Palladium-catalyzed decarboxylative allylic alkylation of diastereomeric β-ketoesters

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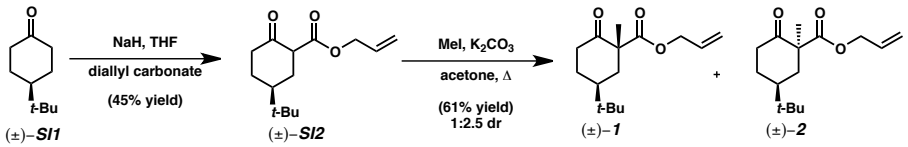
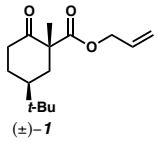
Materials and Methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20 to 23 °C) in flame-dried glassware under a nitrogen or argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Brine solutions are saturated aqueous sodium chloride solutions. Ether refers to diethyl ether. All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, permanganate, or CAM staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively), or a Varian Inova 600 spectrometer (600 MHz and 151 MHz, respectively) spectrometer and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet, bs = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer.

Synthesis of β-Ketoesters



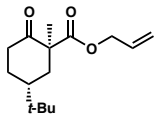
A solution of 4-(*tert)*-butylcyclohexanone (**SI1**) (1.094 g, 7.098 mmol) in THF (2.2 mL) was added dropwise to a cooled suspension of NaH (0.7098 g, 17.75 mmol, 60% dispersion in mineral oil) in THF (10 mL). Upon warming to room temperature, diallyl carbonate (1.5 mL, 10.65 mmol) was added. After 18 hours, the reaction was quenched with saturated aqueous NH_4Cl solution and 1 N HCl to give a pH of 4. The phases were separated and the aqueous phase was extracted with EtOAc (7 x 12 ml). The organic layers were combined, dried with sodium sulfate, and concentrated to afford a yellow oil. The resulting oil was purified by column chromatography (SiO_2, 10 % ether in pentane) to afford the β-ketoester **SI2** as a yellow oil (0.770 g, 45.5%). The β-ketoester **SI2** was then added to K_2CO_3 (1.96 g, 14.20 mmol) in acetone (10 mL). Iodomethane (0.89 mL, 14.20 mmol) was added dropwise, and the reaction was heated at 50 °C for 14 hours. The reaction was filtered and the solids were rinsed with acetone. The resulting organics were collected and purified by column chromatography (SiO_2, 10% → 50% ether in pentane), which allowed for the separation of **1** and **2** (494 mg, 60% yield, 1:2.5 dr (**1**:**2**)).



Allyl (1*R*,5*S*)-5-(*tert*-butyl)-1-methyl-2-oxocyclohexane-1-carboxylate (1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, *J* = 10.2 Hz, 16.2 Hz, 1H), 5.32 (m, *J* = 7.4 Hz, 1.2 Hz, 1H), 5.25 (m, *J* =10.2 Hz, 1.5 Hz, 1H), 4.62 (m, 2H), 2.49 (m, 3H), 2.02 (m, 1H),

1.57–1.18 (m, 3H), 1.29 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 173.2, 131.7, 119.2, 66.0, 56.5, 44.4, 40.6, 39.9, 32.5, 28.6, 27.7, 21.8; IR (Neat Film, NaCl) 2961, 2865, 1717, 1229, 1140 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{24}O_3$ [M]$^+$: 252.1726, found 252.1714.

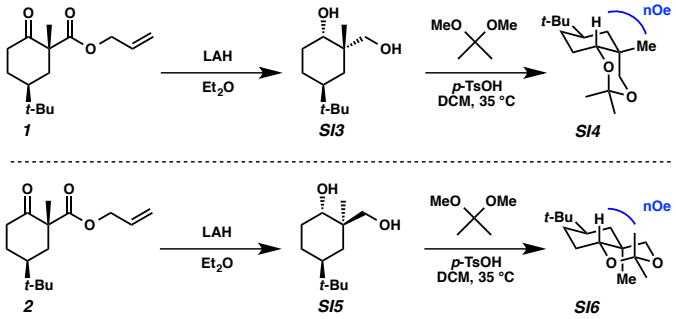


(±)-**2**

Allyl (1*S*,5*S*)-5-(*tert*-butyl)-1-methyl-2-oxocyclohexane-1-carboxylate (2)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dddd, *J* = 17.4 Hz, 10.5 Hz, 5.7 Hz, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.4 Hz, 1.2 Hz, 1H), 5.23 (dq, *J* = 10.5 Hz, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.7 Hz, 1.2 Hz, 2H), 2.45 (m, 2H), 2.21 (t, *J* = 12.6, 1H), 2.02 (m, 1H), 1.84 (dt, *J* =13.5 Hz, 3.3 Hz, 1H), 1.59 (m, 2H), 1.46 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 173.2, 132.2, 118.3, 66.0, 57.4, 41.9, 38.0, 37.0, 32.6, 27.6, 26.8, 21.0; IR (Neat Film, NaCl) 2958, 2876, 1740, 1712, 1459, 1367, 1249, 1227, 1165, 1112 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{24}O_3$ [M]$^+$: 252.1726, found 252.1718.

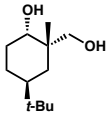
Confirmation of Relative Stereochemistries of β-Ketoesters 1 and 2



General Procedure

β-ketoester **2** (50 mg, 0.21 mmol) in ether (0.4 mL) was added slowly to LAH (23.9 mg, 0.63 mmol) in 0.5 mL ether at –78 °C. The reaction mixture was allowed to warm to ambient temperature (ca. 23 °C) and was stirred for 20 minutes. The workup procedure was carried out as reported by Fieser and Fieser.[i] Water (24 μL), 15% aqueous NaOH (24 μL), and water (72 μL) were added to reaction at 0 °C. A white precipitate was observed, and the reaction was allowed to stir for 30 minutes before filtration. The ether layer was washed with brine (2 x 2 mL) and saturated $NaHCO_3$ (2 x 2 ml). The ether layer was collected, dried with sodium sulfate, and concentrated to give a white solid.

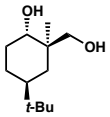
Diol **SI5** (27.1 mg, 0.136 mmol) was dissolved in DCM (2 mL). *p*-TsOH monohydrate (~2 mg) and diomethoxypropane (33 μL, 0.2706 mmol) were added to the reaction. After 24 hours, the reaction mixture was concentrated and purified by column chromatography (SiO_2 pretreated with Et_3N, 10% ether in hexanes) to afford a light yellow oil.



(±)–*SI3*

(1*S*,2*S*,4*S*)-4-(*tert*-butyl)-2-(hydroxymethyl)-2-methylcyclohexan-1-ol (SI3)

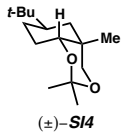
(29.8 mg, 70.9% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, *J* = 10.8 Hz, 1H), 3.46 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H), 3.27 (d, *J* = 11.1 Hz, 1H), 2.74 (bs, 2H), 1.73 (m, 2H), 1.44 (dt, *J* = 13.5 Hz, 2.7 Hz, 1H), 1.30 (m, 2H), 1.19 (s, 3H), 0.81 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.0, 68.0, 42.3, 38.9, 37.9, 32.3, 31.7, 27.6, 26.3, 24.9; IR (KBr pellet) 3272, 2958, 2868, 1459, 1365, 1064, 1039, 1019, 999 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{25}O_2$ [M+H]$^+$: 201.1855, found 201.1854.



(±)–*SI5*

(1*S*,2*R*,4*S*)-4-(*tert*-butyl)-2-(hydroxymethyl)-2-methylcyclohexan-1-ol (SI5)

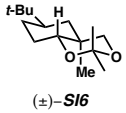
(36.5 mg, 85.7% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (dd, *J* = 11.4 Hz, 3.6 Hz, 1H), 3.50 (d, *J* = 9.3 Hz, 1H), 3.42 (dd, *J* = 10.5 Hz, 4.8 Hz, 1H), 2.84 (bs, 1H), 2.78 (bs, 1H), 1.74 (m, 1H), 1.41 (m, 2H), 1.23 (m, 2H), 0.99–0.78 (m, 2H), 0.99 (s, 3H), 0.82 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.5, 75.6, 41.7, 39.4, 34.7, 32.2, 31.0, 27.7, 25.6, 14.2; IR (KBr pellet) 3325, 2936, 2868, 1462, 1365, 1066, 1039, 991, 687 cm^{-1}; HRMS *m/z* calc'd for $C_{12}H_{25}O_2$ [M+H]$^+$: 201.1855, found 201.1847.



(±)–***SI4***

(4a*R*,6*R*,8a*R*)-6-(*tert*-butyl)-2,2,4a-trimethylhexahydro-4*H*-benzo[*d*][1,3]dioxine (SI4)

(40 mg, 45% yield): ^{1}H NMR (300 MHz, C_6D_6) δ 3.64 (d, *J* = 11.1 Hz, 1H), 3.47 (dd, *J* = 4.5 Hz, 5.1 Hz, 1H), 3.05 (d, *J* = 11.1 Hz, 1H), 1.65 (m, 3H), 1.48 (s, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.14 (m, 1H), 0.94 (m, 1H), 0.89 (s, 3H), 0.78 (s, 9H), 0.69 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 99.6, 74.0, 67.2, 40.3, 35.5, 33.8, 32.7, 27.6, 26.5, 26.3, 25.9, 25.1, 21.4; IR (Neat Film, NaCl) 2951, 2870, 1463, 1365, 1225, 1084, 1067 cm^{-1}; HRMS *m*/*z* calc'd for $C_{15}H_{28}O_2$ $[M+H]^+$: 241.2168, found 241.2173.

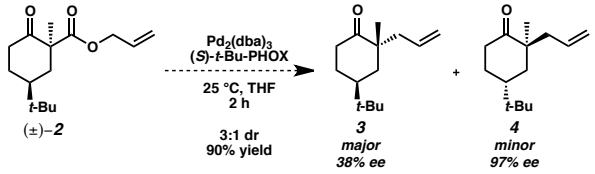


(±)–***SI6***

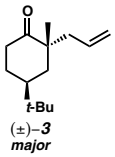
(4a*S*,6*R*,8a*R*)-6-(*tert*-butyl)-2,2,4a-trimethylhexahydro-4*H*-benzo[*d*][1,3]dioxine (SI6)

(40 mg, 71.8% yield): ^{1}H NMR (600 MHz, C_6D_6) δ 3.42 (m, 2H), 3.29 (d, *J* = 10.7 Hz, 1H), 1.60 (m, 2H), 1.55 (d, *J* = 0.8 Hz, 3H), 1.50 (m, 1H), 1.37 (d, *J* = 0.8 Hz, 3H), 1.23 (tt, *J* = 12.5, 3.5 Hz, 1H), 1.17 (t, *J* = 0.7 Hz, 3H), 1.08 (ddd, *J* = 12.7, 3.4, 2.5 Hz, 1H), 0.89 (m, 1H), 0.77 (s, 9H), 0.59 (t, *J* = 12.6 Hz, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 99.4, 76.0, 73.5, 41.6, 34.5, 33.9, 32.2, 30.5, 27.7, 27.5, 26.1, 19.4, 16.0; IR (Neat Film, NaCl) 2992, 2944, 2870, 1462, 1384, 1366, 1270, 1235, 1204, 1104, 1084, 1040 cm^{-1}; HRMS *m*/*z* calc'd for $C_{15}H_{28}O_2$ $[M+H]^+$: 241.2168, found 241.2177.

General Procedures for Pd-Catalyzed Decarboxylative Allylic Alkylation

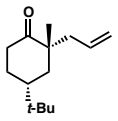


$Pd_2(dba)_3$ (67 mg, 0.0733 mmol) and (*S*)-*t*-BuPHOX (73.8 mg, 0.19045 mmol) were combined in a round bottom flask. The vial was evacuated for 10 minutes prior to addition of THF (88 mL). The reaction mixture was allowed to stir for 30 minutes prior to addition of β-ketoester **2** (739 mg, 2.93 mmol) via syringe. Reaction progress was monitored by TLC. Once the reaction was complete, the mixture was concentrated. Isolation of products was accomplished by column chromatography (SiO_2, 10 % ether in pentane).



(*trans*)-2-allyl-4-(*tert*-butyl)-2-methylcyclohexan-1-one (3)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (m, 1H), 5.04 (m, 2H), 2.38–2.23 (m, 4H), 2.03 (m, 1H), 1.84 (m, 1H), 1.70 (m, 1H), 1.42–1.13 (m, 2H), 1.00 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0, 133.0, 118.5, 48.2, 42.0, 40.1, 38.5, 32.4, 28.3, 27.7, 22.7; IR (Neat Film, NaCl) 2962, 2870, 1709, 1366, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{24}O$ [M^+]: 208.1827, found 208.1825; $[\alpha]_D^{25.6}$ –30.00° (*c* 1.08, hexane).

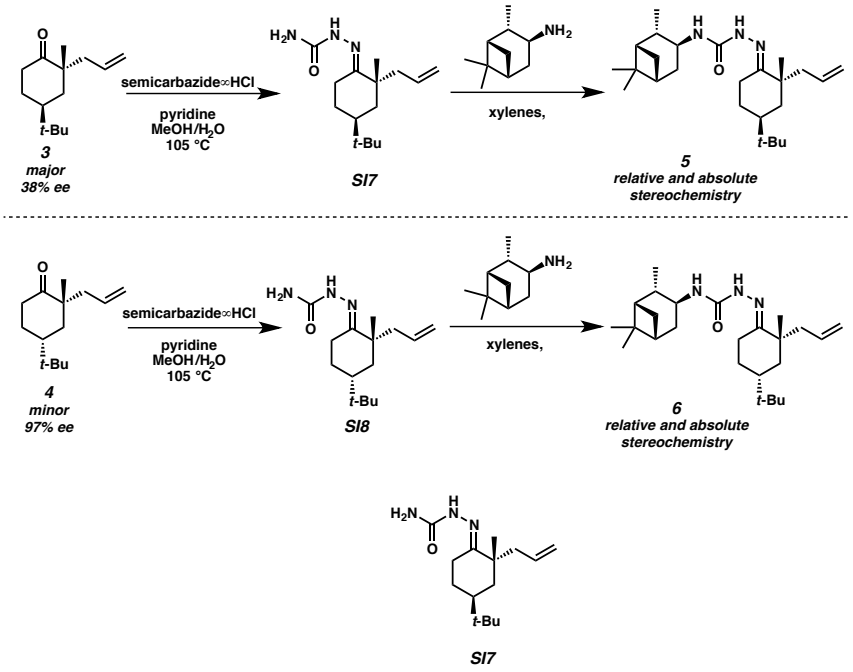


(±)–*4*
minor

(*cis*)-2-allyl-4-(*tert*-butyl)-2-methylcyclohexan-1-one (4)

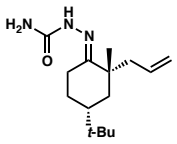
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.03 (m, 2H), 2.50 (m, 1H), 2.28 (m, 2H), 2.16 (m, 1H), 2.00 (m, 1H), 1.64 (m, 2H), 1.42 (m, 2H), 1.14 (s, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 135.0, 117.9, 47.3, 43.3, 42.3, 38.9, 38.5, 32.5, 27.8, 27.7, 24.2; IR (Neat Film, NaCl) 2963, 2870, 1709, 1366, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{14}H_{24}O$ [M^+]: 208.1827, found 208.1836; $[\alpha]_D^{25.7}$ +77.81° (*c* 0.105, hexane).

Determination of Relative Stereochemistries of Ketones 3 and 4



(*E*)-2-((2*R*,4*S*)-2-allyl-4-(*tert*-butyl)-2-methylcyclohexylidene)hydrazine-1-carboxamide (SI7)

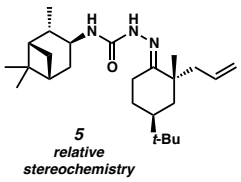
Prepared as reported by Behenna and Stoltz.[ii] (131.7 mg, 69.1% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (bs, 1H), 5.63 (m, 1H), 5.02 (m, 2H), 2.55 (m, 1H), 2.07 (m, 2H), 1.93 (m, 2H), 1.72 (m, 1H), 1.51–1.06 (m, 3H), 1.10 (s, 3H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 157.3, 134.0, 117.8, 42.8, 41.9, 41.9, 40.0, 32.5, 31.2, 27.0, 25.0, 22.8; IR (Neat Film, NaCl) 3470, 3194, 2963, 1689, 1583, 1475, 1366, 1078, 913, 770 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{27}N_3O$ [M^+]: 265.2154, found 265.2149; $[\alpha]_D^{25.7}$ –8.23° (*c* 0.305, methanol).



SI8

(*E*)-2-((2*R*,4*R*)-2-allyl-4-(*tert*-butyl)-2-methylcyclohexylidene)hydrazine-1-carboxamide (SI8)

Prepared as reported by Behenna and Stoltz.[ii] (103.7 mg, 81.4% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 5.89 (m, 1H), 5.03 (app. d, 2H), 2.56 (m, 1H), 2.36 (m, 2H), 1.94 (m, 2H), 1.53 (m, 2H), 1.20–1.11 (m, 2H), 1.11 (s, 3H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.5, 136.0, 117.0, 45.2, 42.3, 41.3, 39.0, 32.5, 27.6, 26.8, 25.8, 23.1; IR (Neat Film, NaCl) 3473, 3199, 2963, 1694, 1578, 1473, 1366, 1101, 912 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{27}N_3O$ [M^+]: 265.2154, found 265.2163; $[\alpha]_D^{25.9}$ –6.67° (*c* 0.995, methanol).



5
relative stereochemistry

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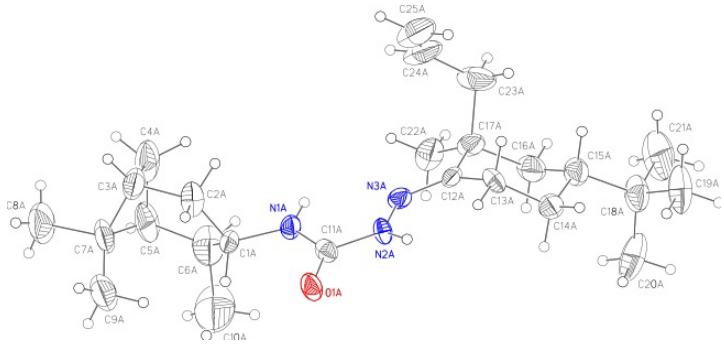
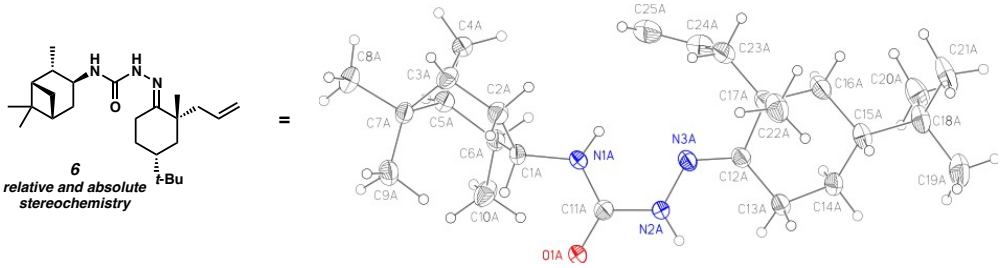


(*E*)-2-((2*R*,4*S*)-2-allyl-4-(*tert*-butyl)-2-methylcyclohexylidene)-*N*-((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)hydrazine-1-carboxamide (5)

Prepared as reported by Behenna and Stoltz.[ii] (40.1 mg, 66.2% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (bs, 1H), 6.08 (d, *J* = 9 Hz, 1H), 5.65 (m, 1H), 5.05 (m, 2H), 4.17 (m, 1H), 2.63 (m, 2H), 2.41 (m, 1H), 2.24 (m, 3H), 1.84 (m, 6H), 1.53 (m, 2H), 1.22 (s, 3H), 1.15 (app. dd, *J* = 7.2 Hz, 1.0 Hz, 4H), 1.10 (s, 3H), 1.05 (s, 3H), 0.88 (d, 1H, *J* =

9.9 Hz), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 156.0, 134.1, 117.8, 48.3, 48.2, 48.0, 47.1, 42.7, 41.9, 41.8, 39.8, 38.6, 38.1, 35.5, 32.5, 28.2, 27.6, 27.0, 25.0, 23.6, 22.6, 21.0; IR (Neat Film, NaCl) 3406, 3194, 3075, 2962, 1672, 1526 cm^{-1}, HRMS *m/z* calc'd for $C_{25}H_{43}N_3O$ $[M+H]^+$: 402.3484, found 402.3487; $[\alpha]_D^{25.0}$ +15.31° (*c* 0.2250, $CHCl_3$). X-Ray structure has been deposited in the Cambridge Database (CCDC) under the deposition number 791823.



(*E*)-2-((2*R*,4*R*)-2-allyl-4-(*tert*-butyl)-2-methylcyclohexylidene)-*N*-((1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)hydrazine-1-carboxamide (6)

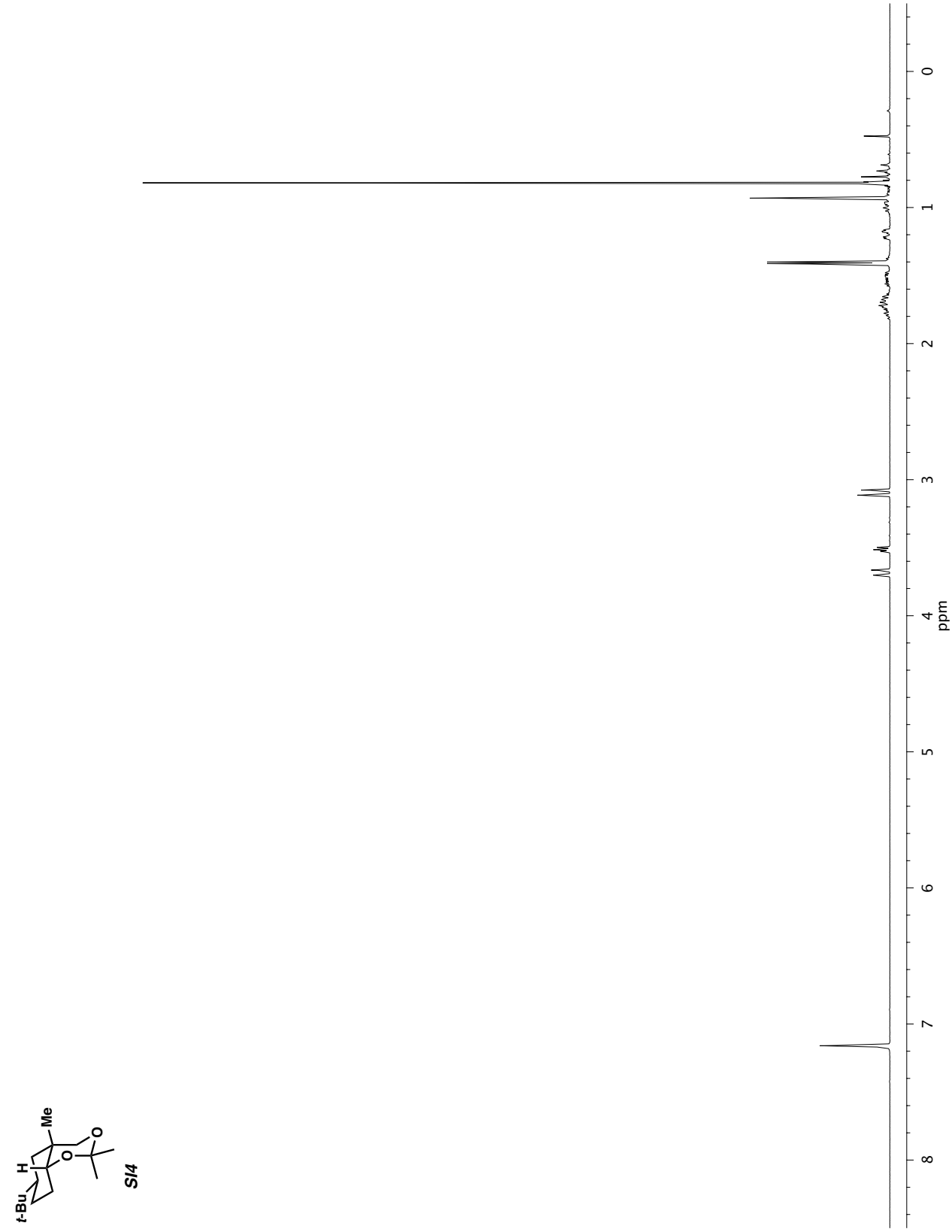
Prepared as reported by Behenna and Stoltz.[ii] (64.1 mg, 84.9% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (bs, 1H), 6.08 (d, *J* = 9 Hz, 1H), 5.94 (m, 1H), 5.04 (m, 2H), 4.17 (m, 1H), 2.71 (m, 2H), 2.37 (m, 3H), 1.91 (m, 5H), 1.55 (m, 3H), 1.21 (s, 3H), 1.12 (d, *J* = 7.5, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.87 (d, *J* = 9.9 Hz, 1H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.1, 136.4, 116.6, 48.2, 46.9, 45.1, 42.3, 41.9, 41.3, 39.4, 38.6, 38.0, 35.5, 32.5, 28.2, 27.6, 26.9, 25.6, 23.6, 22.9, 21.0; IR (Neat Film, NaCl) 3400, 3194, 2952, 2873, 1672, 1526 cm^{-1}; HRMS *m/z* calc'd for $C_{25}H_{43}N_3O$ $[M+H]^+$: 402.3484, found 402.3491; $[\alpha]_D^{25.1}$ +29.73° (*c* 0.2550, hexane). X-Ray structure has been deposited in the Cambridge Database (CCDC) under the deposition number 293396.

References

(i) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581–595.

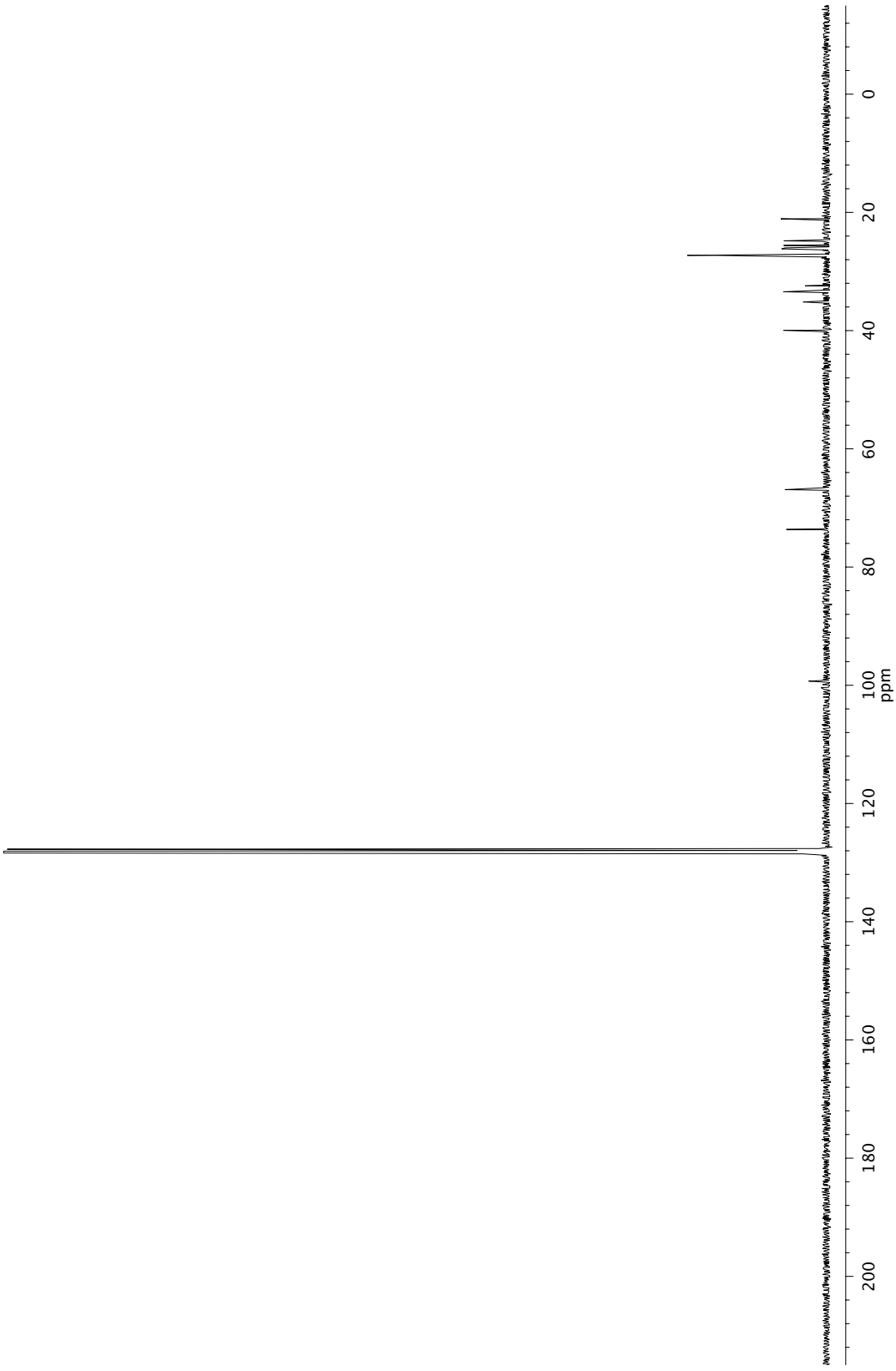
(ii) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15055.

NMR Spectra

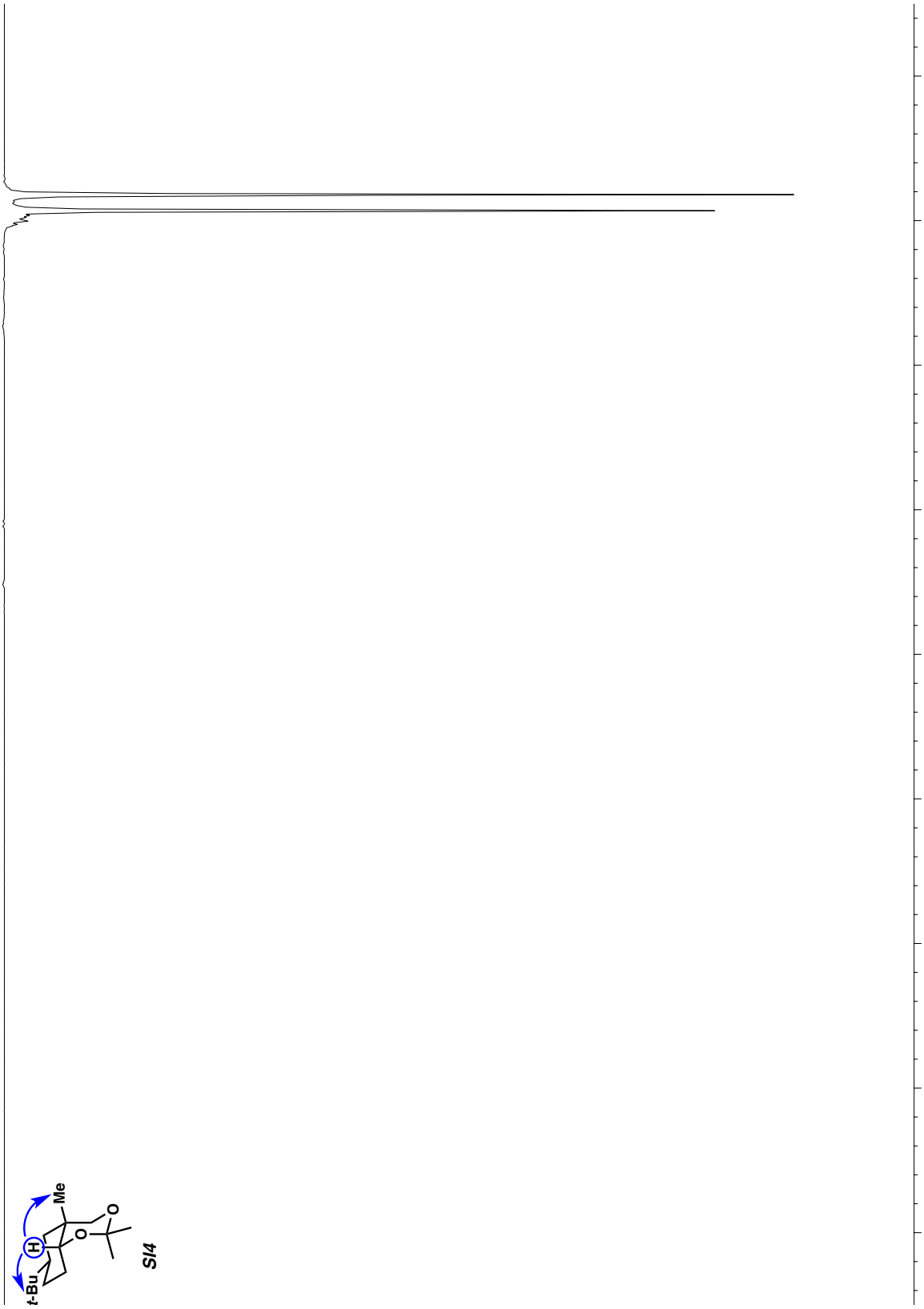


^{1}H NMR (300 MHz, $CDCl_3$) of compound **SI4**.

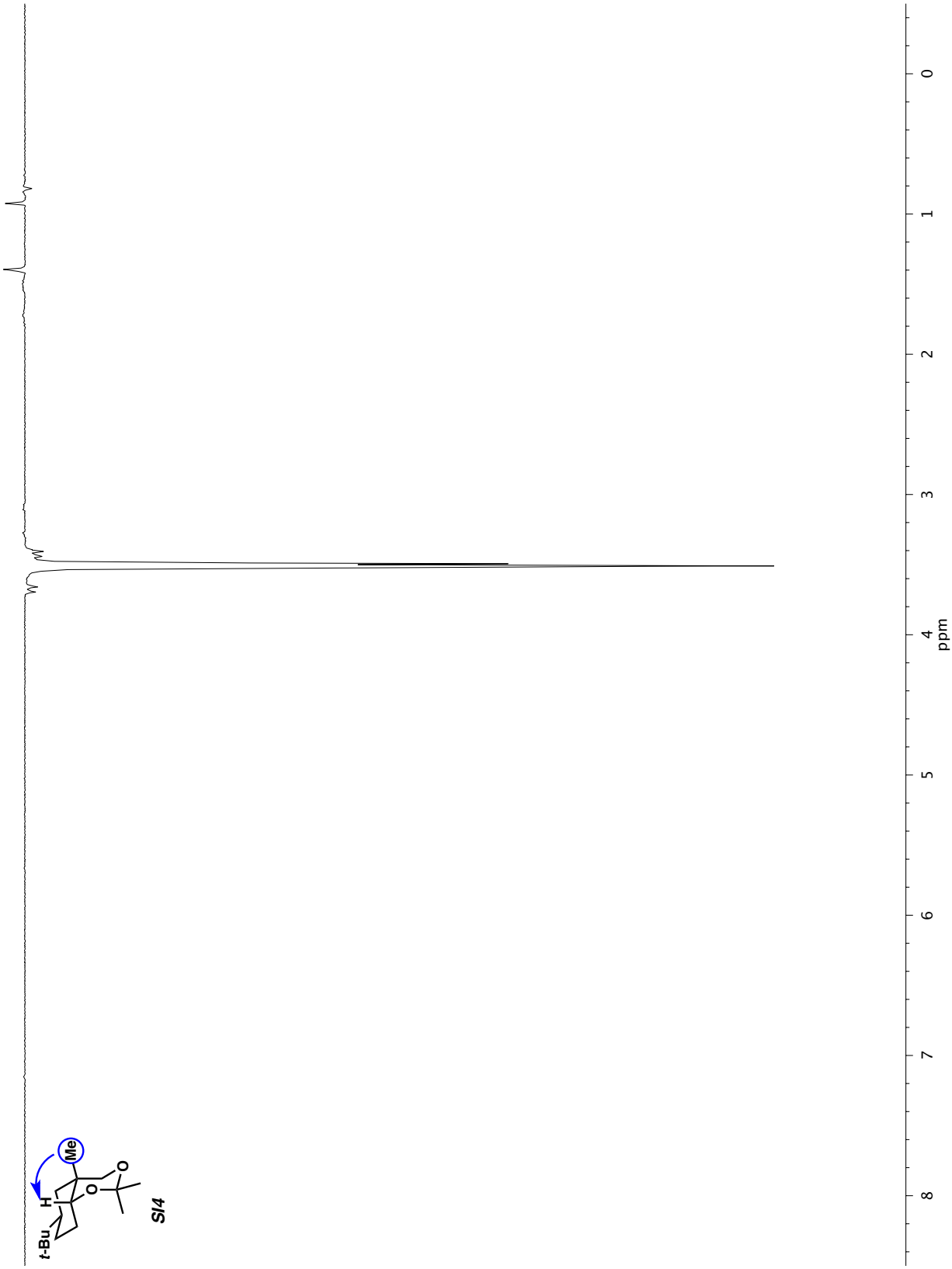
SI4



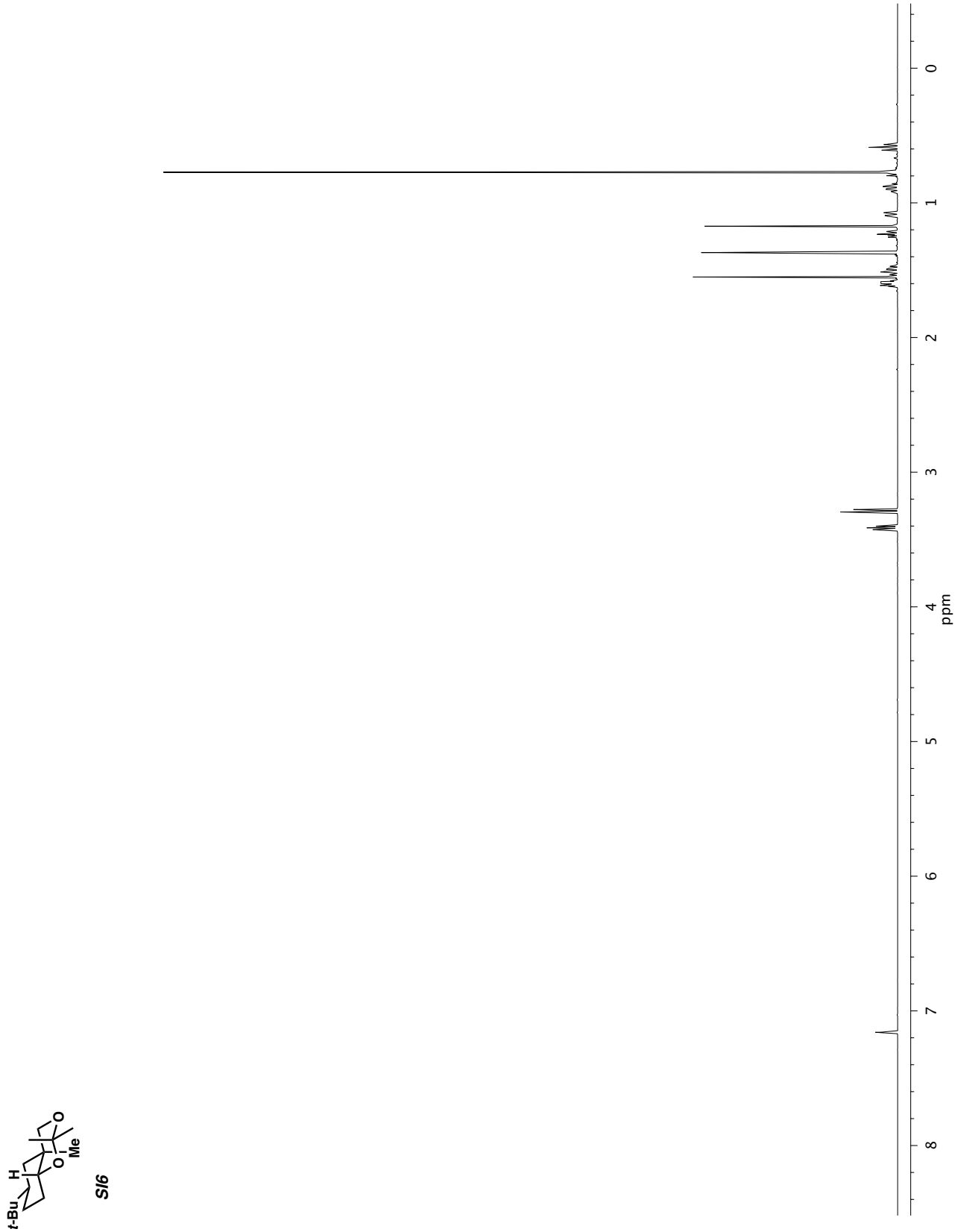
^{13}C NMR (75 MHz, $CDCl_3$) of compound **SI4**.



1-D nOe NMR (300 MHz, $CDCl_3$, Irradiation at 3.47 ppm) of compound **SI4**.

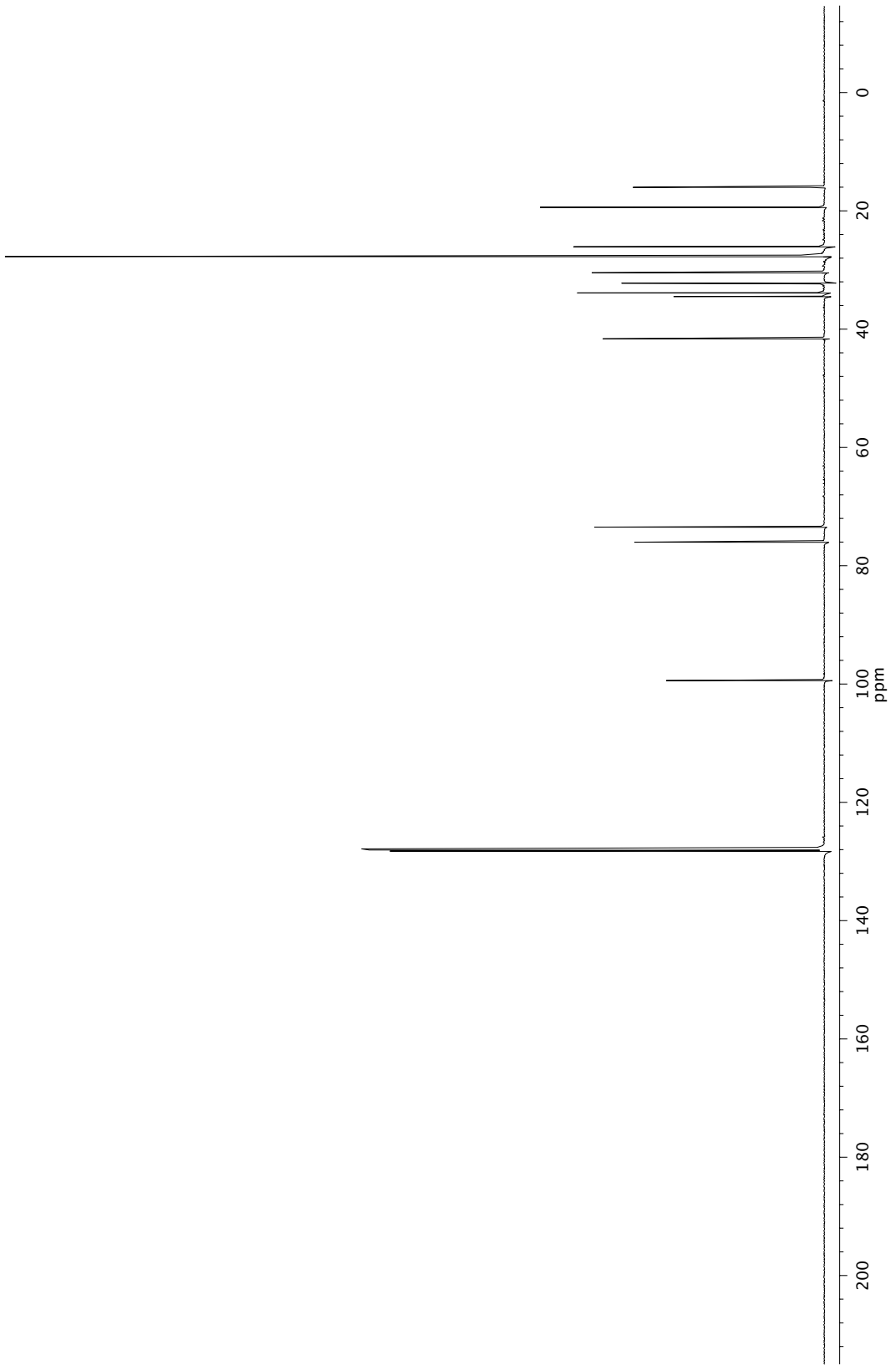


1-D nOe NMR (300 MHz, $CDCl_3$, Irradiation at 0.89 ppm) of compound **SI4**.

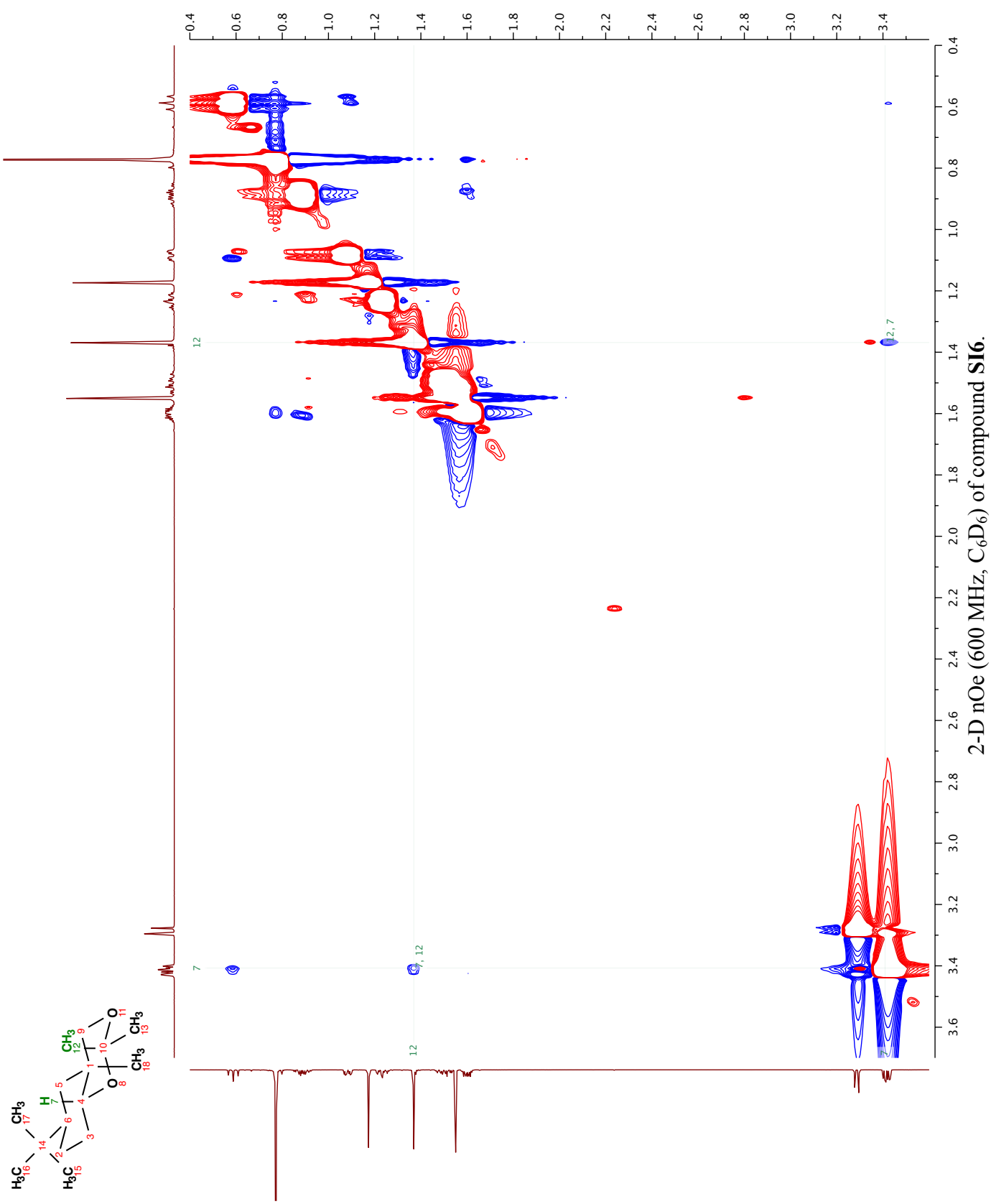


SI6

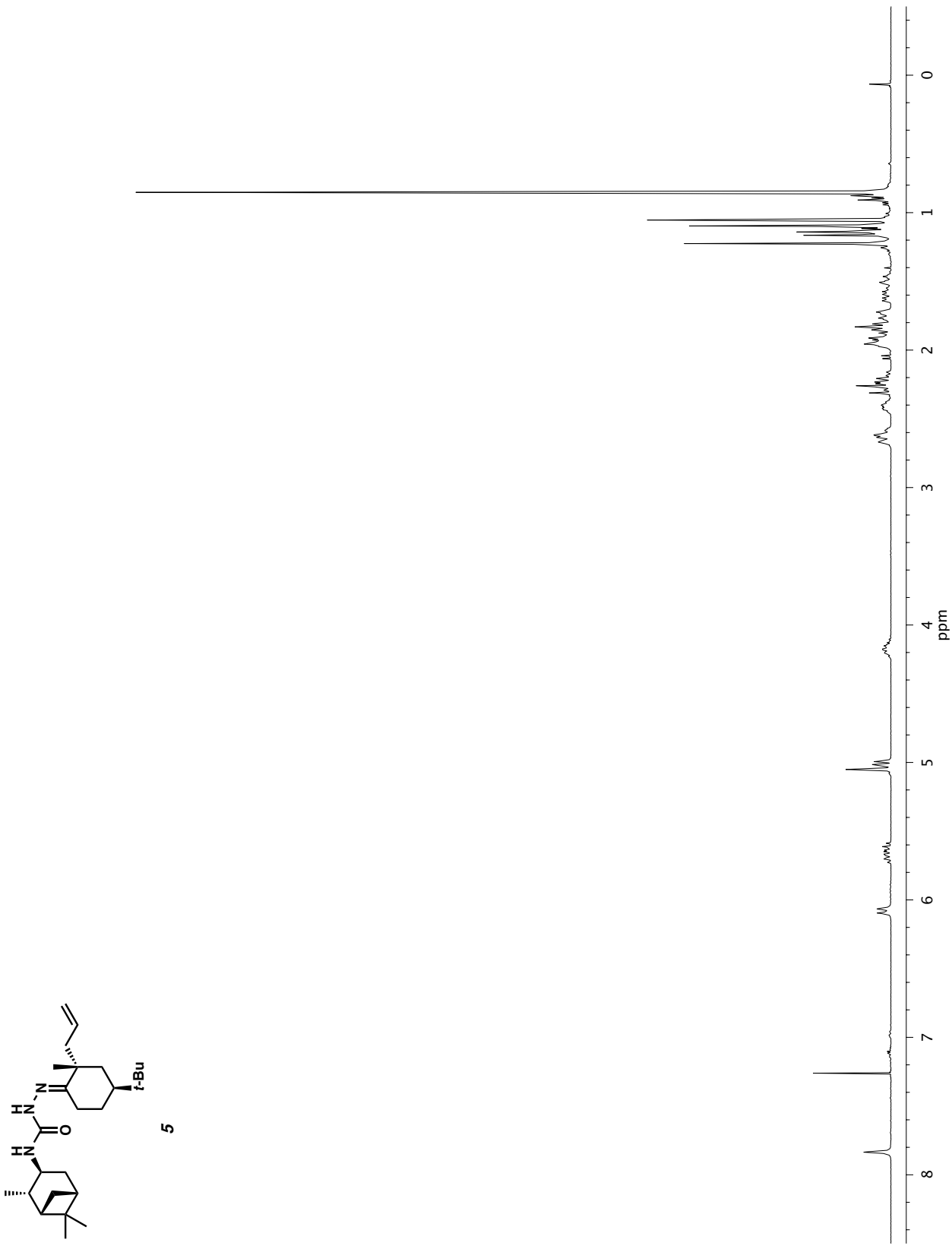
^{1}H NMR (600 MHz, C_6D_6) of compound **SI6**.



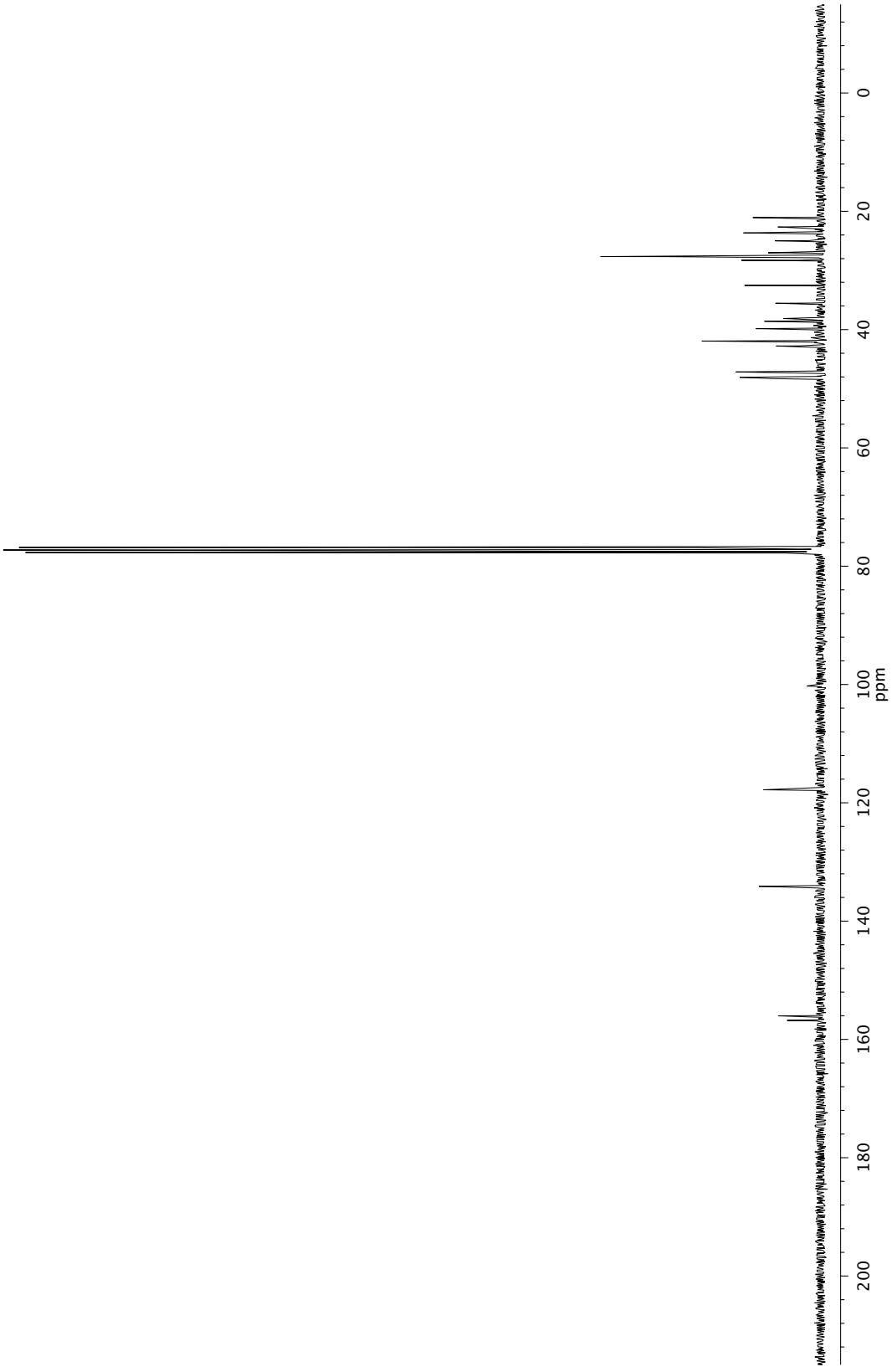
^{13}C NMR (126 MHz, C_6D_6) of compound **SI6**.



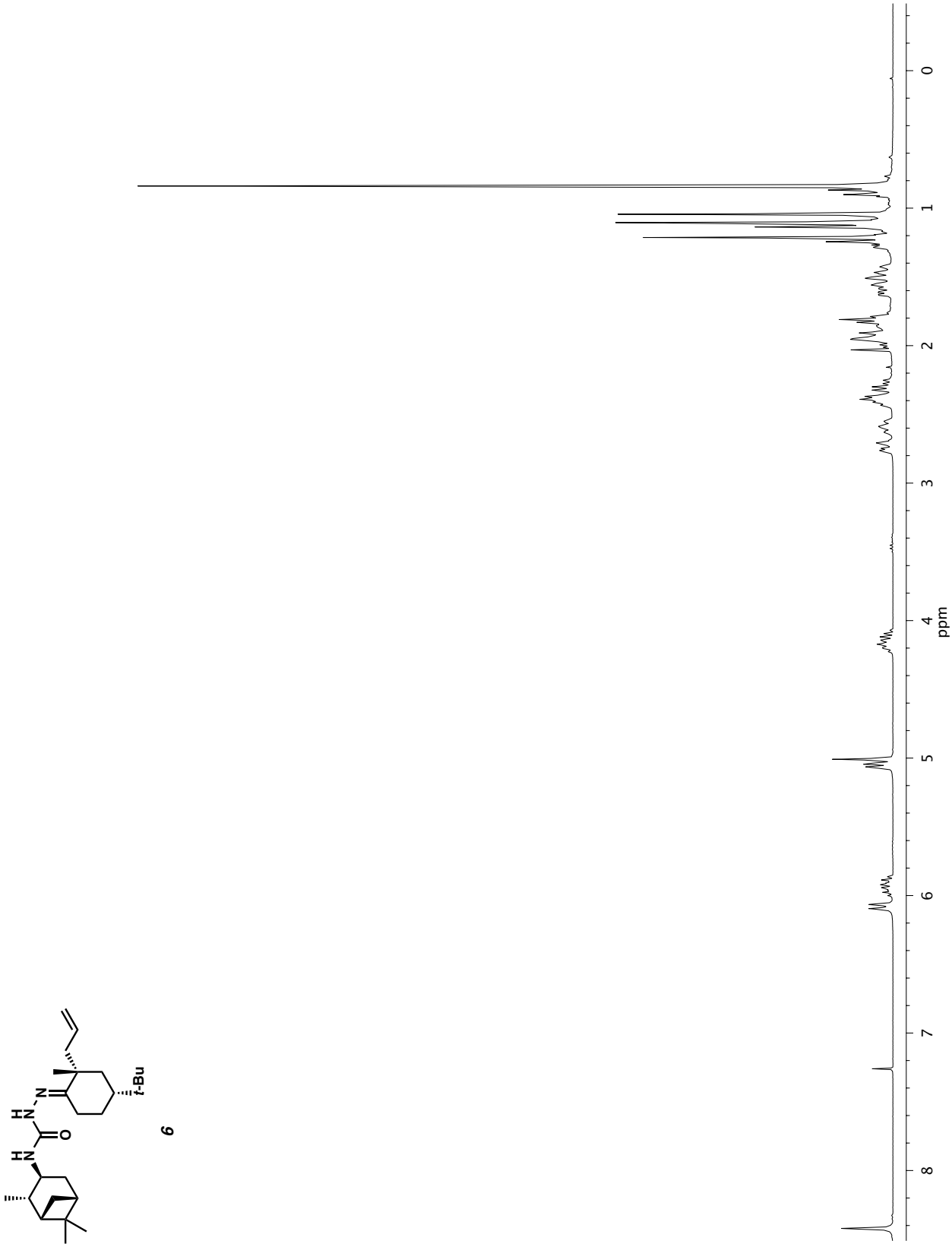
2-D nOe (600 MHz, C_6D_6) of compound **SI6**.



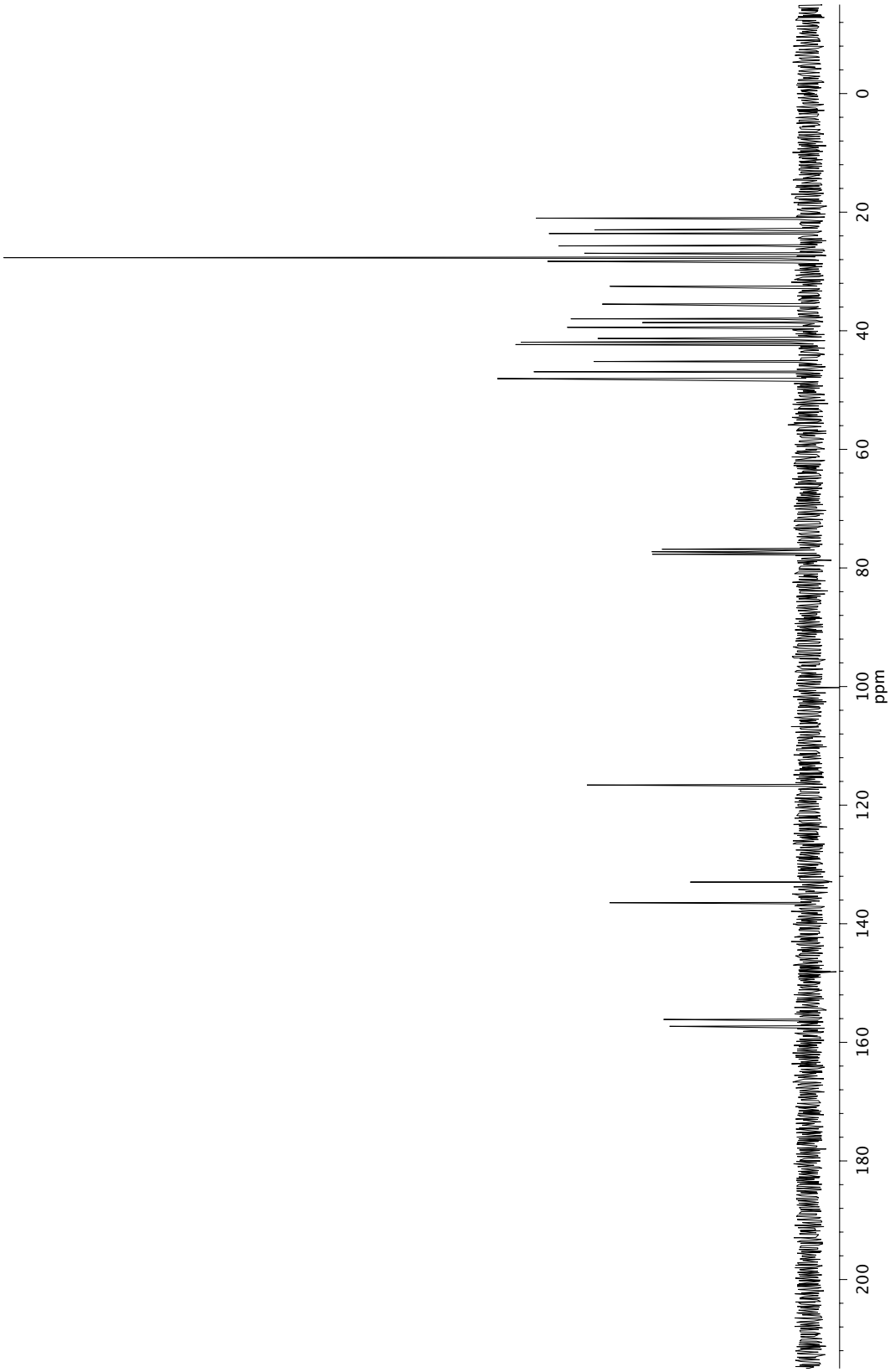
^{1}H NMR (300 MHz, $CDCl_3$) of compound **5**.



^{13}C NMR (75 MHz, $CDCl_3$) of compound **5**.



^{1}H NMR (300 MHz, $CDCl_3$) of compound **6**.



^{13}C NMR (75 MHz, $CDCl_3$) of compound **6**.