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

Electronic Supplementary Information for:

Inexpensive multigram-scale synthesis of cyclic enamines and 3–N spirocyclopropyl systems

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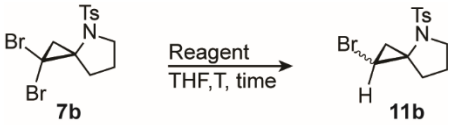
List of abbreviations

Calcd	Calculated
CTAB	Cetyltrimethylammonium bromide
DCM	Dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMF	Dimethylformamide
ESI	Electrospray ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
LAH	Lithium aluminum hydride
MHz	Megahertz
MeCN	Acetonitrile
MeOH	Methanol
M.p.	Melting point
R_f	Retention factor
R_t	Retention time
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet

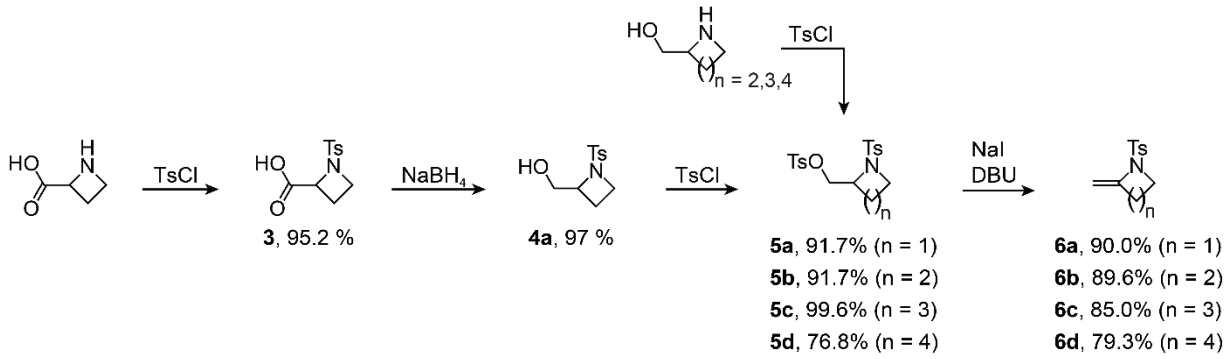
General materials and methods. All chemical reagents were of analytical grade, obtained from commercial suppliers, and used without further purification unless otherwise specified. Reactions were monitored by thin layer chromatography (TLC) on pre-coated glass TLC plates (Analtech UNIPLATE™ silica gel HLF w/ organic binder, 250 μm thickness, with UV254 indicator) or by LC/MS (Agilent LC-MSD, direct-injection mode, 1–10 μL, ESI). TLC plates were visualized by UV illumination or developed with either potassium permanganate stain ($KMnO_4$ stain: 1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL of 10% NaOH dissolved in 200 mL H_2O), ceric ammonium molybdate stain (CAM stain: 12 g $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, 0.5 g $Ce(NH_4)_2(NO_3)_6$ and 15 mL of concentrated H_2SO_4 dissolved in 235 mL H_2O), or ninhydrin stain (1.5 g ninhydrin dissolved in 100 mL of 1-butanol and 3 mL of conc. AcOH). Flash chromatography was carried out using Sorbtech, 60 Å, 40–63 μm or Millipore 60 Å, 35–70 μm silica gel according to the procedure described by Still[1]. HPLC was performed using a Shimadzu HPLC (FCV-200AL) equipped with an Agilent reversed phase Zorbax Sb-Aq C18 column (4.6 × 250 mm or 21.2 × 250 mm) fitted with an Agilent stand-alone prep guard column. NMR spectra (^1H, ^{13}C, COSY, DEPT135, and ^{19}F) were obtained using a 300, 400, 500, or 700 MHz Bruker spectrometer and analyzed using Mestrenova 9.0. ^1H and ^{13}C chemical shifts (δ) were referenced to residual solvent peaks. Low-resolution electrospray ionization (ESI) and High-resolution electrospray ionization (ESI) mass spectra were obtained at the Stony Brook University Institute for Chemical Biology and Drug Discovery (ICB&DD) Mass Spectrometry Facility with an Agilent LC/MSD and LC-UV-TOF spectrometer respectively. Melting points were obtained on Thomas hoover Unimelt capillary melting point apparatus.

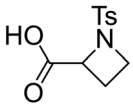
Table S1: Optimisation conditions for converting spirocyclopropyl 3-N dibromo **7b** to spirocyclopropyl 3-N monobromo **11b**. (See page S106 for more details)



Reagent	T (°C)	Time	Yield	Comments
$SnBu_3H$ (1 eq)	rt	3 h	--	No reaction
$SnBu_3H$ (3 eq)	rt	16 h	--	No reaction
$SnBu_3H$ (3 eq)	rt	4d	10%	Unreacted SM
$SnBu_3H$ (1–5 eq)	40–45	1–7 d	15%	Decomposition & unreacted SM
$LiAlH_4$ (4 eq)	rt	18 h	25%	
$LiAlH_4$ (2 eq) + 1% $AgClO_4$	rt	1 h	41%	
EtMgBr (1.3 eq) + $Ti(OiPr)_4$ (1 eq)	rt	4 h	0%	Consumption of SM
EtMgBr (1.3 eq) + $Ti(OiPr)_4$ (0.6 eq)	rt	4 h	0%	Consumption of SM
EtMgBr (1.3 eq) + $Ti(OiPr)_4$ (0.1 eq)	rt	0.5 h	--	Inseparable mixture of SM & product
EtMgBr (2–3 eq)+ $Ti(OiPr)_4$ (0.1 eq)	rt	0.5 h	0%	Allene rearrangement product
n-BuLi	-80	10 min	60%	
iPrMgCl	-50	10 min	55%	

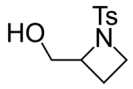
Scheme 1





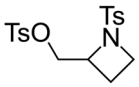
3

To an ice-cold solution of 2-azetidinecarboxylic acid (5.0 g, 49.45 mmol, 1 eq) in NaOH (50 mL, 2M) was added dropwise a solution of TsCl (10.37 g, 54.40 mmol, 1.1 eq) in Et_2O (60 mL). The reaction was stirred at 0 °C for 4 h and then stirred at rt for 16 h. The pH of the reaction mixture was adjusted to 12 using 2M NaOH and the aqueous layer was collected. The aqueous layer was further washed with Et_2O (50 mL), diluted with EtOAc and the pH was adjusted to 1 using 2M HCl. The organic layer was collected and the aqueous layer was further washed with EtOAc (3×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtain **3** as white solid (12 g, 95.2%). R_f = 0.1–0.5 (EtOAc, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.55 (br s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.55–4.51 (m, 1H), 3.74 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.50–2.42 (m, 1H), 2.46 (s, 3H), 2.33–2.26 (m, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.37, 145.10, 131.47, 130.17, 128.51, 60.64, 47.85, 21.77, 19.88. HRMS (ESI): Calcd for $C_{11}H_{14}NO_4S$ $[MH]^+$: 256.0638, found: 256.0642.



4a

To an ice-cold suspension of $NaBH_4$ (3.56 g, 94.08 mmol, 2 eq) in THF (80 mL) was added dropwise $BF_3.Et_2O$ (15.85 mL, 122.93 mmol, 2.6 eq) over a period of 1 h while keeping the reaction mixture ice-cold. **3** (12.0 g, 47.04 mmol, 1 eq) was added as a solution in THF (80 mL) in one portion and the reaction mixture was allowed to warm to rt over 17 h. The reaction mixture was cooled down using an ice-bath and quenched using dropwise addition of MeOH (60 mL). Further, 10% HCl (60 mL) was added in one portion and the reaction mixture (pH 1) was heated at 60 °C for 0.5 h to obtain a clear solution. The pH of the reaction mixture was carefully adjusted to 7–8 using 50% NaOH (w/v). The volatiles were removed under reduced pressure and the crude was diluted with DCM (100 mL). The aqueous layer was washed with DCM (3×50 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain **4a** as white solid (11.0 g, 97%). R_f = 0.36 (50% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.90–3.86 (m, 1H), 3.63 (d, *J* = 4.5 Hz, 2H), 3.59 (td, *J* = 8.9, 8.5, 3.7 Hz, 1H), 3.43–3.33 (m, 1H), 3.16 (s, 1H), 2.34 (s, 3H), 2.05–1.98 (m, 1H), 1.78–1.72 (m, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.17, 130.61, 129.70, 128.18, 65.02, 64.73, 47.71, 21.33, 17.55. HRMS(ESI): Calcd for $C_{11}H_{16}NO_3S$ $[MH]^+$: 242.0845, found: 242.0850.



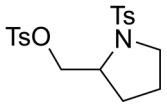
5a

To an ice-cold solution of **4a** (11.0 g, 45.59 mmol, 1 eq) in DCM (60 mL) was added TsCl (10.43 g, 54.70 mmol, 1.2 eq), DMAP (56 mg, 0.45 mmol, 0.01 eq) and Et_3N (6 g, 59.25 mmol, 1.3 eq). The reaction was allowed to warm to rt overnight. The pH of the reaction mixture was adjusted to 1 using 2M HCl. The organic layer was collected and the aqueous layer was washed with DCM (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude **5a**. The off-white crude was refluxed in EtOH (200 mL) for 1 h and allowed to cool down to rt. The precipitated product was filtered using cold EtOH and dried under reduced pressure to obtain **5a** (16.51 g, 91.7%). R_f = 0.57 (50% EtOAc/hexanes, visualized w/ UV). M.p. 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.36 (dd, *J* = 8.1, 6.7 Hz, 4H), 4.18 (d, *J* = 1.1 Hz, 1H), 4.17 (d, *J* = 1.6 Hz, 1H), 4.14–4.06 (m, 1H), 3.65 (ddd,

J = 9.0, 7.7, 4.0 Hz, 1H), 3.55 (q, *J* = 8.0 Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 2.24–2.15 (m, 1H), 2.04–1.96 (m, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.24, 144.47, 132.64, 131.64, 130.09, 129.98, 128.44, 128.14, 70.84, 60.42, 47.98, 21.81, 21.73, 19.16. HRMS (ESI): Calcd for $C_{18}H_{21}NO_5S_2$ [MH]$^+$: 396.0934, found: 396.0939.

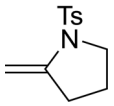
6a

To a solution of **5a** (29.5 g, 74.66 mmol, 1 eq) in glyme (400 mL) was added NaI (33.57 g, 223.99 mmol, 3 eq). To this red solution was added DBU (22.3 mL, 22.73 g, 149.33 mmol, 2 eq) and the greenish-yellow reaction mixture was refluxed for 3 h. The reaction produced foam and insoluble solids which dissolved upon quenching the reaction mixture with water (50 mL). The reaction mixture was reduced to half of its original volume under reduced pressure and diluted with water (300 mL) and Et_2O (200 mL). The organic layer was further washed with sat. $NaHCO_3$ (100 mL) and brine (130 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain beige solid **6a** (15 g, 90%) which was used without further purification. We found the alkene to decompose upon column purification with silica gel. R_f = 0.69 (40% EtOAc/hexanes, visualized w/ UV). The characterization data is in accordance with the previous report of this molecule prepared via copper mediated coupling[2]. M.p. 109–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.82 (q, *J* = 2.6 Hz, 1H), 4.17 (q, *J* = 2.2 Hz, 1H), 3.71 (t, *J* = 6.7 Hz, 2H), 2.58 (td, *J* = 6.6, 3.3 Hz, 2H), 2.39 (s, 3H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.25, 144.29, 132.86, 129.60, 127.68, 89.40, 47.55, 25.52, 21.51. ^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$): δ = (up) 129.68, 127.76, 21.58, (down) 89.48, 47.63, 25.60. HRMS (ESI): Calcd for $C_{11}H_{14}NO_2S$ [MH]$^+$: 224.0740, found: 224.0742.



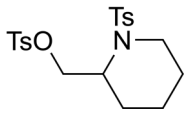
5b

To an ice-cold solution of prolinol (13.0 g, 128.58 mmol, 1.0 eq) in dry pyridine (15 mL) was dropwise added a solution of TsCl (53.9 g, 282.89 mmol, 2.2 eq) in dry pyridine (120 mL) over 1.5 h while maintaining the bath temperature at 0 °C. The red-brown reaction mixture was allowed to warm to rt and stirred for another 17.5 h. The reaction mixture was cooled down to 0 °C and pH was adjusted to 3 using 3M HCl (350 mL). It was then diluted with DCM (300 mL) and the organic layer was collected. The aqueous layer was extracted once more with DCM (50 mL). The combined organic layers were washed with 3M HCl (300 mL), brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude **5b** (~57 g). The crude was refluxed in EtOH (400 mL) for 0.5 h and cooled to rt using an ice bath. The precipitated white solid was filtered and the process was repeated with the mother liquor to obtain **5b** as a white powder (48.3 g, 91.7%). R_f = 0.38 (30% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 8.2 Hz, 4H), 4.20–4.14 (m, 2H), 4.12–4.07 (m, 1H), 3.65 (ddd, J = 8.9, 7.7, 4.1 Hz, 1H), 3.53 (q, J = 8.4 Hz, 1H), 2.46 (d, J = 3.9 Hz, 6H), 2.22–2.14 (m, 1H), 2.02–1.95 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.25, 144.49, 132.62, 131.61, 130.10, 129.99, 128.45, 128.15, 70.84, 60.42, 47.98, 21.82, 21.74, 19.16. HRMS (ESI): Calcd for $C_{19}H_{24}NO_5S_2$ [MH]$^+$: 410.1090, found: 410.1092.



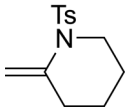
6b

To a solution of **5b** (18.5 g, 45.18 mmol, 1.0 eq) in glyme (250 mL) was added NaI (20.3 g, 135.53 mmol, 3.0 eq). To this red solution was added DBU (27.0 mL, 13.76 g, 90.35 mmol, 2.0 eq) and the greenish-yellow reaction mixture was refluxed for 3 h. The reaction produced foam and insoluble solids that dissolved upon quenching the reaction mixture with water (50 mL). The reaction mixture was reduced to one-quarter of its original volume under reduced pressure and diluted with water (300 mL) and Et_2O (200 mL). The organic layer was further washed with sat. $NaHCO_3$ (100 mL), brine (130 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain **6b** as a beige solid (9.6 g, 89.6%). During attempts at purification, we found that compound **6b** decomposed during silica gel Flash chromatography, and it did not resolve from the impurities when chromatographed using basic alumina eluting with DCM or EtOAc/hexanes. Thus, **6b** was used without further purification. R_f = 0.64 (30% EtOAc/hexanes, visualized w/ UV). M.p. 79–81 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 4.75 (s, 1H), 3.99 (s, 1H), 3.33 (t, J = 6.7 Hz, 2H), 2.07 (s, 3H), 2.00 (t, J = 7.3 Hz, 2H), 1.41 (p, J = 7.0 Hz, 2H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, CDCl3): δ = 143.85, 143.09, 133.63, 128.67, 126.33, 89.23, 53.20, 50.65, 31.80, 21.03, 20.51. ^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$): δ = (up) 129.38, 127.04, 21.21 (down) 89.93, 51.35, 32.50, 21.74. HRMS (ESI): Calcd for $C_{12}H_{16}NO_2S$ [MH]$^+$: 238.0896, found: 238.0897.



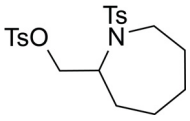
5c

To an ice-cold solution of piperidine-2-methanol (5.0 g, 52.08 mmol, 1.0 eq) in dry pyridine (50 mL) was added TsCl (21.84 g, 114.58 mmol, 2.2 eq) in small portions. The reaction was allowed to warm to rt over 18 h. The reaction was cooled to 0 °C in an ice-bath, diluted with DCM, and the pH of the reaction mixture was adjusted to 1 using conc. HCl. The organic layer was collected and the aqueous layer was washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel (130 g, 10–25% EtOAc/Hexanes) to obtain **5c** as a light-yellow oil (18.3 g, 99.6%). R_f = 0.33 (25% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 4.21 (q, J = 6.2 Hz, 2H), 4.07–3.97 (m, 2H), 3.66 (d, J = 14.1 Hz, 1H), 2.77 (ddd, J = 14.0, 12.6, 2.8 Hz, 1H), 2.41 (s, 3H), 2.36 (s, 3H), 1.64 (d, J = 13.6 Hz, 1H), 1.47–1.42 (m, 2H), 1.40–1.15 (m, 3H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.06, 143.27, 137.77, 132.43, 129.91, 129.70, 127.85, 126.88, 66.82, 50.42, 41.31, 24.34, 24.04, 21.61, 21.45, 18.25. HRMS (ESI): Calcd for $C_{20}H_{26}NO_5S_2$ $[MH]^+$: 424.1247, found: 424.1253.



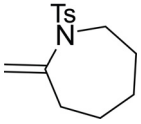
6c

To a solution of **5c** (17.8 g, 42.03 mmol, 1.0 eq) in glyme (280 mL) was added NaI (18.9 g, 126.09 mmol, 3 eq). To this red solution was added DBU (12.57 mL, 12.8 g, 84.06 mmol, 2.0 eq) and the greenish-yellow reaction mixture was refluxed for 24 h. The reaction produced foam and insoluble solids that dissolved upon quenching the reaction mixture with water. The reaction mixture was reduced to one-quarter of its original volume under reduced pressure and diluted with water (300 mL) and Et_2O (200 mL). The combined organic layers were further washed with sat. $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain **6c** as an oil (9.0 g, 85.0%). R_f = 0.50 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.85 (s, 1H), 4.60 (s, 1H), 3.46–3.41 (m, 2H), 2.22 (s, 3H), 1.79 (t, *J* = 6.2 Hz, 2H), 1.42–1.37 (m, 2H), 1.34–1.29 (m, 2H). ^{13}C NMR (126 MHz, CDCl3): δ = 142.68, 137.52, 129.19, 126.74, 107.62, 47.45, 31.44, 24.32, 23.79, 21.03. HRMS (ESI): Calcd for $C_{13}H_{18}NO_2S$ $[MH]^+$: 252.1053, found: 252.1047.



5d

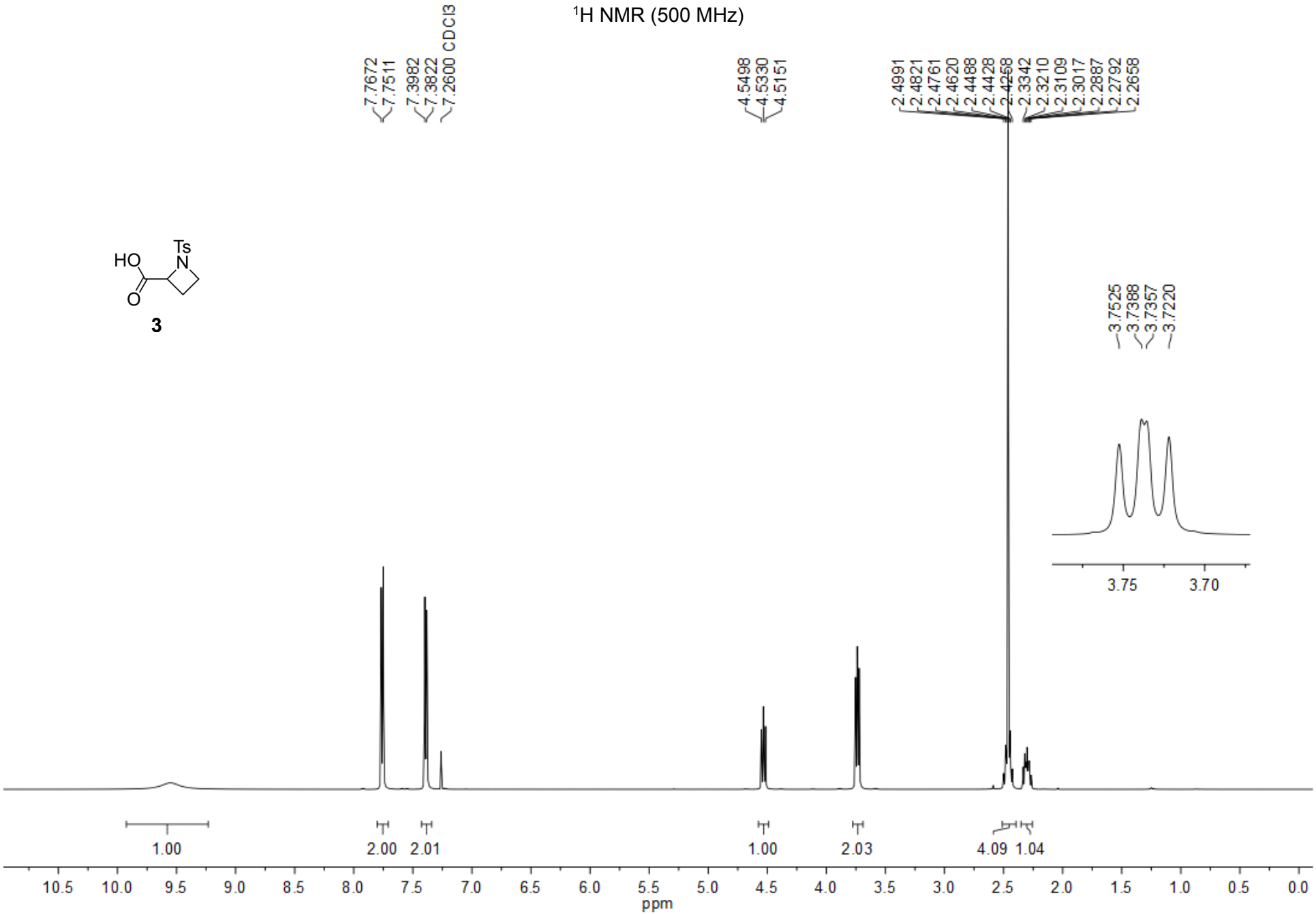
To an ice-cold solution of 2-azepanylmethanol (0.81 g, 6.25 mmol, 1.0 eq) in dry pyridine (14 mL) was added TsCl (3.25 g, 17.03 mmol, 2.7 eq) in one portion. The black reaction was allowed to warm to rt over 24 h. The reaction mixture was concentrated to remove excess pyridine. It was then diluted with DCM and 2M HCl (pH ~1). The organic layer was separated and the aqueous layer was further washed with DCM. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel (60 g, 10–20% EtOAc/Hexanes) to obtain **5d** as a colorless oil (2.1 g, 76.8 %). R_f = 0.26 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.02–3.96 (m, 2H), 3.90–3.87 (m, 1H), 3.75–3.72 (m, 1H), 2.99–2.94 (m, 1H), 2.42 (s, 3H), 2.37 (s, 3H), 2.03–1.97 (m, 1H), 1.66–1.63 (m, 2H), 1.51–1.42 (m, 3H), 1.16–1.08 (m, 1H), 1.02–0.94 (m, 1H) COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.00, 143.25, 138.07, 132.49, 127.87, 127.21, 77.16, 71.88, 55.49, 44.65, 30.89, 29.30, 28.90, 24.18, 21.66, 21.50. HRMS (ESI): Calcd for $C_{21}H_{28}NO_5S_2$ $[MH]^+$: 438.1403, found: 438.1406.



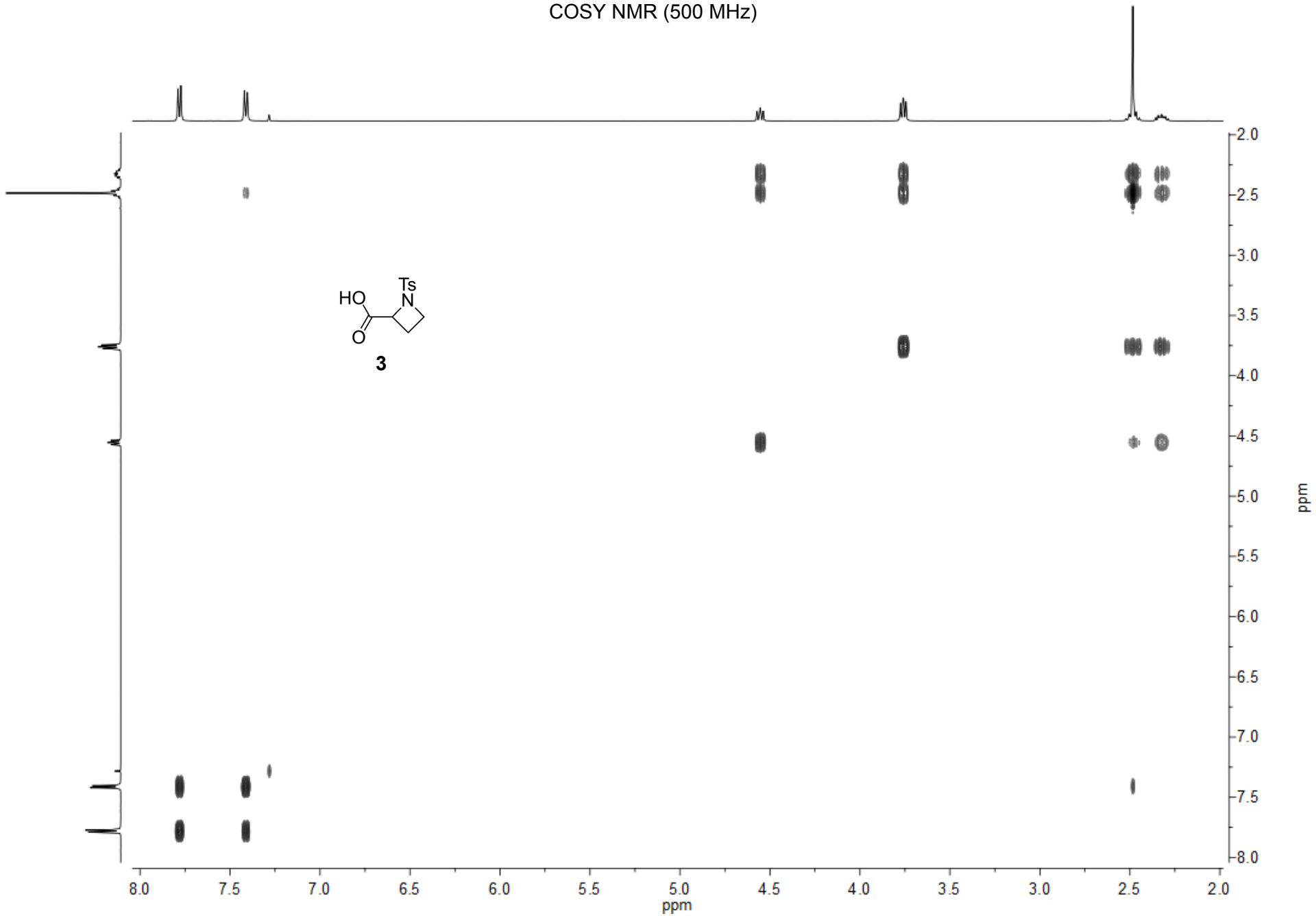
6d

To a solution of **5d** (2.0 g, 4.58 mmol, 1.0 eq) in glyme (40 mL) was added NaI (2.06 g, 13.73 mmol, 3 eq). To this red solution was added DBU (1.37 mL, 1.4 g, 9.15 mmol, 2.0 eq) and the greenish-yellow reaction mixture was refluxed for 4 h. The reaction produced insoluble solids that dissolved upon quenching the reaction mixture with water. The reaction mixture was reduced to a quarter of its original volume under reduced pressure and diluted with water (100 mL) and Et_2O (50 mL). The organic layer was further washed with water (50 mL), sat. $NaHCO_3$ (50 mL×2), brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain **6d** as an oil (0.96 g, 79.3%). R_f = 0.33 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.88 (s, 1H), 4.71 (s, 1H), 3.45– 3.42 (m, 2H), 2.31 (s, 3H), 1.97 (t, *J* = 5.4 Hz, 2H), 1.67–1.40 (m, 2H), 1.46–1.33 (m, 4H). ^{13}C NMR (75 MHz, CDCl3): δ = 145.89, 143.01, 136.43, 129.21, 127.14, 109.69, 57.26, 48.76, 34.51, 28.35, 27.93, 27.67, 21.28. HRMS (ESI): Calcd for $C_{14}H_{20}NO_2S$ $[MH]^+$: 266.1209, found: 266.1211.

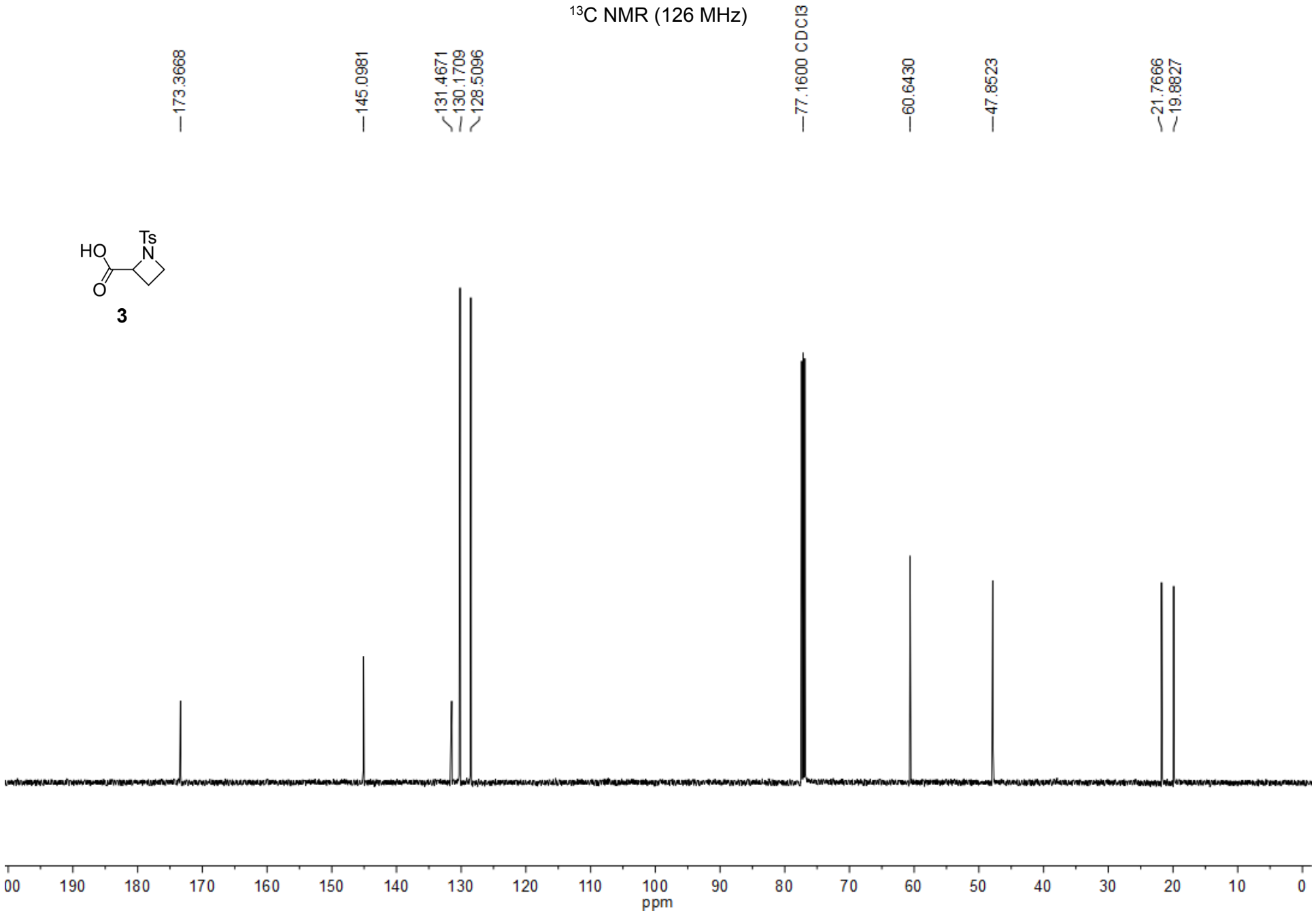
^{1}H NMR (500 MHz)



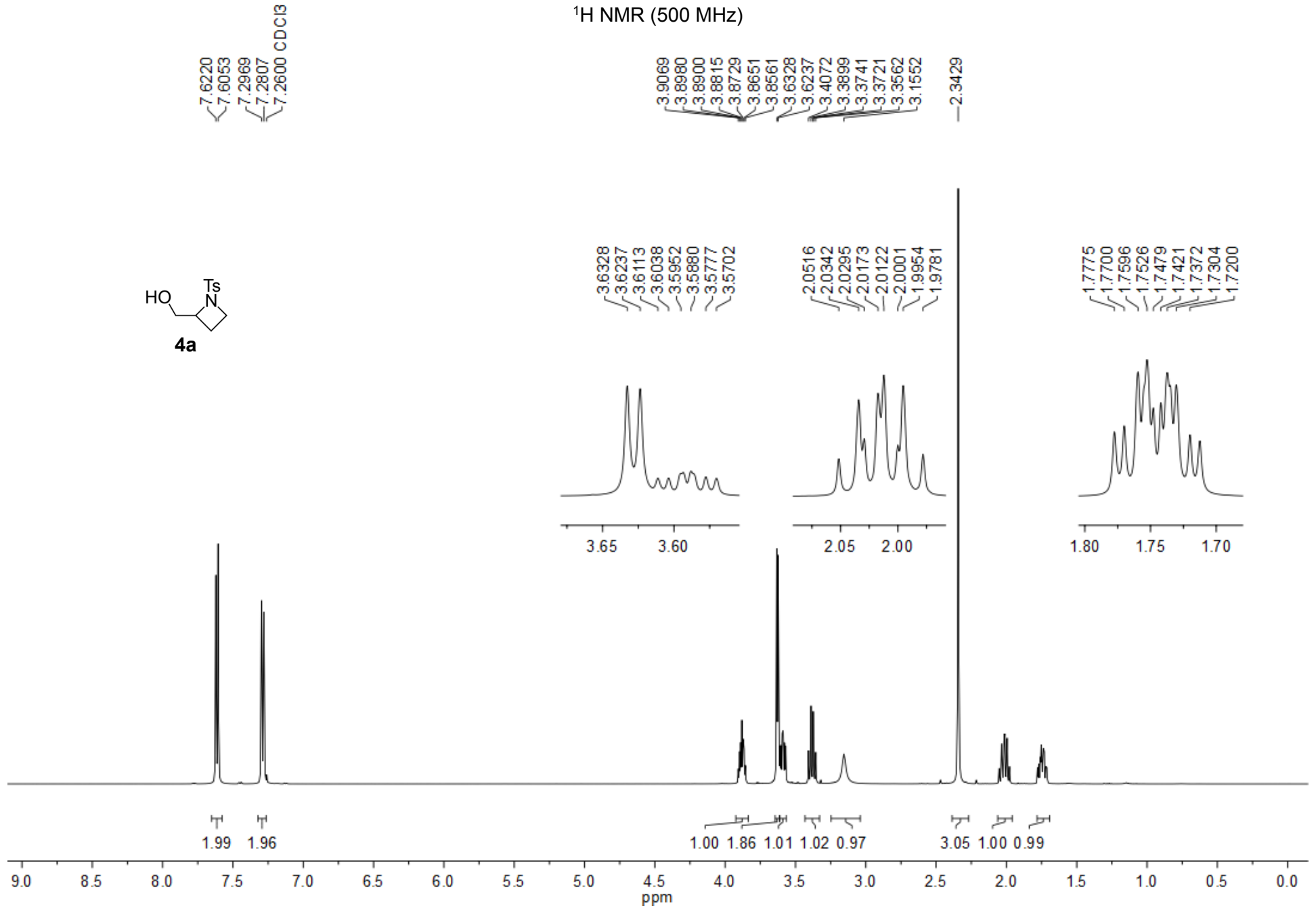
COSY NMR (500 MHz)



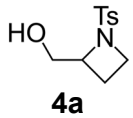
^{13}C NMR (126 MHz)



^{1}H NMR (500 MHz)

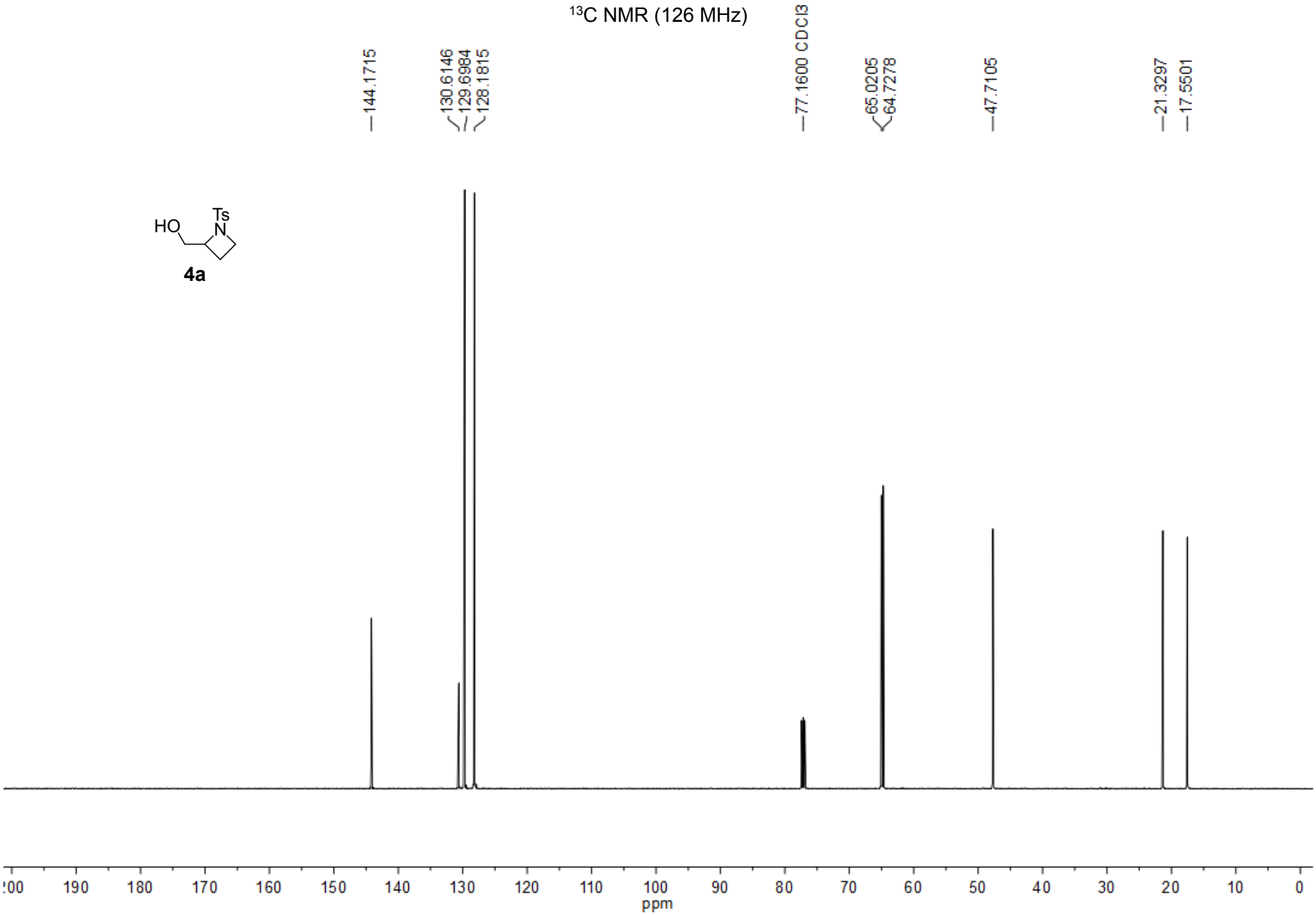


COSY NMR (500 MHz)

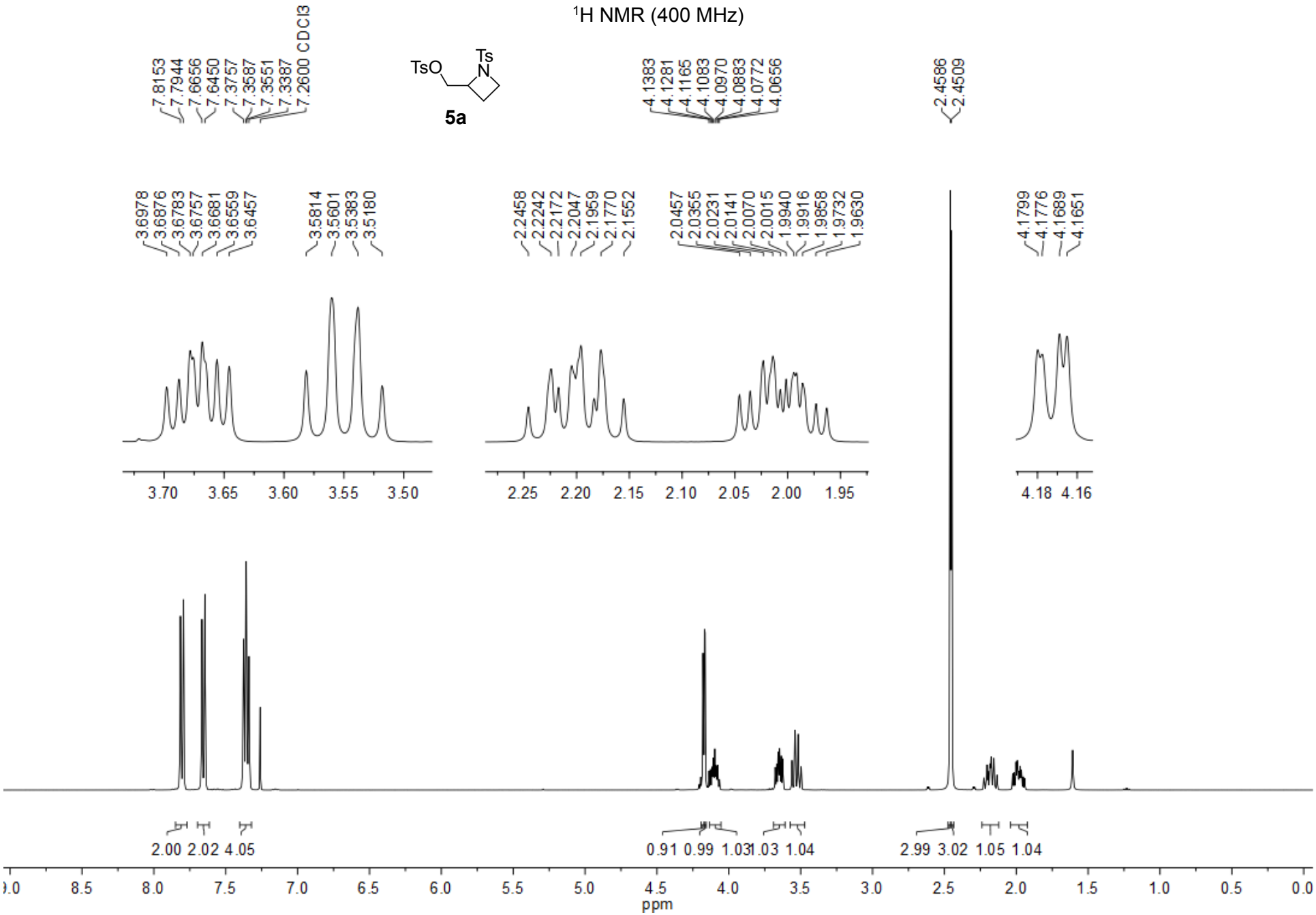


4a

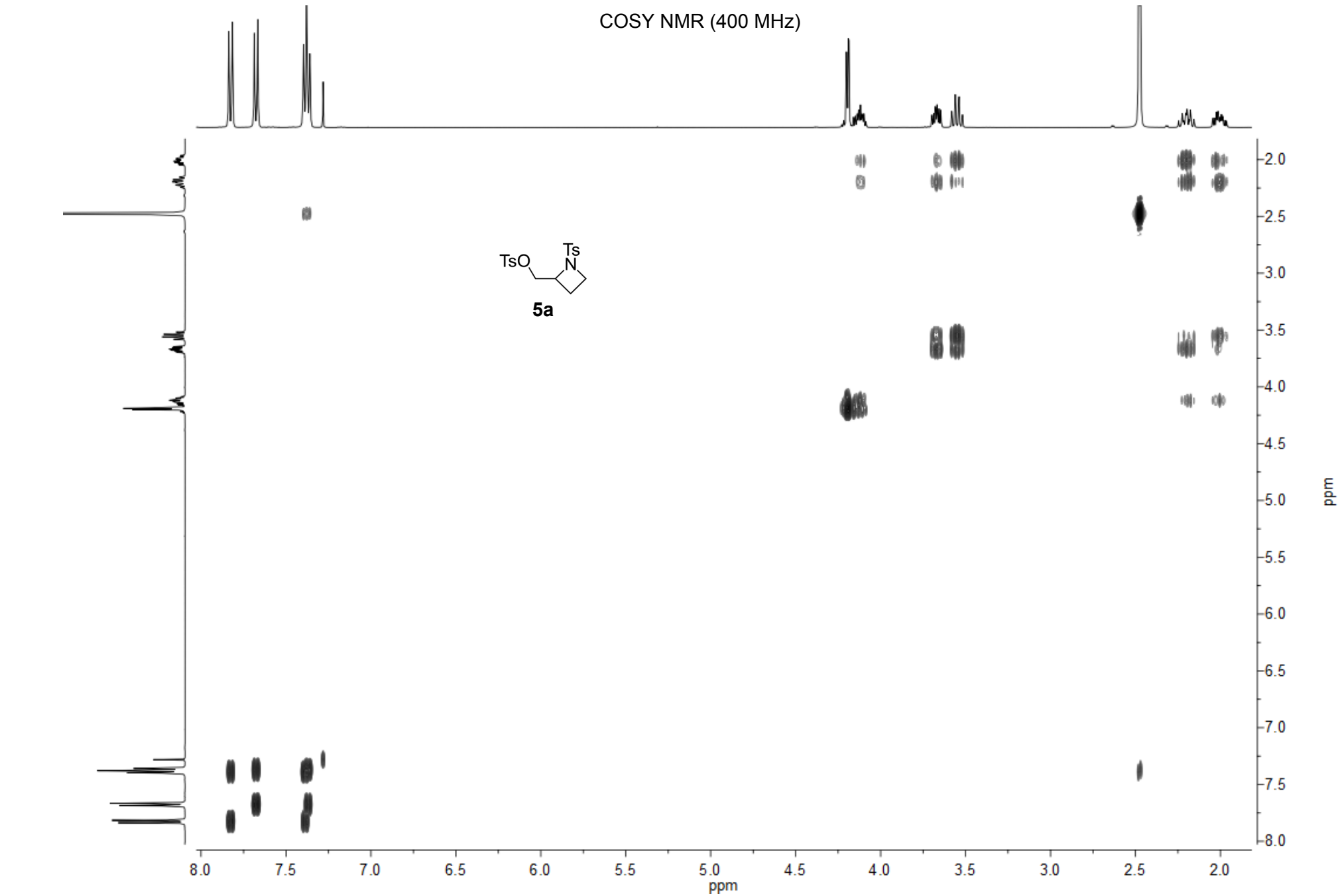
^{13}C NMR (126 MHz)



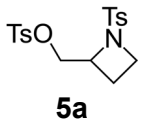
^{1}H NMR (400 MHz)



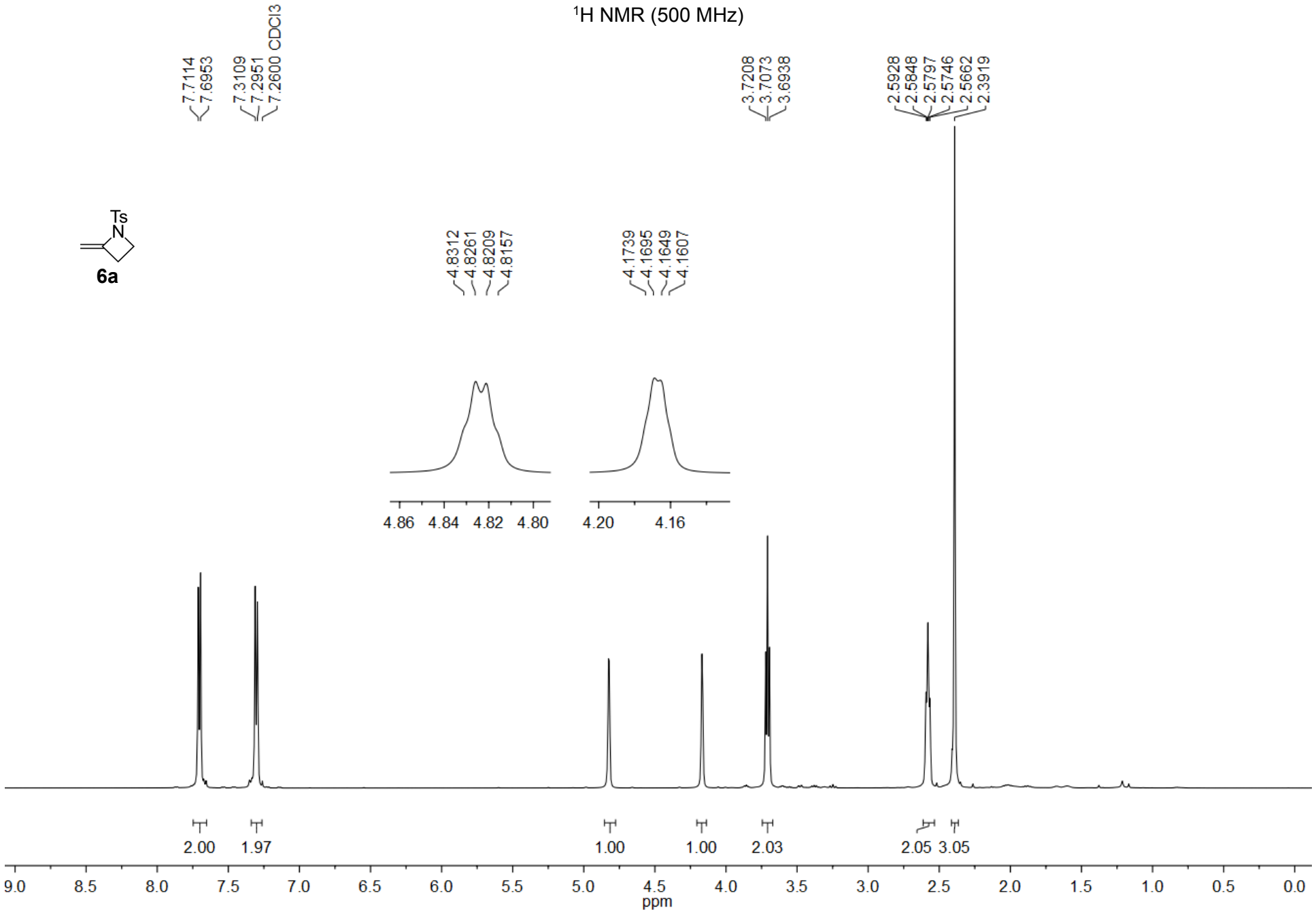
COSY NMR (400 MHz)



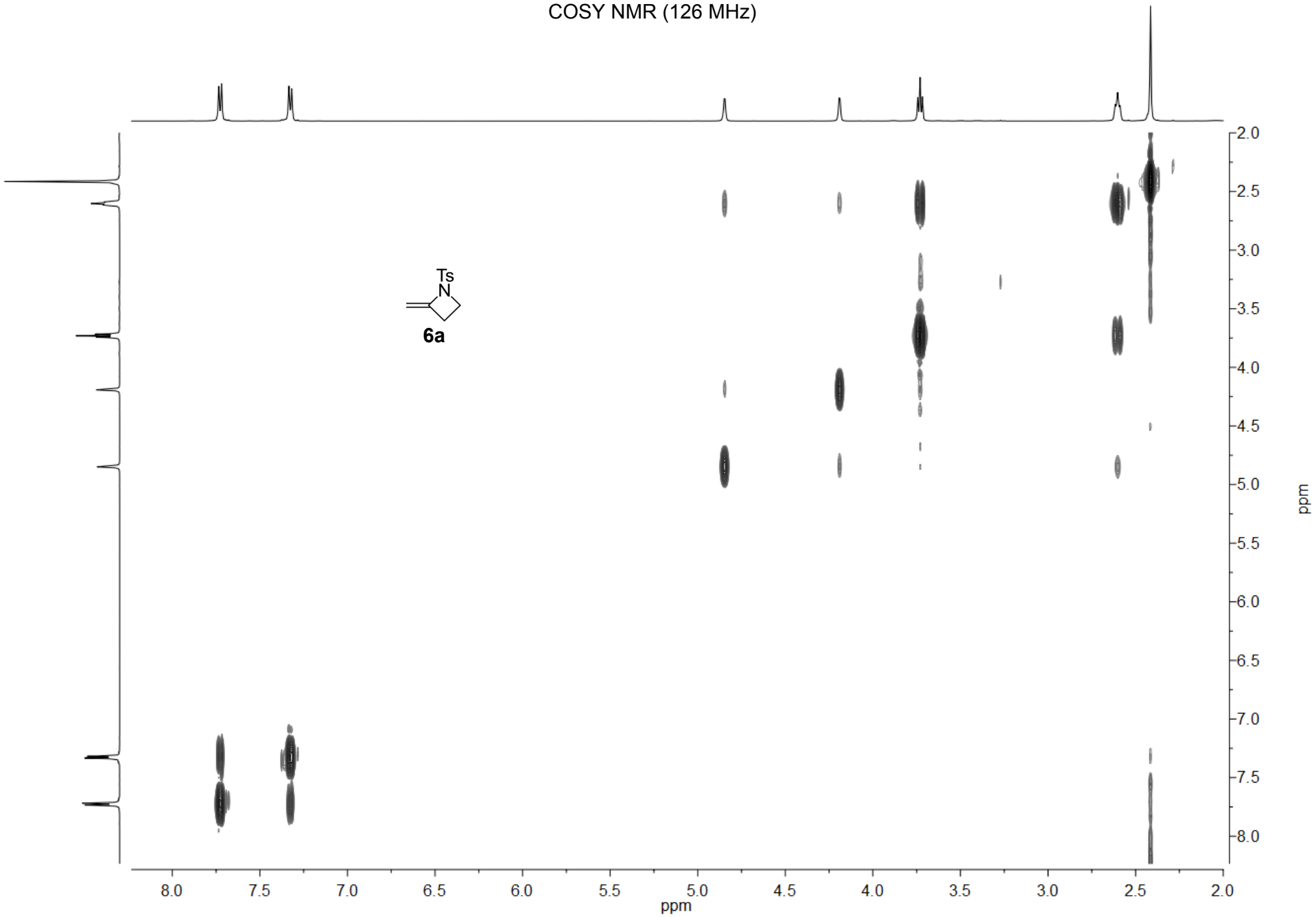
^{13}C NMR (101 MHz)

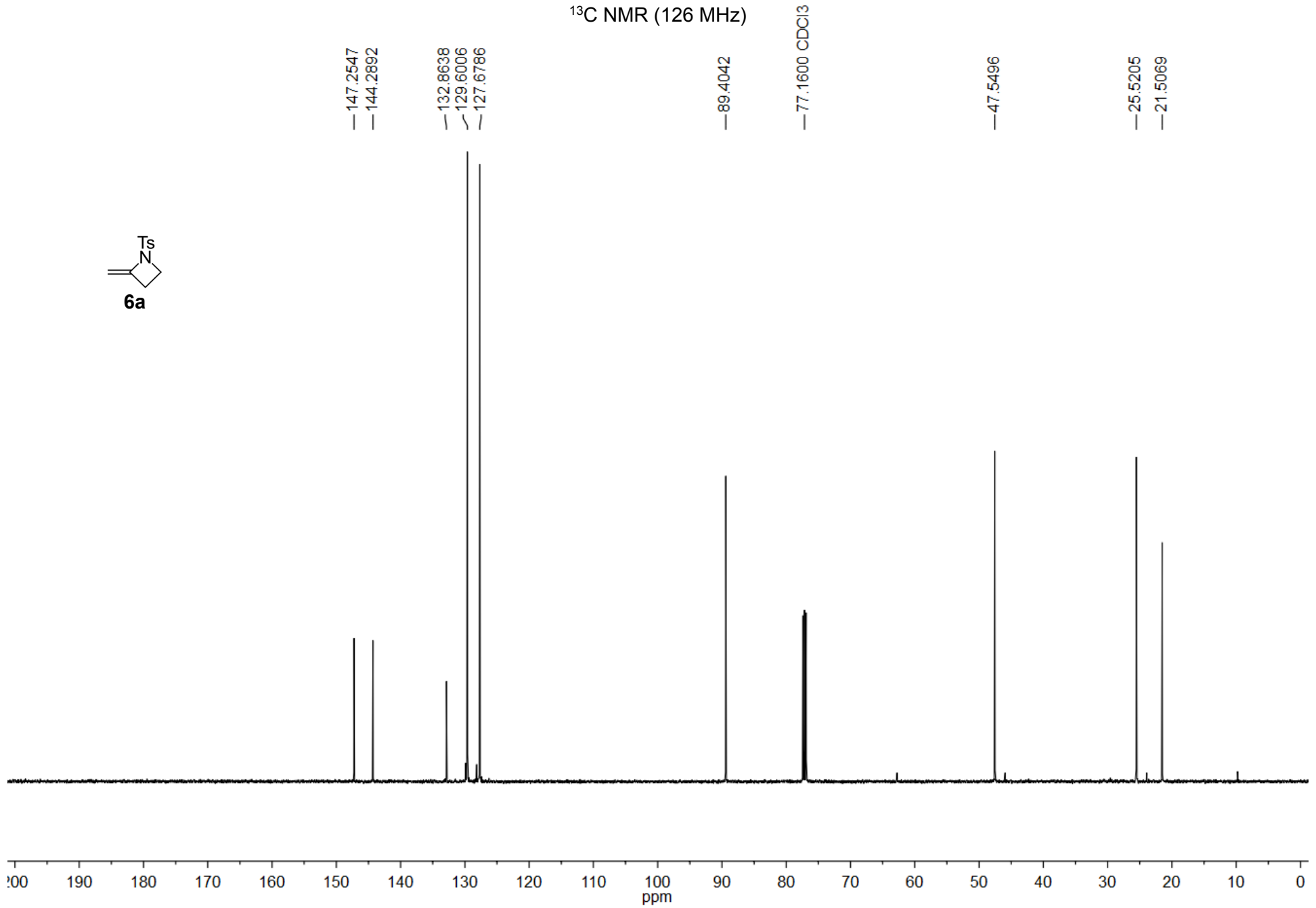


5a

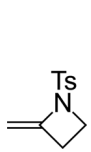

^{1}H NMR (500 MHz)
7.7114
7.6953
7.3109
7.2951
7.2600 CDCl3
3.7208
3.7073
3.6938
2.5928
2.5848
2.5797
2.5746
2.5662
2.3919
Ts
N
6a
4.8312
4.8261
4.8209
4.8157
4.1739
4.1695
4.1649
4.1607
4.86 4.84 4.82 4.80
4.20 4.16
2.00 1.97 1.00 1.00 2.03 2.05 3.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

COSY NMR (126 MHz)



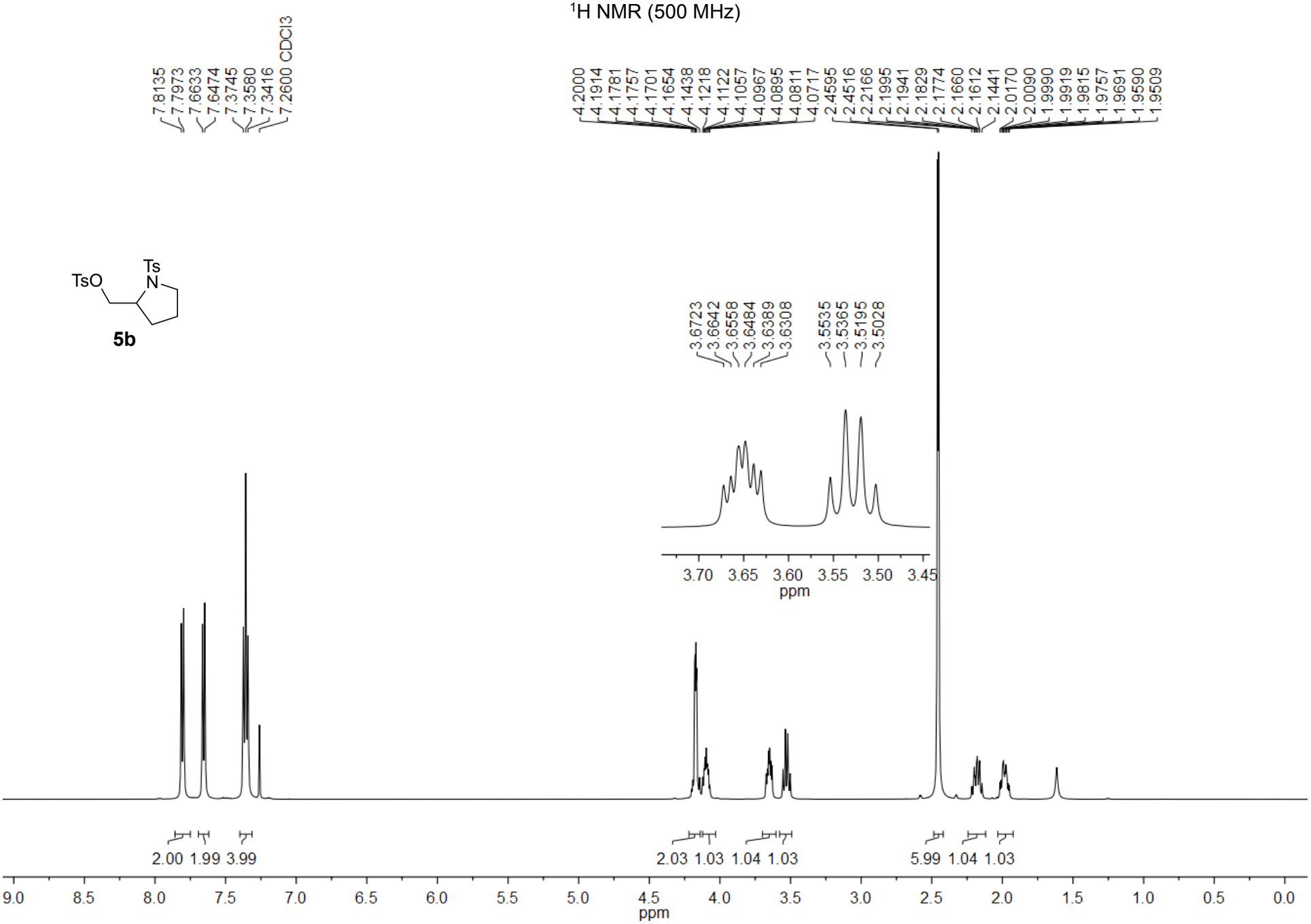

^{13}C NMR (126 MHz)
147.2547
144.2892
132.8638
129.6006
127.6786
89.4042
77.1600 CDCl3
47.5496
25.5205
21.5069
Ts
N
6a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

DEPT-135 NMR (126 MHz)

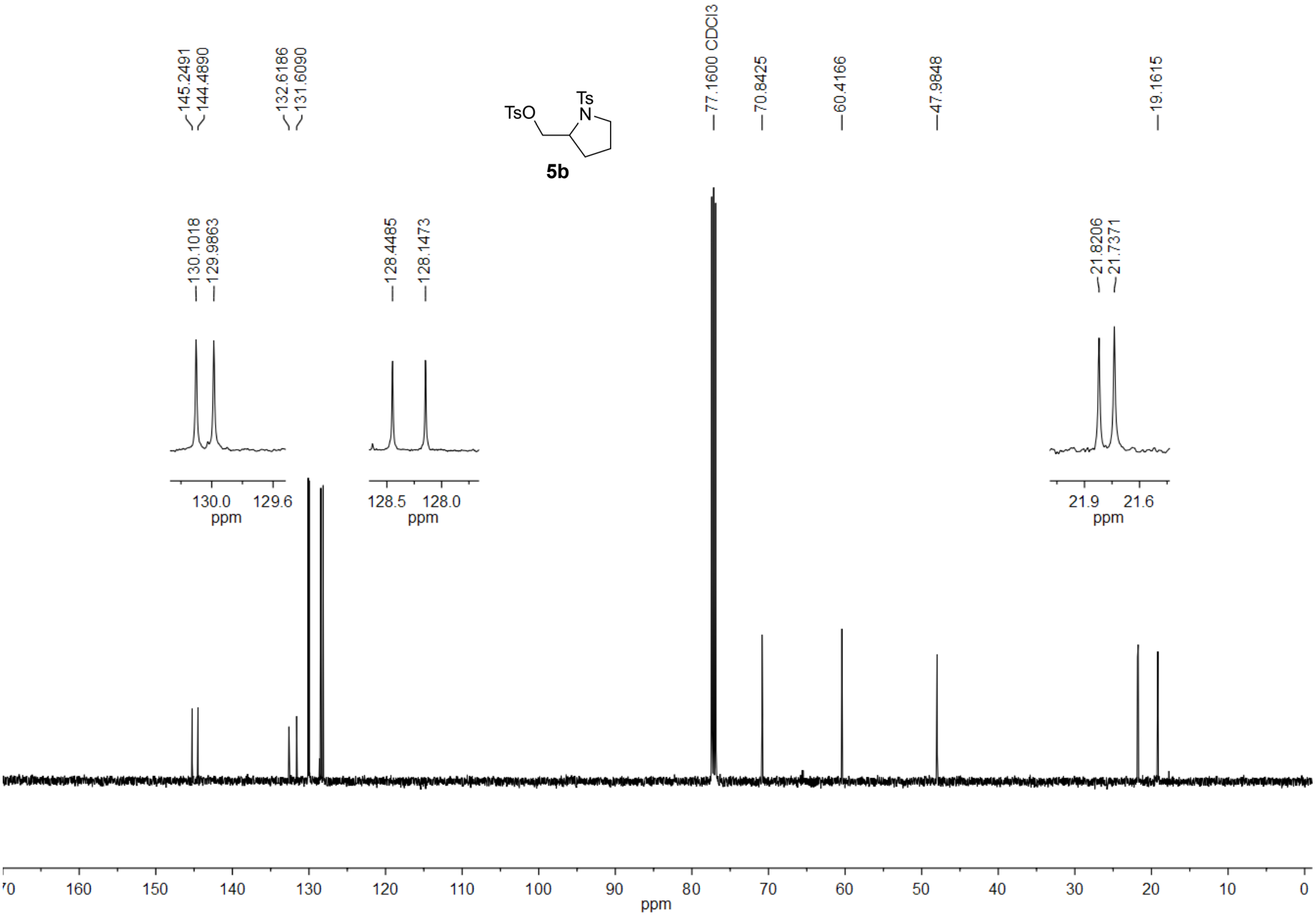


6a

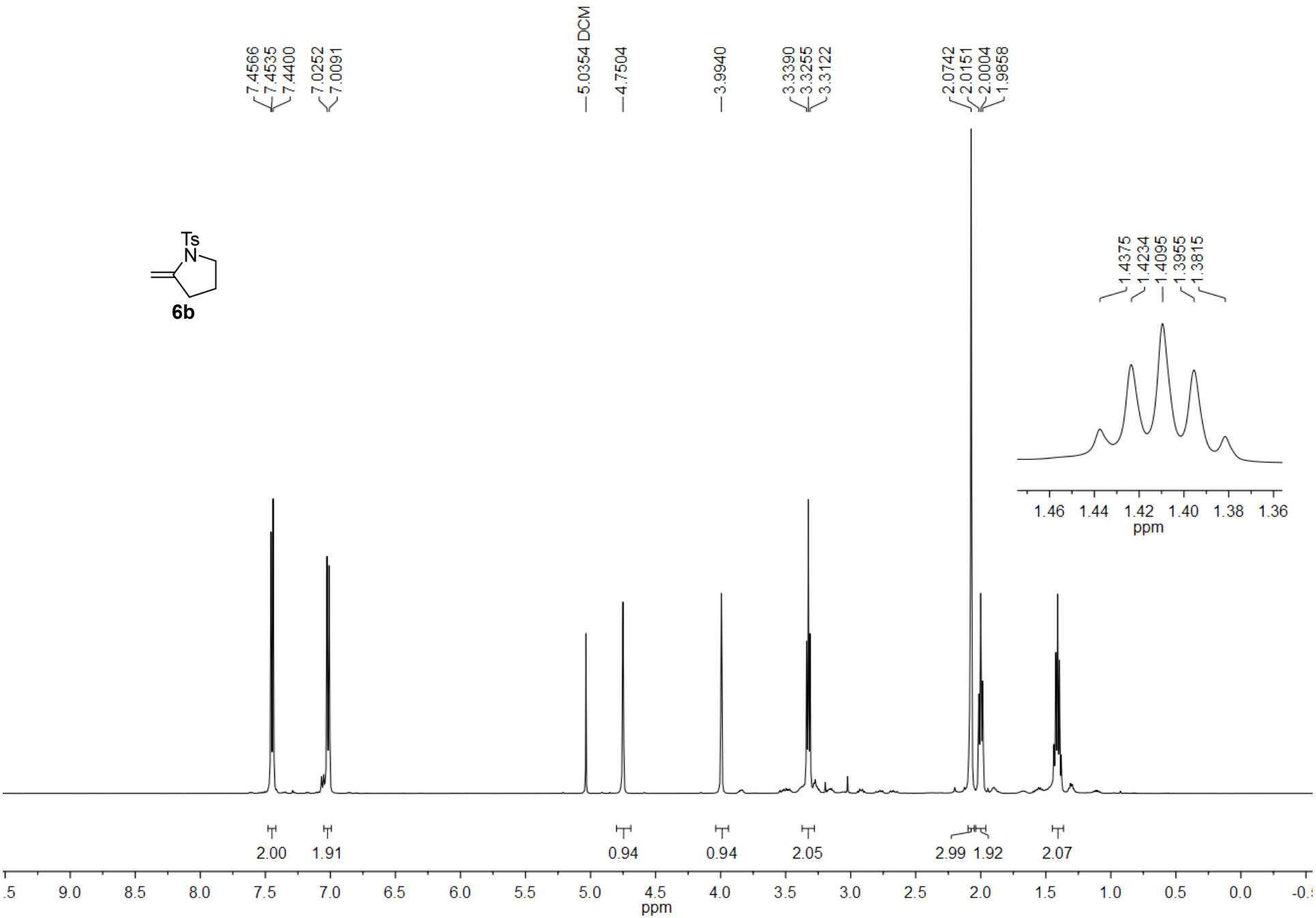
^{1}H NMR (500 MHz)



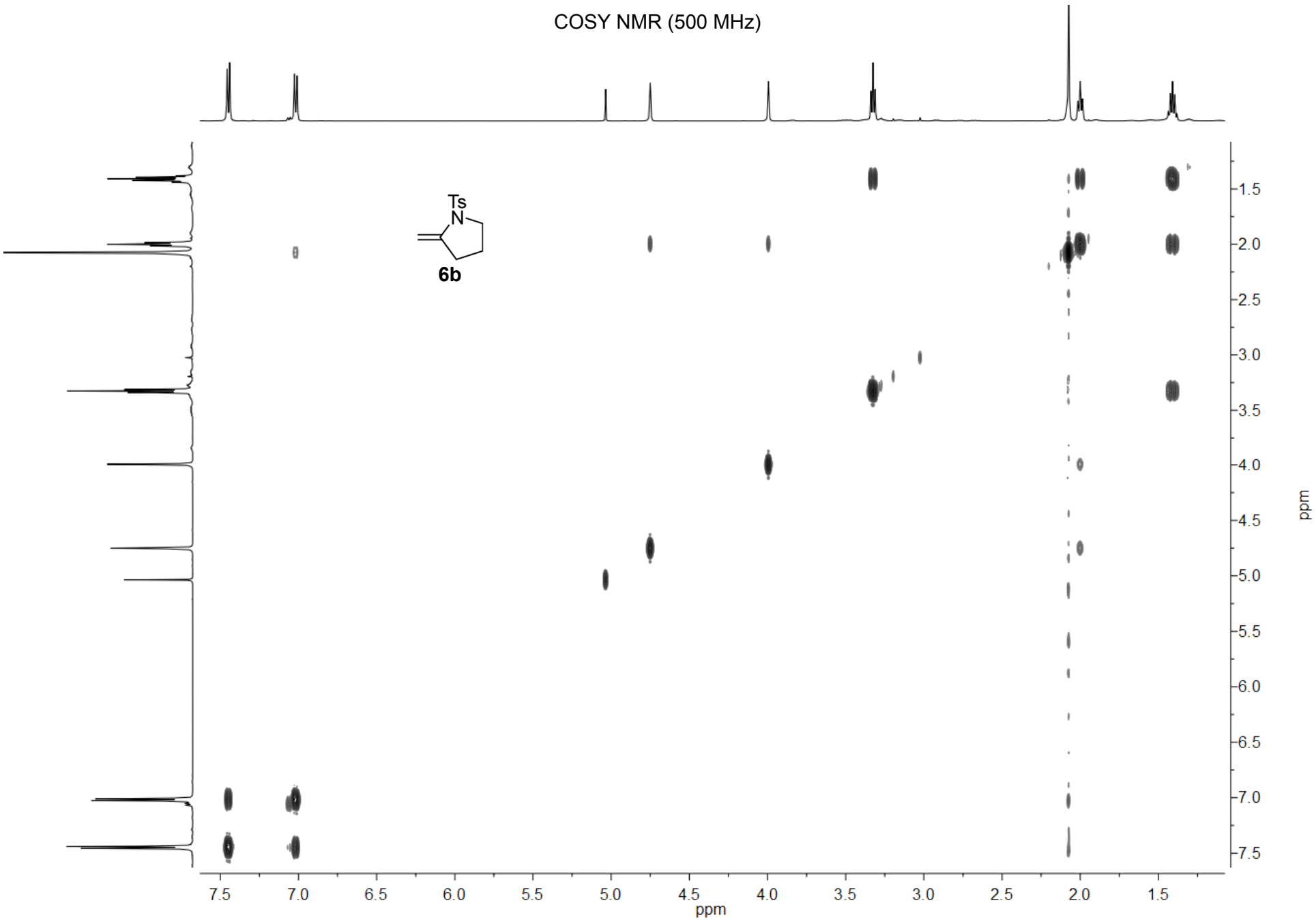
^{13}C NMR (126 MHz)



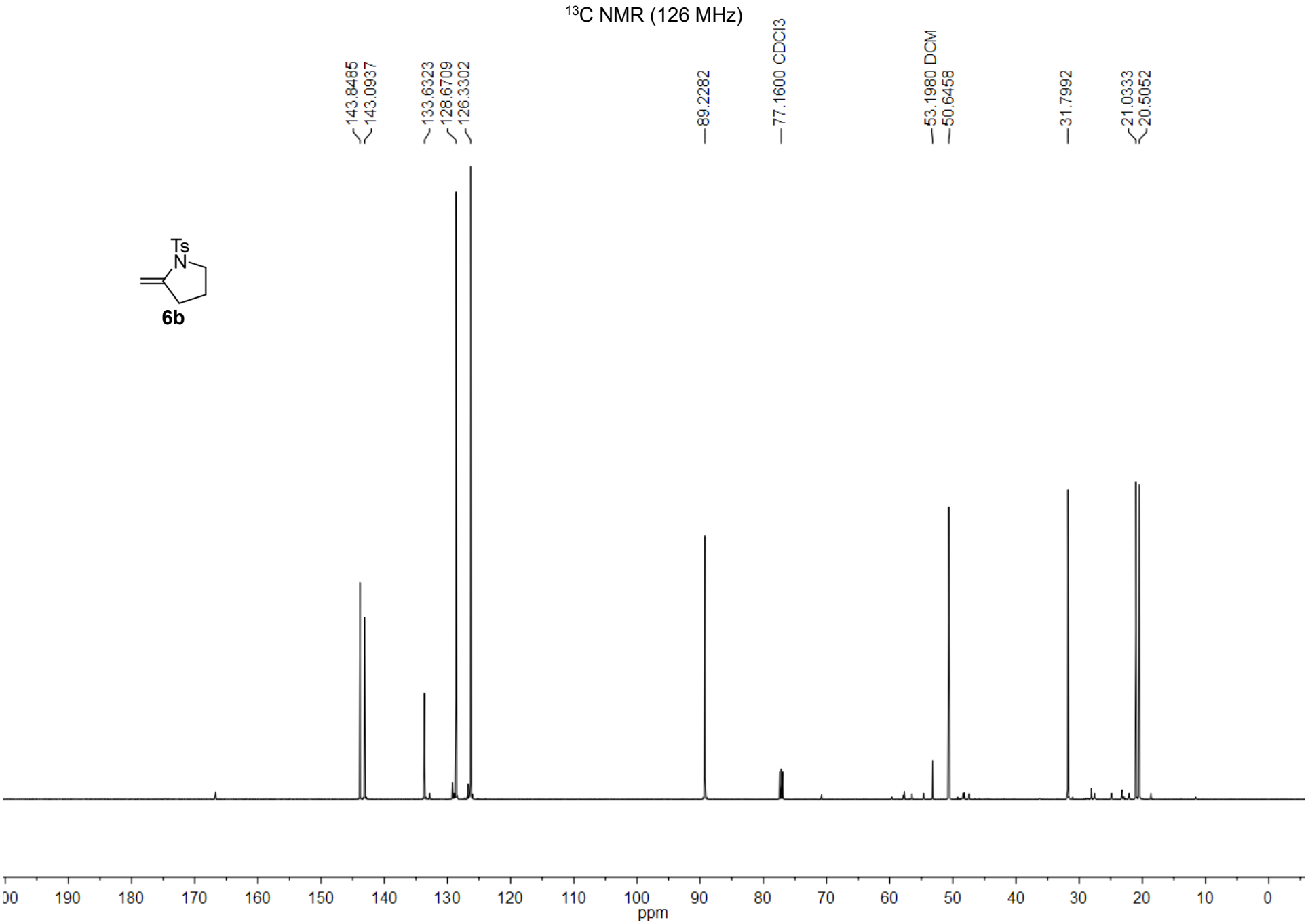
^{1}H NMR (500 MHz)



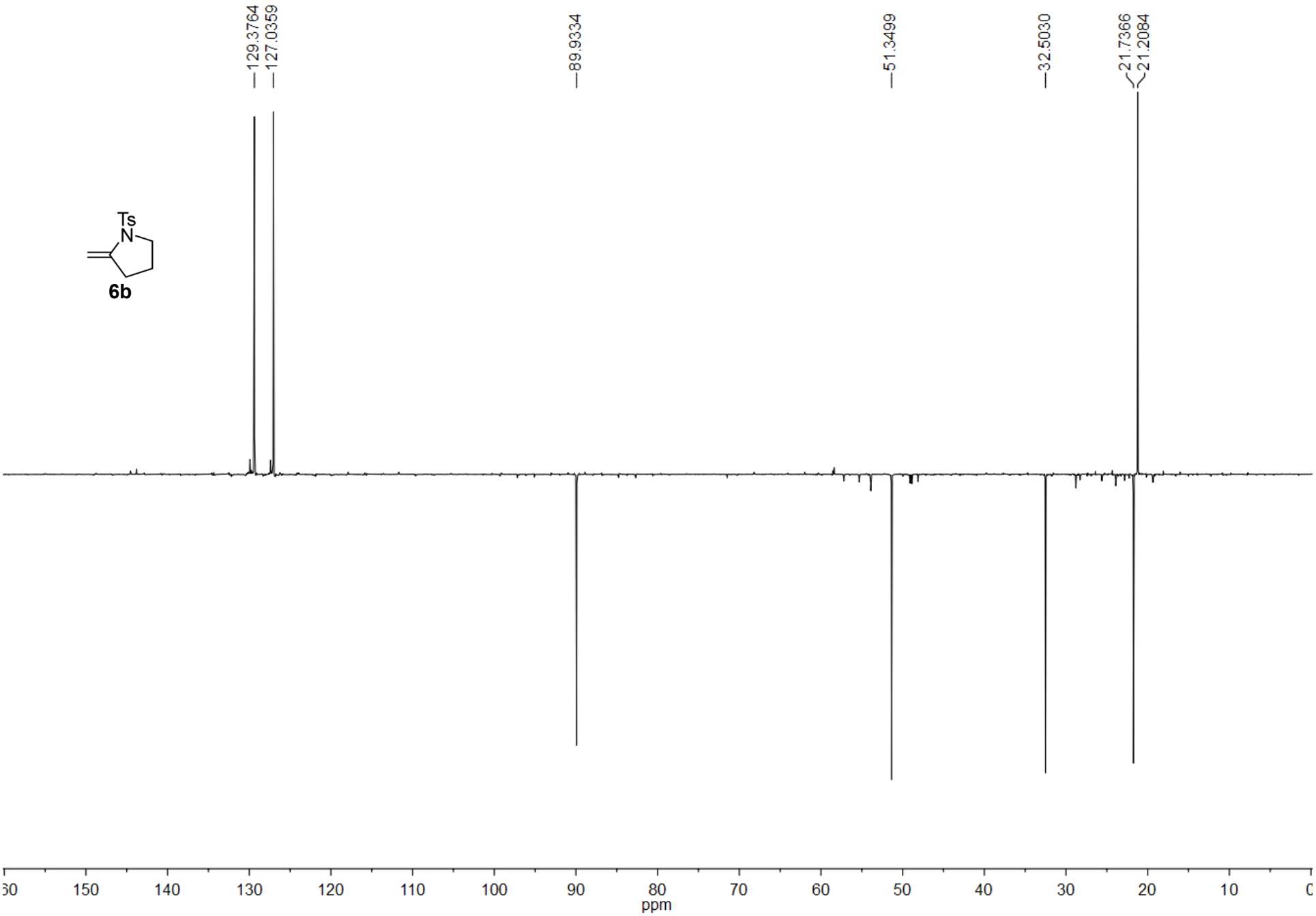
COSY NMR (500 MHz)



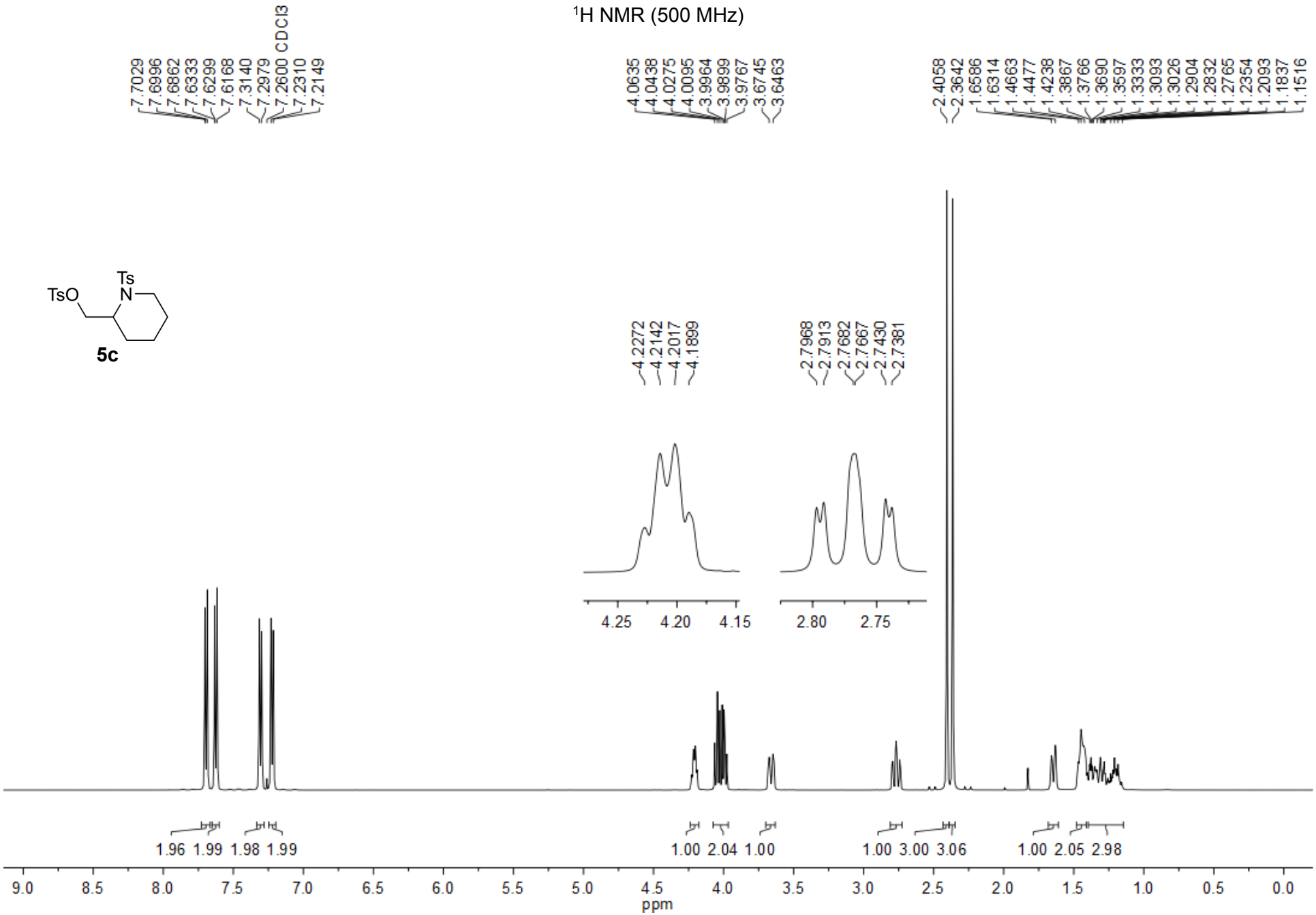
^{13}C NMR (126 MHz)



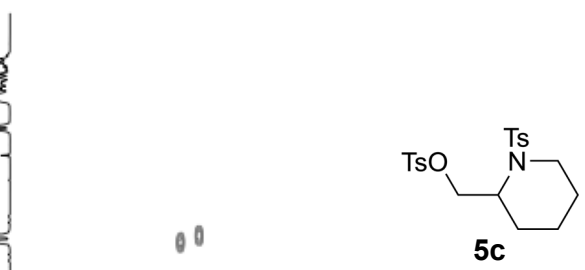
DEPT135 NMR (126 MHz)



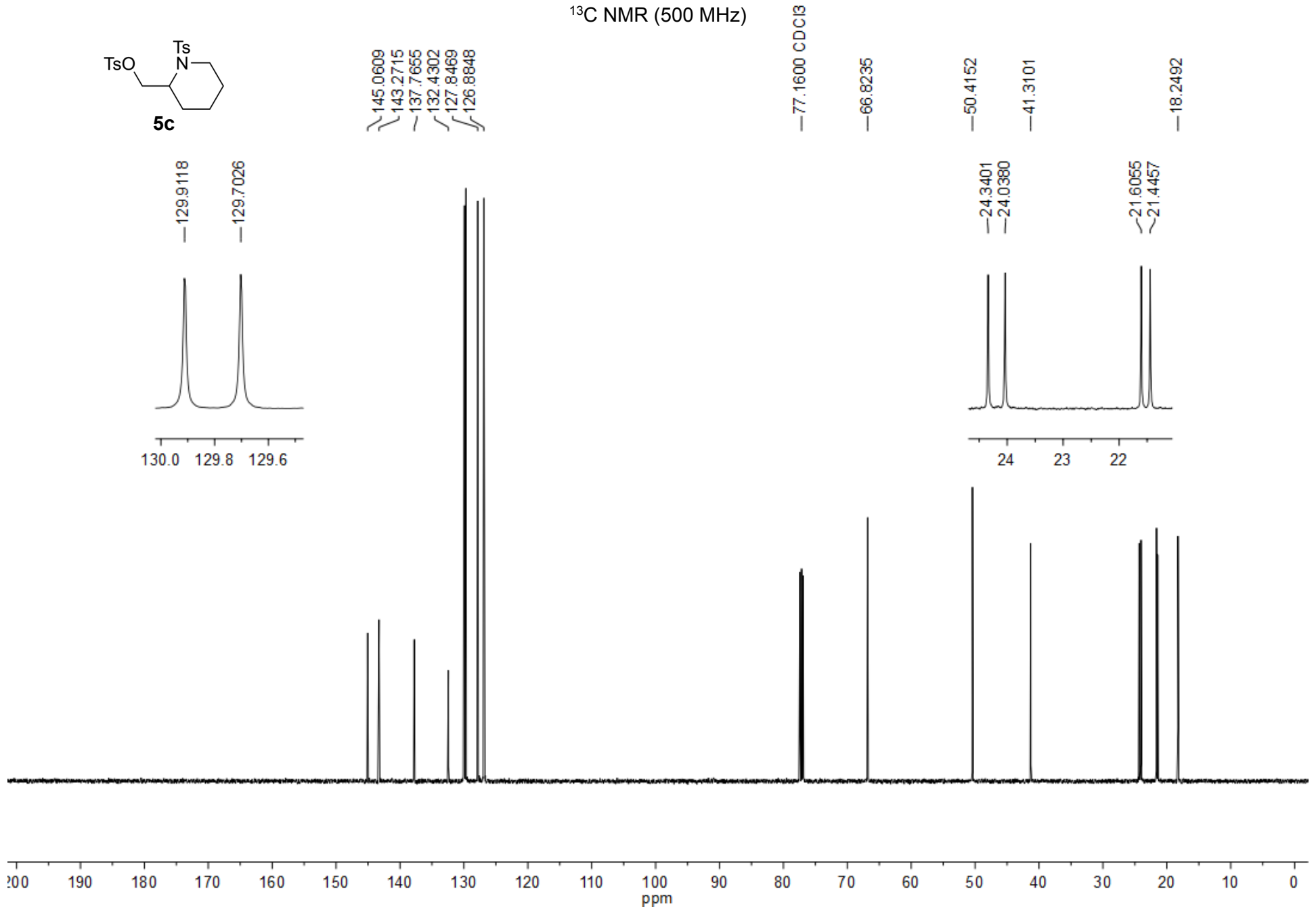
^{1}H NMR (500 MHz)



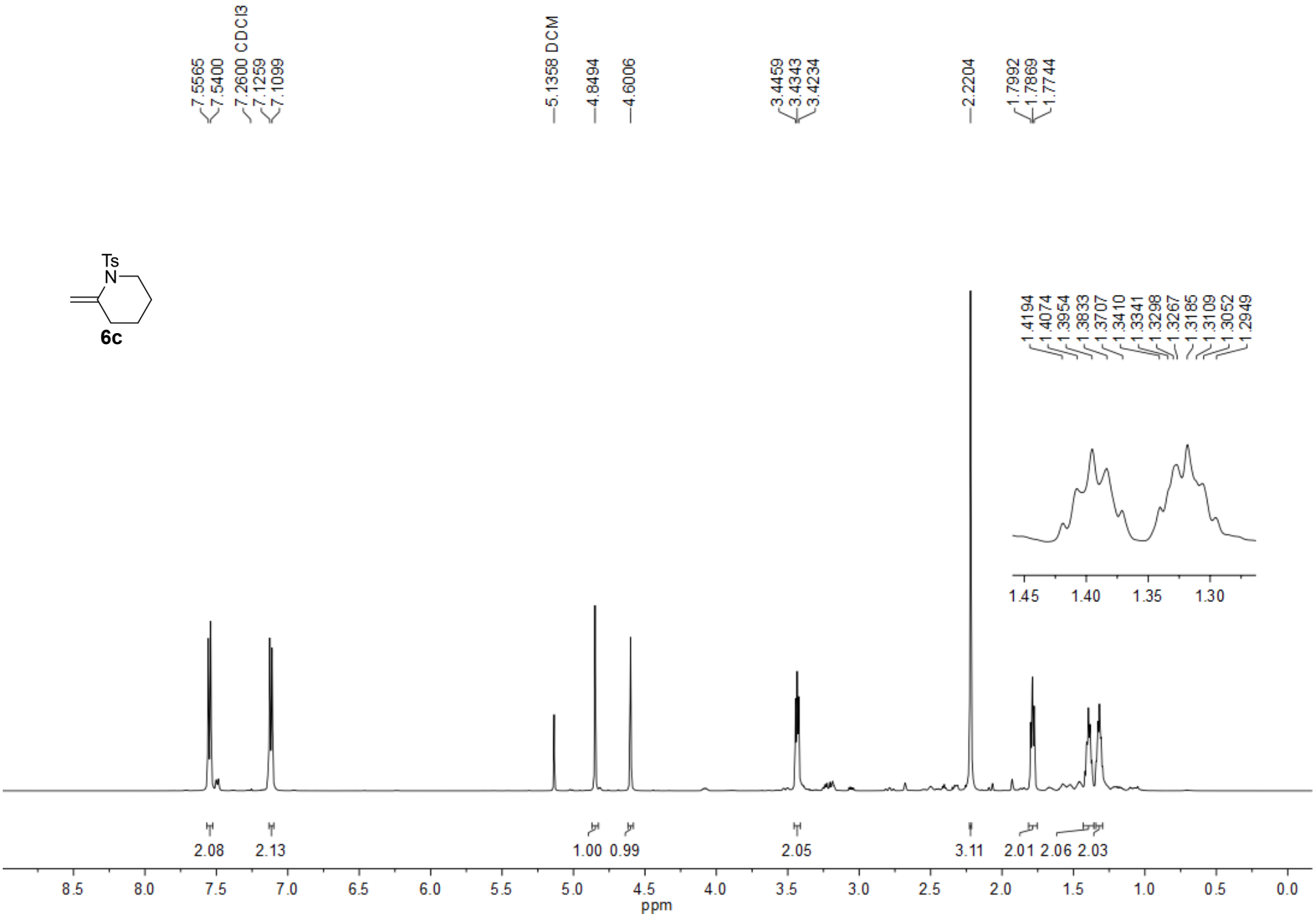
COSY NMR (500 MHz)



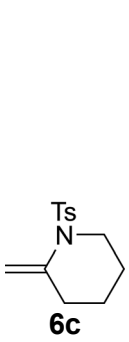
5c


^{13}C NMR (500 MHz)
TsO
Ts
N
5c
145.0609
143.2715
137.7655
132.4302
127.8469
126.8848
77.1600 CDCl3
66.8235
50.4152
41.3101
18.2492
129.9118
129.7026
24.3401
24.0380
21.6055
21.4457
130.0
129.8
129.6
24
23
22
ppm

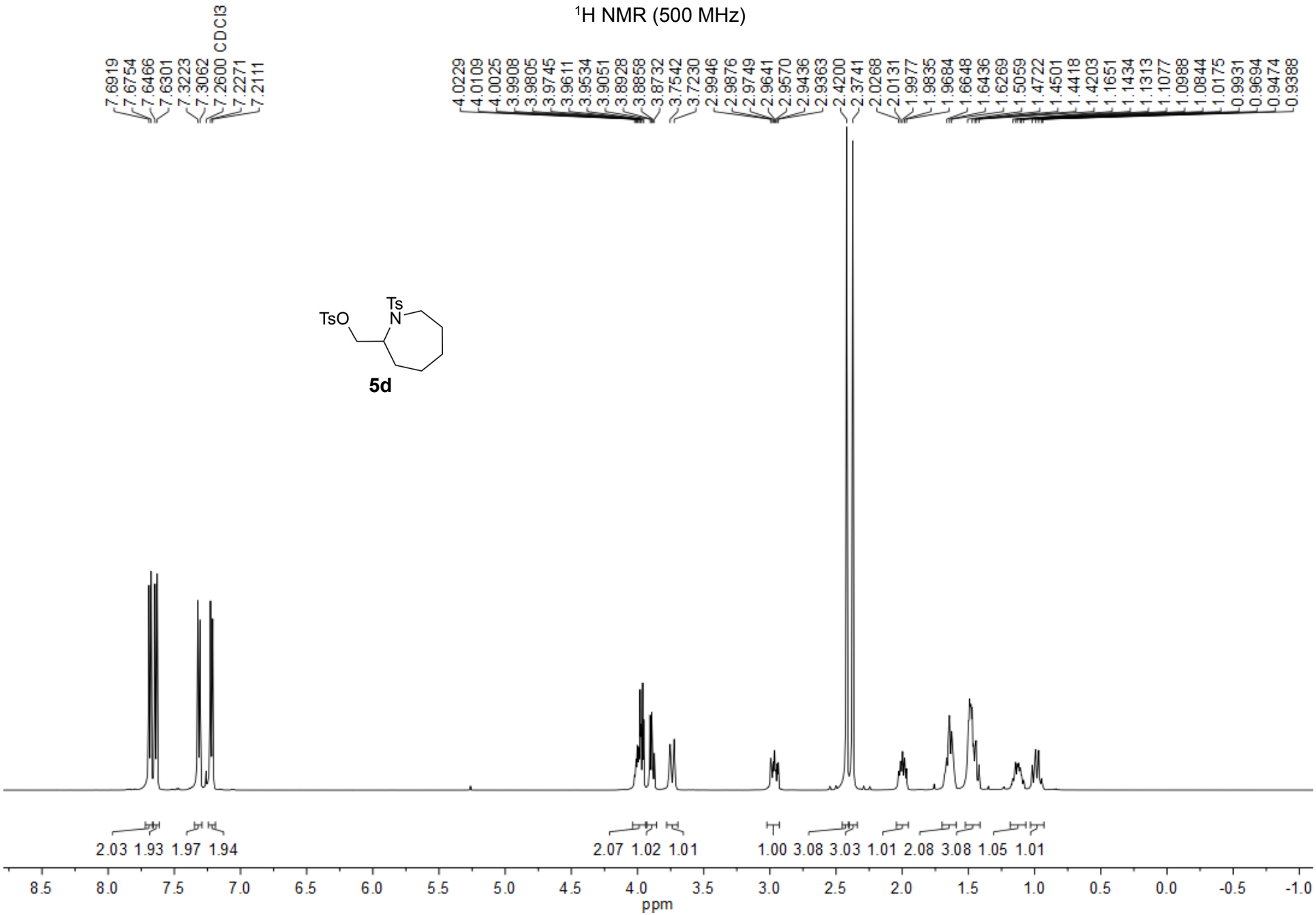
^{1}H NMR (500 MHz)



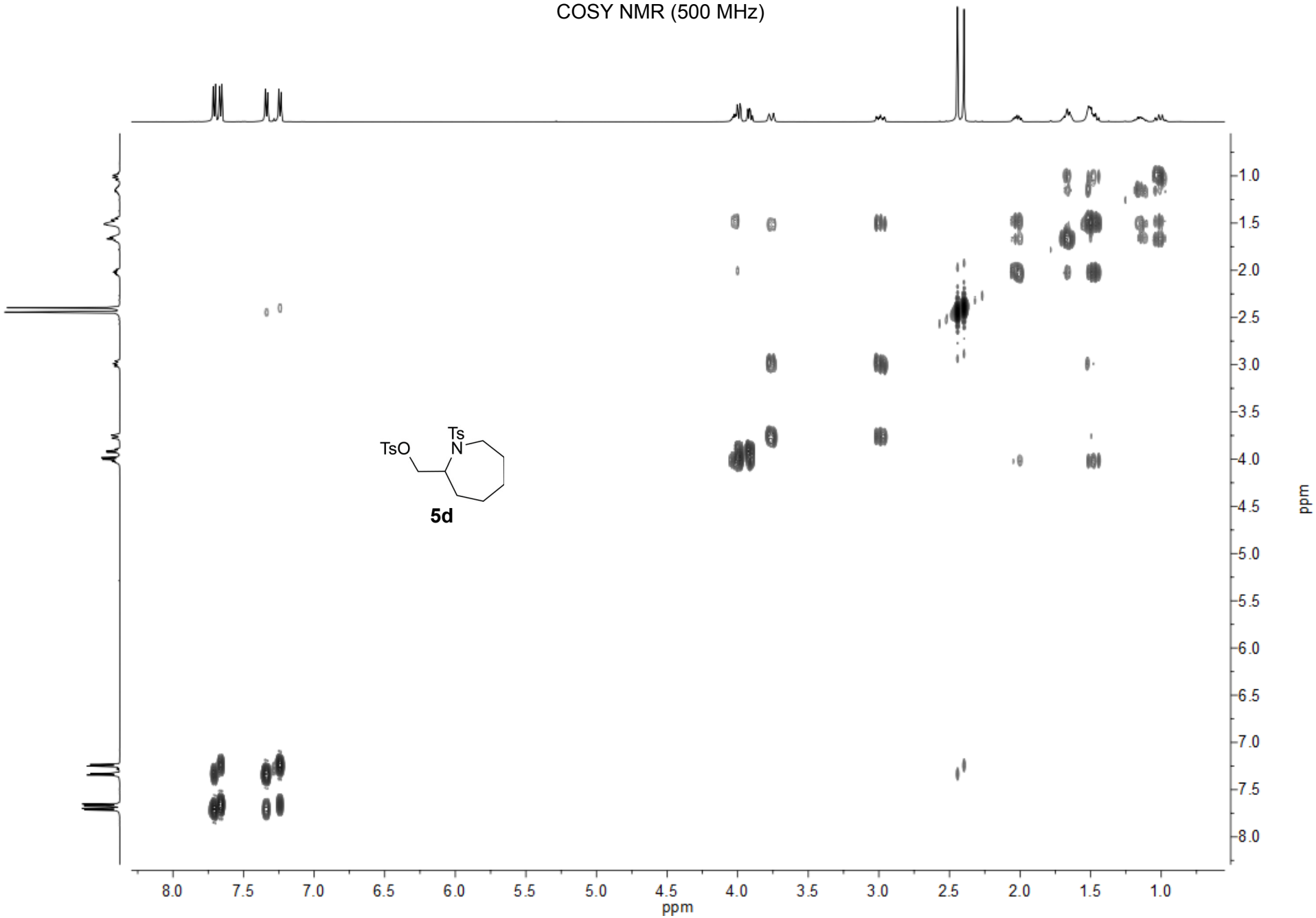
^{13}C NMR (500 MHz)

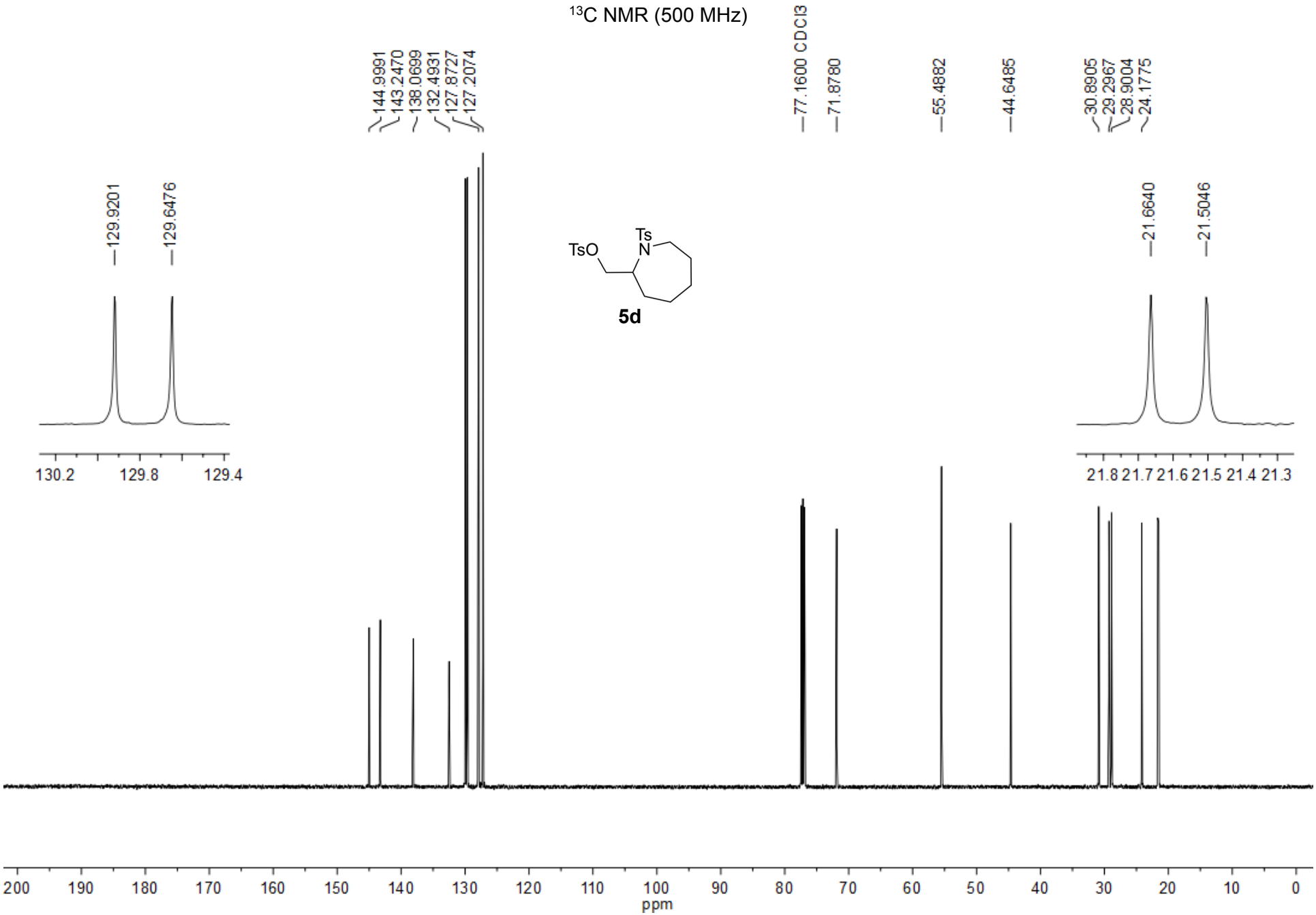


6c

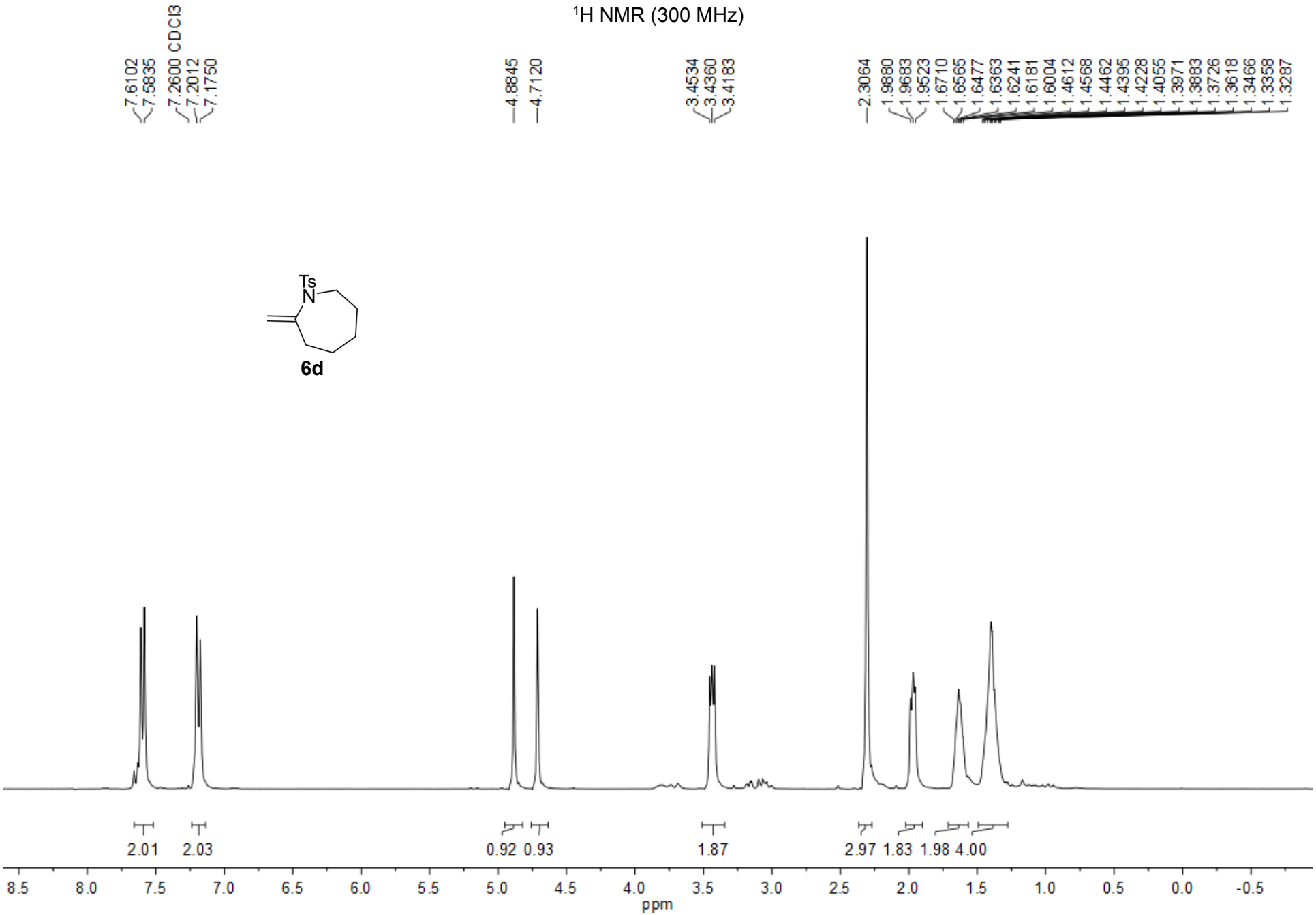

^{1}H NMR (500 MHz)
7.6919
7.6754
7.6466
7.6301
7.3223
7.3062
7.2600 CDCl3
7.2271
7.2111
4.0229
4.0109
4.0025
3.9908
3.9805
3.9745
3.9611
3.9534
3.9051
3.8928
3.8858
3.8732
3.7542
3.7230
2.9946
2.9876
2.9749
2.9641
2.9570
2.9436
2.9363
2.4200
2.3741
2.0268
2.0131
1.9977
1.9835
1.9684
1.6648
1.6436
1.6269
1.5059
1.4722
1.4501
1.4418
1.4203
1.1651
1.1434
1.1313
1.1077
1.0988
1.0844
1.0175
0.9931
0.9694
0.9474
0.9388
TsO
Ts
N
5d
2.03 1.93 1.97 1.94
2.07 1.02 1.01
1.00 3.08 3.03 1.01 2.08 3.08 1.05 1.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
ppm

COSY NMR (500 MHz)

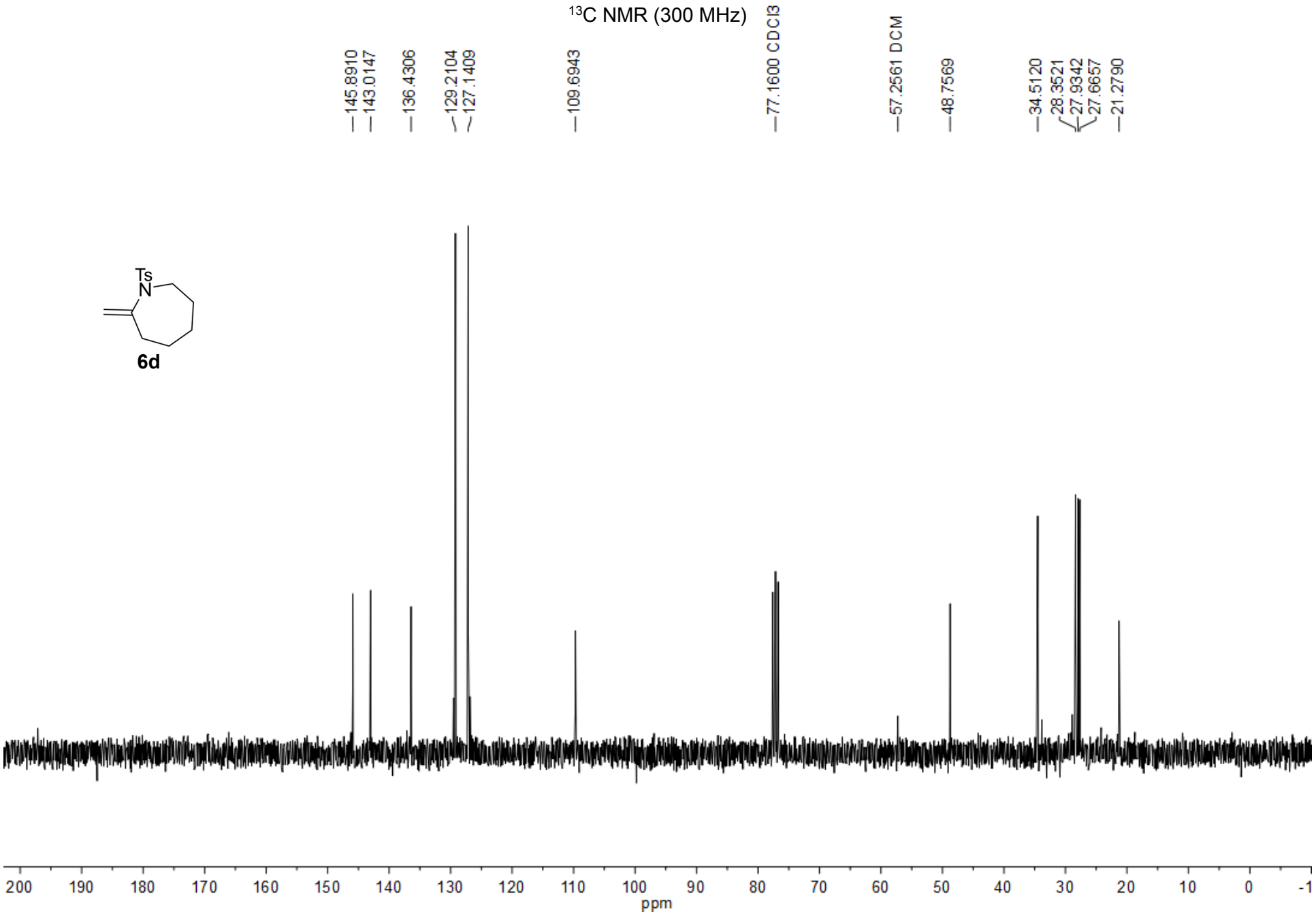



^{13}C NMR (500 MHz)
144.9991
143.2470
138.0699
132.4931
127.8727
127.2074
77.1600 CDCl3
71.8780
55.4882
44.6485
30.8905
29.2967
28.9004
24.1775
129.9201
129.6476
21.6640
21.5046
TsO
Ts
N
5d
130.2
129.8
129.4
21.8 21.7 21.6 21.5 21.4 21.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

^{1}H NMR (300 MHz)

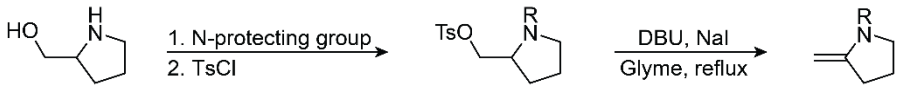


^{13}C NMR (300 MHz)



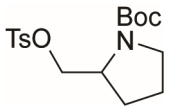
6d

Scheme 2



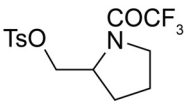
5b, R = Ts, 91.7%
5e, R = Boc, 81%
5f, R = $COCF_3$, 82%
5g, R = Ms, 87%
5h, R = Bz, 38%

6b, R = Ts, 89.6%
6e, R = Boc, 71.2%
6f, R = $COCF_3$, 45%
6g, R = Ms, 55%



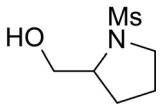
5e

To an ice-cold solution of prolinol (5.1 g, 50.44 mmol, 1.0 eq) and triethylamine (9.1 mL, 65.58 mmol, 1.3 eq) in DCM (65 mL) was added Boc_2O (12.1 g, 55.49 mmol, 1.1 eq) in one portion. The reaction was allowed to warm to rt overnight. The reaction mixture was diluted with 2M HCl (pH =1) and washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude N-Boc prolinol as an oil (12.72 g) which was used without further purification. R_f = 0.5 (50% EtOAc, visualized w/ $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.70 (br s, 1H), 3.75–3.65 (m, 1H), 3.55–3.41 (m, 2H), 3.26–3.21 (m, 1H), 3.16–3.12 (m, 1H), 1.82–1.67 (m, 2H), 1.64–1.57 (m, 1H), 1.48–1.46 (m, 1H), 1.29 (s, 9H). To a solution of crude Boc-Prolinol (12.72 g, 63.25 mmol,1.0 eq) from last step and TsCl (14.47g, 75.90 mmol, 1.2 eq) in DCM (250 mL) at rt was added DMAP (77.3 mg, 0.63 mmol, 0.01 eq) and triethylamine (11.46 mL, 82.22 mmol, 1.3 eq). The reaction was stirred overnight and diluted with 2M HCl (pH =1). The aqueous layer was washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel (100 g, 20% EtOAc/ hexanes (v/v)) to obtain **5e** as an oil (14.54 g, 81% over two steps). R_f = 0.26 (20% EtOAc, visualized w/ UV). ^{1}H NMR (rotational isomers, 400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 4.04 (t, *J* = 5.1 Hz, 2H), 3.92–3.85 (m, 2H), 3.28– 3.22 (m, 2H), 2.39 (s, 3H), 1.91–1.74 (m, 4H), 1.34 (d, *J* = 16.1 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.39, 153.95, 144.92, 144.76, 132.91, 129.89, 127.84, 79.88, 79.52, 69.98, 55.53, 55.48, 53.50, 46.90, 46.52, 28.36, 28.33, 27.59, 23.81, 22.83, 21.61. HRMS(ESI): Calcd for $C_{17}H_{25}NO_5SNa$ [MNa]$^+$: 356.1351, found: 378.1352.



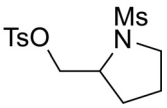
5f

To an ice-cold solution of prolinol (7.0 g, 69.20 mmol, 1.0 eq) and triethylamine (10.2 mL, 72.66 mmol, 1.05 eq) in dry MeOH (40 mL) under inert atmosphere was added ethyl trifluoroacetate (12.35 mL, 103.81 mmol, 1.5 eq) in small portions. The reaction was allowed to warm to rt over 20 h. The reaction mixture was concentrated under reduced pressure and diluted with DCM and 2M HCl. The organic layer was collected and the aqueous layer was further washed with DCM. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude trifluoroacetamide-protected prolinol as a light-yellow oil (13.8 g) which was used without further purification. R_f = 0.19 (30% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.18 (br s, 2H), 3.72–3.58 (m, 4H), 2.02–2.00 (m, 2H), 1.93– 1.80 (m, 2H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.34, 157.06, 156.73, 156.43, 119.85, 117.57, 115.28, 112.99, 63.65, 62.09, 47.76, 47.73, 27.07, 24.53. MS(ESI): Calcd for $C_7H_{11}F_3NO_2$ [MH]$^+$: 352.1, found: 352.1. To an ice-cold solution of crude N-trifluoroacetamide prolinol (13.8 g, 69.20 mmol, 1.0 eq) from last step and TsCl (15.83 g, 83.04 mmol, 1.2 eq) in DCM (80 mL) was added DMAP (0.85 g, 6.92 mmol, 0.1 eq) and triethylamine (12.53 mL, 89.96 mmol, 1.3 eq). The reaction was stirred at this temperature for 30 mins and 2.5 h at rt. It was then diluted with 2M HCl (pH =1) and the aqueous layer was washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel (150 g, 15–20% EtOAc/ hexanes (v/v)) to obtain **5f** as a light-yellow oil (20.0 g, 82 % over two steps). R_f = 0.44 (30% EtOAc/hexanes, visualized w/ UV). M.p. 67–69 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.26 (dd, *J* = 10.2, 4.8 Hz, 1H), 4.21–4.19 (m, 1H), 4.05 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.61–3.53 (m, 2H), 2.39 (s, 3H), 2.08–1.95 (m, 3H), 1.89–1.85 (m, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 156.02, 155.81, 155.60, 155.39, 145.26, 132.25, 130.00, 127.74, 118.38, 116.75, 115.11, 113.48, 68.06, 57.50, 47.46, 47.44, 47.42, 47.40, 26.30, 24.52, 21.53. HRMS (ESI): Calcd for $C_{14}H_{16}F_3NO_4SNa$ [MNa]$^+$: 374.0650, found: 374.0655.



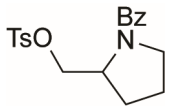
4e

To an ice-cold solution of N-mesyl L-proline ester (3.0 g, 14.45 mmol, 1.0 eq) in THF (45 mL) was added LAH (0.59 g, 15.93 mmol, 1.1 eq) in small portions. The reaction was stirred at the same temperature for 25 mins. The reaction mixture was quenched with sa. NH_4Cl, concentrated under reduced pressure, diluted with DCM and 2M HCl (pH =1). DCM layer was separated and the aqueous layer was further washed with DCM (2×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (20 g**,** 75% EtOAc/ hexanes (v/v)) to obtain **4e** as a colorless oil (2.3 g, 88.7%). R_f = 0.20 (70% EtOAc/hexanes, visualized w/ CAM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.60–3.53 (m, 1H), 3.48–3.35 (m, 2H), 3.31–3.13 (m, 3H), 2.71 (s, 3H), 1.87–1.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.77, 61.12, 49.21, 34.19, 28.35, 24.20. HRMS (ESI): Calcd for $C_6H_{14}NO_3S$ [MH]$^+$: 180.0689, found: 180.0689.



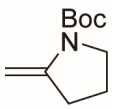
5g

To a solution of **4e** (2.3 g, 12.84 mmol, 1.0 eq) and TsCl (2.7 g, 14.13 mmol, 1.1 eq) in DCM (50 mL) at rt was added DMAP (0.16 g, 1.28 mmol, 0.1 eq) and triethylamine (2.34 mL, 16.7 mmol, 1.3 eq). The reaction was stirred for 20 h at rt. It was then diluted with 2M HCl (pH =1) and the aqueous layer was washed with DCM. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (35 g**,** 40%–80% EtOAc/ hexanes (v/v)) to obtain **5g** a white solid (3.71 g, 86.7%). R_f = 0.30 (50% EtOAc/hexanes, visualized w/ CAM). M.p. 114–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.04 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.92–3.86 (m, 1H), 3.82–3.77 (m, 1H), 3.32–3.15 (m, 2H), 2.74 (s, 3H), 2.38 (s, 3H), 1.99–1.83 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.07, 132.24, 129.90, 127.70, 71.11, 57.53, 48.97, 35.04, 28.50, 24.18, 21.50. HRMS (ESI): Calcd for $C_{13}H_{19}NO_5S_2Na$ [MNa]$^+$: 356.0602, found: 356.0603



5h

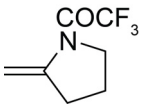
To a solution of prolinol (2.1 g, 20.76 mmol, 1.0 eq) and triethylamine (3.2 mL, 22.83 mmol, 1.1 eq) at -3 °C in DCM (25 mL) was added benzoyl chloride (2.48 g, 17.65 mmol, 0.85 eq) in small portions. The reaction was allowed to warm to rt overnight. The reaction mixture was diluted with 2M HCl (pH =1) and washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain almost pure N-Bz prolinol as an oil (4.2 g) which was used without further purification. R_f = 0.32 (70% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.4 Hz, 2H), 7.31–7.27 (m, 3H), 4.98 (s, 1H), 4.25 (dd, *J* = 7.1, 3.6 Hz, 1H), 3.67–3.64 (m, 1H), 3.62–3.60 (m, 1H), 3.35–3.33 (m, 2H), 2.02–1.98 (m, 1H), 1.77–1.74 (m, 1H), 1.73–1.57 (m, 2H). COSY NMR was obtained under same conditions (attached).^{13}C NMR (176 MHz, $CDCl_3$): δ = 171.38, 136.43, 129.77, 127.98, 126.75, 65.55, 60.59, 50.78, 27.85, 24.67. MS (ESI): Calcd for $C_{12}H_{16}NO_2$ [MH]$^+$: 206.1, found: 206.1. To a solution of crude N-Bz prolinol (4.2 g, 20.48 mmol, 1.0 eq) from last step and TsCl (3.9 g, 20.48 mmol, 1.0 eq) in DCM (50 mL) at rt was added DMAP (0.3 g, 2.48 mmol, 0.1 eq) and triethylamine (3.72 mL, 26.62 mmol, 1.3 eq). The reaction was stirred for 6 h at rt. It was then diluted with 2M HCl (pH =1) and the aqueous layer was washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography over silica gel (50 g**,** 40% EtOAc/ hexanes (v/v)) to obtain **5h** as an oil (38% over two steps). R_f = 0.32 (40% EtOAc/hexanes, visualized w/ UV). We found **5h** to decompose at rt (based on TLC). Hence, it was used immediately for enamine formation.



6e

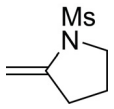
To a solution of **5e** (14.5 g, 41.0 mmol, 1.0 eq) in glyme (150 mL) was added NaI (18.39 g, 122.7 mmol, 3.0 eq). To this red solution was added DBU (12.24 mL, 82.0 mmol, 2.0 eq) and the greenish-yellow reaction mixture was refluxed for 3 h. The reaction produced foam and insoluble solids that dissolved upon quenching the reaction mixture with water (50 mL). The reaction mixture was further diluted with Et_2O and water. The aqueous layer was discarded and the organic layer was washed successively with sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain **6e** (5.33 g, 71.2%). R_f = 0.67 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.99 (s, 1H), 4.06 (s, 1H), 3.37 (t, *J* = 6.9 Hz, 2H), 2.31 (tt, *J* = 7.4, 1.8 Hz, 2H), 1.56 (p, *J* = 7.2 Hz, 2H), 1.27 (s, 9H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.26, 144.38,

88.97, 79.69, 48.98, 32.56, 27.88, 21.25. ^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$): δ = (up) 28.09, (down) 89.19, 49.19, 21.46. HRMS (ESI): Calcd for $C_{10}H_{18}NO_2[MH]^+$: 184.1332, found: 184.1340.



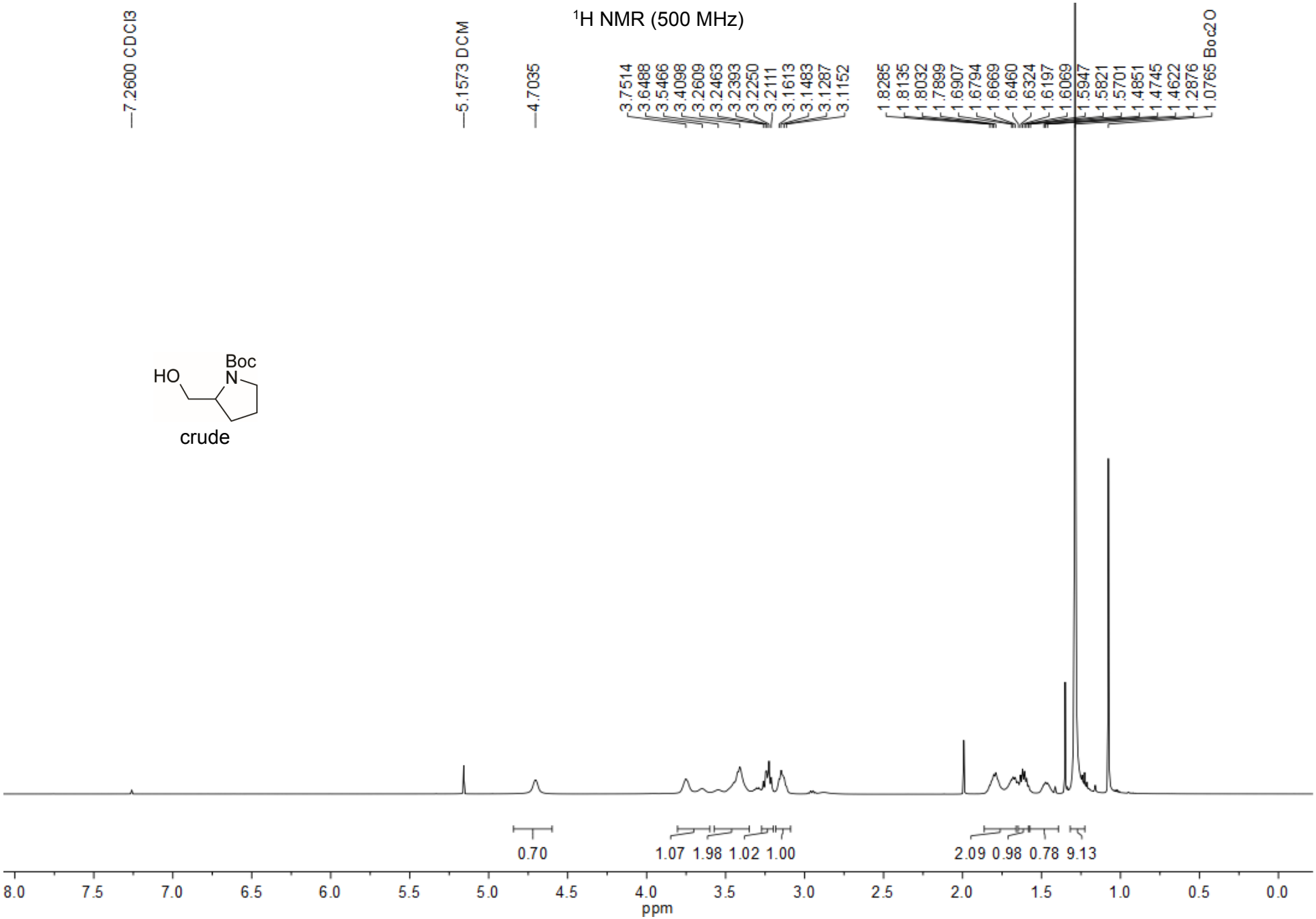
6f

To a solution of **5f** (5.0 g, 12.9 mmol, 1.0 eq) in glyme (80 mL) was added NaI (5.8 g, 38.7 mmol, 3.0 eq). To this red solution was added DBU (3.86 mL, 25.8 mmol, 2.0 eq) and the colorless solution was stirred at 60 °C for 48 h (the final product is an usntable low boiling point oil, hence, when the reaction was performed under refluxing conditions the yields were much lower). The reaction was quenched with water (50 mL). The reaction mixture was further diluted with Et_2O and water. The aqueous layer was discarded and the organic layer was washed successively with sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced under cold conditions and low pressure to obtain **6f** (1.25 g, 45%). Solvents could not be completely removed due to volatile nature of this molecules. We found this enamine to be unstable to silica gel purification. R_f = 0.8 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.29 (s, 1H), 4.78 (s, 1H), 4.10 (q, *J* = 7.2 Hz, 1H), 3.87 (t, *J* = 6.9 Hz, 2H), 3.46 (q, *J* = 6.9 Hz, 1H), 2.59 (tt, *J* = 7.4, 1.8 Hz, 2H), 1.95 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.26, 144.38, 88.97, 79.69, 48.98, 32.56, 27.88, 21.25. HRMS (ESI): Calcd for $C_7H_9F_3NO$ $[MH]^+$: 180.0631, found: 180.0636.

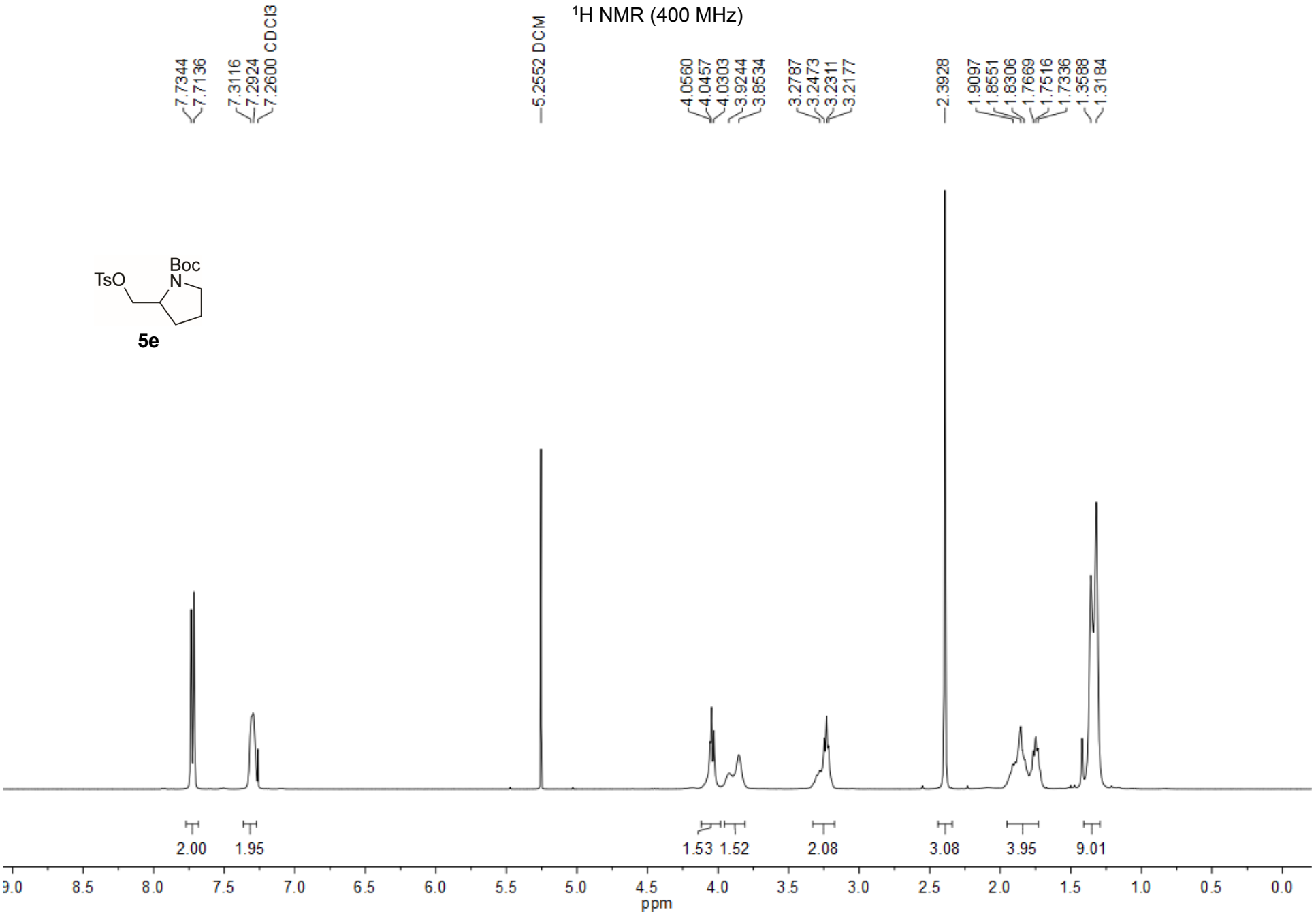


6g

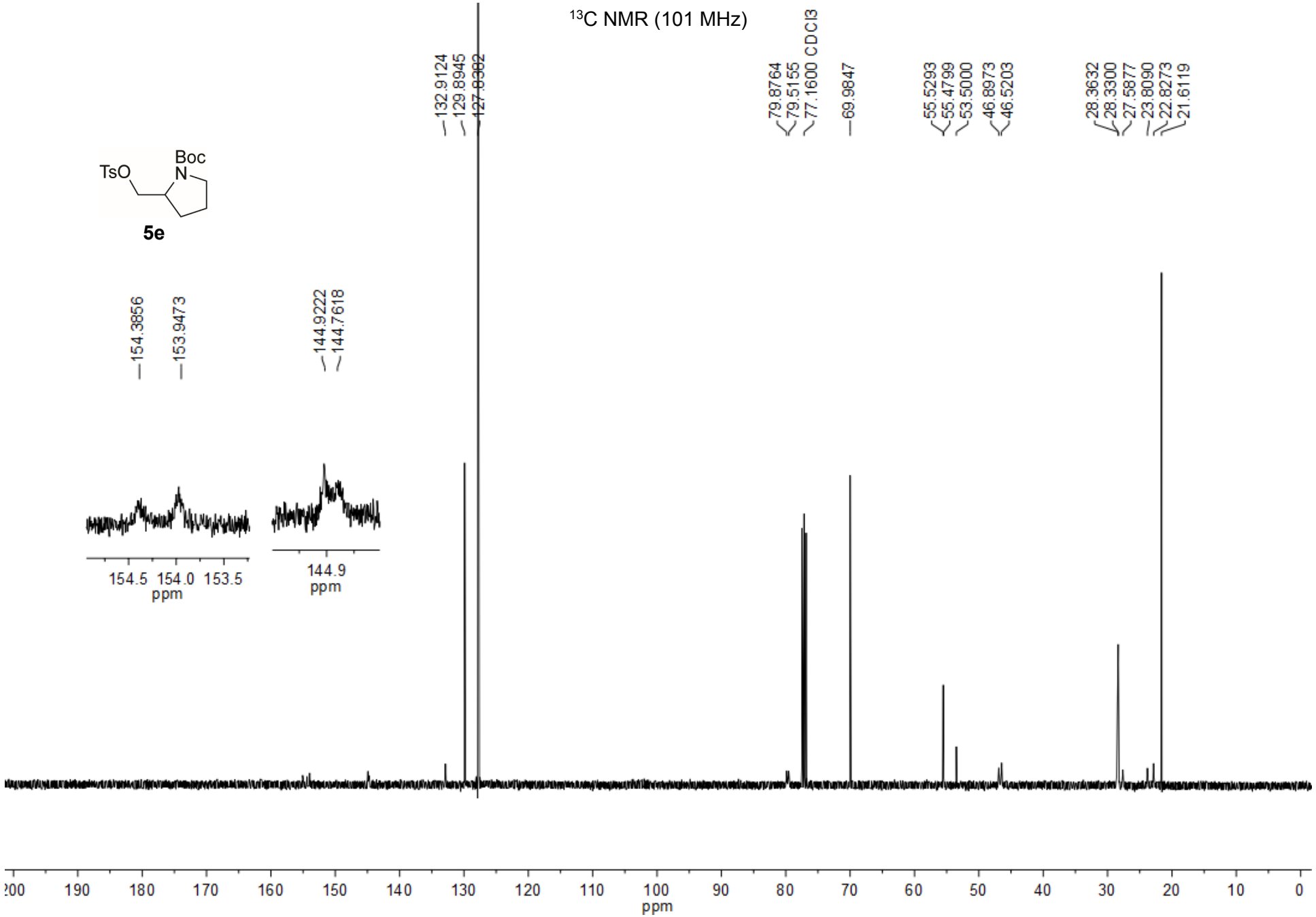
To a solution of **5g** (2.5 g, 7.5 mmol, 1.0 eq) in glyme (50 mL) was added NaI (3.37 g, 22.5 mmol, 3.0 eq). To this red solution was added DBU (2.24 mL, 15 mmol, 2.0 eq) and the colorless solution was refluxed for 7.5 h. Additional NaI (1.0 eq) and DBU (1.0 eq) was added and the reaction was refluxed for another 1 h. The reaction was quenched with water (20 mL). The reaction mixture concentrated and the the reaction was further diluted with Et_2O and water. The aqueous layer was discarded and the organic layer was washed successively with water, sat. $NaHCO_3$ (×2) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced under cold conditions (bath temperature of 16 °C) and low pressure to obtain volatile **6g** (0.66 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.68 (s, 1H), 4.19 (s, 1H), 3.50 (t, *J* = 6.7 Hz, 2H), 2.77 (s, 3H), 2.47 (tt, *J* = 7.5, 1.8 Hz, 2H), 1.75 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.89, 88.48, 51.24, 33.52, 32.42, 21.70. HRMS (ESI): Calcd for $C_6H_{12}NO_2S$ $[MH]^+$: 162.0583, found: 162.0589.


^{1}H NMR (500 MHz)
7.2600 CDCl3
5.1573 DCM
4.7035
3.7514
3.6488
3.5466
3.4098
3.2609
3.2463
3.2393
3.2250
3.2111
3.1613
3.1483
3.1287
3.1152
1.8285
1.8135
1.8032
1.7899
1.6907
1.6794
1.6669
1.6460
1.6324
1.6197
1.6069
1.5947
1.5821
1.5701
1.4851
1.4745
1.4622
1.2876
1.0765 Boc2O
HO
Boc
N
crude
0.70
1.07 1.98 1.02 1.00
2.09 0.98 0.78 9.13
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

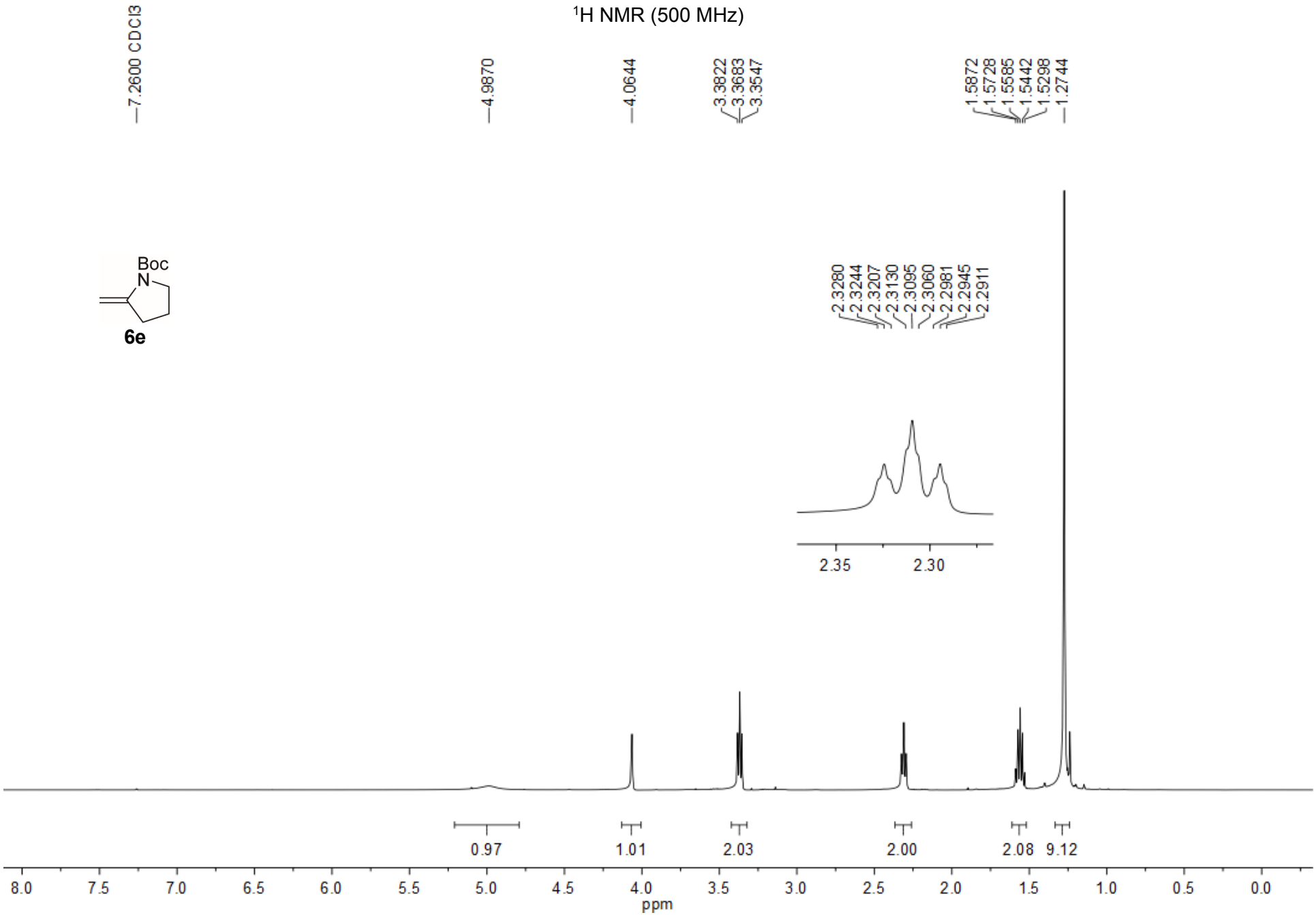
^{1}H NMR (400 MHz)



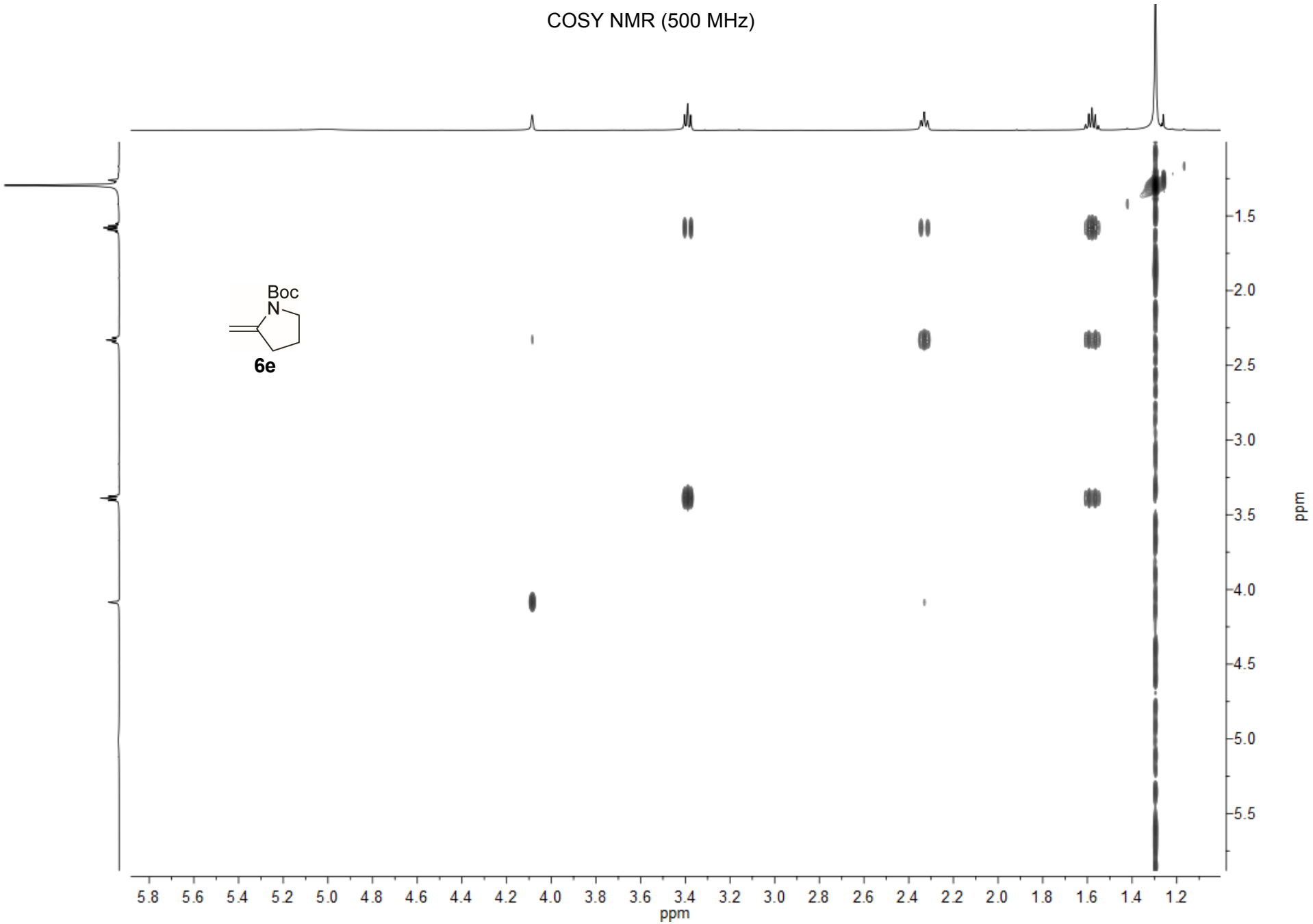
5e

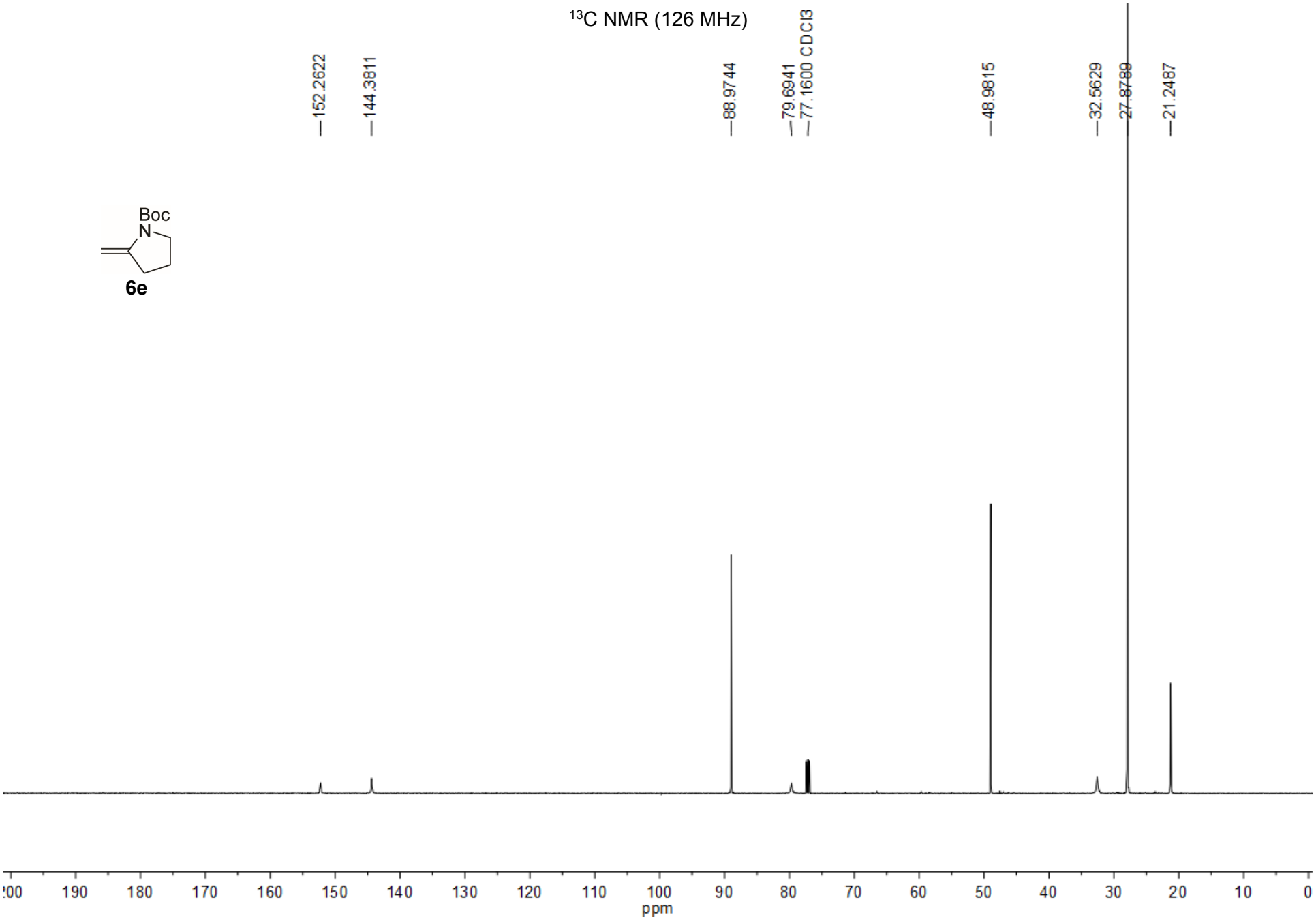

^{13}C NMR (101 MHz)
132.9124
129.8945
127.8362
79.8764
79.5155
77.1600 CDCl3
69.9847
55.5293
55.4799
53.5000
46.8973
46.5203
28.3632
28.3300
27.5877
23.8090
22.8273
21.6119
154.3856
153.9473
144.9222
144.7618
TsO
Boc
N
5e
154.5 154.0 153.5
ppm
144.9
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

^{1}H NMR (500 MHz)

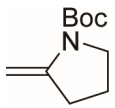


COSY NMR (500 MHz)

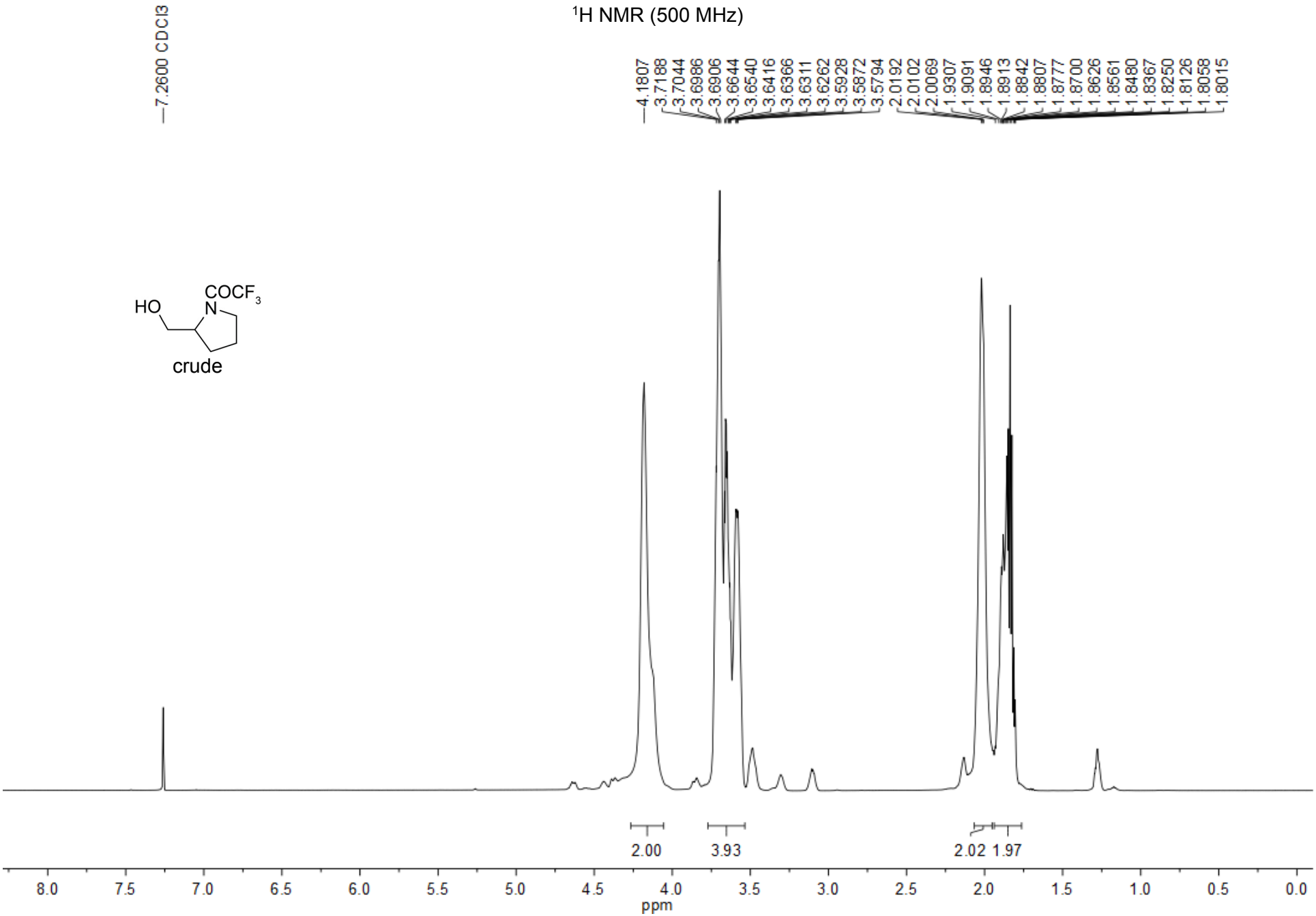



^{13}C NMR (126 MHz)
152.2622
144.3811
88.9744
79.6941
77.1600 CDCl3
48.9815
32.5629
27.8789
21.2487
Boc
N
6e
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

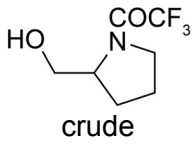
DEPT-135 NMR (126 MHz)



6e

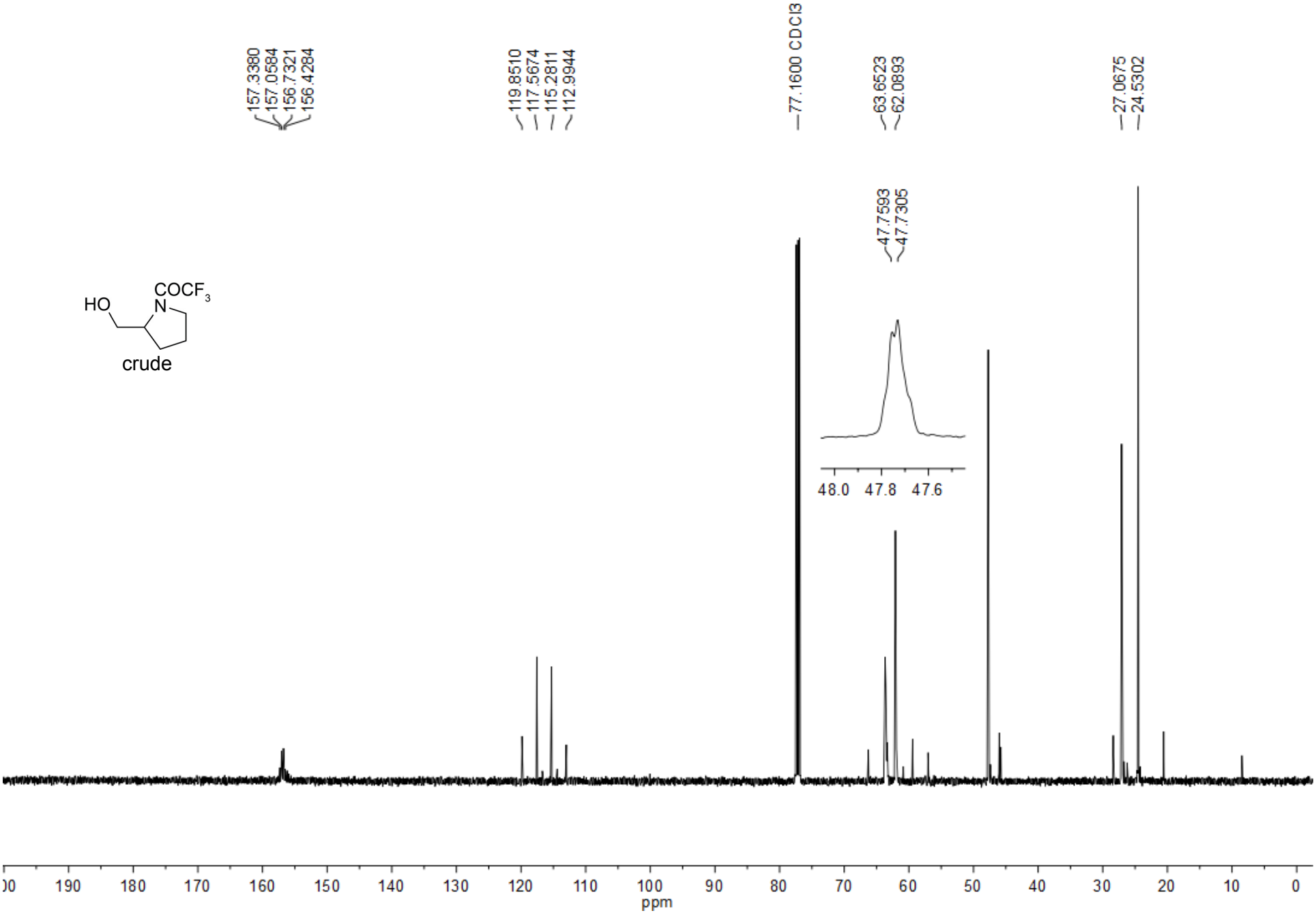

^{1}H NMR (500 MHz)
7.2600 CDCl3
4.1807
3.7188
3.7044
3.6986
3.6906
3.6644
3.6540
3.6416
3.6366
3.6311
3.6262
3.5928
3.5872
3.5794
2.0192
2.0102
2.0069
1.9307
1.9091
1.8946
1.8913
1.8842
1.8807
1.8777
1.8700
1.8626
1.8561
1.8480
1.8367
1.8250
1.8126
1.8058
1.8015
HO
N
COCF3
crude
2.00
3.93
2.02
1.97
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

COSY NMR (500 MHz)

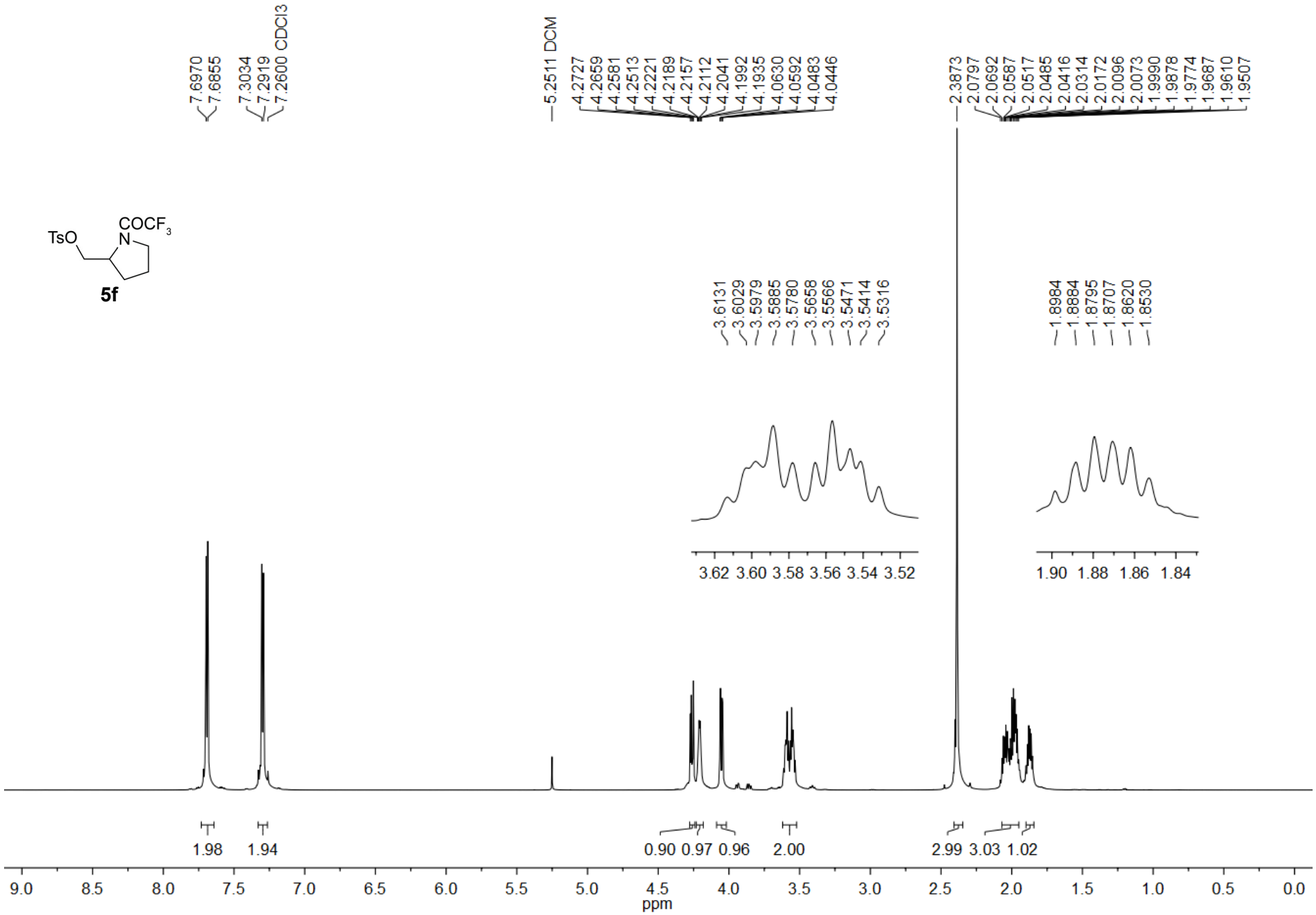


crude

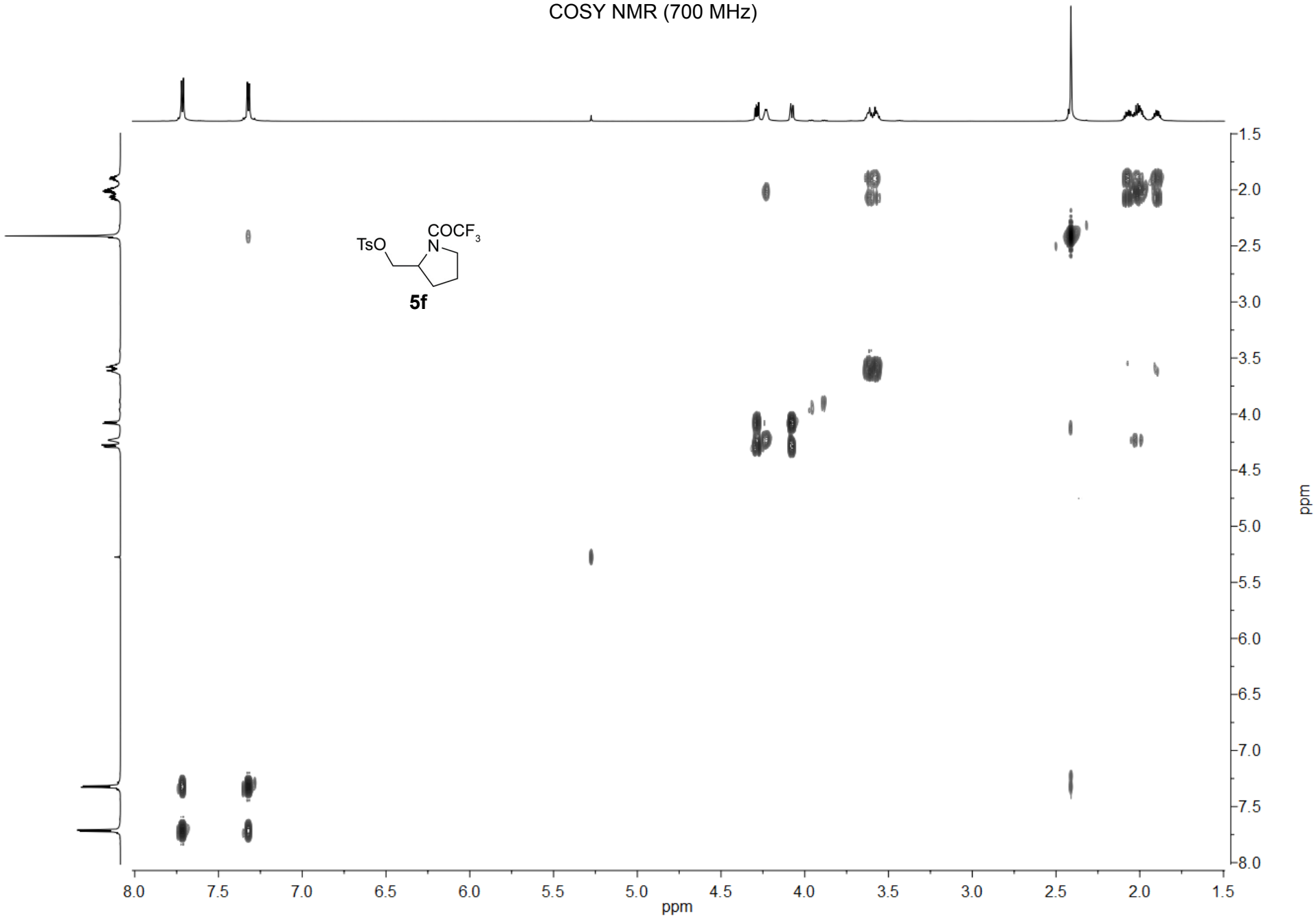
^{13}C NMR (126 MHz)



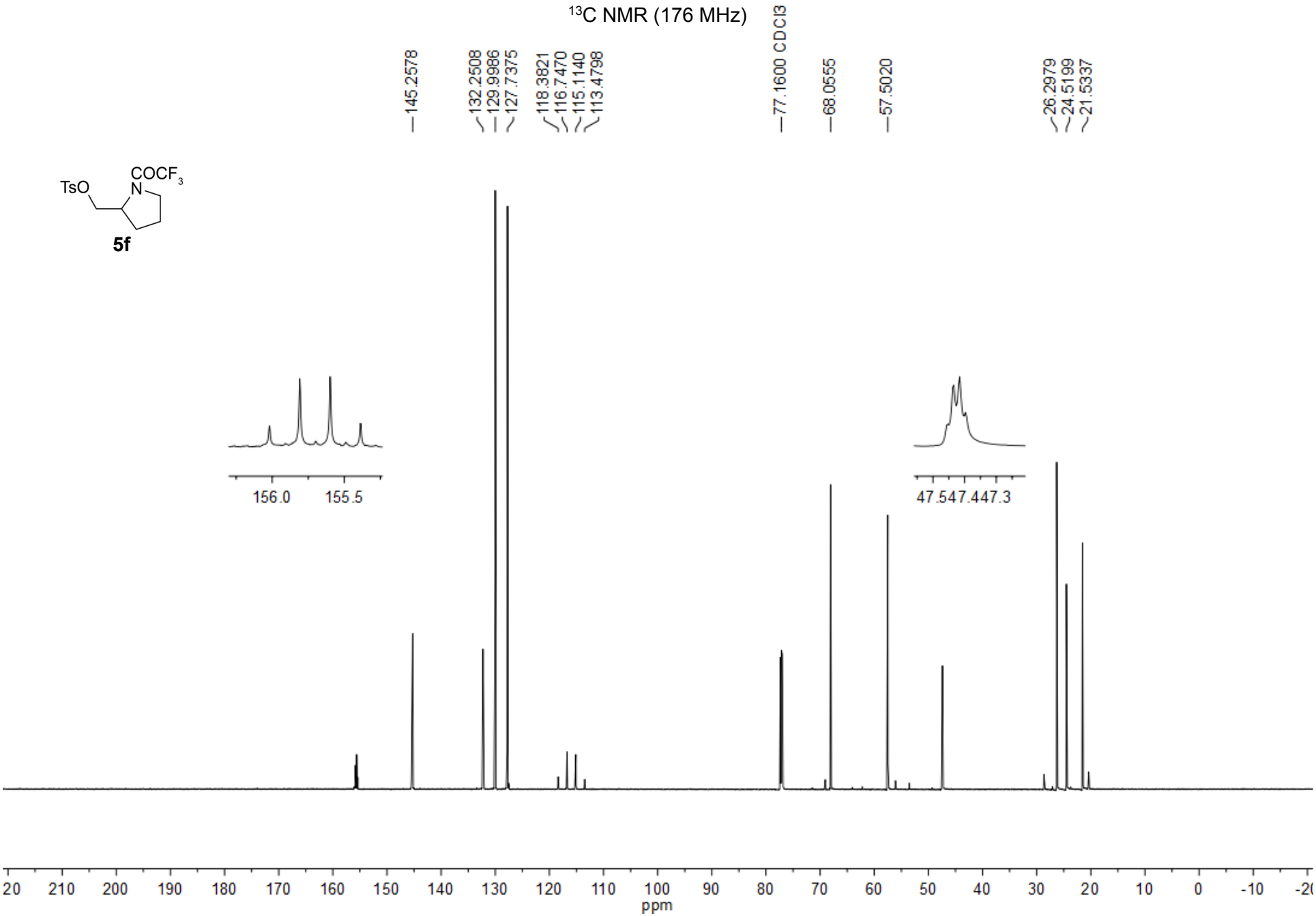
^{1}H NMR (500 MHz)

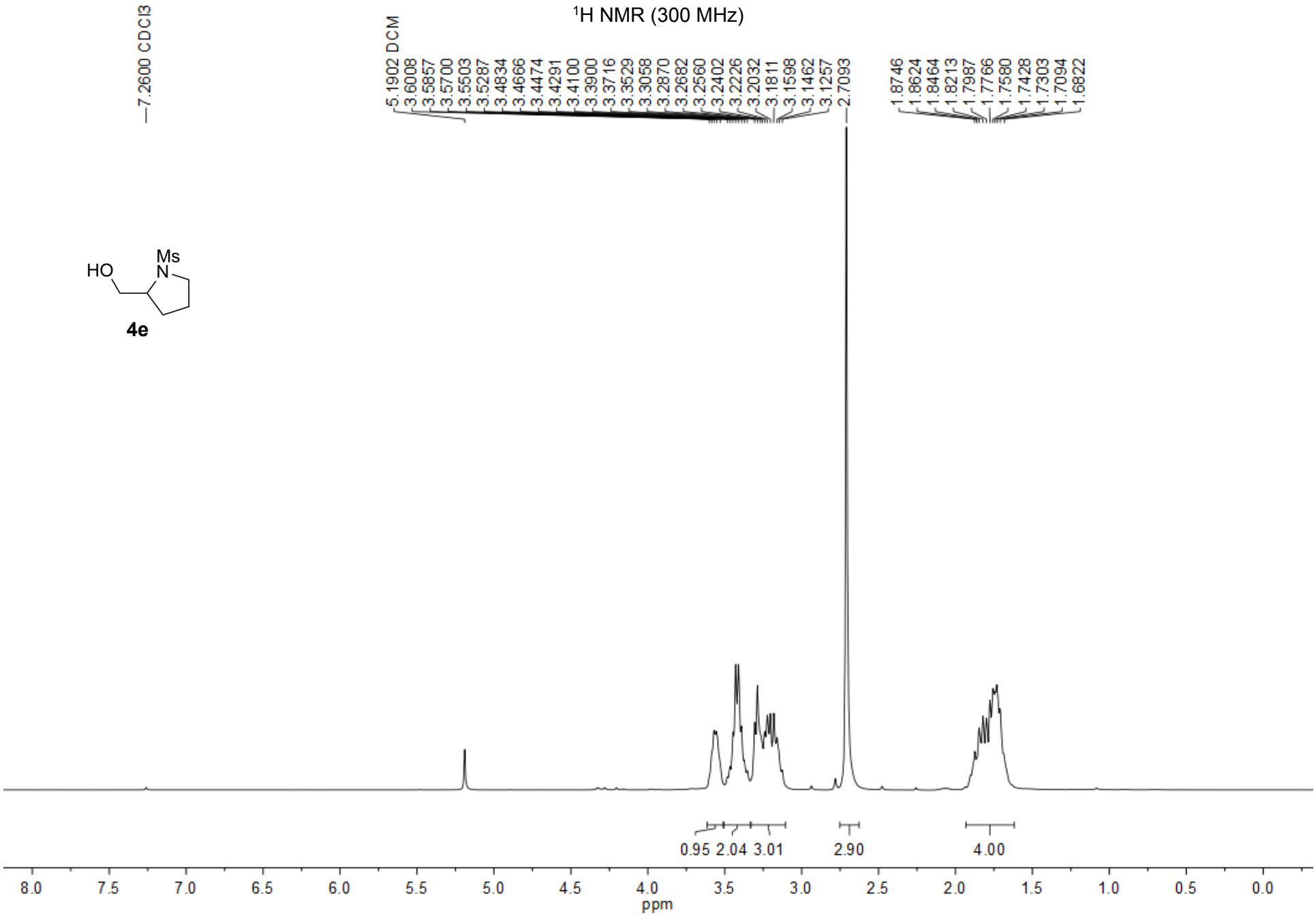


COSY NMR (700 MHz)

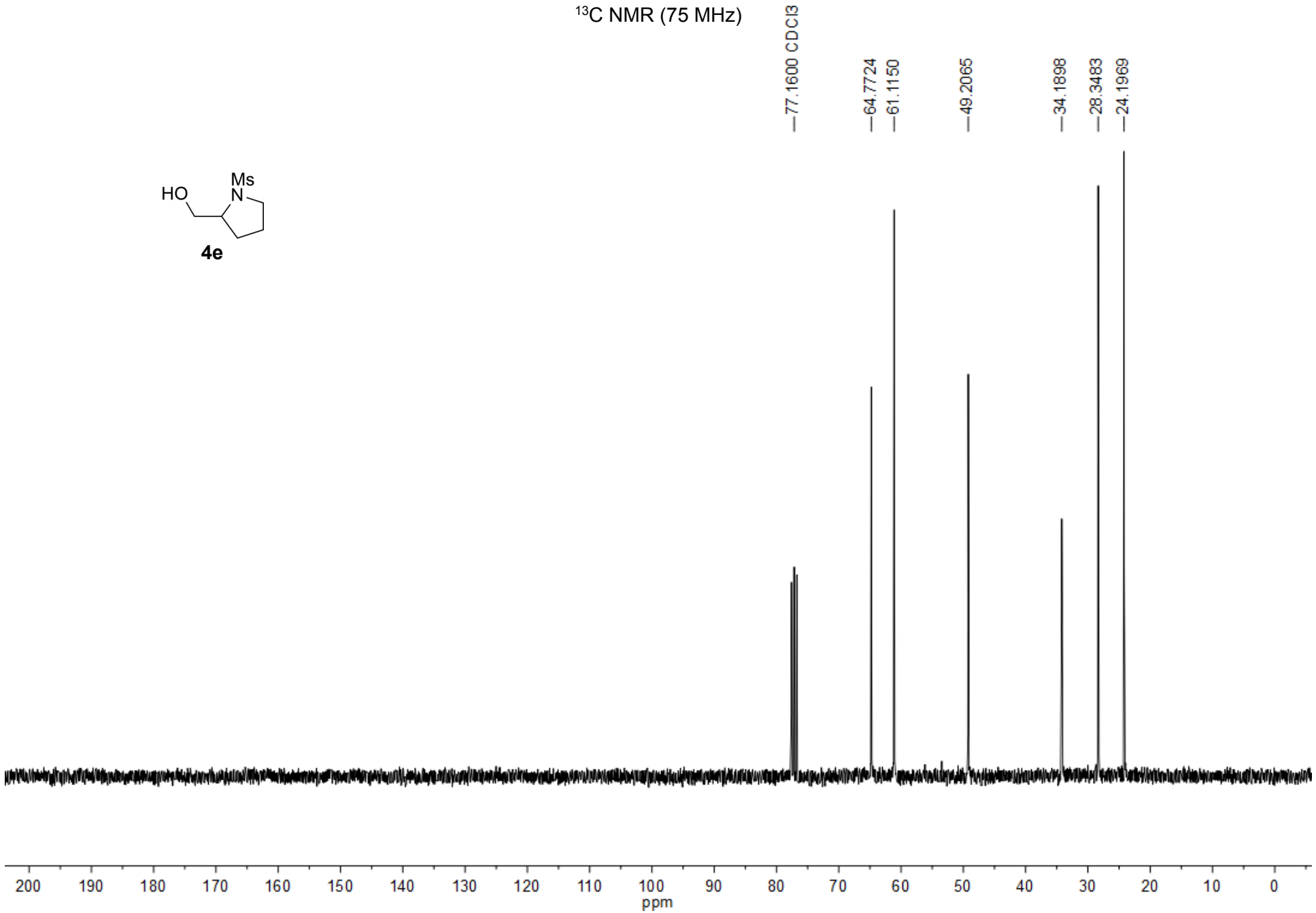


^{13}C NMR (176 MHz)

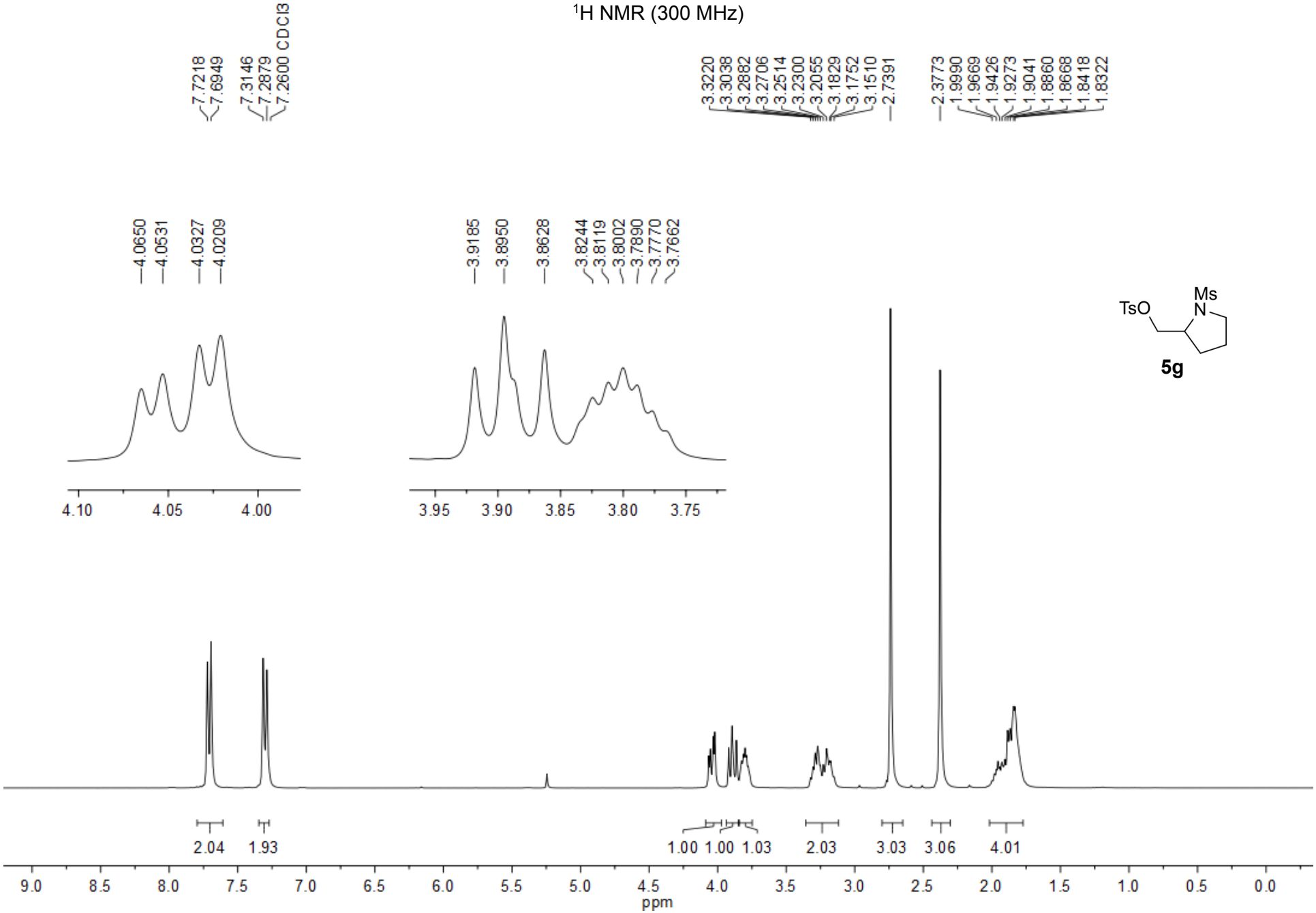



^{1}H NMR (300 MHz)
7.2600 CDCl3
5.1902 DCM
3.6008
3.5857
3.5700
3.5503
3.5287
3.4834
3.4666
3.4474
3.4291
3.4100
3.3900
3.3716
3.3529
3.3058
3.2870
3.2682
3.2560
3.2402
3.2226
3.2032
3.1811
3.1598
3.1462
3.1257
2.7093
1.8746
1.8624
1.8464
1.8213
1.7987
1.7766
1.7580
1.7428
1.7303
1.7094
1.6822
HO
Ms
N
4e
0.95 2.04 3.01
2.90
4.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

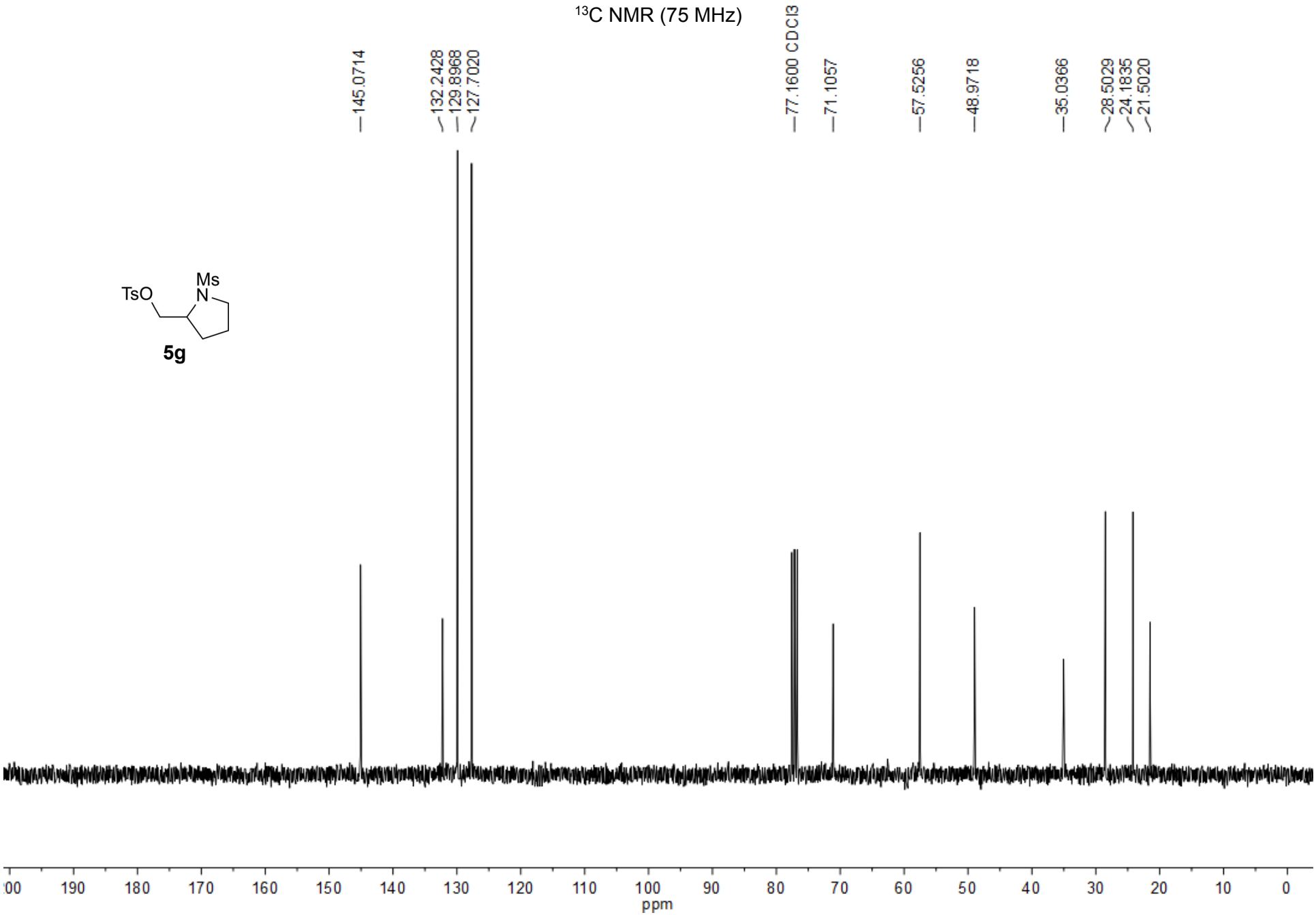
^{13}C NMR (75 MHz)



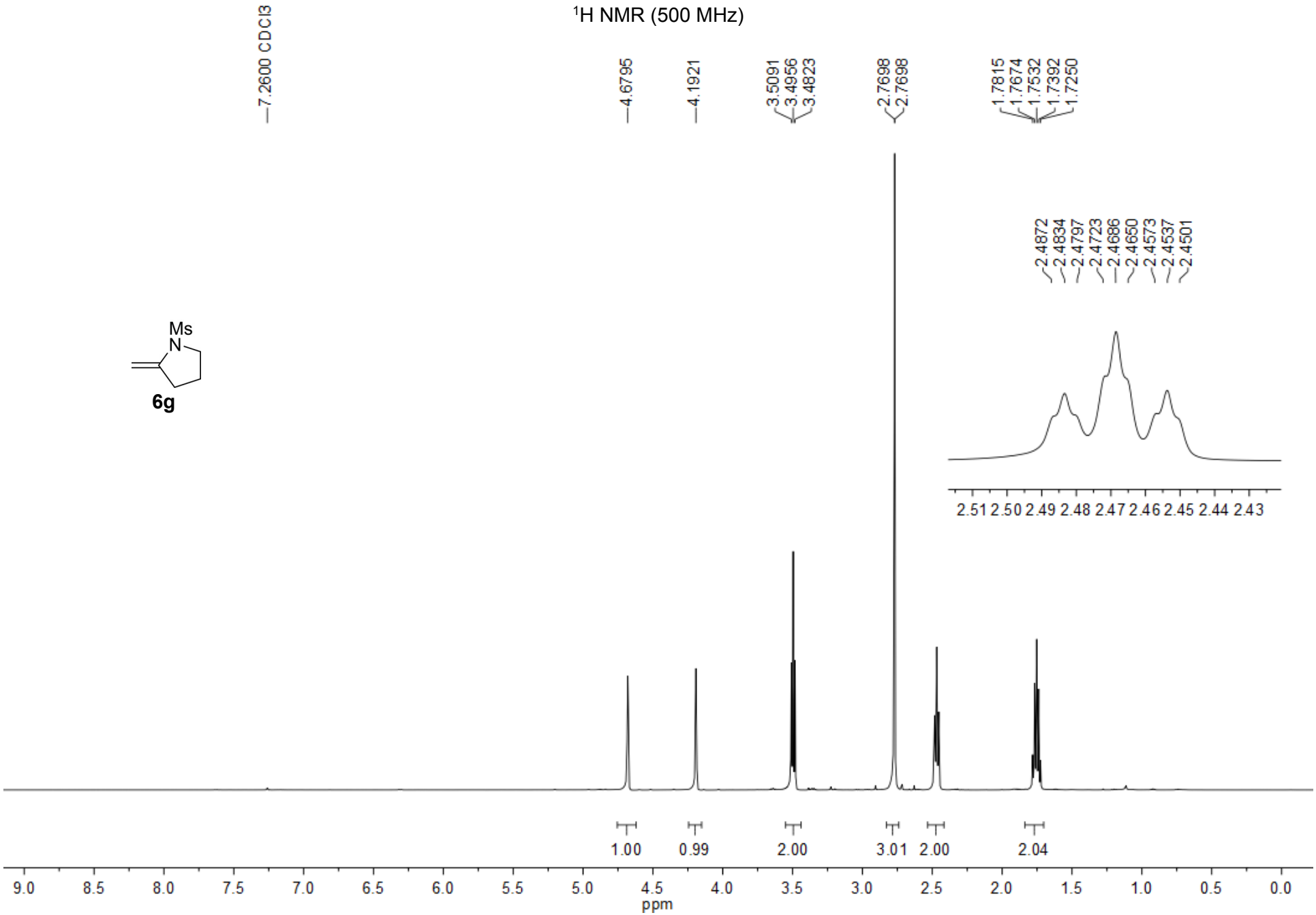
^{1}H NMR (300 MHz)



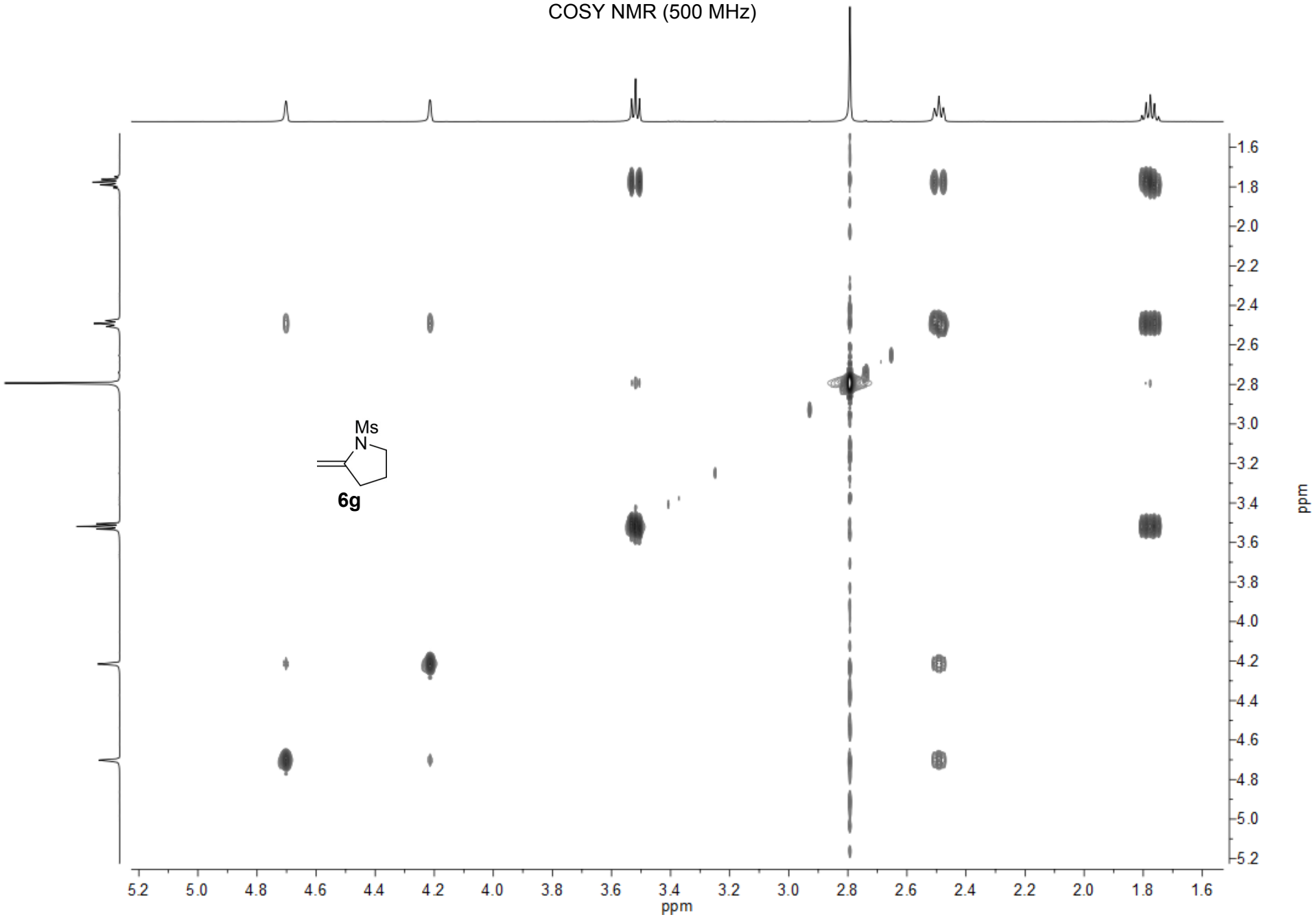
^{13}C NMR (75 MHz)



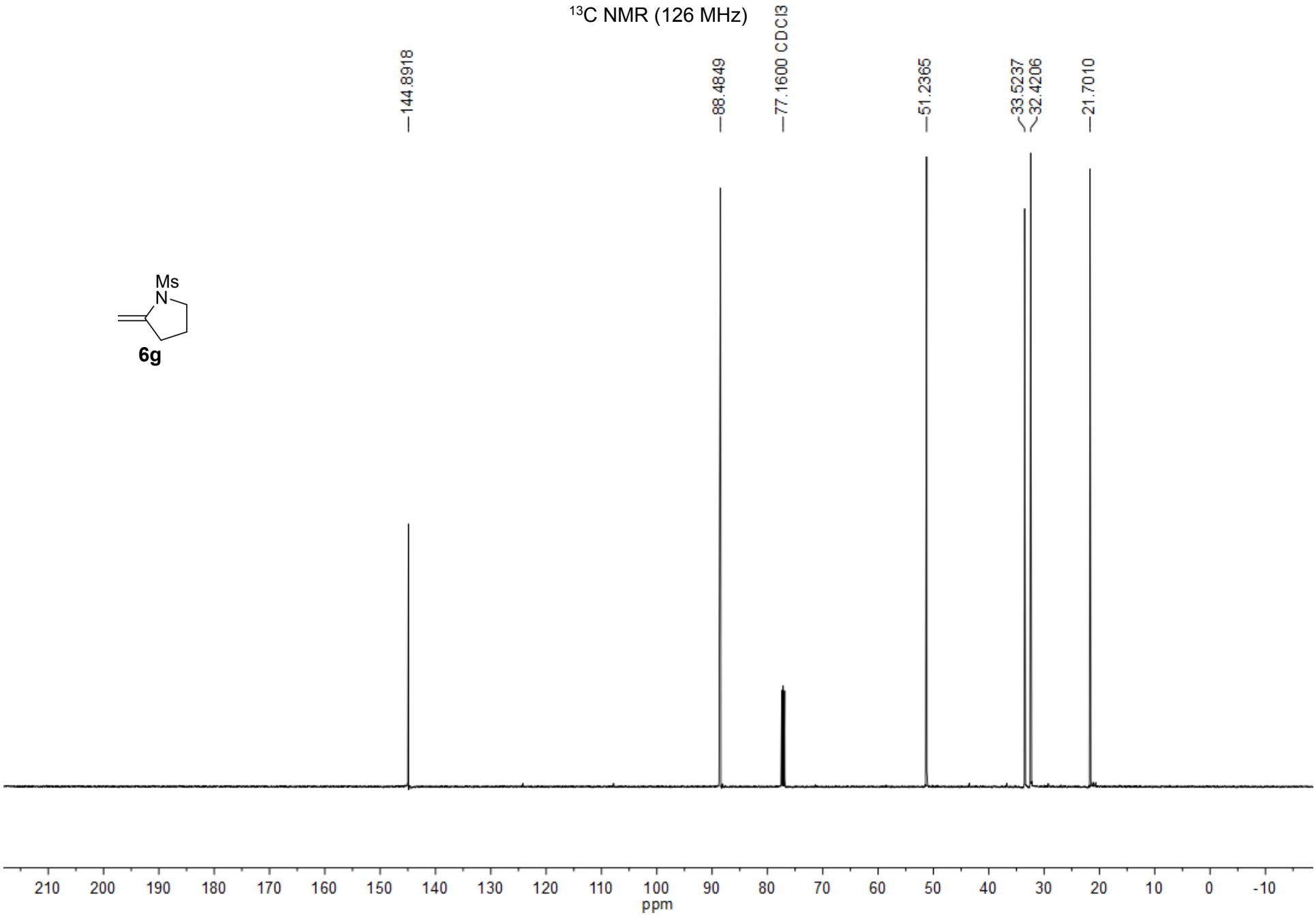
^{1}H NMR (500 MHz)



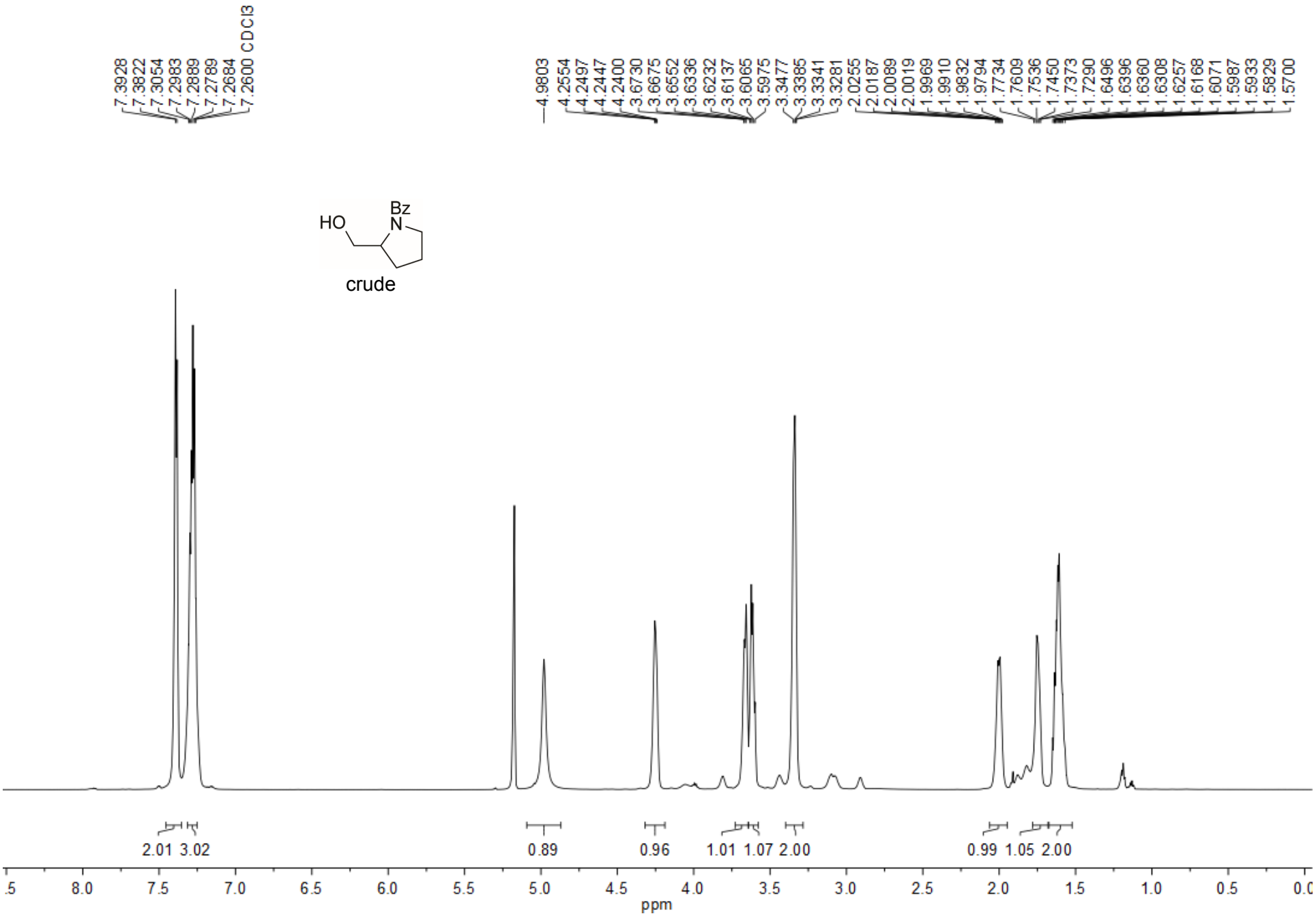
COSY NMR (500 MHz)



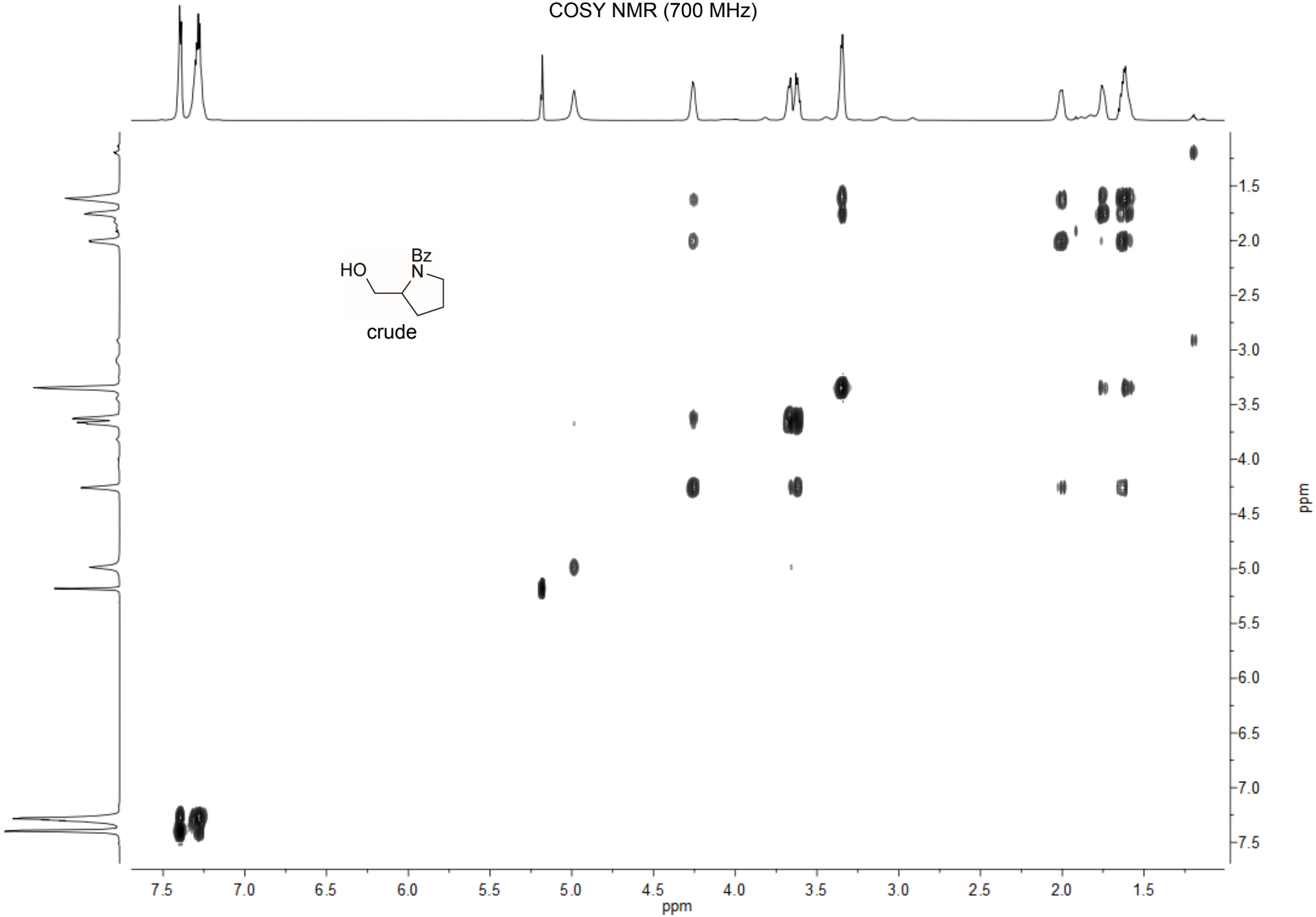
^{13}C NMR (126 MHz)



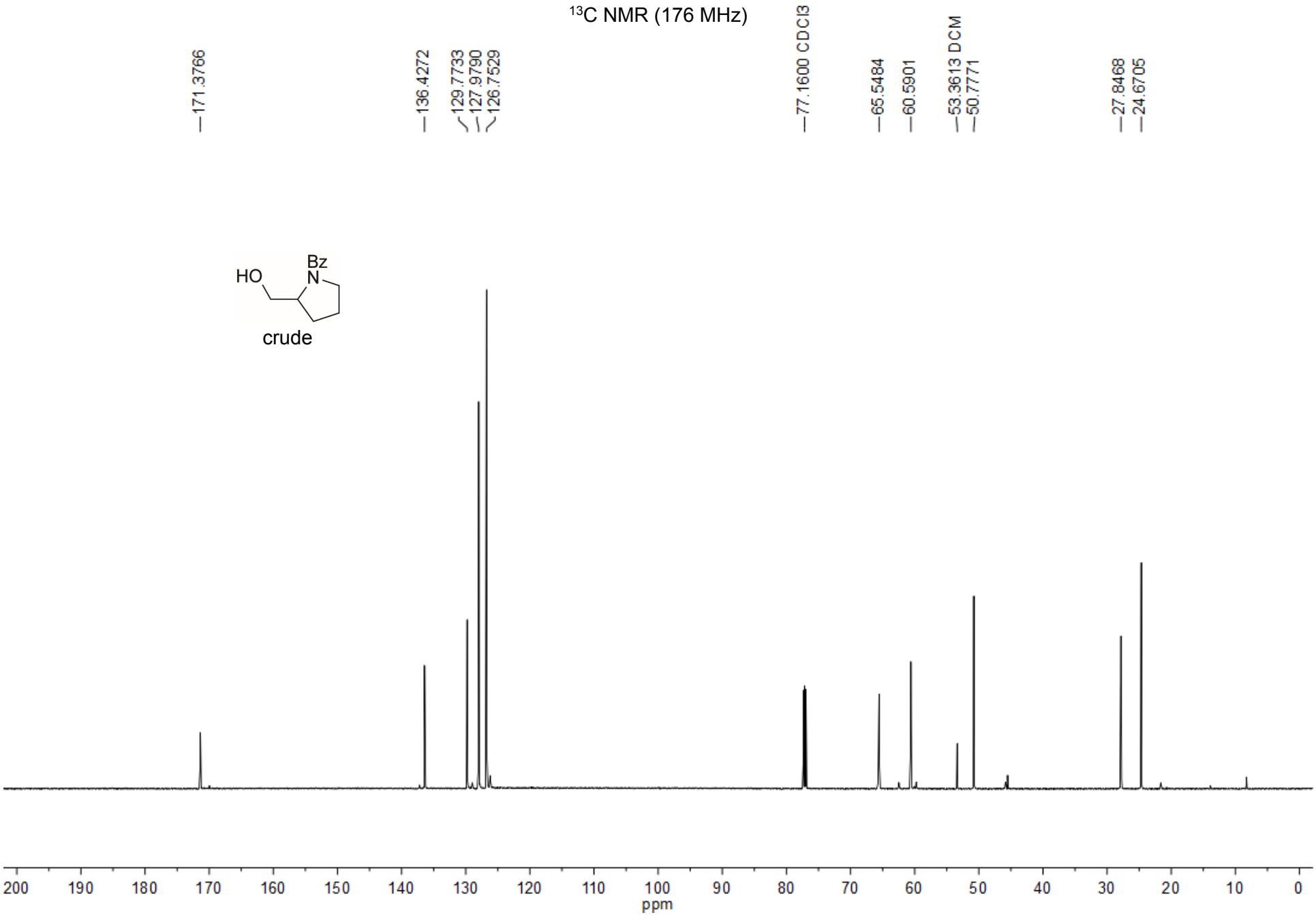
^{1}H NMR (700 MHz)



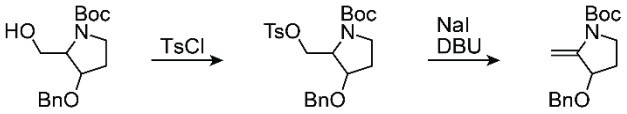
COSY NMR (700 MHz)



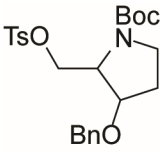
^{13}C NMR (176 MHz)



Scheme 3

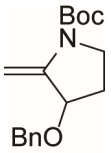


5i, 40% **6i**, 75%



5i

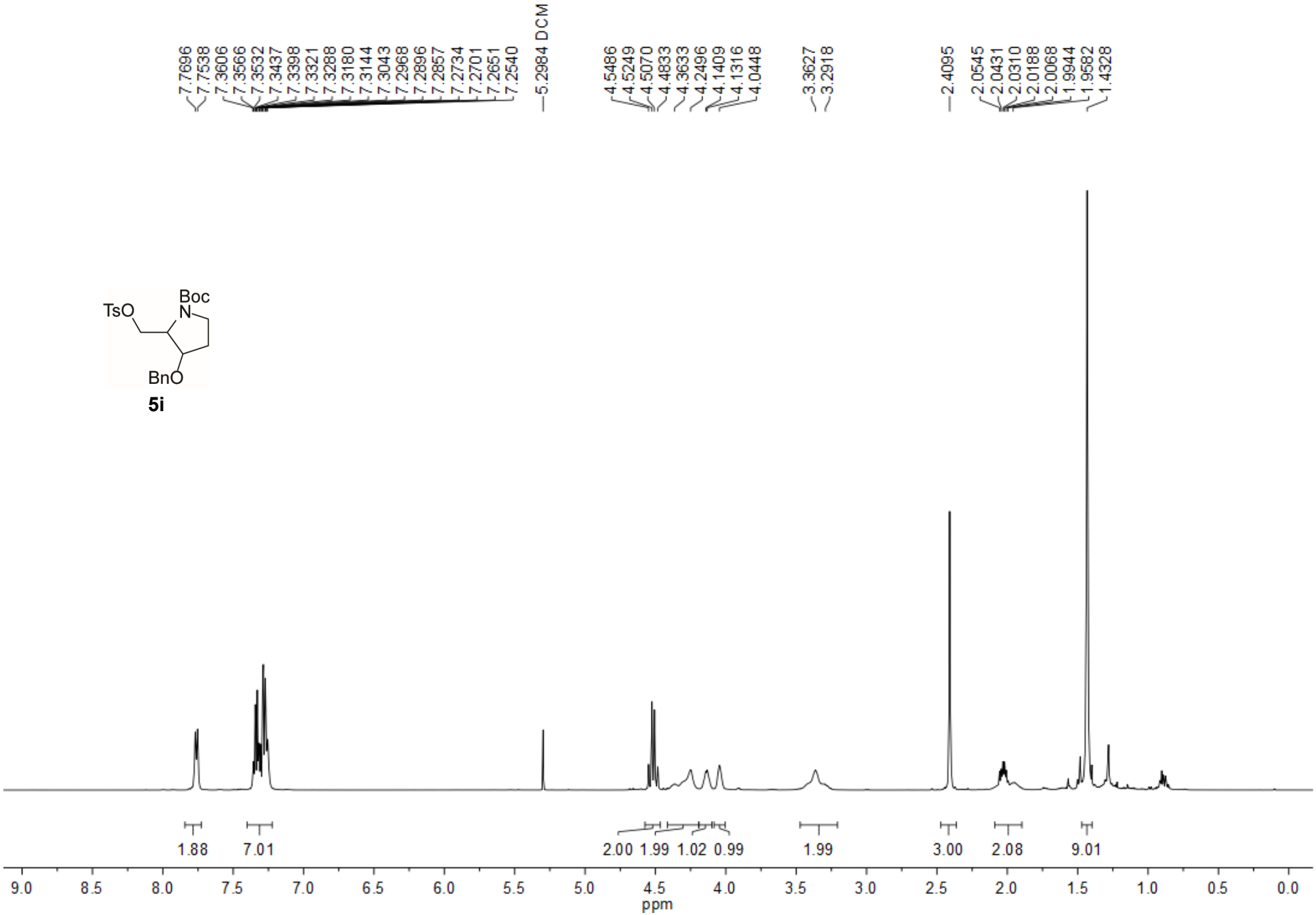
To a solution of N-Boc benzylether prolinol (0.7 g, 2.28 mmol, 1.0 eq) and TsCl (521.3 mg, 2.73 mmol, 1.2 eq) in DCM (10 mL) at 40 °C was added DMAP (3.0 mg, 0.02 mmol, 0.01 eq) and triethylamine (400 µL, 2.96 mmol, 1.3 eq). The reaction was stirred at this temperature for 24 h. It was then diluted with 2M HCl (pH =1) and the aqueous layer was washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel to obtain **5i** (421 mg, 40.0%). R_f = 0.50 (30% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.9 Hz, 2H), 7.36–7.25 (m, 7H), 4.55–4.48 (m, 2H), 4.36–4.25 (m, 2H), 4.14–4.13 (m, 1H), 4.04 (s, 1H), 3.36–3.29 (m, 2H), 2.41 (s, 3H), 2.05–1.96 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.40, 154.22, 144.63, 144.49, 137.83, 133.03, 129.78, 128.43, 127.93, 127.77, 127.55, 80.34, 79.88, 72.00, 67.34, 67.02, 57.34, 57.21, 44.07, 43.51, 28.84, 28.38, 21.65. HRMS (ESI): Calcd for $C_{24}H_{32}NO_6S$ $[MH]^+$: 462.1945, found: 462.1951.



6i

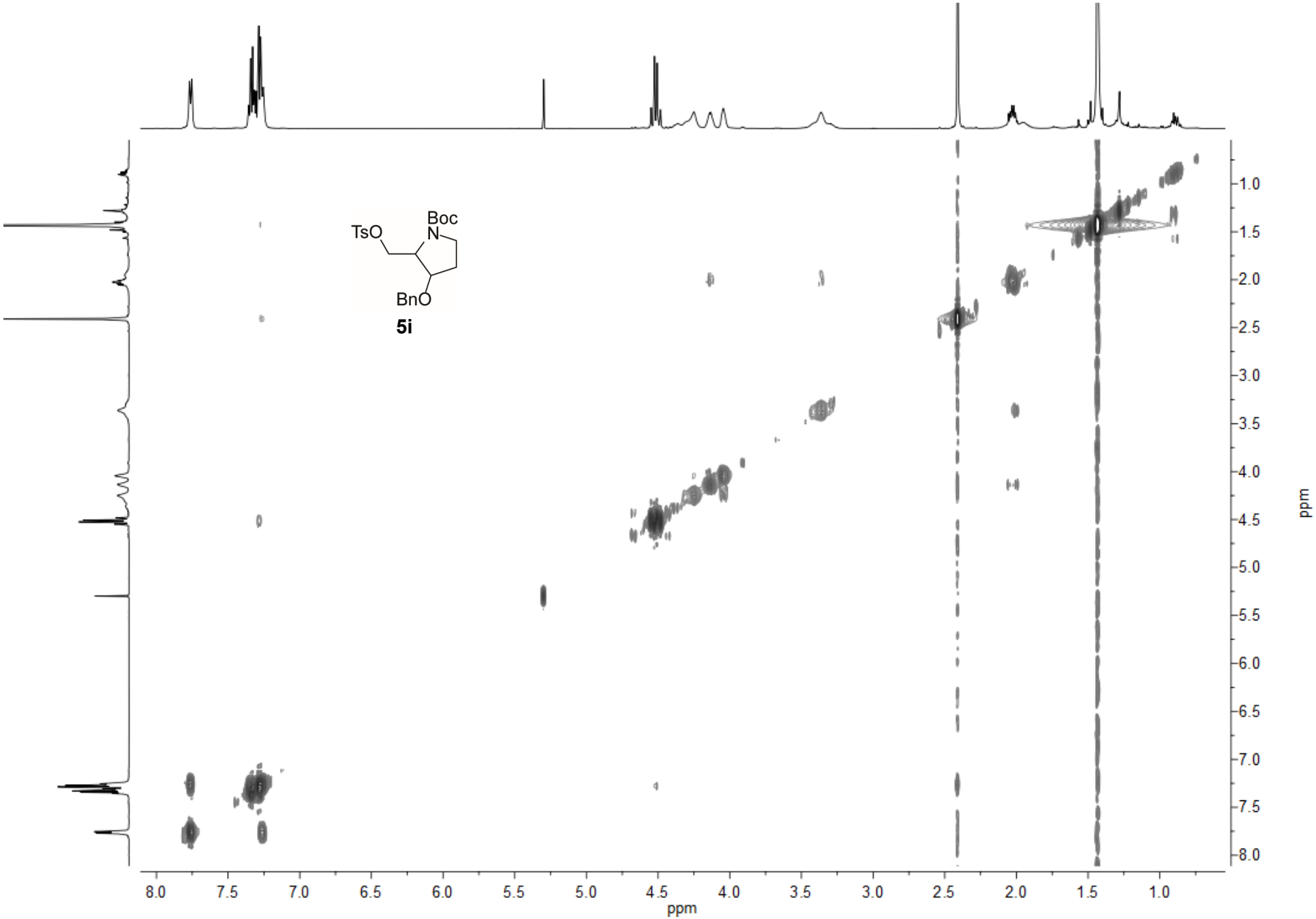
To a solution of **5i** (421 mg, 0.91, 1.0 eq) in glyme (15 mL) was added NaI (410 mg, 2.74 mmol, 3.0 eq). To this red solution was added DBU (273 µL, 1.82 mmol, 2.0 eq) and the greenish-yellow reaction mixture was refluxed for 4 h. The reaction produced foam and insoluble solids that dissolved upon quenching the reaction mixture with water (20 mL). The reaction mixture was further diluted with Et_2O and water. The aqueous layer was discarded and the organic layer was washed successively with sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain **6i** (198 mg, 75%). R_f = 0.75 (15% EtOAc/hexanes, visualized w/ UV). 1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, J = 4.3 Hz, 3.5H), 7.3 –7.27 (m, 1.5 H), 4.67 (d, J = 12.0 Hz, 1H), 4.57–4.51 (m, 2H), 4.22 (dd, J = 5.0, 3.3 Hz, 1H), 3.76–3.69 (m, 1H), 3.63–3.60 (m, 1H), 2.00–1.90 (m, 2H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ =150.00, 138.34, 136.07, 128.55, 127.86, 127.74, 123.89, 93.99, 80.26, 70.08, 60.54, 53.57, 47.03, 28.52. HRMS (ESI): Calcd for $C_{17}H_{24}NO_3[MH]^+$: 290.1751, found: 290.1756.

^{1}H NMR (500 MHz)

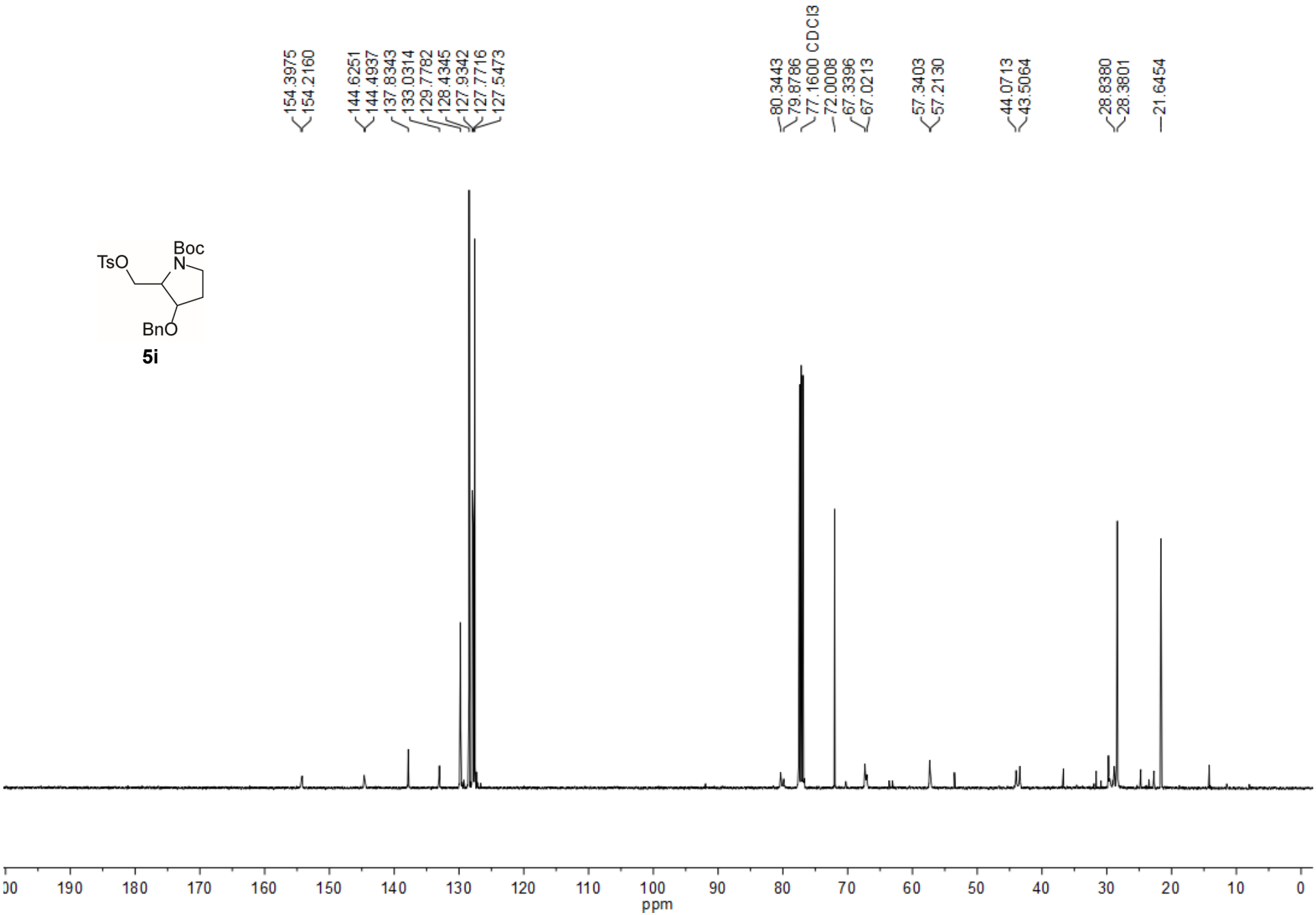


5i

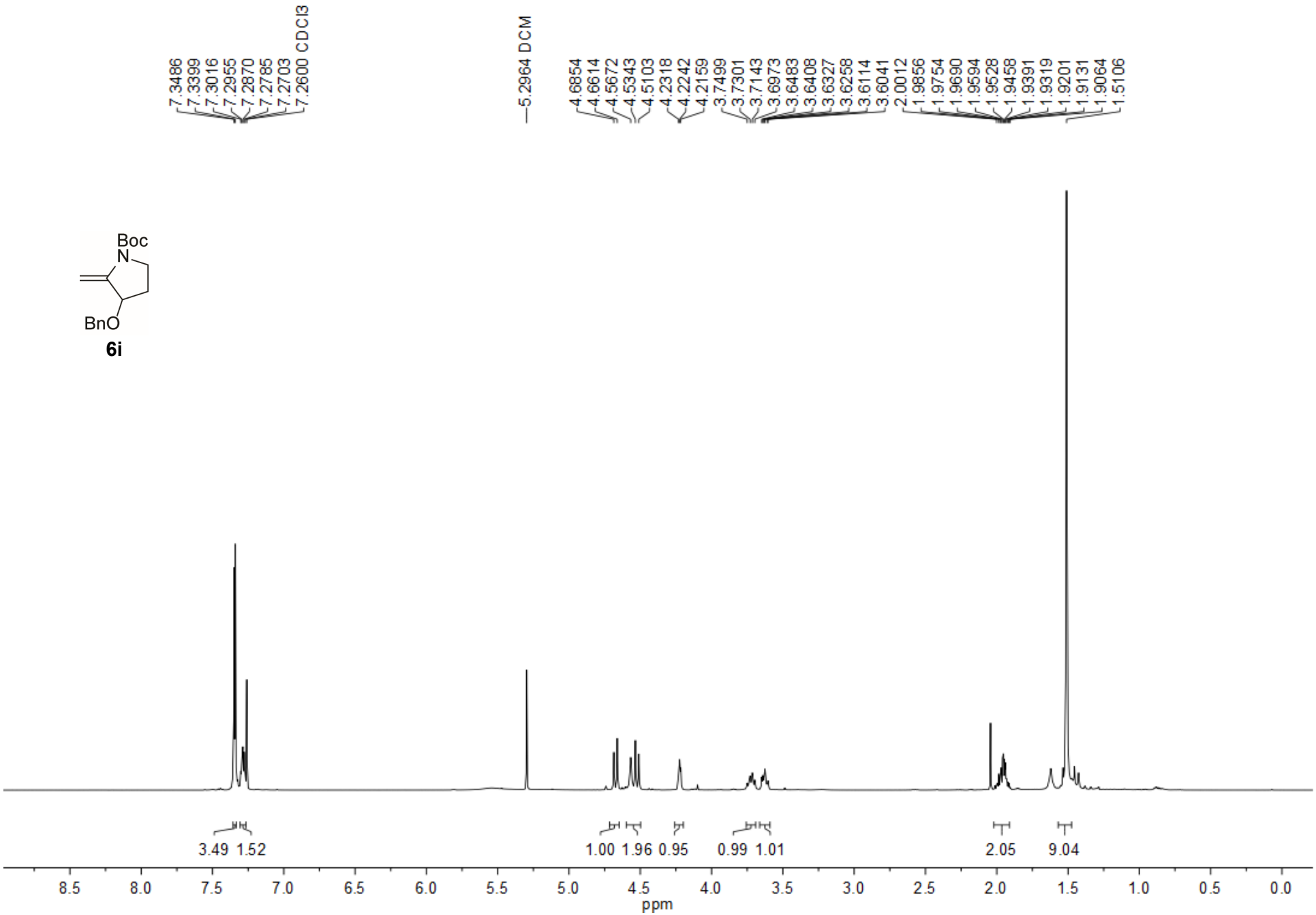
COSY NMR (500 MHz)



^{13}C NMR (500 MHz)

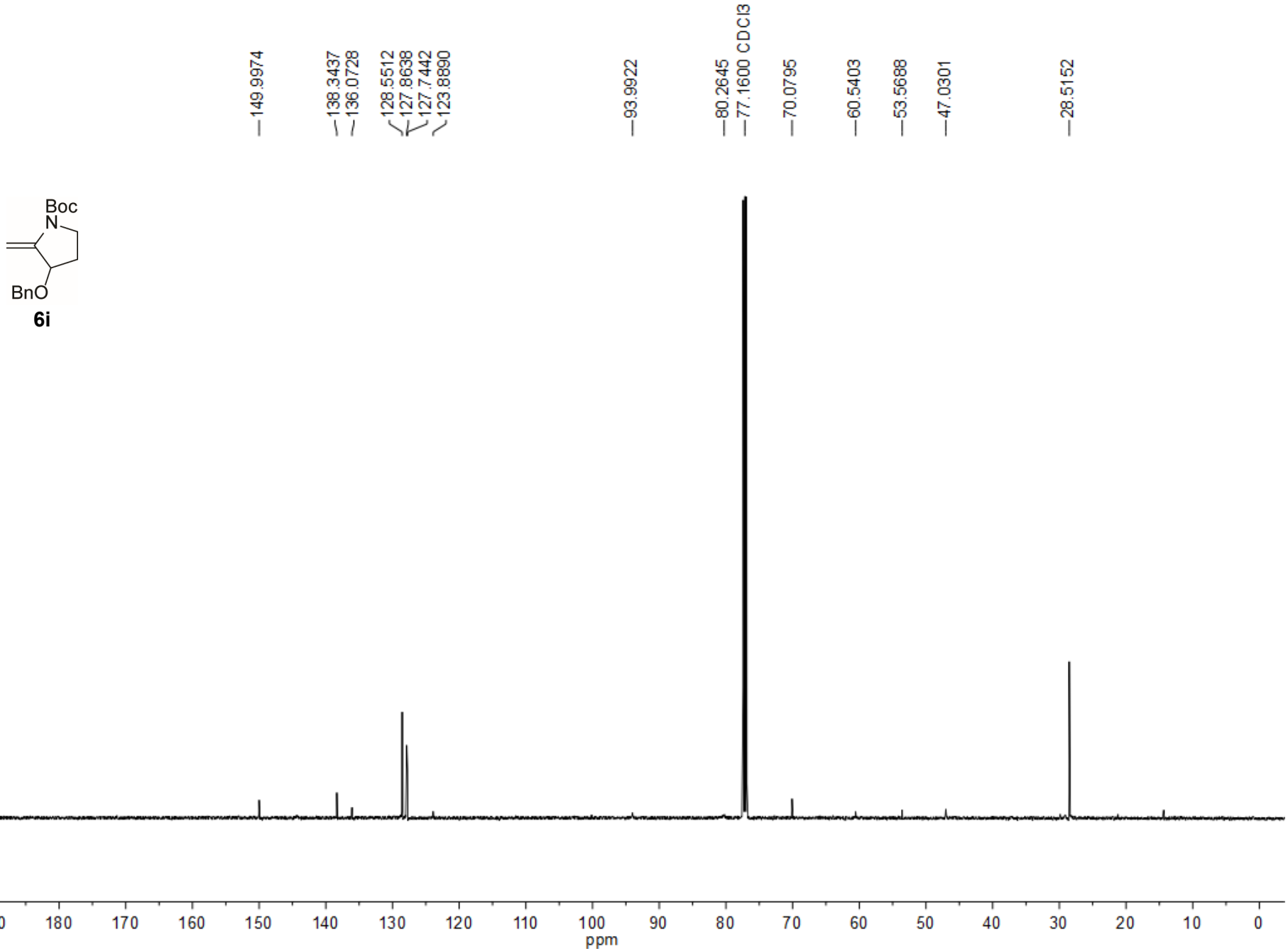


^{1}H NMR (500 MHz)



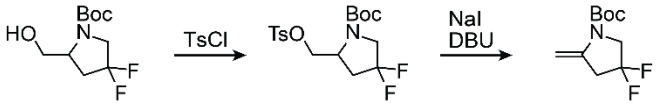
6i

^{13}C NMR (500 MHz)

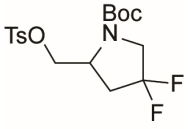


6i

Scheme 4

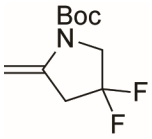


5j, 78.3% **6j**, 87.5%



5j

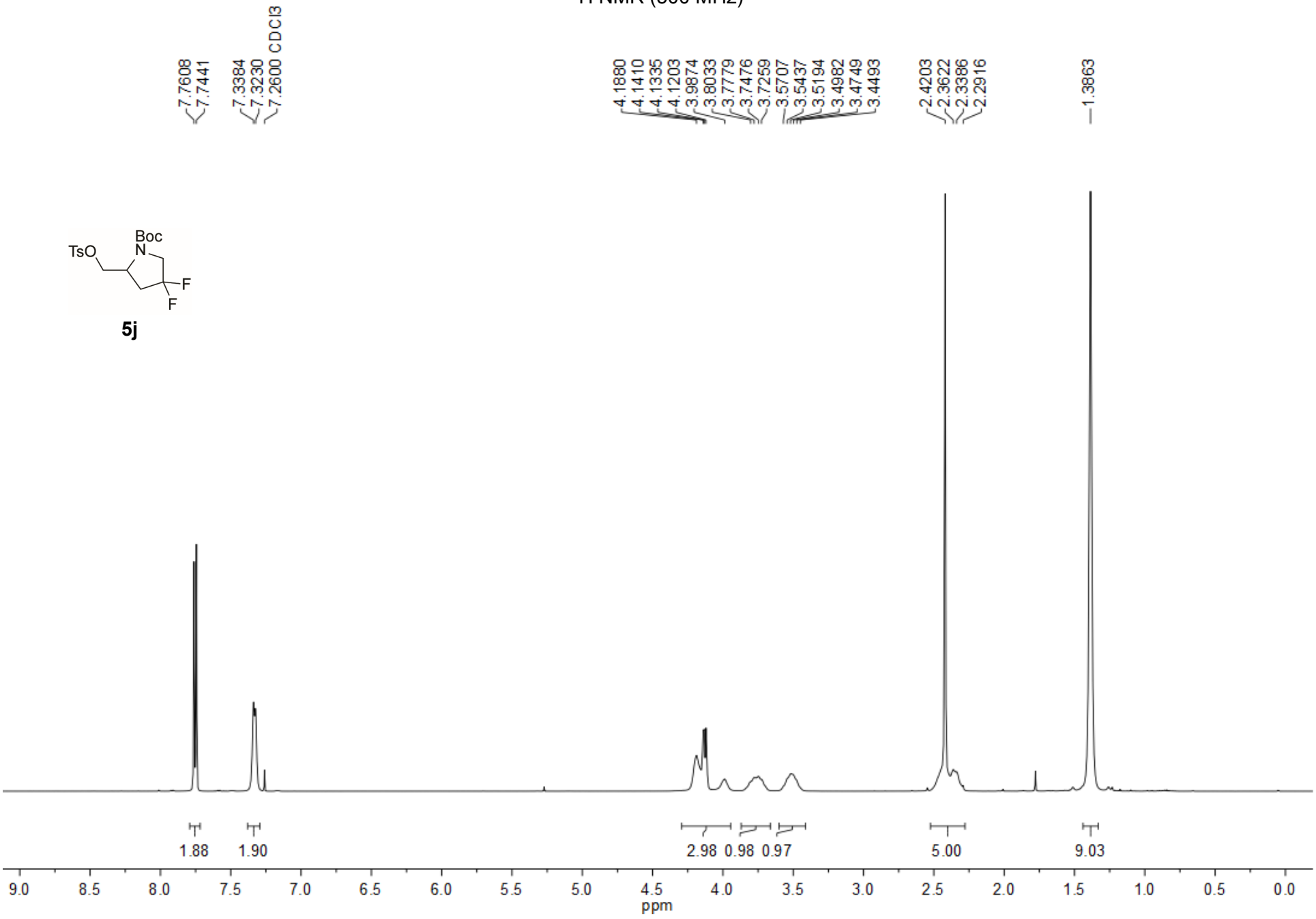
To a solution of N-Boc difluoro prolinol (1.9 g, 8.00 mmol, 1.0 eq) and TsCl (1.83 g, 9.61 mmol, 1.2 eq) in DCM (50 mL) at 40 °C was added DMAP (19.5 mg, 0.16 mmol, 0.02 eq) and triethylamine (1.45 mL, 10.41 mmol, 1.3 eq). The reaction was stirred at this temperature for 24 h. It was then diluted with 2M HCl (pH =1) and the aqueous layer was washed with DCM (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel (100 g, 10–15% EtOAc/ hexanes (v/v)) to obtain **5j** (2.45 g, 78.3%). R_f = 0.42 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 4.19–3.99 (m, 3H), 3.80–3.73 (m, 1H), 3.57–3.45 (m, 1H), 2.42 (s, 3H), 2.42–2.29 (m, 2H) 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.71, 153.28, 145.30, 145.16, 132.64, 130.05, 127.95, 126.50, 126.14, 81.38, 81.13, 68.81, 68.56, 54.25, 54.12, 53.80, 53.55, 53.42, 53.17, 36.87, 36.71, 36.52, 35.99, 35.79, 35.61, 28.26, 21.69. 19F NMR (376 MHz, $CDCl_3$): δ = -97.79, -97.83, -97.87, -98.39, -98.42, -98.46, -98.50, -98.53, -99.01, -99.05, -99.09, -99.12, -99.16, -99.65, -99.68, -99.71, -99.74, -99.78, -100.10, -100.13, -100.17, -100.20, -100.24, -100.30, -100.33, -100.37, -100.76, -100.79, -100.83. HRMS (ESI): Calcd for $C_{17}H_{23}F_2NO_5S$ [MNa]$^+$: 414.1157, found: 414.1159.



6j

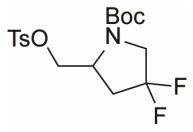
To a solution of **5j** (2.45 g, 6.26 mmol, 1.0 eq) in glyme (40 mL) was added NaI (2.81 g, 18.78 mmol, 3.0 eq). To this red solution was added DBU (1.87 mL, 12.52 mmol, 2.0 eq) and the greenish-yellow reaction mixture was refluxed for 5 h. The reaction produced foam and insoluble solids that dissolved upon quenching the reaction mixture with water (50 mL). The reaction mixture was further diluted with Et_2O and water. The aqueous layer was discarded and the organic layer was washed successively with sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain **6j** (1.2 g, 87.5%). R_f = 0.9 (30% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.28 (s, 1H), 4.18 (s, 1H), 3.75 (t, J = 12.9 Hz, 2H), 2.86 (tt, J = 14.2, 1.9 Hz, 2H), 1.36 (d, J = 5.1 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.79, 151.42, 150.36, 148.99, 139.00, 139.00, 125.82, 123.38, 120.93, 102.70, 102.53, 102.41, 102.35, 92.89, 81.27, 55.92, 55.60, 55.28, 41.11, 40.86, 40.61, 27.85, 27.59. HRMS (ESI): Calcd for $C_{10}H_{16}F_2NO_2$[MH]$^+$: 220.1144, found: 220.1148.

^{1}H NMR (500 MHz)



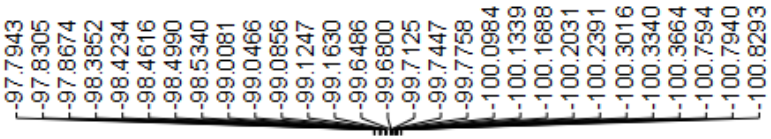
5j

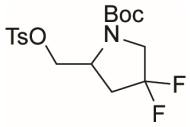
^{13}C NMR (500 MHz)



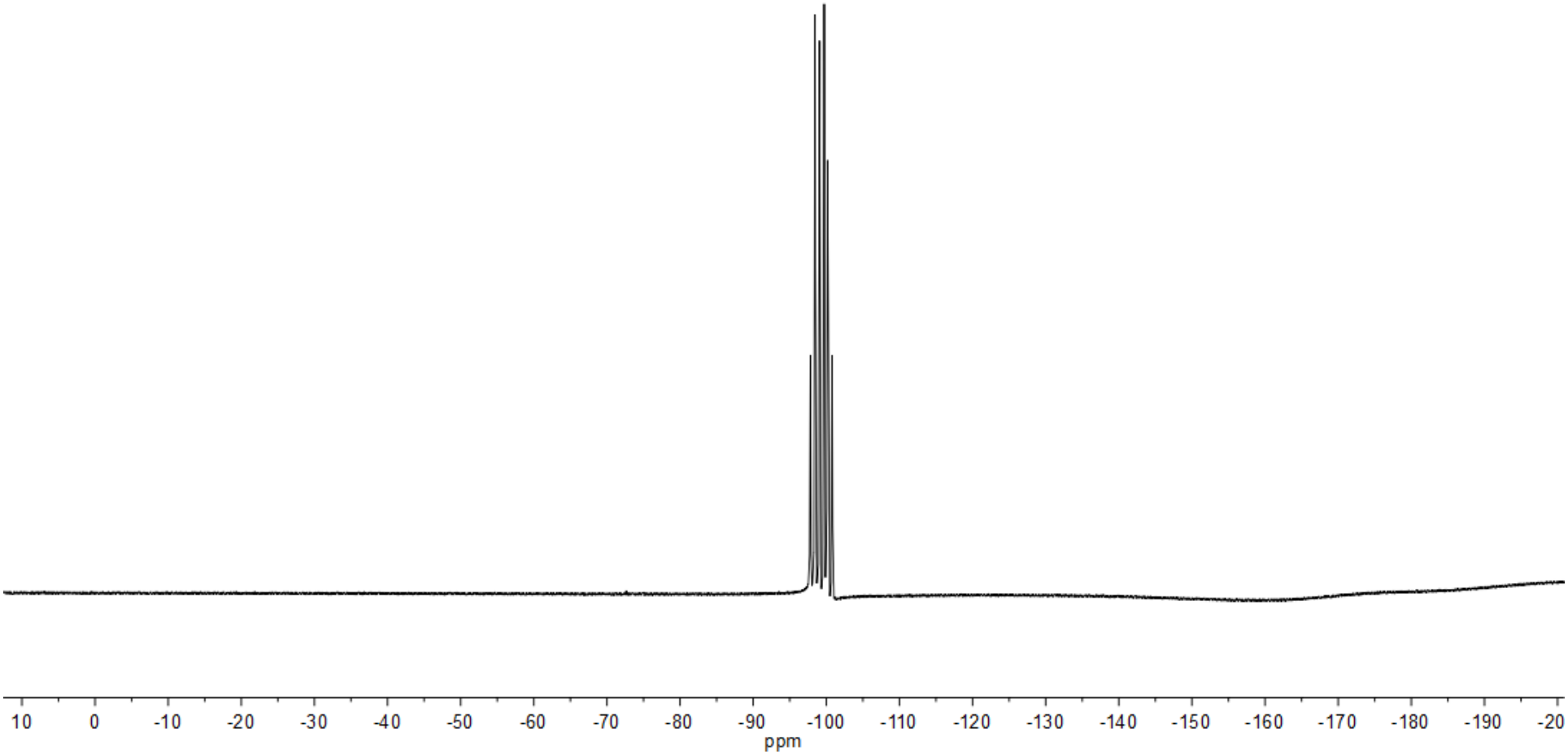
5j

^{19}F NMR (376 MHz)

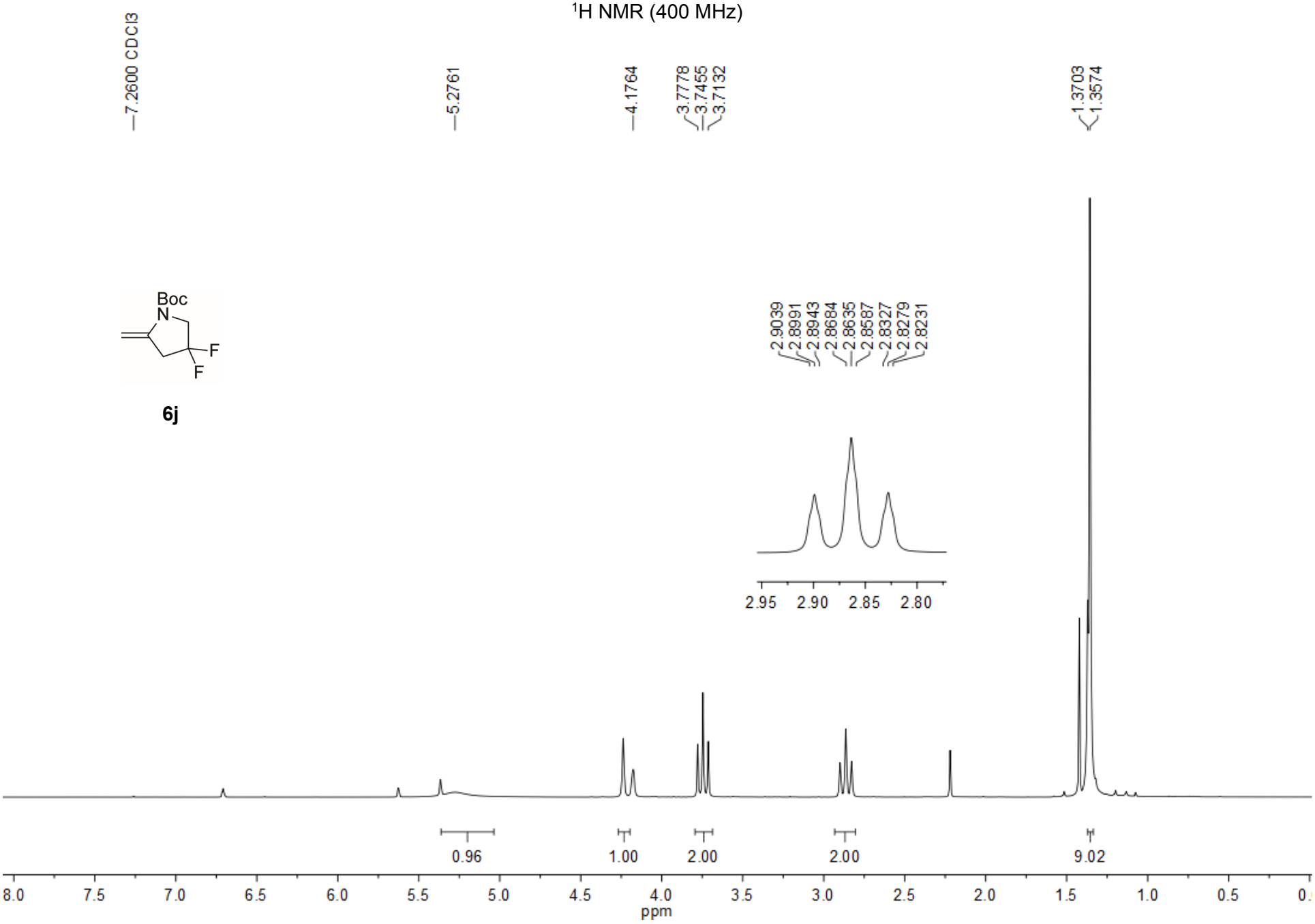




5j

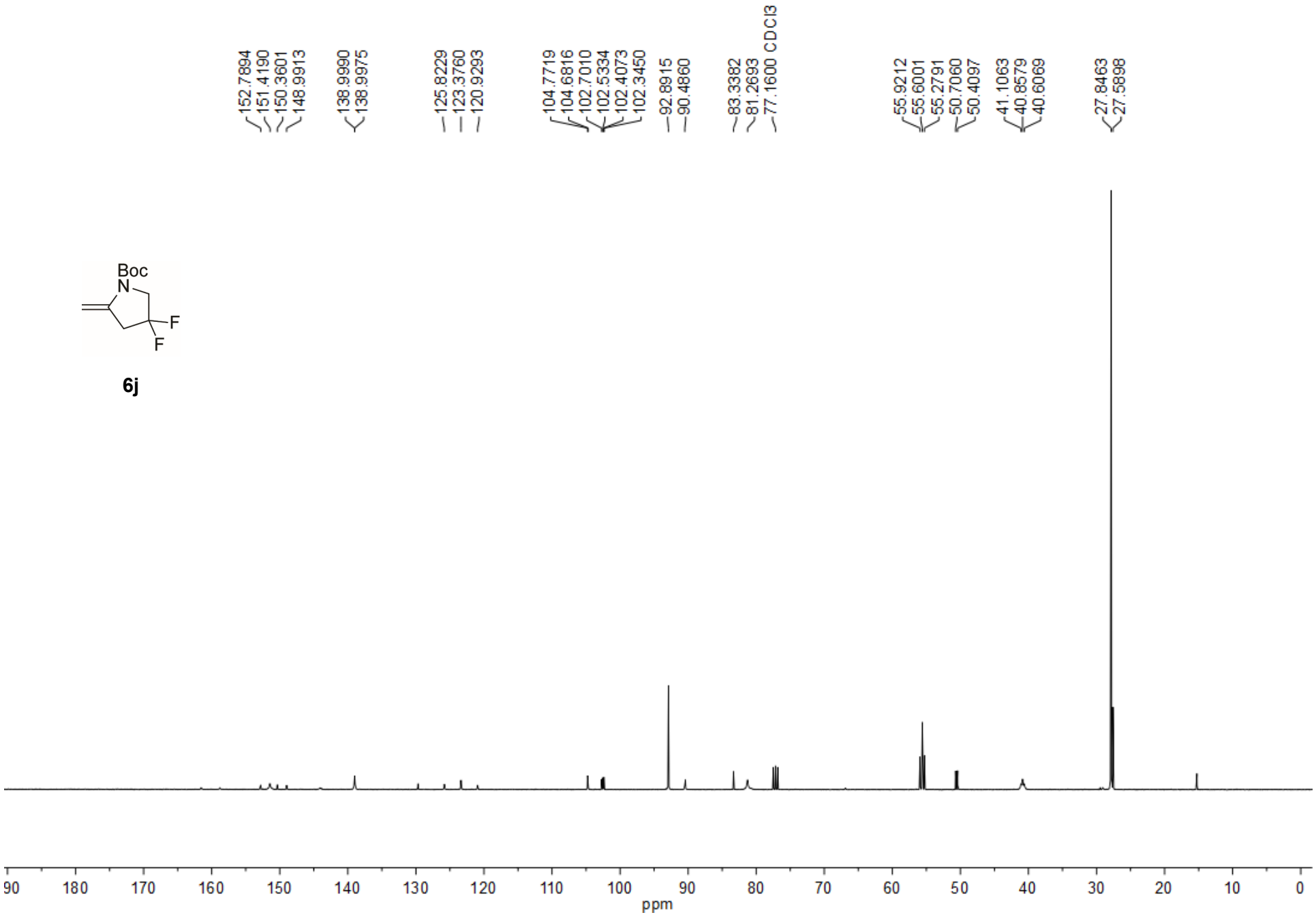


^{1}H NMR (400 MHz)



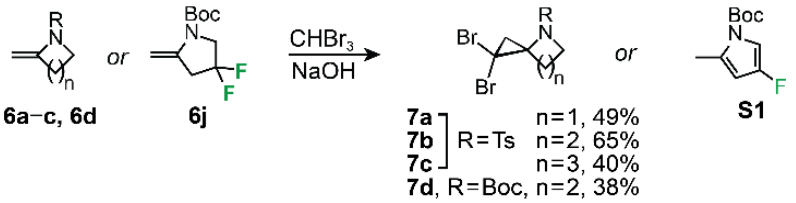
6j

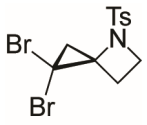
^{13}C NMR (101 MHz)



6j

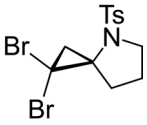
Scheme 5





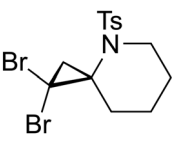
7a

To a solution of **6a** (15.0 g, 67.17 mmol, 1.0 eq) in $CHBr_3$ (12.08 mL, 33.95 g,134.35 mmol, 2.0 eq) and DCM (30 mL) was added CTAB (2.45 g, 6.7 mmol, 0.1 eq) and the mixture was stirred vigorously. To this was added NaOH (11.72 mL, 50% w/v) dropwise over 1.5 h. The brown-black reaction mixture was stirred for 24 h at rt. To this reaction was added additional $CHBr_3$ (0.5 eq) and CTAB (0.025 eq) based on TLC and the process was repeated until complete consumption of reactant. Complete consumption of reactant was a necessity as the product have same R_f as the reactant. Upon completion, the reaction mixture was diluted with DCM and water. The organic layer was collected, washed with brine and concentrated under reduced pressure. The crude was left under high vac overnight to remove excess $CHBr_3$. It was then passed through silica gel (120 g) using DCM and concentrated under reduced pressure. The semi-purified crude was dissolved in DCM (20 mL) and hexanes (150 mL), heated at 45 °C and allowed to cool down to rt. The precipitated product was filtered and the process was repeated with the mother liquor to obtain **7a** as white/beige solid (13 g, 49%). R_f = 0.48 (20% EtOAc/hexanes, visualized w/ UV). HPLC (R_t = 11.0 min, 55-80% MeCN/$H_2$0 + 0.1% TFA over 15 min, flow rate = 20 mL/min). M.p. 134–136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.02–3.98 (m, 1H), 3.86–3.81 (m, 1H), 2.90 (d, J = 9.6 Hz, 1H), 2.62–2.59 (m, 1H), 2.44 (s, 3H), 2.38–2.33 (m, 1H), 1.75 (d, J = 9.6 Hz, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.47, 134.38, 129.86, 128.33, 57.26, 47.13, 31.27, 30.87, 25.56, 21.72. HRMS (ESI): Calcd for $C_{12}H_{13}Br_2NO_2S$ $[MH]^+$: 395.9086, found: 395.9086.



7b

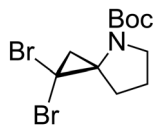
To a solution of **6b** (18.7 g, 78.8 mmol, 1.0 eq) in $CHBr_3$ (14.18 mL, 39.83 g,157.60 mmol, 2.0 eq) and DCM (20 mL) was added CTAB (2.87 g, 7.88 mmol, 0.1 eq) and the mixture was stirred vigorously. To this was added NaOH (14.7 mL, 50% w/v) dropwise over 0.5 h. The brown-black reaction mixture was stirred for 24 h at rt. To this reaction was added additional $CHBr_3$ and CTAB based on TLC and the process was repeated until complete consumption of **6b** occurred. Complete consumption of reactant was necessary because the product and compound **6b** have the same R_f. Upon completion, the reaction mixture was diluted with DCM and water. The organic layer was collected, washed with brine and concentrated under reduced pressure. The crude was left under vacuum overnight to remove excess $CHBr_3$. It was then passed through a silica gel plug (120 g) using DCM and concentrated under reduced pressure. This semi-purified crude was dissolved in DCM (50 mL), and the product was precipitated out of solution by addition of hexanes (150 mL). The process was repeated with the mother liquor to obtain **7b** as a white/beige solid (21 g, 65.2%). R_f = 0.64 (30% EtOAc/hexanes, visualized w/ UV). HPLC (R_t = 14.0 min, 55–100% MeCN/$H_2$0 +0.1% TFA over 15 min, flow rate = 20 mL/min). M.p. 143–145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.77–3.72 (m, 2H), 3.52–3.46 (m, 2H), 3.21 (d, *J* = 9.2 Hz, 1H), 2.43 (s, 3H), 2.05–2.01 (m, 1H), 1.90 (d, *J* = 9.2 Hz, 1H), 1.87–1.78 (m, 1H), 1.75–1.67 (m, 1H), 1.32–1.25 (m, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.10, 135.84, 129.96, 127.69, 53.16, 49.53, 35.34, 31.34, 29.87, 22.28, 21.72. HRMS (ESI): Calcd for $C_{13}H_{15}Br_2NO_2S$ $[MH]^+$: 409.9243, found: 409.9244.



7c

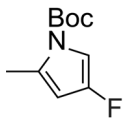
To a solution of **6c** (1.0 g, 3.98 mmol, 1.0 eq) in $CHBr_3$ (0.7 mL, 2.01 g, 7.96 mmol, 2.0 eq) was added CTAB (218 mg, 0.6 mmol, 0.15 eq) and the mixture was stirred vigorously at rt. To this was added NaOH (0.7 mL, 50% w/v) dropwise. The brown-black reaction mixture was stirred for 18 h at rt. To this reaction was added additional $CHBr_3$ and CTAB based on TLC and the process was repeated until complete consumption of **6c** occurred. Complete consumption of reactant was necessary because the product and compound **6c** have the same R_f. Upon completion, the reaction mixture was diluted with DCM and water. The organic layer was collected, washed with brine, concentrated under reduced

pressure, and purified by flash chromatography over silica gel (35.0 g, 5–8% EtOAc/ hexanes (v/v)) to obtain **7c** (0.67 g, 40%). R_f = 0.50 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 6.6 Hz, 2H), 7.29 (d, J = 6.5 Hz, 2H), 4.03–4.00 (m, 1H), 3.31–3.25 (m, 1H), 2.43 (s, 3H), 2.13–2.07 (m, 1H), 1.92–1.81 (m, 4H), 1.68–1.64 (m, 3H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.63, 138.41, 129.66, 127.45, 48.10, 47.39, 35.66, 33.60, 31.96, 23.91, 22.65, 21.67. ^{13}C-DEPT135 NMR (126 MHz, $CDCl_3$): δ = 143.63, 138.41, 129.66, 127.45, 48.10, 47.39, 35.66, 33.60, 31.96, 23.91, 22.65, 21.67. HRMS (ESI): Calcd for $C_{14}H_{18}Br_2NO_2S$ $[MH]^+$: 423.9399, found: 423.9407.



7d

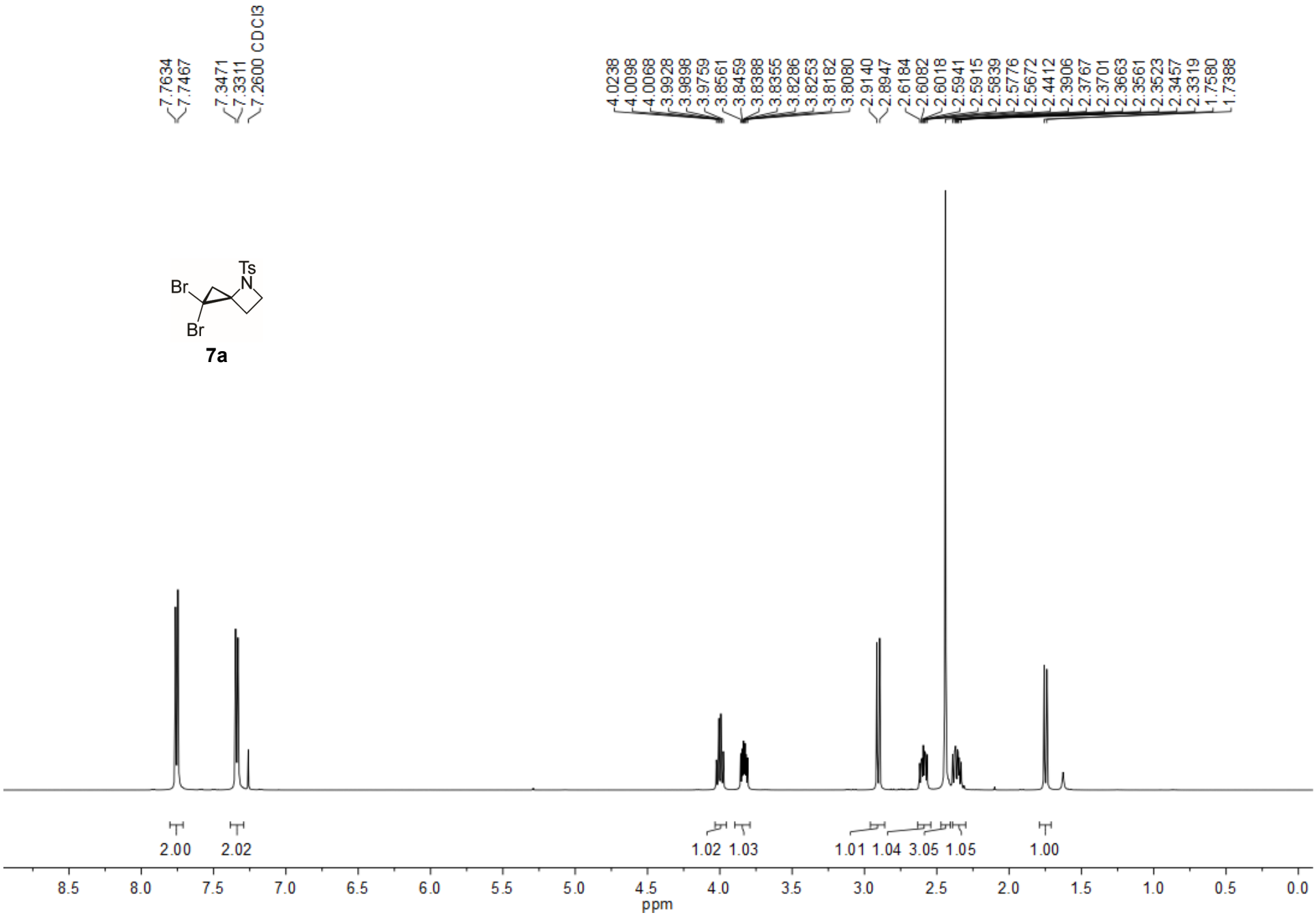
To a solution of **6e** (2.0 g, 10.9 mmol, 1.0 eq) in $CHBr_3$ (5.51 g, 21.8 mmol, 2.0 eq) was added CTAB (596 mg, 1.63 mmol, 0.15 eq) and the mixture was stirred vigorously at rt. To this was added NaOH (0.95 mL, 50% w/v) dropwise. The brown-black reaction mixture was stirred for 24 h at rt. To this reaction was added additional $CHBr_3$ and CTAB based on TLC and the process was repeated until complete consumption of **6e** occurred. Upon completion, the reaction mixture was diluted with DCM and water. The organic layer was collected, washed with brine, concentrated under reduced pressure, and purified by flash chromatography over silica gel (45 g, 5% EtOAc/ hexanes (v/v)) to obtain **7d** (1.46 g, 37.7%). R_f = 0.19 (3% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.53 (q, *J* = 9.1 Hz, 1H), 3.36–3.32 (m, 2H), 2.08–2.01 (m, 2H), 1.85–1.76 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.49, 79.87, 52.14, 47.09, 36.23, 33.71, 30.22, 28.32, 21.08. COSY NMR was obtained under same conditions (attached). ^{13}C-DEPT135 NMR (126 MHz, $CDCl_3$): δ = (up) 28.38, (down) 47.16, 36.23, 33.79, 30.56, 21.14. HRMS (ESI): Calcd for $C_{11}H_{18}Br_2NO_2$ $[MH]^+$: 355.9678, found: 355.9669.



S1

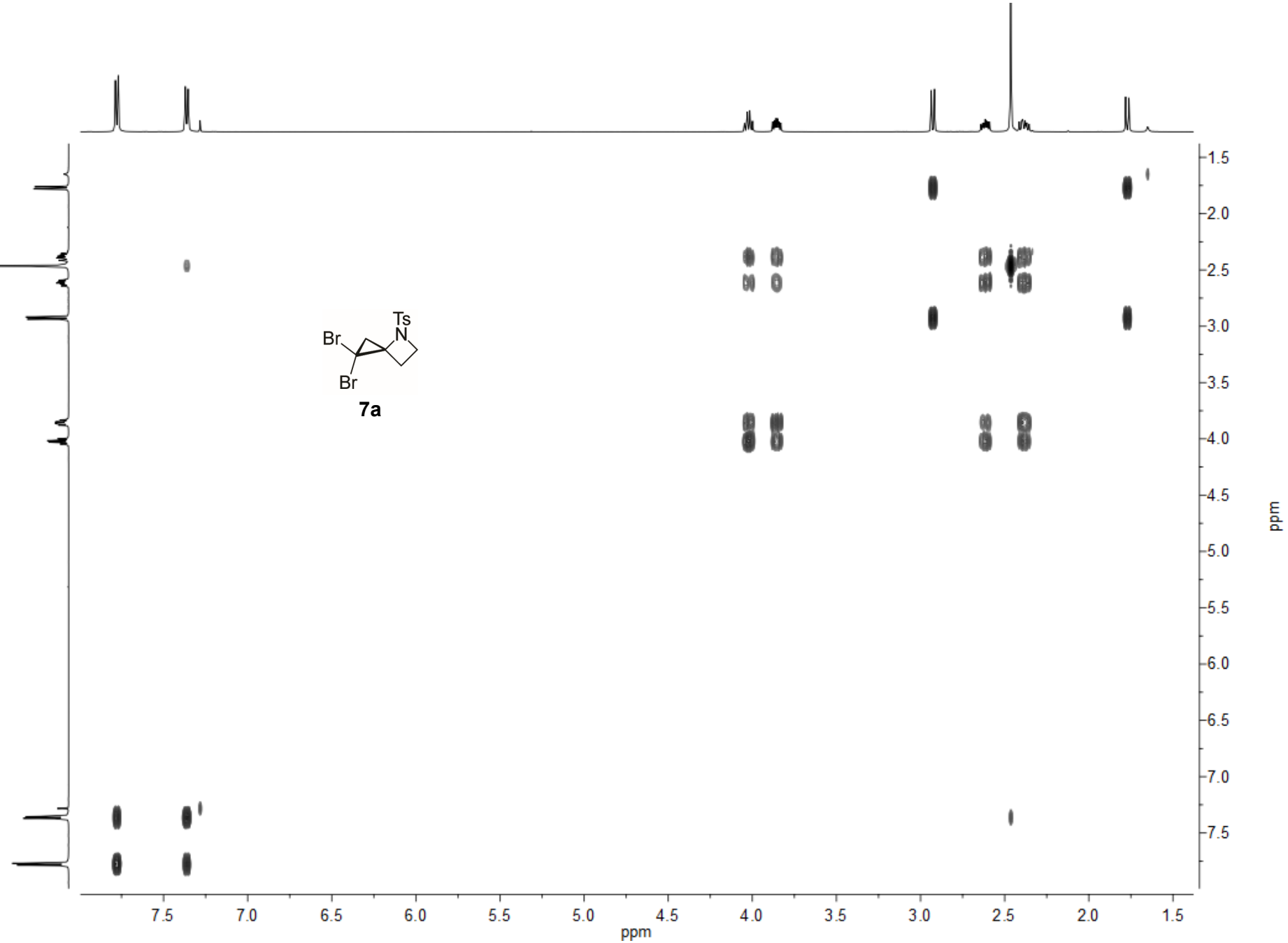
To a solution of **6j** (1.2 g, 5.48 mmol, 1.0 eq) in $CHBr_3$ (1.0 mL, 10.95 mmol, 2.0 eq) was added CTAB (300 mg, 0.82 mmol, 0.15 eq) and the mixture was stirred vigorously at rt. To this was added NaOH (956 µL, 50% w/v) dropwise. The brown-black reaction mixture was stirred for 12 h at rt. The reaction mixture was diluted with DCM and water. The organic layer was collected, washed with brine, concentrated under reduced pressure, and purified by flash chromatography over silica gel (60 g, 2% EtOAc/ hexanes (v/v)) to obtain unstable rearranged pyrrole product **S1** (22.5%) as the major product. R_f = 0.27 (hexanes, visualized w/ UV). ^{1}H NMR (700 MHz, $CDCl_3$): δ(approx.) = 6.8 (t, 1H), 5.8 (s, 1H), 2.4 (s, 3H), 1.56 (s, 9H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (176 MHz, $CDCl_3$): δ (approx.) = 153, 151, 149, 130, 102, 83, 28, 15. ^{13}C-DEPT135 NMR (176 MHz, $CDCl_3$): δ = (up) three CH peaks. MS (ESI): Calcd for $C_{10}H_{15}FNO_2$ $[MH]^+$: 200.1, found: 200.1.

^{1}H NMR (500 MHz)

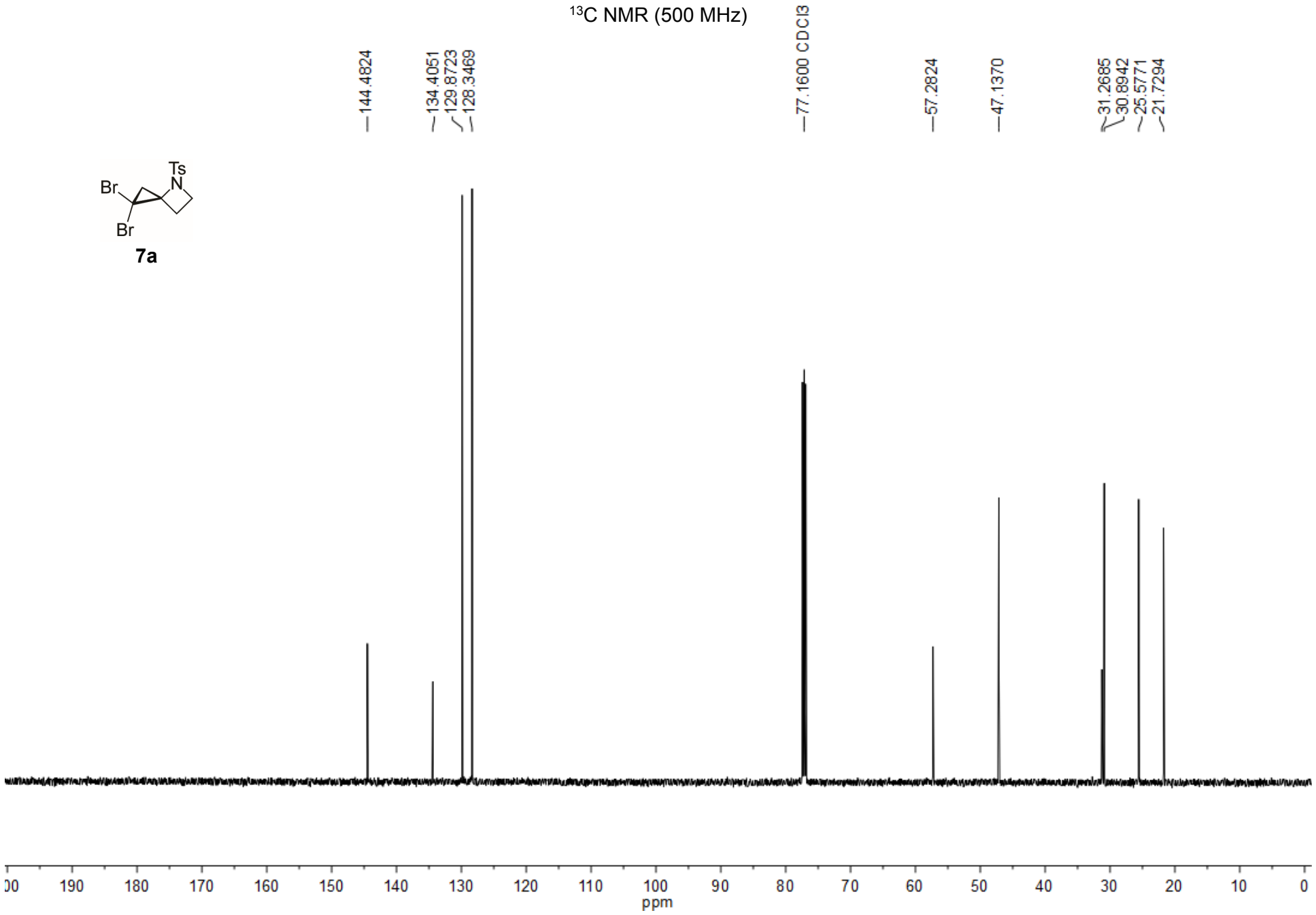


7a

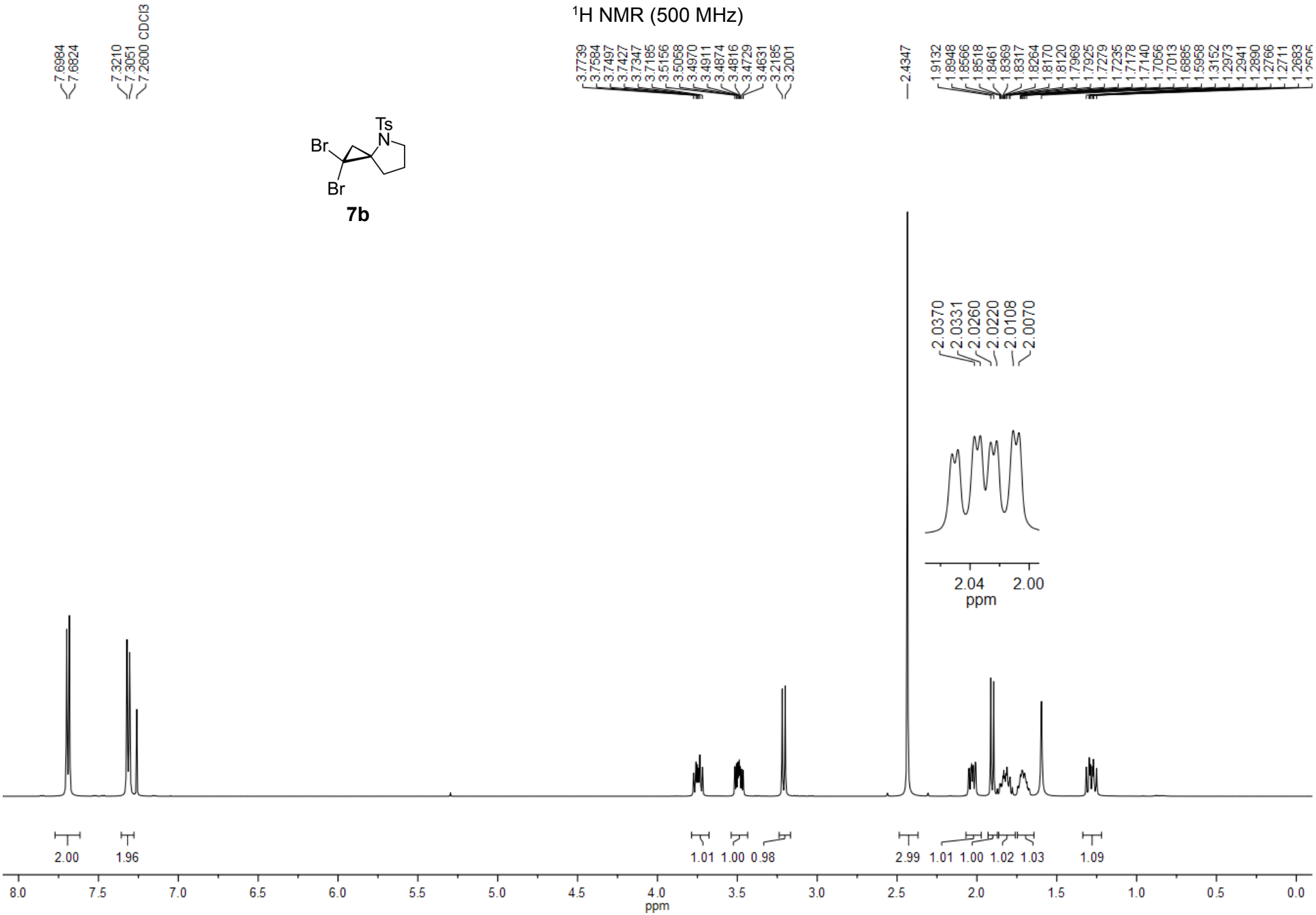
COSY NMR (500 MHz)



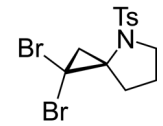
^{13}C NMR (500 MHz)



^{1}H NMR (500 MHz)

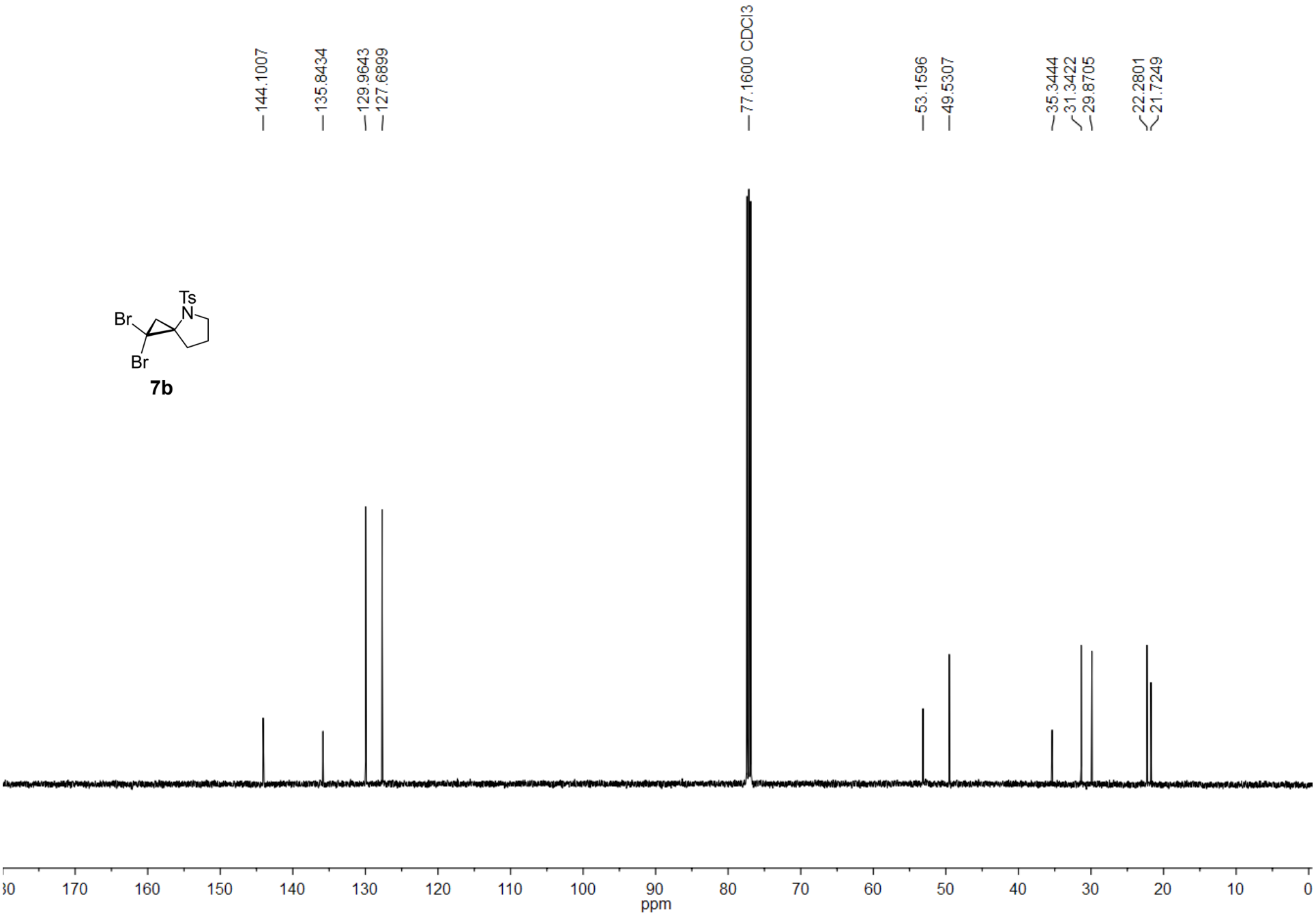


COSY NMR (500 MHz)

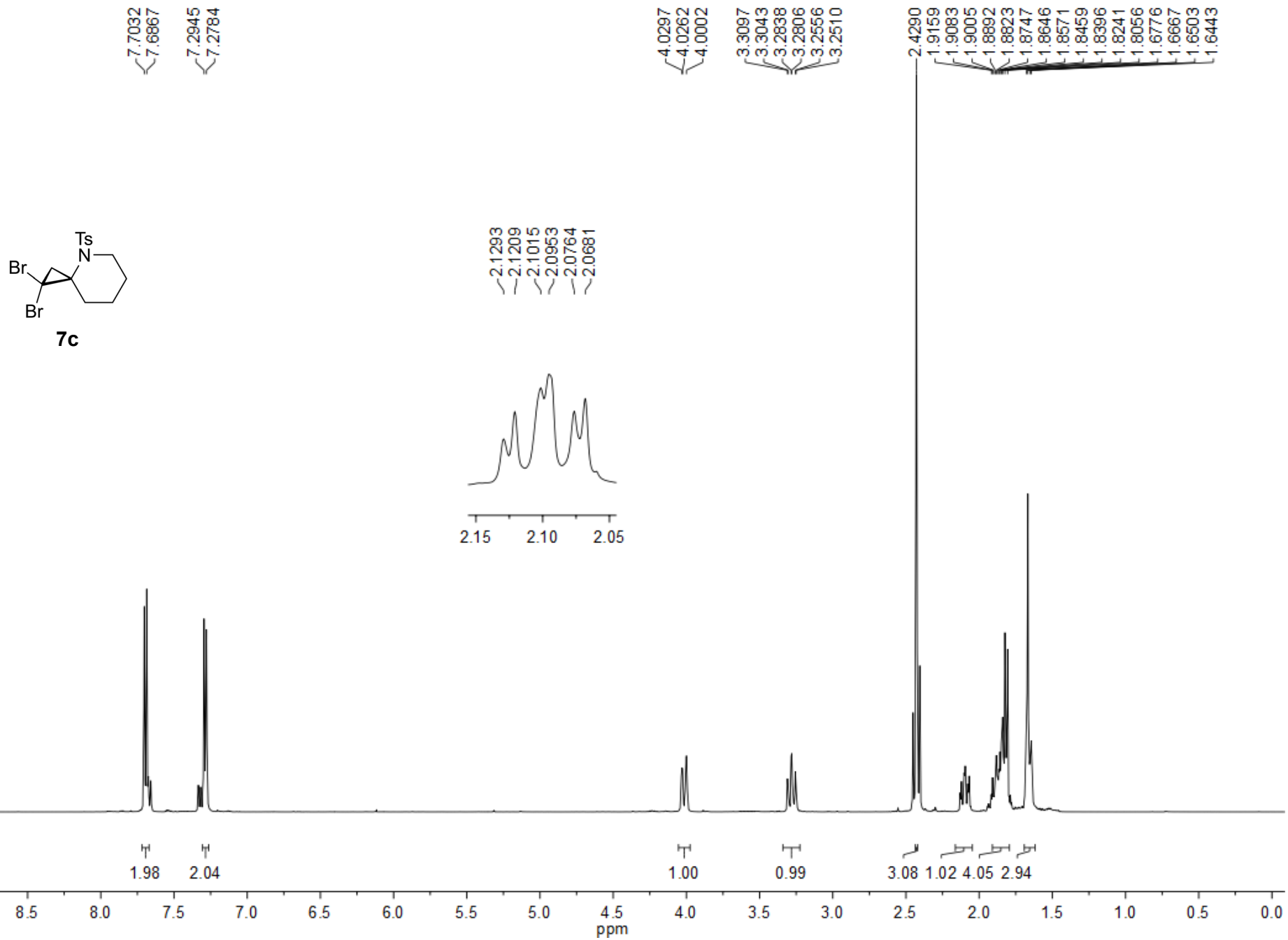


7b

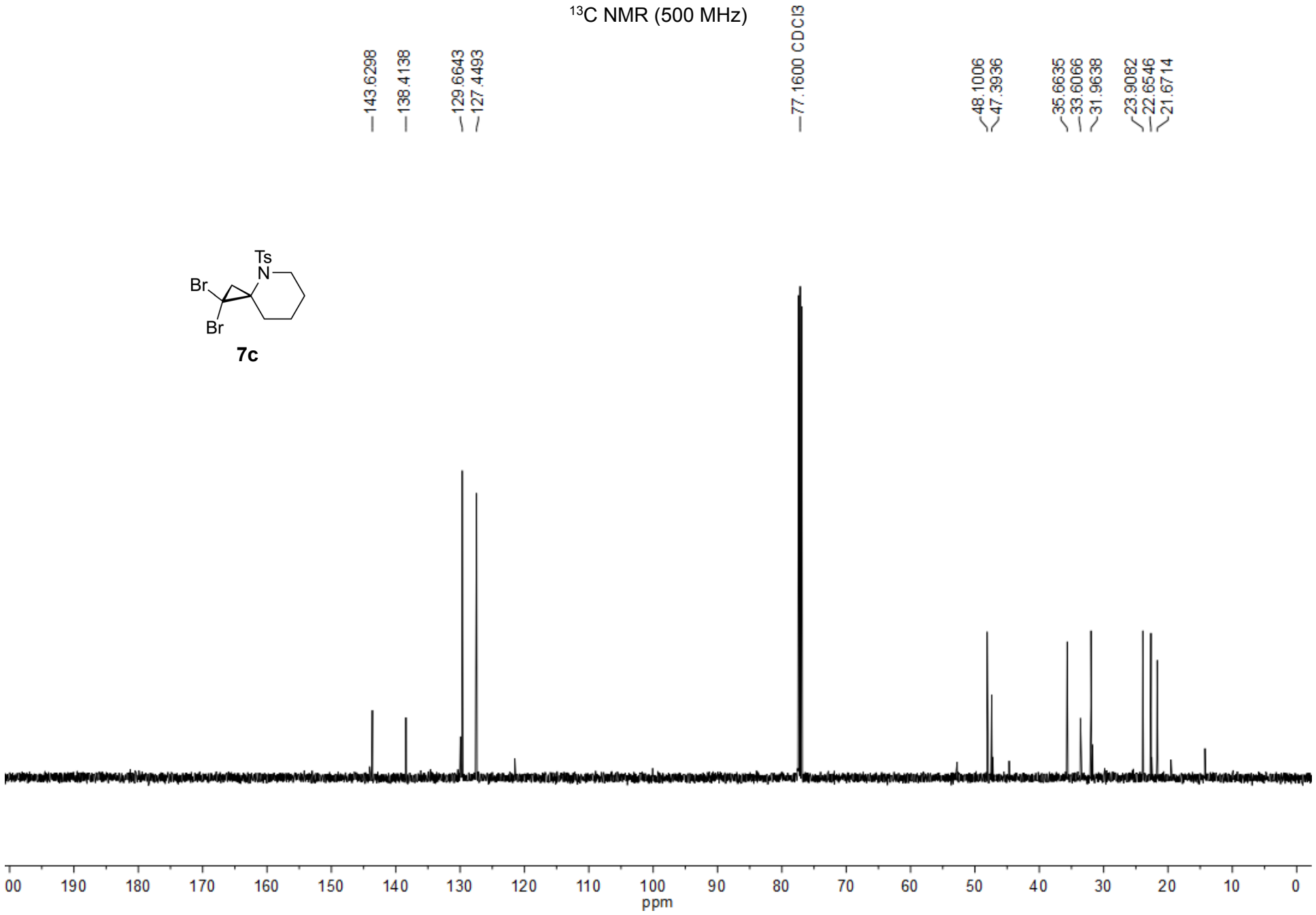
^{13}C NMR (126 MHz)

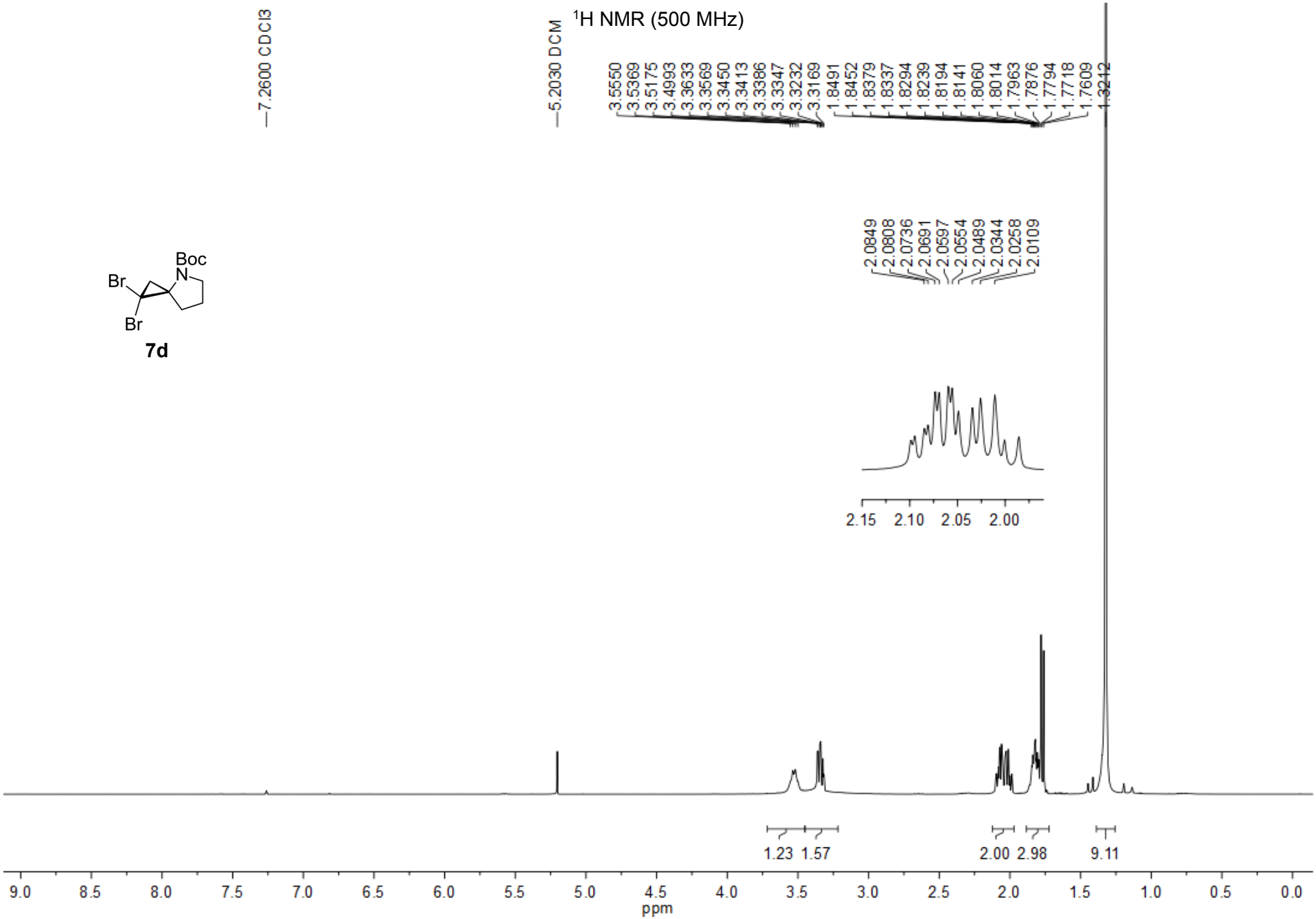


^{1}H NMR (500 MHz)

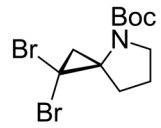


^{13}C NMR (500 MHz)



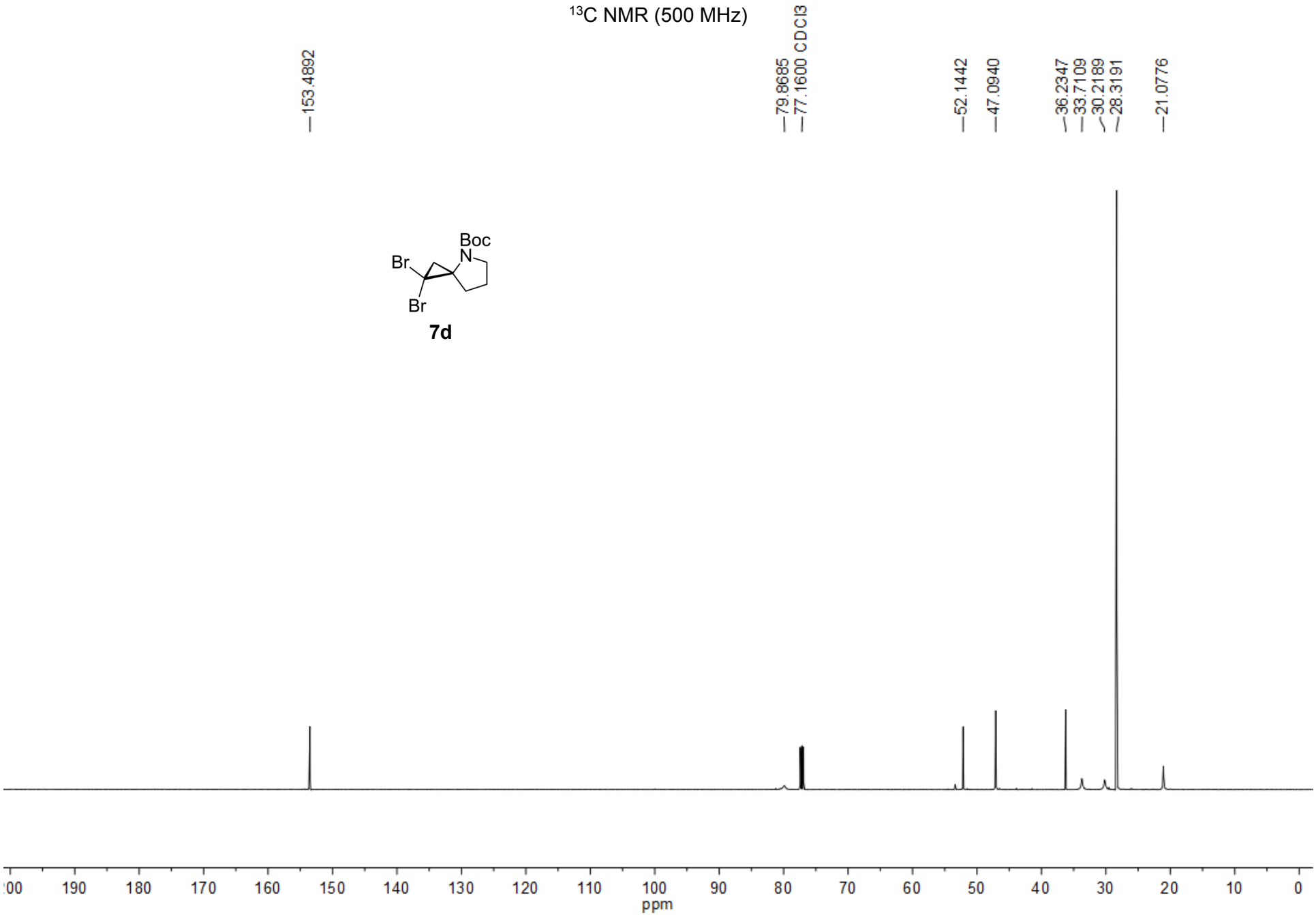

^{1}H NMR (500 MHz)
7.2600 CDCl3
5.2030 DCM
3.5550
3.5369
3.5175
3.4993
3.3633
3.3569
3.3450
3.3413
3.3386
3.3347
3.3232
3.3169
1.8491
1.8452
1.8379
1.8337
1.8294
1.8239
1.8194
1.8141
1.8060
1.8014
1.7963
1.7876
1.7794
1.7718
1.7609
1.3212
2.0849
2.0808
2.0736
2.0691
2.0597
2.0554
2.0489
2.0344
2.0258
2.0109
Boc
N
Br
Br
7d
2.15 2.10 2.05 2.00
1.23 1.57
2.00 2.98
9.11
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

COSY NMR (500 MHz)

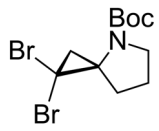


7d

^{13}C NMR (500 MHz)

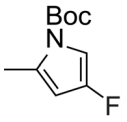


^{13}C-DEPT135 NMR (500 MHz)



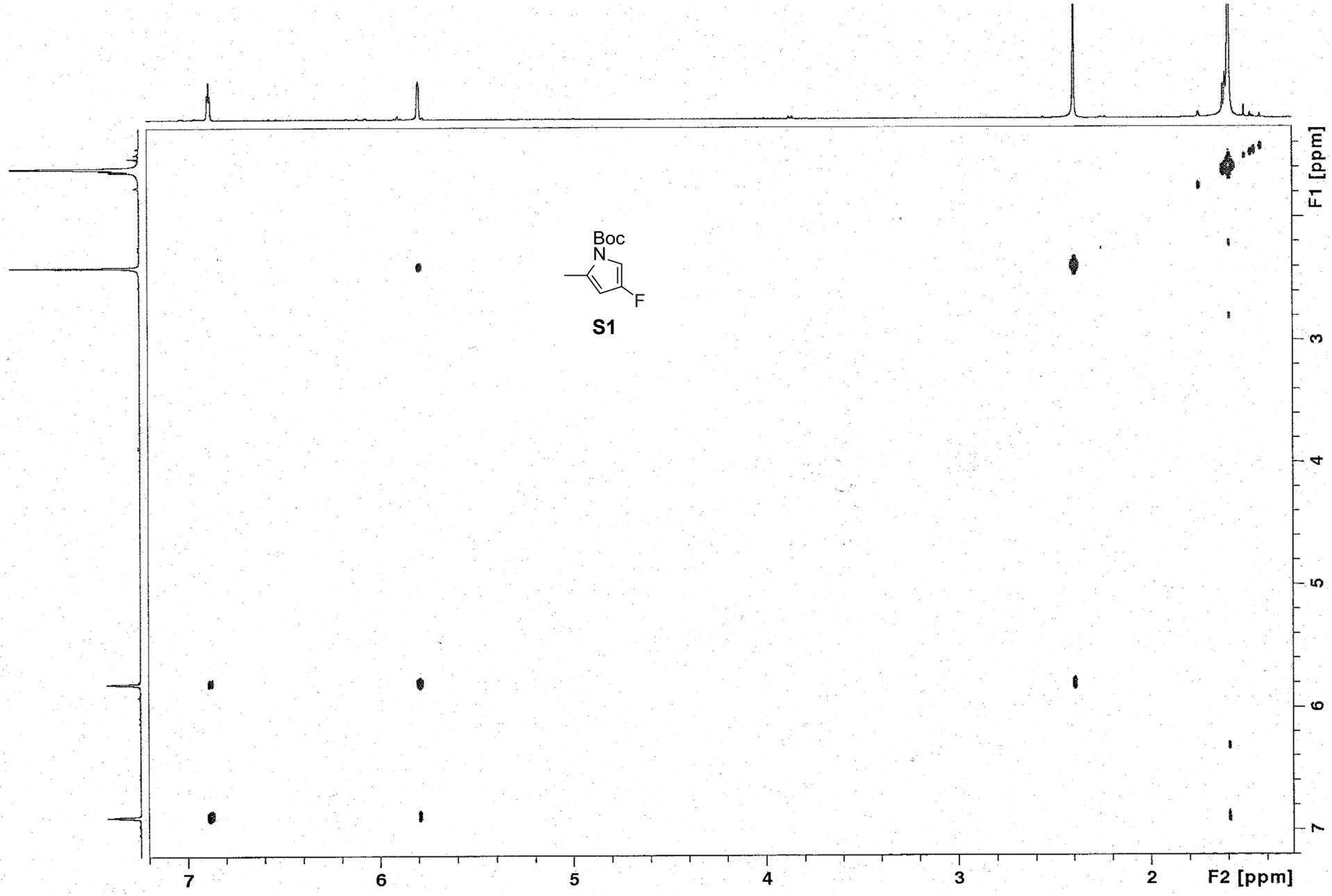
7d

^{1}H NMR (700 MHz)

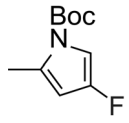


S1

COSY NMR (700 MHz)

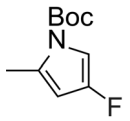


^{13}C NMR (176 MHz)



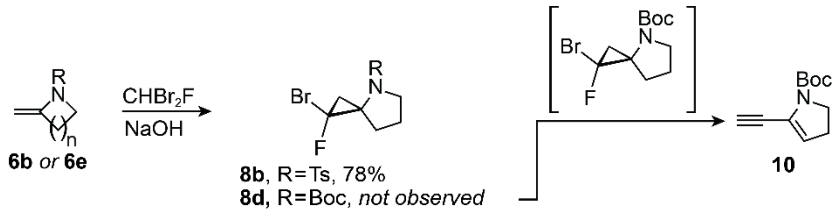
S1

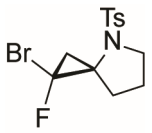
^{13}C-DEPT135 NMR (176 MHz)



S1

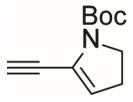
Scheme 6





8b

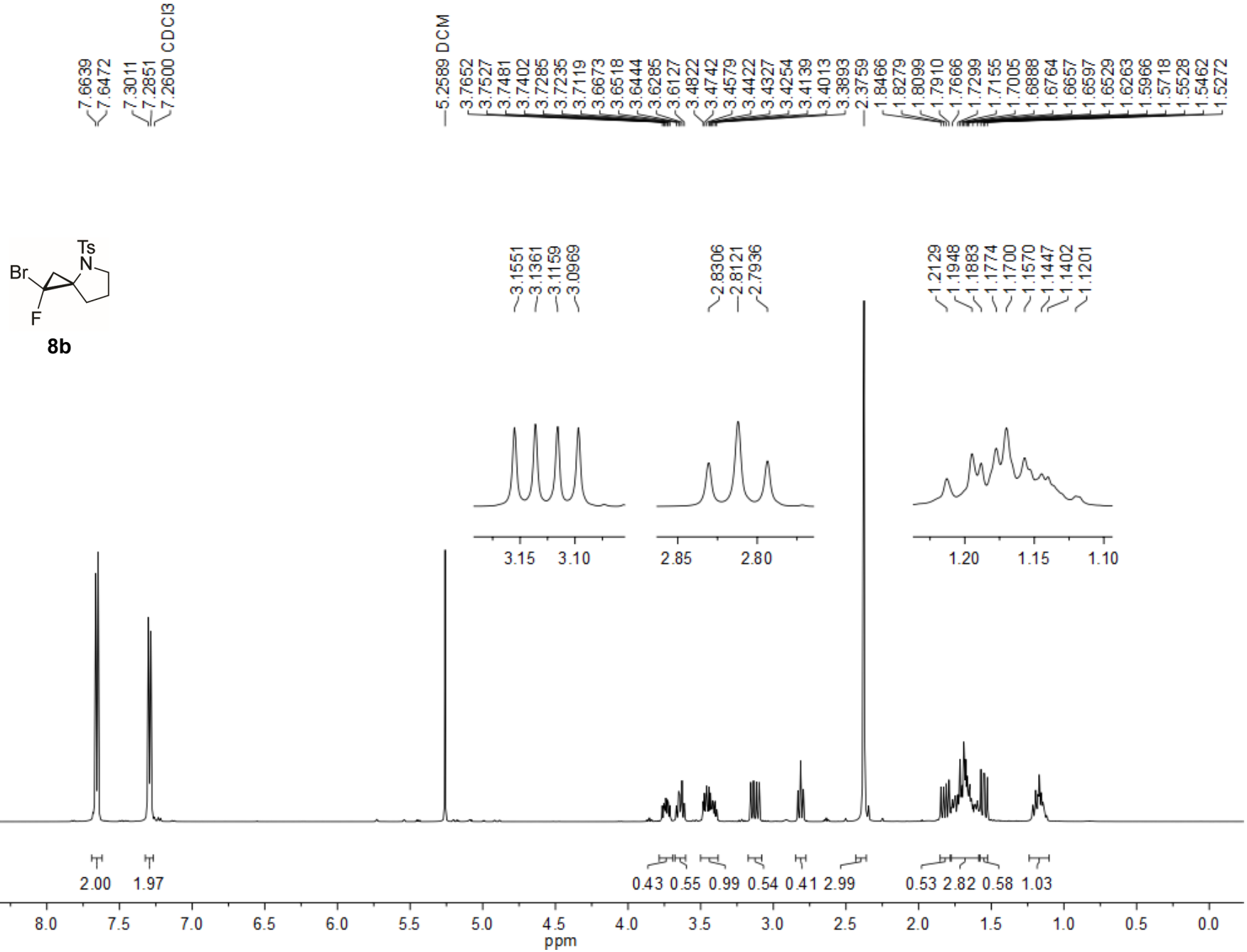
To a solution of **6b** (200 mg, 0.84 mmol, 1.0 eq) and benzyltrimethylammonium chloride (29 mg, 0.13 mmol, 0.15 eq) in DCM (10 mL) was added $CHBr_2F$ (80µl, 1.01 mmol, 1.2 eq) and NaOH (742 µL, 50% w/v) consecutively at rt. The reaction mixture was stirred vigorously at rt for 25.5 h at rt and diluted with DCM and water. The aqueous layer was washed with DCM and the combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography over silica gel (23 g, 15% EtOAc/ hexanes (v/v)) to obtain **8b** (1.0 g, 78%) as a yellow oil. R_f = 0.64 (30% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.76–3.71 (m, 0.5H), 3.67–3.61 (m, 0.5H), 3.48–3.39 (m, 1H), 3.13 (dd, *J* = 19.6, 9.5 Hz, 0.5H), 2.81 (t, *J* = 9.2 Hz, 0.5H), 2.38 (s, 3H), 1.82 (dd, *J* = 18.4, 9.4 Hz, 0.5H), 1.77–1.60 (m, 3H), 1.55 (dd, *J* = 12.8, 9.5 Hz, 0.5H), 1.21–1.12 (m, 1H).^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.98, 143.90, 135.42, 135.07, 129.80, 129.78, 127.28, 127.23, 86.74, 85.85, 84.30, 83.45, 50.92, 50.86, 50.83, 49.85, 49.82, 31.73, 31.71, 26.12, 26.08, 23.72, 23.64, 23.31, 23.22, 22.49, 22.10, 21.37, 21.35. COSY NMR was obtained under same conditions (attached). ^{13}C-DEPT135 NMR (126 MHz, $CDCl_3$): δ = (up) 28.38, (down) 47.16, 36.23, 33.79, 30.56, 21.14. HRMS (ESI): Calcd for $C_{13}H_{16}BrFNO_2S$ $[MH]^+$: 350.0043, found: 350.0050.



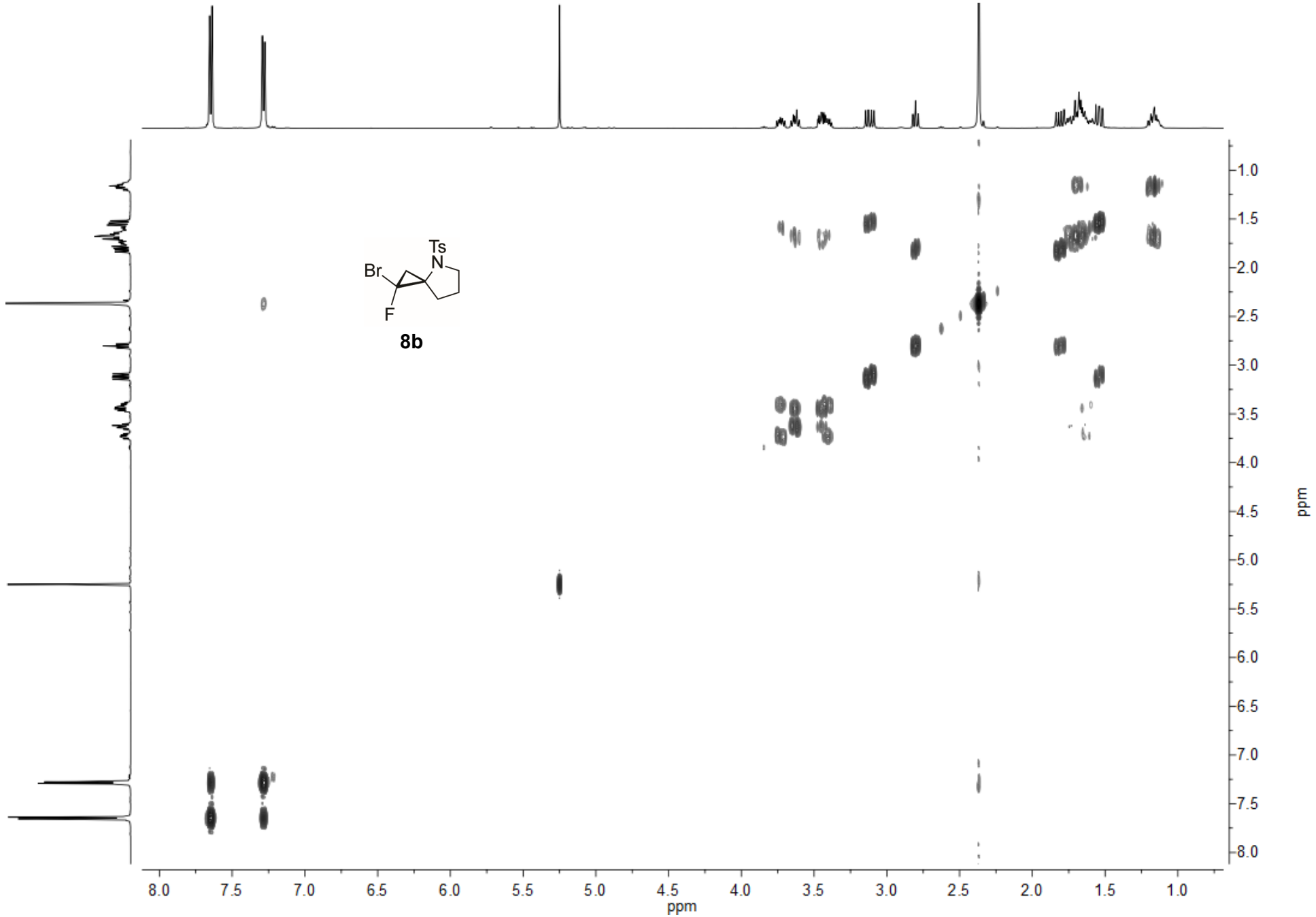
10

To a solution of **6e** (1.0 g, 5.46 mmol, 1.0 eq) and benzyltrimethylammonium chloride (190 mg, 0.83 mmol, 0.15 eq) in DCM (25 mL) was added $CHBr_2F$ (520 µl, 6.55 mmol, 1.2 eq) and NaOH (1.1 mL, 50% w/v) consecutively at rt. The reaction mixture was stirred vigorously for 24 h at rt. The reaction mixture was diluted with DCM and water and the organic layer was collected. The aqueous layer was further washed with DCM and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude turned purple when concentrated. Flash chromatography over silica gel (52 g, 10–15% EtOAc/ hexanes (v/v)) suggested the rearrangement product **10** as the major product, which began decomposing on concentration (1.00g, 30.0%). R_f = 0.67 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (q, *J* = 2.9 Hz, 1H), 4.73 (t, *J* = 3.2 Hz, 1H), 4.69 (d, *J* = 2.8 Hz, 0.5H), 4.61 (d, *J* = 2.8 Hz, 0.5H), 3.90–3.84 (m, 2H), 2.59–2.48 (m, 2H), 1.45 (s, 9H), 1.42 (d, *J* = 5.0 Hz, 3H). COSY NMR was obtained under same conditions (attached). MS (ESI): Calcd for $C_7H_8NO_2$ $[M\text{-}C(CH_3)_3+2H]^+$: 138.1, found: 138.0.

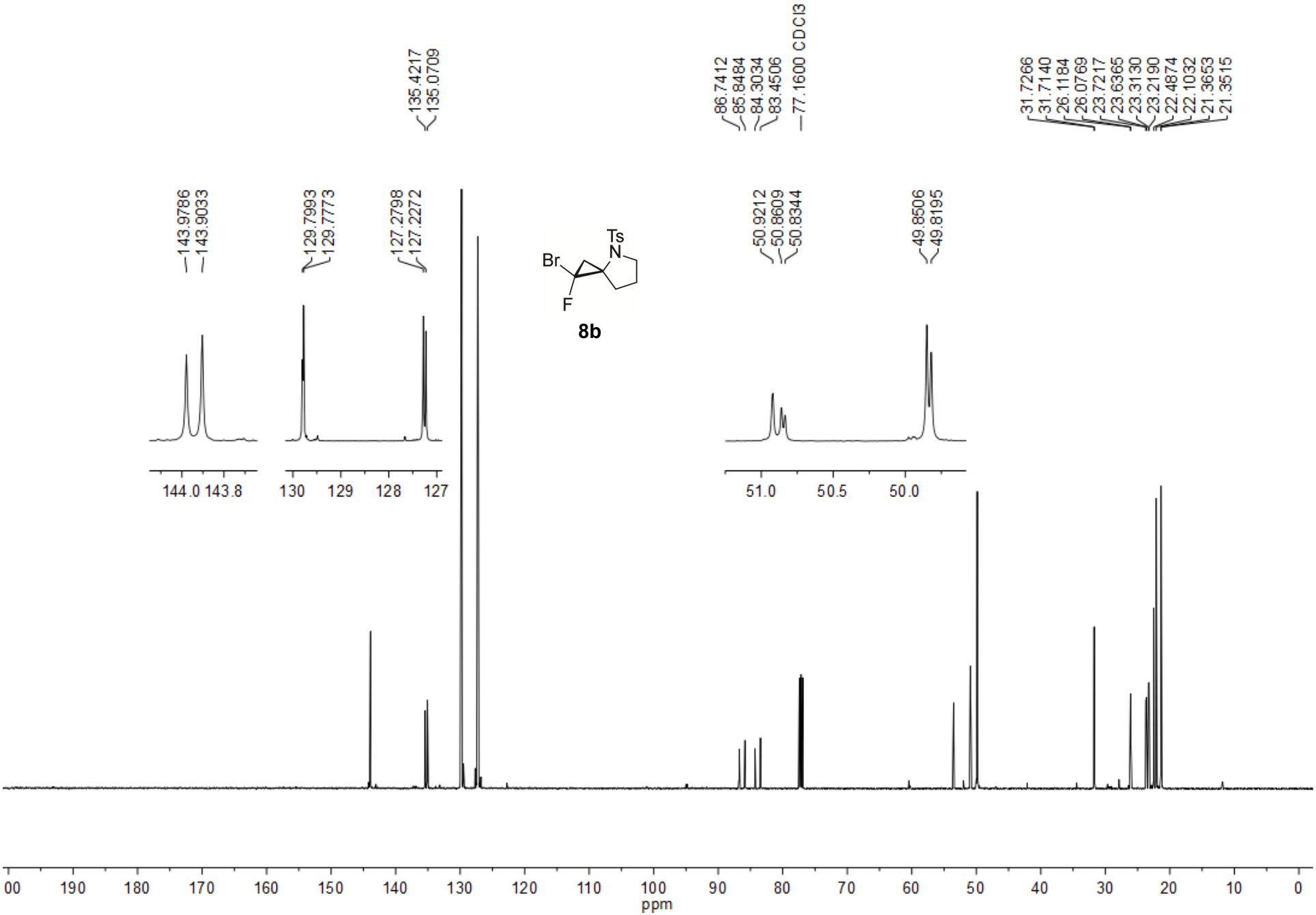
^{1}H NMR (500 MHz)

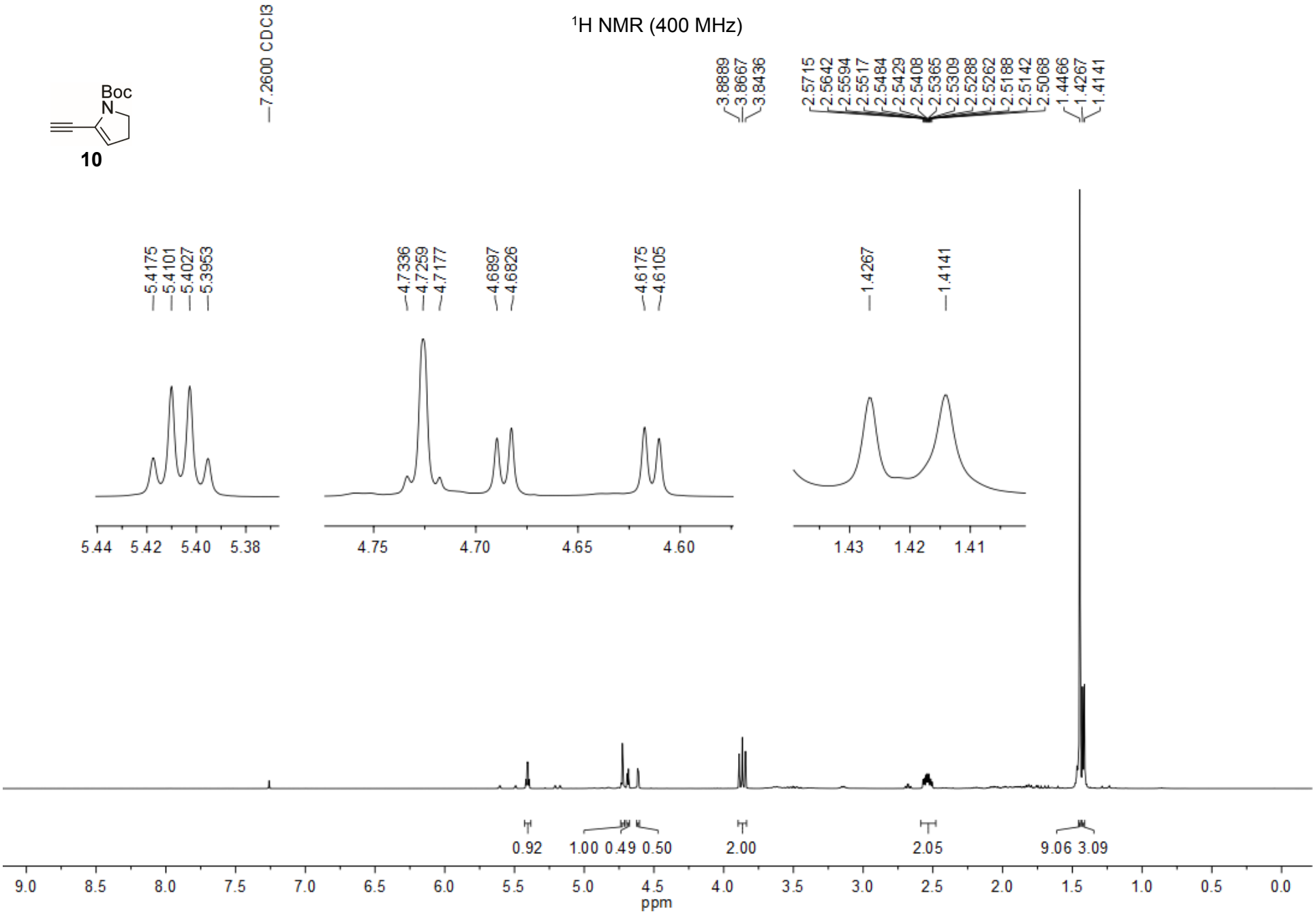


COSY NMR (500 MHz)

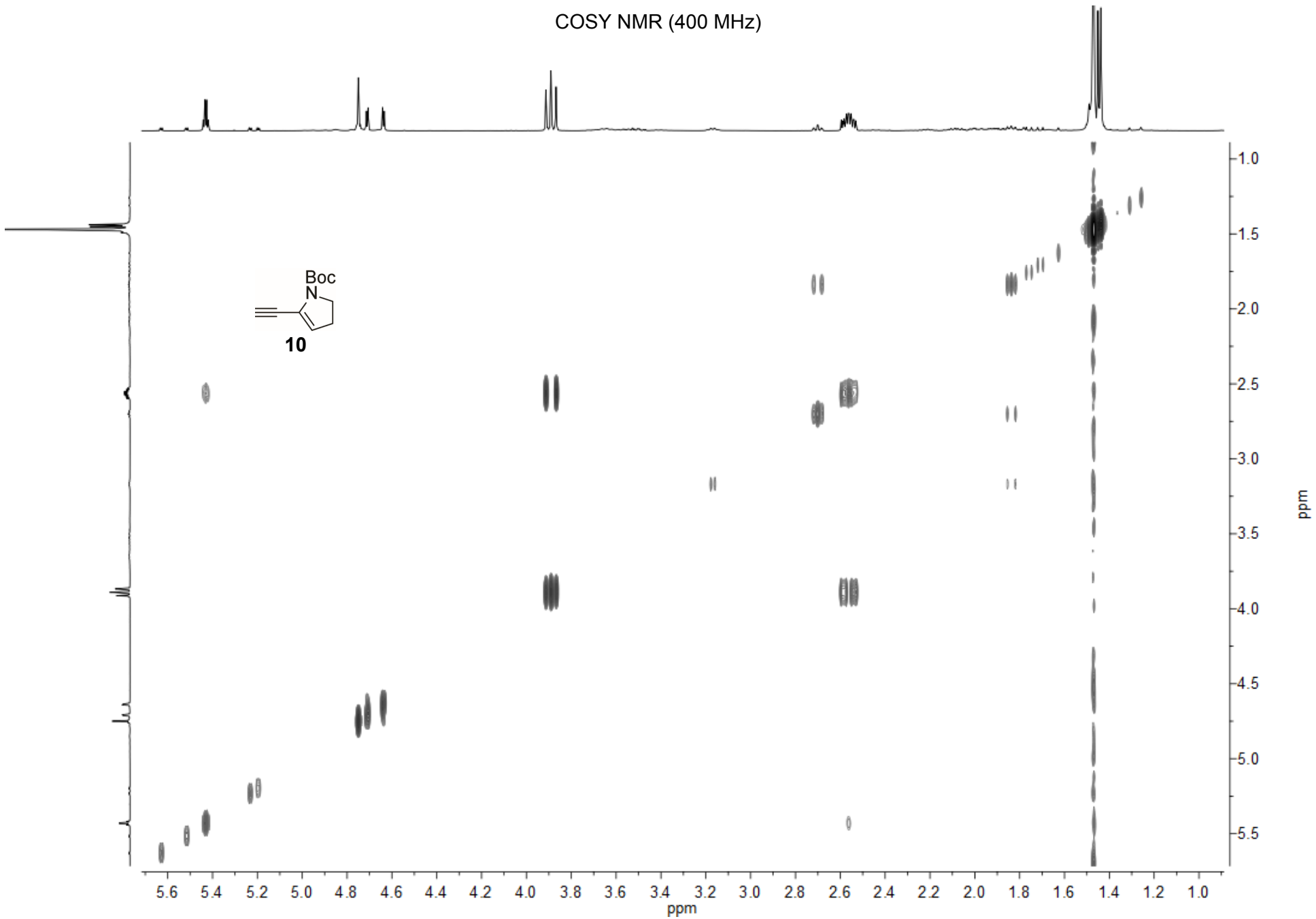


^{13}C NMR (126 MHz)

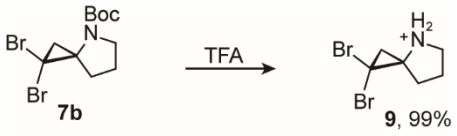


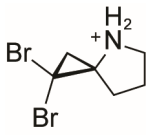

Boc
N
10
^{1}H NMR (400 MHz)
7.2600 CDCl3
3.8889
3.8667
3.8436
2.5715
2.5642
2.5594
2.5517
2.5484
2.5429
2.5408
2.5365
2.5309
2.5288
2.5262
2.5188
2.5142
2.5068
1.4466
1.4267
1.4141
5.4175
5.4101
5.4027
5.3953
4.7336
4.7259
4.7177
4.6897
4.6826
4.6175
4.6105
1.4267
1.4141
5.44 5.42 5.40 5.38
4.75 4.70 4.65 4.60
1.43 1.42 1.41
0.92
1.00 0.49 0.50
2.00
2.05
9.06 3.09
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

COSY NMR (400 MHz)



Scheme 7

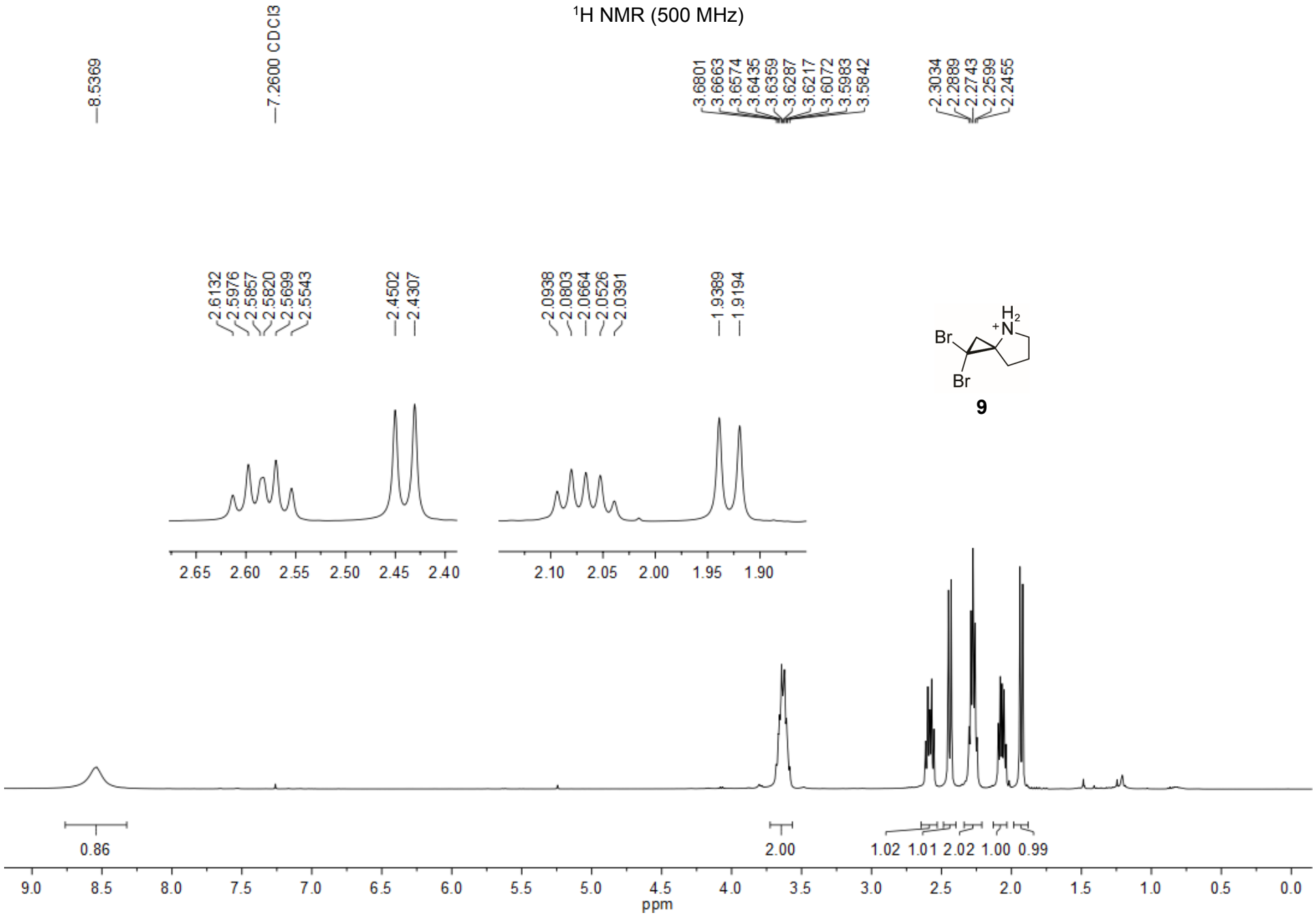




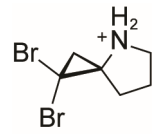
9

To an ice-cold solution of **7d** (1.51 g, 4.25 mmol, 1.0 eq) in DCM (50 mL) was added TFA (10 mL) and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure to obtain **9** (1.55 g, 99%) as a TFA salt. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (br s, 1H), 3.68–3.58 (m, 2H), 2.61–2.55 (m, 1H), 2.44 (d, *J* = 9.8 Hz, 1H), 2.27 (p, *J* = 7.2 Hz, 2H), 2.09–2.04 (m, 1H), 1.93 (d, *J* = 9.8 Hz, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.53, 161.22, 160.91, 160.60, 118.98, 116.69, 114.39, 112.10, 77.16, 52.22, 48.61, 33.26, 32.60, 24.67, 24.08. ^{13}C-DEPT135 NMR (126 MHz, $CDCl_3$): δ = (down) 48.51, 33.15, 32.49, 23.97. HRMS (ESI): Calcd for $C_6H_{10}Br_2N$ $[M]^+$: 255.9154, found: 255.9158.

^{1}H NMR (500 MHz)

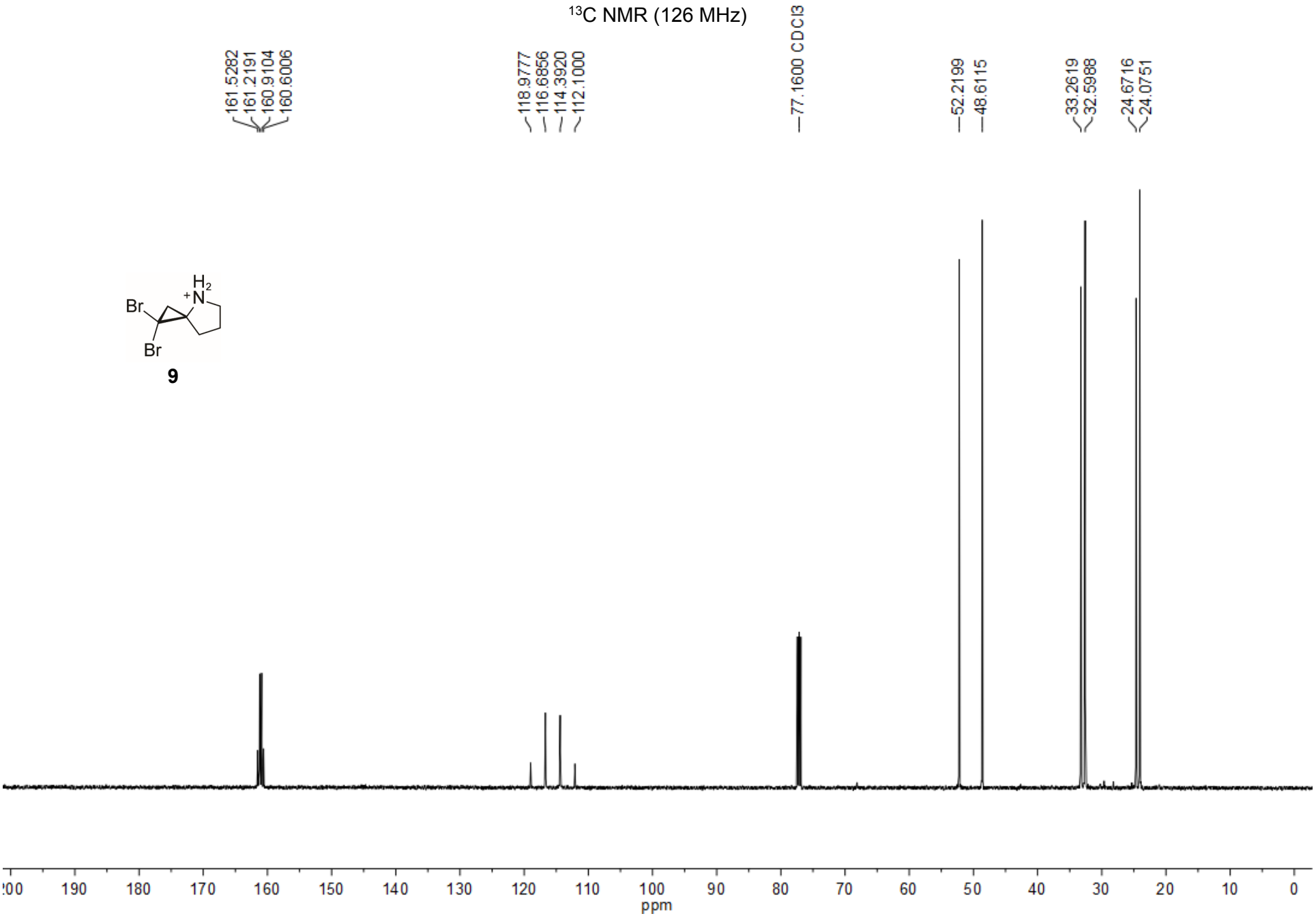


COSY NMR (500 MHz)

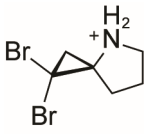


9

^{13}C NMR (126 MHz)

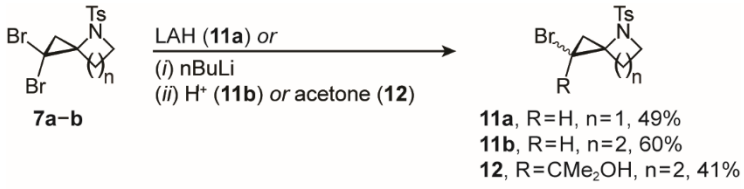


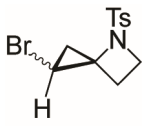
^{13}C-DEPT135 NMR (126 MHz)



9

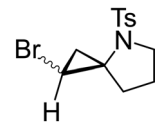
Scheme 8





11a

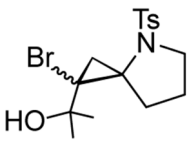
To a solution of **7a** (200 mg, 0.51 mmol, 1 eq) in dry THF (6.0 mL) under N_2 was added LAH (77 mg, 2.02 mmol, 4 eq) at 0 °C and the mixture was allowed to warm to rt over 16 h. The reaction mixture was cooled down to 0 °C, quenched with saturated NH_4Cl, and diluted with DCM and HCl (2M). The organic layer was collected and the aqueous layer was further washed with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (30 g silica, 16% ethyl acetate/hexanes (v/v)) to obtain **11a** as a mixture of diastereomers (111 mg, 49%). R_f = 0.22 and 0.13 (20% EtOAc/hexanes, visualized w/ $KMnO_4$ stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.73 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 3.83 (t, *J* = 7.6 Hz, 2H), 3.59 (dd, *J* = 9.4, 5.5 Hz, 1H), 2.56–2.50 (m, 1H), 2.46 (s, 3H), 2.25–2.20 (m, 1H), 2.12 (t, *J* = 8.8 Hz, 1H), 0.94 (dd, *J* = 8.2, 5.5 Hz, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.26, 134.04, 130.01, 128.14, 52.54, 47.41, 24.18, 22.54, 21.74, 20.36. ^{13}C-DEPT 135 NMR (126 MHz, $CDCl_3$): δ = (up) 129.89, 128.02, 22.41, 21.62, (down) 47.29, 24.06, 20.23. HRMS (ESI): Calcd for $C_{12}H_{15}BrNO_2S$ $[MH]^+$: 316.0001, found: 316.0007.



11b

To a solution of **7b** (200 mg, 0.49 mmol, 1.0 eq) in dry THF (10 mL) at -78 – -85 °C was dropwise added nBuLi (0.59 mmol, 1.2 eq). After stirring the reaction mixture for 10 mins it was stirred at rt for two mins and quenched using sat. NH_4Cl at -78 °C. THF was concentrated *in vacuo,* the reaction was diluted with DCM (10 mL), and the organic layer was collected. The aqueous layer was washed with DCM (2×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified through flash chromatography (30 g silica, 10% ethyl acetate/hexanes (v/v)) to obtain **11b** as a colorless oil and a mixture of diastereomers (60% yield). A similar reaction using iPrMgCl instead of nBuLi in dry DCM at -50 °C afforded similar results (55% yield). Alternative methods (Table **S1**): To a solution of **7b** (200 mg, 0.49 mmol, 1 eq) in dry THF (6.0 mL) under N_2 was added LAH (75 mg, 1.96 mmol, 4 eq) at 0 °C and the mixture was allowed to warm to rt over 16 h. The reaction mixture was cooled down to 0 °C, quenched with saturated NH_4Cl, and diluted with DCM and HCl (2M). The organic layer was collected and the aqueous layer was further washed with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (30 g silica, 15% ethyl acetate/hexanes (v/v)) to obtain **11b** as a mixture of diastereomers (41 mg, 25%). R_f = 0.32 (20% EtOAc/hexanes, visualized w/ $KMnO_4$ stain). A similar reaction starting from **7b** (100 mg, 0.25 mmol, 1 eq) with $AgClO_4$ (1.01 mg, 0.05 mmol, 0.02 eq) as an additional additive completed in 50 mins at -5 °C with a yield of 41%. Our attempts at employing other strategies for this dibromo to monobromo cyclopropane conversion resulted in conversion to allene in high purity when using excess EtMgBr and catalytic $Ti(OiPr)_4$. Upon reducing the equivalents of EtMgBr the reaction produced an inseparable mixture of starting material and product. Negligible product formation was observed with nBu_3SnH. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.88–3.81 (m, 1H), 3.46–3.39 (m, 1H), 2.66 (dd, *J* = 8.2, 5.0 Hz, 1H), 2.45–2.39 (m, 1H), 2.43 (s, 3H), 1.84–1.72 (m, 1H), 1.71–1.63 (m, 1H), 1.60–1.56 (m, 2H), 1.47–1.39 (m, 1H), 1.20–1.14 (m, 1H). COSY NMR was obtained under same conditions (attached). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.77, 136.72, 129.81, 127.83, 49.78, 47.26, 32.83, 26.52, 22.78, 21.72, 17.57. ^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$): δ = (up) 129.68, 127.70, 26.39, 21.58, 49.65, 32.70, 22.64,17.44. HRMS (ESI): Calcd for $C_{13}H_{16}BrNO_2S$ $[MH]^+$: 330.0158, found: 330.0132.

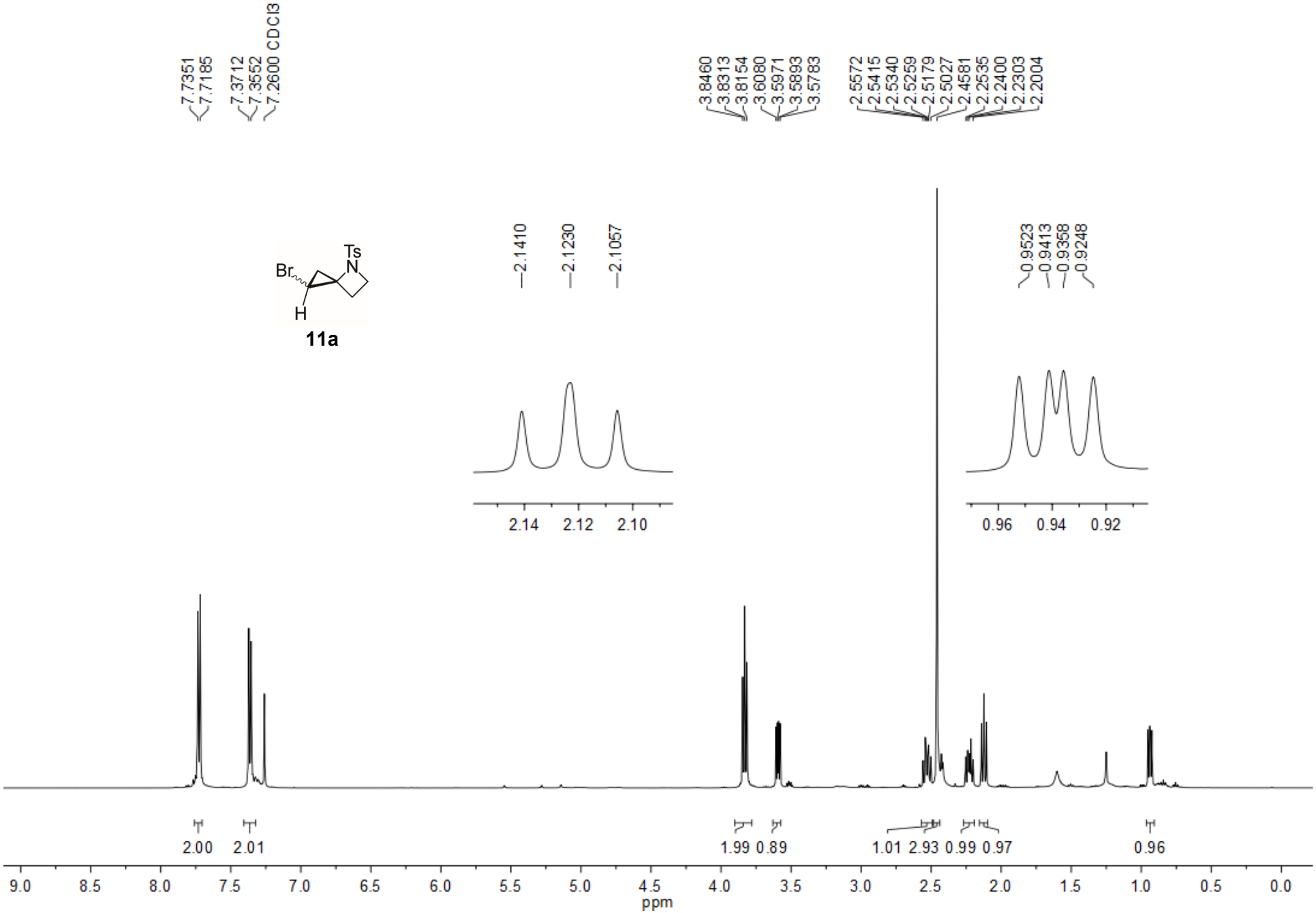
NMR for allene rearrangement product upon using excess EtMgBr. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.33 (t, *J* = 3.8 Hz, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.43–2.38 (m, 2H), 2.40 (s, 3H), 1.80 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.00, 143.81, 133.98, 129.42, 127.59, 110.22, 86.75, 50.54, 30.46, 23.26, 21.50. ^{13}C-DEPT135 NMR (126 MHz, $CDCl_3$): δ: = (up) 129.48, 127.66, 21.57, (down) 86.82, 50.61, 30.53, 23.33.



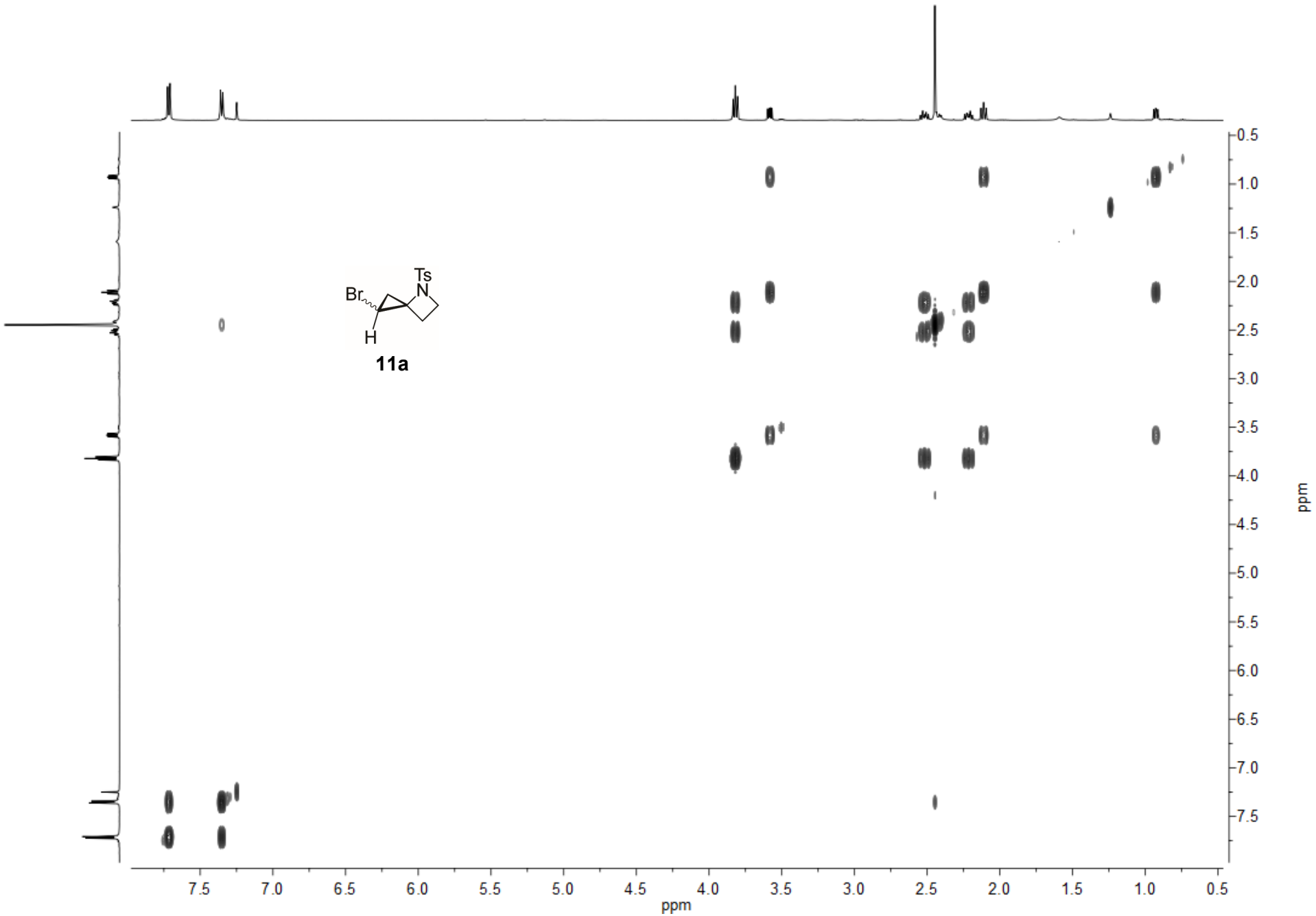
12

To a solution of **7b** (200 mg, 0.49 mmol, 1 eq) at -90 °C was dropwise added nBuLi (306 µL, 0.49 mmol, 1 eq, 1.6 M in hexanes). The solution was allowed to warm up to -70 °C and stirred at this temperature for 20 mins. Dry acetone (1.5 mL) was added to the reaction and it was allowed to gradually warm up to -25 °C. The cooling bath was removed and the reaction was allowed to warm to rt. The reaction was quenched with sat. NH_4Cl, diluted with DCM (10 mL), and the organic layer was collected. The aqueous layer was washed with DCM (2×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified through flash chromatography (25 g silica, 15% ethyl acetate/hexanes (v/v)) to obtain **12** as a colorless oil as a mixture of diastereomers (78 mg, 41.2 %). R_f = 0.35 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (d, J = 8 Hz, 1.6 H), 7.27 (d, J = 8 Hz, 0.42 H), 3.87–3.75 (m, 1H), 3.48–3.35 (m, 1H), 3.24 (s, 1H), 3.18 (d, *J* = 8.3 Hz, 0.83 H), 2.64 (dd, *J* = 8.1, 5.0 Hz, 0.20 H), 2.41(s, 2.5 H), 2.38 (s, 0.63 H), 1.99 (ddd, *J* = 13.0, 6.5, 2.1 Hz, 0.82 H), 1.76–1.58 (m, 2H), 1.49 (s, 3H), 1.43 (s, 3H), 1.30–1.28 (d, 8.3 Hz, 1H), 1.16–1.13 (m, 0.25 H), 0.83–0.74 (m, 0.84 H). HRMS (ESI): Calcd for $C_{16}H_{23}BrNO_3S$ $[MH]^+$: 388.0577, found: 388.0580.

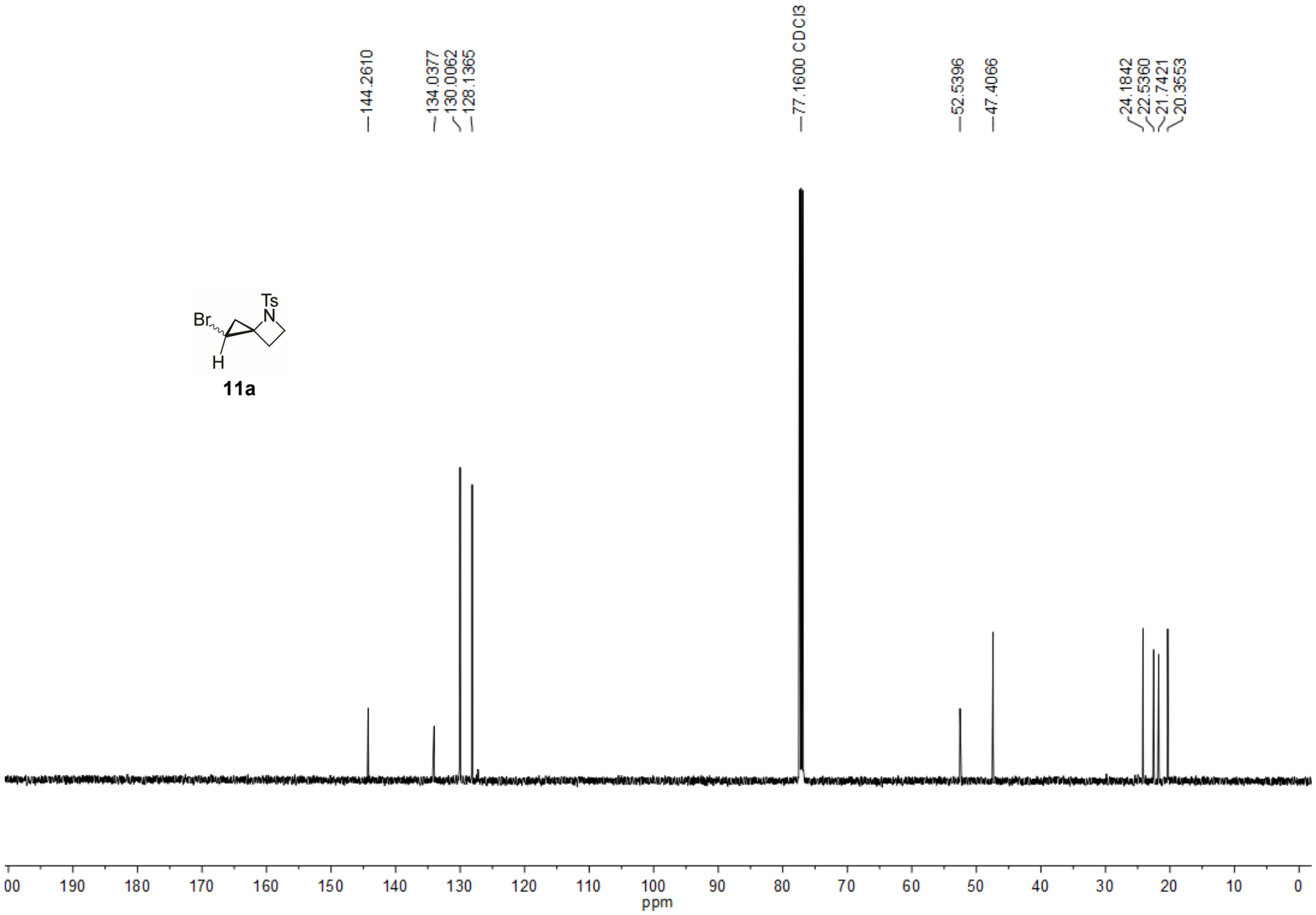
^{1}H NMR (500 MHz)



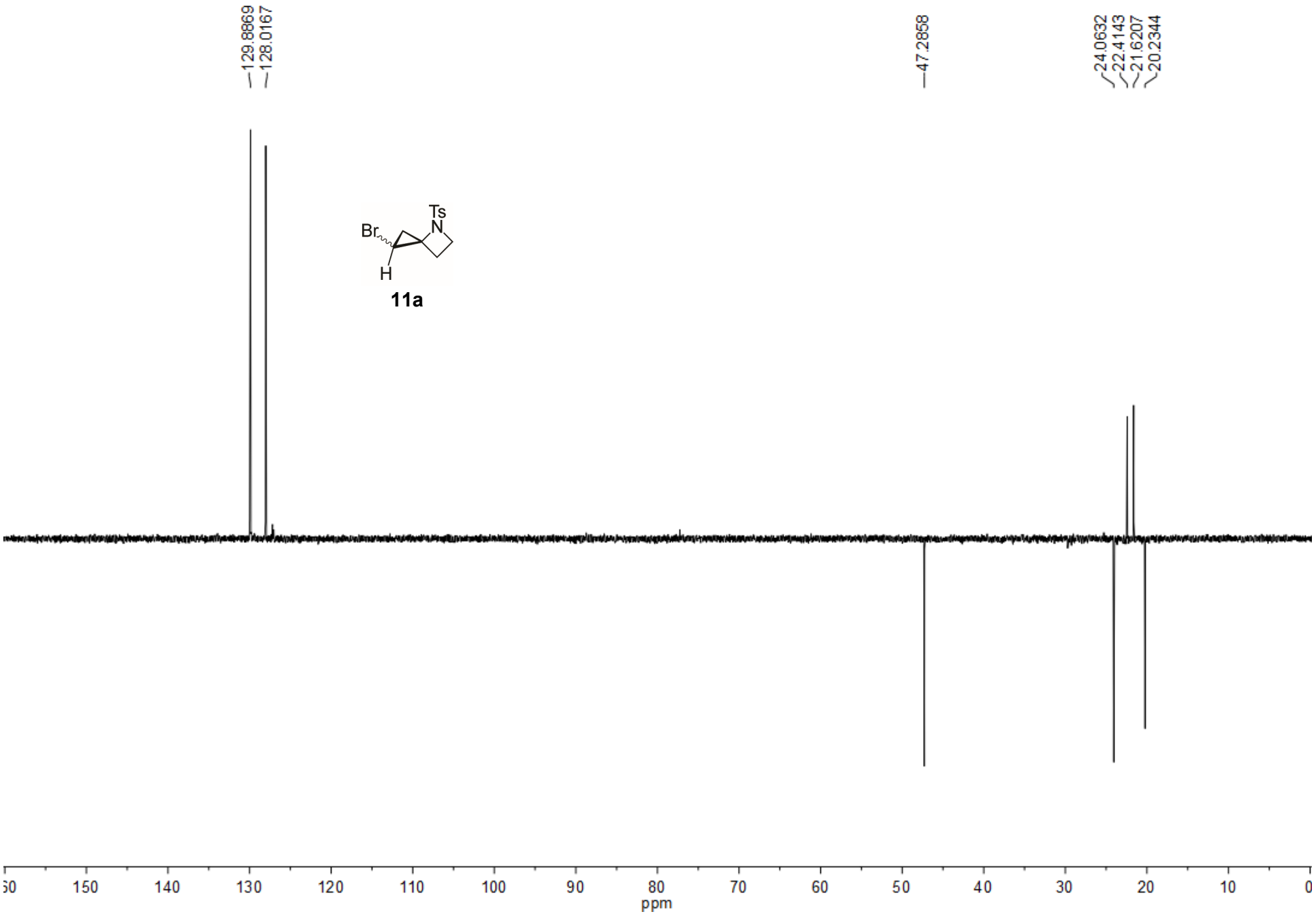
COSY NMR (500 MHz)



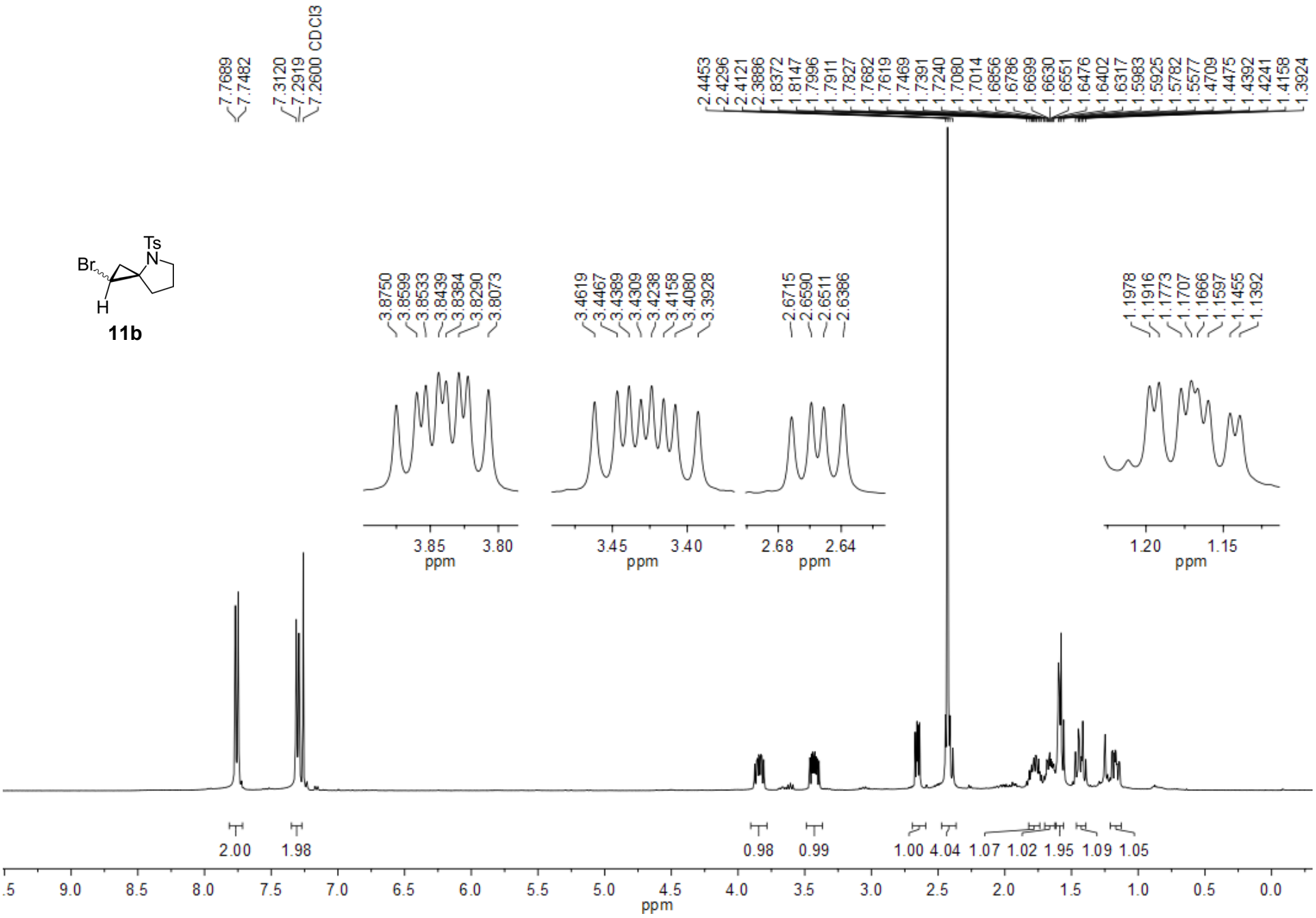
^{13}C NMR (126 MHz)



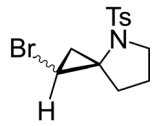
^{13}C-DEPT135 NMR (126 MHz)



^{1}H NMR (500 MHz)

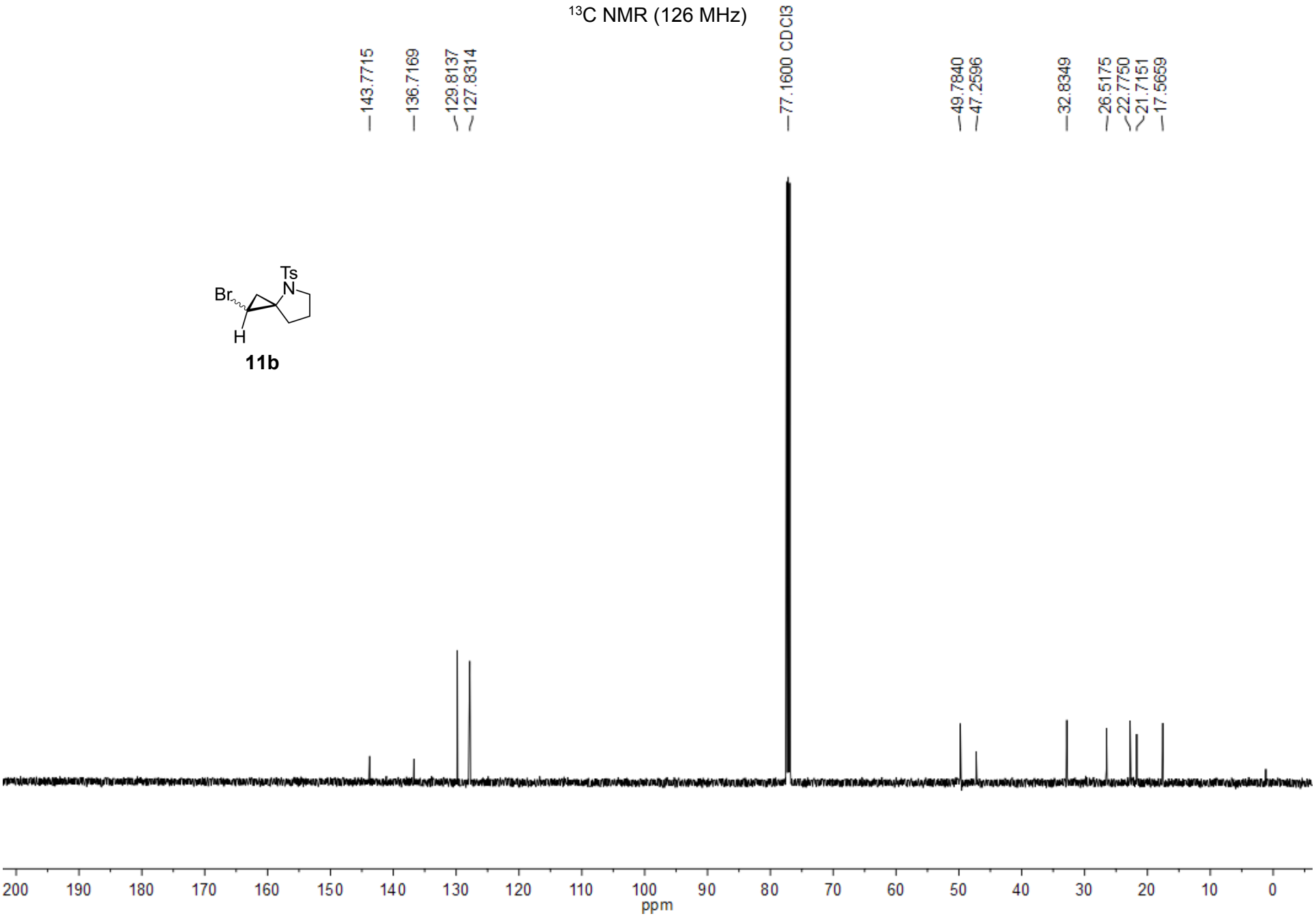


COSY NMR (500 MHz)



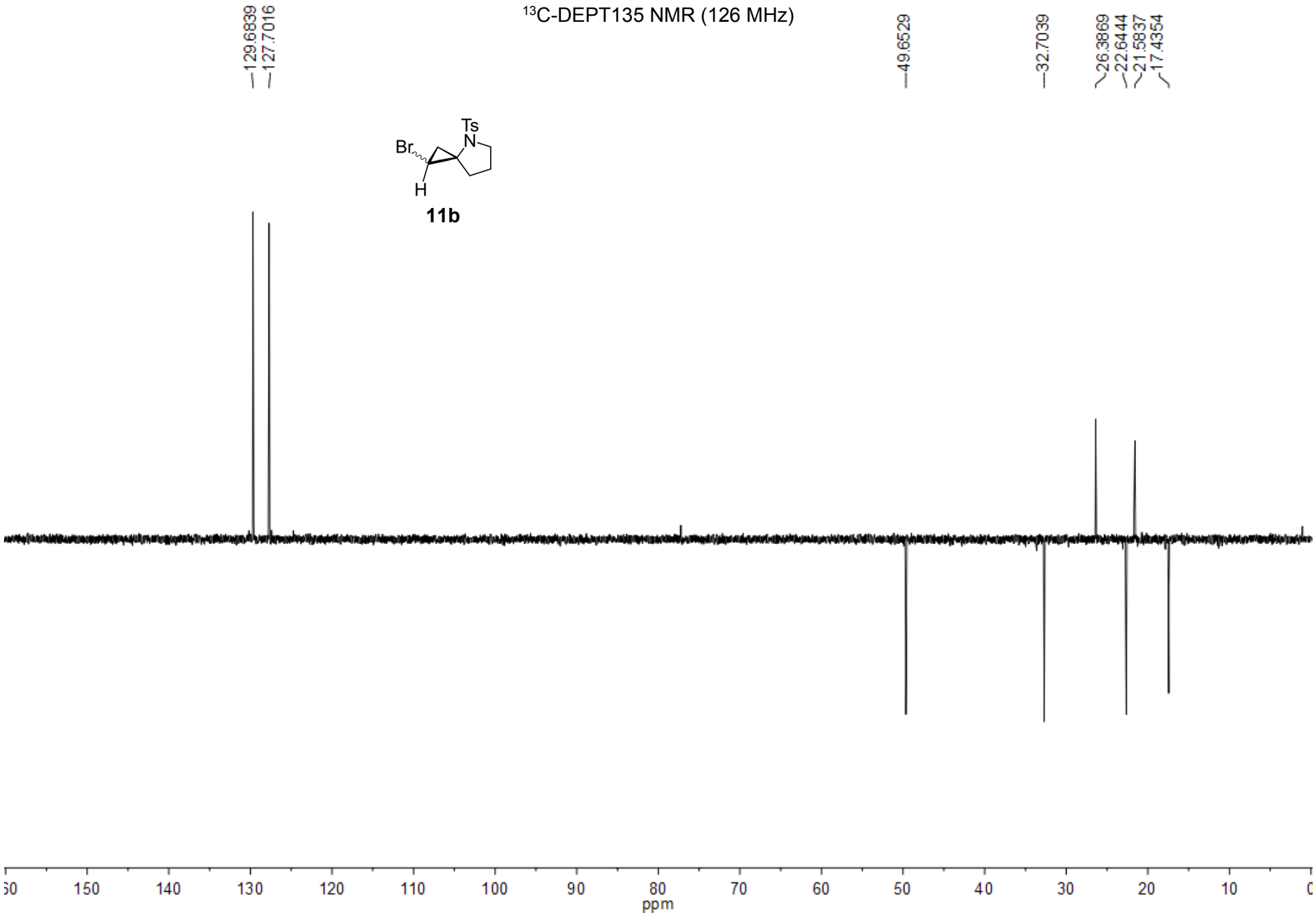
11b

^{13}C NMR (126 MHz)

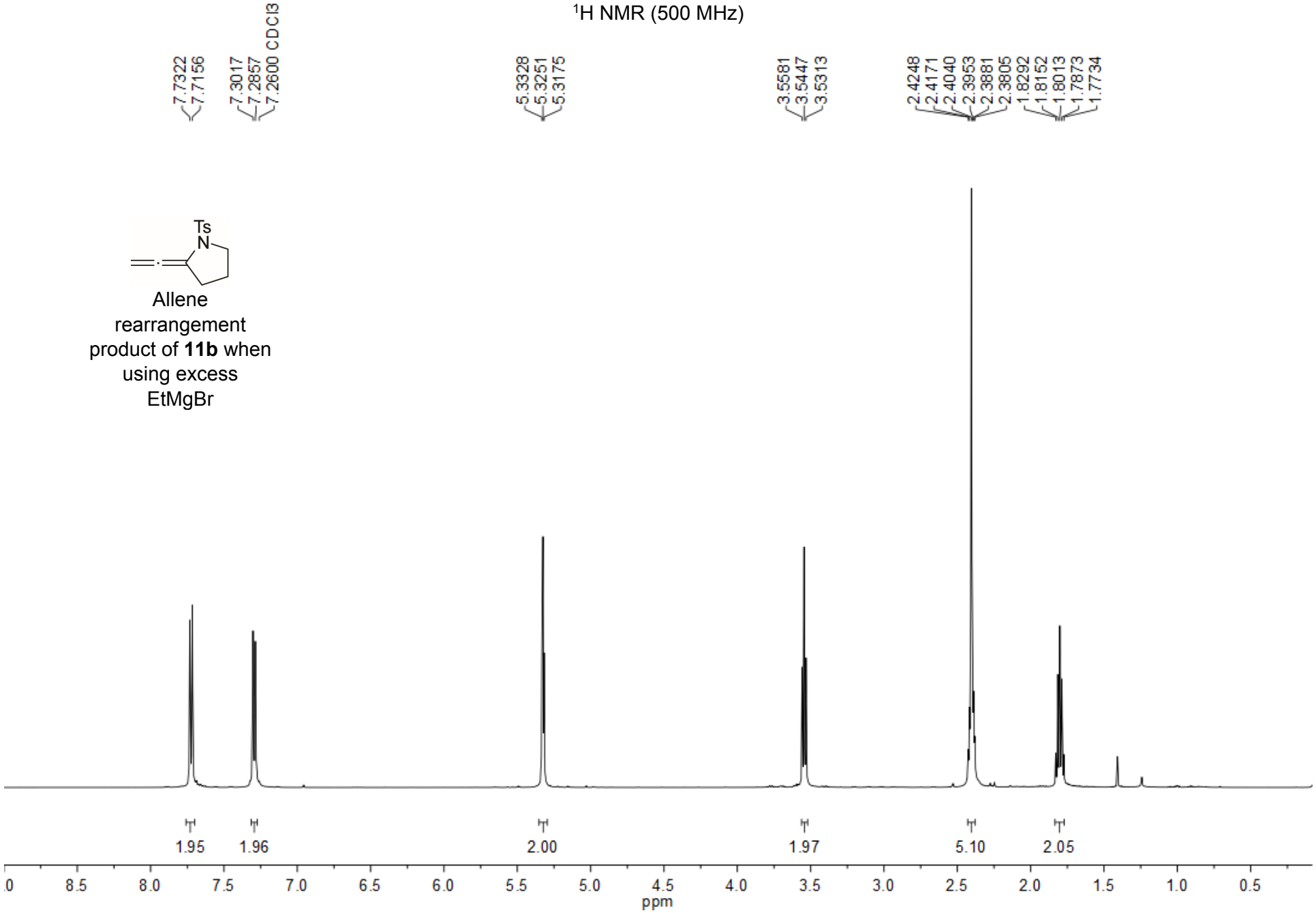


11b

^{13}C-DEPT135 NMR (126 MHz)

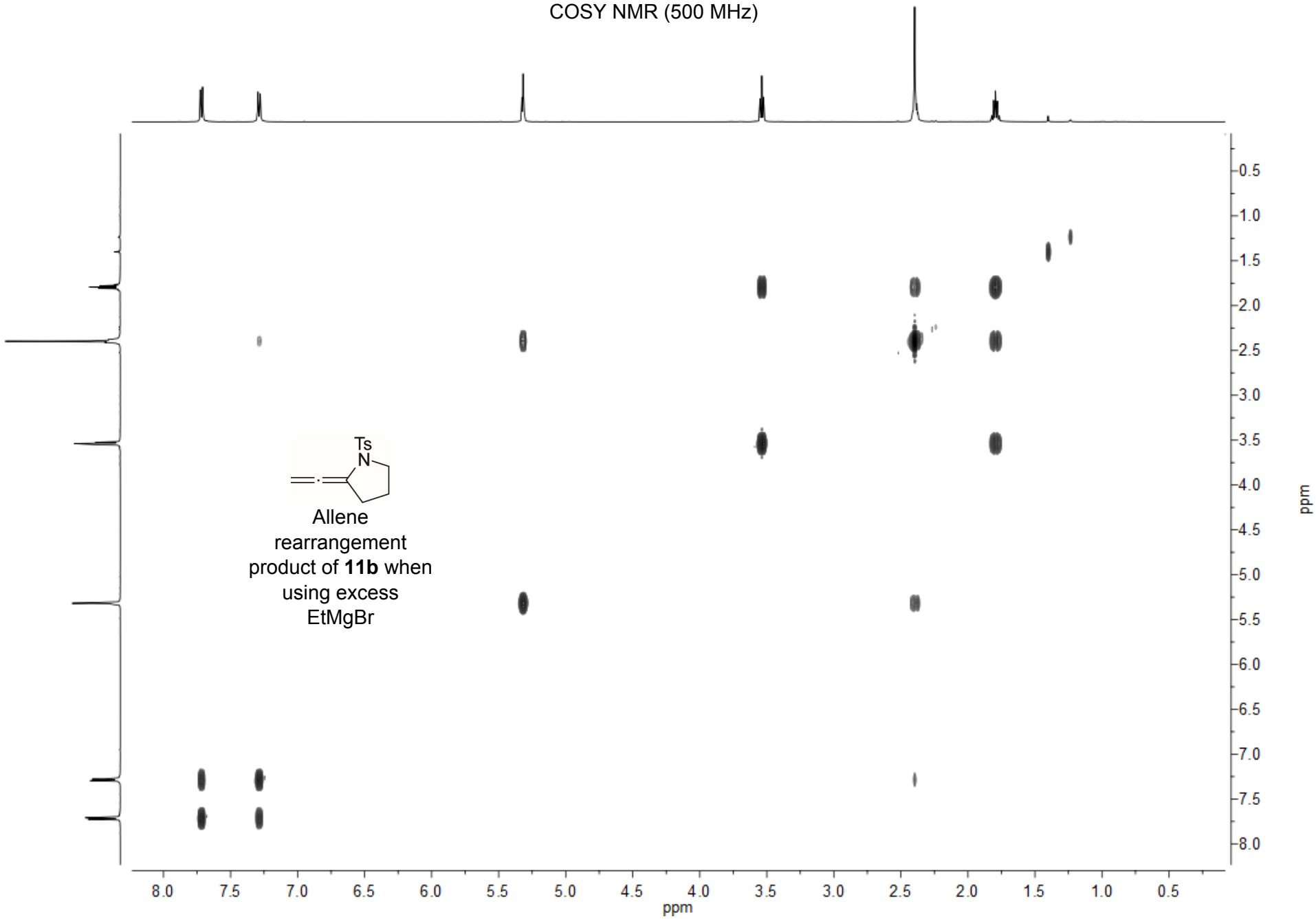


^{1}H NMR (500 MHz)

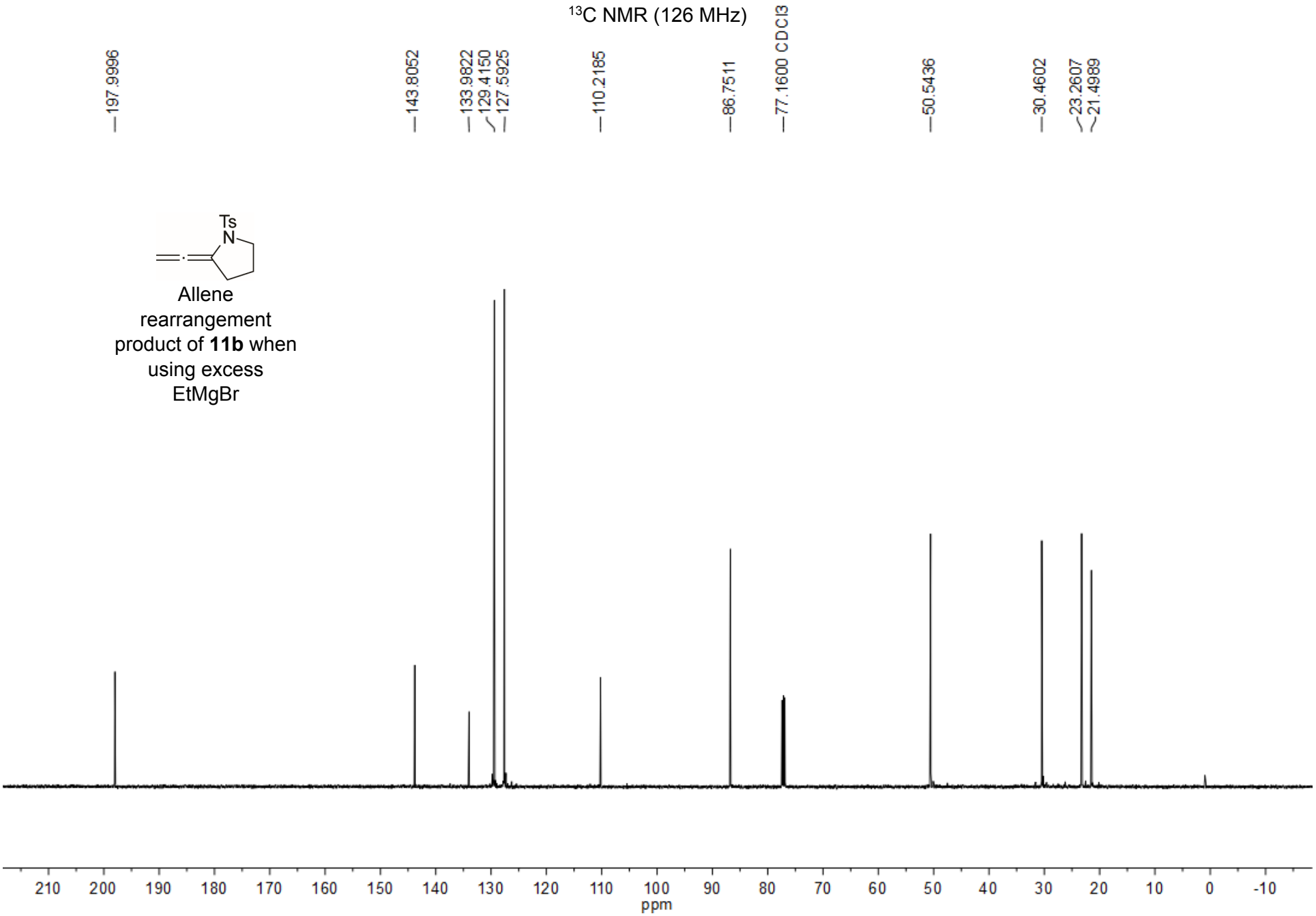


Allene rearrangement product of **11b** when using excess EtMgBr

COSY NMR (500 MHz)

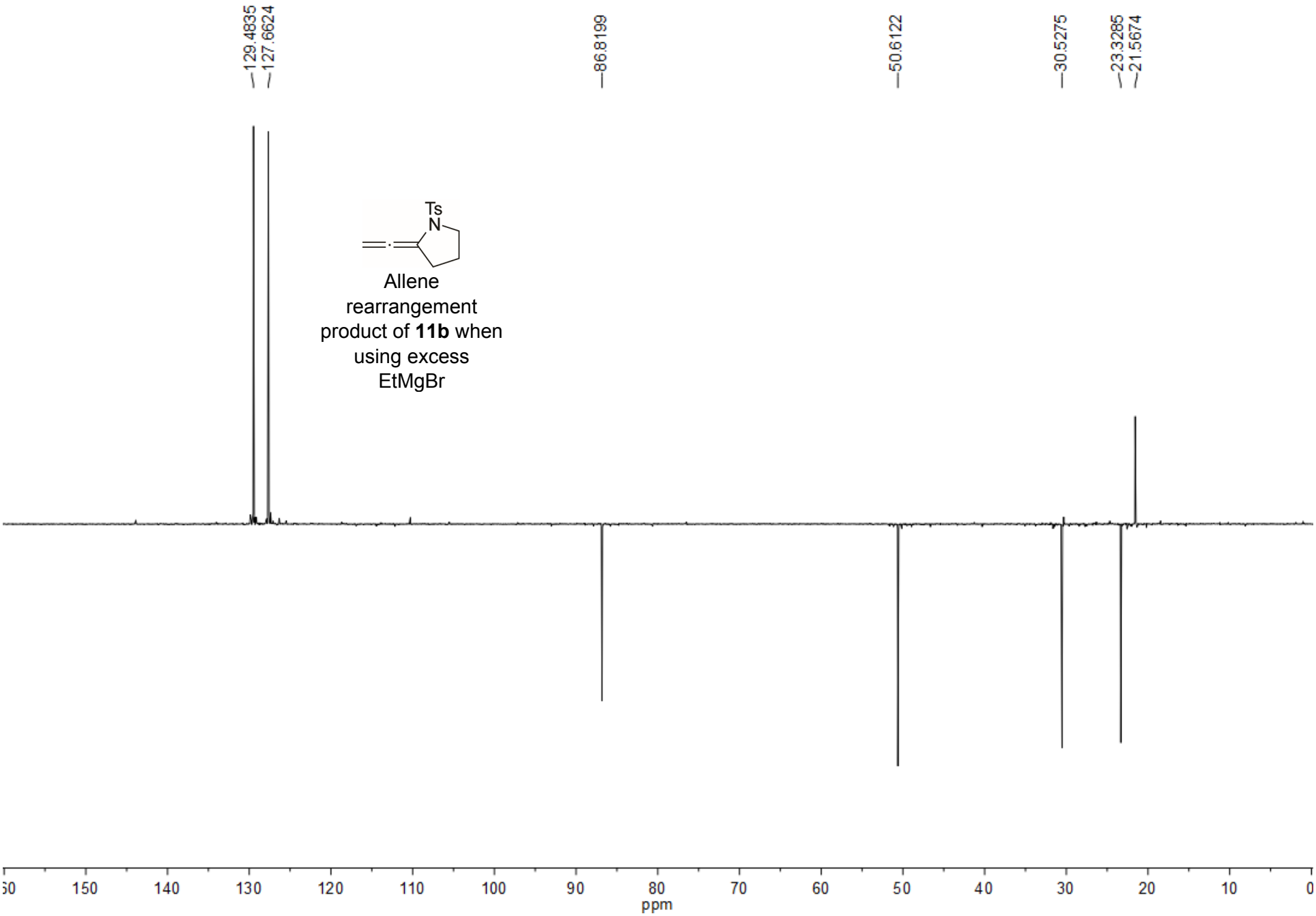


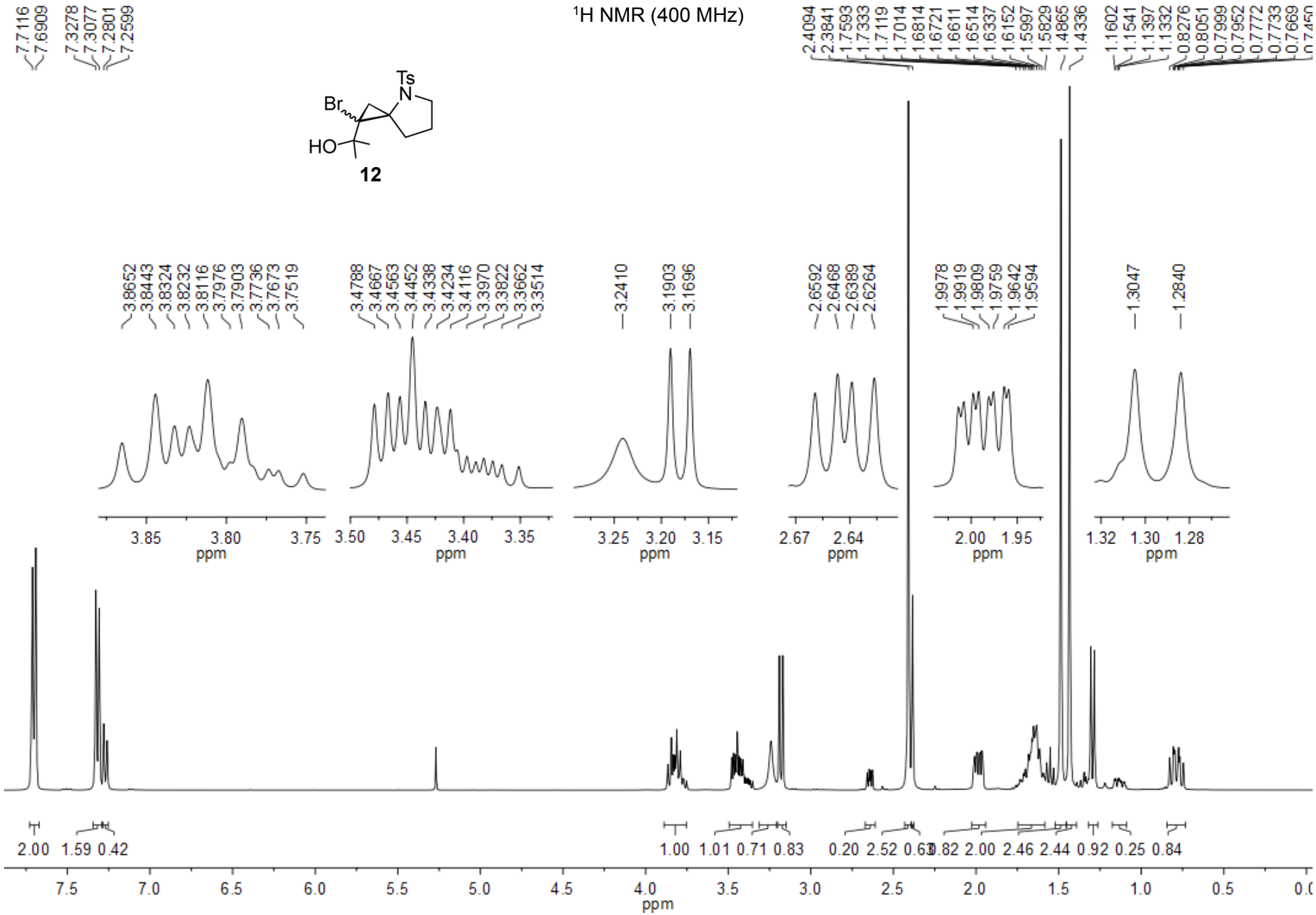
^{13}C NMR (126 MHz)



Allene rearrangement product of **11b** when using excess EtMgBr

^{13}C-DEPT135 NMR (126 MHz)




^{1}H NMR (400 MHz)
Ts
N
Br
HO
12
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7.6909
7.3278
7.3077
7.2801
7.2599
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2.3841
1.7593
1.7333
1.7119
1.7014
1.6814
1.6721
1.6611
1.6514
1.6337
1.6152
1.5997
1.5829
1.4865
1.4336
1.1602
1.1541
1.1397
1.1332
0.8276
0.8051
0.7999
0.7952
0.7772
0.7733
0.7669
3.8652
3.8443
3.8324
3.8232
3.8116
3.7976
3.7903
3.7736
3.7673
3.7519
3.4788
3.4667
3.4563
3.4452
3.4338
3.4234
3.4116
3.3970
3.3822
3.3662
3.3514
3.2410
3.1903
3.1696
2.6592
2.6468
2.6389
2.6264
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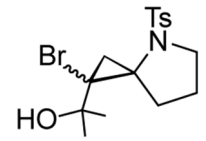
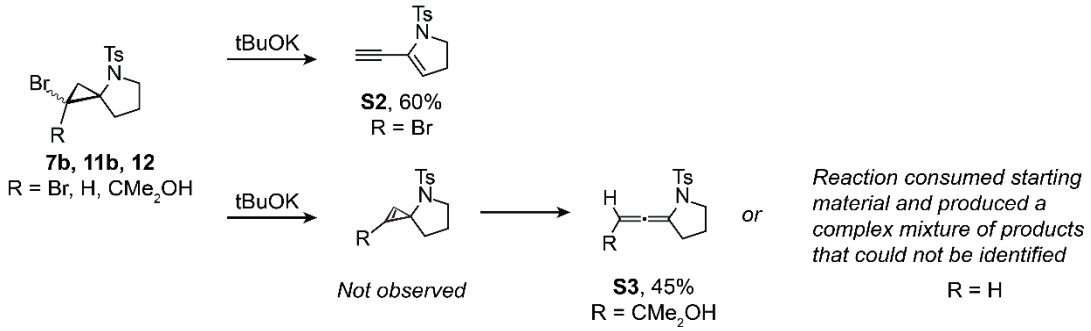
1.9809
1.9759
1.9642
1.9594
1.3047
1.2840
ppm
2.00 1.59 0.42
1.00 1.01 0.71 0.83 0.20 2.52 0.63 0.82 2.00 2.46 2.44 0.92 0.25 0.84

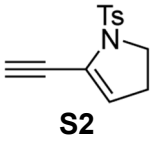
COSY NMR (500 MHz)



12

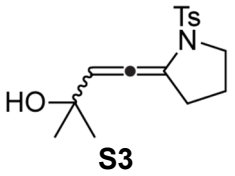
Scheme 9





S2

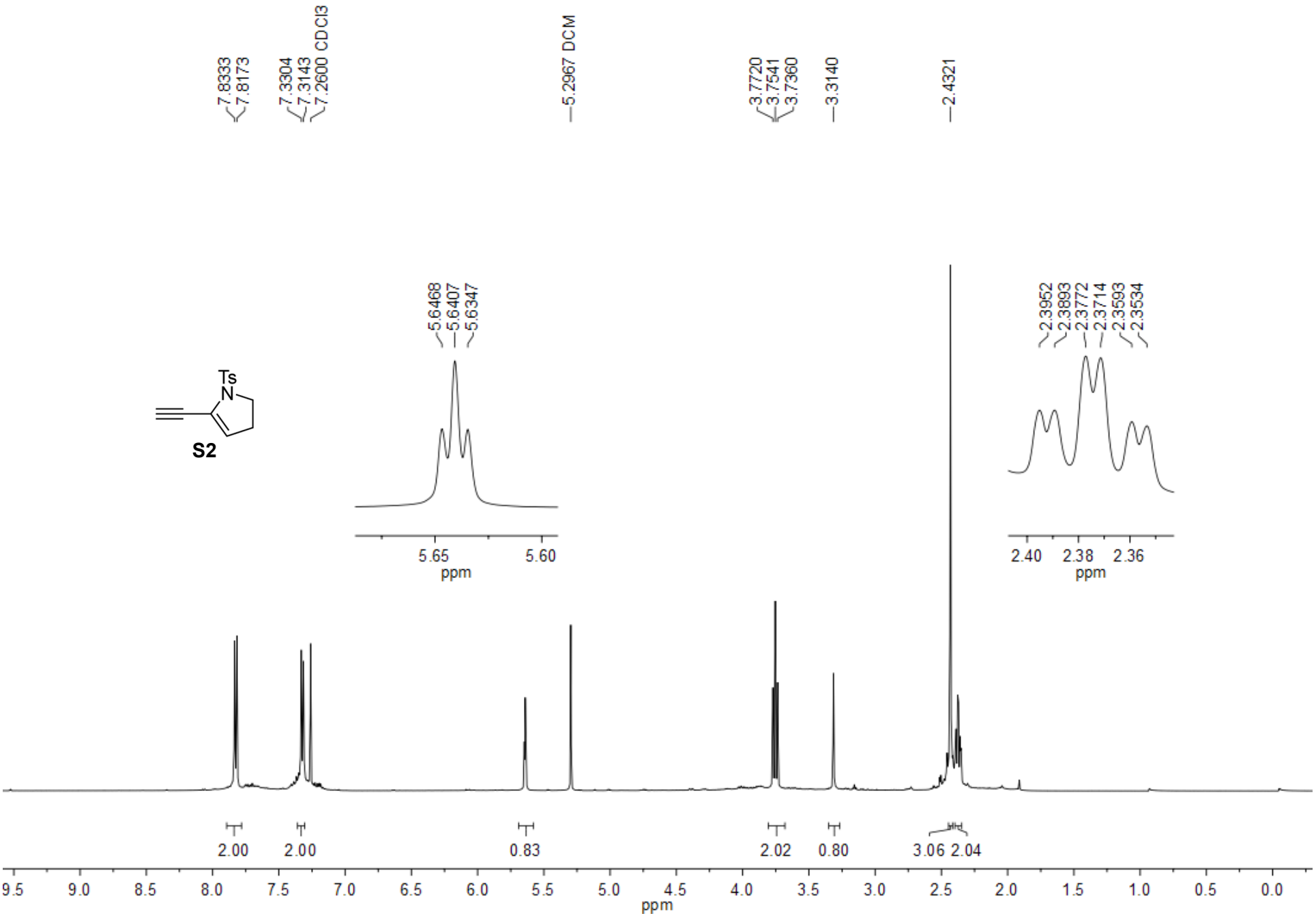
To a solution of **7b** (50 mg, 0.12 mmol, 1 eq) in dry THF (2 mL) at rt was added KOtBu (21 mg, 0.18 mmol,1.5 eq). The solution was stirred for 80 mins at the same temperature and then quenched with dropwise addition of sat. NH_4Cl. It was diluted with DCM (10 mL) and the organic layer was collected. The aqueous layer was washed with DCM (2×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, and quickly concentrated *in vacuo* (T ~ 25 °C) to obtain an oil which was purified through flash chromatography (11 g silica, 15% ethyl acetate/hexanes (v/v)) to obtain unstable **S2** as a colorless oil (18 mg, 60 %) which started turning black upon concentration immediately, likely due to polymerization. R_f = 0.47 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.83 (d, *J* = 6.4 Hz, 2H), 7.32 (d, *J* = 6.4 Hz, 2H), 5.64 (t, *J* = 3.0 Hz, 1H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.31 (s, 1H), 2.43 (s, 3H), 2.37 (dt, *J* = 7.2, 2.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ= 144.08, 133.70, 129.77, 128.29, 124.75, 124.32, 82.94, 74.64, 49.55, 28.42, 21.75. MS (ESI): Calcd for $C_{13}H_{14}NO_2S$ $[MH]^+$: 248.1, found: 248.1 $[MH]^+$, 265.1 (calcd: 265.1) $[M+NH_4]^+$, 512.1 (calcd: 512.1) $[2M+NH_4]^+$.



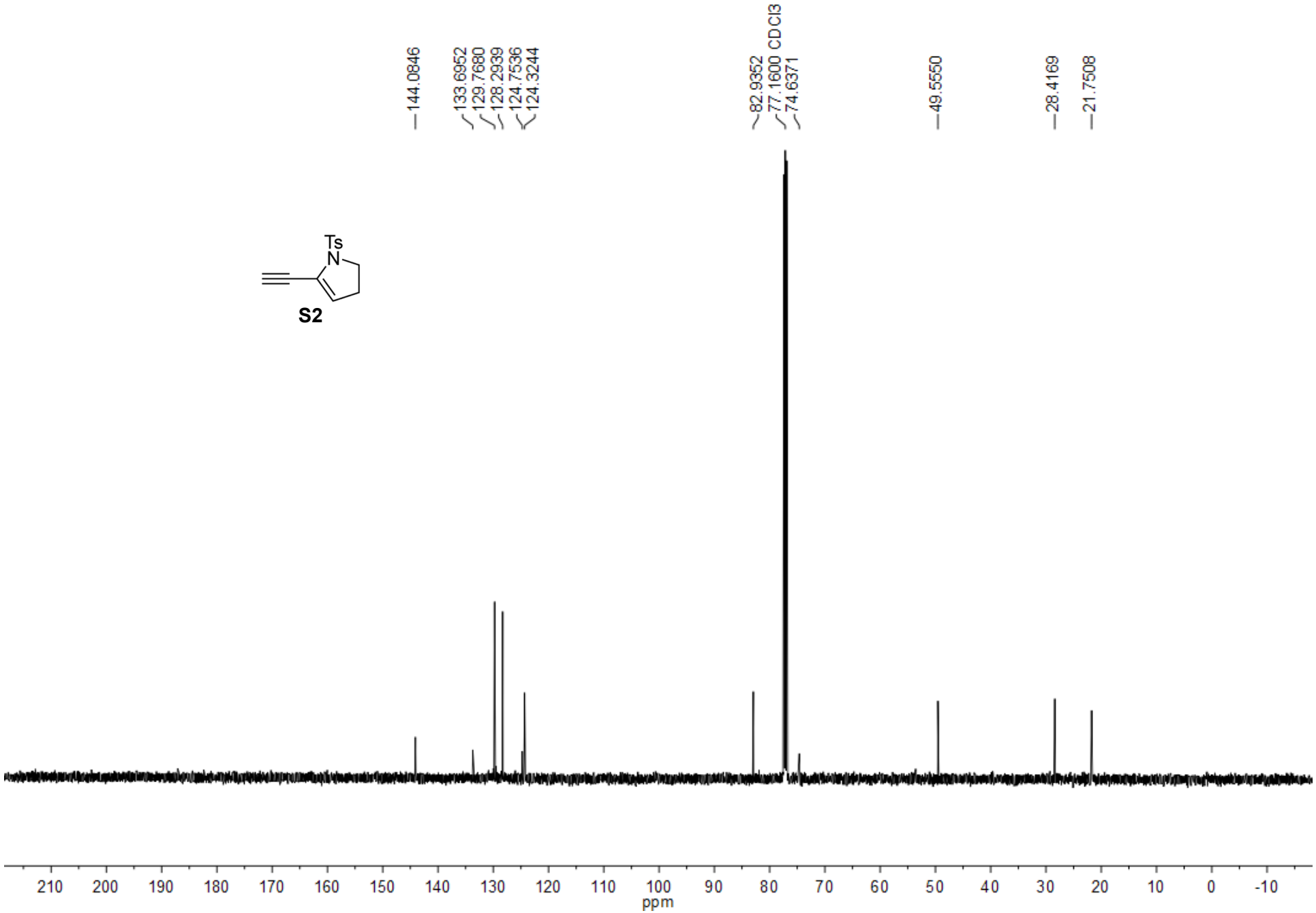
S3

To a solution of **11b** (20 mg, 0.05 mmol, 1 eq) in dry THF (2 mL) at 0 °C was added KOtBu (23.2 mg, 0.21 mmol, 4 eq) and the light-yellow solution was stirred at the same temperature for 15 mins. The reaction was quenched with water, diluted with DCM (10 mL), and the organic layer was collected. The aqueous layer was washed with DCM (2×5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified through flash chromatography (5 g silica, 20% ethyl acetate/hexanes (v/v)) to obtain unstable crude **S3,** a colorless oil, as a mixture of diastereomers (7.1 mg, 45 %). R_f = 0.20 (20% EtOAc/hexanes, visualized w/ UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.73 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 5.46 (s, 1H), 5.26 (m, 1H), 2.94 (m, 2H), 2.41 (s, 3H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.76 (m, 2H), 1.10 (4×s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ= 197.61, 194.68, 145.11, 143.43, 136.94, 134.19, 129.90, 129.76, 127.37, 127.08, 97.35, 42.60, 42.21, 36.68, 36.36, 35.58, 25.64, 25.28, 21.54, 21.28, 19.34, 18.77. ^{13}C DEPT-135 NMR (126 MHz, $CDCl_3$): δ = (up) 129.85, 129.71, 127.32, 127.01, 97.30, 36.31, 21.49, 19.29, 18.71 (down) 42.55, 42.16, 36.63, 35.53, 25.59, 25.22. MS (ESI): Calcd for $C_{16}H_{22}NO_3S$ $[MH]^+$: 308.1, found: 308.1 $[MH]^+$, 325.1 (calcd: 325.1) $[M+NH_4]^+$, 330.1 (calcd: 330.1) $[M+Na]^+$, 632.1 (calcd: 632.1) $[2M+NH_4]^+$.

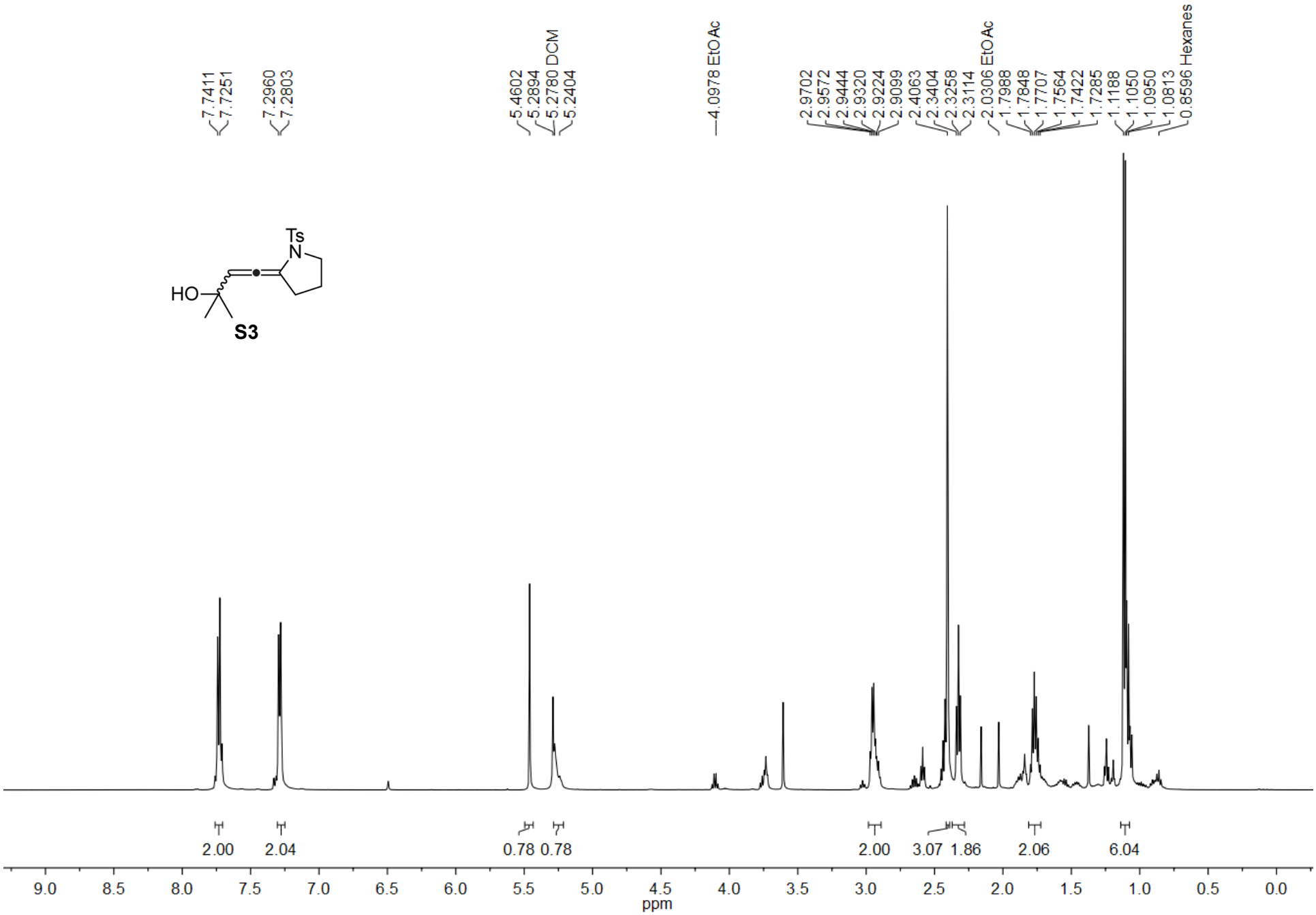
^{1}H NMR (500 MHz)



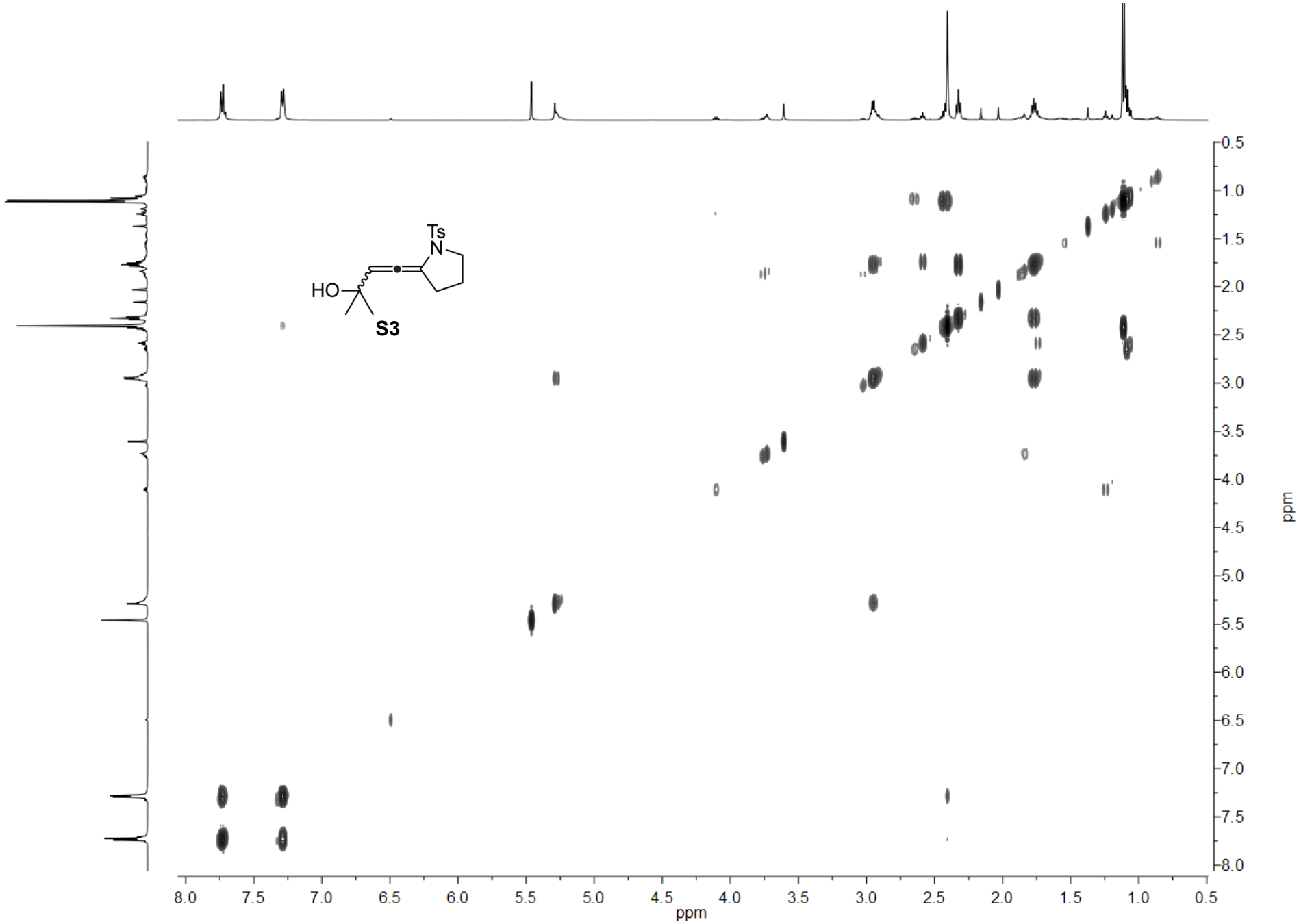
^{13}C NMR (126 MHz)



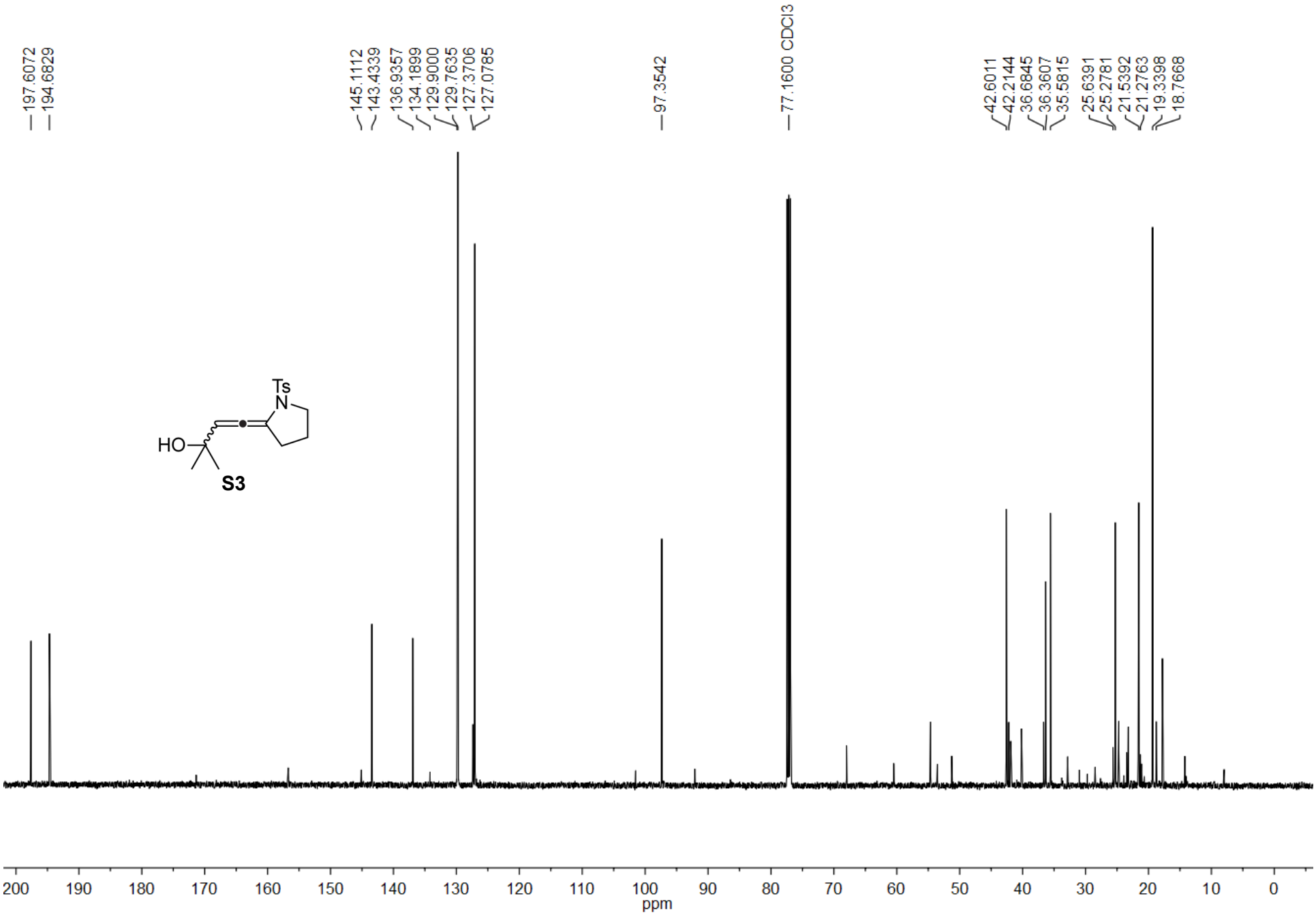
^{1}H NMR (500 MHz)



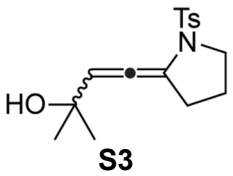
COSY NMR (500 MHz)



^{13}C NMR (126 MHz)



^{13}C-DEPT135 NMR (126 MHz)



References:

(1) Clark, W.; Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43* (14), 2923–2925.

(2) Lu, H.; Li, C. *Org. Lett.* **2006**, *8* (23), 5365–5367.