

4- π -Photocyclization of 1,2-Dihydropyridazines: An Approach to Bicyclic 1,2-Diazetidines with Rich Synthetic Potential

Supporting Information

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1. Synthetic Procedures and Analytical Data of New Compounds

1.1 General Information

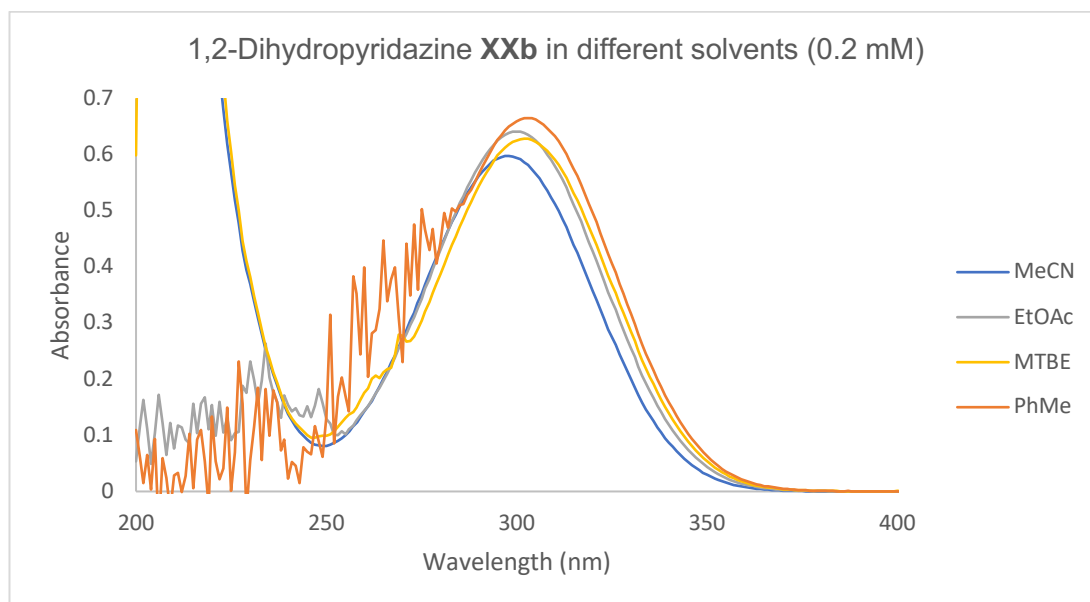
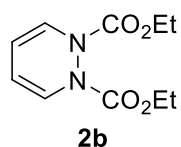
Reagents were purchased in the highest purity available from Acros Organics, Alfa Aesar or Sigma Aldrich. Anhydrous solvents used in reactions were purchased from Acros Organics equipped with AcroSeal™ and all other solvents used were of reagent grade. Reaction vessels were oven dried and cooled under an argon atmosphere prior to use and experiments were performed under argon gas. Reactions were monitored by thin-layer chromatography (TLC) and/or ¹H NMR spectroscopic analysis. Photochemical reactions were performed using a Rayonet RPR-100 Photochemical batch reactor.

Analytical TLC was carried out using Merck pre-coated aluminum-backed TLC silica gel plates (silica gel 60 F₂₅₄) and the plates were visualised by UV light (254 nm) and by staining with either potassium permanganate or aqueous acidic ammonium molybdate(IV). Normal phase flash column chromatography on silica gel was carried out using silica gel from VWR (40-63 microns).

¹H NMR spectroscopic data were obtained on either 300 or 400 MHz instruments and ¹³C{¹H} NMR data were obtained at 100 MHz (Bruker Ultrashield 400 Plus) at 298 K unless otherwise specified. The chemical shifts are reported in parts per million (δ) relative to residual CHCl₃ (δ_H = 7.26 ppm) and CDCl₃ (δ_C = 77.16 ppm, central line), residual *d*₅-DMSO (δ_H = 2.50 ppm) and *d*₆-DMSO (δ_C = 39.52 ppm, central line). The assignment of the signals in the ¹H and ¹³C NMR spectra was achieved through 2D-NMR techniques: COSY, HSQC and HMBC. Coupling constants (*J*) are quoted in Hertz. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer. Melting points were performed on a Sanyo Gallenkamp capillary melting point apparatus and are uncorrected. High resolution mass spectrometry data were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Shimadzu LCMS-IT-TOF mass spectrometer. UV/Vis spectra were recorded using an Agilent Cary 60 UV-Vis spec spectrophotometer. For X-ray crystallography a suitable crystal was selected and mounted on a Mitegen loop using Paratone-N oil on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 100.2(5) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT structure solution program using direct methods and refined with the ShelXL refinement package using least squares minimisation.^{2,3} Figures and tables were prepared using Olex2 software.¹

Bicycles **2b** and **16** were submitted for thermal stability analysis (Process Safety Group, Pharmaceutical Technology and Development, AstraZeneca, Macclesfield, U. K.) using a Mettler differential scanning calorimeter (DSC). The sample crucible together with a reference crucible was heated to 500°C at 5K /minute. Any heat generation (exotherm) or heat absorption (endotherm) was observed as a deviation from the baseline. Exothermic events that exceed 800 J/g were considered to indicate potential explosive properties.

1.2 UV/Vis data for 1,2-Dihydropyridazine **2b**



Entry	Solvent	Cut-off Wavelength (nm)	λ_{max} (nm)
1	MeCN	190	298
2	MTBE	210	302
3	EtOAc	255	300
4	PhMe	285	303
5	Acetone	330	327

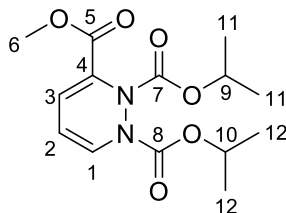
Table 1.1

1.3 General Procedure for 4- π -Photocyclization

A solution of 1,2-dihydropyridazine in either MeCN or PhMe (0.05 M/ 50 mM) was purged with argon for 15 minutes, then irradiated at room temperature ($\lambda = 350$ nm) until complete consumption of starting material (24-44 hours). The solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography using an appropriate solvent system, as described for each individual procedure.

1.4 Synthetic Procedures

3-Methyl 1,2-dipropan-2-yl pyridazine-1,2,3-tricarboxylate **S1**



A solution of methyl 2-oxo-2*H*-pyran-3-carboxylate (697 mg, 4.52 mmol) and diisopropyl azodicarboxylate (890 μ L, 4.52 mmol) in toluene (10 mL) was heated at 100 °C for 48 h. After cooling to room temperature, the resulting solution was evaporated to give the crude product. Purification by flash column chromatography on silica gel (eluent CH₂Cl₂-Et₂O; 95:5) gave dihydropyridazine **S1** (575 mg, 1.84 mmol, 41%) as a pale yellow oil.

R_f (CH₂Cl₂-Et₂O, 95:5) = 0.20

¹H NMR (298 K; 400 MHz, *d*₆-DMSO): δ 7.33 (br d, J = 7.0 Hz, 1H, **H1** or **H3**), 7.08-6.83 (br m, 1H, **H1** or **H3**), 5.92-5.81 (br m, 1H, **H2**), 4.93 (sept, J = 6.2 Hz, 1H, **H9** or **H10**), 4.84 (sept, J = 6.2 Hz, 1H, **H9** or **H10**), 3.73 (s, 3H, **H6**), 1.25 (d, J = 6.2 Hz, 6H, **H11** or **H12**), 1.15 (d, J = 6.2 Hz, 6H, **H11** or **H12**).

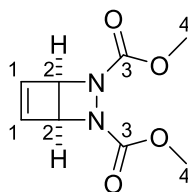
¹H NMR (348 K; 400 MHz, *d*₆-DMSO): δ 7.29 (d, J = 7.0 Hz, 1H, **H1** or **H3**), 6.95 (d, J = 5.6 Hz, 1H, **H1** or **H3**), 5.86 (dd, J = 7.0, 5.6 Hz, 1H, **H2**), 4.95 (sept, J = 6.2 Hz, 1H, **H9** or **H10**), 4.86 (sept, J = 6.2 Hz, 1H, **H9** or **H10**), 3.74 (s, 3H, **H6**), 1.28 (d, J = 6.2 Hz, 6H, **H11** or **H12**), 1.27 (d, J = 6.2 Hz, 6H, **H11** or **H12**), 1.19 (d, J = 6.2 Hz, 6H, **H11** or **H12**), 1.18 (d, J = 6.2 Hz, 6H, **H11** or **H12**).

¹³C NMR (348 K; 100 MHz, *d*₆-DMSO): δ 161.8 (**C5**), 153.9 (**C7** or **C8**), 150.6 (**C7** or **C8**), 133.1 (**C1** or **C3**), 126.0 and 124.7 (**C4**, and **C1** or **C3**), 108.2 (**C2**), 70.8 (**C9** or **C10**), 70.7 (**C9** or **C10**), 51.4 (**C6**), 21.15 (**C11** or **C12**), 21.13 (**C11** and **C12**), 20.96 (**C11** or **C12**).

FTIR (ATR) ν (cm⁻¹): 2984, 1716 (C=O).

HRMS (ESI): m/z calculated for: C₁₄H₂₀N₂O₆ [M+H]⁺ 313.1394, found 313.1406.

Dimethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate **2a**^{4,5}



Using the general procedure, a solution of 1,2-dihydropyridazine **1a** (140 mg, 0.71 mmol) in MeCN (14 mL) was irradiated for 44 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1→2:1) gave the bicycle **2a** (61 mg, 0.31 mmol, 44%) as an off-white solid.

R_f (Hexane-EtOAc, 2:1) = 0.10

mp = 76-78 °C

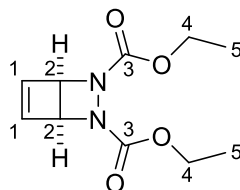
^1H NMR (400 MHz, CDCl_3): δ 6.74-6.71 (m, 2H, **H1**), 5.21-5.18 (m, 2H, **H2**), 3.81 (s, 6H, **H4**).

^{13}C NMR (100 MHz, CDCl_3): δ 160.6 (**C3**), 143.7 (**C1**), 67.4 (**C2**), 53.7 (**C4**).

FTIR (ATR) ν (cm^{-1}): 2961, 1743 (C=O), 1720 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ 221.0533, found 221.0532.

Diethyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate **2b**⁶



Using the general procedure, a solution of 1,2-dihydropyridazine **1b** (170 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 7:1→4:1) gave the bicycle **2b** (121 mg, 0.54 mmol, 71%) as a pale yellow oil.

R_f (Hexane-EtOAc, 1:1) = 0.29

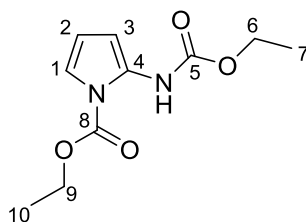
^1H NMR (400 MHz, CDCl_3): δ 6.74-6.71 (m, 2H, **H1**), 5.20-5.17 (m, 2H, **H2**), 4.30-4.19 (m, 4H, **H4**), 1.30 (t, J = 7.1 Hz, 6H, **H5**).

^{13}C NMR (100 MHz, CDCl_3): δ 160.1 (**C3**), 143.6 (**C1**), 67.3 (**C2**), 62.8 (**C4**), 14.6 (**C5**).

FTIR (ATR) ν (cm^{-1}): 2984, 2935, 1746 (C=O), 1703 (C=O).

HRMS (APCI): m/z calculated for: $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 227.1026, found 227.1019.

Ethyl 2-[(ethoxycarbonyl)amino]-1H-pyrrole-1-carboxylate **3b**



R_f (Hexane-EtOAc, 1:1) = 0.57

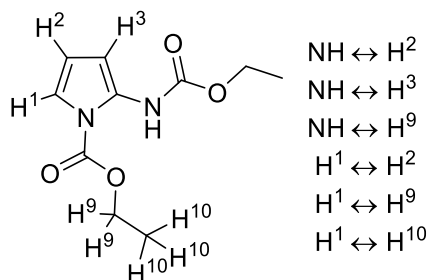
^1H NMR (400 MHz, d_6 -DMSO): δ 8.92 (br s, 1H, **NH**), 7.07 (dd, J = 3.6, 1.9 Hz, 1H, **H1**), 6.15 (t, J = 3.6 Hz, 1H, **H2**), 6.10-6.06 (br m, 1H, **H3**), 4.32 (q, J = 7.1 Hz, 2H, **H9**), 4.08 (q, J = 7.1 Hz, 2H, **H6**), 1.30 (t, J = 7.1 Hz, 3H, **H10**), 1.20 (t, J = 7.1 Hz, 3H, **H7**).

^{13}C NMR (100 MHz, d_6 -DMSO): δ 154.1 (**C5**), 150.0 (**C8**), 128.1 (**C4**), 117.3 (**C1**), 110.1 (**C2**), 105.3 (**C3**), 63.4 (**C9**), 60.6 (**C6**), 14.5 (**C7**), 13.9 (**C10**).

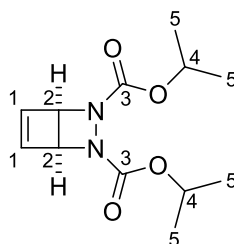
FTIR (ATR) ν (cm^{-1}): 3345 (NH), 3145 (NH), 2980, 1718 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 227.1026, found 227.1024.

Important NOE Contacts (d_6 -DMSO):



Diisopropyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate **2c**



Using the general procedure, a solution of 1,2-dihydropyridazine **1c** (191 mg, 0.75 mmol) in MeCN (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave the bicycle **2c** (159 mg, 0.63 mmol, 83%) as an off-white solid.

R_f (Hexane-EtOAc, 1:1) = 0.35

mp = 48-50 °C

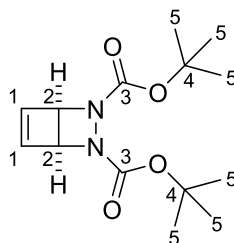
^1H NMR (400 MHz, CDCl_3): δ 6.72-6.69 (m, 2H, **H1**), 5.17-5.14 (m, 2H, **H2**), 5.00 (sept, J = 6.3 Hz, 2H, **H4**), 1.29-1.27 (m, 12H, **H5**).

^{13}C NMR (100 MHz, CDCl_3): δ 159.7 (**C3**), 143.5 (**C1**), 70.6 (**C4**), 67.1 (**C2**), 21.1 (**C5**), 21.1 (**C5**).

FTIR (ATR) ν (cm^{-1}): 2988, 2939, 1698 (C=O).

HRMS (APCI): m/z calculated for: $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ 277.1159, found 277.1147.

Di-*tert*-butyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate **2d**



Using the general procedure, a solution of 1,2-dihydropyridazine **1d** (212 mg, 0.75 mmol) in MeCN (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave the bicycle **2d** (171 mg, 0.61 mmol, 81%) as an off-white solid.

0.85 grams: Using general procedure A, a solution of 1,2-dihydropyridazine **1d** (0.85 g, 3.00 mmol) in MeCN (60 mL, 1 x 60 mL tube) was irradiated for 48 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave the bicycle **2d** (0.69 g, 2.45 mmol, 82%) as an off-white solid.

$$R_f \text{ (Hexane-EtOAc, 1:1)} = 0.46$$
¹H NMR (400 MHz, CDCl₃): δ 6.72-6.69 (m, 2H, **H1**), 5.10-5.07 (m, 2H, **H2**), 1.49 (s, 18H, **H5**).

FTIR (ATR) ν (cm^{-1}): 2982, 2937, 1694 (C=O).

HRMS (APCI): m/z calculated for: $C_{14}H_{22}N_2O_4$ $[M+Na]^+$ 305.1472, found 305.1464.

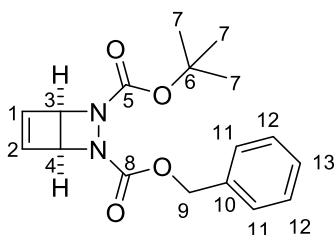
$$R_f \text{ (Hexane-EtOAc, 2:1)} = 0.28$$

¹³C NMR (100 MHz, CDCl₃): δ 159.9 (**C3**), 143.6 (**C1**), 135.7 (**C5**), 128.6 (**C6** or **C7**), 128.4 (**C8**), 128.2 (**C6** or **C7**), 68.2 (**C4**), 67.4 (**C2**).

FTIR (ATR) ν (cm^{-1}): 3032, 2954, 1703 (C=O).

HRMS (ESI): m/z calculated for: $C_{20}H_{18}N_2O_4$ $[M+Na]^+$ 373.1159, found 373.1142.

Benzyl *tert*-butyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate **2f**



Using the general procedure, a solution of 1,2-dihydropyridazine **1f** (237 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1→7:1) gave the bicycle **2f** (179 mg, 0.57 mmol, 75%) as a colourless oil.

R_f (Hexane-EtOAc, 2:1) = 0.26

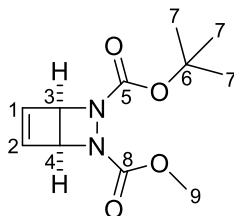
^1H NMR (400 MHz, CDCl_3): δ 7.39-7.31 (m, 5H, **H11**, **H12**, **H13**), 6.70-6.69 (m, 1H, **H1** or **H2**), 6.67-6.65 (m, 1H, **H1** or **H2**), 5.25-5.21 (m, 2H, **H9**), 5.18-5.16 (m, 1H, **H3** or **H4**), 5.13-5.11 (m, 1H, **H3** or **H4**), 1.46 (s, 9H, **H7**).

^{13}C NMR (100 MHz, CDCl_3): δ 159.9 (**C8**), 158.9 (**C5**), 143.5 (**C1** or **C2**), 143.5 (**C1** or **C2**), 135.8 (**C10**), 128.6 (**C11** or **C12**), 128.4 (**C13**), 128.2 (**C11** or **C12**), 82.4 (**C6**), 68.0 (**C9**), 67.1, (**C3** or **C4**), 67.1 (**C3** or **C4**), 28.2 (**C7**).

FTIR (ATR) ν (cm^{-1}): 2978, 2932, 1735 (C=O), 1702 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ 339.1315, found 339.1310.

tert*-Butyl methyl 2,3-diazabicyclo[2.2.0]hex-5-ene-2,3-dicarboxylate **2g*



Using the general procedure, a solution of 1,2-dihydropyridazine **1g** (180 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 24 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1) gave the bicycle **2g** (146 mg, 0.61 mmol, 81%) as an off-white solid.

R_f (Hexane-EtOAc, 2:1) = 0.18

mp = 79-81 °C

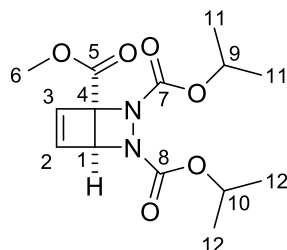
^1H NMR (400 MHz, CDCl_3): δ 6.74-6.72 (m, 1H, **H1** or **H2**), 6.70-6.69 (m, 1H, **H1** or **H2**), 5.17-5.16 (m, 1H, **H3** or **H4**), 5.12-5.10 (m, 1H, **H3** or **H4**), 3.79 (s, 3H, **H9**), 1.49 (s, 9H, **H7**).

^{13}C NMR (100 MHz, CDCl_3): δ 160.6 (**C8**), 158.9 (**C5**), 143.6 (**C1** or **C2**), 143.4 (**C1** or **C2**), 82.5 (**C6**), 67.2 (**C3** or **C4**), 67.0 (**C3** or **C4**), 53.6 (**C9**), 28.3 (**C7**).

FTIR (ATR) ν (cm^{-1}): 2978, 2932, 1735 (C=O), 1702 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ 263.1002, found 263.0991.

1-Methyl 2,3-dipropan-2-yl 2,3-diazabicyclo[2.2.0]hex-5-ene-1,2,3-tricarboxylate 2h



Using the general procedure, a solution of 1,2-dihydropyridazine **1h** (234 mg, 0.75 mmol) in PhMe (15 mL) was irradiated for 12 hours to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 2:1) gave the bicycle **2h** (185 mg, 0.59 mmol, 80%) as a yellow oil. R_f (Hexane-EtOAc, 2:1) = 0.25

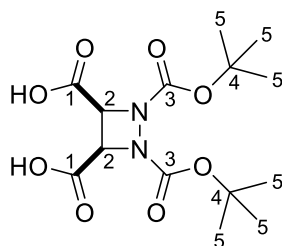
¹H NMR (400 MHz, CDCl₃): δ 6.85 (d, *J* = 2.6 Hz, 1H, **H3**), 6.71 (dd, *J* = 3.3 Hz, 2.6 Hz, 1H, **H2**), 5.14 (d, *J* = 3.3 Hz, 1H, **H1**), 5.06-4.93 (m, 2H, **H9** and **H10**), 3.79 (s, 3H, **H6**), 1.30-1.25 (m, 12H, **H11** and **H12**).

¹³C NMR (100 MHz, CDCl₃): δ 166.0 (**C6**), 159.2 and 158.6 (**C7** and **C8**), 143.8 and 142.0 (**C2** and **C3**), 74.0 (**C4**), 71.17 and 71.12 (**C9** and **C10**), 67.7 (**C1**), 53.0 (**C6**), 22.05 and 21.99 (**C11** and **C12**).

FTIR (ATR) ν (cm^{-1}): 2978, 2932, 1735 (C=O), 1702 (C=O).

HRMS (ESI): m/z calculated for: $C_{14}H_{21}N_2O_6$ $[M+Na]^+$ 313.1394, found 313.1386.

1,2-Bis(*tert*-butoxycarbonyl)-1,2-diazetidene-3,4-dicarboxylic acid 4



An aqueous 10% NaIO₄ solution (20 mL) was added dropwise to a stirred solution of bicyclic 1,2-diazetidene **2d** (402 mg, 1.42 mmol, 1.0 eq) and RuO₂.xH₂O (2 mg, 0.01 mmol, 0.01 eq) in EtOAc (14 mL) at 0 °C, then stirred at room temperature for 41 hours. The organic layer was separated, the aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 10 mL). Isopropanol (2 mL) was added to the combined organic layers and left to stand for 2 hours. The organic layer was dried (MgSO₄), filtered through Celite and evaporated under reduced pressure to give diacid **4** (374 mg, 1.08 mmol, 76%) as a grey solid, which was used without further purification.

R_f (CH₂Cl₂-MeOH, 9:1) = baseline

mp = 168-170 °C (decomposition)

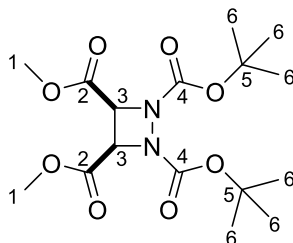
¹H NMR (400 MHz, CDCl₃): δ 10.6 (br s, 2H, **OH**), 5.00 (br s, 2H, **H2**), 1.46 (s, 18H, **H5**).

^{13}C NMR (100 MHz, CDCl_3): δ 170.8 (**C1**), 158.4 (**C3**), 84.2 (**C4**), 61.6 (**C2**), 28.0 (**C5**).

FTIR (ATR) ν (cm^{-1}): 3078 (OH), 2980, 2935, 1718 ($\text{C}=\text{O}$).

HRMS (ESI): m/z calculated for: $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_8$ $[\text{M}+\text{Na}]^+$ 369.1268, found 369.1254.

1,2-Di-*tert*-butyl 3,4-dimethyl 1,2-diazetidene-1,2,3,4-tetracarboxylate **5**



An aqueous 10% NaIO_4 solution (20 mL) was added dropwise to a stirred solution of bicyclic 1,2-diazetidene **2d** (402 mg, 1.42 mmol, 1.0 eq) and $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ (2 mg, 0.01 mmol, 0.01 eq) in EtOAc (14 mL) at 0 °C, then stirred at room temperature for 72 hours. The organic layer was separated and the aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 10 mL). Isopropanol (2 mL) was added to the combined organic layers and left to stand for 2 hours. The organic layer was dried (MgSO_4), filtered through Celite and evaporated under reduced pressure to give the crude diacid **4**, which was taken up in MeOH (10 mL). (Trimethylsilyl)diazomethane (2 M solution in hexanes, 2.1 mL, 4.26 mmol, 3 eq) was added dropwise to the resulting stirred solution of diacid **4** at room temperature, and the resulting mixture was stirred for 10 minutes. The solvent was removed under reduced pressure. The residue was dissolved in CHCl_3 (20 mL), washed with a saturated solution of sodium thiosulfate (10 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1) gave the diester **5** as a colourless film (389 mg, 1.04 mmol, 73% over two steps).

R_f (Hexane-EtOAc, 1:1) = 0.48

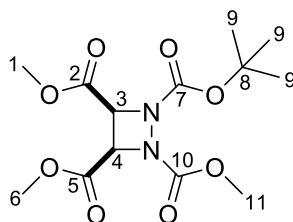
^1H NMR (400 MHz, CDCl_3): δ 4.94 (s, 2H, **H3**), 3.76 (s, 6H, **H1**) 1.46 (s, 18H, **H6**).

^{13}C NMR (100 MHz, CDCl_3): δ 167.7 (**C2**), 158.0 (**C4**), 83.2 (**C5**), 61.4 (**C3**), 52.9 (**C1**), 28.1 (**C6**).

FTIR (ATR) ν (cm^{-1}): 2980, 1752 ($\text{C}=\text{O}_{\text{ester}}$), 1709 ($\text{C}=\text{O}_{\text{carbamate}}$).

HRMS (ESI): m/z calculated for: $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_8$ $[\text{M}+\text{Na}]^+$ 397.1581, found 397.1585; $[2\text{M}+\text{Na}]^+$ 771.3271, found 771.3271.

1-*tert*-Butyl 2,3,4-trimethyl 1,2-diazetidene-1,2,3,4-tetracarboxylate **6**



An aqueous 10% NaIO_4 solution (5 mL) was added dropwise to a stirred solution of bicyclic 1,2-diazetidene **2d** (117 mg, 0.49 mmol, 1.0 eq) and $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ (3 mg, 0.02 mmol, 0.04 eq) in EtOAc (5

mL) at 0 °C, then stirred at room temperature for 72 hours. The organic layer was separated, the aqueous layer was saturated with NaCl and extracted with EtOAc (5 x 10 mL). Isopropanol (2 mL) was added to the combined organic layers and left to stand for 2 hours. The organic layer was dried (MgSO₄), filtered through Celite and evaporated under reduced pressure to give diacid **6** as a grey solid, which was used in the next step without further purification. (Trimethylsilyl)diazomethane (2M solution in hexanes, 2.0 mL, 2.00 mmol, 4.1 eq) was added dropwise to a stirred solution of diacid **6** in MeOH (5 mL) at room temperature, then stirred for 10 minutes. The solvent was removed under reduced pressure. The residue was dissolved in CHCl₃ (2 mL), washed with a saturated solution of sodium thiosulfate (5 mL), dried (Na₂SO₄) and the solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 1:1) gave the diester **6** as a colourless oil (162 mg, 0.37 mmol, 75% over two steps).

R_f (Hexane-EtOAc, 1:1) = 0.35

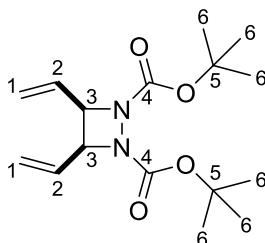
¹H NMR (400 MHz, CDCl₃): δ 5.04-4.98 (m, 2H, **H3** and **H4**), 3.81 (s, 3H, **H11**), 3.78 (s, 6H, **H1** and **H6**), 1.47 (s, 9H, **H9**).

¹³C NMR (100 MHz, CDCl₃): δ 167.5 (**C2** and **C5**), 160.0 (**C10**), 157.7 (**C7**), 83.7 (**C8**), 61.8 (**C3** or **C4**), 61.4 (**C3** or **C4**), 54.0 (**C11**), 53.1 (**C1** or **C6**), 53.0 (**C1** or **C6**), 28.1 (**C9**).

FTIR (ATR) ν (cm⁻¹): 2958, 1735 (C=O).

HRMS (ESI): m/z calculated for: C₁₃H₂₀N₂O₈ [M+Na]⁺ 355.1112, found 355.1117.

Di-*tert*-butyl 3,4-diethenyl-1,2-diazetidine-1,2-dicarboxylate **7**



Ethylene was bubbled (10 s) through a stirred solution of bicyclic 1,2-diazetidine **2g** (44 mg, 0.18 mmol, 1.0 eq) and Hoveyda-Grubbs 2nd generation catalyst (6 mg, 0.01, 0.04 eq) in CH₂Cl₂ (2 mL) at room temperature under nitrogen. The reaction was stirred at room temperature under ethylene atmosphere for 30 mins then the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 5:1) gave the 1,2-diazetidine **7** (42 mg, 0.14 mmol, 76%) as a colourless oil.

R_f (Hexane-EtOAc, 5:1) = 0.28

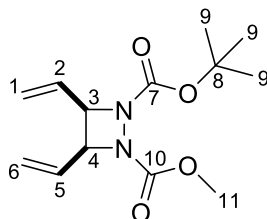
¹H NMR (400 MHz, CDCl₃): δ 5.92-5.80 (m, 2H, **H2**), 5.39-5.33 (m, 4H, **H1**), 4.89-4.84 (m, 2H, **H3**), 1.45 (s, 18H, **H6**).

¹³C NMR (100 MHz, CDCl₃): δ 158.7 (**C5**), 132.5 (**C2**), 120.8 (**C1**), 82.0 (**C5**), 66.6 (**C3**), 28.3 (**C6**).

FTIR (ATR) ν (cm⁻¹): 2978, 1703 (C=O).

HRMS (ESI): m/z calculated for: C₁₆H₂₆N₂O₄ [M+]⁺ 333.1785, found 333.1783.

tert*-Butyl methyl 3,4-diethenyl-1,2-diazetidine-1,2-dicarboxylate **8*



Ethylene was bubbled (10 s) through a stirred solution of bicyclic 1,2-diazetidine **2d** (50 mg, 0.18 mmol, 1.0 eq) and Hoveyda-Grubbs 2nd generation catalyst (6 mg, 0.01, 0.04 eq) in CH₂Cl₂ (2 mL) at room temperature under nitrogen. The reaction was stirred at room temperature under ethylene atmosphere for 1 h, after which time further catalyst (6 mg) was added. After stirring for a further 1 h, the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 5:1→3:1) gave the 1,2-diazetidine **8** (39 mg, 0.15 mmol, 79%) as a colourless oil.

R_f (Hexane-EtOAc, 3:1) = 0.24

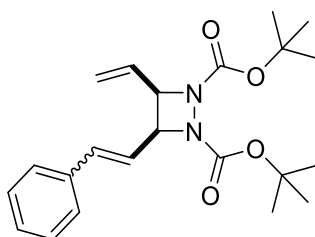
¹H NMR (400 MHz, CDCl₃): δ 5.90-5.79 (m, 2H, **H**), 5.44-5.34 (m, 4H, **H**), 4.98-4.89 (m, 2H, **H**), 3.76 (s, 3H, **H11**), 1.46 (s, 9H, **H9**).

¹³C NMR (100 MHz, CDCl₃): δ 160.2 (**C10**), 158.5 (**C7**), 132.3 (**C2** or **C5**), 131.9 (**C2** or **C5**), 121.0 (**C1** and **C6**), 82.3 (**C8**), 67.0 (**C3** or **C4**), 66.7 (**C3** or **C4**), 53.3 (**C11**), 28.3 (**C9**).

FTIR (ATR) ν (cm⁻¹): 2980, 1709 (C=O).

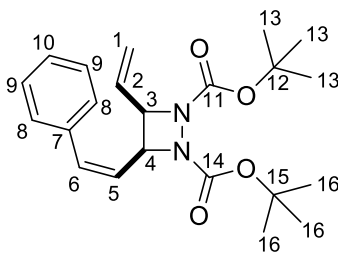
HRMS (ESI): m/z calculated for: C₁₃H₂₀N₂O₄ [M+]⁺ 291.1315, found 291.1306.

Di-*tert*-butyl 3-ethenyl-4-[(*E/Z*)-2-phenylethenyl]-1,2-diazetidine-1,2-dicarboxylate **9a,b**



Styrene (61 μ L, 0.53 mmol, 5.0 eq) was added in one portion to a stirred solution of bicyclic 1,2-diazetidine **2d** (30 mg, 0.11 mmol, 1.0 eq) and Hoveyda-Grubbs 2nd generation catalyst (3 mg, 0.01, 0.05 eq) in CH₂Cl₂ at room temperature under argon, then heated at reflux for 1 hour. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 11:1→7:1) gave the 1,2-diazetidine **9a,b** (30 mg, 0.08 mmol, 73%, *E:Z* 1.0:1.5) as a light brown oil.

Z-isomer 9a



R_f (Hexane-EtOAc, 2:1) = 0.48

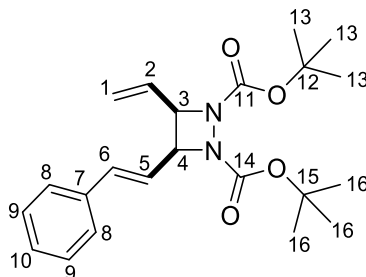
^1H NMR (400 MHz, CDCl_3): δ 7.36-7.28 (m, 3H, **H9** and **H10**), 7.21-7.19 (m, 2H, **H8**), 6.80 (d, J = 11.5 Hz, 1H, **H6**), 5.99-5.84 (m, 2H, **H2** and **H5**), 5.47-5.36 (m, 3H, **H1A**, **H1B** and **H4**), 4.89-4.85 (m, 1H, **H3**), 1.47 (br s, 9H, **H13**), 1.44 (br s, 9H, **H16**).

^{13}C NMR (100 MHz, CDCl_3): δ 159.2 (**C11**), 158.2 (**C14**), 135.8 (**C7**), 135.0 (**C6**), 132.3 (**C2**), 128.7 (**C8**), 128.5 (**C9**), 127.9 (**C10**), 126.1 (**C5**), 120.6 (**C1**), 82.1 (**C12** and **C15**), 66.8 (**C3**), 61.9 (**C4**), 28.3 (**C13** or **C16**), 28.3 (**C13** or **C16**).

FTIR (ATR) ν (cm^{-1}): 2978, 2932, 1702 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ 409.2098, found 409.2096; $[\text{2M}+\text{Na}]^+$ 795.4303, found 795.4299.

E-isomer 9b



R_f (Hexane-EtOAc, 2:1) = 0.44

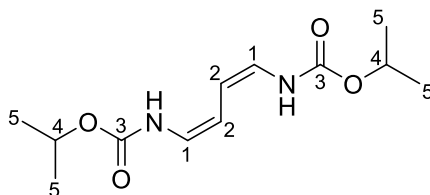
^1H NMR (400 MHz, CDCl_3): δ 7.40-7.25 (m, 5H, **H8**, **H9**, **H10**), 6.65 (d, J = 15.7 Hz, 1H, **H6**), 6.24 (dd, J = 15.7, 8.6 Hz, 1H, **H5**), 5.97-5.88 (m, 1H, **H2**), 5.45-5.34 (m, 2H, **H1A** and **H1B**), 5.07-5.01 (m, 1H, **H4**), 4.97-4.92 (m, 1H, **H3**), 1.48-4.41 (m, 18H, **H13** and **H16**).

^{13}C NMR (100 MHz, CDCl_3): δ 158.9 (**C**), 158.6 (**C**), 136.1 (**C7**), 135.9 (**C6**), 132.5 (**C2**), 128.8 (**C9**), 128.4 (**C10**), 126.9 (**C8**), 123.5 (**C5**), 120.8 (**C1**), 82.1 (**C12** or **C15**), 81.9 (**C12** or **C15**), 66.8 (**C3**), 66.5 (**C4**), 28.3 (**C13** or **C16**), 28.2 (**C13** or **C16**).

FTIR (ATR) ν (cm^{-1}): 2980, 2932, 1709 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_4$ $[\text{M}+\text{Na}]^+$ 409.2098, found 409.2092; $[\text{2M}+\text{Na}]^+$ 795.4303, found 795.4296.

Di-propan-2-yl (1Z,3Z)-buta-1,3-diene-1,4-diylbiscarbamate **11c**



Sml₂ prepared according to a previously reported procedure.⁷ *Note: It was essential for dry THF without stabilisers to be used for the preparation of Sml₂.* A solution of Sml₂ in THF (0.072 M, 13.7 mL, 0.98 mmol, 2.5 eq) was added dropwise to a stirred deoxygenated solution of bicyclic 1,2-diazetidine **2c** (100 mg, 0.39 mmol, 1.0 eq) in THF (2 mL) at room temperature under argon, then stirred at room temperature for 30 minutes. The reaction mixture was purged with air until the colour changed from blue to yellow and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-Et₂O, 1:1) gave diene **11c** (69 mg, 0.27 mmol, 68%) as a white solid.

R_f (Hexane-Et₂O, 1:1) = 0.35

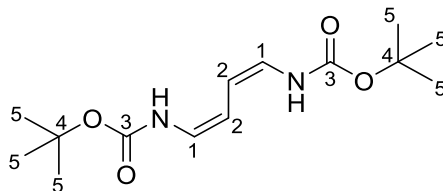
mp = 190-193 °C

¹H NMR (400 MHz, CDCl₃): δ 6.60-6.44 (br m, 4H, **H1** and **H2**), 5.29 (br s, 2H, **NH**), 4.99 (sept, *J* = 6.2 Hz, 2H, **H4**), 4.99 (d, *J* = 6.2 Hz, 12H, **H5**).

¹³C NMR (100 MHz, CDCl₃): δ 153.2 (**C3**), 122.5 (**C1**), 100.6 (**C2**), 69.5 (**C4**), 22.2 (**C5**).

FTIR (ATR) *v* (cm⁻¹): 3278 (NH), 3000, 1690 (C=O), 1623 (C=O).

Di-*tert*-butyl (1Z,3Z)-buta-1,3-diene-1,4-diylbiscarbamate **11d**



Sml₂ prepared according to a previously reported procedure.⁷ *Note: It was essential for dry THF without stabilisers to be used for the preparation of Sml₂.* A solution of Sml₂ in THF (0.075 M, 21.0 mL, 1.57 mmol, 2.2 eq) was added in one portion to a stirred deoxygenated solution of bicyclic 1,2-diazetidine **2d** (202 mg, 0.72 mmol, 1.0 eq) in MeOH (7.2 mL) at room temperature under argon, then stirred at room temperature for 30 minutes. The reaction mixture was purged with air until the colour changed from blue to yellow and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 14:1→9:1) gave diene **11d** (48 mg, 0.17 mmol, 24%) as a white solid.

R_f (Hexane-EtOAc, 2:1) = 0.48

mp = 206-208 °C (decomposition)

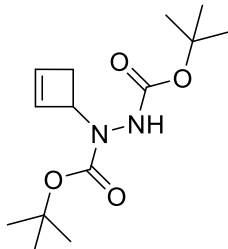
¹H NMR (400 MHz, *d*₆-DMSO): δ 9.07-8.77 (br m, 2H, **NH**), 6.15-6.08 (br m, 2H, **H1**), 5.65-5.54 (br m, 2H, **H2**), 1.43 (br s, 18H, **H5**).

¹³C NMR (100 MHz, *d*₆-DMSO): δ 153.1 (**C3**), 121.0 (**C1**), 102.2 (**C2**), 79.2 (**C4**), 28.0 (**C5**).

FTIR (ATR) ν (cm⁻¹): 3325 (NH), 2980, 2935, 1690 (C=O), 1621 (C=O).

HRMS (ESI): m/z calculated for: C₁₄H₂₄N₂O₄ [M+Na]⁺ 307.1628, found 307.1628.

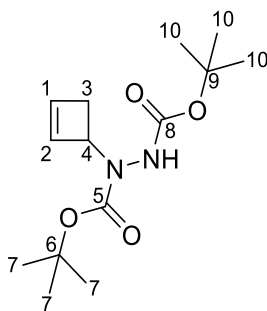
Di-*tert*-butyl 1-(cyclobut-2-en-1-yl)hydrazine-1,2-dicarboxylate **12d**



A solution of bicyclic 1,2-diazetidine **2d** (50 mg, 0.18 mmol, 1.0 eq) in THF (3 mL) was added to liquid ammonia (3 mL) at -78 °C under argon. Sodium metal (41 mg, 1.77 mmol, 10 eq) was added portion wise at -78 °C, then the reaction mixture was warmed to room temperature. The reaction mixture was left at room temperature overnight to remove the ammonia. The residue was dissolved in EtOAc (5 mL), dried (MgSO₄) and the solvent removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 9:1→4:1) gave a mixture of cyclobutene **12d** and diene **13d** (44 mg, 0.16 mmol, 87%, 2.4:1.0 **12d**:**13d**) as a white cloudy oil.

Note: Diene 13d can be isolated as a white solid with careful purification. The purification of cyclobutene 12d always resulted in the presence of diene 13d.

Cyclobutene **12d**



R_f (Hexane-EtOAc, 2:1) = 0.46

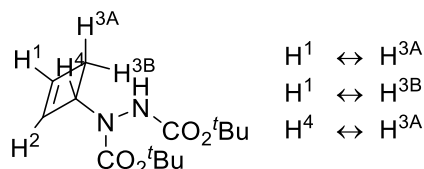
¹H NMR (400 MHz, *d*₆-DMSO): δ 8.92-8.44 (br m, 1H, **NH**), 6.14-6.09 (br m, 1H, **H1**), 5.92-5.83 (br m, 1H, **H2**), 5.06-4.86 (br m, 1H, **H4**), 2.69-2.40 (br m, 2H, **H3A** and **H3B**), 1.43-1.35 (br m, 18H, **H7** and **H10**).

¹³C NMR (100 MHz, *d*₆-DMSO, additional peaks due to rotamers annotated by an asterisk): δ 155.6* (**C5** or **C8**), 155.4 (**C5** or **C8**), 154.0* (**C5** or **C8**), 153.8 (**C5** or **C8**), 137.2 (**C1**), 136.4* (**C2**), 136.2 (**C2**), 80.0* (**C6** or **C9**), 79.6 (**C6** or **C9**), 79.1 (**C6** or **C9**), 56.3* (**C4**), 55.9 (**C4**), 55.6* (**C4**), 36.3 (**C3**), 28.0 (**C7** or **C10**), 27.9 (**C7** or **C10**).

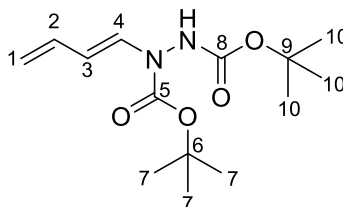
FTIR (ATR) ν (cm⁻¹): 3301 (NH), 2976, 2928, 1702 (C=O).

HRMS (ESI): m/z calculated for: C₁₄H₂₄N₂O₄ [M+Na]⁺ 307.1628, found 307.1637.

Important NOE contacts:



Diene **13d**



R_f (Hexane-EtOAc, 2:1) = 0.52

mp = 96-98 °C

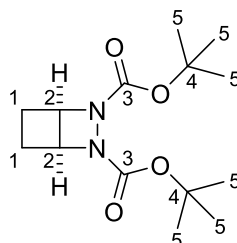
^1H NMR (400 MHz, 348 K, d_6 -DMSO): δ 9.24-8.8.69 (br m, 1H, **NH**), 7.06 (br d, J = 13.6 Hz, 1H, **H4**), 6.41-6.32 (m, 1H, **H2**), 5.68-5.62 (m, 1H, **H3**), 5.06-5.01 (m, 1H, **H1A**), 4.89-4.86 (m, H, **H1B**), 1.47-1.41 (br m, 18H, **H7** and **H10**).

^{13}C NMR (100 MHz, 348 K, d_6 -DMSO): δ 153.7 (**C5** and **C8**), 134.3 (**C2**), 130.2 (**C4**), 112.7 (**C1**), 109.6 (**C2**), 81.4 (**C6** or **C9**), 79.5 (**C6** or **C9**), 27.7 (**C7** or **C10**), 27.4 (**C7** or **C10**).

FTIR (ATR) ν (cm^{-1}): 3289 (NH), 2978, 2932, 1715 (C=O), 1649 (C=O).

HRMS (ESI or APCI): target mass not found.

Di-*tert*-butyl 2,3-diazabicyclo[2.2.0]hexane-2,3-dicarboxylate **14d**



Hydrazine hydrate (2.6 mL, 53.1 mmol, 66 eq) was added in one portion to a solution of bicyclic 1,2-diazetidene **2d** (250 mg, 0.88 mmol, 1.0 eq) in EtOH (2 mL). The resulting solution was cooled to 0 °C, then H_2O_2 (295 μL of a 50% w/v aqueous solution, 17.7 mmol, 20 eq). was added dropwise over 20 mins at 0 °C. The resulting solution was stirred at 0 °C for one hour, then water (20 mL) was added. The mixture was extracted with EtOAc (3 \times 10 mL), dried (MgSO_4) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1) gave bicycle **14d** (250 mg, 0.88 mmol, 99%) as a colourless oil.

R_f (Hexane-EtOAc, 4:1) = 0.31

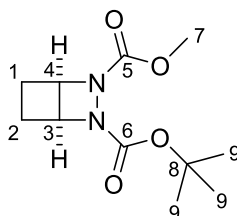
^1H NMR (400 MHz, CDCl_3): δ 4.68-4.66 (br m, 2H, **H2**), 2.55-2.49 (br m, 4H, **H1**), 1.49 (br s, 18H, **H5**).

^{13}C NMR (100 MHz, CDCl_3): δ 158.7 (**C3**), 81.9 (**C4**), 64.1 (**C2**), 28.3 (**C5**), 27.4 (**C1**).

FTIR (ATR) ν (cm^{-1}): 2980, 2945, 1737 (C=O), 1711 (C=O).

HRMS (ESI): m/z calculated for: $C_{14}H_{24}N_2O_4$ $[M+Na]^+$ 307.1628, found 307.1617.

tert*-Butyl methyl 2,3-diazabicyclo[2.2.0]hexane-2,3-dicarboxylate **14g*



A solution of acetic acid (715 μ L, 12.5 mmol, 30 eq) in CH_2Cl_2 (5 mL) was added dropwise over 1 hour at 0 °C to a stirred suspension of dipotassium azodicarboxylate (1.21 g, 6.24 mmol, 15 eq) and bicyclic 1,2-diazetidine **2g** (100 mg, 0.42 mmol, 1.0 eq) in CH_2Cl_2 (5 mL). The resulting suspension was stirred and allowed to warm gradually to room temperature over 12 hours, then filtered and washed with CH_2Cl_2 (5 \times 5 mL). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 3:1) gave bicycle **14g** (99 mg, 0.41 mmol, 98%) as a colourless oil.

R_f (Hexane-EtOAc, 3:1) = 0.23

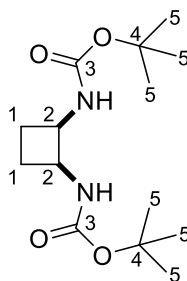
1H NMR (400 MHz, $CDCl_3$): δ 4.77-4.73 (m, 1H, **H3** or **H4**), 4.71-4.68 (m, 1H, **H3** or **H4**), 3.79 (s, 3H, **H7**), 2.58-2.50 (m, 4H, **H1** and **H2**), 1.49 (br s, 9H, **H9**).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 and 158.6 (**C5** and **C6**), 82.3 (**C8**), 64.53 and 64.49 (**C3** and **C4**), 53.4 (**C7**), 28.3 (**C9**), 27.40 and 27.38 (**C1** and **C2**).

FTIR (ATR) ν (cm^{-1}): 2952, 2980, 1702 (C=O).

HRMS (ESI): m/z calculated for: $C_{11}H_{18}N_2O_4$ $[M+Na]^+$ 265.1159, found 265.1151.

Di-*tert*-butyl (1*R*,2*S*)-cyclobutane-1,2-diylbiscarbamate **15d**



A solution of bicyclic 1,2-diazetidine **14d** (136 mg, 0.48 mmol, 1.0 eq) in THF (5 mL) was added to liquid ammonia (5 mL) at –78 °C under argon. Sodium metal (110 mg, 4.78 mmol, 10 eq) was added portion wise at –78 °C, then the reaction mixture was stirred at –78 °C for 15 mins. Solid NH_4Cl (100 mg) was added at –78 °C, and the mixture was allowed to warm slowly to room temperature. The reaction mixture was left at room temperature overnight to allow complete evaporation of the ammonia. The residue was

dissolved in CH₂Cl₂ (5 mL) and filtered, then washed with further CH₂Cl₂ (4 × 5 mL). The solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 3:1) gave diamine **15d** (111 mg, 0.39 mmol, 81%) as a white solid.

mp = 165-168 °C

R_f (Hexane-EtOAc, 3:1) = 0.30

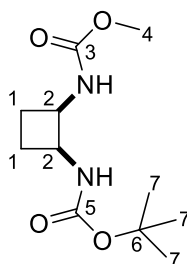
¹H NMR (400 MHz, *d*₆-DMSO; rotamers present): δ 7.16-7.10, 6.84-6.66 and 6.33-6.26 (all br m, 2H, **NH**), 4.14-3.92 and 3.86-3.65 (both br m, 2H, **H2**), 2.07-1.92 and 1.87-1.66 (both br m, 2H, 3 × **H1**), 1.52-1.19 (br m, 19H, **H5** and 3 × **H1**).

¹³C NMR (100 MHz, *d*₆-DMSO; rotamers present): δ 155.1 and 154.9 (**C3**), 79.2 and 77.8 (**C4**), 52.2 and 49.2 (**C2**), 28.2 (**C5**), 25.0 and 22.7 (**C1**).

FTIR (ATR) ν (cm⁻¹): 3330 (NH), 2976, 1681 (C=O).

HRMS (ESI): *m/z* calculated for: C₁₄H₂₆N₂O₄ [M+Na]⁺ 309.1785, found 309.1780.

tert*-Butyl methyl *cis*-cyclobutane-1,2-diylbiscarbamate **15g*



A solution of bicyclic 1,2-diazetidene **14g** (87 mg, 0.36 mmol, 1.0 eq) in THF (3 mL) was added to liquid ammonia (5 mL) at -78 °C under argon. Sodium metal (83 mg, 3.59 mmol, 10 eq) was added portion wise at -78 °C, then the reaction mixture was stirred at -78 °C for 15 mins. Solid NH₄Cl (100 mg) was added at -78 °C, and the mixture was allowed to warm slowly to room temperature. The reaction mixture was left at room temperature overnight to allow complete evaporation of the ammonia. The residue was dissolved in CH₂Cl₂ (5 mL), filtered, washed with further CH₂Cl₂ (4 × 5 mL) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 2:1) gave diamine **15g** (67 mg, 0.27 mmol, 76%) as a white solid.

mp = 124-126 °C

R_f (Hexane-EtOAc, 2:1) = 0.20

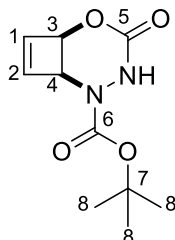
¹H NMR (400 MHz, *d*₆-DMSO; 5:4:2:1 mixture of rotamers); δ 7.43 (br d, *J* = 7.2 Hz, 0.7H, **NH**), 7.12 (br d, *J* = 7.8 Hz, 0.8H, **NH**), 7.01 (br d, *J* = 8.1 Hz, 0.2H, **NH**), 6.72 (br d, *J* = 7.4 Hz, 0.3H, **NH**), 4.19-3.67 (br m, 2H, **H3** and **H4**), 3.51 and 3.49 (s, 3H, **H6**), 2.07-1.94 and 1.90-1.68 (br m, 2.5H, **H1** and **H2**), 1.51-1.20 (br m, 10.5H, **H9** and **H1** and/or **H2**).

¹³C NMR (100 MHz, CDCl₃; rotamers present); δ 155.8, 155.6, 154.7 and 154.5 (**C5** and **C7**), 77.9 and 77.6 (**C8**), 52.6, 52.0, 51.1, 51.3, 49.7 and 49.2 (**C6**, **C3** and **C4**), 28.22 and 28.16 (**C9**), 25.1, 22.8 and 22.6 (**C1** and **C2**).

FTIR (ATR) ν (cm⁻¹): 3319 (NH), 2978, 2950, 1696 (C=O), 1683 (C=O).

HRMS (ESI): m/z calculated for: $C_{11}H_{20}N_2O_4$ $[M+Na]^+$ 267.1315, found 267.1314.

tert*-Butyl 4-oxo-5-oxa-2,3-diazabicyclo[4.2.0]oct-7-ene-2-carboxylate **16*



A solution of bicyclic 1,2-diazetidine **2d** (512 mg, 1.81 mmol) in 1,4-dioxane (3.5 mL) was heated at reflux for 24 hours. The reaction mixture was cooled to room temperature, then a 1 M aqueous solution of HCl (1 mL) was added and the mixture stirred for at room temperature for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 2:1) gave bicycle **16** (366 mg, 1.62 mmol, 89%) as a white solid.

R_f (Hexane-EtOAc, 2:1) = 0.07

mp = 134-136 °C

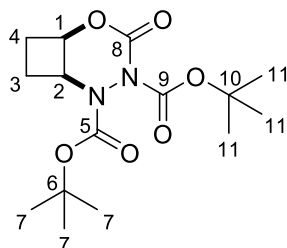
1H NMR (400 MHz, $CDCl_3$); δ 7.21 (br s, 1H, **NH**), 6.42-6.41 (br m, 1H, **H1** or **H2**), 6.34-6.33 (br m, 1H, **H1** or **H2**), 5.44-5.42 (br m, 2H, **H3** and **H4**), 1.50 (s, 9H, **H8**).

^{13}C NMR (100 MHz, $CDCl_3$); δ 153.6 (**C5** or **C6**), 151.9 (**C5** or **C6**), 141.5 (**C1** or **C2**), 140.2 (**C1** or **C2**), 83.6 (**C7**), 81.5 (**C3**), 60.2 (**C4**), 28.3 (**C8**).

FTIR (ATR) ν (cm^{-1}): 3293 (NH), 2982, 2933, 1728 (C=O), 1683 (C=O).

HRMS (ESI): m/z calculated for: $C_{10}H_{14}N_2O_4$ $[M+Na]^+$ 249.0846, found 249.0839.

rac*-Di-*tert*-butyl (1*S*,6*R*)-4-oxo-5-oxa-2,3-diazabicyclo[4.2.0]octane-2,3-dicarboxylate **17*



A solution of acetic acid (2.5 mL, 44.2 mmol, 100 eq) in CH_2Cl_2 (5 mL) was added dropwise over 1 hour at 0 °C to a stirred suspension of dipotassium azodicarboxylate (4.29 g, 22.1 mmol, 50 eq) and bicyclic 1,2-diazetidine **2g** (100 mg, 0.44 mmol, 1.0 eq) in CH_2Cl_2 (10 mL). The resulting suspension was stirred and allowed to warm gradually to room temperature over 12 hours, then filtered and washed with CH_2Cl_2

(5 × 5 mL). The filtrate was evaporated under reduced pressure to give the crude product, which consisted of starting material and product (~1:1). The residue was re-subjected twice to the reduction conditions, leading to complete conversion to the cyclobutane, then dissolved in THF (5 mL). Triethylamine (123 μ L, 0.88 mmol, 2.0 eq) and DMAP (5 mg, 0.04 mmol, 0.1 eq) were added, and the resulting solution was stirred at room temperature for 12 h, then evaporated under reduced pressure. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 4:1) gave bicycle **17** (118 mg, 0.36 mmol, 81%) as a white solid.

R_f (Hexane-EtOAc, 4:1) = 0.20

mp = 126-128 °C

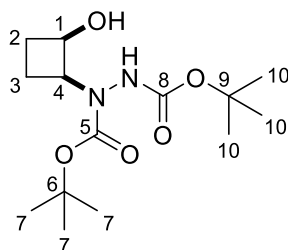
^1H NMR (400 MHz, CDCl_3); δ 5.18-5.08 (br m, 1H, **H4**), 5.03 (dt, J = 8.0 Hz, 7.6 Hz, 1H, **H1**), 2.56-2.41 (m, 2H, **H2** and/or **H3**), 2.32-2.13 (m, 2H, **H2** and/or **H3**), 1.58 (s, 9H, **H7** or **H11**), 1.49 (s, 9H, **H7** or **H11**).

^{13}C NMR (100 MHz, CDCl_3); δ 153.5, 149.7 and 148.4 (**C5**, **C8** and **C9**), 84.7 and 83.6 (**C1**, **C6** and **C10**), 55.0 (**C4**), 28.7 (**C2** or **C3**), 28.11 and 28.09 (**C7** and **C11**), 21.8 (**C2** or **C3**).

FTIR (ATR) ν (cm^{-1}): 2980, 1804 (C=O), 1776 (C=O), 1722 (C=O).

HRMS (ESI): m/z calculated for: $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_6$ $[\text{M}+\text{Na}]^+$ 351.1527, found 351.1524.

rac-Di-tert-butyl 1-[(1S,2R)-2-hydroxycyclobutyl]hydrazine-1,2-dicarboxylate 18



$\text{LiOH}\cdot\text{H}_2\text{O}$ (76 mg, 1.81 mmol, 10 eq) was added in one portion to a stirred solution of bicycle **17** (60 mg, 0.18 mmol, 1 eq) in THF (3 mL) and water (1.5 mL). The resulting mixture was stirred for 14 h at room temperature, then evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), filtered, washed with further CH_2Cl_2 (4 × 5 mL) and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography on silica gel (eluent: hexane-EtOAc, 2:1) gave cyclobutanol **18** (41 mg, 0.14 mmol, 74%) as a white solid.

R_f (Hexane-EtOAc, 2:1) = 0.29

mp = 111-113 °C

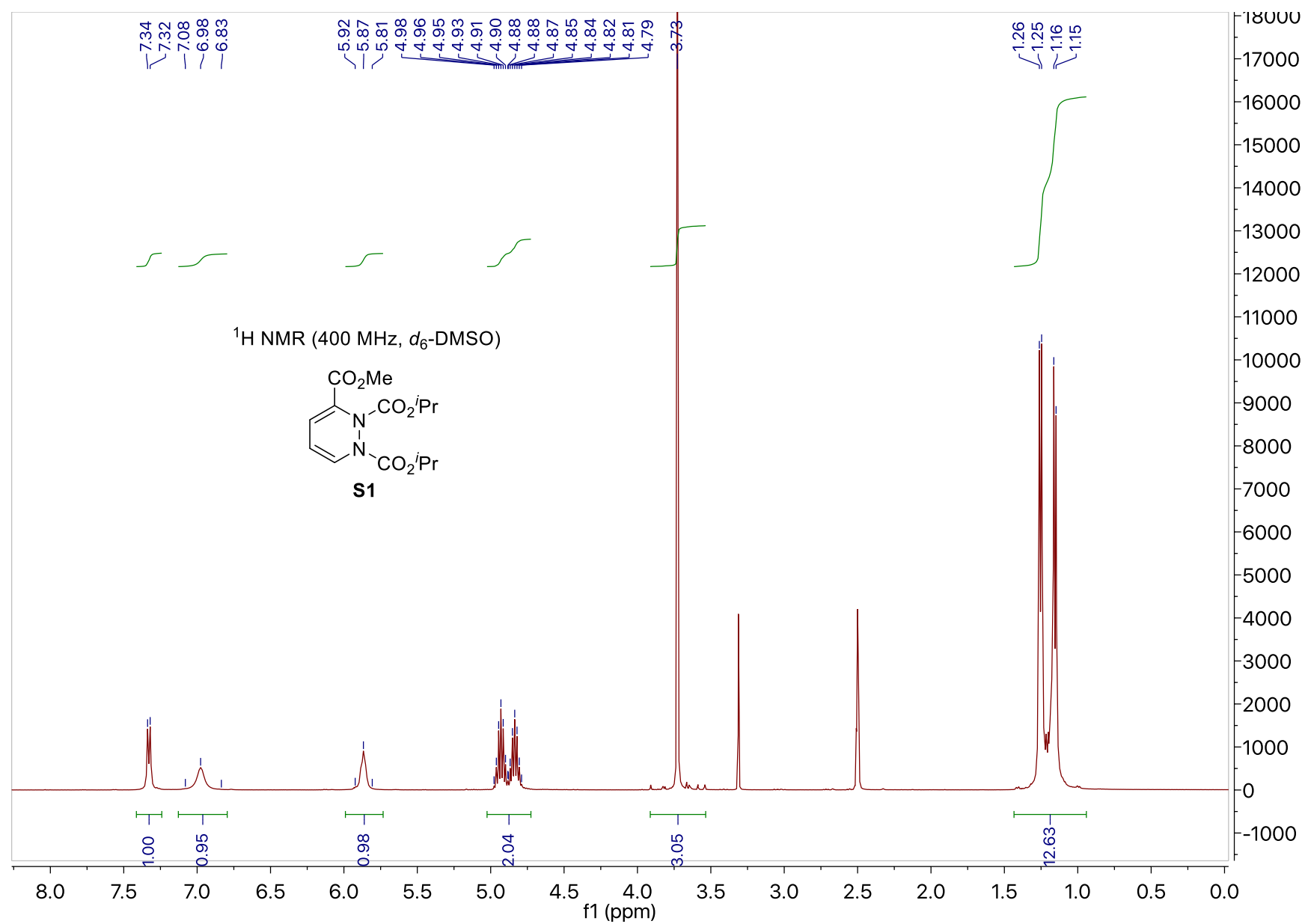
The ^1H and ^{13}C NMR spectra of cyclobutanol **18** are very complex, due to the presence of a number of rotamers. Attempts to simplify the spectra by running samples in different solvents and by using variable-temperature NMR (up to 348 K) were unsuccessful, and no improvement was observed.

^1H NMR (400 MHz, d_6 -DMSO; complex mixture of rotamers): δ 9.39, 9.26, 8.40 and 8.02 (br s, 1H, **OH**), 5.33-3.92 (br m, 3H, **H1**, **H4** and **NH**), 2.16-1.81 (br m, 3H, **H2** and **H3**), 1.73-0.71 (br m, 21H, **H2** or **H3** plus **H7** and **H10**), 1.49 (br s, 18H, **H5**).

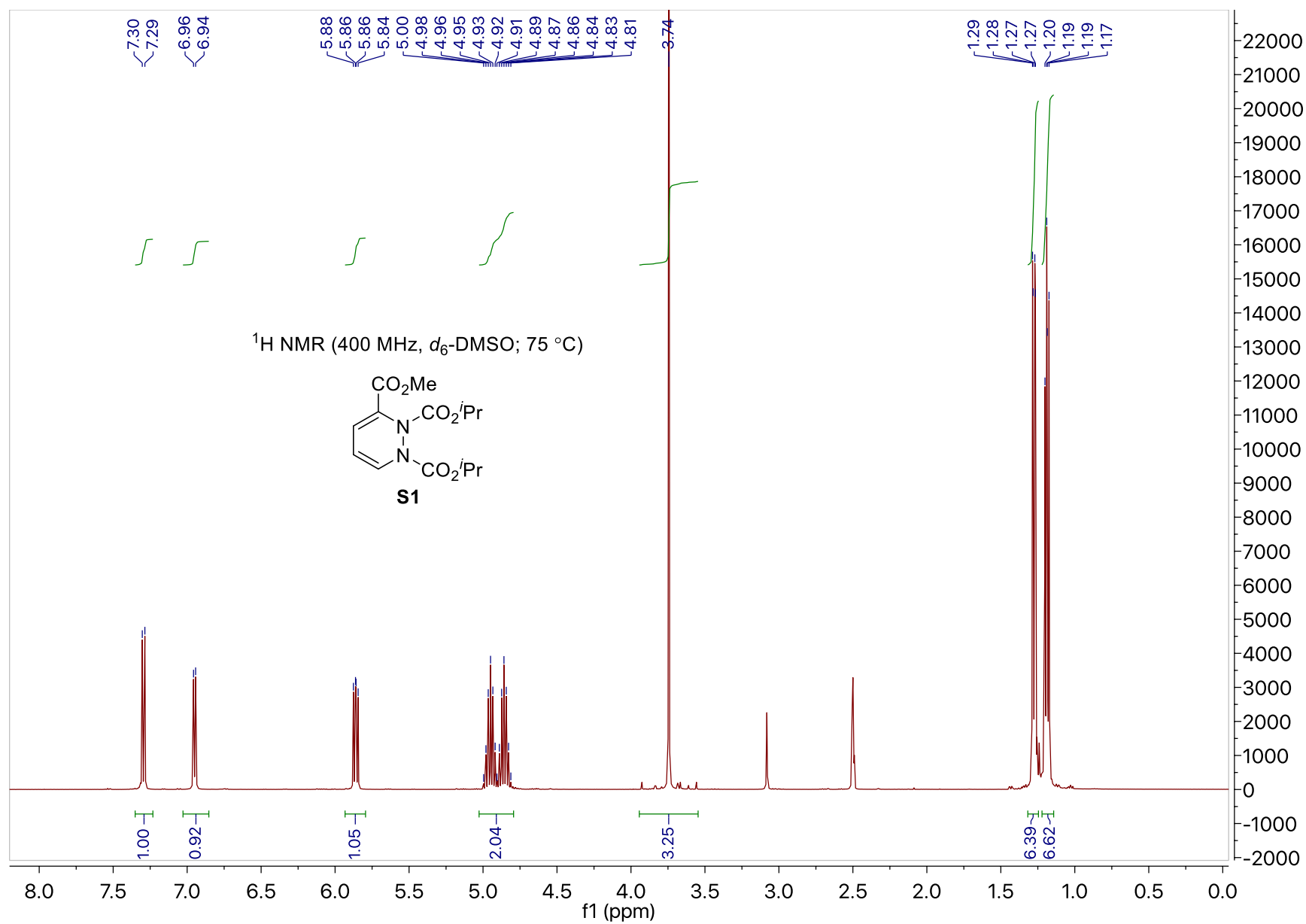
^{13}C NMR (100 MHz, d_6 -DMSO; complex mixture of rotamers); δ 157.8, 155.3, 154.7 and 154.0 (**C5** and **C8**), 80.9, 80.2, 80.0, 79.6, 79.3 and 79.2 (**C1**, **C6** and **C9**), 69.7, 69.3, 67.9, 67.8, 58.3 (**C4**), 31.3, 30.8, 29.0, 28.7, 28.2 (**C2** and **C3**), 28.0 and 27.9 (**C7** and **C10**), 22.1, 20.2, 20.1, 17.9, 14.0 (**C2** and **C3**). FTIR (ATR) ν (cm^{-1}): 3384 (OH), 3299 (NH), 2976, 2928, 1701 (C=O). HRMS (ESI): m/z calculated for: $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$ 325.1734, found 325.1719.

2. References

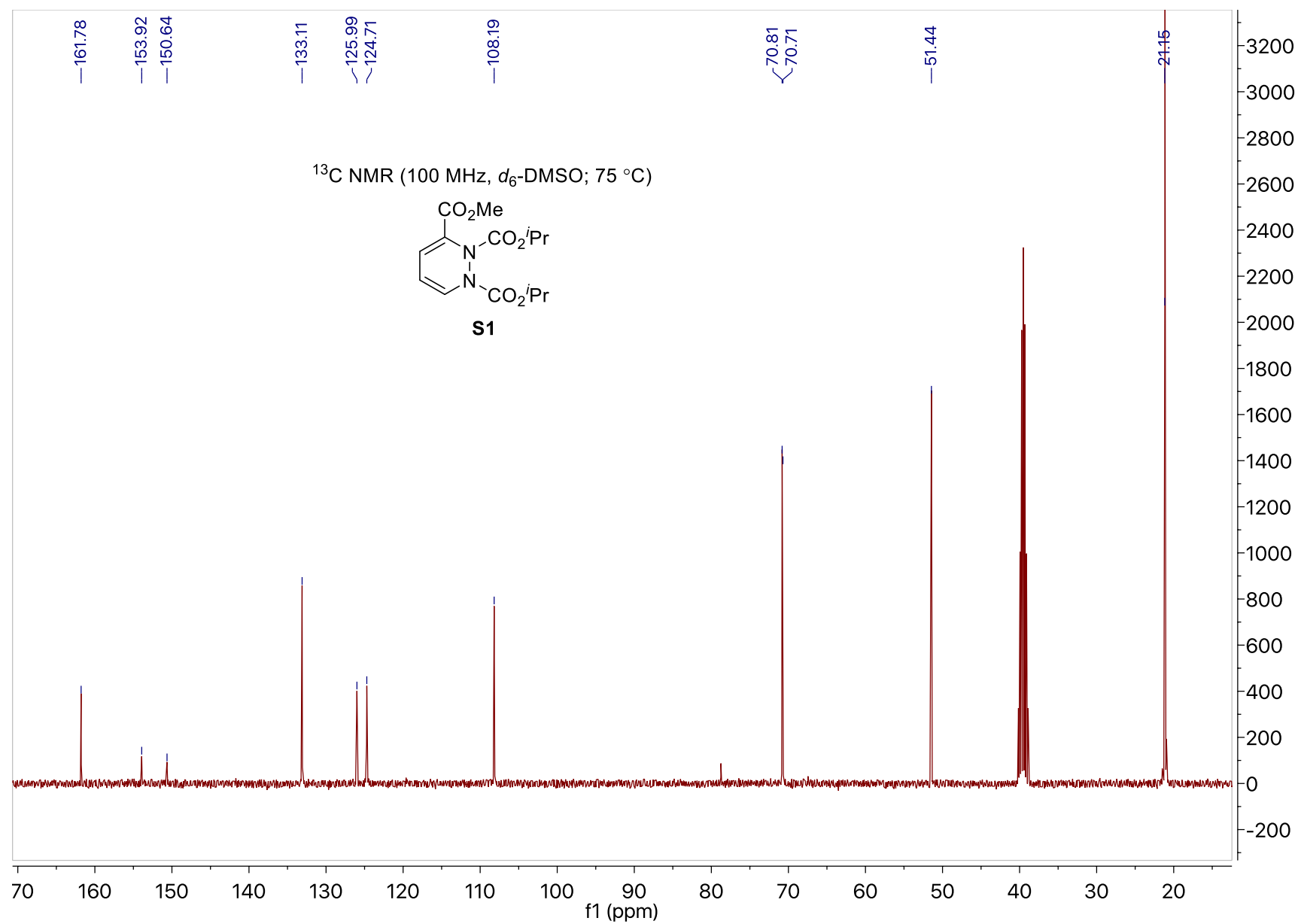
- (1) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341.
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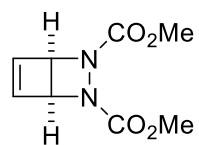
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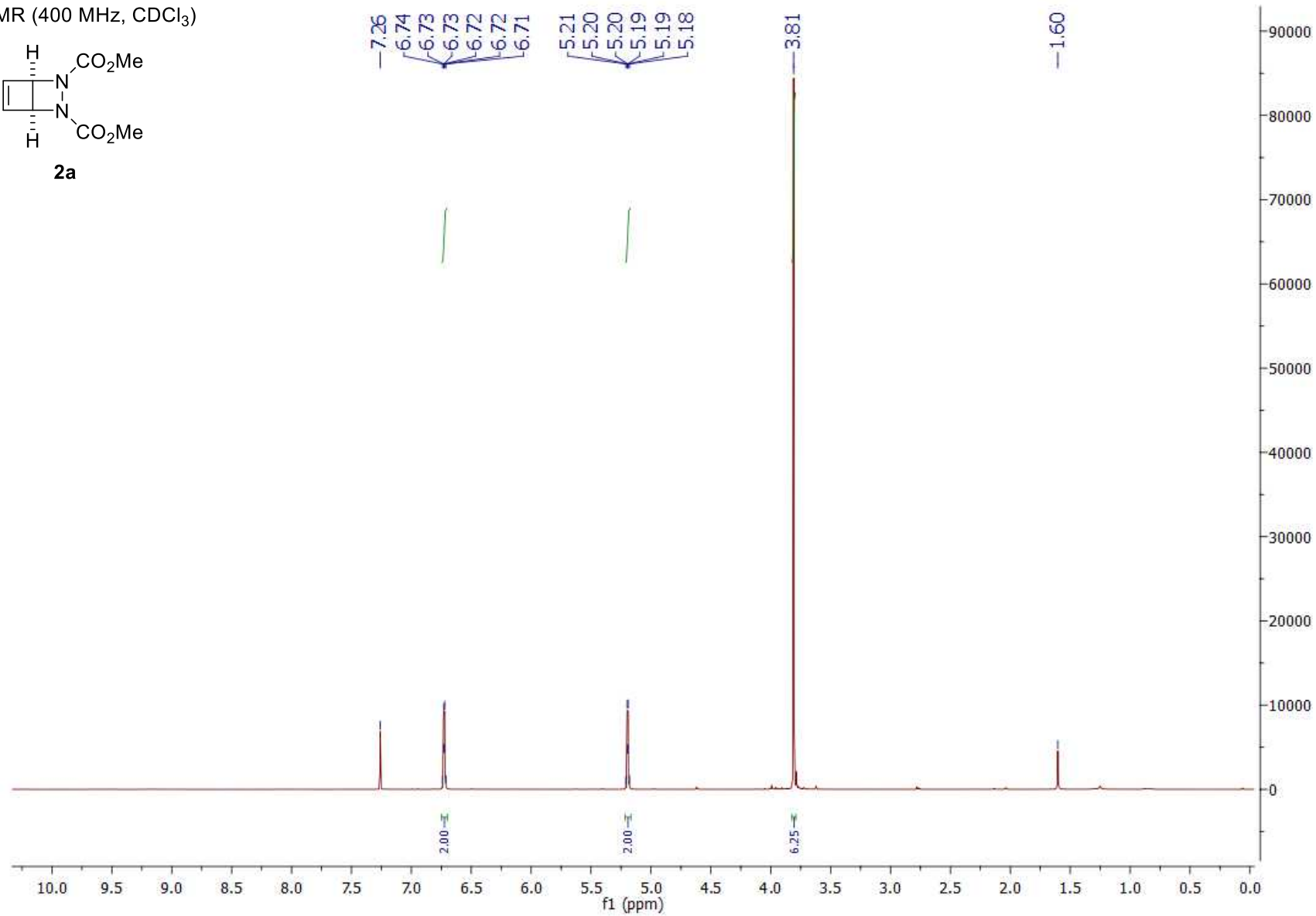
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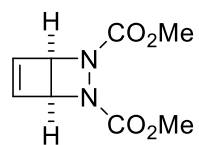
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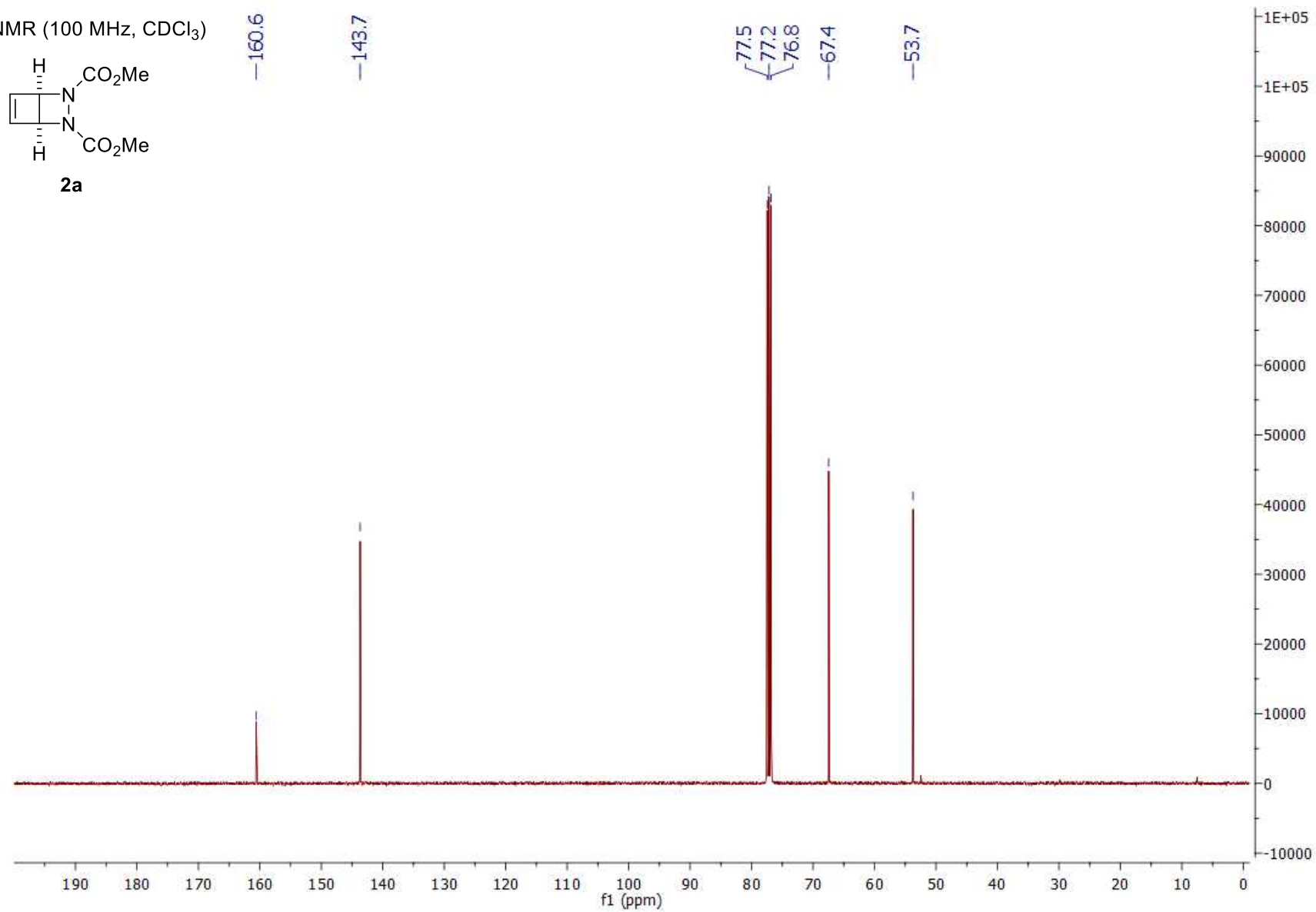
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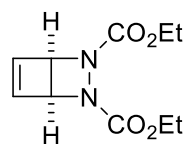
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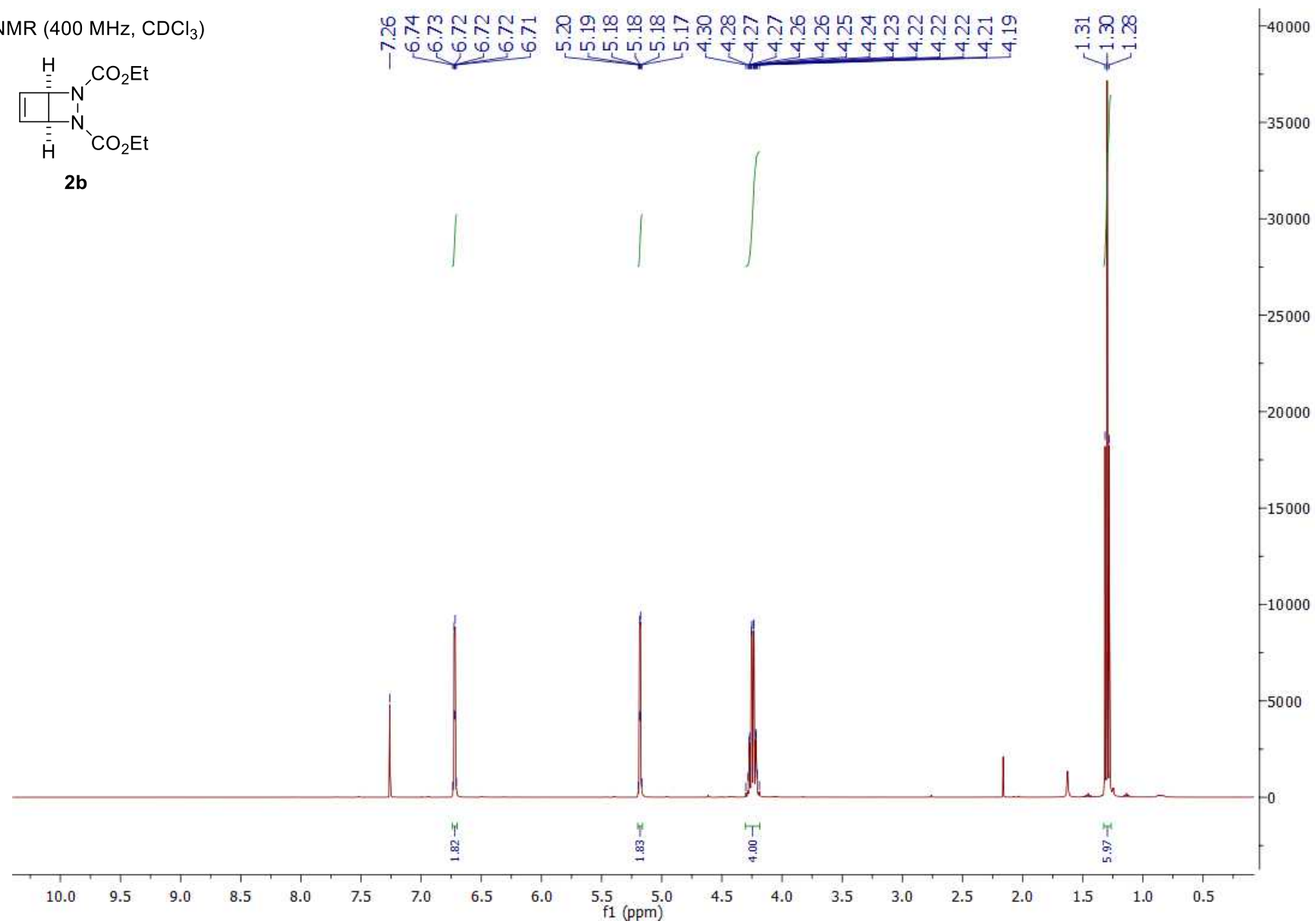
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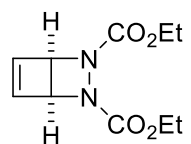
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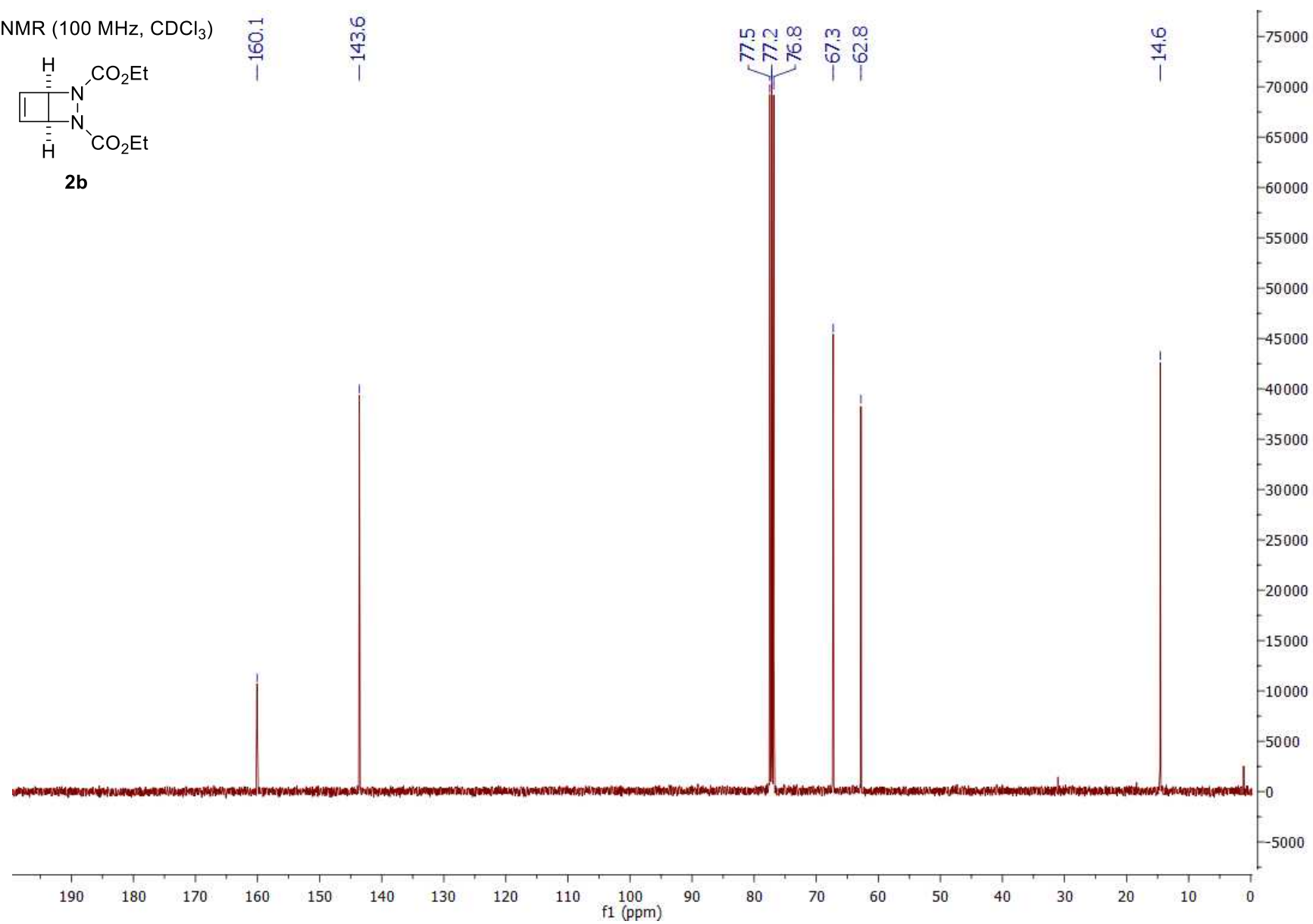
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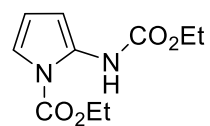
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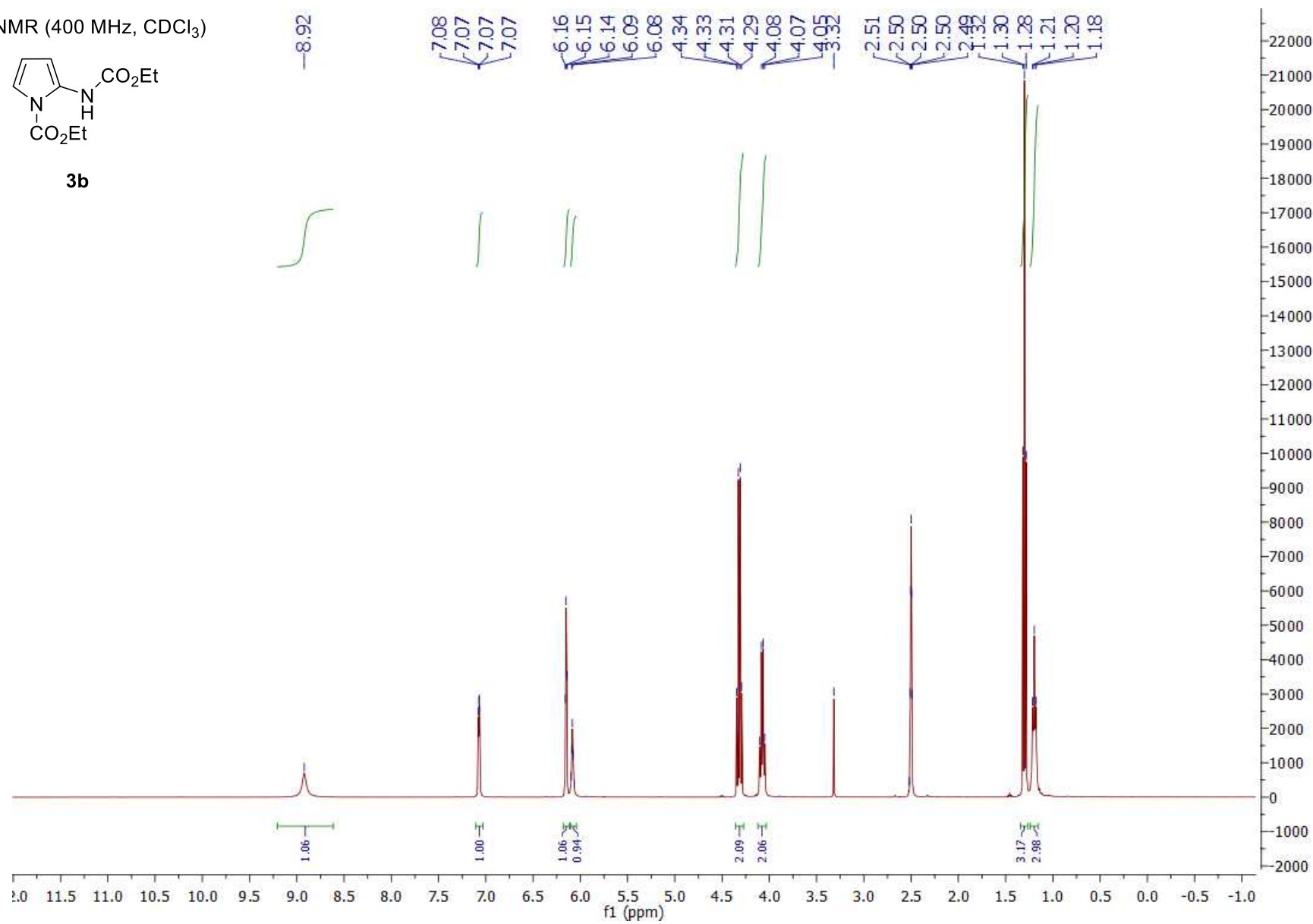
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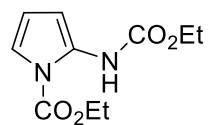
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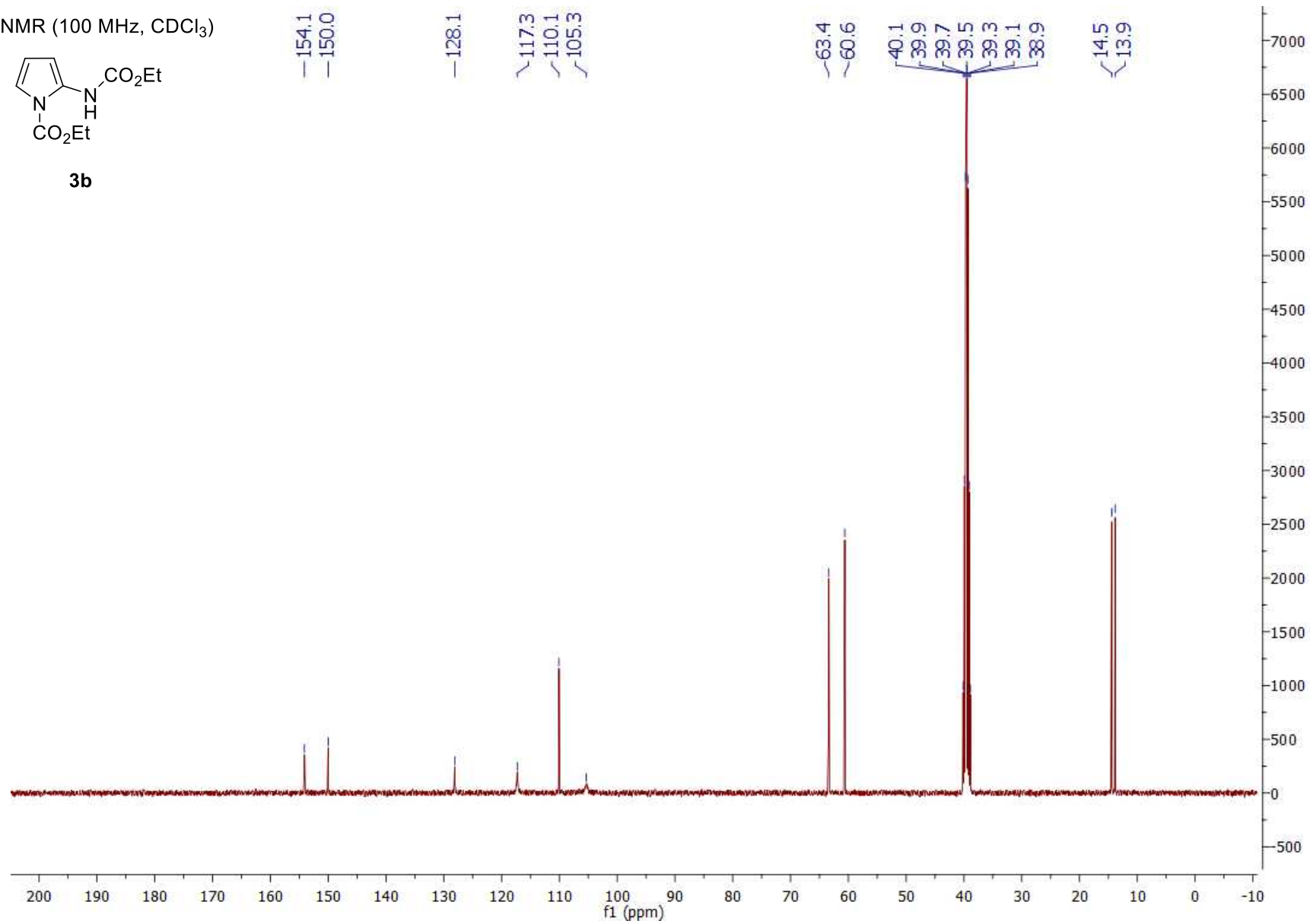
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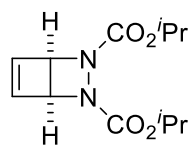
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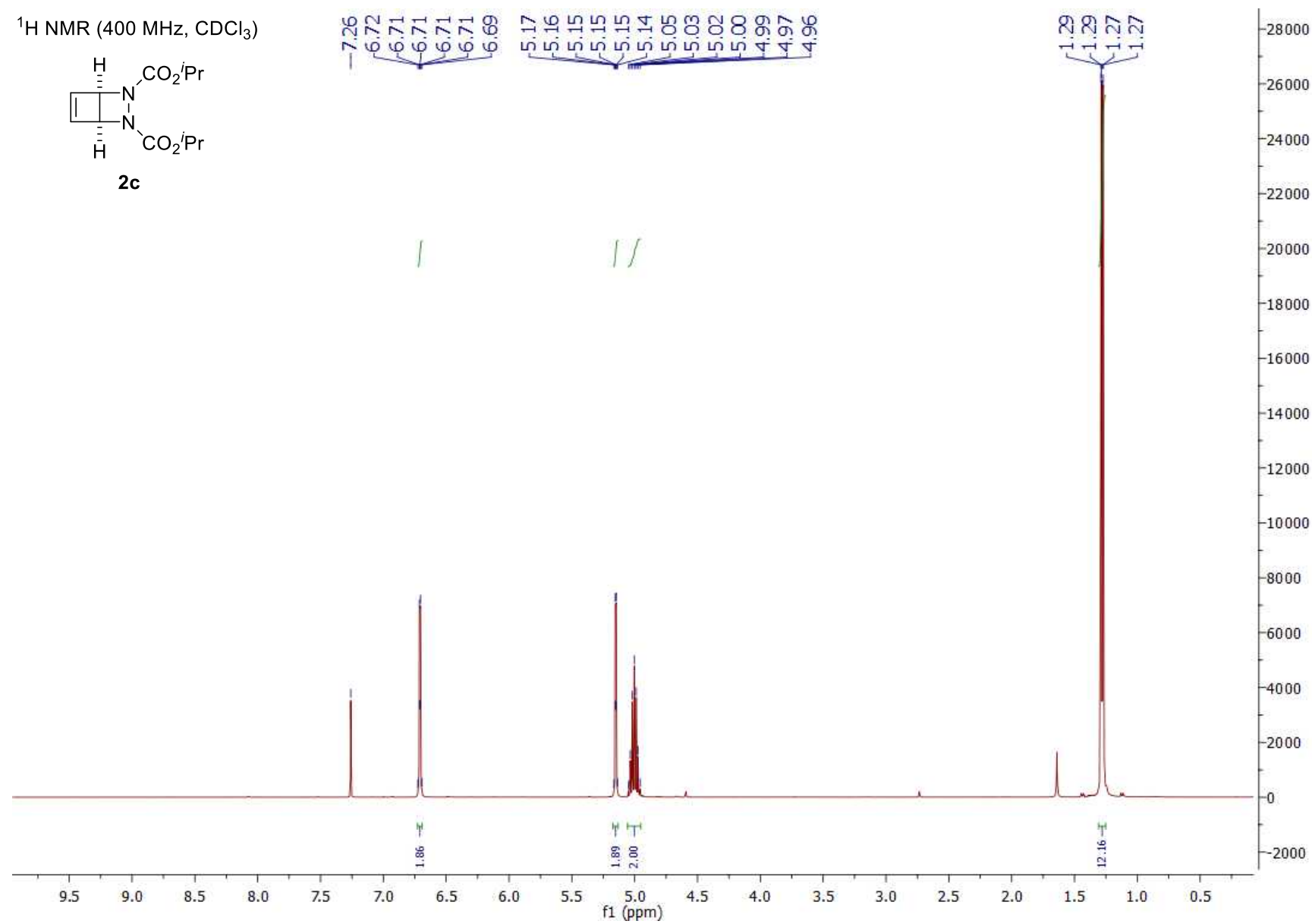
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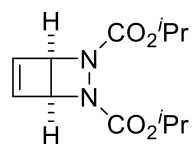
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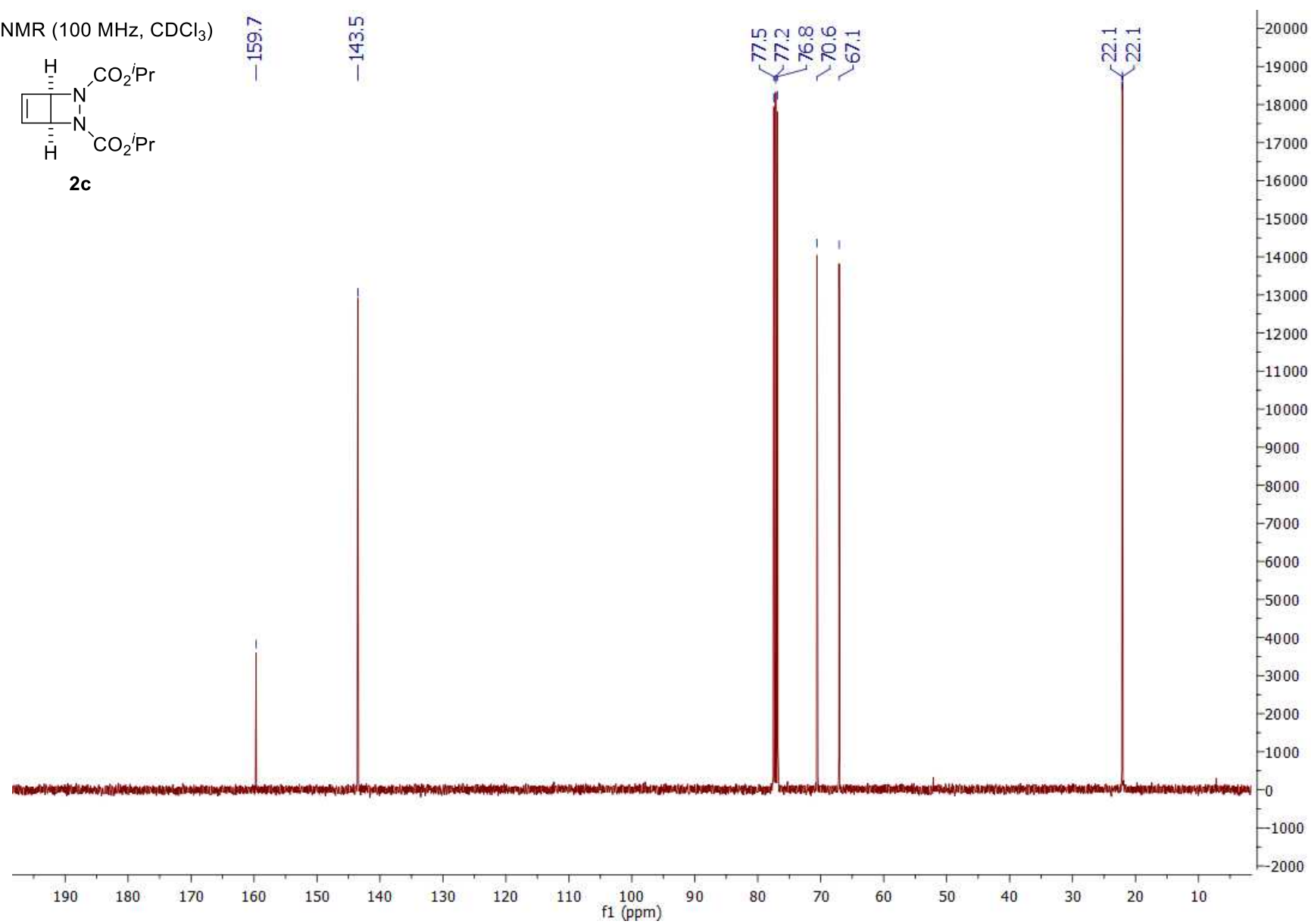
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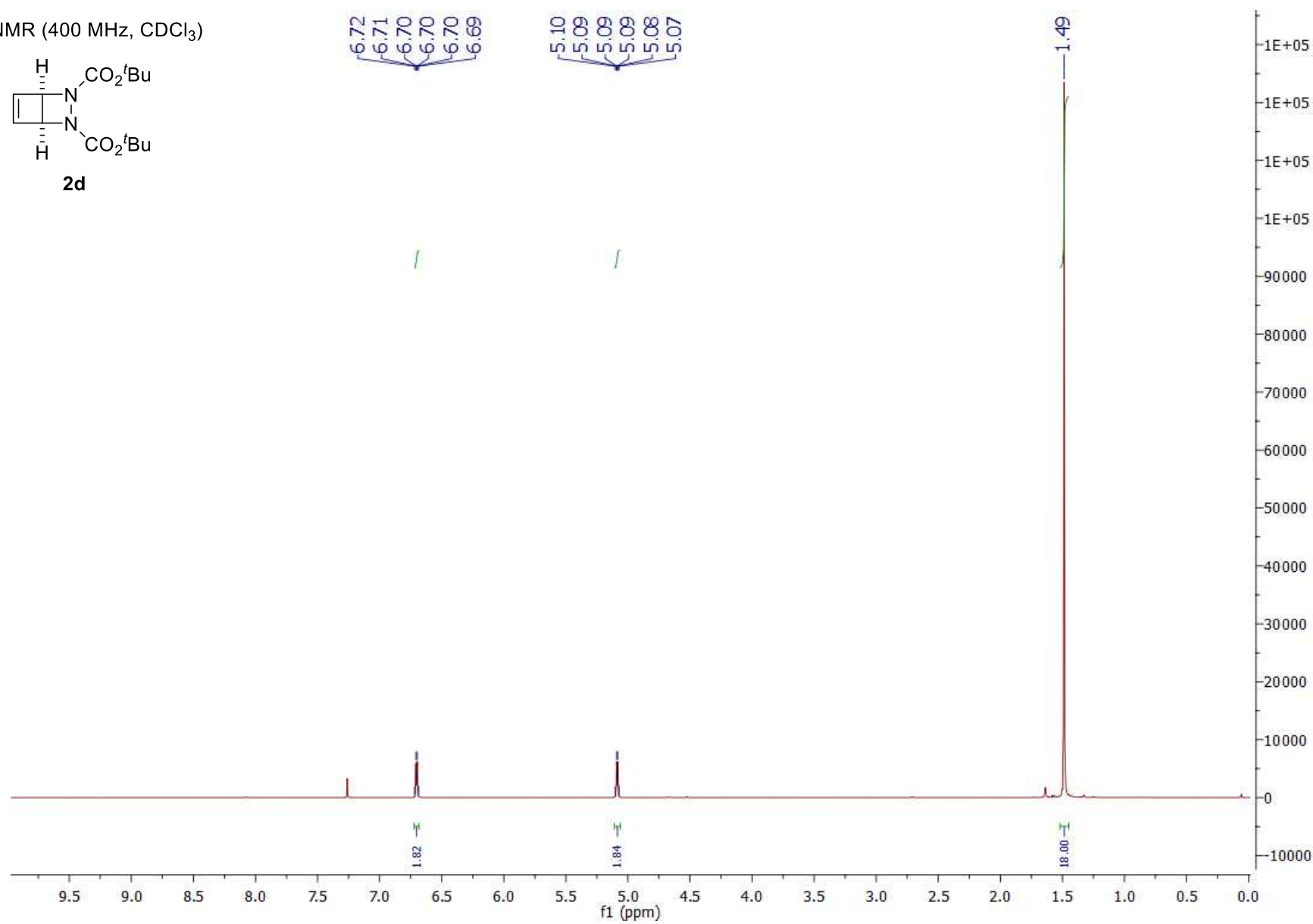


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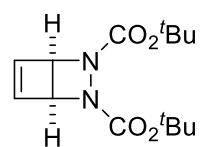


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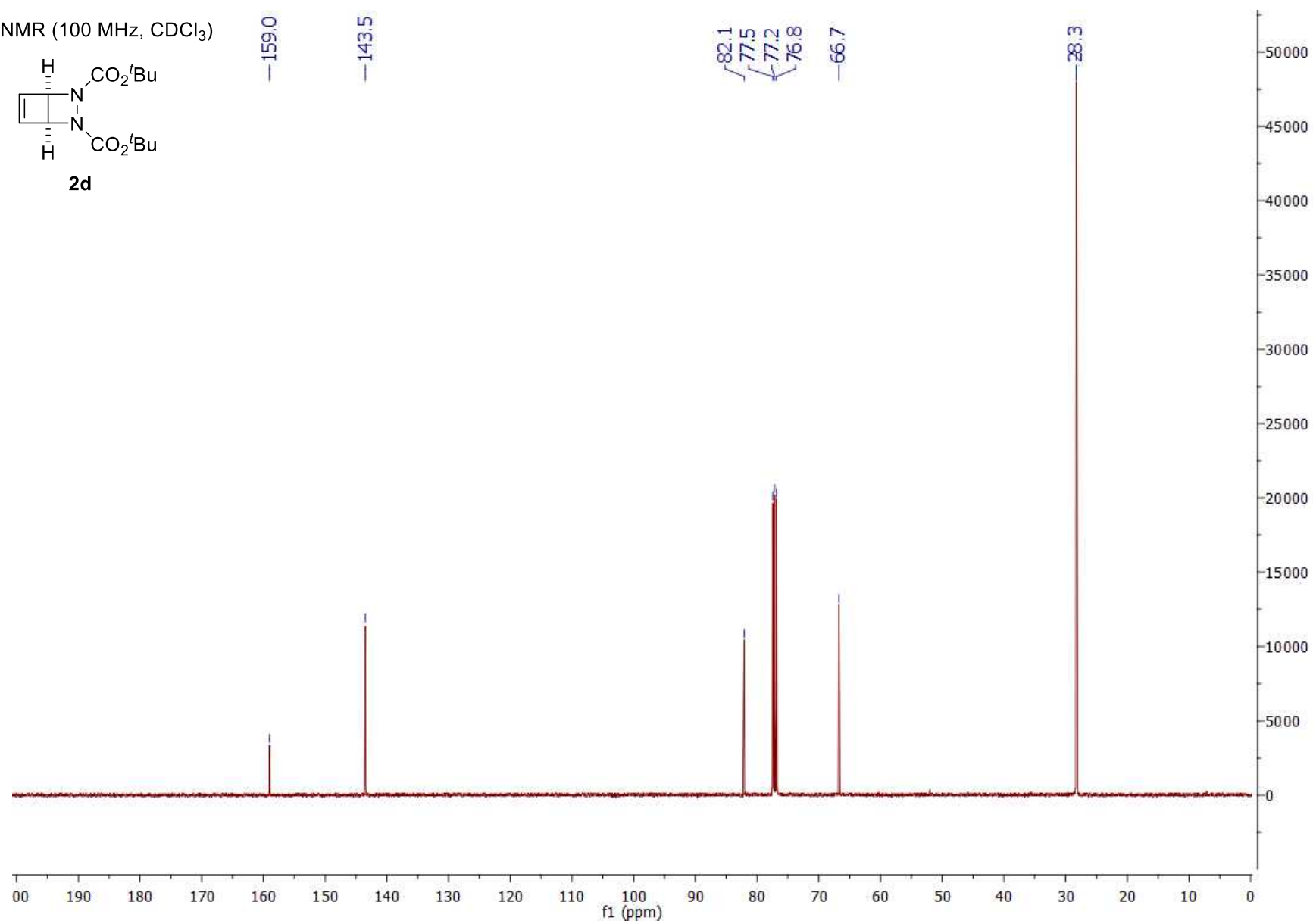




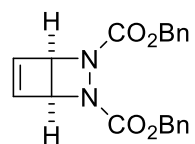
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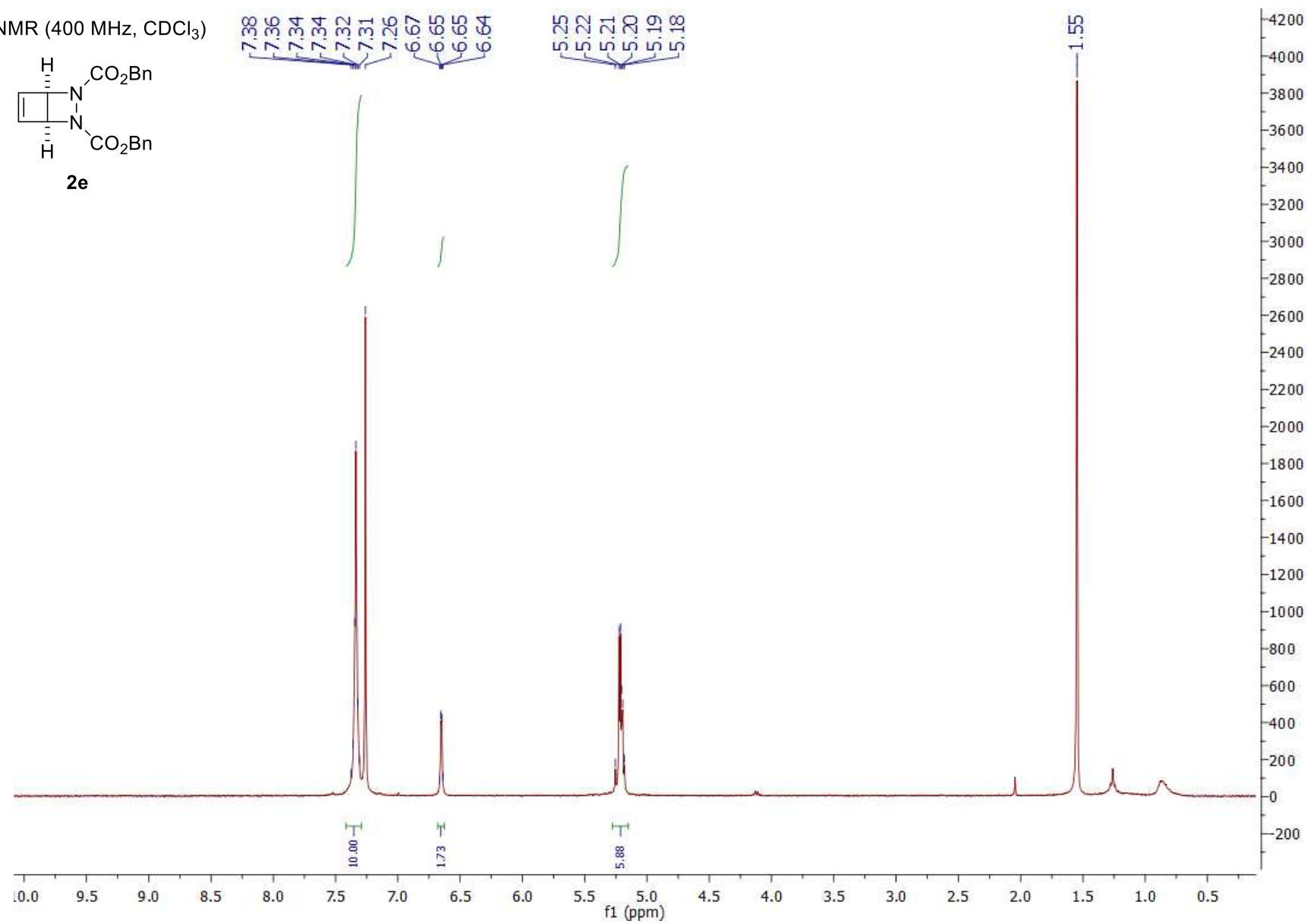
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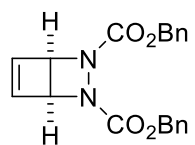
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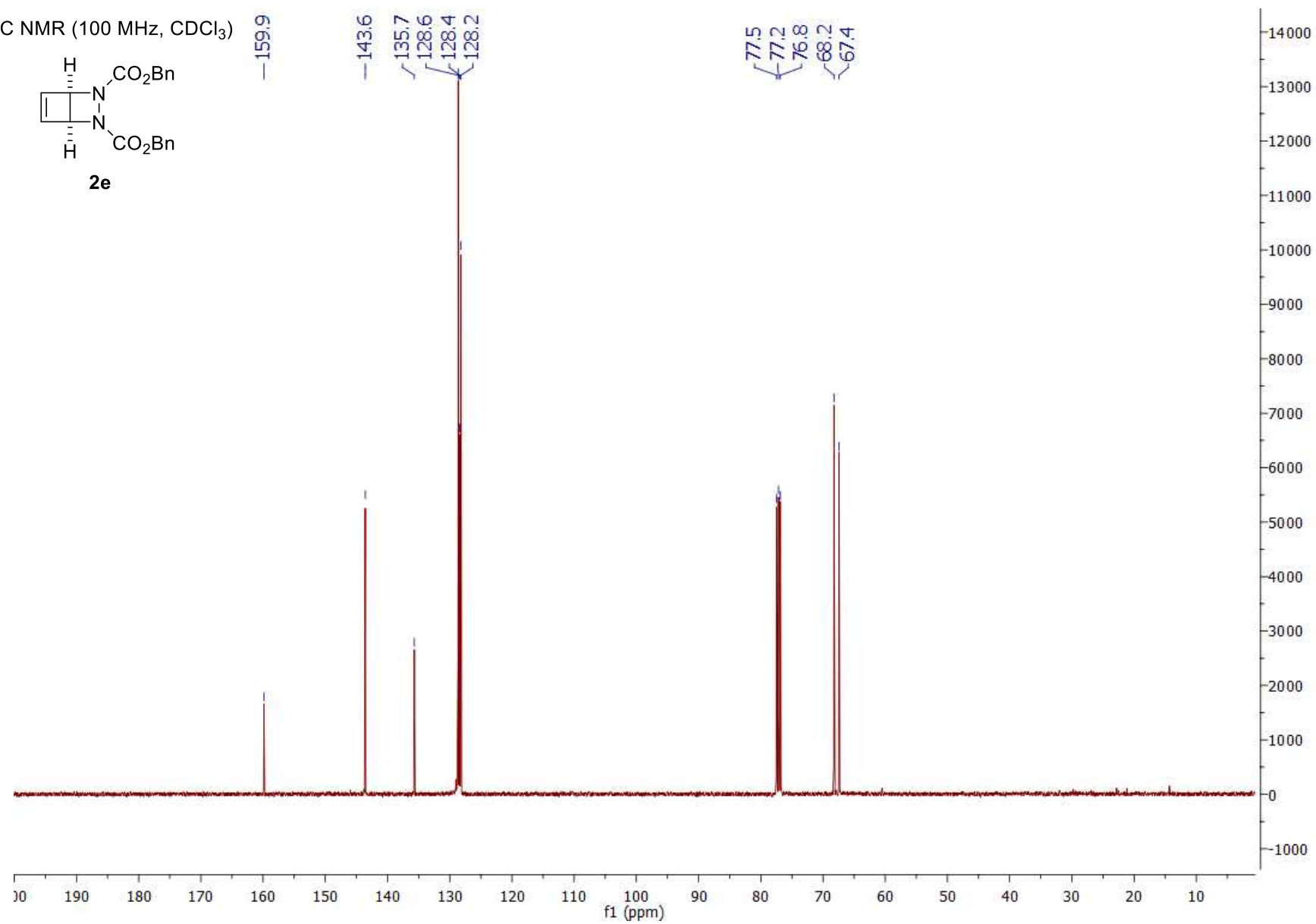
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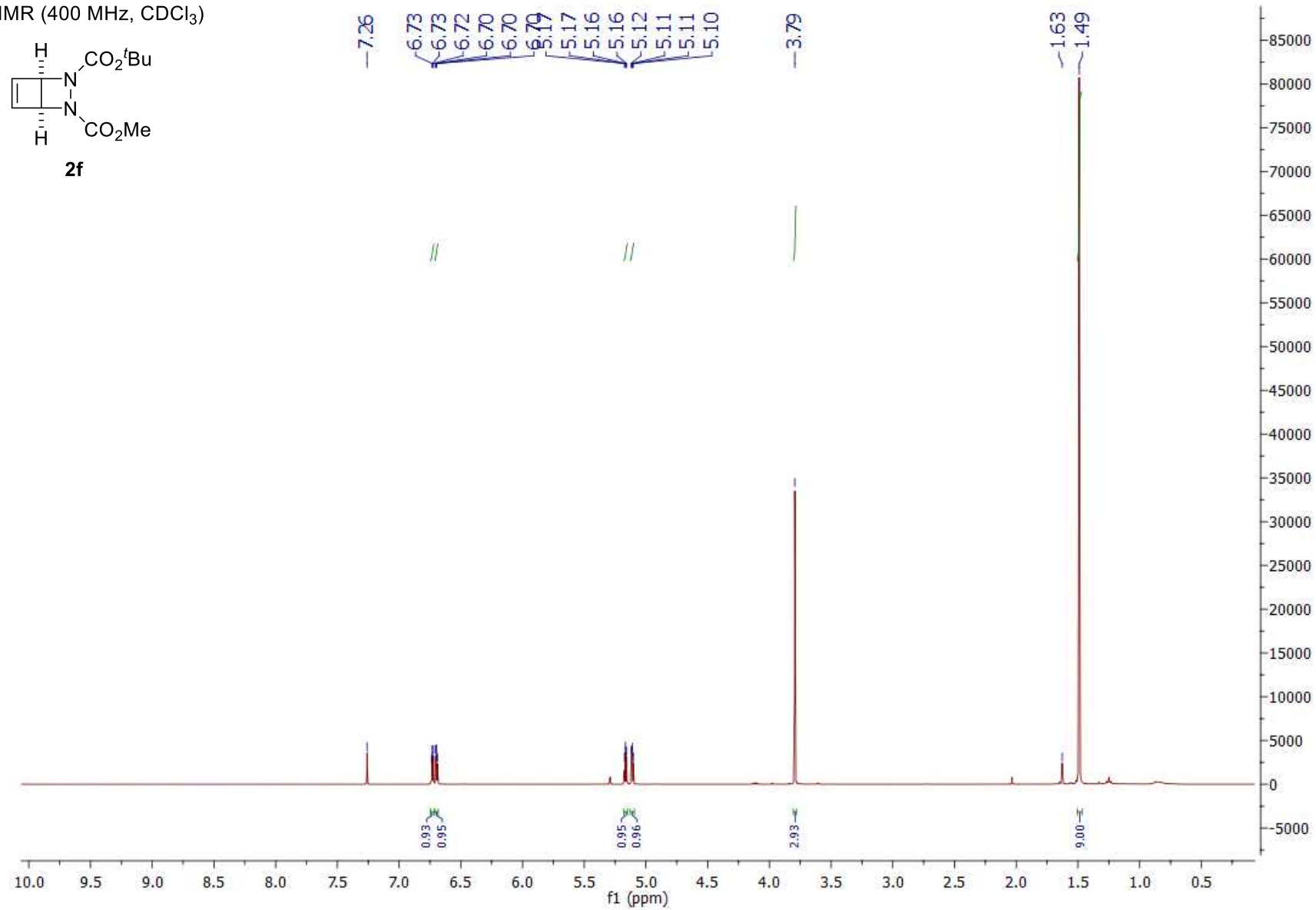
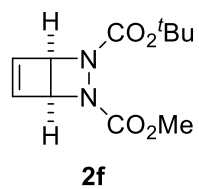
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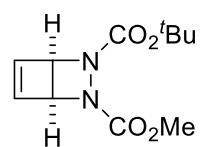
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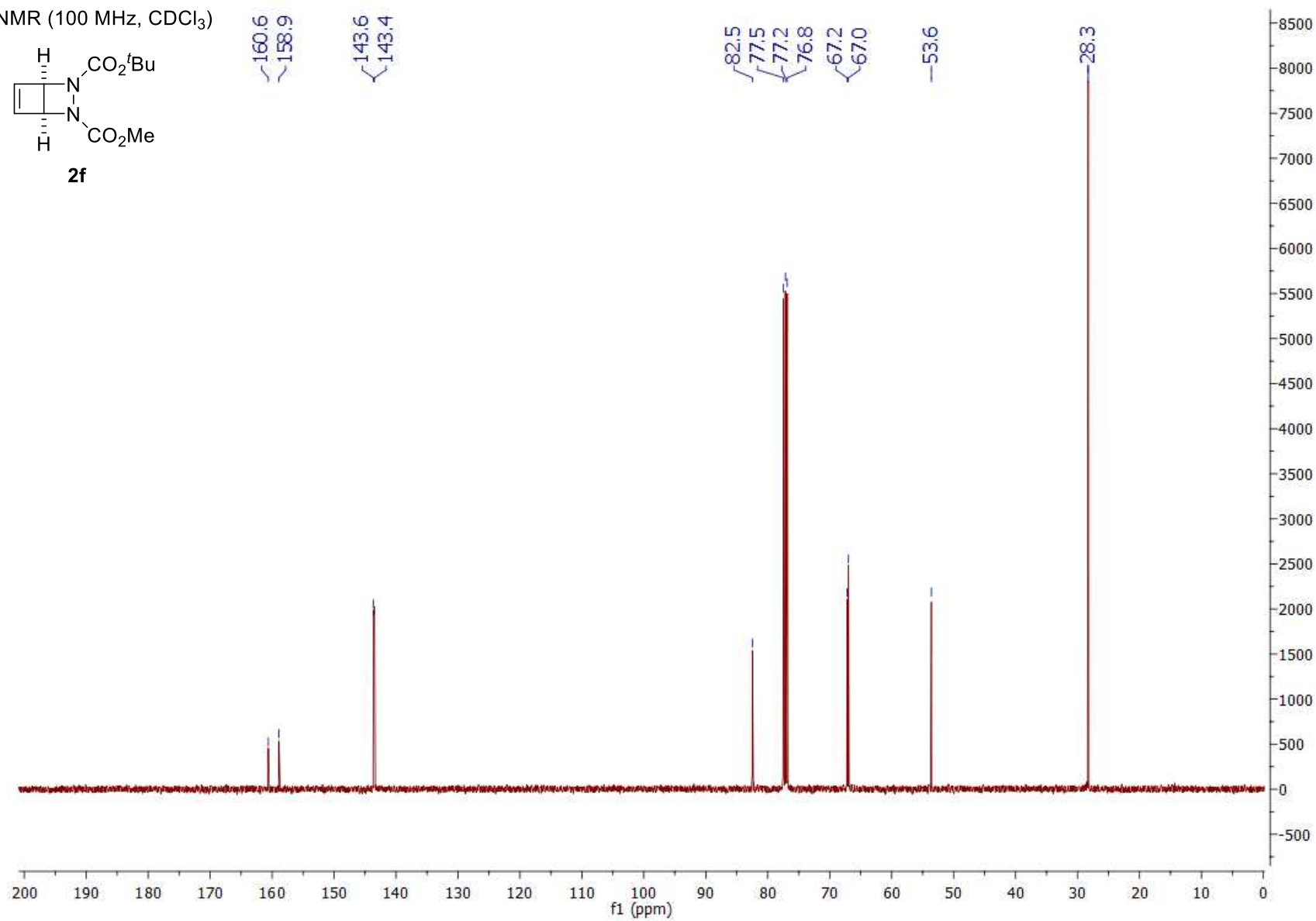
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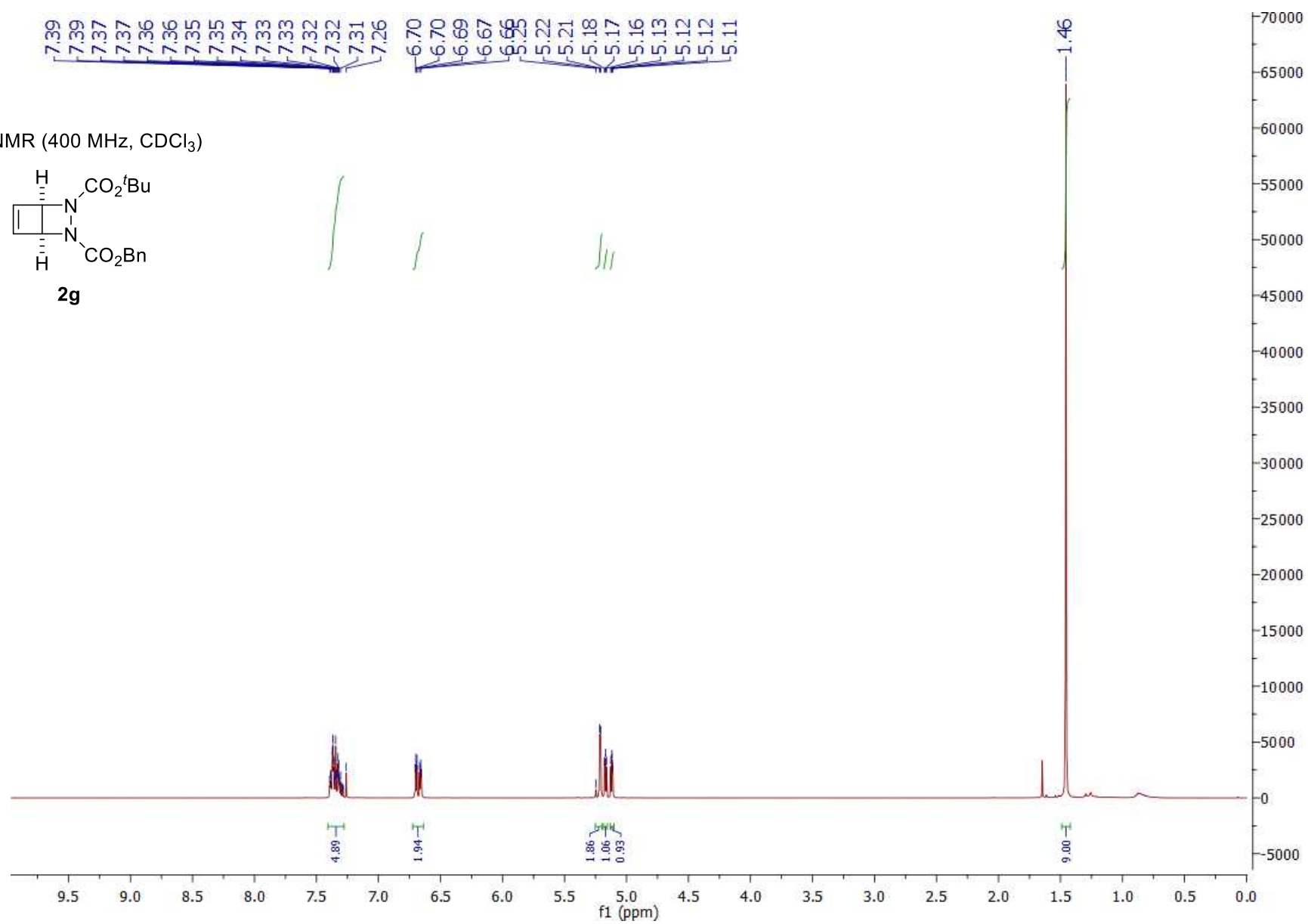
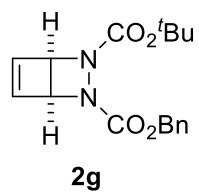
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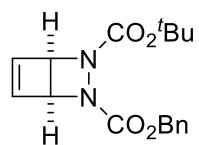
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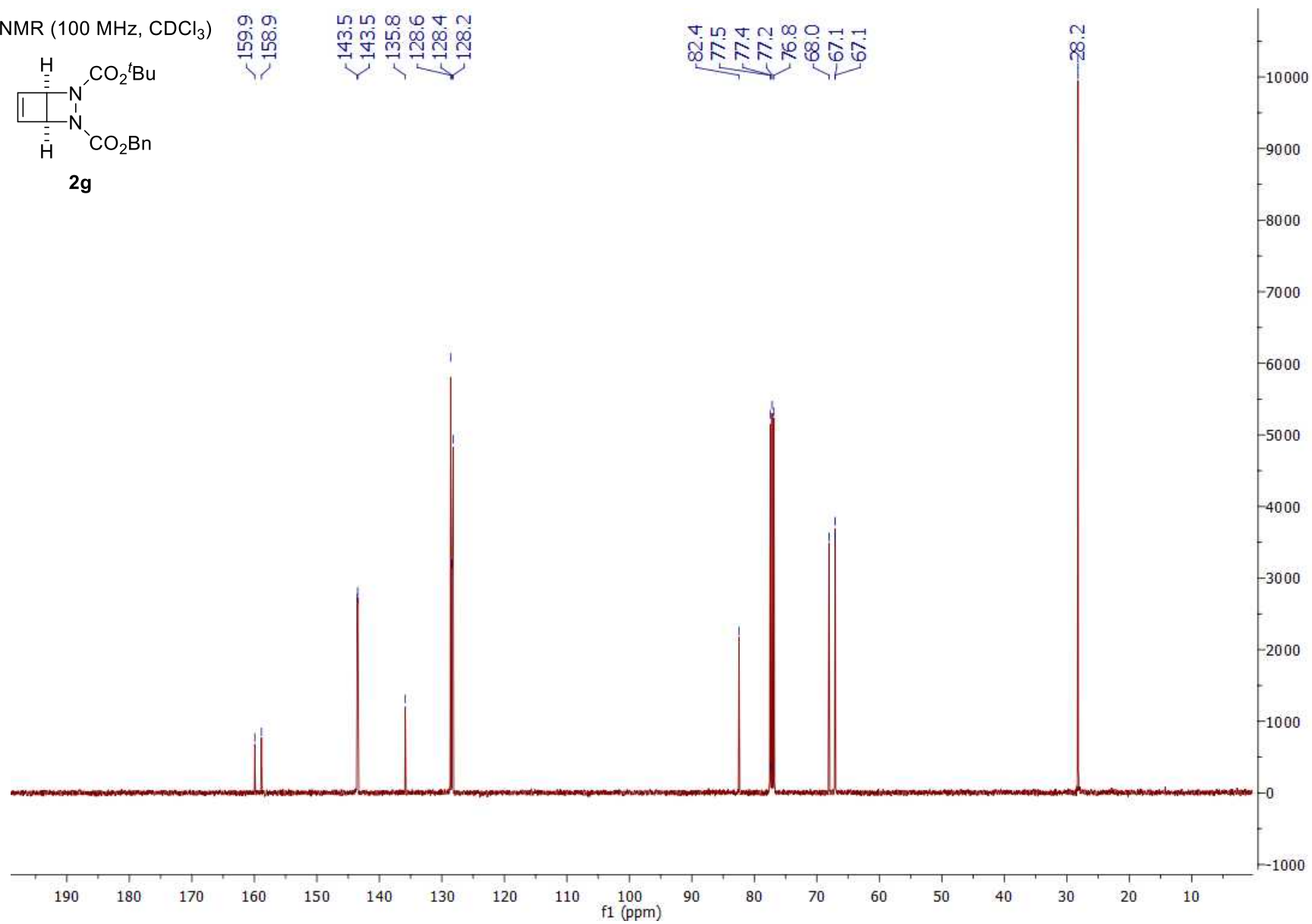
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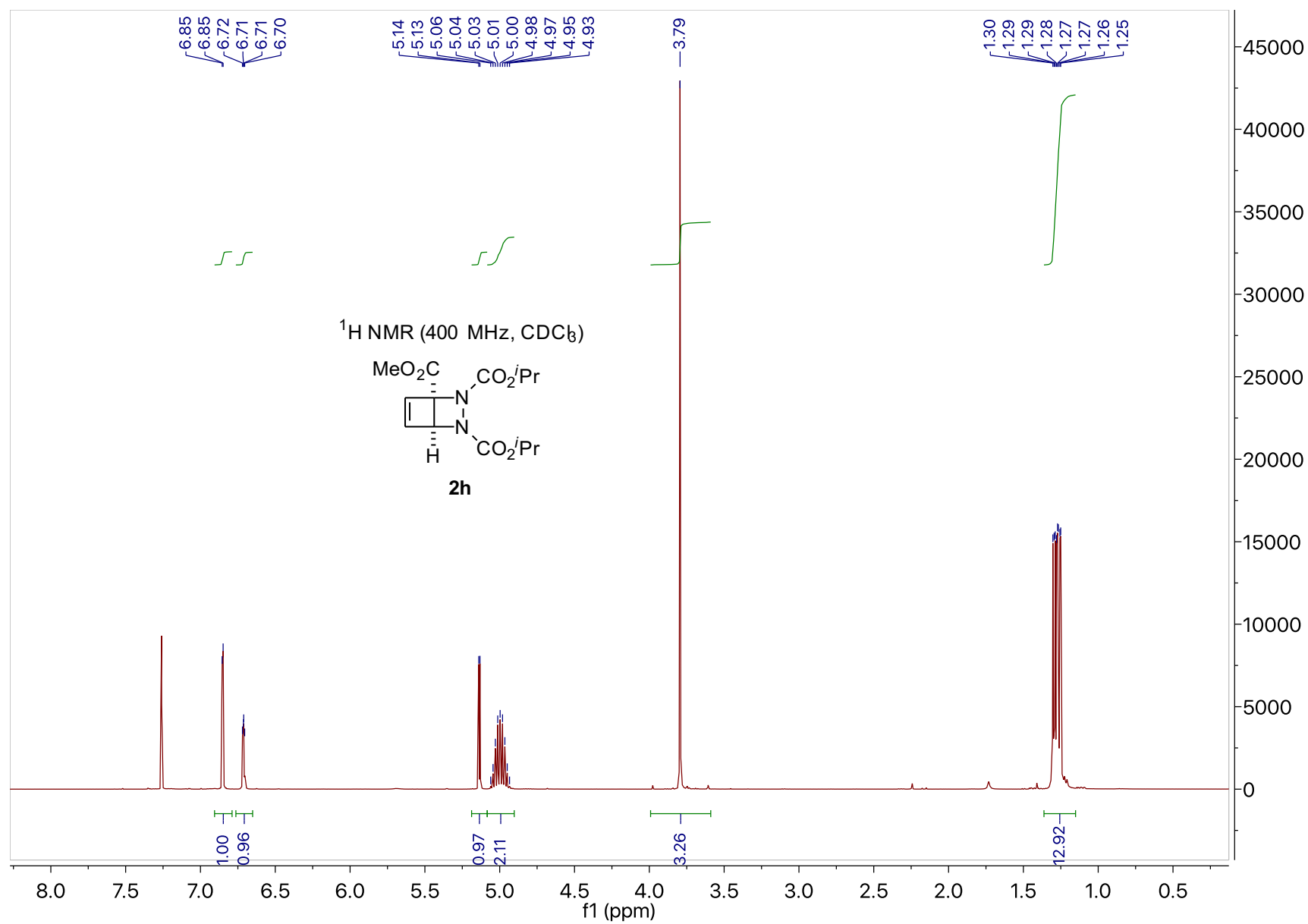


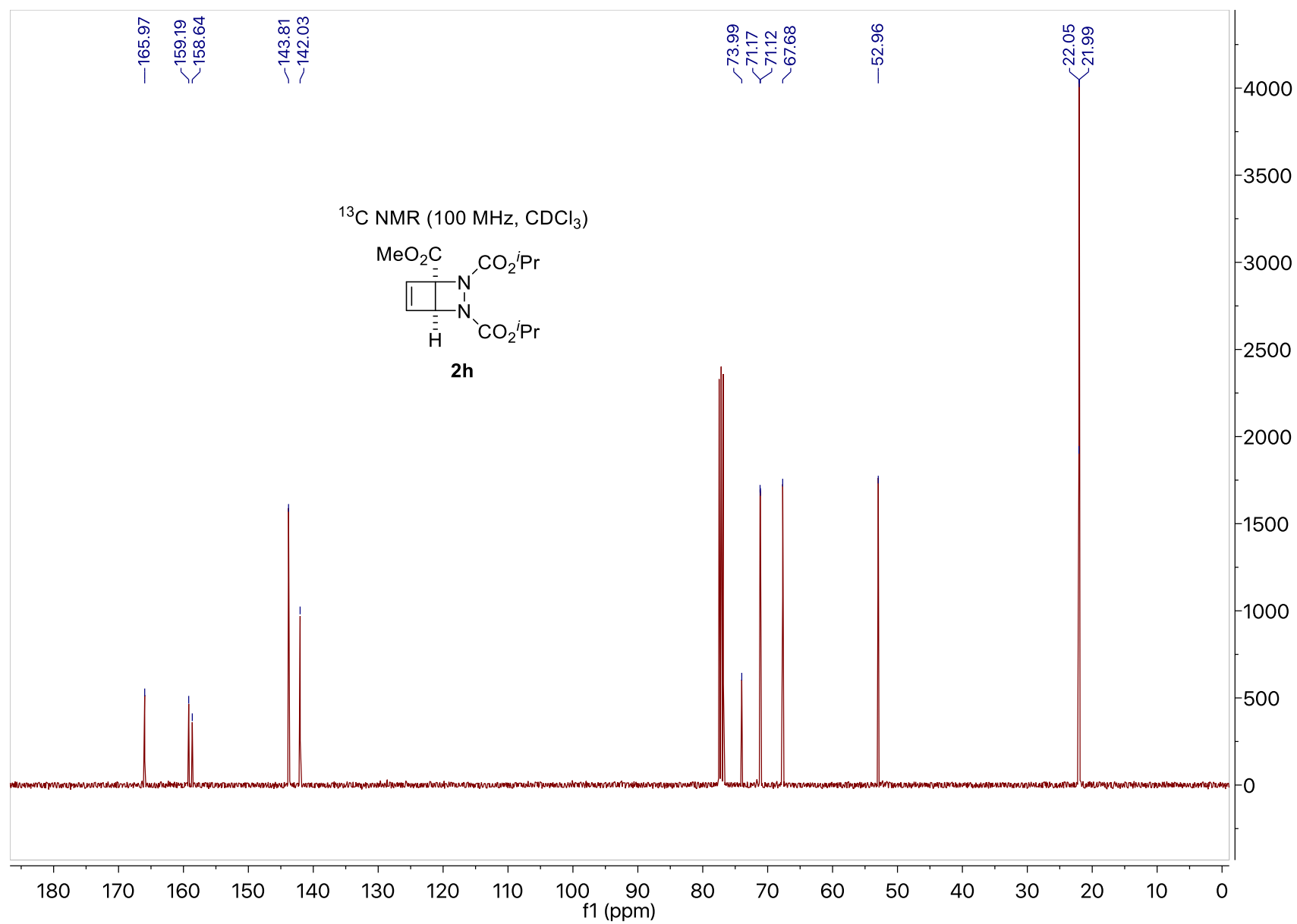
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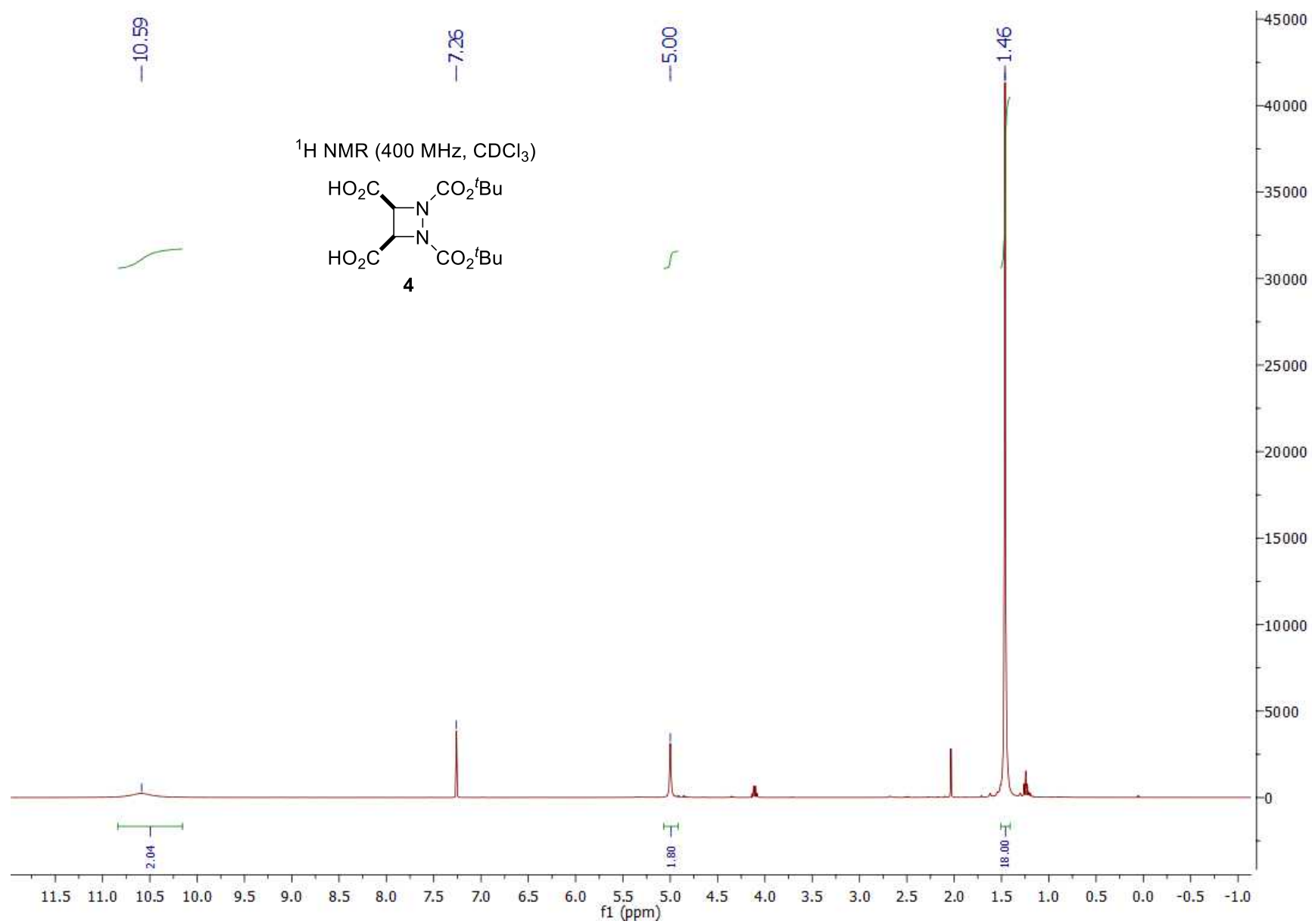


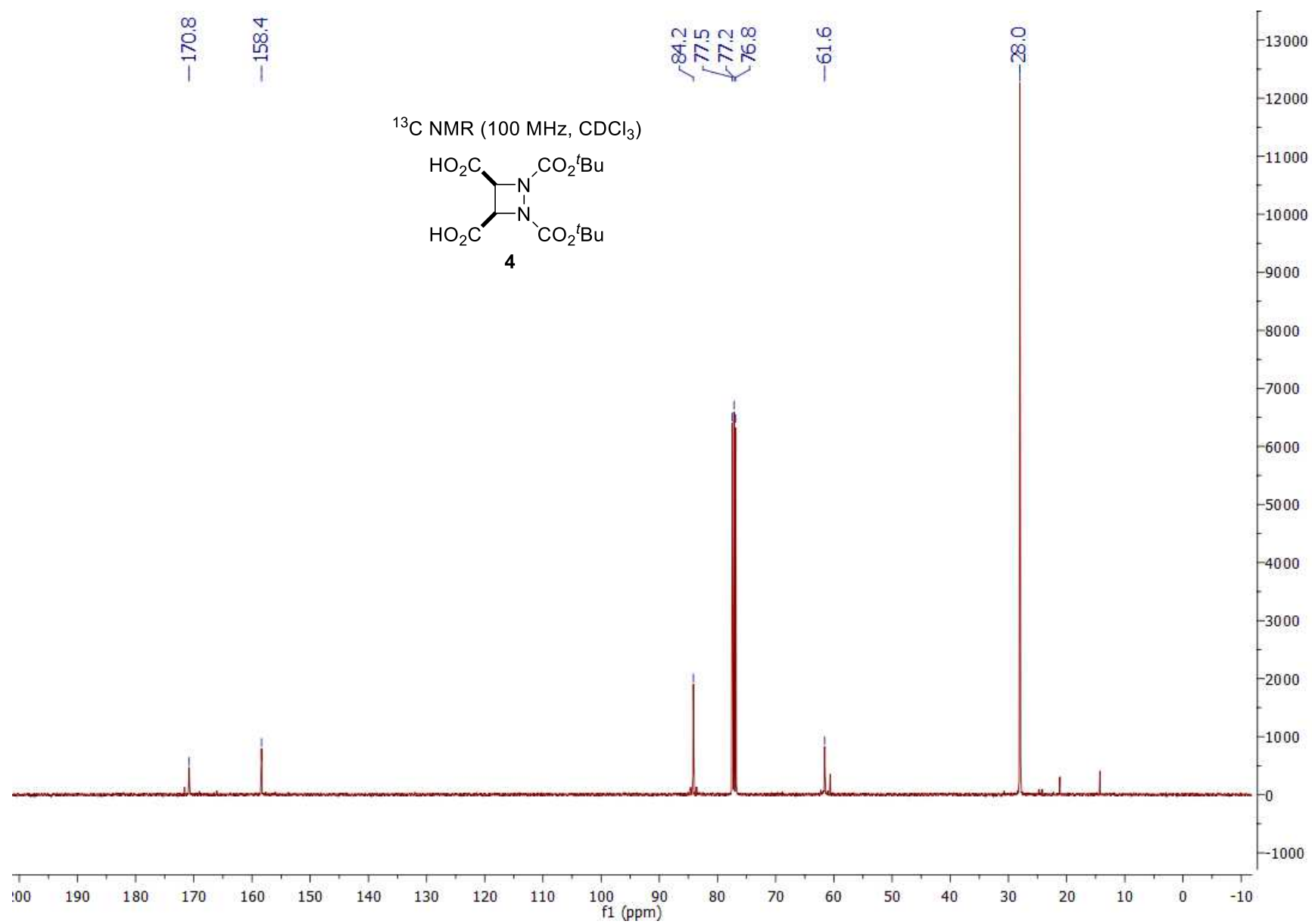
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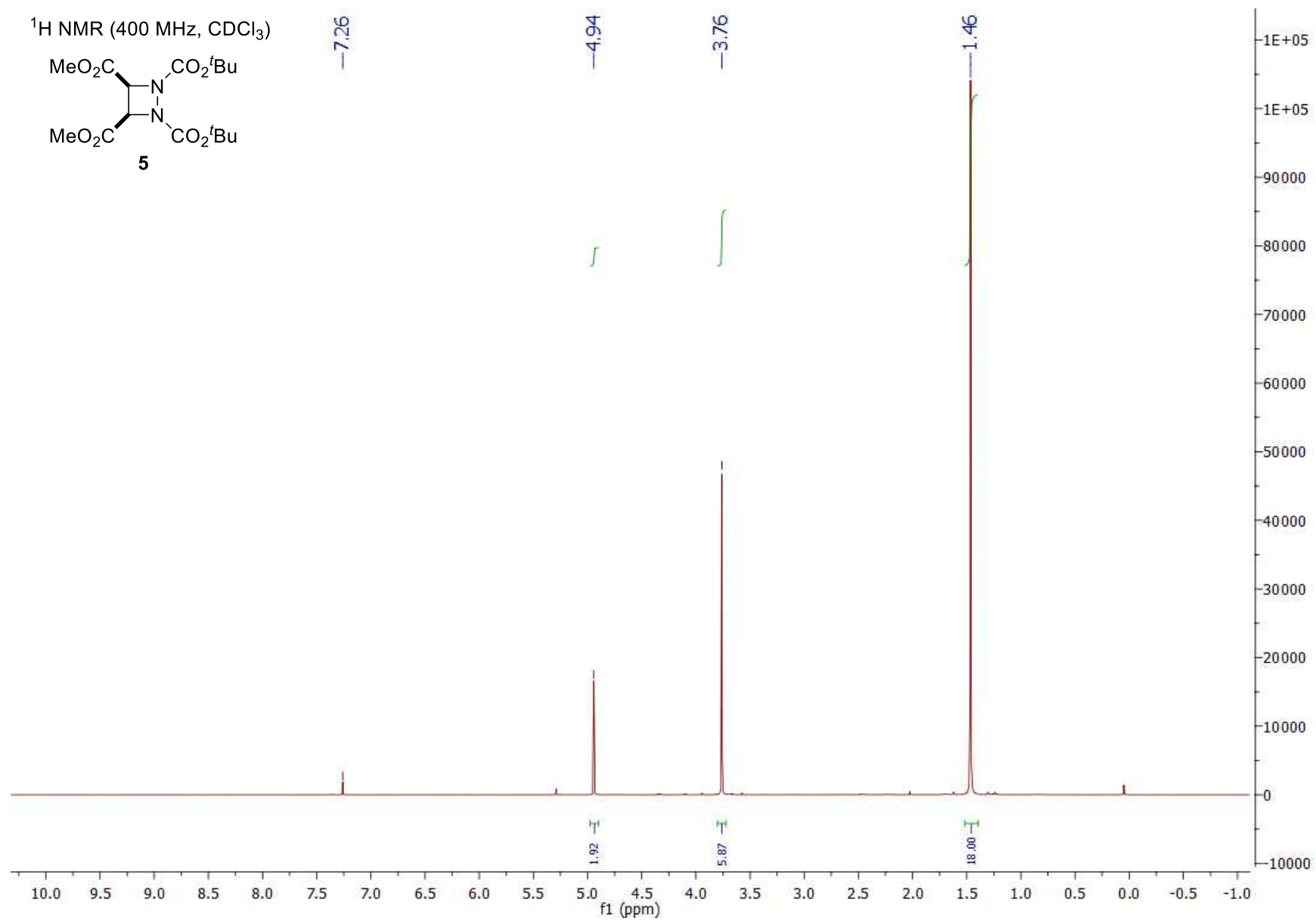
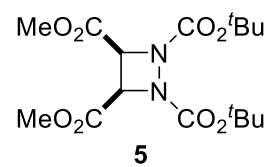


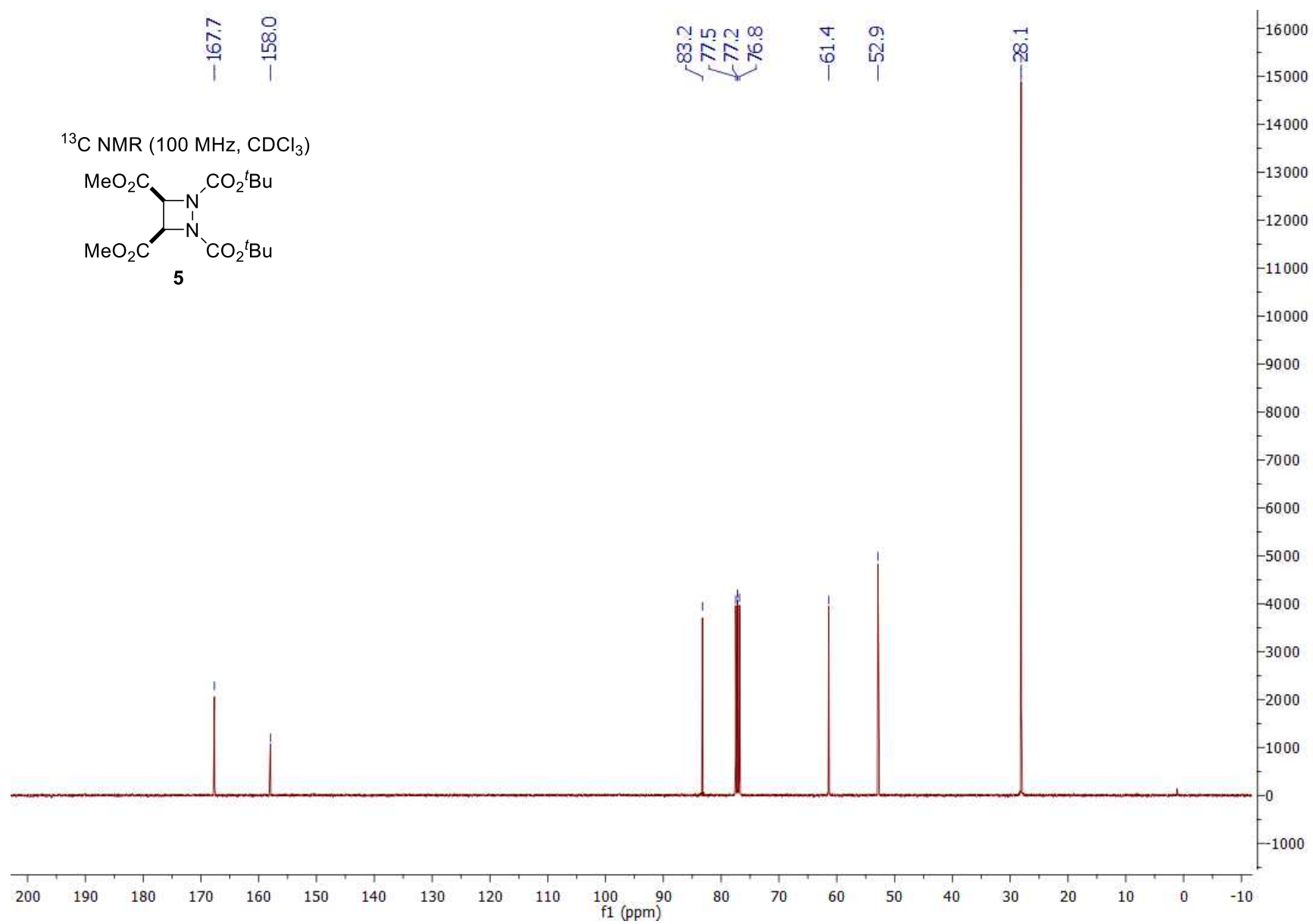


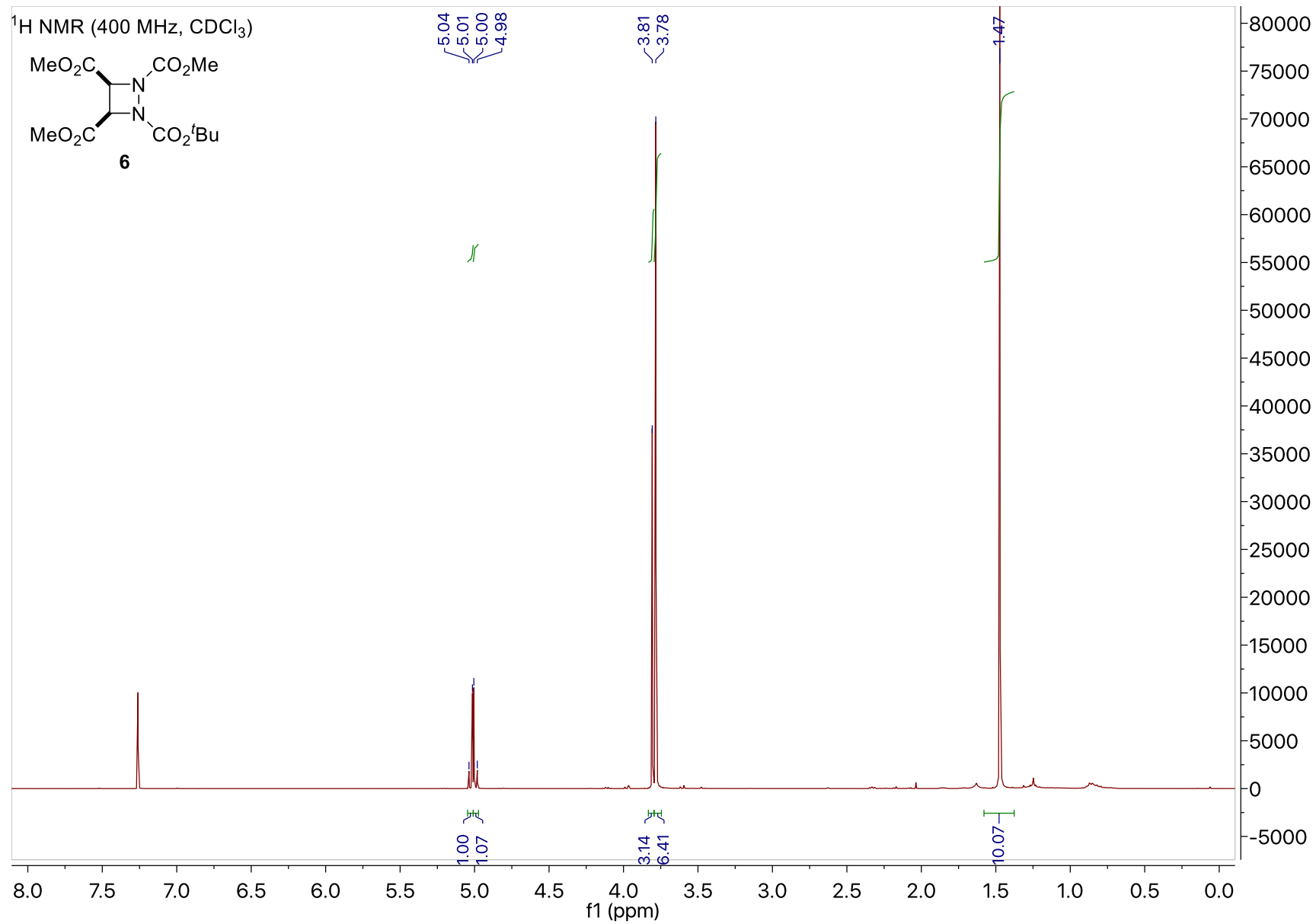




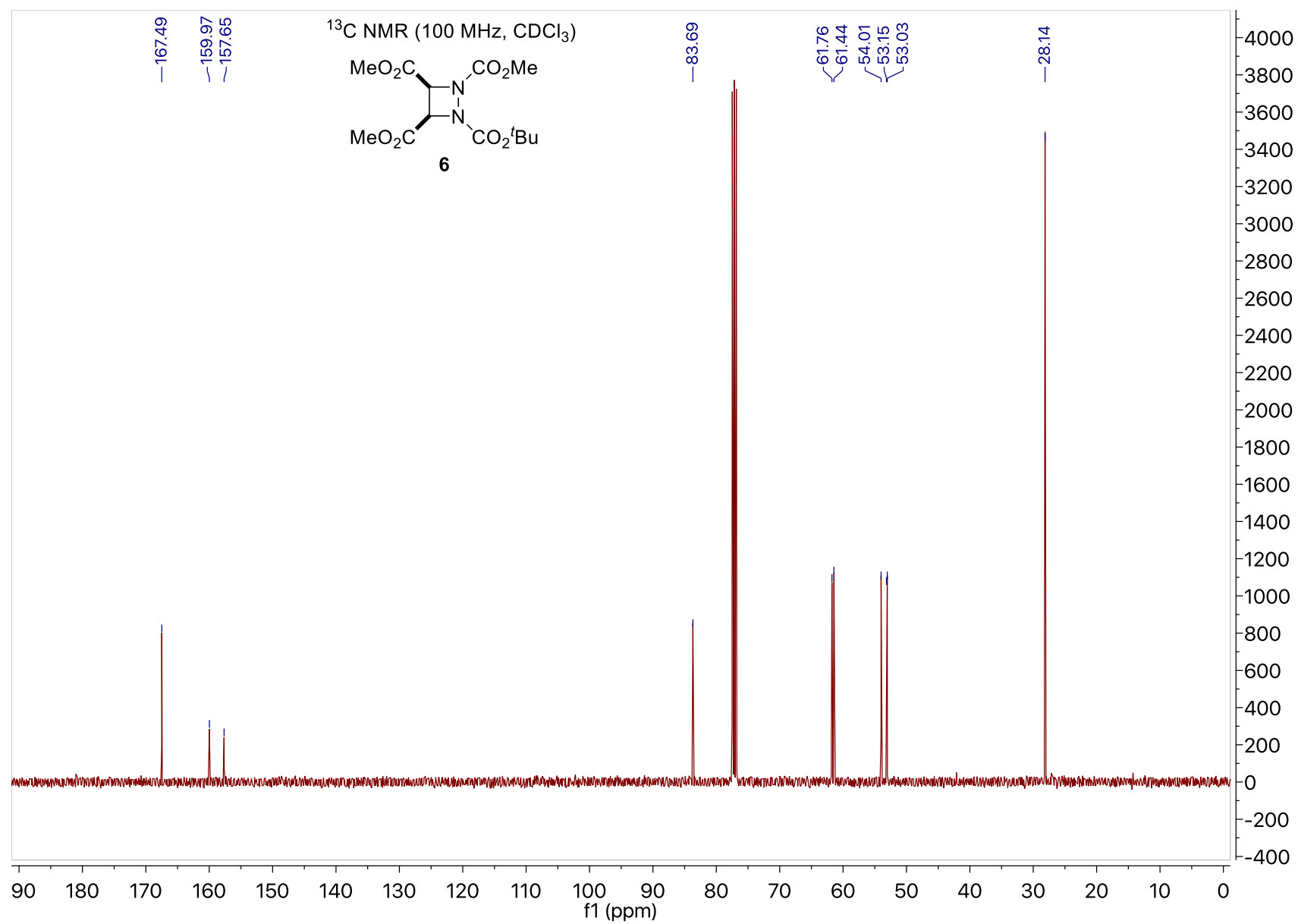
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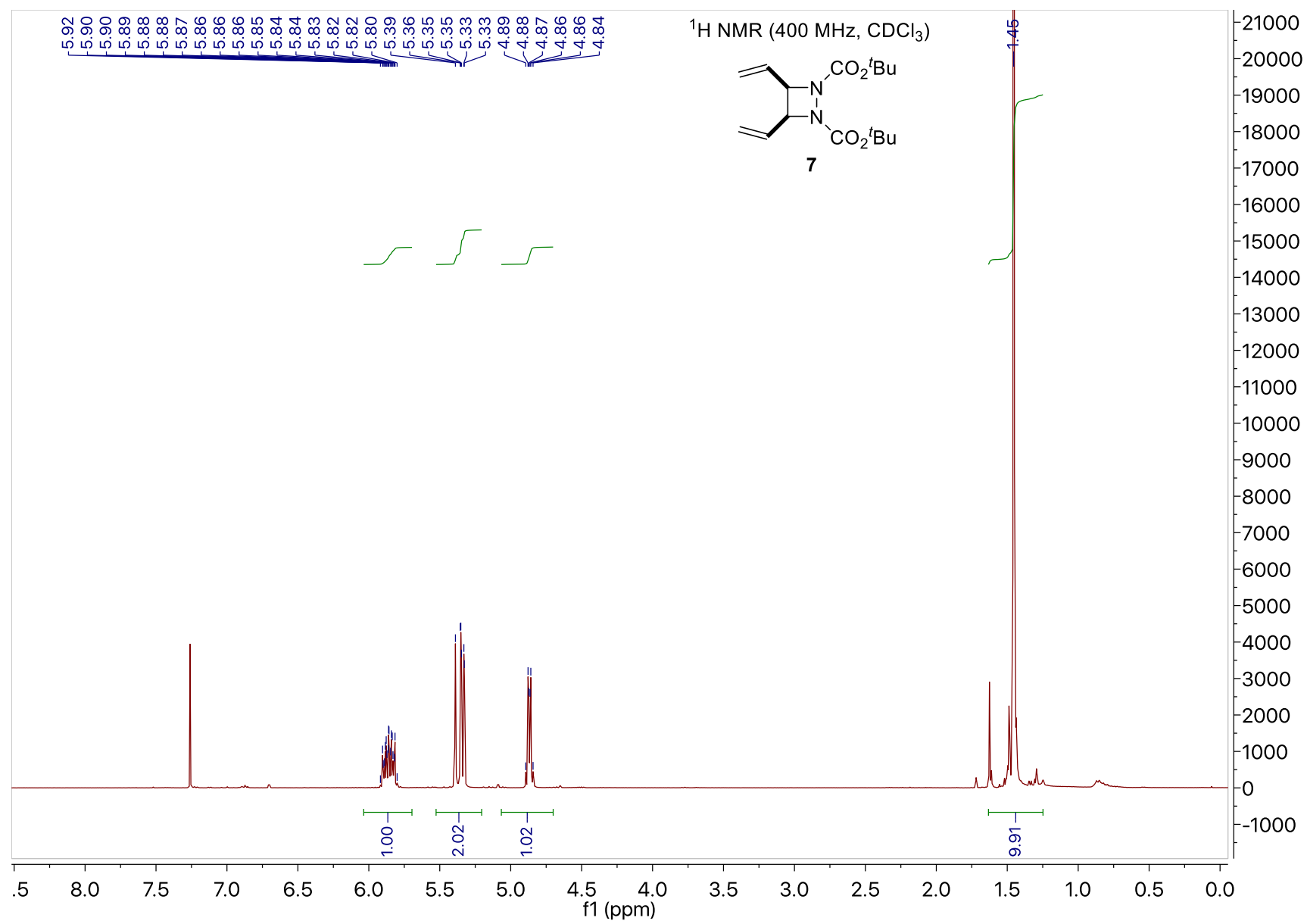


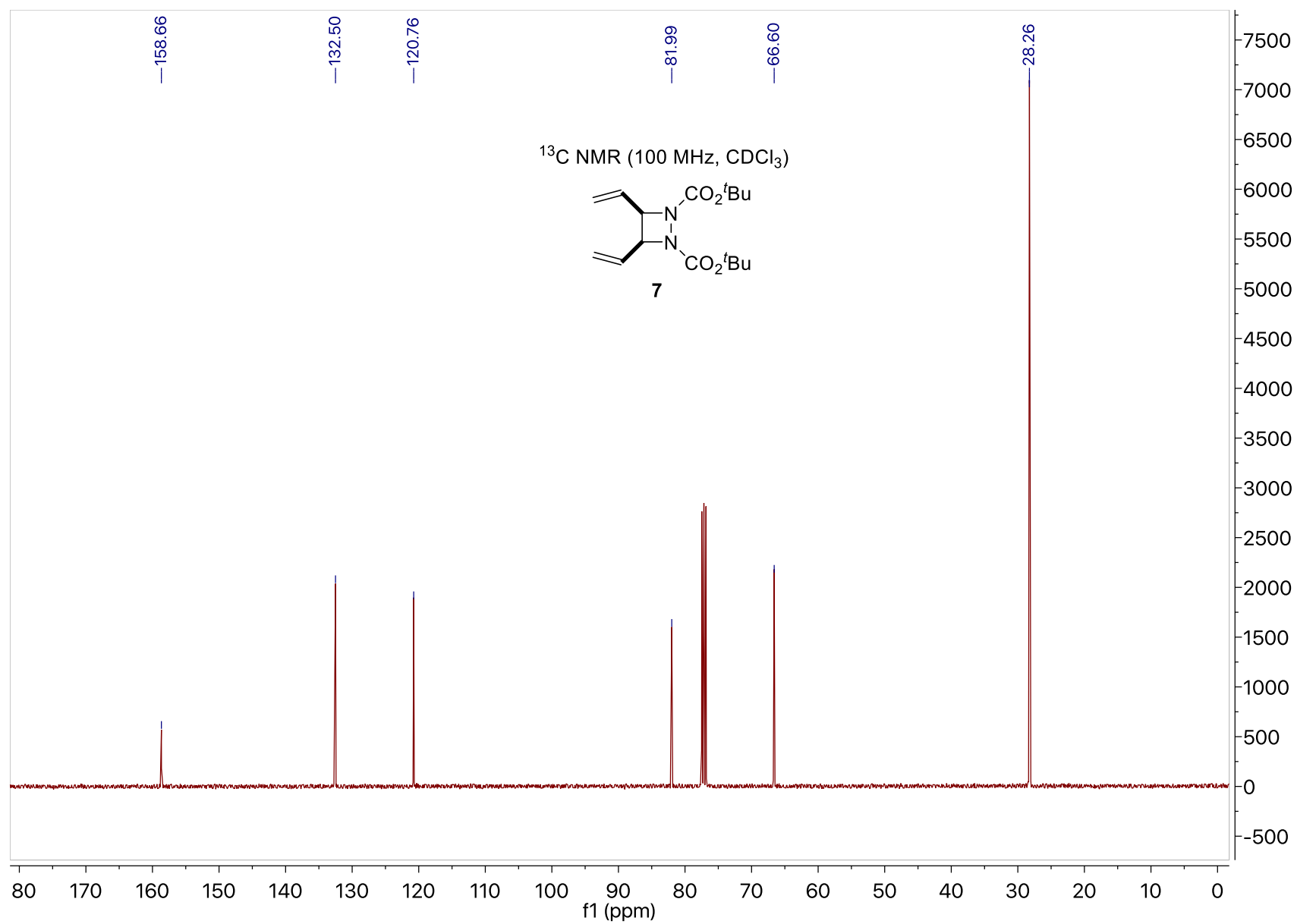




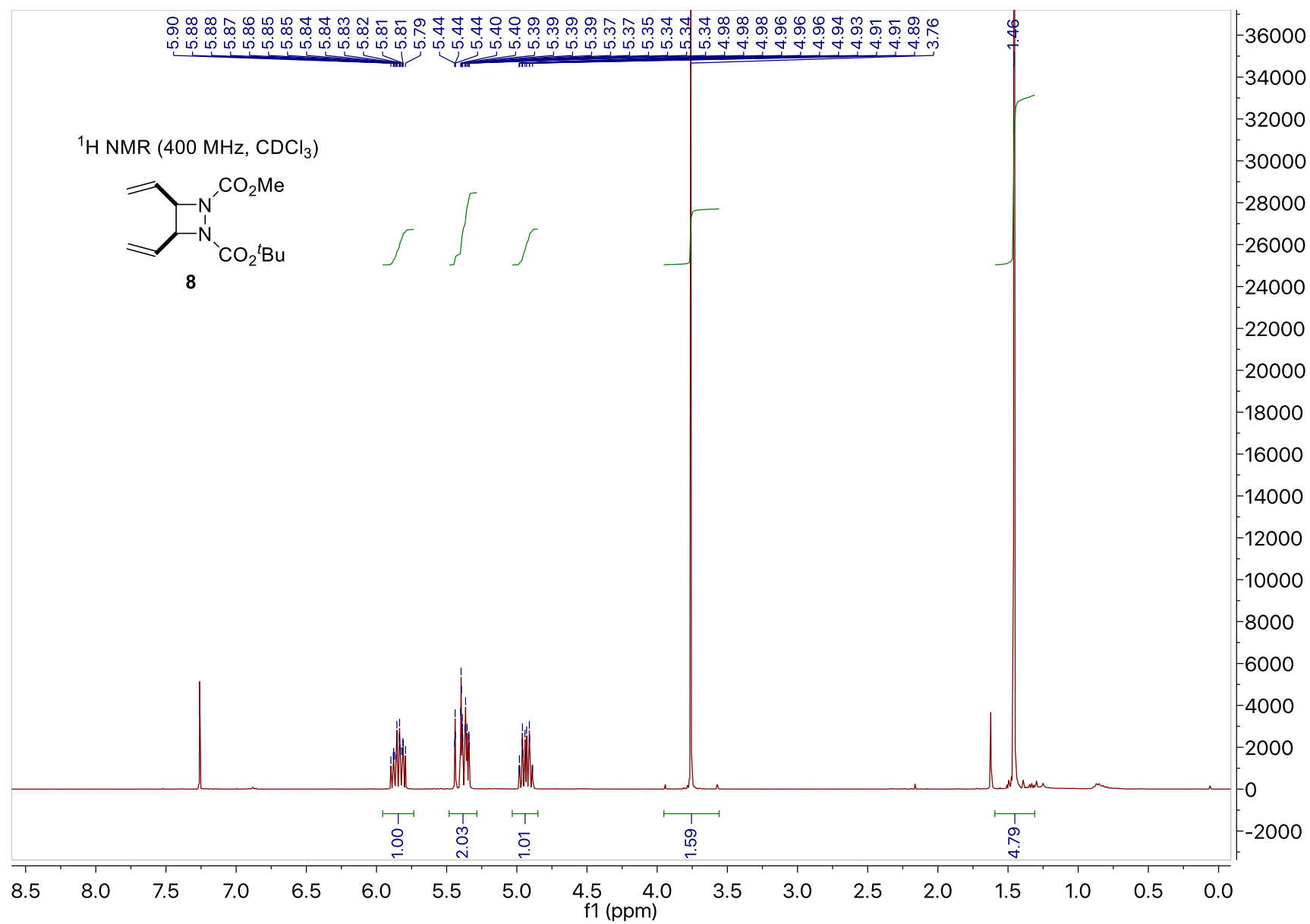
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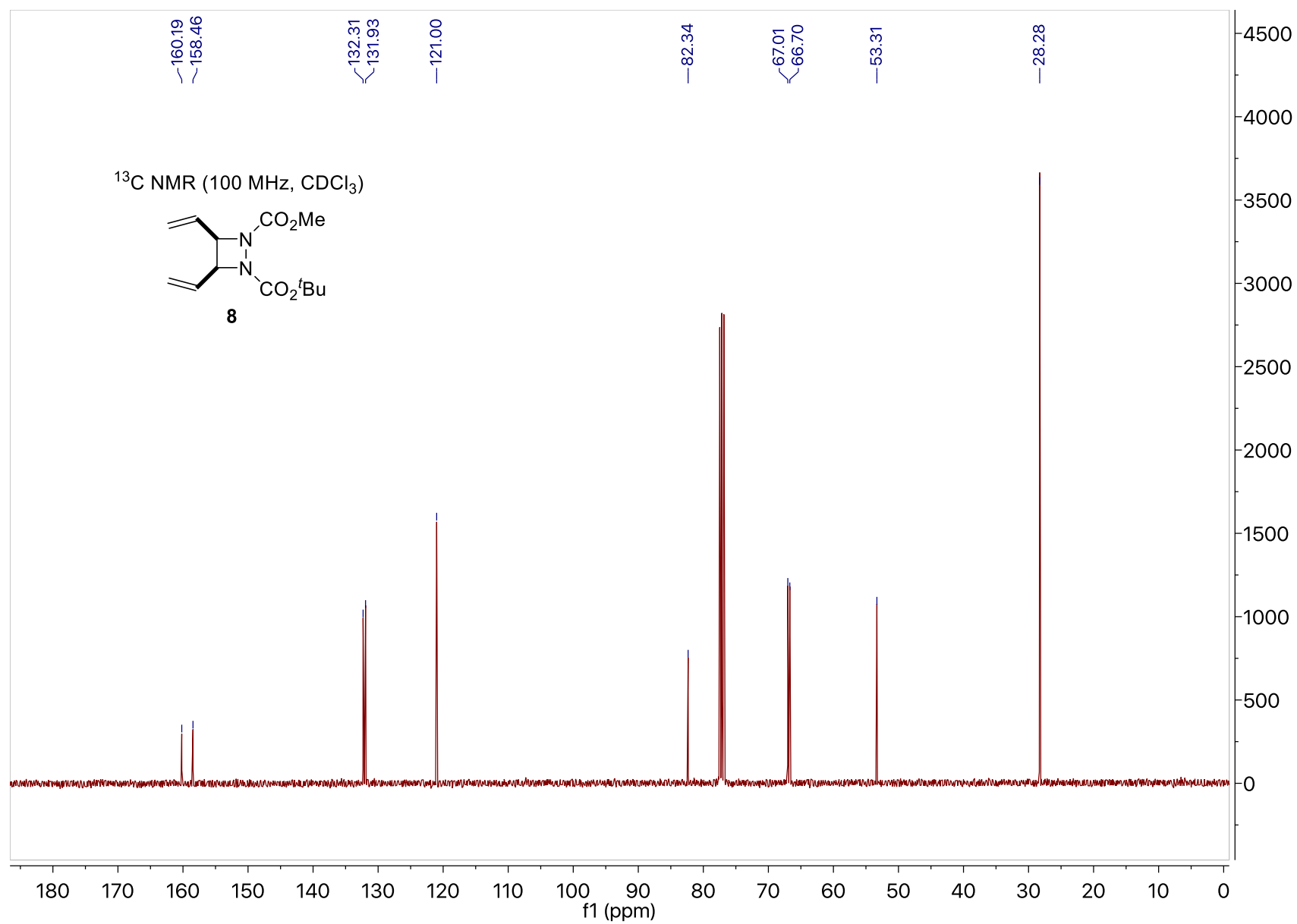




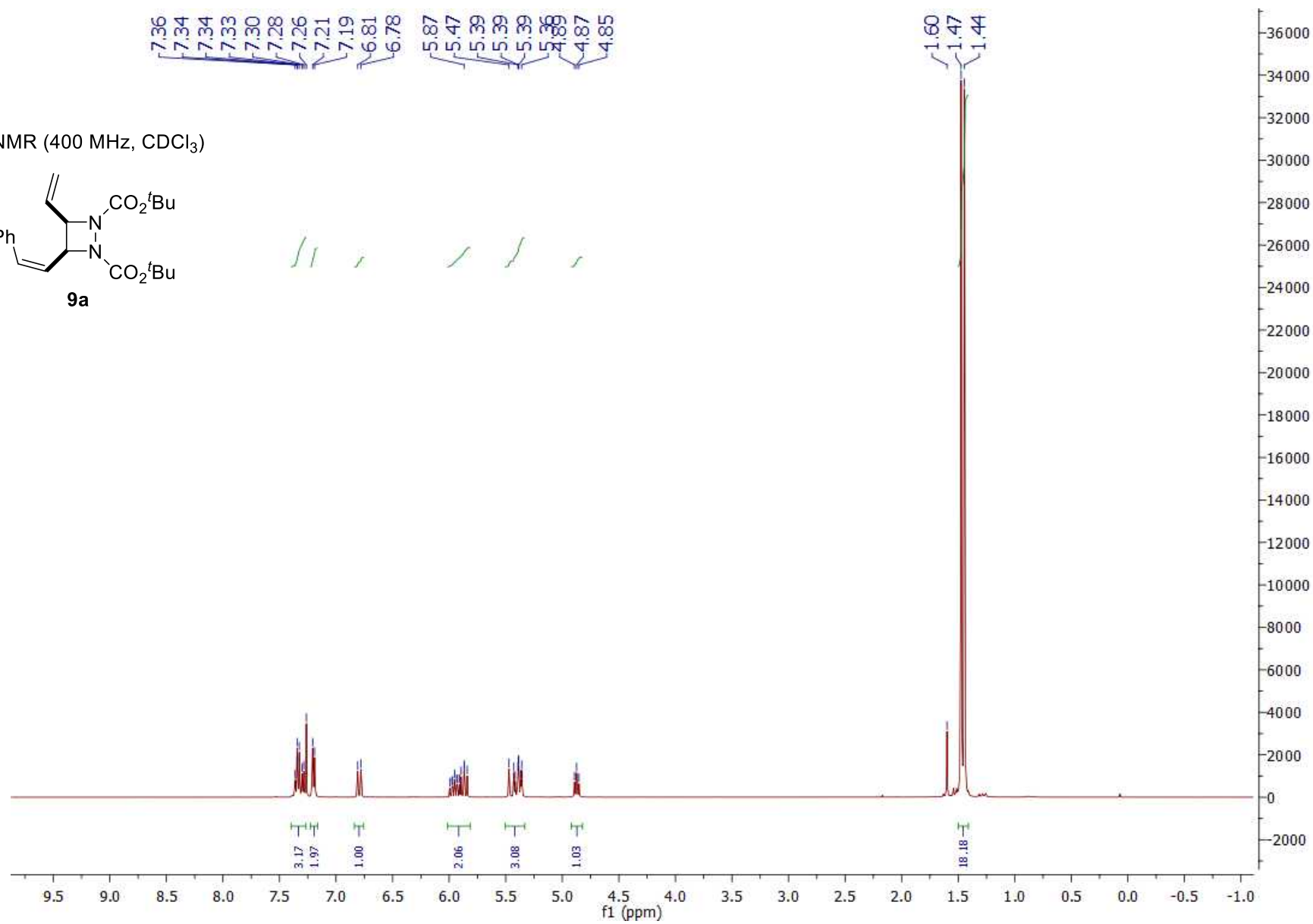
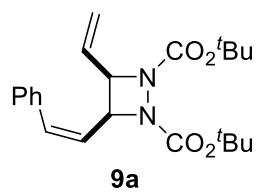


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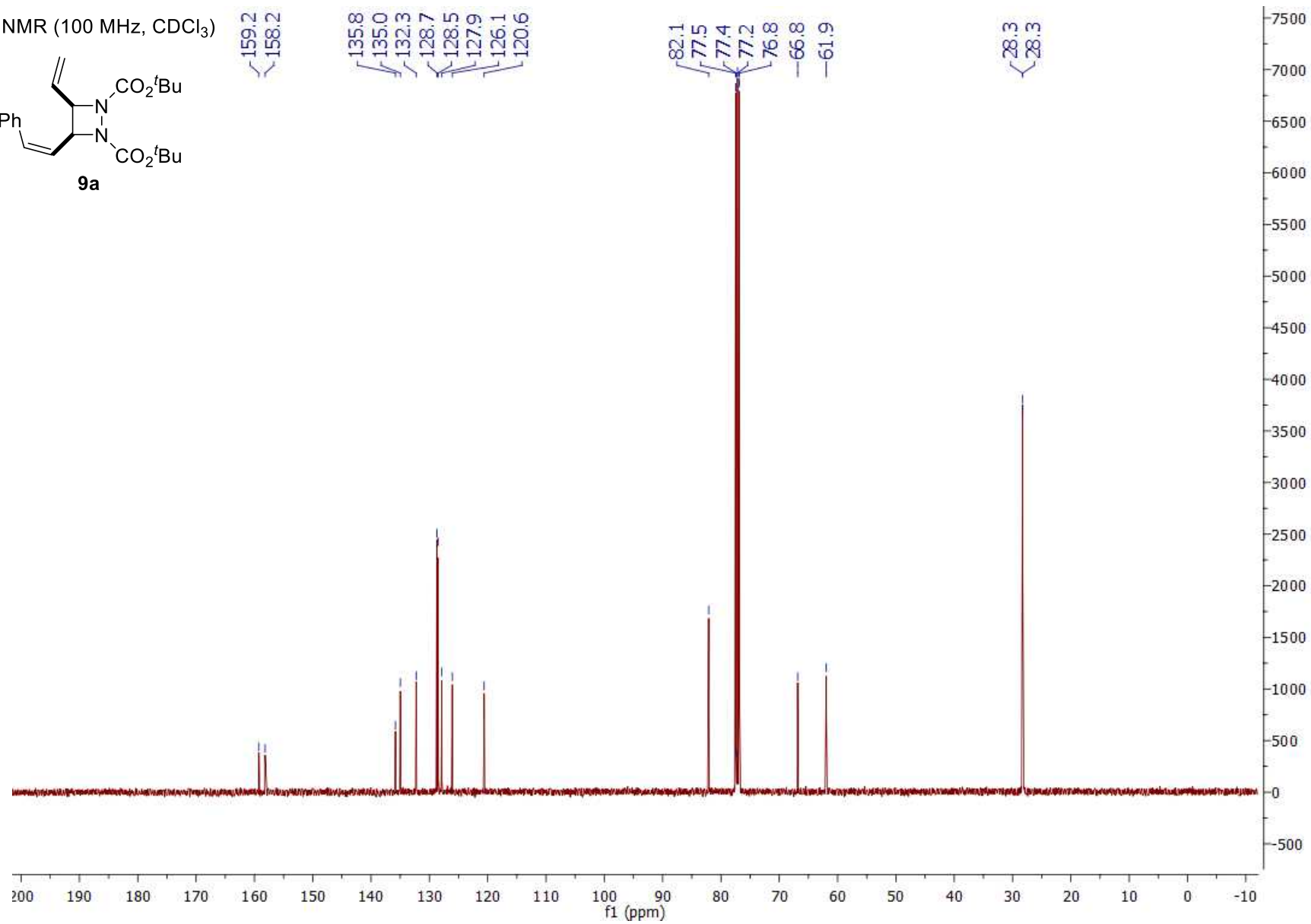
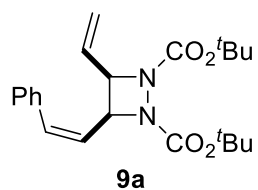




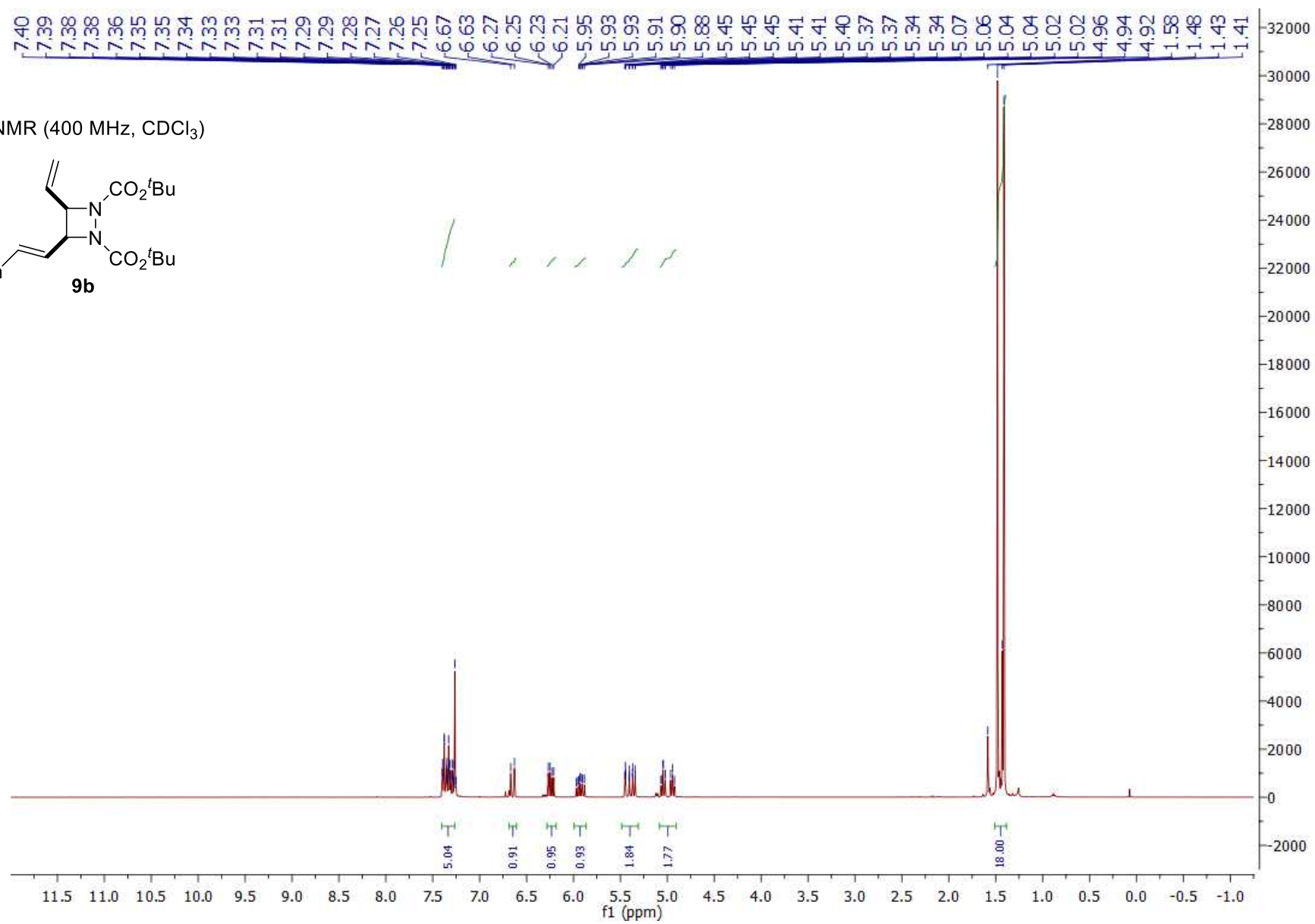
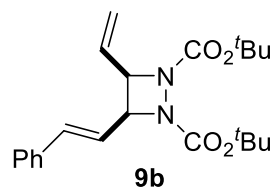
¹H NMR (400 MHz, CDCl₃)



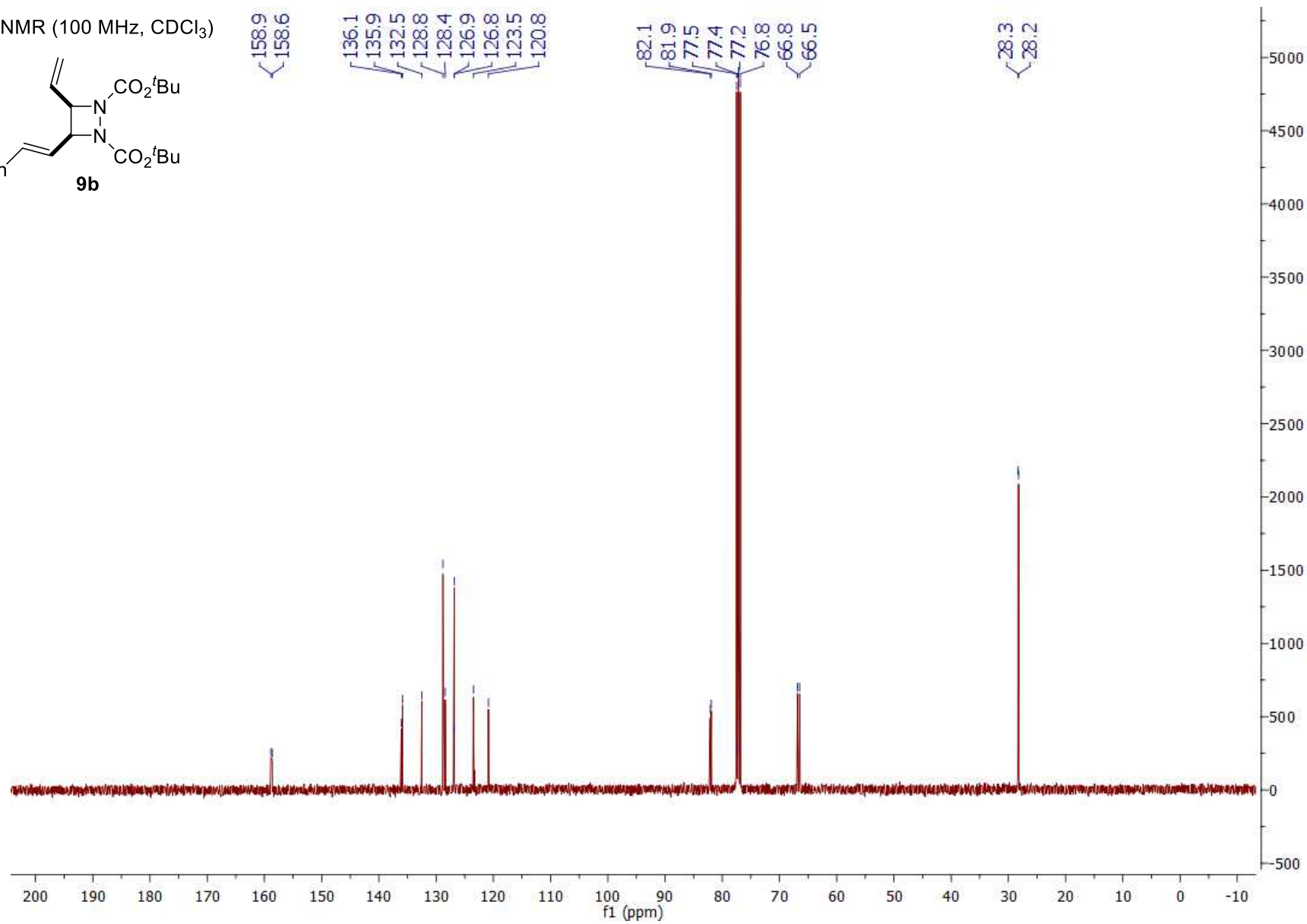
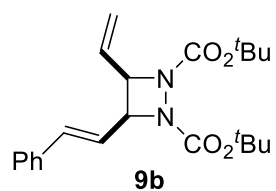
^{13}C NMR (100 MHz, CDCl_3)

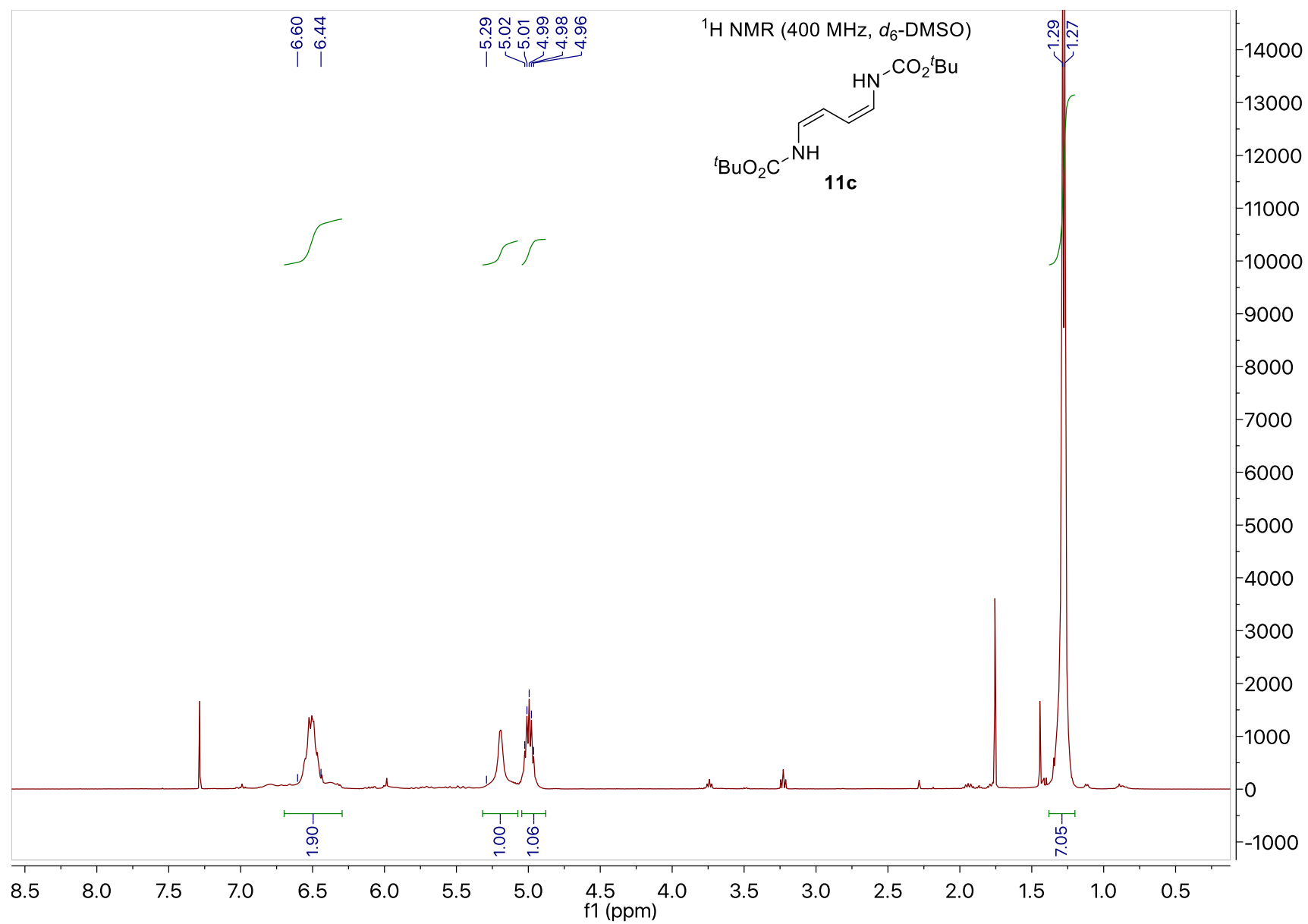


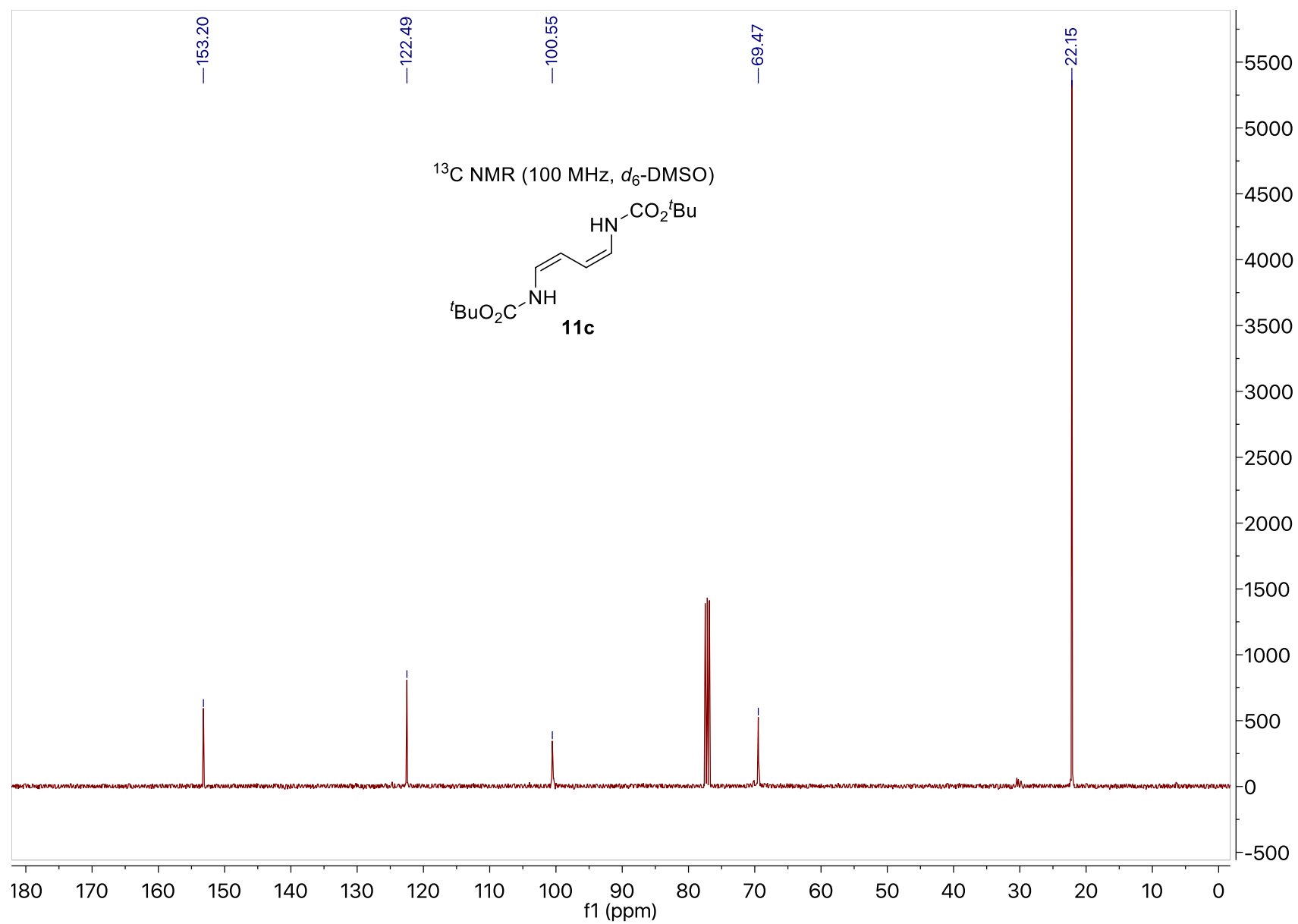
¹H NMR (400 MHz, CDCl₃)



^{13}C NMR (100 MHz, CDCl_3)

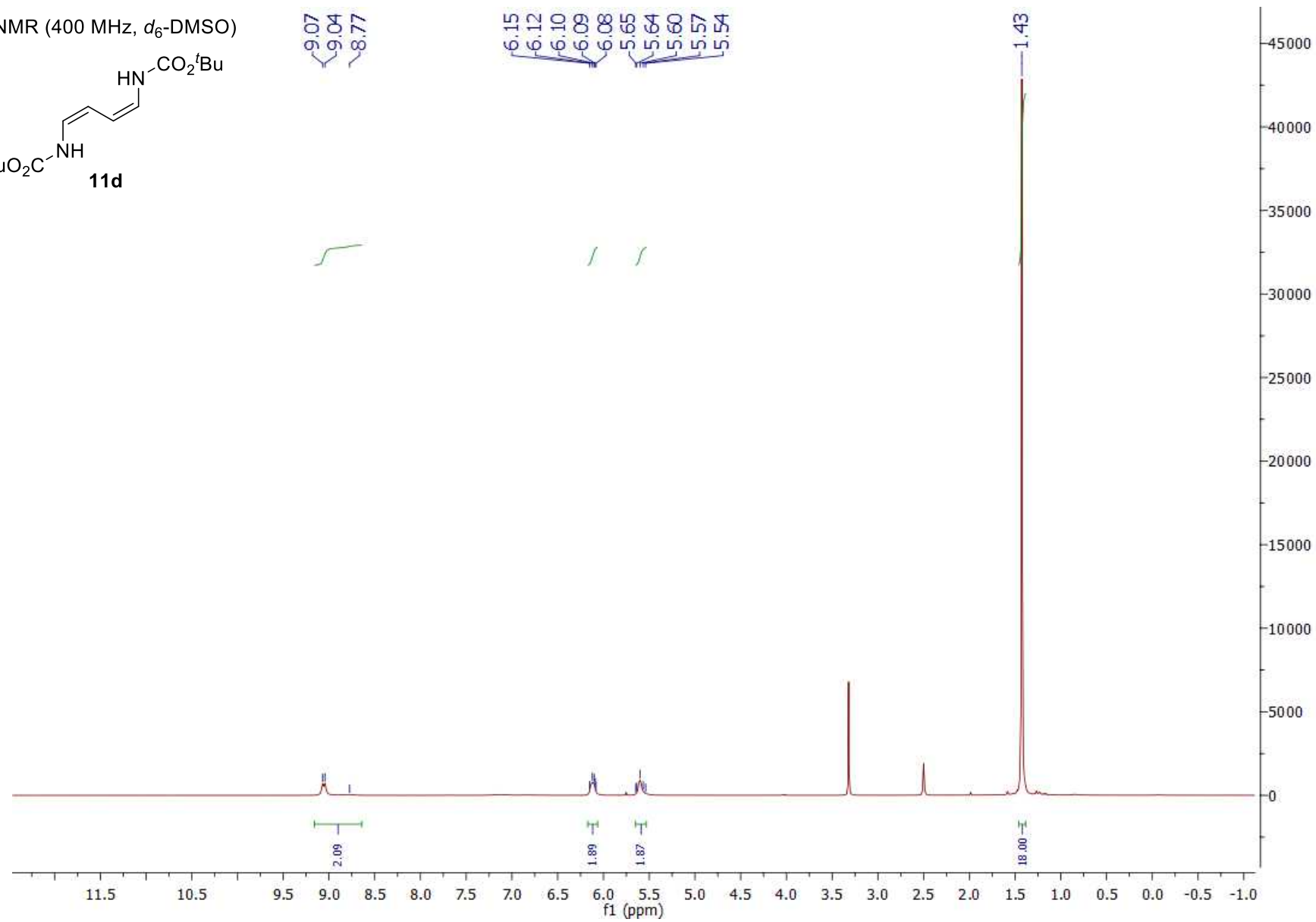
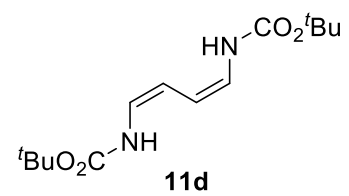


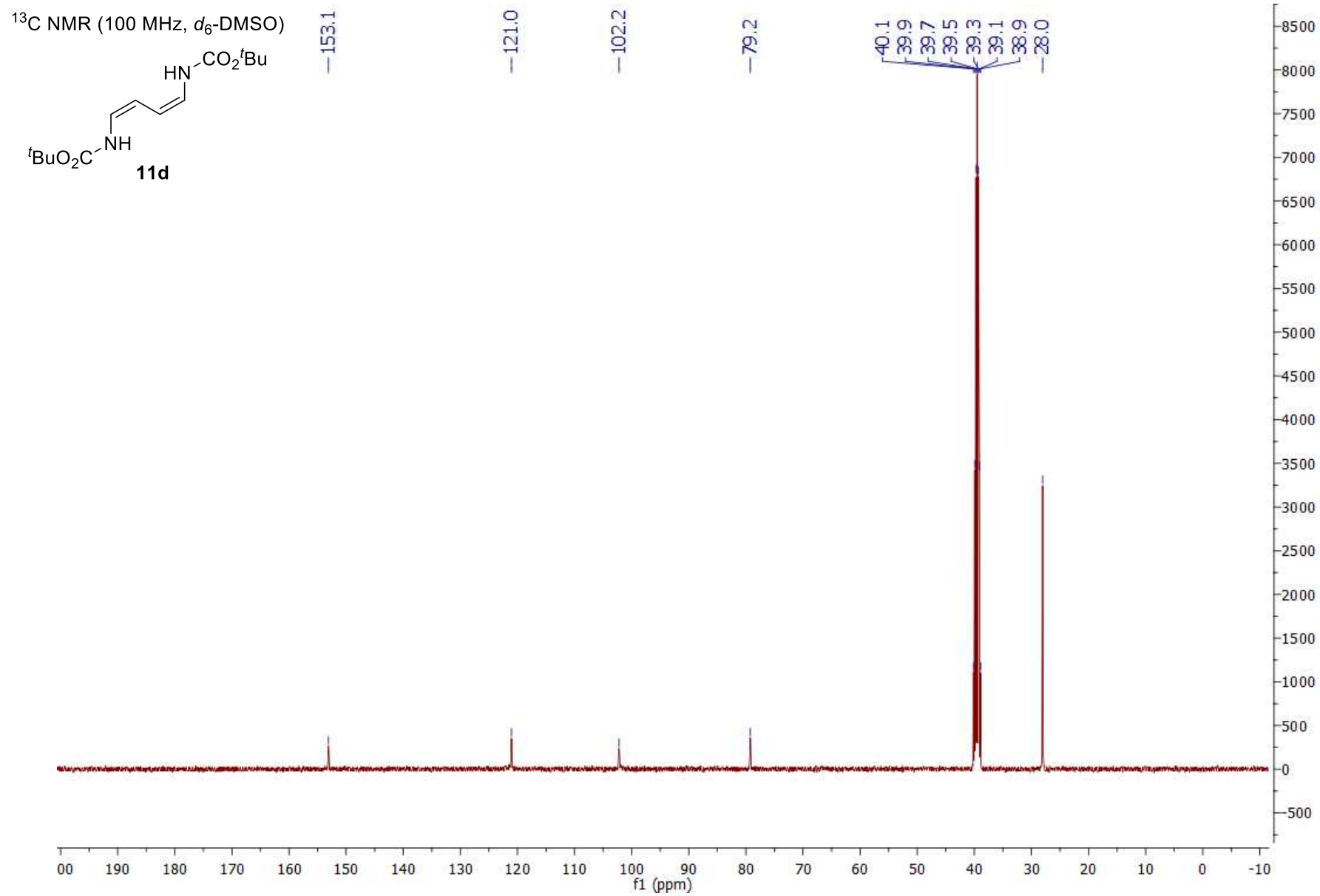




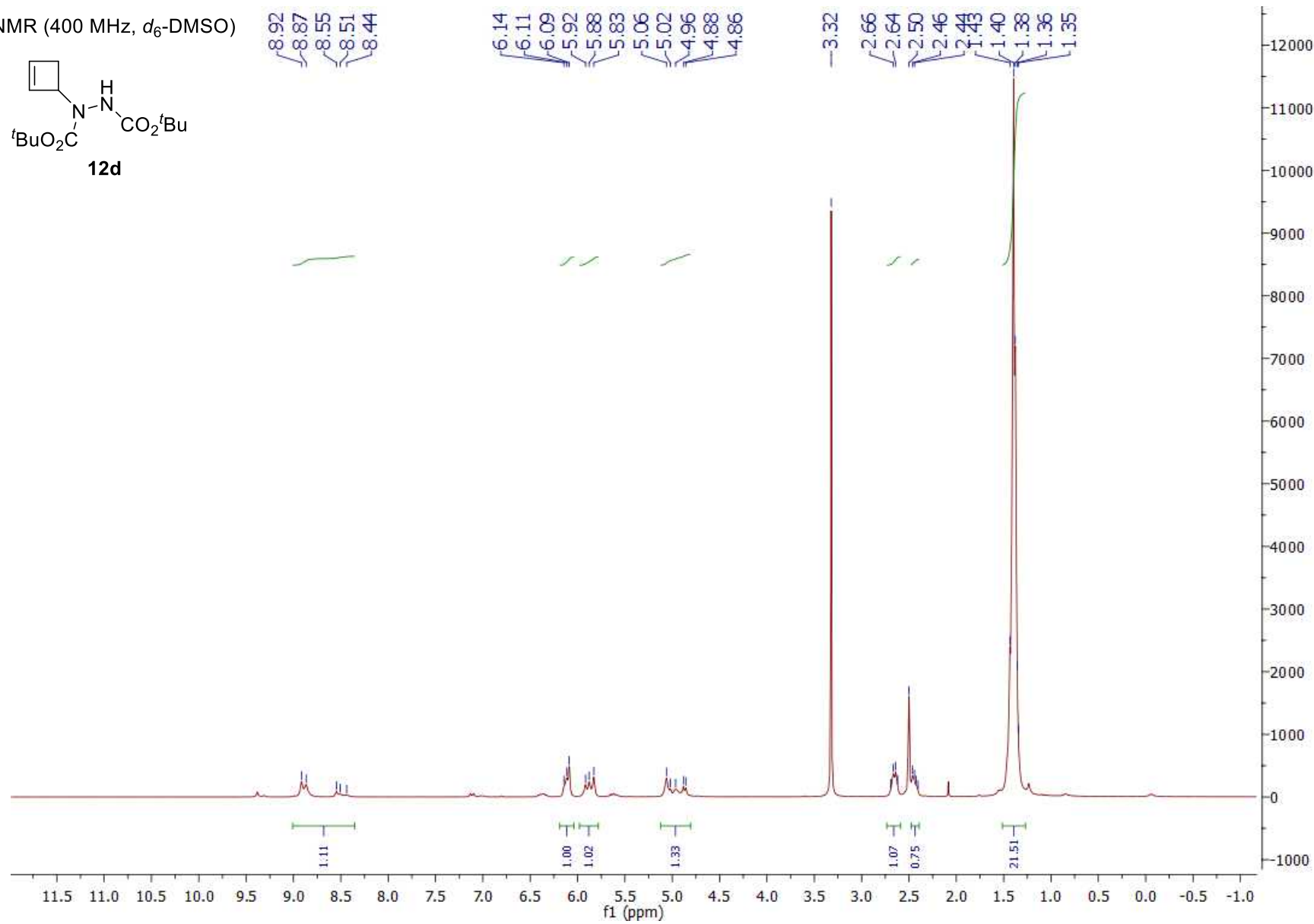
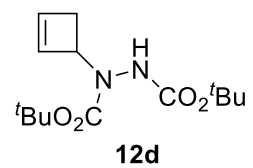
S58

^1H NMR (400 MHz, d_6 -DMSO)

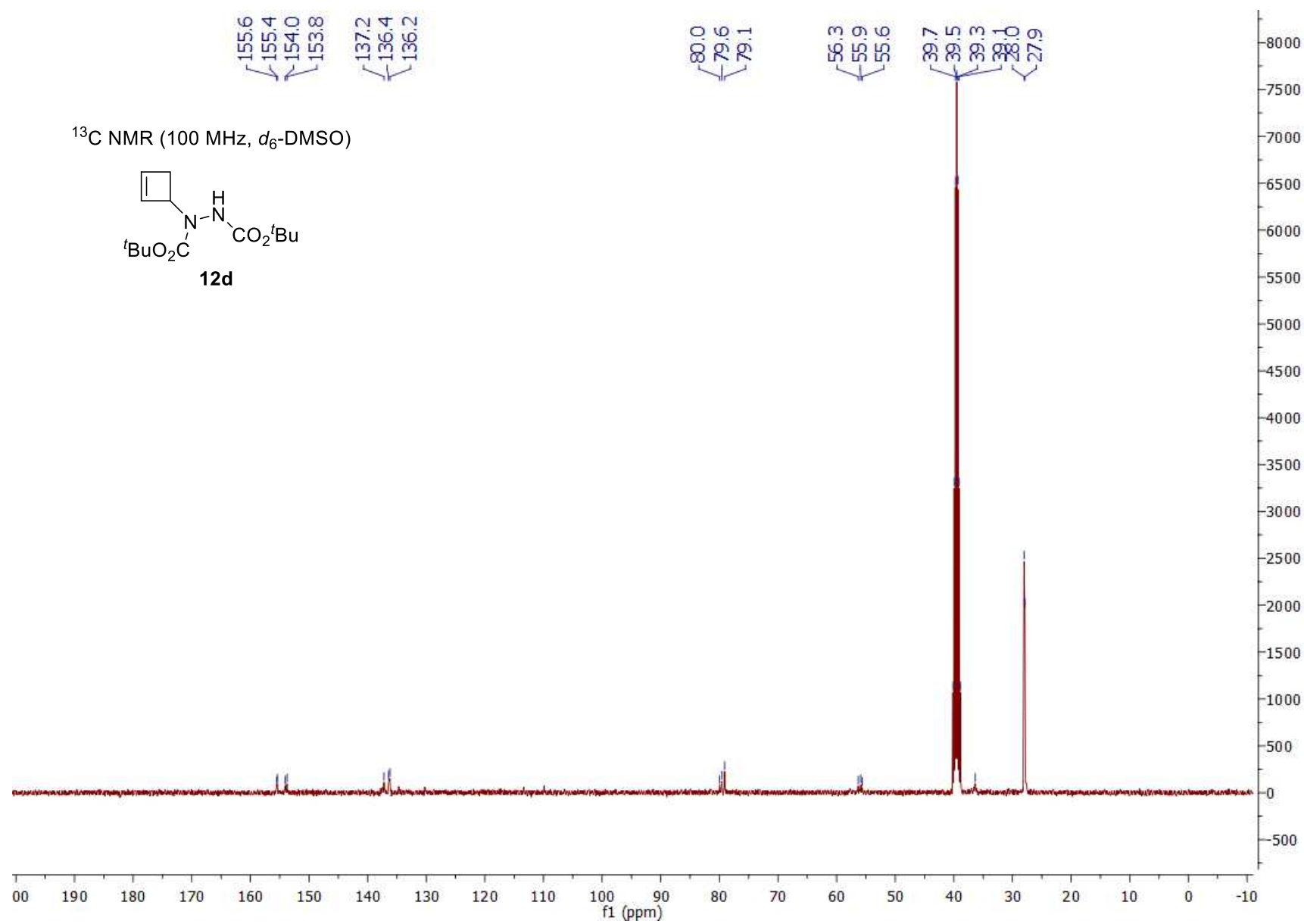
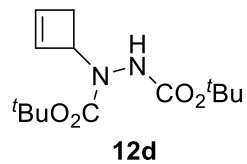




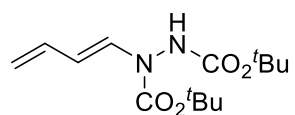
¹H NMR (400 MHz, d₆-DMSO)



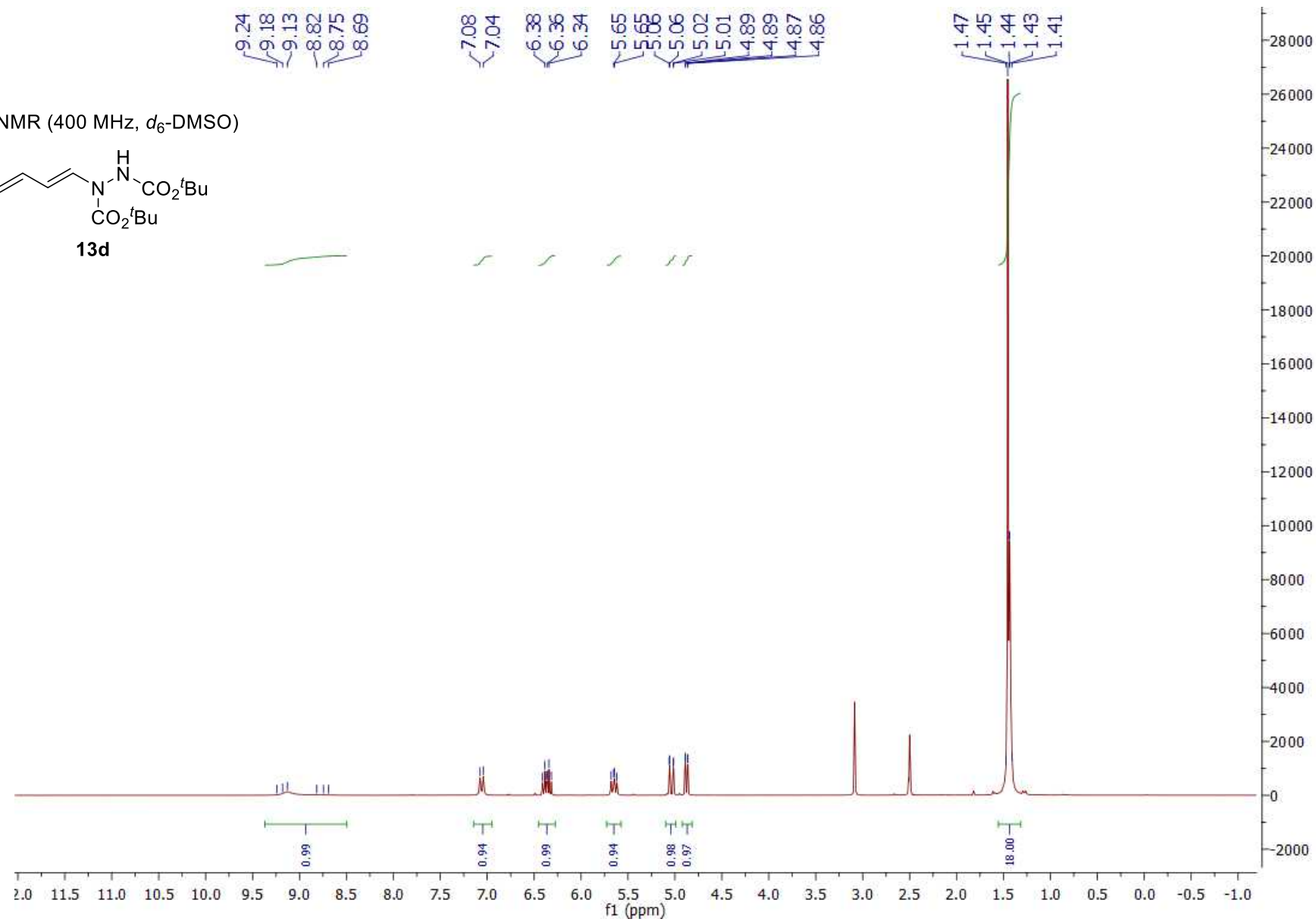
^{13}C NMR (100 MHz, d_6 -DMSO)



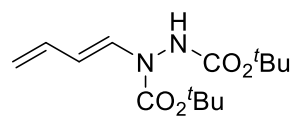
¹H NMR (400 MHz, d₆-DMSO)



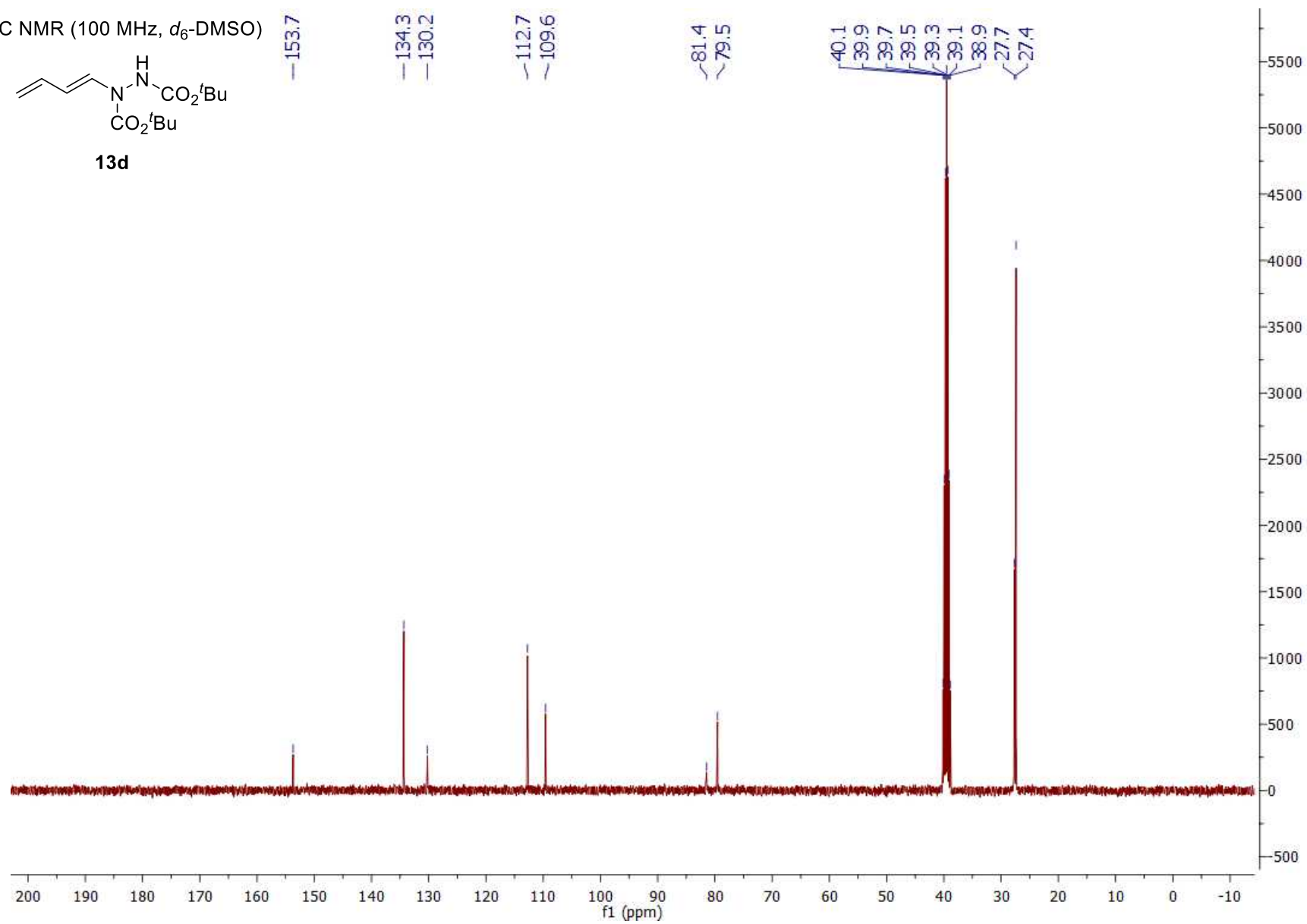
13d



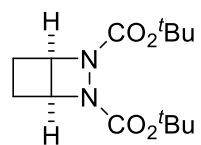
^{13}C NMR (100 MHz, d_6 -DMSO)



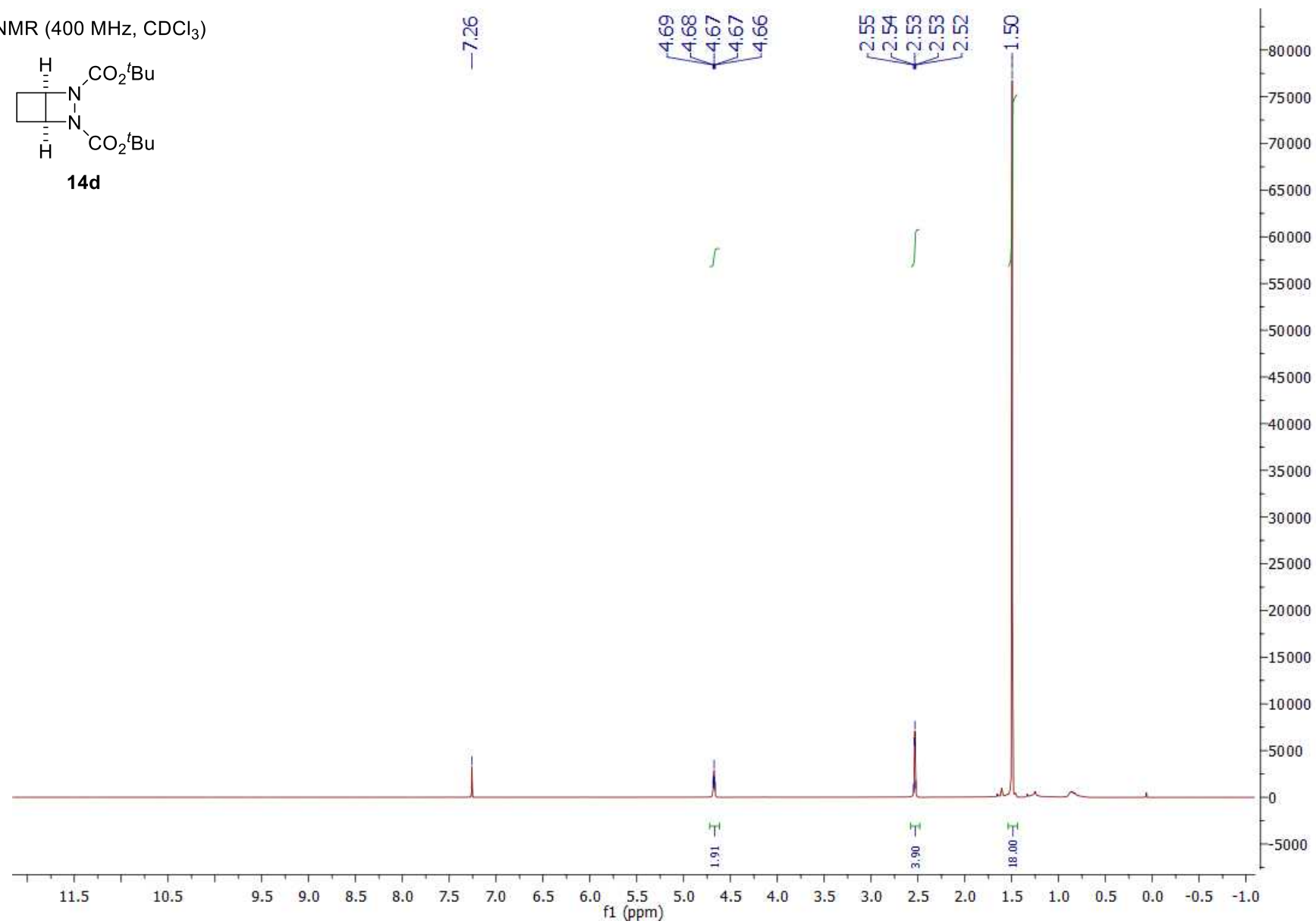
13d



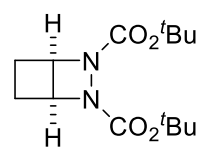
¹H NMR (400 MHz, CDCl₃)



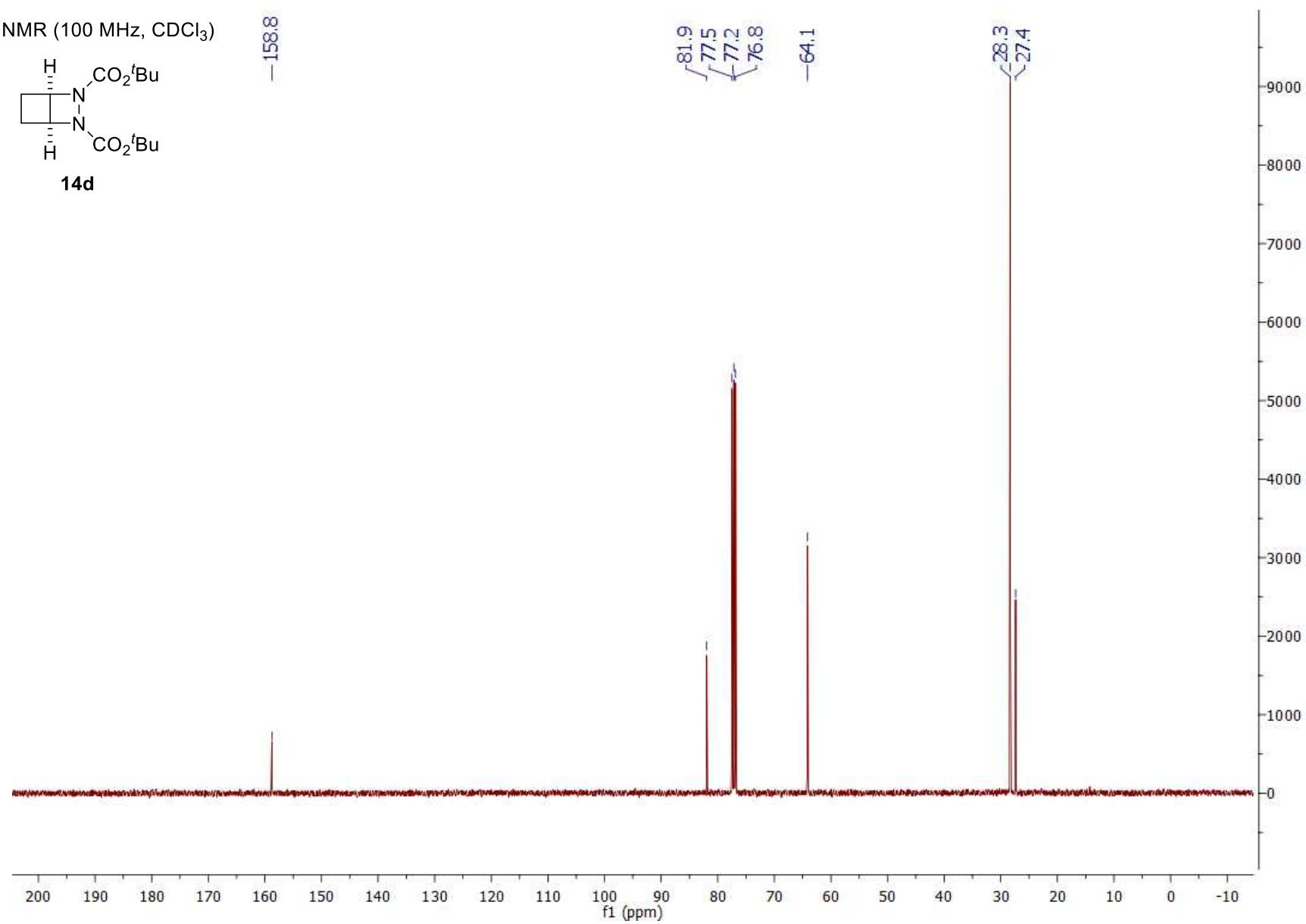
14d



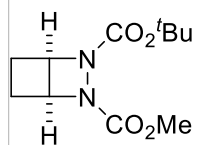
^{13}C NMR (100 MHz, CDCl_3)



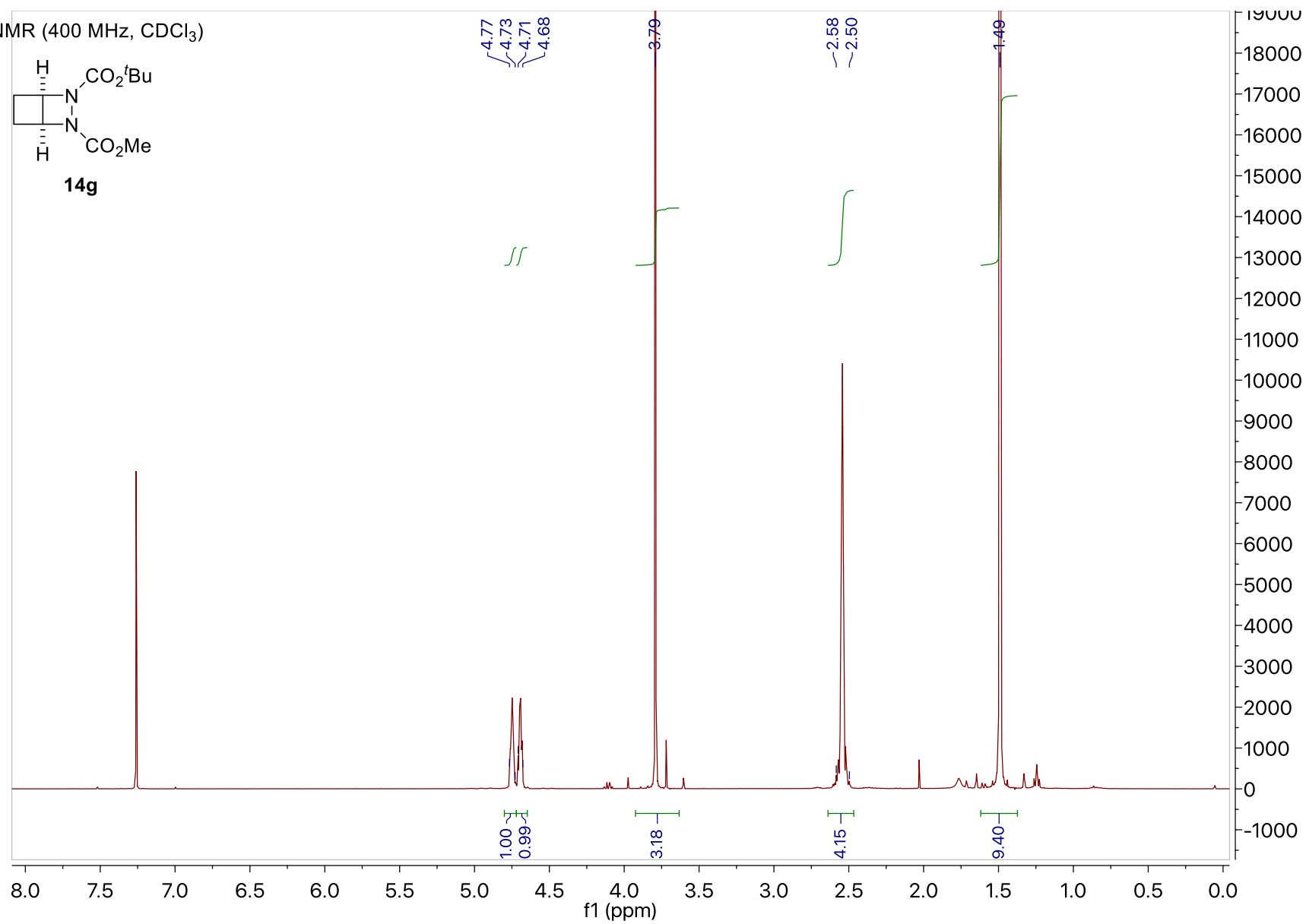
14d

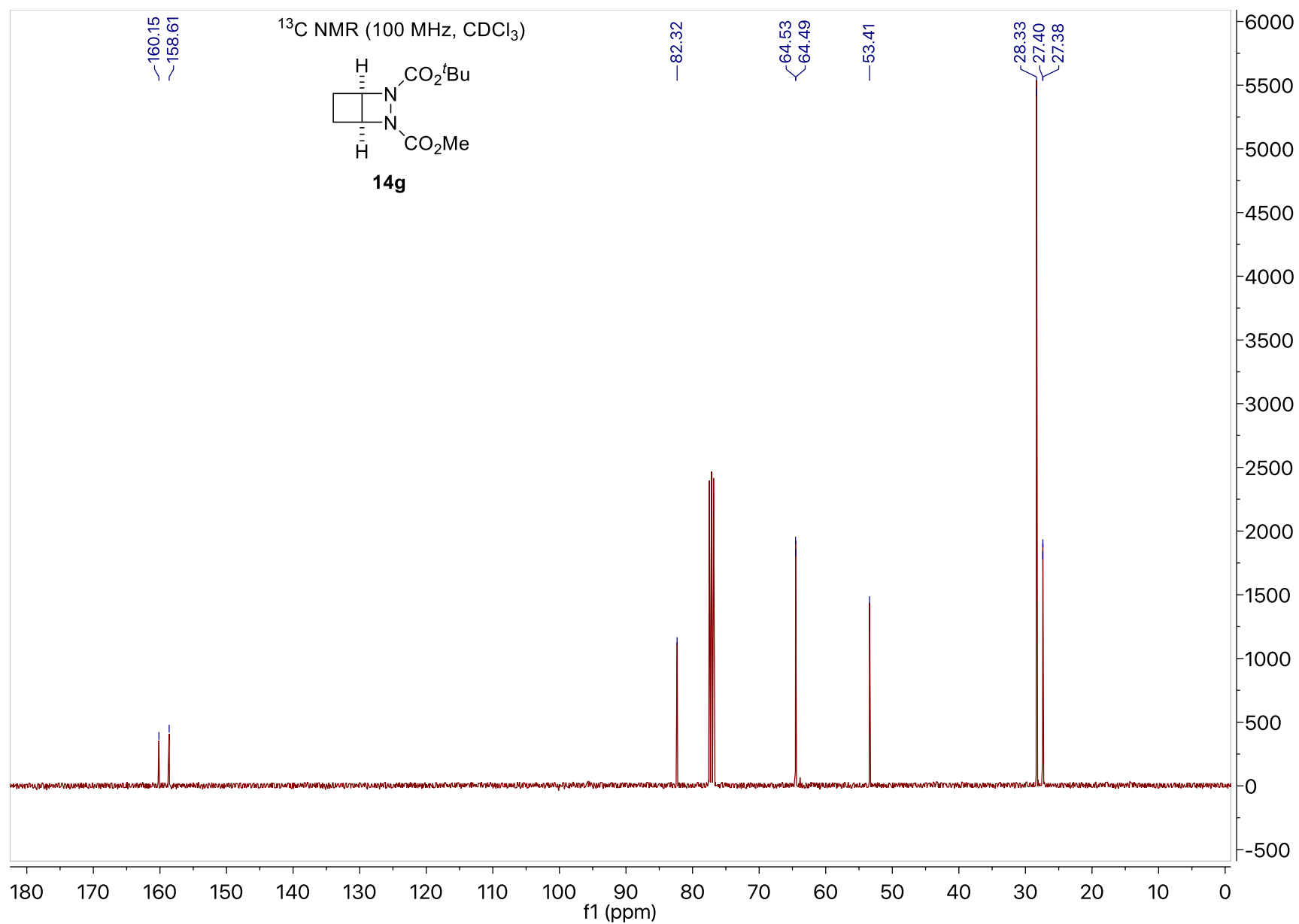


¹H NMR (400 MHz, CDCl₃)

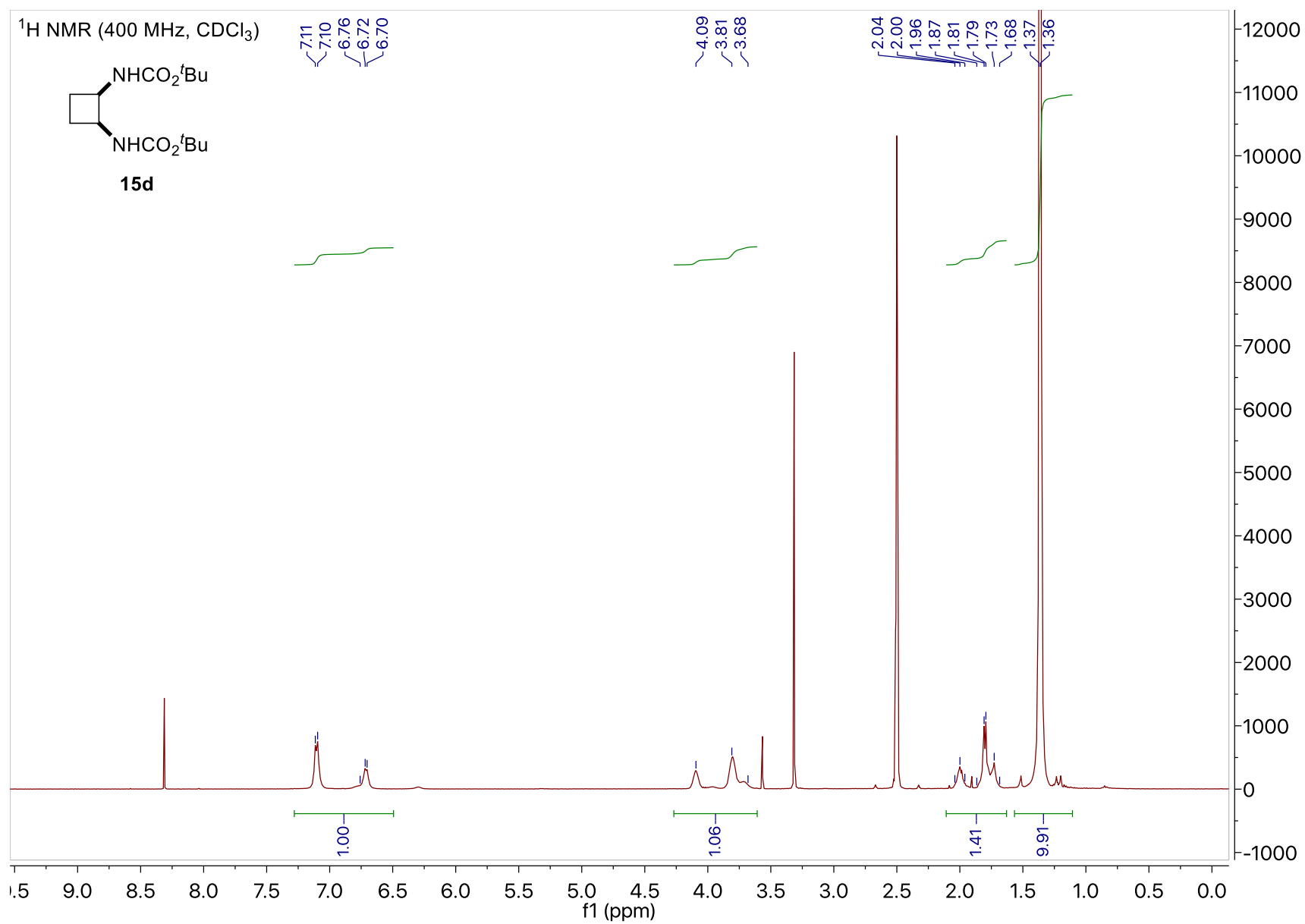


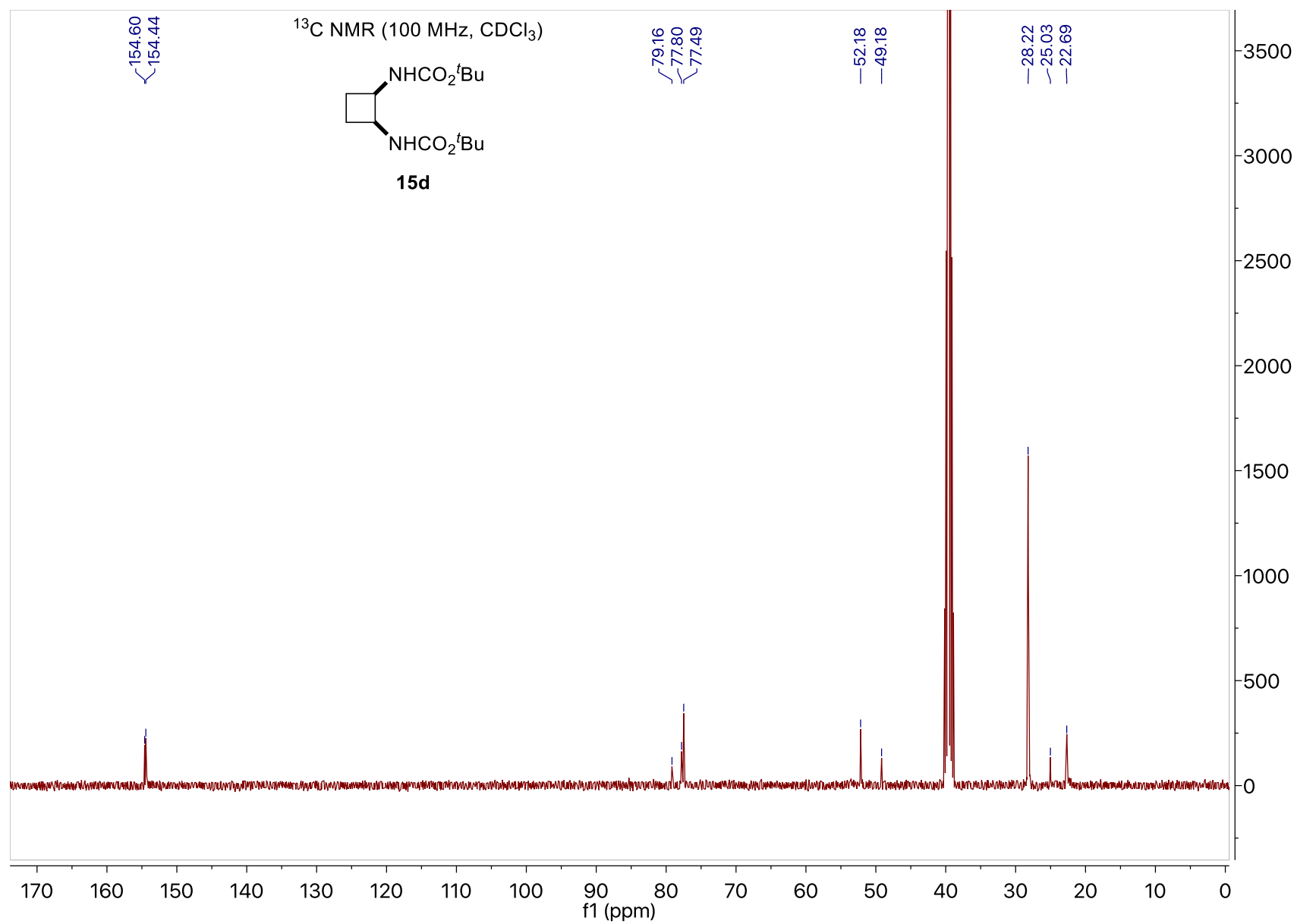
14g

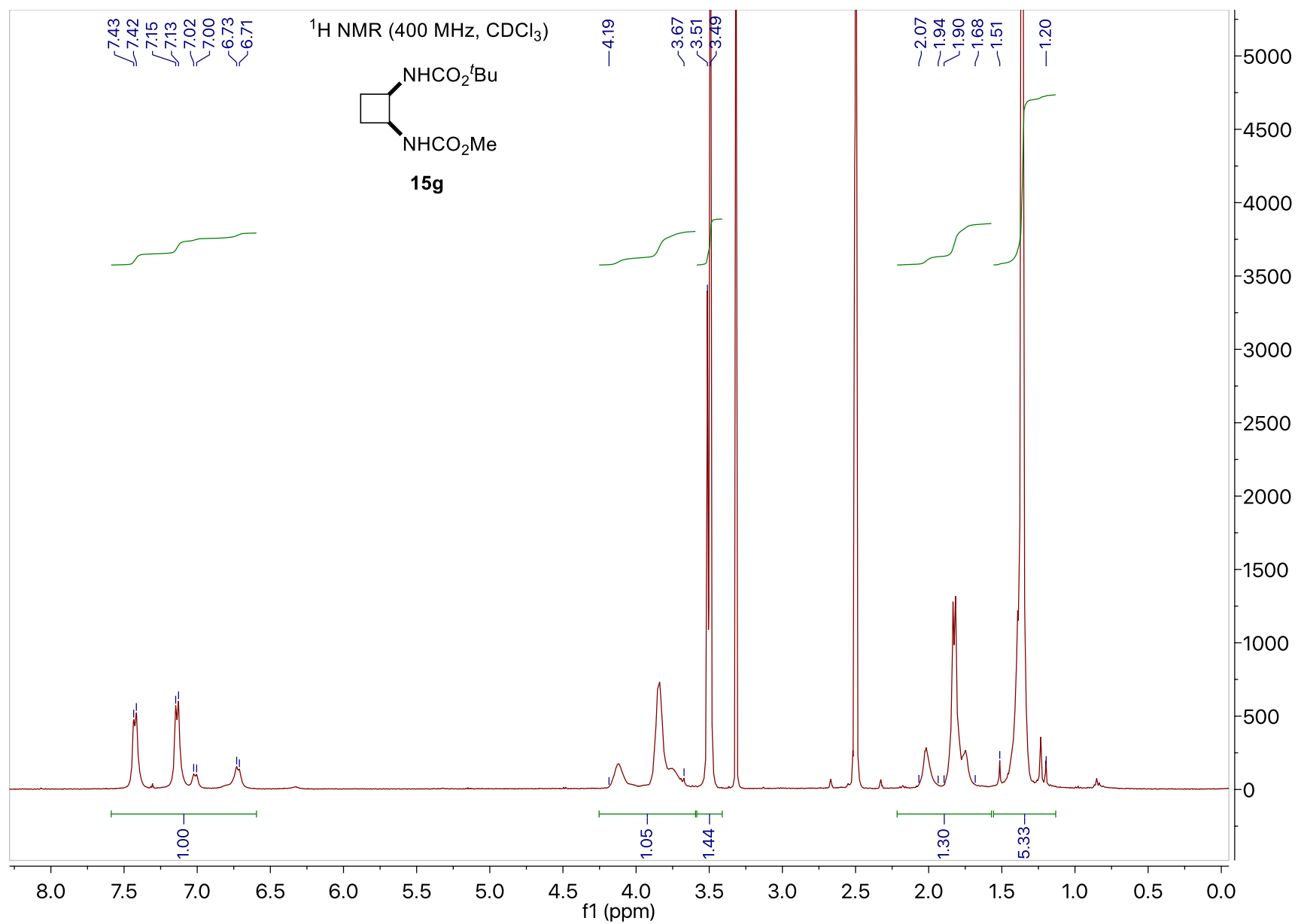


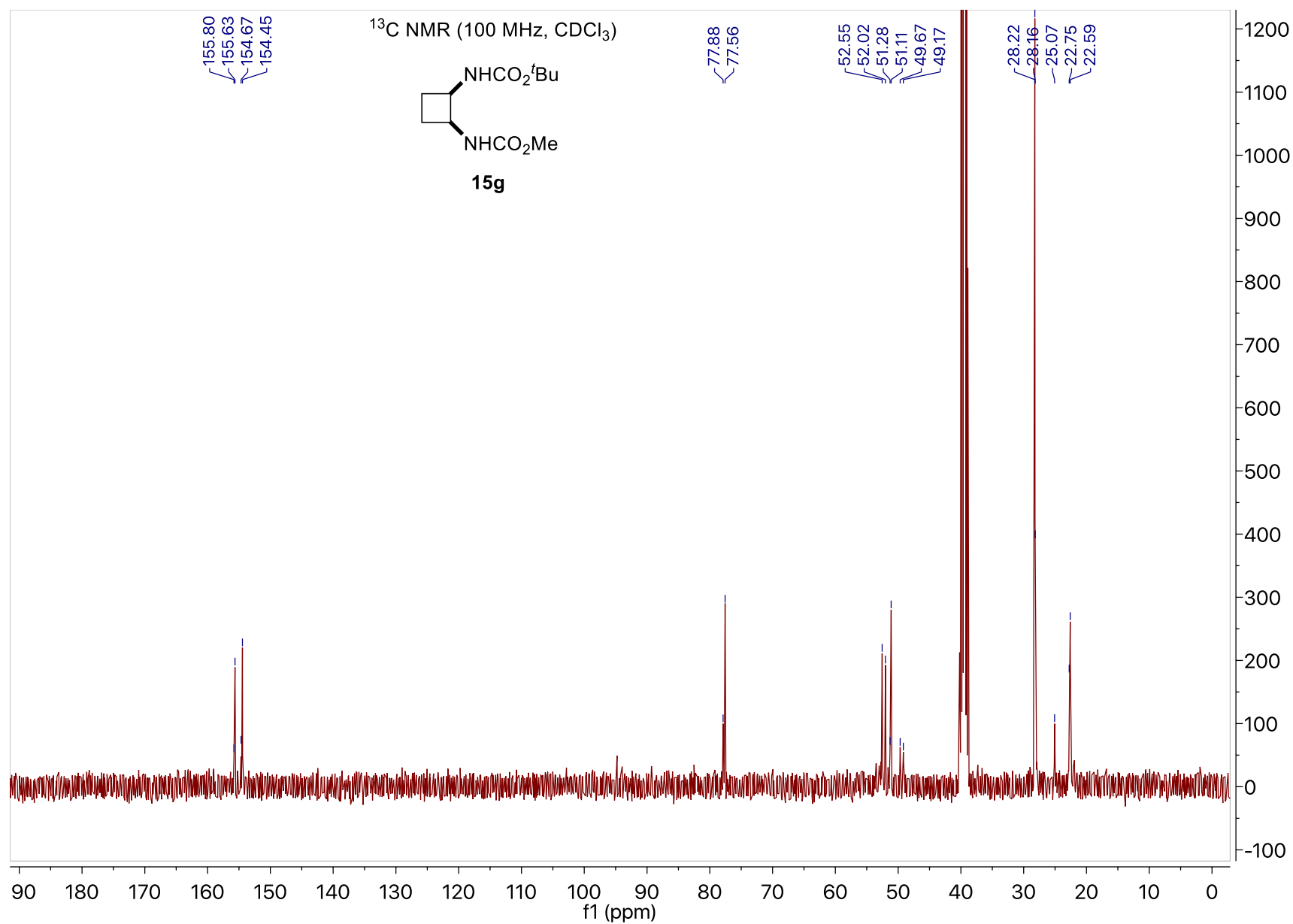


S68

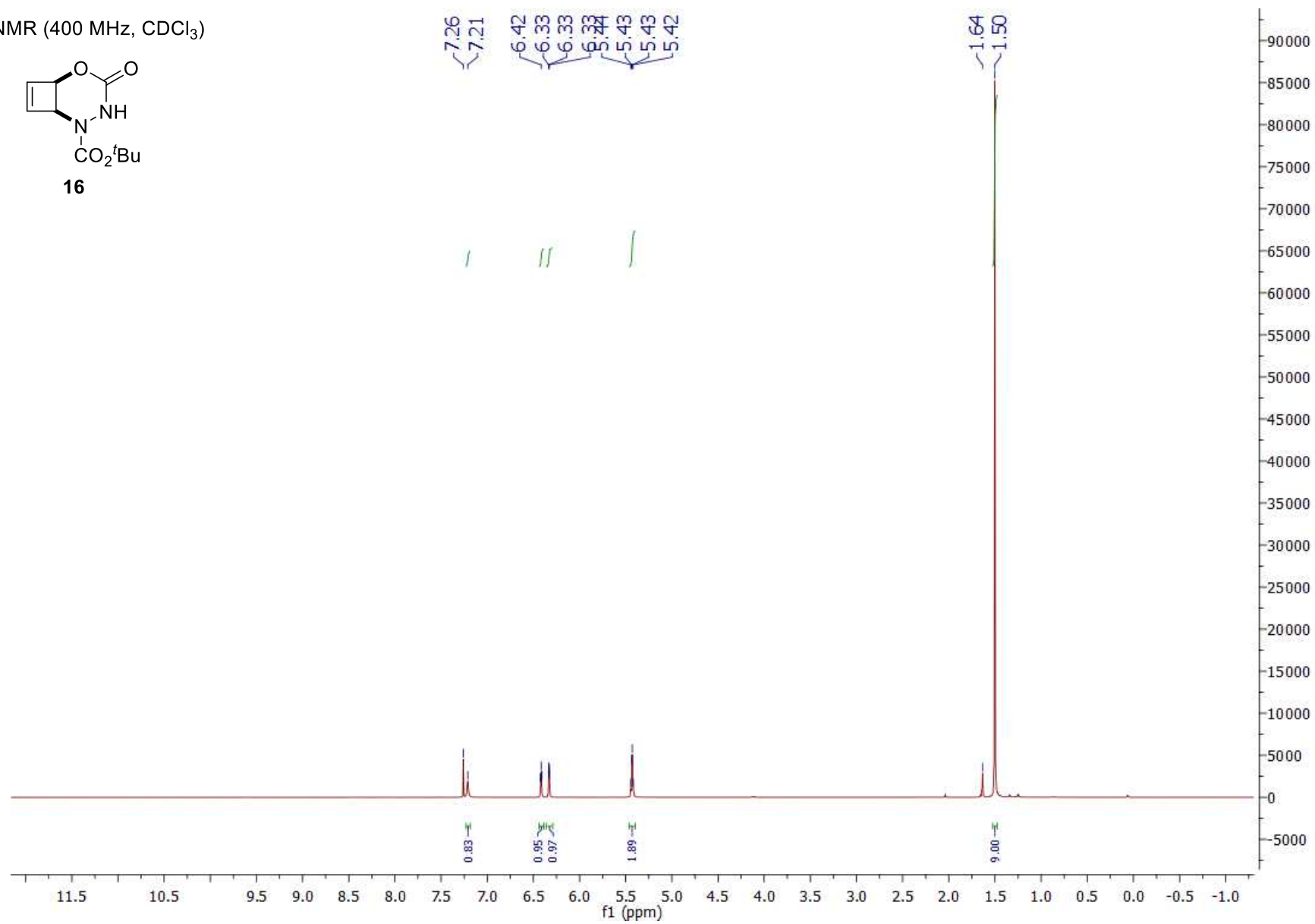
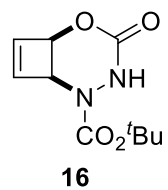




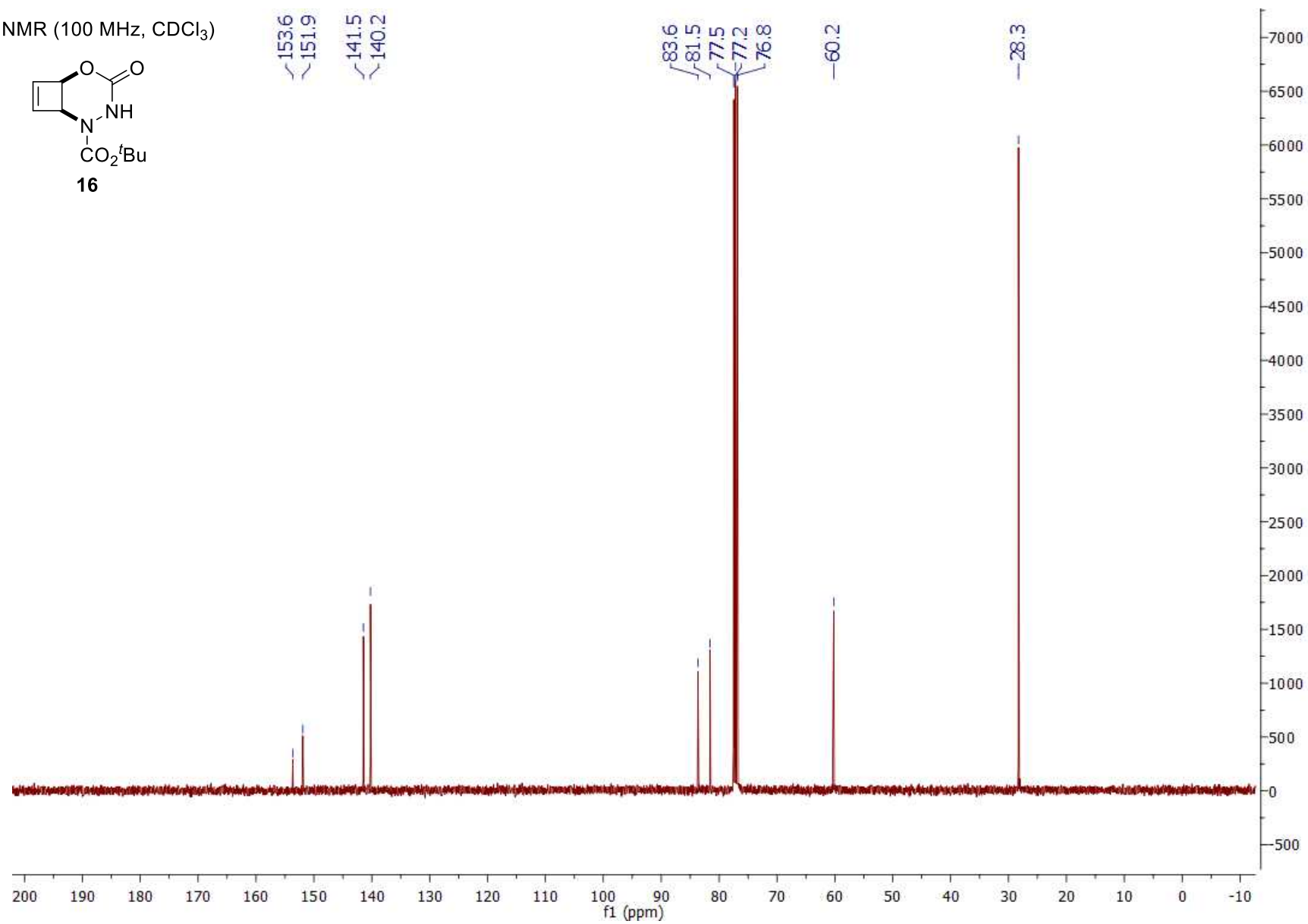
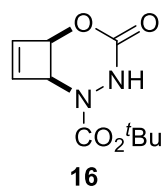


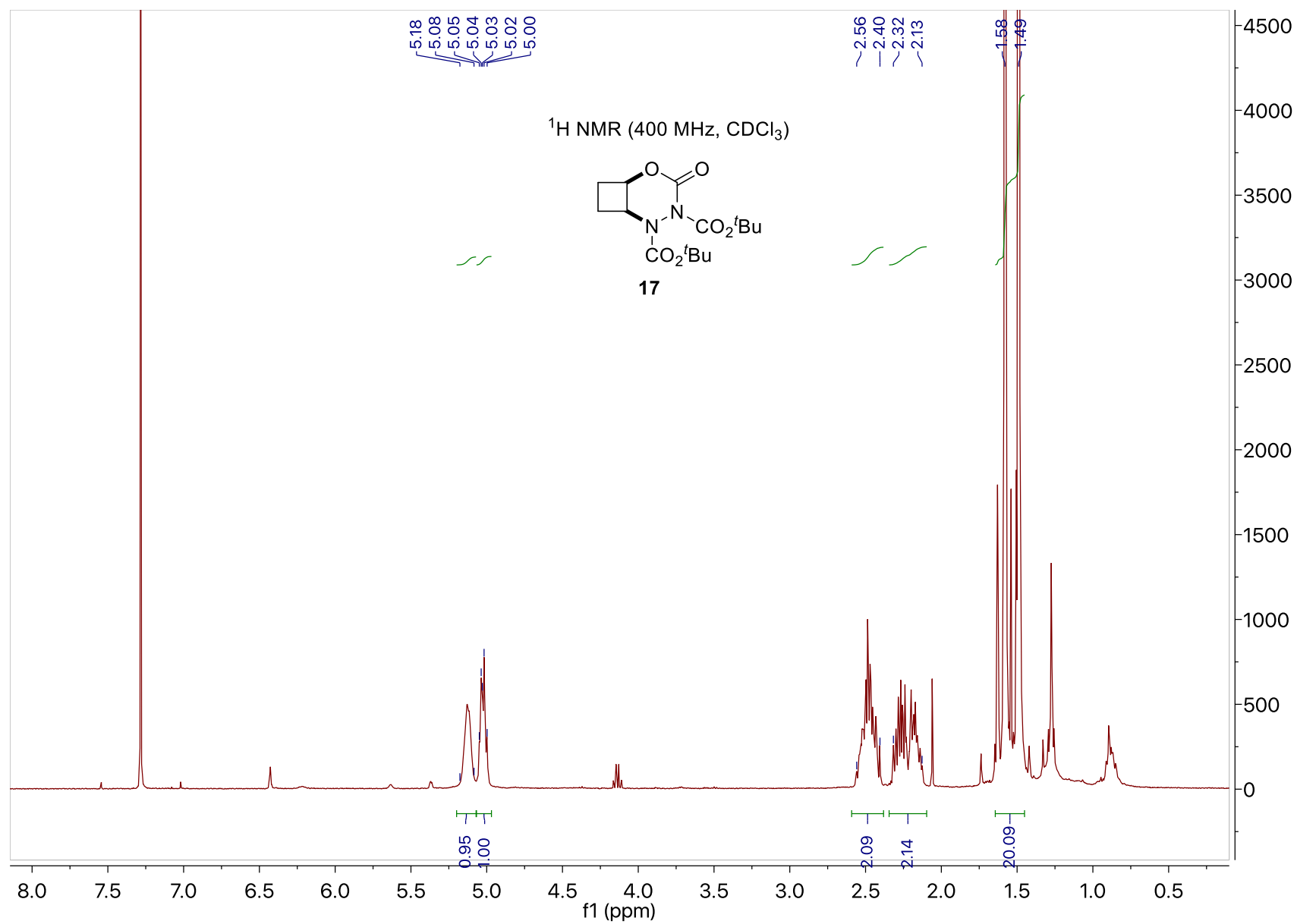


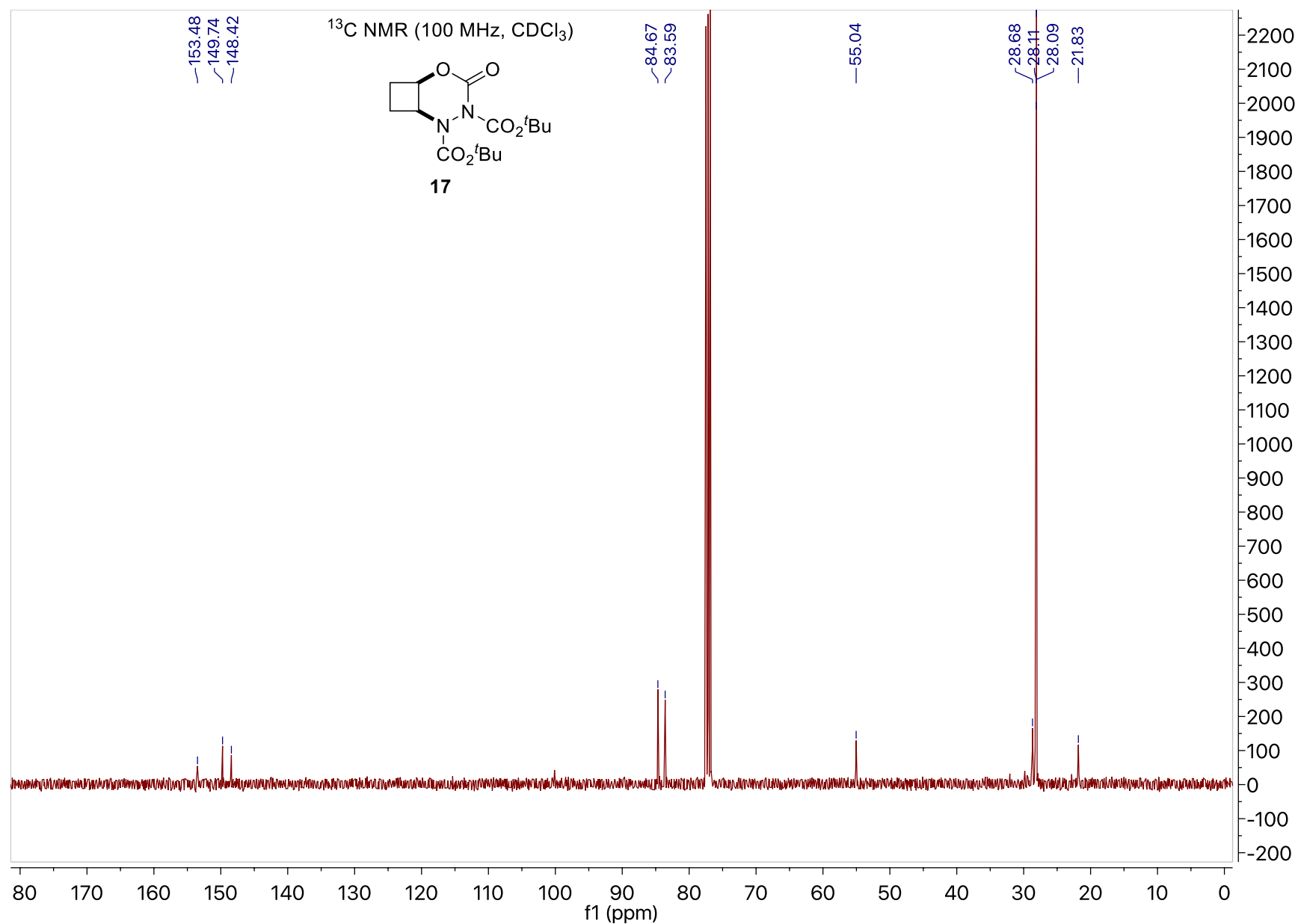
^1H NMR (400 MHz, CDCl_3)

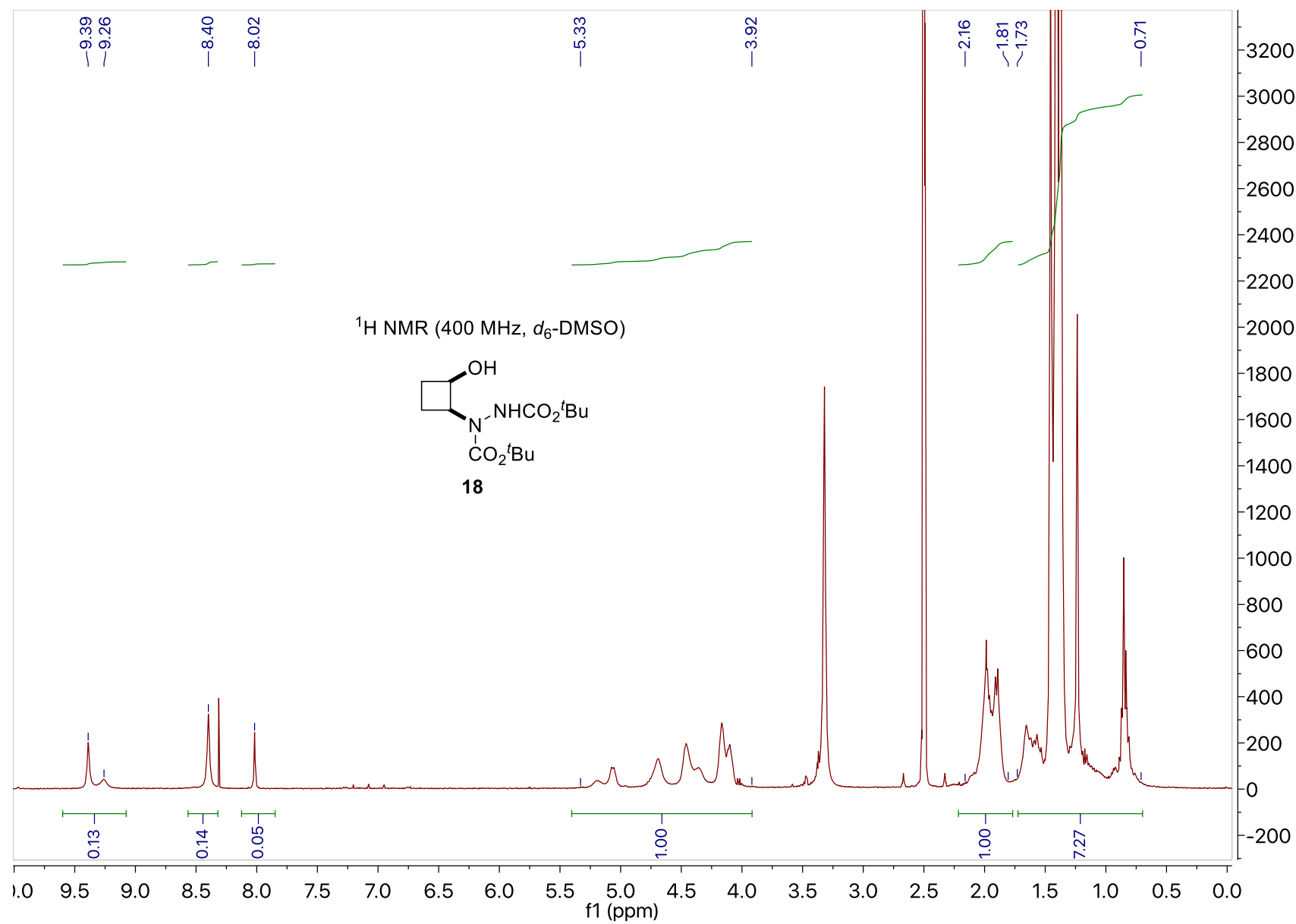


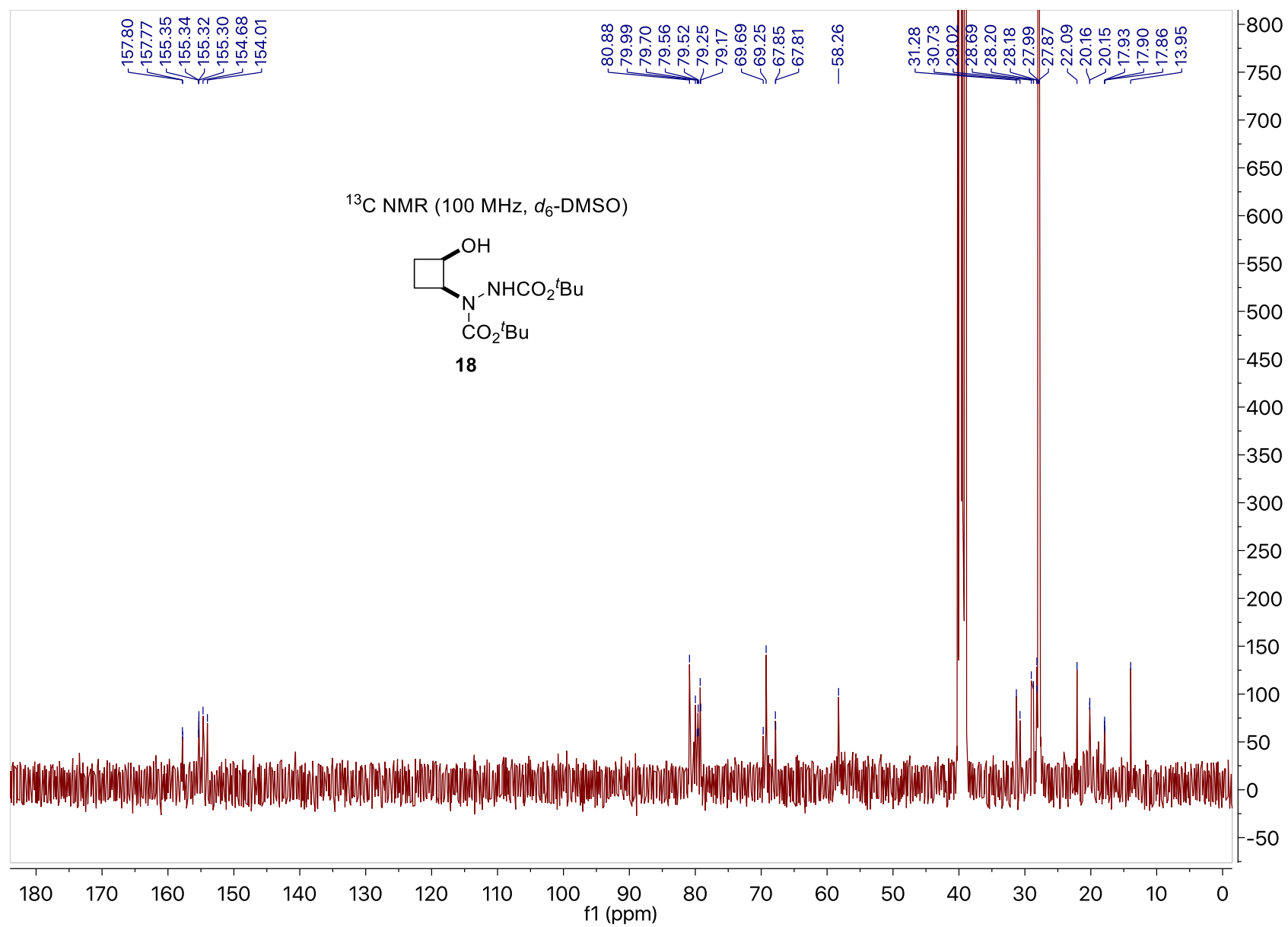
^{13}C NMR (100 MHz, CDCl_3)





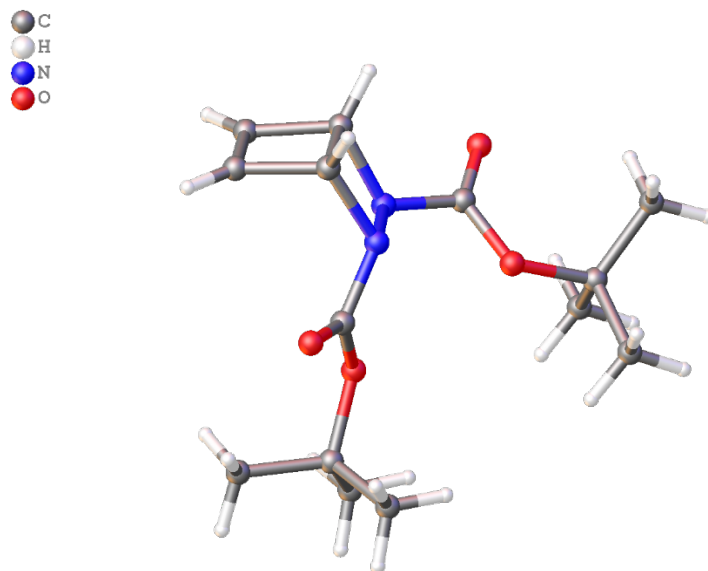






4. X-Ray Diffraction Data for 2d, 11d, 16 and 18

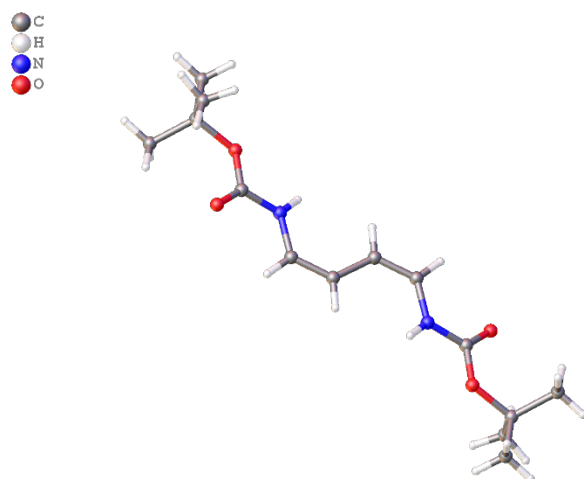
X-Ray Crystal Structure Data for **2d** (CCDC 1941740)



Identification code	SC107
Empirical formula	C ₁₄ H ₂₂ N ₂ O ₄
Formula weight	282.33
Temperature/K	99.99(10)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	8.95843(13)
b/Å	19.3911(2)
c/Å	9.66742(12)
α/°	90
β/°	114.1195(17)
γ/°	90
Volume/Å ³	1532.75(4)
Z	4
ρ _{calc} /cm ³	1.223
μ/mm ⁻¹	0.740
F(000)	608.0

Crystal size/mm ³	0.433 × 0.309 × 0.26
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	9.122 to 153.564
Index ranges	-11 ≤ h ≤ 11, -23 ≤ k ≤ 24, -12 ≤ l ≤ 12
Reflections collected	17499
Independent reflections	3203 [R _{int} = 0.0248, R _{sigma} = 0.0127]
Data/restraints/parameters	3203/0/187
Goodness-of-fit on F ²	1.027
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0369, wR ₂ = 0.0913
Final R indexes [all data]	R ₁ = 0.0374, wR ₂ = 0.0918
Largest diff. peak/hole / e Å ⁻³	0.25/-0.24

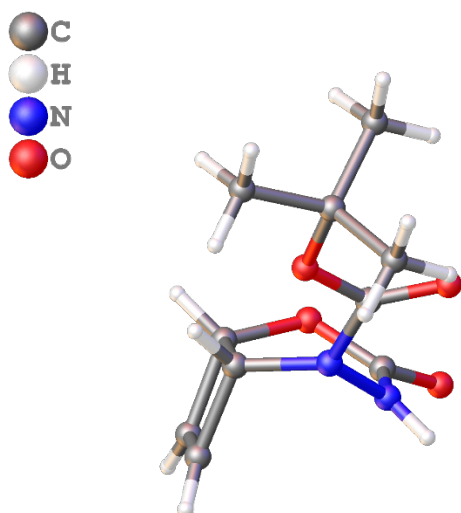
X-Ray Crystal Structure Data for **11b** (CCDC 1941741)



Identification code	SC117
Empirical formula	C ₁₄ H ₂₄ N ₂ O ₄
Formula weight	284.35
Temperature/K	99.9(2)
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	5.23750(9)
b/Å	8.83307(15)

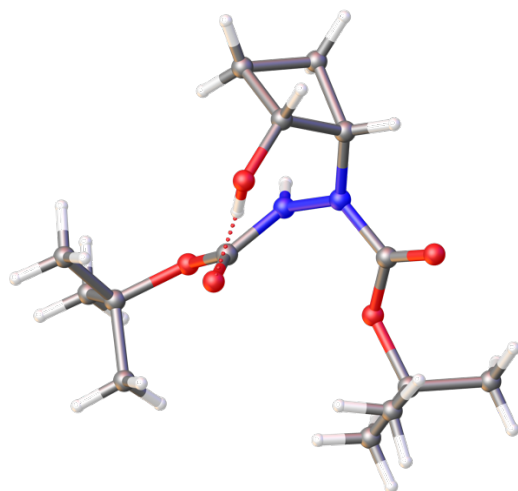
c/Å	16.5180(3)
$\alpha/^\circ$	90
$\beta/^\circ$	92.6082(17)
$\gamma/^\circ$	90
Volume/Å ³	763.39(2)
Z	2
$\rho_{\text{calc}}/\text{g}/\text{cm}^3$	1.237
μ/mm^{-1}	0.743
F(000)	308.0
Crystal size/mm ³	0.109 × 0.098 × 0.082
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/ $^\circ$	10.724 to 153
Index ranges	-6 ≤ h ≤ 6, -11 ≤ k ≤ 11, -17 ≤ l ≤ 20
Reflections collected	9639
Independent reflections	1589 [R_{int} = 0.0415, R_{sigma} = 0.0201]
Data/restraints/parameters	1589/0/94
Goodness-of-fit on F^2	1.058
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0369, wR_2 = 0.0961
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.0977
Largest diff. peak/hole / e Å ⁻³	0.21/-0.23

X-Ray Crystal Structure Data for **16** (CCDC 1941742)



Identification code	SC108
Empirical formula	C ₁₀ H ₁₄ N ₂ O ₄
Formula weight	226.23
Temperature/K	100.2(4)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	10.3330(6)
b/Å	9.5174(5)
c/Å	11.5317(7)
α/°	90
β/°	102.715(7)
γ/°	90
Volume/Å ³	1106.26(11)
Z	4
ρ _{calc} /g/cm ³	1.358
μ/mm ⁻¹	0.893
F(000)	480.0
Crystal size/mm ³	0.171 × 0.142 × 0.07
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.772 to 152.362
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 11, -14 ≤ l ≤ 8
Reflections collected	6952
Independent reflections	2281 [R _{int} = 0.0313, R _{sigma} = 0.0277]
Data/restraints/parameters	2281/0/148
Goodness-of-fit on F ²	1.056
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0545, wR ₂ = 0.1455
Final R indexes [all data]	R ₁ = 0.0604, wR ₂ = 0.1504
Largest diff. peak/hole / e Å ⁻³	0.65/-0.28

X-Ray Crystal Structure Data for **18** (CCDC 1950846)



Identification code	SC121
Empirical formula	C ₁₄ H ₂₆ N ₂ O ₅
Formula weight	302.37
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	P2 ₁ /c
a/Å	10.58050(10)
b/Å	10.87620(10)
c/Å	15.39660(10)
α/°	90
β/°	98.9080(10)
γ/°	90
Volume/Å ³	1750.40(3)
Z	4
ρ _{calc} /g/cm ³	1.147
μ/mm ⁻¹	0.718
F(000)	656.0
Crystal size/mm ³	0.301 × 0.273 × 0.142
Radiation	CuKα (λ = 1.54184)

2 θ range for data collection/° 8.46 to 153.16

Index ranges -13 $\leq h \leq 13$, -13 $\leq k \leq 11$, -19 $\leq l \leq 19$

Reflections collected 31493

Independent reflections 3663 [$R_{\text{int}} = 0.0330$, $R_{\text{sigma}} = 0.0124$]

Data/restraints/parameters 3663/0/197

Goodness-of-fit on F^2 1.058

Final R indexes [$I \geq 2\sigma(I)$] $R_1 = 0.0425$, $wR_2 = 0.1107$

Final R indexes [all data] $R_1 = 0.0433$, $wR_2 = 0.1114$

Largest diff. peak/hole / e \AA^{-3} 0.39/-0.40

5. Differential Scanning Calorimetry (DSC) Trace for 2d

