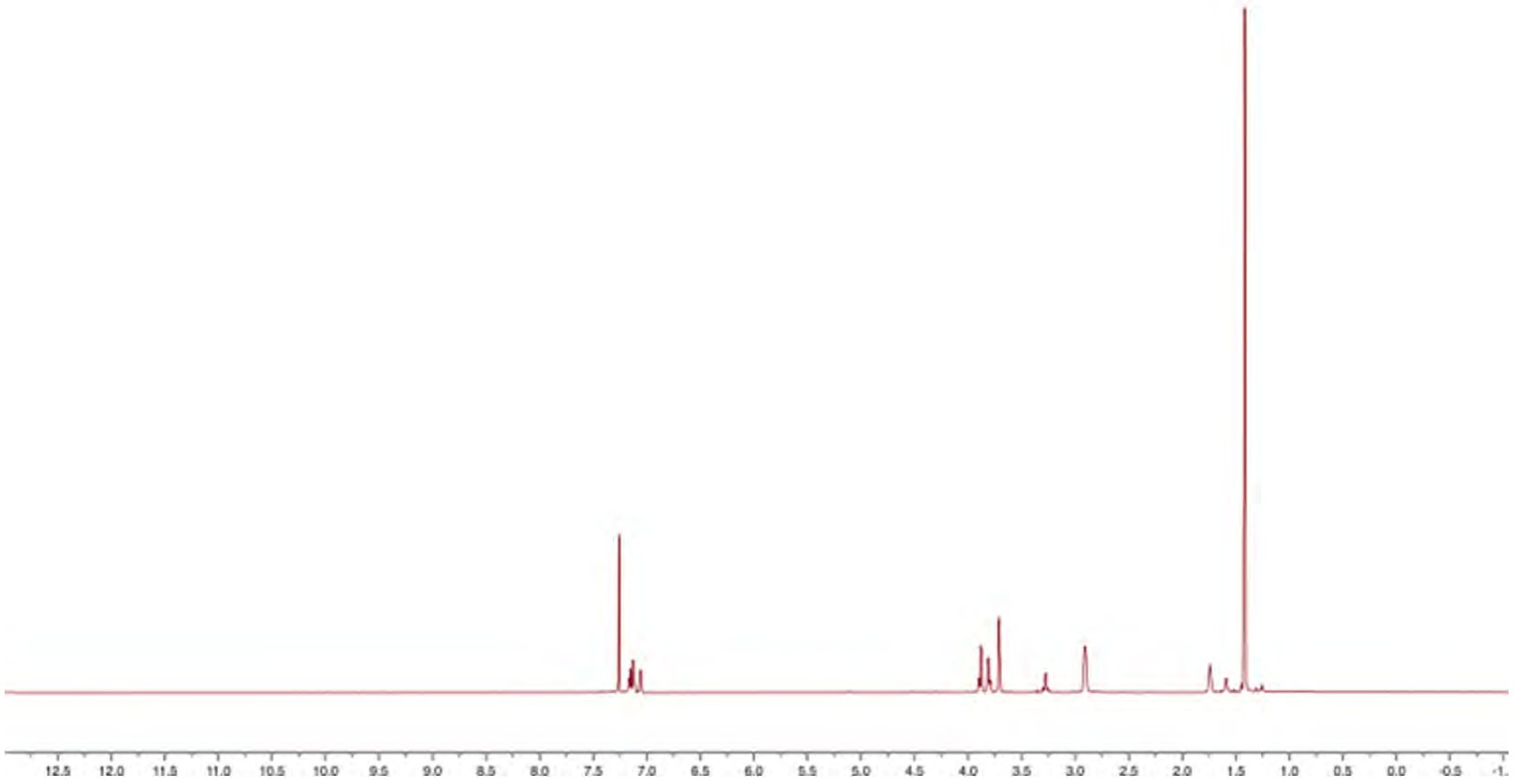
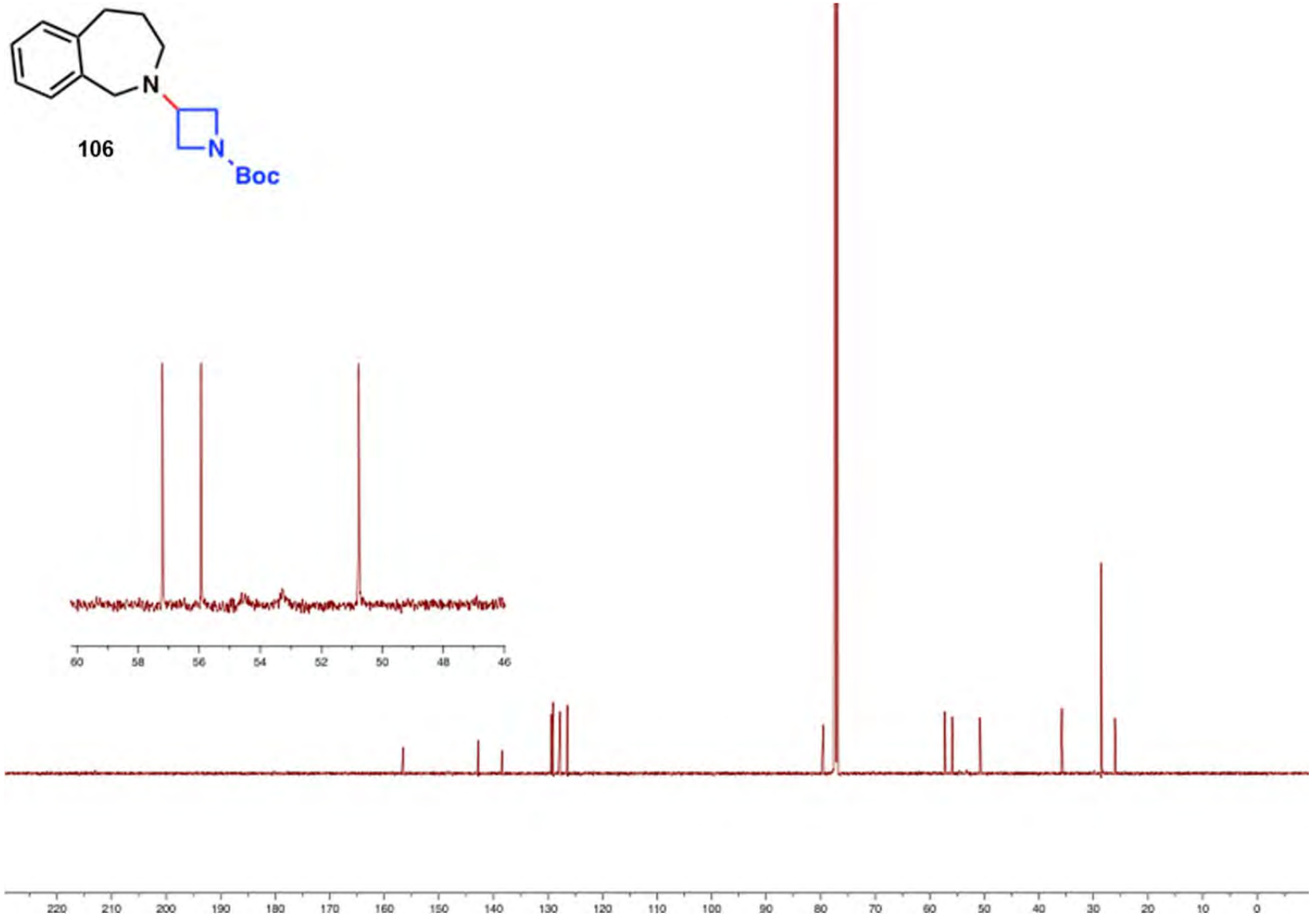
10
0


N
N
Boc

106


12.5 12.0 11.5 11.0 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


N
N
Boc
106
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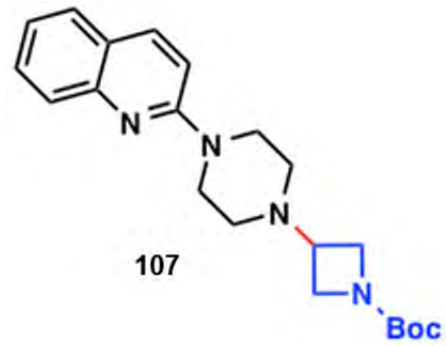
10
0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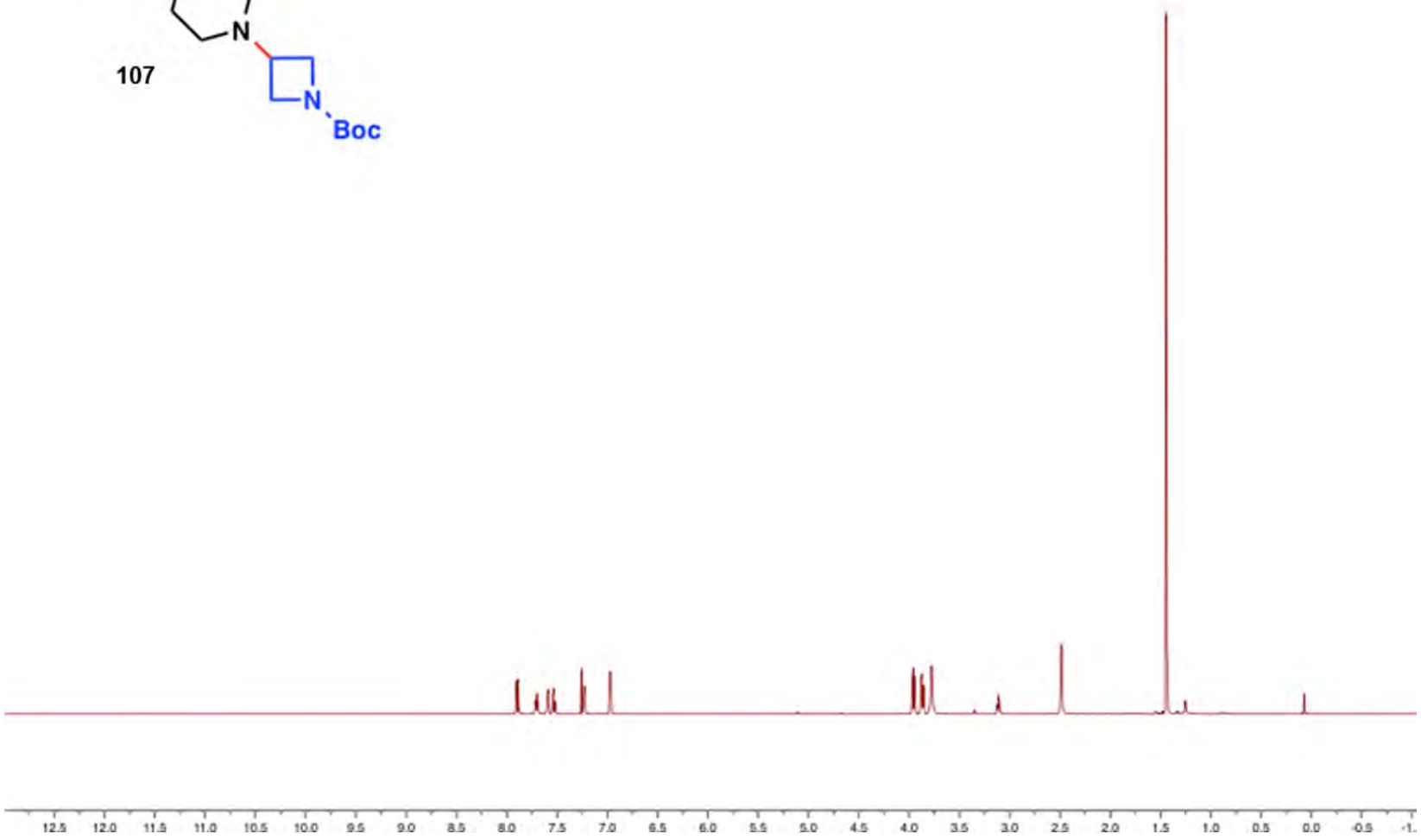
N
N
N
Boc

107


12.5
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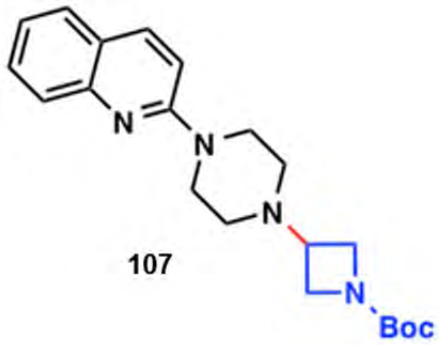
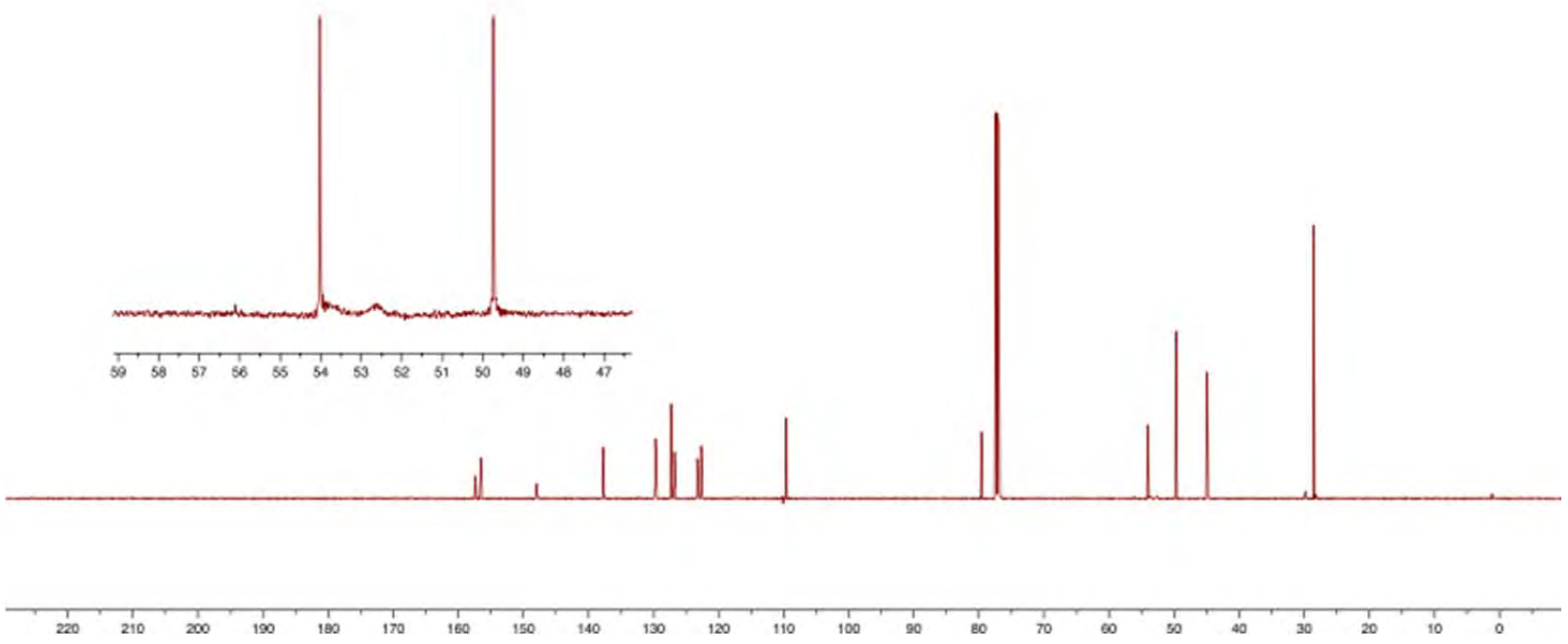
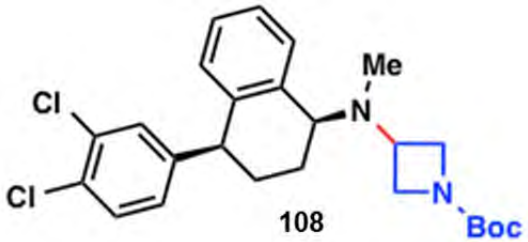
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


N
N
N
N
Boc

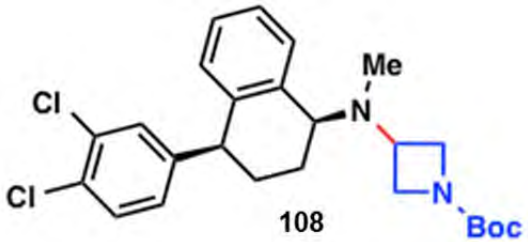
107


59 58 57 56 55 54 53 52 51 50 49 48 47
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

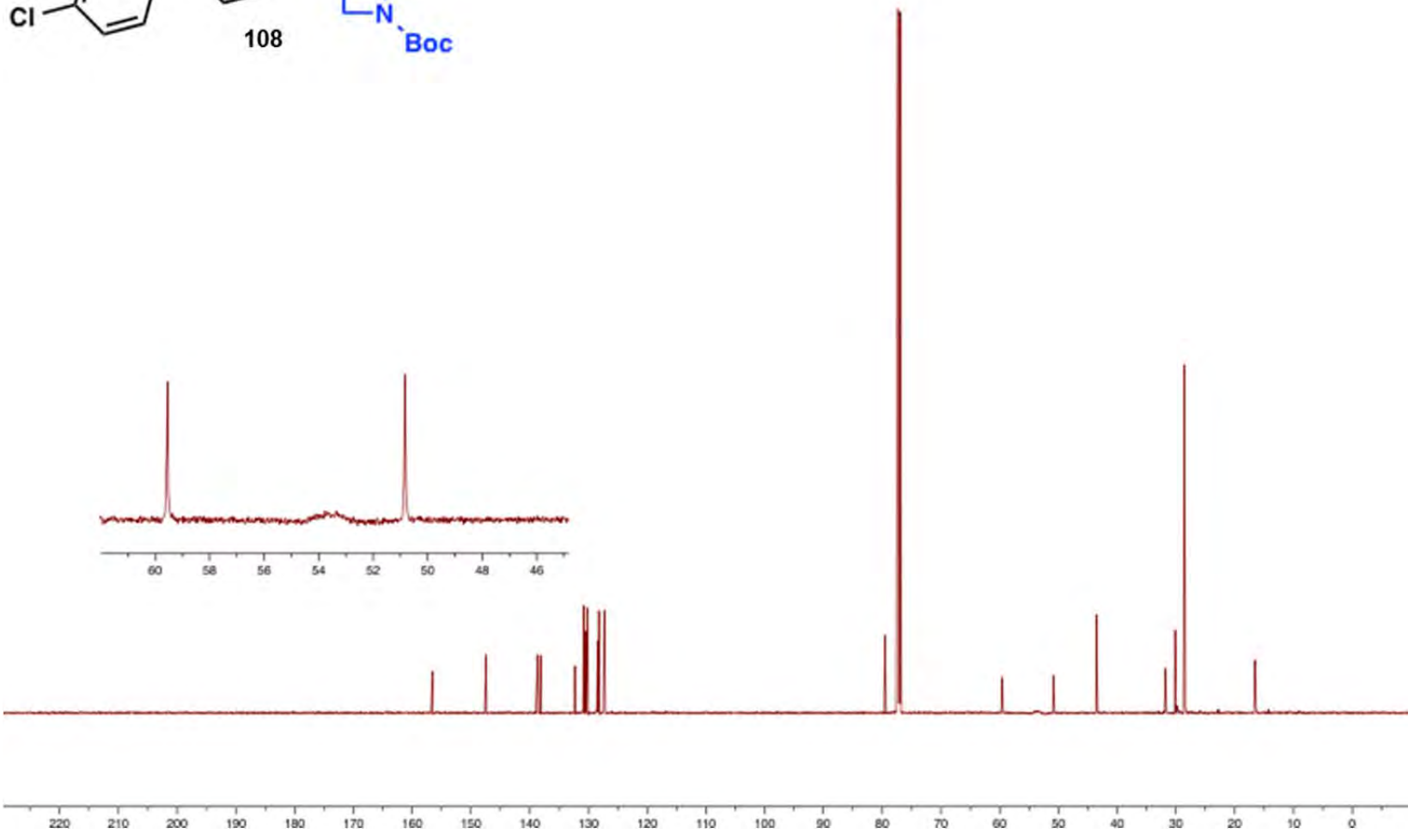

Me
N
Cl
Cl
N
Boc

108

12.5 12.0 11.5 11.0 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


Me
N
Cl
Cl
N
Boc

108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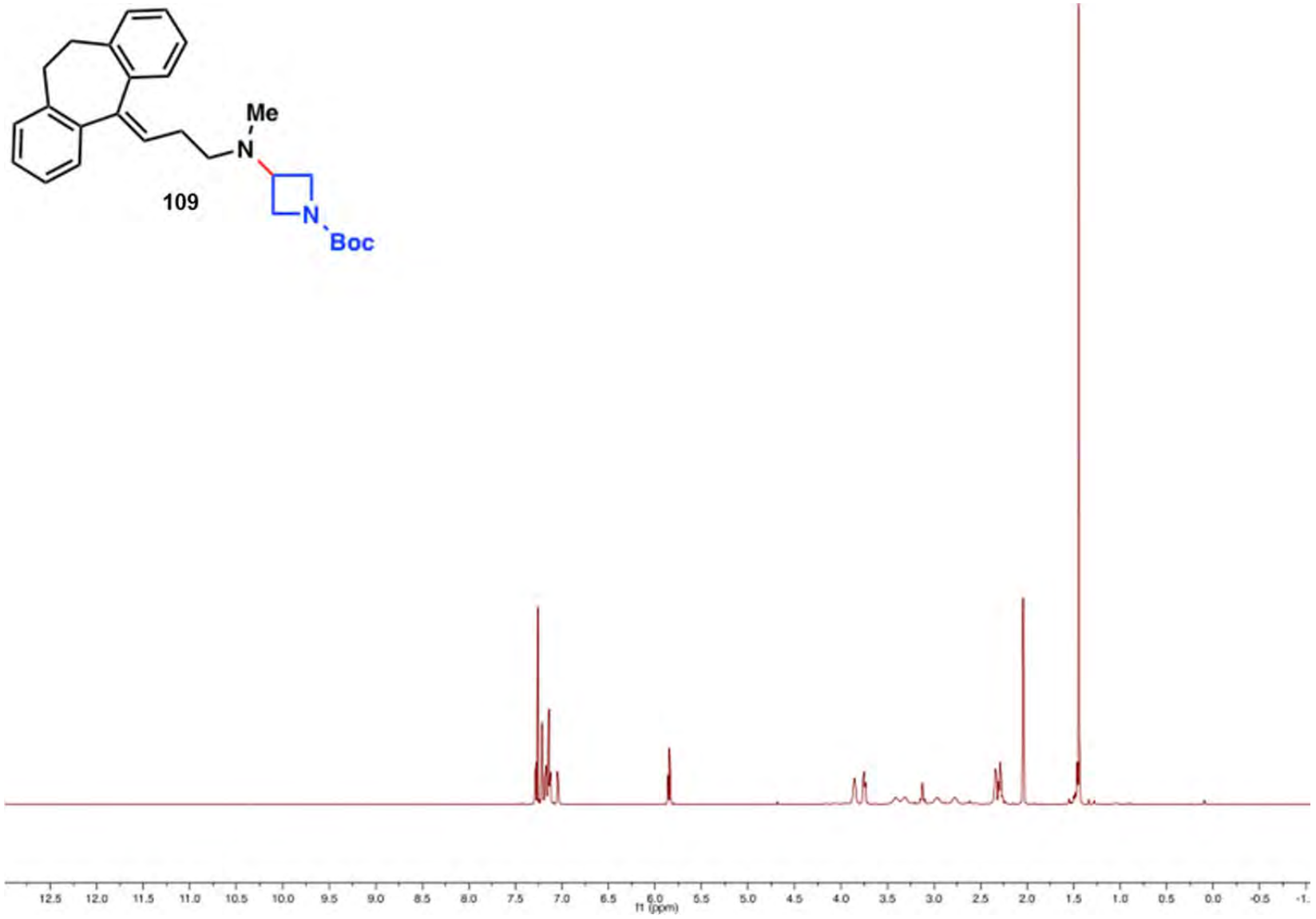
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N
109
N
Boc
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8.0
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7.0
6.5
6.0
f1 (ppm)
5.5
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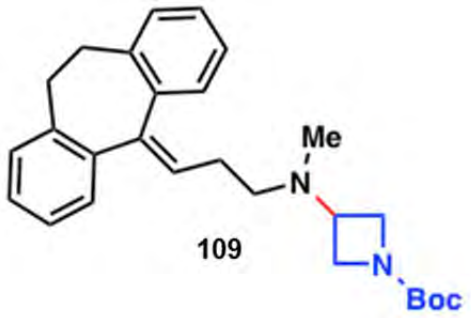
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N
Boc

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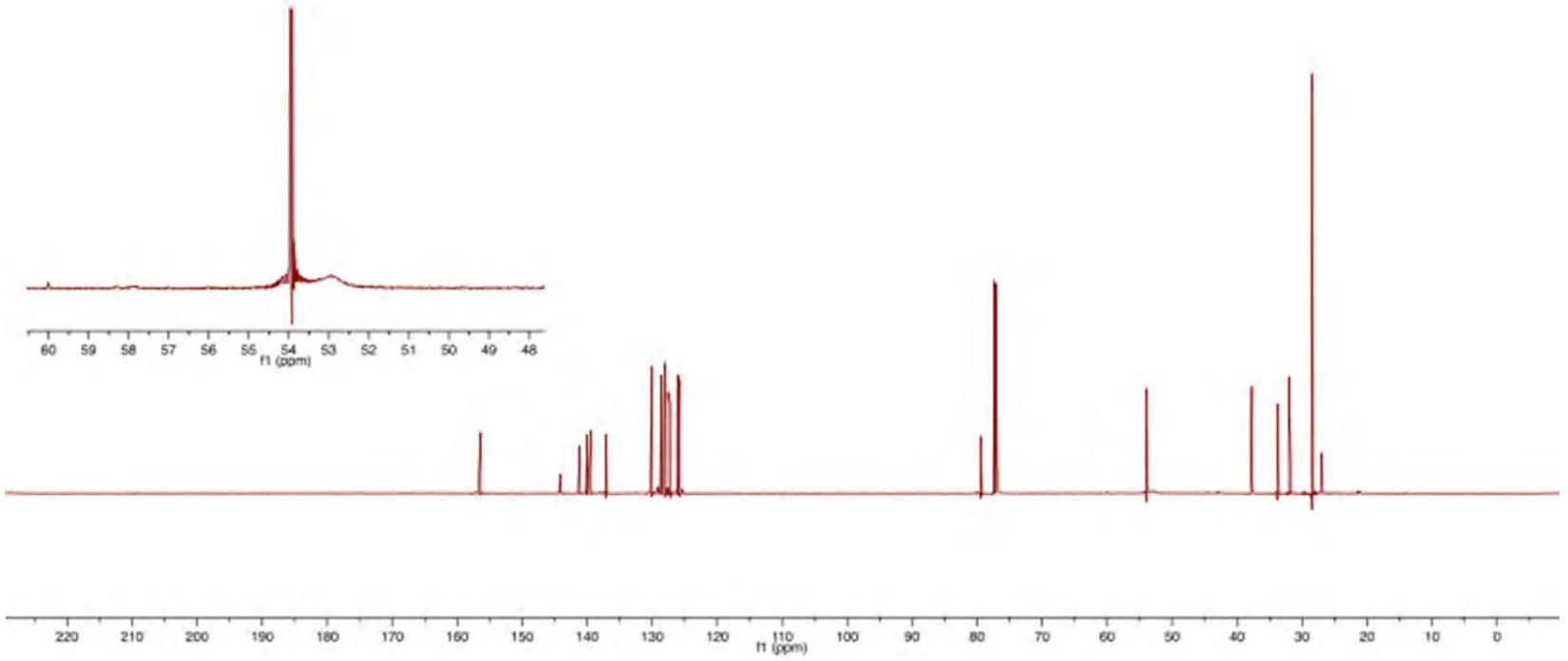
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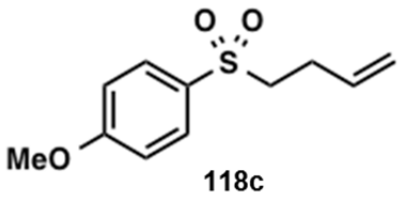
f1 (ppm)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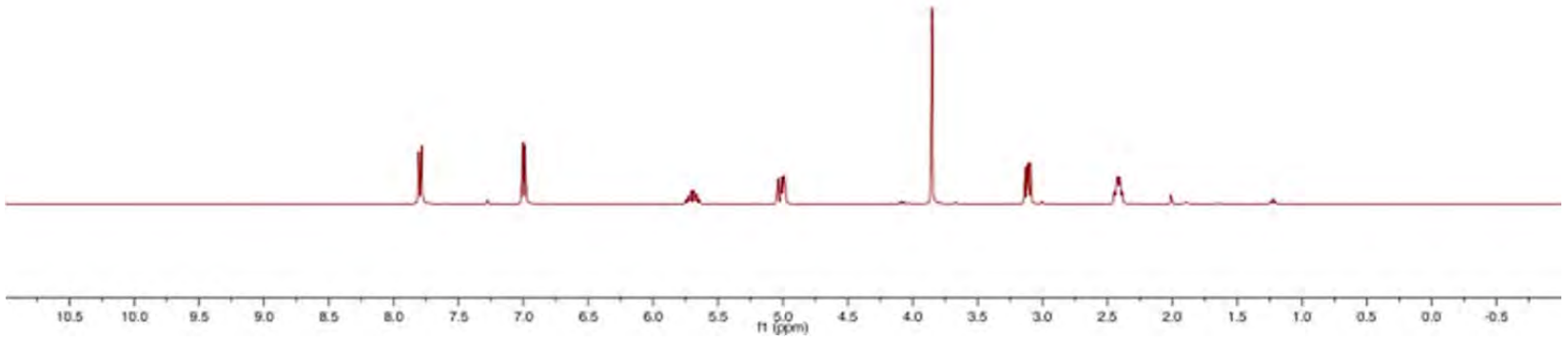
118c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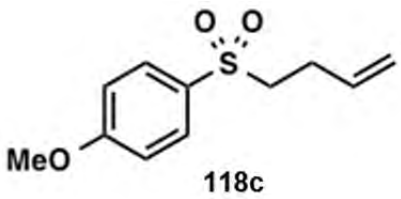
f1 (ppm)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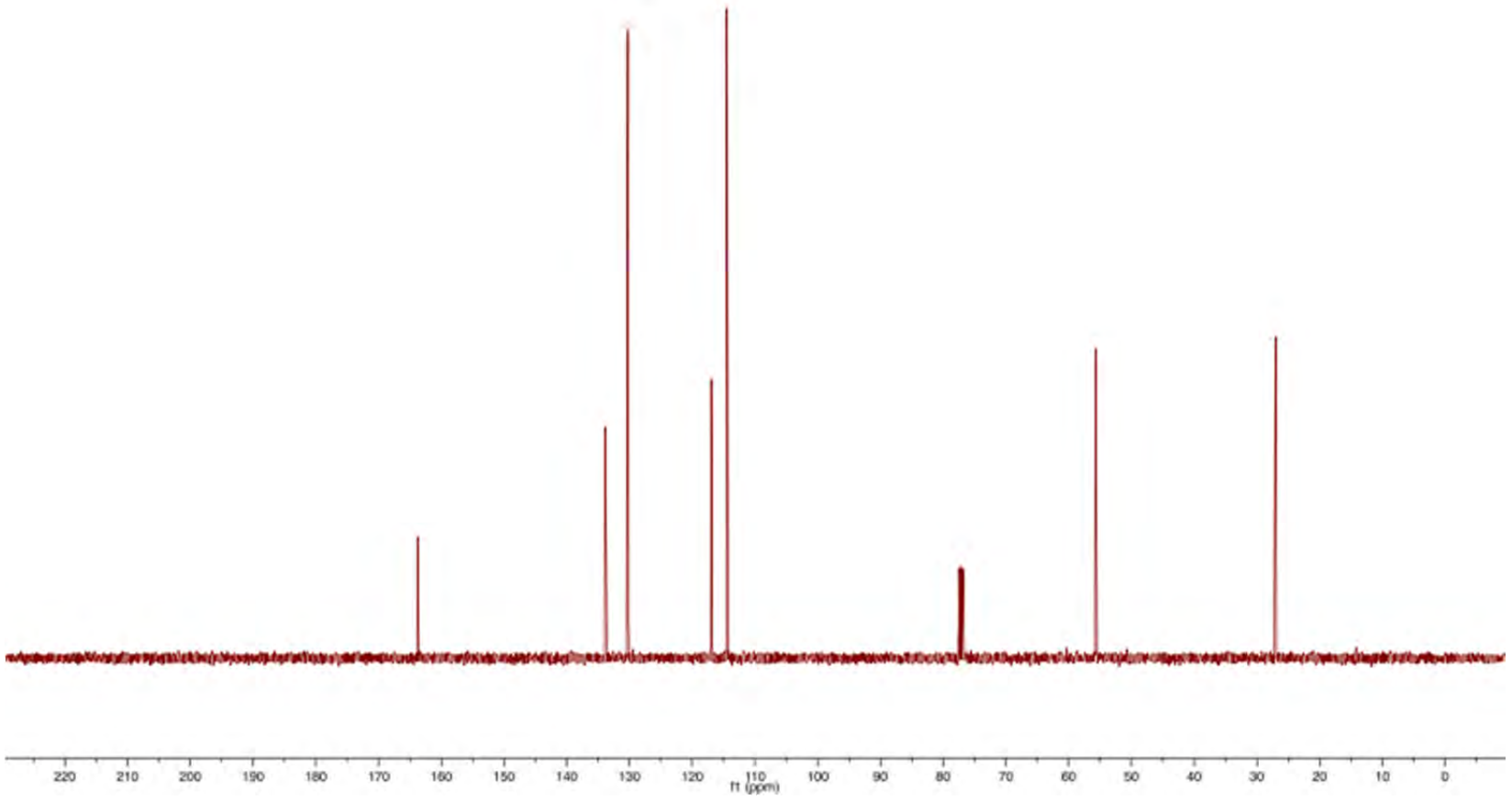
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10
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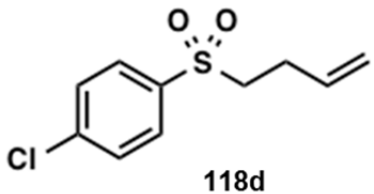
f1 (ppm)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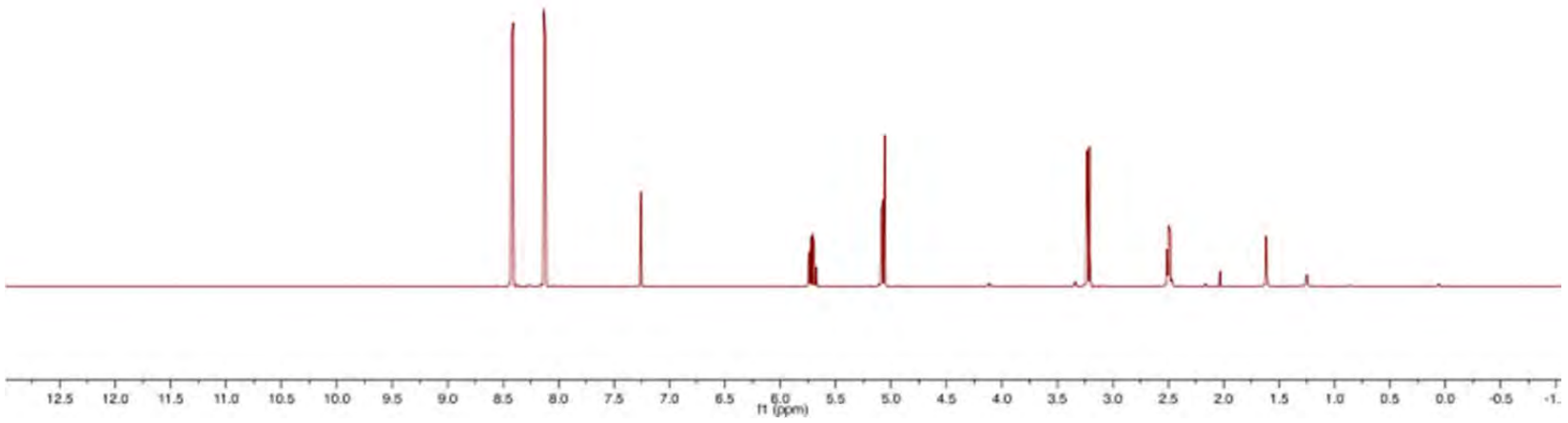
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7.5
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6.0
f1 (ppm)
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4.5
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3.0
2.5
2.0
1.5
1.0
0.5
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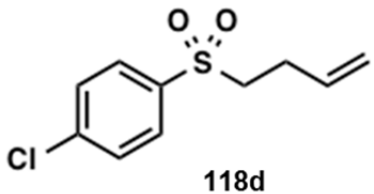
-0.5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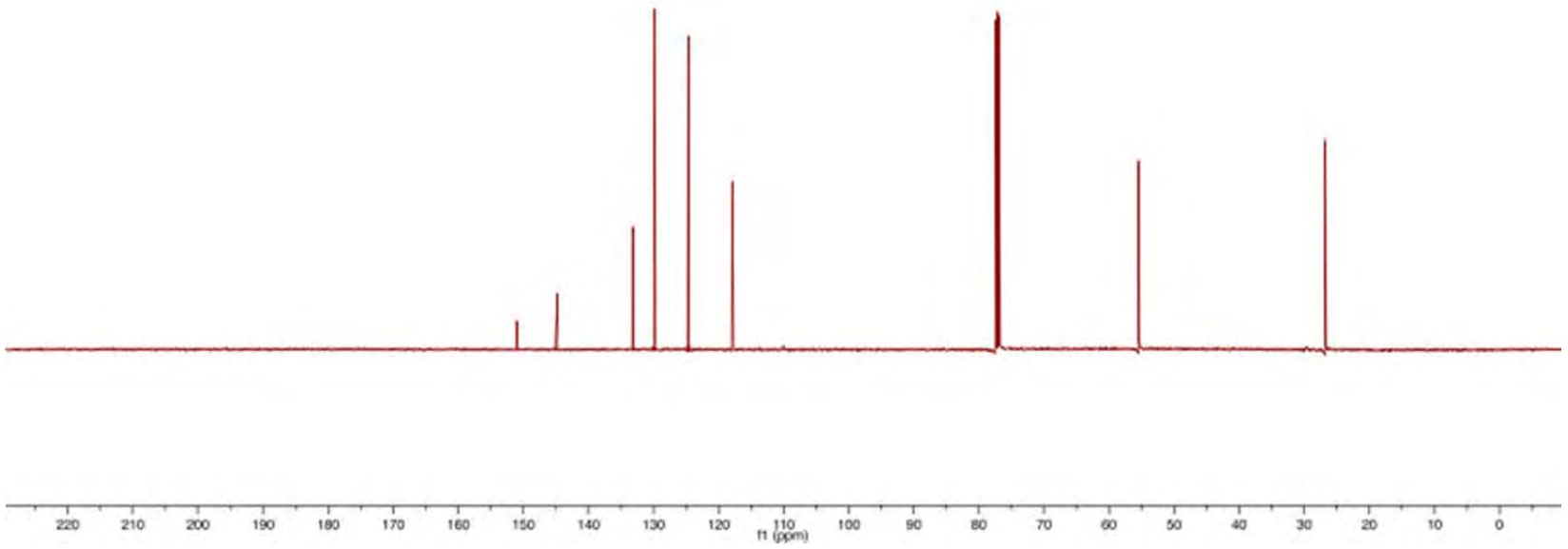
Cl

118d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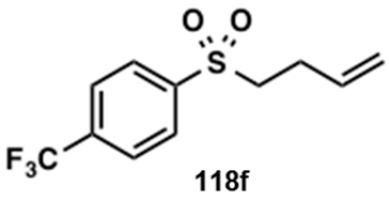
f1 (ppm)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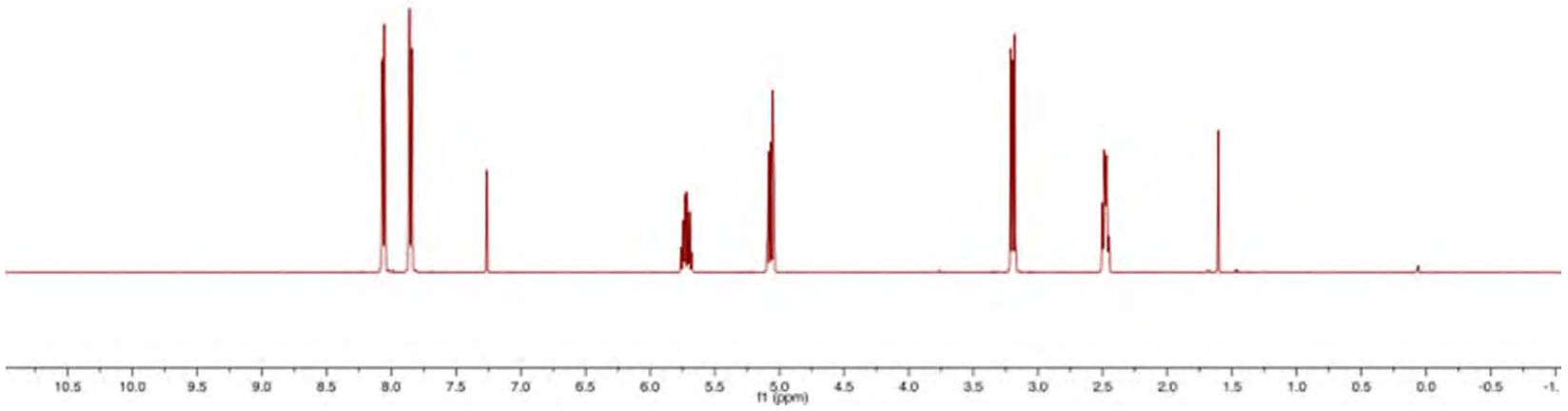
S
F3C

118f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5.0
4.5
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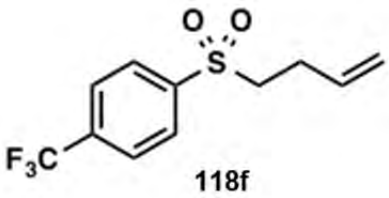
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.
f1 (ppm)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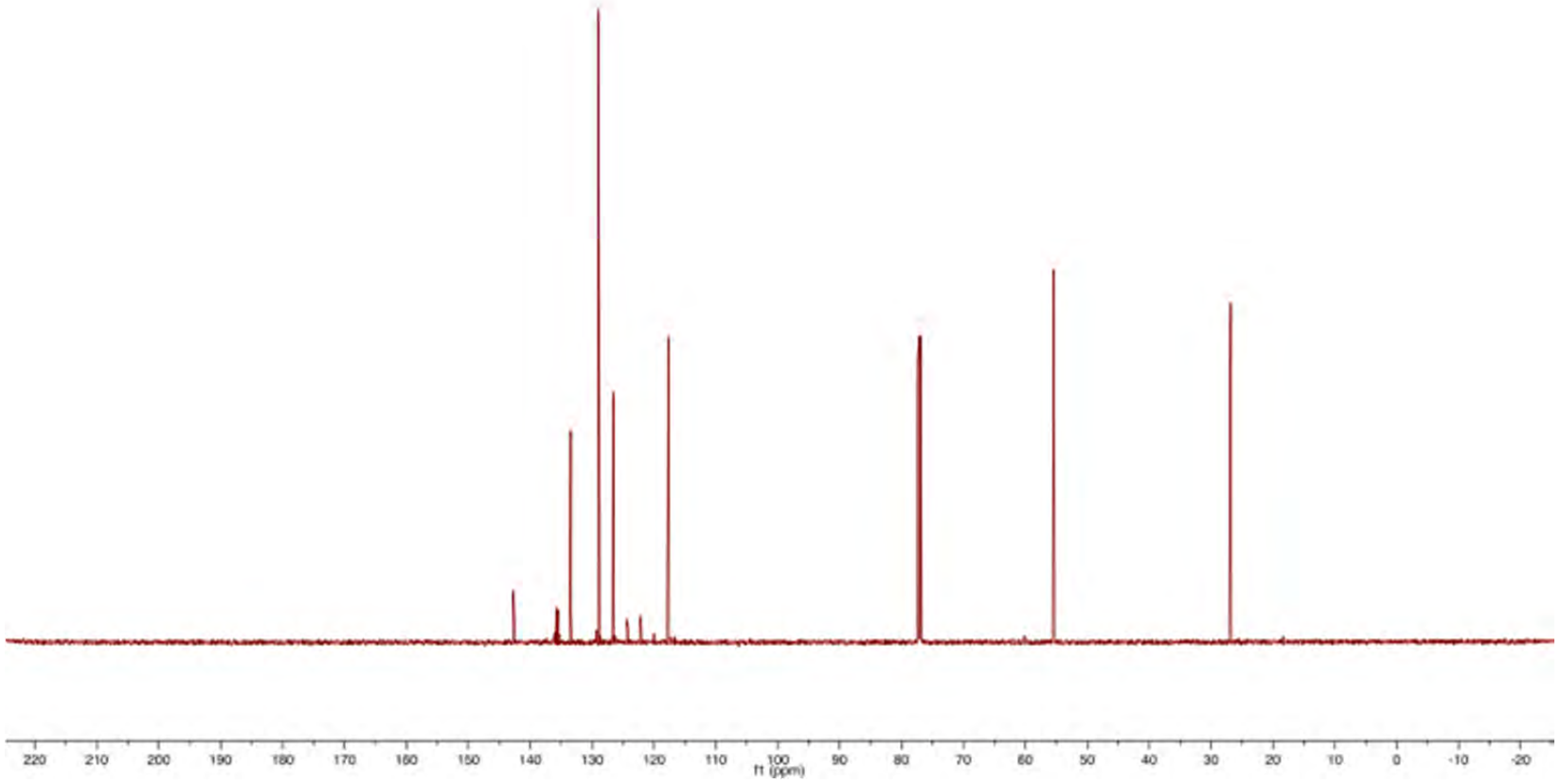
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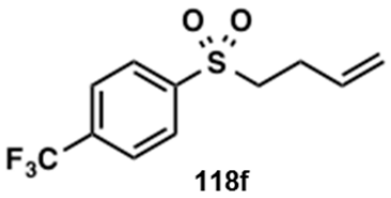
-20
f1 (ppm)


O
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S
F3C

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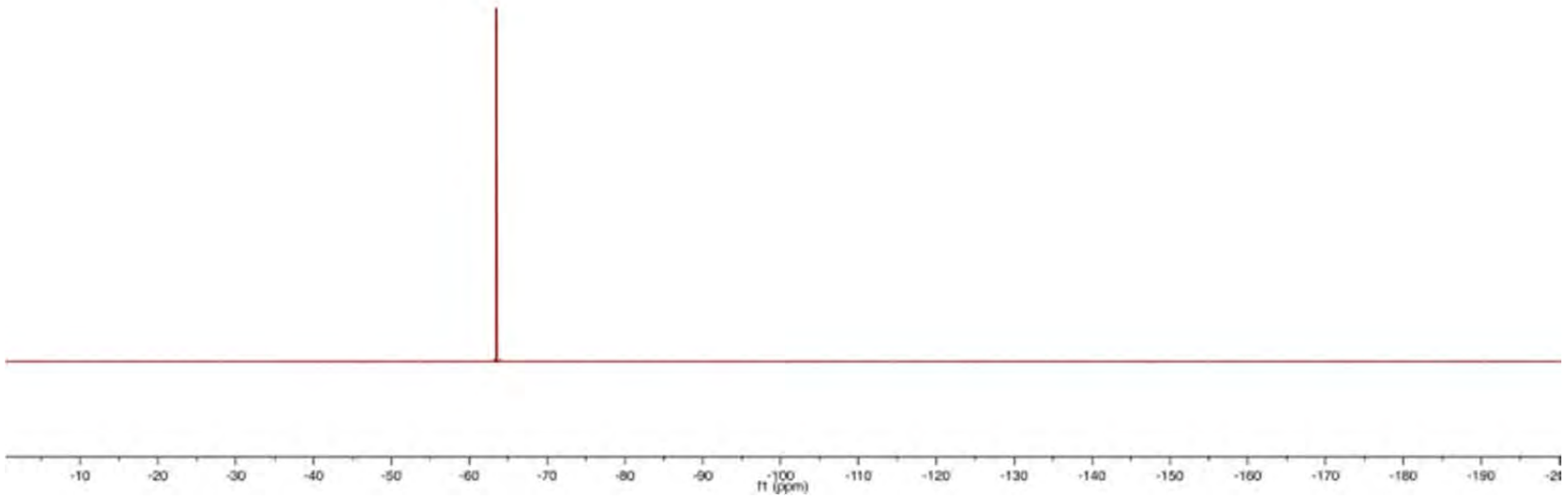
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f1 (ppm)
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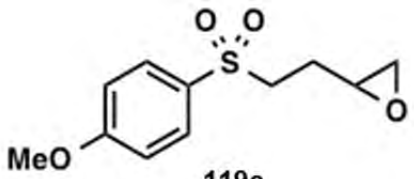
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S
O
MeO

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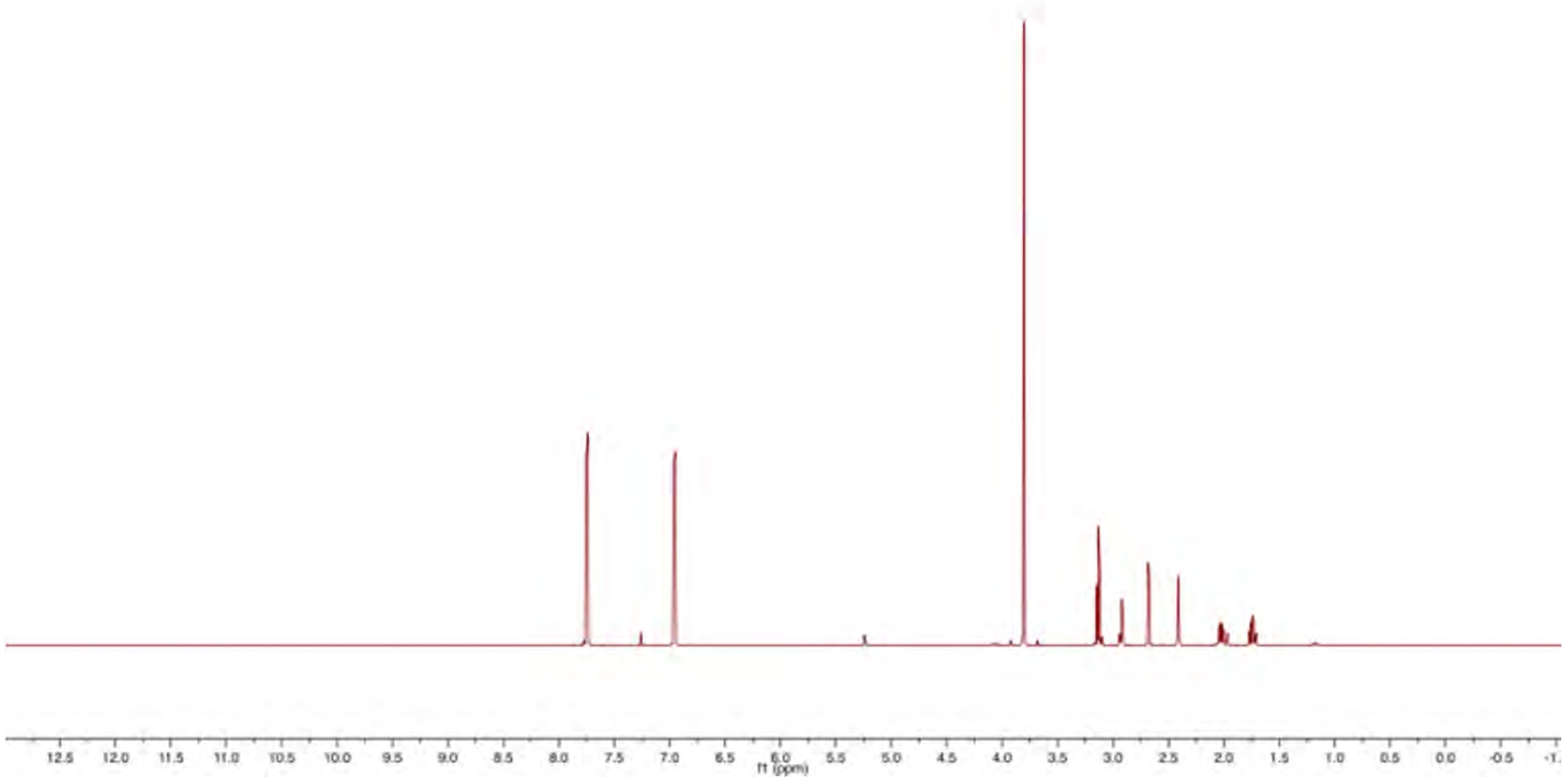
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7.5
7.0
6.5
6.0
f1 (ppm)
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3.5
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2.5
2.0
1.5
1.0
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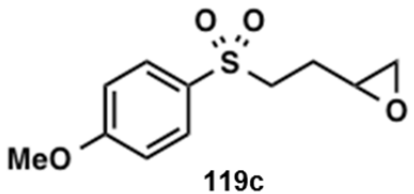
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MeO

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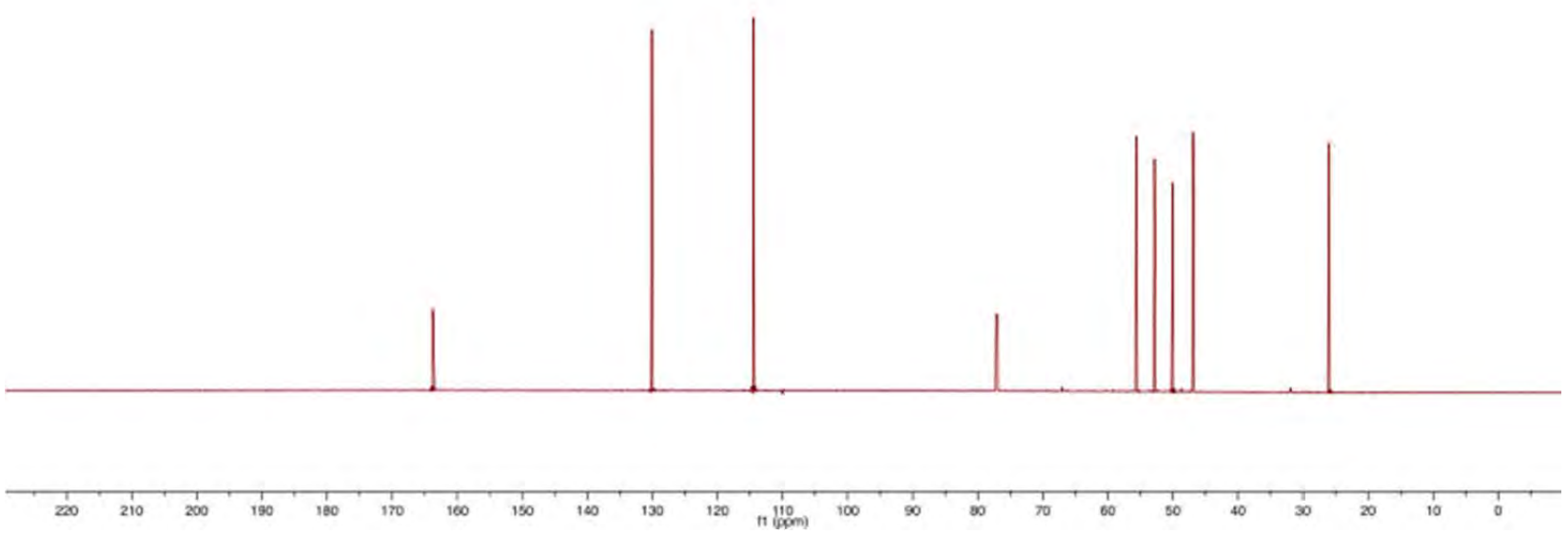
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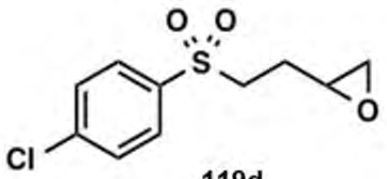
f1 (ppm)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S
O
Cl

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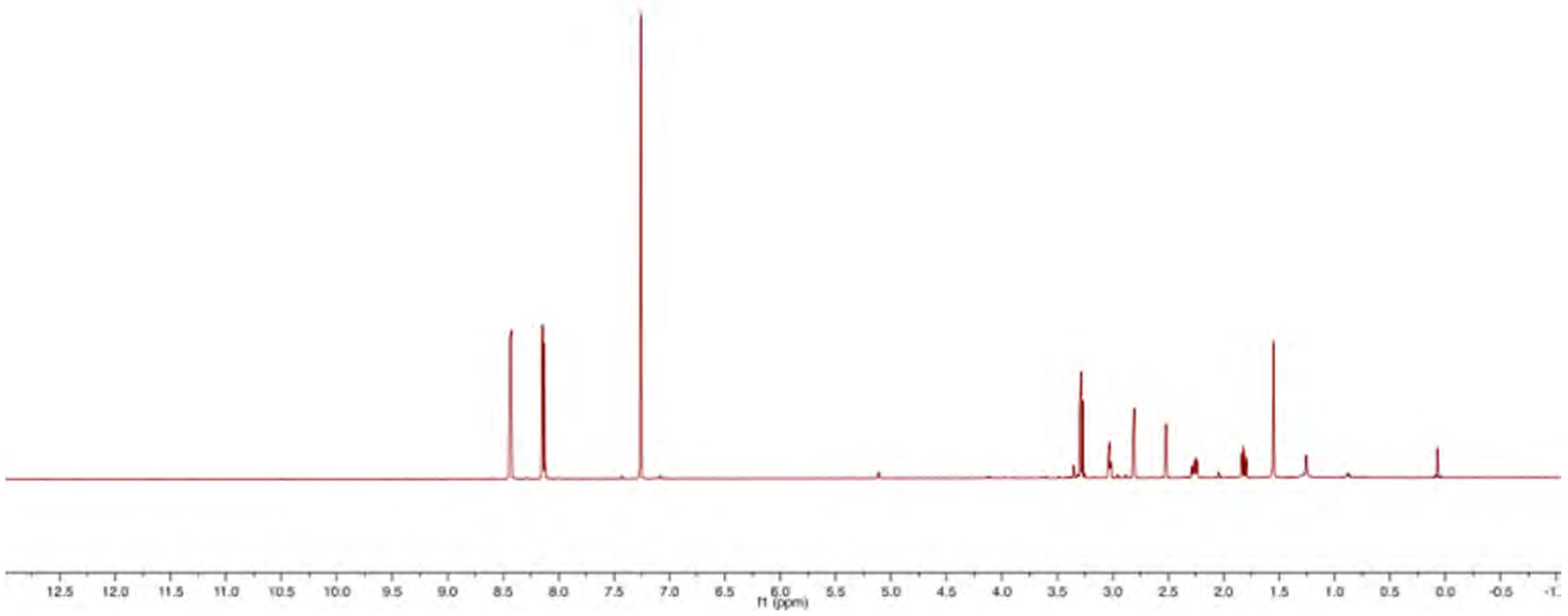
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6.0
f1 (ppm)
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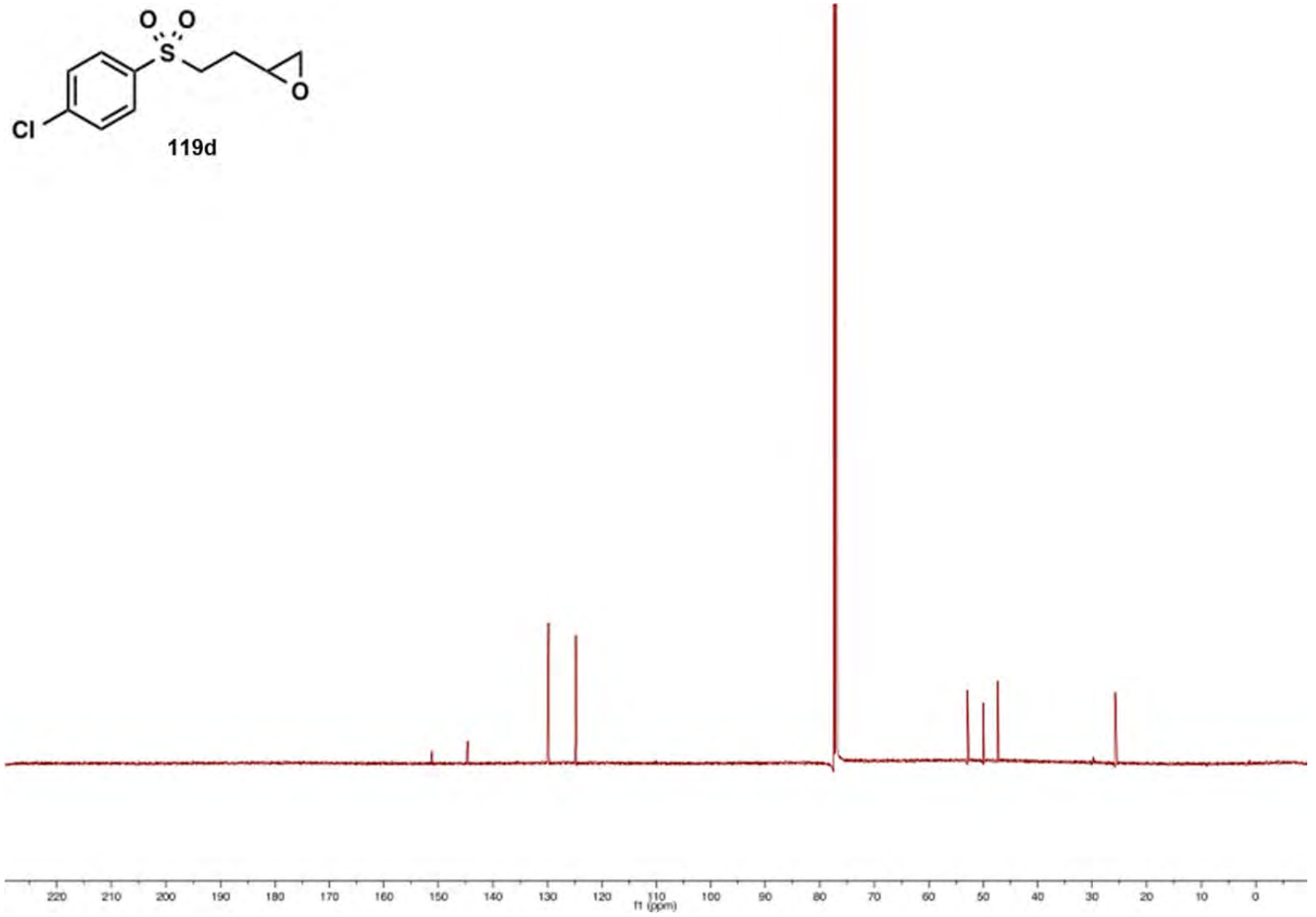
O
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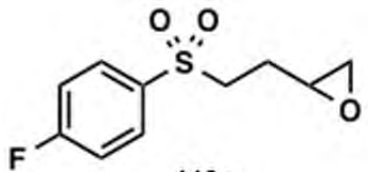
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F

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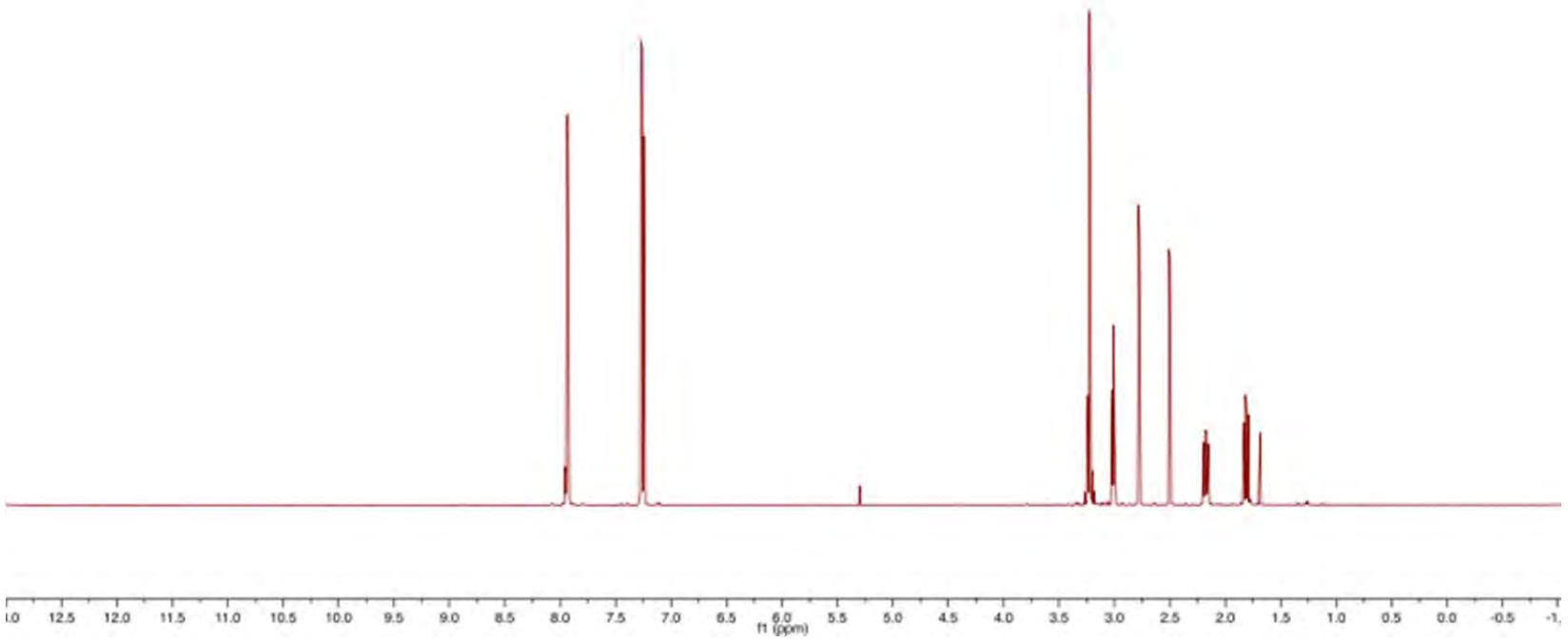
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f1 (ppm)
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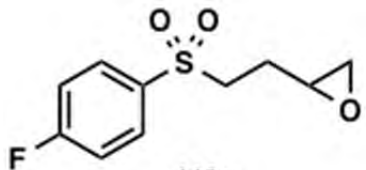
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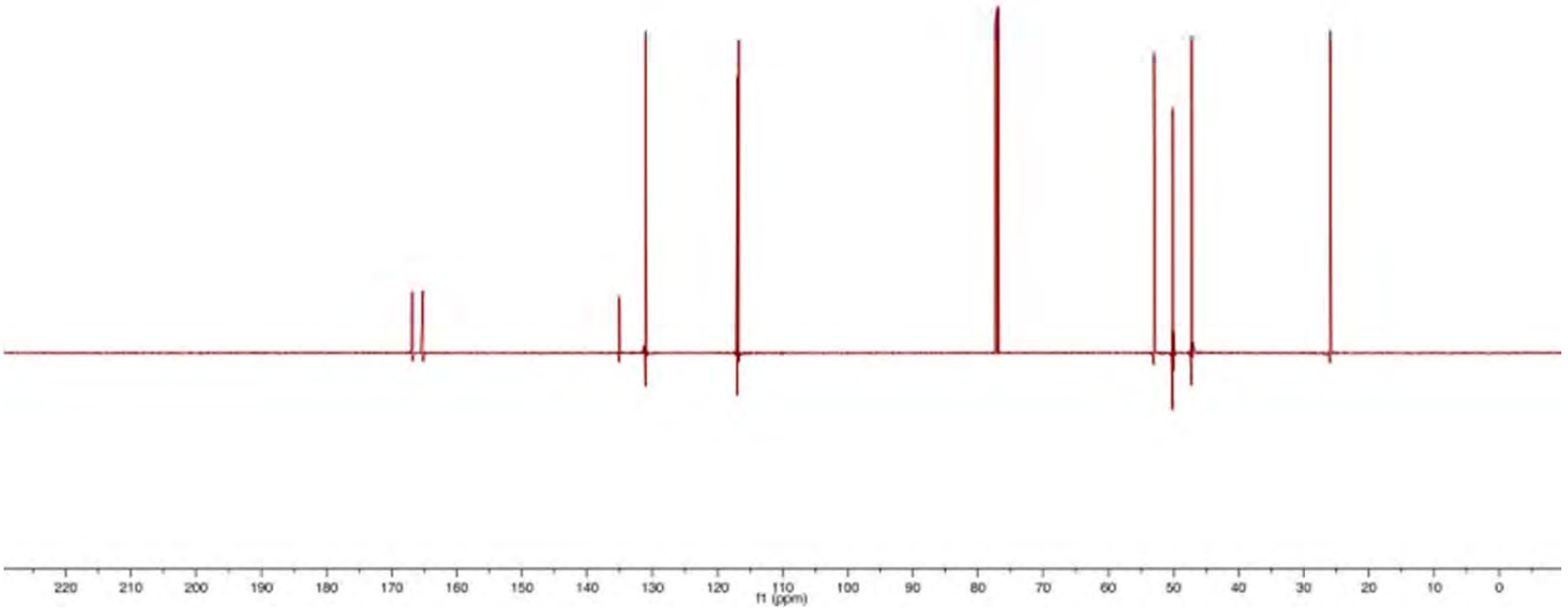
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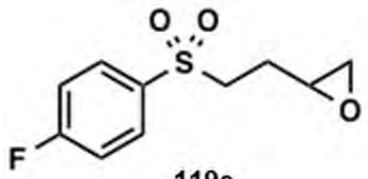
f1 (ppm)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F

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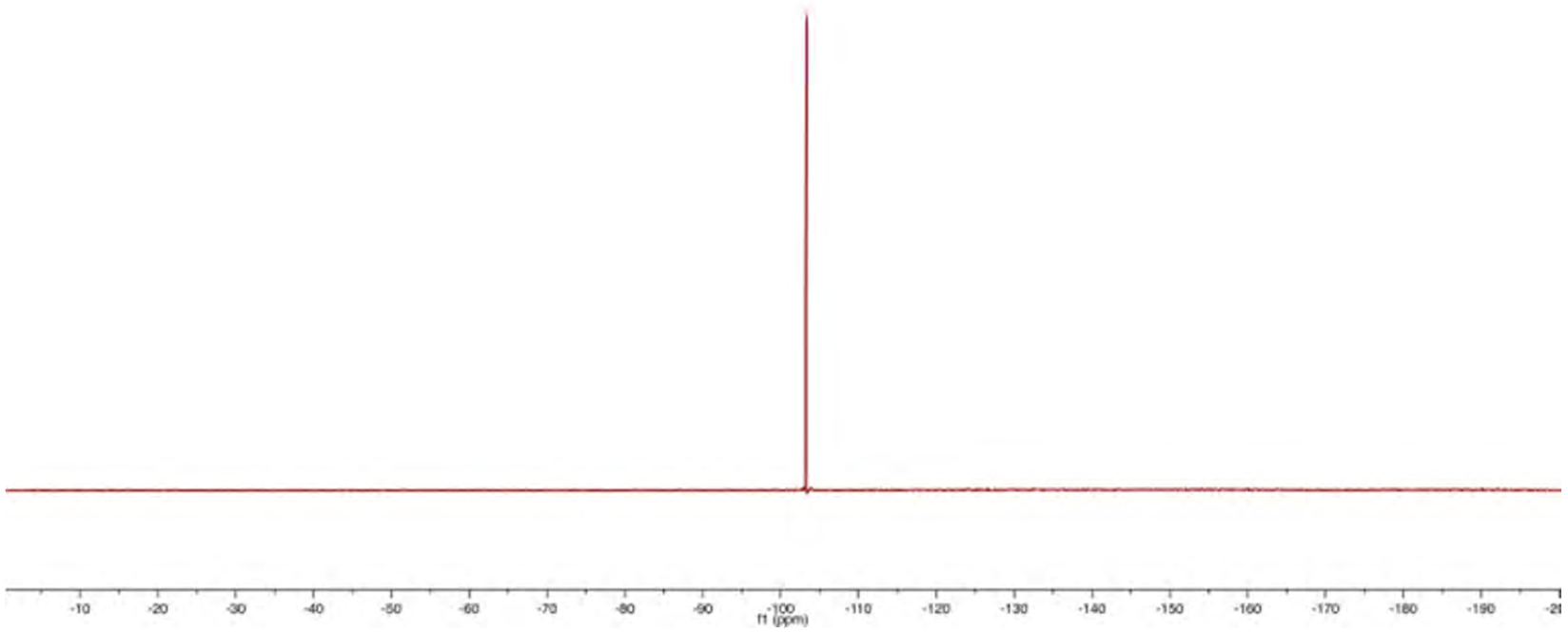
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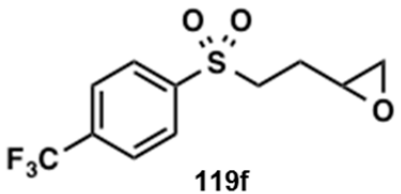
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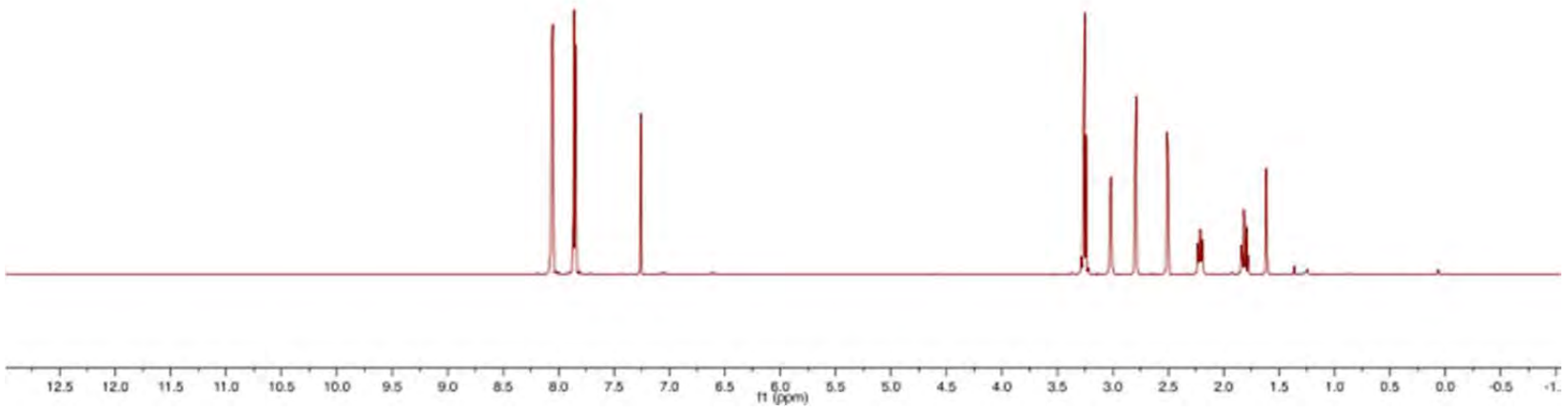
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f1 (ppm)
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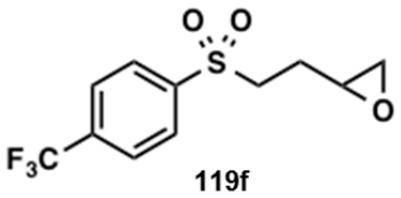
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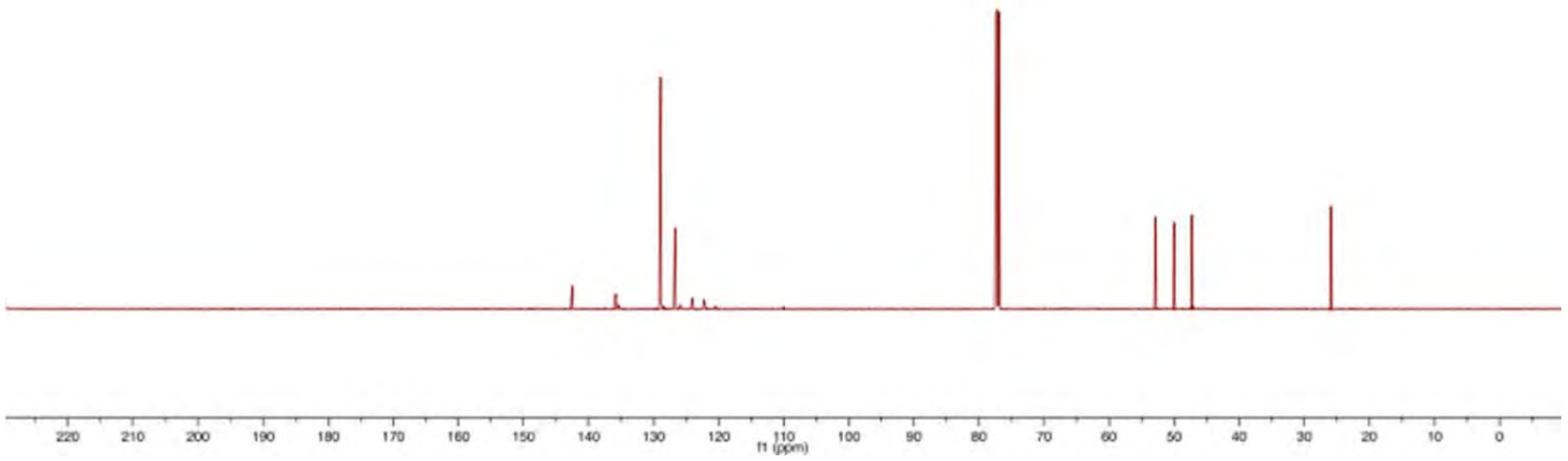
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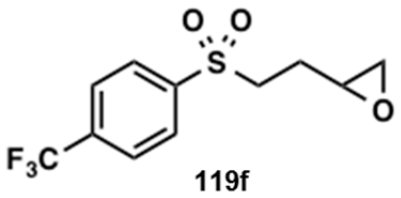
0
f1 (ppm)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S
O
F3C

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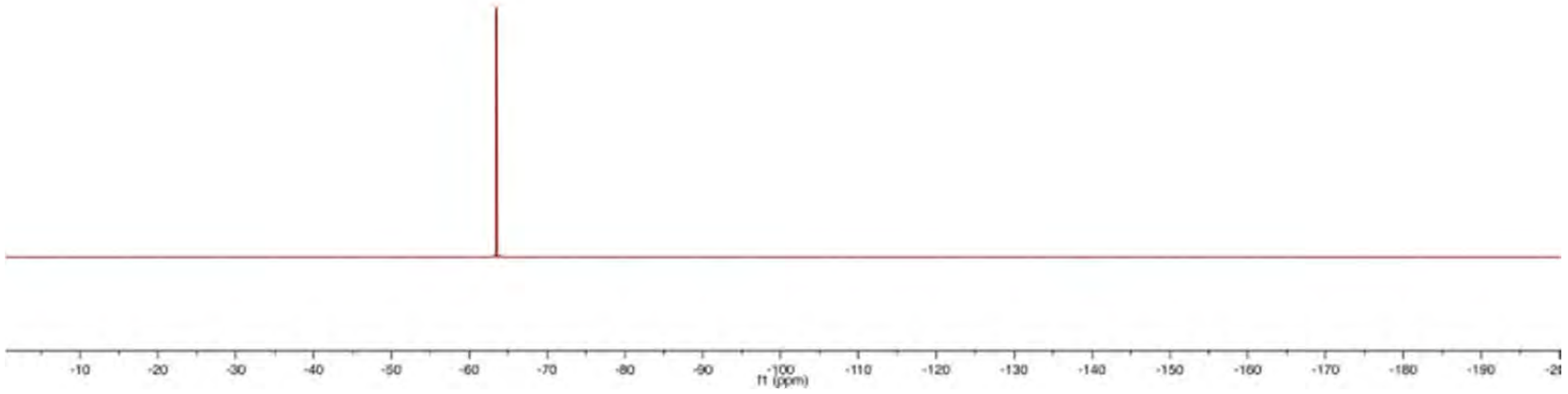
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-70
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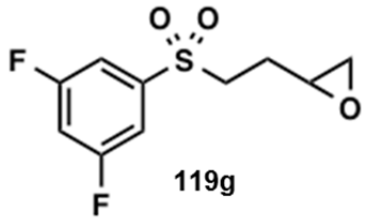
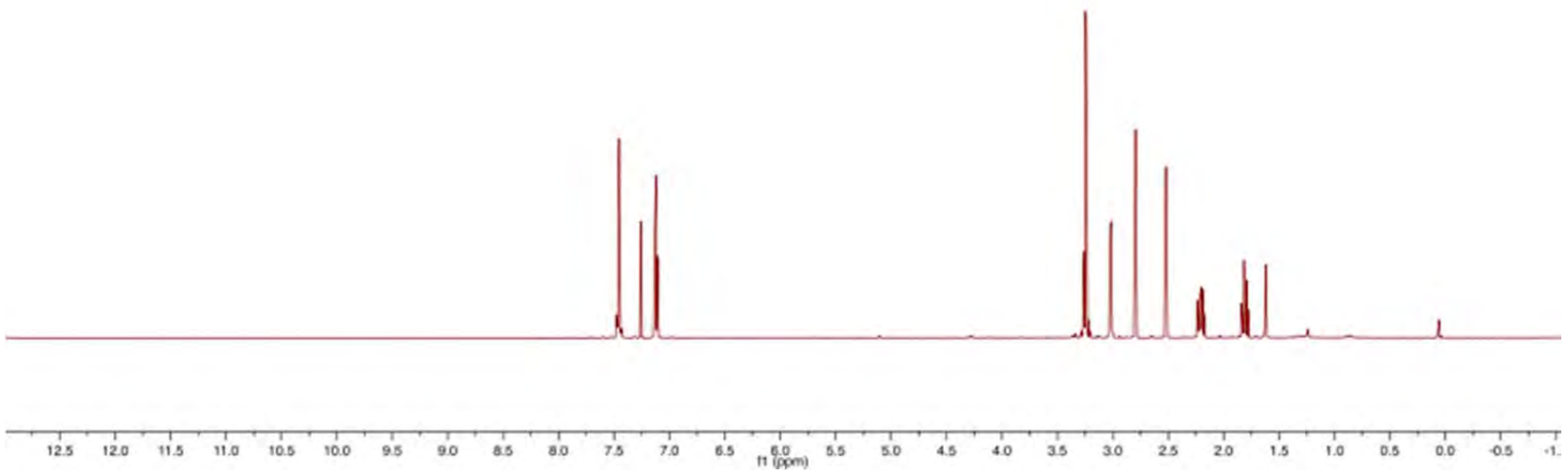
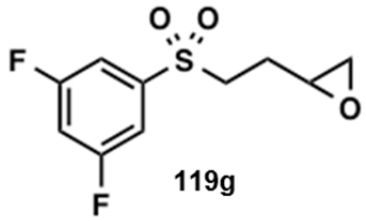
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190

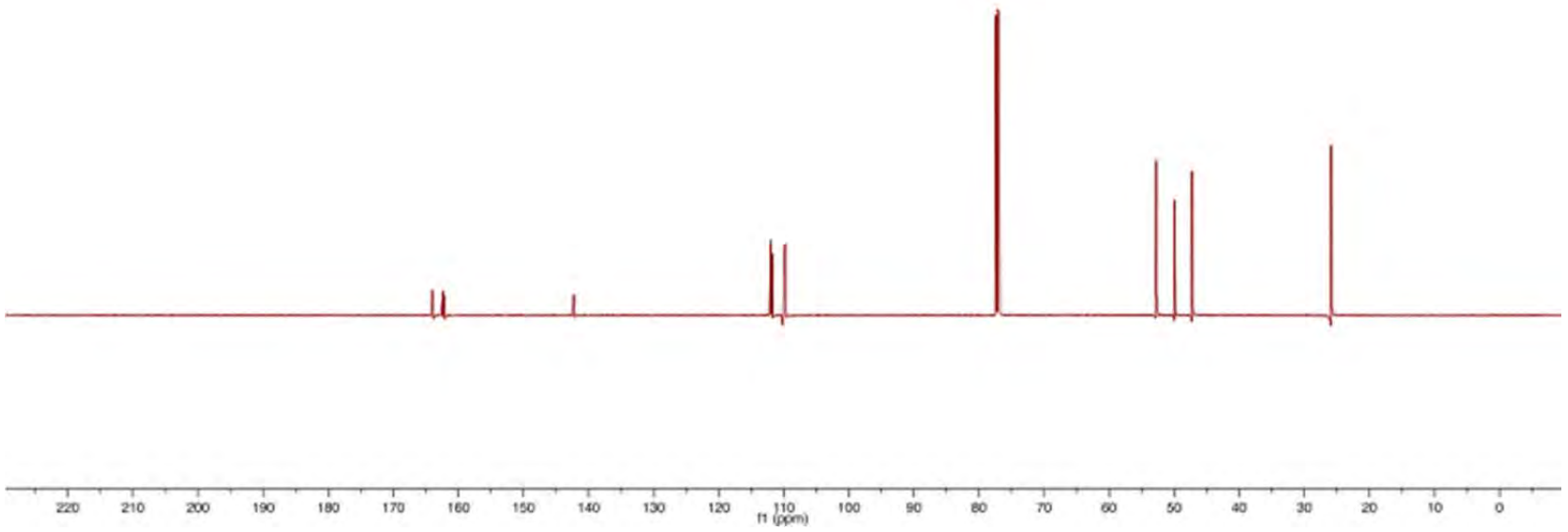

O
O
S
F
O
F

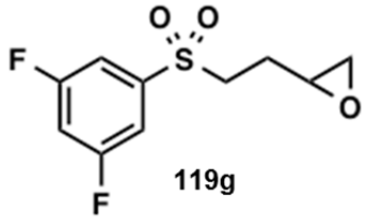
119g


12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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

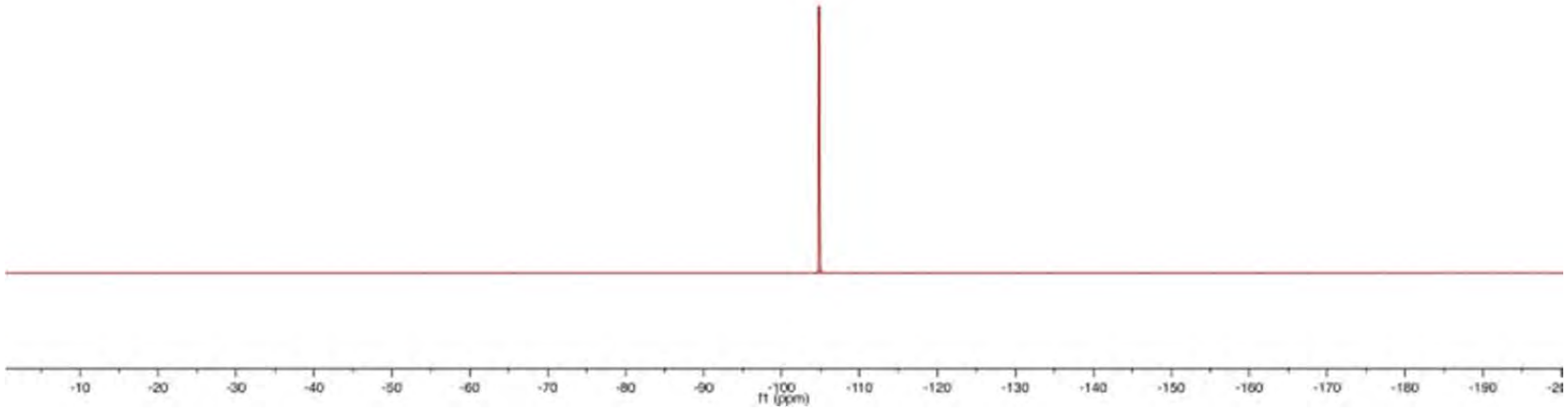

O
O
S
F
O
F

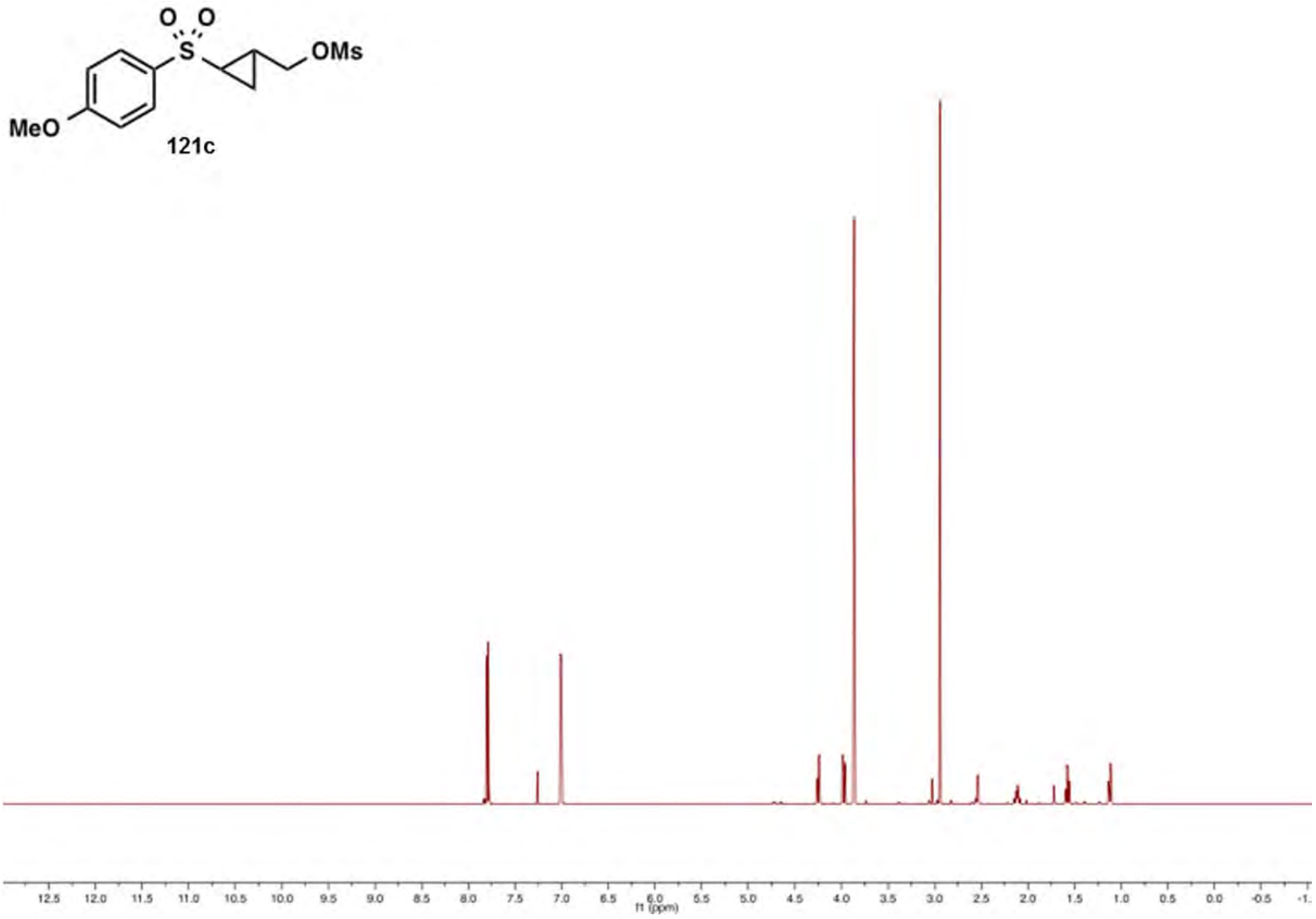
119g

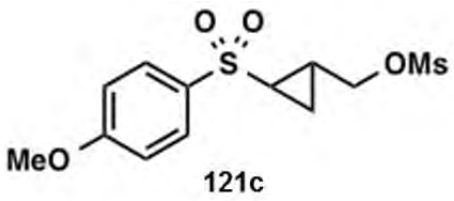

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
F
F
O

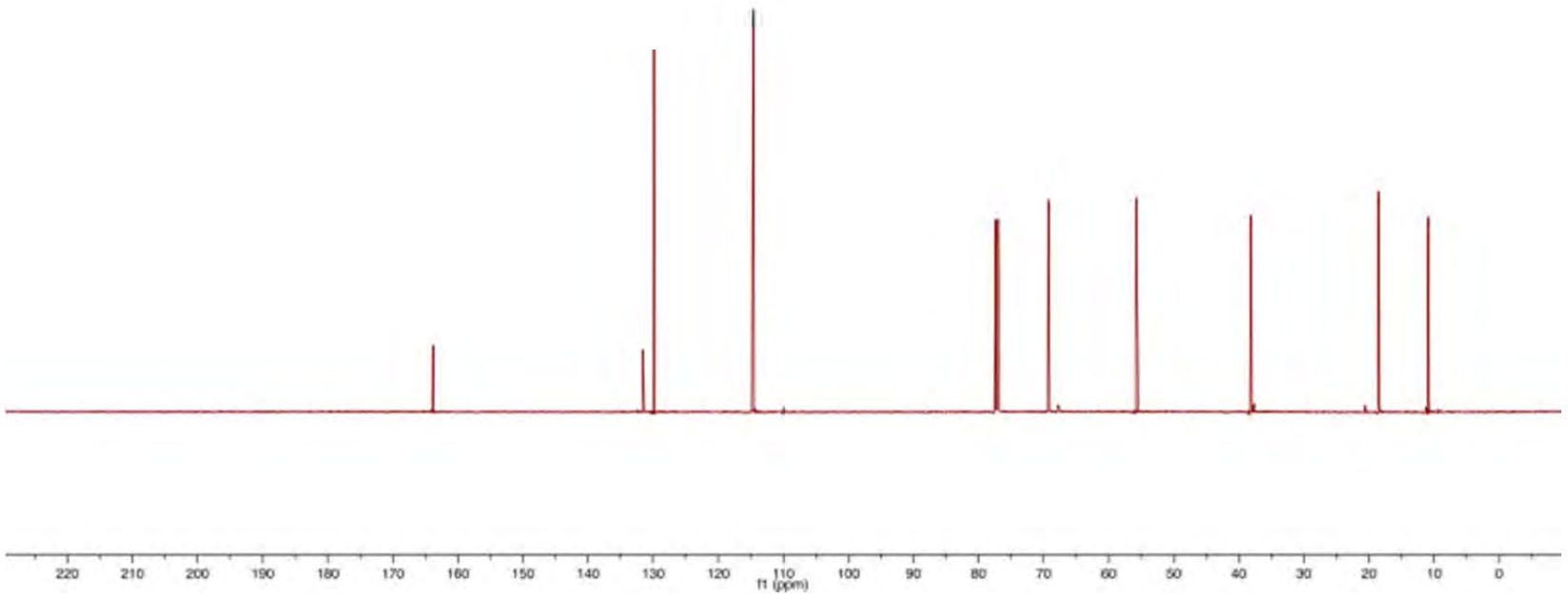
119g

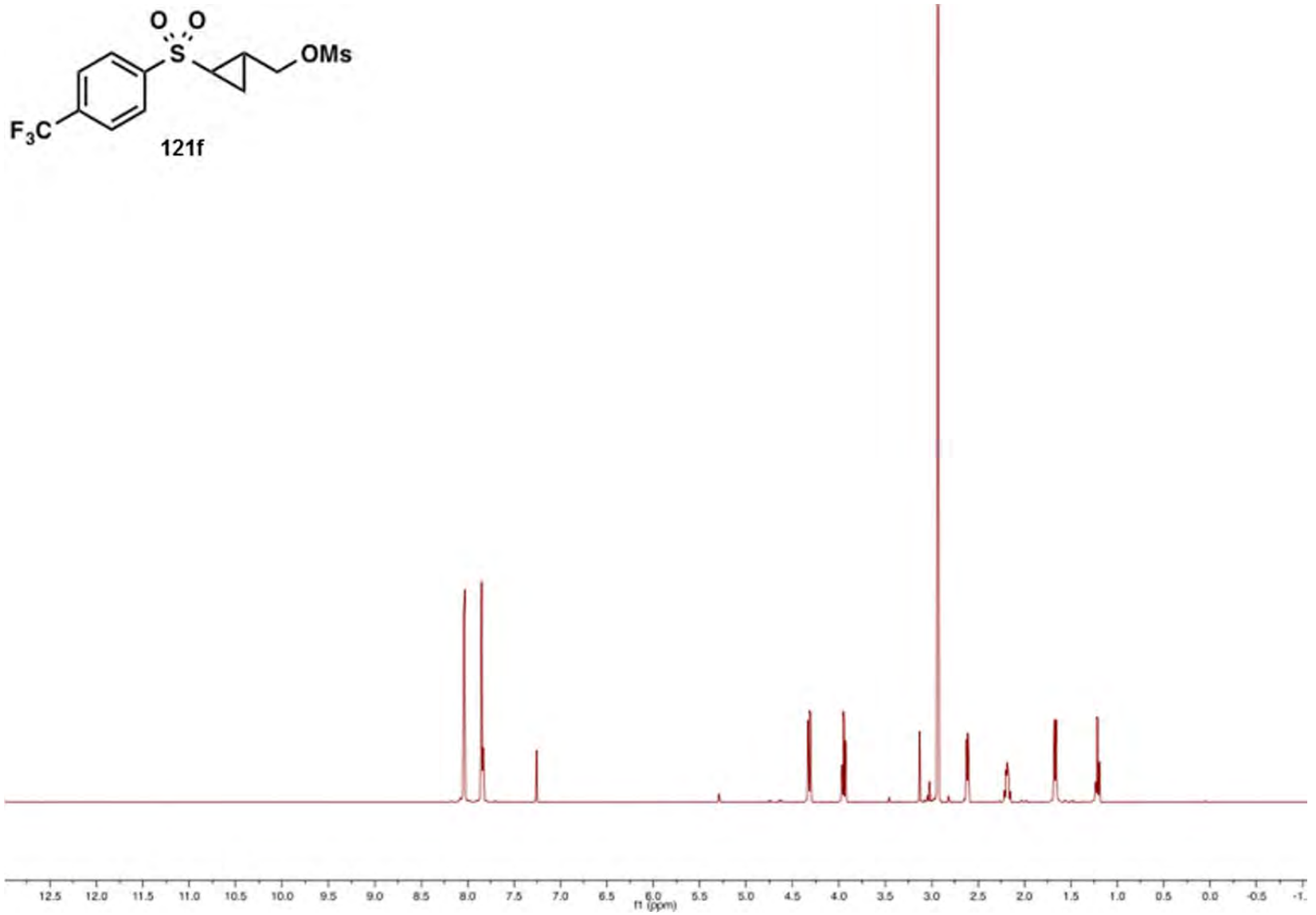

-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190

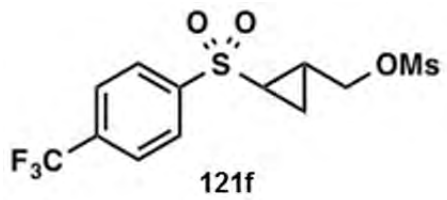

O
O
S
OMs
MeO
121c
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


O
O
S
OMs
MeO

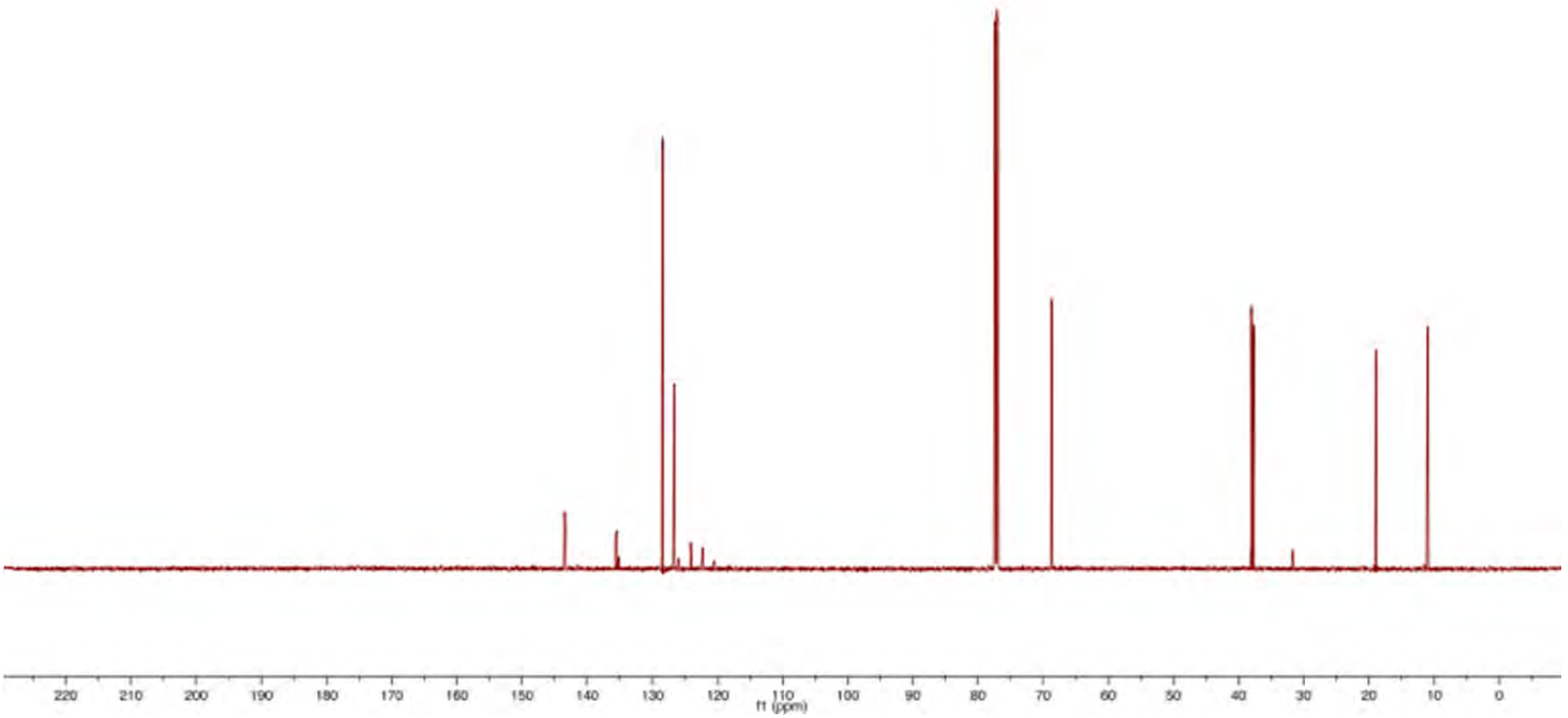
121c

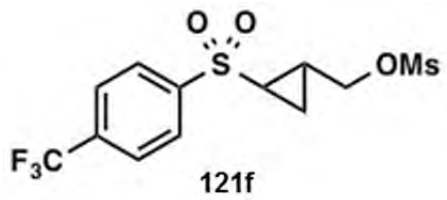

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
OMs
F3C
121f
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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

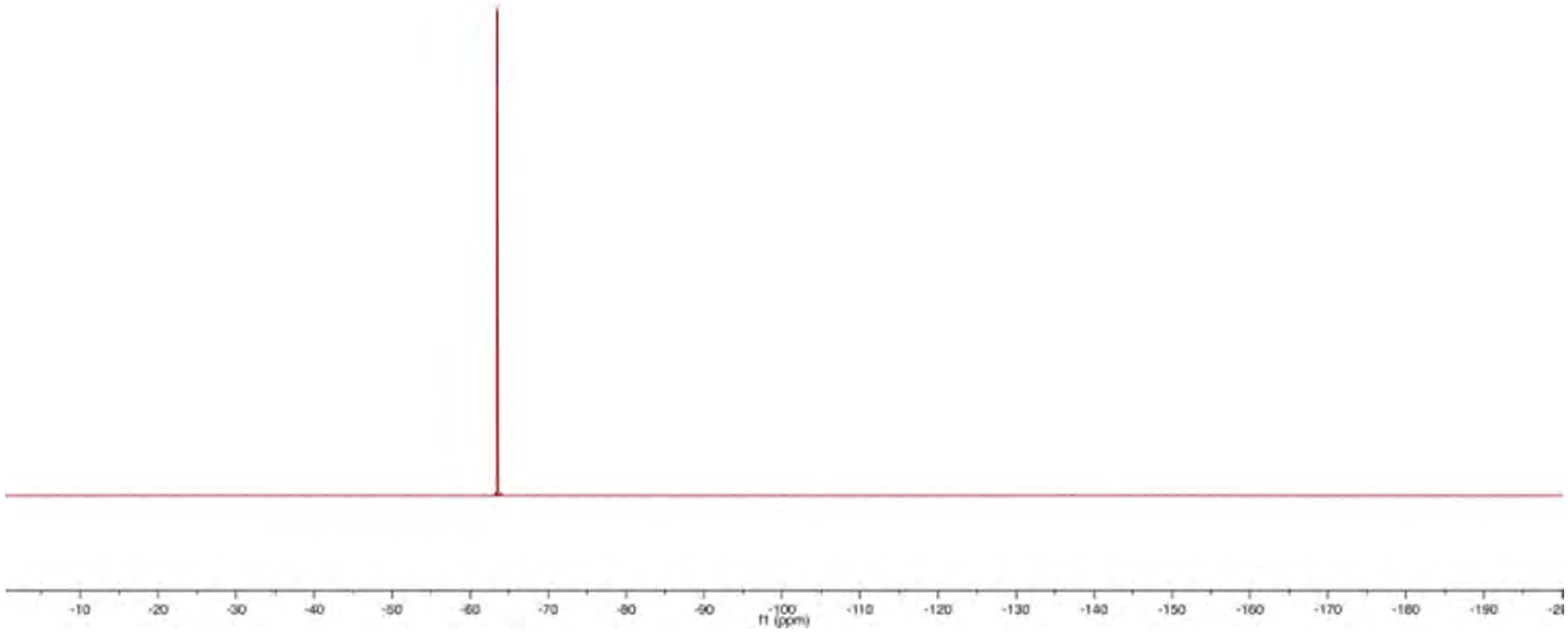

O
O
S
OMs
F3C

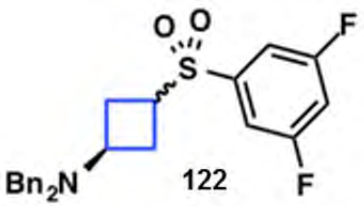
121f


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)

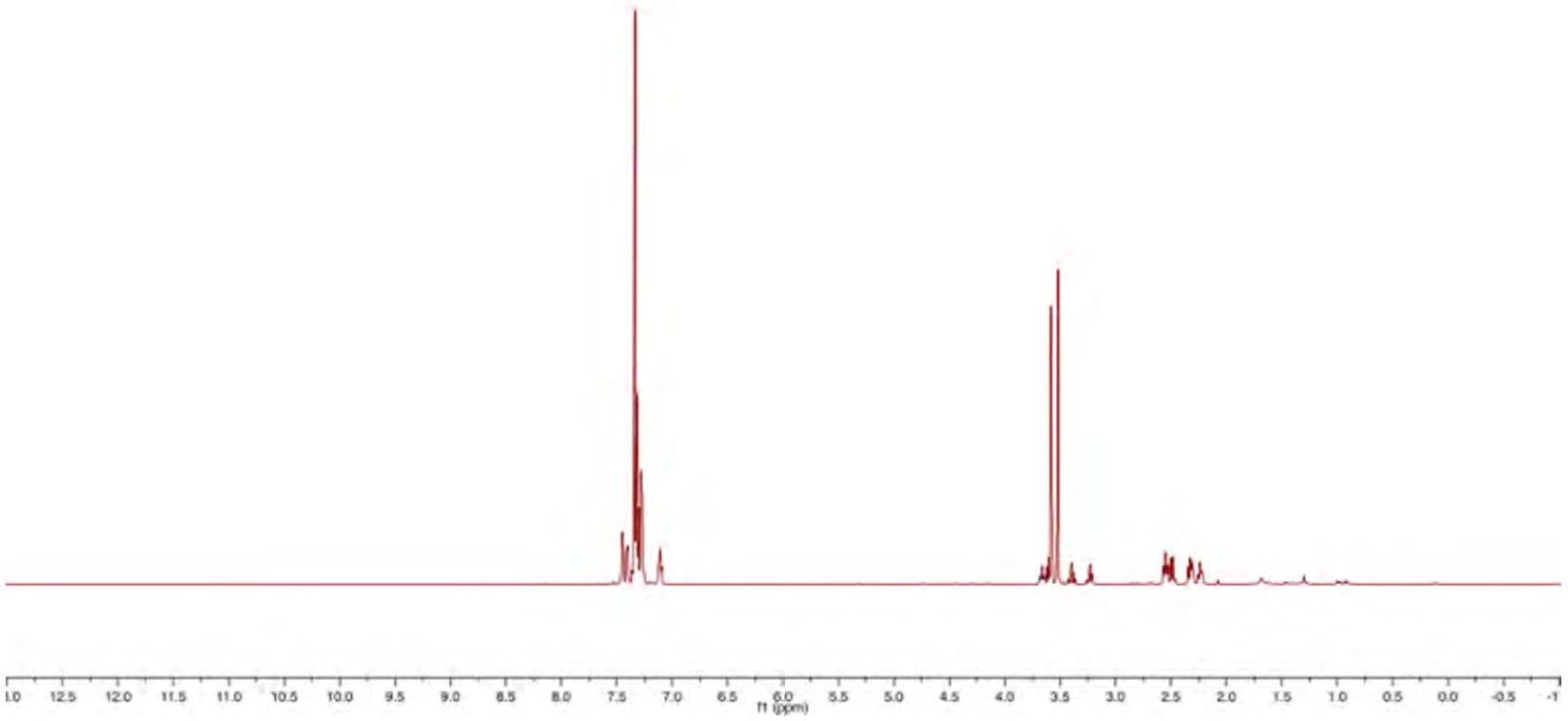

O
O
S
OMs
F3C

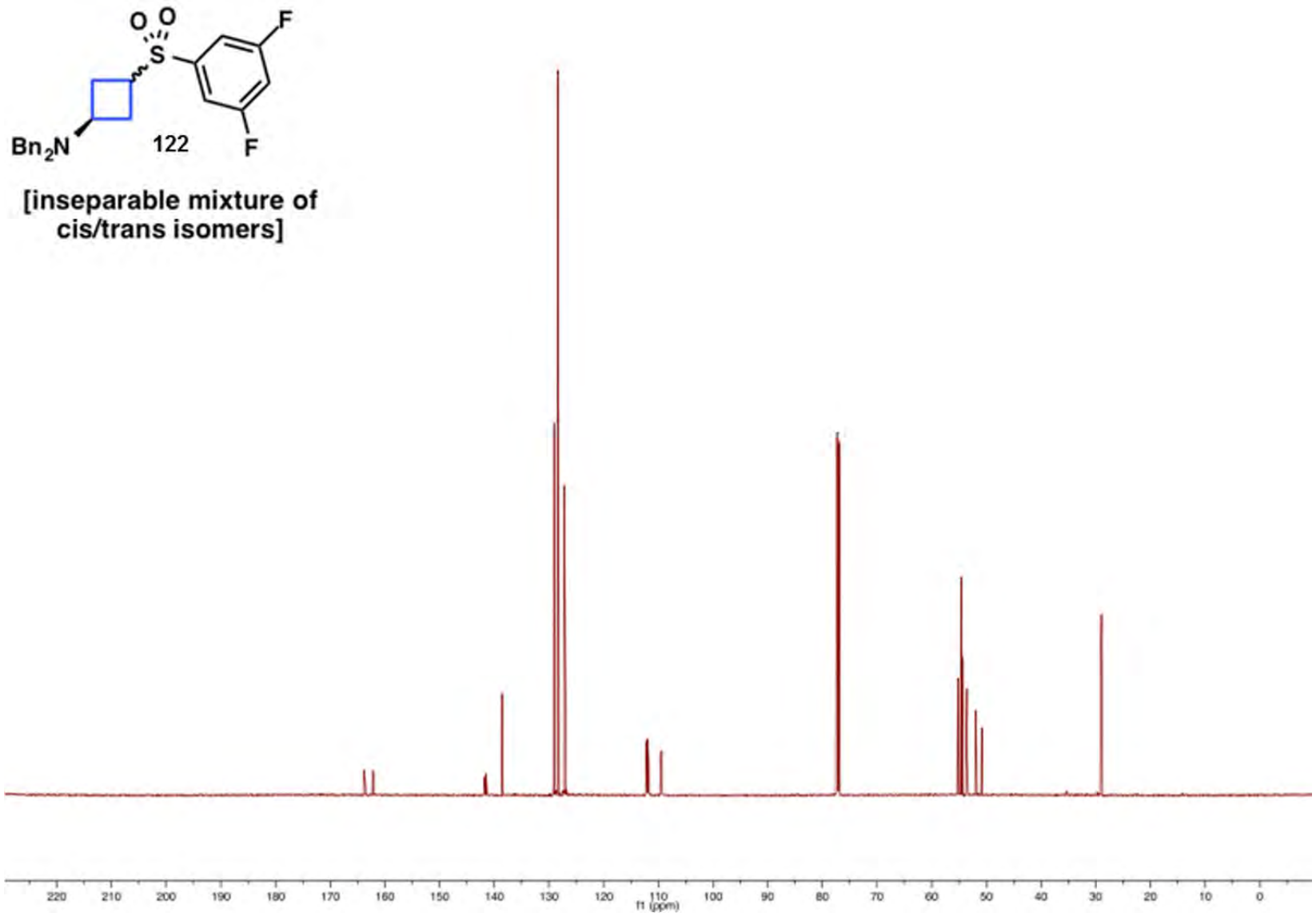
121f

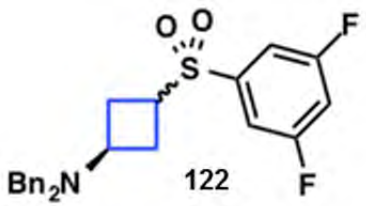

-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190



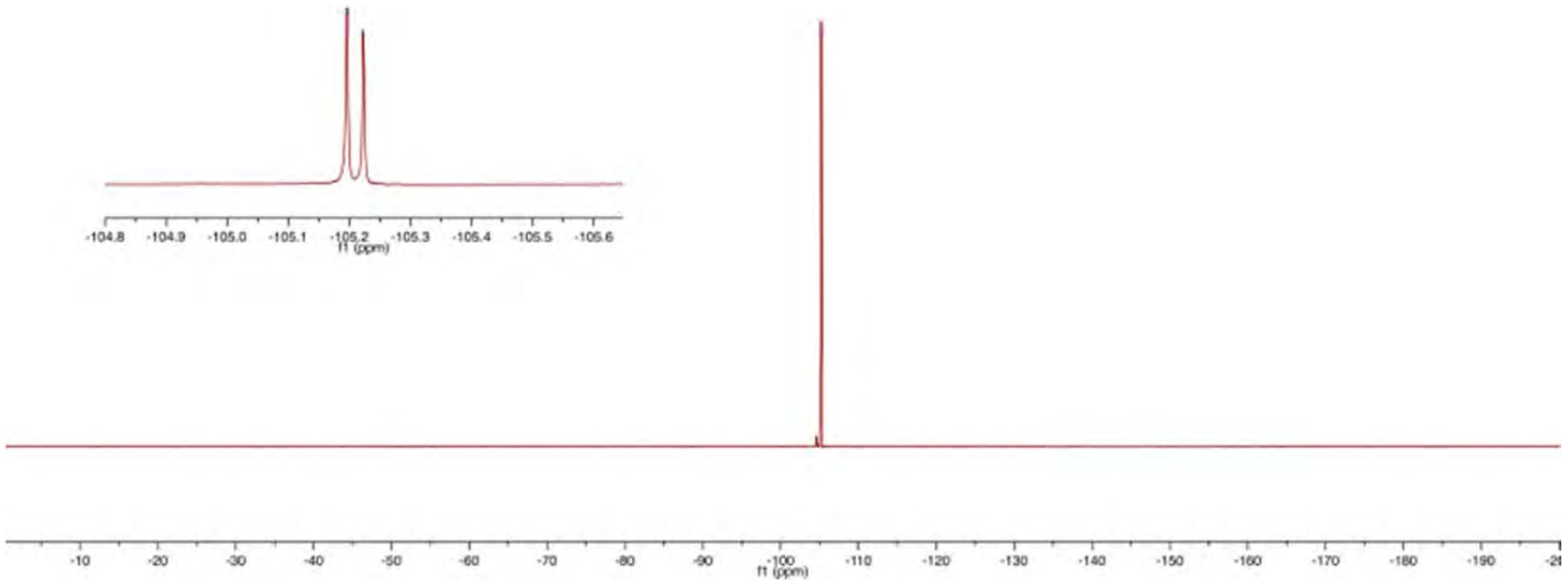
[inseparable mixture of cis/trans isomers]

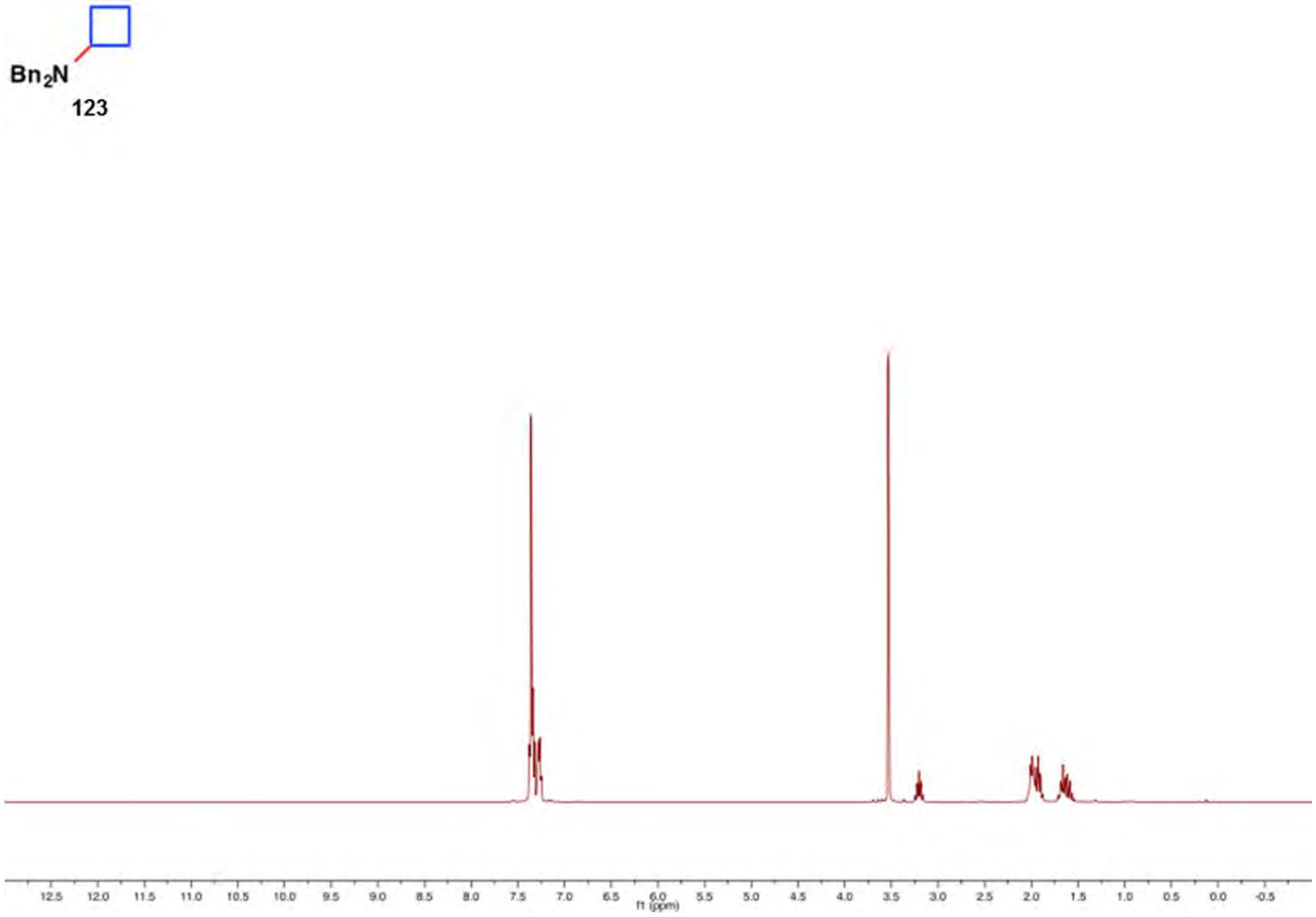


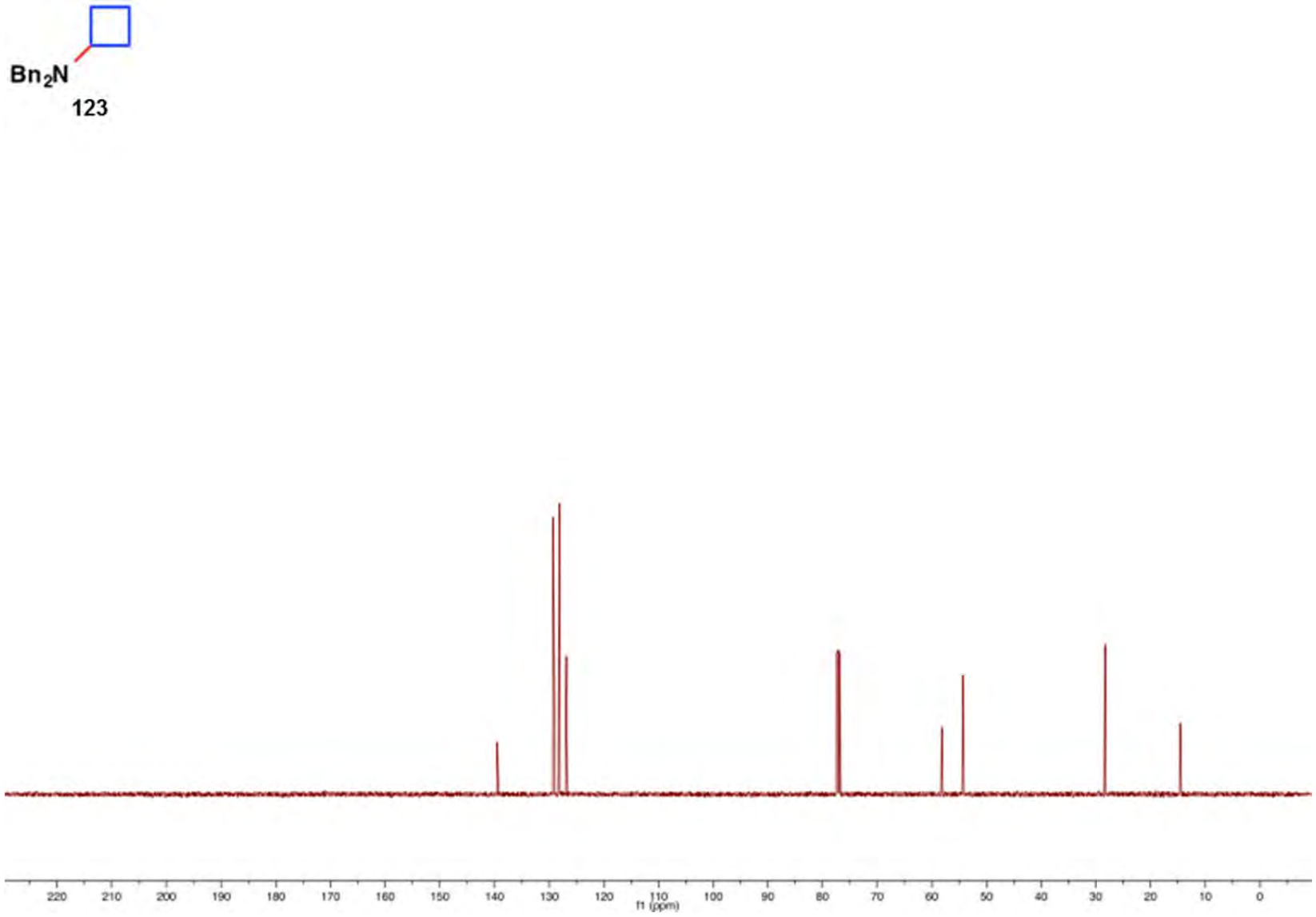

O
O
S
F
F
Bn2N
122
[inseparable mixture of cis/trans isomers]
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

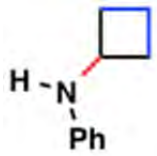


[inseparable mixture of cis/trans isomers]

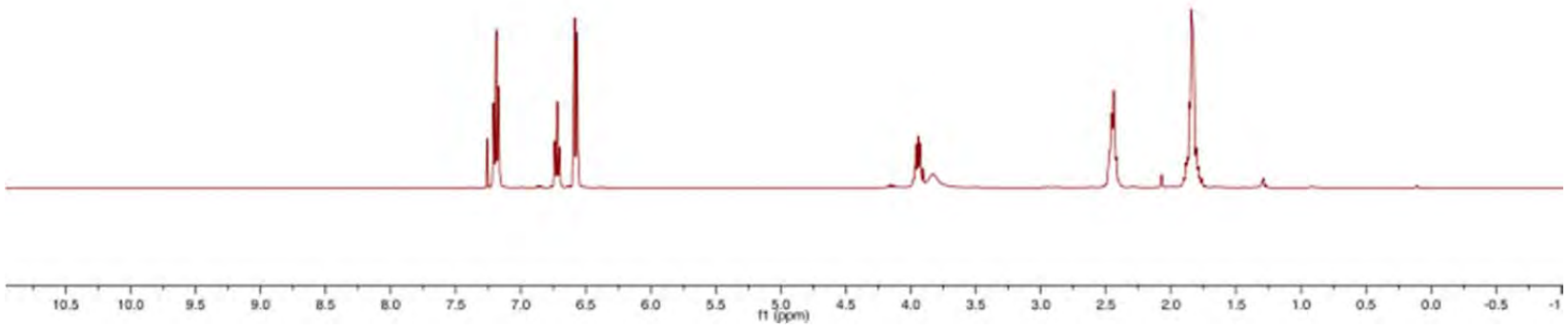


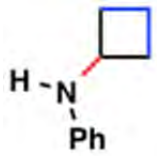

Bn2N
123
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Bn2N
123
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)

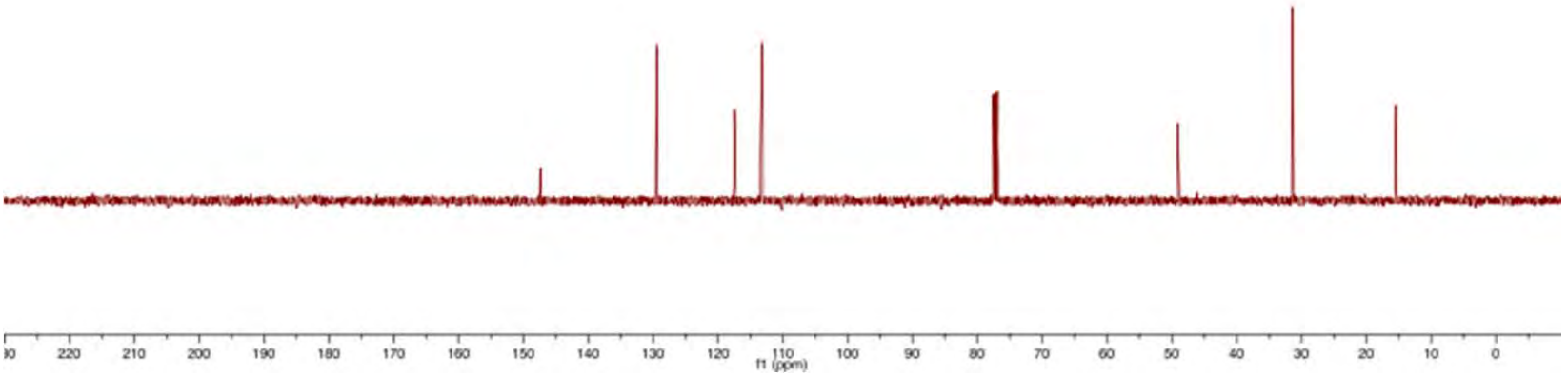

H
N
Ph

124


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

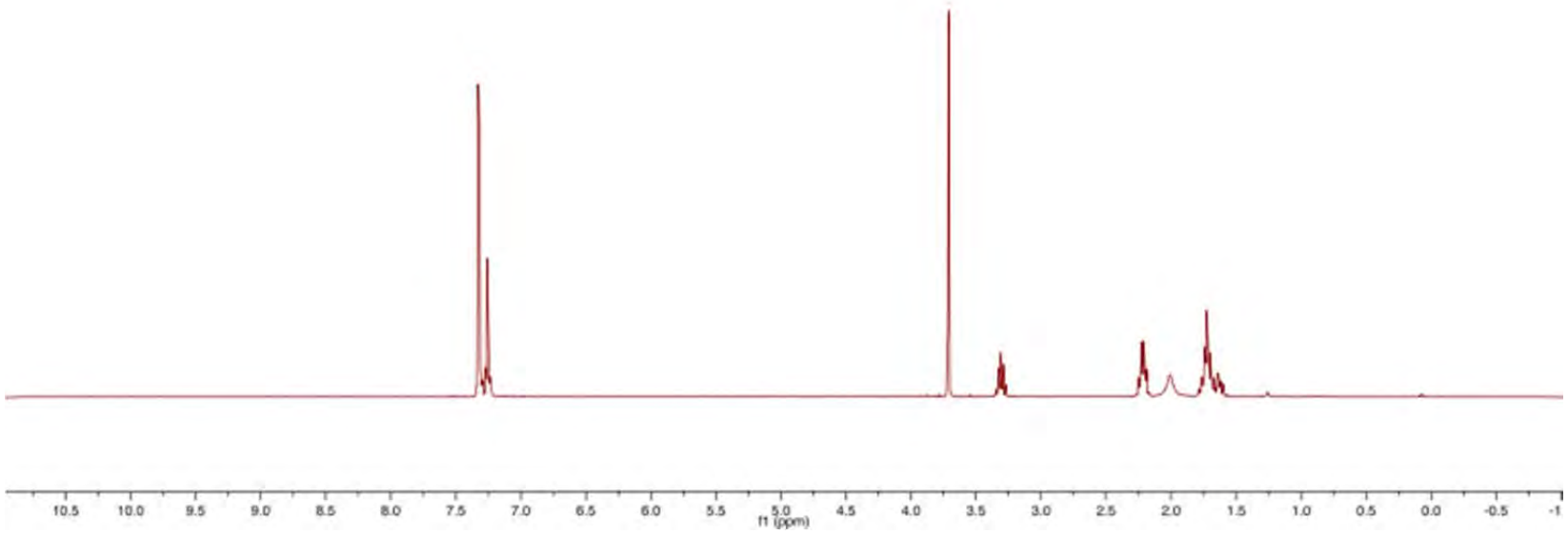

H
N
Ph

124


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)

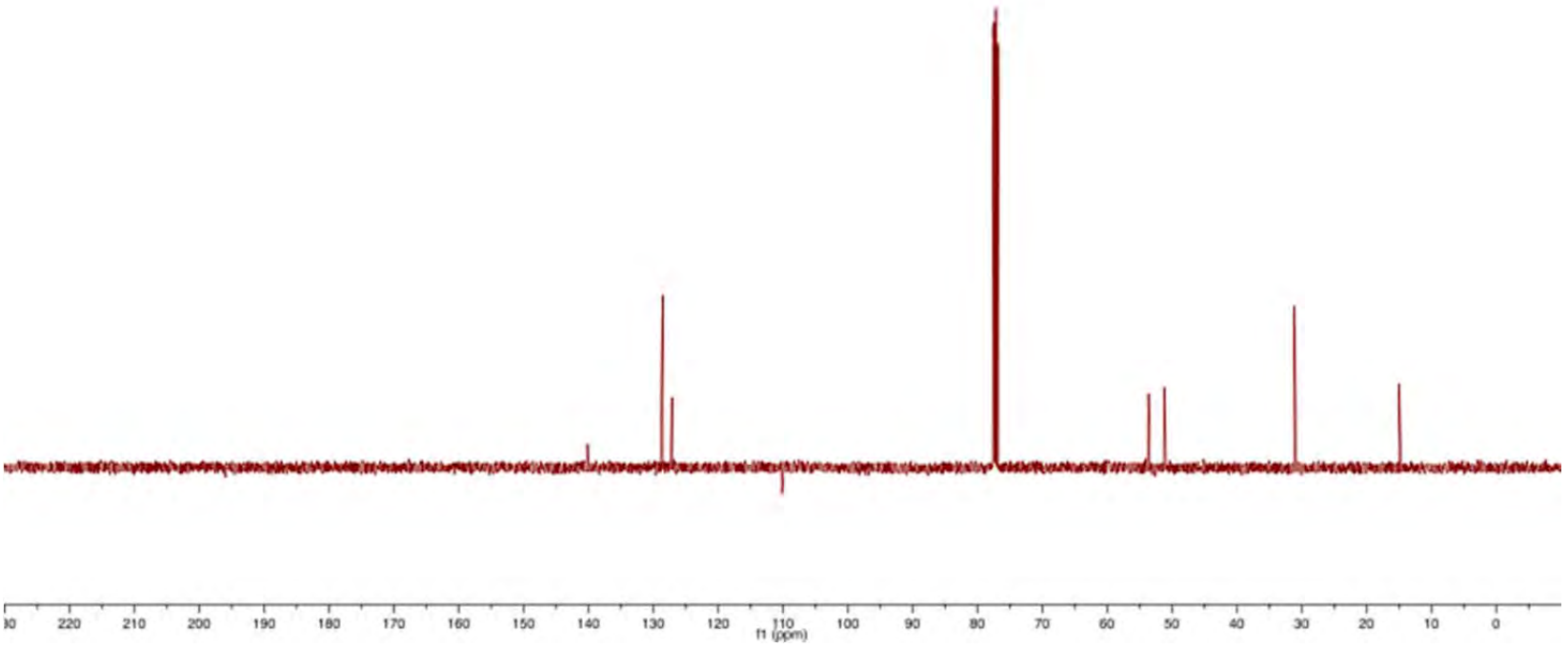

H
N
Bn

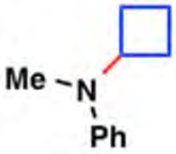
125


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1

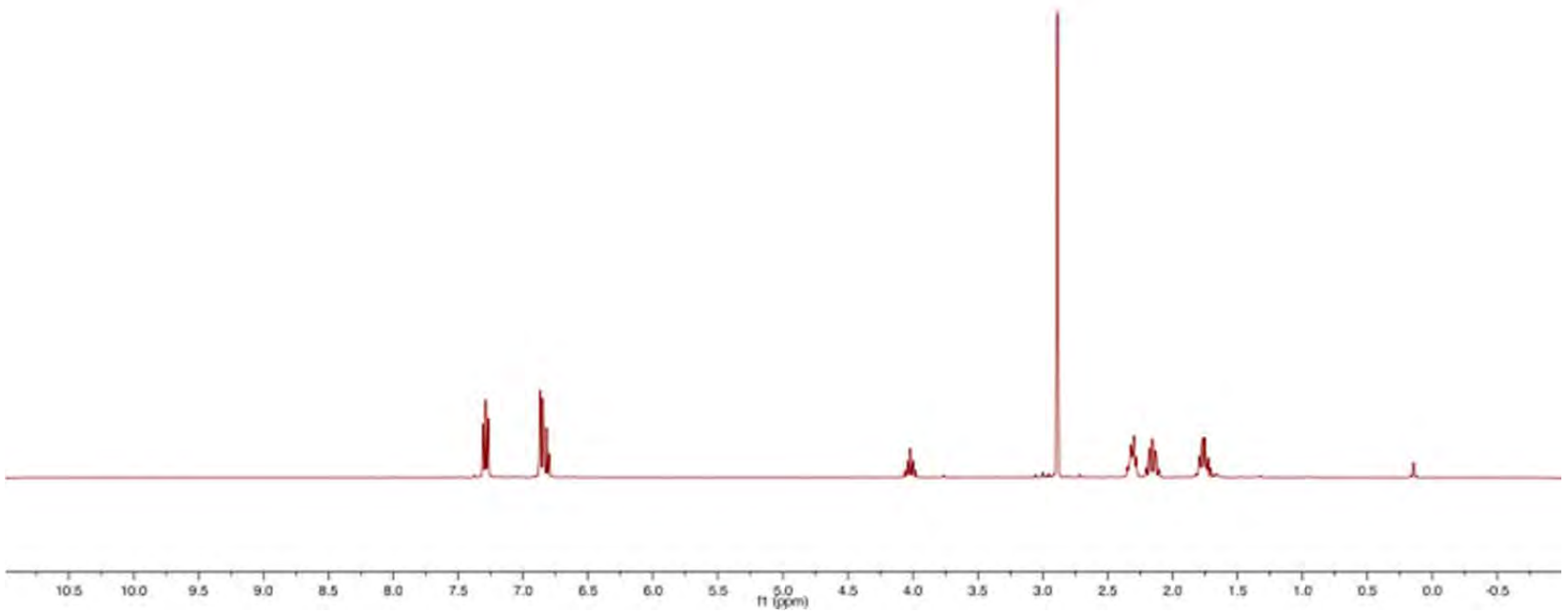

H
N
Bn

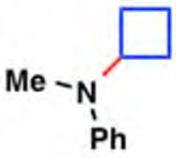
125


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)

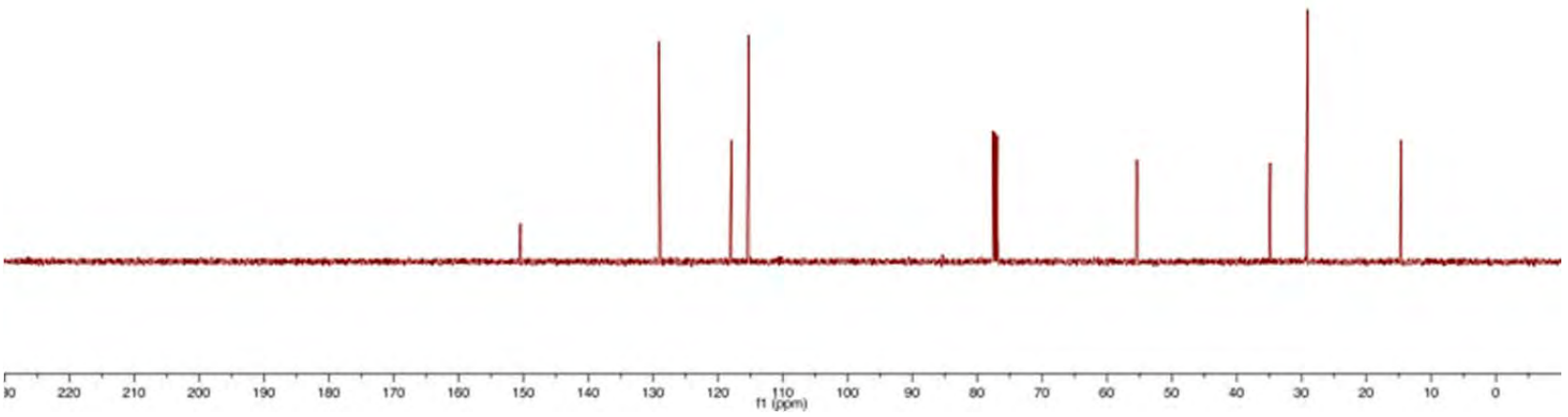

Me
N
Ph

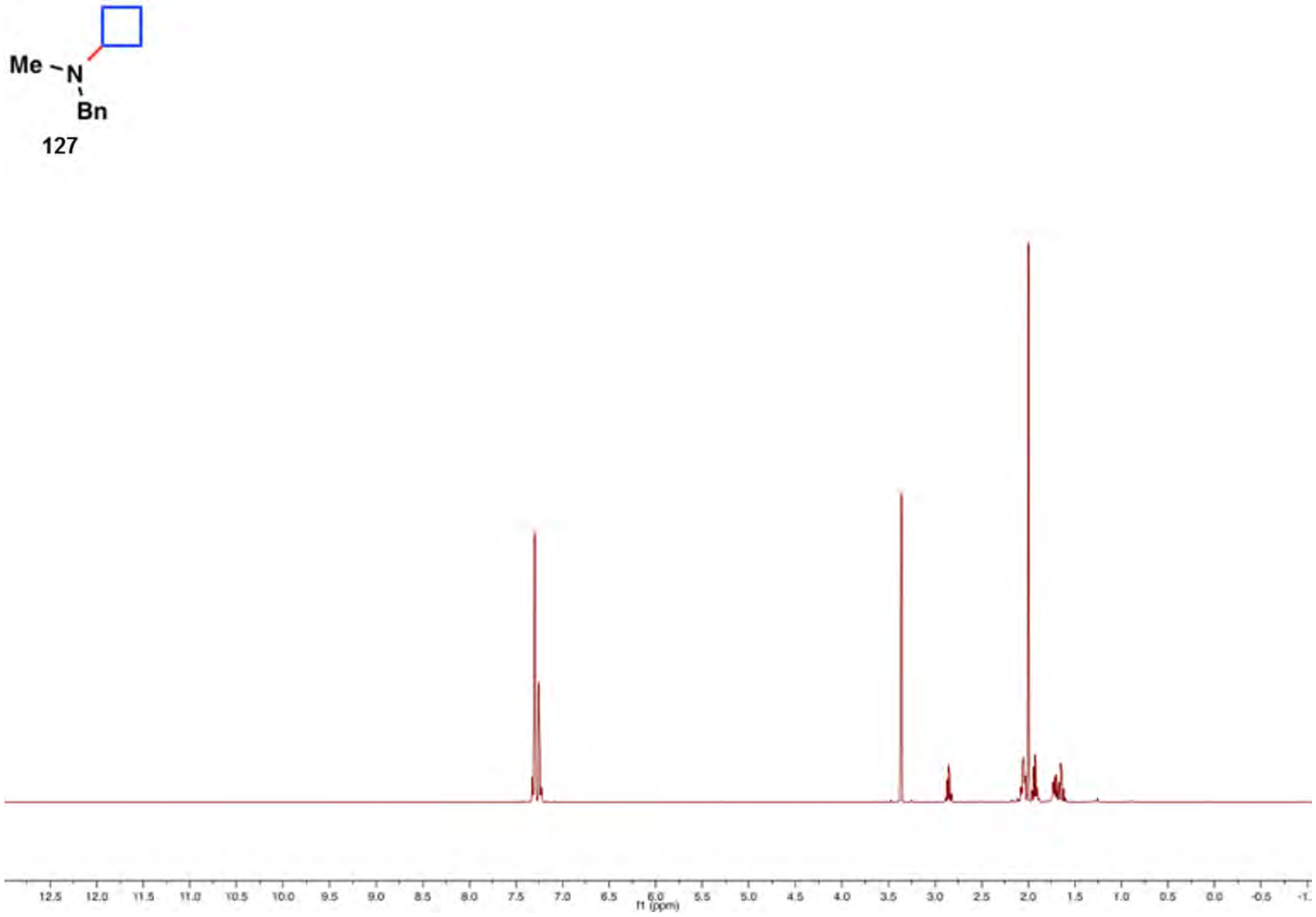
126


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
N
Ph

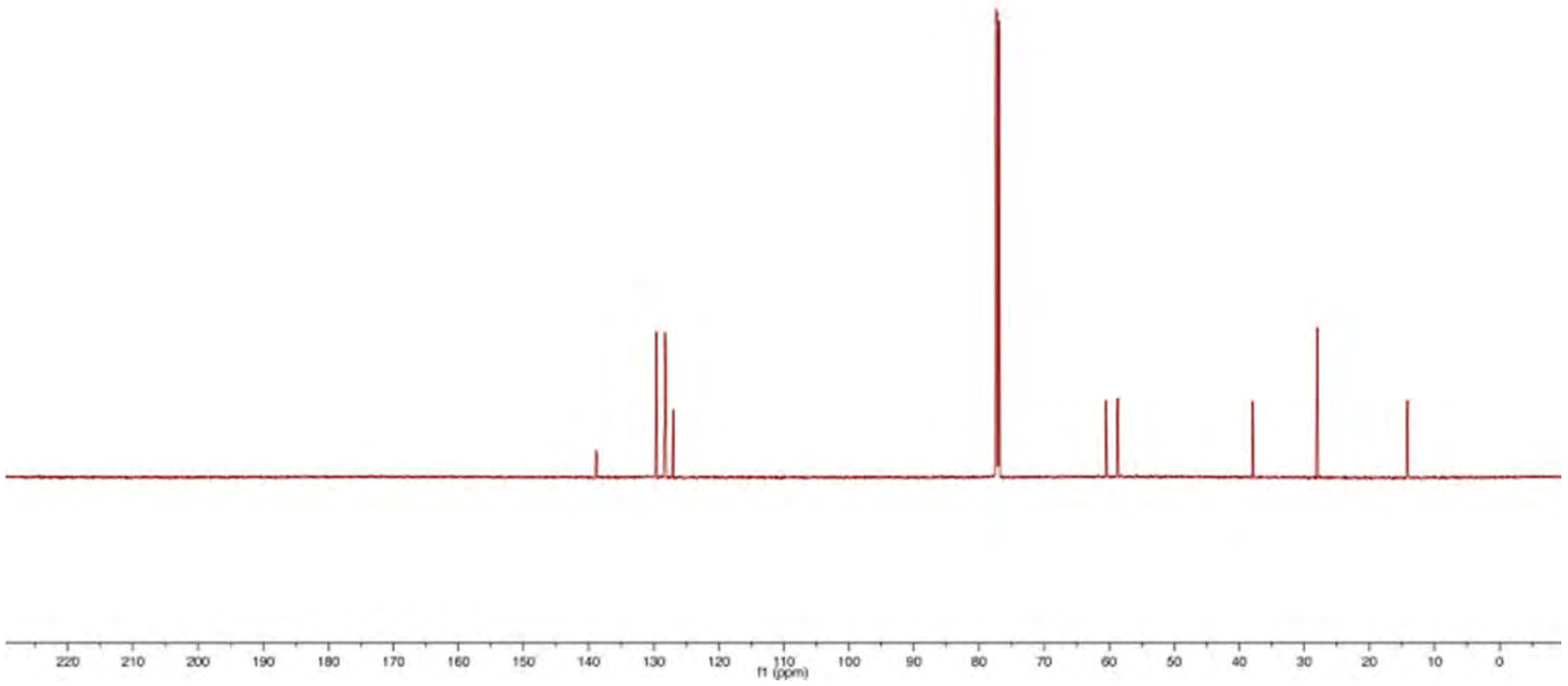
126

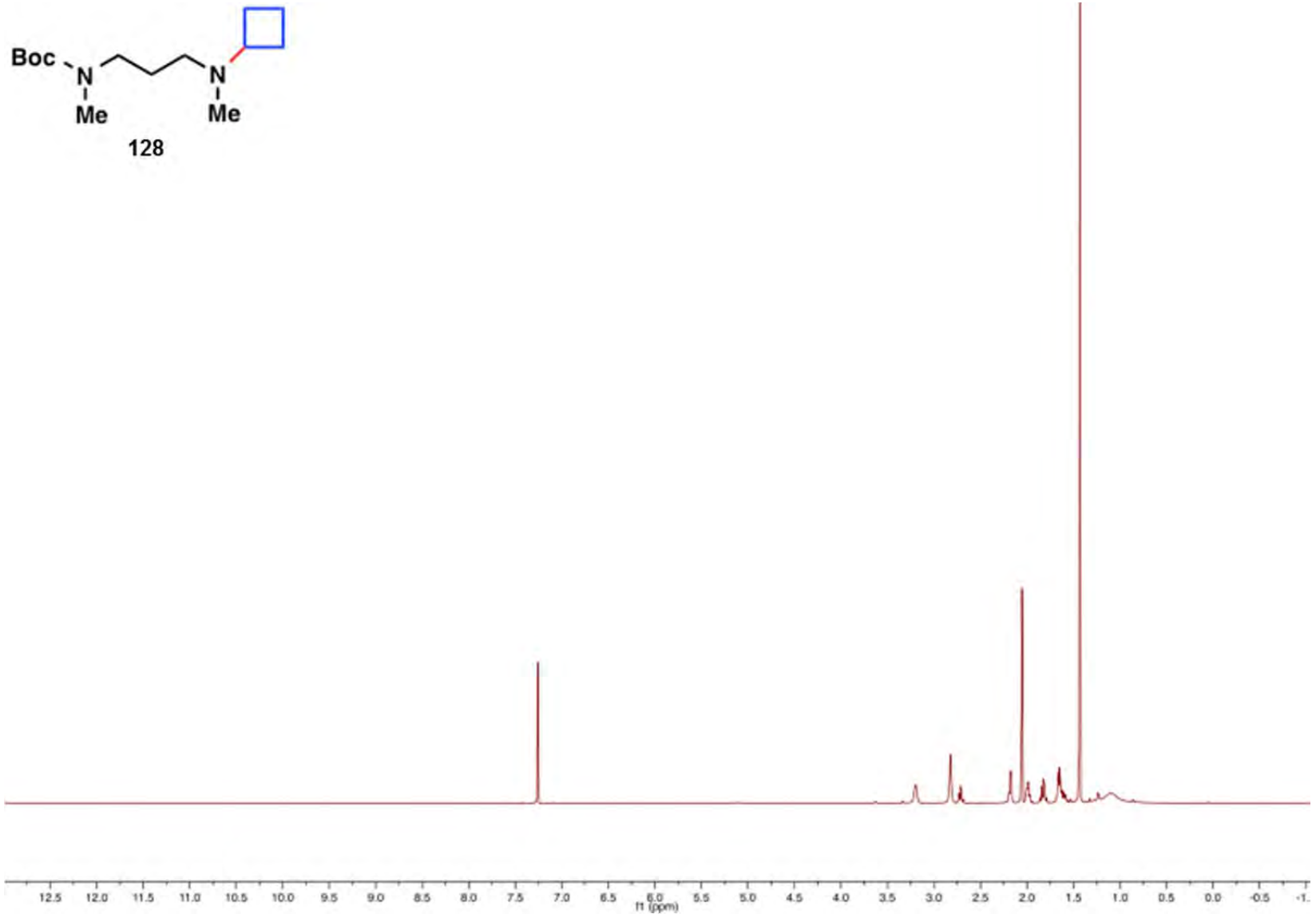

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

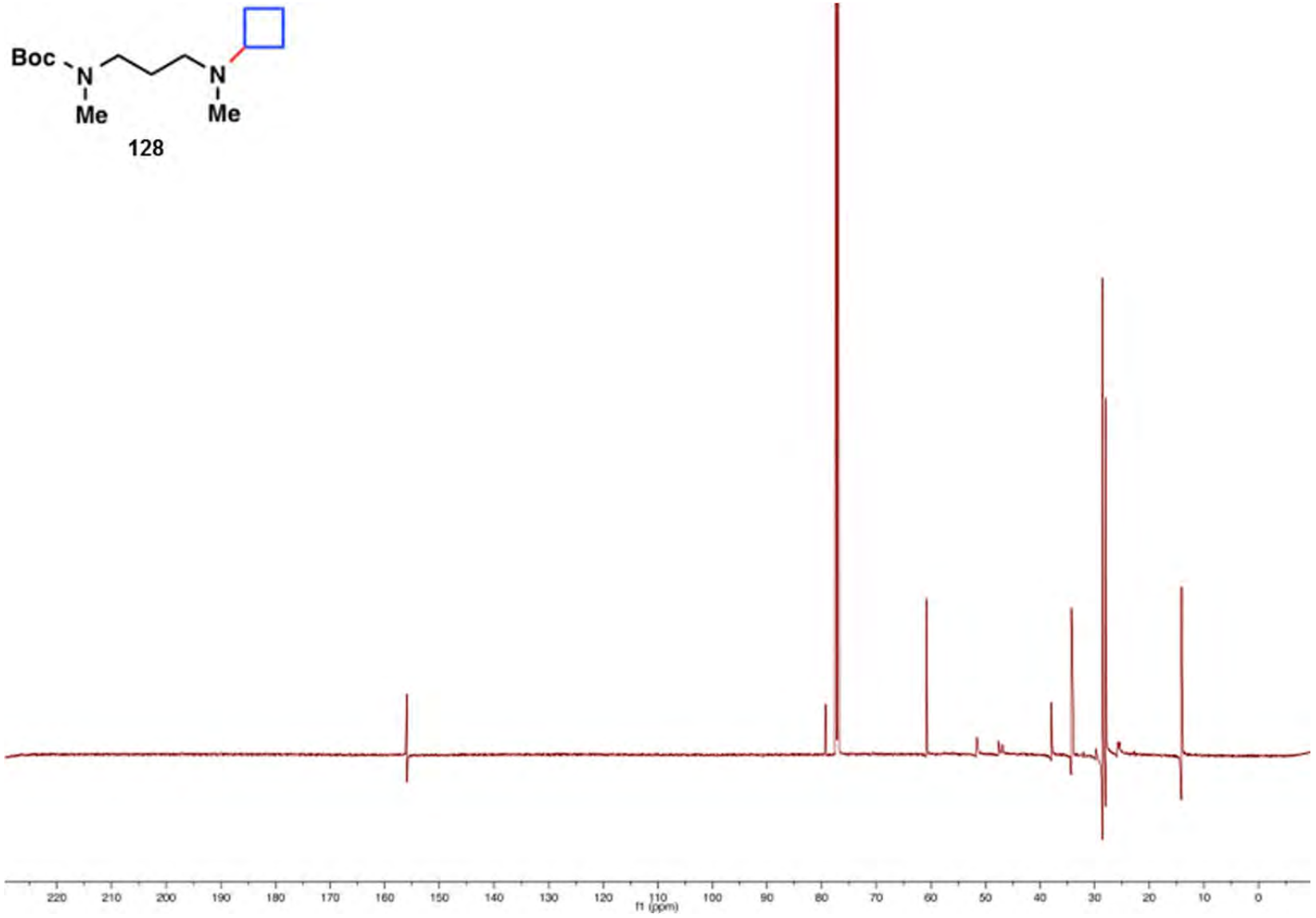

Me
N
Bn
127
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

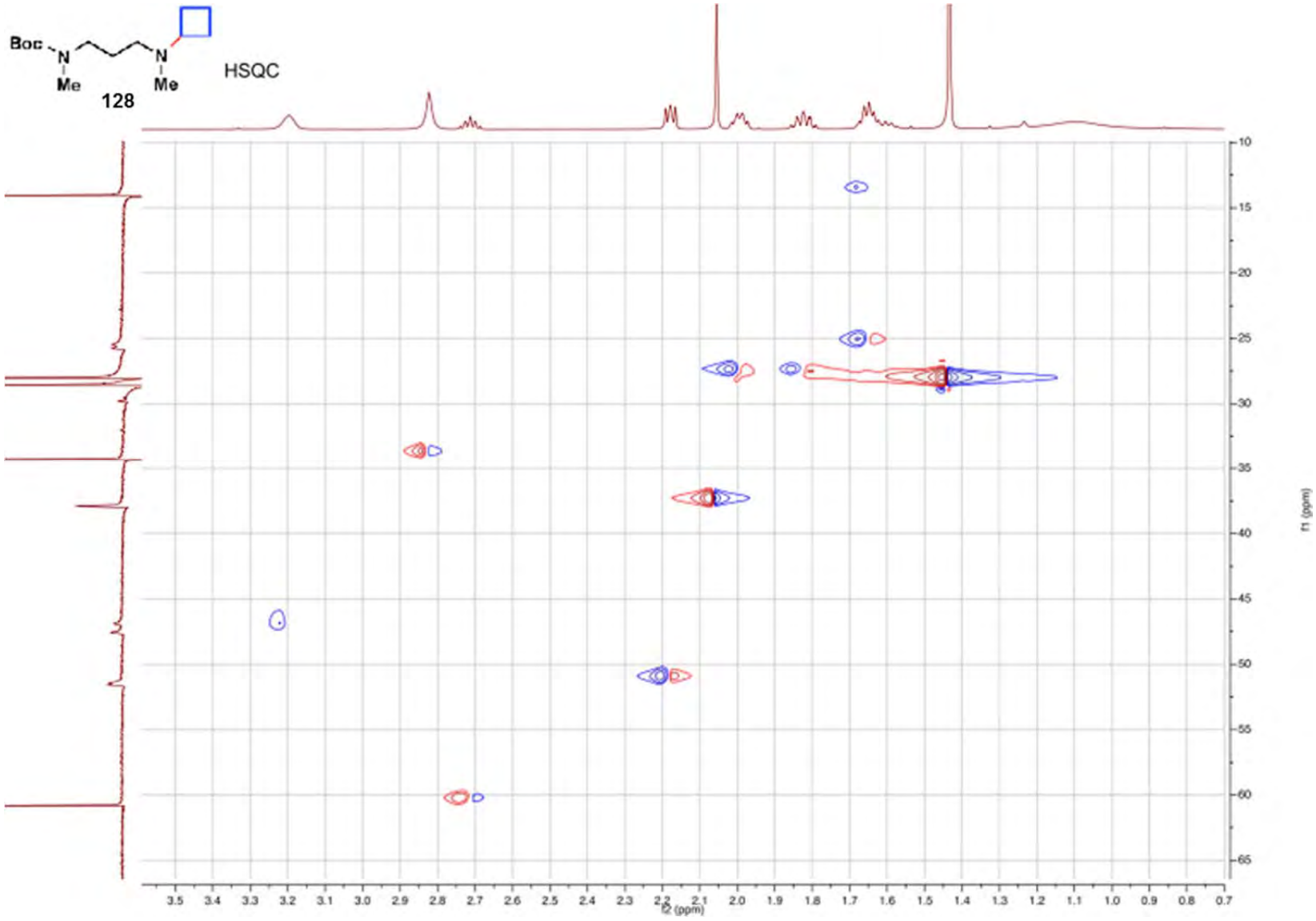

Me
N
Bn

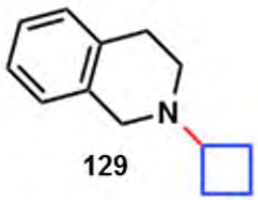
127


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)

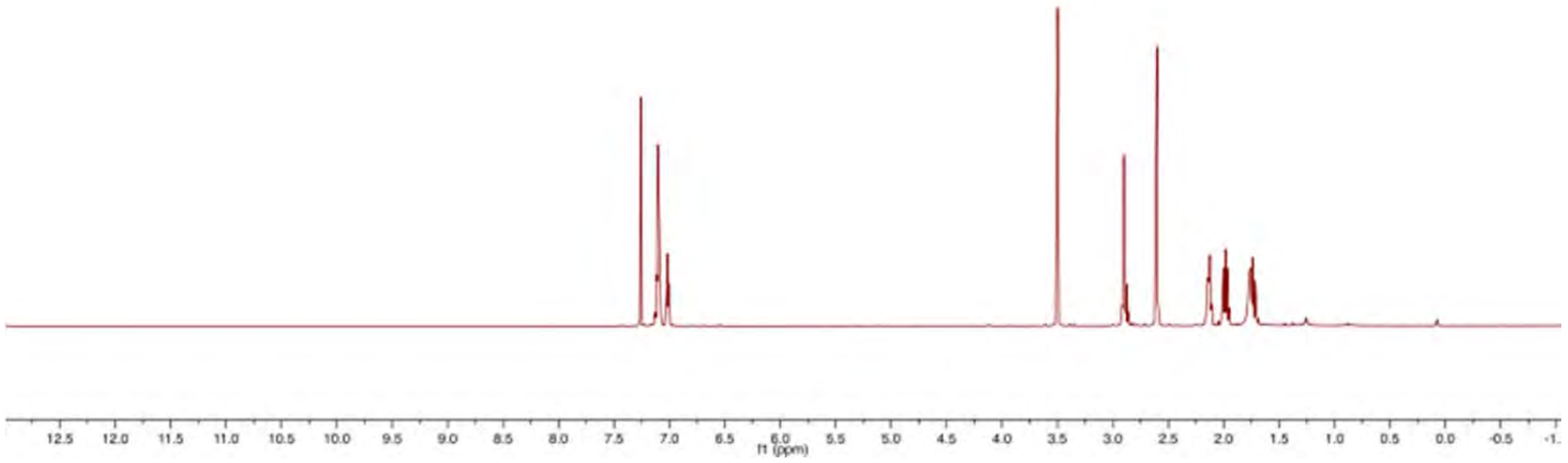

Boc
N
Me
N
Me
128
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Boc
N
Me
N
Me
128
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)


Boc
N
Me
N
Me
128
HSQC
f1 (ppm)
f2 (ppm)


N

129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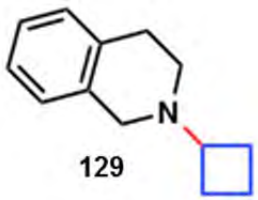
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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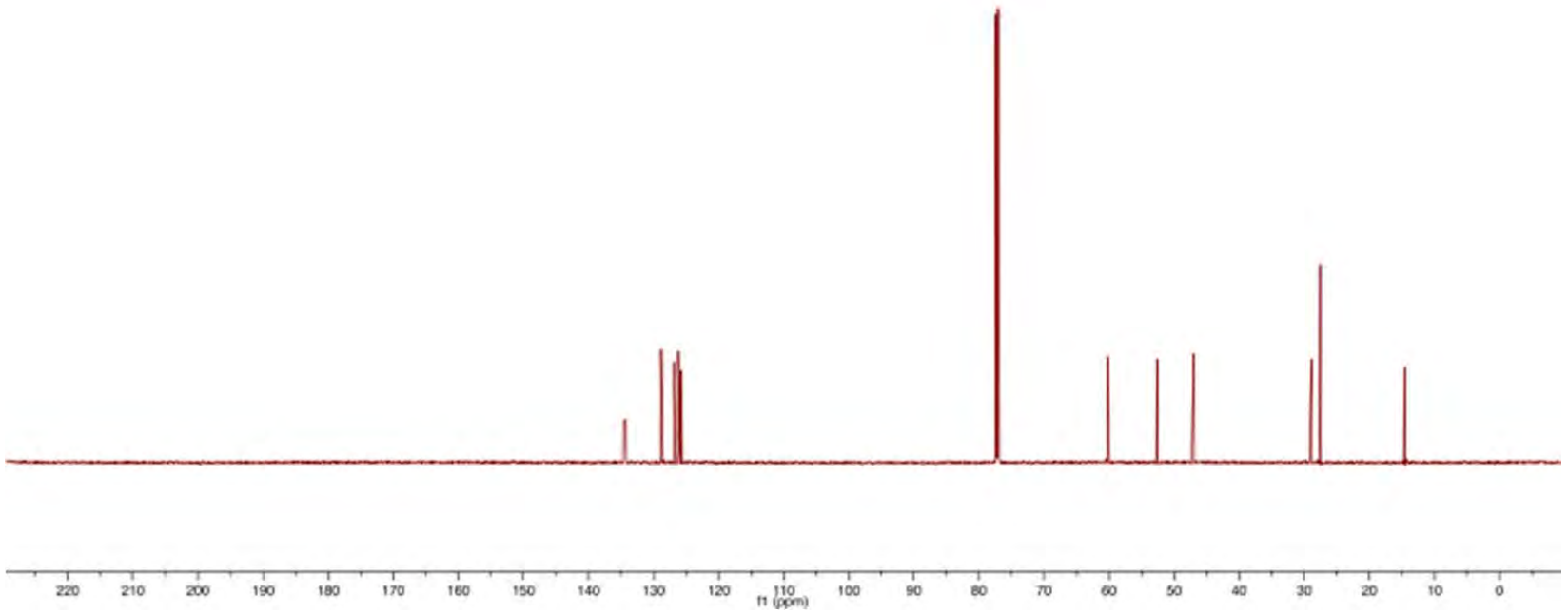
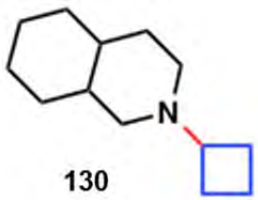

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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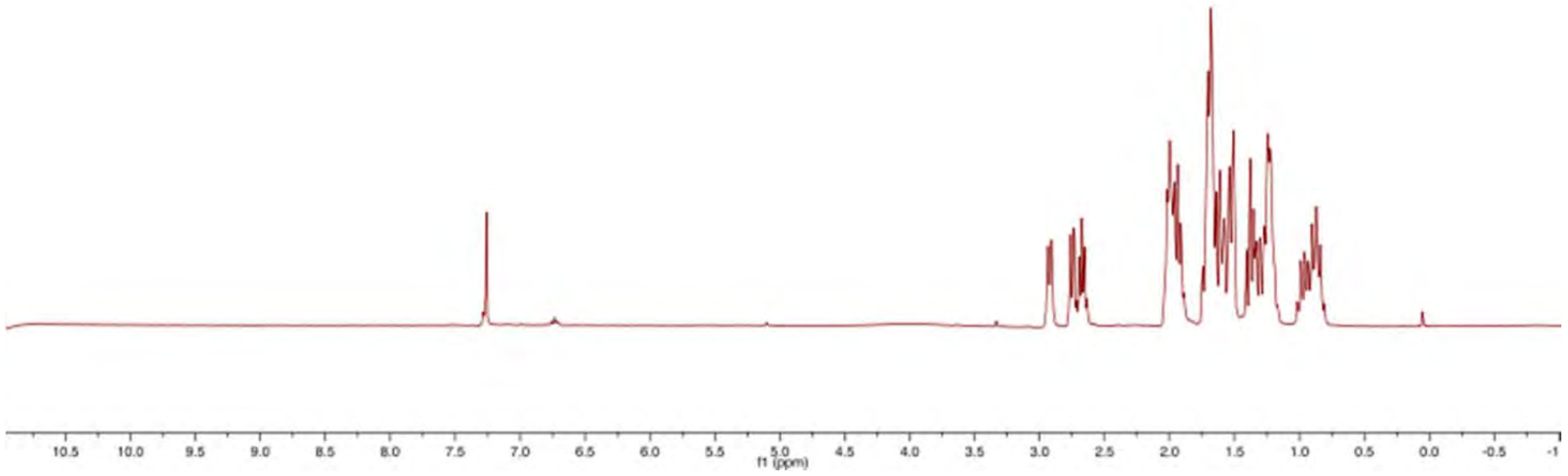
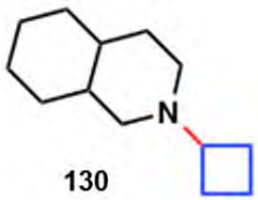

10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1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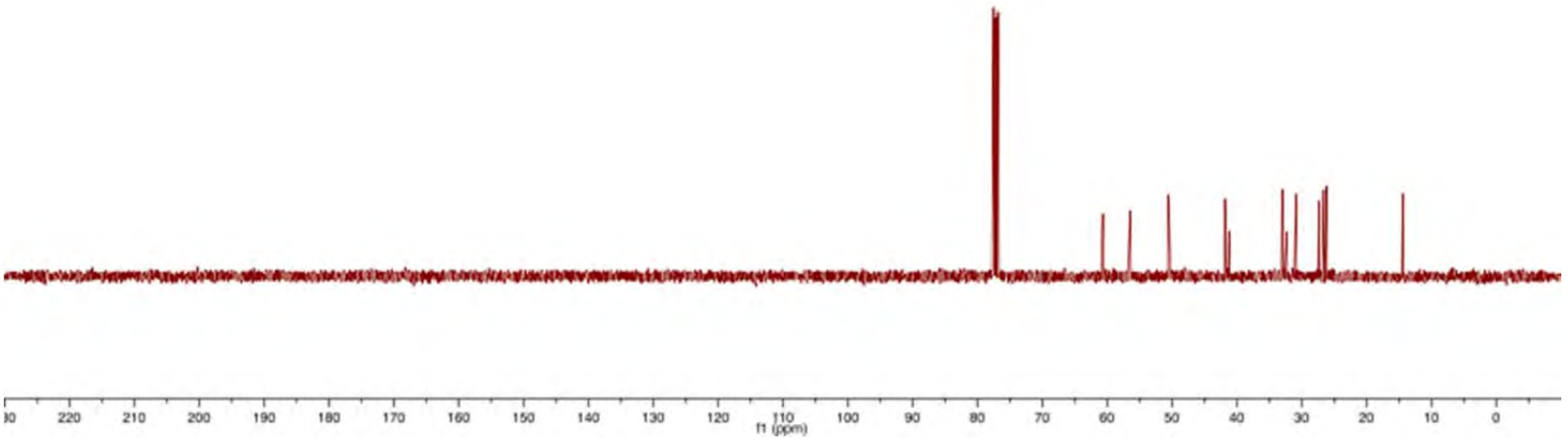
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210
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180
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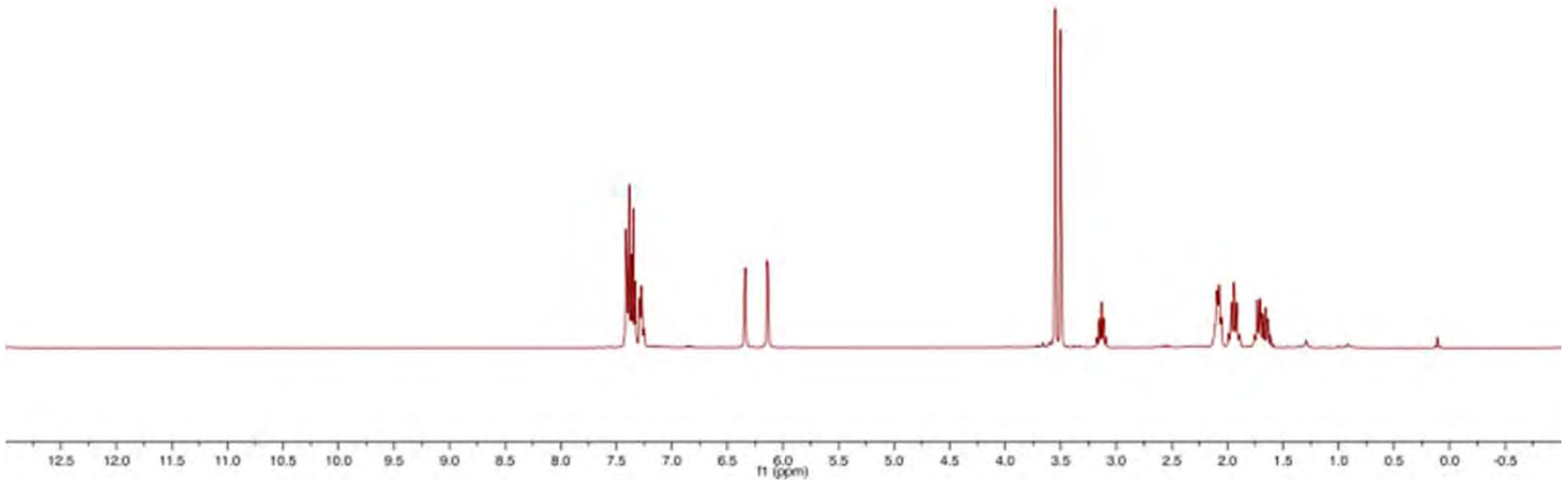
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
Bn

131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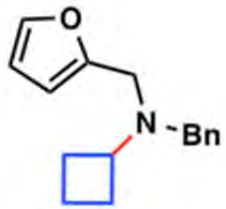
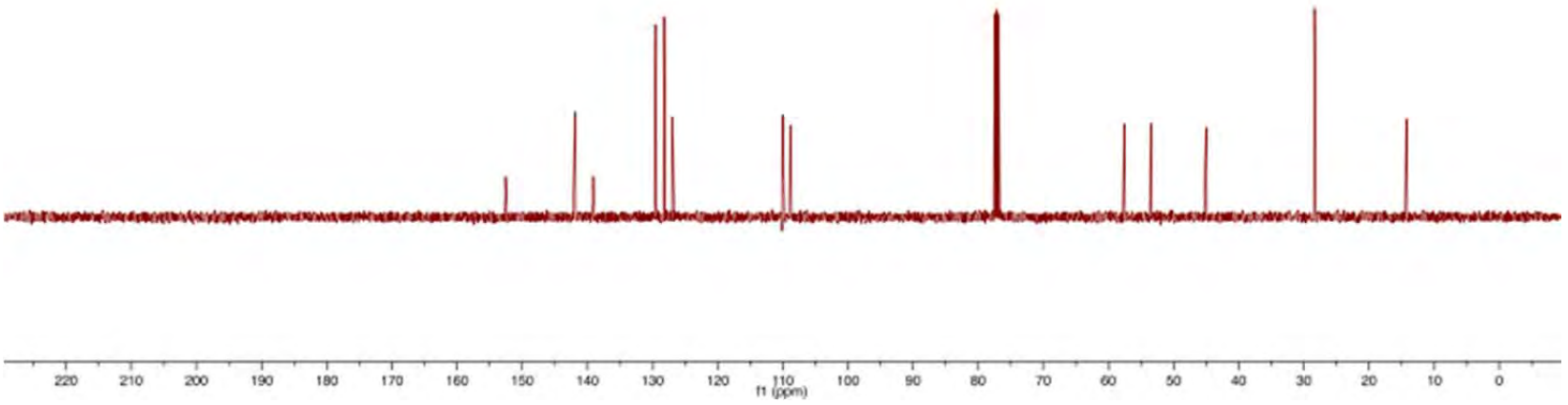
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


O
N
Bn

131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210
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190
180
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100
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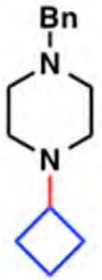
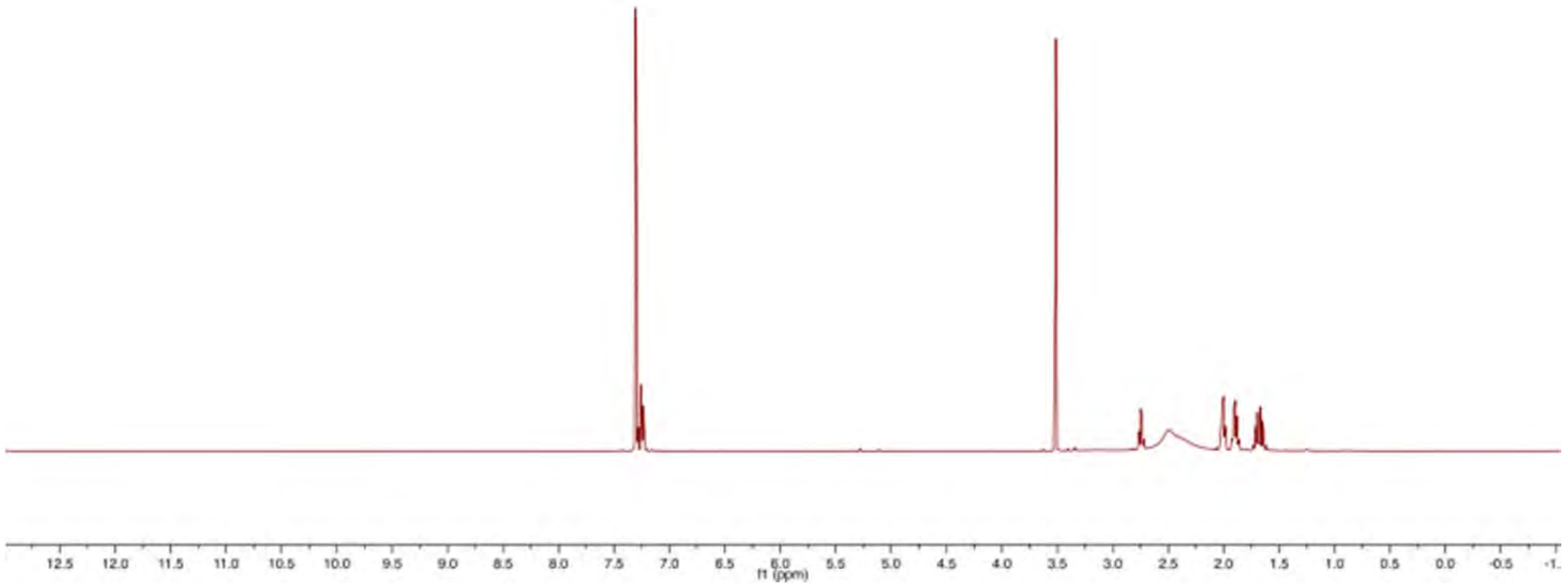
70
60
50
40
30
20
10
0
f1 (ppm)


Bn
N
N

132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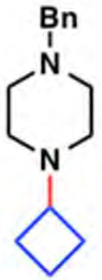
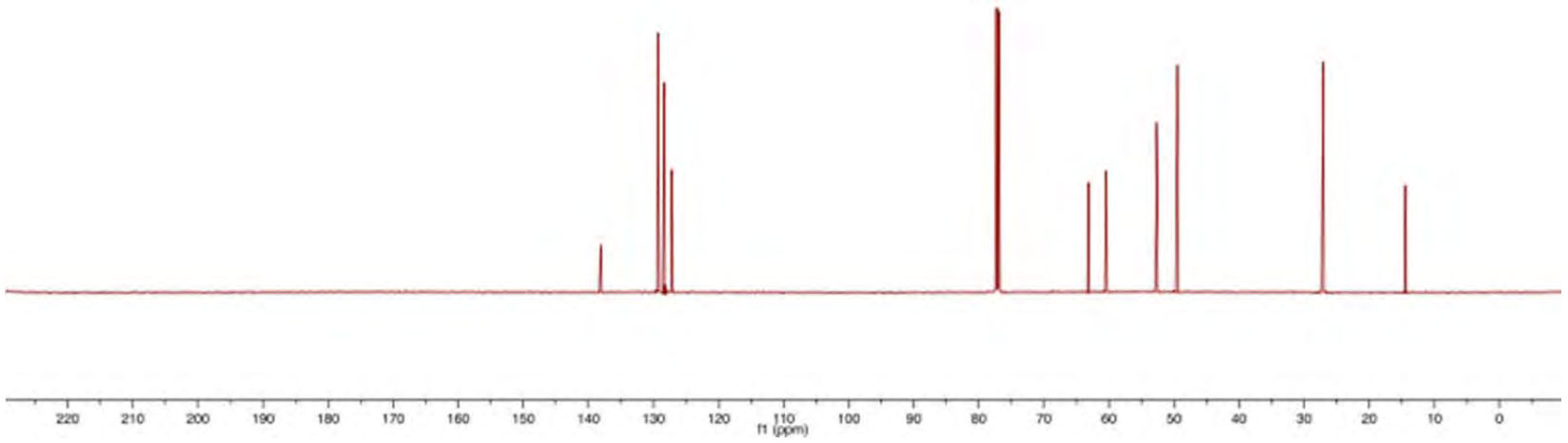
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Bn
N
N

132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210
200
190
180
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160
150
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120
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100
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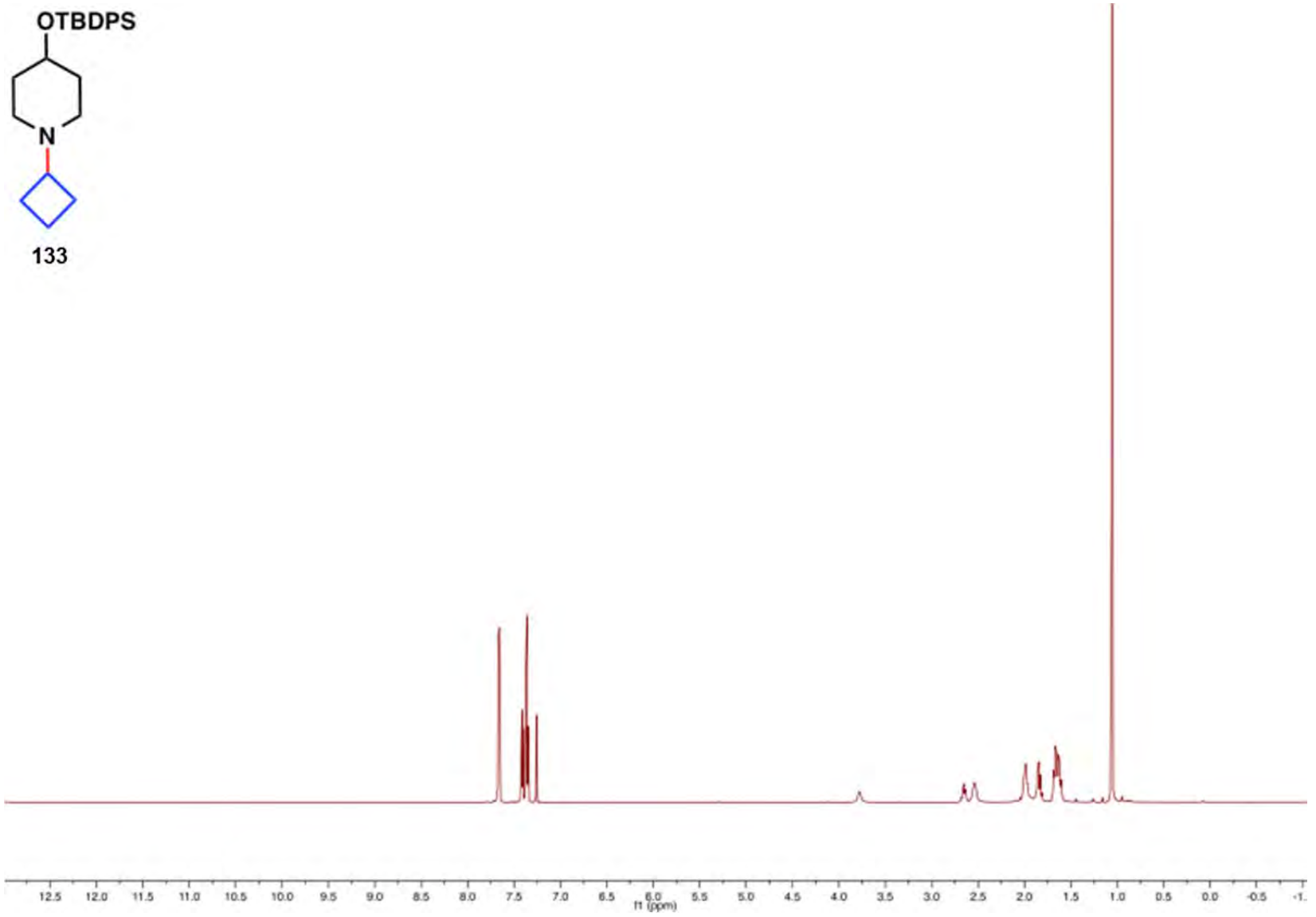
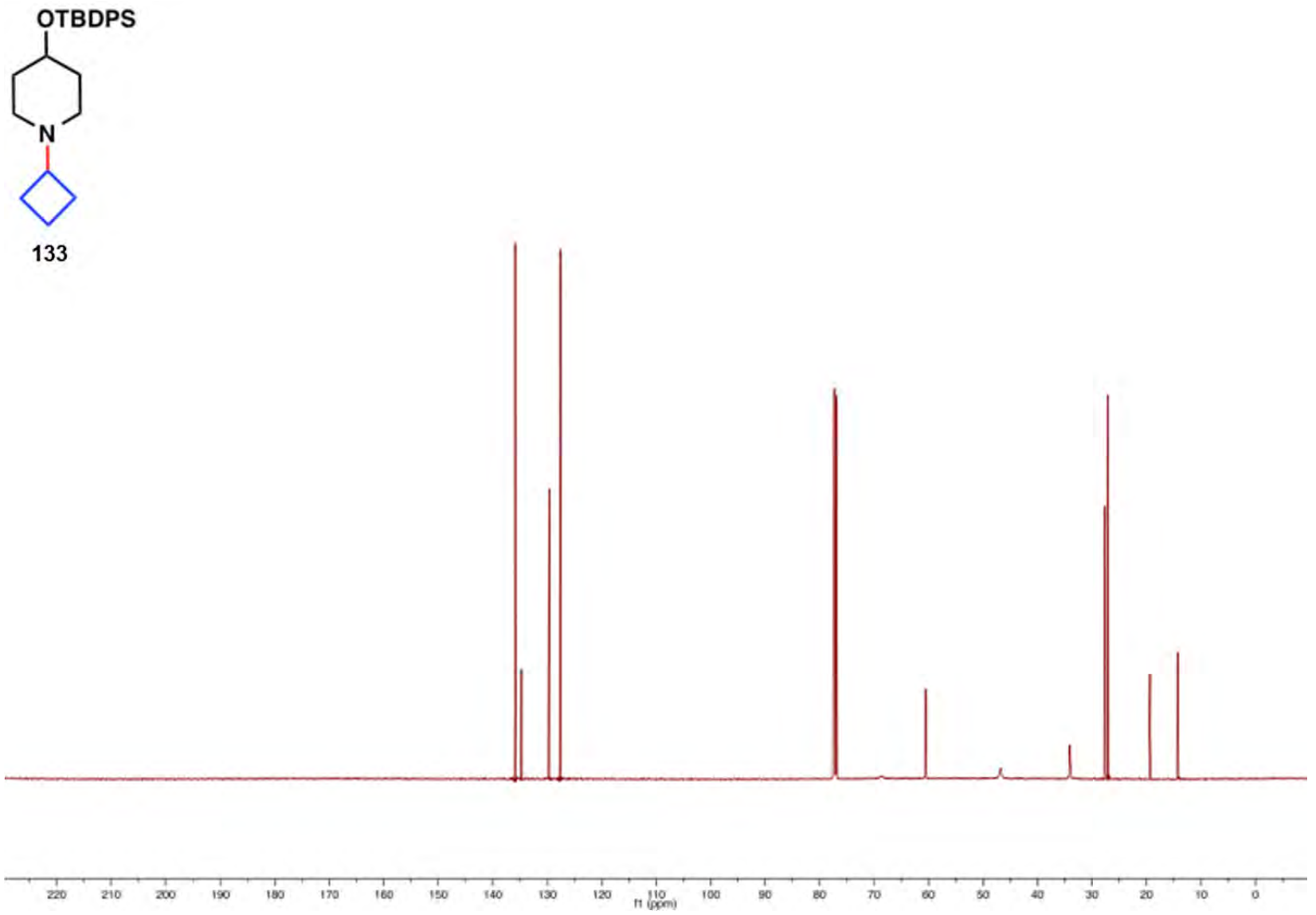
80
70
60
50
40
30
20
10
0
f1 (ppm)


OTBDPS
N
133
12.5 12.0 11.5 11.0 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)


OTBDPS
N
133
220
210
200
190
180
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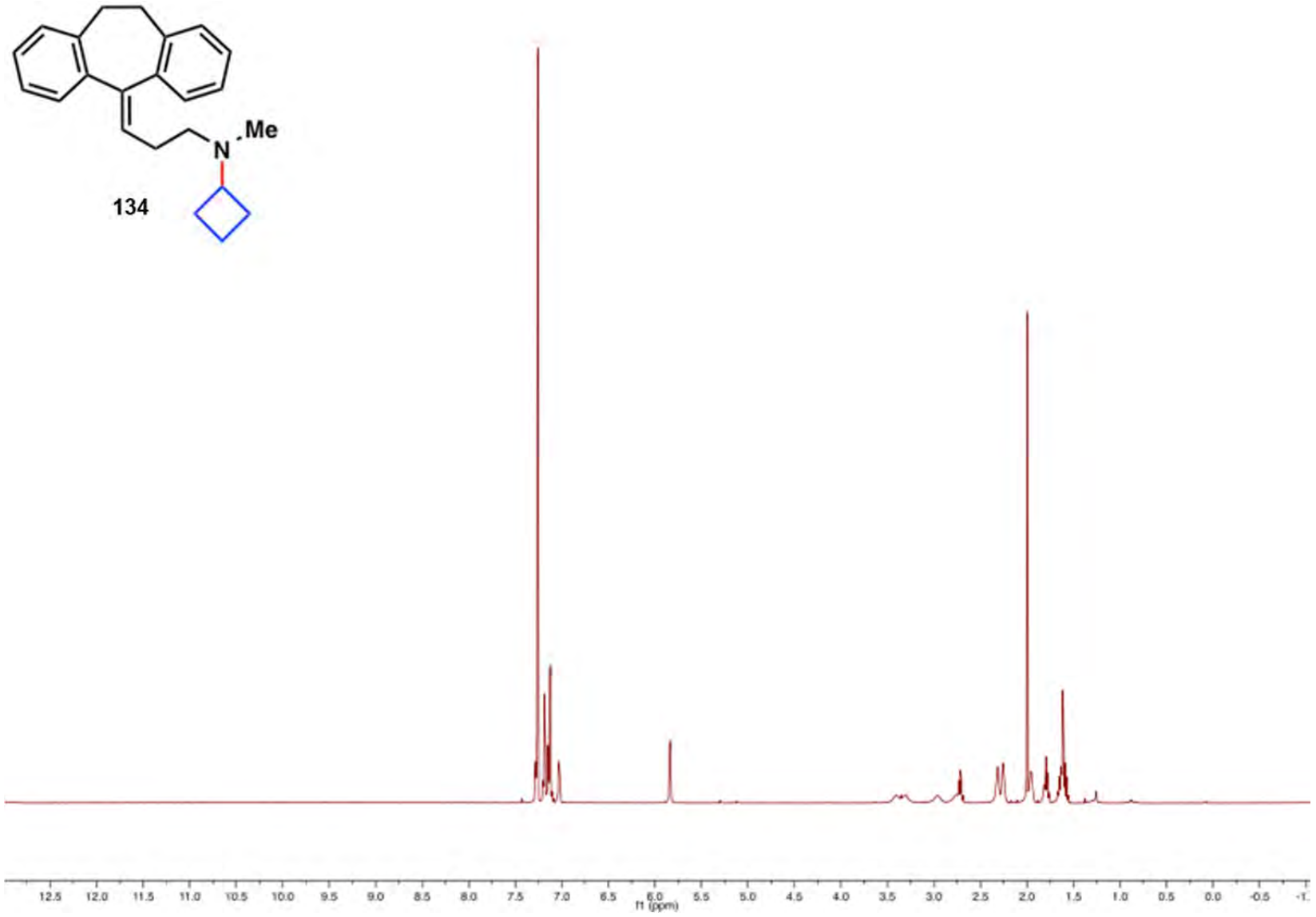
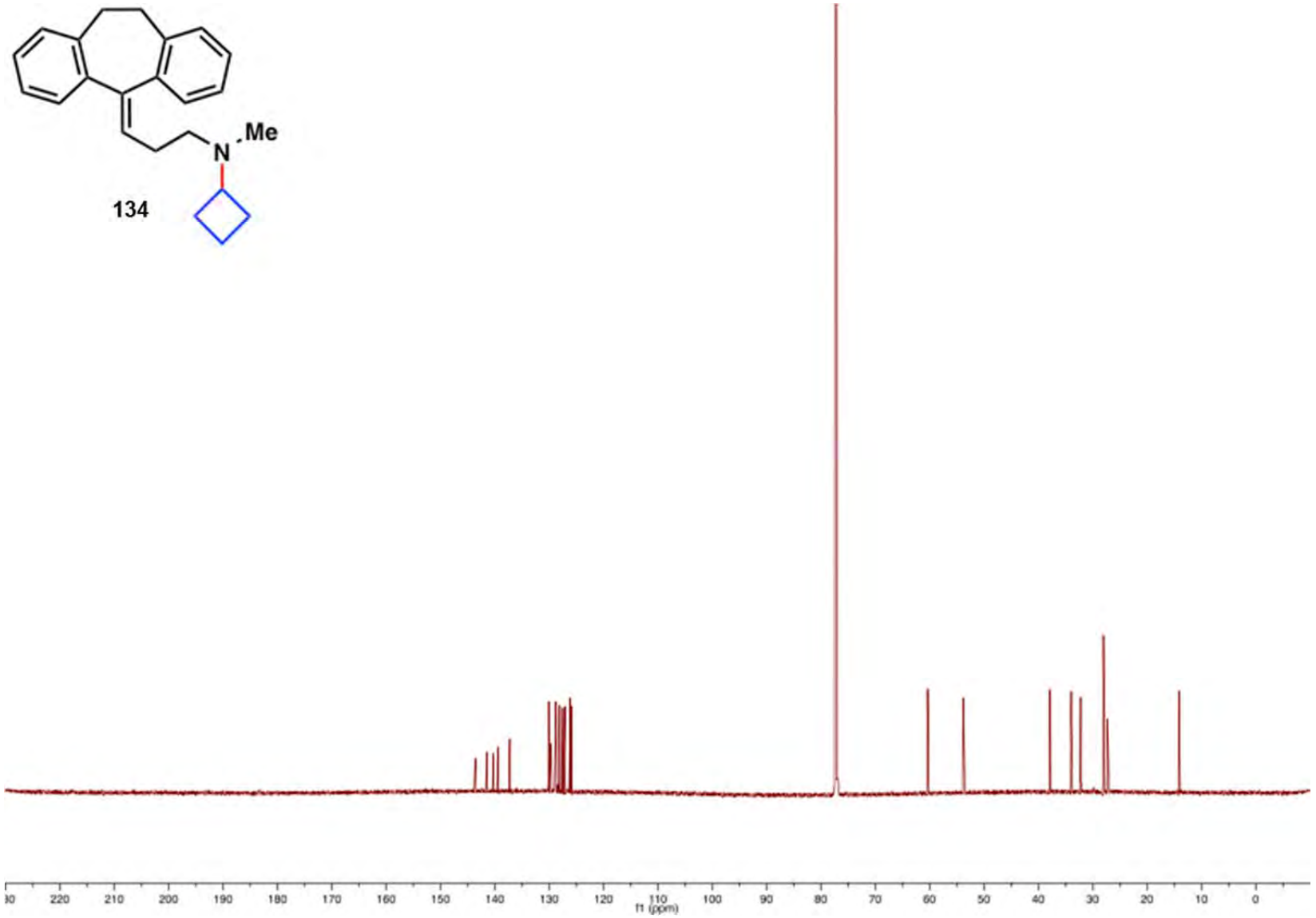
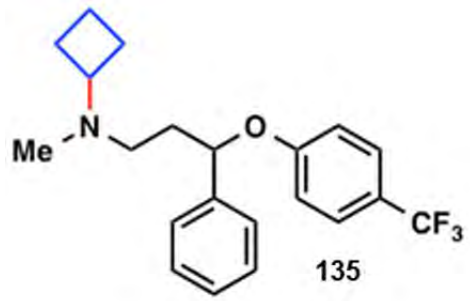
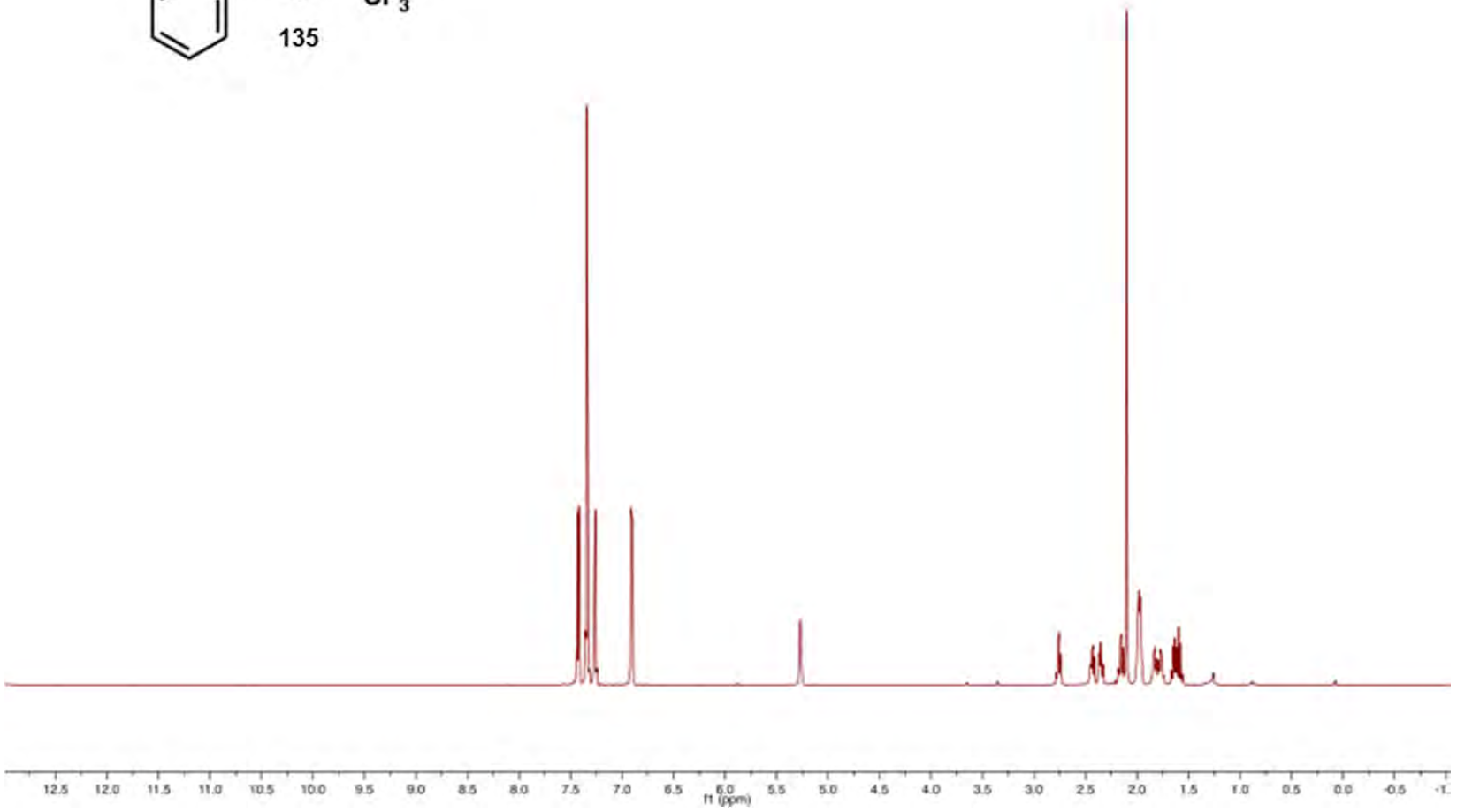
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
N
134
12.5
12.0
11.5
11.0
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
N
134
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)


Me
N
O
CF3

135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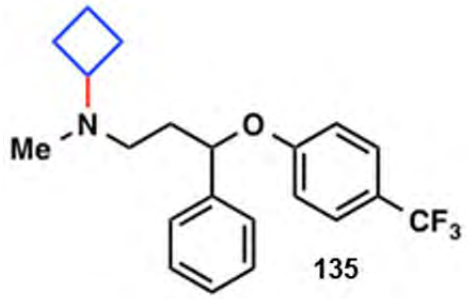
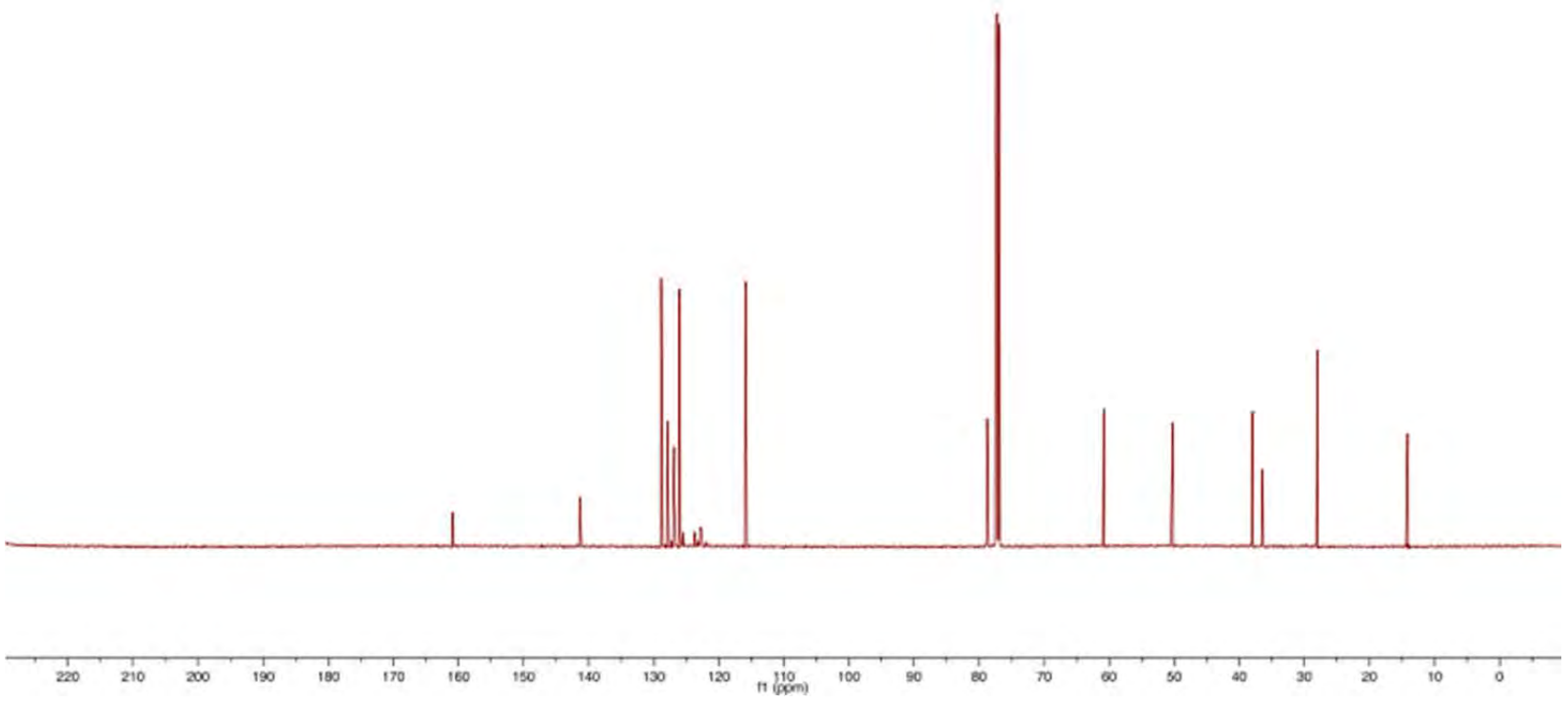
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Me
N
O
CF3

135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180
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100
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80
70
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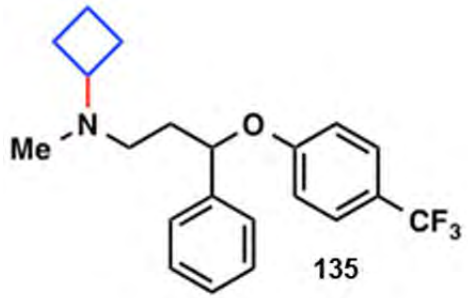
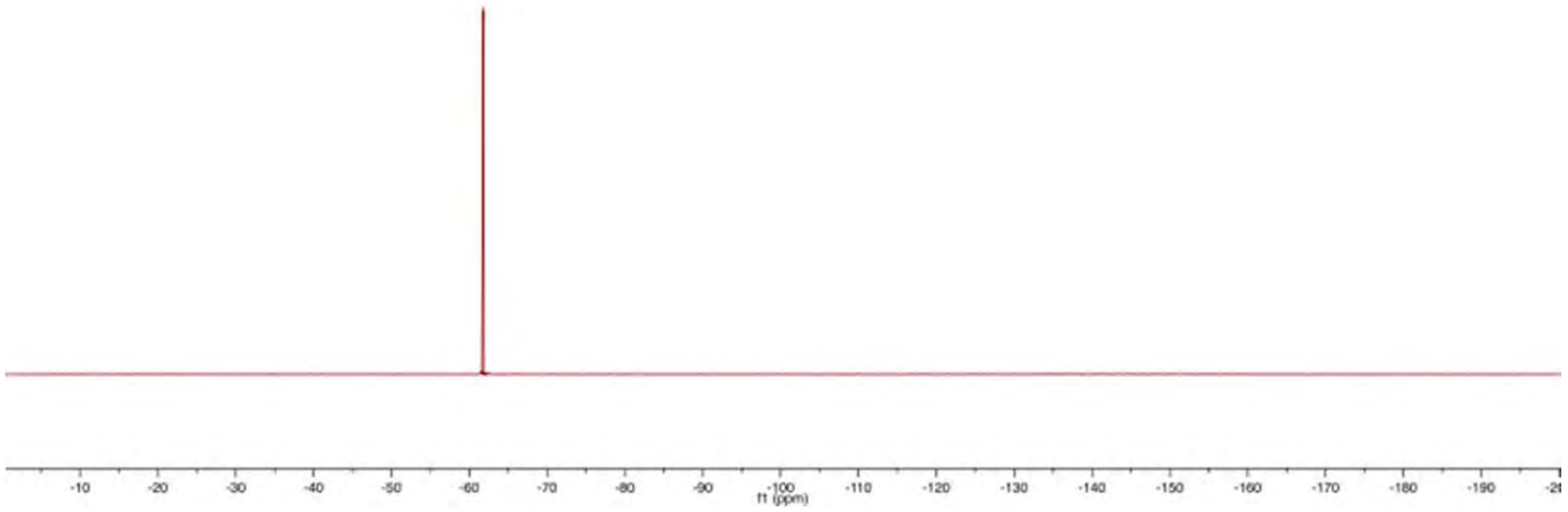
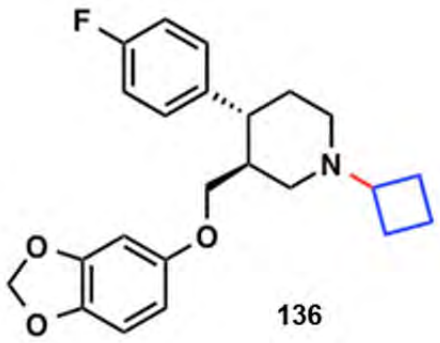
50
40
30
20
10
0
f1 (ppm)

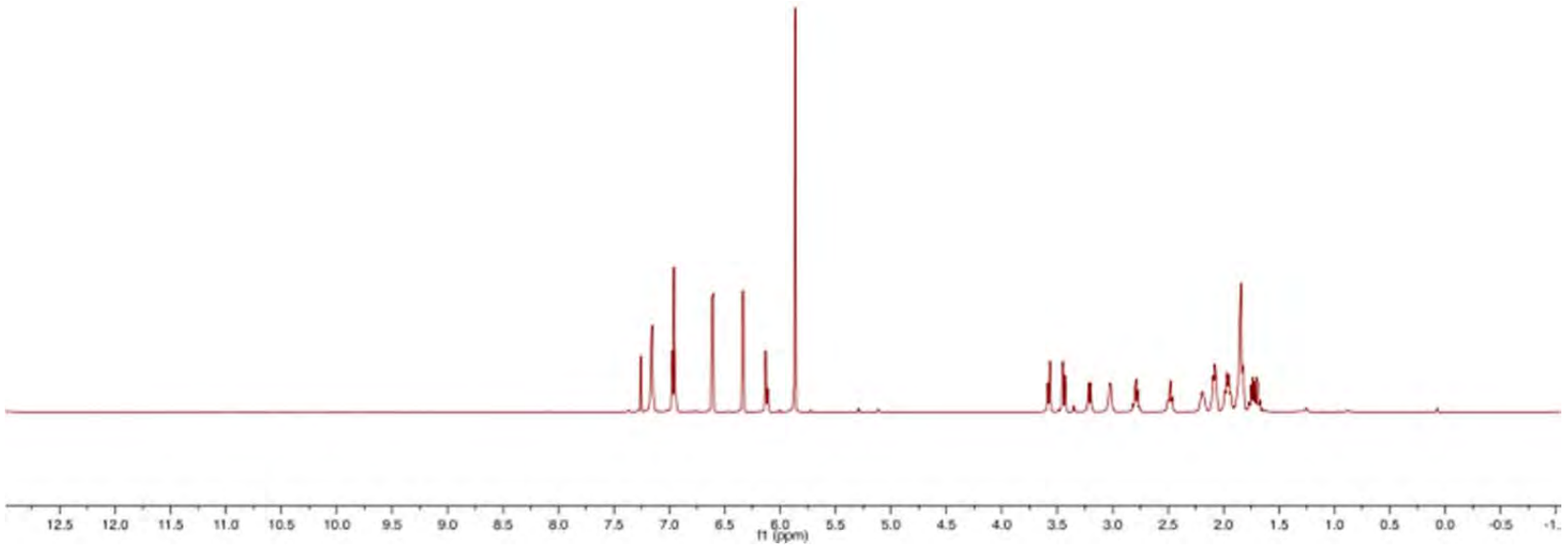

Me
N
O
CF3

135


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190


F
N
O
O
O

136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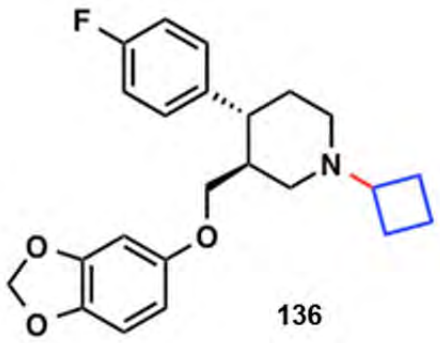
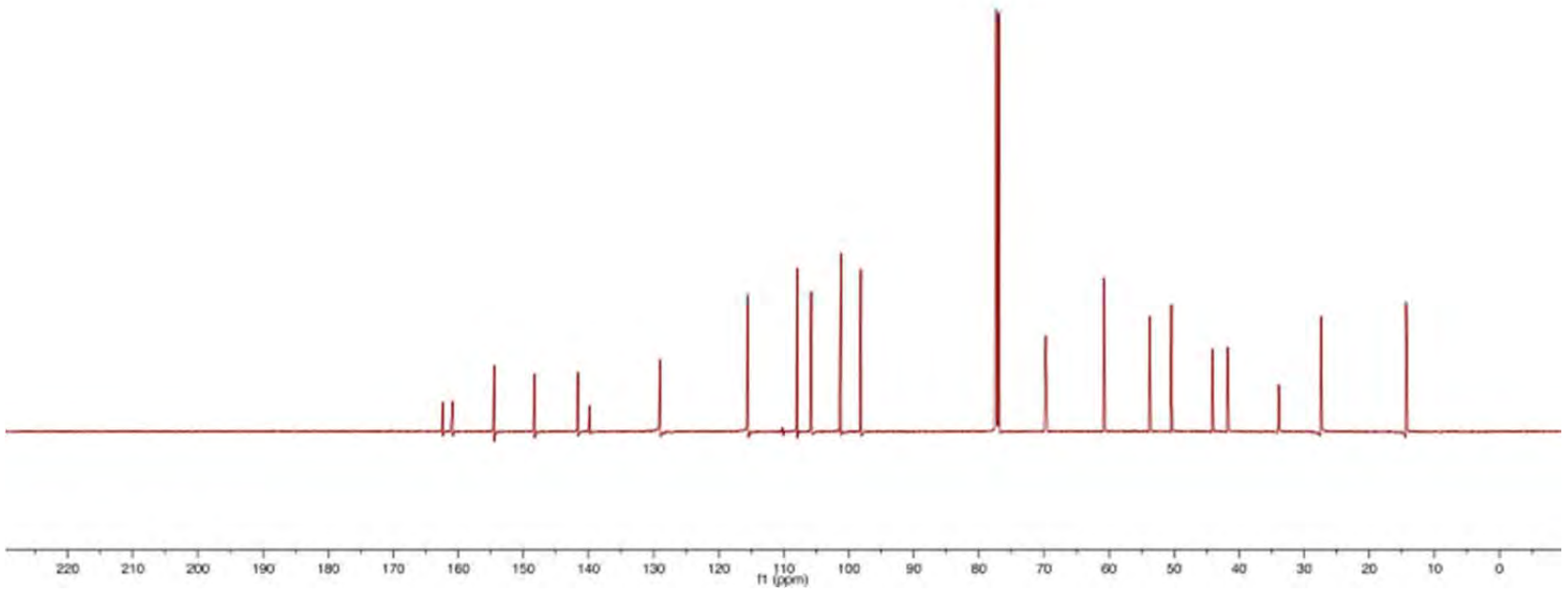
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


F
N
O
O
O
O

136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210
200
190
180
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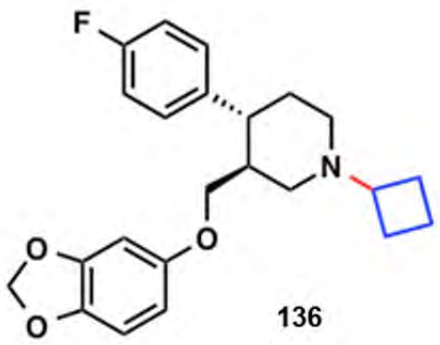
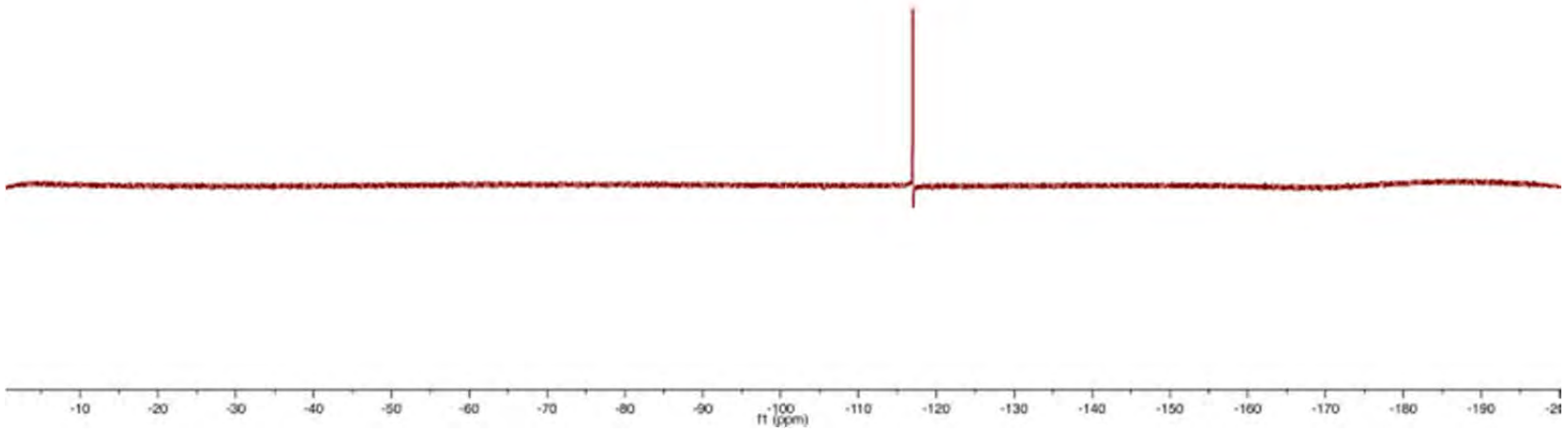
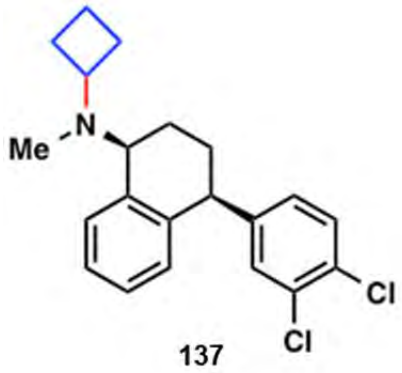
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

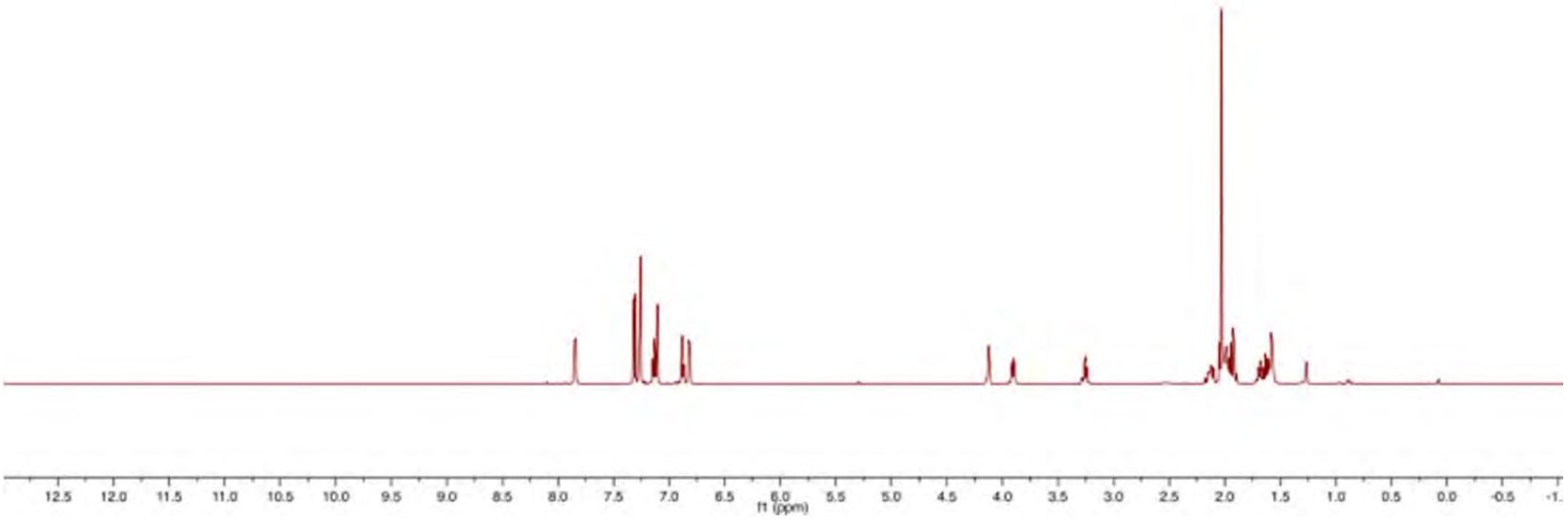

F
N
O
O
O

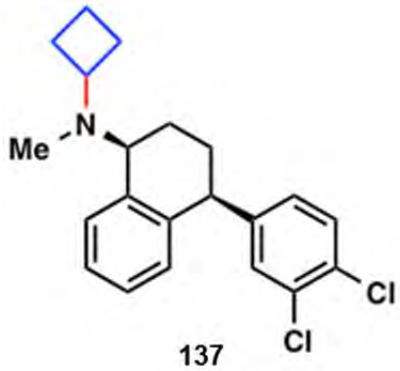
136


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190

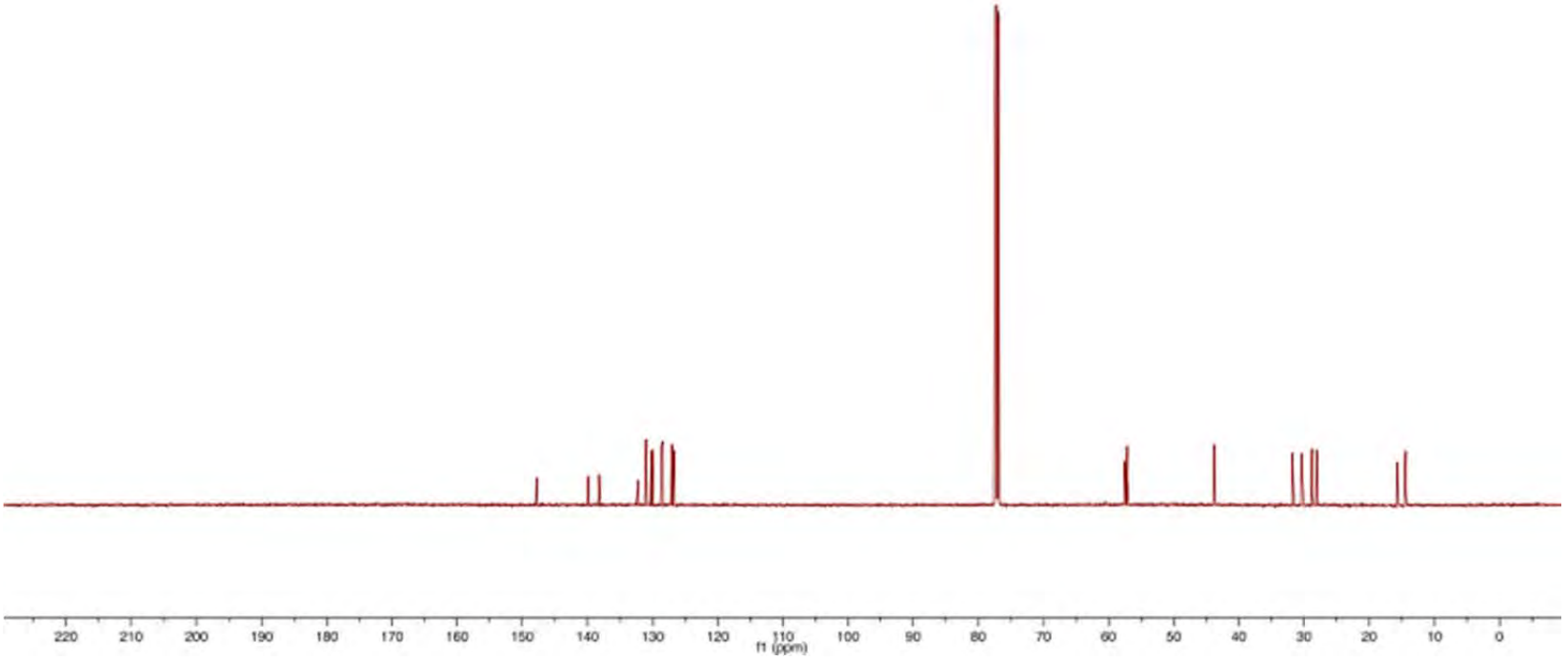

Me
N
Cl
Cl

137


12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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


Me
N
Cl
Cl

137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210
200
190
180
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150
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130
120
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100
90
80
70
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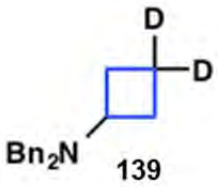
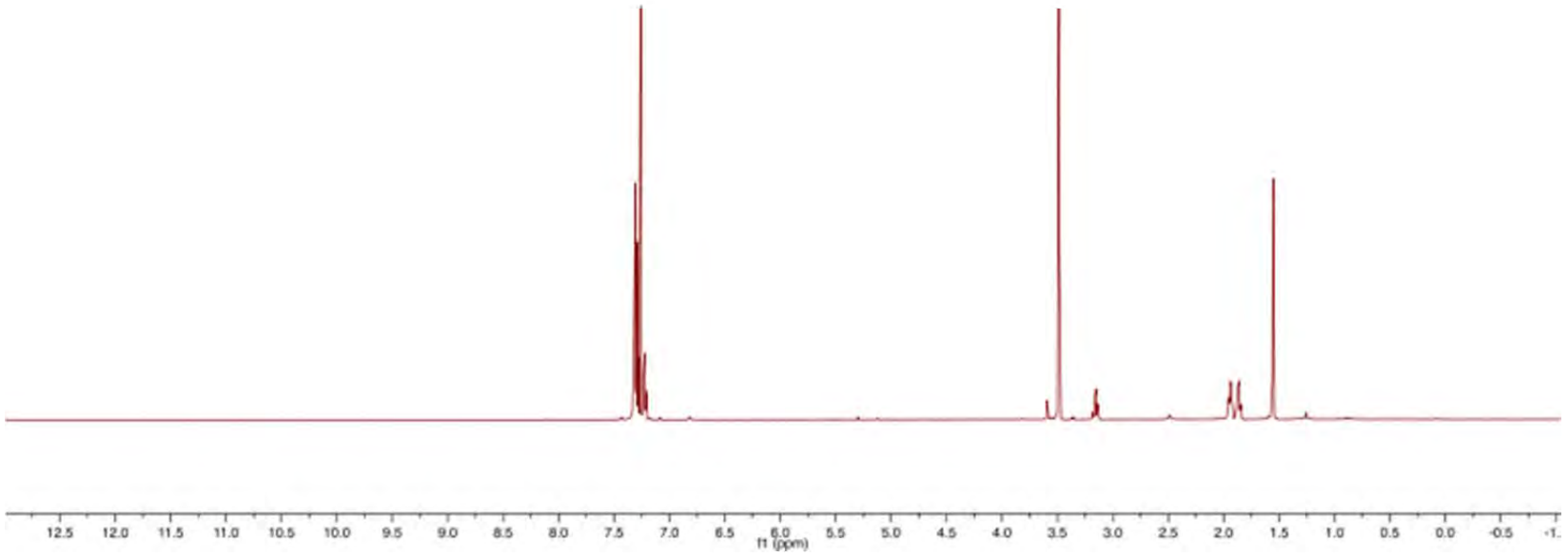
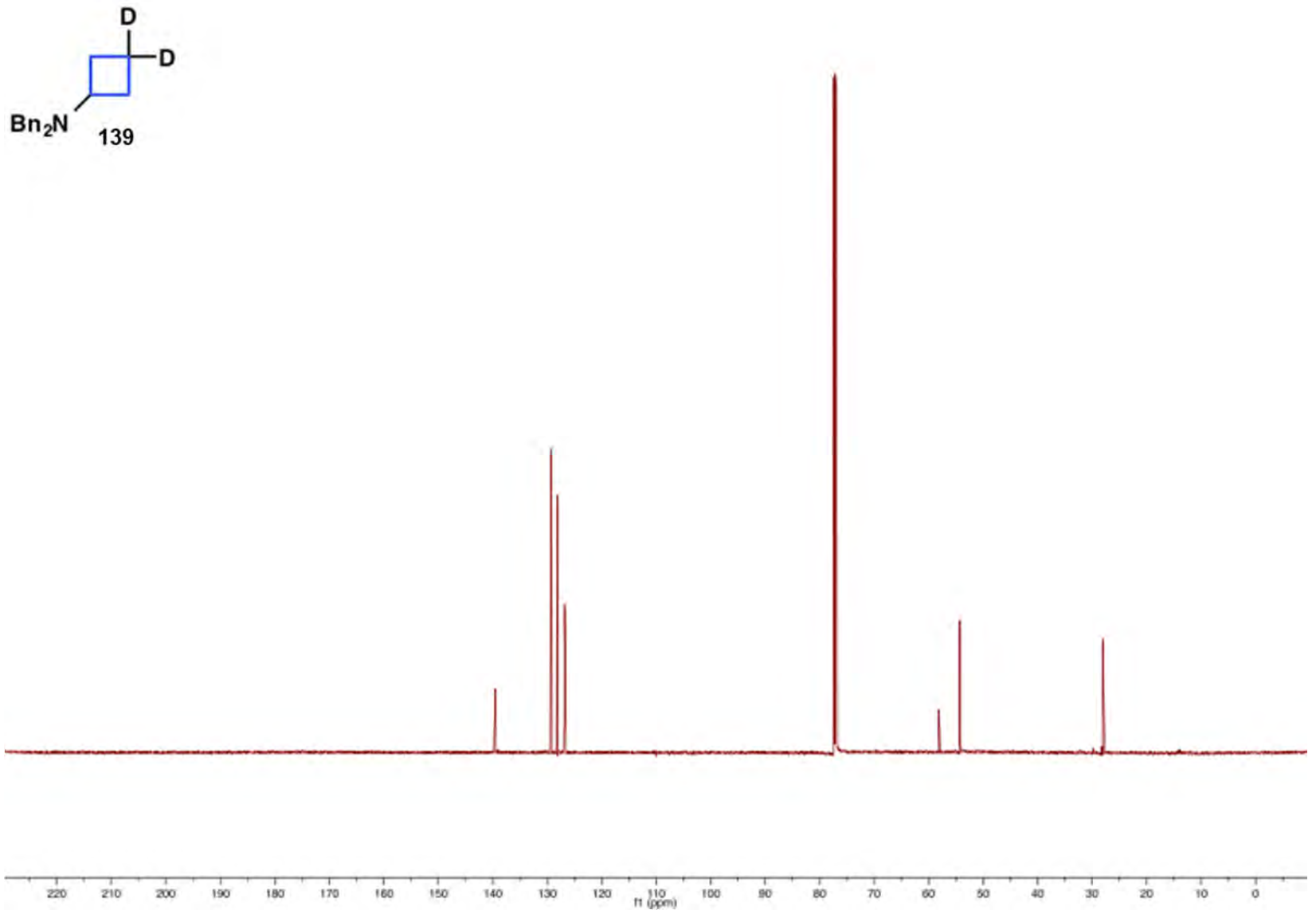
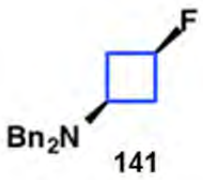
50
40
30
20
10
0
f1 (ppm)


D
D
Bn2N

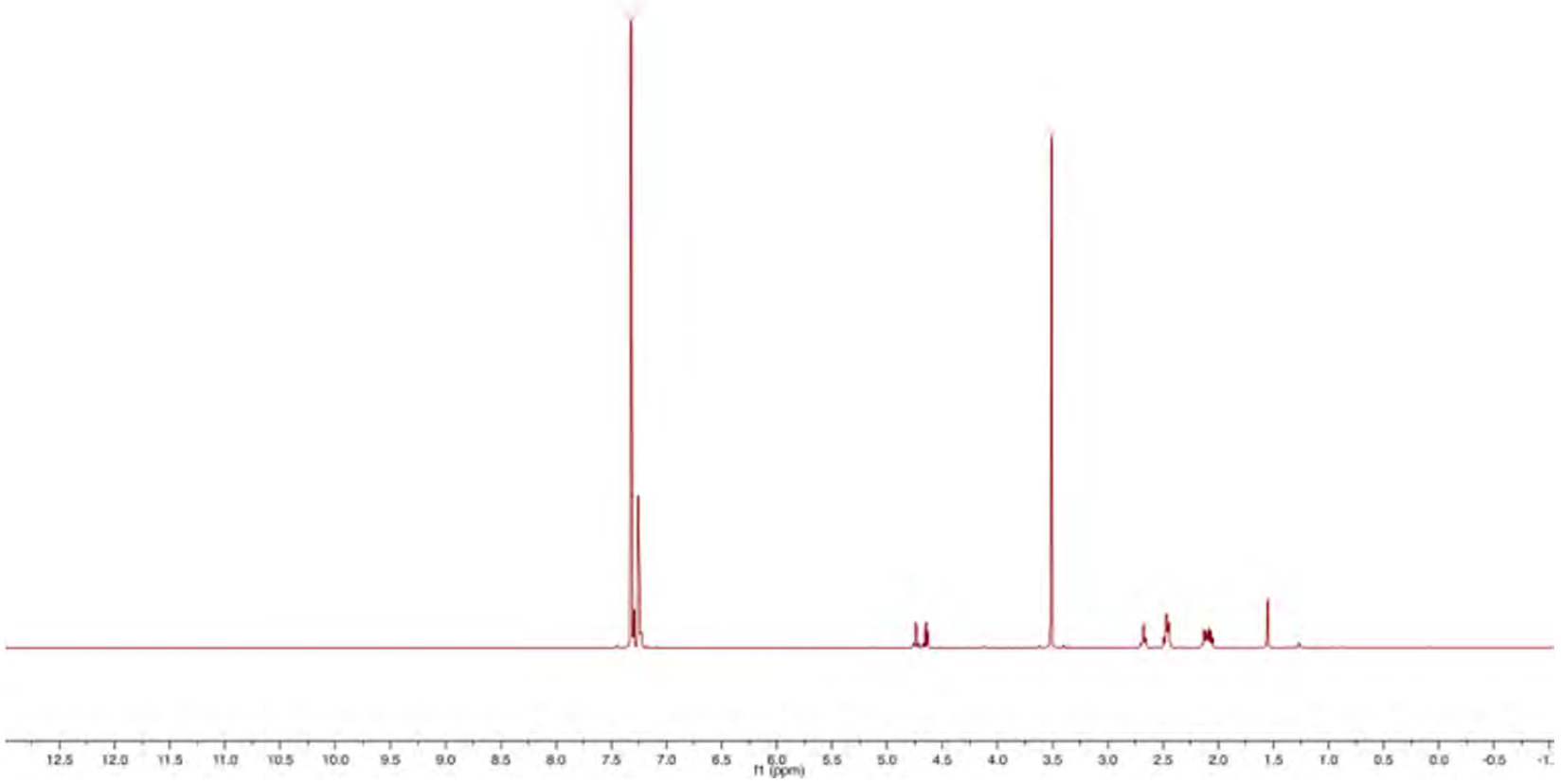
139

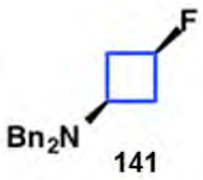

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


D
D
Bn2N
139
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)

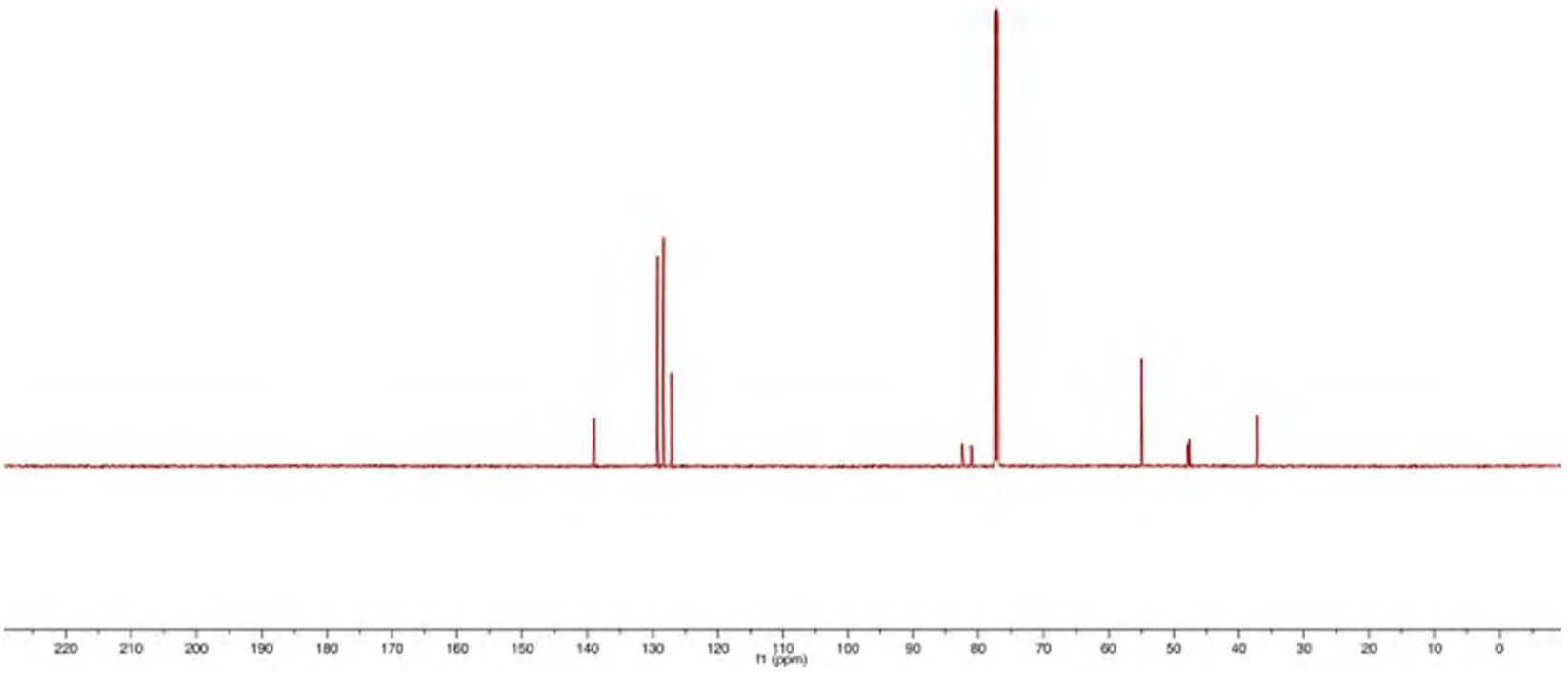

F
Bn2N

141


12.5 12.0 11.5 11.0 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)


F
Bn2N

141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210
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190
180
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150
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120
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100
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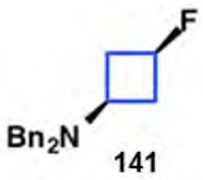
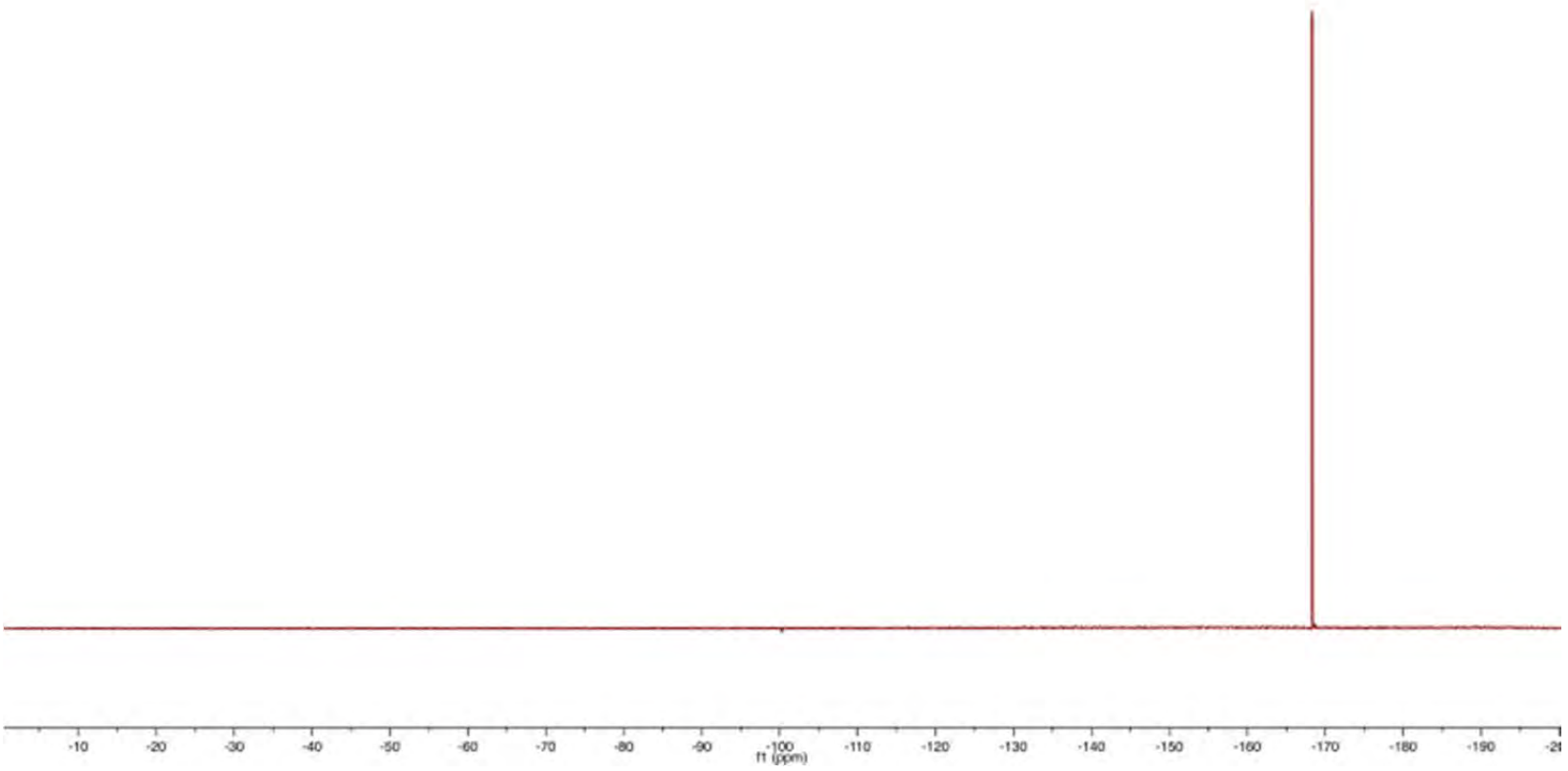
70
60
50
40
30
20
10
0
f1 (ppm)


F
Bn2N

141


-10
-20
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-50
-60
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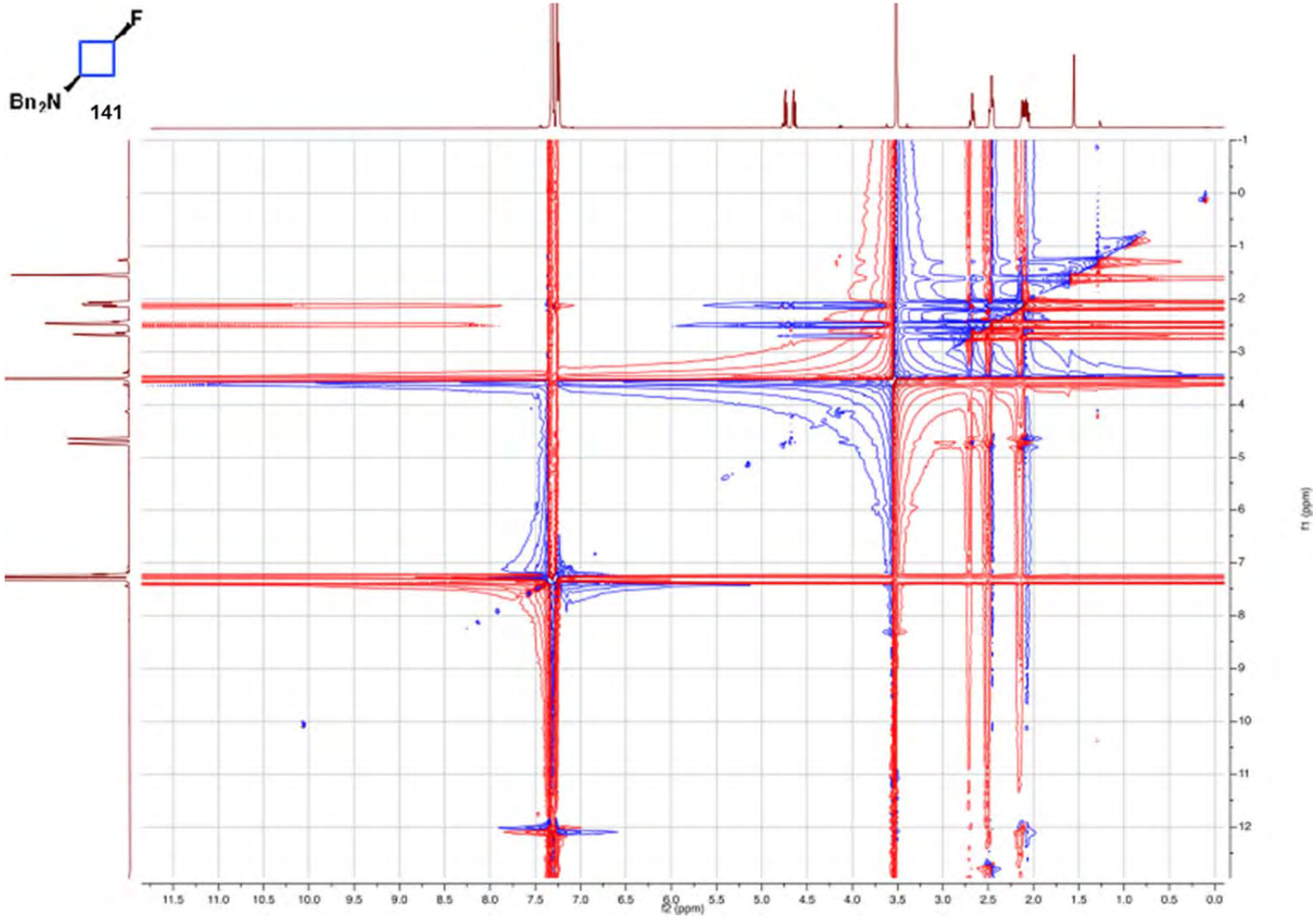
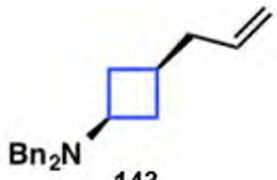
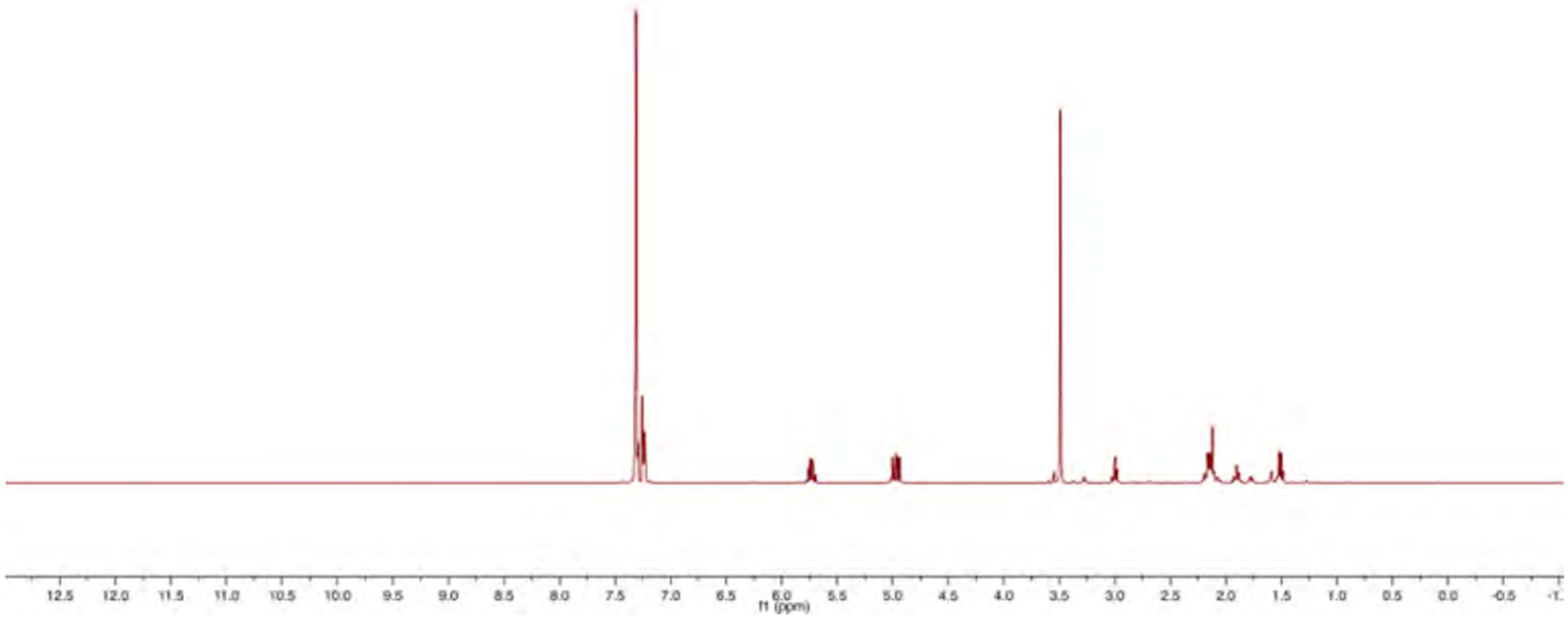
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190

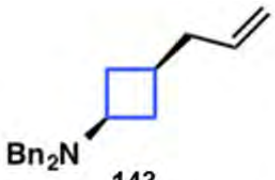

F
Bn2N
141
f2 (ppm)
f1 (ppm)



143

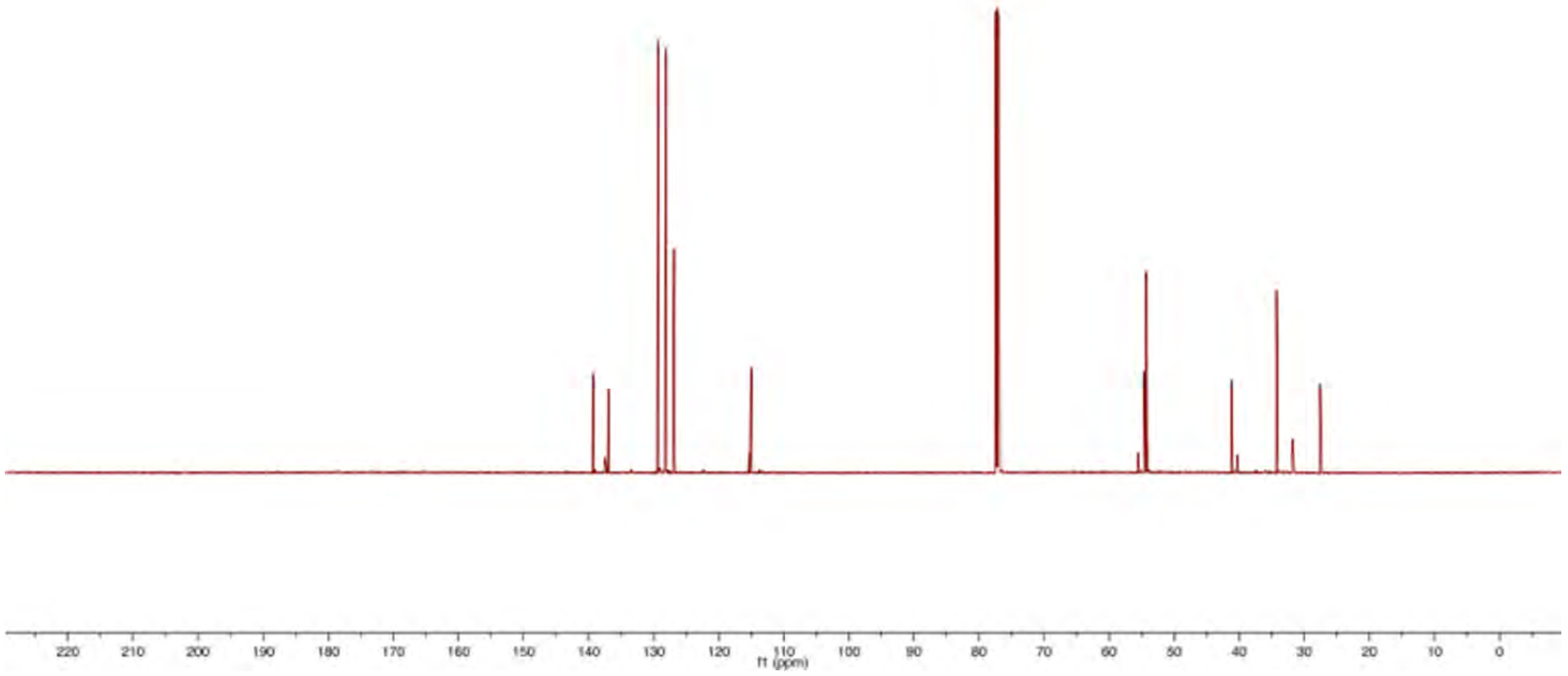
[+ minor amt. of trans isomer]

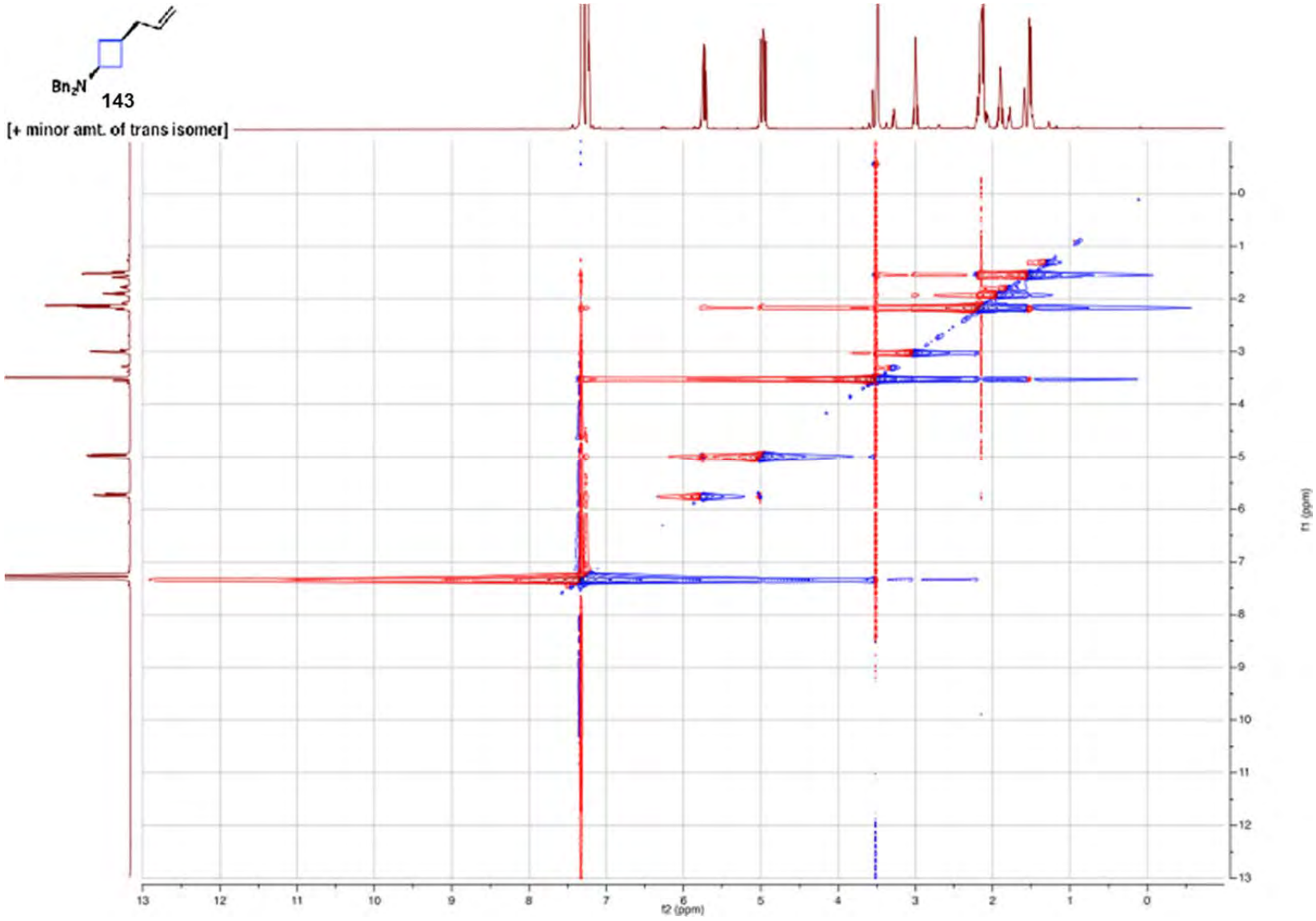


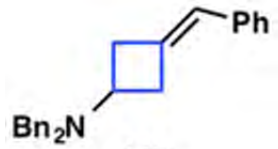


143

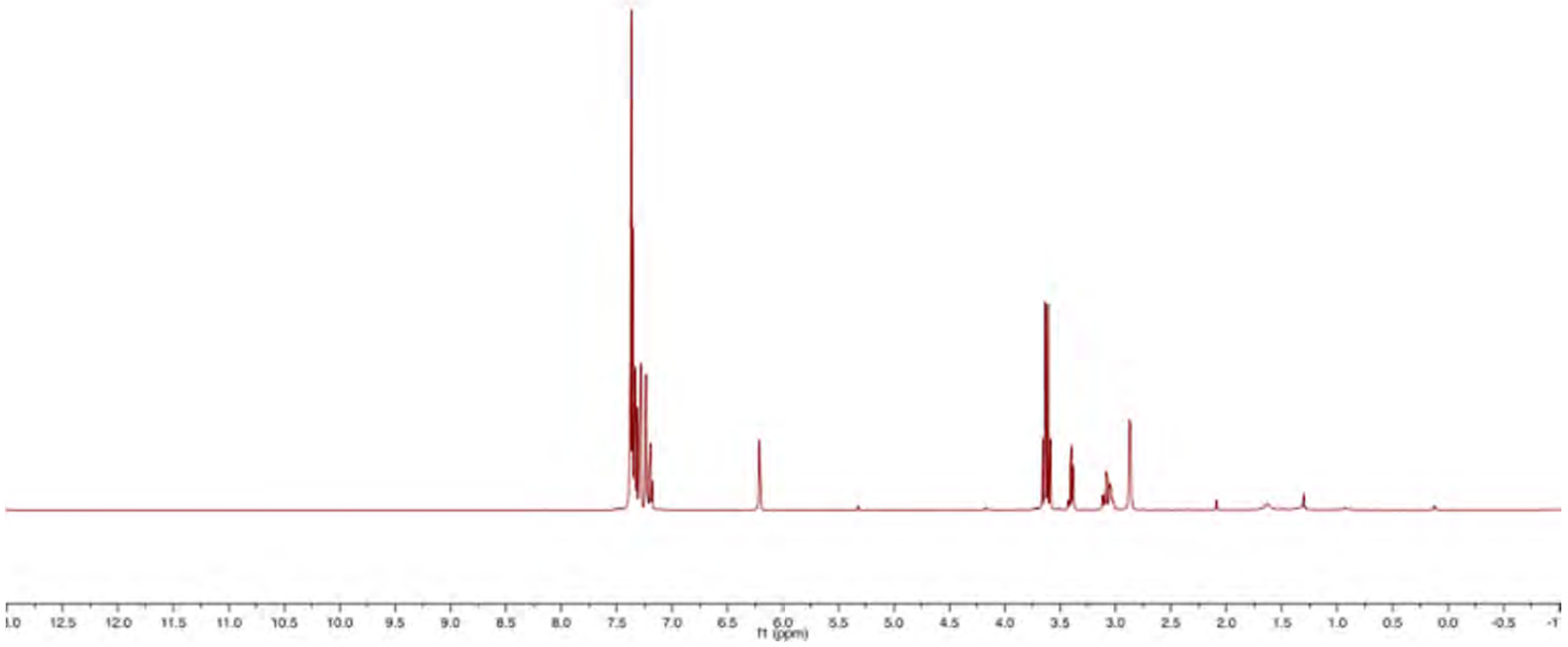
[+ minor amt. of trans isomer]

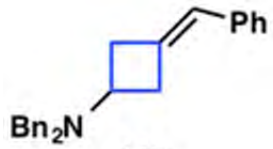



Bn2N
143
[+ minor amt. of trans isomer]
f2 (ppm)
f1 (ppm)

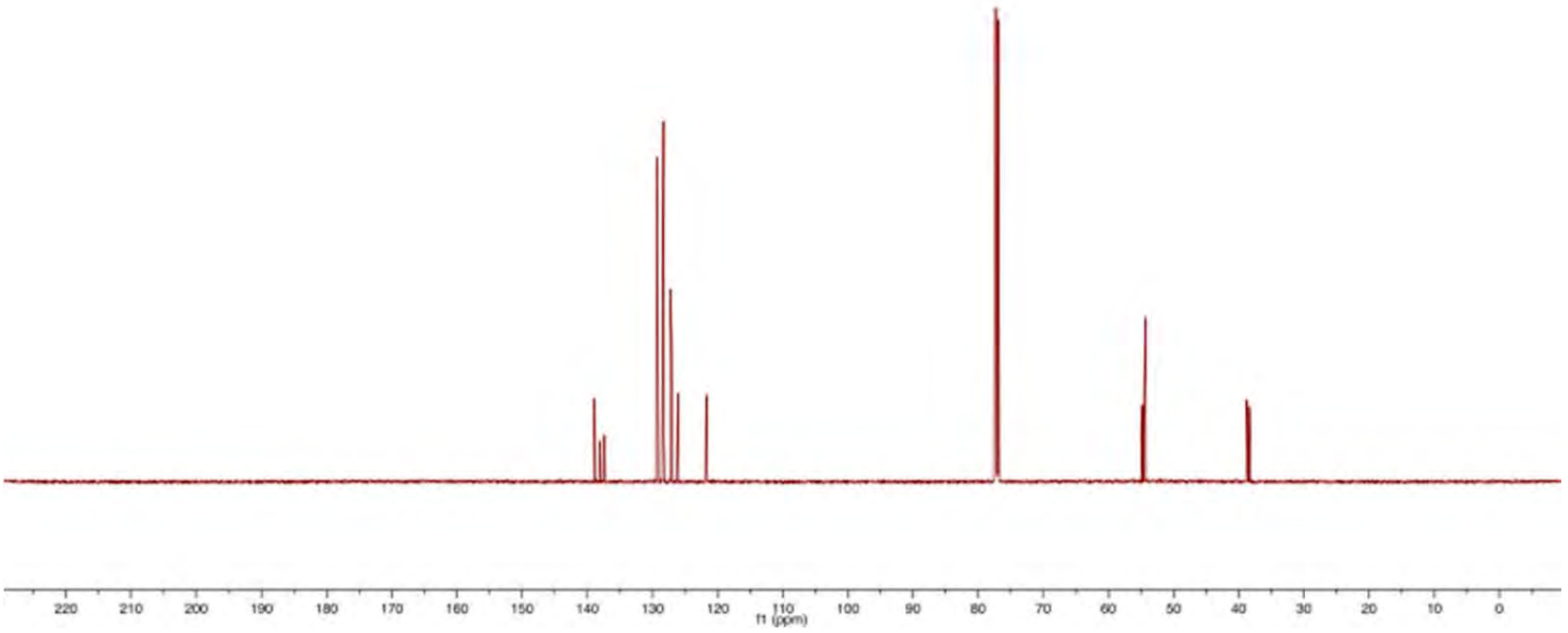


145




Ph
Bn2N

145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130
120
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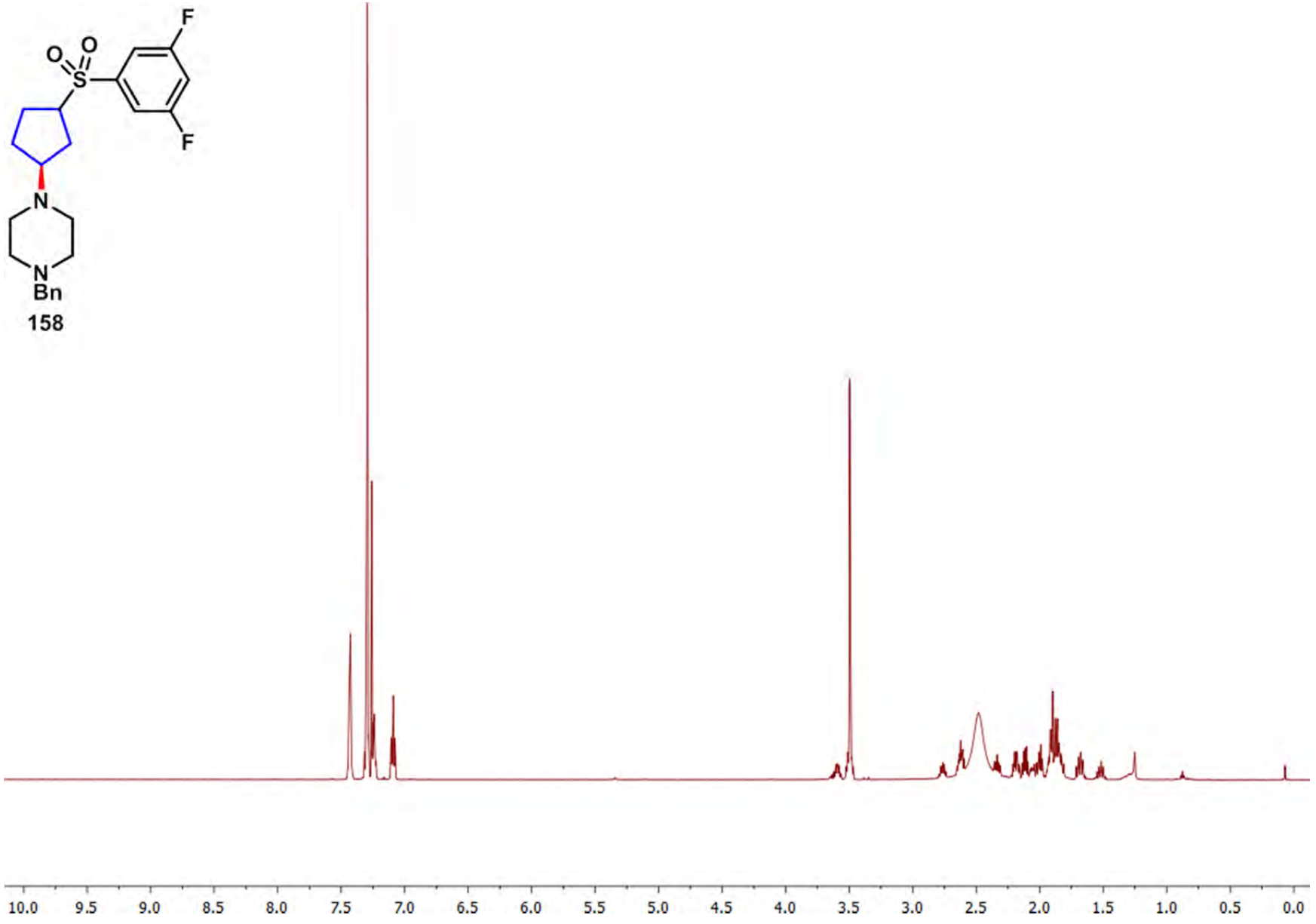
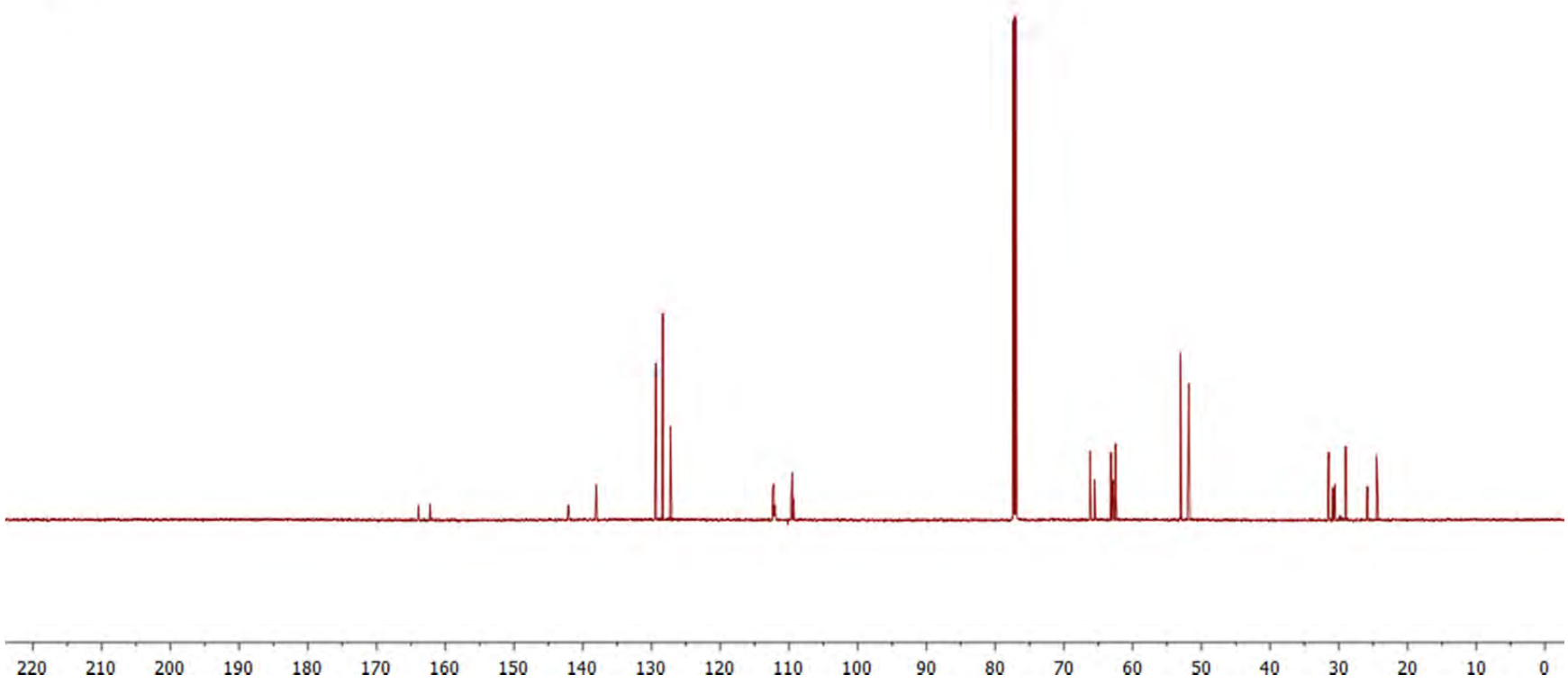
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
O
O
S
F
N
N
Bn
158
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


F
O
O
S
F
N
N
Bn

158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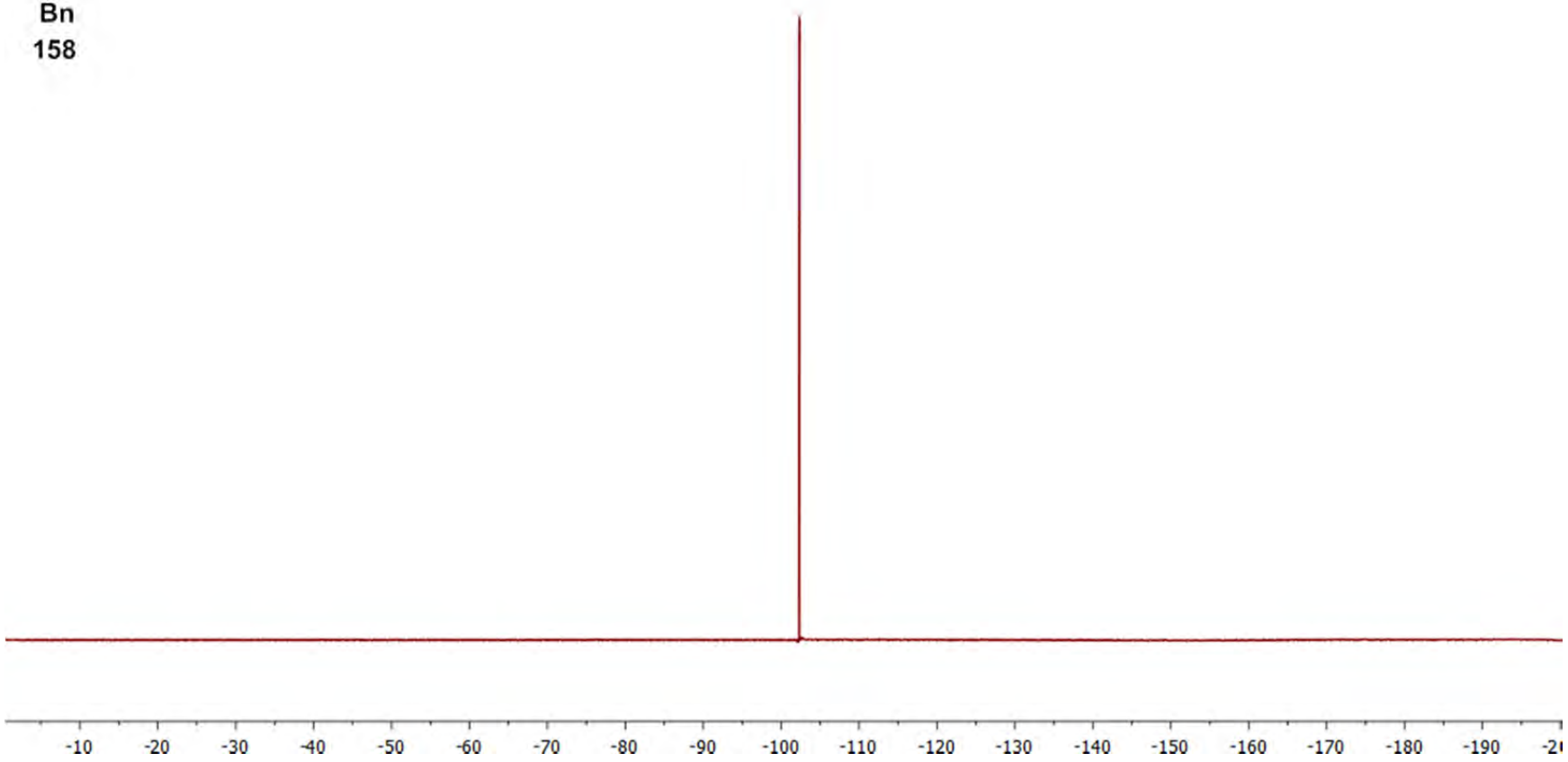
0


F
O
O
S
F
N
N
Bn

158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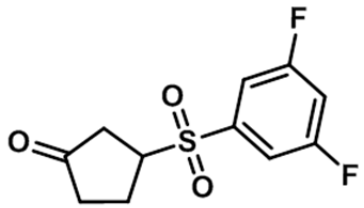
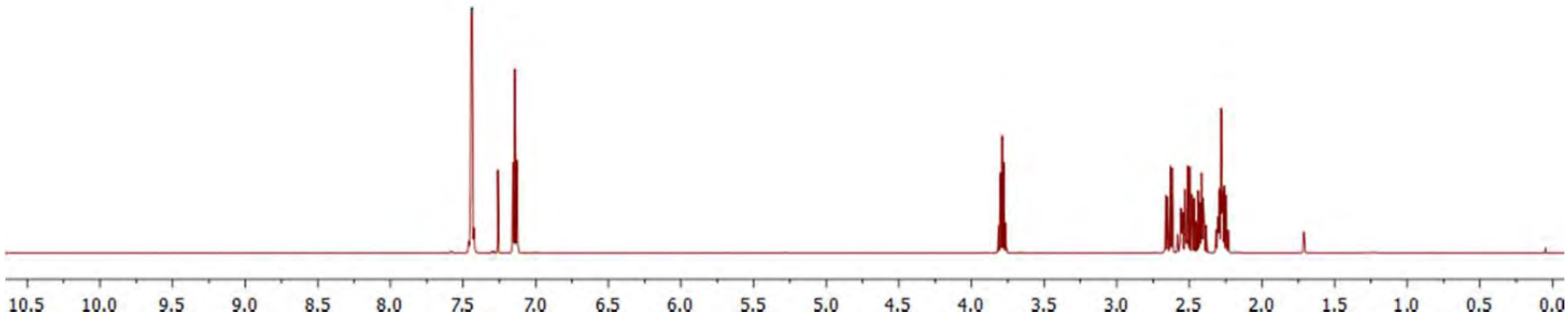
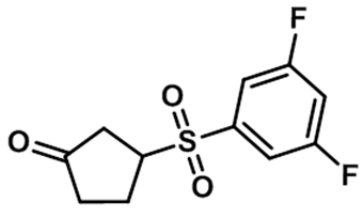
-160
-170
-180
-190

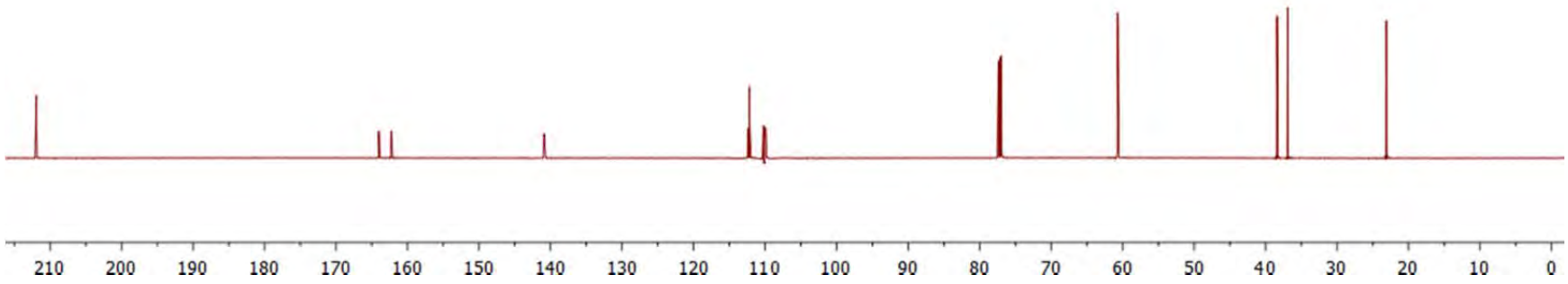

F
O
S
O
O
F

163


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


F
O
S
O
O
F

163


210
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190
180
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150
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110
100
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80
70
60
50
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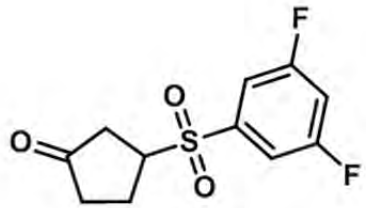
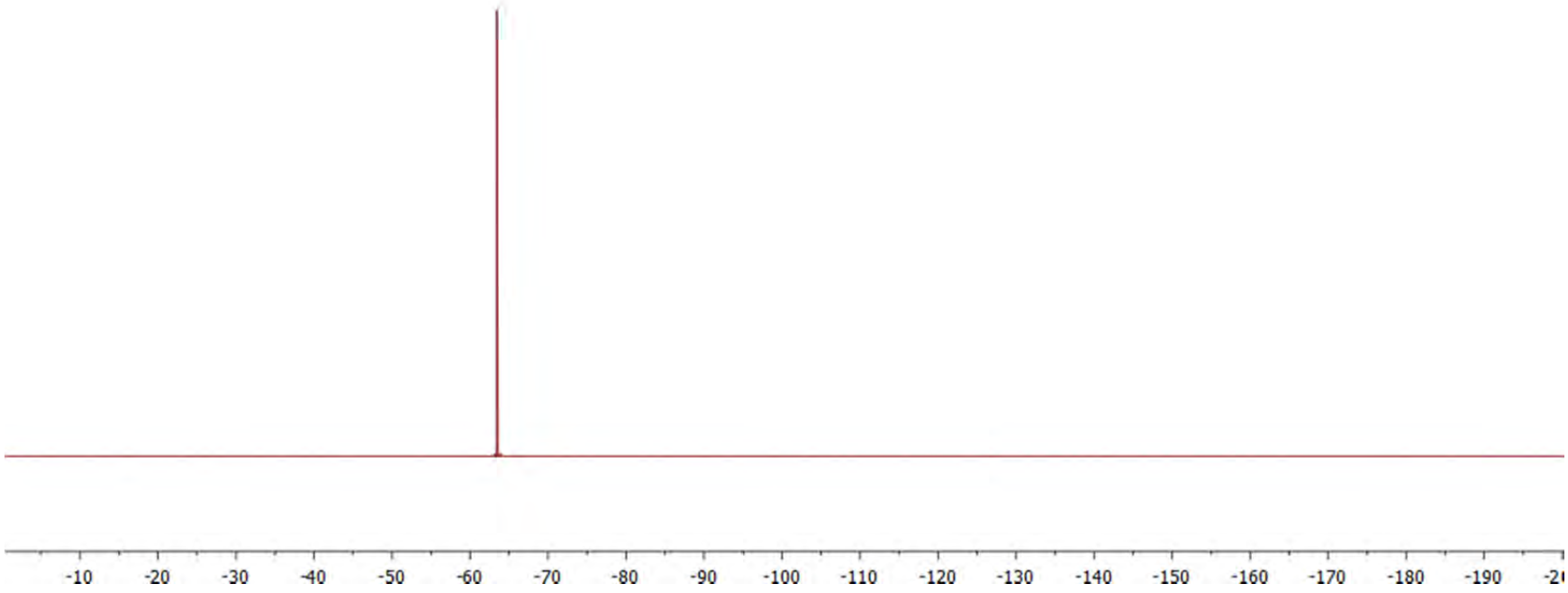
30
20
10
0


F
O
S
O
O
F

163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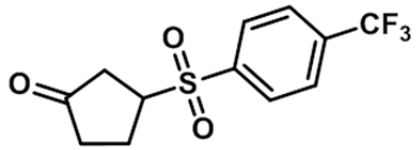
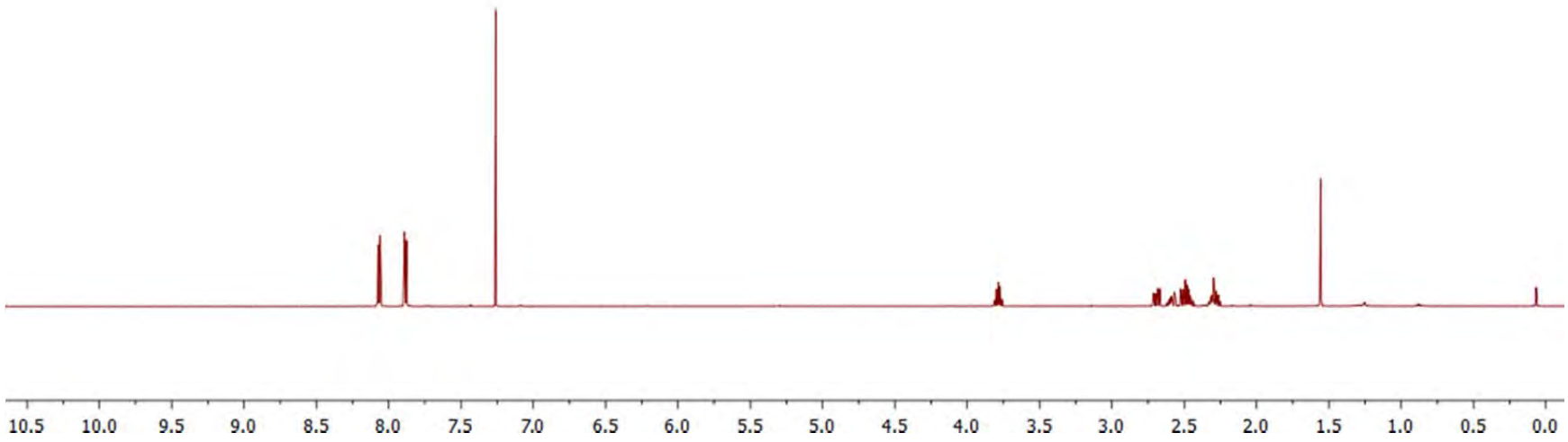
-180
-190


O
O
S
O
CF3

164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10.0
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8.0
7.5
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6.0
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4.5
4.0
3.5
3.0
2.5
2.0
1.5
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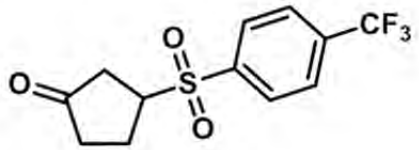
O
O
S
O
CF3

164

220
210
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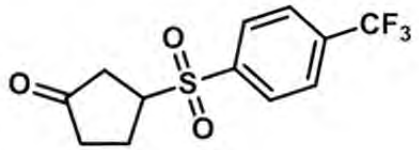
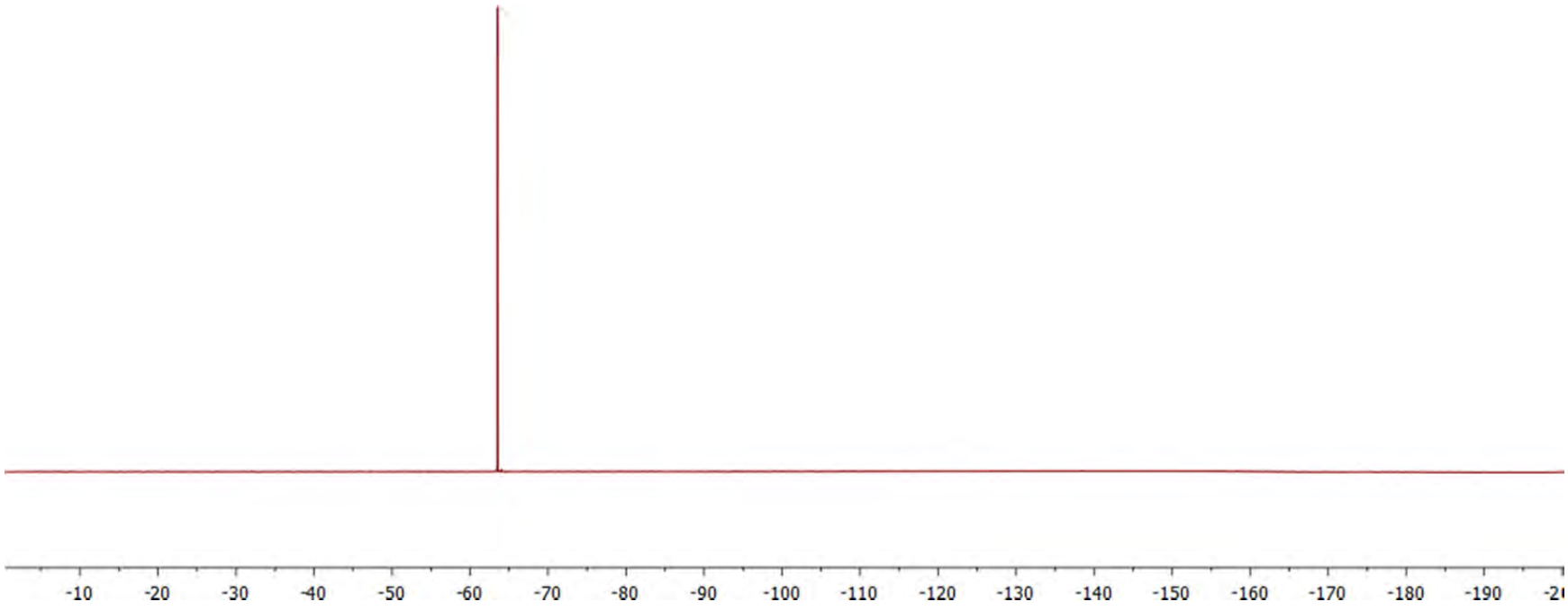
0


O
O
S
O
CF3

164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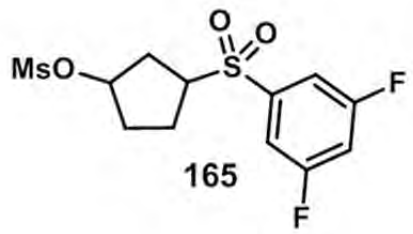
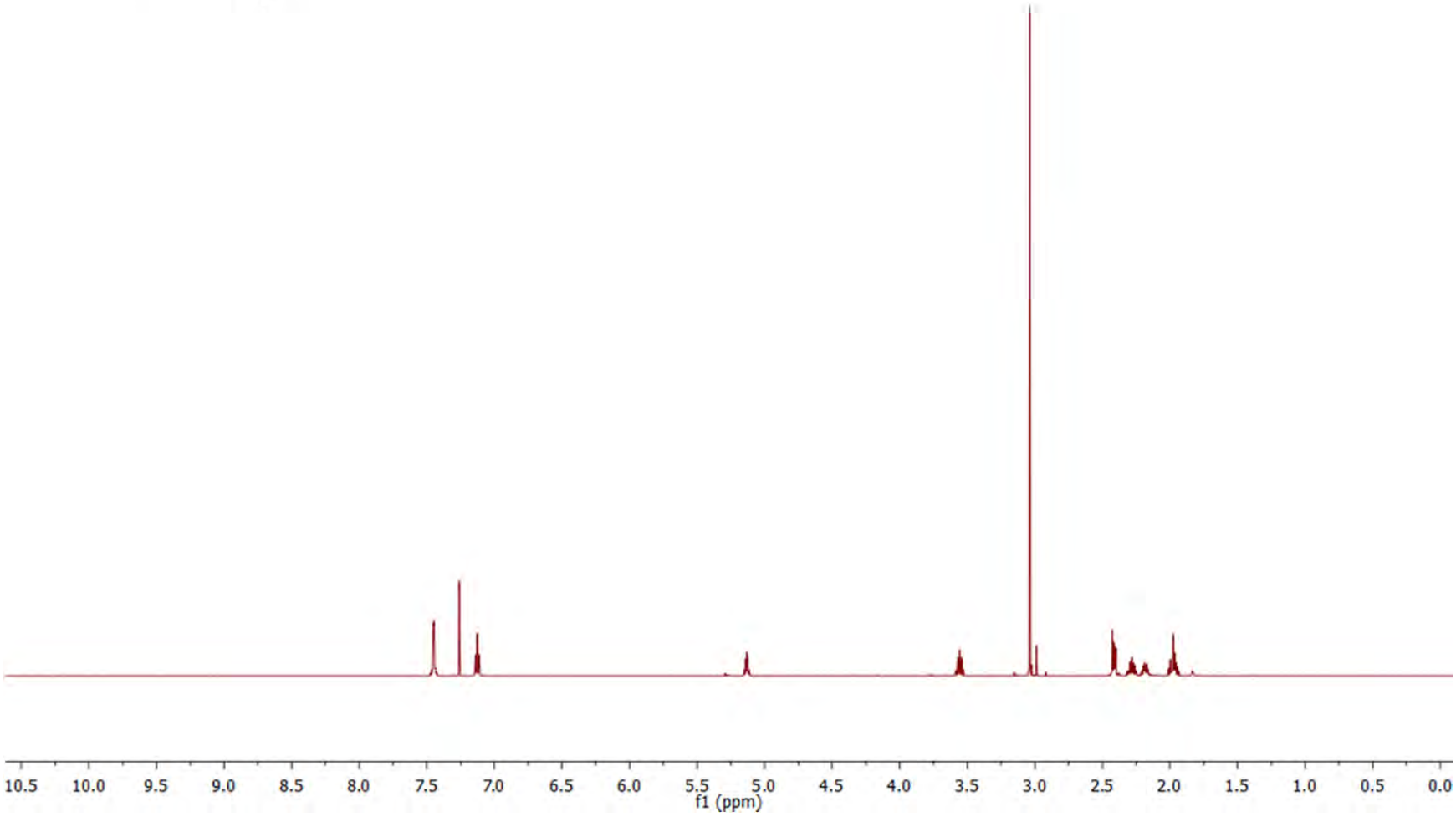

MsO
O
O
S
F
F

165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10.0
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9.0
8.5
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6.0
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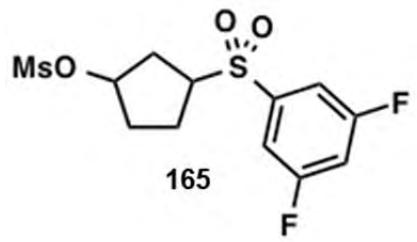
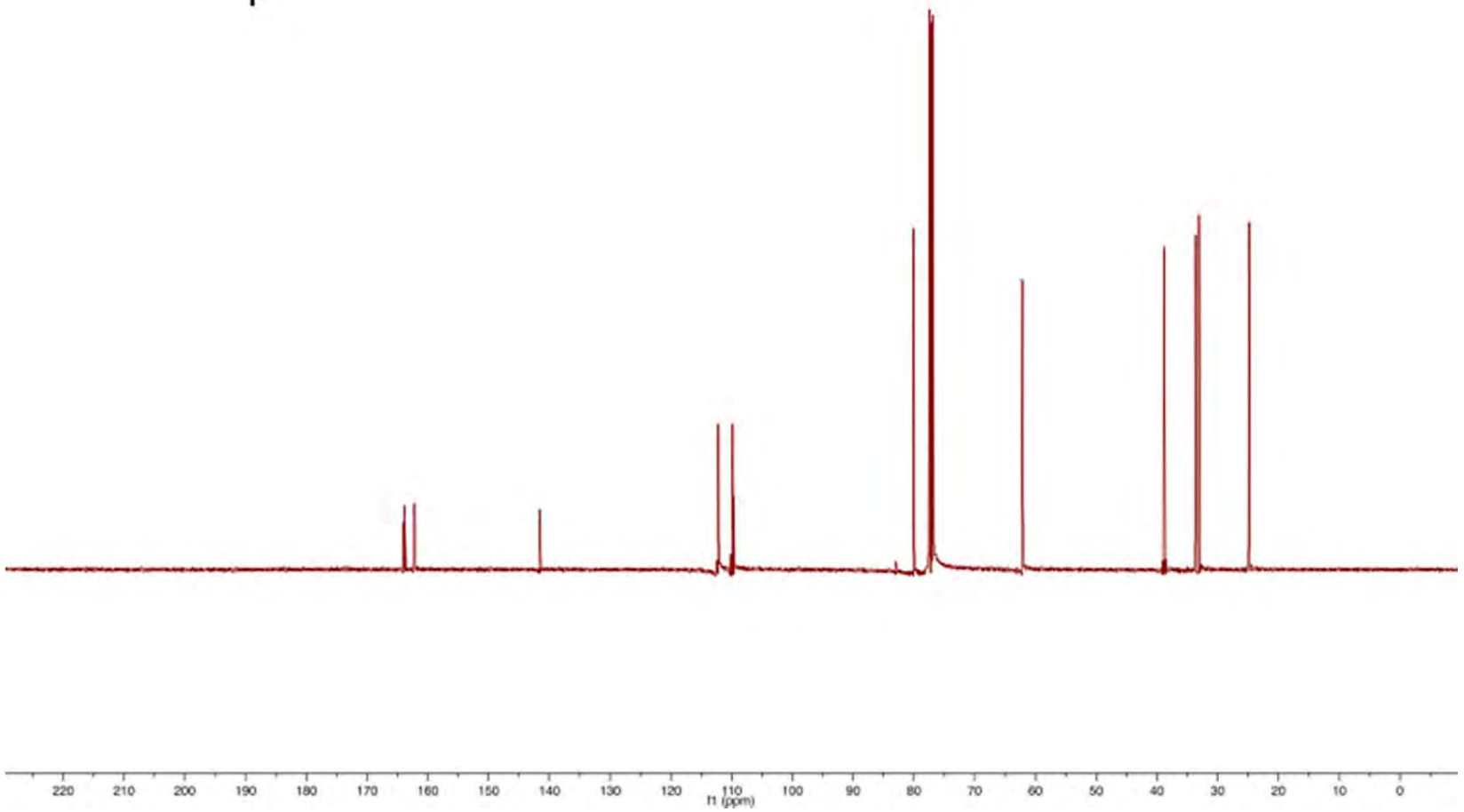
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MsO
O
O
S
F
F

165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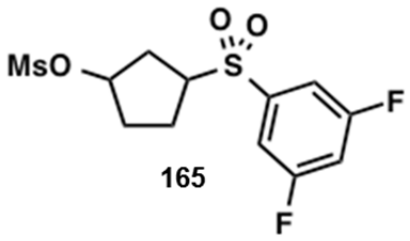
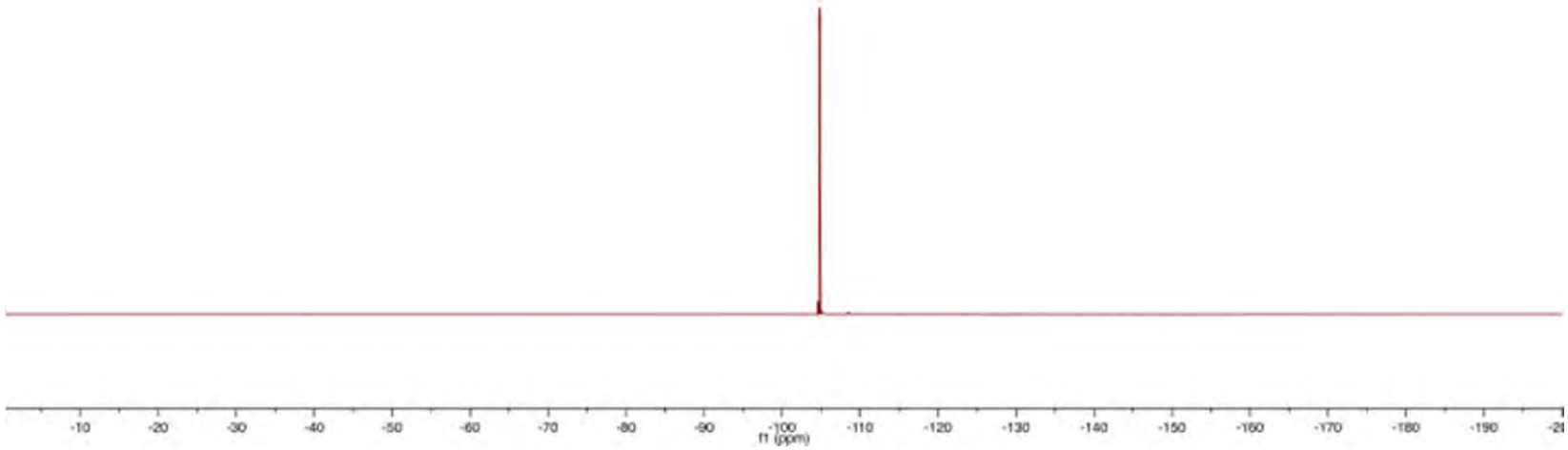
10
0
f1 (ppm)


MsO
O
O
S
F
F

165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-50
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-70
-80
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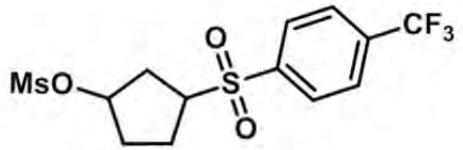
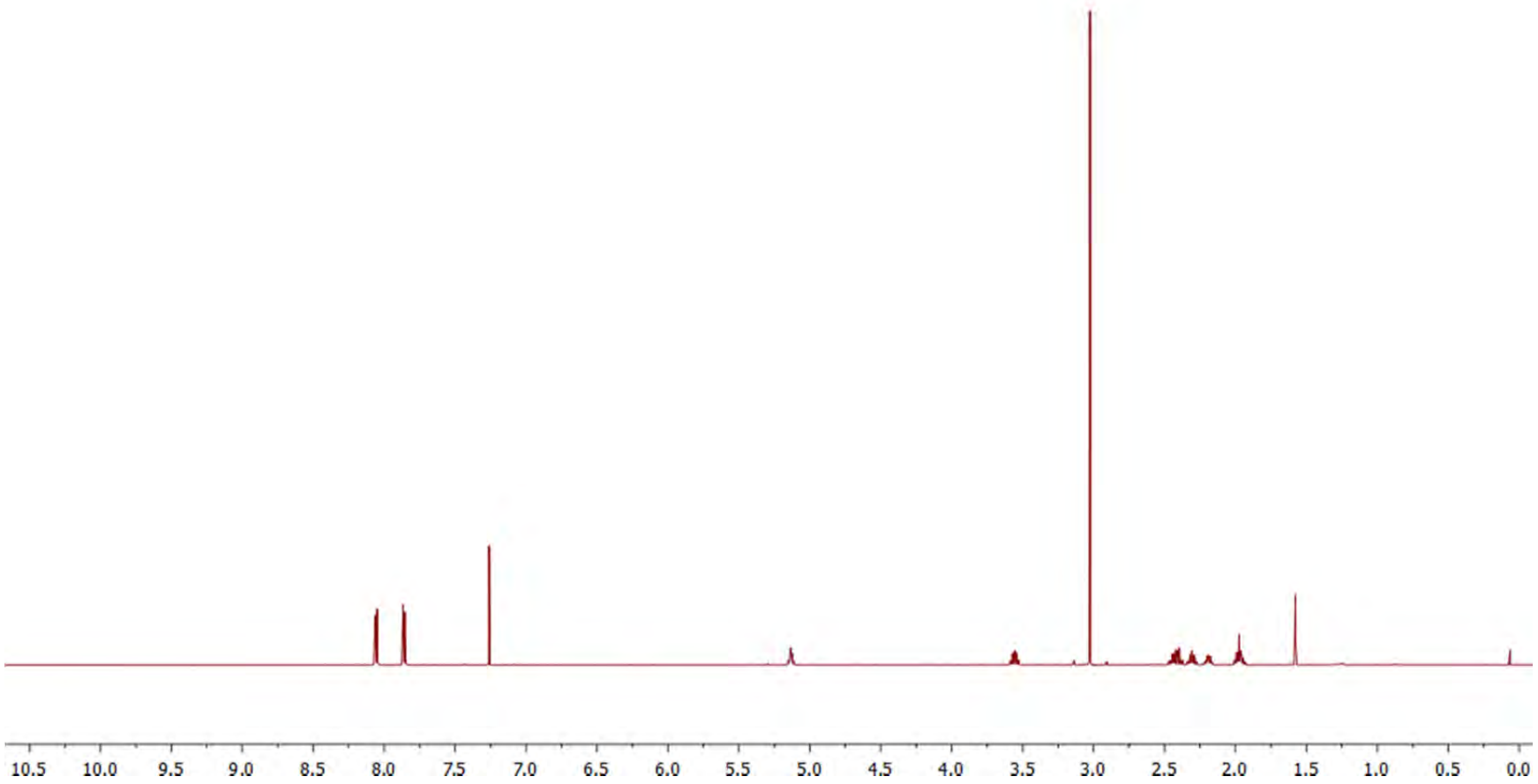
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190


MsO
O
S
O
CF3

166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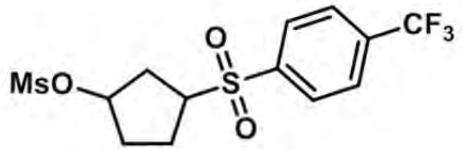
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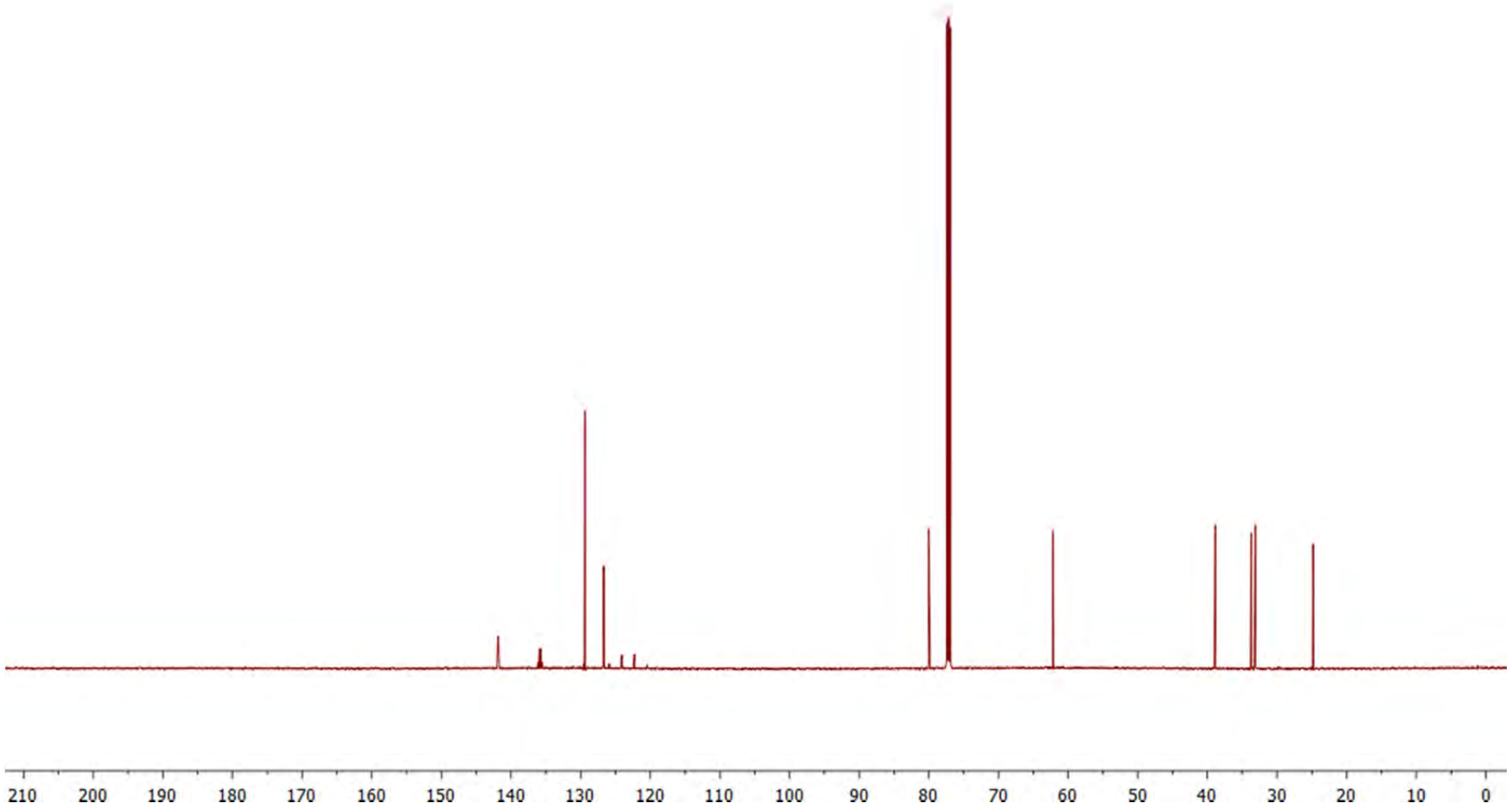
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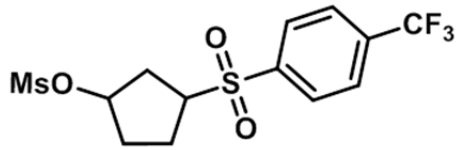
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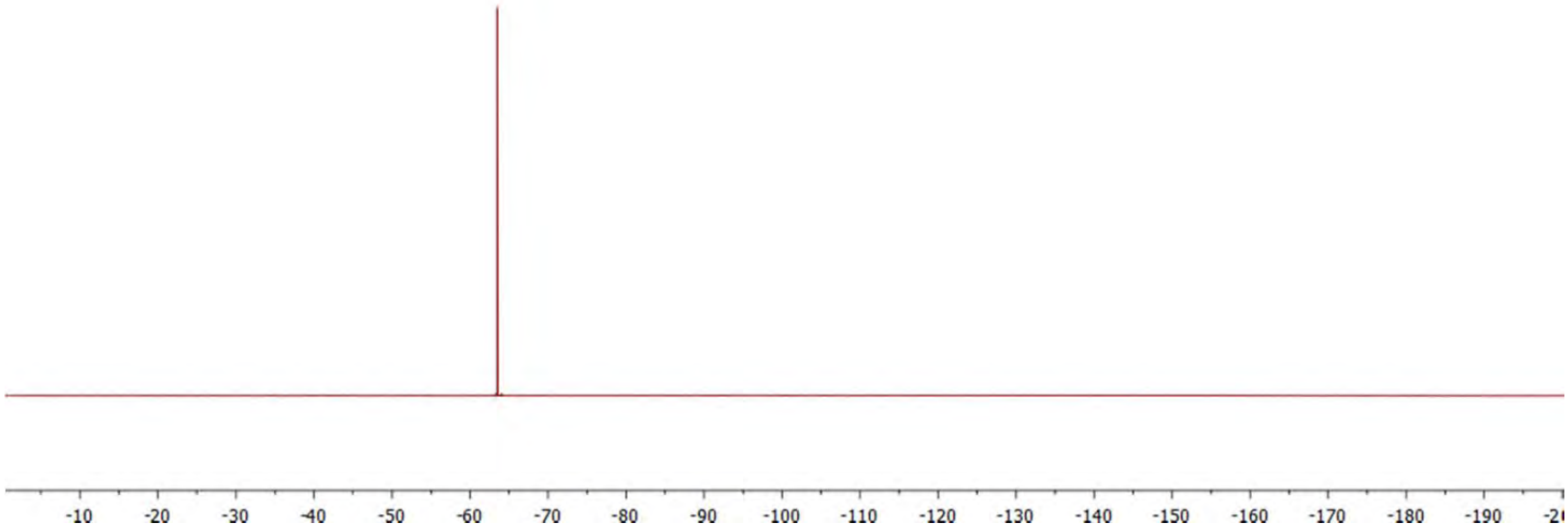
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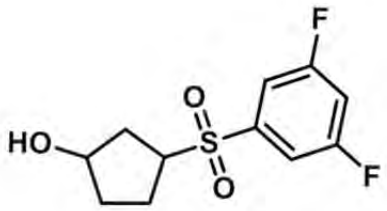
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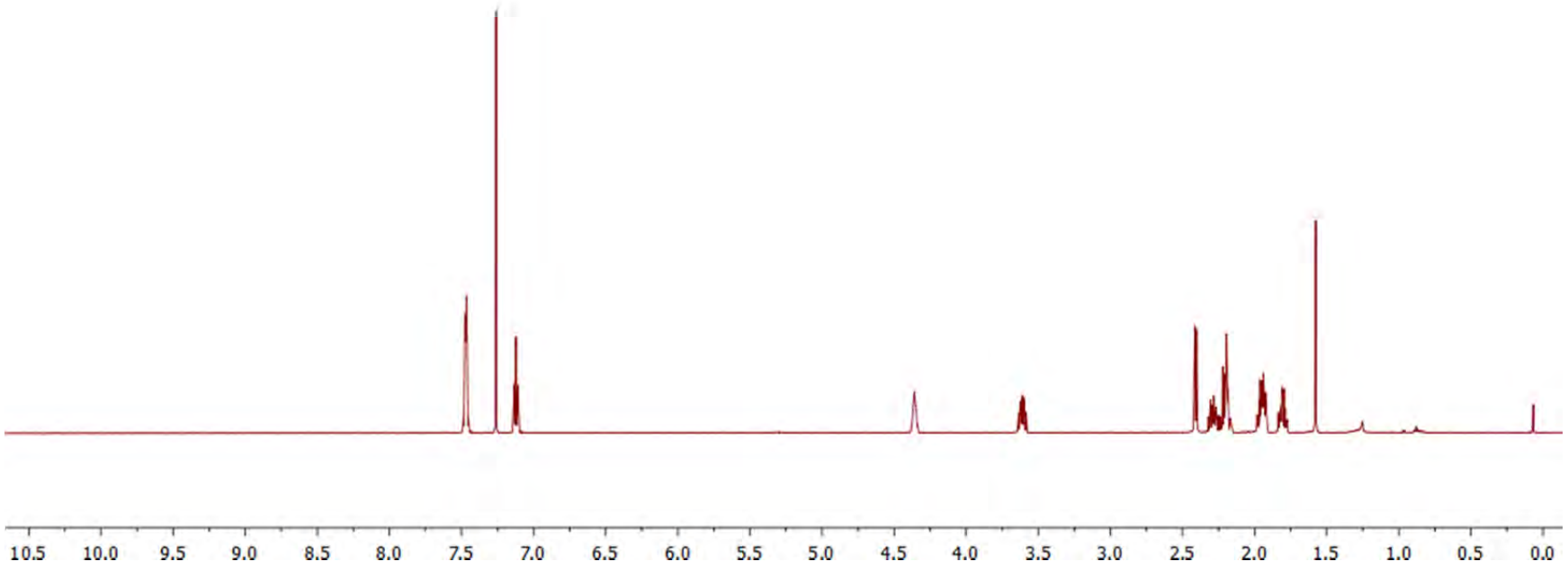
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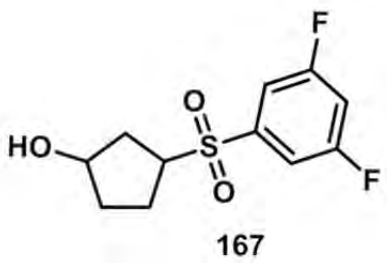
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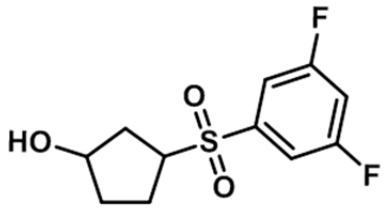
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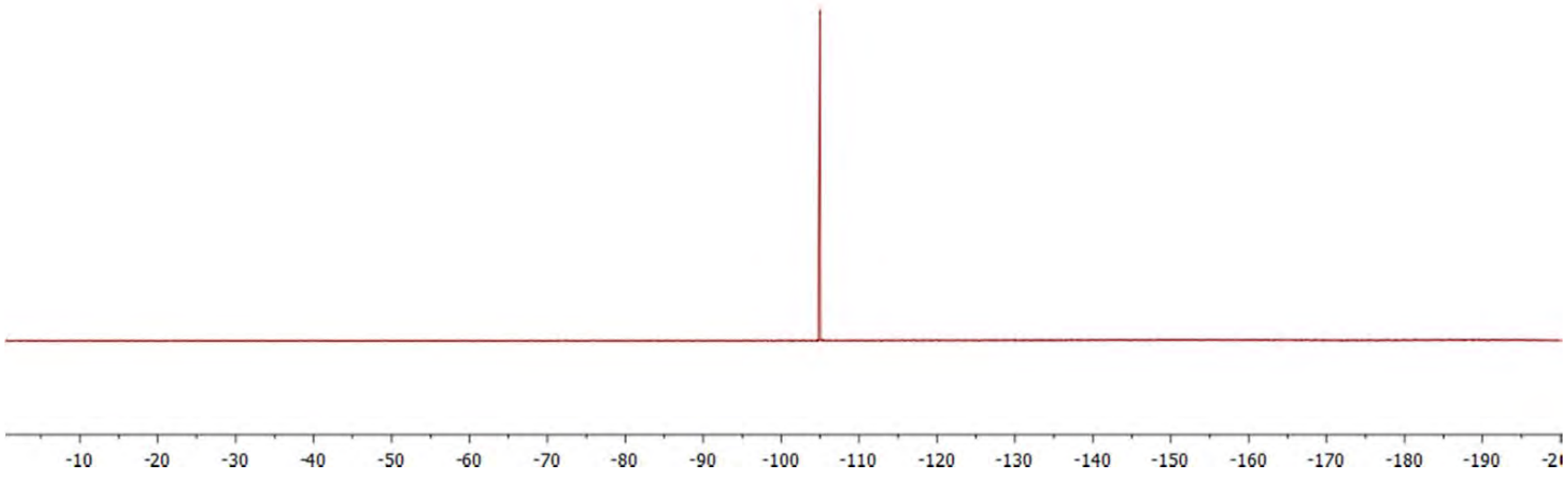
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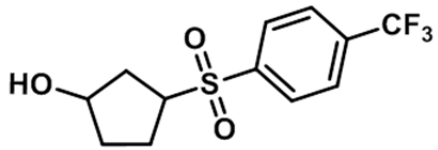
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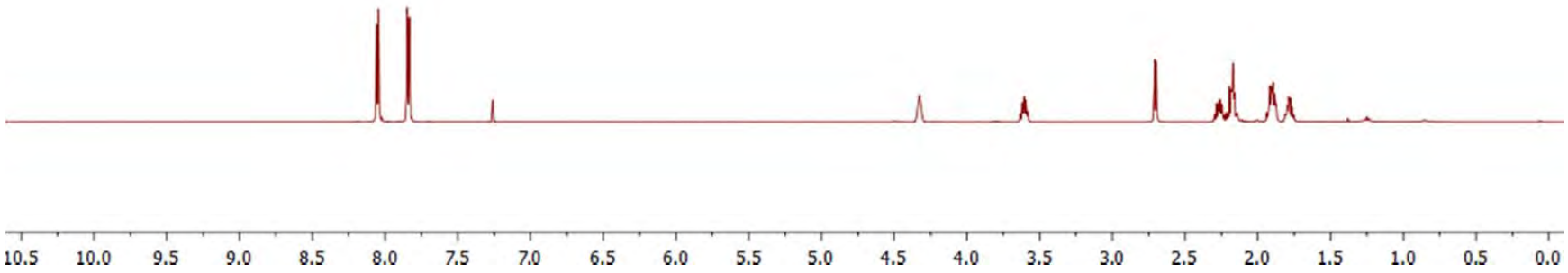
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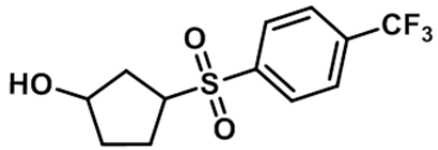
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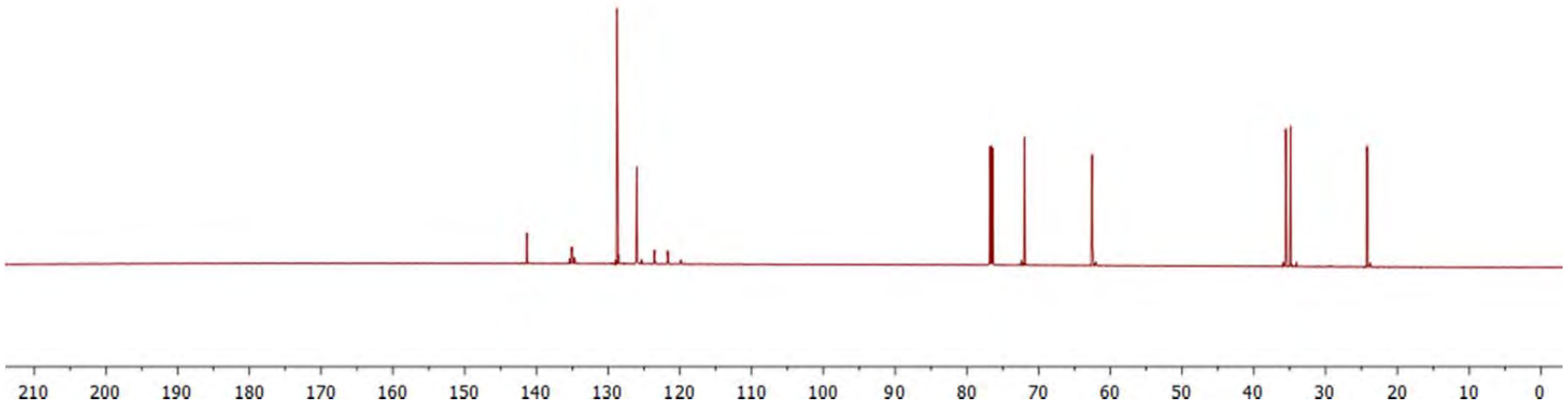
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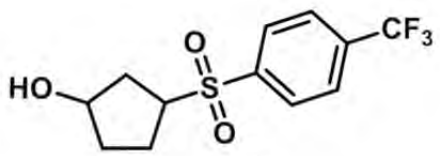
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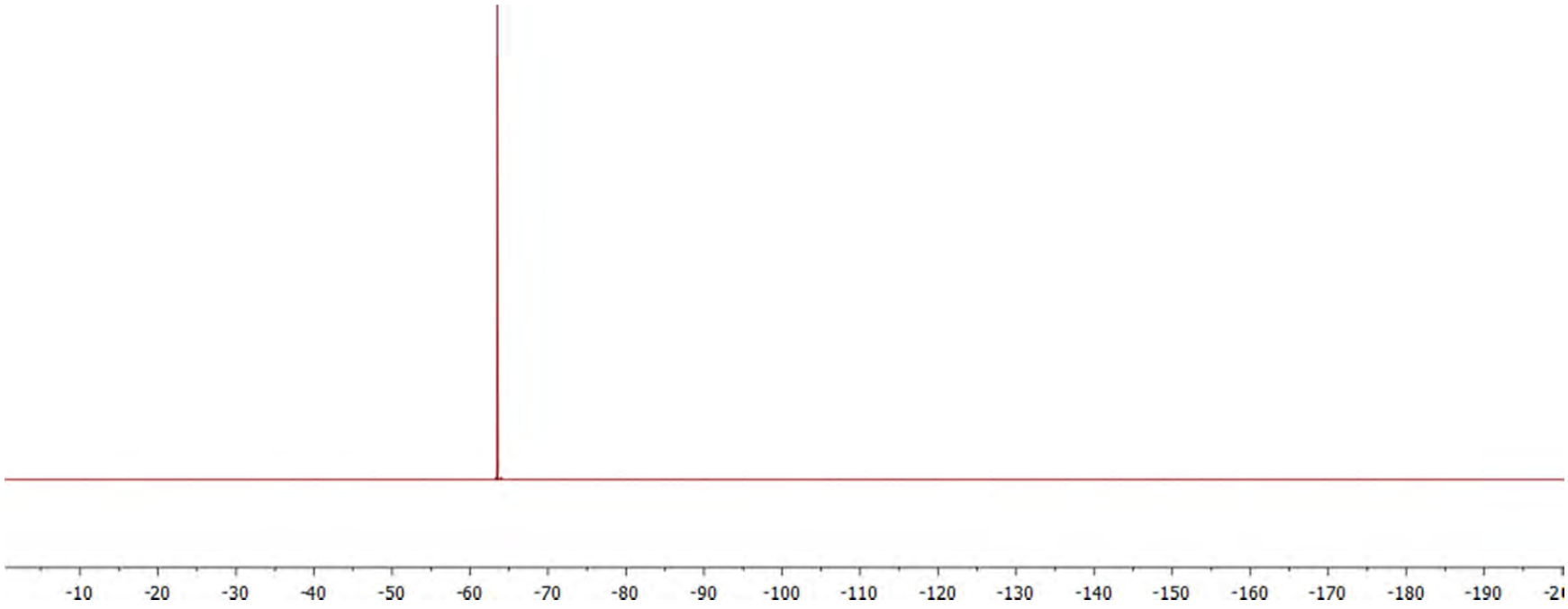
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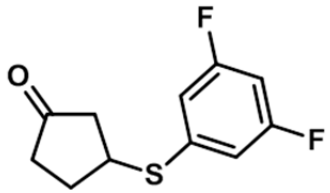

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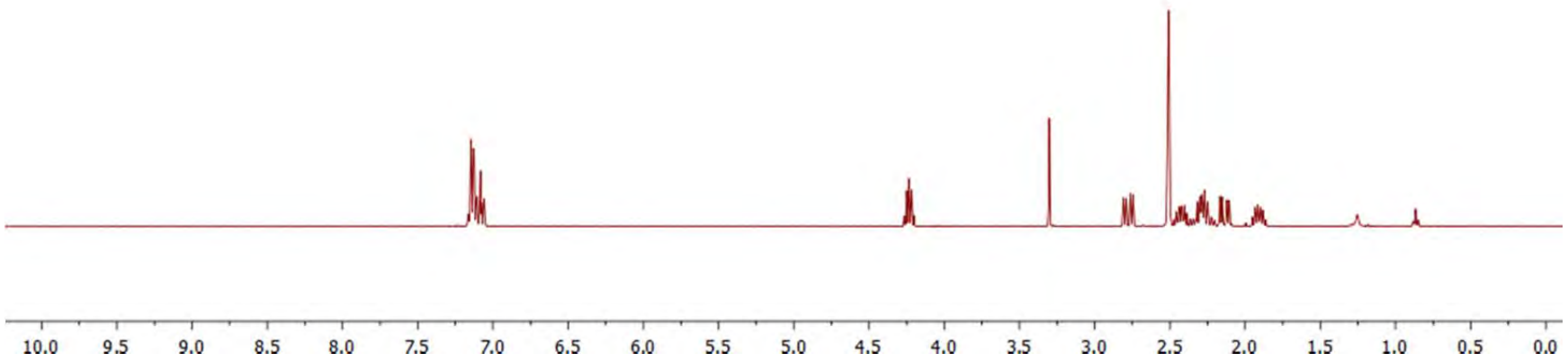

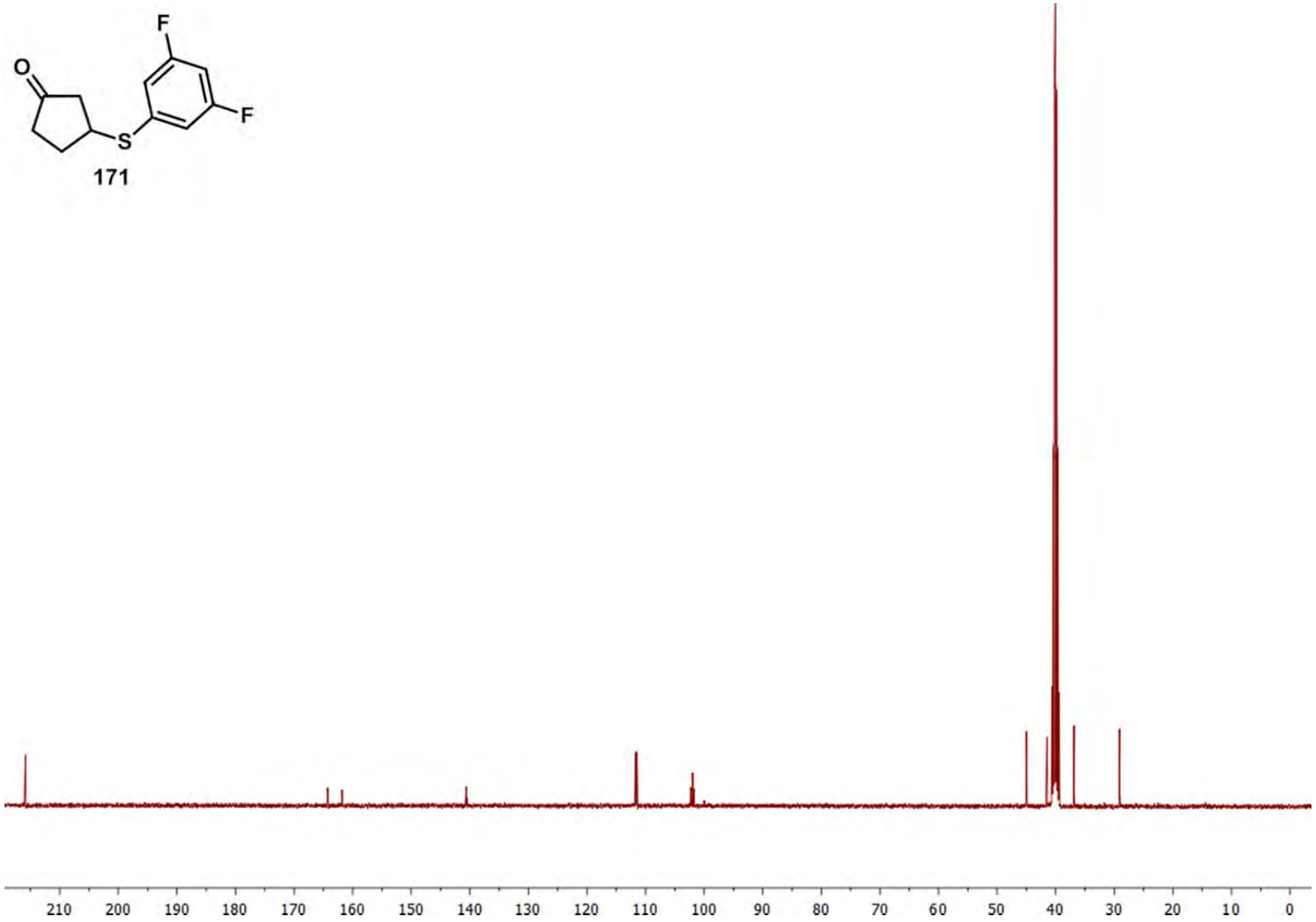
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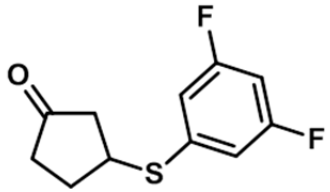
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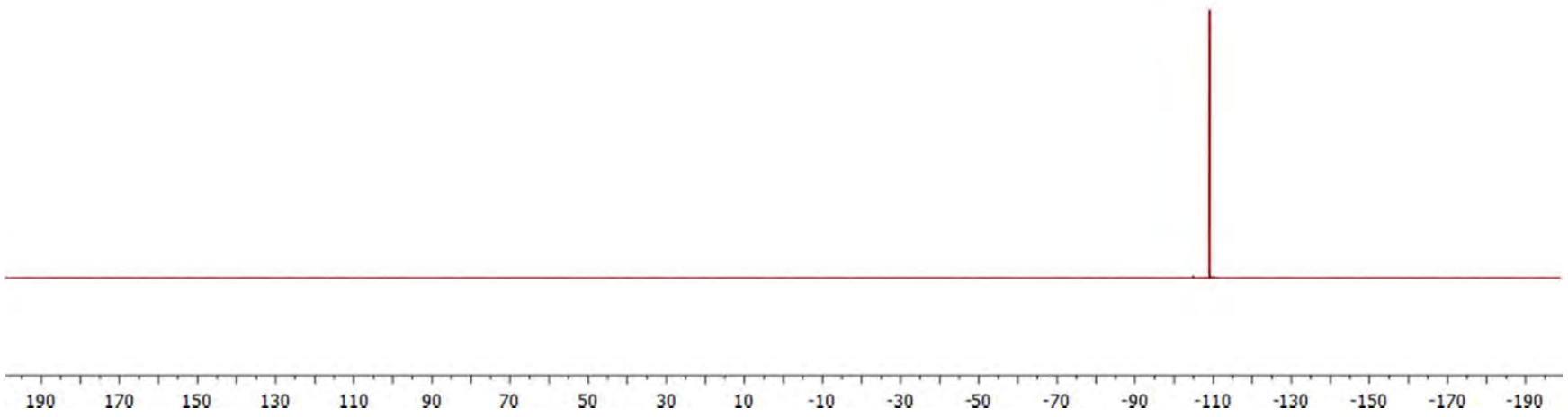
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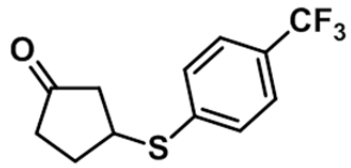
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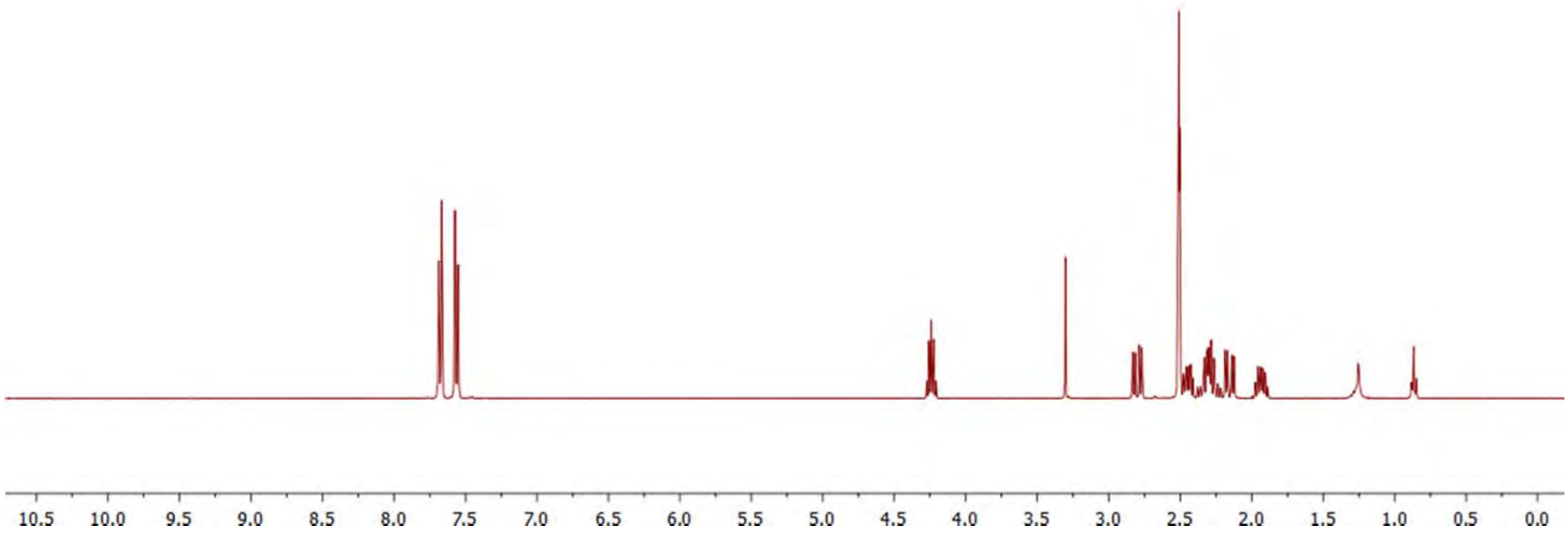
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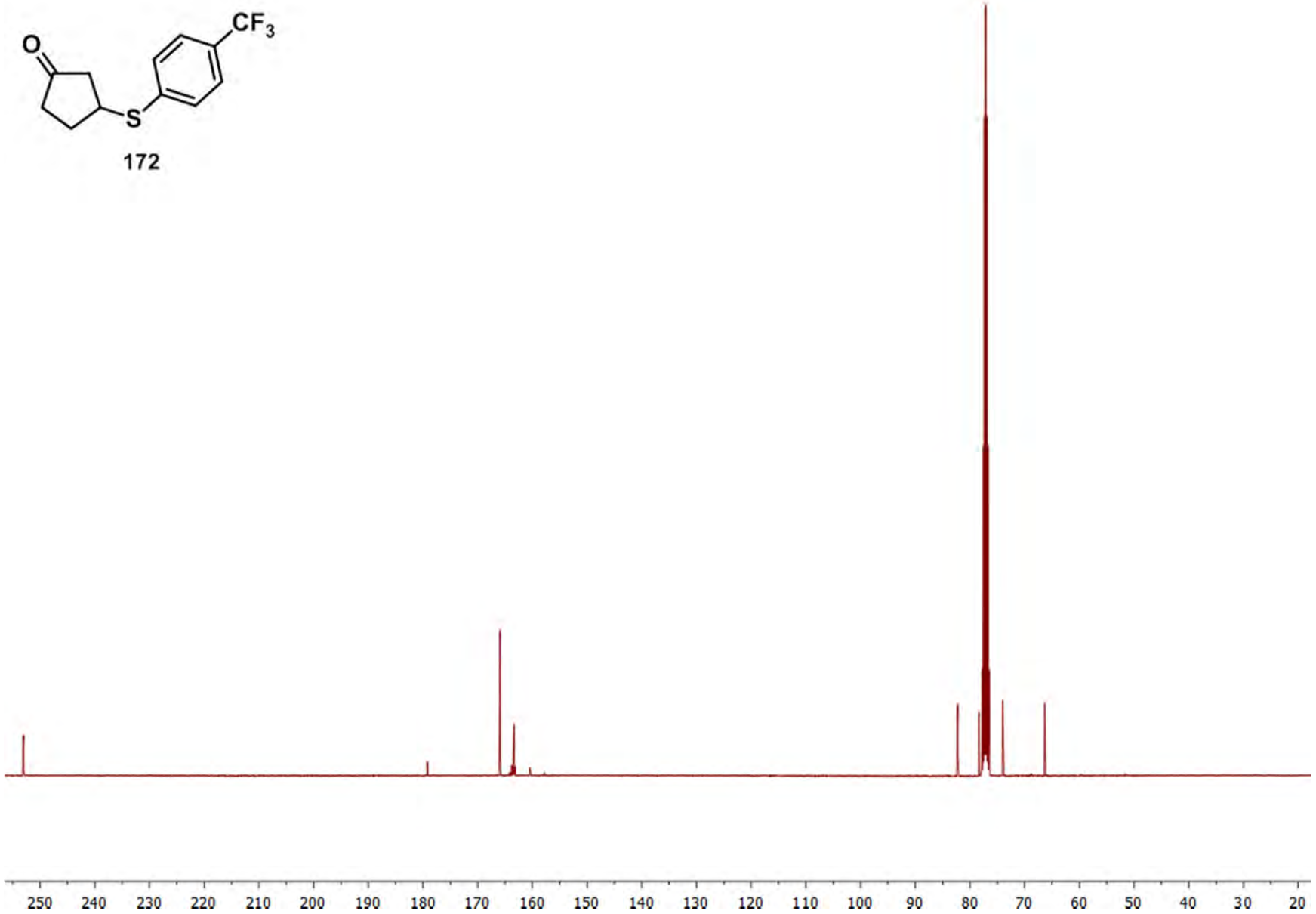
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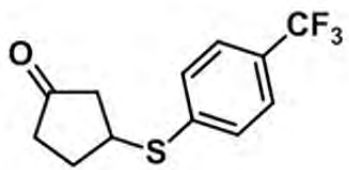
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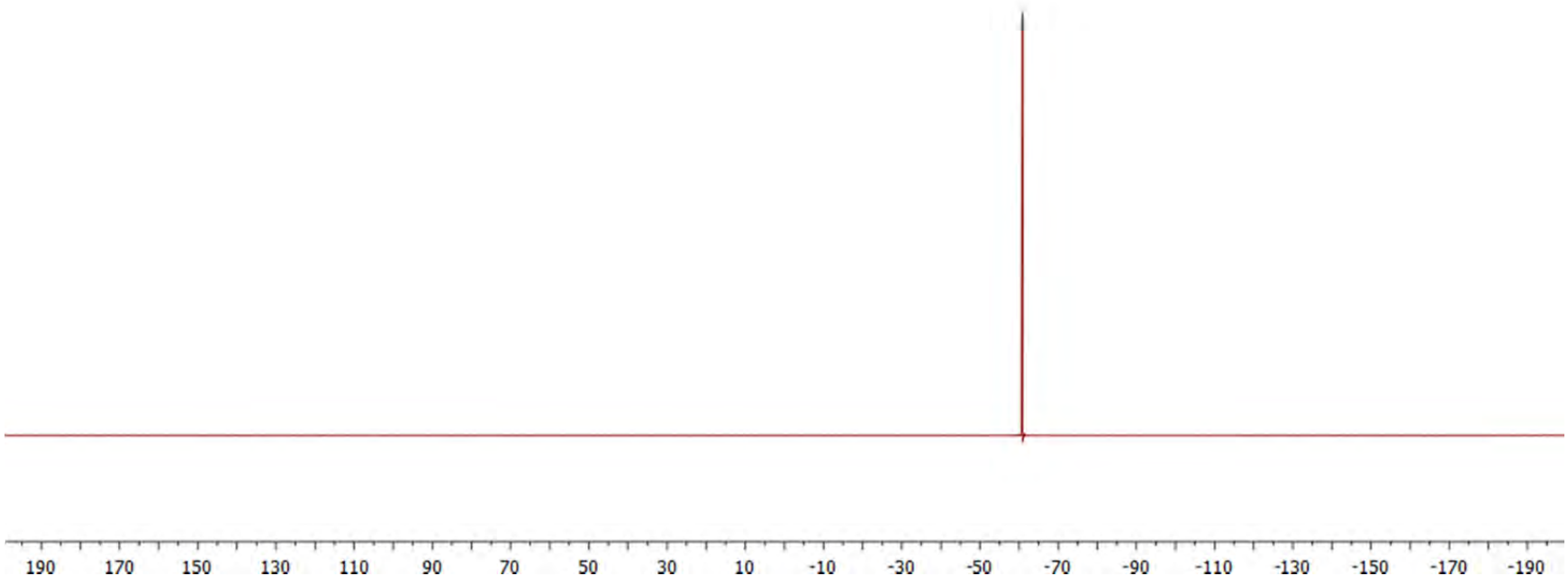
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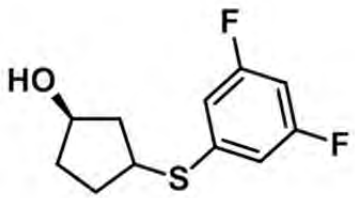
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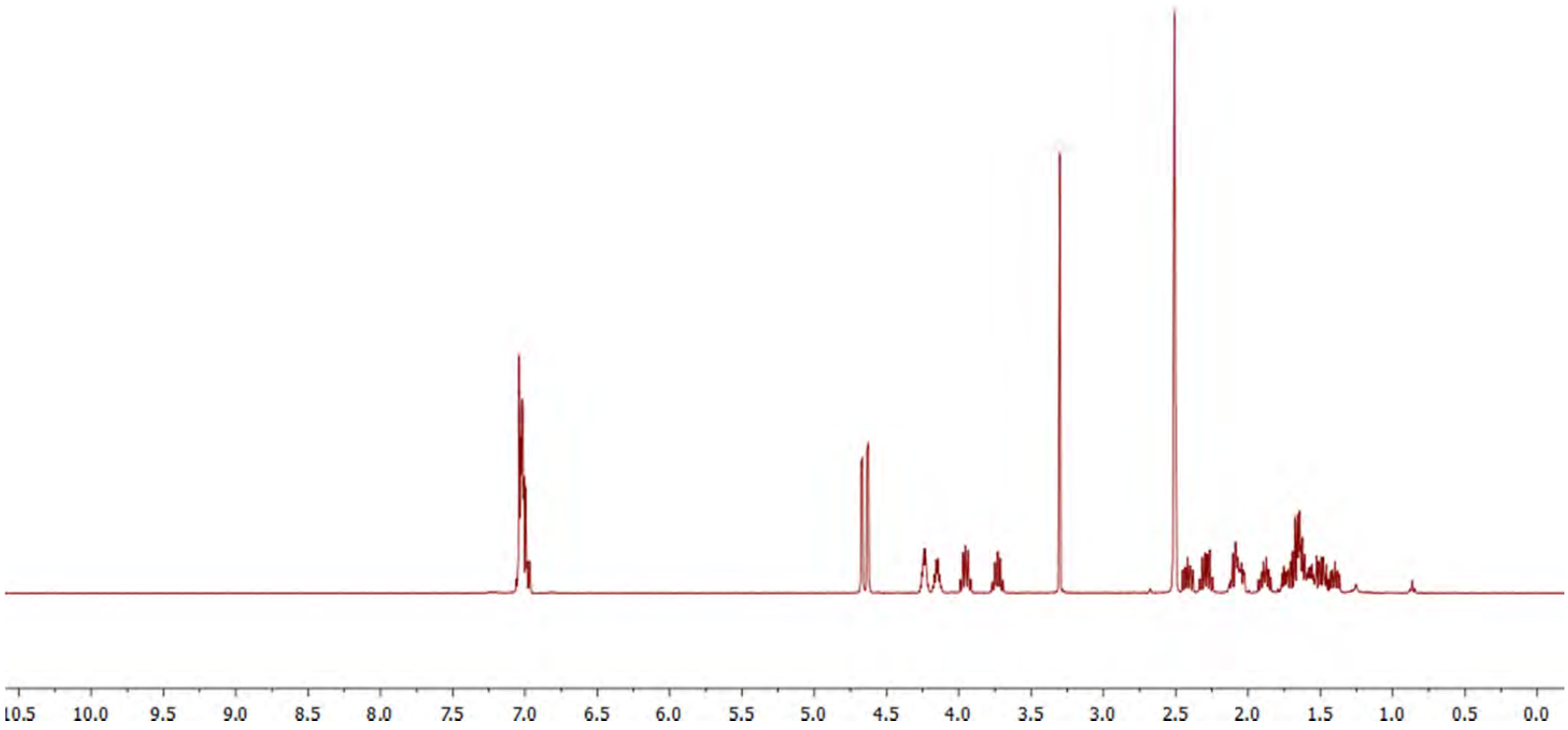
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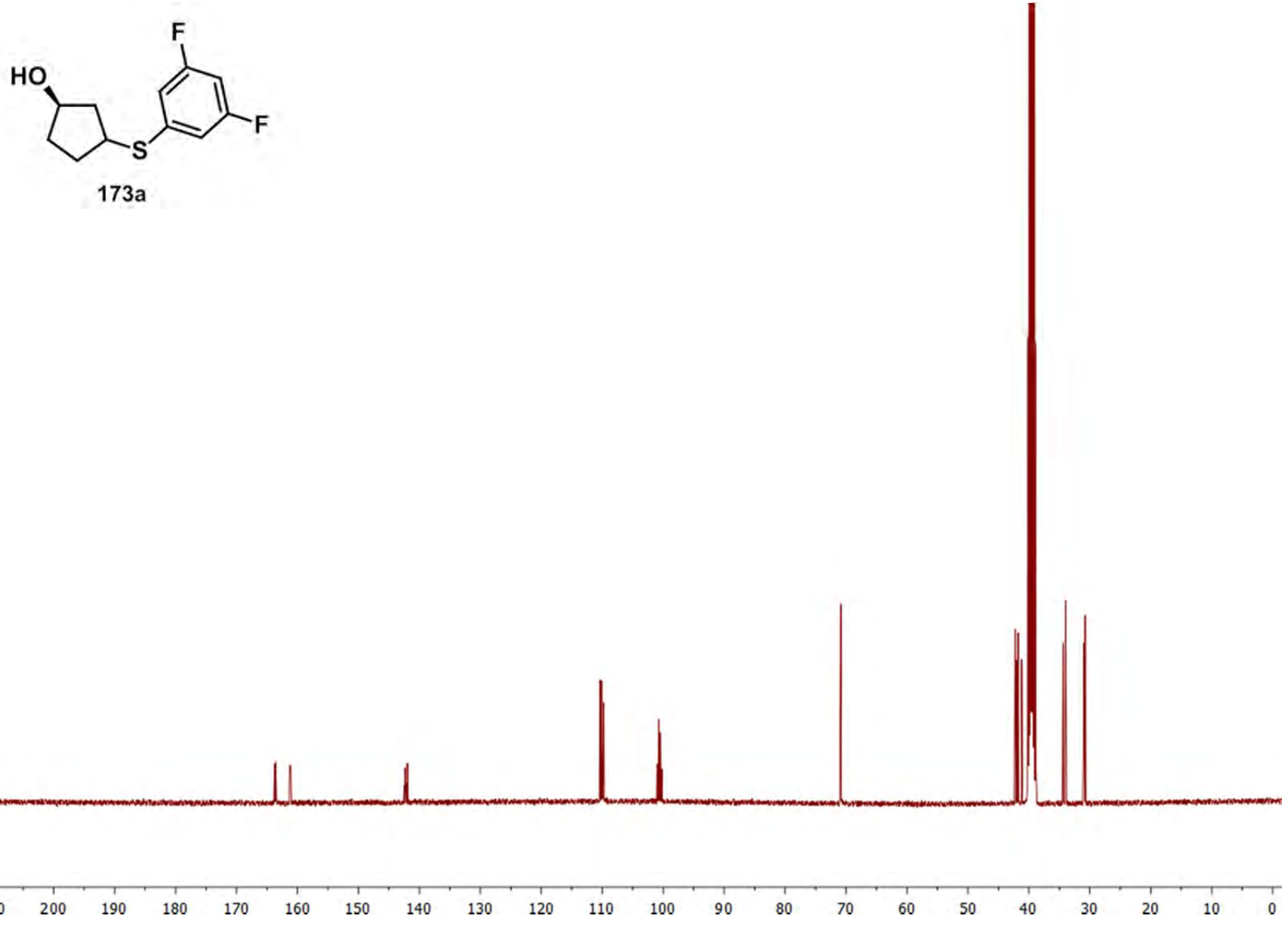
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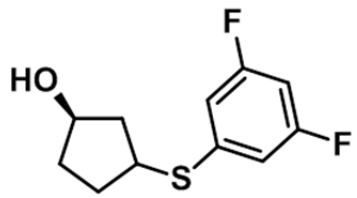
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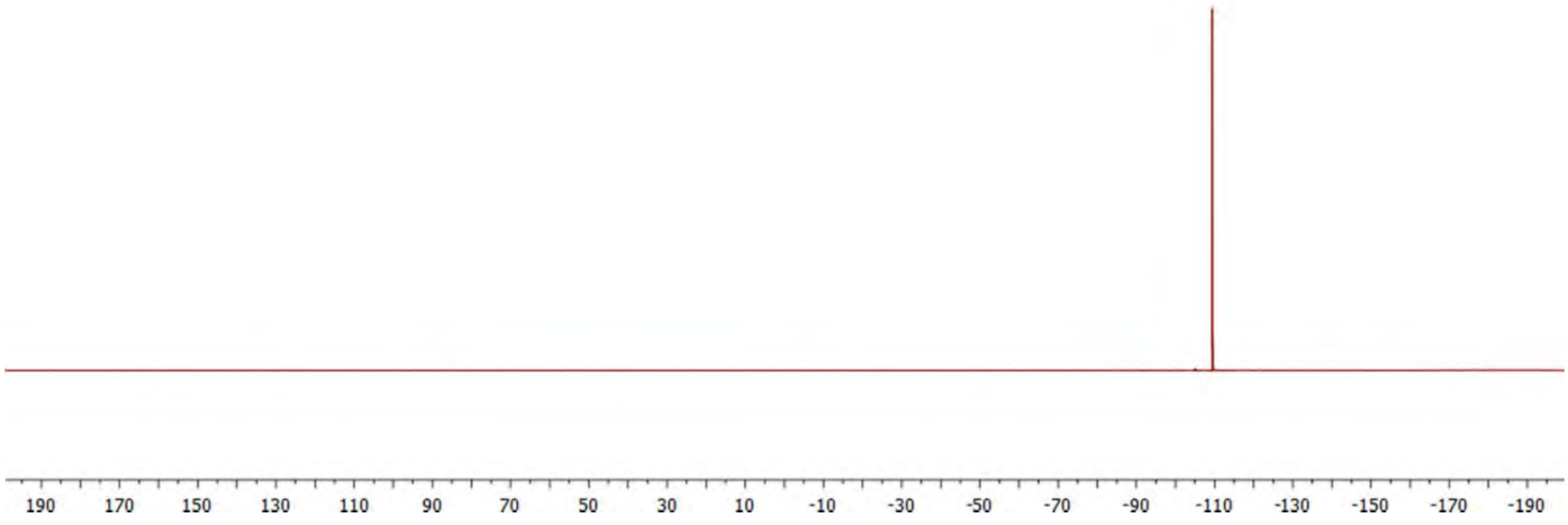
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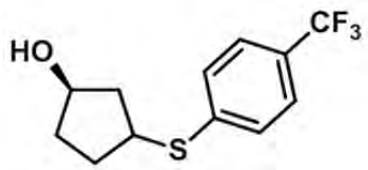
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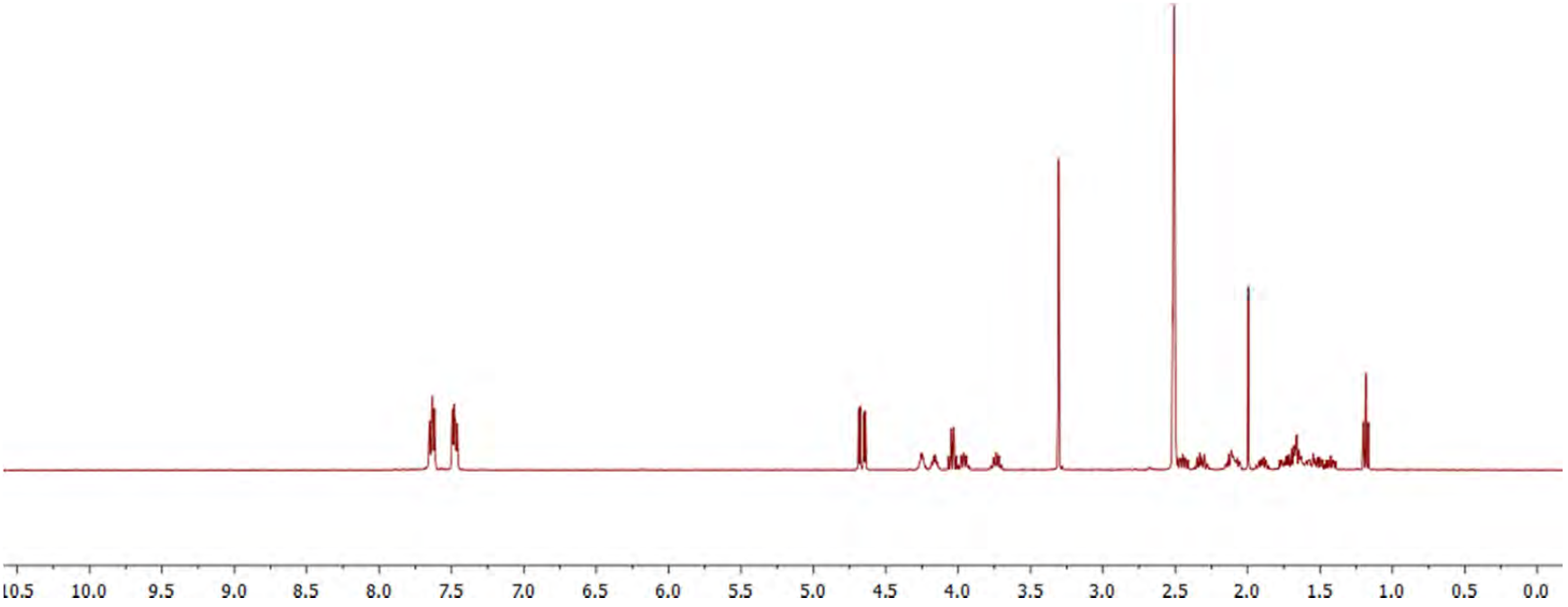
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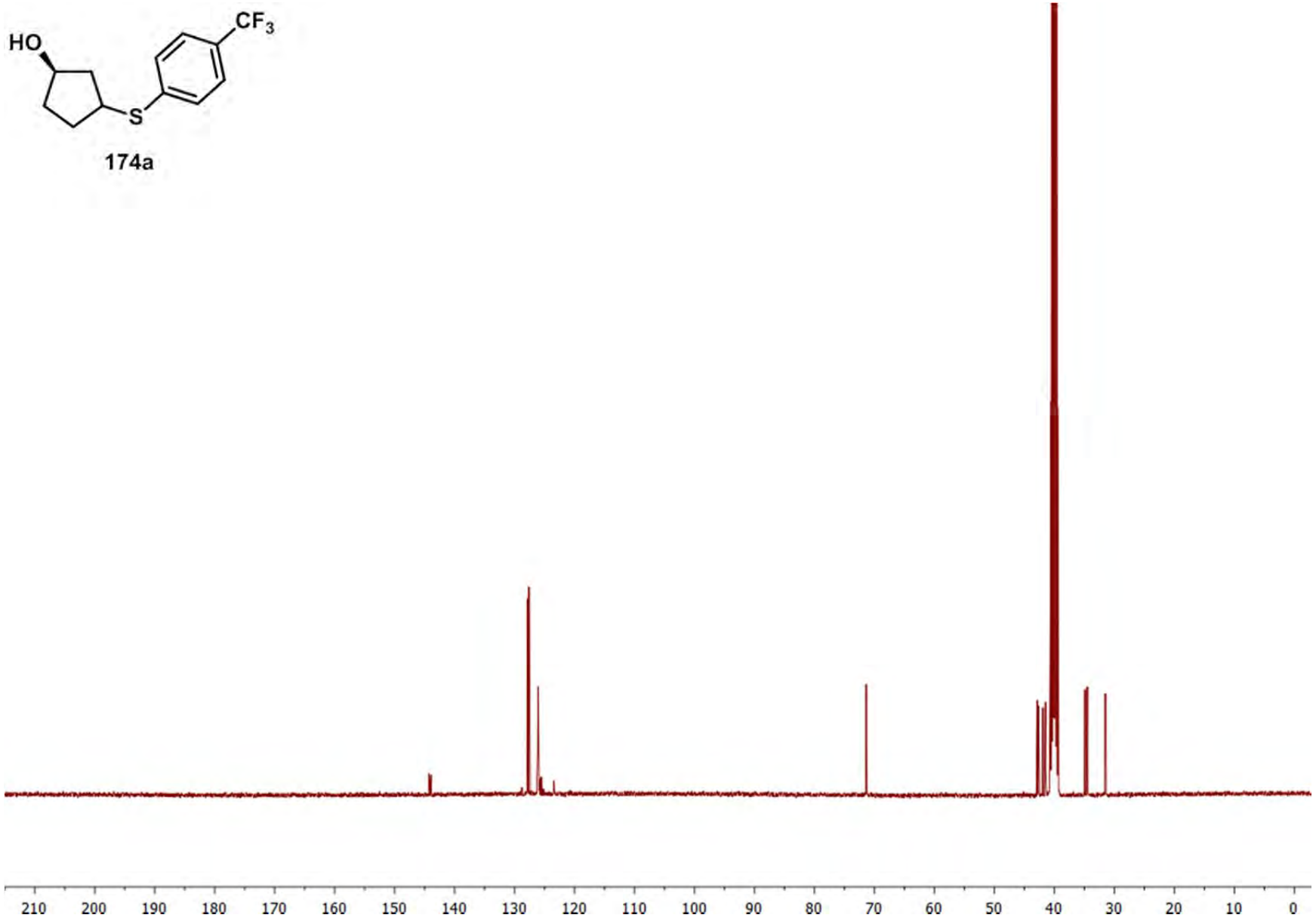
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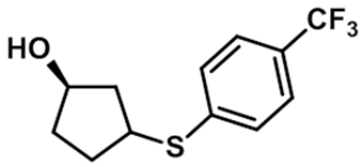
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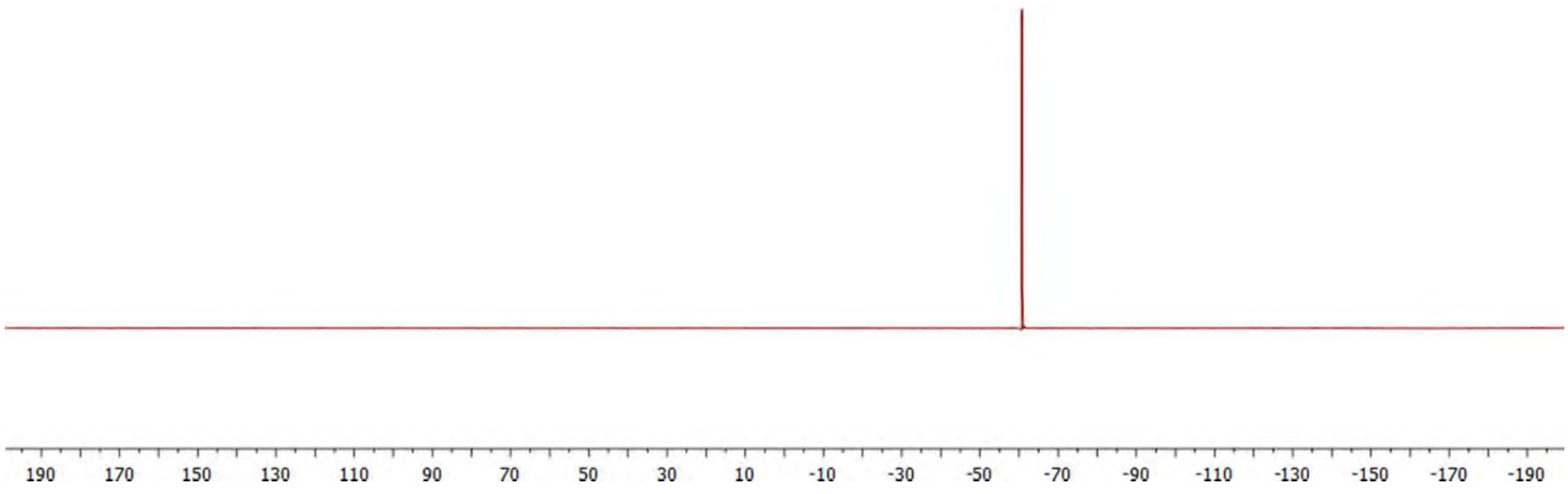
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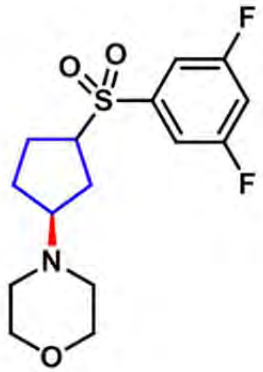

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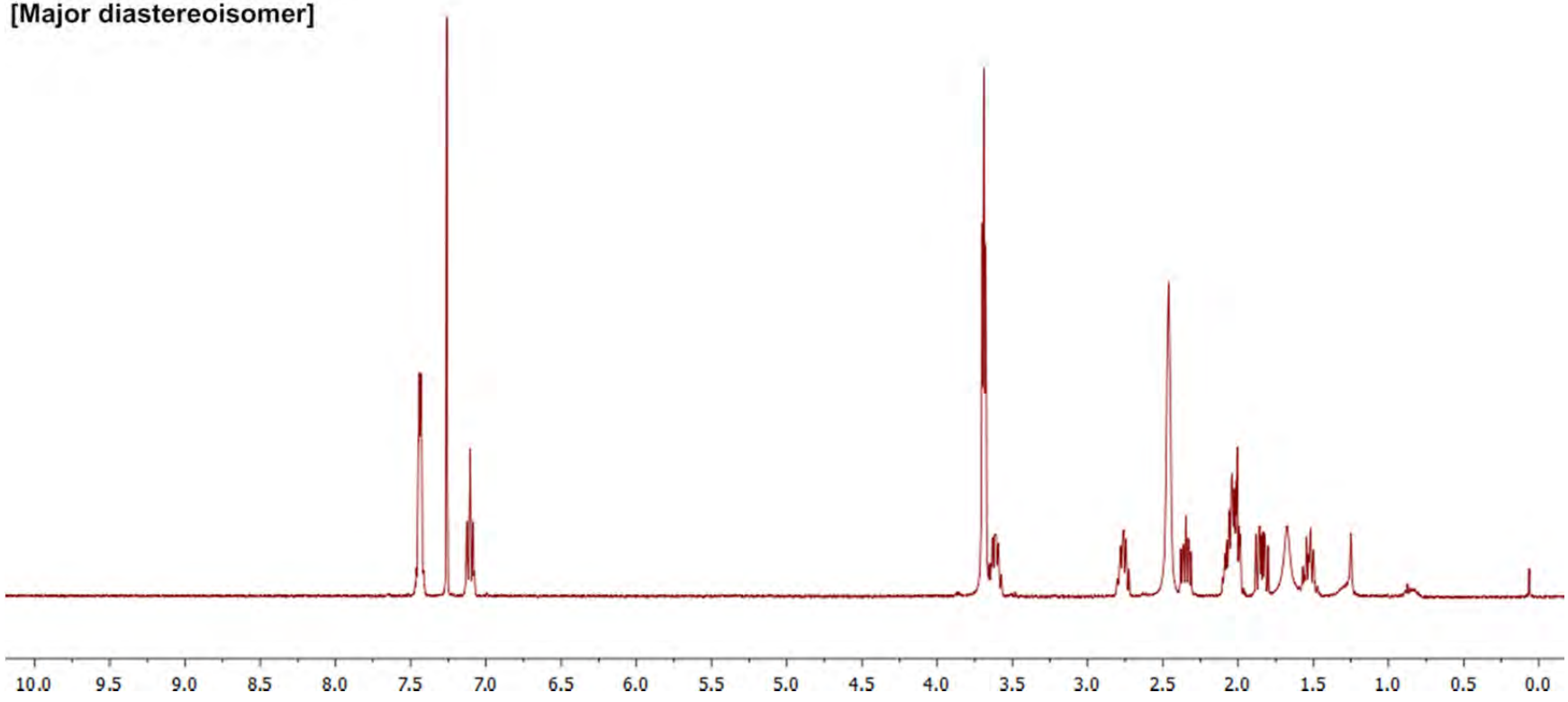

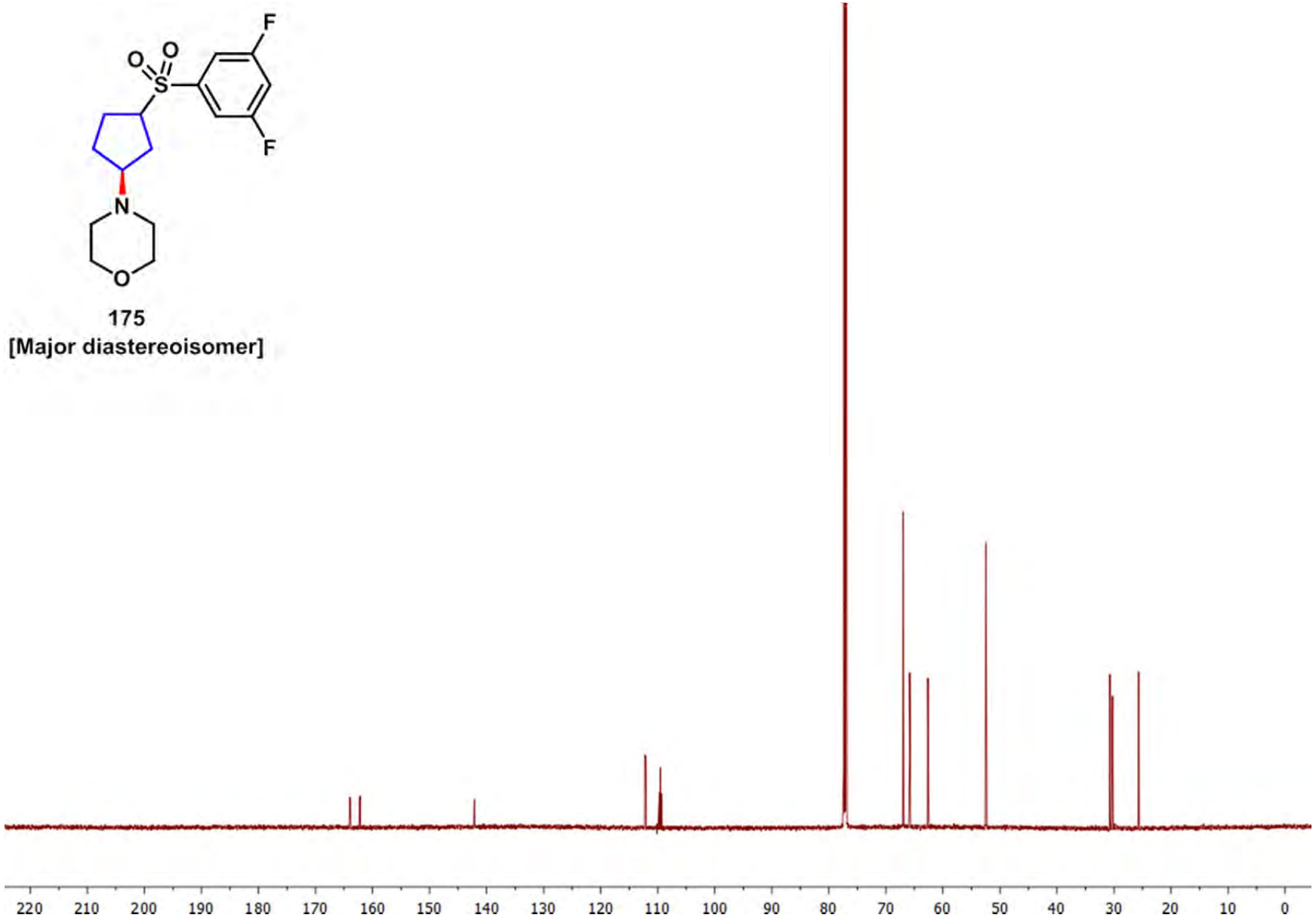

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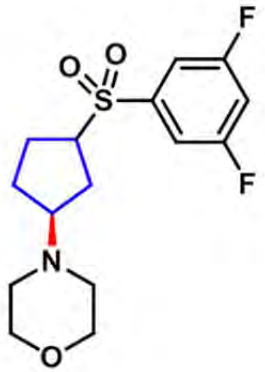
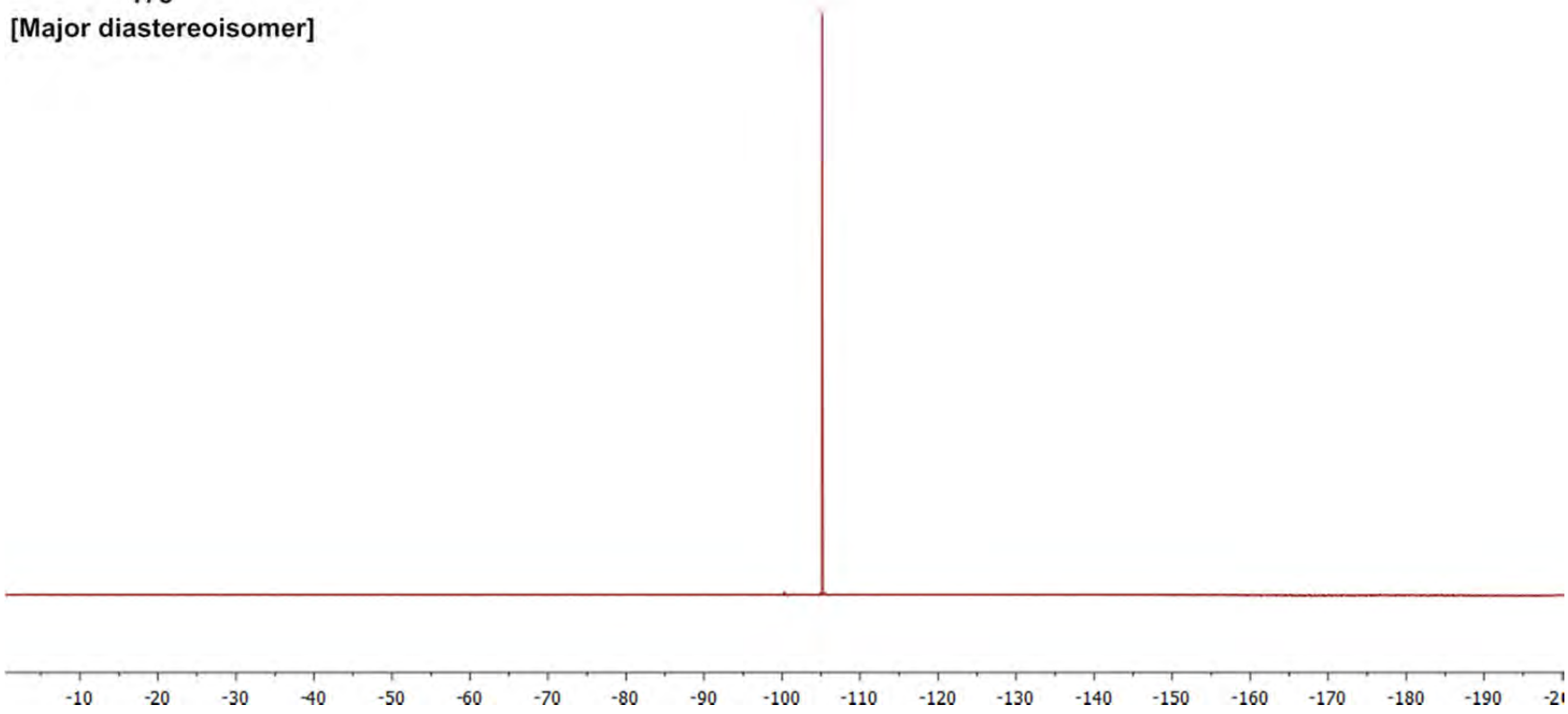
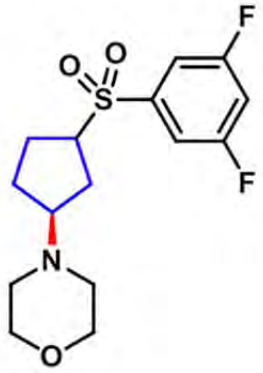
[Major diastereoisomer]



175
[Major diastereoisomer]





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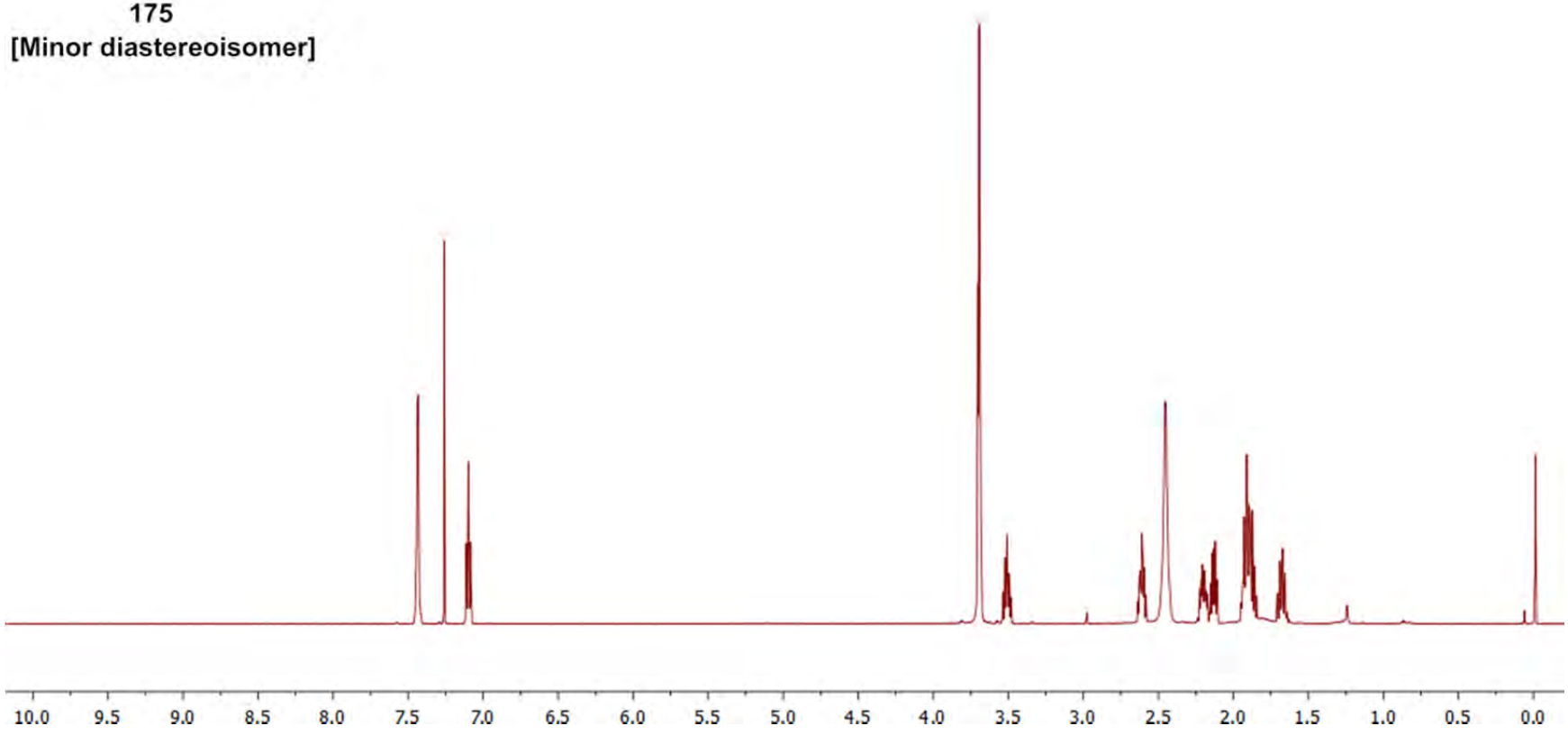

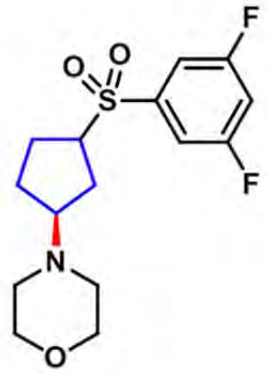

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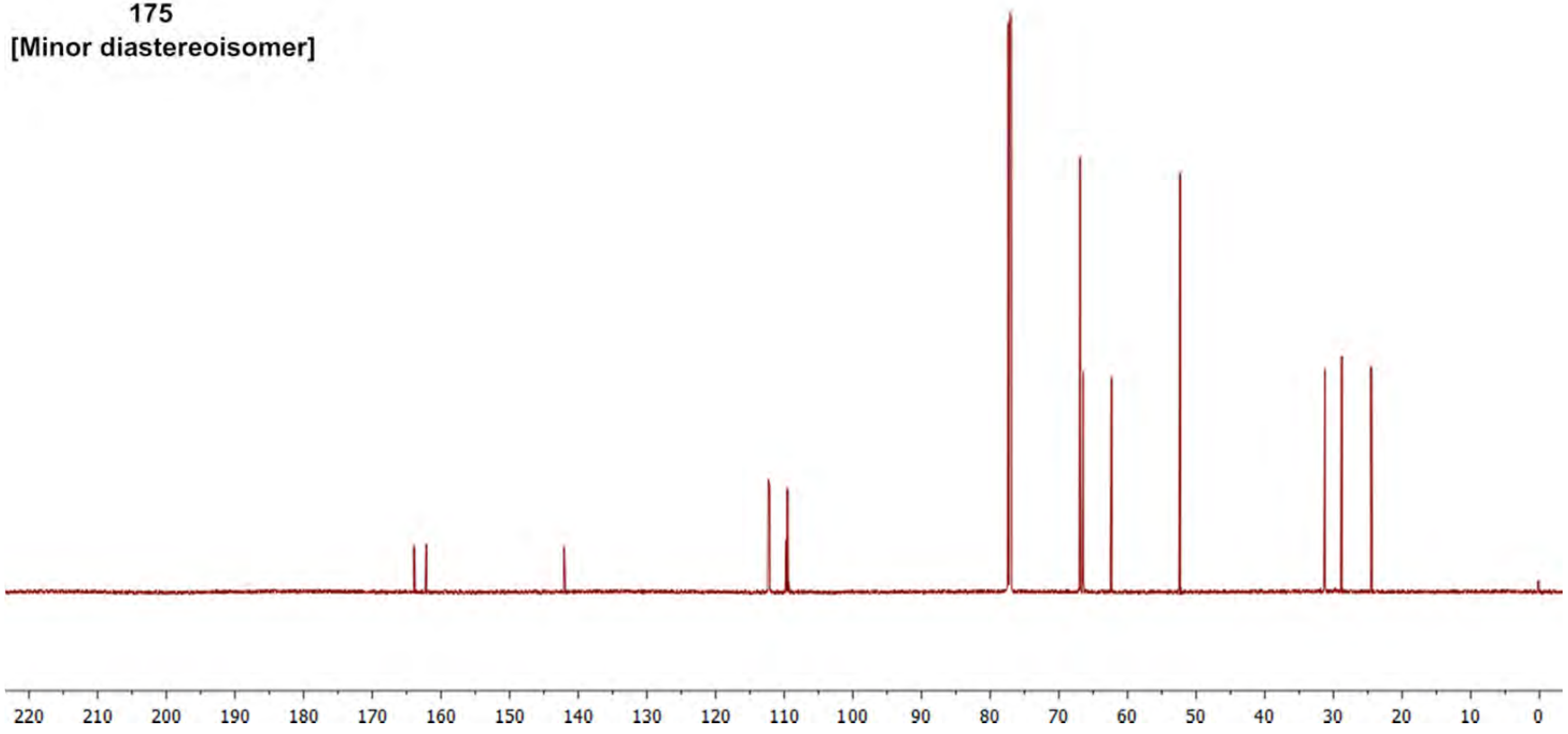

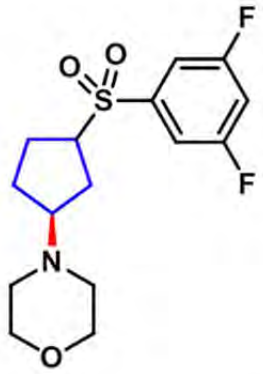

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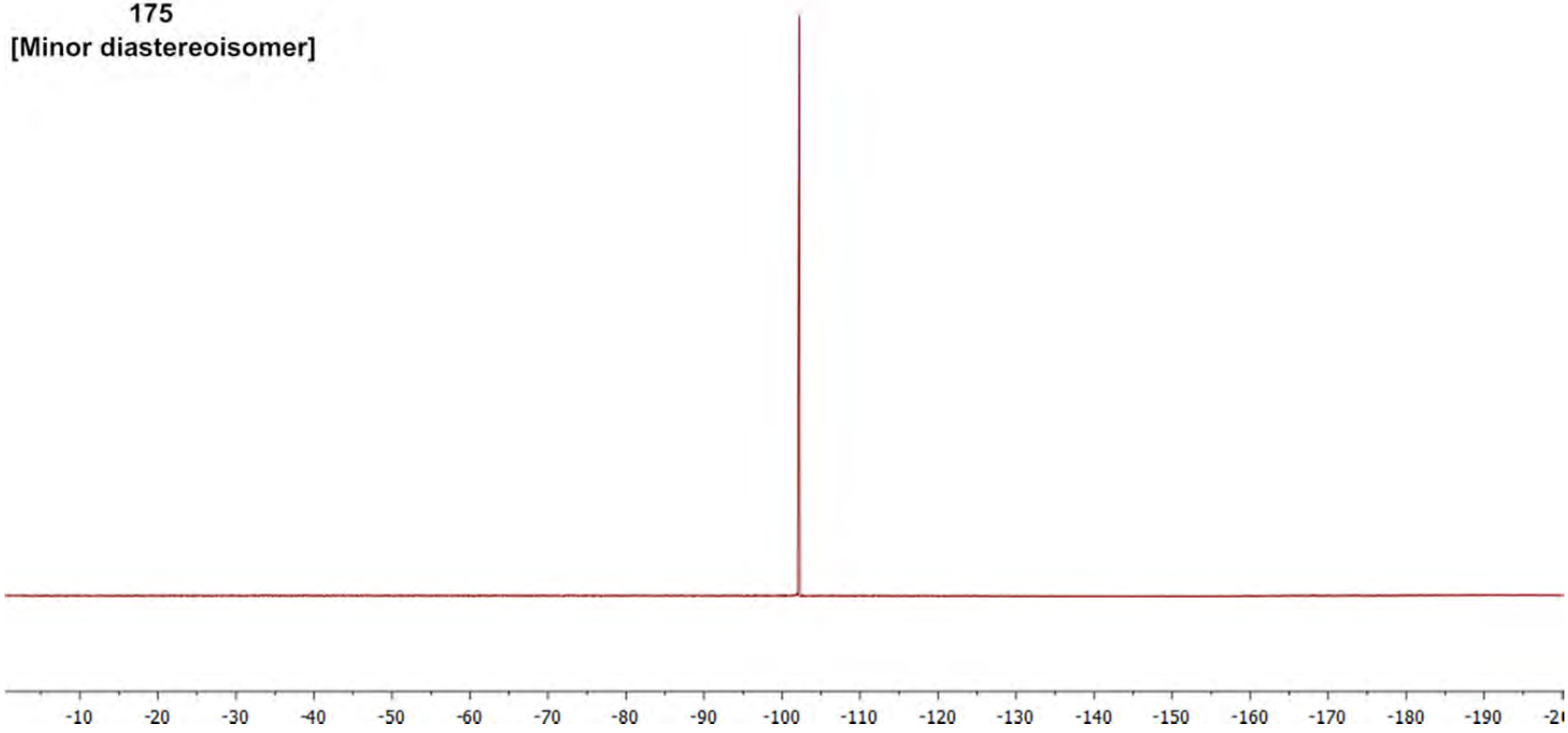

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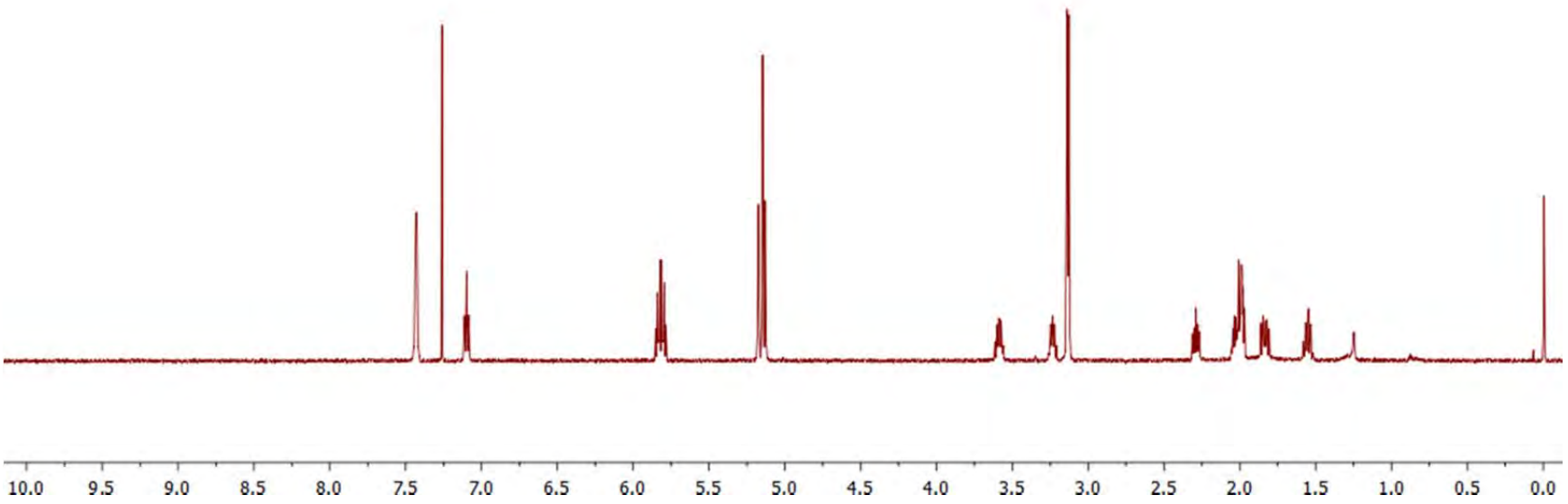

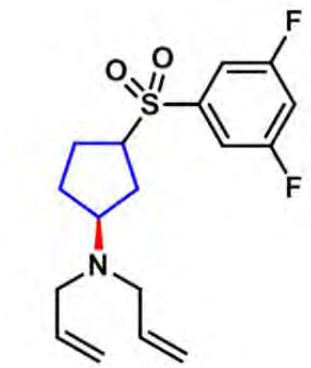

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[Major diastereoisomer]

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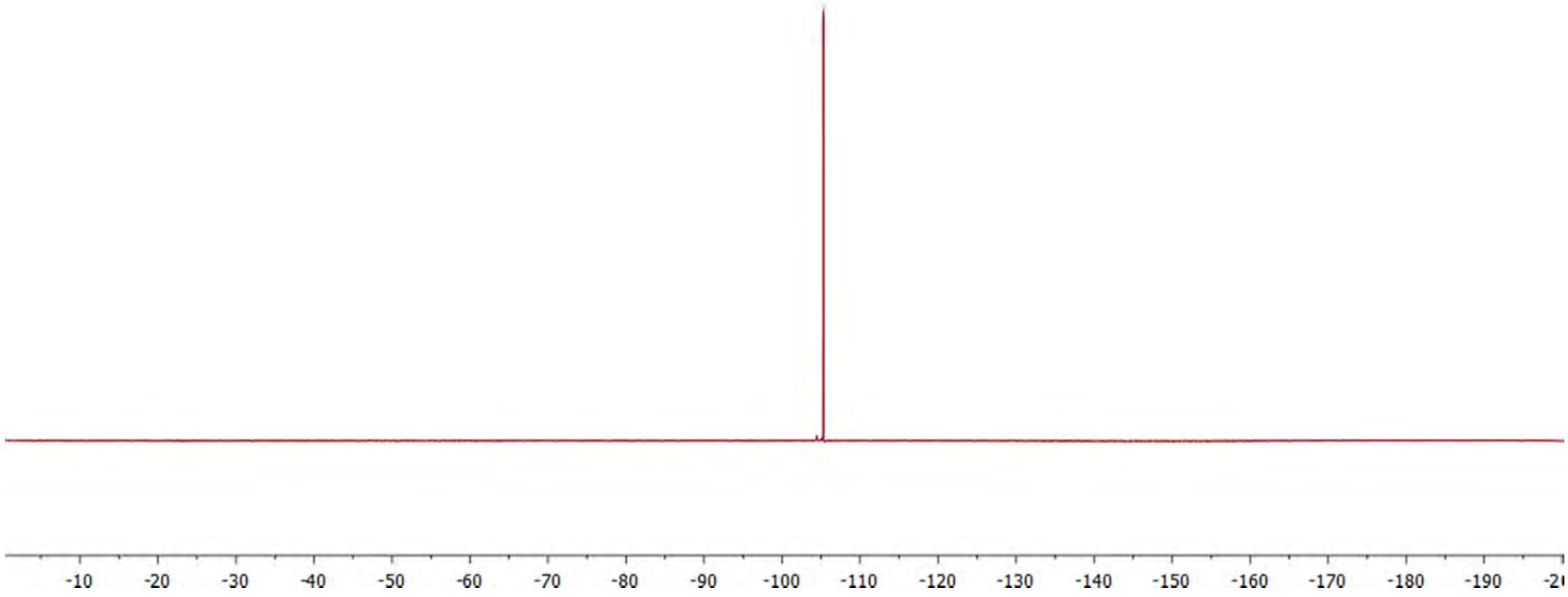
[Major diastereoisomer]



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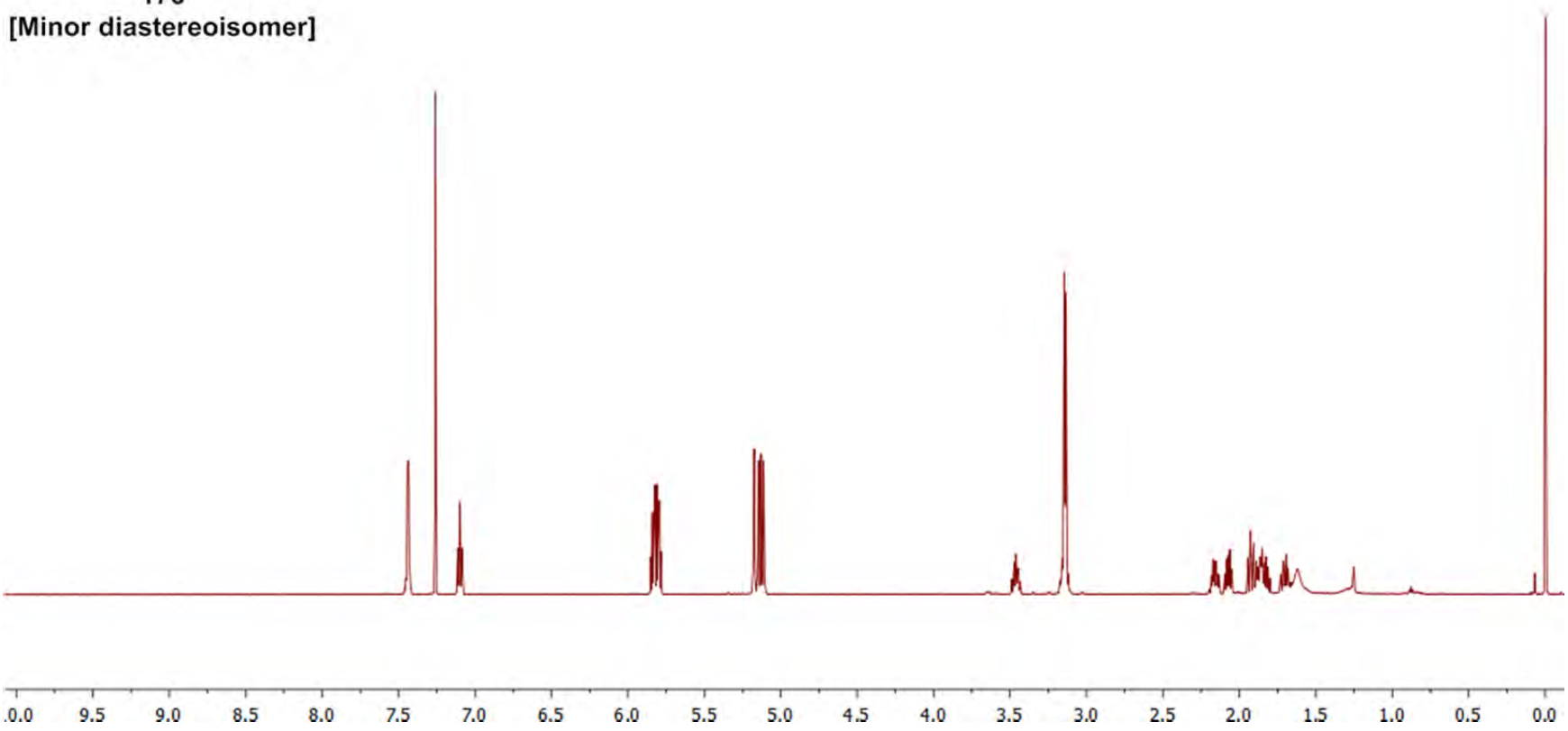

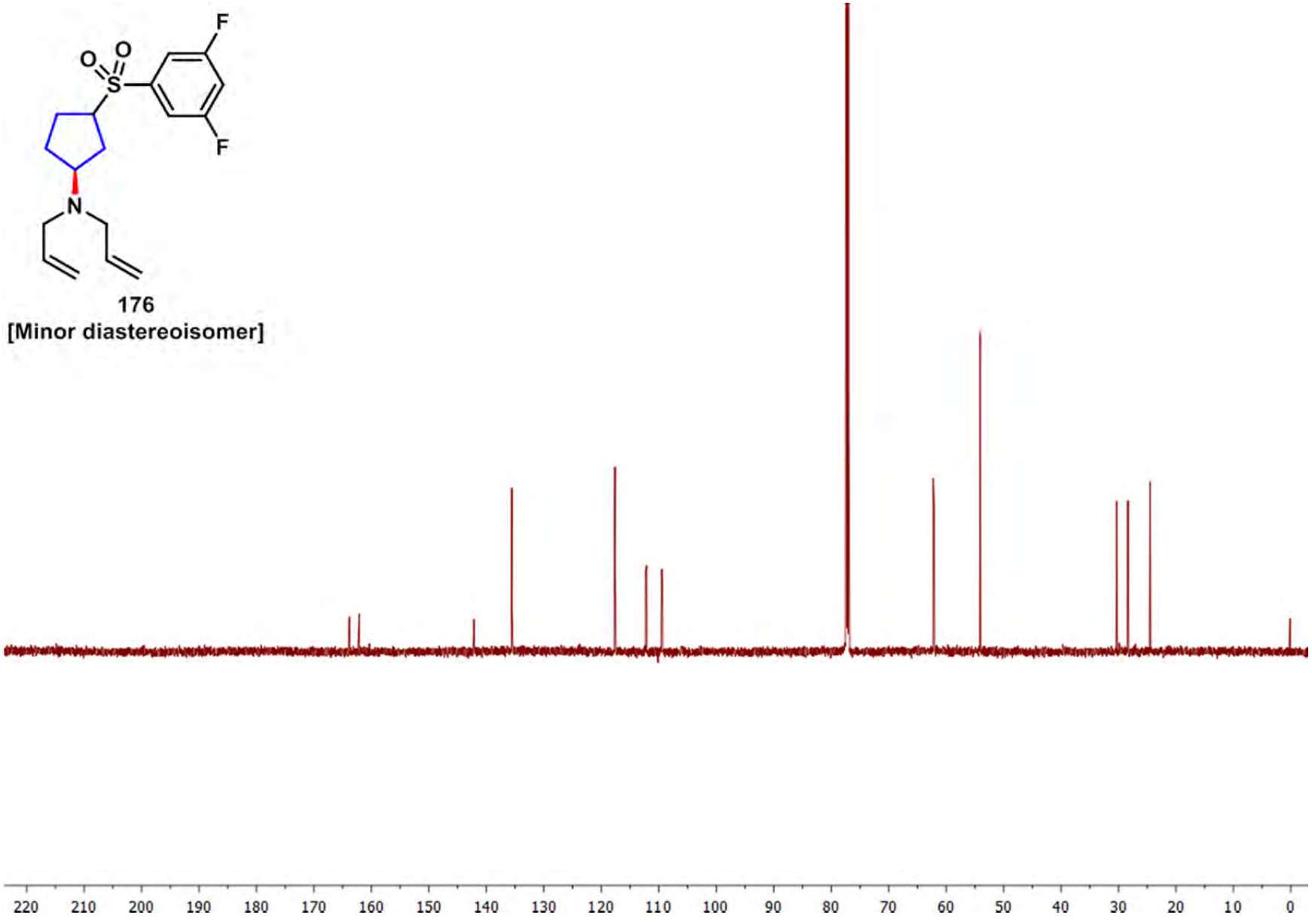

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[Minor diastereoisomer]

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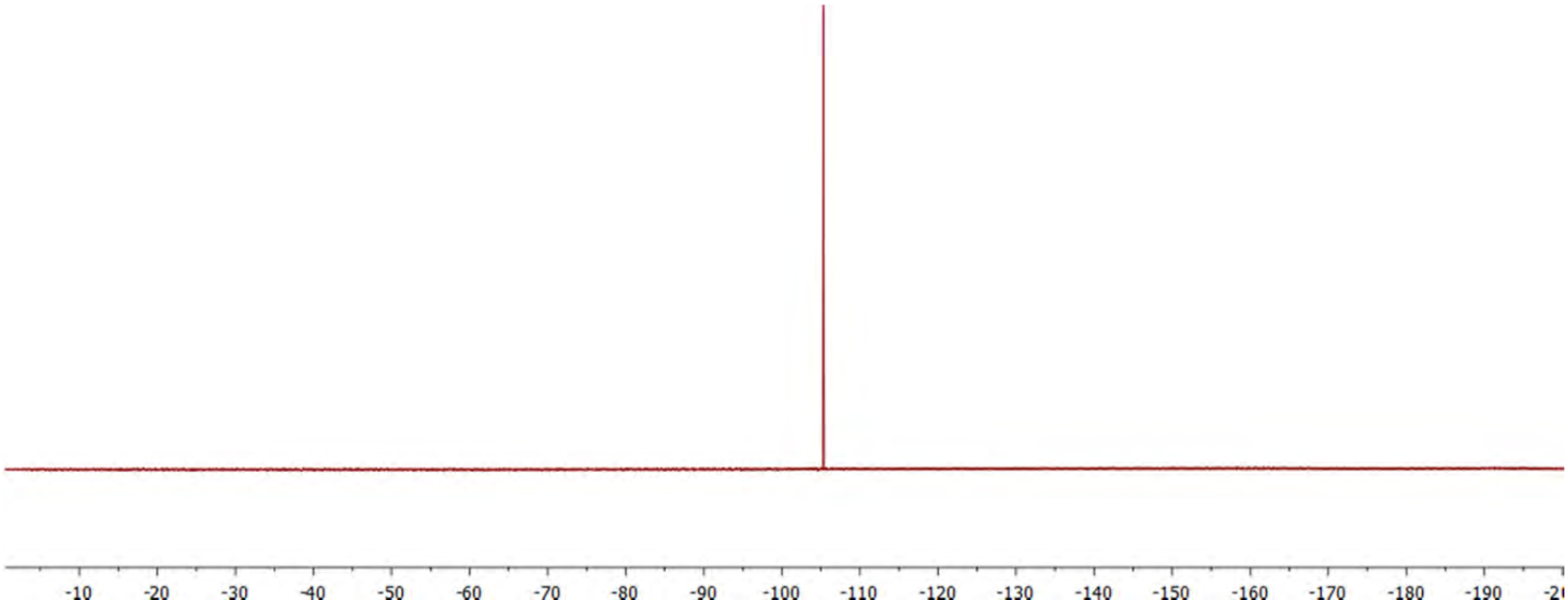
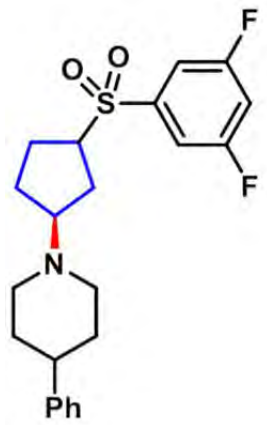
[Minor diastereoisomer]

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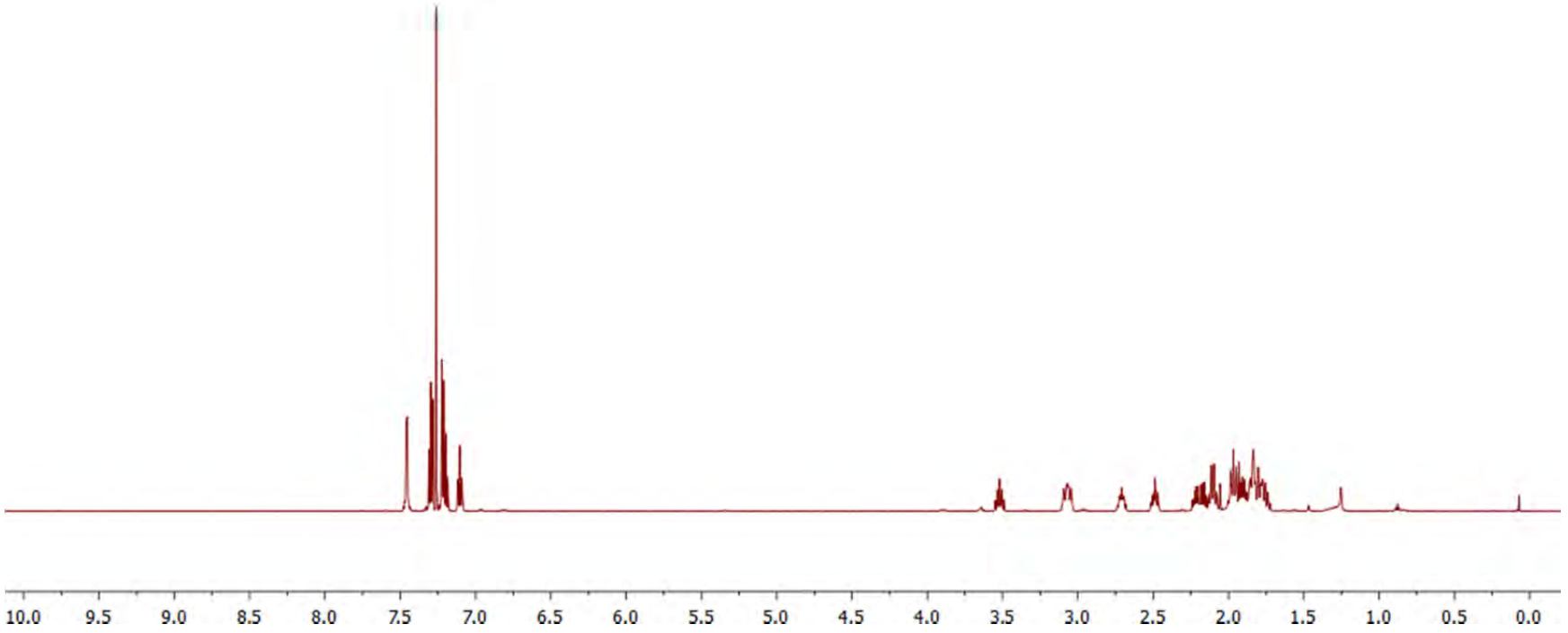
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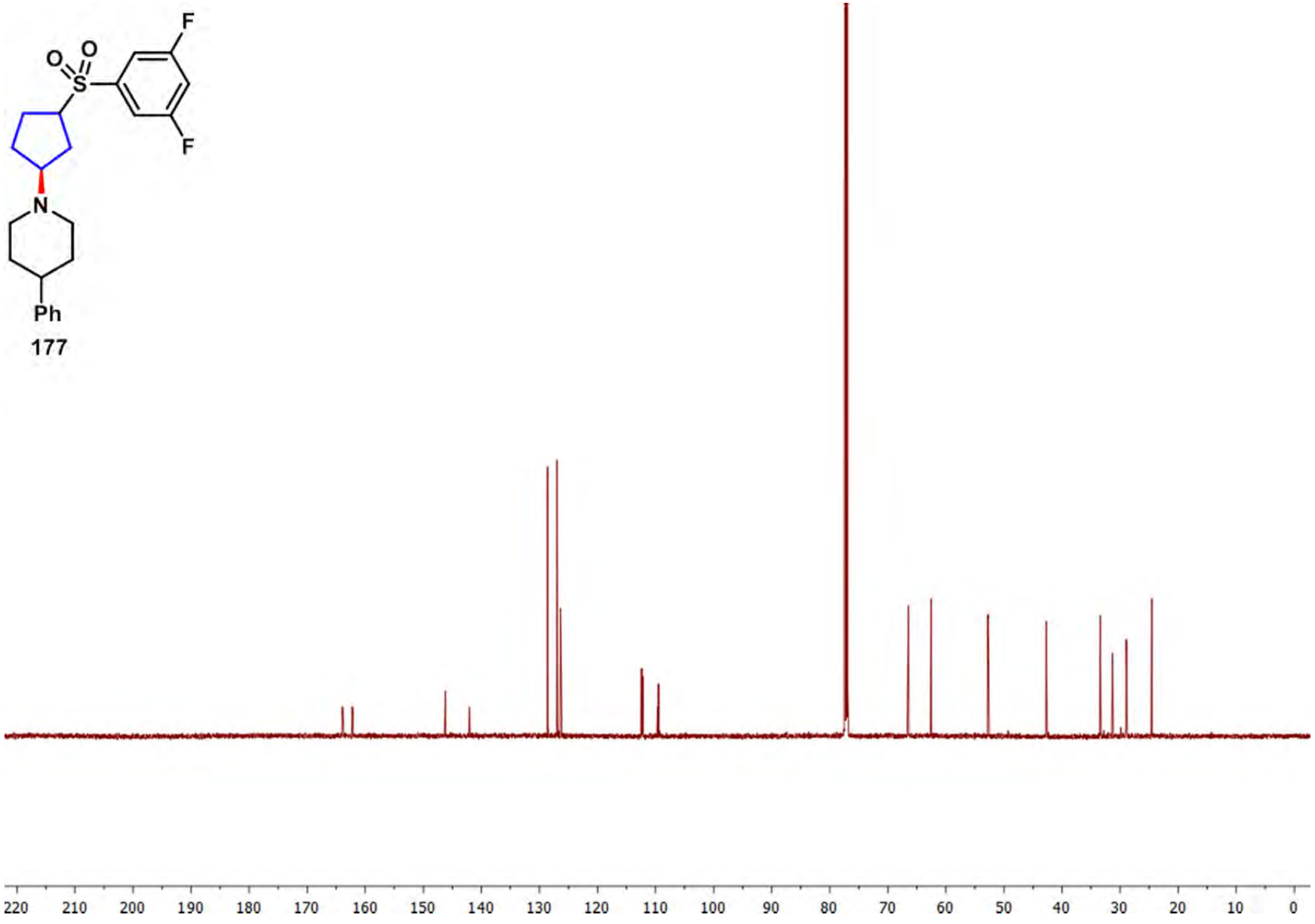
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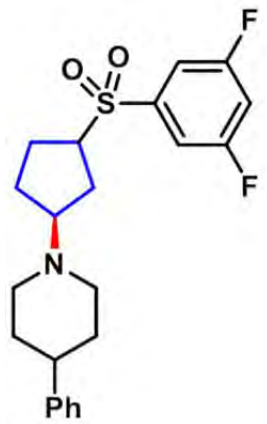
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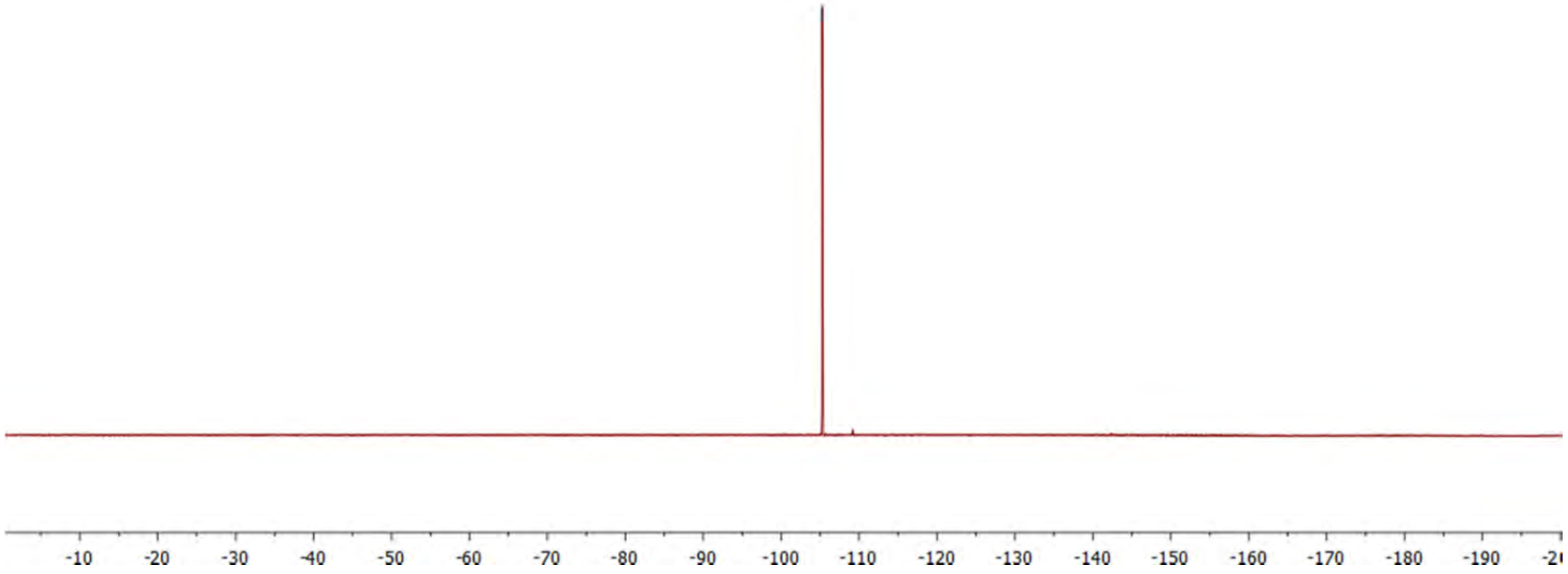
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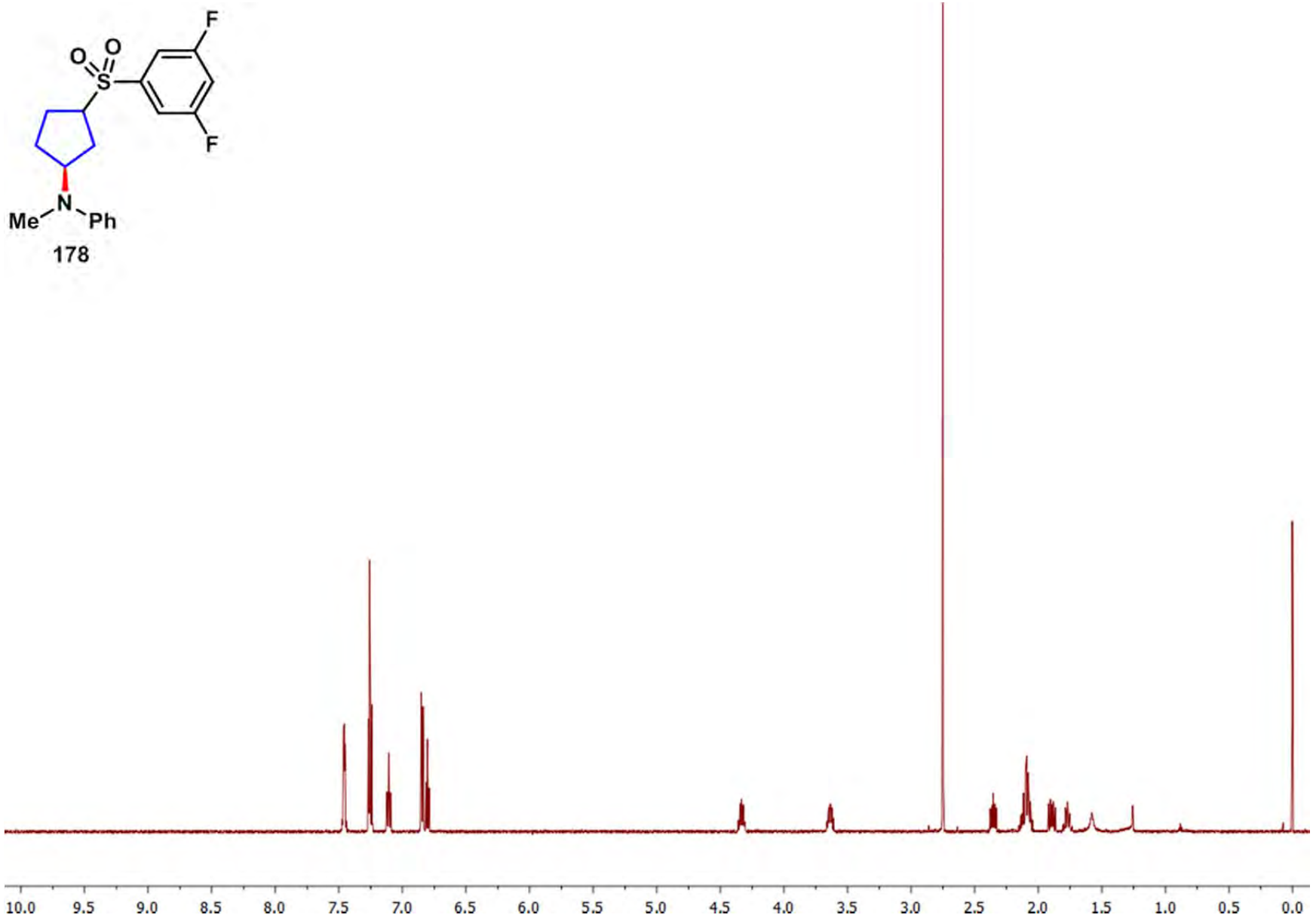
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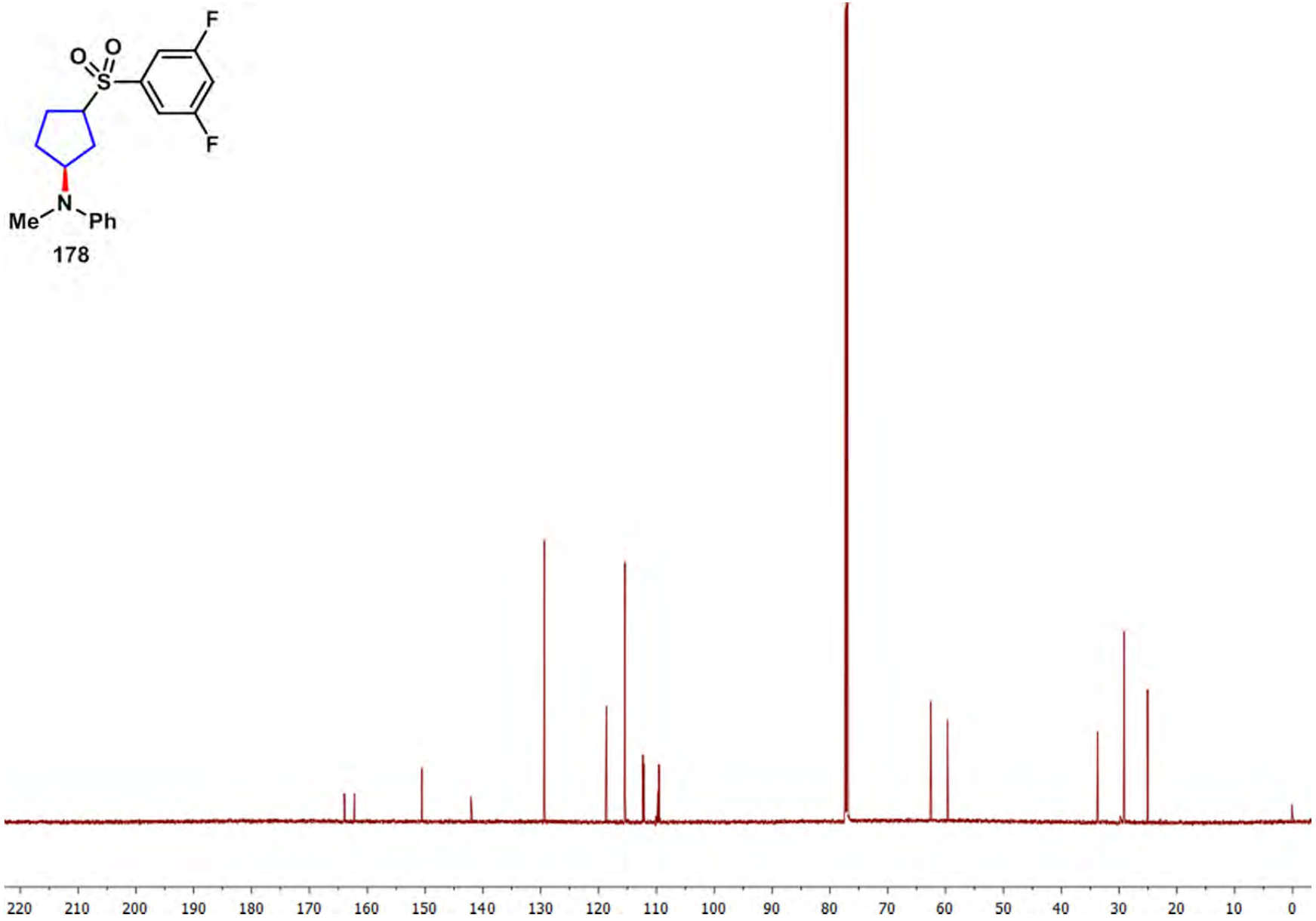
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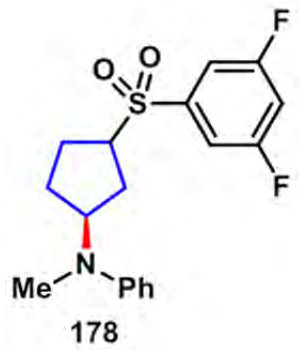
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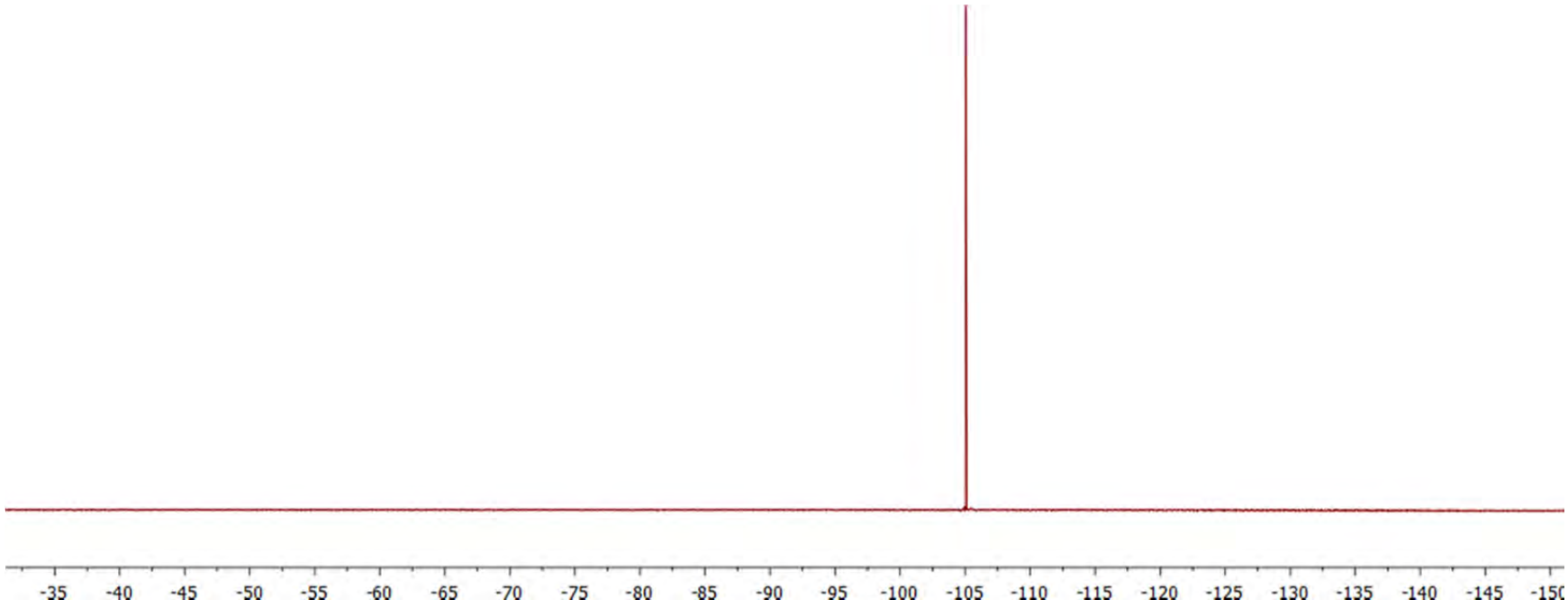
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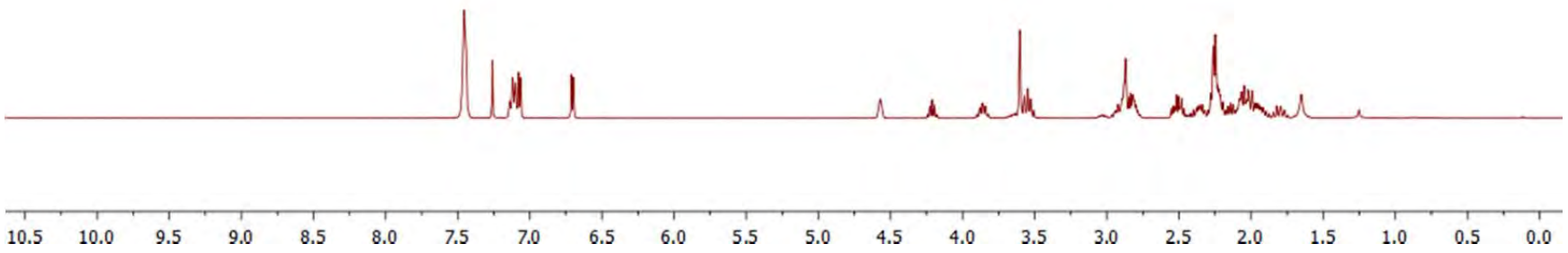
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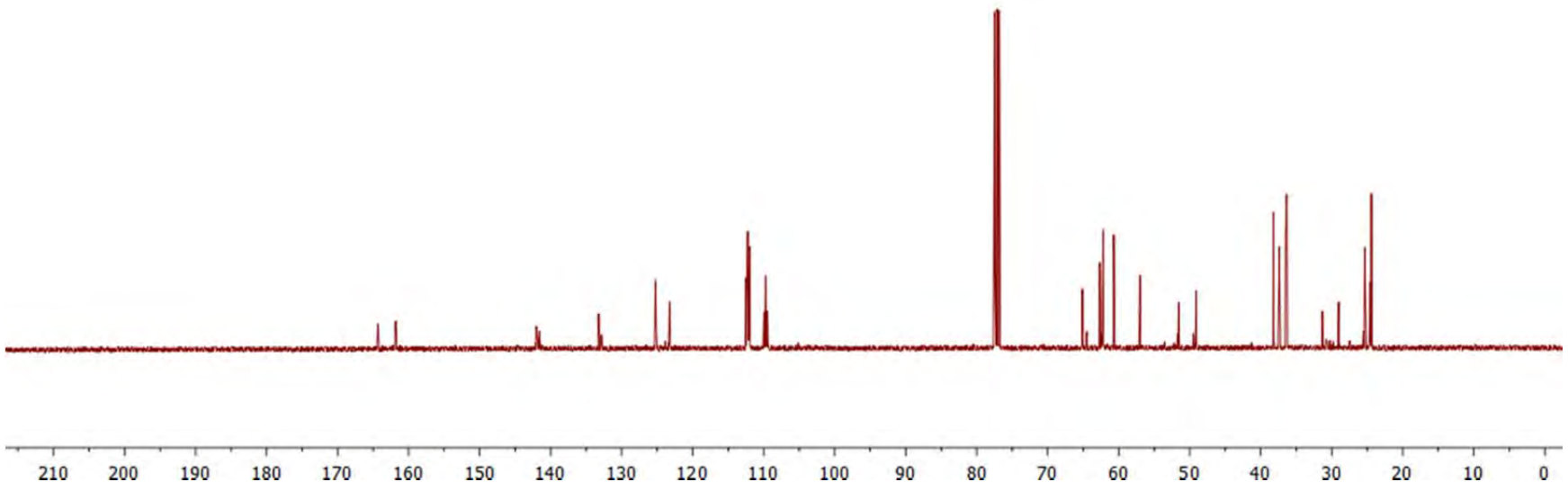
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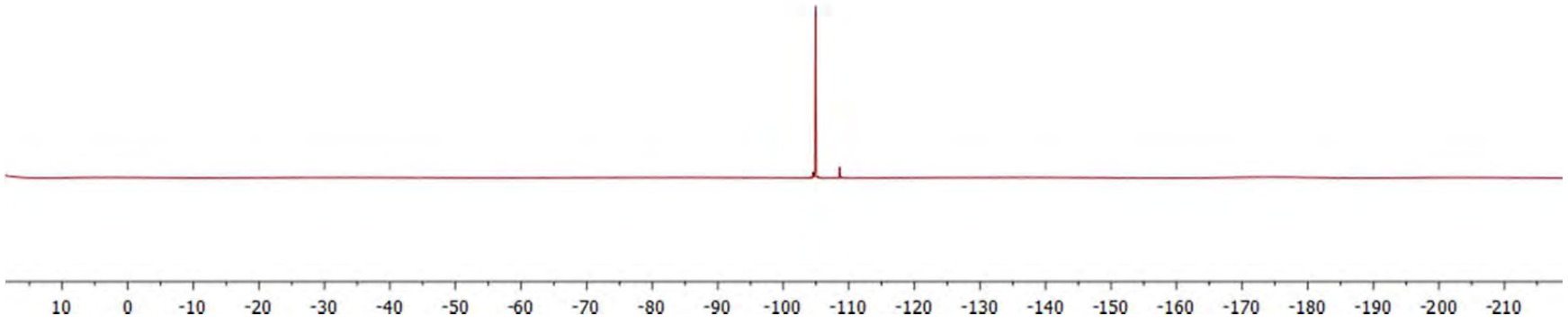
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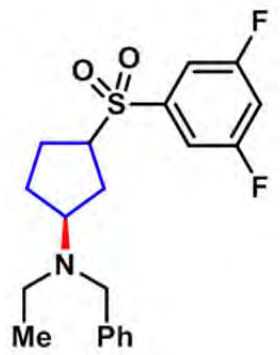
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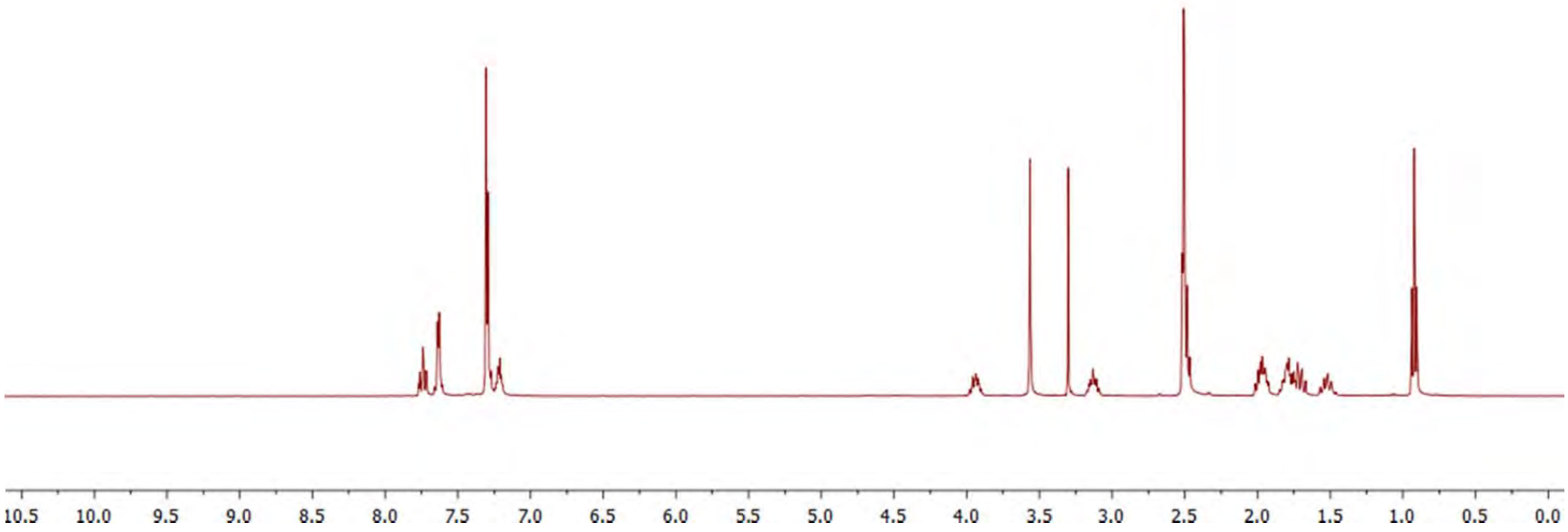
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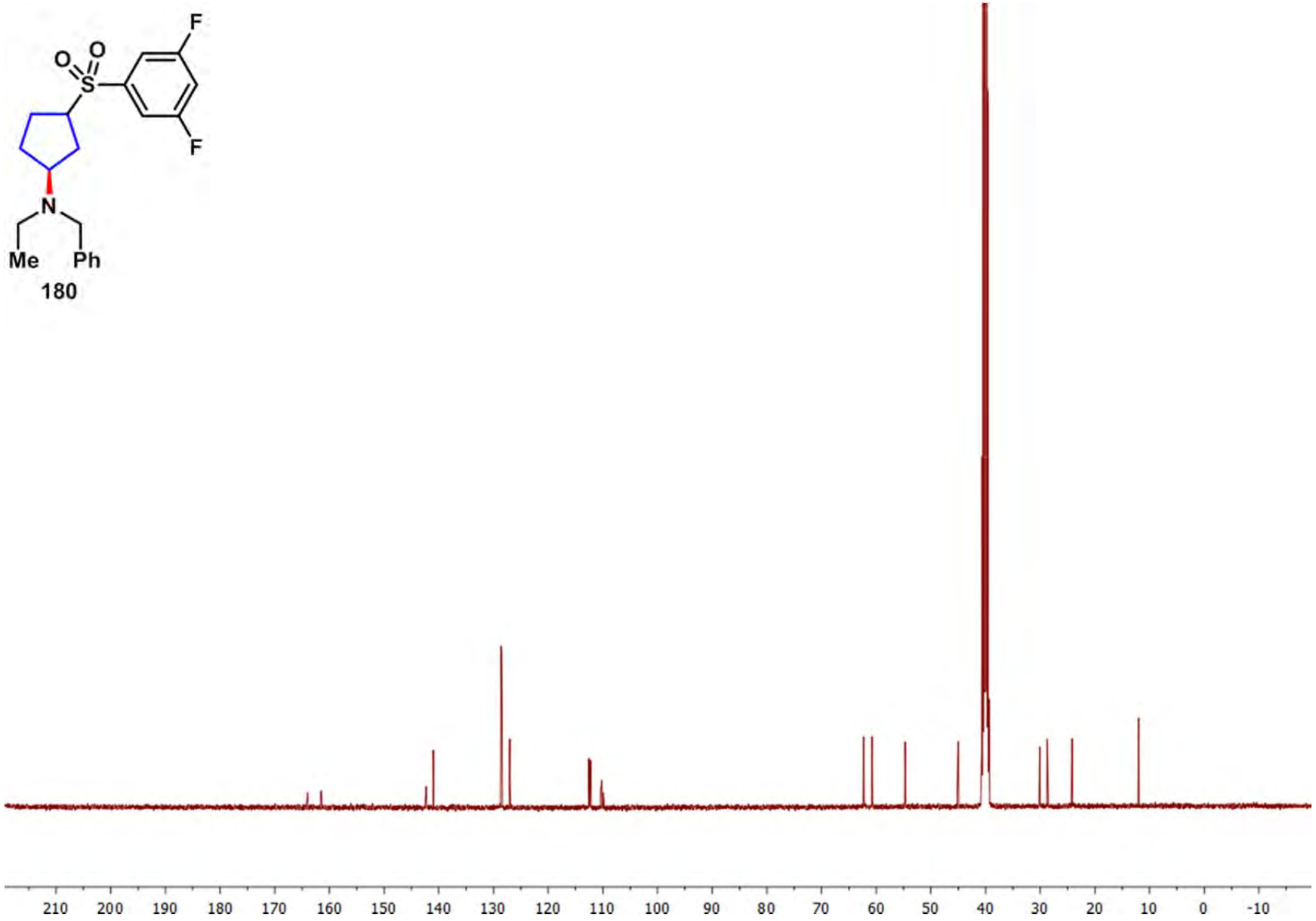
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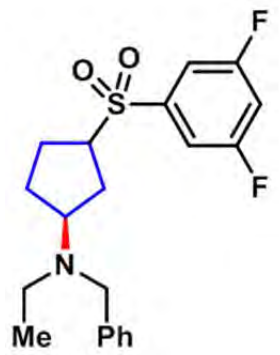
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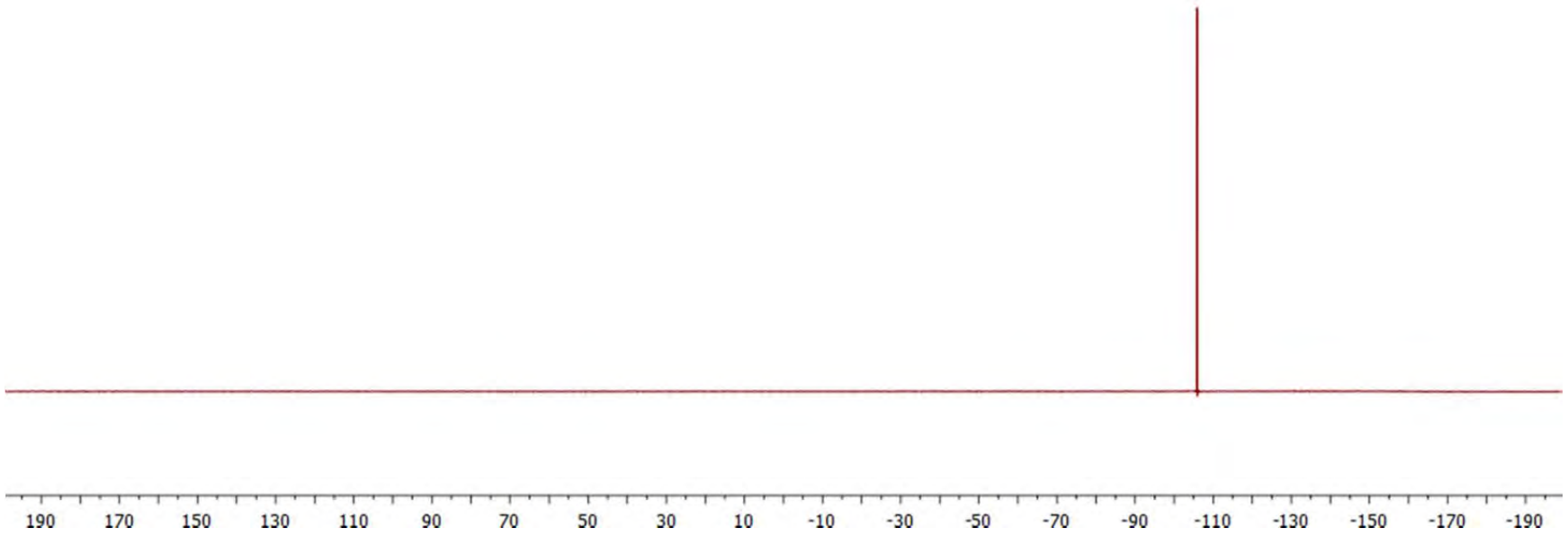
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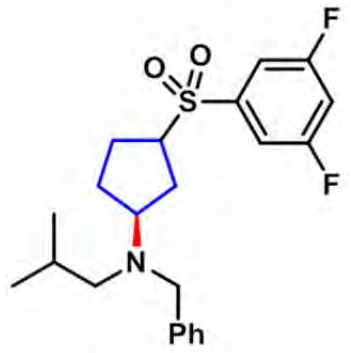
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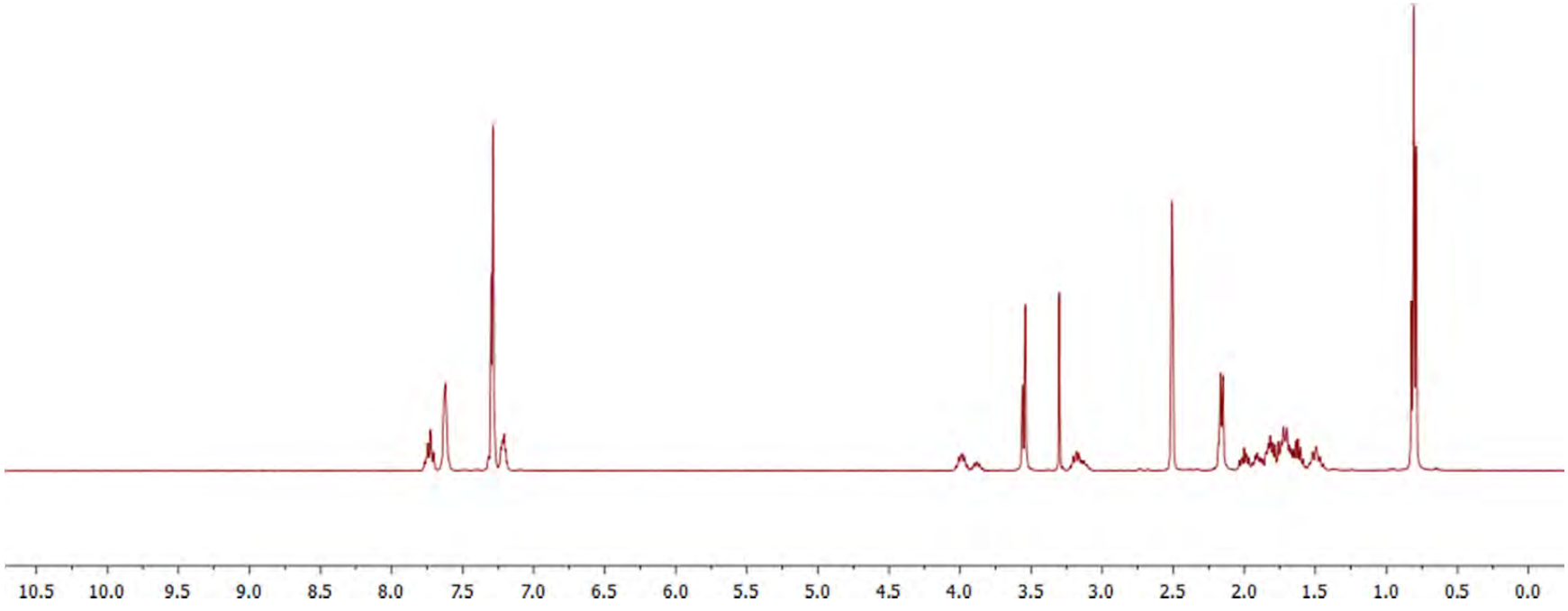
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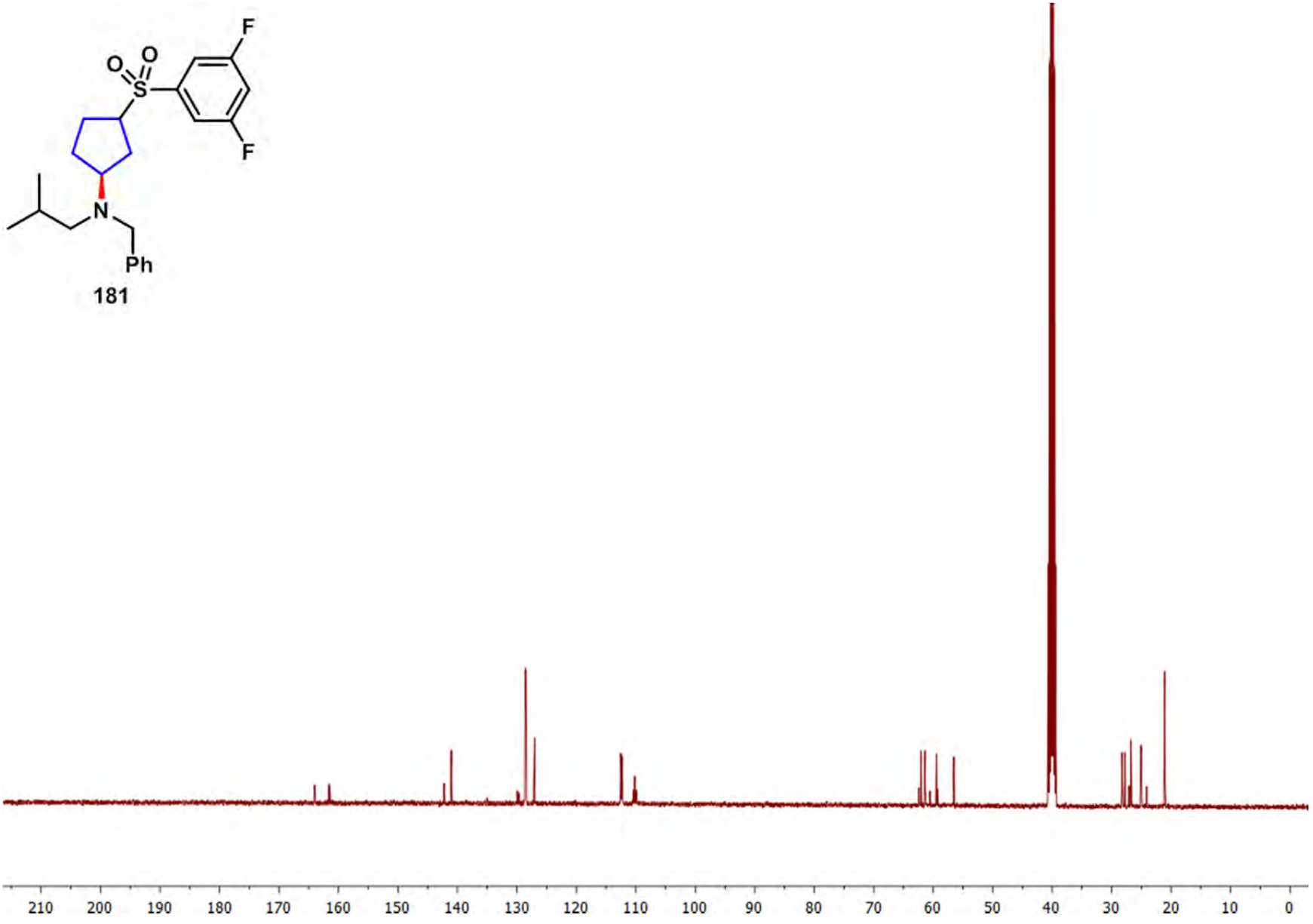
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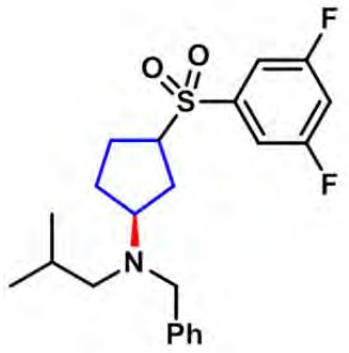
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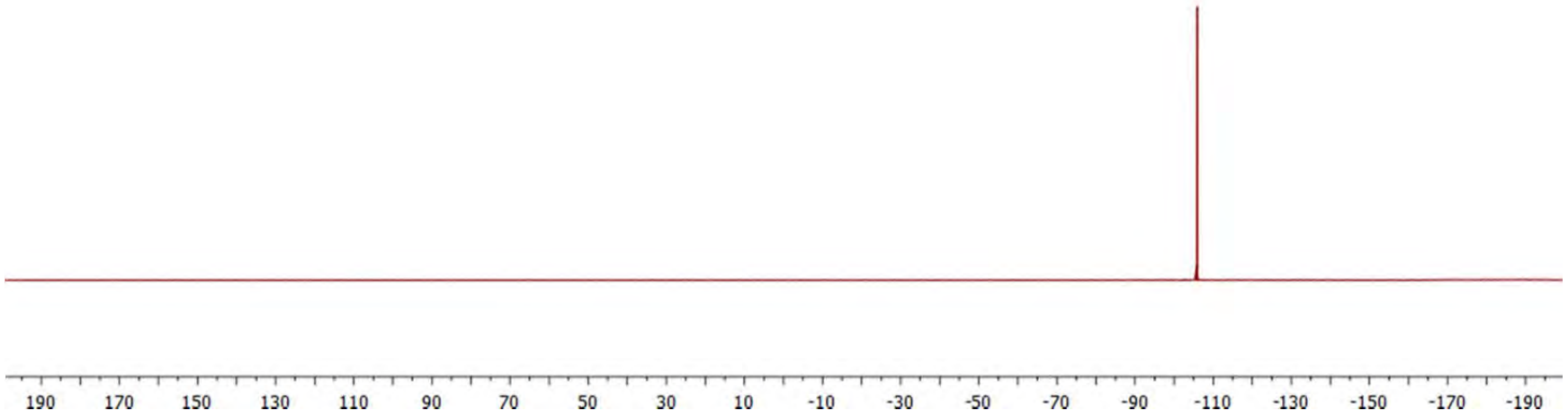
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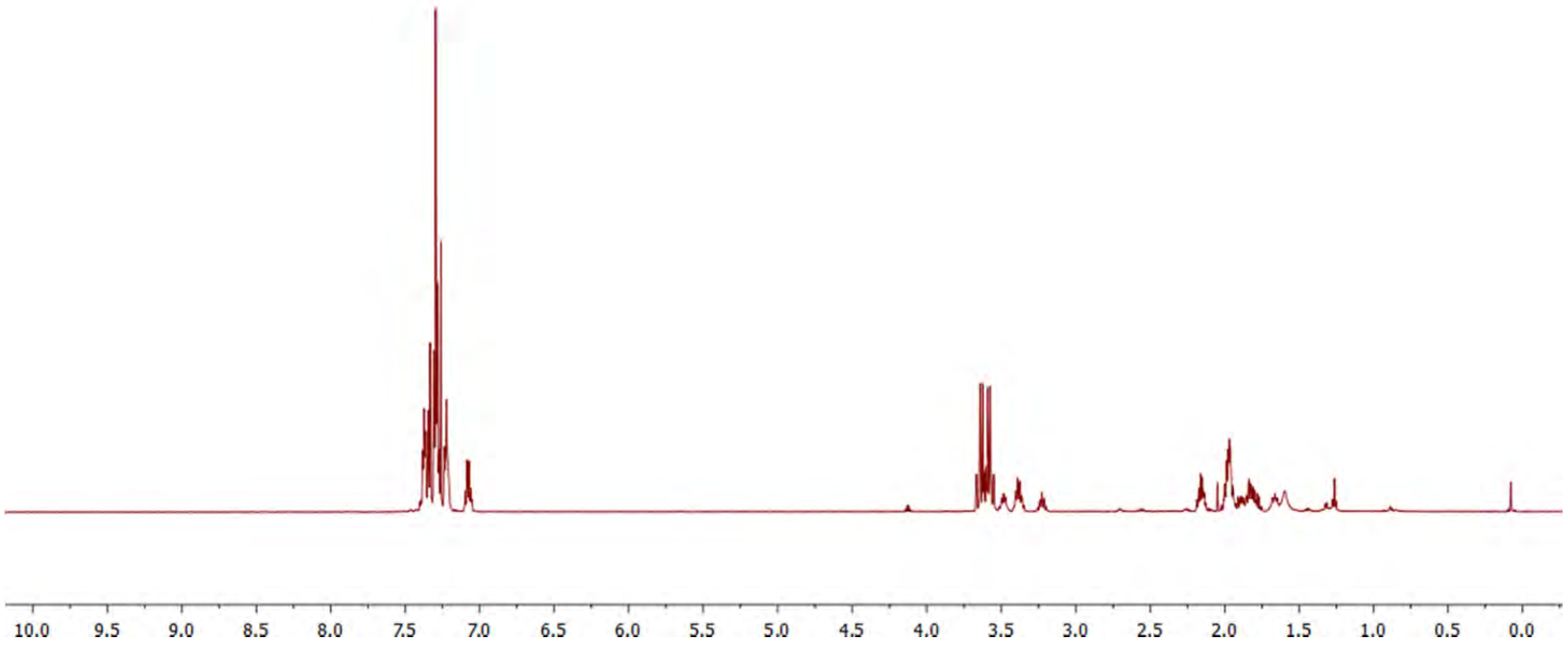
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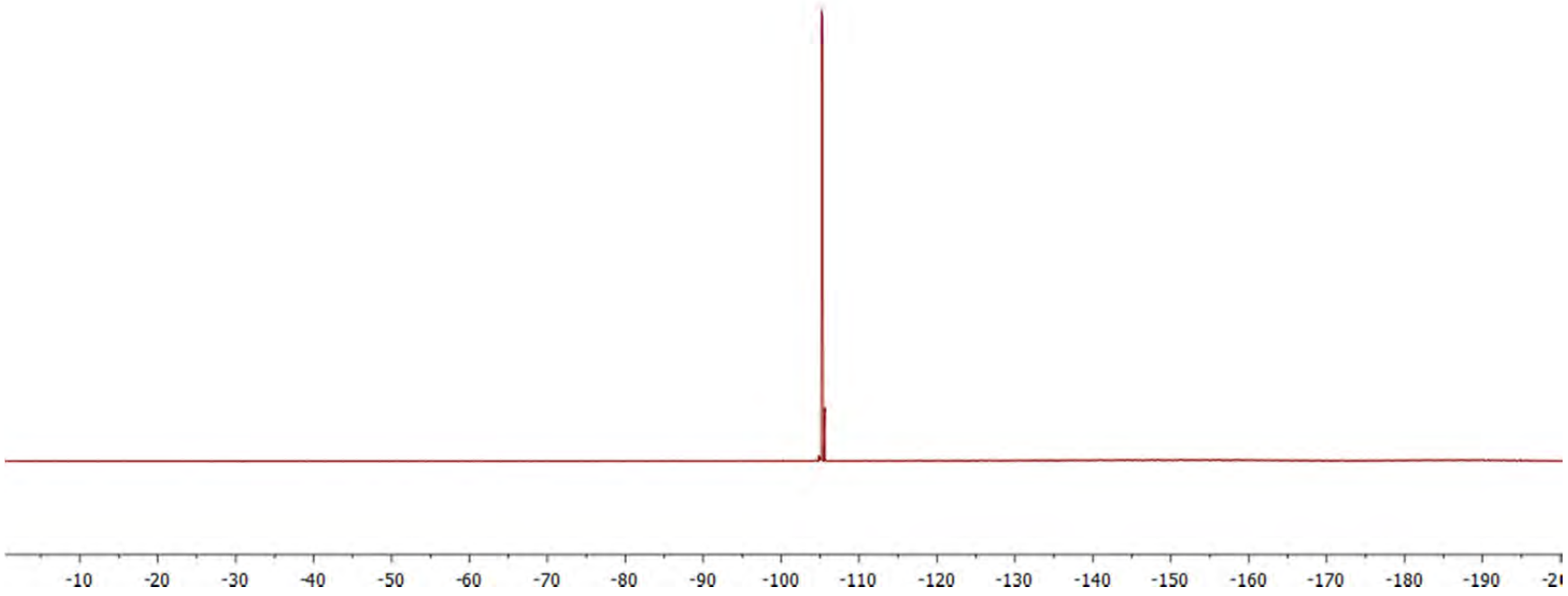
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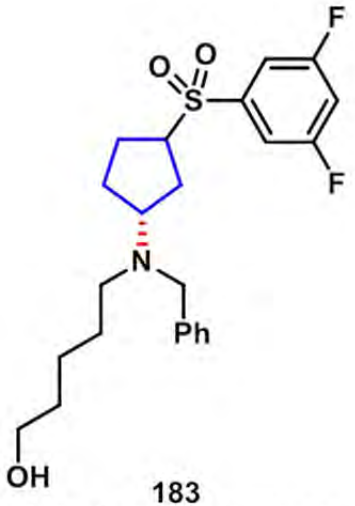
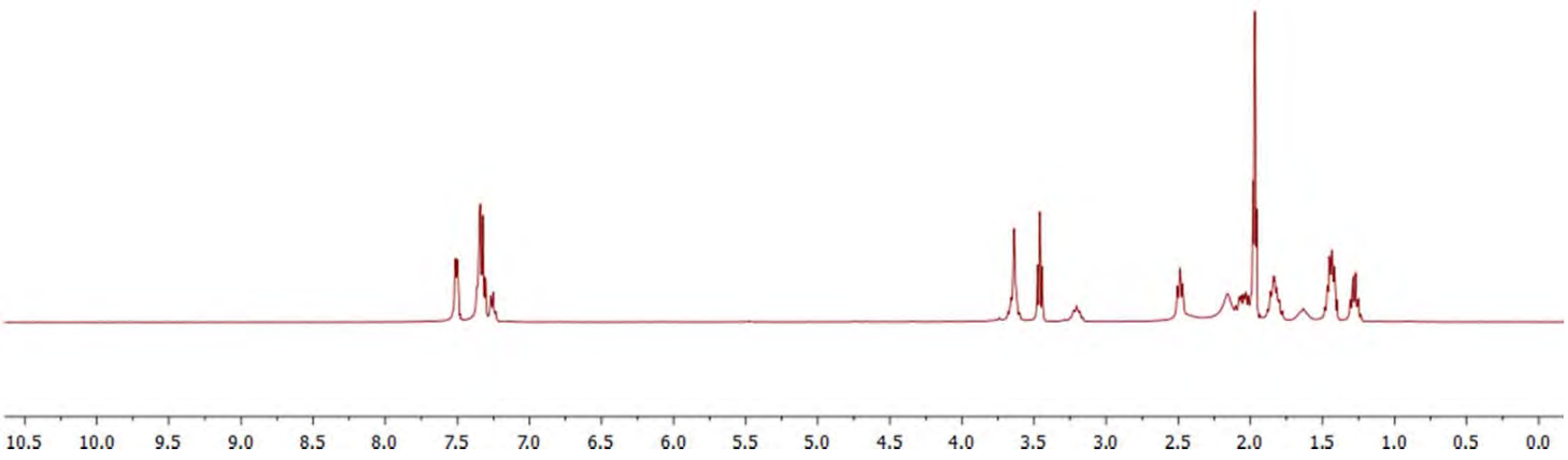
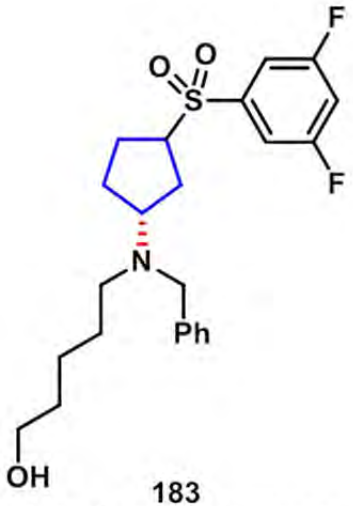


183
[*cis*-diastereoisomer]





183
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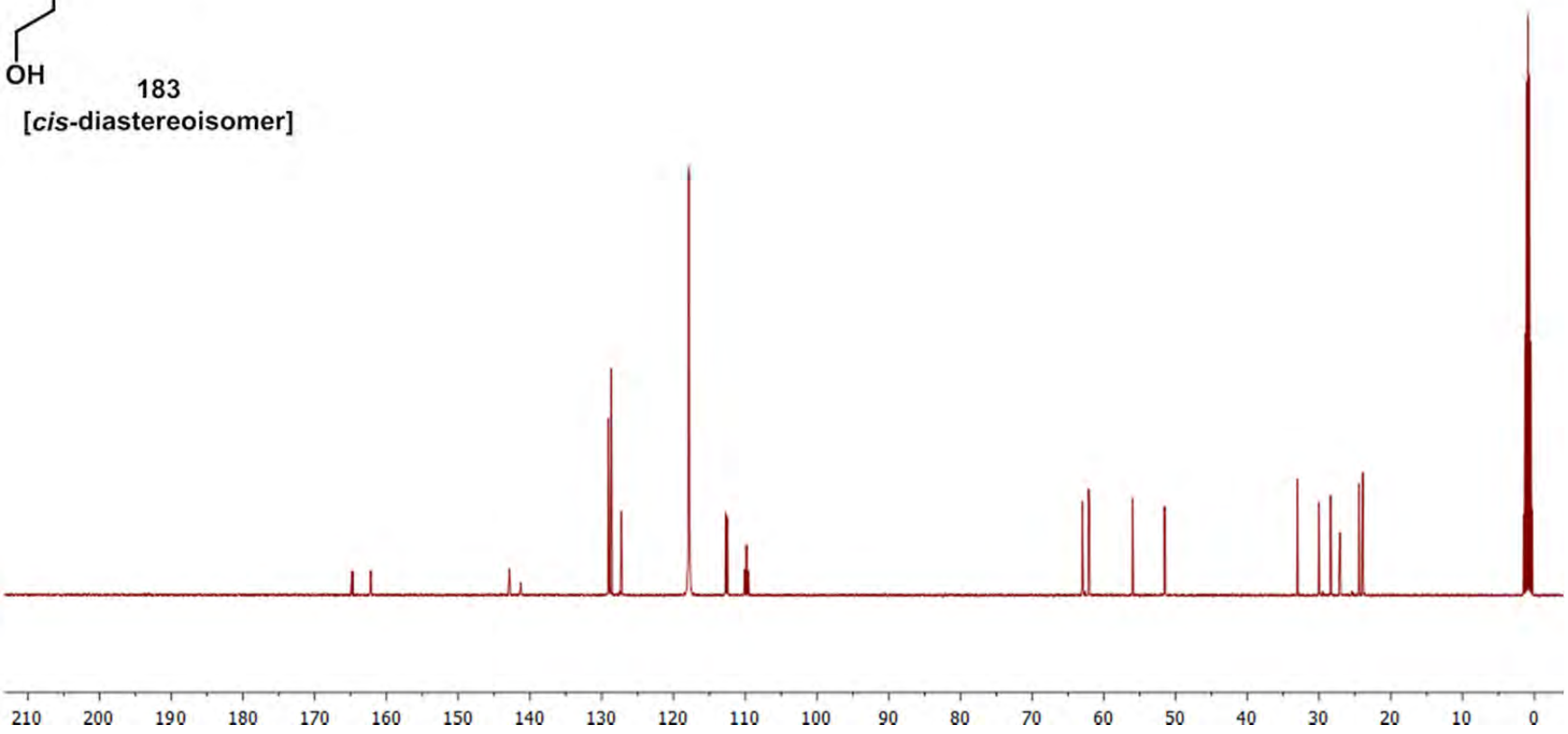
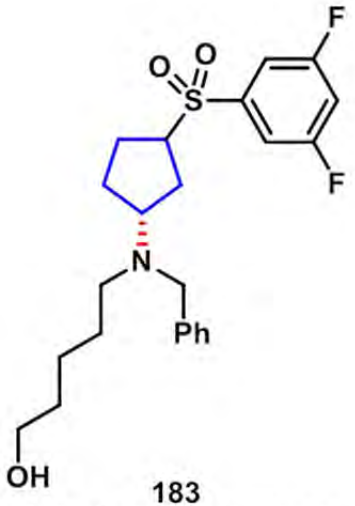
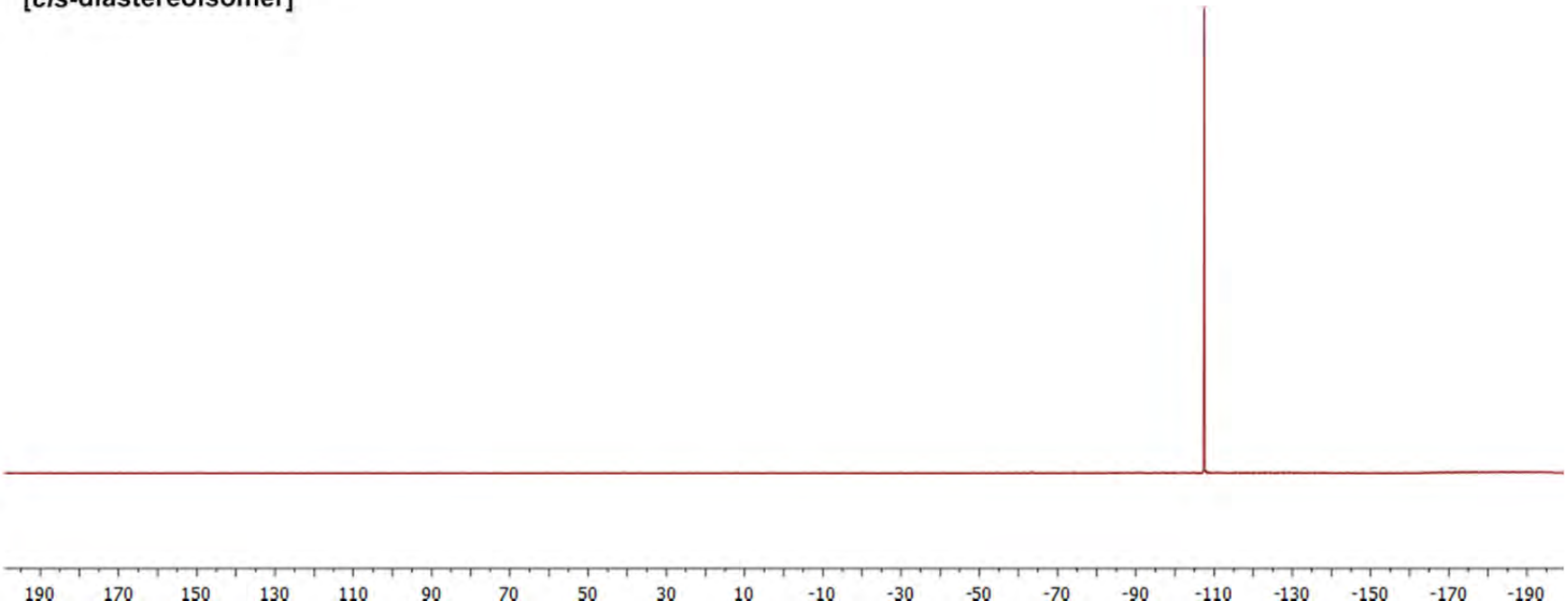
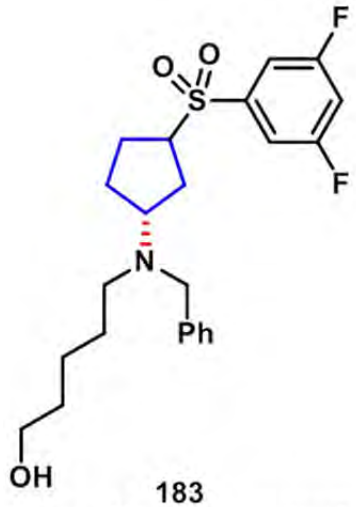


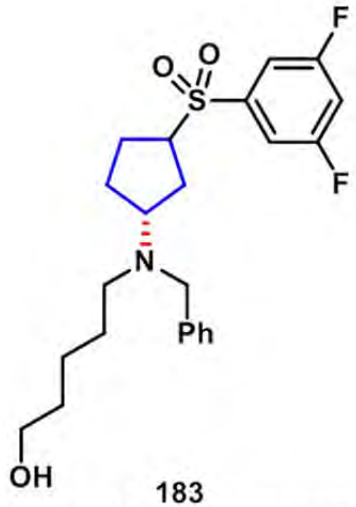


183
[*cis*-diastereoisomer]

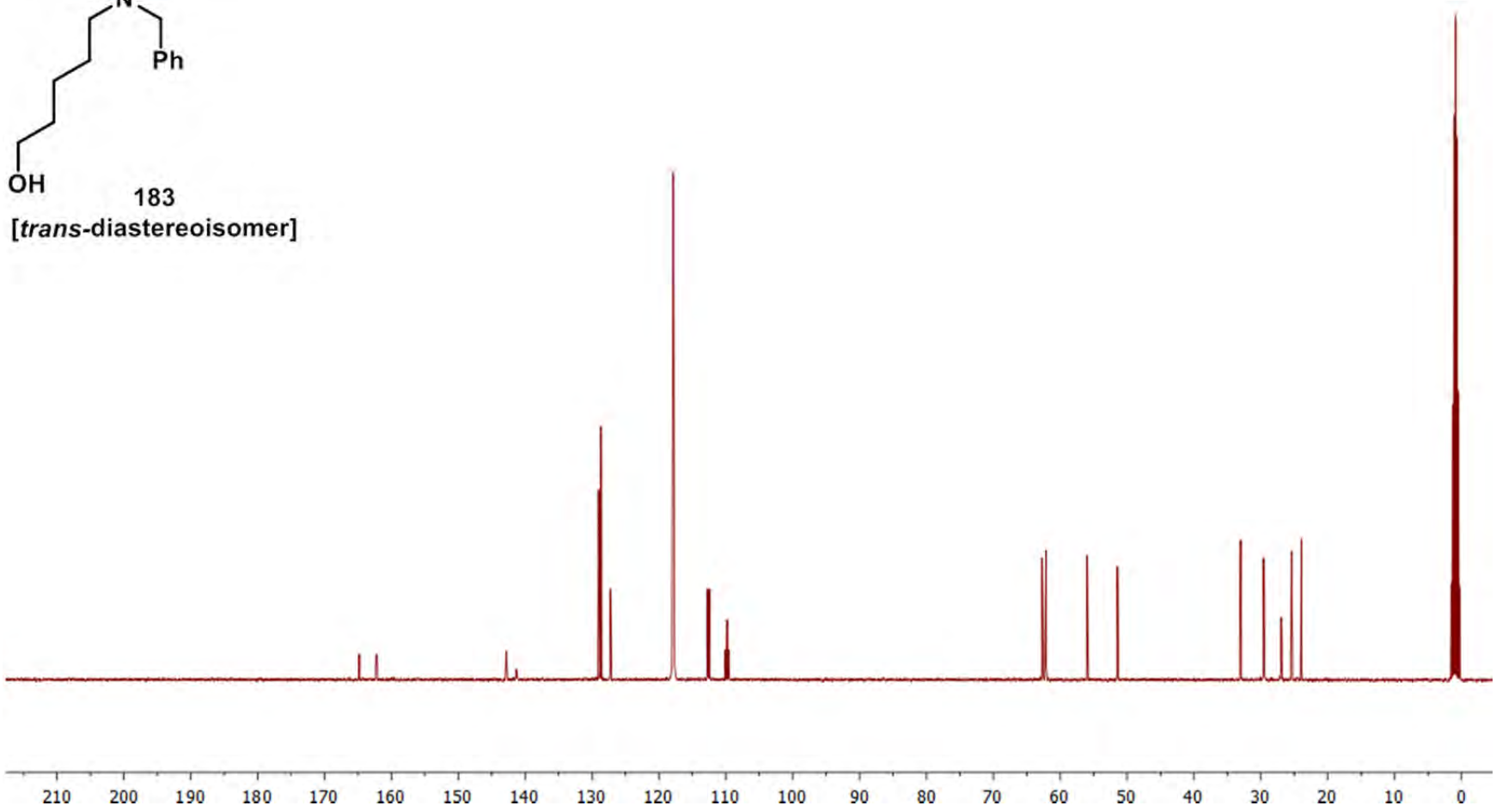


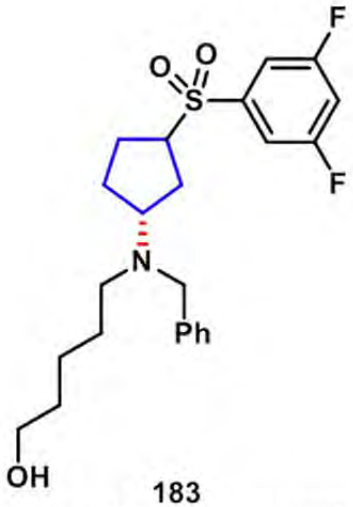


183
[*trans*-diastereoisomer]



183
[*trans*-diastereoisomer]





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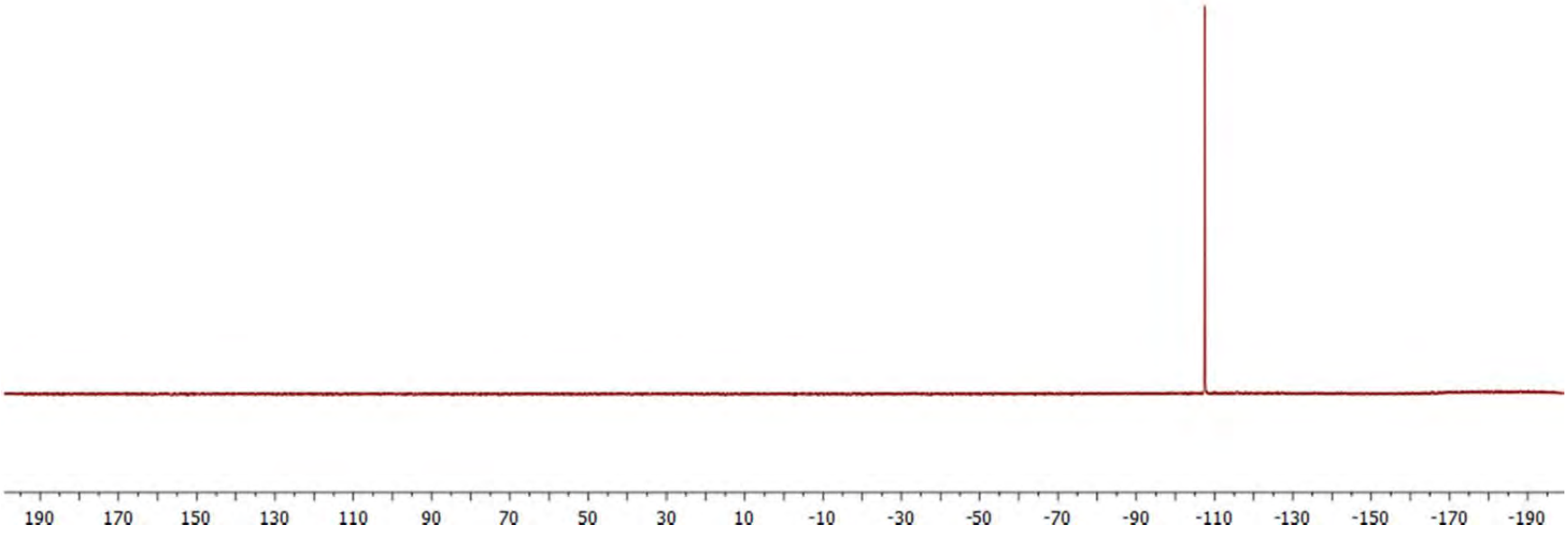
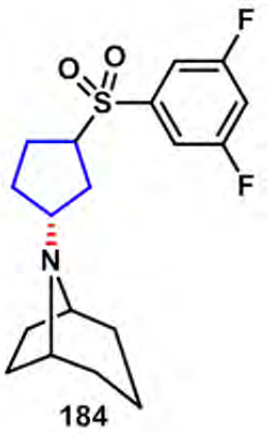
[*trans*-diastereoisomer]

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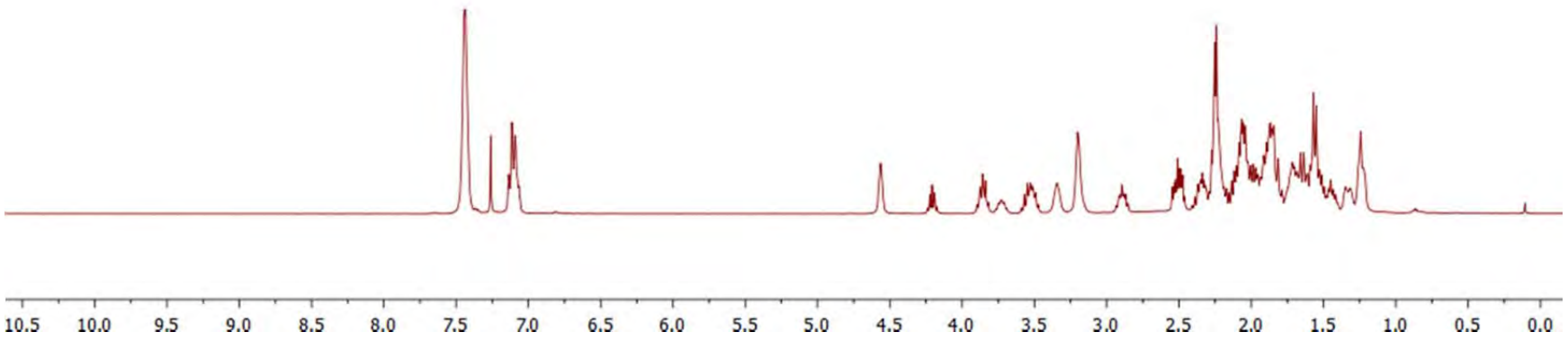
184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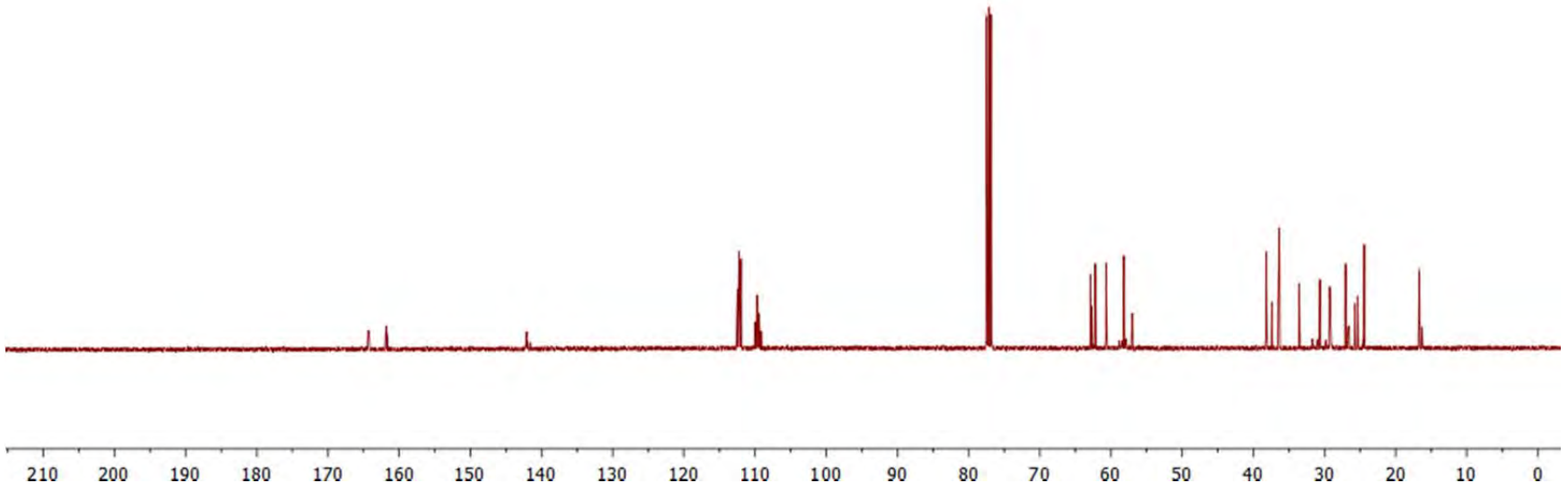
184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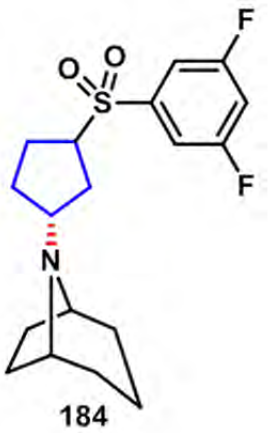
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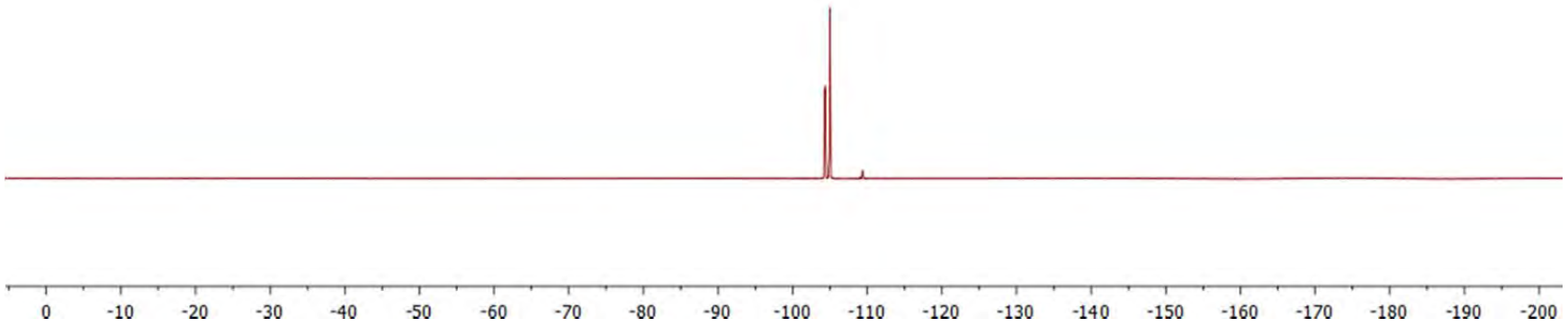
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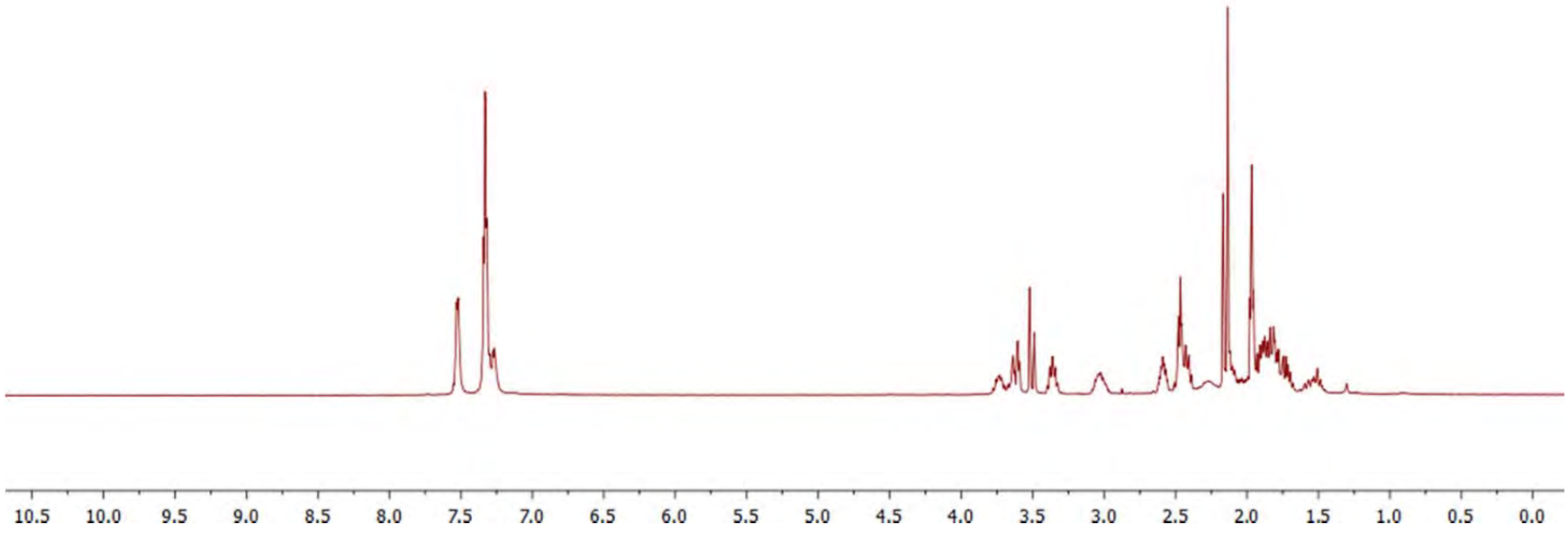
185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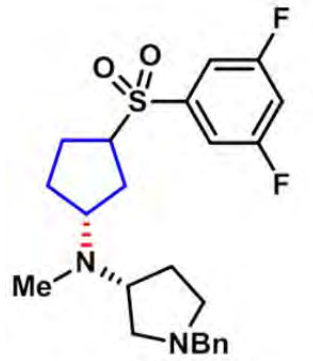
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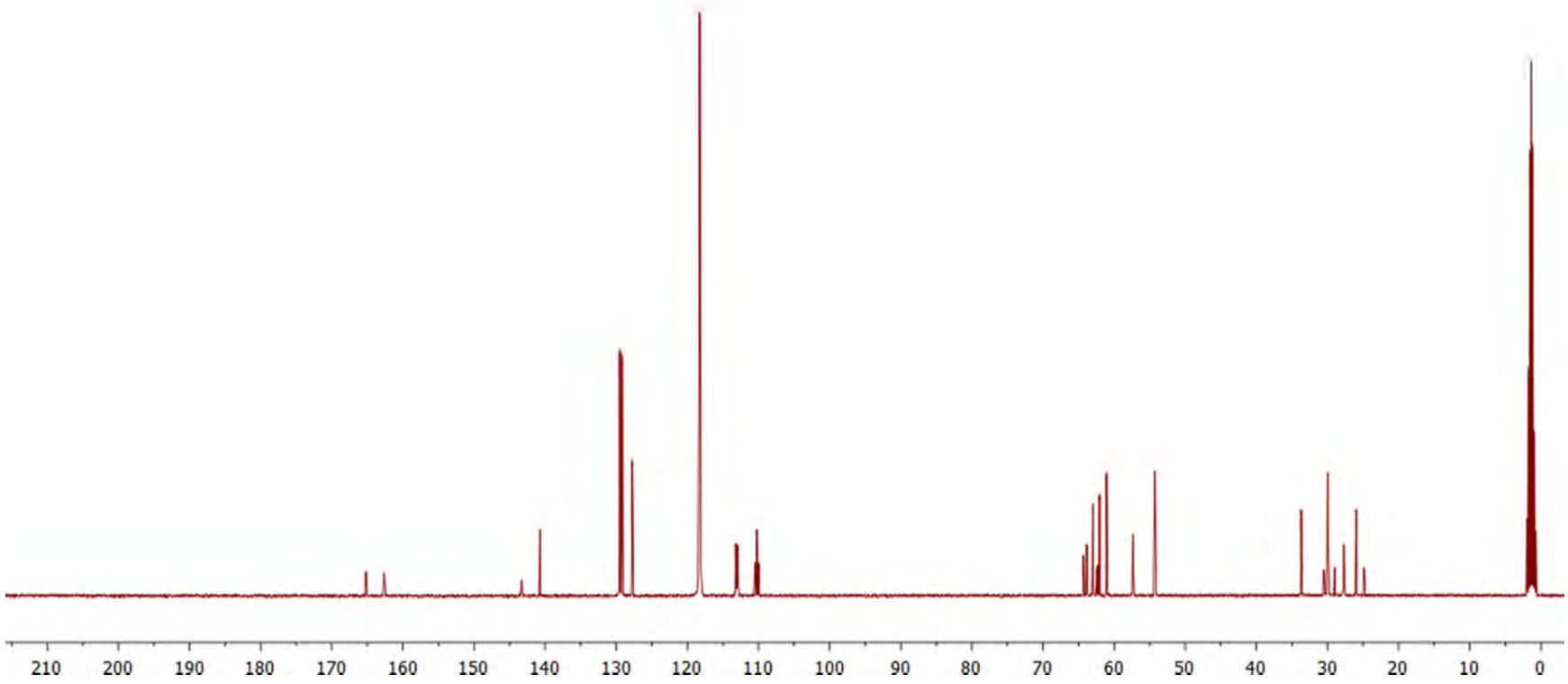
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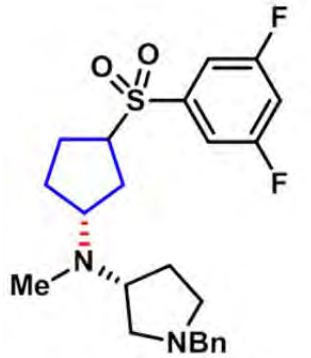
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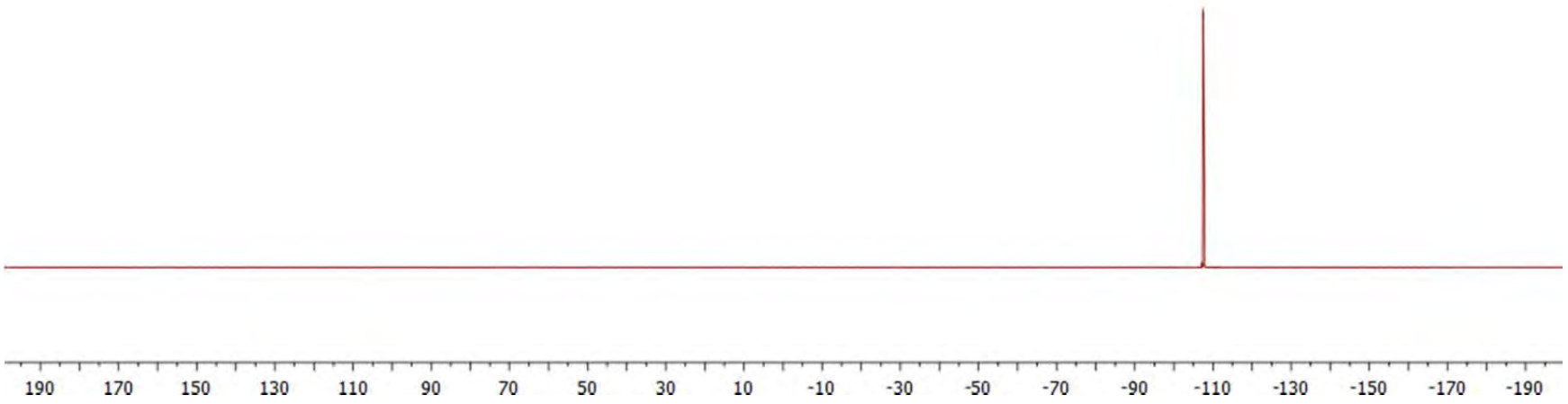
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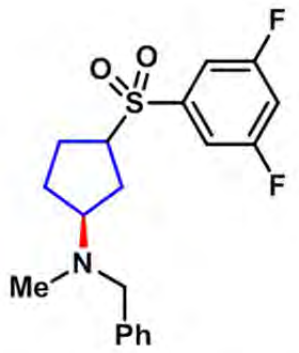
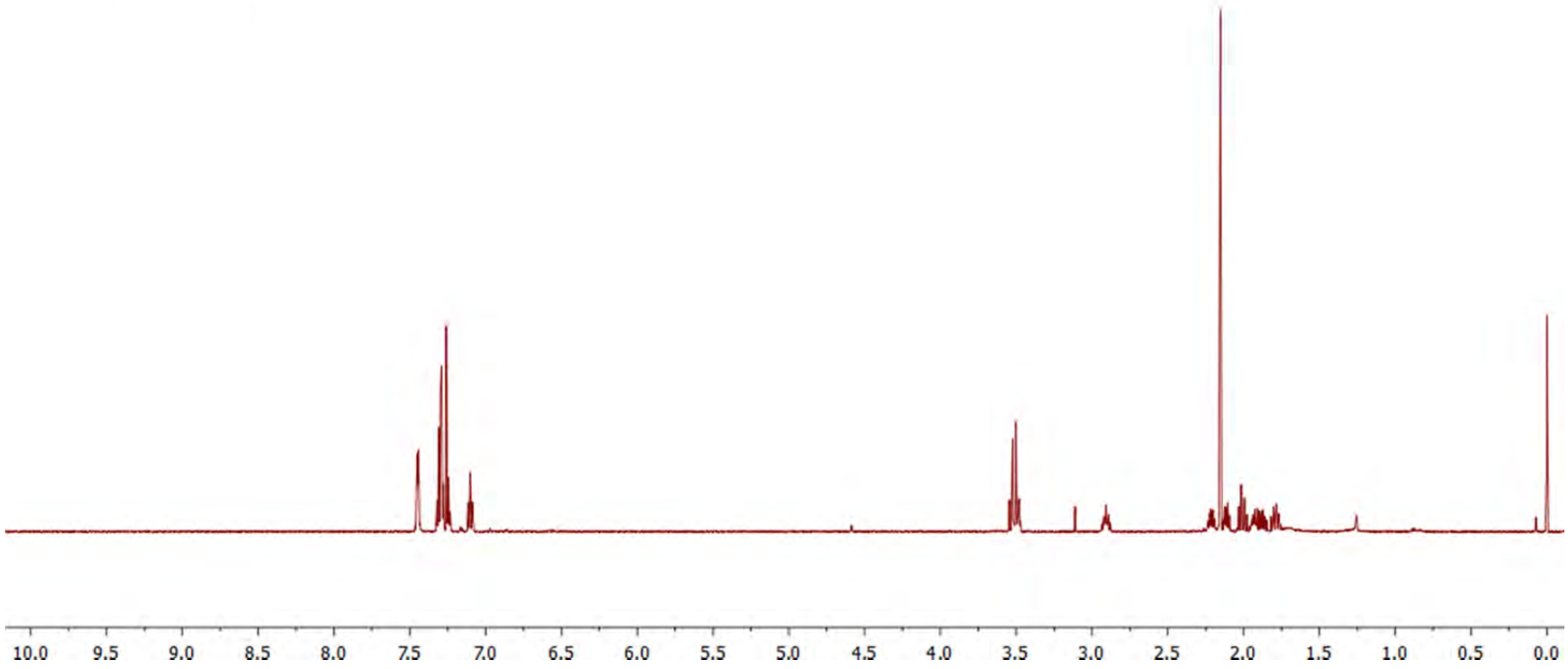
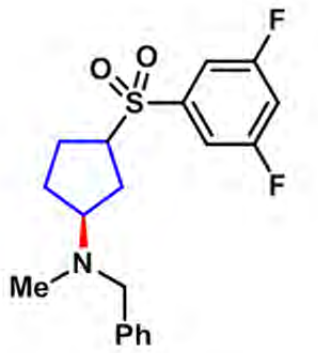


186

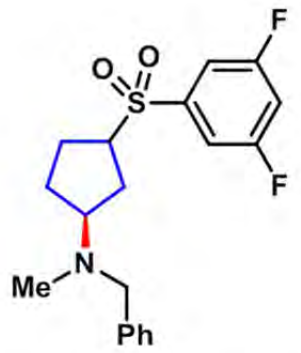
[Major diastereoisomer]





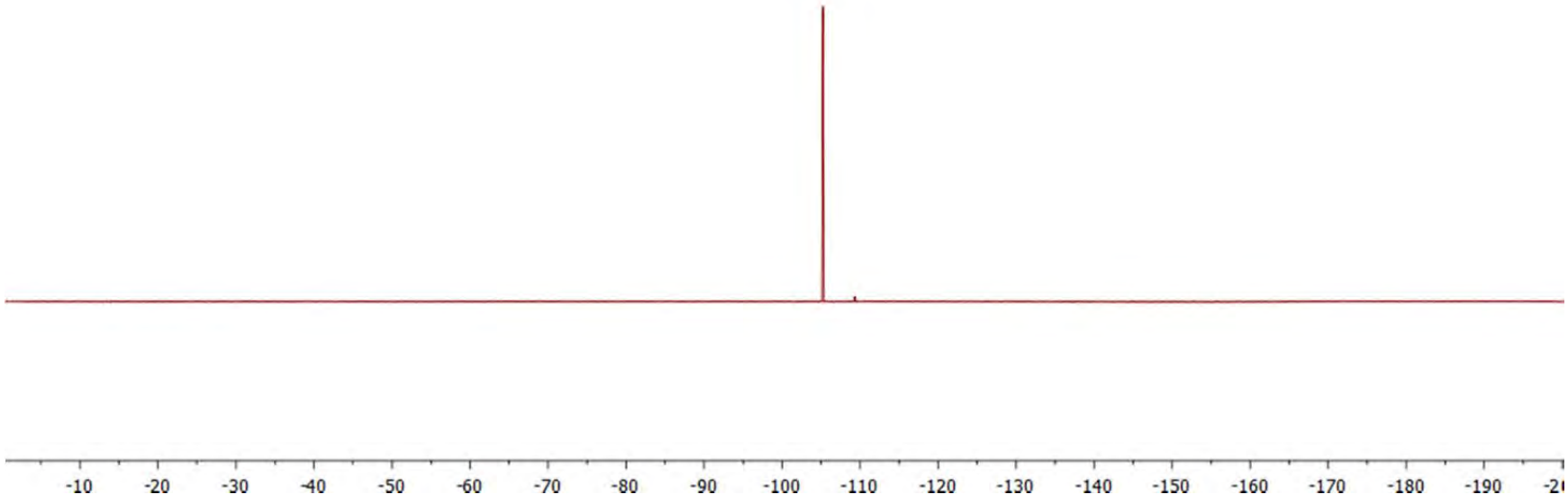
186

[Major diastereoisomer]



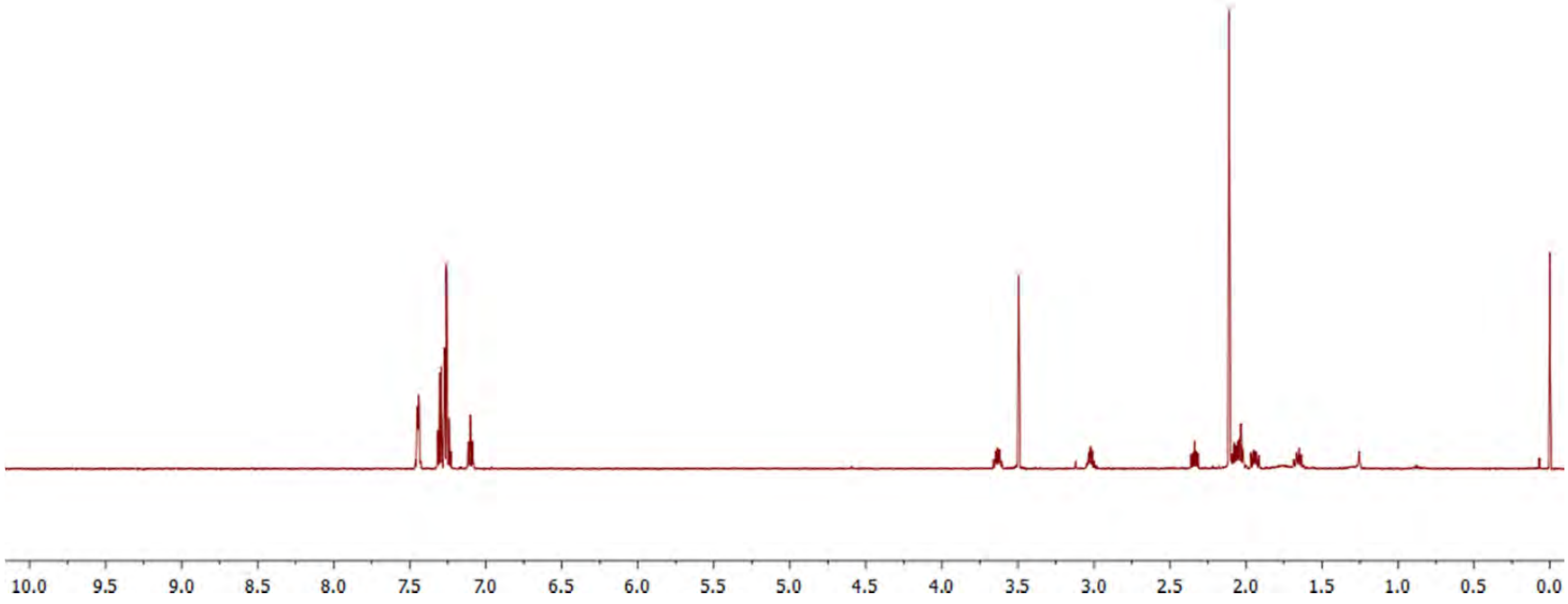
186

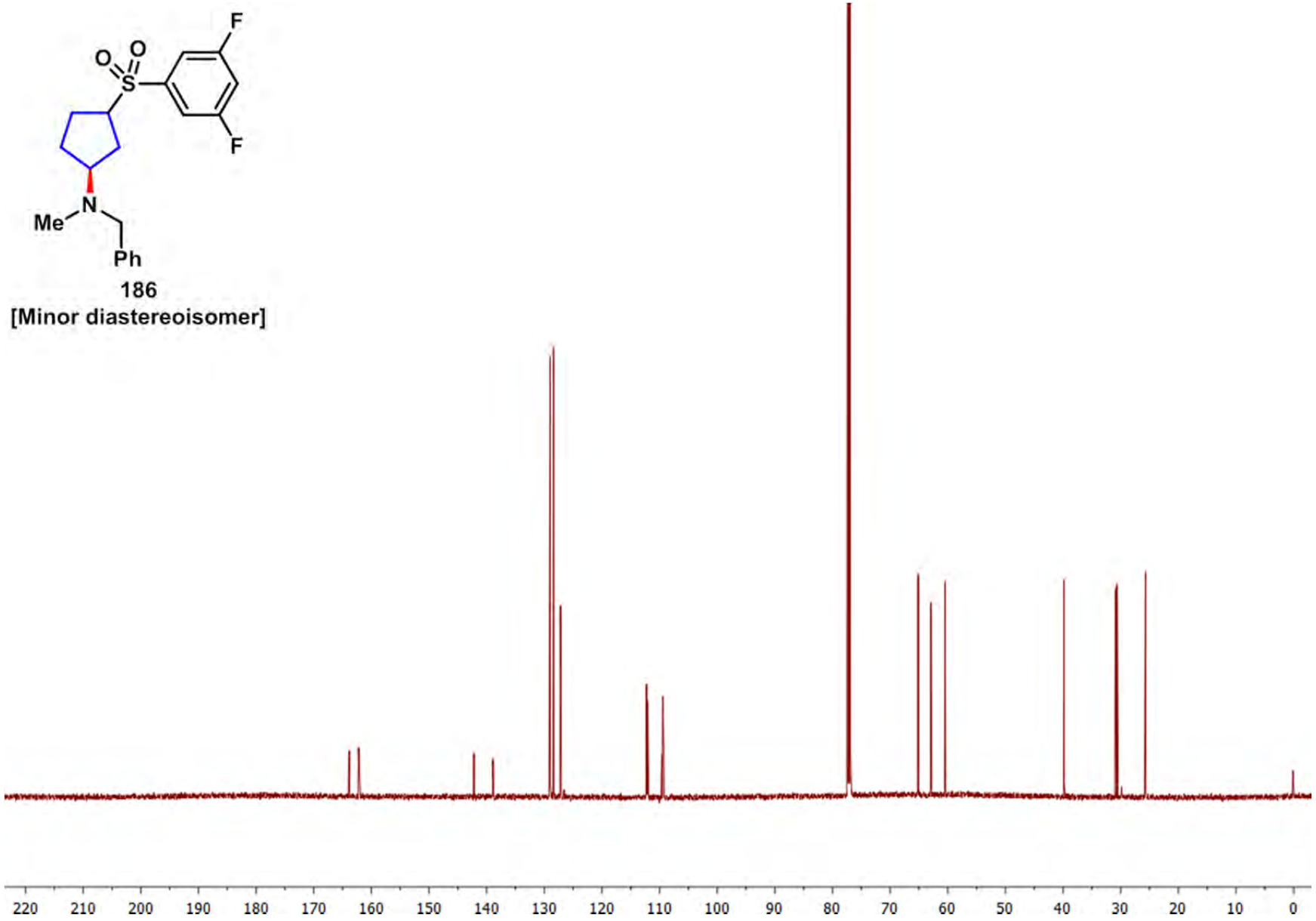
[Major diastereoisomer]



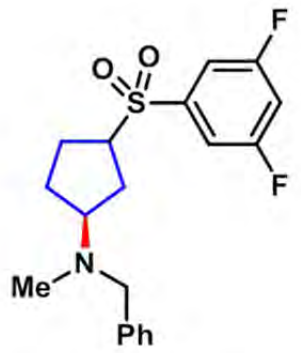
186

[Minor diastereoisomer]



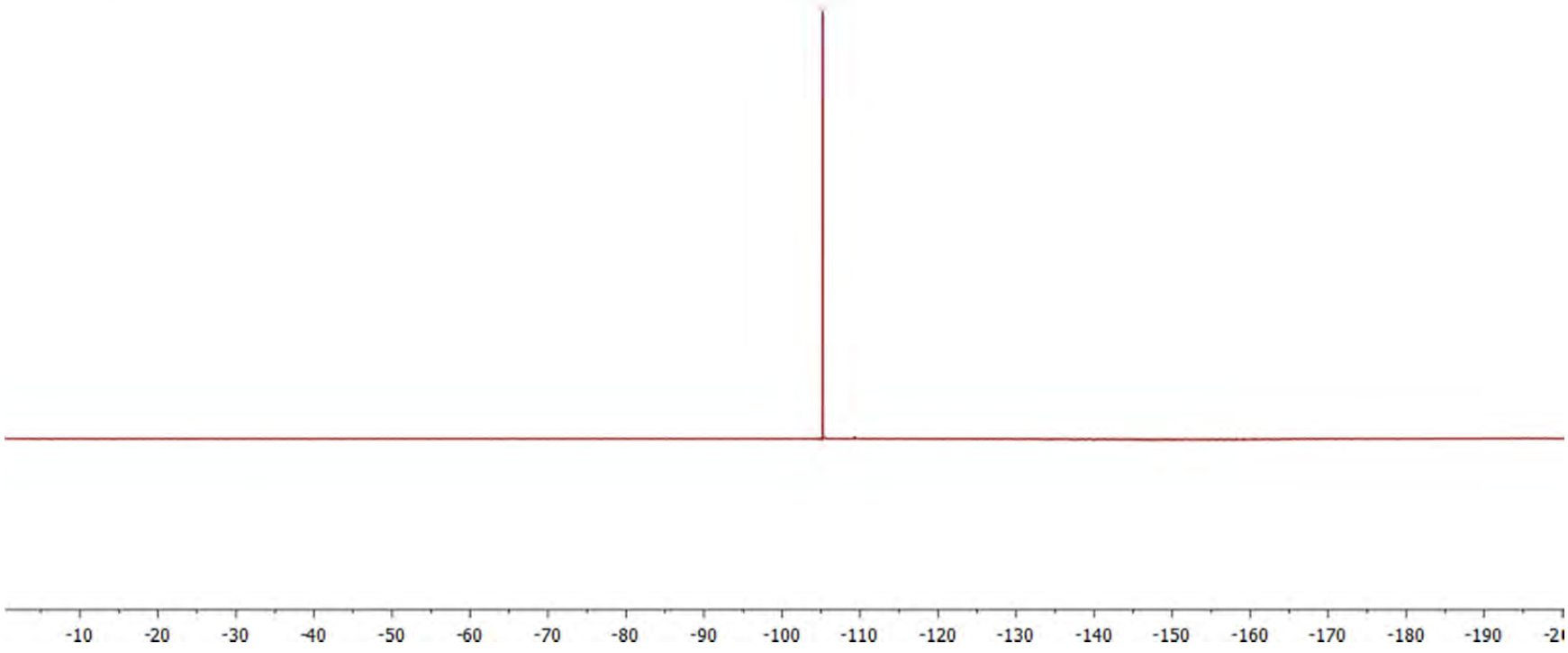


186
[Minor diastereoisomer]



186

[Minor diastereoisomer]

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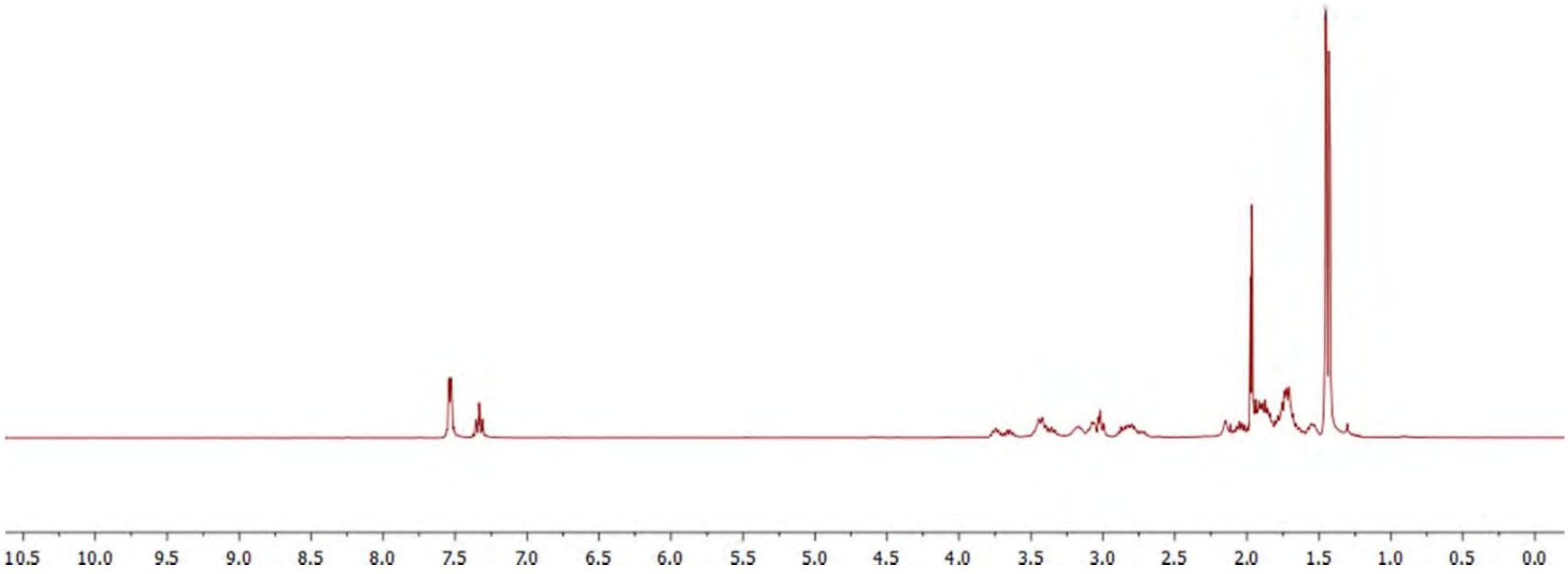
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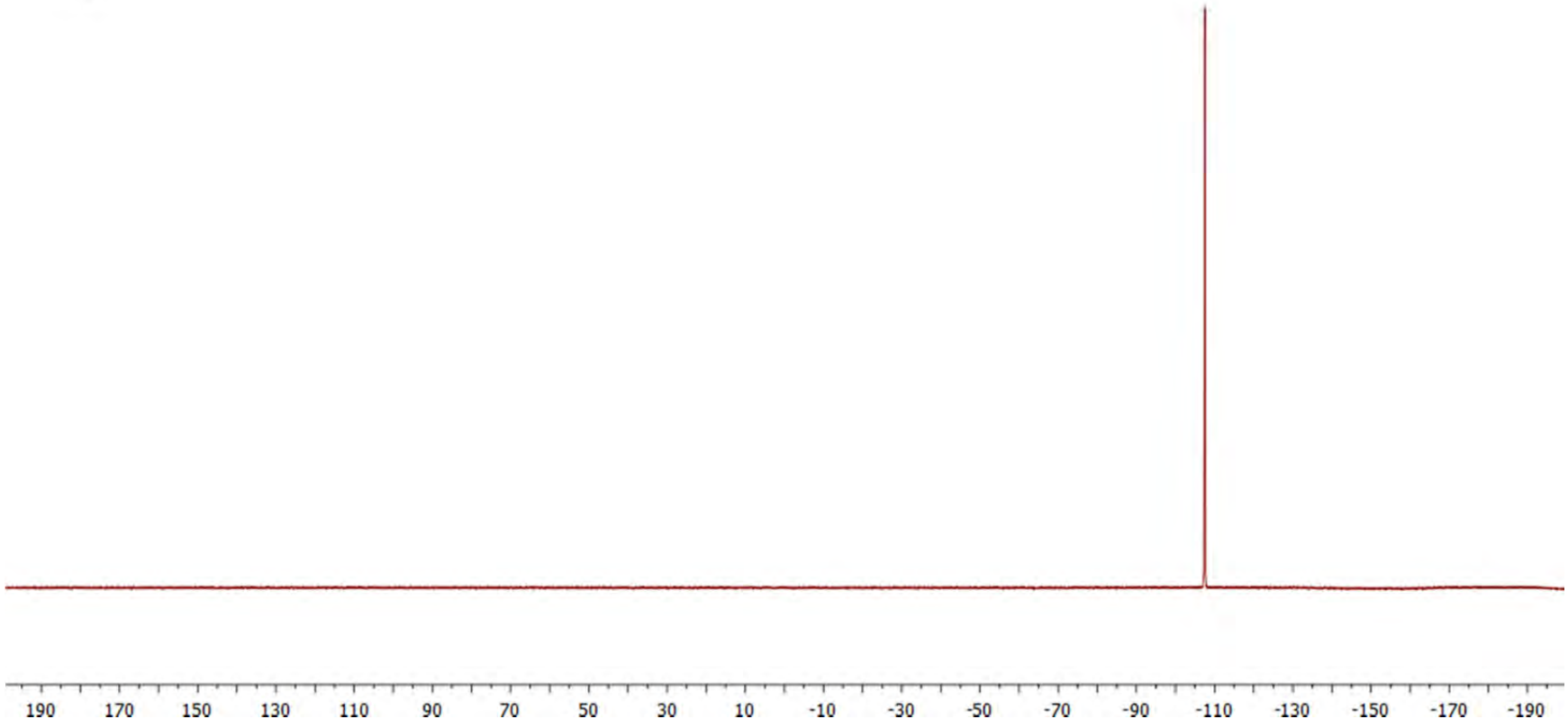
187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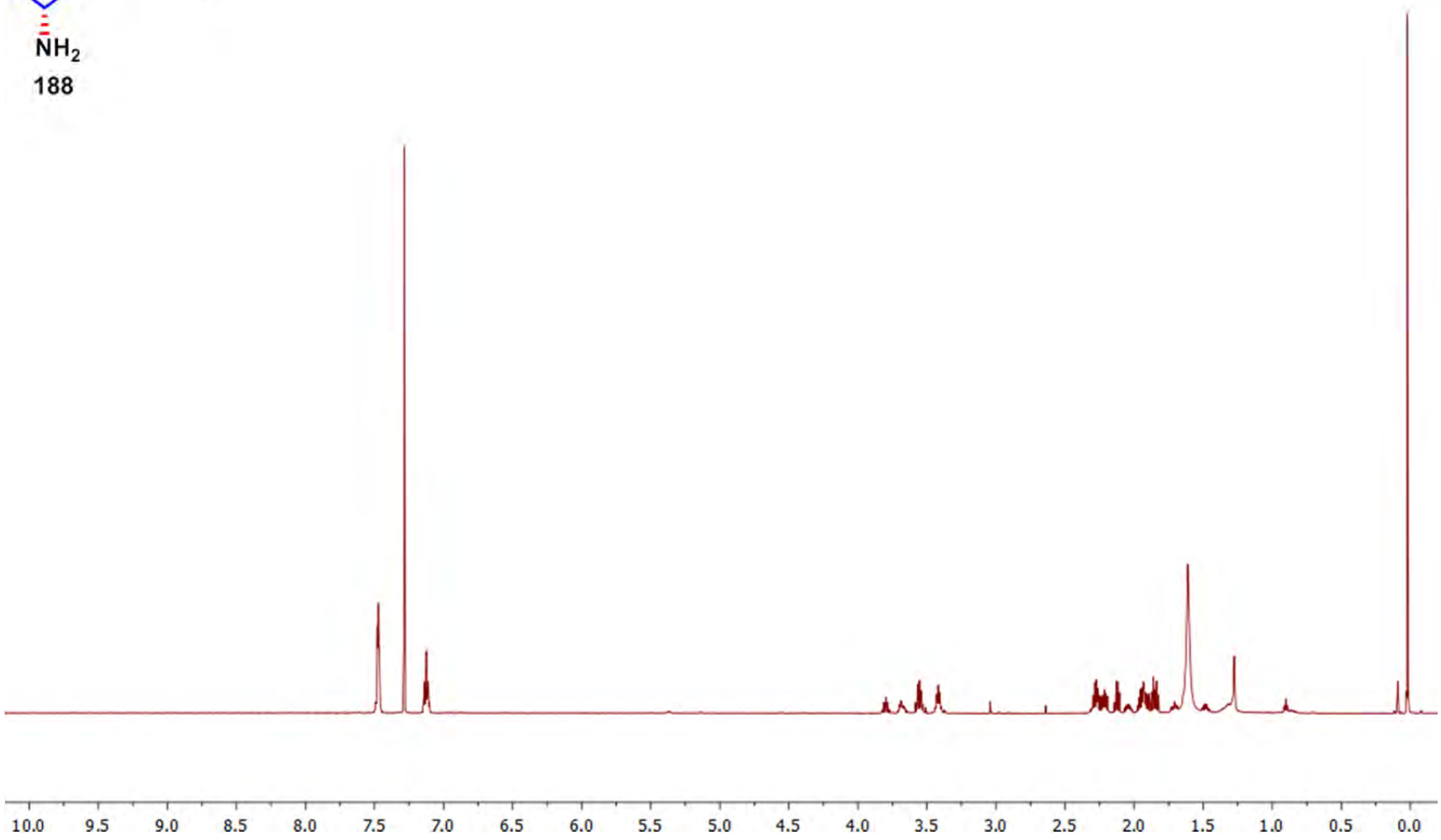
188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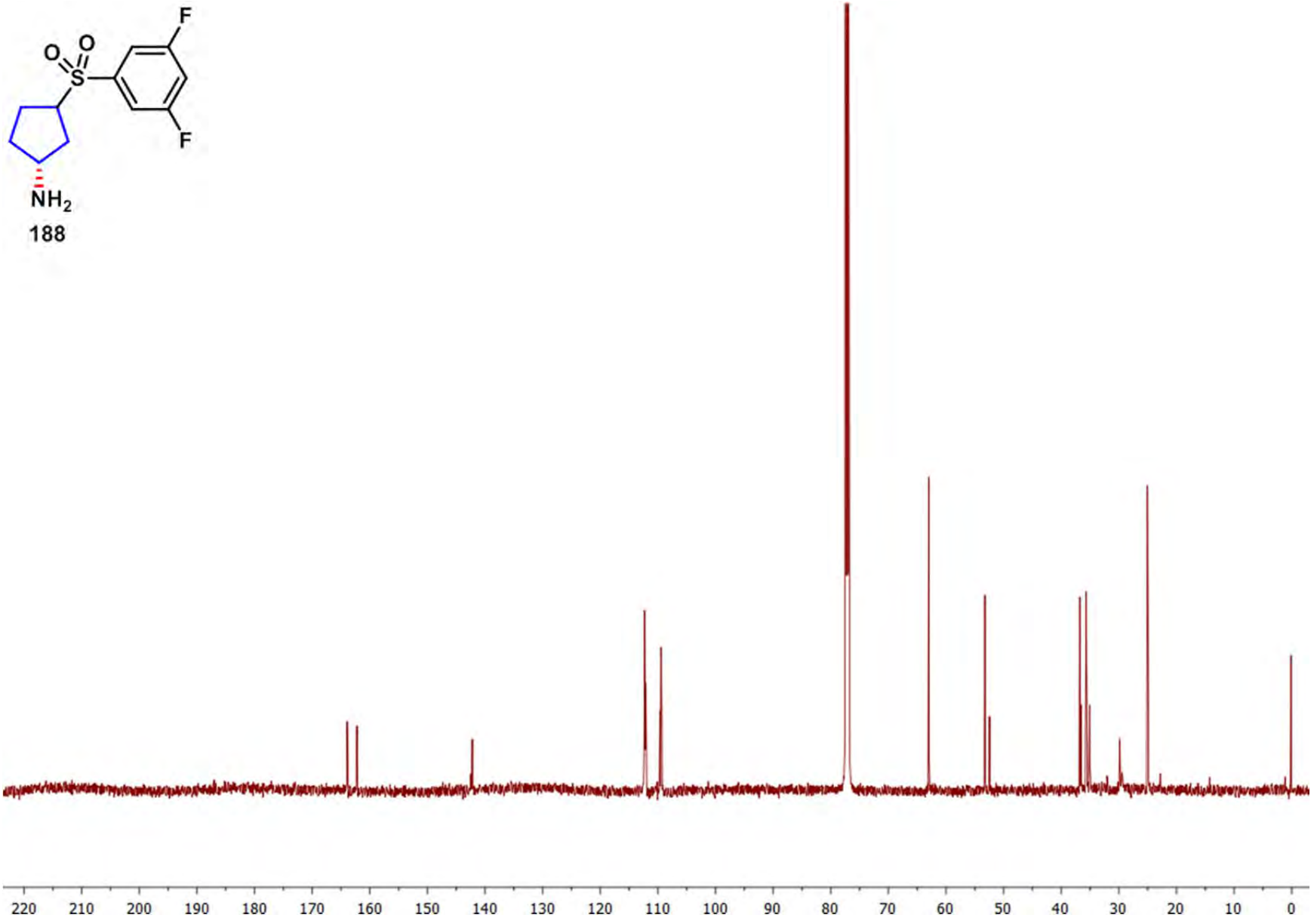
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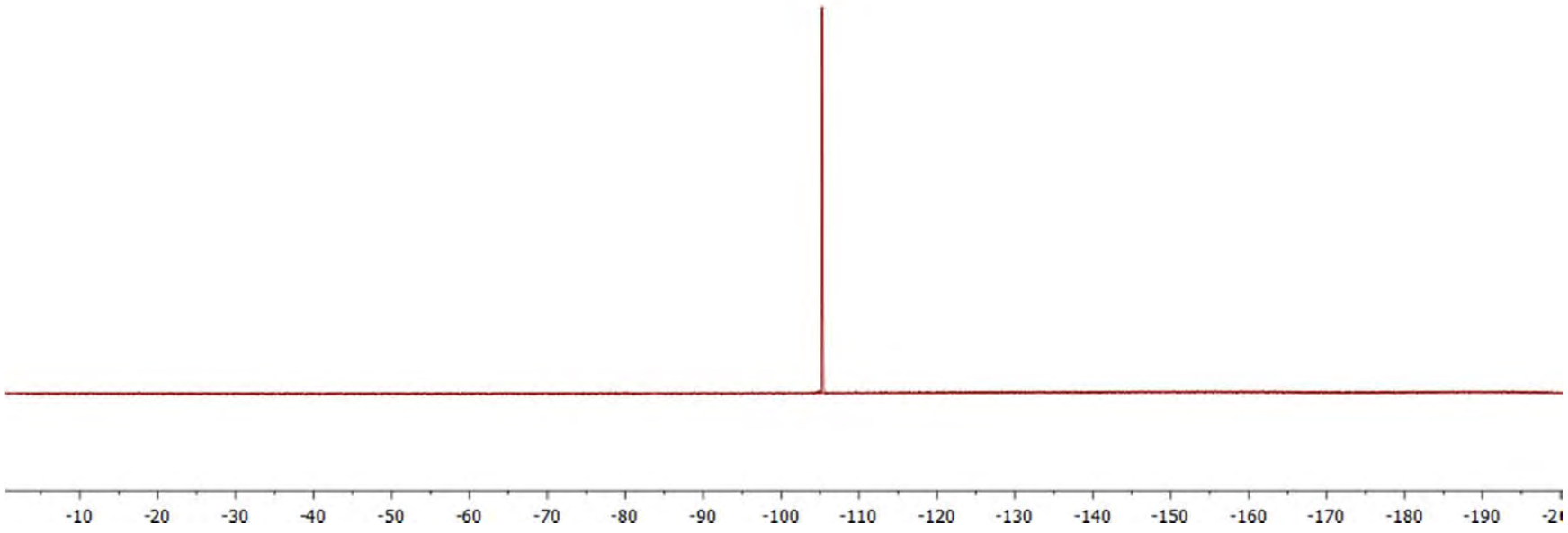
188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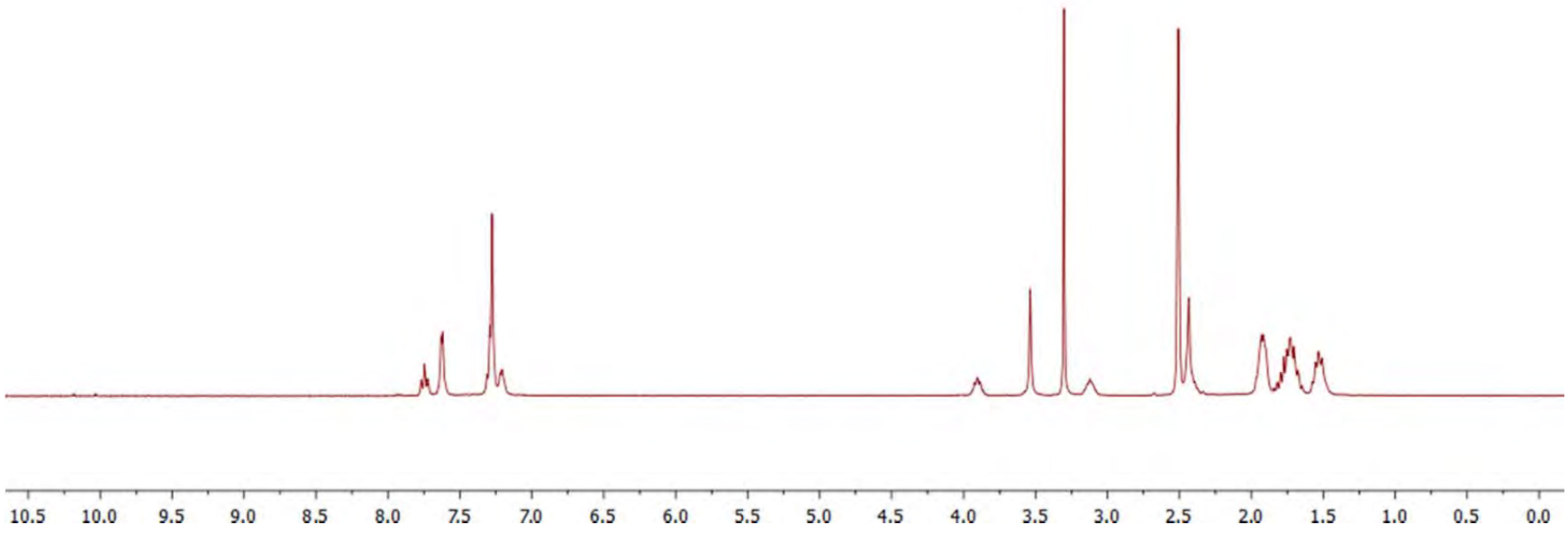
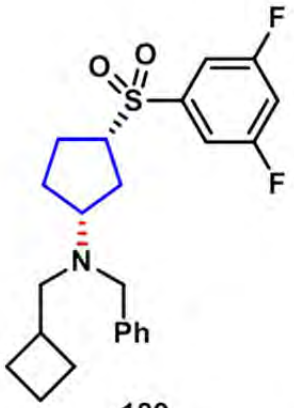
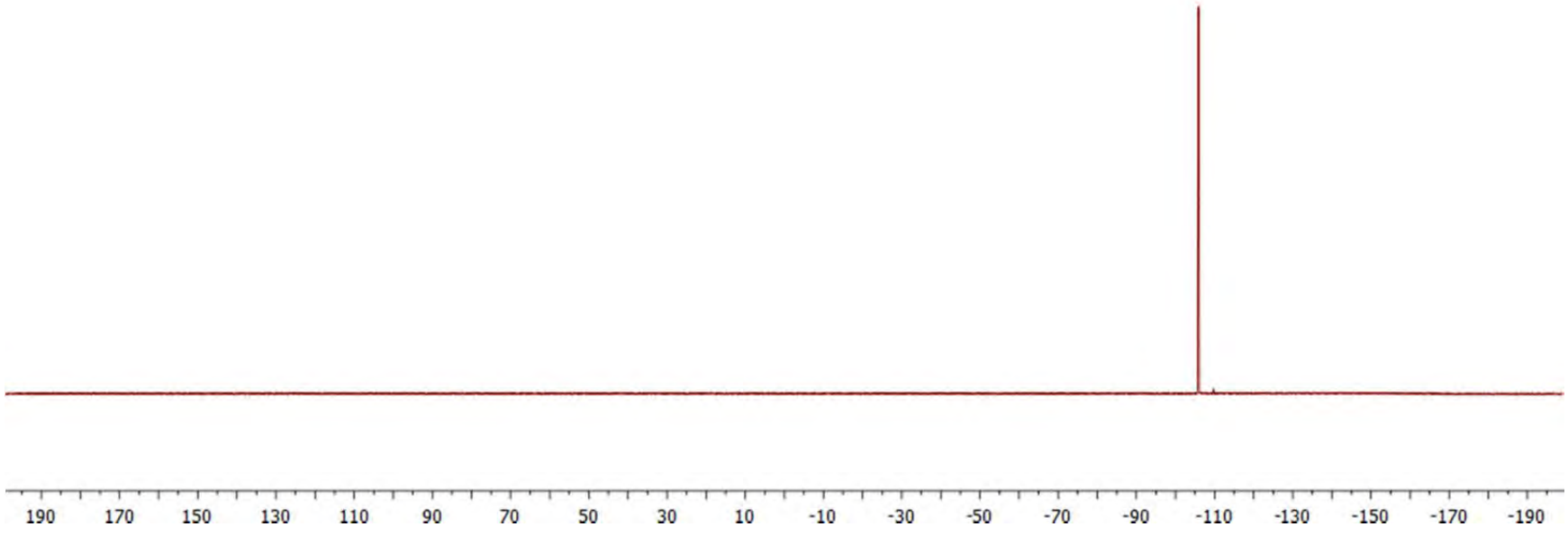
189
[*cis*-diastereoisomer]

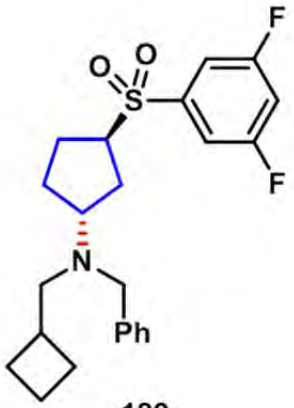


189
[*cis*-diastereoisomer]

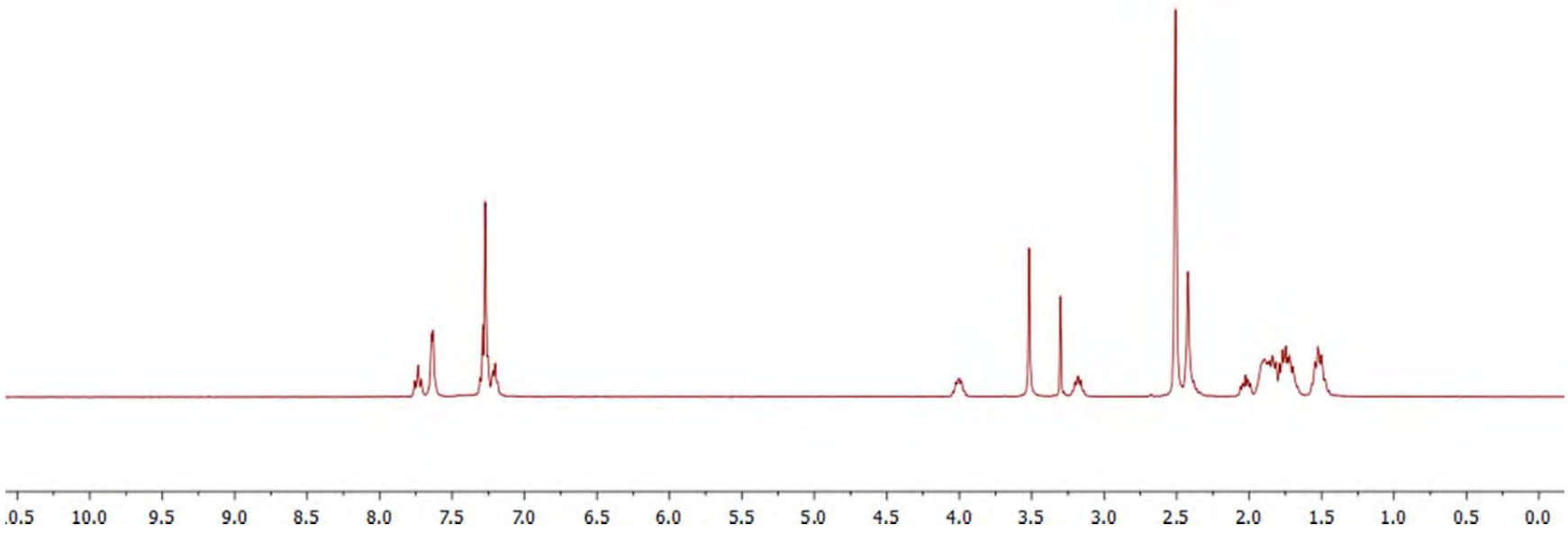


189
[*cis*-diastereoisomer]





189
[*trans*-diastereoisomer]



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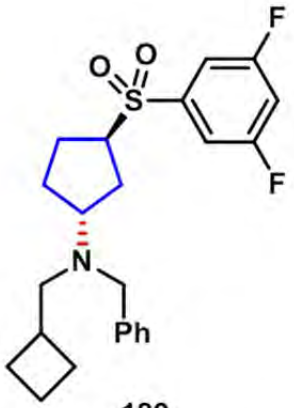

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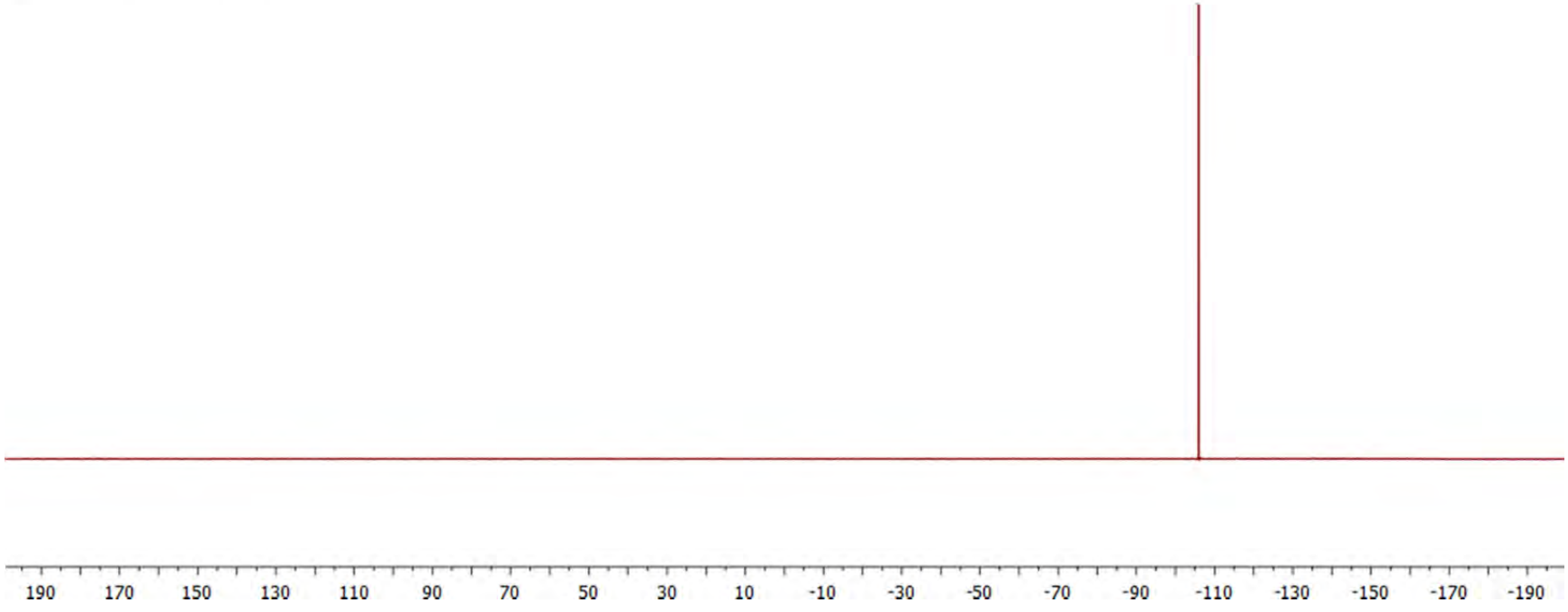
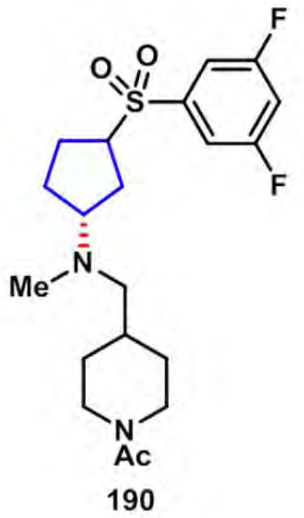
[*trans*-diastereoisomer]

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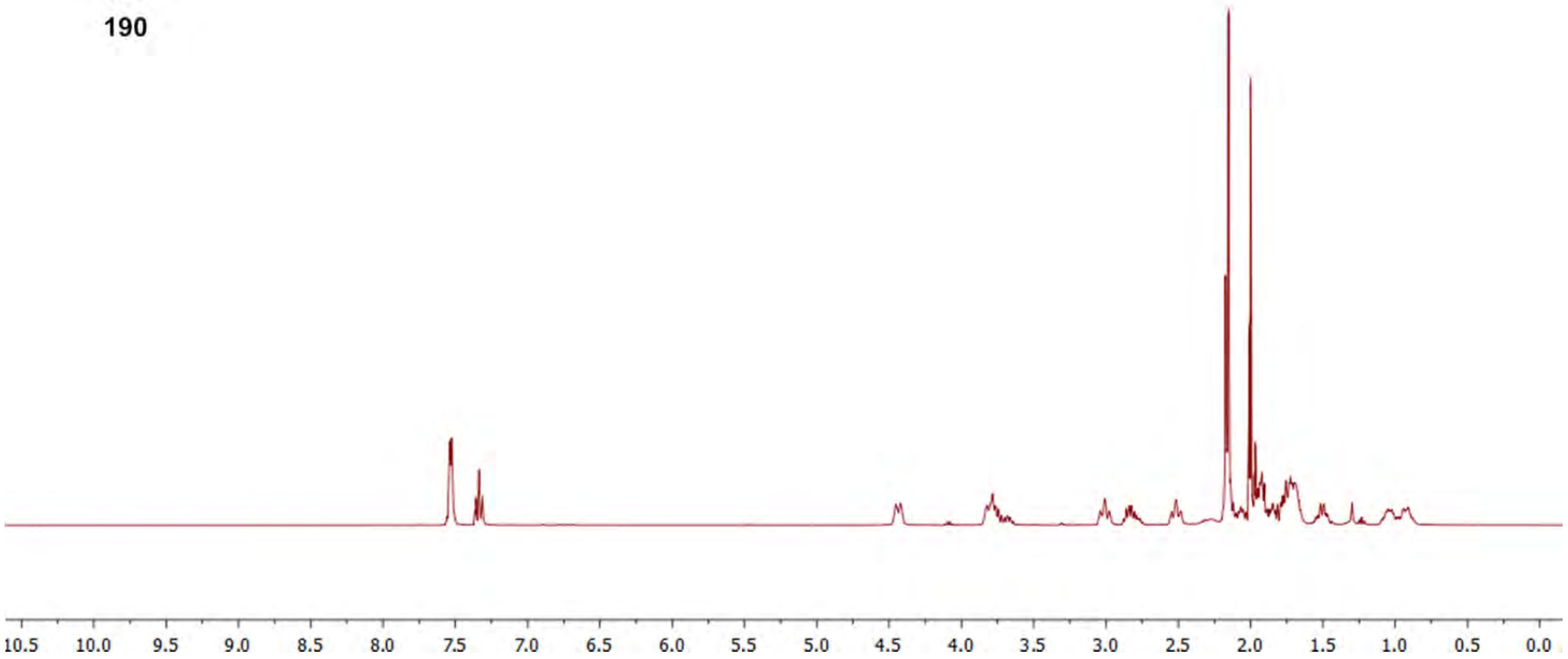
Ac

190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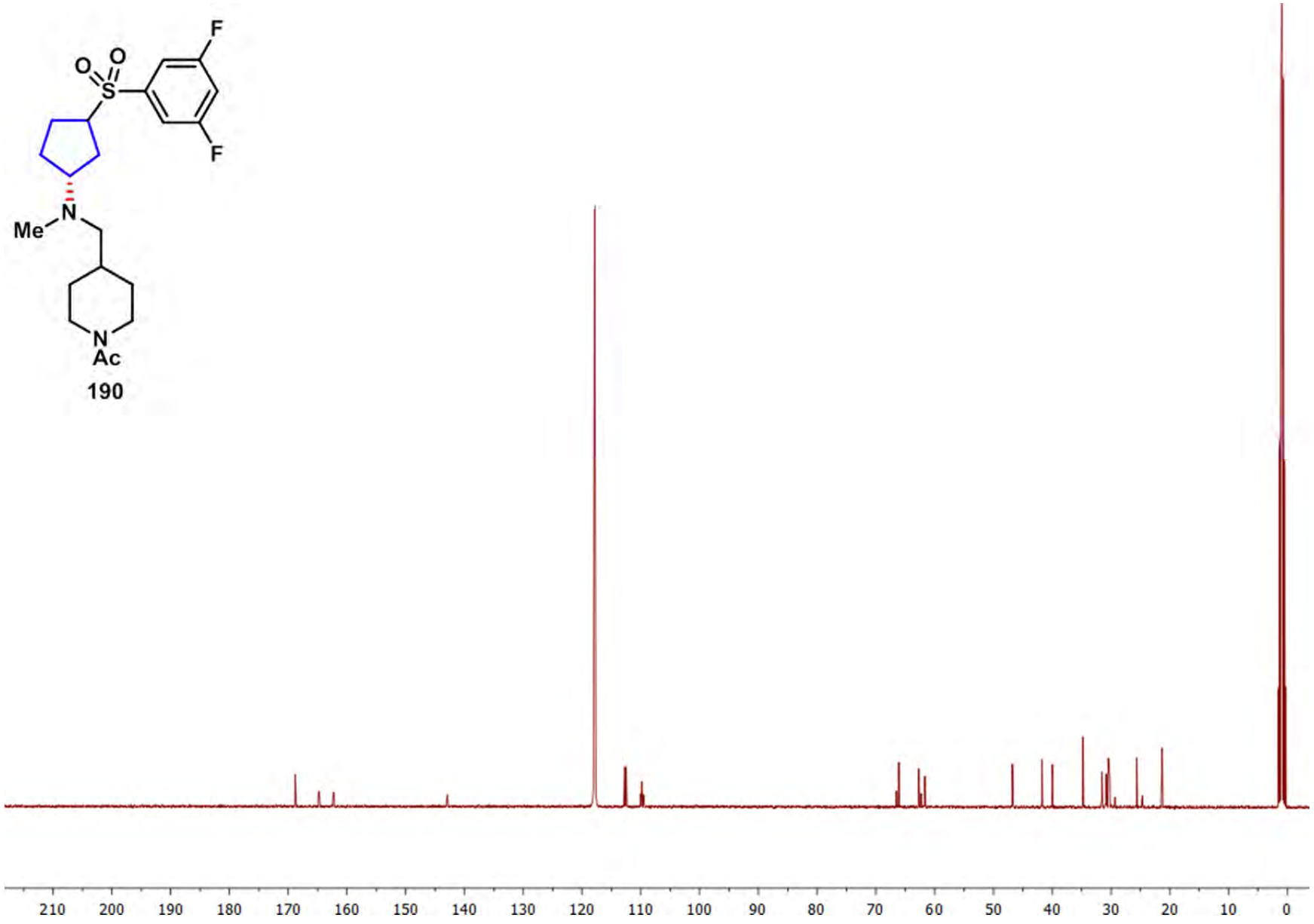
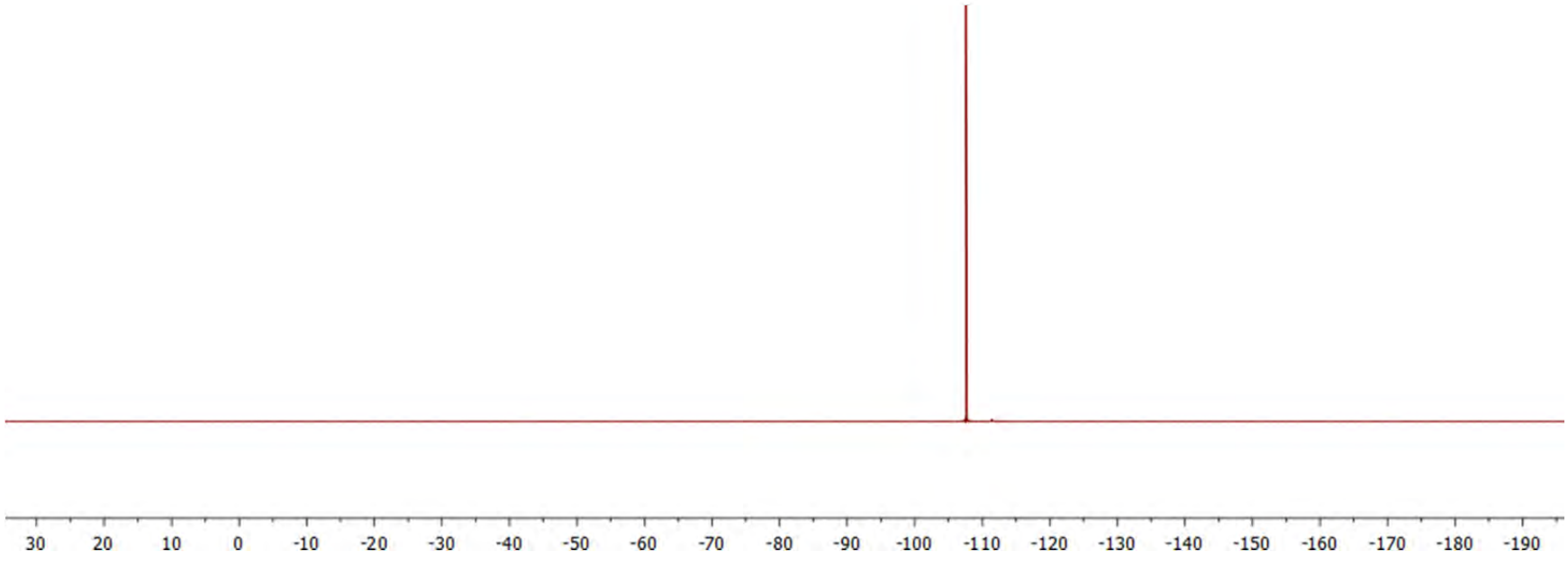
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


F
O
O
S
F
N
Me
N
Ac
190
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F
O
O
S
F
N
Me
N
Ac

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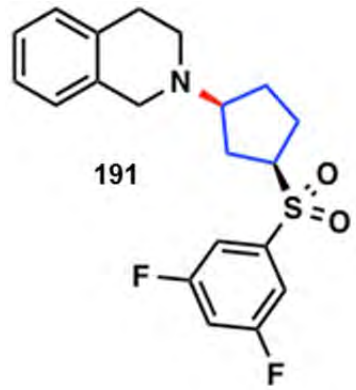
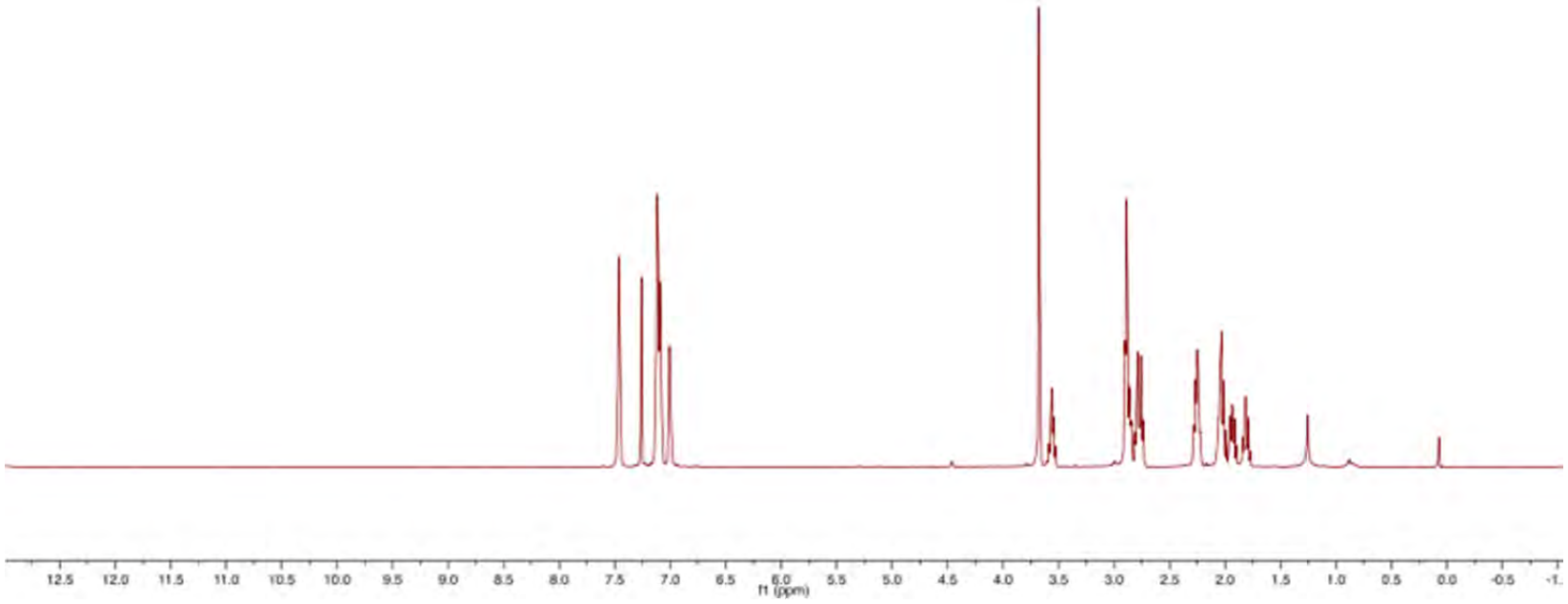
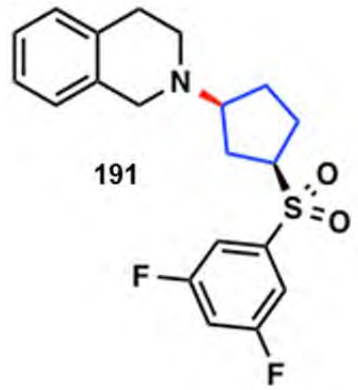
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

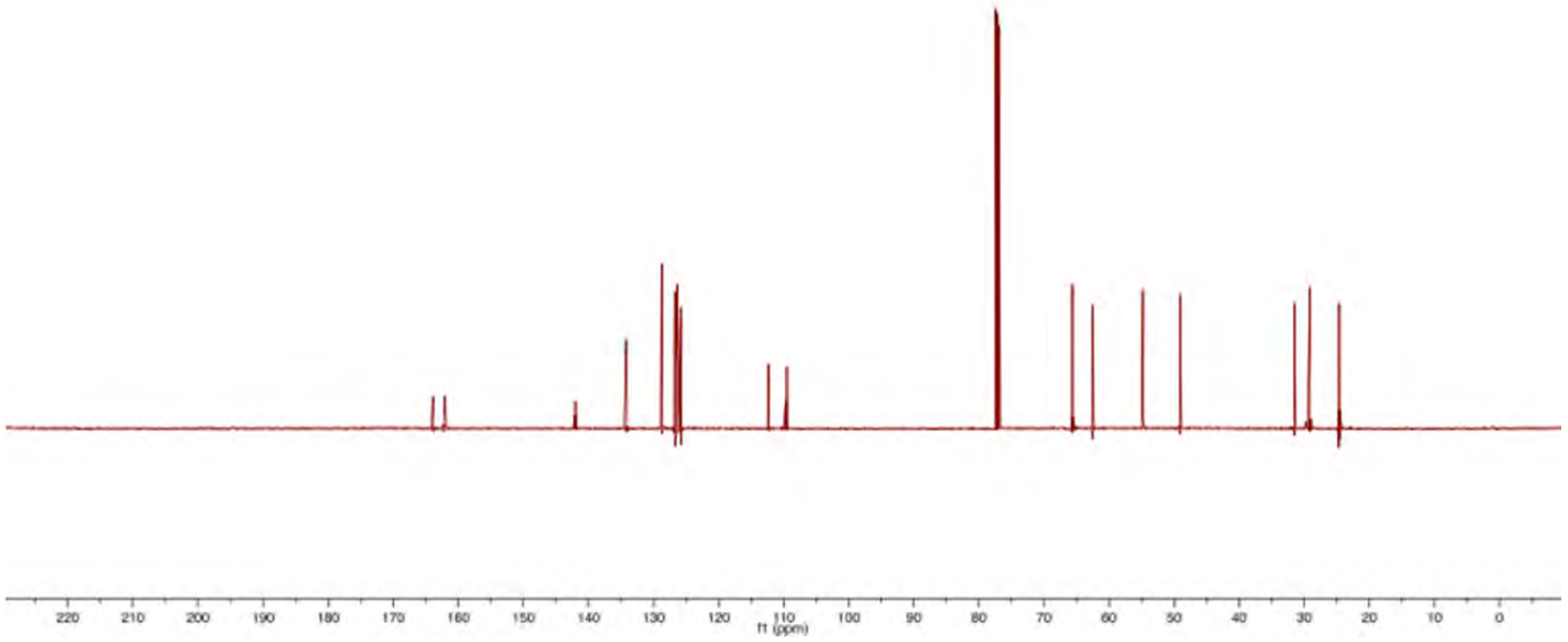

N
O
S
O
F
F

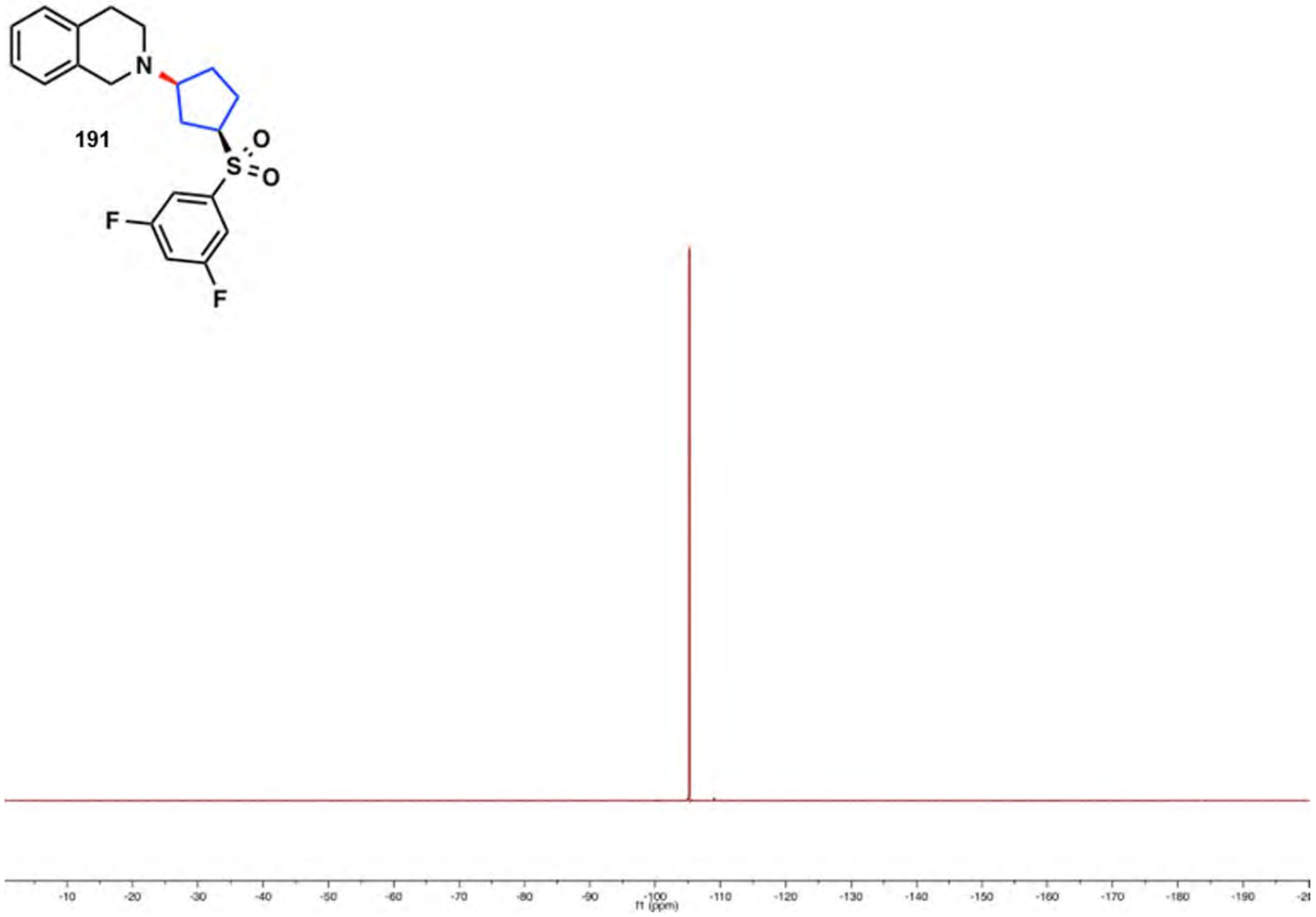
191

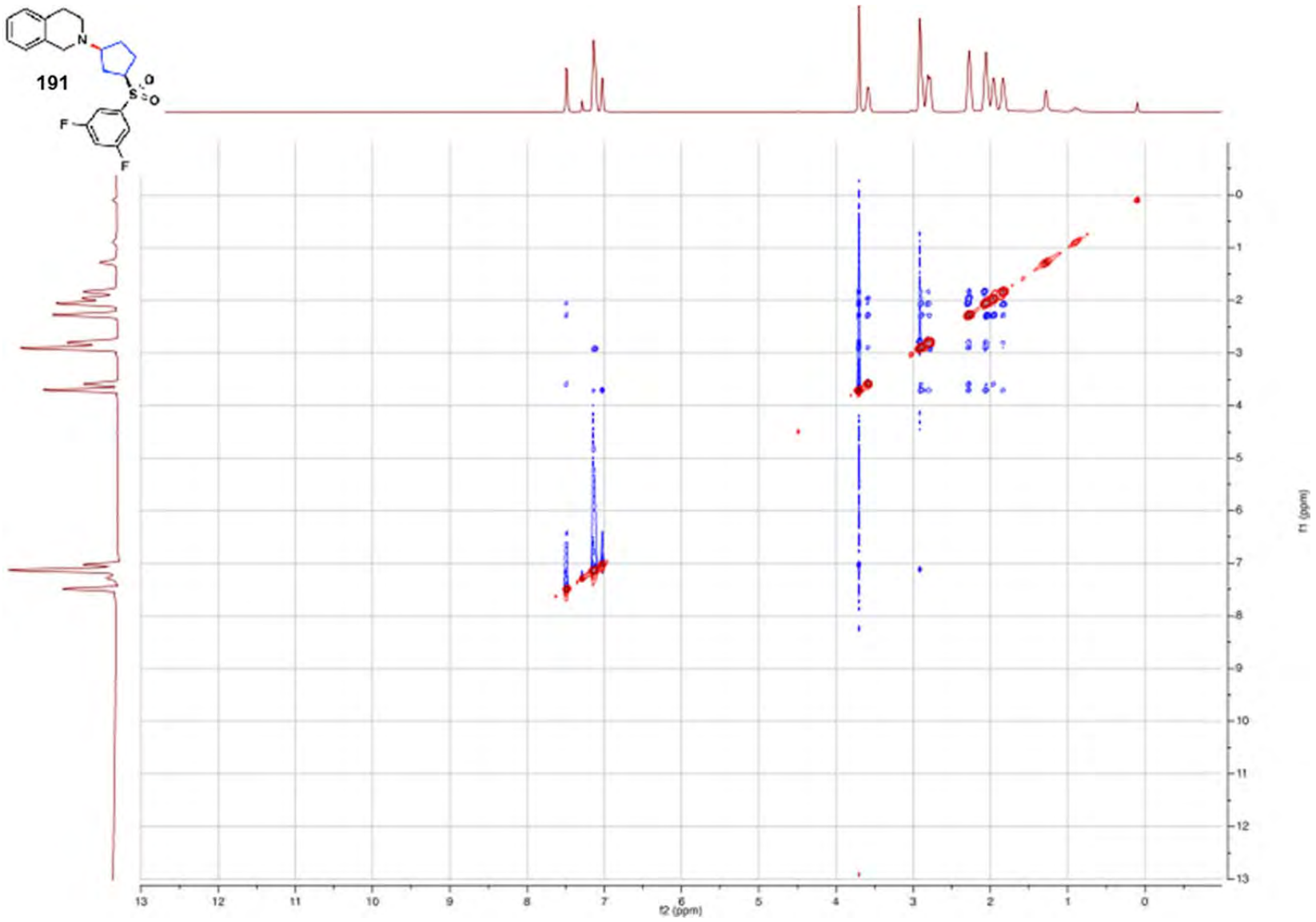

12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


N
O
S
O
F
F

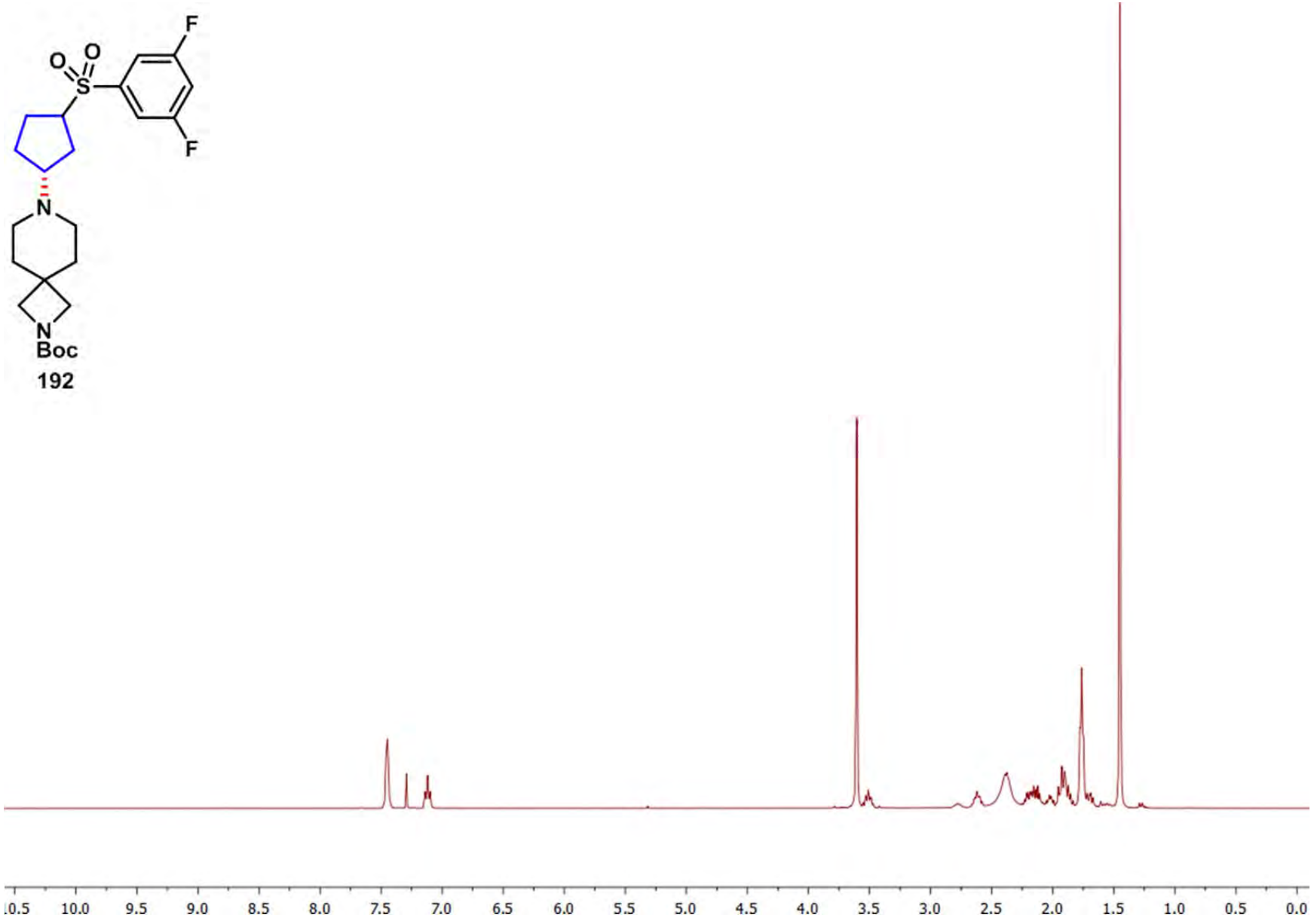
191


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)


191
N
O
S
O
F
F
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


191
F
F
O
S
O
N
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)
f1 (ppm)

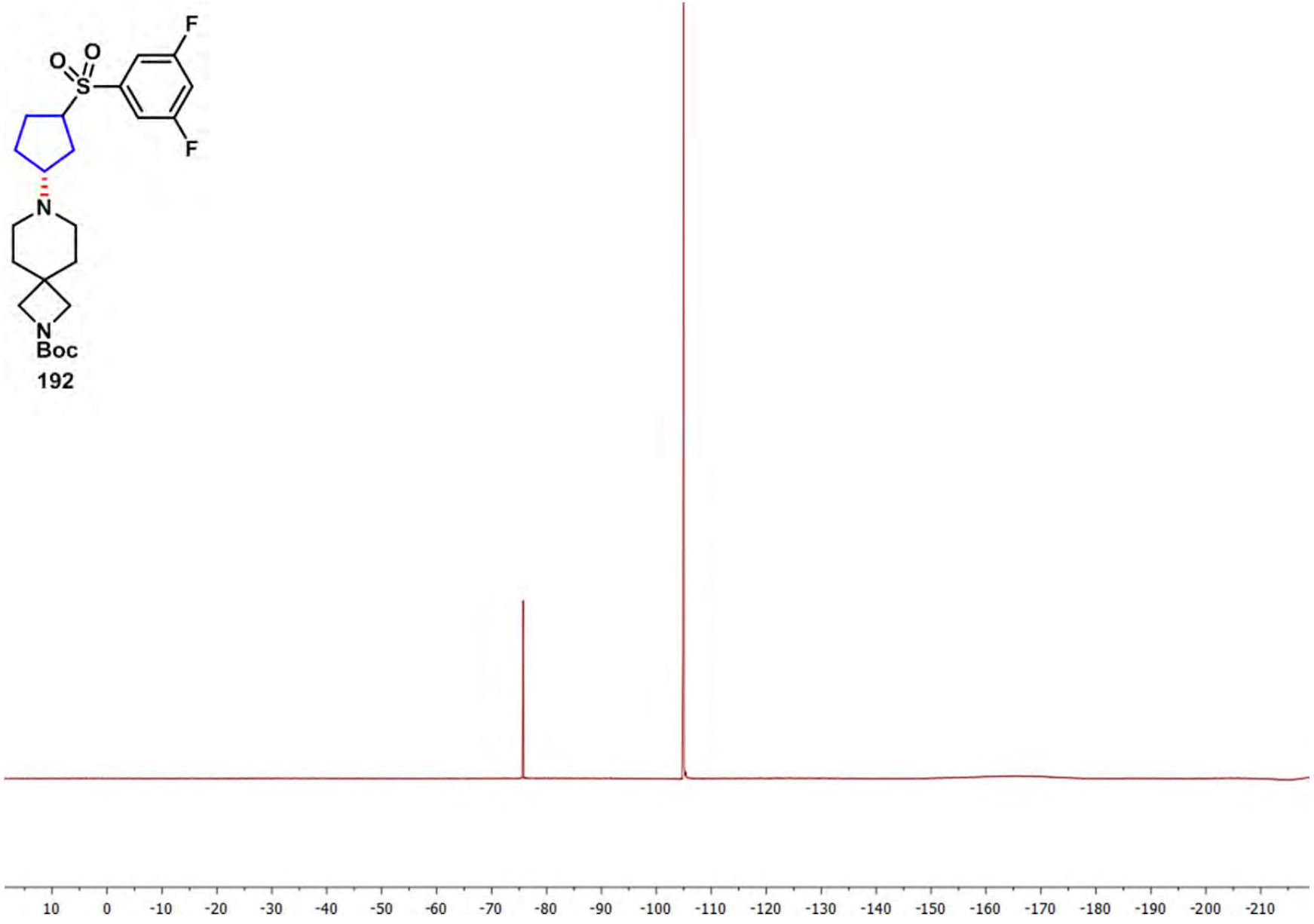

191
F
F
O
S
O
f2 (ppm)
f1 (ppm)

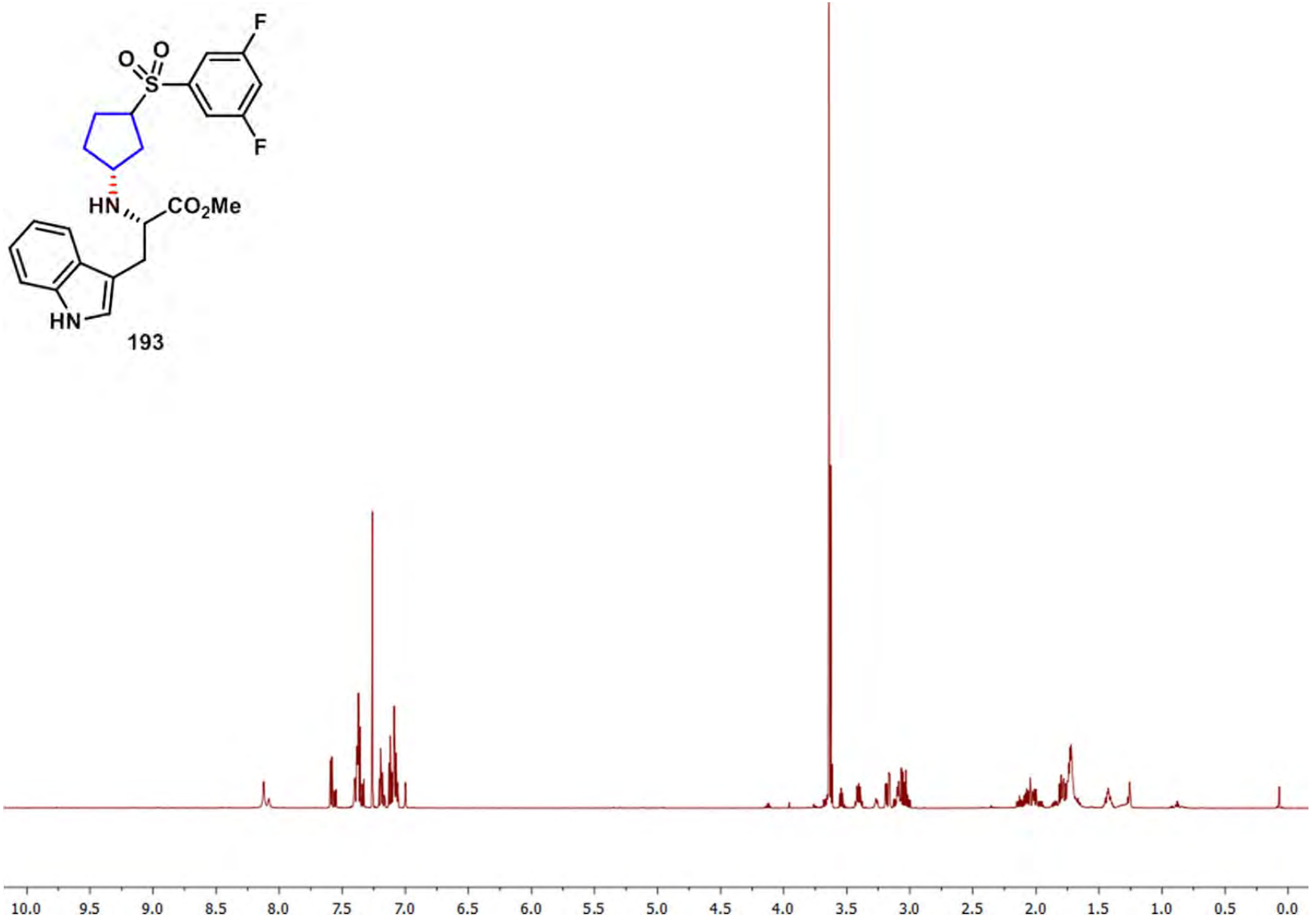

F
O
O
S
F
N
N
Boc
192
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

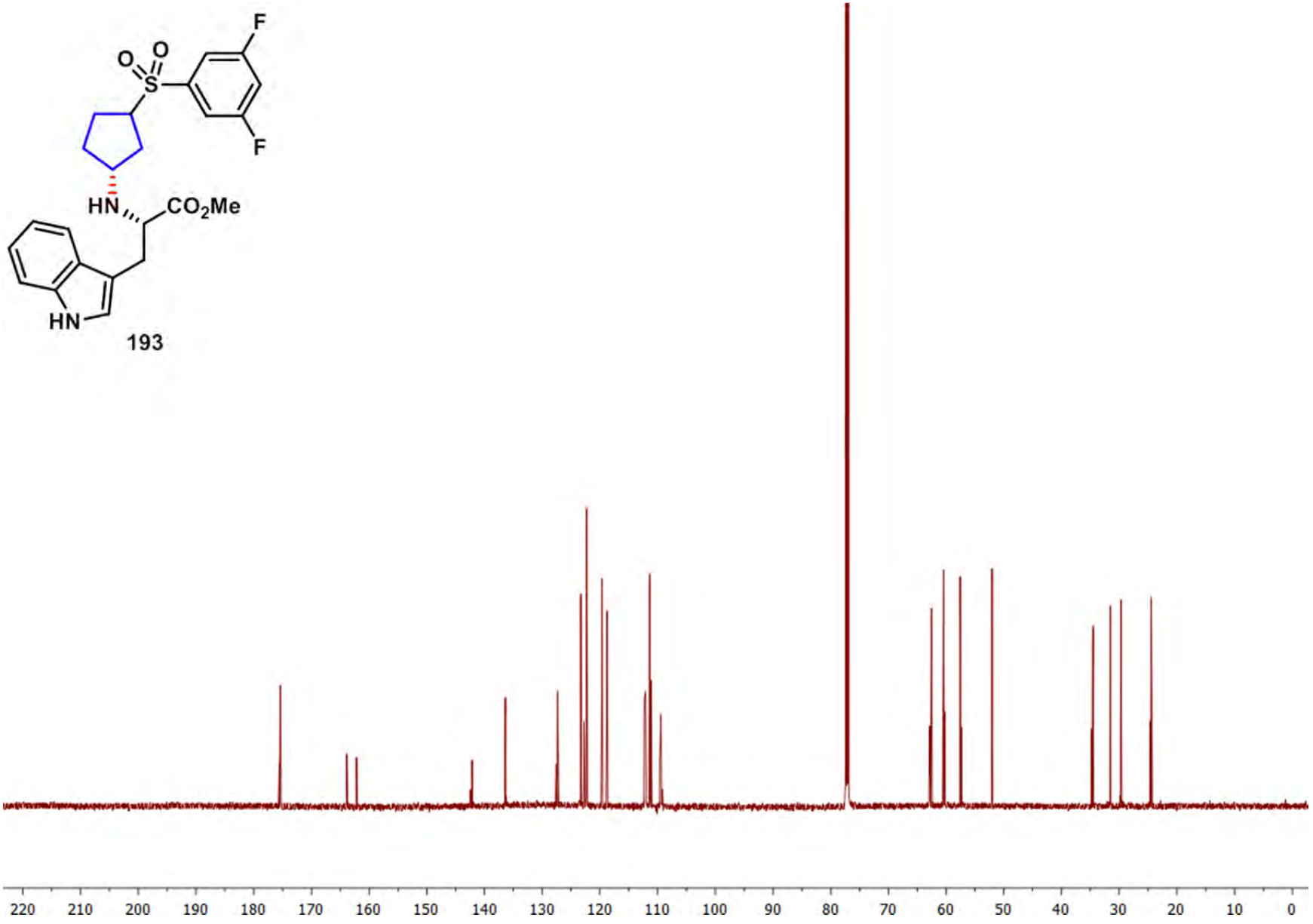

F
O
O
S
F
N
N
Boc

192

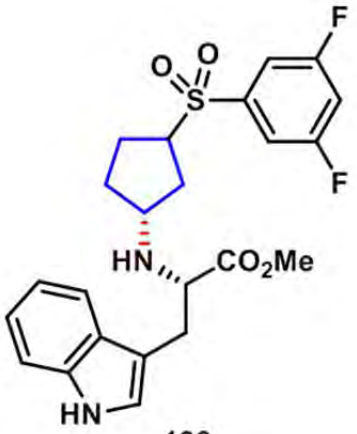
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F
O
O
S
F
N
N
Boc
192
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

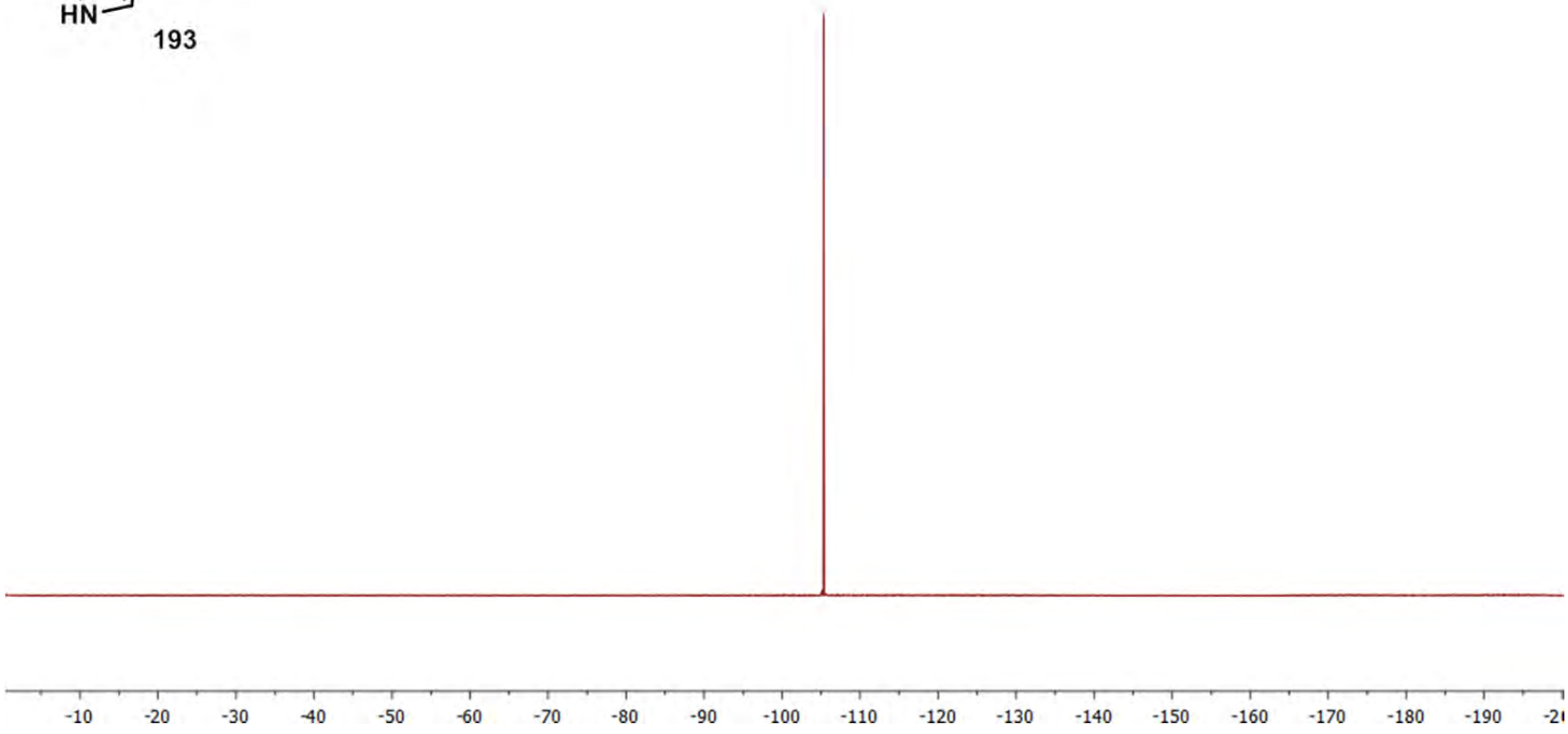

F
O
O
S
F
HN
CO2Me
HN
193
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


F
O
O
S
F
HN
CO2Me
HN
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

193

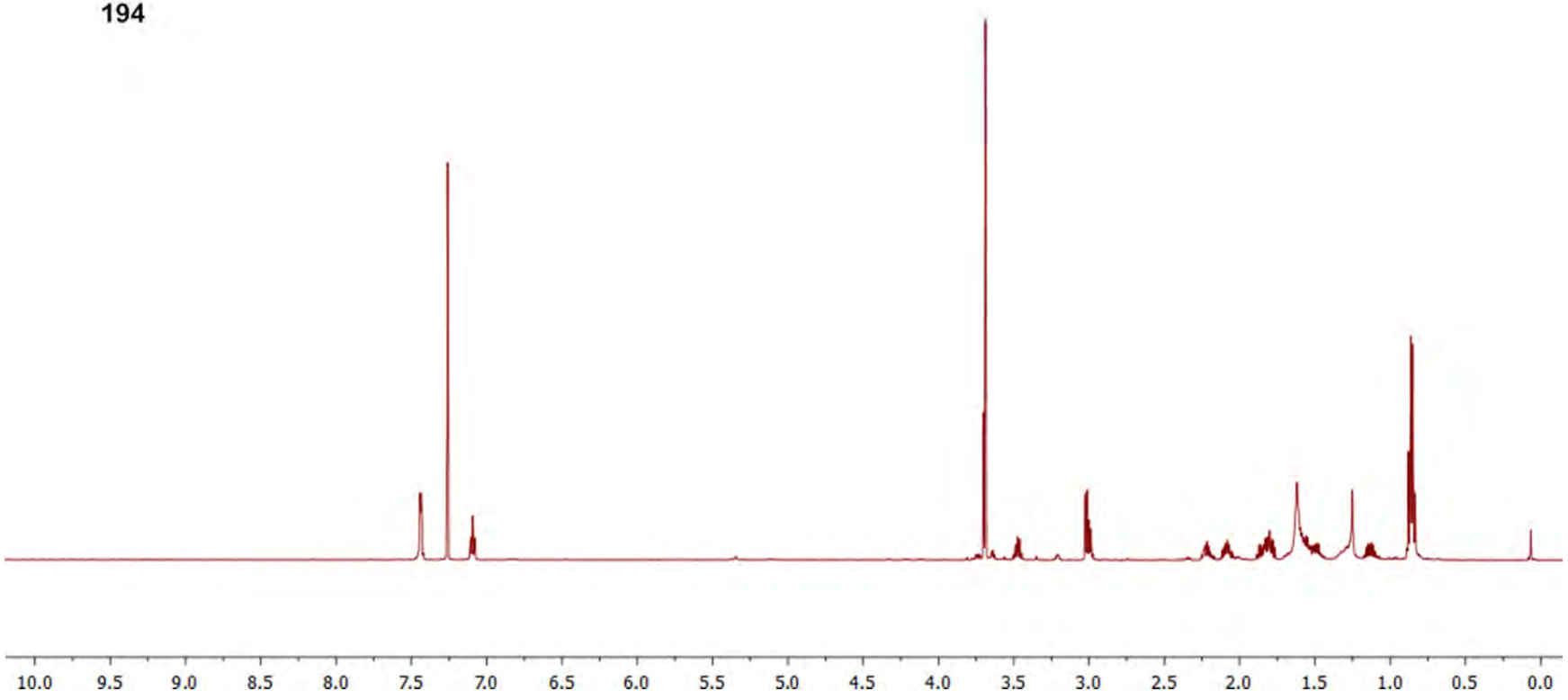

F
O
O
S
F
HN
CO2Me
HN

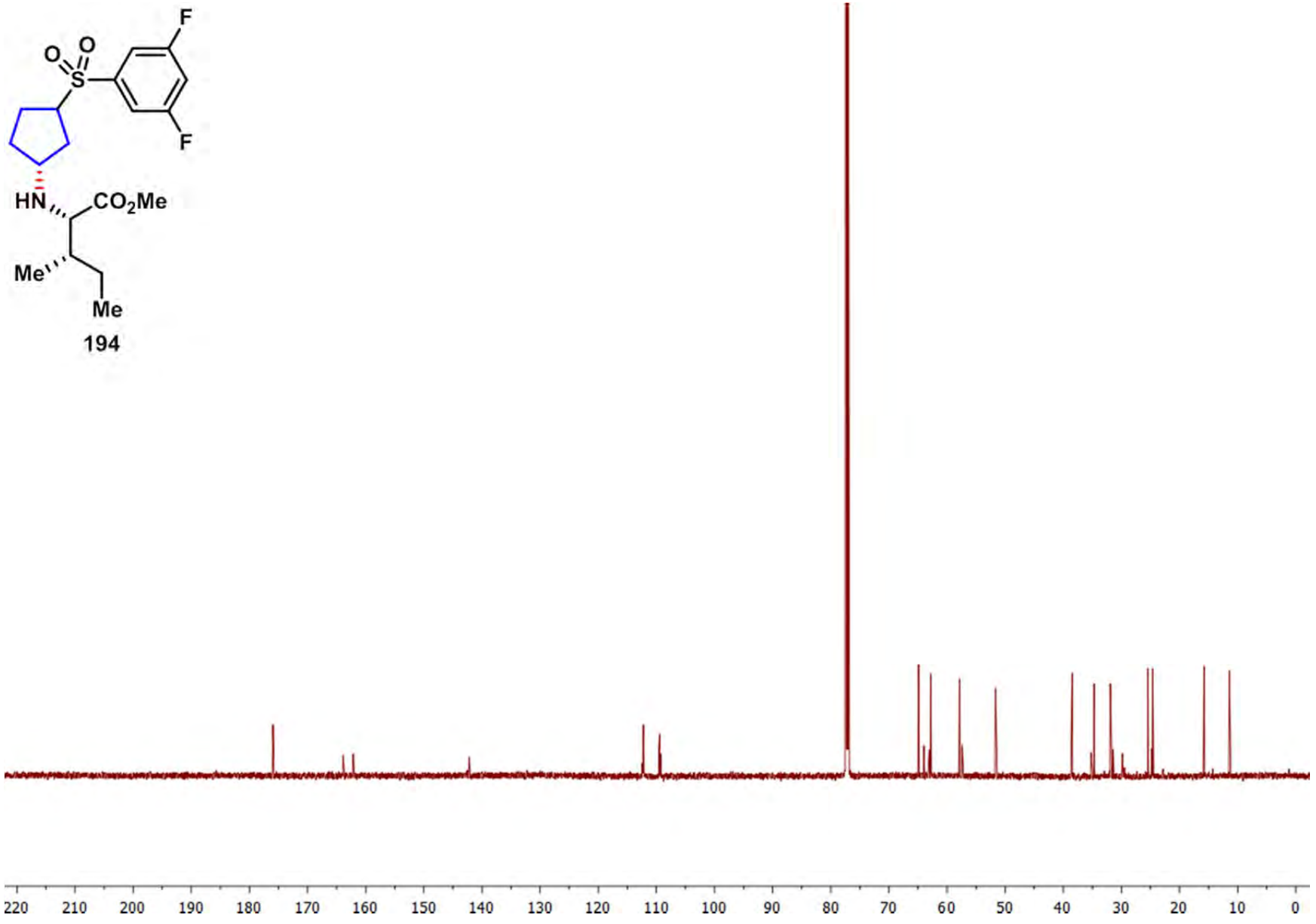
193


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190


F
O
O
S
F
HN
CO2Me
Me
Me

194

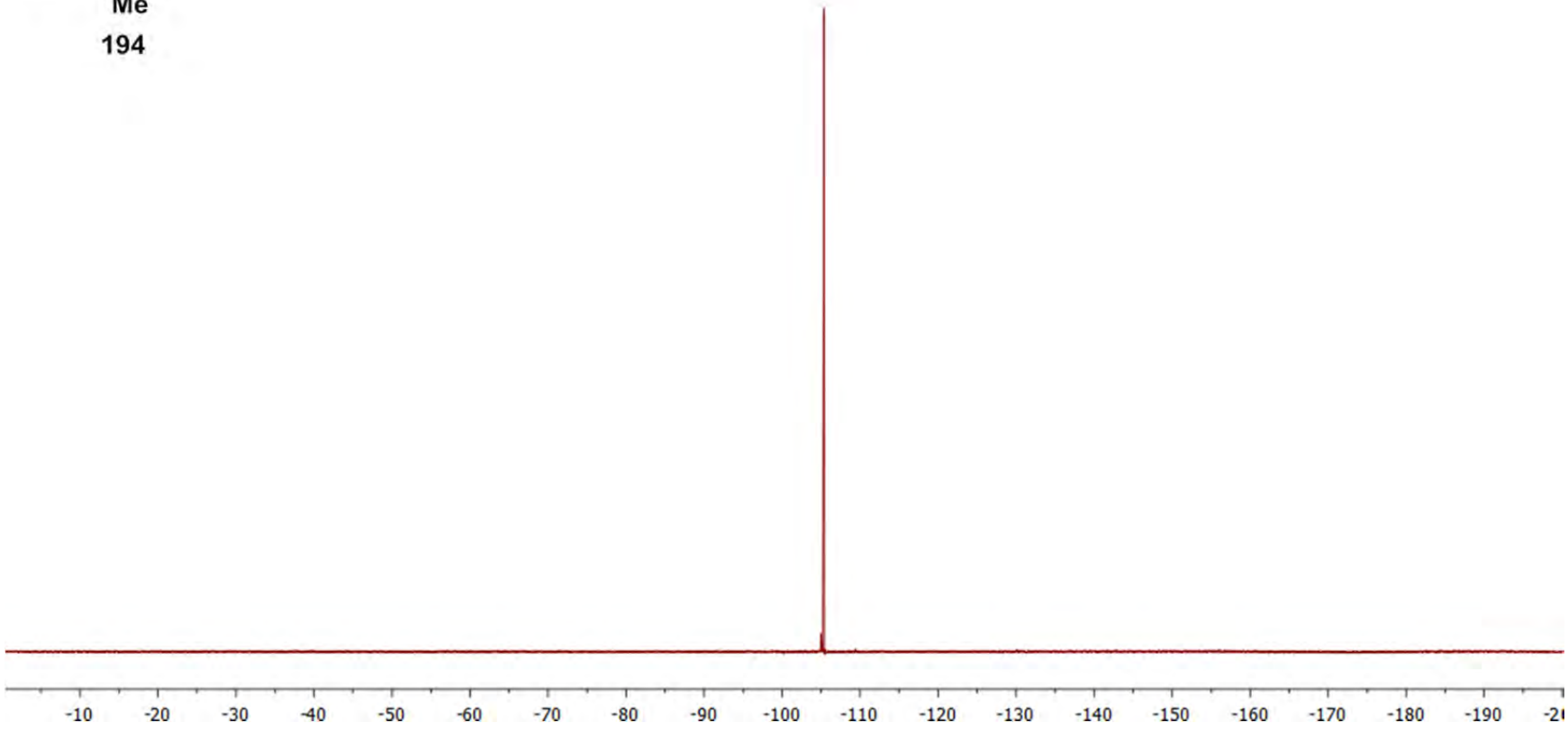

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


F
O
O
S
F
HN
CO2Me
Me
Me
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

194

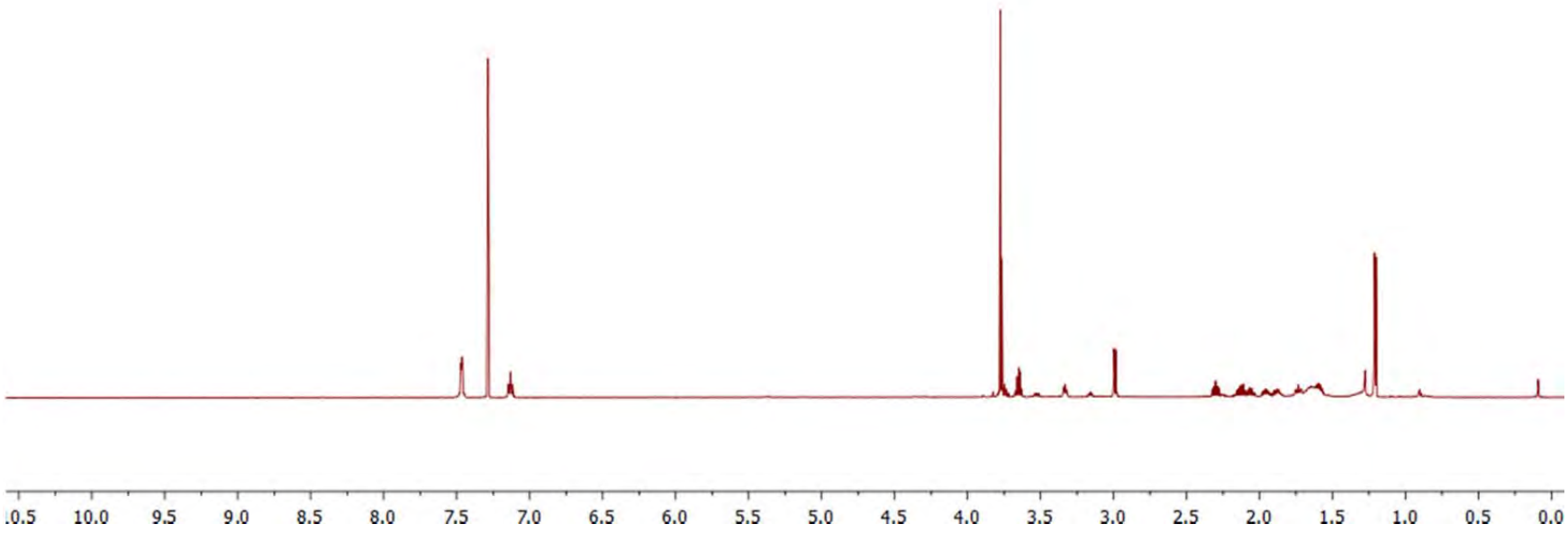

F
O
O
S
F
HN
CO2Me
Me
Me

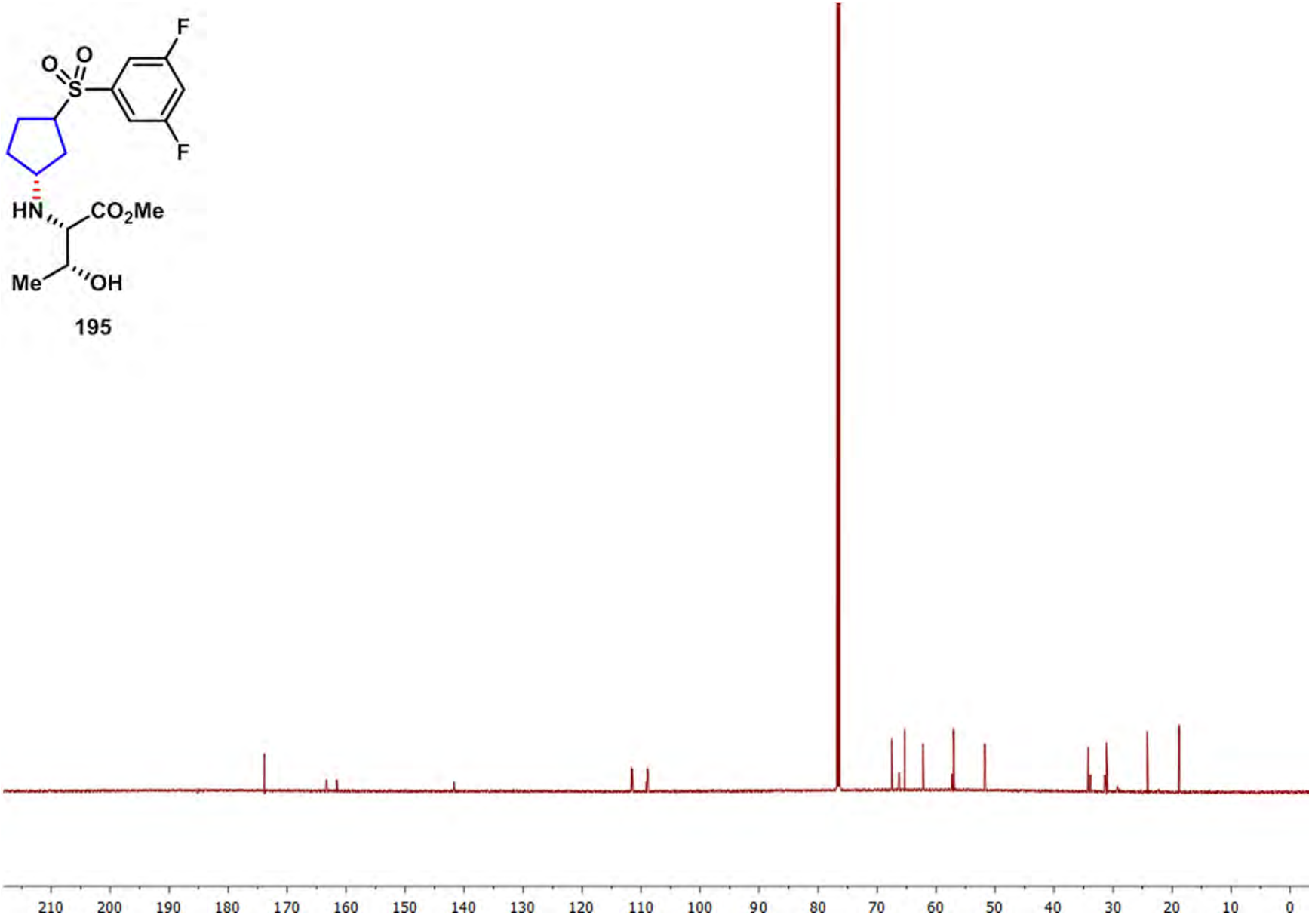
194


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190


F
O
O
S
F
HN
CO2Me
Me
OH

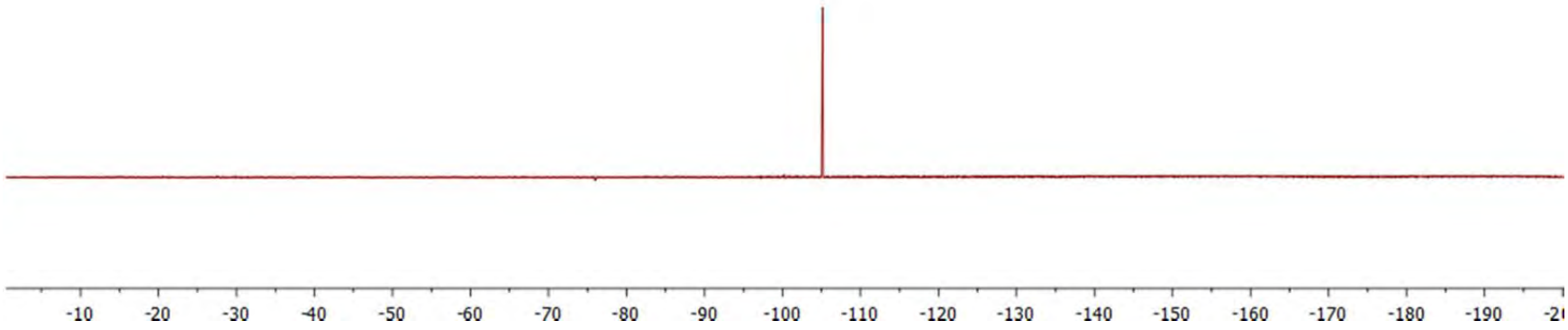
195


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


F
O
O
S
F
HN
CO2Me
Me
OH
195
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F
O
O
S
F
HN
CO2Me
Me
OH

195


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

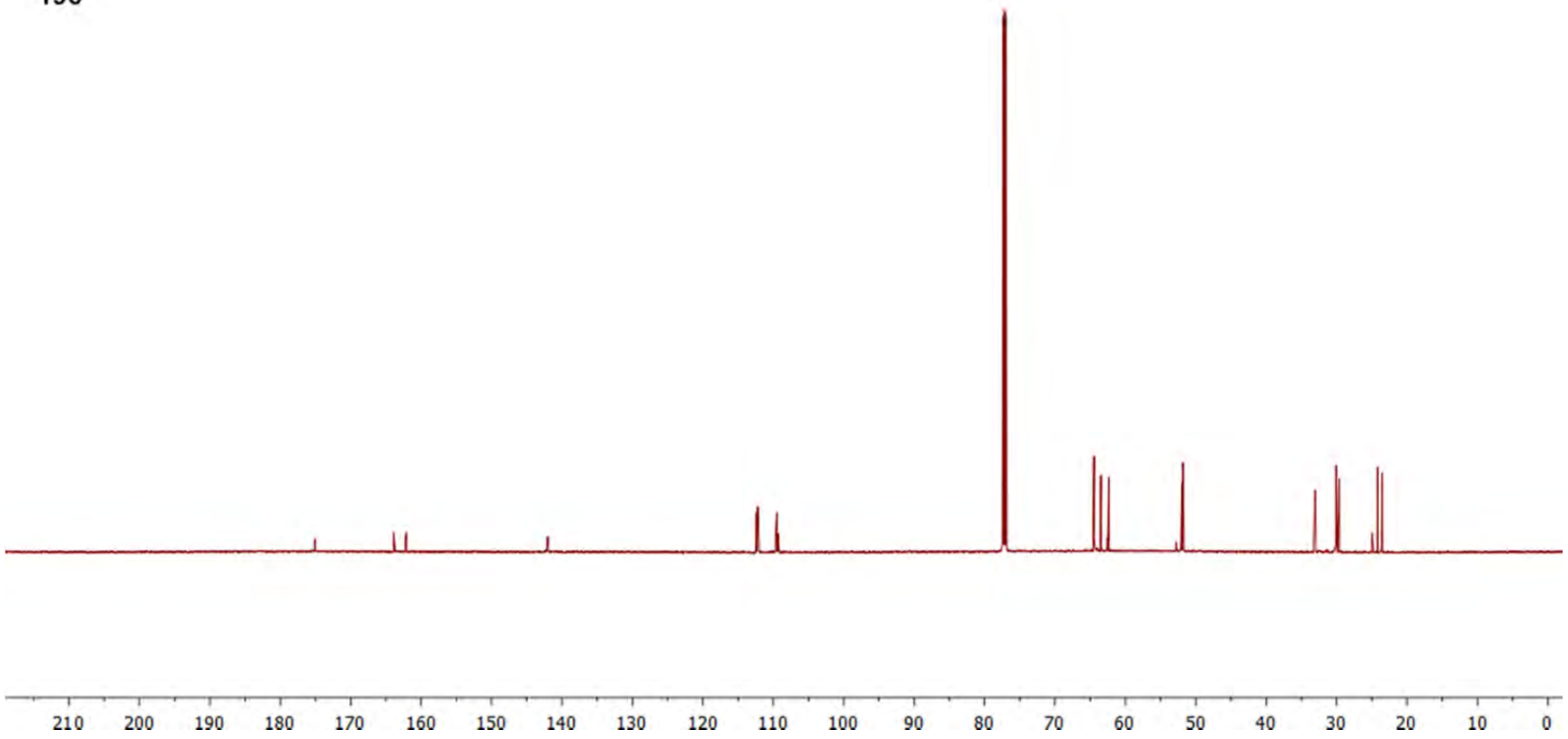

F
O
O
S
F
N
CO2Me

196

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

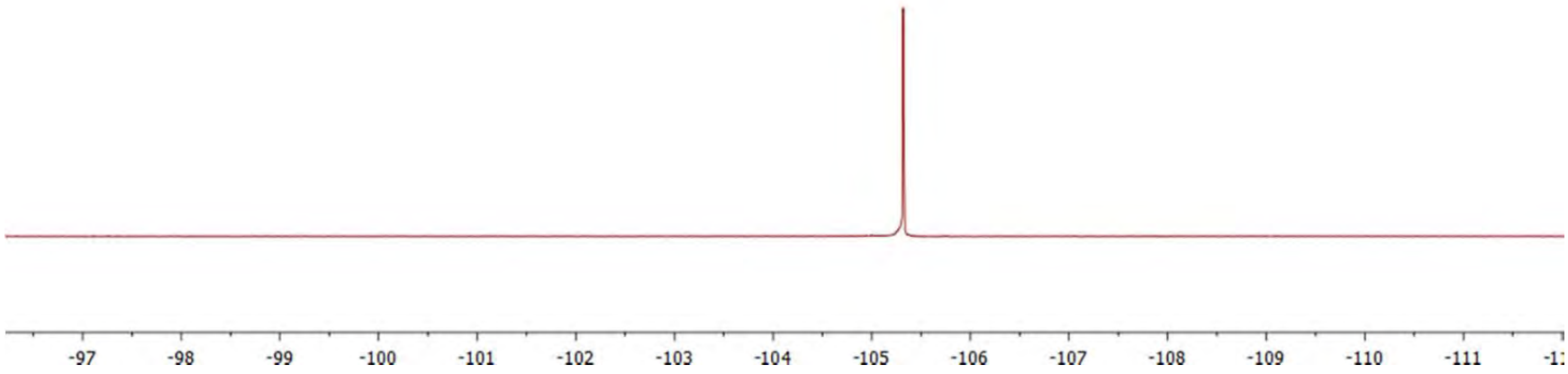

F
O
O
S
F
N
CO2Me

196


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


F
O
O
S
F
N
CO2Me

196


-97
-98
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-100
-101
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-103
-104
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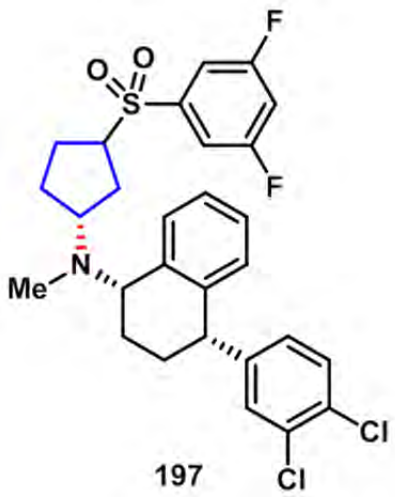
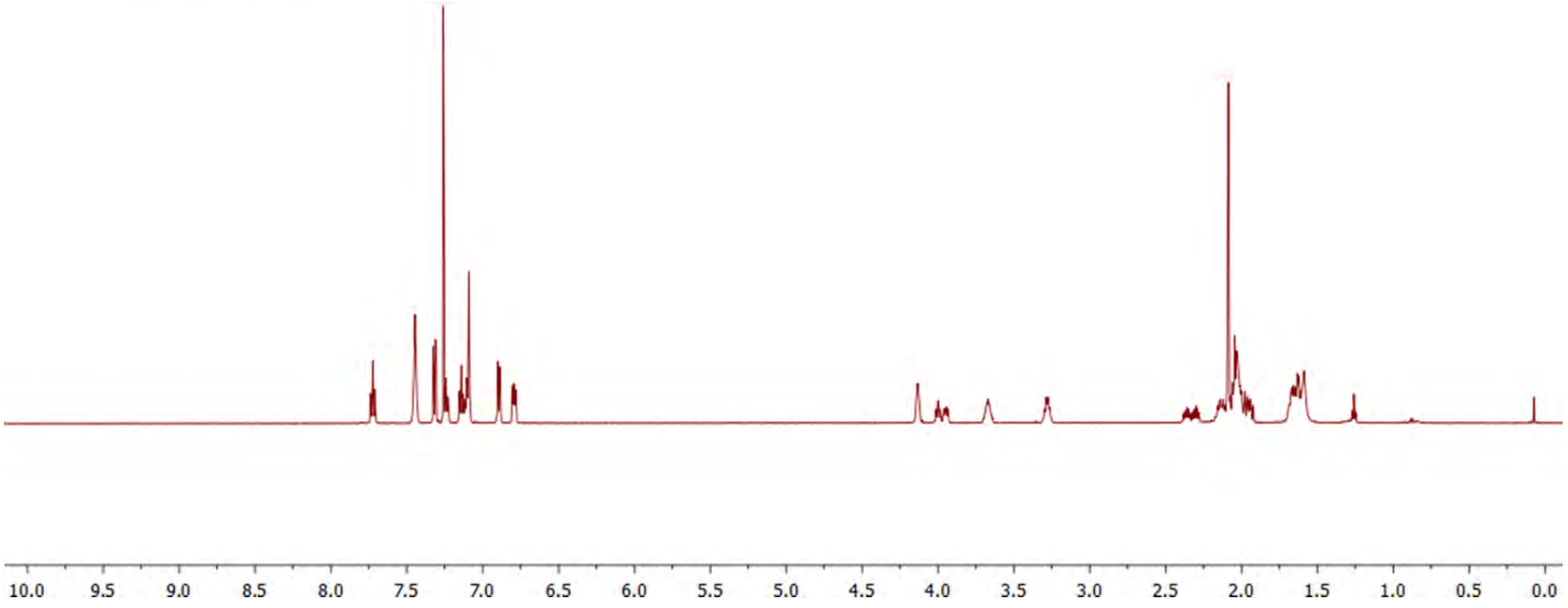
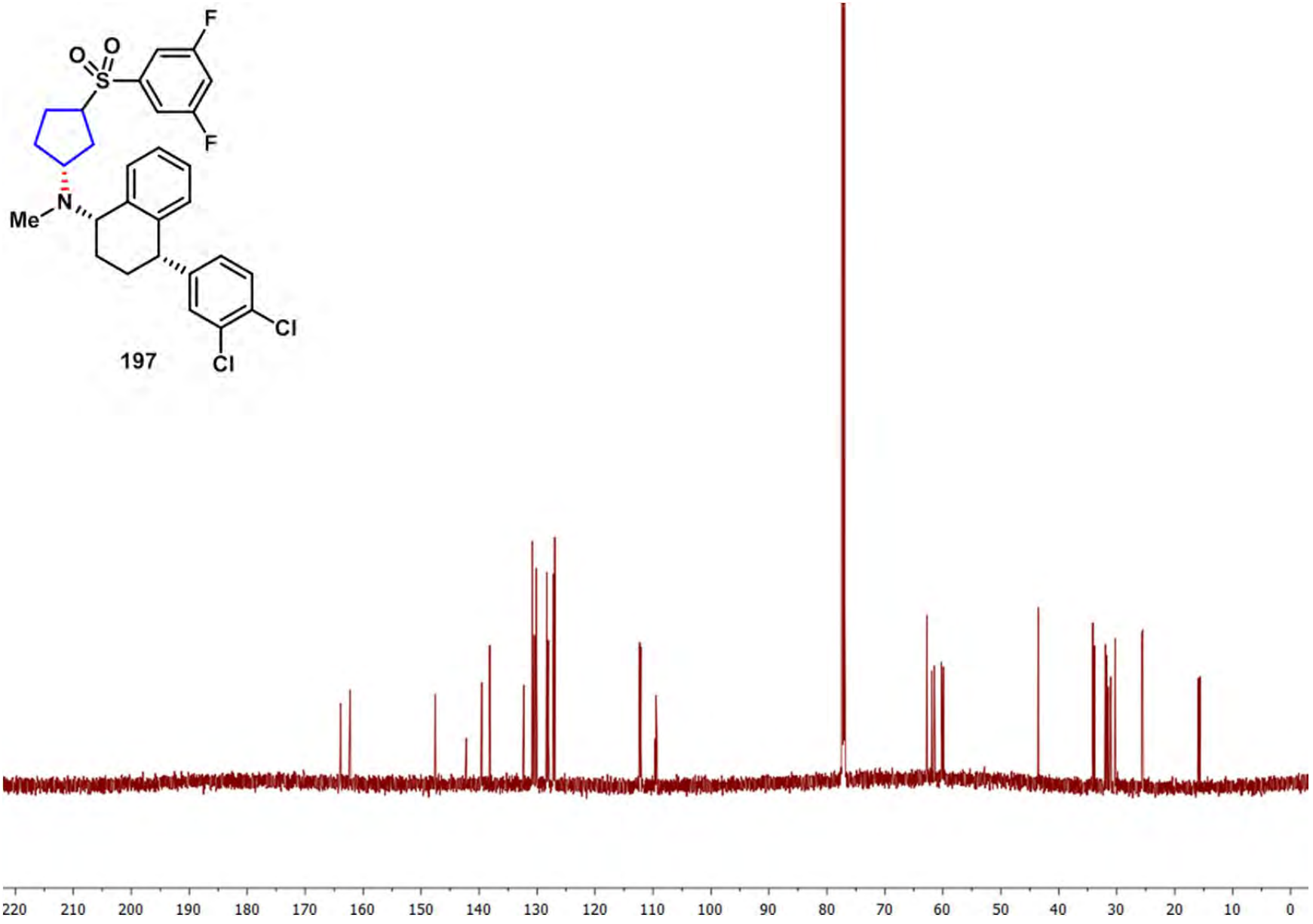
-106
-107
-108
-109
-110
-111


F
O
O
S
F
Me
N
Cl
Cl

197


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


F
O
O
S
F
Me
N
Cl
Cl
197
220
210
200
190
180
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150
140
130
120
110
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70
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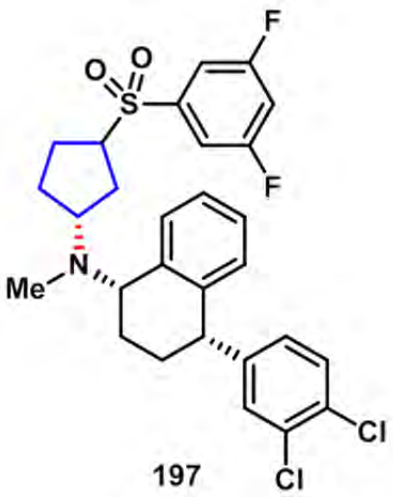
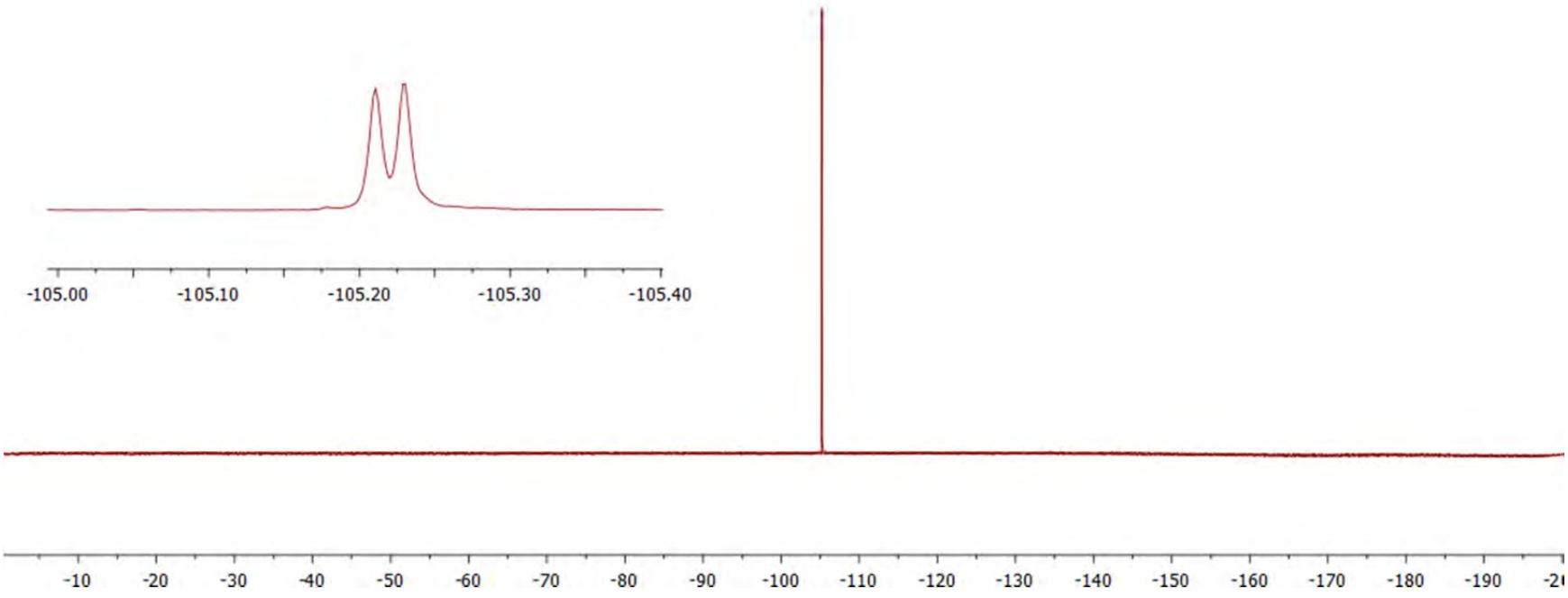
30
20
10
0


F
O
O
S
F
N
Me
Cl
Cl

197


-105.00
-105.10
-105.20
-105.30
-105.40
-10
-20
-30
-40
-50
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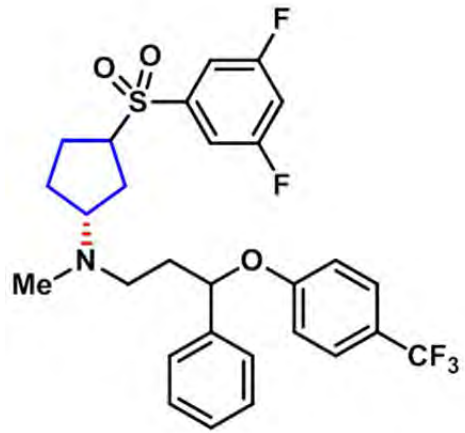
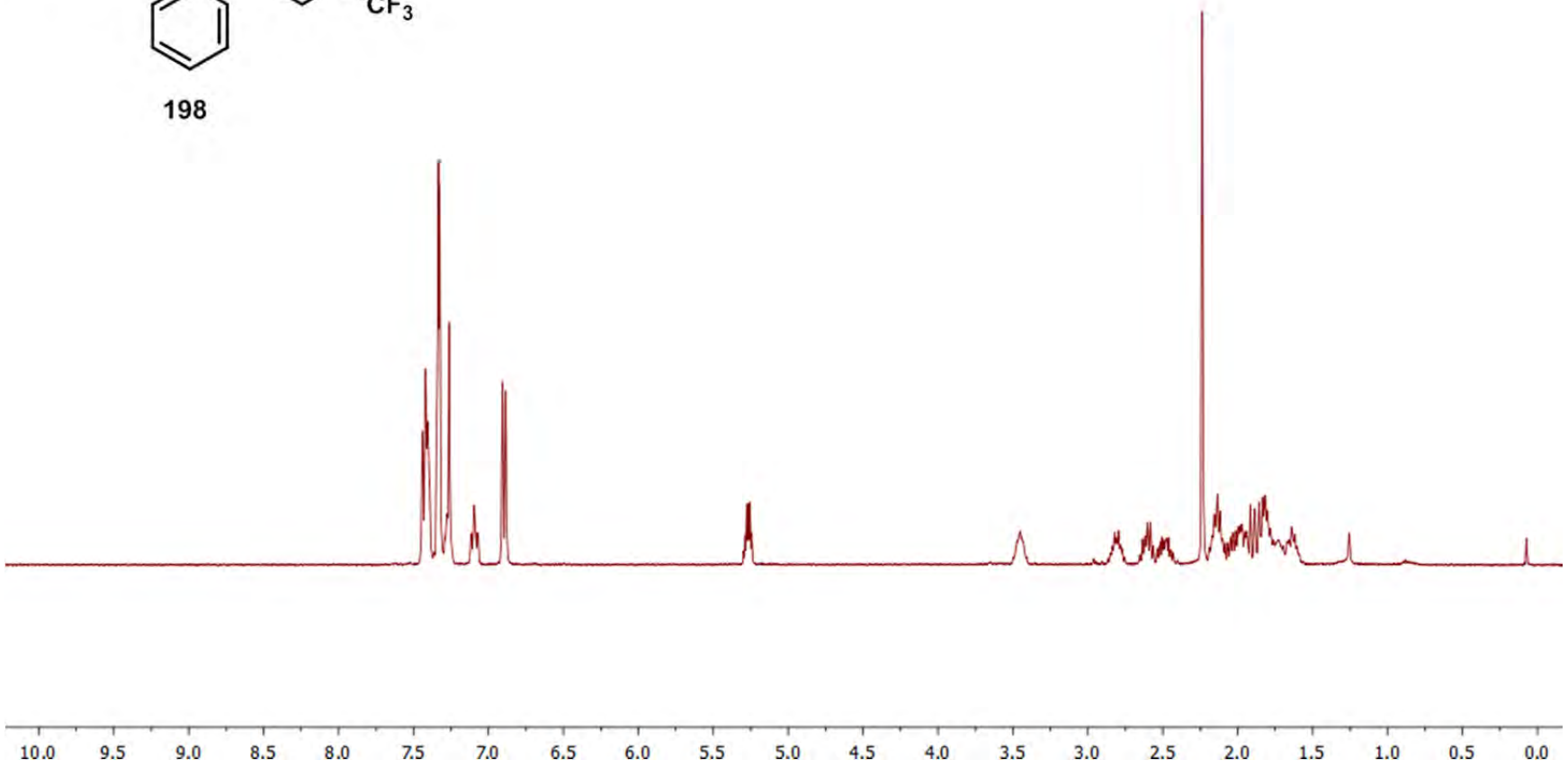
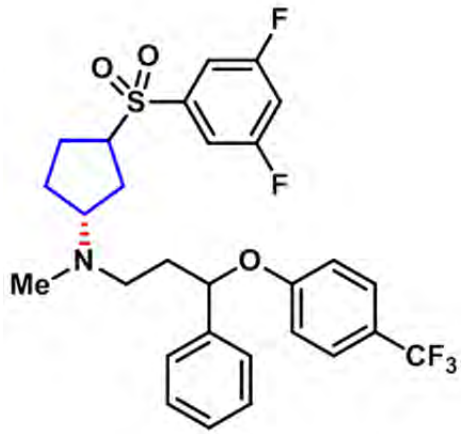
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190


F
O
O
S
F
N
Me
O
CF3

198


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


F
O
O
S
F
N
Me
O
CF3

198

220
210
200
190
180
170
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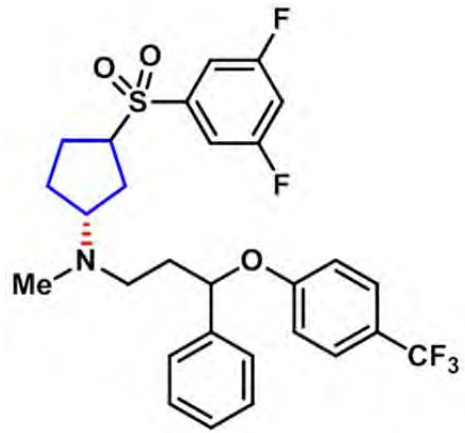
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F
O
O
S
F
N
Me
O
CF3

198

-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
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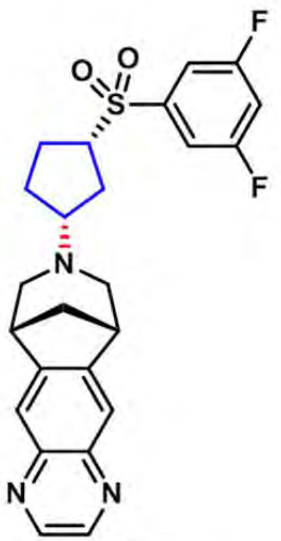
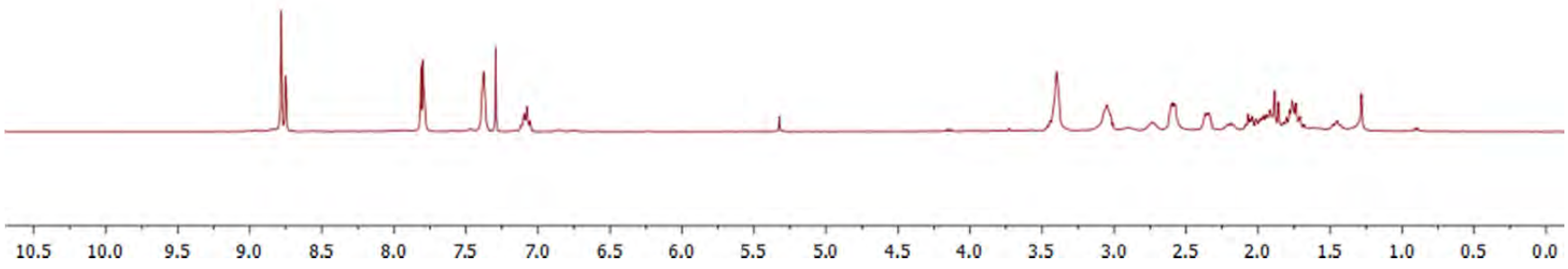
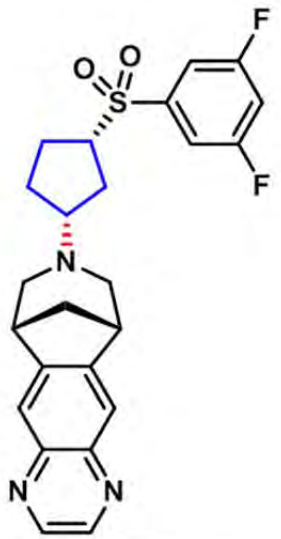
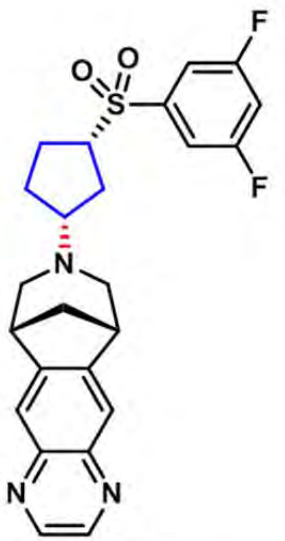


199
[*cis*-diastereoisomer]





199
[*cis*-diastereoisomer]



199
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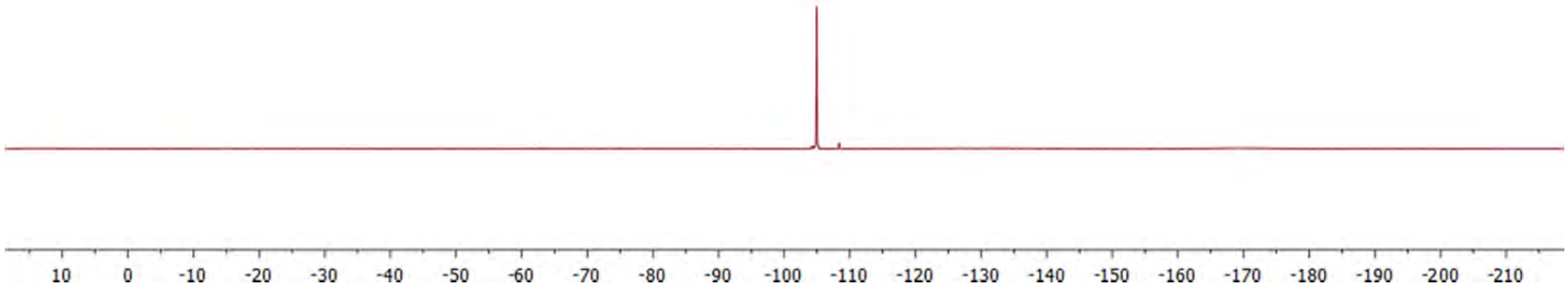

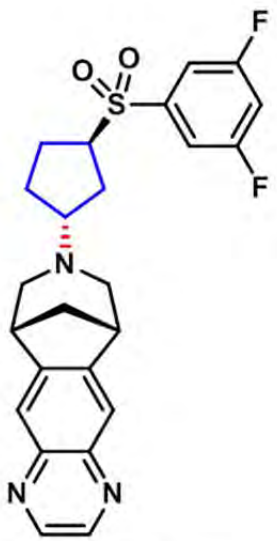

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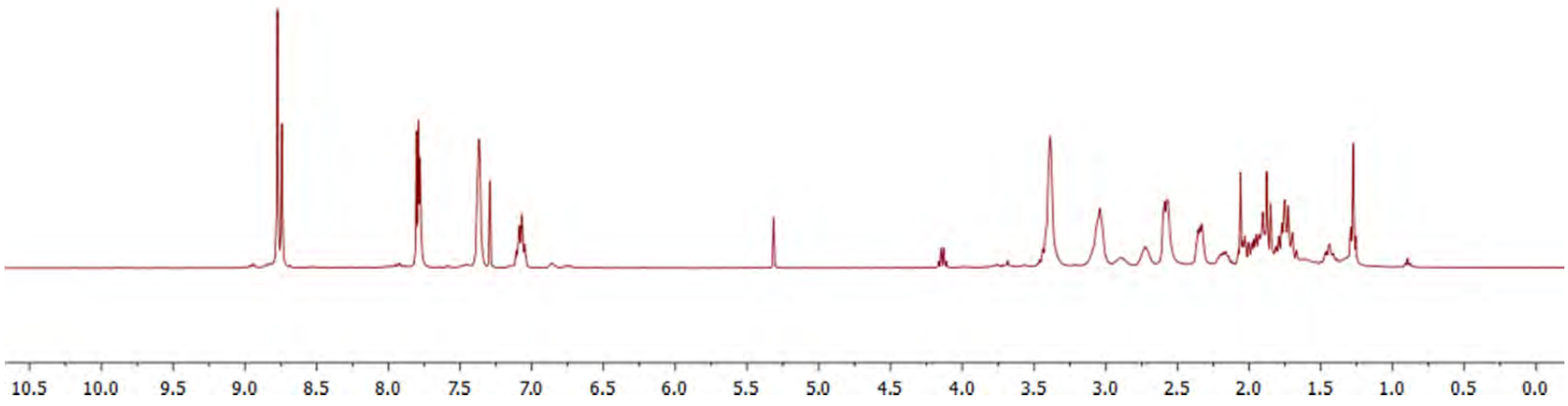

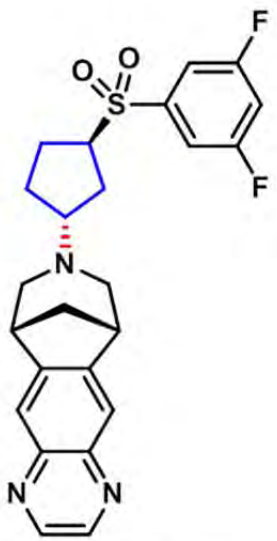

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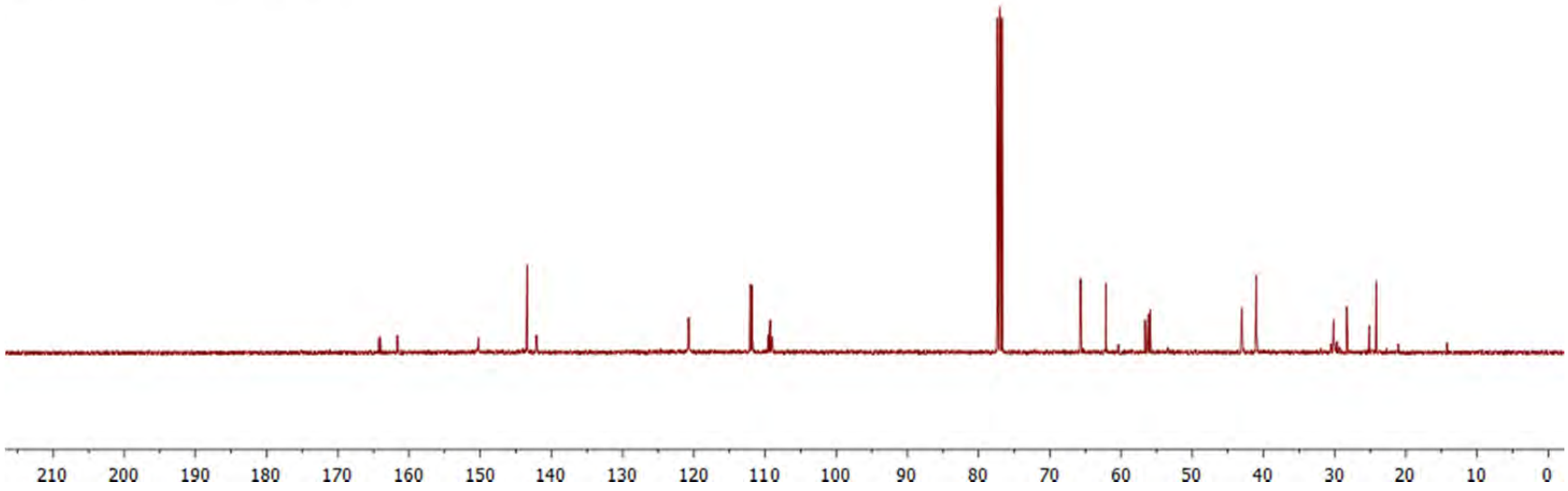
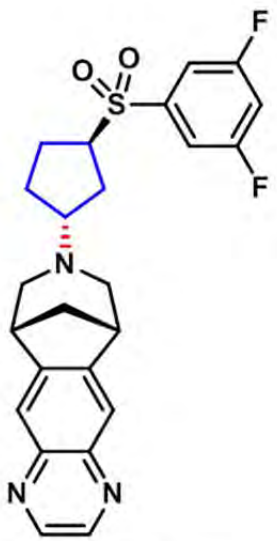
[*trans*-diastereoisomer]





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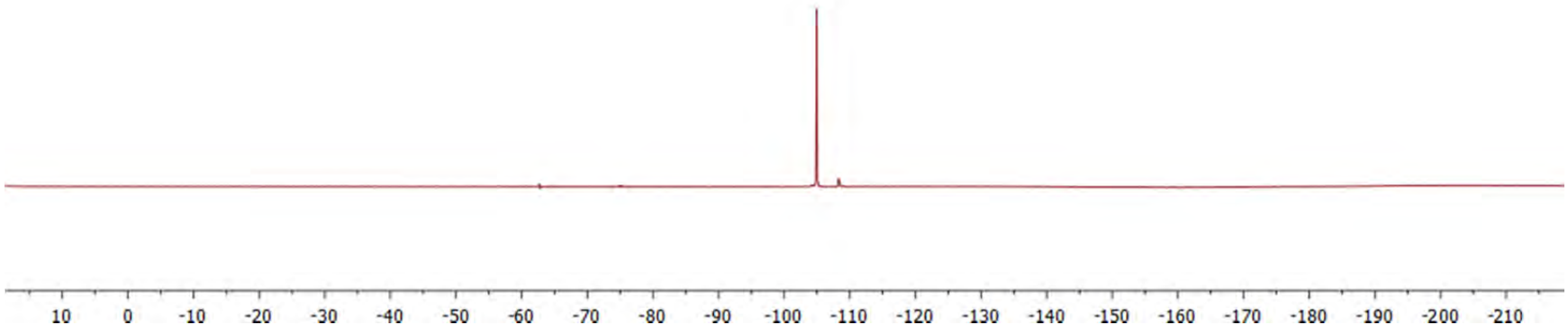
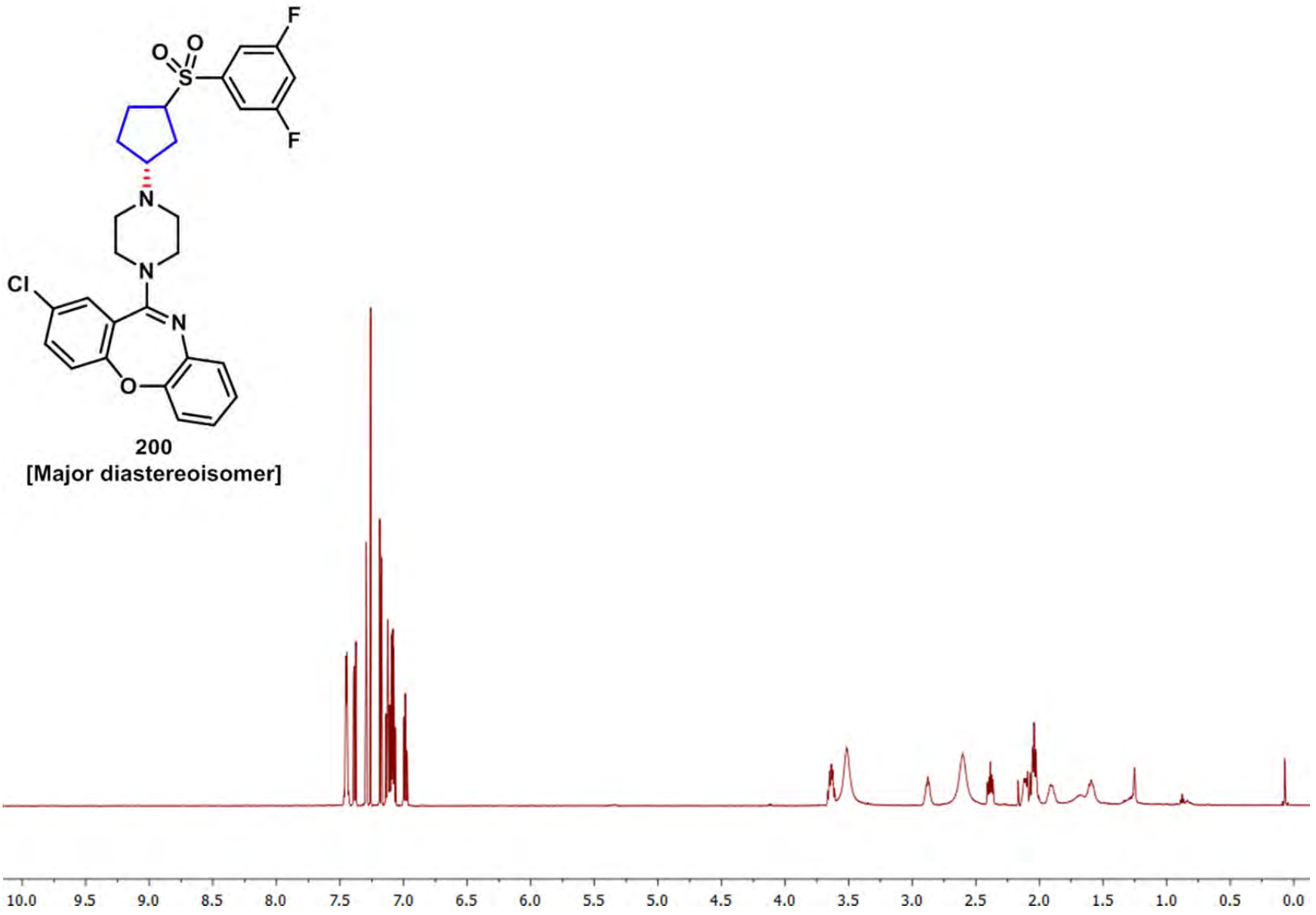
[*trans*-diastereoisomer]





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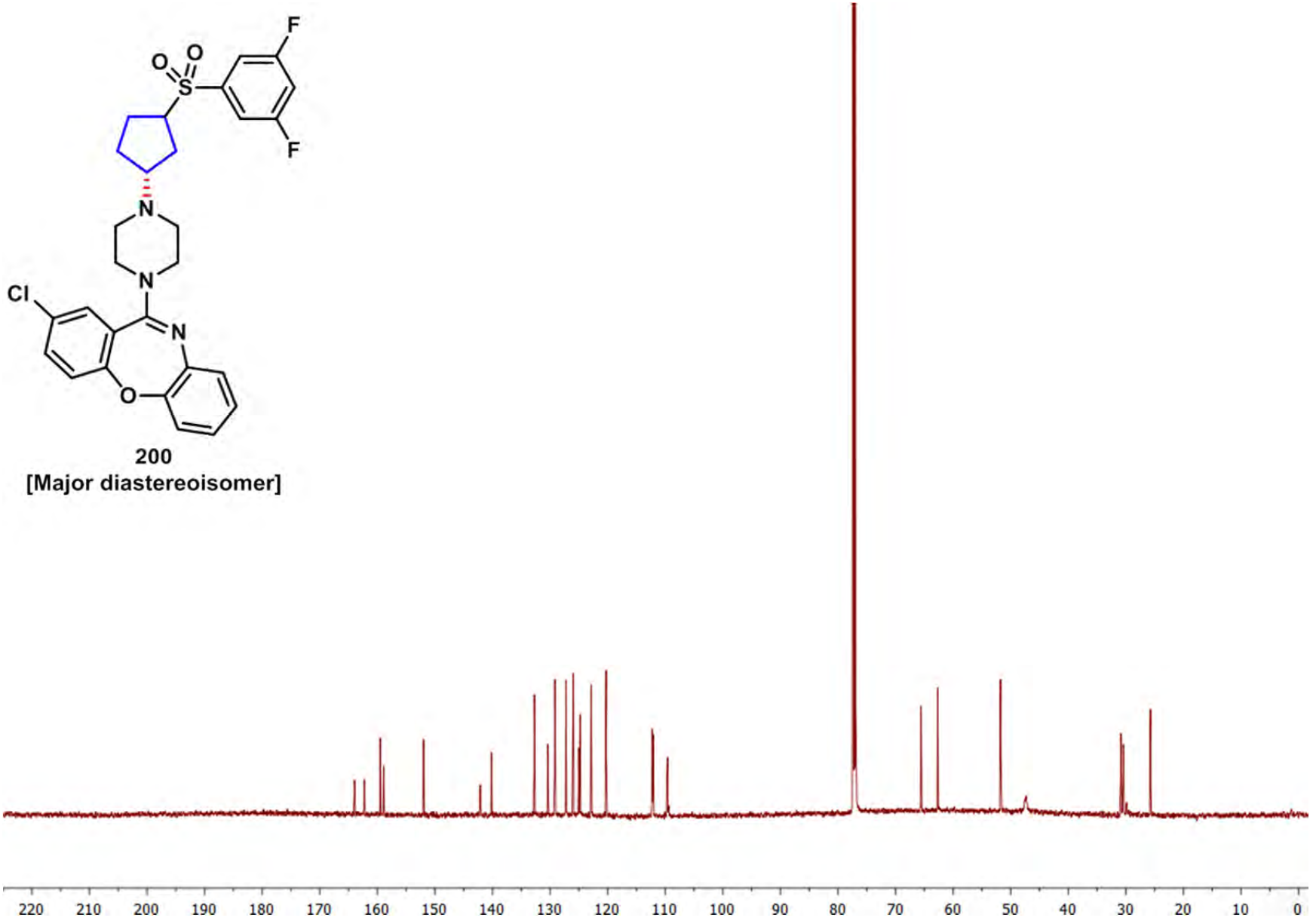
[Major diastereoisomer]



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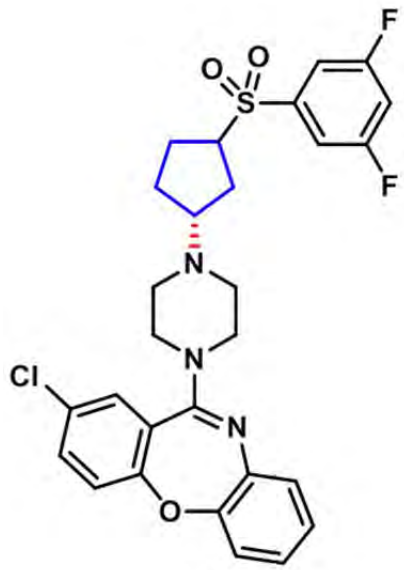
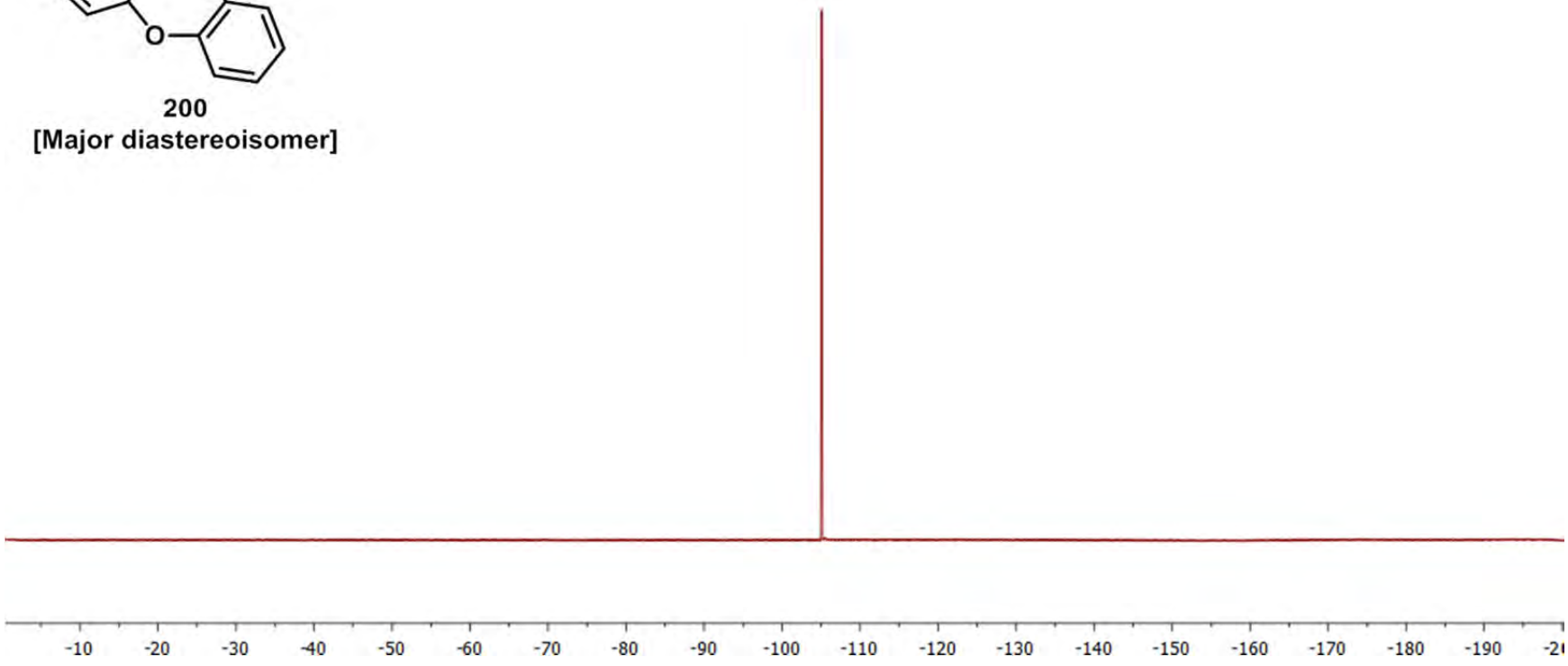
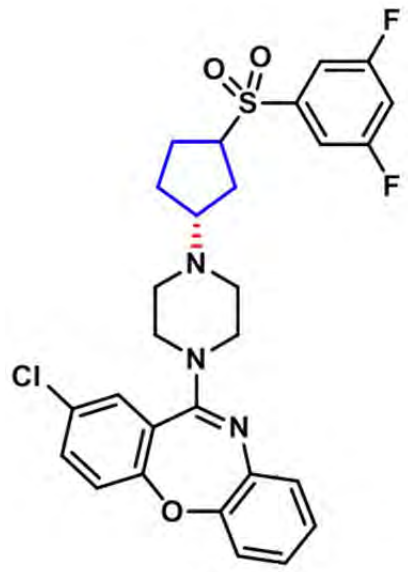
[Major diastereoisomer]



200
[Major diastereoisomer]





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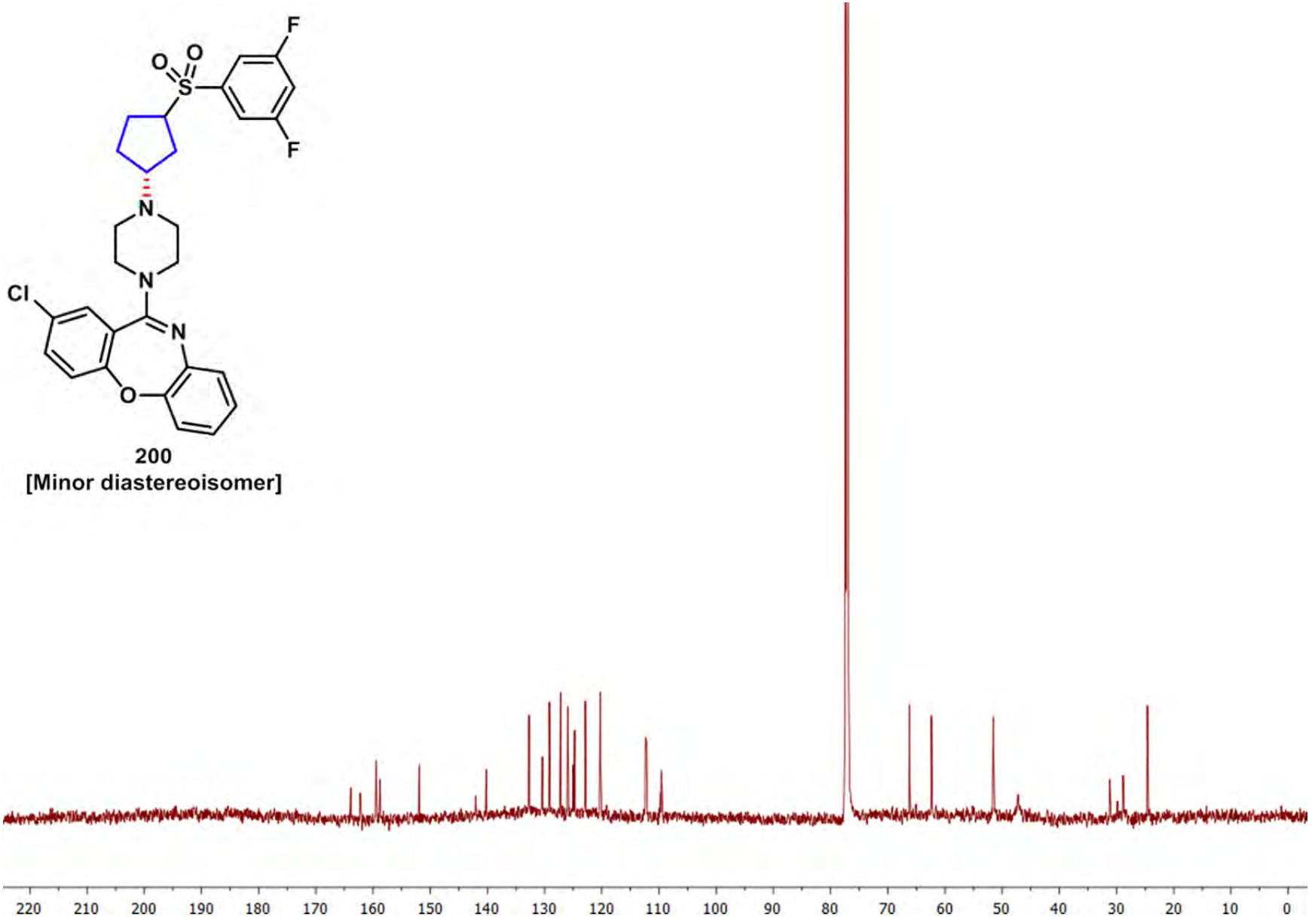
[Minor diastereoisomer]



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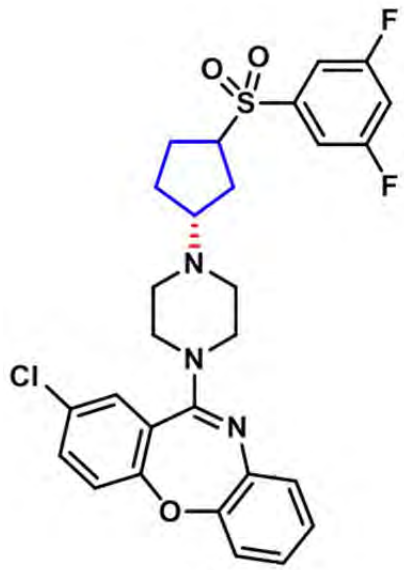

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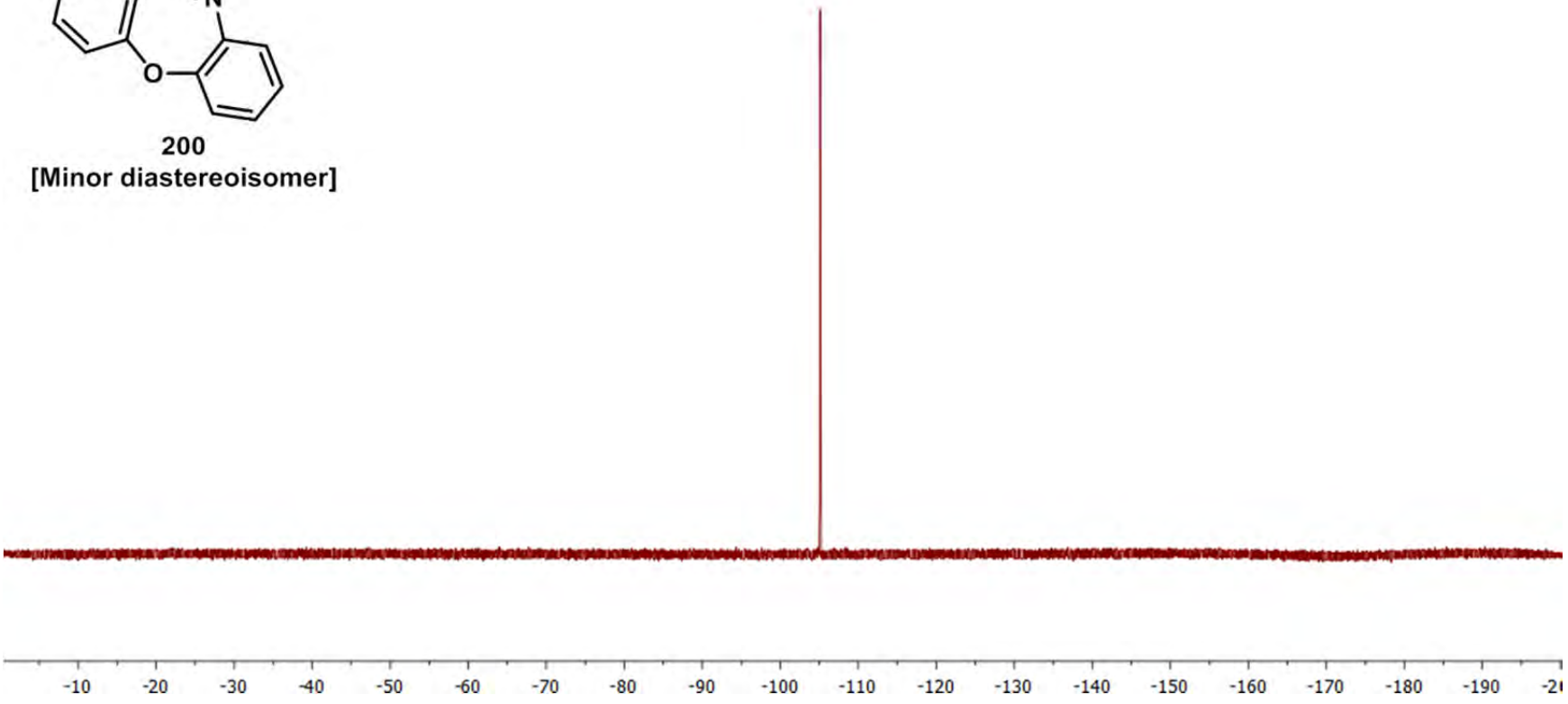
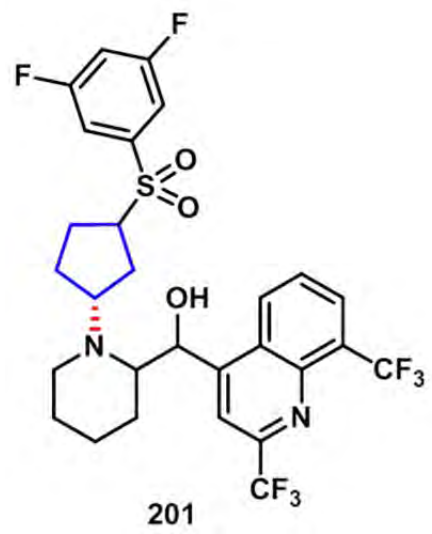
[Minor diastereoisomer]




F
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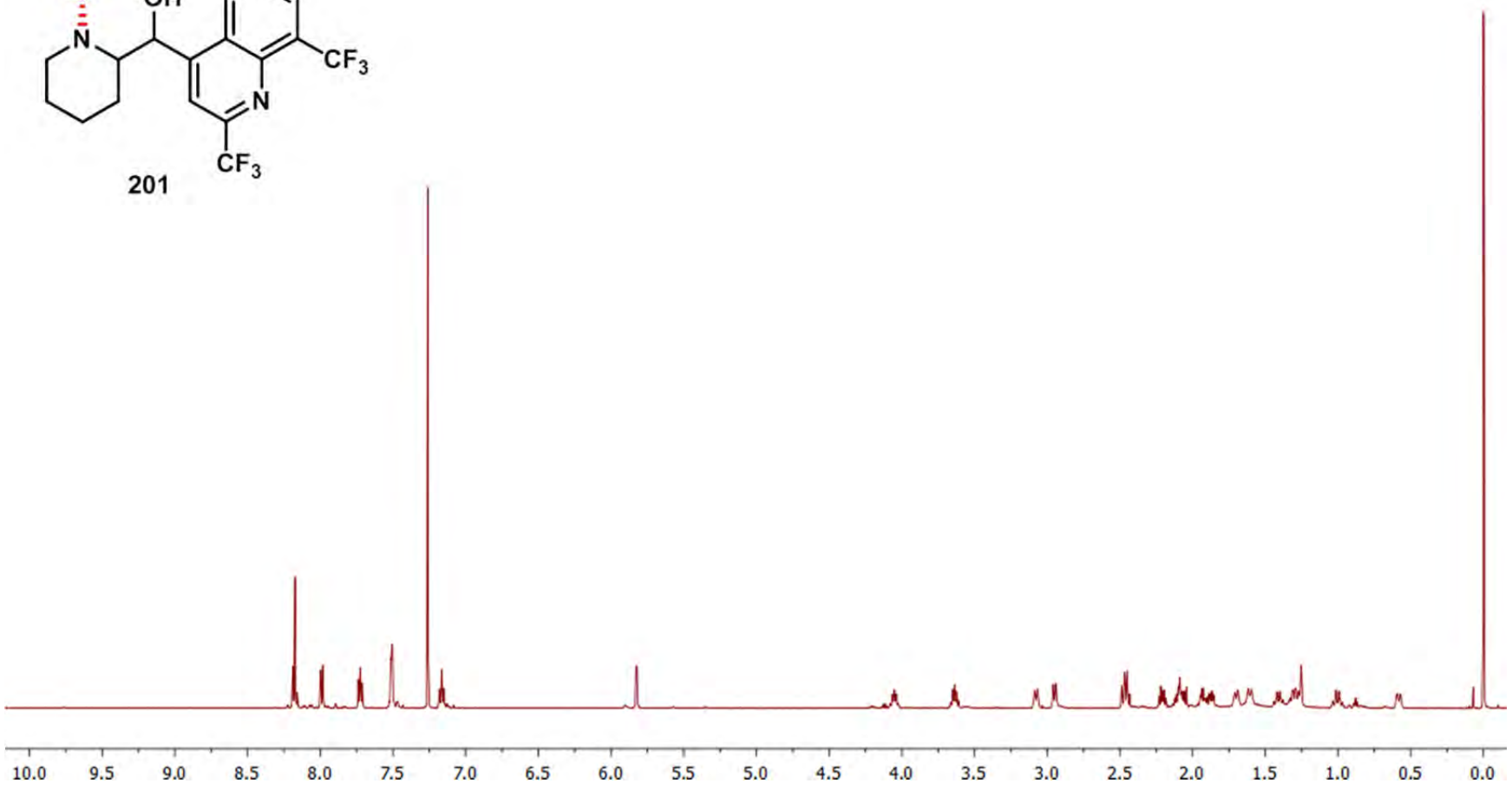
OH
N
CF3
N
CF3

201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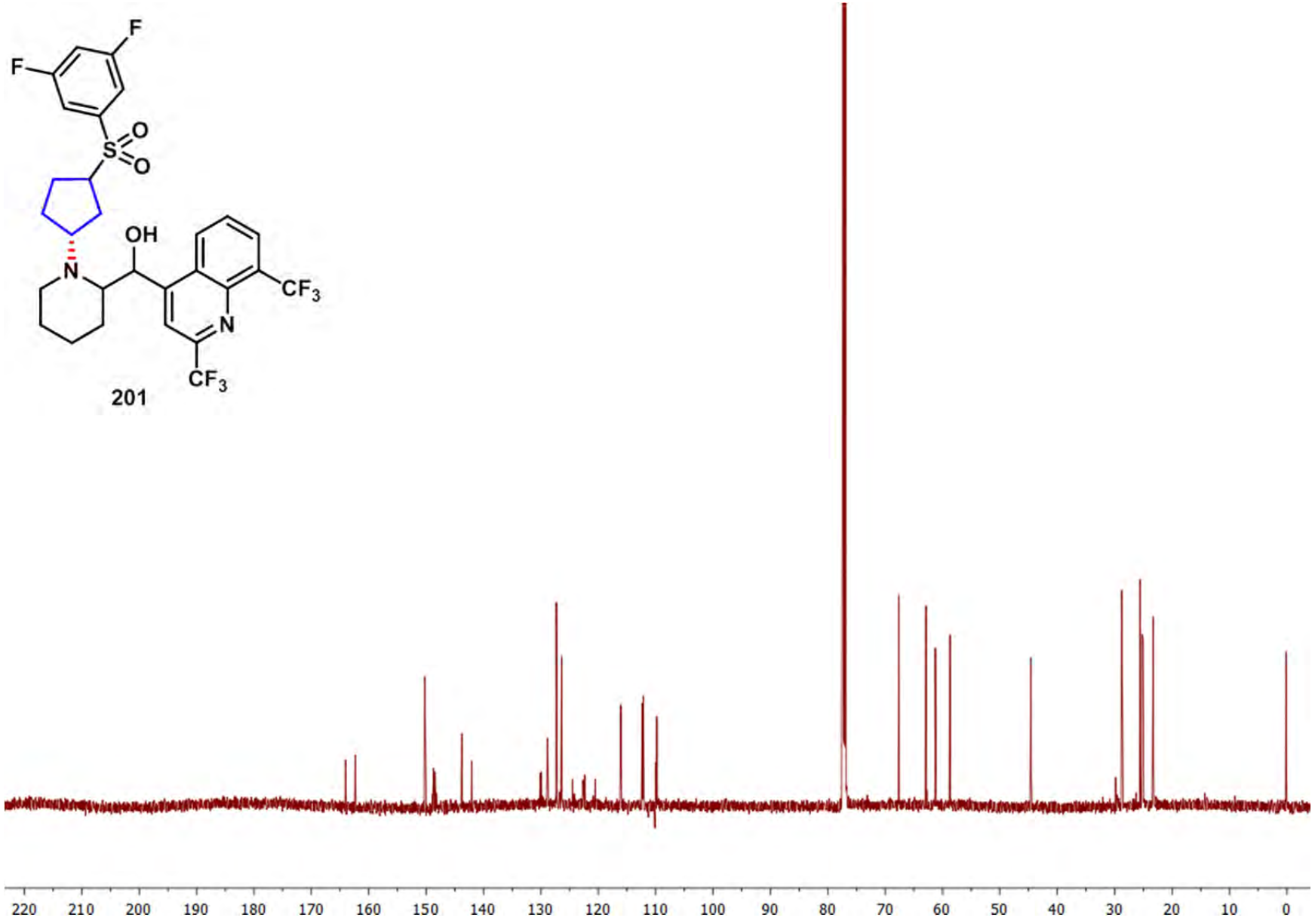
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CF3
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CF3
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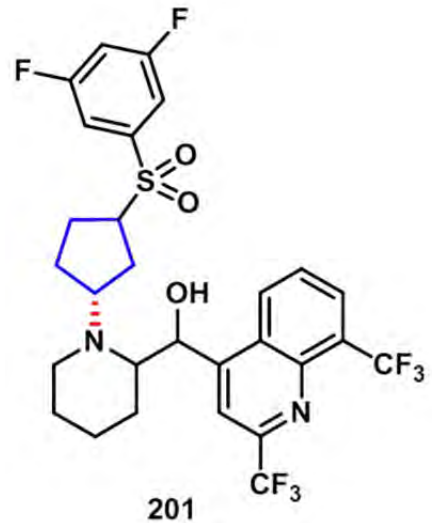
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CF3
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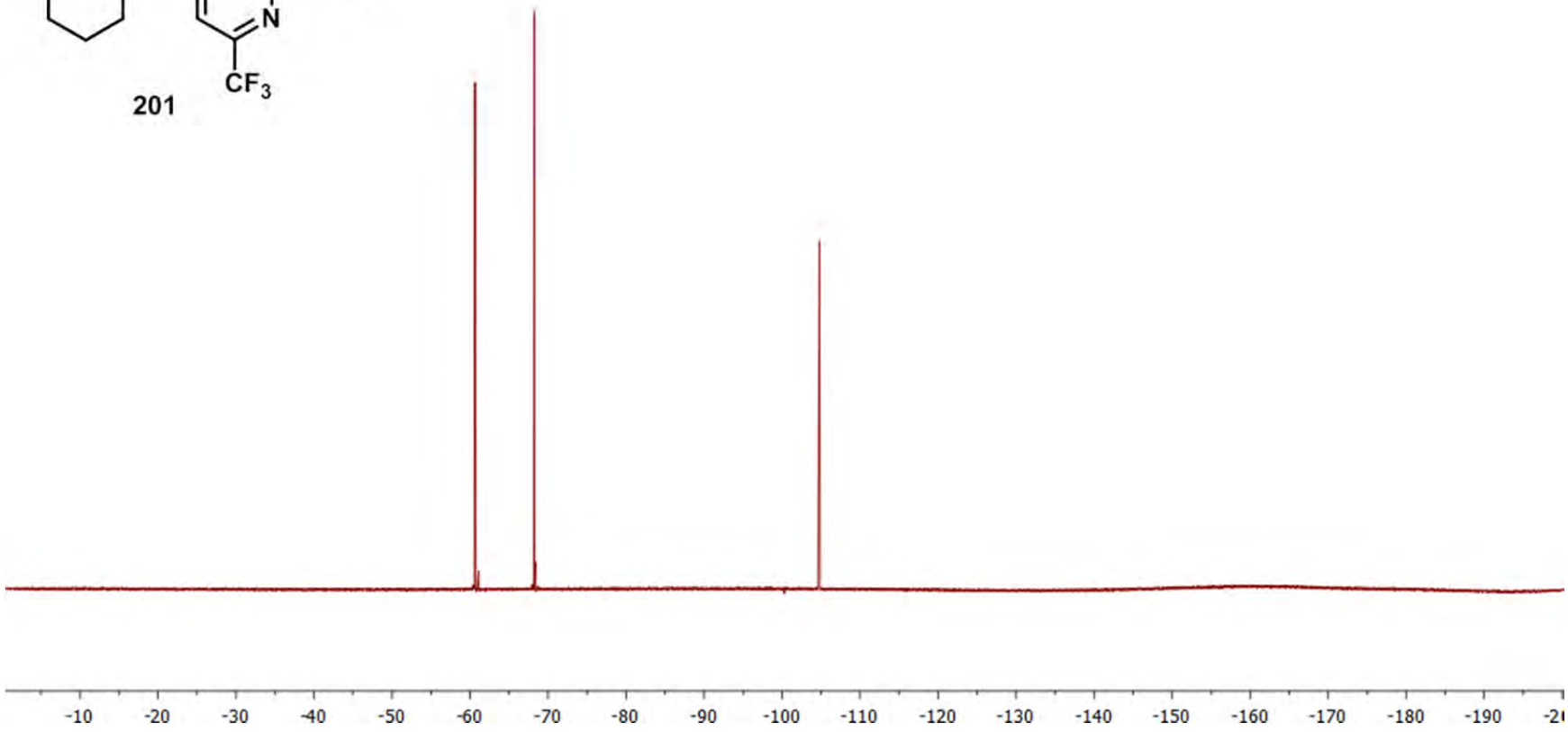
CF3

201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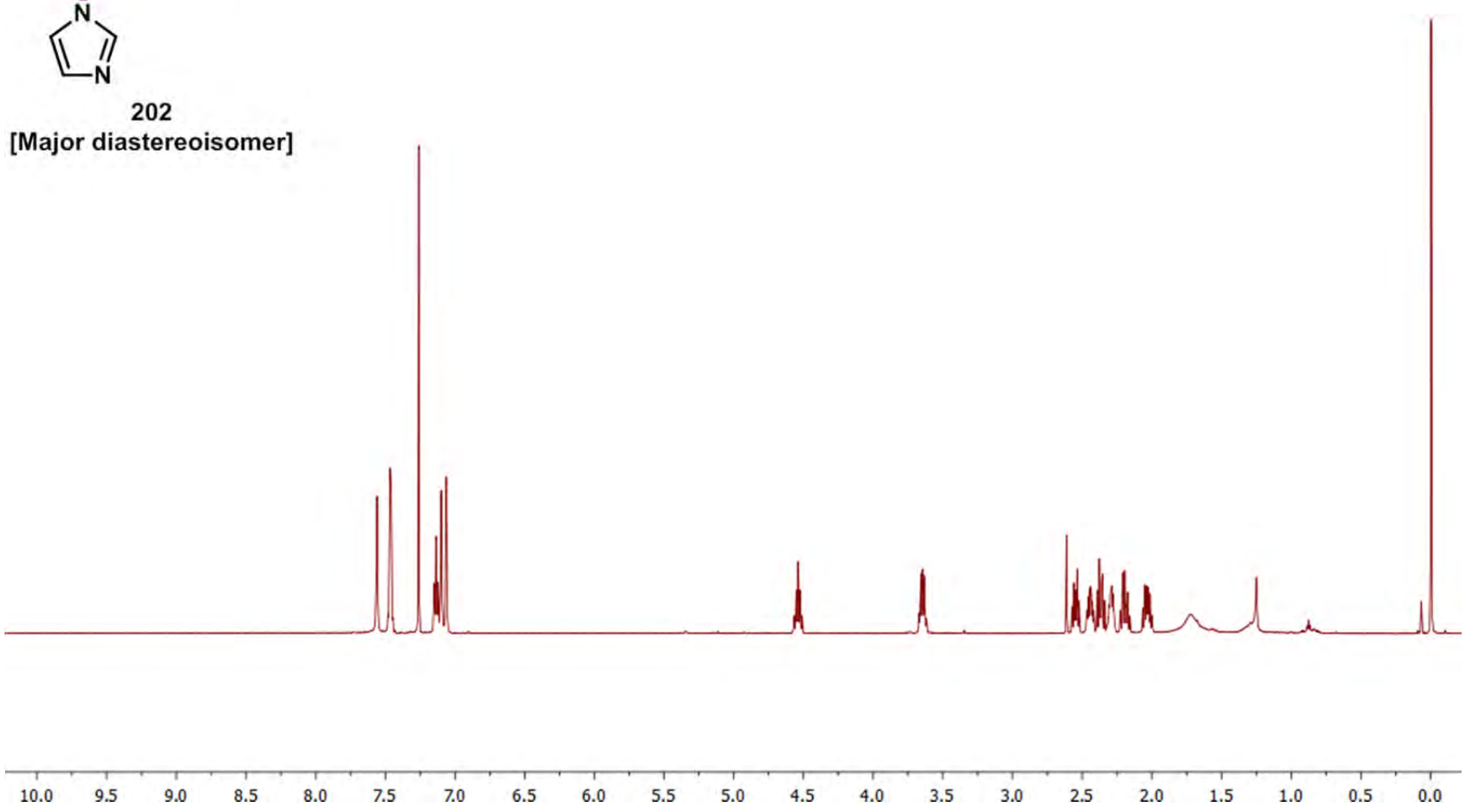
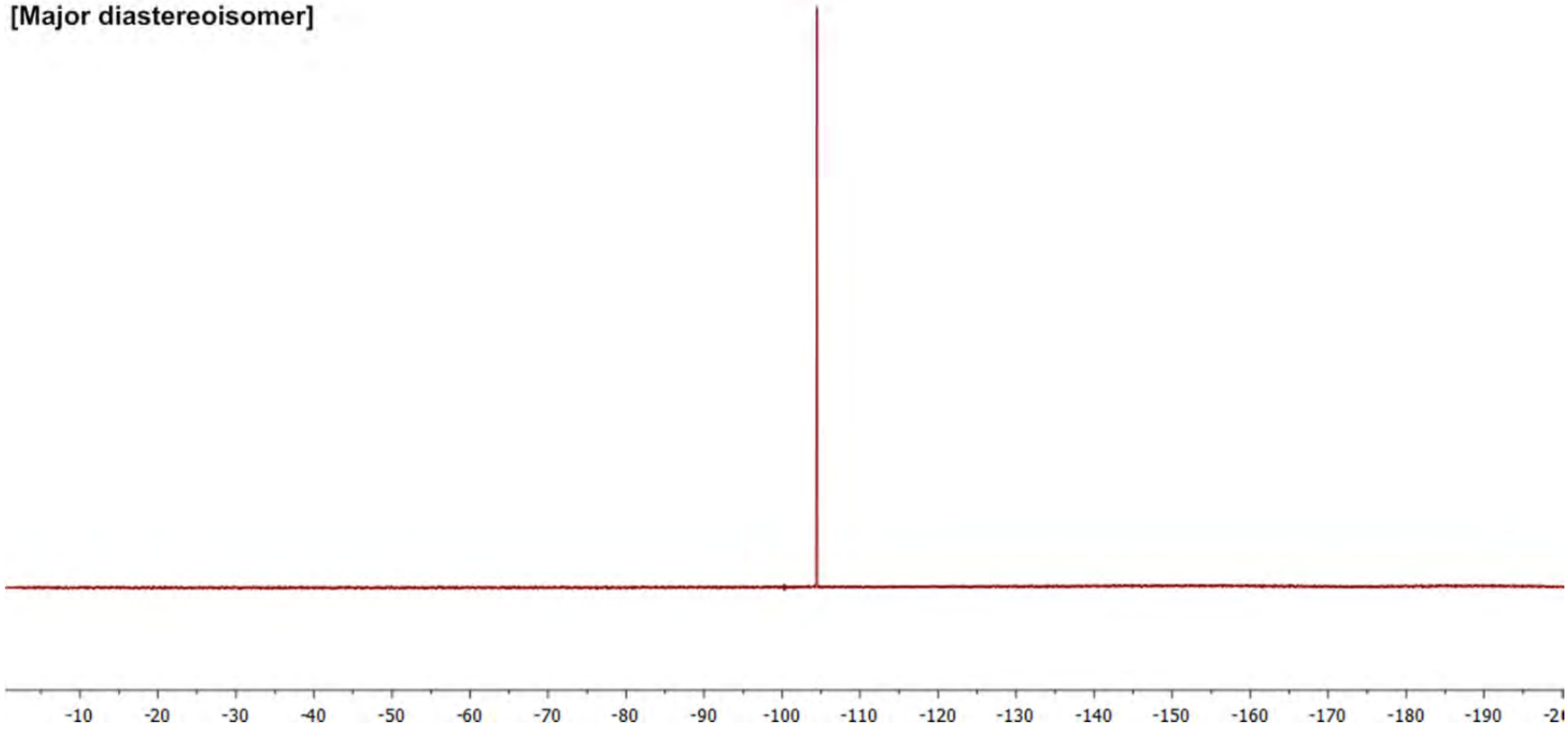
-190

202
[Major diastereoisomer]



202
[Major diastereoisomer]

202
[Major diastereoisomer]



202
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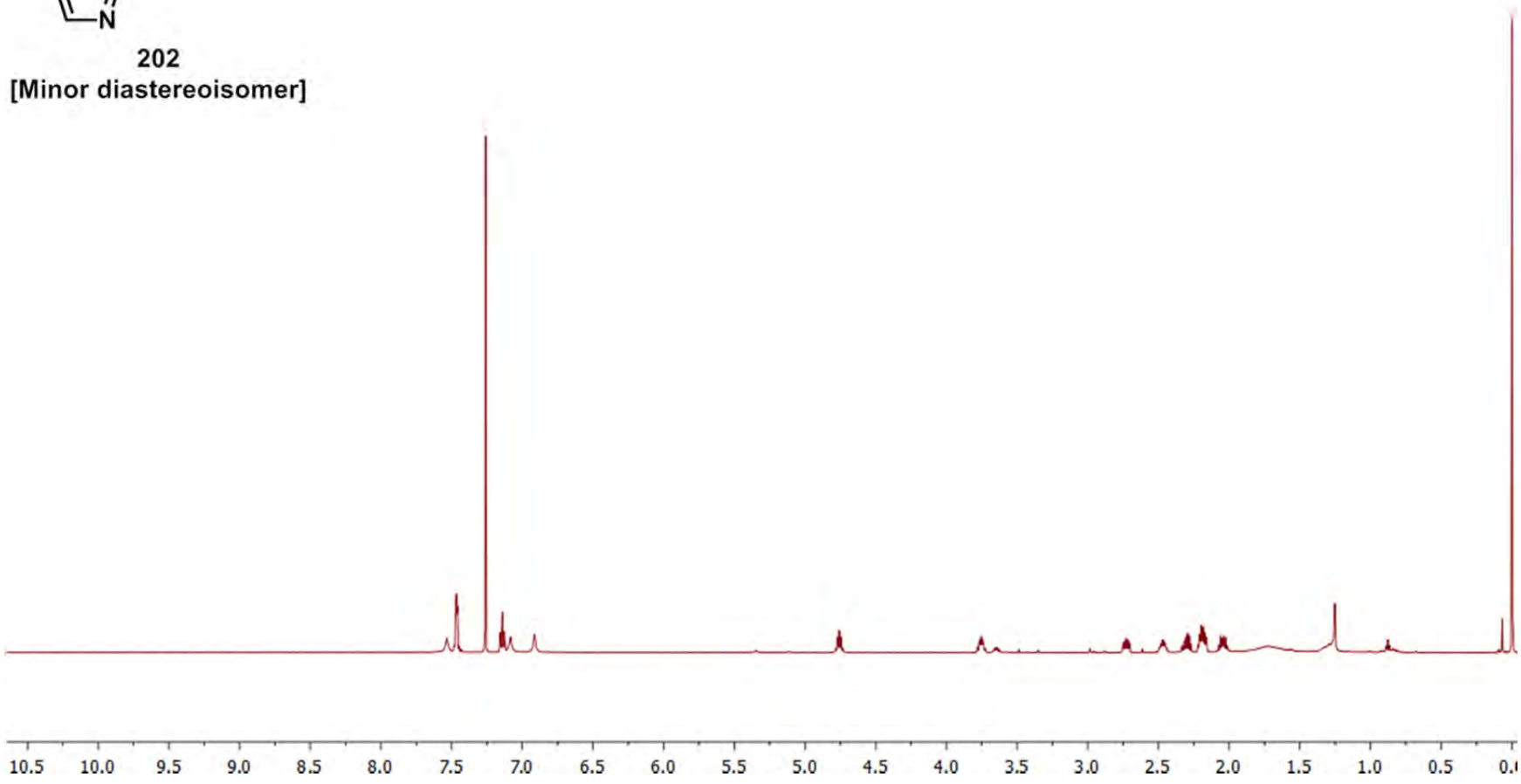
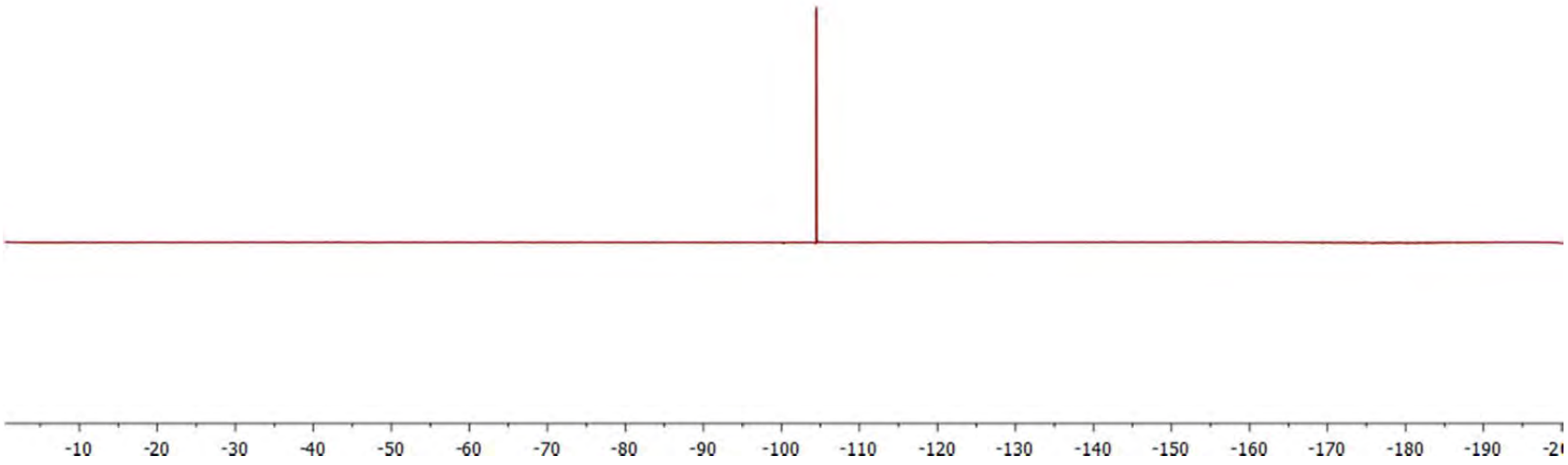


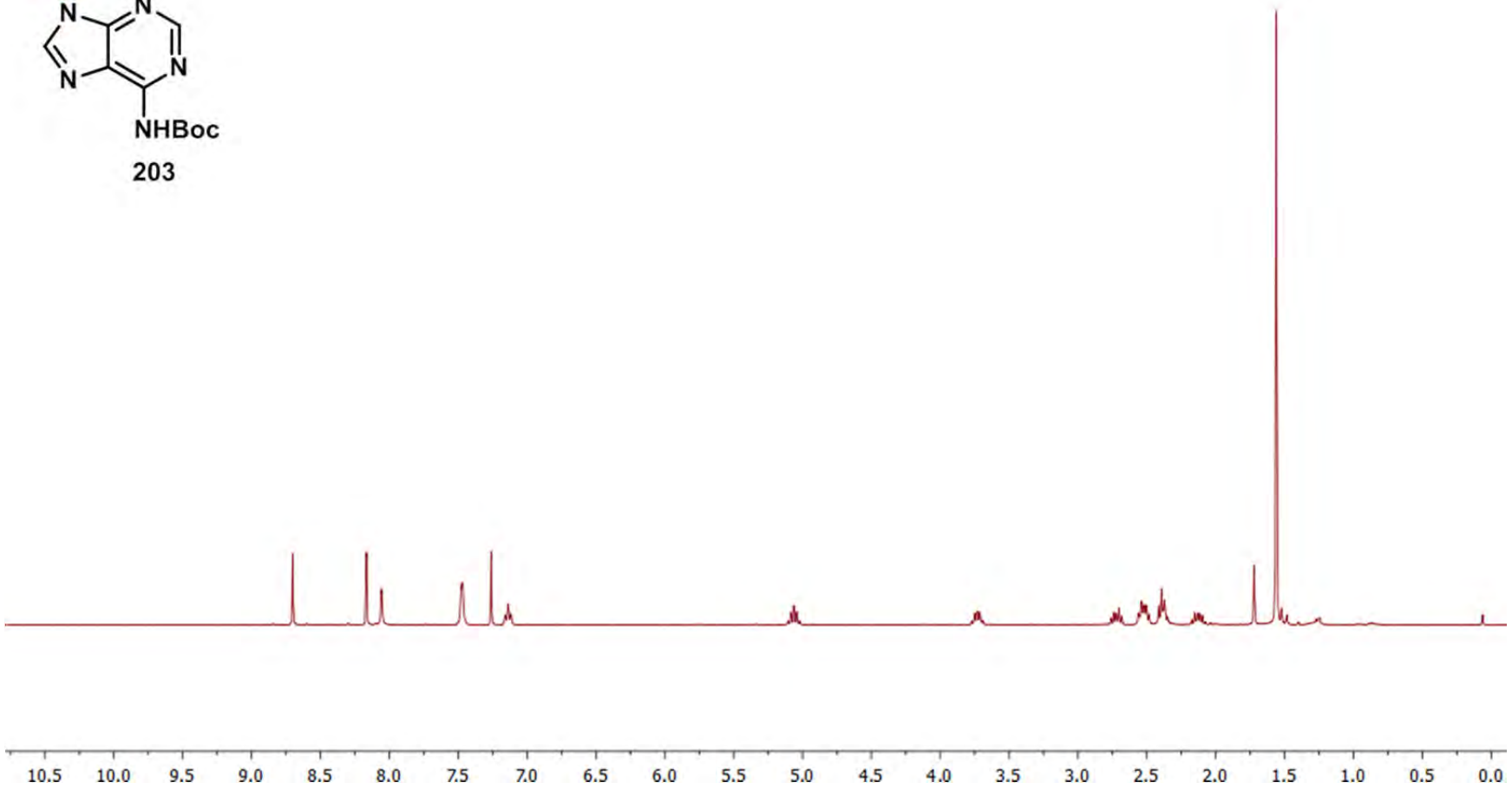
202
[Minor diastereoisomer]

202
[Minor diastereoisomer]




F
O
O
S
F
N
N
N
N
NHBoc

203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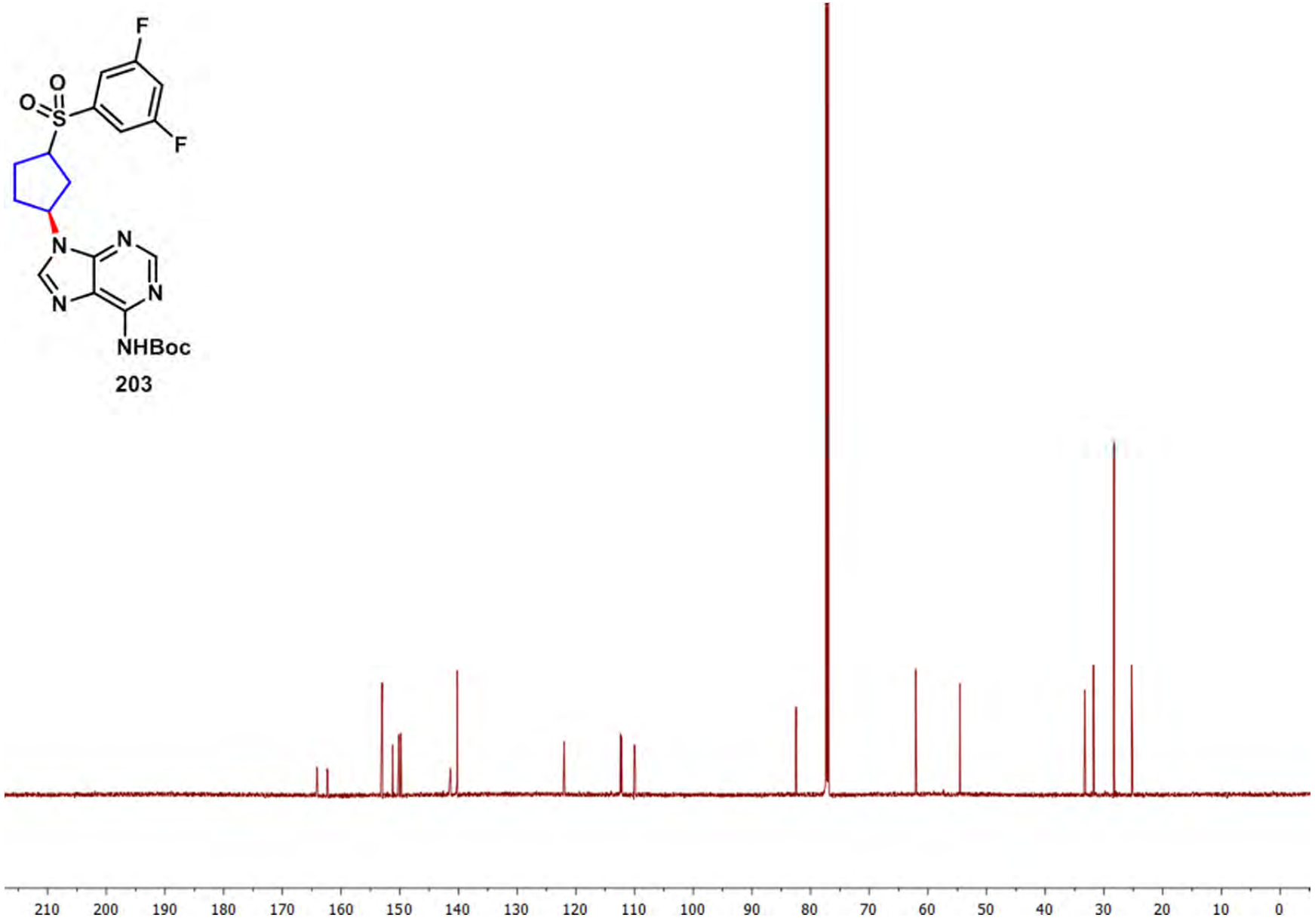
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NHBoc
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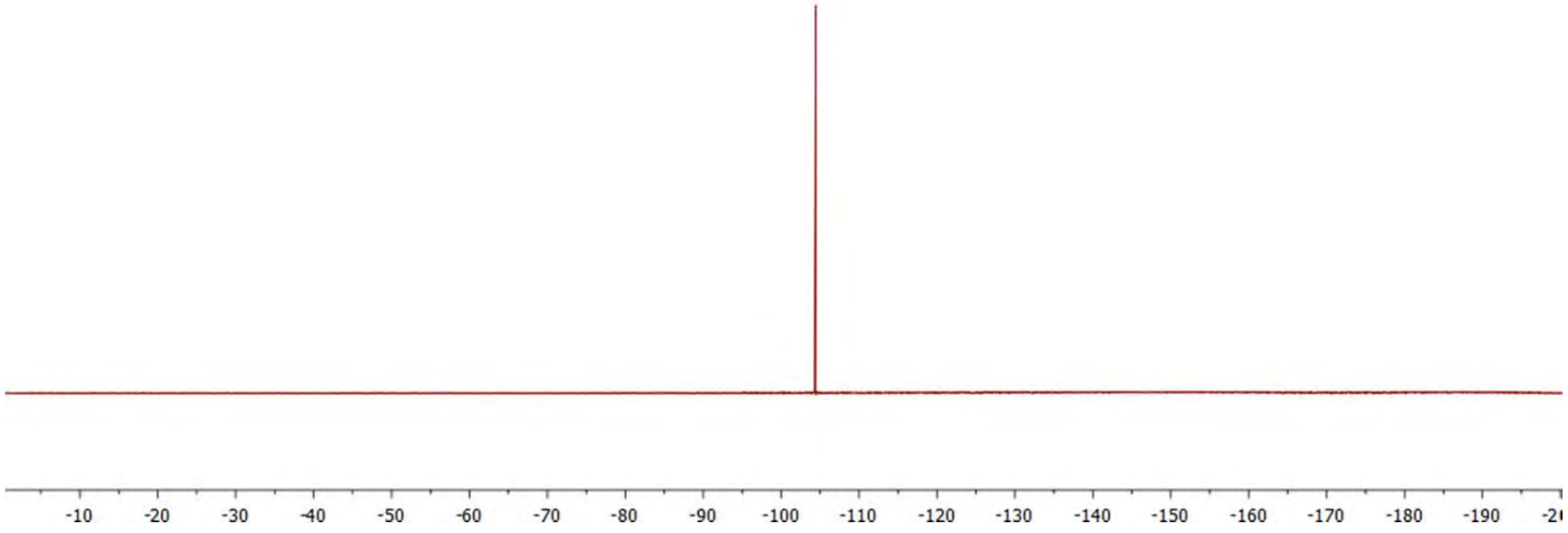
NHBoc

203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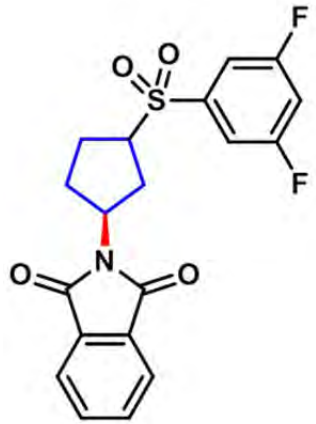
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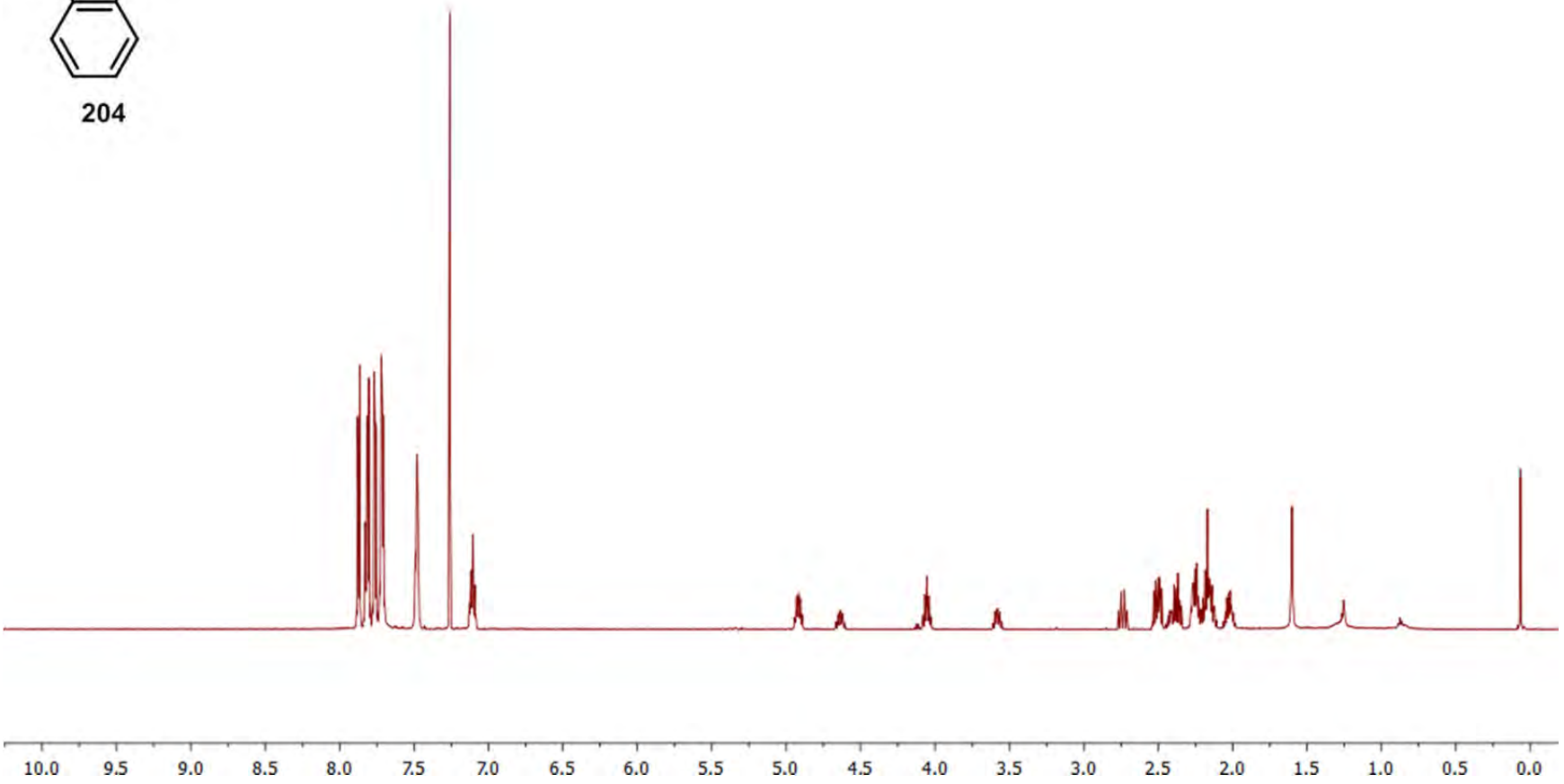
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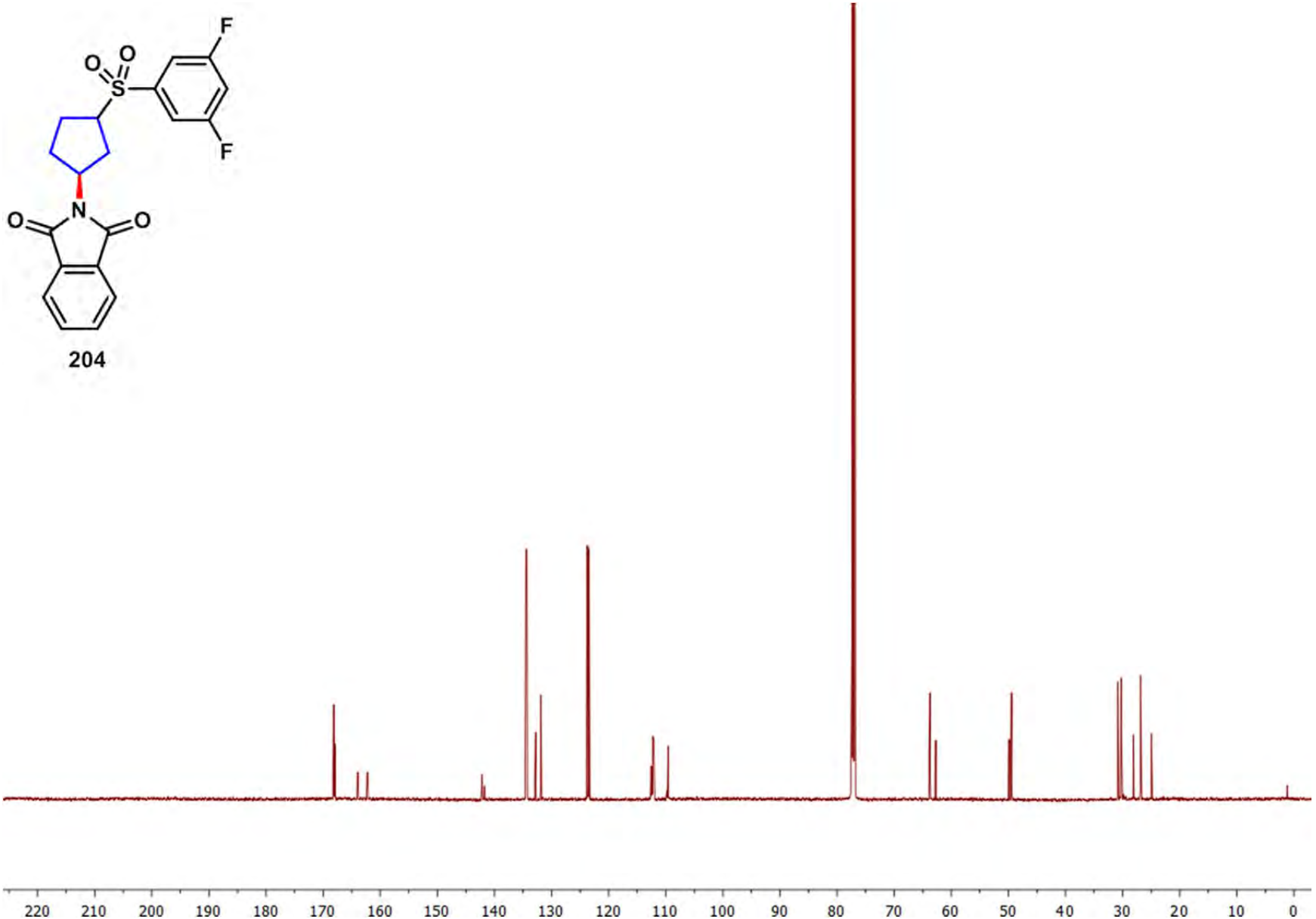
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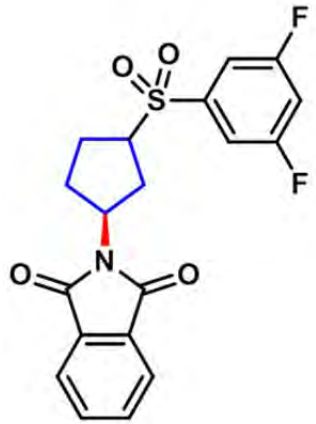
204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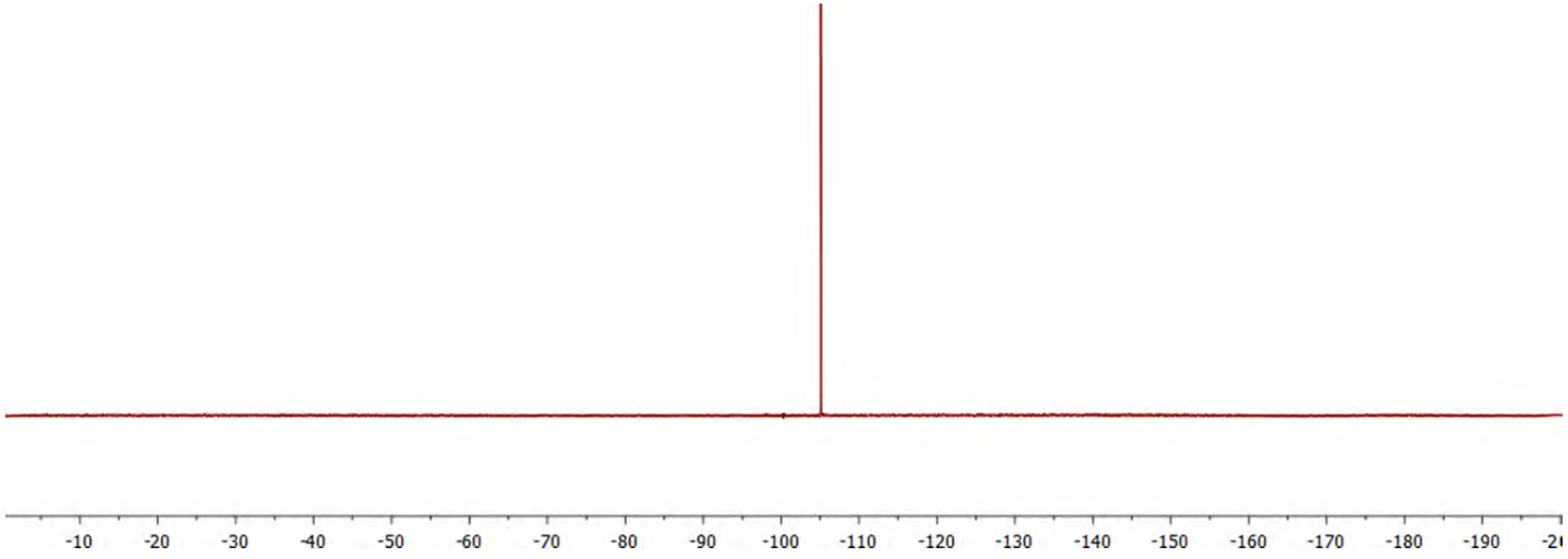
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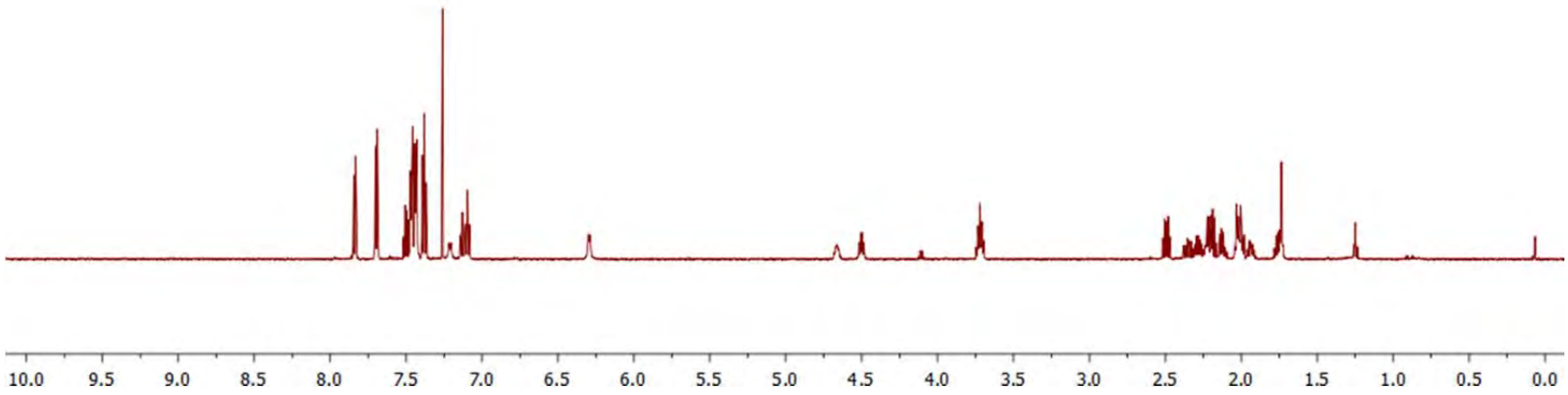
205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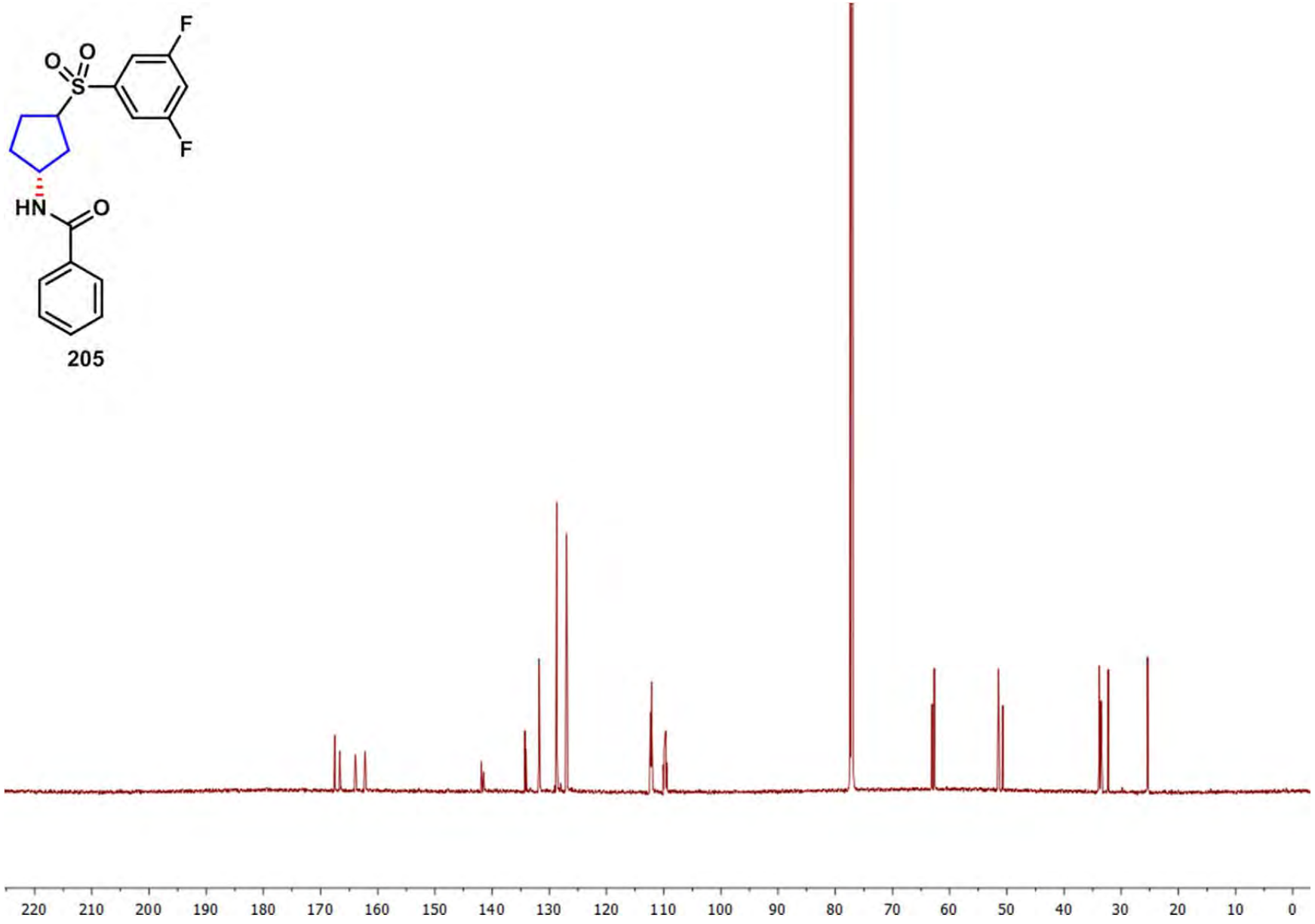
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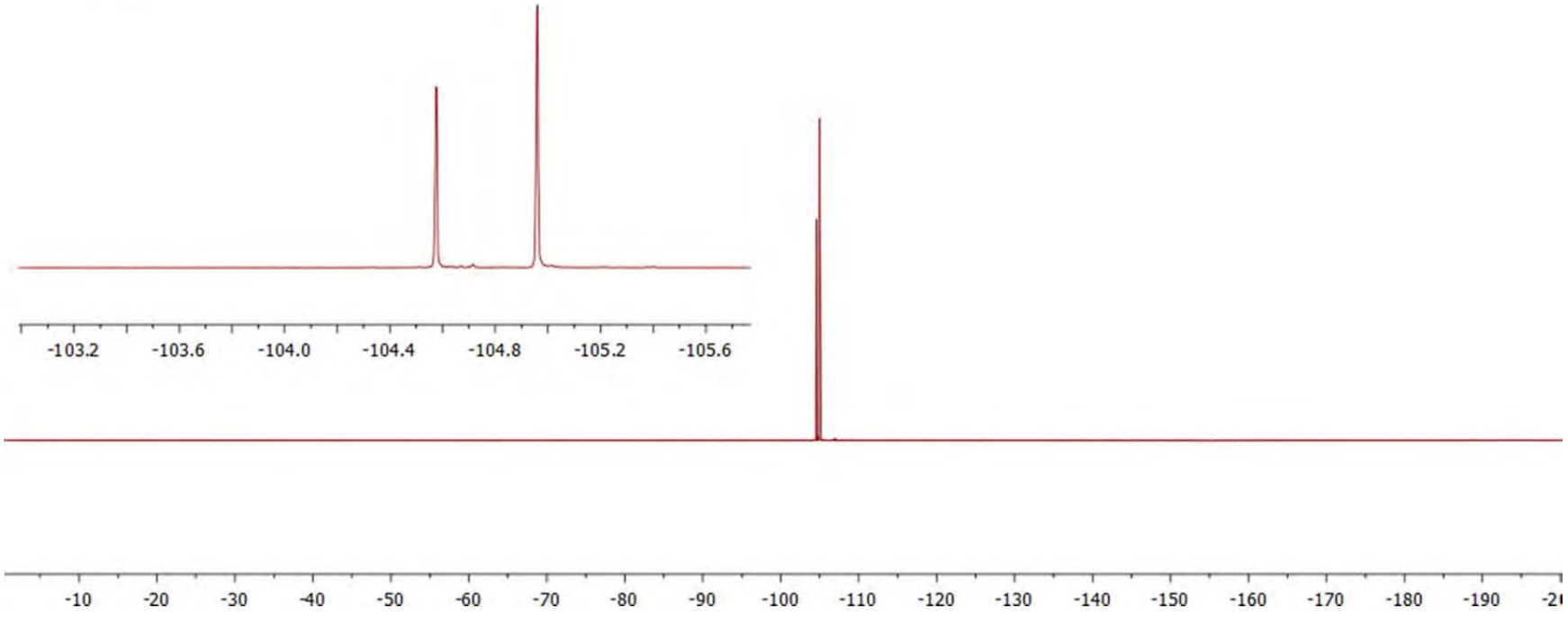
205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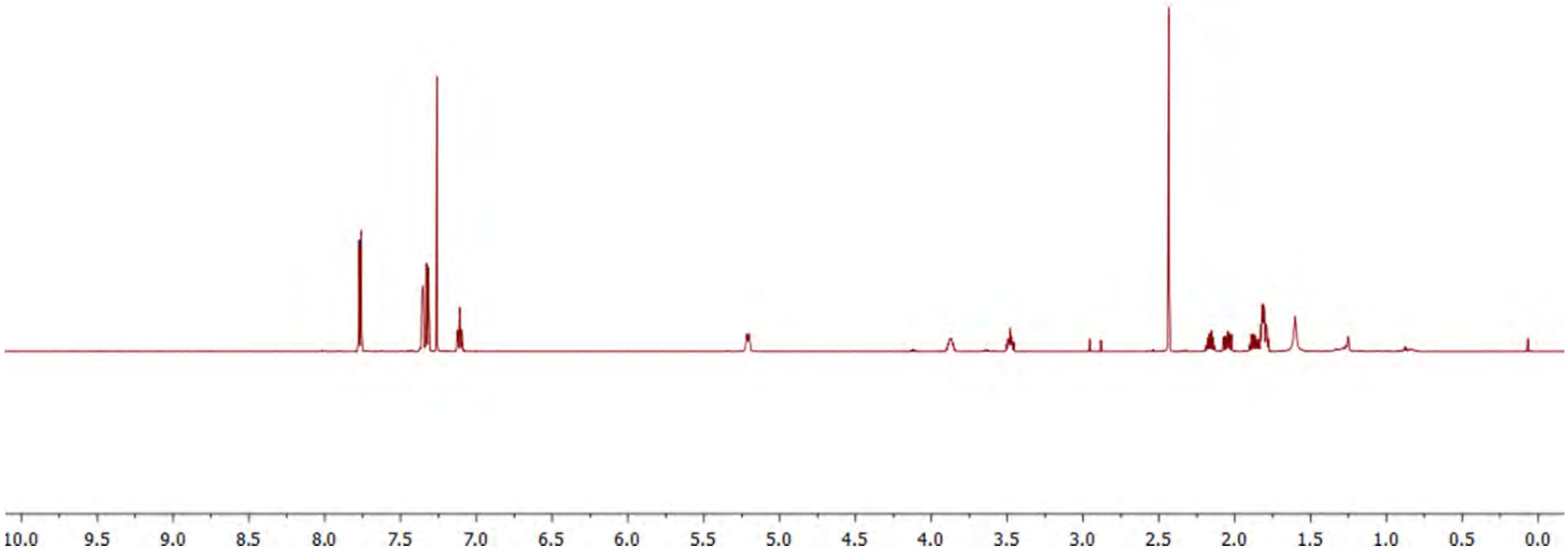
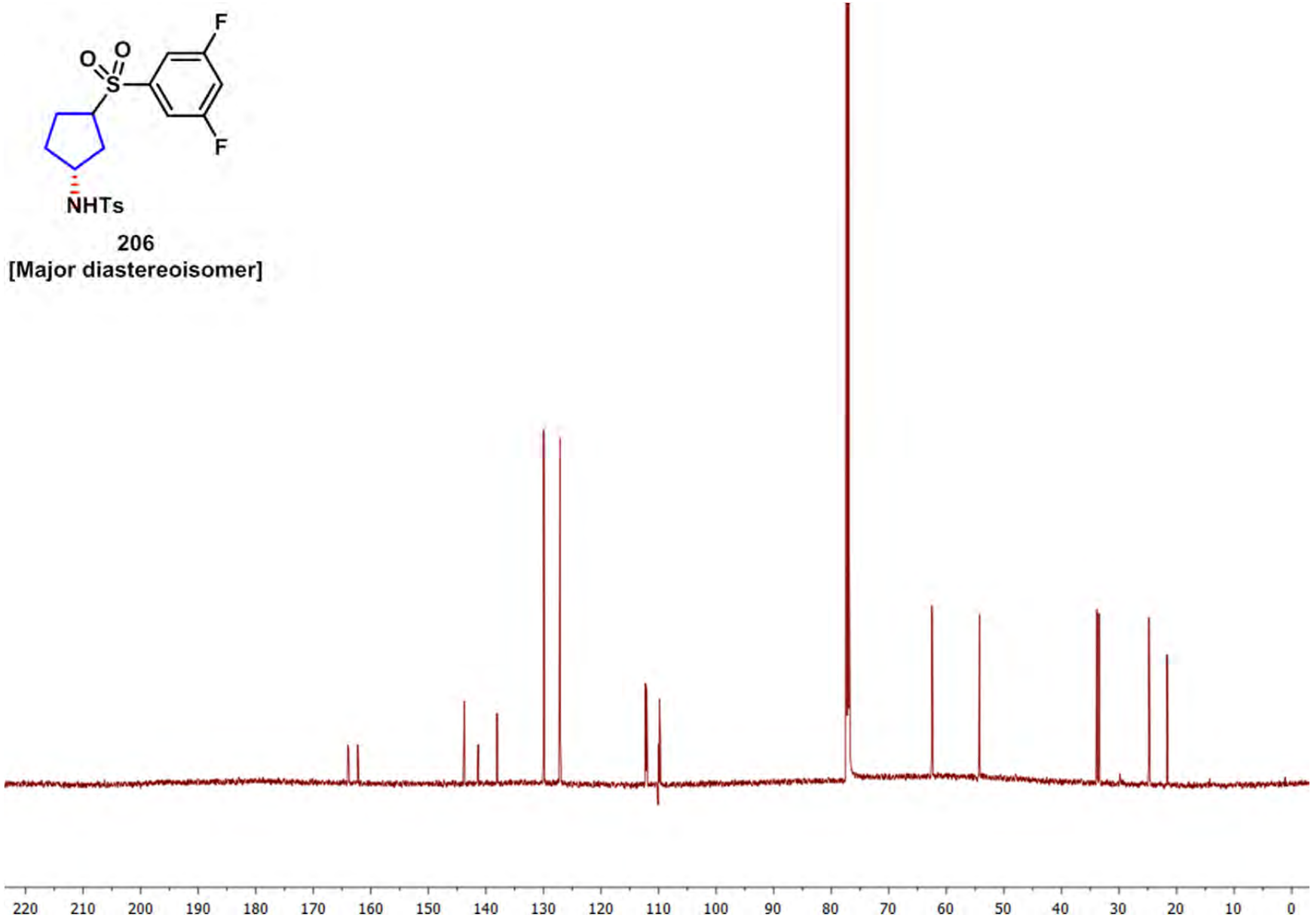
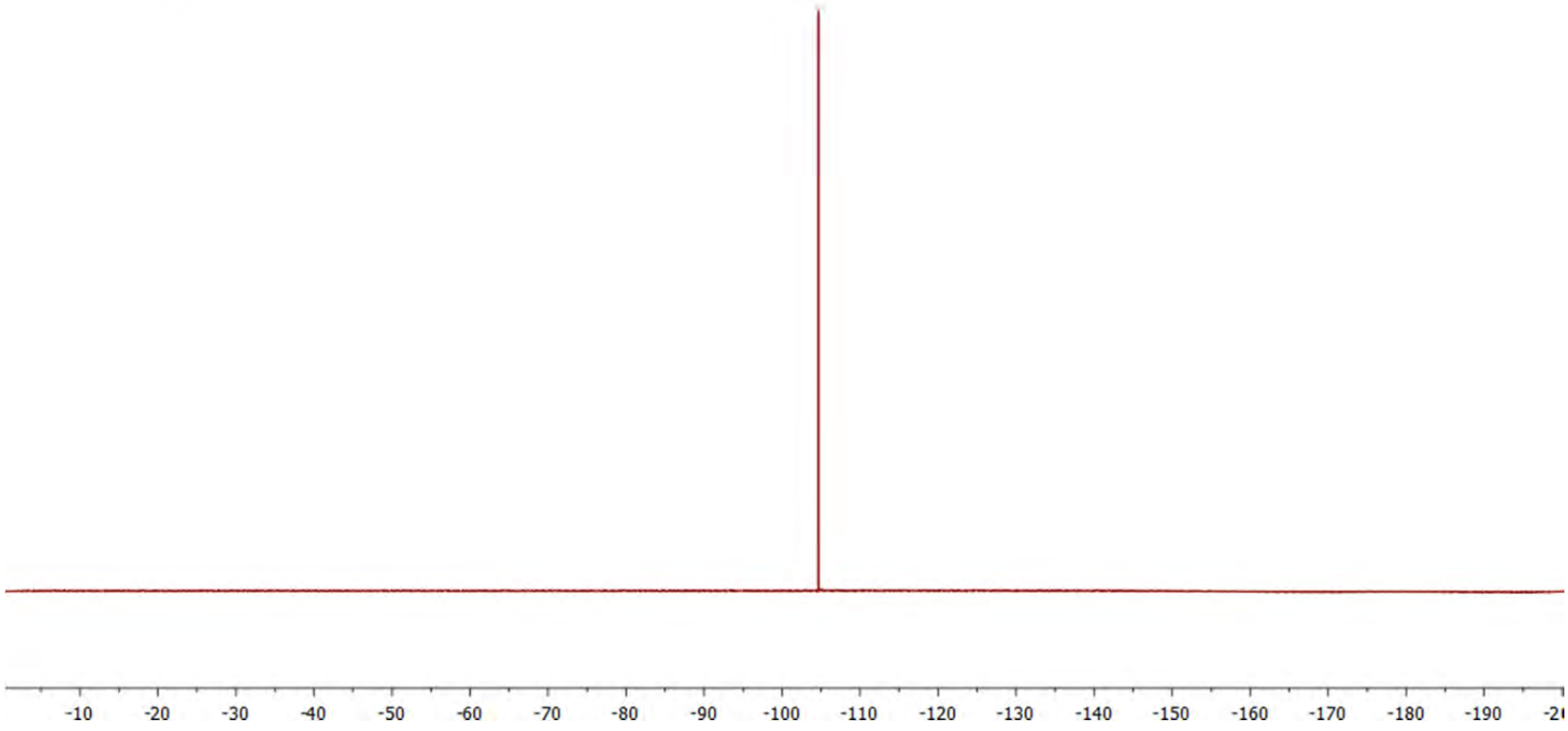
206
[Major diastereoisomer]





206
[Major diastereoisomer]

206
[Major diastereoisomer]



206
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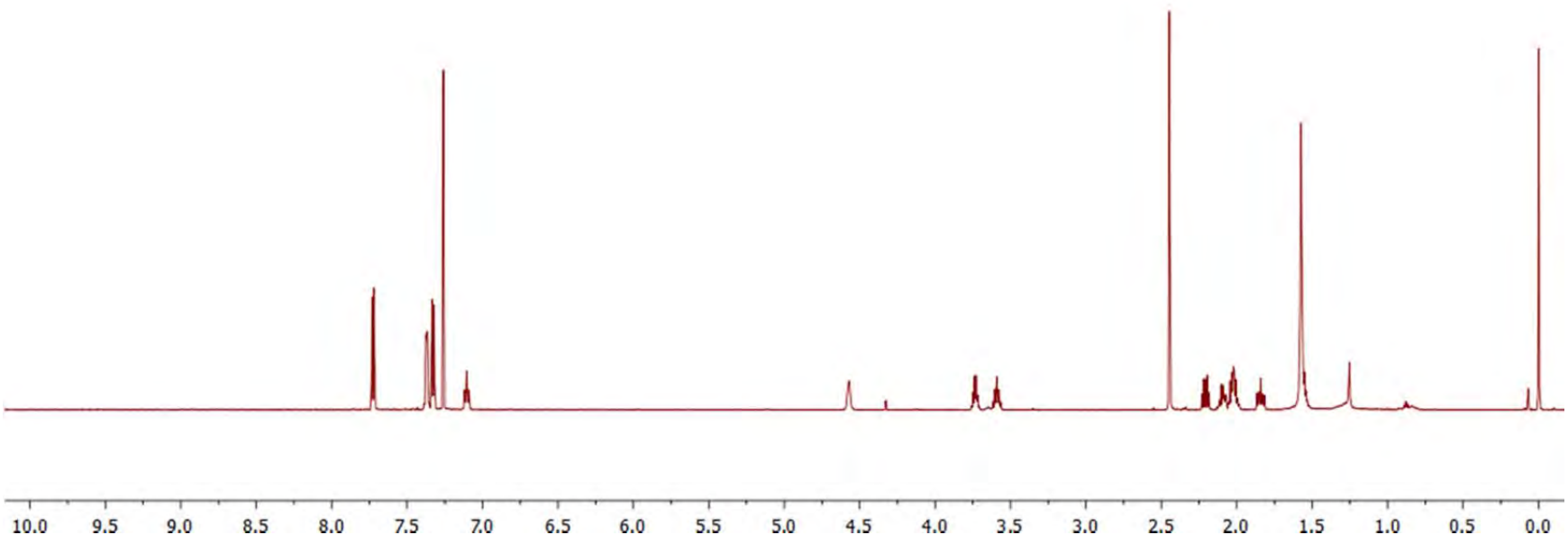
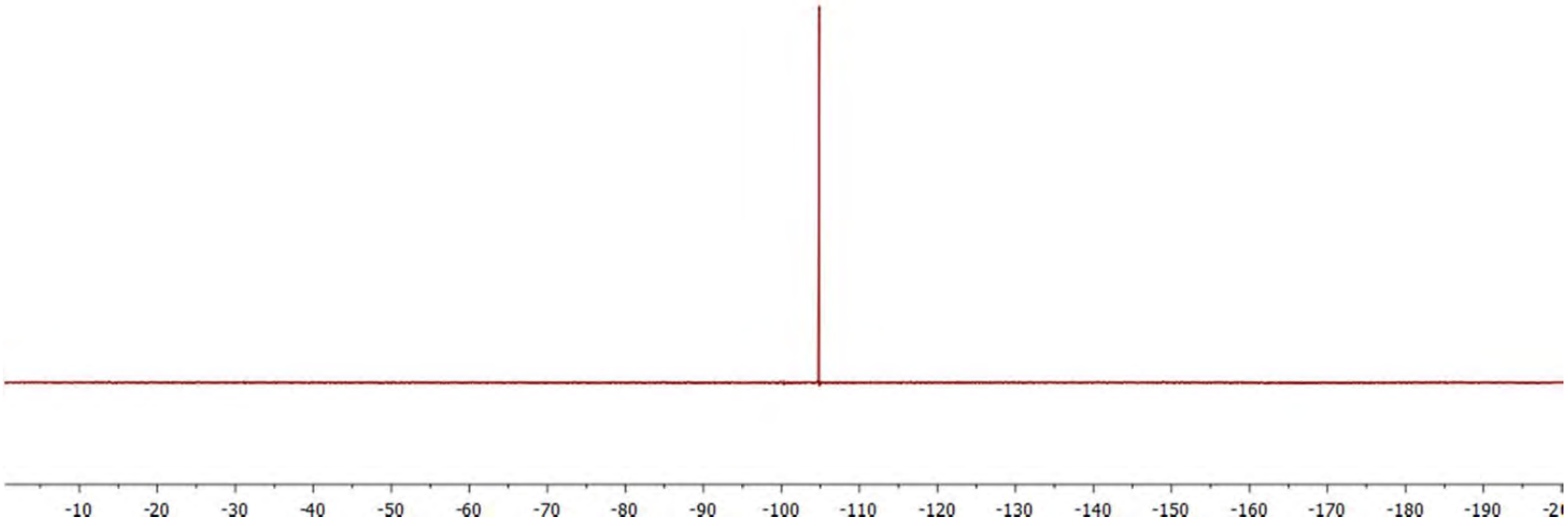
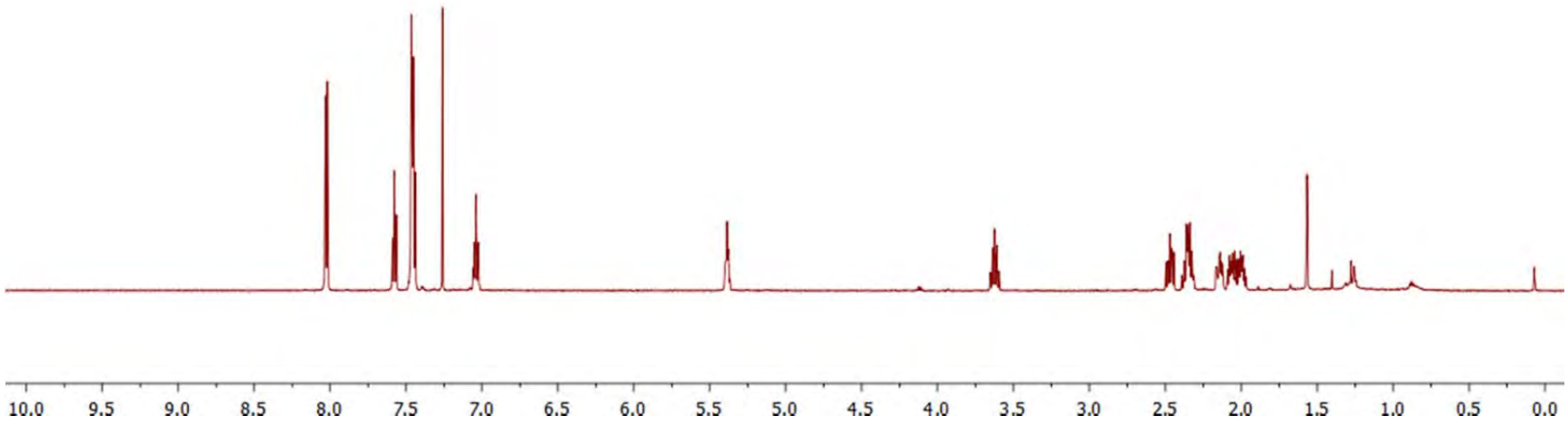


206
[Minor diastereoisomer]

206
[Minor diastereoisomer]

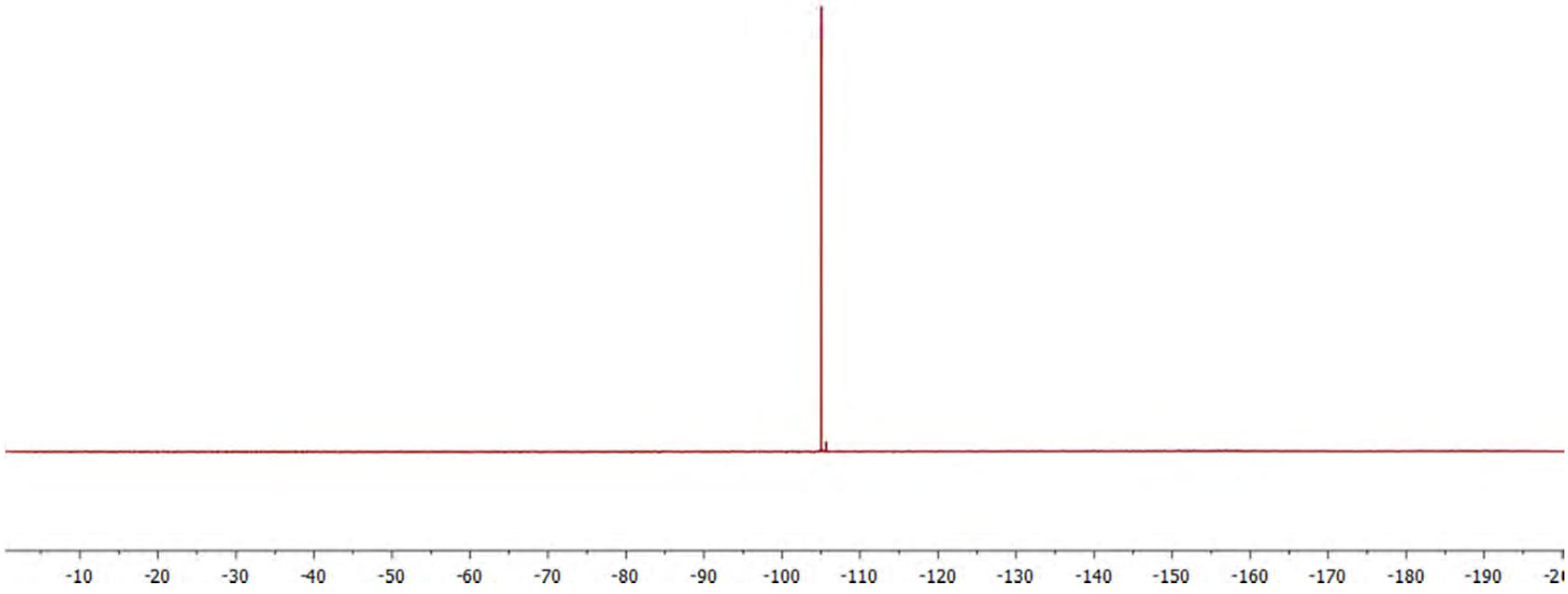


207
[Major diastereoisomer]



207
[Major diastereoisomer]

207
[Major diastereoisomer]



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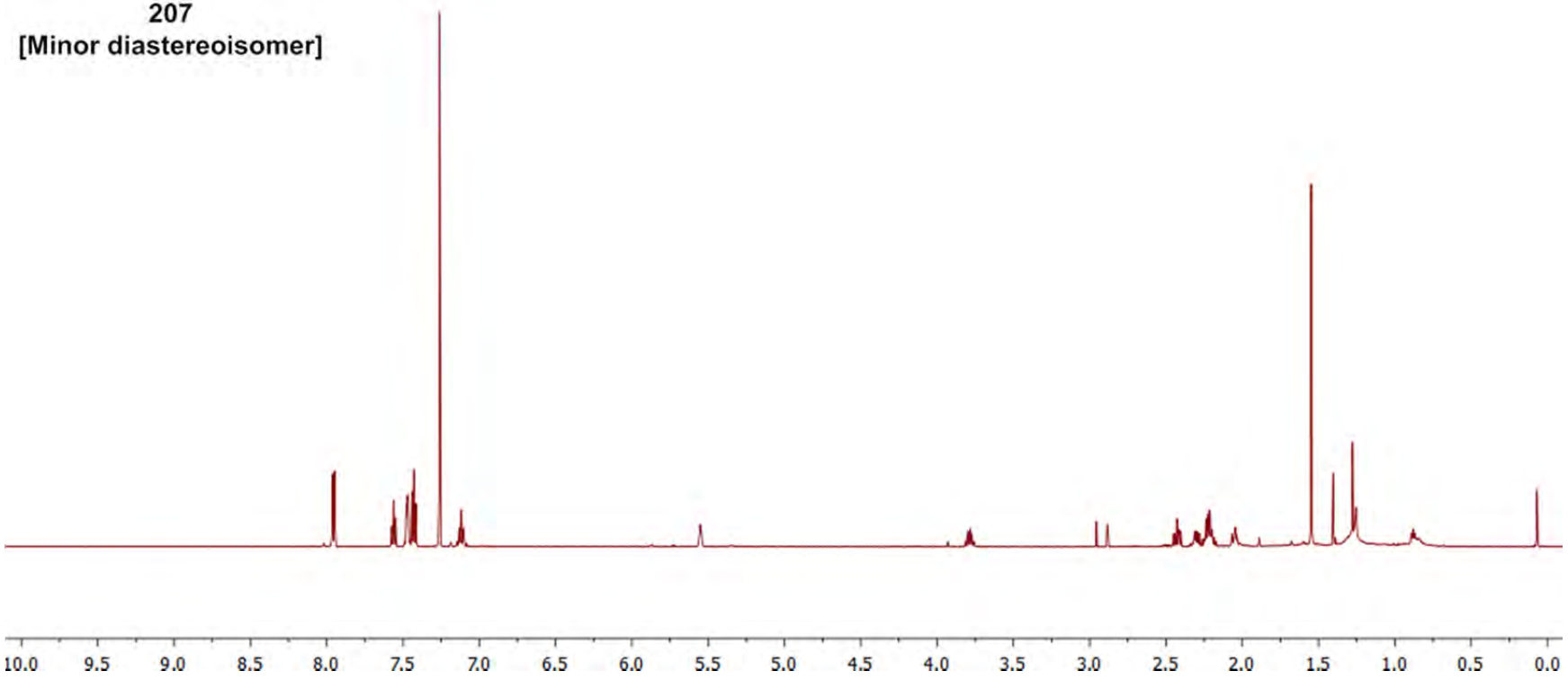

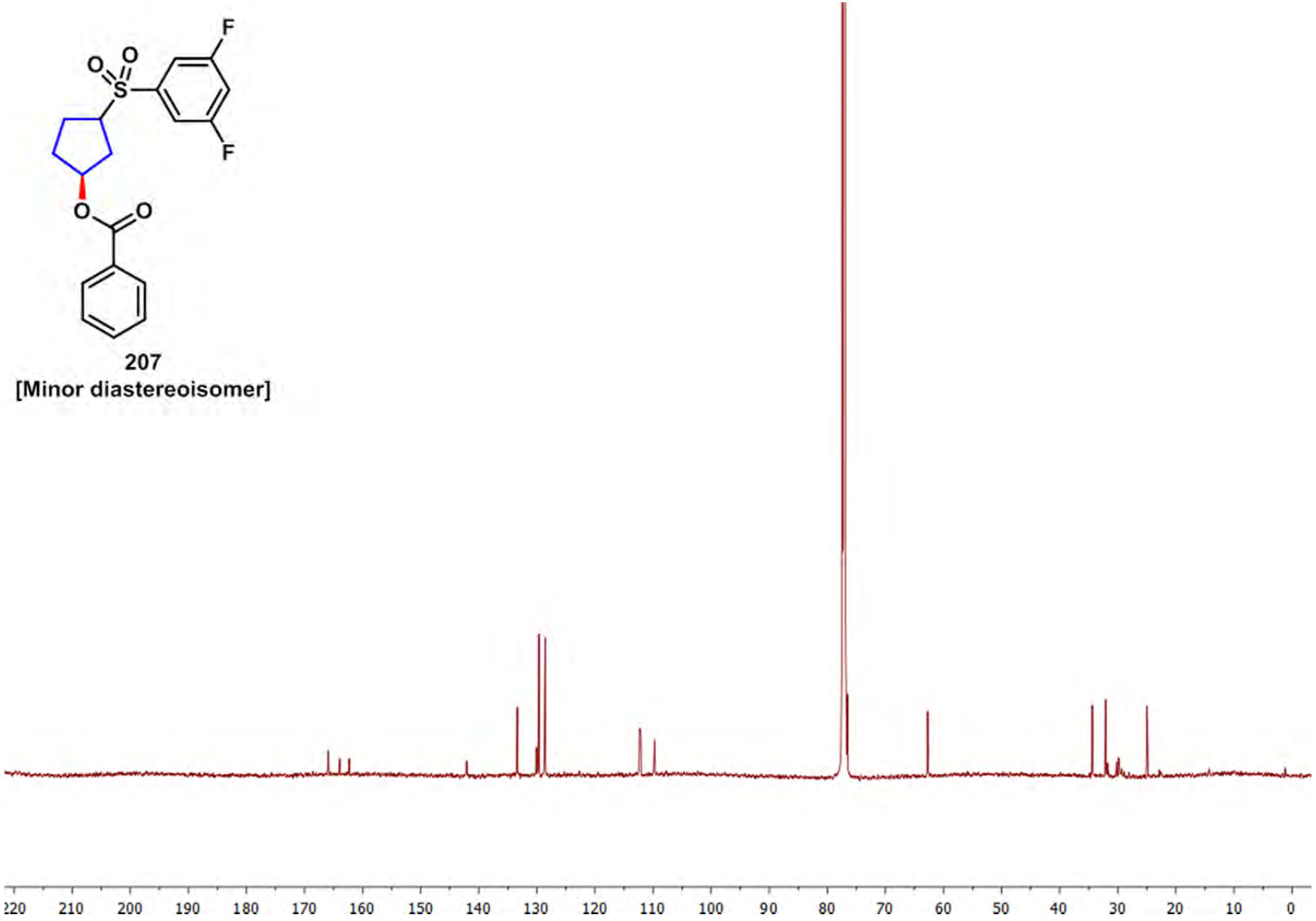

207
[Minor diastereoisomer]

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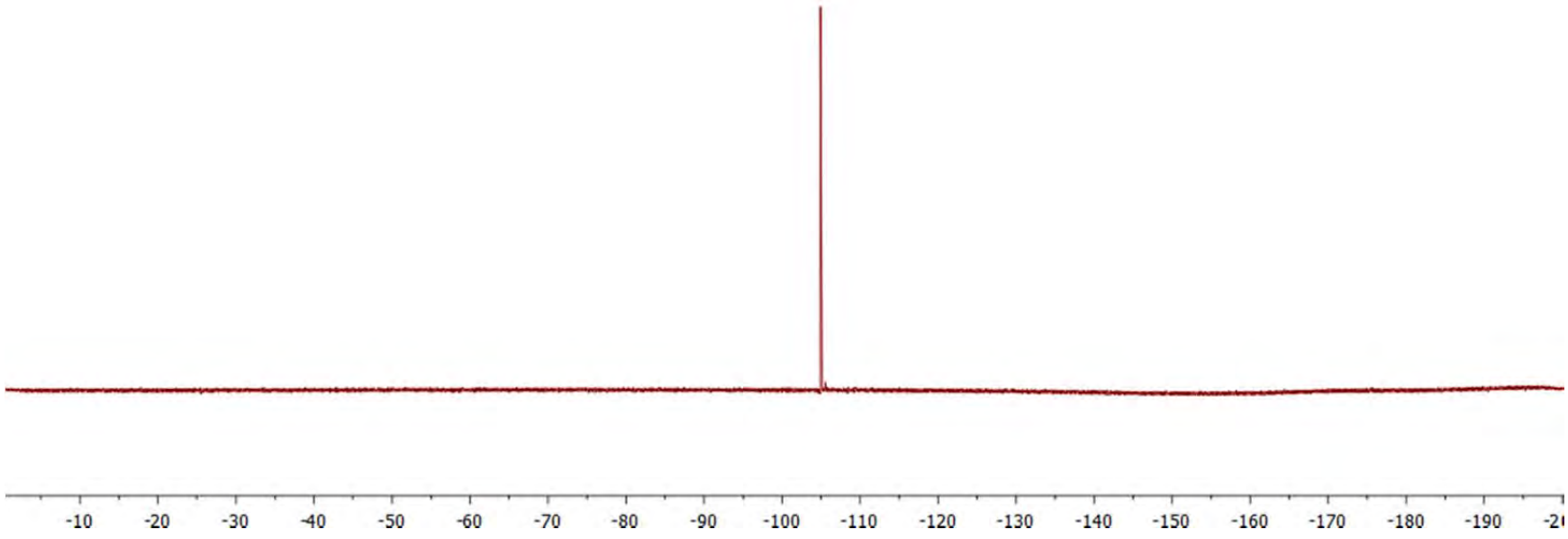
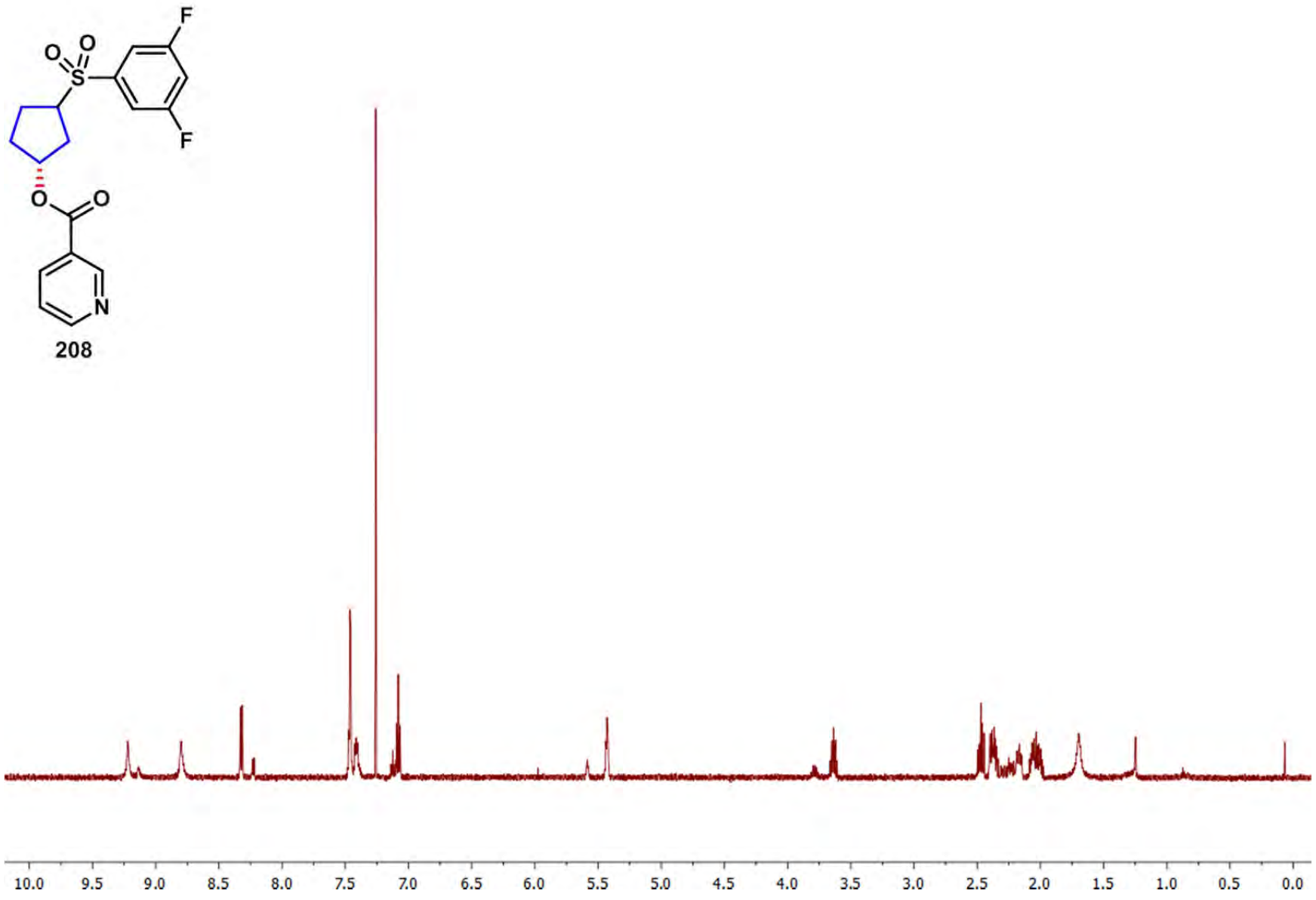
[Minor diastereoisomer]

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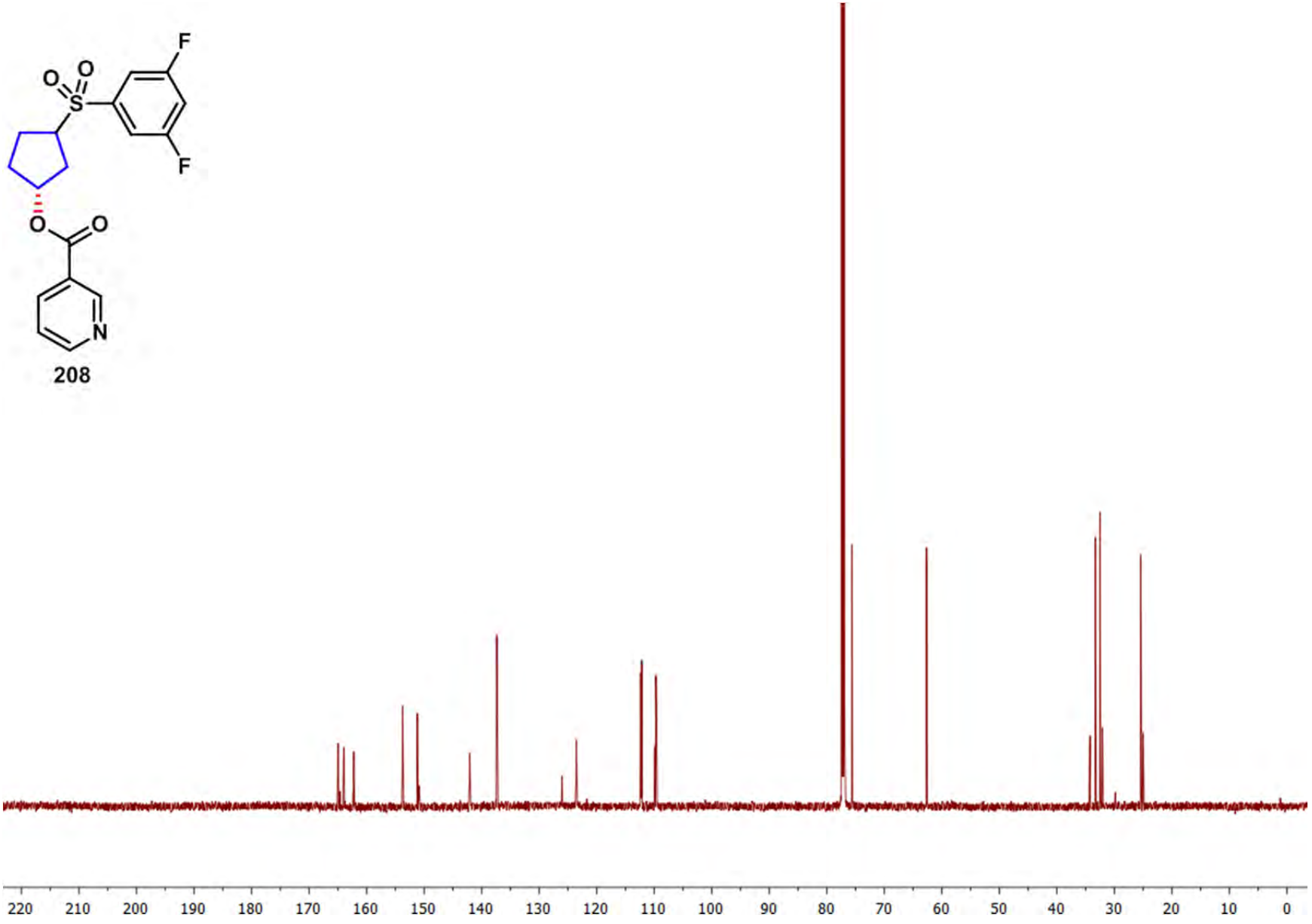
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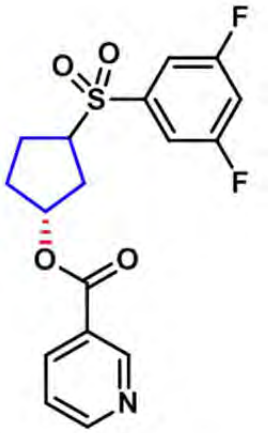
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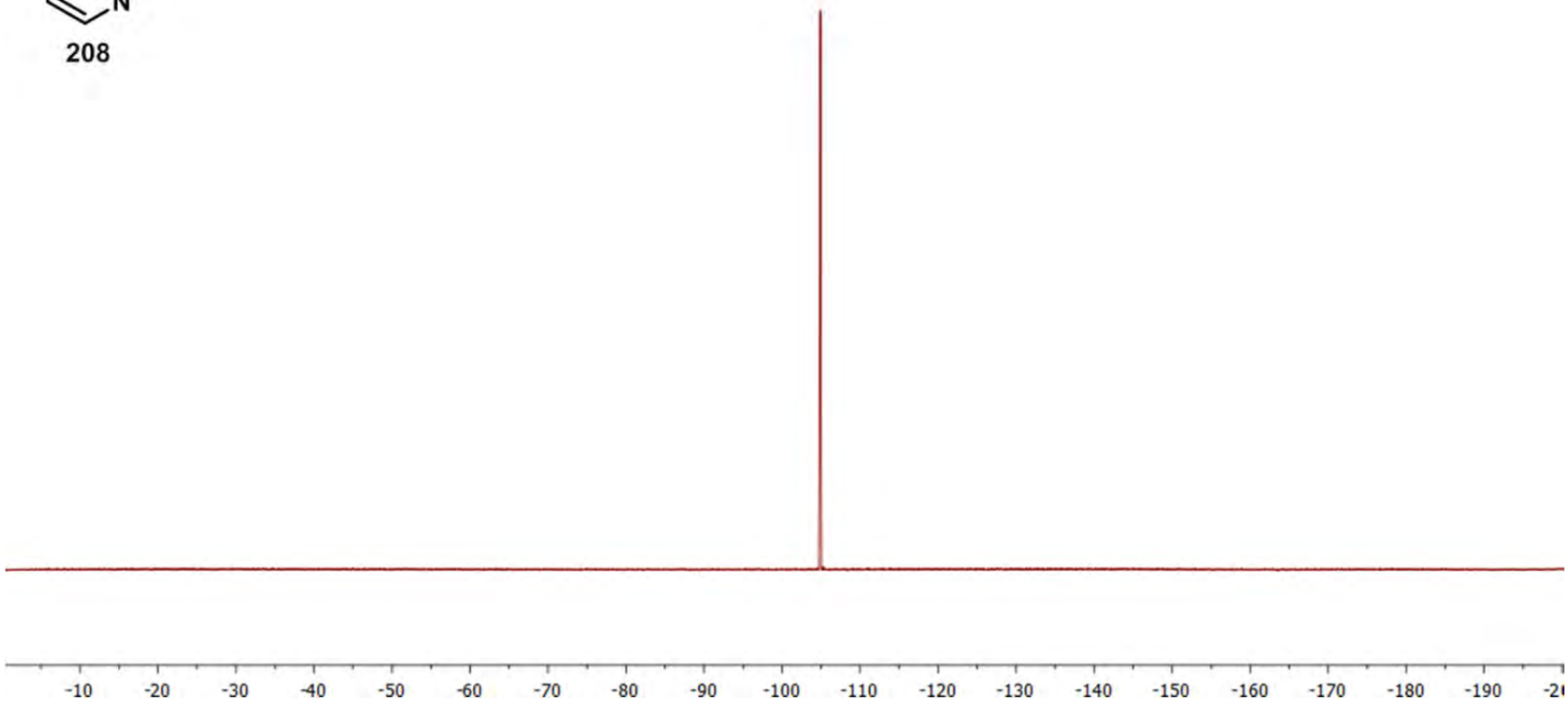
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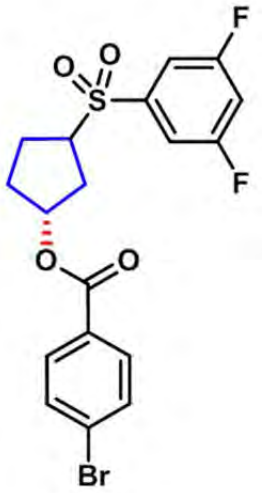
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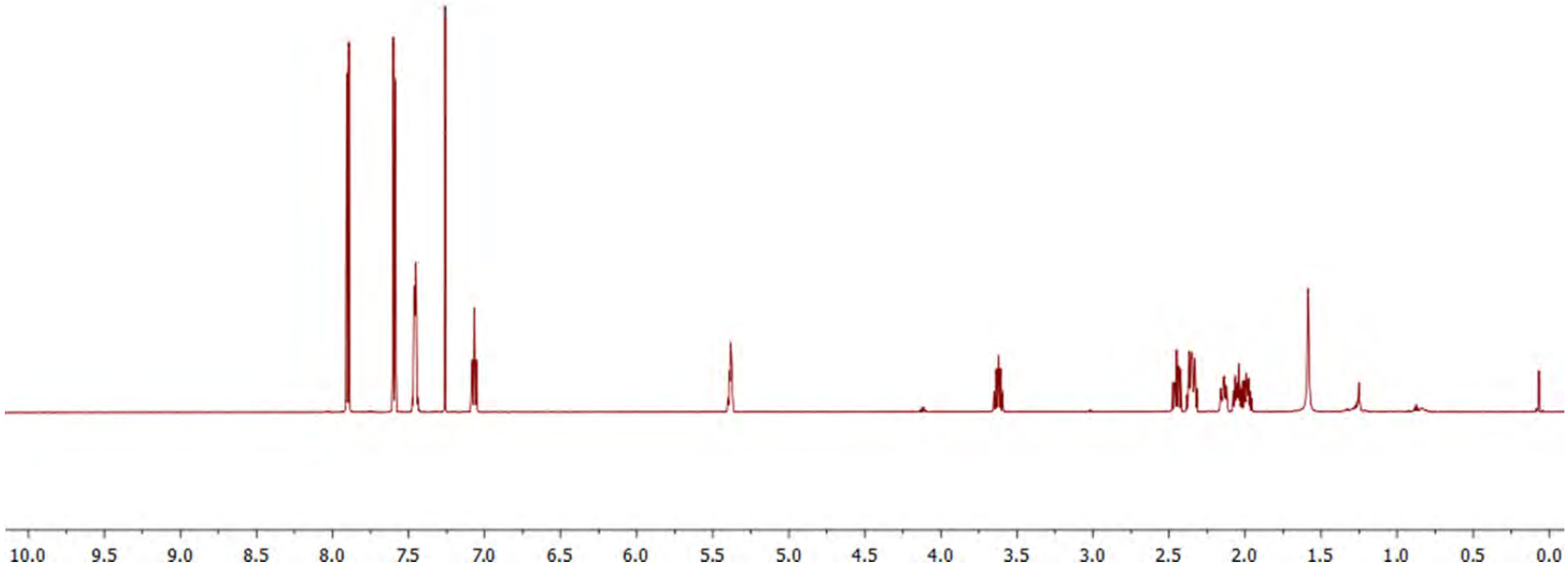
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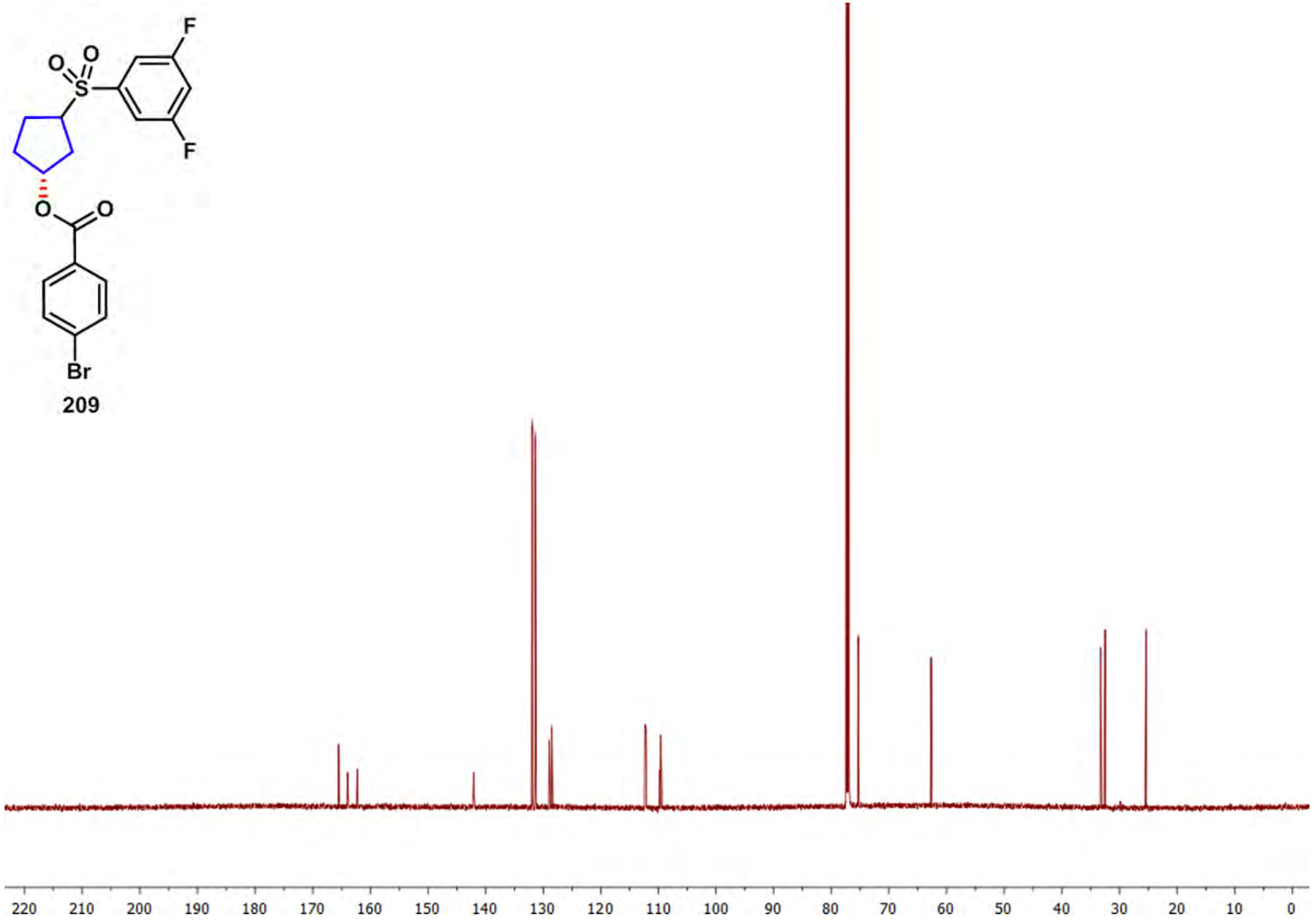
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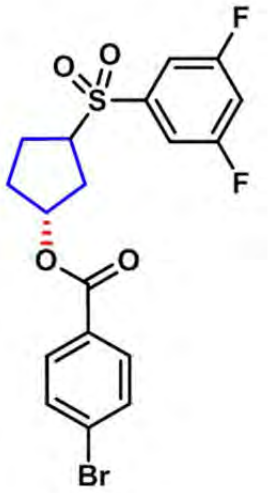
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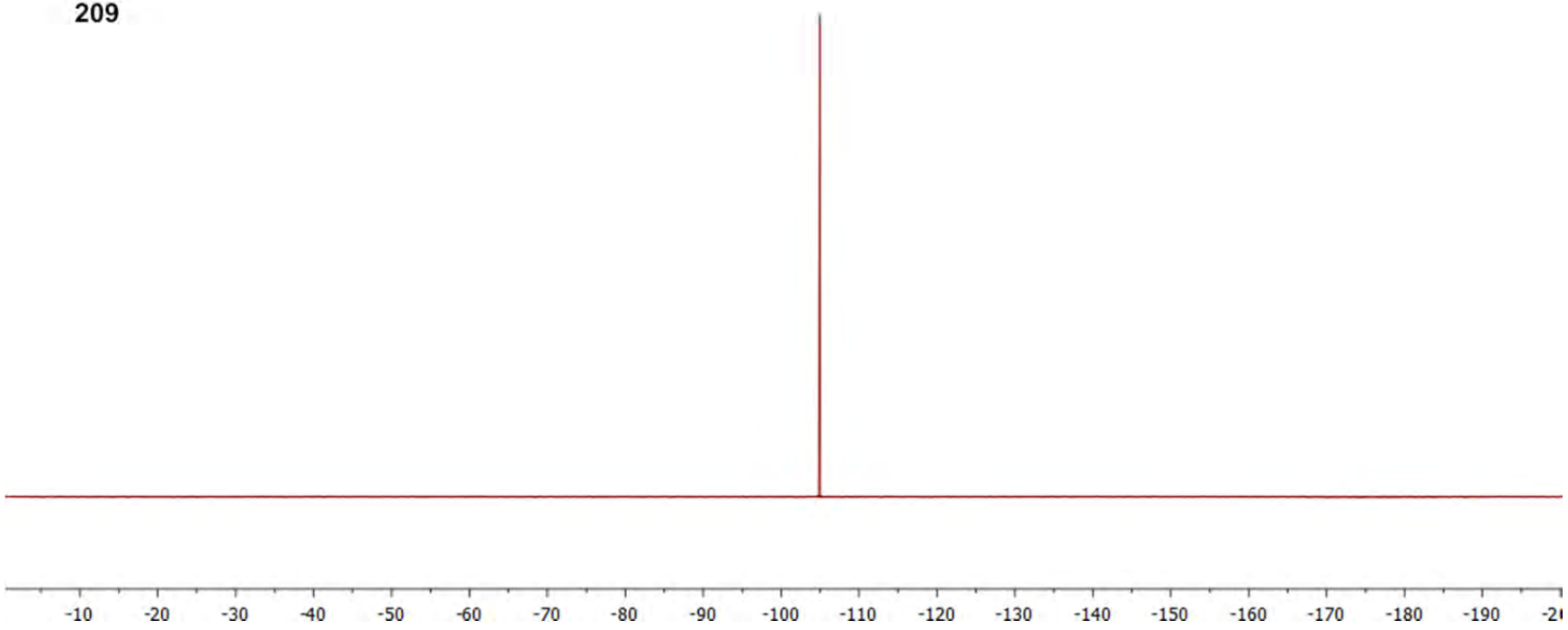
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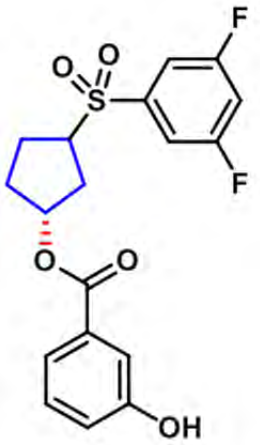
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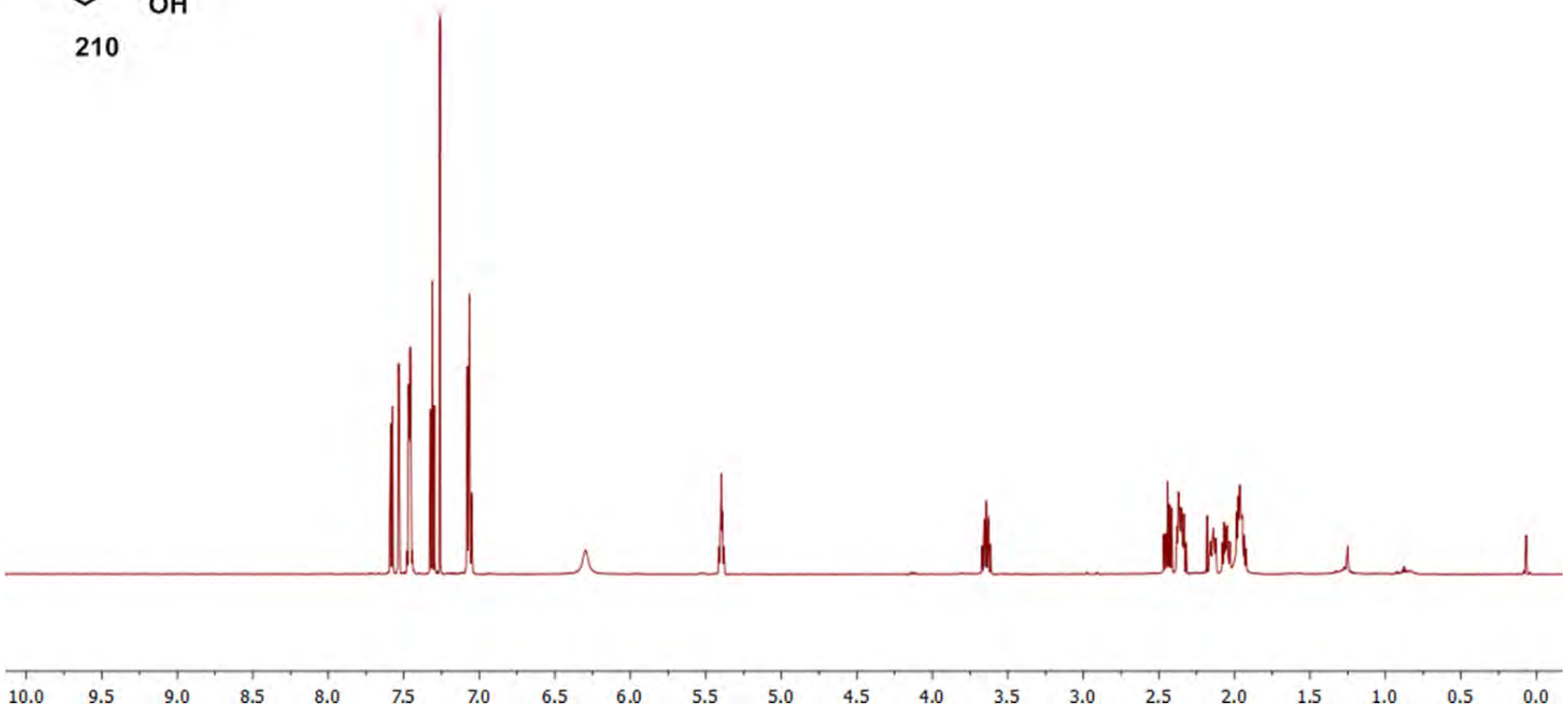
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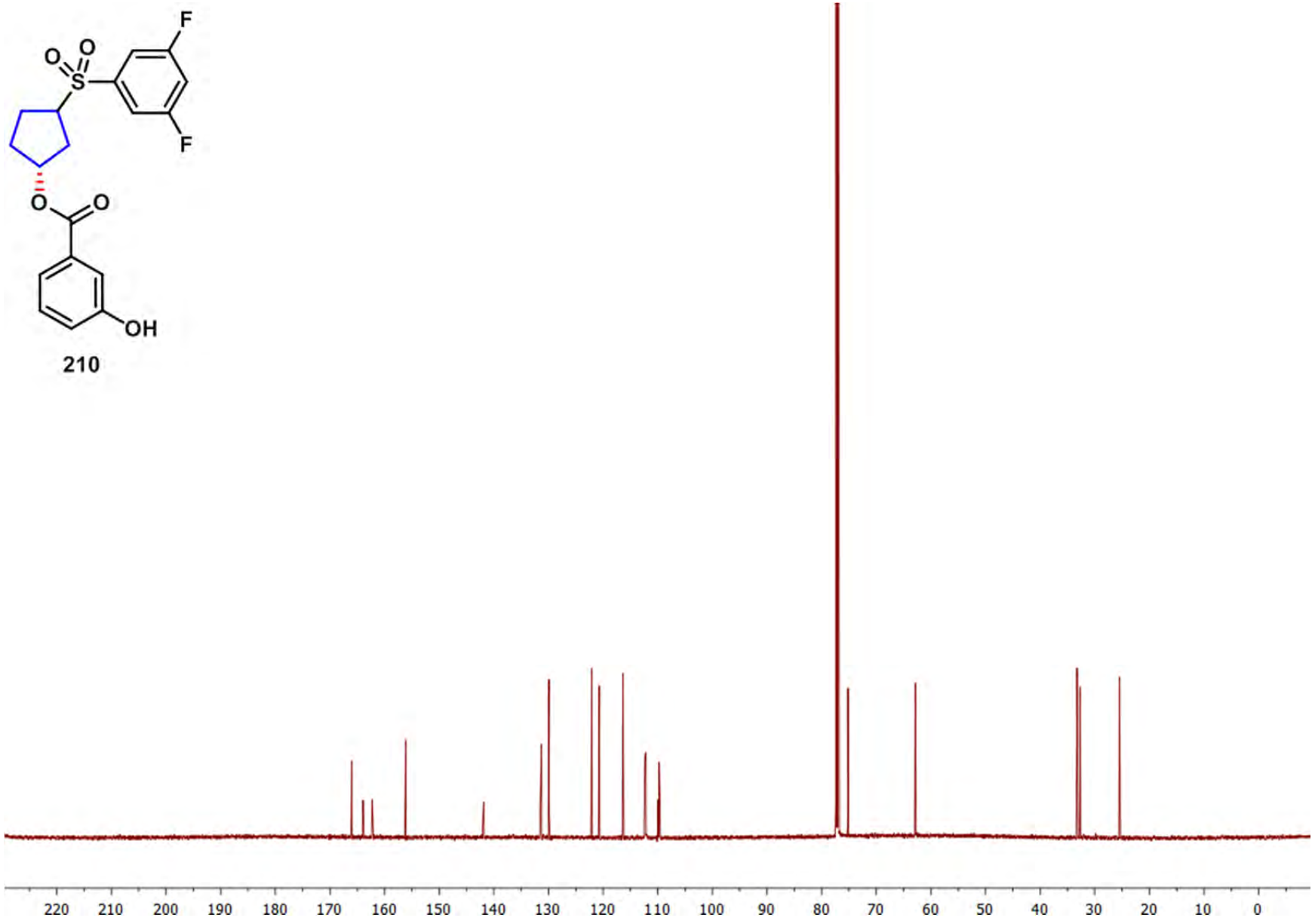
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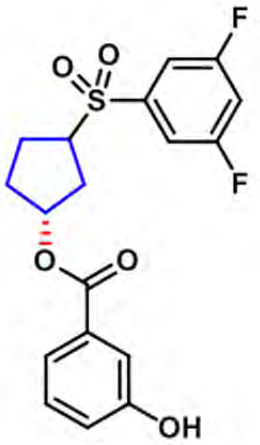
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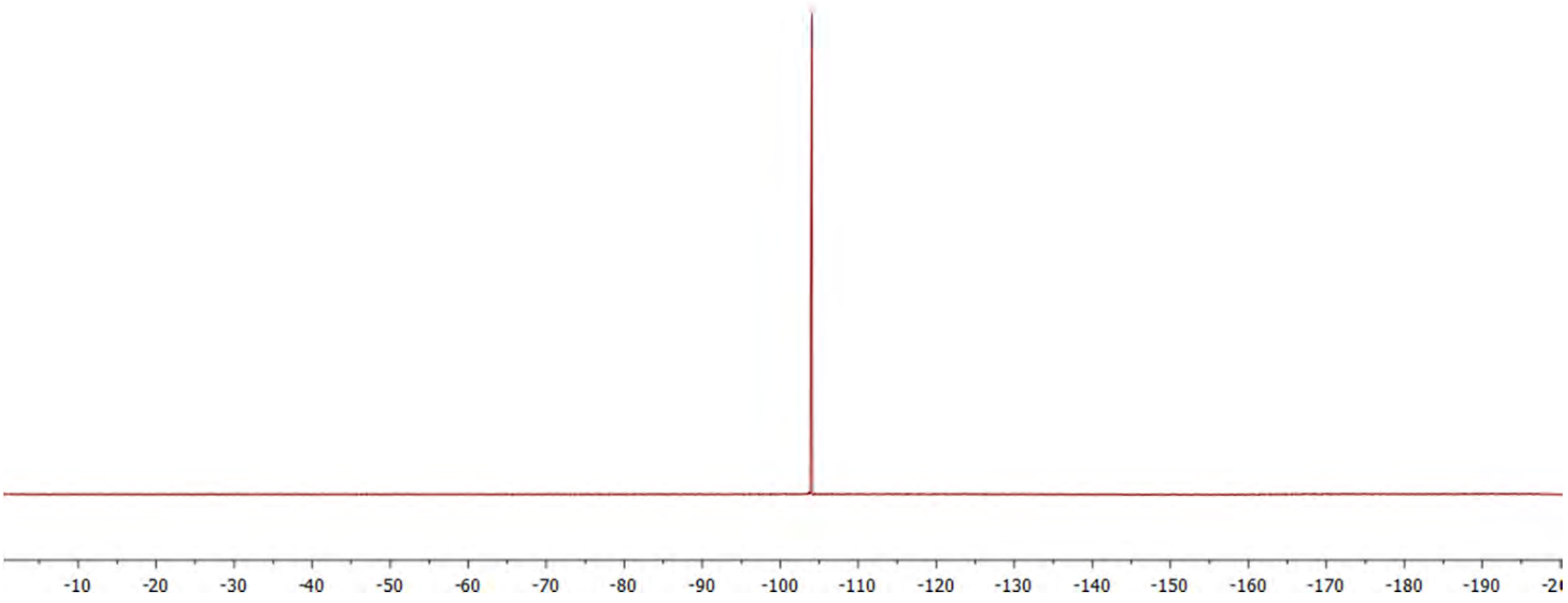
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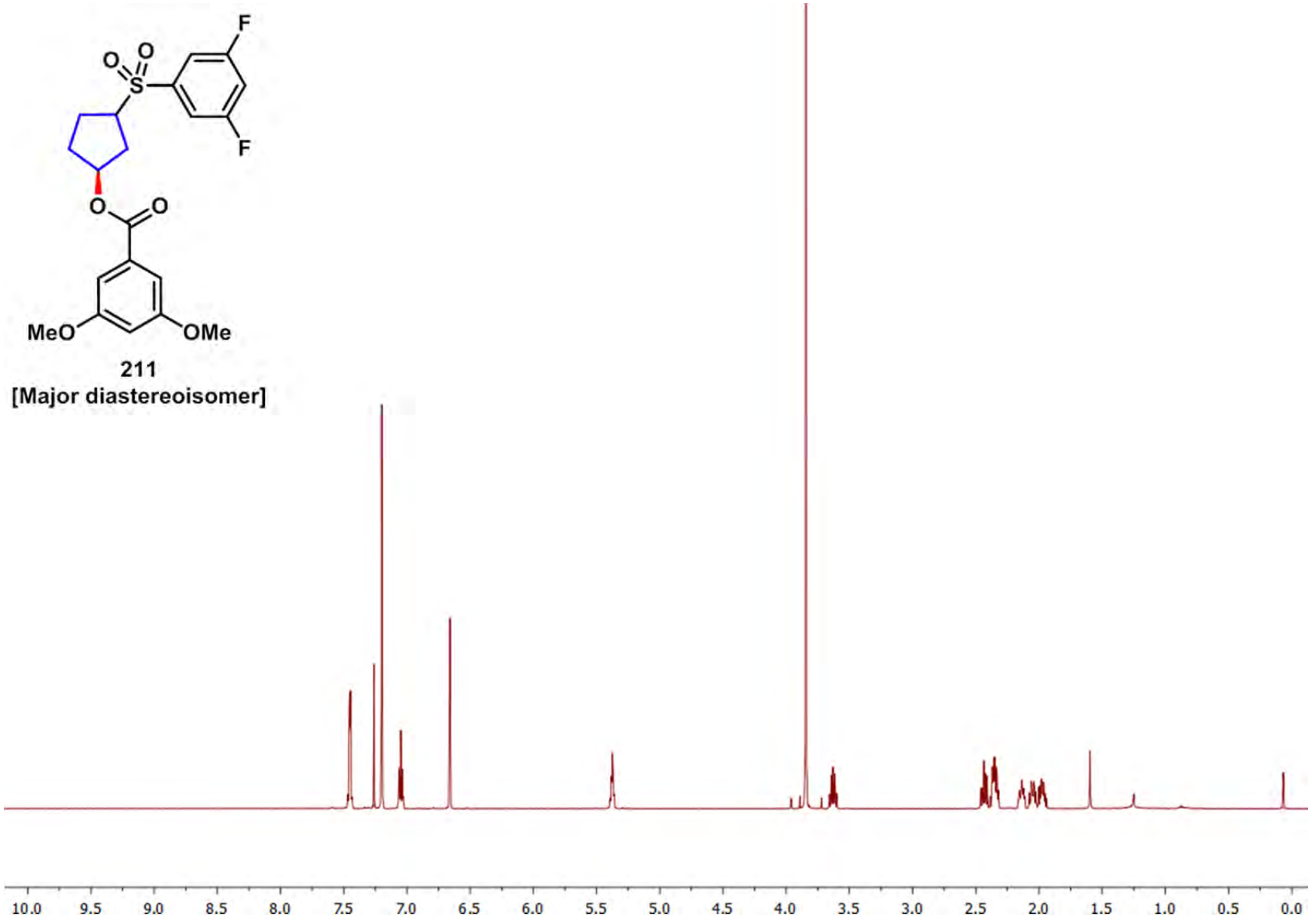
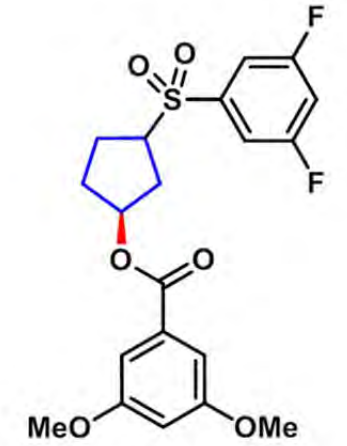
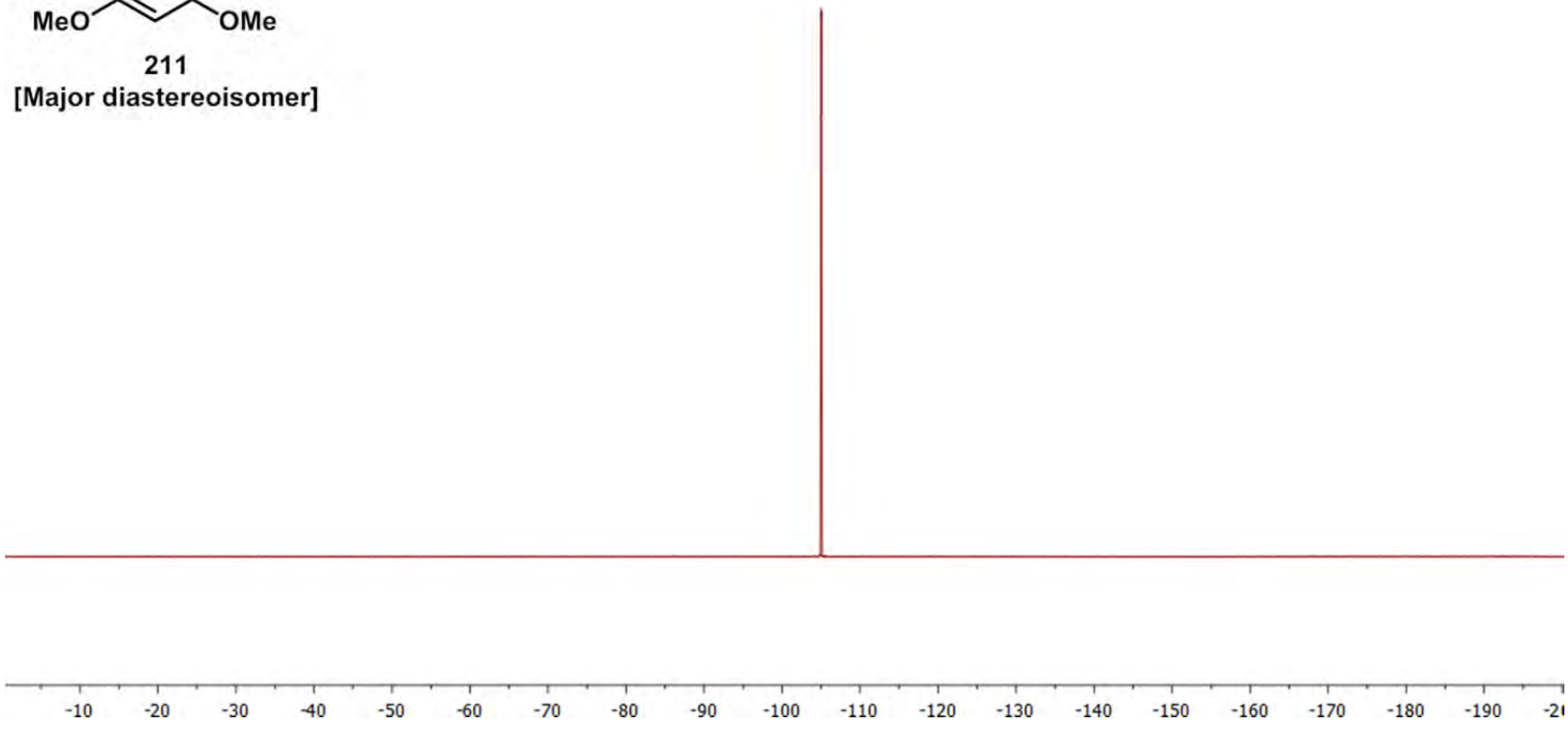


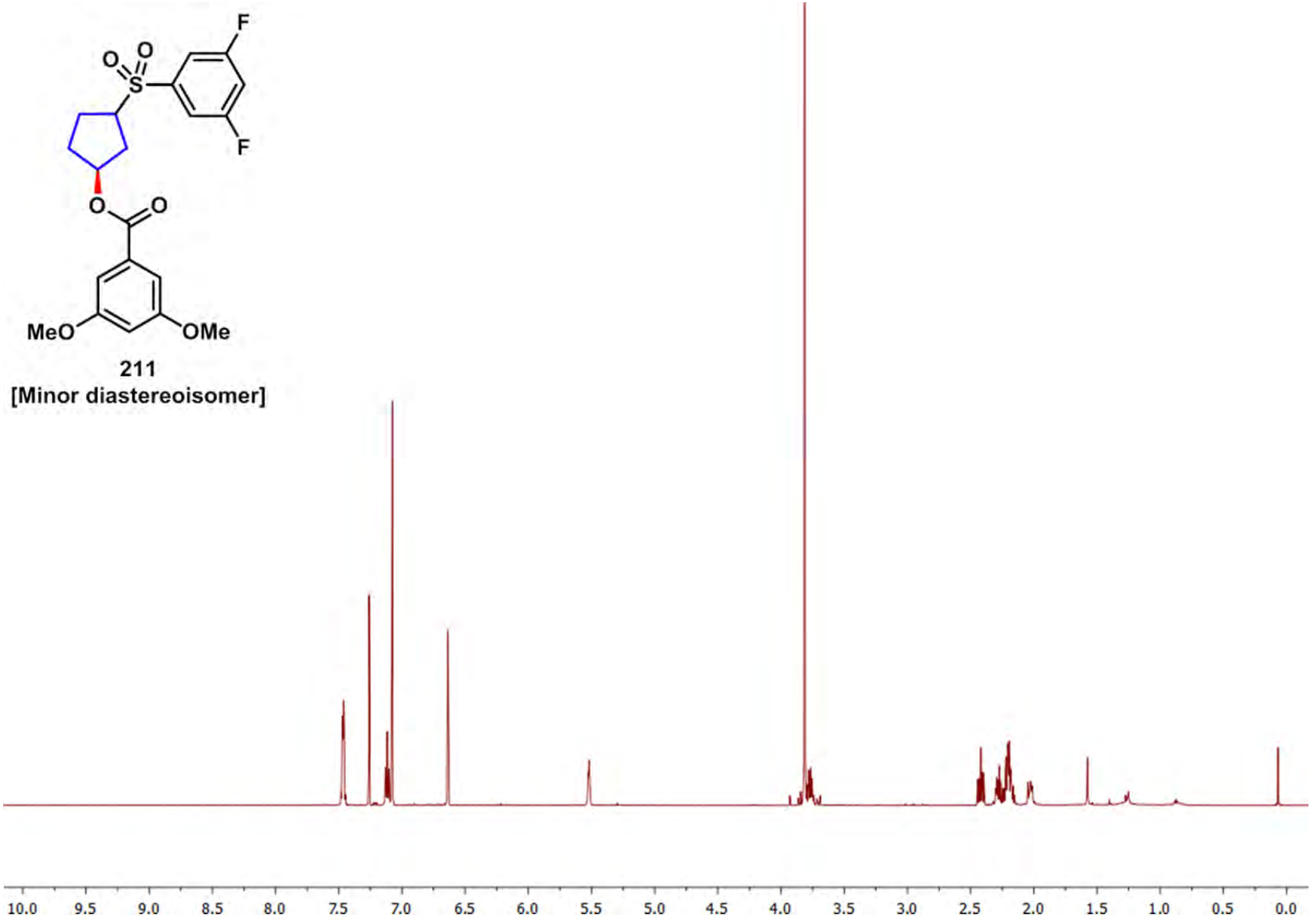
211
[Major diastereoisomer]



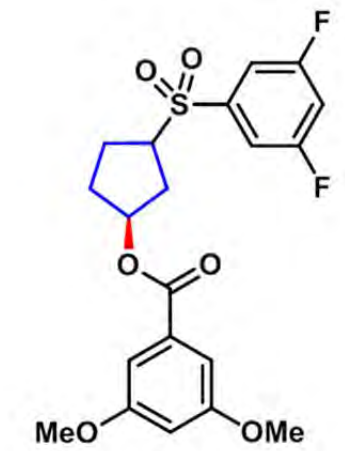
211
[Major diastereoisomer]

211
[Major diastereoisomer]

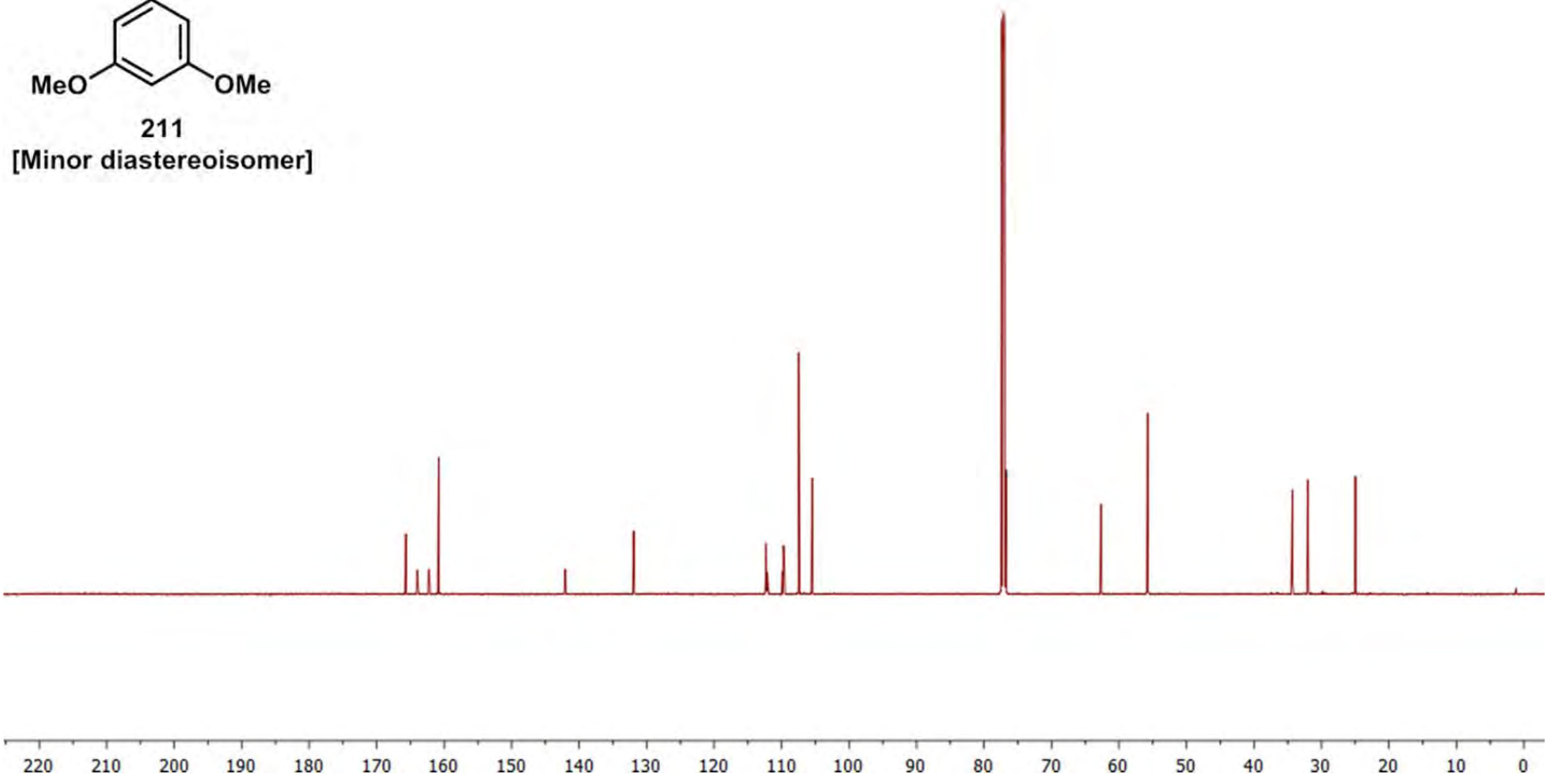


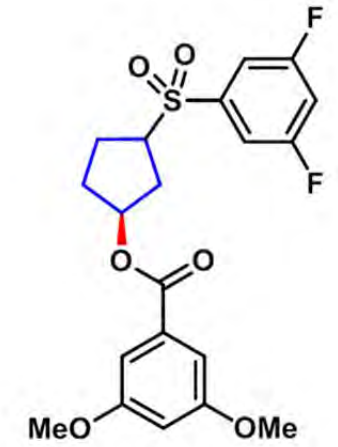


211
[Minor diastereoisomer]

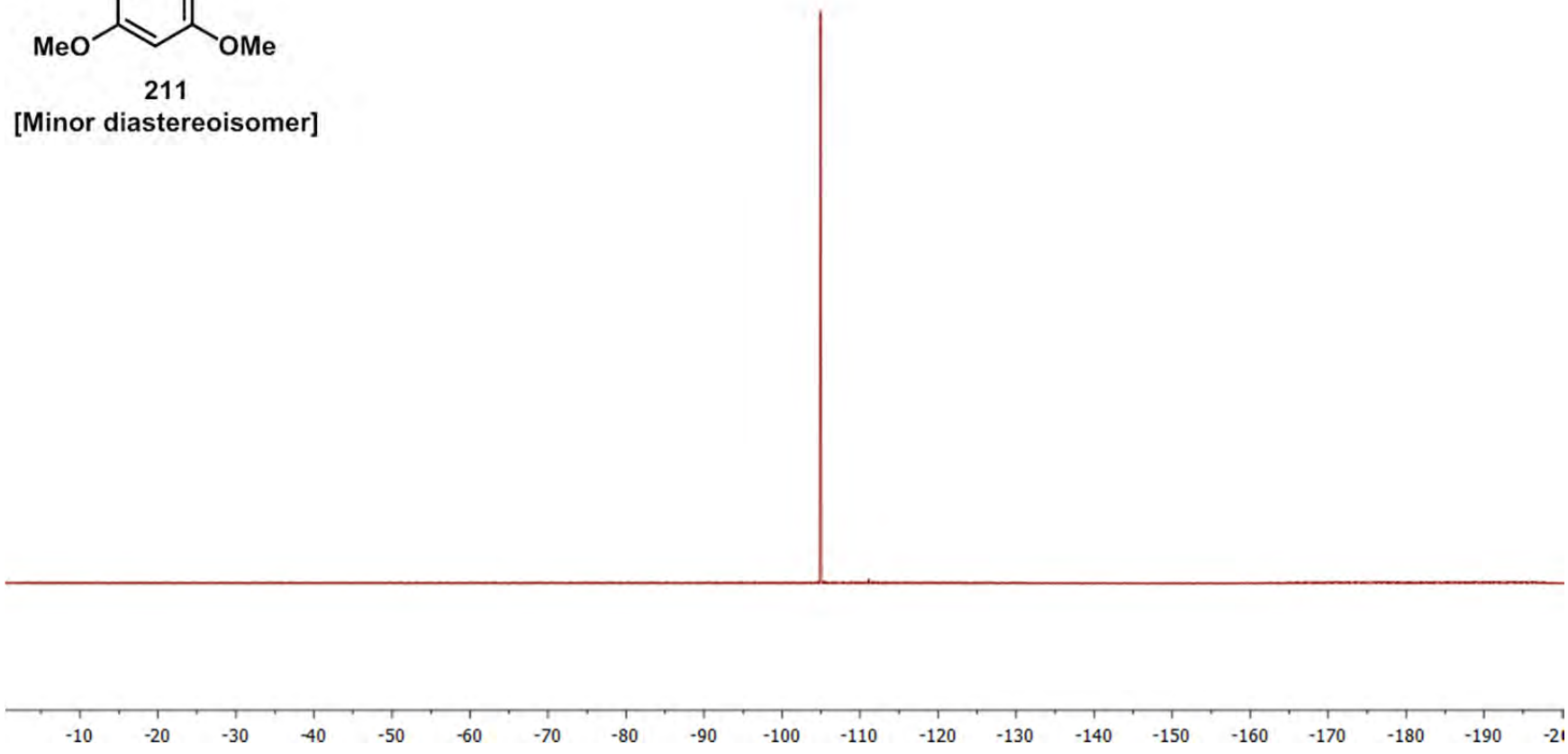


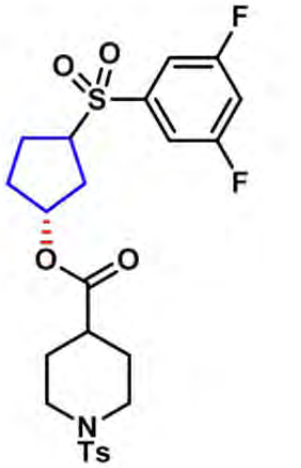
211
[Minor diastereoisomer]



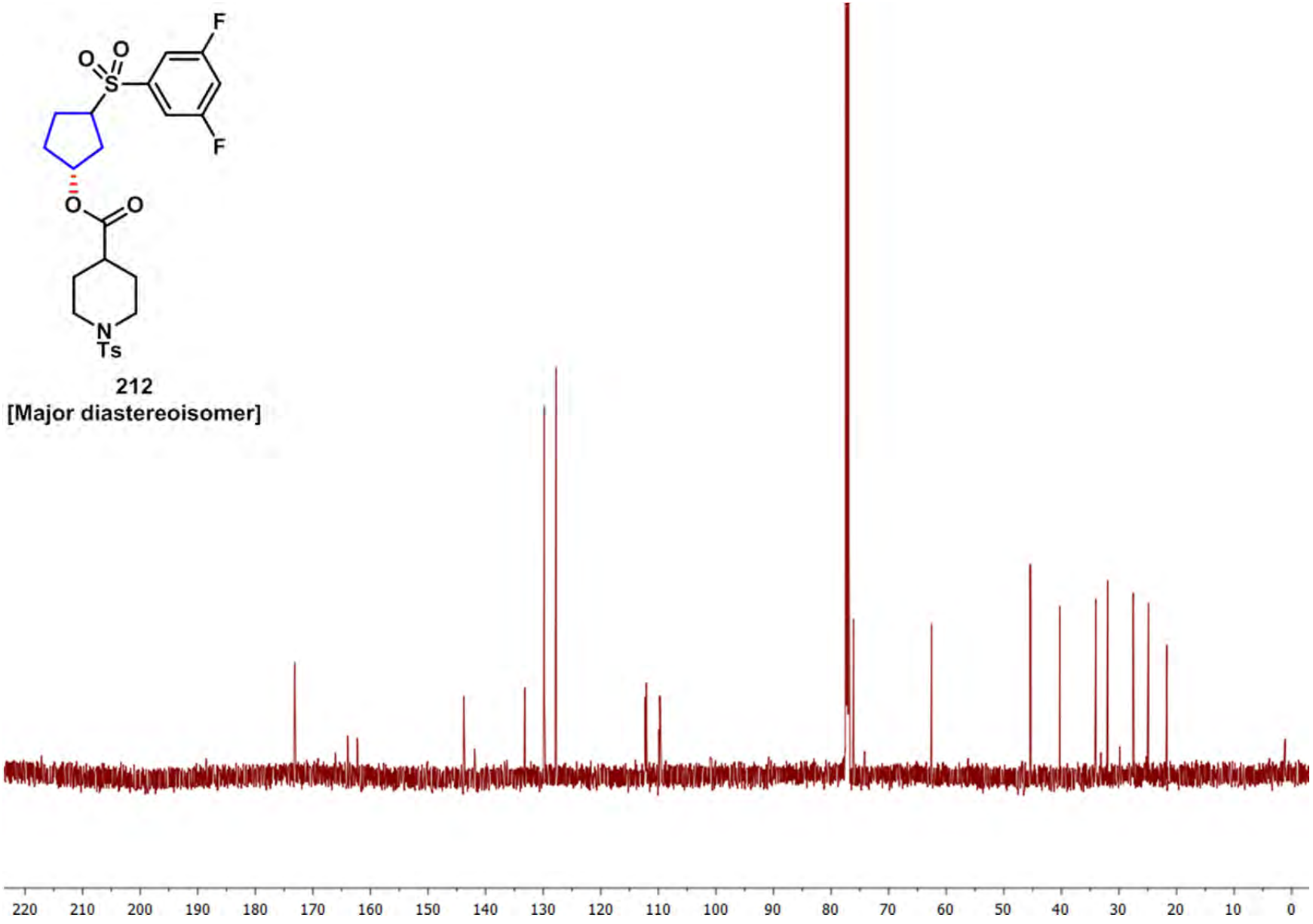


211
[Minor diastereoisomer]

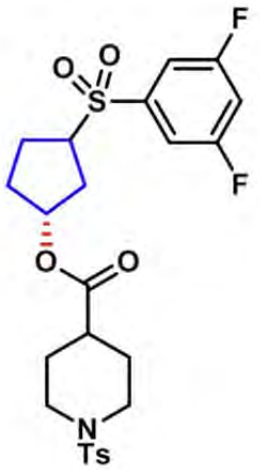




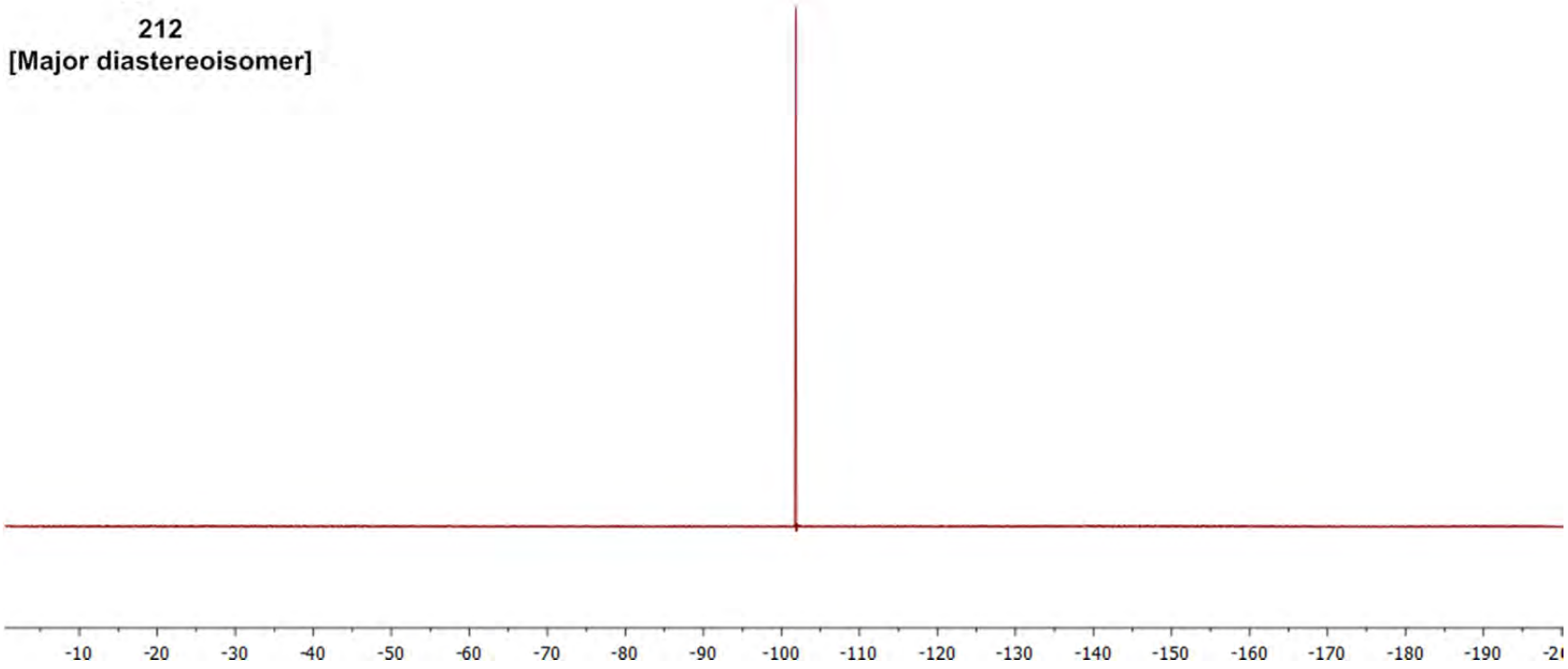
212
[Major diastereoisomer]

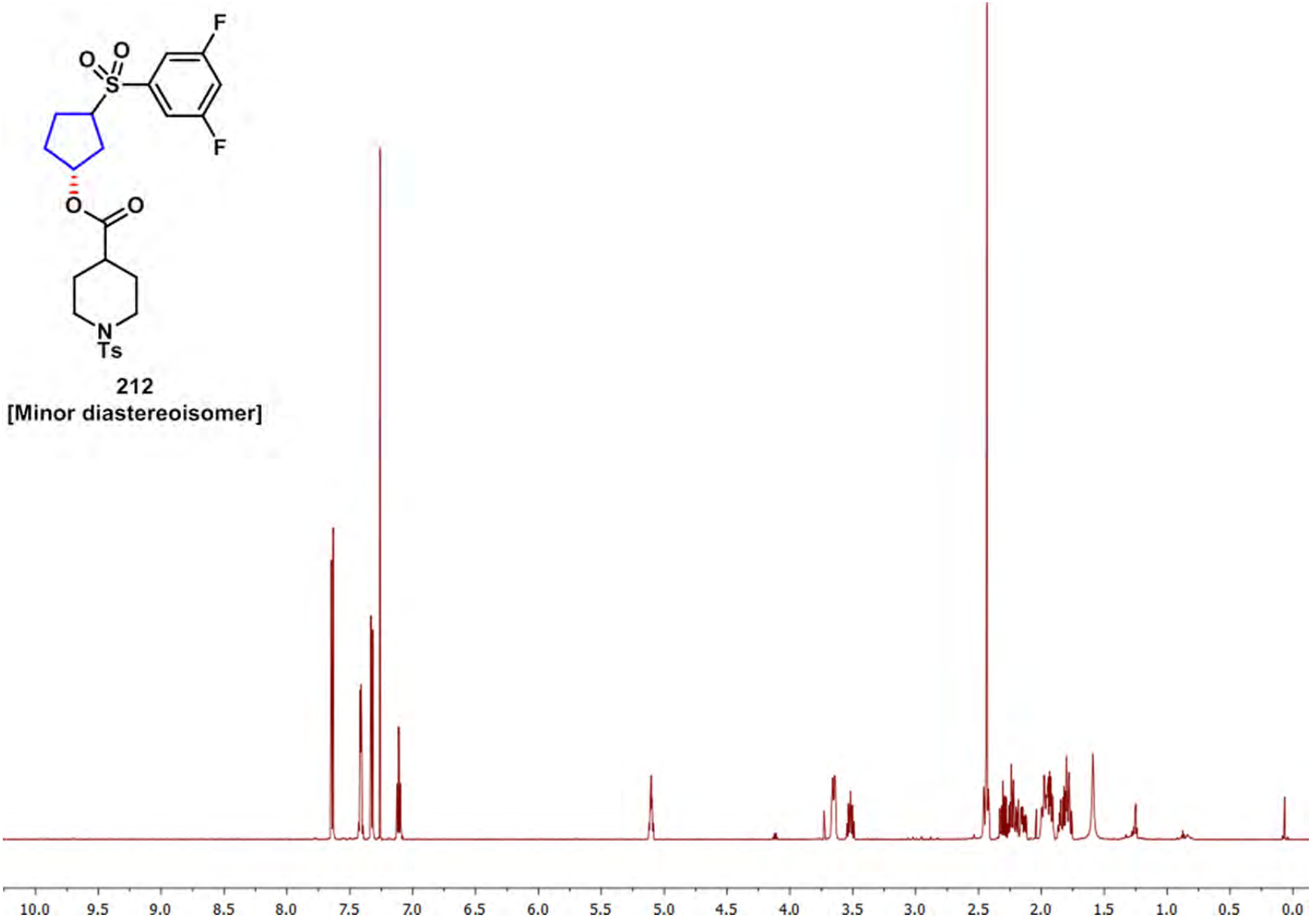


212
[Major diastereoisomer]

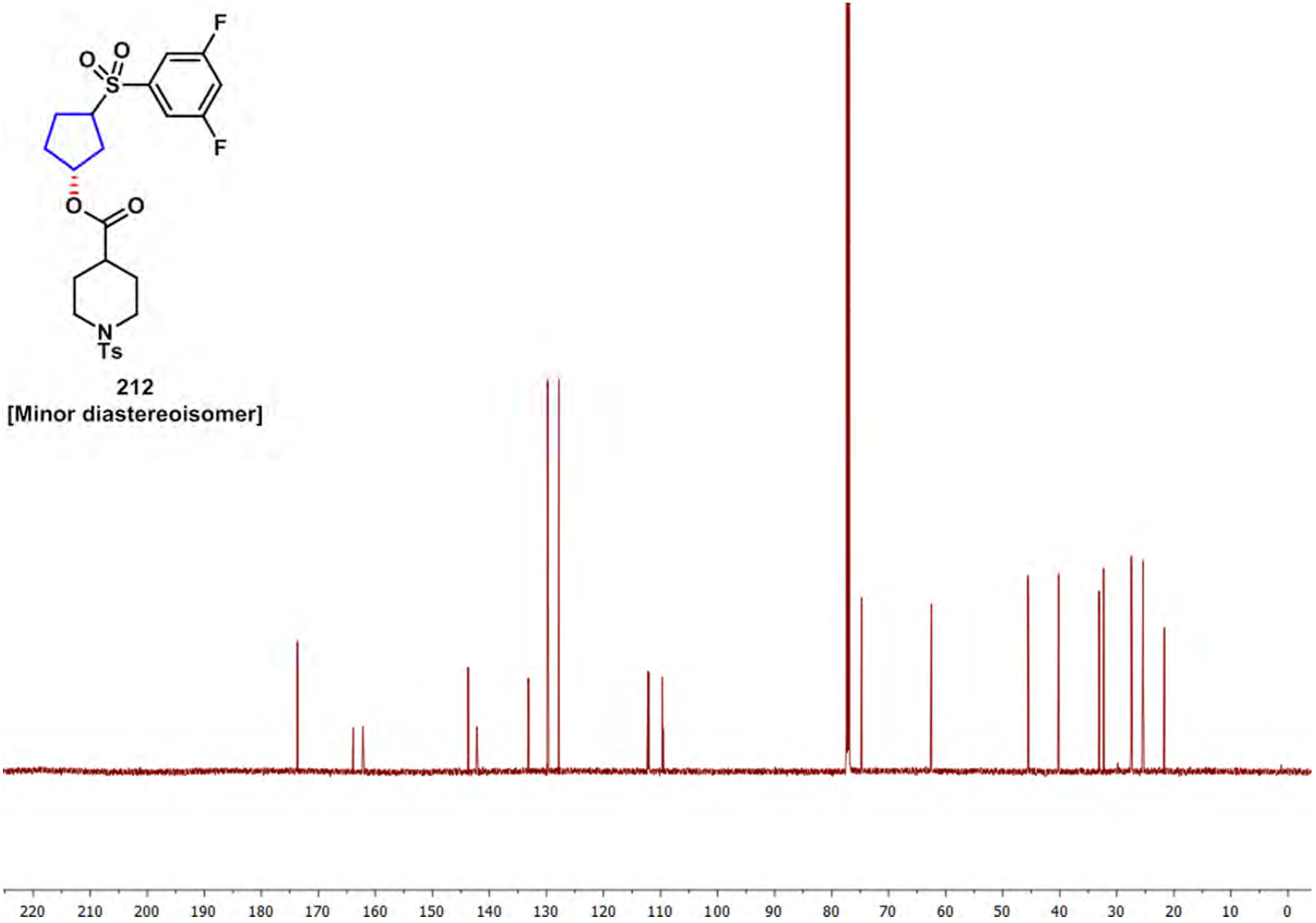


212
[Major diastereoisomer]

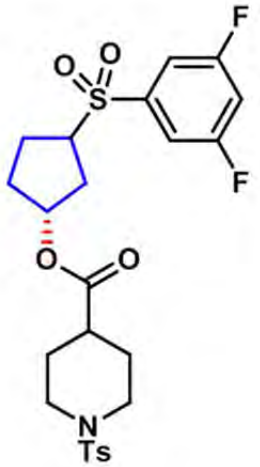




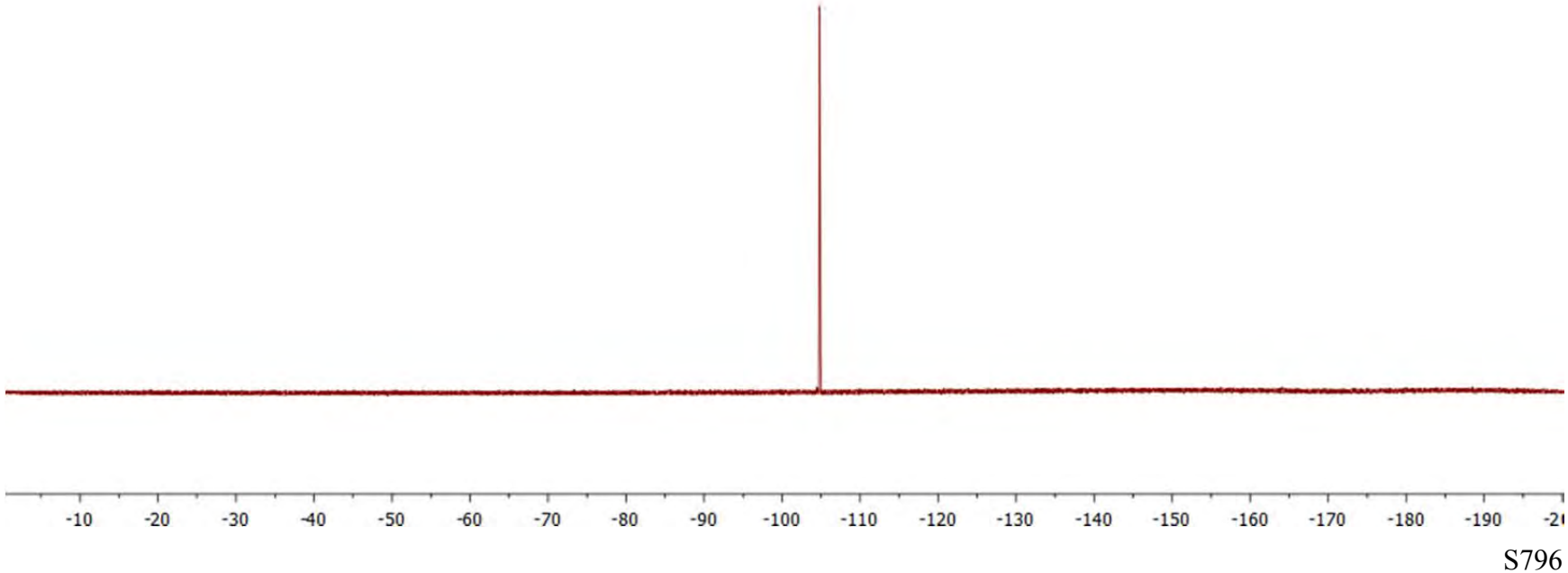
212
[Minor diastereoisomer]



212
[Minor diastereoisomer]



212
[Minor diastereoisomer]



213
[Major diastereoisomer]

213
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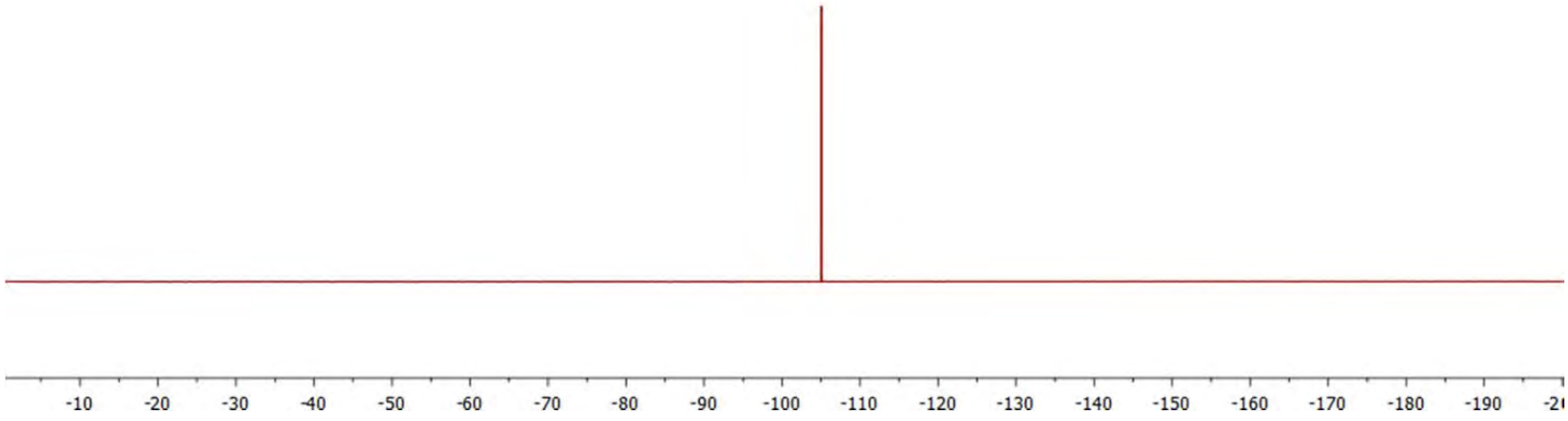
[Major diastereoisomer]



213
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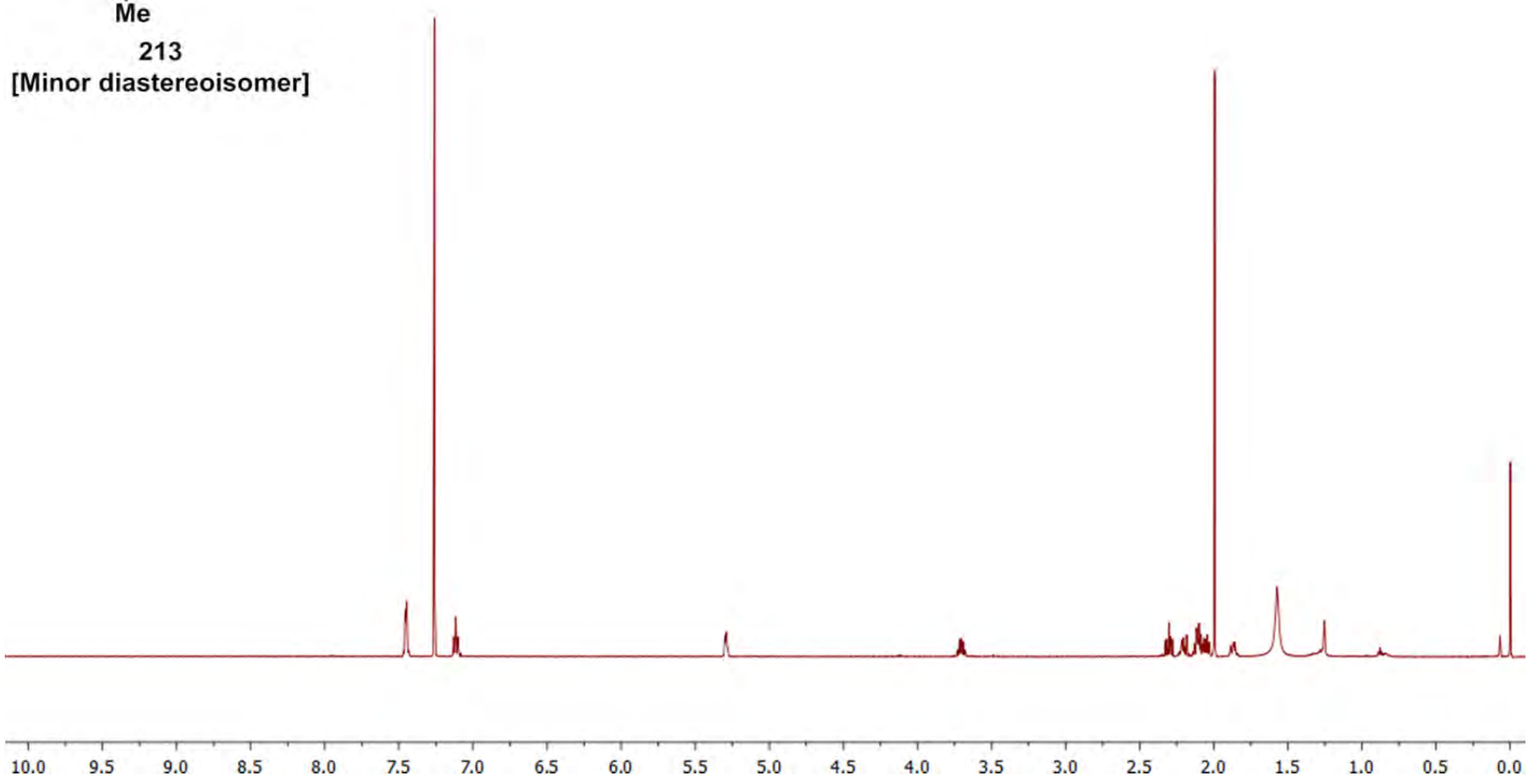
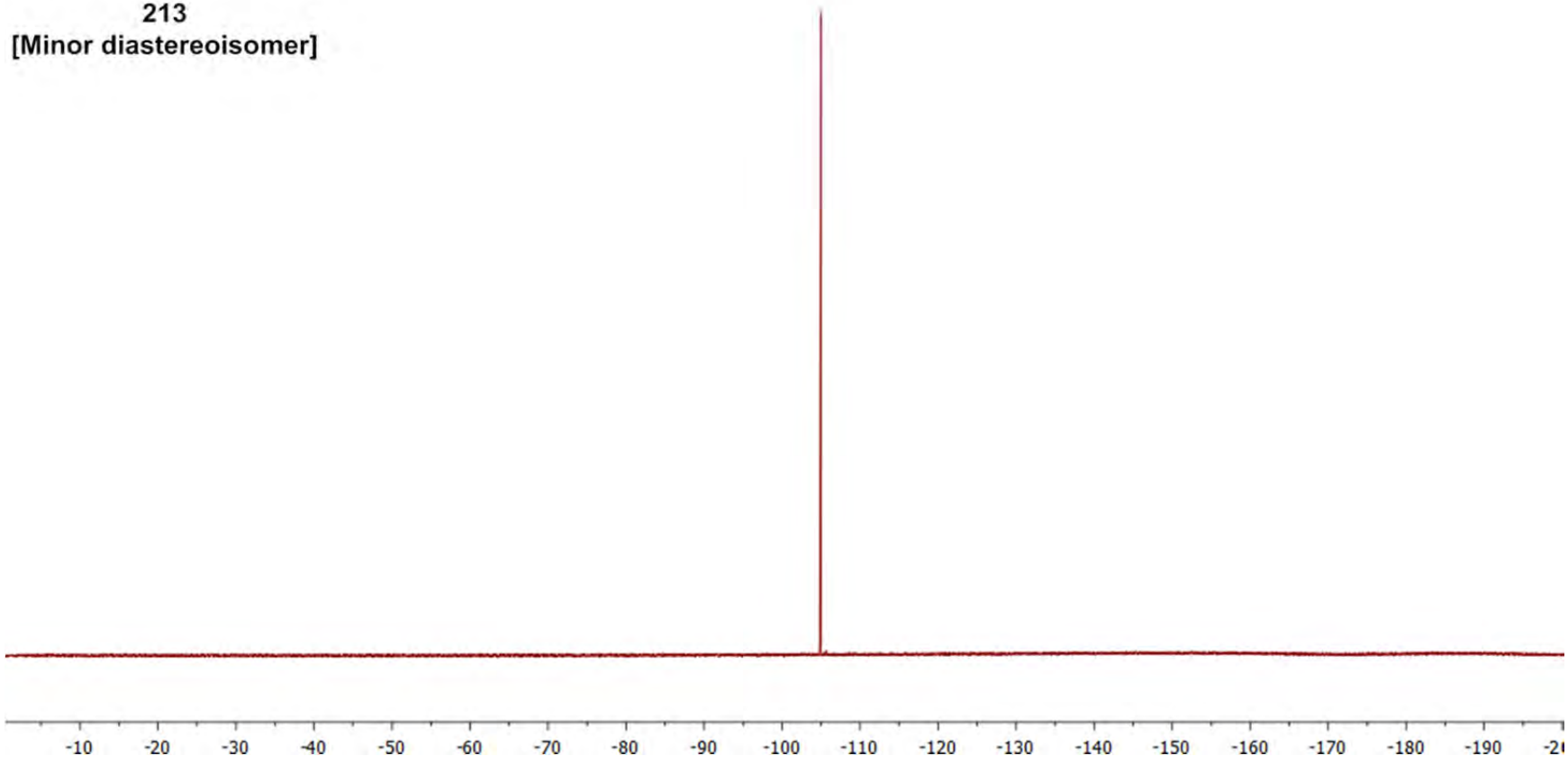
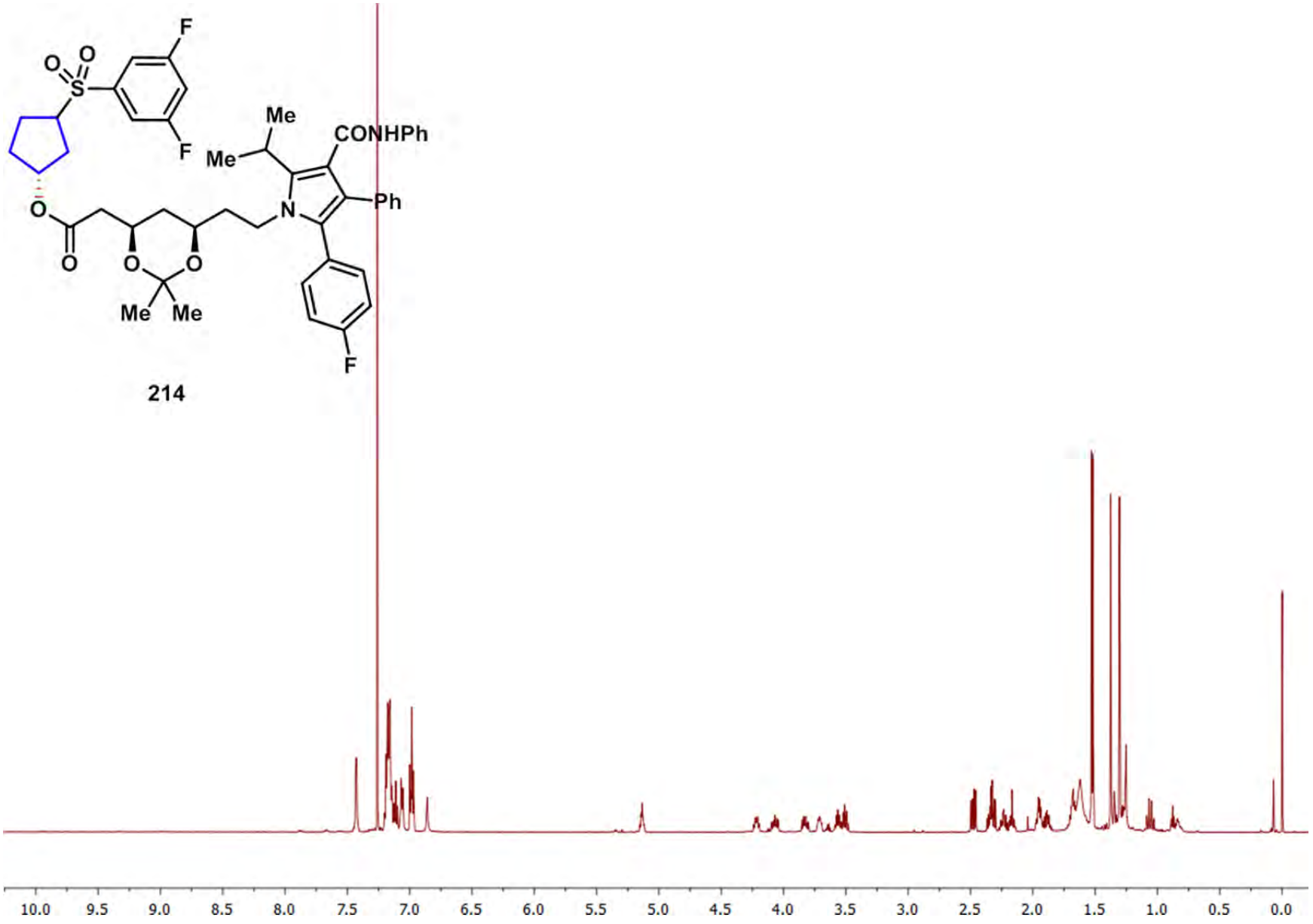


213
[Minor diastereoisomer]

213
[Minor diastereoisomer]

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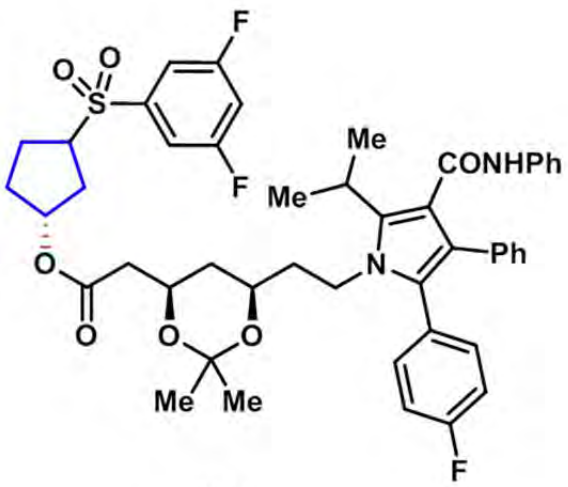
214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F
Me
Me
CONHPh
Ph
N
O
O
O
O
O
Me
Me
F

214

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210
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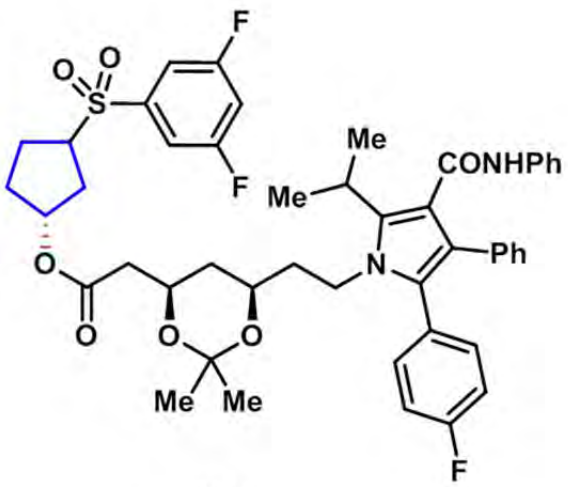
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Me
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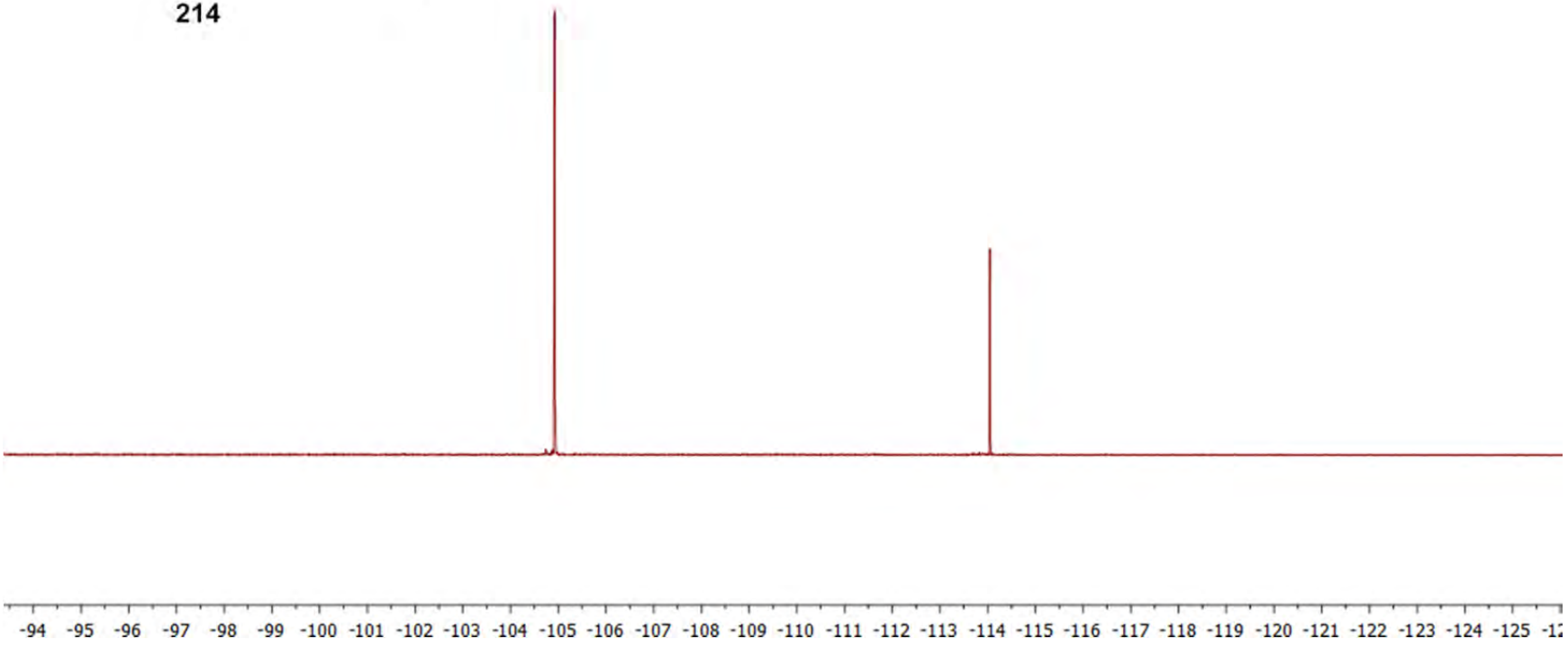
CONHPh
Ph
N
O
O
O
O
O
Me
Me
F

214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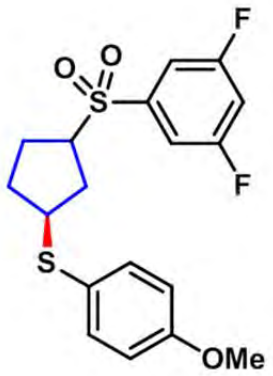
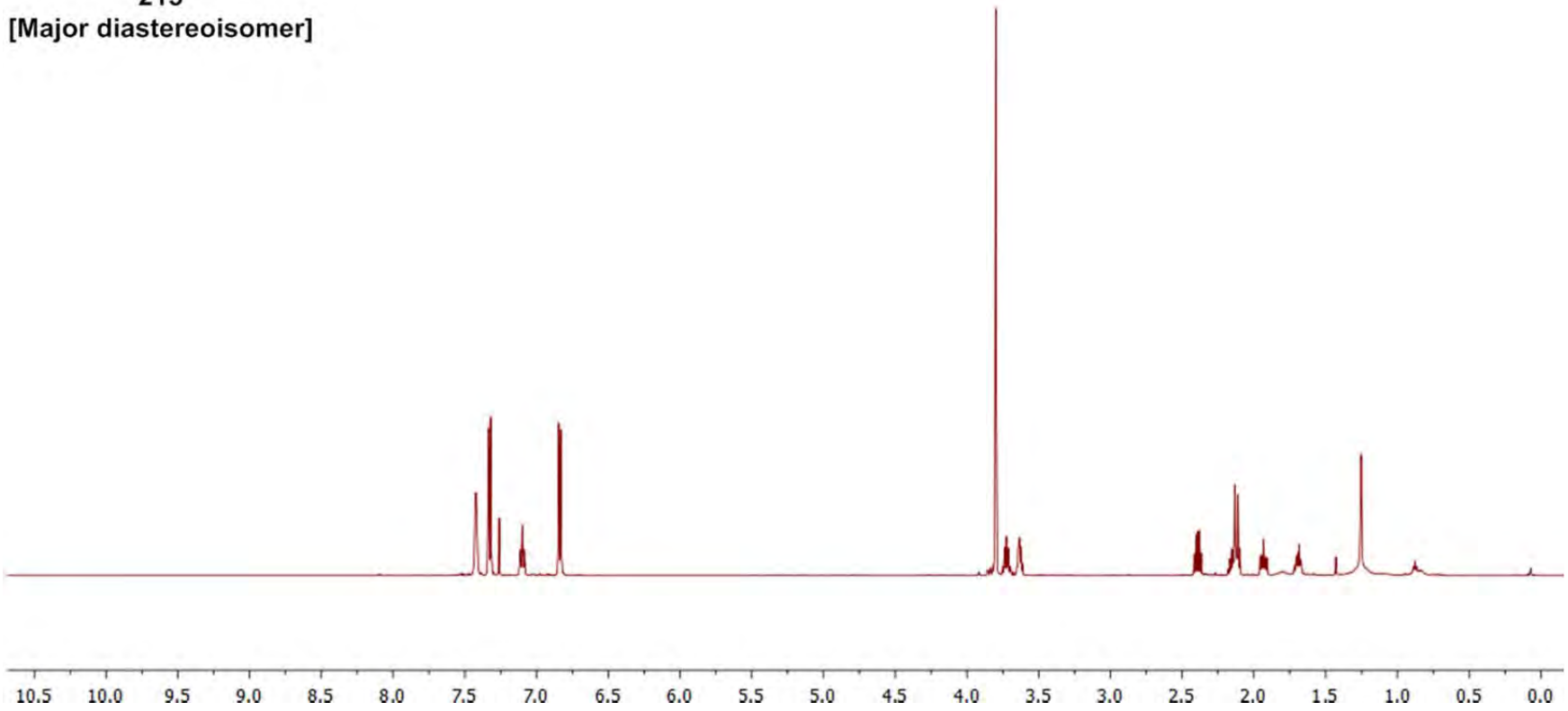
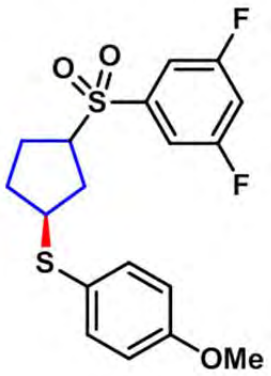


215
[Major diastereoisomer]





215
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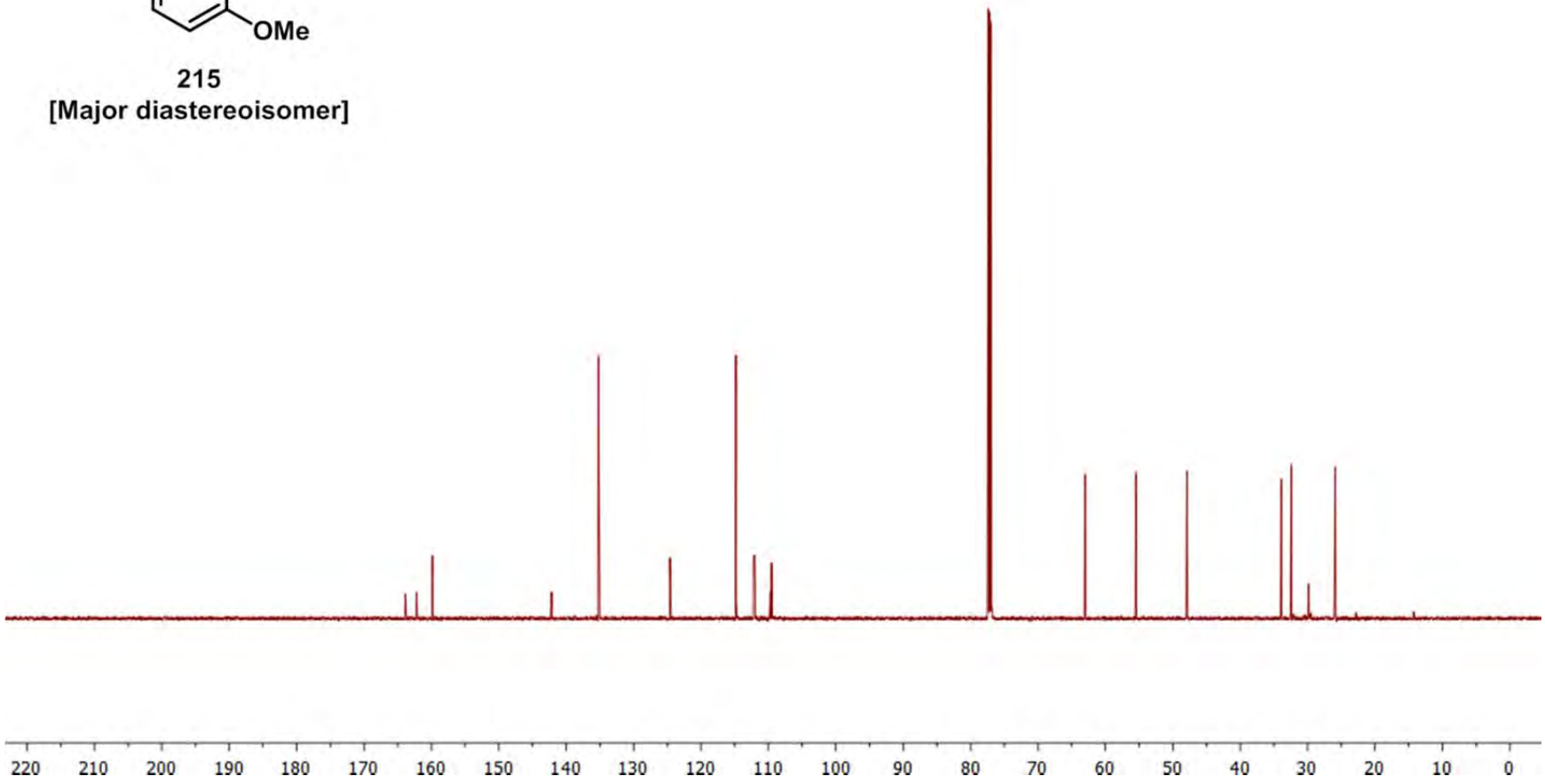
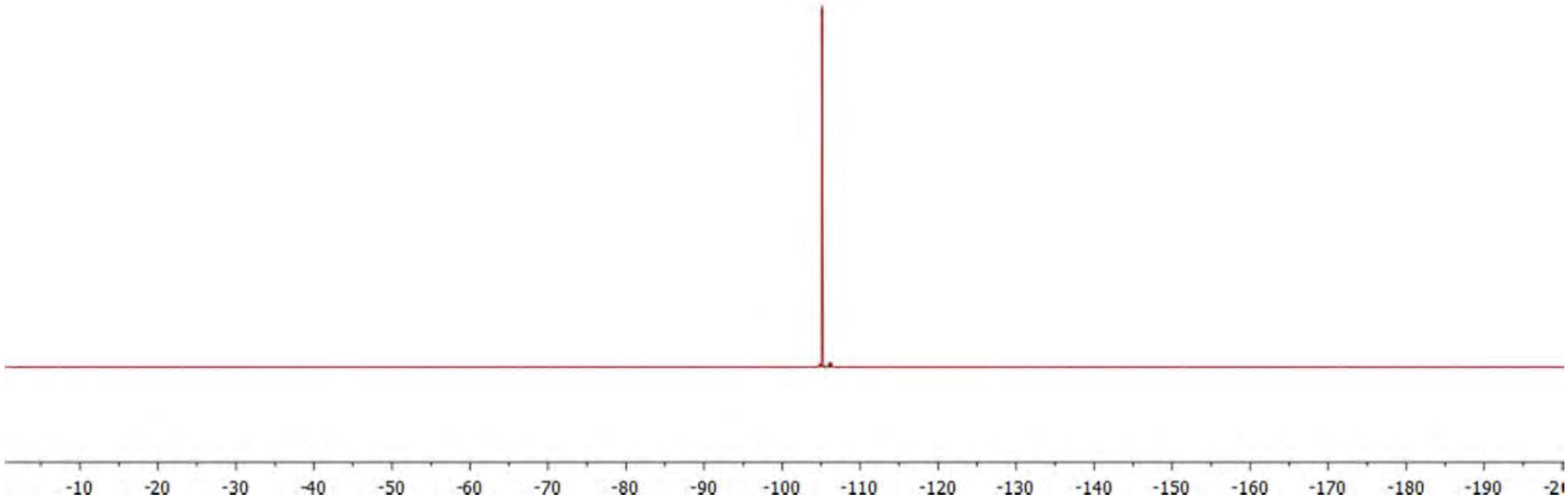
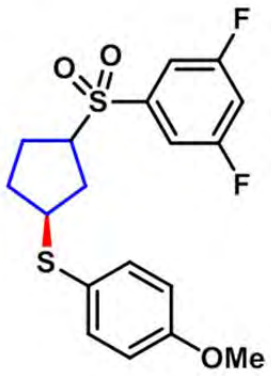


215
[Major diastereoisomer]





215
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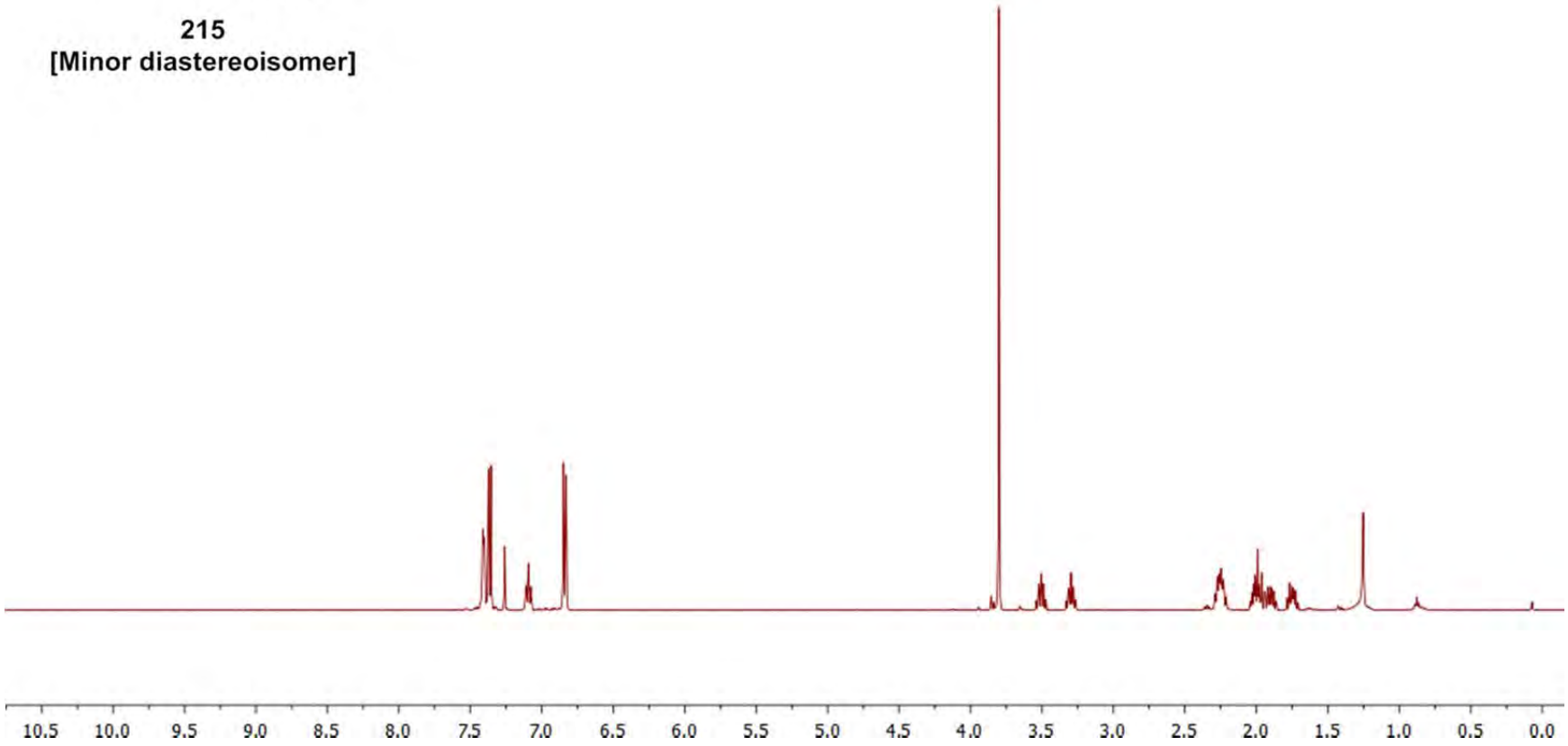
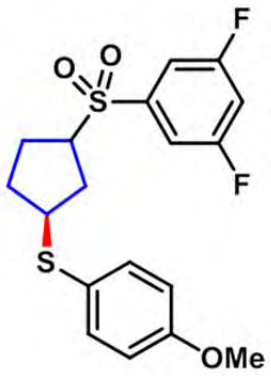
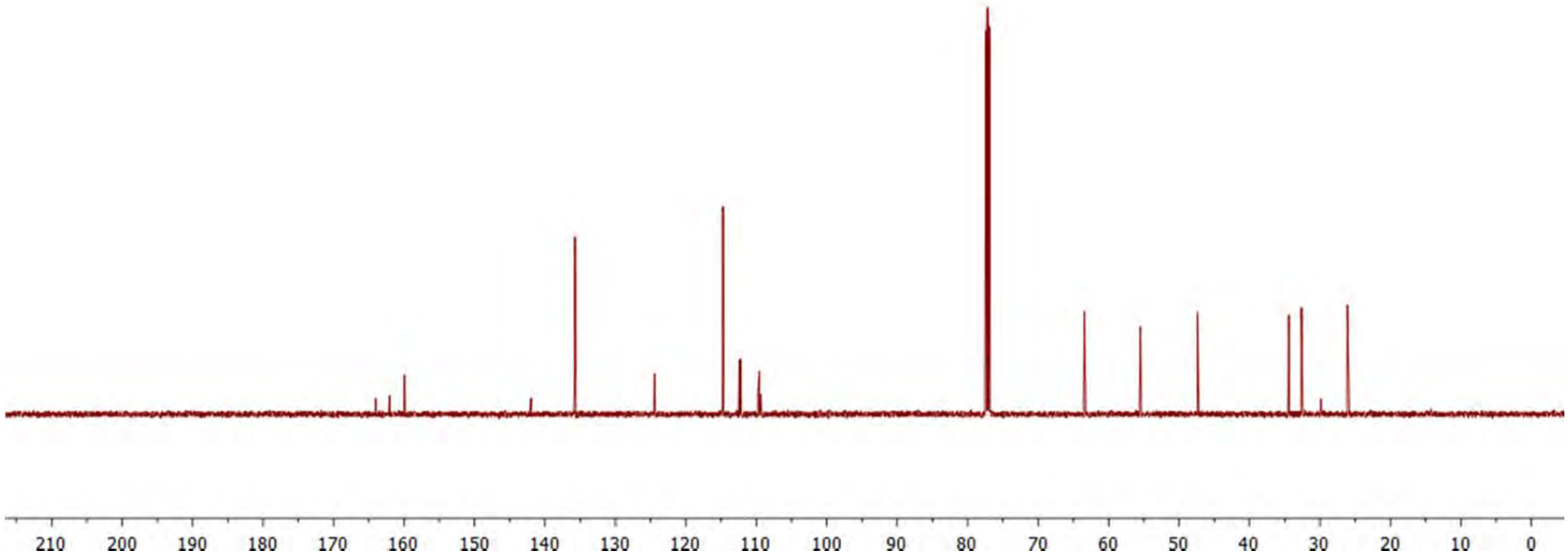
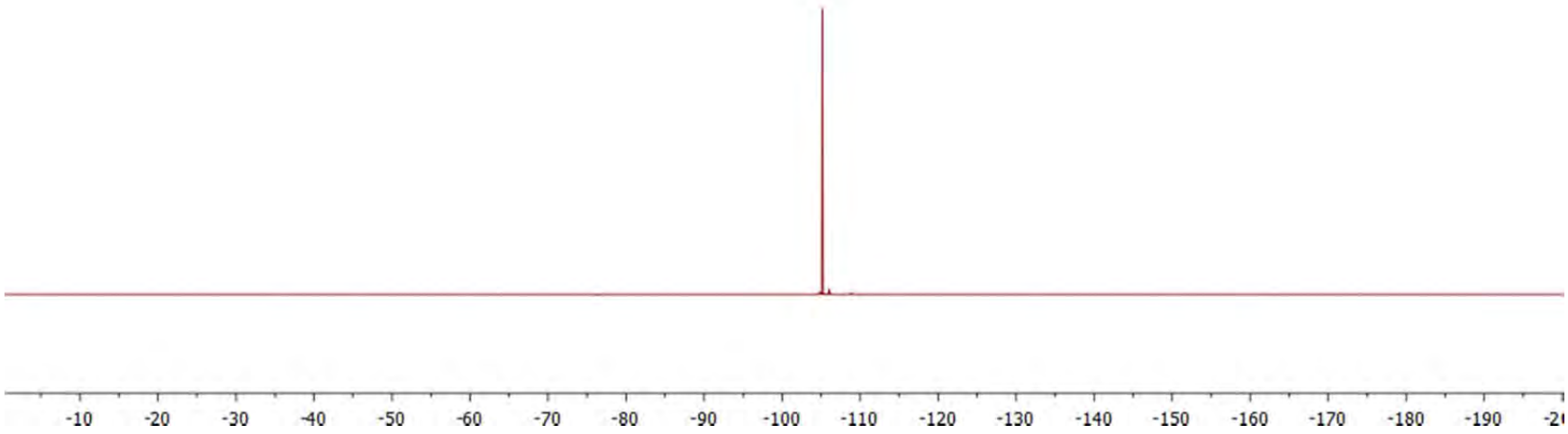




215
[Minor diastereoisomer]



215
[Minor diastereoisomer]

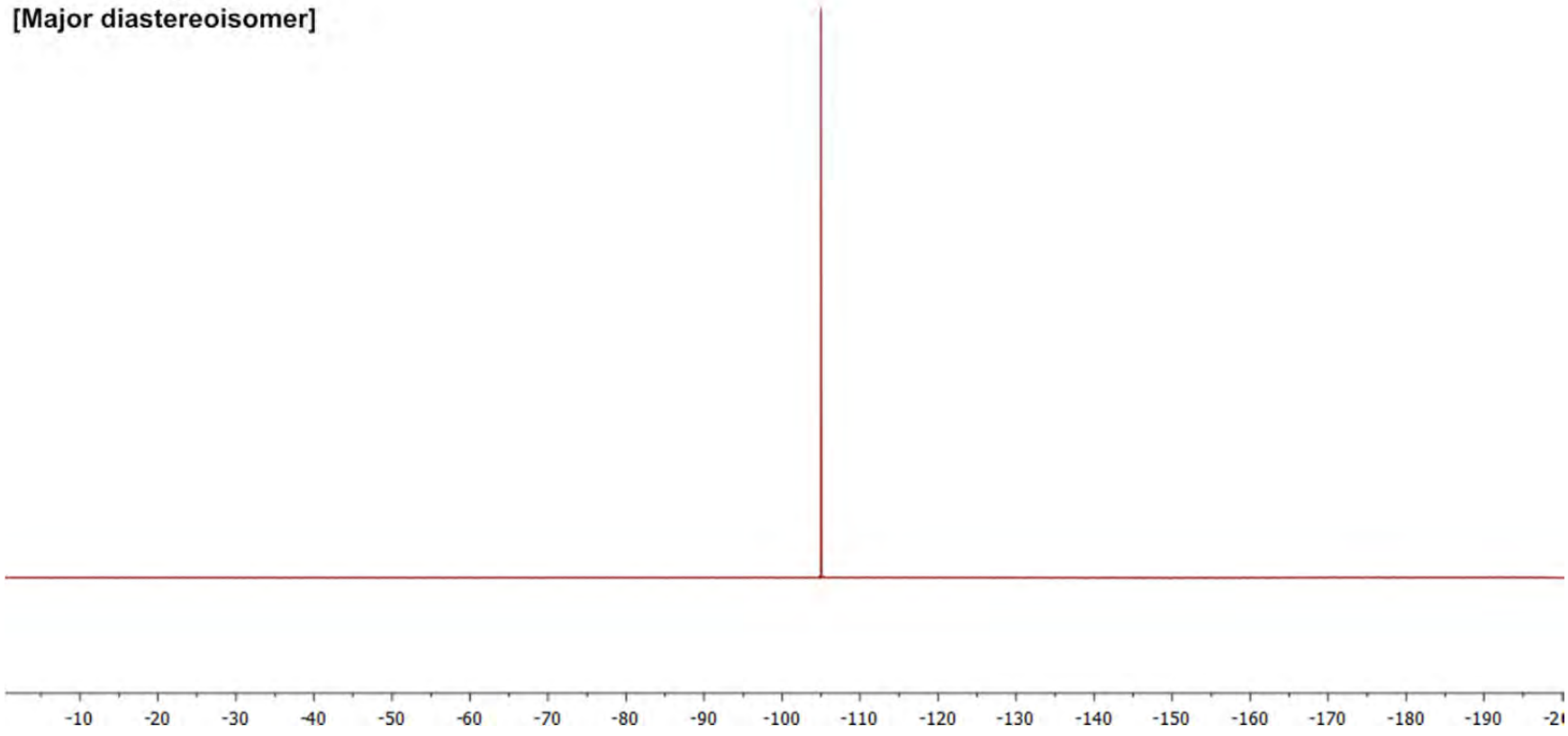


216
[Major diastereoisomer]

216
[Major diastereoisomer]

216

[Major diastereoisomer]



216
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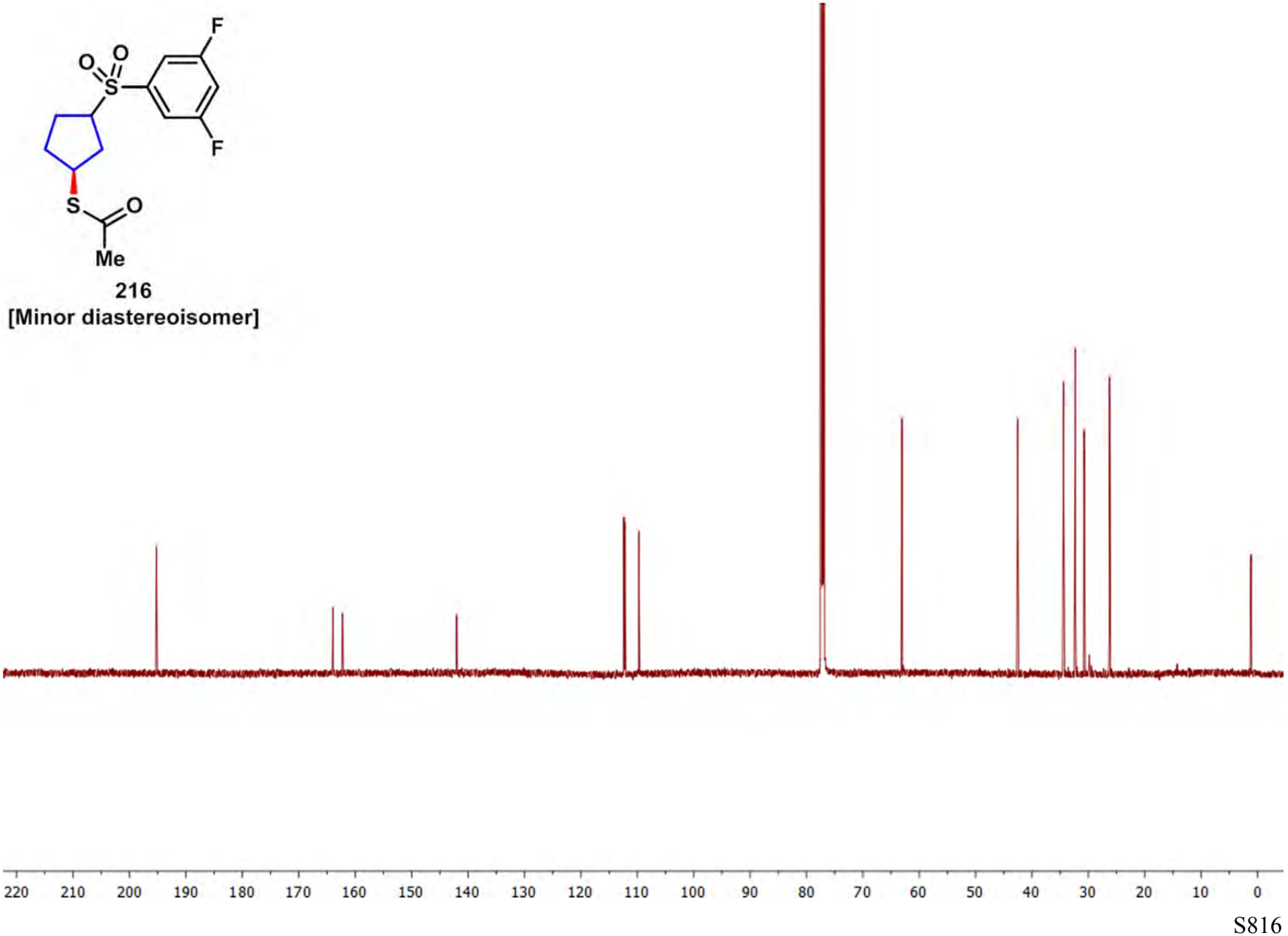
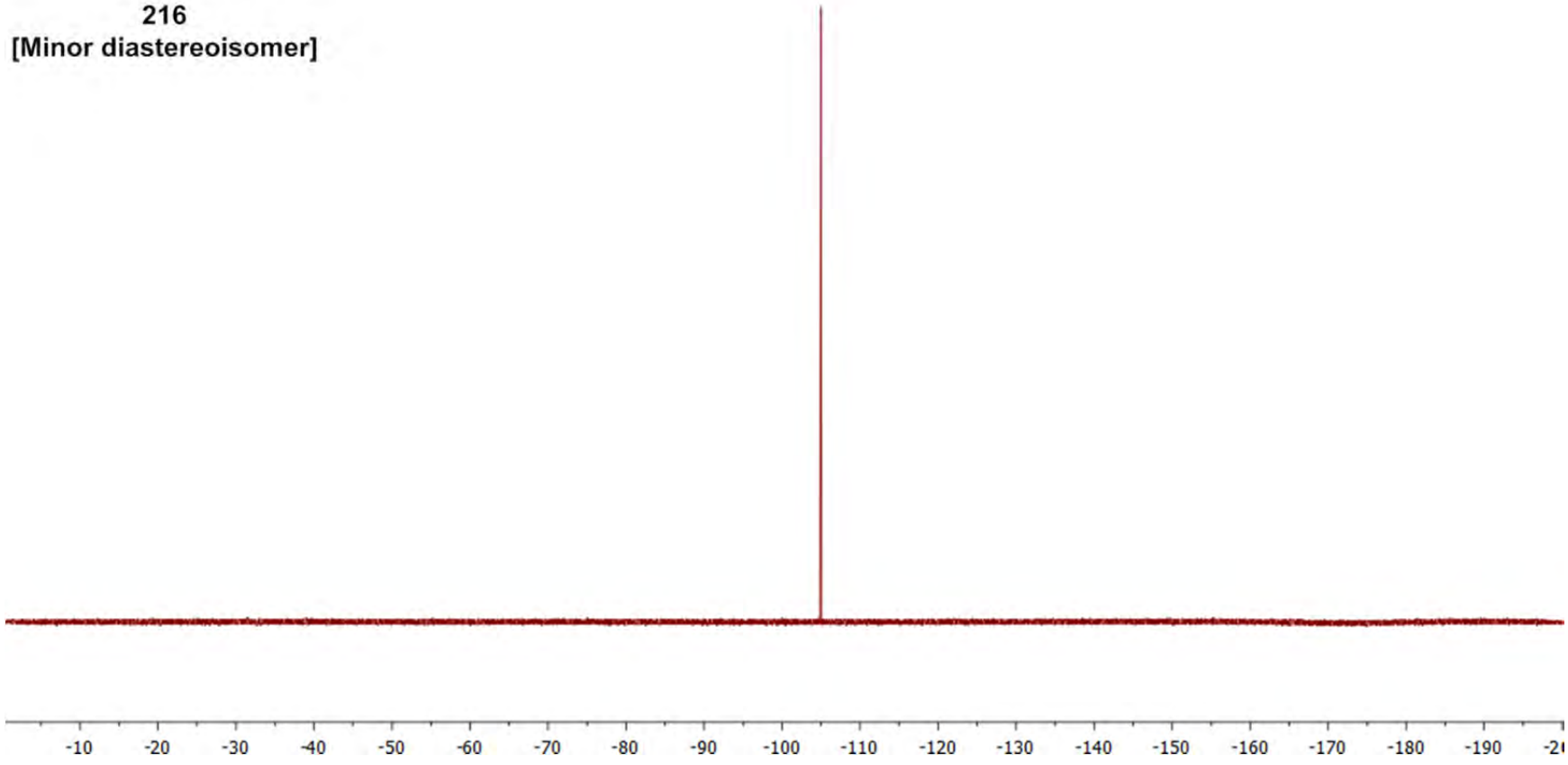
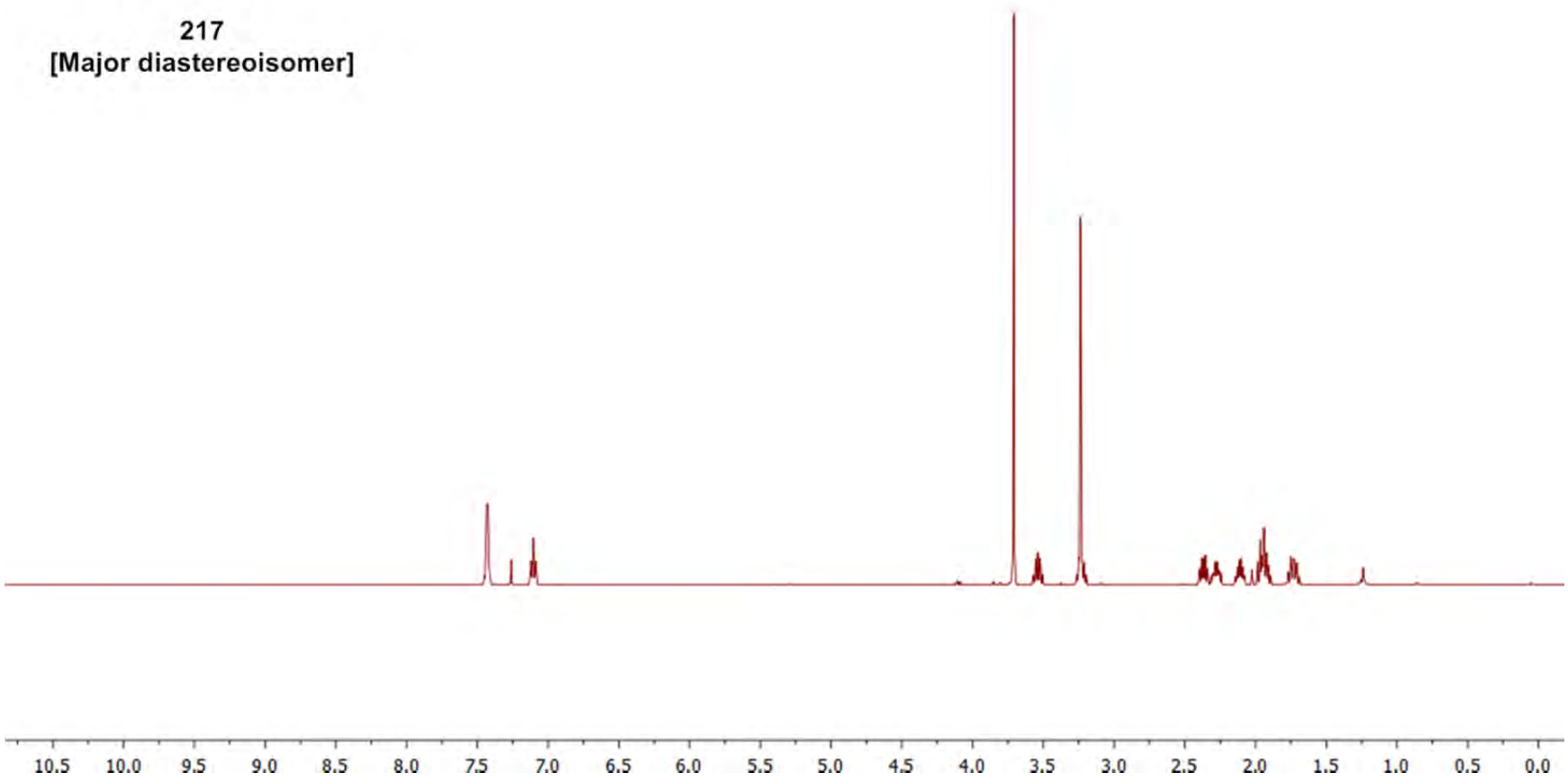


216
[Minor diastereoisomer]

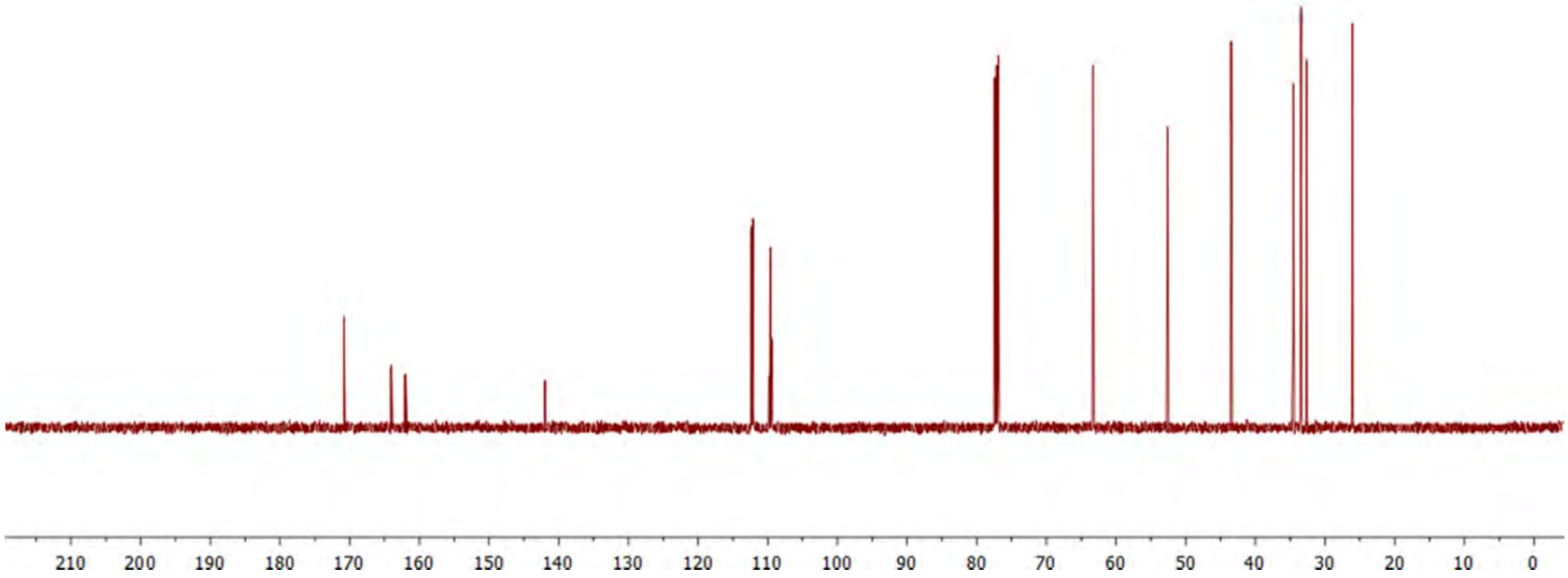
216
[Minor diastereoisomer]



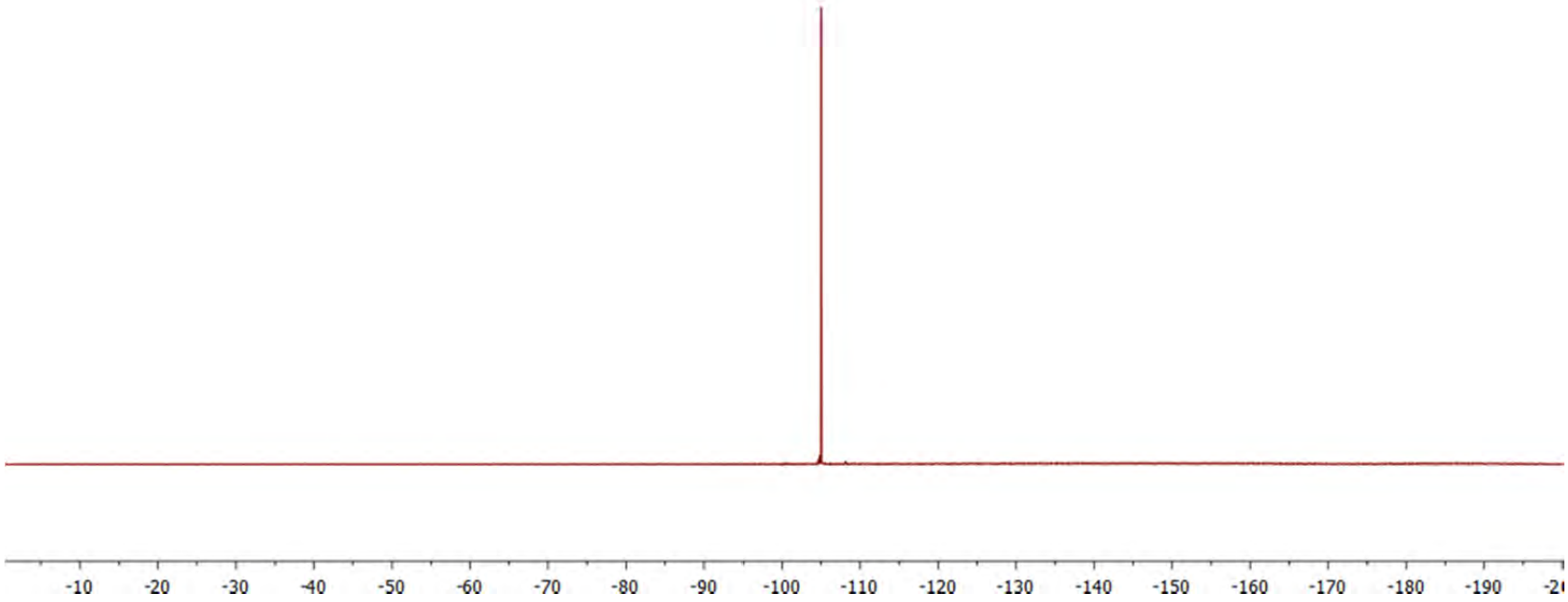
217
[Major diastereoisomer]



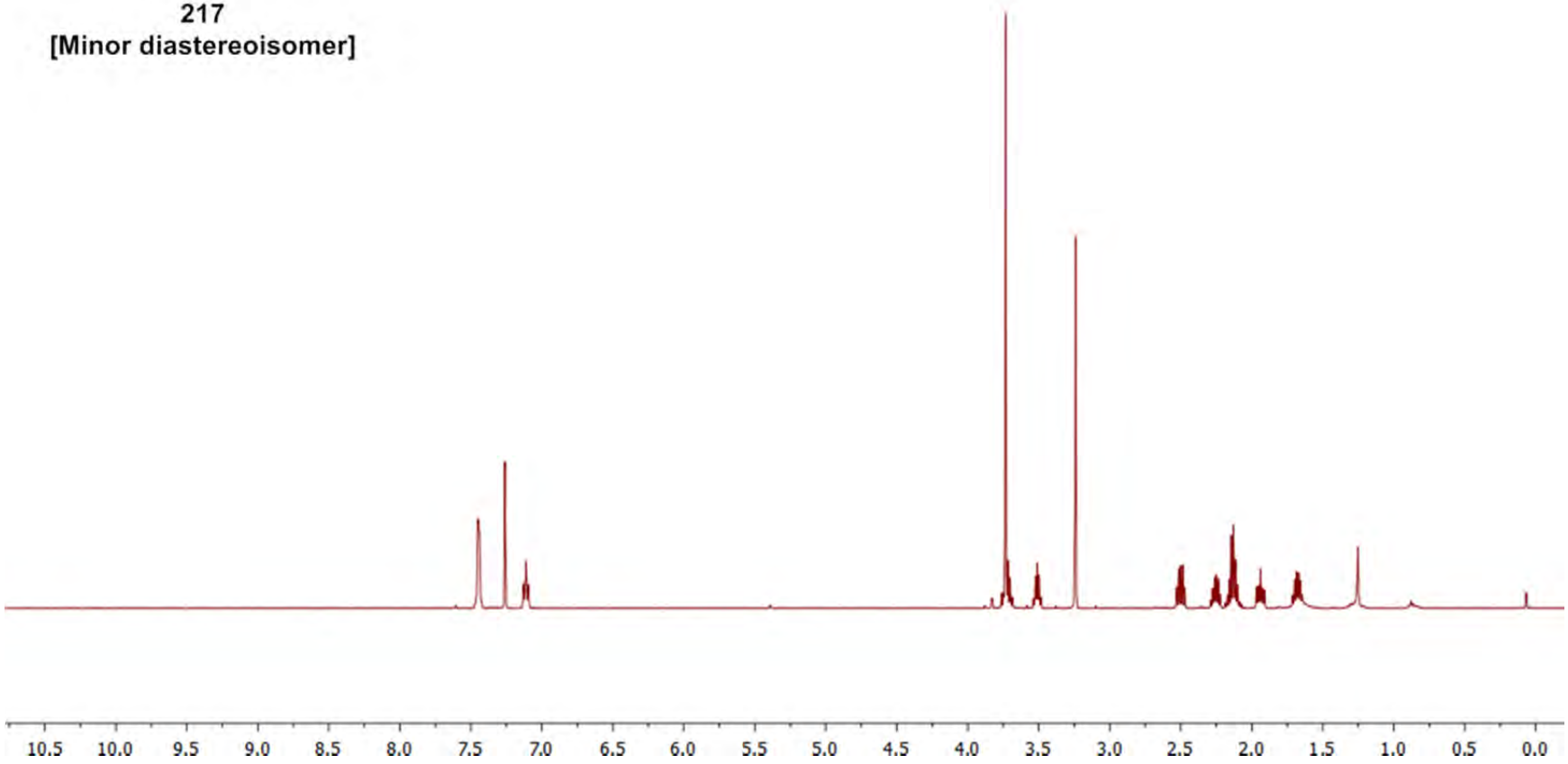
217
[Major diastereoisomer]



217
[Major diastereoisomer]

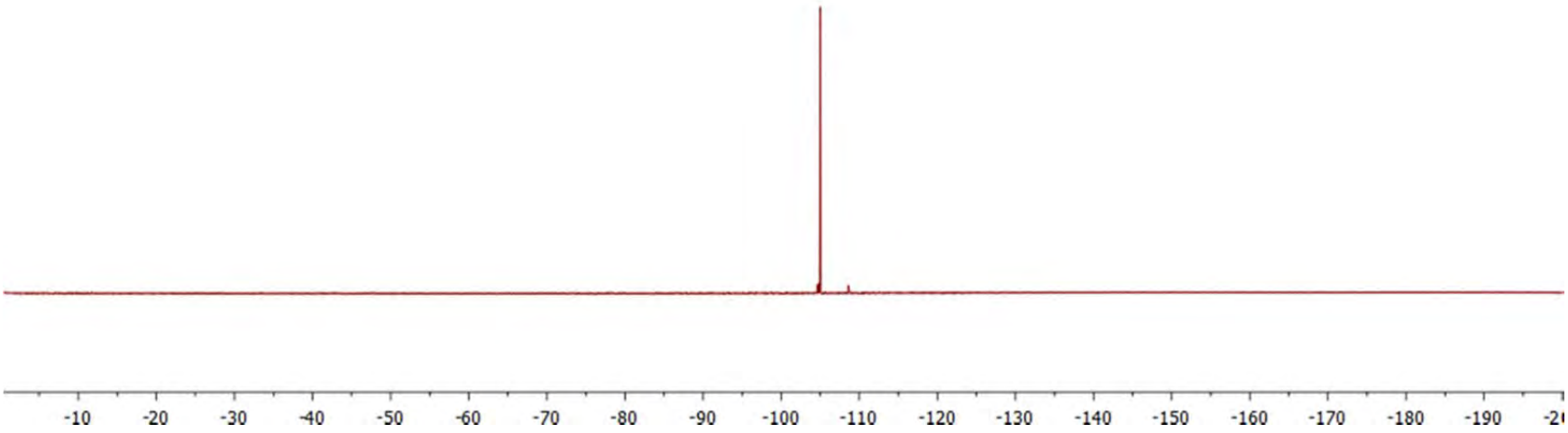


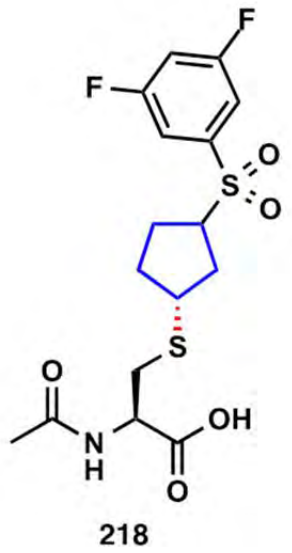
217
[Minor diastereoisomer]



217
[Minor diastereoisomer]

217
[Minor diastereoisomer]




F
F
O
S
O
S
O
N
H
OH
O

218

10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.0
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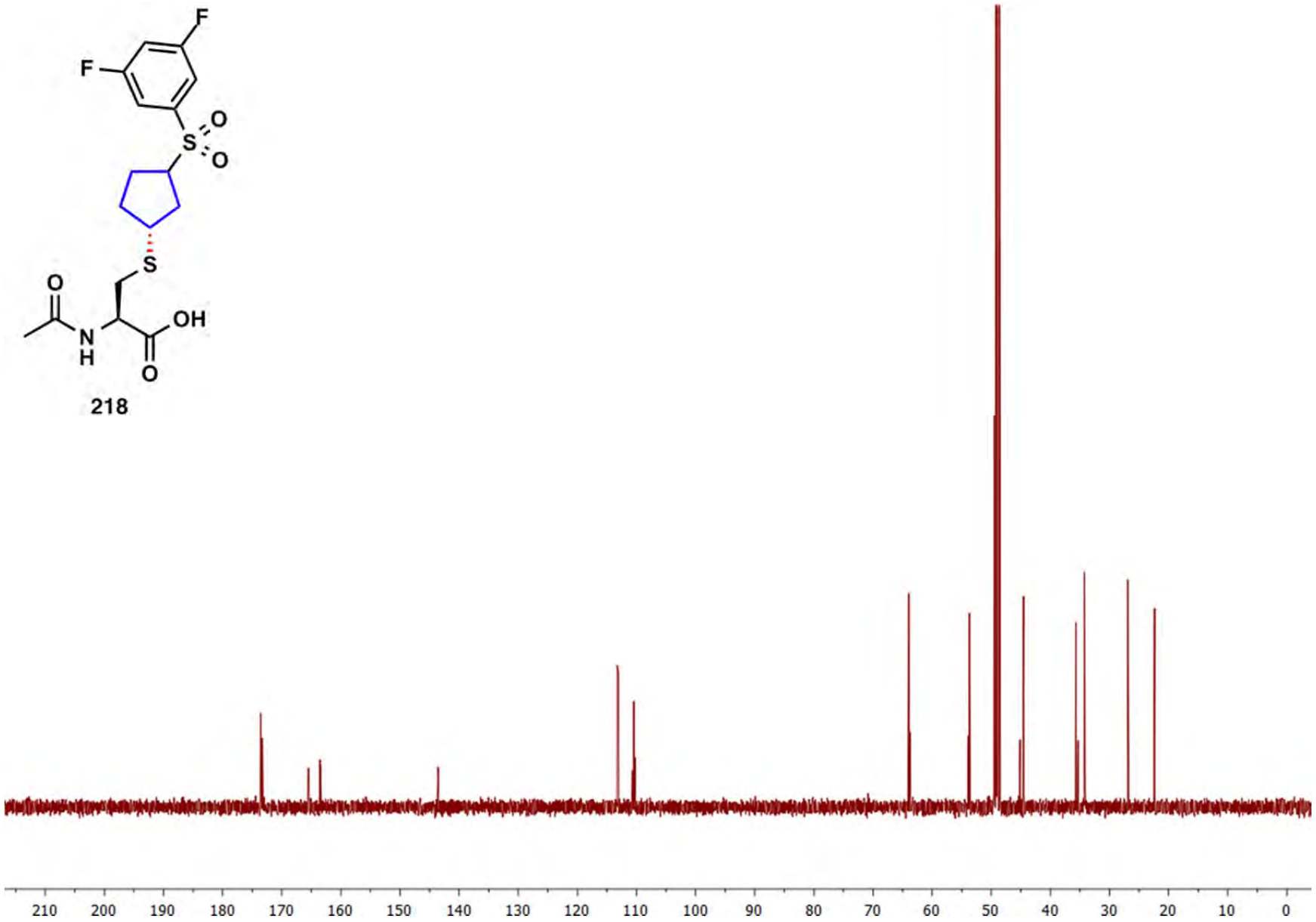
F
F
O
S
O
S
O
N
H
OH
O
218
210
200
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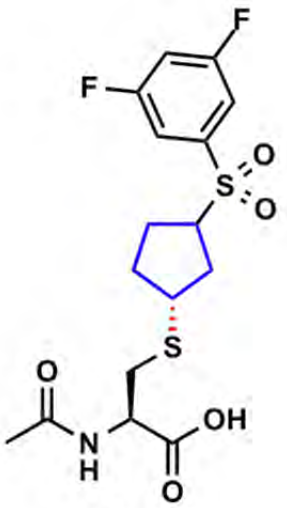
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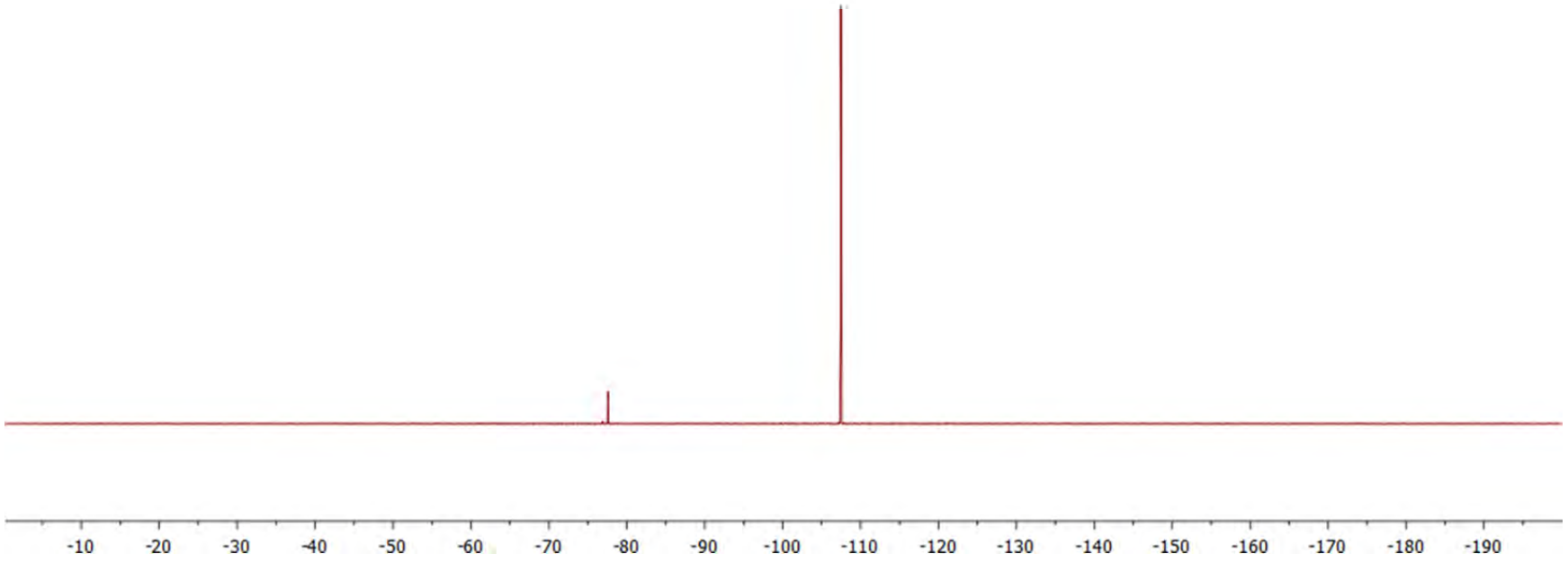
S
O
S
O
N
H
OH
O

218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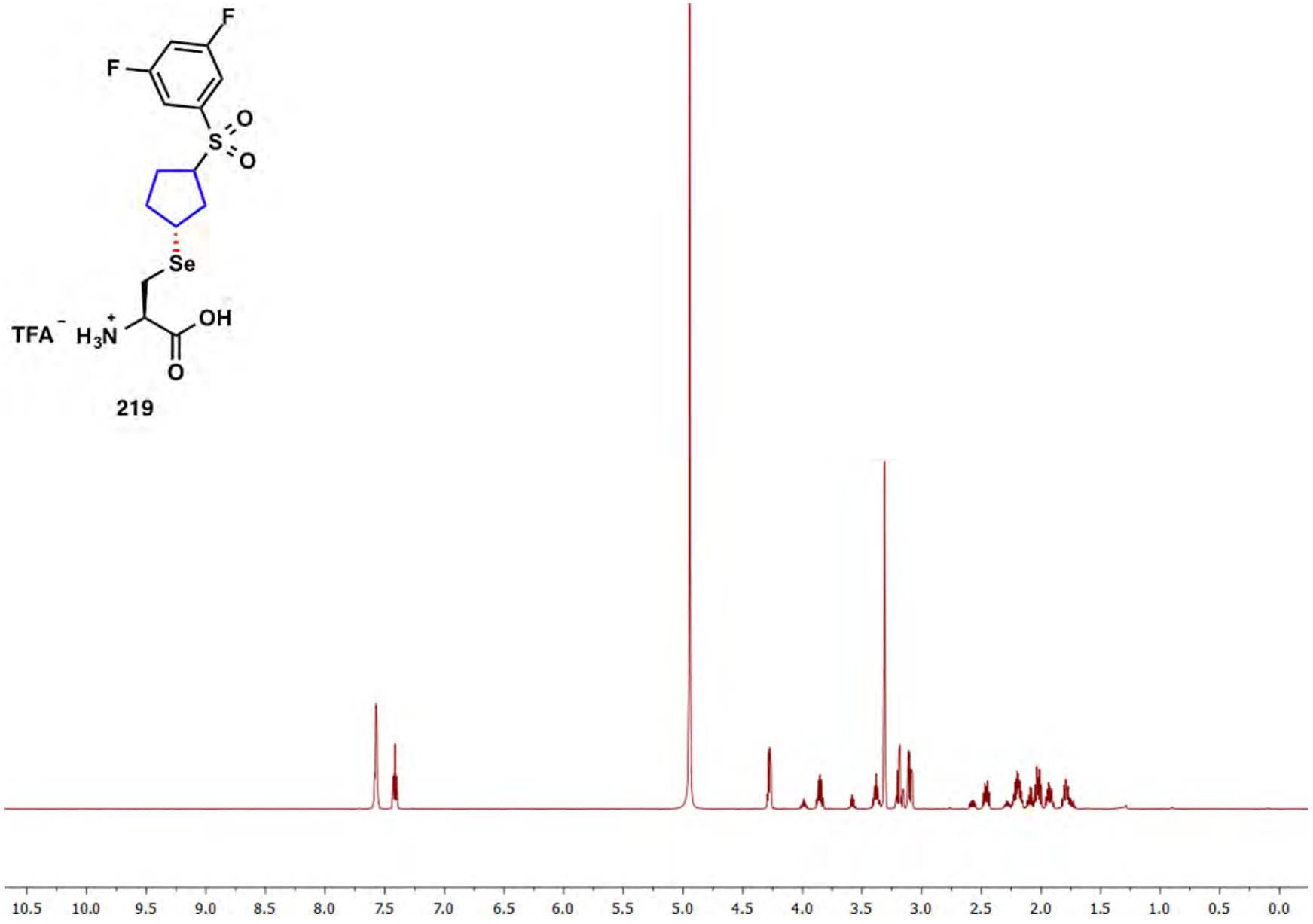
F
F
O
S
O
Se
TFA
H3N
OH
O
219
10.5
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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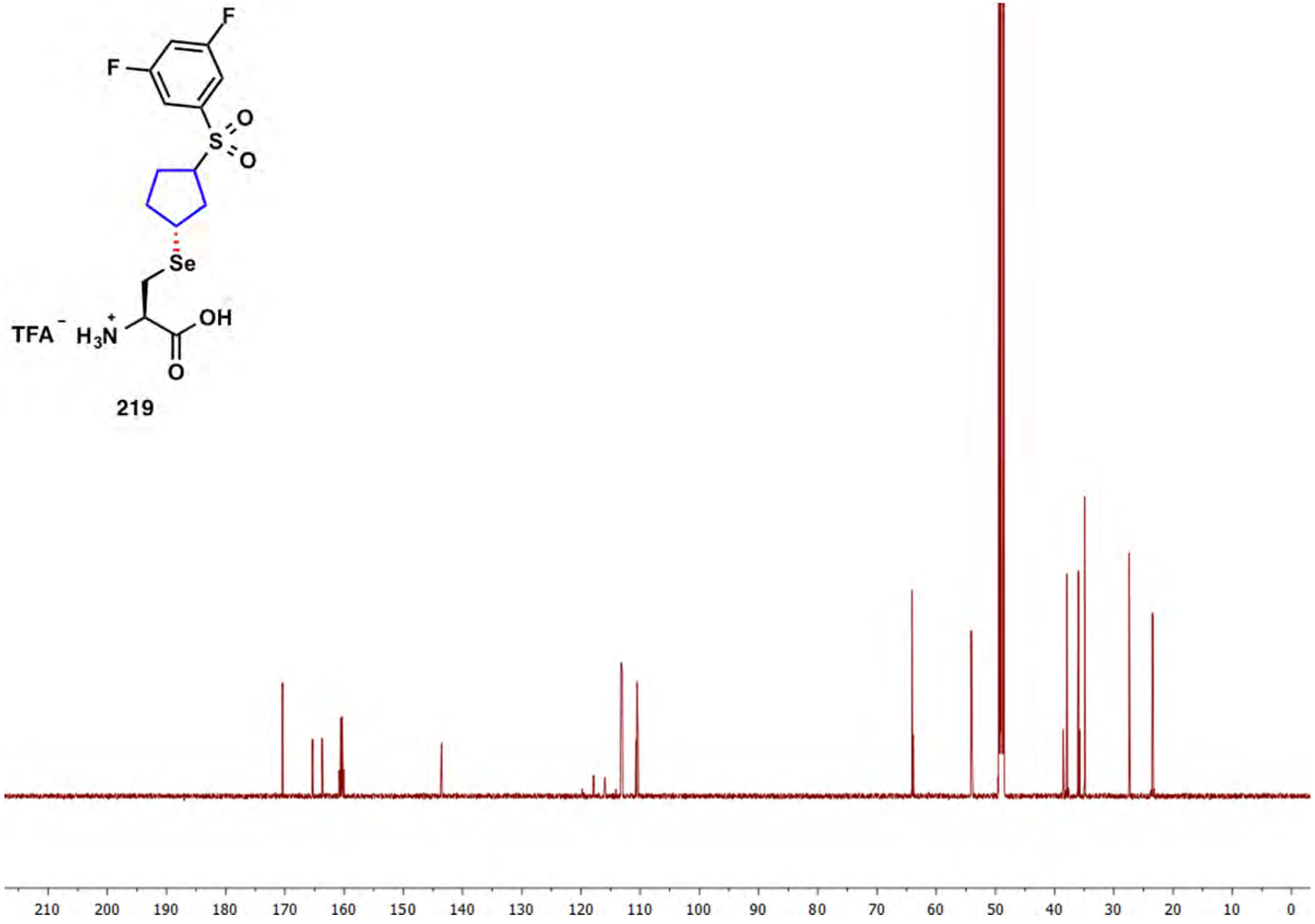
F
F
O
S
O
Se
TFA
H3N
OH
O
219
210
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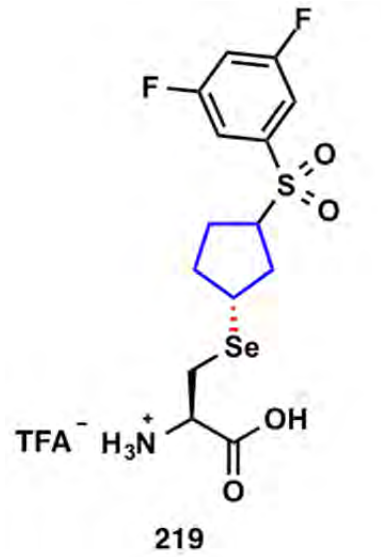
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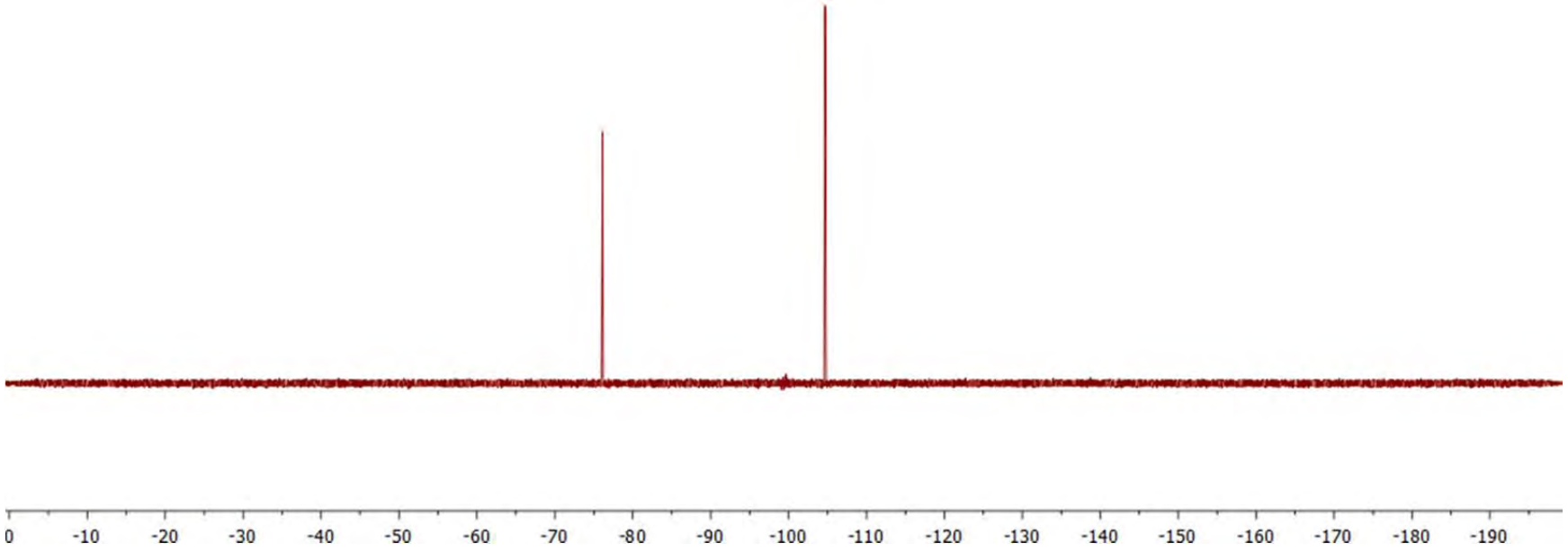
O
S
O
Se
TFA
H3N
OH
O

219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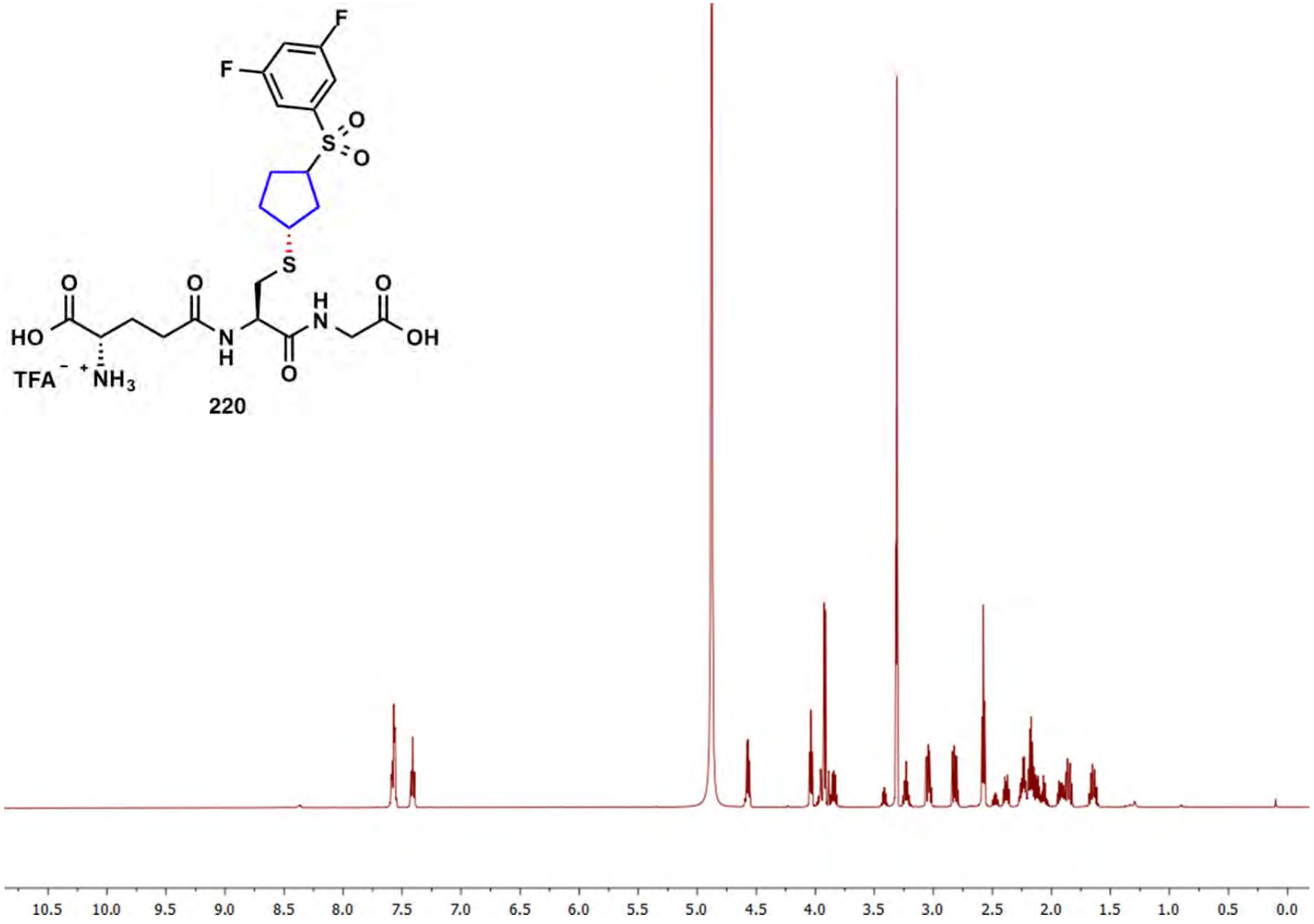
F
F
O
S
O
S
O
HO
O
N
H
O
H
N
O
OH
TFA
NH3
O
220
10.5
10.0
9.5
9.0
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8.0
7.5
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6.5
6.0
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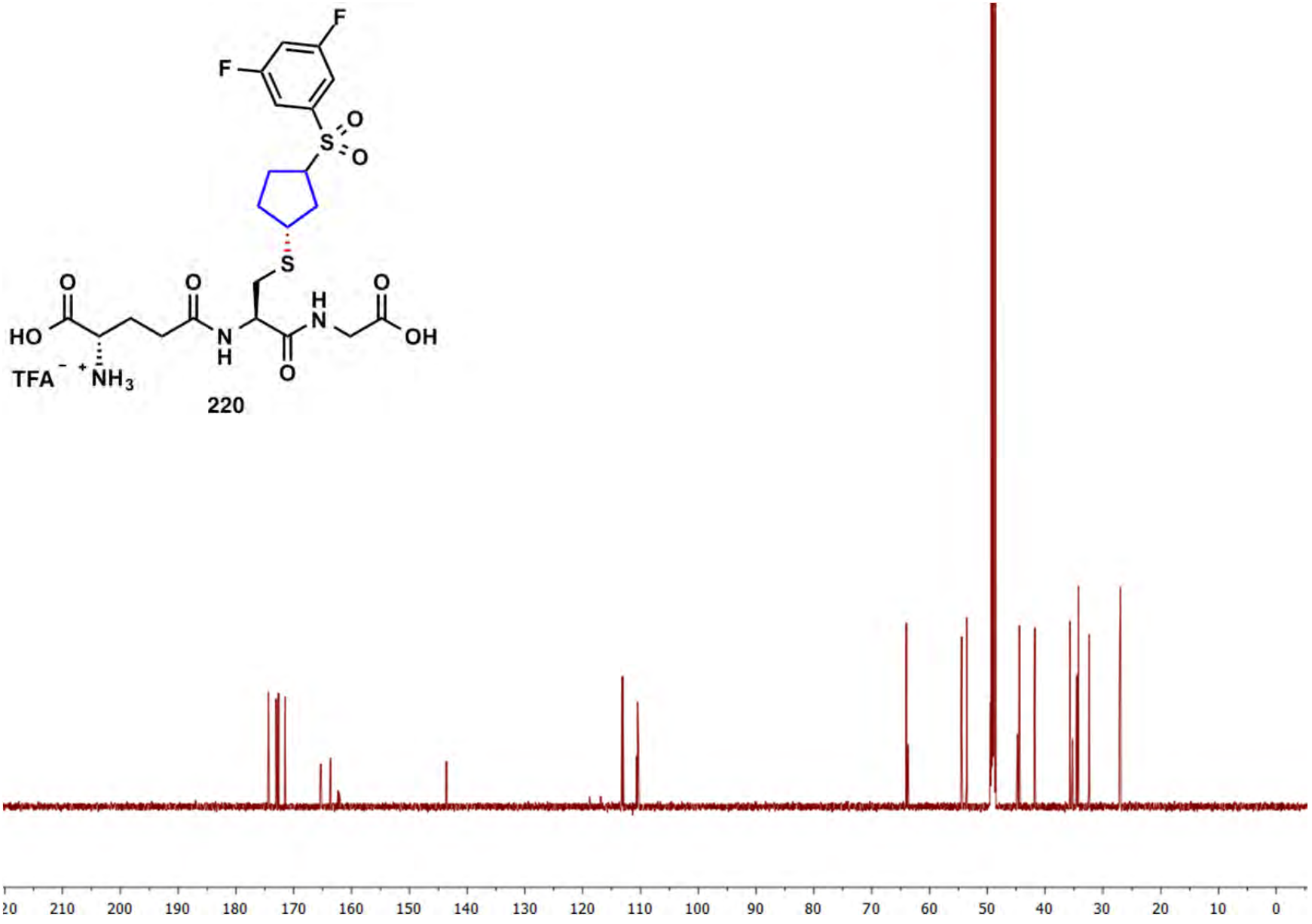
F
F
O
S
O
S
O
HO
O
N
H
O
H
N
O
OH
TFA
NH3
O
220
210
200
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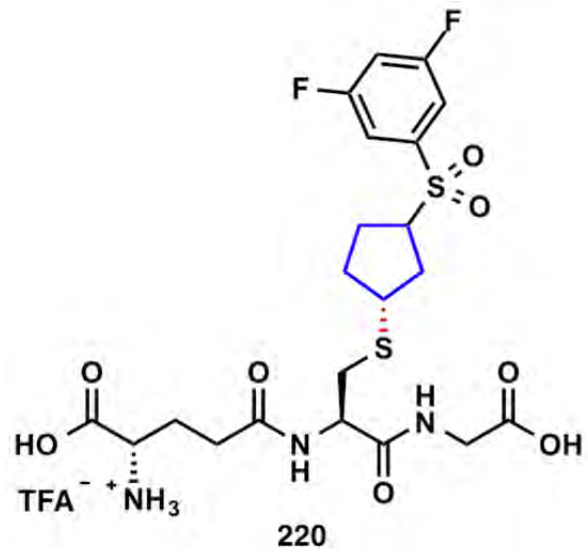
10
0


F
F
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S
O
HO
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N
H
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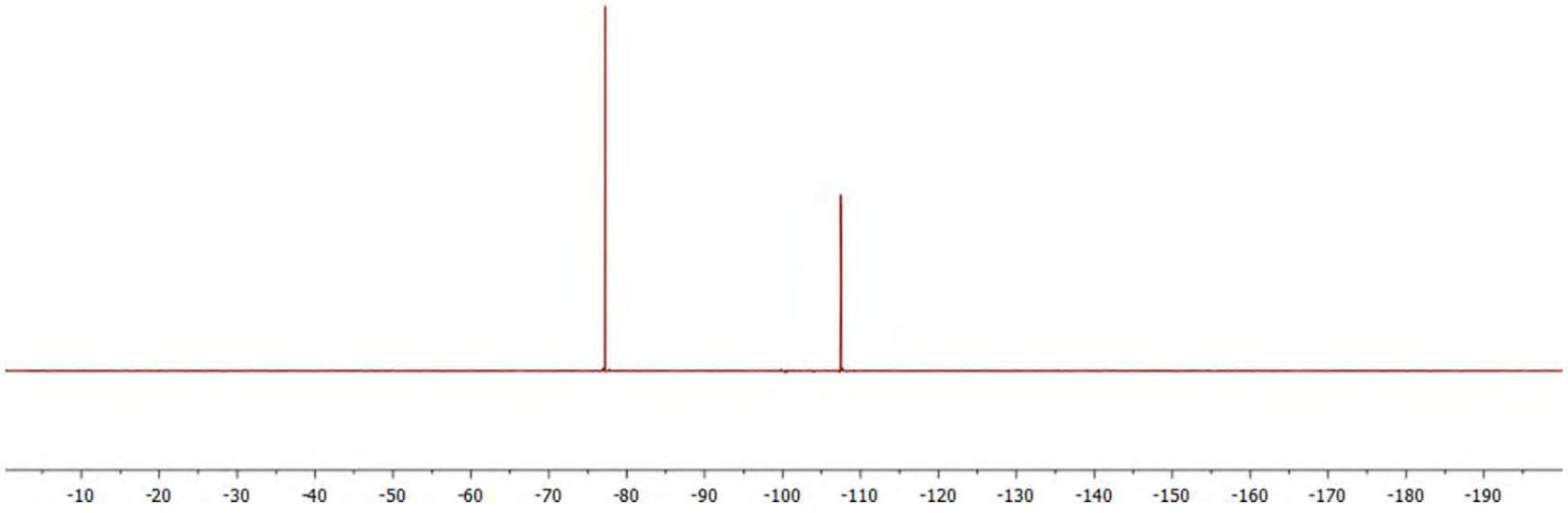
H
N
O
OH
TFA
NH3

220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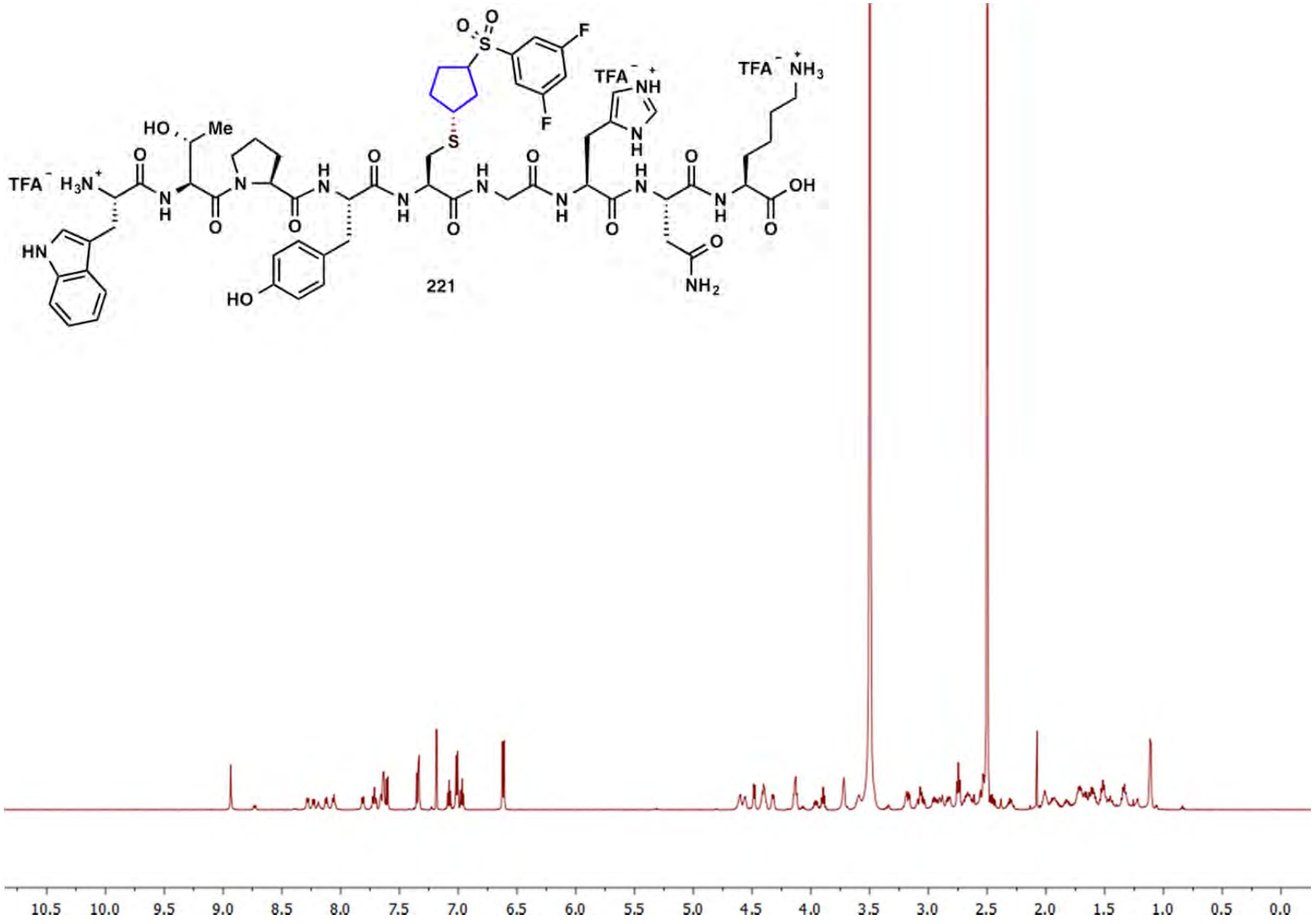
221
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
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3.0
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2.0
1.5
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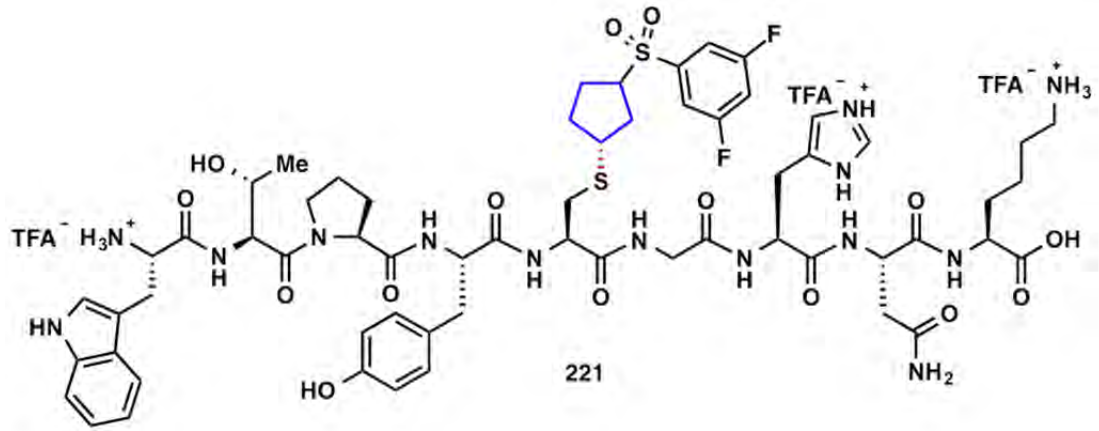
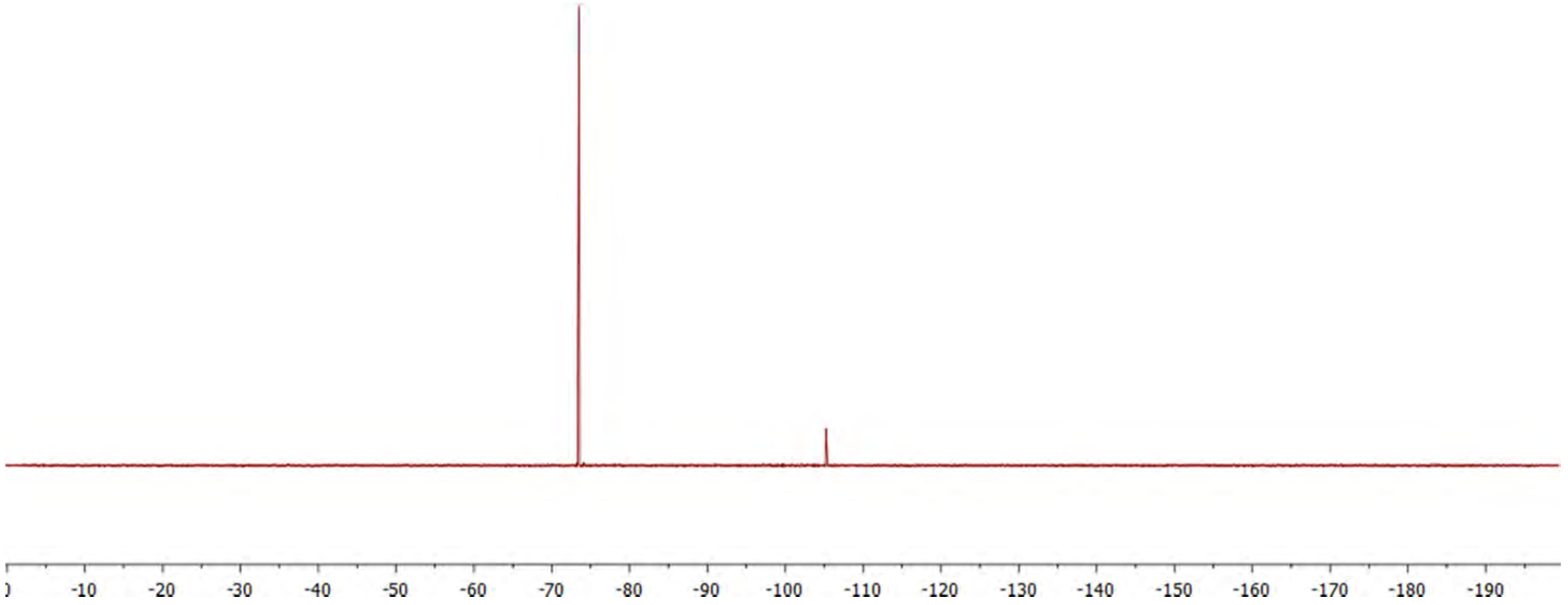
0.0


TFA⁻ H3N+
HO
Me
HN
HO
TFA⁻ NH
TFA⁻ NH3
OH
NH2
F
F
221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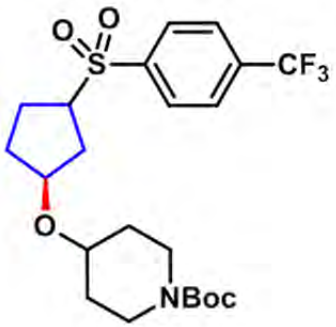
O
O
S
CF3
O
NBoc

225

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9.0
8.5
8.0
7.5
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6.5
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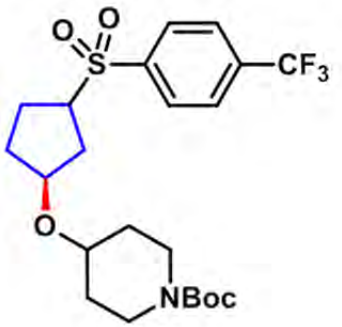
O
O
S
CF3
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NBoc

225

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210
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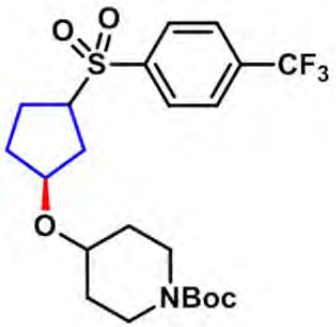
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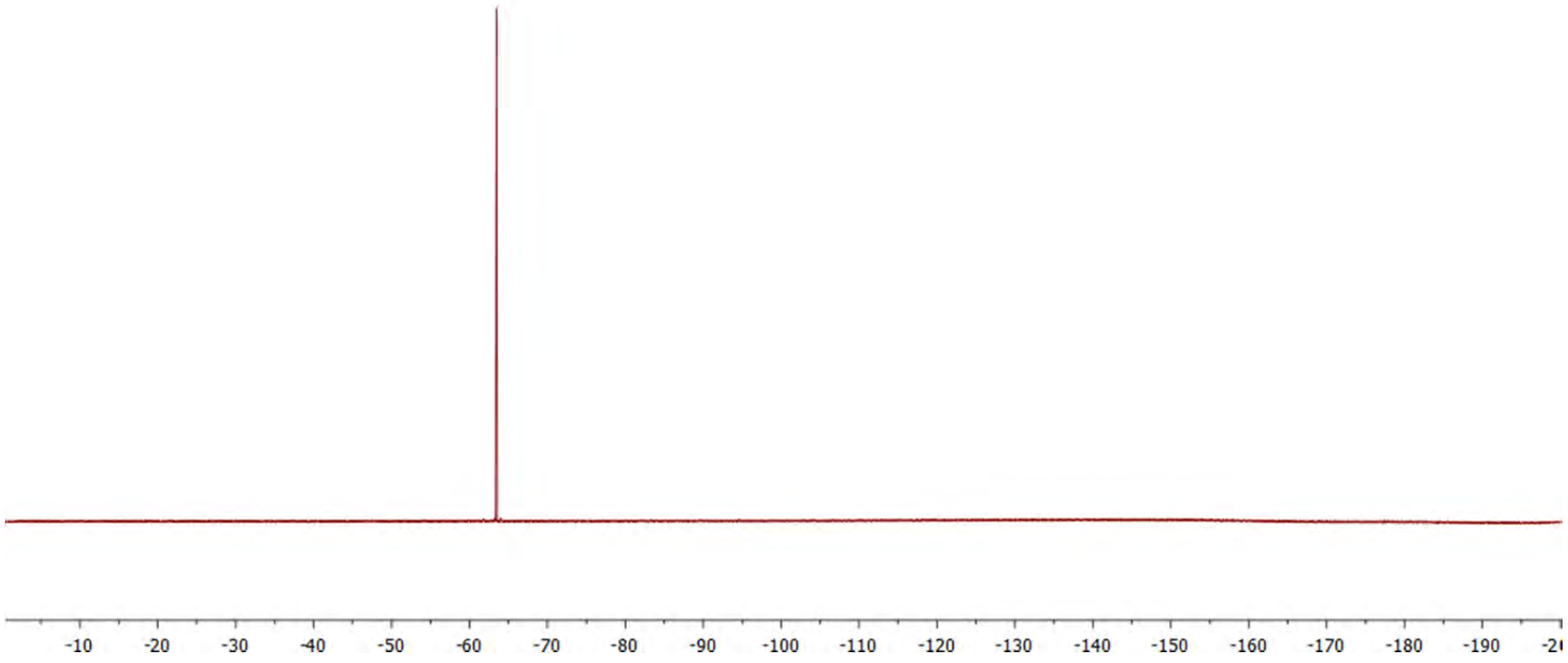
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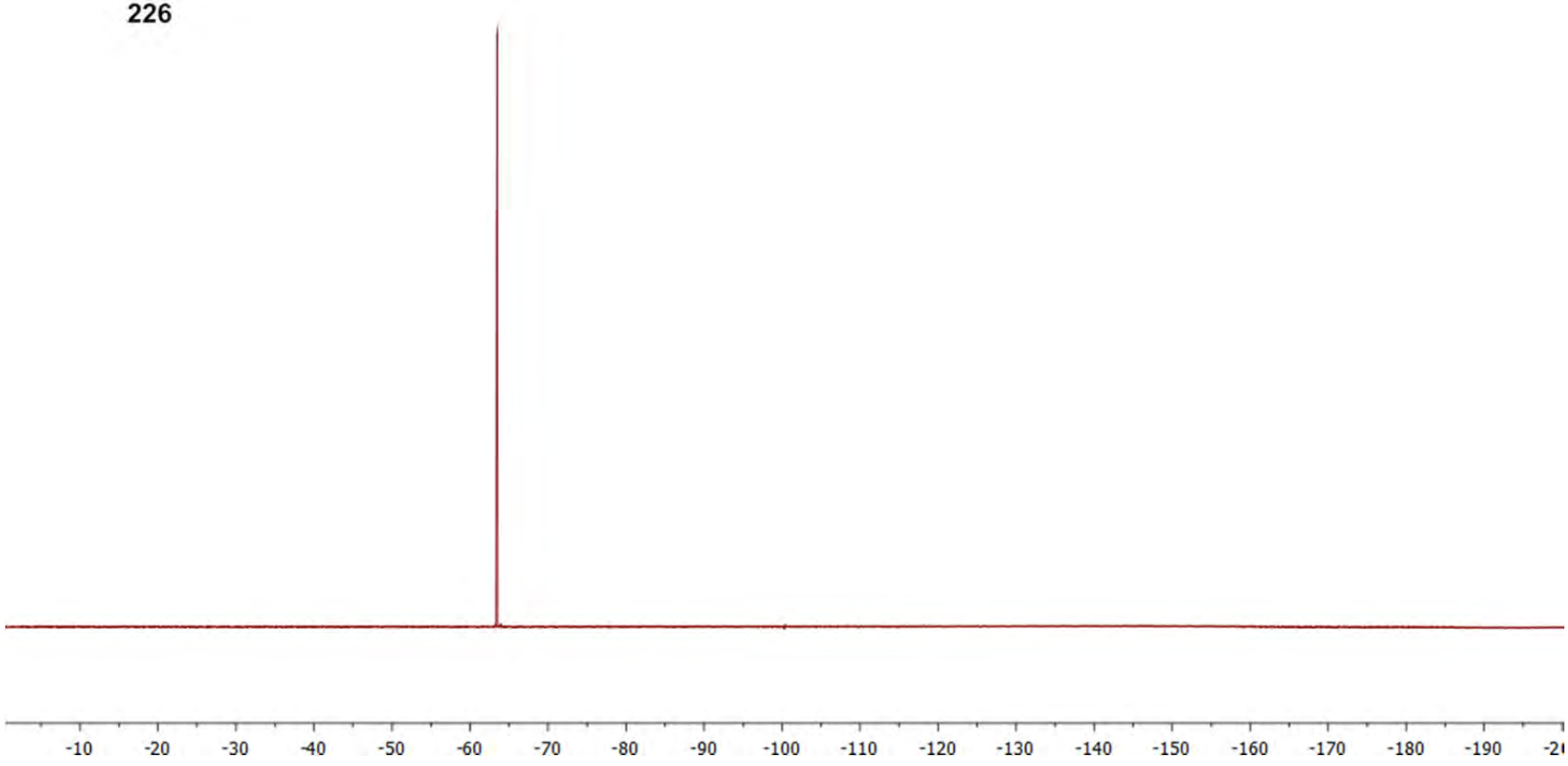
226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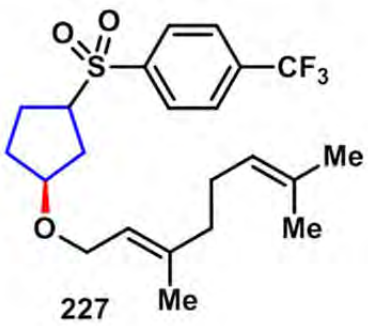
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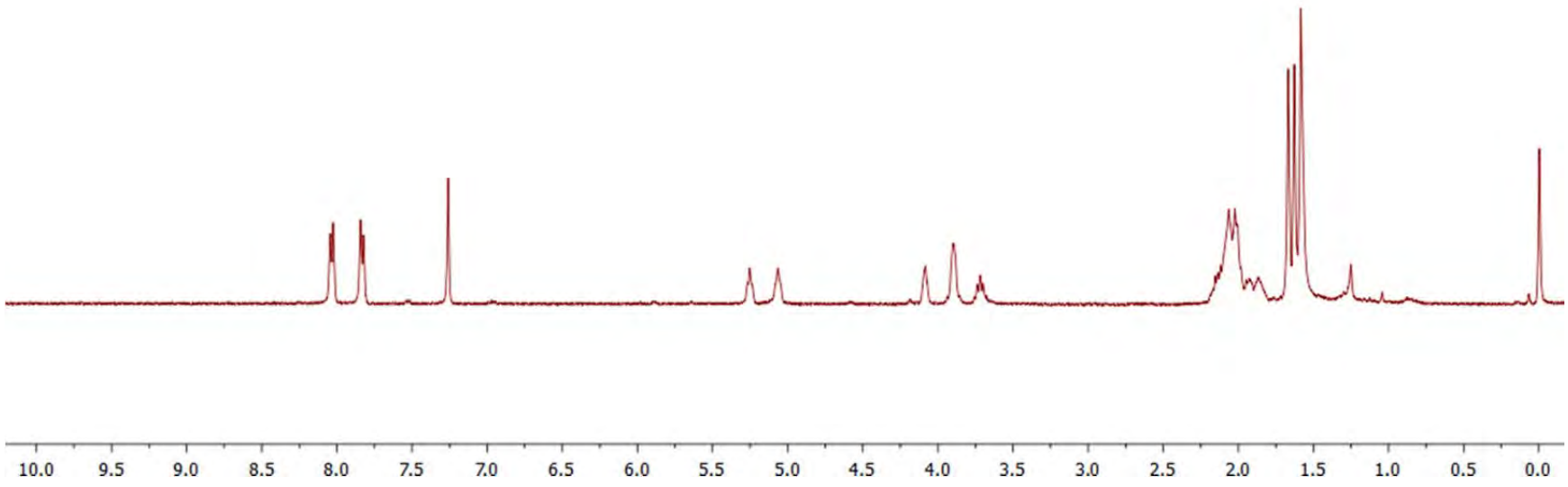
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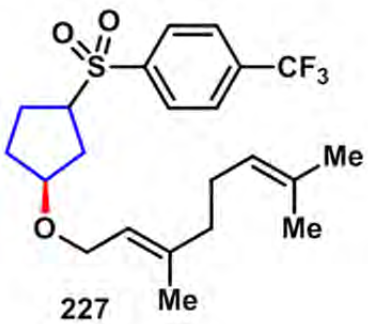
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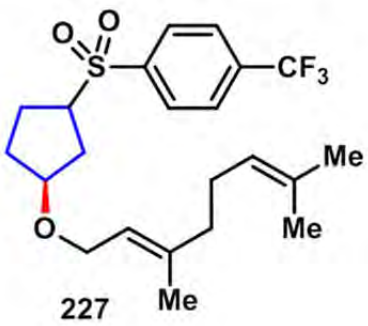
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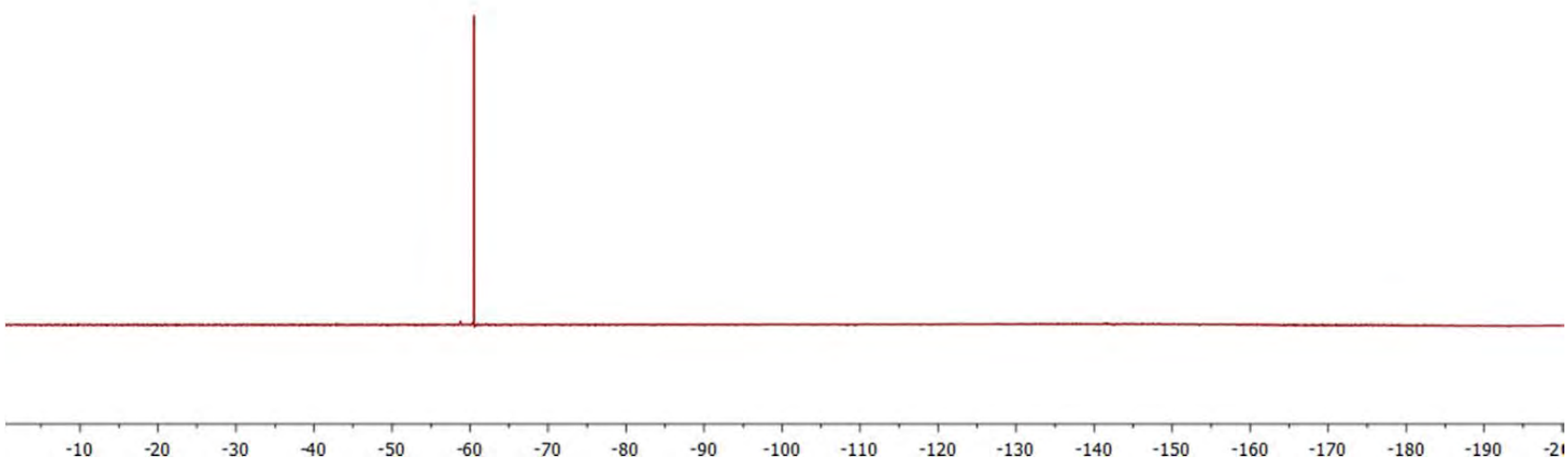
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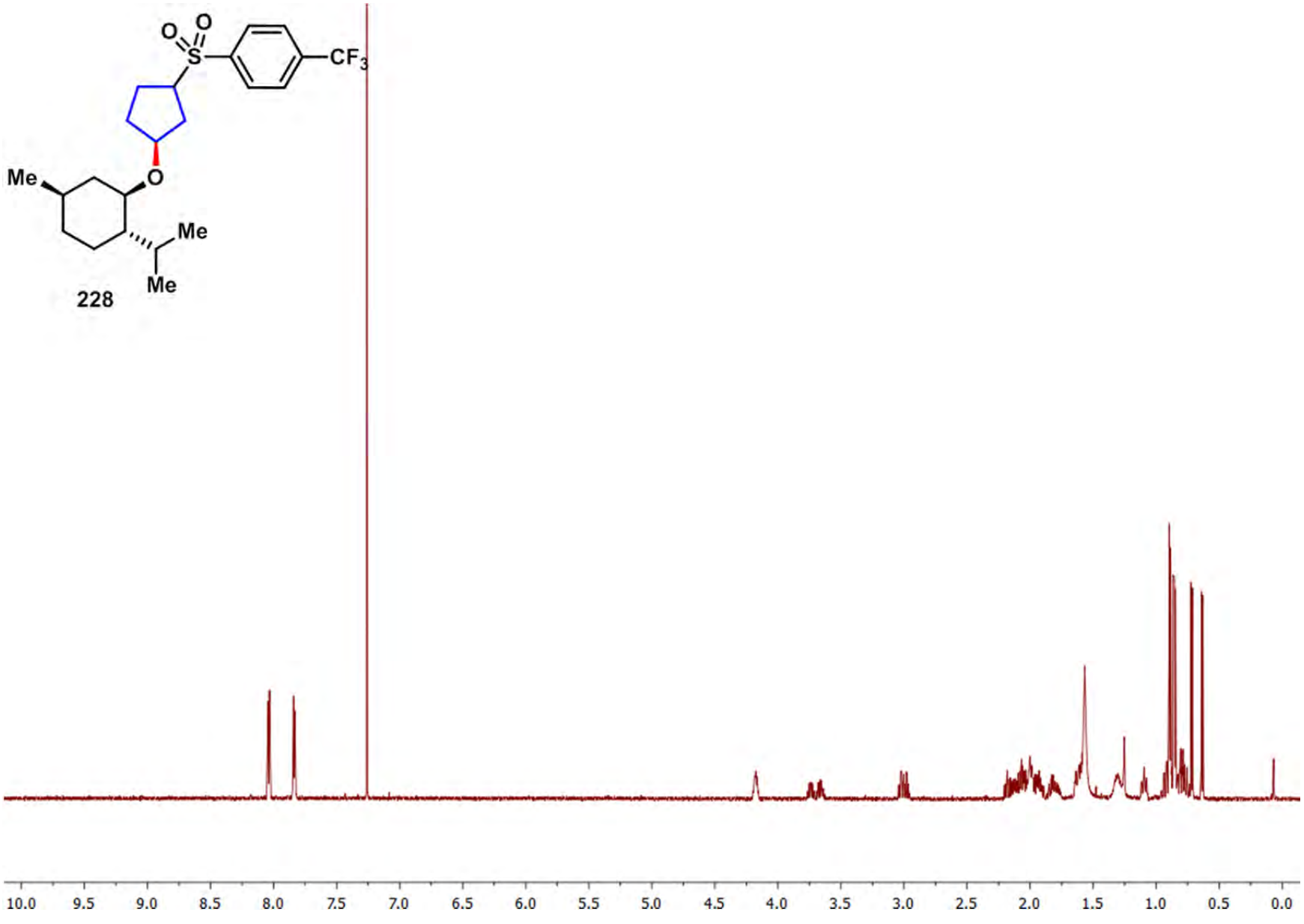
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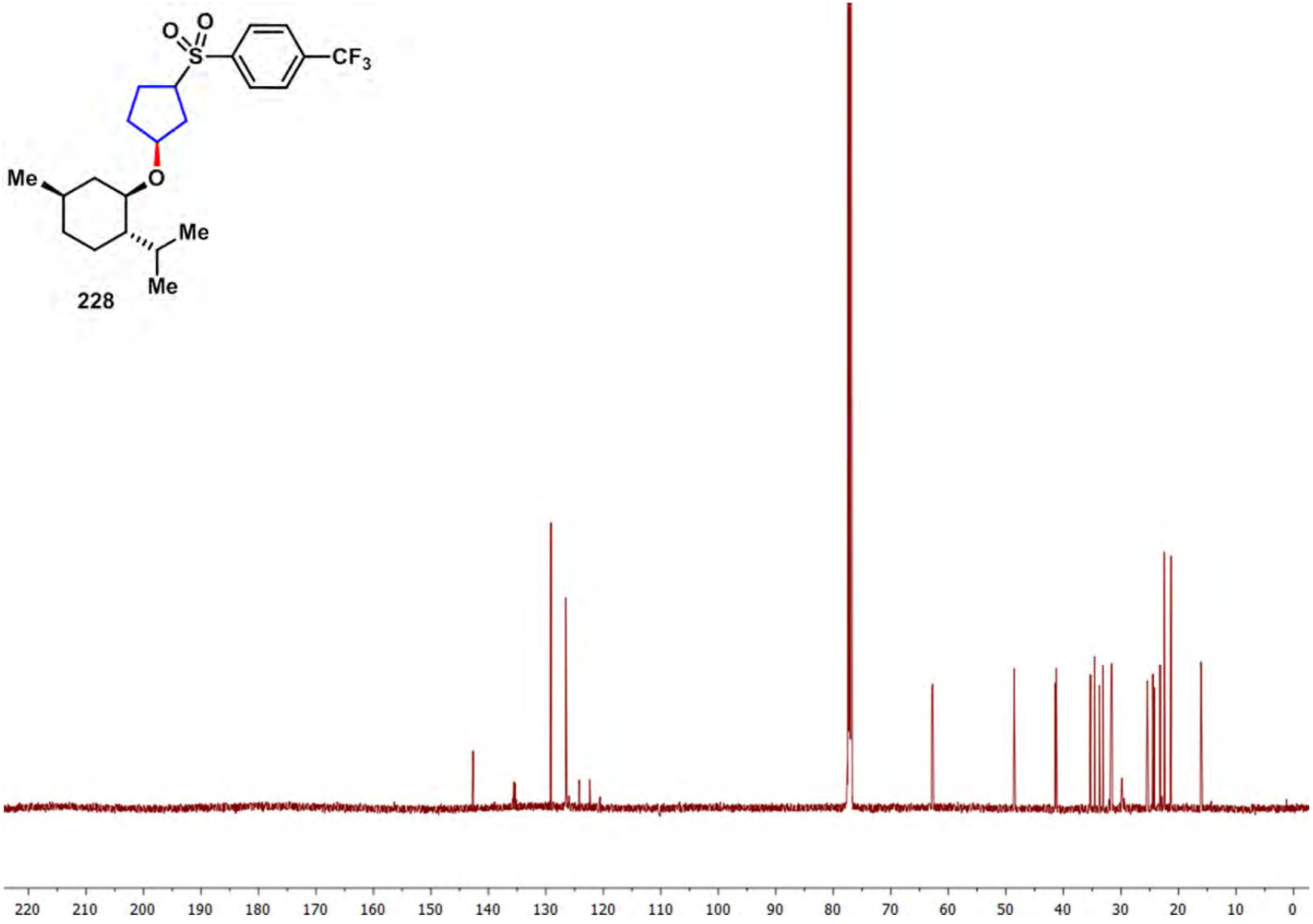
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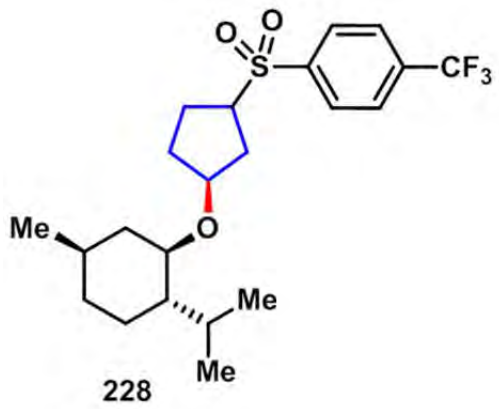
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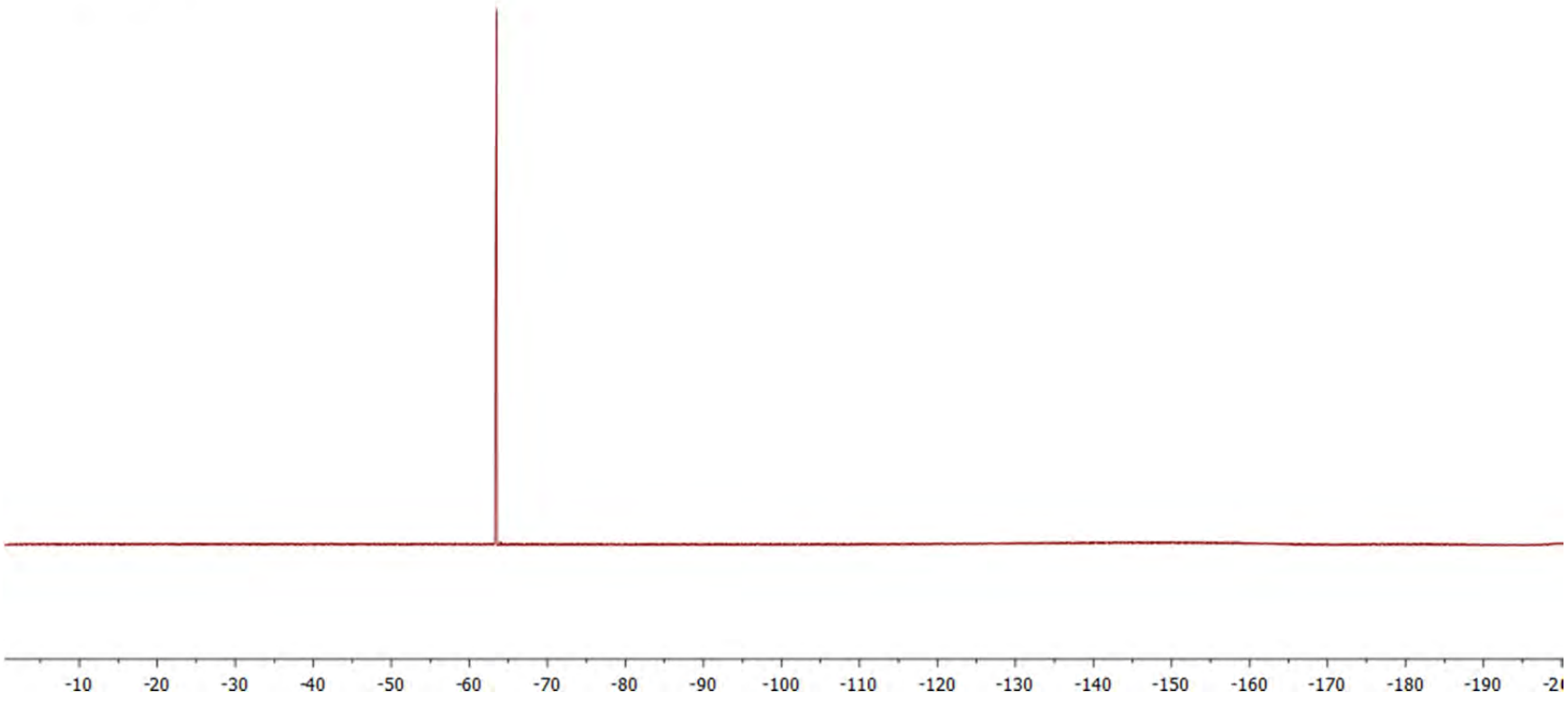
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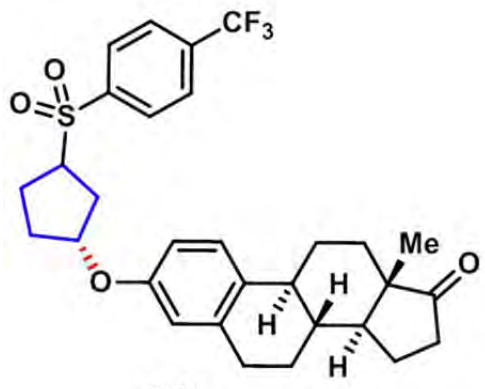
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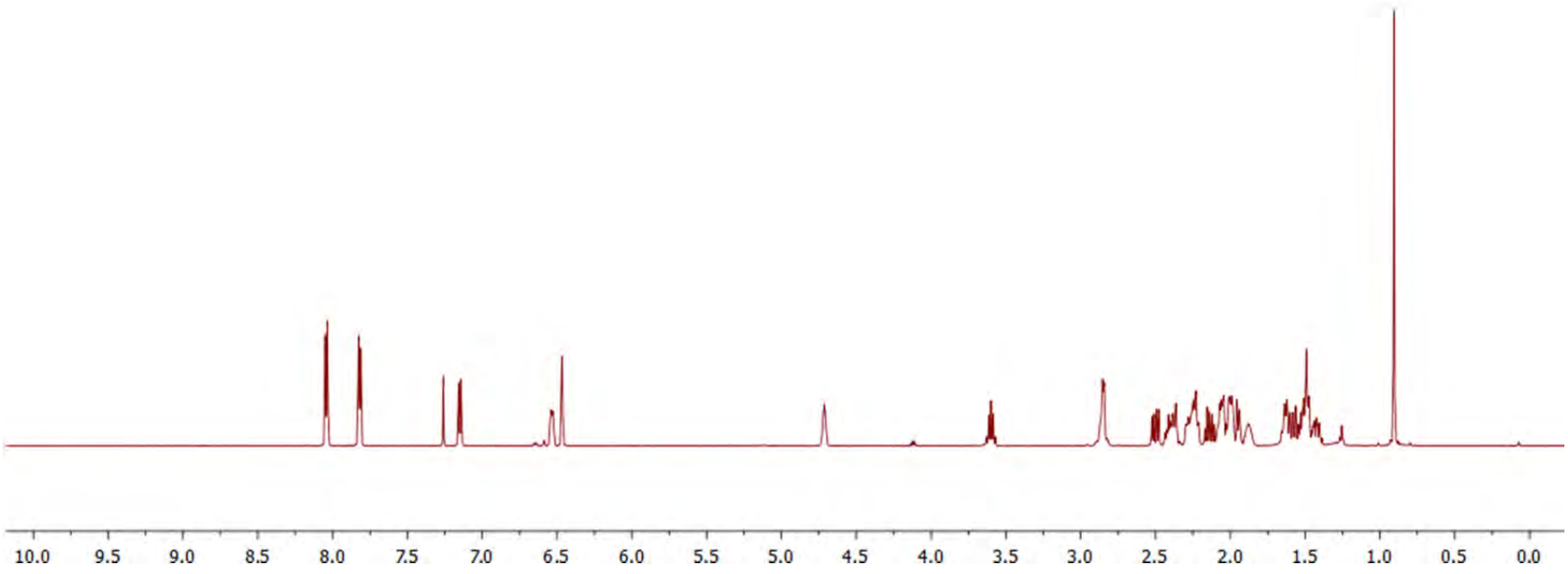
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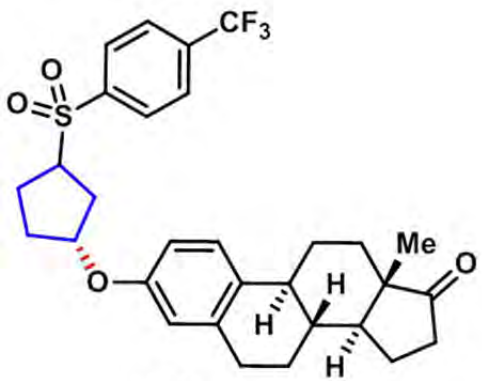
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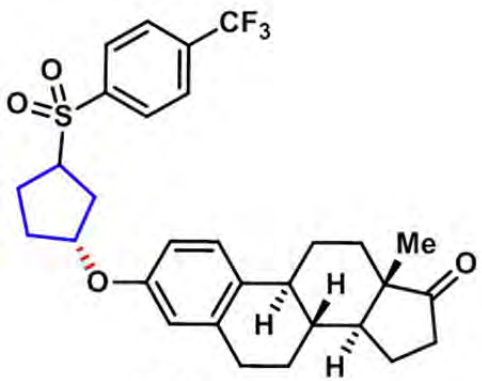
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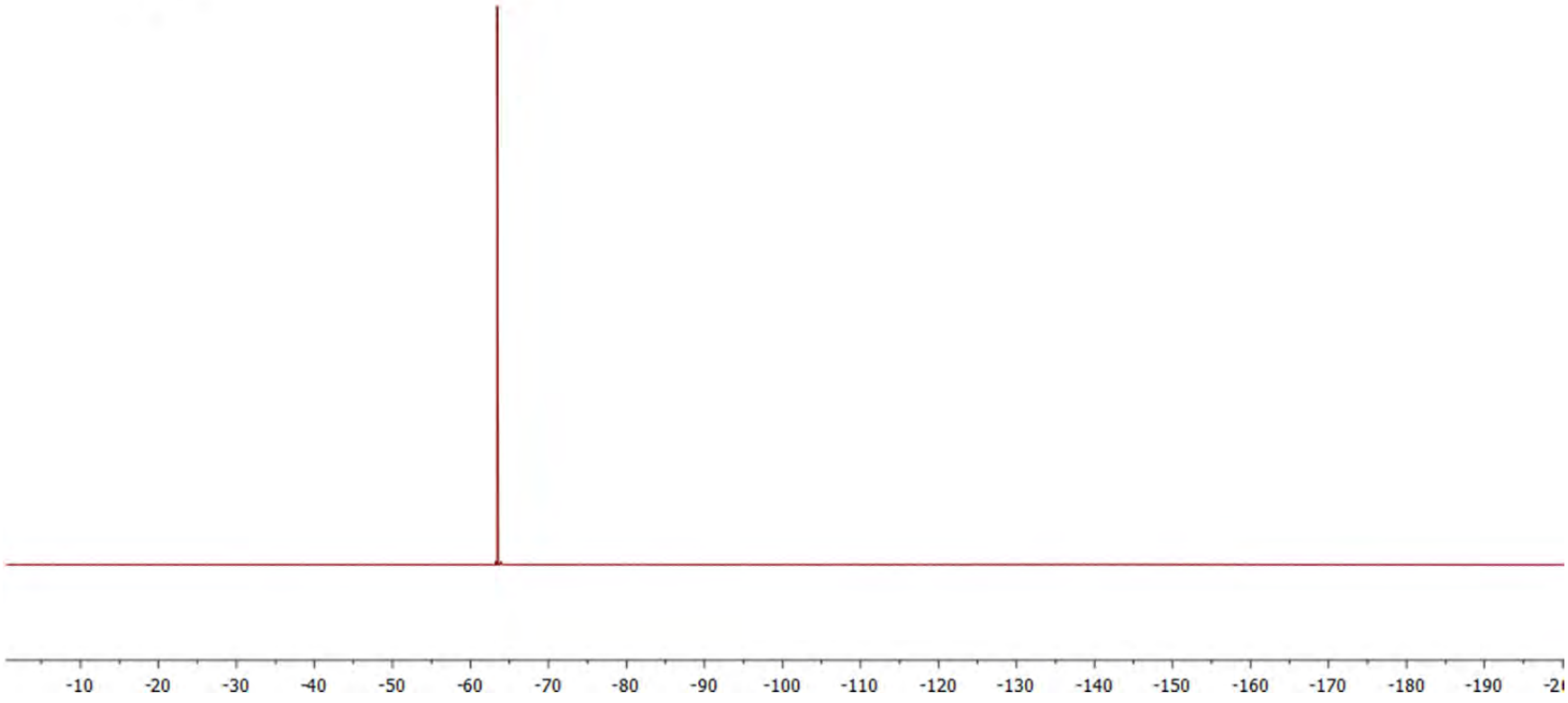
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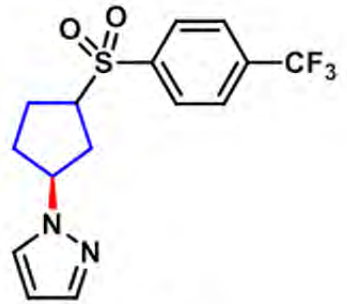

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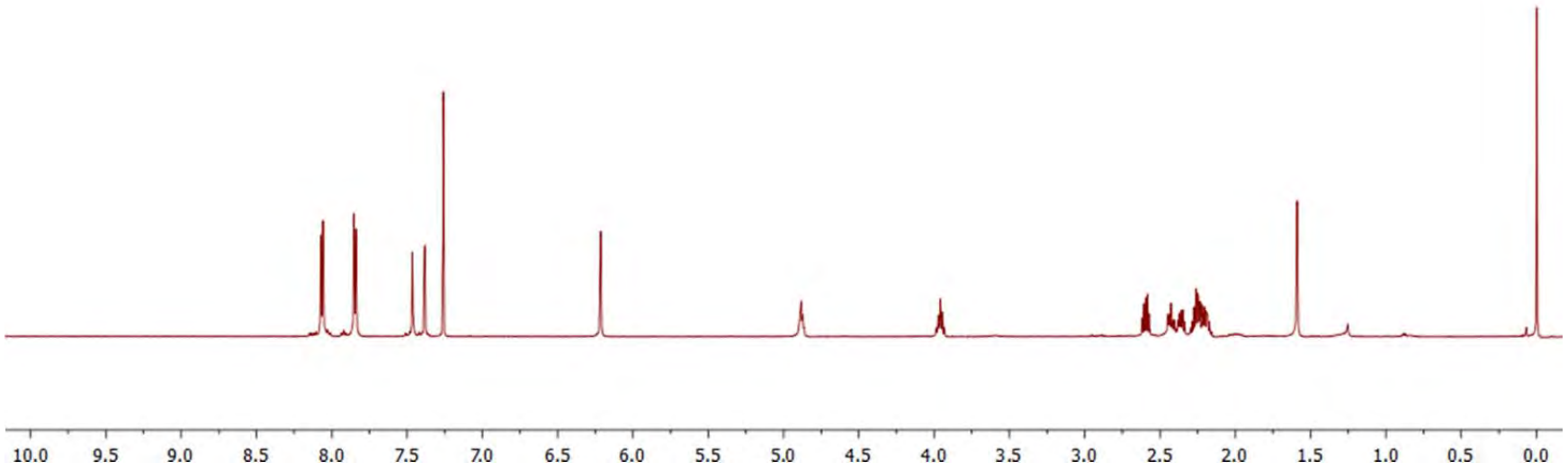

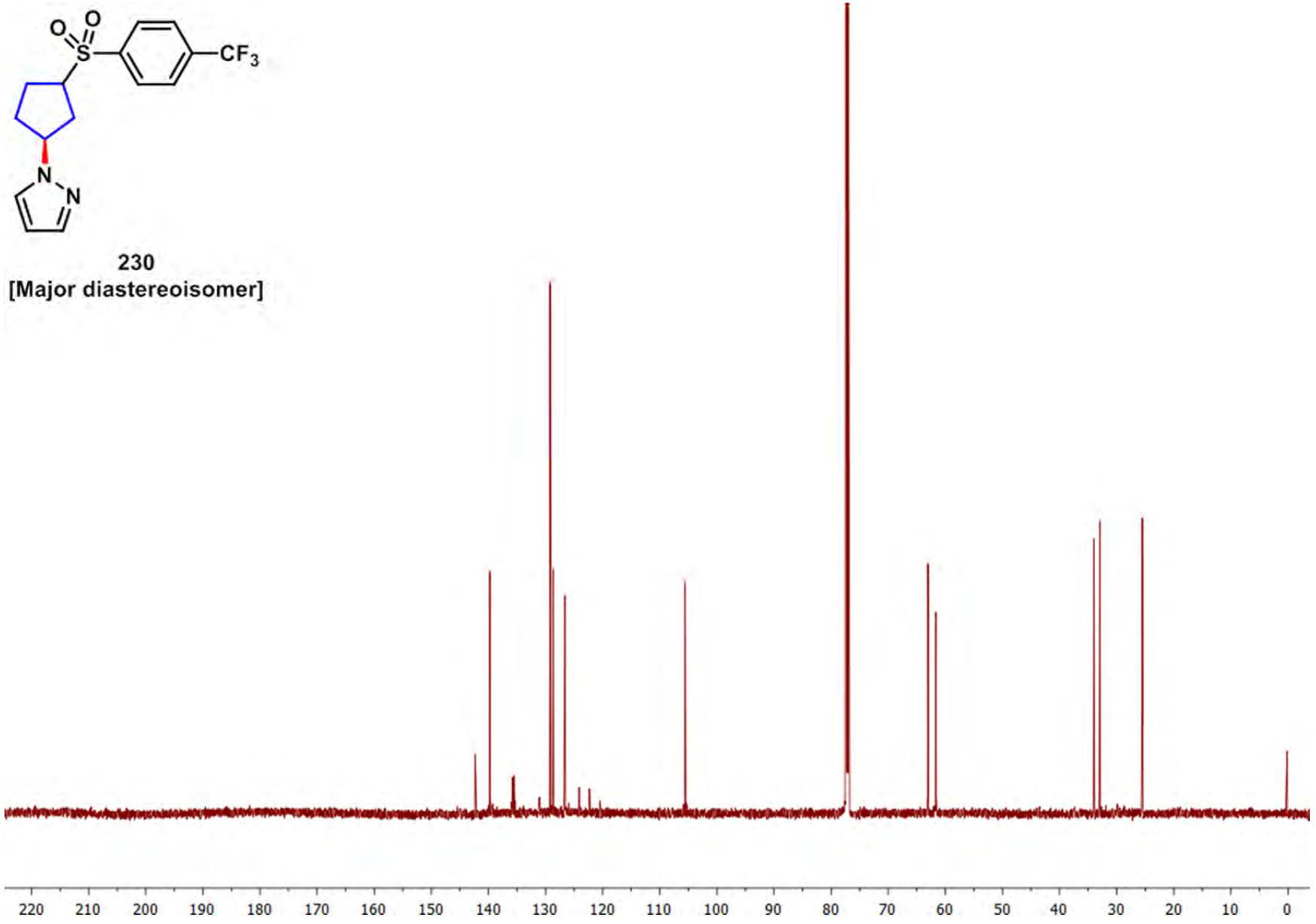
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[Major diastereoisomer]
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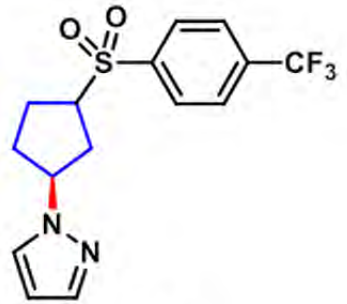

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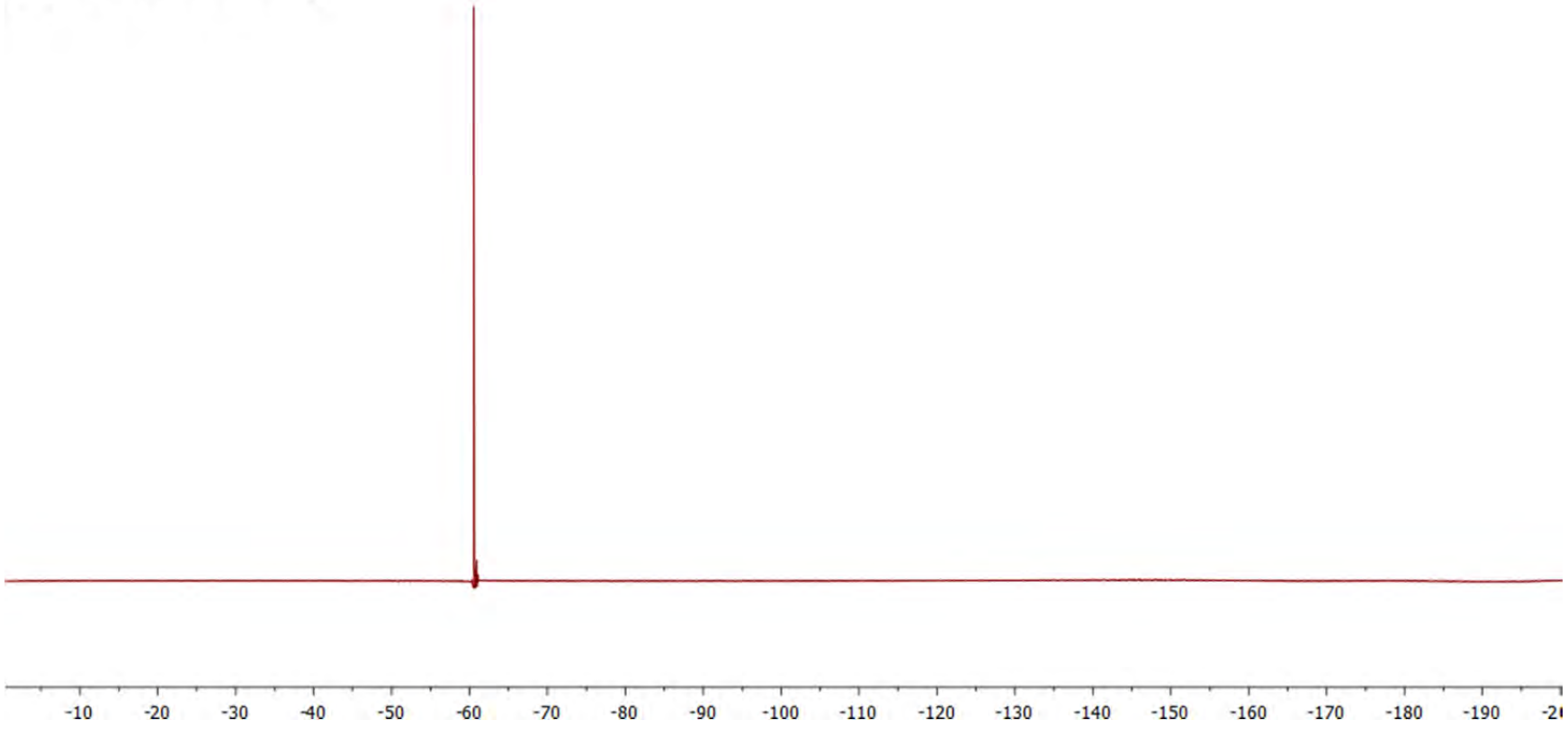

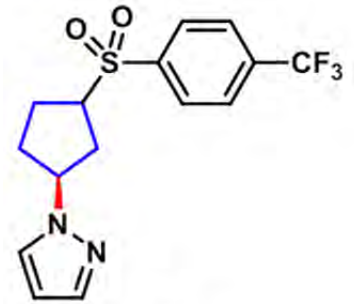

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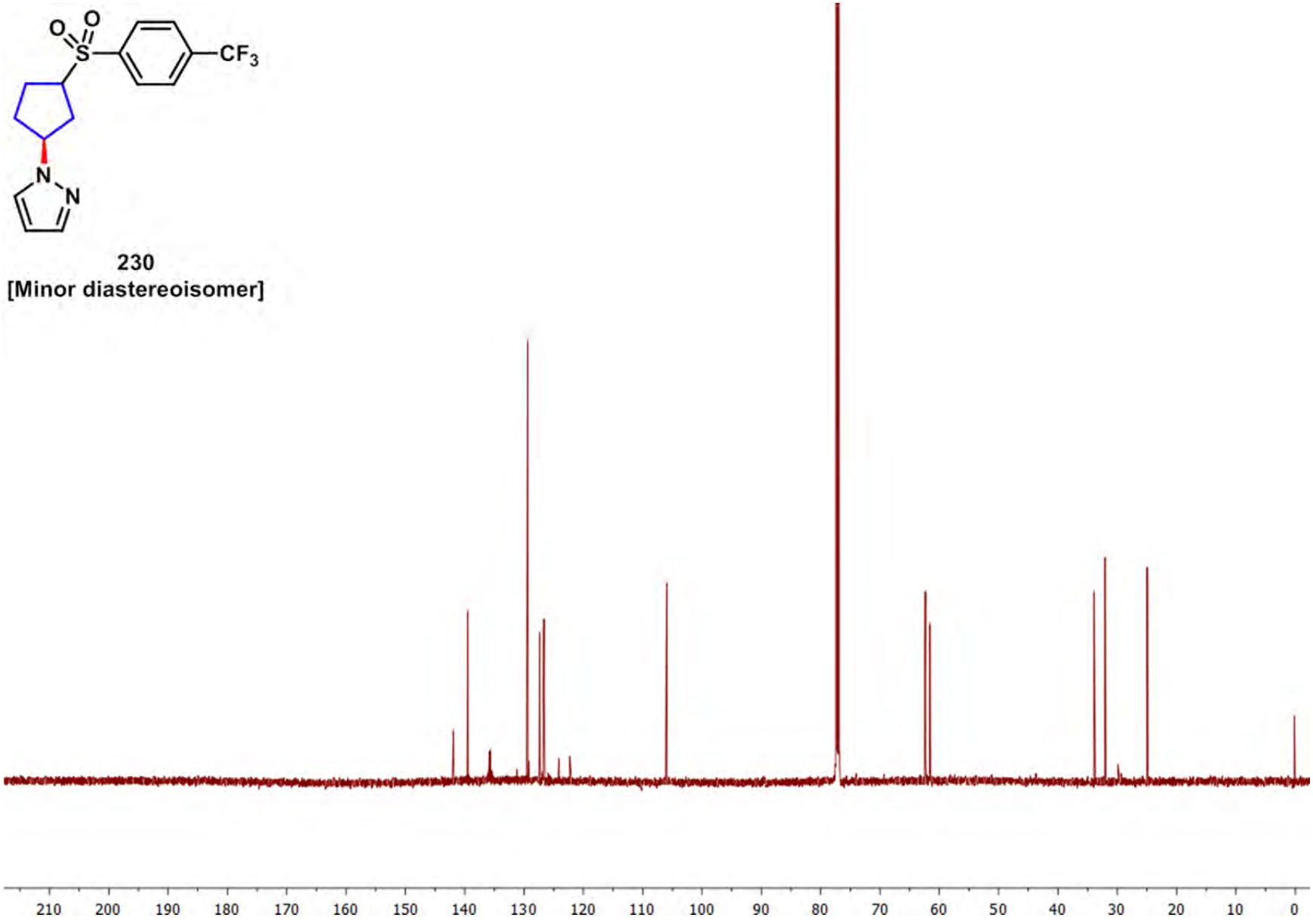
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[Minor diastereoisomer]
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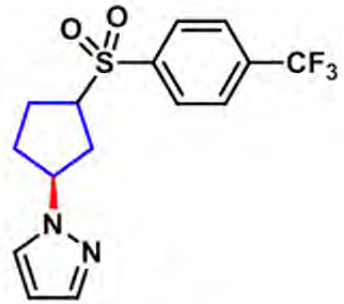

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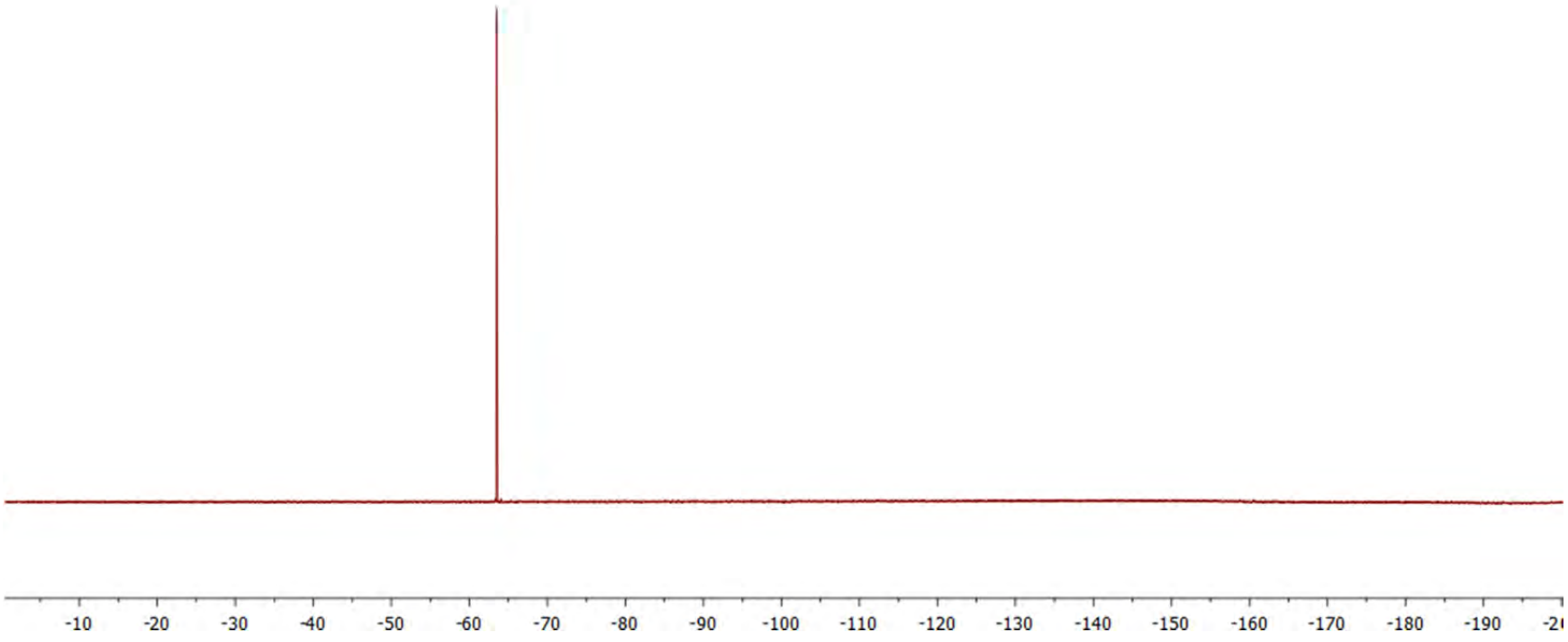


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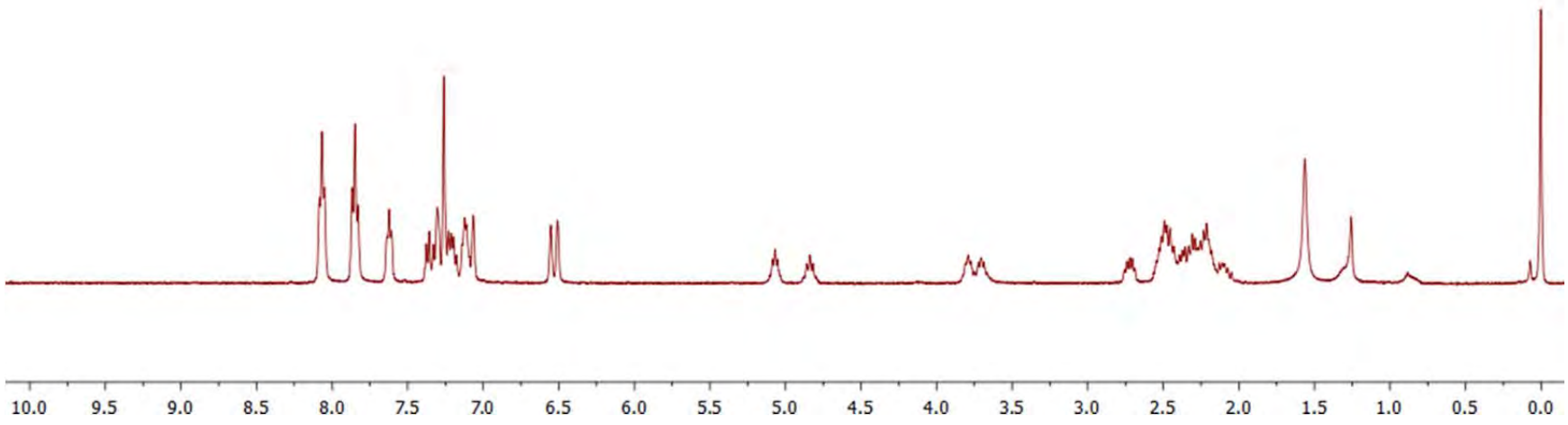
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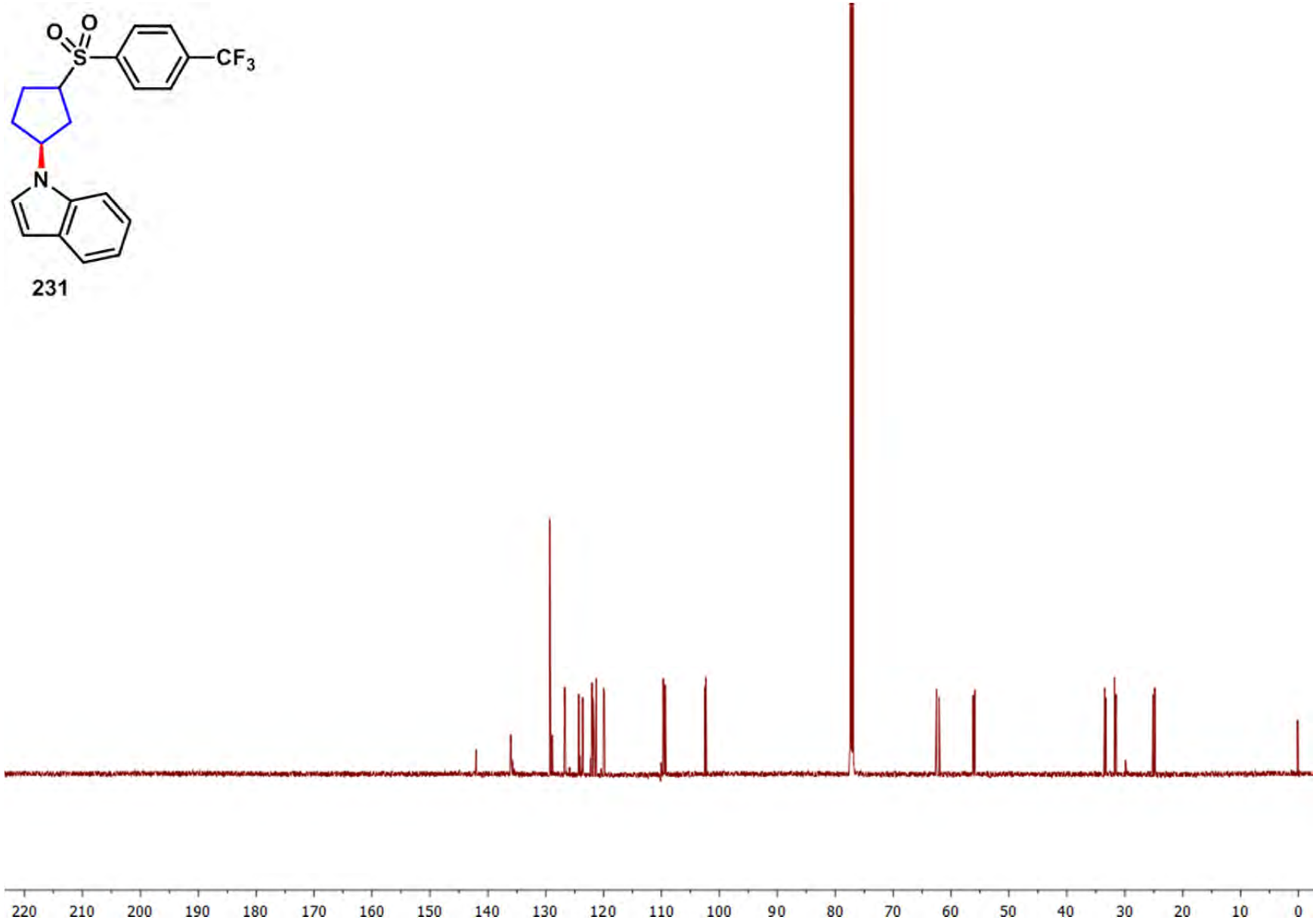
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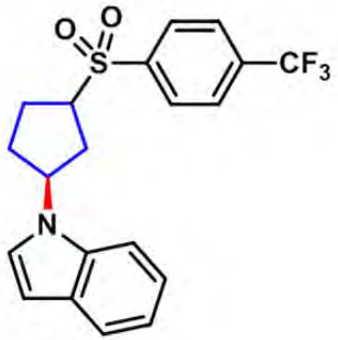
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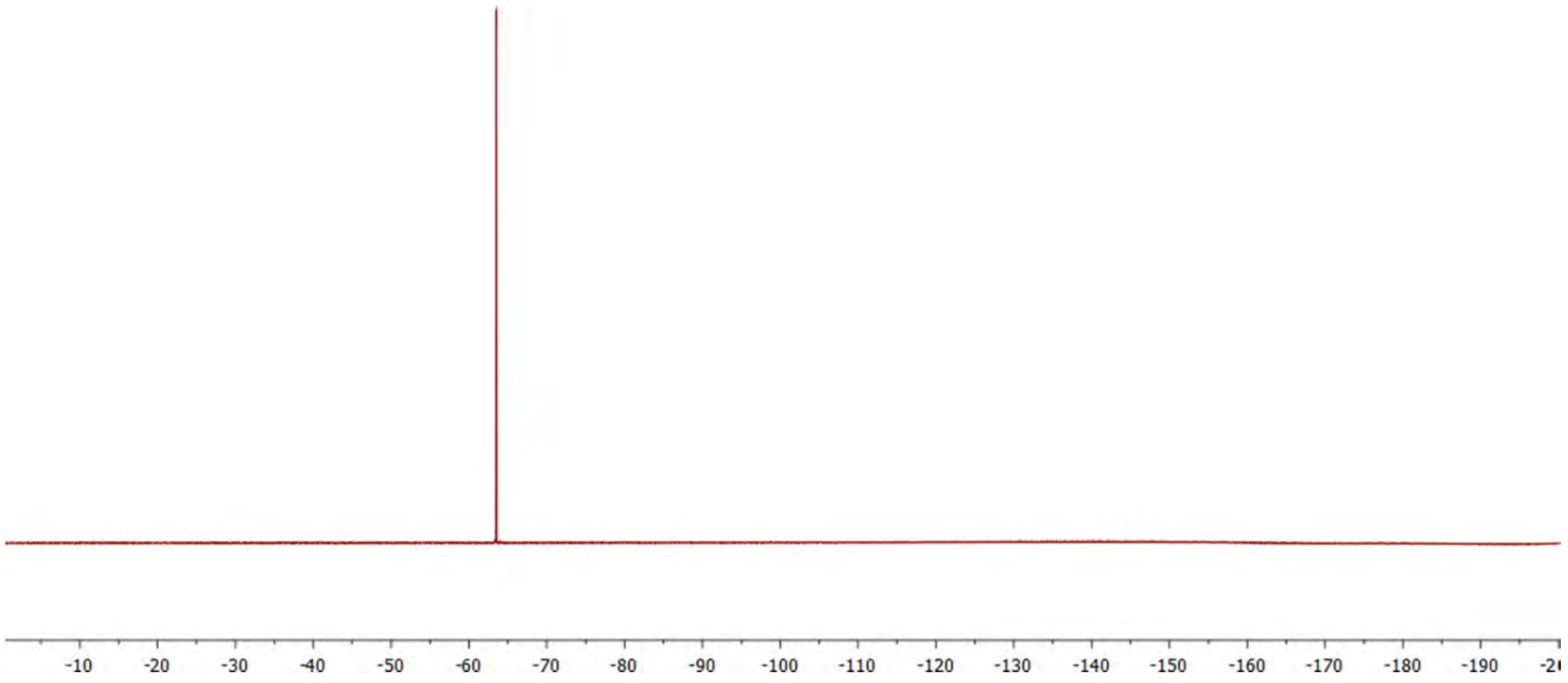
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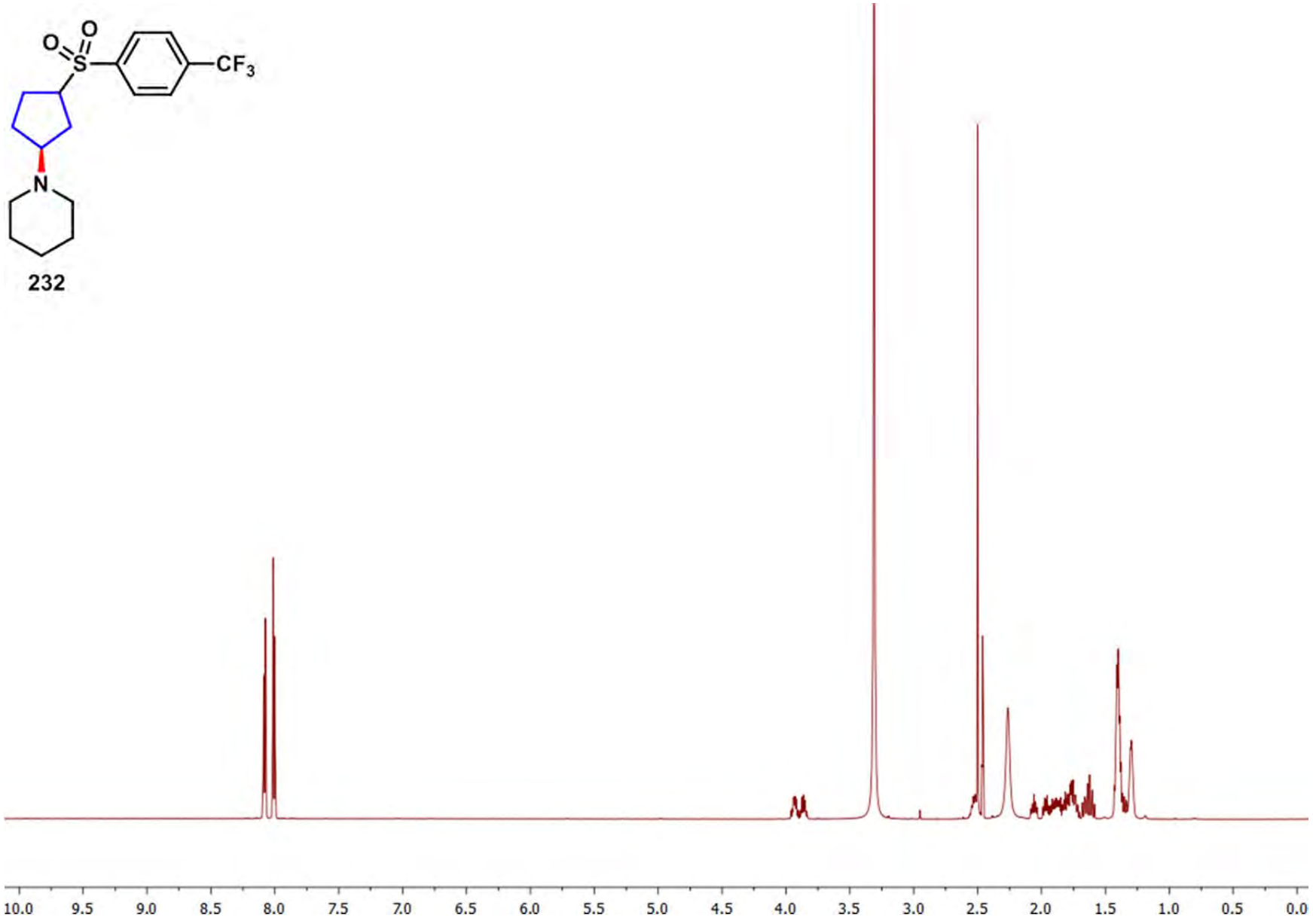
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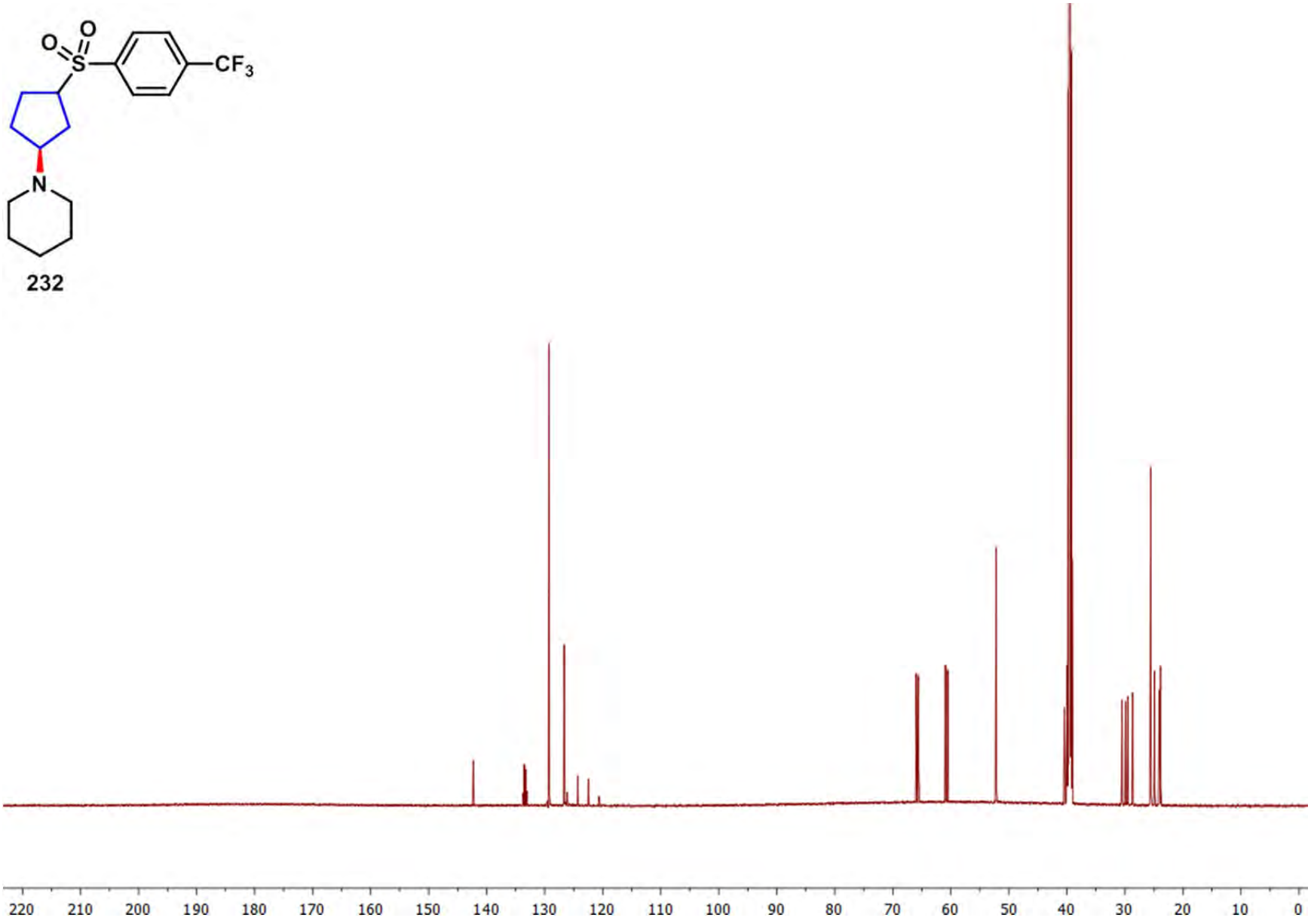
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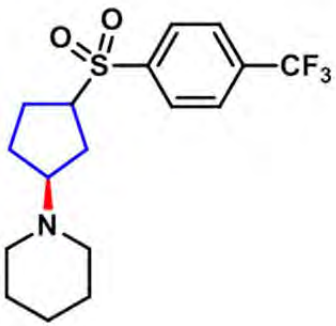
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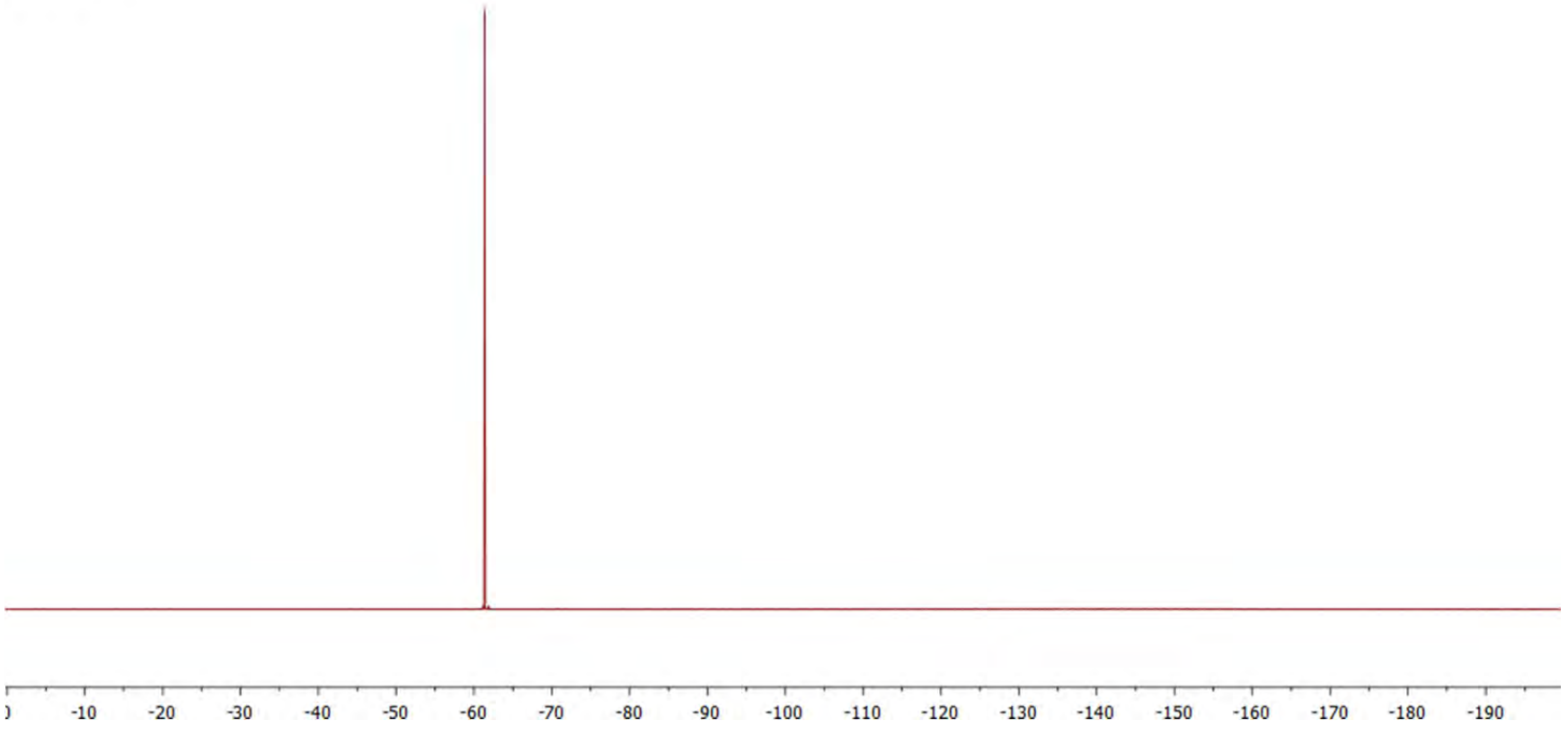
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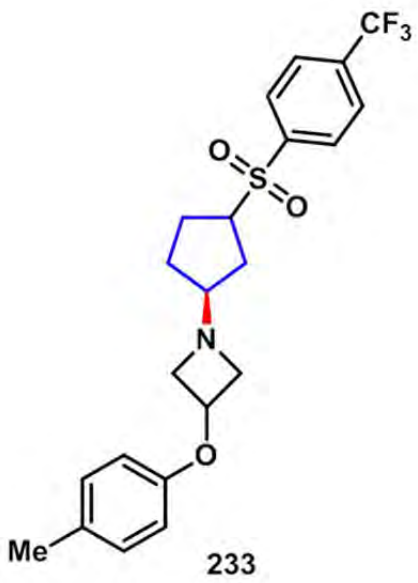
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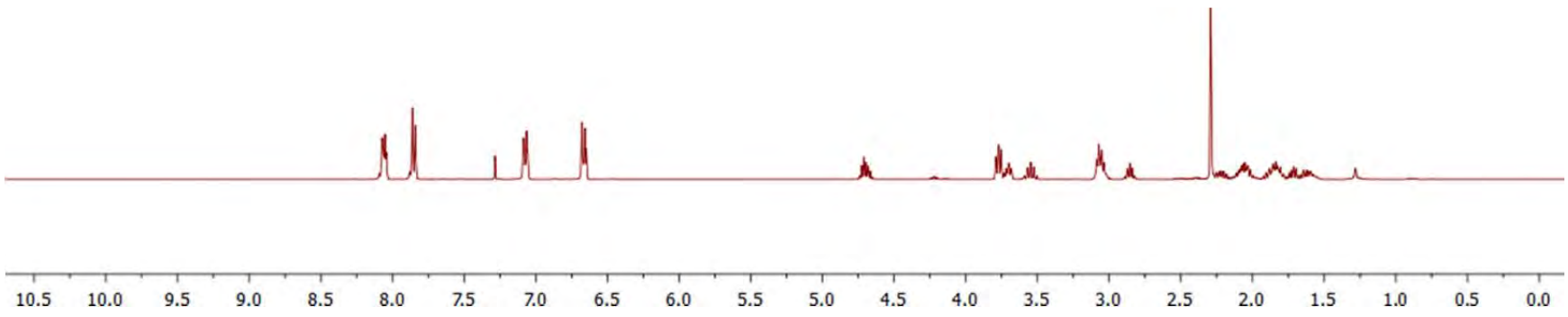
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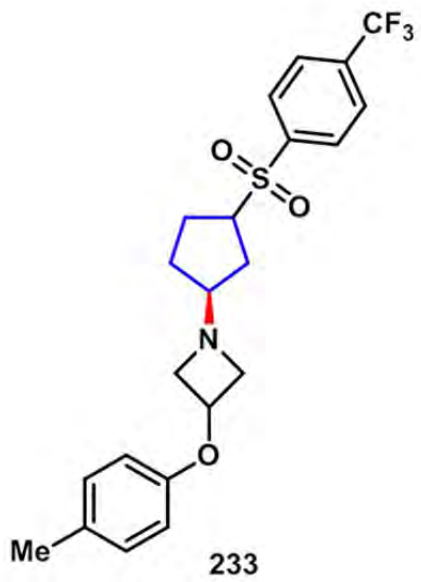
CF3
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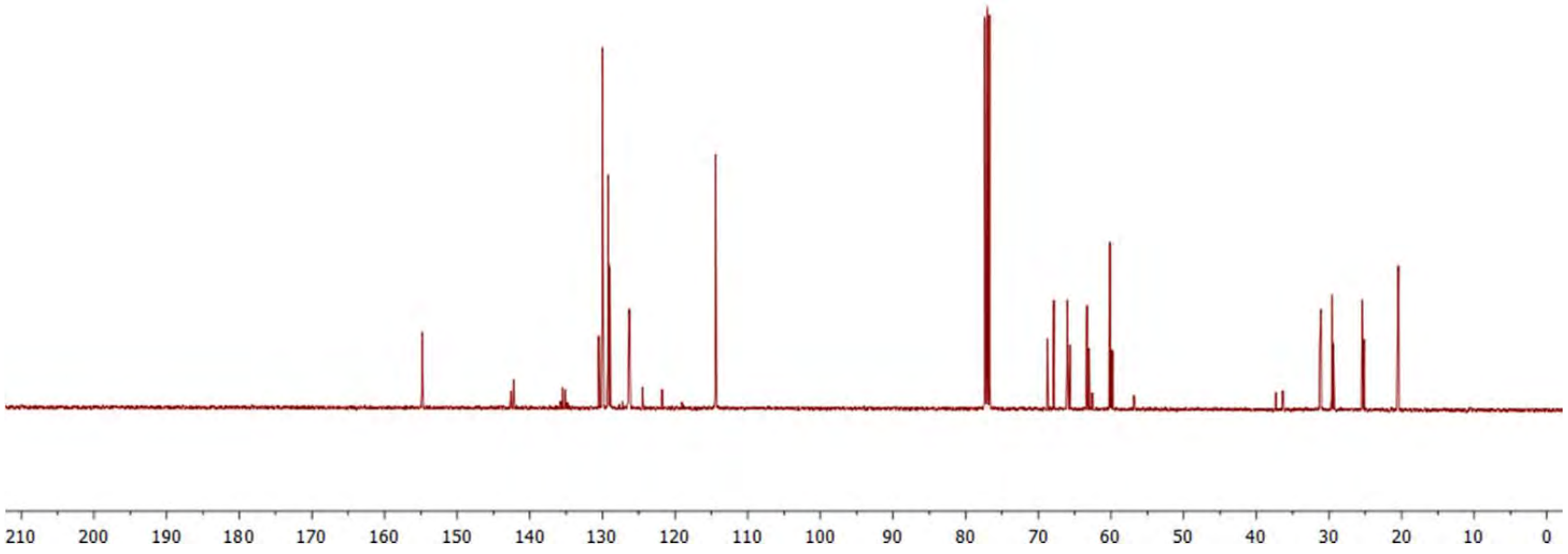
233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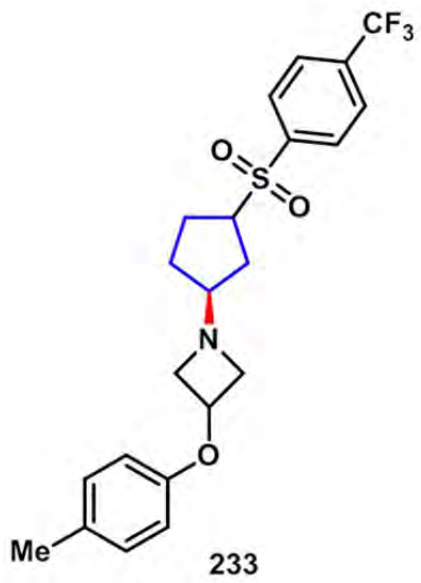
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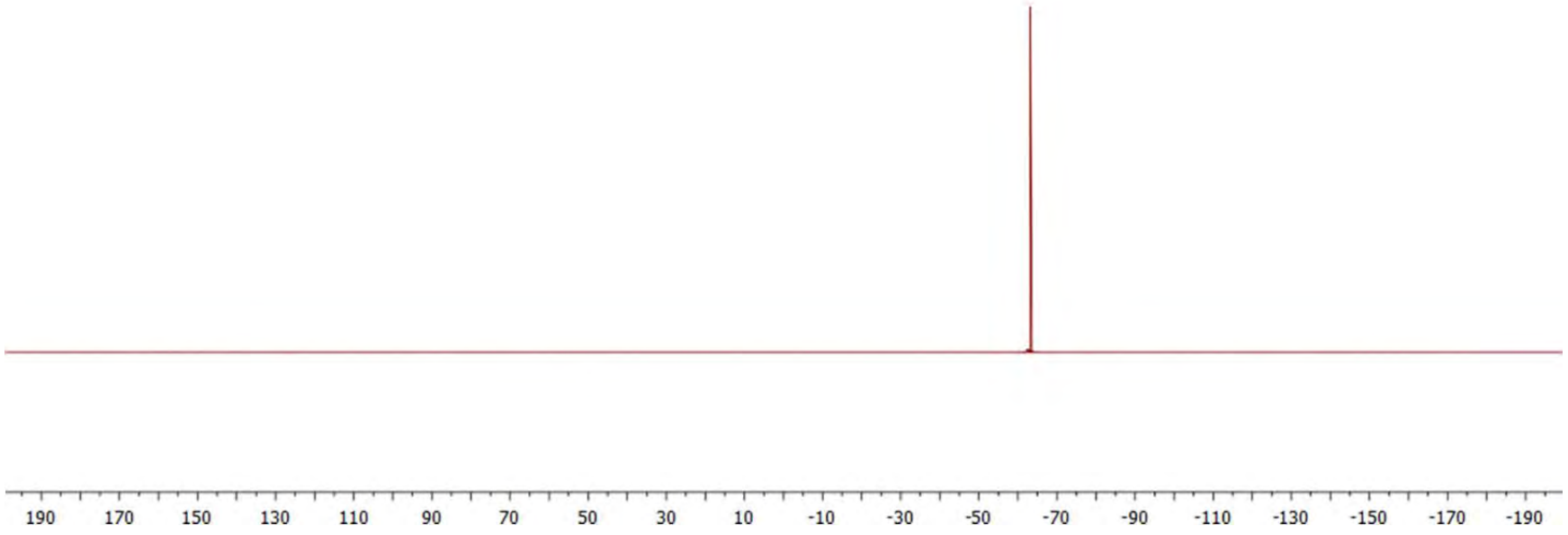
233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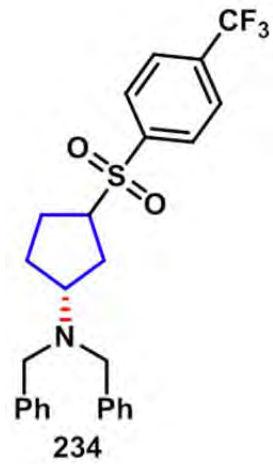
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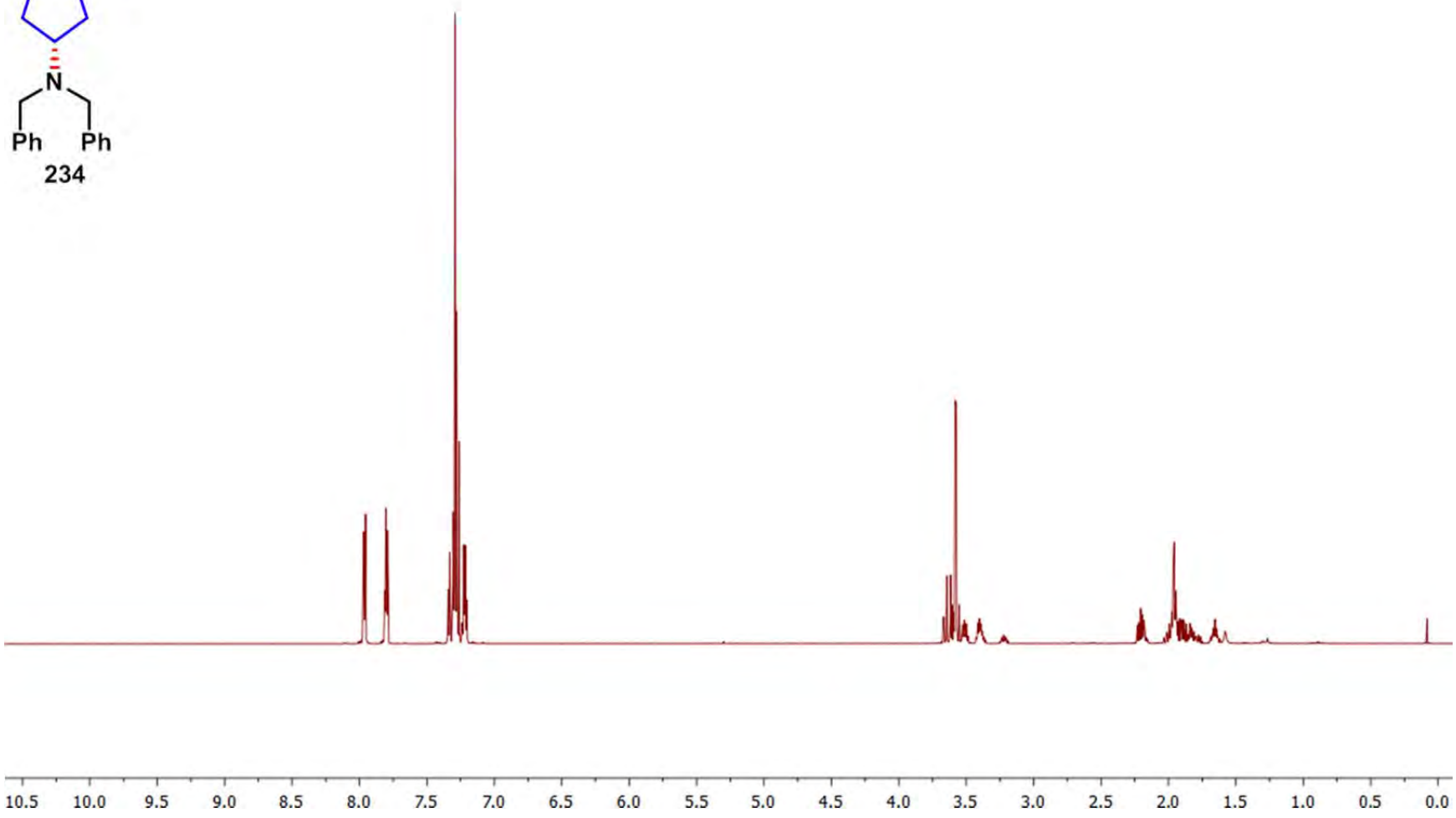
234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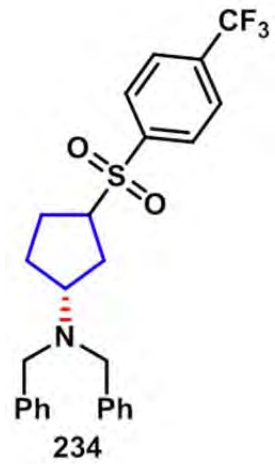
CF3
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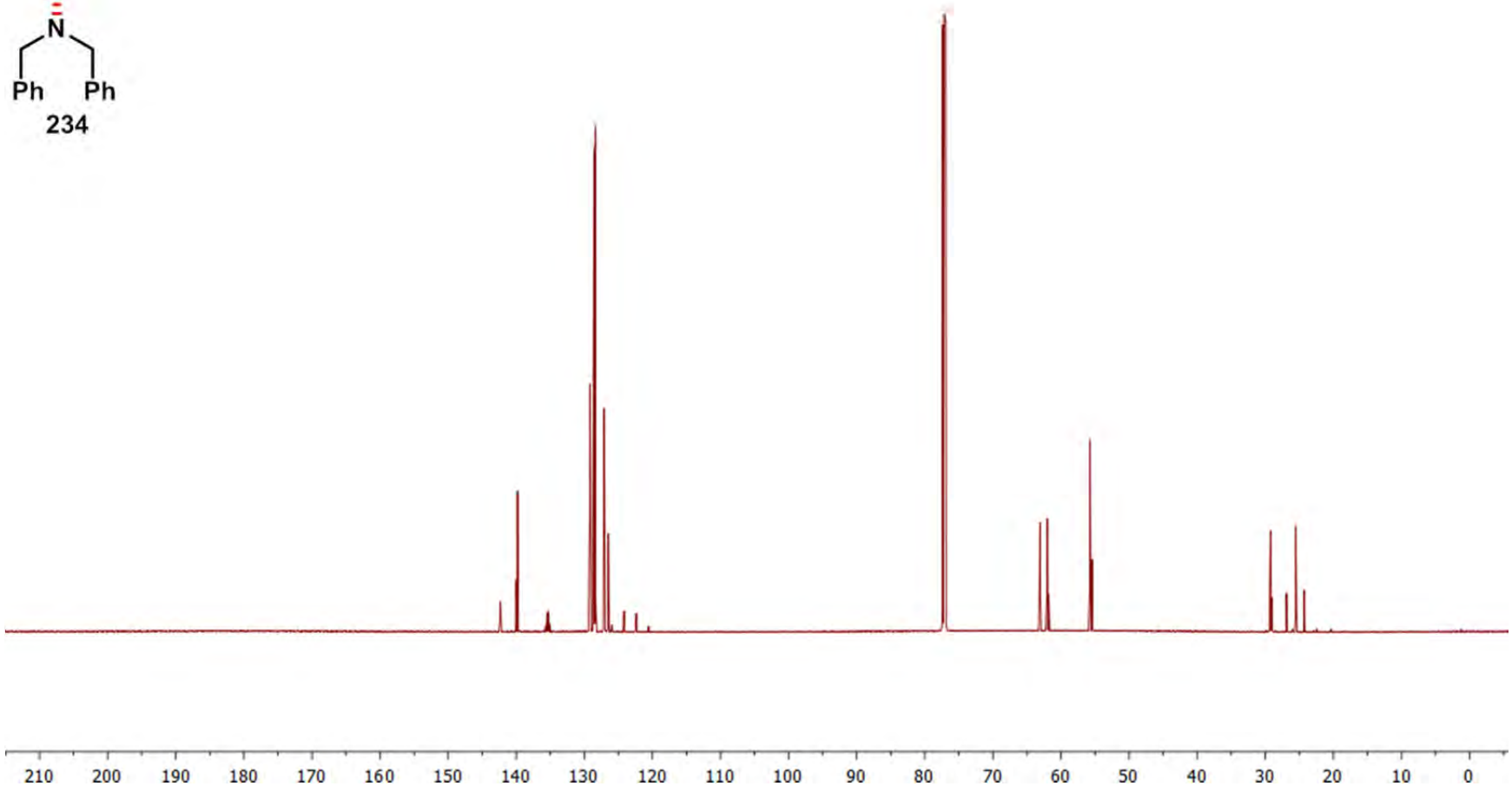
N
Ph
Ph

234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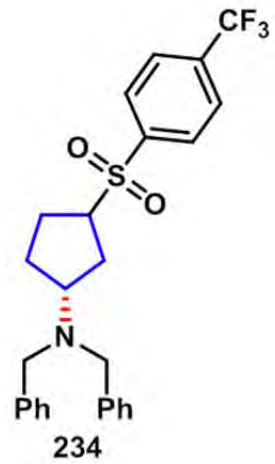
CF3
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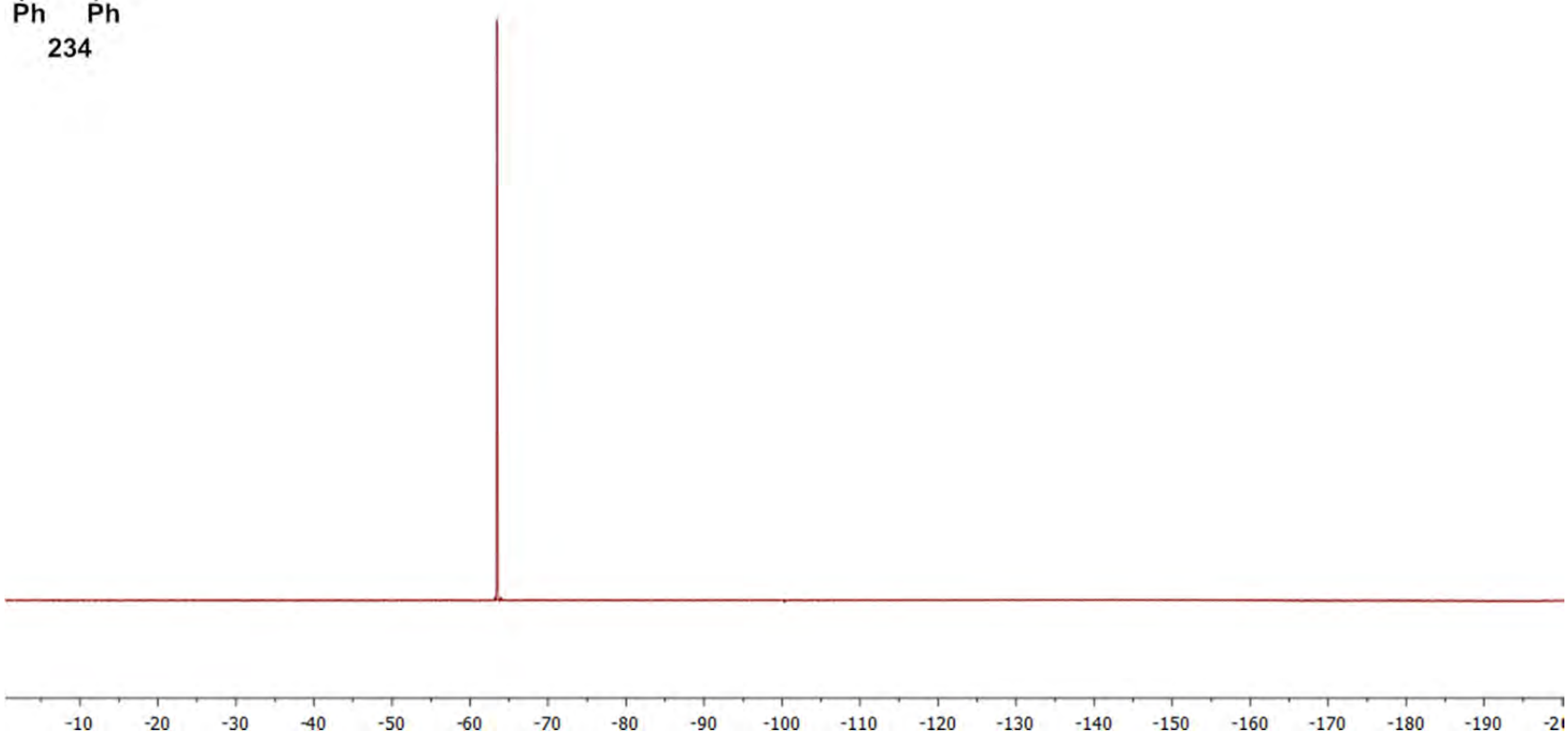
234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Ph
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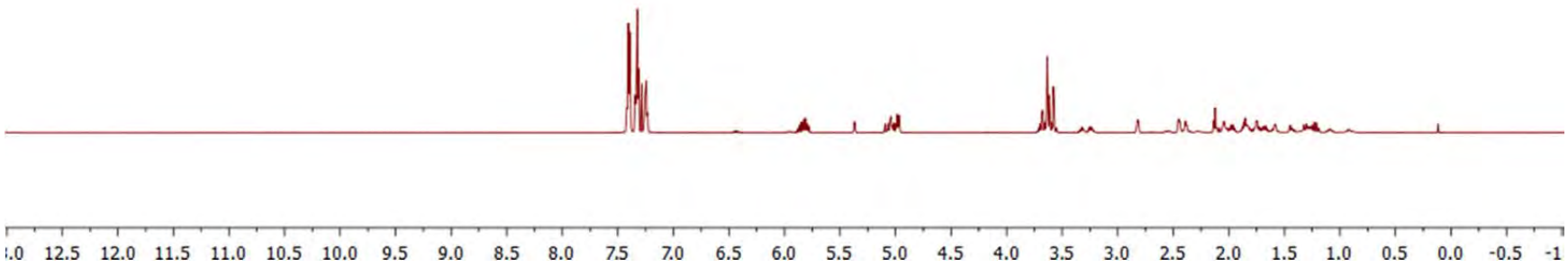
Ph

236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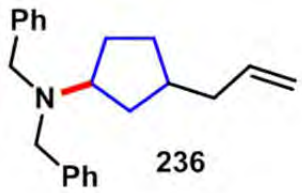
Ph
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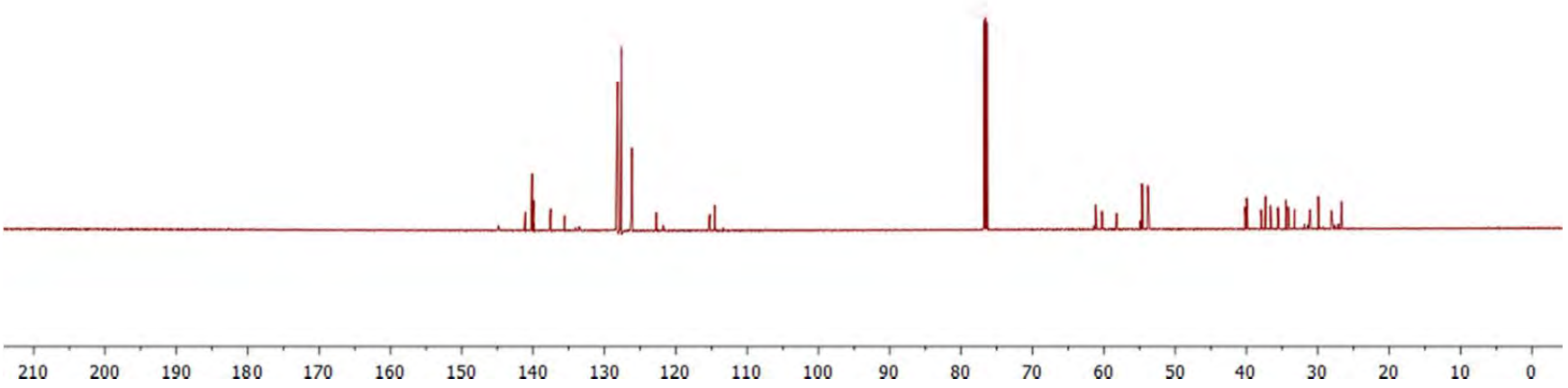
Ph

236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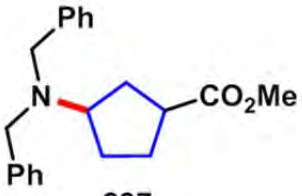
Ph
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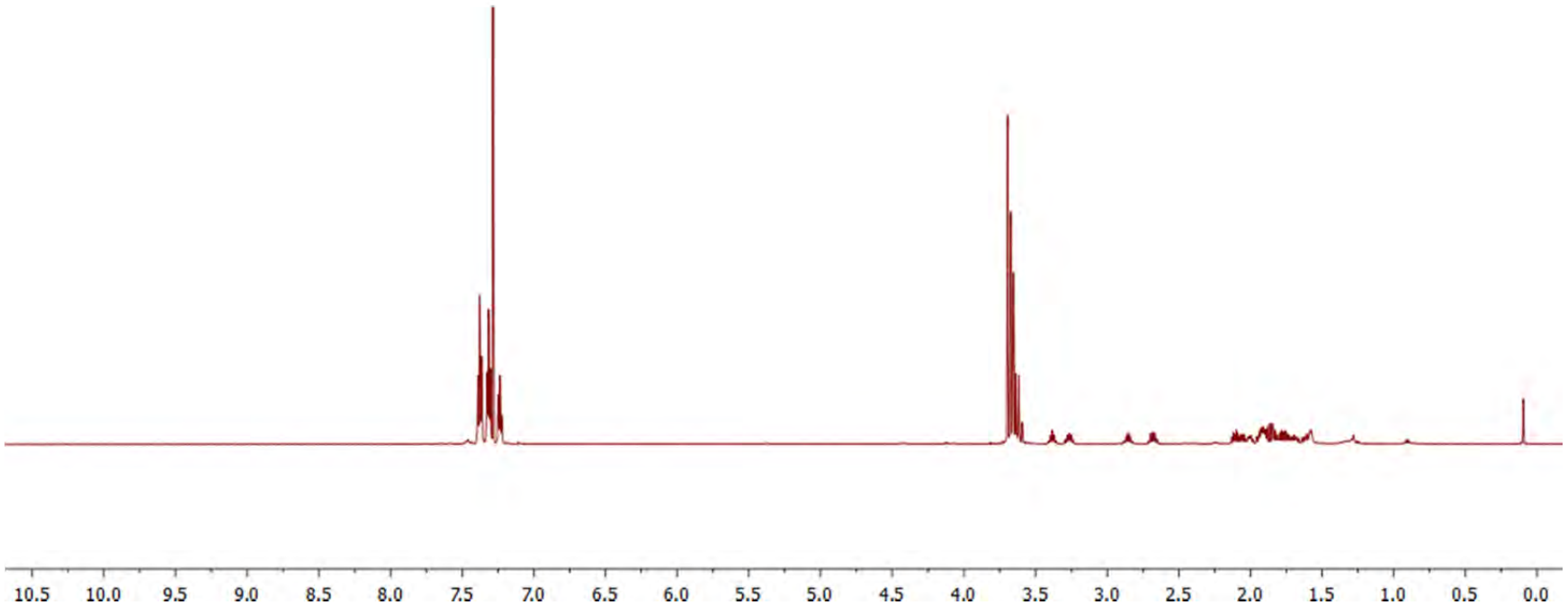
CO2Me
Ph

237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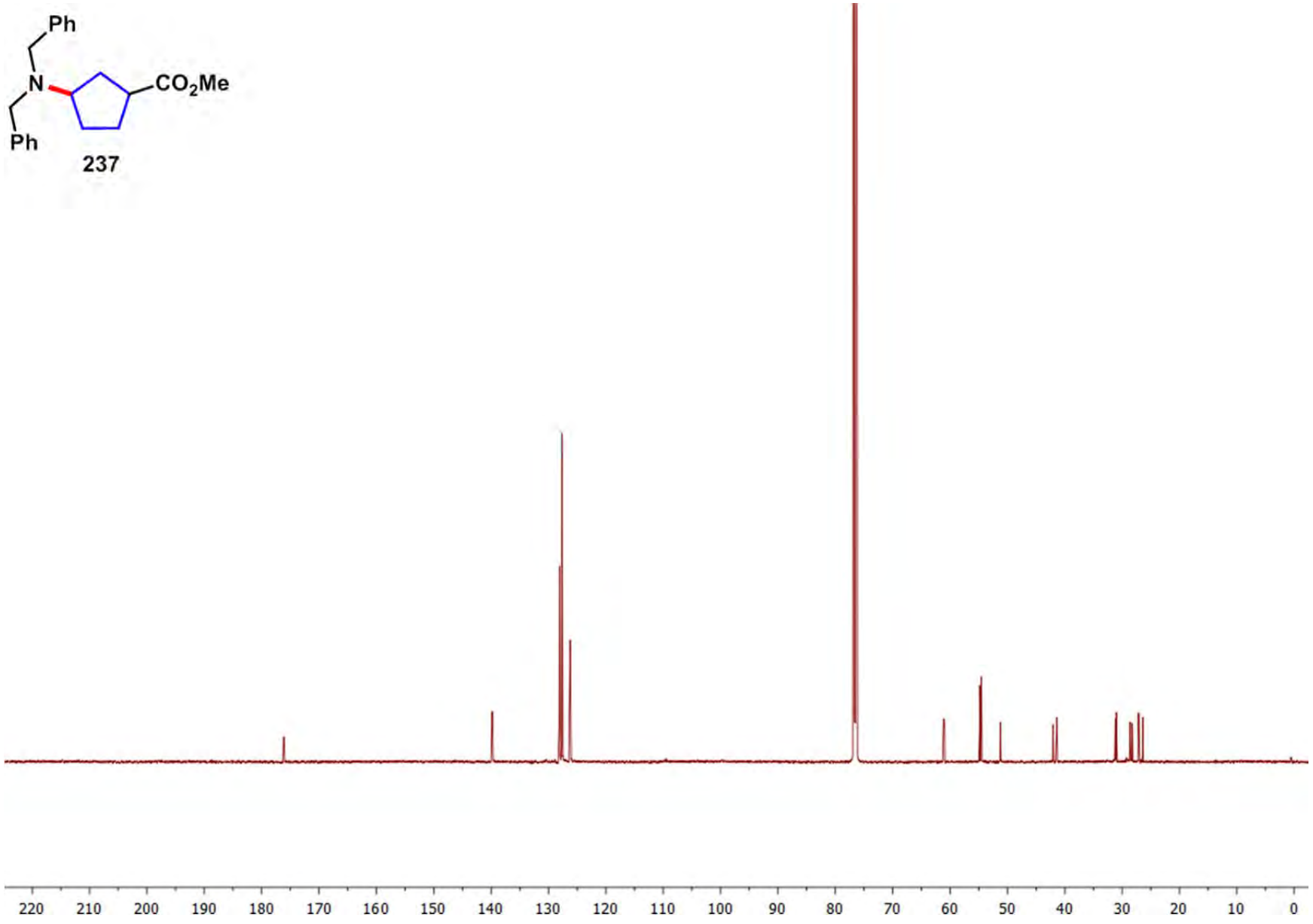
Ph
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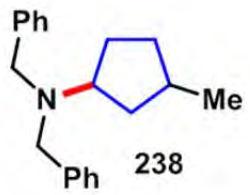
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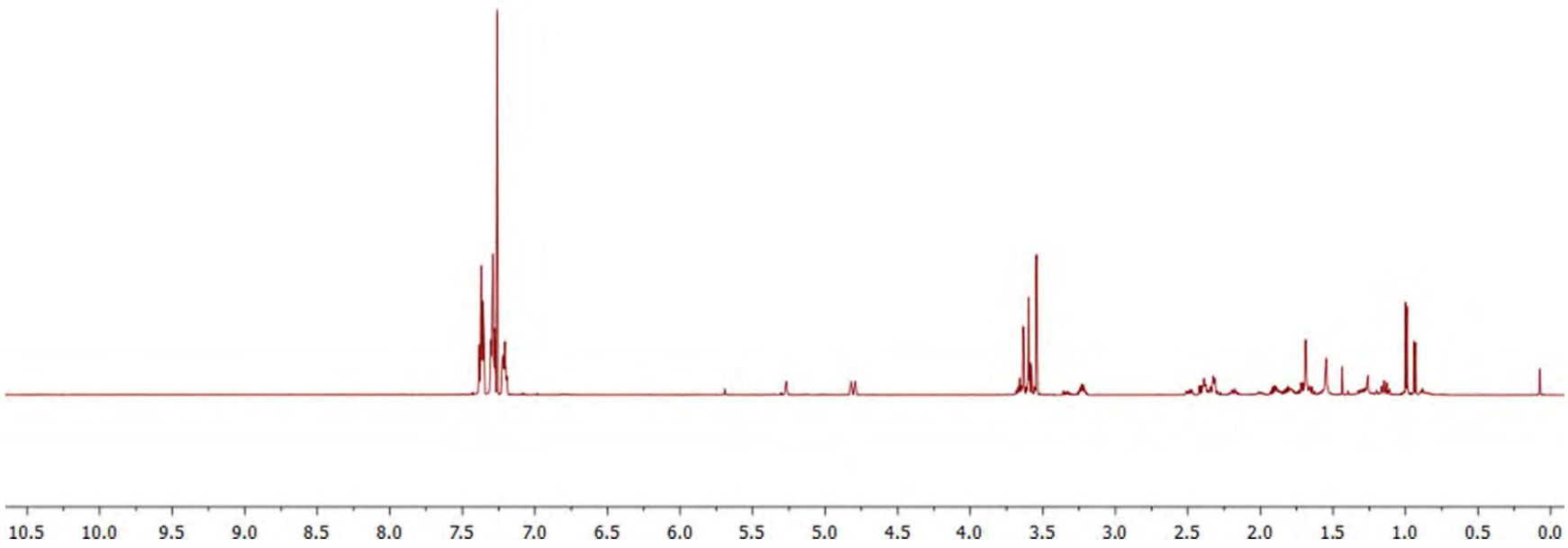
Me
Ph

238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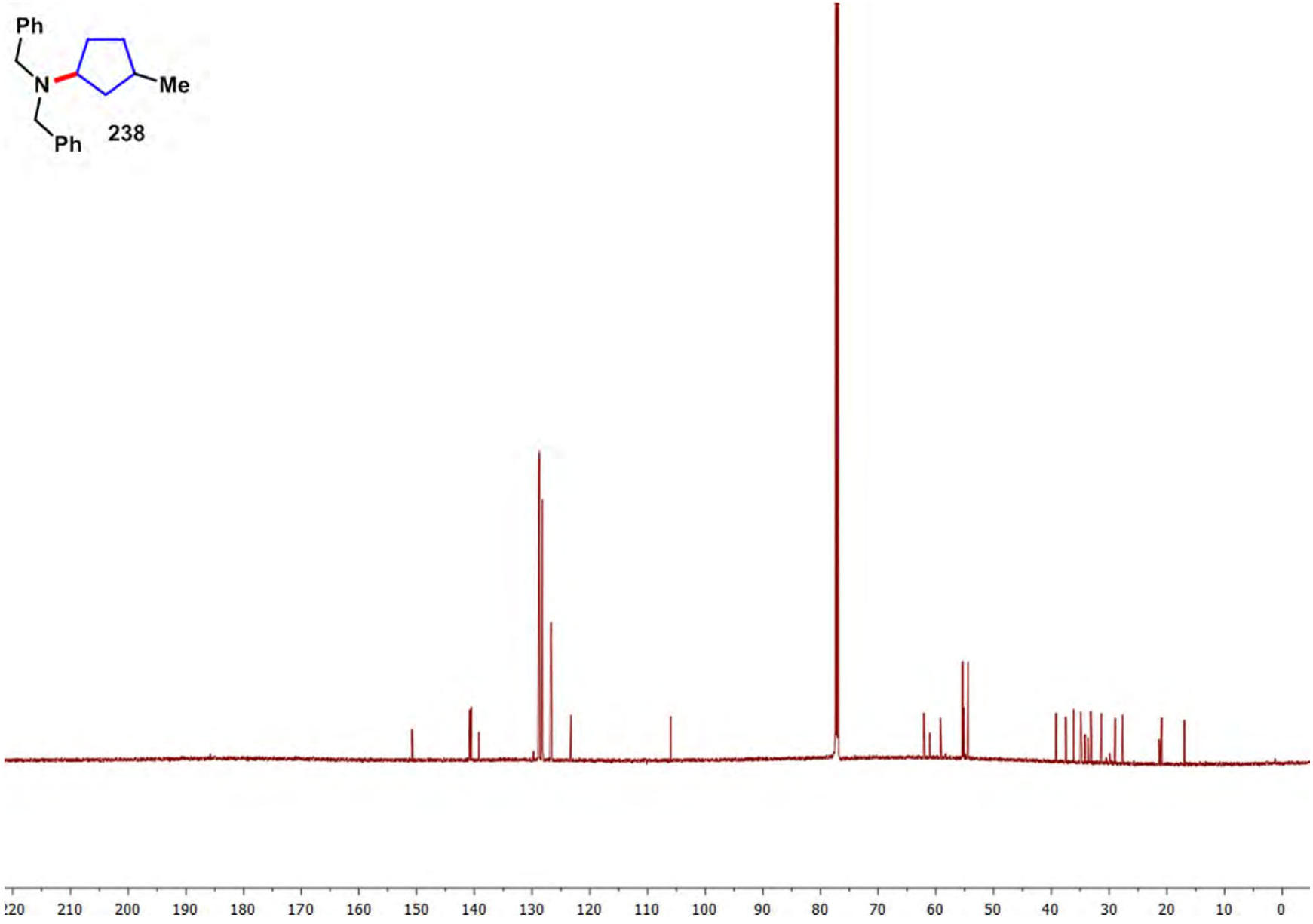
Ph
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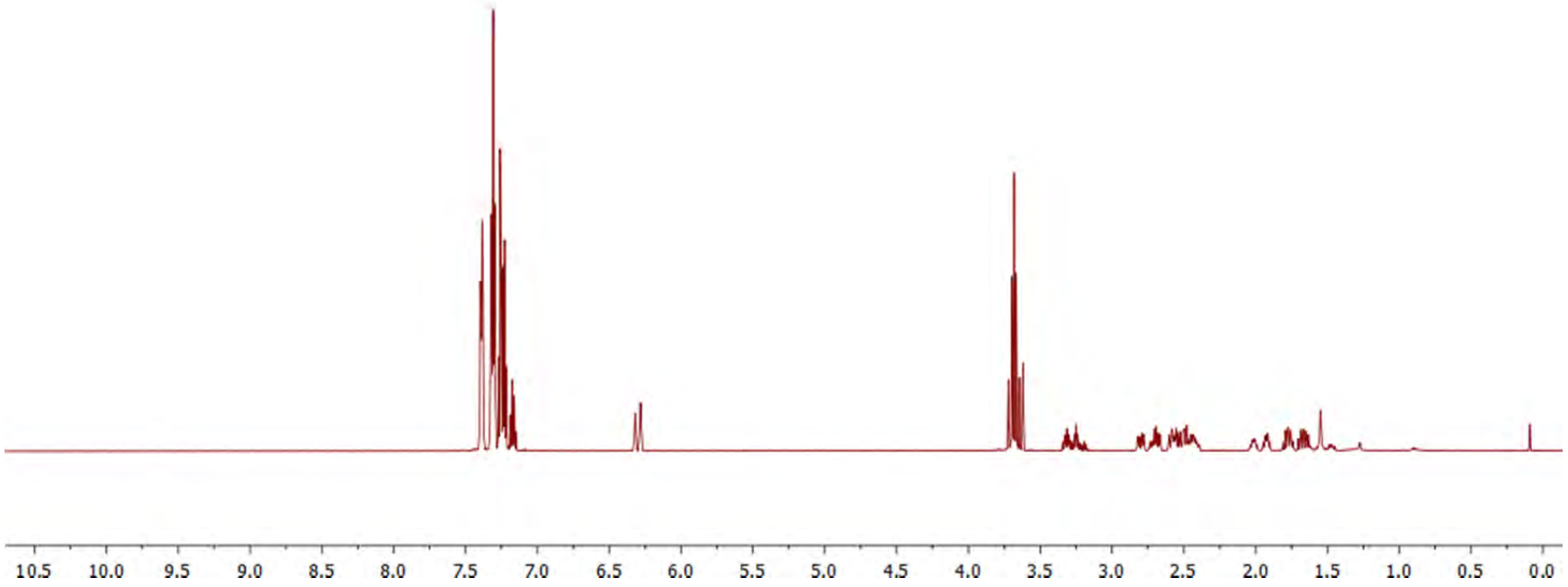
239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1.5
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Ph
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239

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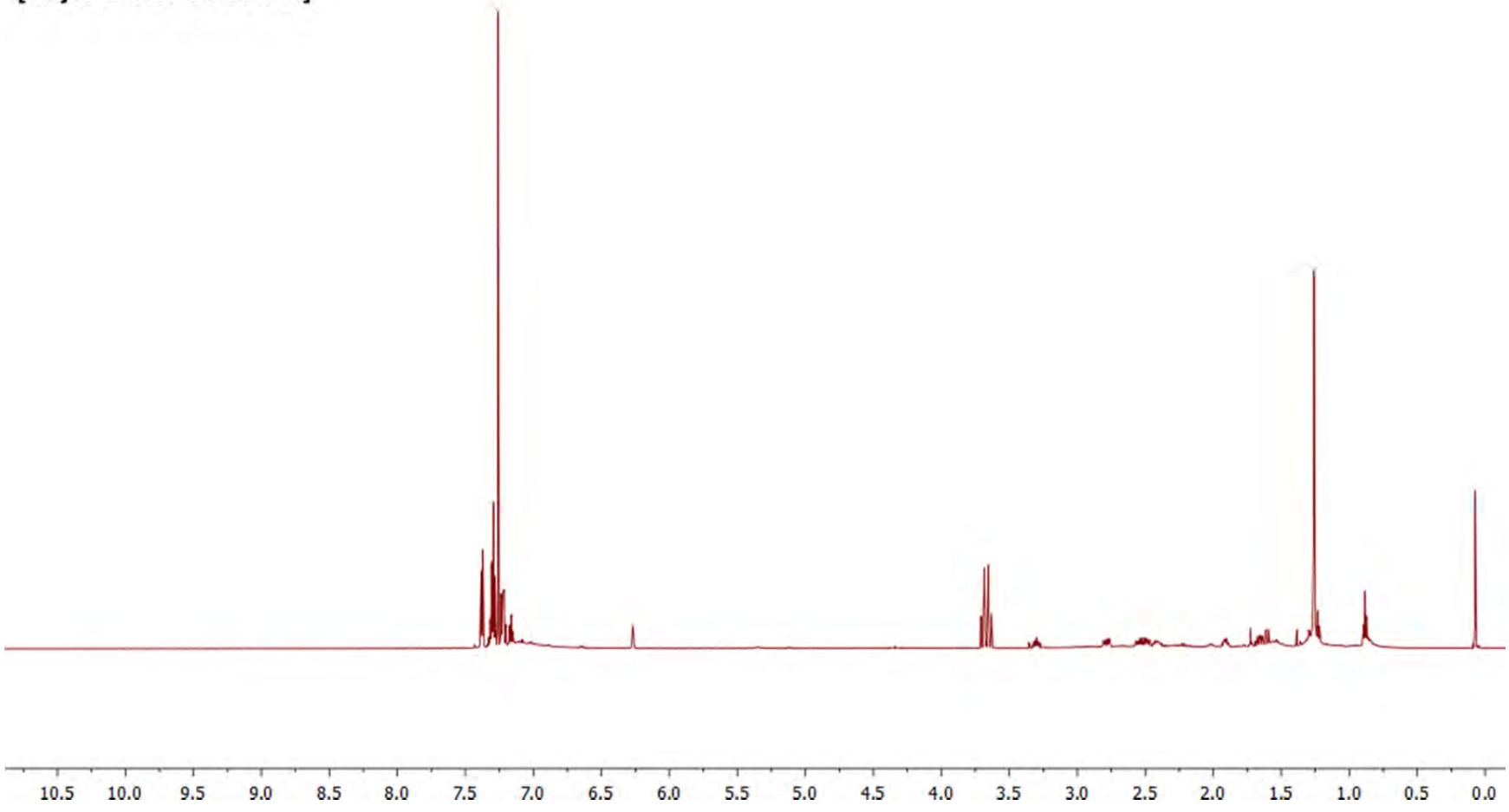
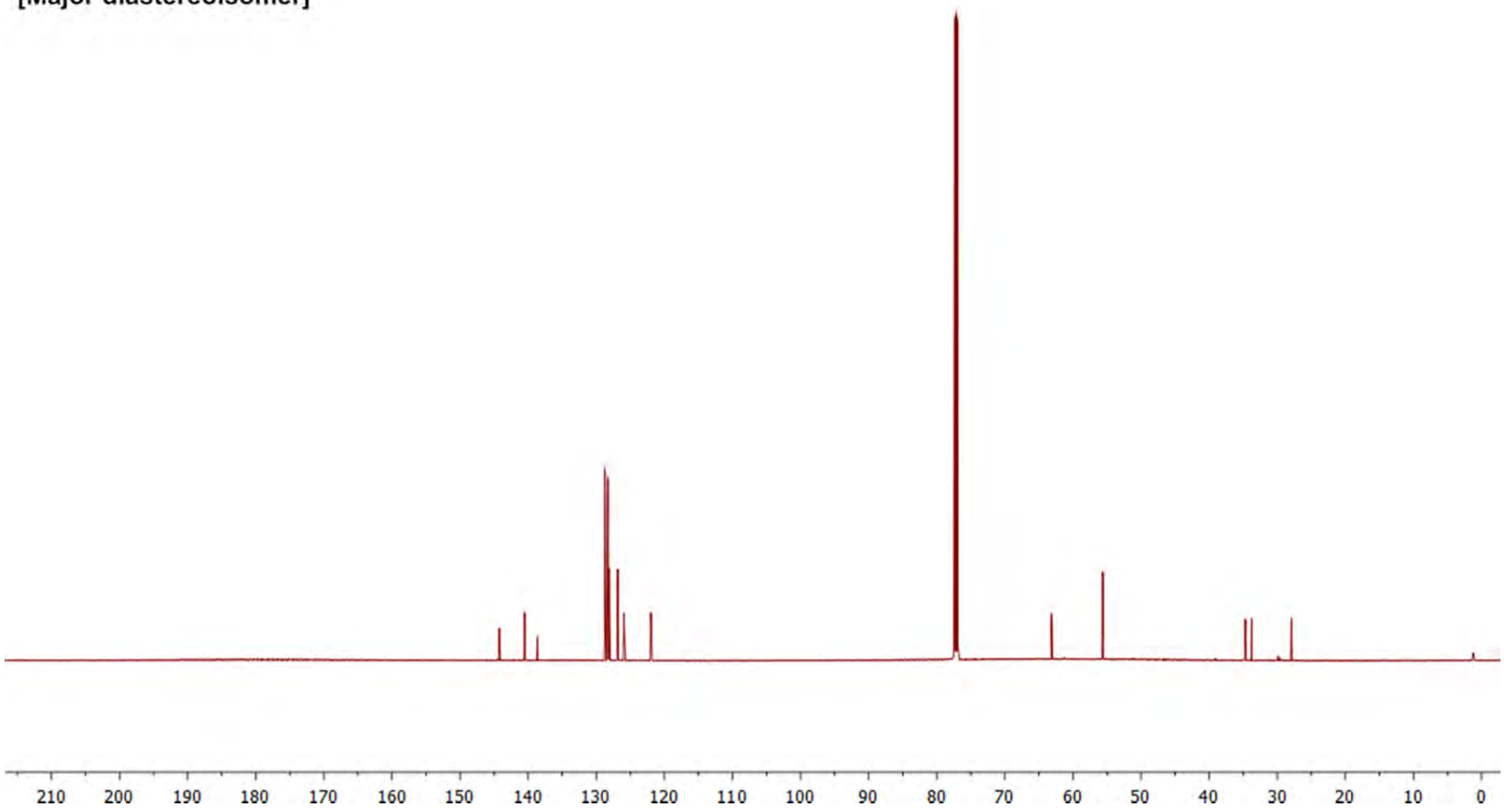
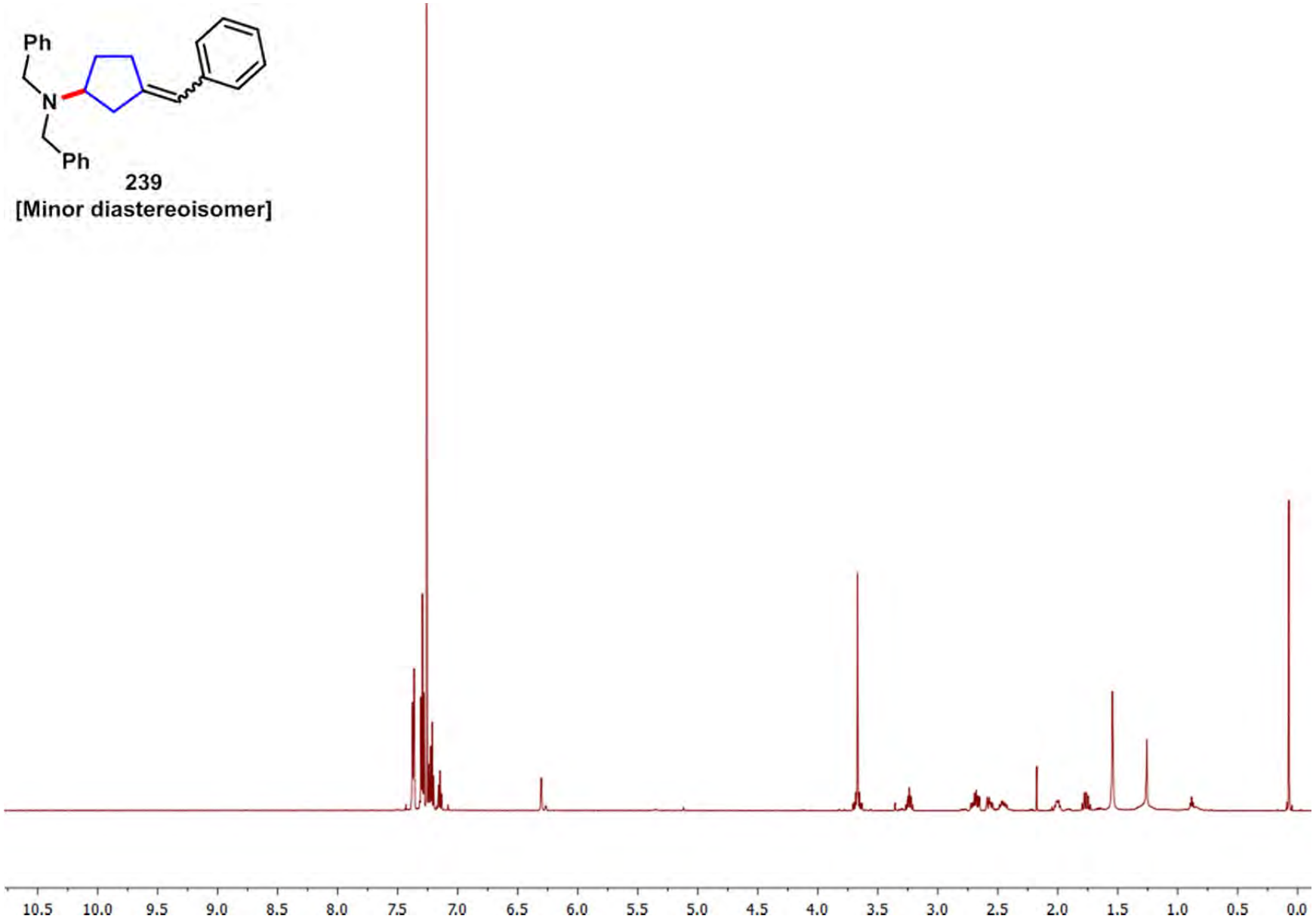
239
[Major diastereoisomer]



239
[Major diastereoisomer]




Ph
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239
[Minor diastereoisomer]
10.5
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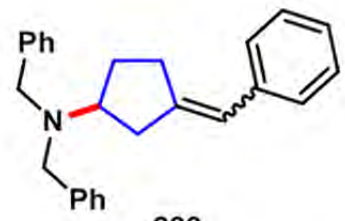
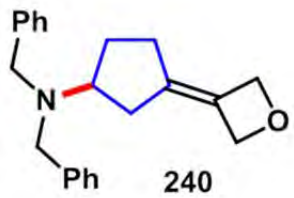


239
[Minor diastereoisomer]



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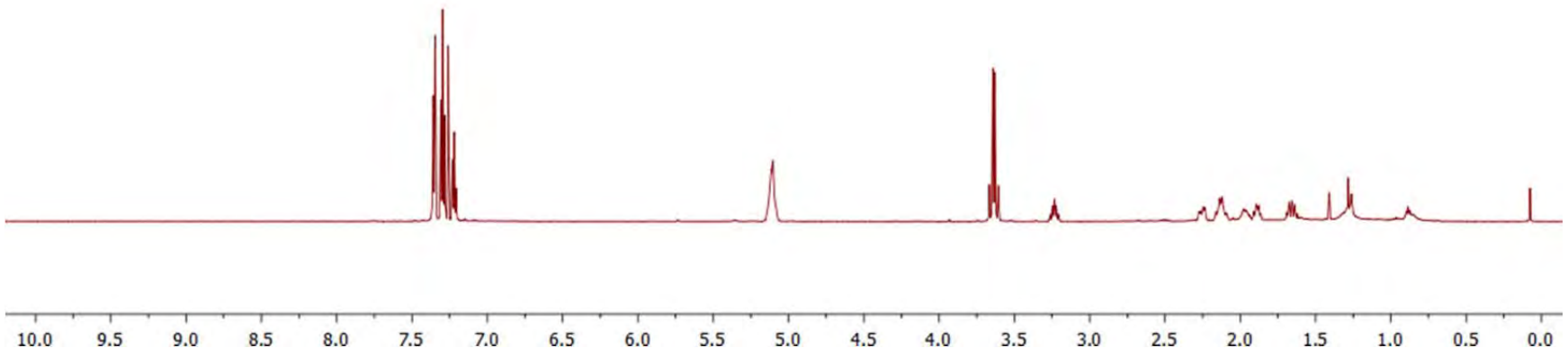


Ph
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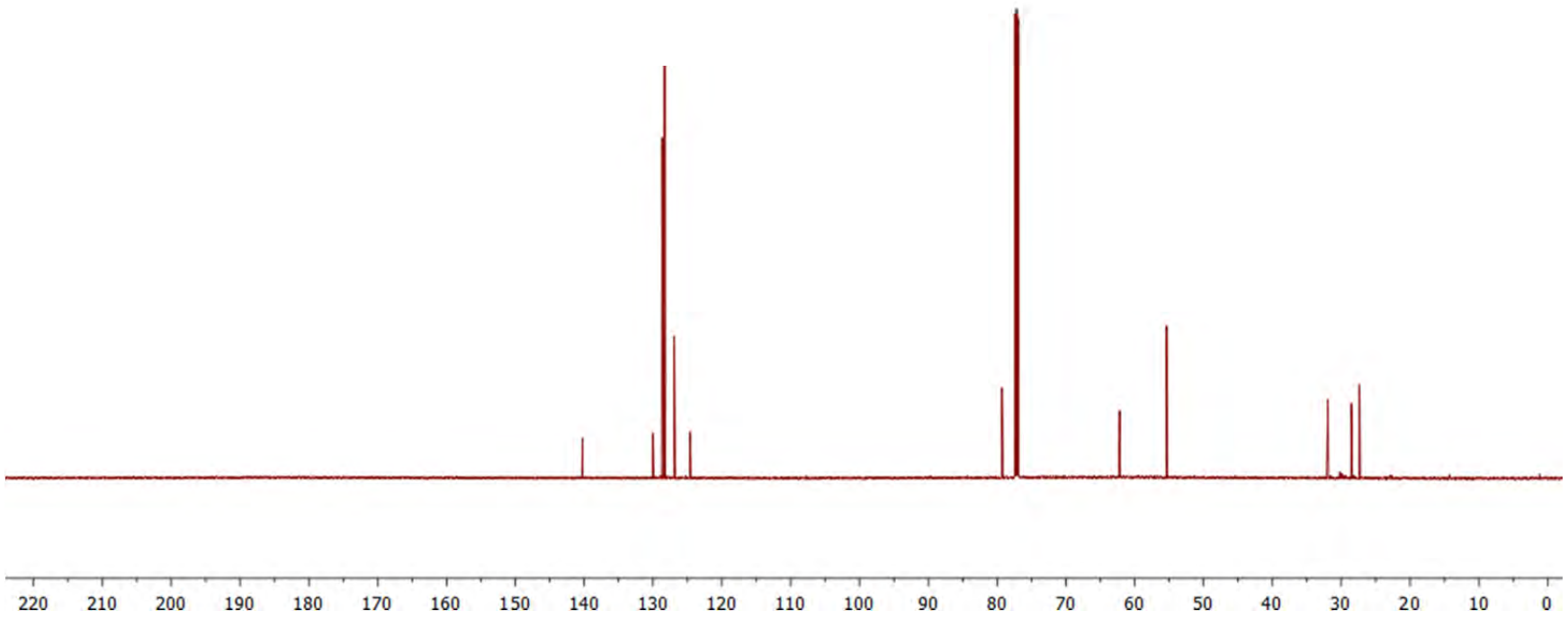
240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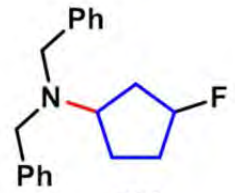

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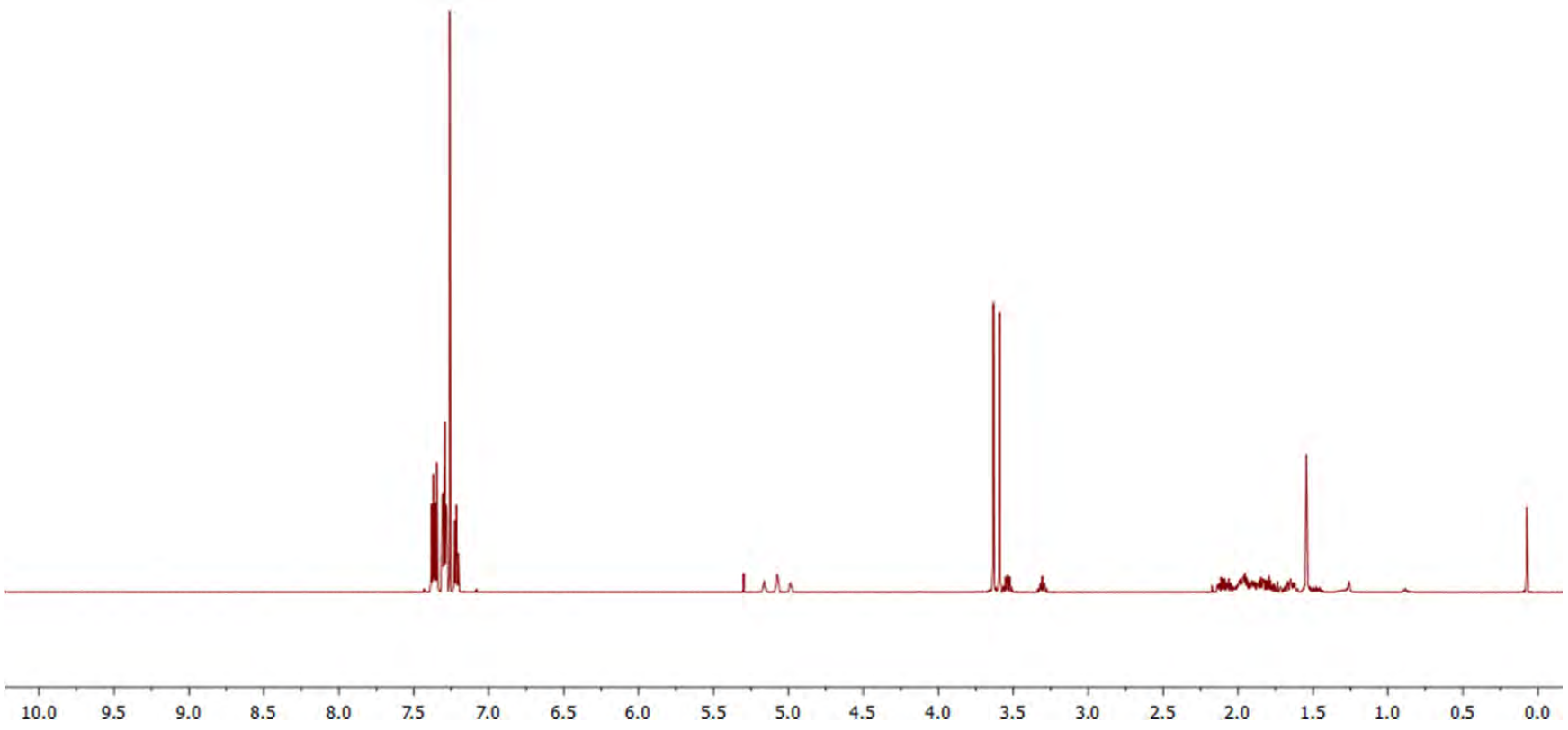

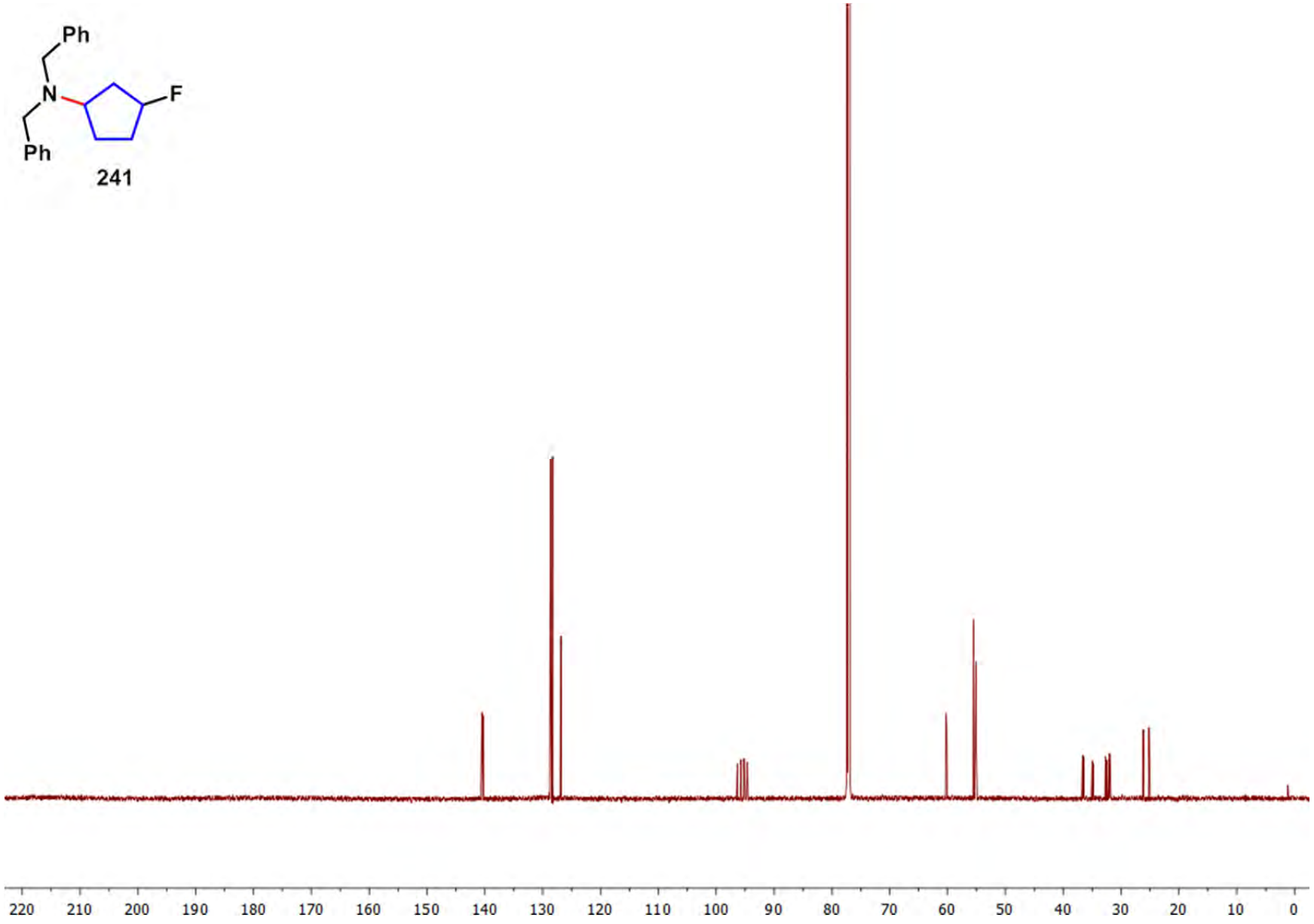
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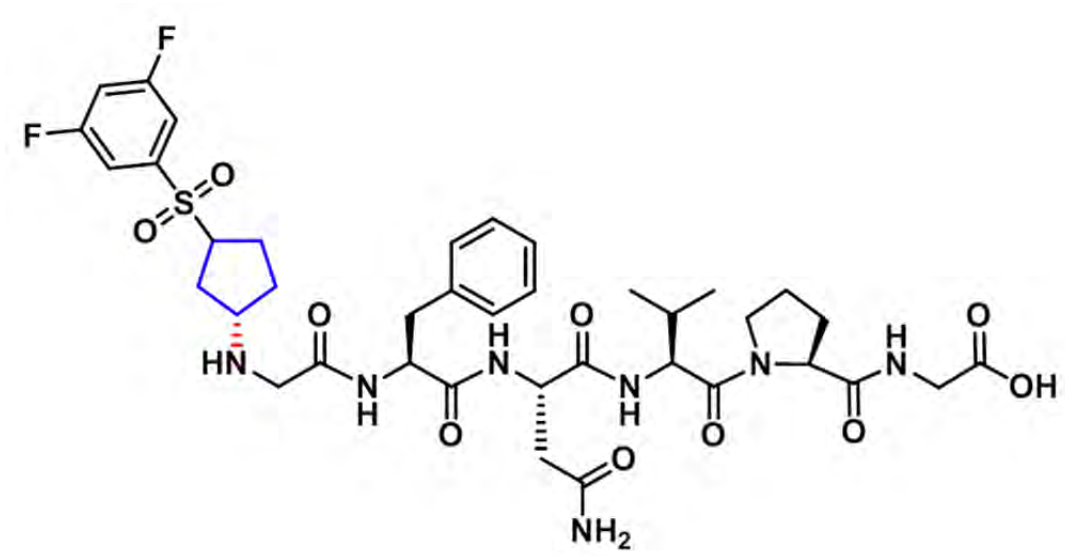
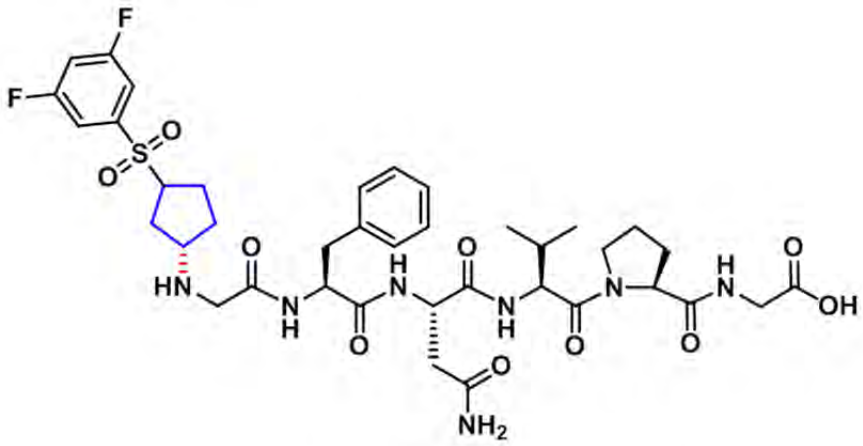
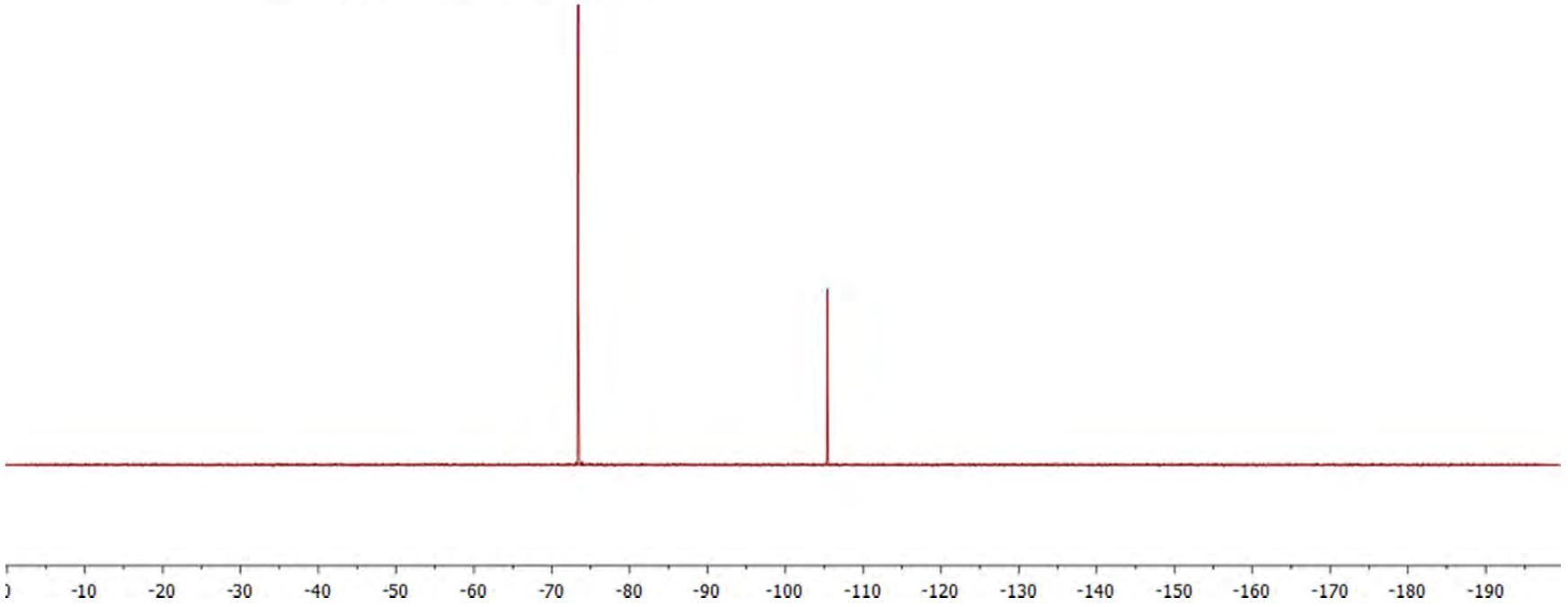
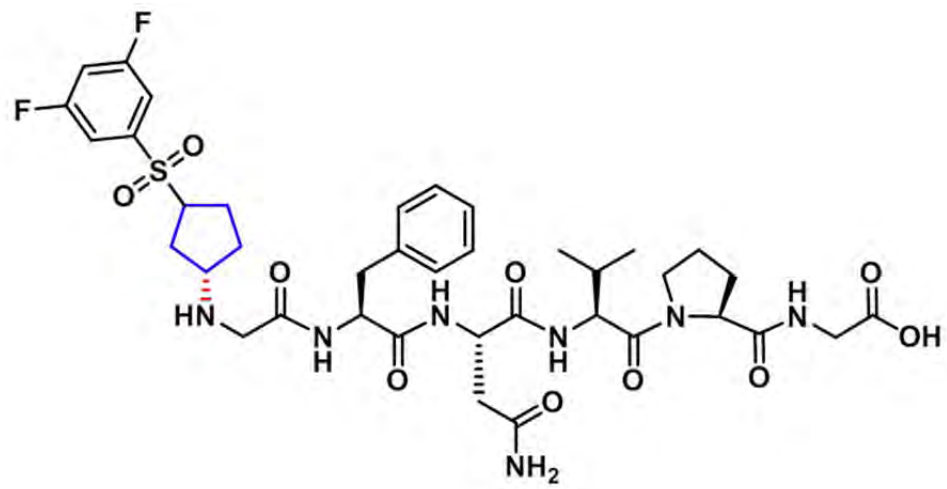


245
[Major diastereoisomer]



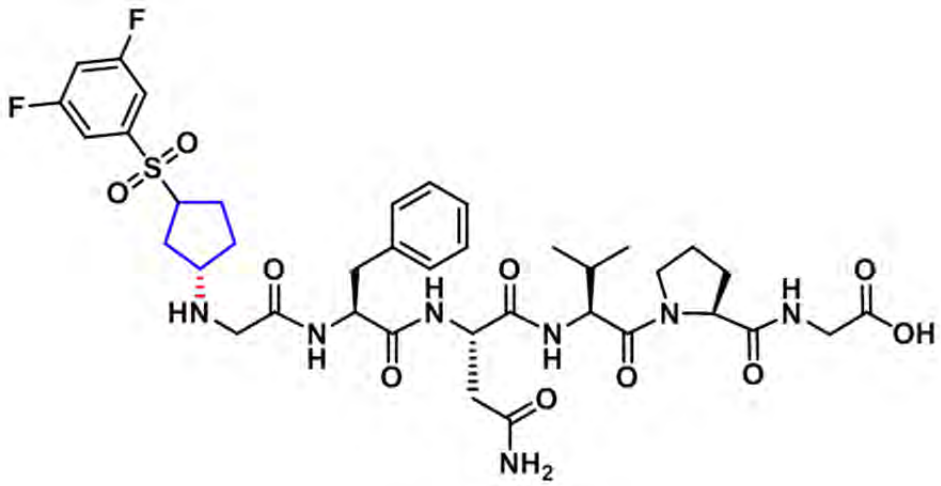
245
[Major diastereoisomer]



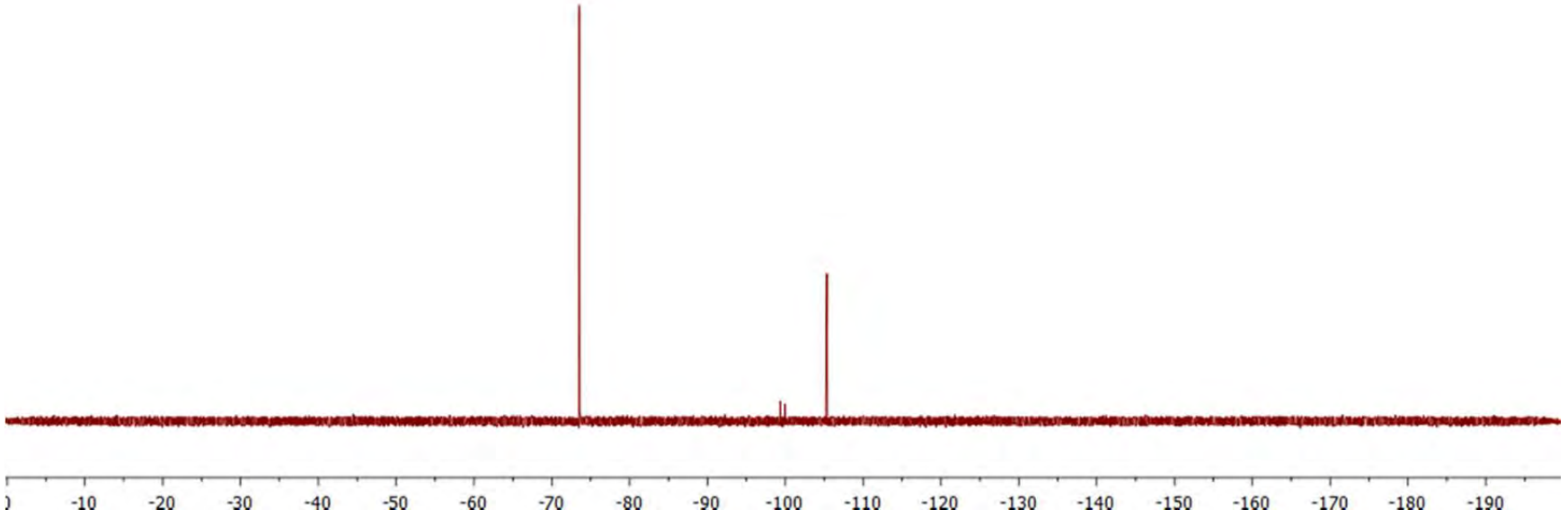


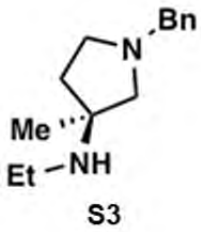
245

[Minor diastereoisomer]



245
[Minor diastereoisomer]





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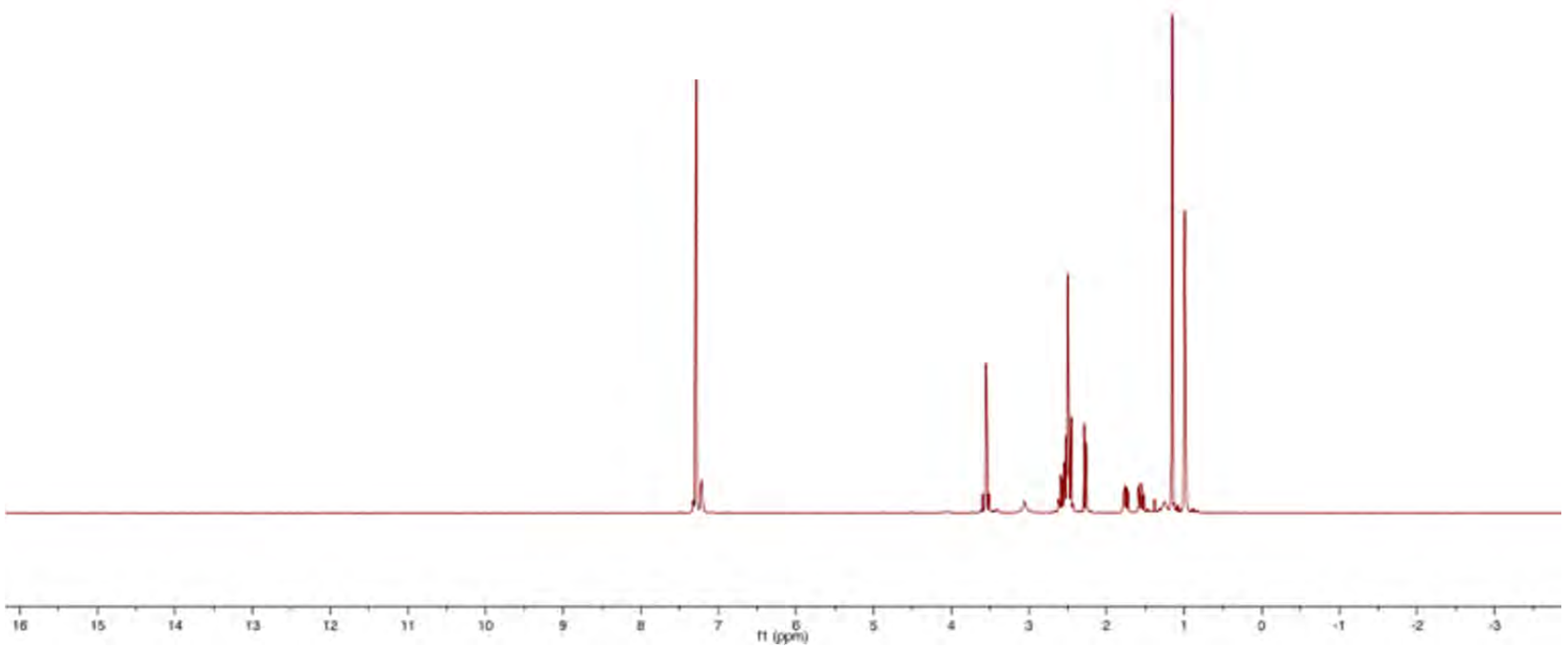

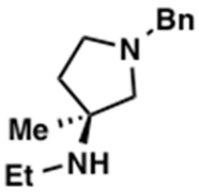
Bn
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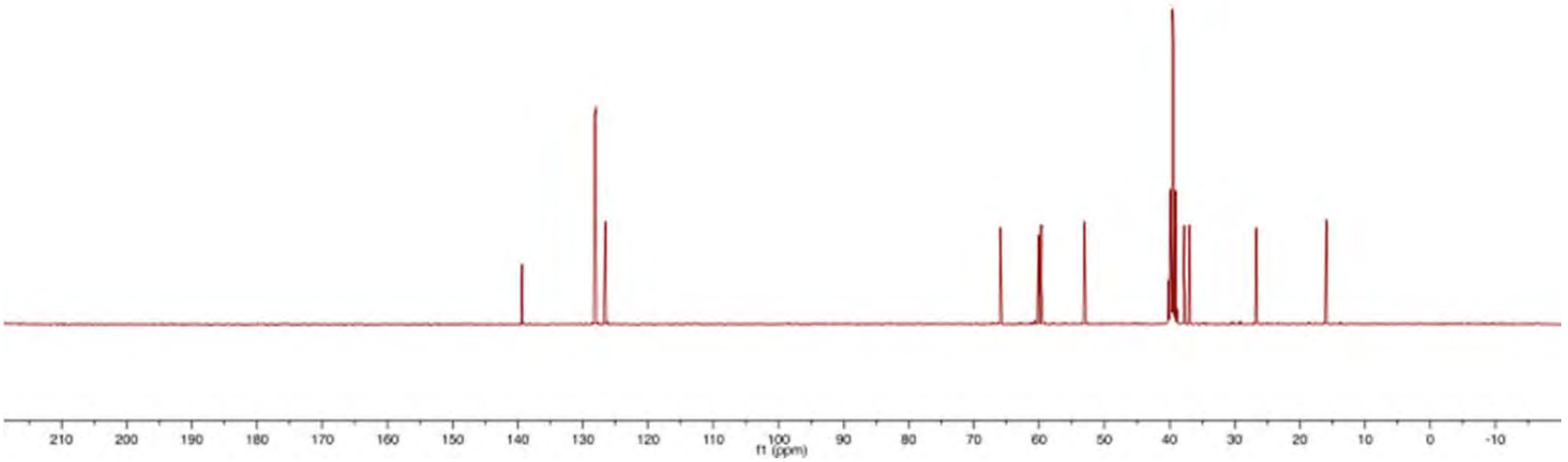
S3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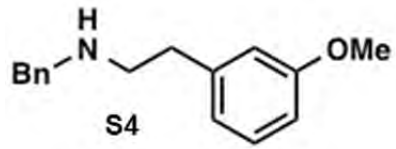
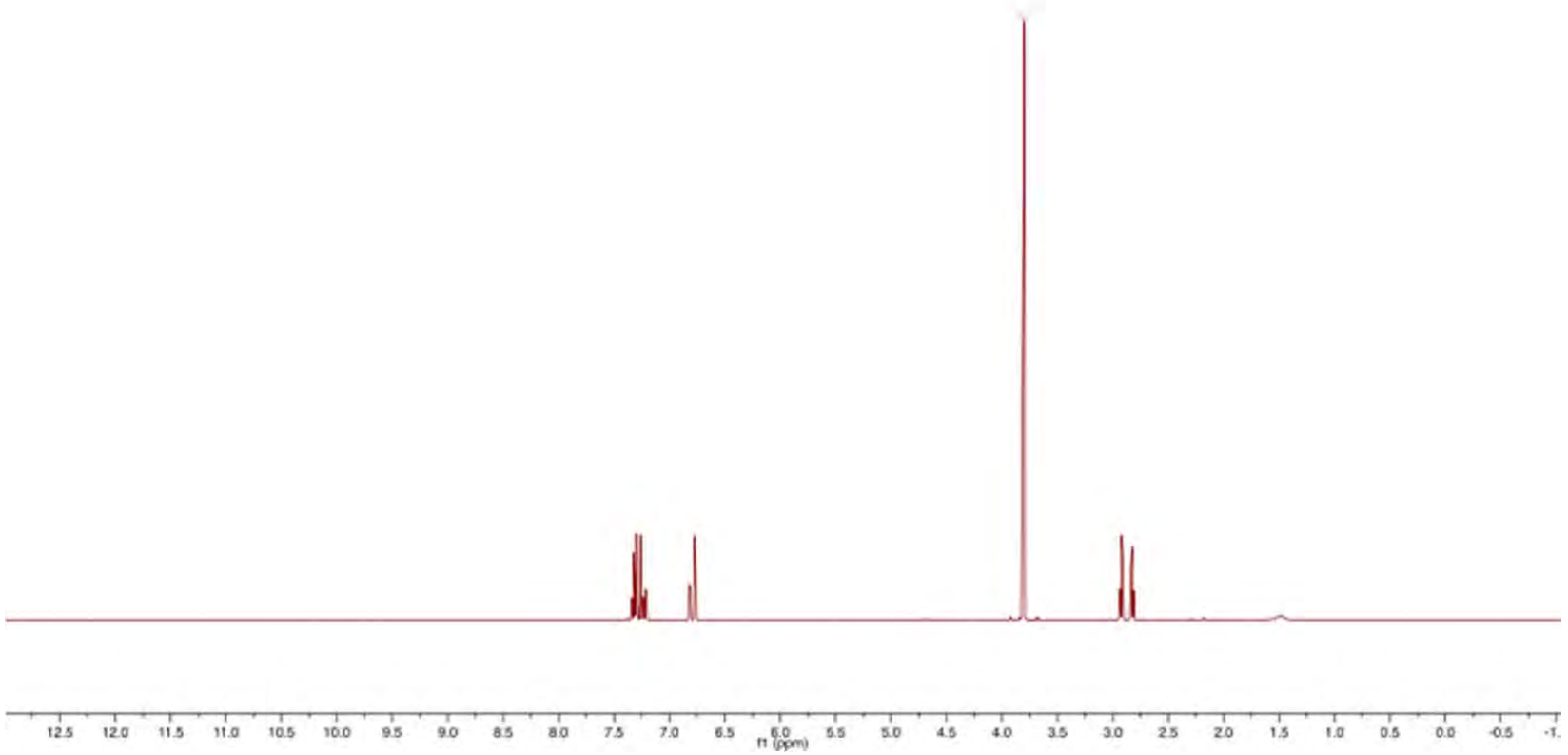
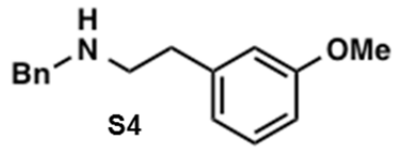
-10
f1 (ppm)

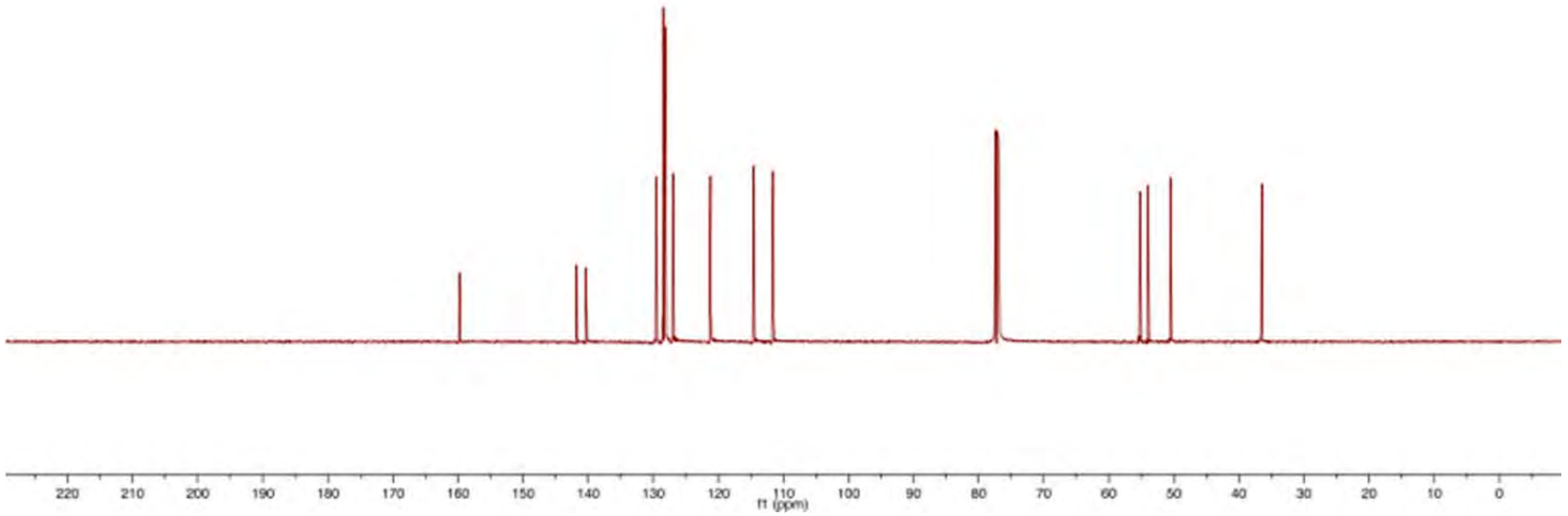

H
N
Bn
OMe

S4


12.5 12.0 11.5 11.0 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)


H
N
Bn
OMe

S4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210
200
190
180
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100
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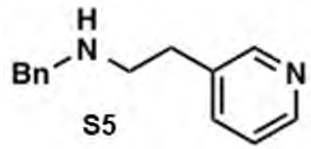
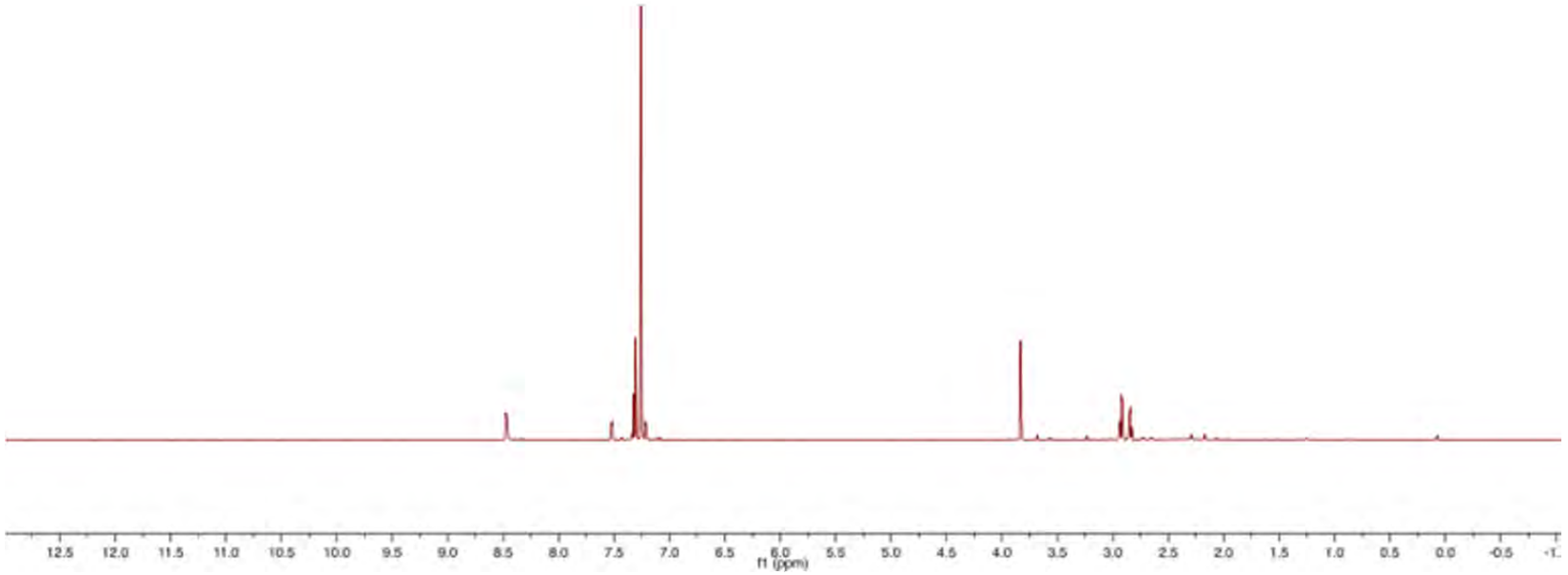
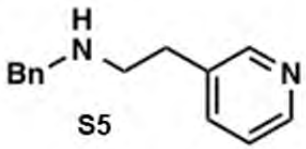
20
10
0
f1 (ppm)

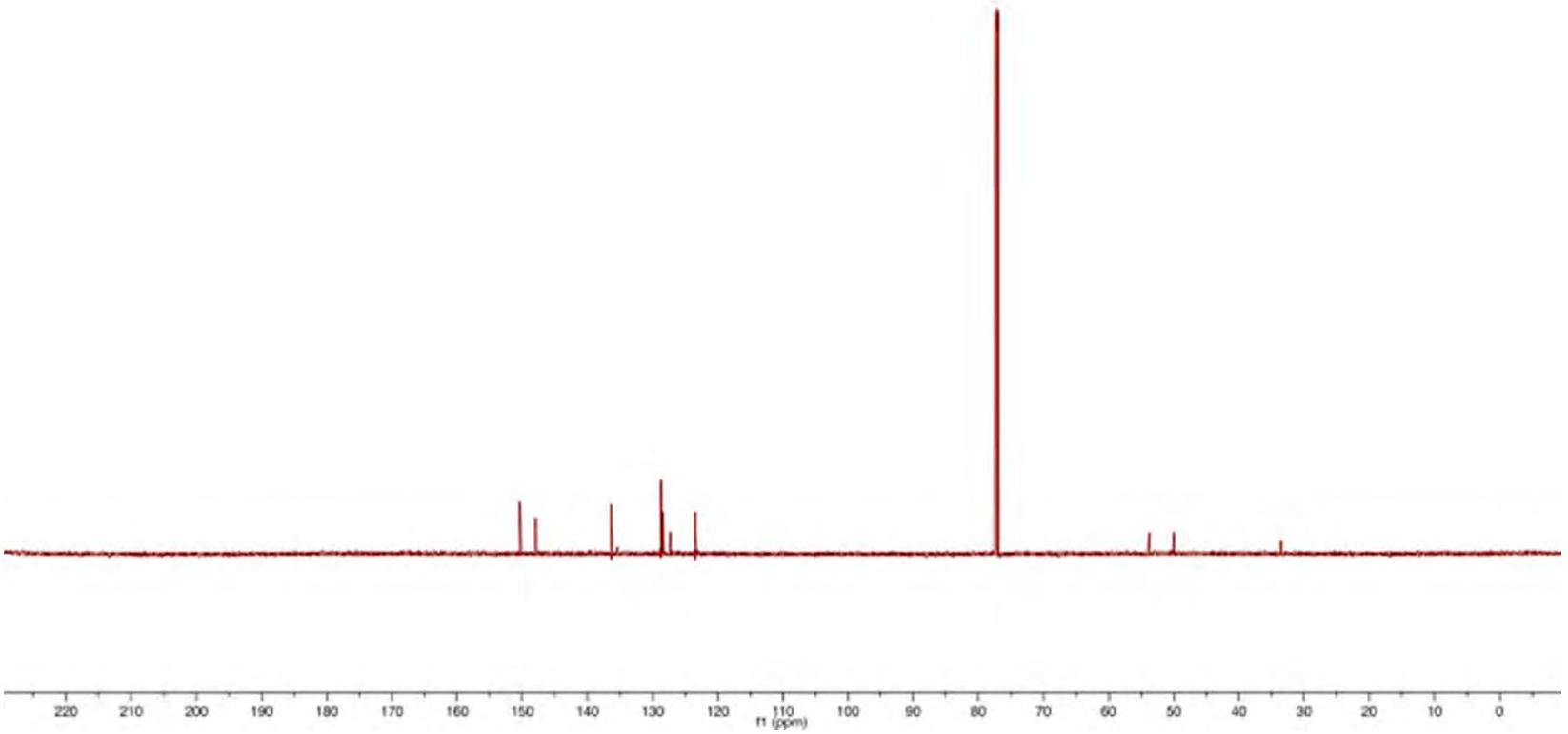

H
N
Bn
N

S5


12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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


H
N
Bn
N

S5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210
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180
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100
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70
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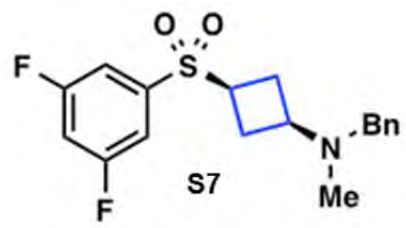
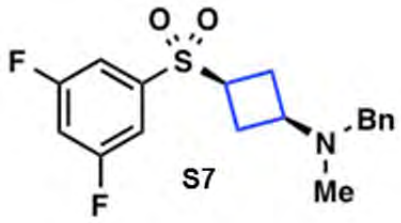
50
40
30
20
10
0
f1 (ppm)

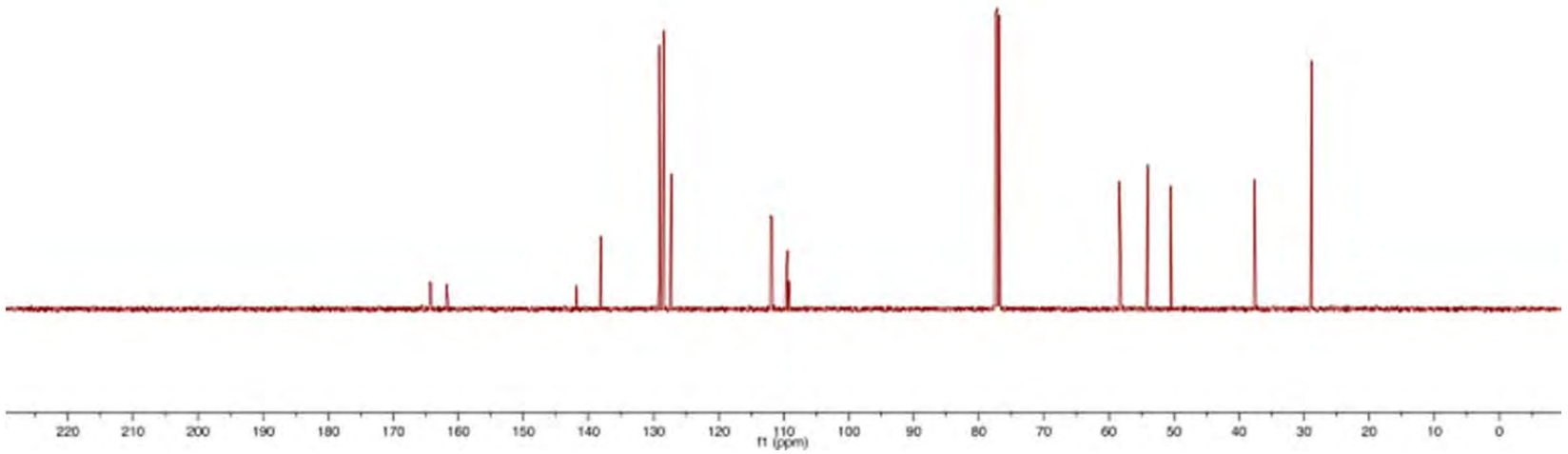

O
O
S
F
F
N
Bn
Me

S7

12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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


O
O
S
F
F
N
Bn
Me

S7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180
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100
90
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70
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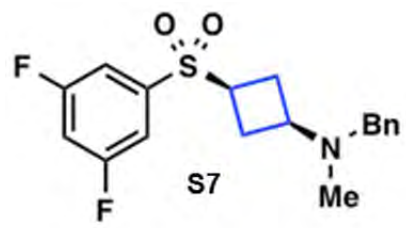
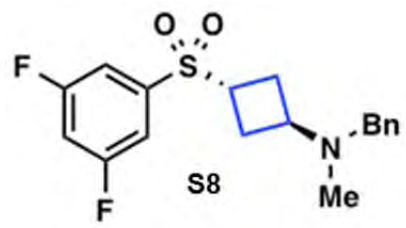
50
40
30
20
10
0
f1 (ppm)


O
O
S
F
F
Bn
N
Me

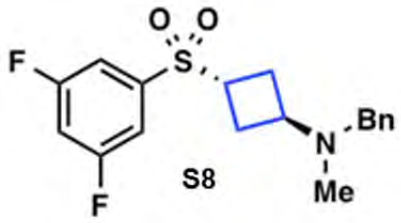
S7

-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190

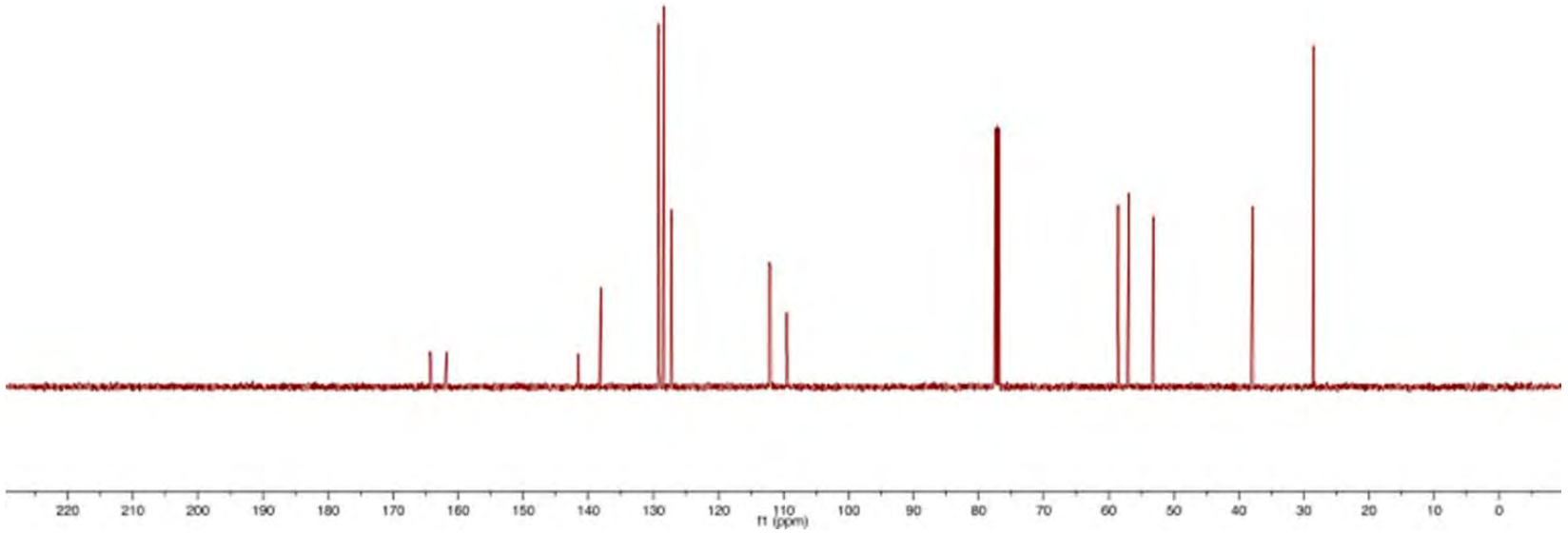

O
O
S
F
F
Bn
N
Me

S8

12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
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


O
O
S
F
F
Bn
N
Me

S8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100
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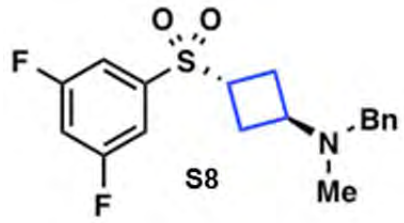
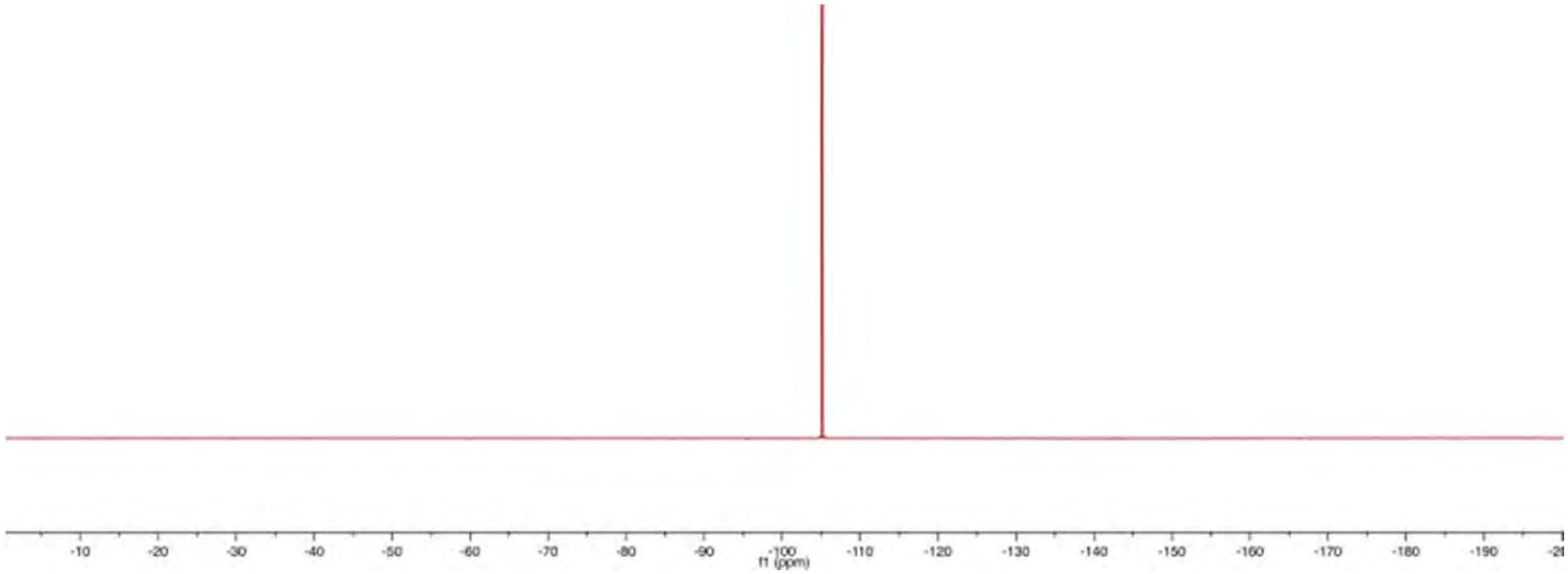
50
40
30
20
10
0
f1 (ppm)


O
O
S
F
F
N
Bn
Me

S8


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190