Counterion Effects in the Catalytic Stereoselective Synthesis of 2,3'-Pyrrolidinyl Spirooxindoles

Jacob P. MacDonald, Benjamin H. Shupe, John D. Schreiber, Annaliese K. Franz*

University of California, Department of Chemistry, One Shields Ave, Davis, CA 95616 USA
akfranz@ucdavis.edu

Supporting Information

I. General Information

Materials. Commercially available reagents were obtained from (Aldrich, Acros, AKSci) and used without further purification. Iminooxindoles were synthesized according to the literature.[1] Crotylsilane **2** was synthesized according to the literature procedure.[2] Racemic standards were prepared using a racemic variant of crotylsilane **2**. Dry CH_2Cl_2 was dispensed from a solvent purification system that passes CH_2Cl_2 through two columns of dry neutral alumina. Anhydrous acetonitrile was purchased from EMD (drisolv® bottle). The following abbreviations are used throughout: ethyl acetate (EtOAc), dichloromethane (DCM), dimethylformamide (DMF), diastereomeric ratio (dr), *para*-methoxyphenyl (PMP), *para*-methoxybenzyl (PMB), benzyl (Bn), enantiomeric excess (ee), isopropyl alcohol (IPA), *N*-*tert*-butoxycarbonyl (Boc), sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (NaBArF).

Synthesis, Purification, and Analysis. All reactions were performed in oven-dried and Ar-purged glassware (including 4- and 8-mL vials fitted with PTFE caps). All ^{1}H and ^{13}C spectra were recorded at ambient temperature at 400 (or 300, 600) and 100 (or 75, 150) MHz, respectively, using a Varian Mercury 300, Varian Inova 400, or Varian 600 spectrometer. The ^{1}H spectral data are reported as follows: chemical shift in ppm downfield from tetramethylsilane on the δ scale, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet; dd, doublet of doublets; dt, doublets of triplets; td, triplet of doublets, and b, broadened), coupling constant (Hz), and integration. Carbon NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent reference employed as the internal standard (deuterochloroform ($CDCl_3$) at 77.16 ppm).

Compounds were analyzed for MS (ESI) using an Applied Biosystems Qtrap (Foster City, CA) in the positive ion mode. Source parameters were 5kV spray voltage, with a curtain plate temperature of 275 ˚C and sheath gas setting of 15. Samples were analyzed via flow injection analysis by injecting 20 µL samples into a stream of 80% MeOH/20% aqueous solution of 0.1% formic acid, flowing at 200 µL/min. When indicated, the progress of reactions was monitored by analytical thin layer chromatography using glass or aluminum backed plates pre-coated with EMD silica gel 60 F254 and visualized with UV light. Flash chromatography was performed either on Acros silica gel 60 Å (0.035-0.070 mm), Aldrich silica gel 150 Å grade 62 (60-200 mesh), or using a CombiFlash Companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica columns (RediSep, Rf®). All HPLC analyses were performed on a Shimadzu LC-20AB system with a Daicel CHIRALPAK® AD-H column (4.6 x 250 mm, 5 µm), CHIRALPAK® AS-H column (4.6 x 250 mm, 5 µm) or CHIRALPAK® OD-H column (4.6 x 250 mm, 5 µm), each attached to a guard column, at a flow rate of 1 mL/min (isopropanol/hexanes isocratic system) using a Shimadzu SPD-M20A photodiode array detector and 40 °C column oven temperature. Optical rotations were obtained on a Rudolph AUTOPOL IV polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell. Specific rotations are reported in degrees per decimeter at 23 °C and the concentrations are given in grams per 100 mL of solvent. Solvents used for optical rotations were MeOH (reagent grade), and $CHCl_3$ (stabilized with 0.5% - 1% EtOH, and filtered through basic alumina). X-ray powder diffraction was measured on a Bruker D8 Advance diffractometer with Cu Ka radiation (λ=1.5418 Å) operating at 40 kV and 40 mA. Samples were collected on a zero background quartz plate.

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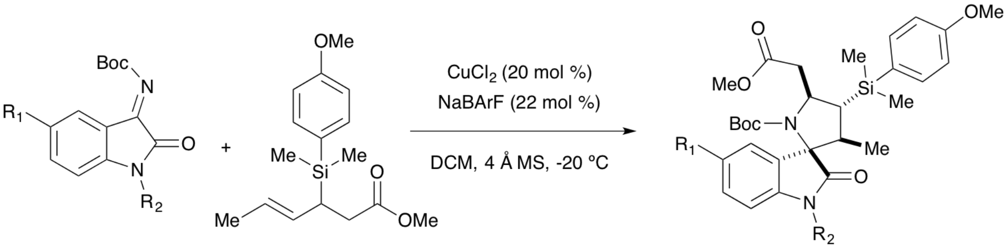
[1] (a) Cali, P.; Begtrup, M. *Synthesis* **2002**, *1*, 63. (b) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512.

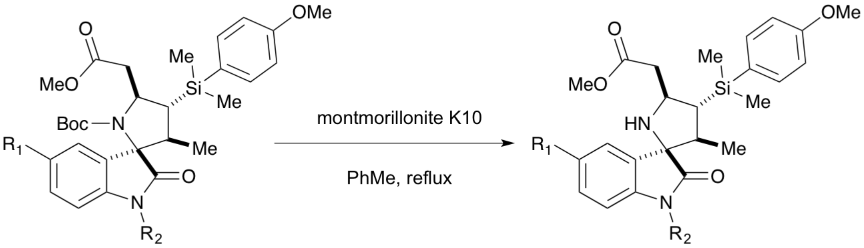
[2] (a) Beresis, R.; Solomon, J.; Yang, M.; Fain, N.; Panek, J. *Org. Synth.* **1998**, *75*, 78. (b) Franz, A.; Dreyfuss, P.; Schreiber, S. *J. Am. Chem. Soc.* **2007**, *129*, 1020.

II. Experimental Procedures and Characterization Data

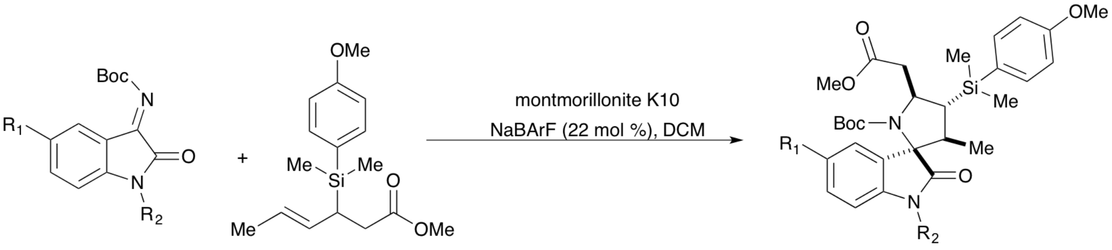
a. General Procedures



General Procedure for the Cu(II)-catalyzed Preparation of Spiropyrrolidine-oxindoles: To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated 4 Å molecular sieves (100 mg/mmol), $CuCl_2$ (20 mol %) and NaBArF (22 mol %) in dry CH_2Cl_2 (0.1 M). This solution was stirred at room temperature for 0.5-1 h, then cooled to – 20 ºC where the appropriate *N*-Boc-iminooxindole (1 equiv) and crotylsilane (3 equiv) were added to the solution. The reaction was monitored by TLC until full consumption of the iminooxindole was observed, then the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc.

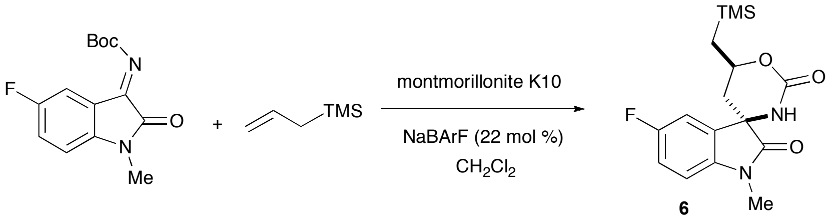


General Procedure for the deprotection of *N*-Boc Protected Spiropyrrolidines: Montmorillonite K10 was activated under vacuum at 200 ºC for 1 h. To a flame dried, Ar-purged 4-mL vial charged with a stir bar was added the appropriate *N*-Boc spiropyrrolidine (1 equiv), dry toluene (0.24 M) and activated Montmorillonite K10 (1 equiv by weight). The reaction mixture was heated to 110 ºC and stirred overnight. The reaction mixture was cooled to room temperature, filtered through a pad of celite, and the solvent removed under reduced pressure. No further purification was necessary.



General Procedure for the Montmorillonite-promoted Synthesis of Spiropyrrolidine-oxindoles: Montmorillonite K10 was activated under vacuum at 200 ºC for 1 h. To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated montmorillonite K10 (1 equiv by weight) and NaBArF (22 mol %), and then dry CH_2Cl_2 (0.1 M). Crotylsilane (3 equiv) and *N*-Boc-iminooxindole (1 equiv) were then added to the solution. The reaction was monitored by TLC and when full consumption of the iminooxindole was observed, the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc.

Procedure for montmorillonite-promoted synthesis of spirocarbamate 6:



5-Fluoro-1-methyl-6'-((trimethylsilyl)methyl)spiro[*trans*-indoline-3,4'-[1,3]oxazinane]-2,2'-dione (6): Montmorillonite K10 was activated under vacuum at 200 ºC for 1 h. Imine **4a** (0.12 mmol, 32 mg), montmorillonite K10 (1 equiv by weight, 32 mg), NaBArF (0.024 mmol, 21 mg) were added to an Ar-purged flame dried 4-mL vial equipped with a stir bar. The reagents were then dissolved in dry CH_2Cl_2 (0.1 M, 1.2 mL). Next, allyltrimethylsilane (0.36 mmol, 57 μL) was added to the reaction mixture and allowed to stir at room temperature for 2 days until the imine was consumed. At this point the reaction was loaded on to a silica plug and was eluted with 10 mL of 70:30 DCM/EtOAc and concentrated in vacuo. The diastereomeric ratio was determined to be 60:40 based on analysis of the unpurified (filtered) reaction mixture using ^{1}H NMR spectroscopy. These spectral data match those reported previously in literature.[3] *trans*-**6** (major diastereomer): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 7.5, 2.5, 1H), 7.08 (td, *J* = 8.7, 2.5, 1H), 6.83 (dd, *J* = 8.7, 4.0, 1H), 5.98 (s, 1H), 4.74 (dddd, *J* = 13.2, 11.1, 8.8, 1.4, 1H), 3.23 (s, 3H), 2.21 (dd, *J* = 13.2, 11.1 1H), 1.80 (d, *J* = 13.2, 1H), 1.23 (dd, *J* = 11.1, 4.1 1H), 0.96 (dd, *J* = 13.2, 8.8, 1H), 0.06 (s, 9H).

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[3] Shupe, B. S.; Allen, E. A.; MacDonald, J. P.; Franz, A. K. *Org. Lett.* **2013**, 15, 3218.

b. Full Optimization Table For Annulation Reaction:

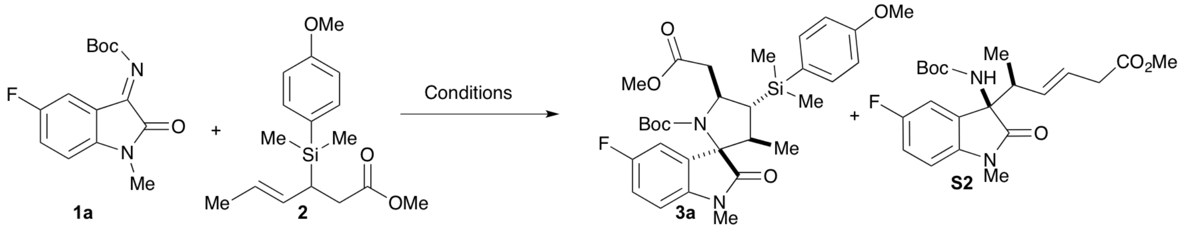
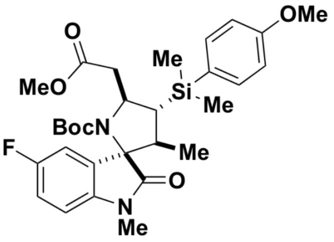


Table S1. Optimization of conditions for spiropyrrolidine **3a**

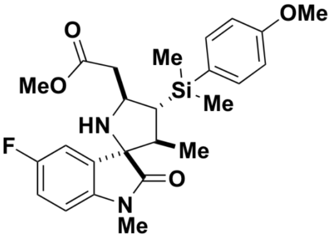
entry	catalyst[a]	counterion source[b]	temp. (ºC)	solvent	time	yield of **3a** (%)[c]	yield of **5** (%)[c]
1	TfOH	--	23	DCM	21 h	27[d]	0
2	TfOH	--	–78	DCM	20 h	68[e]	10[f]
3	$Sc(OTf)_3$	--	23	DCM	3 h	61[f]	8
4	$ScCl_3$	--	23	DCM	7 d	37	0
5	$ScCl_3$	$NaSbF_6$	23	DCM	5 d	28	0
6	$ScCl_3$	NaBArF	23	MeCN	7 d	10	0
7	$ScCl_3$	NaBArF	23	DCM	22 h	61	14
8	$ScCl_3$	NaBArF	23	DCM	7 d	51[g]	0
9	$InCl_3$	NaBArF	23	DCM	5h	42	0
10	$ZnCl_2$	--	23	DCM	5 d	42	0
11	$ZnCl_2$	NaBArF	23	DCM	3 d	61	17
12	$SnCl_2$	NaBArF	23	DCM	12 h	51	31
13	$CuCl_2$	NaBArF	23	DCM	2 h	64	27
14	$CuCl_2$	NaBArF	-20	DCM	24 h	79	0
15	--	NaBArF	-20	DCM	7 d	0	0
16	$CuCl_2$	$NaSbF_6$	-20	DCM	3 d	41	0
17	$CuCl_2$	--	-20	DCM	3 d	0	0
18	$CuCl_2$	NaBArF	23	DCM	3 d	56[h]	0
19	Mont. K10[i]	NaBArF	23	DCM	< 1 h	60	0
20	Mont. K10[i]	$NaSbF_6$	23	DCM	5 d	0	0
21	Mont. K10[i]	--	23	DCM	5 d	0	0

[a] Reactions run with 20 mol % of catalyst unless otherwise noted. [b] Reaction performed with 22 mol % of counterion source. [c] Isolated yield. [d] The NH spiropyrrolidine **4a** was also isolated in 31% yield. [e] The NH spiropyrrolidine **4a** was also isolated in 8 % yield. [f] Reaction gave ~10 % yield of the free NH_2 crotylation **S1**. [g] Reaction performed in the presence 20 mol % indapybox. [h] Reaction performed with 10 mol % $CuCl_2$ and 11 mol % NaBArF. [i] Reaction performed with 1.0 equiv of montmorillonite K10

c. Characterization Data for Spiropyrrolidine Scaffolds

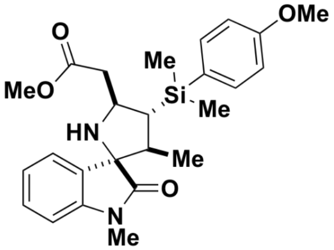


tert-butyl (3_R_,3'_S_,4'_R_,5'_S_)-5-fluoro-5'-(2-methoxy-2-oxoethyl)-4'-((4-methoxyphenyl)-dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidine]-1'-carboxylate (3a): The general procedure for the preparation of spiropyrrolidine-oxindoles was followed using 0.0278 g of iminooxindole **1a** and 0.083 g of enantioenriched crotylsilane (_S_)-**2** (>95% ee). The reaction was monitored by TLC and stopped after 24 h to give product **3a** as a single stereoisomer as judged by ^{1}H NMR spectroscopy and with 96% ee based on HPLC. The reaction mixture was purified to afford **3a** a yellow oil (0.0451 g, 79%). $[\alpha]_D^{23}$ –53.2° (_c_ 0.40, $CHCl_3$). Enantiomeric excess was determined using HPLC with a Daicel CHIRALPAK® AD-H column (5% IPA/hexanes), 1.0 mL/min. t_R (major) = 23.2 min, t_R (minor) = 8.9 min. 96% _ee_. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 6.92 (dd, J = 8.7, 2.2, 1H), 6.91 – 6.87 (m, 2H), 6.63 (dd, _J_ = 8.5, 4.0, 1H), 6.60 (dd, _J_ = 7.8, 2.2, 1H), 4.54 (ddd, _J_ = 10.4, 6.3, 1.8, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.10 (s, 3H), 2.73 (dd, J = 15.6, 6.3, 1H), 2.61 (dd, _J_ = 15.6, 1.8, 1H), 2.14 (dq, _J_ = 13.0, 6.7, 1H), 1.74 (dd, _J_ = 13.0, 10.4, 1H), 0.92 (s, 9H), 0.54 (d, _J_ = 6.7, 3H), 0.39 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.0, 172.6, 160.9, 159.6 (d, J_{FC} = 241.2 Hz), 152.6, 139.8, 135.7, 133.7, 127.4, 114.4 (d, J_{FCC} = 23.5 Hz), 114.0, 109.9 (d, J_{FCC} = 24.5 Hz), 108.3 (d, J_{FCCC} = 7.9 Hz), 72.6, 59.4, 55.2, 51.7, 48.4, 41.5, 35.9, 28.3, 27.9, 26.2, 13.4, -2.8, -3.5; FT IR (neat): 2954, 2372, 2335, 2161, 1708, 1617, 1459 cm^{-1}; LRMS (ESI) _m/z_ $[M + H]^+$ calcd for $C_{30}H_{40}FN_2O_6Si$, 571.26; found 571.4.

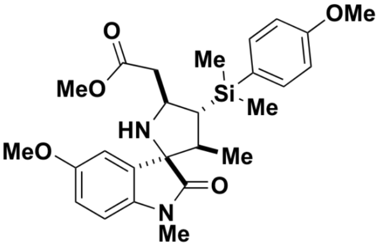


methyl 2-((3_R_,3'_S_,4'_R_,5'_S_)-5-fluoro-4'-((4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4a): The general procedure for the deprotection of _N_-Boc-spiropyrrolidines was followed using 0.045 g of spiropyrrolidine **3a** and 0.045 g of montmorillonite K10, and spiropyrrolidine was obtained as a yellow oil (0.0335 g, 90%) as a single stereoisomer as judged by ^{1}H NMR spectroscopy, and 95% ee based on HPLC. $[\alpha]_D^{23}$ –17.4° (_c_ 0.40, $CHCl_3$). Enantiomeric excess was determined using HPLC with a Daicel CHIRALPAK® OD-H column (10% IPA/hexanes), 1.0 mL/min. t_R (major) = 6.0 min, t_R (minor) = 8.4 min. 95% _ee_. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, _J_ = 8.6 Hz, 2H), 6.93 (d, _J_ = 8.6 Hz, 3H), 6.89 (dd, _J_ = 7.6, 2.4 Hz, 1H), 6.65 (dd, _J_ = 7.6, 3.9 Hz, 1H), 3.93 (ddd, _J_ = 10.5, 9.5, 2.1 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.10 (s, 3H), 2.86 (dd, _J_ = 16.1, 10.5 Hz, 1H), 2.29 (dd, _J_ = 16.1, 2.1 Hz, 1H), 2.22 (dq, _J_ = 13.2, 6.8 Hz, 1H), 1.70 (dd, _J_ = 12.5, 9.5 Hz, 1H), 0.62 (d, _J_ = 6.8 Hz, 3H), 0.39 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 160.7, 159.4 (d, J_{FC} = 241.4 Hz), 139.7, 135.2, 127.7, 115.0 (d, J_{FCC} = 23.4 Hz), 113.8, 110.9, 110.7, 108.3 (d,

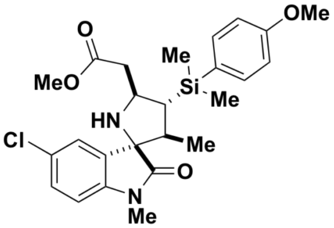
J_{FCCC} = 7.8 Hz), 72.8, 57.9, 55.0, 51.5, 49.5, 42.4, 36.8, 26.1, 13.6, –0.01, –3.5, –3.6; FT IR (neat): 3436, 2946, 2164, 1719, 1577, 1497, 1454 cm^{-1}; LRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{25}H_{32}FN_2O_4Si$, 471.21; found 471.4.



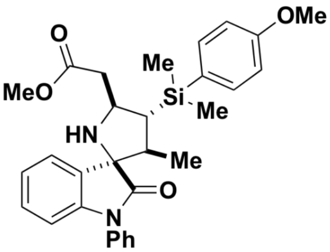
methyl 2-((3*R*,3'*S*,4'*R*,5'*S*)-4'-((4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro-[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4b): The general procedure for the synthesis of *N*-Boc-protected spiropyrrolidines was followed using 0.037 g of iminooxindole **1b**, and 0.124 g of enantioenriched crotylsilane (*S*)-**2** (>95% ee). The reaction was monitored by TLC and stopped after 24 h to give spiropyrrolidine **3b** as a single stereoisomer as judged by ^{1}H NMR spectroscopy. The reaction mixture was purified by flash chromatography (SiO_2, DCM/EtOAc) and product **3b** (0.0546 g, 80%) was confirmed by LRMS and ^{1}H NMR spectroscopy and directly deprotected. Following the general procedure for the deprotection of spiropyrrolidines, 0.0546 g of **3b** was heated in the presence of 0.0546 g of montmorillonite K10. The reaction was monitored by TLC, and when complete (24 h) the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine **4b** as a yellow oil (0.038 g, 85%), which was determined to be a single stereoisomer as judged by ^{1}H NMR spectroscopy and with 99% ee based on HPLC. $[\alpha]_D^{23}$ –31.9° (*c* 0.41, $CHCl_3$). Enantiomeric excess was determined using HPLC with a Daicel CHIRALPAK® AD-H column (5% IPA/hexanes), 1.0 mL/min. t_R (major) = 12.6 min, t_R (minor) = 4.7 min. 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.24 (td, *J* = 7.8, 1.3 Hz, 1H), 7.14 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.01 – 3.90 (m, 1H), 3.82 (s, 3H), 3.59 (s, 3H), 3.11 (s, 3H), 2.86 (dd, *J* = 16.1, 10.5 Hz, 1H), 2.39 – 2.20 (m, 2H), 1.73 (dd, *J* = 12.6, 9.6 Hz, 1H), 0.63 (d, *J* = 6.7 Hz, 3H), 0.39 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 161.1, 143.9, 135.4, 135.0, 129.9, 125.7, 123.5, 123.1, 117.7, 114.2, 108.5, 72.7, 64.6, 55.3, 52.1, 49.4, 37.1, 26.4, 19.3, 13.8, –3.2, –3.8; FT IR (neat): 3336, 2956, 2524, 2148, 1980, 1704, 1592, 1502, 1349, 1276, 1157 cm^{-1}; LRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{25}H_{33}N_2O_4Si$, 453.22; found 453.3.



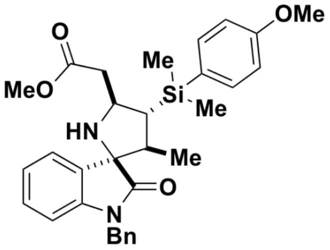
methyl 2-((3*R*,3'*S*,4'*R*,5'*S*)-5-methoxy-4'-((4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4c): The general procedure for the synthesis of *N*-Boc-protected spiropyrrolidines was followed using 0.087 g of iminooxindole **1c**, and 0.262 g of enantioenriched crotylsilane (*S*)-**2** (>95% ee). The reaction was monitored by TLC and after 24h the reaction mixture was purified by column chromatography (SiO_2, DCM/EtOAc) to afford spiropyrrolidine **3c** (0.140 g, 88%) as a single stereoisomer as determined by ^{1}H NMR spectroscopy. Product was confirmed by LRMS and ^{1}H NMR sepectroscopy and directly deprotected. Following the general procedure for the deprotection of spiropyrrolidines, 0.140 g of **3c** was heated in the presence of 0.140 g of montmorillonite K10. The reaction was monitored by TLC. After 48 h the reaction was not complete and was filtered through a pad of celite using 10% MeOH/DCM. The mixture was purified via column chromatography (SiO_2, DCM/EtOAc) to afford spiropyrrolidine **4c** as a yellow oil (0.076 g, 66%), which was a single stereoisomer as judged by ^{1}H NMR spectroscopy. $[\alpha]_D^{23}$ –60.0° (*c* 0.40, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.79 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.58 (s, 3H), 3.10 (s, 3H), 2.81 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.37 – 2.26 (m, 2H), 1.66 (dd, *J* = 12.3, 10.0 Hz, 1H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.42 (s, 3H), 0.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.8, 173.7, 160.7, 156.3, 137.1, 135.2, 134.8, 127.6, 113.8, 113.0, 110.0, 108.3, 76.8, 72.9, 64.4, 58.2, 55.7, 55.0, 51.6, 49.6, 42.1, 37.0, 26.0, 13.8, –3.4, –3.7; FT IR (neat): 2952, 2929, 2165, 2046, 1704, 1500, 1353 cm^{-1}; LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_5Si$ 483.23; found 483.3.



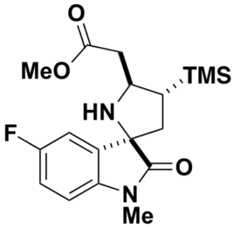
methyl 2-((3*R*,3'*S*,4'*R*,5'*S*)-5-chloro-4'-((4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4d): The general procedure for the synthesis of *N*-Boc-protected spiropyrrolidines was followed using 0.088 g of iminooxindole **1d**, and 0.262 g of enantioenriched crotylsilane (*S*)-**2** (>95% ee). The reaction was monitored by TLC and after 24h the reaction mixture was purified via flash chromatography (SiO_2, DCM/EtOAc) to afford spiropyrrolidine **3d** (0.140 g, 81%) as a single diastereomer as judged by ^{1}H NMR spectroscopy. Product was confirmed by LRMS and ^{1}H NMR spectroscopy and then directly deprotected to access the NH compound. Following the general procedure for the deprotection of spiropyrrolidines, 0.334 g of **3d** was heated in the presence of 0.34 g of montmorillonite K10. The reaction was monitored by TLC, and when complete (24 h) the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine **4d** as a brown oil (0.027 g, 99%), which was a single stereoisomer as judged by ^{1}H NMR spectroscopy. $[\alpha]_D^{23}$–44.8° (*c* 0.38, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.78 (s, 1H), 6.58 (d, *J* = 8.1 Hz, 2H), 6.32 (d, *J* = 8.2 Hz, 1H), 3.62 - 3.56 (m, 1H), 3.47 (s, 3H), 3.25 (s, 3H), 2.75 (s, 3H), 2.49 (dd, *J* = 15.6, 10.0 Hz, 1H), 2.20 (bs, 1H), 1.93 (d, *J* = 15.6 Hz, 1H), 1.90 (dd, *J* = 12.8, 6.7 Hz, 1H), 1.35 (dd, *J* = 10.0, 2.6 Hz, 1H), 0.27 (d, *J* = 6.7 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.0, 173.4, 160.7, 142.5, 135.2, 133.1, 128.5, 128.04, 127.97, 123.2, 113.8, 108.6, 72.7, 57.8, 55.0, 51.4, 49.5, 42.8, 36.7, 26.0, 13.6, –3.49, –3.52; FT IR (neat): 3403, 2952, 2215, 2046, 1710, 1608, 1245 cm^{-1}; LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}ClN_2O_4Si$ 487.18; found 487.2.



methyl 2-((3*R*,3'*S*,4'*R*,5'*S*)-4'-((4-methoxyphenyl)dimethylsilyl)-3'-methyl-2-oxo-1-phenylspiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4e): The general procedure for the synthesis of Boc-protected spiropyrrolidines was followed using 0.064 g of iminooxindole **1e**, and 0.174 g of enantioenriched crotylsilane (*S*)-**2** (>95% ee). The reaction was monitored by TLC and after 24h the reaction mixture was purified via flash chromatography (SiO_2, DCM/EtOAc) to afford spiropyrrolidine **3e** (0.108 g, 88%) as a single stereoisomer as determined by ^{1}H NMR spectroscopy. Product was confirmed by LRMS and ^{1}H NMR spectroscopy and then directly deprotected to access the NH compound. Following the general procedure for the deprotection of spiropyrrolidines, 0.140 g of **3e** was heated in the presence of 0.108 g of montmorillonite K10. The reaction was monitored by TLC, and when complete the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine **4e** as a yellow oil (0.072 g, 80%), which was a single stereoisomer as judged by ^{1}H NMR spectroscopy. $[\alpha]_D^{23}$ –18.1° (*c* 0.39, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.82 (s, 3H), 3.57 (s, 3H), 2.84 – 2.74 (m, 2H), 2.35 (dq, *J* = 13.0, 6.7 Hz, 1H), 2.25 (d, *J* = 15.7 Hz, 1H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.38 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 177.2, 164.2, 147.3, 138.8, 138.0, 134.4, 133.0, 132.1, 131.7, 131.3, 129.9, 126.7, 126.4, 117.3, 112.6, 76.3, 61.3, 58.6, 55.0, 54.0, 46.3, 40.1, 17.2, 0.2, 0.00; FT IR (neat): 2954, 2892, 2385, 2524, 1997, 1724, 1592, 1500, 1612, 1463, 1369, 1276, 1247, 1180, 1126, 1047, 910 cm^{-1}; LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{30}H_{35}N_2O_4Si$, 515.23; found 515.3.



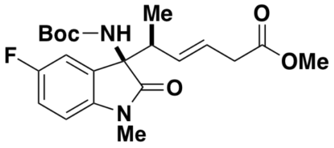
methyl 2-((3*R*,3'*S*,4'*R*,5'*S*)-1-benzyl-4'-((4-methoxyphenyl)dimethylsilyl)-3'-methyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4f): The general procedure for the synthesis of Boc-protected spiropyrrolidines was followed using 0.0124 g of iminooxindole **1f**, and 0.040 g of enantioenriched crotylsilane (*S*)-**2**. The reaction was monitored by TLC and after 24h the reaction mixture was purified via flash chromatography (SiO_2, DCM/EtOAc) to afford spiropyrrolidine **3f** (0.0153 g, 53%) as a single stereoisomer as determined by ^{1}H NMR spectroscopy. Product was confirmed by LRMS and ^{1}H NMR. Following the general procedure for the deprotection of spiropyrrolidines, 0.0153 g of **3f** was heated in the presence of 0.015 g of montmorillonite K10. The reaction was monitored by TLC, and when complete (24h) the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine **4f** as a yellow oil (0.0098 g, 93%), which was a single stereoisomer as judged by ^{1}H NMR spectroscopy. $[\alpha]_D^{23}$ -32.0° (*c* 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.6 Hz, 2H), 7.32-7.22 (m, 5H), 7.17 – 7.07 (m, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 7.7 Hz, 1H), 5.10 (d, *J* = 15.6 Hz, 1H), 4.52 (d, *J* = 15.6 Hz, 1H), 3.98 (td, *J* = 10.4, 2.0 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 2.87 (dd, *J* = 16.1, 10.5 Hz, 1H), 2.33 – 2.25 (m, 2H), 1.77 (dd, *J* = 12.6, 9.7 Hz, 1H), 0.69 (d, *J* = 6.8 Hz, 3H), 0.40 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0 177.1, 164.1, 146.8, 139.6, 138.7, 134.6, 132.13, 132.10, 131.6, 130.9, 130.8, 126.1, 123.0, 117.2, 112.2, 75.9, 61.2, 58.5, 54.9, 53.1, 47.3, 46.4, 40.3, 17.5, 0.03, 0.00; FT IR (neat): 2958, 2524, 2362, 2335, 2159, 1712, 1592, 1612, 1502 cm^{-1}; LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{31}H_{37}N_2O_4Si$, 529.72; found 529.5.



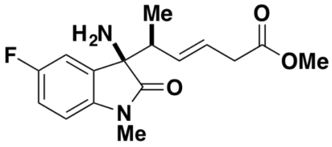
methyl 2-((3*R*,4'*R*,5'*S*)-5-fluoro-1-methyl-2-oxo-4'-(trimethylsilyl)spiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (8): To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated 4 Å molecular sieves (10 mg), $ScCl_3$ (3 mg and NaBArF (19.6 mg in dry CH_2Cl_2 (0.1 M). This solution was stirred at room temperature for 0.5-1 h. Iminooxindole **1a** (28 mg) and allylsilane **7** (56 mg) were then added to the solution. The reaction was monitored by TLC until full consumption of the iminooxindole was observed (19 h), then the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc to afford the spiropyrrolidine as a yellow oil (19.6 mg, 42%) as a single diastereomer as determined by ^{1}H NMR spectroscopy. Product was confirmed by LRMS and ^{1}H NMR spectroscopy. NOTE: No allylation was observed. Next, the general procedure for the deprotection of spiropyrrolidines was followed using 19.6 mg of the spiropyrrolidine and 19.6 mg of montmorillonite k10 to give compound **8** as a yellow oil (0.0154 g, 99%) after 24 h, which was a single diastereomer as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 7.7, 2.6 Hz, 1H), 6.92 (td, *J* = 9.0, 2.6 Hz, 1H), 6.66 (dd, *J* = 9.0, 4.0 Hz, 1H), 3.85 (ddd, *J* = 12.6, 9.9, 2.7 Hz, 1H), 3.63 (s, 3H), 3.11 (s, 3H), 2.70 (dd, *J* = 16.5, 9.9 Hz, 1H), 2.64 (dd, *J* = 16.5, 2.7 Hz, 1H), 2.24 (dd, *J* = 13.2, 7.2 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.71 (ddd, *J* = 13.8, 10.2, 7.2 Hz, 1H), 1.66 (ddd, *J* = 13.5, 10.4, 7.1 Hz, 1H), 0.05 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.6, 173.4, 159.5 (d, J_{FC} = 241.2 Hz), 139.4, 135.2, 114.7 (d, J_{FCC} = 23.5 Hz), 110.7 (d, J_{FCC} = 24.7 Hz), 108.4 (d, J_{FCCC} = 8.0 Hz), 67.8, 58.9, 51.8, 42.4, 42.2, 32.0, 26.5, –2.3; FT IR (neat): 3366, 2960, 2178, 1715, 1826, 1493, 1475 cm^{-1}; LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{26}FN_2O_3Si$, 365.50; found 365.1.

e. Selected Characterization Data for Crotylation Side Products

During the course of this study, two crotylation side-products were identified under several of the Lewis acid-catalyzed conditions. Selected characterization data is provided below.



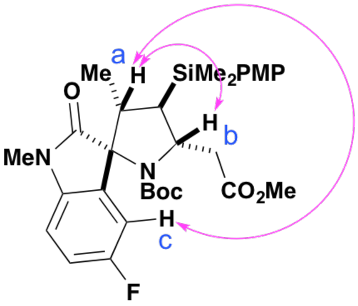
methyl (*S*,*E*)-5-((*R*)-3-((*tert*-butoxycarbonyl)amino)-5-fluoro-1-methyl-2-oxoindolin-3-yl)hex-3-enoate (5): During the optimization study, this product was isolated as a colorless oil for several of the conditions. To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated 4 Å molecular sieves (10 mg), $CuCl_2$ (2.7 mg) and NaBArF (19.6 mg) in dry CH_2Cl_2 (0.1 M). This solution was stirred at room temperature for 0.5-1 h. The iminooxindole **1a** (27.8 mg) and crotylsilane (*S*)-**2** (83 mg) were then added to the solution at room temperature. The reaction was monitored by TLC until full consumption of the iminooxindole was observed (2 h), then the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc to give annulation product **3a** as the major product and crotylation product **5** as a minor product as a colorless oil (11 mg, 27%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 5.9, 4.5 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.72 (dd, *J* = 8.4, 4.5 Hz, 1H), 5.73 (dt, *J* = 15.1, 6.7 Hz, 1H), 5.66 (dd, *J* = 15.1, 9.4 Hz, 1H), 5.31 (bs, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 3.14 – 3.07 (m, 2H), 2.81 – 2.42 (m, 1H), 1.25 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H); LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{28}N_2O_5$ 407.30; found 407.0.



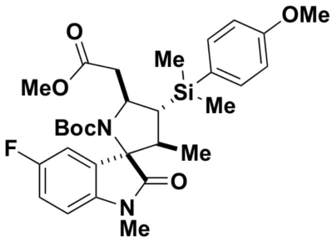
methyl (*E*)-5-(3-amino-5-fluoro-1-methyl-2-oxoindolin-3-yl)hex-3-enoate (S1):
To a flame dried 4 mL vial equipped with a stir bar was added 0.0278 g of iminooxindole **1a**, 1 mL of CH_2Cl_2 (0.1M) 0.083 g of crotylsilane (*S*)-**2**. The reaction was cooled to -78 ºC, and 0.017 mL of TfOH was added. This reaction was allowed to slowly warm up to – 60 ºC in a cryocool. Upon completion (as determined by TLC), the reaction was placed directly on the silica, and eluted with DCM/EtOAc to give 0.003 g of **S1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.7, 2.6 Hz, 1H), 7.10 (td, *J* = 8.8, 2.6 Hz, 1H), 6.80 (dd, *J* = 8.8, 4.0 Hz, 1H), 6.02 – 5.78 (m, 1H), 5.73 (bs, 2H), 5.54 (dd, *J* = 15.4, 9.6 Hz, 1H), 3.66 (s, 3H), 3.15 (s, 3H), 3.06 (d, *J* = 6.6 Hz, 2H), 2.99 – 2.86 (m, 1H), 0.86 (d, *J* = 6.9 Hz, 5H); LRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{16}H_{20}FN_2O_3$, 307.15; found 307.3.

f. nOe Experiments to Determine Relative Stereochemistry for spiropyrrolidine 3a

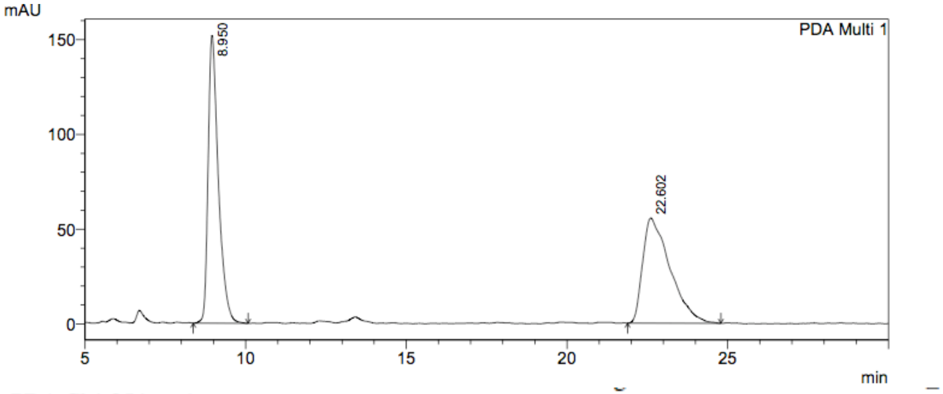
One dimensional nOe experiments were performed on *N*-Boc-protected annulation product **3a** using a 400 MHz NMR spectrophotometer. Proton **a** was found to interact with both protons **b** and **c**, indicating that they are on the same face of the pyrrolidine ring system. The reaction is highly stereoselective and the absolute stereochemistry was assigned based on the starting configuration of the crotylsilane, which has been previously demonstrated and attributed to an anti-S_E’ addition.



f. Selected HPLC Spectra



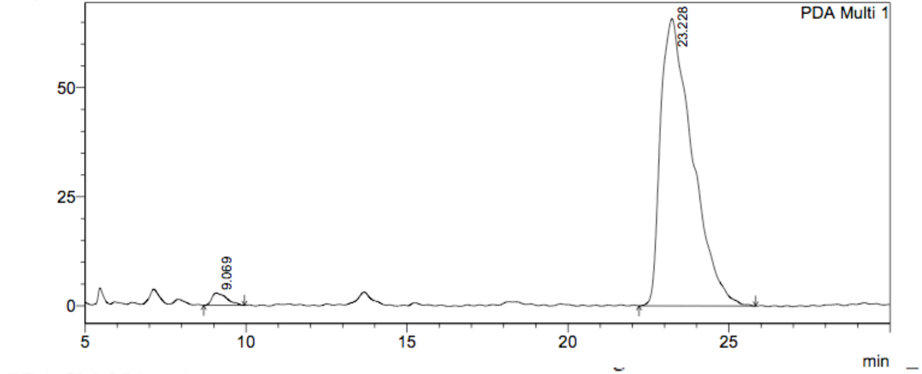
Racemic Standard for **3a**:



PDA Ch1 254nm 4nm

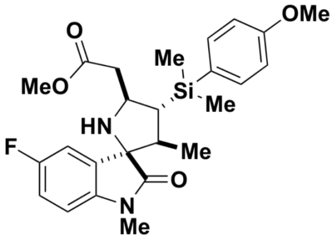
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.950	3370577	151900	50.641	73.245
2	22.602	3285291	55486	49.359	26.755
Total		6655868	207386	100.000	100.000

Enantiomerically-enriched **3a** (96% *ee*):

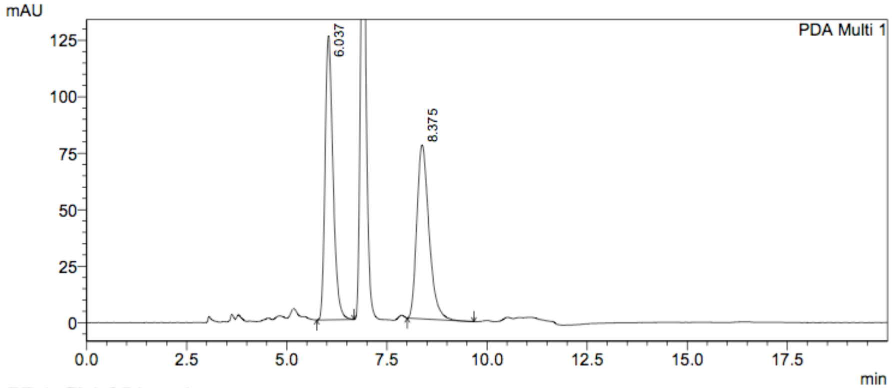


PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.069	90919	2792	1.965	4.070
2	23.228	4536661	65813	98.035	95.930
Total		4627580	68605	100.000	100.000



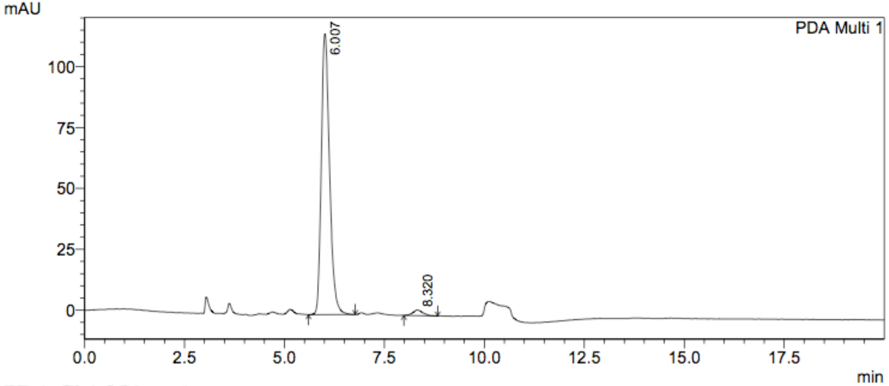
Racemic standard for **4a**:



PDA Ch1 254nm 4nm

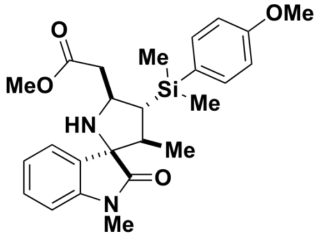
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.037	1736998	125777	51.579	62.039
2	8.375	1630674	76960	48.421	37.961
Total		3367672	202737	100.000	100.000

Enantiomerically-enriched **4a** (95% *ee*):

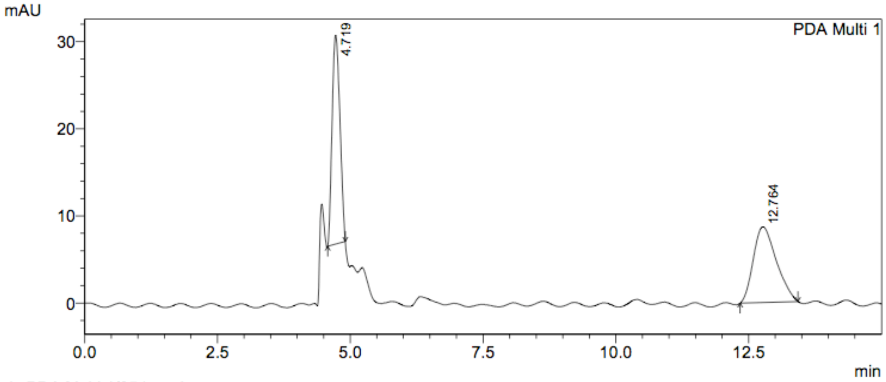


PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.007	1655778	115356	97.640	98.067
2	8.320	40020	2274	2.360	1.933
Total		1695799	117631	100.000	100.000



Racemic standard for **4b**:

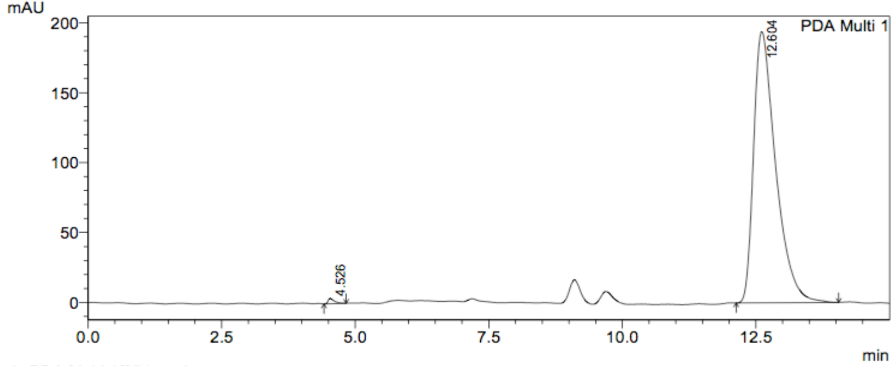


1 PDA Multi 1/254nm 4nm

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.719	245555	24007	48.368	73.436
2	12.764	262123	8684	51.632	26.564
Total		507679	32691	100.000	100.000

Enantiomerically-enriched **4b** (99% *ee*):

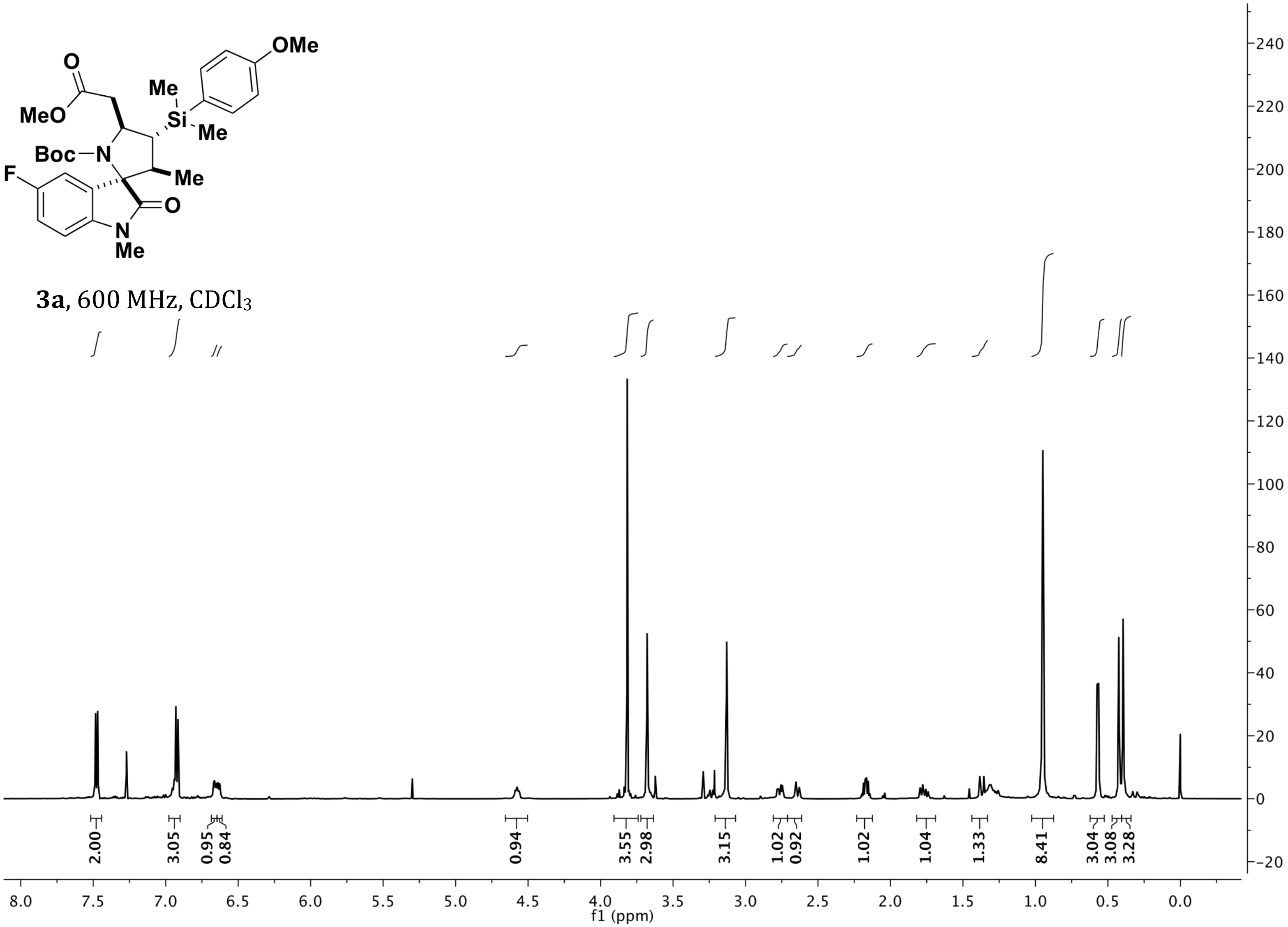


1 PDA Multi 1/254nm 4nm

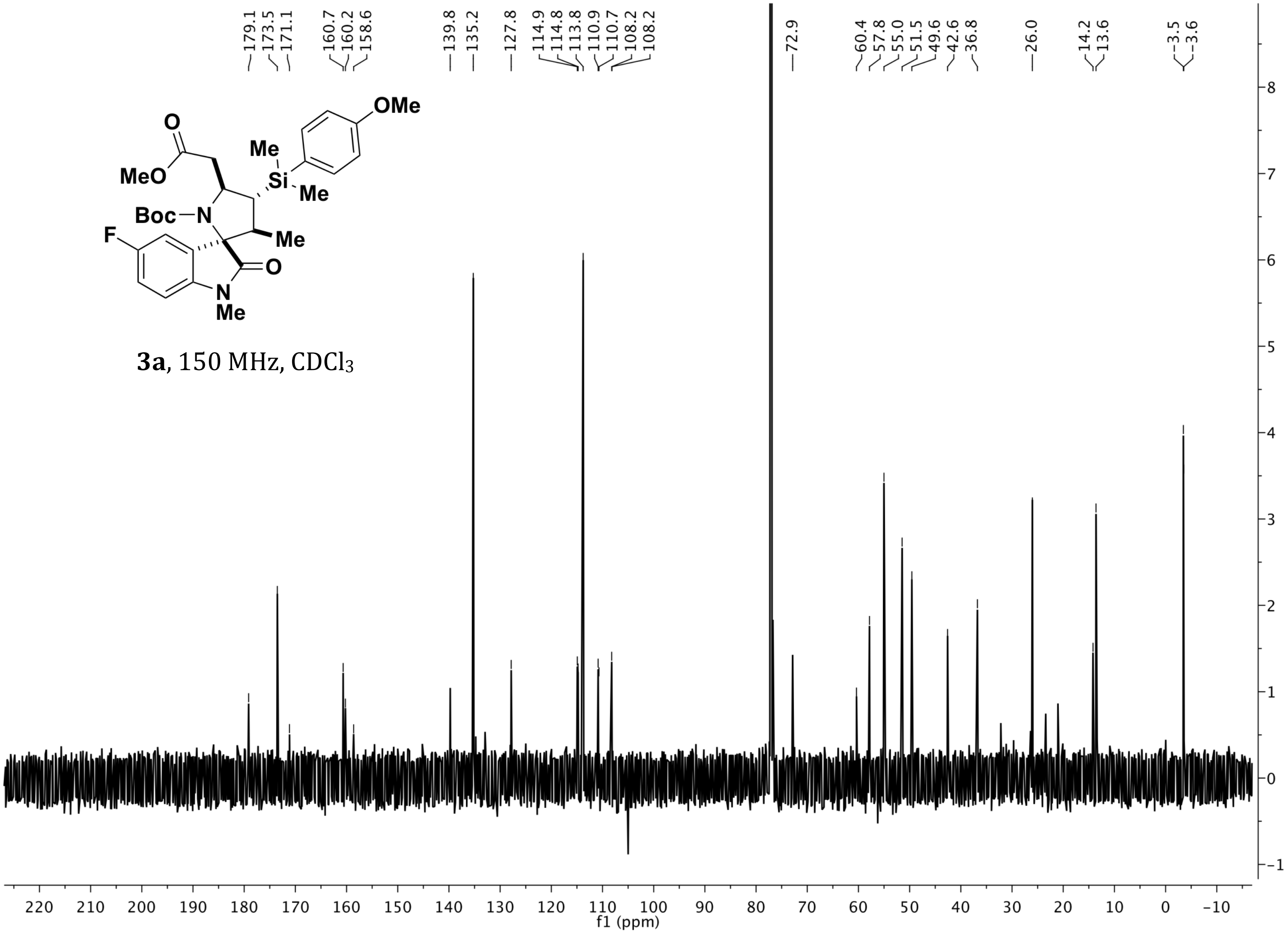
PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.526	30148	3712	0.538	1.878
2	12.604	5568998	194010	99.462	98.122
Total		5599146	197722	100.000	100.000

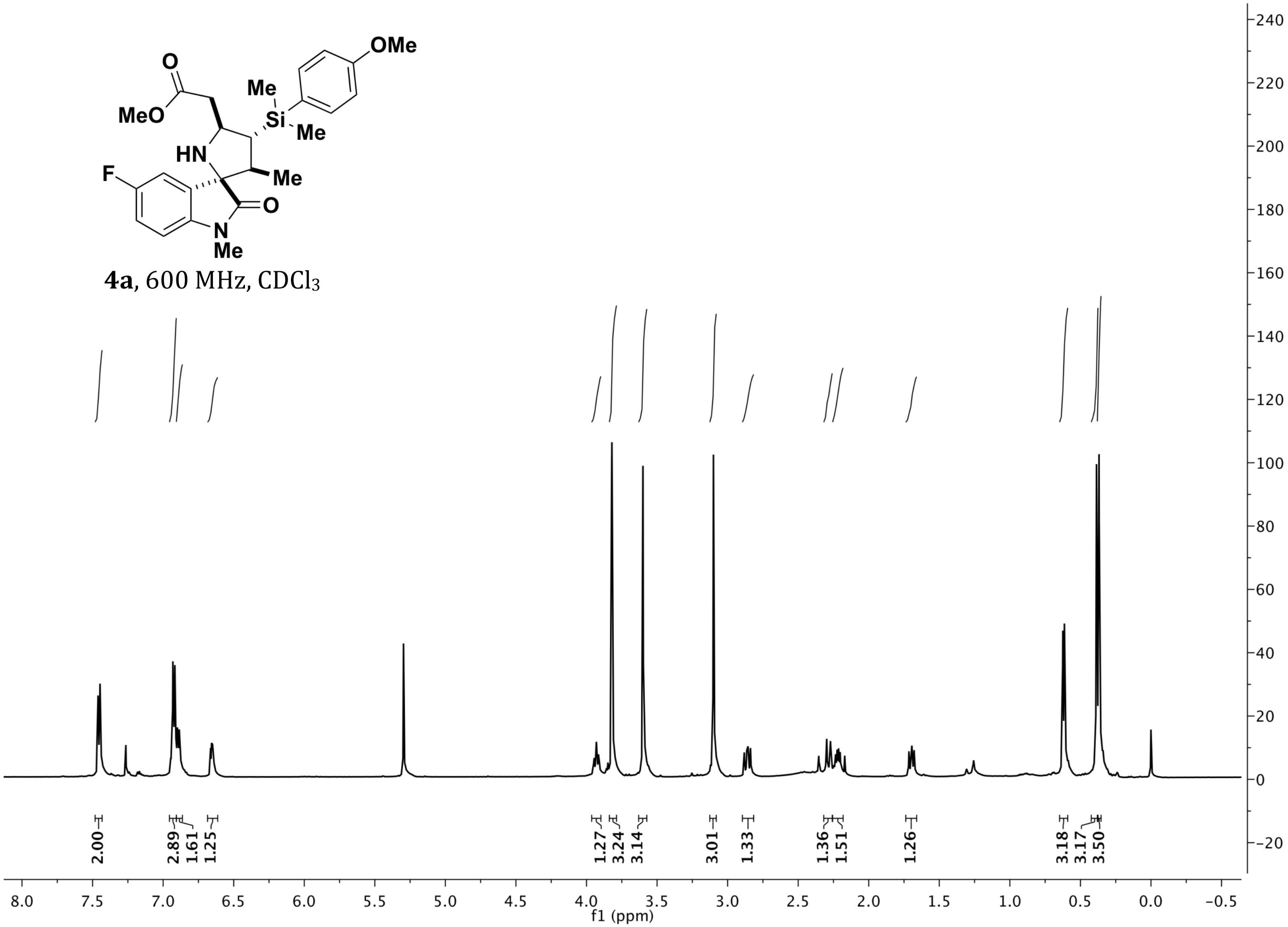
III. ^{1}H and ^{13}C NMR Spectra



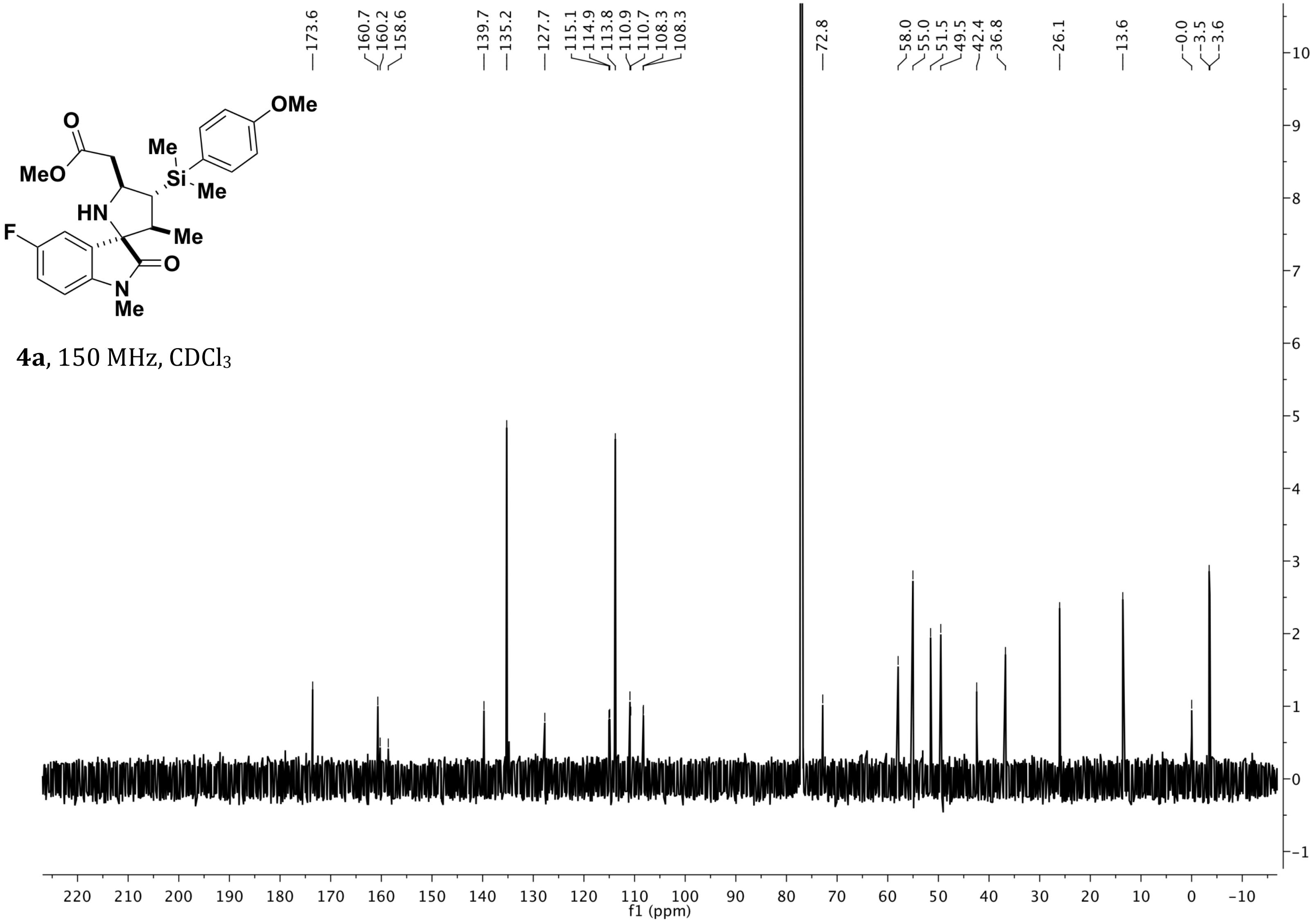
3a, 600 MHz, $CDCl_3$



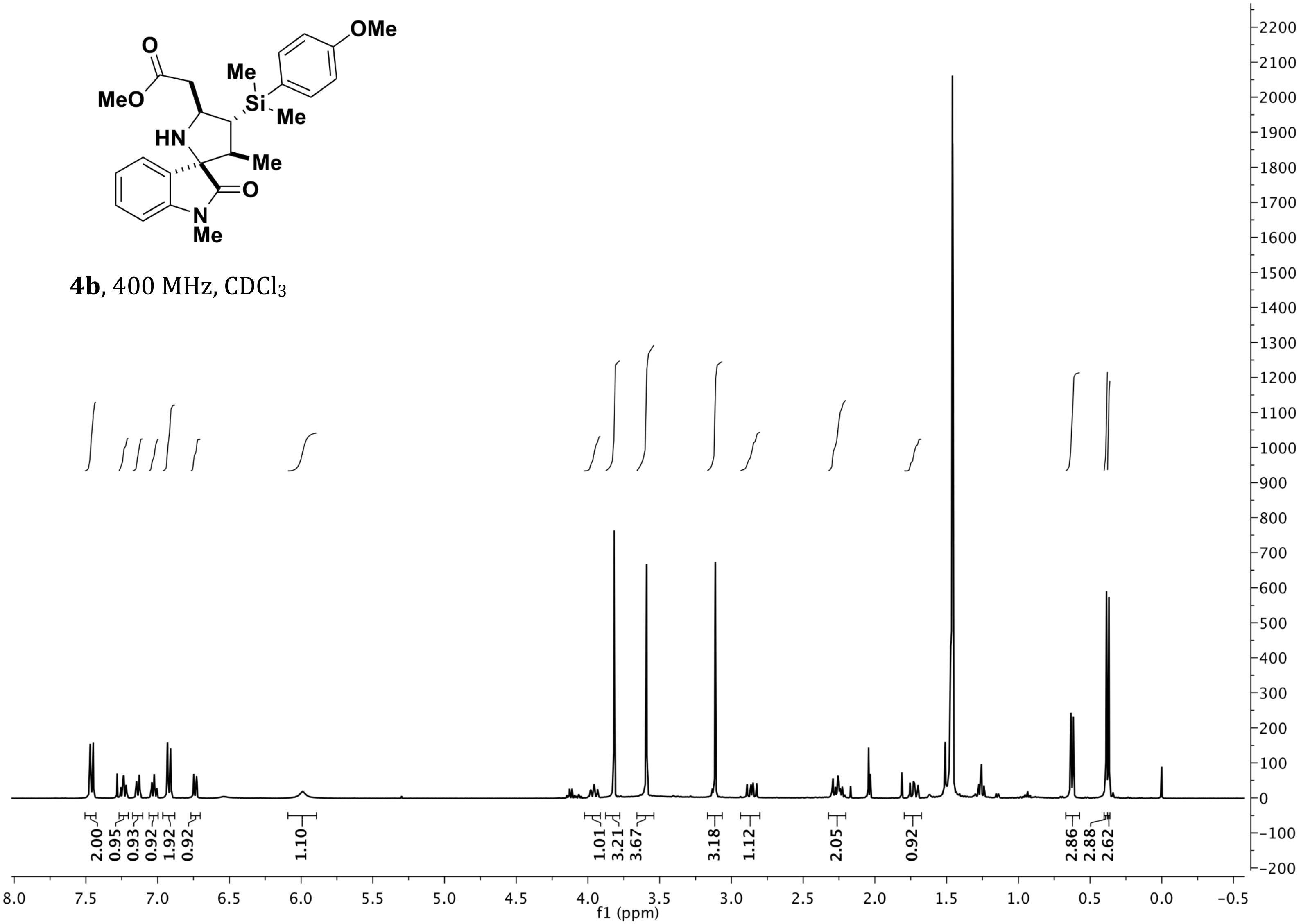
3a, 150 MHz, $CDCl_3$



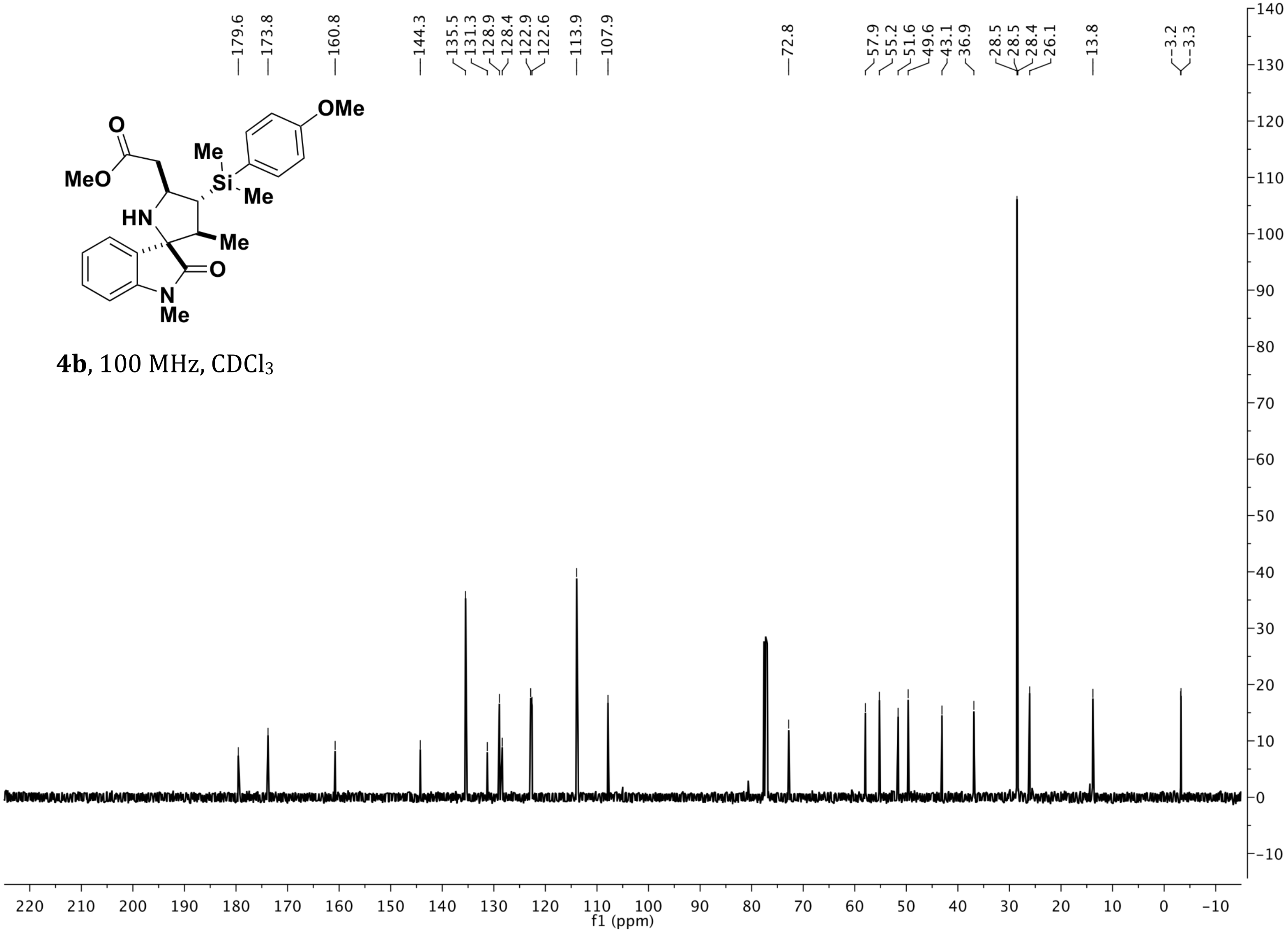
4a, 600 MHz, CDCl$_3$

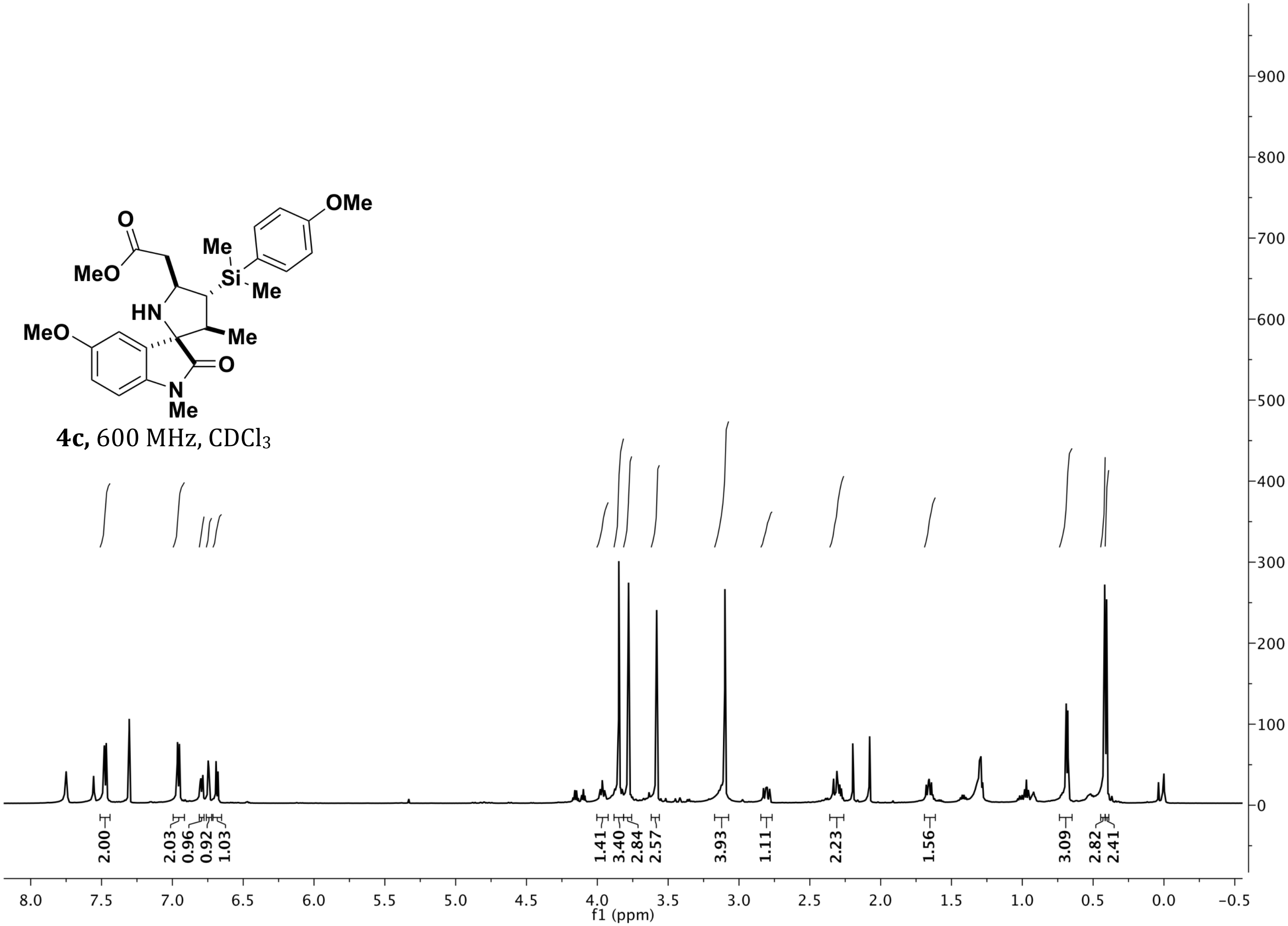


4a, 150 MHz, $CDCl_3$

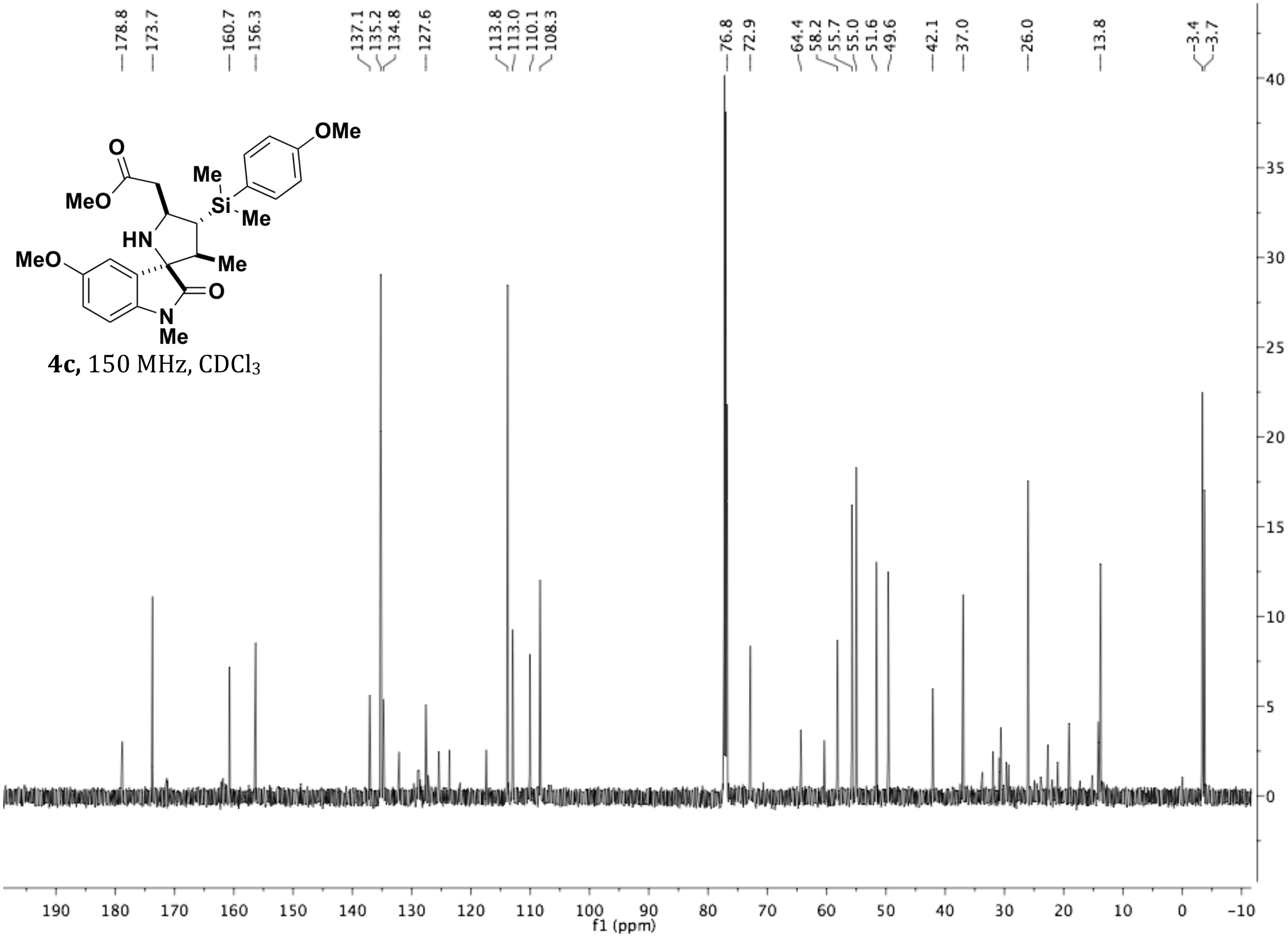


4b, 400 MHz, CDCl$_3$

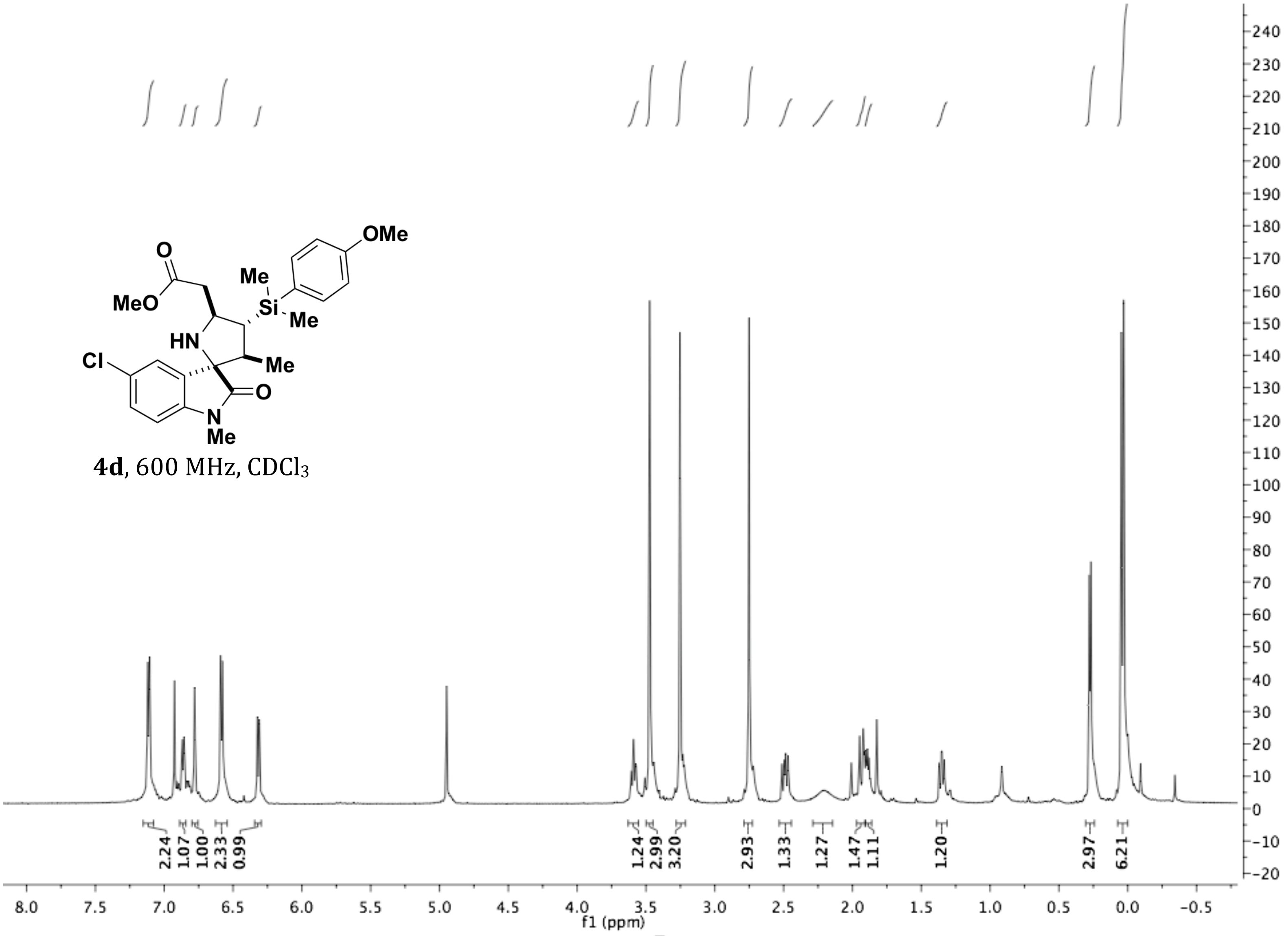

4b, 100 MHz, $CDCl_3$



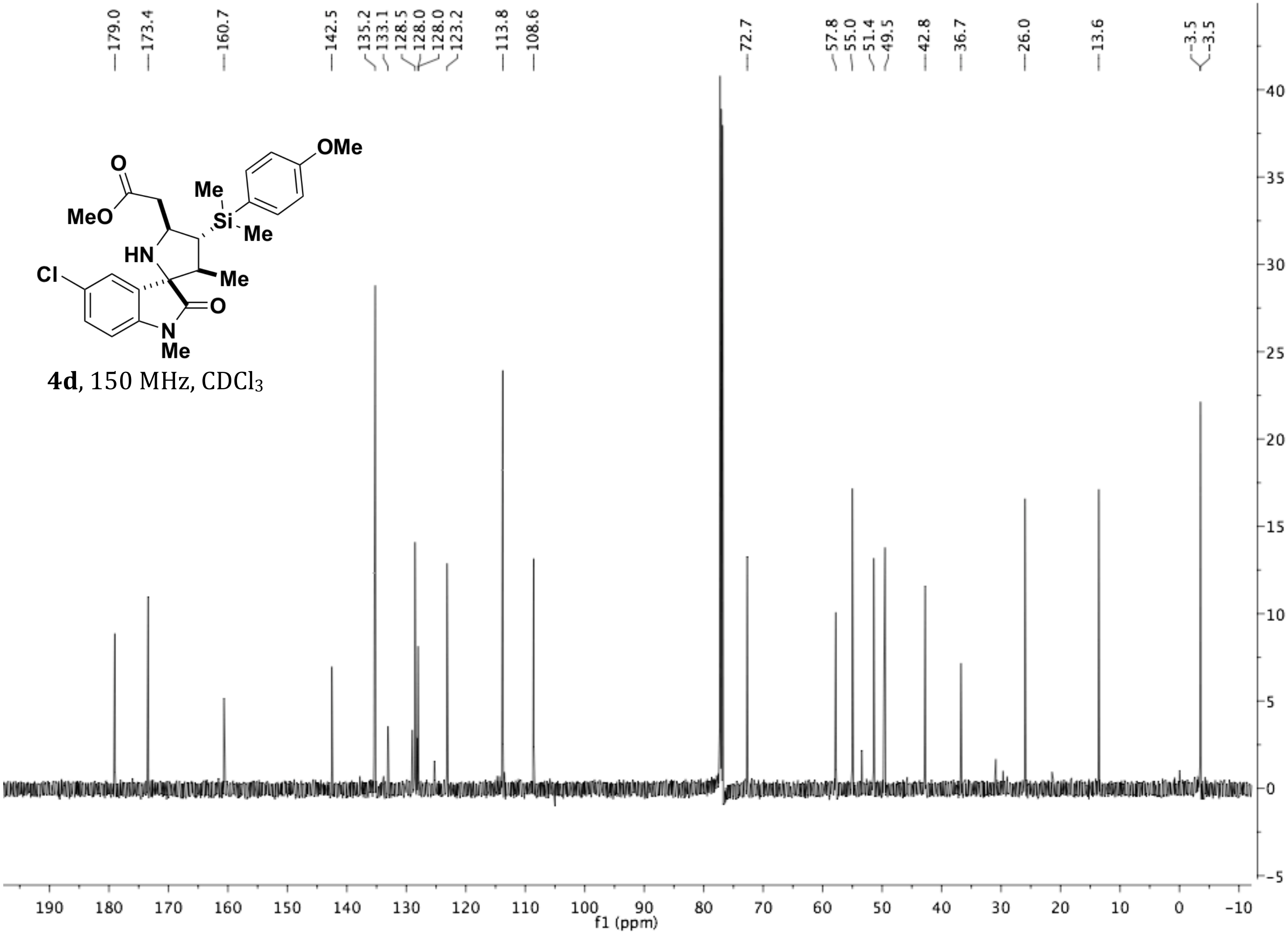
4c, 600 MHz, CDCl$_3$



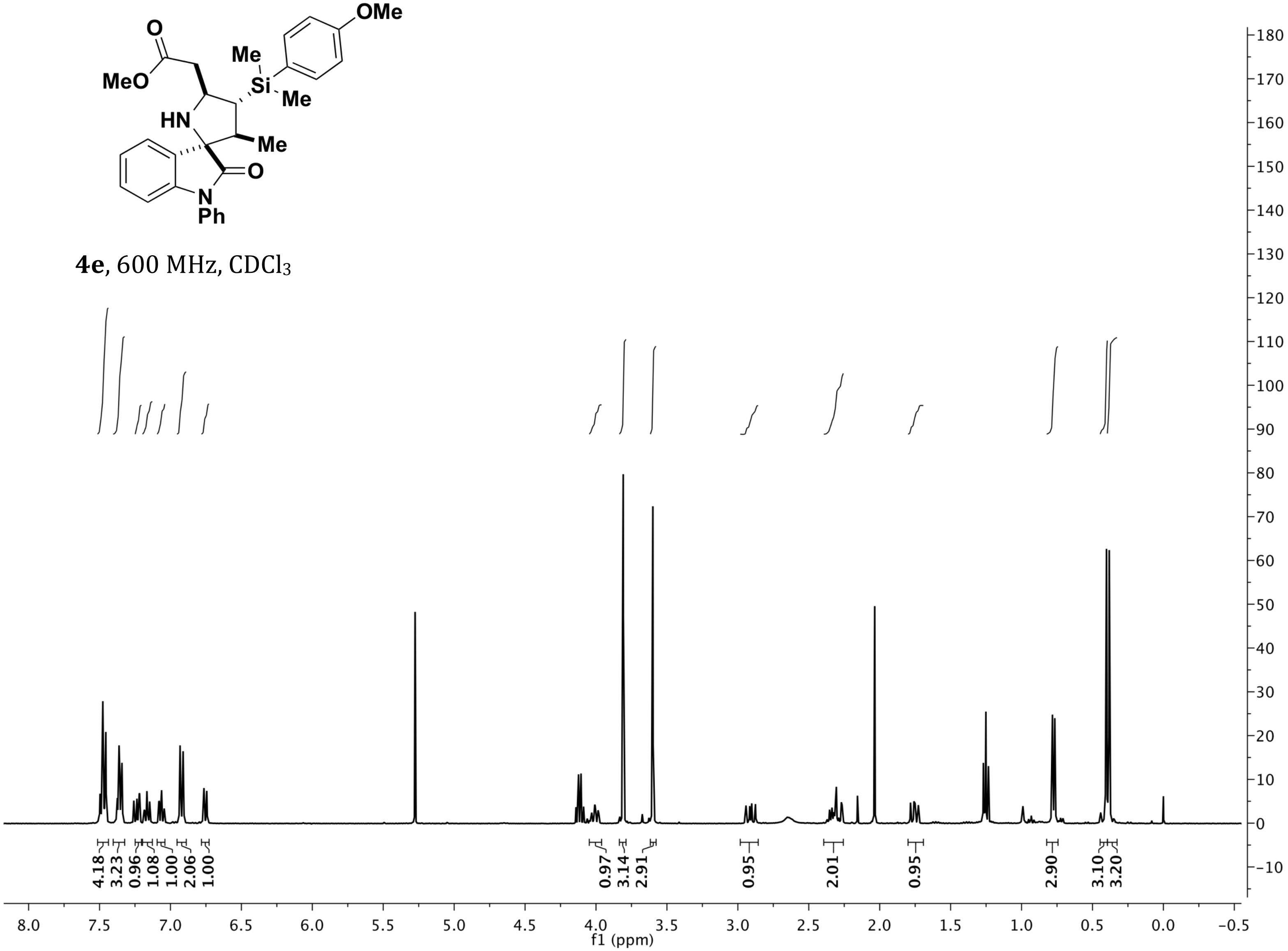
4c, 150 MHz, $CDCl_3$



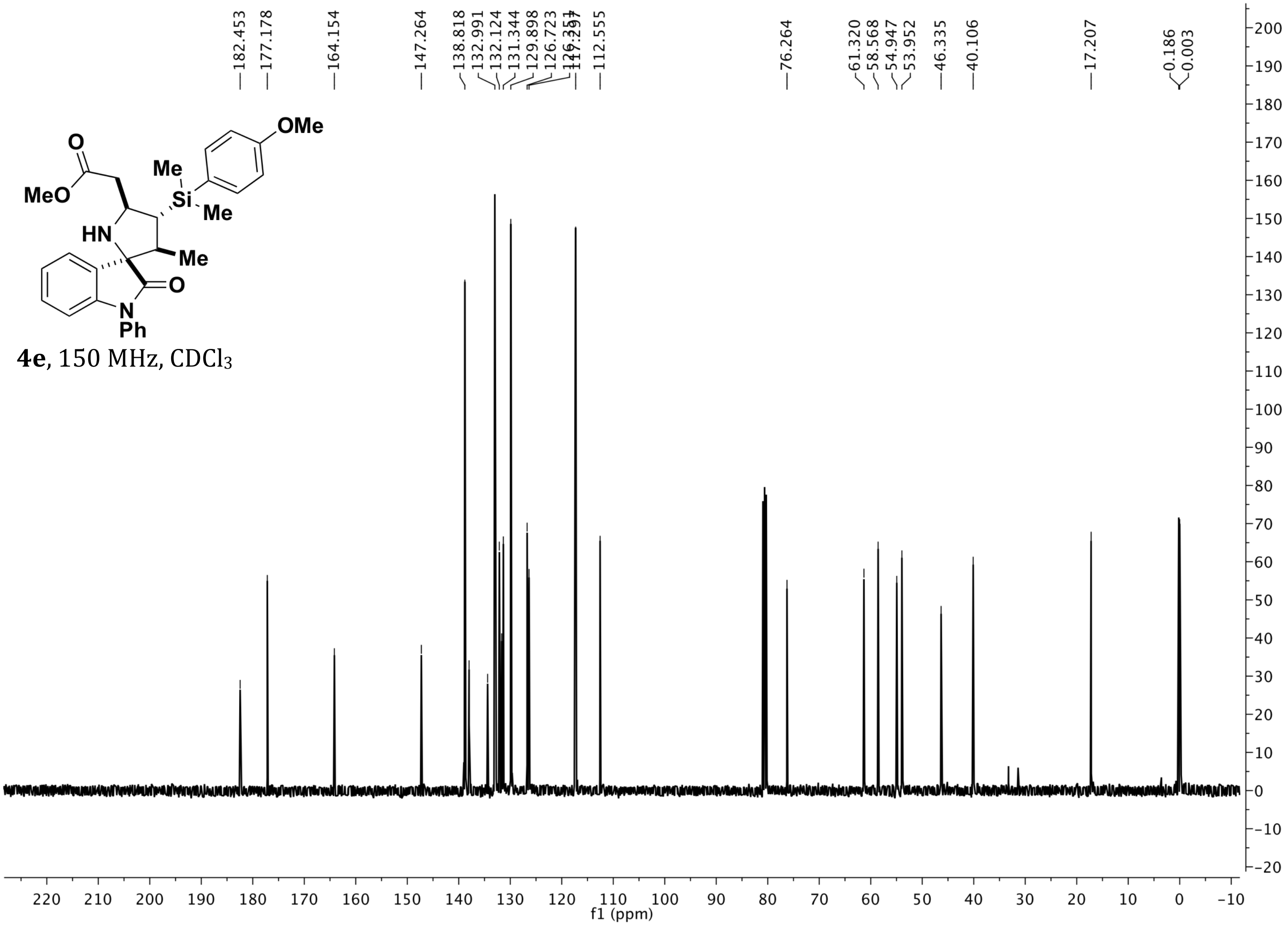
4d, 600 MHz, $CDCl_3$



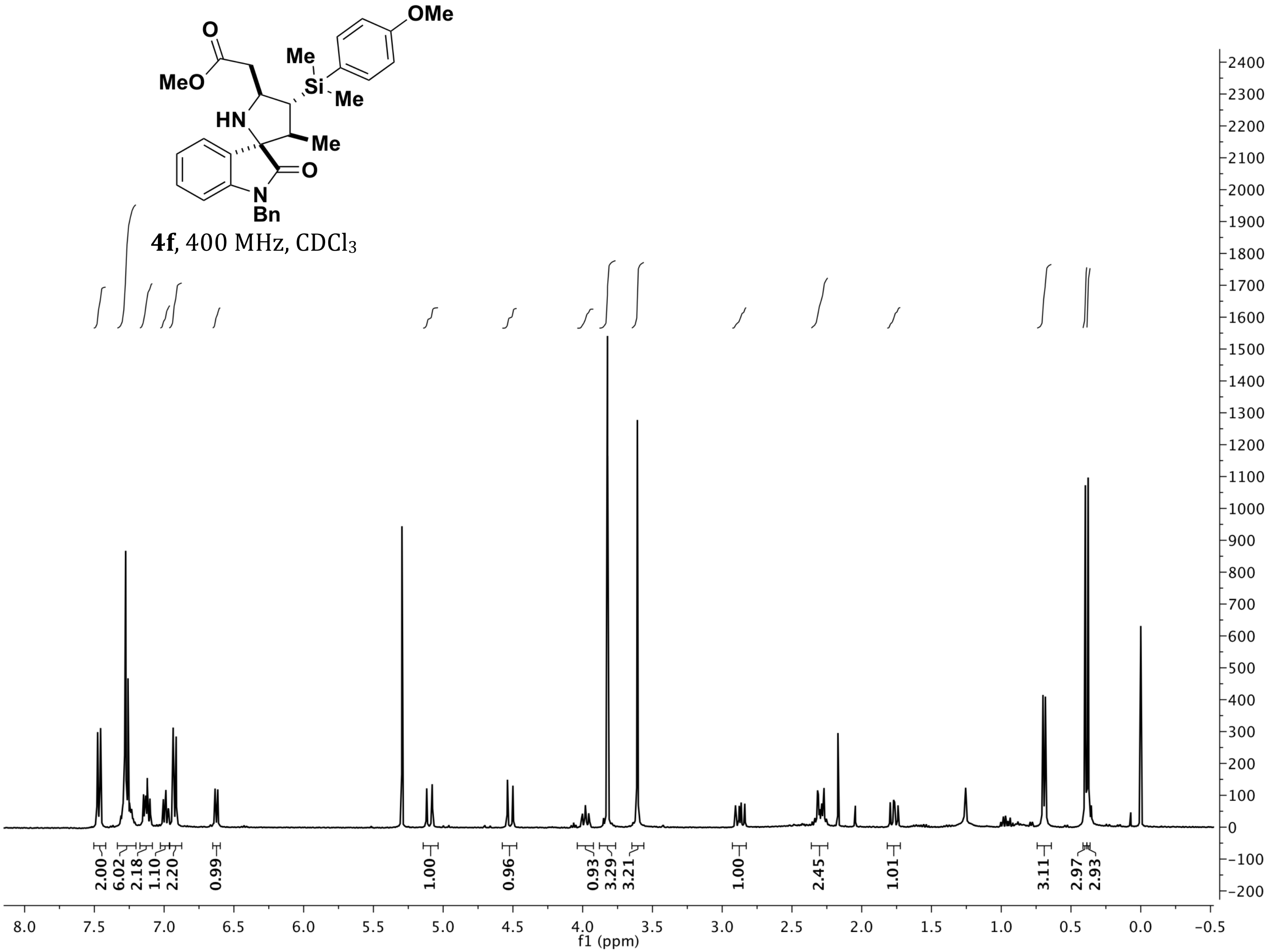
4d, 150 MHz, $CDCl_3$



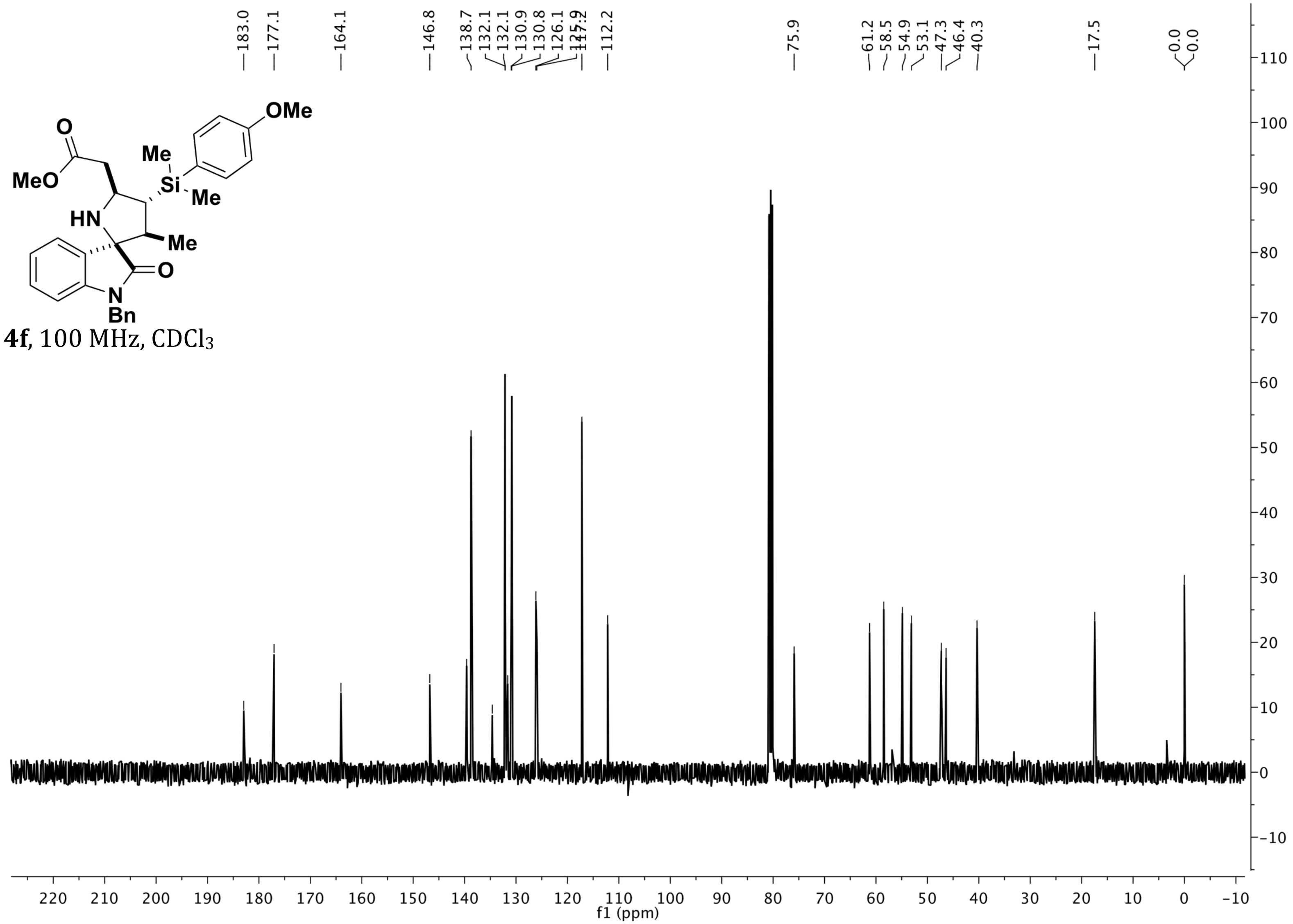
4e, 600 MHz, $CDCl_3$



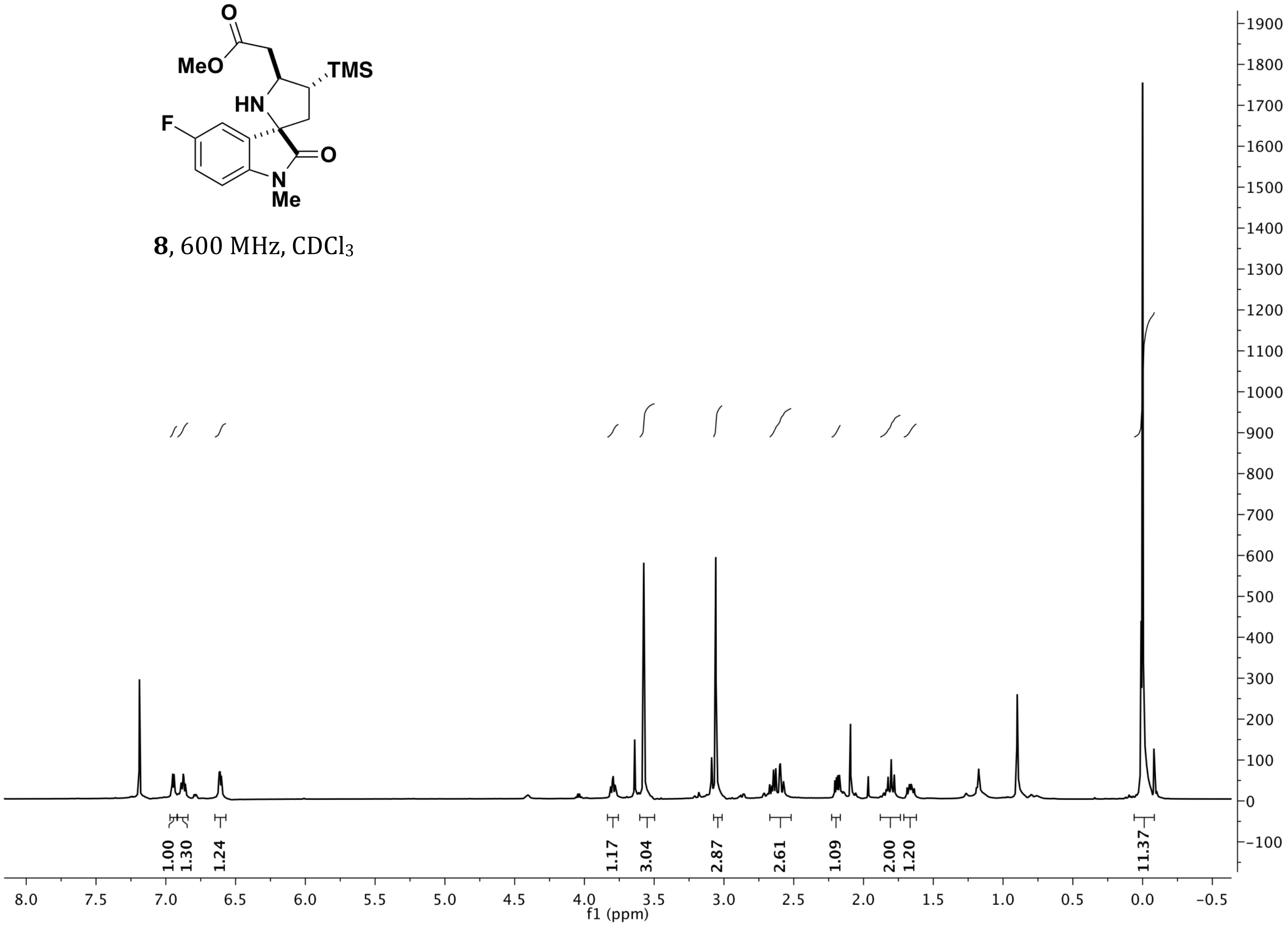
4e, 150 MHz, CDCl$_3$



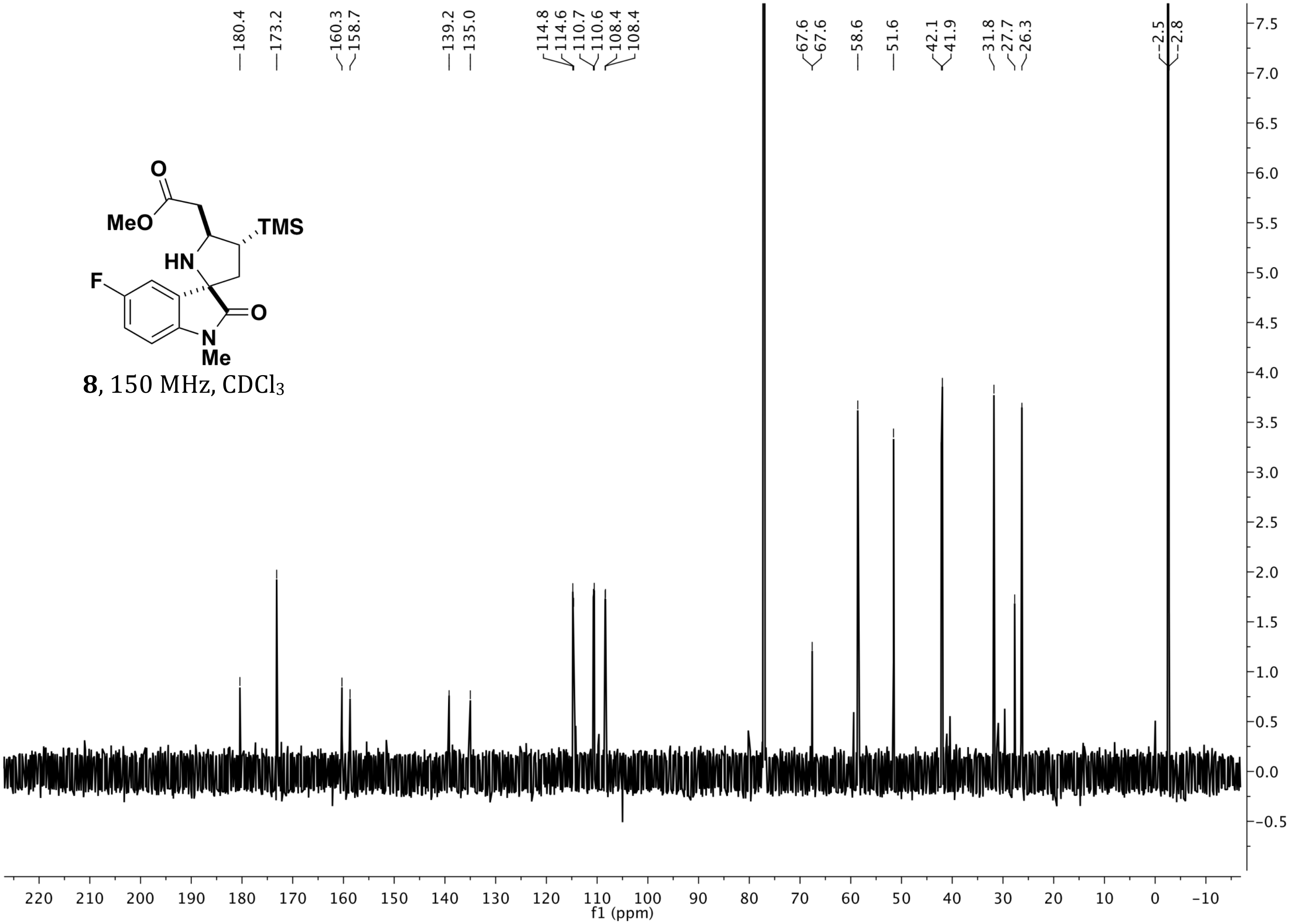
4f, 400 MHz, $CDCl_3$



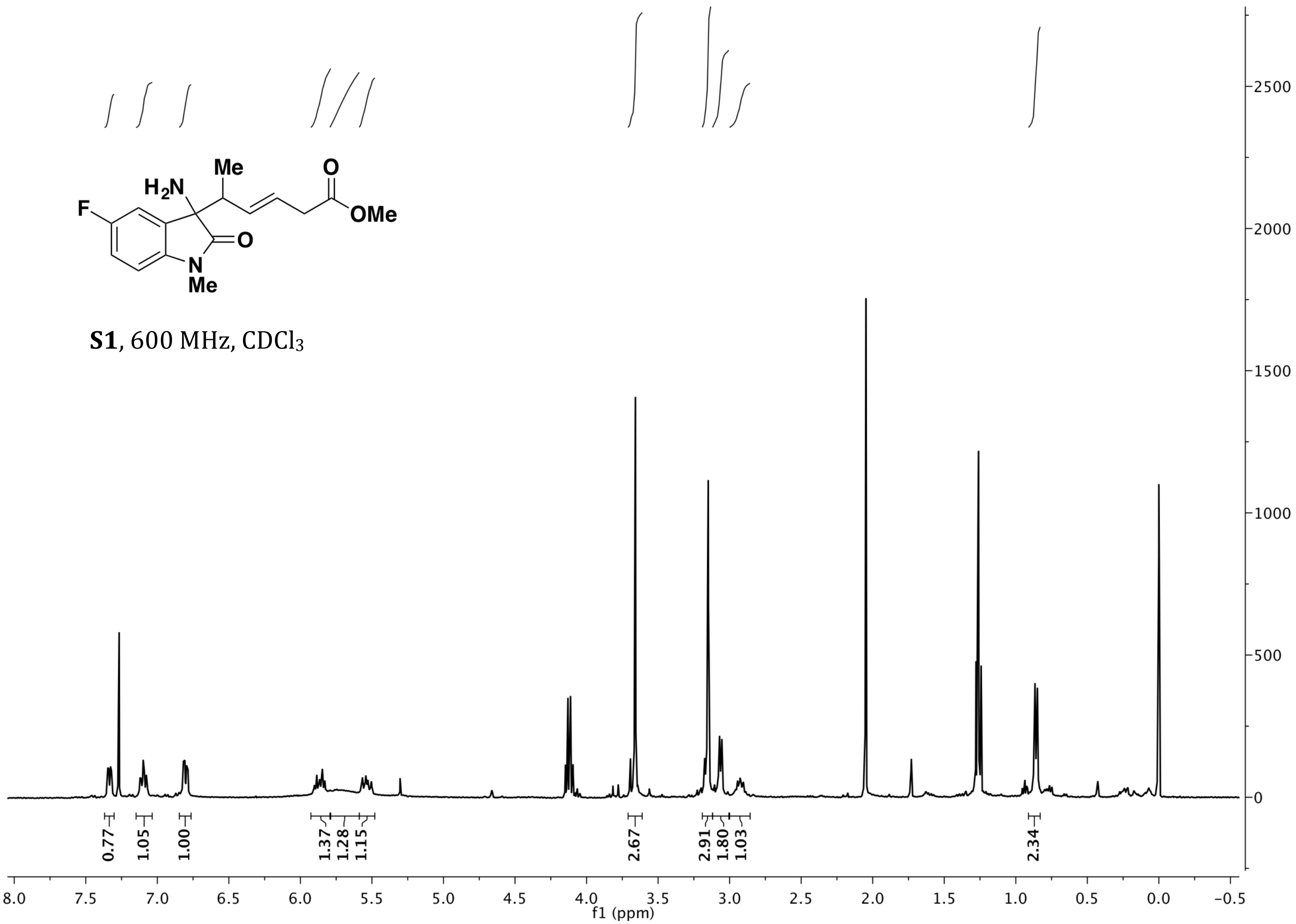
4f, 100 MHz, $CDCl_3$



8, 600 MHz, $CDCl_3$



8, 150 MHz, CDCl$_3$



S1, 600 MHz, $CDCl_3$