Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information for

Solvent-Free, Uncatalyzed Asymmetric "Ene" Reactions of N-tert-Butylsulfinyl-3,3,3-trifluoroacetaldimines: General Approach to Enantiomerically Pure α-(Trifluoromethyl)tryptamines

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Experimental General

If not specified otherwise, ^{1}H NMR and ^{1}H-decoupled ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution using tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded at 376 MHz in $CDCl_3$ solution using $CFCl_3$ as a reference standard. *J* values are expressed in Hz. Mass spectra were obtained by electron impact fragmentation at 70 eV ionization potential. The purity of all final products was testified by elemental analyses of the diastereomeric mixtures performed on Carlo Erba Elemental Analyzer Mod. 1106. VCD experiments were performed with a Jasco FVS6000 spectrometer on 0.1 M/$CDCl_3$ solutions in 0.200 mm BaF_2 cells. DFT calculations were carried out using Gaussian09 set of programs[1] (for further details see SI). Further information about working routine and technical details can be found in previous publications from this laboratory. The starting fluoro-, trifluoromethyl- and trifluoromethoxy substituted anilines and 2-bromo-5-fluoroaniline were commercial products and were used without further purification.

New starting material used in this work:

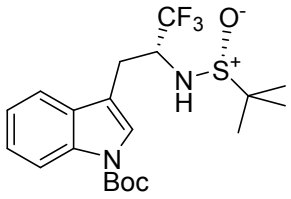
tert-Butyl N-(2-bromo-4-methoxyphenyl)-N-(prop-2-yn-1-yl)carbamate. It was obtained in 75% of yield from *p*-anisidine following the same protocol previously reported.[2] Chromatography of the crude on silica gel (eluent 9:1 v/v petroleum ether/diethyl ether) allowed to recover a colorless oil consisting of a 3:1 mixture of two conformers exhibiting the following spectral characteristics. Major conformer: ^{1}H NMR δ 7.28 (d, *J* = 8.6 Hz, 1 H), 7.14 (d, *J* = 2.7 Hz, 1 H), 6.84 (dd, *J* = 8.6 and 2.7, 1 H), 4.76 (dd, *J* = 17.6 and 2.3 Hz, 1 H), 3.91 (dd, *J* = 17.6 and 2.3 Hz, 1 H), 3.81 (s, 3 H), 2.20 (bs, 1 H), 1.36 (s, 9 H); ^{13}C NMR δ 159.1, 154.0, 132.9, 131.0, 123.8, 117.8, 113.5, 80.7, 72.2, 55.6, 38.2, 28.1. Minor conformer, typical absorptions: ^{1}H NMR δ 7.35 (d, *J* = 8.6 Hz, 1 H), 7.15 (b, 1 H), 4.61 (d, *J* = 17 Hz, 1 H), 3.79 (s, 3 H), 2.22 (bs, 1 H), 1.52 (s, 9 H) ^{13}C NMR δ 156.7, 154.3, 133.2, 131.3, 118.2, 114.0, 81.3, 71.9, 39.5. Anal.: calcd for $C_{15}H_{18}BrNO_3$ (340.22) C, 52.96; H, 5.33; N, 4.12. Found C, 53.13; H, 5.36; N, 4.17.

1-tert-Butoxycarbonyl-5-metoxy-3-methyleneindoline. It was prepared in 53% yield by tributyltin hydride-promoted radical cyclization of the above 2-bromoarylcarbamate as previously reported.[2] Chromatography of the crude product on silica gel (eluent, 9:1 petroleum ether/diethyl ether mixture) allowed to get a pale yellow solid exhibiting the following spectroscopic and analytical characteristics. Mp 40-42 °C; ^{1}H NMR δ 7.86 (d, *J* = 8.4 Hz, 1 H), 6.95 (s, 1 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 5.43 (bs, 1 H), 5.03 (bs, 1 H), 4.56 (bs, 2 H), 3.81 (s, 3 H), 1.55 (s, 9 H). ^{13}C NMR δ 155.5, 151.5, 141.1, 130.0, 116.1, 116.0, 105.2, 101.6, 101.2, 80.5, 55.7, 53.6, 28.4. Anal.: calcd for $C_{15}H_{19}NO_3$ (261.32) C, 68.94; H, 7.33; N, 5.36. Found C, 68.67; H, 7.45; N, 5.41.

General Procedure for (*R*)-1-*tert*-butoxycarbonyl-3-[2-((*R*)-*tert*-butanesulfin-ylamido)-3,3,3-trifluoropropyl]indoles.

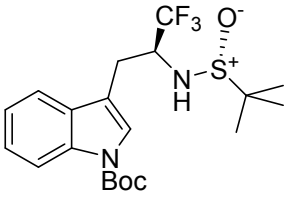
3-methyleneindoline **1a-f** (1.0 mmol) and (*R*)- or (*S*)-*tert*-butanesulfinyltrifluoacetaldimine were mixed in a sealed vial without solvent and heated at 70-80°C in a oil bath for the time reported in the

Table. After cooling, the diastereomeric ratio was determined by ^{19}F NMR analysis before the crude mixture was take up with dichloromethane (1 mL) and chromatographed on silica gel using 65:35 petroleum ether-ethyl acetate mixture as the eluent. Yields are reported in the Table. For irresolvable diastereomeric mixture, the structure of each diastereomer was inferred from the specific ^{1}H, ^{13}C and ^{19}F NMR signals in the spectrum of the mixture.



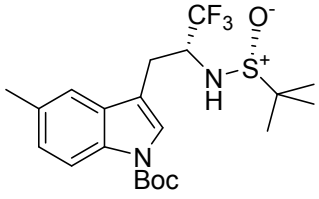
6a$_{(R)}$

*(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]indole (**6a**$_{(R)}$).* ^{1}H NMR δ 8.14 (bd, *J* = 7.6 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.50 (s, 1 H), 7.35 (t, *J* = 8.5 Hz, 1 H), 7.28 (t, *J* = 8.5 Hz, 1 H) 4.05 (m, 1 H), 3.74 (d, *J* = 9.6 Hz, 1 H), 3.26 (dd, *J* = 15 and 4.0 Hz, 1 H), 3.03 (dd, *J* = 15 and 9.2 Hz, 1 H), 1.68 (s, 9 H), 1.01 (s, 9 H); ^{13}C NMR δ 148.9, 134.9, 129.4, 124.6 (q, *J* = 281 Hz), 124.3, 124.2, 123.2, 117.9, 114.9, 113.8, 83.3, 57.6 (q, *J* = 29 Hz), 56.6, 27.6, 24.8, 21.6; ^{19}F NMR δ −75.33 (d, *J* = 7.1 Hz, 3 F).



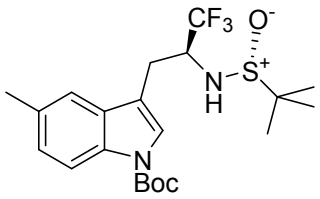
6a$_{(S)}$

*(S,R$_S$)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]indole (**6a**$_{(S)}$).* ^{1}H NMR δ 7.91 (m, 1 H), 7.55 (s, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 8.5 Hz, 1 H), 7.19 (t, *J* = 8.5 Hz, 1 H), 4.05 (quint, *J* = 6.8 Hz, 1H), 3.53 (d, *J* = 9.6 Hz, 1 H), 3.24 (dd, *J* = 15 and 6.0 Hz, 1 H), 3.10 (dd, *J* = 15 and 6.4 Hz, 1 H), 1.59 (s, 9 H), 0.93 (s, 9 H); ^{19}F NMR δ −75.52 (d, *J* = 7.1 Hz, 3 F). Analysis of the diastereomeric mixture: calcd for $C_{20}H_{27}F_3N_2O_3S$ (432.50) C, 55.54; H, 6.29; N, 6.48. Found C, 55.41; H, 6.34; N, 6.51.



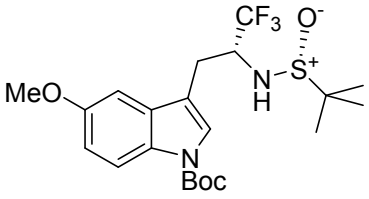
6b$_{(R)}$

(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methylindole ***(6b$_{(R)}$).*** ^{1}H NMR δ 8.00 (bd, *J* = 8.3 Hz, 1 H), 7.44 (s, 1 H), 7.27 (s, 1 H), 7.16 (d, *J* = 8.3 Hz, 1 H), 4.04 (m, 1 H), 3.58 (d, *J* = 9.6 Hz, 1 H), 3.24 (dd, *J* = 15 and 3.9 Hz, 1 H), 2.98 (dd, *J* = 15 and 9.6 Hz, 1 H), 2.47 (s, 3 H), 1.67 (s, 9 H), 1.01 (s, 9 H); ^{13}C NMR δ 149.4, 133.7, 132.3, 130.0 (d, *J* = 9.5 Hz), 126.0, 125.1 (q, *J* = 282 Hz), 124.5, 118.3, 115.0, 114.0, 83.6, 58.2 (q, *J* = 29 Hz), 57.1, 28.1 (3 C), 25.3, 22.1 (3 C), 21.3; ^{19}F NMR δ −75.34 (d, *J* = 7.0 Hz, 3 F).



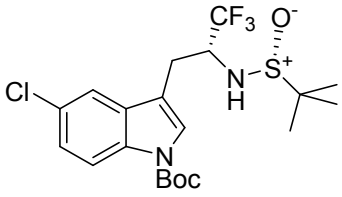
6b$_{(S)}$

(S,R$_S$)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methylindole ***(6b$_{(S)}$).*** ^{1}H NMR δ 7.92 (bs, 1 H), 7.52 (s, 1 H), 7.20 (s, 1 H), 7.09 (d, *J* = 8.3 Hz, 1 H), 4.06 (quint, *J* = 5.8 Hz, 1 H), 3.54 (d, *J* = 6.0 Hz, 1 H), 3.21 (dd, *J* = 15 and 5.8 Hz, 1 H), 3.07 (dd, *J* = 15 and 6.8 Hz, 1 H), 2.39 (s, 3 H), 1.59 (s, 9 H), 0.93 (s, 9 H); ^{13}C NMR δ 149.4, 133.6, 132.3, 130.6, 126.5, 125.1 (q, *J* = 282 Hz), 124.8, 118.3, 115.0, 114.0, 83.6, 58.2 (q, J = 29 Hz), 57.1, 28.1 (3 C), 25.3, 22.3 (3 C), 21.3; ^{19}F NMR δ −75.47 (d, *J* = 7.0 Hz, 3 F). Analysis of the diastereomeric mixture: calcd for $C_{21}H_{29}F_3N_2O_3S$ (446.53) C, 56.49; H, 6.55; N, 6.27. Found C, 56.47; H, 6.60; N, 6.37.



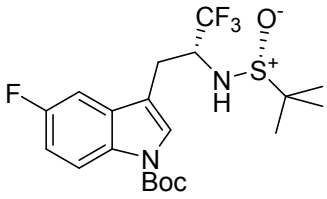
6c

(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methoxyindole ***(6c).*** ^{1}H NMR δ 7.94 (bd, 8.0 Hz, 1 H), 7.39 (s, 1 H), 6.88 (s, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 3.96 (m, 1 H), 3.81 (s, 3 H), 3.72 (d, *J* = 9.4 Hz, 1 H), 3.15 (dd, *J* = 15 and 4.3 Hz, 1 H), 2.92 (dd, *J* = 15 and 9.1 Hz, 1 H), 1.59 (s, 9 H), 0.96 (s, 9 H); ^{13}C NMR δ 155.5, 148.9, 130.2, 129.5, 124,9, 124.6 (q, *J* = 282 Hz), 115.7, 113.5, 112.7, 100.7, 83.1, 57.3 (q, *J* = 29 Hz), 56.7, 55.2, 27.6 (3 C), 25.0, 21.6 (3 C); ^{19}F NMR δ −75.25 (d, *J* = 7.1 Hz, 3 F). Analysis: calcd for $C_{21}H_{29}F_3N_2O_4S$ (462.53) C, 54.53; H, 6.32; N, 6.06. Found C, 55.40; H, 6.41; N, 6.12.



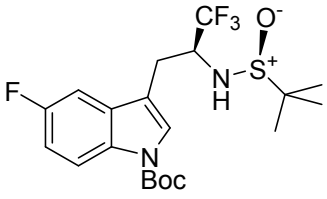
6d

(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-chloroindole ***(6d)***. ^{1}H NMR δ 8.07 (d, *J* = 8.4 Hz, 1 H), 7.53 (s, 1 H), 7.49 (d, *J* = 1.5 Hz, 1 H), 7.30 (dd, *J* = 9.0 and 1.9 H, 1 H), 4.01 (m, 1 H), 3.85 (d, *J* = 9.4 Hz, 1 H), 3.21 (dd, *J* = 15 and 3.5 Hz, 1 H), 3.02 (dd, *J* = 15 and 9.2 Hz, 1 H), 1.68 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR δ 149.0, 133.7, 131.2, 128.5, 126.1, 125.0 (q, *J* = 282 Hz), 124.8, 118.2, 116.4, 113.7, 84.3, 58.1 (q, *J* = 29 Hz), 57.1, 28.1 (3 C), 25.1, 22.2 (3 C); ^{19}F NMR δ, −75.18 (d, *J* = 6.3 Hz, 3 F). Analysis: calcd for $C_{20}H_{26}ClF_3N_2O_3S$ (466.94) C, 51.44; H, 5.61; N, 6.00. Found C, 51.54; H, 5.71; N, 6.09.



(*R*,*R*$_S$)-6e

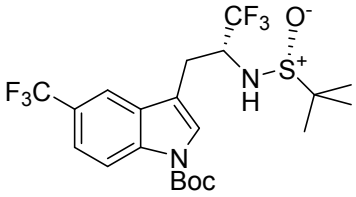
*(R,R$_S$)-1-tert-butoxycarbonyl-3-[2-((R)-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-fluoroindole (**6e**$_{(R)}$).* ^{1}H NMR δ 8.03 (bs, 1 H), 7.49 (s, 1 H), 7.14 (dd, *J* = 8.4 and 2.4 Hz, 1 H), 7.06 (td, *J* = 9.2 and 2.8 Hz, 1 H), 4.16 (m, 1 H), 3.71 (d, *J* = 9.6 Hz, 1 H), 3.39 (dd, *J* = 15 and 4.0 Hz, 1 H), 3.19 (dd, *J* = 15 and 9.2 Hz, 1 H), 1.93 (s, 9 H), 1.34 (s, 9 H); ^{13}C NMR δ 159.3 (d, *J* = 240 Hz), 149.2, 131.8, 130.9 (d, *J* = 9.5 Hz), 126.4, 125.1 (q, *J* = 282 Hz), 116.5 (d, *J* = 9.1 Hz), 113.9 (d, *J* = 4.0 Hz), 112.6 (d, *J* = 25 Hz), 104.2 (d, *J* = 24 Hz), 84.2, 57.9 (q, *J* = 29 Hz), 57.1, 28.2 (3 C), 25.5 (q, *J* = 1.9 Hz), 22.2 (3 C); ^{19}F NMR δ −75.72 (d, *J* = 7.0 Hz, 3 F), −120.01 (s, 1 F).



(*S*,*S*$_S$)-6e

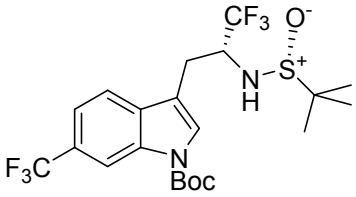
*(S,S$_S$)-1-tert-butoxycarbonyl-3-[2-((R)-tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-fluoroindole (**6e**$_{(S)}$).* ^{1}H NMR δ 8.10 (bs, 1 H), 7.55 (s, 1 H), 7.18 (dd, *J* = 8.7 and 2.5 Hz, 1 H), 7.09 (td, *J* = 9.1 and 2.6 Hz, 1 H), 4.03 (m, 1 H), 3.55 (d, *J* = 7.4 Hz, 1 H), 3.22 (dd, *J* = 15 and 5.6 Hz, 1 H), 3.02 (dd, *J* = 15 and 6.8 Hz, 1 H), 1.68 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR δ 159.3 (d, *J* = 239 Hz), 149.2, 131.8, 130.9 (d, *J* = 9.5 Hz), 126.4, 125.1 (q, *J* = 281 Hz), 116.5 (d, *J* = 9.1 Hz), 114.0 (d, *J* = 4.0 Hz), 112.6 (d, *J* = 25

Hz), 104.2 (d, *J* = 24 Hz), 84.2, 57.9 (q, *J* = 29 Hz), 57.1, 28.2 (3 C), 25.5 (q, *J* = 1.9 Hz), 22.2 (3 C); ^{19}F NMR δ −74.71 (d, *J* = 6.7 Hz, 3 F), −120.01 (s, 1 F). Analysis of the diastereomeric mixture: calcd for $C_{20}H_{26}F_4N_2O_3S$ (450.49) C, 53.32; H, 5.82; N, 6.22. Found C, 53.21; H, 5.90; N, 6.37.



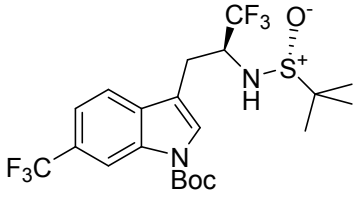
6f

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-trifluoro-methylindole (**6f**).* ^{1}H NMR δ 8.25 (d, *J* = 8.6 Hz, 1 H), 7.79 (s, 1 H), 7.61 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 4.02 (m, 1 H), 3.77 (d, *J* = 9.5 Hz, 1 H), 3.26 (dd, *J* = 15 and 4.3 Hz, 1 H), 3.09 (dd, *J* = 15 and 9.1 Hz, 1 H), 1.68 (s, 9 H), 1.03 (s, 9 H); ^{13}C NMR δ 148.4, 136.4, 129.3, 125.9, 124.8 (q, *J* = 280 Hz), 124.6 (q, *J* = 32 Hz), 124.1 (q, *J* = 270 Hz), 121.0, 115.3, 115.2, 114.0, 84.2, 57.7 (q, *J* = 29 Hz), 56.6, 27.5 (3 C), 24.6, 21.5 (3 C); ^{19}F NMR δ −61.48 (3 F), −75.12 (d, *J* = 6.8 Hz, 3 F). Analysis: calcd for $C_{21}H_{26}F_6N_2O_3S$ (500.50) C, 50.39; H, 5.24; N, 5.60. Found C, 50.31; H, 5.28; N, 5.69.



6g$_{(R)}$

*(R,R_S)-1-tert-butoxycarbonyl-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-6-trifluoro-methylindole (**6g**$_{(R)}$).* ^{1}H NMR δ 8.87 (bs, 1 H), 7.57 (s, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 3.98 (m, 1 H), 3.66 (d, *J* = 9.7 Hz, 1 H), 3.20 (dd, *J* = 15 and 4.2 Hz, 1 H), 3.01 (dd, *J* = 15 and 8.9, 1 H), 1.62 (s, 9 H), 0.97 (s, 9 H); ^{13}C NMR δ 148.4, 134.0, 131.8, 126.8, 126.2 (q, *J* = 32 Hz), 124.6 (q, *J* = 282 Hz), 124.2 (q, *J* = 270 Hz), 119.0 (q, *J* = 3.0 Hz), 118.4, 113.7, 112.5 (q, *J* = 4.1 Hz), 84.3, 57.6 (q, *J* = 29 Hz), 56.7, 27.5 (3 C), 24.6, 21.6 (3 C); ^{19}F NMR δ −61.56 (3 F), −75.12 (d, *J* = 7.1 Hz, 3 F).



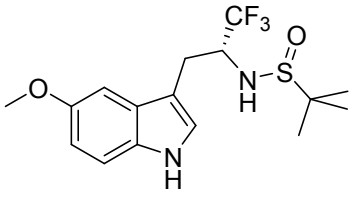
6g$_{(S)}$

*(S,R_S)-1-tert-butoxycarbonyl-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-6-trifluoro-methylindole (**6g**$_{(S)}$).* ^{1}H NMR δ 8.41 (bs, 1 H), 7.73 (s, 1 H), 7.63 (d, *J* = 8.3 Hz, 1 H), 7.45 (d, *J* = 8.3 Hz, 1

H), 4.06 (quint, *J* = 5.9 Hz, 1 H), 3.71 (d, *J* = 7.7 Hz, 1 H), 3.26 (dd, *J* = 15 and 5.4 Hz, 1 H), 3.13 (dd, *J* = 15 and 6.4 Hz, 1 H), 1.63 (s, 9 H), 1.15 (s, 9 H); ^{13}C NMR δ 148.5, 134.2, 132.0, 127.4, 126.2 (q, *J* = 32 Hz), 124.6 (q, *J* = 282 Hz), 124.2 (q, *J* = 270 Hz), 119.1, 118.8112.6, 112.5, 84.3, 57.0 (q, *J* = 29 Hz), 56.4, 27.6 (3 C), 25.0, 21.9 (3 C); ^{19}F NMR δ −61.6 (3 F), −75.52 (d, *J* = 7.1 Hz, 3 F). Analysis of the diastereomeric mixture: calcd for $C_{21}H_{26}F_6N_2O_3S$ (500.50) C, 50.39; H, 5.24; N, 5.60. Found C, 50.24; H, 5.31; N, 5.72.

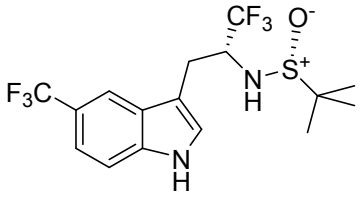
Selective deprotection of the adduct 6f by removal of tert-butoxycarbonyl (Boc) group.[3]

Adduct **6c** (or **6f)** (0.50 mmol) was added to a 1:9 dioxane/H_2O mixture (20 mL)and the resulting suspension was refluxed until the starting material was completely disappeared (48 h, *tlc*, SiO_2, eluent, 1:1 petroleum ether/ethyl acetate). After cooling, the reaction mixture was poured into water (30 mL), extracted with dichloromethane (3 × 50 mL) and the collected organic phases were dried with Na_2SO_4. After the solvent evaporation at reduced pressure, chromatography of the crude product on silica gel (eluent, 1:1 petroleum ether/ethyl acetate) allowed to get pure indole **7**



7c

*(R,R$_S$)-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-methoxyindole (**7c**, 96%)*. White solid, mp 92-94 °C; ^{1}H NMR δ 8.13 (bs, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.11 (s, 1 H), 6.99 (d, *J* = 2.4 Hz, 1 H), 6.87 (dd, *J* = 8.8 and 2.4 Hz, 1 H), 4.02 (m, 1 H), 3.88 (s, 3 H), 3.60 (d, *J* = 9.1 Hz, 1 H), 3.30 (dd, *J* = 15 and 3.4 Hz, 1 H), 3.09 (dd, *J* = 15 and 9.1 Hz, 1 H), 0.98 (s, 9 H); ^{13}C NMR δ 154.2, 131.2, 127.6, 125.3 (q, *J* = 281 Hz), 124.4, 123.9, 112.4, 112.1, 108.9, 57.9 (q, *J* = 29 Hz), 56.9, 55.8, 25.4, 22.0 (3 C); ^{19}F NMR δ −75.00 (d, *J* = 7.5 Hz, 3 F); MS (70 eV) m/z (%) 304 (M^+–C_4H_{10}, 20), 160 (100), 145 (21), 117 (14). Analysis: calcd for $C_{16}H_{21}F_3N_2O_2S$ (362,41) C, 53.03; H, 5.84; N, 7.73. Found C, 53.17; H, 5.91; N, 7.66.

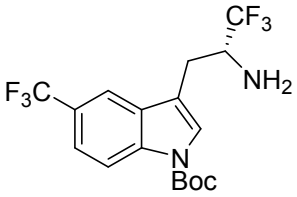


7f

*(R,R$_S$)-3-[2-(tert-butanesulfinylamido)-3,3,3-trifluoropropyl]-5-trifluoromethylindole (**7f**)* (0.19 g, 96%). ^{1}H NMR (acetone-d_6) δ 10.1 (s, 1 H), 8.16 (s, 1 H), 7.59 (d, *J* = 8.4 Hz, 1 H), 7.56 (s, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 4.19 (m, 1 H), 3.39 (dd, *J* = 14 and 3.4 Hz, 1 H), 3.26 (dd, *J* = 14 and 11 Hz, 1 H), 2.1 (bs, 1 H), 0.83 (s, 9 H); ^{13}C NMR (acetone-d_6) δ 137.9, 130.1, 127.3, 126.5, 125.8 (q, *J* = 282 Hz), 120.6, 117.7, 116.2, 111.9, 110.7, 59.5 (q, *J* = 28 Hz), 56.3, 24.3, 21.3 (3 C); ^{19}F NMR (acetone-d_6) δ −60.66 (s, 3 F), −75.93 (d, *J* = 7.3 Hz, 3 F); MS (70 eV) m/z (%) 342 (M^+–C_4H_{10}, 10), 198 (100), 178 (6), 151 (8). Analysis: calcd for $C_{16}H_{18}F_6N_2OS$ (400.38) C, 48.00; H, 4.53; N, 7.00. Found C, 48.17; H, 5.40; N, 5.78.

Selective deprotection of the adduct 6f by removal of tert-butanesulfinyl group.[4]

Iodine (25 mg, 0.05 mmol) was added to a solution of the adduct 6f (0.25 g, 0.50 mmol) in 5:1 THF/H2O (15 mL) and the mixture was stirred at 50 °C until the complete disappearance of the starting material was observed (24 h, *tlc*, SiO_2, eluent, 1:1 petroleum ether/ethyl acetate). After cooling, 1 M aqueous NaOH (1 mL) was added and the mixture was poured into water (20 mL), extracted with dichloromethane (3 × 25 mL) and the collected organic phases were dried with Na_2SO_4. After the solvent was evaporated at reduced pressure, chromatography of the residue on silica gel (eluent, 6:4 petroleum ether/ethyl acetate) allowed to collect pure indole **8f**.as a pale yiellow oil (0.19 g, 95%).

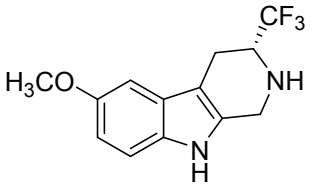


8f

*(R,R$_S$)-1-(tert-butoxycarbonyl)-3-(2-amino-3,3,3-trifluoropropyl)-5-(trifluoromethyl)-1H-indole (**8f**).* ^{1}H NMR δ 8.25 (d, *J* = 8.7 Hz, 1 H), 7.81 (s, 1 H), 7.66 (s, 1 H), 7.59 (d, *J* 8.7 Hz, 1 H), 3.56 (m, 1 H), 3.20 (dd, *J* = 15 and 2.3 Hz, 1 H), 2.80 (dd, *J* = 15 and 10 Hz, 1 H), 1.70 (s, 9 H), 1.43 (bs, 2 H); ^{13}C NMR δ 148.6, 136.6, 129.3, 125.8 (q, *J* = 280 Hz), 125.5, 124.5 (q, *J* = 32 Hz), 124.2 (q, *J* = 270 Hz), 120.9, 115.5, 115.2, 115.1, 84.0, 53.1 (q, *J* = 29 Hz), 27.6 (3C), 25.1; ^{19}F NMR δ –61.45 (s, 3 F), –79.06 (d, *J* = 7.1 Hz, 3 F). Analysis: calcd for $C_{17}H_{18}F_6N_2O_2$ (396.33) C, 51.52; H, 4.58; N, 7.07. Found C, 51.38; H, 4.65; N, 7.12.

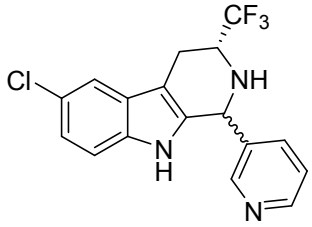
General procedure for the synthesis of tetrahydrocarbolines 9c and 10d

Conc. HCl (0.5 mL) was cautiously added to a solution of the indole derivative **6** (0.50 mmol) and the aldehyde (1.2 equiv.) and the mixture was made to react at 75 °C until the starting indole was disappeared (48 h, by tlc, SiO_2, 1:3 petroleum ether/ethyl acetate). After cooling at room temperature, aqueous 1 M KOH was added until the pH 11-12 was reached, the mixture was extracted with dichloromethane (3 × 20 mL) and the collected organic phases were dried with Na_2SO_4. Alter the solvent was evaporated at reduced pressure, chromatography of the residue on silica gel (eluent, petroleum ether/ethyl acetate 1:3) allowed to get the expected product which was characterized as follows:



9c

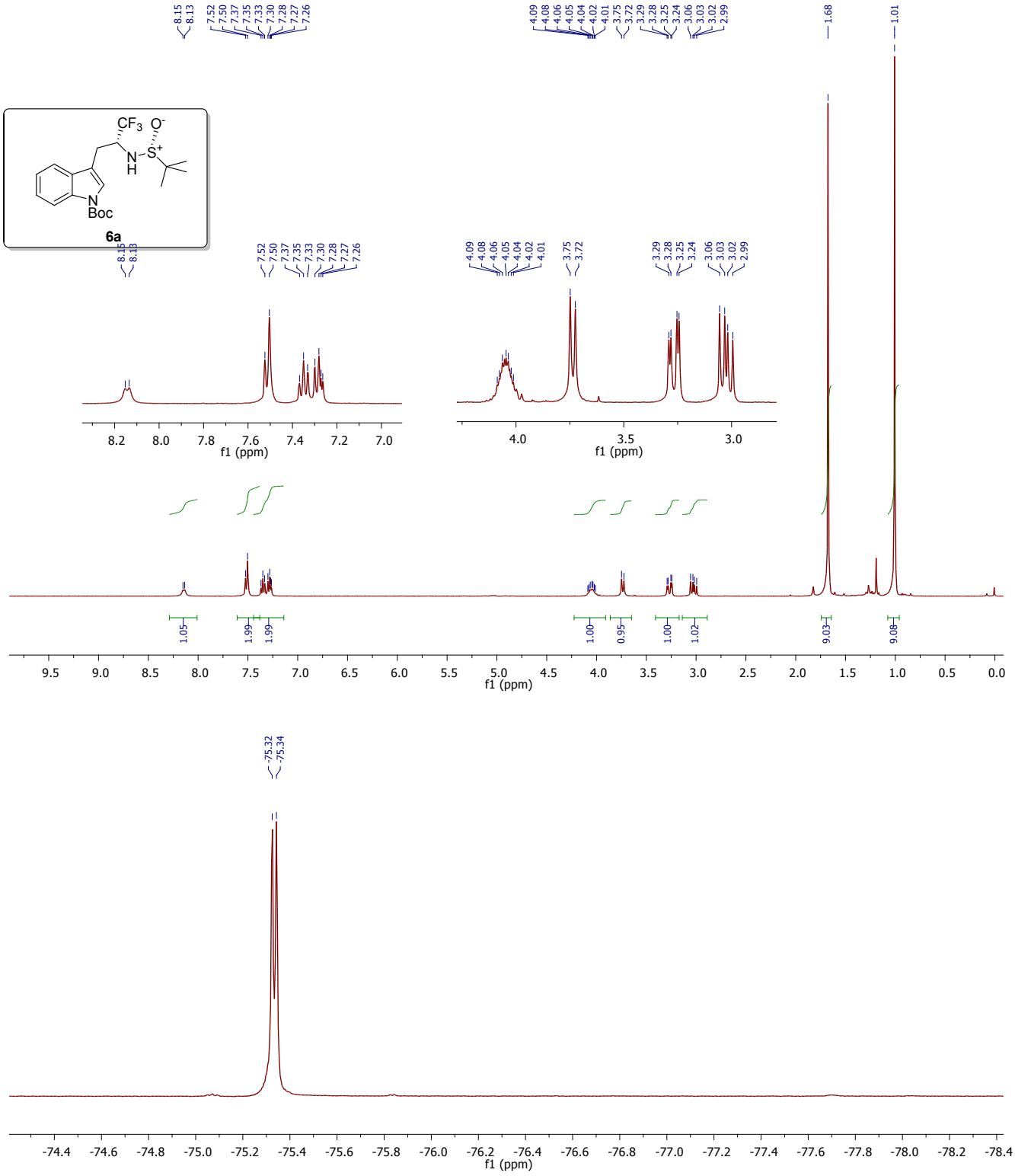
*(R)-6-methoxy-3-(trifluoromethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**9c**)*. (54%) From **7c** (0.23 g, 0.50 mmol) and formaldehyde (37% in H_2O, 50 μL, 18 mg, 0.6 mmol); ^{1}H NMR (DMSO-d_6) δ 7.18 (d, 8.6 Hz, 1 H), 6.93 (d, 1.7 Hz, 1 H), 6.67 (d, *J* = 8.6 and 1.7 Hz, 1 H), 3.94 (s, 2 H), 3.74 (s, 3 H), 3.6 (m, 1 H), 2.86 (dd, *J* = 3.2 and 14.0 Hz 1 H), 2.66 (dd, *J* =10.6 and 14.0 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 153.5, 134.8, 131.2, 127.6, 127.0 (q, *J* = 278 Hz), 111.9, 110.6, 104.9, 100.0, 55.7, 55.2 (q, *J* = 28 Hz), 42.3, 21.8; ^{19}F NMR (DMSO-d_6) δ −75.16 (t, *J* = 3.5 Hz, 3 F). Analysis: calcd for $C_{13}H_{13}F_3N_2O$ (270,26) C, 57.78; H, 4.85; N, 10.37. Found C, 57.59; H, 5.00; N, 10.22.



10d

(1*R*,3*R*)- and (1*S*,3*R*)-*(R)-6-chloro-3-(trifluoromethyl)-2,3,4,9-tetrahydro-1-(pyrid-3-yl)-1H-pyrido[3,4-b]indole (**10d**$_{(R)}$)* (63%). From **6d** (0.23 g, 0.5 mmol) and 3-pyridinecarbaldehyde (65 mg, 0.61 mmol). Diastereomeric mixture of (1*R*,3*R*)-**10d** and (1*S*,3*R*)-**10d**, dr = 2.2 (by integration of the signals at δ −74.98 and −74.63, respectively, in the ^{19}F NMR spectrum of the crude reaction mixture). (1*R*,3*R*)-**10d**: ^{1}H NMR (DMSO-d_6) δ 10.74 (s, 1 H), 8.63 (s, 1 H), 8.55 (d, *J* = 4,4 Hz, 1 H), 8.51 (s, 1 H), 7.74 (d, *J* = 7.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz), 7.42 (dd, *J* = 8.1 and 4.4 Hz, 1 H), 7.23(d, *J* = 8.5 Hz, 1 H), 7.04 (d, *J* = 8.6 Hz, 1 H), 5.31 (s, 1 H), 3.87 (m, 1 H), 3.5 (bs, 1 H), 2.9 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 150.4, 149.5, 137.0, 136.9, 136.8, 135.2, 128.0, 126.6 (q, *J* = 276 Hz), 124.1, 123.7, 121.4, 117.6, 113.1,

106.7, 55.5 (q, *J* = 23 Hz), 55.3, 21.7; ^{19}F NMR (DMSO-d_6) δ −74.98 (d, *J* = 7.8 Hz). (1*S*,3*R*)-**10d**: ^{1}H NMR δ 11.14 (s, 1 H), 8.6 (s, 1 H), 8.55 (d, *J* = 4,4 Hz, 1 H), 8.50 (s, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.57 (d, *J* = 8 Hz, 1 H), 7.37 (dd, *J* = 8.1 and 4.4 Hz, 1 H), 7.33(d, *J* = 8.5 Hz, 1 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 5.33 (s, 1 H), 3.72 (m, 1 H), 3.5 (bs, 1 H),), 3.03 (dd, *J* = 16 and 5.3 Hz, 1 H), 2.76 (dd, *J* = 16 and 10 Hz, 1 H); ^{13}C NMR δ 149.9, 148.9, 137.6, 137.0, 136.1, 135.6, 134.9, 127.0 (q, *J* = 276 Hz), 123.9, 123.7, 121.6, 117.7, 113.1, 107.0, 52.0, 50.8 (q, *J* = 28 Hz), 21.4; ^{19}F NMR δ −74.63 (d, *J* = 7.8 Hz). Analysis of the diastereomeric mixture: calcd for $C_{17}H_{13}ClF_3N_3$ (351.76) C, 58.05; H, 3.73; N, 11.95. Found C, 58.13; H, 3.82; N, 12.10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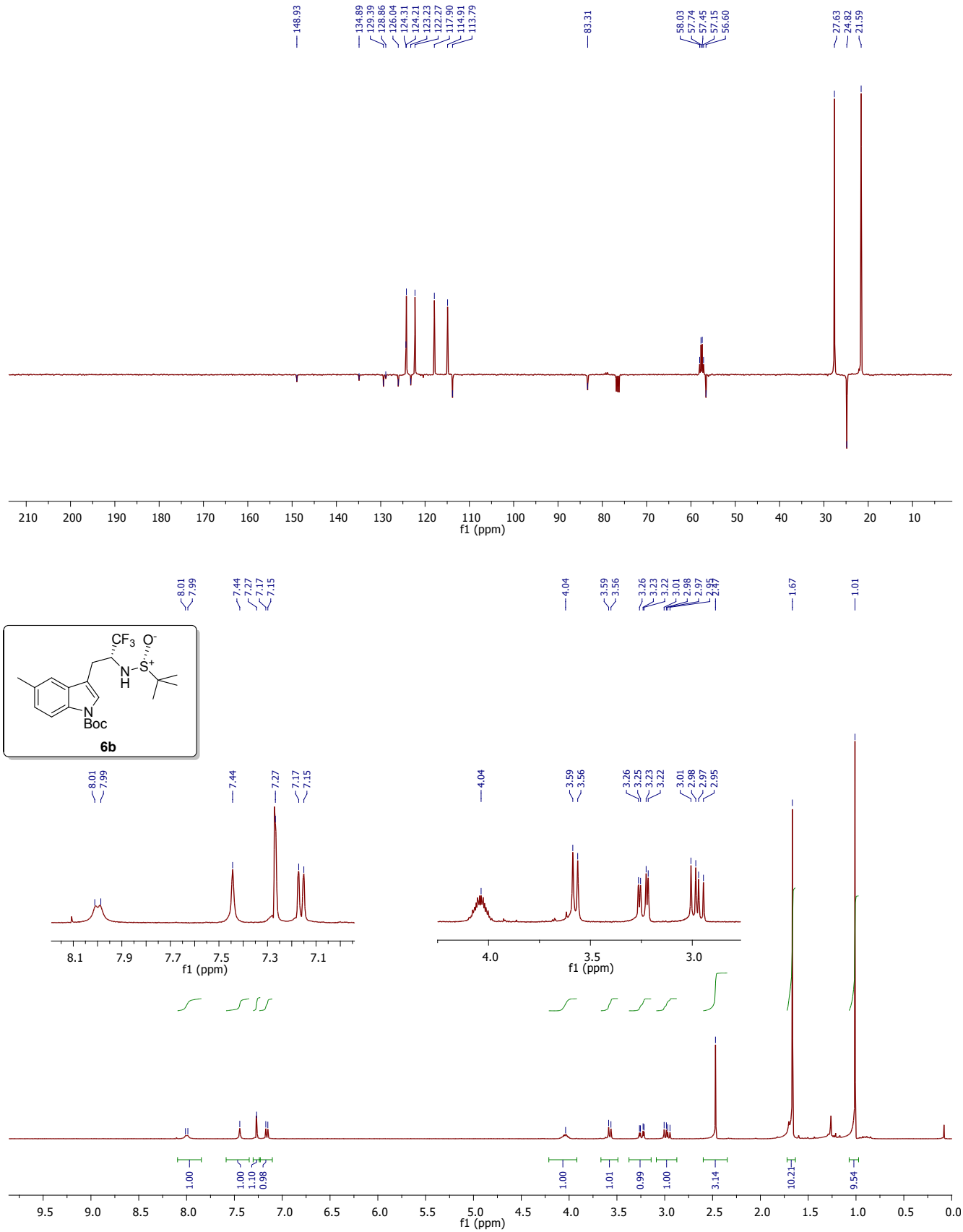
f1 (ppm)
f1 (ppm)
f1 (ppm)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58.03
57.74
57.45
57.15
56.60
27.63
24.82
21.59
f1 (ppm)
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7.99
7.44
7.27
7.17
7.15
4.04
3.59
3.56
3.26
3.25
3.23
3.22
3.01
2.98
2.97
2.95
1.67
1.01
CF3
O-
S+
N
H
N
Boc
6b
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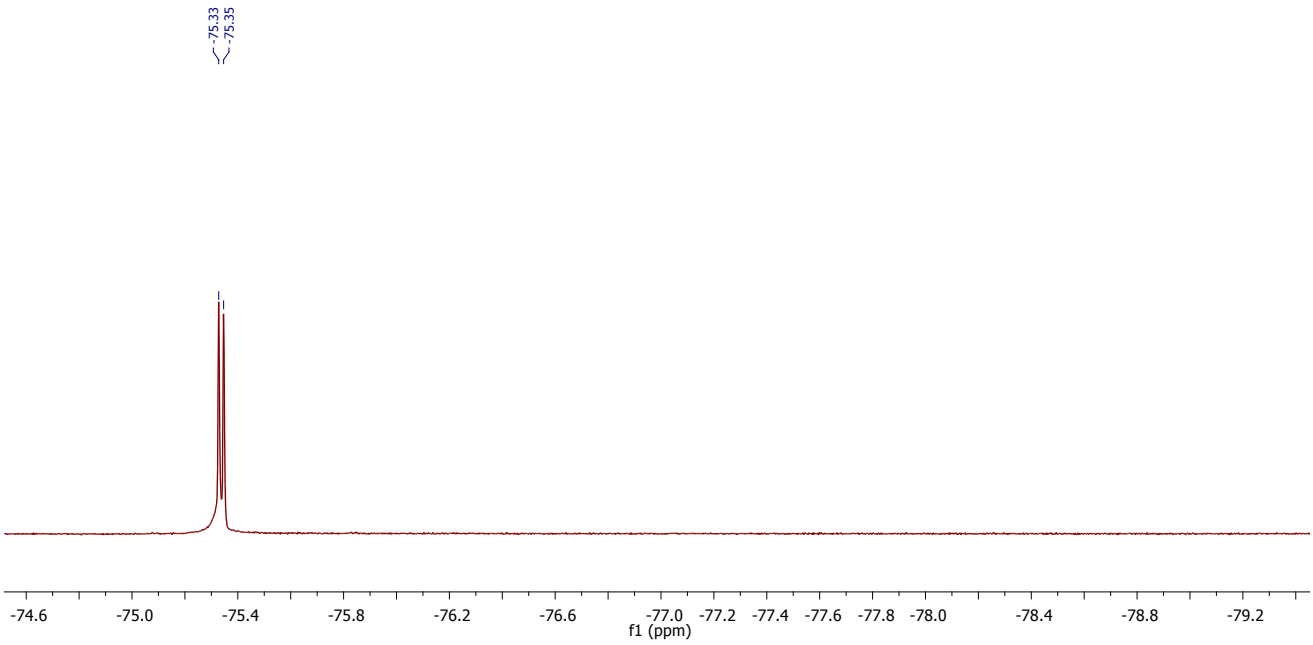
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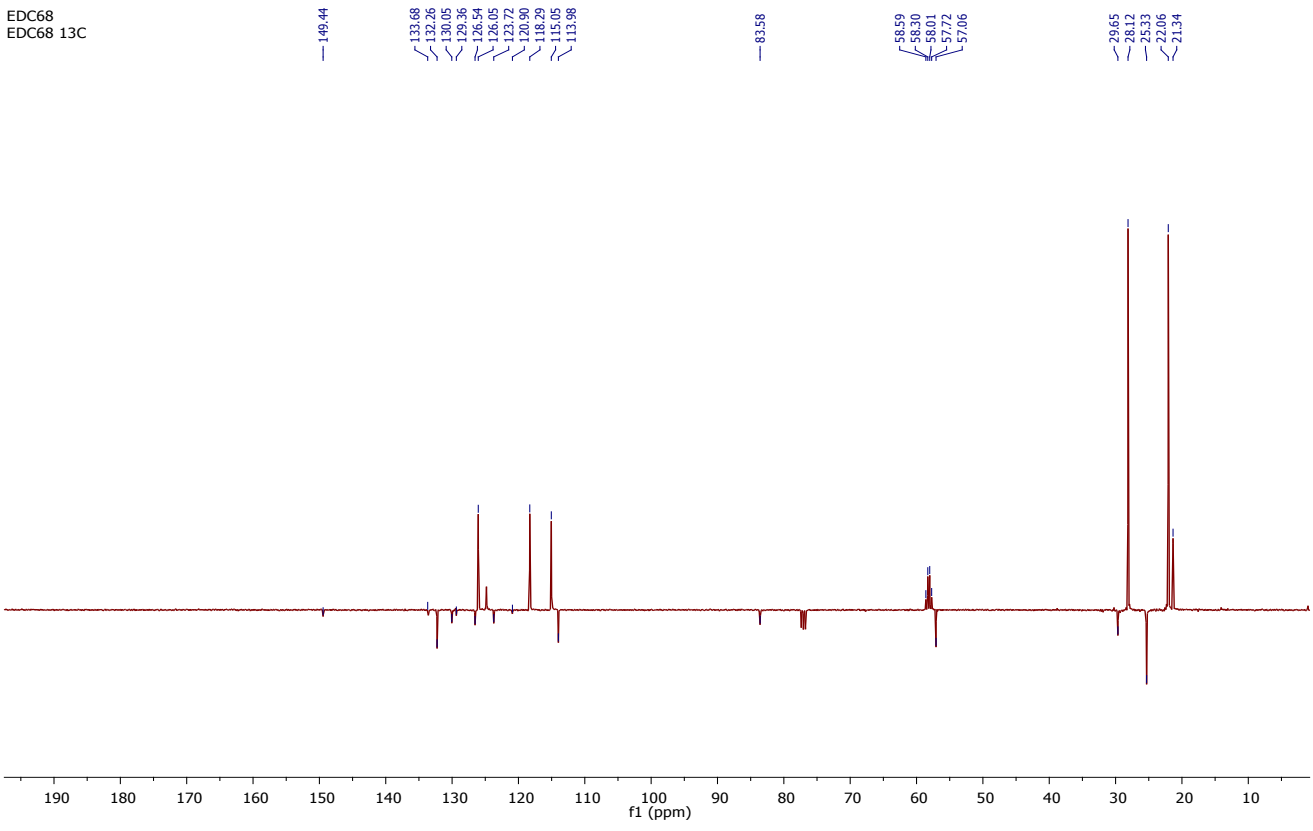
f1 (ppm)


EDC68
EDC68 13C
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133.68
132.26
130.05
129.36
126.54
126.05
123.72
120.90
118.29
115.05
113.98
83.58
58.59
58.30
58.01
57.72
57.06
29.65
28.12
25.33
22.06
21.34
190
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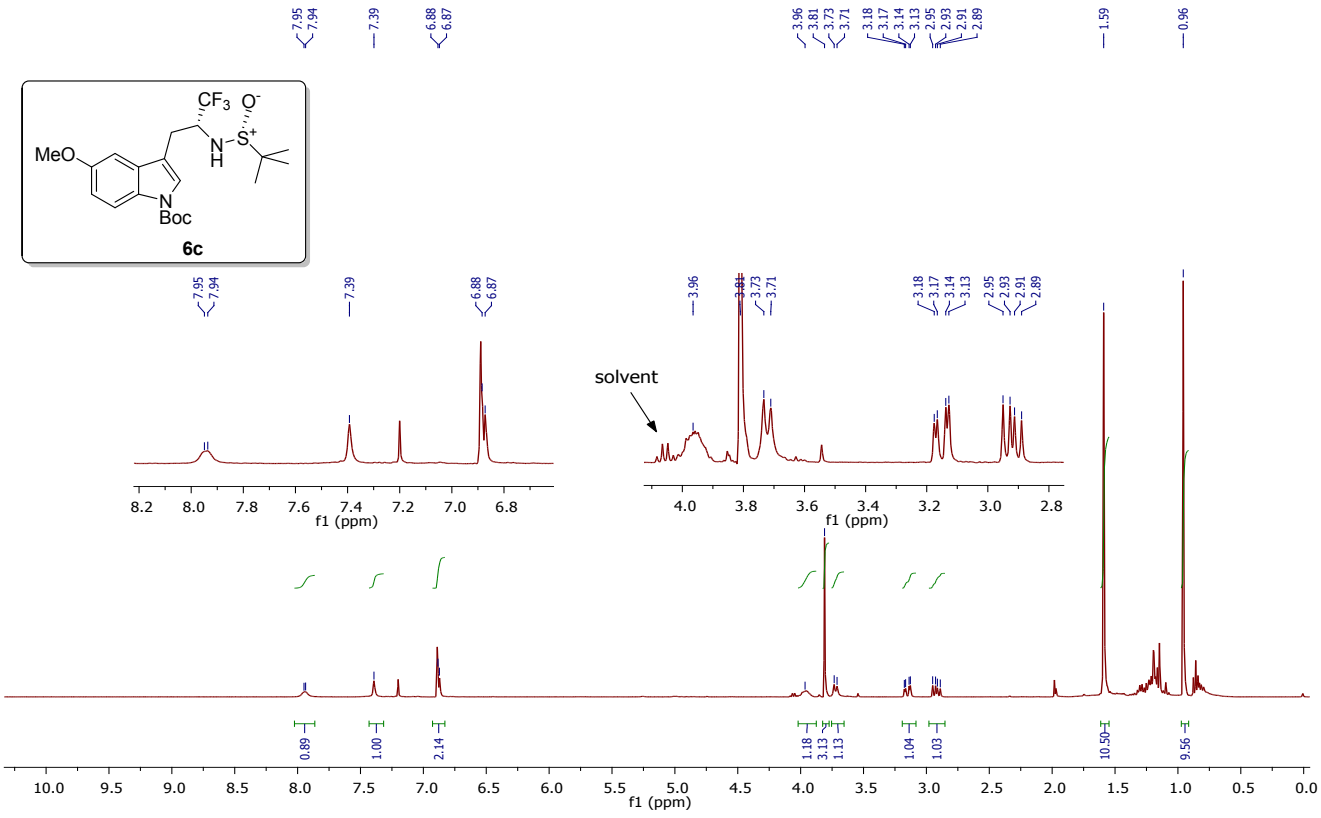
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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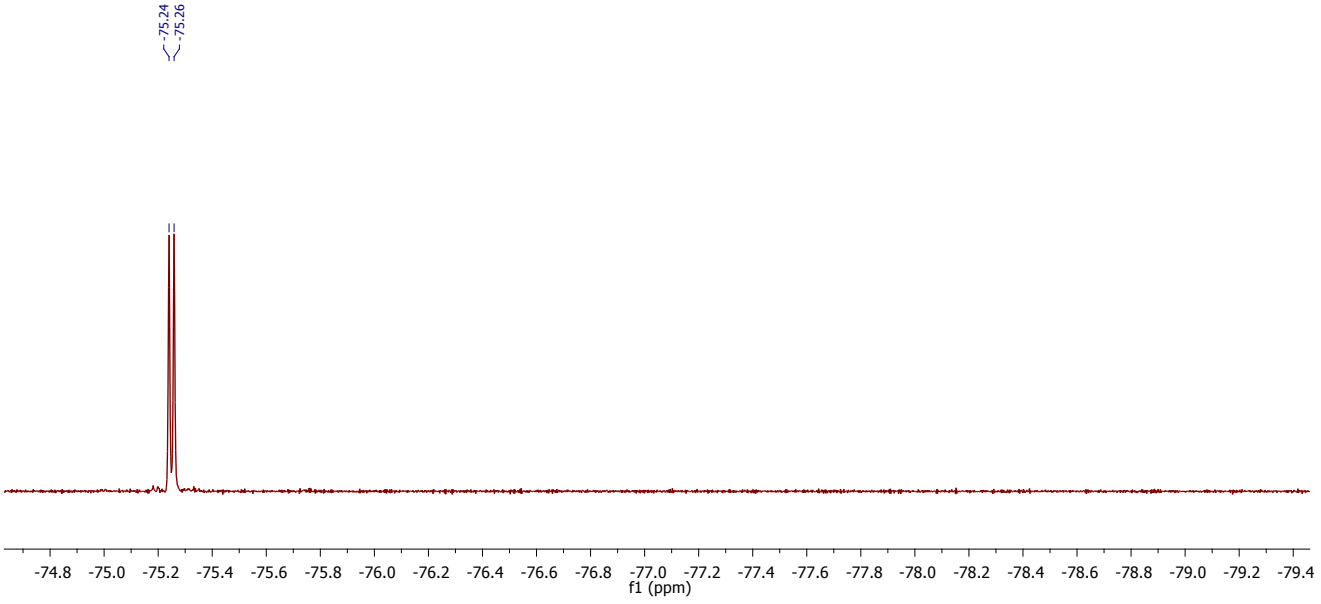
O-
S+
N
H
N
Boc
6c
solvent
f1 (ppm)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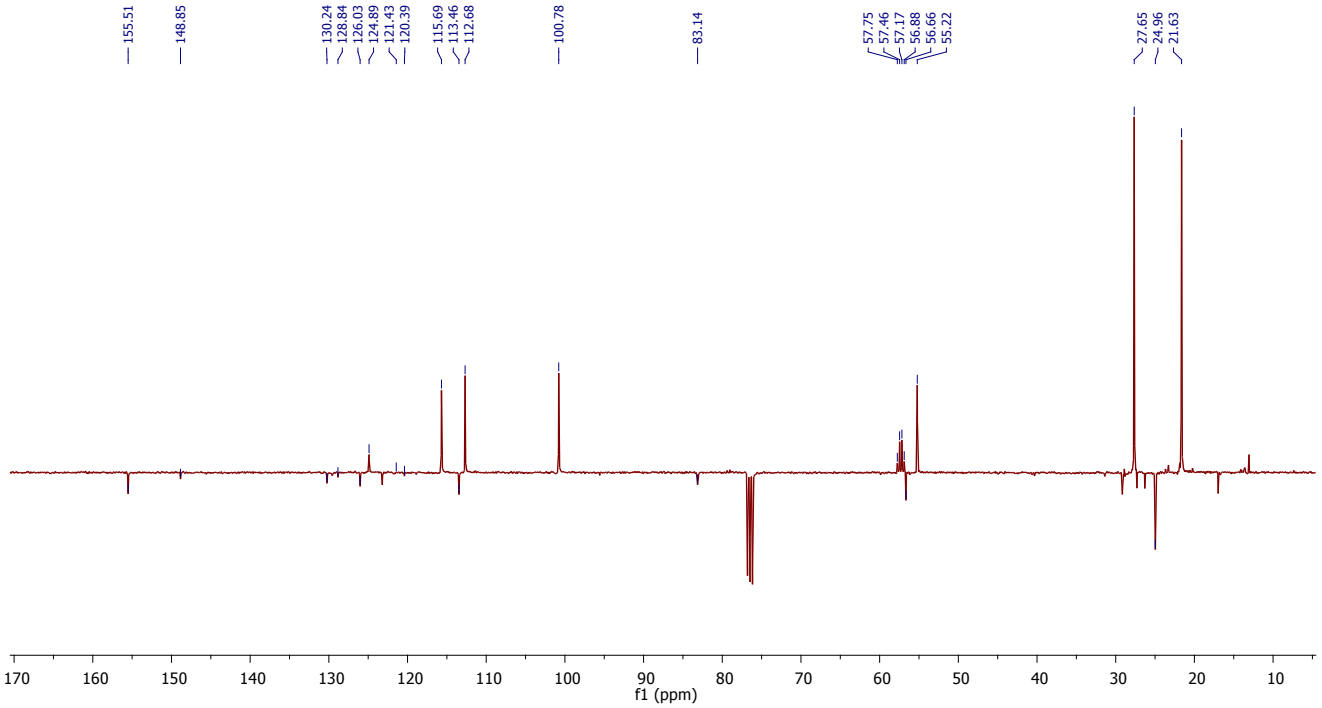
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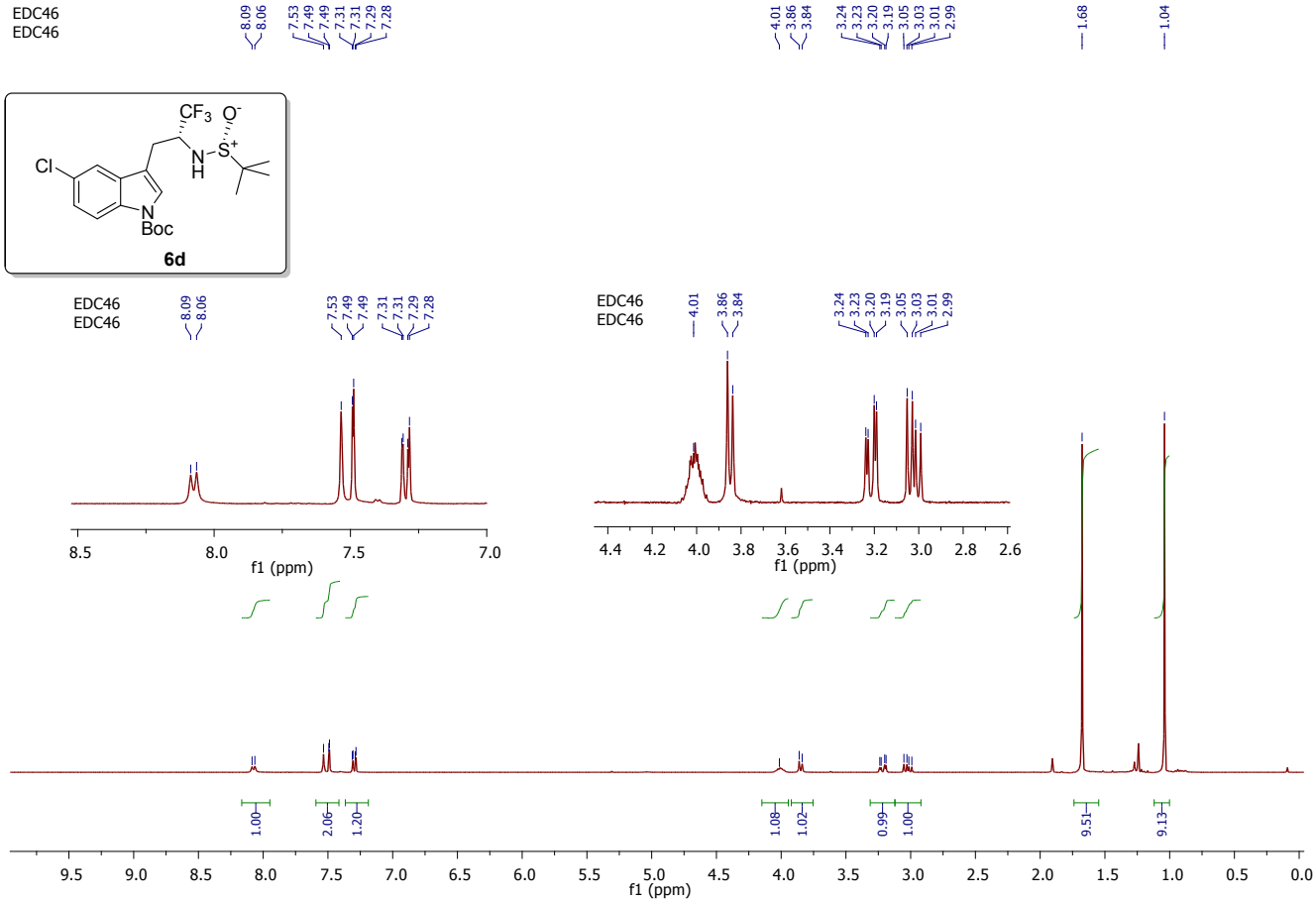
f1 (ppm)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8.06
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7.49
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7.31
7.31
7.29
7.28
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3.84
3.24
3.23
3.20
3.19
3.05
3.03
3.01
2.99
1.68
1.04
CF3
O-
S+
N
H
Cl
N
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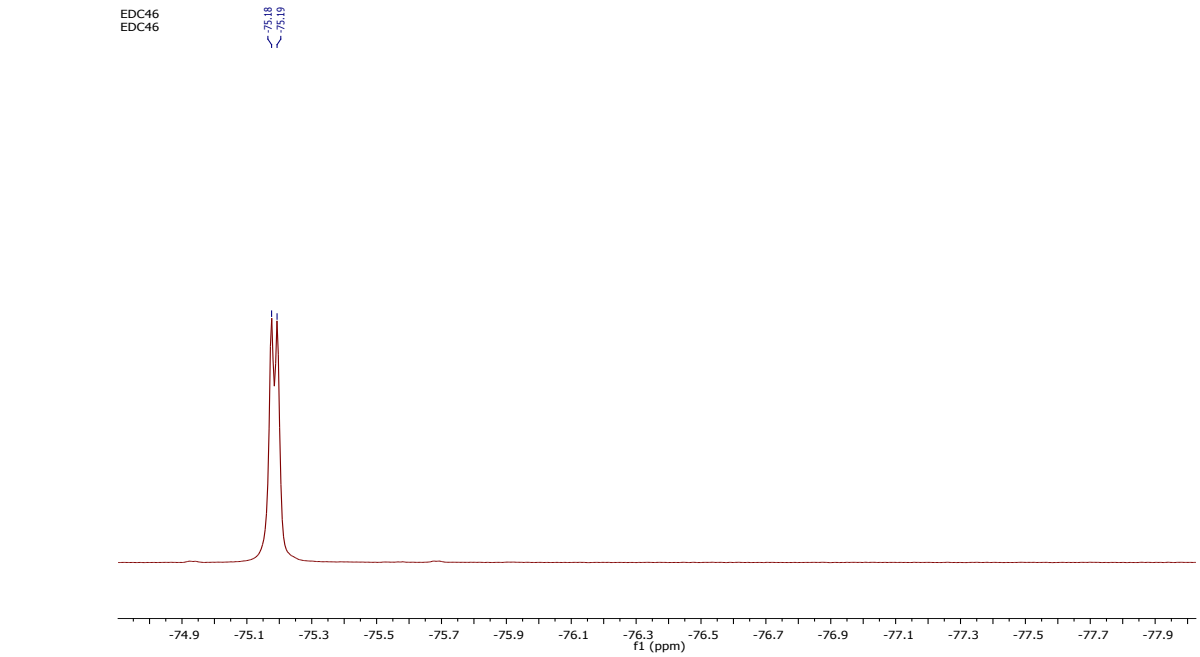
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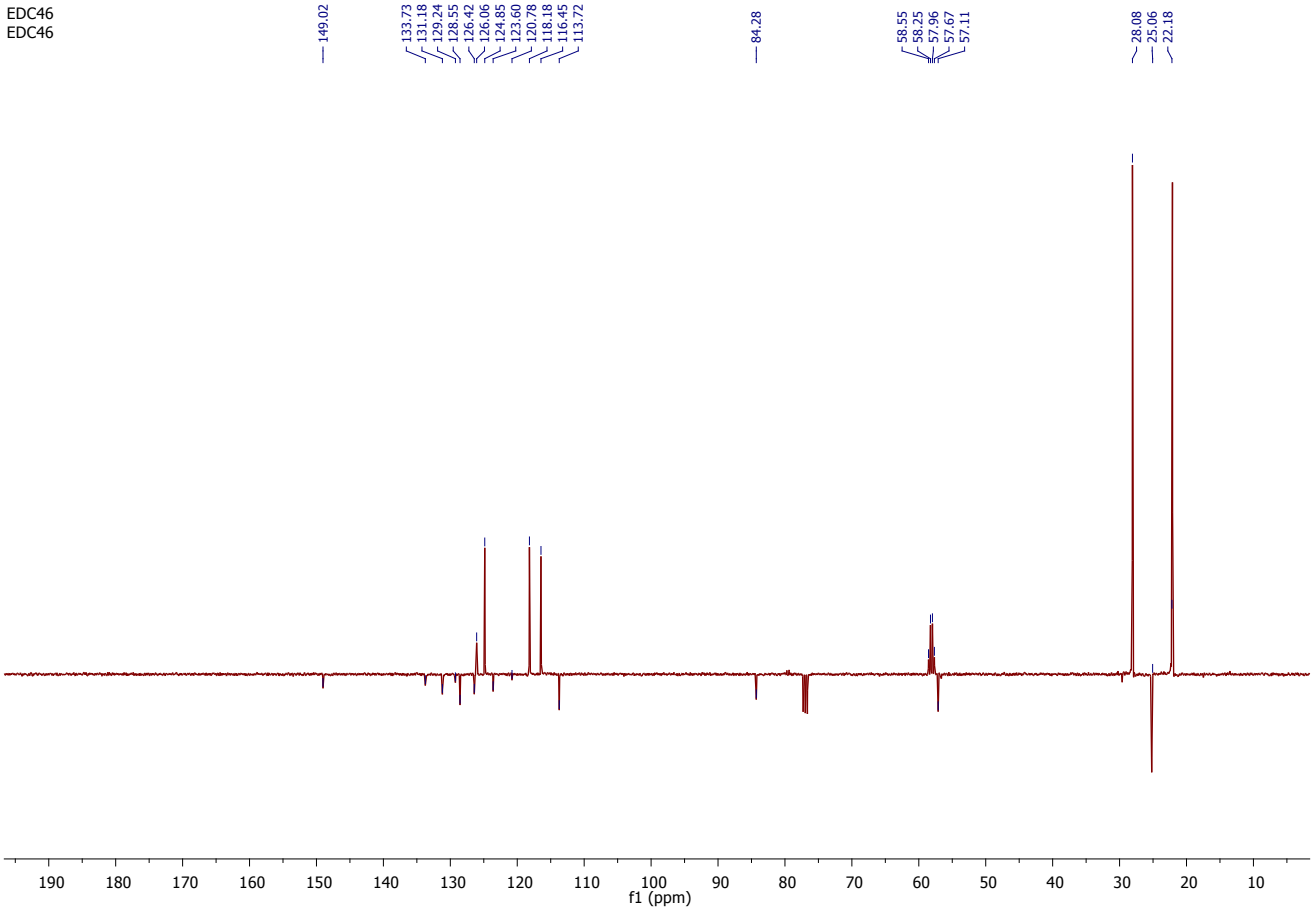
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28.08
25.06
22.18
190
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60
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30
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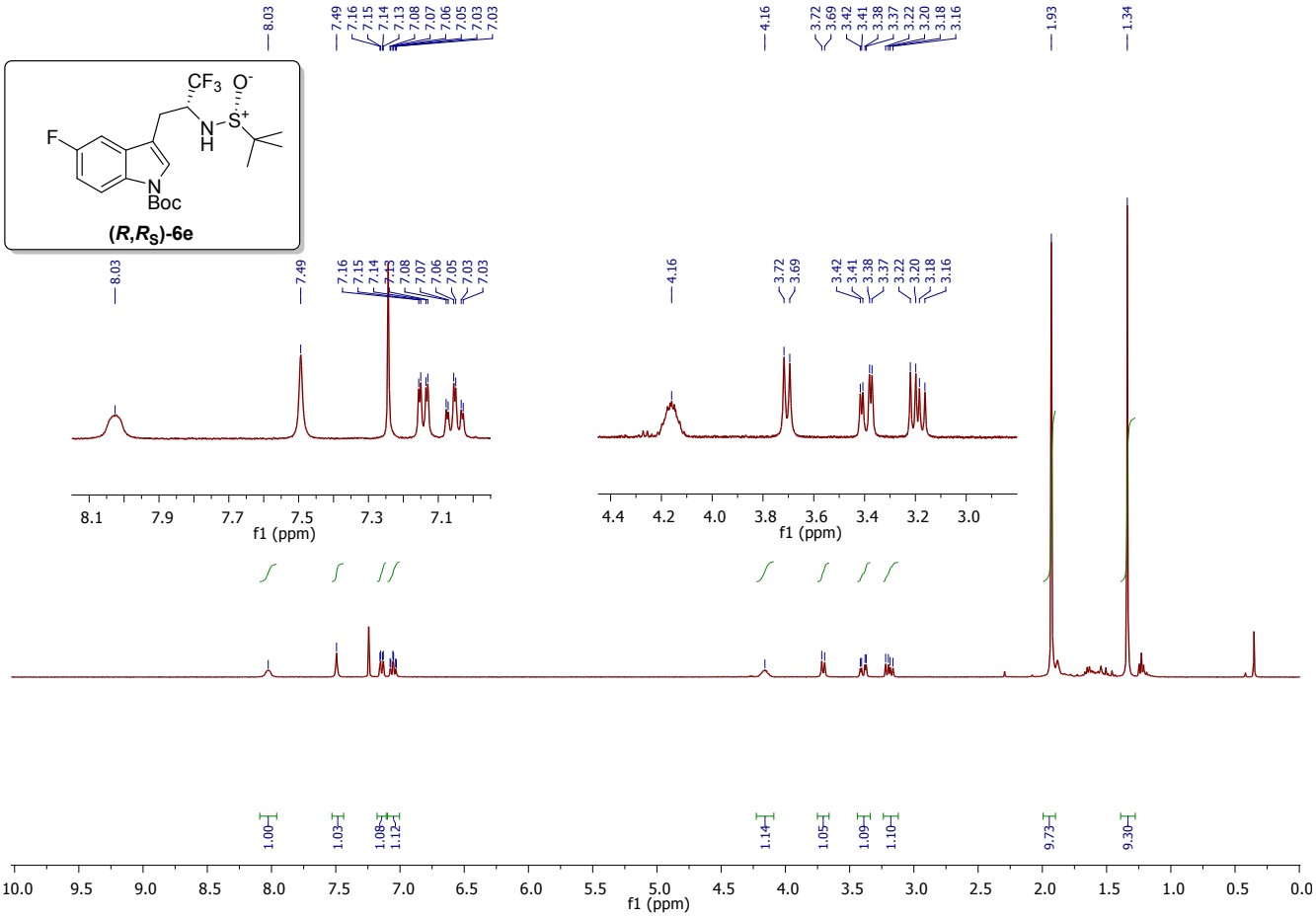
10
f1 (ppm)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3.22
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F
CF3
O-
N
S+
H
N
Boc
(R,RS)-6e
f1 (ppm)
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1.09
1.10
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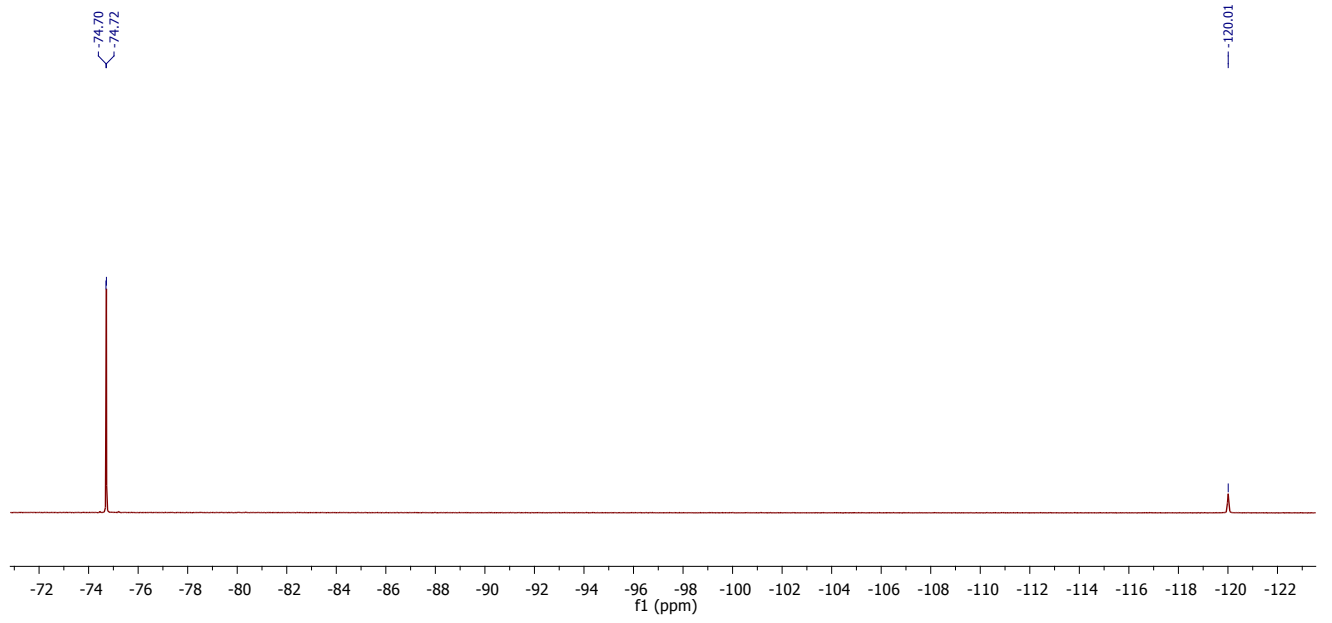
9.30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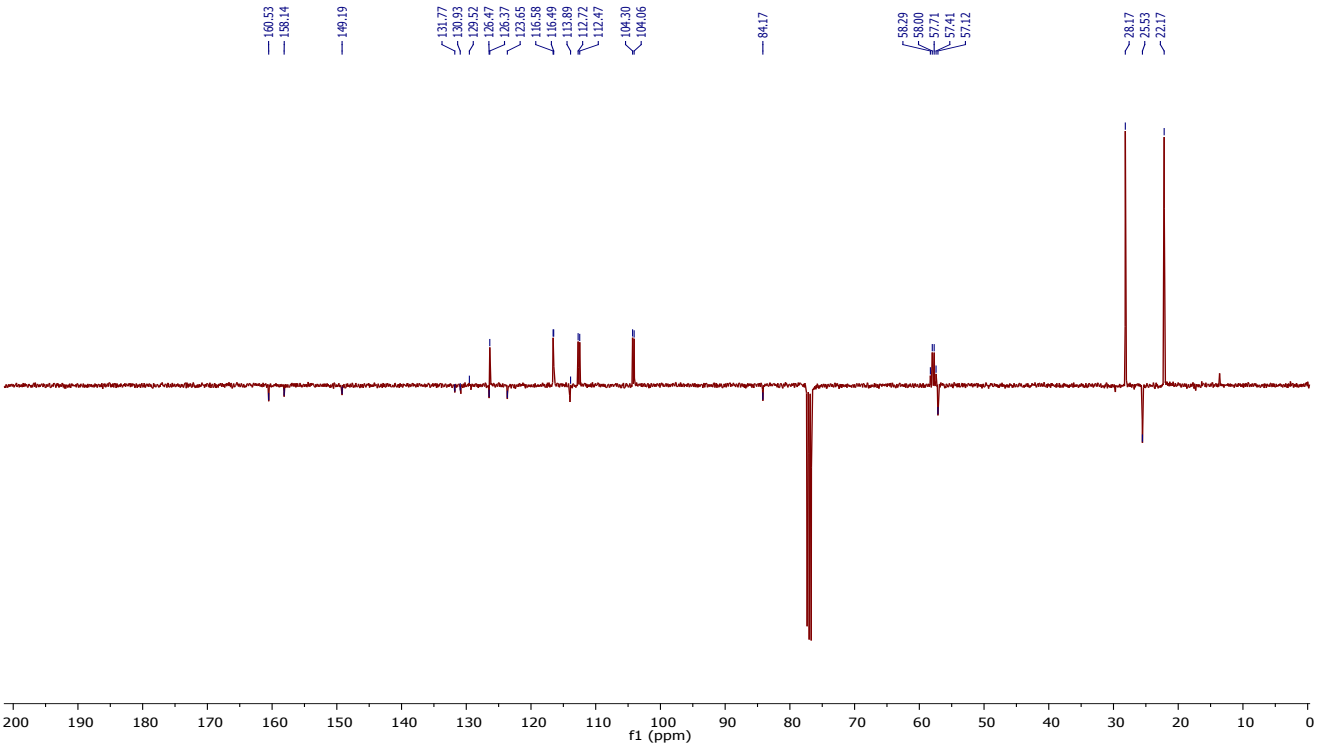
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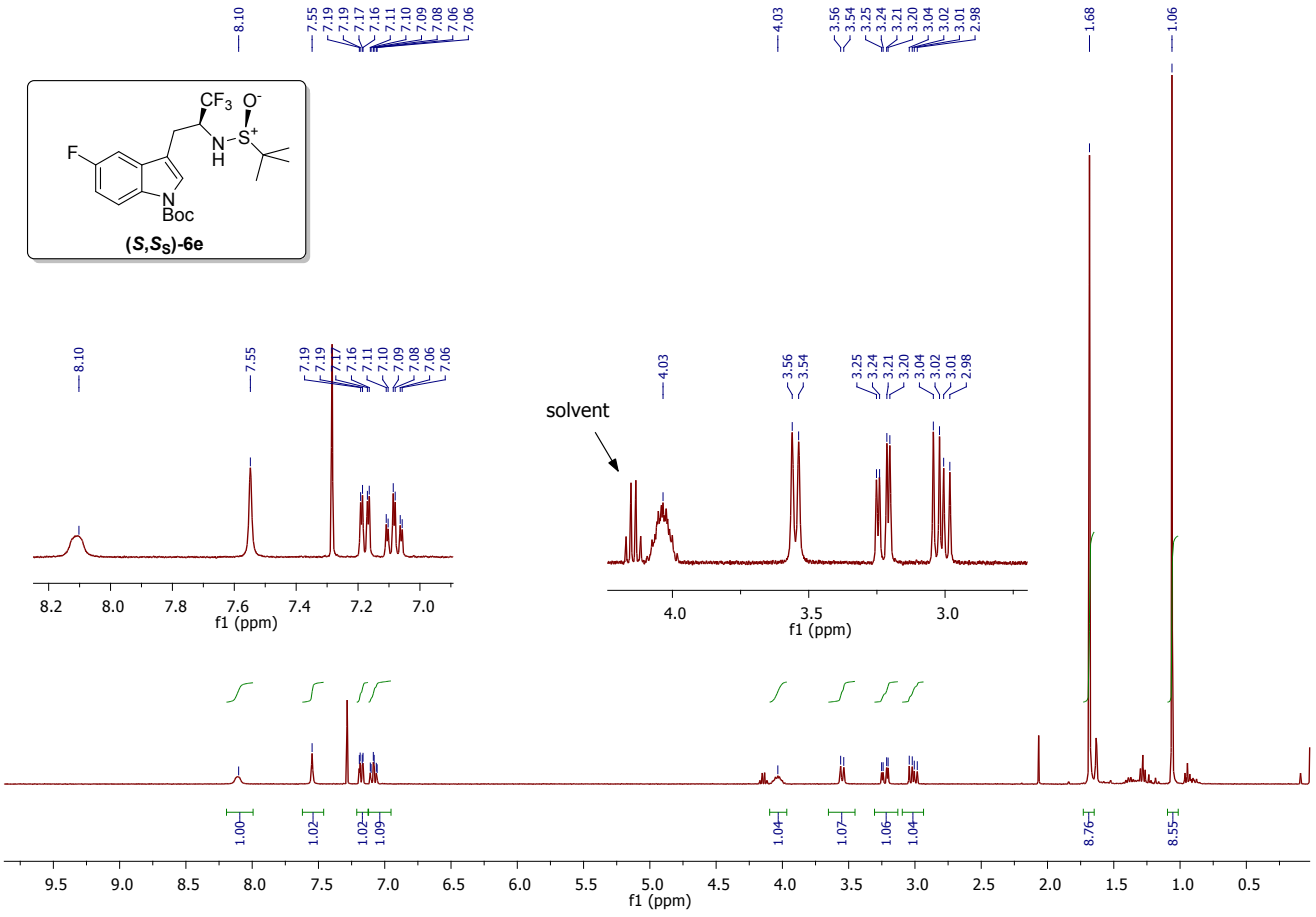
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3.24
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3.20
3.04
3.02
3.01
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CF3
O-
N
H
S+
N
Boc
(S,SS)-6e
solvent
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1.04
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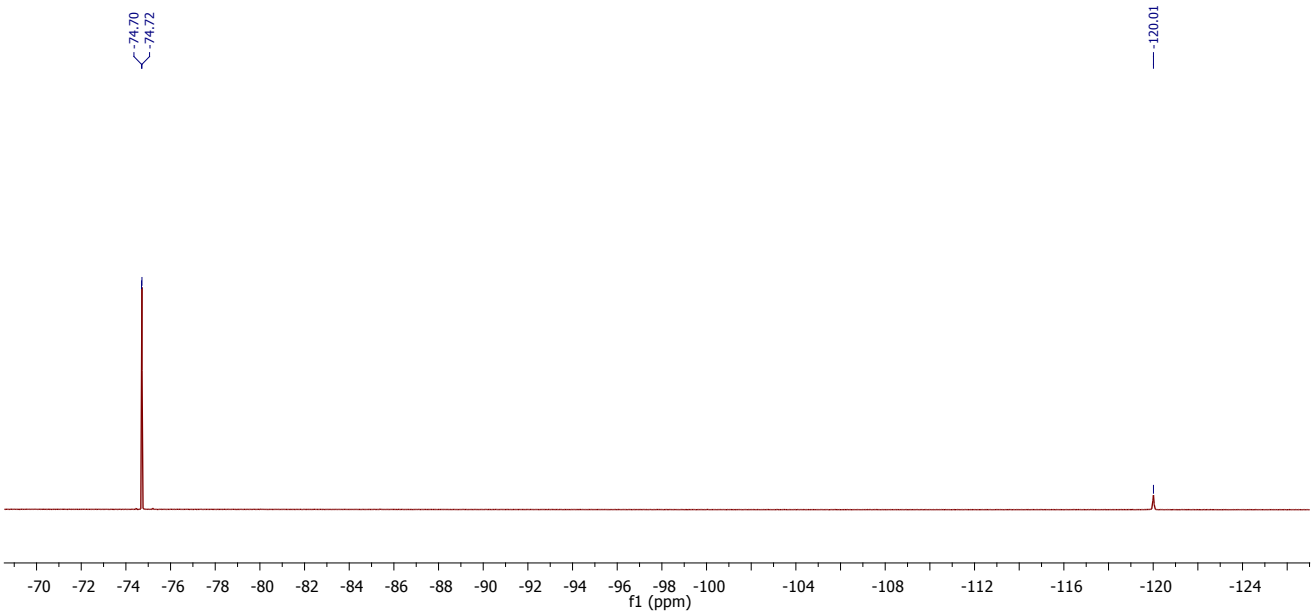
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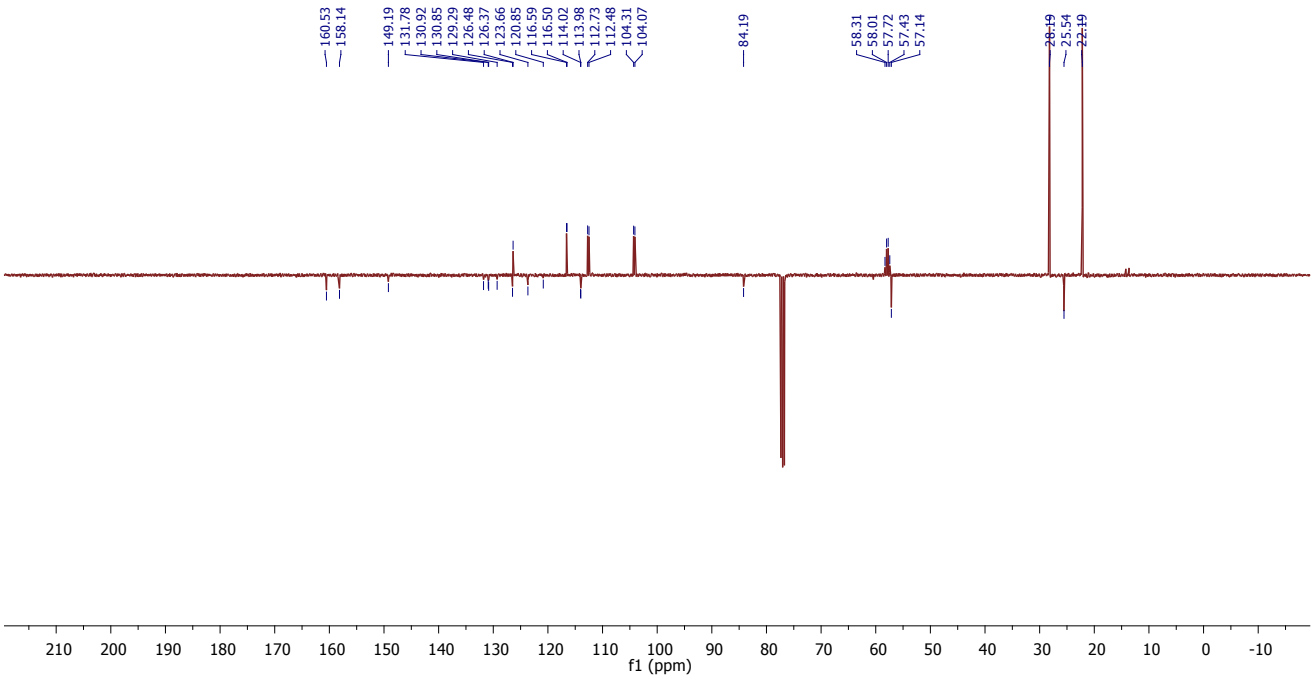
f1 (ppm)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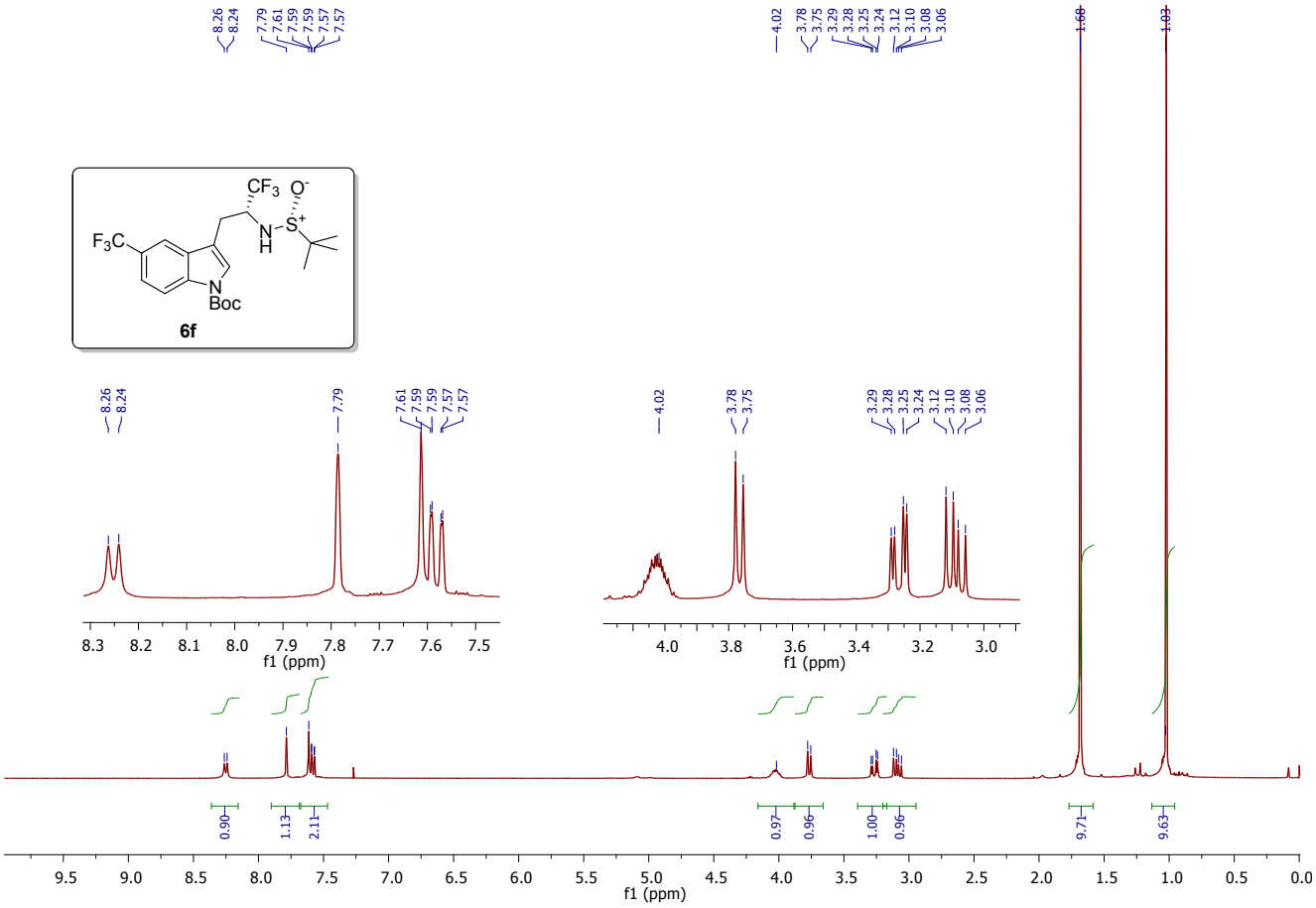
f1 (ppm)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3.06
1.60
1.03
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CF3
O-
N
H
S+
N
Boc
6f
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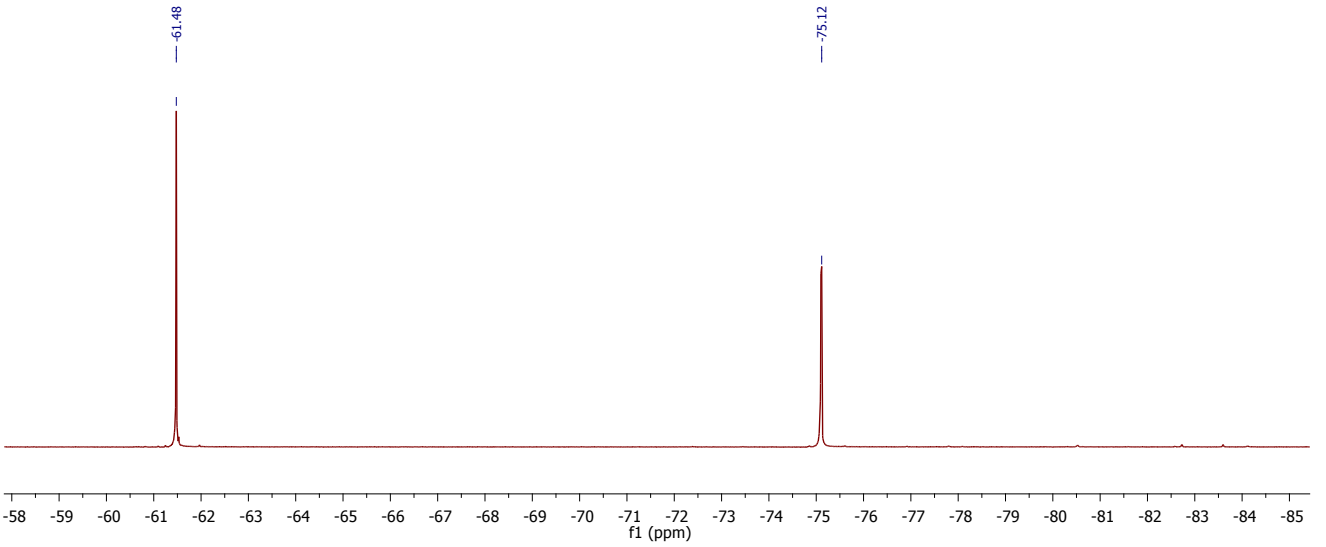
2.11
0.97
0.96
1.00
0.96
9.71
9.63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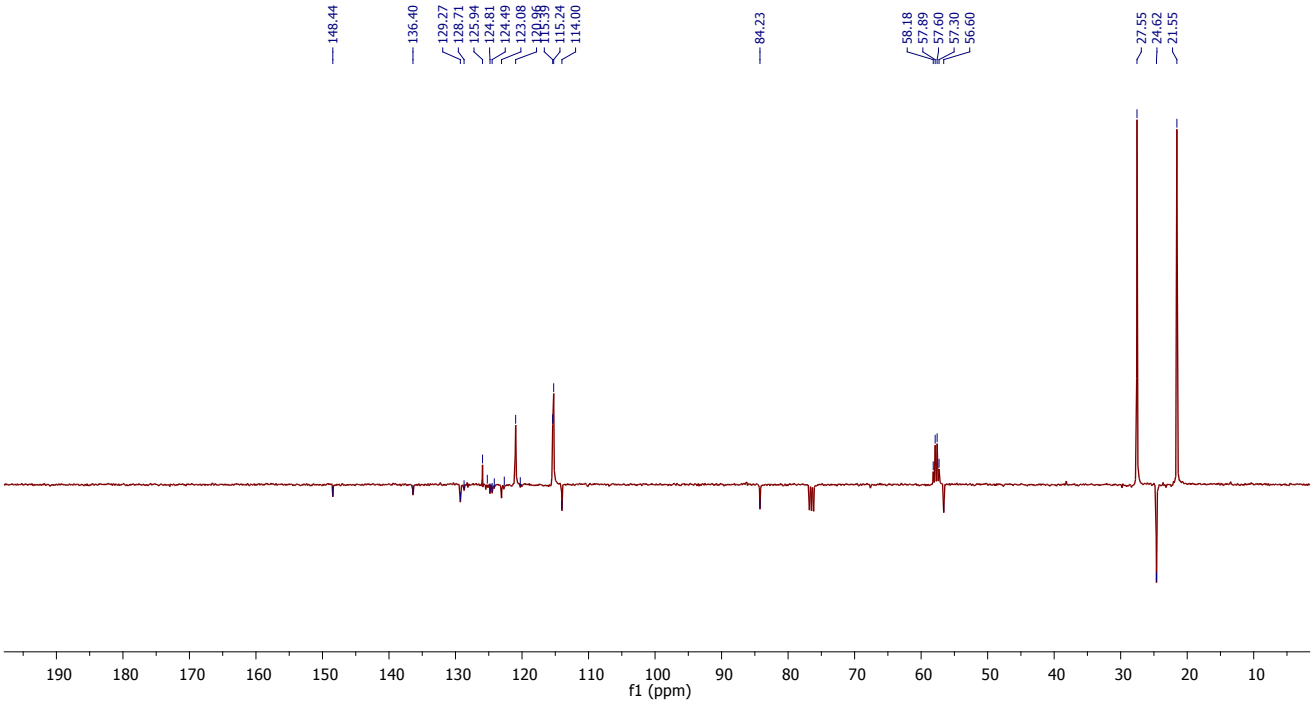
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123.08
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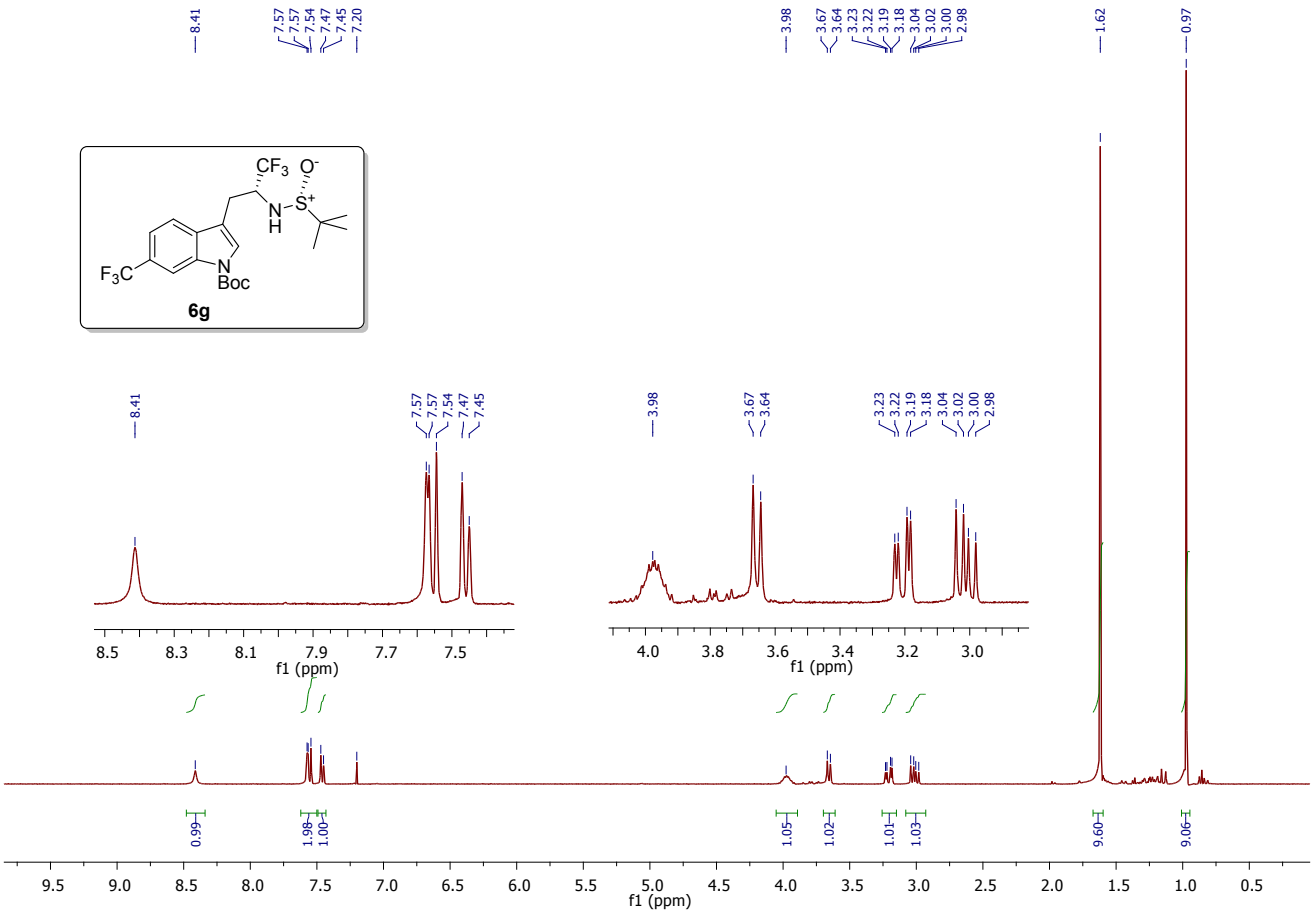
57.89
57.60
57.30
56.60
27.55
24.62
21.55
f1 (ppm)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7.45
7.20
3.98
3.67
3.64
3.23
3.22
3.19
3.18
3.04
3.02
3.00
2.98
1.62
0.97
CF3
O-
N
H
S+
F3C
N
Boc
6g
f1 (ppm)
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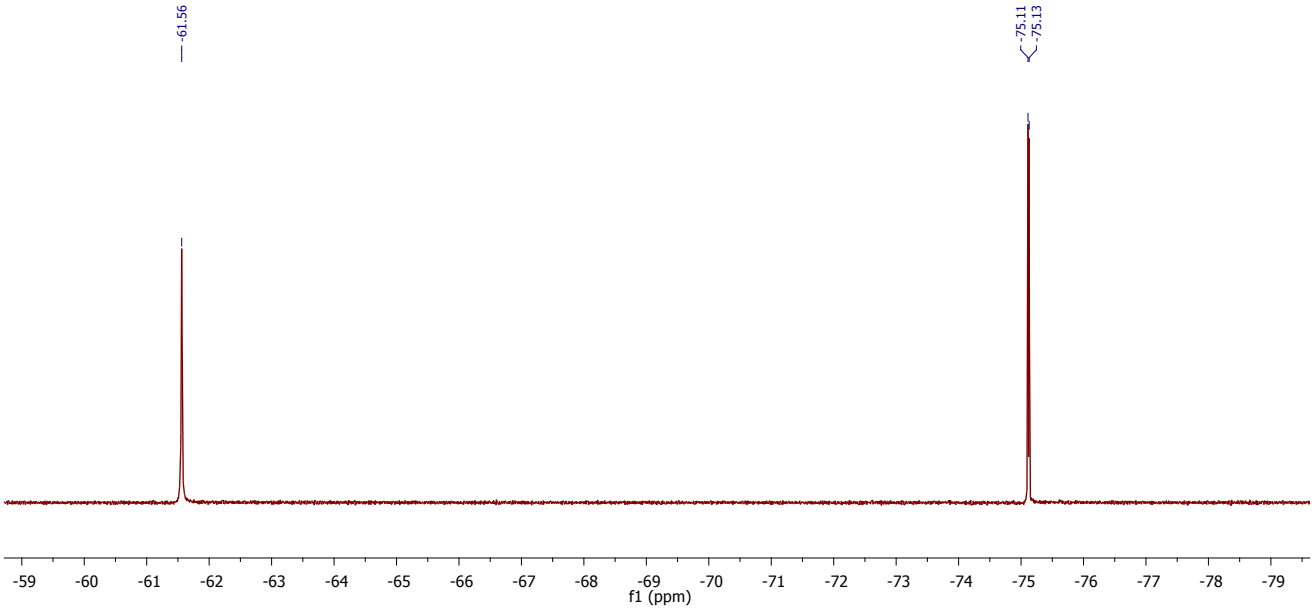
1.98
1.00
1.05
1.02
1.01
1.03
9.60
9.06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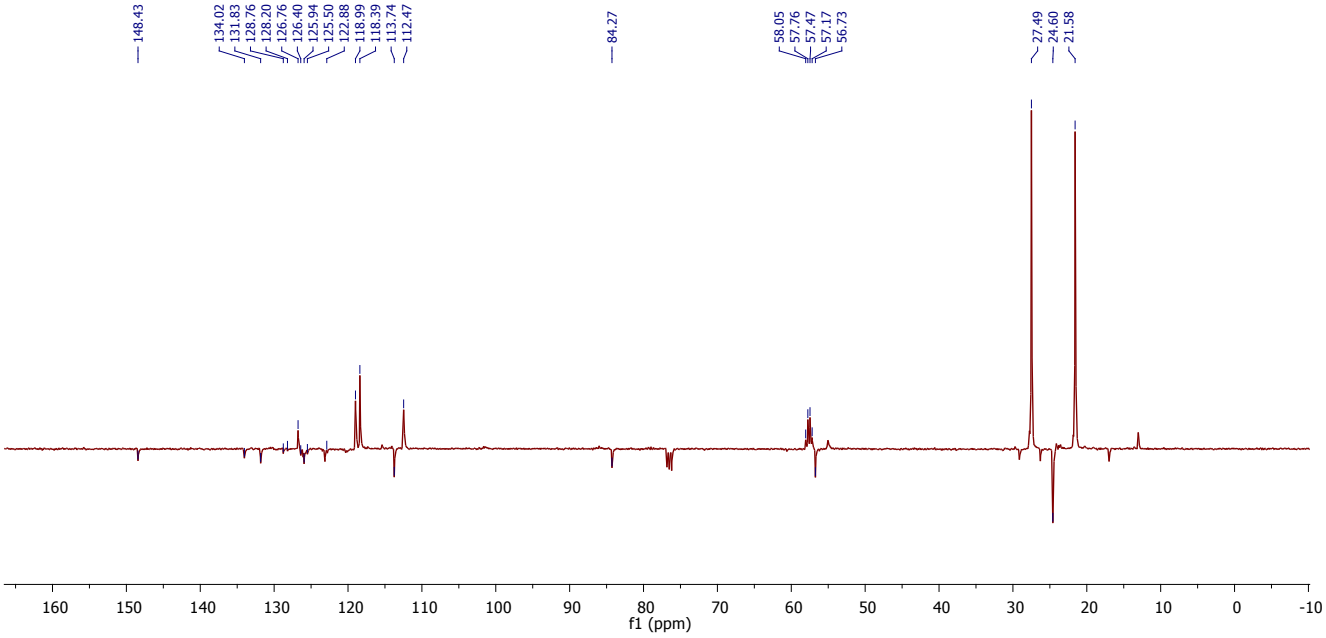
-75.11
-75.13
-59 -60 -61 -62 -63 -64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79
f1 (ppm)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128.20
126.76
126.40
125.94
125.50
122.88
118.99
118.39
113.74
112.47
84.27
58.05
57.76
57.47
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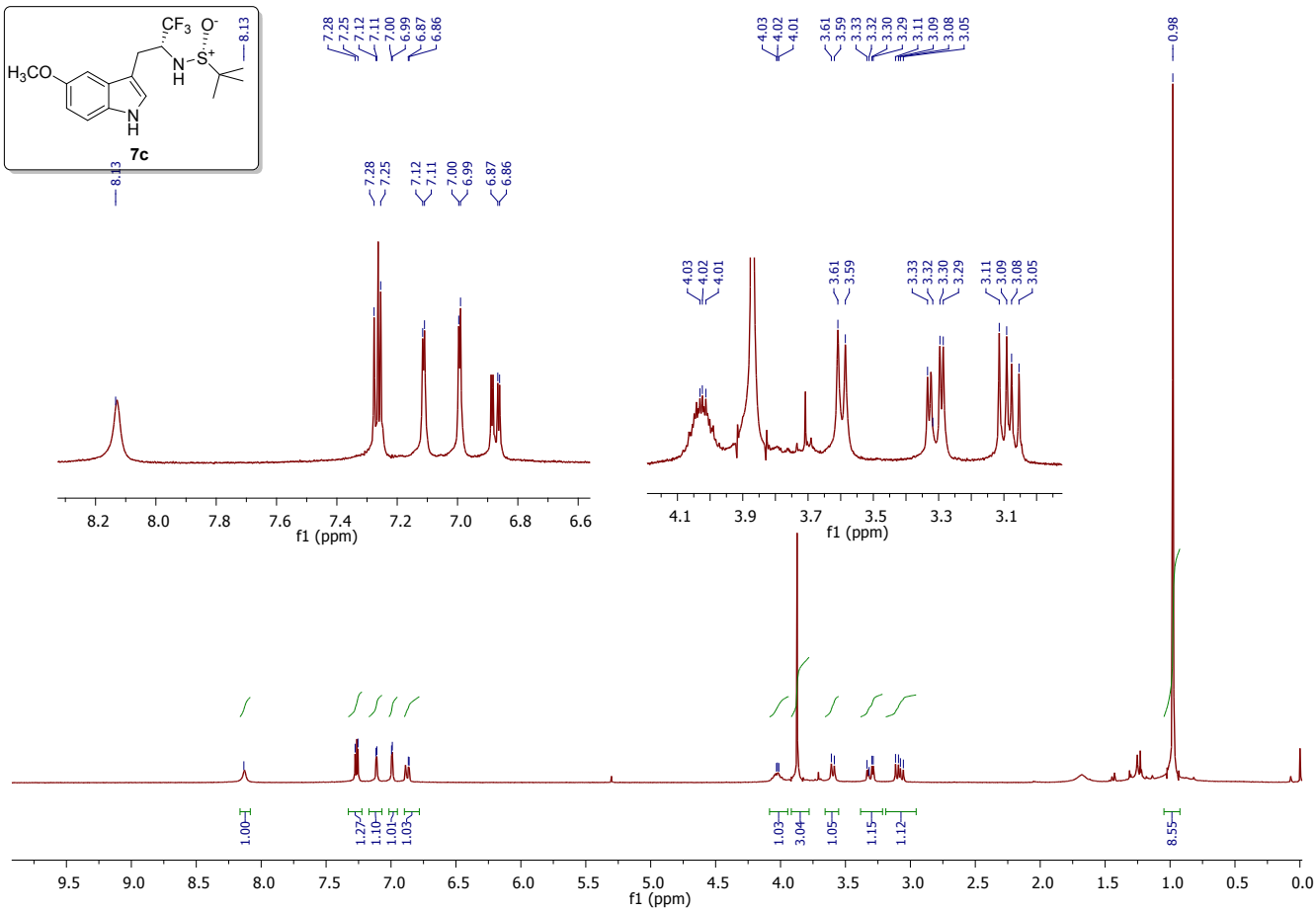
56.73
27.49
24.60
21.58
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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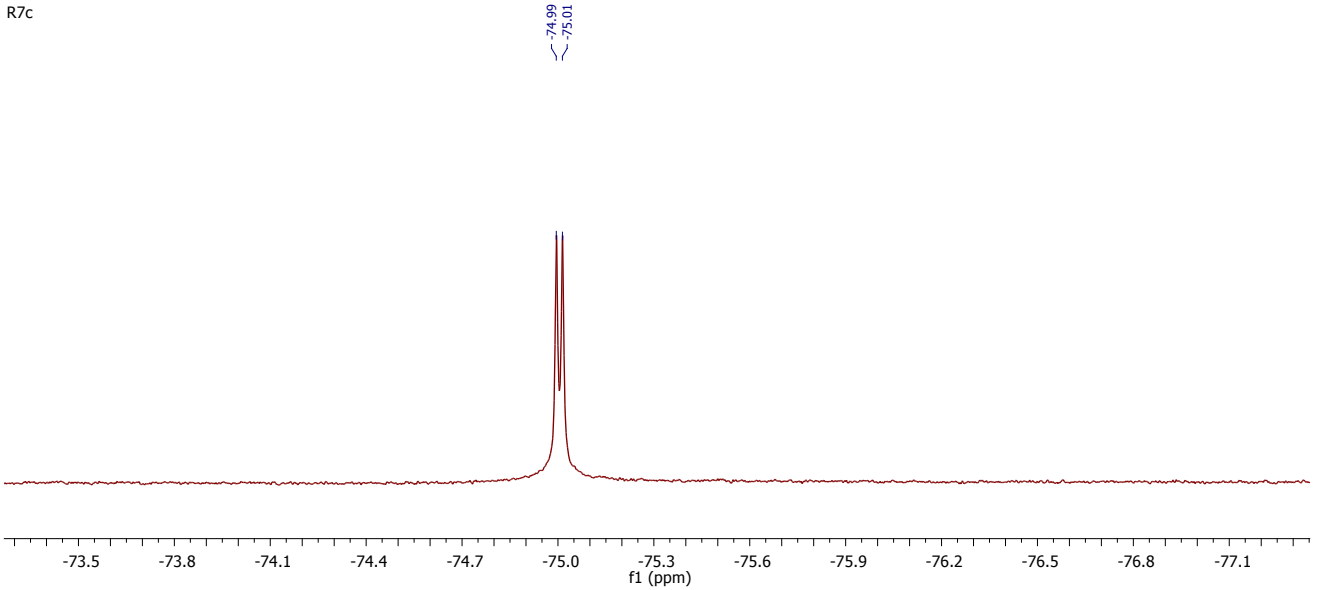
7.12
7.11
7.00
6.99
6.87
6.86
4.03
4.02
4.01
3.61
3.59
3.33
3.32
3.30
3.29
3.11
3.09
3.08
3.05
0.98
f1 (ppm)
1.00
1.27
1.10
1.01
1.03
1.03
3.04
1.05
1.15
1.12
8.55


R7c
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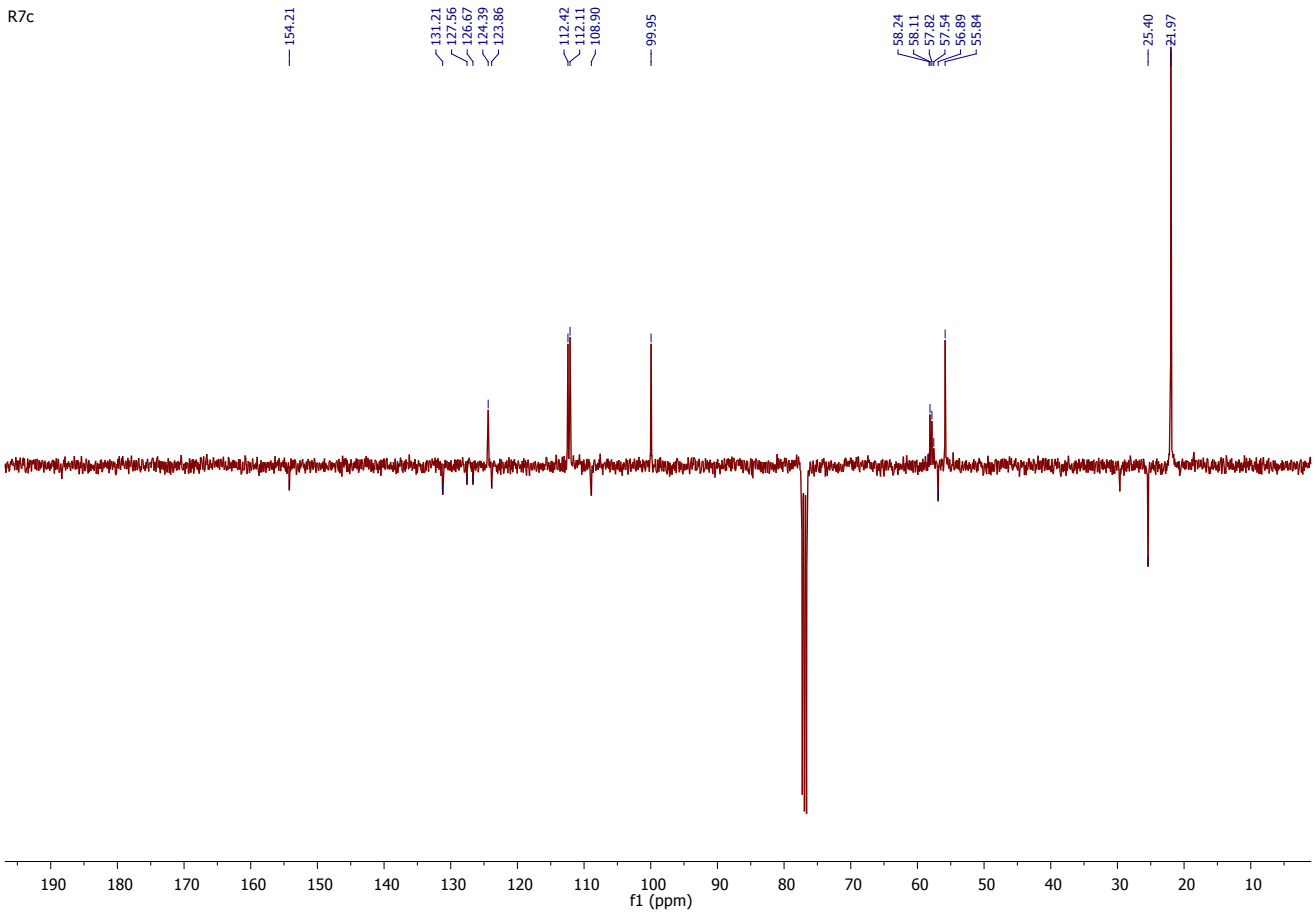
-75.01
f1 (ppm)


R7c
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131.21
127.56
126.67
124.39
123.86
112.42
112.11
108.90
99.95
58.24
58.11
57.82
57.54
56.89
55.84
25.40
21.97
190
180
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120
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100
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60
50
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30
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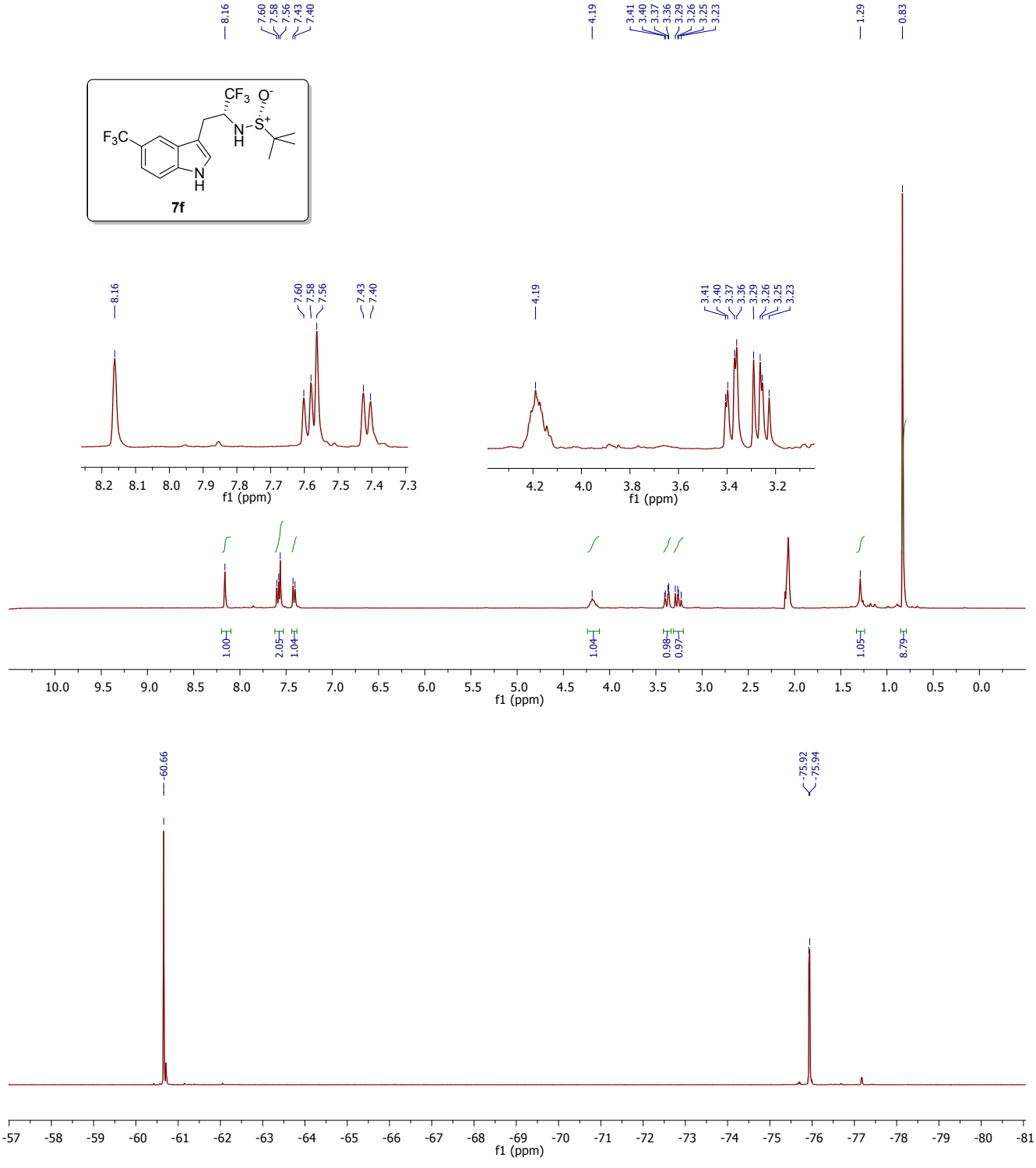
10
f1 (ppm)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7.56
7.43
7.40
4.19
3.41
3.40
3.37
3.36
3.29
3.26
3.25
3.23
1.29
0.83
CF3
O-
F3C
N
H
S+
N
H
7f
f1 (ppm)
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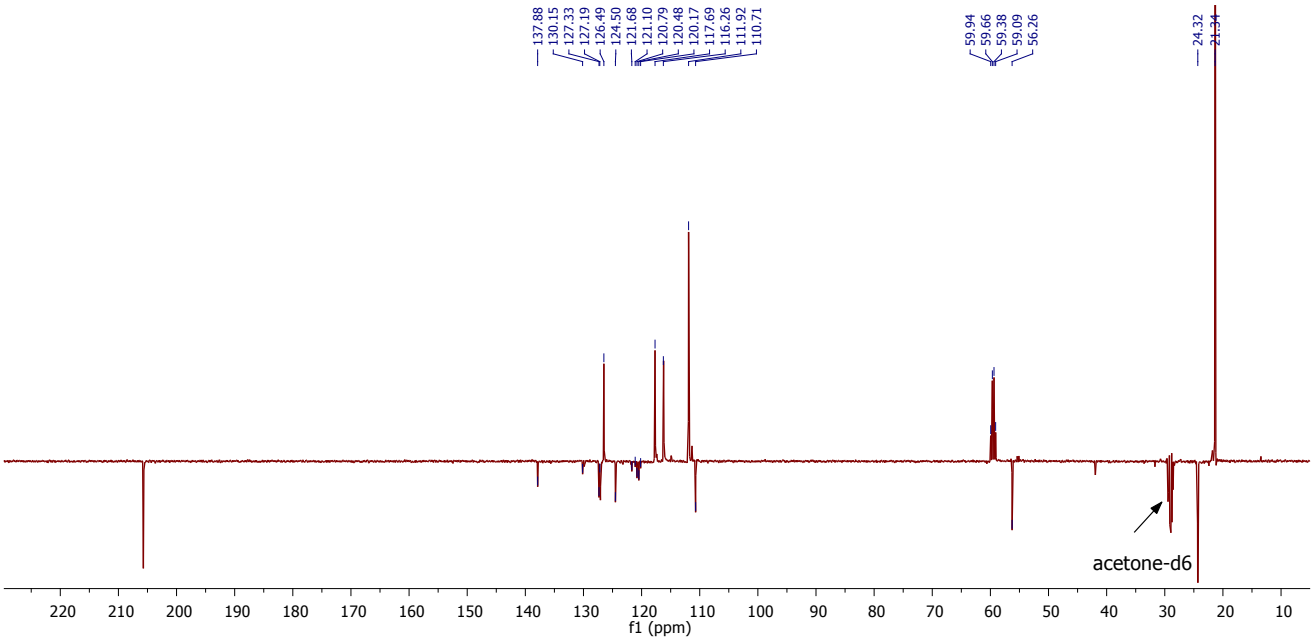
2.05
1.04
1.04
0.98
0.97
1.05
8.79
-60.66
-75.92
-75.94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124.50
121.68
121.10
120.79
120.48
120.17
117.69
116.26
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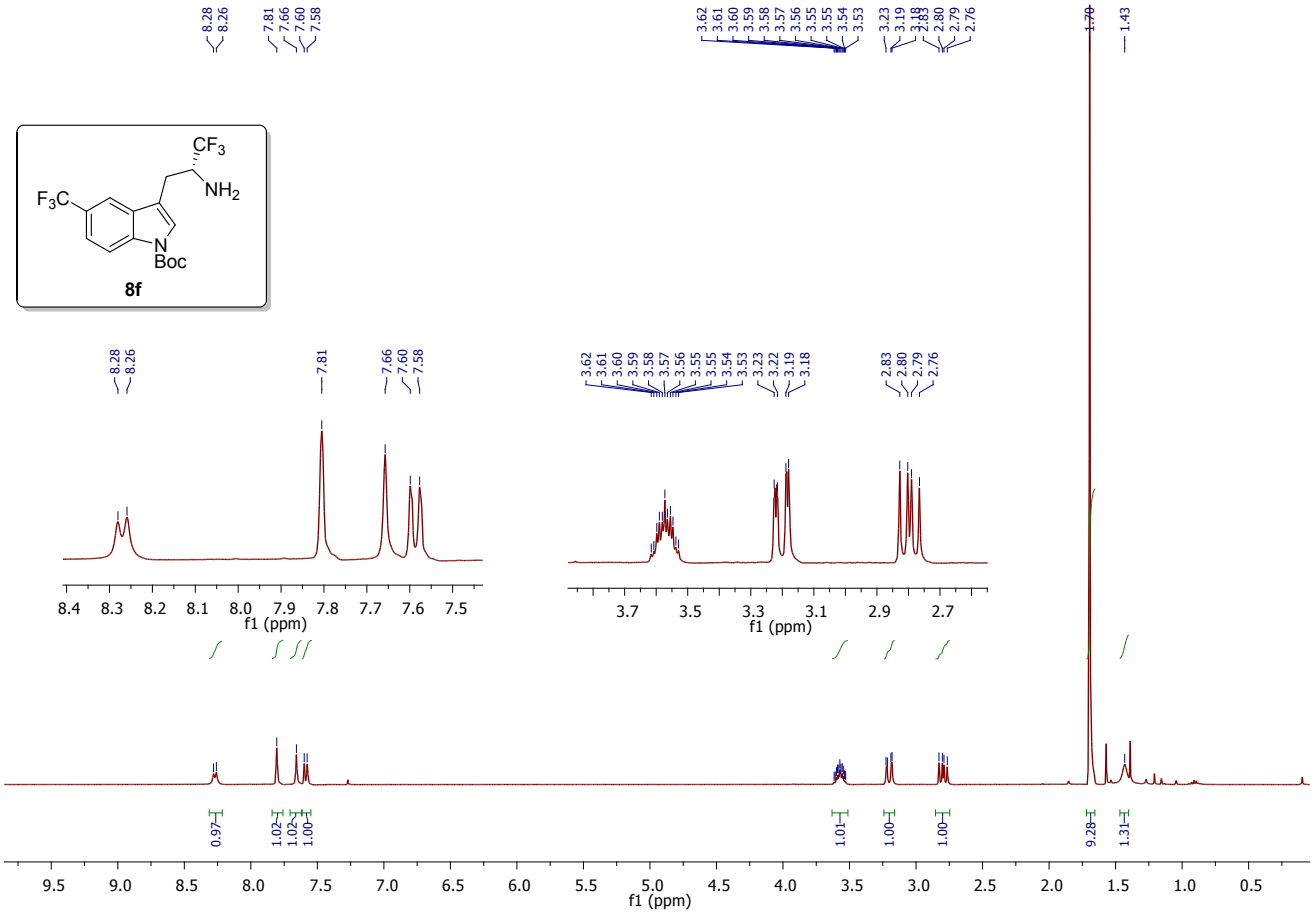
59.94
59.66
59.38
59.09
56.26
24.32
21.34
acetone-d6
f1 (ppm)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7.66
7.60
7.58
3.62
3.61
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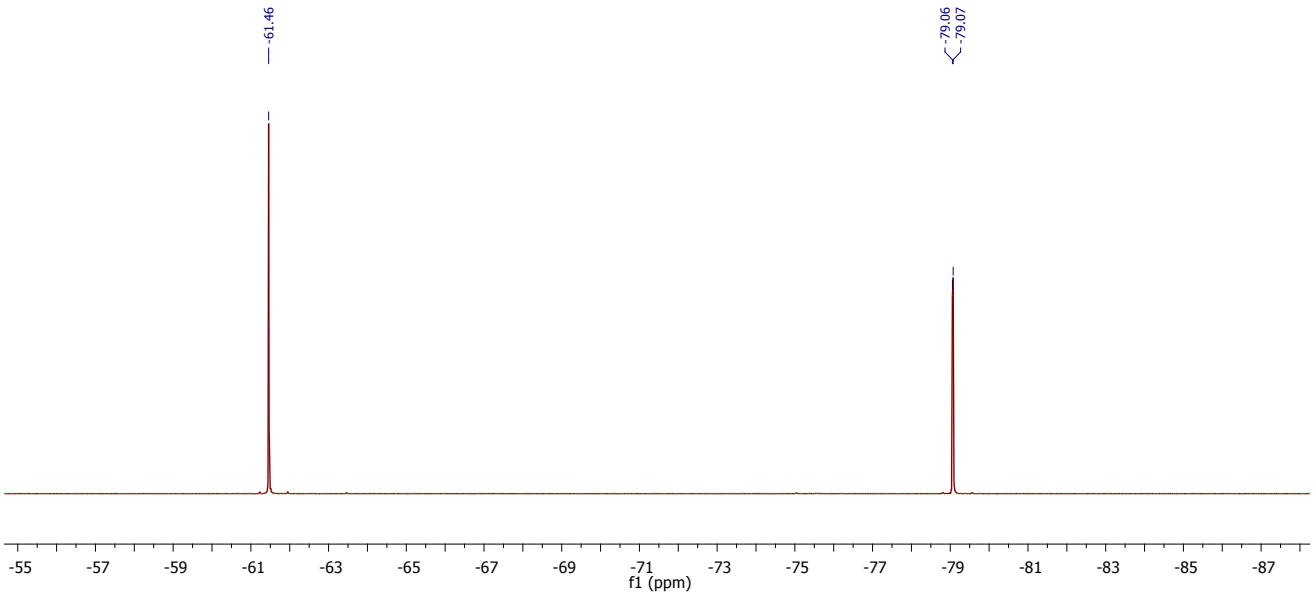
3.59
3.58
3.57
3.56
3.55
3.54
3.53
3.23
3.19
2.83
2.80
2.79
2.76
1.70
1.43
CF3
NH2
F3C
N
Boc
8f
f1 (ppm)
0.97
1.02
1.02
1.00
1.01
1.00
1.00
9.28
1.31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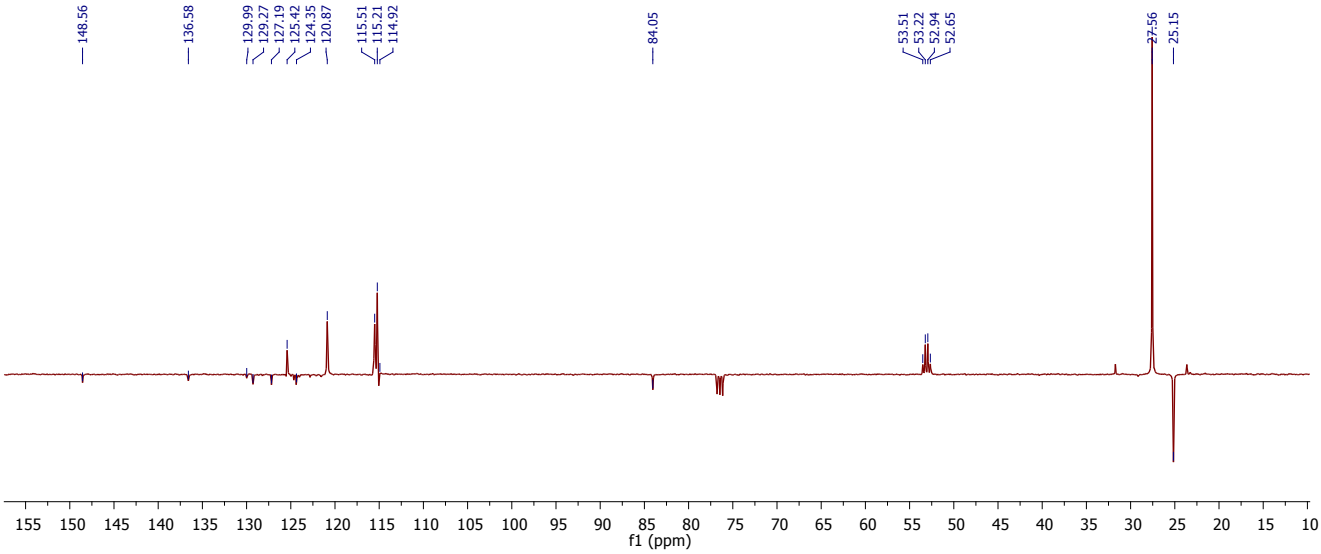
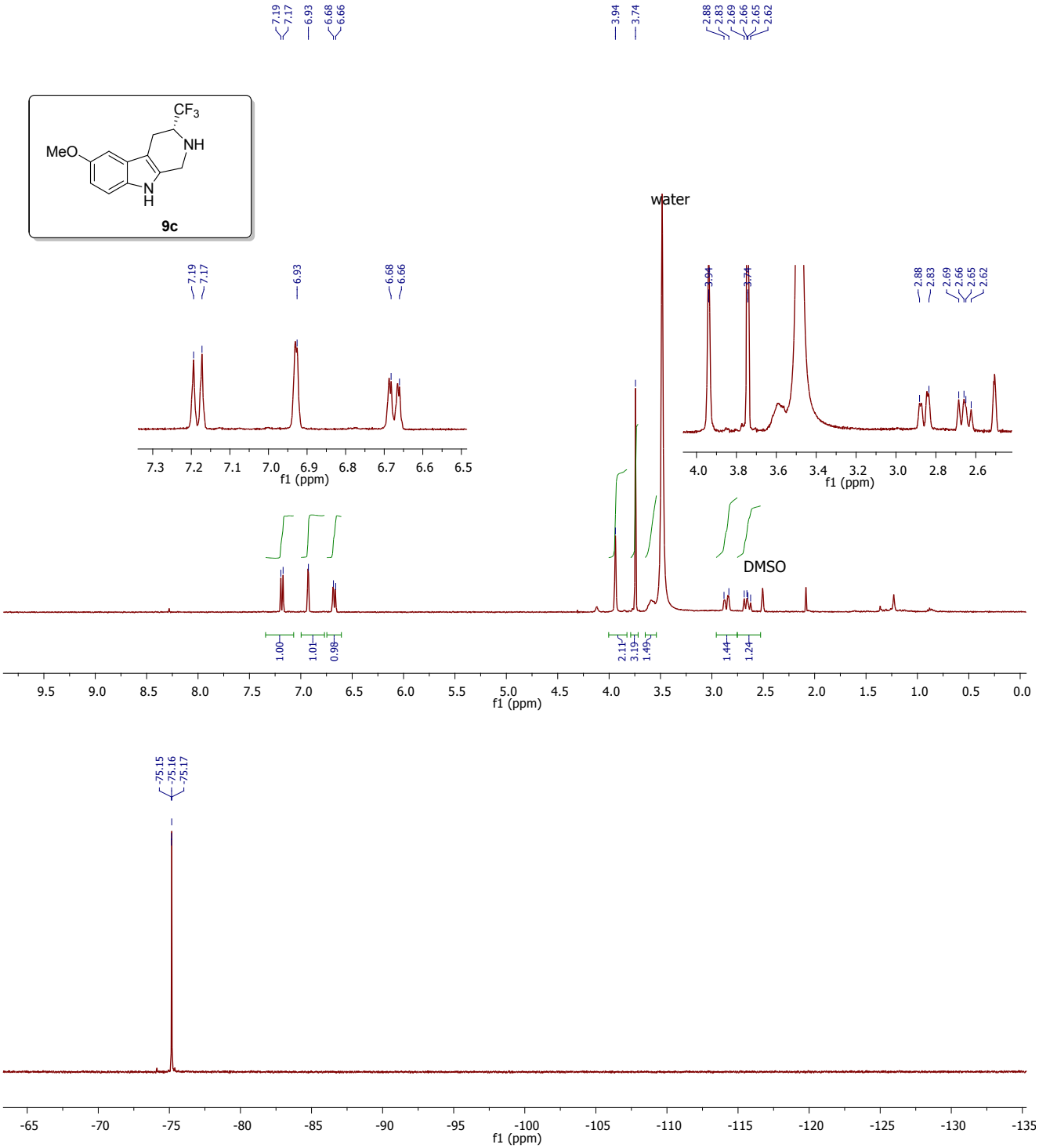
-79.06
-79.07
-55 -57 -59 -61 -63 -65 -67 -69 -71 -73 -75 -77 -79 -81 -83 -85 -87
f1 (ppm)


148.56
136.58
129.99
129.27
127.19
125.42
124.35
120.87
115.51
115.21
114.92
84.05
53.51
53.22
52.94
52.65
27.56
25.15
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)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3.94
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2.69
2.66
2.65
2.62
CF3
NH
MeO
N
H
9c
water
DMSO
f1 (ppm)
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3.19
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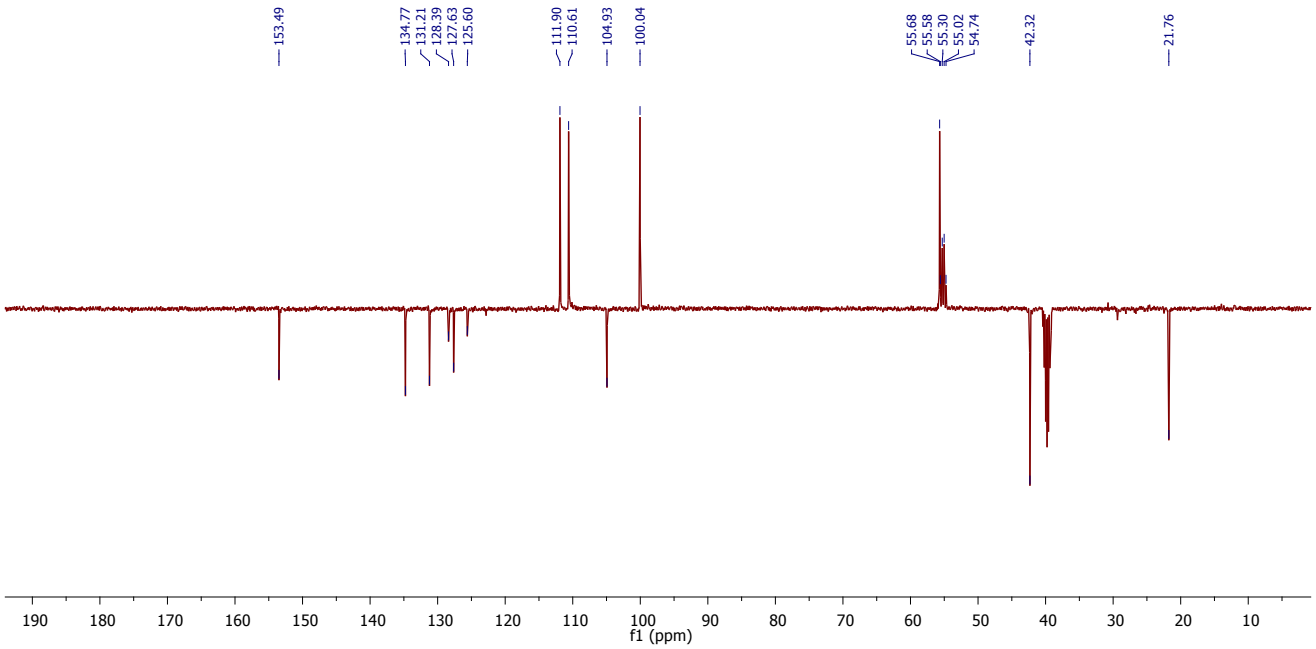
1.24
-75.15
-75.16
-75.17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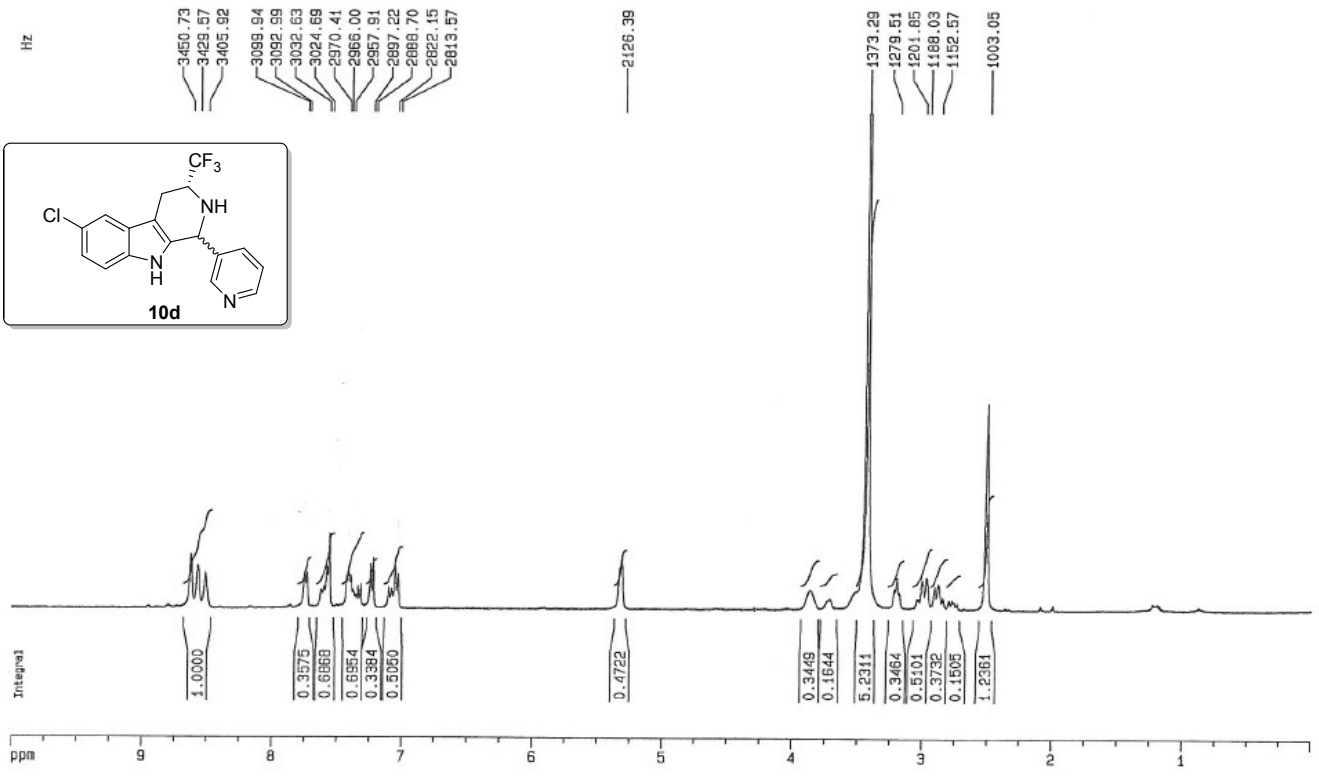
55.02
54.74
42.32
21.76
f1 (ppm)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2966.00
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2897.22
2868.70
2822.15
2813.57
2126.39
1373.29
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1201.85
1188.03
1152.57
1003.05
CF3
NH
Cl
N
H
N
10d
Integral
1.0000
0.3575
0.6868
0.6954
0.3384
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0.1644
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0.1505
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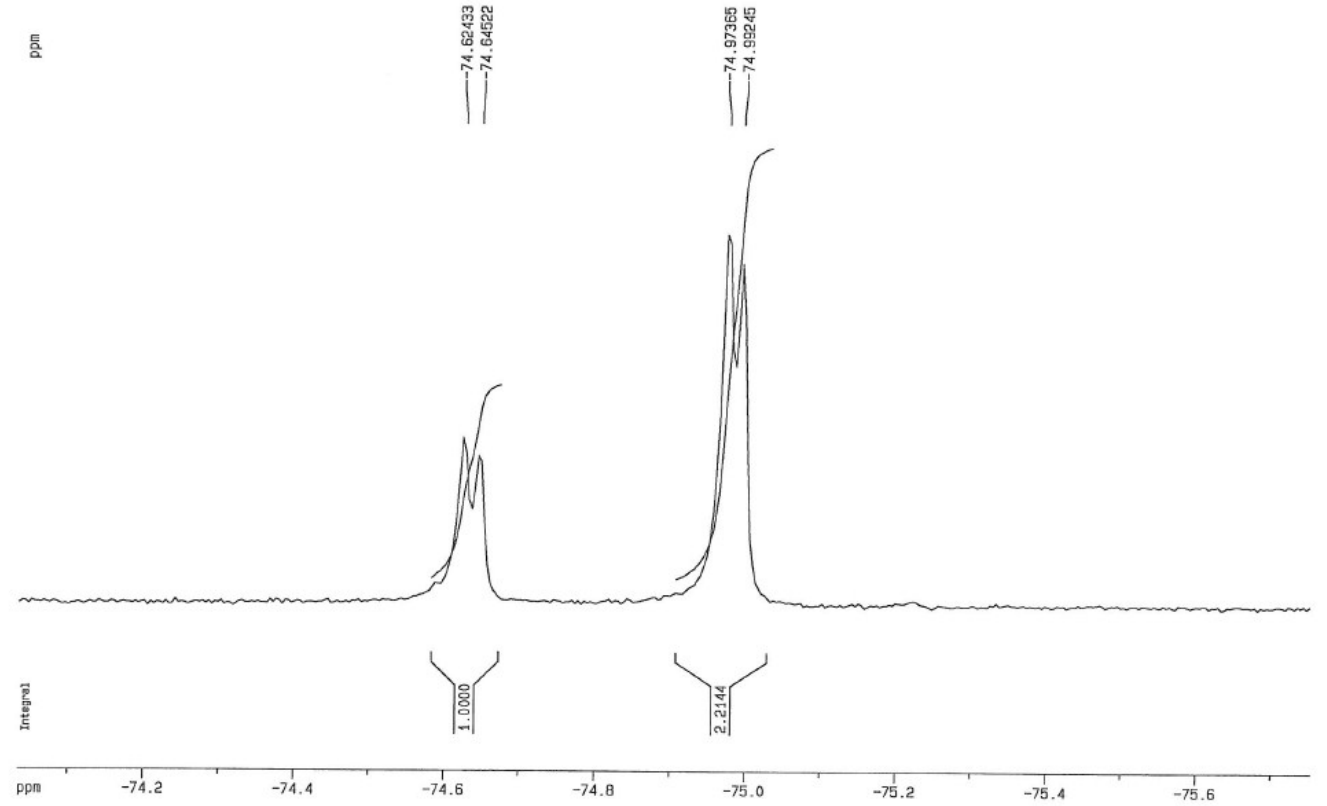
ppm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Integral
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2.2144
ppm
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-74.6
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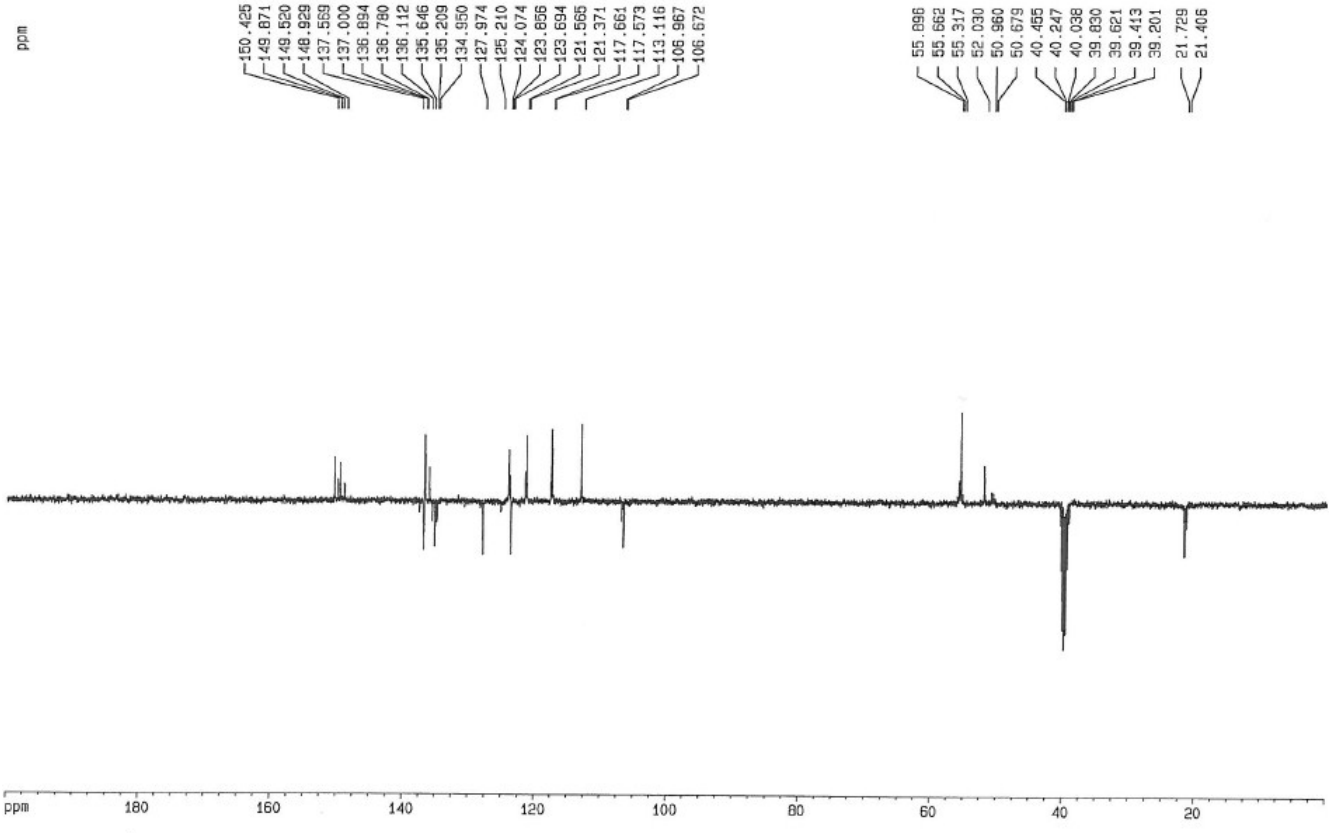
-75.0
-75.2
-75.4
-75.6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124.074
123.856
123.694
121.565
121.371
117.661
117.573
113.116
106.967
106.672
55.896
55.662
55.317
52.030
50.960
50.679
40.455
40.247
40.038
39.830
39.621
39.413
39.201
21.729
21.406
ppm
180
160
140
120
100
80
60
40
20

Comments on VCD-IR analysis for absolute configuration assignment

Experimentals

Experimental VCD and IR spectra were recorded in CCl_4 solution for enantiomers (R_S)-**6e** and (S_S)-**6e** (in a 200 μm BaF_2 cell at concentration of ca. 0.075M). All spectra were recorded with a Jasco FVS-6000 VCD spectrometer at 4 wavenumber resolution. 6000 scans were taken for each spectrum and subtraction of IR and VCD spectra of the solvent (CCl_4) was performed.

Computationals

Molecular Mechanics (MM) conformational search (with MMFFs force field) was performed for both possible diastereomers of **6e.** Geometry optimization and VCD spectra calculations were performed by means of Density Functional Theory (DFT) approach.

In **Figure SI-1** we report, for all relevant conformers of (S,S_S)-**1** and for (R,S_S)-**1**, the electronic and free energy values and relative population factors obtained by DFT calculations. Dihedral angles φ and ψ reported therein and describing, respectively, the orientations of sulfoxide group and the aromatic moiety with respect to CF_3 group are defined in **Figure SI-2**.

Absolute Configuration of 1

Conformational analysis

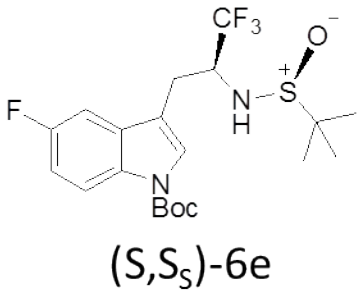
S configuration at sulfur atom was fixed in setting up the calculations. The search provided 67 conformers for (S,S_S)-**6e** and 69 conformers for (R,S_S)-**6e** within 10 kcal/mol in relative energy with respect to the lowest energy conformer. These two set of conformations were fully optimized at DFT level of theory using PBE0 functional and 6-31G* as basis set. 13 conformations within 2.1 kcal/mol in relative energy were further optimized at higher level with PBE0/TZVP functional and basis set providing 7 conformers for (S,S_S)-**6e** and 8 for (R,S_S)-**6e** within 2 kcal/mol. In **Figure SI-3** the optimized structures of (S,S_S)-**6e** and (R,S_S)-**6e** are depicted.

The VCD and IR spectra are reported as average spectra over Boltzamnn's population percentage listed in **Figure SI-1**.

In **Figure SI-4** it is reported the normal modes description for modes involved in the 1180 cm^{-1} VCD doublet (*see text*).

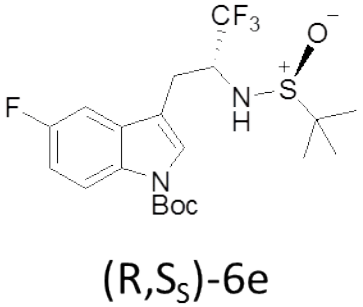
VCD-IR computational analysis approach started in using the most used B3LYP functional, with 6-31G* and TZVP basis sets. In that case, VCD doublet at 1180 cm^{-1} (*see text*) was not satisfactorily predicted. Also smaller basis set 6-31G* appeared to be more qualitatively similar to the experimental VCD spectrum than the larger TZVP basis set (see **Figure SI-5**).

Then we decided to change functional to PBE0 which provided better results (*see text*).



(S,S_S)-6e

Conformer	ΔE (%pop)	ΔG (%pop)	φ (°)	ψ (°)
1a	0 (30.5)	0 (54.9)	78	161
1b	0.18 (27.3)	0.97 (10.6)	-148	73
1c	0.07 (27.3)	1.11 (8.4)	-148	-82
1d	1.60 (2.1)	1.16 (7.7)	-78	170
1e	0.56 (11.8)	1.31 (6.0)	-149	-77
1f	1.83 (1.4)	1.72 (3.0)	-173	80
1g	2.16 (0.8)	1.74 (2.9)	-81	173



(R,S_S)-6e

Conformer	ΔE (%pop)	ΔG (%pop)		
1a'	0.19 (29.3)	0 (26.4)	-106	75
1b'	0 (40.5)	0.05 (24.4)	95	-172
1c'	1.50 (3.2)	0.25 (17.3)	140	-160
1d'	0.37 (21.8)	0.34 (14.8)	141	66
1e'	1.62 (2.6)	0.91 (5.7)	146	-89
1f'	2.03 (1.3)	0.95 (5.3)	94	-176
1g'	2.34 (0.8)	1.02 (4.7)	98	-176
1h'	2.93 (0.3)	1.86 (1.1)	97	-180

Figure SI-1. Conformers relative energy and free energy values with respect to the most stable conformer of the two diastereomers of **6e**. Population factors (in brackets) are Boltzmann factors. Dihedral angles φ and ψ are defined in Figure SI-2.(DFT/PBE0/TZVP level of theory)

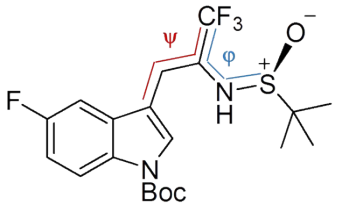


Figure SI-2. Definition of dihedral angles **φ** and **ψ** reported in Figure SI-1.

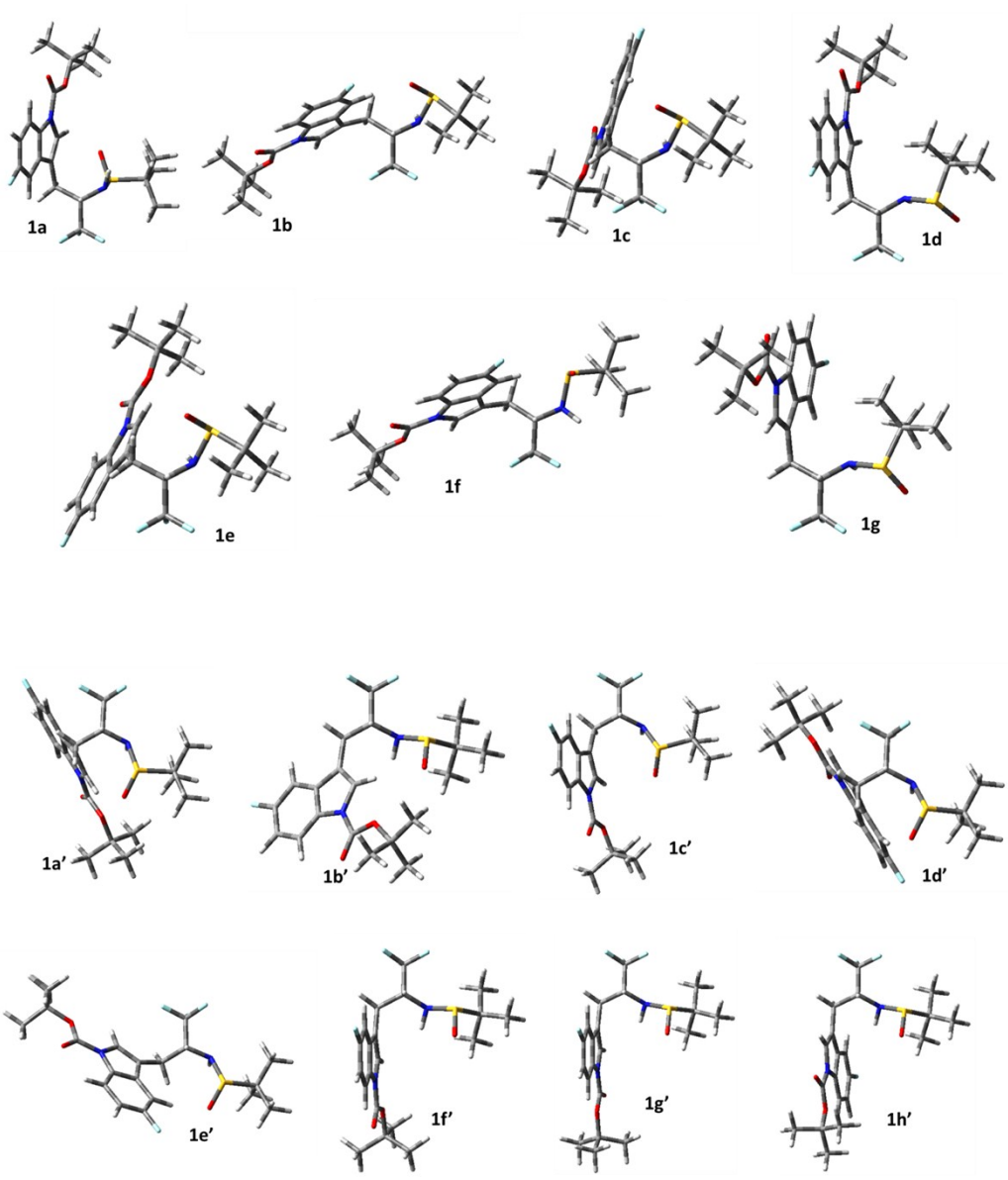


Figure SI-3. Most populated conformers structures of (*S*,S_S)-**6e** and (*R*,S_S)-**6e** optimized at DFT/PBE0/TZVP level of theory.

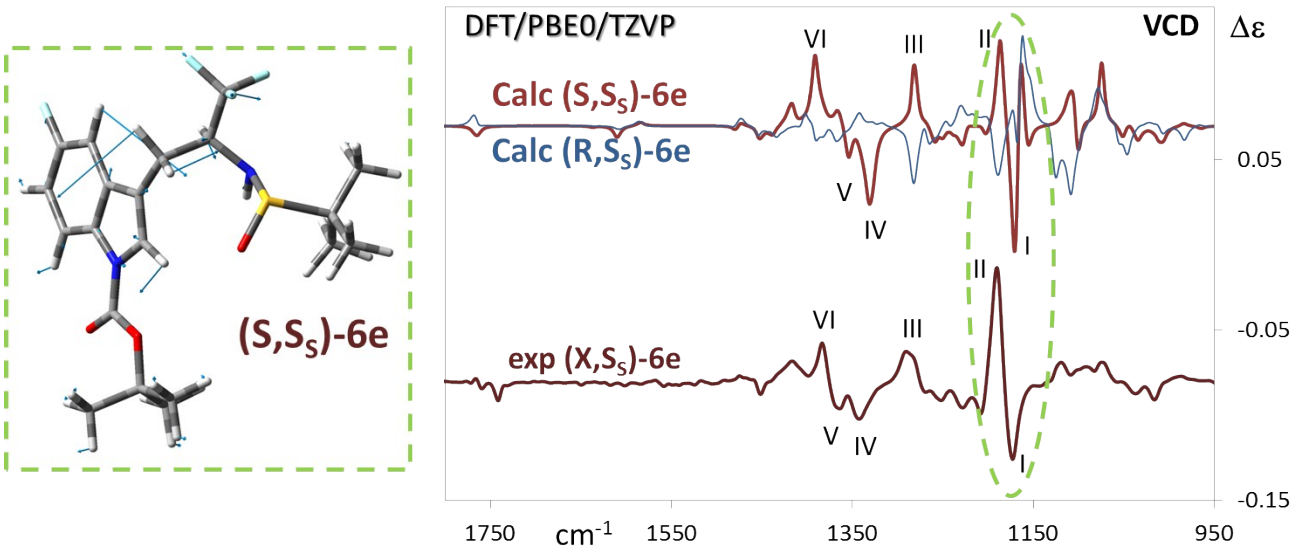


Figure SI-4. Normal modes involved in absolute configuration of carbon stereocenter. Normal mode highlighted in green is related to doublet I-II (*see text*).

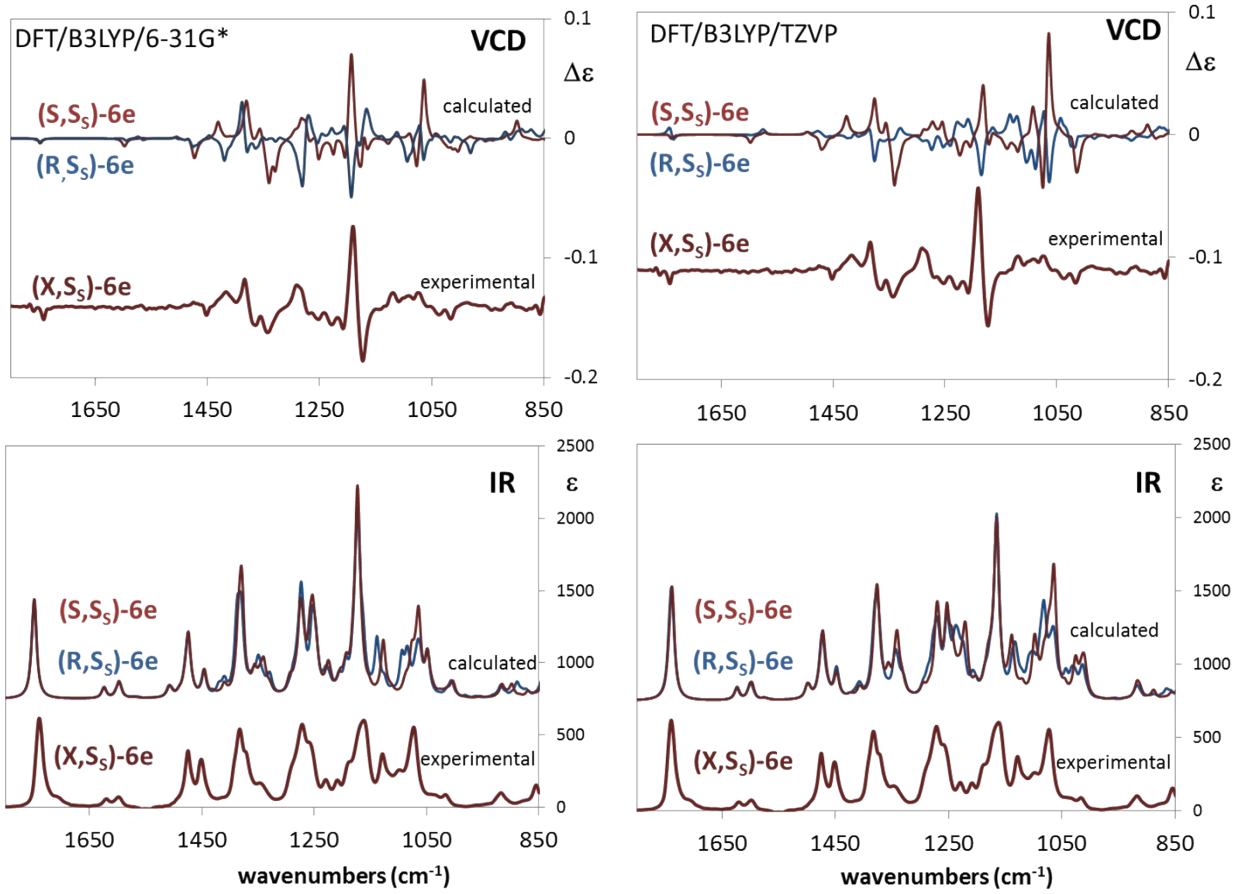


Figure SI-5. Comparison of experimental IR (bottom panels) and VCD (top panels) spectra (CCl_4) with calculated ones: (left) DFT/B3LYP/6-31G* level; (right) DFT/B3LYP/TZVP level.