Highly Diastereoselective and General Synthesis of Primary β-Fluoroamines.

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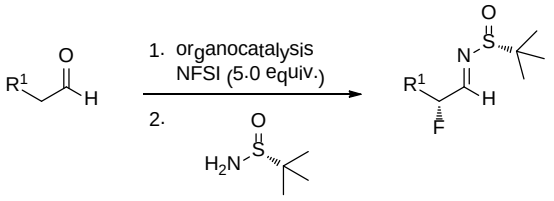
General Experimental

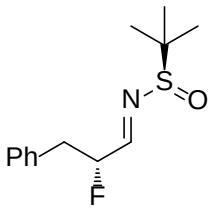
All reagents were purchased from commercial suppliers and purified as needed according to the procedures of Armarego and Chai[1]. Analytical thin-layer chromatography (TLC) was performed on 250 μm silica gel plates from Sorbent Technologies. Visualization was accomplished via UV light, and/or the use of ninhydrin and potassium permanganate solutions followed by application of heat. Chromatography was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies or Silica RediSep Rf flash columns on a CombiFlash Rf automated flash chromatography system. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 MHz and 100 MHz respectively). All ^{19}F NMR spectra were recorded on a Bruker DPX-300 (282 MHz). All 1H and 13C chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 ($CDCl_3$). All ^{19}F chemical shifts are reported in ppm relative to CCl_3F as an internal standard set to δ 0.00. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad, m = multiplet), coupling constant (Hz), integration. Low resolution mass spectra (LCMS) were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra (HRMS) were recorded on a Waters Qtof-API-US plus Acquity system with ES as the ion source.

General Procedure for the Synthesis of β-Fluoro-*N*-sulfinyl Aldimines.



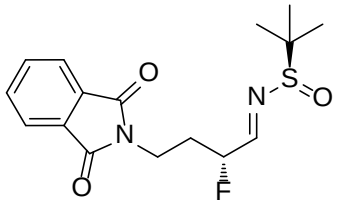
The enantioselective α-fluorination of aldehydes was accomplished using the procedure established by MacMillan and co-workers[2]. To a vial equipped with a stir bar was added (R)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (0.40 mmol, 0.2 eq.) and *N*-fluorobenzenesulfonimide (10.0 mmol, 5.0 eq.) followed by THF (9.0 mL) and *i*PrOH (1.0 mL). This solution was allowed to stir at rt until homogeneous then cooled to -20°C. The aldehyde (2.0 mmol, 1.0 eq.) was added and the reaction stirred at -20°C for 12 h. The

solution was then cooled to -78°C, diluted with 10 mL Et_2O, and filtered through a plug of Davisil® Silica Gel, eluting with ether at -78°C. 5.0 mL of Me_2S was then added to the filtrate resulting in a white precipitate. The resulting suspension was washed with sat. $NaHCO_3$ (3x), brine (1x), and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting α-fluoroaldehyde was dissolved in THF (5mL) and $Ti(OEt)_4$ (4.0 mmol, 2 eq.) was added followed by (R)-(+)-2-methyl-2-propanesulfinamide (2.0 mmol, 1.0 eq.). The mixture was stirred at rt for 5 h. The reaction is then quenched by addition of an equal volume of sat. $NaHCO_3$. The resulting mixture is filtered through a pad of Celite® and the filter cake rinsed washed with EtOAc. The filtrate is extracted with EtOAc, dried over $MgSO_4$, and concentrated. The α-fluorosulfinimines were purified by flash column chromatography and their diastereomeric ratio determined by ^{19}F NMR experiments.



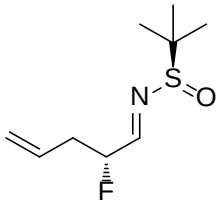
(*R*)-*N*-((*R*)-2-fluoro-3-phenylpropylidene)-2-methylpropane-2-sulfinamide (4)

The product was prepared according to the general procedure and purified by silica chromatography (3:1 hexanes/EtOAc) to afford the product as a clear oil (72%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.17 (dd, J_1 = 3.5Hz, J_2 = 9.4 Hz, 1H); 7.38-7.25 (m, 5H); 5.53-5.35 (dm, 1H); 3.25-3.14 (m, 2H); 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.37 (d, J = 30.1 Hz); 135.36 (d, J = 3.2 Hz); 129.71; 129.02; 127.49; 93.41 (d, J = 177.5 Hz); 57.53; 39.57 (d, J = 21.6 Hz); 22.64. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11 (s). HRMS (TOF, ES+) $C_{13}H_{18}NOFS$ $[M+H]^+$ calc. mass 256.1171, found 256.1173.



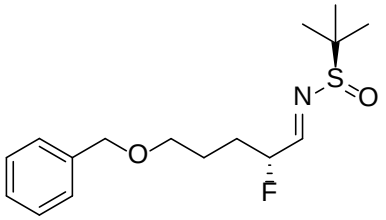
(*R*)-*N*-((*R*)-4-(1,3-dioxoisoindolin-2-yl)-2-fluorobutylidene)-2-methylpropane-2-sulfinamide (5)

The product was prepared according to the general procedure and purified by silica chromatography (3:1 hexanes/EtOAc) to afford the product as a clear oil (67%), which was determined to have a d.r. of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (dd, J_1 = 3.1 Hz, J_2 = 9.8 Hz, 1H); 7.85 (m, 2H); 7.72 (m, 2H); 5.30 (dm, 1H); 3.94 (m, 2H); 2.27 (m, 2H); 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.45; 166.05 (d, J = 30.1 Hz); 134.44; 132.32; 123.71; 91.36 (d, J = 175.3 Hz); 57.71; 34.21 (d, J = 3.8 Hz); 32.03 (d, J = 20.8 Hz); 22.68. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -190.92 (s). HRMS (TOF, ES+) $C_{16}H_{19}N_2O_3FS$ $[M+H]^+$ calc. mass 339.1179, found 339.1178.



(*R*)-*N*-((*R*)-2-fluoropent-4-en-1-ylidene)-2-methylpropane-2-sulfinamide (6)

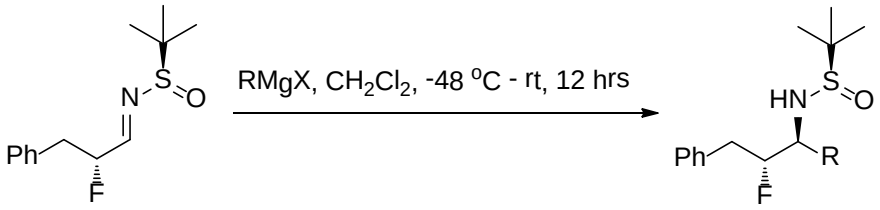
The product was prepared according to the general procedure and purified by silica chromatography (3:1 Hexanes/EtOAc) to afford the product as a clear oil (68%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (dd, J_1 = 3.2 Hz, J_2 = 10.3 Hz, 1H); 5.84 (m, 1H); 5.39-4.98 (m, 3H); 2.75-2.56 (m, 2H); 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.32 (d, J = 28.5 Hz); 131.30 (d, J = 4.7 Hz); 119.86; 92.28 (d, J = 177.7 Hz); 57.64; 37.62 (d, J = 21.5 Hz); 22.76. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -189.48 (s). HRMS (TOF, ES+) $C_9H_{16}NOFS$ $[M+H]^+$ calc. mass 206.1015, found 206.1017.



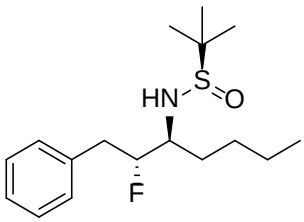
(*R*)-*N*-((*R*)-5-(benzyloxy)-2-fluoropentylidene)-2-methylpropane-2-sulfinamide (7)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear yellow oil (75%), which was determined to have a d.r. of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (dd, J_1 = 3.35 Hz, J_2 = 10.33 Hz, 1H); 7.30-7.19 (m, 5H); 5.16 (dm, 1H); 4.44 (s, 2H); 3.45 (m, 2H); 2.04-1.68 (m, 4H); 1.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 199.87 (d, J = 33.9 Hz); 166.51 (d, J = 28.6 Hz); 138.37; 128.42; 127.64; 92.77 (d, J = 175.0 Hz); 72.93; 69.34; 57.26; 29.92 (d, J = 20.6 Hz); 24.78; 22.40. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -187.88 (s). HRMS (TOF, ES+) $C_{16}H_{24}NO_2FS$ $[M+H]^+$ calc. mass 314.1590, found 314.1590.

General Procedure for Grignard Addition

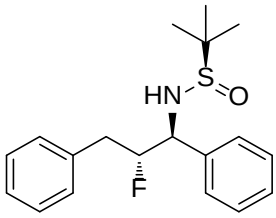


Grignard additions were done according to the general procedure by Ellman and co-workers[3]. To a solution of the *N*-*tert*-butanesulfinyl aldimine, at -48°C was added the Grignard reagent in either Et_2O or THF. The reaction stirred at -48°C for 5 h. and was then warmed to rt and stirred overnight. The reaction was quenched by the addition of sat. NH_4Cl and extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash column chromatography. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



(*R*)-*N*-((2*R*,3*S*)-2-fluoro-1-phenylheptan-3-yl)-2-methylpropane-2-sulfinamide (8a)

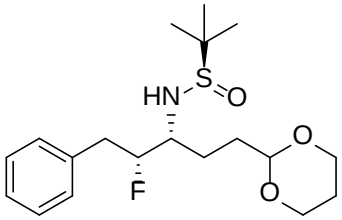
The product was prepared according to the general procedure and purified by silica chromatography (4:1 – 1:1 gradient EtOAc/hexane) to afford the product as a clear oil (92%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37-7.22 (m, 5H); 5.05 (dm, 1H); 3.57 (d, J = 9.2 Hz, 1H); 3.33 (m, 1H); 3.08 (td, J_1 = 8.6 Hz, J_2 = 14.8 Hz, 1H); 2.89 (ddd, J_1 = 4.7 Hz, J_2 = 14.5 Hz, J_3 = 31.2 Hz, 1H); 1.74-1.58 (m, 2H); 1.42-1.27 (m, 4H); 1.25 (s, 9H); 0.93 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.95 (d, J = 4.7 Hz); 129.48; 128.95; 127.09; 97.43 (d, J = 175.1 Hz); 59.86 (d, J = 20.1 Hz); 56.62; 38.13 (d, J = 21.5 Hz); 58.07 (d, J = 4.5 Hz); 28.32; 23.04; 22.68; 14.31. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11 (s). HRMS (TOF, ES+) $C_{17}H_{28}NOFS$ $[M+H]^+$ calc. mass 314.1876, found 314.1876.



(*R*)-*N*-((*1S*,2*R*)-2-fluoro-1,3-diphenylpropyl)-2-methylpropane-2-sulfinamide (8b)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (89%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46-7.35 (m, 4H); 7.35-7.22 (m, 4H); 7.21-7.13 (d, J_1 = 7.24 Hz, 2H); 5.11 (dm, 1H); 4.51 (dm, 1H); 3.81 (d, J = 5.4 Hz, 1H); 2.87-2.69 (m, 2H); 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.56; 136.80 (d, J = 3.1 Hz); 129.30, 128.90; 128.71; 128.65; 126.94; 95.15 (d, J = 182.3 Hz); 61.72 (d, J = 19.2 Hz); 56.53; 38.30; 29.83; 22.68. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11 (s). HRMS

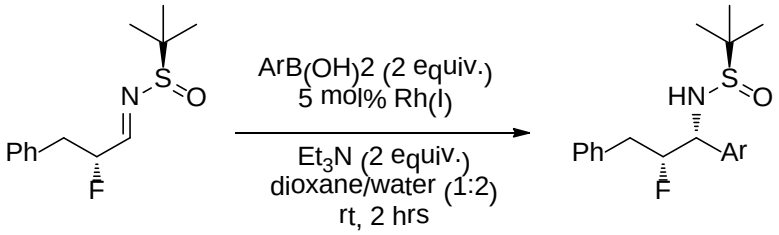
(TOF, ES+) $C_{19}H_{24}NOFS$ $[M+H]^+$ calc. mass 334.1641, found 334.1639.



(*R*)-*N*-((2*R*,3*R*)-5-(1,3-dioxan-2-yl)-2-fluoro-1-phenylpentan-3-yl)-2-methylpropane-2-sulfinamide (8c)

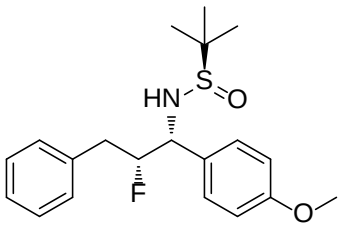
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a white solid (81%), which was determined to have a d.r. of >9:1 by ^{19}F NMR. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33-7.20 (m, 5H); 5.03 (dm, *J* = 47.6 Hz, 1H); 4.54 (t, *J* = 4.3 Hz, 1H); 4.16-4.02 (m, 4H); 3.22-3.00 (m, 2H); 294-2.79 (m, 1H); 2.17-1.56 (m, 6H); 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 129.71; 129.32; 128.74; 126.85 (d, *J* = 8.6 Hz); 101.85 (d, *J* = 6.8 Hz); 97.23 (d, *J* = 175.9 Hz); 67.03 (d, *J* = 5.6 Hz); 59.73 (d, *J* = 7.6 Hz); 38.04 (d, *J* = 22.6 Hz); 31.54 (d, *J* = 5.70 Hz); 28.03; 25.89 (d, *J* = 3.9 Hz); 23.51; 22.88. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.11. HRMS (TOF, ES+) $C_{19}H_{30}NO_3FS$ $[M+H]^+$ calc. mass 372.2009, found 372.2006.

General Procedure for Boronic Acid Addition



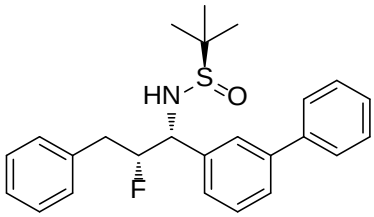
Addition of Boronic Acids to β-fluorosulfinimines were achieved using the methods shown by Batey and co-workers[4]. To a vial containing sulfinimine (0.25 mmol, 1.0 eq.), $[Rh(COD)(CH_3CN)_2]BF_4$ (0.0125 mmol, 0.05 eq.), and boronic acid (0.50 mmol, 2.0 eq.) in dioxane (0.6 mL) was added Et_3N (0.50 mmol, 2.0 eq.) and H_2O (1.2 mL). The resulting mixture

was stirred at rt for 2 h. The aqueous layer was then extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. The products were purified using flash column chromatography. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



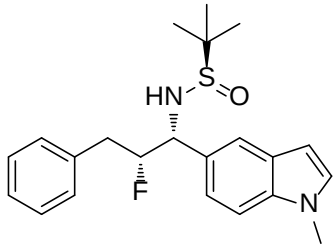
(*R*)-*N*-((1*R*,2*R*)-2-fluoro-1-(4-methoxyphenyl)-3-phenylpropyl)-2-methylpropane-2-sulfinamide (9a)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a yellow solid (80%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.20 (m, 5H); 7.19-7.10 (m, 2H); 6.95 (d, *J* = 8.60 Hz, 2H); 5.04 (dm, 1H); 4.55-4.49 (m, 1H); 3.95 (d, *J* = 4.1 Hz, 1H); 3.86 (s, 3H); 2.85-2.69 (m, 2H); 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 159.64 (d, *J* = 32.2 Hz); 136.35; 129.97 (d, *J* = 22.47 Hz); 129.20 (d, *J* = 14.2 Hz); 128.51; 126.69 (d, *J* = 7.49 Hz); 114.23; 113.83; 96.45 (d, *J* = 180.6 Hz); 61.07 (d, *J* = 19.3 Hz); 58.34; 55.49 (d, *J* = 63.8 Hz); 37.60 (d, *J* = 21.0 Hz); 29.62; 22.47. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -184.63 (s). HRMS (TOF, ES+) $C_{20}H_{26}NO_2FS$ $[M+H]^+$ calc. mass 364.1747, found 364.1748.



(*R*)-*N*-((1*R*,2*R*)-1-([1,1'-biphenyl]-3-yl)-2-fluoro-3-phenylpropyl)-2-methylpropane-2-sulfinamide (9b)

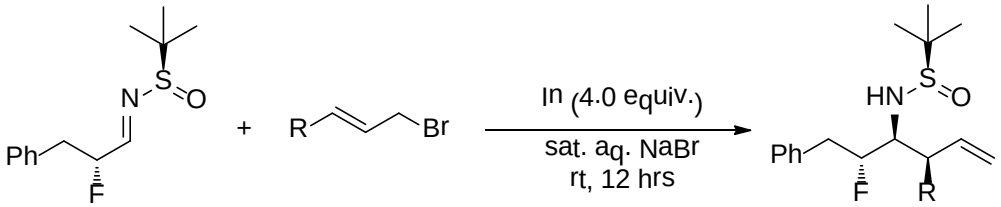
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (87%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65-7.56 (m, 4H); 7.52-7.45 (m, 3H); 7.43-7.22 (m, 5H); 7.17-7.13 (m, 2H); 4.90 (dm, 1H); 4.64 (m, 1H); 4.20 (s, 1H); 2.91 (d, *J* = 5.8 Hz, 1H); 2.88-2.82 (m, 1H); 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 141.99; 140.66; 137.88 (d, *J* = 5.80 Hz); 136.42; 129.50; 129.47; 129.01; 128.62; 127.75; 127.68; 127.65; 127.60; 127.25; 126.94; 97.12 (d, *J* = 180.0 Hz); 61.75 (d, *J* = 18.5 Hz); 55.84; 37.96 (d, *J* = 20.0 Hz); 22.68. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -185.00 (s). HRMS (TOF, ES+) $C_{25}H_{28}NOFS$ $[M+H]^+$ calc. mass 410.1954, found 410.1953.



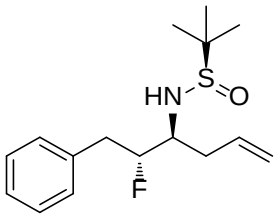
(*R*)-*N*-((1*R*,2*R*)-2-fluoro-1-(1-methyl-1H-indol-5-yl)-3-phenylpropyl)-2-methylpropane-2-sulfinamide (9c)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a dark brown oil (65%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (s, 1H); 7.40-7.08 (m, 8H); 6.53 (d, *J* = 3.1 Hz, 1H); 4.91 (dm, *J* = 49.3 Hz, 1H); 4.68 (t, *J* = 8.7 Hz, 1H); 3.84 (s, 3H); 2.86-2.68 (m, 2H); 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.74; 129.53; 129.29; 129.15; 128.56; 128.43; 128.35; 128.26; 126.52; 121.78; 109.68; 101.19; 97.49 (d, *J* = 177.1 Hz); 61.89 (d, *J* = 18.3 Hz); 55.29; 37.73 (d, *J* = 20.3 Hz); 32.87; 22.50. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -184.26 (s). HRMS (TOF, ES+) $C_{22}H_{27}N_2OFS$ $[M+H]^+$ calc. mass 387.1906, found 387.1908.

General Procedure for In-Mediated Allylation

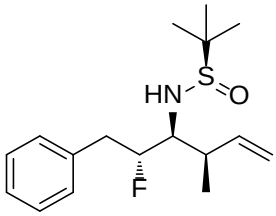


In-Mediated allylation were done according to procedures published by Lin and co-workers.[5] To a vial containing sulfinimine (0.25 mmol, 1.0 eq.) and indium powder (1.0 mmol, 4.0 eq.) was added saturated aqueous NaBr solution (5 mL) followed by the allylic bromide (1.0 mmol, 4.0 eq.). The resulting suspension stirred at rt for 12 h. The reaction was quenched by the addition of 15 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography to afford the allylation product. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



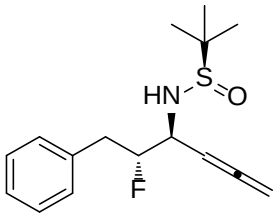
(*R*)-*N*-((2*R*,3*S*)-2-fluoro-1-phenylhex-5-en-3-yl)-2-methylpropane-2-sulfinamide (10a)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (90%), which was determined to have a d.r. of >9:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (s, 2H); 7.31 (s, 2H); 7.27-7.21 (m, 1H); 5.79-5.67 (m, 1H); 5.11 (s, 1H); 5.07 (d, *J* = 2.96 Hz, 1H); 4.76 (dtd, J_1 = 2.60 Hz, J_2 = 6.9 Hz, J_3 = 46.5 Hz, 1H); 3.66 (d, *J* = 7.5 Hz, 1H); 3.47-3.33 (m, 1H); 3.21-3.13 (m, 1H); 3.11 (d, *J* = 6.9 Hz, 1H); 2.50-2.31 (m, 2H); 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.68; 133.97; 129.67; 128.77; 126.87; 118.54; 95.14 (d, *J* = 175.8 Hz); 57.83 (d, *J* = 19.2 Hz); 56.57; 38.21 (d, *J* = 2.5 Hz); 37.78 (d, *J* = 21.6 Hz); 22.93. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.35 (s). HRMS (TOF, ES+) $C_{16}H_{24}NOFS$ $[M+H]^+$ calc. mass 298.1641, found 298.1642.



(*R*)-N-((2*R*,3*S*,4*R*)-2-fluoro-4-methyl-1-phenylhex-5-en-3-yl)-2-methylpropane-2-sulfinamide (10b)

The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (82%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.15 (m, 5H); 5.97-5.86 (m, 1H); 5.85-5.55 (m, 1H); 5.09-4.98 (m, 1H); 4.62-4.43 (dm, *J* = 47.7 Hz, 1H); 3.52-2.78 (m, 4H); 1.29 (s, 9H); 1.05 (dd, J_1 = 4.2 Hz, J_2 = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.24; 137.48; 129.42; 128.68; 126.88; 118.14; 94.96 (d, *J* = 178.7 Hz); 62.23 (d, *J* = 22.9 Hz); 60.35; 38.24 (d, *J* = 20.8 Hz); 36.62 (d, *J* = 4.4 Hz); 23.04; 16.40. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -184.09 (s). HRMS (TOF, ES+) $C_{17}H_{26}NOFS$ $[M+H]^+$ calc. mass 312.1797, found 312.1798.

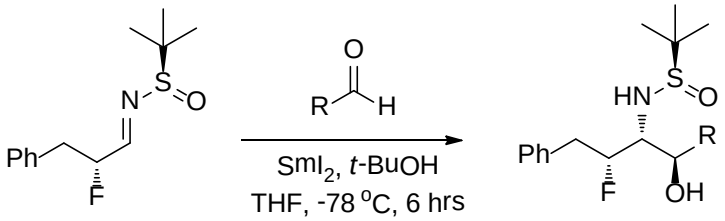


(*R*)-*N*-((2*R*,3*S*)-2-fluoro-1-phenylhexa-4,5-dien-3-yl)-2-methylpropane-2-sulfinamide (10c)

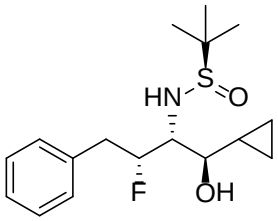
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a yellow oil (78%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38-7.18 (m, 5H); 5.48-5.31 (m, 1H); 5.05-4.97 (m, 2H); 4.82-4.63 (dm, *J* = 47.2 Hz, 1H); 3.86 (d, *J* = 9.06 Hz,1H); 3.25-3.08 (m, 1H); 3.02-2.86 (m,1H); 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 208.62; 136.62; 129.35; 128.47; 126.76; 93.15 (d, *J* = 179.0 Hz); 88.32 (d, *J* = 7.1 Hz); 72.31; 57.47; 56.29 (d, *J* = 25.7 Hz); 37.68 (d, *J* = 20.4 Hz); 22.62. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -

187.09 (s). HRMS (TOF, ES+) $C_{16}H_{22}NOFS$ $[M+H]^+$ calc. mass 296.1484, found 296.1483.

General Procedure for the SmI_2-Induced Reductive Aldehyde Coupling



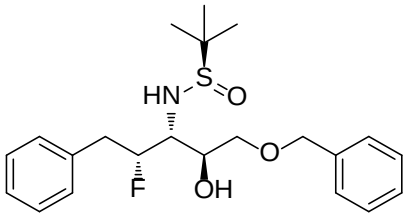
Reductive coupling of aldehydes was accomplished using the procedure established by Lu and Xin.[6] To a flame dried flask under an argon atmosphere was added a solution of 0.1M SmI_2 in THF (1.0 mmol, 2.0 eq.). The solution was cooled to -78°C and a mixture of sulfinimine (0.5 mmol, 1.0 eq.), *t*-butyl alcohol (1.0 mmol, 2.0 eq.), and aldehyde (0.75 mmol, 1.5 eq.) in 6 mL of THF was added dropwise. The reaction was stirred at -78°C for 4-6 h. The reaction was quenched with the addition of 5 mL of saturated aqueous $Na_2S_2O_3$ followed by extraction with EtOAc (3x) and purification by reverse-phase column chromatography to afford the product. The diastereomeric ratio of the sulfinamide-protected primary β-fluoroamines was determined by ^{19}F NMR experiments.



(*R*)-*N*-((1*R*,2*R*,3*R*)-1-cyclopropyl-3-fluoro-1-hydroxy-4-phenylbutan-2-yl)-2-methylpropane-2-sulfinamide (11a)

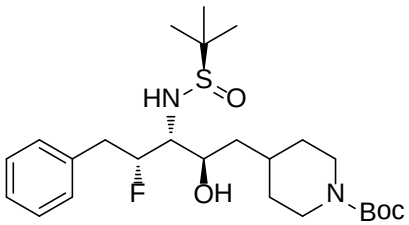
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (87%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38-7.17 (m, 5H); 5.19 (dm, J = 46.7 Hz, 1H); 4.07 (dd, J_1 = 1.8 Hz, J_2 = 8.2 Hz, 1H); 3.44-3.02 (m, 5H); 1.32 (s, 9H); 0.62-0.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 136.65 (d, J = 7.32 Hz); 129.69;

128.75; 126.86; 93.22 (d, *J* = 175.6 Hz); 62.23 (d, *J* = 16.8 Hz); 56.72; 38.3; 22.99; 14.68; 3.81; 21.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -194.35 (s). HRMS (TOF, ES+) $C_{17}H_{26}NO_2FS$ $[M+H]^+$ calc. mass 328.1747, found 328.1749.



(*R*)-*N*-((2*S*,3*R*,4*R*)-1-(benzyloxy)-4-fluoro-2-hydroxy-5-phenylpentan-3-yl)-2-methylpropane-2-sulfinamide (11b)

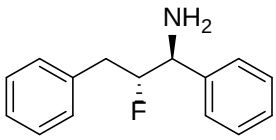
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (83%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44-7.27 (m, 10H); 4.63 (dm, 1H); 4.55 (s, 2H); 3.97-3.93 (m, 2H); 3.54 (m, 1H); 2.97-2.60 (m, 3H); 1.55 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.58; 137.72; 129.29; 129.19; 128.47 (d, *J* = 3.2 Hz); 127.83; 127.75; 126.57; 93.54 (d, *J* = 169.7 Hz); 73.43; 71.53; 70.81; 55.90 (d, *J* = 21.7 Hz); 55.52; 55.33; 38.18 (d, *J* = 22.0 Hz); 21.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -189.07 (s). HRMS (TOF, ES+) $C_{13}H_{19}NOFS$ $[M+H]^+$ calc. mass 408.1930, found 408.1931.



***tert*-butyl-4-((2*R*,3*R*,4*R*)-3-((*R*)-1,1-dimethylethylsulfinamido)-4-fluoro-2-hydroxy-5-phenylpentyl)piperidine-1-carboxylate (11c)**

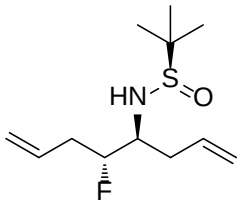
The product was prepared according to the general procedure and purified by silica chromatography (2:1 hexanes/EtOAc) to afford the product as a clear oil (80%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35-7.16

(m, 5H); 4.84 (dm, *J* = 47.9 Hz, 1H); 4.07 (br, 1H); 3.67 (m, 1H); 3.16-2.85 (m, 3H); 2.77-2.58 (m, 4H); 1.83-1.51 (m, 5H); 1.45 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.81; 136.63; 129.18; 128.58; 126.75; 94.14 (d, *J* = 173.0 Hz); 79.17; 64.23 (d, *J* = 22.1 Hz); 62.57; 57.43; 39.57; 38.44 (d, *J* = 20.1 Hz); 33.25; 32.32; 31.19; 28.39. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -188.40 (s). HRMS (TOF, ES+) $C_{25}H_{41}N_2O_4FS$ $[M+H]^+$ calc. mass 485.2771, found 485.2771.



(1*S*,2*R*)-2-fluoro-1,3-diphenylpropan-1-amine (12)

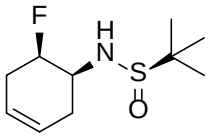
The product was prepared by treatment of (*R*)-*N*-((*1S*,2*R*)-2-fluoro-1,3-diphenylpropyl)-2-methylpropane-2-sulfinamide with excess HCl in dioxane to afford analytically pure product as a yellow solid (92%) which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42-7.11 (m, 10H); 4.91 (dm, *J* = 47.7 Hz, 1H); 4.14 (d, *J* = 15.7 Hz, 1H); 2.97-2.67 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 140.80; 137.42 (d, *J* = 2.2 Hz); 129.38; 128.75; 128.59; 127.92; 127.71; 126.70; 97.49 (d, *J* = 177.8 Hz); 58.59 (d, *J* = 20.9 Hz); 37.21 (d, *J* = 21.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -186.59 (s). HRMS (TOF, ES+) $C_{15}H_{16}NF$ $[M+H]^+$ calc. mass 230.1345, found 230.1346.



(*R*)-*N*-((*4S,5R*)-5-fluoroocta-1,7-dien-4-yl)-2-methylpropane-2-sulfinamide (15)

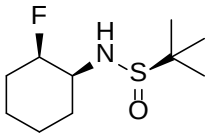
The product was prepared according to the general procedure and purified by silica chromatography (4:1 – 1:1 gradient EtOAc/hexane) to afford the product as a clear oil (90%), which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.90-5.77 (m, 2H); 5.27-5.11 (m, 4H); 4.54-4.36 (dm, 1H); 3.54-3.38 (m, 2H); 2.53-2.38 (m, 4H);

1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 133.51; 133.08 (d, *J* = 4.6 Hz); 120.49; 118.71; 93.97 (d, *J* = 177.7 Hz); 57.25 (d, *J* = 23.2 Hz); 56.52; 36.18 (d, *J* = 21.5 Hz); 35.57 (d, *J* = 4.6 Hz); 22.95. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -189.74 (s). HRMS (TOF, ES+) $C_{12}H_{22}NOFS$ $[M+H]^+$ calc. mass 248.1484, found 248.1483.



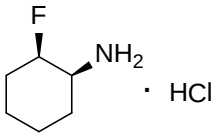
(*R*)-*N*-((1*S*,6*R*)-6-fluorocyclohex-3-en-1-yl)-2-methylpropane-2-sulfinamide (16)

The product was prepared by treatment of (*R*)-*N*-((*4S,5R*)-5-fluoroocta-1,7-dien-4-yl)-2-methylpropane-2-sulfinamide with Grubbs 2nd generation catalyst to afford the cyclized product in 85% yield as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.67 (m, 1H); 5.57 (m, 1H); 4.84 (dm, 1H); 3.54 (m, 1H); 3.36 (d, *J* = 8.52 Hz, 1H); 2.61-2.25 (m, 4H); 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 124.83; 122.48; 90.37 (d, *J* = 174.13 Hz); 56.18; 54.54 (d, *J* = 19.17 Hz); 30.91 (d, *J* = 22.10 Hz); 30.41 (d, *J* = 6.03 Hz); 22.71. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -193.57 (s). HRMS (TOF, ES+) $C_{10}H_{18}NOFS$ $[M+H]^+$ calc. mass 220.1171, found 220.1171.



(*R*)-*N*-((1*S*,2*R*)-2-fluorocyclohexyl)-2-methylpropane-2-sulfinamide (17)

The product was prepared by treatment of (*R*)-*N*-((1*S*,6*R*)-6-fluorocyclohex-3-en-1-yl)-2-methylpropane-2-sulfinamide with 10% Pd/C in a H_2 atmosphere to afford the product as an off-white solid (95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.29 (dm, *J* = 49.2 Hz); 3.33-3.22 (m, 2H); 2.20-2.07 (m, 2H); 1.83-1.65 (m, 2H); 1.57-1.37 (m, 2H); 1.36-1.26 (m, 2H); 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 95.19 (d, *J* = 177.7 Hz); 59.45 (d, *J* = 17.0 Hz); 56.11; 32.32; 31.25 (d, *J* = 17.2 Hz); 24.33; 23.38 (d, *J* = 10.8 Hz); 22.65. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -175.84 (s) HRMS (TOF, ES+) $C_{10}H_{20}NOFS$ $[M+H]^+$ calc. mass 222.1328, found 222.1326.



(1*S*,2*R*)-2-fluorocyclohexanamine hydrochloride (18)

The product was prepared by treatment of (*R*)-*N*-((1*S*,2*R*)-2-fluorocyclohexyl)-2-methylpropane-2-sulfinamide with excess HCl in dioxane to afford analytically pure product as an off-white solid (98%) which was determined to have a d.r. of >20:1 by ^{19}F NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.78 (br s, 1H); 3.83-3.61 (m, 1H); 3.56–3.07 (br s, 1H); 2.68-0.70 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 55.39; 30.78; 29.60; 28.71; 23.52; 22.91. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): -175.98 (br s). HRMS (TOF, ES+) $C_6H_{12}NF$ $[M+H]^+$ calc. mass 118.0954, found 118.0954.

References:

1) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th Ed.; Elsevier: Burlington, MA, 2009.
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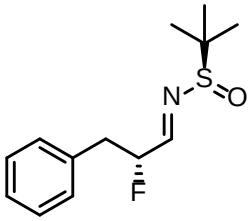
5) Sun, X-W.; Liu, M.; Xu, M-H.; Lin, G-Q. *Org. Lett.* **2008**, *10*, 1259-1262
6) Zhong, Y-W.; Dong, Y-Z.; Fang, K.; Izumi, K.; Xu, M-H.; Lin G-Q. *J. Am. Chem. Soc.* **2005,** *127*, 11956-11957

^{1}H



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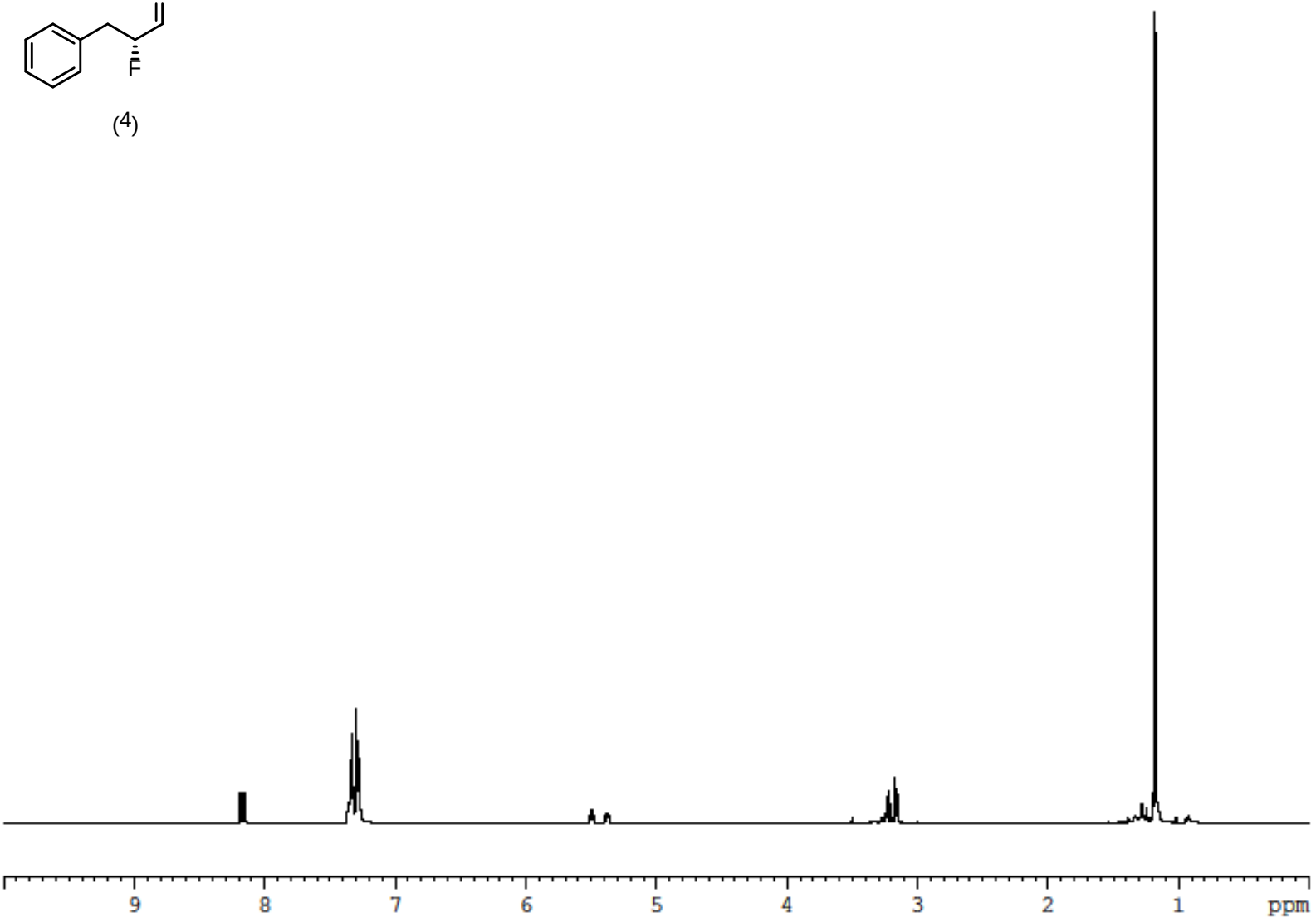
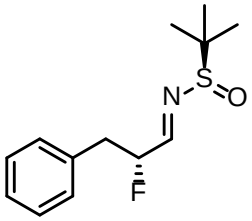


^{13}C



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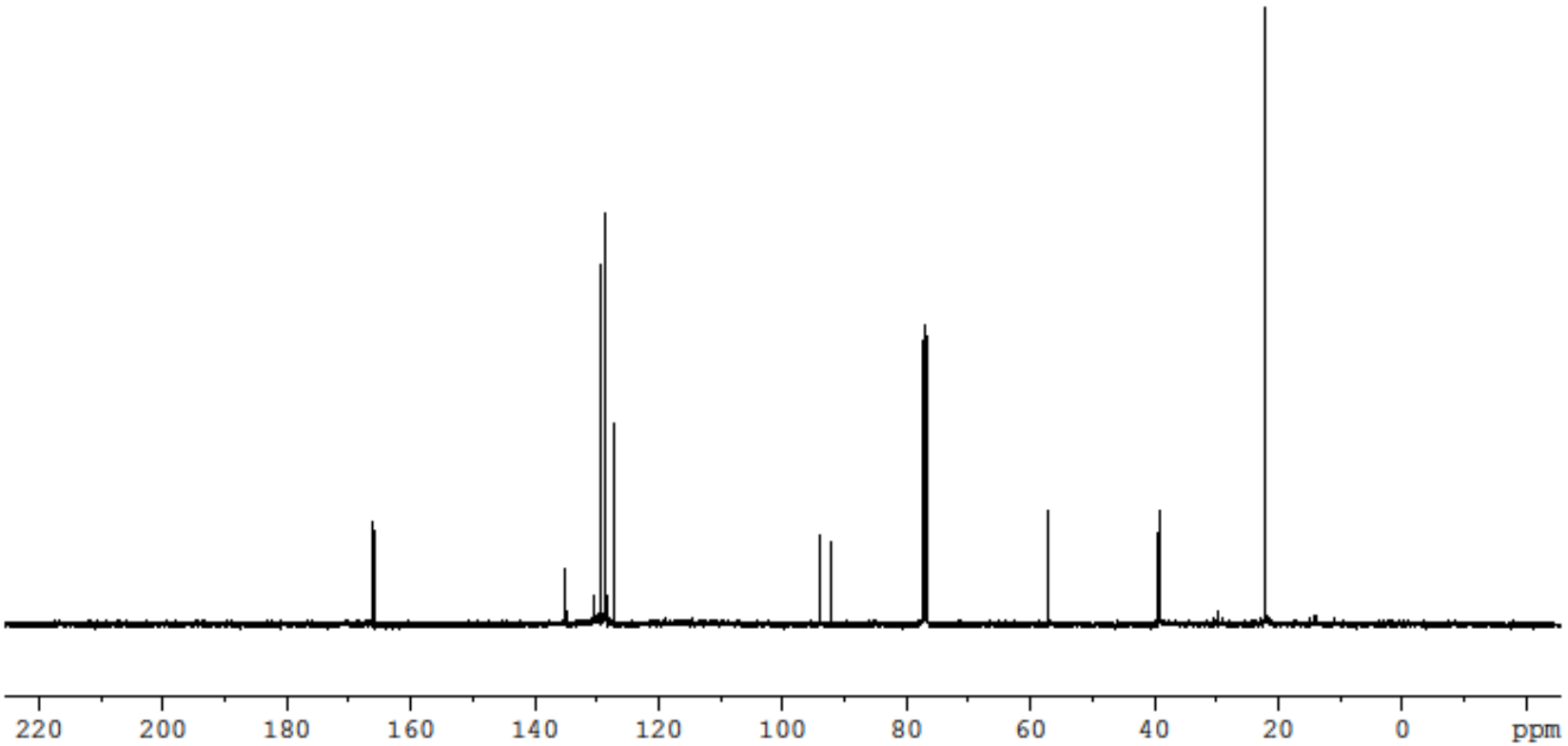
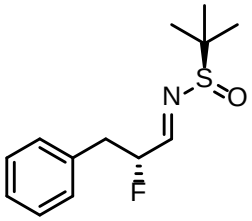


^{19}F



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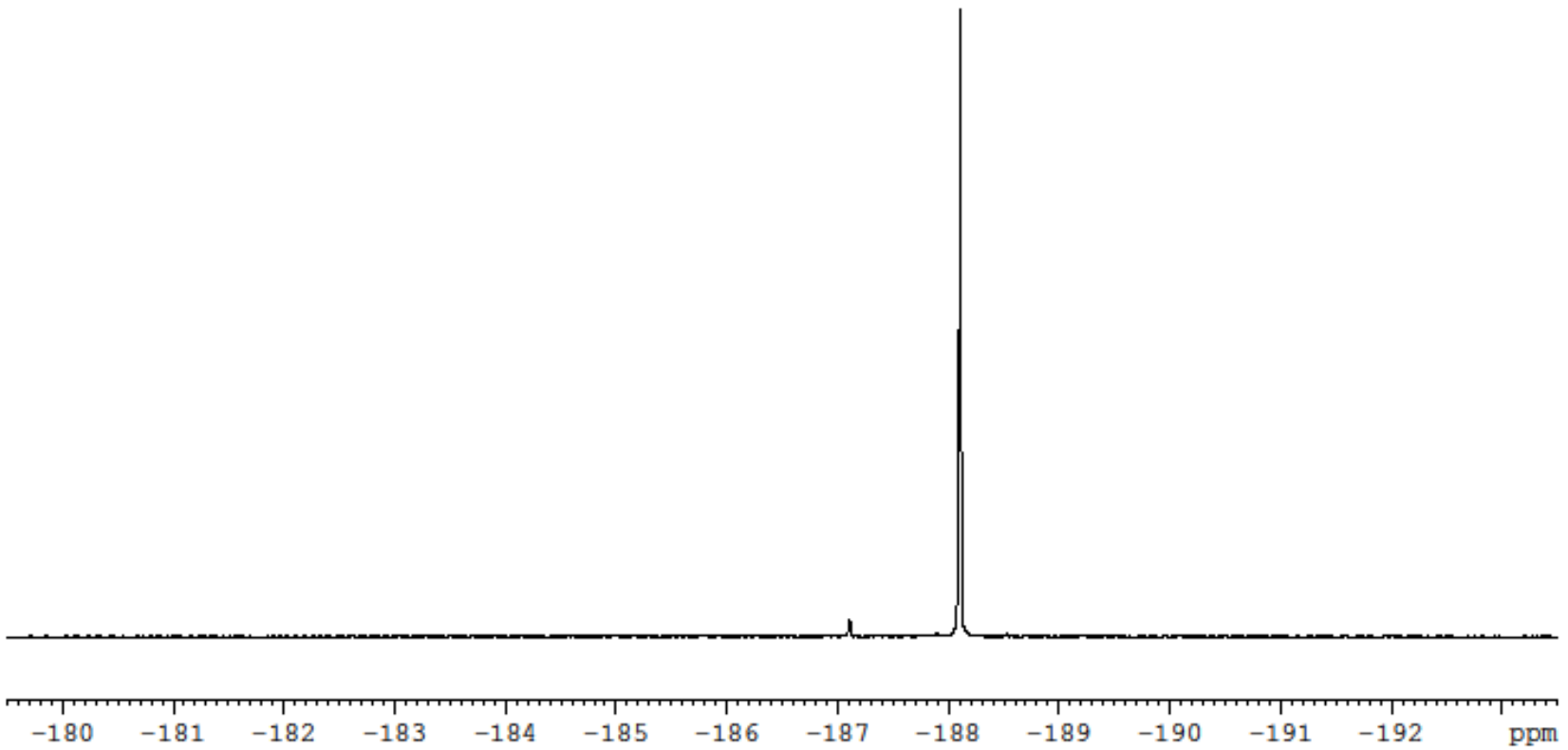
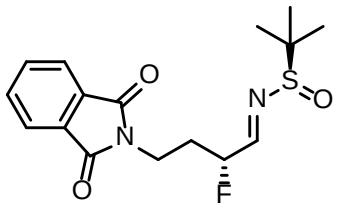
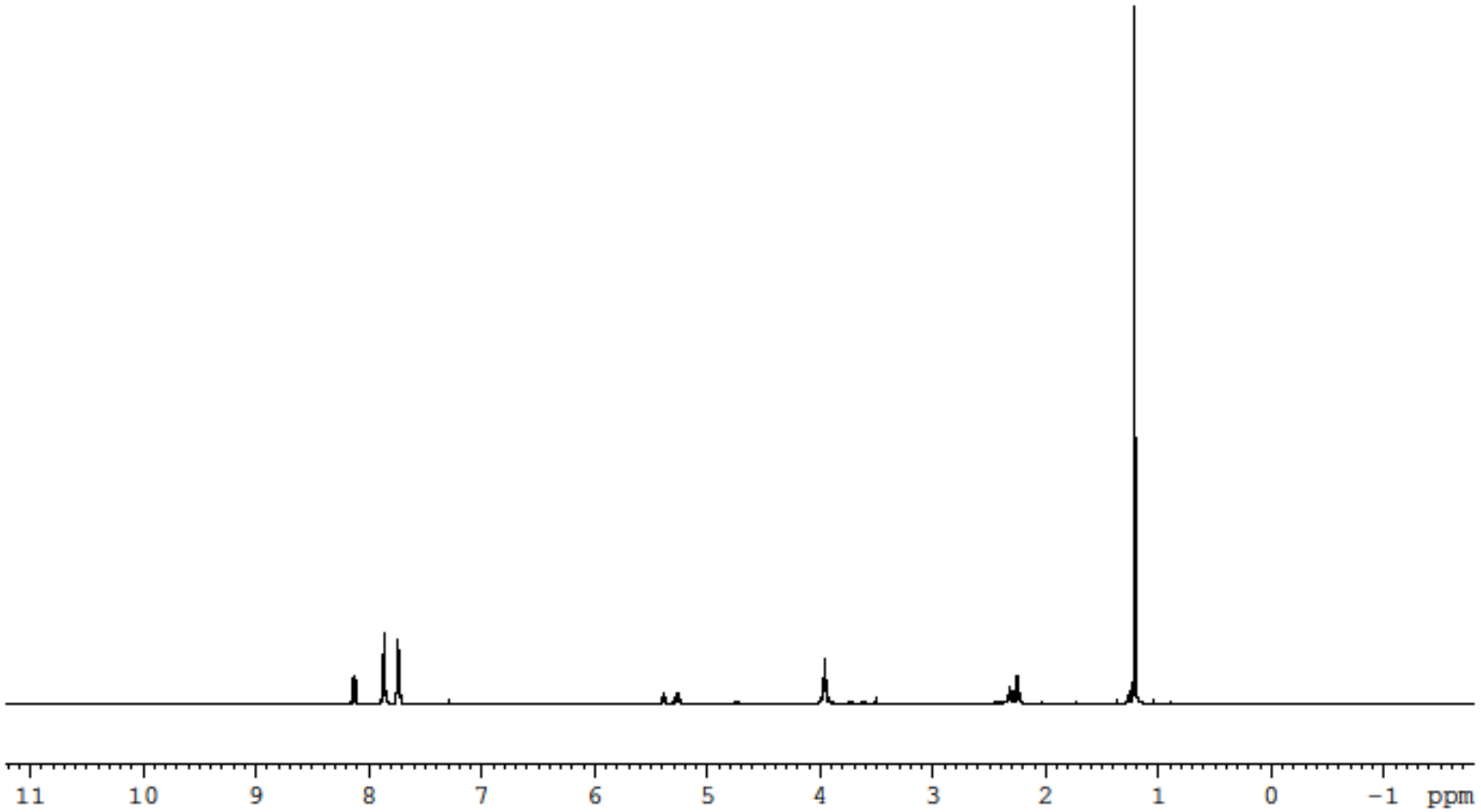


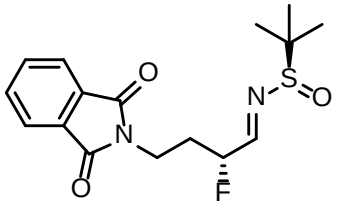
^{1}H



(5)



^{13}C



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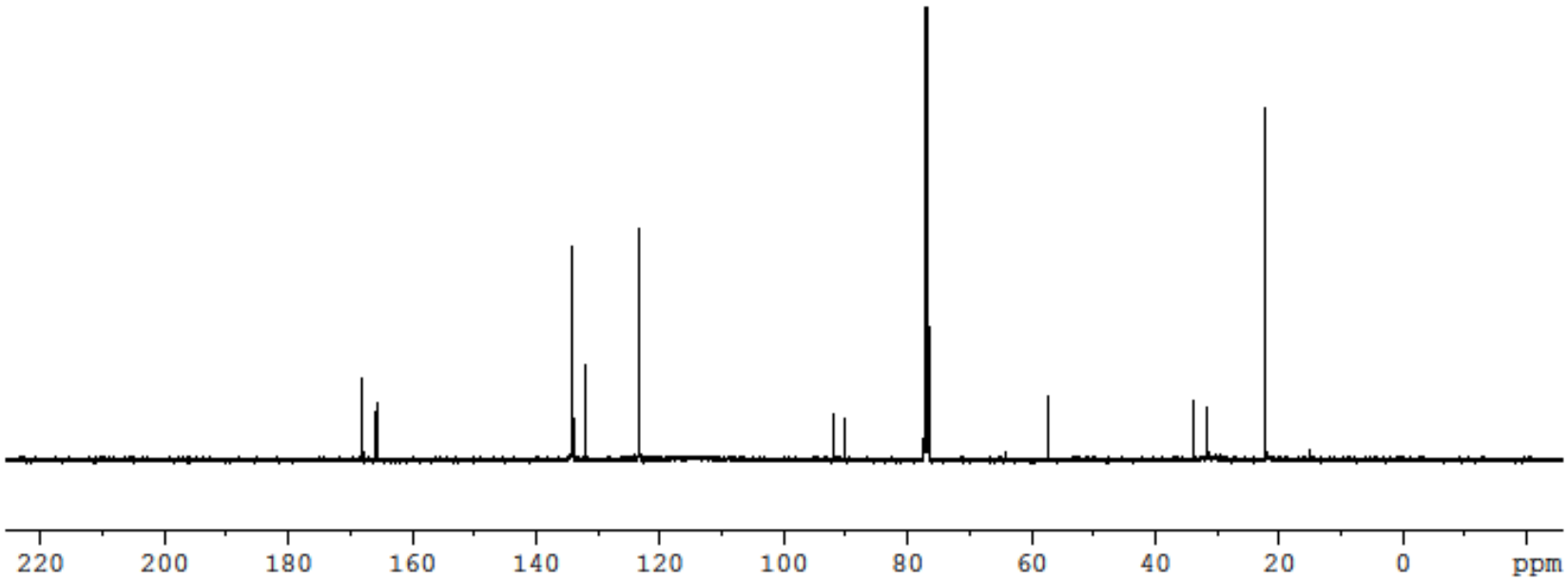
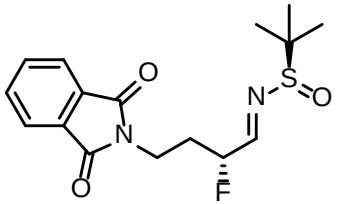


^{19}F



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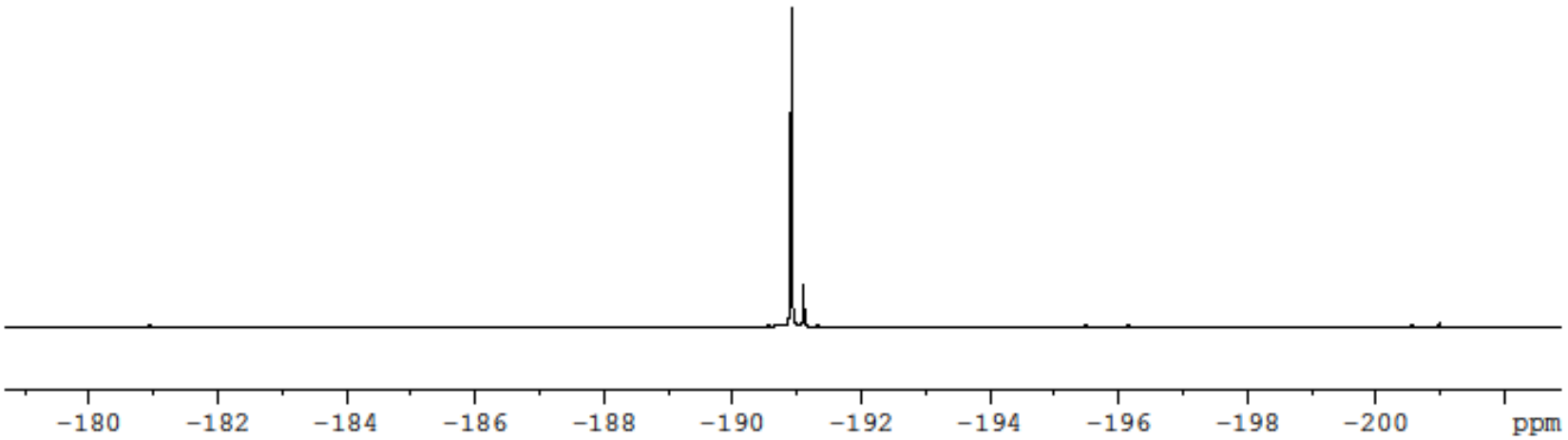

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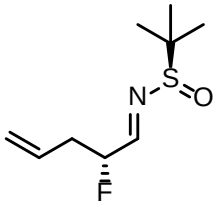

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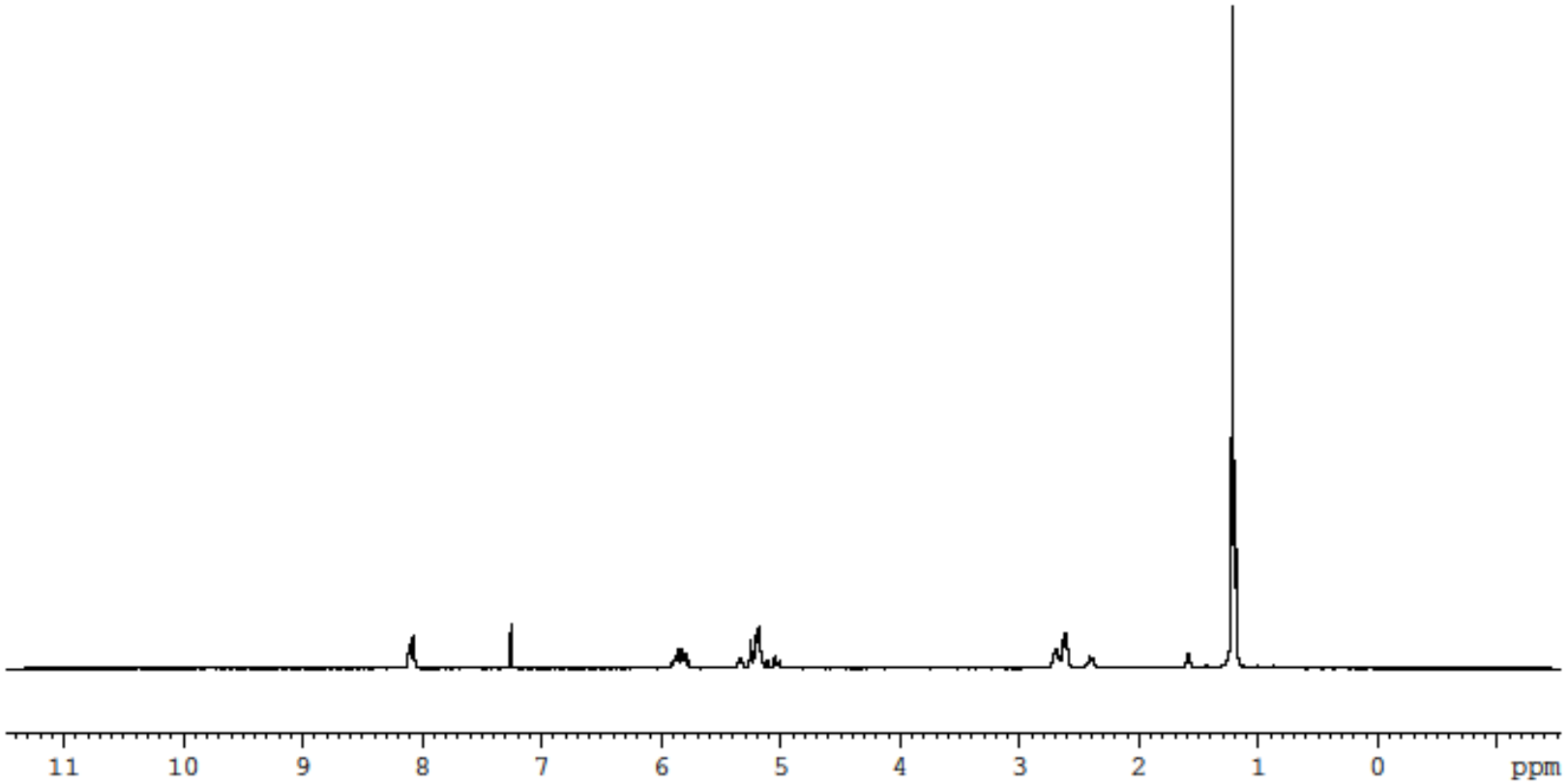

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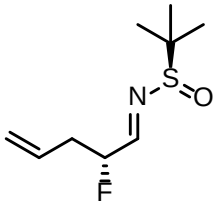

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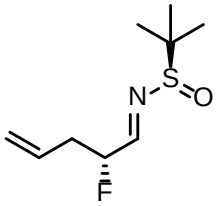

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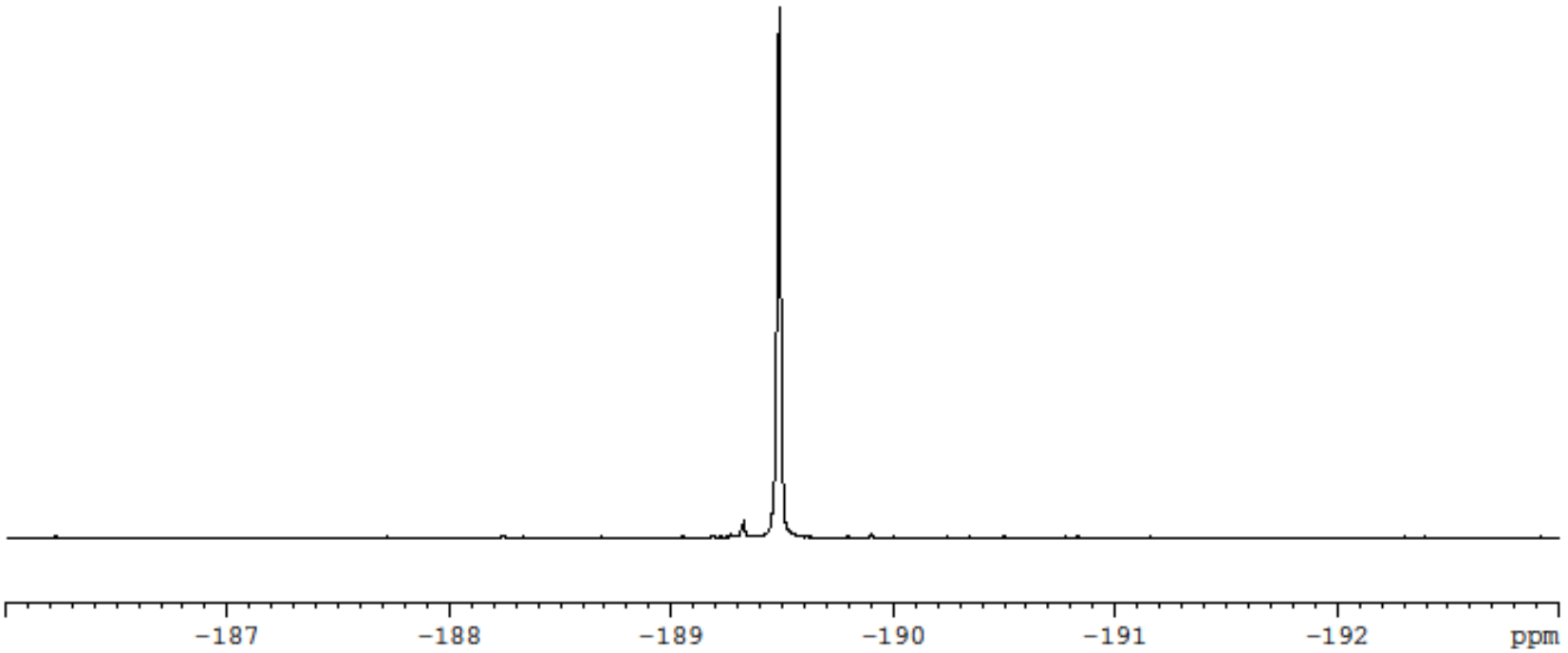

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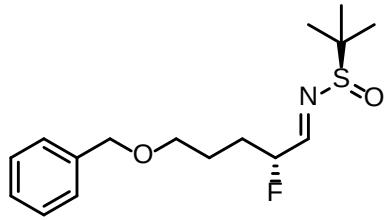

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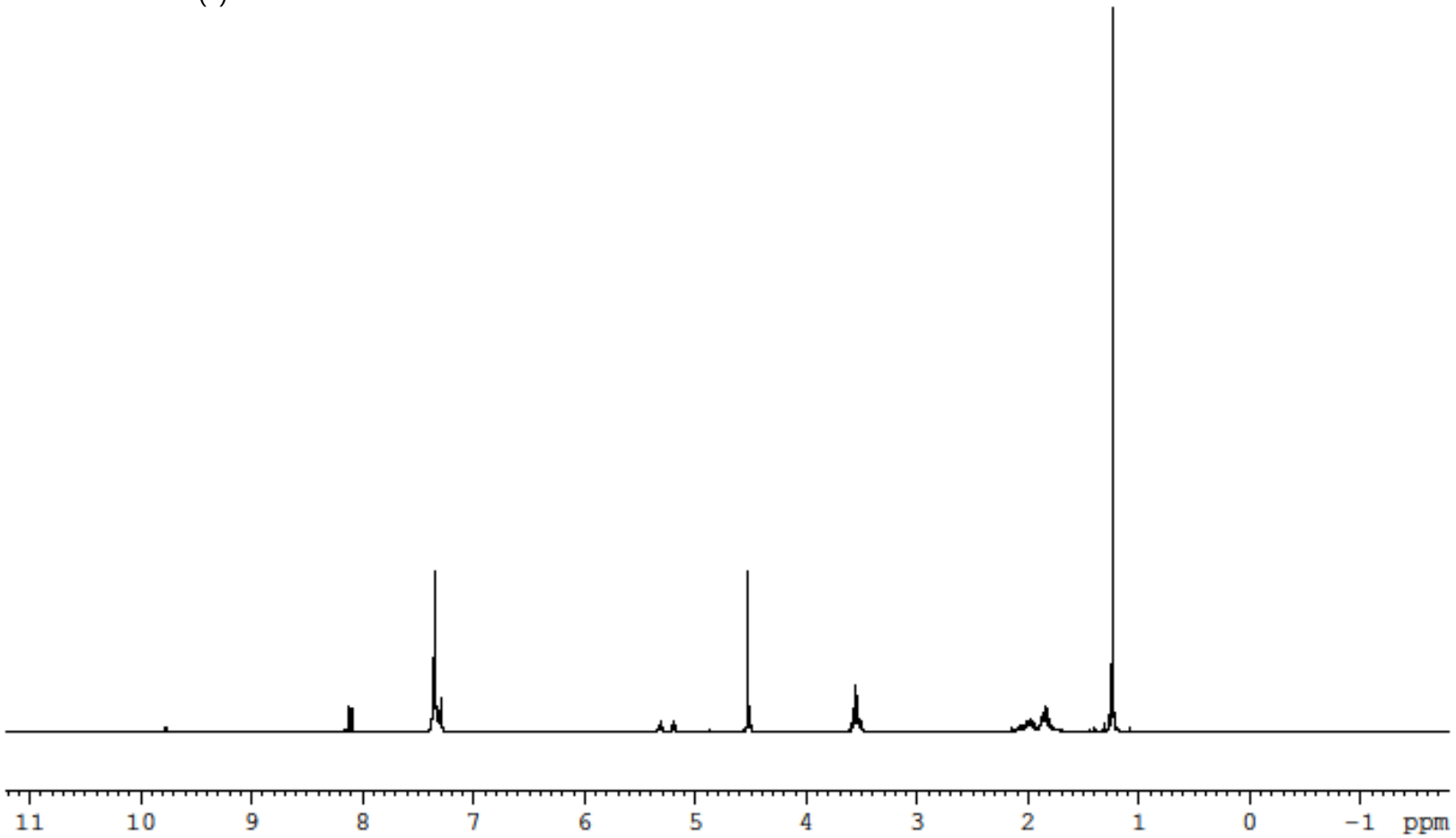

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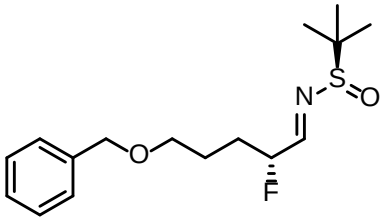

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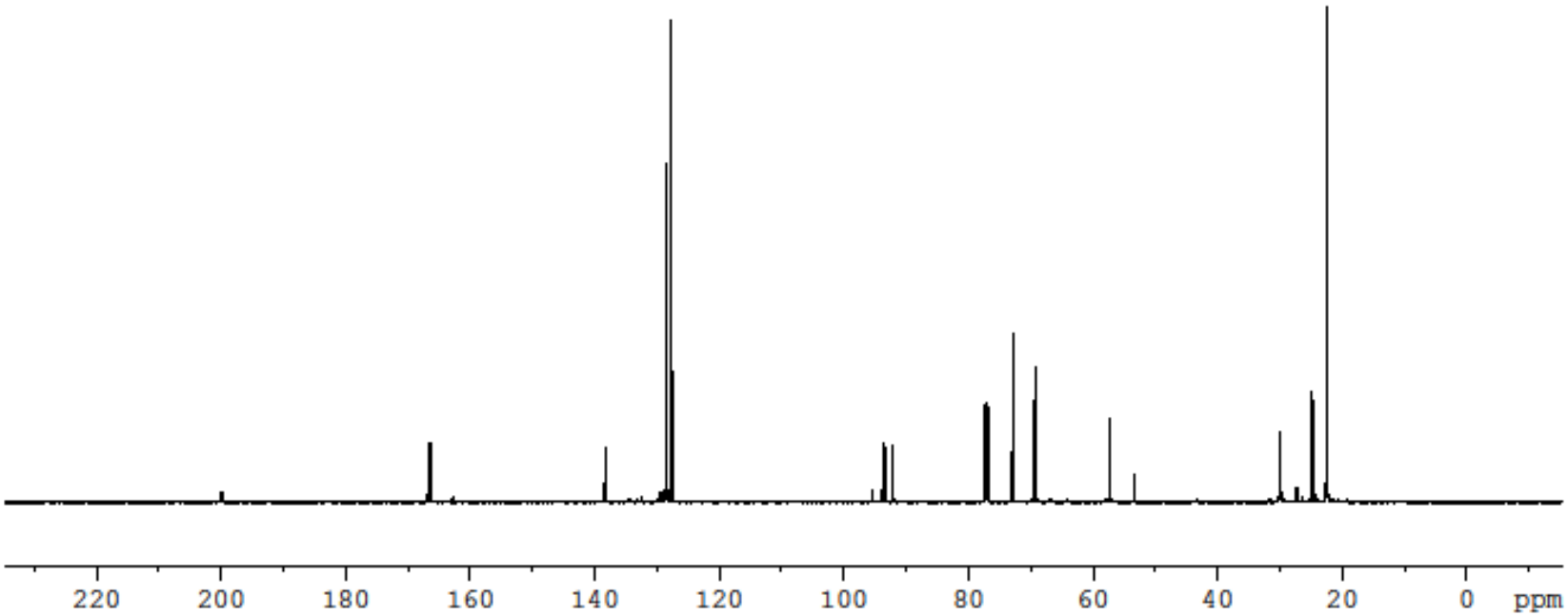

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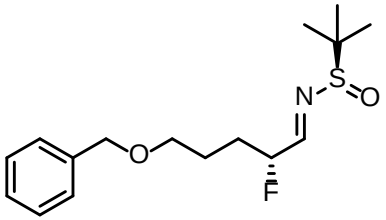

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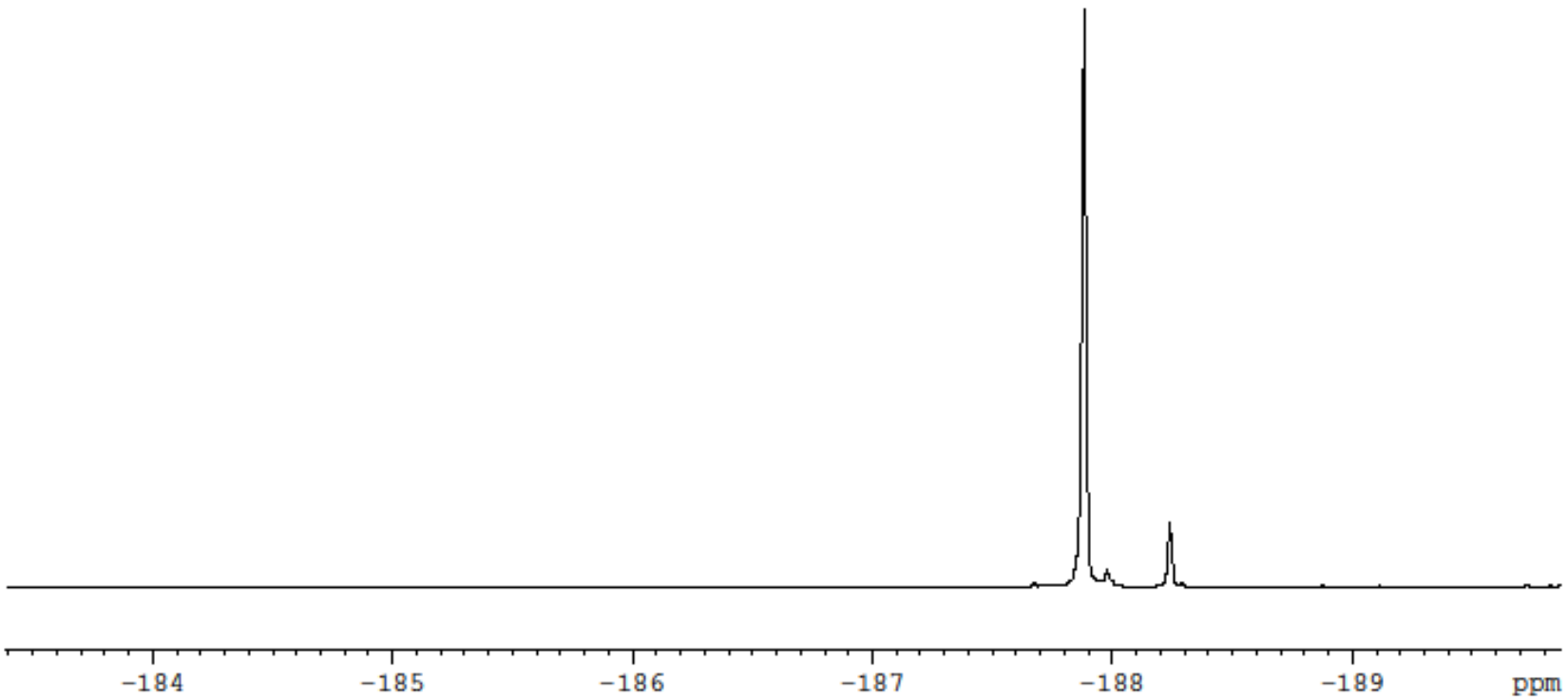

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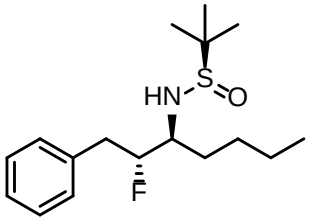

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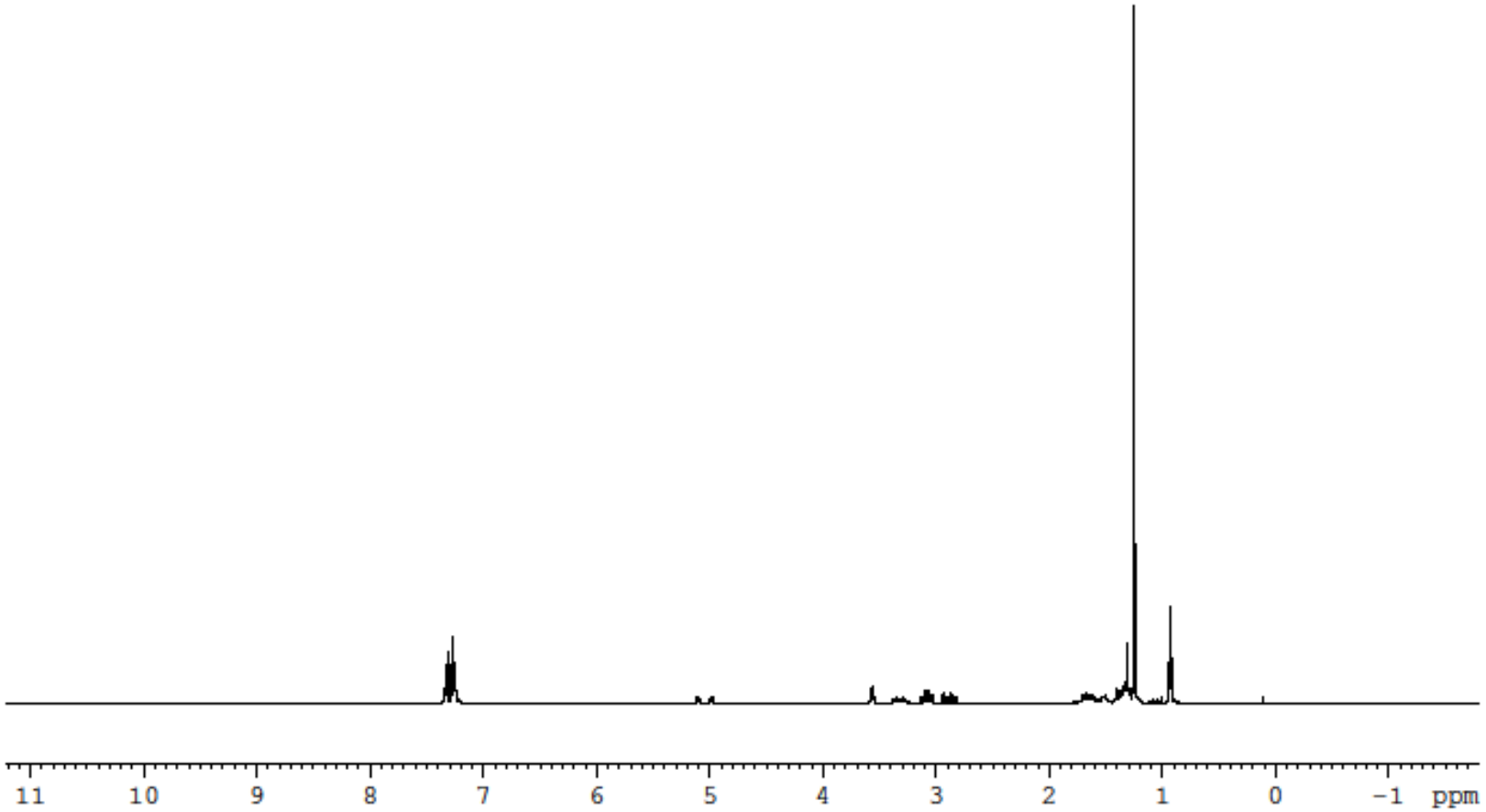

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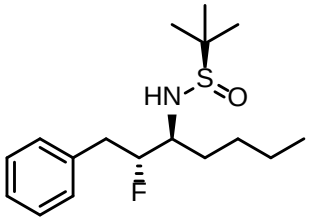

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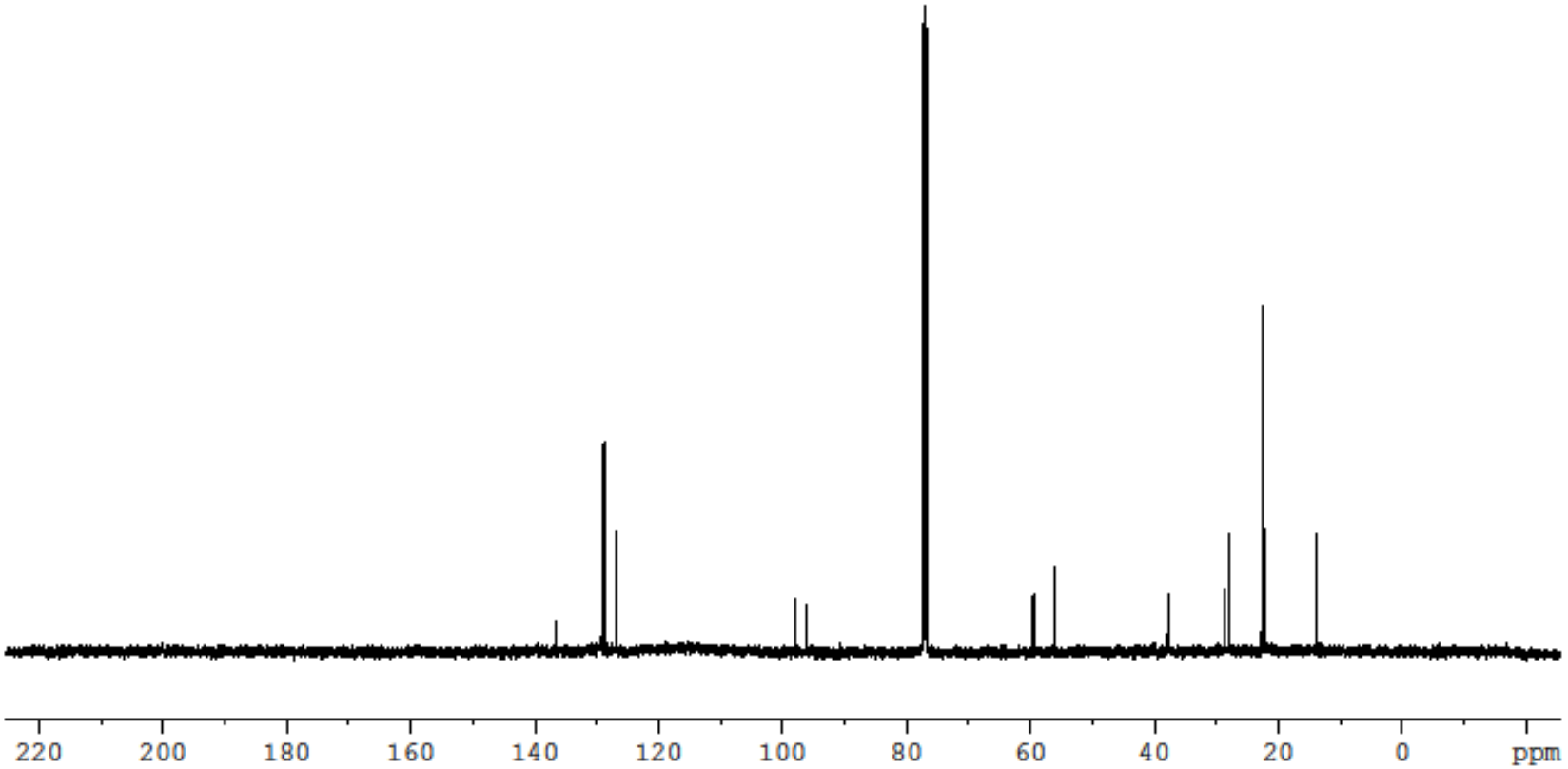

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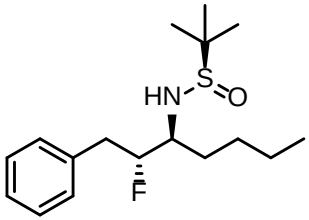

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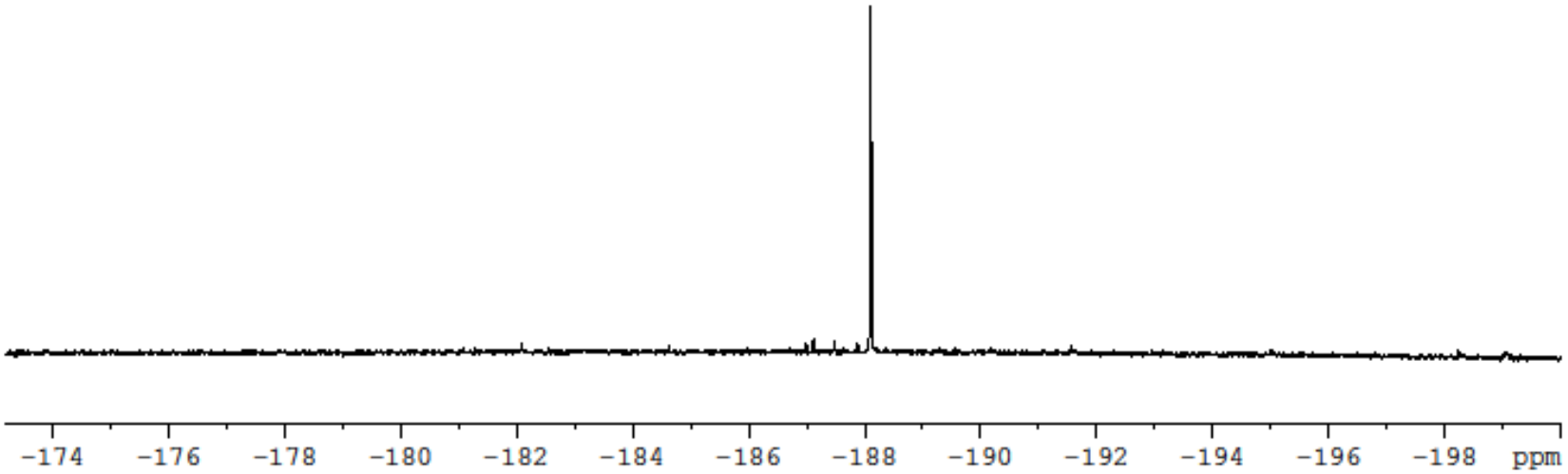

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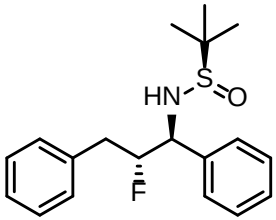

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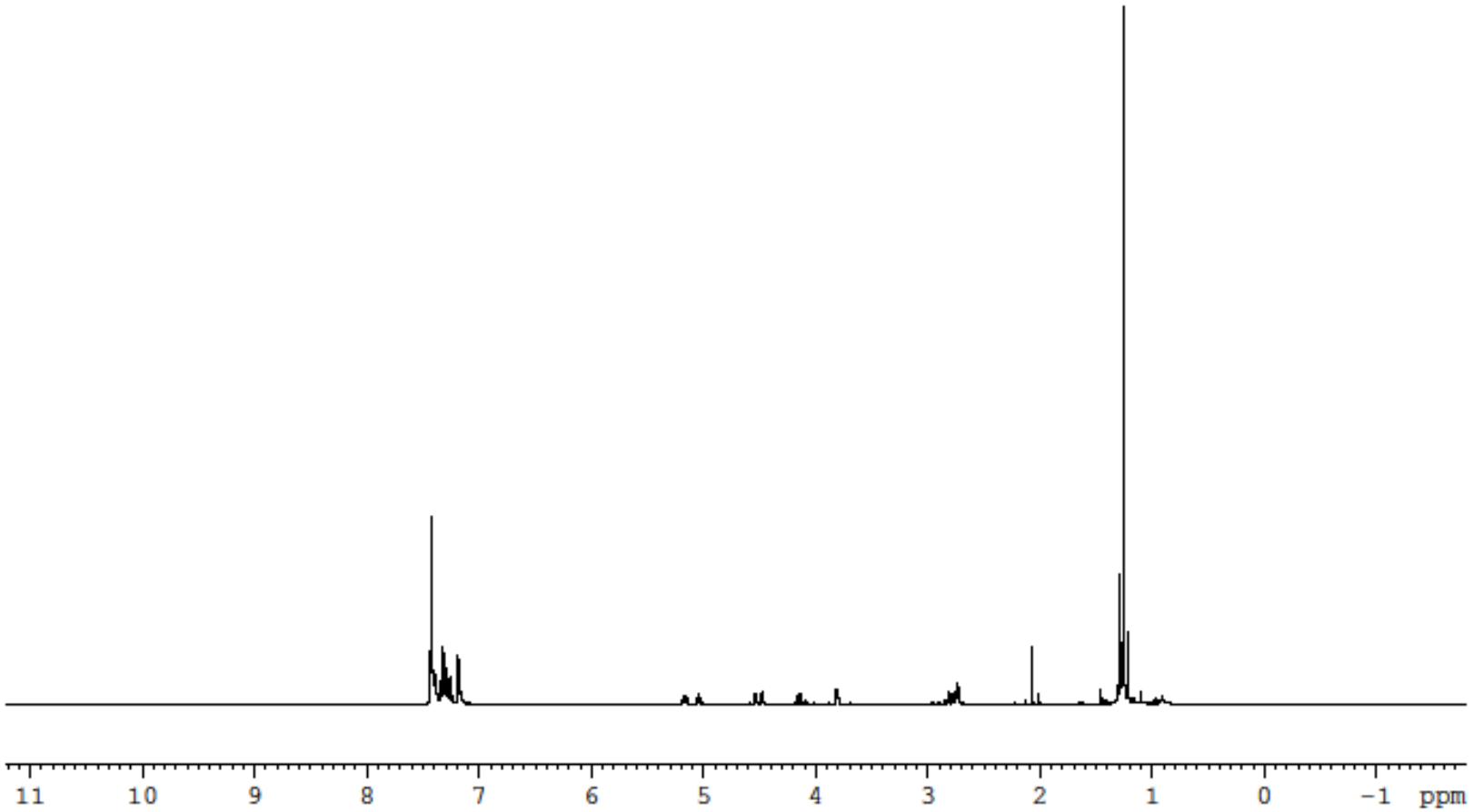

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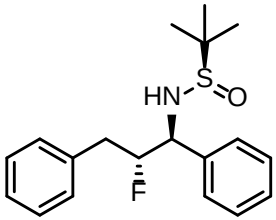

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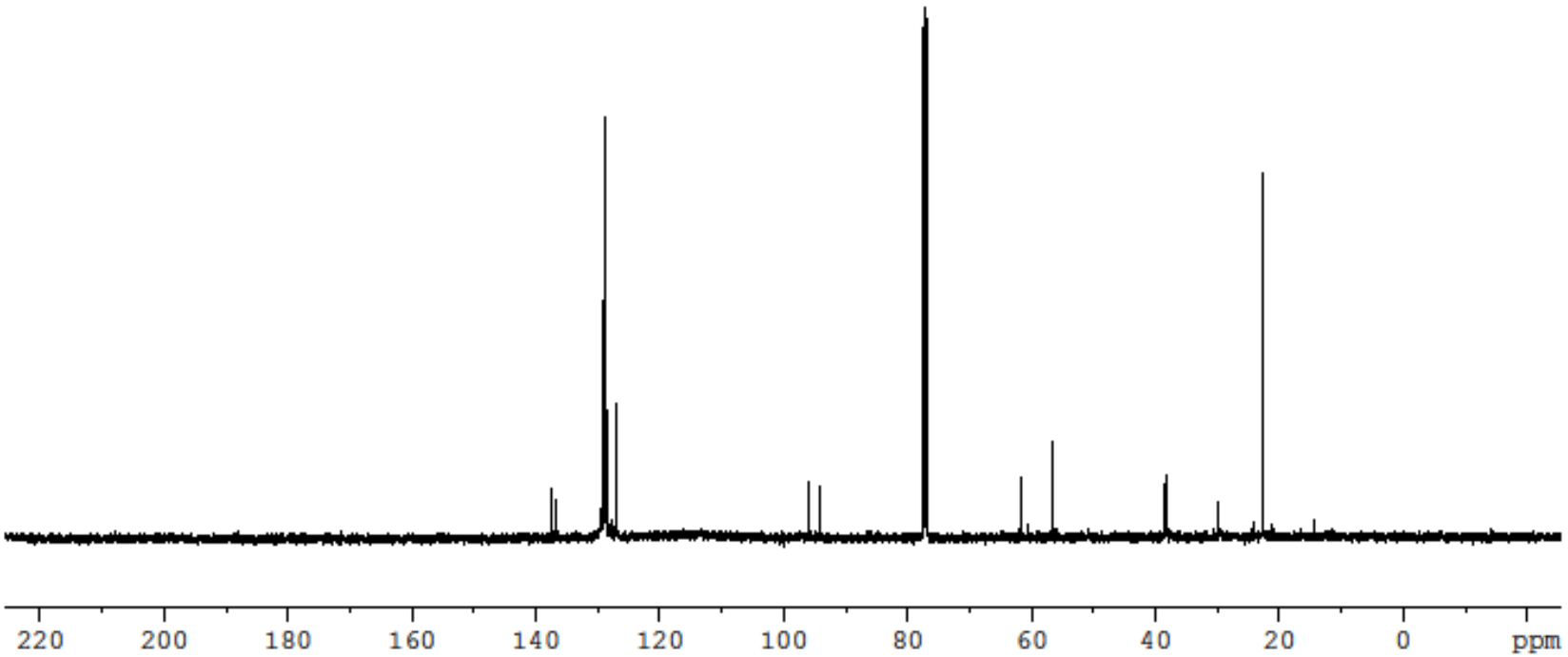

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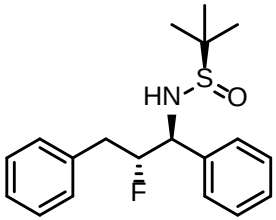

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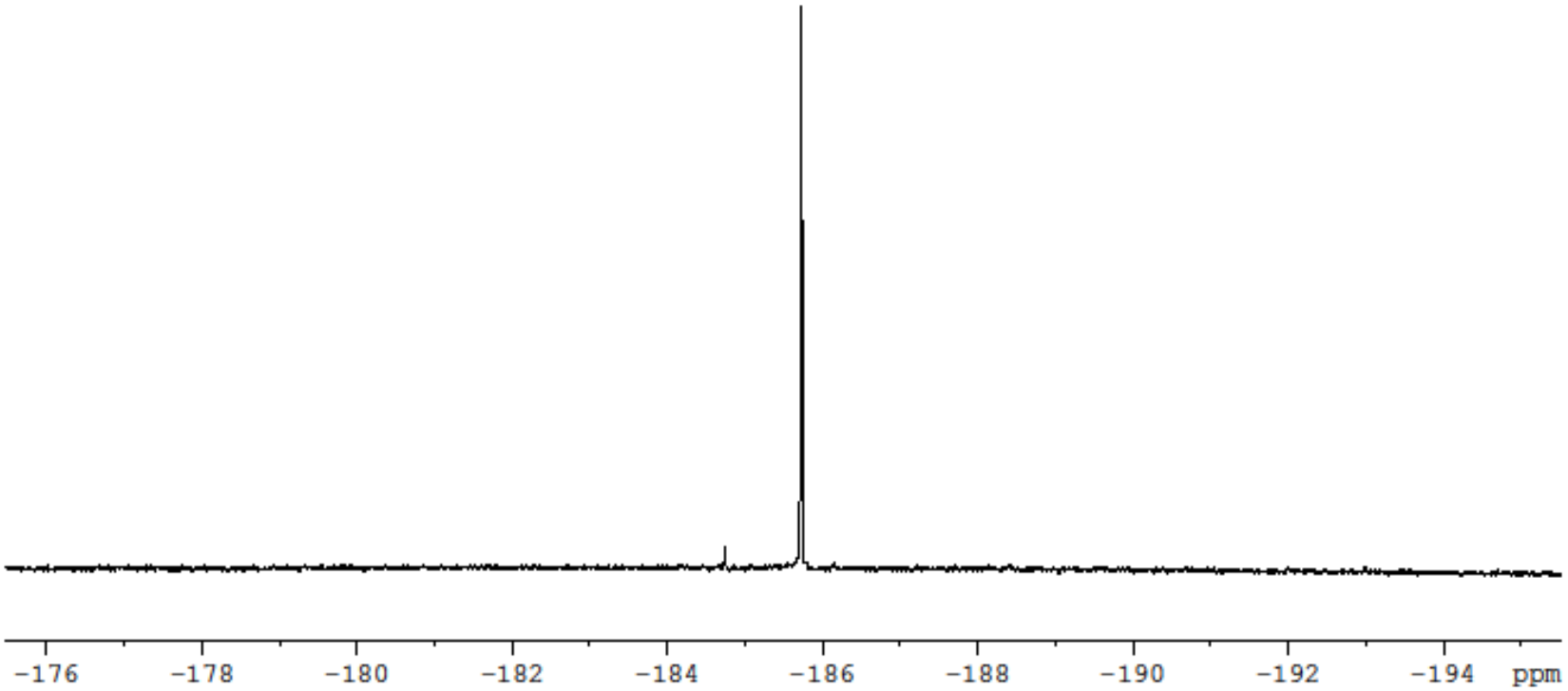

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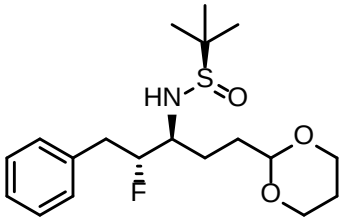

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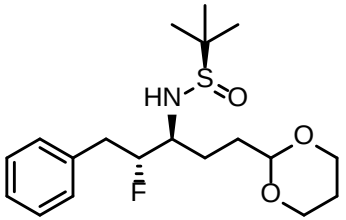

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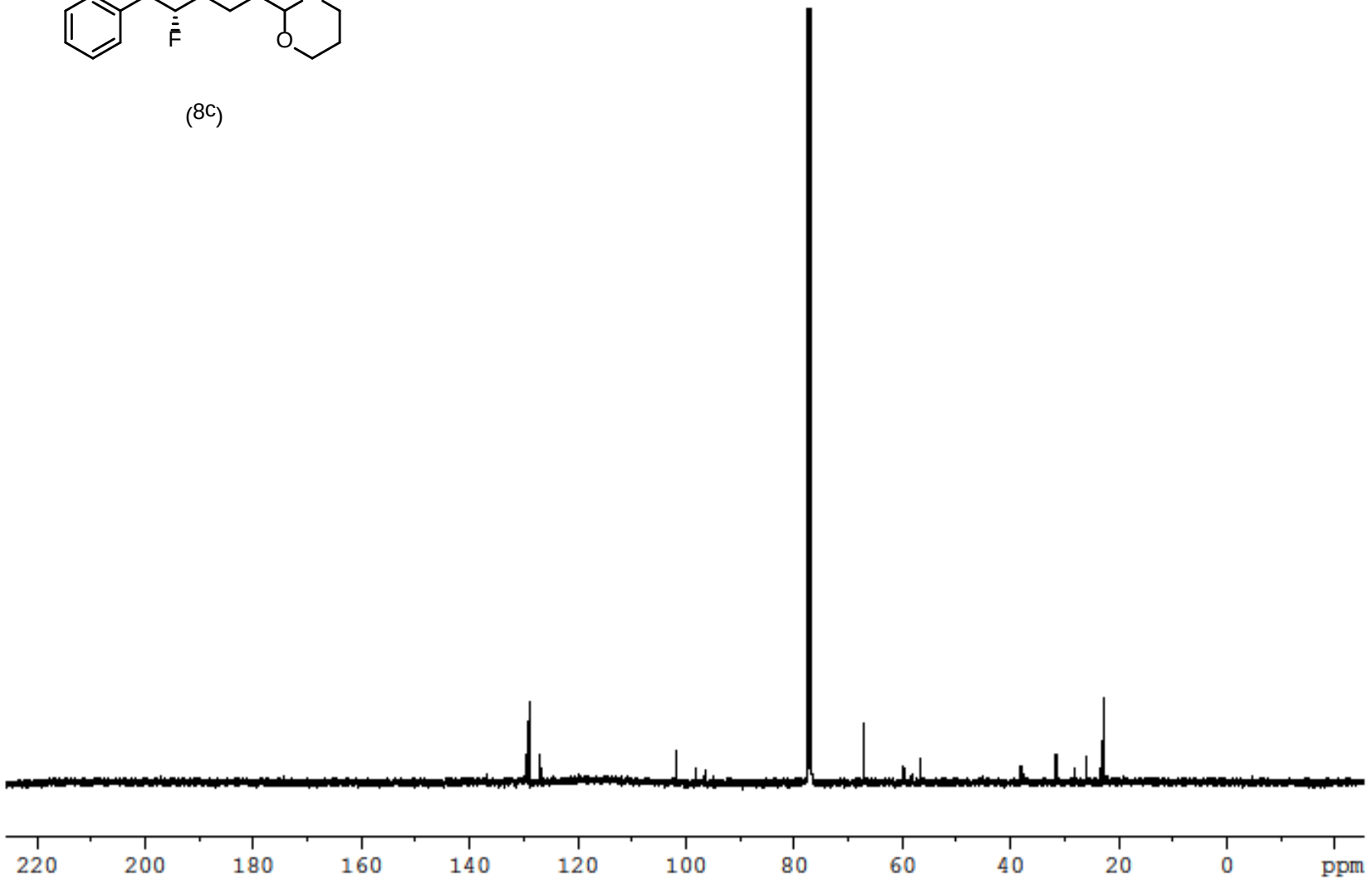

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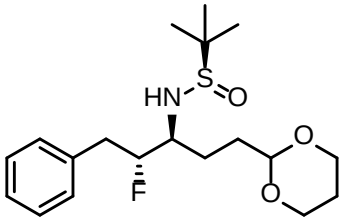

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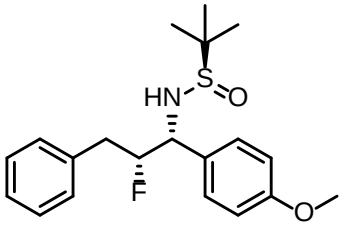

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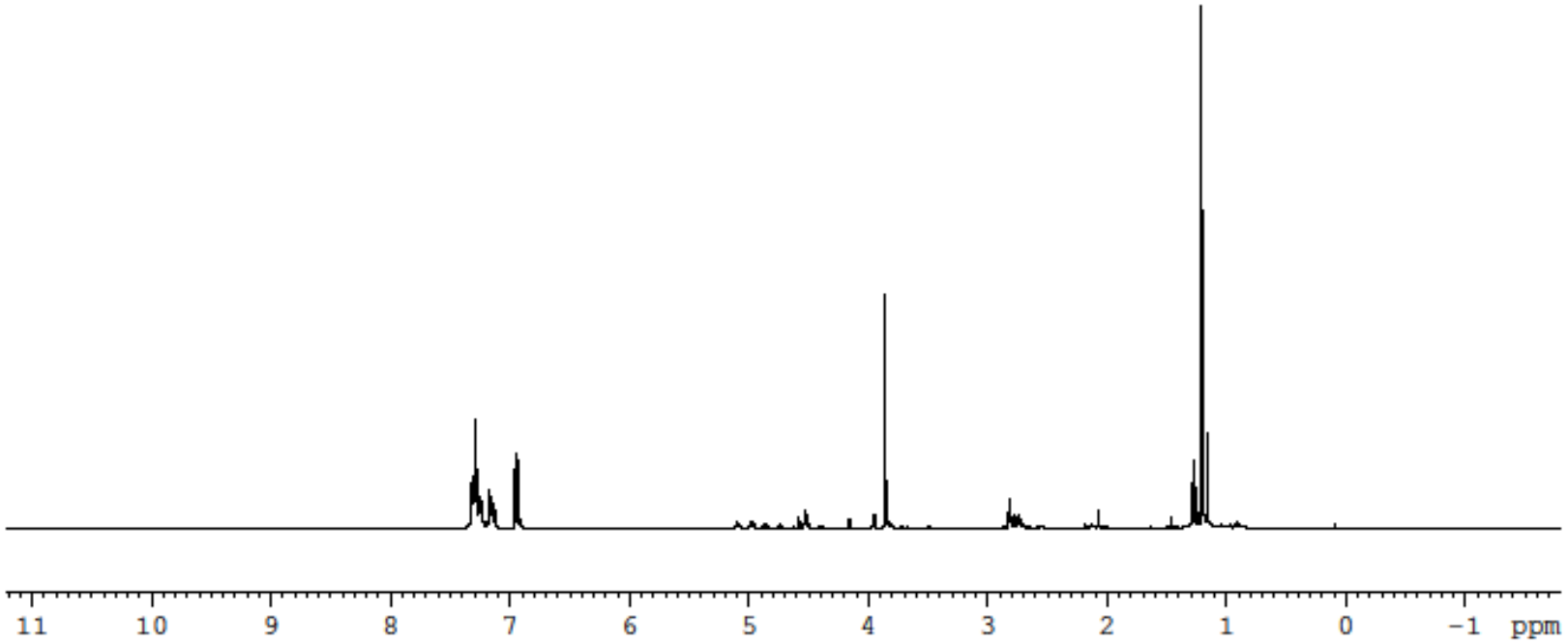

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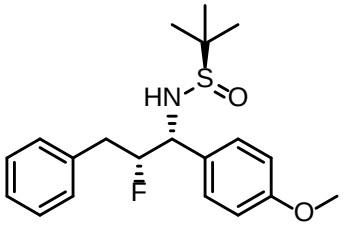

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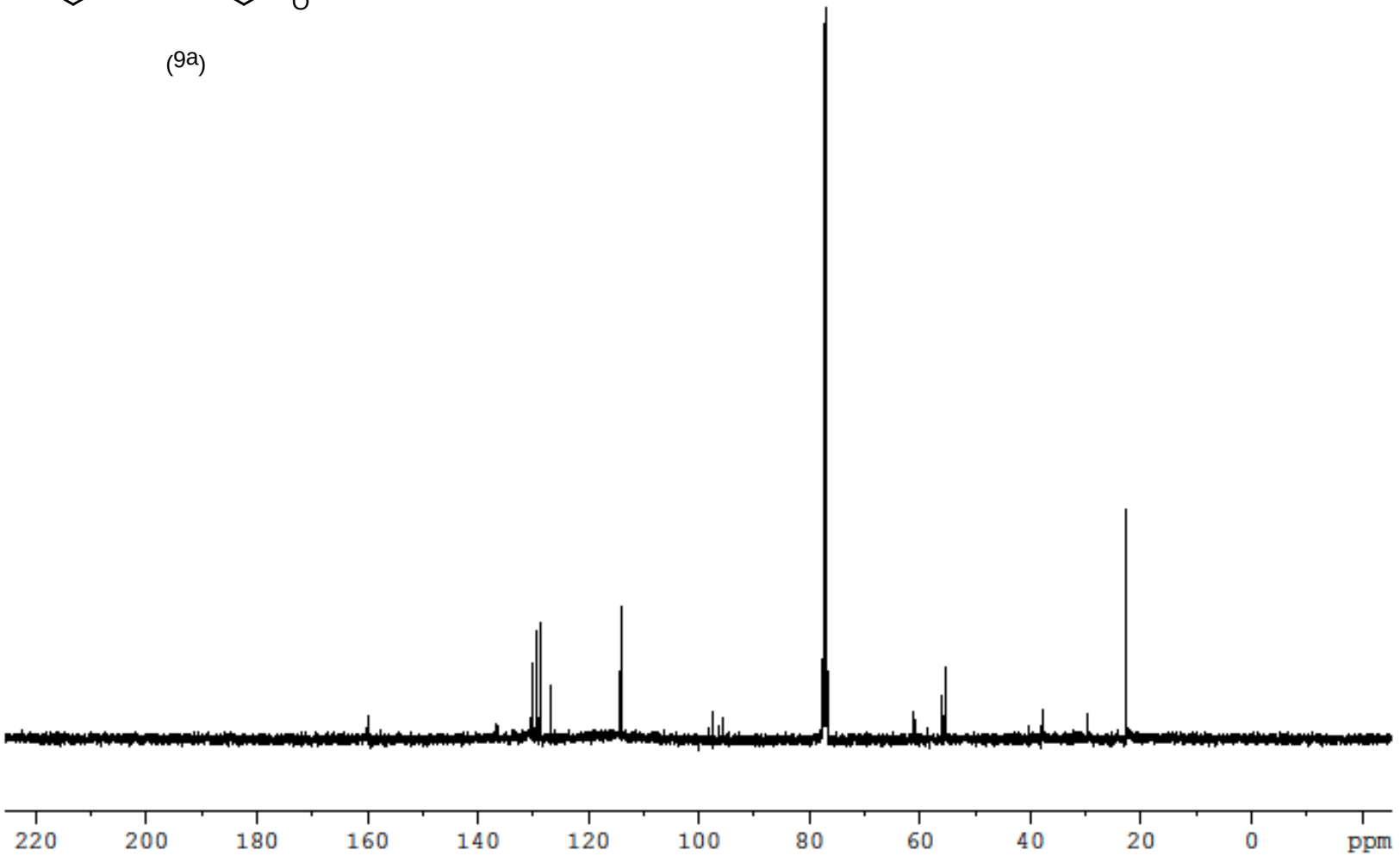

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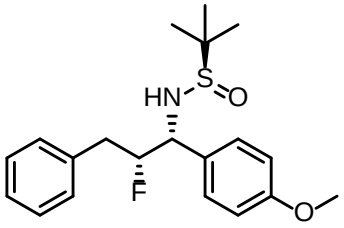

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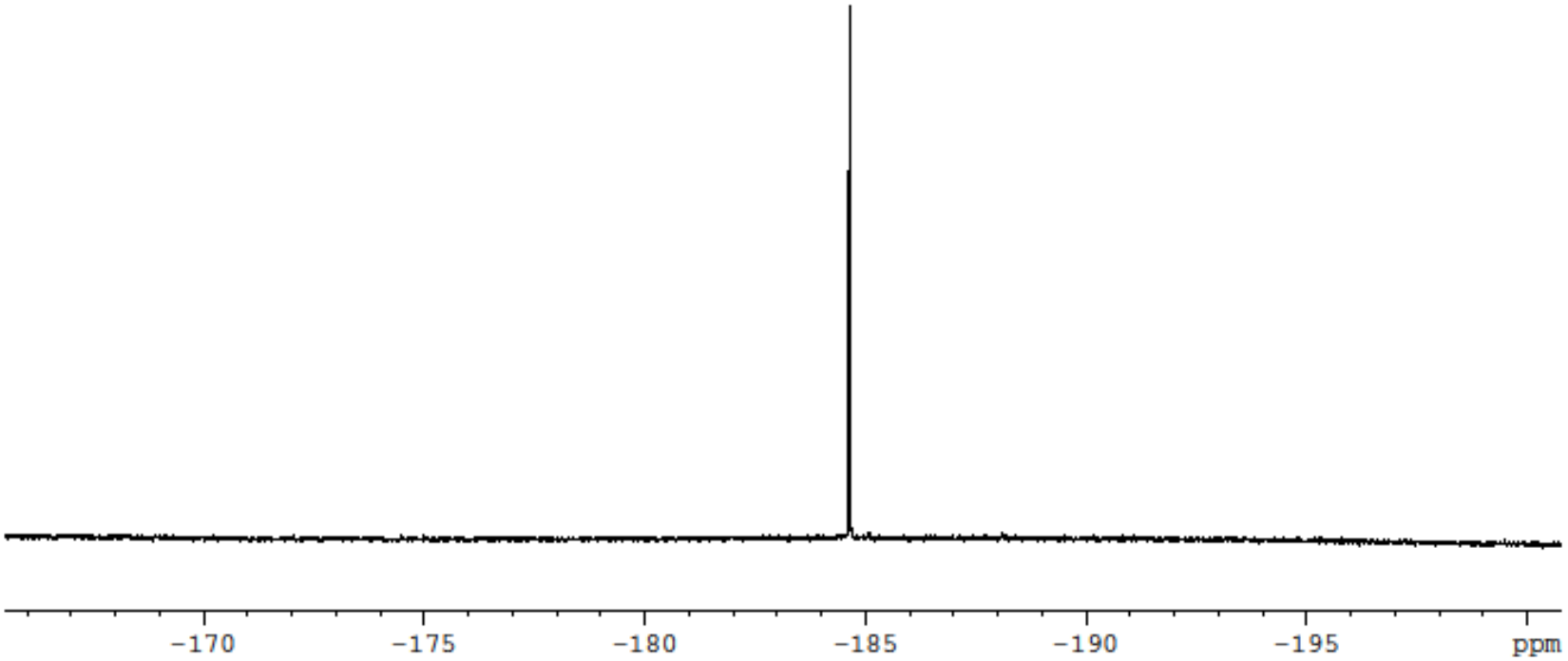

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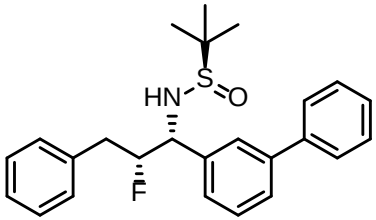

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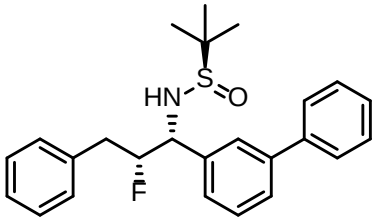

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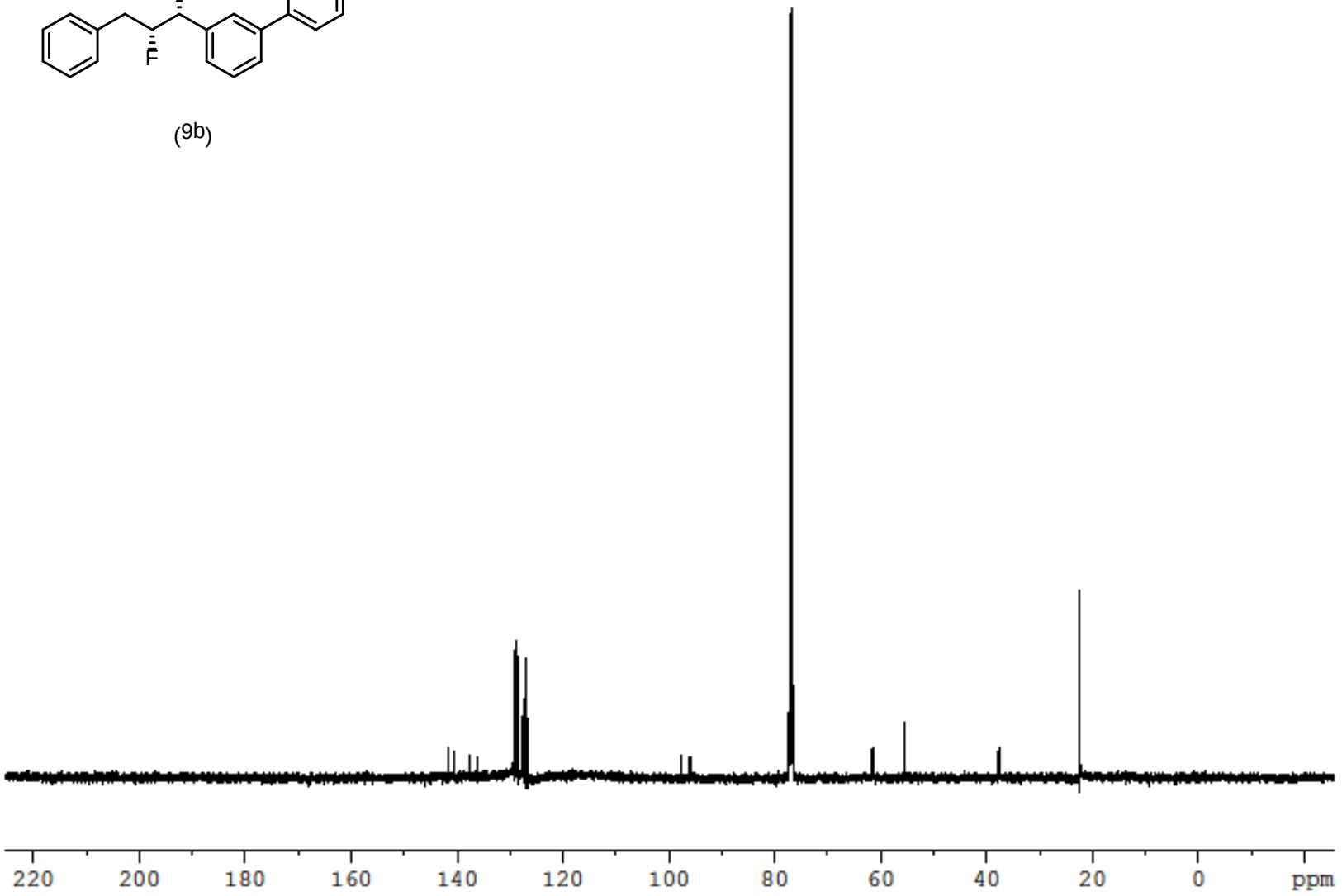

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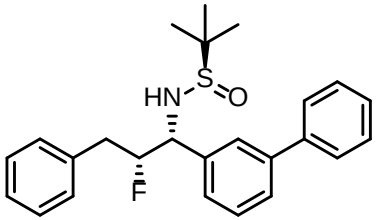
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(9b)

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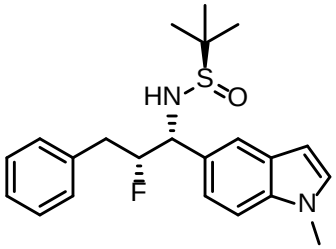

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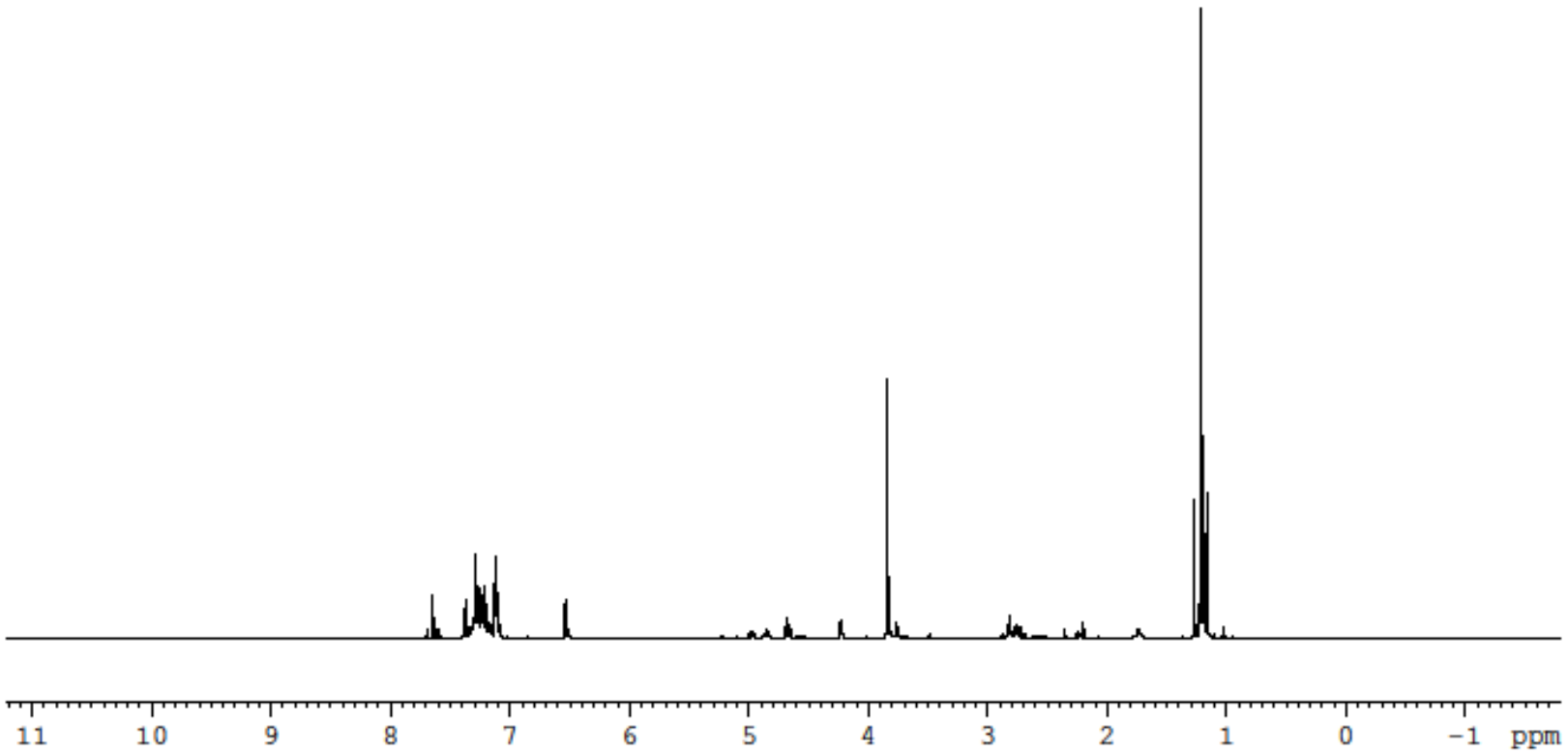

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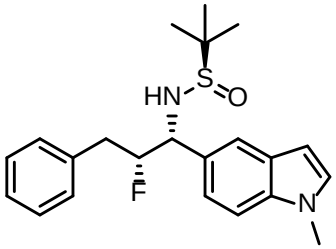

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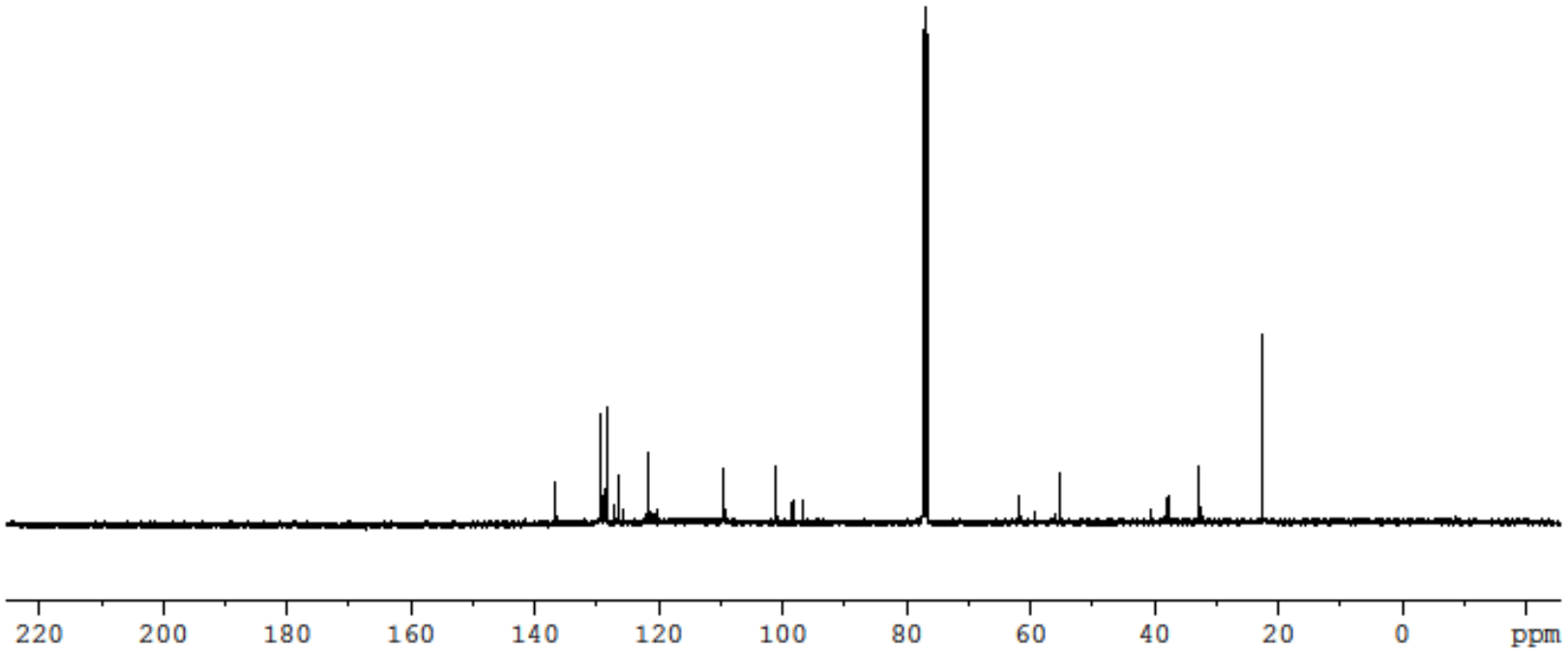

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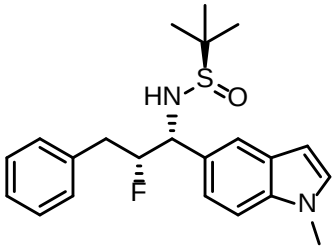

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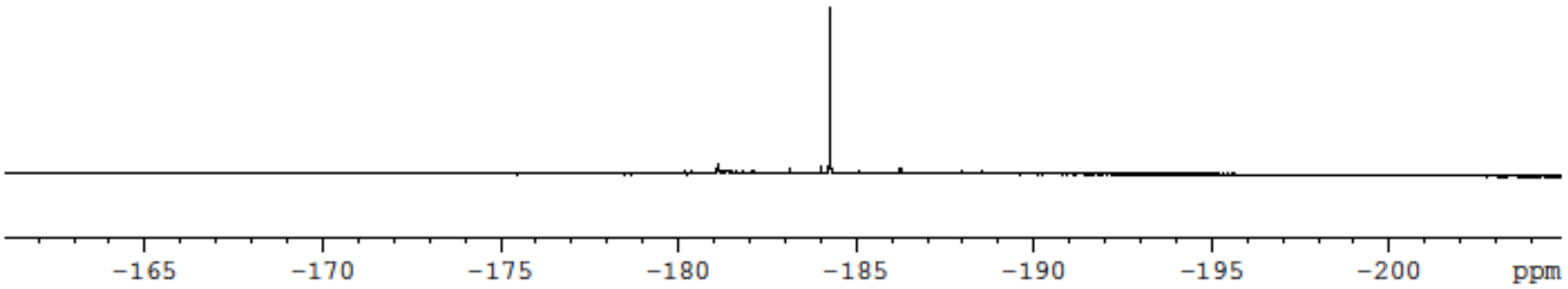

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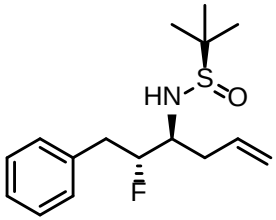

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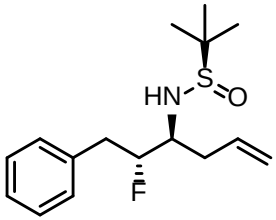

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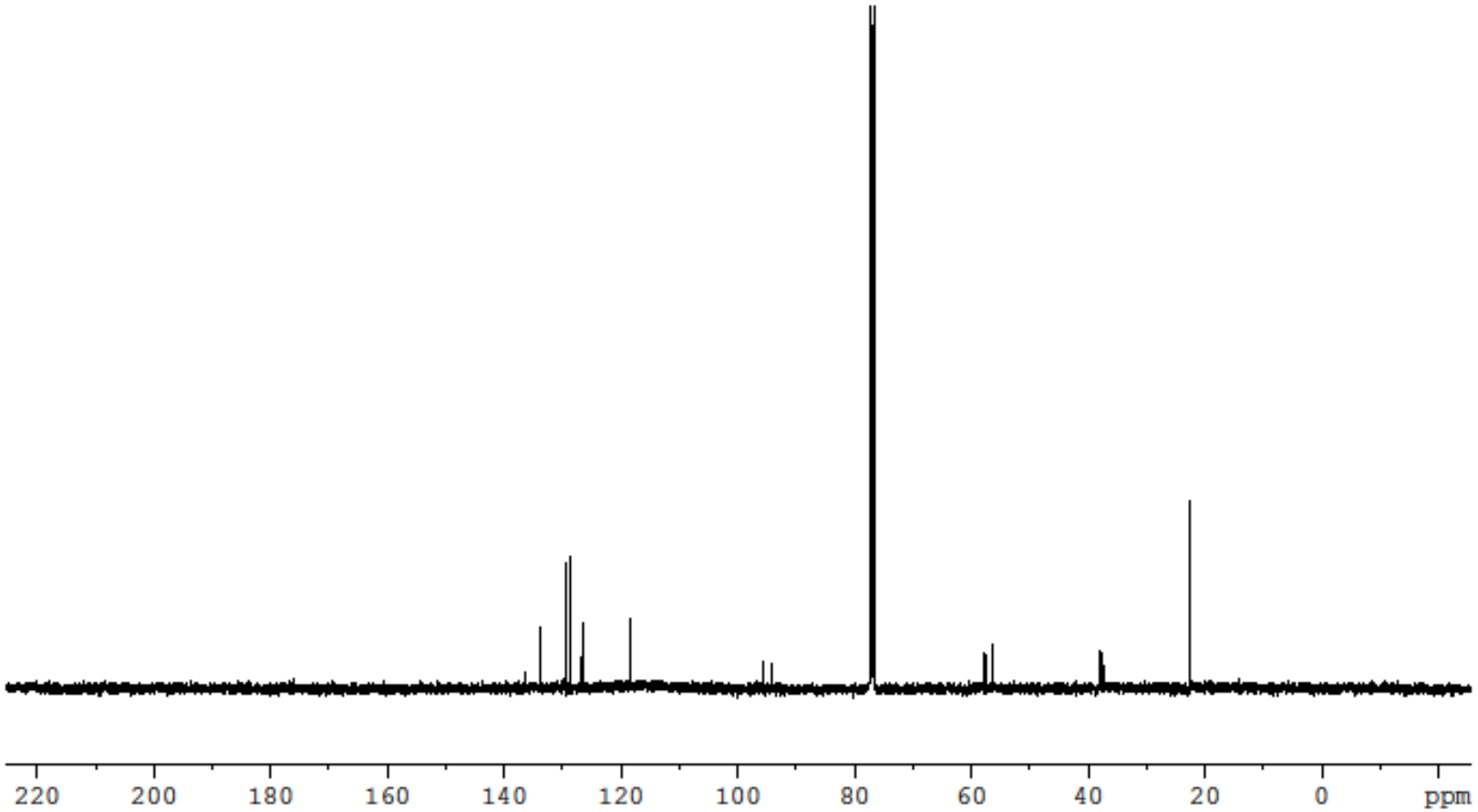

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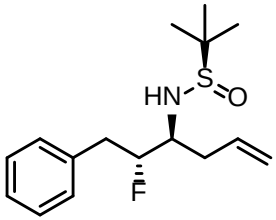

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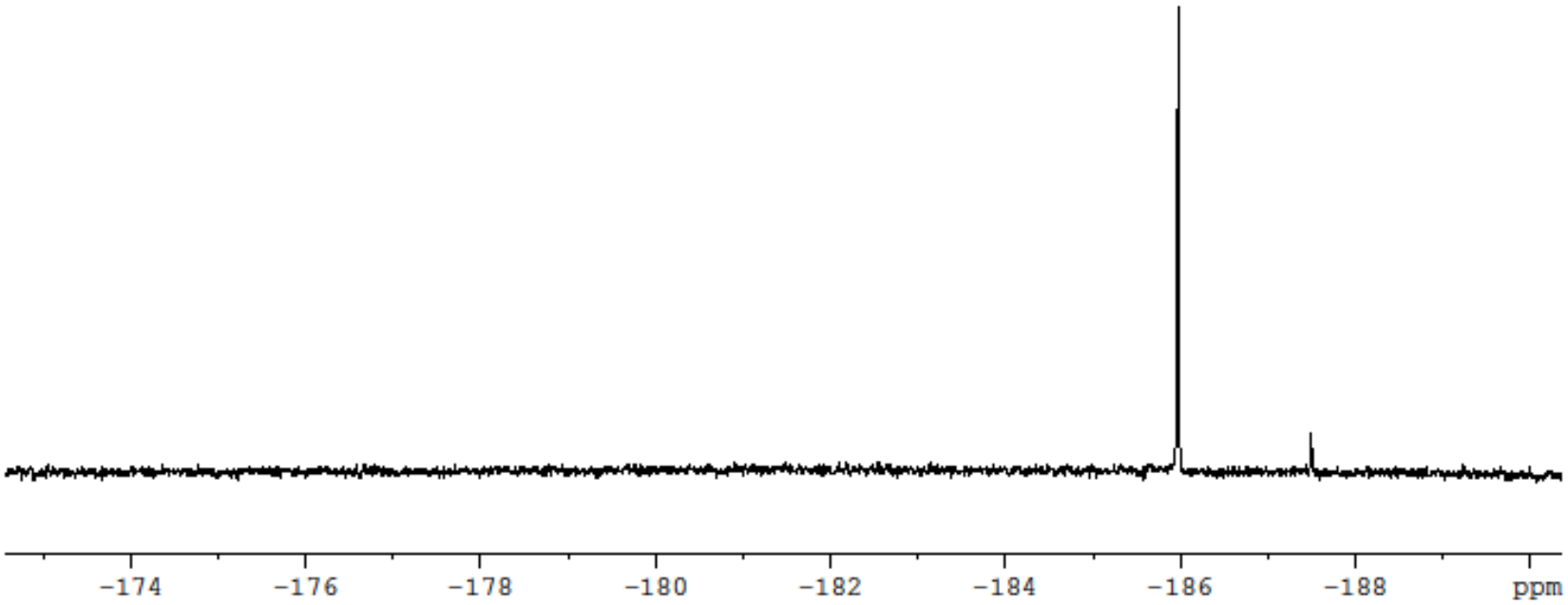

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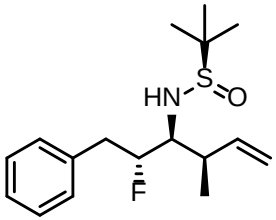

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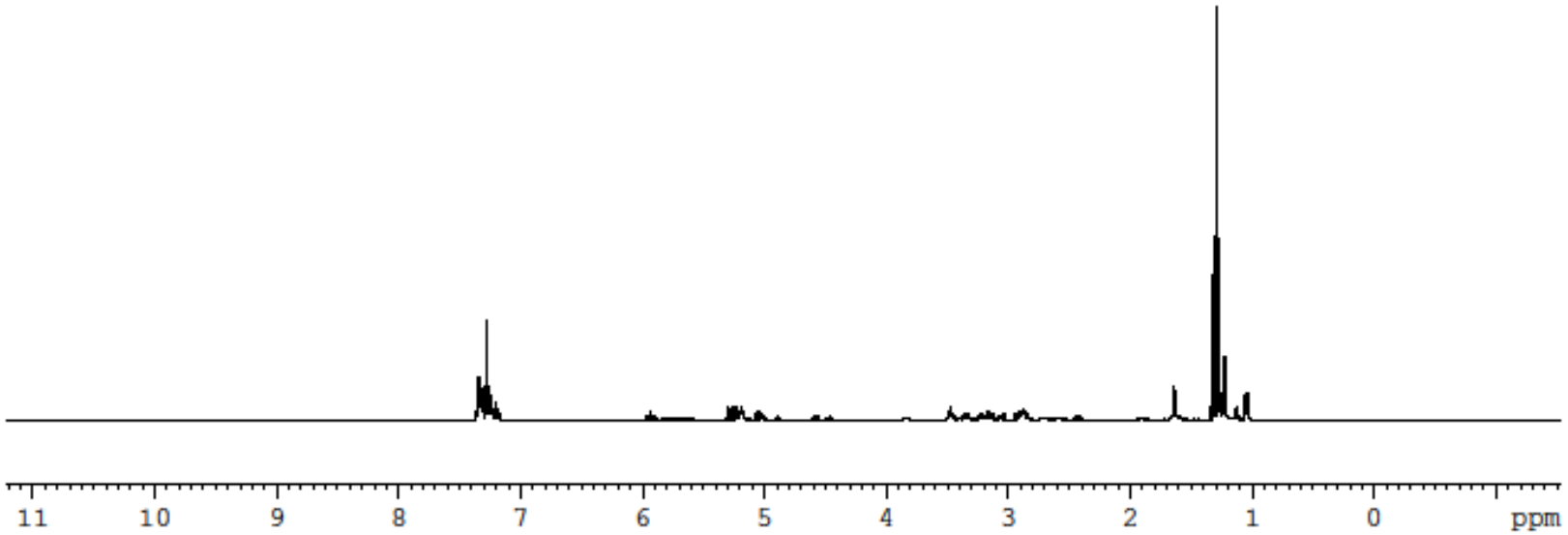

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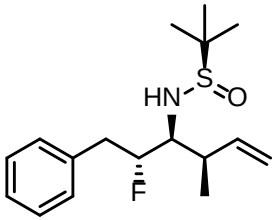

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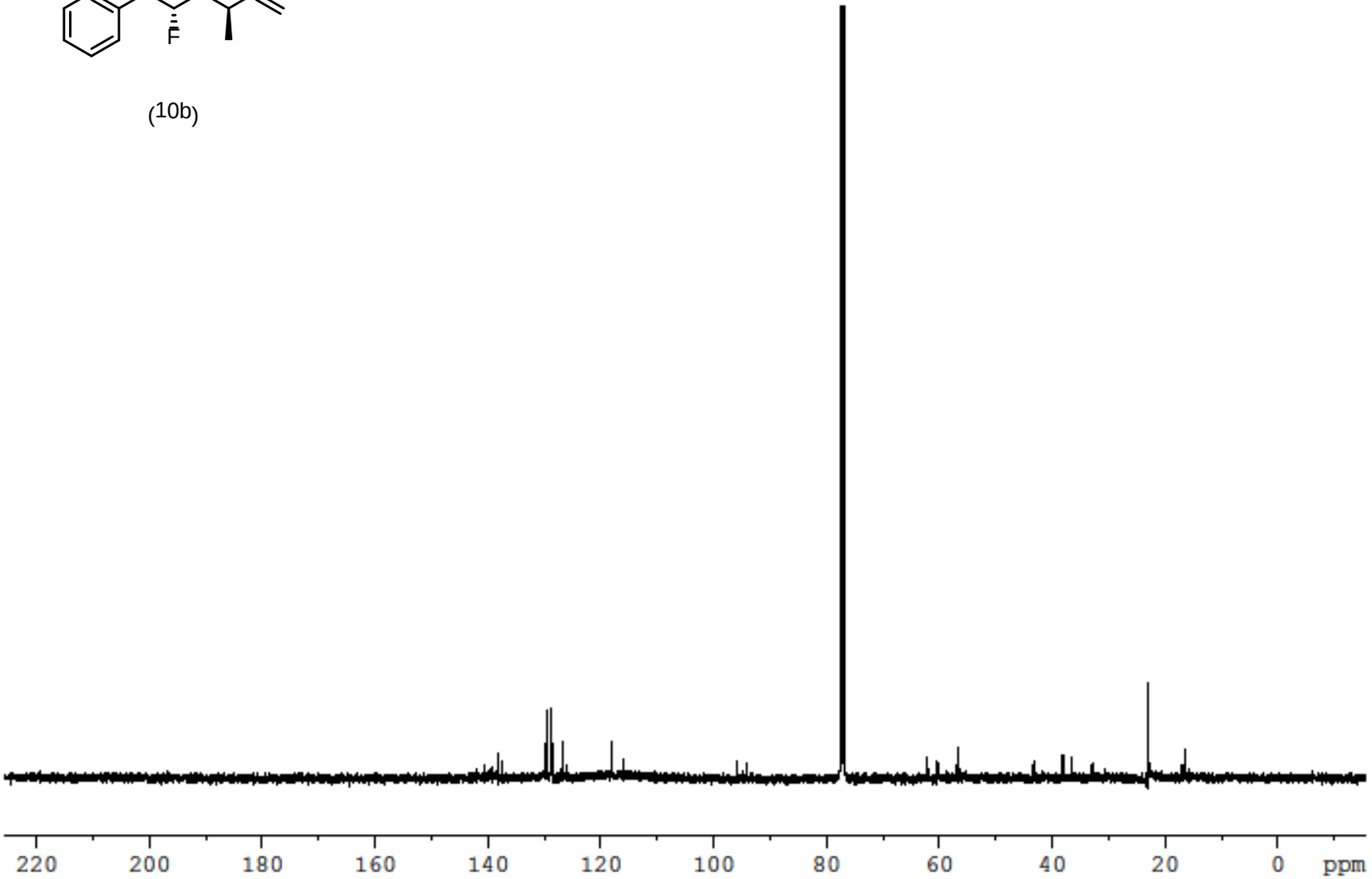

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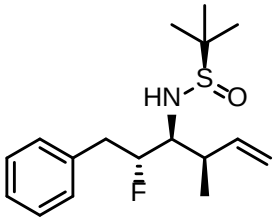

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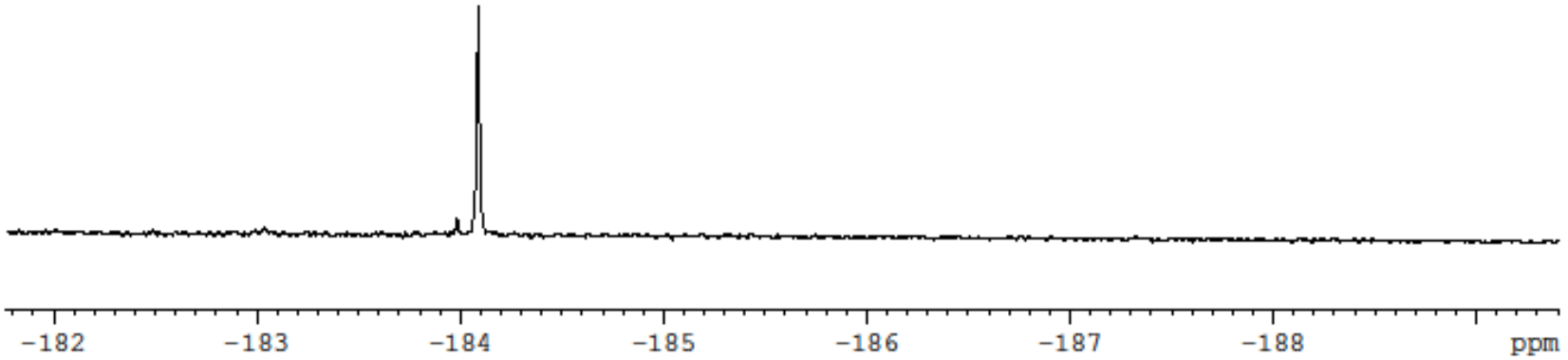

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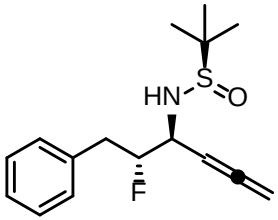

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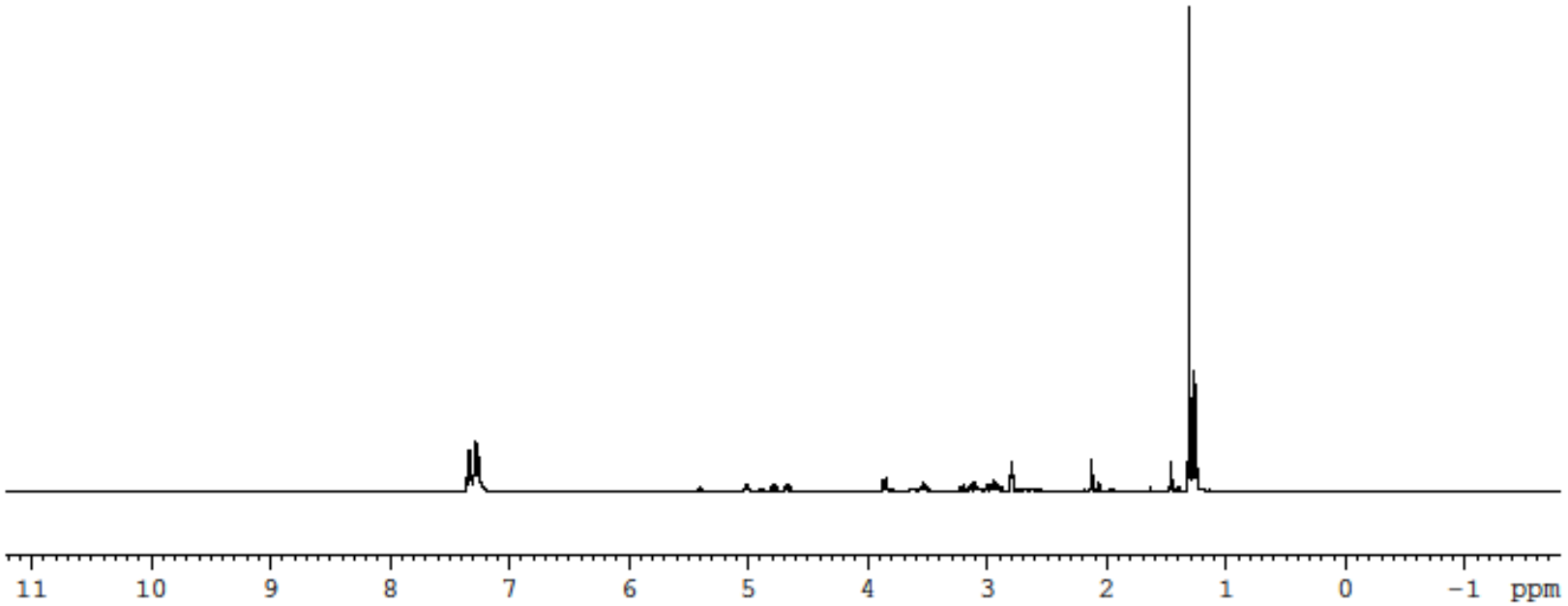

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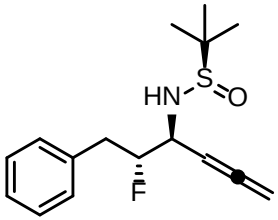

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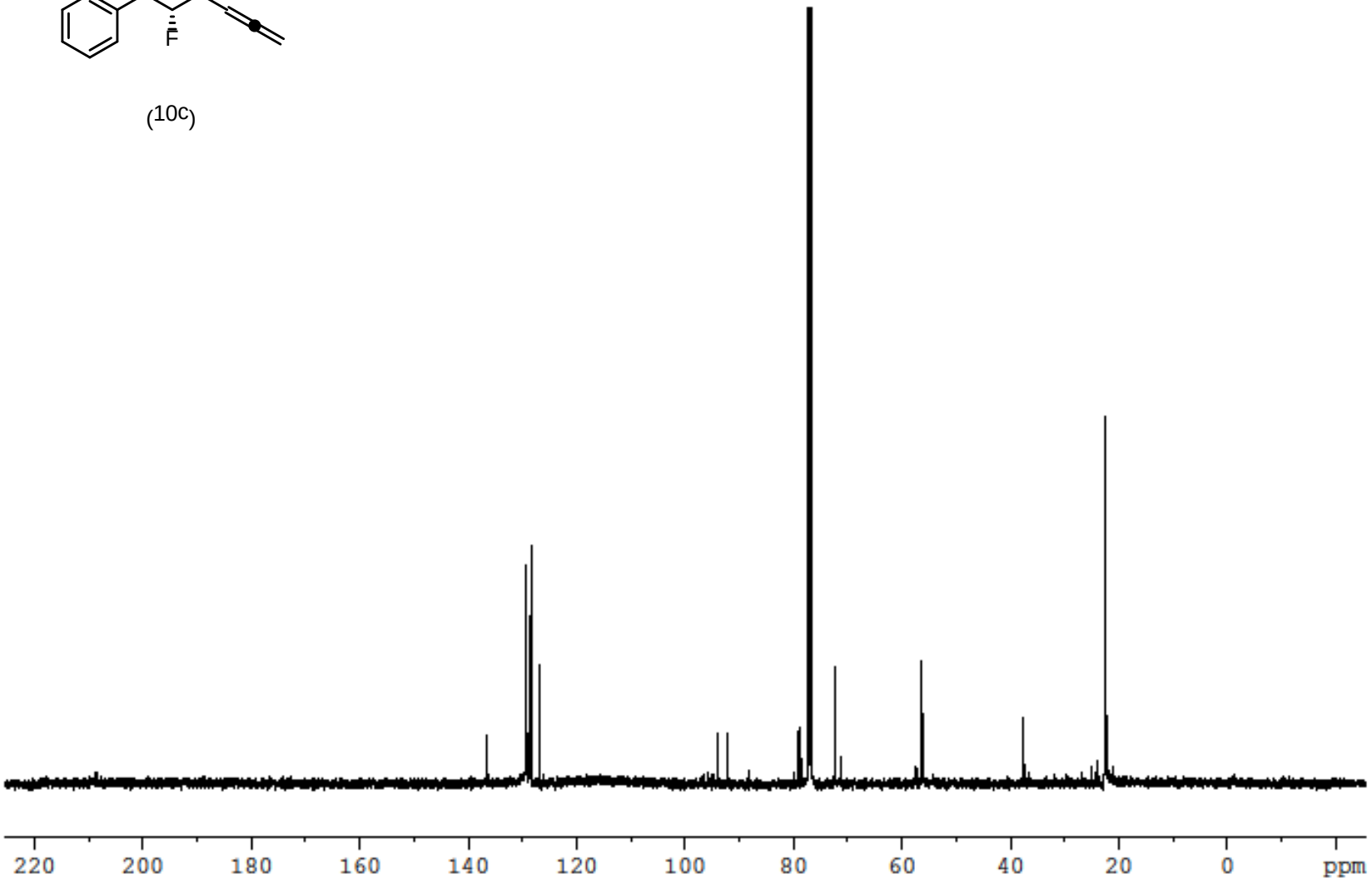

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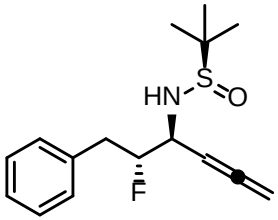
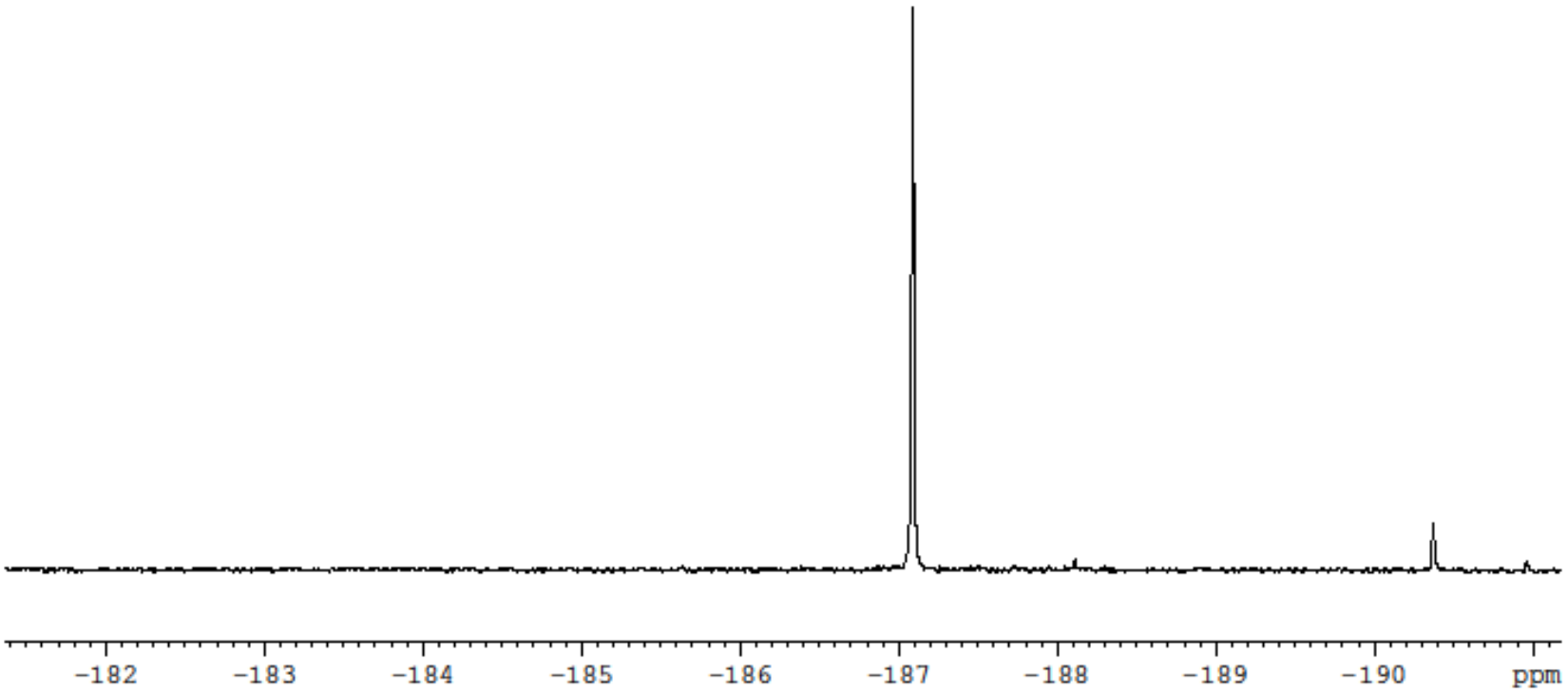


($10c$)



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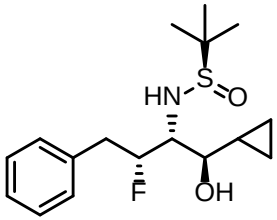

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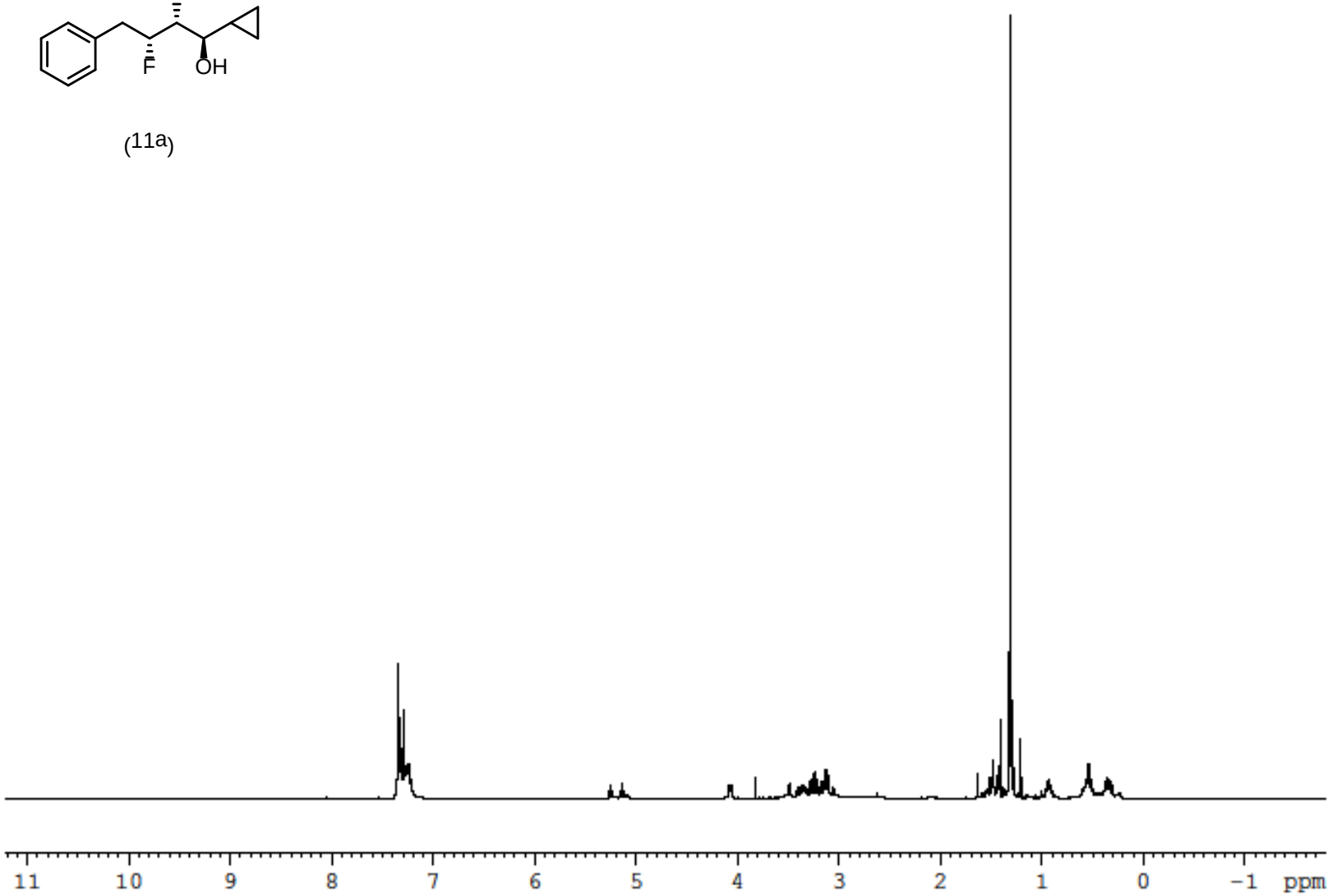

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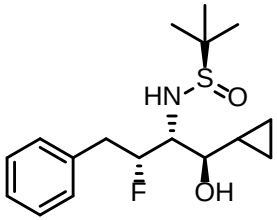

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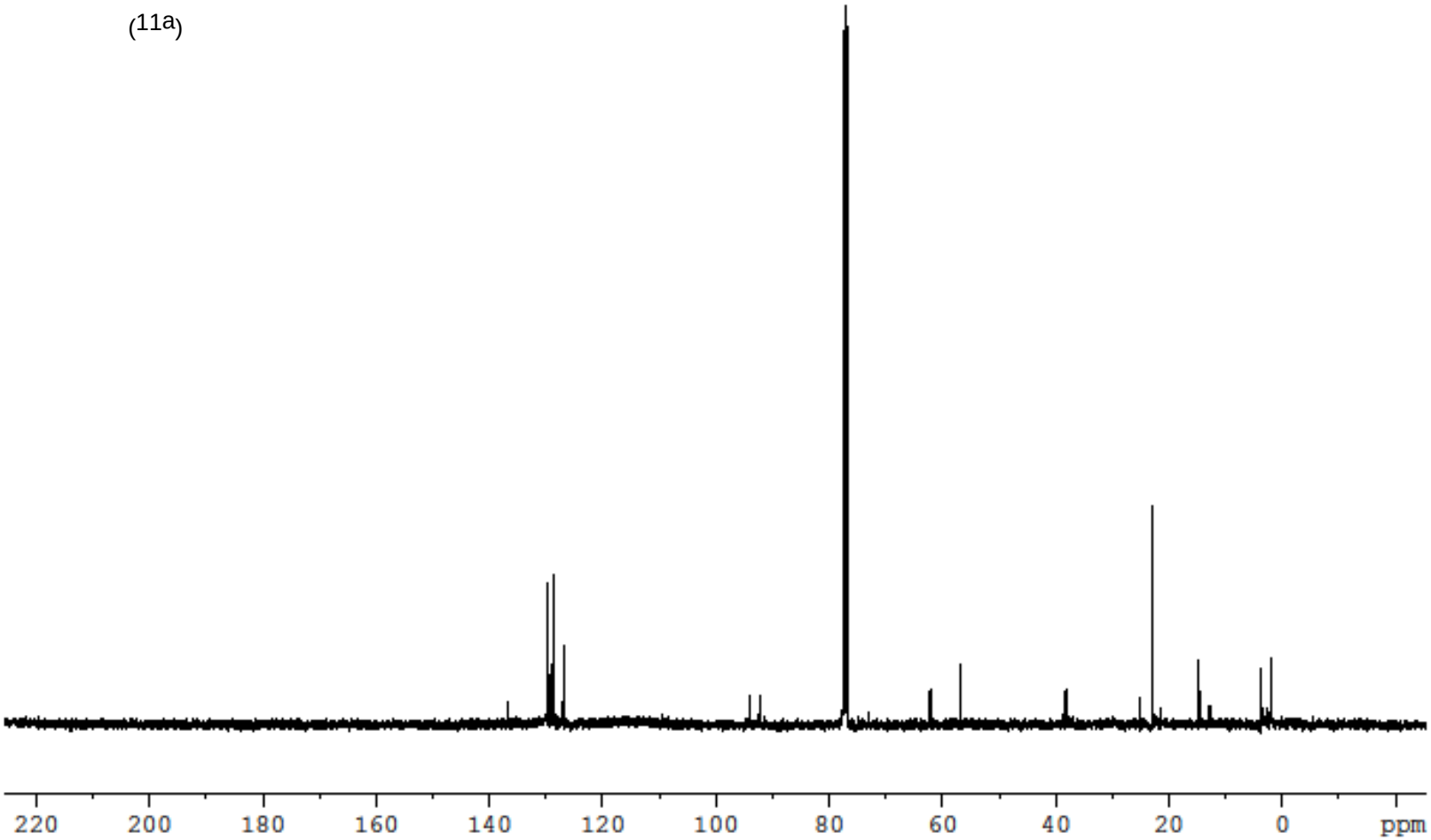

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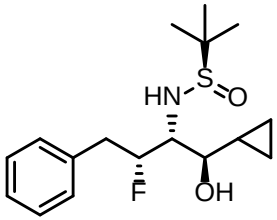

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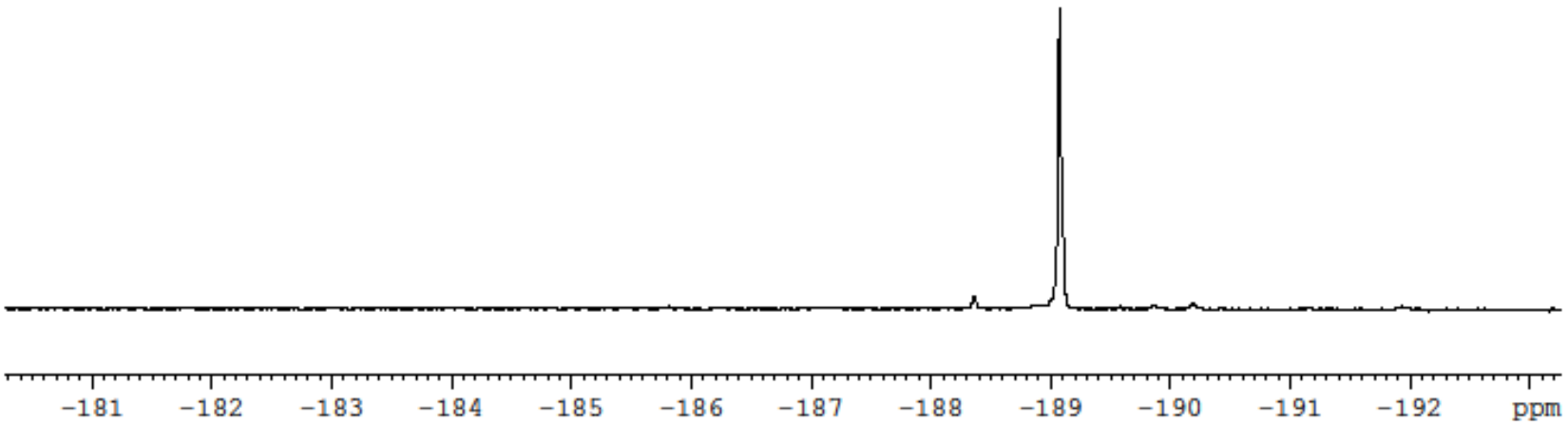

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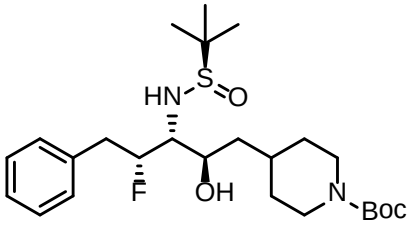

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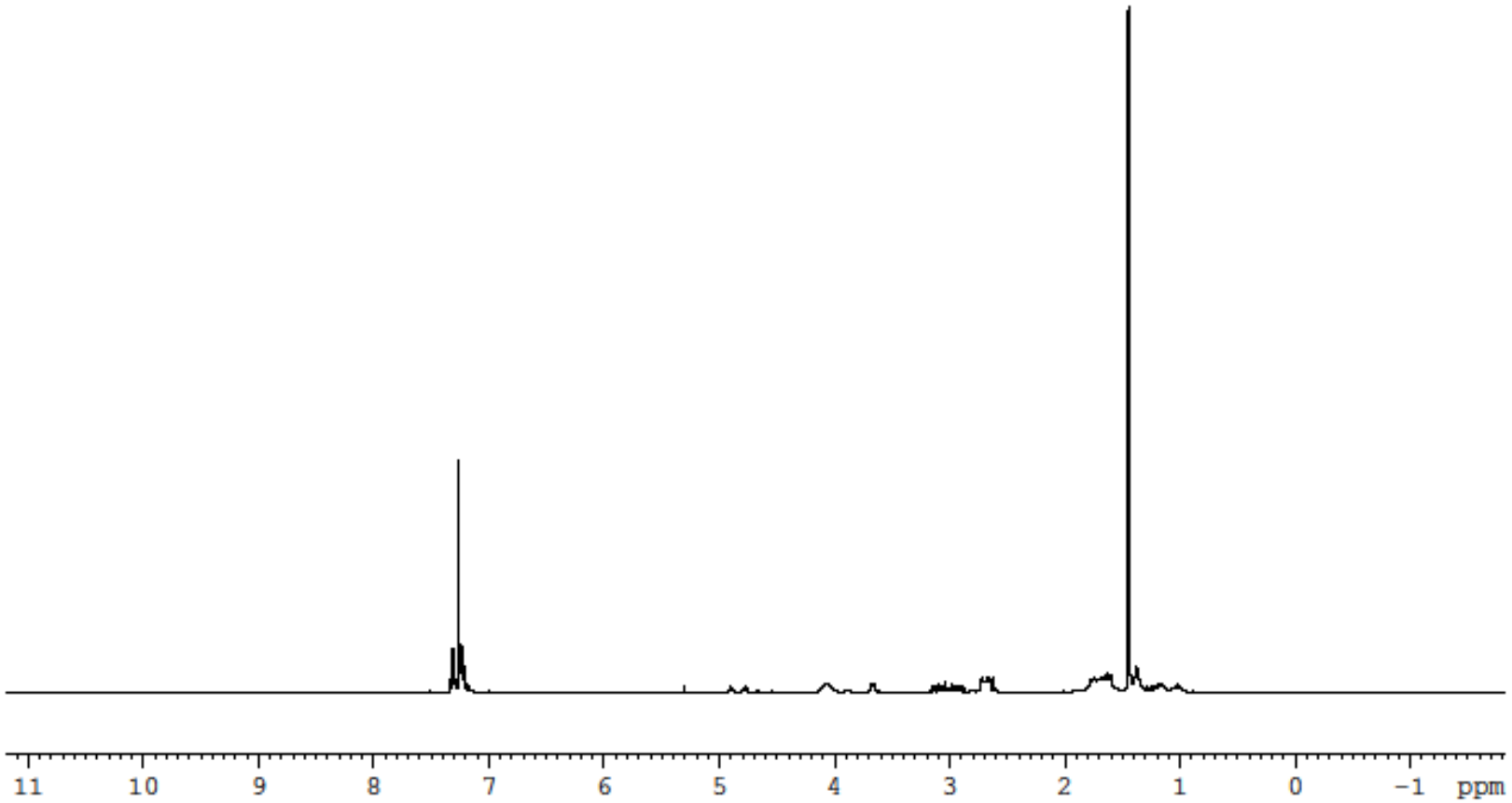

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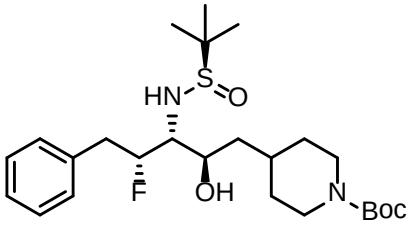

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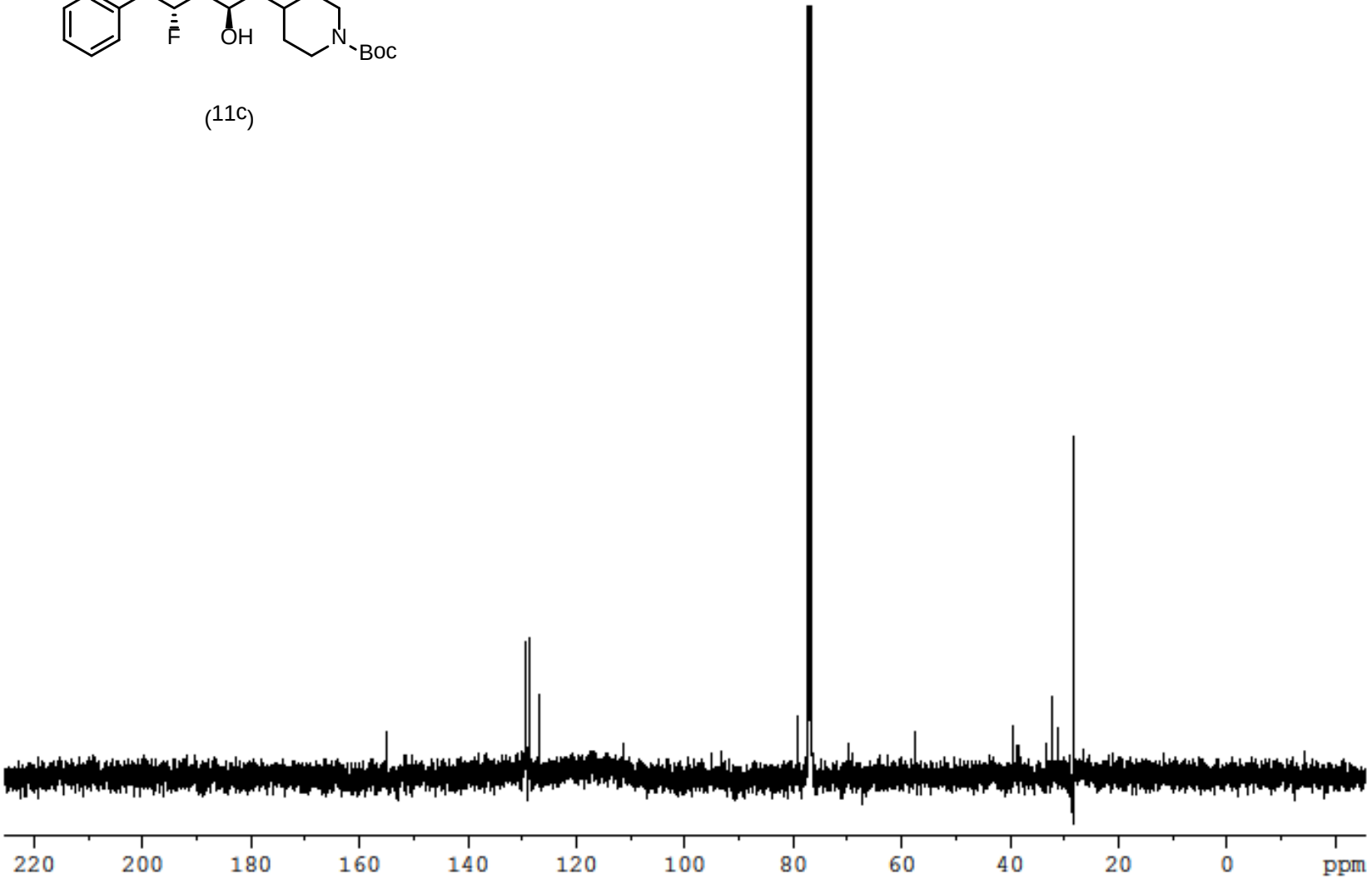

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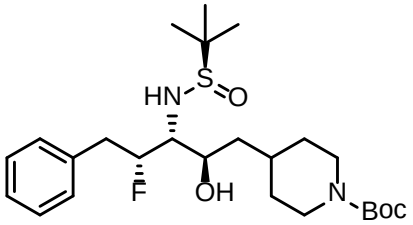

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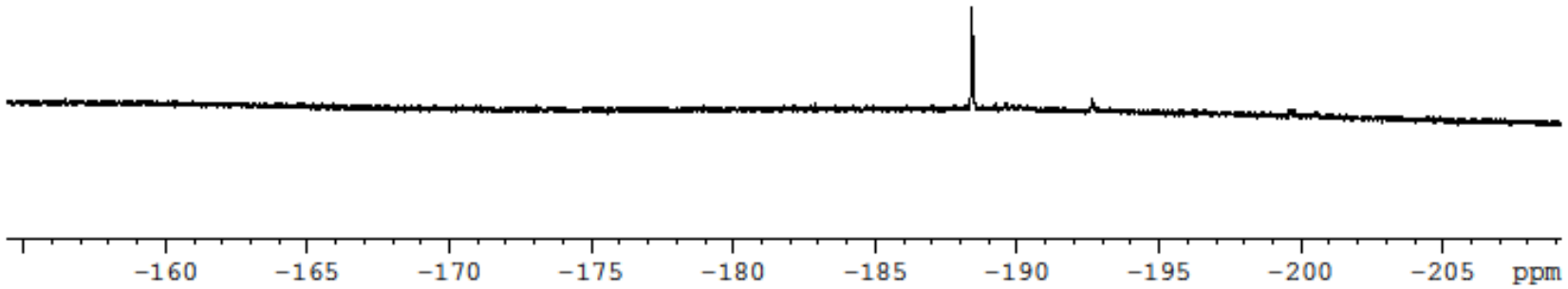

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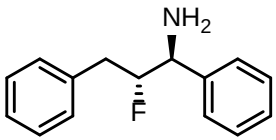

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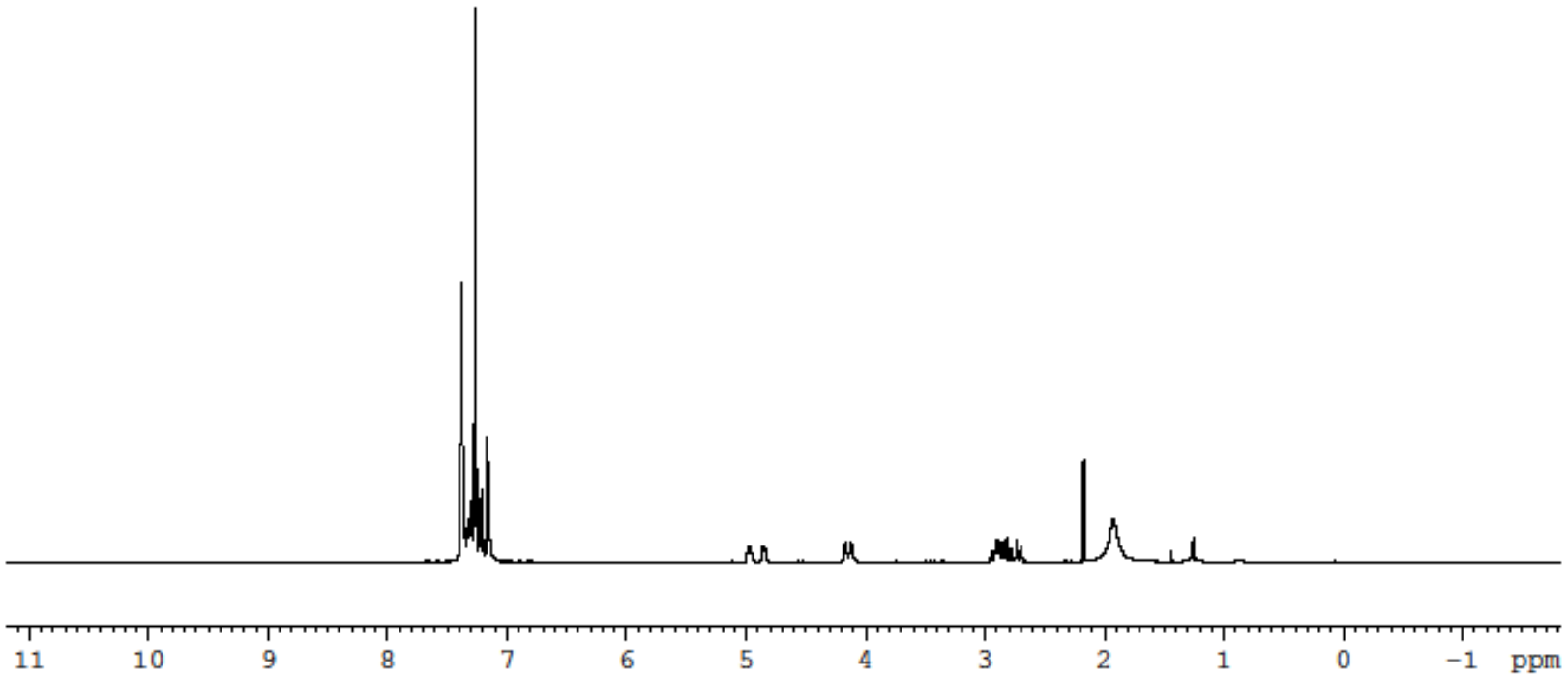

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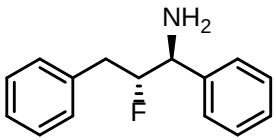

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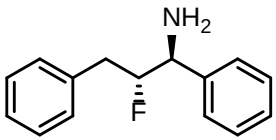

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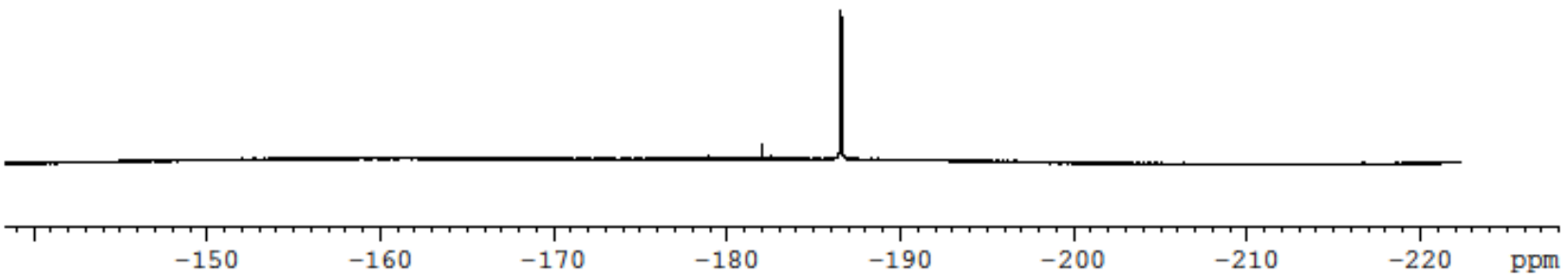

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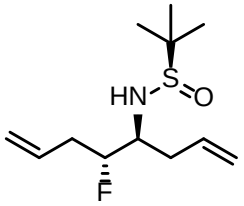

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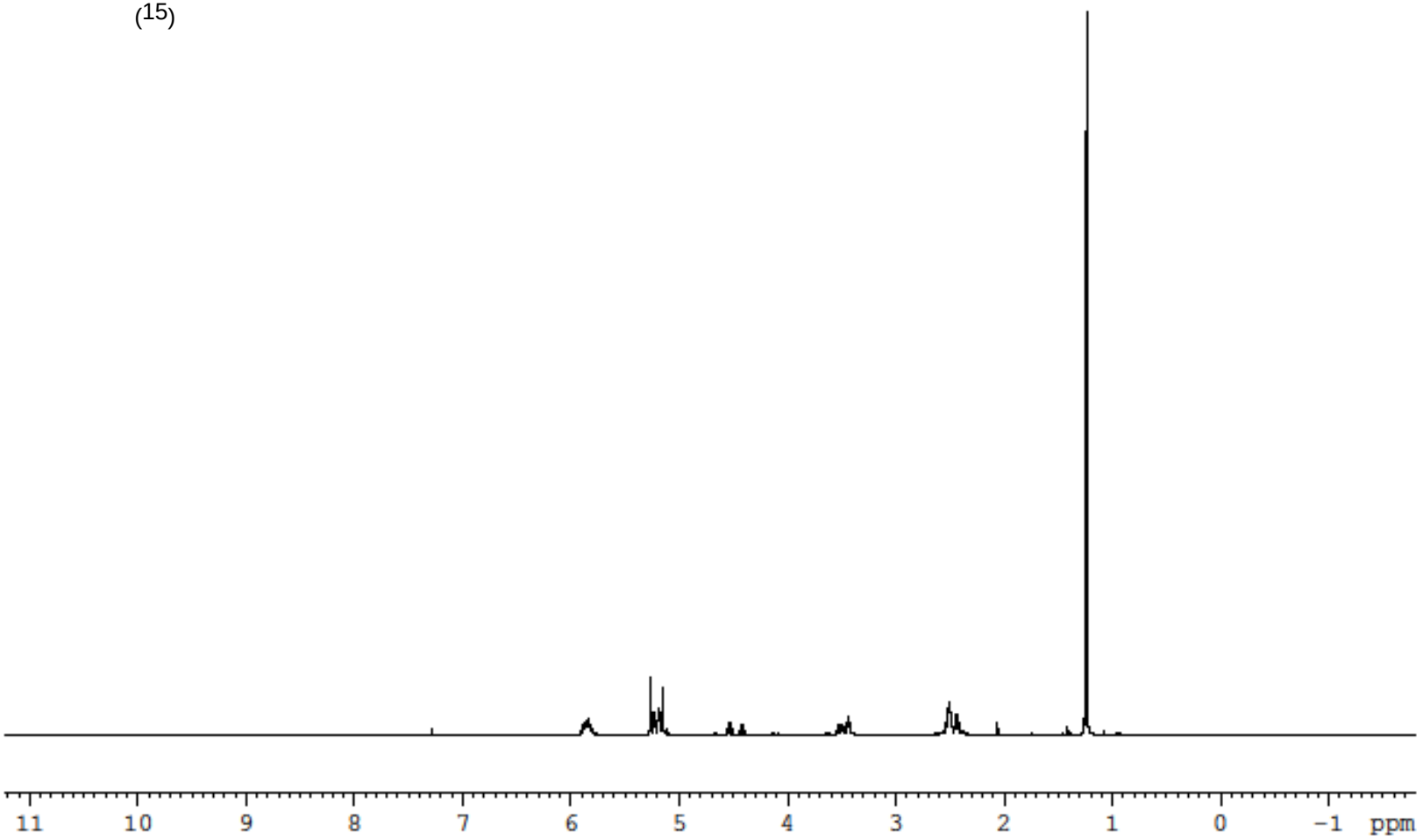

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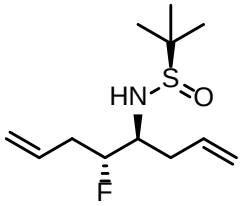

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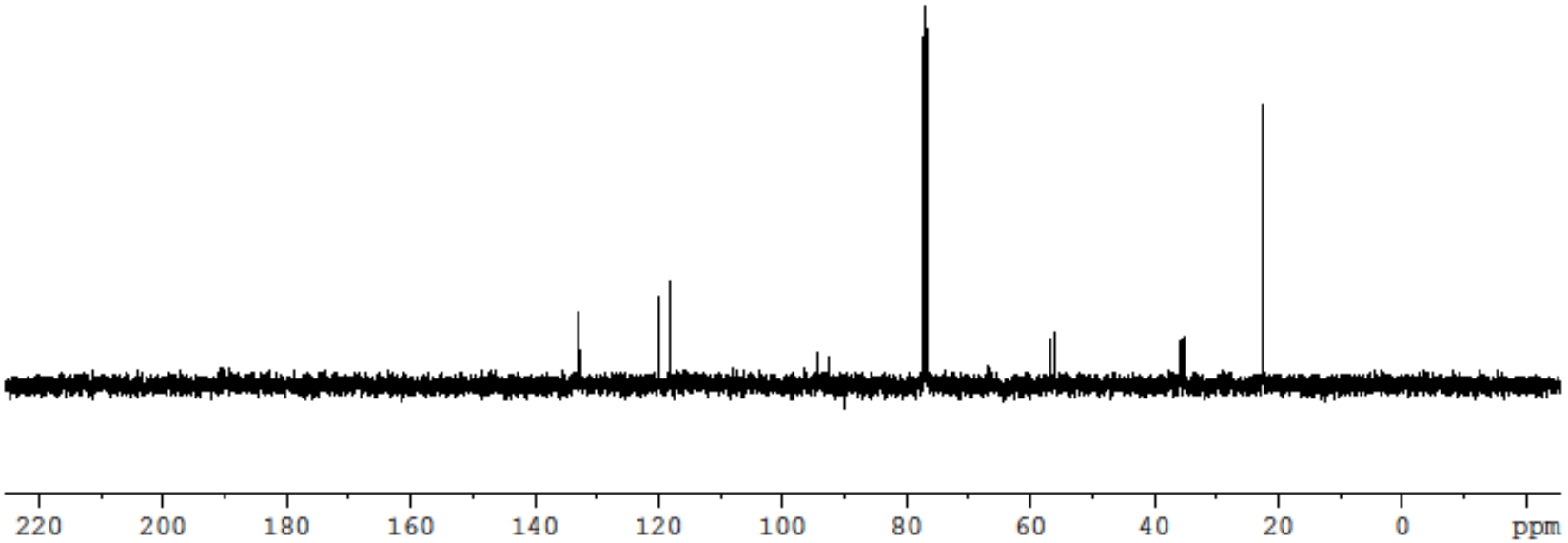

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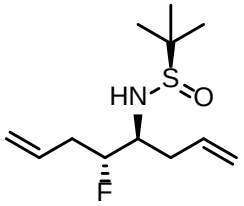

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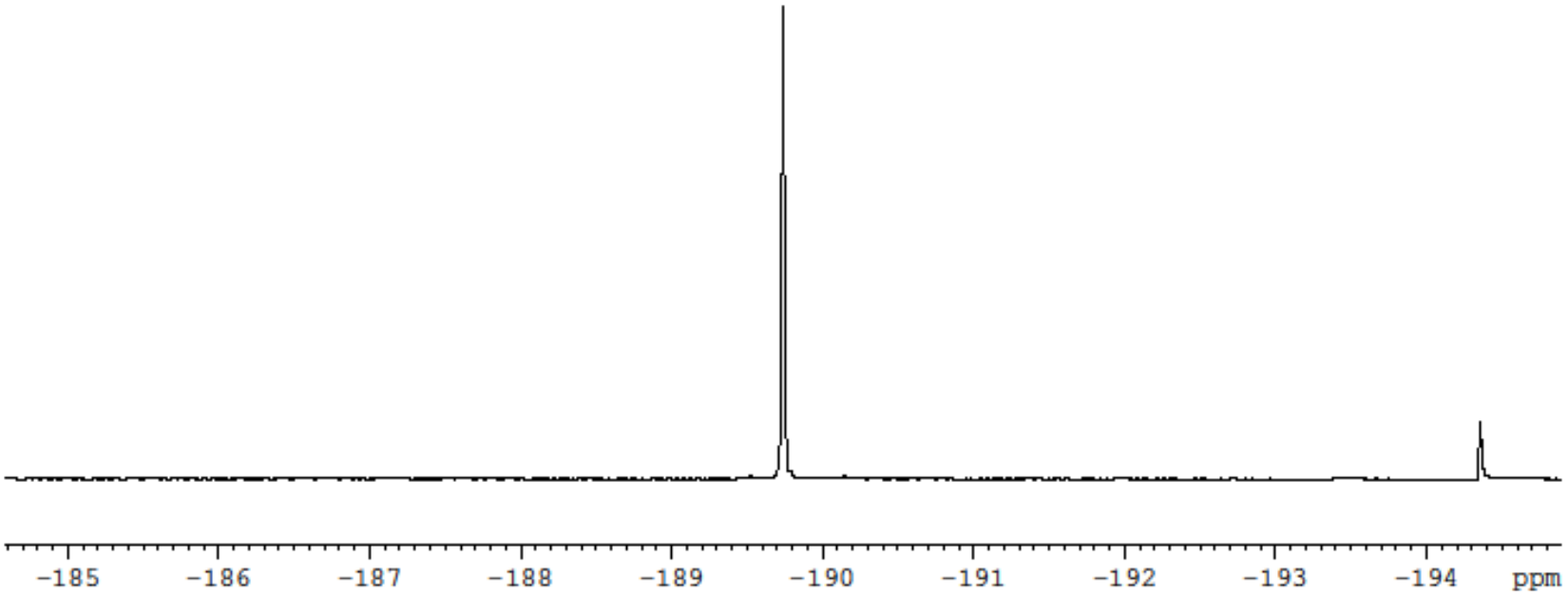

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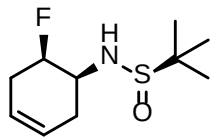

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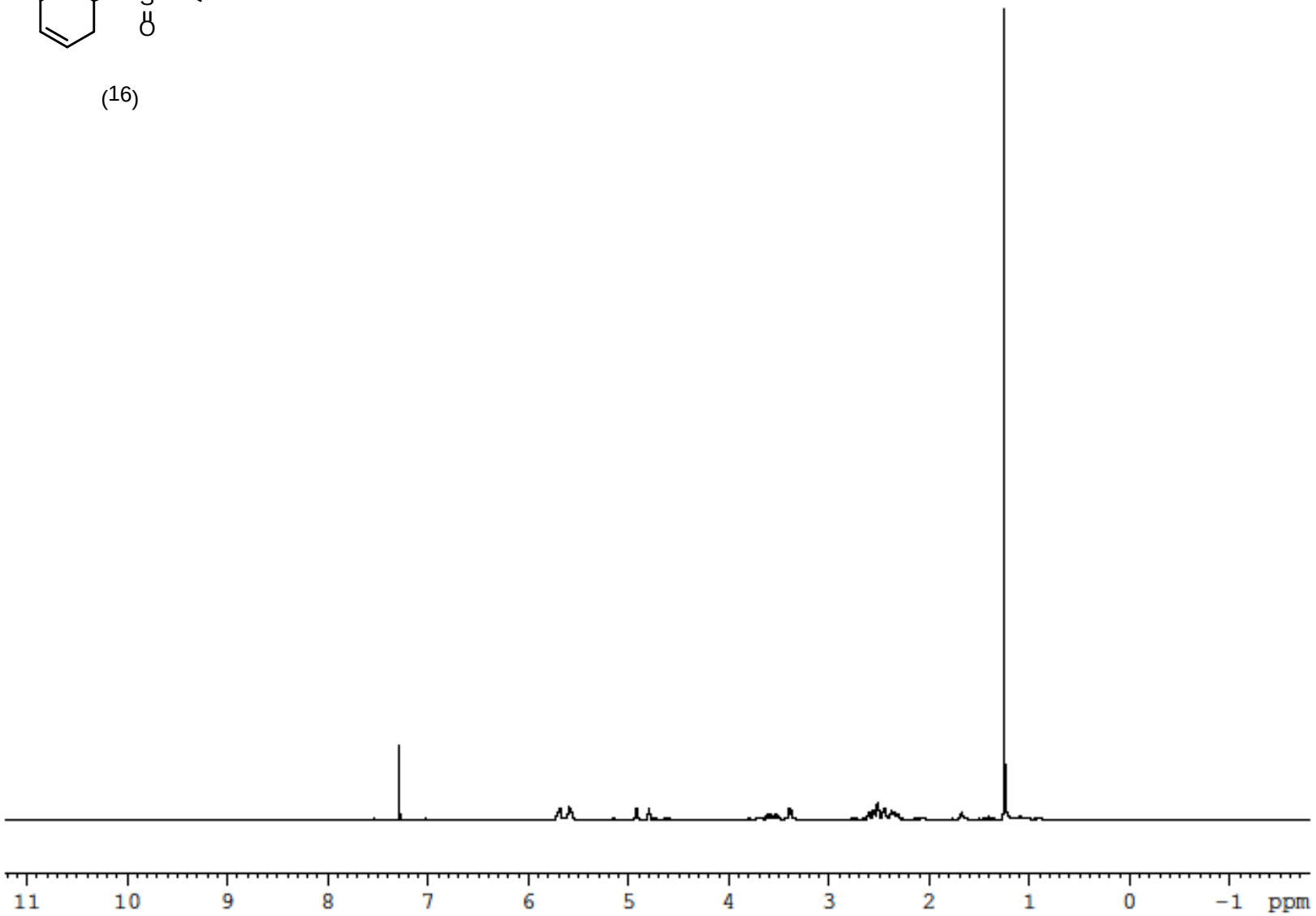

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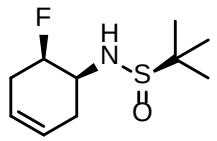

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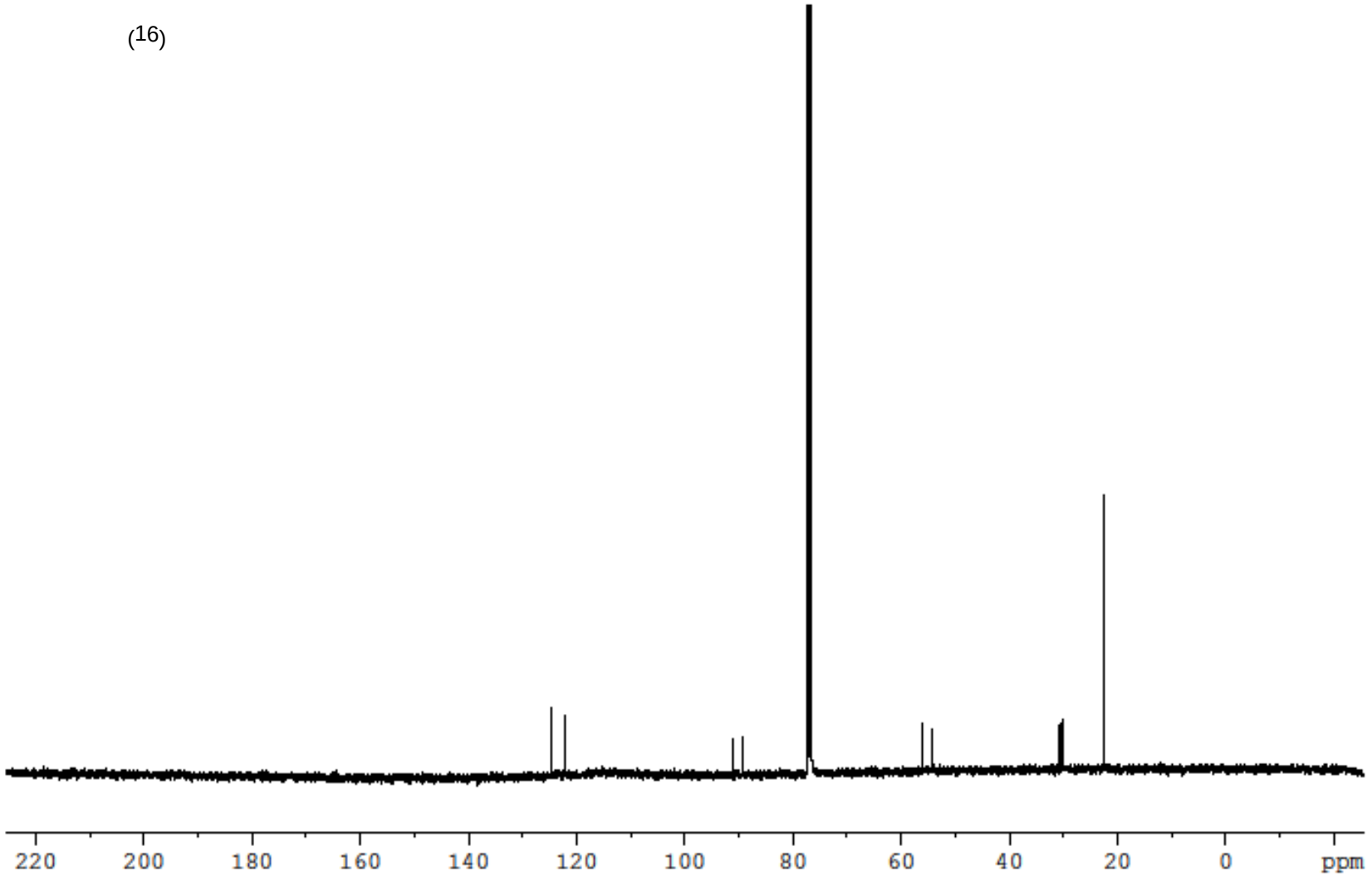

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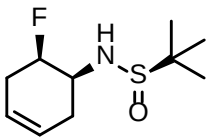

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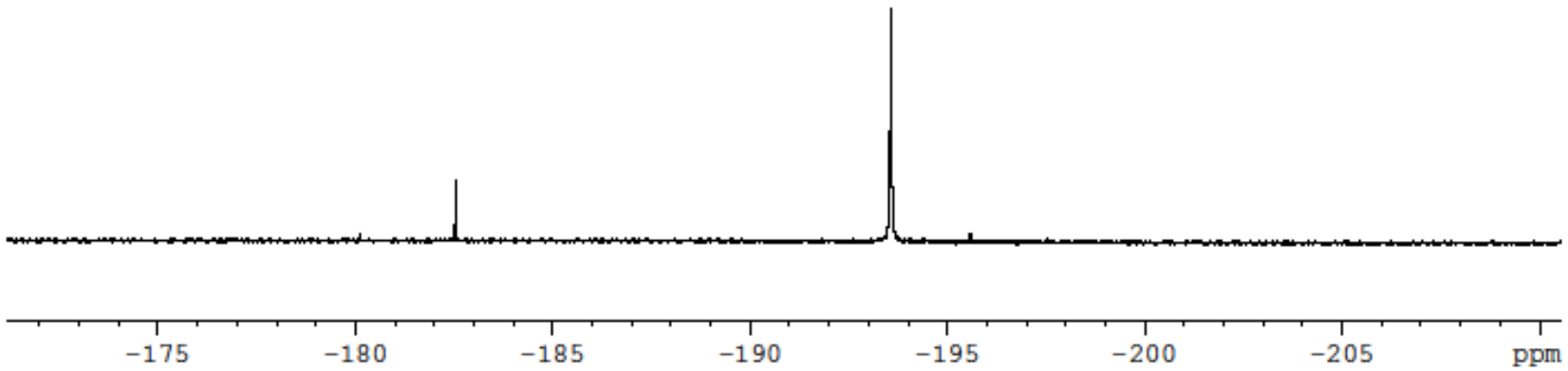

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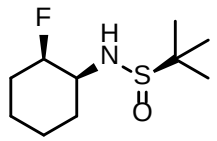

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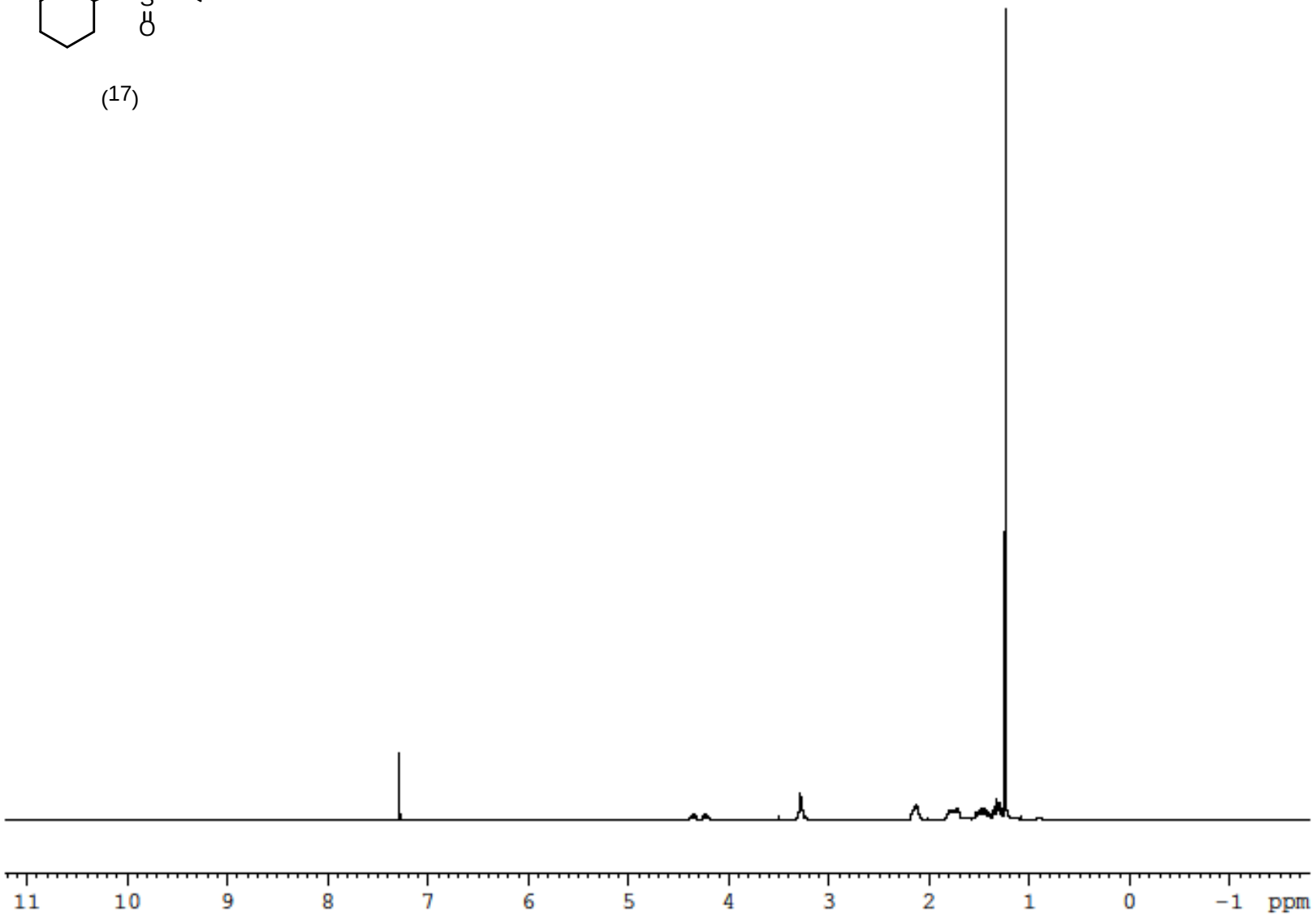

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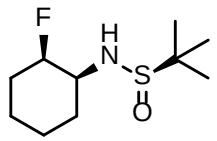

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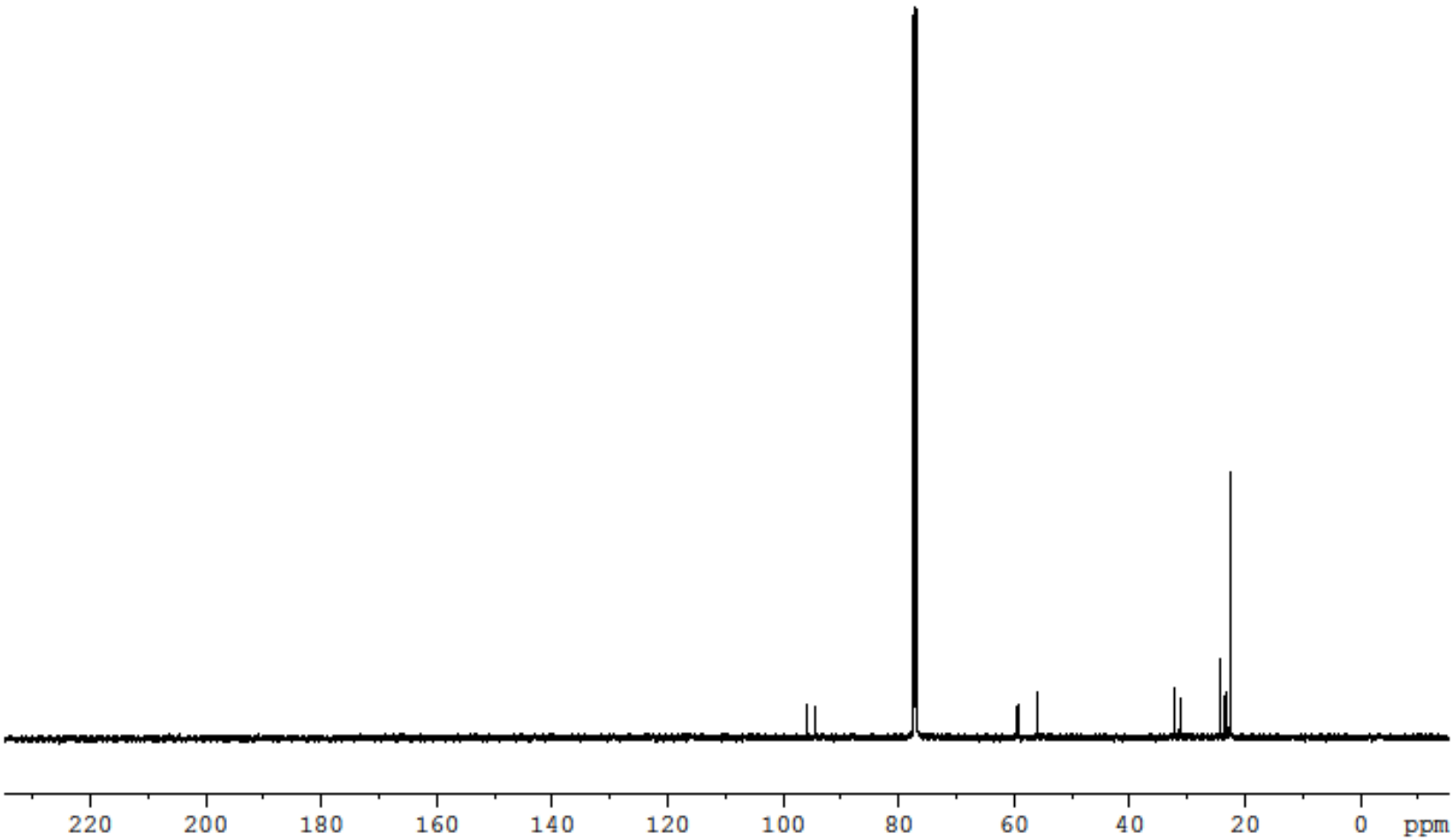

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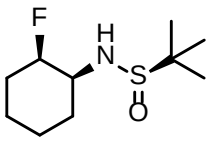

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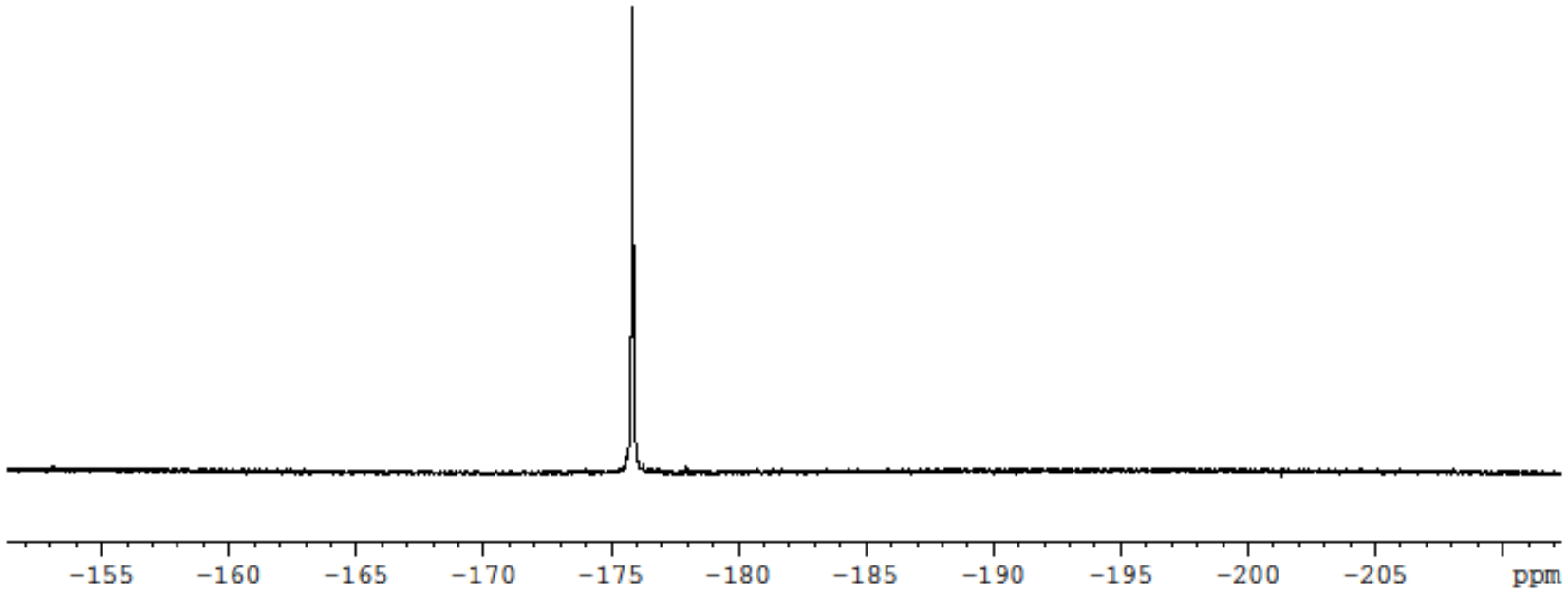

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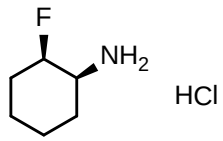

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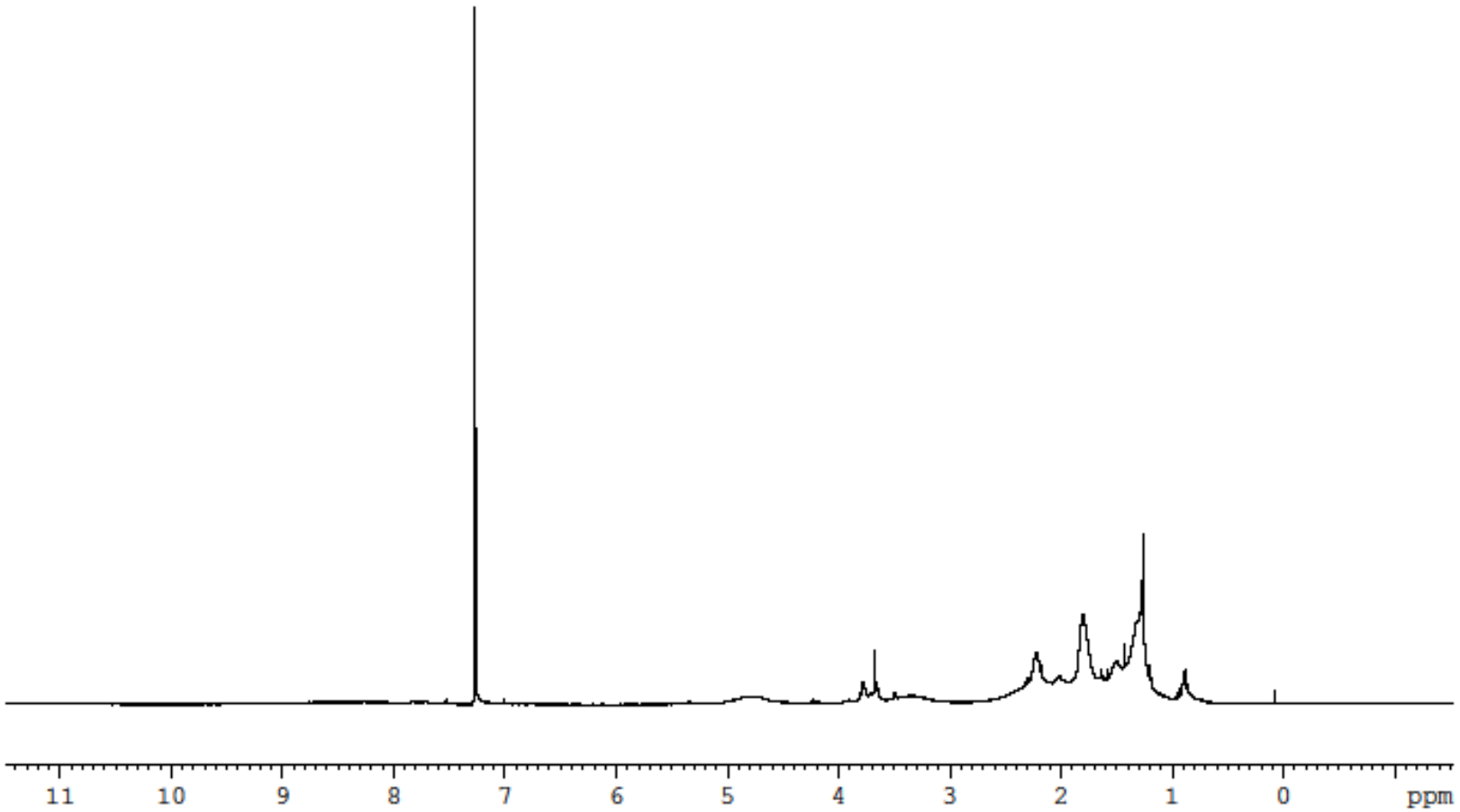

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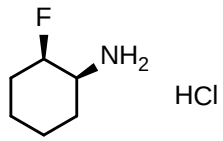

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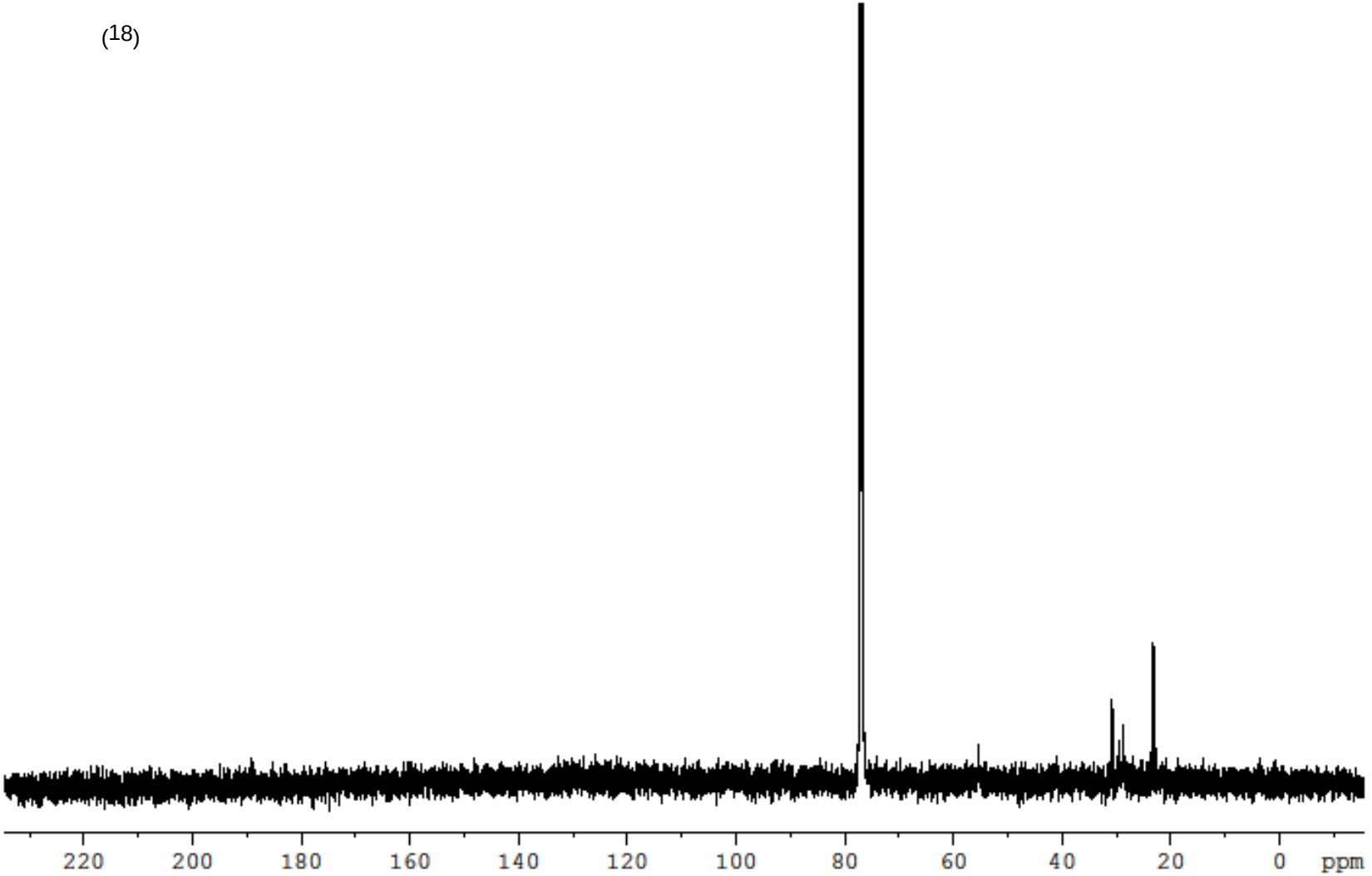

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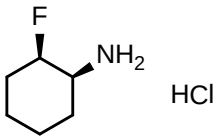

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