Supporting Information for:

Fine-tuning Strain and Electronic Activation of Strain-promoted 1,3-Dipolar Cycloadditions with Endocyclic Sulfamates in SNO-OCTs

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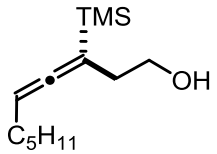
I. General Information.

Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran and diethyl ether were freshly distilled from purple Na/benzophenone ketyl. Dichloromethane, acetonitrile and toluene were dried over CaH2 and freshly distilled prior to use. All other solvents were purified in accordance with "Purification of Laboratory Chemicals".[1] Air- and moisture sensitive reactions were performed using standard Schlenk techniques under an atmosphere of nitrogen. Analytical thin layer chromatography (TLC) was performed utilizing pre-coated silica gel 60 F254 plates containing a fluorescent indicator, while preparative chromatography was performed using SilicaFlash P60 silica gel (230-400 mesh) via Still's method.[2] Unless otherwise stated, the mobile phases for column chromatography were mixtures of hexanes/ethyl acetate. Columns were typically run using a gradient method, beginning with 100% hexanes and gradually increasing the polarity using ethyl acetate. Various stains were used to visualize reaction products, including *p*-anisaldehyde, KMnO4, ceric ammonium molybdate (CAM stain) and iodine powder.

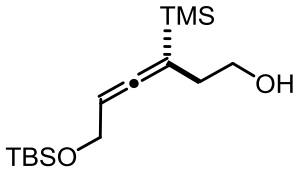
^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker-300, Varian-300, Varian Inova-500, or Varian Unity-500 spectrometers. For ^{1}H NMR, chemical shifts are reported relative to residual protiated solvent peaks (δ 7.26, 2.49, 7.15 and 7.09 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6 and $CD_3C_6D_5$ respectively). ^{13}C NMR spectra were measured ateither 125 MHz or 75 MHz on the same instruments noted above for recording ^{1}H NMR spectra. Chemical shifts were again reported in accordance to residual protiated solvent S3 peaks (δ 77.2, 39.5, 128.0 and 137.9 ppm for $CDCl_3$, $(CD_3)_2SO$, C_6D_6, and $CD_3C_6D_5$, respectively). High-pressure liquid chromatography (HPLC) analyses were performed at 215 and 235 nm using a Shimadzu HPLC, Model LC-20AB. Further details are given in Section VIII. Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization, time-of-flight analyzer or electron impact methods). When two or more significant isotopes were present in the molecule, a monoisotopic approach was used, focusing on the isotope with the lowest mass (35Cl and 79Br). IR spectra were obtained using a Bruker ALPHA Platinum ATR FT-IR spectrometer. The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-9974839, CHE-9304546, CHE-9208463, CHE-9629688) and the University of Wisconsin, as well as the NIH (RR08389-01).

II. Preparation of homoallenic alcohols.

General procedure. A three-neck round bottom flask was charged with lithium aluminum hydride (1 equiv) in dry THF (0.4 M) under a nitrogen atmosphere. The suspension was cooled to 0 °C and the corresponding homoallenic ester (1 equiv), dissolved in THF, was added dropwise. The reaction mixture was stirred for 30 min, quenched at 0 °C with 2.1 equiv of H_2O, followed by 2.1 equiv of 1 M aqueous NaOH and 6.3 equiv of H_2O. The organics were dried over Na_2SO_4, the mixture filtered and the volatiles removed under reduced pressure. The residual oil was purified via column chromatography.



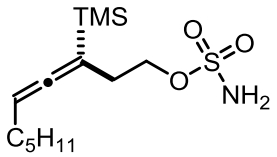
Homoallenic alcohol precursor to compounds 5, 6 and 7. The homoallenic alcohol was prepared from the corresponding homoallenic ester (1.9 g, 7.2 mmol) according to the general procedure. The crude product was purified via column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) to yield the alcohol (1.3 g, 5.9 mmol) as a clear oil in a yield of 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (tt, *J* = 6.6, 3.0 Hz, 1H), 3.74 (t, *J* = 6.3 Hz, 2H), 2.22 (tdd, *J* = 6.2, 3.0, 0.8 Hz, 2H), 2.02 – 1.89 (m, 2H), 1.72 (d, *J* = 5.1 Hz, 1H), 1.44 – 1.23 (m, 6H), 0.88 (td, *J* = 5.6, 4.5, 3.0 Hz, 3H), 0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.28, 93.46, 86.55, 32.56, 31.59, 29.56, 28.60, 22.65, 14.19, -1.44. HRMS (ESI) *m/z* calculated for $C_{13}H_{27}OSi$ $[M+H]^+$ 227.1826; found, 227.1829.



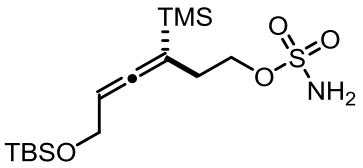
Homoallenic alcohol precursor to compound 8. The homoallenic alcohol was prepared from the corresponding homoallenic ester (2.22 g, 6.4 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 10% EtOAc/hexanes, gradient) to yield the alcohol (1.92 g, 6.4 mmol) as a clear oil in a yield of 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (tt, *J* = 4.8, 2.9 Hz, 1H), 4.19 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.13 (dd, *J* = 12.4, 5.0 Hz, 1H), 3.83 (m, 1H), 3.71 – 3.62 (m, 1H), 2.83 (s, 1H), 2.29 – 2.15 (m, 2H), 0.91 (s, 9H), 0.11 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$ HRMS δ 204.20, 96.48, 87.22, 61.37, 60.65, 32.44, 26.08, 25.80, 18.62, -1.53, -5.18, -5.24. (ESI) *m/z* calculated for $C_{15}H_{32}O_2Si_2Na$ $[M+Na]^+$ 323.1833; found, 323.1830.

III. Preparation of homoallenic sulfamates.

General procedure. In a 3-neck round bottom flask, chlorosulfonyl isocyanate (2.5 equiv) was cooled to 0 °C. Formic acid (2.5 equiv) was added dropwise to this mixture, resulting in vigorous gas evolution. The resulting white solid was dissolved in CH_3CN to yield a 0.5 M solution. This solution was stirred at 0 °C for 30 min, warmed to 23 °C and stirred for an additional 4-12 h. The reaction mixture was then cooled to 0 °C, at which point the homoallenic alcohol (1 equiv) was added as a solution in N,N-dimethylacetamide (0.6 M). The reaction was stirred for 1 h at 23 °C and then quenched by the addition of an equal volume of H_2O. The aqueous phase was extracted with three portions of EtOAc and the combined organic phases washed with five portions of H_2O. The combined organics were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude material was purified via column chromatography.

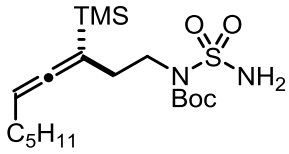


Precursor to compounds 5 and 6. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (4.8 g, 21 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield the product (3.6 g, 11 mmol) as a waxy white solid in 55% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (tt, *J* = 6.6, 3.0 Hz, 1H), 4.65 (s, 2H), 4.28 (td, *J* = 7.5, 1.4 Hz, 2H), 2.44 – 2.33 (m, 2H), 1.95 (dt, *J* = 7.9, 6.7 Hz, 2H), 1.44 – 1.27 (m, 6H), 0.94 – 0.85 (m, 3H), 0.10 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 205.86, 91.54, 87.28, 70.90, 31.60, 31.08, 29.45, 28.38, 28.36, 22.64, 14.19, -1.52. HRMS (ESI) *m/z* calculated for $C_{13}H_{28}NO_3SSi$ [M+H$^+$] 306.1554; found, 306.1545.



Precursor to compound 8. The homoallenic sulfamate was prepared from the corresponding homoallenic alcohol (1.1 g, 3.7 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield the product (0.65 g, 1.7 mmol) as a waxy white solid in 47% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (s, 2H), 5.01 (ddt, *J* = 8.9, 5.0, 3.4 Hz, 1H), 4.34 (ddd, *J* = 9.2, 8.2, 4.5 Hz, 1H), 4.32 (ddd, *J*= 8.2, 3.6, 3.1 Hz, 1H), 4.29 (dd, *J* = 11.5, 5.3 Hz, 1H), 4.14 (dd, *J* = 11.5, 9.1 Hz, 1H), 2.43 (ddd, *J* = 16.7, 4.5, 3.1 Hz, 1H), 2.36 (ddd, *J* = 16.8, 9.2, 3.6 Hz, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.63, 94.11, 87.26, 69.42, 62.57, 27.55, 26.11, 18.64, -1.67, -5.10. HRMS (ESI) *m/z* calculated for $C_{15}H_{33}NO_4SSi_2$ [M+H$^+$] 380.1742; found, 380.1739.

IV. Preparation of homoallenic sulfamides.

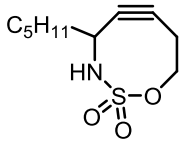


Precursor to compound 7. A dry, 50 mL round bottom flask was placed under a nitrogen atmosphere and charged with the desired alcohol (500 mg, 2.2 mmol, 1 equiv), triphenylphosphine (754 mg, 2.9 mmol, 1.3 equiv), and *tert*-butyl aminosulfonylcarbamate (563 mg, 2.9 mmol, 1.3 equiv) were combined in dry THF (8.5 mL, 0.3 M) and cooled to 0 °C. Diisopropyldicarboxylate (0.57 mL, 2.9 mmol. 1.3 equiv) was added in a dropwise fashion to the resulting solution. The reaction mixture was warmed to room temperature and stirred for 4 h

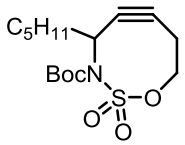
before the solvent was removed under reduced pressure. The resulting oil was diluted with hexanes and the solvent again removed under reduced pressure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure homoallenic sulfamide (677 mg, 1.7 mmol) as a white solid in a yield of 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 2H), 4.85 (tt, *J* = 6.7, 2.8 Hz, 1H), 3.74 (ddd, *J* = 8.7, 7.3, 1.3 Hz, 2H), 2.34 – 2.19 (m, 2H), 1.97 – 1.89 (m, 2H), 1.53 (s, 9H), 1.43 – 1.28 (m, 6H), 0.94 – 0.86 (m, 3H), 0.09 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.13, 152.45, 93.14, 86.58, 84.35, 47.60, 31.62, 29.51, 29.10, 28.45, 28.27, 22.66, 14.20, -1.42. HRMS (ESI) *m/z* calculated for $C_{18}H_{40}N_3O_4SSi$ [M+NH_4^+] 427.2057; found, 427.2055.

V. Preparation of cycloalkynes.

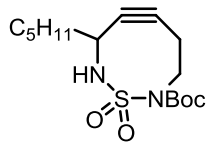
General procedure. The following procedure was adapted from our previously reported syntheses of endocyclic bicyclic methyleneaziridines.[3] The homoallenic sulfamate (1 equiv) and $Rh_2(OAc)_4$ (0.05 equiv) were placed in a dry round bottom flask. The solids were dissolved in CH_2Cl_2 to prepare a 0.2 M solution and stirred for 5 min at rt. PhIO (1.2 equiv) was added in a single portion and the reaction mixture was stirred for 30 min while monitoring by TLC. When TLC indicated complete consumption of the starting material, 1 M TBAF in THF (2 equiv) was added. After 5 min at rt, the reaction was checked for completion by TLC. The reaction was then quenched by the addition of an equal volume of water and extracted with 3 portions of EtOAc. The combined organics were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product purified by column chromatography.



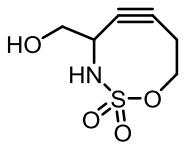
Compound 5. The cyclic alkyne was prepared from the corresponding homoallenic sulfamate (1.3 g, 4.3 mmol). Purification by column chromatography (0% EtOAc/hexanes to 15% EtOAc/hexanes, gradient) furnished pure **5** (0.90 g, 3.9 mmol) as a white solid in a yield of 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (d, *J* = 7.2 Hz, 1H), 4.92 (ddd, *J* = 10.6, 10.5, 4.2 Hz, 1H), 4.66 (ddd, *J* = 11.0, 5.3, 3.0 Hz, 1H), 4.23 (dtd, *J* = 8.8, 6.8, 3.5 Hz, 1H), 2.75 (dddd, *J* = 17.7, 10.1, 5.3, 2.6 Hz, 1H), 2.41 (ddt, *J* = 17.0, 4.6, 2.5 Hz, 1H), 1.77 – 1.59 (m, 2H), 1.44 – 1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 97.38, 96.84, 76.47, 49.62, 32.80, 31.23, 25.63, 22.55, 21.87, 14.06. HRMS (ESI) *m/z* calculated for $C_{10}H_{21}N_2O_3S$ [M+NH_4^+] 249.1267; found, 249.1265.



Compound 6. Compound **5** (0.25 g, 1.1 mmol) was dissolved in CH_2Cl_2 (0.2 M). To this solution was added di-*tert*-butyl dicarbonate (0.35 g, 1.6 mmol) and triethylamine (0.23 mL, 1.6 mmol), followed by 4-dimethylaminopyridine (13 mg, 0.11 mmol). The reaction was stirred at ambient temperature under a N_2 atmosphere until TLC indicated complete consumption of **5**. The reaction mixture was quenched by the addition of an equal volume of saturated aqueous NH_4Cl. The aqueous phase was extracted with 3 x 10 mL portions of CH_2Cl_2 and the combined organic phases dried over Na_2SO_4. The solution was filtered and the volatiles removed under reduced pressure. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure cyclic alkyne **6** (0.28 g, 0.84 mmol) as a white solid in 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (ddd, *J* = 12.4, 11.1, 4.0 Hz, 1H), 4.97 (td, *J* = 8.0, 2.8 Hz, 1H), 4.62 (dd, *J* = 11.1, 6.0 Hz, 1H), 2.92 (dddd, *J* = 17.1, 12.4, 6.1, 2.9 Hz, 1H), 2.30 (dd, *J* = 17.1, 3.9 Hz, 1H), 2.04 – 1.89 (m, 2H), 1.54 (s, 9H), 1.40 – 1.28 (m, 6H), 0.89 (td, *J* = 6.8, 5.7, 3.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.01, 96.15, 94.46, 85.29, 75.03, 55.61, 33.48, 31.15, 28.51, 26.00, 22.61, 21.72, 14.09. HRMS (ESI) *m/z* calculated for $C_{15}H_{26}NO_5S$ [M+H$^+$] 332.1526; found, 332.1515.



Compound 7. The cyclic alkyne **7** was prepared from the corresponding homoallenic sulfamide (1.7 g, 4.1 mmol). The general procedure was employed, with the exception that $Rh_2(TPA)_4$ was substituted for $Rh_2(OAc)_4$ to improve the selectivity between endocyclic and exocyclic methyleneaziridines. The crude product was purified via column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure **7** (0.90 g, 3.9 mmol) as a white solid in 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), δ 4.37 (dtt, *J* = 11.7, 8.6, 5.7 Hz, 2H), 4.03 (ddd, *J* = 14.1, 6.2, 2.3 Hz, 1H), 2.74 (dddd, *J* = 17.1, 11.5, 6.0, 3.2 Hz, 1H), 2.30 – 2.18 (m, 1H), 1.56 (s, 9H), 1.54 – 1.22 (m, 8H), 0.89 (td, *J* = 7.0, 4.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.29, 96.98, 92.81, 84.45, 51.59, 49.31, 35.95, 32.40, 31.31, 28.25, 25.86, 25.23, 22.58, 14.04.HRMS (ESI) *m/z* calculated for $C_{15}H_{30}N_3O_4S$ [M+NH_4^+] 348.1952; found, 348.1947.

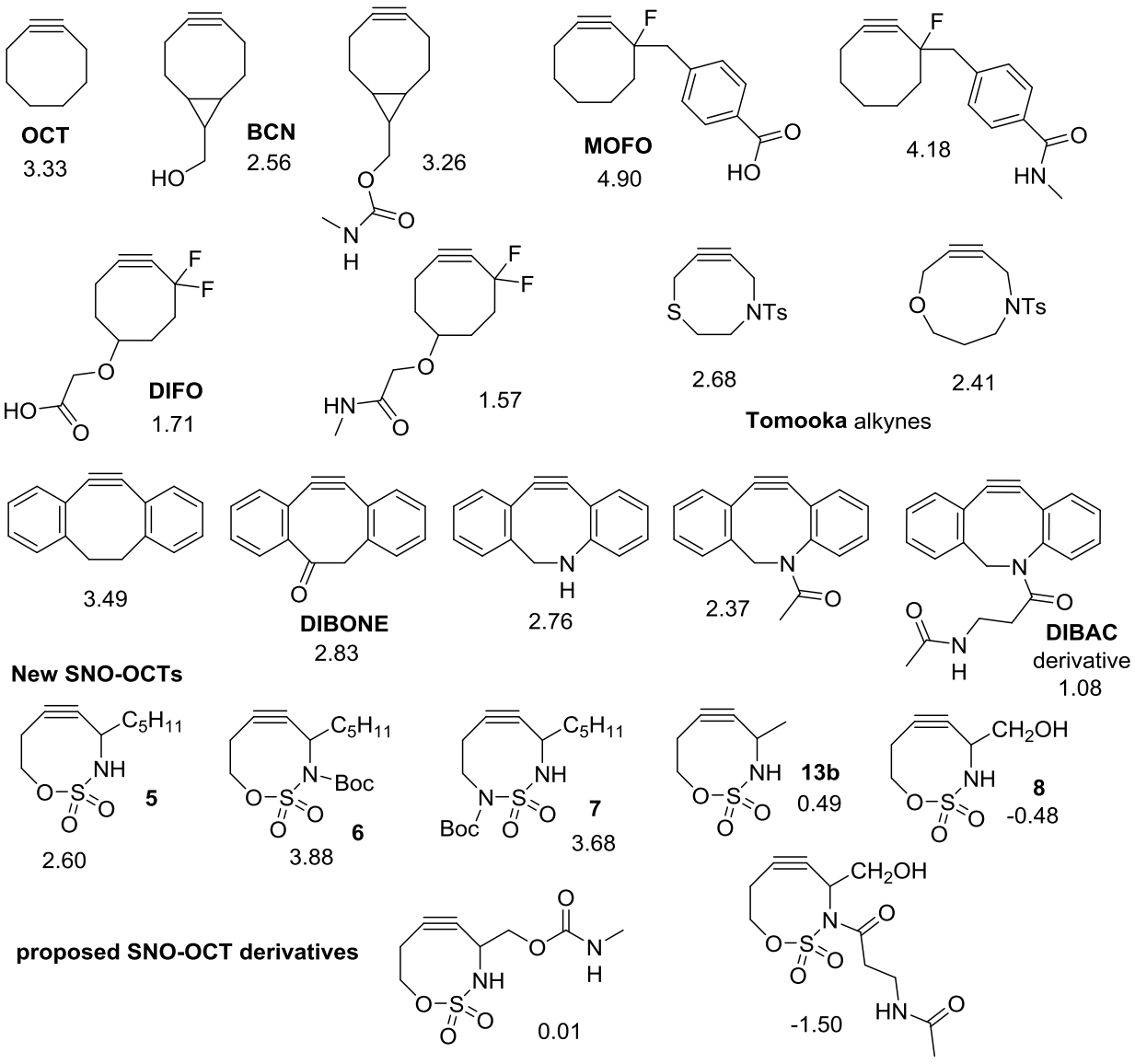


Compound 8. The cyclic alkyne **8** was prepared from the corresponding homoallenic sulfamate (28 mg, 0.074 mmol). The crude product was purified via column chromatography (0% EtOAc/hexanes to 50% EtOAc/hexanes, gradient) to yield pure **8** (9 mg, 0.047 mmol) as a white

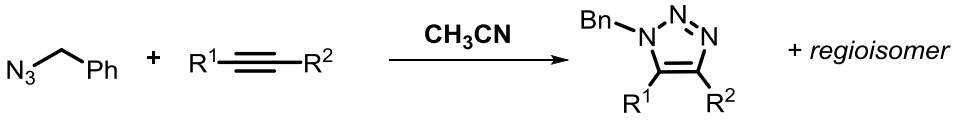
solid in 66% yield. The general procedure was adapted to use 5 equiv of 1 M TBAF in THF to allow for complete deprotection of the tethered alcohol in addition to the desilylation and ring expansion process. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (d, *J* = 7.2 Hz, 1H), 4.93 (ddd, *J* = 11.0, 9.2, 4.4 Hz, 1H), 4.73 (ddd, *J* = 11.1, 5.2, 4.0 Hz, 1H), 4.32 (qd, *J* = 7.2, 6.0, 2.6 Hz, 1H), 3.83 (dt, *J* = 11.4, 3.9 Hz, 1H), 3.71 (ddd, *J* = 11.4, 7.7, 3.7 Hz, 1H), 2.77 (dddd, *J* = 16.9, 9.1, 5.1, 2.4 Hz, 1H), 2.50 (dtd, *J* = 17.0, 4.1, 2.1 Hz, 1H), 2.05 (d, *J* = 9.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.10, 93.13, 76.33, 62.03, 50.89, 21.76. HRMS (ESI) *m/z* calculated for $C_6H_{10}NO_4S$ $[M+H^+]$ 192.0325; found, 192.0324.

VI. Comparison of calculated log *P* values for known *vs.* new SNO-OCT alkynes. The log *P* values were calculated for known cycloalkynes and our new SNO-OCTs. In addition, calculations were carried out on SNO-OCT analogs that could be easily accessed from our new cycloalkynes using http://www.molinspiration.com/cgi-bin/properties (Scheme S1).

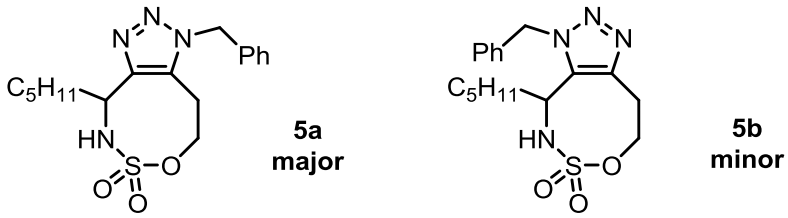
Scheme S1. Calculated log *P* values for known cycloalkynes and new SNO-OCTs.



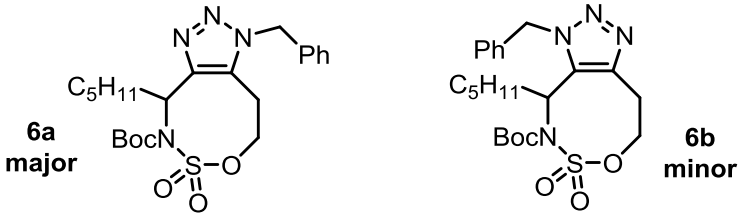
VII. Reactions with benzylazide.



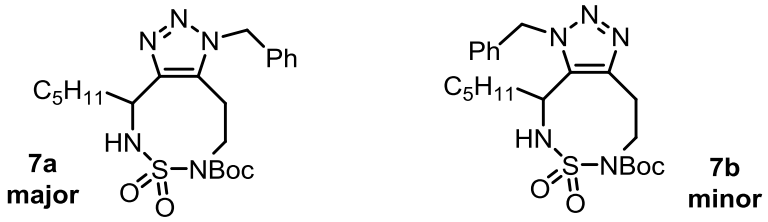
General Procedure. The cyclic alkyne (1 equiv) was dissolved in CH_3CN (0.1 M). Benzyl azide (1.1 equiv) was added to the resulting solution and the reaction mixture stirred for 1 h to ensure full conversion. The solvent was then removed under reduced pressure and the resulting oil dissolved in a minimum volume of CH_2Cl_2. The solvent was again removed under reduced pressure and the triazole products characterized without further purification.



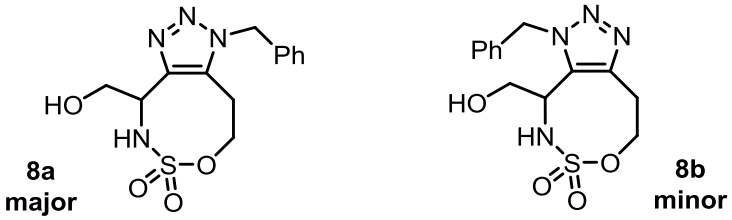
Triazoles 5a and 5b from 5. The triazole was prepared from alkyne **5** (15 mg, 0.065 mmol). The resulting triazoles **5a** and **5b** were obtained as a clear oil (24 mg, 0.065 mmol) in quantitative yield as a mixture of regioisomers (**5a:5b** 2.2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4.45H), 7.17 – 7.08 (m, 2.8H), 5.65 – 5.42 (m, 4.35H), 4.59 (major, dd, *J* = 9.1, 4.9 Hz, 1H), 4.56 (minor, m, 0.45H), 4.15 (minor, td, *J* = 11.8, 5.5 Hz, 0.45H), 3.88 (major, ddd, *J* = 11.7, 6.4, 5.3 Hz, 1H), 3.80 (major, ddd, *J* = 11.9, 7.8, 5.2 Hz, 1H), 3.74 – 3.63 (minor, m, 0.45H), 3.34 – 3.15 (m, 1.9H), 3.01 (major, ddd, *J* = 16.1, 6.5, 5.2 Hz, 1H), 2.35 – 2.22 (major, m, 1H), 1.96 (major, ddd, *J* = 14.2, 9.6, 5.0 Hz, 1H), 1.75 – 1.59 (m, 0.45H), 1.59 – 1.43 (m, 2.2H), 1.43 – 1.19 (m, 6.9H), 0.89 (major, td, *J* = 6.9, 4.8 Hz, 3H), 0.80 (minor, t, *J* = 7.2 Hz, 1.4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.79, 134.36, 129.41, 128.86, 127.07, 126.87, 69.25 (minor), 67.46 (major), 52.70, 52.50, 51.14 (major), 50.22(minor), 34.11, 33.39 (major), 31.40, 31.05, 26.41, 25.58, 24.86, 24.79, 22.59, 22.36, 14.12 (major), 13.99 (minor). HRMS (ESI) *m/z* calculated for $C_{17}H_{25}N_4O_3S$ [M+H$^+$] 365.1642; found, 365.1638.



Triazoles 6a and 6b from 6. The triazoles were prepared from alkyne **6** (10 mg, 0.031 mmol). The product was obtained (14 mg, 0.030 mmol) as a clear oil as a mixture of regioisomers (**6a:6b** 2.0:1) in a quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 7.26 – 7.21 (m, 0.5H), 7.14 – 7.05 (m, 2H), 5.80 (minor, d, J = 15.6 Hz, 0.5H), 5.69 – 5.59 (m, 2H), 5.51 (major, dd, J = 10.4, 4.9 Hz, 1H), 5.43 (major, d, J = 15.8 Hz, 1H), 4.76 (minor, td, J = 10.6, 3.0 Hz, 0.5H), 4.68 (minor, dt, J = 11.0, 3.8 Hz, 0.5H), 4.18 (major, ddd, J = 12.2, 6.2, 3.2 Hz, 1H), 3.90 (major, ddd, J = 11.2, 6.9, 2.9 Hz, 1H), 3.30 (minor, tdt, J = 17.1, 9.6, 3.1 Hz, 1H), 3.04 – 2.90 (major, m, 2H), 2.61 – 2.49 (major, m, 1H), 2.43 – 2.29 (major, m, 1H), 2.19 (minor, dddd, J = 13.5, 10.5, 8.4, 4.8 Hz, 0.5H), 1.68 (minor, dddd, J = 13.7, 10.3, 7.2, 5.7 Hz, 1H), 1.54 (minor, s, 6H), 1.45 (major, s, 9H), 1.38 (tt, J = 9.8, 6.1 Hz, 3H), 1.32 – 1.19 (m, 2H), 1.10 – 0.94 (m, 2H), 0.90 (major, dt, J = 14.4, 7.0 Hz, 3H), 0.74 (minor, t, J = 7.2 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) 152.04, 150.76, 135.14, 134.81, 129.44, 128.90, 127.47, 127.03, 86.20, 85.37, 74.78 (minor), 69.47 (major), 57.35 (major), 52.78 (minor), 52.66 (minor), 52.50 (major), 32.15 (major), 31.78, 31.50 (major), 31.09, 27.99 (minor), 27.93, 27.18, 25.83, 25.60, 23.31 (major), 22.62, 22.33, 14.15 (major), 13.96 (minor). HRMS (ESI) *m/z* calculated for $C_{22}H_{33}N_4O_5S$ [M+H$^+$] 465.2166; found, 465.2163.

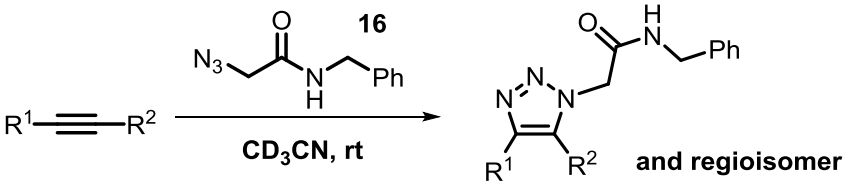


Triazoles 7a and 7b from 7. The triazoles were prepared from alkyne **7** (17 mg, 0.052 mmol) and obtained as a clear oil (22 mg, 0.048 mmol) as a mixture of regioisomers (**7a:7b** 3.2:1) in a quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 3.5H), 7.25 – 7.13 (m, 3H), 5.81 (major, d, *J* = 15.6 Hz, 1H), 5.71 (minor, d, *J* = 16.1 Hz, 0.31H), 5.54 (minor, d, *J* = 15.9 Hz, 0.32H), 5.23 (major, d, *J* = 15.6 Hz, 1H), 5.09 (major, s, 1H), 4.36 (p, *J* = 6.7, 5.5 Hz, 2H), 4.16 (major, s, 1H), 4.11 – 3.88 (m, 0.6H), 3.79 (major, dd, *J* = 14.4, 7.9 Hz, 1H), 3.34 – 3.20 (m, 1H), 3.15 (minor, dt, *J* = 14.6, 5.8 Hz, 0.3H), 2.67 (major, dd, *J* = 15.2, 6.3 Hz, 1H), 2.31 – 2.10 (m, 2H), 1.68 (p, *J* = 8.0, 7.5 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.47 (ddq, *J* = 9.4, 5.9, 2.8, 2.3 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 9H), 1.28 (ddd, *J* = 35.1, 17.1, 9.8 Hz, 4H), 1.17 – 1.08 (m, 0.3H), 1.03 (dp, *J* = 7.2, 4.6, 2.7 Hz, 0.3H), 0.93 – 0.85 (major, m, 3H), 0.79 (minor, t, *J* = 7.2 Hz, 0.9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ151.82, 151.09, 145.88, 134.95, 134.68, 132.31, 129.33, 129.24, 128.94, 128.78, 128.70, 128.32, 127.29, 127.02, 85.28 (major), 84.49 (minor), 52.37, 52.37, 50.09, 48.95, 47.30(minor), 44.49 (major), 31.66, 31.43 (major), 31.04, 28.01, 27.87, 26.21 (minor), 22.59, 21.33 (major), 14.12 (major), 13.99 (minor). HRMS (ESI) *m/z* calculated for $C_{22}H_{34}N_5O_4S$ [M+H$^+$] 464.2333; found, 464.2323.

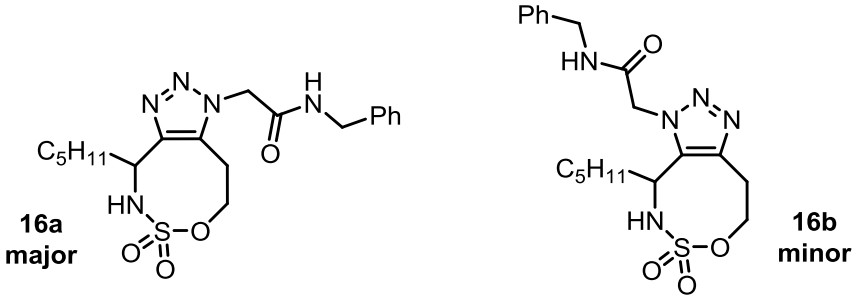


Triazoles 8a and 8b from 8. The triazoles **8a** and **8b** were prepared from alkyne **8** (12 mg, 0.063 mmol). The resulting compounds were obtained as a clear oil (20 mg, 0.061 mmol) as a mixture of regioisomers (**8a:8b** 3.3:1) in quantitative yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.45 – 7.29 (m, 4.5H), 7.23 – 7.16 (m, 2H), 6.36 (minor, d, J = 6.6 Hz, 0.30H), 6.27 (major, d, J = 9.1 Hz, 1H), 5.64 – 5.47 (m, 2.6H), 4.62 (ddd, J = 9.5, 5.8, 4.1 Hz, 1.3H), 4.53 (minor, ddd, J = 11.9, 7.2, 1.5 Hz, 0.3H), 4.22 (major, dt, J = 12.2, 5.1 Hz, 1H), 4.13 – 4.01 (m, 1.3H), 3.97 (major, dd, *J* = 11.5, 5.9 Hz, 1H), 3.92 (major, ddd, *J* = 12.1, 9.5, 4.7 Hz, 1H),3.75 – 3.58 (m, 1H), 3.40 (major, ddd, J = 16.5, 9.5, 5.3 Hz, 1H), 3.16 – 3.06 (m, 1H), 3.03 (major, dt, J = 16.5, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 145.29, 136.64, 136.36 131.62, 129.95, 129.85, 129.72, 129.36, 129.24, 129.13, 128.13, 128.04, 69.53 (minor), 68.33 (major), 64.27 (major), 63.41, 55.28, 53.79, 52.79, 52.41, 24.94 (minor), 23.05 (major). HRMS (ESI) *m/z* calculated for $C_{13}H_{17}N_4O_4S$ [M+H$^+$] 325.0965; found, 325.0959.

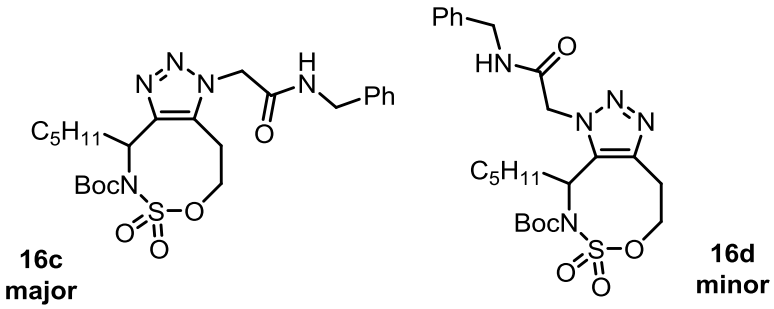
VIII. Reactions of cycloalkynes with azidoacetamide 16.



General Procedure. The cyclic alkyne (1 equiv) was dissolved in CH_3CN (0.1 M) and azidoacetamide[4] **16** (1.1 equiv) was added to the resulting solution. The reaction was stirred for 1 h to ensure full conversion by TLC, then the volatiles were removed under reduced pressure. The resulting oil was dissolved in a minimum volume of CH_2Cl_2, the solvent was again removed under reduced pressure and the triazole products were characterized without further purification.



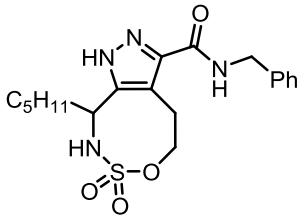
Triazoles 16a and 16b from reaction of 16 with 5. The triazoles **16a** and **16b** were prepared from cycloalkyne **5** (10 mg, 0.044 mmol). A mixture was obtained (20.0 mg, 0.061 mmol) as a clear oil as a mixture of regioisomers (**16a:16b** 2.2:1) in quantitative yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.29 – 7.21 (m, 3H), 7.18 (dt, *J* = 7.5, 2.0 Hz, 4.25H), 5.02 – 4.89 (m, 2.9H), 4.53 (minor, dd, *J* = 10.1, 3.3 Hz, 0.45H), 4.44 (major, dd, *J* = 9.6, 4.6 Hz, 1H), 4.41 – 4.36 (minor, m, 0.45H), 4.32 – 4.24 (m, 3.4H), 4.19 (major, ddd, *J* = 11.9, 9.3, 4.6 Hz, 1H), 4.00 (minor, td, *J* = 11.7, 5.8 Hz, 0.45H), 3.77 (minor, s, 0.9H), 3.52 (minor, ddd, *J* = 15.3, 11.5, 6.8 Hz, 0.45H), 3.31 (major, ddd, *J* = 16.5, 9.4, 5.2 Hz, 1H), 3.03 (minor, ddd, *J* = 15.3, 5.8, 2.2 Hz, 0.45H), 2.94 (major, dt, *J* = 16.5, 4.8 Hz, 1H), 2.20 – 2.00 (m, 1.45H), 1.78 – 1.64 (m, 1H), 1.54 (minor, dtd, *J* = 14.8, 9.8, 5.3 Hz, 0.45H), 1.48 – 1.04 (m, 5H), 0.79 (ddd, *J* = 14.6, 8.9, 6.8 Hz, 4.4H). ^{13}C NMR (126 MHz, CD_3CN) δ 166.48 (major), 166.41(minor), 147.11, 140.20, 139.50, 139.46, 137.70, 131.88, 129.46, 129.40, 128.44, 128.39, 128.17, 128.16, 70.15 (minor), 68.91 (minor), 52.63 (minor), 52.03, 52.00, 51.25 (major), 50.75 (minor), 43.86 (major), 34.42 (major), 34.14 (minor), 31.99, 31.72, 26.10, 25.82 (major), 24.98, 23.20, 23.18 (major), 23.11, 14.28, 14.25. HRMS (ESI) *m/z* calculated for $C_{19}H_{26}N_5O_4S$ [M-H$^-$] 420.1711; found, 420.1712.



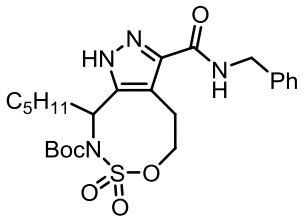
Triazoles 16c and 16d from reaction of 16 with 6. The triazoles **16c** and **16d** were prepared from alkyne **6** (16 mg, 0.048 mmol). The resulting mixture was obtained as a clear oil (25 mg, 0.048 mmol) as a mixture of regioisomers (**16c:16d** 2.2:1) in quantitative yield. ^{1}H NMR (500 MHz, CD_3CN) δ 7.39 – 7.23 (m, 4.25H), 7.20 (ddd, *J* = 14.4, 7.9, 1.6 Hz, 3H), 6.80 (major, t, *J* = 5.8 Hz, 1H), 6.33 (minor, t, *J* = 5.9 Hz, 0.45H), 5.65 (minor, dd, *J* = 9.6, 6.0 Hz, 0.45H), 5.50 (major, dd, *J* = 10.5, 4.9 Hz, 1H), 5.26 (minor, d, *J* = 16.6 Hz, 0.45H), 5.15 (minor, d, *J* = 16.6 Hz, 0.45H), 4.99 (major, d, *J* = 16.2 Hz, 1H), 4.92 (major, d, *J* = 16.2 Hz, 1H), 4.72 (minor, ddd, *J* = 11.1, 9.1, 3.4 Hz, 0.45H), 4.62 (minor, dt, *J* = 11.1, 4.2 Hz, 0.45H), 4.55 – 4.43 (m, 2H), 4.43 – 4.30 (m, 2.9H), 3.37 – 3.22 (minor, m, 1H), 3.20 – 3.05 (major, m, 2H), 2.46 (ddq, *J* = 14.6, 9.6, 4.9, 4.1 Hz, 1H), 2.31 (dtd, *J* = 15.0, 10.2, 5.1 Hz, 1H), 1.53 (minor, s, 6H), 1.49 (major, s, 9H), 1.43 – 1.32 (m, 3H), 1.32 – 1.18 (m, 3H), 0.96 – 0.80 (m, 4.35H). ^{13}C NMR (126 MHz, CD_3CN) δ 166.62, 164.99, 151.85, 150.84, 146.48, 142.14, 137.50, 137.26, 134.67, 130.40, 128.93, 128.91, 128.86, 127.94, 127.93, 127.89, 86.43 (minor), 85.54 (major), 74.46 (minor), 70.45 (major), 57.12 (major), 53.27 (minor), 52.77, 51.29, 43.92, 43.58, 32.18, 31.68, 31.44, 31.14, 27.94, 26.83, 26.09, 25.54, 23.13, 22.60, 22.50, 14.12, 14.05. HRMS (ESI) *m/z* calculated for $C_{24}H_{36}N_5O_6S$ [M+H$^+$] 522.2381; found, 522.2375.

IX. Reactions of cycloalkynes with diazoacetamide 17.

General Procedure. The cyclic alkyne (1 equiv) was dissolved in CH_3CN (0.1 M). To the resulting solution was added *N*-benzyl-2-diazoacetamide **17** (1.1 equiv). The reaction was stirred for 1 h to ensure full conversion, then the volatiles removed under reduced pressure. The resulting oil was dissolved in a minimum volume of CH_2Cl_2, then solvent was again removed under reduced pressure and the diazole products characterized without further purification.



Diazole 17a from reaction of 17 with 5. The diazole **17a** was prepared from cycloalkyne **5** (10 mg, 0.044 mmol). The product was obtained (14 mg, 0.033 mmol) as a clear oil as a single regioisomer in 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.40 – 7.21 (m, 5H), 5.38 (d, J = 9.0 Hz, 1H), 4.63 – 4.45 (m, 2H), 4.43 – 4.29 (m, 2H), 3.50 (t, J = 6.4 Hz, 2H), 1.82 (ddtt, J = 23.3, 14.1, 9.4, 5.4 Hz, 2H), 1.55 – 1.17 (m, 6H), 0.94 – 0.79 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 162.77, 138.11, 137.86, 128.85, 127.79, 127.68, 127.03, 115.62, 72.34, 49.53, 43.15, 33.06, 31.28, 25.45, 22.55, 21.33, 14.08. HRMS (ESI) *m/z* calculated for $C_{19}H_{27}N_4O_4S$ [M+H$^+$] 407.1748; found, 407.1739.

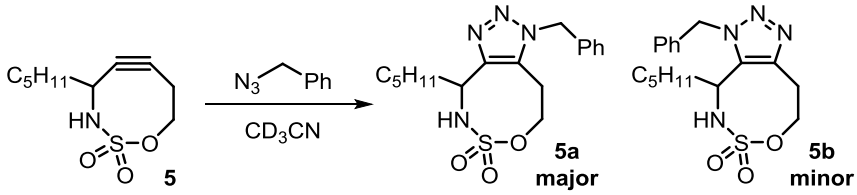


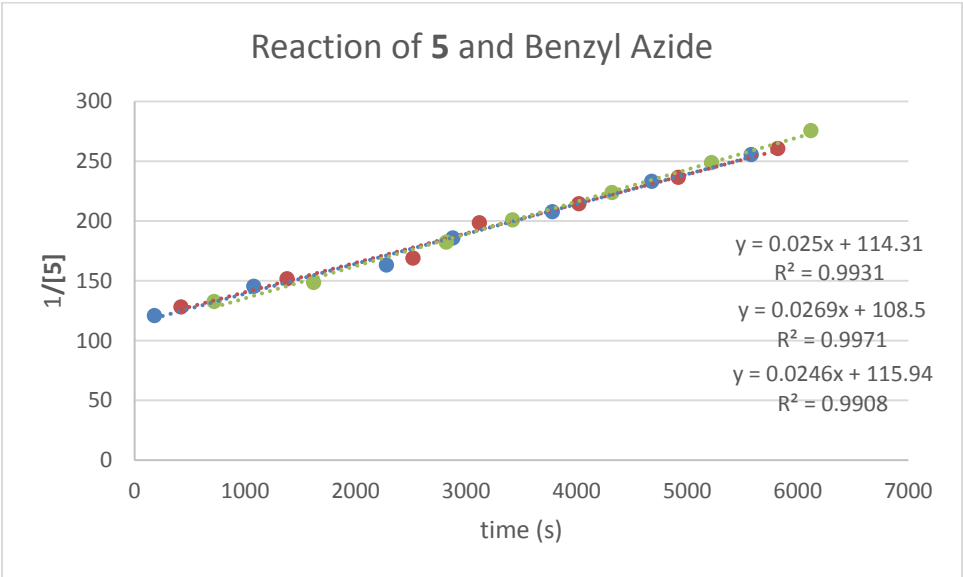
Diazole 17c from reaction of 17 with 6. The diazole **17c** was prepared from the cycloalkyne **6** (16 mg, 0.048 mmol). The product was obtained (24 mg, 0.047 mmol) as a clear oil as a single regioisomer in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.37 – 7.21 (m, 5H), 5.38 (dd, J = 10.0, 5.7 Hz, 1H), 4.63 (ddd, J = 11.5, 6.4, 2.2 Hz, 1H), 4.53 (d, J = 6.1 Hz, 2H), 4.49 (ddd, J = 11.5, 9.3, 1.9 Hz, 1H), 3.90 (ddd, J = 16.8, 6.4, 1.8 Hz, 1H), 3.27 (ddd, J = 16.8, 9.2, 2.3 Hz, 1H), 2.36 (dtd, J = 13.3, 10.0, 5.1 Hz, 1H), 2.15 – 2.03 (m, 1H), 1.50 (s, 9H), 1.39 – 1.22 (m, 6H), 0.91 – 0.86 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 162.98, 150.97, 138.24, 128.78, 128.73, 127.95, 127.71, 127.55, 116.27, 85.58, 75.35, 54.76, 42.99, 31.40, 30.93, 27.99,

27.92, 25.58, 22.61, 22.50, 14.05. HRMS (ESI) *m/z* calculated for $C_{24}H_{35}N_4O_6S$ [M+H$^+$] 507.2272; found, 507.2264.

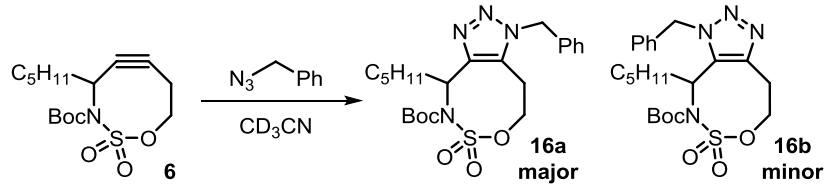
X. Kinetic data for the reactions of 5-8 with benzyl azide.

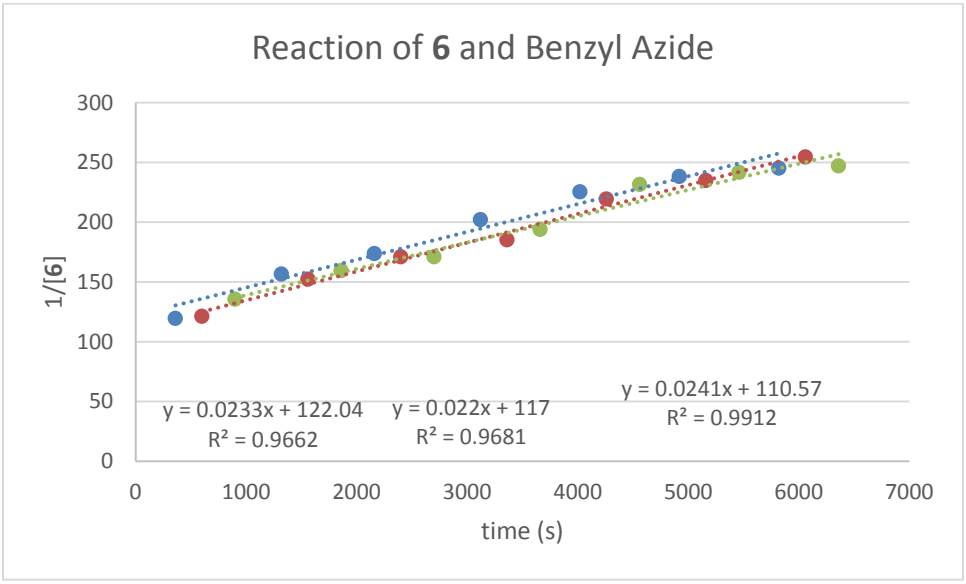
General Procedure. A stock solution of cycloalkyne (0.02 M) and a stock solution of benzyl azide and mesitylene (0.02 M with respect to both solutes) were combined in equal volumes in a small cuvette, then rapidly mixed. The resulting solution was transferred to an NMR tube and the reaction progress was monitored by ^{1}H-NMR at 25 °C, with spectra taken once every 15 min over the course of several hours. The k_2 values were determined by measuring the decrease in cycloalkyne signal integrations which were standardized relative to the mesitylene standard. Inverse concentration of cycloalkyne was plotted against time, and the points were fitted by linear regression. The slope of the resulting line corresponded to the k_2 value. Each experiment was run in triplicate and the k_2 values for each trial were averaged.



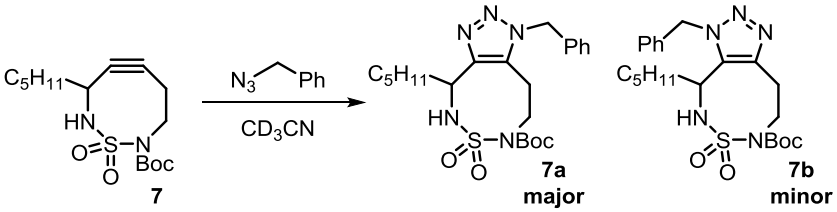


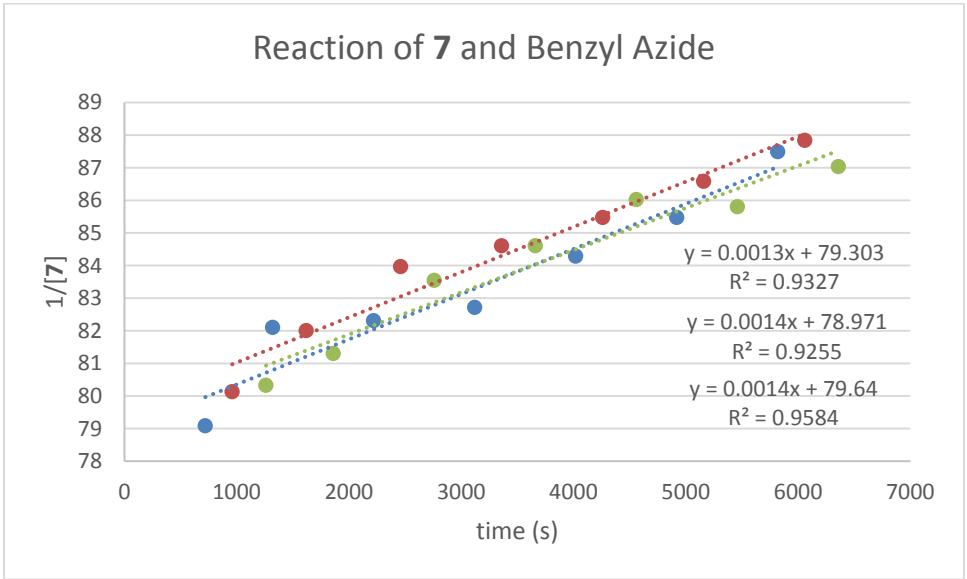
k_2=0.026±0.001M^{-1}s^{-1}



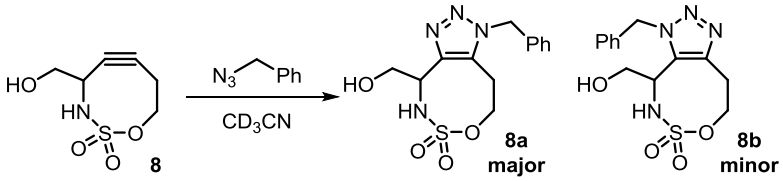


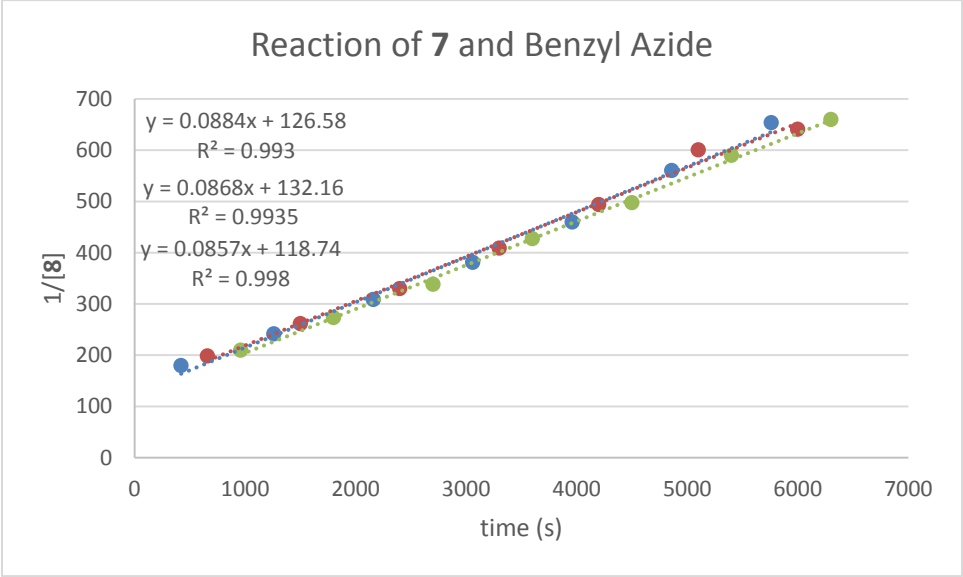
k_2=0.023±0.0009 $M^{-1}s^{-1}$





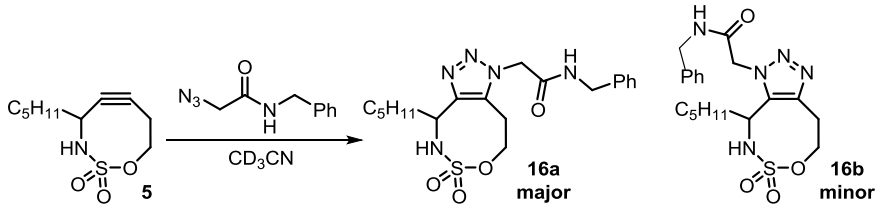
k_2=0.0014±0.00005 $M^{-1}s^{-1}$

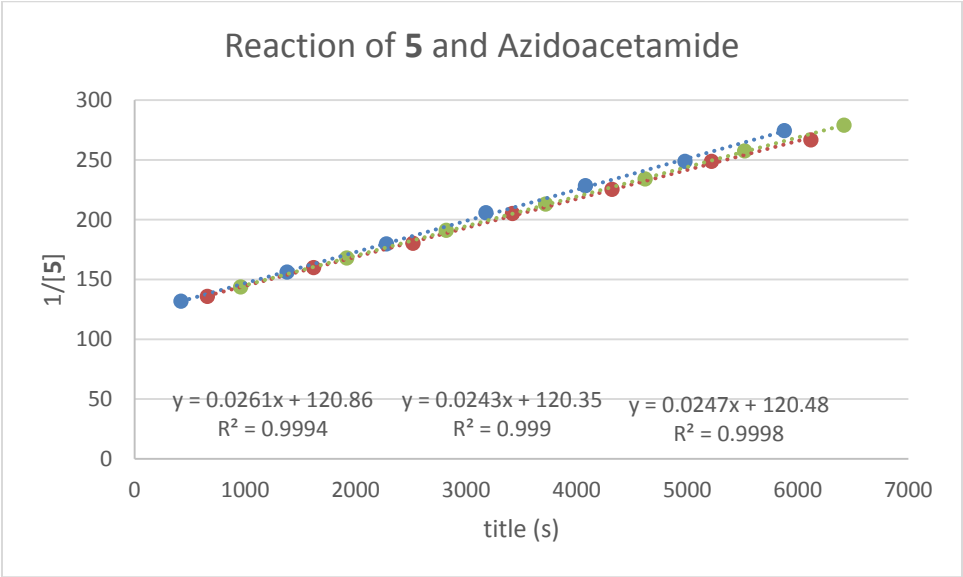




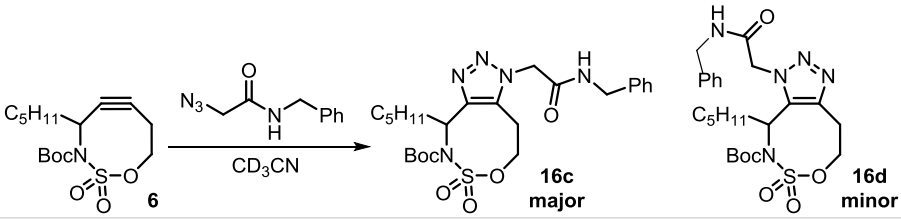
k_2=0.087±0.001 $M^{-1}s^{-1}$

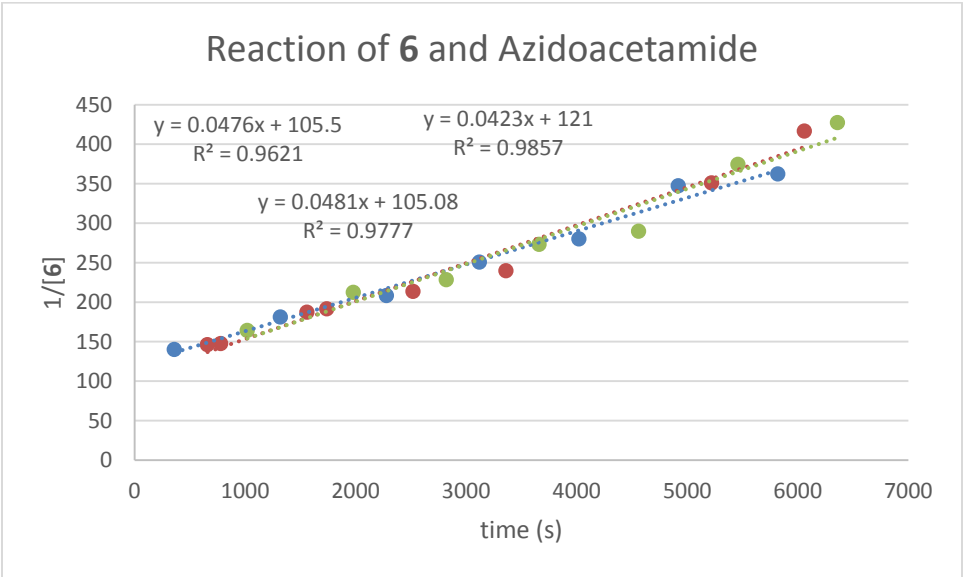
XI. Kinetic data for the reaction of 5 and 6 with azidoacetamide.





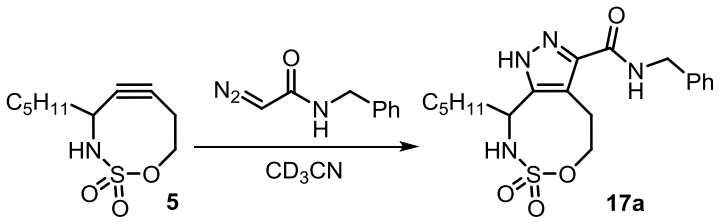
k_2=0.025±0.0008 $M^{-1}s^{-1}$

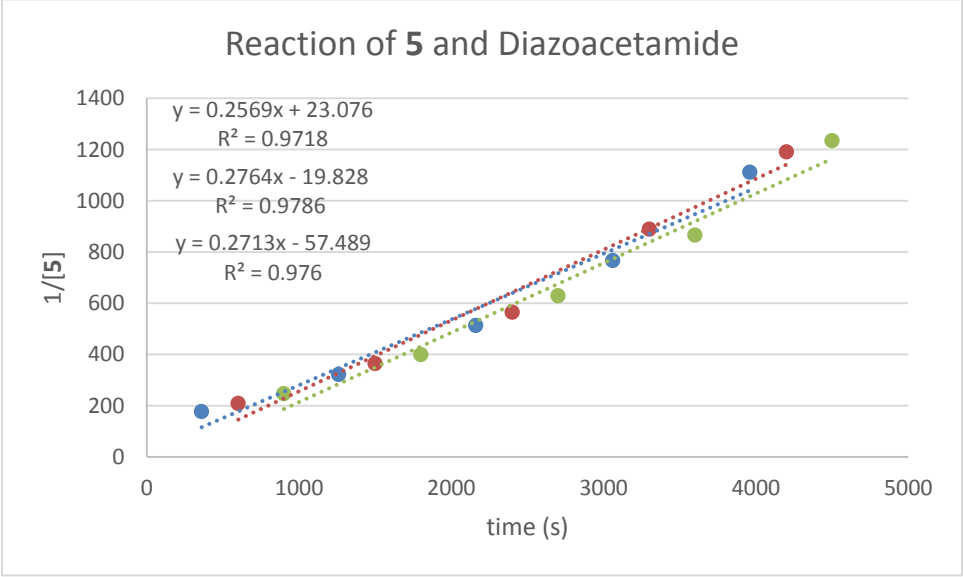




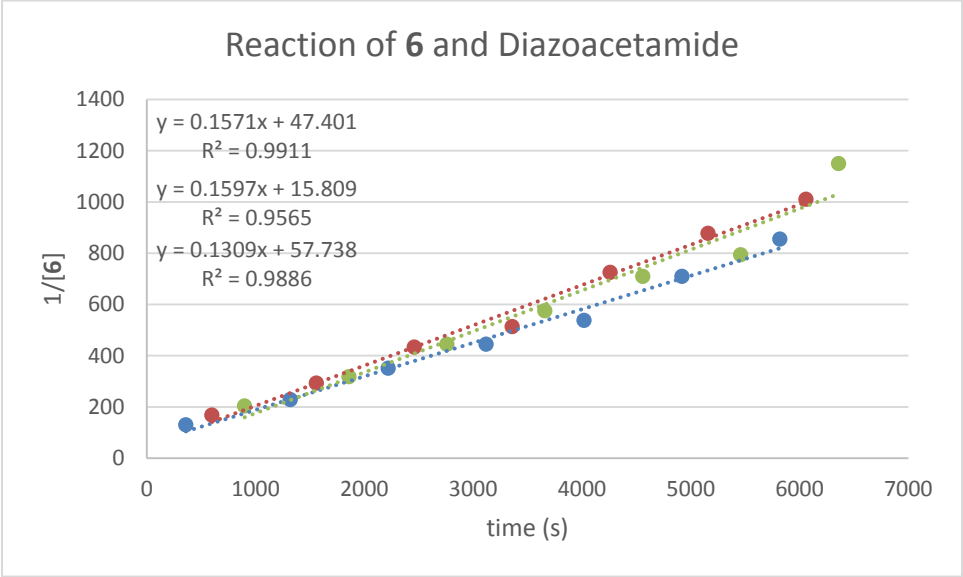
k_2=0.046±0.003 $M^{-1}s^{-1}$

XII. Kinetic data for the reaction of 5 and 6 with diazoacetamide.



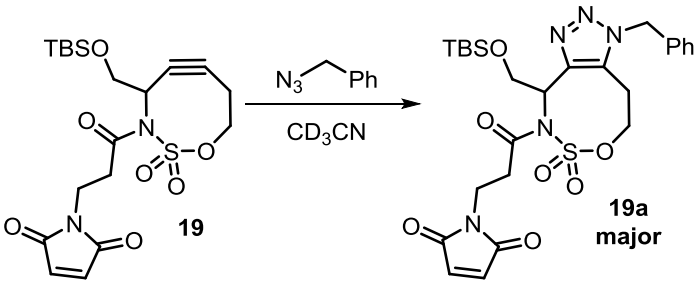


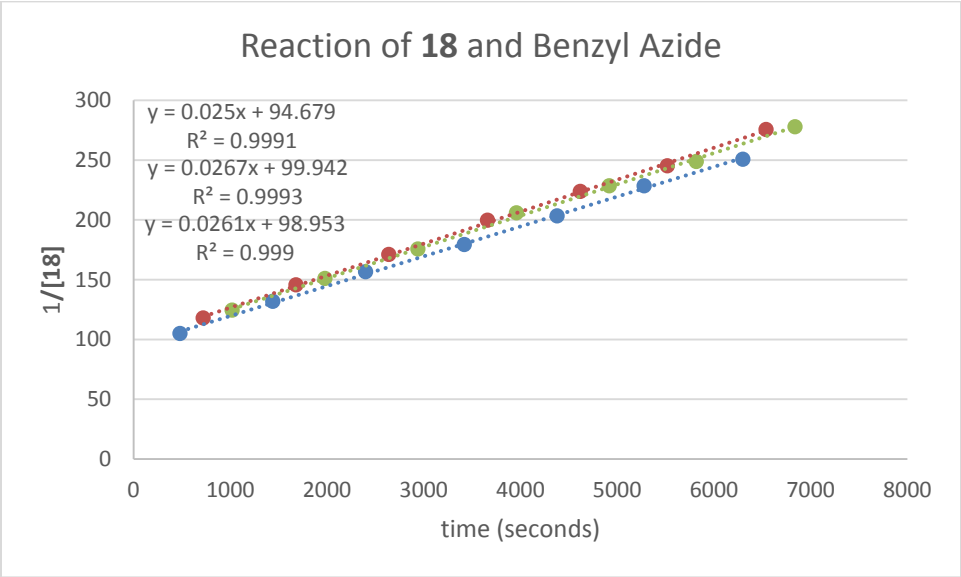
k_2=0.27±0.008 $M^{-1}s^{-1}$



k_2=0.15±0.01 $M^{-1}s^{-1}$

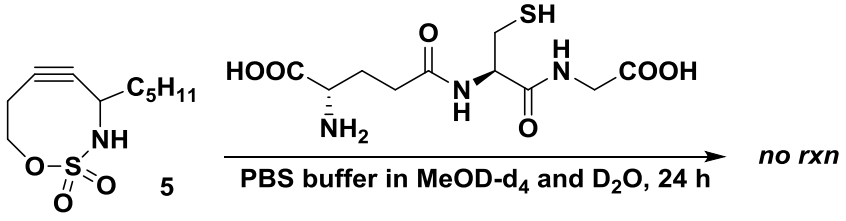
XIII. Kinetic data for the reaction of 19 with benzyl azide.





k_2=0.026±0.0007 $M^{-1}s^{-1}$

XIV. Reaction of glutathione with 5. An issue with DIFO and related strained cycloalkynes is competing reaction with thiol nucleophiles in biological systems. To test whether our new SNO-OCT **5** are stable to sulfur nucleophiles, **5** was incubated with a 0.15 M solution of glutathione in pH 7 phosphate-buffered saline and the reaction monitored by ^{1}H NMR spectroscopy over 24 h. No reaction was noted.



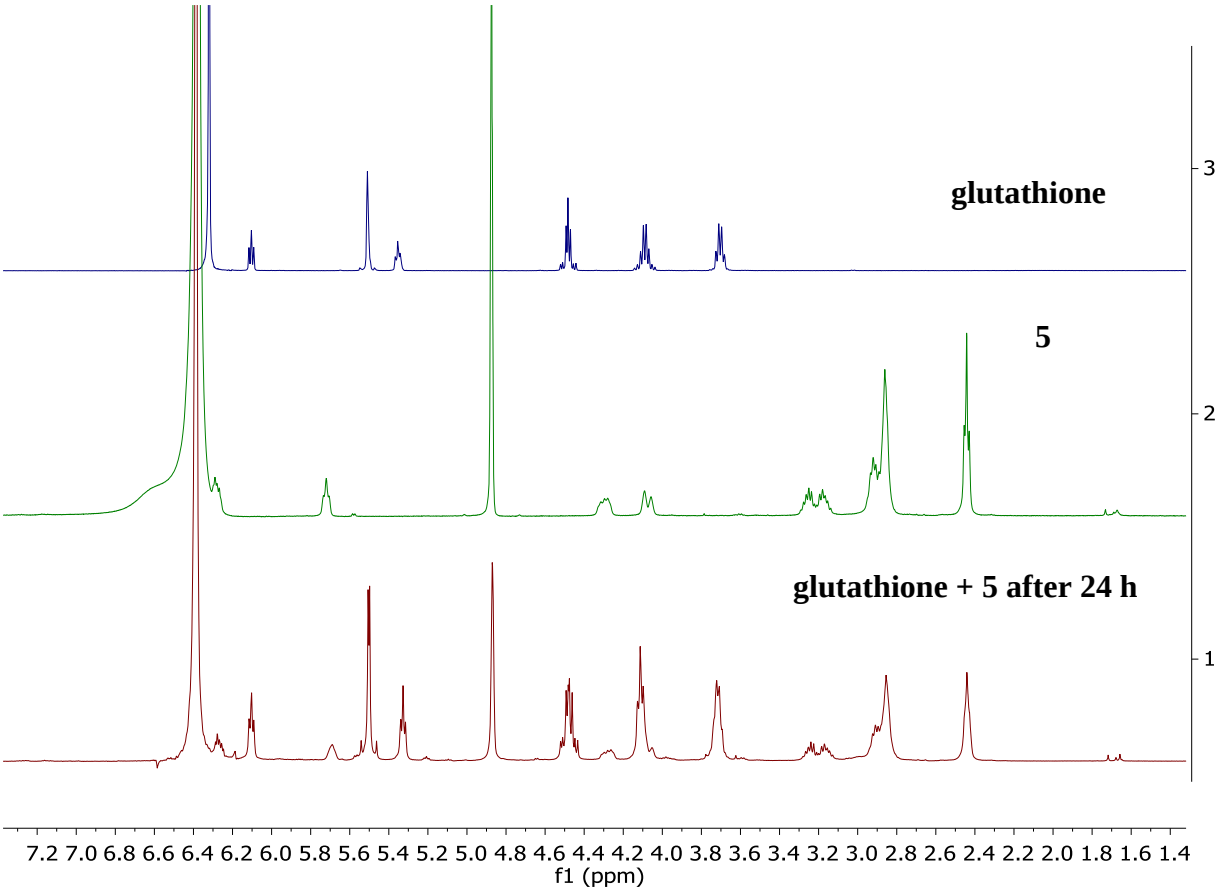
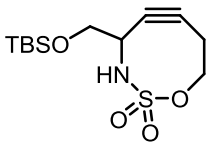


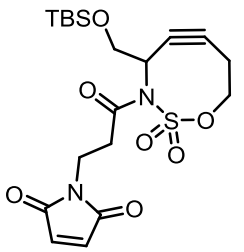
Figure S1. NMR spectra of glutathione, **5** and a mixture of glutathione and **5** at rt for 24 h.

XV. Bioconjugation Studies.

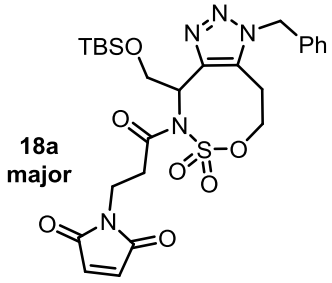


Compound 18. Cyclic alkyne **18** was prepared from the corresponding homoallenic sulfamate (300 mg, 0.79 mmol) following the general procedure from Section V. The general procedure was adapted to use 1 equiv of 1 M TBAF in THF to minimize deprotection of the tethered alcohol in addition to the desilylation and ring expansion process. The crude product was purified via column chromatography (0% EtOAc/hexanes to 20% EtOAc/hexanes, gradient) to yield pure alkyne (69 mg, 0.29 mmol) as a white solid in 29% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, *J* = 6.7 Hz, 1H), 4.94 (td, *J* = 10.9, 4.1 Hz, 1H), 4.64 (ddd, *J* = 11.0, 5.5, 2.4 Hz, 1H), 4.29 (dtt, *J* = 6.7, 4.3, 2.4 Hz, 1H), 3.79 – 3.62 (m, 2H), 2.81 (dddd, *J* = 16.9, 10.7, 5.4, 2.8 Hz, 1H), 2.38 (ddt, *J* = 16.9, 4.3, 2.2 Hz, 1H), 0.91 (s, 8H), 0.10 (d, *J* = 6.9 Hz, 6H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 99.96, 94.24, 76.24, 62.56, 50.81, 25.95, 21.90, 18.49, -5.18. HRMS (ESI) *m/z* calculated for $C_{12}H_{23}NO_4SSi$ [M-H^+] 304.1044; found, 304.1044.



Compound 19. Compound **18** (20 mg, 0.066 mmol) was dissolved in CH_2Cl_2 (0.3 M). To this solution was added sodium hydroxide (4.2 mg, 0.10 mmol), and benzyltriethylammonium chloride (1.5 mg, 0.007 mmol). The suspension was stirred cooled to 0 °C under a N_2 atmosphere at which point 3-maleimidopropropionyl chloride (14 mg, 0.075 mmol) in CH_2Cl_2 (0.6 M) was added dropwise. The reaction was stirred at 0 °C until TLC indicated complete consumption of starting materials. The solution was diluted with an equal volume of hexanes, then filtered through a small celite pad. Filtrate was concentrated *via* rotary evaporation. The crude product was purified *via* column chromatography (0% EtOAc/hexanes to 25% EtOAc/hexanes, gradient) to yield pure alkyne **18** (17 mg, 0.036 mmol) as a white solid in 55% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 2H), 5.62 (td, *J* = 7.4, 2.9 Hz, 1H), 5.05 (ddd, *J* = 12.4, 11.0, 4.0 Hz, 1H), 4.67 (dd, *J* = 11.1, 6.1 Hz, 1H), 3.99 – 3.88 (m, 3H), 3.83 (ddd, *J* = 14.3, 8.9, 5.6 Hz, 1H), 3.29 (ddd, *J* = 17.6, 8.9, 5.9 Hz, 1H), 3.08 (ddd, *J* = 17.6, 8.9, 5.6 Hz, 1H), 2.95 (dddd, *J* = 17.2, 12.4, 6.2, 3.0 Hz, 1H), 2.34 (dd, *J* = 17.2, 4.0 Hz, 1H), 0.88 (s, 9H), 0.07 (d, *J* = 1.3 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 170.92, 170.50, 134.40, 94.59, 94.41, 75.85, 63.14, 52.59, 36.13, 33.94, 25.91, 21.85, 18.34, 1.17, 0.15, -5.19. HRMS (ESI) *m/z* calculated for $C_{19}H_{28}N_2NaO_7SSi$ [M+Na^+] 479.1279; found 479.1276.



Triazole 18a from 18. The triazole **18a** was prepared from alkyne **18** (13 mg, 0.027 mmol) following the general procedure from Section VII. The resulting compounds were obtained as a white solid (18 mg, 0.027 mmol) as a single regioisomer in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 3H), 7.06 – 6.94 (m, 2H), 6.57 (s, 2H), 5.76 (m, 1H), 5.51 (d, *J* =

15.8 Hz, 1H), 5.38 (d, *J* = 15.8 Hz, 1H), 4.54 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.22 (t, *J* = 10.3 Hz, 1H), 3.97 (dt, *J* = 12.0, 4.6 Hz, 1H), 3.75 (ddt, *J* = 12.9, 8.4, 4.2 Hz, 3H), 3.21 – 2.98 (m, 2H), 2.88 (t, *J* = 5.1 Hz, 2H), 0.83 – 0.76 (m, 9H), -0.01 (d, *J* = 5.5 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 170.76, 170.47, 143.73, 134.79, 134.38, 129.52, 128.98, 128.80, 127.04, 70.05, 61.36, 56.91, 52.53, 35.51, 33.65, 25.88, 23.04, 18.19, 0.15, -5.33, -5.44. HRMS (ESI) *m/z* calculated for $C_{26}H_{36}N_5O_7SSi$ [$M+H^+$] 590.2099; found, 590.2101.

Semisynthesis of RNase 1 conjugates. DNA fragment encoding human P19C RNase 1 was inserted into the pET22b expression vector from Addgene (Cambridge, MA) for tagless expression in *Escherichia coli* strain BL21(DE3). The production and purification of P19C RNase 1 was performed as described previously.[5] A SNO-OCT–RNase 1 conjugate was prepared by reaction of P19C RNase 1 with 15-fold molar excess of SNO-OCT **19** in 0.10 M Tris–HCl buffer, pH 8.0, containing DMSO (5% v/v) for 3 h at ambient temperature. Purification using a HiTrap SP HP cation-exchange column (GE Healthcare, Chicago, IL) afforded the desired conjugate. Next, a biotin–RNase 1 conjugate was prepared by reaction of SNO-OCT–RNase 1 with a 5-fold molar excess of azide-PEG3-biotin (Sigma–Aldrich, St. Louis, MO) in phosphate-buffered saline containing DMSO (5% v/v) for 2 h at ambient temperature. Purification using monomeric avidin agarose (Pierce, Waltham, MA) afforded the desired conjugate. The molecular mass of each protein conjugate was confirmed by MALDI–TOF mass spectrometry using a Voyager instrument (Applied Biosystems).

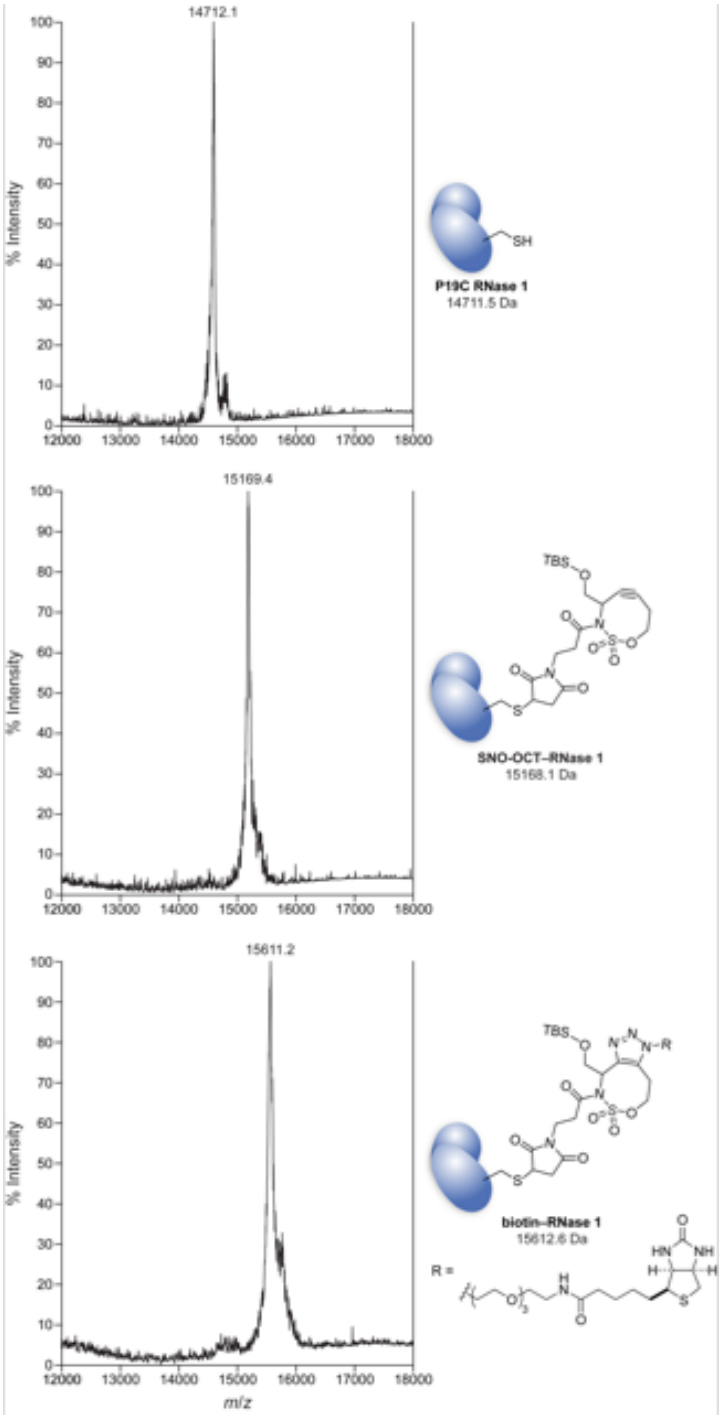
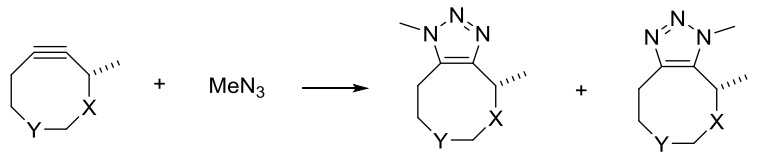


Figure S2. MALDI–TOF spectra of P19C RNase 1 (top), the SNO-OCT–RNase 1 conjugate (middle), and the biotin-RNase 1 conjugate (bottom).

XVI. Computational details.

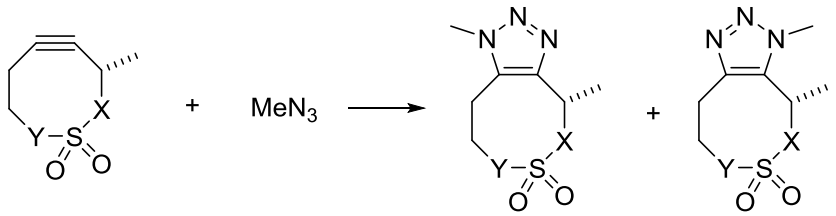
Optimizations were performed with Gaussian 09 software[6] at the M06-2X level of theory[7] and the 6-311+G(d,p) basis set. M06-2X has been shown to describe trends in reactivity accurately for cycloadditions.[8] Optimizations were performed utilizing IEFPCM dielectric continuum solvent model for water with UFF radii.[9] Frequency calculations were performed to confirm stationary points as minima or first-order saddle points. All ΔE and $\Delta E^{\ddagger}$ values include zero-point corrections.

Table S1. Energies and free energies of activation (kcal/mol) for cycloadditions of methyl azide with alkynes of various substitution patterns. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). CT = NBO charge on the dipole (initial charge—0 or +1—minus CT resides on alkyne).



		Regioisomer 1			Regioisomer 2			Regioselectivity (Regio. 2 – 1)	
X	Y	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta G^{\ddagger}$
CH_2	CH_2	14.5	26.3	0.020	13.7	26.4	0.015	–0.8	0.1
NH	CH_2	13.1	25.0	0.033	13.1	25.1	0.027	0.0	0.1
NH_2^+	CH_2	11.3	23.7	0.091	12.2	24.5	0.079	0.9	0.8
O	CH_2	11.8	23.9	0.053	12.5	24.5	0.045	0.7	0.6
CH_2	O	12.8	24.8	0.035	12.3	24.5	0.028	–0.5	–0.3
CH_2	NH	13.4	25.2	0.027	12.8	24.9	0.021	–0.6	–0.3
CH_2	NH_2^+	13.3	25.5	0.061	12.4	24.6	0.059	–0.9	–0.9

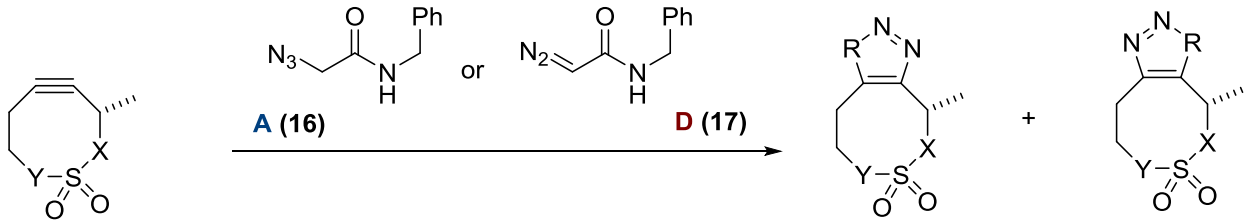
Table S2. Free energies of activation (kcal/mol) of the lowest energy TSs for each regioisomeric cycloaddition of methyl azide with alkynes of various substitution patterns. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). CT = NBO charge on the dipole (initial charge—0, +1, or +2—minus CT resides on alkyne). Bold signifies compounds synthesized and tested experimentally (with benzyl azide).



		Regioisomer 1			Regioisomer 2			Regioselectivity (Regio. 2 –1)	
X	Y	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta G^{\ddagger}$
CH_2	CH_2	15.5	27.0	0.042	15.3	27.9	0.034	–0.2	0.9
NH	CH_2	13.6	25.4	0.059	14.1	26.7	0.047	0.5	1.3

NH_2^+	CH_2	12.8	25.1	0.102	14.4	26.7	0.084	1.6	1.6
O	CH_2	11.7	23.7	0.080	13.5	26.1	0.066	1.8	2.4
CH_2	O	13.0	24.9	0.059	13.1	25.7	0.050	0.1	0.8
CH_2	NH	14.0	25.6	0.049	14.2	26.8	0.040	0.2	1.2
CH_2	NH_2^+	14.5	26.5	0.077	14.1	26.6	0.072	–0.4	0.1
NH	NH	12.4	24.4	0.064	13.2	25.8	0.052	0.8	1.4
NH	**O**	**11.2**	**23.0**	**0.076**	**12.1**	**24.7**	**0.064**	**0.9**	**1.7**
NH	NH_2^+	11.8	23.8	0.097	12.1	24.7	0.088	0.3	0.9
O	NH	10.9	23.1	0.086	12.7	25.4	0.069	1.8	2.3
O	O	9.4	21.4	0.101	11.2	23.7	0.083	1.8	2.3
O	NH_2^+	9.2	21.5	0.135	11.1	23.8	0.111	1.9	2.3
NH_2^+	NH	11.1	23.1	0.108	13.1	25.6	0.089	2.0	2.5
NH_2^+	O	9.5	21.5	0.126	11.7	24.2	0.107	2.2	3.7
NH_2^+	NH_2^+	10.4	22.5	0.155	12.5	25.3	0.128	2.1	2.8
NBoc	**O**	**10.7**	**24.9**	**0.080**	**11.0**	**23.8**	**0.075**	**0.3**	**–1.1**

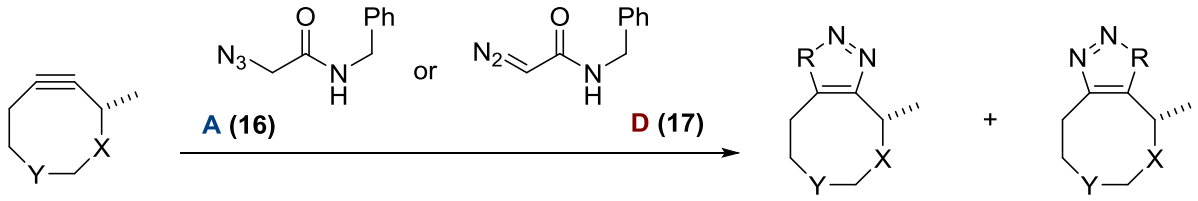
Table S3. Free energies of activation (kcal/mol) of the lowest energy TSs for each regioisomeric cycloaddition of diazoacetamide (R = CHCONHMe) and azidoacetamide (R = $NCH_2CONHMe$) with alkynes of various substitution patterns. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). CT = NBO charge on the dipole (initial charge—0, +1, or +2—minus CT resides on alkyne). Bold signifies compounds synthesized and tested experimentally.



		Diazo			Azide			Diazo			Azide			Regioselect.–$\Delta\Delta G^‡$		Chemoselect.	
X	Y	$\Delta E^‡$	$\Delta G^‡$	CT	$\Delta E^‡$	$\Delta G^‡$	CT	$\Delta E^‡$	$\Delta G^‡$	CT	$\Delta E^‡$	$\Delta G^‡$	CT	Diazo	Azide	$\Delta\Delta E^‡$	$\Delta\Delta G^‡$
CH_2	CH_2	15.4	26.9	0.108	15.3	27.2	0.031	15.6	27.9	0.100	15.1	28.0	0.026	1.0	0.8	–0.3	0.3
NH	CH_2	13.5	25.8	0.125	13.5	25.6	0.050	14.2	26.8	0.112	13.9	27.0	0.038	1.0	1.4	0.0	–0.2
NH_2^+	CH_2	11.8	23.2	0.185	12.5	24.0	0.094	13.9	26.4	0.162	14.5	27.6	0.072	3.2	3.6	0.7	0.8
O	CH_2	11.3	21.3	0.152	11.6	24.1	0.074	13.2	25.9	0.131	13.4	26.4	0.056	2.6	2.3	0.3	0.7
CH_2	O	12.8	24.7	0.122	13.0	25.6	0.052	12.9	25.0	0.113	12.9	26.0	0.043	0.3	0.4	0.1	0.9
CH_2	NH	13.8	25.0	0.111	14.1	26.6	0.041	14.2	26.3	0.103	13.9	26.7	0.031	1.3	0.1	0.1	1.6
CH_2	NH_2^+	14.3	27.3	0.151	14.5	26.9	0.067	14.2	26.5	0.149	13.7	25.5	0.064	–0.8	–1.4	0.3	–1.0
NH	NH	12.3	24.4	0.134	12.5	25.3	0.059	13.0	25.7	0.116	13.0	26.1	0.04	1.3	0.8	0.2	0.9
NH	**O**	**10.7**	**21.9**	**0.143**	**11.5**	**23.8**	**0.063**	**11.6**	**24.0**	**0.127**	**11.9**	**25.2**	**0.056**	**2.1**	**1.5**	**0.8**	**1.9**
NH	NH_2^+	11.3	23.2	0.174	12.0	24.8	0.087	11.9	24.6	0.161	11.9	24.8	0.079	1.4	0.0	0.6	1.6
O	NH	10.1	21.8	0.156	10.8	23.5	0.080	12.0	24.7	0.134	12.5	25.5	0.059	2.9	2.0	0.7	1.7
O	O	8.4	20.2	0.174	9.4	21.9	0.096	10.3	22.8	0.149	11.1	23.9	0.073	2.6	2.0	1.0	1.7
O	NH_2^+	7.9	19.9	0.227	9.3	21.8	0.127	10.3	23.2	0.180	11.0	24.1	0.102	3.3	2.3	1.4	1.9
NH_2^+	NH	10.6	22.5	0.188	11.3	23.9	0.101	12.5	24.7	0.163	13.0	26.0	0.163	2.2	2.1	0.7	1.4
NH_2^+	O	8.6	20.4	0.208	9.6	23.4	0.119	10.7	23.4	0.180	11.7	25.0	0.094	3.0	1.6	1.0	3.0
NH_2^+	NH_2^+	8.9	21.1	0.265	10.3	23.8	0.142	11.4	24.4	0.218	12.1	25.3	0.218	3.3	1.5	1.4	2.7
NBoc	**O**	**10.1**	**23.1**	**0.144**	**10.6**	**24.1**	**0.074**	**10.4**	**24.0**	**0.140**	**10.4**	**25.0**	**0.068**	**0.9**	**0.9**	**0.3**	**1.0**

Table S4. Energies and free energies of activation (kcal/mol) for cycloadditions of of diazoacetamide (R = CHCONHMe) and azidoacetamide (R = $NCH_2CONHMe$) with alkynes of various substitution patterns. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory

using an IEFPCM solvent model for water (radii = UFF). CT = NBO charge on the dipole (initial charge—0 or +1—minus CT resides on alkyne).



		Diazoacetamide						Azide					
		Regio. 1			Regio. 2			Regio. 1			Regio. 2		
X	Y	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	CT
CH_2	CH_2	14.5	26.5	0.076	14.1	26.1	0.071	14.4	26.8	0.016	13.4	25.9	0.007
NH	CH_2	12.9	24.7	0.091	13.0	25.0	0.083	13.2	25.9	0.023	12.7	25.3	0.019
NH_2^+	CH_2	10.9	23.3	0.163	11.9	24.7	0.147	11.3	23.9	0.081	12.5	25.5	0.067
O	CH_2	11.4	23.6	0.113	12.3	24.6	0.103	11.8	24.4	0.049	12.6	24.8	0.037
CH_2	O	12.7	24.8	0.090	12.6	24.9	0.085	12.9	25.3	0.029	12.1	24.8	0.023
CH_2	NH	13.4	25.5	0.083	13.1	25.2	0.079	13.5	25.9	0.022	12.5	25.0	0.015
CH_2	NH_2^+	13.0	24.8	0.128	12.7	24.8	0.125	13.5	25.9	0.052	12.1	24.9	0.052

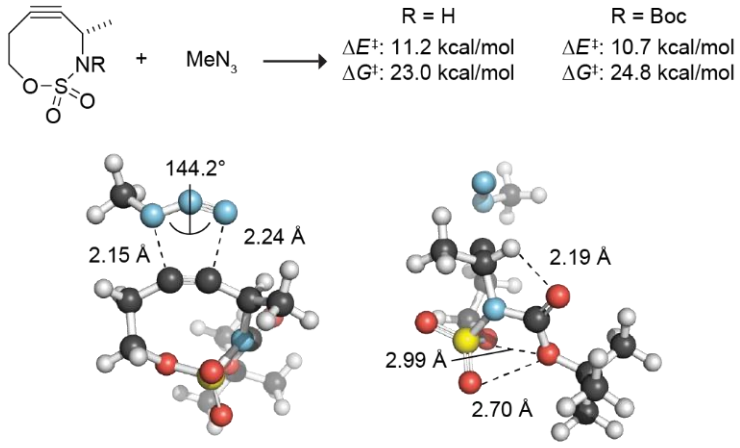


Figure S3. Energies and free energies of activation (kcal/mol, 298 K) for the lowest energy TSs for cycloadditions methyl azide to alkynes **13b** and **13j**. Favorable electronics as a result of the Boc group are outweighed by increased rigidity and a higher $\Delta S^{\ddagger}$. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF).

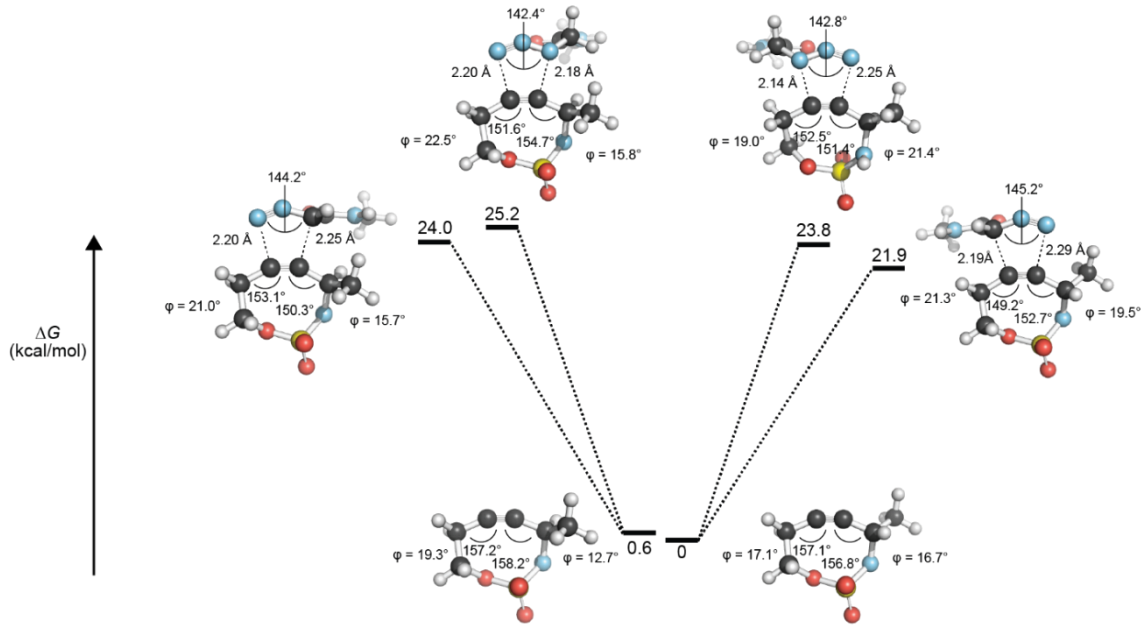
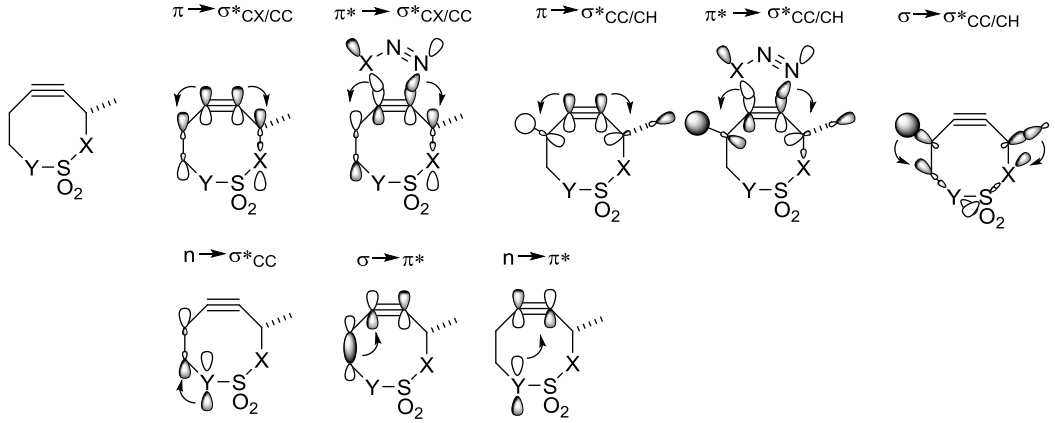


Figure S4. Free energies of activation (kcal/mol, 298 K) for the lowest energy TSs for each regioisomeric cycloaddition of diazo- and azidoacetamide to alkyne **13b**. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). φ is the dihedral angle around the acetylenic C–C bonds (CC–C≡C and C≡C–CN).

Table S5. Second order perturbation energies (kcal/mol) provided by NBO analysis[10] in the starting geometry, the alkyne distorted to the TS geometry in the absence of the dipole, and in the full TS. All values are for the *anti*-TS. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF).



		Int. Orb.	SM	Diazo			Azide			Δ (TS–SM)[c]	
X	Y			TS Geom.	Full TS	Δ (TS–SM)	TS Geom.	Full TS	Δ (TS–SM)	Diazo	Azide
CH_2	CH_2	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	2.27(0.84)[a] /2.47	3.44 /0.84(2.25)[a]	2.42 /1.83(0.60)[a]	–0.73	3.11(0.54)[a] /0.66(2.48)[a]	3.11 /1.80(0.77)[a]	0.1	π/π*→	π/π*→
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	1.23/0.78	2.01	<0.5	2.30/1.61	3.91	3.6	6.3
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	1.23(3.00)[a] /3.38(0.68)[a]	4.47/ <0.5(3.74)[a]	3.03(1.03)[a] /1.68(1.93)[a]	–0.62	4.28/ <0.5(4.00)[a]	2.72(1.07)[a] /1.88(2.07)[a]	–0.55		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.45/0.59	2.04	<0.5	1.39/0.57	1.96		
		$\sigma_{CC}\rightarrow\sigma^*_{XS}$	3.46	3.97	3.89	0.43	3.92	3.94	0.48		

		$\sigma_{CH}\rightarrow\sigma^*_{CY}$	3.52	4.10	3.99	0.47	3.99	3.89	0.37		
		$\sigma_{CH(Y)}\rightarrow\sigma^*_{CC}$	1.33	2.97	2.47	1.14	2.95	2.62	1.29	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CC}\rightarrow\pi^*_{CC}$	7.99	2.73(4.10)[a]	6.88(1.19)[a]	0.08	2.03(4.89)[a]	7.07(1.30)[a]	0.38	1.2	1.7
		Total	30.17	32.61	34.99	4.82	32.85	38.11	7.94		
NH	CH_2	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	5.33 /1.72(1.12)[a]	6.87/ 1.63(1.38)[a]	3.78 /1.96(0.51)[a]	–1.92	6.87/ 1.71(1.29)[a]	5.72(0.52)[a] /1.91	–0.02	$\pi/\pi^*\rightarrow$	$\pi/\pi^*\rightarrow$
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	1.64/1.82	3.46	<0.5	3.85/1.83	5.68	4.1	9.2
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	3.59 /0.75(2.55)[a]	3.98/ 0.94(3.09)[a]	2.60(1.42)[a] /1.51(1.75)[a]	0.39	3.71/ 1.14(2.98)[a]	2.17(1.61)[a] /2.25(1.66)[a]	0.8		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.23/<0.5	1.23	<0.5	1.13/0.71	1.84		
		$\sigma_{CC}\rightarrow\sigma^*_{XS}$	3.81	4.30	4.33	0.52	4.27	4.38	0.57		
		$\sigma_{CH}\rightarrow\sigma^*_{CY}$	3.47	4.06	3.93	0.46	3.95	3.79	0.32		
		$n_X\rightarrow\pi^*_{CC}$	1.55	1.07	0.84	–0.71	1.07	0.83	–0.72	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CH(Y)}\rightarrow\sigma^*_{CC}$	3.88	2.75	2.79	–1.09	2.77	2.54	–1.34	–0.9	–0.4
		$\sigma_{CC}\rightarrow\pi^*_{CC}$	4.51(3.18)[a]	4.66(2.45)[a]	7.73(0.85)[a]	0.89	4.67(2.55)[a]	8.53(0.83)[a]	1.67		
		Total	35.46	37.18	38.69	3.23	36.98	44.26	8.80		
NH_2^+	CH_2	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	7.75 /1.46(1.24)[a]	9.48/ 1.35(1.57)[a]	9.13 /1.62(0.82)[a]	1.12	9.07/ 1.39(1.58)[a]	8.06 /1.58(0.86)[a]	0.05	$\pi/\pi^*\rightarrow$	$\pi/\pi^*\rightarrow$
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	10.82/1.74	12.56	<0.5	8.12/1.66	9.78	16.9	12.3
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	3.42 /0.73(3.37)[a]	3.90/ 0.93(3.36)[a]	2.87(0.90)[a] /1.60(2.32)[a]	0.17	3.69	2.64(0.92)[a] /1.77(2.32)[a]	0.13		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.61/0.60	2.21	<0.5	1.50/<0.5	1.50		
		$\sigma_{CC}\rightarrow\sigma^*_{XS}$	2.86	3.06	3.11	0.25	3.05	3.16	0.30		
		$\sigma_{CH}\rightarrow\sigma^*_{CY}$	3.69	4.38	4.27	0.58	4.34	4.22	0.53		
		$\sigma_{CH(Y)}\rightarrow\sigma^*_{CC}$	2.72	2.79	2.74	0.02	2.91	2.86	0.14	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CC}\rightarrow\pi^*_{CC}$	4.78(3.41)[a]	4.63(2.53)[a]	7.01(1.29)[a]	0.11	4.46(2.69)[a]	7.16(1.44)[a]	0.41	0.1	0.5
		Total	35.43	37.98	52.45	17.02	37.46	48.27	12.84		
O	CH_2	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	9.14 /1.91(0.76)[a]	10.27/ 1.78(1.14)[a]	9.73 /1.84(0.58)[a]	0.34	10.23/ 1.82(1.08)[a]	9.48 /1.79(0.53)[a]	–0.01	$\pi/\pi^*\rightarrow$	$\pi/\pi^*\rightarrow$
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	10.15/1.84	11.99	<0.5	8.10/1.78	9.88	13.6	11.0
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	3.11(0.94)[a] /0.87(2.96)[a]	3.68(0.59)[a] /0.91(3.05)[a]	2.62(1.30)[a] /1.35(2.22)[a]	–0.39	3.42(0.68)[a] /0.97(3.00)[a]	2.29(1.45)[a] /1.46(2.10)[a]	–0.58		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.32/<0.5	1.32	<0.5	1.20/<0.5	1.20		
		$\sigma_{CC}\rightarrow\sigma^*_{XS}$	2.98	3.01	2.89	–0.09	3.02	3.08	0.10		
		$\sigma_{CH}\rightarrow\sigma^*_{CY}$	3.52	4.09	3.97	0.45	3.98	3.89	0.37		
		$n_X\rightarrow\pi^*_{CC}$	1.07	0.80	0.70	–0.37	0.79	0.67	–0.40	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CH(Y)}\rightarrow\sigma^*_{CC}$	2.77	2.79	2.75	–0.02	2.79	2.75	–0.02	0.1	0.6
		$\sigma_{CC}\rightarrow\pi^*_{CC}$	6.20(2.07)[a]	5.50(1.86)[a]	7.79(0.93)[a]	0.45	5.49(1.99)[a]	8.33(0.99)[a]	1.05		
		Total	38.30	39.47	51.98	13.68	39.26	49.89	11.59		
CH_2	O	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	1.29 /2.54(0.53)[a]	3.78/ 1.70(1.58)[a]	2.51 /1.88	0.03	3.70/ 2.19(1.07)[a]	3.27 /1.98(0.68)[a]	1.57	$\pi/\pi^*\rightarrow$	$\pi/\pi^*\rightarrow$
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	1.66/0.80	2.46	<0.5	2.43/1.68	4.11	4.9	8.2
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	2.02(1.14)[a] /2.02(1.87)[a]	4.29/ 1.14(3.07)[a]	2.64(1.24)[a] /2.03(1.29)[a]	0.15	3.67(0.75)[a] /1.77(2.46)[a]	2.65(1.25)[a] /2.24(1.81)[a]	0.90		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	0.83/0.56	1.39	<0.5	1.26/0.67	1.93		
		$\sigma_{CC}\rightarrow\sigma^*_{XS}$	3.49	3.89	3.92	0.43	3.83	3.15	–0.34		
		$\sigma_{CH}\rightarrow\sigma^*_{CY}$	5.04	5.66	5.44	0.40	5.44	5.03	–0.01		
		$n_Y\rightarrow\sigma^*_{CC}$	5.93	5.42	3.77	–2.16	5.49	5.35	–0.58	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CC}\rightarrow\pi^*_{CC}$	6.98(1.32)[a]	4.34(2.66)[a]	7.58(0.89)[a]	0.17	5.46(1.84)[a]	7.90(1.18)[a]	0.78	–2.0	0.2
		Total	34.17	37.53	37.04	2.87	37.67	42.53	8.36		
CH_2	NH	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	3.05 /2.53(0.51)[a]	3.63/ 1.17(2.05)[a]	3.53 /1.86(0.88)[a]	0.18	3.54/ 2.21(1.00)[a]	3.30 /1.88(0.74)[a]	–0.17	$\pi/\pi^*\rightarrow$	$\pi/\pi^*\rightarrow$
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	2.87/1.64	4.51	<0.5	2.32/1.72	4.04	6.9	5.8
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	2.96(1.41)[a] /2.19(1.95)[a]	4.57/ 0.75(3.42)[a]	3.19(0.90)[a] /1.69(1.92)[a]	–0.81	3.57(0.84)[a] /2.09(2.17)[a]	2.68(1.16)[a] /2.33(1.74)[a]	–0.60		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.49/0.67	2.16	<0.5	1.36/0.71	2.07		
		$\sigma_{CC}\rightarrow\sigma^*_{XS}$	3.51	3.93	3.93	0.42	3.85	3.68	0.17		
		$\sigma_{CH}\rightarrow\sigma^*_{CY}$	4.49	5.09	4.94	0.45	4.97	4.82	0.33		
		$n_Y\rightarrow\sigma^*_{CC}$	9.96	8.39	8.59	–1.37	8.42	8.40	–1.56	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CC}\rightarrow\pi^*_{CC}$	6.99(1.40)[a]	3.46(3.74)[a]	7.03(1.52)[a]	0.16	5.67 (1.78)[a]	7.81(1.36)[a]	0.78	–1.2	–0.78
		Total	40.95	40.20	46.65	5.70	40.11	46.01	5.06		
CH_2	NH_2^+	Endocyclic $\pi_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	1.74(1.56)[a] 3.00	3.78/ 1.46(2.02)[a]	3.85 /2.22(0.69)[a]	0.46	3.64/ 1.47(2.06)[a]	3.51 /2.14(0.73)[a]	0.08	$\pi/\pi^*\rightarrow$	$\pi/\pi^*\rightarrow$
		$\pi^*_{CC}\rightarrow\sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	3.27/1.96	5.23	<0.5	2.78/1.85	4.63	8.9	7.8
		Exocyclic[b] $\pi_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5(3.93)[a] /3.52	4.48/ 0.53(3.52)[a]	2.86(1.26)[a] 1.57(1.99)[a]	0.23	4.28/ <0.5(3.62)[a]	2.59(1.25)[a] /1.56(2.28)[a]	0.23		
		$\pi^*_{CC}\rightarrow\sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.45/0.53	1.98	<0.5	1.39/0.52	1.91		

		$\sigma_{CC} \rightarrow \sigma^*_{XS}$	4.34	4.65	4.58	0.24	4.63	4.70	0.36		
		$\sigma_{CH} \rightarrow \sigma^*_{CY}$	5.11	6.09	5.87	0.76	5.87	5.67	0.56		
		$\sigma_{NH(Y)} \rightarrow \sigma^*_{CC}$	1.24	1.32	1.74	0.50	1.32	1.67	0.43	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$\sigma_{CC} \rightarrow \pi^*_{CC}$	7.19	3.46(2.81)[a]	6.51(0.85)[a]	0.17	3.32(3.13)[a]	6.80(1.02)[a]	0.63	0.7	1.1
		Total	31.63	34.12	41.20	9.57	33.34	40.46	8.83		
NH	O	Endocyclic $\pi_{CC} \rightarrow \sigma^*_{CX}/\sigma^*_{CC}$	6.53 /1.95(0.99)[a]	7.17/ 1.93(1.27)[a]	6.34(0.67)[a] /2.19	–0.27	7.12/ 1.99(1.18)[a]	6.10(0.72)[a] /2.12	–0.53	$\pi/\pi^* \rightarrow$	$\pi/\pi^* \rightarrow$
		$\pi^*_{CC} \rightarrow \sigma^*_{CX}/\sigma^*_{CC}$	<0.5	<0.5	4.62/2.00	6.62	<0.5	3.71/1.94	5.65	8.3	6.7
		Exocyclic[b] $\pi_{CC} \rightarrow \sigma^*_{CH}/\sigma^*_{CC}$	3.59(0.72)[a] /1.04(2.99)[a]	3.92(0.52)[a] /1.32(2.82)[a]	2.29(1.73)[a] /2.26(1.46)[a]	–0.60	3.77(1.18)[a] /1.39(2.77)[a]	2.00(1.93)[a] /2.36(1.38)[a]	–0.67		
		$\pi^*_{CC} \rightarrow \sigma^*_{CH}/\sigma^*_{CC}$	<0.5	<0.5	1.06/0.78	1.84	<0.5	0.96/0.63	1.59		
		$\sigma_{CC} \rightarrow \sigma^*_{XS}$	3.80	4.09	4.09	0.29	4.09	4.12	0.32		
		$\sigma_{CH} \rightarrow \sigma^*_{CY}$	4.95	5.59	5.41	0.46	5.48	5.25	0.30		
		$n_X \rightarrow \pi^*_{CC}$	1.33	1.06	0.65	–0.68	1.05	0.78	–0.55	$\rightarrow\pi^*$	$\rightarrow\pi^*$
		$n_Y \rightarrow \sigma^*_{CC}$	5.71	5.38	5.24	–0.47	5.46	5.36	–0.35	–0.93	0.2
		$\sigma_{CC} \rightarrow \pi^*_{CC}$	5.98(2.67)[a]	4.99(2.22)[a]	8.27(0.60)[a]	0.22	5.34(2.25)[a]	9.22(0.57)[a]	1.14		
		Total	42.25	42.28	49.66	7.41		49.15	6.9		

[a] Donation from/to both in plane and (out of plane) π-bonds. [b] Double hyperconjugation/induction: Values given for exocyclic C–H and C–C bonds that are antiperiplanar to X–S and C–Y bonds. [c] Δ (TS – SM) provided as both a sum of interactions that increase the electrophilicity of the alkyne ($\pi/\pi^* \rightarrow$) and a sum of interactions that increase the nucleophilicity of the alkyne ($\rightarrow\pi^*$).

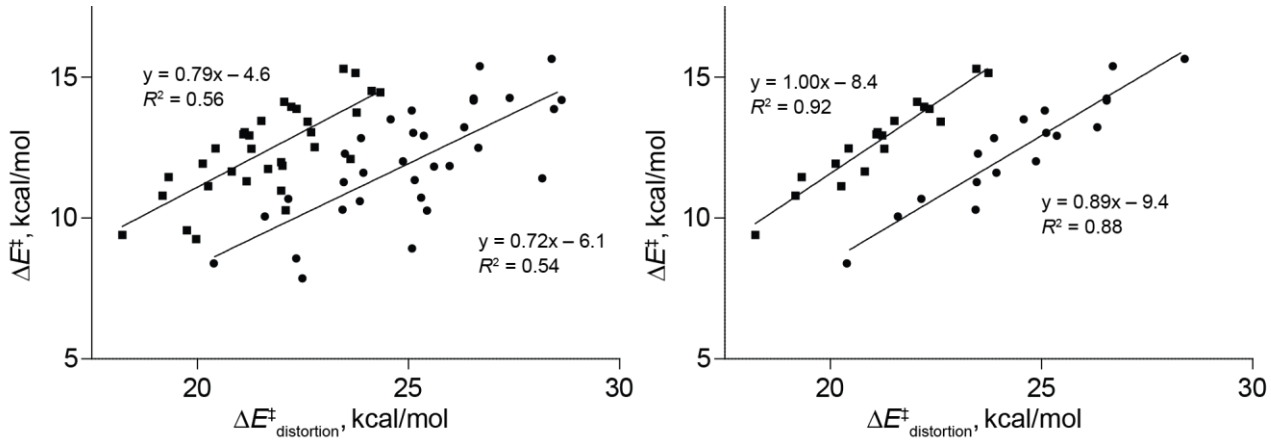


Figure S5. Plots of activation energies versus distortion energies split by the diazoacetamide (circles) and azidoacetamide (squares) for all cycloadditions from Table S3 (left) and removing charged alkynes (right).

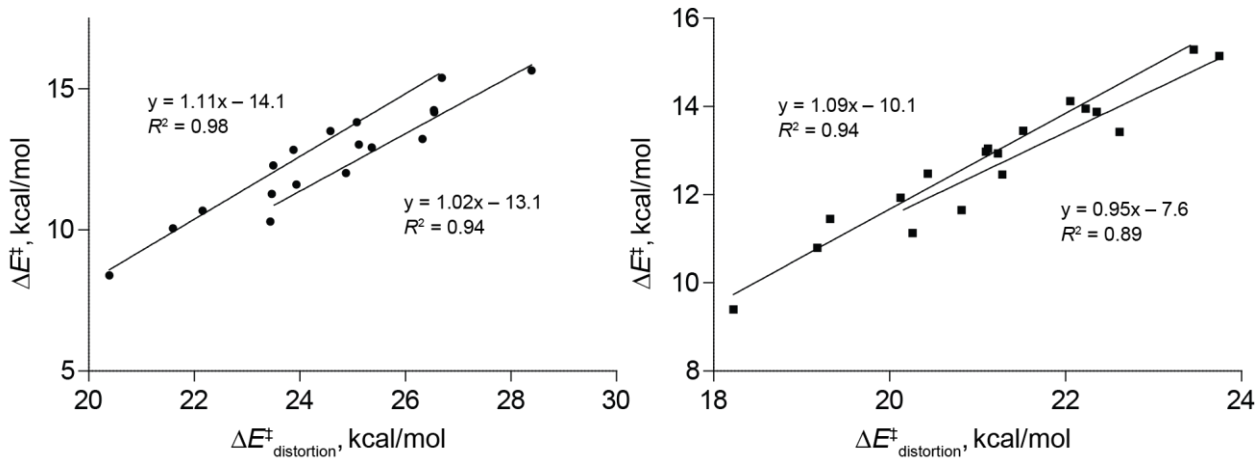


Figure S6. Plots of activation energies versus distortion energies for each of the dipoles from Figure S2 (right). Each dipole is further split into each regioisomeric transition state for the diazoacetamide (left) and azidoacetamide (right).

Table S6. Distortion/interaction analysis for cycloadditions of methyl azide with alkynes of various substitution patterns (from Table S2). Calculated at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). Energies in kcal/mol.

		Regio. 1					Regio. 2				
X	Y	$\Delta E^{\ddagger}_{dist.}$ (dipole)	$\Delta E^{\ddagger}_{dist}$ (alkyne)	$\Delta E^{\ddagger}_{dist}$ total	$\Delta E^{\ddagger}_{int.}$	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{dist.}$ (dipole)	$\Delta E^{\ddagger}_{dist}$ (alkyne)	$\Delta E^{\ddagger}_{dist}$ total	$\Delta E^{\ddagger}_{int.}$	$\Delta E^{\ddagger}$
CH_2	CH_2	19.2	4.4	23.6	–8.1	15.5	19.2	4.5	23.7	–8.4	15.3
NH	CH_2	17.9	3.9	21.8	–8.2	13.6	17.9	3.9	21.8	–7.7	14.1
NH_2^+	CH_2	18.1	5.0	23.1	–10.3	12.8	19.6	5.0	24.6	–10.1	14.4
O	CH_2	17.1	3.7	20.9	–9.2	11.7	18.3	4.3	22.6	–9.1	13.5
CH_2	NH	18.2	4.0	22.2	–8.2	14.0	18.1	4.1	22.2	–8.0	14.2
CH_2	O	17.8	3.4	21.2	–8.2	13.0	17.7	3.5	21.2	–8.1	13.1
CH_2	NH_2^+	19.5	4.8	24.3	–9.8	14.5	19.4	4.5	23.9	–9.9	14.1
NH	NH	17.1	3.4	20.5	–8.0	12.4	17.5	3.7	21.2	–7.9	13.2
NH	O	16.6	2.9	19.5	–8.3	11.2	17.1	3.0	20.1	–8.0	12.1
NH	NH_2^+	18.0	4.3	22.4	–10.6	11.8	18.4	3.5	22.0	–9.9	12.1
O	NH	16.2	3.1	19.3	–8.4	10.9	17.2	4.1	21.3	–8.6	12.7
O	O	15.5	2.7	18.3	–8.9	9.4	16.8	3.5	20.2	–9.1	11.2
O	NH_2^+	16.4	3.9	20.2	–11.0	9.2	18.0	4.1	22.1	–11.0	11.1
NH_2^+	NH	17.0	4.2	21.2	–10.0	11.1	18.2	4.5	22.8	–9.7	13.1
NH_2^+	O	16.1	3.8	19.9	–10.4	9.5	17.5	4.3	21.8	–10.1	11.7
NH_2^+	NH_2^+	17.5	4.5	22.0	–11.6	10.4	19.7	4.2	23.9	–11.4	12.5

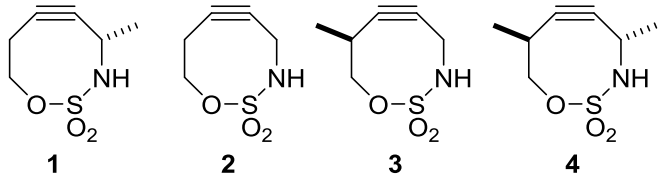
Table S7. Distortion/interaction analysis for cycloadditions of diazoacetamide with alkynes of various substitution patterns (from Table S3). Calculated at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). Energies in kcal/mol.

		Regio. 1					Regio. 2				
X	Y	$\Delta E^{\ddagger}_{dist.}$ (dipole)	$\Delta E^{\ddagger}_{dist}$ (alkyne)	$\Delta E^{\ddagger}_{dist}$ total	$\Delta E^{\ddagger}_{int.}$	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{dist.}$ (dipole)	$\Delta E^{\ddagger}_{dist}$ (alkyne)	$\Delta E^{\ddagger}_{dist}$ total	$\Delta E^{\ddagger}_{int.}$	$\Delta E^{\ddagger}$
CH_2	CH_2	20.9	5.8	26.7	–11.3	15.4	22.1	6.3	28.4	–12.7	15.6
NH	CH_2	19.7	4.9	24.6	–11.1	13.5	21.1	5.4	26.5	–12.3	14.2
NH_2^+	CH_2	19.4	6.2	25.6	–13.8	11.8	21.7	6.7	28.4	–14.6	13.9
O	CH_2	18.5	5.0	23.5	–12.2	11.3	20.7	5.6	26.3	–13.1	13.2
CH_2	NH	19.9	5.2	25.1	–11.3	13.8	20.8	5.8	26.5	–12.4	14.2
CH_2	O	19.4	4.5	23.9	–11.0	12.8	20.4	5.0	25.4	–12.4	12.9
CH_2	NH_2^+	21.2	6.2	27.4	–13.1	14.3	22.0	6.6	28.6	–14.4	14.2
NH	NH	18.5	5.0	23.5	–11.2	12.3	19.9	5.2	25.1	–12.1	13.0
NH	**O**	18.0	4.1	22.2	–11.5	10.7	19.4	4.5	23.9	–12.3	11.6
NH	NH_2^+	19.6	5.6	25.1	–13.8	11.3	20.8	5.1	26.0	–14.1	11.9
O	NH	17.4	4.2	21.6	–11.5	10.1	19.6	5.3	24.9	–12.9	12.0
O	O	16.6	3.8	20.4	–12.0	8.4	18.8	4.6	23.4	–13.1	10.3
O	NH_2^+	17.2	5.3	22.5	–14.6	7.9	20.0	5.4	25.4	–15.2	10.3
NH_2^+	NH	18.2	5.7	23.9	–13.2	10.6	20.4	6.2	26.7	–14.2	12.5
NH_2^+	O	17.1	5.2	22.3	–13.8	8.6	19.5	5.8	25.3	–14.6	10.7
NH_2^+	NH_2^+	18.0	7.1	25.1	–16.2	8.9	21.2	6.9	28.2	–16.8	11.4

Table S8. Distortion/interaction analysis for cycloadditions of azidoacetamide with alkynes of various substitution patterns (from Table S3). Calculated at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF). Energies in kcal/mol.

		Regio. 1					Regio. 2				
X	Y	$\Delta E^{\ddagger}_{dist.}$ (dipole)	$\Delta E^{\ddagger}_{dist}$ (alkyne)	$\Delta E^{\ddagger}_{dist}$ total	$\Delta E^{\ddagger}_{int.}$	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{dist.}$ (dipole)	$\Delta E^{\ddagger}_{dist}$ (alkyne)	$\Delta E^{\ddagger}_{dist}$ total	$\Delta E^{\ddagger}_{int.}$	$\Delta E^{\ddagger}$
CH_2	CH_2	19.3	4.2	23.5	–8.2	15.3	19.5	4.2	23.7	–8.6	15.1
NH	CH_2	17.8	3.7	21.5	–8.1	13.5	18.7	3.7	22.4	–8.5	13.9
NH_2^+	CH_2	17.9	4.9	22.8	–10.3	12.5	19.5	4.8	24.3	–9.9	14.5
O	CH_2	17.2	3.6	20.8	–9.2	11.6	18.5	4.1	22.6	–9.2	13.4
CH_2	NH	18.2	3.9	22.1	–7.9	14.1	18.3	3.9	22.2	–8.3	13.9
CH_2	O	17.8	3.3	21.1	–8.1	13.0	17.8	3.4	21.2	–8.3	12.9
CH_2	NH_2^+	19.5	4.6	24.1	–9.6	14.5	19.5	4.3	23.8	–10.0	13.7
NH	NH	16.9	3.5	20.4	–8.0	12.5	17.6	3.5	21.1	–8.1	13.0
NH	**O**	16.5	2.8	19.3	–7.9	11.5	17.1	3.0	20.1	–8.2	11.9
NH	NH_2^+	17.9	4.1	22.0	–10.0	12.0	18.6	3.4	22.0	–10.2	11.9
O	NH	16.2	3.0	19.2	–8.4	10.8	17.4	3.9	21.3	–8.8	12.5
O	O	15.6	2.6	18.2	–8.8	9.4	16.9	3.4	20.3	–9.1	11.1
O	NH_2^+	16.3	3.7	20.0	–10.7	9.3	18.1	3.9	22.0	–11.0	11.0
NH_2^+	NH	17.0	4.1	21.2	–9.9	11.3	18.3	4.4	22.7	–9.7	13.0
NH_2^+	O	16.2	3.6	19.8	–10.2	9.6	17.5	4.2	21.7	–9.9	11.7
NH_2^+	NH_2^+	17.5	4.6	22.1	–11.8	10.3	19.6	4.1	23.6	–11.5	12.1

Table S9. Energies and free energies of activation (kcal/mol) for cycloadditions of diazoacetamide to alkynes of various substitution patterns. Geometries optimized at the M06-2X/6-311+G(d,p) level of theory using an IEFPCM solvent model for water (radii = UFF).



1 **2** **3** **4**

	Regio. 1		Regio. 2	
Y	$\Delta E^{‡}$	$\Delta G^{‡}$	$\Delta E^{‡}$	$\Delta G^{‡}$
1	10.7	21.9	11.5	23.8
2	10.1	22.0	10.8	23.6
3	10.8	23.7	11.0	23.6
4	11.8	24.5	11.6	24.7

XVII. References.

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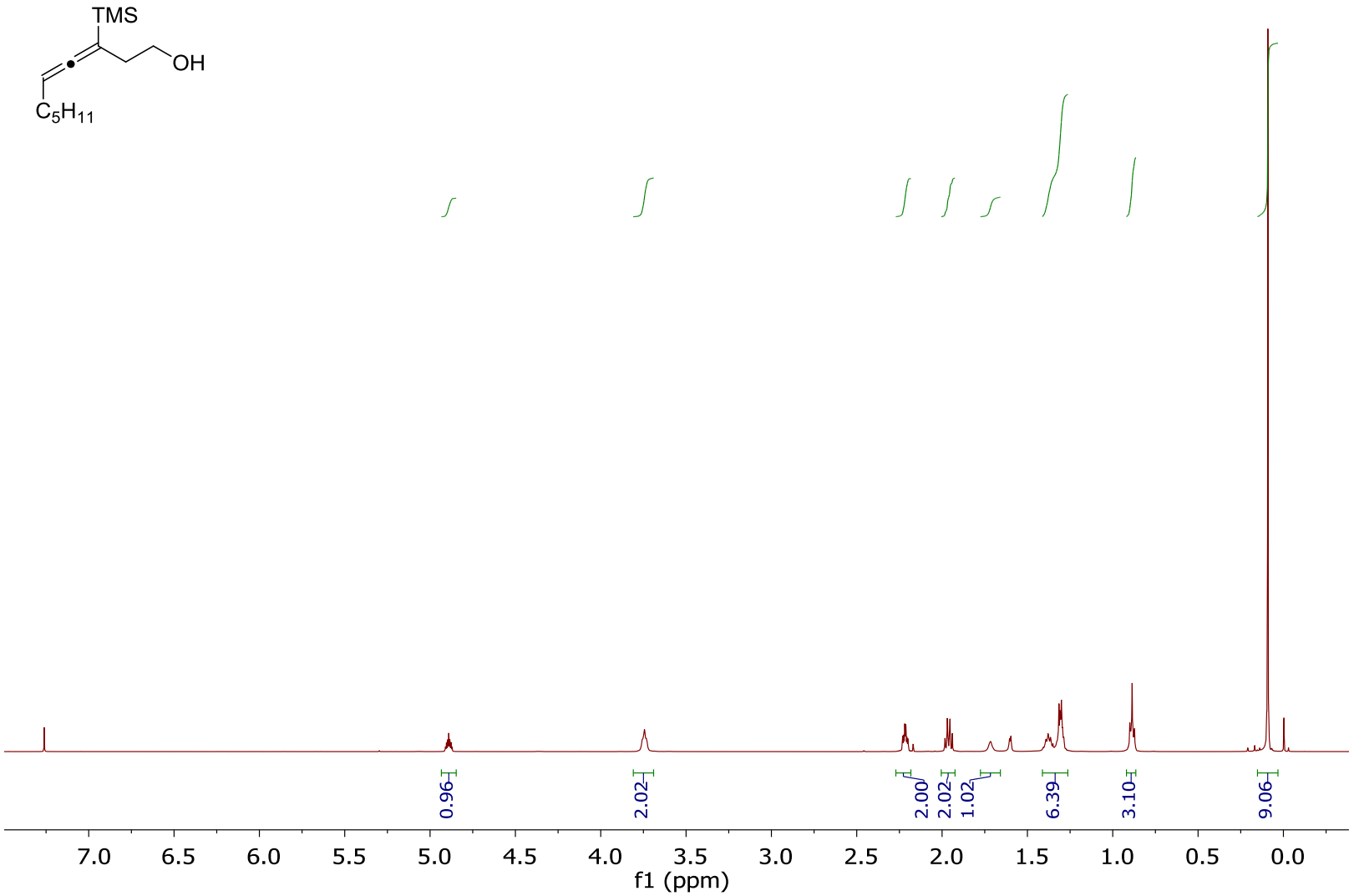
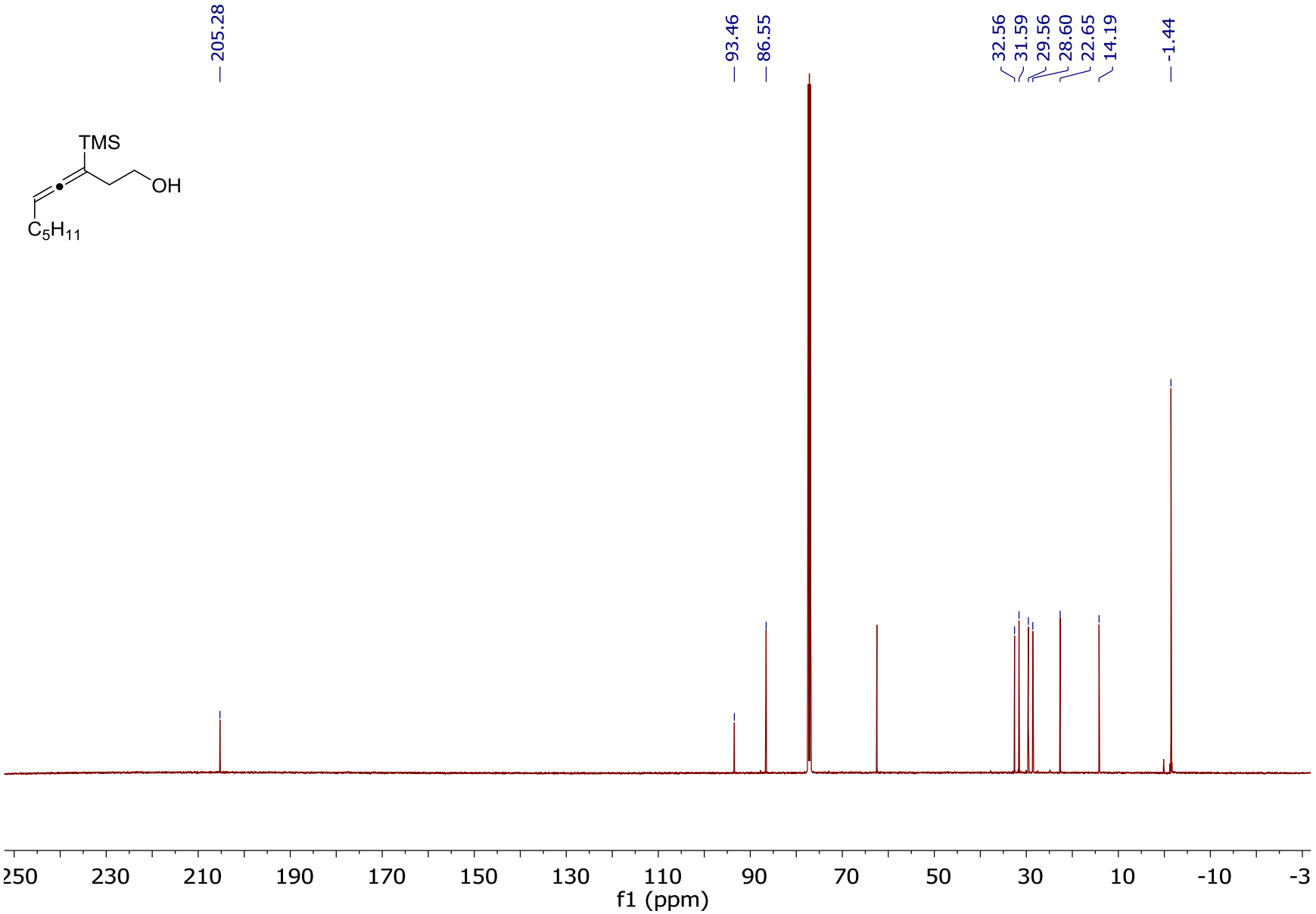
XVIII. NMR Spectra.

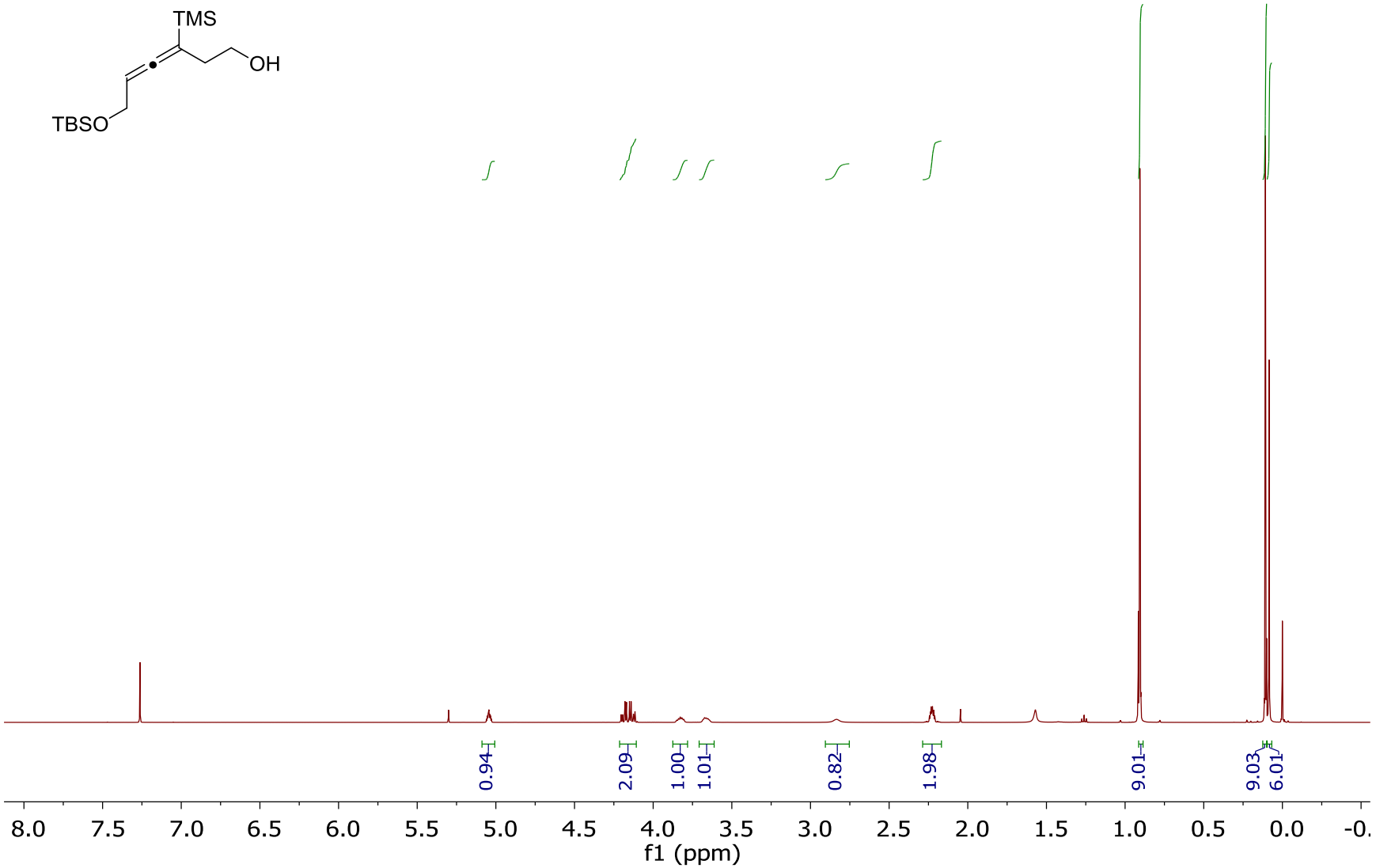
^{1}H NMR of the homoallenic alcohol precursor to compounds 5, 6 and 7.



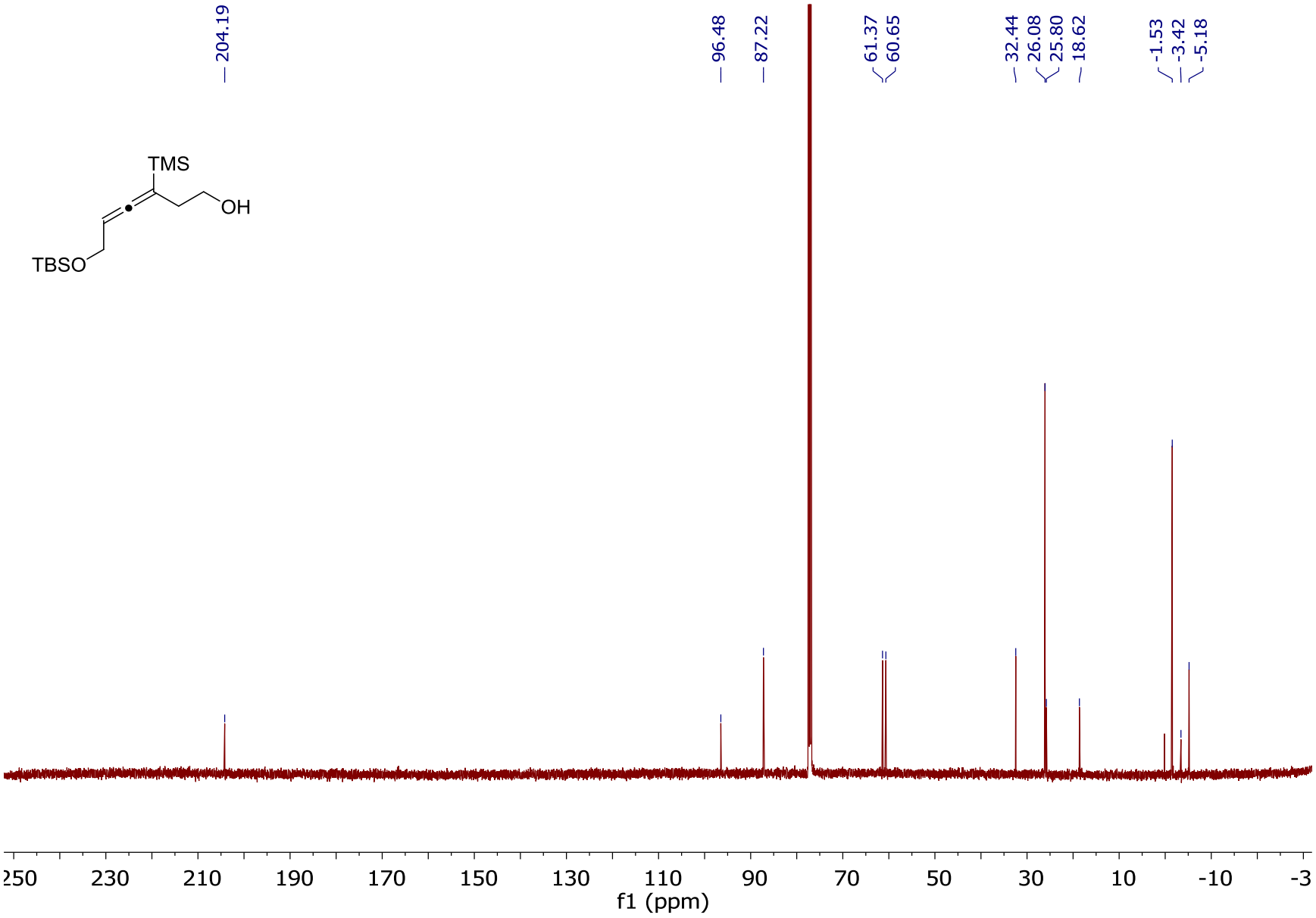
^{13}C NMR of the homoallenic alcohol precursor to compounds 5, 6 and 7.



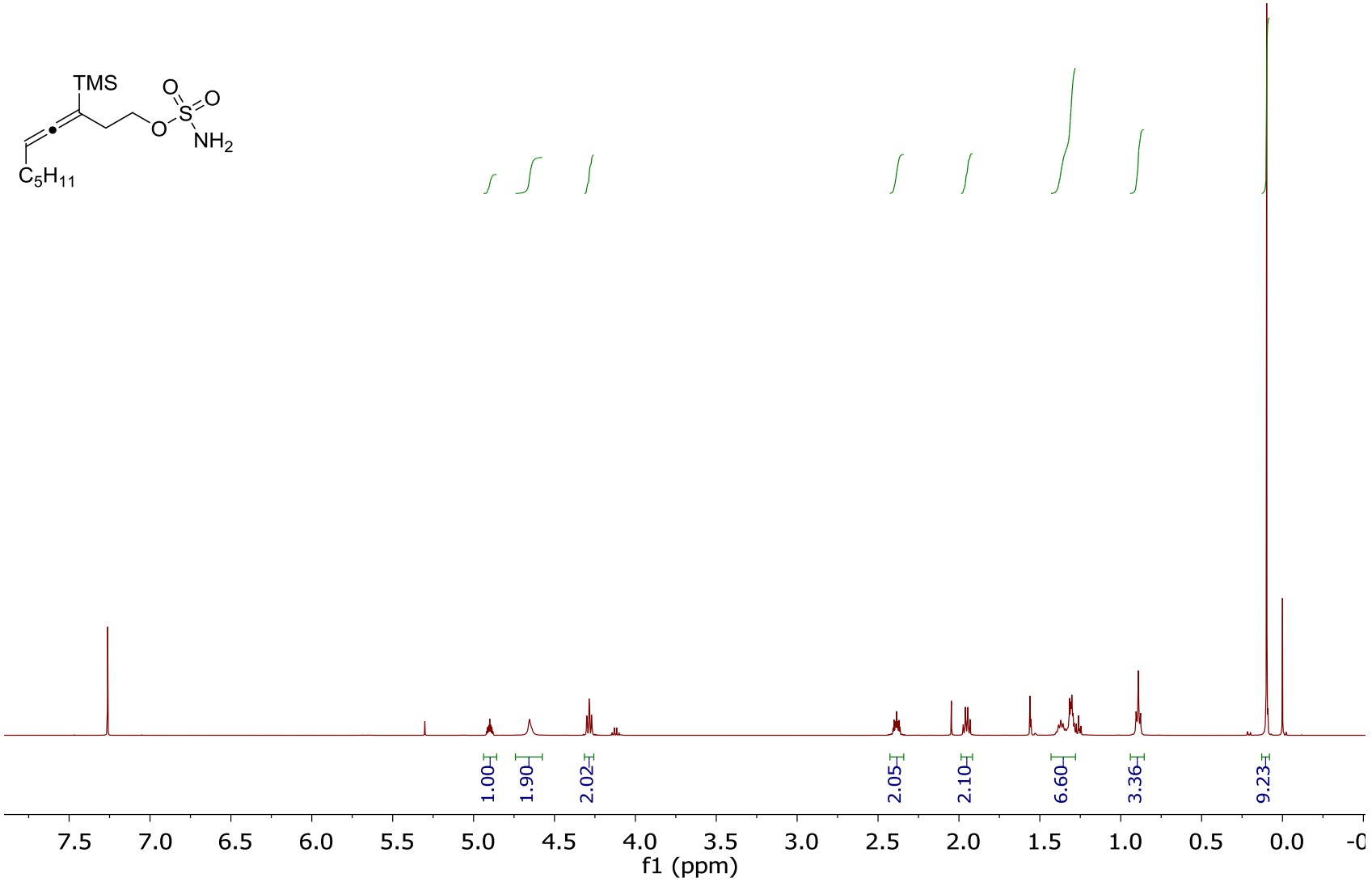
^{1}H NMR of the homoallenic alcohol precursor to compound 8.



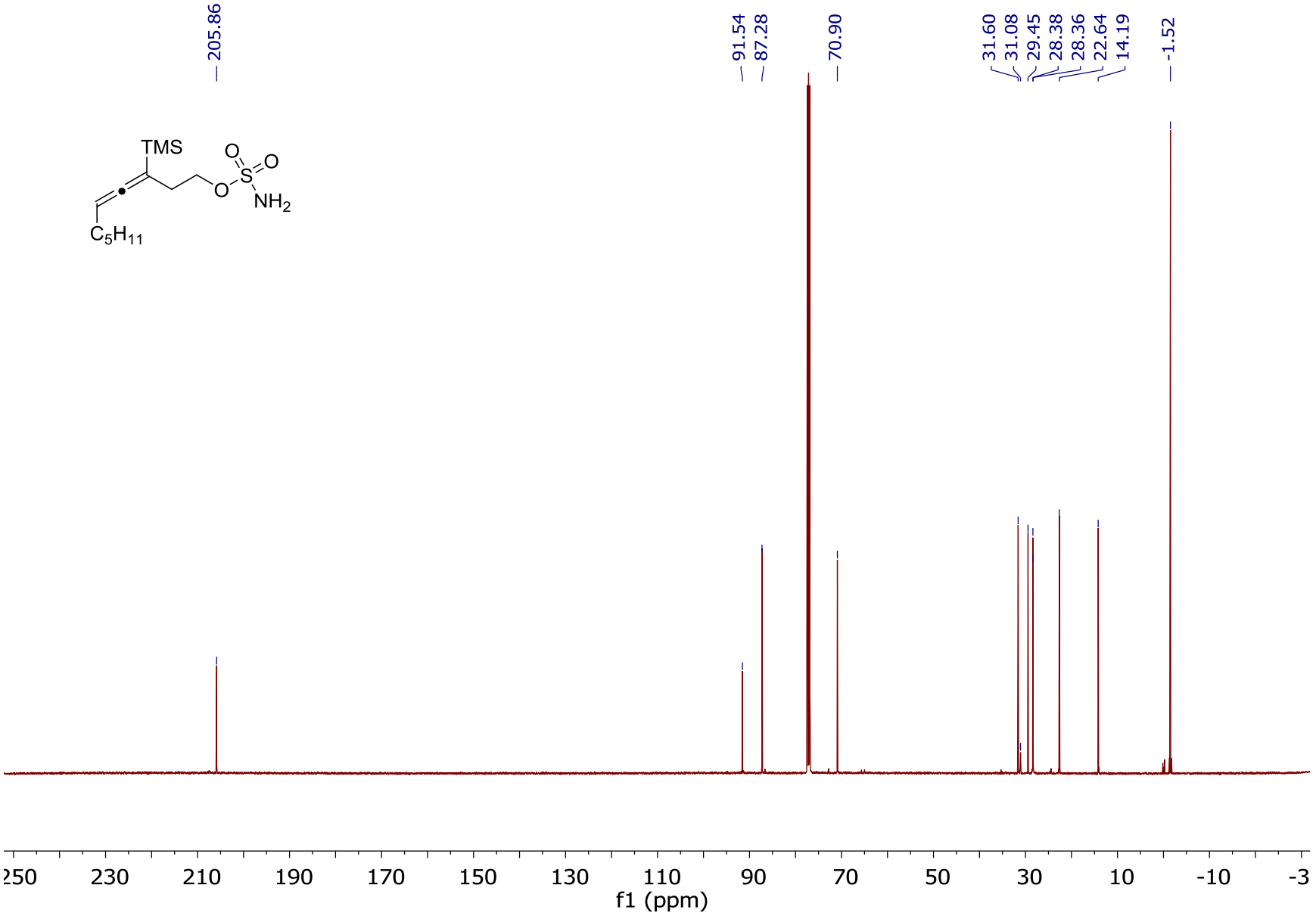
^{13}C NMR of the homoallenic alcohol precursor to compound 8.



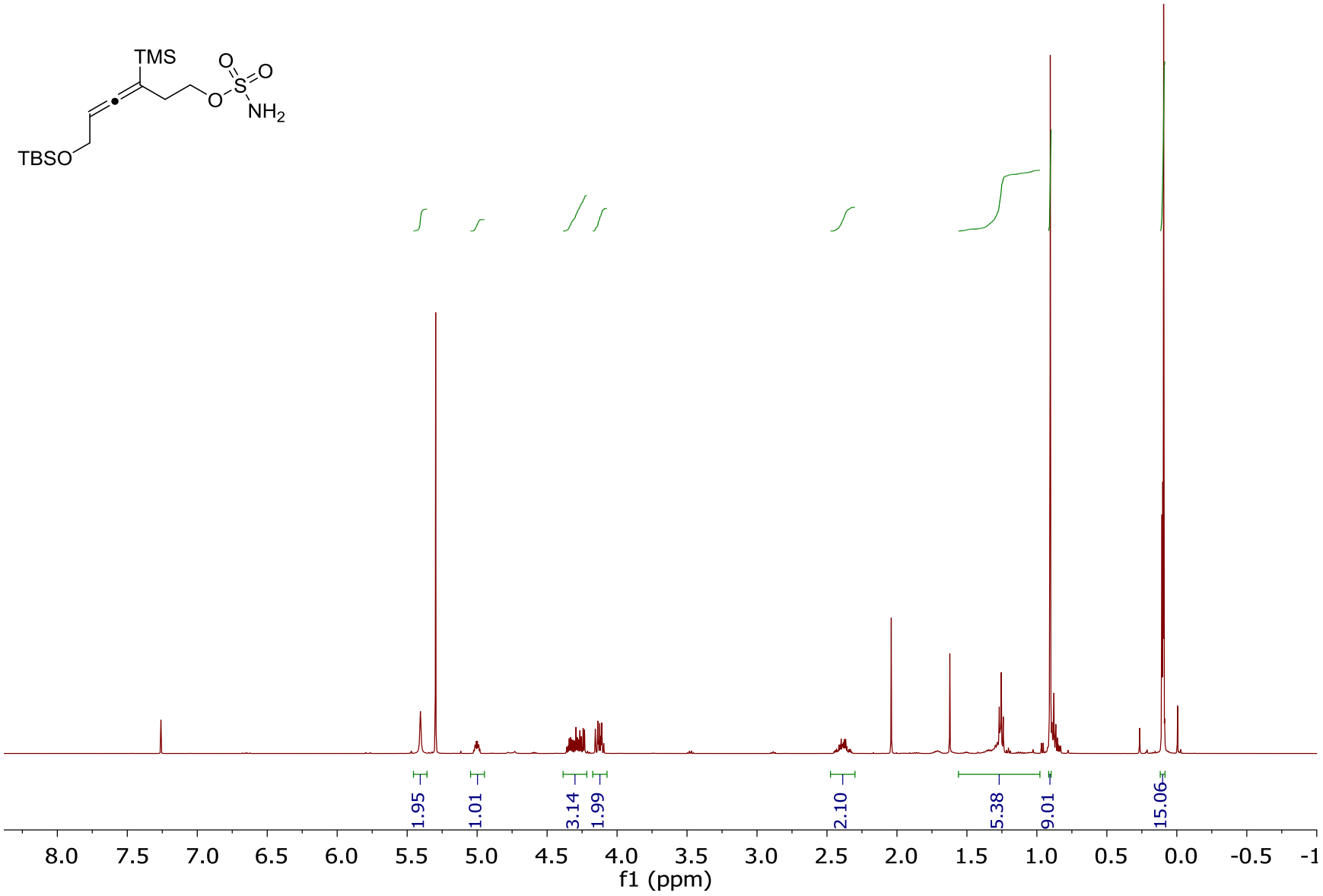
^{1}H NMR of the precursor to compounds 5 and 6.



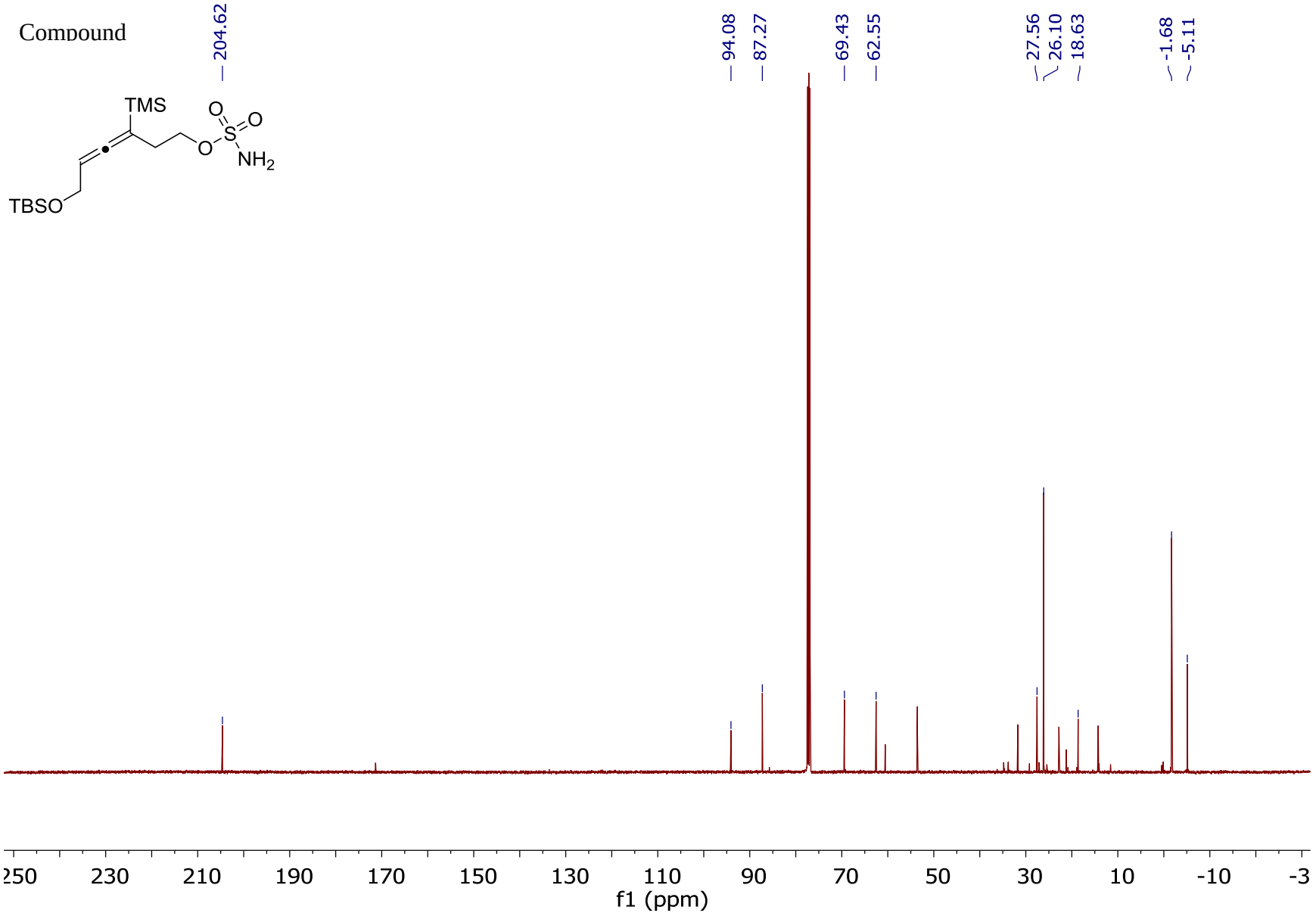
^{13}C NMR of the precursor to compounds 5 and 6.



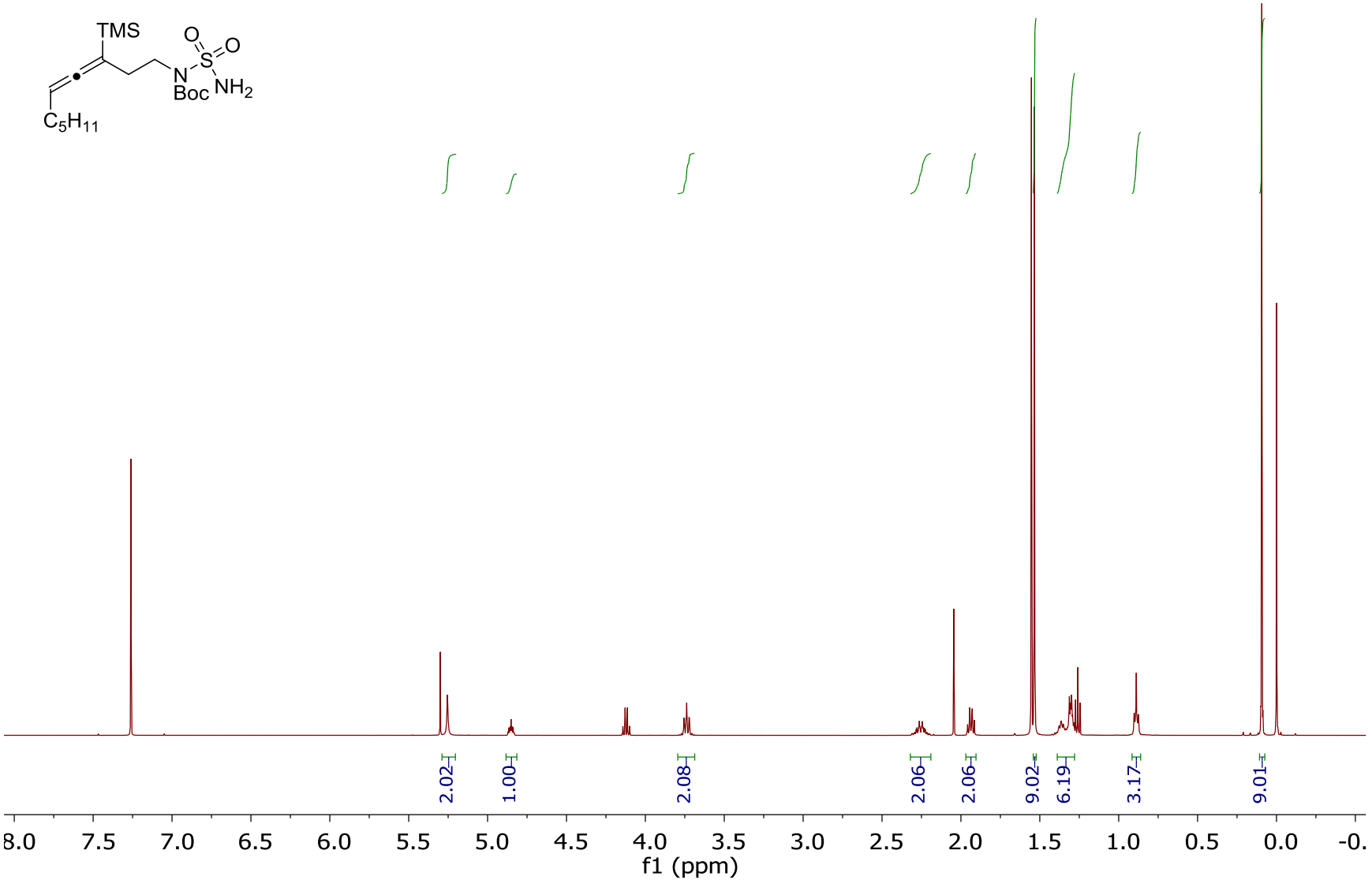
^{1}H NMR of the precursor to compound 8.



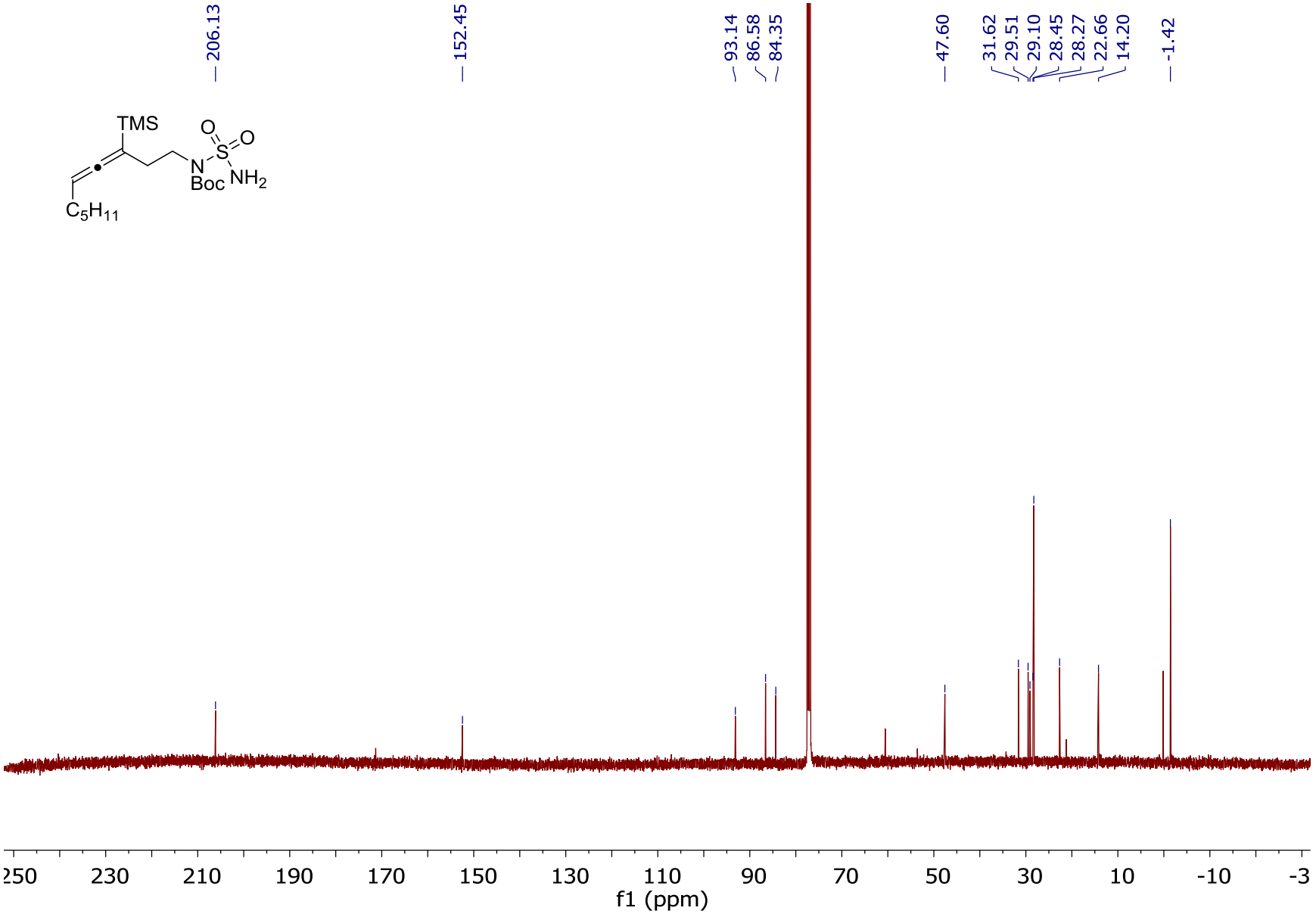
^{13}C NMR of the precursor to compound 8.



^{1}H NMR of the precursor to compound 7.



^{13}C NMR of the precursor to compound 7.



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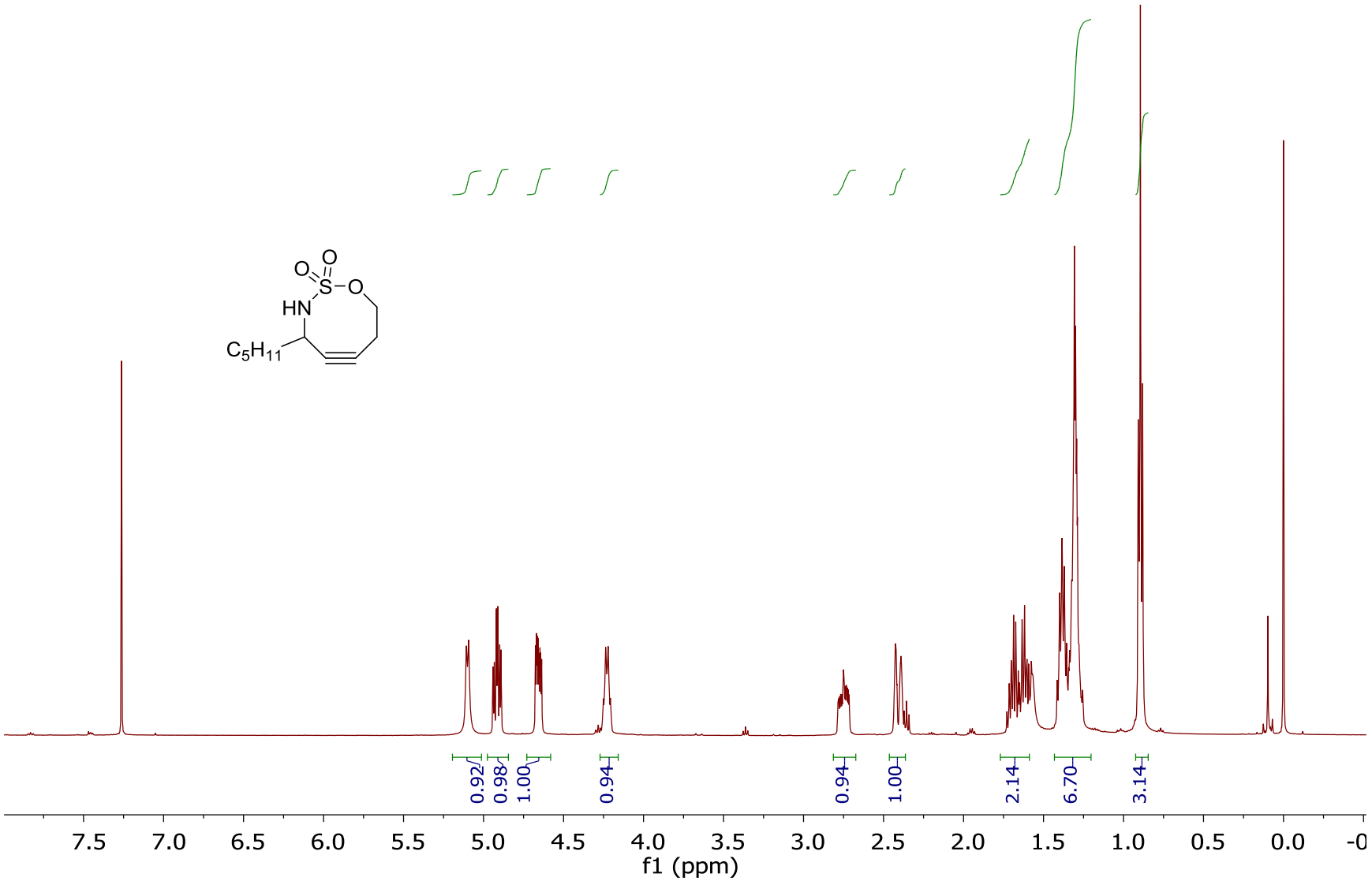

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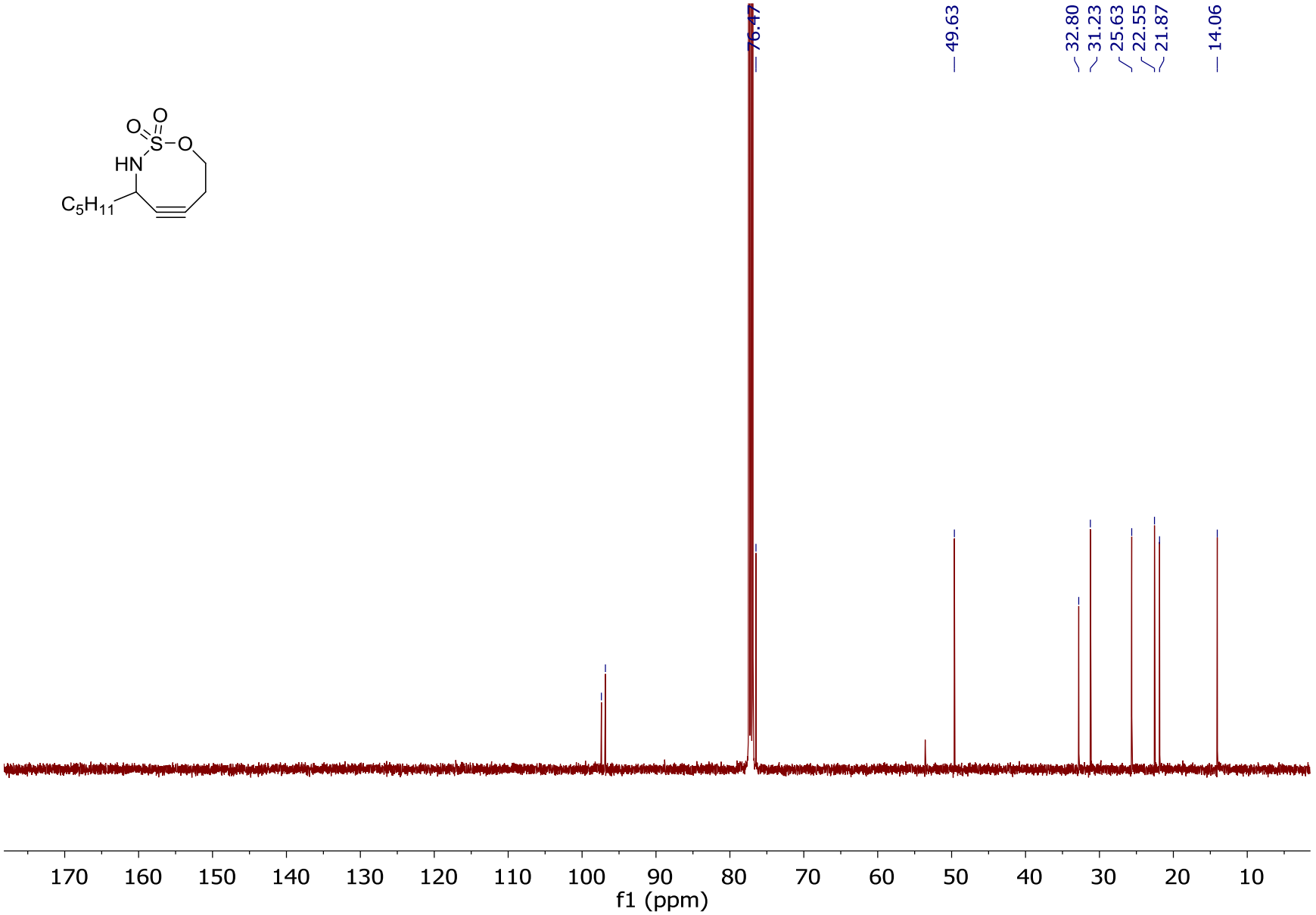
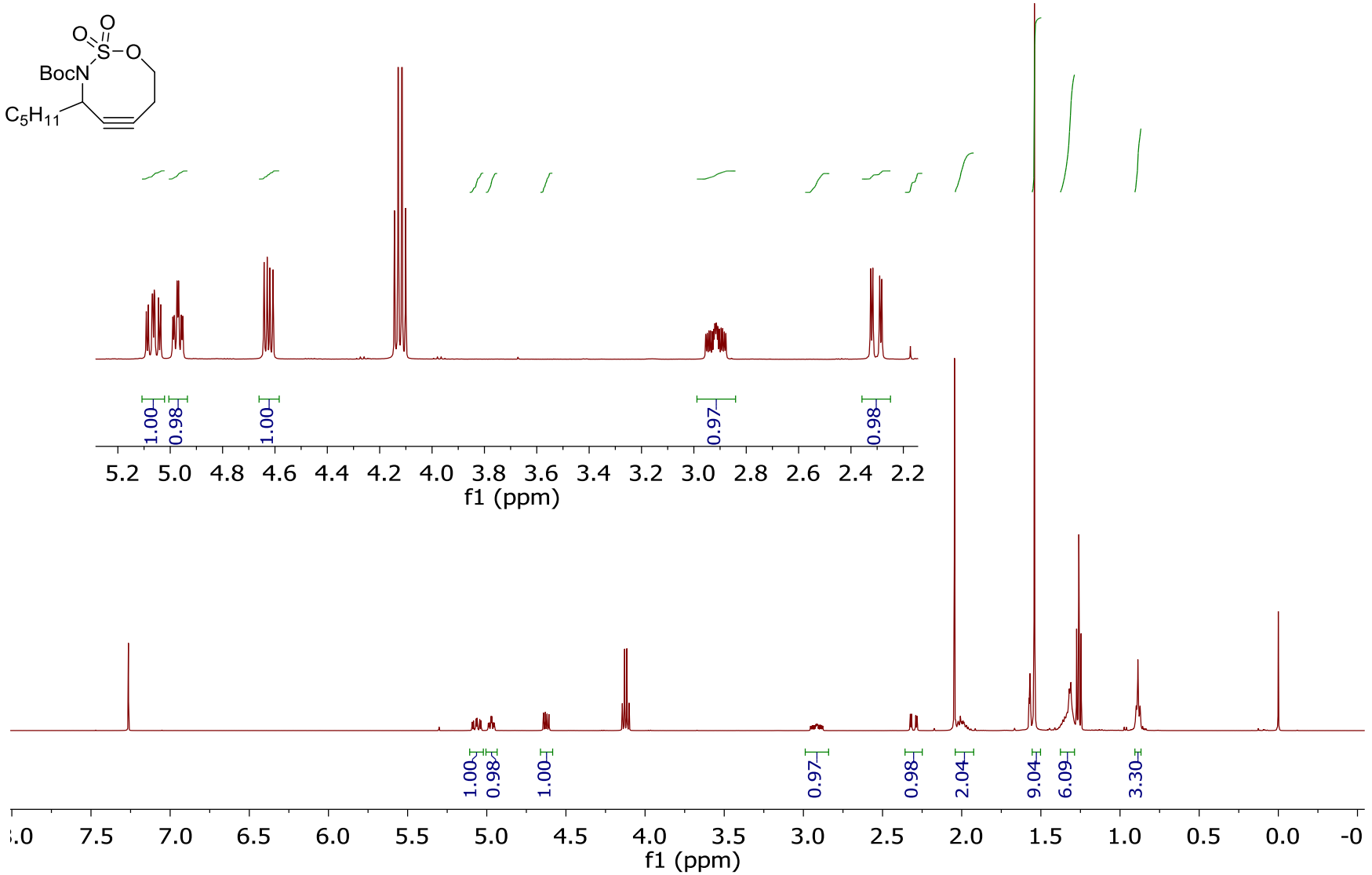


^{1}H NMR of compound 6.



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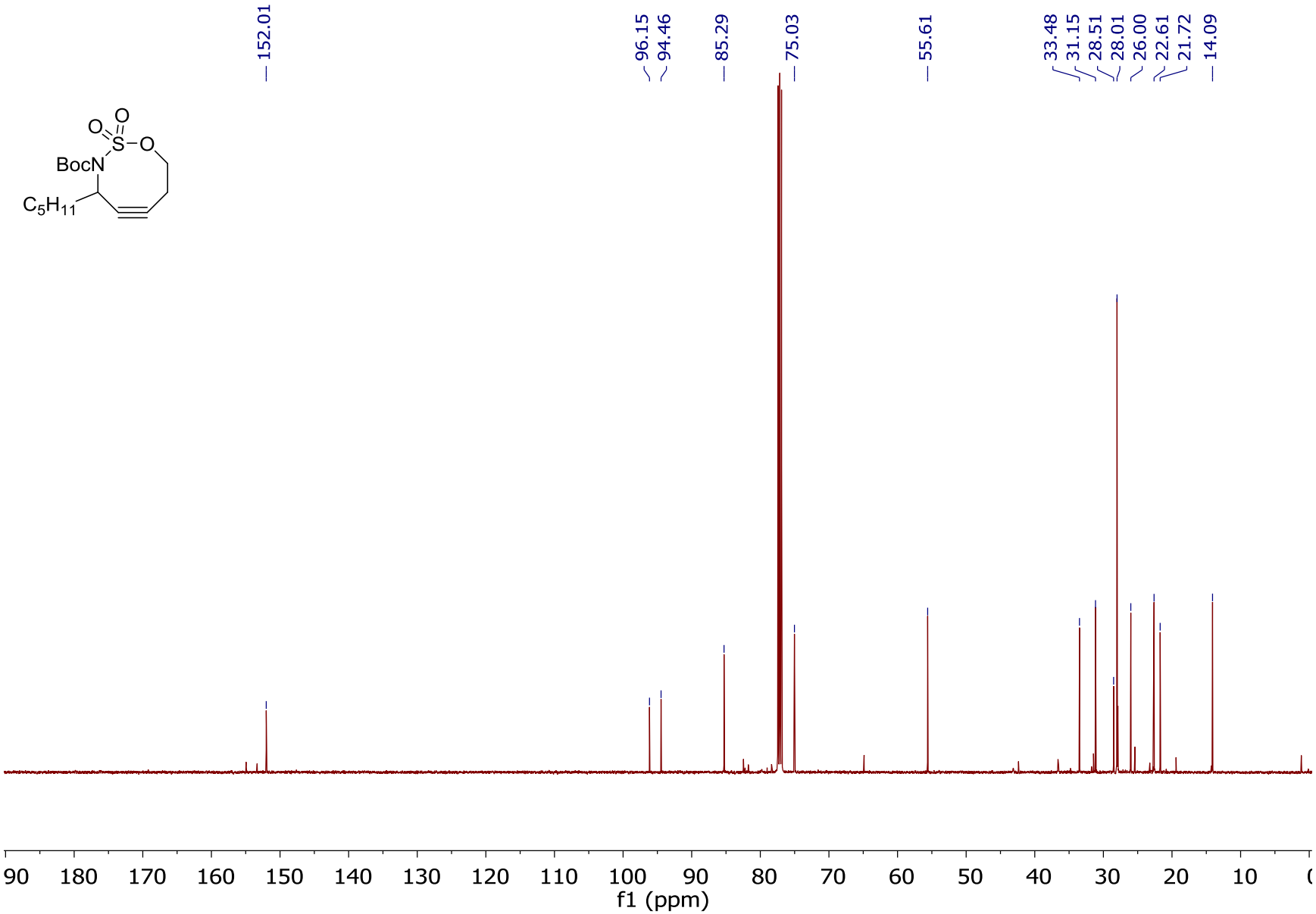

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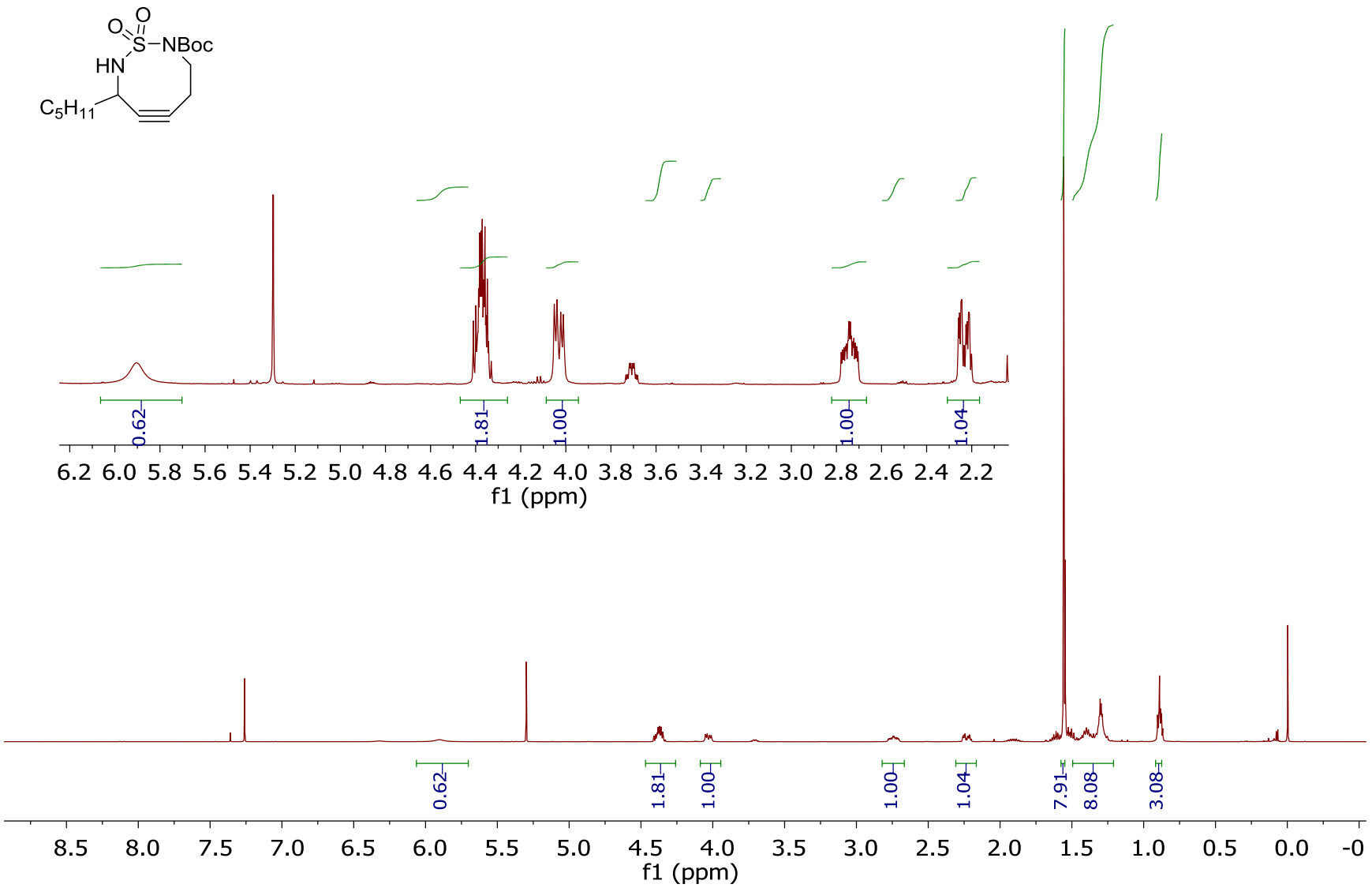

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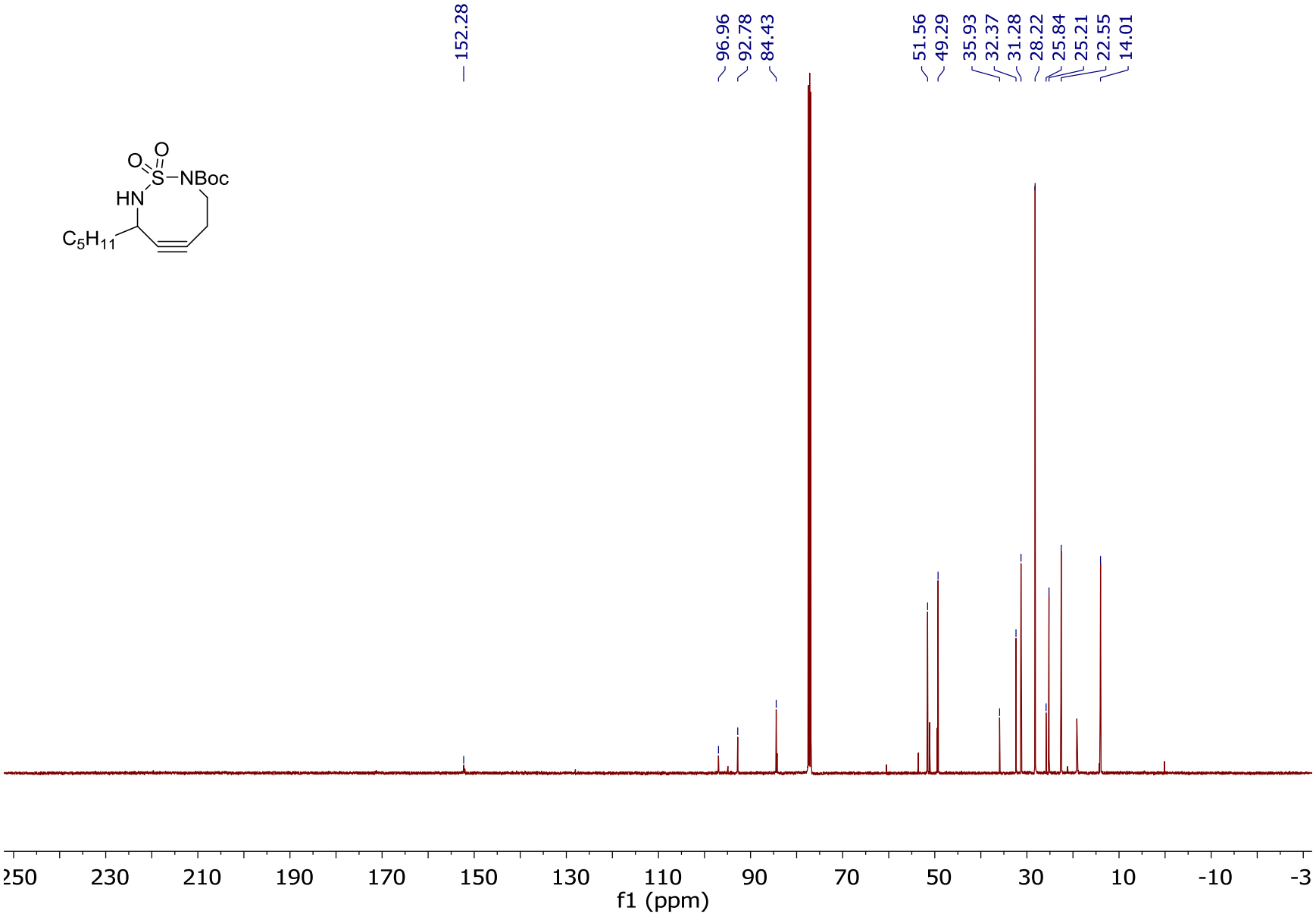
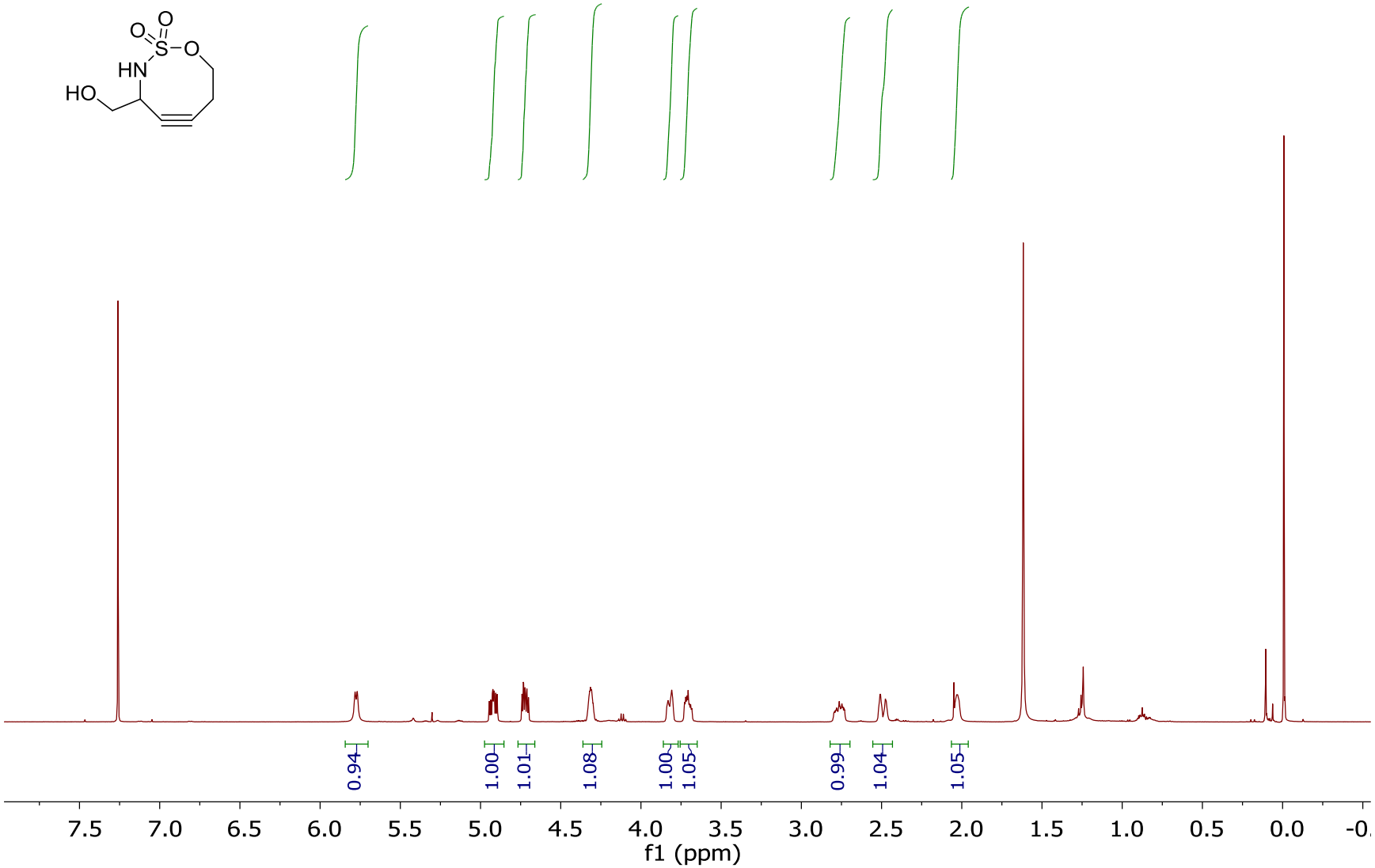


^{1}H NMR of compound 8.



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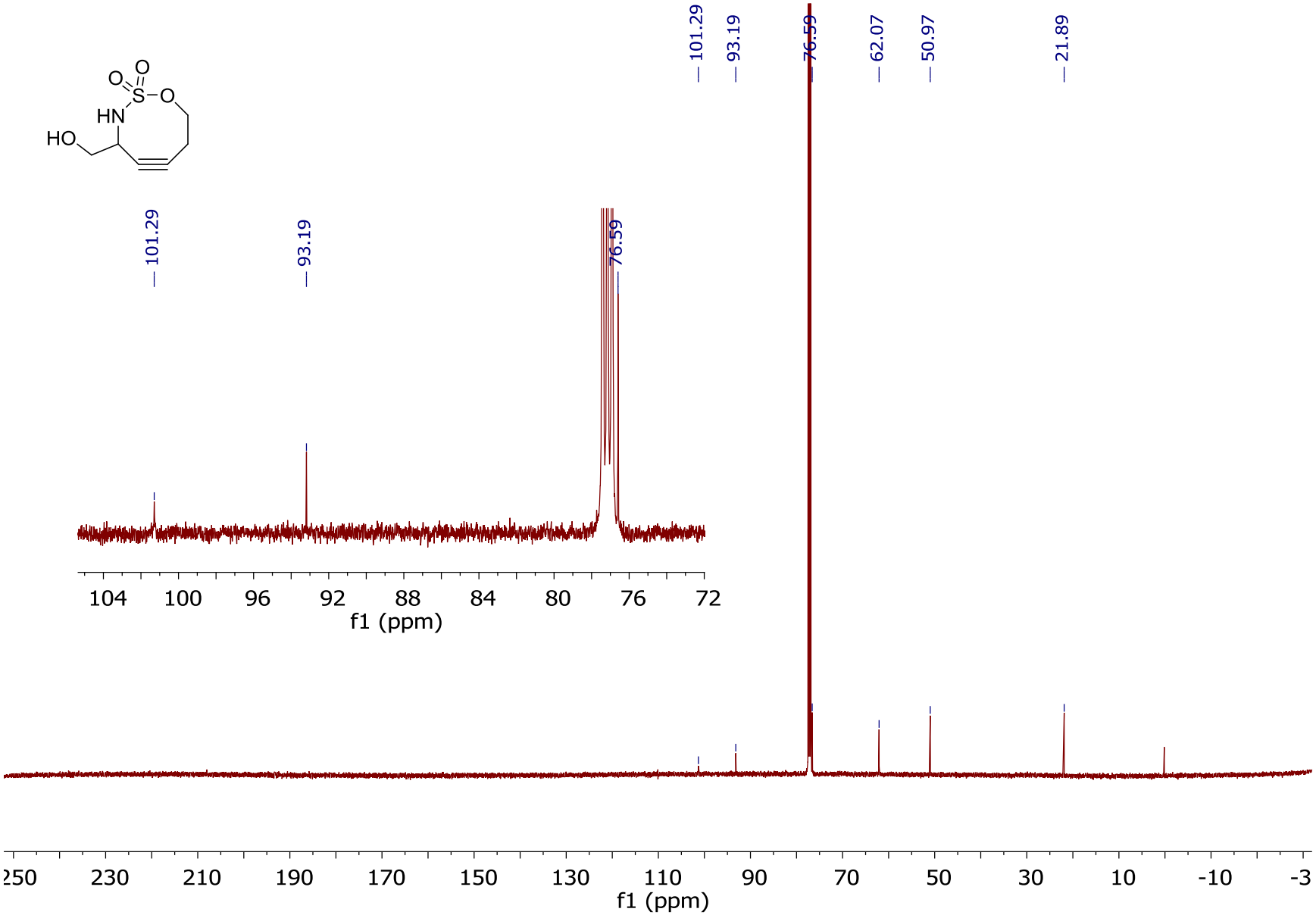
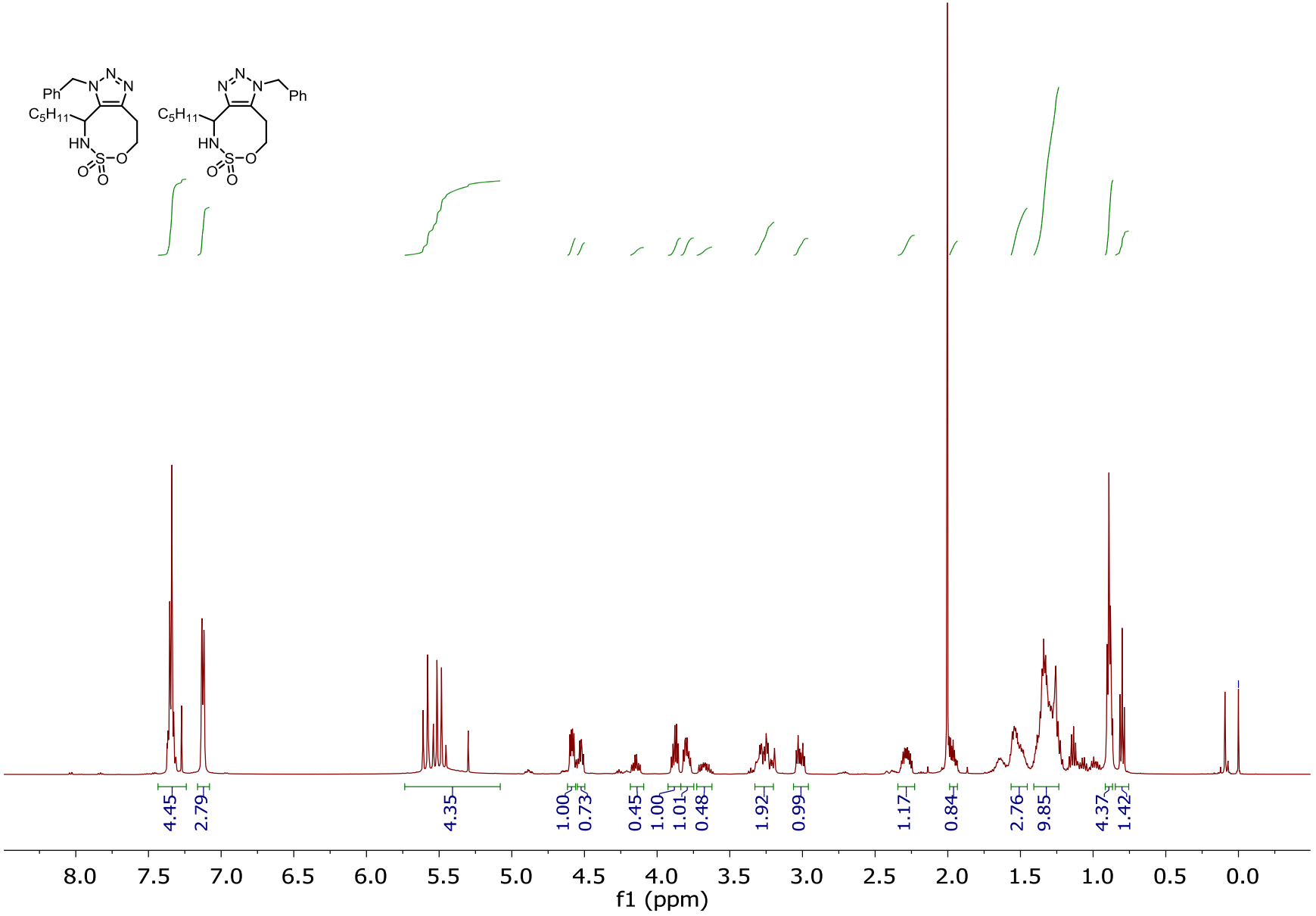


^{1}H NMR of compounds 5b and 5a.



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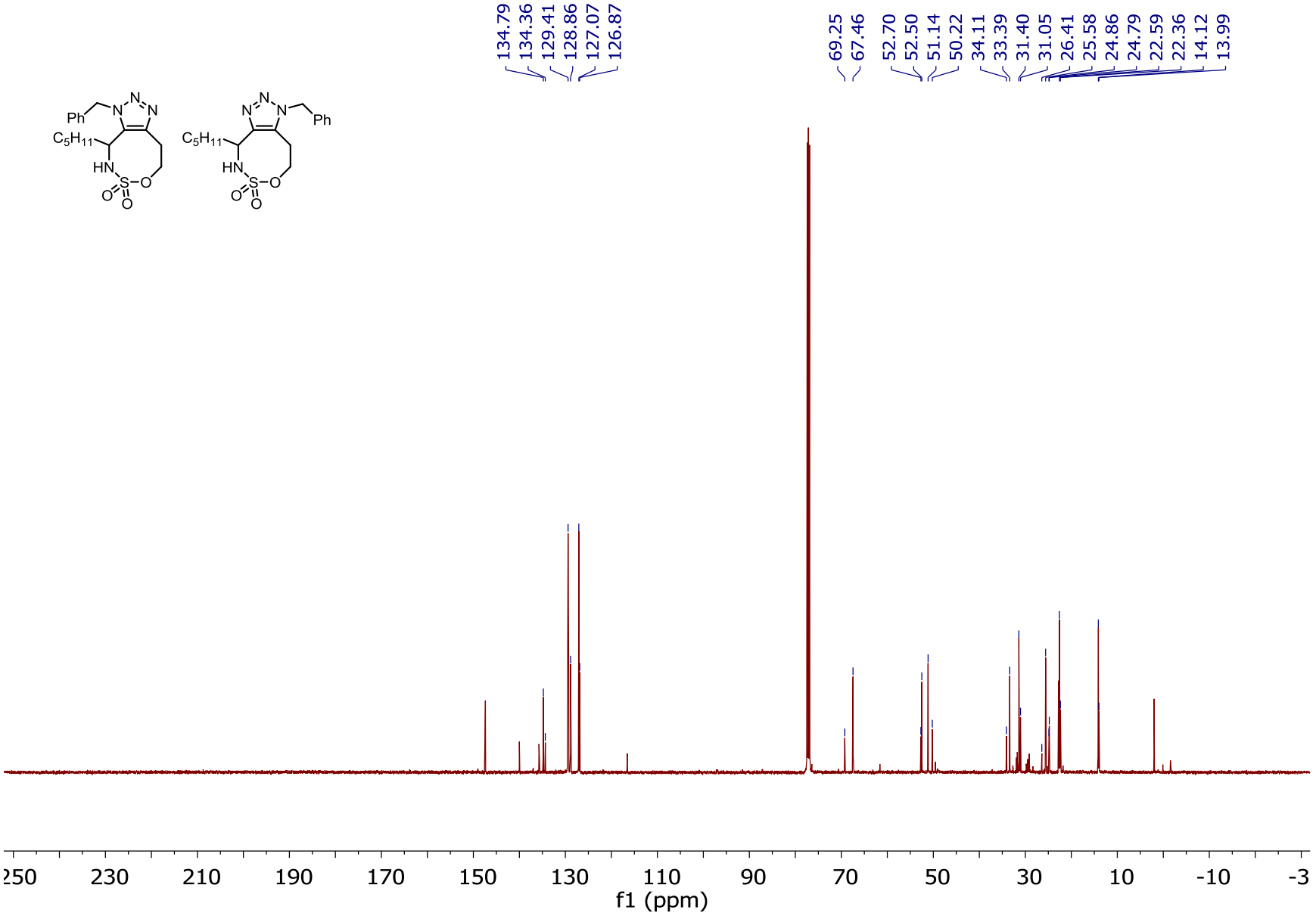

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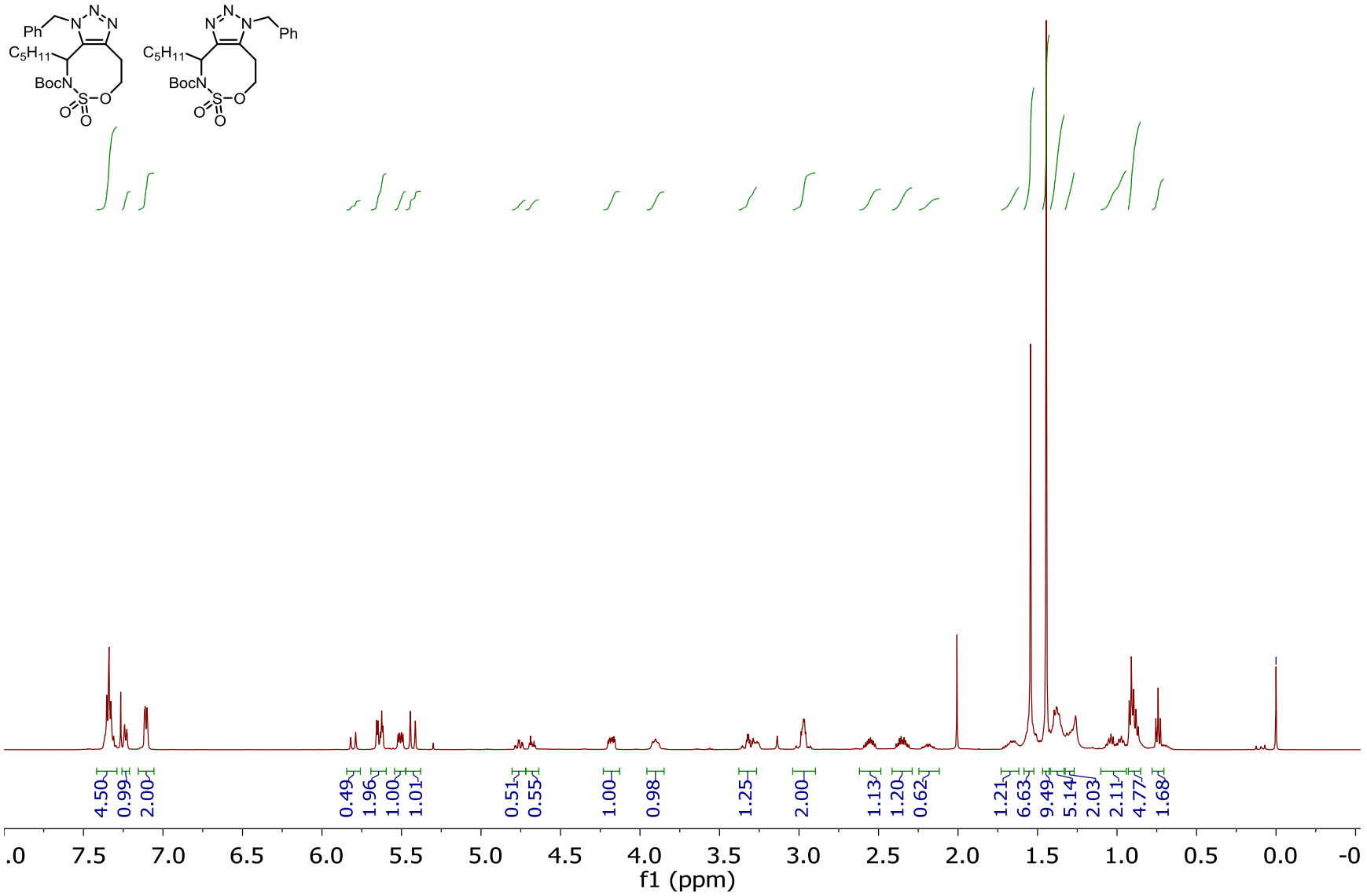

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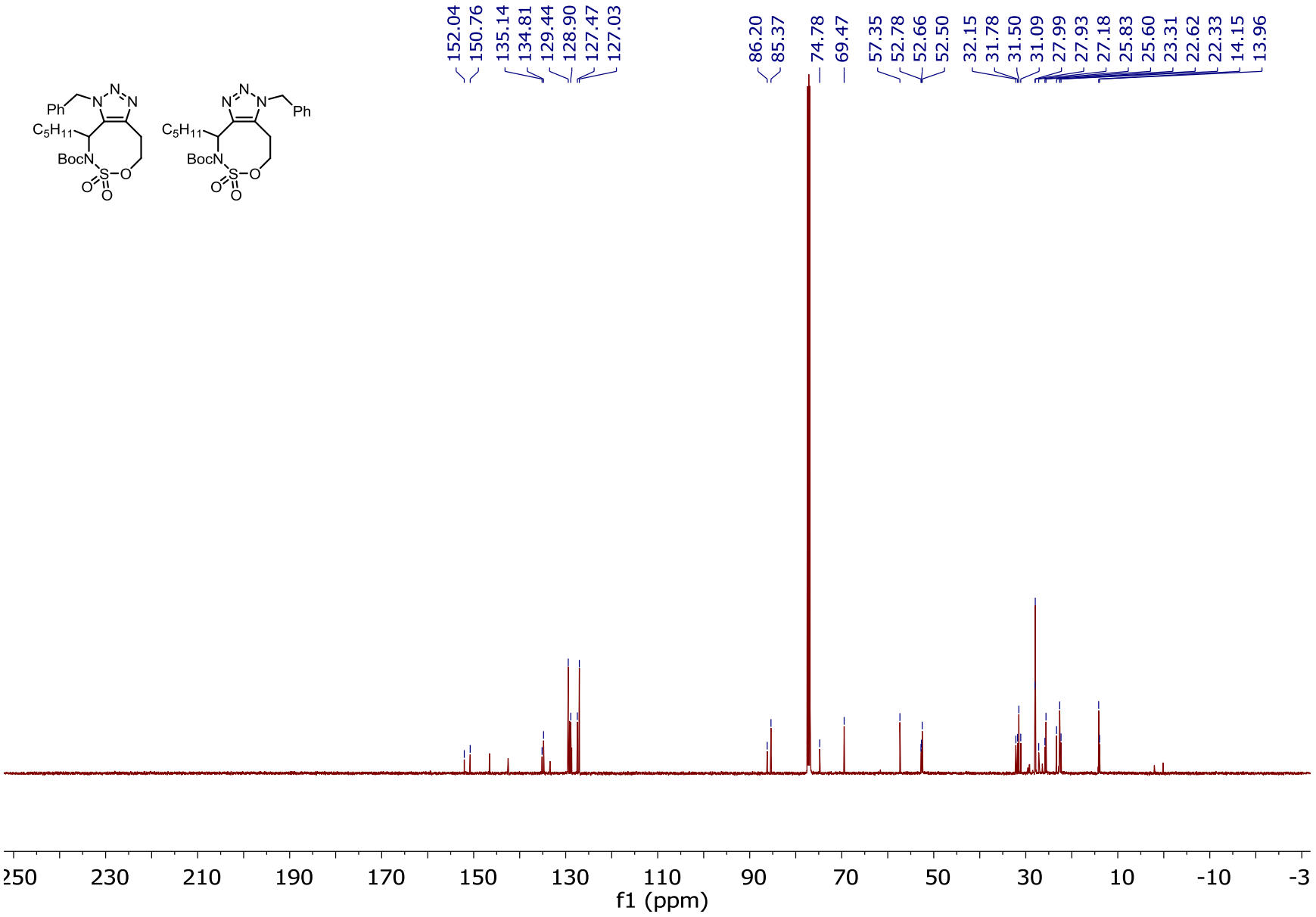
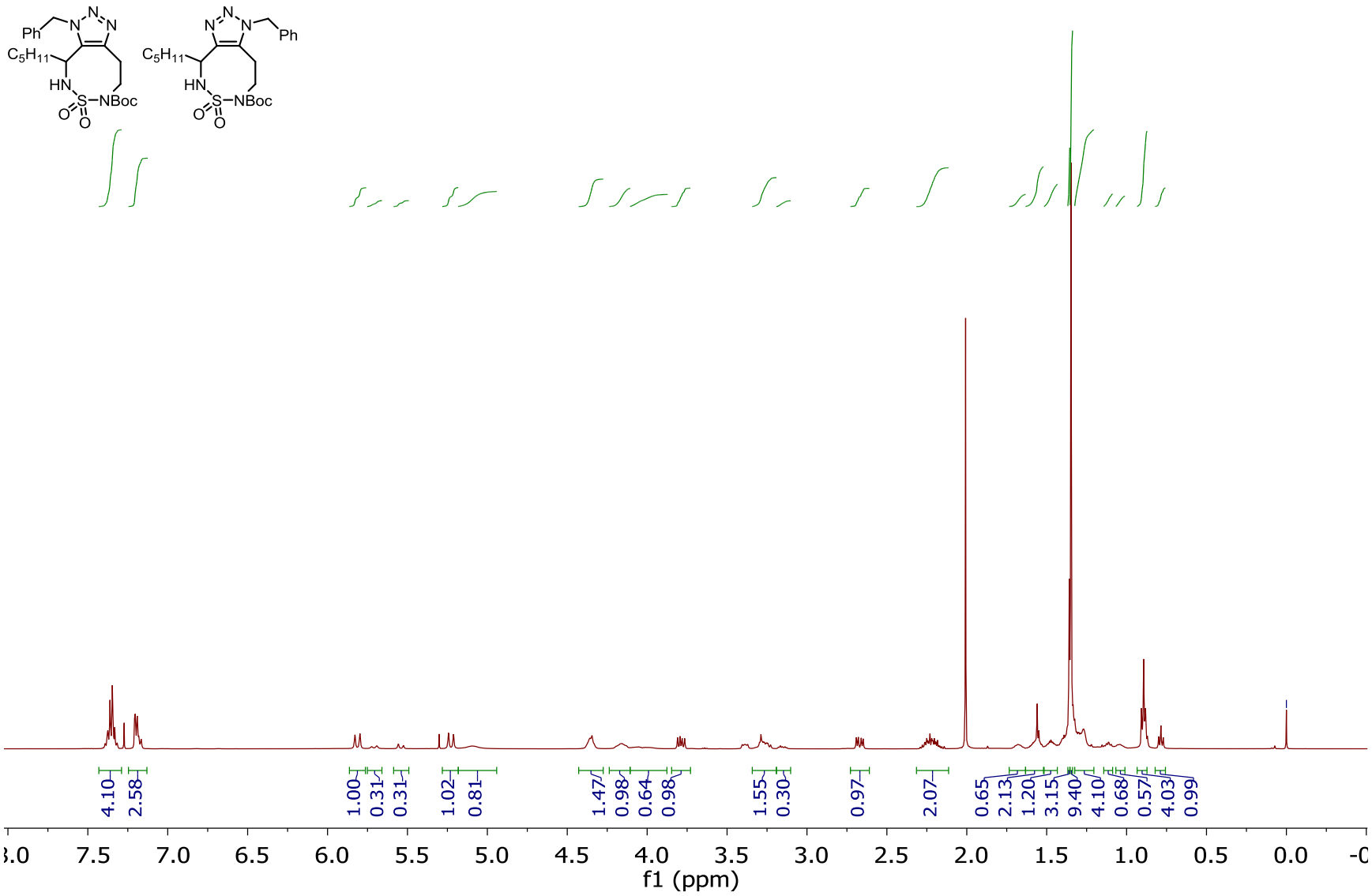
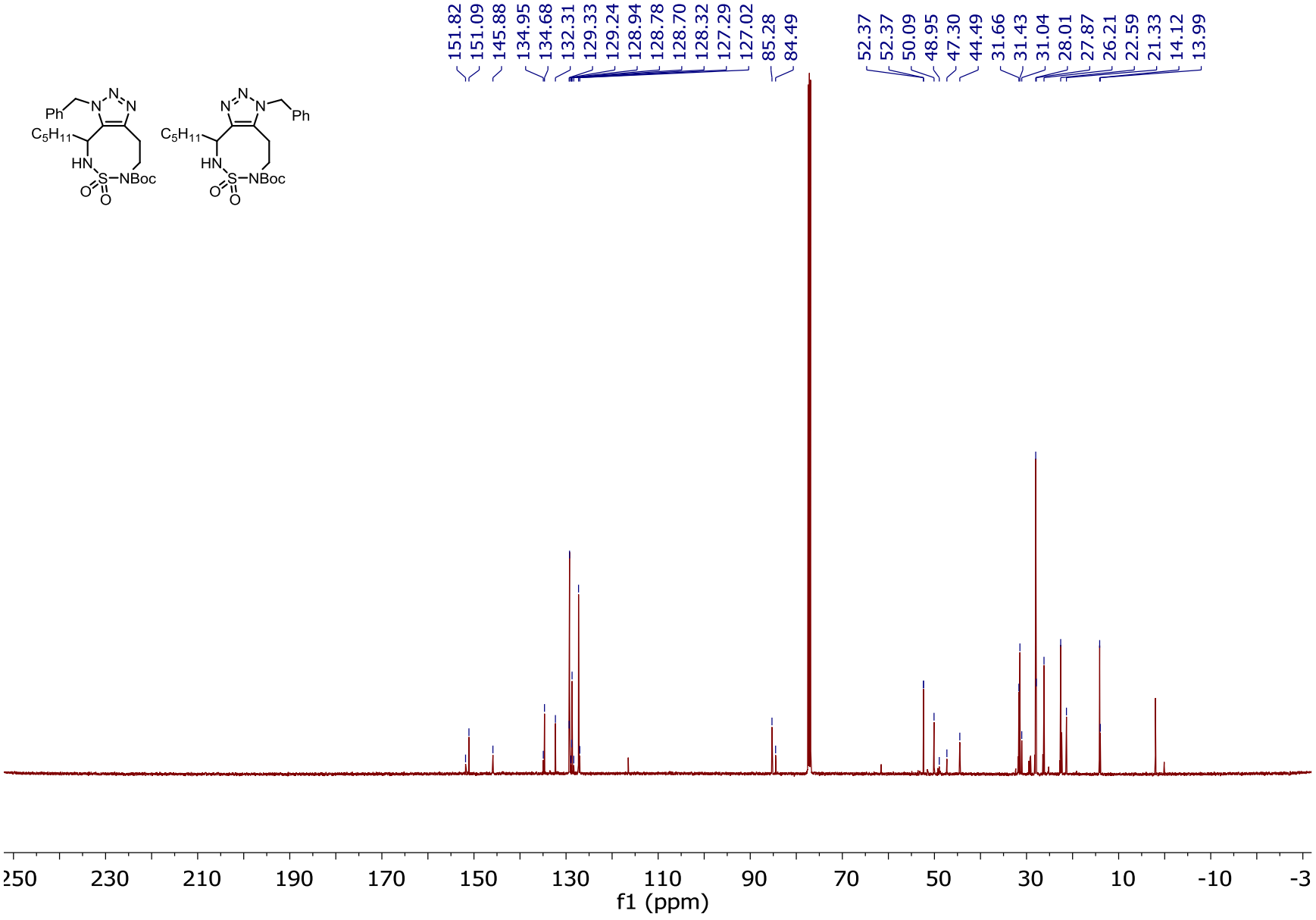


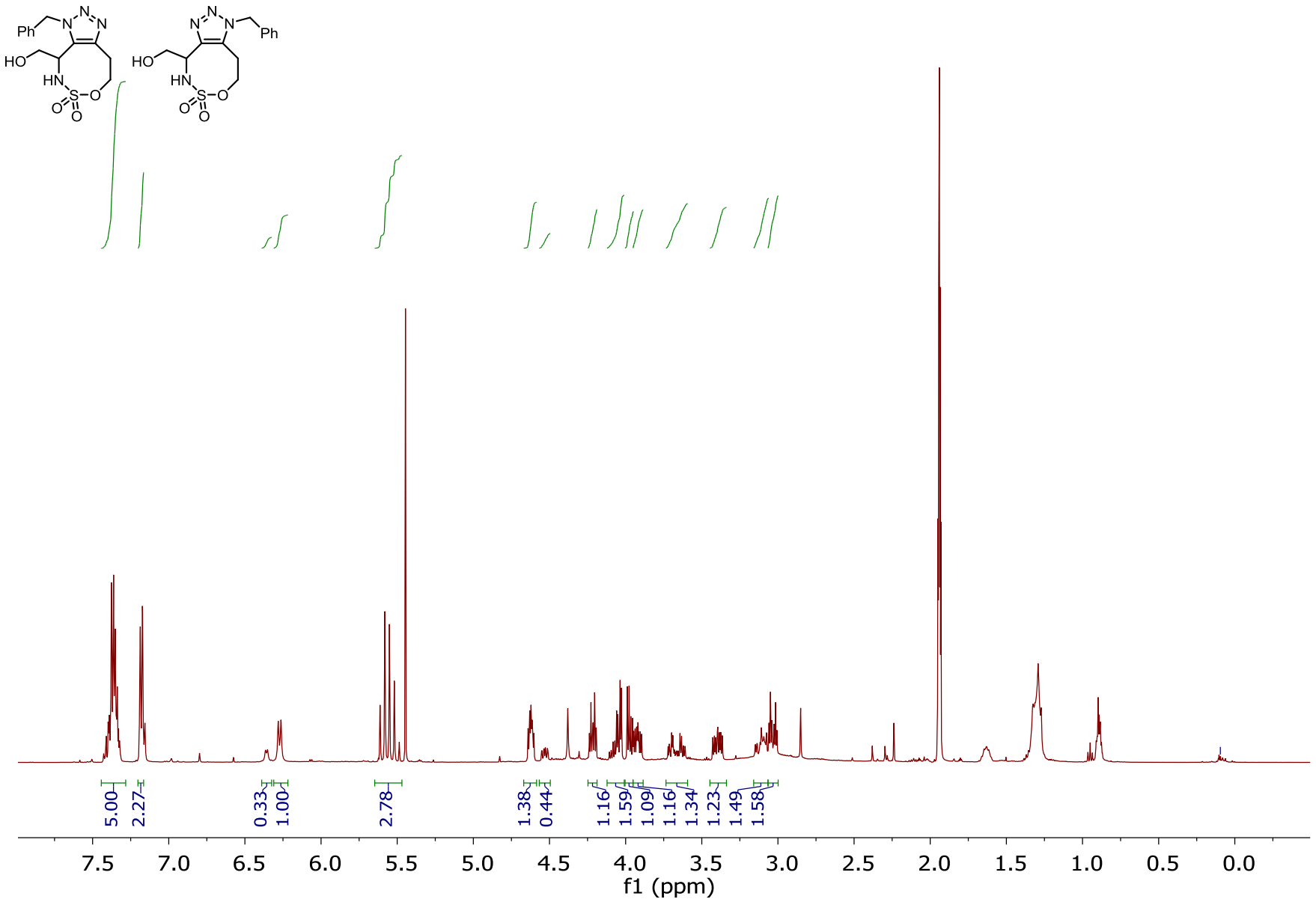
^{1}H NMR of compounds 7b and 7a.



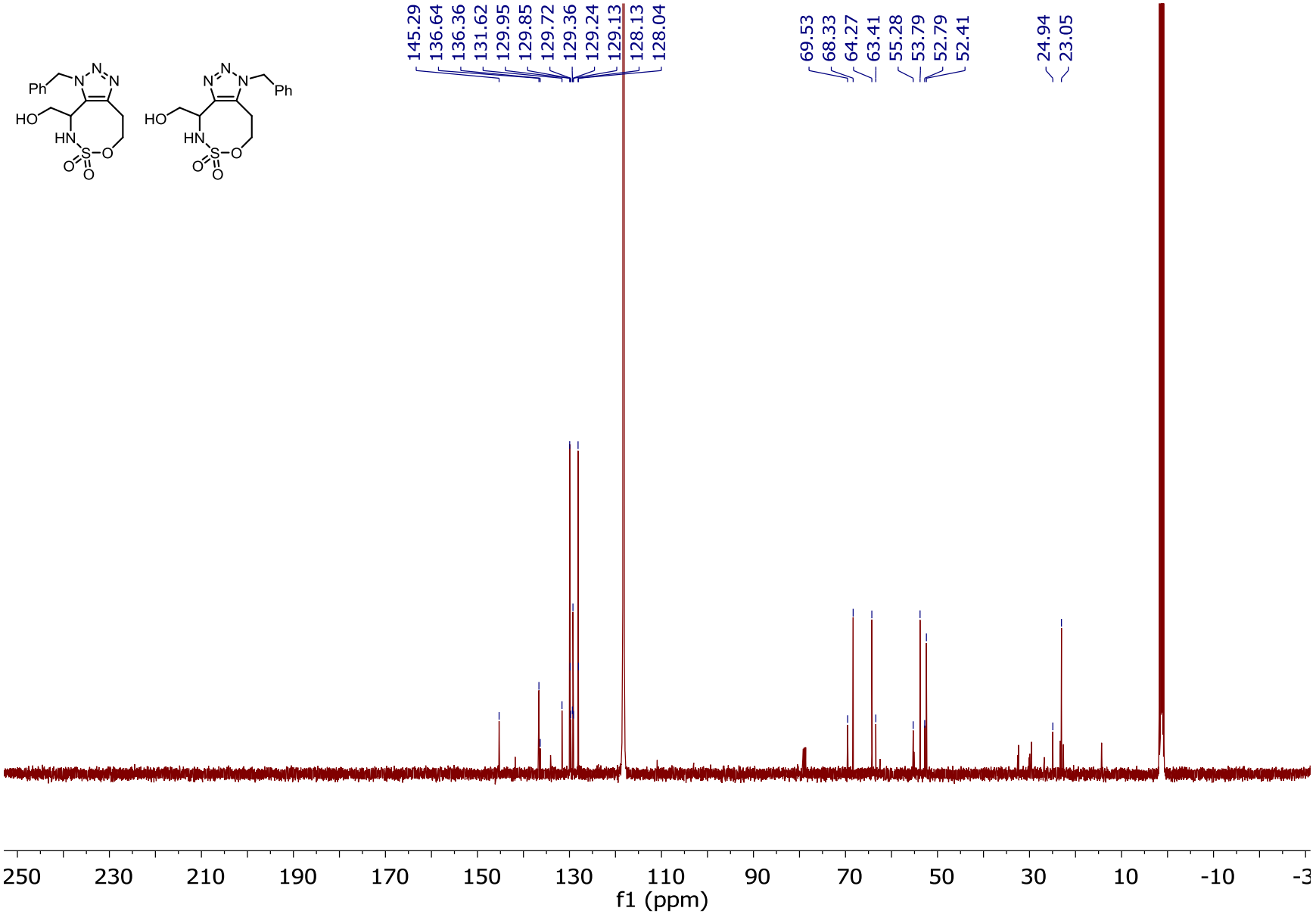
^{13}C NMR of compounds 7b and 7a.



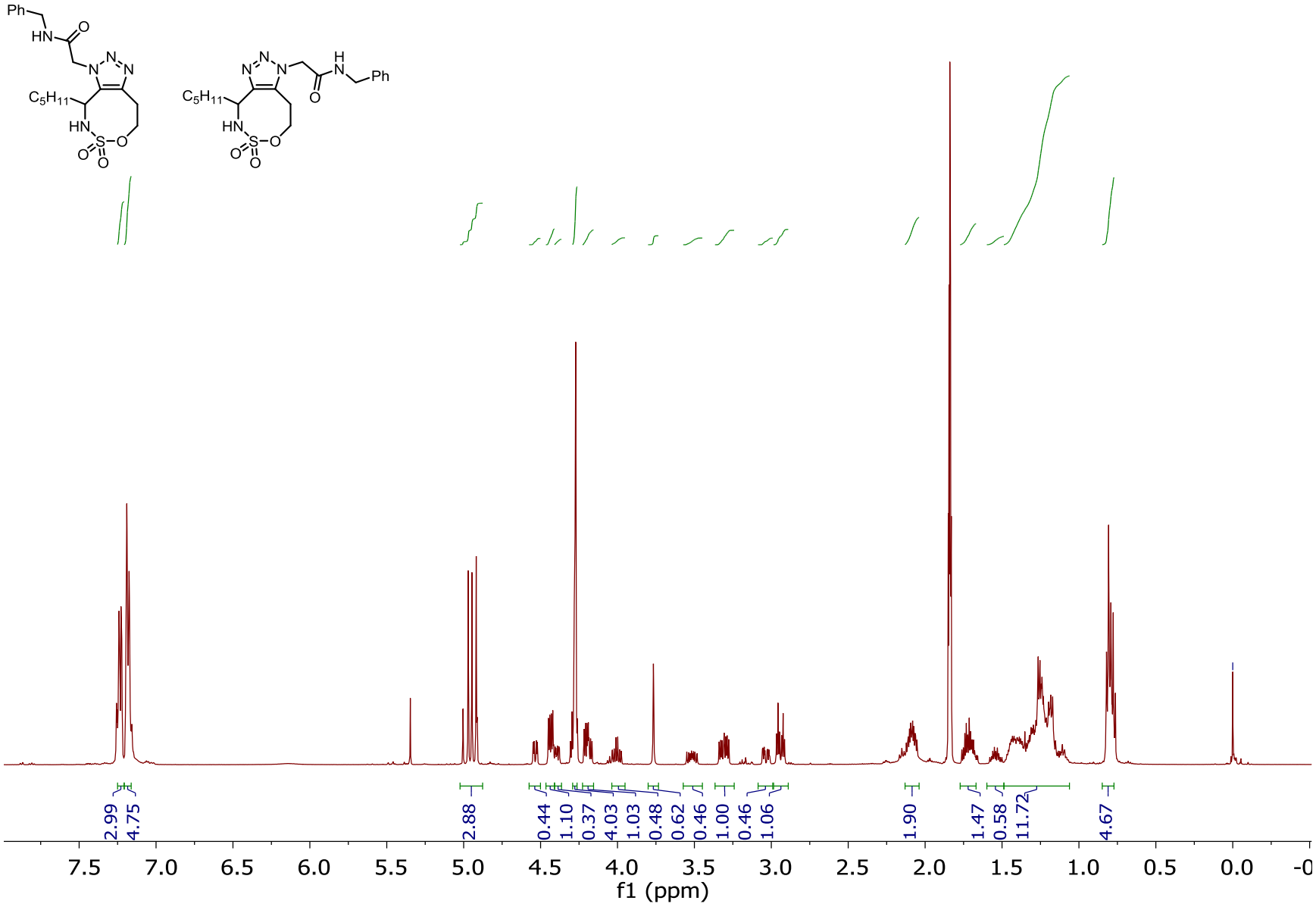
^{1}H NMR of compounds 8b and 8a.



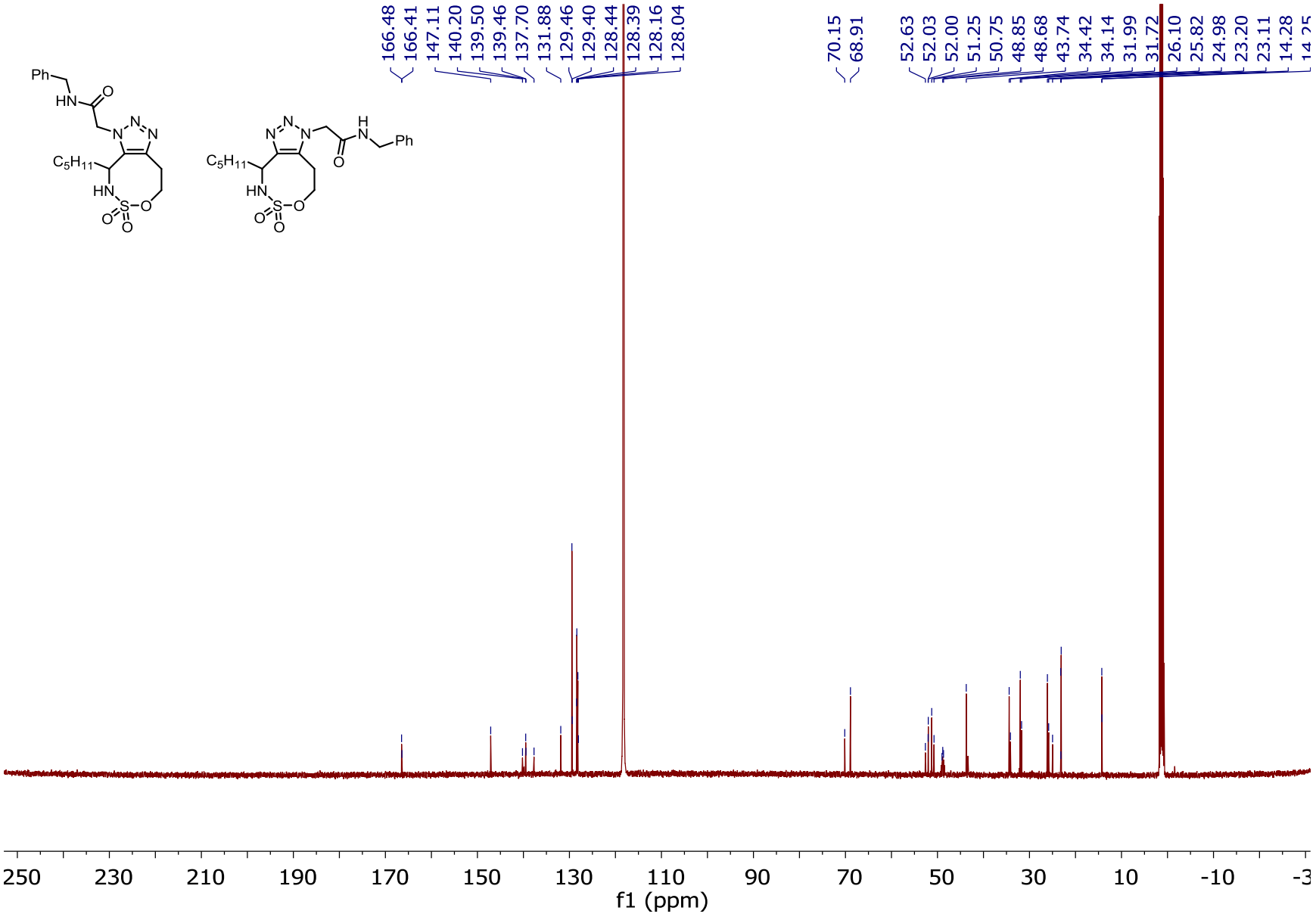
^{13}C NMR of compounds 8b and 8a.



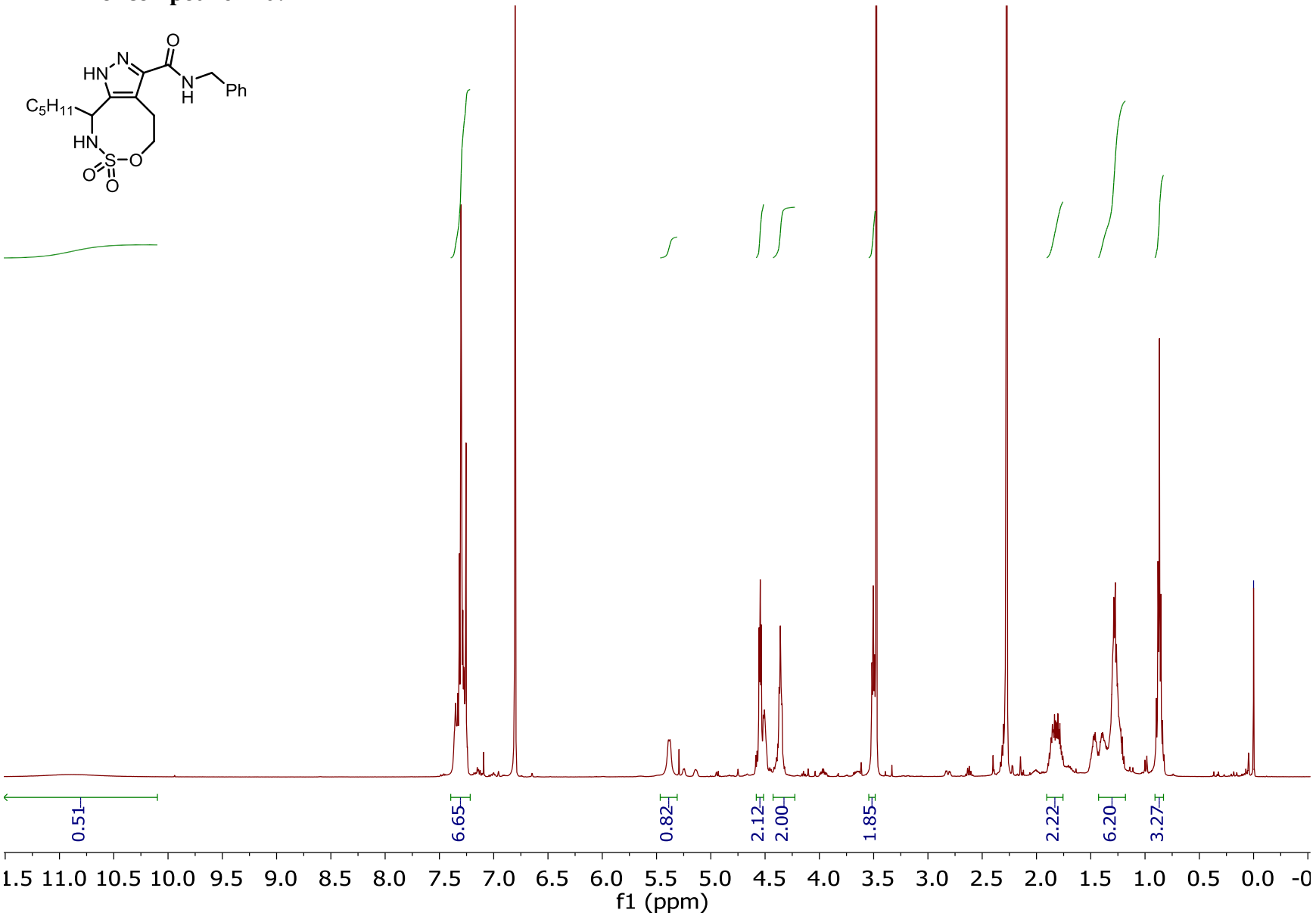
^{1}H NMR of compounds 16b and 16a.



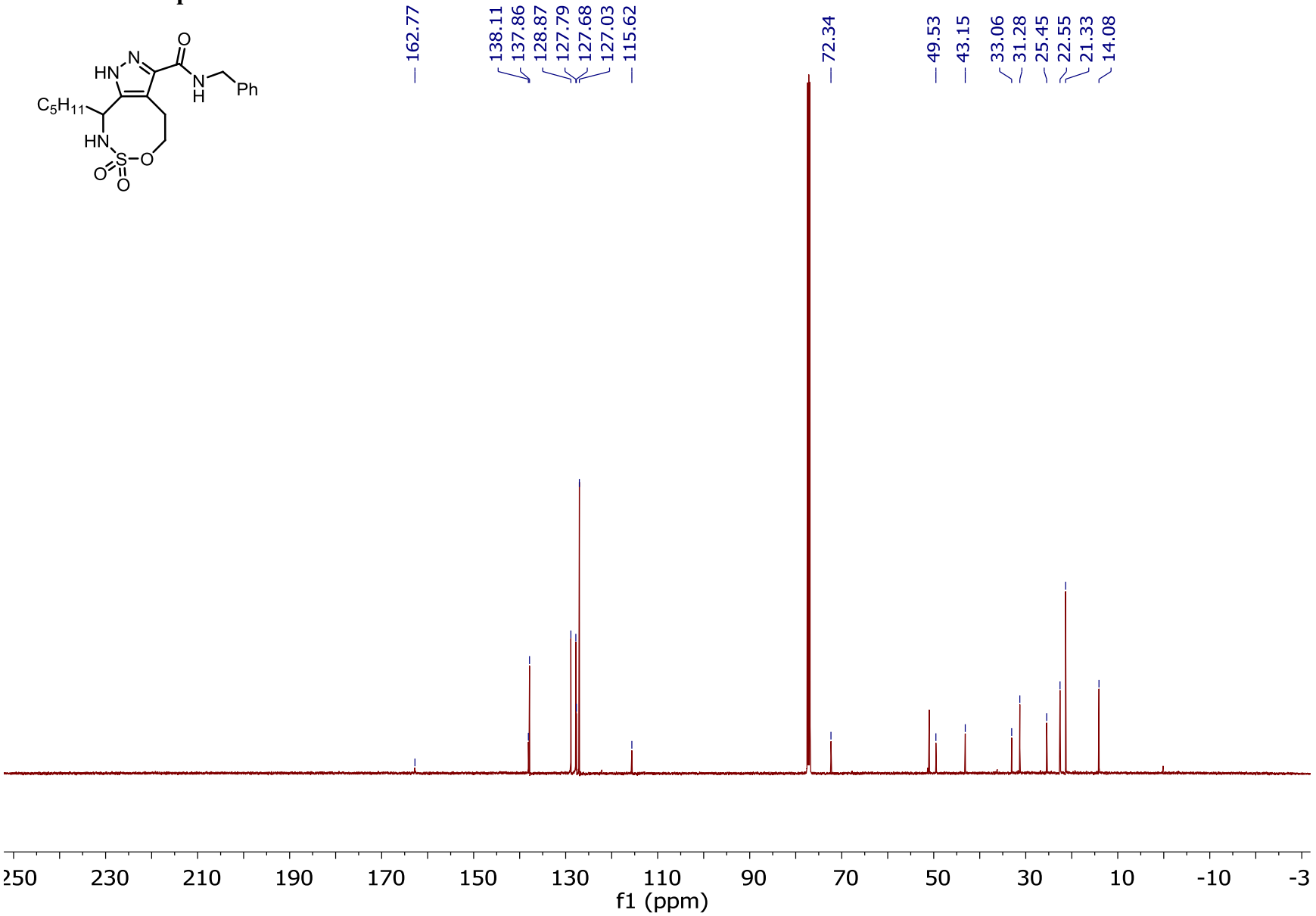
^{13}C NMR of compounds 16b and 16a.



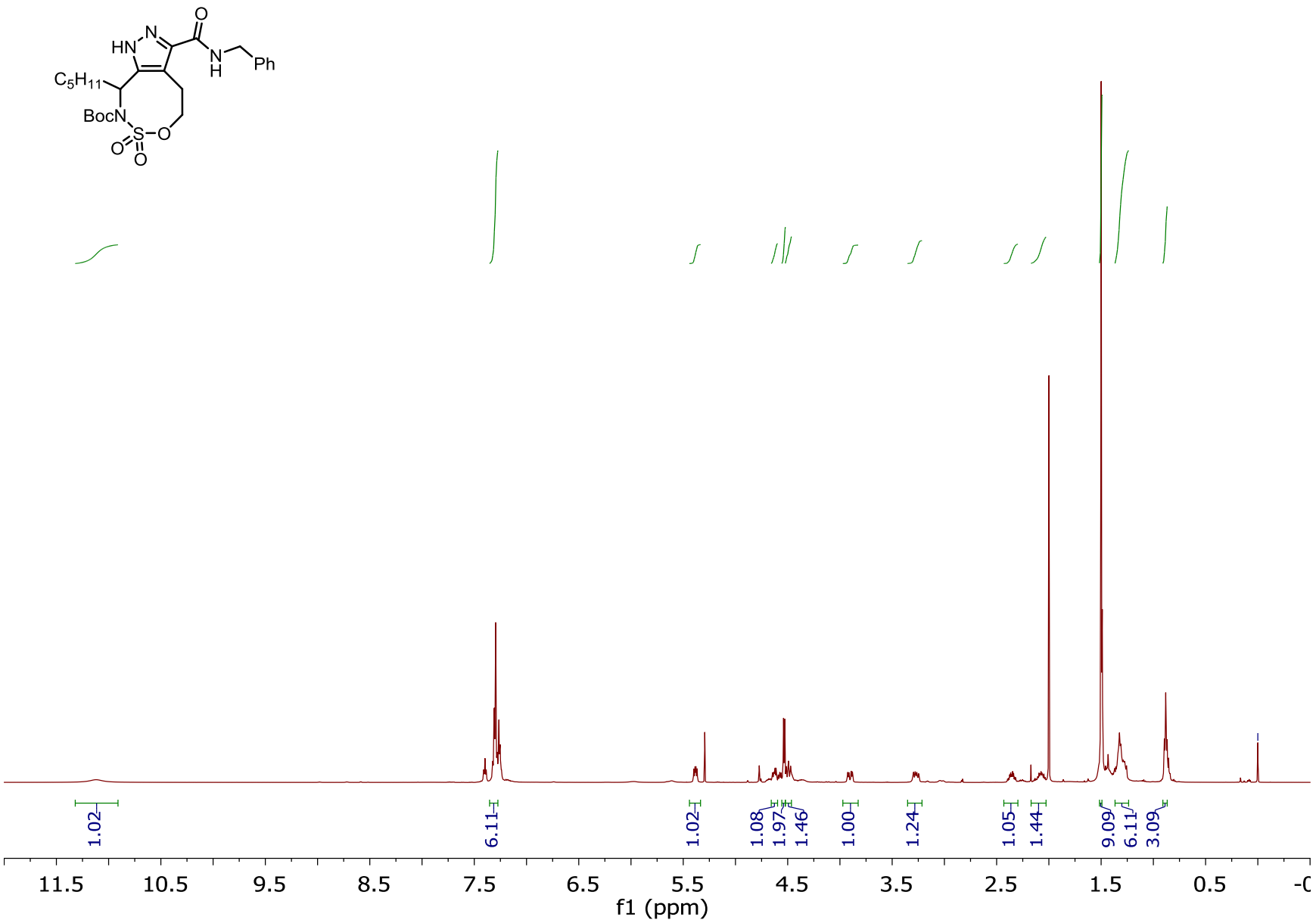
^{1}H NMR of compound 17a.



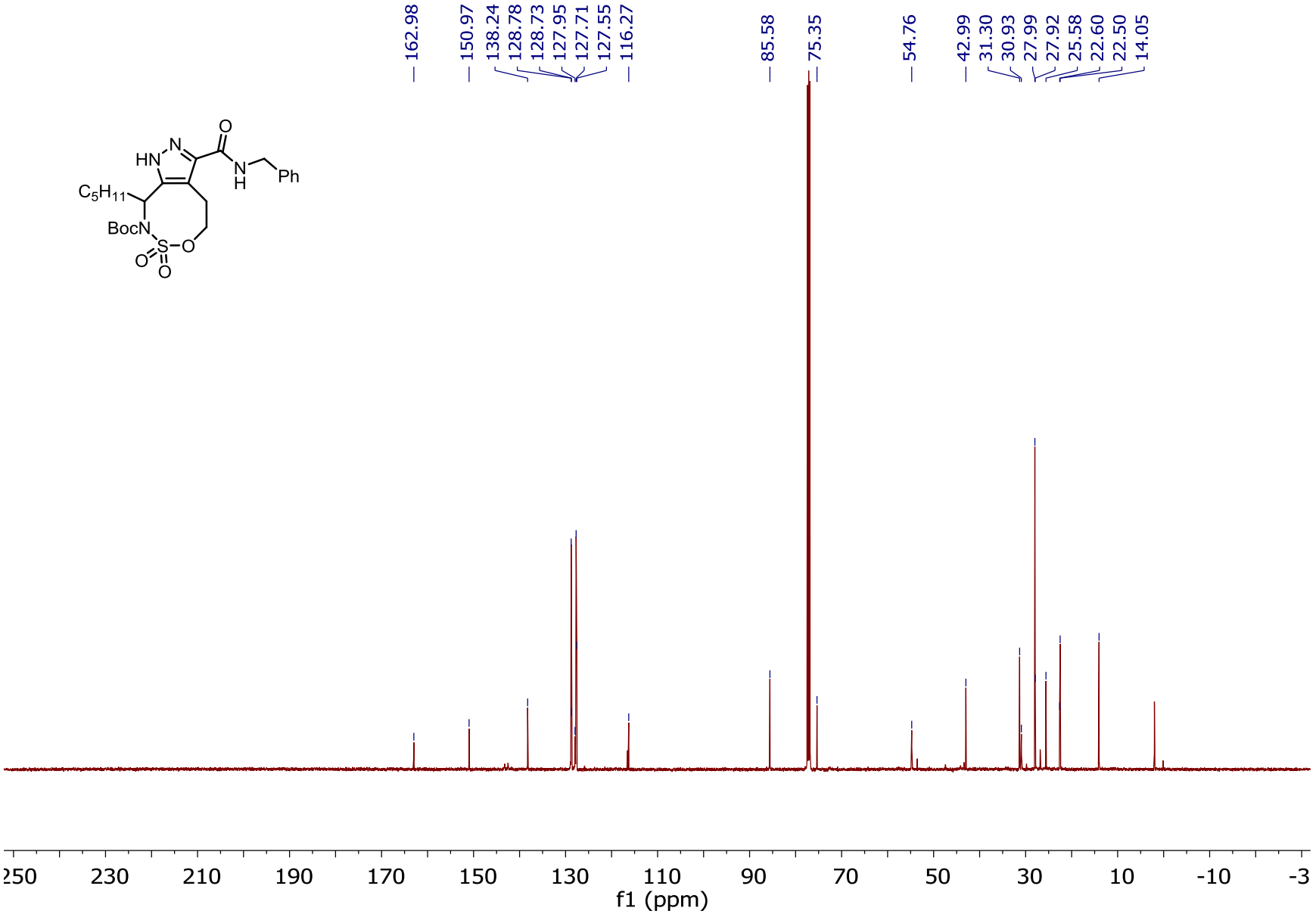
^{13}C NMR of compound 17a.



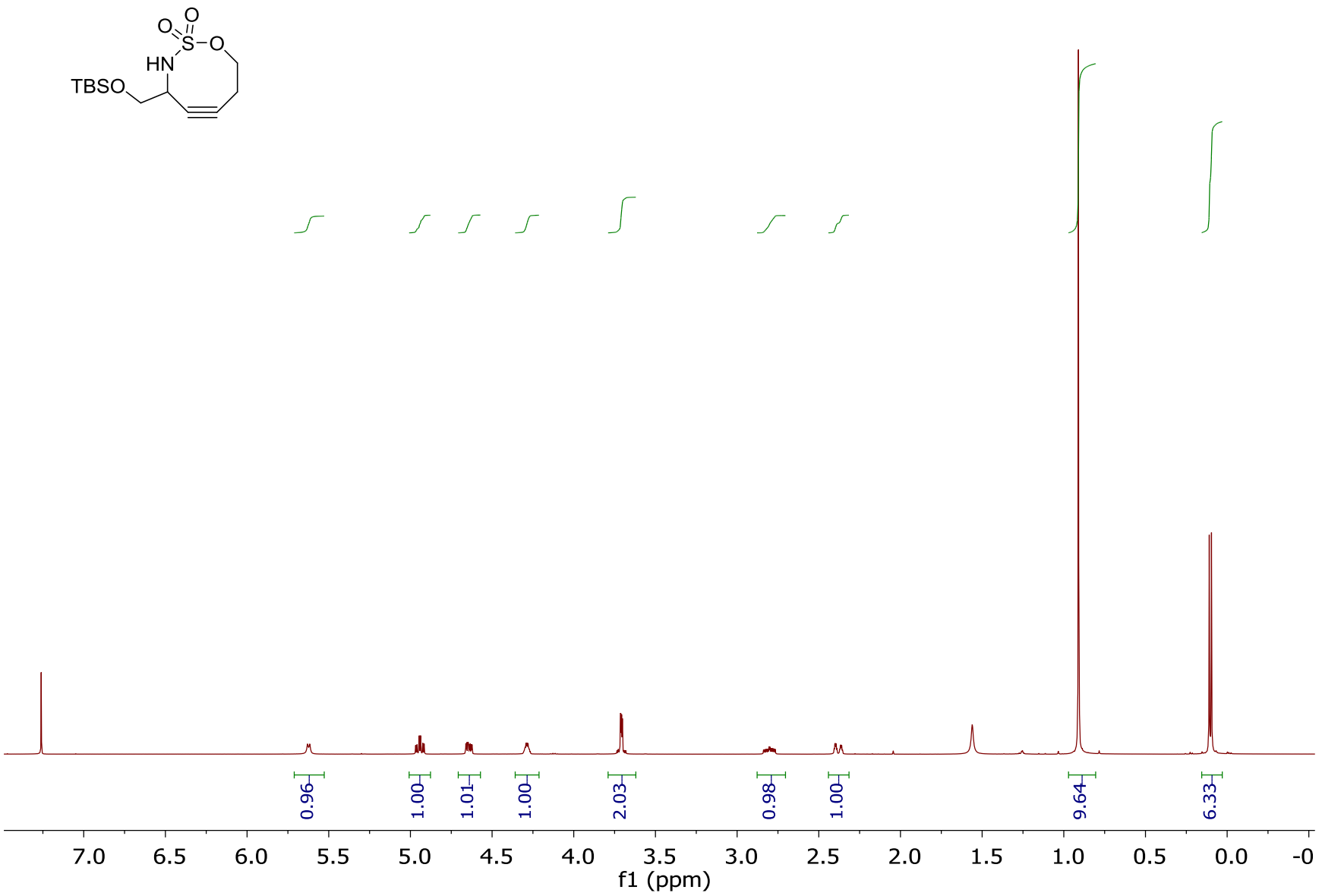
^{1}H NMR of compound 17c.



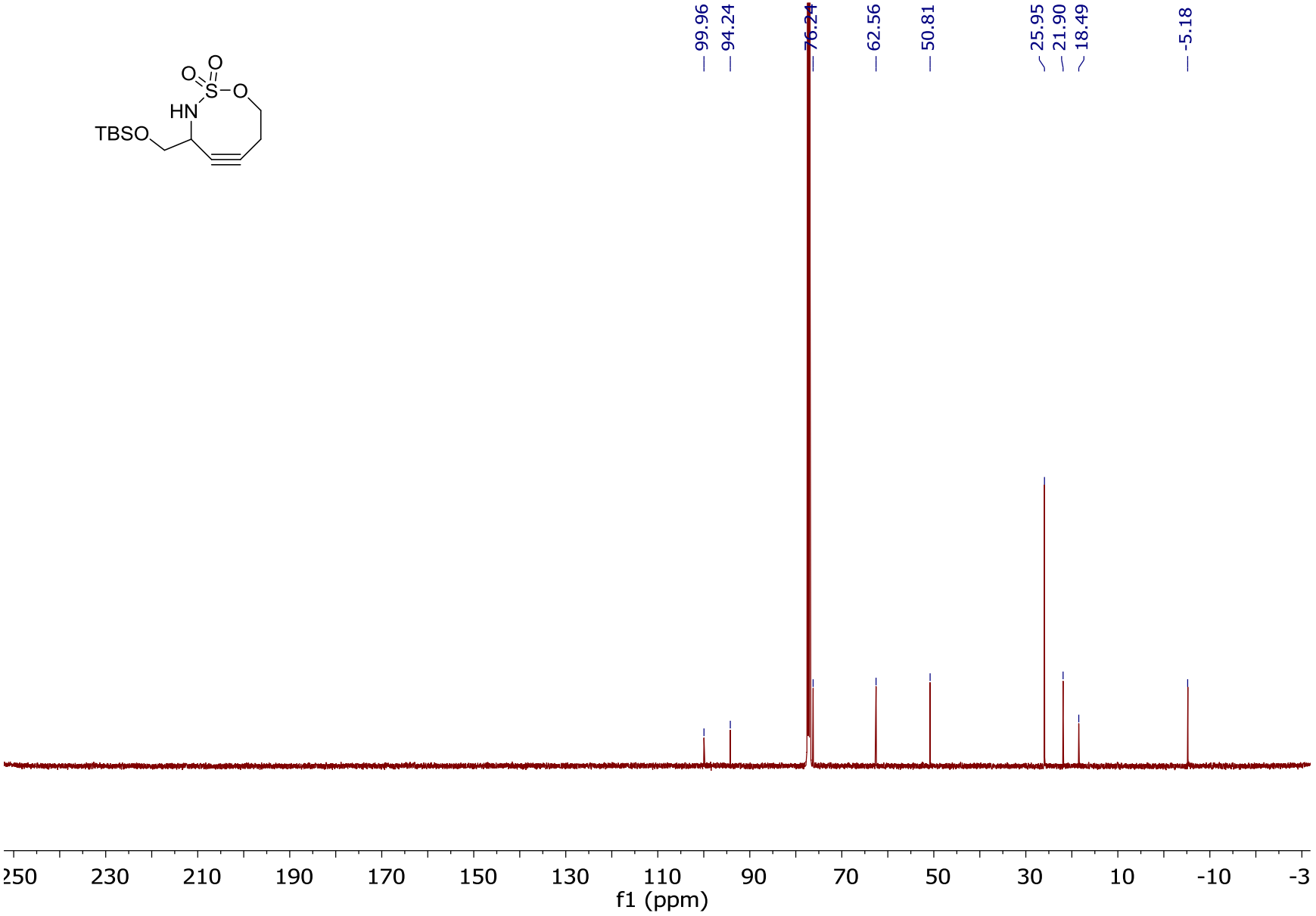
^{13}C NMR of compound 17c.



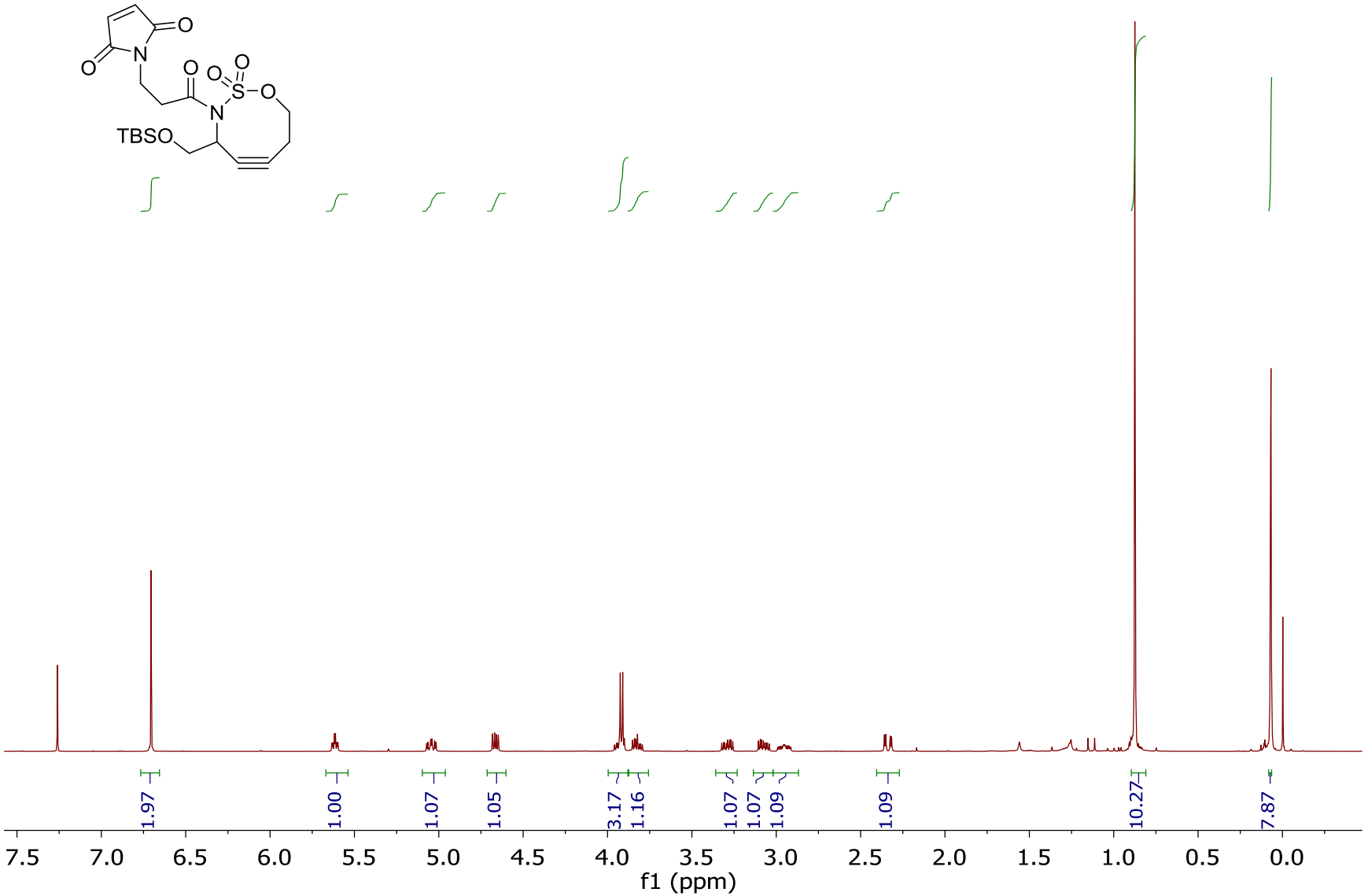
^{1}H NMR of the precursor to compound 18.



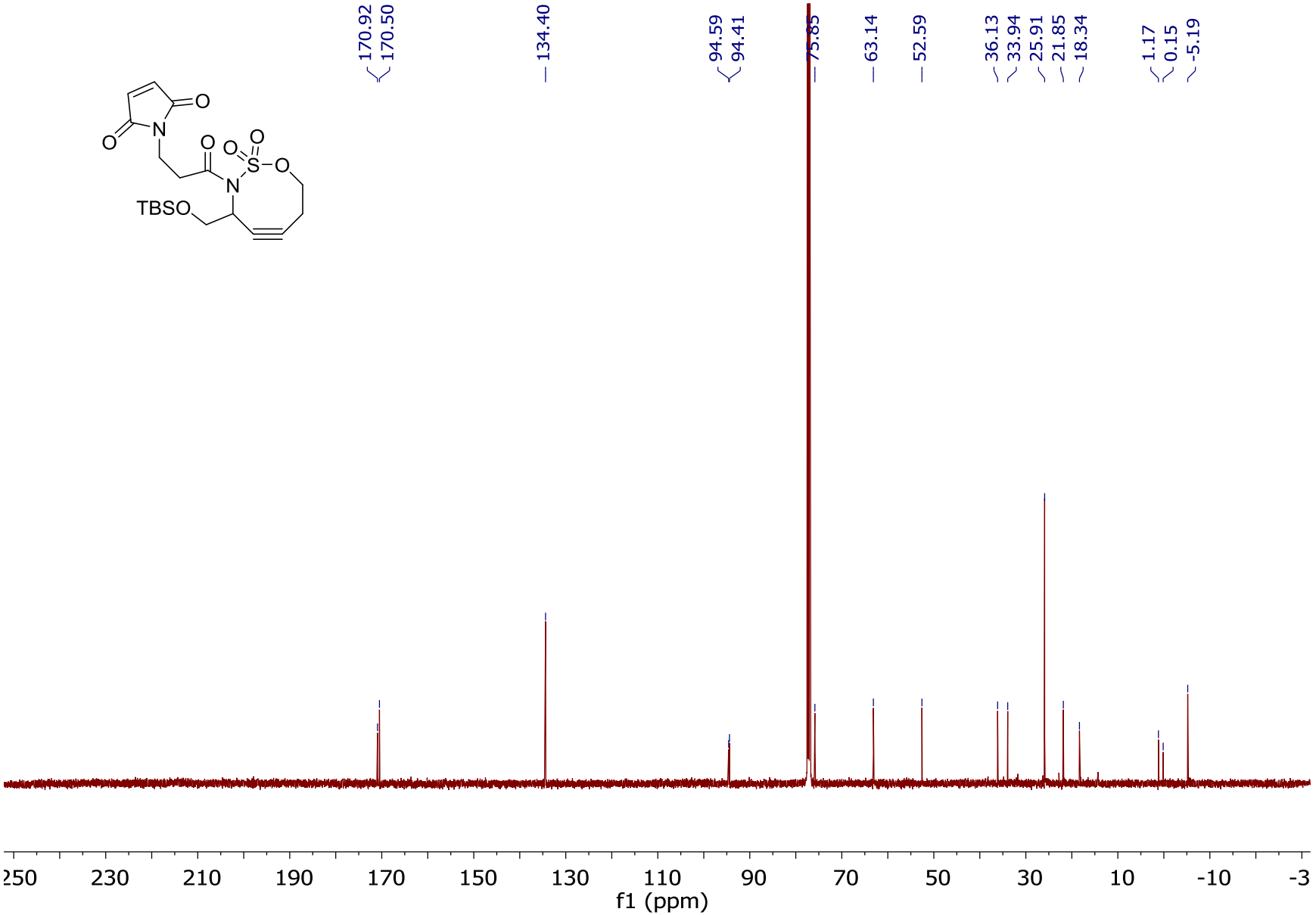
^{13}C NMR of the precursor to compound 18.



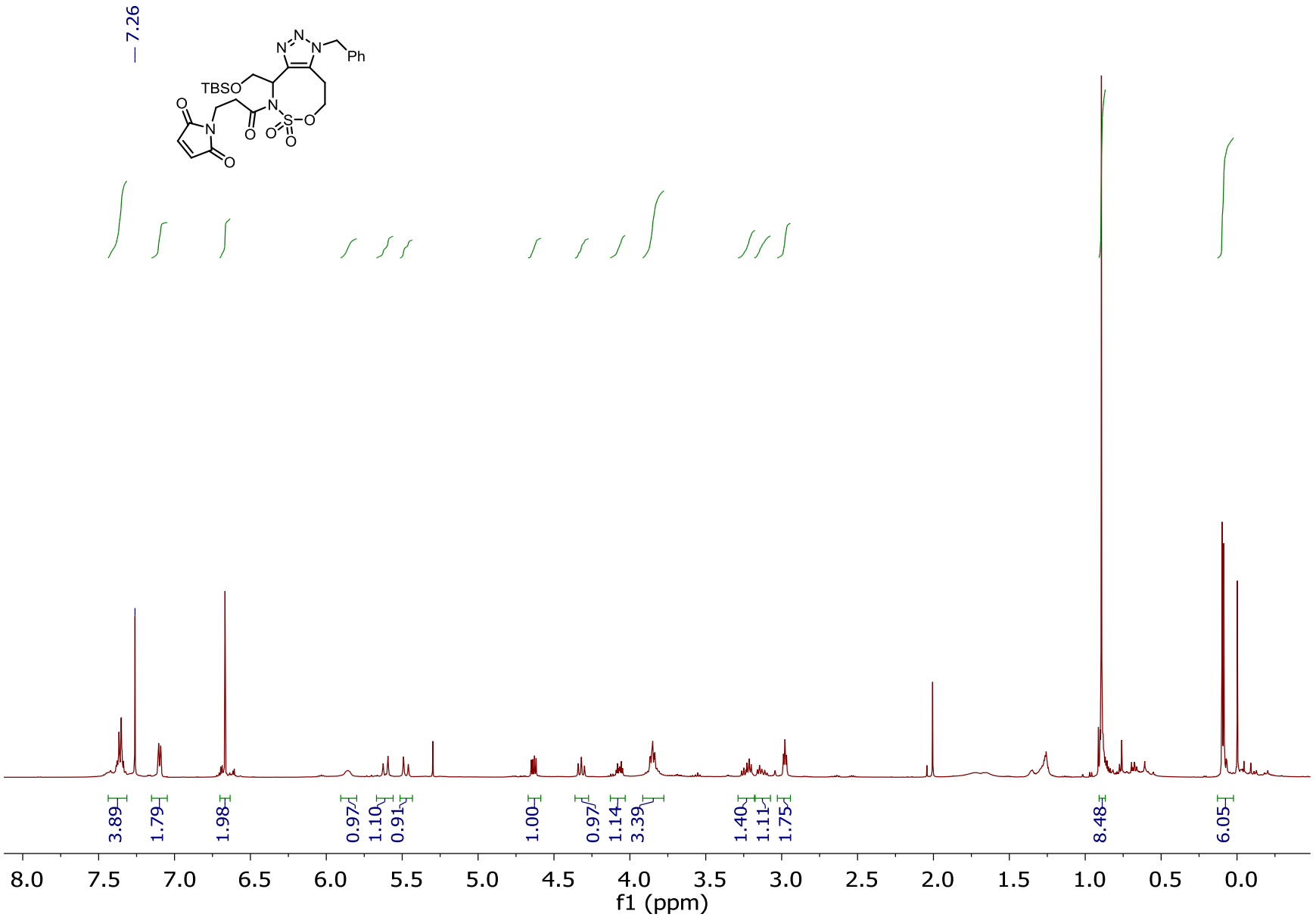
^{1}H NMR of compound 18.



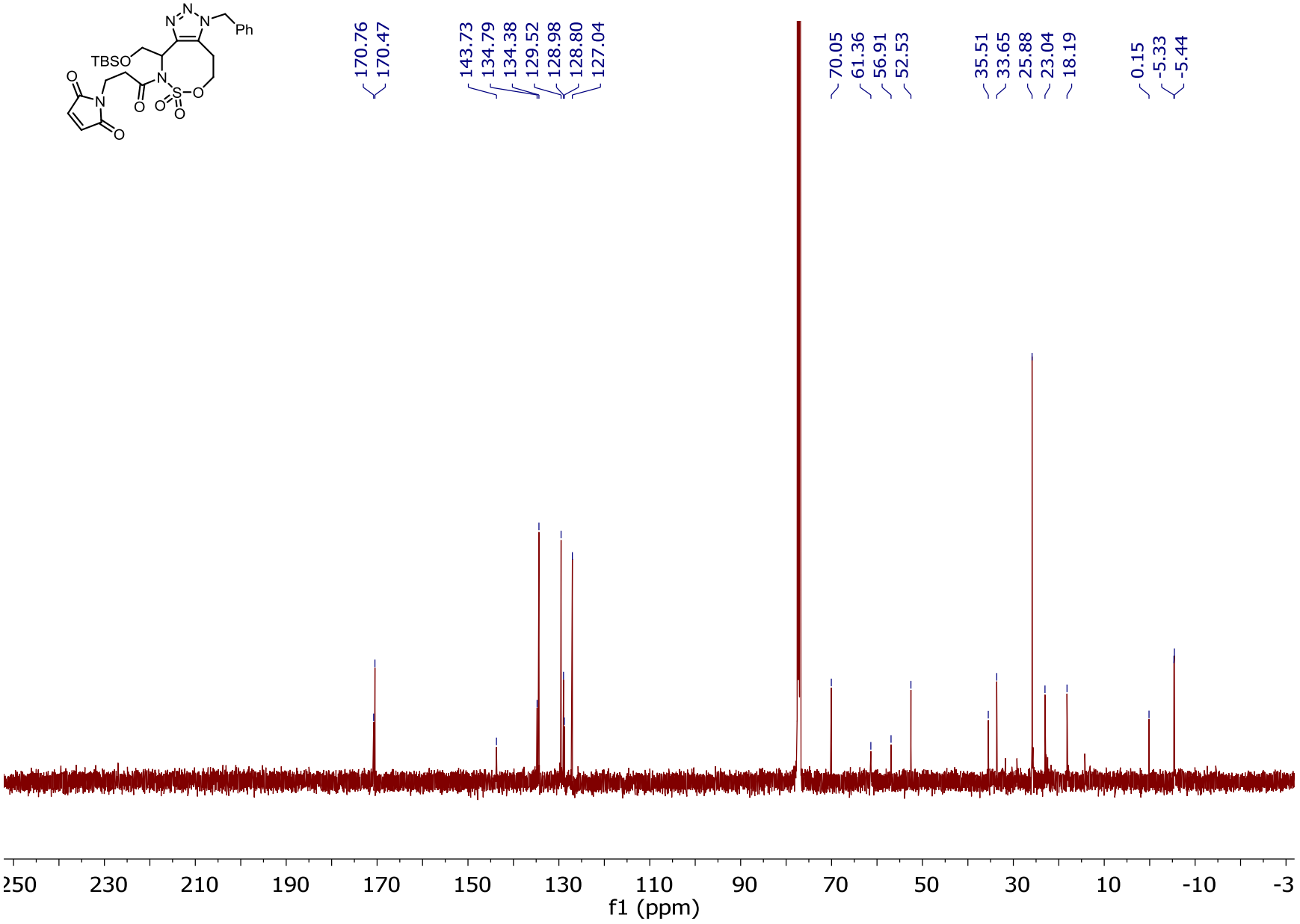
^{13}C NMR of the precursor to compound 18.



^{1}H NMR of compound 18a.



^{13}C NMR of compound 18a.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128.80
127.04
70.05
61.36
56.91
52.53
35.51
33.65
25.88
23.04
18.19
0.15
-5.33
-5.44
250
230
210
190
170
150
130
110
90
70
50
30
10
-10
-3
f1 (ppm)