Electronic Supplementary Information (ESI)

Novel Protection-Deprotection Strategies in Diazeniumdiolate Chemistry: Synthesis of V-IPA/NO

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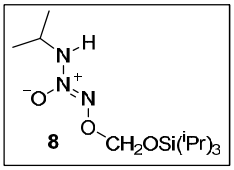
General. Starting materials were purchased from Aldrich Chemical Co. (Milwaukee, WI) unless otherwise indicated. NMR spectra were recorded on a 400 MHz Varian UNITY INOVA spectrometer; chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Ultraviolet (UV) spectra were recorded on an Agilent Model 8453 or a Hewlett-Packard model 8451A diode array spectrophotometer. Elemental analyses were performed by Midwest Microlab (Indianapolis, IN). Chromatography was performed on a Biotage SP1 Flash Purification System. Prepacked silica gel flash chromatography columns were purchased from Silicycle (Quebec City, Canada) or Universal Column (Yamazen Coporation). Compounds **2**[1], **12**[2]were prepared by using the reported procedures. Analytical data of compounds **14**[2], **15**[2] and JS-K (**18**)[3] prepared by procedures reported in this manuscript were comparable to the literature data.

***Caution**: Primary amine diazeniumdiolate salts such as **2** have been known to decompose explosively and without warning or obvious provocation on isolation or storage.*

Experimental.

***O*^{2}-(Triisopropylsilyloxy)methyl 1-(Isopropylamino)diazen-1-ium-1,2-diolate (8)**. Sodium 1-(isopropylamino)diazen-1-ium-1,2-diolate (**2**) (1.0 g, 7.1 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (1.31 mL, 7.81 mmol) were dissolved in dry DMSO (20 mL). To this solution, (triisopropylsilyloxy)methyl chloride (TOMCl) (1.81 mL, 7.81 mmol) was slowly added (the reaction is exothermic, needs vigorous stirring and cooling in a water bath). After 6 h, the reaction was diluted with water (25 mL) and extracted with ether (3 X 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate 11:1) to obtain compound **8** as a pale oil (1.50 g, 69%). UV (ethanol) λ_{max} (ε) 240 nm (6.1 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05-1.15 (m, 3H), 1.08 (d, *J* = 6.0 Hz, 18H), 1.18 (d, *J* = 6.5 Hz, 6H), 3.97-4.02 (m, 1H), 5.42 (s, 2H), 6.08 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 90.90, 49.11, 20.36, 17.63, 11.86.



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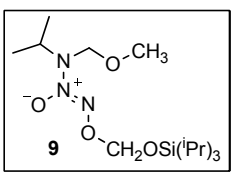
Anal. Calcd for $C_{13}H_{31}N_3O_3$·0.1 Et_2O: C, 51.44; H, 10.31; N, 13.43, Found: C, 51.82; H, 10.08; N, 13.53.

***O*^{2}-(Triisopropylsilyloxy)methyl 1-(*N*-Isopropyl-*N*-methoxymethyl)aminodiazen-1-ium-1,2-diolate (9)**. Under an inert atmosphere of N_2, a 1.6 M solution of *n*BuLi in hexane (1.61 mL, 2.57 mmol) was added to a solution of **8** (654 mg, 2.14 mmol) in THF (10 mL) at 0 °C. After 20 min, chloromethyl methyl ether (MOMCl) (0.2 mL, 2.57 mmol) was added at 0 °C, and the reaction mixture was stirred at rt for 12 h. The reaction was diluted with cold distilled water (10 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine, dried over



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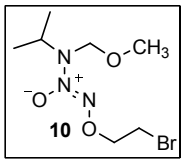
anhydrous sodium sulfate and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate 11:1) to obtain compound **9** as an oil (440 mg, 59%). UV (ethanol) λ_{max} (ε) 236 nm (7.9 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05-1.16 (m, 3H), 1.07 (d, *J* = 6.0 Hz, 18H), 1.21(d, *J* = 6.5 Hz, 6H), 3.40 (s, 3H), 3.79 (septet, *J* = 6.5 Hz, 1H), 4.65 (s, 2H), 5.49 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 91.22, 81.58, 56.76, 51.49, 19.94, 17.70, 12.29, 11.91.

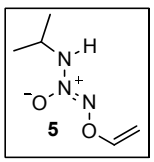
Anal. Calcd for $C_{15}H_{35}N_3O_4Si$: C, 51.54; H, 10.09; N, 12.02, Found: C, 51.71; H, 10.17; N, 12.08.

***O*^{2}-(2-Bromoethyl) 1-(*N*-Isopropyl-*N*-methoxymethyl)aminodiazen-1-ium-1,2-diolate (10)**. To a solution of **9** (280 mg, 0.8 mmol), triethylamine (TEA) (0.35 mL, 2.4 mmol), 2-bromo-l-[((trifluoromethane)sulfonyl)oxy]ethane[4] (617 mg, 2.4 mmol) in THF (6 mL), was added tetrabutylammonium fluoride trihydrate (TBAF) (316 mg, 1.0 mmol) in THF (2 mL) at rt. After stirring the reaction at rt for 2 h, the solvent was evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate 4:1) to obtain **10** as an oil (250 mg, 62%). UV (ethanol) λ_{max} (ε) 232 nm (6.4 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, *J* = 6.4 Hz, 6H), 3.41 (s, 3H), 3.58 (t, *J* = 7.0 Hz, 2H), 3.76 (septet, *J* = 6.4 Hz, 1H), 4.52 (t, *J* = 7.0 Hz, 2H), 4.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 81.48, 72.52, 56.78, 51.51, 27.68, 19.89.



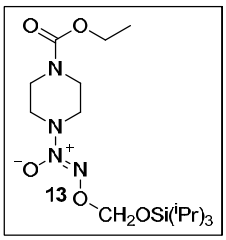
Anal. Calcd for $C_7H_{16}BrN_3O_3$: C, 31.12; H, 5.97; Br, 29.58; N, 15.56, Found: C, 30.74; H, 5.92; Br, 30.22; N, 14.99.

***O*^{2}-Vinyl 1-(Isopropylamino)diazen-1-ium-1,2-diolate (5)**. To a solution of **10** (202 mg, 0.74 mmol) in acetonitrile (3 mL), a solution of Verkade's super base (**11**) (242 mg, 0.11 mmol) in acetonitrile (3 mL) was added at rt. After 30 min at rt, the solvent was evaporated and the residue was extracted with ether (10 mL). The slurry that formed was filtered, and the residue was washed with ether (3 X 10 mL). The filtrate was evaporated to get the crude product, used for the next step without further purification. To this crude product was added CH_2Cl_2 (5 mL) and 1 M HCl solution in ether (1.48 mL), and the resulting mixture was stirred at rt for 5 h. The reaction was neutralized by saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate 10:1) to obtain compound **5** as an oil (77 mg, 71% for 2 steps). UV (ethanol) λ_{max} (ε) 261 nm (7.1 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, *J* = 6.5 Hz, 6H), 3.98-4.07 (m, 1H), 4.40 (dd, *J* = 6.7, 2.5 Hz, 1H), 4.84 (dd, *J* = 14.1, 2.5 Hz, 1H), 6.15 (d, *J* = 9.2 Hz, 1H), 6.77 (dd, *J* = 14.1, 6.7 Hz, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.40, 92.15, 49.32, 20.44.



Anal. Calcd for $C_5H_{11}N_3O_2$: C, 41.37; H, 7.64; N, 28.95, Found: C, 41.30; H, 7.52; N, 28.96.

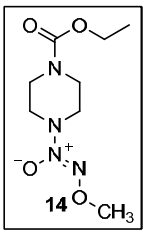
***O*^{2}-Triisopropylsilyloxymethyl 1-[4-(Ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (13)**. To a suspension of sodium 1-[4-(ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (**12**) (1.0 g, 4.6 mmol), 15-crown-5 (0.3 mL), and DIPEA (0.9 mL, 5.52 mmol) in THF (15 mL) was slowly added TOMCl (1.6 mL, 5.52 mmol). The reaction mixture was stirred at rt for 12 h. The reaction was diluted with distilled water (20 mL) and extracted with ethyl acetate (3 X 15mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate 3:1) to obtain compound **13** as a pale oil (1.41 g, 76%). UV (ethanol) λ_{max} (ε) 234 nm (5.1 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02-1.18 (m, 3H), 1.07 (d, *J* = 6.1 Hz, 18H), 1.28 (t, *J* = 7.1 Hz, 3H), 3.42 (t, *J* = 5.3 Hz, 4H), 3.66 (t, *J* = 5.3 Hz, 4H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.47 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.08, 91.24, 61.76, 51.03, 42.35, 17.64, 14.55, 11.87.



Anal. Calcd for $C_{17}H_{36}N_4O_5Si$: C, 50.47; H, 8.97; N, 13.85, Found: C, 50.53; H, 9.01; N, 13.87.

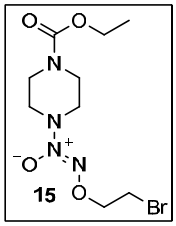
General procedure for synthesis of compounds (14)-(17) and JS-K (18).

To a solution of compound **13** (1 equiv), electrophile RX (1.5-4 equiv), TEA (1.2-4 equiv) (required in synthesis of compounds **15** and **16**) in THF (10 mL/ mmol of compound **7**) was added a solution of TBAF (1.2 equiv) in THF (3 mL/ mmol of TBAF). The reaction mixture was stirred at rt for 2 h, then the solvent was evaporated. The crude mixture was purified by flash column chromatography.



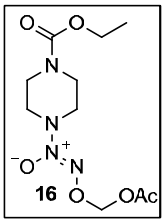
***O*^{2}-Methyl 1-[4-(Ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (14)**. Starting from **13** (100 mg, 0.25 mmol), dimethyl sulfate (36 µL, 0.38 mmol) and TBAF (95 mg, 0.3 mmol), **14** was isolated as an oil (45 mg, 78%). Analytical data of compound **14** were comparable to the literature report.[2]

***O*^{2}-(2-Bromoethyl) 1-[4-(Ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (15)**.



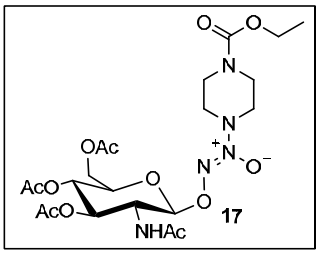
Starting from **13** (100 mg, 0.25 mmol), 2-bromo-l-[((trifluoromethane)sulfonyl)oxy]ethane[4] (257 mg, 1.0 mmol), TEA (0.14 mL, 1.0 mmol) and TBAF (95 mg, 0.3 mmol), **15** was isolated as an oil (52 mg, 65%). Analytical data of compound **15** were comparable to the literature report.[2]

***O*^{2}-Acetoxymethyl 1-[4-(Ethyloxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (16)**. Starting from **13** (100 mg, 0.25 mmol), bromomethyl acetate (98 μL, 1.0 mmol), TEA (0.14 mL, 1.0 mmol) and TBAF (95 mg, 0.3 mmol), **16** was isolated as an oil (53 mg, 74%). UV (ethanol) λ_{max} (ε) 232 nm (5.6 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.1 Hz, 3H), 2.12 (s, 3H), 3.45 (t, *J* = 5.3 Hz, 4H), 3.66 (t, *J* = 5.3 Hz, 4H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.79 (s, 2H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.32, 155.02, 87.24, 61.82, 50.77, 42.27, 20.78, 14.55.



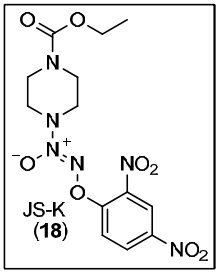
Anal. Calcd for $C_{10}H_{18}N_4O_6 \cdot 0.5H_2O$: C, 40.13; H, 6.40; N, 18.67, Found: C, 40.47; H, 6.09; N, 18.67.

***O*^{2}-(3,4,6-Tri-*O*-acetyl-β-D-*N*-acetylglucosaminyl) 1-[4-(Ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (17)**. Starting from **13** (100 mg, 0.25 mmol), 1-chloro-*N*-acetylglucosamine triacetate (110 mg, 0.3 mmol), and TBAF (95 mg, 0.3 mmol), **17** was isolated as a white solid (80 mg, 59%). UV (ethanol) λ_{max} (ε) 232 nm (6.1 $mM^{-1}cm^{-1}$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.93 (s, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 3.47 (t, *J* = 5.1 Hz, 4H), 3.66 (t, *J* = 5.1 Hz, 4H), 3.82-3.86 (m, 1H), 4.02-4.09 (m, 1H), 4.13-4.17 (m, 3H), 4.28 (dd, *J* = 12.4, 4.7 Hz, 1H), 5.11 (t, *J* = 9.7 Hz, 1H), 5.46-5.55 (m, 2H), 5.78 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.76, 170.69, 170.50, 169.52, 155.22, 100.22, 72.77, 71.79, 68.26, 62.00, 53.38, 50.91, 42.48, 23.51, 20.90, 20.79, 20.77, 14.76.



Anal. Calcd for $C_{21}H_{33}N_5O_{12}$: C, 46.07; H, 6.08; N, 12.79, Found: C, 45.89; H, 6.11; N, 12.72.

***O*^{2}-(2,4-Dinitrophenyl) 1-[4-(Ethoxycarbonyl)piperazin-1-yl]diazen-1-ium-1,2-diolate (JS-K) (18)**. Starting from **13** (100 mg, 0.25 mmol), 2,4-dinitro fluorobenzene (68 mg, 0.3 mmol), and TBAF (95 mg, 0.3 mmol), JS-K (**18**) was isolated as a yellow solid (88 mg, 92%). Analytical data of compound JS-K (**18**) were comparable to the literature report.[3]



References.

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2. Saavedra, J. E.; Booth, M. N.; Hrabie, J. A.; Davies, K. M.; Keefer, L. K. *J. Org. Chem.* **1999**, *64*, 5124-5131.
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4. Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658–664.

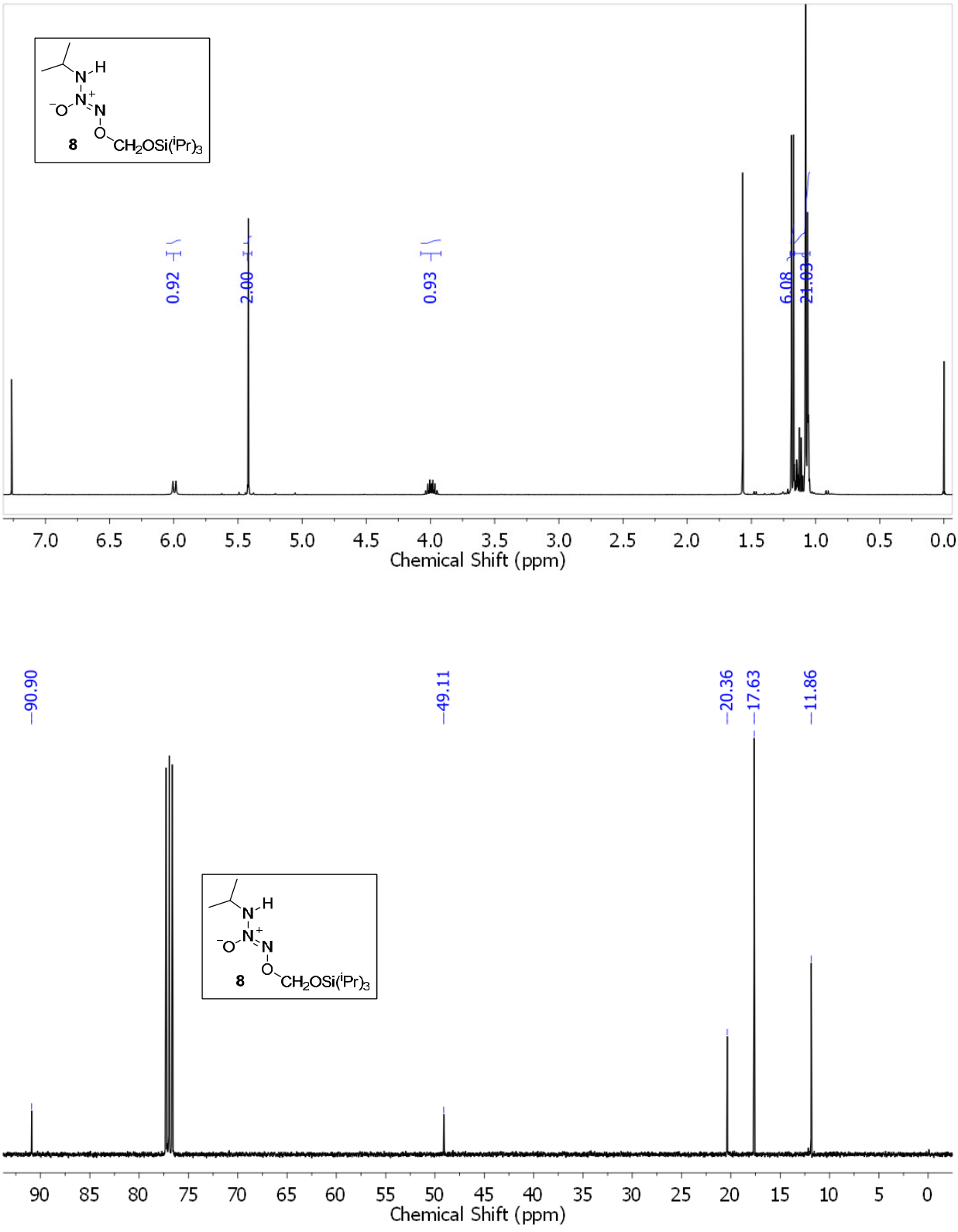

Figure S-1. ^{1}H and ^{13}C NMR of compound **8**.

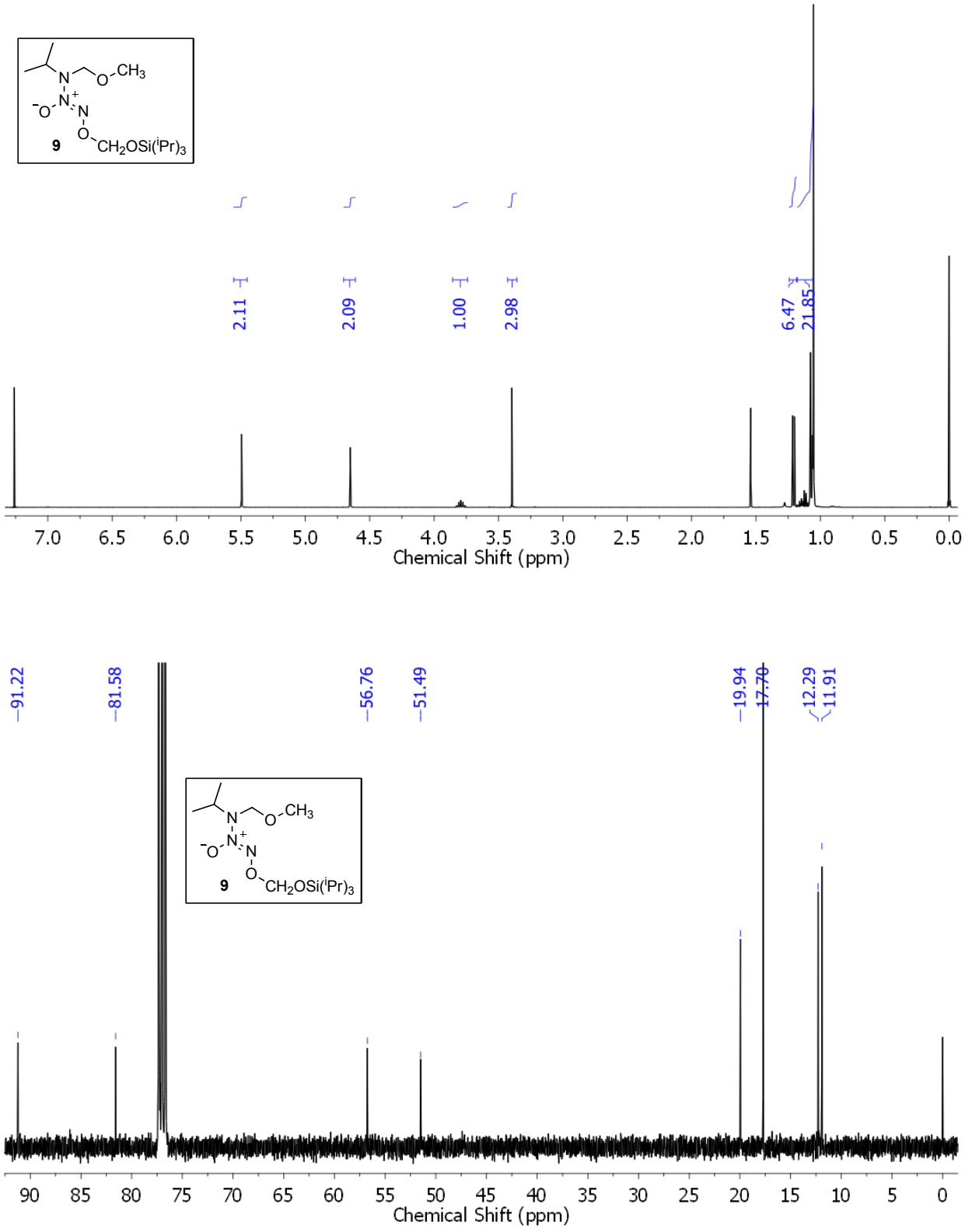

Figure S-2. ^{1}H and ^{13}C NMR of compound **9**.

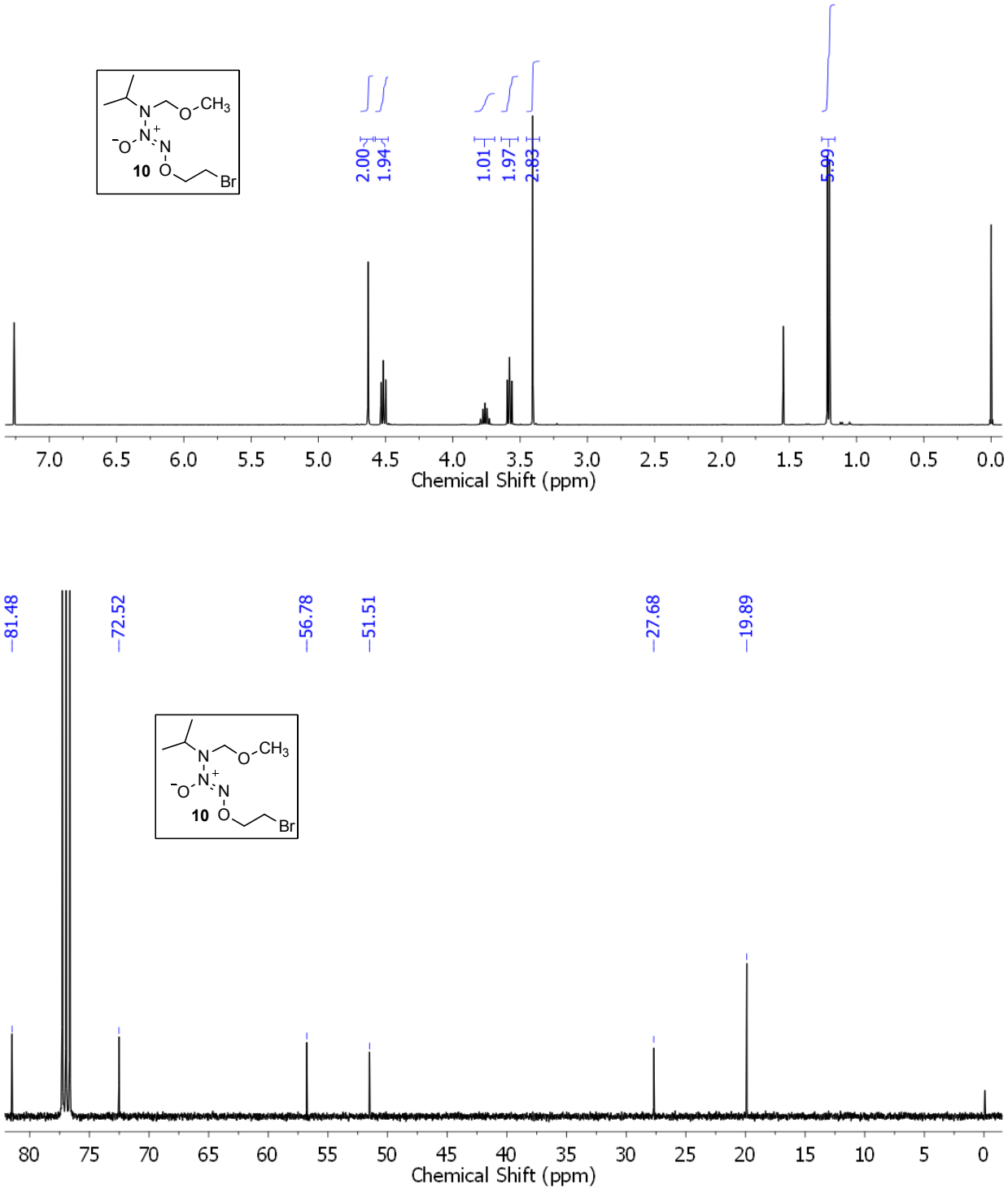

Figure S-3. ^{1}H and ^{13}C NMR of compound **10**.

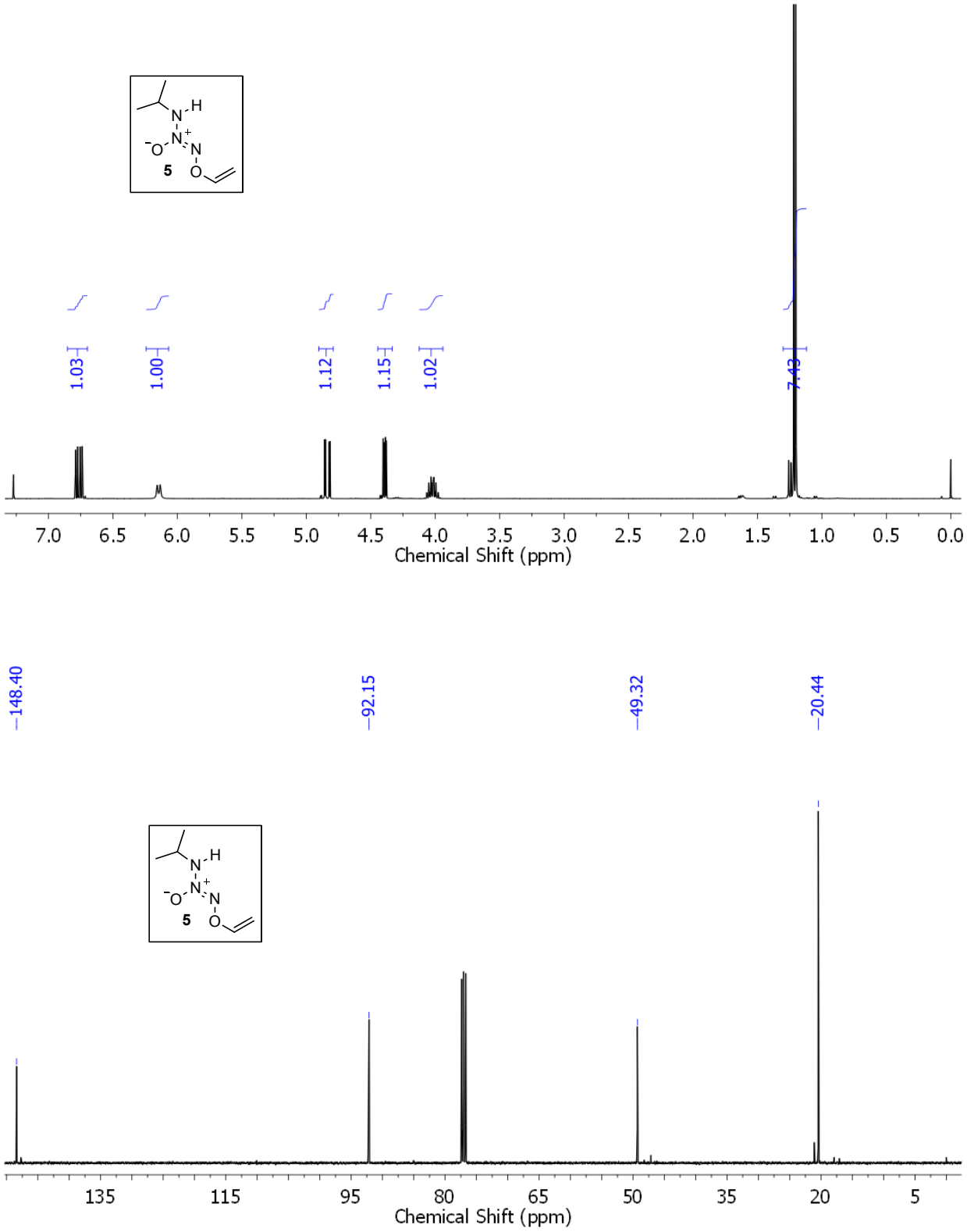

Figure S-4. ^{1}H and ^{13}C NMR of compound **5**.

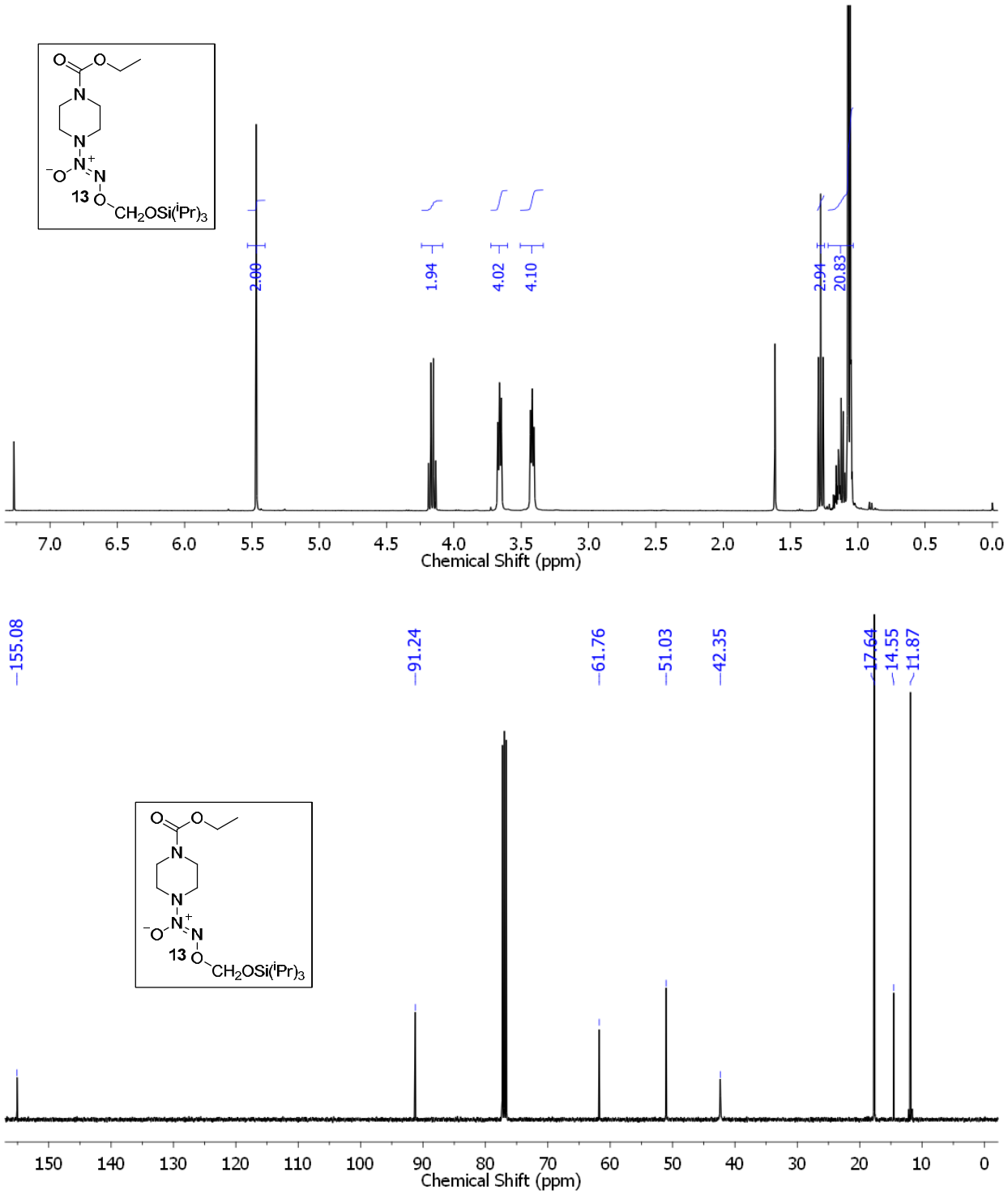

Figure S-5. ^{1}H and ^{13}C NMR of compound **13**.

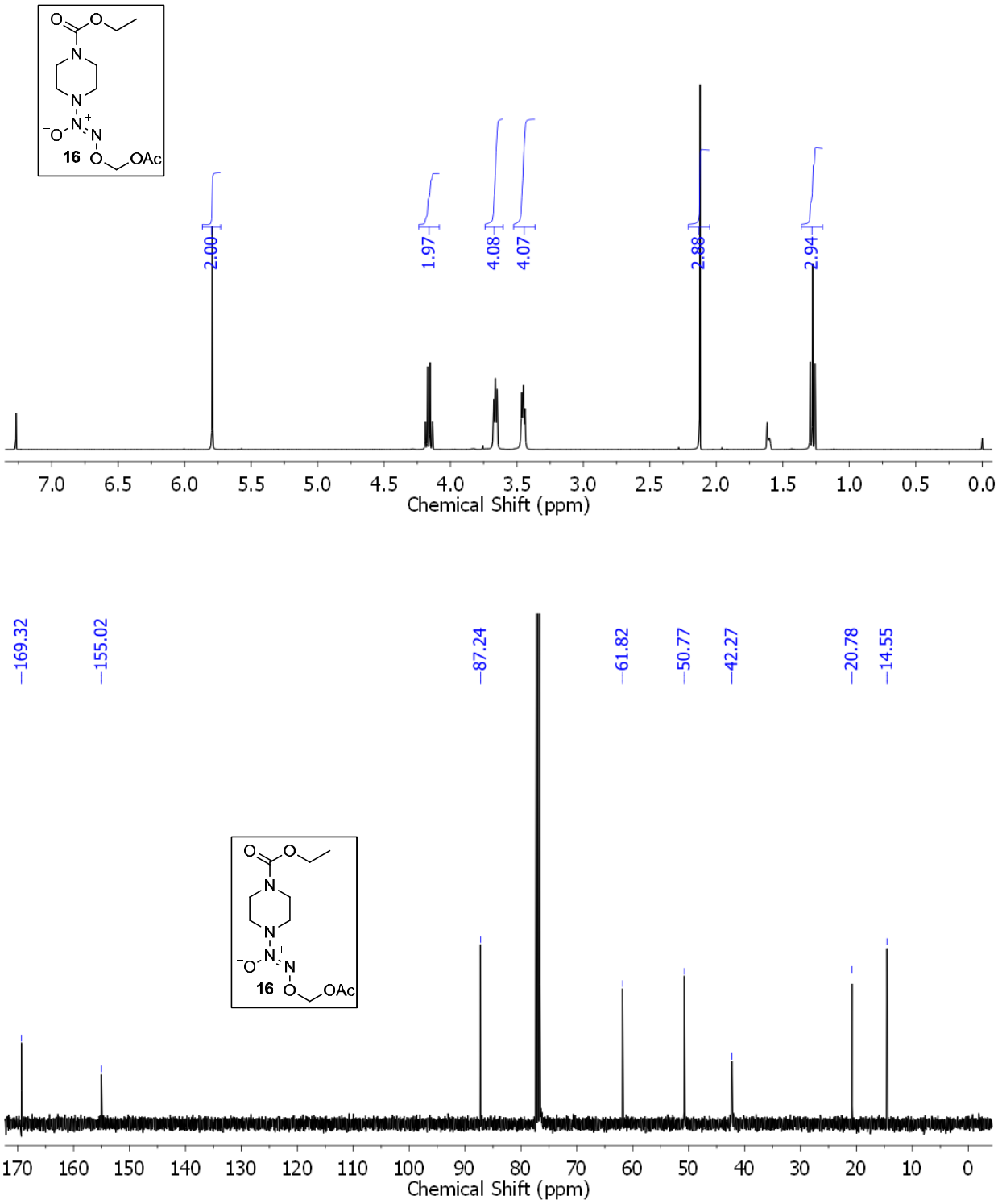

Figure S-6. ^{1}H and ^{13}C NMR of compound **16**.

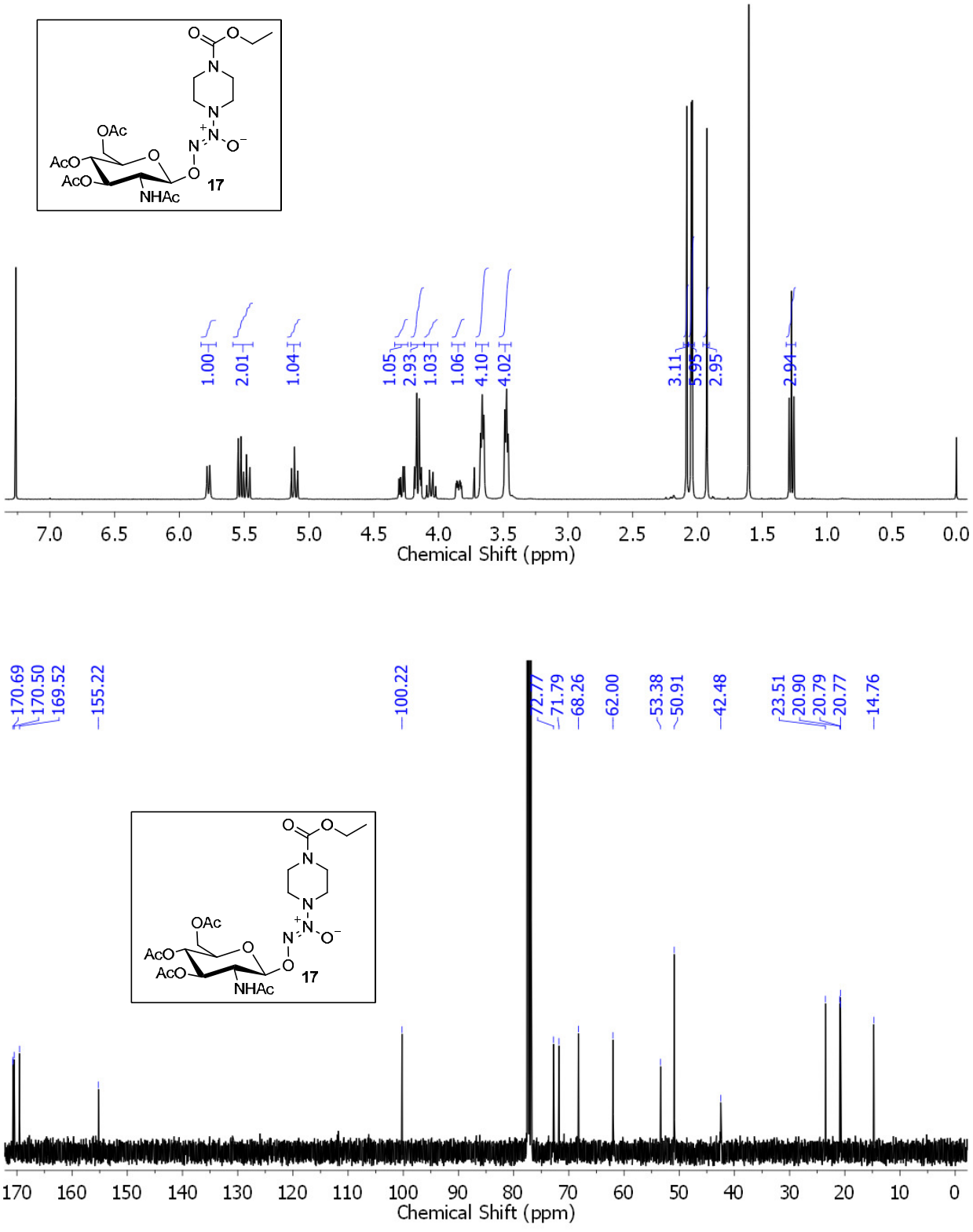

Figure S-7. ^{1}H and ^{13}C NMR of compound **17**.