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Supporting Information

Hydrazone and Oxime Olefination via Ruthenium Alkylidenes

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Experimental

1. General Information

General Laboratory Procedures. All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks or glass vials fitted with rubber septa and/or septa equipped screw caps. All reactions setup in NMR tubes were performed in oven-dried 5 mm x 7 inch 600 MHz frequency Wilmad screw-cap NMR tubes (535-TR-7) with either solid PTFE lined caps or septa equipped screw caps. Stainless steel syringes were used to transfer air or moisture-sensitive liquids. Gas chromatography (GC) was conducted on a Shimadzu GC-2010 Plus system using a Shimadzu SHRXI-5MS column. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates using UV light (254 or 366 nm), iodine, $KMnO_4$, or CAM stain for visualization. Column chromatography was performed using silica gel Silia Flash® 40-63 micron (230-400 mesh) from Silicycle eluting with ethyl acetate/hexanes or diethyl ether/pentane. HPLC purification was performed using an Agilent 1260 Infinity II equipped with a Phenomenex Luna 5 μm C18 column (10 mm x 250 mm).

Materials and Instrumentation. All chemicals were purchased from Sigma-Aldrich, VWR, Alfa Aesar, Acros Organics, Oakwood, TCI America, Frontier Scientific, Matrix Scientific, Ark Pharm, and Strem and were used as received unless otherwise stated. THF, CH_2Cl_2, Et_2O, MeOH, MeCN and DMF were dried by being passed through a column of activated alumina under argon using a JCMeyer Solvent Systems. Triethylamine and diisopropylamine were freshly distilled prior to use over CaH_2. O-(adamantan-1-yl)hydroxylamine[1], O-*tert*-butylhydroxylamine hydrochloride[1], 2-iodoxybenzoic acid[2], diethyl 2-(2,2-dimethoxyethyl)propanedioate[3], and **G3**[4] were prepared according to literature procedures. **HG-2**, **G1**, and **G2** used in this publication were generously donated by Umicore. Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra and Carbon Nuclear Magnetic Resonance (^{13}C NMR) spectra were recorded on a Varian Unity Plus 400, Varian MR400, Varian vnmrs 500, Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for protons are reported in parts per million and are referenced to the NMR solvent peak ($CDCl_3$: δ 7.26, CD_2Cl_2: δ 5.32, C_6D_6: δ 7.16, CD_3OD: δ 3.31, DMSO-d_6 δ 3.31, toluene-d_8: δ 2.09). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.16 $CDCl_3$, CD_2Cl_2: δ 53.84, C_6D_6: δ 128.06, CD_3OD: δ 49.00, DMSO-d_6 δ 39.52). Chemical shifts for other nuclei (^{19}F, ^{31}P, ^{15}N) are reported in parts per million and referenced to the ^{1}H NMR solvent. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet), and coupling constants in Hertz (Hz). GC-MS analysis was performed on a Shimadzu GCMS QP2010 gas chromatograph mass spectrometer. The products were separated on a 30 m length by 0.25 mm id Restek Rxi-5Sil MS column coated with a 0.25 μm film. Helium was employed as the carrier gas with a constant column flow of 0.98 mL/min. The injector temperature was held constant at 320 °C. One GC oven temperature method was used: 60 °C hold for 1 min, ramp at 20 °C/min to 310 °C, and hold at 310 °C for 3 min (total run time = 16.5 min). High resolution mass spectroscopic (MS) data was recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer or Micromass AutoSpec Ultima Magnetic Sector mass spectrometer (ESI, EI). Infrared (IR) spectra were obtained using either an Avatar 360 FT-IR or Perkin Elmer Spectrum BX FT-IR spectrometer. IR data are represented as frequency of absorption (cm^{-1}).

Abbreviations used: APCI = atmospheric pressure chemical ionization, aq. = aqueous, CAM = cerium ammonium molybdate, CaH_2 = calcium hydride, CD_2Cl_2 = deuterated dichloromethane, $CDCl_3$ = deuterated chloroform, C_6D_6 = deuterated benzene, DCM = dichloromethane, DIBAL-H = diisobutylaluminium hydride, DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide, EI = electron ionization, ESI = electrospray ionization, Et_2O = diethyl ether, Et_3N = triethylamine, EtOAc = ethyl acetate, EtOH = ethanol, GC = gas chromatography, HCl = hydrochloric acid, IBX = 2-iodoxybenzoic acid, IR = infrared, K_2CO_3 = potassium carbonate, $KMnO_4$ = potassium permanganate, LDA = lithium diisopropylamide, MeCN = acetonitrile, MeOH = methanol, $MgSO_4$ = magnesium sulfate, MS = mass

spectrometry, *n*-Bu_4NBr = tetrabutylammonium bromide, Na_2SO_4 = sodium sulfate, NaH = sodium hydride, $NaHCO_3$ = sodium bicarbonate, NaCl = sodium chloride, NaOH = sodium hydroxide, NH_4Cl = ammonium chloride, NMR = nuclear magnetic resonance, PTSA = p-toluenesulfonic acid monohydrate, p-TsCl = p-toluenesulfonyl chloride, PhTMS = phenyltrimethylsilane, PPTS = pyridinium p-toluenesulfonate, sat. = saturated, TBAI = tetrabutylammonium iodide, THF = tetrahydrofuran, TLC = thin-layer chromatography, UV = ultraviolet.

2. Experimental Procedures for Hydrazone and Oxime Olefination[1]

Representative Procedure A for Olefination Reactions (Tables 1 and 2)

A 13x100mm test tube was charged with substrate (0.012 mmol), alkylidene (0.01 mmol), and C_6D_6 (0.6 mL). Then, 90 µL of PhTMS (~0.1 M in C_6D_6) was added as an internal standard. The solution was transferred to an NMR tube by pipette and was allowed to react for the time and at the temperature indicated in the figure or table before the yield and conversion were measured by ^{1}H-NMR. This procedure was utilized for the metathesis reaction of substrates **14** and **22-32** to give the corresponding product **15**. Complete conversion of **20** required prologed reaction times greater than 24 h (relying on 1.2 equiv. of substrates). However, yield of the desired olefin product formed does not increase beyond the yield indicated in the table.

Representative Procedure B for Solvent and robustness screen[5] (Table 3)

A 5mm x 7 inch screw-cap NMR tube was charged with **14** (3.0 eq), **20** (0.01 mmol, 1.0 eq), additive (0.0 or 1.0 eq) and deuterated solvent (0.6 mL). Then, 90 µL of PhTMS (~0.1 M in the same solvent) was added as an internal standard. The mixture was shaken and briefly sonicated (~15 s) to allow dissolution of substrate. The solution was allowed to react for the time and at the temperature indicated in the figure or table before the yield and conversion were measured by ^{1}H-NMR.

Representative Procedure C for Olefination Reactions (Table 4)

A 5mm x 7 inch screw-cap NMR tube was charged with substrate (0.012 mmol), alkylidene (0.01 mmol), and C_6D_6 (0.6 mL). Then, 90 µL of PhTMS (~0.1 M in C_6D_6) was added as an internal standard. The mixture was shaken and briefly sonicated (~15 s) to allow dissolution of substrate. The solution was allowed to react for the time and at the temperature indicated in the figure or table before the yield and conversion were measured by ^{1}H-NMR. This procedure was utilized for the metathesis reaction of substrates **26**, **33**, **35**, **37**, **39**, **41**, **43**, **45**, **47**, **49-51**, **52**, **54**, **56**, **58**, **60**, **62**, **64**, and **66** to give the corresponding olefin products.

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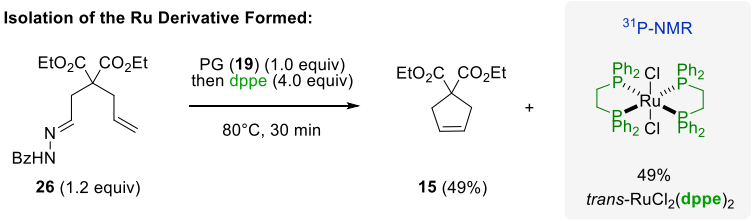
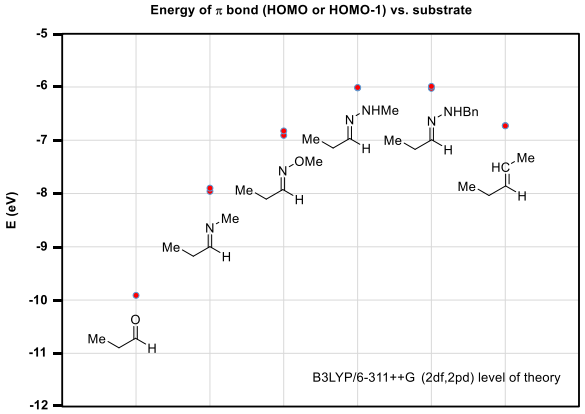
[1] For representative procedures that describe the measurement of NMR-yields relying on internal standards, see: 1) L. Griffiths, *Analyst* **1998**, *123*, 1061–1068. https://pubs.rsc.org/en/content/articlepdf/1998/an/a800625c?page=search
2) T. Saito, S. Nakaie, M. Kinoshita, T. Ihara, S. Kinugasa, A. Nomura, T. Maeda, *Metrologia* **2004**, *41*, 213–218. https://iopscience.iop.org/article/10.1088/0026-1394/41/3/015/pdf
3) Pauli, G.F.; Jaki, B.U.; Lankin, D.C. A routine experimental protocol for qHNMR illustrated with taxol. *J. Nat. Prod.* **2007**, *70*, 589-595. https://pubs.acs.org/doi/pdf/10.1021/np060535r
4) Pauli, G.F.; Jaki, B.U.; Lankin, D.C. Quantitative ^{1}H NMR: Development and Potential of a Method for Natural Products Analysis. *J. Nat. Prod.* **2005**, *68*, 133-149. https://pubs.acs.org/doi/pdf/10.1021/np0497301

3. Isolation of Ru Derivative Formed



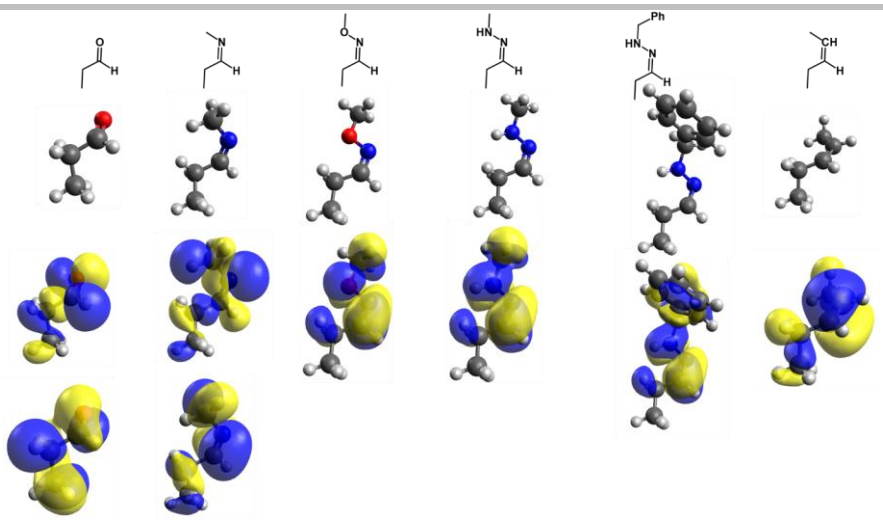
When substrate **26** is converted under optimal reaction conditions followed by the addition of 1,2-bis(diphenylphosphino)ethane (dppe) (4.0 equiv), the metathesis product **15** is isolated in 49% yield together with equal amounts of trans-$RuCl_2(dppe)_2$ as a stable, metathesis inactive Ru(II) complex that is literature reported [M. A. Fox, J. E. Harris, S. Heider, V. Pérez-Gregorio, M. E. Zakrzewska, J. D. Farmer, D. S. Yufit, J. A. K. Howard, P. J. Low, *J. Organomet. Chem*. 2009, 694, 2350–2358. https://doi.org/10.1016/j.jorganchem.2009.03.033.]. This result suggests that the ruthenium metal can be recovered after the olefination reaction has occurred.

4. Computational Investigations Evaluating the Frontier Orbital Energies



entry	fragment	HOMO	LUMO	π bond	HOMO-1	relevant π bond
1	O=CHEt	-7.22	-1.13	HOMO-1	-9.914	-9.914
2	MeN=CHEt (Z-isomer)	-6.634	-0.408	HOMO-1	-7.961	-7.961
3	MeN=CHEt (E-isomer)	-6.94	-0.412	HOMO-1	-7.898	-7.898
4	MeON=CHEt (Z-isomer)	-6.909	-0.322	HOMO		-6.909
5	MeON=CHEt (E-isomer)	-6.826	-0.447	HOMO		-6.826
6	MNHN=CHEt (Z-isomer)	-6.017	-0.335	HOMO		-6.017
7	MNHN=CHEt (E-isomer)	-6.008	-0.27	HOMO		-6.008
8	BnNHN=CHEt (Z-isomer)	-6.025	-0.615	HOMO		-6.025
9	BnNHN=CHEt (E-isomer)	-5.988	-0.639	HOMO		-5.988
10	HCMe=CHEt (Z-isomer)	-6.724	-0.238	HOMO		-6.724
11	HCMe=CHEt (E-isomer)	-6.73	-0.155	HOMO		-6.73

The orbital manifolds of a series of π-systems (C=X where X = CH_2, NOMe, NNHBn, NNHMe, NMe, and O) were computed (B3LYP/6-311++G (2df,2pd) level of theory). The orbital that is primarily of π-bonding character is lowest for carbonyl and imine variants. Importantly, hydrazone and oxime variants have higher HOMO energies, compared to carbonyl and imine substrates, which are more similar to the HOMO energy of an olefin substrate. These calculations support our hypothesis that incorporating additional heteroatoms adjacent to a C=N unit increases the HOMO energy, and enables productive reactions with Ru-alkylidenes.



5. Control Experiments: Investigation of Metathesis Reactivity of Ru-alkylidenes

A recent report by Roy and coworkers[6] disclosed the observation of ring-closing carbonyl-olefin metathesis (COM) activity mediated by Ru-alkylidenes (Grubbs' Second Generation catalyst) to result in the formation of 8- and 9-membered medium-sized rings. We attempted to replicate their results using aldehyde **22** and ketone **S1**. Using the conditions reported by Roy and coworkers[6], we observed no formation of the desired ring-closing metathesis products **15** and **S2**, respectively (Supplementary Figure 1), by ^{1}H-NMR spectroscopy and gas-chromatography mass spectrometry (see below).

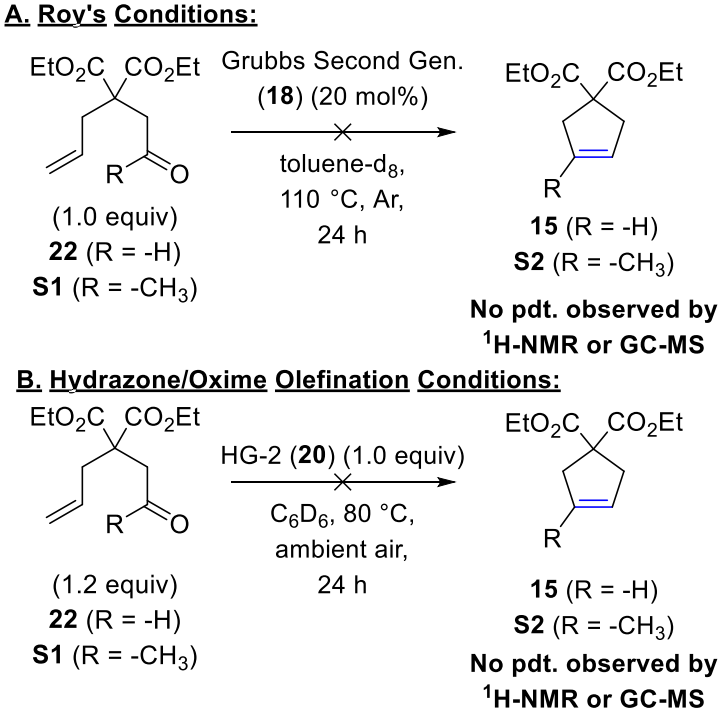


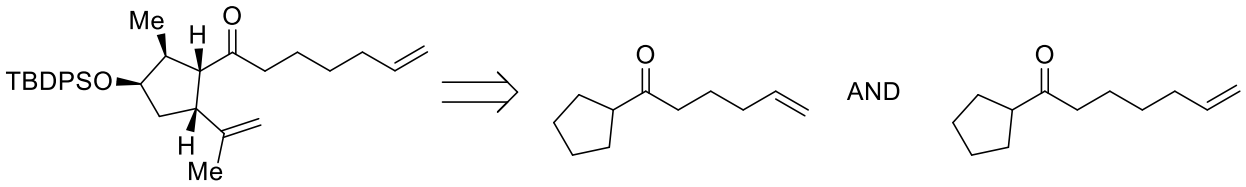
Figure S1. Investigation of Ru-alkylidene mediated COM for malonate-derived aldehyde **22** and ketone **S1** under Roy's conditions[6] (**A**) and hydrazone and oxime olefination conditions (**B**).

Based on these results, we designed a set of additional control experiments. First, we focused on substrates that showed promising reactivity under our conditions developed for ring-closing olefination as their oxime or hydrazine derivatives. Specifically, we compared the reactivity of diethyl malonate-

derived substrates **22** and **S1** under the conditions reported by Roy and coworkers[6] for carbonyl-olefin metathesis and our own conditions for olefination of hydrazones and oximes, and assessed the reaction outcome using *in situ* ^{1}H-NMR and GC-MS analyses (see Section 3 of the Supporting Information for details). The product standards were synthesized from dialkene precursors using Hoveyda-Grubbs Second Generation catalyst (**20**).[7–9] Importantly, comparison of reaction mixtures with independently synthesized product standards by ^{1}H-NMR and GC-MS revealed that neither aldehyde **22** nor ketone **S1** formed metathesis products **15** or **S2**, respectively. Similarly, we observed no formation of **15** and **S2** when aldehyde **22** and ketone **S1** were used as reactants and applied to conditions developed for olefination of hydrazones and oximes (Supplementary Figure 1B).

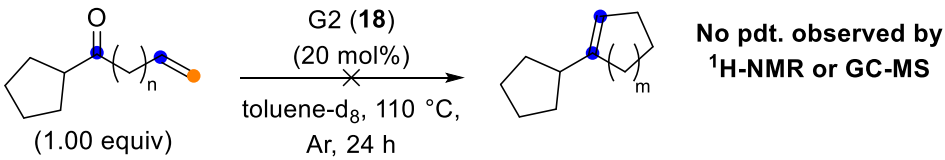
Next, we attempted to convert two ketone substrates (**S4** and **S5**) bearing a terminal olefin functionality that more closely resembles the substrate reported by Roy and coworkers[6] (Supplementary Figure 2A). Notably, when substrates **S4** and **S5** were subjected to the reaction conditions reported by Roy and coworkers, none of the carbonyl-olefin metathesis products **S6** or **S7**, respectively, were formed (Supplementary Figure 2B), as assessed by comparisons with authentic product standards. We independently prepared product standards of cyclopentene **S6** and cyclohexene **S7** following the conditions reported for carbonyl-olefin metathesis using Schrock's catalyst **72** (CAS 139220-25-0) as developed by Grubbs and Fu in 1993 (Supplementary Figure 2C).[10]

A. Truncated Substrate: Probing COM activity



Roy's substrate[6] (**S3**) **S4** **S5**

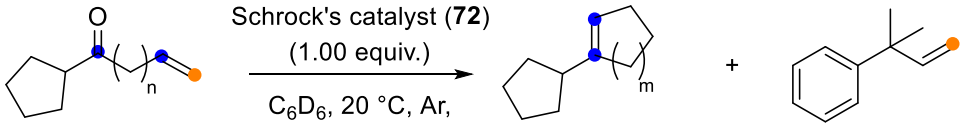
B. Roy's Conditions:



(1.00 equiv)
S4 (n = 3)
S5 (n = 4)

S6 (m = 1)
S7 (m = 2)

C. Grubbs' conditions for COM with Schrock's Catalyst:



(1.00 equiv)
S4 (n = 3)
S5 (n = 4)

S6 (m = 1) 69%[a]
(13% IY)
S7 (m = 2) 41%[a]
(24% IY)

S8

[a]Yield determined by ^{1}H-NMR using phenyltrimethylsilane as an internal standard.

Figure S2. A. Ketone substrates for investigation of Ru-alkylidene mediated carbonyl-olefin metathesis. B. Attempted metathesis under Roy's conditions. C. Application of Grubbs' conditions[10] for carbonyl olefin metathesis using Schrock's catalyst to access product standards.

Experimental Procedures for Control Reactions

GC-MS Method:

GC-MS analysis was performed on a Shimadzu GCMS QP2010 gas chromatograph mass spectrometer. The products were separated on a 30 m length by 0.25 mm id Restek Rxi-5Sil MS column coated with a 0.25 µm film. Helium was employed as the carrier gas with a constant column flow of 0.98 mL/min. The injector temperature was held constant at 320 °C. One GC oven temperature method was used: 60 °C hold for 1 min, ramp at 20 °C/min to 310 °C, and hold at 310 °C for 3 min (total run time = 16.5 min).

GC-MS Standard Preparation:

Product and substrate standards for GC-MS analysis were prepared by filtration of a 1.0 mg/mL solution of each standard (**15**, **22**, **S1**, **S2**, and **S4-S7**) in benzene which was then analyzed by GC-MS.

General Procedure for COM reactions under Roy's Conditions[6] (General Procedure D, GP-D): Monitoring by ^{1}H-NMR and GC-MS

An oven-dried 1-dram glass vial was charged with substrate (0.010 mmol), Grubbs' Second Generation catalyst **18** (20 mol%), PhTMS (~1.00 equiv.), and toluene-d_8 (690 µL) in a N_2 glovebox. This solution was transferred by Pasteur pipette to a screw-cap NMR tube equipped with a PTFE septum, capped, and sealed under N_2 with electrical tape. The NMR tube was transferred out of the glove box and the N_2 atmosphere exchanged for Ar via 3 cycles of vacuum/Ar. The reaction was allowed to react at 110 °C for 24 h, before the yield and conversion were measured by ^{1}H-NMR spectroscopy.

Samples for GC-MS analysis were prepared by removal of a 100 µL aliquot of the NMR tube reactions at the last time point recorded (24 h), allowed to stand for 5 min, filtered through a 30 micron syringe filter, and then analyzed by GC-MS. The chromatograms and mass spectra obtained were compared to the retention times of 1.0 mg/mL substrate standards (**22**, **S1**, **S4**, and **S5**) and product standards (**15**, **S2**, **S6**, and **S7**).

This procedure was used for the attempted metathesis reactions of substrates **22** → **15**, **S1** → **S2**, **S4** → **S6**, and **S5** → **S7** on a 0.01 mmol scale.

General Procedure for COM reactions under Hydrazone and Oxime Olefination Conditions (General Procedure E, GP-E): Monitoring by ^{1}H-NMR and GC-MS

A 1-dram glass vial was charged with substrate (0.012 mmol), Hoveyda-Grubbs Second Generation catalyst **20** (0.01 mmol), and C_6D_6 (0.6 mL). Then, 90 µL of PhTMS (~0.1 M in C_6D_6) was added as an internal standard. The solution was transferred to an screw-cap NMR tube by pipette, sealed under ambient air, and was allowed to react for 24 h at 80 °C after which time the yield and conversion were measured by ^{1}H-NMR.

Samples for GC-MS analysis were prepared by removal of a 100 µL aliquot of the NMR tube reactions at the last time point recorded (24 h), allowed to stand for 5 min, filtered through a 30 micron syringe filter, and then analyzed by GC-MS. The retention times and mass spectra of product peaks were compared to the retention times of 1.0 mg/mL known substrate standards (**22** and **S1**) and product standards (**15** and **S2**).

This procedure was used for the attempted metathesis reactions of substrates **22** → **15** and **S1** → **S2** on a 0.01 mmol scale.

General Procedure for COM reactions under Grubbs's Conditions[10] (General Procedure F, GP-F): Monitoring by ^{1}H-NMR and GC-MS

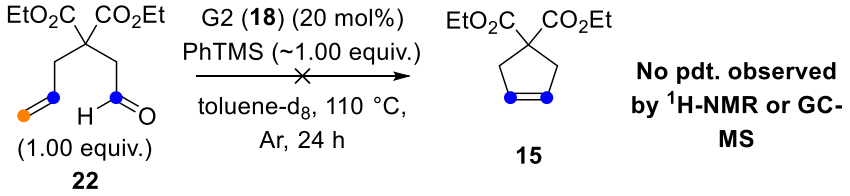
An oven-dried 1-dram glass vial was charged with substrate **S4** or **S5** (0.01 mmol), PhTMS (~0.01 mmol), and C_6D_6 (300 µL) in a N_2 glovebox. This solution was transferred by Pasteur pipette to a homogeneous solution of Schrock's Catalyst **72** (CAS 139220-25-0) (7.7 mg, 0.01 mmol) in C_6D_6 (600 µL) and thoroughly mixed by either pipette or stirring at 400 rpm with a Teflon-coated stirbar. The solution was transferred to a screw-cap NMR tube equipped with a PTFE septum, capped, and sealed

under N_2 with electrical tape. The NMR tube was transferred out of the glove box and the N_2 atmosphere exchanged for Ar via 3 cycles of vacuum/Ar. The reaction was allowed to react at 25 °C for 30 min after which time the yield and conversion were measured by ^{1}H-NMR spectroscopy.

Samples for GC-MS analysis were prepared by removal of a 100 µL aliquot of the NMR tube reactions at the last time point recorded (0.5 h), allowed to stand for 5 min, filtered through a 30 micron syringe filter, and then analyzed by GC-MS. The chromatograms and mass spectra obtained were were compared to the retention times of 1.0 mg/mL substrate standards (**S4** and **S5**) and product standards (**S6** and **S7**).

This procedure was used for the metathesis reactions of substrates **S4** → **S6** and **S5** → **S7** on a 0.01 mmol scale. Product standards **S6** and **S7** were synthesized by a scale-up of this procedure in 25 mL Schlenk tubes on a 0.10 mmol and 0.13 mmol scale respectively (see Characterization section for details).

A. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **22** under Roy's conditions (**GP-D**)



General Procedure D was employed with substrate **22** (2.5 mg, 0.0103 mmol), G2 (**18**) (1.7 mg, 0.002 mmol, 19.4 mol%) and PhTMS (1.00 equiv.). After 24 h at 110 °C, 96% of starting material **22** was consumed and cyclic olefin product **15** was not formed by ^{1}H-NMR.

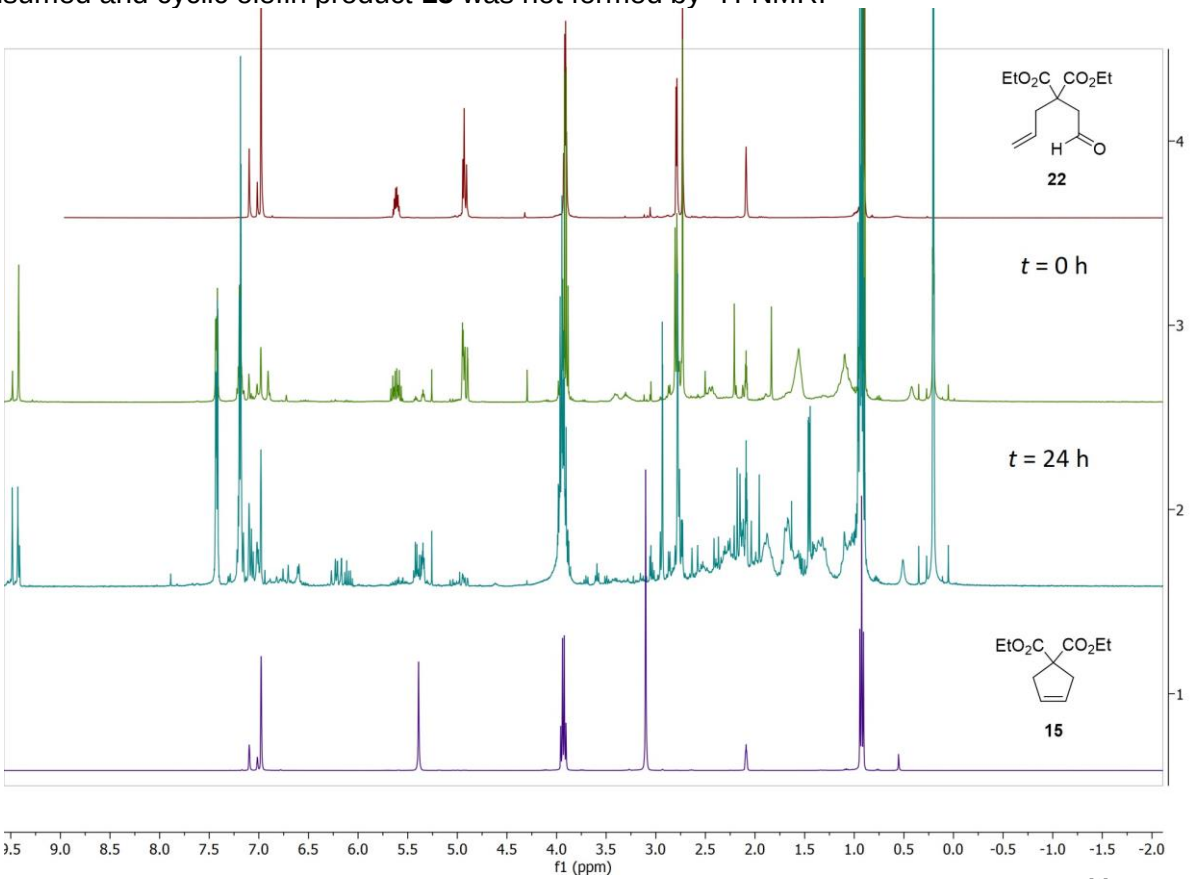


Figure S3. In situ ^{1}H-NMR experiment for substrate **22** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) ^{1}H-NMR of substrate **22** in toluene-d_8. 2) Reaction mixture of substrate **22** and 20 mol% G2 (**18**) in toluene-d_8 after 0 h. 3) Same reaction

mixture after 24 h at 110 °C. 4) ^{1}H-NMR of product standard **15** independently synthesized by olefin metathesis.[11]

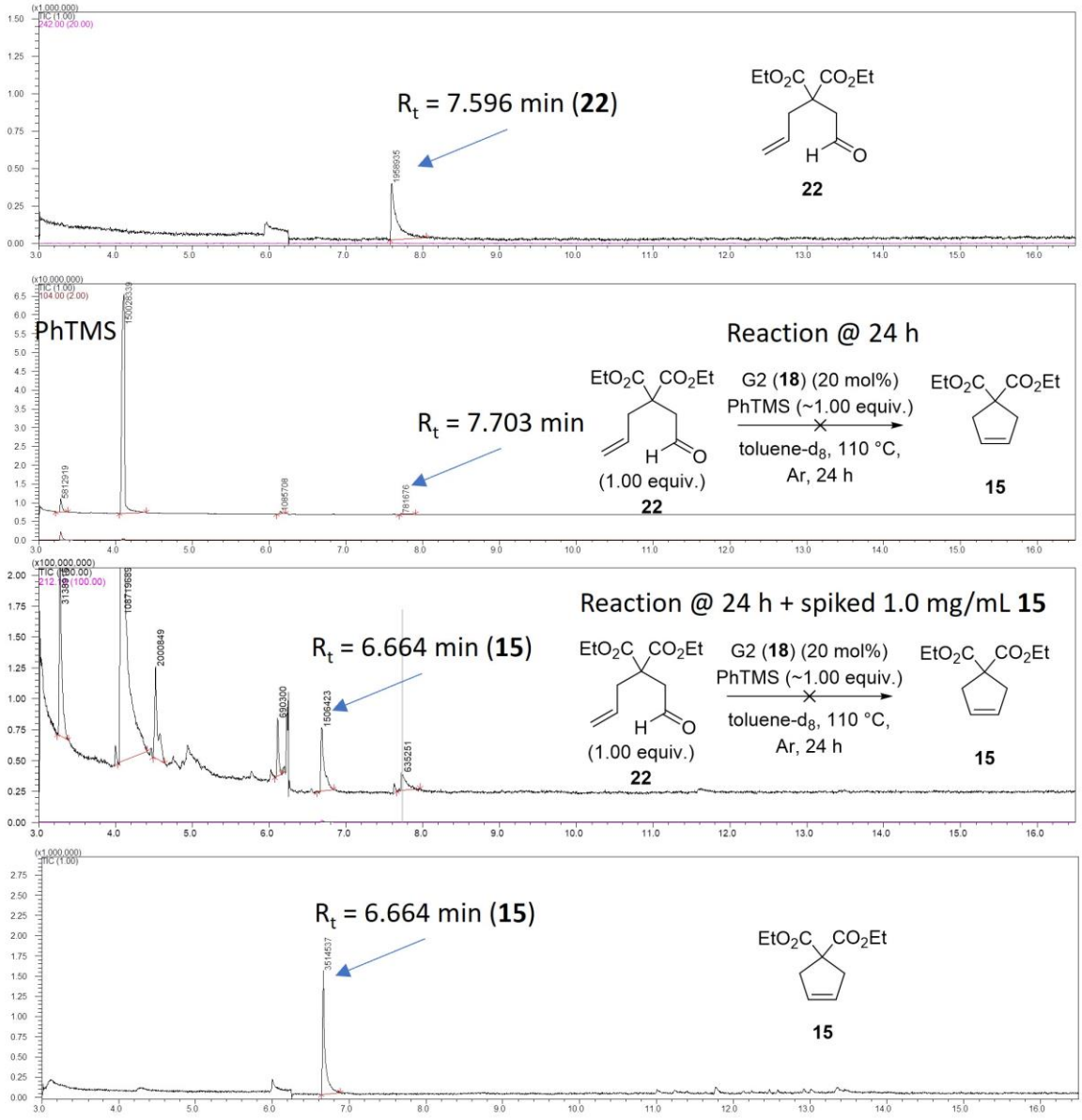
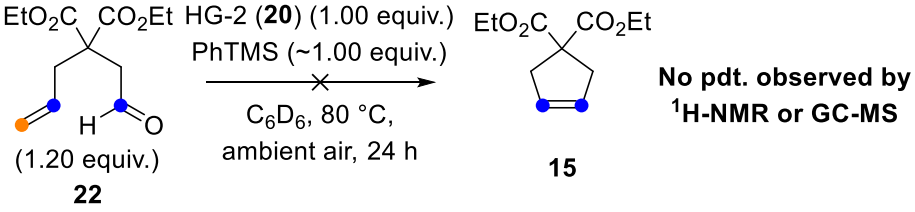


Figure S4. GC-MS reaction monitoring for substrate **22** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) GC-MS trace of substrate **22**. 2) Reaction mixture of substrate **22** and 20 mol% G2 (**18**) in toluene-d$_8$ after 24 h at 110 °C. 3) Same reaction mixture with addition of standard solution of **15** (at 1.0 mg/mL). 4) GC-MS trace of product standard **15** independently synthesized by olefin metathesis.[11]

B. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **22** under hydrazone/oxime olefination conditions (**GP-E**)



General Procedure E was employed with substrate **22** (2.9 mg, 0.0120 mmol, 1.20 equiv.), HG-2 (**20**) (6.30 mg, 0.0101 mmol, 1.00 equiv.) and PhTMS (1.00 equiv.). After 24 h at 80 °C, 8% of starting material **22** remained and cyclic olefin product **15** was not formed by ^{1}H-NMR.

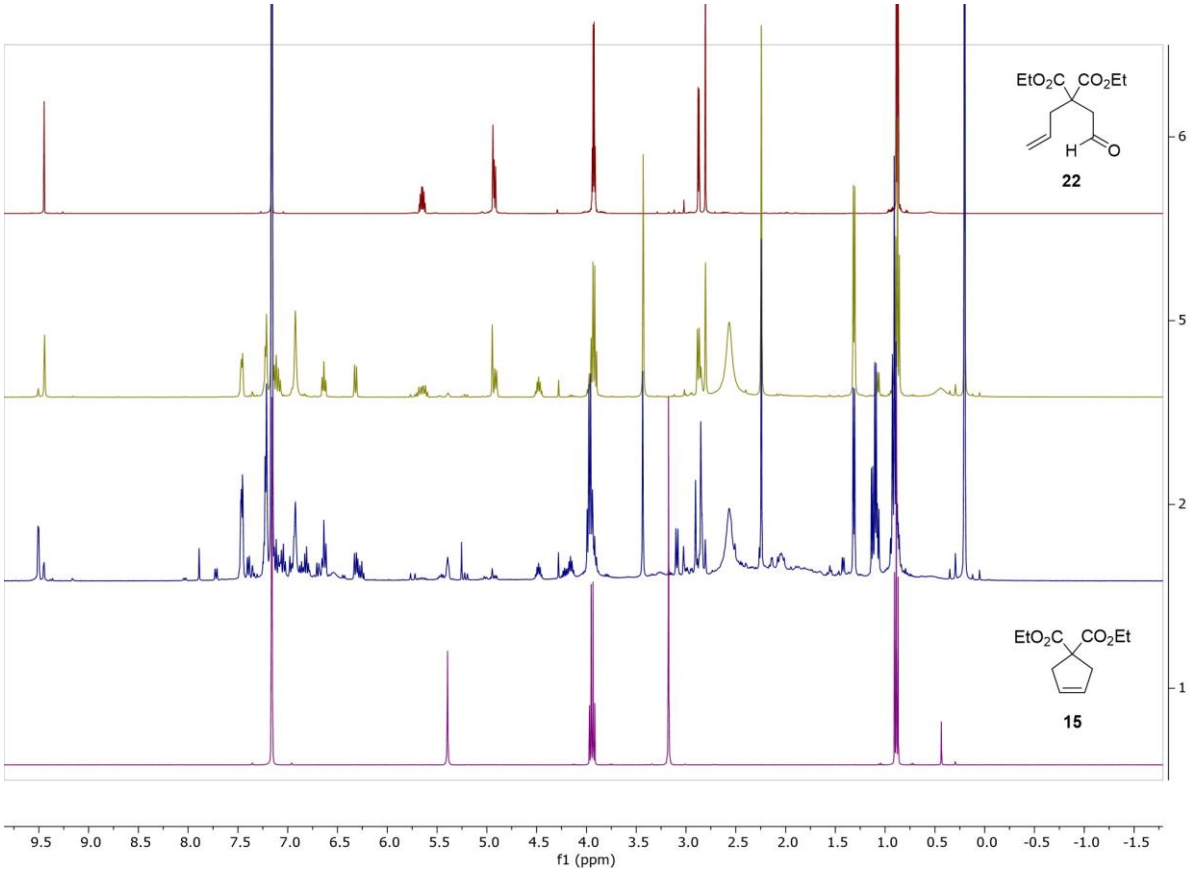


Figure S5. In situ ^{1}H-NMR experiment for substrate **22** under hydrazone/oxime olefination conditions using HG-2 (**20**). From top to bottom: 1) ^{1}H-NMR of substrate **22** in C_6D_6. 2) Reaction mixture of substrate **22** and HG-2 (**20**) in C_6D_6 after 0 h. 3) Same reaction mixture after 24 h at 80 °C. 4) ^{1}H-NMR of product standard **15** independently synthesized by olefin metathesis. [11]

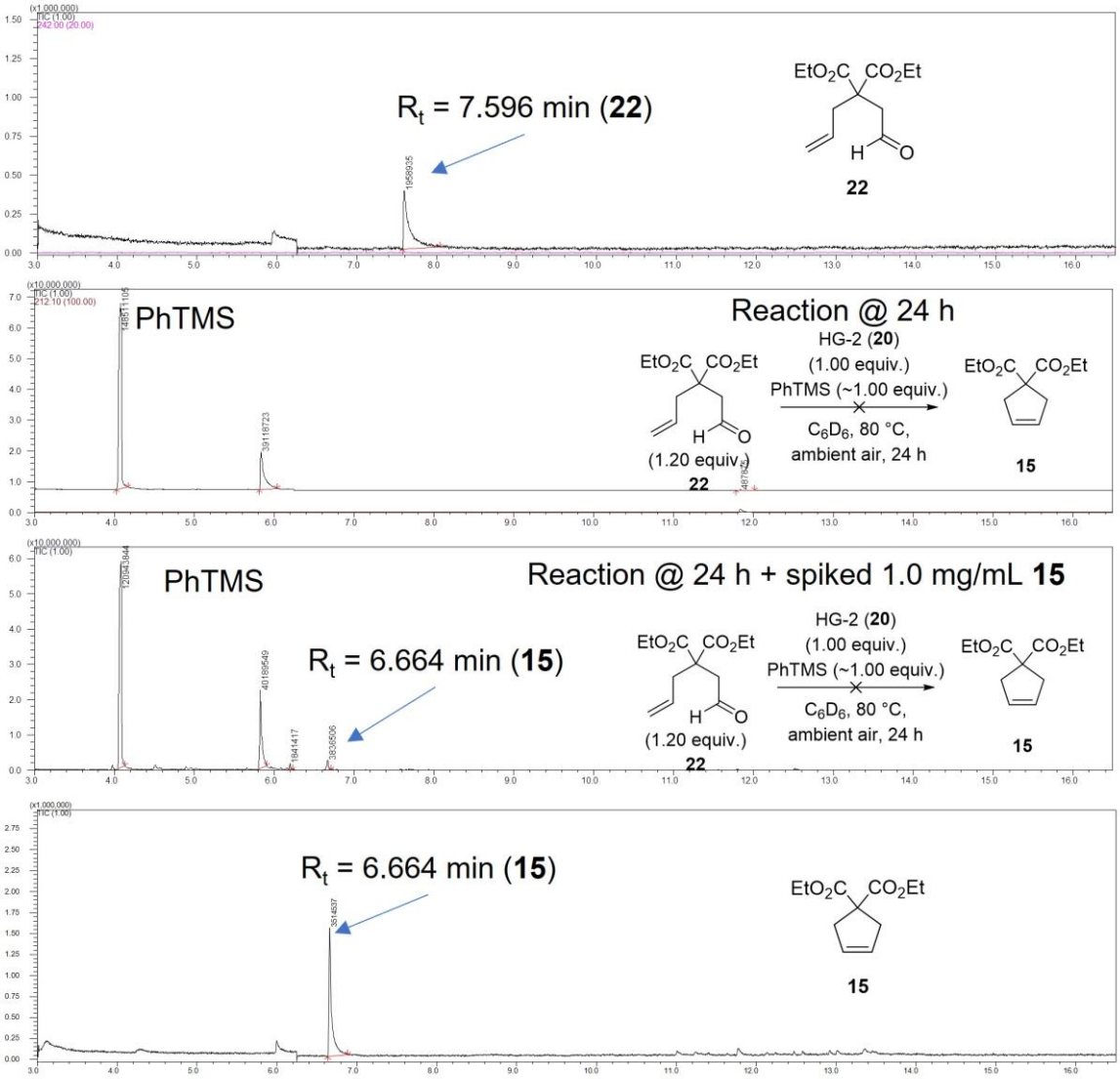
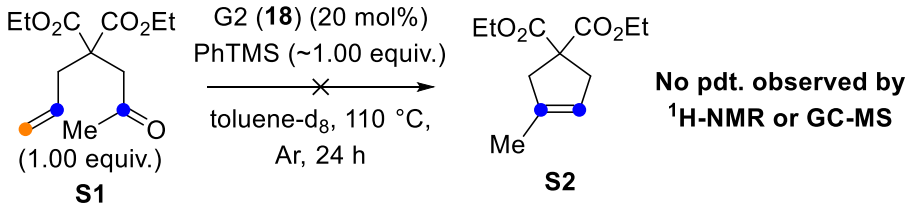


Figure S6. GC-MS reaction monitoring for substrate **22** under hydrazone/oxime olefination conditions using HG-2 (**20**). From top to bottom: 1) GC-MS trace of substrate **22**. 2) Reaction mixture of substrate **22** and HG-2 (**20**) in C_6D_6 after 24 h at 80 °C. 3) Same reaction mixture with addition of standard solution of **15** (at 1.0 mg/mL). 4) GC-MS trace of product **15** independently synthesized by olefin metathesis.[11]

C. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **S1** under Roy's conditions (**GP-D**)



General Procedure D was employed with substrate **S1** (2.65 mg, 0.0103 mmol), G2 (**18**) (1.70 mg, mmol, 19.4 mol%) and PhTMS (1.00 equiv.). After 24 h at 110 °C, 94% of starting material **S1** was consumed and cyclic olefin product **S2** was not formed by ^{1}H-NMR.

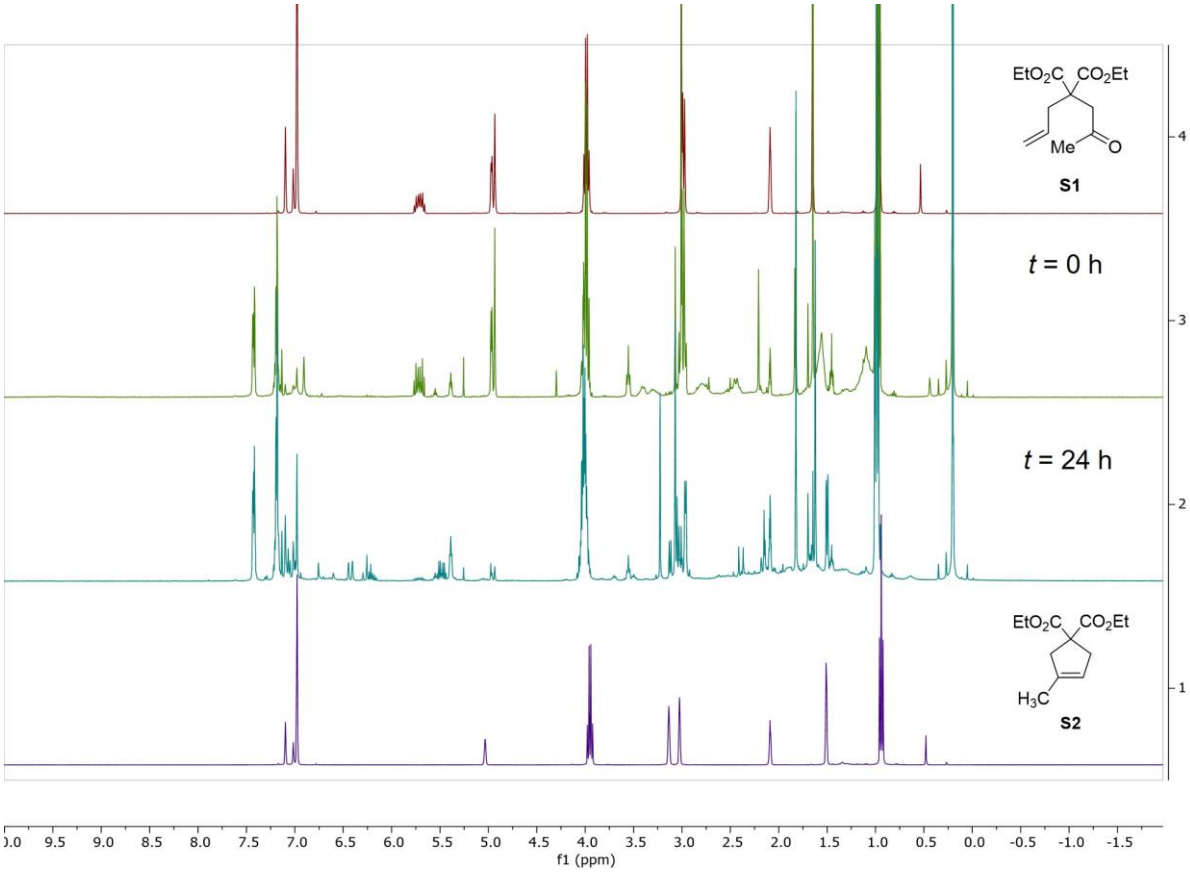


Figure S7. In situ ^{1}H-NMR experiment for substrate **S1** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) ^{1}H-NMR of substrate **S1** in toluene-d_8. 2) Reaction mixture of substrate **S1** and 20 mol% G2 (**18**) in toluene-d_8 after 0 h. 3) Same reaction mixture after 24 h at 110 °C. 4) ^{1}H-NMR of product standard **S2** independently synthesized by olefin metathesis.[11]

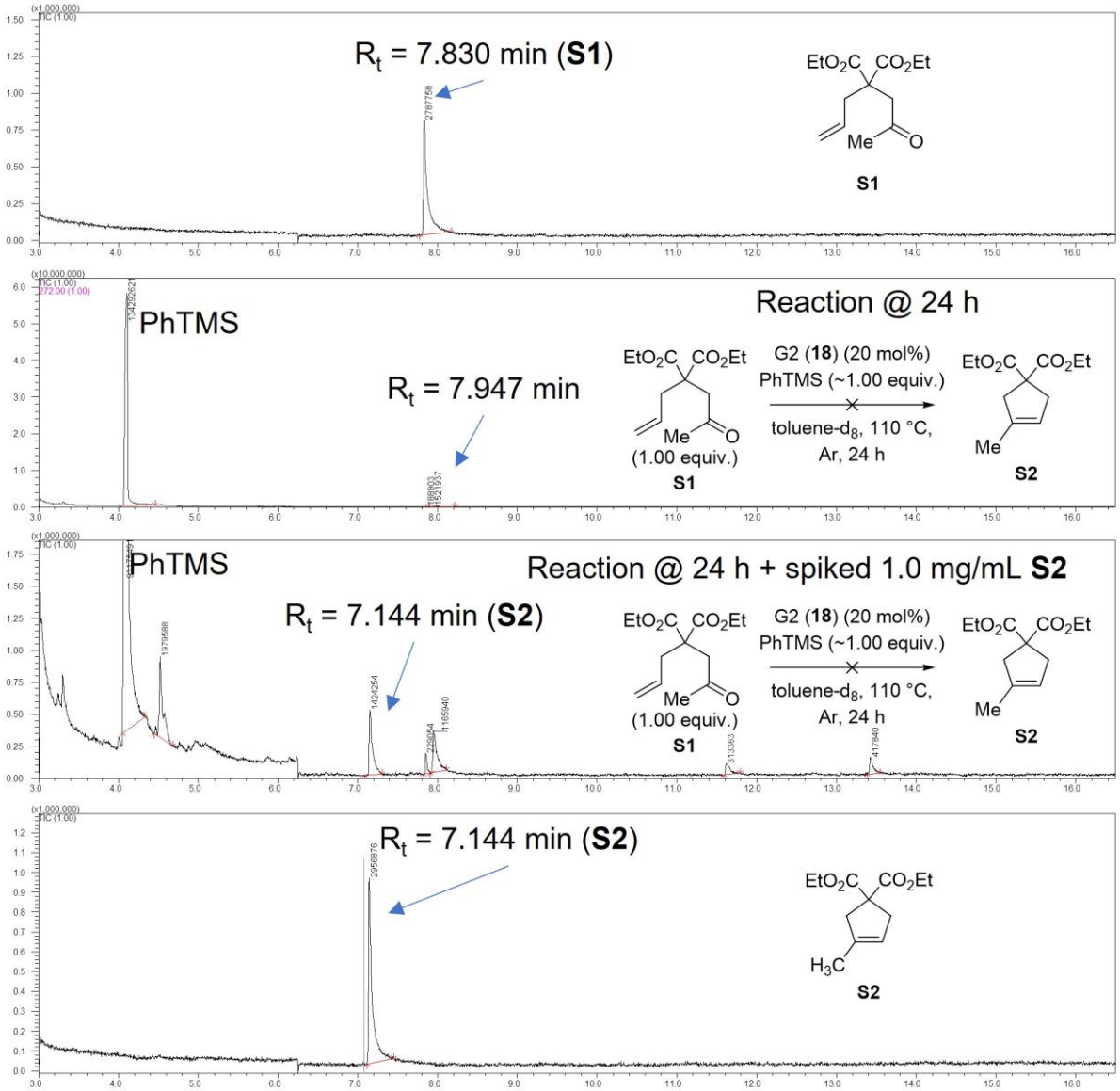
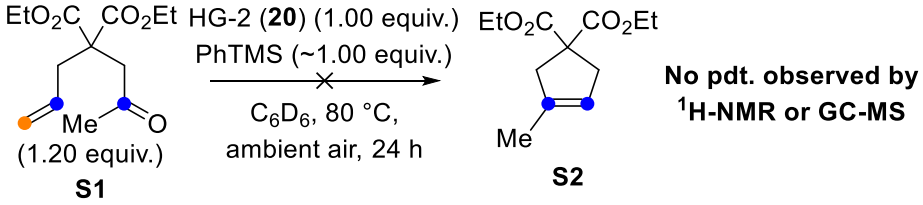


Figure S8. GC-MS reaction monitoring for substrate **S1** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) GC-MS trace of substrate **S1**. 2) Reaction mixture of substrate **S1** and 20 mol% G2 (**18**) in toluene-d_8 after 24 h at 110 °C. 3) Same reaction mixture with addition of standard solution of **S2** (at 1.0 mg/mL). 4) GC-MS trace of product standard **S2** independently synthesized by olefin metathesis.[11]

D. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **S1** under hydrazone/oxime olefination conditions (**GP-E**)



General Procedure E was employed with substrate **S1** (3.1 mg, 0.0121 mmol, 1.20 equiv.), HG-2 (**20**) (6.3 mg, 0.0101 mmol, 1.00 equiv.) and PhTMS (1.00 equiv.). After 24 h at 80 °C, 7% of starting material **S1** remained and cyclic olefin product **S2** was not formed by ^{1}H-NMR.

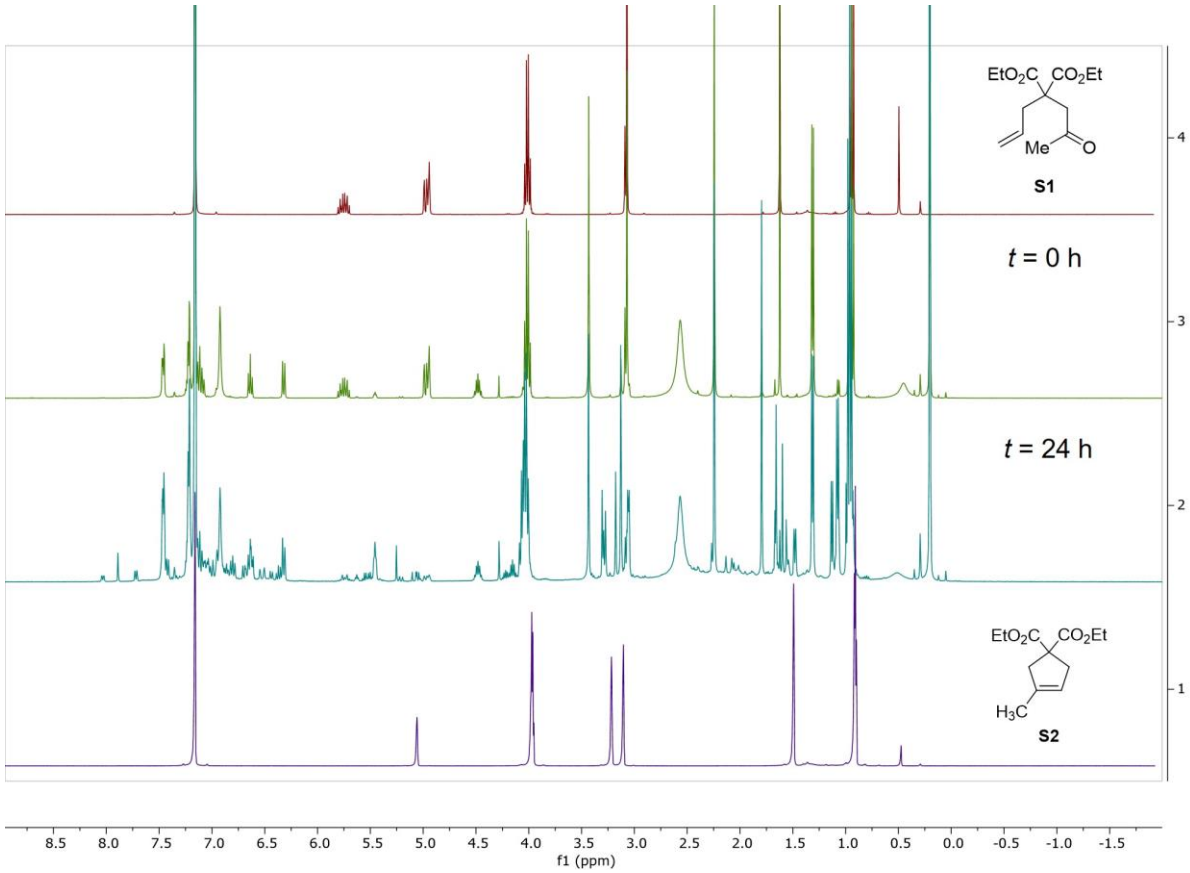


Figure S9. In situ ^{1}H-NMR experiment for substrate **S1** under hydrazone/oxime olefination conditions using HG-2 (**20**). From top to bottom: 1) ^{1}H-NMR of substrate **S1** in C_6D_6. 2) Reaction mixture of substrate **S1** and HG-2 (**20**) in C_6D_6 after 0 h. 3) Same reaction mixture after 24 h at 80 °C. 4) ^{1}H-NMR of product standard **S2** independently synthesized by olefin metathesis.[11]

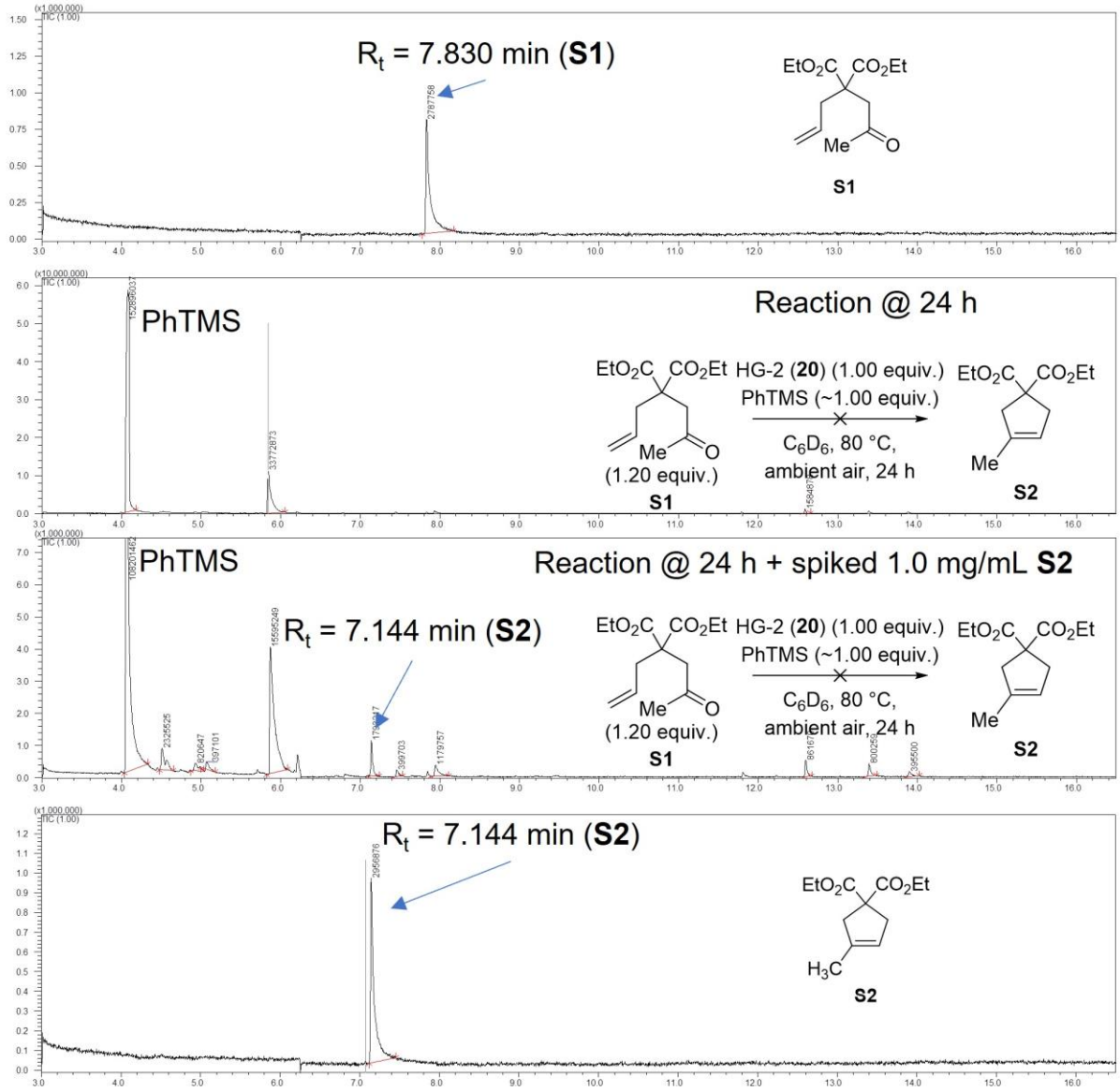
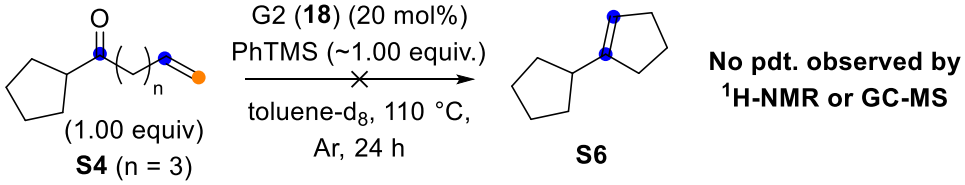


Figure S10. GC-MS reaction monitoring for substrate **S1** under hydrazone/oxime olefination conditions using HG-2 (**20**). From top to bottom: 1) GC-MS trace of substrate **S1**. 2) Reaction mixture of substrate **S1** and HG-2 (**20**) in C_6D_6 after 24 h at 80 °C. 3) Same reaction mixture with addition of standard solution of **S2** (at 1.0 mg/mL). 4) GC-MS trace of product **S2** independently synthesized by olefin metathesis.[11]

E. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **S4** under Roy's conditions (**GP-D**)



General Procedure D was employed with substrate **S4** (1.7 mg, 0.0102 mmol), G2 (**18**) (1.70 mg, mmol, 19.6 mol%) and PhTMS (1.00 equiv.). After 24 h at 110 °C, starting material **S4** was completely consumed and cyclic olefin product **S6** was not formed by ^{1}H-NMR.

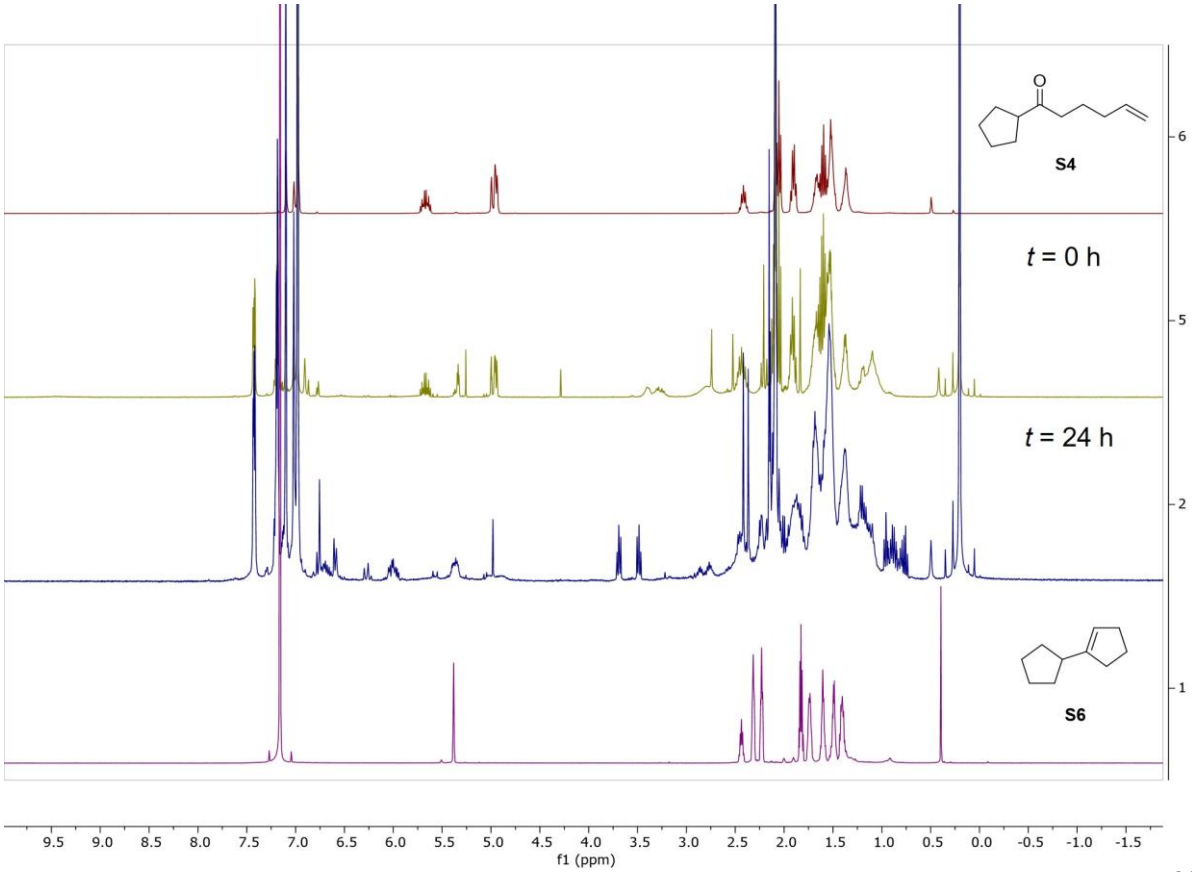


Figure S11. In situ ^{1}H-NMR experiment for substrate **S4** under Roy's reported conditions[6] for Ru alkylidene-mediated COM. From top to bottom: 1) ^{1}H-NMR of substrate **S4** in toluene-d_8. 2) Reaction mixture of substrate **S4** and 20 mol% G2 (**18**) in toluene-d_8 after 0 h. 3) Same reaction mixture after 24 h at 110 °C. 4) ^{1}H-NMR of product standard **S6** independently synthesized from **S4** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10]

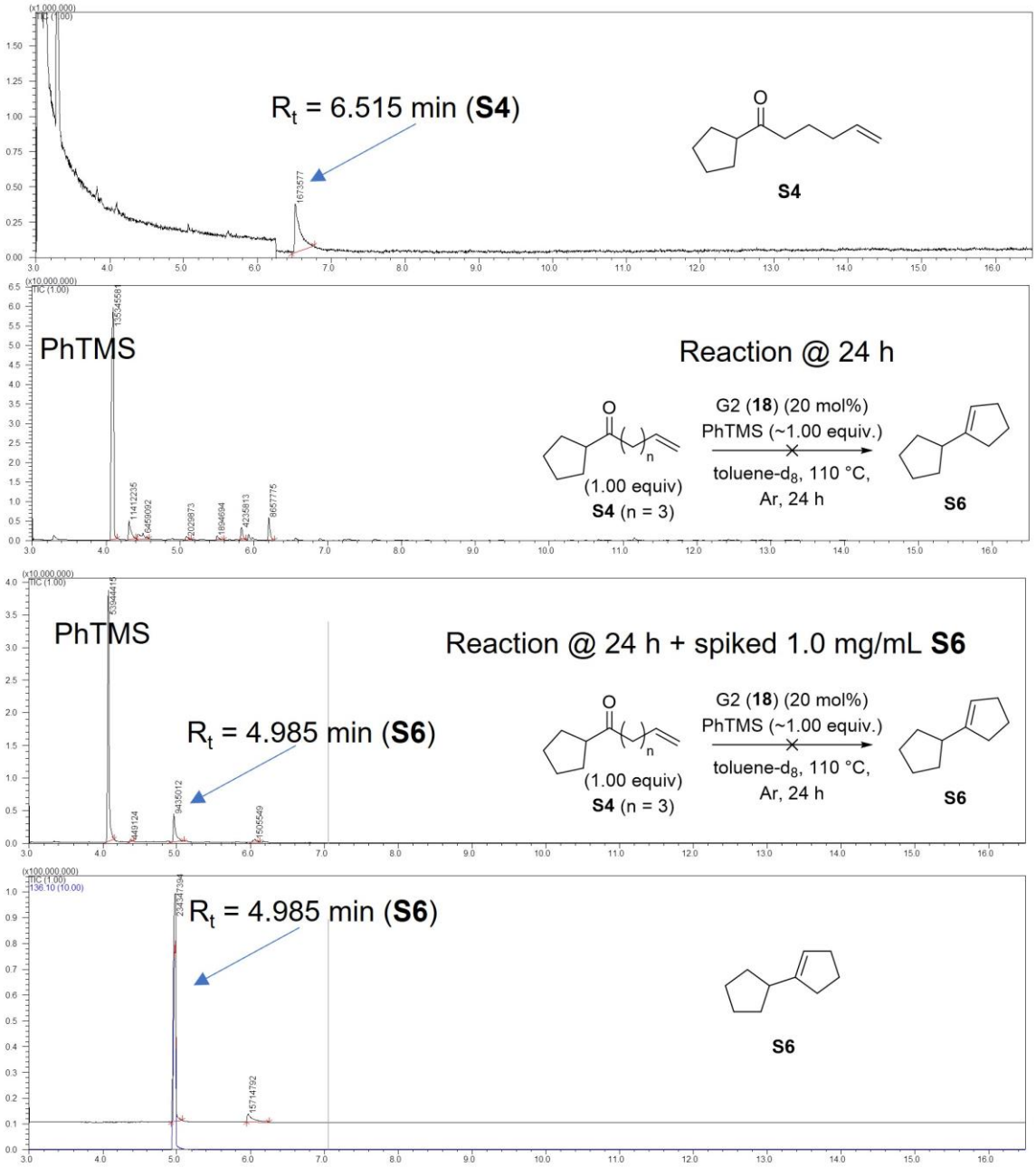
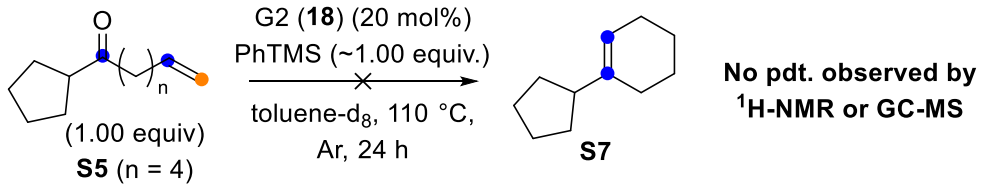


Figure S12. GC-MS reaction monitoring for substrate **S4** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) GC-MS trace of substrate **S4**. 2) Reaction mixture of substrate **S4** and 20 mol% G2 (**18**) in toluene-d_8 after 24 h at 110 °C. 3) Same reaction mixture with addition of standard solution of **S6** (at 1.0 mg/mL). 4) GC-MS trace of product standard **S6** independently synthesized from **S4** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10]

F. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **S5** under Roy's conditions (**GP-D**)



General Procedure D was employed with substrate **S5** (1.8 mg, 0.01 mmol), G2 (**18**) (1.70 mg, mmol, 20 mol%) and PhTMS (1.00 equiv.). After 24 h at 110 °C, starting material **S5** was completely consumed and cyclic olefin product **S7** was not formed by ^{1}H-NMR.

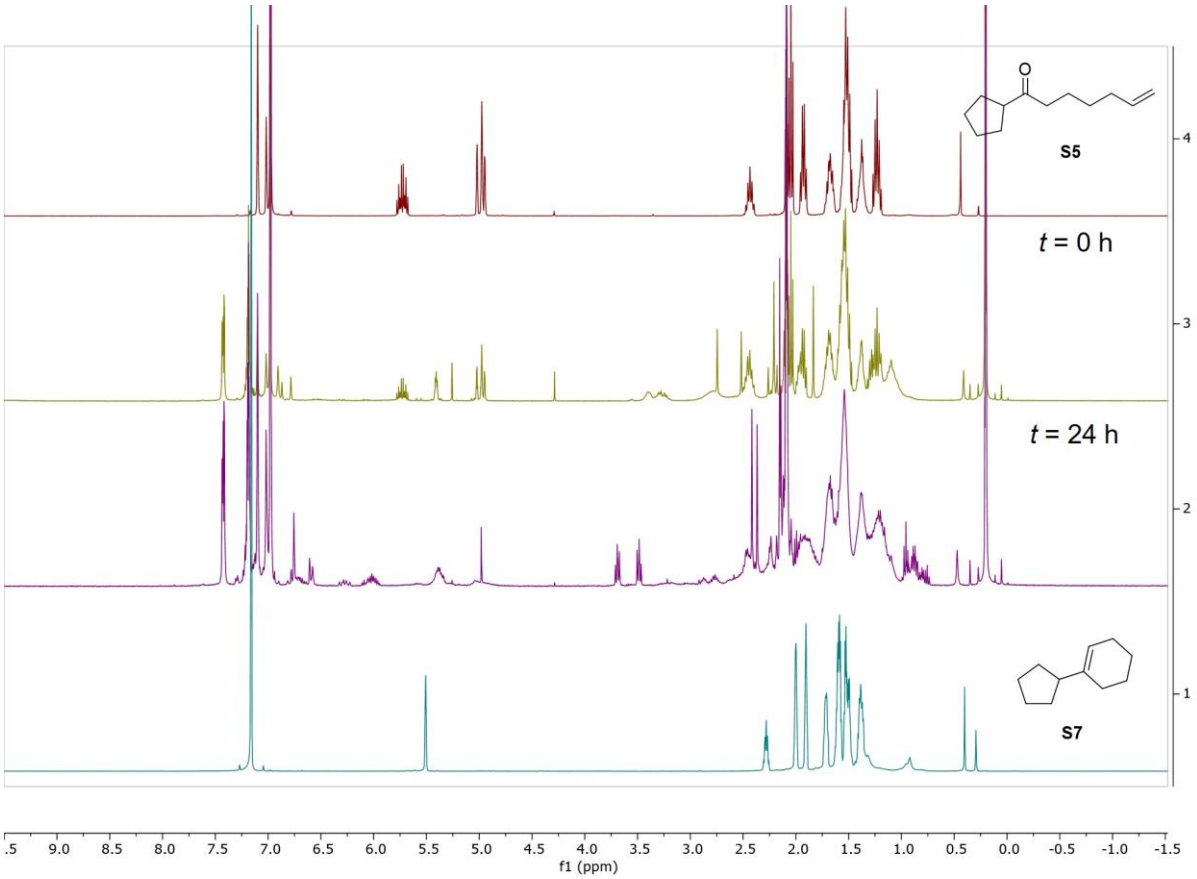


Figure S13. In situ ^{1}H-NMR experiment for substrate **S5** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) ^{1}H-NMR of substrate **S5** in toluene-d_8. 2) Reaction mixture of substrate **S5** and 20 mol% G2 (**18**) in toluene-d_8 after 0 h. 3) Same reaction mixture after 24 h at 110 °C. 4) ^{1}H-NMR of product standard **S7** independently synthesized from **S5** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10]

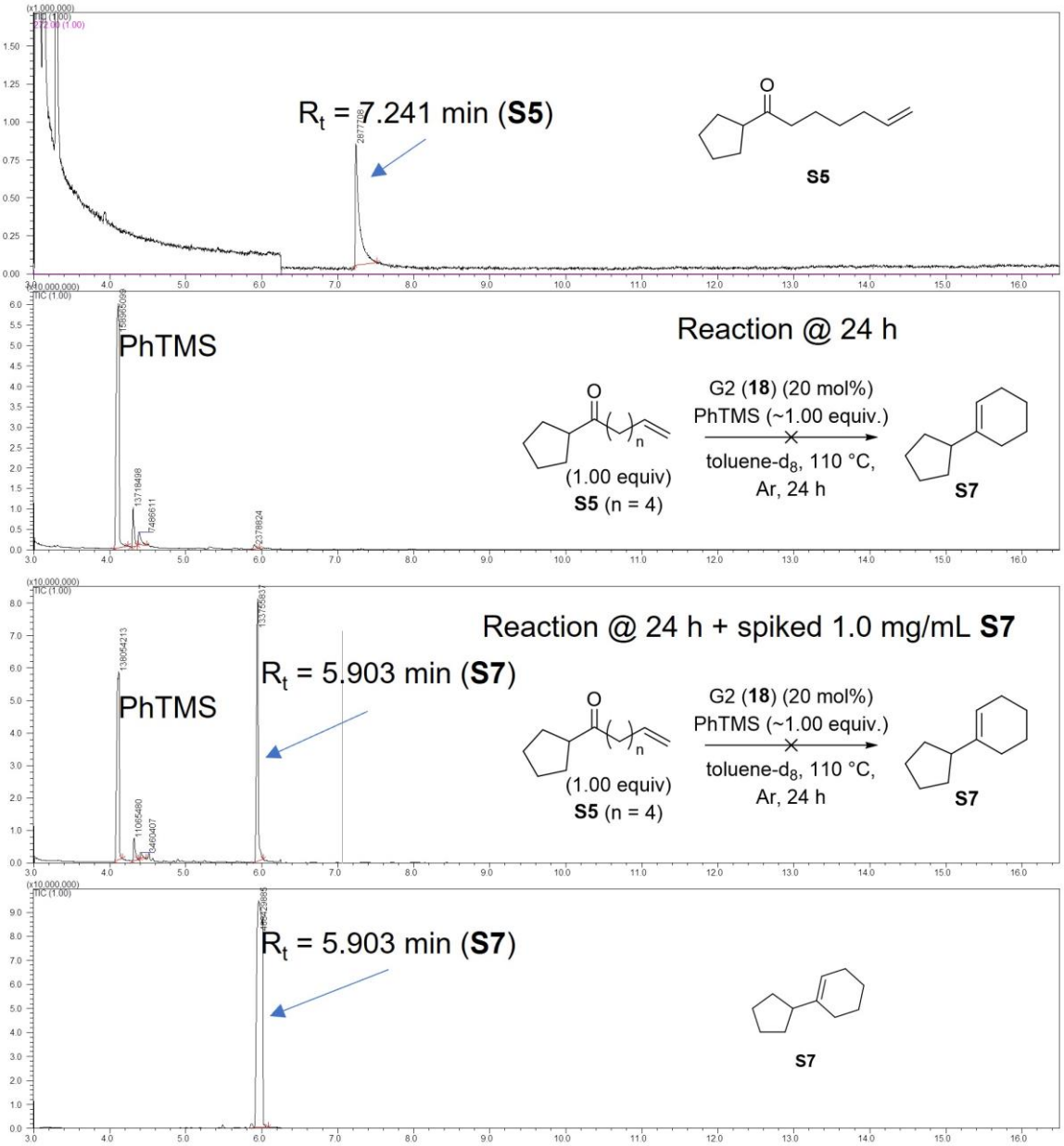


Figure S14. GC-MS reaction monitoring for substrate **S5** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**). From top to bottom: 1) GC-MS trace of substrate **S5**. 2) Reaction mixture of substrate **S5** and 20 mol% G2 (**18**) in toluene-d_8 after 24 h at 110 °C. 3) Same reaction mixture with addition of standard solution of **S7** (at 1.0 mg/mL). 4) GC-MS trace of product standard **S7** independently synthesized from **S5** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10]

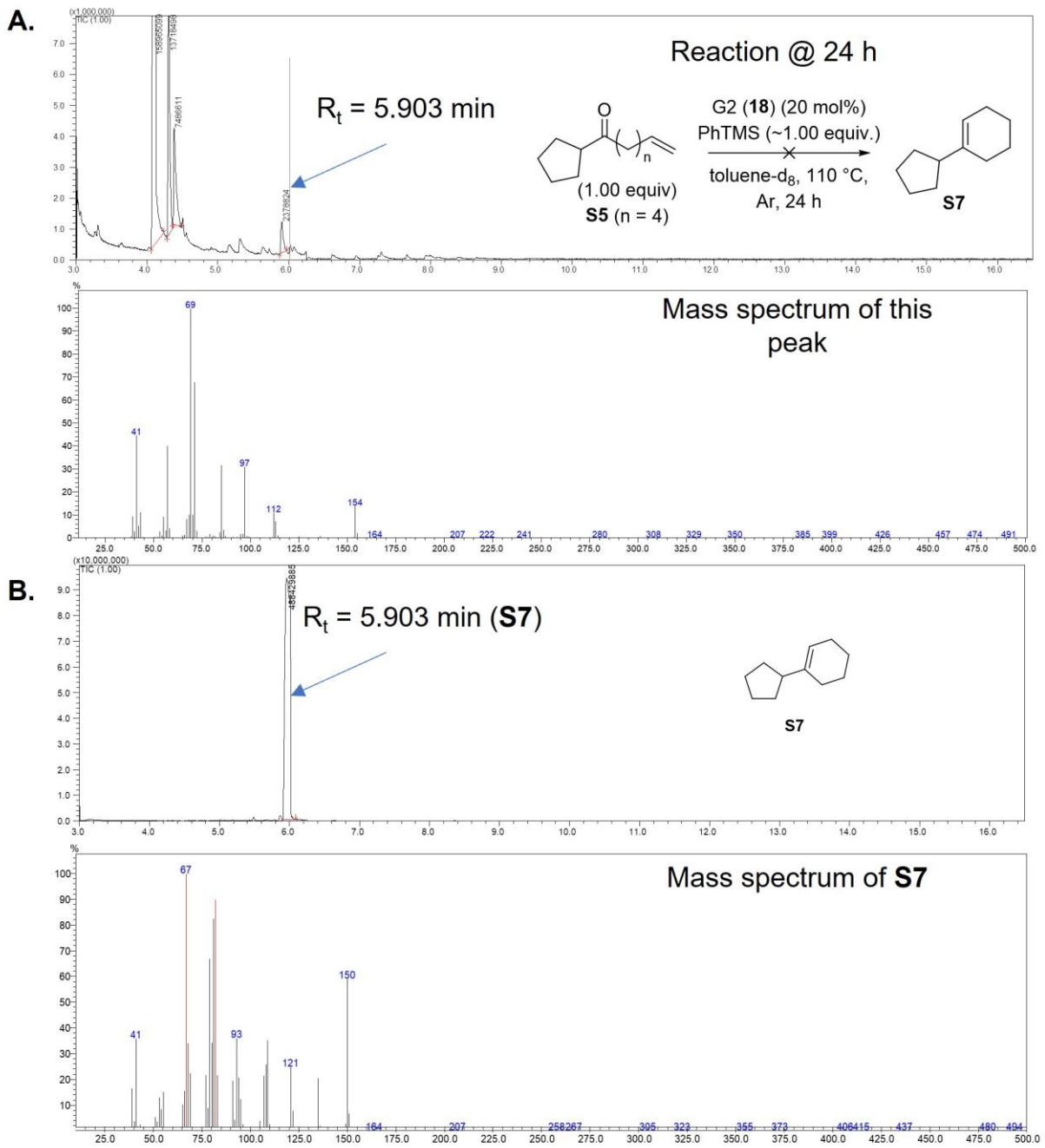
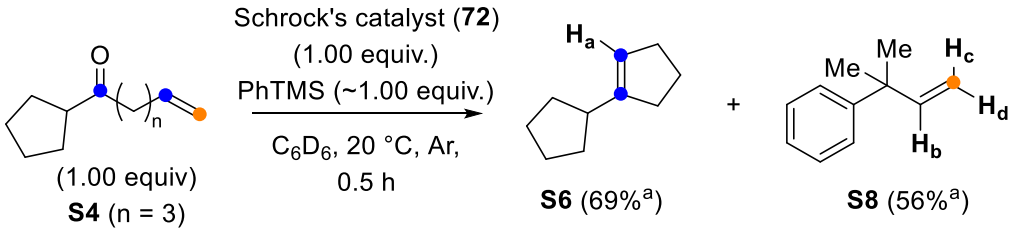


Figure S15. Comparison of mass spectra between **S7** and a small peak in GC-MS trace with identical retention time from the reaction of **S5** under Roy's reported conditions[6] for carbonyl-olefin metathesis using G2 (**18**).

G. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **S4** under Grubbs' conditions (**GP-F**)



[a]Yield determined by ^{1}H-NMR using phenyltrimethylsilane as an internal standard.

General Procedure F was employed with substrate **S4** (1.7 mg, 0.0102 mmol), Schrock's catalyst (**72**) (7.7 mg, 0.0101 mmol) and PhTMS (1.00 equiv.). After 0.5 h at 25 °C, Schrock's catalyst was completely consumed and cyclic olefin product **S6** was formed in 69% by ^{1}H-NMR spectroscopy.

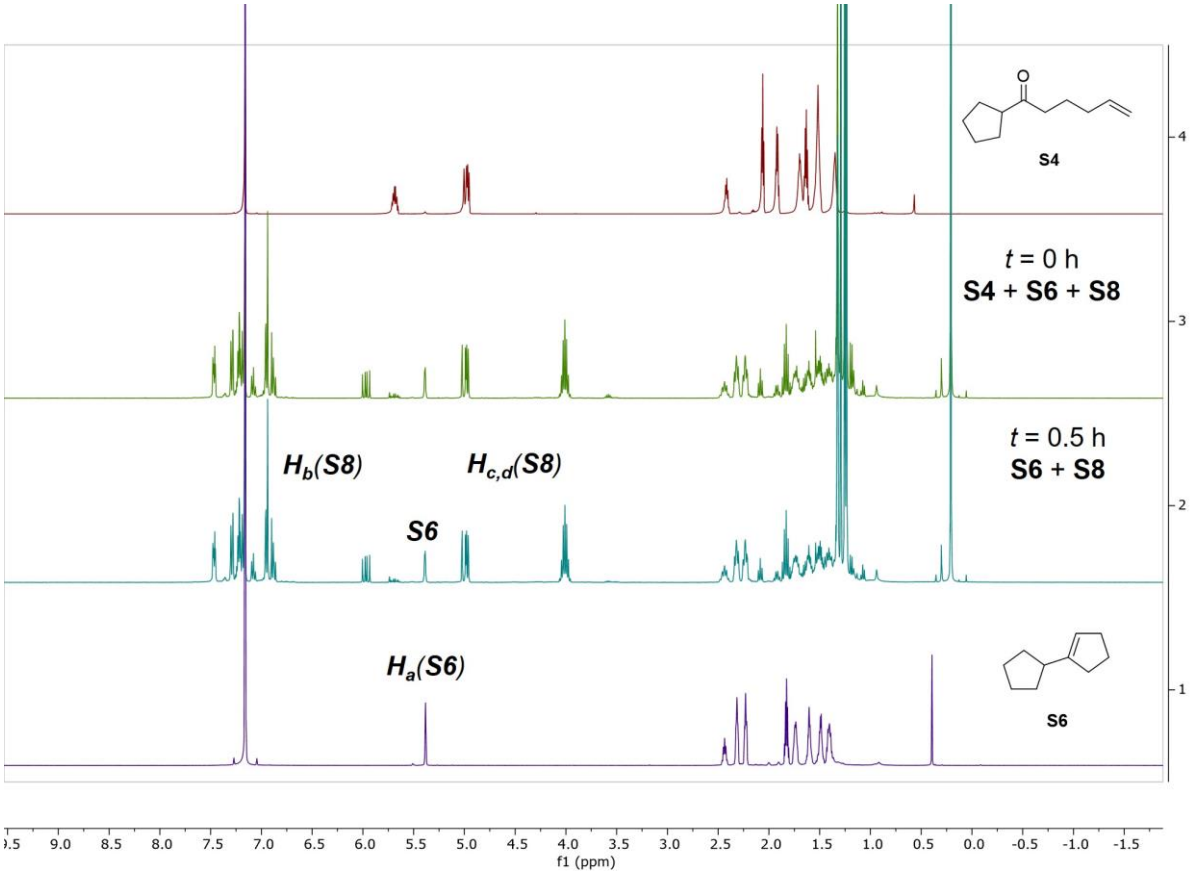


Figure S16. In situ ^{1}H-NMR experiment for substrate **S4** following reported conditions for carbonyl olefin metathesis using Schrock's catalyst.[10] From top to bottom: 1) ^{1}H-NMR of substrate **S4** in C_6D_6. 2) Reaction mixture of substrate **S4** and Schrock's catalyst (**72**) in C_6D_6 after 0 h. 3) Same reaction mixture after 0.5 h at 25 °C. 4) ^{1}H-NMR of product standard **S6** synthesized from **S4** under identical conditions on a 0.1 mmol scale.

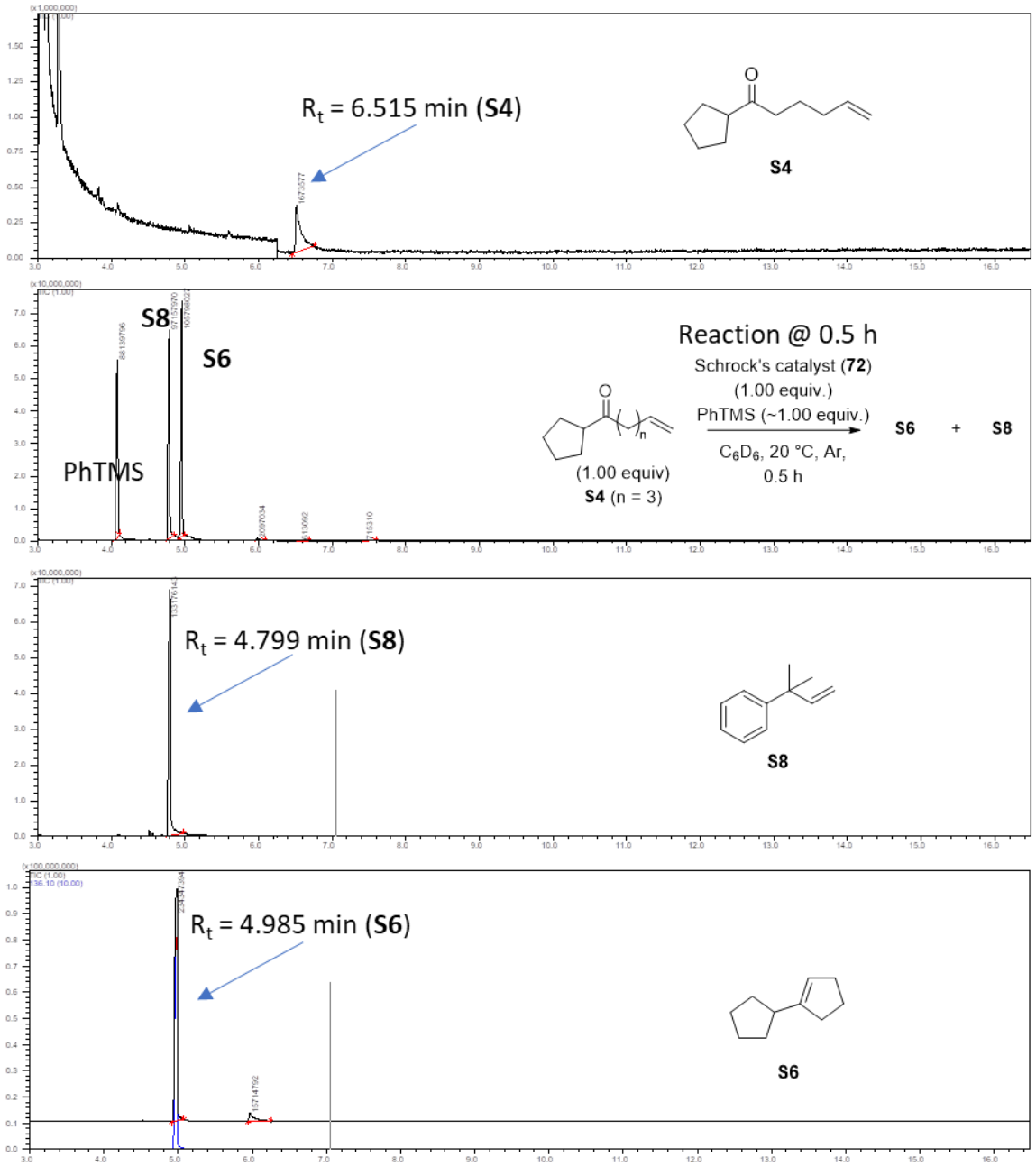
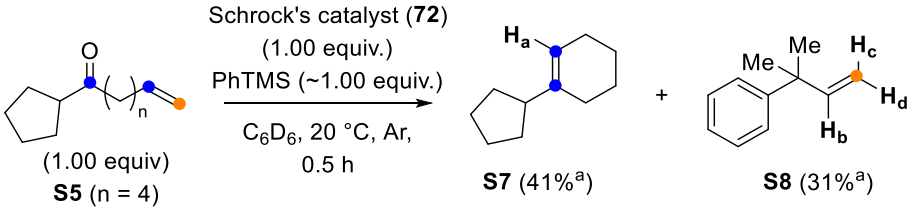


Figure S17. GC-MS reaction monitoring for substrate **S4** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10] From top to bottom: 1) GC-MS trace of substrate **S4**. 2) Reaction mixture of substrate **S4** and Schrock's catalyst (**72**) in C_6D_6 after 0.5 h at 25 °C. 3) GC-MS trace of byproduct **S8**. 4) GC-MS trace of product standard **S6** synthesized from **S4** under identical conditions on a 0.1 mmol scale.

H. *In situ* ^{1}H-NMR Experiment and subsequent GC-MS analysis of COM reaction of **S5** under Grubbs' conditions (**GP-F**)



[a]Yield determined by ^{1}H-NMR using phenyltrimethylsilane as an internal standard.

General Procedure F was employed with substrate **S5** (1.9 mg, 0.0105 mmol), Schrock's catalyst (**72**) (7.8 mg, 0.0102 mmol) and PhTMS (1.00 equiv.). After 0.5 h at 25 °C, Schrock's catalyst was completely consumed and cyclic olefin product **S7** was formed in 41% by ^{1}H-NMR.

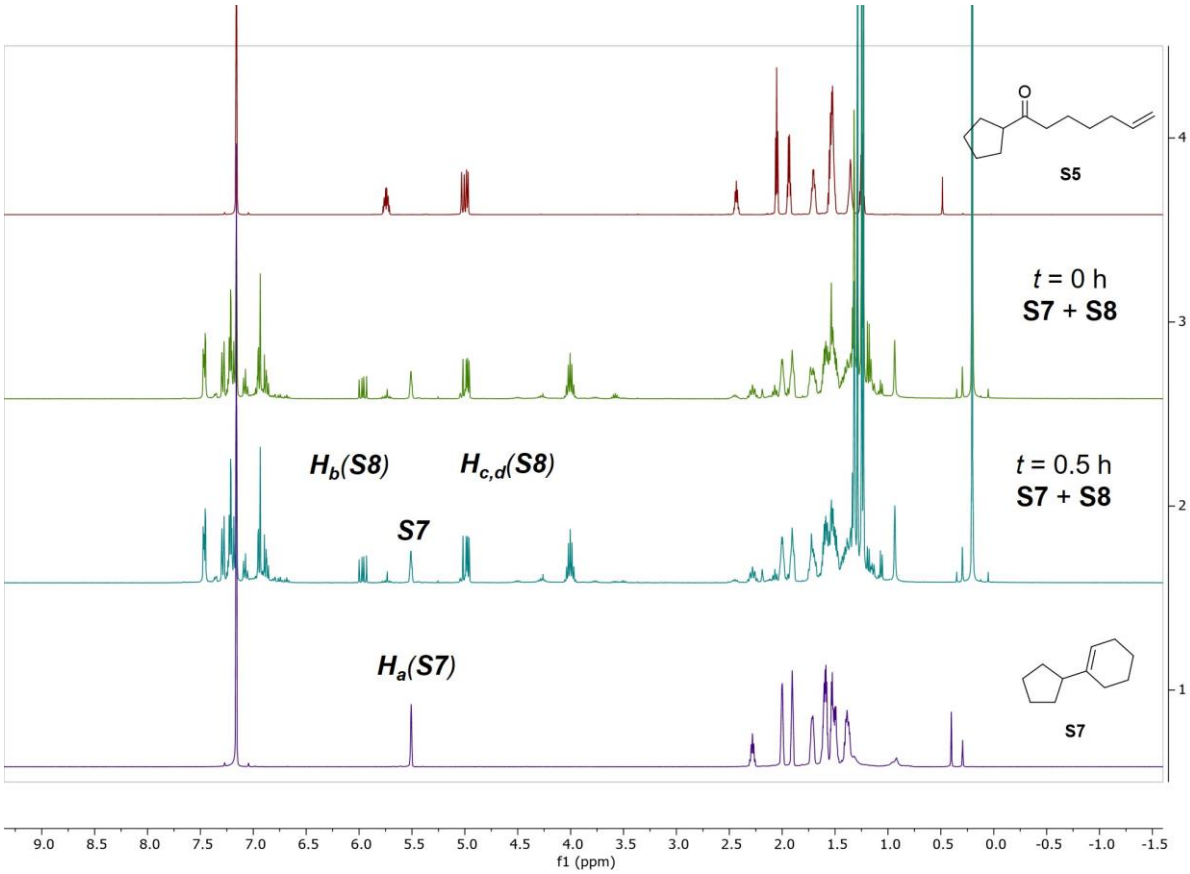


Figure S18. In situ ^{1}H-NMR experiment for substrate **S5** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10] From top to bottom: 1) ^{1}H-NMR of substrate **S5** in C_6D_6. 2) Reaction mixture of substrate **S5** and Schrock's catalyst (**72**) in C_6D_6 after 0 h. 3) Same reaction mixture after 0.5 h at 25 °C. 4) ^{1}H-NMR of product standard **S7** synthesized from **S5** under identical conditions on a 0.13 mmol scale.

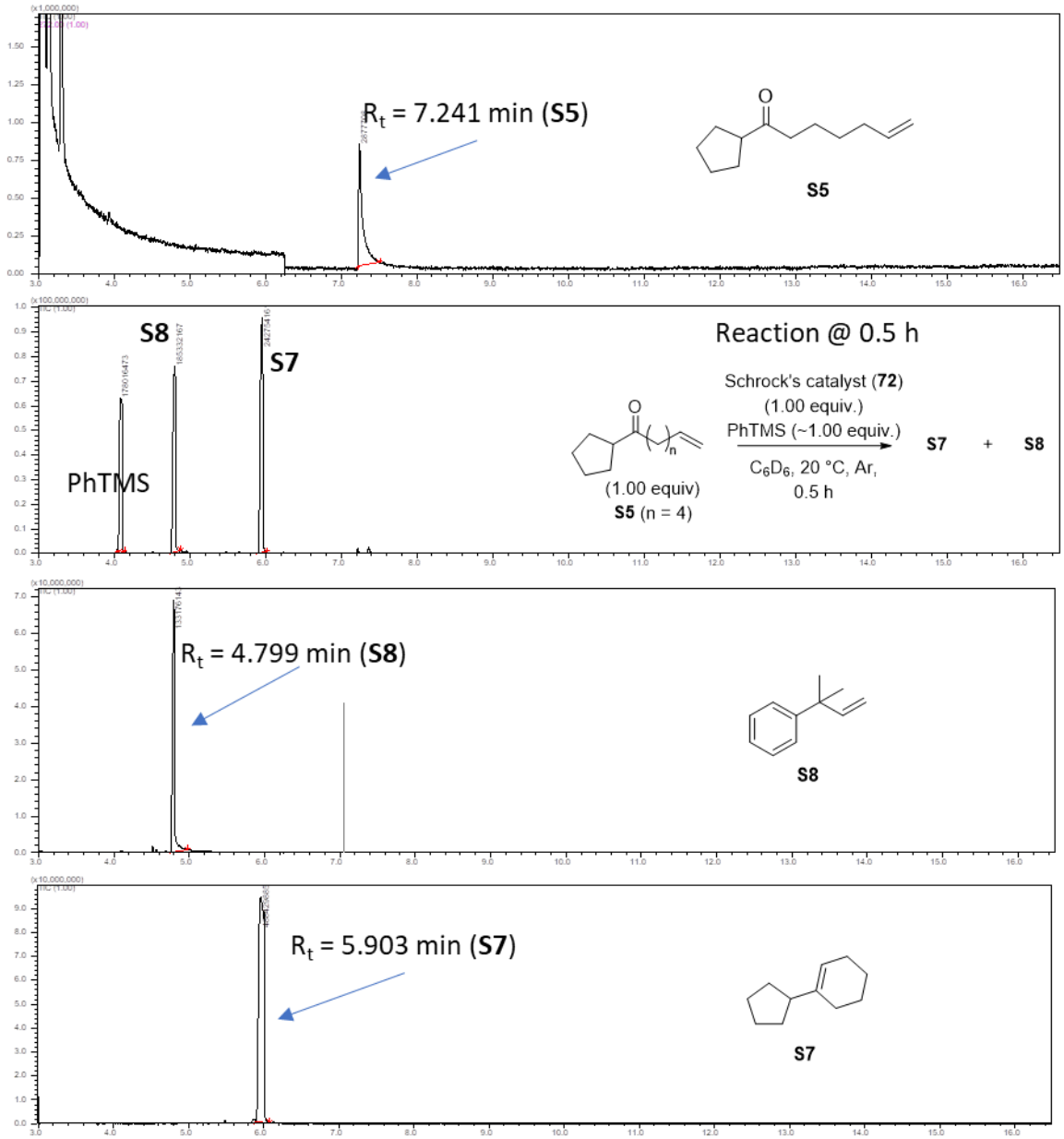
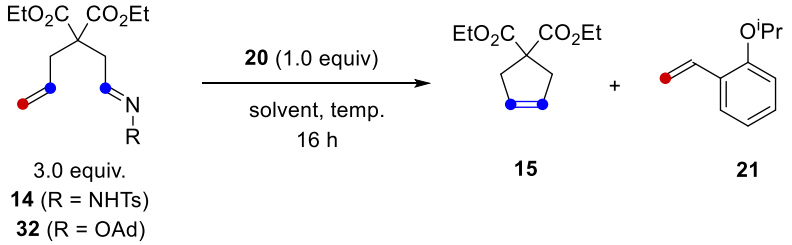


Figure S19. GC-MS reaction monitoring for substrate **S5** following reported conditions for carbonyl-olefin metathesis using Schrock's catalyst.[10] From top to bottom: 1) GC-MS trace of substrate **S5**. 2) Reaction mixture of substrate **S5** and Schrock's catalyst (**72**) in C_6D_6 after 0.5 h at 25 °C. 3) GC-MS trace of byproduct **S8**. 4) GC-MS trace of product standard **S7** synthesized from **S5** under identical conditions on a 0.13 mmol scale.

6. Solvent evaluation for olefination of oximes and hydrazones (expanded Table 3 from manuscript)

Evaluation of solvents for both substrates **14** and **32** under the conditions of **Representative Procedure B** (page 5) is shown below as a supplement to **Table 3** in the manuscript.

Table S1. Solvent evaluation of the ruthenium-meditated olefination of hydrazones and oximes.[a]



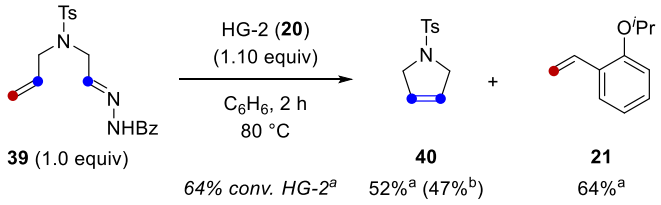
entry	solvent	substrate	temp. (°C)	yield **15** at 2h (%)[b]	yield **15** at 16h (%)[b]
1	benzene-d_6	**14**	80[c]	85	-
2	benzene-d_6	**32**	80[d]	79	87
3	toluene-d_8	**14**	80[c]	84	-
4	toluene-d_8	**32**	80[d]	75	85
5	$CDCl_3$	**14**	60[c]	71	81
6	$CDCl_3$	**32**	60[d]	38	72
7	CD_2Cl_2	**14**	40[c]	-	77
8	CD_2Cl_2	**32**	40[d]	17	61[e]
9	acetonitrile-d_3	**14**	80[c]	18	-
10	acetonitrile-d_3	**32**	80[d]	55	59
11	THF-d_8	**14**	60[c]	-	76
12	THF-d_8	**32**	60[d]	64	66
13	acetone-d_6	**14**	60[c]	-	72
14	acetone-d_6	**32**	60[d]	50	74
15	DMSO-d_6	**14**	80[c]	24	-
16	DMSO-d_6	**32**	80[d]	47	51
17	methanol-d_4	**14**	60[c]	-	64
18	methanol-d_4	**32**	60[d]	47	35[f]

[a] Conditions: **20** (0.01 mmol), **14** or **32** (3.0 equivalents), in deuterated solvent (0.0145 M) at various temperatures (40, 60, or 80 °C) for 0.5-16 h in screw-top NMR tubes. [b] Yield and conversion based on **20** were determined by ^{1}H-NMR with phenyltrimethylsilane as the internal standard. [c] Under N_2 atmosphere. [d] 40 °C for 40 h. [e] Addition of MeOH to Grubbs type Ru alkylidene catalysts leads to formation of Ru hydride species which isomerize the olefin product **15** resulting in lower yield at extended reaction times.[12,13]

7. Comparison of Isolated and NMR yields for olefination of substrate 39 under conditions with limiting substrate compared to limiting HG-2 (20):

To verify that our NMR yields match the isolated yields, a direct comparison was conducted for substrate **39** (under condtions with limiting substrate and HG-2 (**20**)) and the results are shown below. Reaction times for both experiments (2 h) were selected due the tendency of the product **40** to isomerize upon heating for extended period (16 h) leading to lower yields by NMR. Specifically, they show that the reported NMR yield matches the isolated yield for conditions with limiting substrate (52% by NMR / 47% IY) and limiting Ru-alkylidene **20** (51% by NMR / 49% IY) respectively. This result suggests that the use of NMR yields represents isolated yields appropriately.

Comparison of ^{1}H-NMR yield and IY for limiting substrate:



39 (1.0 equiv) | **40** | **21**

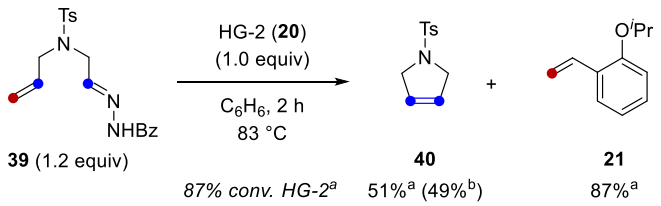
64% conv. HG-2[a] | 52%[a] (47%[b]) | 64%[a]

Conditions: HG-2 (**20**) (1.10 equivalents), **39** (0.40 mmol), phenyltrimethylsilane (PhTMS) (1.00 equivalents) in benzene (0.0145 M) at 80°C for 2 h in screw-top pressure flasks. [a]Yield and conversion based on Ru alkylidene **20** were determined by ^{1}H-NMR with phenyltrimethylsilane (PhTMS) as the internal standard using ^{1}H-NMR with solvent suppression. [b]Isolated yield.

Olefination of 39 (1.00 equiv.) with HG-2 (20) (1.10 equiv.) to form 1-tosyl-2,5-dihydro-1H-pyrrole (40): An oven-dried 48 mL glass pressure flask equipped with a Teflon-coated stir bar was charged with **20** (284 mg, 1.10 equiv., 444 µmol) in a N_2-filled glovebox, transferred outside the glovebox and opened to air. Then, the flask was charged with **39** (149.4 mg, 1.00 equiv., 402 µmol), phenyltrimethylsilane (61.0 mg, 70.0 µL, 1.00 equiv., 406 µmol, PhTMS), and anhydrous benzene (27.6 mL, 14.50 µM), sealed and heated at 80 °C for 2 h with stirring at 450 RPM. The reaction was cooled to 25 °C and a 0.40 mL aliquot was removed by syringe and examined by ^{1}H-NMR for conversion and yield against the internal standard PhTMS (referenced to δ 0.20 ppm, the observed -$SiMe_3$ shift in C_6D_6). A standard ^{1}H-NMR experiment (16 scans, 10 sec. relaxation delay, gradient shimming on ^{1}H) was obtained and used to setup a ^{1}H {PRESAT} solvent suppression experiment (presaturation at 7.09 ppm, 16 scans, 2 sec. relaxation delay, 10 sec. pulse delay, 8 steady state scans). After 2 h at 80 °C, complete consumption of **39** was observed in addition to 46% HG-2 (**20**) (64% conversion), 63% 1-isopropoxy-2-vinylbenzene (**19**), and 52% of 1-tosyl-2,5-dihydro-1H-pyrrole (**40**) (-CH_2- resonance of **40**).

Then, Snatchcat™(1,4-bis(3-isocyanopropyl)piperazine) (433.3 mg, 4.89 Eq, 1.97 mmol) was added in one portion and the reaction mixture stirred at 25 °C for 0.5 hour. The reaction mixture was transferred to a 100 mL round bottom flask and concentrated under reduced pressure (37 °C rotovap bath temperature, 20 torr) to give a thick brown oil which was dissolved in DCM (3-4 mL) and dry loaded onto silica (2.5 g). The crude residue was purified by flash column chromatography (SiO_2/5%EtOAc–Hexanes). Fractions containing the desired compound by TLC (R_f = 0.38, 30% EtOAc in hexanes, UV 254 nm and $KMnO_4$, 42.0 mg total) were combined to give 1-tosyl-2,5-dihydro-1H-pyrrole **40** (42.0 mg, 0.19 mmol, 47 %). The ^{1}H-NMR spectra obtained for this reaction was consistent with those obtained for compound **40** (see Page 40) and with literature values.[14]

Comparison of ^{1}H-NMR yield and Isolated Yield for limiting HG-2



39 (1.2 equiv) | **40** | **21**

87% conv. HG-2[a] | 51%[a] (49%[b]) | 87%[a]

Conditions: HG-2 (**20**) (0.20 mmol), **39** (1.20 equivalents), phenyltrimethylsilane (PhTMS) (1.00 equivalents) in benzene (0.0145 M) at 80°C for 2 h in screw-top pressure flasks. [a]Yield and conversion based on Ru alkylidene **20** were determined by ^{1}H-NMR with phenyltrimethylsilane (PhTMS) as the internal standard using ^{1}H-NMR with solvent suppression. [b]Isolated yield.

Olefination of 39 (1.20 equiv.) with HG-2 (20) to form 1-tosyl-2,5-dihydro-1H-pyrrole (40): An oven-dried 48 mL glass pressure flask equipped with a Teflon-coated stir bar was charged with HG-2 (**20**) (125.4 mg, 1.00 equiv., 200.1 µmol) in a N_2-filled glovebox, transferred outside the glovebox, and opened to air. Then, the flask was charged with **39** (89.4 mg, 1.20 Eq, 241 µmol), phenyltrimethylsilane (30.5 mg, 35.0 µL, 1.00 equiv., 203 µmol, PhTMS), and anhydrous benzene (13.8 mL, 14.50 µM),

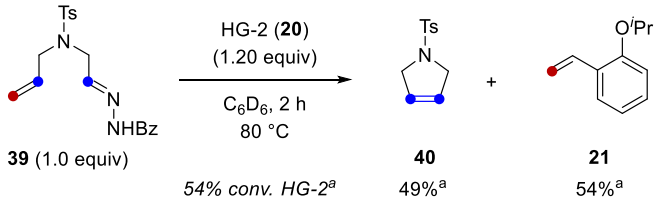
sealed and heated at 83 °C for 2 h. The reaction was cooled to 25 °C and a 0.40 mL aliquot was removed by syringe and examined by ^{1}H-NMR for conversion and yield against the internal standard PhTMS (referenced to δ 0.20 ppm, the observed -$SiMe_3$ shift in C_6D_6). A standard ^{1}H-NMR experiment (16 scans, 2 sec. relaxation delay, gradient shimming on ^{1}H) was obtained and used to setup a ^{1}H {PRESAT} solvent suppression experiment (presaturation at 7.5637 ppm, 16 scans, 2 sec. relaxation delay, 10 sec. pulse delay, 8 steady state scans). After 2 h at 83 °C, 87% conversion of HG-2 (**20**) was observed along with 87% of 1-isopropoxy-2-vinylbenzene (**19**) and 51% 1-tosyl-2,5-dihydro-1H-pyrrole (**40**) (-CH_2- resonance of **40**).
Then, Snatchcat™ (1,4-bis(3-isocyanopropyl)piperazine) (194.0 mg, 4.40 equiv., 880 µmol) (Strem) was added in one portion and the reaction mixture stirred at 25 °C for 0.5 h. The reaction mixture was transferred to a 50 mL pear-shaped round bottom flask and concentrated under reduced pressure (25 °C rotovap bath temperature, 50 torr) to give a thick brown oil which was dissolved in DCM (3-4 mL) and dry loaded onto silica (1 g). The crude residue was purified by flash column chromatography (SiO_2/5%EtOAc–Hexanes). Fractions containing the desired compound by TLC (R_f = 0.38, 30% EtOAc in hexanes, UV 254 nm and $KMnO_4$) were combined to give **40** (21.9 mg, 98.1 µmol, 49 %) as a white solid. The ^{1}H-NMR spectra obtained for this reaction was consistent with those obtained for compound **40** (see Page 40) and with literature values.[14]

8. Investigation of portion-wise addition method for olefination of oximes and hydrazones:

Olefination of substrate 39 with portion-wise addition of excess HG-2 (20):

Portion-wise addition of Ru-alkylidene HG-2 (**20**) in olefination of **39** was investigated due the reported beneficial effect for olefin-olefin metathesis of substrates with terminal olefins at high temperatures.[15] Notably, the yield observed of product **40** (49%) was comparable to previous experiments which did not rely on portion-wise addition.

Portionwise Addition of HG-2 (0.3 equiv / 0.5 h) with limiting substrate:



39 (1.0 equiv) | **40** | **21**

54% conv. HG-2[a] | 49%[a] | 54%[a]

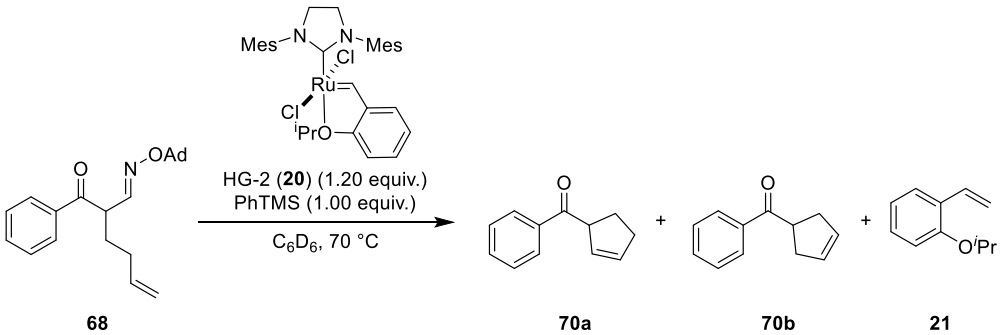
Conditions: HG-2 (**20**) (0.30 equivalents), **39** (0.03 mmol), in benzene-d_6 (0.0145 M) at 80°C for 2 h in 1-dram vial under a N_2 atmosphere with subsequent portionwise addition of HG-2 (**20**) (0.30 equivalents) at 0.5, 1.0, and 1.5 h of heating. [a]Yield and conversion based on Ru alkylidene **20** were determined by ^{1}H-NMR with phenyltrimethylsilane (PhTMS) as the internal standard using ^{1}H-NMR.

Olefination of 39 (1.00 equiv.) with HG-2 (20) (1.20 equiv., 4 portions of 0.30 equiv.) to form 1-tosyl-2,5-dihydro-1H-pyrrole (40): An oven-dried 1-dram glass vial equipped with a Teflon-coated stir bar was charged with **39** (11.10 mg, 1.00 equiv., 29.88 µmol), **20** (5.78 mg, 0.30 equiv., 9.03 µmol), and anhydrous C_6D_6 (2.06 mL, 14.50 µM) in a N_2-filled glovebox. The vial was capped, sealed with electrical tape, and stirred in a pre-heated Al block (80 °C, 250 RPM). The remainder of the HG-2 (**20**) was added in 3 equal portions of 5.78 mg) portions in 0.5 h intervals (0.5, 1.0, and 1.5 h), after removing the reaction mixture from heating and subsequently re-sealed. After 2 h at 80 °C, the reaction was cooled to 25 °C, transferred outside the glovebox, and opened to air. Then, the reaction mixture was charged with a solution of phenyltrimethylsilane (4.428 mg, 1.00 equiv., 29.46 µmol, 0.090 mL aliquot of 49.2 mg / mL solution, PhTMS) in C_6D_6 as an internal standard and briefly mixed at 500 RPM (30 s). An aliquot of the reaction mixture was transferred to an NMR tube for measurement of the yield and conversion by ^{1}H-NMR. A standard ^{1}H-NMR experiment (16 scans, 5 sec. relaxation delay, gradient shimming on ^{1}H) was obtained and after 2 h at 80 °C, complete consumption of **39** was observed in addition to 66% HG-2 (**20**) (conversion of 54% of theoretical HG-2 available), 54% 1-isopropoxy-2-vinylbenzene (**19**), and 49% of 1-tosyl-2,5-dihydro-1H-pyrrole (**40**) (based on integration

of -CH_2- resonance of **40** in C_6D_6) (see compound **40** on page 40 for ^{1}H-NMR spectra).

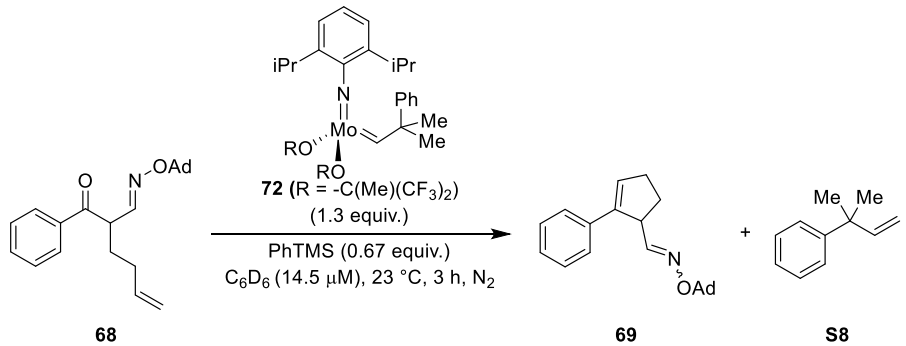
9. Investigation of divergent reactivity of carbonyls and oximes with Mo-, Ru-, and Ti-alkylidenes:

Trifunctional substrate **68** was designed to demonstrate the divergent reactivity afforded by our method of hydrazone/oxime olefination mediated by Ru-alkylidenes compared to existing olefinations reliant on Mo- and Ti-alkylidenes (summarized in **Figure 4** of manuscript). Notably, when **68** reacted with HG-2 (**20**), ring-closed oxime olefination product **70** was exclusively formed in 37% yield. In contrast, application of other metal alkylidene reagents afforded either carbonyl-olefination product **71** (49% from Tebbe's reagent (**73**)) or carbonyl-olefin metathesis product **69** (61% from Schrock's reagent (**72**)).



68 **70a** **70b** **21**

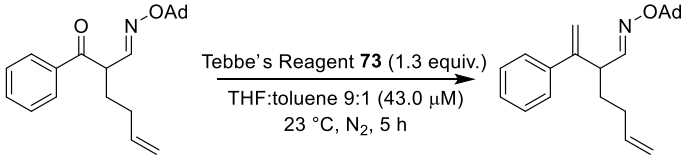
Cyclopent-2-en-1-yl(phenyl)methanone (70a): An oven-dried 1-dram vial was charged with **20** (6.3 mg, 0.010 mmol, 1.0 equiv.), anhydrous C_6D_6 (0.69 mL, 14.5 µM), and phenyltrimethylsilane (1.5 mg, 0.01 mmol, 1.0 equiv., PhTMS) as an internal standard. The solution was transferred by Pasteur pipette to a 1-dram vial containing substrate **68** (4.2 mg, 0.012 mmol, 1.20 equiv.). The solution was then transferred to a screw cap NMR tube, sealed, and heated to 70 °C. After 16 hours, ^{1}H-NMR analysis indicated a 37% combined yield of oxime-olefination product as a mixture of **70a** (26%) and alkene regio-isomer **70b** (11%). The identity of these products was confirmed by comparison to literature ^{1}H-NMR spectra.[16]



68 **69** **S8**

(*E*)-2-phenylcyclopent-2-ene-1-carbaldehyde *O*-((3*s*,5*s*,7*s*)-adamantan-1-yl) oxime (69): An oven-dried 1-dram vial was charged with **72** (11.2 mg, 0.014 mmol, 1.3 equiv.), anhydrous C_6D_6 (benzene (0.69 mL, 14.5 µM), and PhTMS (1.2 mg, 0.0079 mmol, 0.67 equiv.) as an internal standard under inert atmosphere in a glovebox. The solution was transferred by Pasteur pipette to a 1-dram vial containing substrate **68** (4.2 mg, 0.012 mmol, 1.0 equiv.). The solution was transferred to a screw cap NMR tube, sealed with electrical tape, and removed from the glovebox. After 3 h at 25 °C, ^{1}H-NMR analysis indicated a 61% yield of **69** relative to internal standard (PhTMS). Upon completion, the reaction mixture was concentrated, and purified via flash column chromatography (SiO_2/EtOAc–Hexanes gradient) to provide **69** (9.29:1.00 mixture of *E:Z* isomers in C_6D_6) as a colorless oil. Characterization data was obtained for the 9.29:1 mixture of *E*-isomer (major) and *Z*-isomer (minor). **^{1}H NMR** (major + minor, 500 MHz, C_6D_6) δ 7.54 (d, *J* = 7.8 Hz, 21.0H, major + minor), 7.38 (d, *J* = 8.1 Hz, 9.8H, major),

7.20 (t, *J* = 7.6 Hz, 24.5H, major + minor), 7.07 (t, *J* = 7.5 Hz, 10.6H, major + minor), 6.61 (d, *J* = 8.0 Hz, 0.9H, minor), 6.00 (d, *J* = 2.5 Hz, 1H, minor), 5.95 (q, *J* = 2.3 Hz, 9.4H, major), 4.82 (t, *J* = 6.9 Hz, 0.9H, minor), 3.99 (tdd, *J* = 8.3, 4.3, 2.2 Hz, 9.7H, major), 2.21 (ddt, *J* = 17.8, 8.9, 4.5 Hz, 13.2H, major + minor), 2.17 – 2.11 (m, 16.1H, major + minor), 2.06 (s, 97.7H, major + minor), 2.03 – 1.95 (m, 10.9H, major + minor), 1.78 (ddt, *J* = 13.3, 9.0, 4.6 Hz, 10.3H, major + minor), 1.55 (t, *J* = 9.8 Hz, 67.7H, major + minor); **^{13}C NMR** (major isomer, 125 MHz, C_6D_6) δ 151.2, 142.6, 136.2, 128.7, 128.5, 127.4, 126.8, 77.1, 46.8, 42.1, 36.8, 36.8, 31.9, 31.0, 29.5.; **IR** (Neat) 2908, 2851, 1496, 1453, 1352, 1302, 1111, 1075, 974, 946, 812, 756, 693.; **HRMS**: calcd for $C_{22}H_{28}NO^+$ $[M+H]^+$: 322.2166 found: 322.2169.

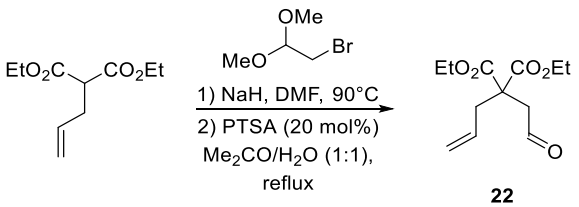


68 **71**

***E*)-2-phenylcyclopent-2-ene-1-carbaldehyde *O*-((3*s*,5*s*,7*s*)-adamantan-1-yl) oxime (71):** An oven-dried 1-dram vial equipped with a Teflon-coated stir bar was charged with **68** (35.1 mg, 0.100 mmol, 1.00 equiv) inside of a glove box. Then, anhydrous THF (2.00 mL, 43.0 µM total) and a 0.5 M solution of **73** (Tebbe's reagent) in toluene (0.260 mL, 0.130 mmol, 1.30 equiv.) were sequentially added and the reaction was capped and stirred inside the glovebox at room temperature. After 5 hours, the reaction was removed from the glovebox and quenched via the addition of 0.1 mL of 1 M NaOH.[17,18] The reaction mixture was filtered through a bed of Celite and concentrated. ^{1}H-NMR yield (49%) was determined by crude ^{1}H-NMR with phenyltrimethylsilane (1.51 mg, 0.0100 mmol, 0.10 equiv) as an NMR standard that was added following the concentration of the crude mixture. Purification via flash column chromatography (SiO_2/DCM/Hexanes gradient) provided the pure product **71** (2.25:1.00 mixture of *E:Z* isomers in CD_3OD) as a colorless oil. Characterization data was obtained for the 2.25:1 mixture of *E*-isomer (major) and *Z*-isomer (minor). **^{1}H NMR** (major + minor, 500 MHz, CD_3OD) δ 7.43 – 7.35 (m, 7.2H, major + minor), 7.34 – 7.24 (m, 13.1H, major + minor), 6.58 (d, *J* = 7.7 Hz, 1H, minor), 5.87 – 5.72 (m, 3.2H, major + minor), 5.37 – 5.30 (m, 3.7H, major + minor), 5.14 (dt, *J* = 18.3, 1.0 Hz, 3.6H, major + minor), 5.02 – 4.92 (m, 6.5H, major + minor), 4.24 (dddd, *J* = 8.7, 7.0, 5.8, 1.0 Hz, 1H, minor), 3.50 (q, *J* = 7.6, 7.1 Hz, 2.2H, major), 2.17 – 2.01 (m, 18H, major + minor), 1.83 (app. d, *J* = 2.9 Hz, 21.5H, major + minor), 1.78 – 1.62 (m, 129.7H, major + minor).;**^{13}C NMR** (major + minor, 125 MHz, CD_3OD) δ 153.8, 152.5, 150.9, 143.2, 142.9, 139.2, 139.2, 129.3, 129.2, 128.6, 128.6, 127.7, 127.6, 115.6, 114.2, 113.4, 78.3, 78.1, 45.7, 42.7, 42.7, 40.7, 37.6, 37.5, 33.1, 32.5, 32.5, 32.5, 32.1, 32.1.; **IR** (Neat) 2909, 2853, 1459, 1352, 1302, 1110, 1077, 974, 946, 907, 777.; **HRMS**: calcd for $C_{24}H_{32}NO^+$ $[M+H]^+$: 350.2479 found: 350.2474.

10. Synthesis and Characterization of Compounds

New Compounds Synthesized:

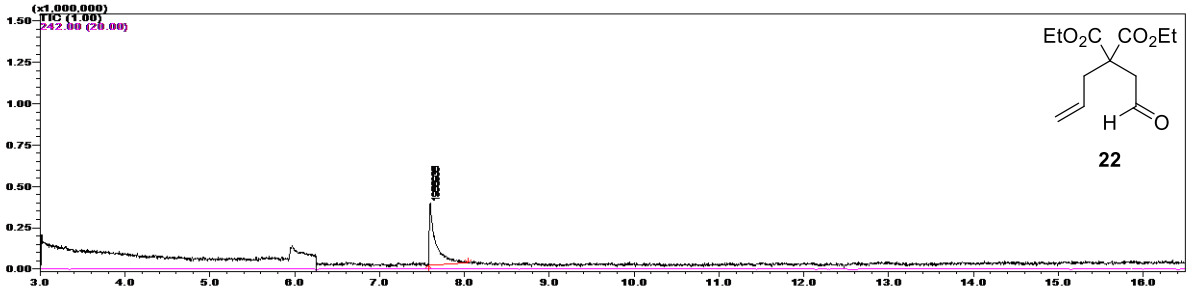


22

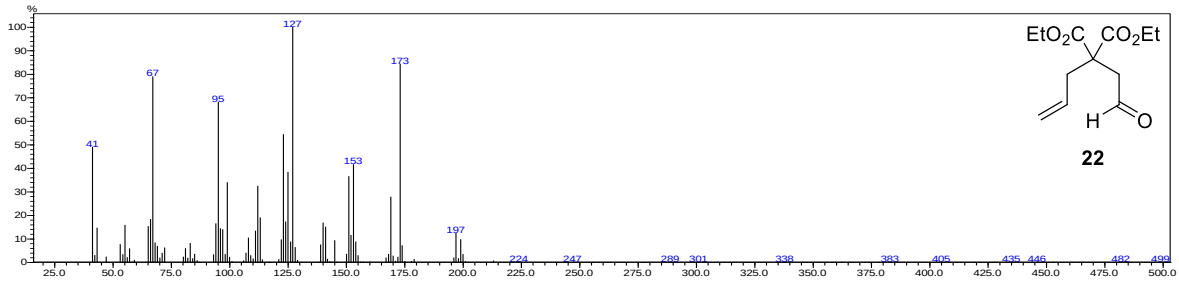
diethyl 2-allyl-2-(2-oxoethyl)malonate (22): Sodium hydride (5.00 g, 125 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 250 mL round-bottom flask containing a Teflon coated stir bar followed by 130 mL DMF (0.75 M). The flask was cooled to 0 °C with an ice bath and diethyl allylmalonate (20 mL, 100 mmol) was added dropwise to the reaction as H_2 gas formed. After stirring at 0 °C for 5 min, 2-bromo-1,1-dimethoxy-ethane (14.2 mL, 120 mmol) was added, and the reaction was allowed to warm to 25 °C. Then the reaction was heated to 90 °C for 16 h. After 16 h, the reaction was

cooled to 25 °C and a few drops of water were added to quench the excess sodium hydride followed by an additional 100 mL of water. The desired product was extracted with EtOAc (5 x 100 mL) and washed with water (5 x 20 mL) to remove residual DMF. The organic layer was dried with magnesium sulfate, filtered, and put under reduced pressure to remove the solvent. The crude material was used in the next step without further purification. To the crude reaction mixture from the previous step was added a 50:50 mixture of acetone and water (100 mL each, 0.5 M) and a Teflon coated stir bar. PTSA (3.8 g, 20 mmol) was added, and the reaction was allowed to stir at 85 °C for 2 h. The reaction was worked up by extracting with EtOAc (3 x 80 mL), dried over anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 12.1 g (50% over 2 steps) of **22** as a colorless liquid. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 9.72 (t, *J* = 1.5 Hz, 1H), 5.65 (ddt, *J* = 16.7, 10.3, 7.5 Hz, 1H), 5.18 – 5.02 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 4H), 2.95 (d, *J* = 1.5 Hz, 2H), 2.76 (dt, *J* = 7.4, 1.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; $CDCl_3$) δ 199.1, 170.1, 132.2, 120.2, 62.1, 54.8, 46.3, 38.5, 14.1.; **IR** (Neat) 2983, 1722, 1445, 1390, 1284, 1192, 1093, 1019, 925, 858. **HRMS**: calcd for $C_{12}H_{19}O_5^+$ $[M+H]^+$: 243.1227 found: 243.1214. **GC-MS** (EI) m/z: $[M\text{-}OCH_2CH_3]^+$ = 197.0808 calculated for $C_{12}H_{17}O^+$; Found 196.95.

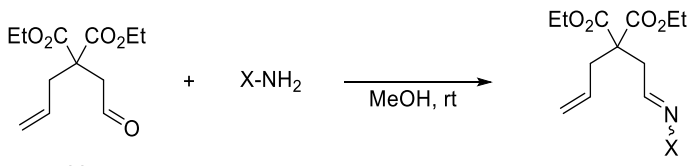
GC-MS trace of **22**:



Mass Spectrum of product peak (7.596 min):

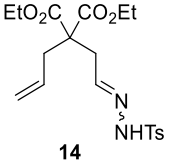


General Procedure (A): Condensation of free-base hydroxylamines and hydrazines onto aldehyde 22



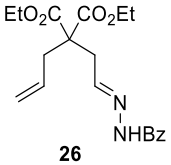
22

A round bottom flask equipped w/ a magnetic stir bar was charged with **22** (1.0 eq.) and methanol (0.2 M). The hydroxylamine or hydrazine freebase was added (1.5 eq.) and the mixture was allowed to stir until judged complete by TLC. Upon completion, the reaction was concentrated under reduced pressure and directly purified by column chromatography to give pure hydrazone or oxime.



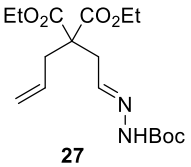
14

diethyl 2-allyl-2-(2-(2-tosylhydrazineylidene)ethyl)malonate (14): General procedure A (**GP-A**) was employed with p-toluenesulfonyl hydrazide on 1.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 309 mg (75%) of **14** (3:1 mixture of *E:Z* isomers in $CDCl_3$) as a viscous pale yellow oil. **^{1}H NMR** (700 MHz; $CDCl_3$, major + minor isomer) δ 8.80 (s, 1.0H, minor isomer), 8.11 (s, 3.0H, major isomer), 7.82 (d, *J* = 8.0 Hz, 2.0H, minor isomer), 7.78 (d, *J* = 8.0 Hz, 6.2H, major isomer), 7.29 (d, *J* = 8.0 Hz, 6.7H, major + minor isomer), 7.14 (t, *J* = 5.6 Hz, 3.4H, major isomer), 6.73 (t, *J* = 6.2 Hz, 1.0H, minor isomer), 5.59 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1.1H, minor isomer), 5.53 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 3.2H, major isomer), 5.09 (dd, *J* = 21.9, 13.6 Hz, 2.2H, minor isomer), 5.02 (d, *J* = 9.9 Hz, 3.4H, major isomer), 4.95 (d, *J* = 16.9 Hz, 3.4H, major isomer), 4.15 – 4.11 (m, 4.5H, minor isomer), 4.11 – 4.03 (m, 13.5H, major isomer), 2.71 (d, *J* = 5.6 Hz, 6.7H, major isomer), 2.64 (d, *J* = 7.4 Hz, 2.4H, minor isomer), 2.59 (d, *J* = 6.2 Hz, 2.4H, minor isomer), 2.50 (s, 7.0H, major + minor isomer), 2.40 (s, 13.1H, major + minor isomer), 1.20 – 1.15 (m, 26.3H, major + minor isomer); **^{13}C NMR** (175 MHz; $CDCl_3$) δ 170.5, 170.2, 147.6, 145.9, 144.2, 144.0, 135.4, 131.8, 131.4, 129.7, 129.6, 128.2, 128.1, 120.6, 119.9, 62.3, 61.8, 56.4, 39.0, 37.8, 35.7, 31.2, 21.7, 21.7, 14.1, 14.0; **IR** (Neat) 3200, 2981, 2936, 1727, 1641, 1598, 1444, 1366, 1288, 1197, 1164, 1093, 1063, 1010, 916, 814. **HRMS**: calcd for $C_{19}H_{26}N_2O_6SNa^+$ [M+Na]$^+$: 433.1404 found: 433.1406.



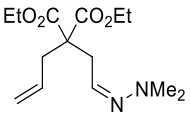
26

diethyl (E)-2-allyl-2-(2-(2-benzoylhydrazineylidene)ethyl)malonate (26): General procedure A was employed with benzhydrazide on a 2.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 584 mg (81%) of **26** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.75 (t, *J* = 5.9 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 5.77 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.21 – 5.13 (m, 2H), 4.26 – 4.16 (m, 4H), 2.88 (d, *J* = 5.9 Hz, 2H), 2.70 (d, *J* = 7.4 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; CD_3OD) δ 171.5, 166.6, 150.7, 134.0, 133.21, 133.17, 129.7, 128.7, 120.3, 62.8, 57.9, 39.3, 37.2, 14.4.; **IR** (Neat) 3222, 3067, 2982, 1727, 1645, 1562, 1422, 1360, 1283, 1212, 1190, 1126, 1029, 999, 924, 889. **HRMS**: calcd for $C_{19}H_{25}N_2O_5^+$ [M+H]$^+$: 361.1758 found: 361.1766.



27

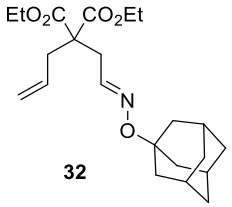
diethyl (E)-2-allyl-2-(2-(2-(tert-butoxycarbonyl)hydrazineylidene)ethyl)malonate (27): General procedure A was employed with *tert*-butyl carbazate on a 1.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 292 mg (82%) of **27** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.25 (t, *J* = 5.9 Hz, 1H), 5.72 (ddt, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.17 – 5.11 (m, 2H), 4.18 (p, *J* = 6.6 Hz, 4H), 2.75 (d, *J* = 5.9 Hz, 2H), 2.64 (d, *J* = 7.3 Hz, 2H), 1.48 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; CD_3OD) δ 171.6, 155.2, 144.7, 133.3, 120.2, 81.5, 62.7, 58.0, 39.1, 36.8, 28.6, 14.4; **IR** (Neat) 2981, 2935, 1719, 1525, 1367, 1244, 1216, 1159, 1044, 1013, 911. **HRMS**: calcd for $C_{17}H_{29}N_2O_6^+$ [M+H]$^+$: 357.2020 found: 357.2011.



28

diethyl (Z)-2-allyl-2-(2-(2,2-dimethylhydrazineylidene)ethyl)malonate (28): General procedure A was employed with N,N-dimethylhydrazine on a 1.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 253 mg (89%) of **28** (1:>20 mixture of *E:Z* isomers in $CDCl_3$) as a clear oil. **^{1}H NMR** (700 MHz; $CDCl_3$) δ 6.47 (bs, 1H), 5.71 (ddt, *J* = 17.5, 10.2,

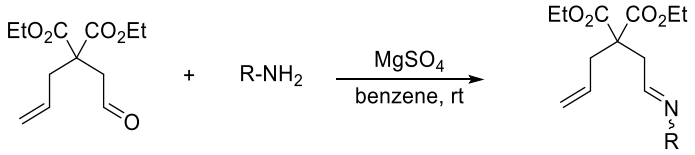
7.4 Hz, 1H), 5.14 – 5.07 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 2.79 (d, *J* = 5.6 Hz, 2H), 2.72 (s, 6H), 2.67 (dt, *J* = 7.4, 1.2 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; $CDCl_3$) δ 170.8, 132.5, 132.2, 119.4, 61.4, 57.2, 43.2, 37.7, 36.1, 14.3; **IR** (Neat) 2981, 1727, 1467, 1444, 1283, 1250, 1209, 1189, 1139, 1052, 1032, 920, 857. **HRMS**: calcd for $C_{14}H_{25}N_2O_4^+$ $[M+H]^+$: 285.1809 found: 285.1823.



32

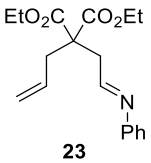
diethyl 2-((E)-2-((((1s,3s)-adamantan-1-yl)oxy)imino)ethyl)-2-allylmalonate (32): General procedure A was employed on a 4.13 mmol scale with the following modifications: 1.2 equivalents of O-(adamantan-1-yl)hydroxylamine were used and the reaction was allowed to stir overnight at room temperature. Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 1.54 g (95%) of **32** (>20:1 mixture of *E:Z* isomers in C_6D_6) as a waxy solid. **^{1}H NMR** (700 MHz; C_6D_6) δ 7.58 (t, *J* = 6.0 Hz, 1H), 5.79 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 5.07 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.00 (dd, *J* = 10.1, 2.0 Hz, 1H), 3.96 (m, 4H), 2.98 (d, *J* = 6.1 Hz, 2H), 2.94 (d, *J* = 7.4 Hz, 2H), 2.05 (s, 9H), 1.54 (q, *J* = 12.3 Hz, 6H), 0.91 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; C_6D_6) δ 170.3, 145.0, 132.7, 119.5, 77.4, 61.4, 56.9, 42.1, 38.0, 36.8, 33.6, 31.0, 14.1; **IR** (Neat) 2981, 2908, 2853, 1731, 1453, 1303, 1283, 1213, 1191, 1142, 1104, 1074, 957, 858. **HRMS**: calcd for $C_{22}H_{34}NO_5^+$ $[M+H]^+$: 392.2431 found: 392.2443.

General Procedure (B): Condensation of amines onto aldehyde 22



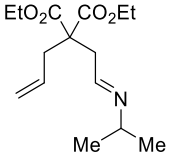
22

A 1-dram screw cap vial equipped with a magnetic stir bar was charged with **22** (50 mg, 0.19 mmol), benzene (1.5 mL), $MgSO_4$ (115 mg, 0.96 mmol), and amine (0.29 mmol). The reaction was allowed to stir overnight at room temperature. The next day, the mixture was filtered over celite, washed with DCM, and concentrated to give crude imine that was used without further purification.



23

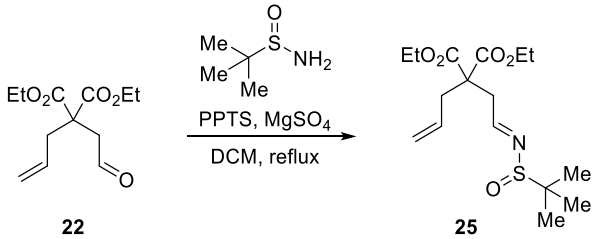
diethyl (E)-2-allyl-2-(2-(phenylimino)ethyl)malonate (23): General procedure B was employed with the following modification: 1 equivalent of aniline was used, and the crude ^{1}H-NMR showed only imine and leftover aldehyde starting material. Due to the instability of this compound, it was used without further purification. This modified procedure gave 54 mg of **23** (>20:1 mixture of *E:Z* isomers in C_6D_6) as a pale yellow oil that was estimated as 71% pure (63% overall yield) by ^{1}H-NMR using PhTMS as an internal standard. **^{1}H NMR** (700 MHz; C_6D_6) δ 7.82 (t, *J* = 4.6 Hz, 1H), 7.14 – 7.10 (m, 2H), 7.05 – 7.03 (m, 2H), 7.00 – 6.97 (m, 1H), 5.82 (ddt, *J* = 17.3, 10.2, 7.4 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.97 (q, *J* = 7.1 Hz, 4H), 3.14 (d, *J* = 4.6 Hz, 2H), 3.01 (d, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.1 Hz, 6H).



24

diethyl (E)-2-allyl-2-(2-(isopropylimino)ethyl)malonate (24): General procedure B was employed with isopropylamine to give 54 mg (~99%) of **24** (>20:1 mixture of *E:Z* isomers in C_6D_6) as a clear oil. **^{1}H NMR** (700 MHz; C_6D_6) δ 7.56 (t, *J* = 4.5 Hz, 1H), 5.85 (ddt, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.09 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.04 – 3.94 (m, 4H), 3.08 (p, *J* = 6.3 Hz, 1H), 3.03 – 3.00 (m, 4H), 1.10 (d, *J* = 6.3 Hz, 6H), 0.94 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; C_6D_6) δ 170.5, 156.6, 133.2, 119.3, 61.9, 61.2, 56.8, 38.5, 38.0, 24.3, 14.1.; **IR** (Neat) 2969, 2937, 1730, 1669, 1382, 1283, 1191, 1145, 1095, 1032, 921, 857. **HRMS**: calcd for $C_{15}H_{26}NO_4^+$ $[M+H]^+$: 284.1856 found: 284.1854.

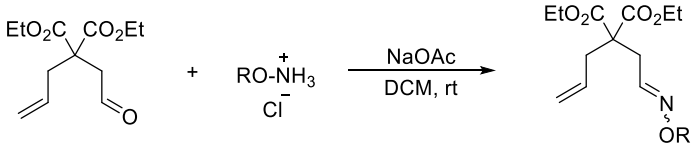
Condensation for the synthesis of sulfinyl imine 25



22 **25**

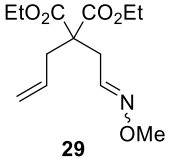
To a solution of aldehyde **22** (242 mg, 1.0 mmol) in DCM (10 mL) was added racemic 2-methylpropane-2-sulfinamide (145 mg, 1.2 mmol), PPTS (13 mg, 0.05 mmol), and $MgSO_4$ (602 mg, 5.0 mmol). The resulting mixture was allowed to reflux overnight. The next day, the suspension was filtered, washed with DCM, and concentrated. Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 150 mg (43%) of **25** (>20:1 mixture of *E:Z* isomers in $CDCl_3$) as a clear oil. **^{1}H NMR** (700 MHz; $CDCl_3$) δ 8.39 (t, *J* = 4.3 Hz, 1H), 5.79 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1H), 5.12 – 5.05 (m, 2H), 4.06 – 3.98 (m, 4H), 3.21 (dd, *J* = 16.9, 4.2 Hz, 1H), 3.14 (dd, *J* = 16.9, 4.5 Hz, 1H), 3.03 (ddd, *J* = 47.2, 14.2, 7.5 Hz, 2H), 1.17 (s, 9H), 0.99 (td, *J* = 7.1, 4.2 Hz, 6H); **^{13}C NMR** (175 MHz; $CDCl_3$) δ 170.1, 170.0, 165.8, 132.1, 120.1, 61.9, 61.9, 56.9, 56.0, 38.6, 37.7, 22.4, 14.2, 14.2; **IR** (Neat) 2981, 1730, 1619, 1475, 1445, 1365, 1284, 1190, 1084, 923, 857. **HRMS**: calcd for $C_{16}H_{28}NO_5S^+$ $[M+H]^+$: 346.1683, found: 346.1692.

General Procedure (C): Condensation of hydroxylamine salts onto aldehyde 22



22

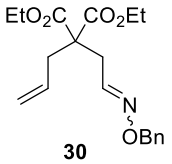
A round bottom flask equipped with a magnetic stir bar was charged with **22** (1 eq.) and DCM (0.2M). The hydroxylamine salt was added (1.5 eq.), followed by sodium acetate (2.5 eq.) and the mixture was allowed to stir until judged complete by TLC. Upon completion, the reaction was quenched with saturated sodium bicarbonate and diluted with water and DCM. The layers were separated and the aqueous was further extracted with DCM (x2). The combined organics were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography to give pure oxime.



29

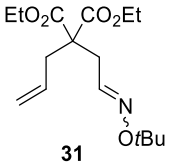
diethyl 2-allyl-2-(2-(methoxyimino)ethyl)malonate (29): General procedure C was employed with methoxyamine hydrochloride on a 1.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 234 mg (86%) of **29** (3:2 mixture of *E:Z* isomers in $CDCl_3$) as a clear oil. **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.33 (t, *J* = 6.4 Hz, 3H), 6.69 (t, *J* = 5.3 Hz, 2H), 5.67 (dq, *J* = 16.4, 8.2, 7.6 Hz, 5H), 5.15 – 5.10 (m, 10H), 4.20 (q, *J* = 7.1 Hz, 20H), 3.86 (s, 6H), 3.80 (s, 9H), 2.87

(d, *J* = 5.3 Hz, 4H), 2.73 (d, *J* = 6.4 Hz, 6H), 2.69 – 2.65 (m, 10H), 1.25 (t, *J* = 7.1 Hz, 30H); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 170.4, 170.2, 146.5, 146.5, 131.9, 119.9, 61.8, 61.7, 61.7, 61.5, 56.4, 55.6, 38.3, 37.8, 32.8, 29.0, 14.1, 14.1; **IR** (Neat) 2982, 2940, 1729, 1466, 1444, 1283, 1213, 1193, 1144, 1046, 1028, 922, 851. **HRMS**: calcd for $C_{13}H_{21}NO_5Na^+$ [M+Na]$^+$: 294.1312, found: 294.1308.



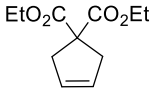
30

diethyl 2-allyl-2-(2-((benzyloxy)imino)ethyl)malonate (30): General procedure C was employed with O-benzylhydroxylamine hydrochloride on a 1.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 297 mg (85%) of **30** (3:2 mixture of *E:Z* isomers in $CDCl_3$) as a clear oil. **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.41 (t, *J* = 6.3 Hz, 3H), 7.38 – 7.27 (m, 25H), 6.73 (t, *J* = 5.4 Hz, 2H), 5.70 – 5.57 (m, 5H), 5.13 – 5.01 (m, 20H), 4.23 – 4.11 (m, 20H), 2.93 (d, *J* = 5.3 Hz, 4H), 2.74 (d, *J* = 6.3 Hz, 6H), 2.69 – 2.62 (m, 10H), 1.28 – 1.19 (m, 30H); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 170.4, 170.2, 147.2, 147.1, 137.9, 137.8, 131.9, 128.5, 128.4, 128.1, 127.94, 127.92, 119.93, 119.90, 76.1, 75.9, 61.8, 61.7, 56.5, 55.7, 38.3, 37.7, 32.9, 29.3, 14.18, 14.16; **IR** (Neat) 2981, 2935, 1728, 1454, 1444, 1367, 1283, 1211, 1192, 1144, 1013, 922, 856. **HRMS**: calcd for $C_{19}H_{25}NO_5Na^+$ [M+Na]$^+$: 370.1625, found: 370.1626.



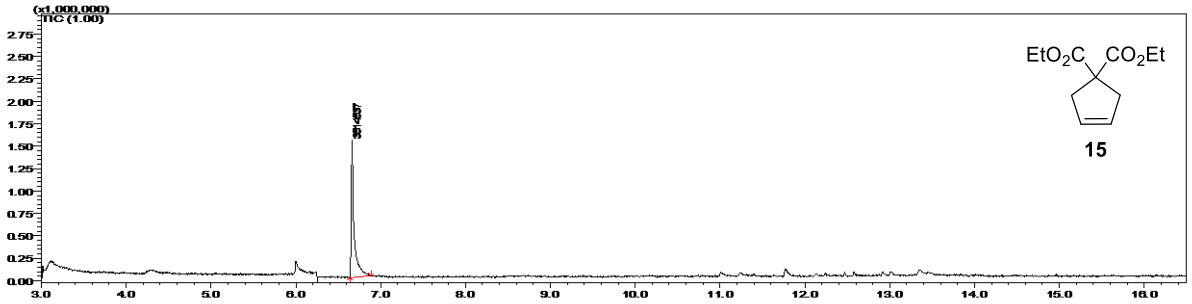
31

diethyl 2-allyl-2-(2-(tert-butoxyimino)ethyl)malonate (31): General procedure C was employed with O-*tert*-butylhydroxylamine hydrochloride on a 1.0 mmol scale and purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 215 mg (69%) of **31** (2:1 mixture of *E:Z* isomers in $CDCl_3$) as a pale yellow oil. **^{1}H NMR** (500 MHz; $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 6.63 (t, *J* = 5.4 Hz, 1H), 5.74 – 5.61 (m, 3H), 5.16 – 5.07 (m, 6H), 4.25 – 4.14 (m, 12H), 2.90 (d, *J* = 5.3 Hz, 2H), 2.77 (d, *J* = 6.0 Hz, 4H), 2.72 – 2.63 (m, 6H), 1.28 – 1.21 (m, 45H); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 170.4, 144.9, 144.6, 132.2, 119.69, 119.67, 78.5, 78.4, 61.7, 61.6, 56.5, 55.9, 38.0, 37.4, 32.9, 28.9, 27.62, 27.56, 14.2; **IR** (Neat) 2979, 2934, 1731, 1444, 1364, 1283, 1190, 1144, 1034, 943, 919, 857. **HRMS**: calcd for $C_{16}H_{27}NO_5Na^+$ [M+Na]$^+$: 336.1781, found: 336.1787.

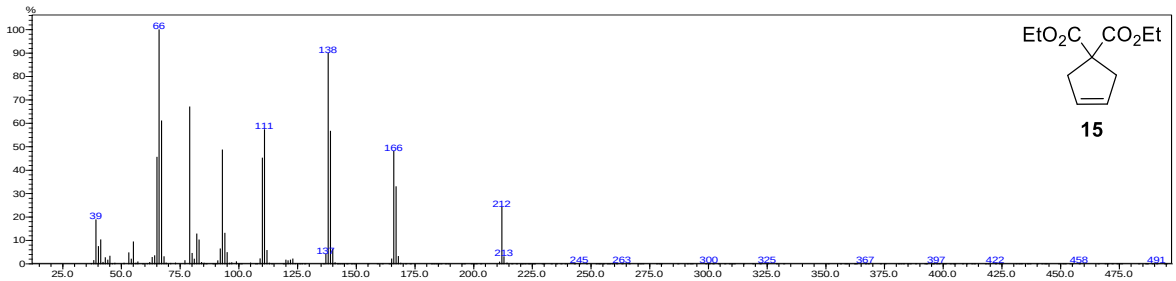


15

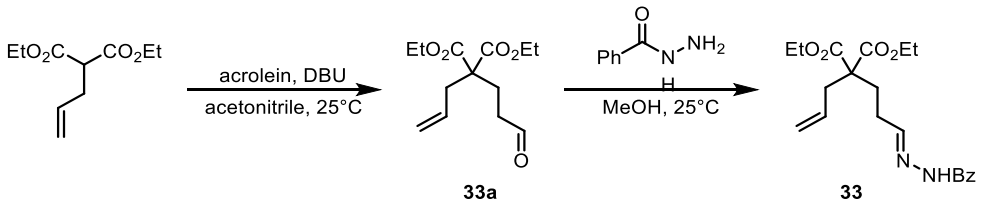
diethyl cyclopent-3-ene-1,1-dicarboxylate (15): Colorless oil. The ^{1}H-NMR spectral data was consistent with literature data.[19] ^{1}H NMR spectral data in toluene-d_8 and C_6D_6 has not previously been reported. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.61 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.01 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{1}H-NMR** (400 MHz, C_6D_6) δ 5.39 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 4H), 3.18 (s, 4H), 0.89 (t, *J* = 7.1 Hz, 6H); **^{1}H-NMR** (400 MHz, toluene-d_8) δ 5.39 (s, 2H), 3.93 (q, *J* = 7.1 Hz, 4H), 3.10 (s, 4H), 0.93 (t, *J* = 7.1 Hz, 6H); **GC-MS** (EI) m/z: M^+ = 212.1043 calculated for $C_{11}H_{16}O_4^+$; Found 212.00.
GC-MS trace of **15**:



Mass Spectrum of product peak (6.664 min):

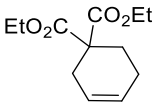


2 step sequence for the synthesis of substrate 33



diethyl 2-allyl-2-(3-oxopropyl)malonate (**33a**): This compound was prepared using a modification of a literature method.[20] Diethyl allyl malonate (2.040 g, 10.18 mmol) and acrolein (698 mg, 11.20 mmol, 90 wt% from Sigma-Aldrich) were added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 35 mL anhydrous acetonitrile (0.30 M). The flask was cooled to 0 °C with an ice bath and DBU (0.026 mL, 0.20 mmol) was added. The mixture was allowed to warm to 25 °C and stirred until judged complete by TLC (12 h). After 12 h, the reaction was quenched with sat. aq. NH_4Cl solution (30 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. aq. NaCl solution (30 mL), dried with anhydrous Na_2SO_4, filtered and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.2760 g (48%) of diethyl 2-allyl-2-(3-oxopropyl)malonate **33a** as a colorless oil. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature data.[21] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.3 Hz, 1H), 5.74 – 5.56 (m, 1H), 5.15 – 5.06 (m, 2H), 4.18 (qd, *J* = 7.1, 3.2 Hz, 4H), 2.64 (dt, *J* = 7.5, 1.2 Hz, 2H), 2.47 (ddt, *J* = 7.8, 6.3, 1.3 Hz, 2H), 2.21 – 2.14 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 6H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.9, 170.9, 132.1, 119.60, 61.6, 56.6, 39.2, 38.0, 25.0, 14.2.

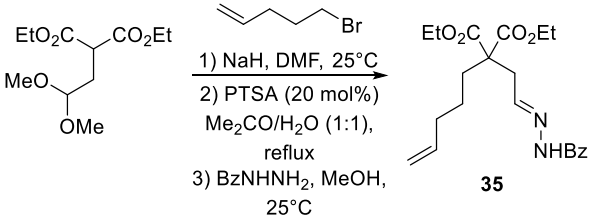
diethyl (E)-2-allyl-2-(3-(2-benzoylhydrazineylidene)propyl)malonate (33): This compound was prepared by a modification of general procedure A (**GP-A**): diethyl 2-allyl-2-(3-oxopropyl)malonate **33a** (256 mg, 1.00 mmol, 1.00 equiv.) and benzoyl hydrazide (204 mg, 1.50 mmol, 1.50 equiv.) in MeOH (5.00 mL, 0.20 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 160.4 mg (42%) of **33** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.65 (t, *J* = 5.4 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 5.71 (ddt, *J* = 17.3, 10.2, 7.4 Hz, 1H), 5.16 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 4.22 – 4.17 (m, 4H), 2.69 (d, *J* = 7.4 Hz, 2H), 2.36 – 2.31 (m, 2H), 2.14 – 2.11 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; CD_3OD) δ 172.2, 166.7, 153.7, 134.2, 133.5, 133.2, 129.7, 128.7, 128.7, 119.7, 62.6, 58.3, 38.2, 30.1, 28.6, 14.4; **IR** (Neat): 3196, 3029, 2979, 1738, 1722, 1646, 1626, 1335, 1240, 1211, 1185, 1149, 1118, 1094, 1079, 929, 697, 660; **HRMS**: calcd for $C_{20}H_{26}N_2O_5Na^+$ $[M+Na]^+$: 397.1734, found: 397.1731.



34

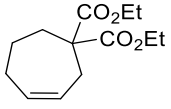
diethyl cyclohex-3-ene-1,1-dicarboxylate (34): Colorless oil. The ^{1}H-NMR spectral data in $CDCl_3$ was consistent with literature data.[11] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.67 (m, 2H), 4.23 – 4.14 (m, 4H), 2.55 (s, 2H), 2.13 (t, *J* = 6.0 Hz, 2H), 2.10 (d, *J* = 5.5 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{1}H-NMR** (700 MHz, C_6D_6) δ 5.63 – 5.59 (m, 1H), 5.59 – 5.55 (m, 1H), 4.00 – 3.91 (m, 4H), 2.74 (s, 2H), 2.27 (t, *J* = 6.4 Hz, 2H), 2.07 – 2.03 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 6H).

3 step sequence for the synthesis of substrate 35



35

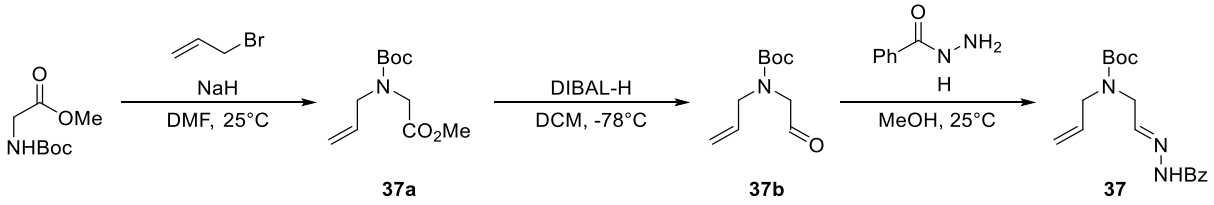
Sodium hydride (155 mg, 3.88 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 10 mL THF (0.19 M total). The flask was cooled to 0 °C with an ice bath and a solution of diethyl 2-(2,2-dimethoxyethyl)propanedioate[3] (750 mg, 3.02 mmol) in THF (5.0 mL) was added dropwise to the reaction as H_2 gas formed. After stirring at 0 °C for 2 h, 5-bromo-1-pentene (0.47 mL, 3.97 mmol) was added dropwise over 5 min followed by sodium iodide (679 mg, 4.53 mmol) and the reaction was allowed to warm to 25 °C. Then the reaction was stirred at 25 °C for 16 h. After 16 h, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (4 x 10 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent to afford crude acetal (333 mg). The crude material was used in the next step without further purification. To the crude acetal (333 mg) from the previous step was added a 50:50 mixture of acetone and water (5.25 mL each, 0.1 M) and a Teflon coated stir bar. PTSA (42.0 mg, 0.22 mmol) was added, and the reaction was allowed to stir at 85 °C for 3 h. The reaction was concentrated to remove the acetone, extracted with EtOAc (3 x 15 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude aldehyde (267 mg) was used in the next step without further purification. The crude aldehyde (267 mg, 1.20 equiv.) from the previous step was dissolved in MeOH (2.7 mL, 0.30 M) and benzoyl hydrazide (112 mg, 0.82 mmol, 1.00 equiv.) was added and the reaction stirred at 25 °C for 16 h. Upon consumption of aldehyde by TLC analysis, the reaction was concentrated under reduced pressure and directly purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 274 mg (24% over 3 steps) of **35** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.86 (d, *J* = 7.7 Hz, 2H), 7.71 (t, *J* = 5.9 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 5.79 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.02 (d, *J* = 17.1 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 4.25 – 4.16 (m, 4H), 2.89 (d, *J* = 5.9 Hz, 2H), 2.08 (q, *J* = 7.0 Hz, 2H), 1.95 – 1.90 (m, 2H), 1.43 – 1.36 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (175 MHz; CD_3OD) δ 172.0, 166.7, 150.7, 139.2, 134.1, 133.2, 129.7, 128.7, 115.6, 62.7, 58.0, 37.2, 34.8, 34.2, 24.4, 14.4, 14.3; **IR** (Neat) 3219, 2981,2934, 1729, 1648, 1604, 1568, 1448, 1367, 1293, 1266, 1228, 1130, 1022, 907, 856, 800. 692, 677; **HRMS**: calcd for $C_{21}H_{29}N_2O_5^+$ $[M+H]^+$: 389.2071, found: 389.2064.



36

diethyl cyclohept-3-ene-1,1-dicarboxylate (36): Colorless oil. The ^{1}H-NMR spectral data in $CDCl_3$ was consistent with literature data.[22] The ^{1}H NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.85 (dt, *J* = 11.4, 6.1 Hz, 1H), 5.68 (dt, *J* = 10.8, 6.3 Hz, 1H), 4.21 – 4.12 (m, 4H), 2.67 (d, *J* = 6.4 Hz, 2H), 2.25 – 2.21 (m, 2H), 2.16 (q, *J* = 5.9 Hz, 2H), 1.67 – 1.61 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{1}H-NMR** (400 MHz, C_6D_6) δ 5.83 – 5.76 (m, 1H), 4.02 – 3.92 (m, 2H), 2.88 (d, *J* = 5.1 Hz, 1H), 2.40 – 2.32 (m, 1H), 1.97 (q, *J* = 5.2 Hz, 1H), 1.69 – 1.58 (m, 1H), 0.92 (t, *J* = 7.1 Hz, 3H).

3 step sequence for the synthesis of substrate 37



37a **37b** **37**

methyl N-allyl-N-(tert-butoxycarbonyl)glycinate (37a): This compound was synthesized by a modification of a literature method.[23] *N*-(*tert*-butoxycarbonyl)glycine methyl ester (0.94 mL, 1.014 g, 5.36 mmol) was added to a flame dried 50 mL round-bottom flask containing a Teflon coated stir bar followed by 10.5 mL DMF (0.51 M). The flask was cooled to 0 °C with an ice bath and sodium hydride (304 mg, 7.93 mmol, 60 wt% dispersion in mineral oil) was added in 3 portions. The reaction mixture was stirred at 0 °C for 10 min, then allyl bromide (0.71 mL, 8.20 mmol) was added dropwise over 10 min. The mixture was held at 0 °C for 2 h and then allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with deionized water (3 x 20 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 0.862 g (70%) of **37a** as a colorless oil. The ^{1}H-NMR spectral data was consistent with literature data.[23] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 – 5.72 (m, 1H), 5.21 – 5.08 (m, 2H), 3.95 (s, 2H), 3.87 (d, *J* = 20.7 Hz, 2H), 3.73 (s, 3H), 1.45 (d, *J* = 13.1 Hz, 9H).

tert-butyl allyl(2-oxoethyl)carbamate (37b): This compound was synthesized by a modification of a literature method.[24] A flame dried 200 mL round-bottom flask containing a Teflon coated stir bar was charged with **37a** (862 mg, 3.767 mmol) followed by 15.0 mL anhydrous DCM (0.25 M). After cooling the solution to –78 °C, DIBAL-H (7.50 mL, 7.52 mmol, 1.0 M in hexanes) was added via syringe pump over 1 h. After stirring for 4 h at –78 °C, the flask was transferred to an ice bath and allowed to warm to 0 °C. The reaction was quenched with the addition of Glauber's salt (>3.00 equiv., sodium sulfate decahydrate), diluted with water (10 mL), sat. aq. Rochelle's salt solution (30 mL), Et_2O (100 mL), and stirred overnight to obtain two distinct layers. The biphasic mixture was partitioned, and the aqueous layer extracted with DCM (2 x 100 mL). The combined organic layers were washed with deionized water (2 x 20 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 0.135 g (18%) of **37b** as a colorless oil. The ^{1}H-NMR spectral data was consistent with literature data.[24] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, *J* = 7.6 Hz, 1H), 5.77 (ddd, *J* = 16.9, 10.4, 5.3 Hz, 1H), 5.29 – 5.02 (m, 2H), 4.04 – 3.74 (m, 4H), 1.45 (d, *J* = 14.5 Hz, 9H).

tert-butyl (E)-allyl(2-(2-benzoylhydrazineylidene)ethyl)carbamate (**37**): This compound was prepared by a modification of general procedure A (**GP-A**): **37b** (65 mg, 0.32 mmol, 1.00 equiv.) and benzoyl hydrazide (66.6 mg, 0.49 mmol, 1.50 equiv.) in MeOH (1.60 mL, 0.20 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 68.9 mg (66%) of **37** (>20:1 mixture of *E:Z* isomers in DMSO-d_6) as a light brown gum. The *E:Z* isomeric ratio of this compound was assigned based on the singlet at δ 7.71 ppm. **^{1}H NMR** (major rotamer, 700 MHz; DMSO-d_6, 25 °C) δ 11.59 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.71 (s, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 5.79 (s, 1H), 5.13 (t, *J* = 14.5 Hz, 2H), 4.09 – 3.69 (m, 4H), 1.41 (s, 9H); **^{13}C NMR** (rotamers present, 175 MHz; DMSO-d_6, 25 °C) δ 163.0, 154.7 (rotamer), 154.4 (rotamer), 147.9, 134.0 (rotamer), 133.3 (rotamer), 131.7, 128.4, 127.5, 116.8 (rotamer), 116.3 (rotamer), 79.3, 49.6 (rotamer), 49.0 (rotamer),

48.1 (rotamer), 47.9 (rotamer), 28.0. Variable temperature experiments were performed in DMSO-d_6 at 25 and 80 °C to obtain ^{13}C-NMR spectra of the major rotamer. The peak at 3.09 in the ^{1}H-NMR spectrum at 80 °C has been assigned as water. **^{1}H NMR** (major rotamer, 700 MHz; DMSO-d_6, 80 °C) δ 11.34 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.72 (s, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 5.86 – 5.77 (m, 1H), 5.18 – 5.12 (m, 2H), 3.96 (d, *J* = 4.8 Hz, 2H), 3.84 (d, *J* = 5.6 Hz, 2H), 1.43 (s, 9H); **^{13}C NMR** (major rotamer, 175 MHz; DMSO-d_6, 80 °C) δ 154.3, 147.5, 133.7, 133.3, 131.0, 127.8, 127.3, 116.1, 49.1, 47.7, 27.7; **IR** (Neat): 3329, 3065, 2978, 1692, 1651, 1580, 1548, 1477, 1455, 1422, 1365, 1281, 1246, 1140, 1103, 1077, 1051, 993, 914, 858, 800. 692, 676; **HRMS**: calcd for $C_{17}H_{23}N_3O_3Na^+$ $[M+Na]^+$: 340.1632, found: 340.1628.

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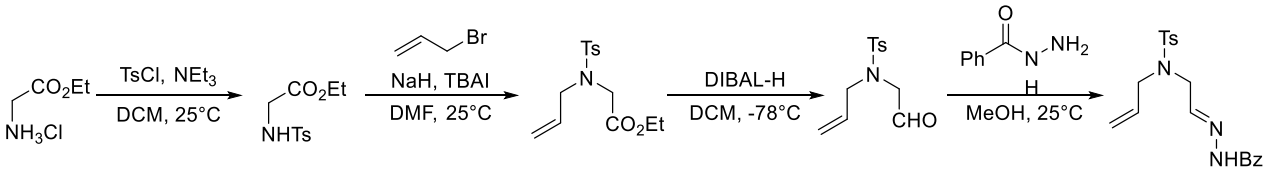
tert-butyl 2,5-dihydro-1H-pyrrole-1-carboxylate (38): Colorless oil. The ^{1}H-NMR spectral data is consistent with literature data.[25] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.81 – 5.77 (m, 1H), 5.76 – 5.72 (m, 1H), 4.15 – 4.12 (m, 2H), 4.10 – 4.07 (m, 2H), 1.48 (s, 9H); **^{1}H-NMR** (700 MHz, C_6D_6) δ 5.24 – 5.15 (m, 2H), 4.09 (m, 2H), 3.86 (m, 2H), 1.49 (d, *J* = 1.0 Hz, 9H).

4 step sequence for the synthesis of substrate 39



39a **39b** **39c** **39**

ethyl tosylglycinate (39a): This compound was prepared using a modification of a literature method.[26] A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with glycine ethyl ester hydrochloride (1.00 g, 7.16 mmol) followed by 25.0 mL of anhydrous DCM (0.28 M). After cooling the solution to 0 °C, freshly distilled triethylamine (2.50 mL, 17.90 mmol, 2.50 equiv.) was added dropwise over 2 min and the suspension stirred for 5 min at 0 °C. Then para-toluenesulfonyl chloride (1.890 g, 9.91 mmol, p-TsCl) was added in one portion and the mixture allowed to warm to 25 °C under a nitrogen atmosphere. After stirring for 16 h at 25 °C, the reaction was quenched with deionized H_2O (12 mL), diluted with Et_2O (30 mL) and partitioned. The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.3009 g (70%) of **39a** as a white solid. The ^{1}H-NMR spectral data was consistent with literature data.[26] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.70 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.12 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 2.42 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

ethyl N-allyl-N-tosylglycinate (39b): A flame dried 100 mL round-bottom flask containing a Teflon coated stir bar was charged with **39a** (1.242 g, 4.83 mmol) followed by 25.0 mL of anhydrous DMF (0.19 M). After cooling the solution to 0 °C, sodium hydride (212 mg, 5.31 mmol, 60 wt% dispersion in mineral oil) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min, then allyl bromide (0.50 mL, 5.81 mmol) and tetrabutylammonium iodide (1.7829 g, 4.83 mmol) were added and the mixture allowed to warm to 25 °C under a nitrogen atmosphere. After stirring for 16 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (2 x 20 mL), sat. aq. NaCl (20 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.2321 g (85%) of **39b** as a pale-yellow oil. The ^{1}H-NMR spectral data was consistent with literature data.[26] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.69 (ddt, *J* =

16.9, 10.4, 6.5 Hz, 1H), 5.22 – 5.12 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 2H), 3.90 (dt, *J* = 6.5, 1.4 Hz, 2H), 2.42 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

N-allyl-4-methyl-N-(2-oxoethyl)benzenesulfonamide (39c): This compound was prepared using a modification of a literature method.[24] A flame dried 100 mL round-bottom flask containing a Teflon coated stir bar was charged with **39b** (1.2321 g, 4.14 mmol) followed by 20.7 mL of anhydrous DCM (0.20 M). After cooling the solution to –78 °C, DIBAL-H (4.14 mL, 4.14 mmol, 1.0 M in hexanes) was added via syringe pump over 1 h. After stirring for 2.5 h at –78 °C, the reaction was quenched with dropwise addition of EtOAc (10.0 mL) and was transferred to an ice bath and allowed to warm to 0 °C. The reaction was diluted with sat. aq. Rochelle's salt solution (50 mL), Et_2O (100 mL), and stirred overnight to obtain two distinct layers. The biphasic mixture was partitioned, and the aqueous layer extracted with Et_2O (2 x 100 mL) and EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaCl solution (50 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 955.4 mg (91%) of **39c** as a pale-yellow oil which crystallized to a pale-yellow solid upon storage for 6 months at 0 °C. The ^{1}H-NMR spectral data was consistent with literature data.[27] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 5.68 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.19 (dd, *J* = 24.1, 13.6 Hz, 2H), 3.82 – 3.78 (m, 4H), 2.44 (s, 3H).

(E)-N-allyl-N-(2-(2-benzoylhydrazineylidene)ethyl)-4-methylbenzenesulfonamide (**39**): This compound was prepared by a modification of general procedure A (**GP-A**): **39c** (333 mg, 1.32 mmol, 1.29 equiv.) and benzoyl hydrazide (138.7 mg, 1.02 mmol, 1.00 equiv.) in MeOH (3.30 mL, ~0.31 M). Purification by filtration of precipitated **39** from the reaction mixture provided 133.3 mg (35%) of **39** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. Spectral overlap was observed between the hydrazone C-H and another aryl C-H resonance in the ^{1}H-NMR spectrum. **^{1}H NMR** (700 MHz, CD_3OD) δ 7.86 (d, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 5.71 (ddt, *J* = 16.8, 11.8, 6.3 Hz, 1H), 5.23 (d, *J* = 17.1 Hz, 1H), 5.18 (d, *J* = 10.2 Hz, 1H), 3.99 (d, *J* = 5.3 Hz, 2H), 3.85 (d, *J* = 6.2 Hz, 2H), 2.42 (s, 3H); **^{13}C NMR** (175 MHz, CD_3OD) δ 166.9, 149.6, 145.3, 137.6, 134.0, 133.9, 133.4, 131.0, 129.7, 128.7, 128.6, 119.9, 52.4, 50.1, 21.5; **IR** (Neat): 3242, 1652, 1630, 1600, 1542, 1323, 1304, 1155, 1091, 1040, 979, 935, 861, 812, 798, 763, 691, 675, 657; **HRMS** (ESI+): calcd for $C_{19}H_{22}N_3O_3S^+$ $[M+H]^+$: 372.1376, found 373.1367.

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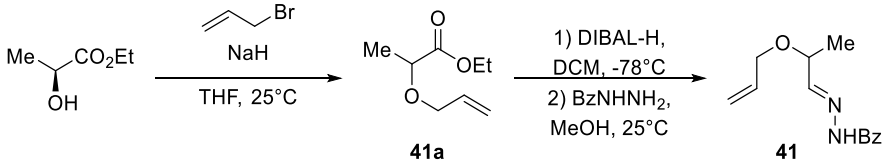
1-tosyl-2,5-dihydro-1H-pyrrole (40): White solid. The ^{1}H-NMR spectral data was consistent with literature data.[14] The ^{1}H NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.65 (s, 2H), 4.11 (s, 4H), 2.42 (s, 3H); **^{1}H-NMR** (400 MHz, C_6D_6) δ 7.72 (d, *J* = 7.8 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 2H), 4.92 (s, 2H), 3.90 (s, 4H), 1.87 (s, 3H).

3 step sequence for the synthesis of substrate 41



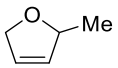
41a **41**

ethyl 2-(allyloxy)propanoate (41a): This compound was prepared using a modification of a literature method.[28] A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with ethyl-(L)-lactate (1.0040 g, 8.49 mmol) followed by 6.0 mL of anhydrous THF (1.41 M). After cooling the solution to 0 °C, sodium hydride (356 mg, 8.92 mmol, 60 wt% dispersion in mineral oil) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min, then allyl bromide (0.81 mL, 9.36 mmol) was added dropwise over 5 min while stirring and the reaction allowed to warm to 25 °C. After stirring for 16 h at 25 °C, the reaction was quenched with deionized water (25 mL), diluted with

EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 0.454 g (33%) of **41a** as a pale-yellow oil. The ^{1}H-NMR spectral data was consistent with literature data.[28] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 16.2, 10.3, 5.8 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.25 – 4.17 (m, 2H), 4.14 (ddt, *J* = 12.5, 5.5, 1.5 Hz, 1H), 4.01 (q, *J* = 6.8 Hz, 1H), 3.94 (ddt, *J* = 12.5, 6.1, 1.4 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

(E)-N'-(2-(allyloxy)propylidene)benzohydrazide (41): A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with **41a** (454 mg, 2.87 mmol) followed by 11.0 mL of anhydrous Et_2O (0.26 M). After cooling the solution to –78 °C, DIBAL-H (2.90 mL, 2.90 mmol, 1.0 M in hexanes) was added via syringe pump over 1 h. After stirring for 2 h at –78 °C, the reaction was quenched with the addition of Glauber's Salt (>3.00 equiv., sodium sulfate decahydrate), stirred for 5 min at -78 °C, and allowed to warm to 25 °C. The reaction was diluted with Et_2O (20 mL), and solids were filtered off through a Celite plug. The plug was washed with Et_2O (300 mL) and DCM (100 mL) and the filtrate put under reduced pressure to give crude aldehyde in ~3.0 mL Et_2O which was carried forward without further purification.

The solution of crude aldehyde (1.00 equiv., 3.00 mL) in Et_2O was diluted with MeOH (6.00 mL, 0.32 M in total) and benzoyl hydrazide (596 mg, 4.38 mmol, 1.50 equiv.) was added and the reaction stirred at 25 °C for 3 h. Upon consumption of aldehyde by TLC analysis, the reaction was concentrated under reduced pressure and directly purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 517.7 mg (76% over 2 steps) of **41** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a light tan solid. **^{1}H NMR** (700 MHz, CD_3OD) δ 7.89 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 6.7 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 5.91 (ddt, *J* = 16.2, 10.7, 5.5 Hz, 1H), 5.29 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 4.16 (p, *J* = 6.6 Hz, 1H), 4.06 (dd, *J* = 12.9, 5.1 Hz, 1H), 4.00 (dd, *J* = 13.1, 5.7 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (175 MHz, CD_3OD) δ 167.1, 154.7, 136.0, 134.0, 133.4, 129.7, 128.7, 117.2, 75.8, 70.8, 19.3; **IR** (Neat): 3203, 3087, 2882, 1645, 1567, 1496, 1450, 1350, 1287, 1181, 1112, 1072, 1045, 1001, 885, 869, 806, 714, 681; **HRMS** (ESI+): calcd for $C_{13}H_{16}N_2O_2Na^+$ $[M+Na]^+$: 255.1104, found 255.1095.



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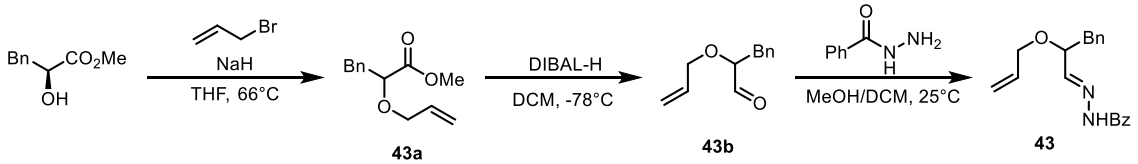
2-methyl-2,5-dihydrofuran (42): The ^{1}H-NMR spectral data was consistent with literature data.[29] The ^{1}H NMR spectral data in C_6D_6 has not previously been reported. The singlet at δ 4.28 ppm was assigned as DCM and the singlets at δ 1.60 ppm and δ 4.75 ppm were assigned as isobutylene respectively.[30] **^{1}H-NMR** (700 MHz, C_6D_6) δ 5.43 – 5.38 (m, 2H), 4.85 (h, *J* = 6.0 Hz, 1H), 4.53 (dd, *J* = 13.1, 5.9 Hz, 1H), 4.47 – 4.43 (m, 1H), 1.16 (d, *J* = 6.3 Hz, 3H).

3 step sequence for the synthesis of substrate 43



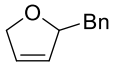
43a **43b** **43**

methyl 2-(allyloxy)-3-phenylpropanoate (43a): This compound was prepared using a modification of a literature method.[28] Sodium hydride (660 mg, 17.2 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 250 mL round-bottom flask containing a Teflon coated stir bar followed by 30 mL anhydrous THF (0.22 M in total). The flask was cooled to 0 °C with an ice bath. Then a solution of methyl (S)-2-hydroxy-3-phenylpropanoate (2.509 g, 13.92 mmol) in 15.0 mL anhydrous THF was added dropwise over 15 min. The reaction mixture was warmed to 25 °C for 30 min, diluted with 15.0 mL anhydrous THF and heated to reflux for 30 min. The reaction mixture was removed from heat and allyl bromide (1.57 mL, 18.10 mmol) was added dropwise over 2 min and the mixture was heated to reflux. After refluxing for 16 h, the reaction was cooled to 25 °C, quenched with MeOH (1.00 mL),

diluted with Et_2O (20 mL), and put under reduced pressure to remove THF. The residue was taken up in Et_2O (100 mL) and filtered through a Celite plug to remove NaBr. The filtrate was washed with H_2O (3 x 20 mL). The combined aqueous washes were extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.70 g (55%) of **43a** as a colorless oil. The ^{1}H-NMR spectral data was consistent with literature data.[31] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 (d, *J* = 7.1 Hz, 3H), 5.77 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.14 – 4.06 (m, 2H), 3.86 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.71 (s, 3H), 3.08 – 2.98 (m, 2H).

2-(allyloxy)-3-phenylpropanal (43b): A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with **43a** (503 mg, 2.28 mmol), followed by 11.5 mL anhydrous hexanes and 4.0 mL of anhydrous DCM (0.147 M in total). After cooling the solution to –78 °C, DIBAL-H (2.50 mL, 2.50 mmol, 1.0 M in hexanes) was added slowly over 1 h by syringe pump. After stirring for 3 h at –78 °C, the flask was transferred to an ice bath and allowed to warm to 0 °C. The mixture was diluted with Et_2O (25 mL), then water (0.02 mL) was added dropwise, followed by the sequential addition of 15% NaOH (aq., 0.02 mL) and water (0.06 mL) with 5 min between each addition. The mixture was allowed to warm to 25 °C and stirred for 15 min. Anhydrous $MgSO_4$ was added, and the mixture stirred for an additional 15 min. Solids were filtered off through a Celite plug, the plug washed with Et_2O (300 mL) and DCM (200 mL), and the filtrate concentrated in vacuo to afford the corresponding crude aldehyde. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 337 mg (77%) of **43b** as a pale-yellow oil which was carried forward immediately to the next step. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.9 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.23 (d, *J* = 2.9 Hz, 3H), 5.79 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.10 – 4.04 (m, 1H), 3.99 – 3.92 (m, 2H), 3.02 (dd, *J* = 14.2, 4.8 Hz, 1H), 2.92 (dd, *J* = 14.2, 8.2 Hz, 1H).

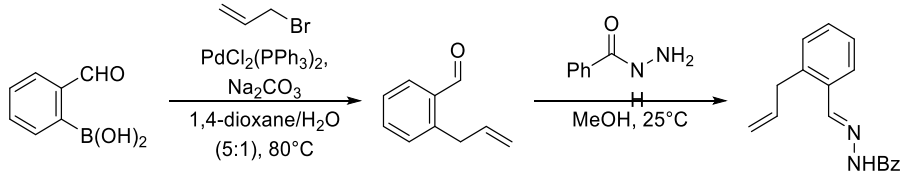
(E)-N'-(2-(allyloxy)-3-phenylpropylidene)benzohydrazide (**43**): This compound was prepared by a modification of general procedure A (**GP-A**): **43b** (200 mg, 1.05 mmol, 1.00 equiv.) and benzoyl hydrazide (215 mg, 1.58 mmol, 1.50 equiv.) in MeOH (3.50 mL, 0.30 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 197.1 mg (60%) of **43** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. Spectral overlap was observed between the hydrazone C-H and another aryl C-H resonance in the ^{1}H-NMR spectrum. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 4.5 Hz, 4H), 7.19 (p, *J* = 4.3 Hz, 1H), 5.80 (ddd, *J* = 22.6, 10.6, 5.3 Hz, 1H), 5.19 (d, *J* = 17.3 Hz, 1H), 5.09 (d, *J* = 11.2 Hz, 1H), 4.24 (q, *J* = 6.8 Hz, 1H), 4.04 (dd, *J* = 13.2, 5.0 Hz, 1H), 3.91 (dd, *J* = 13.1, 5.4 Hz, 1H), 3.01 – 2.97 (m, 2H); **^{13}C NMR** (175 MHz; CD_3OD) δ 167.0, 153.6, 138.4, 135.8, 133.9, 133.4, 130.8, 129.7, 129.3, 128.7, 127.5, 117.1, 80.5, 71.1, 41.0; **IR** (Neat): 3233, 3066, 1650, 1603, 1581, 1544, 1495, 1456, 1361, 1282, 1197, 1155, 1125, 1051, 1030, 951, 913, 867, 798, 7520, 690; **HRMS**: calcd for $C_{19}H_{20}N_2O_2Na^+$ $[M+Na]^+$: 331.1417, found: 331.1419.



44

2-benzyl-2,5-dihydrofuran (44): Pale-yellow oil. The ^{1}H NMR spectra data in $CDCl_3$ was consistent with literature data.[32] The ^{1}H NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.19 (m, 3H), 5.88 – 5.85 (m, 1H), 5.79 – 5.75 (m, 1H), 5.08 – 5.03 (m, 1H), 4.63 – 4.58 (m, 2H), 2.91 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.83 (dd, *J* = 13.5, 6.5 Hz, 1H); **^{1}H-NMR** (700 MHz, C_6D_6) δ 7.15 – 7.11 (m, 4H), 7.07 (t, *J* = 6.9 Hz, 1H), 5.46 – 5.42 (m, 1H), 5.39 – 5.36 (m, 1H), 5.00 (p, *J* = 5.9 Hz, 1H), 4.42 (dd, *J* = 3.7, 1.7 Hz, 2H), 2.84 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.72 (dd, *J* = 13.4, 6.4 Hz, 1H).

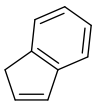
2 step sequence for the synthesis of substrate 45



45a **45**

2-allylbenzaldehyde (45a): This compound was synthesized by a literature procedure.[33] A flame-dried 250 mL round bottom flask equipped with a Teflon-coated stir bar was charged with $PdCl_2(PPh_3)_2$ (304 mg, 0.433 mmol, 2.5 mol%), 2-formylphenyl boronic acid (2.60 g, 17.3 mmol) followed by anhydrous THF (50 mL, 0.2 M) under a nitrogen atmosphere. Then allyl bromide (2.25 mL, 26.0 mmol) and aq. Na_2CO_3 (34.7 mL, 34.7 mmol, 1.0 M) were added and the mixture heated to reflux for 5 h. The reaction was diluted with H_2O (50 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were washed with sat. aq. NaCl (30 mL), dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The crude material was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.1251 g (44%) of **45a** as a yellow oil. The ^{1}H-NMR spectral data was consistent with literature data.[33] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.03 (ddt, *J* = 16.4, 10.2, 6.2 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 4.98 (d, *J* = 17.1 Hz, 1H), 3.82 (d, *J* = 6.1 Hz, 2H).

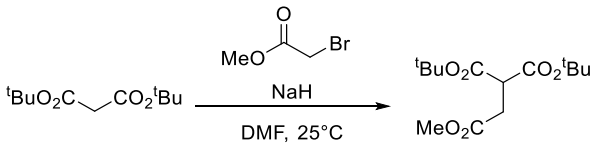
(E)-N'-(2-allylbenzylidene)benzohydrazide (**45**): This compound was prepared by a modification of general procedure A (**GP-A**): **45a** (100 mg, 0.684 mmol, 1.00 equiv.) and benzoyl hydrazide (140 mg, 1.03 mmol, 1.50 equiv.) in MeOH (3.50 mL, 0.30 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) and subsequent trituration from ice-cold pentane (3 x 1 mL) provided 23.9 mg (13%) of **43** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a cream solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 8.70 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.01 (ddt, *J* = 16.5, 11.2, 6.1 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.94 (d, *J* = 17.1 Hz, 1H), 3.58 (d, *J* = 5.9 Hz, 2H); **^{13}C NMR** (175 MHz; CD_3OD) δ 167.0, 148.9, 140.6, 138.5, 134.2, 133.4, 133.3, 131.6, 131.5, 129.7, 128.8, 127.9, 127.8, 116.5, 37.8; **IR** (Neat): 3187, 3027, 2852, 1643, 1604, 1558, 1482, 1407, 1368, 1288, 1145, 1062, 610, 754, 691; **HRMS**: calcd for $C_{17}H_{16}N_2ONa^+$ $[M+Na]^+$: 287.1155, found: 287.1153.



46

1*H*-indene (46): An authentic sample of 1*H*-indene **46** was obtained from Tokyo Chemical Company (Product number: I0016, >93% purity by G.C.) and characterized by NMR for use as a product standard. The ^{1}H-NMR spectral data in $CDCl_3$ was consistent with literature data.[34] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.28 (s, 1H), 7.20 (td, *J* = 7.4, 1.0 Hz, 1H), 6.90 (dt, *J* = 5.4, 1.6 Hz, 1H), 6.57 (dt, *J* = 5.5, 1.9 Hz, 1H), 3.41 (s, 2H); **^{1}H NMR** (400 MHz, C_6D_6) δ 7.30 (t, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 14.7 Hz, 1H), 7.15 – 7.09 (m, 1H), 6.73 (dd, *J* = 5.1, 2.0 Hz, 1H), 6.24 (dt, *J* = 5.5, 1.9 Hz, 1H), 3.03 (s, 2H).

Synthesis of common intermediate 47a for di-tertbutyl ester backbone substrates (47, 49-51)

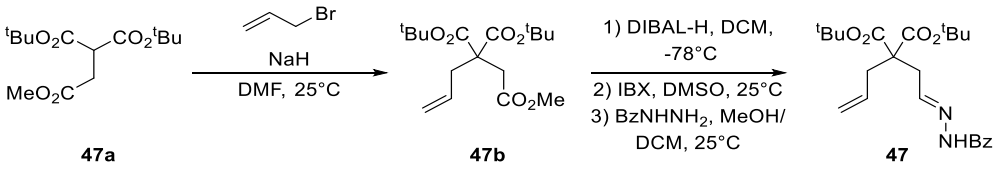


47a

1,1-di-tert-butyl 2-methyl ethane-1,1,2-tricarboxylate (47a): This compound was synthesized according to a literature method.[35] Sodium hydride (730 mg, 19.05 mmol, 60 wt% dispersion in

mineral oil) was added to a flame dried 250 mL round-bottom flask containing a Teflon coated stir bar followed by 53 mL DMF (0.30 M). The flask was cooled to 0 °C with an ice bath and di-tert-butyl malonate (3.60 mL, 16.11 mmol) was added dropwise over 2 min. The reaction mixture was stirred at 0 °C for 30 min, then methyl bromoacetate (1.50 mL, 15.85 mmol) was added dropwise while stirring and the reaction allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl (20 mL), diluted with deionized water (80 mL) and EtOAc (60 mL) and partitioned. The aqueous layer was extracted with EtOAc (5 x 60 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (2 x 30 mL), sat. aq. NaCl solution (30 mL), dried with anhydrous Na_2SO_4, filtered and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 3.172 g (69%) of **47a** as a pale-yellow oil that solidified to a white solid on standing. The ^{1}H NMR and ^{13}C NMR spectral data were consistent with literature data.[36] HRMS and IR spectra were not previously reported. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.64 (t, J = 7.5 Hz, 1H), 2.82 (d, J = 7.4 Hz, 2H), 1.46 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.71, 167.84, 82.12, 77.41, 77.16, 76.91, 52.05, 49.99, 33.20, 28.00; **IR** (Neat): 2977, 1727, 1720, 1370, 1345, 1282, 1141, 997, 884, 847, 752; **HRMS** (ESI+): calcd for $C_{14}H_{24}O_6Na^+$ $[M+Na]^+$: 311.1465, found 311.1464.

4 step sequence for the synthesis of allyl substrate 47 from 47a



47a **47b** **47**

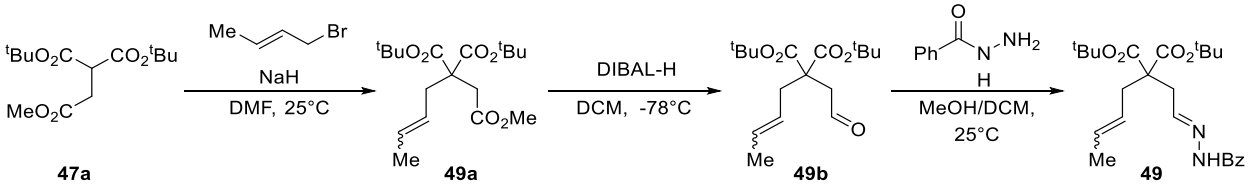
2,2-di-tert-butyl 1-methyl pent-4-ene-1,2,2-tricarboxylate (47b): This compound was prepared using a modification of a literature method.[37] Sodium hydride (162 mg, 4.24 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 10 mL DMF (0.20 M in total). The flask was cooled to 0 °C with an ice bath. Then a solution of **47a** (1.0030 g, 3.48 mmol) in 7.4 mL DMF was added dropwise over 2 min. The reaction mixture was stirred at 0 °C for 30 min, then allyl bromide (0.40 mL, 4.62 mmol) was added dropwise over 5 min while stirring and the reaction allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (2 x 20 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 0.801 g (70%) of **47b** as a colorless oil. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.68 (ddt, *J* = 16.3, 10.6, 7.5 Hz, 1H), 5.14 – 5.08 (m, 2H), 3.65 (s, 3H), 2.87 (s, 2H), 2.68 (dt, *J* = 7.5, 1.1 Hz, 2H), 1.45 (s, 18H).; **^{13}C NMR** (175 MHz, $CDCl_3$) δ 171.19, 169.15, 132.69, 119.56, 81.93, 77.34, 77.16, 76.98, 56.32, 51.69, 37.51, 37.15, 27.97.; **IR** (Neat): 2979, 1729, 1438, 1369, 1298, 1196, 1142, 996, 920, 845, 749; **HRMS** (ESI+): calcd for $C_{17}H_{28}O_6Na^+$ $[M+Na]^+$: 351.1778, found 351.1776.

di-tert-butyl (E)-2-allyl-2-(2-(2-benzoylhydrazineylidene)ethyl)malonate (47): A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with **47b** (443 mg, 1.35 mmol) and followed by 18.5 mL anhydrous DCM (0.10 M). After cooling the solution to –78 °C, DIBAL-H (2.90 mL, 2.90 mmol, 1.0 M in hexanes) was added slowly over 10 min. After stirring for 2 h at –78 °C, the flask was transferred to an ice bath and allowed to warm to 0 °C. The mixture was diluted with Et_2O (25 mL), then water (0.02 mL) was added dropwise, followed by the sequential addition of 15 wt% NaOH (aq.) (0.02 mL) and water (0.05 mL) with 5 min between each addition. The mixture was allowed to warm to 25 °C and stirred for 15 min. Anhydrous $MgSO_4$ was added, and the mixture stirred for an additional 15 min. Solids were filtered off through a Celite plug, the plug washed with Et_2O (300 mL) and DCM (100 mL), and the filtrate concentrated in vacuo to afford the corresponding crude alcohol as a white semisolid (180 mg) which was used without further purification.

A 50 mL round-bottom flask containing a Teflon coated stir bar was charged with IBX[2] (257 mg, 2.23 mmol, 1.53 equiv.) and 3.0 mL DMSO (0.1 M) and stirred at 25 °C for 30 min until the IBX dissolved. A solution of the crude alcohol (180 mg) in 7.0 mL DMSO (7.0 mL) was added dropwise over 2 min and the mixture stirred at 25 °C until judged complete by TLC analysis (8 h), after which Et_2O (25 mL) and

water (20 mL) were added. The biphasic mixture was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 60 mL) and EtOAc (3 x 60 mL), and the combined organic layers were washed with sat. aq. NaCl solution (2 x 30 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude white semisolid residue containing the aldehyde obtained (208 mg) was carried forward without further purification.
The crude aldehyde (208 mg) was dissolved in 1:1 MeOH/DCM (v/v) (12.0 mL, 0.17 M) and benzoyl hydrazide (150 mg, 1.10 mmol, 1.83 equiv.) was added and the reaction stirred at 25 °C for 12 h. Upon consumption of aldehyde by TLC analysis, the reaction was concentrated under reduced pressure and directly purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) and then HPLC (C18) eluting with water/acetonitrile to give 137 mg (24% over 3 steps) of **47** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.77 (t, *J* = 5.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 5.81 – 5.72 (m, 1H), 5.17 (dd, *J* = 22.9, 13.6 Hz, 2H), 2.78 (d, *J* = 6.0 Hz, 2H), 2.61 (d, *J* = 7.4 Hz, 2H), 1.47 (s, 18H); **^{13}C NMR** (175 MHz; CD_3OD) δ 170.8, 166.7, 151.4, 134.1, 133.4, 133.2, 129.7, 128.6, 120.1, 83.3, 58.6, 39.6, 37.3, 28.2; **IR** (Neat): 3198, 2976, 2934, 1725, 1656, 1570, 1448, 1393, 1369, 1291, 1249, 1225, 1140, 1120, 1078, 996, 923, 840, 797, 749, 736, 702; **HRMS**: calcd for $C_{23}H_{32}N_2O_5Na^+$[M+Na]$^+$: 439.2203, found: 439.2207.

4 step sequence for the synthesis of crotyl substrate 49 from 47a

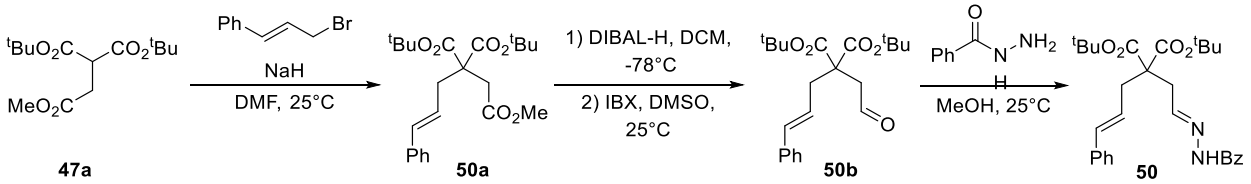


2,2-di-tert-butyl 1-methyl hex-4-ene-1,2,2-tricarboxylate (47a): This compound was prepared using a modification of a literature method.[37] Sodium hydride (91.7 mg, 2.29 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 14.0 mL DMF (0.20 M in total). The flask was cooled to 0 °C with an ice bath. Then a solution of **47a** (529 mg, 1.83 mmol) in 7.1 mL DMF was added dropwise over 2 min. The reaction mixture was stirred at 0 °C for 30 min, then trans-crotyl bromide (0.25 mL, 2.39 mmol, 85% technical grade from Sigma-Aldrich) was added portion wise while stirring and the reaction allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with aqueous 5 wt% LiCl solution (2 x 20 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 223 mg (35%) of **49a** (6.59:1 mixture of *E:Z* isomers in $CDCl_3$) as a colorless oil. **^{1}H NMR** (major + minor isomer, 500 MHz, $CDCl_3$) δ 5.61 (dq, *J* = 13.4, 7.1 Hz, 1H, minor), 5.51 (dq, *J* = 13.2, 6.2 Hz, 6.6H, major), 5.35 – 5.20 (m, 7.4H, major + minor), 3.65 (s, 21.5H, major + minor), 2.87 (s, 2H, minor), 2.85 (s, 13.2H, major), 2.71 (d, *J* = 7.8 Hz, 2H, minor), 2.59 (d, *J* = 7.5 Hz, 13.3H, major), 1.64 (d, *J* = 6.4 Hz, 20.9H, major), 1.59 (d, *J* = 6.9 Hz, 3H, minor), 1.45 (s, 133.5H, major + minor); **^{13}C NMR** (major isomer, 125 MHz, $CDCl_3$) δ 171.3, 169.3, 130.2, 125.0, 81.7, 56.6, 51.7, 37.2, 36.4, 28.0, 18.1; **IR** (Neat): 2979, 2936, 1729, 1477, 1438, 1394, 1298, 1252, 1216, 1195, 1142, 1082, 1057, 1033, 1003, 969, 938, 893, 846, 745, 697; **HRMS** (ESI+): calcd for $C_{18}H_{30}O_6Na^+$ [M+Na]$^+$: 365.1935, found 365.1930.
di-tert-butyl 2-(but-2-en-1-yl)-2-(2-oxoethyl)malonate (49b): A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with **49a** (215 mg, 0.63 mmol) and followed by 6.5 mL anhydrous Et_2O (0.096 M). After cooling the solution to –78 °C, DIBAL-H (1.38 mL, 1.38 mmol, 1.0 M in hexanes) was added slowly over 30 min. After stirring for 3 h at –78 °C, the reaction was quenched with dropwise addition of EtOAc (0.13 mL) and was transferred to an ice bath and allowed to warm to 0 °C. The reaction was diluted with sat. aq. Rochelle's salt solution (15 mL), Et_2O (25 mL), and stirred overnight to obtain two distinct layers. The biphasic mixture was partitioned, and the aqueous layer extracted with Et_2O (2 x 30 mL) and EtOAc (3 x 30 mL). The combined organic layers were washed with sat. aq. NaCl solution (10 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 129 mg (65%) of **49b** (5.39:1 mixture of *E:Z* isomers in $CDCl_3$)

as a colorless oil. Characterization data was obtained for the 5.39:1 mixture of *E*-isomer (major) and *Z*-isomer (minor). The peak at δ 29.84 ppm in the ^{13}C-NMR spectrum was assigned as an unknown impurity which was removed in the next step. **^{1}H NMR** (major + minor isomer, 700 MHz, $CDCl_3$) δ 9.73 (s, 5.8H, major + minor), 5.67 – 5.60 (m, 1H, minor), 5.51 (dq, *J* = 13.1, 6.4 Hz, 5.4H, major), 5.27 (dt, *J* = 14.8, 7.3 Hz, 6.4H, major + minor), 2.77 (s, 2.1H, minor), 2.76 (s, 10.6H, major), 2.67 (d, *J* = 7.8 Hz, 2.1H, minor), 2.58 (d, *J* = 7.4 Hz, 10.6H, major), 1.65 (d, *J* = 6.5 Hz, 16.8H, major), 1.60 (d, *J* = 6.9 Hz, 3.1H, minor), 1.45 (s, 115.5H, major + minor); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 200.2 (major), 200.1 (minor), 169.5 (minor), 169.5 (major), 130.7 (major), 128.7 (minor), 124.7 (major), 123.7 (minor), 82.4 (minor), 82.4 (major), 56.2 (major), 56.0 (minor), 46.5 (major), 46.5 (minor), 37.6 (major), 31.5 (minor), 28.0 (major), 28.0 (minor), 18.1 (major), 13.2 (minor); **IR** (Neat): 2979, 2934, 1722, 1478, 1457, 1394, 1369, 1285, 1251, 1216, 1146, 1094, 1069, 1039, 970, 929, 845, 736; **HRMS** (ESI+): calcd for $C_{17}H_{28}O_5Na^+$ $[M+Na]^+$: 335.1829, found 335.1829.

di-tert-butyl 2-((E)-2-(2-benzoylhydrazineylidene)ethyl)-2-((E)-but-2-en-1-yl)malonate (49): This compound was prepared by a modification of general procedure A (**GP-A**): **49b** (100 mg, 0.32 mmol, 1.00 equiv.) and benzoyl hydrazide (70.9 mg, 0.52 mmol, 1.63 equiv.) in MeOH (3.00 mL, 0.10 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) and subsequent trituration from ice-cold pentane (4 x 1 mL) provided 133.5 mg (96%) of **49** (>20:1 mixture of *E:Z* hydrazone isomers and 4.68:1 mixture of E:Z olefin isomers in CD_3OD) as a white solid. Characterization data was obtained for the 4.68:1 mixture of (*E*-hydrazone*, E*-olefin) diastereomer (major) and (*E*-hydrazone*, Z*-olefin) diastereomer (minor). **^{1}H NMR** (major + minor diastereomer, 700 MHz, CD_3OD) δ 7.85 (d, *J* = 7.6 Hz, 9.8H, major + minor), 7.76 (t, *J* = 6.0 Hz, 5.3H, major + minor), 7.57 (t, *J* = 7.4 Hz, 4.9H, major + minor), 7.49 (t, *J* = 7.6 Hz, 10.4H, major + minor), 5.68 – 5.57 (m, 5.3H, major + minor), 5.41 – 5.30 (m, 5.30H, major + minor), 2.80 – 2.75 (m, 10.7H, major + minor), 2.63 (d, *J* = 7.5 Hz, 2.0H, minor), 2.53 (d, *J* = 7.3 Hz, 9.4H, major), 1.69 – 1.64 (m, 16.2H, major + minor), 1.46 (s, 93.8H, major + minor); **^{13}C NMR** (175 MHz, CD_3OD) δ 171.0, 170.9, 166.6, 151.5, 151.4, 134.1, 133.2, 131.3, 129.7, 129.0, 128.6, 125.7, 124.7, 83.2, 83.1, 58.9, 58.8, 38.4, 37.4, 37.4, 32.4, 28.2, 28.2, 18.2, 13.4; **IR** (Neat) 2925, 1725, 1650, 1568, 1454, 1393, 1367, 1296, 1215, 1146, 1126, 1075, 1057, 969, 908, 846, 798, 705, 678; **HRMS**: calcd for $C_{24}H_{34}N_2O_5Na^+$ $[M+Na]^+$: 453.2360, found: 453.2359.

4 step sequence for the synthesis of cinnamyl substrate 50 from 47a



2,2-di-tert-butyl 1-methyl (E)-5-phenylpent-4-ene-1,2,2-tricarboxylate (50a): This compound was prepared using a modification of a literature method.[37] Sodium hydride (163 mg, 4.25 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 10 mL DMF (0.20 M in total). The flask was cooled to 0 °C with an ice bath. Then, a solution of **47a** (1.0057 g, 3.49 mmol) in 7.4 mL DMF was added dropwise over 2 min. The reaction mixture was stirred at 0 °C for 30 min, then trans-cinnamyl bromide (895 mg, 4.54 mmol) was added portion wise while stirring and the reaction allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (2 x 20 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.275 g (90%) of **50a** (22.46:1 mixture of *E:Z* styrene isomers in $CDCl_3$) as a viscous yellow oil. The minor *Z*-styrene isomer was only observed in the ^{1}H-NMR spectrum for **50a**. **^{1}H NMR** (minor isomer, 700 MHz, $CDCl_3$) δ 6.62 (d, *J* = 15.9 Hz, 1H), 6.24 (dt, *J* = 16.0, 6.5 Hz, 1H), 2.96 (d, *J* = 1.1 Hz, 2H), 2.86 (d, *J* = 7.6 Hz, 2H), 1.46 (s, 18H). Characterization data shown for the major isomer (*E*). **^{1}H NMR** (major isomer, 700 MHz, $CDCl_3$) δ 7.30 (dt, *J* = 14.7, 7.6 Hz, 4H), 7.21 (t, *J* = 7.1 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.10 (dt, *J* = 15.6, 7.6 Hz, 1H), 3.65 (s, 3H), 2.91 (s, 2H), 2.83 (d, *J* = 7.6 Hz, 2H), 1.46 (s, 18H); **^{13}C NMR** (major isomer, 175 MHz, $CDCl_3$) δ 171.2, 169.2, 137.3, 134.3, 128.6, 127.5, 126.4, 124.4, 82.0, 56.8, 51.7, 37.5, 36.9, 28.0; **IR** (Neat): 2978, 1727, 1437, 1393, 1368, 1295,

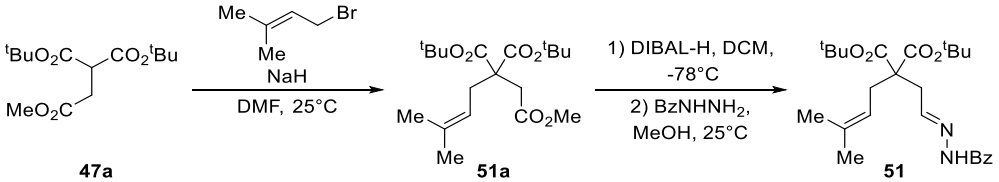
1252, 1142, 1096, 1070, 1003, 968, 847, 740, 692; **HRMS** (ESI+): calcd for $C_{23}H_{32}O_6Na^+$ $[M+Na]^+$: 427.2091, found 427.2091.

di-tert-butyl 2-cinnamyl-2-(2-oxoethyl)malonate (50b): A flame dried 50 mL round-bottom flask containing a Teflon coated stir bar was charged with **50a** (747 mg, 1.85 mmol) and followed by 18.5 mL anhydrous DCM (0.10 M). After cooling the solution to –78 °C, DIBAL-H (4.10 mL, 4.10 mmol, 1.0 M in hexanes) was added slowly over 30 min. After stirring for 1.5 h at –78 °C, the flask was transferred to an ice bath and allowed to warm to 0 °C. The mixture was diluted with Et_2O (25 mL), then water (0.2 mL) was added dropwise, followed by the sequential addition of 15% NaOH (aq., 0.2 mL) and water (0.4 mL) with 5 min between each addition. The mixture was allowed to warm to 25 °C and stirred for 15 min. Anhydrous $MgSO_4$ was added, and the mixture stirred for an additional 15 min. Solids were filtered off through a Celite plug, the plug washed with Et_2O (300 mL) and DCM (100 mL), and the filtrate concentrated in vacuo to afford the corresponding crude alcohol.

A 100 mL round-bottom flask containing a Teflon coated stir bar was charged with the crude alcohol (1.0 equiv.) and dissolved in 18.5 mL DMSO (0.10 M). IBX[2] (776 mg, 2.77 mmol, 1.5 equiv.) was added and the mixture stirred at 25 °C until judged complete by TLC analysis (24 h), after which Et_2O (30 mL) and water (20 mL) were added. The biphasic mixture was filtered through celite, and the plug washed with Et_2O (20 mL). The organic layer was separated from the biphasic filtrate. The aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 100 mg (14% over 2 steps) of **50b** as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.30 (d, *J* = 6.5 Hz, 4H), 7.25 – 7.19 (m, 1H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.07 (dt, *J* = 15.4, 7.7 Hz, 1H), 2.87 – 2.79 (m, 4H), 1.47 (s, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.77, 169.32, 137.01, 134.64, 128.71, 127.69, 126.36, 124.00, 82.61, 77.41, 76.91, 56.38, 46.80, 38.02, 28.01; **IR** (Neat): 2978, 2934, 1721, 1456, 1369, 1252, 1144, 958, 847, 746, 593; **HRMS** (ESI+): calcd for $C_{22}H_{30}O_5Na^+$ $[M+Na]^+$: 397.1985, found 397.1988.

di-tert-butyl 2-((E)-2-(2-benzoylhydrazineylidene)ethyl)-2-cinnamylmalonate (50): This compound was prepared by a modification of general procedure A (**GP-A**): **50b** (98.2 mg, 0.262 mmol, 1.00 equiv.) and benzoyl hydrazide (57.0 mg, 0.419 mmol, 1.60 equiv.) in 4:3 MeOH/DCM (v/v) (3.50 mL, 0.075 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 93.0 mg (72%) of **50** (>20:1 mixture of *E:Z* hydrazone isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) 7.84 (d, *J* = 7.7 Hz, 2H), 7.79 (t, *J* = 5.9 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.20 (dt, *J* = 15.4, 7.6 Hz, 1H), 2.86 (d, *J* = 6.0 Hz, 2H), 2.75 (d, *J* = 7.6 Hz, 2H), 1.47 (s, 18H); **^{13}C NMR** (175 MHz; CD_3OD) δ 170.9, 166.7, 151.4, 138.4, 135.8, 134.1, 133.2, 129.7, 129.6, 128.7, 128.5, 127.2, 124.7, 83.4, 59.2, 38.9, 37.8, 28.2; **IR** (Neat): 3228, 2978, 1726, 1646, 1565, 1370, 1295, 1144, 1121, 971, 844, 799, 751, 706, 691; **HRMS**: calcd for $C_{29}H_{36}N_2O_5Na^+$ $[M+Na]^+$: 515.2516, found: 515.2513.

3 step sequence for the synthesis of dimethallyl substrate 51 from 47a:

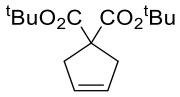


2,2-di-tert-butyl 1-methyl 5-methylhex-4-ene-1,2,2-tricarboxylate (51a): This compound was prepared using a modification of a literature method.[37] Sodium hydride (232 mg, 5.81 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 15.0 mL DMF (~0.20 M in total). The flask was cooled to 0 °C with an ice bath. Then, a solution of **47a** (1.3394 g, 4.64 mmol) in 8.0 mL DMF was added dropwise over 2 min. The reaction mixture was stirred at 0 °C for 30 min, then prenyl bromide (0.70 mL, 6.04 mmol) was added dropwise over 15 min while stirring and the reaction allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (4 x 40 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (2 x 20 mL), sat. aq.

NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.340 g (80%) of **51a** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.02 – 4.93 (m, 1H), 3.64 (s, 3H), 2.85 (s, 2H), 2.63 (d, *J* = 7.7 Hz, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.44 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.4, 169.5, 135.9, 118.2, 81.6, 56.7, 51.6, 37.1, 31.7, 27.9, 26.2, 18.1; **IR** (Neat): 2978, 2933, 1729, 1477, 1455, 1437, 1393, 1368, 1298, 1252, 1141, 1069, 1054, 1003, 895, 847, 750; **HRMS** (ESI+): calcd for $C_{19}H_{32}O_6Na^+$ [M+Na]$^+$: 379.2091, found 379.2087.

di-tert-butyl (E)-2-(2-(2-benzoylhydrazineylidene)ethyl)-2-(3-methylbut-2-en-1-yl)malonate (51): A flame dried 250 mL round-bottom flask containing a Teflon coated stir bar was charged with **51a** (1.261 g, 354 mmol) followed by 34.0 mL anhydrous DCM (0.10 M). After cooling the solution to –78 °C, DIBAL-H (3.90 mL, 4.10 mmol, 1.0 M in hexanes) was added slowly over 2 h with a syringe pump. After stirring for 2 h at –78 °C, the flask was transferred to an ice bath and allowed to warm to 0 °C. The mixture was diluted with Et_2O (50 mL), then H_2O (0.25 mL) was added dropwise, followed by the sequential addition of 15 wt% NaOH (aq., 0.25 mL) and H_2O (0.6 mL) with 5 min between each addition. The mixture was allowed to warm to 25 °C and stirred for 15 min. Anhydrous $MgSO_4$ was added and the mixture stirred for an additional 15 min. Solids were filtered off through a Celite plug, the plug washed with Et_2O (200 mL) and the filtrate concentrated in vacuo to afford the corresponding crude aldehyde (203 mg).

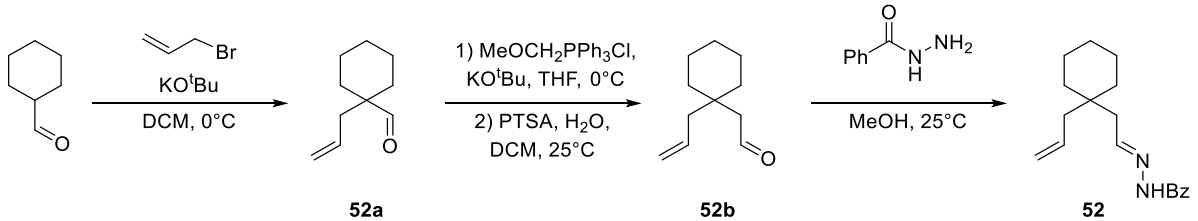
The crude aldehyde (203 mg, 0.392 mmol, 1.00 equiv.) was dissolved in MeOH (2.7 mL, 0.145 M) and benzoyl hydrazide (67.4 mg, 0.495 mmol, 1.26 equiv.) was added and the reaction stirred at 25 °C for 3 h. Upon consumption of aldehyde by TLC analysis, the reaction was concentrated under reduced pressure and purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 168.2 mg (10% over 2 steps) of **51** (>80:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.76 (t, *J* = 5.9 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 5.08 (t, *J* = 7.6 Hz, 1H), 2.77 (d, *J* = 6.2 Hz, 2H), 2.56 (d, *J* = 7.5 Hz, 2H), 1.72 (s, 3H), 1.66 (s, 3H), 1.46 (s, 18H); **^{13}C NMR** (175 MHz; CD_3OD) δ 171.2, 166.7, 151.6, 136.8, 134.2, 133.2, 129.7, 128.6, 118.9, 83.1, 59.1, 37.5, 33.7, 28.2, 26.2, 18.3; **IR** (Neat): 3194, 2982, 1723, 1655, 1565, 1451, 1369, 1297, 1252, 1230, 1147, 1074, 896, 845, 698; **HRMS** (ESI+): calcd for $C_{25}H_{36}N_2O_5Na^+$ [M+Na]$^+$: 467.2516, found: 467.2511.



48

di-tert-butyl cyclopent-3-ene-1,1-dicarboxylate (48): White solid. **^{1}H NMR** (400 MHz, C_6D_6) δ 5.41 (s, 2H), 3.15 (s, 4H), 1.35 (s, 18H); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.58 (s, 2H), 2.91 (s, 4H), 1.45 (s, 18H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 171.63, 127.96, 81.21, 60.14, 40.79, 28.00; **IR** (Neat): 2985, 1711, 1366, 1280, 1138, 1055, 954, 845, 777, 713; **HRMS** (ESI+): *m/z* calculated for $C_{15}H_{24}O_5Na^+$ [M+Na]$^+$: 291.1567; found: 291.1569.

3 step sequence for the synthesis of substrate 52



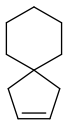
52a **52b** **52**

1-allylcyclohexane-1-carbaldehyde (**52a**): This compound was prepared using a modification of a literature method.[38] A flame dried 250 mL round bottom flask containing a Teflon coated stir bar was charged with allyl bromide (4.52 g, 37.3 mmol), anhydrous DCM (140 mL, 0.21 M), and cyclohexanecarbaldehyde (3.77 mL, 31.1 mmol). The resulting mixture was cooled to 0 ˚C before solid potassium tert-butoxide (4.19 g, 37.3 mmol) was added in a single portion. The reaction was allowed to warm to 25 °C and stir until judged complete by TLC analysis (1.5 h). After stirring at 25 °C for 1.5 h, the reaction quenched with sat. aq. NH_4Cl solution (30 mL) and partitioned. The organic layer was collected, and the aqueous layer was further extracted with DCM (2 x 50 mL). The combined organic

layers were washed with sat. aq. NaCl solution (30 mL), dried over Na_2SO_4, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 3.63 g (76%) of **52a** as a colorless oil. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature data.[39] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 5.65 (ddt, *J* = 17.6, 10.4, 7.5 Hz, 1H), 5.09 – 4.98 (m, 2H), 2.18 (d, *J* = 7.5 Hz, 2H), 1.94 – 1.83 (m, 2H), 1.64 – 1.47 (m, 2H), 1.31 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.0, 132.8, 118.4, 49.7, 40.9, 30.9, 25.8, 22.6.

2-(1-allylcyclohexyl)acetaldehyde (**52b**): This compound was prepared using a modification of a literature method.[40] A flame dried 100 mL round bottom flask containing a Teflon coated stir bar was charged with (methoxymethyl)triphenylphosphonium chloride (3.3776 g, 9.85 mmol) followed by anhydrous THF (26.0 mL, 0.25 M). The suspension was cooled to 0 °C, solid potassium tert-butoxide was added in one portion and the resulting mixture was allowed to warm to room temperature for 0.5 h. The suspension was then cooled to 0 °C and a solution of **52a** (1.00 g, 6.57 mmol) in THF (4.00 mL) was added. The mixture was allowed to warm to room temperature and stirred until judged complete by TLC (16 h). After stirring at 25 °C for 16 h, the reaction was quenched with sat. aq. NH_4Cl solution (20 mL), diluted with deionized H_2O (20 mL) and EtOAc (40 mL) and partitioned. The aqueous layer was further extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried over Na_2SO_4, and put under reduced pressure to remove the solvent. The crude material was used in the next step without further purification. To the crude reaction mixture from the previous step was added a 50:50 mixture of acetone and water (30 mL each, 0.11 M) and a Teflon coated stir bar. PTSA (250 mg, 1.31 mmol) was added and the reaction was allowed to stir at 95 °C for 6 h. After the reaction is complete, quenched with sat. aq. $NaHCO_3$ (20 mL), diluted with EtOAc (50 mL) and H_2O (50 mL), and partitioned. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were sat. aq. NaCl solution (20 mL), dried over Na_2SO_4, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 380 mg (24% over 2 steps) of **52b** as a colorless liquid. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature data.[39] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.85 (t, *J* = 3.1 Hz, 1H), 5.81 (ddt, *J* = 17.5, 10.1, 7.5 Hz, 1H), 5.13 – 4.99 (m, 2H), 2.32 (d, *J* = 3.1 Hz, 2H), 2.20 (d, *J* = 7.5 Hz, 2H), 1.53 – 1.39 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.8, 134.0, 118.4, 50.7, 42.8, 37.0, 36.0, 26.1, 21.6.

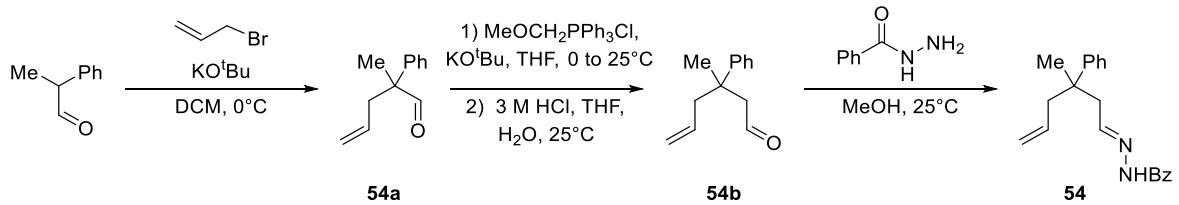
(E)-N'-(2-(1-allylcyclohexyl)ethylidene)benzohydrazide (52): This compound was prepared by a modification of general procedure A (**GP-A**): **52b** (200 mg, 1.20 mmol, 1.00 equiv.) and benzoyl hydrazide (246 mg, 1.80 mmol, 1.50 equiv.) in MeOH (6.00 mL, 0.2 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 192.6 mg (56%) of **52** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.90 – 7.86 (m, 2H), 7.80 (t, *J* = 6.2 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 5.90 (ddt, *J* = 17.5, 10.5, 7.5 Hz, 1H), 5.11 – 5.05 (m, 2H), 2.34 (d, *J* = 6.3 Hz, 2H), 2.14 (d, *J* = 7.5 Hz, 2H), 1.55 – 1.51 (m, 4H), 1.45 – 1.38 (m, 6H); **^{13}C NMR** (175 MHz; CD_3OD) δ 166.6, 153.6, 135.5, 134.2, 133.1, 129.7, 128.7, 118.2, 37.6, 36.7, 27.2, 22.5; **IR** (Neat): 3195, 3056, 2919, 2850, 1660, 1559, 1373, 1295, 1153, 915, 893, 883, 792, 695; **HRMS (ESI+)**: calcd for $C_{18}H_{24}N_2ONa^+$[M+Na]$^+$: 307.1781, found: 307.1781.



53

spiro[4.5]dec-2-ene (53): This compound was not isolated in neat form due to volatility. **^{1}H NMR** (700 MHz, C_6D_6) δ 5.60 (s, 2H), 2.12 (s, 4H), 1.39 (d, *J* = 3.1 Hz, 8H), 1.35 – 1.32 (m, 2H); **^{13}C NMR** (175 MHz, C_6D_6) δ 129.3, 46.0, 42.2, 39.0, 26.5, 23.9; **IR** (Neat): 2924, 2854, 1455, 1261, 1019, 802; **HRMS** (EI+): *m/z* calculated for $C_{10}H_{16}$ [M]$^+$: 136.1252; found: 136.1251.

4 step sequence for the synthesis of substrate 54

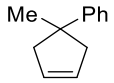


2-methyl-2-phenylpent-4-enal (54a): This compound was prepared using a modification of a literature method.[38] A flame dried 250 mL round bottom flask containing a Teflon coated stir bar was charged with allyl bromide (4.27 mL, 49.3 mmol), anhydrous DCM (125 mL, 0.19 M), and 2-phenylpropanal (3.30 mL, 24.6 mmol). The resulting mixture was cooled to 0 ˚C before solid potassium tert-butoxide (3.594 g, 32.0 mmol) was added in a single portion. The reaction was allowed to warm to 25 °C and stir until judged complete by TLC analysis (3 h). After stirring at 25 °C for 3 h, the reaction quenched with sat. aq. NH_4Cl solution (30 mL) and partitioned. The organic layer was collected, and the aqueous layer was further extracted with DCM (3 x 50 mL). The combined organic layers were washed with sat. aq. NaCl solution (30 mL), dried over Na_2SO_4, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.9684 g (45%) of **54a** as a pale-yellow oil. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature data.[41] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 6.9 Hz, 2H), 5.59 – 5.51 (m, 1H), 5.05 (dd, *J* = 18.5, 13.7 Hz, 2H), 2.70 (dd, *J* = 14.1, 6.8 Hz, 1H), 2.63 (dd, *J* = 14.1, 7.7 Hz, 1H), 1.45 (s, 3H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 202.3, 139.8, 133.5, 129.2, 127.6, 127.5, 118.9, 53.9, 40.9, 19.1.

3-methyl-3-phenylhex-5-enal (54b): This compound was prepared using a modification of a literature method.[40] A flame dried 100 mL round bottom flask containing a Teflon coated stir bar was charged with (methoxymethyl)triphenylphosphonium chloride (4.37 g, 12.7 mmol) followed by anhydrous THF (30.0 mL, 0.15 M in total). The suspension was cooled to 0 °C, a solution of potassium tert-butoxide (1.43 g, 12.7 mmol) in 20.0 ml THF was added dropwise and then this mixture was stirred for 1 h at 0 °C. A solution of **54a** (888 mg, 3.84 mmol) in 5.00 ml THF was added at 0 °C and the mixture was allowed to warm to 25 °C and stirred until judged complete by TLC/^{1}H-NMR (16 h). After stirring at 25 °C for 16 h, the reaction was quenched via the addition of deionized H_2O (30 mL) and the solution extracted with Et_2O (4 x 75 ml). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent to give crude enol ether as a brown semicrystalline mass. The crude enol ether was carried forward into the hydrolysis without further purification. To the crude reaction mixture from the previous step was added 34.0 mL THF and aq. 3.0 M HCl (8.5 mL, 25.5 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred until judged complete by TLC (24 h). The reaction mixture was diluted with Et_2O (80 mL) and washed in a separating funnel with aq. $NaHCO_3$ solution (20 mL), deionized H_2O (20 mL), sat. aq. NaCl solution (20 mL) and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford crude product (3.75 g) as a brown oil. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 846 mg (88%) of **54b** as a pale-yellow oil. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 9.52 (t, *J* = 2.9 Hz, 1H), 7.35 (d, *J* = 3.9 Hz, 4H), 7.23 (dt, *J* = 8.5, 4.2 Hz, 1H), 5.58 – 5.49 (m, 1H), 5.03 – 5.00 (m, 1H), 2.86 (dd, *J* = 15.5, 2.3 Hz, 1H), 2.56 (ddd, *J* = 20.3, 14.7, 5.0 Hz, 2H), 2.42 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.48 (s, 3H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 203.1, 145.7, 133.9, 128.7, 126.5, 126.2, 118.6, 54.6, 48.0, 39.8, 25.2; **IR** (Neat): 3061, 2976, 2922, 2837, 1719, 1497, 1446, 1417, 1381, 1134, 1077, 1031, 998, 916, 763, 746, 698, 659; **HRMS** (GC-APCI): calcd for $C_{13}H_{16}O^+$ $[M+H]^+$: 189.1274, found 189.1268.

(E)-N'-(3-methyl-3-phenylhex-5-en-1-ylidene)benzohydrazide (54): This compound was prepared by a modification of general procedure A (**GP-A**): **54b** (107.4 mg, 0.57 mmol, 1.00 equiv.) and benzoyl hydrazide (116.5 mg, 0.86 mmol, 1.50 equiv.) in MeOH (1.90 mL, 0.30 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 127.3 mg (72%) of **54** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white crystalline foam. **^{1}H NMR** (700 MHz; CD_3OD) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.39 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 5.58 – 5.51 (m, 1H), 4.99 (dd, *J* = 26.9, 13.6 Hz, 2H), 2.87 (dd, *J* = 14.5, 5.2 Hz, 1H), 2.62 (dd, *J* = 14.4, 6.8 Hz, 1H), 2.58 (dd, *J* = 13.9, 6.6 Hz, 1H), 2.39 (dd, *J* = 13.8, 7.9 Hz, 1H), 1.38 (s, 3H); **^{13}C NMR** (175 MHz, CD_3OD) δ 166.6, 153.3, 147.3, 135.6, 134.0, 133.1, 129.6, 129.4, 128.6, 127.5, 127.2, 118.2,

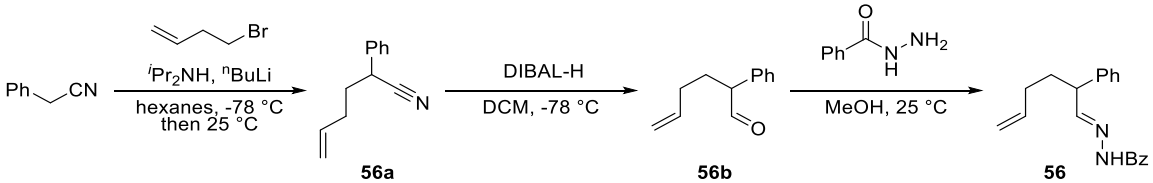
48.8, 45.8, 41.6, 24.9; **IR** (Neat): 3228, 3062, 2974, 1645, 1603, 1579, 1562, 1496, 1450, 1420, 1358, 1288, 1189, 1075, 1043, 1028, 998, 916, 797, 766, 698, 677; **HRMS** (ESI+): calcd for $C_{20}H_{22}N_2ONa^+$ $[M+Na]^+$: 329.1624, found: 329.1625.



55

(1-methylcyclopent-3-en-1-yl)benzene (55): This compound was not isolated in neat form due to volatility. The peak visible in the ^{1}H-NMR spectrum at δ 5.25 ppm was assigned as ethylene. **^{1}H NMR** (700 MHz, C_6D_6) δ 7.19 (d, *J* = 4.0 Hz, 4H), 7.10 – 7.05 (m, 1H), 5.63 (s, 2H), 2.70 (d, *J* = 14.4 Hz, 2H), 2.36 – 2.30 (m, 2H), 1.30 (s, 4H); **^{13}C NMR** (175 MHz, C_6D_6) δ 151.7, 129.5, 128.6, 126.3, 125.7, 47.9, 46.3, 31.5; **IR** (Neat): 3057, 3026, 2960, 2846, 1600, 1580, 1495, 1445, 1262, 1089, 1069, 1030, 980, 901, 764, 751, 698, 672; **HRMS** (EI+): *m/z* calculated for $C_{12}H_{14}$ $[M]^+$: 158.1096; found: 158.1099.

3 step sequence for the synthesis of substrate 56



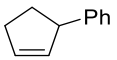
56a **56b** **56**

2-phenylhex-5-enenitrile (56a): This compound was prepared using a modification of a literature method.[42] To a solution of diisopropylamine (4.83 mL, 34.5 mmol, 1.75 equiv.) in THF (25 mL, 0.75 M) was added n-butyllithium (15.0 mL, 37.4 mmol, 1.85 equiv., 2.5 M in hexanes) at −78 °C. The resulting solution was stirred for 30 min at −78 °C and immediately used. To a solution of freshly prepared LDA (34.5 mmol, 1.75 equiv,), was added benzyl cyanide (3.41 mL, 29.6 mmol) followed by 4-bromo-1-butene (2.00 mL, 19.7 mmol, 1.0 equiv.). After stirring for 2 h at −78 °C, the reaction was allowed to warm to 25 °C and stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl solution (30 mL) and the resulting mixture extracted with DCM (3 x 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.234 g (36%) of **56a** as a colorless oil. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature reported values.[43] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 5.8 Hz, 3H), 5.82 – 5.74 (m, 1H), 5.09 (dd, *J* = 23.5, 13.7 Hz, 2H), 3.80 (t, *J* = 7.3 Hz, 1H), 2.25 (d, *J* = 6.8 Hz, 2H), 2.05 (dq, *J* = 15.4, 7.8 Hz, 1H), 1.95 (dq, *J* = 14.3, 7.2 Hz, 1H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 136.2, 135.9, 129.3, 128.3, 127.5, 120.8, 116.8, 36.7, 35.1, 31.1.

2-phenylhex-5-enal (56b): This compound was prepared using a modification to the method of Widenhoefer et al.[44] A flame dried 250 mL round-bottom flask containing a Teflon coated stir bar was charged with **56a** (678 mg, 3.96 mmol), followed by 40.0 mL anhydrous Et_2O (0.10 M). After cooling the solution to –78 °C, DIBAL-H (4.75 mL, 4.75 mmol, 1.0 M in hexanes) was added slowly over 2 h by syringe pump. After stirring for 4 h at –78 °C, the flask was transferred to an ice bath and allowed to warm to 0 °C. The mixture was diluted with Et_2O (25 mL), then water (0.03 mL) was added dropwise, followed by the sequential addition of aq. 15 wt% NaOH solution (0.03 mL) and water (0.06 mL) with 5 min between each addition. The mixture was allowed to warm to 25 °C and stirred for 15 min. Anhydrous $MgSO_4$ was added, and the mixture stirred for an additional 15 min. Solids were filtered off through a Celite plug, the plug washed with Et_2O (300 mL) and DCM (200 mL), and the filtrate put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 431.8 mg (62%) of **54b** as a viscous pale-yellow oil which was carried forward immediately to the next step. The ^{1}H-NMR spectral data was consistent with literature reported values.[45] This material contained ~20% of diallylated aldehyde as an impurity which was removed in the next step. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.8 Hz, 1H), 7.42 – 7.27 (m, 3H), 7.23 – 7.16 (m, 2H), 5.77 (ddt, *J* = 18.2, 9.6, 6.6 Hz, 1H), 5.05 – 4.96 (m, 2H), 3.55 (ddd, *J* = 8.3, 6.2, 1.8 Hz, 1H), 2.26 – 2.12 (m, 1H), 2.12 – 1.93 (m, 2H), 1.89 – 1.76 (m, 1H).

(E)-N'-(3-methyl-3-phenylhex-5-en-1-ylidene)benzohydrazide (56): This compound was prepared by a modification of general procedure A (**GP-A**): **56b** (65 mg, 0.32 mmol, 1.00 equiv.) and benzoyl

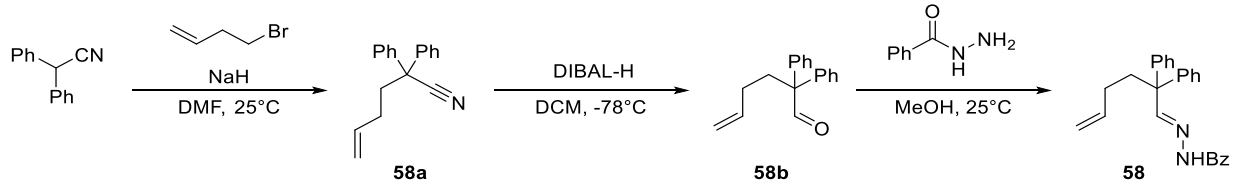
hydrazide (66.6 mg, 0.49 mmol, 1.50 equiv.) in MeOH (5.20 mL, 0.50 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 233.1 mg (30%) of **56** (68.6:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (700 MHz, CD_3OD) δ 7.87 – 7.84 (m, 2H), 7.76 (d, *J* = 6.9 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 5.84 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 1H), 5.00 (dd, *J* = 17.3, 1.9 Hz, 1H), 4.97 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.65 (q, *J* = 7.2 Hz, 1H), 2.11 – 2.01 (m, 3H), 1.98 – 1.90 (m, 1H); **^{13}C NMR** (175 MHz, CD_3OD) δ 166.8, 156.8, 141.9, 139.1, 134.1, 133.2, 129.9, 129.7, 129.0, 128.7, 128.1, 115.6, 49.5, 33.7, 32.3; **IR** (Neat): 3194, 3029, 2925, 1646, 1619, 1603, 1558, 149, 1451, 1361, 1292, 1183, 1152, 1076, 1056, 976, 953, 906, 878, 799, 765, 697, 676; **HRMS** (ESI+): calcd for $C_{19}H_{21}N_2O^+$ $[M+H]^+$: 293.1648, found: 293.1642.



57

cyclopent-2-en-1-ylbenzene (57): Colorless oil. The ^{1}H-NMR spectral data in $CDCl_3$ is consistent with literature data.[45] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.17 (m, 3H), 5.97 – 5.93 (m, 1H), 5.81 – 5.77 (m, 1H), 3.92 – 3.88 (m, 1H), 2.54 – 2.48 (m, 1H), 2.45 – 2.38 (m, 2H), 1.77 – 1.70 (m, 1H); **^{1}H NMR** (700 MHz, C_6D_6) ^{1}H NMR (700 MHz, C_6D_6) δ 7.18 (t, *J* = 7.6 Hz, 5H), 7.13 (d, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 5.78 (dd, *J* = 5.5, 2.5 Hz, 1H), 5.72 (dd, *J* = 5.4, 2.1 Hz, 1H), 3.78 – 3.73 (m, 1H), 2.33 – 2.27 (m, 1H), 2.25 – 2.16 (m, 2H), 1.70 – 1.64 (m, 1H).

3 step sequence for the synthesis of substrate 58



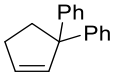
58a **58b** **58**

2,2-diphenylhex-5-enenitrile (58a): This compound was prepared using a modification of a literature method.[44] Sodium hydride (303 mg, 7.58 mmol, 60% in mineral oil) was added to a flame dried 50 mL round-bottom flask containing a Teflon coated stir bar followed by 7.5 mL DMF (0.69 M in total). The flask was cooled to 0 °C with an ice bath. Then, diphenylacetonitrile (1.0057 g, 3.49 mmol) was added in 2 portions to the reaction as H_2 gas formed. After stirring at 0 °C for 3 h, the reaction was warmed to 25 °C for 1 h. Then, the reaction was cooled to 0 °C and 4-bromo-1-butene (0.58 mL, 5.71 mmol) was added dropwise over 10 min while stirring and the reaction allowed to warm to 25 °C. After stirring for 12 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (20 mL) and EtOAc (30 mL) and partitioned. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (3 x 20 mL), sat. aq. NaCl solution (20 mL), dried with anhydrous $MgSO_4$, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.1499 g (89%) of **58a** as a viscous pale-yellow oil. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature reported values.[44] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 4H), 7.36 (t, *J* = 7.6 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 2H), 5.81 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.00 (dd, *J* = 10.5, 1.8 Hz, 1H), 2.49 – 2.44 (m, 2H), 2.21 – 2.15 (m, 2H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 140.2, 136.8, 129.1, 128.1, 127.0, 122.4, 115.8, 51.6, 39.0, 30.0.

2,2-diphenylhex-5-enal (58b): This compound was prepared using the method of Widenhoefer et al.[44] A flame dried 250 mL round-bottom flask containing a Teflon coated stir bar was charged with **58a** (1.00 g, 4.04 mmol), followed by 168.0 mL anhydrous hexanes (0.02 M in total). After cooling the solution to –78 °C, DIBAL-H (16.0 mL, 16.0 mmol, 1.0 M in hexanes) was added slowly over 1 h by syringe pump. After stirring for 1.5 h at –78 °C, the mixture was quenched by slow addition of EtOAc (16 mL). The resulting suspension was stirred for 30 min at –78 °C, treated with an aqueous suspension of silica gel in water [5% w/w, 25 mL], allowed to stand for 30 min, and then warmed slowly to room temperature. The resulting mixture was filtered through a plug of Celite, which was eluted with

Et_2O (100 mL). The resulting solution was washed with water (100 mL), 1.0 M aq. HCl solution (2 × 100 mL), sat. aq. $NaHCO_3$ solution (100 mL), and brine (100 mL), dried over anhydrous $MgSO_4$ and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 651.8 mg (64%) of **58b** as a viscous pale-yellow oil which was carried forward immediately to the next step. The ^{1}H-NMR spectral data was consistent with literature reported values.[44] This material contained a small amount of **58a** as an impurity which was removed in the next step. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.37 (t, *J* = 7.5 Hz, 4H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 4H), 5.79 (ddt, *J* = 16.9, 10.5, 6.6 Hz, 1H), 5.02 – 4.91 (m, 2H), 2.41 – 2.34 (m, 2H), 1.80 (q, *J* = 7.4 Hz, 2H).

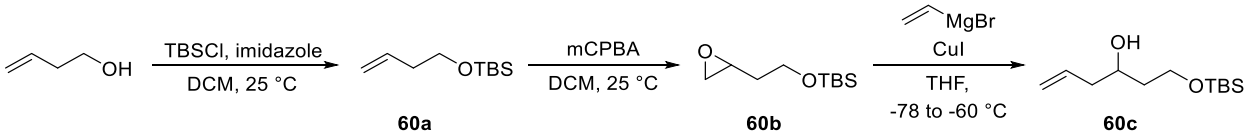
(E)-N'-(2,2-diphenylhex-5-en-1-ylidene)benzohydrazide (58): This compound was prepared by a modification of general procedure A (**GP-A**): **58b** (360.9 mg, 1.44 mmol, 1.29 equiv.) and benzoyl hydrazide (151.6 mg, 1.11 mmol, 1.00 equiv.) in MeOH (3.70 mL, 0.30 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 231 mg (56%) of **58** (>20:1 mixture of *E:Z* isomers in DMSO-d_6) as a white solid. **^{1}H NMR** (700 MHz; DMSO-d_6) δ 11.54 (s, 1H), 8.25 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 4H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 4H), 5.83 (ddt, *J* = 16.9, 11.3, 6.5 Hz, 1H), 4.94 (dd, *J* = 37.7, 13.7 Hz, 2H), 2.49 – 2.44 (m, 2H), 1.82 (t, *J* = 7.7 Hz, 2H); **^{13}C NMR** (175 MHz, DMSO-d_6) δ 162.8, 155.5, 144.5, 138.7, 133.4, 131.6, 128.4, 128.4, 128.1, 127.5, 126.6, 114.5, 54.1, 35.1, 29.0; **IR** (Neat): 3232, 2979, 2932, 1725, 1646, 1564, 1369, 1143, 1121, 971, 844, 751, 692; **HRMS**(ESI+): calcd for $C_{25}H_{25}N_2O^+$ $[M+H]^+$: 369.1961, found: 369.1959.



59

cyclopent-2-ene-1,1-diyldibenzene (59): Colorless oil. The ^{1}H-NMR spectral data in $CDCl_3$ was consistent with literature data.[46,47] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 4H), 7.22 (d, *J* = 7.0 Hz, 4H), 7.18 (t, *J* = 7.2 Hz, 2H), 6.18 (dt, *J* = 5.7, 2.0 Hz, 1H), 5.93 (dt, *J* = 5.9, 2.3 Hz, 1H), 2.56 (t, *J* = 6.2 Hz, 2H), 2.52 – 2.49 (m, 2H); **^{1}H NMR** (400 MHz, C_6D_6) δ 7.25 (d, *J* = 7.0 Hz, 4H), 7.19 (t, *J* = 7.5 Hz, 4H), 7.09 (t, *J* = 7.1 Hz, 2H), 6.21 – 6.07 (m, 1H), 5.82 – 5.71 (m, 1H), 2.48 (t, *J* = 6.8 Hz, 2H), 2.33 – 2.28 (m, 2H).

Synthesis of common intermediate 60c for substrates 60, 62, 64, and 66



60a **60b** **60c**

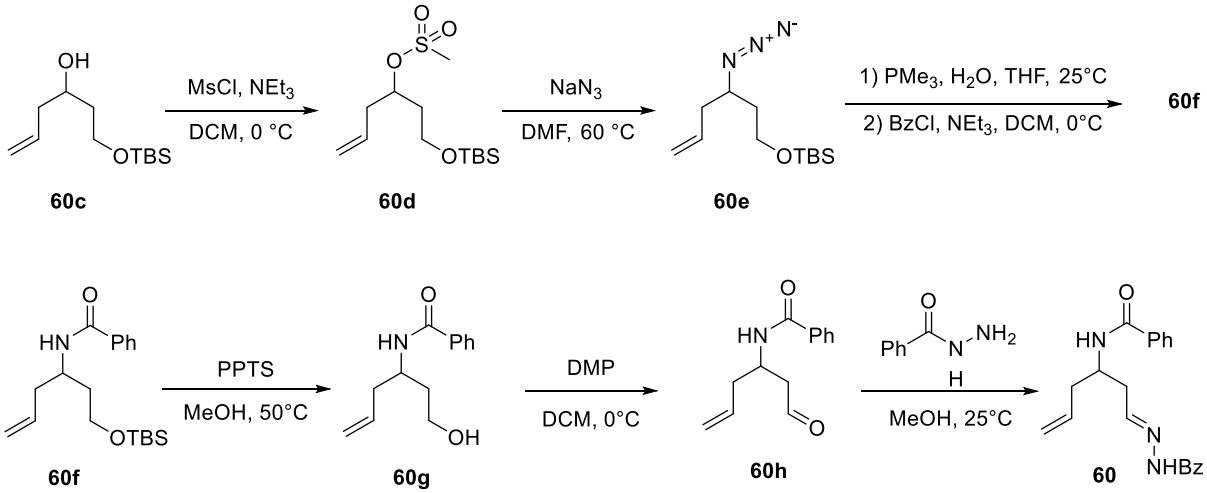
(but-3-en-1-yloxy)(tert-butyl)dimethylsilane (60a): This compound was synthesized according to a literature method.[48] A flame-dried 250 mL round bottom flask equipped with a PTFE-coated stir bar was charged with but-3-en-1-ol (8.39 g, 10.00 mL, 116 mmol, 1.00 equiv.) followed by anhydrous DCM (130 mL) and flushed with dry nitrogen for 5 min. Then, imidazole (8.7131 g, 128.0 mmol, 1.10 equiv.) and tert-butyldimethylchlorosilane (19.3350 g, 128.28 mmol, 1.10 equiv) were sequentially added to the stirred mixture and the mixture stirred for 16 h (white suspension with complete consumption of 3-buten-1-ol by TLC). The white suspension was poured into sat. aq. NH_4Cl solution (80 mL) and partitioned. The organic layer was further washed with sat. aq. NH_4Cl solution (80 mL) and sat. aq. NaCl solution (30 mL), dried over anhydrous Na_2SO_4, filtered and put under reduced pressure to yield a cloudy liquid. The crude residue was transferred into a 100-mL round-bottomed flask and distilled using a short-path distillation apparatus under vacuum (0.06 mm Hg) with a heating block temperature of 30 °C. The fractions distilling at 30 °C (pre-pump trap and fractions 1-2) were combined and collected to afford 20.226 g (93%) of **60a** as a clear oil. The ^{1}H and ^{13}C-NMR spectral data in $CDCl_3$ were consistent with literature data.[48] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 2.28 (qt, *J* = 6.8, 1.3 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.6, 116.4, 63.0, 37.6, 26.1, 18.5, -5.1.

tert-butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (60b): This compound was synthesized according to a literature method.[48] A flame-dried 500 mL round bottom flask equipped with a PTFE-coated stir bar was charged with **60a** (20.0796 g, 107.74 mmol, 1.00 equiv.) followed by anhydrous DCM (158 mL)

and placed under a nitrogen atmosphere. Then, 3-chloroperbenzoic acid (75%, 29.747 g, 129.29 mmol, 1.20 equiv.) was added portion wise to the stirred solution and the mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered through a pad of Celite 545 to remove the white precipitate and the pad washed with an additional portion of DCM (300 mL). The filtrate was washed with a 1:1 mixture of sat. aq. $NaHCO_3$ and Na_2SO_3 (2 × 150 mL). The organic layer was separated, dried (Na_2SO_4), filtered and put under reduced pressure to remove the solvent. The crude residue was purified by flash column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 18.2061 g (83%) of **60b** as a colorless oil. The ^1H and ^{13}C-NMR spectral data in $CDCl_3$ were consistent with literature data.[48] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.83 – 3.73 (m, 2H), 3.04 (dtd, *J* = 6.6, 4.6, 2.7 Hz, 1H), 2.78 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.51 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.83 – 1.73 (m, 1H), 1.69 (dq, *J* = 14.1, 5.7 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 60.2, 50.2, 47.3, 36.0, 26.0, 18.4, -5.3, -5.3.

1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-ol (60c): This compound was prepared by modification of a literature method.[49] A flame-dried 3-neck 250 mL round bottom flask equipped with a PTFE-coated stir bar was charged with cuprous iodide (188 mg, 988 µmol, 0.10 equiv.) in a nitrogen glovebox. The flask was transferred out of the glovebox and heated lightly with a heat gun under high vacuum and then cooled to 25 °C. Then, anhydrous THF (20.00 mL) was added, and the light brown suspension cooled to -78 °C under nitrogen. To the suspension was added vinyl magnesium bromide (2.59 g, 28.2 mL, 0.7 M in THF from Acros Organics, 19.8 mmol, 2.00 equiv.) dropwise over 1 h with a 50 mL addition funnel. The orange-brown suspension was stirred at -78 °C for 10 min. Then, a solution of **60b** (2.00 g, 9.88 mmol, 1.00 equiv.) in anhydrous THF (14.00 mL) was added dropwise over 1 h with a 25 mL addition funnel. After addition of the epoxide, the yellow suspension was allowed to warm up to -60 °C over 3 h (**60b** was consumed by TLC in 10% EtOAc in hexanes). The reaction was slowly quenched at -40 °C with the dropwise addition of sat. aq. NH_4Cl solution (25 mL) followed by deionized H_2O (8 ml). The cooling bath was removed, and the mixture was stirred for 15 min. Then, 25 wt% aq, NH_4OH solution (6 mL) was added, and the brown suspension stirred for an additional 10 min. The layers were separated, the blue aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and put under reduced pressure to give a crude yellow oil (2.3350 g). The crude reaction mixture was purified by flash column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.2283 g (54%) of **60c** as a pale-yellow oil. After running this reaction several times, we discovered the presence of small amounts of Mg-hydride impurities in commercially available MeMgBr solutions led to inferior results (polymerization). The ^1H and ^{13}C-NMR spectral data in $CDCl_3$ were consistent with literature data.[48] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.15 – 5.06 (m, 2H), 3.90 (dt, *J* = 10.1, 4.9 Hz, 2H), 3.81 (ddd, *J* = 10.2, 7.3, 5.6 Hz, 1H), 3.35 (d, *J* = 2.3 Hz, 1H), 2.32 – 2.19 (m, 2H), 1.67 (td, *J* = 7.6, 7.0, 4.8 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.2, 117.4, 71.5, 62.8, 42.1, 37.9, 26.0, 18.3, -5.4, -5.4.

7 step sequence for the synthesis of amide backbone substrate 60 from 60c



1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl methanesulfonate (60d): This compound was prepared using a modification of a literature method.[50] A flame-dried 50 mL round bottom flask was charged with **60c** (1.0016 g, 4.3468 mmol, 1.00 equiv.) followed by anhydrous DCM (13.00 mL)(freshly N_2-sparged). Then, triethylamine (659.79 mg, 909 µL, 6.5203 mmol, 1.50 equiv.) was added followed

by methanesulfonyl chloride (547.68 mg, 370 µL, 4.7815 mmol, 1.10 equiv.) at 0 °C. The reaction was stirred at 0 °C for 1.5 h and allowed to warm to 25 °C over 30 min. When TLC analysis showed completion of the reaction, the reaction was diluted with DCM (20 mL), washed with deionized H_2O (2 x 10 mL) and sat. aq. NaCl solution (2 x 10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and put under reduced pressure to give a crude yellow oil (1.679 g). The crude residue was purified by flash column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.243 g (92%) of **60d** as a pale-yellow oil. A portion of mesylate **60d** was immediately used in the next step but remained stable at 0 °C for 3 months. **^{1}H NMR** (500 MHz, C_6D_6) δ 5.72 – 5.57 (m, 1H), 5.00 – 4.93 (m, 2H), 4.90 (dtd, *J* = 7.9, 5.9, 4.6 Hz, 1H), 3.56 (ddd, *J* = 10.5, 8.0, 5.1 Hz, 1H), 3.50 (dt, *J* = 10.5, 5.4 Hz, 1H), 2.36 – 2.23 (m, 5H), 1.73 – 1.58 (m, 2H), 0.94 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).; **^{13}C NMR** (125 MHz, C_6D_6) δ 133.0, 118.7, 79.0, 58.9, 39.7, 37.9, 37.3, 26.1, 18.4, -5.3, -5.3.; **IR** (Neat): 2955, 2930, 2886, 2858, 1644, 1473, 1417, 1389, 1356, 1255, 1174, 1091, 1005, 973, 904, 834, 811, 775, 711, 682, 662; **HRMS** (ESI+): calcd for $C_{13}H_{29}O_4SSi^+$ $[M+H]^+$: 309.155, found: 309.1538.

((3-azidohex-5-en-1-yl)oxy)(tert-butyl)dimethylsilane (60e): This compound was prepared using a modification of a literature method.[50] A flame-dried 50 mL round bottom flask was charged with **60d** (569.3 mg, 1.845 mmol, 1.00 equiv.) followed by anhydrous DMF (6.30 mL) and placed under a nitrogen atmosphere. Then, sodium azide (367 mg, 5.65 mmol, 3.06 equiv.) was added in one portion at room temperature and the mixture heated to 60 °C for 1.5 h. The reaction was cooled to 25 °C, quenched with deionized H_2O (20 mL), and extracted with Et_2O (5 x 25 mL). The combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried over anhydrous $MgSO_4$, filtered, and put under reduced pressure to give a crude pale-yellow oily residue (509.5 mg). The crude residue was purified by flash column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 400 mg (85%) of **60e** as a pale-yellow oil. The presence of an azide in this compound was confirmed by the strong diagnostic IR absorptions at 2099 and 1255 cm^{-1} respectively which are also in accordance with literature for other alkyl azides.[51] The $[M+H–N_2]^+$ molecular ion was observed by HRMS (ESI+) which has previous precedent in the literature.[50] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.21 – 5.10 (m, 2H), 3.77 – 3.67 (m, 2H), 3.63 – 3.55 (m, 1H), 2.40 – 2.27 (m, 2H), 1.75 (dddd, *J* = 14.3, 8.1, 6.4, 4.3 Hz, 1H), 1.62 (ddt, *J* = 14.0, 9.4, 4.8 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).; **^{1}H NMR** (500 MHz, C_6D_6) δ 5.64 (ddt, *J* = 17.2, 10.3, 7.1 Hz, 1H), 5.03 – 4.95 (m, 2H), 3.59 (ddd, *J* = 10.1, 8.7, 4.7 Hz, 1H), 3.48 (ddd, *J* = 10.3, 5.7, 4.6 Hz, 1H), 3.46 – 3.40 (m, 1H), 2.11 – 1.96 (m, 2H), 1.51 (dddd, *J* = 14.2, 8.6, 5.7, 4.1 Hz, 1H), 1.38 (ddt, *J* = 14.0, 9.3, 4.7 Hz, 1H), 0.96 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).; **^{13}C NMR** (125 MHz, C_6D_6) δ 134.2, 118.1, 59.7, 59.1, 39.2, 37.1, 26.1, 18.5, -5.3, -5.4.; **IR** (Neat): 3082, 2955, 2930, 2858, 2099 (N≡N asymmetric), 1644, 1472, 1464, 1438, 1388, 1362, 1344, 1255 (N≡N symmetric), 1091, 1006, 994, 960, 939, 918, 832, 812, 775, 733, 664.; **HRMS** (ESI+): calcd for $C_{12}H_{26}NOSi^+$ $[M+H\text{-}N_2]^+$: 228.1778, found: 228.1775.

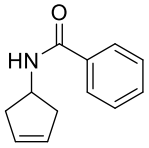
***N*-(1-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)benzamide (60f)**: This compound was prepared using a modification of a literature method.[52] A flame dried 25 mL round bottom flask equipped with a PTFE-coated stir bar and septa was charged with **60e** (101 mg, 0.395 mmol, 1.0 equiv.) followed by anhydrous THF (5.00 mL) and deionized H_2O (71.3 µL, 3.95 mmol, 10 equiv.) and the reaction was allowed to equilibrate in an ice bath for five minutes. After cooling, trimethylphosphine (1.0 M in THF, 0.79 mL, 0.79 mmol, 2.00 equiv.) was added via syringe. The reaction extruded nitrogen (as indicated via the septa popping off) and complete consumption of **60e** was observed by TLC. The reaction solvent, excess phosphine, and phosphine oxide were removed via a gentle N_2 stream, and the amine was used without further purification. Anhydrous DCM (3.00 mL) and triethylamine (0.53 mL, 3.8 mmol, 4.00 equiv.) were added to the crude amine and the reaction mixture was cooled to 0 °C in an ice bath. After cooling for 10 minutes, benzoyl chloride (0.12 mL, 1.0 mmol, 1.10 equiv.) was added via syringe and the reaction was allowed to slowly warm to room temperature. Reaction progress was monitored via TLC, upon completion, MeOH (0.20 mL) and DMAP (3.0 mg) were added to quench the excess benzoyl chloride. After 15 minutes of stirring, water (5 mL) was added, and the layers were separated. The aqueous phase was further extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed with sat. aq. NaCl solution (5 mL), dried over anhydrous $MgSO_4$, and put under reduced pressure to remove the solvent. The crude product was further purified via flash column chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 79 mg (60 % over 2 steps) of **60f** as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.0 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.43 – 7.36 (m, 2H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.91 – 5.76 (m, 1H), 5.14 – 5.04 (m, 2H), 4.30 (dtd, *J* = 13.6, 7.2, 4.5 Hz, 1H), 3.88 (ddd, *J* = 10.5, 8.5, 4.4 Hz, 1H), 3.76 (dt, *J* = 10.5, 5.3 Hz, 1H), 2.50 (dt, *J* = 12.7, 6.4 Hz, 1H),

2.38 (dt, *J* = 13.8, 7.4 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.81 – 1.71 (m, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.1, 135.2, 134.8, 131.3, 128.5, 127.0, 117.8, 60.9, 48.2, 38.6, 35.3, 26.1, 18.5, -5.3.: **IR** (Neat): 3301, 3075, 2953, 2929, 2285, 2857, 1634, 1579, 1536, 1490, 1360, 1308, 1234, 1094, 883, 774, 693, 664.; **HRMS** (ESI+): calcd for $C_{19}H_{31}NO_2SiNa^+$ $[M+Na]^+$: 356.2017, found: 356.2011

***N*-(1-hydroxyhex-5-en-3-yl)benzamide (60g):** A flame-dried 25 mL round bottom equipped with a rubber septum and a PTFE-coated stir bar was charged with **60f** (75 mg, 0.22 mmol, 1.00 equiv.) was charged to a 25 mL round bottom flask equipped with a rubber septum and Teflon-coated stir bar. Then, MeOH (5.00 mL) was added, and the reaction was allowed to stir at room temperature for 10 minutes. Then, pyridinium p-toluenesulfonate (85 mg, 0.34 mmol, 1.50 equiv.) was added and the reaction was heated to 50 °C. After complete consumption of **60f** by TLC, the reaction mixture was concentrated and then diluted with water (5 mL) and DCM (5 mL). The layers were separated, and aqueous phase was further extracted with DCM (2 x 5 mL). The combined organic layers were washed with sat.aq. NaCl solution (10 mL), dried over anhydrous $MgSO_4$, and put under reduced pressure to remove the solvent. The crude product was further purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 45 mg (93%) of the deprotected alcohol **60g** as a clear oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.0 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.15 (d, *J* = 7.7 Hz, 1H), 5.87 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.33 – 5.10 (m, 2H), 4.44 (d, *J* = 18.5 Hz, 1H), 3.83 – 3.55 (m, 2H), 2.43 (qt, *J* = 14.2, 6.7 Hz, 2H), 1.98 (ddt, *J* = 14.4, 8.5, 4.6 Hz, 1H), 1.49 (dd, *J* = 14.0, 11.0 Hz, 1H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.5, 134.1, 134.0, 131.8, 128.7, 126.9, 118.7, 58.7, 45.9, 39.5, 37.9.; **IR** (Neat): 3285, 3073, 2947, 2924, 2260, 1635, 1604, 1579, 1533, 1488, 1353, 1313, 1272, 1048, 917, 801, 697, 668.; **HRMS** (ESI+): calcd for $C_{13}H_{17}NO_2Na^+$ $[M+Na]^+$: 242.1152, found: 242.1151.

***N*-(1-oxohex-5-en-3-yl)benzamide (60h):** A flame dried 50 mL round bottom flask equipped with a rubber septum and Teflon-coated stir bar was charged with alcohol **60g** (140 mg, 0.64 mmol, 1.00 equiv.) under a nitrogen atmosphere. Then, anhydrous DCM (5.00 mL) was added, and the reaction was cooled to 0 °C in an ice bath. After 15 minutes of cooling, Dess-Martin periodiane[53] (379 mg, 0.89 mmol, 1.40 equiv.) was added and the reaction was allowed to warm to room temperature and reaction progress was monitored by TLC. Upon completion, the reaction was concentrated under reduced pressure and purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 134 mg (96%) of aldehyde **60h**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.72 (d, *J* = 7.0 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.80 (ddt, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.16 (d, *J* = 6.1 Hz, 1H), 5.14 (s, 1H), 4.59 (h, *J* = 7.4, 6.9 Hz, 1H), 2.90 – 2.73 (m, 2H), 2.58 – 2.36 (m, 2H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.1, 167.0, 134.3, 133.8, 131.6, 128.6, 126.9, 118.8, 47.3, 45.0, 38.6.; **IR** (Neat): 3302, 3067, 2977, 2920, 2838, 1721, 1635, 1604, 1579, 1531, 1489, 1351, 1314, 1297, 1149, 1075, 994, 919, 710, 693, 670.; **HRMS** (ESI+): calcd for $C_{13}H_{15}NO_2Na^+$ $[M+Na]^+$: 240.0995, found: 240.0995.

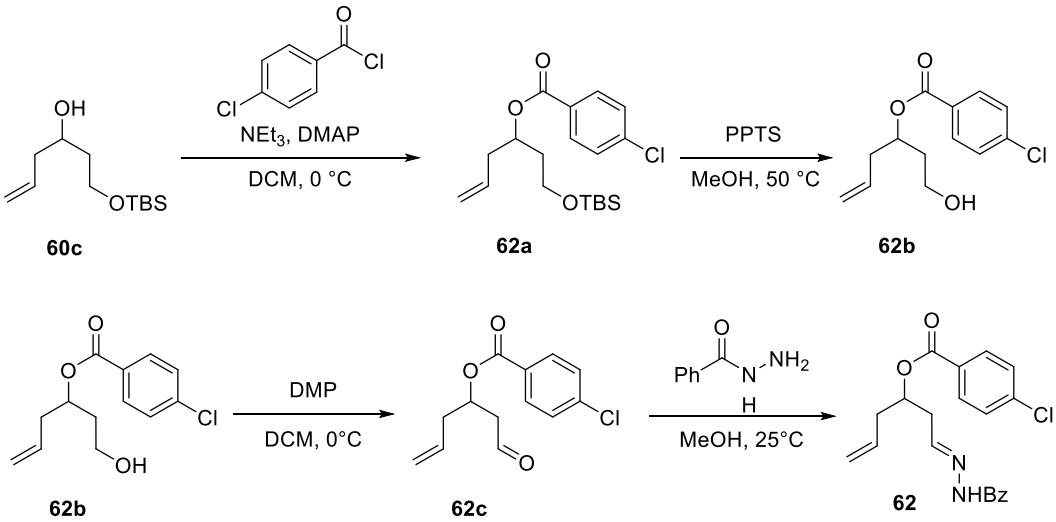
(*E*)-*N*-(1-(2-benzoylhydrazineylidene)hex-5-en-3-yl)benzamide (60): This compound was prepared by a modification of general procedure A (**GP-A**): Aldehyde **60h** (120 mg, 0.55 mmol, 1.00 equiv.) and benzoyl hydrazide (75 mg, 0.55 mmol, 1.00 equiv.) in MeOH (3.00 mL, 0.20 M). Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 72 mg (39 %) of **60** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.83 (d, *J* = 6.9 Hz, 2H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.71 (t, *J* = 5.8 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.40 (m, 5H), 5.88 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.16 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.47 – 4.35 (m, 1H), 2.71 (dt, *J* = 14.5, 4.9 Hz, 1H), 2.59 (ddd, *J* = 14.4, 9.6, 6.5 Hz, 1H), 2.51 – 2.40 (m, 2H).; **^{13}C NMR** (125 MHz, CD_3OD) δ 170.4, 166.9, 152.1, 135.9, 135.9, 134.1, 133.2, 132.6, 129.7, 129.5, 128.6, 128.3, 118.2, 48.5, 40.2, 38.8.; **IR** (Neat): 3302, 3067, 2977, 2920, 2838, 1721, 1635, 1604, 1579, 1531, 1489, 1351, 1314, 1297, 1149, 1075, 994, 919, 710, 693, 670.; **HRMS** (ESI+): calcd for $C_{20}H_{21}N_3O_2Na^+$ $[M+Na]^+$: 358.1526, found: 358.1529.



61

***N*-(cyclopent-3-en-1-yl)benzamide (61):** The ^{1}H-NMR spectral data in DMSO-d_6 was consistent with literature data.[54] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (600 MHz, C_6D_6) 7.62 (d, *J* = 6.9 Hz, 2H), 7.12 – 7.08 (m, 1H), 7.03 (t, *J* = 7.7 Hz, 2H), 5.73 (s, 1H), 5.47 (s, 2H), 4.80 (qt, *J* = 7.9, 4.2 Hz, 1H), 2.57 (dd, *J* = 15.1, 7.9 Hz, 2H), 2.00 (dd, *J* = 14.9, 4.2 Hz, 2H).

4 step sequence for the synthesis of para-chlorobenzoyl ester substrate 62 from 60c



60c **62a** **62b** **62b** **62c** **62**

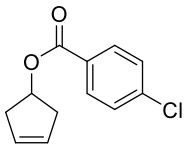
1-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl 4-chlorobenzoate (62a): An oven-dried 25mL flask equipped with a rubber septum and a Teflon-coated stir bar was charged with **60c** (800 mg, 3.47 mmol, 1.00 equiv.) under nitrogen. Then, anhydrous DCM (10.00 mL), triethylamine (0.73 mL, 5.21 mmol, 1.50 equiv.), and DMAP (106 mg, 0.87 mmol, 0.25 equiv.) were added and the reaction was cooled to 0 °C. Then, 4-chlorobenzoyl chloride (0.53 mL, 4.4 mmol, 1.10 equiv.) was added. After 2 h of stirring at 0 °C, **60c** was completely consumed by TLC and the reaction was quenched by the addition of water (5 mL). The aqueous phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and put under reduced pressure to remove the solvent. Purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 950 mg (74%) of **62a** as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 5.81 (ddt, *J* = 17.3, 10.2, 7.1 Hz, 1H), 5.28 (p, *J* = 6.1 Hz, 1H), 5.16 – 4.99 (m, 2H), 3.70 (td, *J* = 6.2, 1.9 Hz, 2H), 2.48 (q, *J* = 7.1 Hz, 2H), 2.02 – 1.82 (m, 2H), 0.87 (s, 9H), 0.00 (s, 6H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.3, 139.4, 133.5, 131.1, 129.3, 128.8, 118.2, 71.9, 59.6, 39.0, 36.8, 26.0, 18.4, -5.3, -5.3.; **IR** (Neat): 2955, 2929, 2857, 1720, 1643, 1594, 1488, 1463, 1269, 1153, 1090, 1015, 843, 811, 775, 758.; **HRMS** (APCI+): calcd for $C_{19}H_{30}ClO_3Si^+$ $[M+H]^+$: 369.1647, found: 369.1649.

1-hydroxyhex-5-en-3-yl 4-chlorobenzoate (62b): A 25 mL round bottom flask equipped with a rubber septum and Teflon-coated stir bar was charged with **62a** (100 mg, 0.27 mmol, 1.0 equiv.) followed by MeOH (3.00 mL) and the reaction was allowed to stir at room temperature for 10 minutes. Then, pyridinium p-toluenesulfonate (85 mg, 0.34 mmol, 1.25 equiv.) was added and the reaction was heated to 50 °C. Upon completion (SM consumed by TLC), the reaction mixture was concentrated and then diluted with water (5 mL) and DCM (3 mL). The layers were separated, and aqueous phase was further extracted with DCM (2 x 5 mL). The combined organics were washed with sat. aq. NaCl, dried over anhydrous $MgSO_4$, and put under reduced pressure to remove the solvent. The crude product was further purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 64 mg (93%) of **62b** as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 5.81 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.33 (dtd, *J* = 9.7, 6.2, 3.4 Hz, 1H), 5.13 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.08 (dd, *J* = 10.2, 1.7 Hz, 1H), 3.69 (ddd, *J* = 11.5, 5.9, 4.3 Hz, 1H), 3.60 (ddd, *J* = 11.5, 9.3, 4.5 Hz, 1H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.29 (s, 1H), 1.96 (dddd, *J* = 15.0, 9.4, 6.0, 3.5 Hz, 1H), 1.84 (ddt, *J* =

14.2, 9.1, 4.4 Hz, 1H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 139.7, 133.3, 131.2, 128.9, 128.6, 118.4, 71.7, 58.7, 39.2, 37.1.; **IR** (Neat): 3419, 3078, 2955, 2887, 1715, 1643, 1594, 1488, 1463, 1269, 1172, 1116, 1015, 849, 811, 758.; **HRMS** (APCI+): calcd for $C_{13}H_{16}ClO_3^+$ $[M+H]^+$: 255.0782, found: 255.0787.

1-oxohex-5-en-3-yl 4-chlorobenzoate (62c): A flame-dried 50 mL round bottom flask equipped with a rubber septum and Teflon stir bar was charged with **62b** (100 mg, 0.39 mmol, 1.0 equiv.) under nitrogen atmosphere. Then, anhydrous DCM (5 mL) was added, and the reaction was cooled to 0 °C in an ice bath. After 15 minutes of cooling, Dess-Martin periodiane[53] (250 mg, 0.59 mmol, 1.50 equiv.) was added and the reaction was allowed to warm to room temperature and reaction progress was monitored by TLC. Upon completion, the reaction was concentrated under reduced pressure and purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 70 mg (71%) of aldehyde **62c** as a colorless oil. We were unable to obtain a HRMS for this compound due to difficulty ionizing under ESI, APCI, and EI conditions. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 5.87 – 5.75 (m, 1H), 5.61 (pd, *J* = 6.2, 1.2 Hz, 1H), 5.20 – 5.12 (m, 2H), 2.90 – 2.75 (m, 2H), 2.55 (dtd, *J* = 6.9, 4.1, 3.3, 1.4 Hz, 2H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.1, 165.1, 139.8, 132.4, 131.2, 128.9, 128.5, 119.4, 69.3, 47.5, 38.7.; **IR** (Neat): 3078, 2980, 2914, 2837, 1720, 1643, 1594, 1488, 1270, 1115, 1092, 1015, 851, 760.

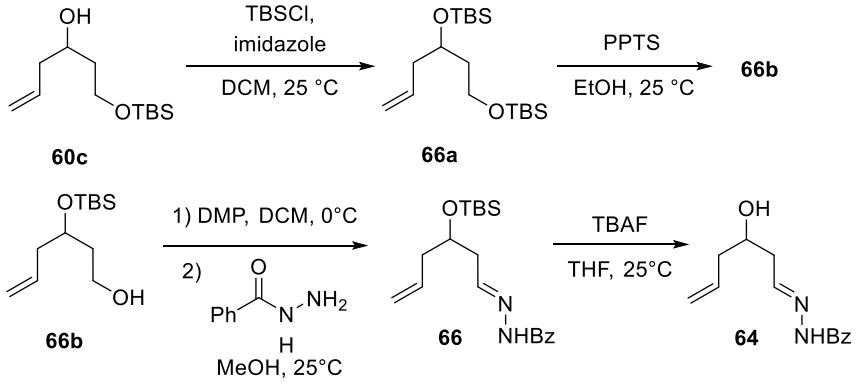
(*E*)-1-(2-benzoylhydrazineylidene)hex-5-en-3-yl 4-chlorobenzoate (62): This compound was prepared by a modification of general procedure A (**GP-A**): Aldehyde **62c** (200 mg, 0.79 mmol, 1.0 equiv.) and benzoyl hydrazide (162 mg, 1.2 mmol, 1.50 equiv.) in MeOH (4.00 mL, 0.20 M) purification by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 151 mg (51 %) of **62** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (500 MHz, CD_3OD) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.76 (t, *J* = 5.8 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.50 – 7.42 (m, 4H), 5.88 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.39 (p, *J* = 6.3 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.3 Hz, 1H), 2.79 (td, *J* = 6.7, 6.0, 3.3 Hz, 2H), 2.56 (t, *J* = 6.7 Hz, 2H).; **^{13}C NMR** (125 MHz, CD_3OD) δ δ 166.7, 166.5, 150.9, 140.6, 134.3, 134.0, 133.2, 132.2, 130.1, 129.9, 129.7, 128.6, 119.0, 73.3, 39.6, 38.1.; **IR** (Neat): 3326, 3066, 3037, 2980, 2847, 1718, 1650, 1593, 1578, 1268, 1114, 1092, 1015, 759.; **HRMS** (ESI+): calcd for $C_{20}H_{19}ClN_2O_3Na^+$ $[M+Na]^+$: 393.0977, found: 393.0975.



63

cyclopent-3-en-1-yl benzoate (63): White solid. **^{1}H NMR** (500 MHz, C_6D_6) δ 7.80 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 5.53 – 5.42 (m, 3H), 2.51 (dd, *J* = 16.9, 7.0 Hz, 2H), 2.42 – 2.28 (m, 2H).; **^{13}C NMR** (125 MHz, C_6D_6) δ 165.3, 139.2, 131.3, 129.7, 128.8, 128.5, 75.1, 40.0. **IR** (Neat): 3069, 3037, 2968, 2920, 2850, 1705, 1690, 1619, 1590, 1478, 1400, 1297, 1272, 1086, 1011, 853, 759, 684.; **HRMS** (EI+): calcd for $C_{12}H_{11}ClO_2^{\cdot+}$ $[M]^{\cdot+}$: 222.0442, found: 222.0452.

4 step sequence for the synthesis of free alcohol and TBS protected substrates 64 and 66 from 60c



5-allyl-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (66a): A flame-dried 50 mL round bottom flask containing a Teflon-coated stir bar was charged with **60c** (325 mg, 1.41 mmol, 1.00

equiv.) followed by anhydrous DCM (5.00 mL), imidazole (192 mg, 2.82 mmol, 2.00 equiv.), and tert-butyldimethylchlorosilane (319 mg, 2.12 mmol, 1.50 equiv.). This reaction was stirred at room temperature until **60c** was completely consumed by TLC. Upon completion, water (5.00 mL) was added, the reaction mixture was transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted with DCM (2 x 10 mL). The combined organics were washed with sat. aq. NaCl solution, dried over anhydrous $MgSO_4$, and put under reduced pressure. The crude product was further purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 393 mg (81%) of the protected alcohol **66a** as a colorless oil. The ^{1}H spectral data was consistent with literature.[55] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.4, 10.7, 7.2 Hz, 1H), 5.15 – 4.90 (m, 2H), 3.87 (p, *J* = 5.8 Hz, 1H), 3.66 (td, *J* = 6.7, 2.4 Hz, 2H), 2.30 – 2.14 (m, 2H), 1.71 – 1.58 (m, 2H), 0.88 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H).

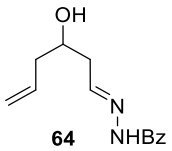
3-((*tert*-butyldimethylsilyl)oxy)hex-5-en-1-ol (66b): A flame-dried 50 mL round bottom equipped with a Teflon-coated stir bar and charged with **66a** (700 mg, 2.03 mmol, 1.00 equiv.) by the addition of ethanol (10 mL) and pyridinium p-toluenesulfonate (510 mg, 2.03 mmol, 1.00 equiv.). The reaction mixture was stirred at room temperature until **66a** was completely consumed by TLC. The reaction mixture was concentrated, and DCM (5 mL) and water (5 mL) were added to the crude reaction mixture. The reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with DCM (2 x 10 mL). The combined organic layers were washed with sat. aq. NaCl solution (10 mL), dried over anhydrous $MgSO_4$, and put under reduced pressure to remove the solvent. The crude product was further purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 245 mg (52%) of **66b** as a colorless oil. The ^{1}H spectral data was consistent with literature.[56] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.5, 10.4, 7.2 Hz, 1H), 5.15 – 4.96 (m, 2H), 3.97 (qd, *J* = 6.4, 4.0 Hz, 1H), 3.83 (ddd, *J* = 10.8, 8.1, 4.4 Hz, 1H), 3.72 (ddd, *J* = 10.8, 5.9, 5.0 Hz, 1H), 2.40 – 2.20 (m, 2H), 1.88 – 1.75 (m, 1H), 1.67 (dddd, *J* = 14.3, 6.8, 5.9, 4.4 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

(*E*)-*N*'-(3-((*tert*-butyldimethylsilyl)oxy)hex-5-en-1-ylidene)benzohydrazide (66): A flame-dried 50 mL round bottom flask equipped with a rubber septum and Teflon-coated stir bar was charged with **66b** (110 mg, 0.48 mmol, 1.00 equiv.) under a nitrogen atmosphere. Then, anhydrous DCM (4.00 mL) was added, and the reaction was cooled to 0 °C in an ice bath. After 15 minutes of cooling, Dess-Martin periodiane[53] (263 mg, 0.62 mmol, 1.30 equiv.) was added and the reaction was allowed to warm to room temperature and reaction progress was monitored by TLC. Upon completion, the reaction was concentrated under reduced pressure and purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient). Due to concerns with volatility, the eluent compound mixture was put under reduced pressure to give the aldehyde in ~2 mL EtOAc/hexane which was used directly in the next step.

The solution of aldehyde from the previous step (200 mg, 0.79 mmol, 1.00 equiv.) in EtOAc/hexane was diluted in MeOH (2.00 mL, 0.20 M) and benzoyl hydrazide (162 mg, 1.20 mmol, 1.50 equiv.) was added. Upon consumption of the aldehyde by TLC analysis, the reaction was concentrated under reduced pressure and purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) provided 120 mg (73%) of **66** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a white solid. **^{1}H NMR** (600 MHz, CD_3OD) δ 7.85 (d, *J* = 7.1 Hz, 2H), 7.76 (t, *J* = 5.9 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 5.87 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.21 – 4.98 (m, 2H), 4.08 (p, *J* = 5.9 Hz, 1H), 2.63 – 2.42 (m, 2H), 2.42 – 2.20 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** (125 MHz, CD_3OD) δ 165.4, 151.4, 134.3, 132.8, 131.7, 128.3, 127.2, 116.6, 70.3, 41.8, 39.4, 24.9, 17.5, -5.7, -5.9. **IR** (Neat): 3195, 3065, 2927, 2885, 1649, 1604, 1562, 1494, 1361, 1293, 1251, 1111, 1076, 1002, 938, 835, 713, 674. **HRMS** (ESI+): calcd for $C_{19}H_{30}N_2O_2SiNa^+$ $[M+Na]^+$: 369.1974, found: 369.1971.

67

***tert*-butyl(cyclopent-3-en-1-yloxy)dimethylsilane (67):** Colorless oil. The ^{1}H-NMR spectral data in $CDCl_3$ was consistent with literature data.[57] The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (500 MHz, C_6D_6) δ 5.57 (s, 2H), 4.41 (tt, *J* = 7.1, 3.8 Hz, 1H), 2.44 (dd, *J* = 15.3, 6.9 Hz, 2H), 2.33 (dd, *J* = 15.2, 3.9 Hz, 2H), 0.96 (s, 9H), 0.05 (s, 6H).



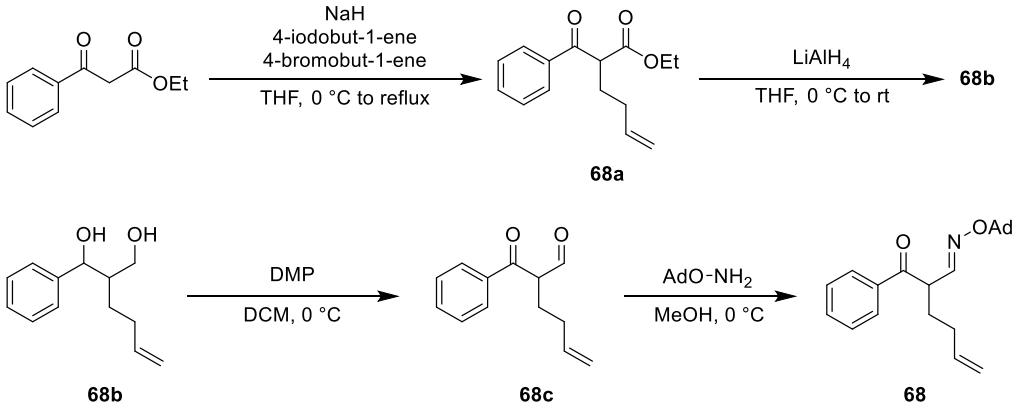
64

(*E*)-*N*'-(3-hydroxyhex-5-en-1-ylidene)benzohydrazide (64): A flame-dried 50 mL round bottom flask equipped with a rubber septum and Teflon-coated stir bar was charged with the protected alcohol **66** (120 mg, 0.35 mmol, 1.00 equiv.) under a nitrogen atmosphere. The reaction was cooled to 0 °C in an ice bath and a 1.0 M solution of TBAF in THF (0.70 mL, 0.70 mmol, 2.00 equiv.) was added and the reaction was allowed to warm to room temperature and reaction progress was monitored by TLC. Upon completion, the reaction mixture was concentrated, and DCM (5.00 mL) and water (5.00 mL) were added to the crude reaction mixture. The reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with sat. aq. NaCl, dried over anhydrous $MgSO_4$, and put under reduced pressure to remove the solvent. The crude product was further purified via flash chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 32 mg (40%) of deprotected alcohol **64** (>20:1 mixture of *E:Z* isomers in CD_3OD) as a yellowish oil. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.77 (t, *J* = 5.6 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 5.90 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.20 – 5.02 (m, 2H), 3.93 (p, *J* = 6.2 Hz, 1H), 2.57 (dt, *J* = 15.1, 4.9 Hz, 1H), 2.46 (ddd, *J* = 14.6, 8.1, 5.7 Hz, 1H), 2.31 (t, *J* = 6.7 Hz, 2H). **^{13}C NMR** (125 MHz, CD_3OD) δ 166.8, 153.0, 135.9, 134.2, 133.2, 129.7, 128.7, 117.8, 70.2, 42.9, 40.6.; **IR** (Neat): 3420, 3197, 3067, 2923, 2853, 1648, 1628, 1539, 1447, 1366, 1302, 1286, 1179, 1074, 1026, 905, 870, 835, 794, 690, 674. **HRMS** (ESI+): calcd for $C_{13}H_{16}N_2O_2Na^+$ $[M+Na]^+$: 255.1104, found: 255.1106.

65

cyclopent-3-en-1-ol (65): An authentic sample of cyclopent-3-en-1-ol **65** was obtained from Oakwood Chemical Company (Product number: 011611) and characterized by ^{1}H-NMR for use as a product standard. The ^{1}H-NMR spectral data in C_6D_6 has not previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.52 (s, 2H), 4.19 (td, J = 6.4, 5.1, 3.1 Hz, 1H), 2.35 (dd, J = 16.1, 6.5 Hz, 2H), 2.21 – 2.05 (m, 2H), 1.12 (s, 1H).; **^{1}H NMR** (500 MHz, C_6D_6) δ 5.52 (s, 2H), 4.19 (td, J = 6.4, 5.1, 3.1 Hz, 1H), 2.35 (dd, J = 16.1, 6.5 Hz, 2H), 2.21 – 2.05 (m, 2H), 1.12 (s, 1H).

4 step sequence for synthesis of 68



ethyl 2-benzoylhex-5-enoate (68a): This compound was prepared using a modification of a literature method.[58] Sodium hydride (1.95 g, 48.7 mmol, 1.10 equiv., 60 wt% dispersion in mineral oil) was added to a flame dried 500 mL flask with a stir bar and fitted with a rubber septum under nitrogen. Anhydrous THF (100 mL) was added, and the reaction was cooled to 0 °C in an ice bath. Then, a solution of ethyl 3-oxo-3-phenylpropanoate (8.52 g, 44.3 mmol, 1.00 equiv.) in anhydrous THF (50 mL) was added dropwise over 30 minutes. The reaction was then warmed to room temperature for 30 minutes. It was then returned to the ice bath for 15 minutes after which a solution of 4-iodobut-1-ene

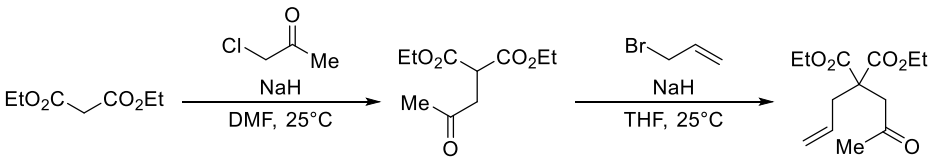
(8.87 g, 48.8 mmol, 1.10 equiv.) in anhydrous THF (50 mL) was added dropwise over 30 minutes. The reaction was removed from the ice bath and refluxed for 48 hours. Due to the sluggish nature of the reaction, additional sodium hydride (0.887 g, 22.2 mmol, 0.50 equiv.) and 4-bromobutene (2.99 g, 22.2 mmol, 0.50 equiv.) were added and the reaction was heated for 24 hours. The reaction was cooled to 0 °C and quenched with aq. sat. NH_4Cl solution (75 mL). The biphasic mixture was separated, and the aqueous layer was extracted with DCM (3 x 75 mL). The combined organic layers were washed with aq. sat. NaCl (50 mL), dried with anhydrous Na_2SO_4, and concentrated. The crude reaction mixture (inseparable mixture of mono and poly alkylation) was carried to the next step without further purification.

2-(but-3-en-1-yl)-1-phenylpropane-1,3-diol (68b): This compound was prepared by application of a literature method for reduction of alkylated β-keto-esters.[59] A flame-dried 250 mL round bottom flask equipped with a Teflon-coated stir bar was charged with lithium aluminum hydride (1.29 g, 34.1 mmol, 2.1 equiv.), placed under a nitrogen atmosphere, and then anhydrous THF (50 mL) was added. The gray suspension was cooled to -78 °C and then a solution of crude **68a** (4.00 g, 16.2 mmol, 1.00 equiv.) in anhydrous THF (6.20 mL) was added dropwise over 5 min with a vent needle. After addition was complete, the stirred reaction was sealed under N_2 with electrical tape and was allowed to warm up to room temperature overnight (10 h). After 10 h, a small amount of SM was present by TLC. The reaction was cooled to 0 °C (ice/water bath), and additional lithium aluminum hydride (616 mg, 16.2 mmol, 1.00 equiv.) was added and the reaction was stirred at 0 °C for 1 hour and then warmed to 25 °C over 0.5 hour (complete consumption of SM by TLC). The reaction was cooled to 0 °C and quenched by the successive dropwise addition of water (1.90 mL), 15 wt% aq. NaOH solution (1.90 mL), and water (5.70 mL). The suspension was warmed to RT and stirred for 30 min. Anhydrous $MgSO_4$ was added, and the mixture was stirred an additional 15 min. Solids were filtered off through a Celite plug (2.0 cm, 100 mL capacity, medium porosity frit), the plug washed with DCM (300 mL), and the filtrate concentrated in vacuo (35 °C, 60 mbar) to afford the corresponding crude diol as a yellow oil. Flash column chromatography (SiO_2/EtOAc–Hexanes gradient) provided an inseparable mixture of presumed diastereomers that were used in the next step of the reaction. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.33 – 7.25 (m, 1H), 5.70 (ddtd, *J* = 16.9, 10.2, 6.6, 1.8 Hz, 1H), 5.03 (d, *J* = 3.9 Hz, 0.7H), 5.00 – 4.88 (m, 2H), 4.75 (d, *J* = 6.8 Hz, 0.4H), 3.84 (dd, *J* = 11.0, 2.7 Hz, 0.4H), 3.76 (d, *J* = 4.9 Hz, 1.3H), 3.68 (dd, *J* = 11.1, 6.1 Hz, 0.4H), 2.41 (s, 2H), 2.10 (ddddd, *J* = 15.0, 8.8, 7.6, 4.0, 1.6 Hz, 1H), 2.04 – 1.91 (m, 1.7H), 1.90 – 1.83 (m, 0.4H), 1.49 – 1.34 (m, 2H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.5, 142.6, 138.6, 138.4, 128.6, 128.4, 127.9, 127.5, 126.5, 126.3, 115.1, 114.9, 79.0, 77.3, 64.3, 64.2, 45.9, 45.7, 31.6, 31.4, 27.4, 24.1.

2-benzoylhex-5-enal (68c): This compound was prepared by application of a literature method.[60] Diol **69b** (825 mg, 4.00 mmol, 1.00 equiv.) was added to a flame dried 250 mL round bottom flask with stir bar under nitrogen followed by anhydrous DCM (25 mL). The reaction was cooled to 0° C in an ice bath. After cooling for 15 minutes, Dess-Martin periodinane[53] (4.24 g, 10.0 mmol, 2.5 equiv.) was added and the reaction was warmed to room temperature. Once the reaction was complete by TLC analysis, the mixture was concentrated. Flash column chromatography (SiO_2/EtOAc–Hexanes gradient provided 625 mg (77%) of aldehyde **68c** as a mixture of the presumed enol-ether. This compound rapidly decomposes and should be used immediately.

(*E*)-2-benzoylhex-5-enal *O*-((3*s*,5*s*,7*s*)-adamantan-1-yl) oxime (68): Aldehyde **68c** (209 mg, 1.04 mmol, 1.15 equiv.) was charged to a 50 mL round bottom flask with stir bar, dissolved in methanol (10 mL), and cooled to 0 °C. After cooling, a solution of O-(adamantan-1-yl) hydroxylamine (151 mg, 0.900 mmol, 1.00 equiv.) in methanol (3.00 mL) was added dropwise over 5 minutes. After 45 minutes, the reaction was concentrated and purified via column chromatography (SiO_2/EtOAc–Hexanes gradient) to provide 261 mg (83%) of **68** (15:1 mixture of *E:Z* isomers in C_6D_6) as an tan solid. **^{1}H NMR** (500 MHz, C_6D_6) δ 7.98 (d, *J* = 6.9 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.12 – 6.96 (m, 3H), 5.63 (ddt, *J* = 16.9, 10.1, 6.4 Hz, 1H), 5.02 – 4.91 (m, 2H), 4.30 – 4.20 (m, 1H), 2.04 – 1.90 (m, 12H), 1.72 – 1.63 (m, 1H), 1.54 – 1.46 (s, 6H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.8, 148.1, 137.8, 137.0, 133.0, 129.0, 128.7, 115.8, 47.9, 42.0, 36.7, 31.4, 31.0, 29.7.; **IR** (Neat) 2907, 2850, 1673, 1641, 1448, 1349, 1300, 1286, 1111, 972, 956, 927 896, 801.; **HRMS**: calcd for $C_{23}H_{30}NO_2^+$ $[M+H]^+$: 352.2272 found: 352.2273.

Procedures for Substrate and Product synthesis for RuCOM Control experiments

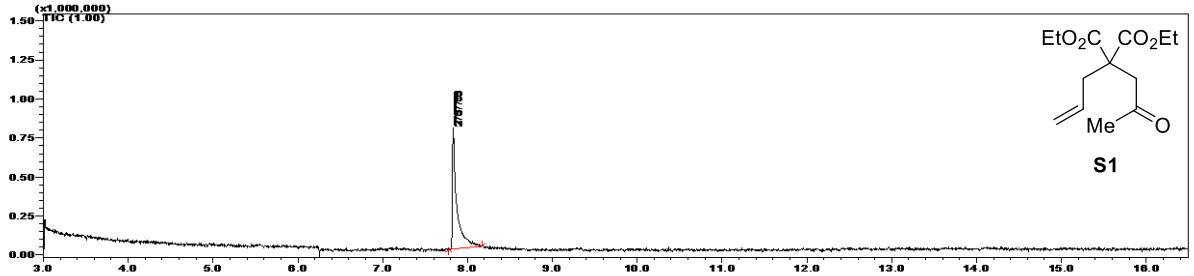


S1a **S1**

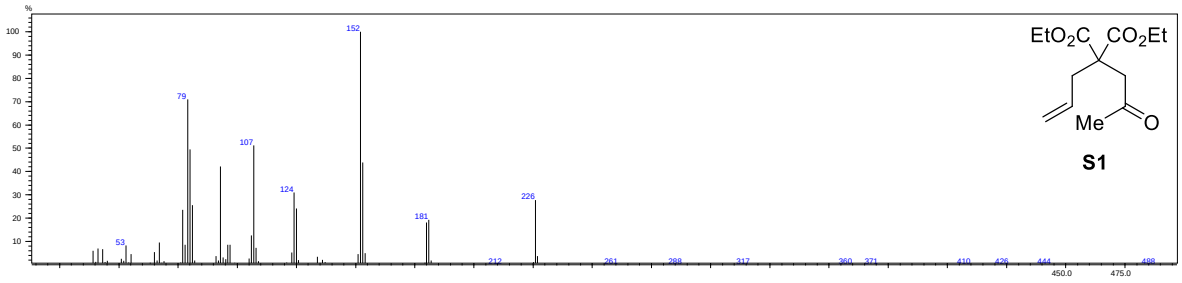
diethyl acetonyl malonate (S1a): Sodium hydride (722 mg, 18.03 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 100 mL round-bottom flask containing a Teflon coated stir bar followed by 25.0 mL DMF (0.55 M). The flask was cooled to 0 °C with an ice bath and diethylmalonate (2.50 mL, 16.39 mmol) was added dropwise to the reaction as H_2 gas formed. After stirring at 0 °C for 30 min, chloroacetone (2.00 mL, 24.86 mmol) was added and the reaction was allowed to warm to 25 °C. Then the reaction was heated to 50 °C for 23 h. After 23 h, the reaction was cooled to 25 °C, quenched with sat. aq. NH_4Cl solution (40 mL), diluted with deionized water (20 mL) and EtOAc (50 mL) and partitioned. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with aq. 5 wt% LiCl solution (3 x 20 mL), with deionized water (2 x 20 mL), sat. aq. NaCl solution (30 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 1.6404 g (46%) of **S1a** as a colorless oil. The ^{1}H-NMR spectral data were consistent with literature reported values.[61] **^{1}H NMR** (500 MHz; $CDCl_3$) δ 4.26 – 4.13 (m, 4H), 3.85 (t, *J* = 7.1 Hz, 1H), 3.05 (d, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H).

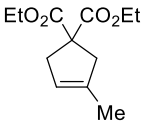
diethyl 2-allyl-2-(2-oxopropyl)malonate (S1): Sodium hydride (26.8 mg, 0.70 mmol, 60 wt% dispersion in mineral oil) was added to a flame dried 25 mL round-bottom flask containing a Teflon coated stir bar followed by 1.80 mL anhydrous THF (0.124 M in total). The flask was cooled to 0 °C with an ice bath and a solution of **S1a** (108.9 mg, 0.50 mmol) in THF (2.20 mL) was added dropwise to the reaction as H_2 gas formed. After stirring at 0 °C for 30 min, allyl bromide (0.60 mL, 0.69 mmol) was added, and the reaction was allowed to warm to 25 °C. After 16 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (5 mL) and EtOAc (15 mL) and partitioned. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with sat. aq. NaCl solution (30 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 84.7 mg (65%) of **S1** as a colorless oil. The ^{1}H-NMR spectral data in $CDCl_3$ was consistent with literature reported values.[62] **^{1}H NMR** (400 MHz; toluene-d_8) δ 5.79 – 5.63 (m, 1H), 5.00 – 4.91 (m, 2H), 3.99 (q, *J* = 7.1 Hz, 4H), 3.02 – 2.96 (m, 4H), 1.65 (s, 3H), 0.97 (t, *J* = 7.1 Hz, 6H); **^{1}H NMR** (400 MHz; C_6D_6) δ 5.75 (ddt, *J* = 17.6, 10.2, 7.5 Hz, 1H), 5.01 – 4.92 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 4H), 3.11 – 3.07 (m, 4H), 1.62 (s, 3H), 0.94 (t, *J* = 7.1 Hz, 6H); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 5.71 – 5.58 (m, 1H), 5.11 – 5.02 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.10 (s, 2H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); **GC-MS** (EI) m/z: M+ = 256.1305 calculated for $C_{13}H_{20}O_5^{\cdot+}$; found 255.90.

GC-MS trace of Product **S1**:



Mass Spectrum of product peak (7.830 min):

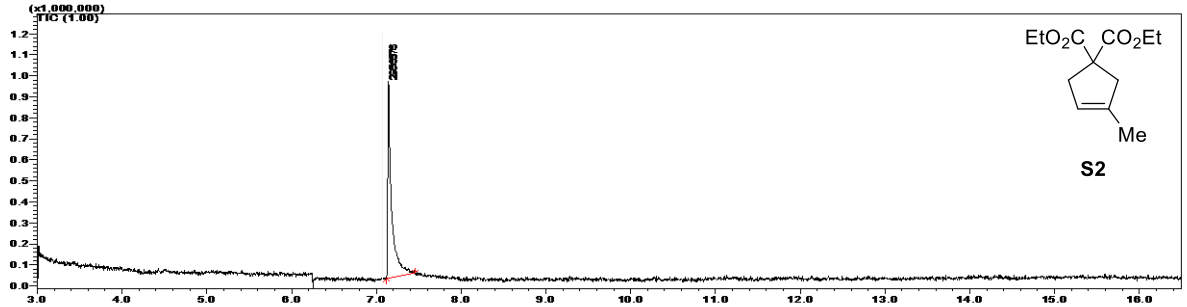




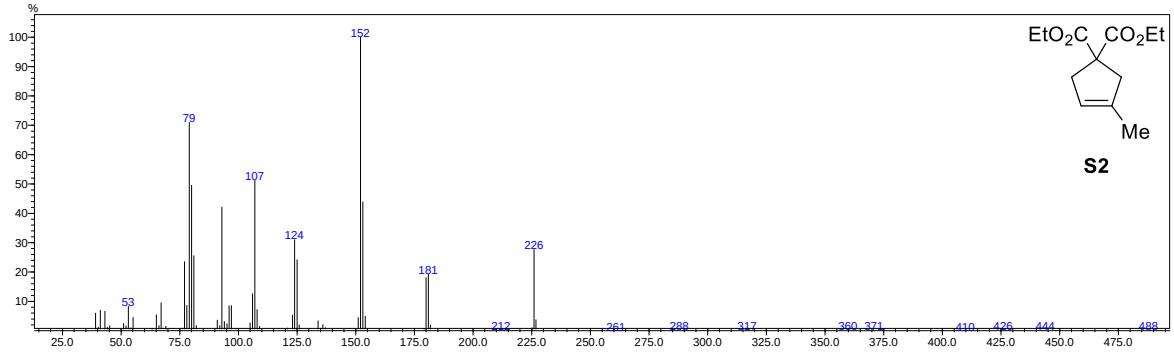
S2

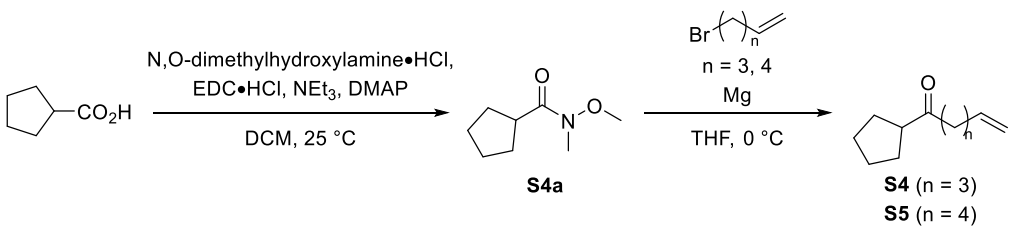
diethyl 3-methylcyclopent-3-ene-1,1-dicarboxylate (S2): Colorless oil. The ^{1}H NMR spectra data in $CDCl_3$ was consistent with literature data.[11] The ^{1}H-NMR spectral data in C_6D_6 and toluene-d_8 have not previously been fully reported. **^{1}H NMR** (400 MHz, toluene-d_8) δ 5.11 – 4.97 (m, 1H), 3.95 (q, *J* = 7.1 Hz, 4H), 3.16 – 3.11 (m, 2H), 3.03 (s, 2H), 1.53 – 1.49 (m, 3H), 0.94 (t, *J* = 7.1 Hz, 6H); **^{1}H NMR** (700 MHz, C_6D_6) δ 5.06 (s, 1H), 3.97 (q, *J* = 6.9 Hz, 4H), 3.22 (s, 2H), 3.10 (s, 2H), 1.49 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 6H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.18 (h, *J* = 1.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 2.96 (hept, *J* = 2.3 Hz, 2H), 2.90 (s, 2H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H); **GC-MS** (EI) m/z: M+ = 226.1043 calculated for $C_{12}H_{16}O_4^{\cdot+}$; found 225.95.

GC-MS trace of Product **S2**:



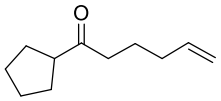
Mass Spectrum of product peak (7.144 min):





N-methoxy-N-methylcyclopentanecarboxamide (S4a): A flame dried 250 mL round-bottom flask containing a Teflon-coated stir bar was charged with cyclopentanecarboxylic acid (2.20 mL,

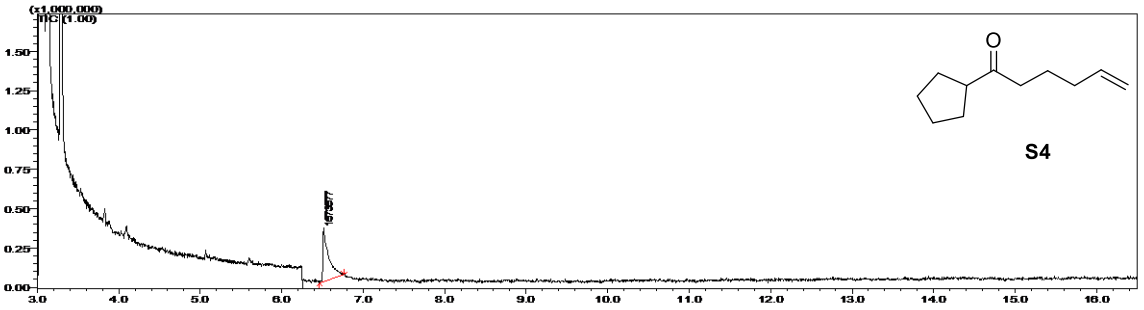
20.1 mmol), followed by 70.0 mL of anhydrous DCM (0.285 M) at 25 °C. To this solution was successively added N,O-dimethylhydroxylamine hydrochloride (2.352 g, 24.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.622 g, 24.1 mmol, EDC·HCl), 4-dimethylaminopyridine (244 mg, 9.95 mol%, DMAP), and freshly distilled triethylamine (7.00 mL, 50.2 mmol). The resulting mixture was stirred at 25 °C overnight (16 h). Upon completion, the reaction mixture was quenched with water (50 mL) and extracted with DCM (4 × 80 mL). The combined organic layers were washed with 1.0 M aq. HCl solution (40 mL), sat. aq. $NaHCO_3$ solution (40 mL), sat. aq. NaCl solution (30 mL), dried over Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 2.1417 g (67%) of **S4a** as a pale-yellow oil. The ^{1}H-NMR and ^{13}C-NMR spectral data were consistent with literature reported values.[63] **^{1}H NMR** (700 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.14 (s, 3H), 3.06 (s, 1H), 1.84 – 1.77 (m, 2H), 1.77 – 1.67 (m, 4H), 1.58 – 1.49 (m, 2H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 178.0, 61.4, 40.2, 32.3, 30.2, 26.2.



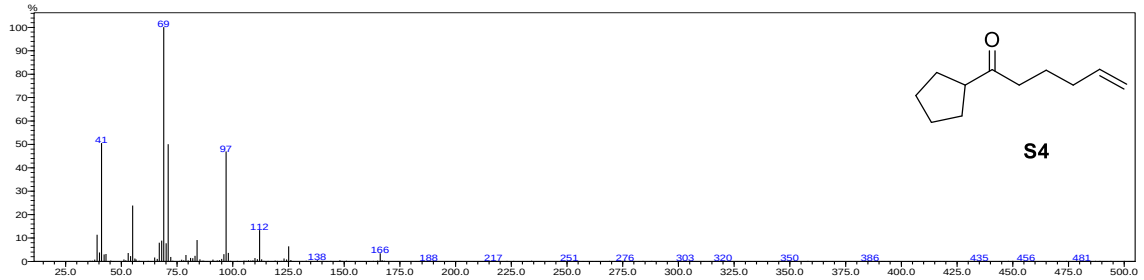
S4

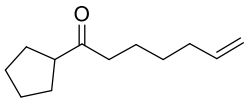
1-cyclopentylhex-5-en-1-one (S4): This compound was prepared using a modification of a literature method.[64] A flame dried 50 mL round-bottom flask containing a Teflon-coated stir bar was charged with magnesium turnings (234 mg, 9.63 mmol), followed by 10.50 mL of anhydrous THF and a small crystal of iodine (~3 mg) under nitrogen. Then, neat 5-bromo-1-pentene (1.20 mL, 10.13 mmol) was slowly added dropwise to the stirred reaction mixture while monitoring for the loss of iodine color (yellow). Once the reaction has started, as evidenced by the disappearance of iodine color, the resulting solution was stirred for 30 min at 25 °C until the magnesium dissolved. A flame dried 50 mL round-bottom flask containing a Teflon-coated stir bar was charged with Weinreb amide **S4a** (500 mg, 3.18 mmol), followed by 10.5 mL of anhydrous THF under nitrogen and was cooled to 0 °C with an ice bath. The freshly generated Grignard reagent from the previous step was added dropwise over 15 min and the reaction was allowed to stir for 2 h (complete consumption of starting material by TLC). The reaction was quenched by the dropwise addition of sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (5 mL) and EtOAc (25 mL), and partitioned. The aqueous layer was extracted with EtOAc (4 x 25 mL). The combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 427 mg (80%) of **S4** as a colorless oil. **^{1}H NMR** (400 MHz, toluene-d_8) δ 5.79 – 5.56 (m, 1H), 5.10 – 4.86 (m, 2H), 2.42 (p, J = 7.8 Hz, 1H), 2.05 (t, J = 7.2 Hz, 2H), 1.91 (q, J = 7.1 Hz, 2H), 1.72 – 1.56 (m, 4H), 1.56 – 1.45 (m, 4H), 1.42 – 1.34 (m, 2H); **^{1}H NMR** (700 MHz, C_6D_6) δ 5.68 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 4.98 (dd, J = 21.3, 13.9 Hz, 2H), 2.42 (p, J = 7.7 Hz, 1H), 2.06 (t, J = 7.2 Hz, 2H), 1.92 (q, J = 7.2 Hz, 2H), 1.73 – 1.60 (m, 4H), 1.56 – 1.48 (m, 4H), 1.38 – 1.32 (m, 2H). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.77 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (dq, J = 17.1, 1.7 Hz, 1H), 4.96 (dt, J = 10.1, 1.6 Hz, 1H), 2.85 (p, J = 8.1 Hz, 1H), 2.45 (t, J = 7.3 Hz, 2H), 2.05 (q, J = 7.1 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.74 – 1.61 (m, 6H), 1.60 – 1.52 (m, 2H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 213.4, 138.3, 115.2, 51.6, 41.0, 33.3, 29.1, 26.1, 23.0; **IR** (Neat): 3078, 2951, 2870, 1708, 1641, 1504, 1450, 1410, 1368, 1313, 1123, 993, 910, 850, 797, 743, 671; **HRMS** (GCMS-APCI+): calcd for $C_{11}H_{19}O^+$ $[M+H]^+$: 167.1430, found: 167.1438. **GC-MS** (EI) m/z: M+ = 166.1352 calculated for $C_{11}H_{18}O$; Found 166.1.

GC-MS trace of **S4**:



Mass Spectrum of product peak (6.515 min):



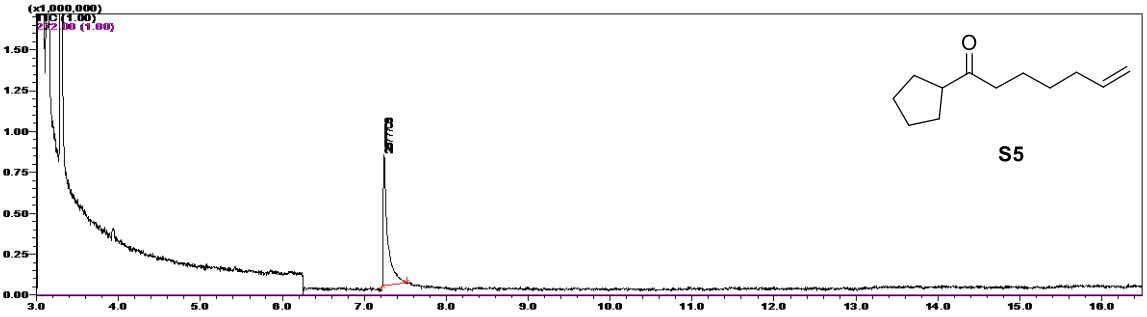


S5

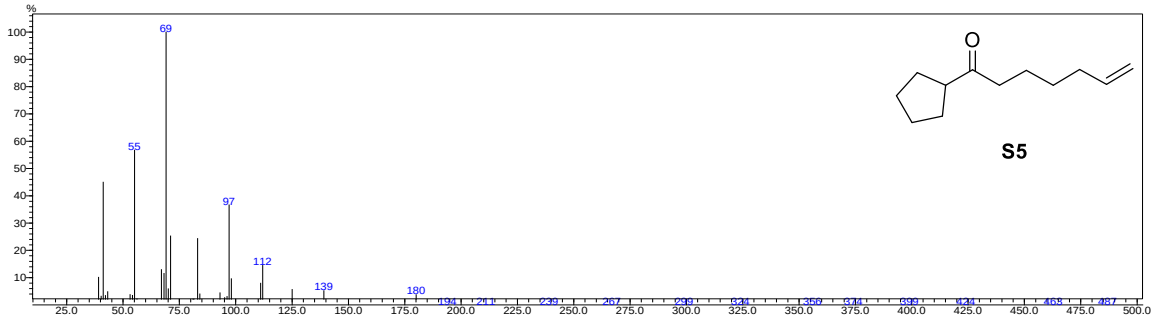
1-cyclopentylhept-6-en-1-one (S5): This compound was prepared using a modification of a literature method.[64] A flame dried 50 mL round-bottom flask containing a Teflon-coated stir bar was charged with magnesium turnings (232 mg, 9.56 mmol), followed by 10.50 mL of anhydrous THF and a small crystal of iodine (~3 mg) under nitrogen. Then, neat 6-bromo-1-hexene (1.36 mL, 10.20 mmol) was slowly added dropwise to the stirred reaction mixture while monitoring for the loss of iodine color (yellow). Once the reaction has started, as evidenced by the disappearance of iodine color, the resulting solution was stirred for 30 min at 25 °C until the magnesium dissolved.

A flame dried 50 mL round-bottom flask containing a Teflon-coated stir bar was charged with Weinreb amide **S4a** (501 mg, 3.19 mmol), followed by 10.5 mL of anhydrous THF under nitrogen and was cooled to 0 °C with an ice bath. The freshly generated Grignard reagent from the previous step was added dropwise over 15 min and the reaction was allowed to stir for 2 h (complete consumption of starting material by TLC). The reaction was quenched by the dropwise addition of sat. aq. NH_4Cl solution (10 mL), diluted with deionized water (5 mL) and EtOAc (25 mL), and partitioned. The aqueous layer was extracted with EtOAc (4 x 25 mL). The combined organic layers were washed with sat. aq. NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered, and put under reduced pressure to remove the solvent. The crude reaction mixture was purified by column chromatography (SiO_2/EtOAc–Hexanes gradient) to give 497 mg (86%) of **S5** as a colorless oil. **^{1}H NMR** (400 MHz, toluene-d_8) δ 5.73 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.12 – 4.86 (m, 2H), 2.44 (p, *J* = 7.9 Hz, 1H), 2.05 (t, *J* = 7.3 Hz, 2H), 1.93 (q, *J* = 7.2 Hz, 2H), 1.73 – 1.64 (m, 2H), 1.58 – 1.48 (m, 6H), 1.42 – 1.33 (m, 2H), 1.27 – 1.19 (m, 2H); **^{1}H NMR** (700 MHz, C_6D_6) δ 5.74 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.02 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.98 (dd, *J* = 9.9, 2.0 Hz, 1H), 2.43 (p, *J* = 7.8 Hz, 1H), 2.05 (t, *J* = 7.3 Hz, 2H), 1.94 (q, *J* = 7.3 Hz, 2H), 1.73 – 1.67 (m, 2H), 1.57 – 1.49 (m, 6H), 1.40 – 1.32 (m, 2H), 1.25 (p, *J* = 7.6 Hz, 2H); **^{1}H NMR** (700 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.02 – 4.96 (m, 1H), 4.96 – 4.91 (m, 1H), 2.85 (p, *J* = 8.1 Hz, 1H), 2.46 – 2.42 (m, 2H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.76 – 1.67 (m, 2H), 1.69 – 1.61 (m, 2H), 1.62 – 1.53 (m, 4H), 1.41 – 1.34 (m, 2H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 213.5, 138.7, 114.7, 51.5, 41.7, 33.7, 29.0, 28.7, 26.1, 23.5; **IR** (Neat): 3078, 2941, 2869, 1708, 1641, 1504, 1451, 1409, 1369, 1101, 992, 849, 778, 734, 671; **HRMS** (GCMS-APCI+): calcd for $C_{12}H_{21}O^+$ $[M+H]^+$: 181.1587, found: 181.1595. **GC-MS** (EI) m/z: M+ = 180.1509 calculated for $C_{12}H_{20}O$; found 180.1.

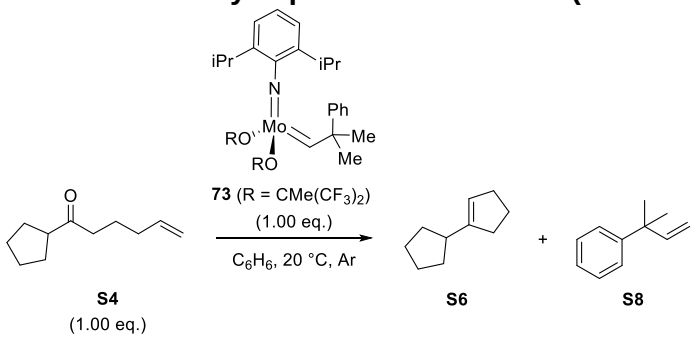
GC-MS trace of **S5**:



Mass Spectrum of product peak (7.241 min):



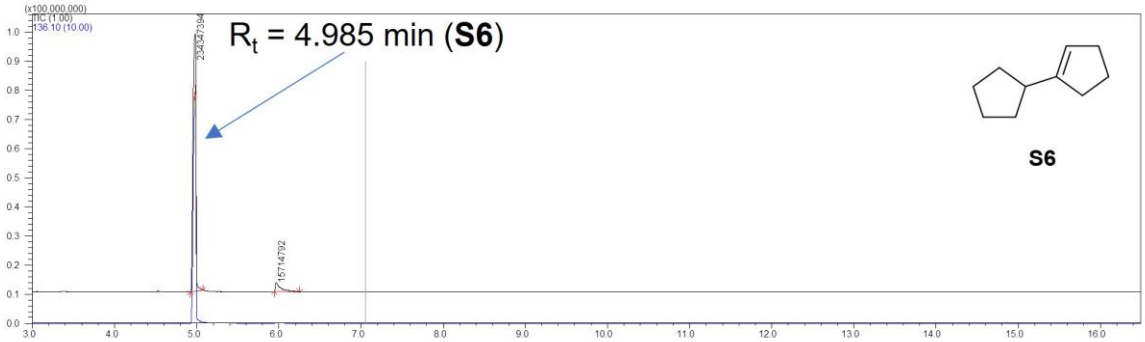
Preparation of COM Product standard cyclopentene S6 from S4 (0.1 mmol scale)



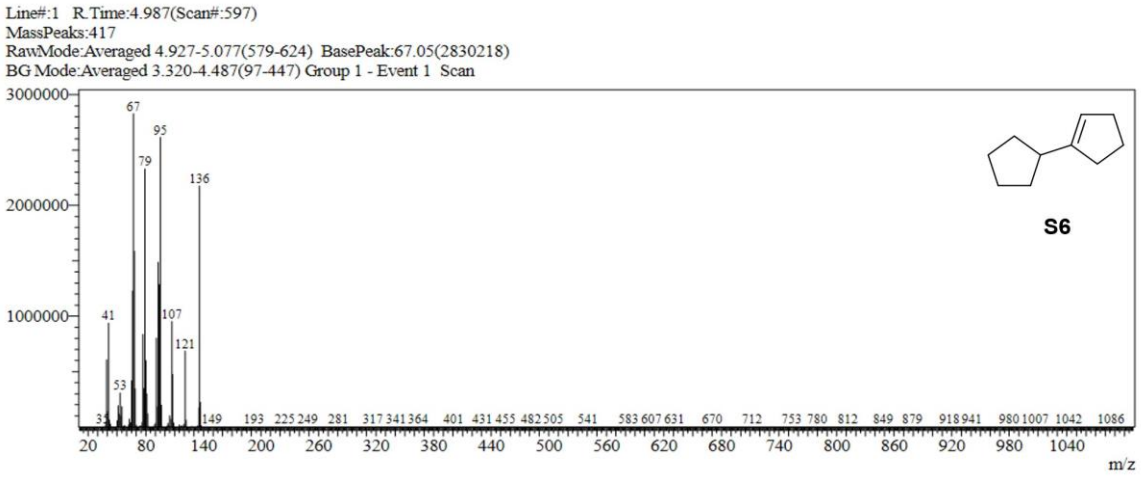
1-cyclopentylcyclopentene (S6): This compound was prepared using a modification of a literature method.[10] An oven-dried 1-dram glass vial was charged with substrate **S4** (16.2 mg, 0.0974 mmol) and anhydrous benzene (2.00 mL) in a N_2 glovebox. This solution was transferred by Pasteur pipette to a homogeneous stirred solution of Schrock's Catalyst **72** (CAS 139220-25-0) (74.2 mg, 0.0969 mmol) in anhydrous benzene (7.00 mL, 0.0108 M in total) in an oven-dried 25 mL Schlenk flask and thoroughly mixed by stirring at 400 rpm with a Teflon-coated stir bar. The solution was capped and sealed under N_2 with electrical tape. The reaction was transferred out of the glove box and the N_2 atmosphere exchanged for Ar via 3 cycles of vacuum with a Schlenk line and Ar balloon. The reaction was allowed to react at 25 °C for 2 h, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by exposure to air, carefully concentrated and purified by column chromatography (SiO_2/100% pentane) to give 8.5 mg of a mixture of 1-cyclopentylcyclopentene[65] (**S6**) and 1,1-dimethylallyl benzene[66] (**S8**) and 0.8 mg (5%) of **S8** alone. The mixture was immediately purified by gravity column chromatography (SiO_2/100% pentane) and concentrated under a gentle stream of dry N_2 to give 1.8 mg (13%) of **S6** as a volatile, colorless oil. Spectroscopic data for **S6** and **S8** were consistent with those reported in the literature.[65,66] Characterization data was obtained for the pure sample of **S6** which contains some trace pentane. **^{1}H NMR** (700 MHz, C_6D_6) δ 5.38 (s, 1H), 2.44 (p, *J* = 8.5 Hz, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.26 – 2.20 (m, 2H), 1.83 (p, *J* = 7.5 Hz, 2H), 1.74 (h, *J* = 6.4 Hz, 2H), 1.64 – 1.56 (m, 2H), 1.53 – 1.45 (m, 2H), 1.44 – 1.37 (m, 2H); **^{13}C NMR** (175 MHz, C_6D_6) δ 148.3, 121.9, 42.1, 34.1, 32.7, 31.8, 25.5, 23.9; **GC-MS** (EI) m/z: M+ = 136.1 calculated for $C_{10}H_{16}$; Found 136.1.

^{1}H-NMR spectroscopic data and low resolution GC-MS data were also obtained for the small amount of pure **S8** isolated in the first column. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.29 (d, *J* = 7.4 Hz, 1H), 7.19 (d, *J* =

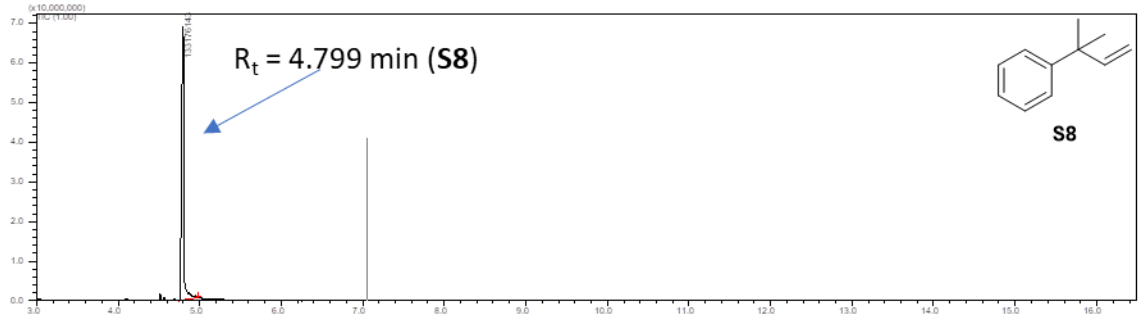
7.6 Hz, 3H), 7.07 (t, *J* = 7.3 Hz, 1H), 5.96 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.04 – 4.94 (m, 2H), 1.29 (s, 6H);
GC-MS (EI) m/z: M+ = 146.1096 calculated for $C_{11}H_{14}$; found 146.1.
GC-MS trace of Product **S6**:



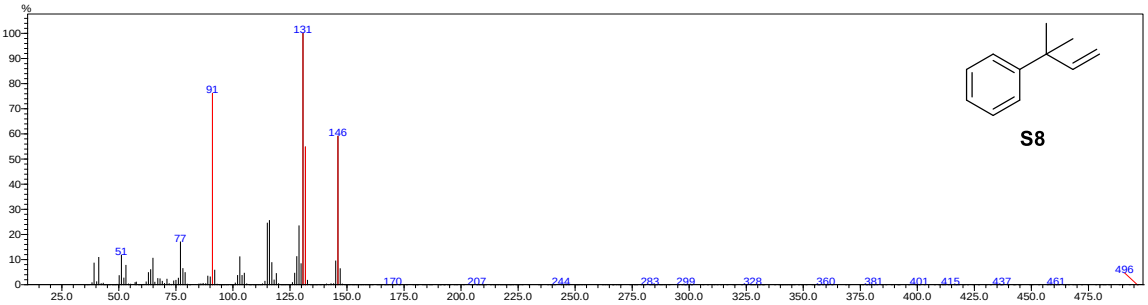
Mass Spectrum of product peak (4.987 min):



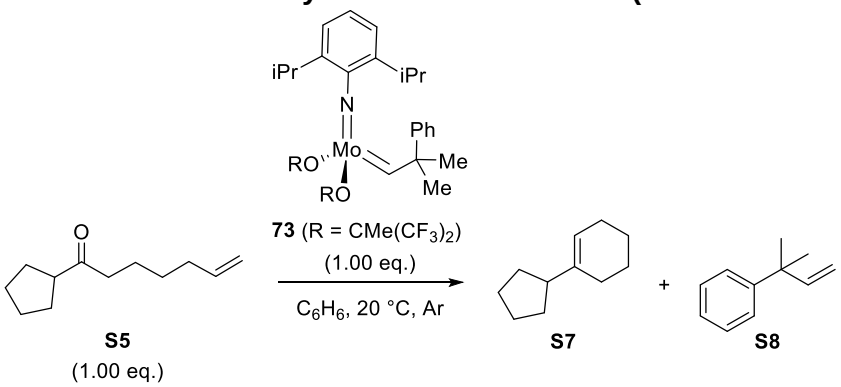
GC-MS trace of Product **S8**:



Mass Spectrum of product peak (4.799 min):



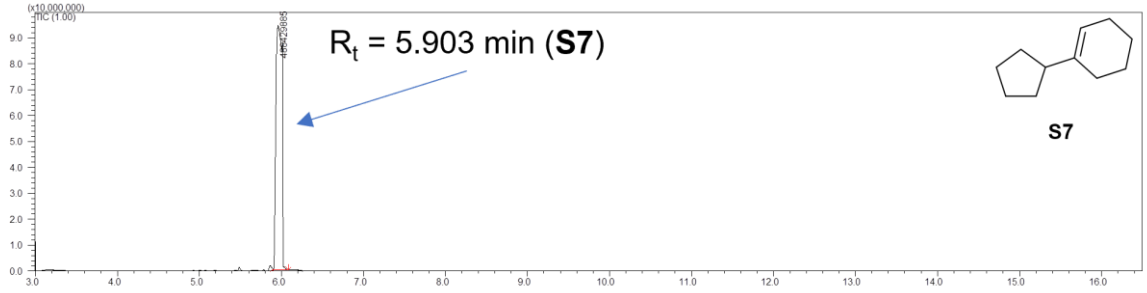
Preparation of COM Product standard cyclohexene S7 from S5 (0.13 mmol scale)



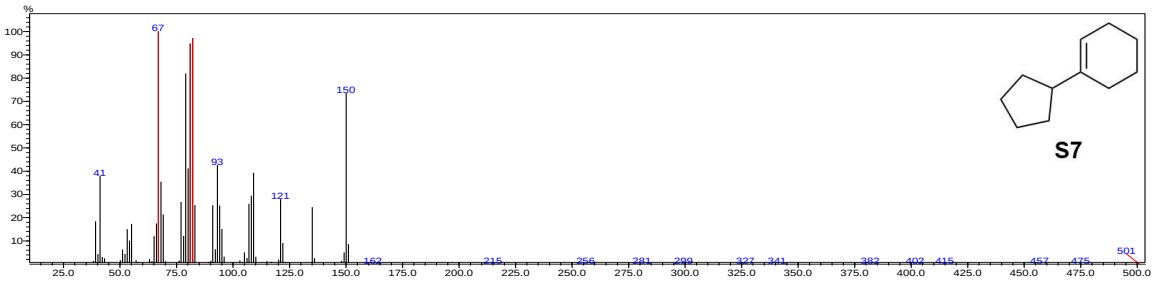
1-cyclopentylcyclohexene (S7): This compound was prepared using a modification of a literature method.[10] An oven-dried 1-dram glass vial was charged with substrate **S5** (23.4 mg, 0.13 mmol) and anhydrous benzene (1.00 mL) in a N_2 glovebox. This solution was transferred by Pasteur pipette to a homogeneous stirred solution of Schrock's Catalyst **72** (CAS 139220-25-0) (99.8 mg, 0.13 mmol) in anhydrous benzene (11.00 mL, 0.0108 M in total) in an oven-dried 25 mL Schlenk flask and thoroughly mixed by stirring at 400 rpm with a Teflon-coated stir bar. The solution was capped and sealed under N_2 with electrical tape. The reaction was transferred out of the glove box and the N_2 atmosphere exchanged for Ar via 3 cycles of vacuum with a Schlenk line and Ar balloon. The reaction was allowed to react at 25 °C for 2 h, at which time TLC showed the reaction to be complete. The reaction mixture was quenched by exposure to air, carefully concentrated and purified by column chromatography (SiO_2/0-10% Et_2O/Hexanes gradient) to give 13.1 mg of a mixture of 1-cyclopentylcyclohexene[65] (**S7**) and 1,1-dimethylallyl benzene[66] (**S8**) (1.38:1 ratio by ^{1}H-NMR). This mixture was purified by gravity column chromatography (SiO_2/100% pentane) and concentrated under a gentle stream of dry N_2 to give 4.7 mg (24%) of **S7** as a volatile, colorless oil. Spectroscopic data for **S7** and **S8** were consistent with those reported in the literature.[65,66] Characterization data was obtained for the 1.38:1 mixture of **S7** (major product) and **S8** (minor product). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.8 Hz, 0.8H, minor), 7.30 (t, *J* = 7.6 Hz, 0.8H, minor), 7.19 (t, *J* = 7.3 Hz, 0.4H, minor), 6.04 (dd, *J* = 17.4, 10.6 Hz, 0.4H, minor), 5.46 – 5.40 (s, 1H, major), 5.10 – 5.01 (m, 0.8H, minor), 2.30 (p, *J* = 8.7 Hz, 1H, major), 2.03 – 1.97 (m, 2H, major), 1.95 (m, 2H, major), 1.72 (m, 2H, major), 1.68 – 1.59 (m, 4H, major), 1.55 (m, 4H, major), 1.41 (s, 2.7H, minor), 1.39 – 1.32 (m, 2H, major); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 148.7 (minor), 148.2 (minor), 141.0 (major), 128.2 (minor), 126.3 (minor), 125.9 (minor), 118.9 (major), 110.8 (minor), 47.7 (major), 41.3 (minor), 31.0 (major), 28.4 (minor), 27.1 (major), 25.4 (major), 25.3 (major), 23.3 (major), 23.0 (major).

Characterization data was also obtained for the pure sample of **S7** which contains some trace pentane. **^{1}H NMR** (700 MHz, C_6D_6) δ 5.51 (s, 1H), 2.28 (p, *J* = 8.7 Hz, 1H), 2.02 – 1.98 (m, 2H), 1.92 – 1.89 (m, 2H), 1.72 (dq, *J* = 9.1, 5.6, 5.1 Hz, 2H), 1.63 – 1.57 (m, 4H), 1.55 – 1.48 (m, 4H), 1.41 – 1.36 (m, 2H); **^{1}H NMR** (700 MHz; $CDCl_3$) δ 5.42 (s, 1H), 2.29 (p, *J* = 8.6 Hz, 1H), 2.00 – 1.98 (m, 2H), 1.96 – 1.92 (m, 2H), 1.74 – 1.69 (m, 2H), 1.66 – 1.60 (m, 4H), 1.58 – 1.52 (m, 4H), 1.39 – 1.31 (m, 2H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ 141.1, 118.9, 47.7, 31.0, 27.1, 25.4, 25.3, 23.3, 23.0; **GC-MS** (EI) m/z: M+ = 150.1409 calculated for $C_{11}H_{18}$; found 150.1.

GC-MS trace of Product **S7**:



Mass Spectrum of product peak (5.903 min):



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12. ^{1}H and ^{13}C NMR Spectra

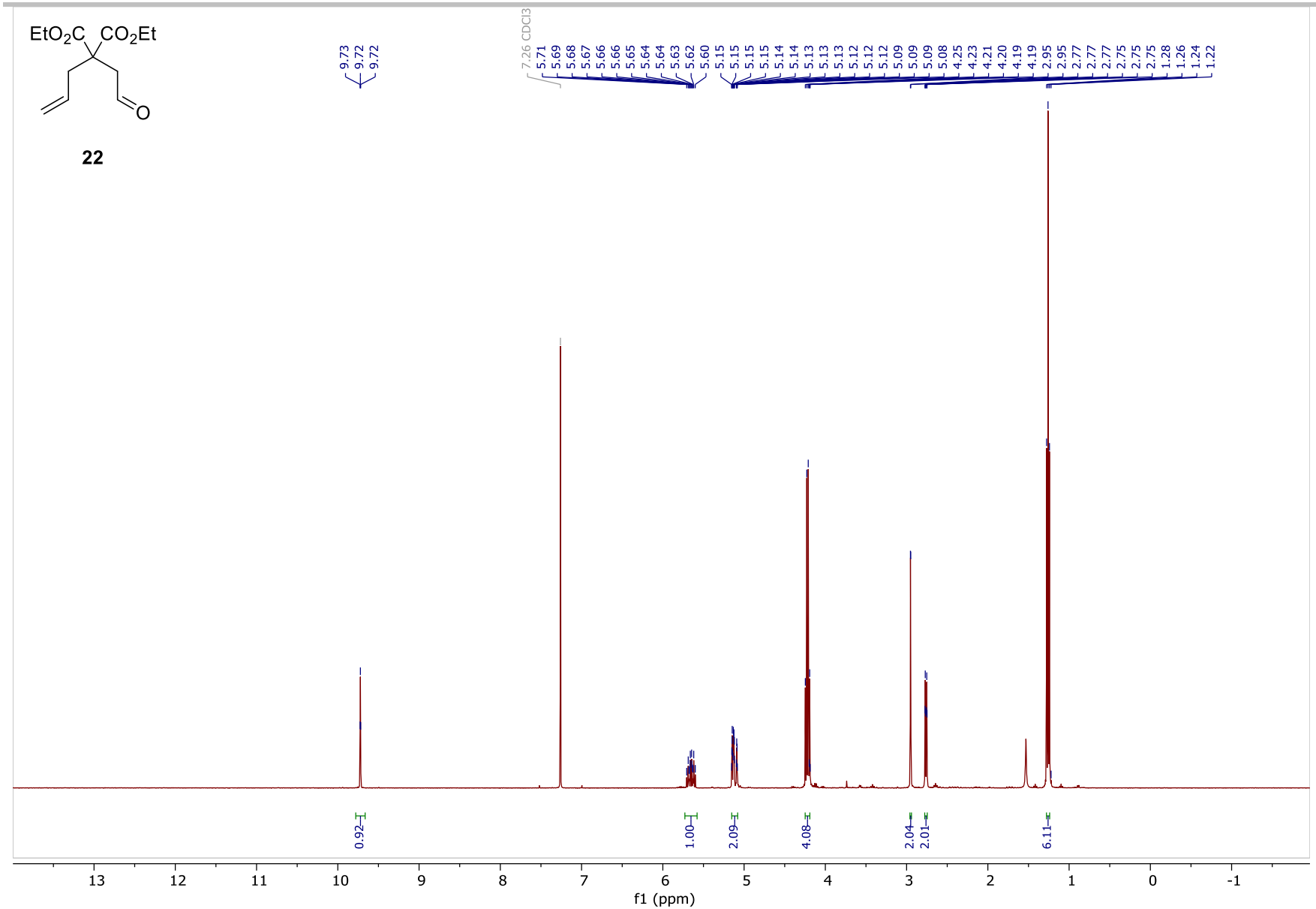

Figure S20. ^{1}H NMR (400 MHz, $CDCl_3$) of **22.**

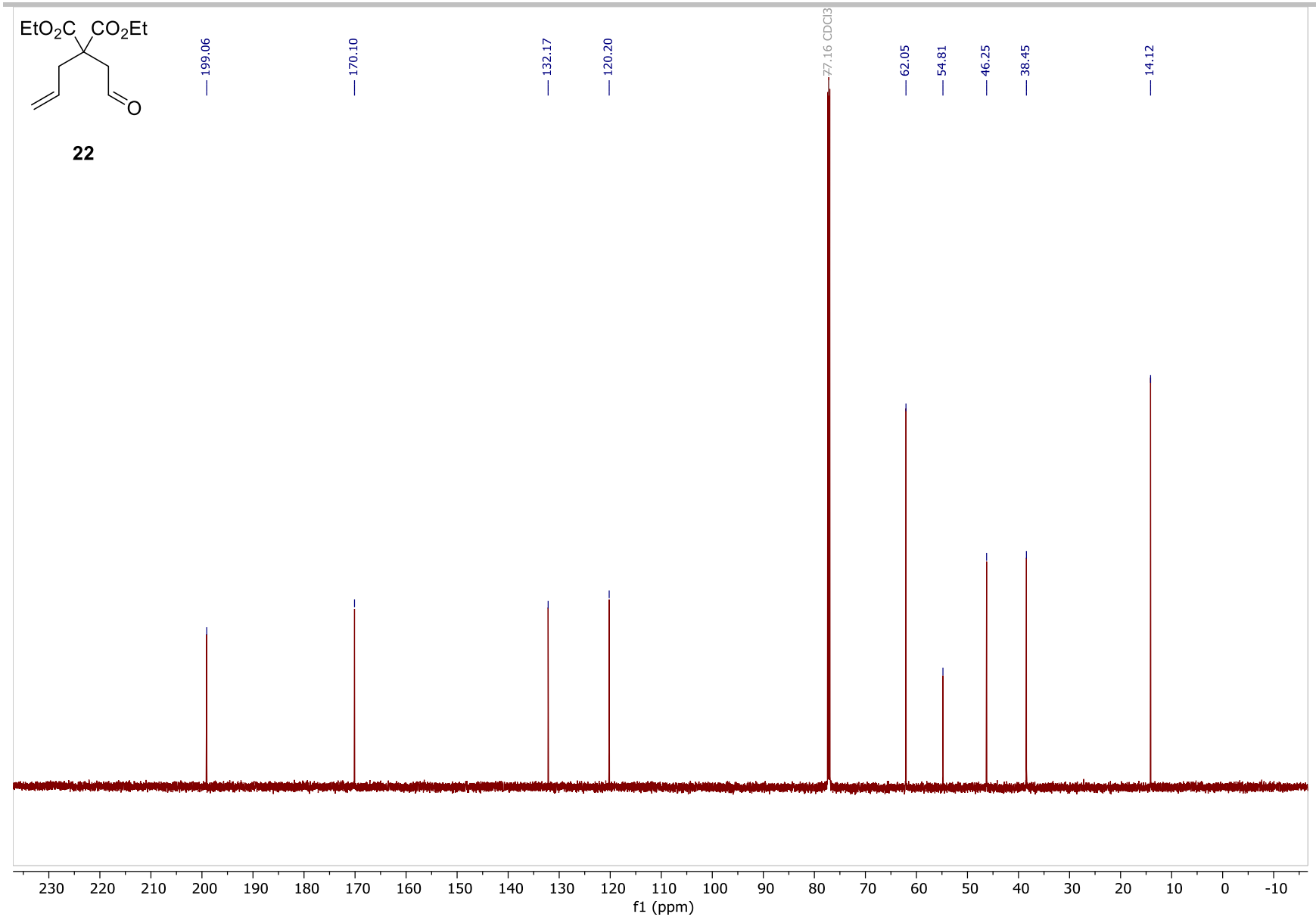

Figure S21. ^{13}C NMR (175 MHz, $CDCl_3$) of **22.**

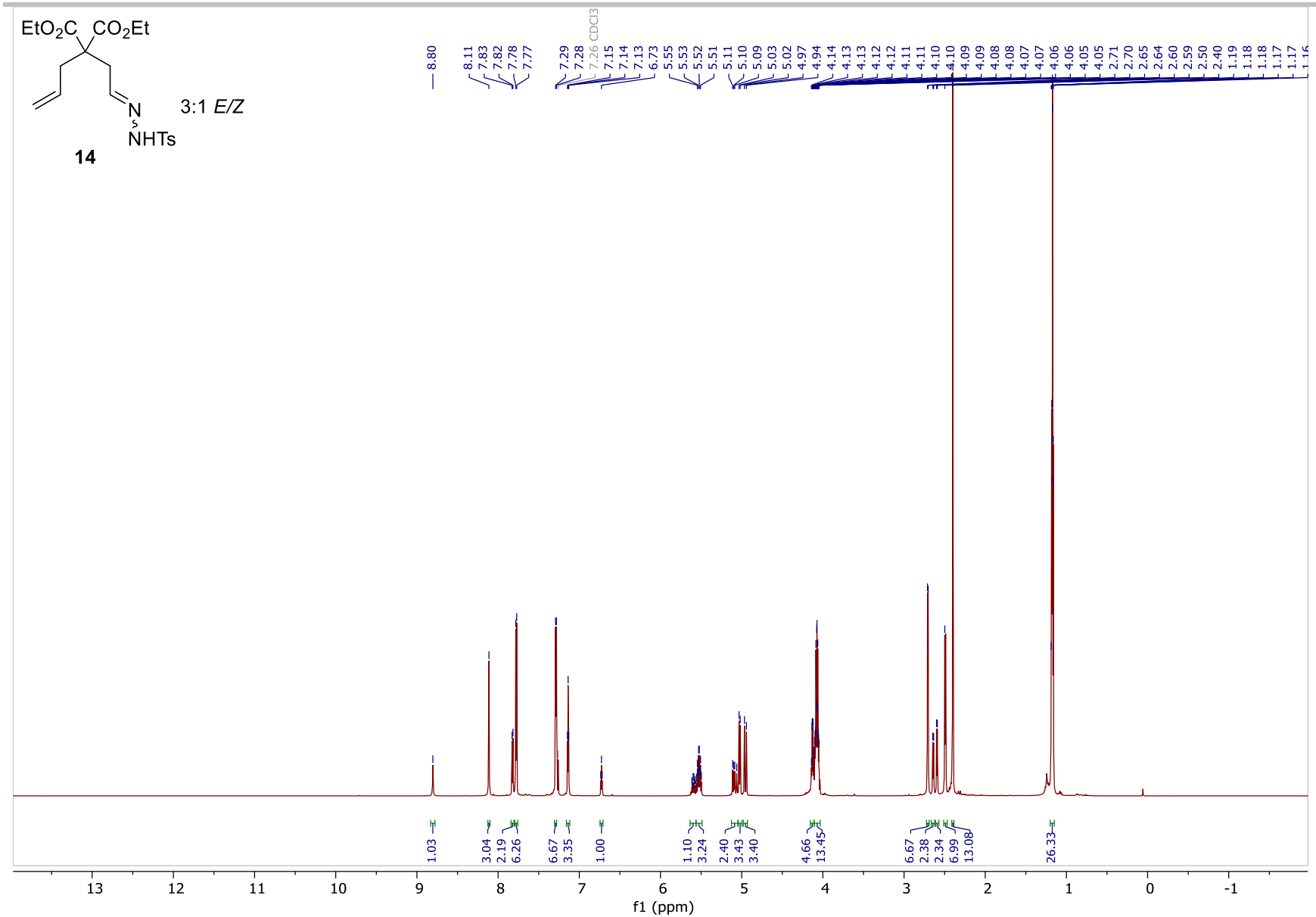

Figure S22. ^{1}H NMR (700 MHz, $CDCl_3$) of **14.**

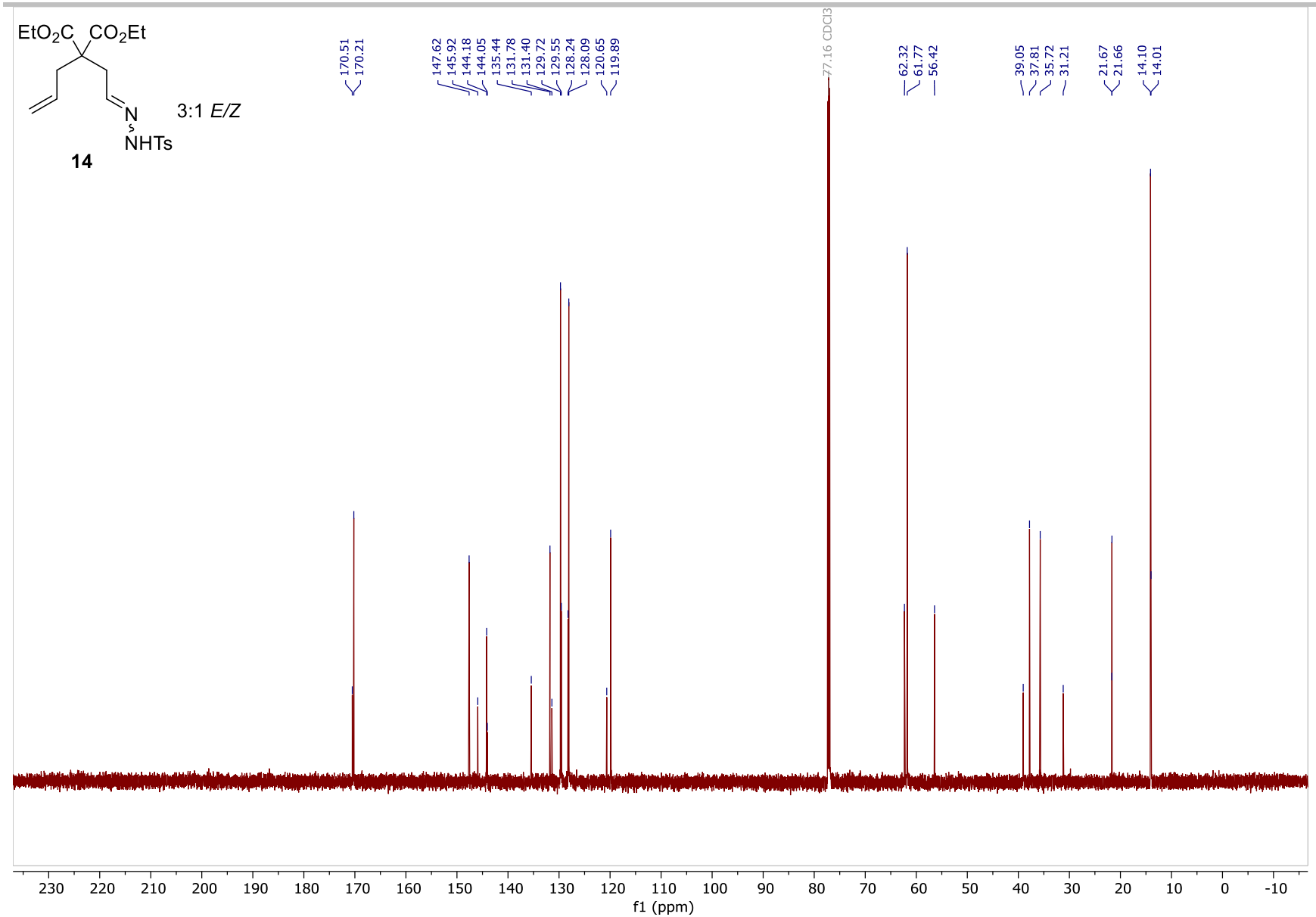

Figure S23. ^{13}C NMR (175 MHz, $CDCl_3$) of **14.**

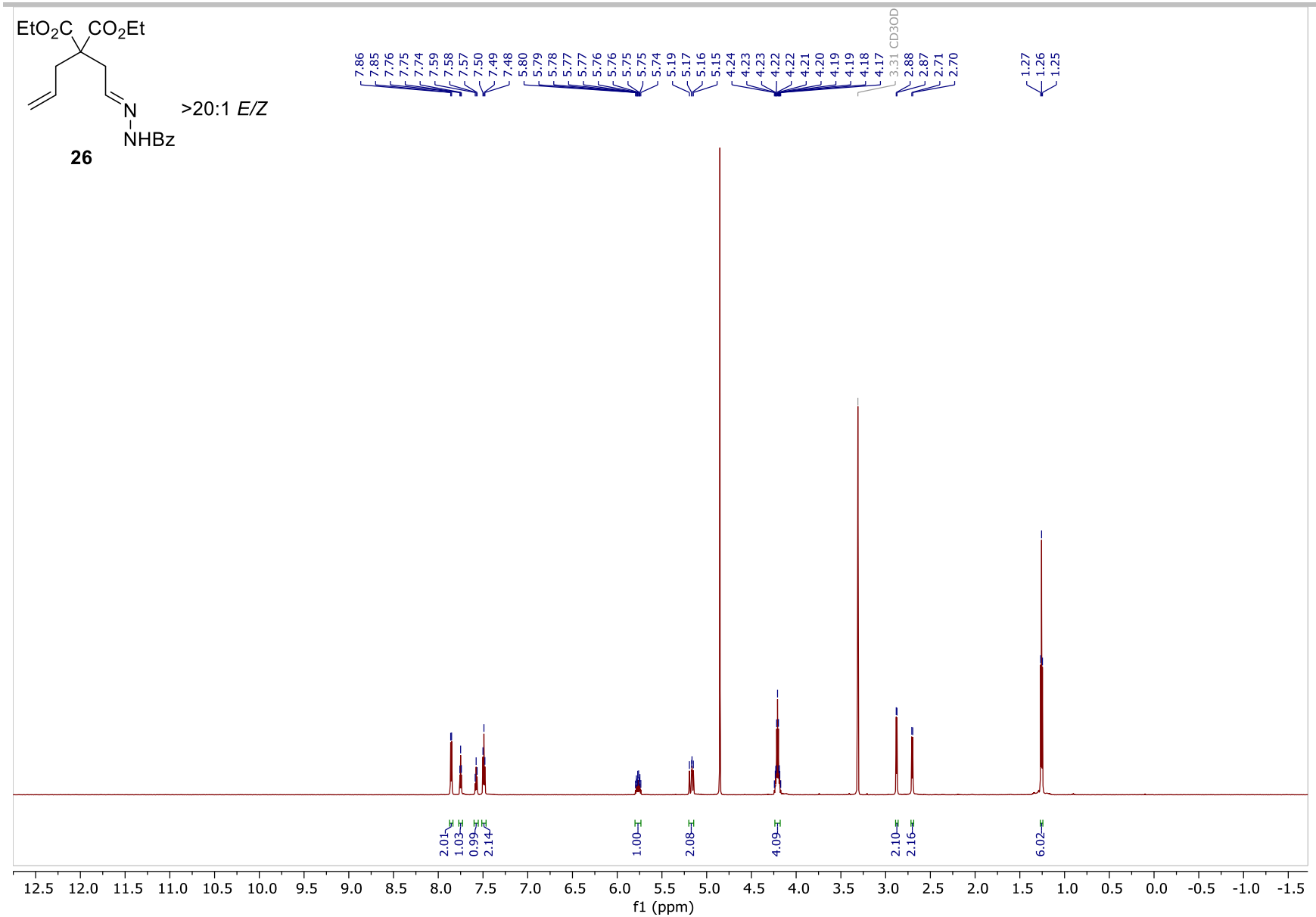

Figure S24. ^{1}H NMR (700 MHz, CD_3OD) of **26.**

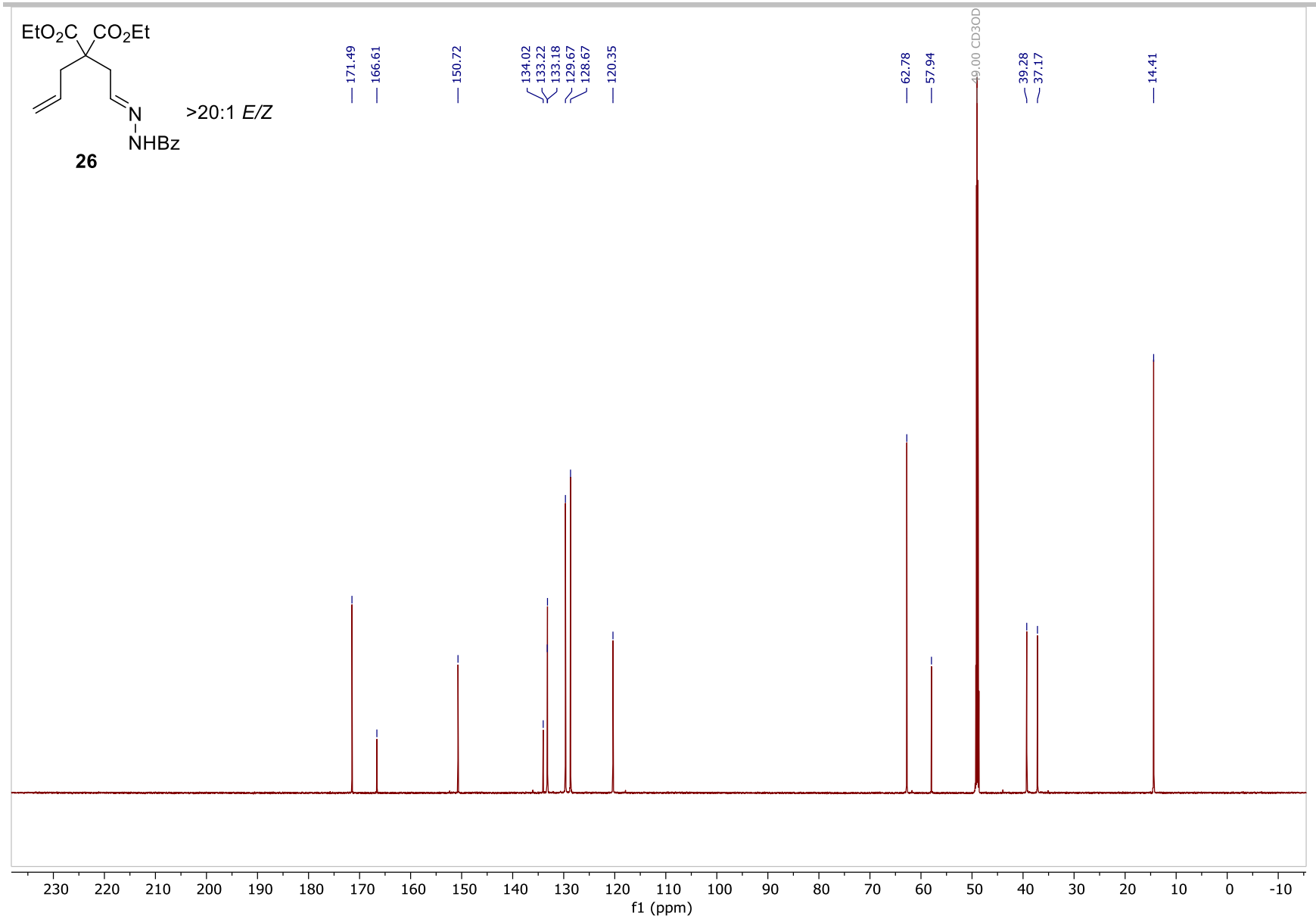

Figure S25. ^{13}C NMR (175 MHz, CD_3OD) of **26.**

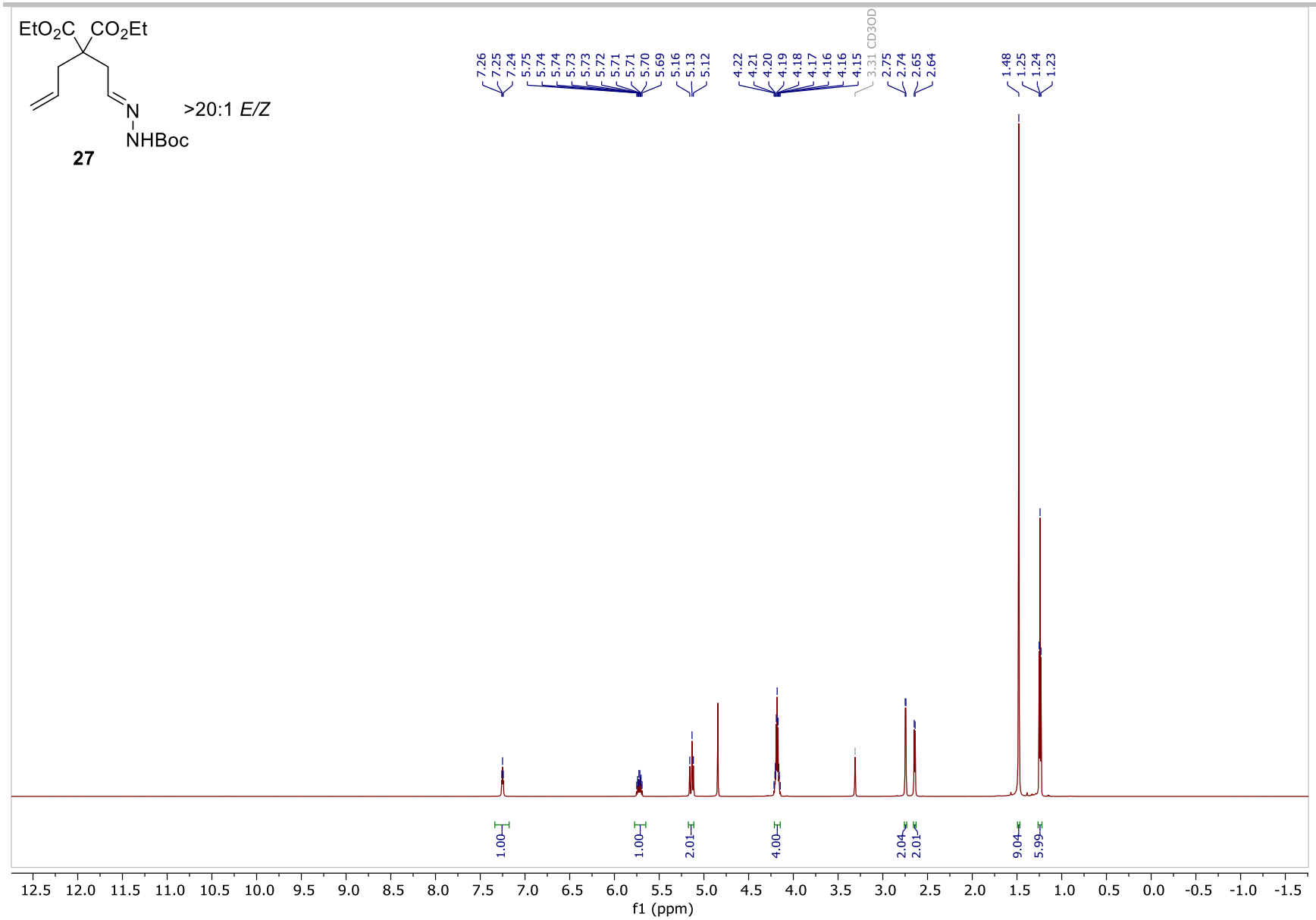

Figure S26. ^{1}H NMR (700 MHz, CD_3OD) of **27.**

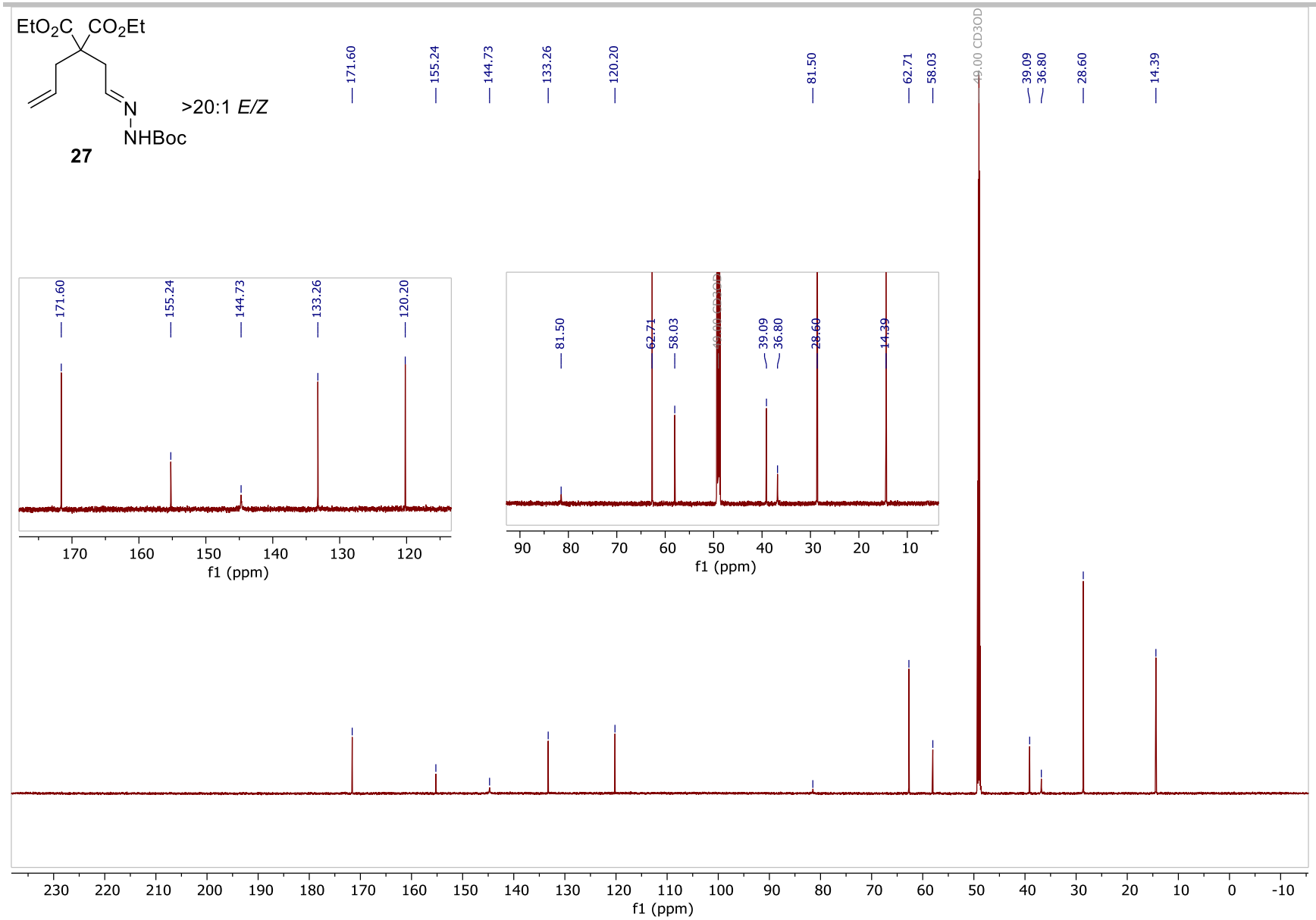

Figure S27. ^{13}C NMR (175 MHz, CD_3OD) of **27.**

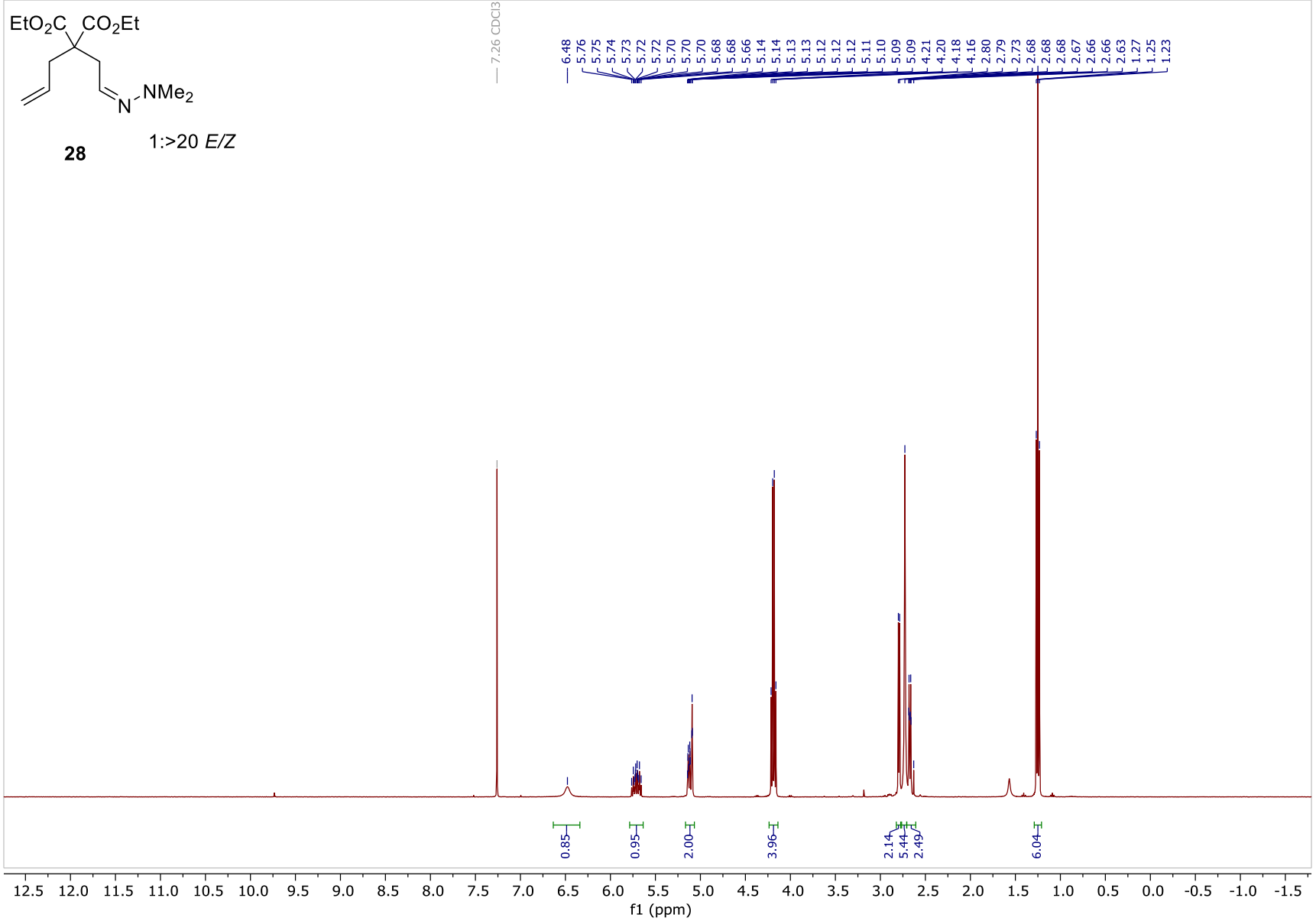

Figure S28. ^{1}H NMR (700 MHz, $CDCl_3$) of **28.**

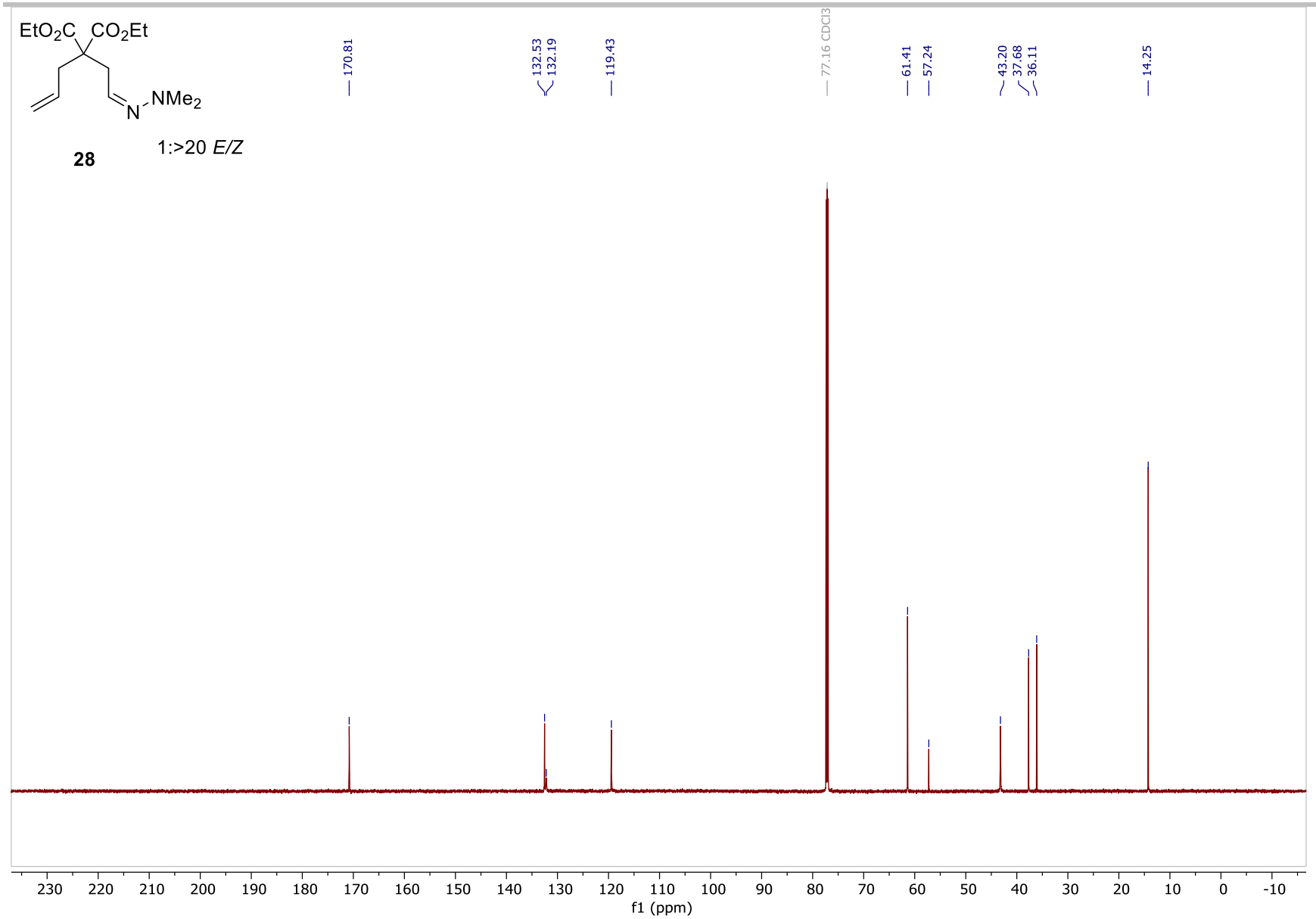

Figure S29. ^{13}C NMR (175 MHz, $CDCl_3$) of **28.**

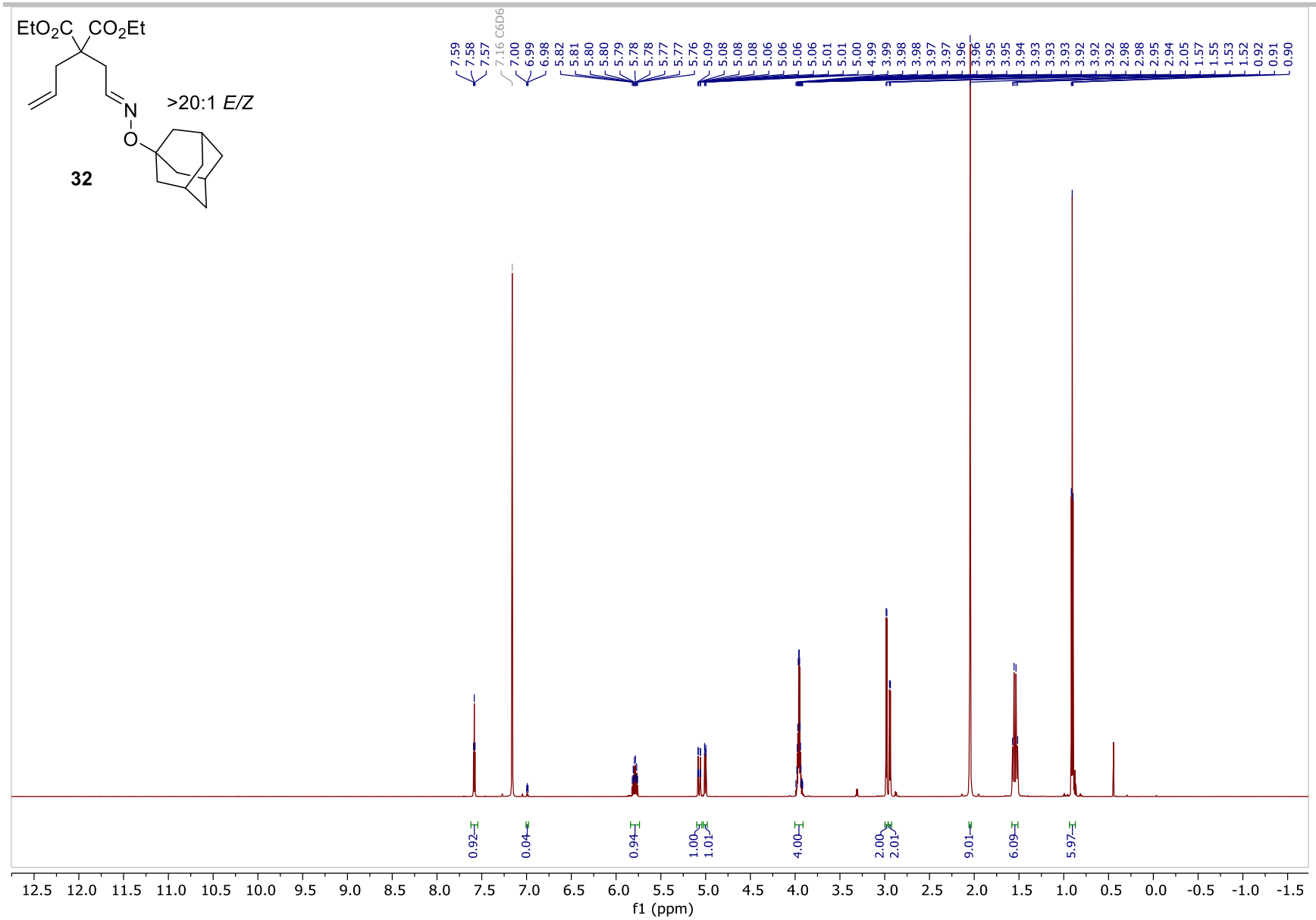

Figure S30. ^{1}H NMR (700 MHz, C_6D_6) of **32.**

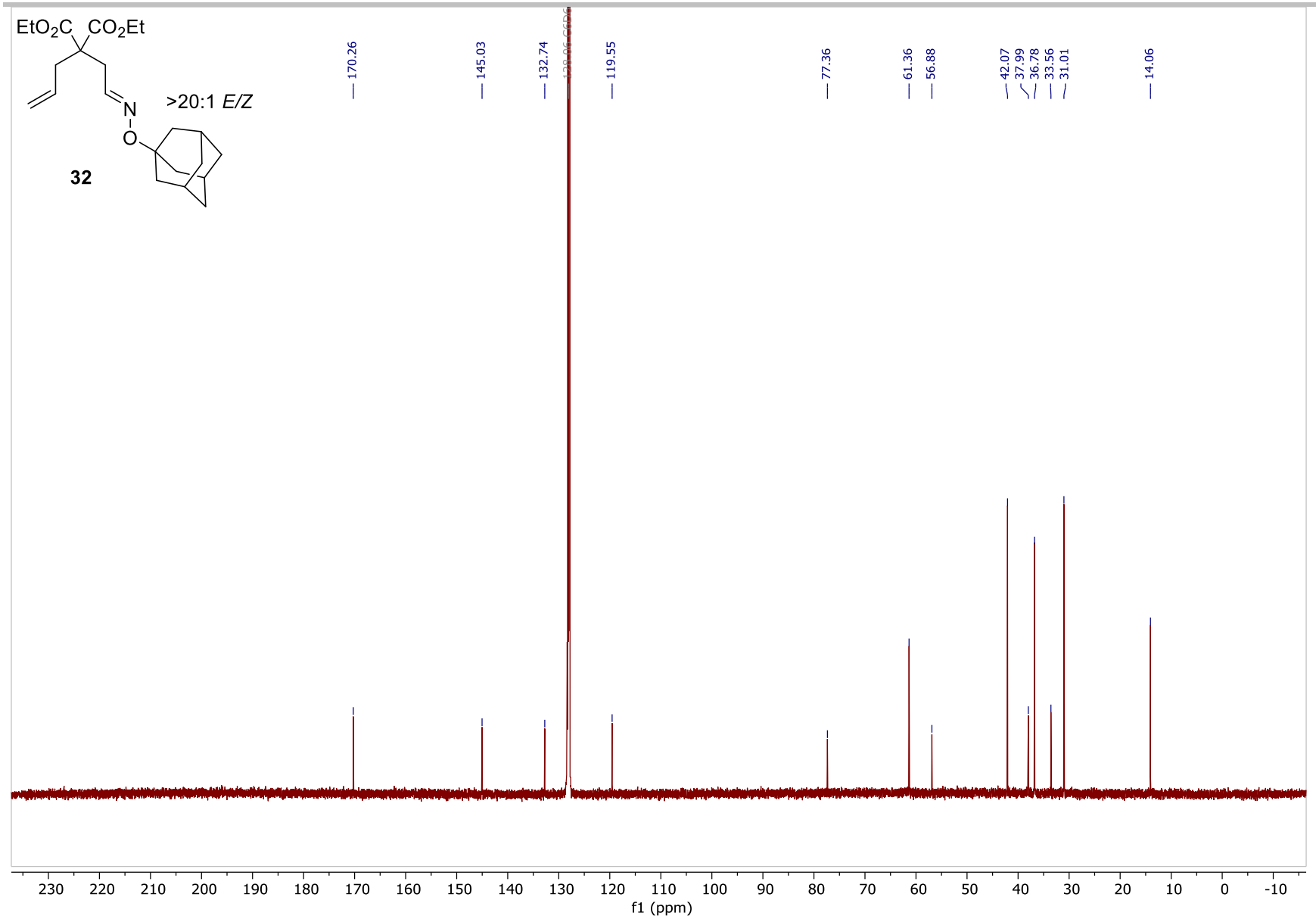

Figure S31. ^{13}C NMR (175 MHz, C_6D_6) of **32.**

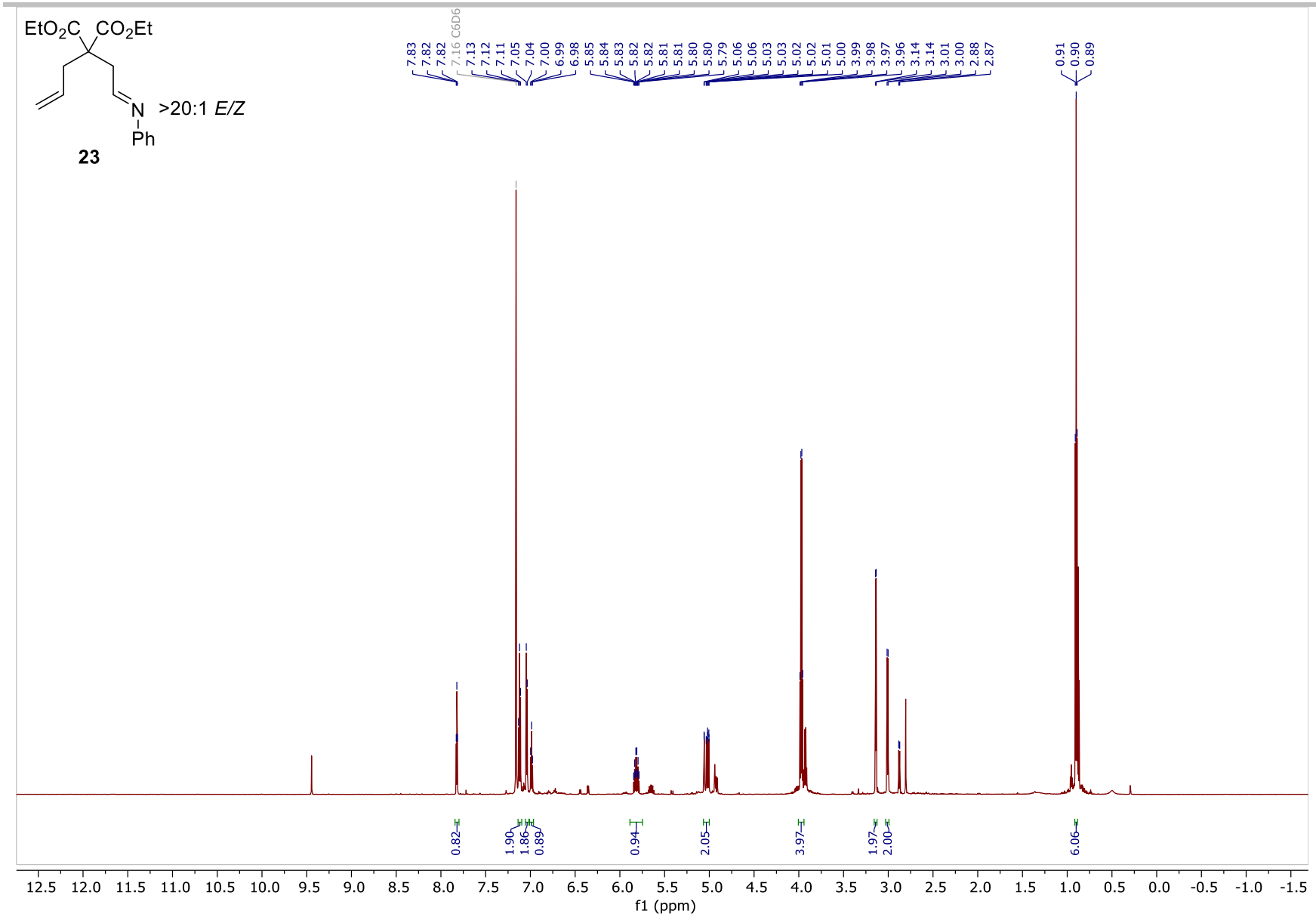

Figure S32. ^{1}H NMR (700 MHz, C_6D_6) of **23** (71% purity by ^{1}H-NMR).

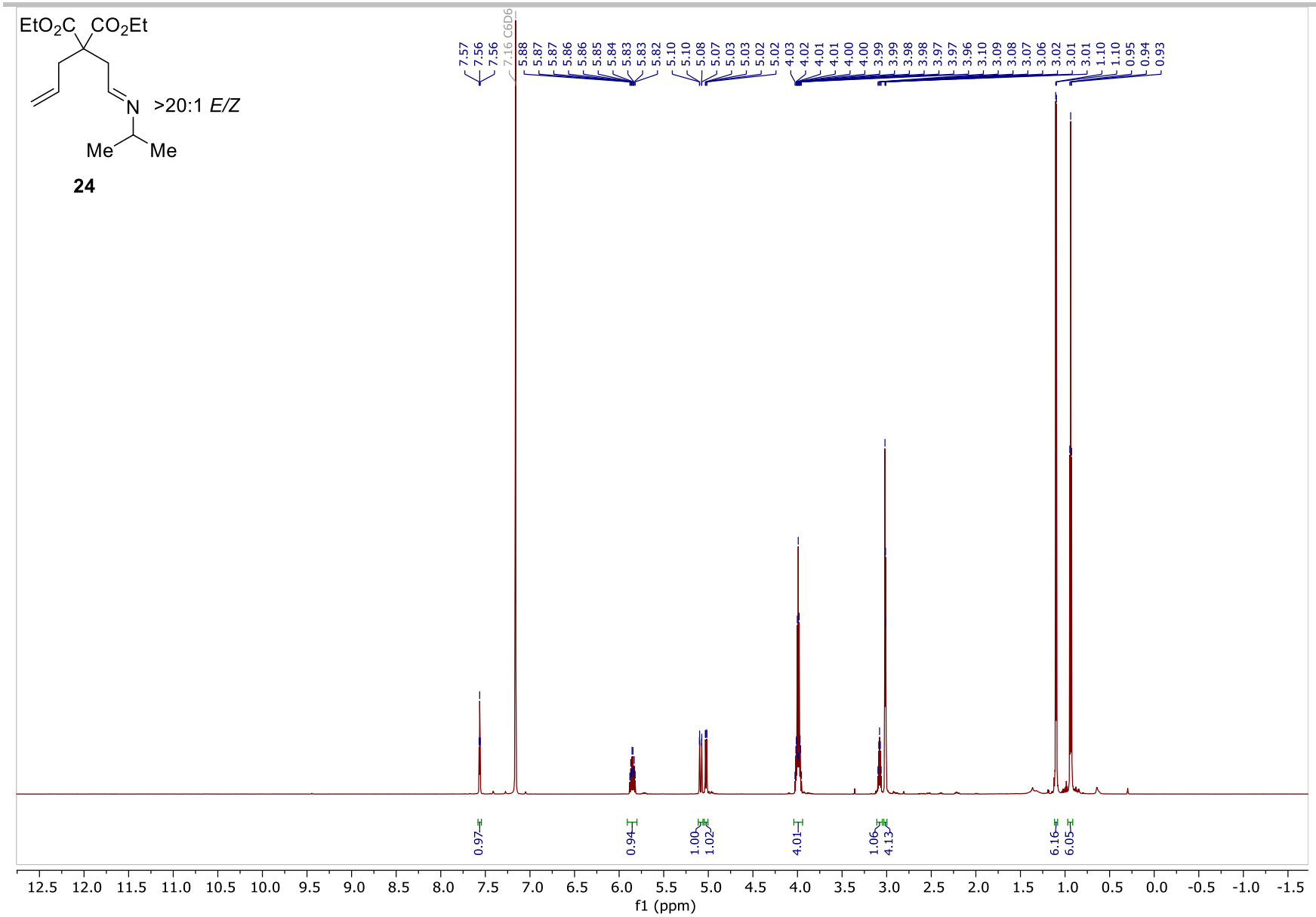

Figure S33. ^{1}H NMR (700 MHz, C_6D_6) of **24.**

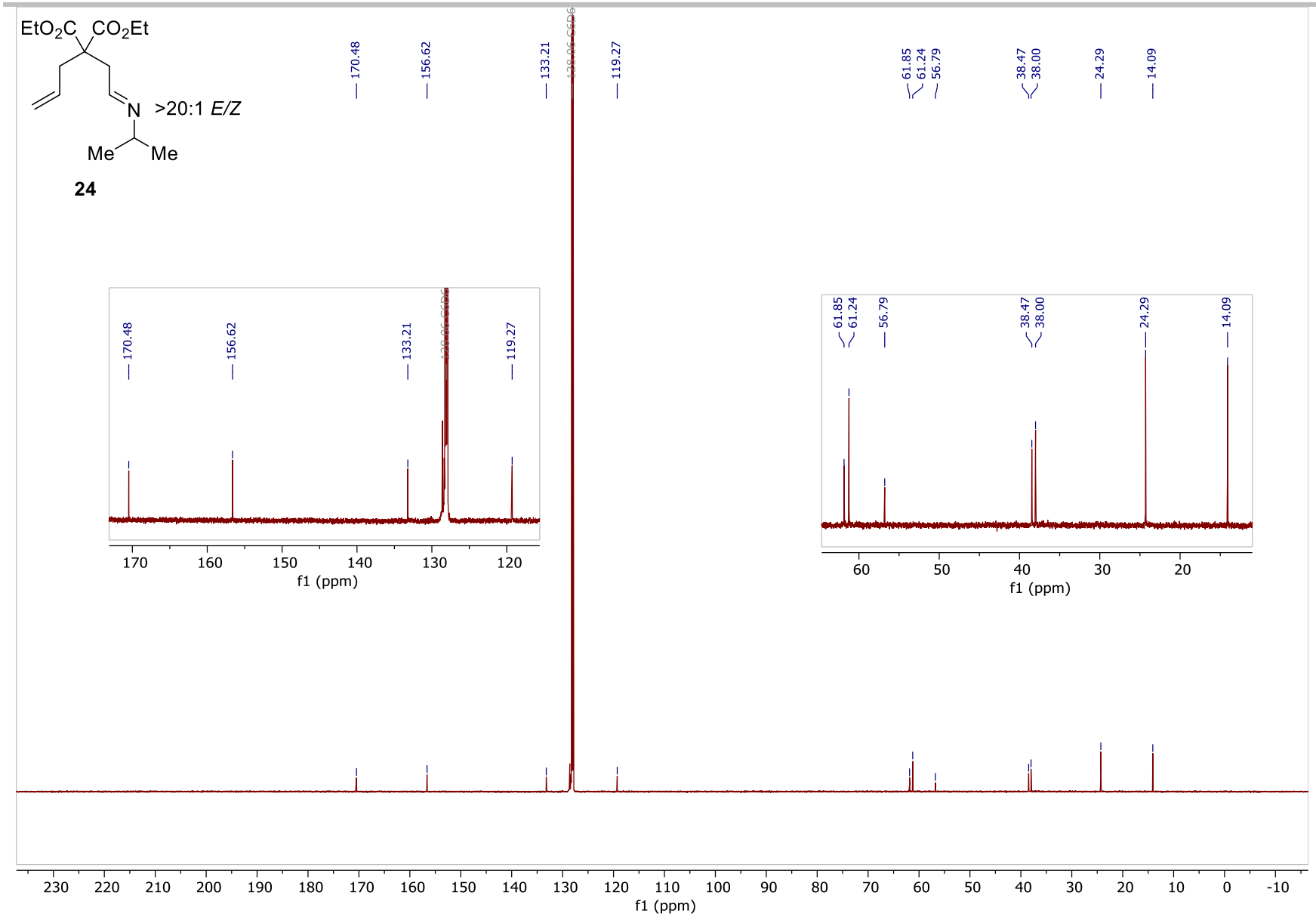

Figure S34. ^{13}C NMR (175 MHz, C_6D_6) of **24.**

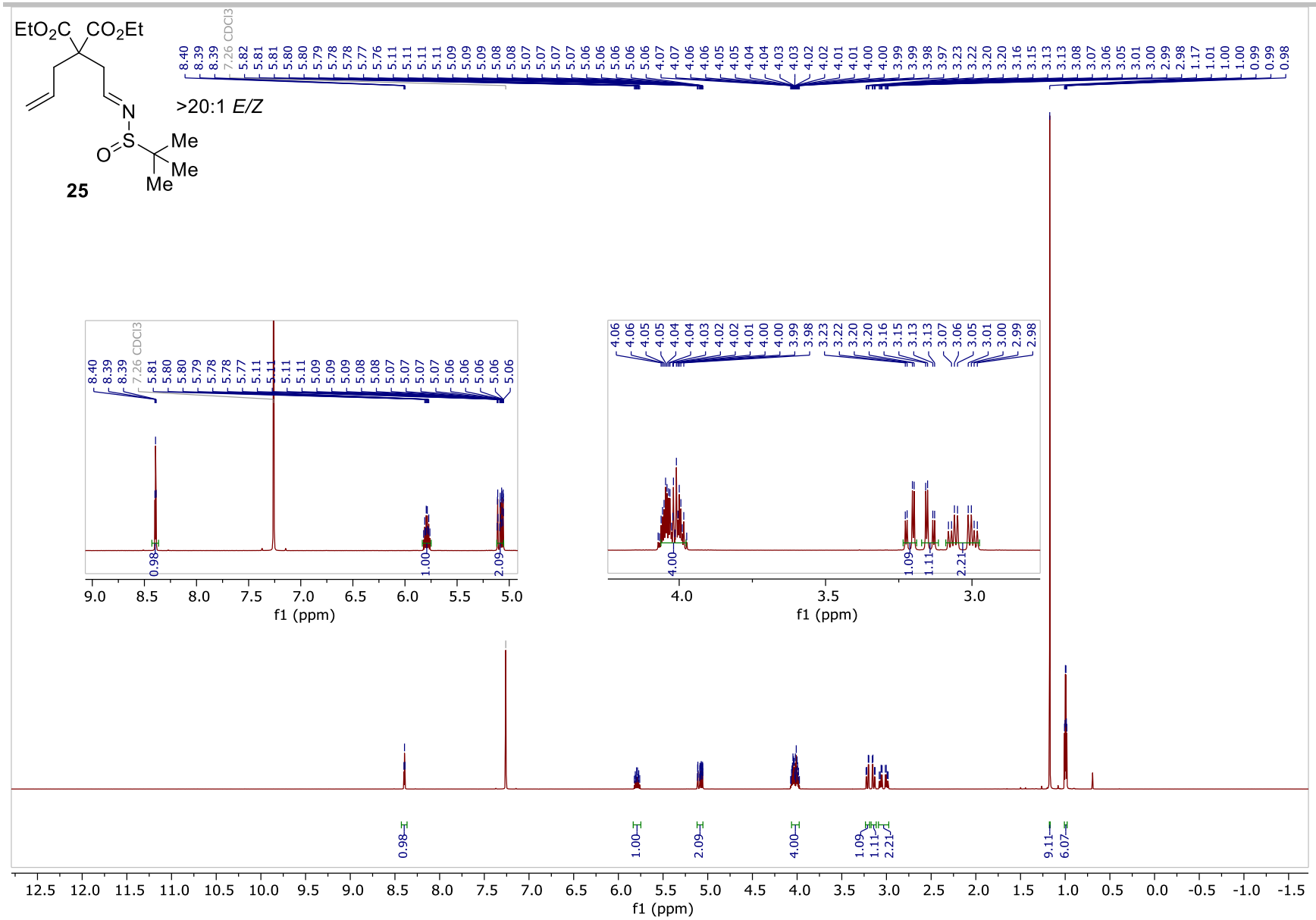

Figure S35. ^{1}H NMR (700 MHz, $CDCl_3$) of **25.**

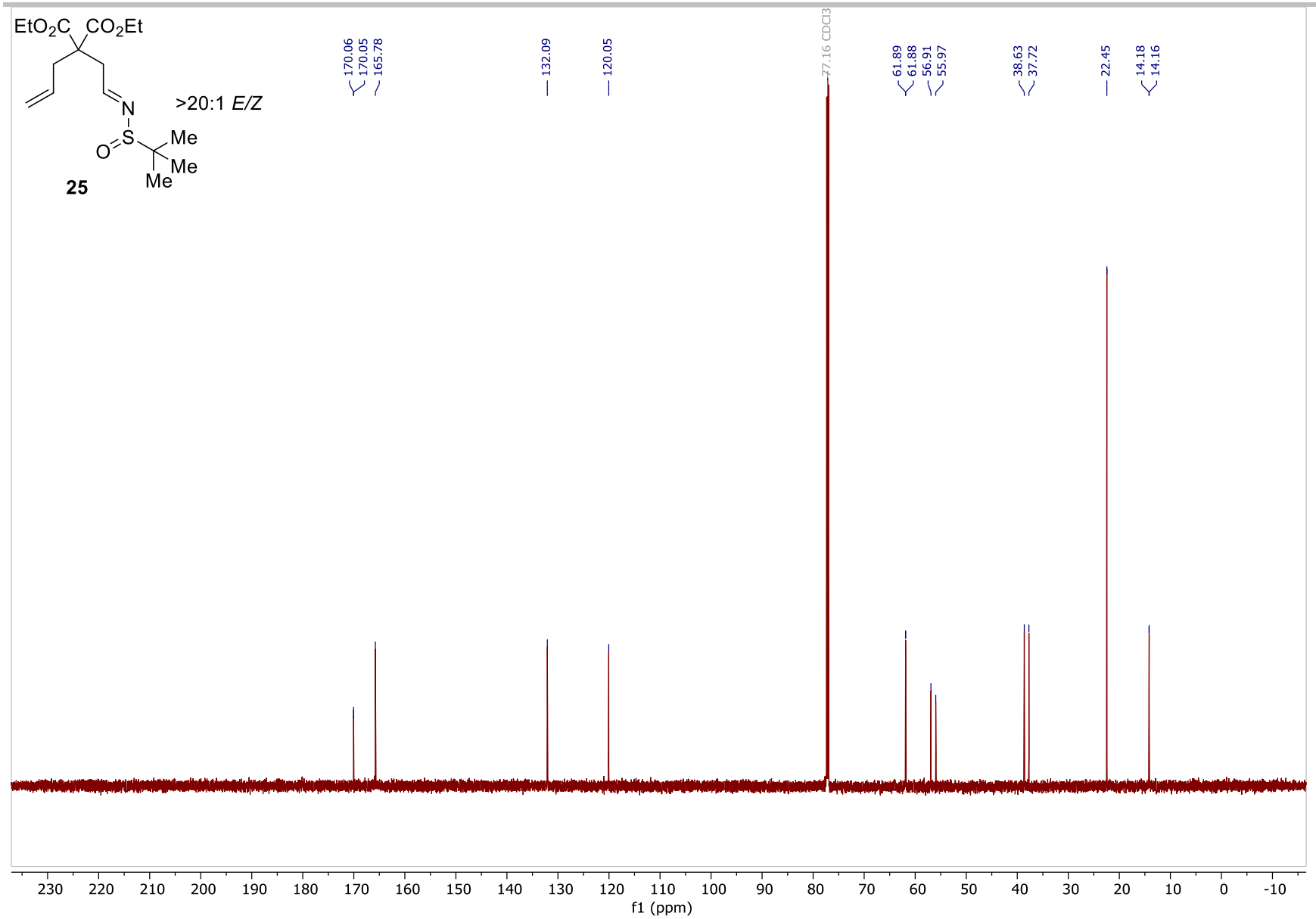

Figure S36. ^{13}C NMR (175 MHz, $CDCl_3$) of **25.**

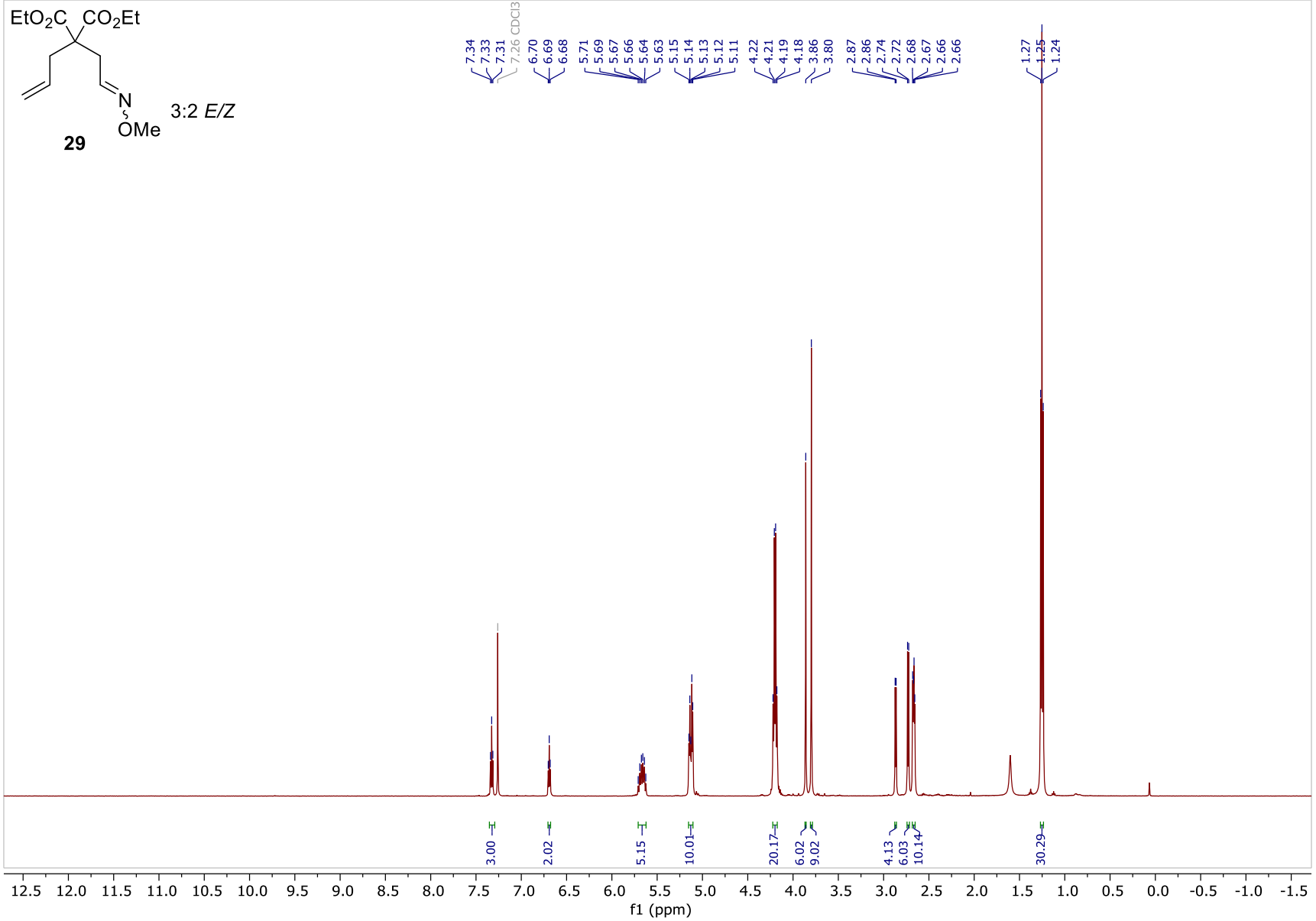

Figure S37. ^{1}H NMR (500 MHz, $CDCl_3$) of **29.**

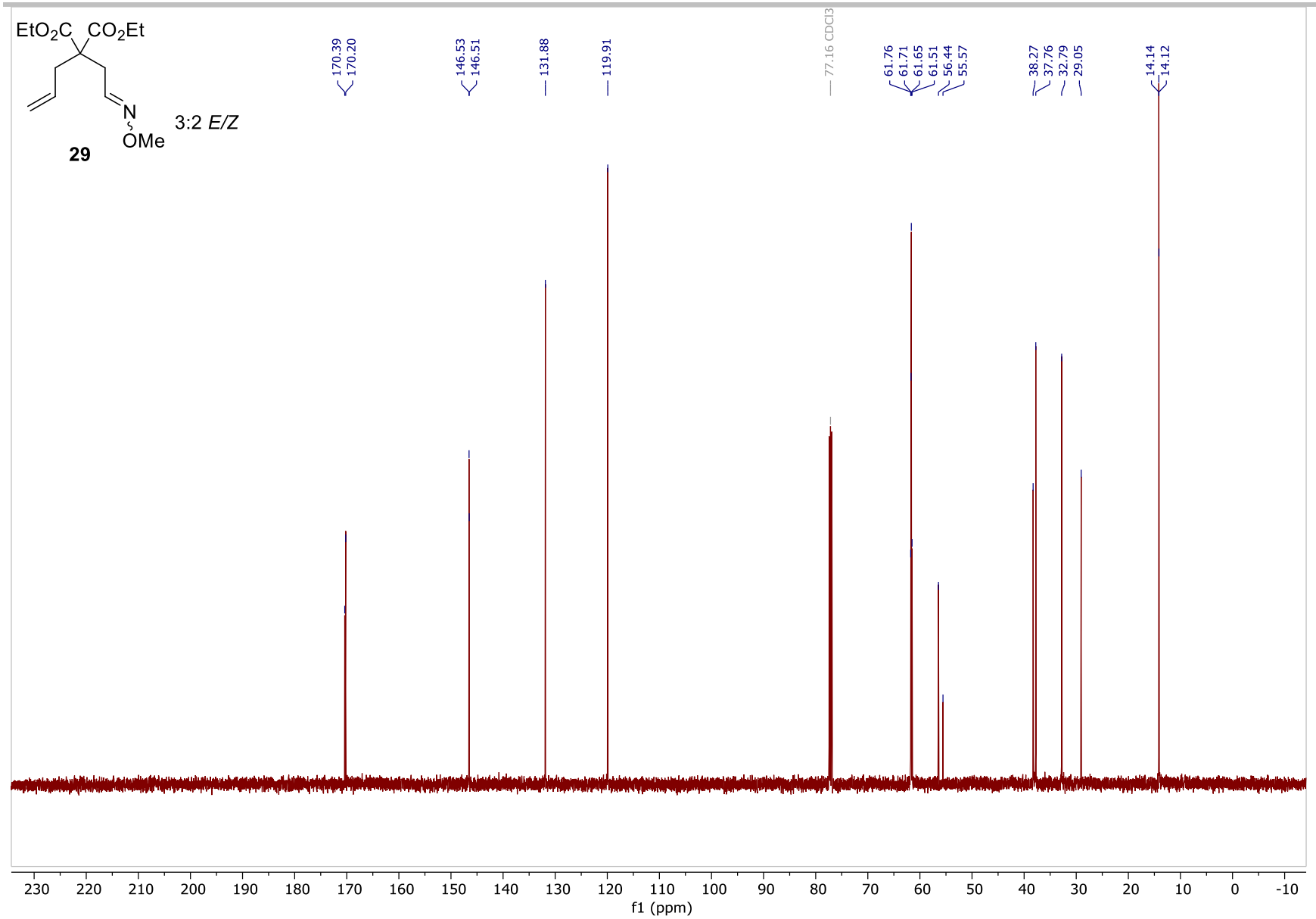

Figure S38. ^{13}C NMR (125 MHz, $CDCl_3$) of **29.**

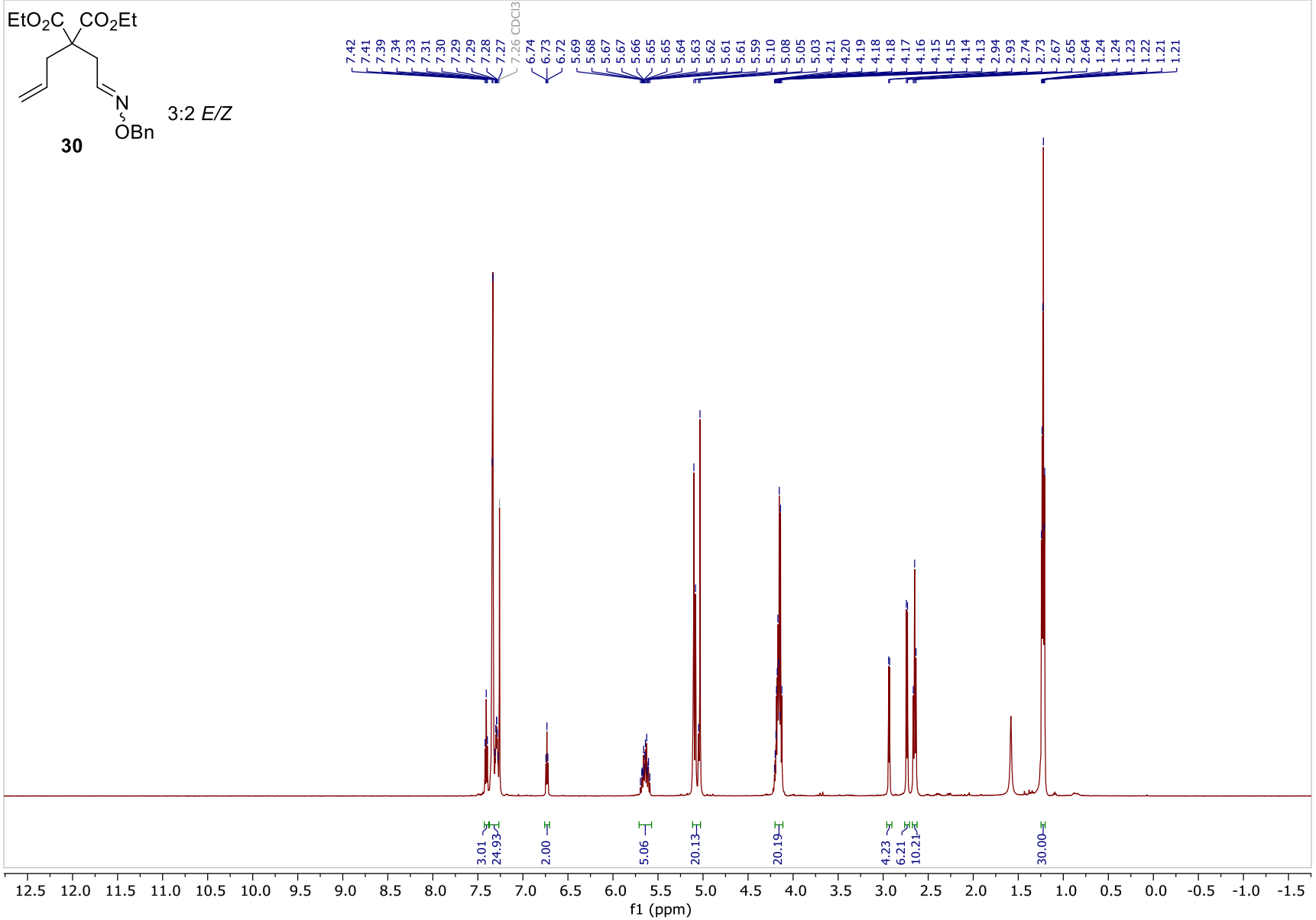

Figure S39. ^{1}H NMR (500 MHz, $CDCl_3$) of **30.**

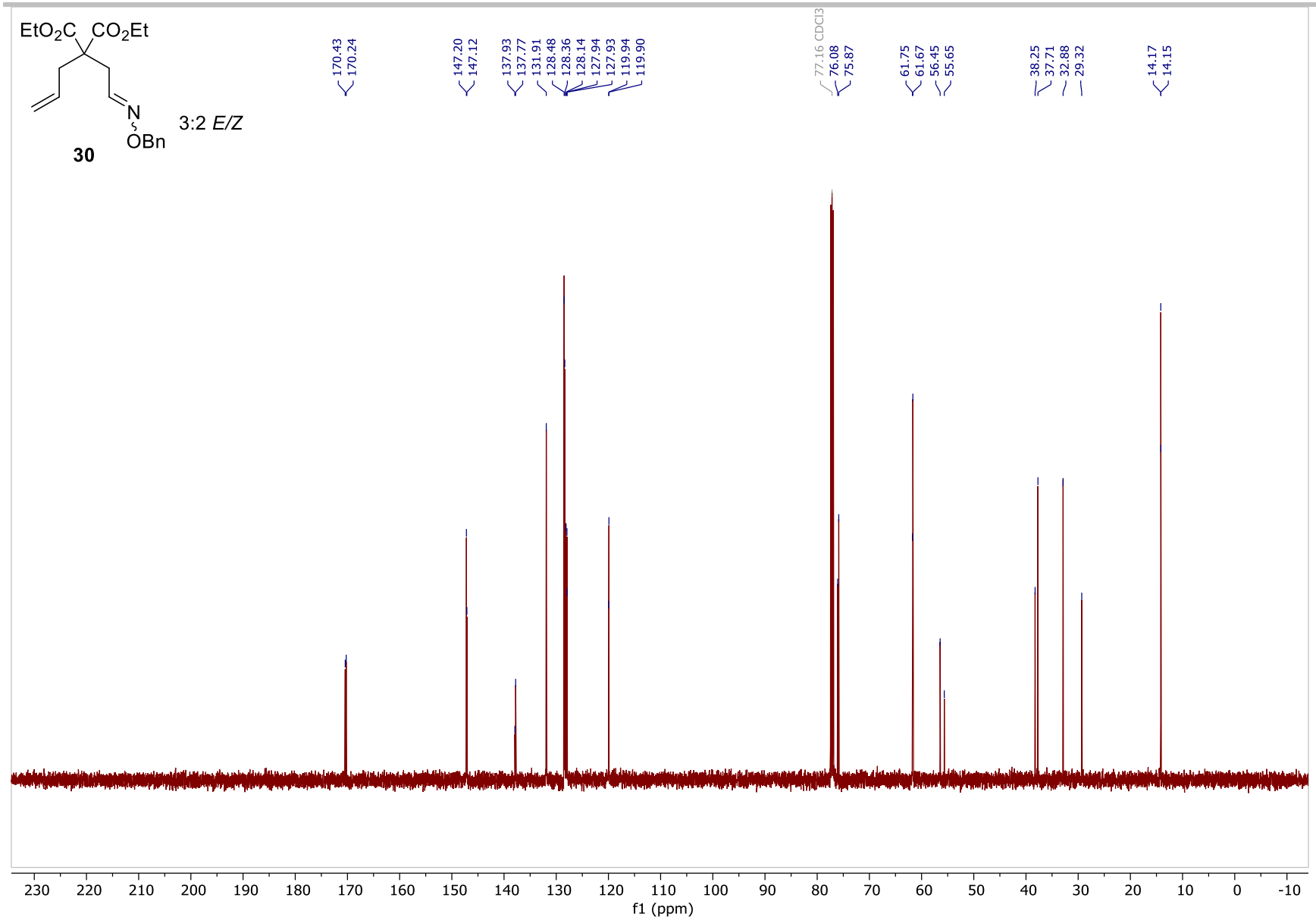

Figure S40. ^{13}C NMR (125 MHz, $CDCl_3$) of **30.**

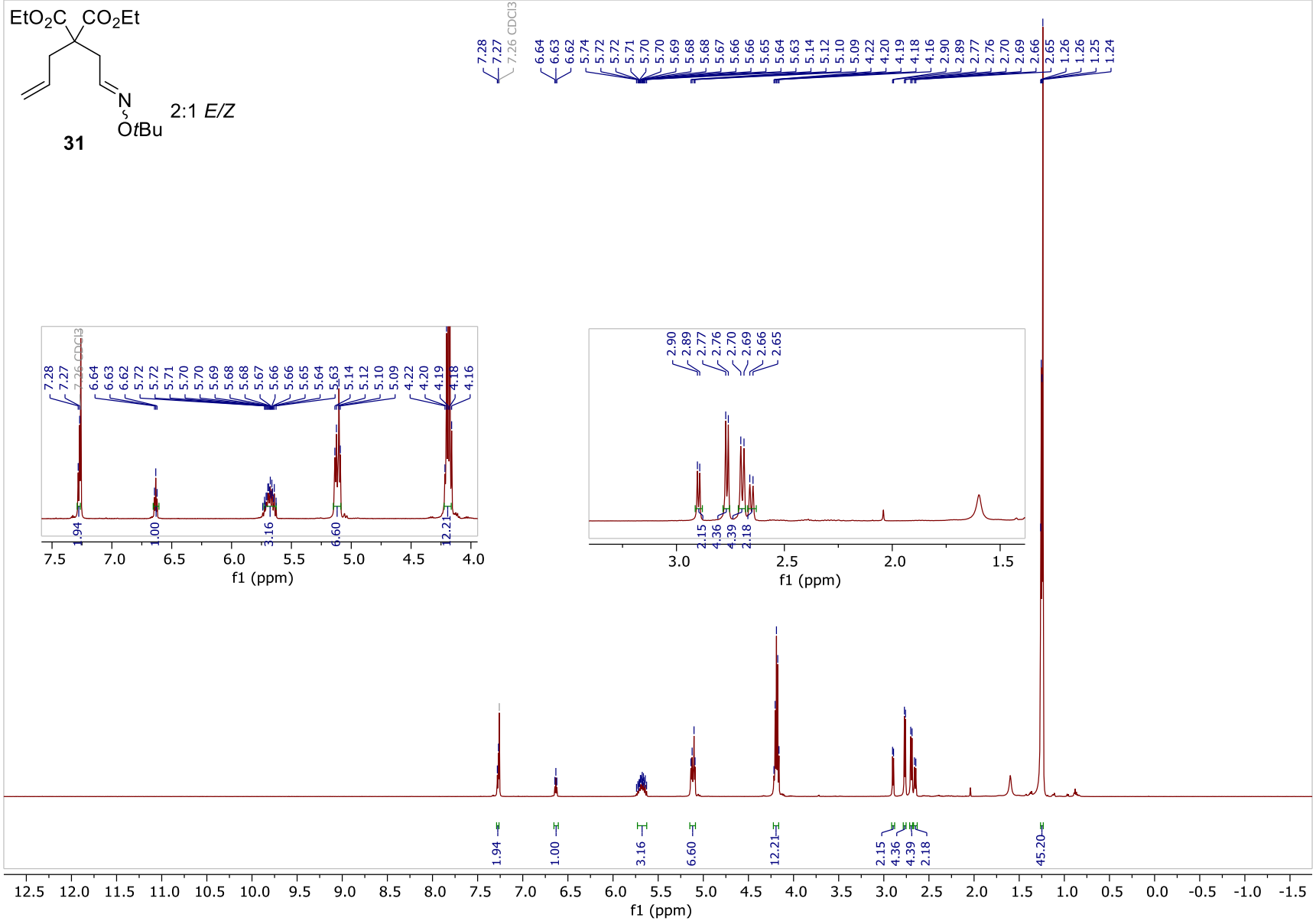

Figure S41. ^{1}H NMR (500 MHz, $CDCl_3$) of **31.**

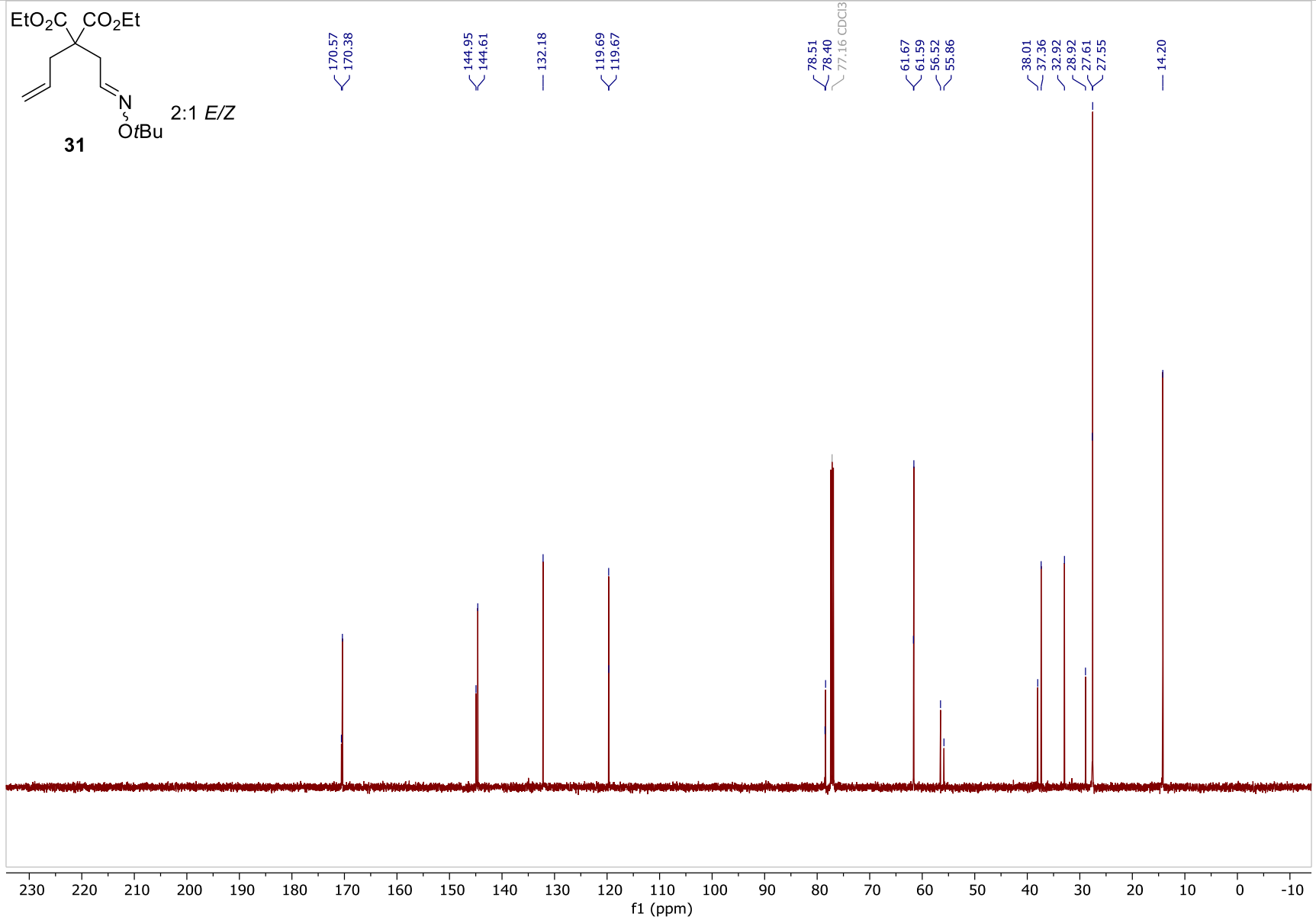

Figure S42. ^{13}C NMR (125 MHz, $CDCl_3$) of **31.**

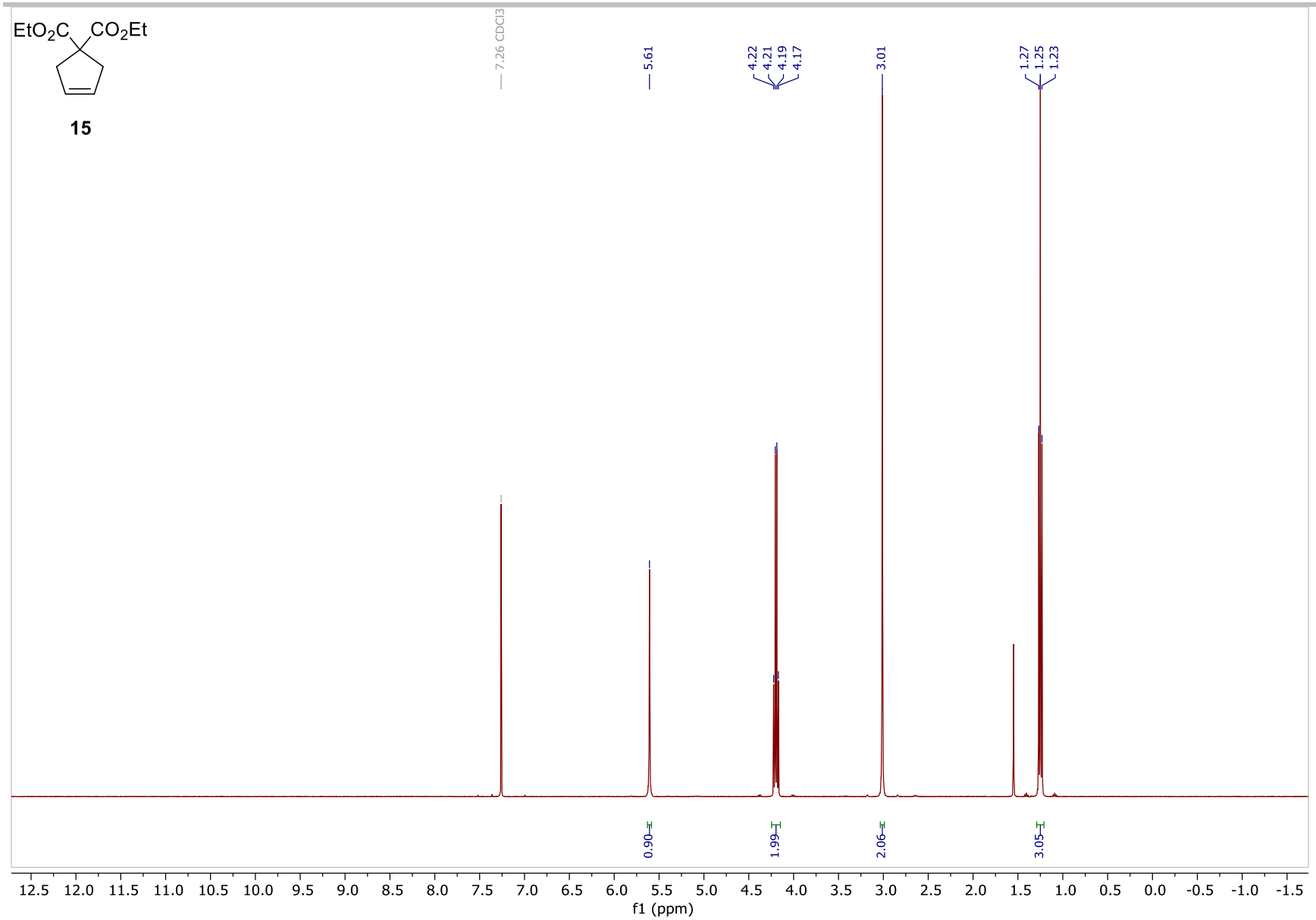

Figure S43. ^{1}H NMR (400 MHz, $CDCl_3$) of **15.**

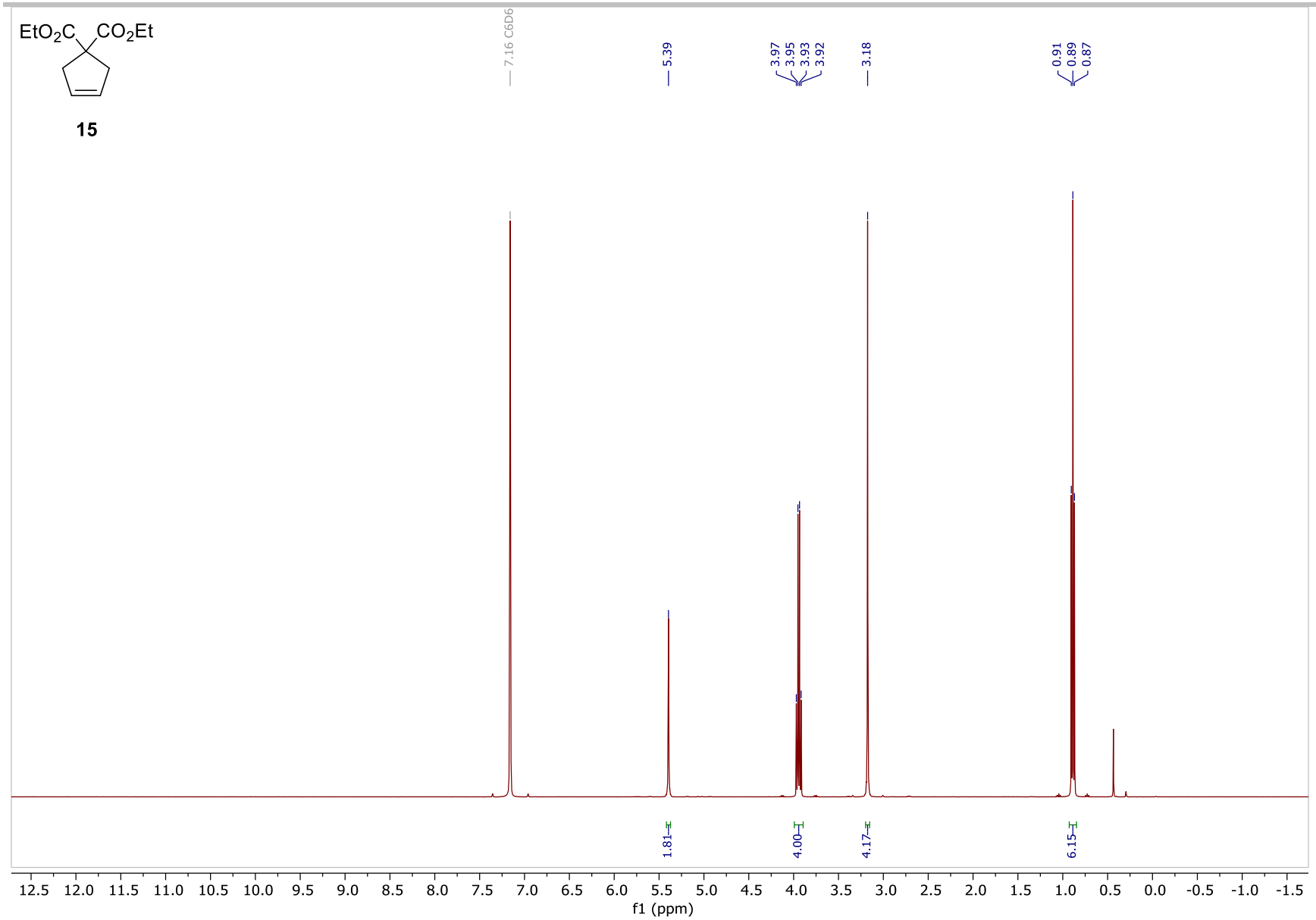

Figure S44. ^{1}H NMR (400 MHz, C_6D_6) of **15.**

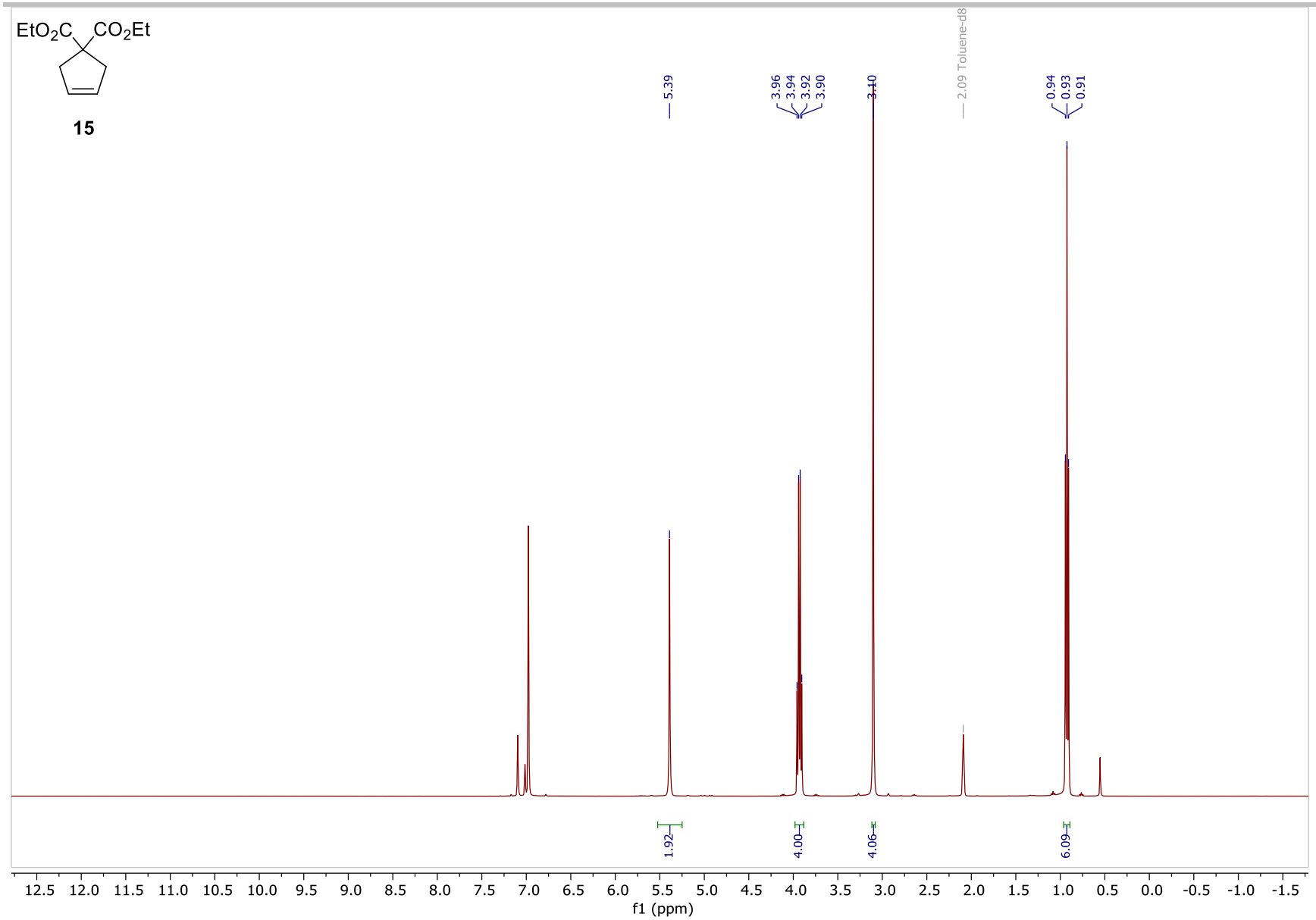

Figure S45. ^{1}H NMR (400 MHz, toluene-d_8) of **15.**

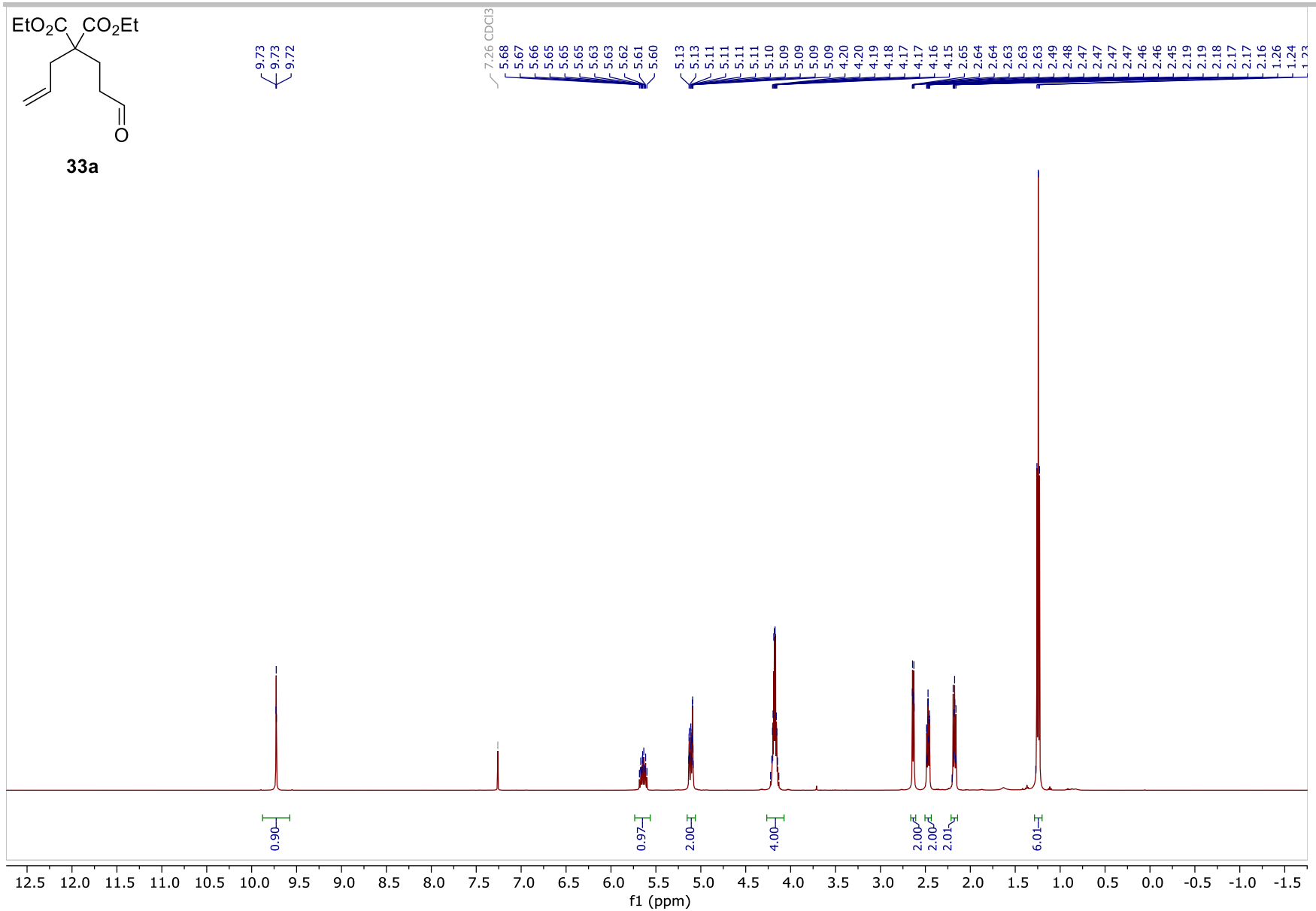

Figure S46. ^{1}H NMR (500 MHz, $CDCl_3$) of **33a**.

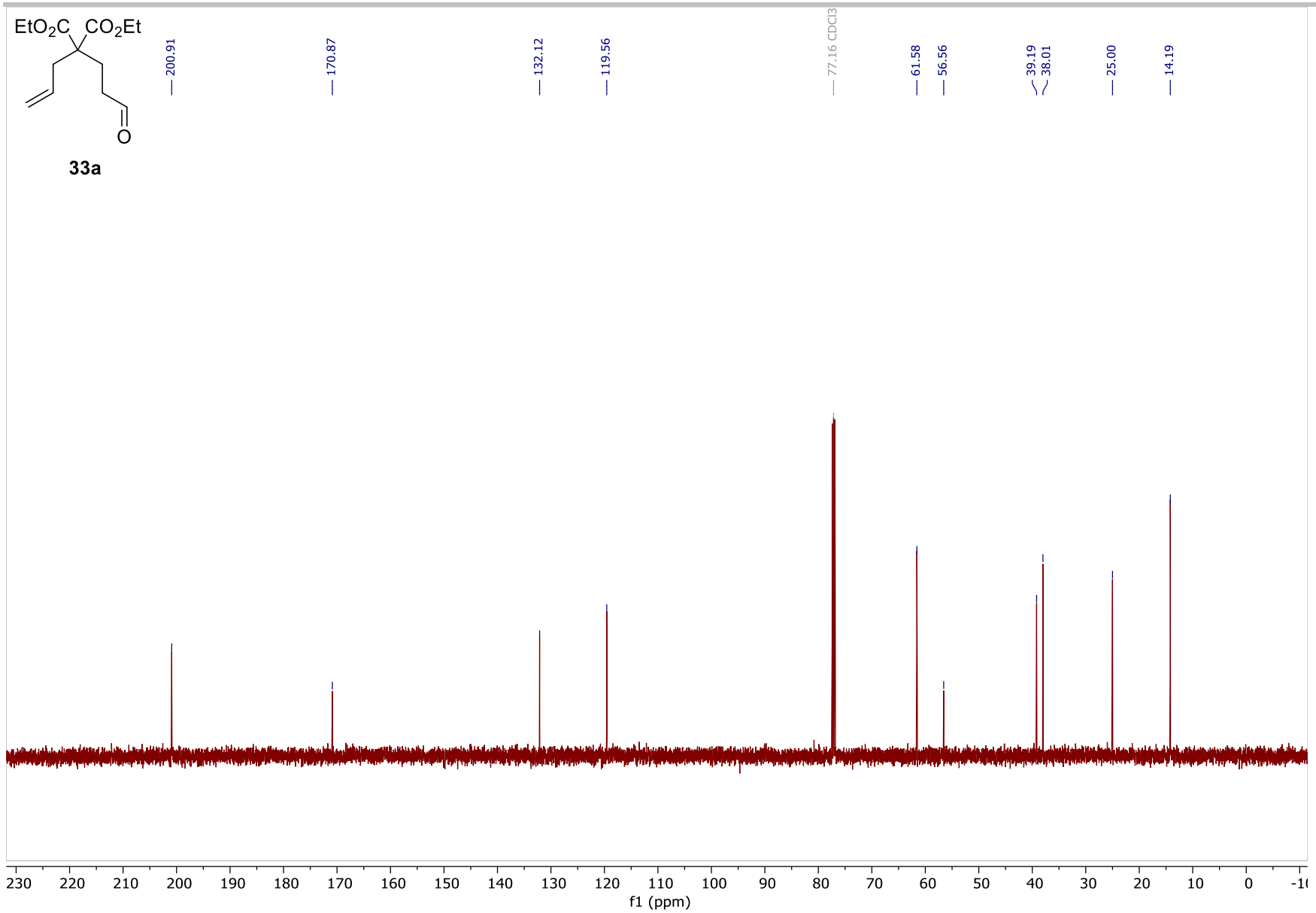

Figure S47. ^{13}C NMR (125 MHz, $CDCl_3$) of **33a.**

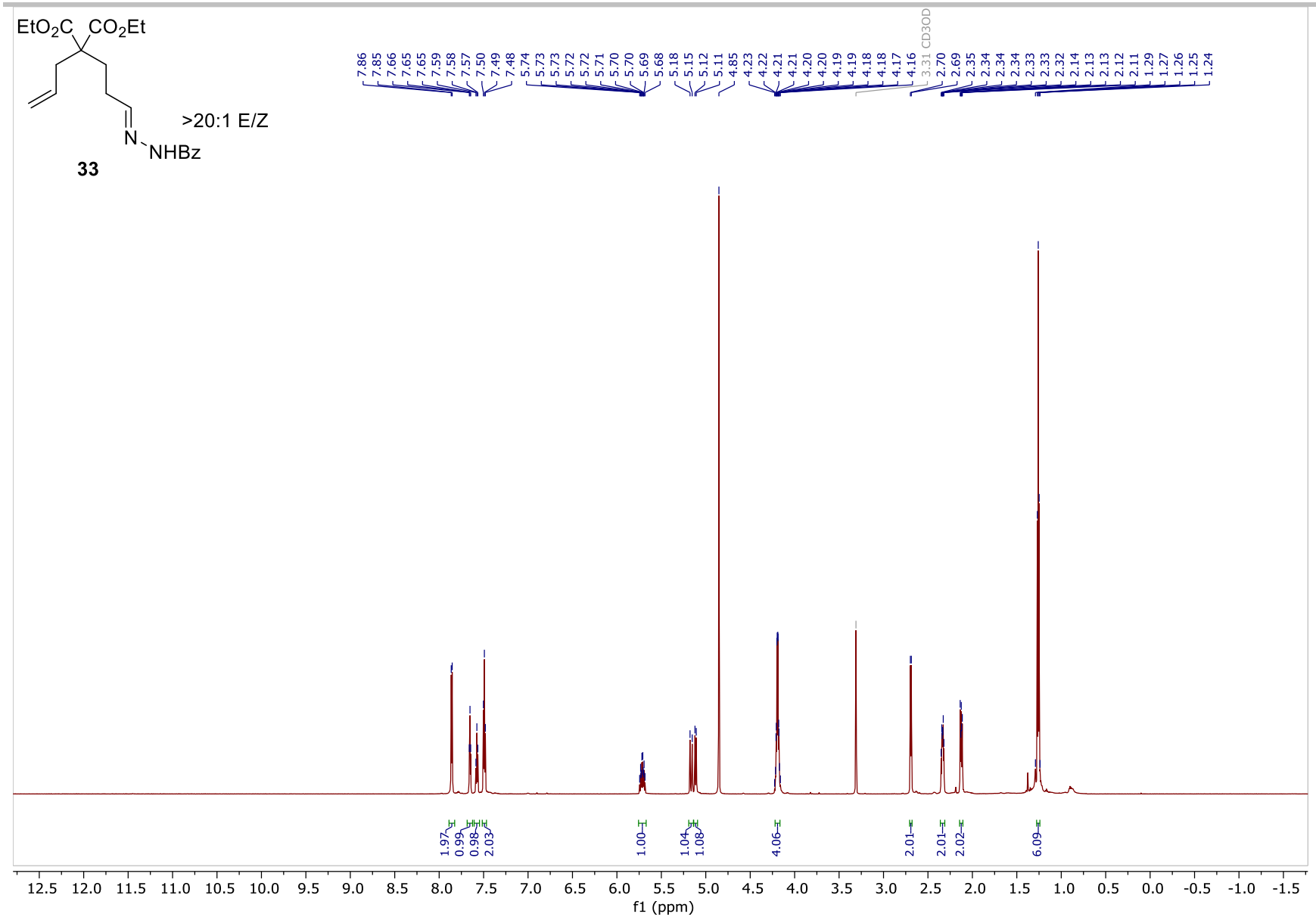

Figure S48. ^{1}H NMR (700 MHz, CD_3OD) of **33.**

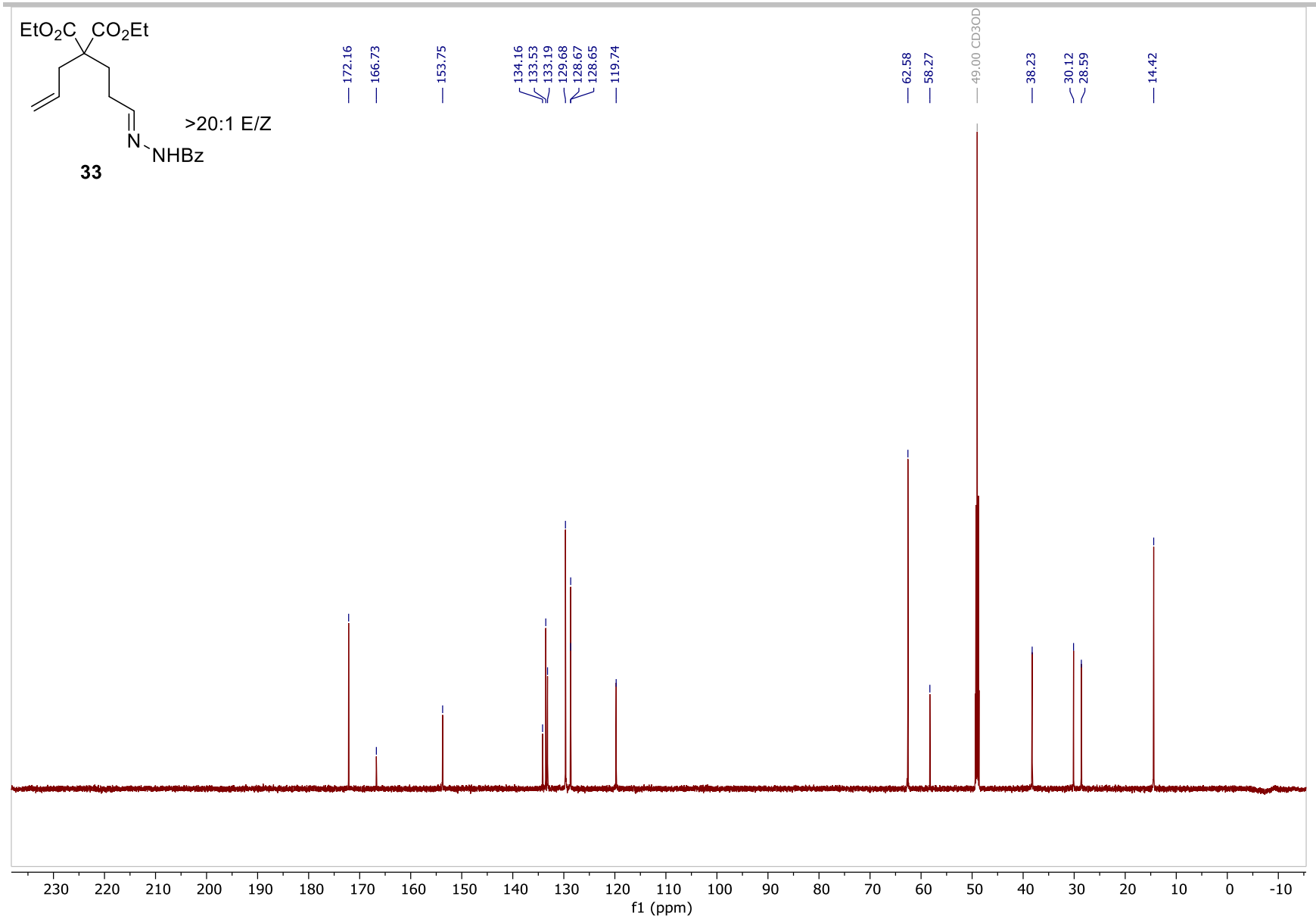

Figure S49. ^{13}C NMR (175 MHz, CD_3OD) of **33.**

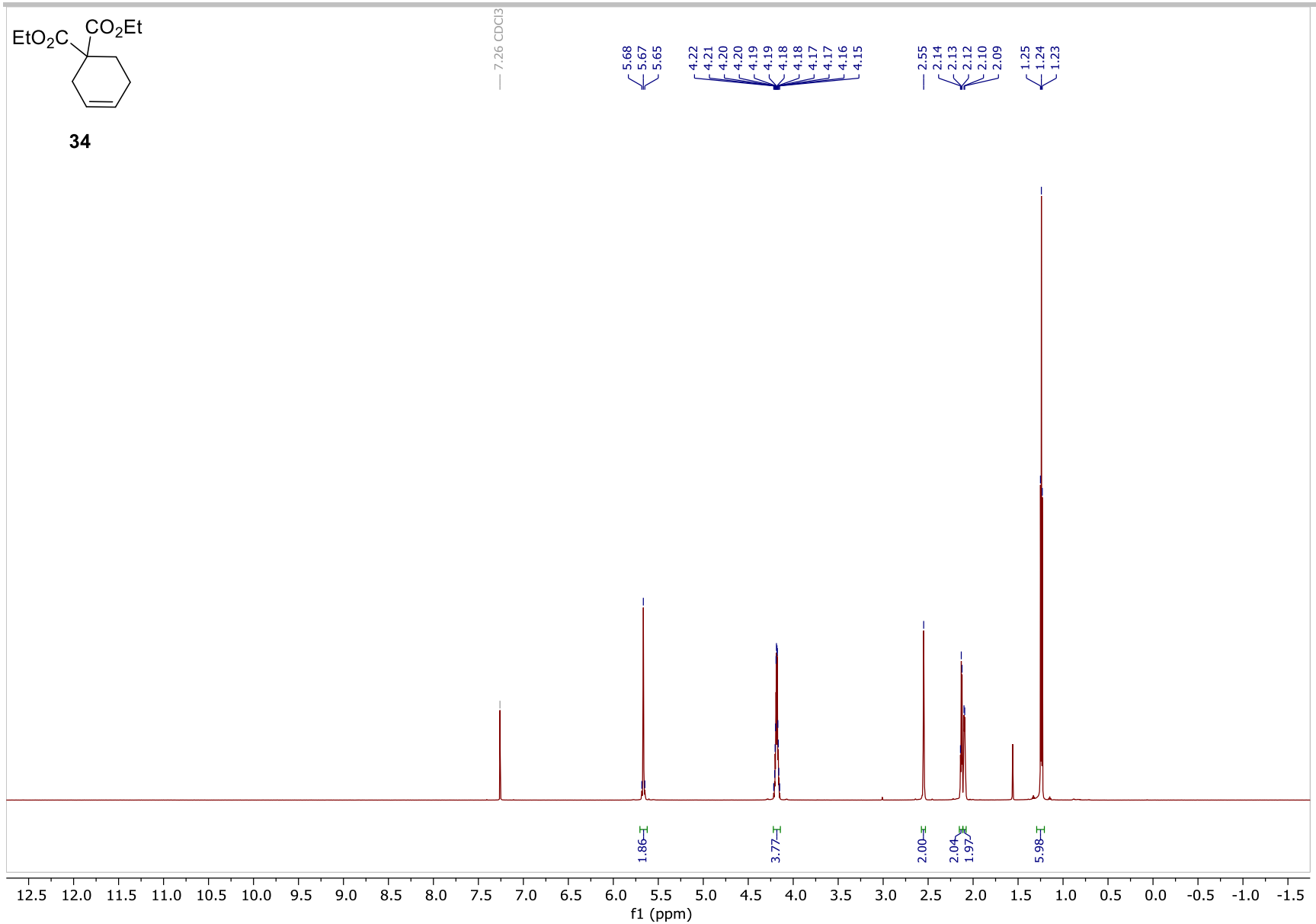

Figure S50. ^{1}H NMR (700 MHz, $CDCl_3$) of **34**.

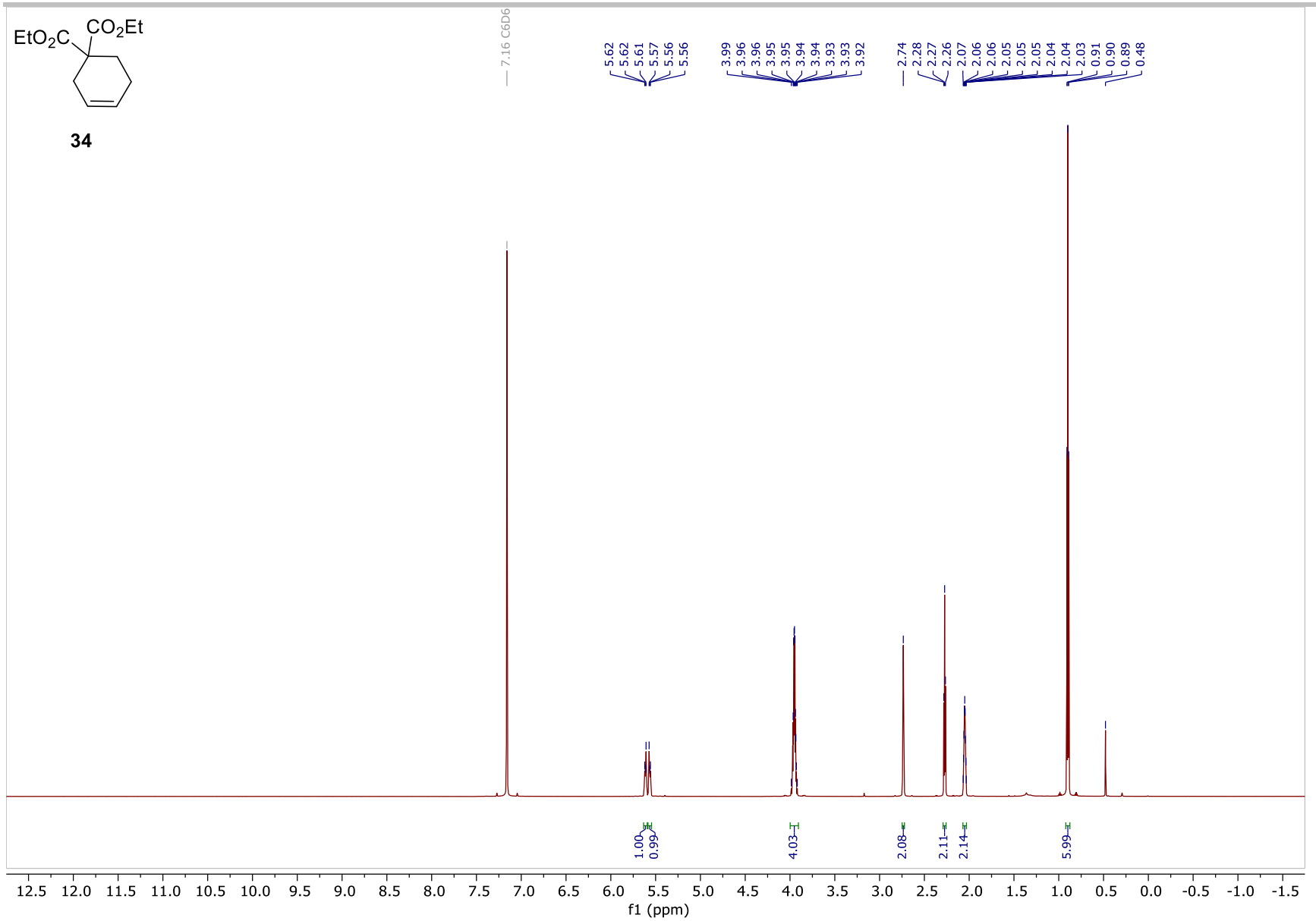

Figure S51. ^{1}H NMR (700 MHz, C_6D_6) of **34.**

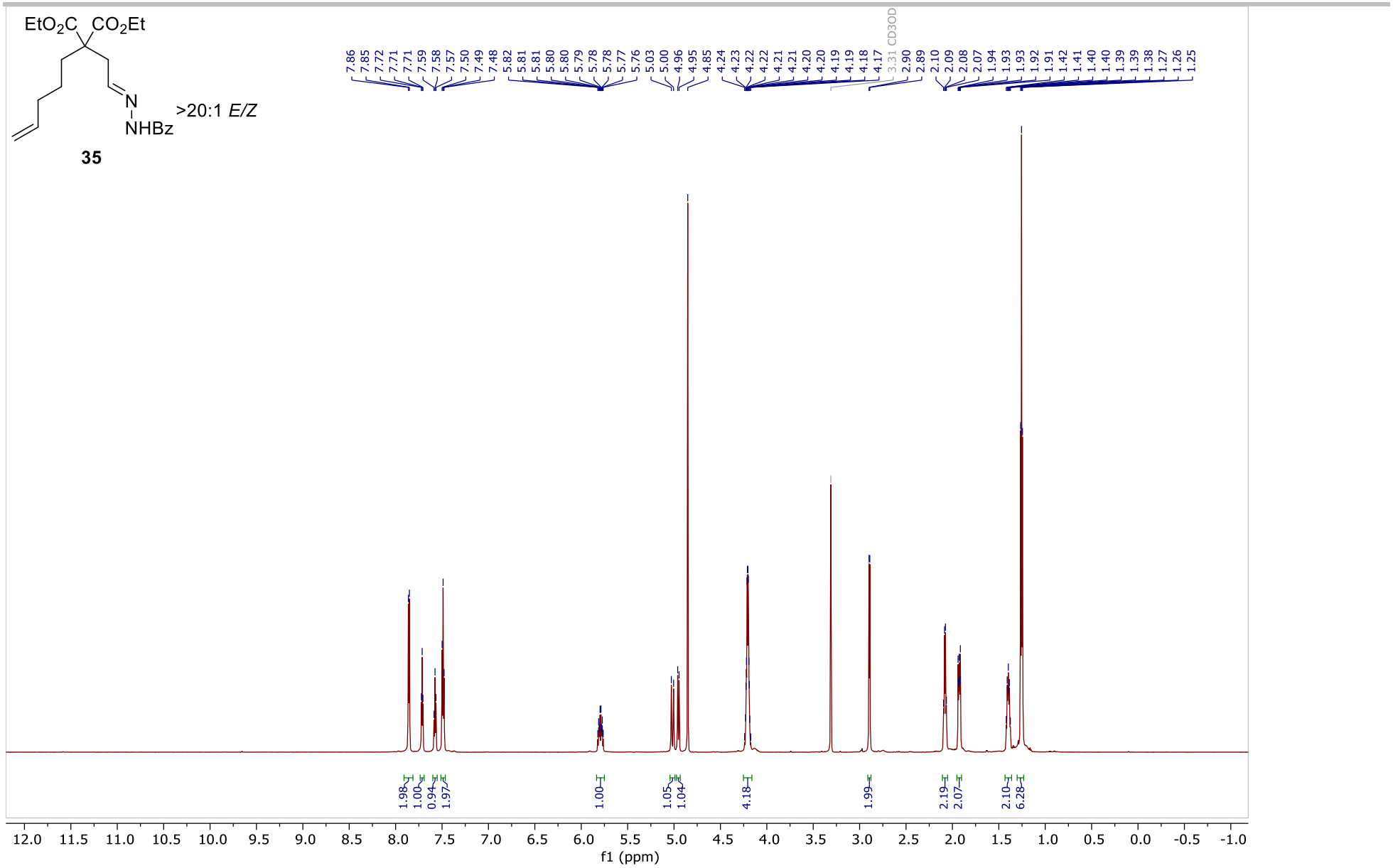

Figure S52. ^{1}H NMR (700 MHz, CD_3OD) of **35**.

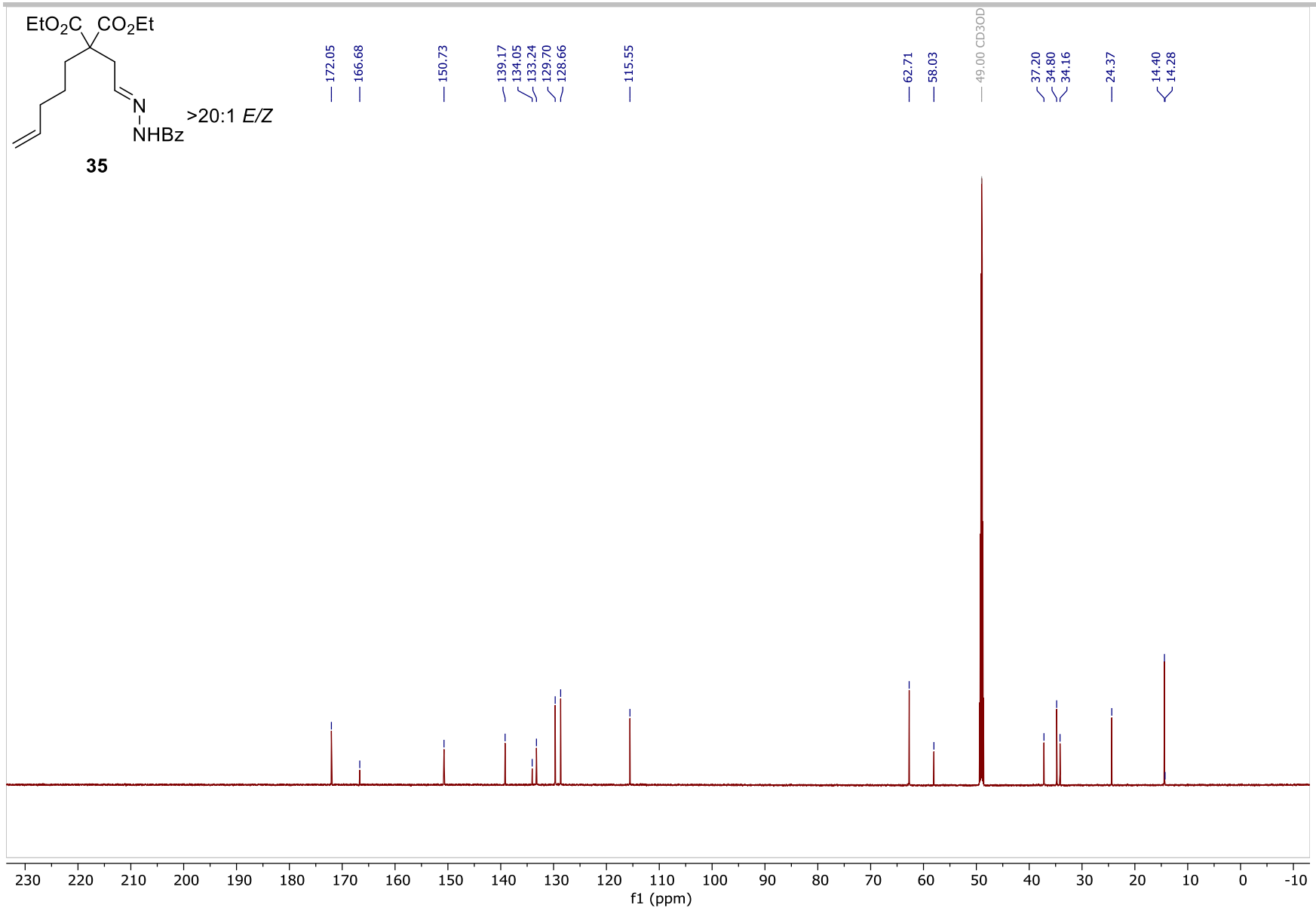

Figure S53. ^{13}C NMR (175 MHz, CD_3OD) of **35.**

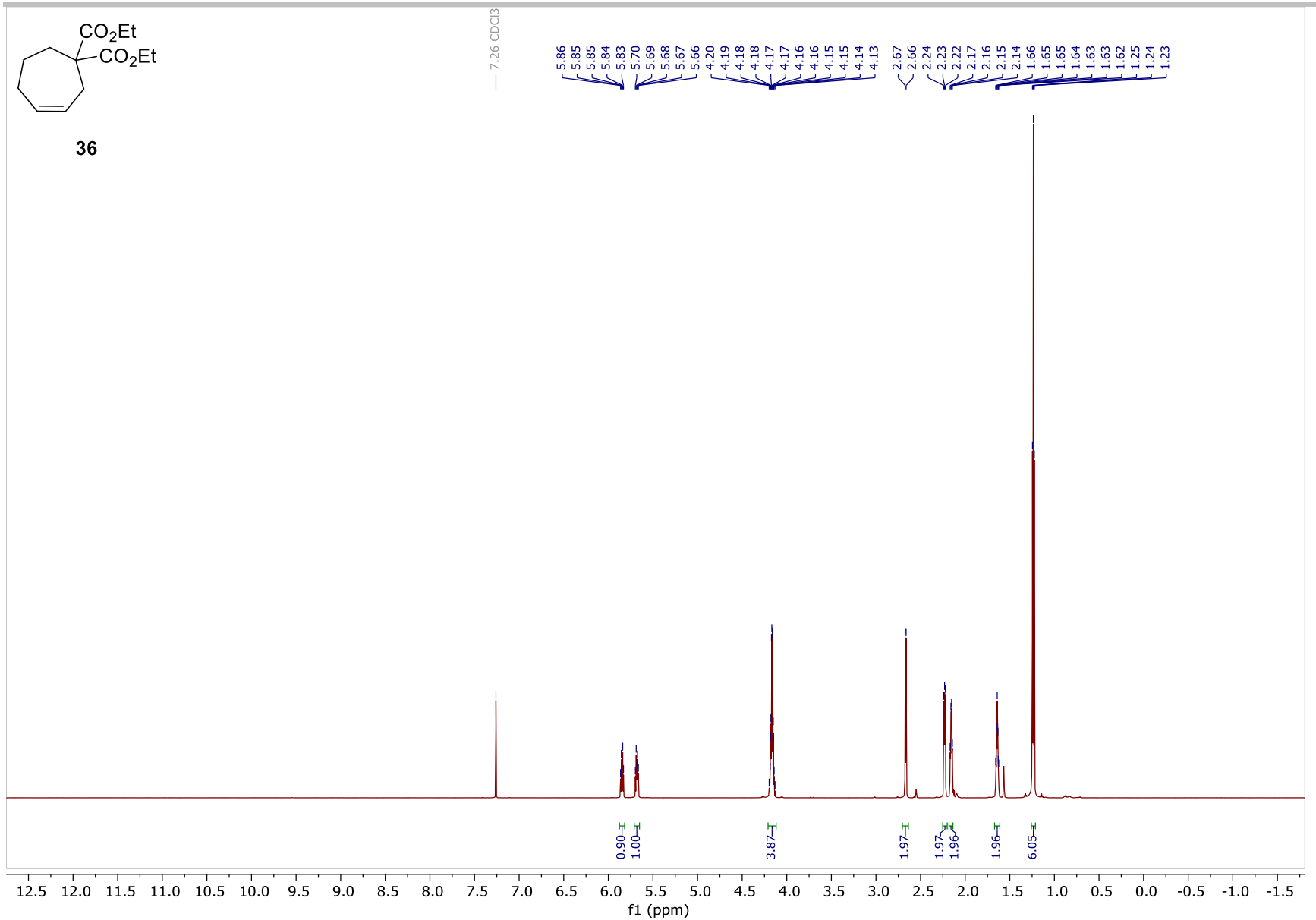

Figure S54. ^{1}H NMR (700 MHz, $CDCl_3$) of **36**.

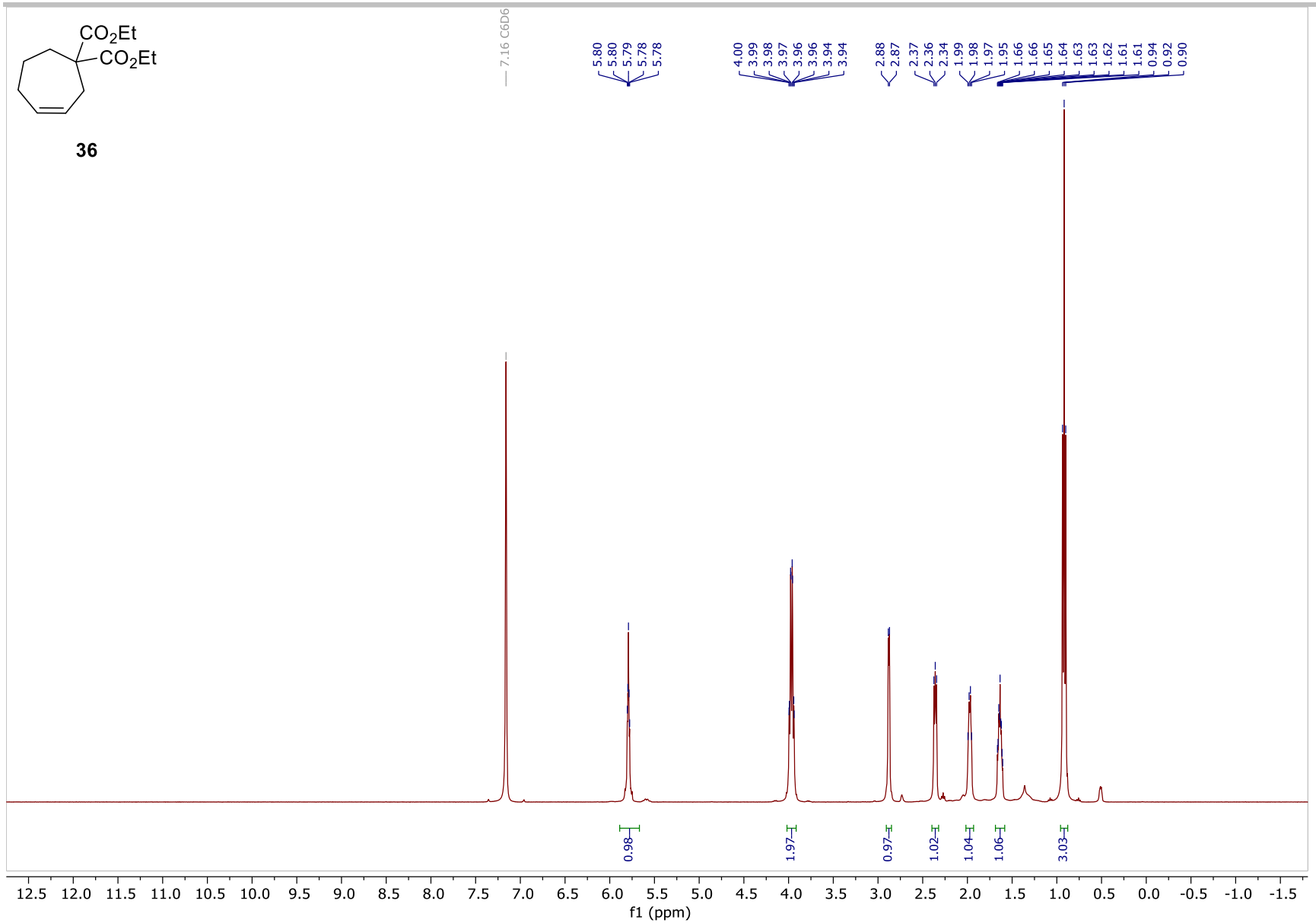

Figure S55. ^{1}H NMR (400 MHz, C_6D_6) of **36.**

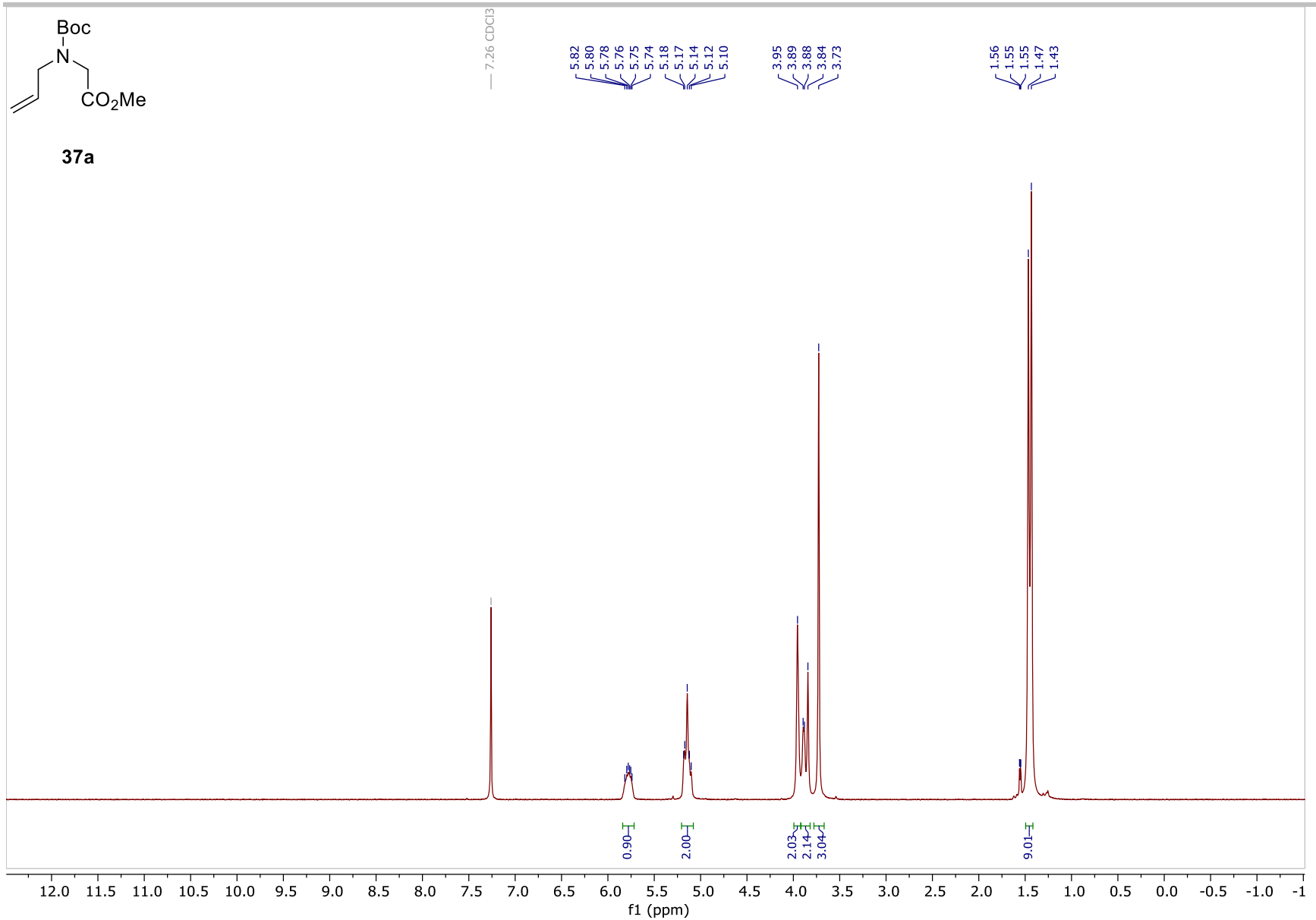

Figure S56. ^{1}H NMR (400 MHz, $CDCl_3$) of **37a**.

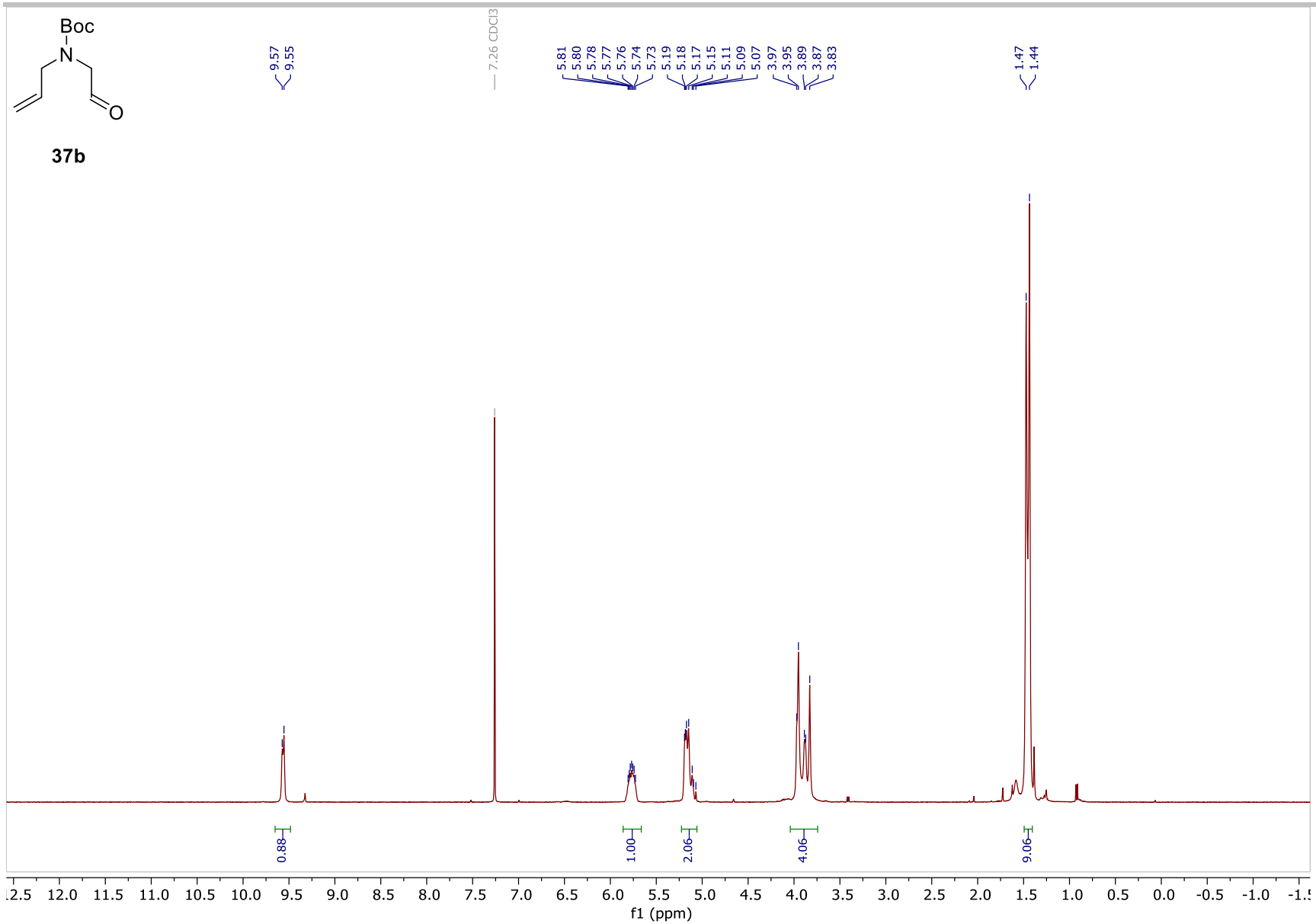

Figure S57. ^{1}H NMR (400 MHz, $CDCl_3$) of **37b**.

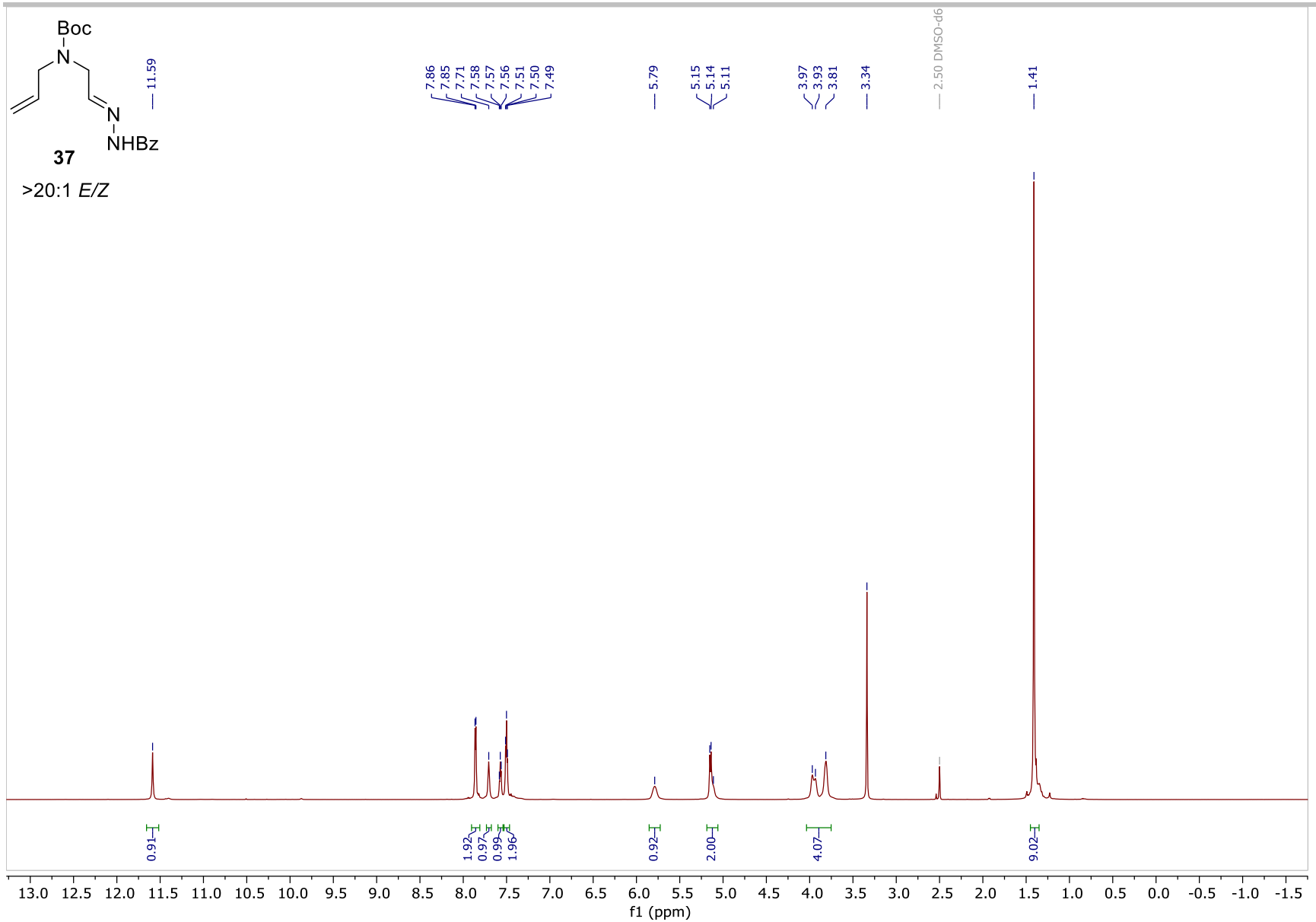

Figure S58. ^{1}H NMR (700 MHz, DMSO-d_6, 25 °C) of **37**.

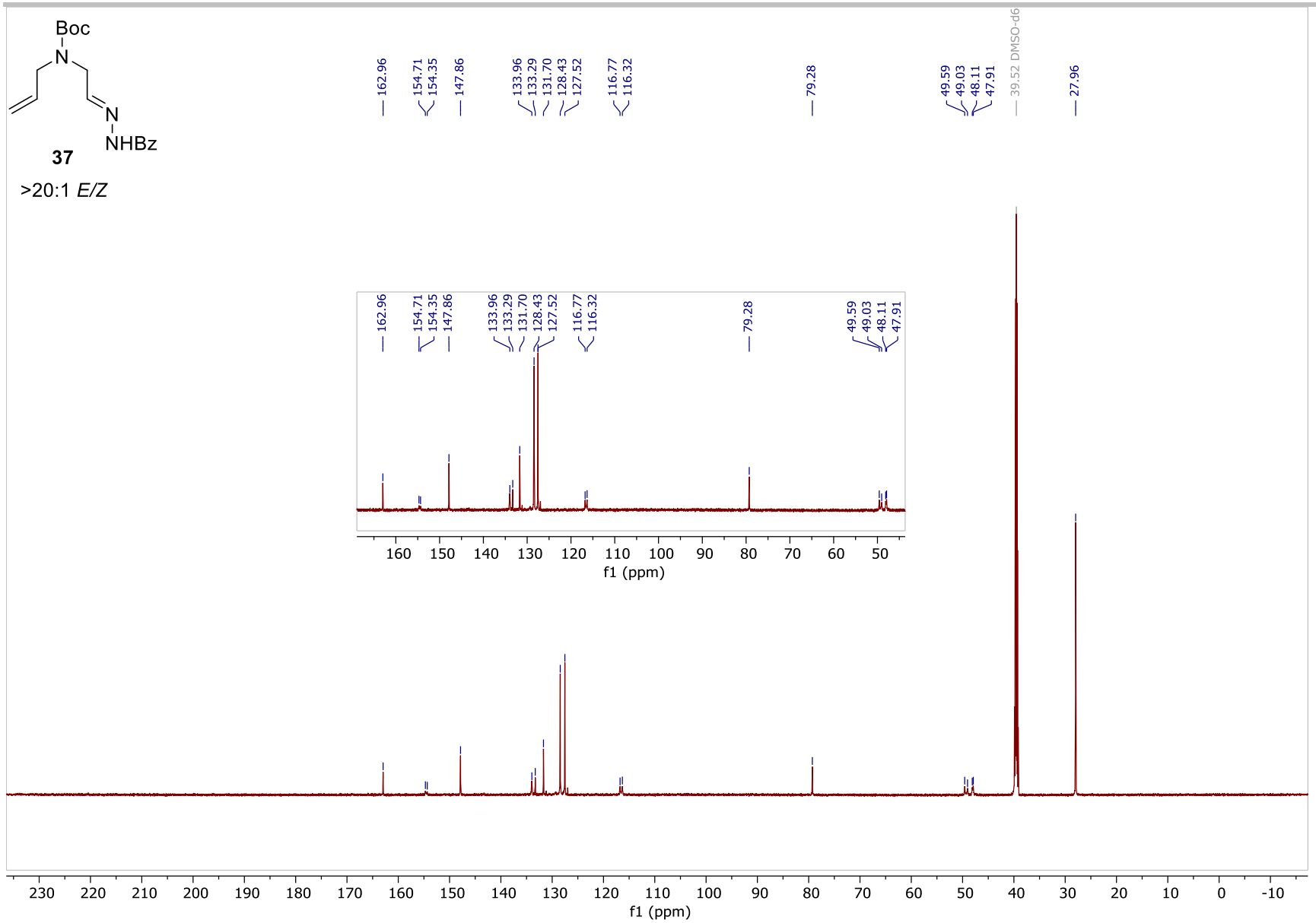

Figure S59. ^{13}C NMR (175 MHz, DMSO-d_6, 25 °C) of **37.**

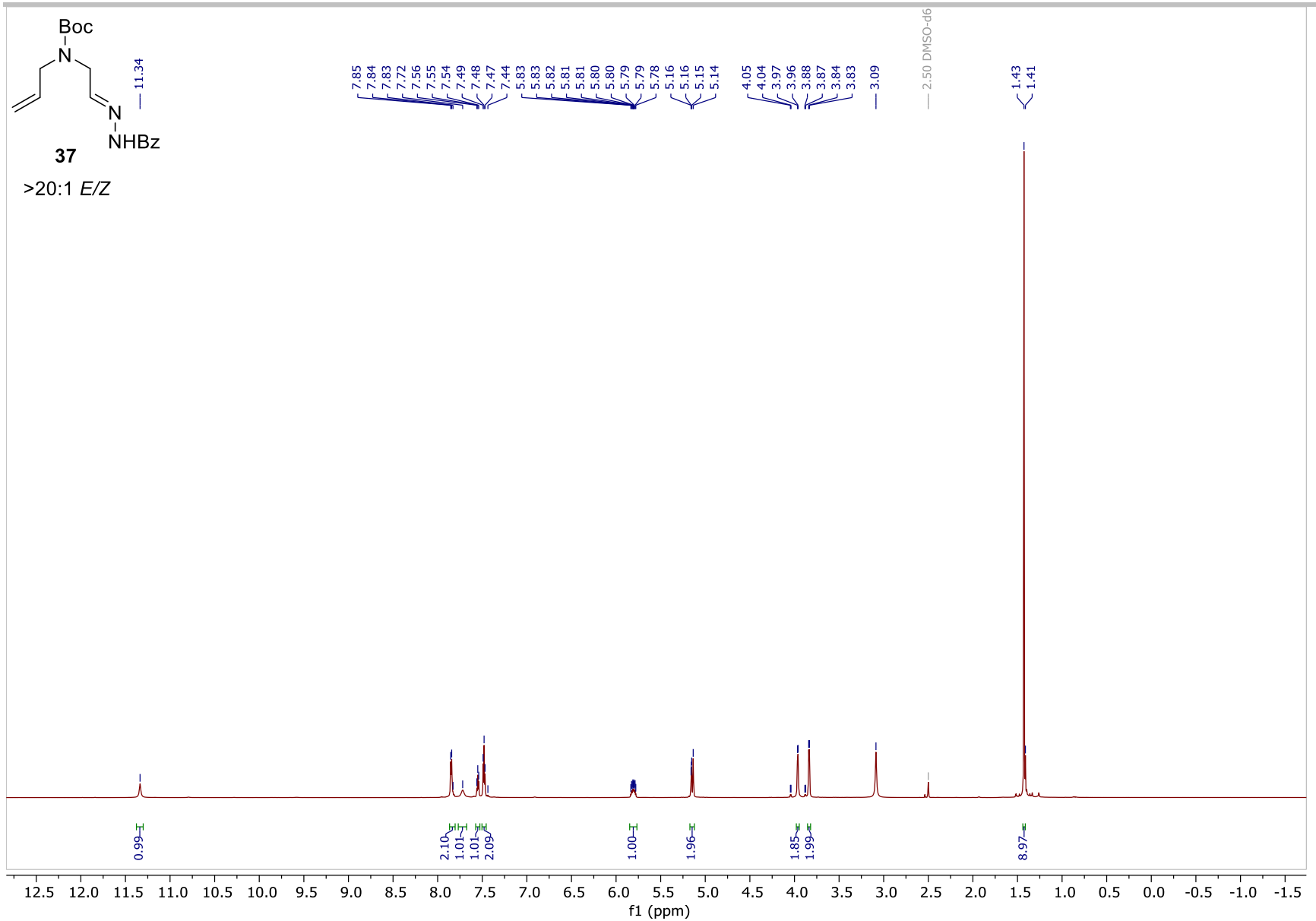

Figure S60. ^{1}H NMR (700 MHz, DMSO-d_6, 80 °C) of **37**.

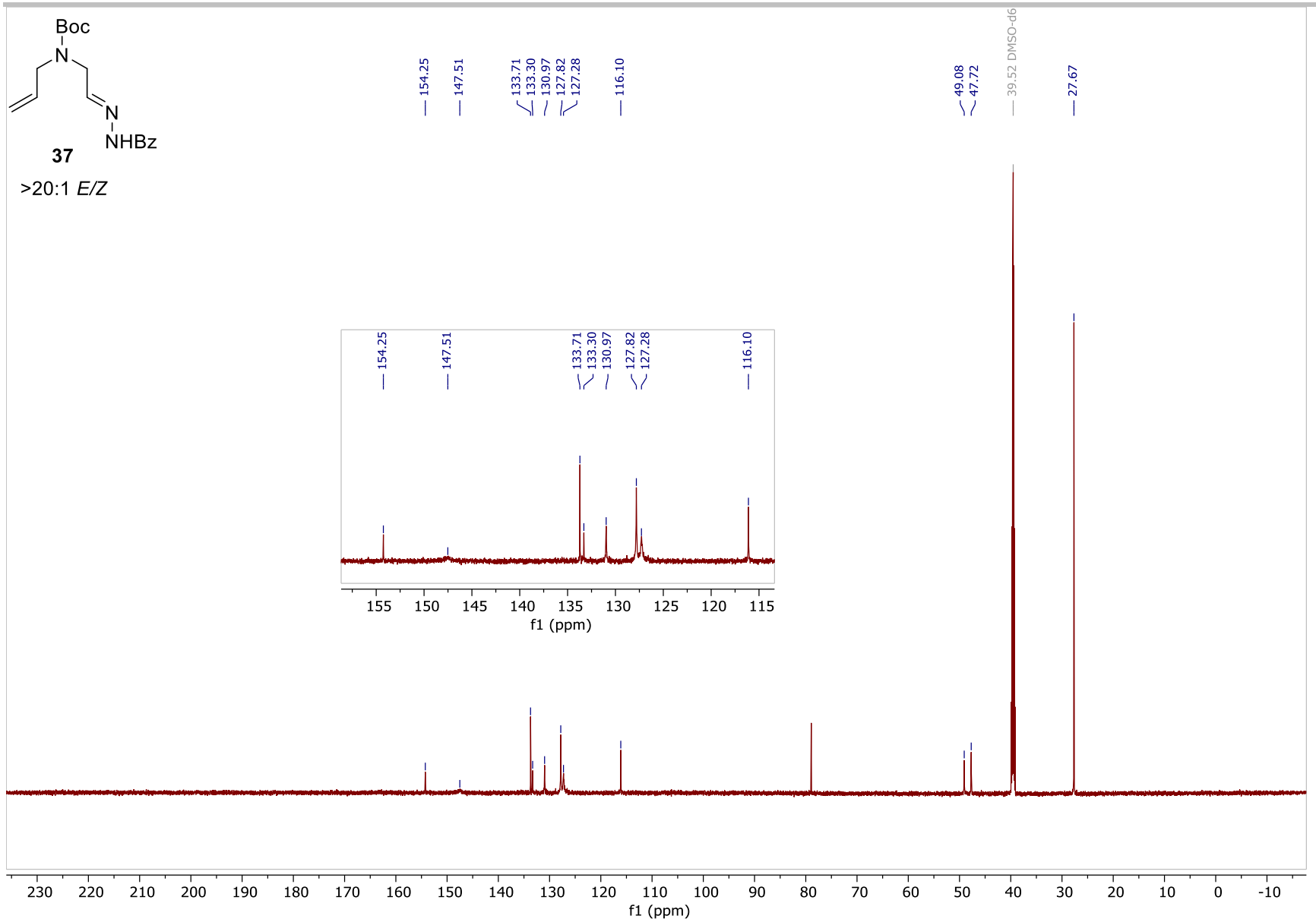

Figure S61. ^{13}C NMR (175 MHz, DMSO-d_6, 80 °C) of **37.**

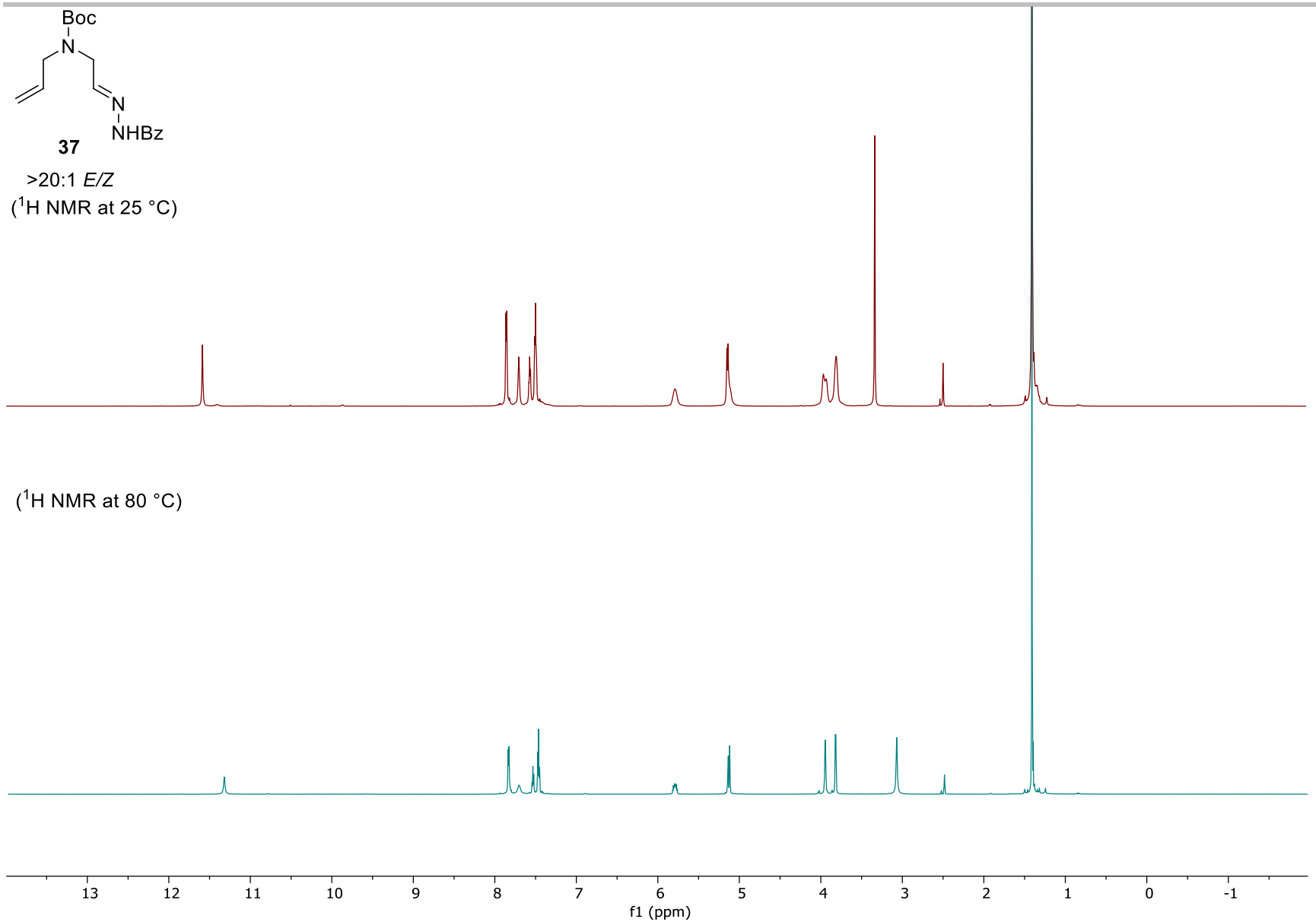

Figure S62. Comparison of variable temperature ^{1}H NMR (700 MHz, DMSO-d_6) spectra of **37**.

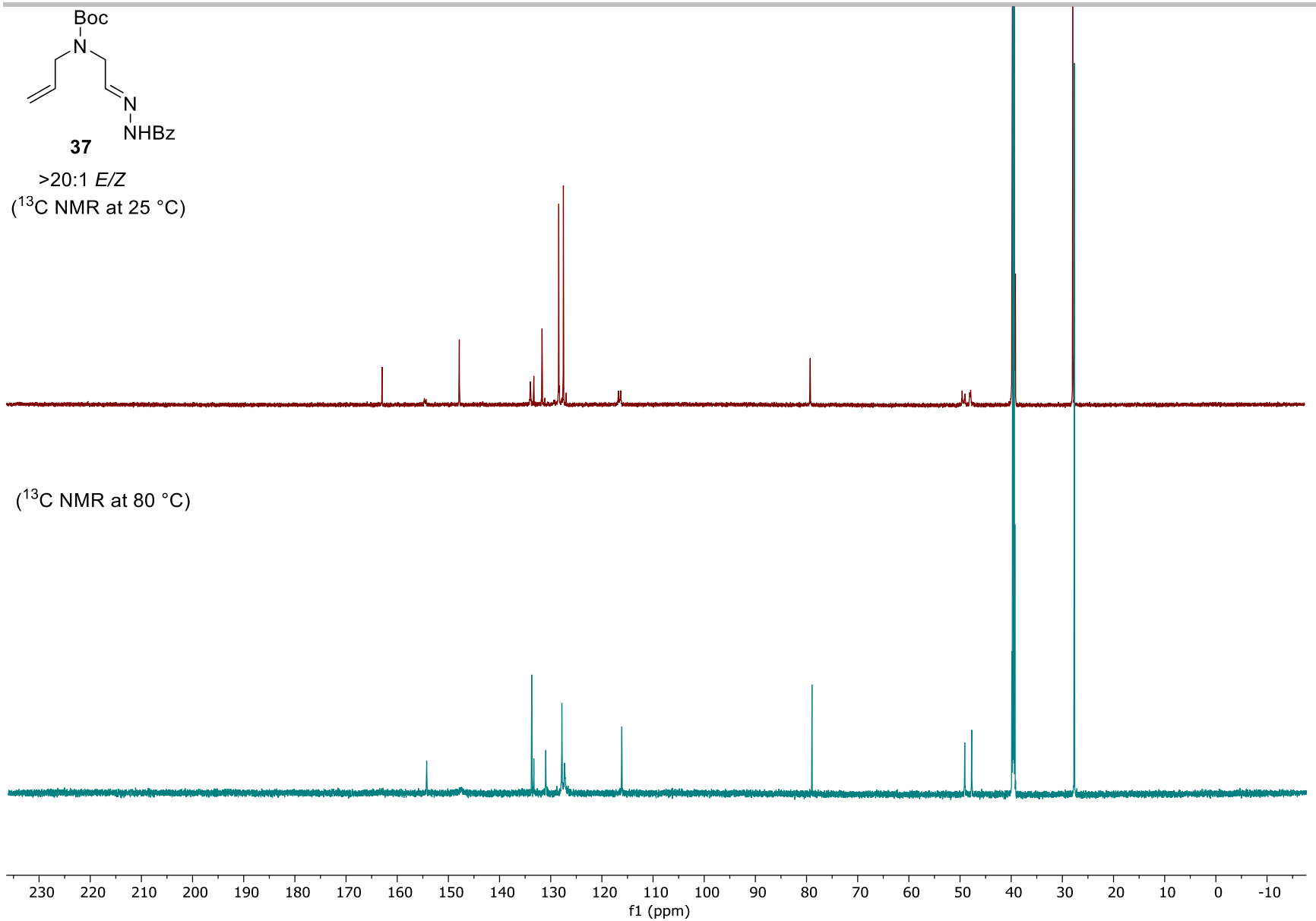

Figure S63. Comparison of variable temperature ^{13}C NMR (175 MHz, DMSO-d_6) spectra of **37**.

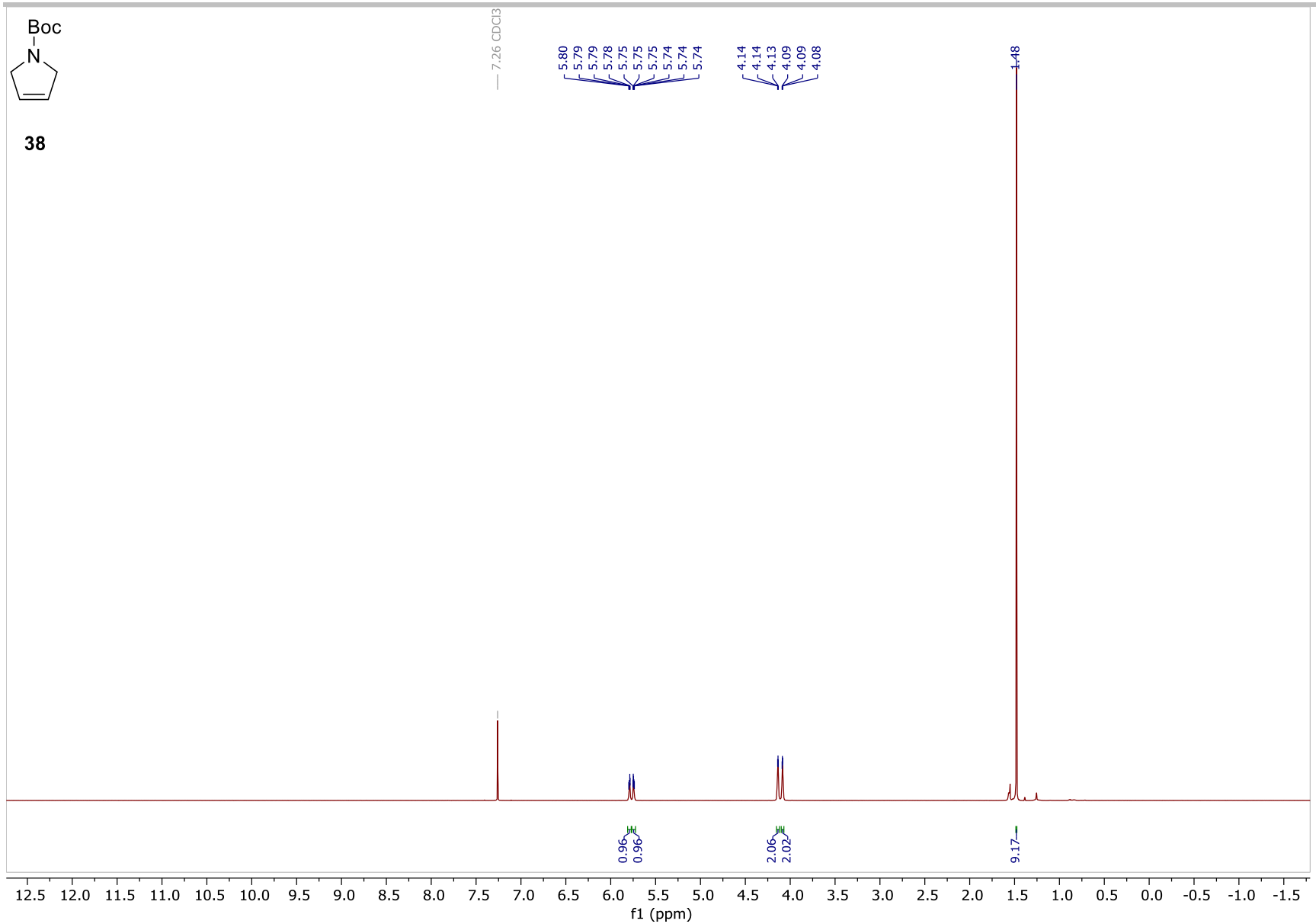

Figure S64. ^{1}H NMR (700 MHz, $CDCl_3$) of **38**.

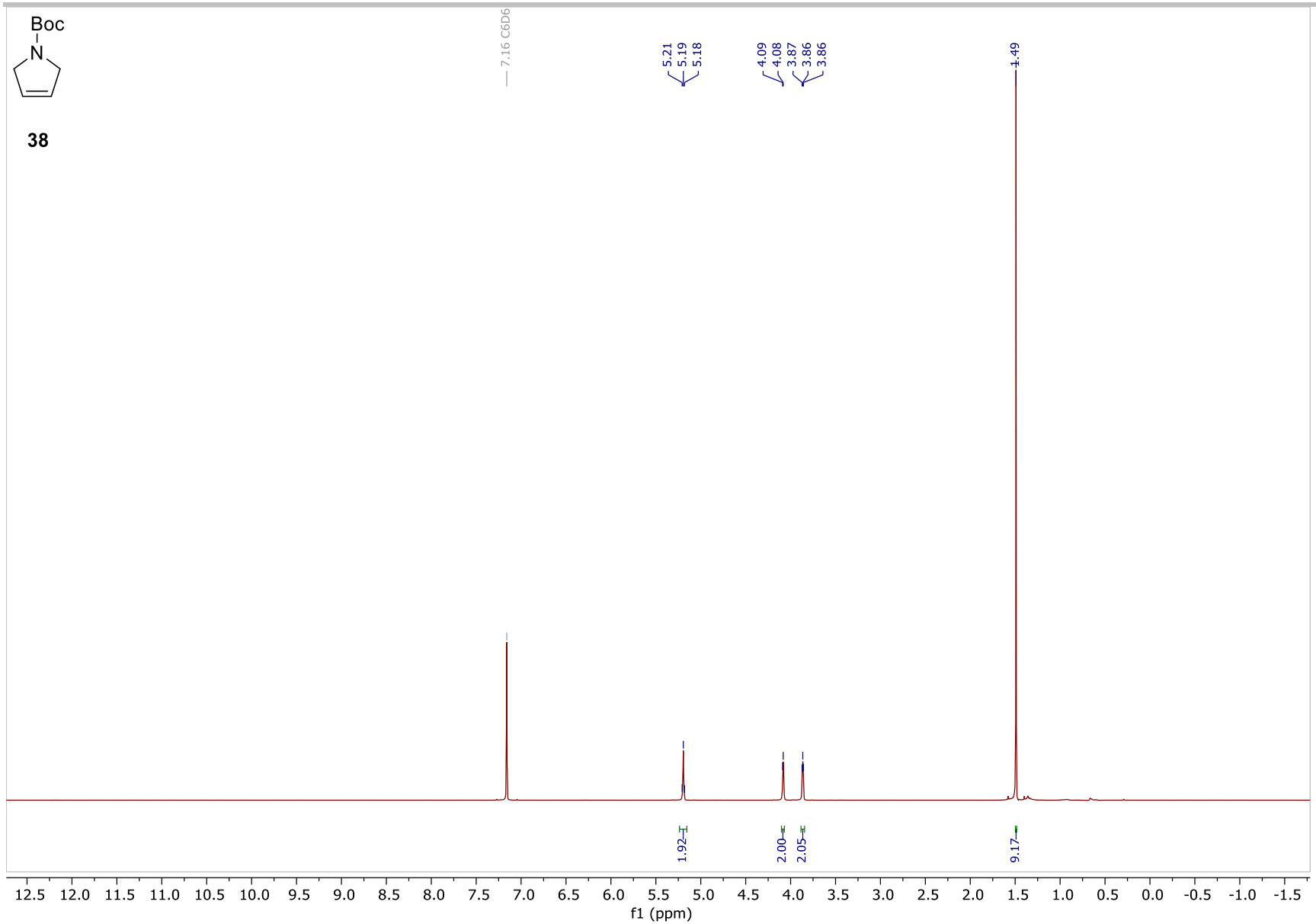

Figure S65. ^{1}H NMR (700 MHz, C_6D_6) of **38.**

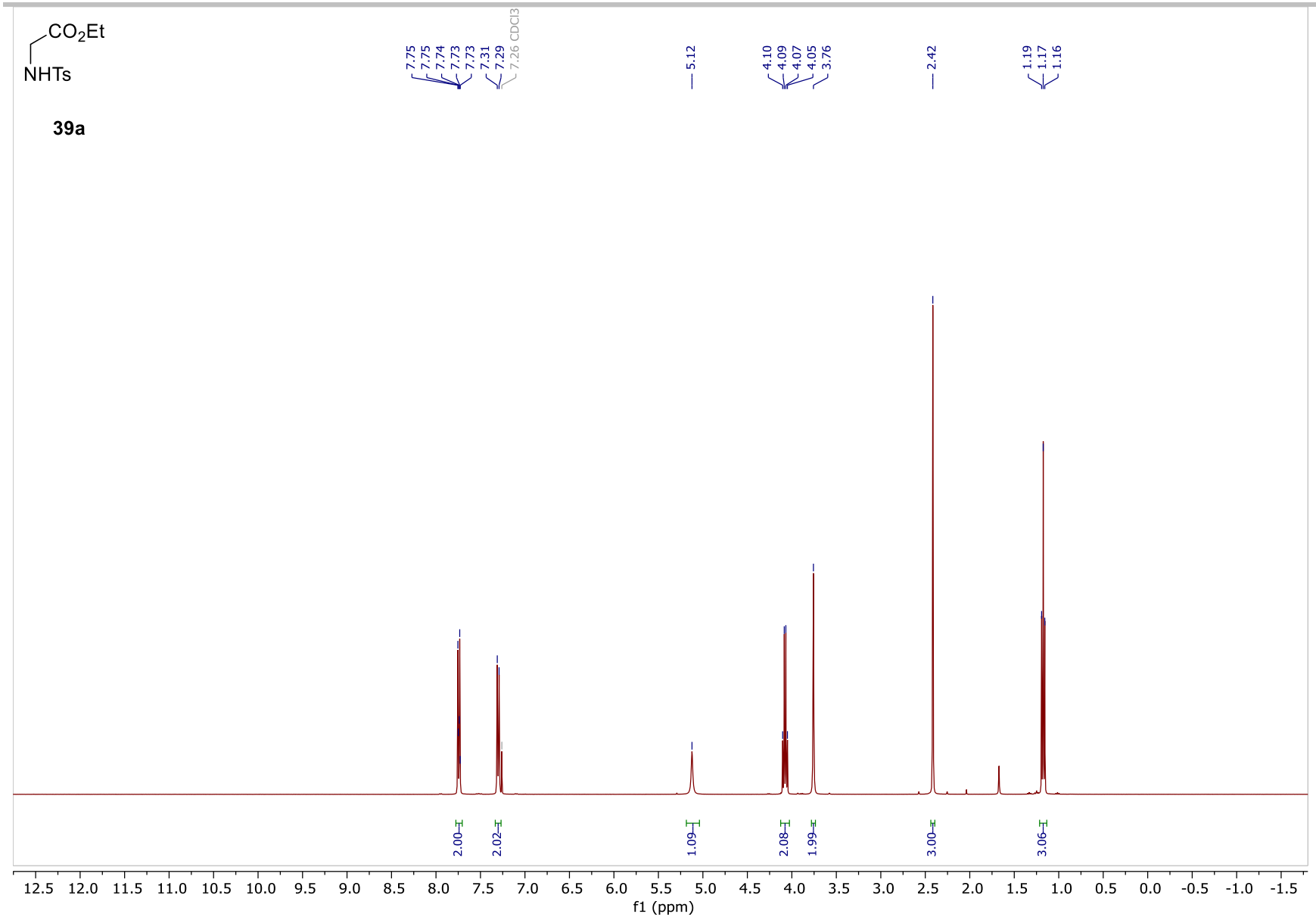

Figure S66. ^{1}H NMR (400 MHz, $CDCl_3$) of **39a**.

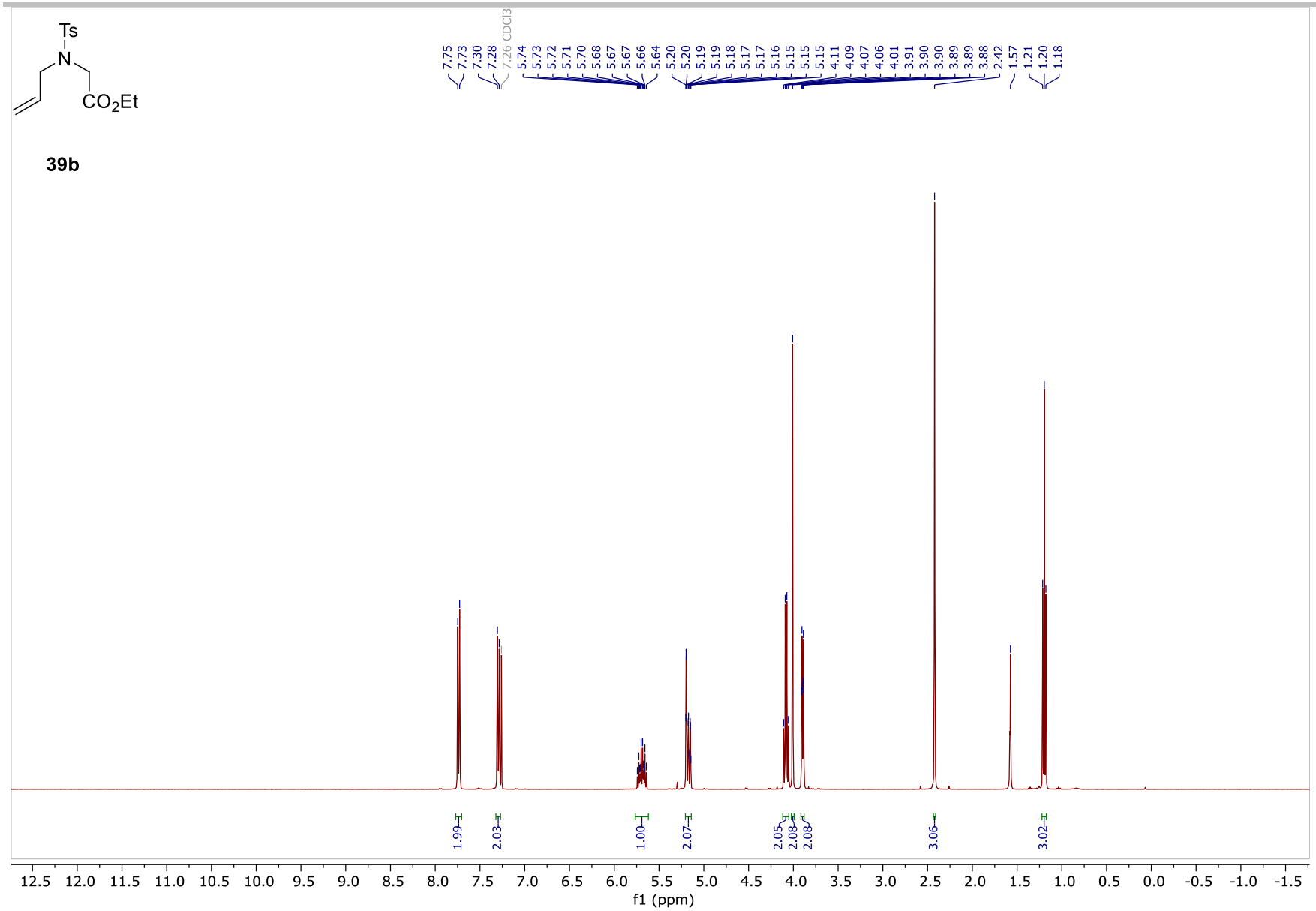

Figure S67. ^{1}H NMR (400 MHz, $CDCl_3$) of **39b**.

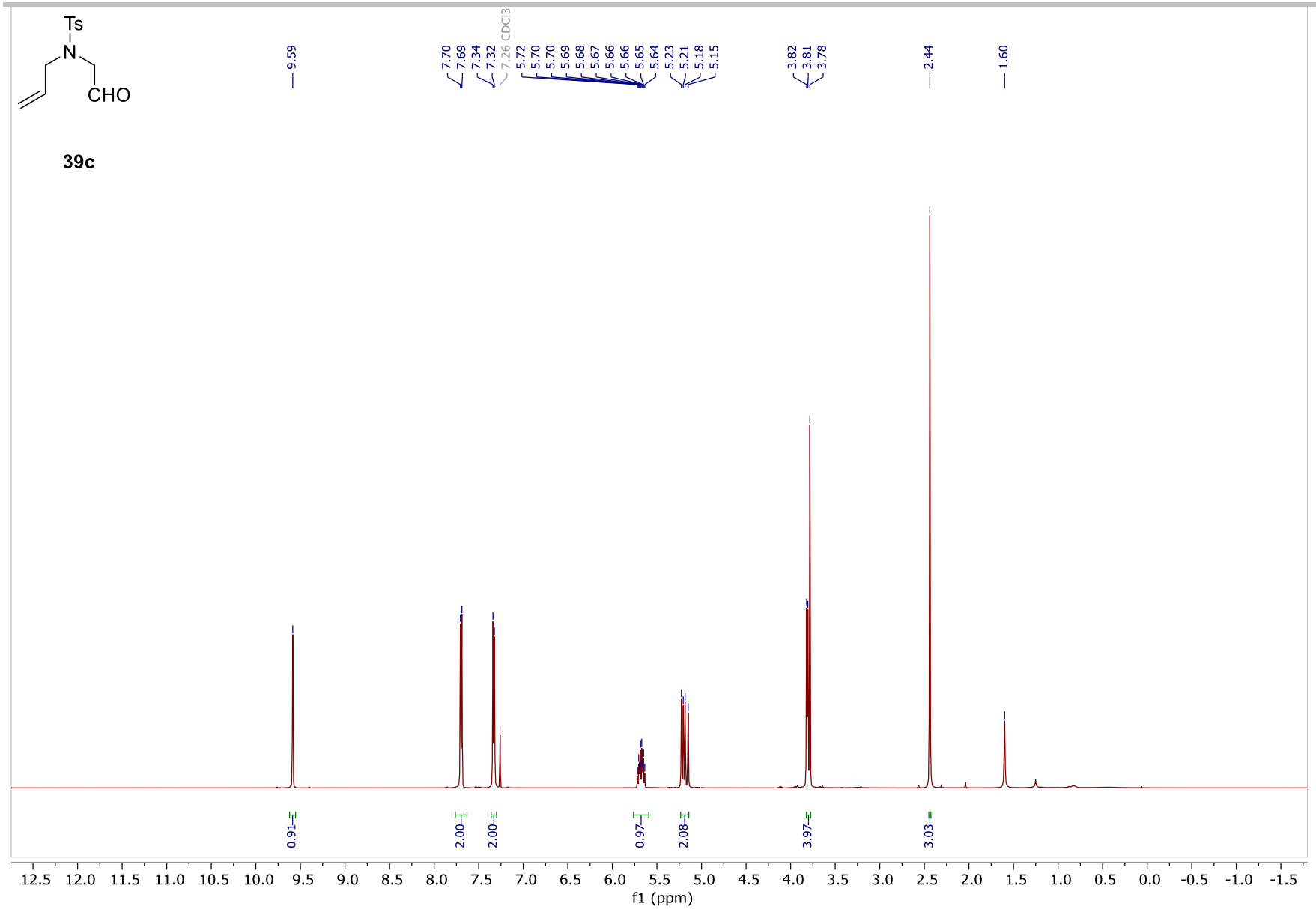

Figure S68. ^{1}H NMR (500 MHz, $CDCl_3$) of **39c**.

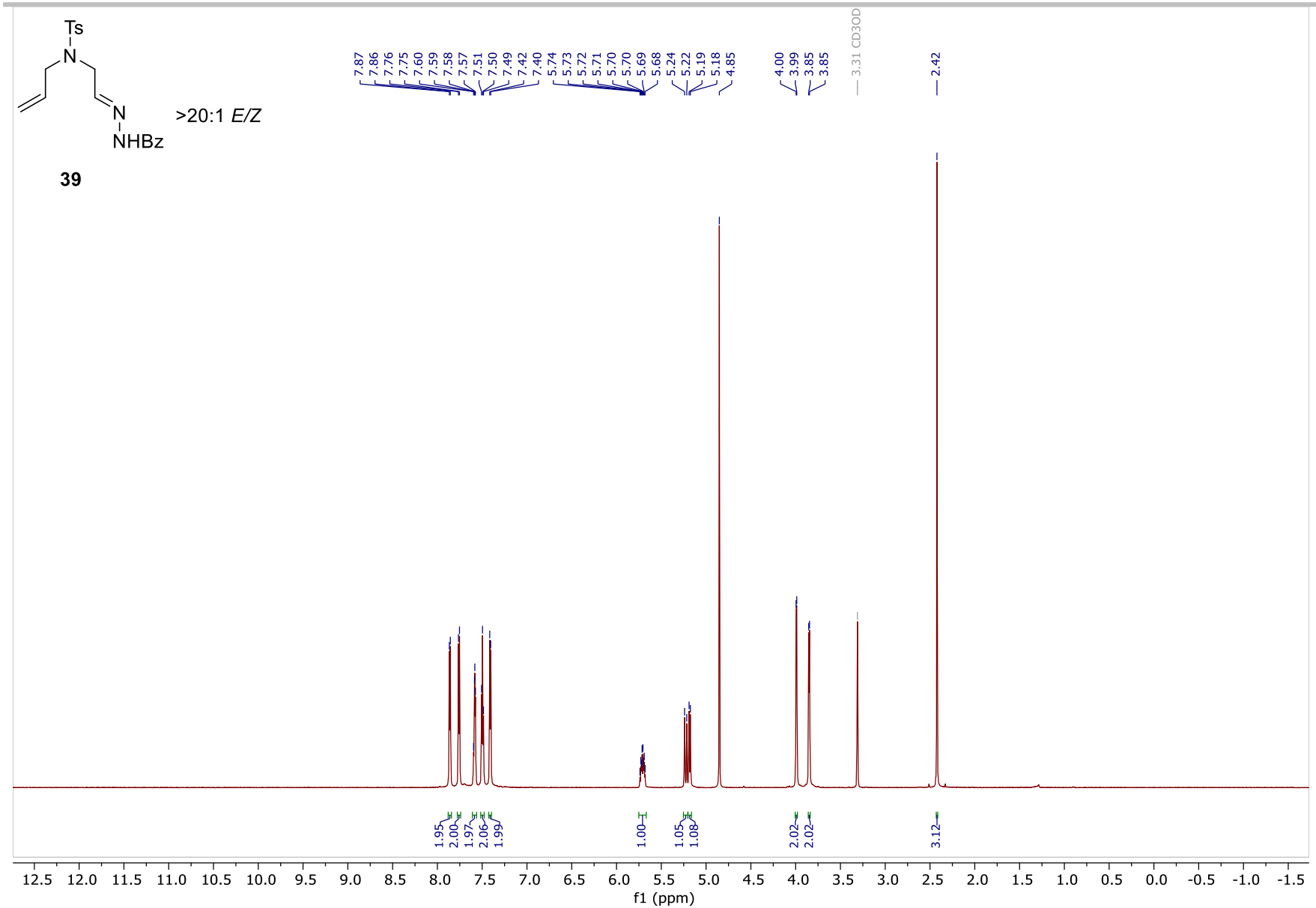

Figure S69. ^{1}H NMR (700 MHz, CD_3OD) of **39**.

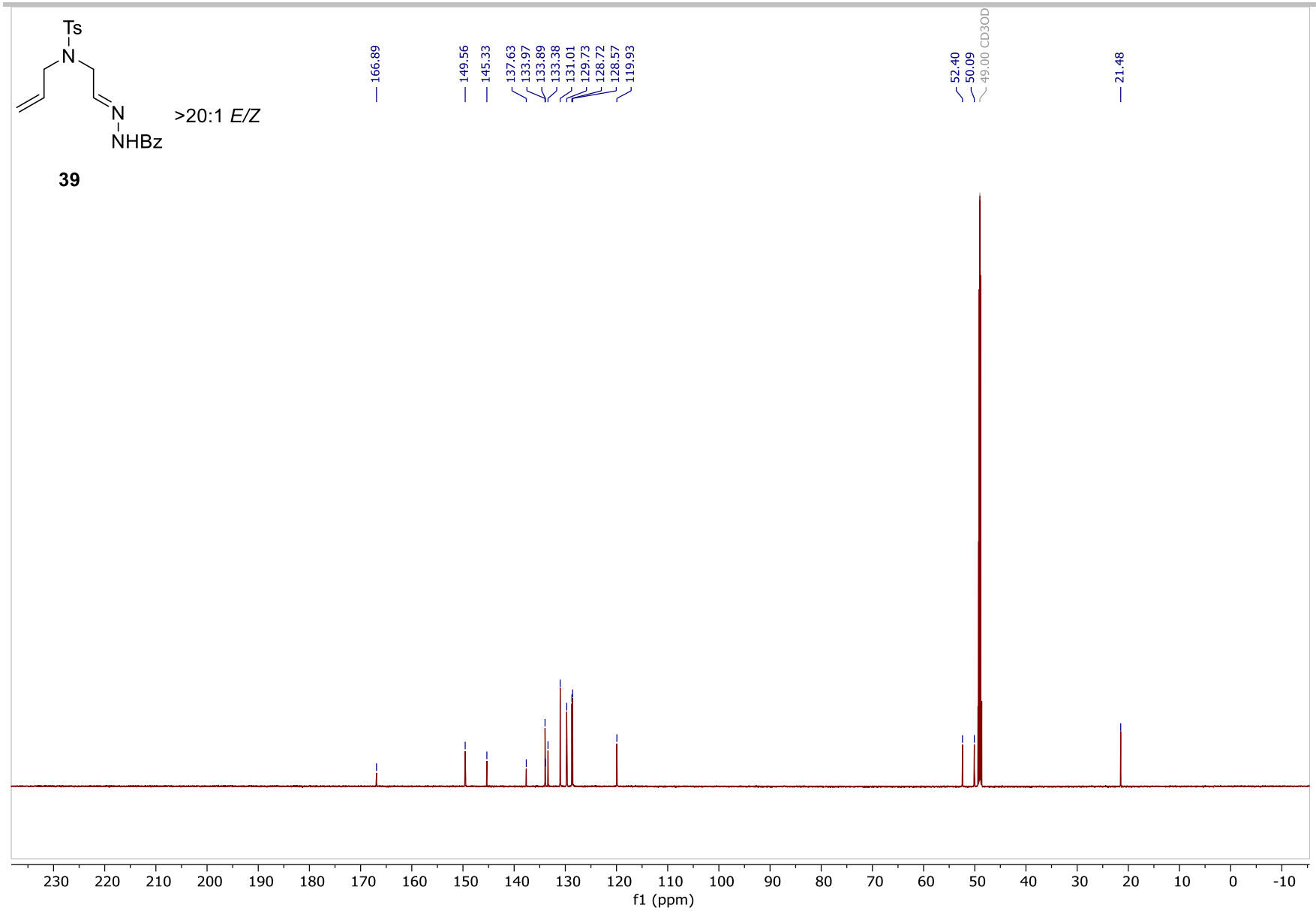

Figure S70. ^{13}C NMR (175 MHz, CD_3OD) of **39.**

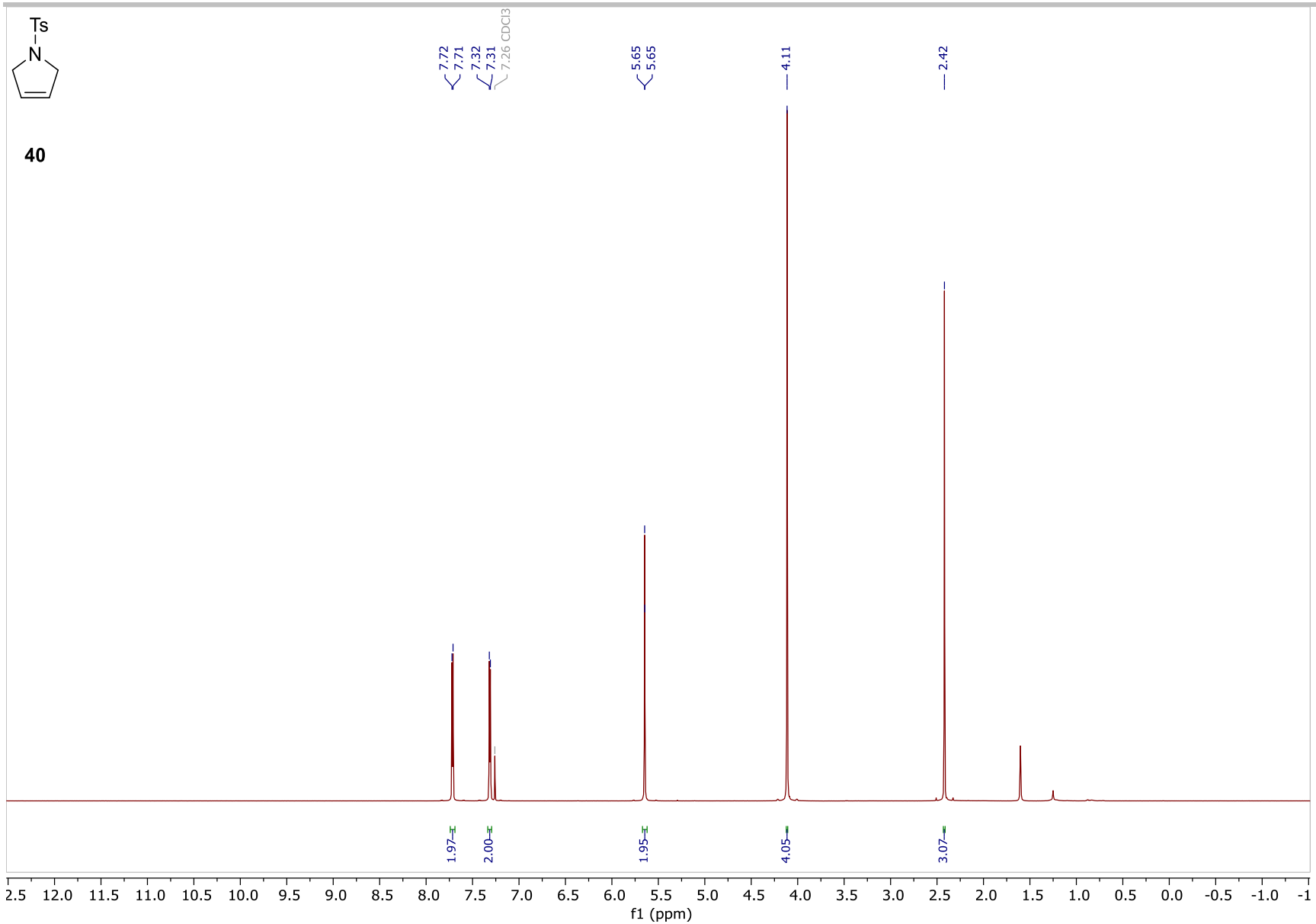

Figure S71. ^{1}H NMR (700 MHz, $CDCl_3$) of **40**.

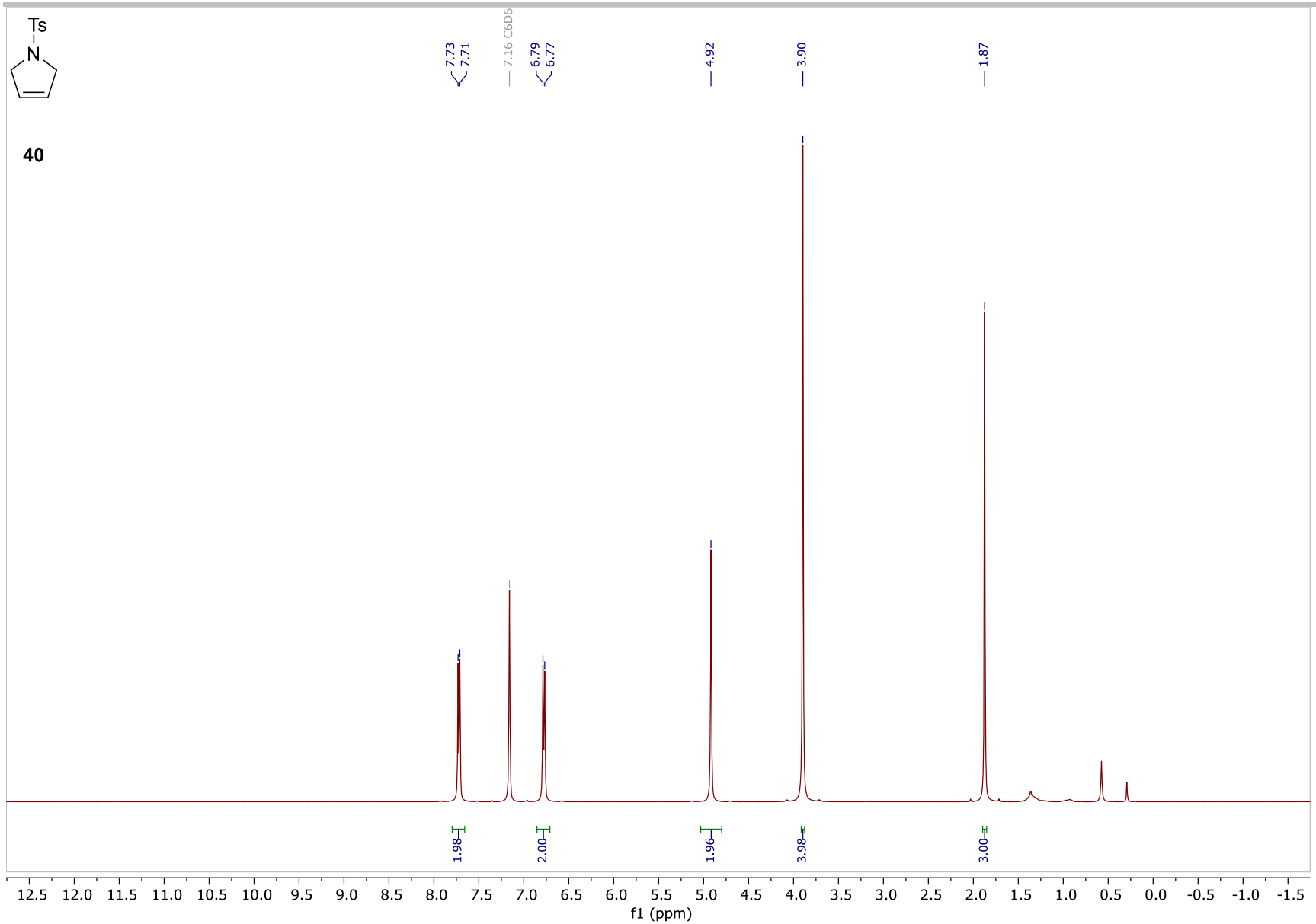

Figure S72. ^{1}H NMR (400 MHz, C_6D_6) of **40.**

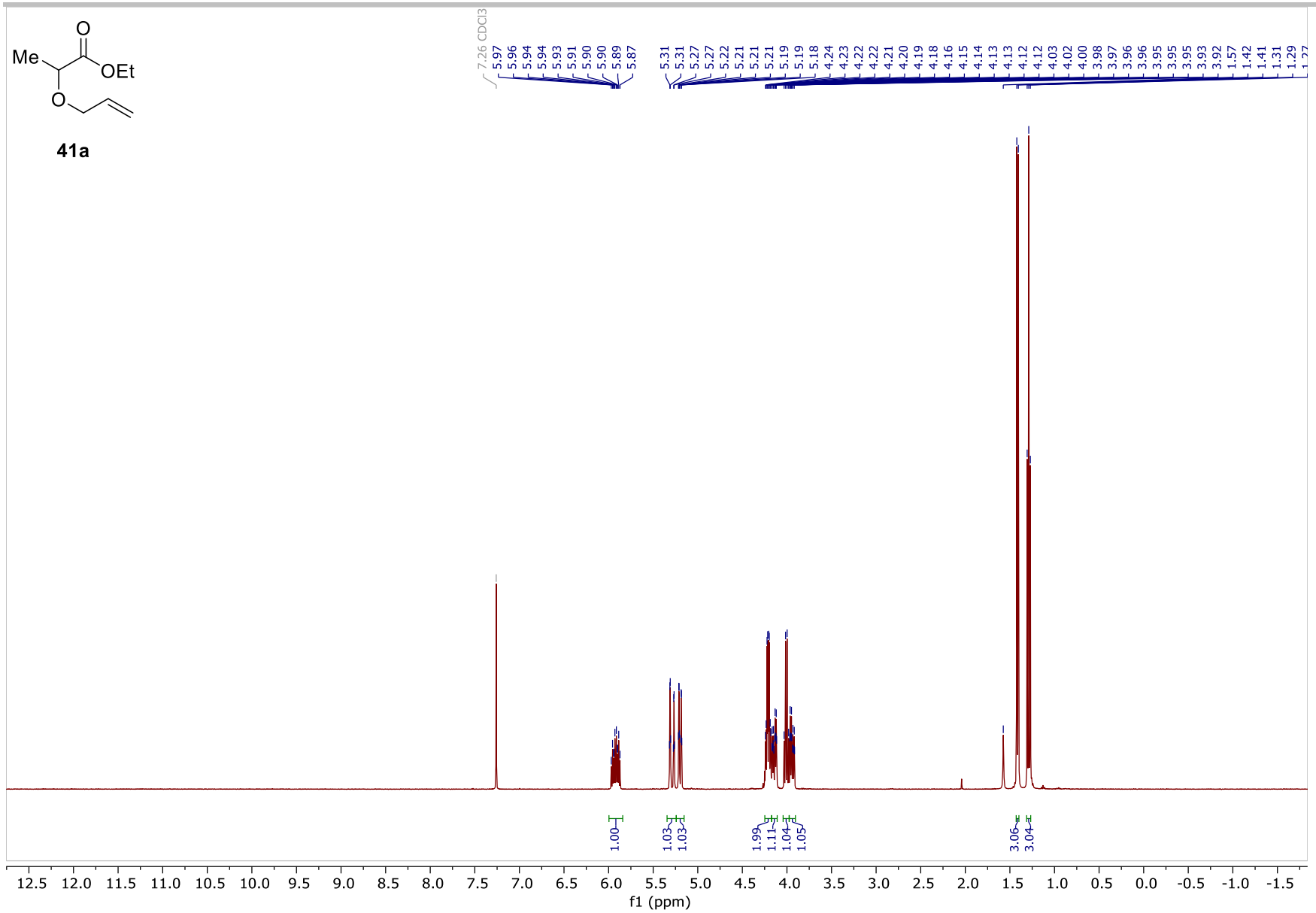

Figure S73. ^{1}H NMR (400 MHz, $CDCl_3$) of **41a**.

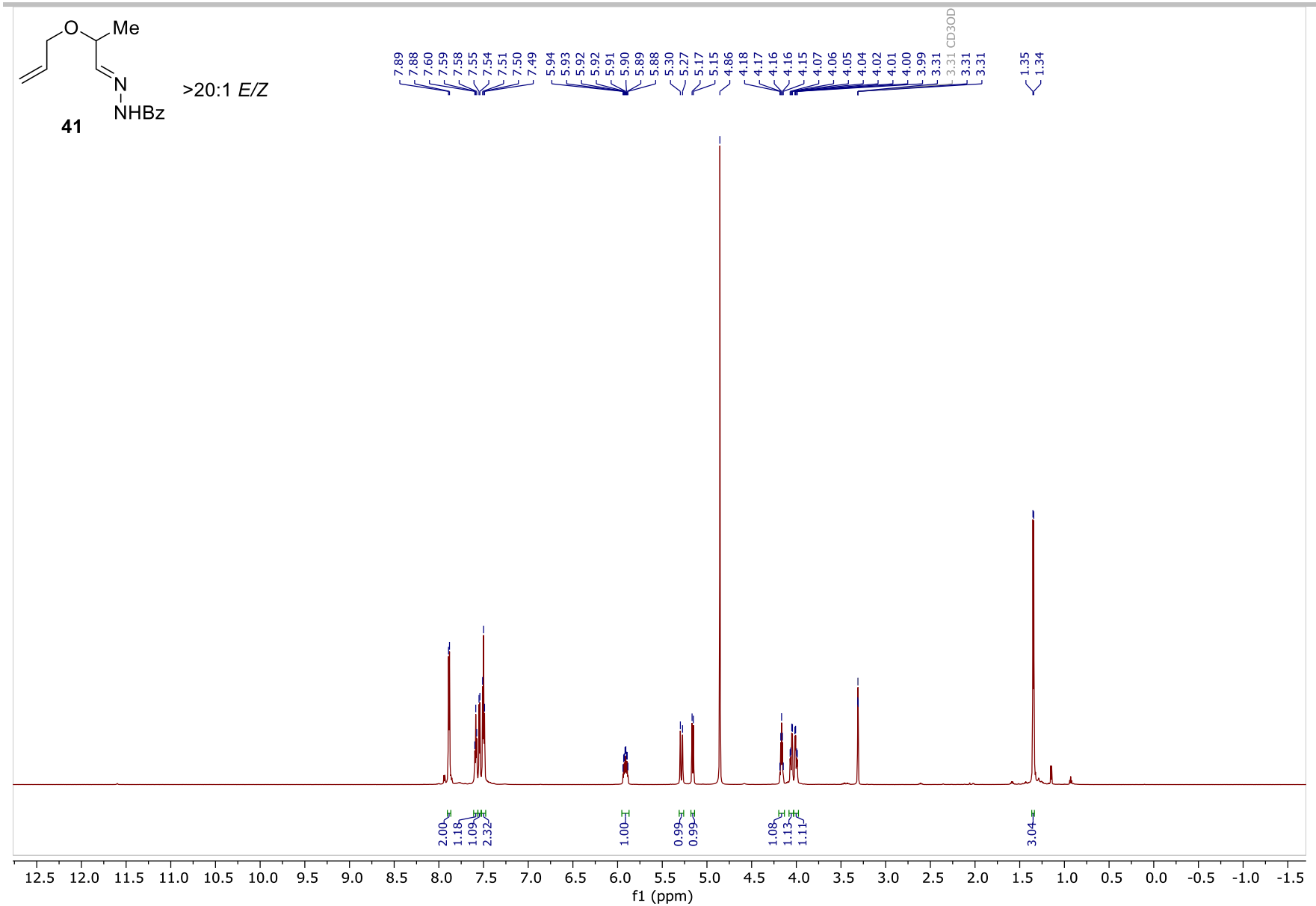

Figure S74. ^{1}H NMR (700 MHz, CD_3OD) of **41**.

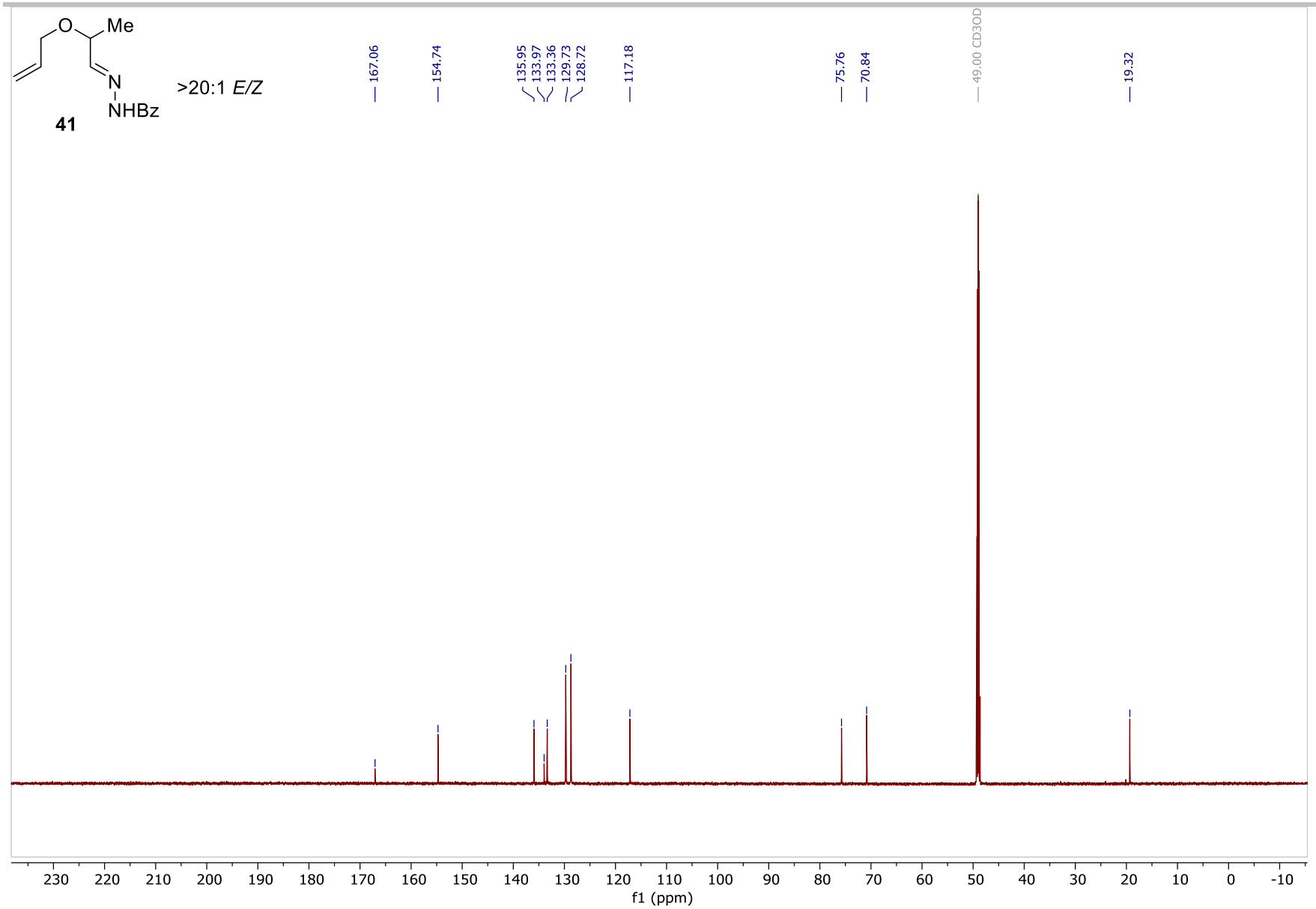

Figure S75. ^{13}C NMR (175 MHz, CD_3OD) of **41.**

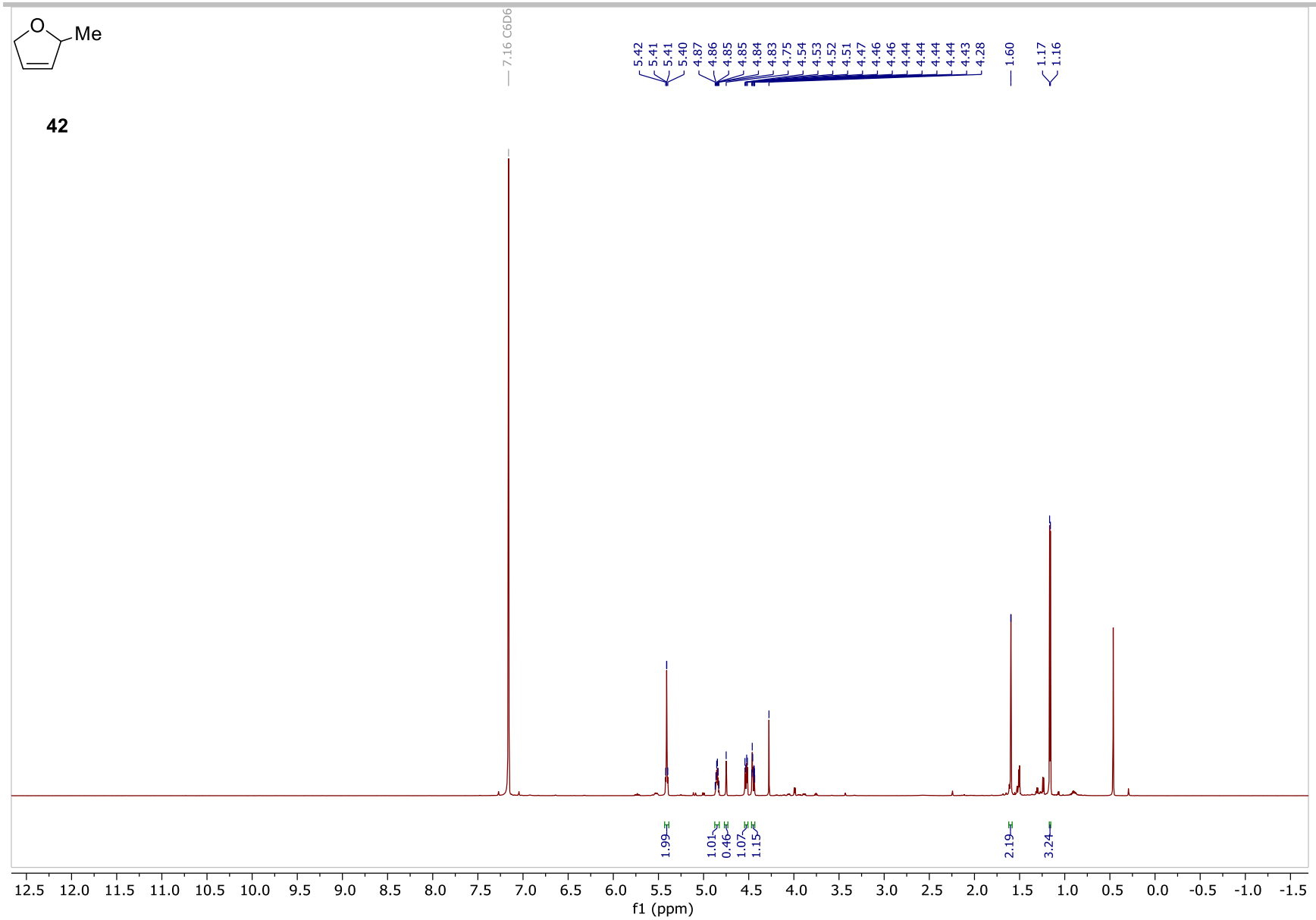

Figure S76. ^{1}H NMR (700 MHz, C_6D_6) of **42**.

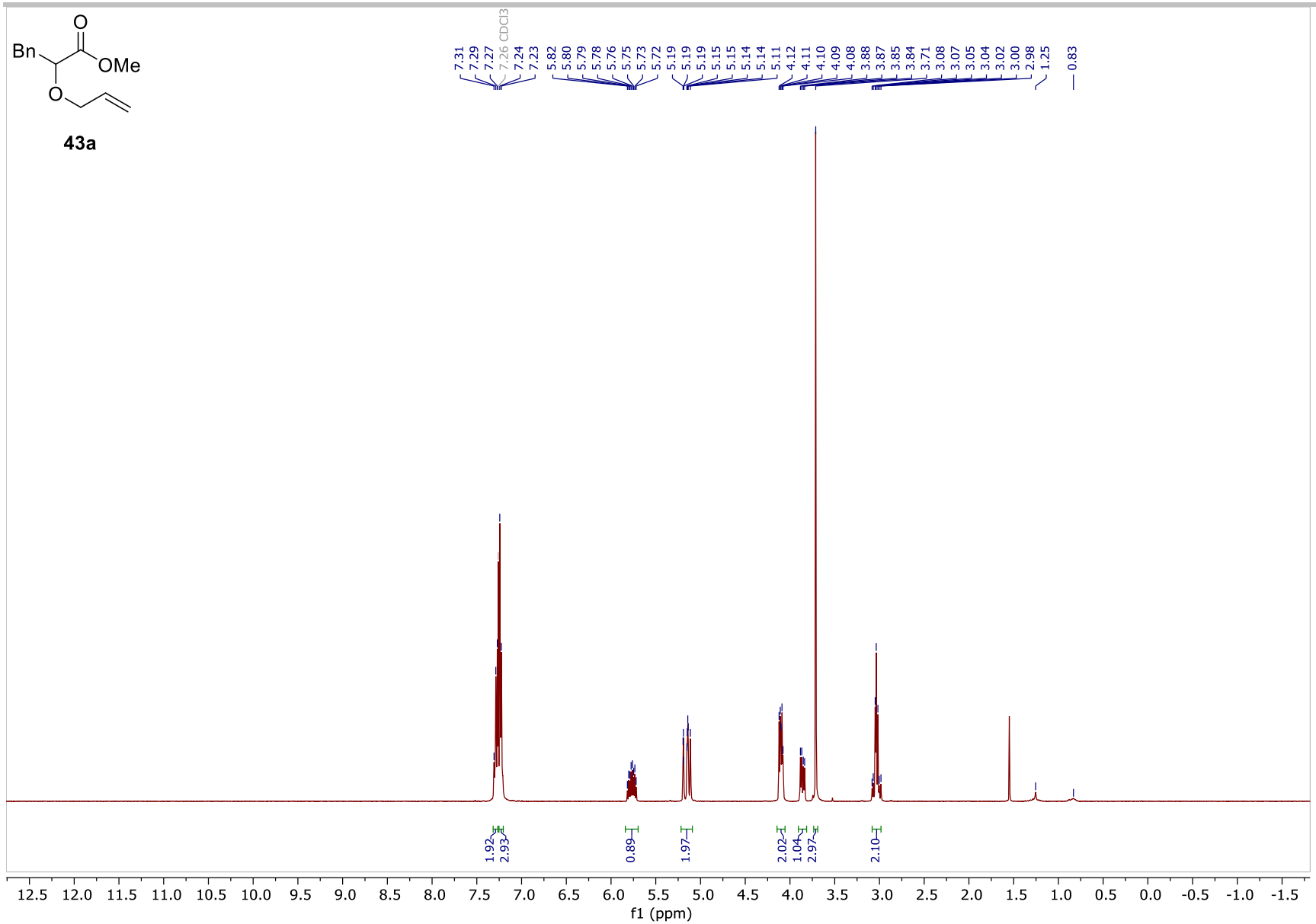

Figure S77. ^{1}H NMR (400 MHz, $CDCl_3$) of **43a**.

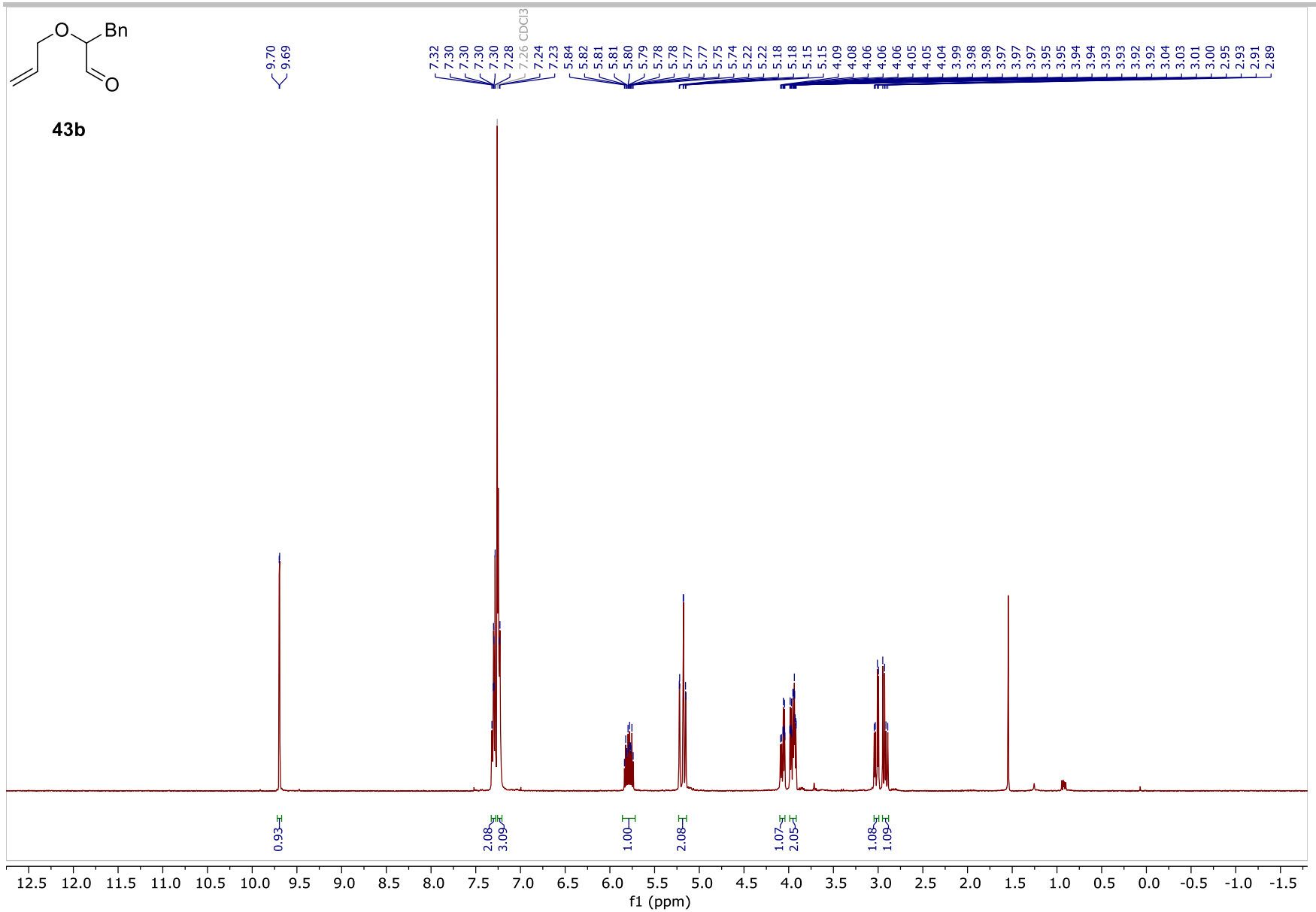

Figure S78. ^{1}H NMR (400 MHz, $CDCl_3$) of **43b**.

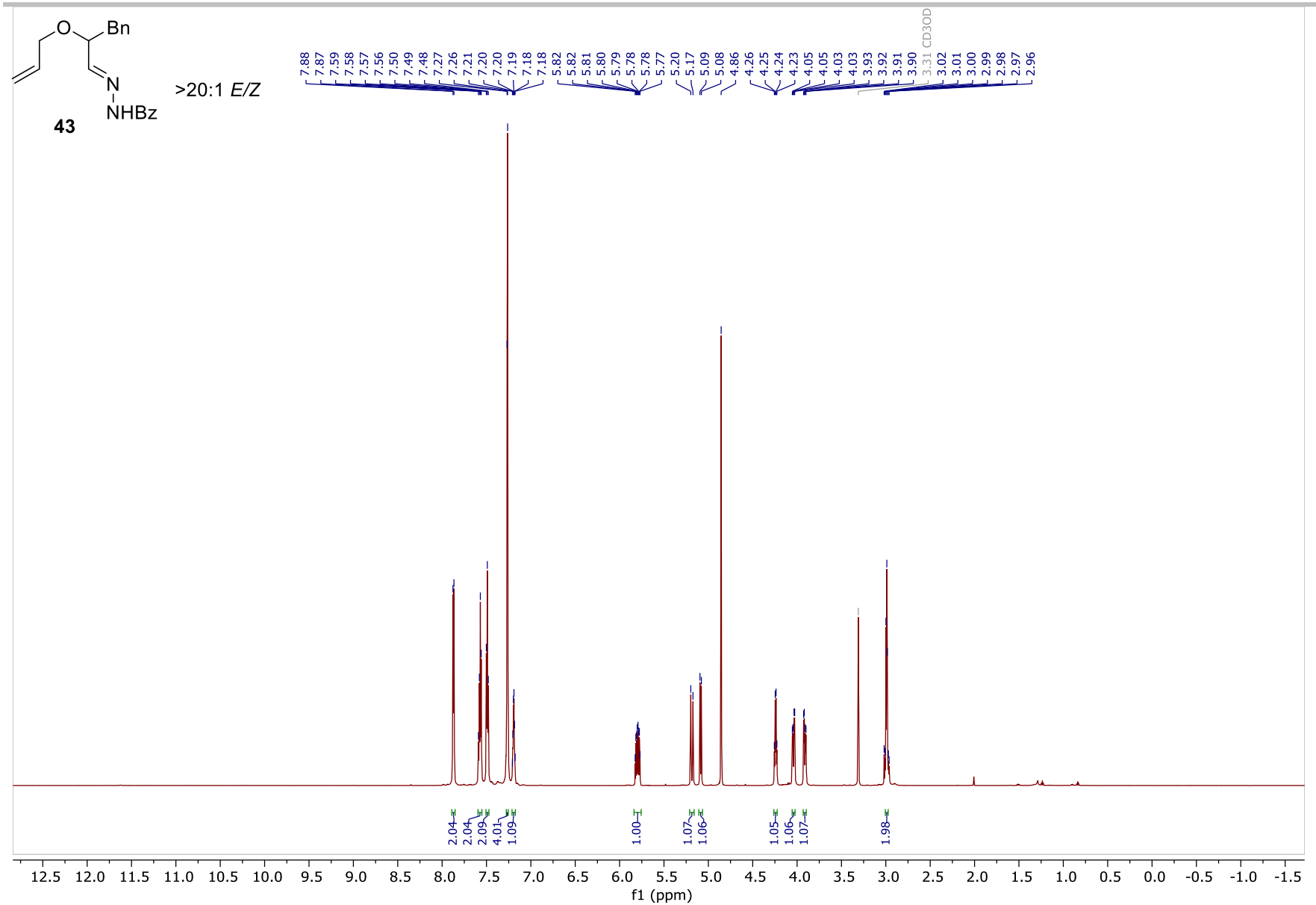

Figure S79. ^{1}H NMR (700 MHz, CD_3OD) of **43**.

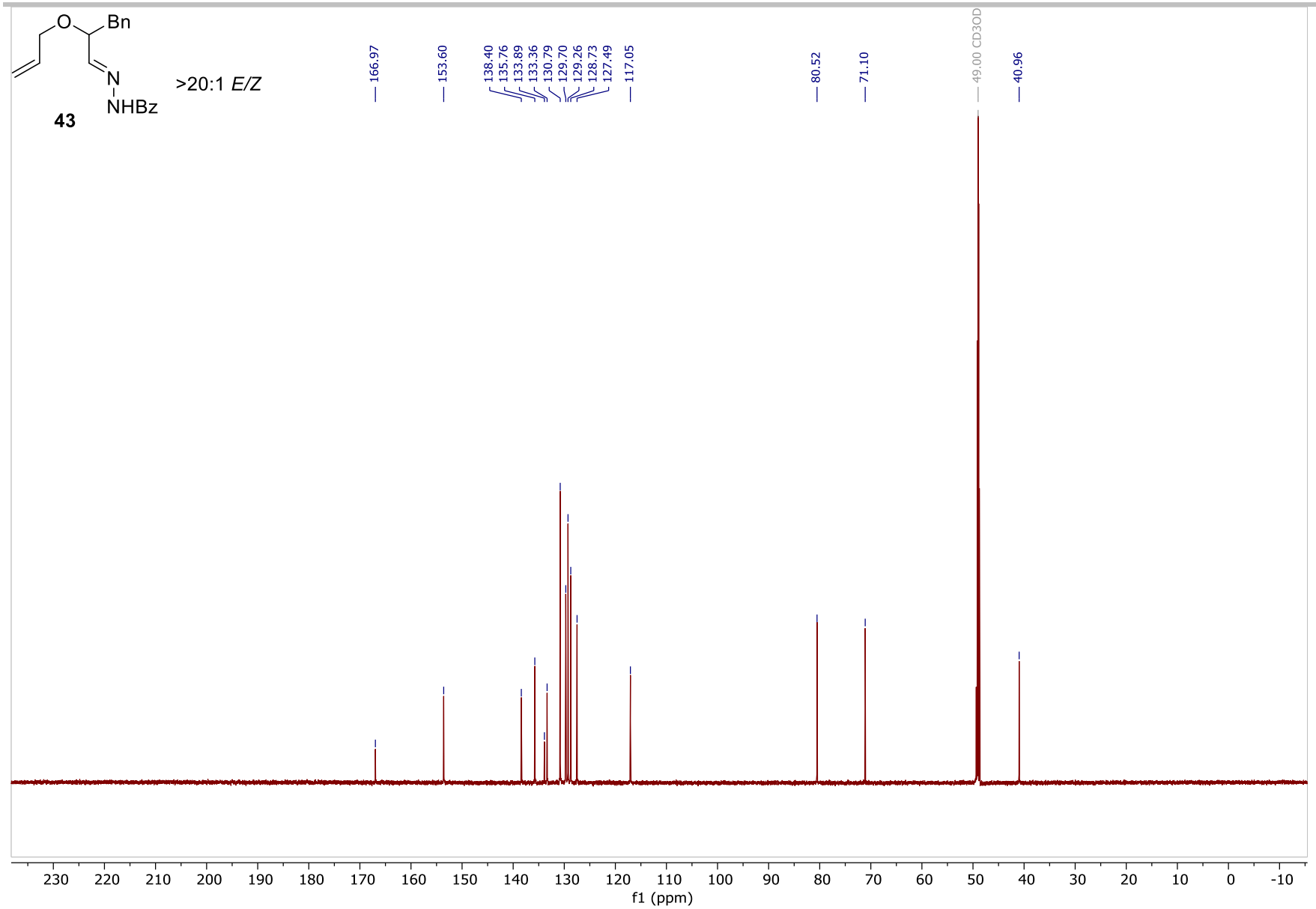

Figure S80. ^{13}C NMR (175 MHz, CD_3OD) of **43.**

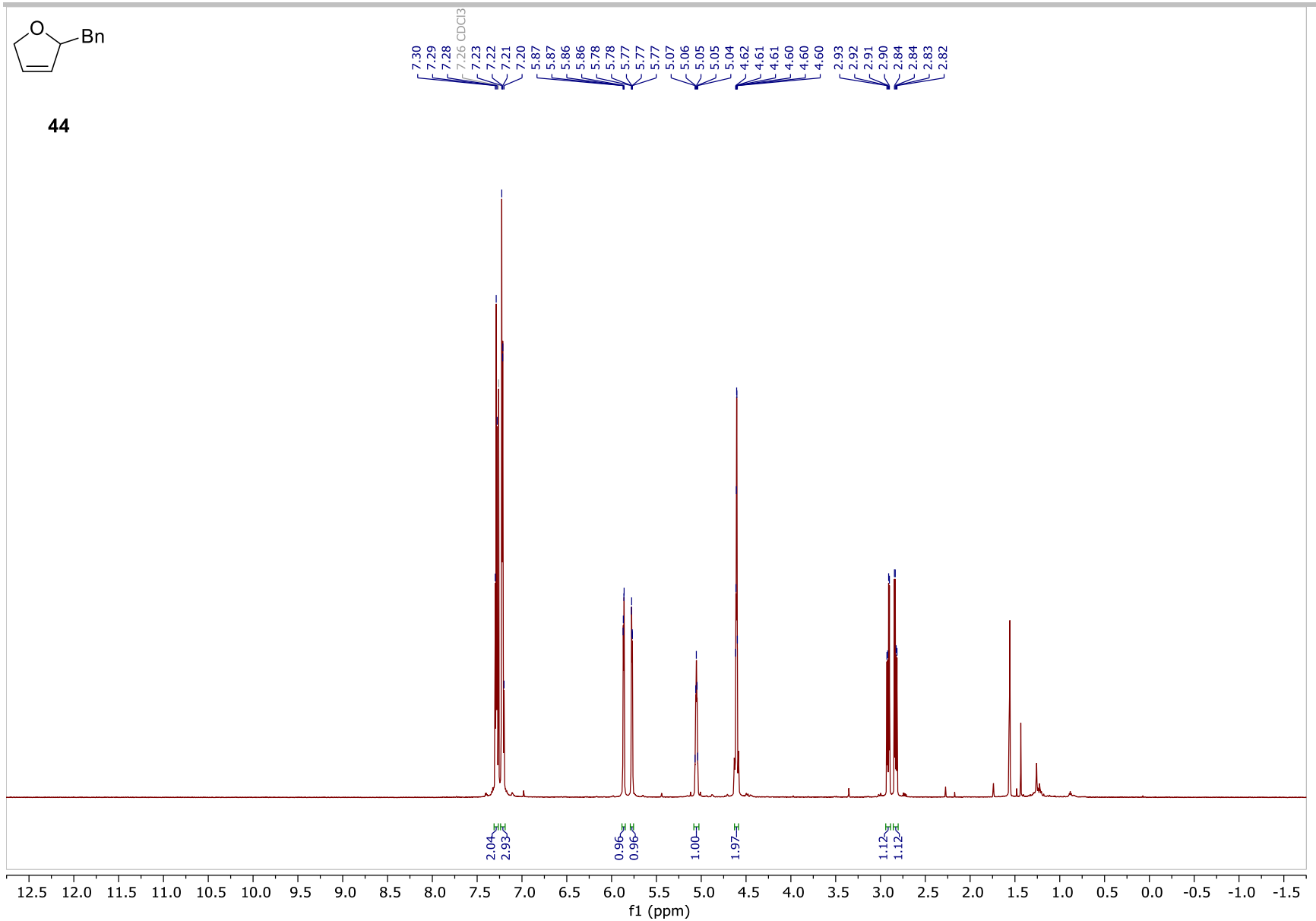

Figure S81. ^{1}H NMR (700 MHz, $CDCl_3$) of **44**.

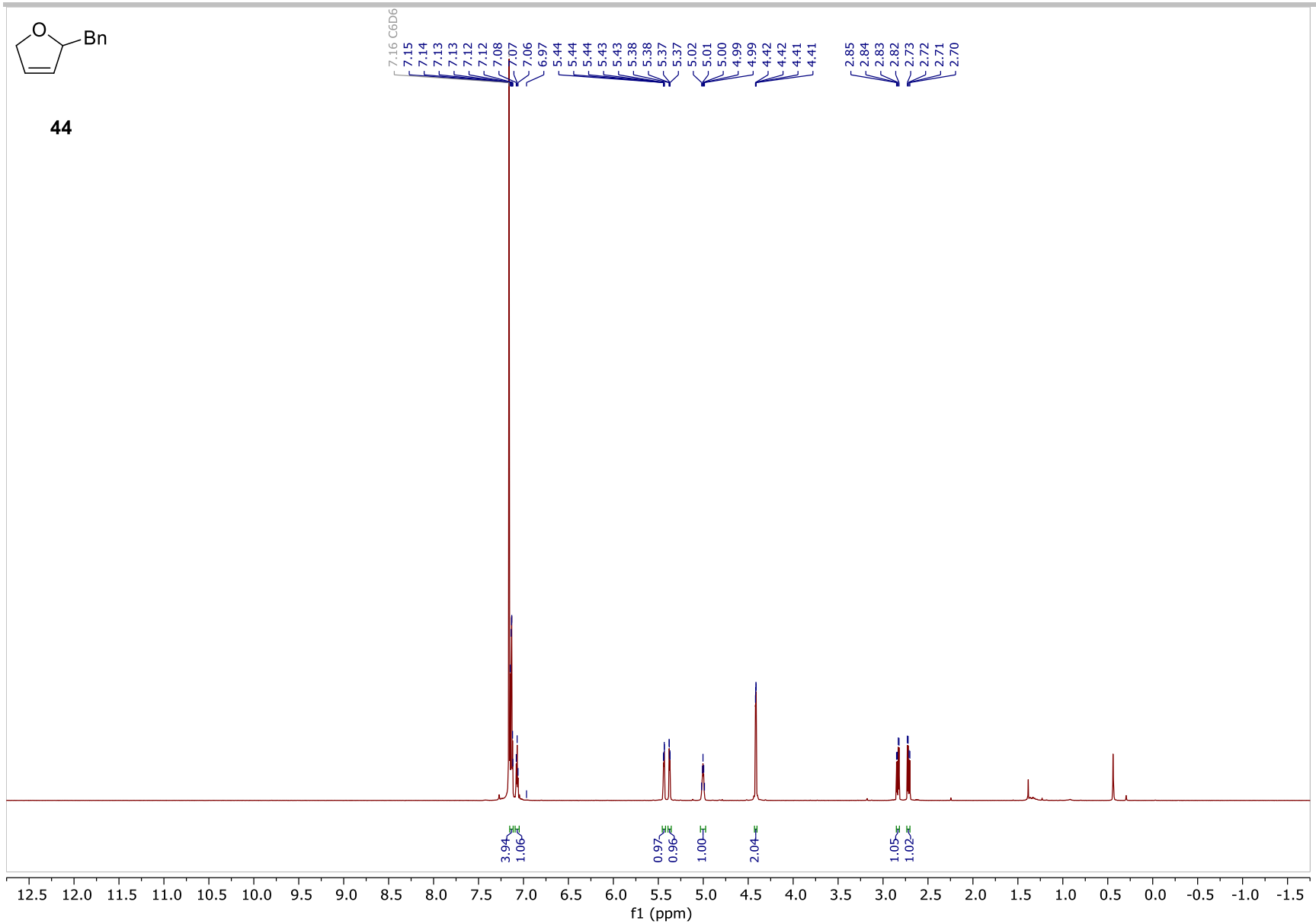

Figure S82. ^{1}H NMR (700 MHz, C_6D_6) of **44.**

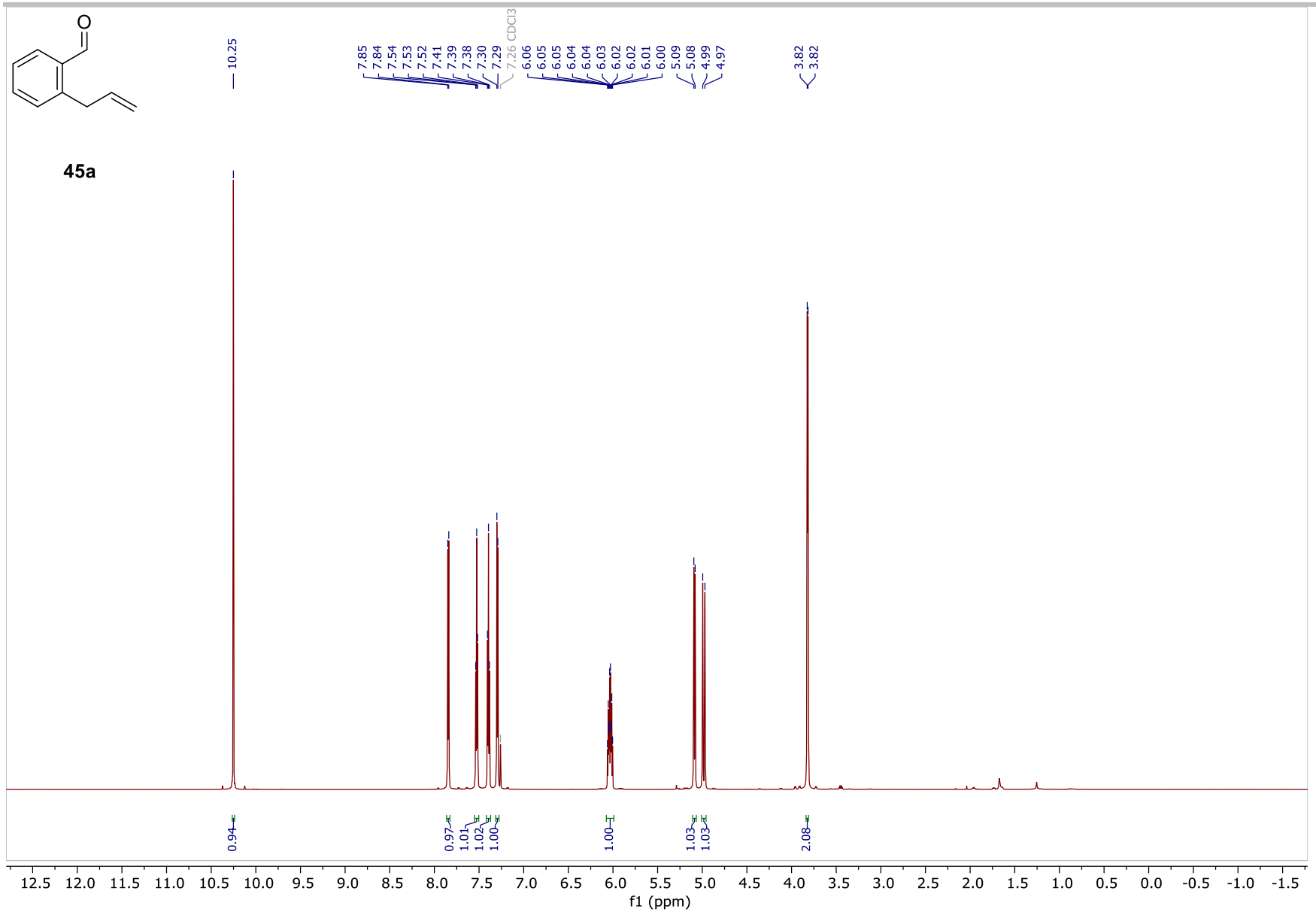

Figure S83. ^{1}H NMR (700 MHz, $CDCl_3$) of **45a**.

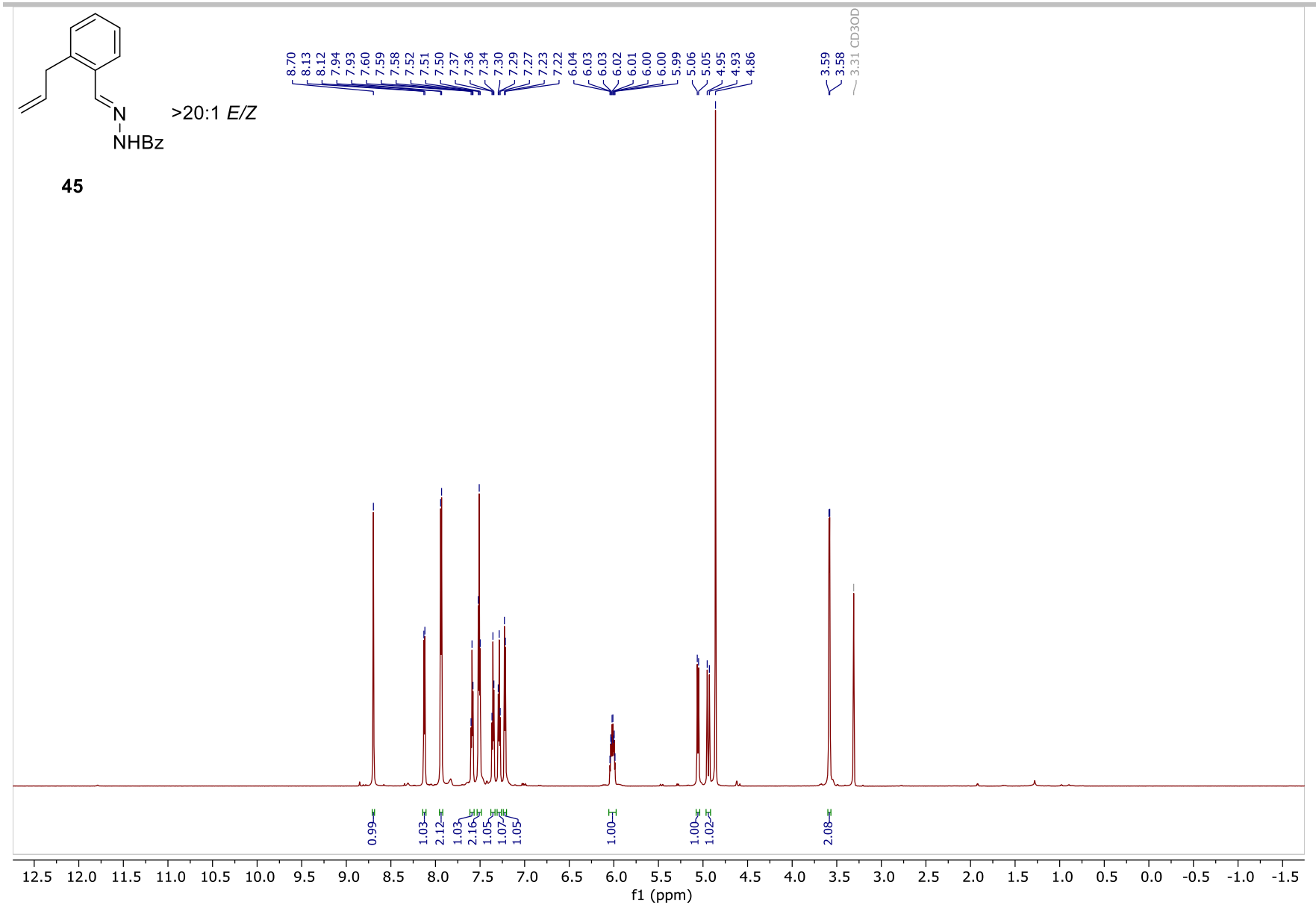

Figure S84. ^{1}H NMR (700 MHz, CD_3OD) of **45**.

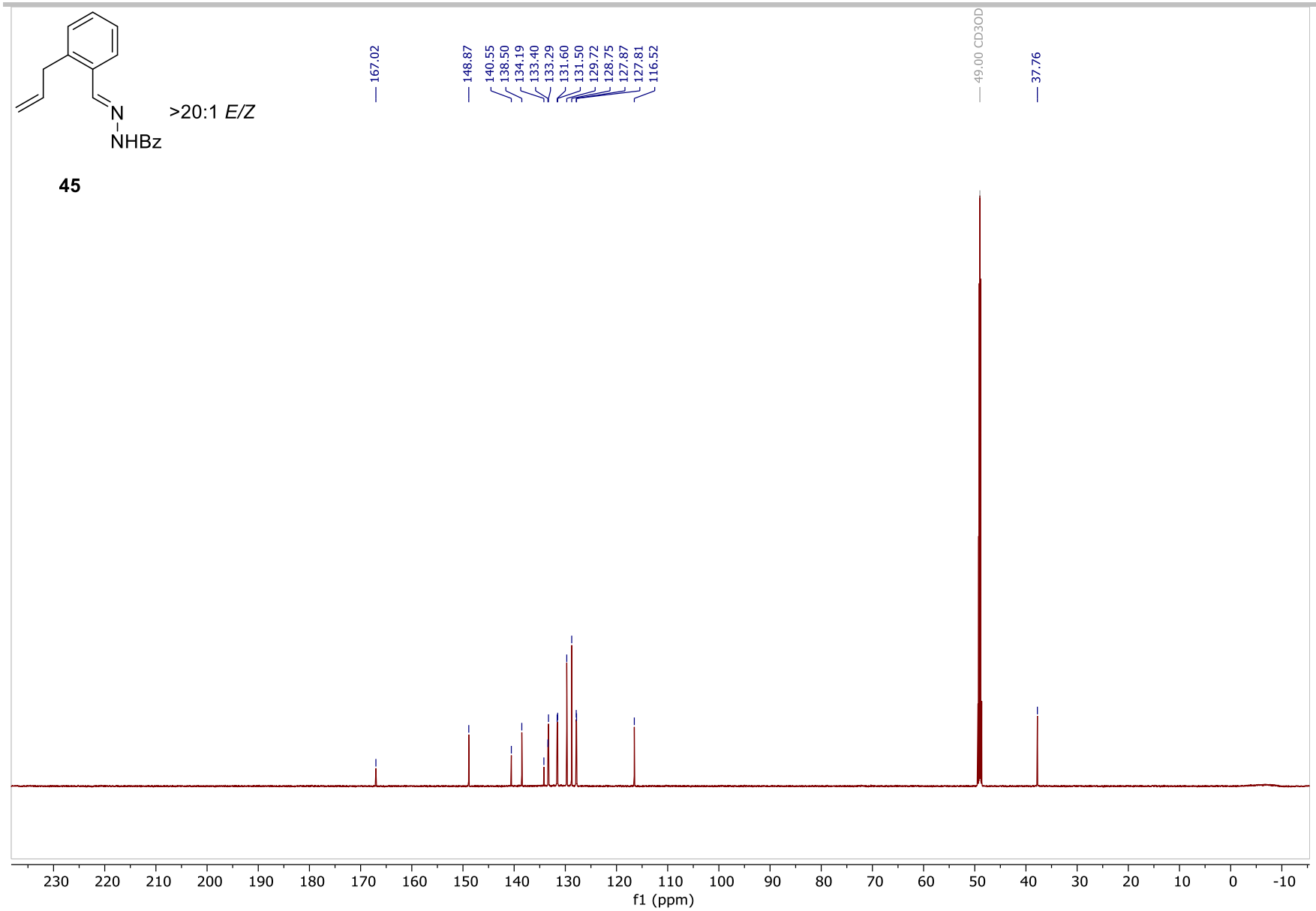

Figure S85. ^{13}C NMR (175 MHz, CD_3OD) of **45.**

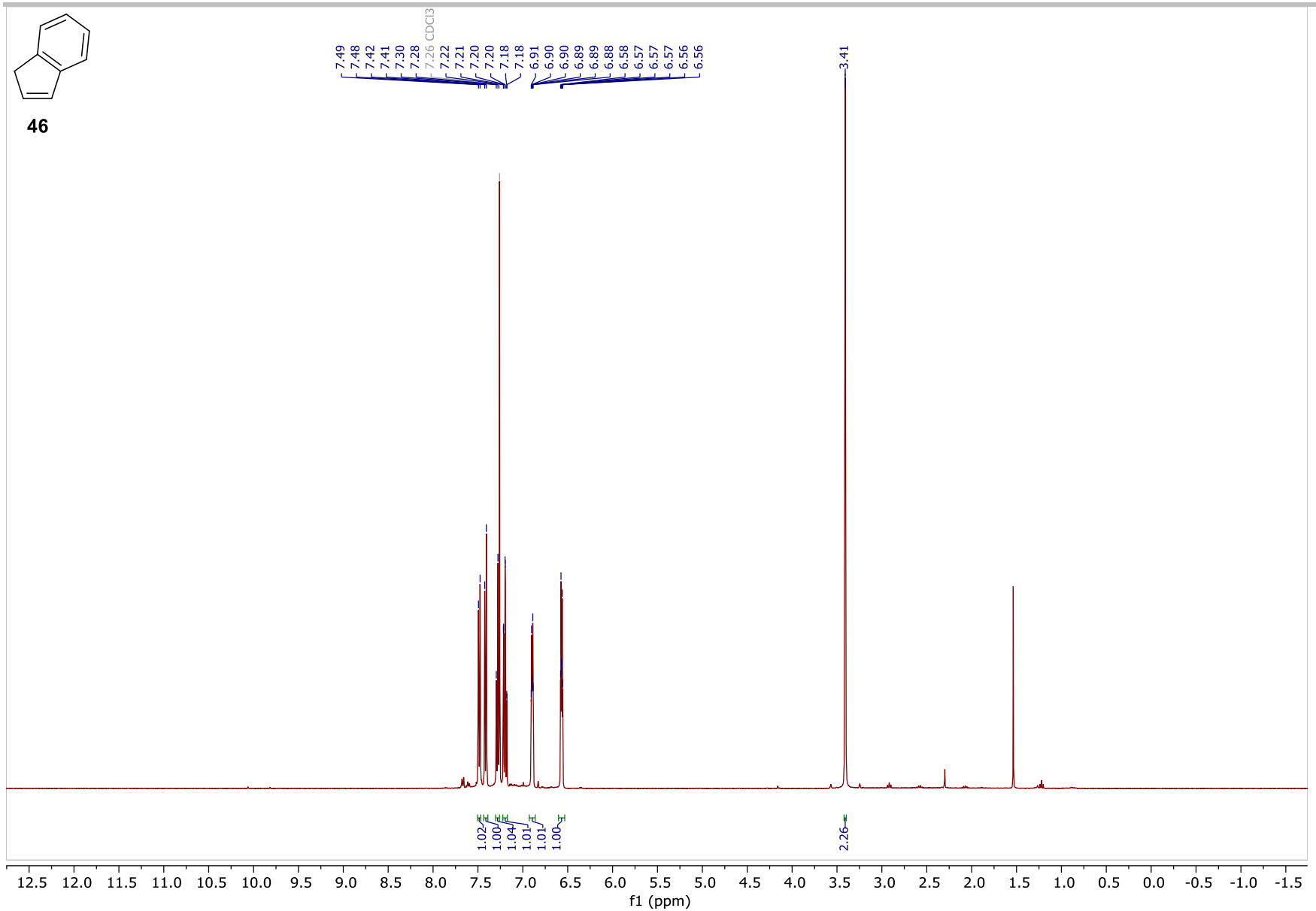

Figure S86. ^{1}H NMR (400 MHz, $CDCl_3$) of **46**.

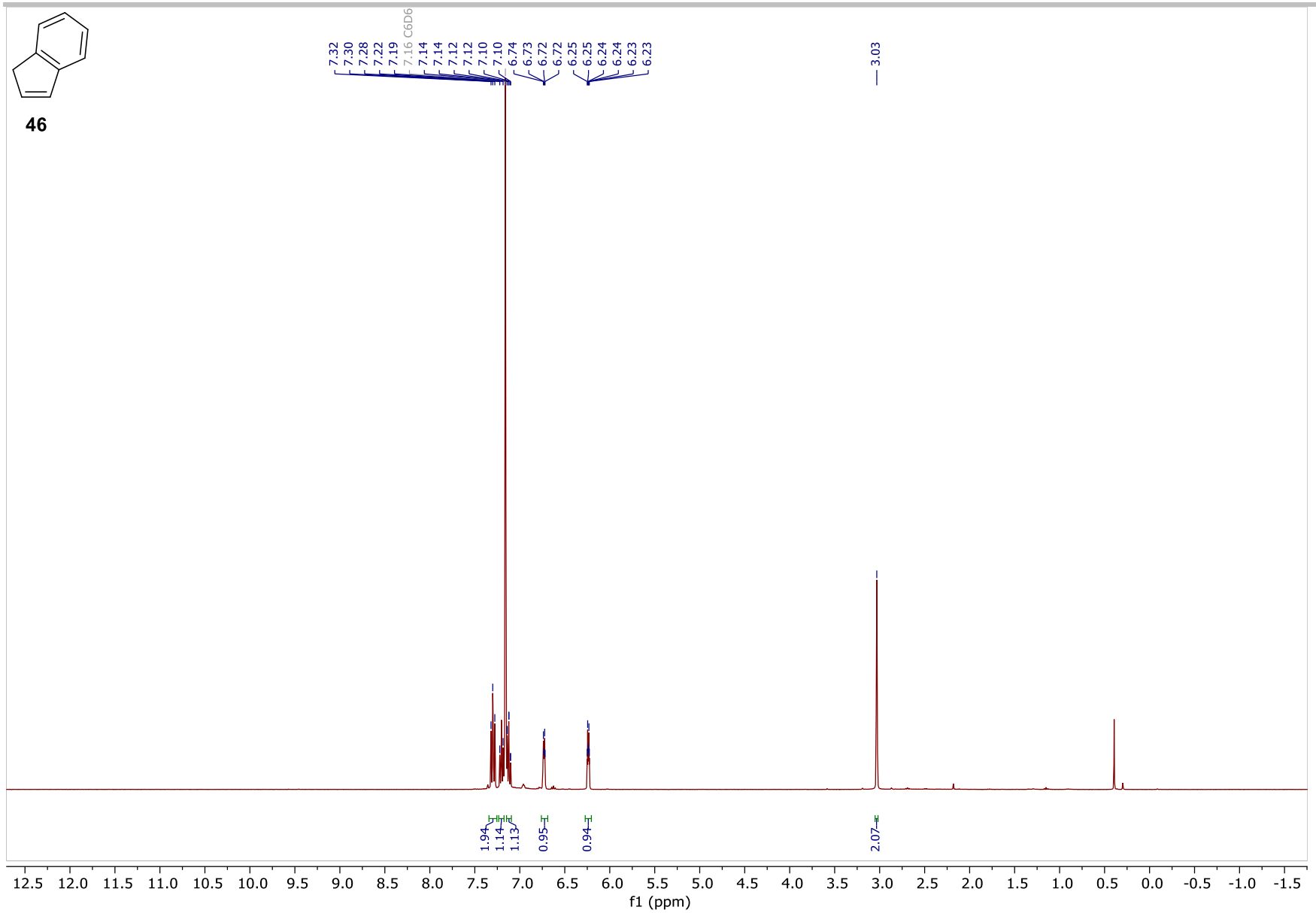

Figure S87. ^{1}H NMR (400 MHz, C_6D_6) of **46.**

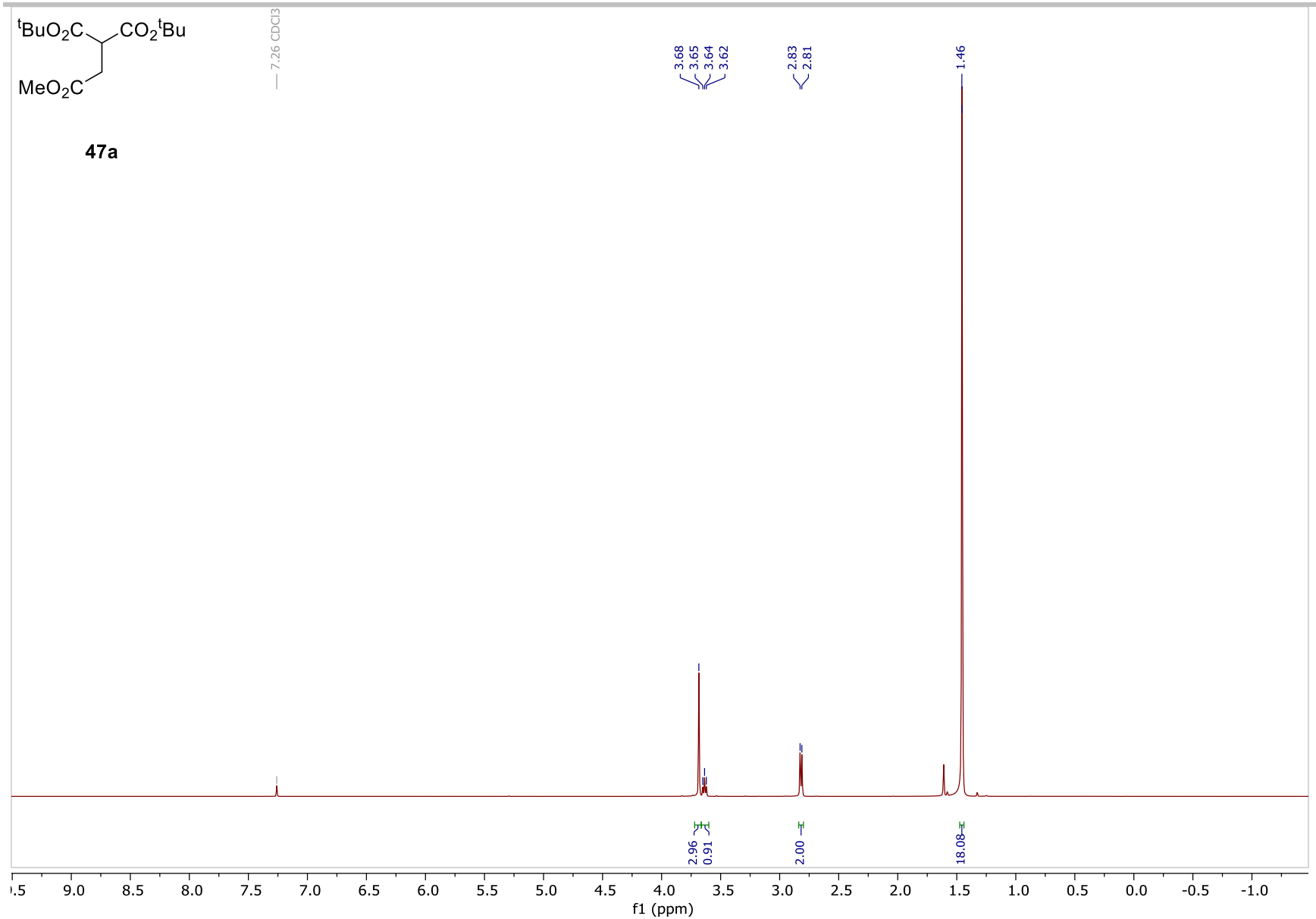

Figure S88. ^{1}H NMR (500 MHz, $CDCl_3$) of **47a**.

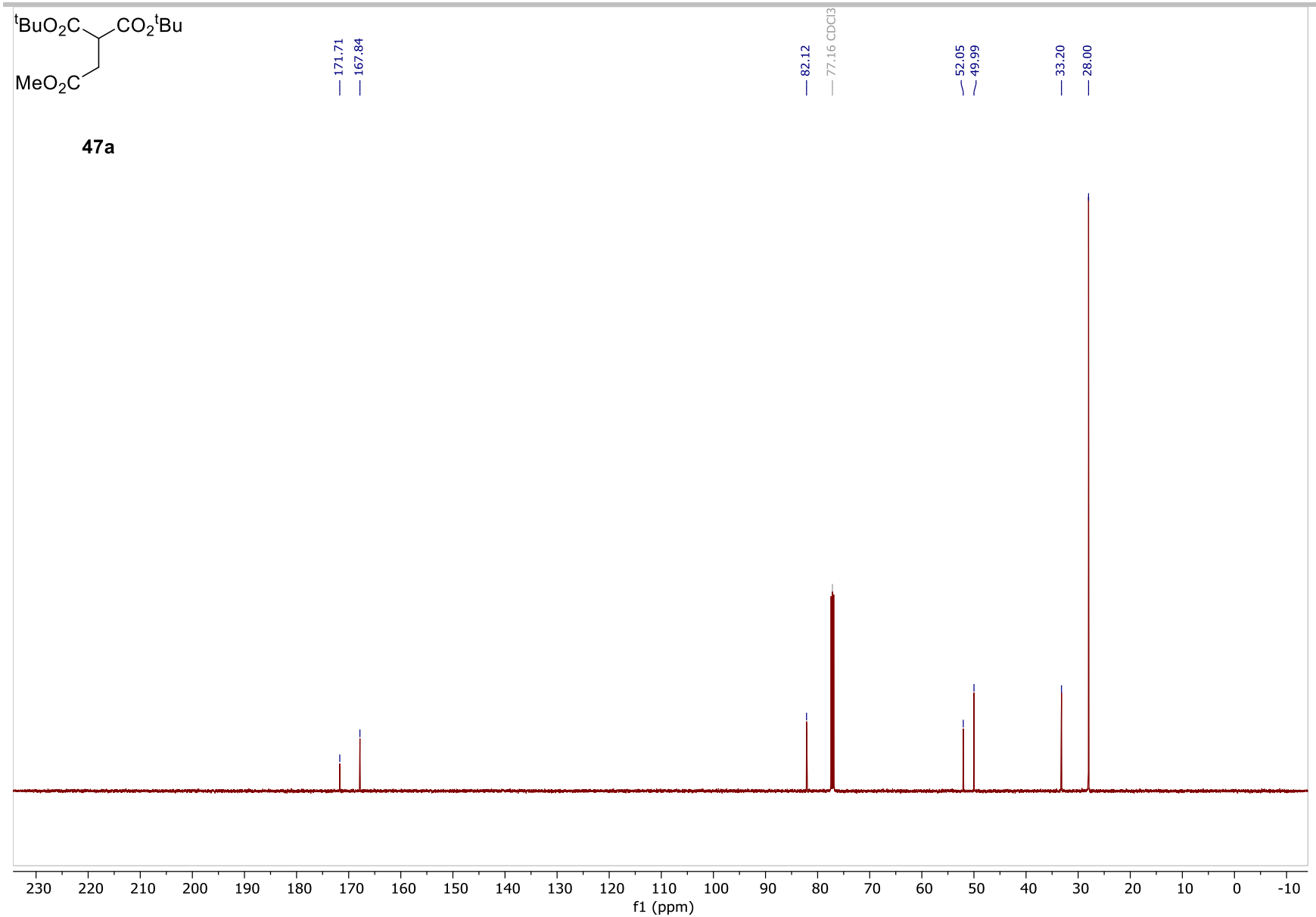

Figure S89. ^{13}C NMR (125 MHz, $CDCl_3$) of **47a**.

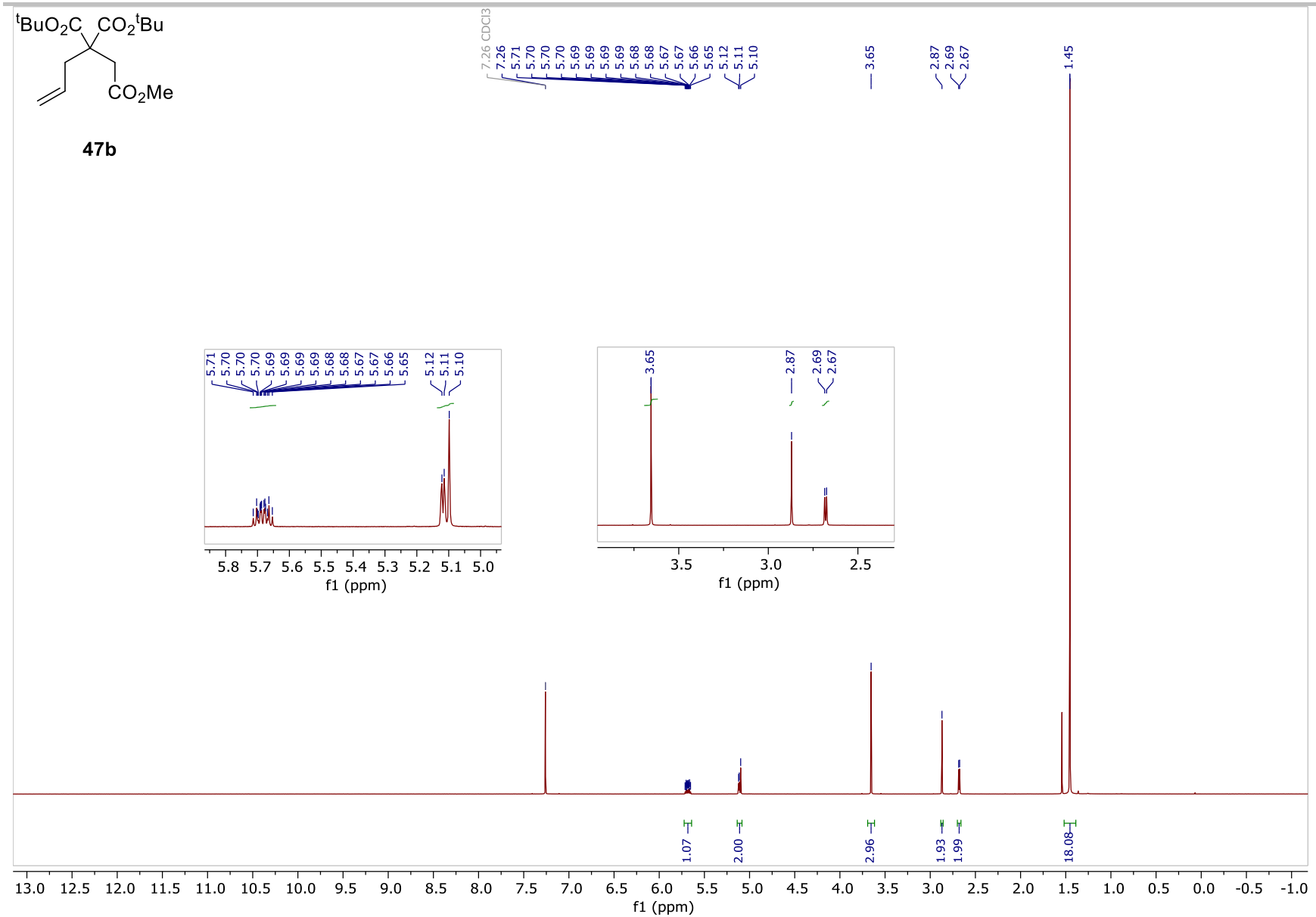

Figure S90. ^{1}H NMR (700 MHz, $CDCl_3$) of **47b**.

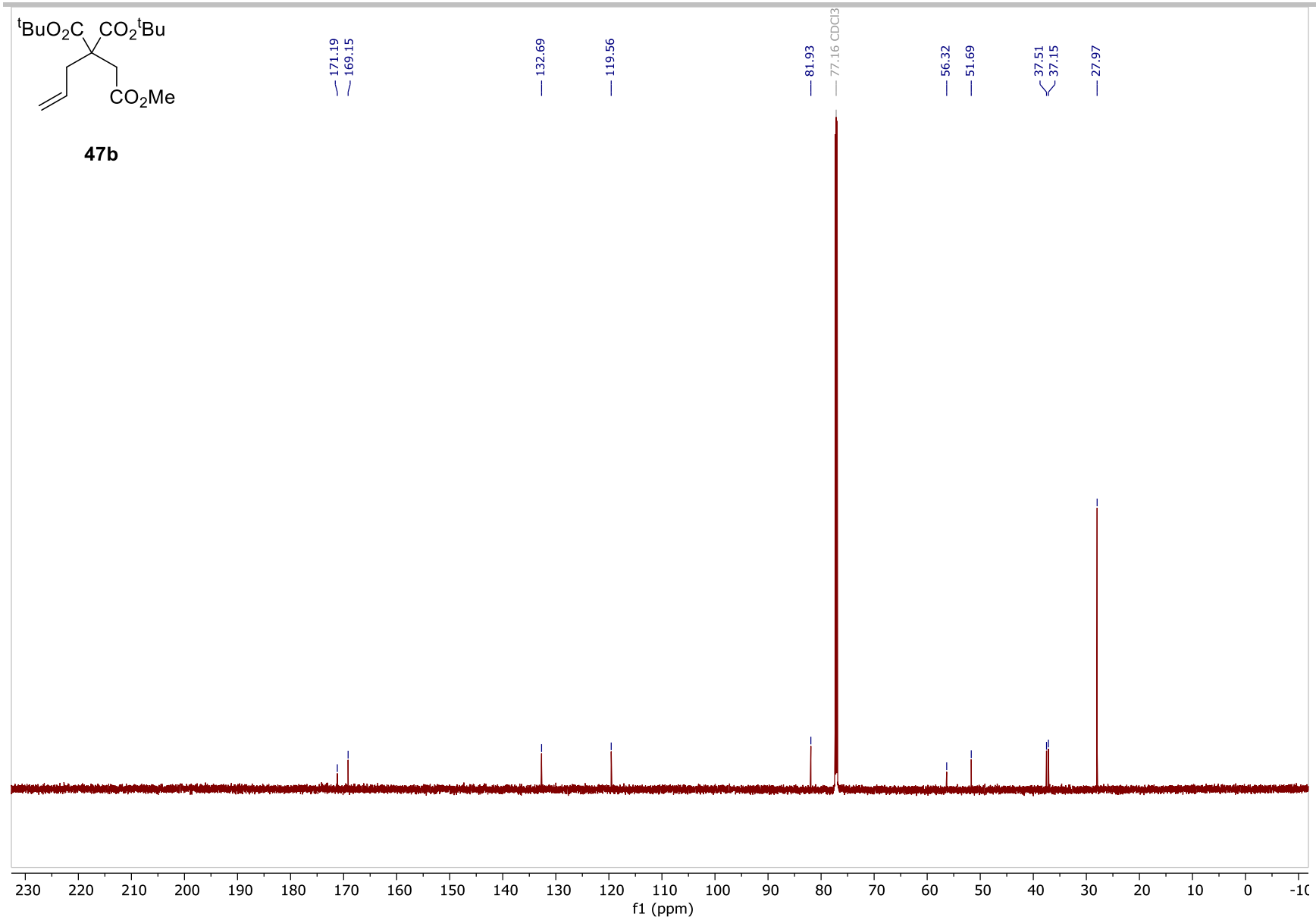

Figure S91. ^{13}C NMR (175 MHz, $CDCl_3$) of **47b**.

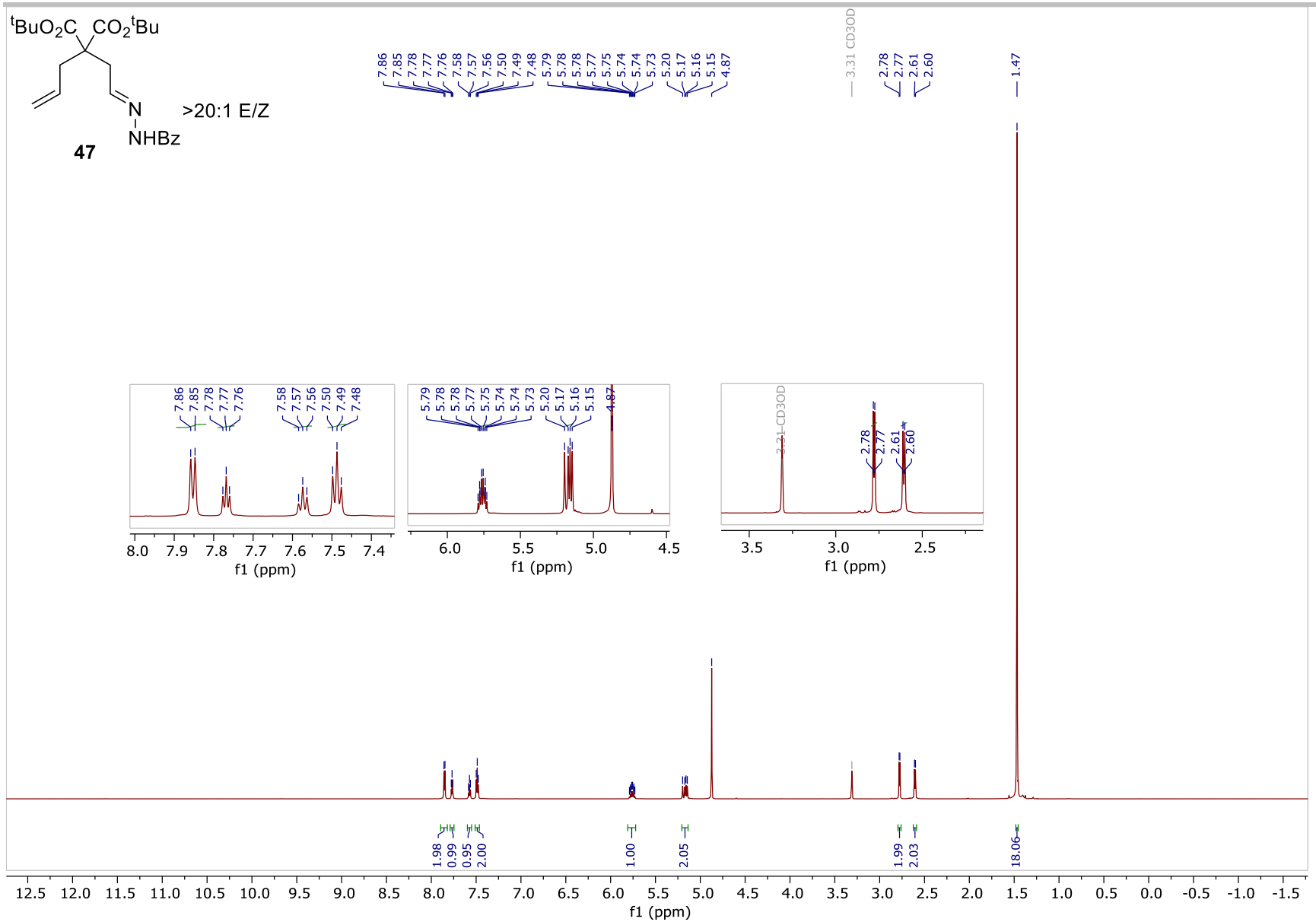

Figure S92. ^{1}H NMR (700 MHz, CD_3OD) of **47**.

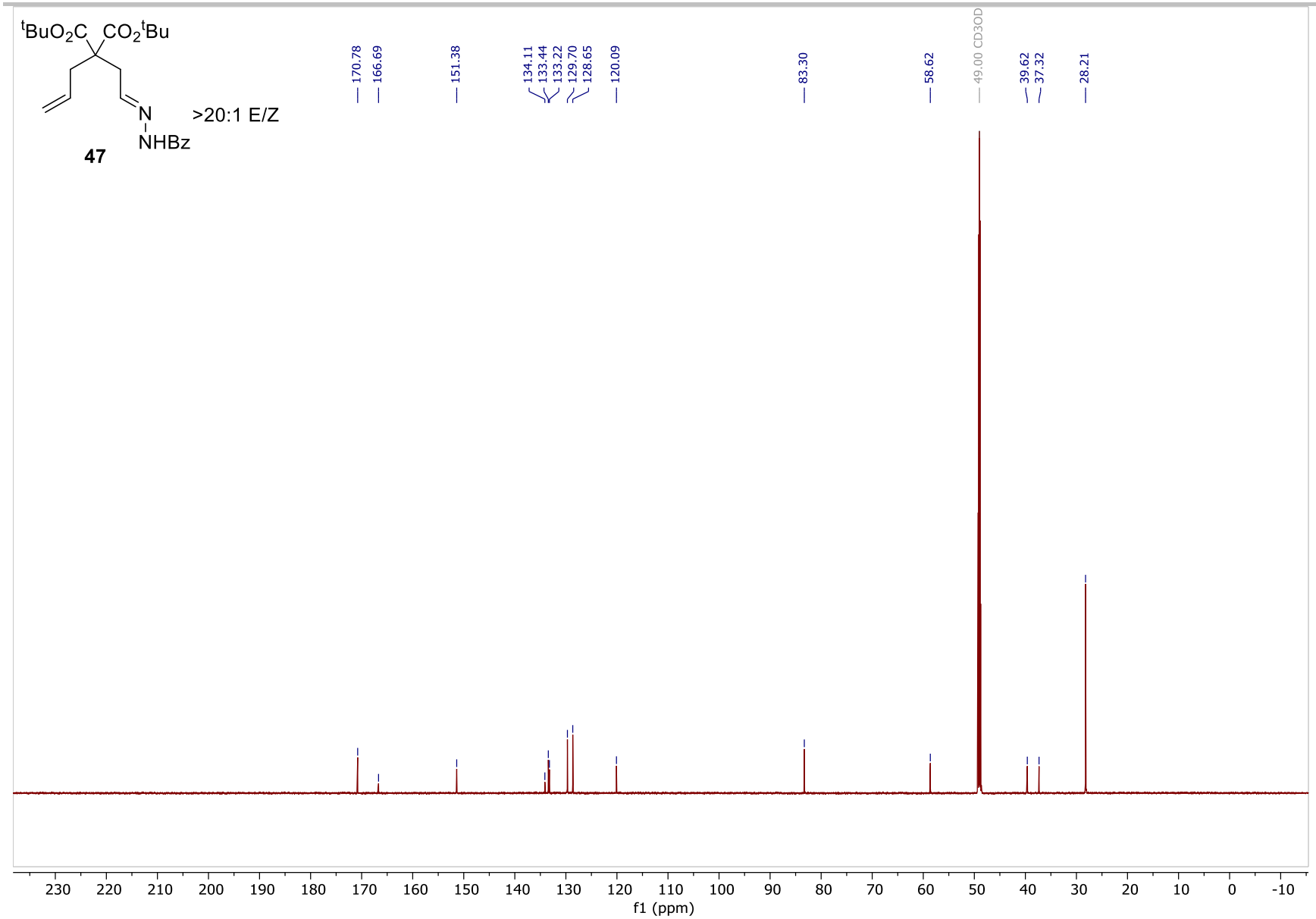

Figure S93. ^{13}C NMR (175 MHz, CD_3OD) of **47**.

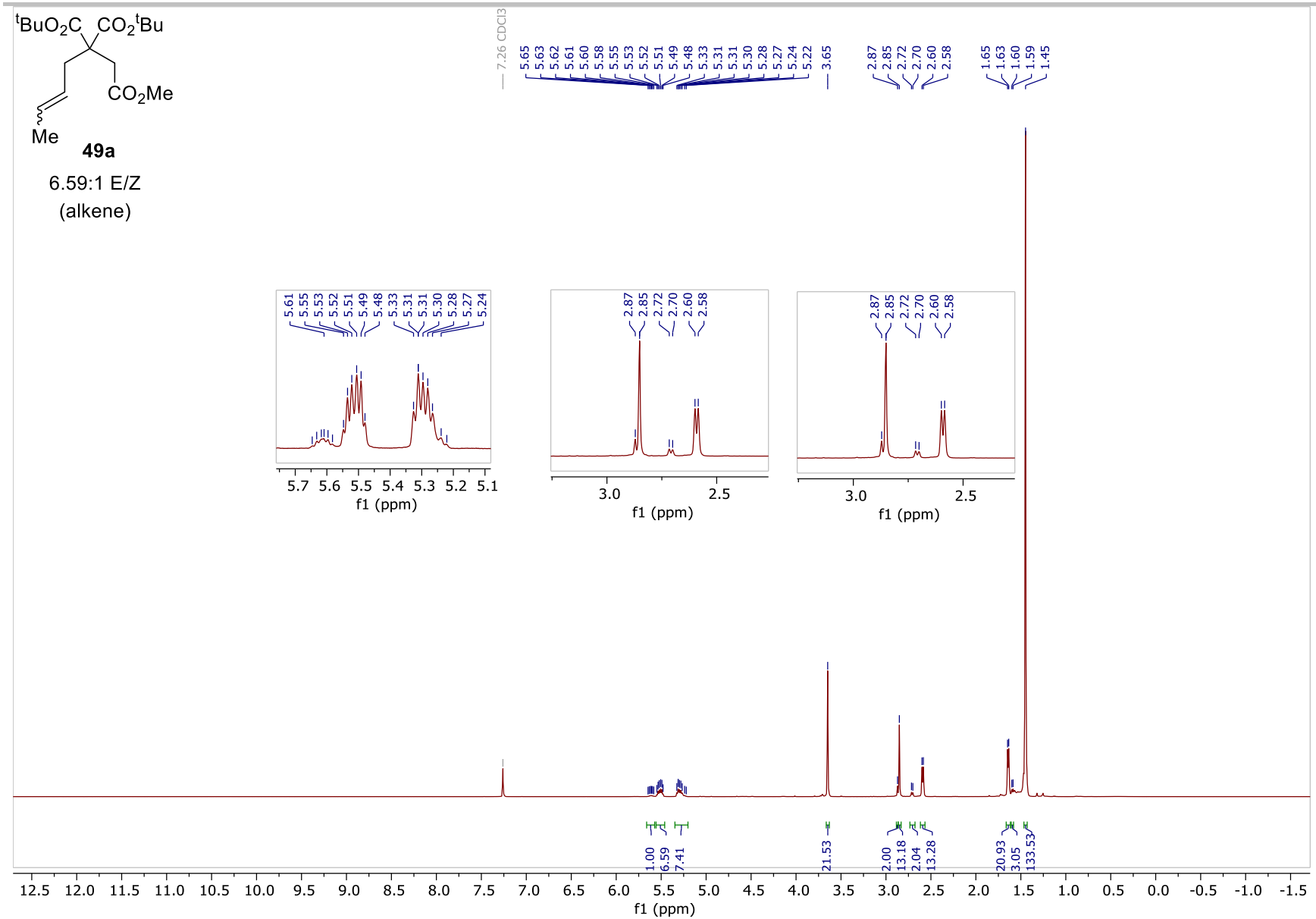

Figure S94. ^{1}H NMR (500 MHz, $CDCl_3$) of **49a**.

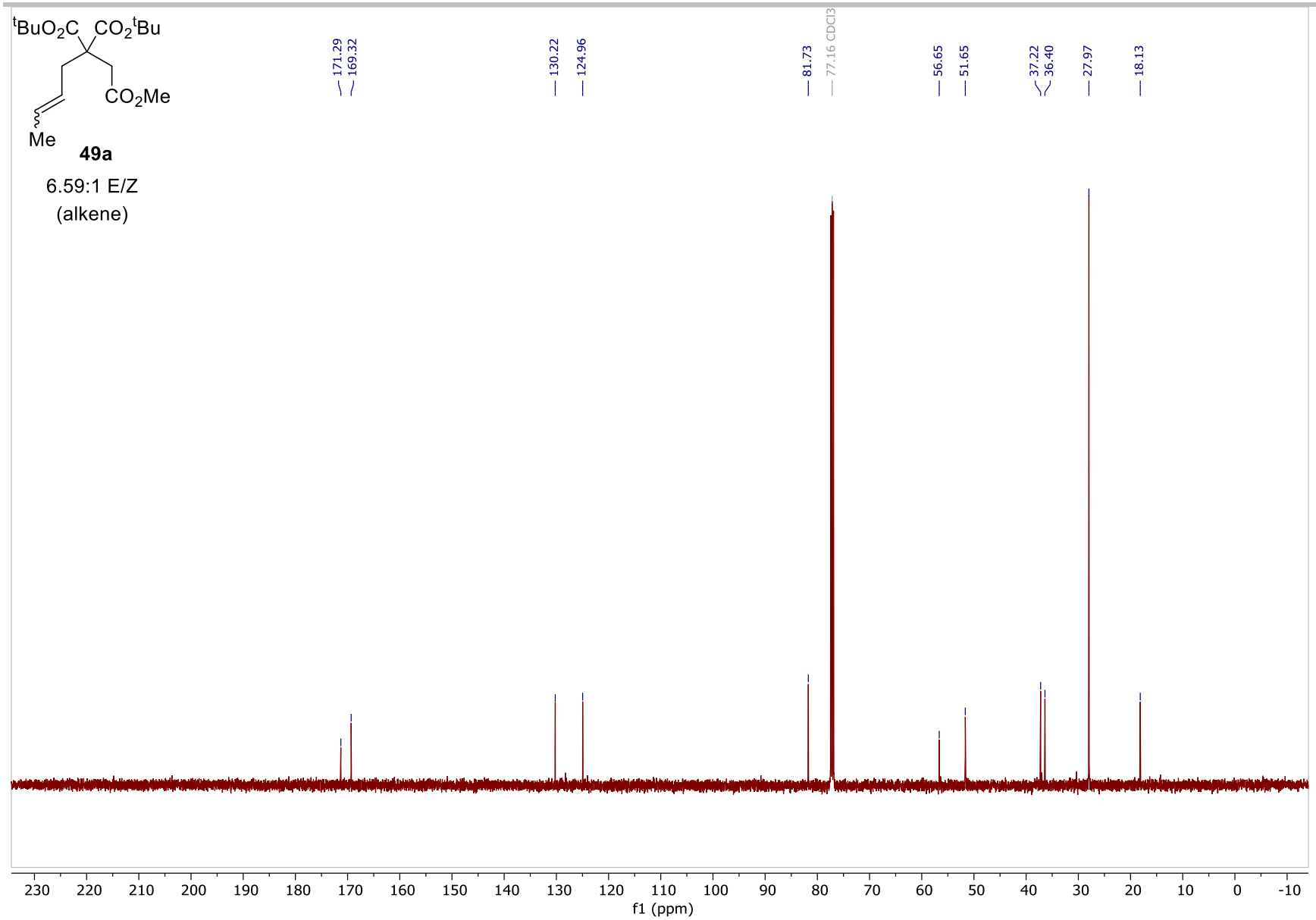

Figure S95. ^{13}C NMR (125 MHz, $CDCl_3$) of **49a**.

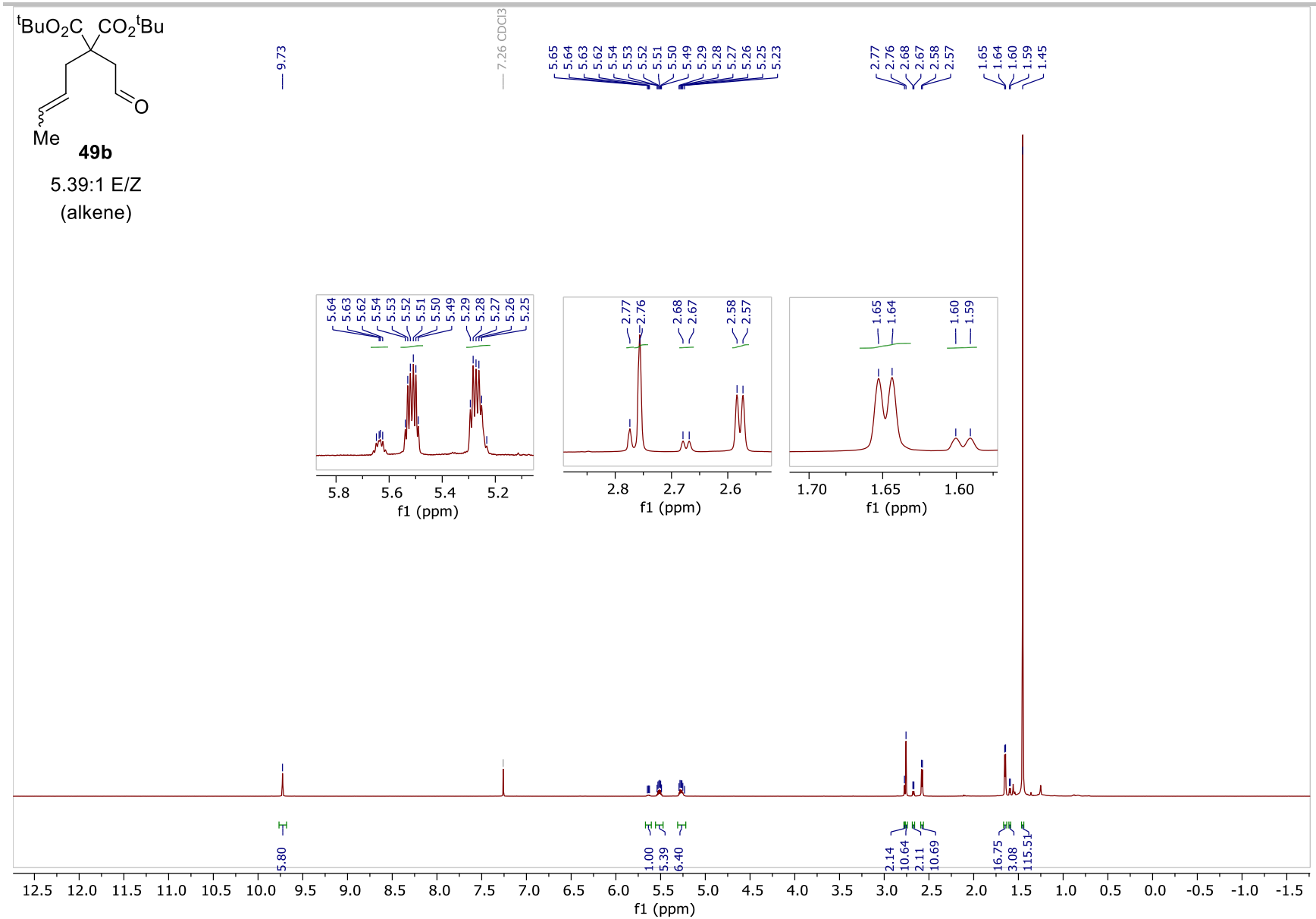

Figure S96. ^{1}H NMR (700 MHz, $CDCl_3$) of **49b**.

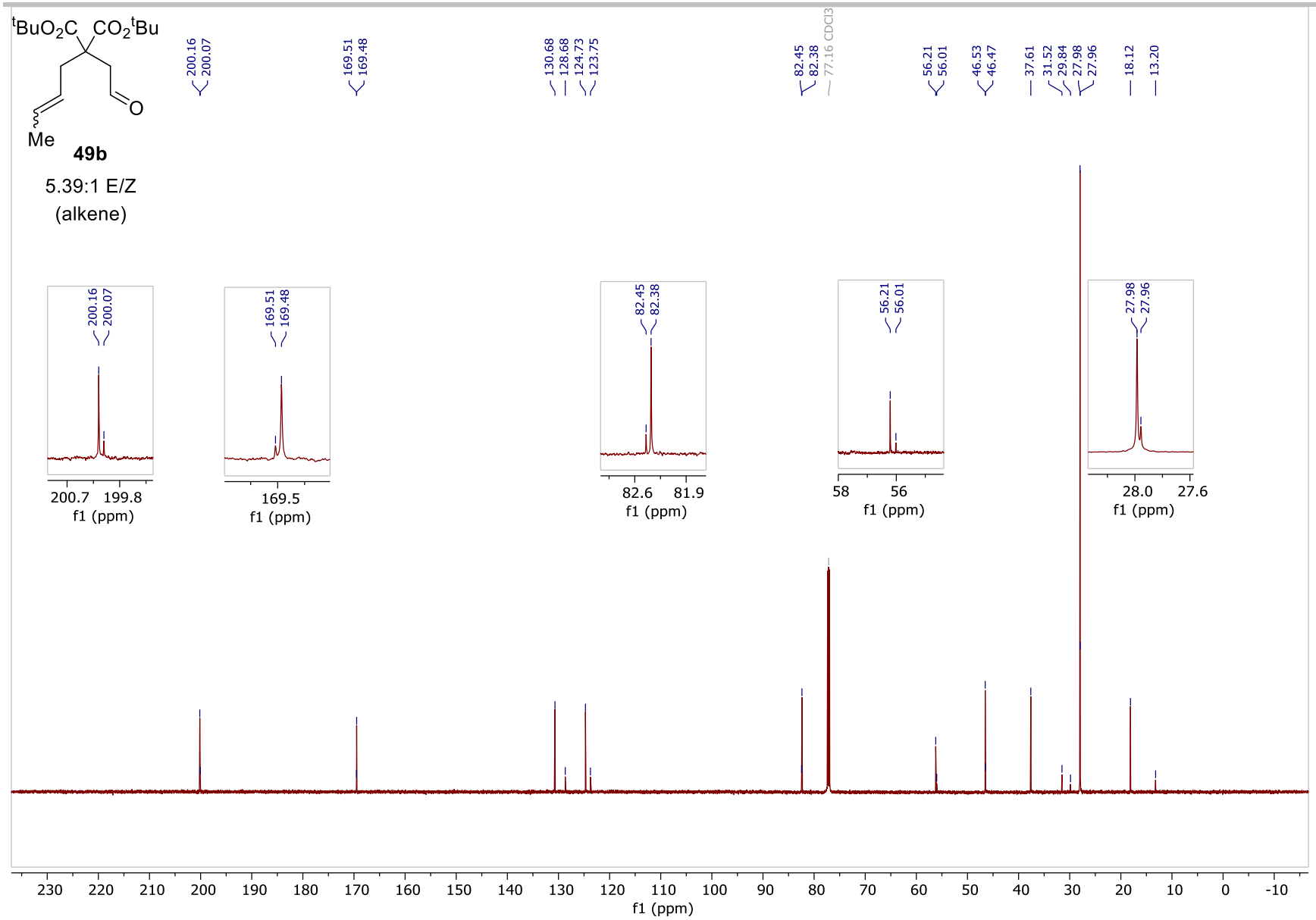

Figure S97. ^{13}C NMR (175 MHz, $CDCl_3$) of **49b**.

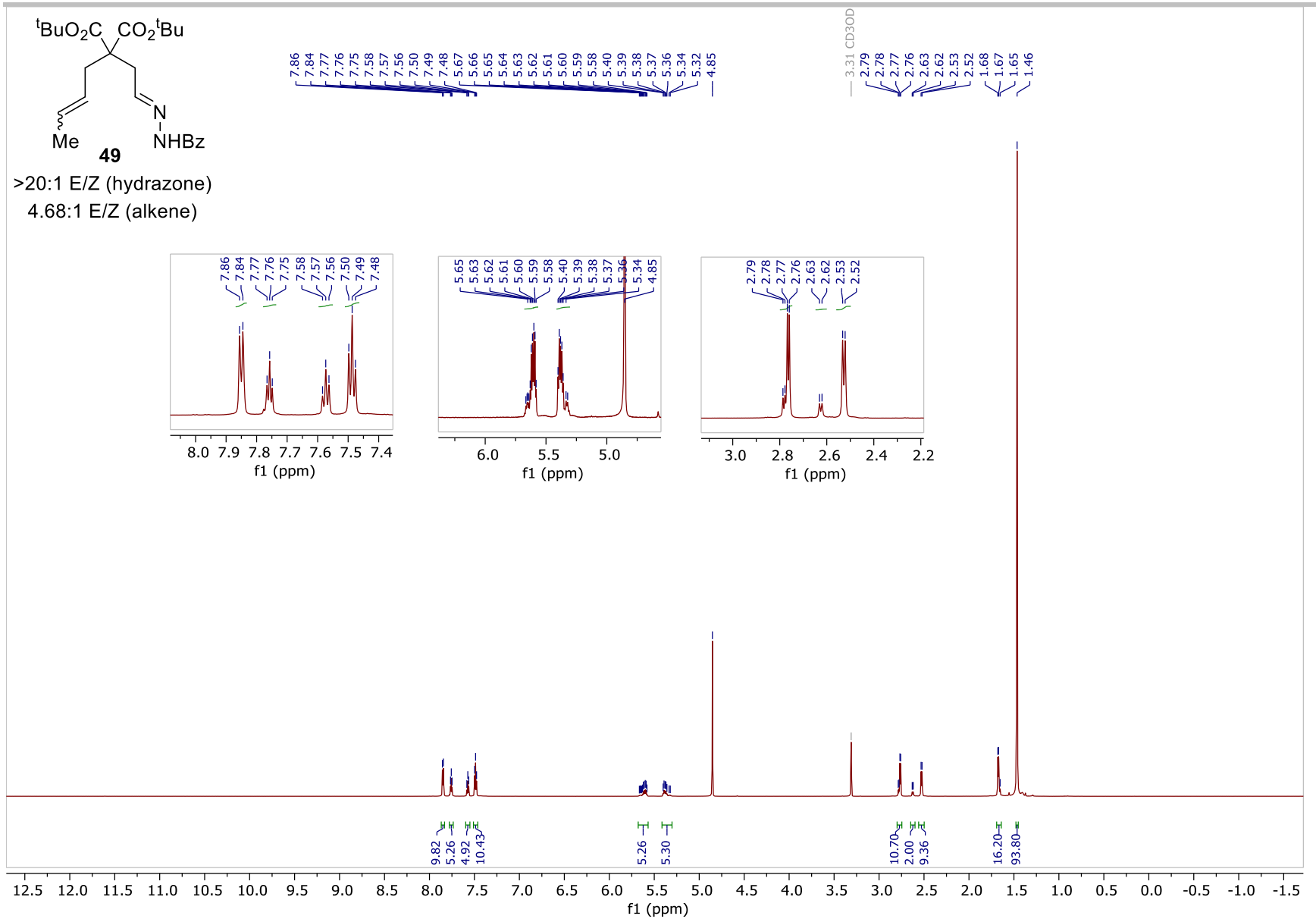

Figure S98. ^{1}H NMR (700 MHz, CD_3OD) of **49**.

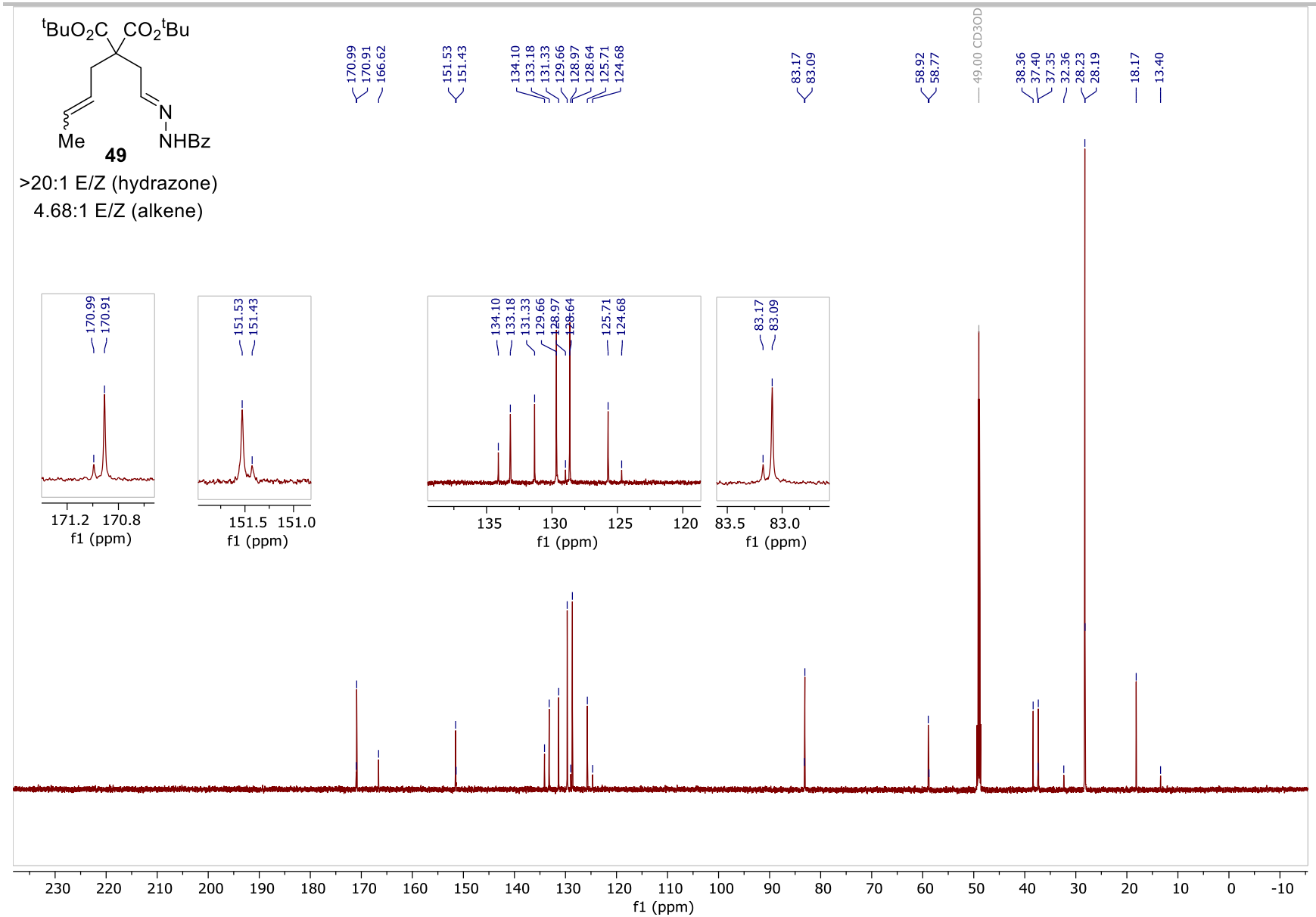

Figure S99. ^{13}C NMR (175 MHz, CD_3OD) of **49**.

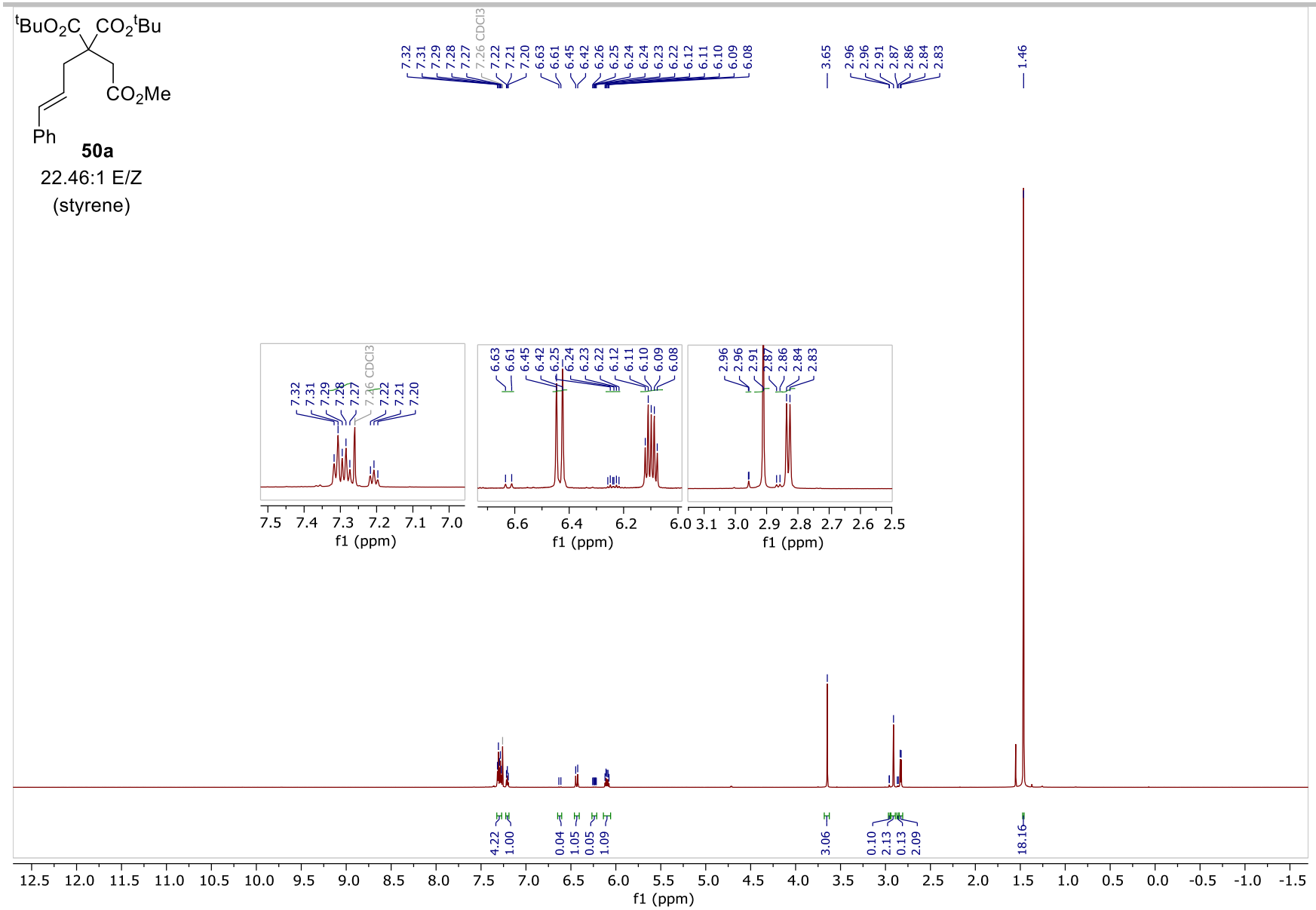

Figure S100. ^{1}H NMR (700 MHz, $CDCl_3$) of **50a**.

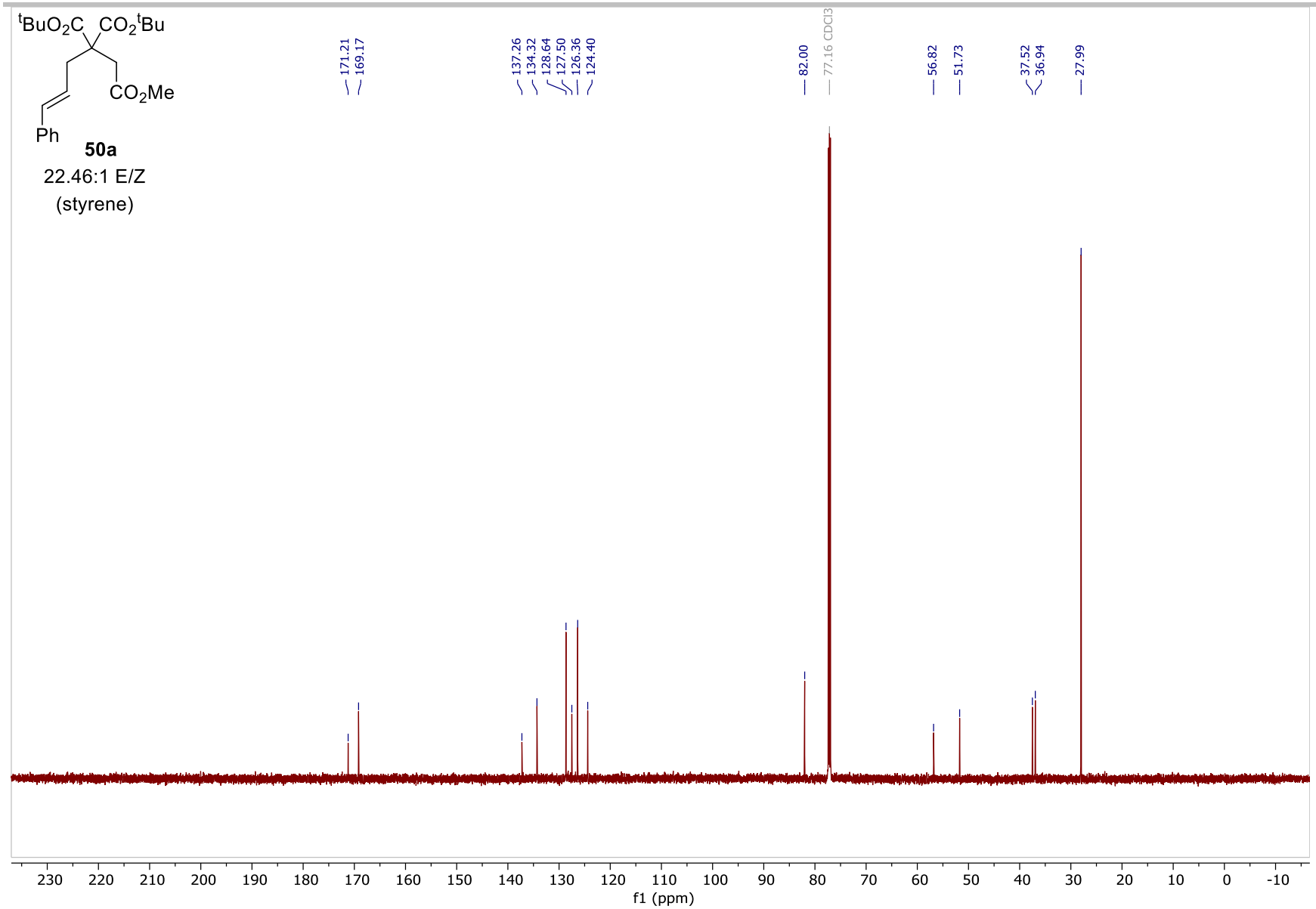

Figure S101. ^{13}C NMR (175 MHz, $CDCl_3$) of **50a**.

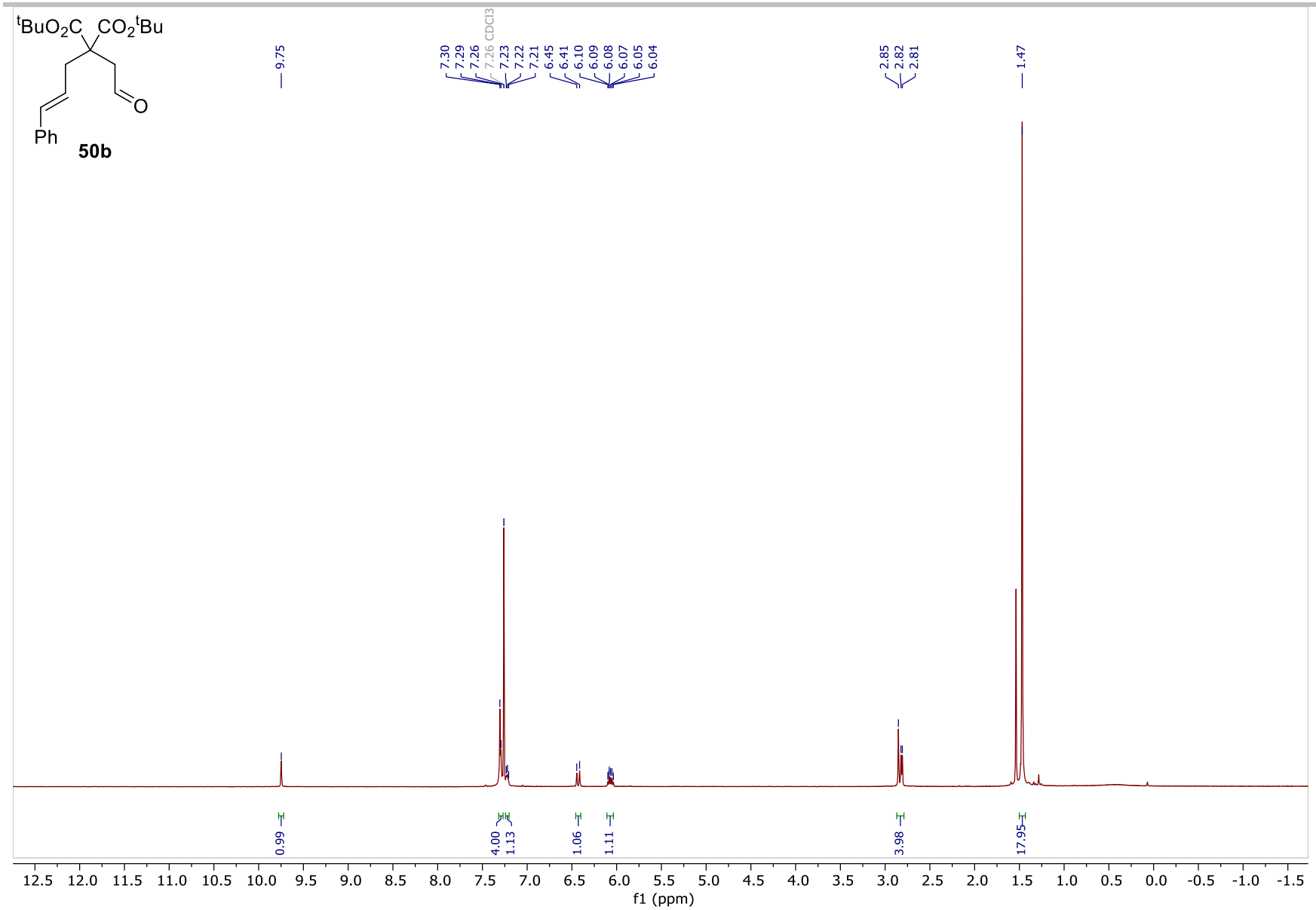

Figure S102. ^{1}H NMR (500 MHz, $CDCl_3$) of **50b**.

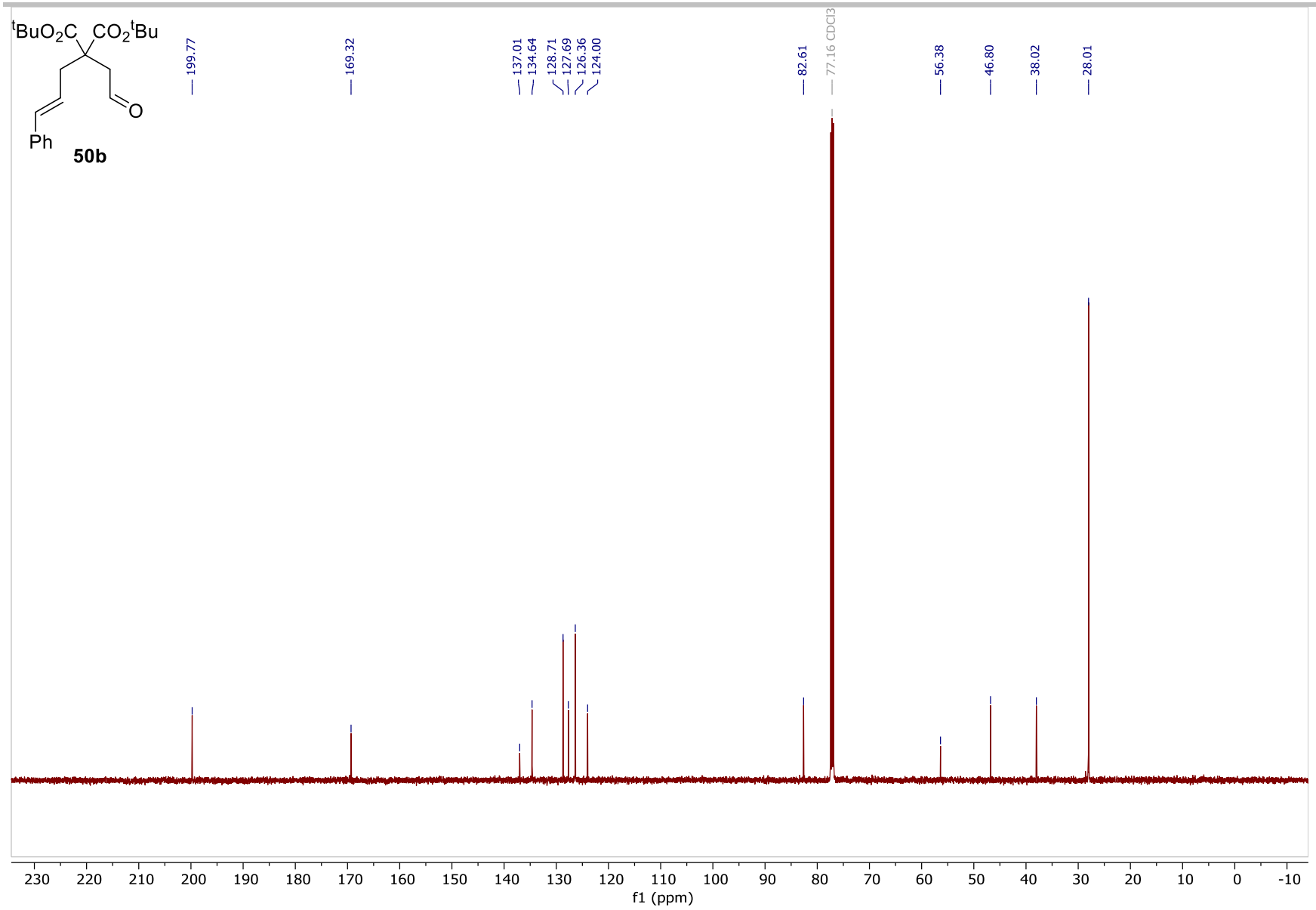

Figure S103. ^{13}C NMR (125 MHz, $CDCl_3$) of **50b**.

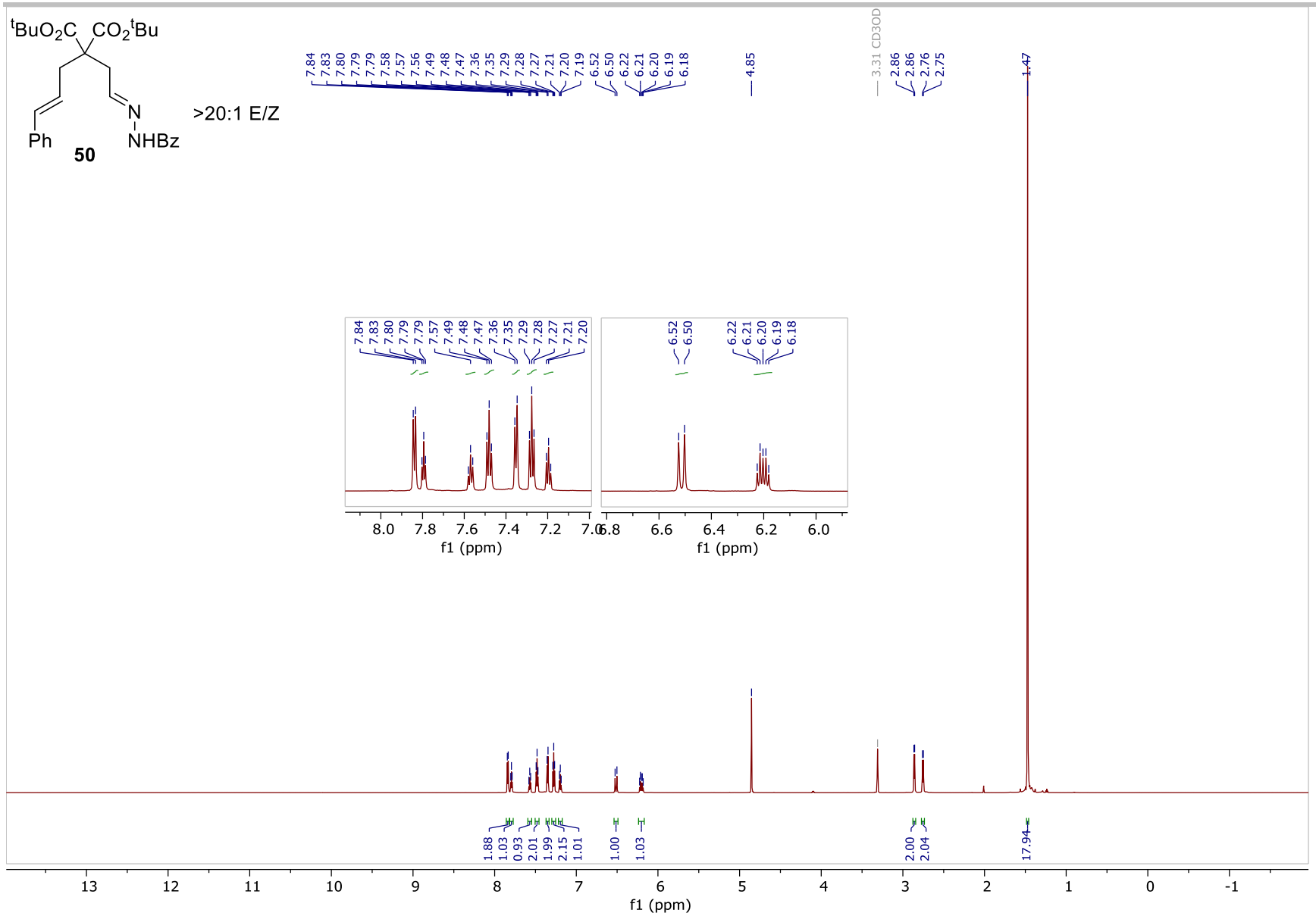

Figure S104. ^{1}H NMR (700 MHz, CD_3OD) of **50**.

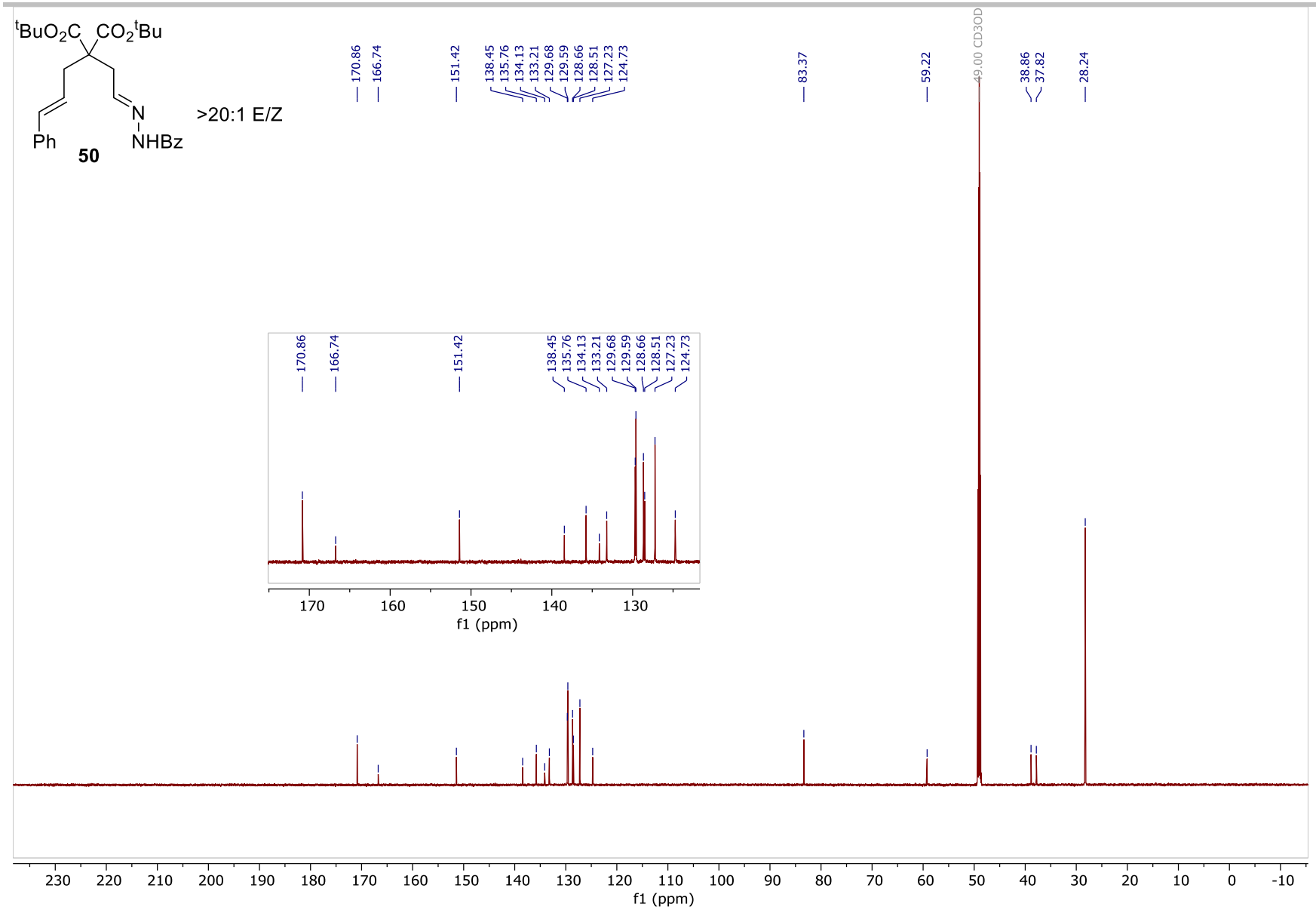

Figure S105. ^{13}C NMR (175 MHz, CD_3OD) of **50**.

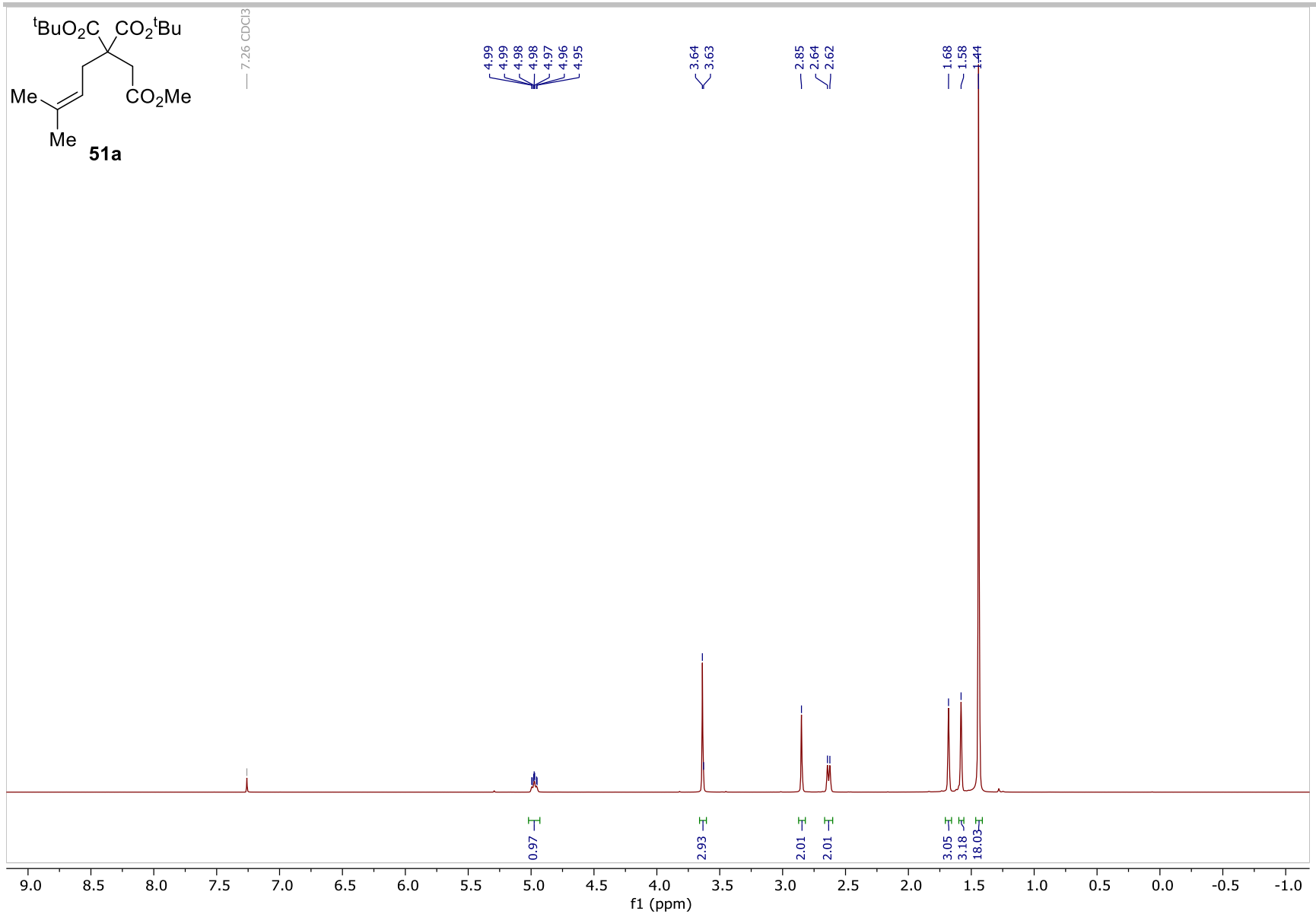

Figure S106. ^{1}H NMR (400 MHz, $CDCl_3$) of **51a**.

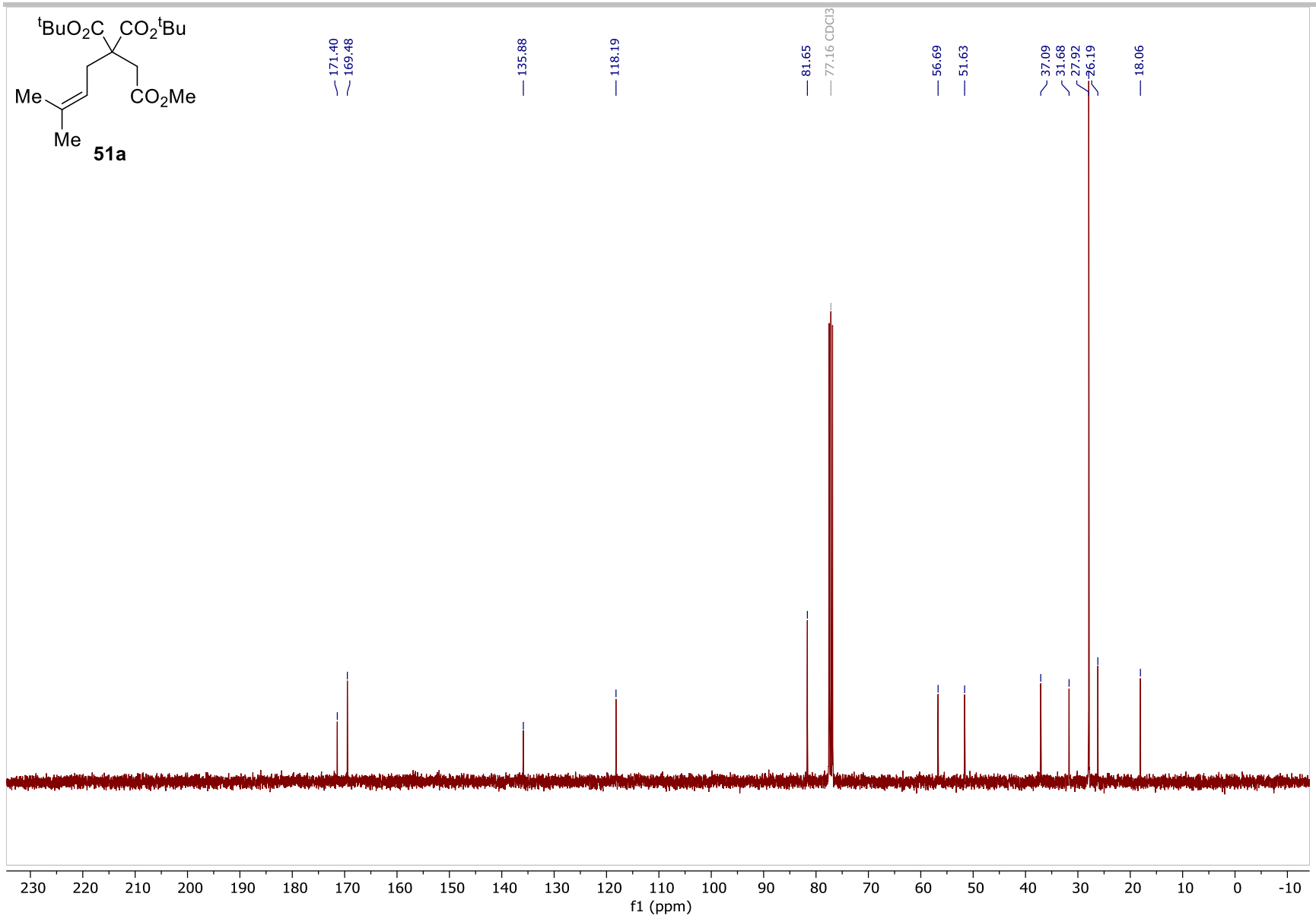

Figure S107. ^{13}C NMR (100 MHz, $CDCl_3$) of **51a**.

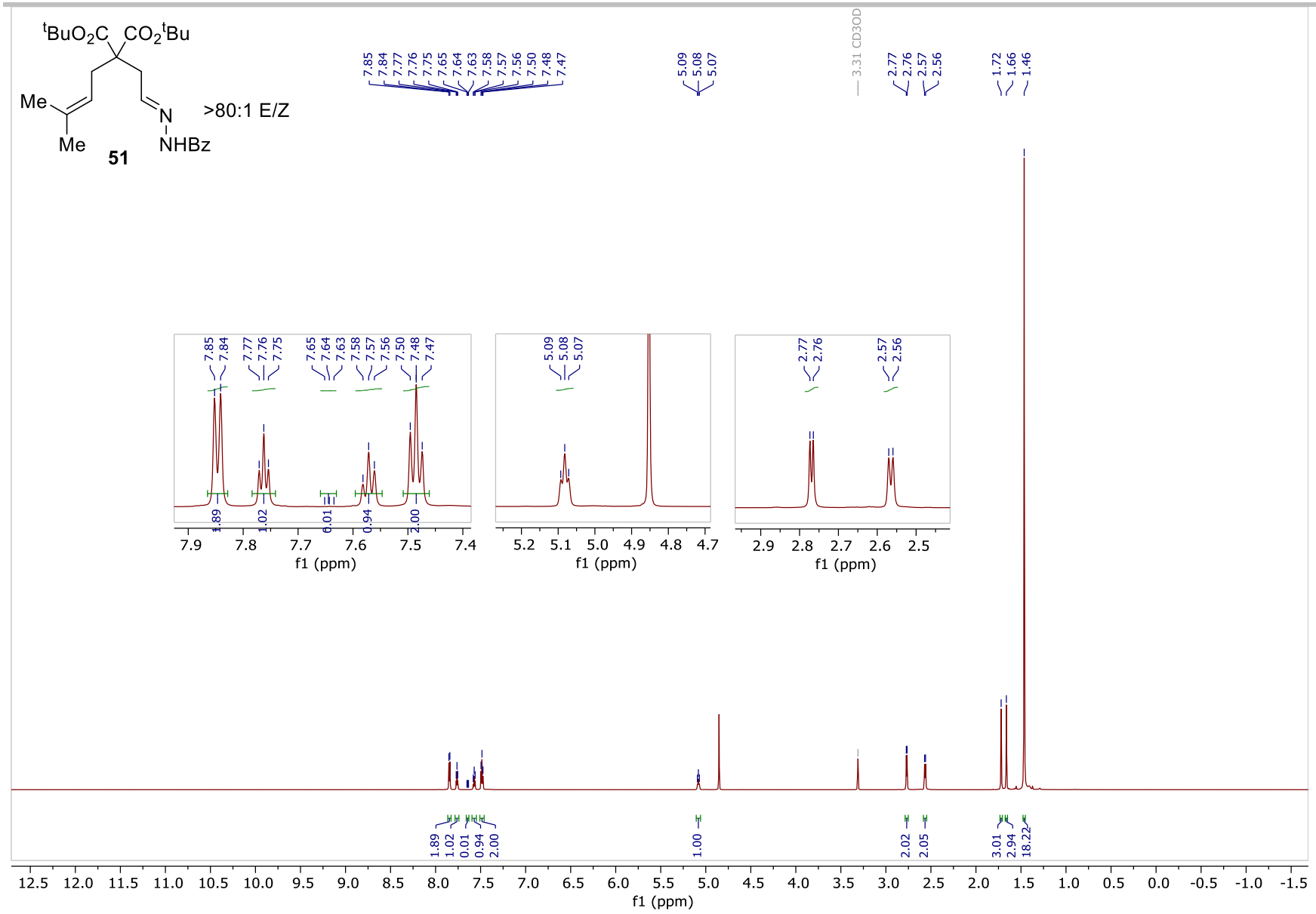

Figure S108. ^{1}H NMR (700 MHz, CD_3OD) of **51**.

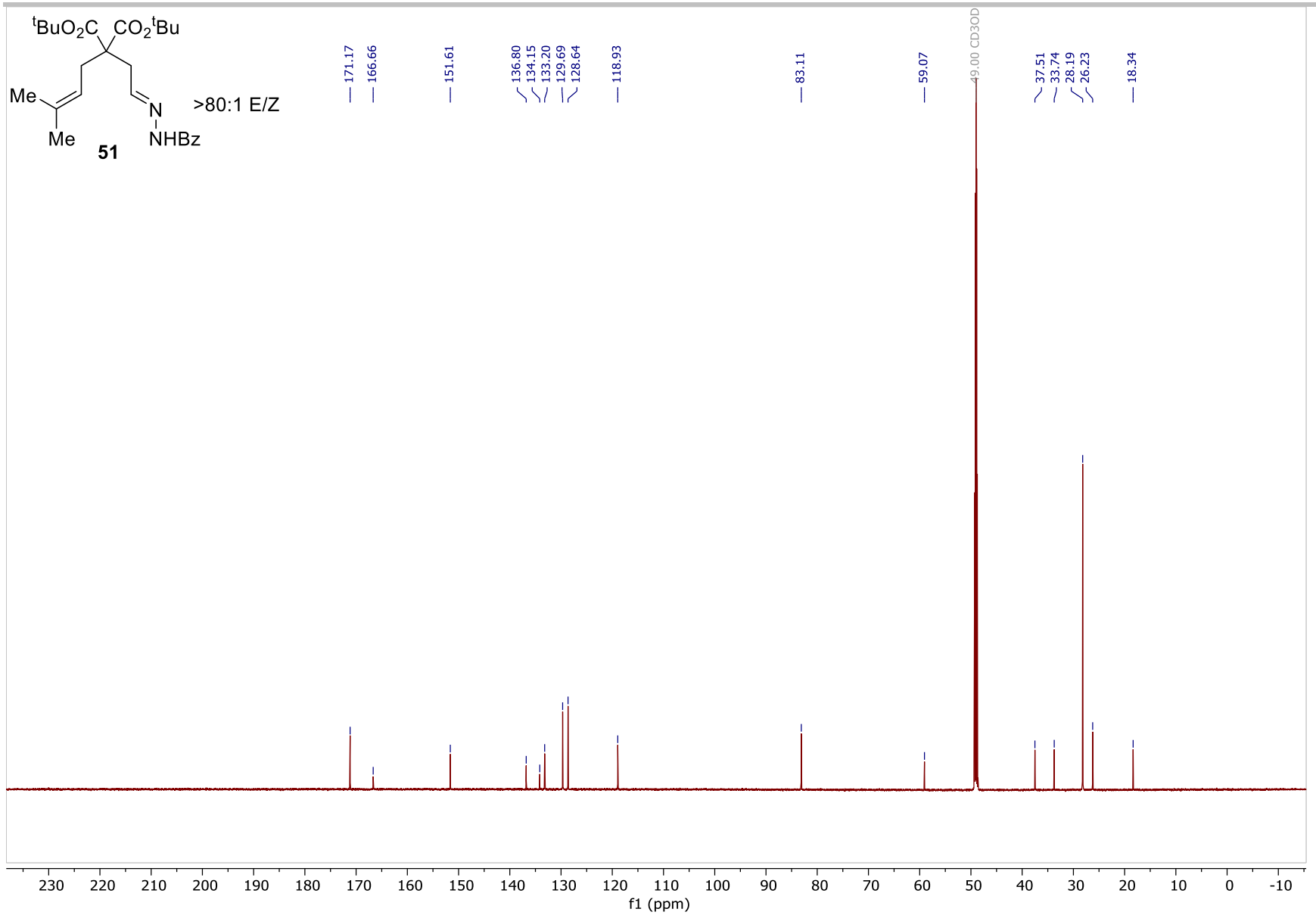

Figure S109. ^{13}C NMR (175 MHz, CD_3OD) of **51**.

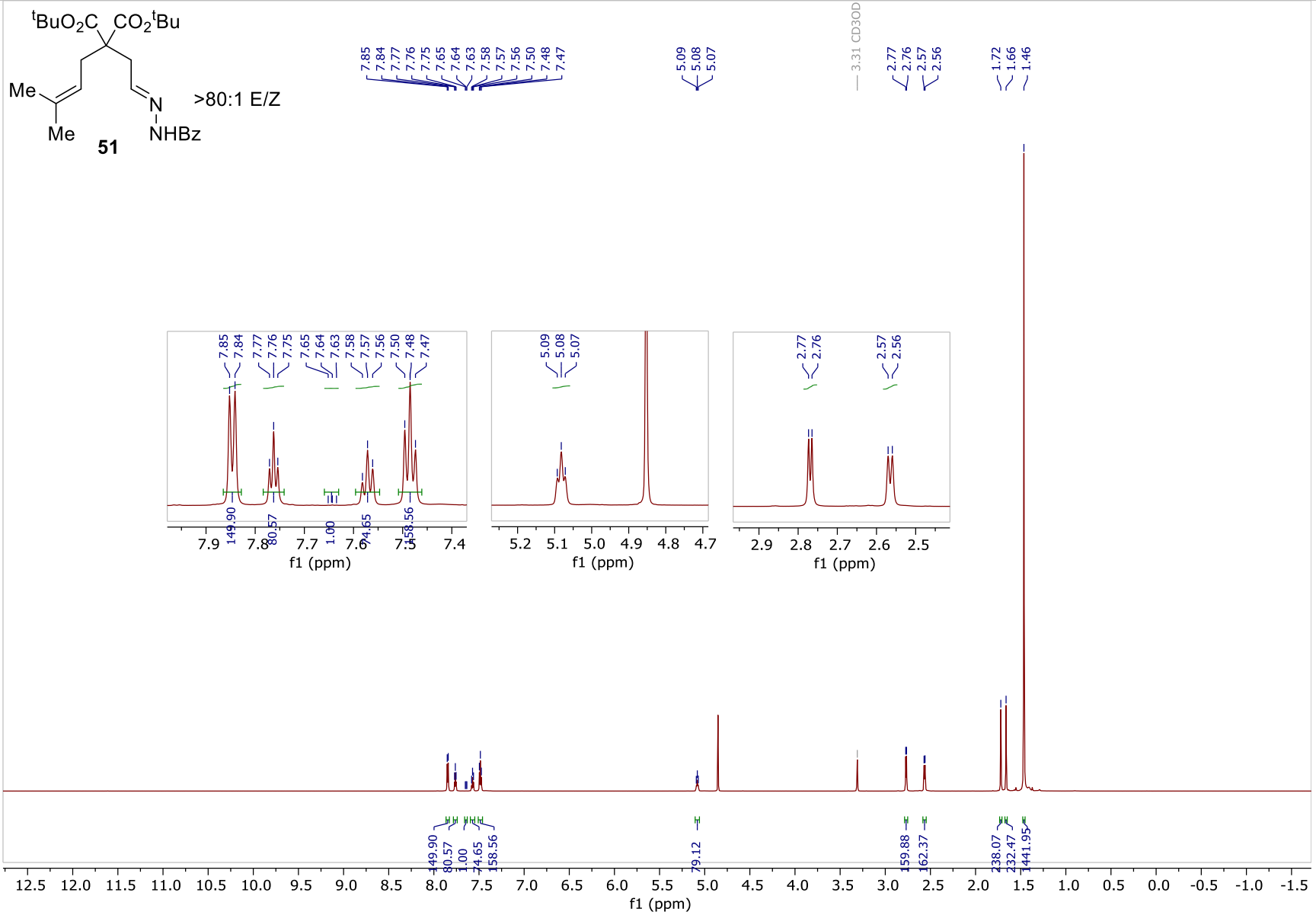

Figure S110. ^{1}H NMR (700 MHz, CD_3OD) showing >80:1 E/Z ratio of **51**.

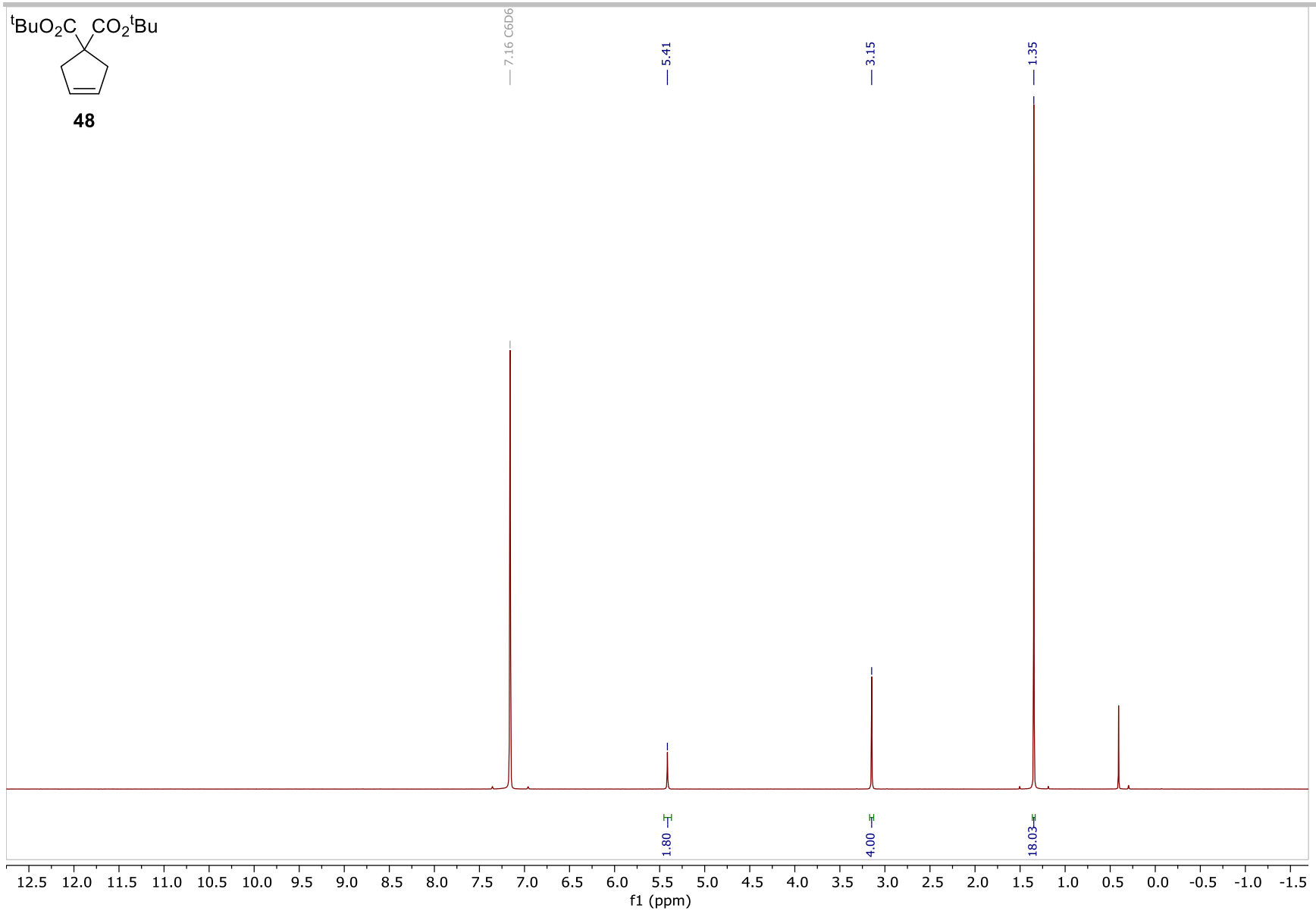

Figure S111. ^{1}H NMR (400 MHz, C_6D_6) of **48**.

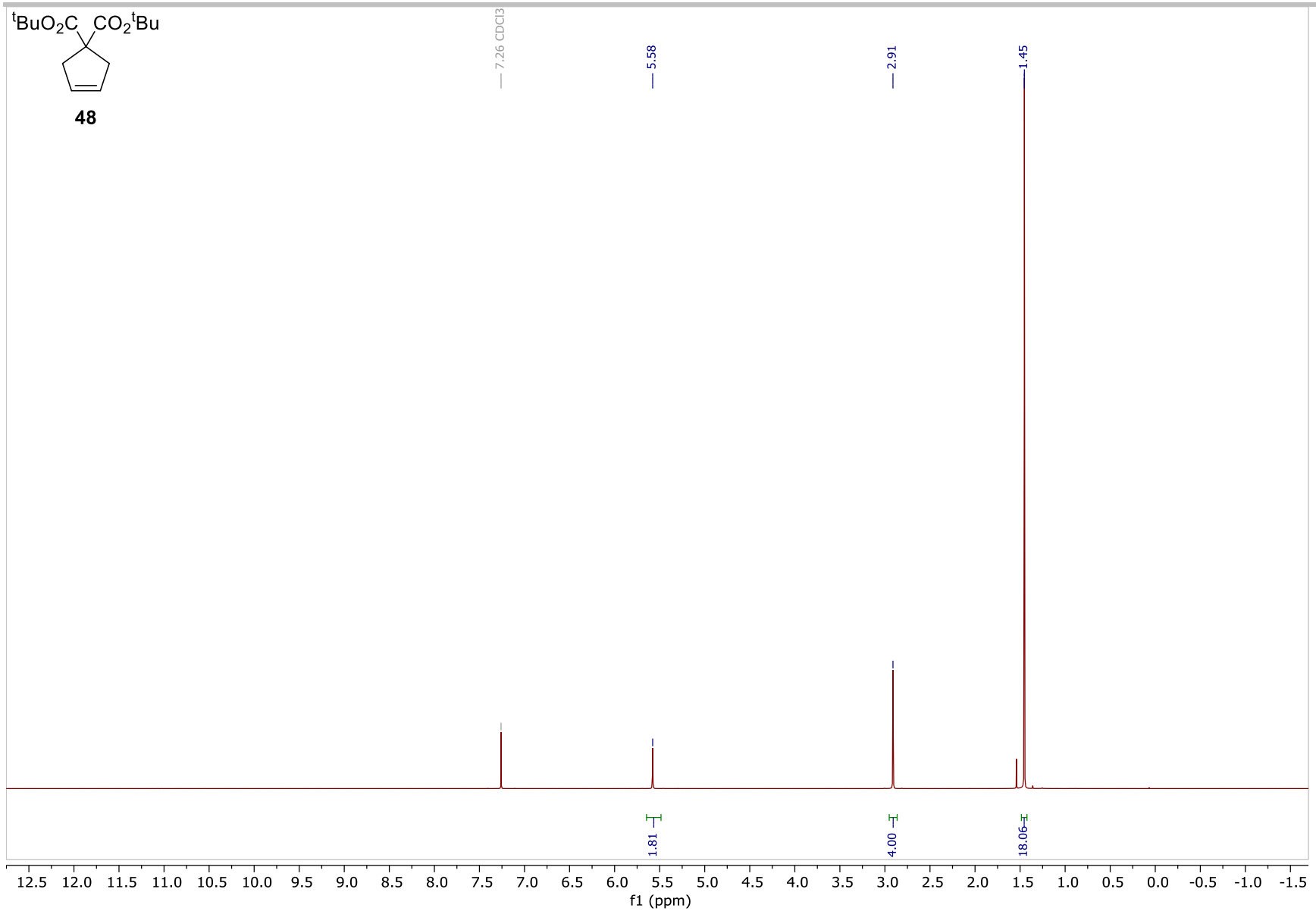

Figure S112. ^{1}H NMR (700 MHz, $CDCl_3$) of **48**.

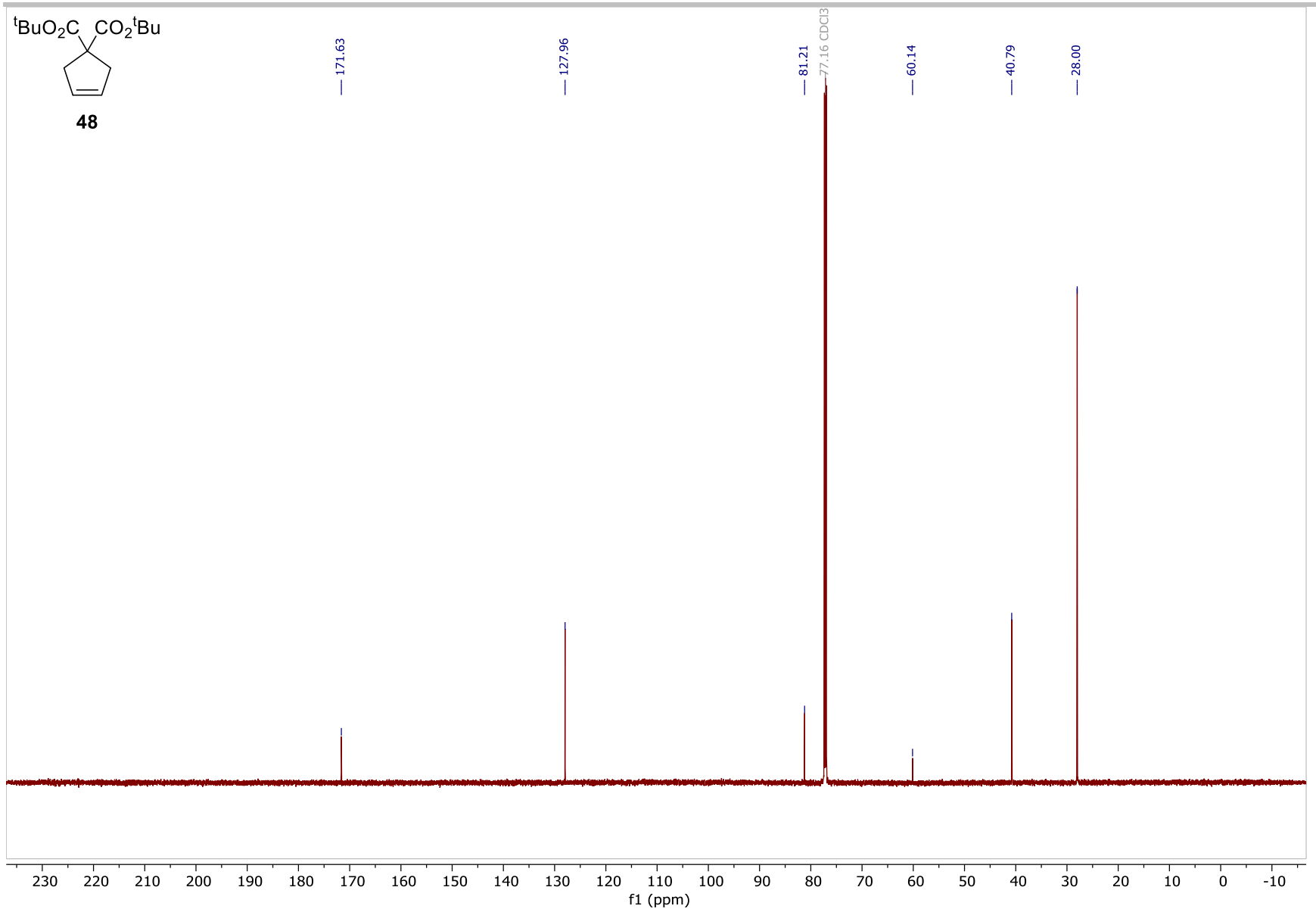

Figure S113. ^{13}C NMR (175 MHz, $CDCl_3$) of **48.**

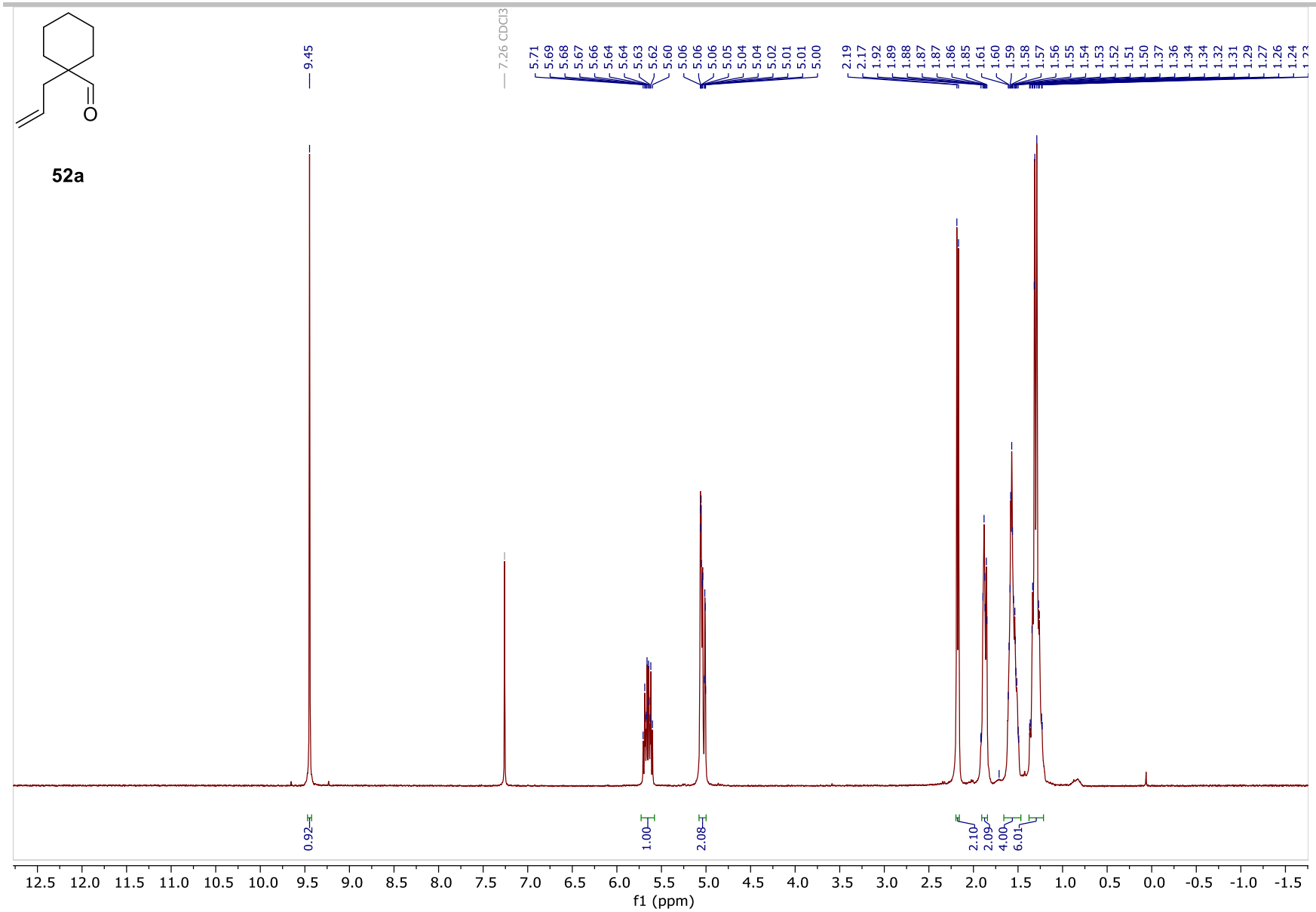

Figure S114. ^{1}H NMR (500 MHz, $CDCl_3$) of **52a**.

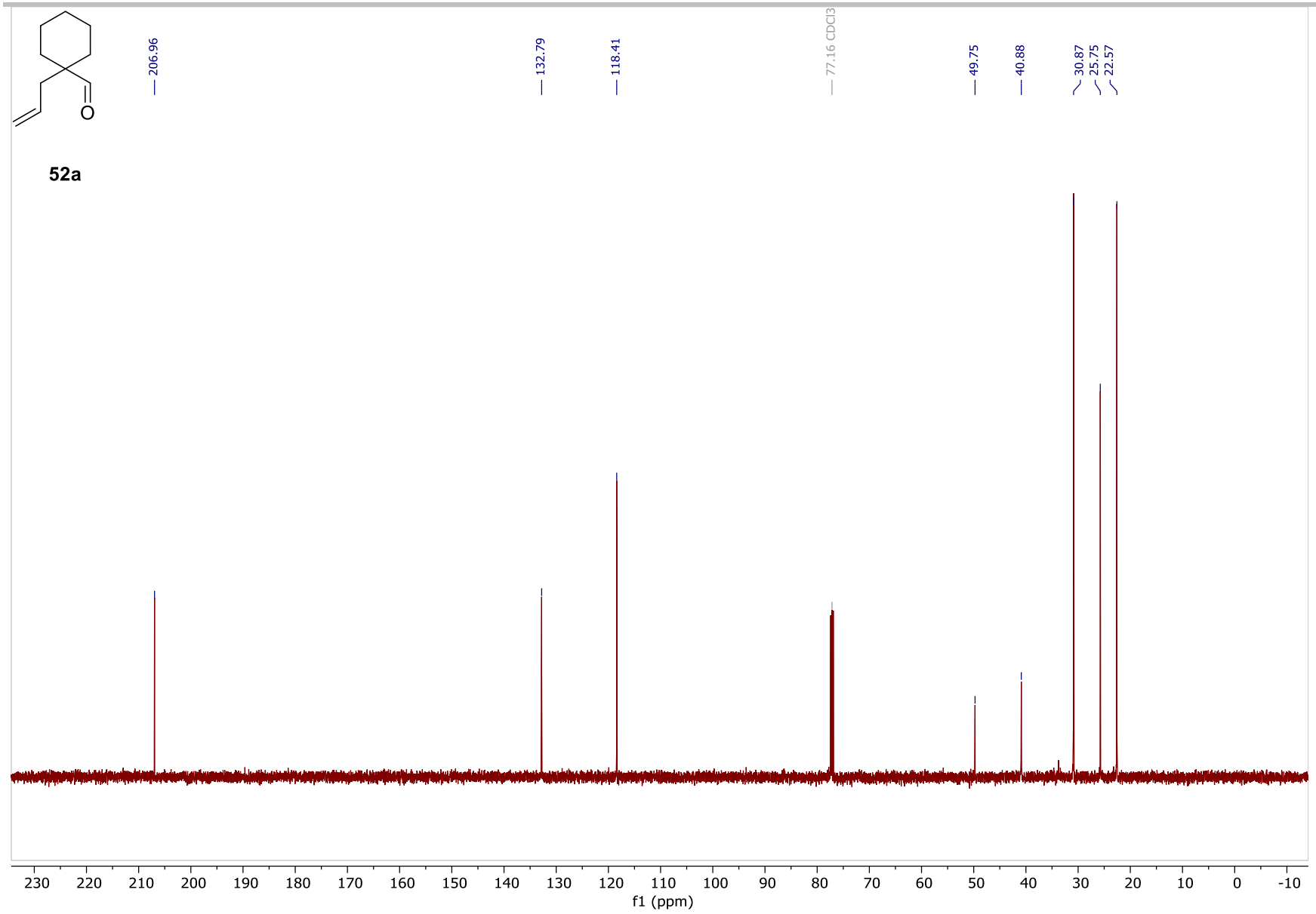

Figure S115. ^{13}C NMR (125 MHz, $CDCl_3$) of **52a**.

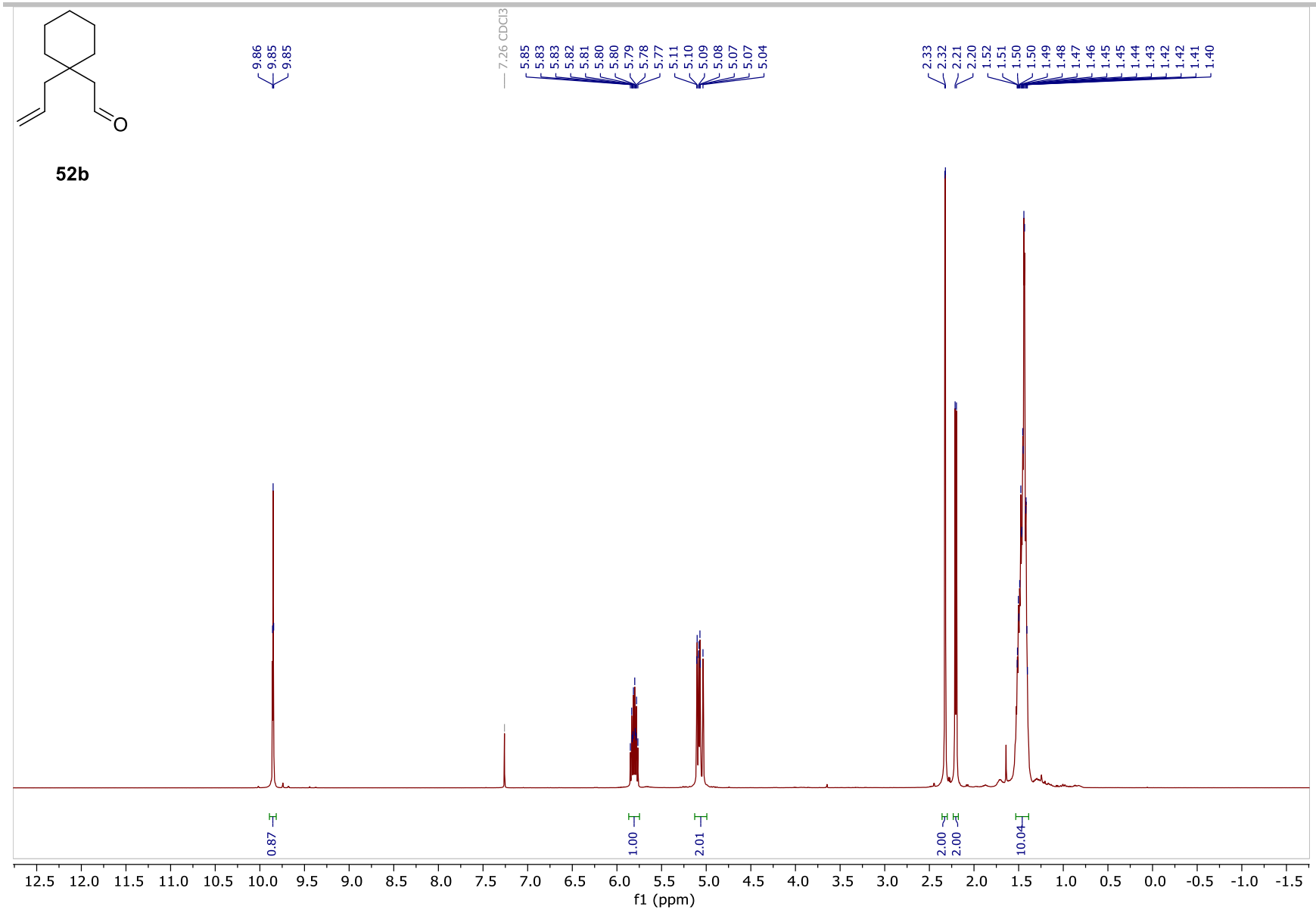

Figure S116. ^{1}H NMR (500 MHz, $CDCl_3$) of **52b**.

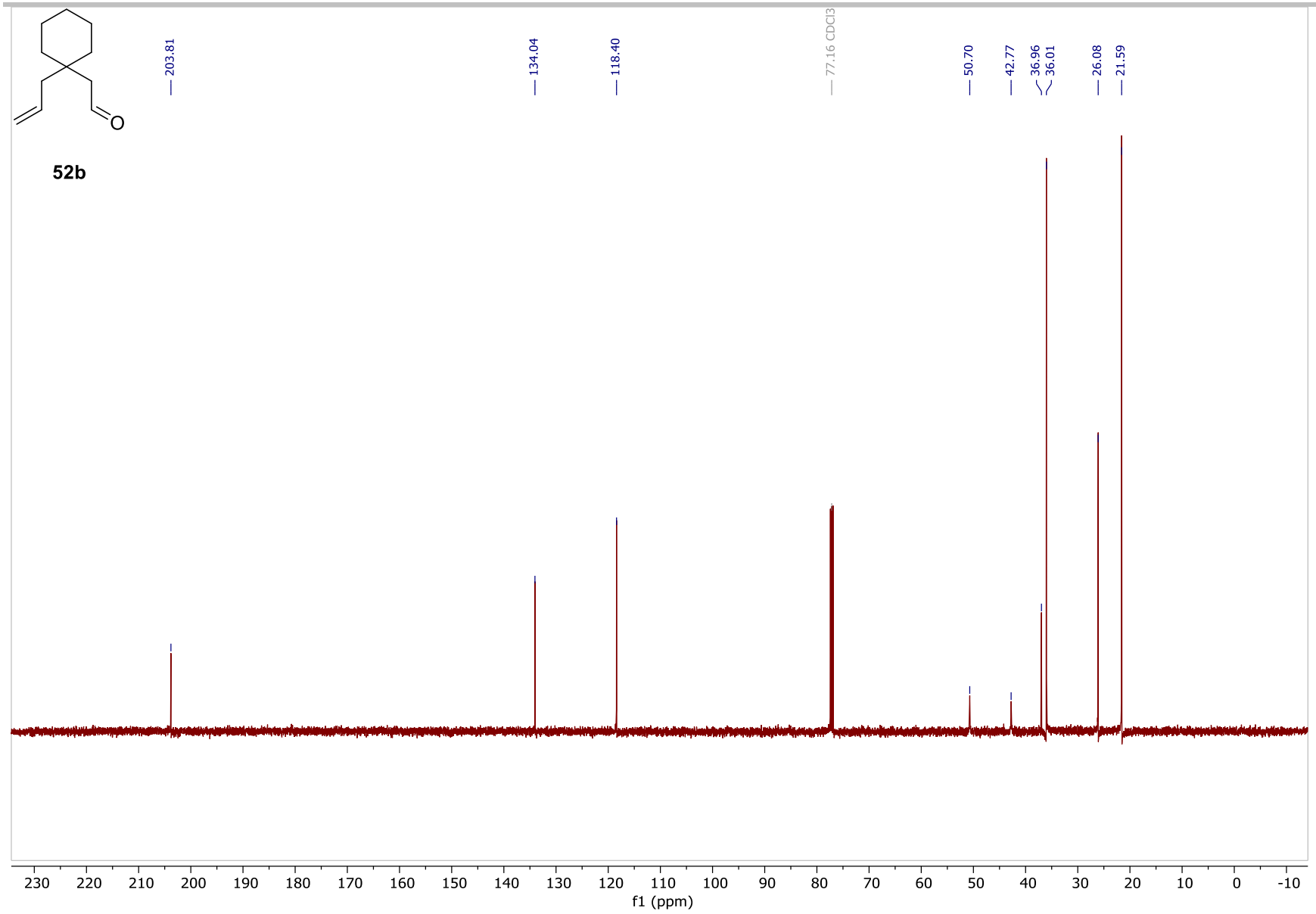

Figure S117. ^{13}C NMR (125 MHz, $CDCl_3$) of **52b**.

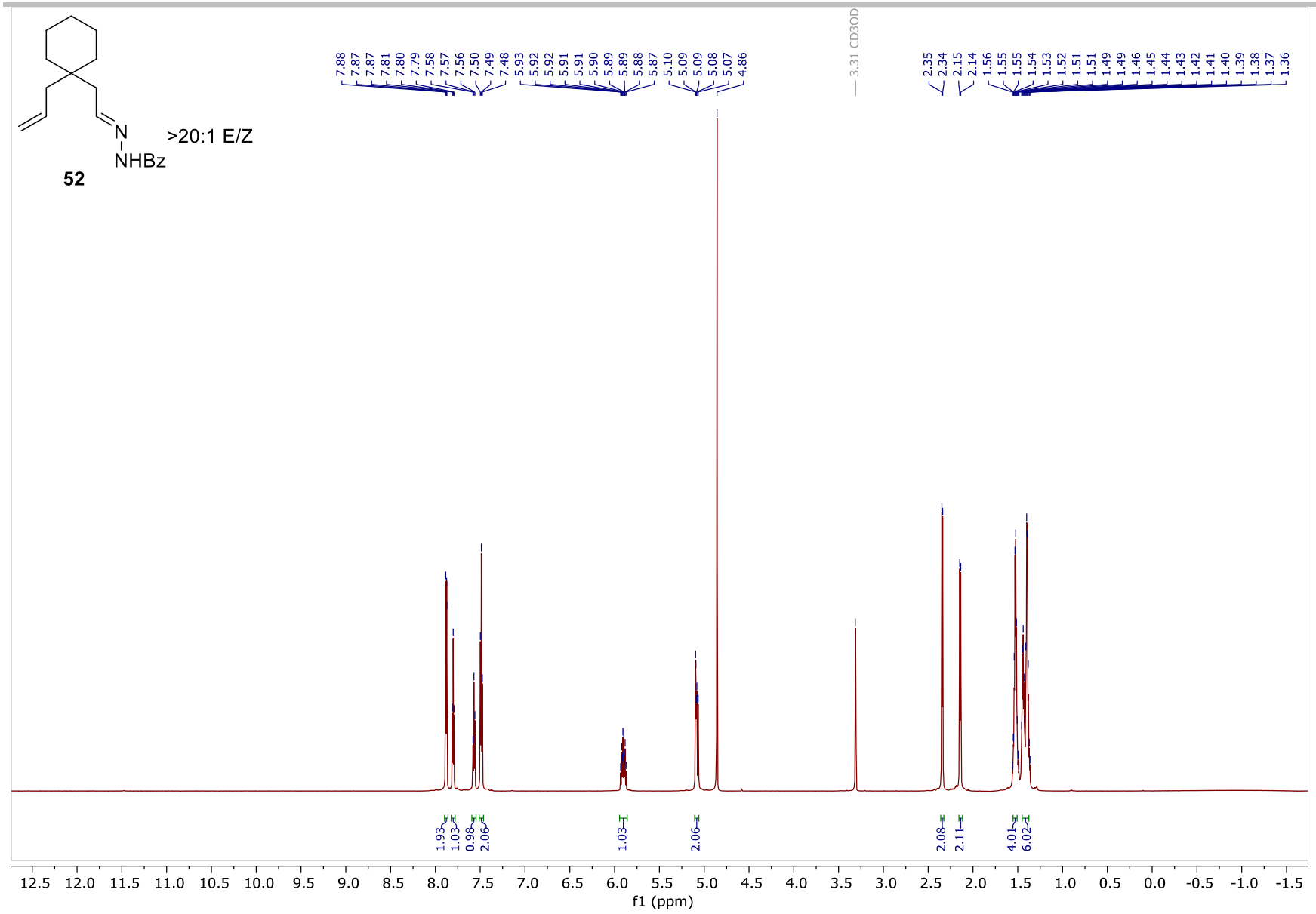

Figure S118. ^{1}H NMR (700 MHz, CD_3OD) of **52**.

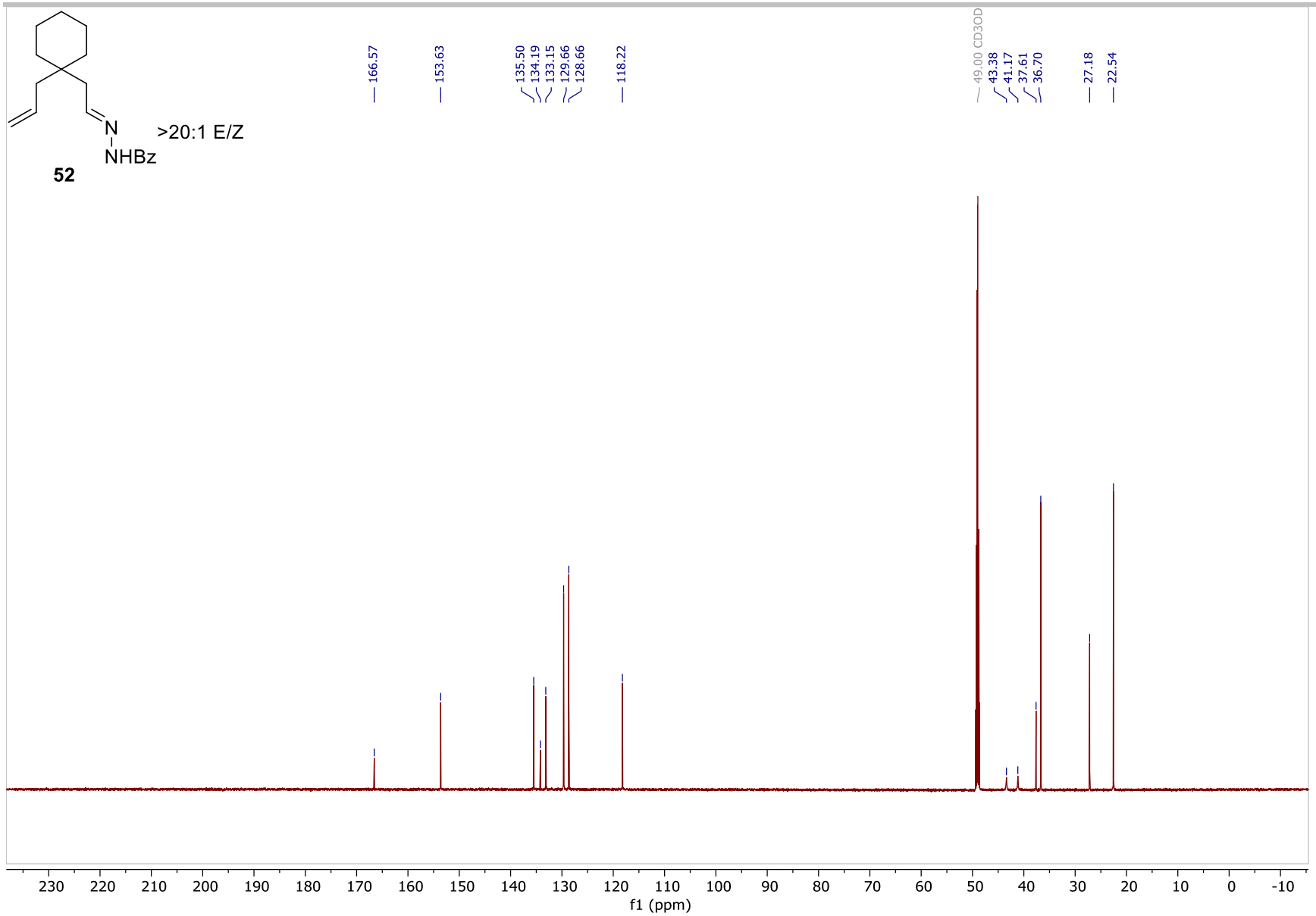

Figure S119. ^{13}C NMR (175 MHz, CD_3OD) of **52**.

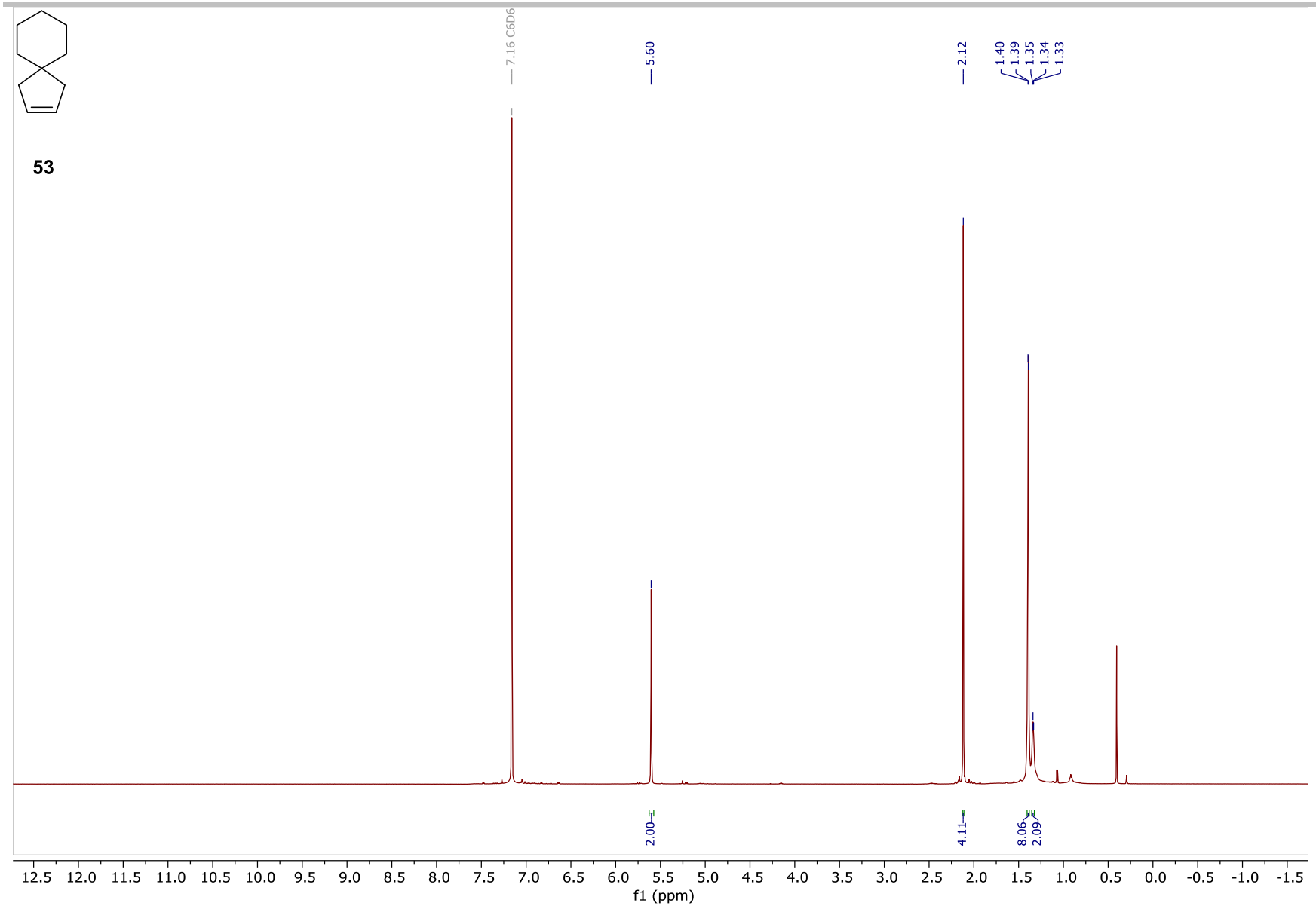

Figure S120. ^{1}H NMR (700 MHz, C_6D_6) of **53**.

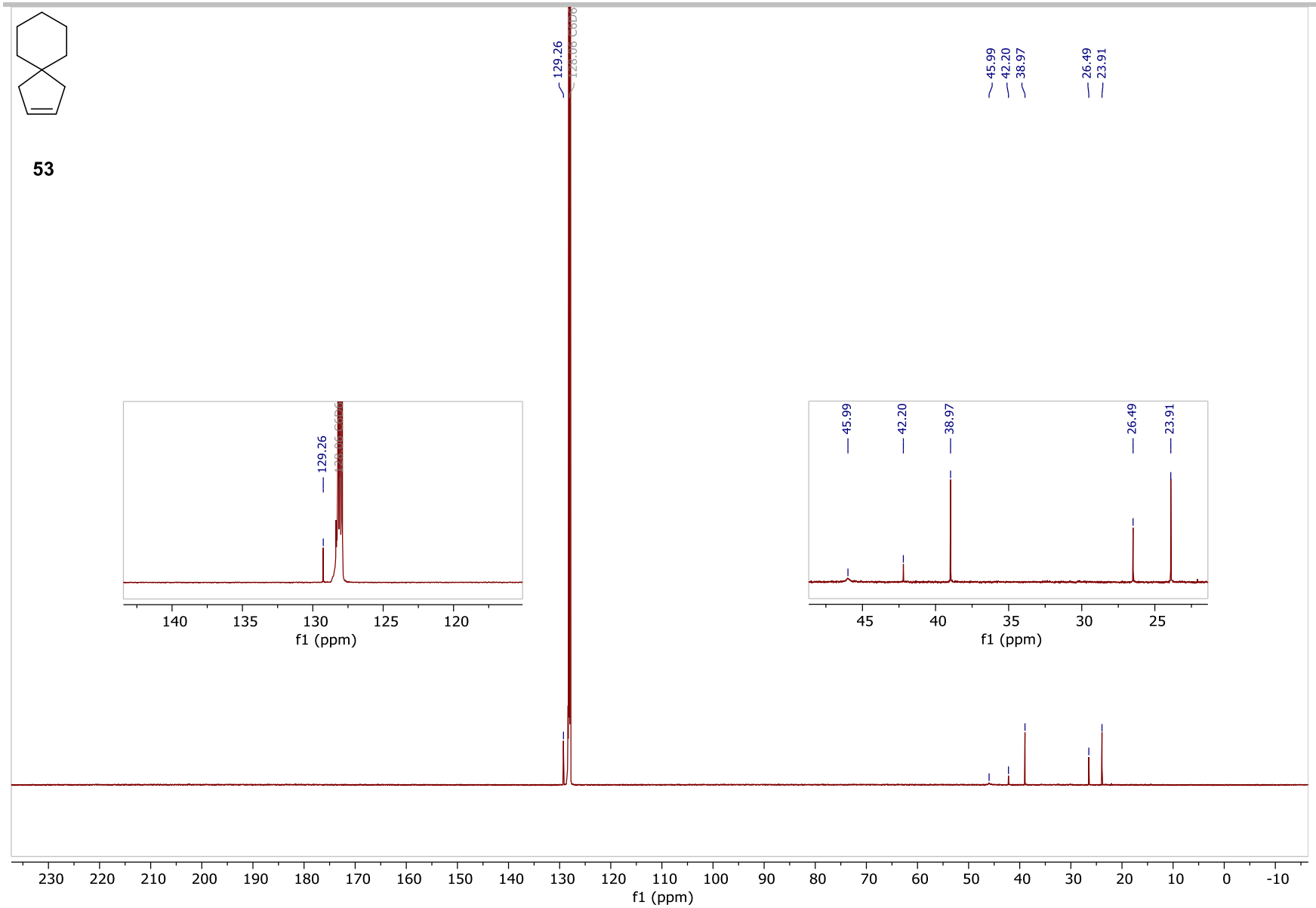

Figure S121. ^{13}C NMR (175 MHz, C_6D_6) of **53.**

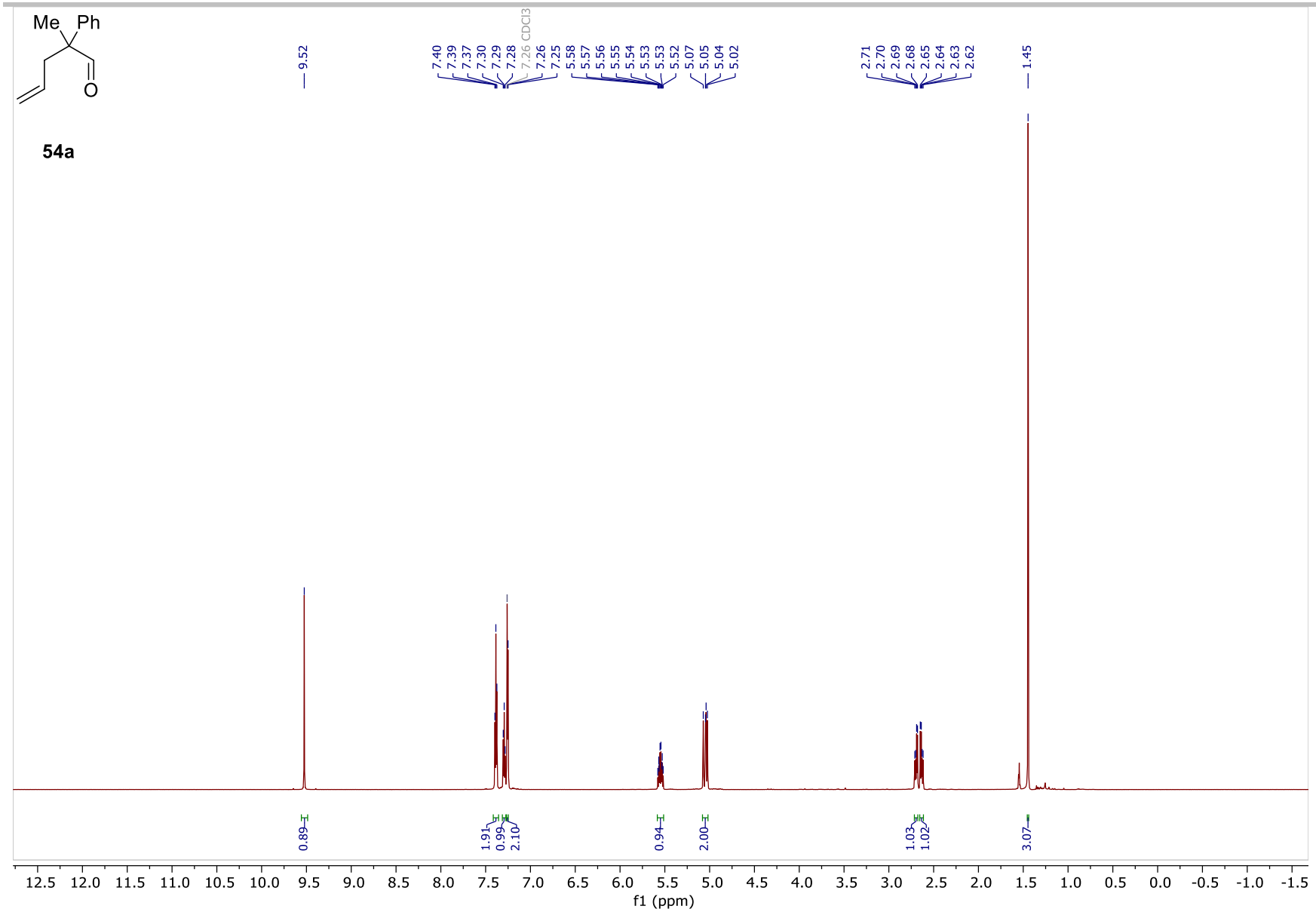

Figure S122. ^{1}H NMR (700 MHz, $CDCl_3$) of **54a**.

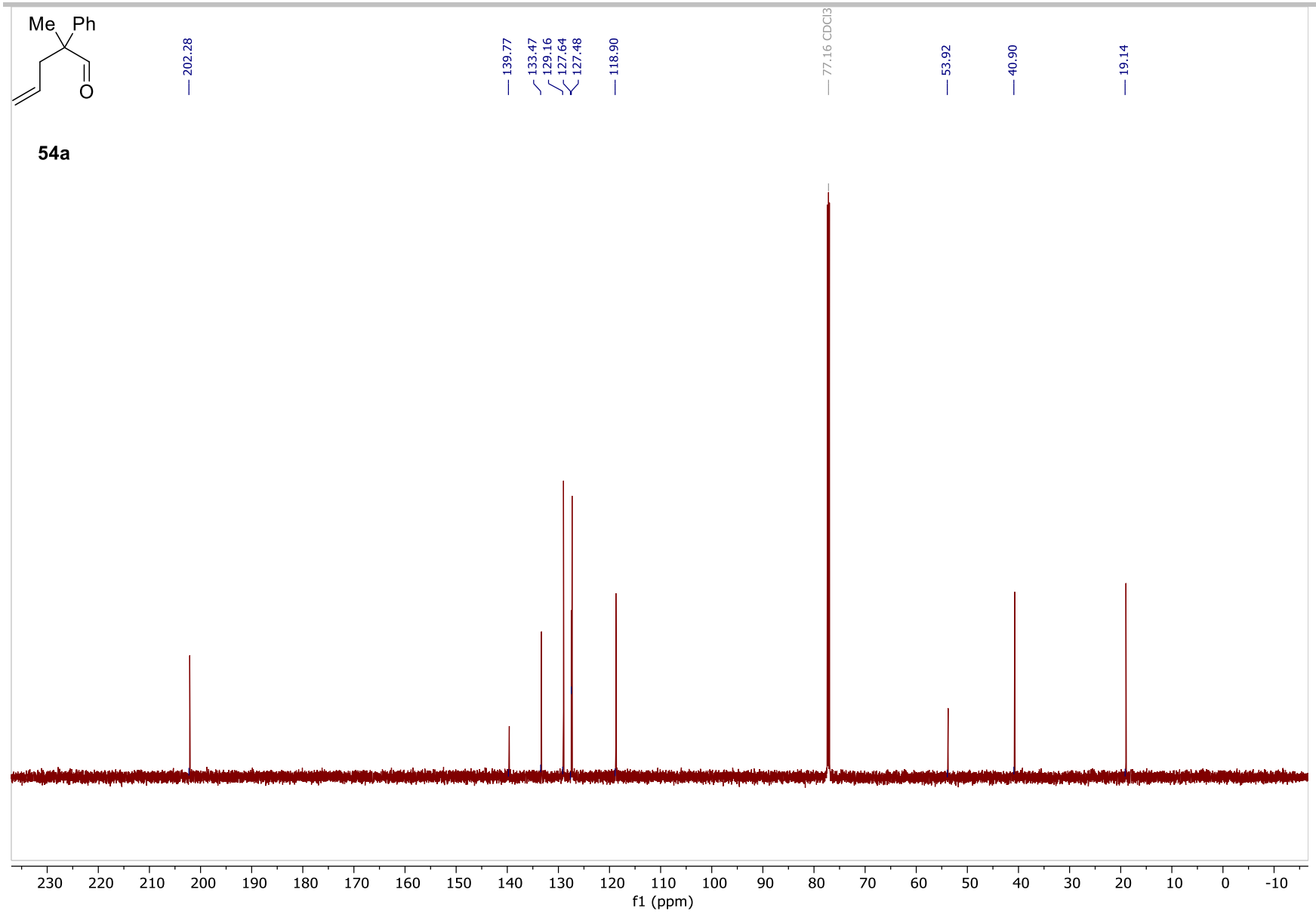

Figure S123. ^{13}C NMR (175 MHz, $CDCl_3$) of **54a**.

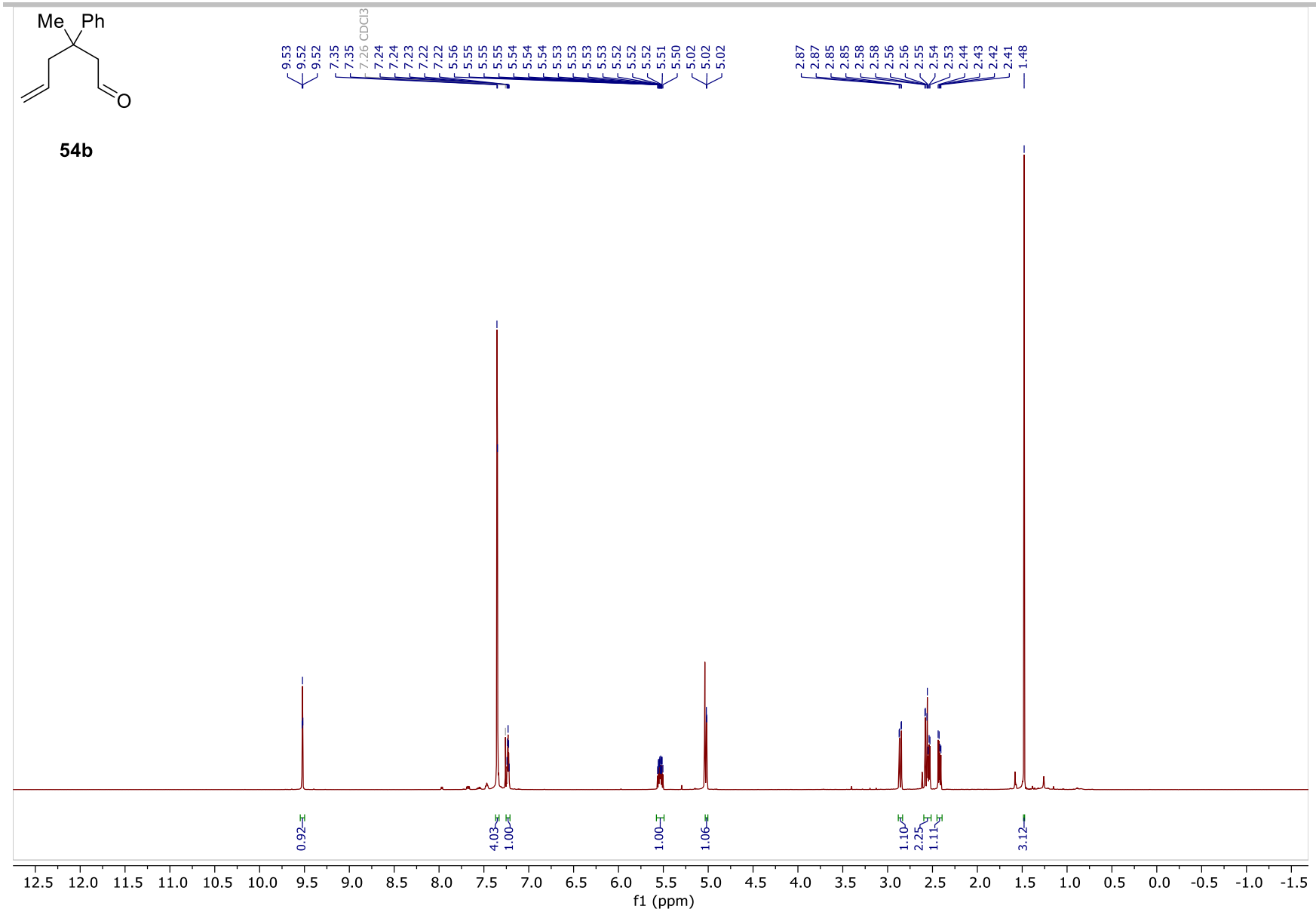

Figure S124. ^{1}H NMR (700 MHz, $CDCl_3$) of **54b**.

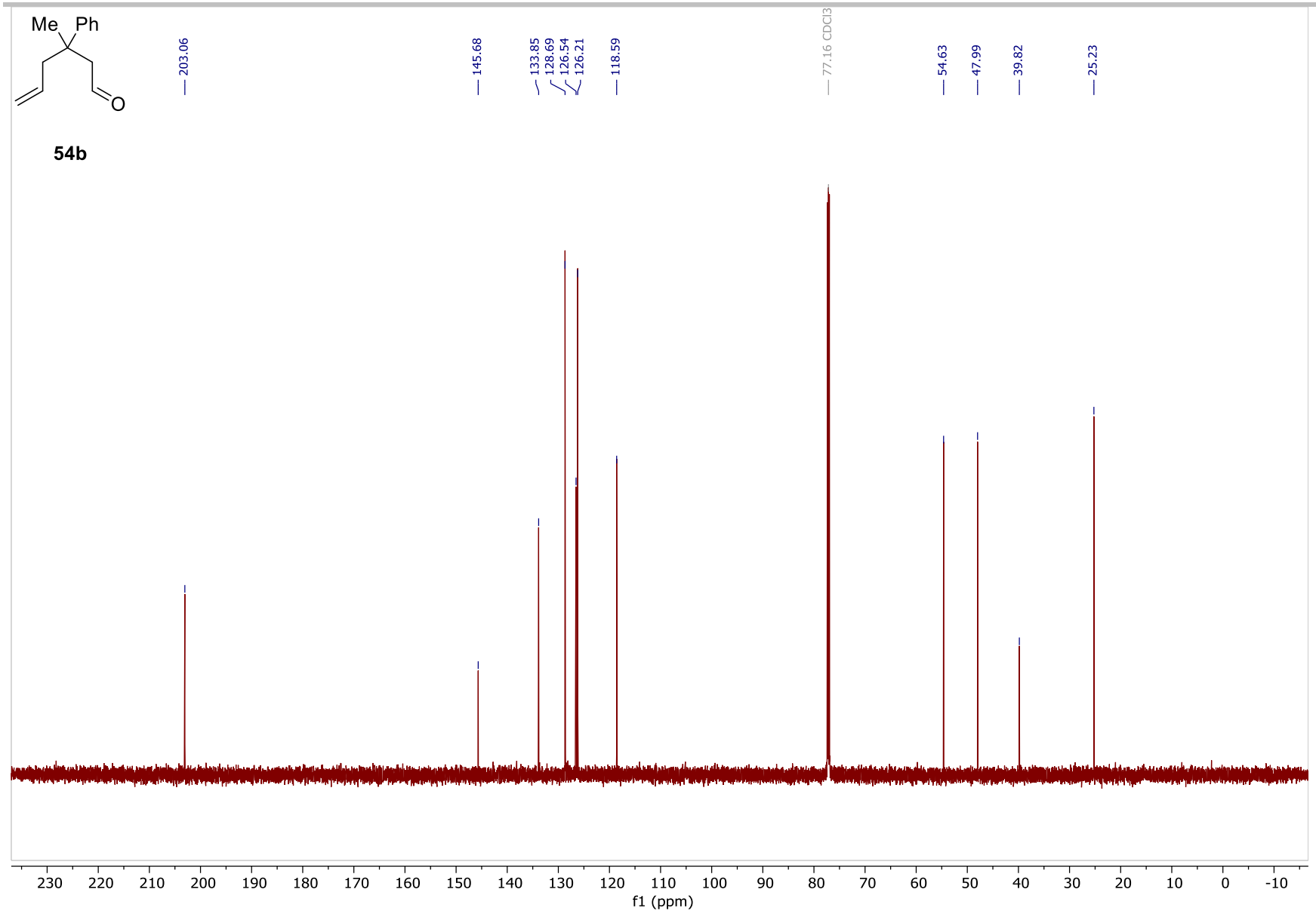

Figure S125. ^{13}C NMR (175 MHz, $CDCl_3$) of **54b**.

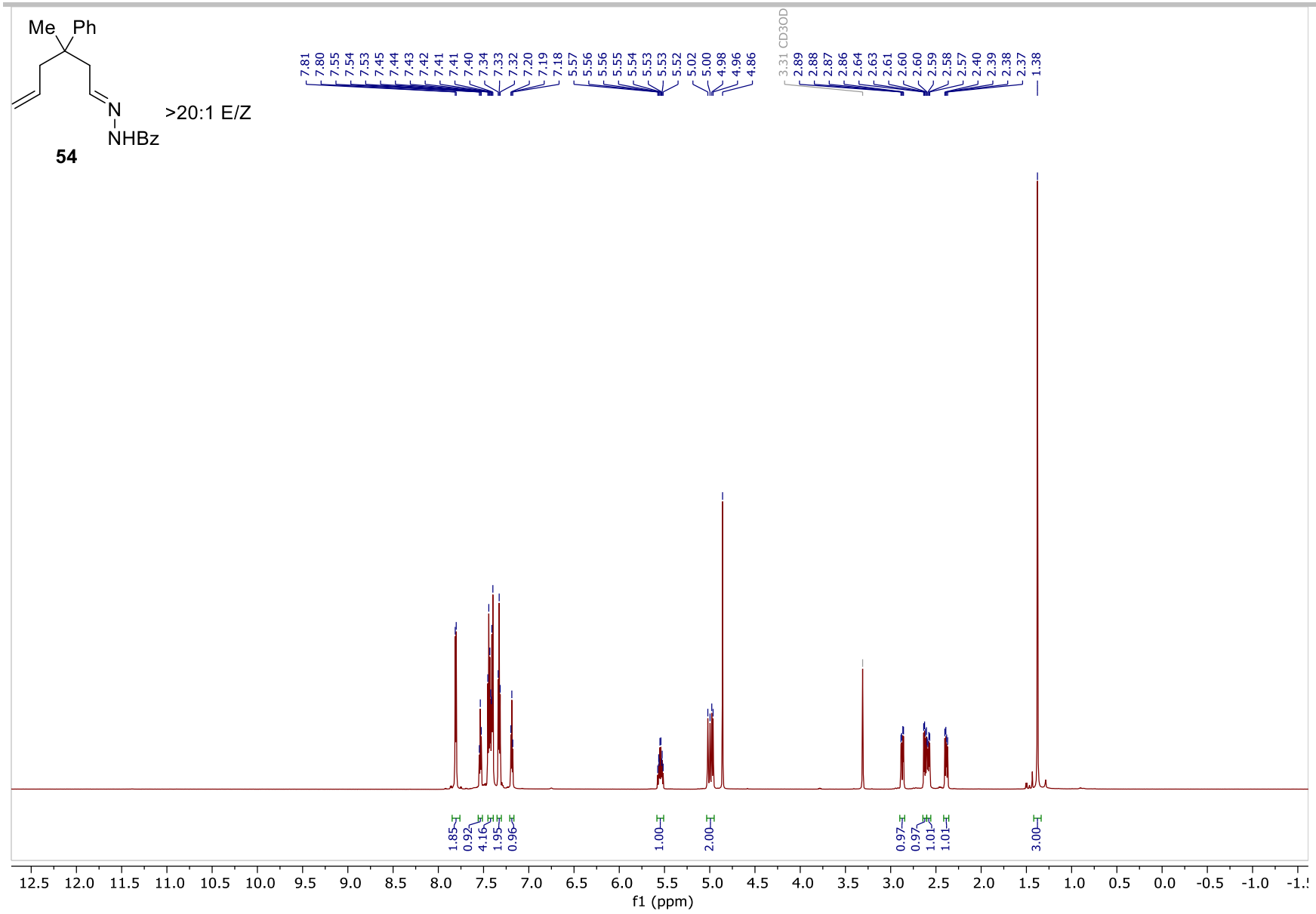

Figure S126. ^{1}H NMR (700 MHz, CD_3OD) of **54**.

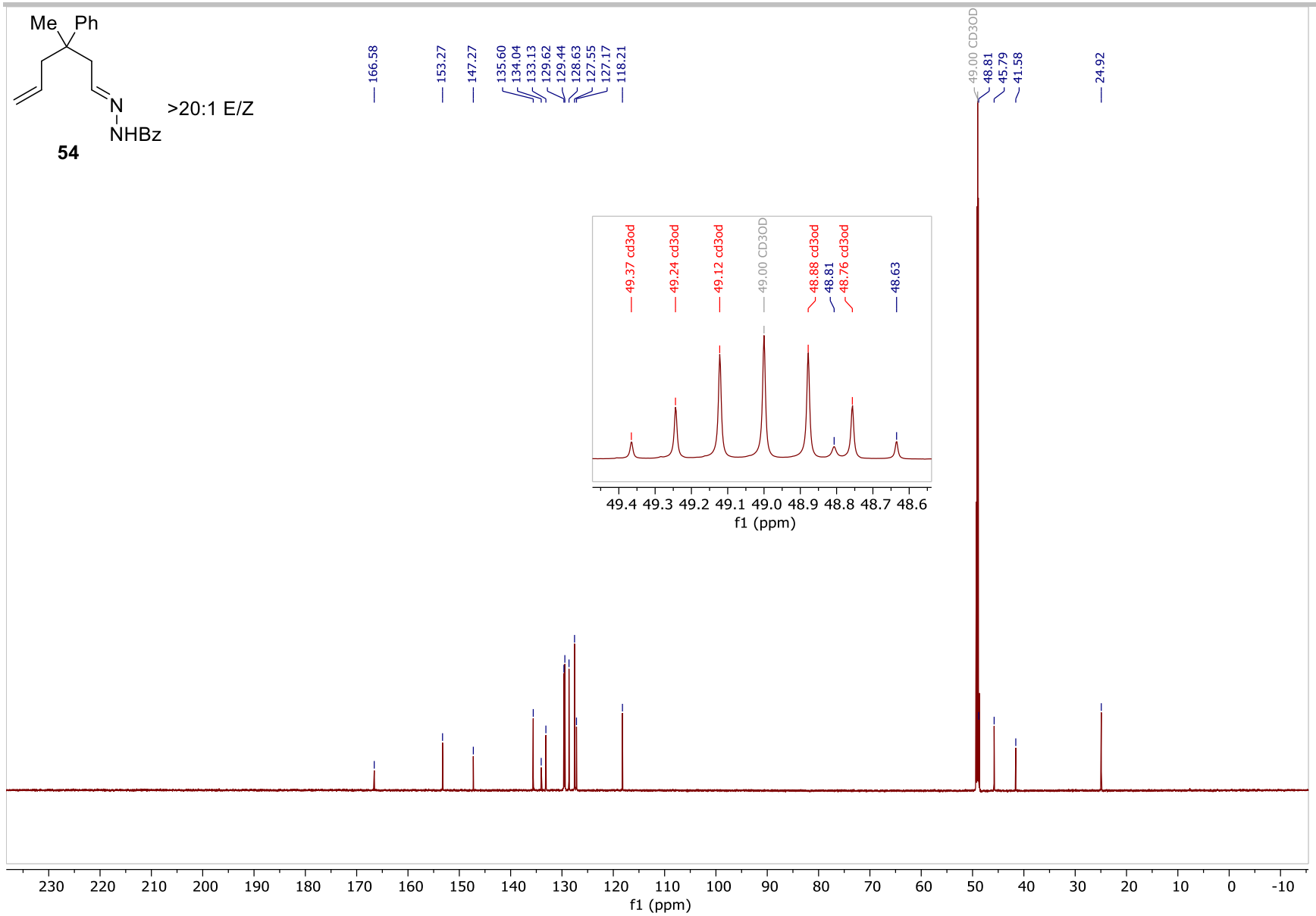

Figure S127. ^{13}C NMR (175 MHz, CD_3OD) of **54**.

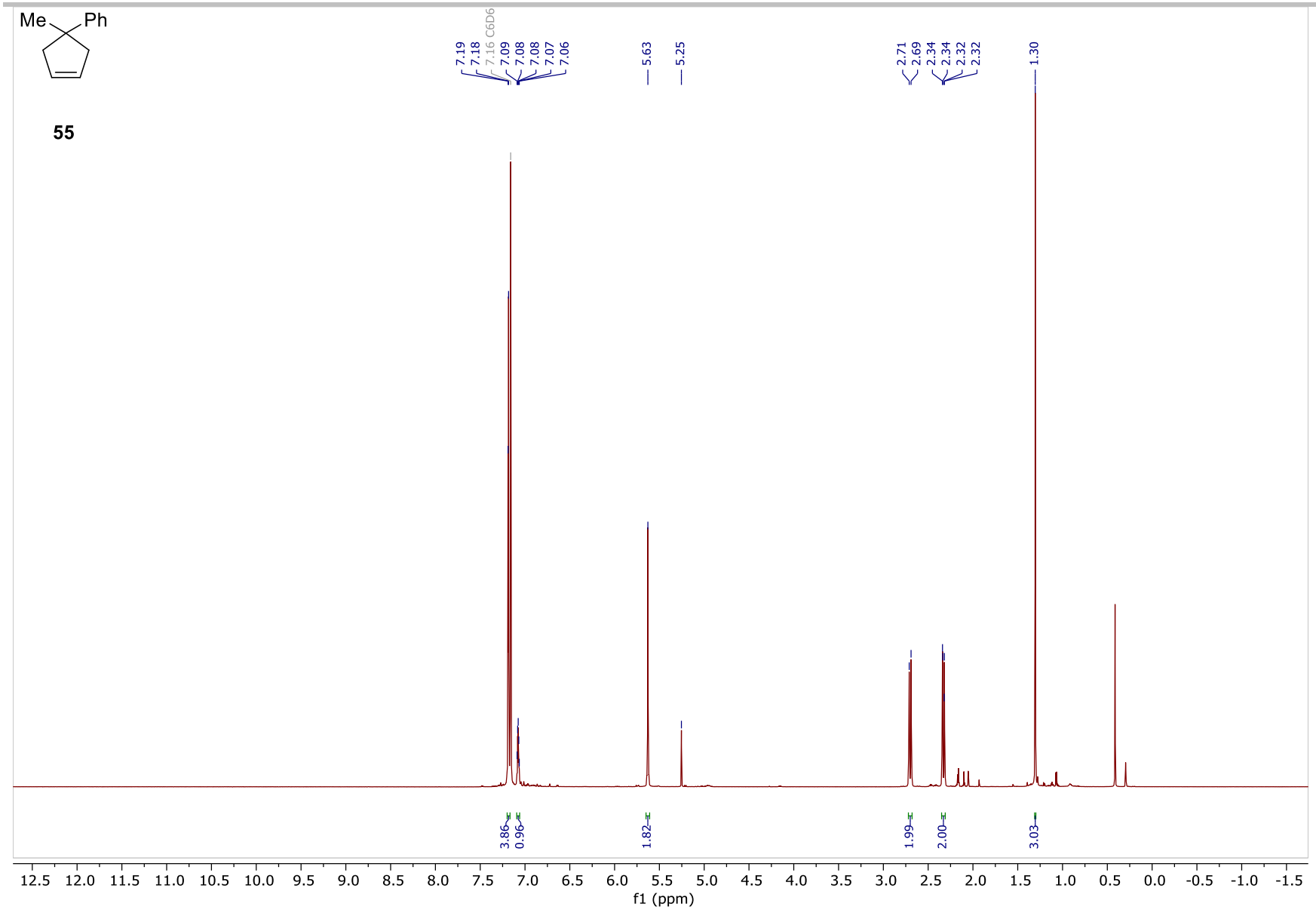

Figure S128. ^{1}H NMR (700 MHz, C_6D_6) of **55**.

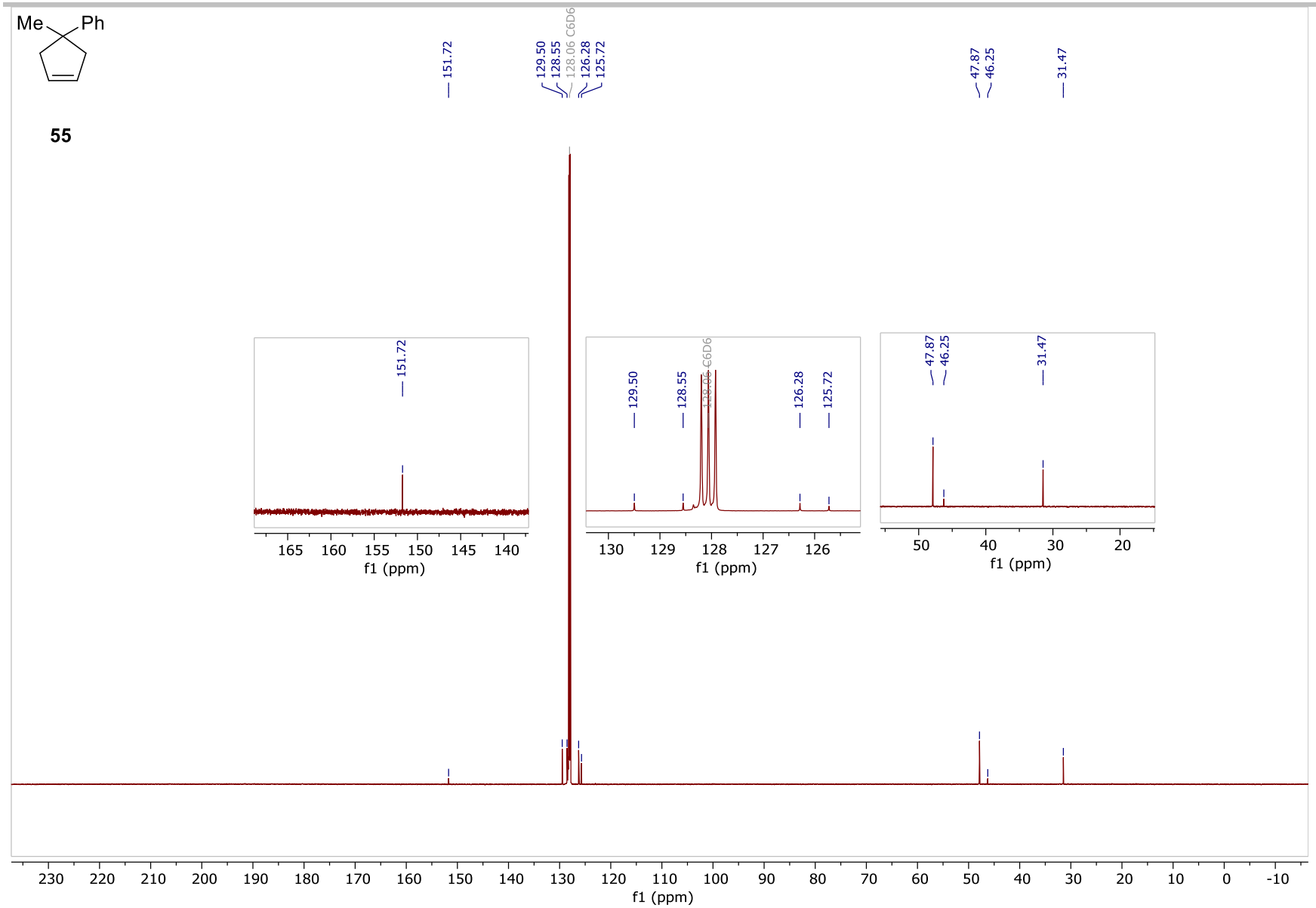

Figure S129. ^{13}C NMR (175 MHz, C_6D_6) of **55.**

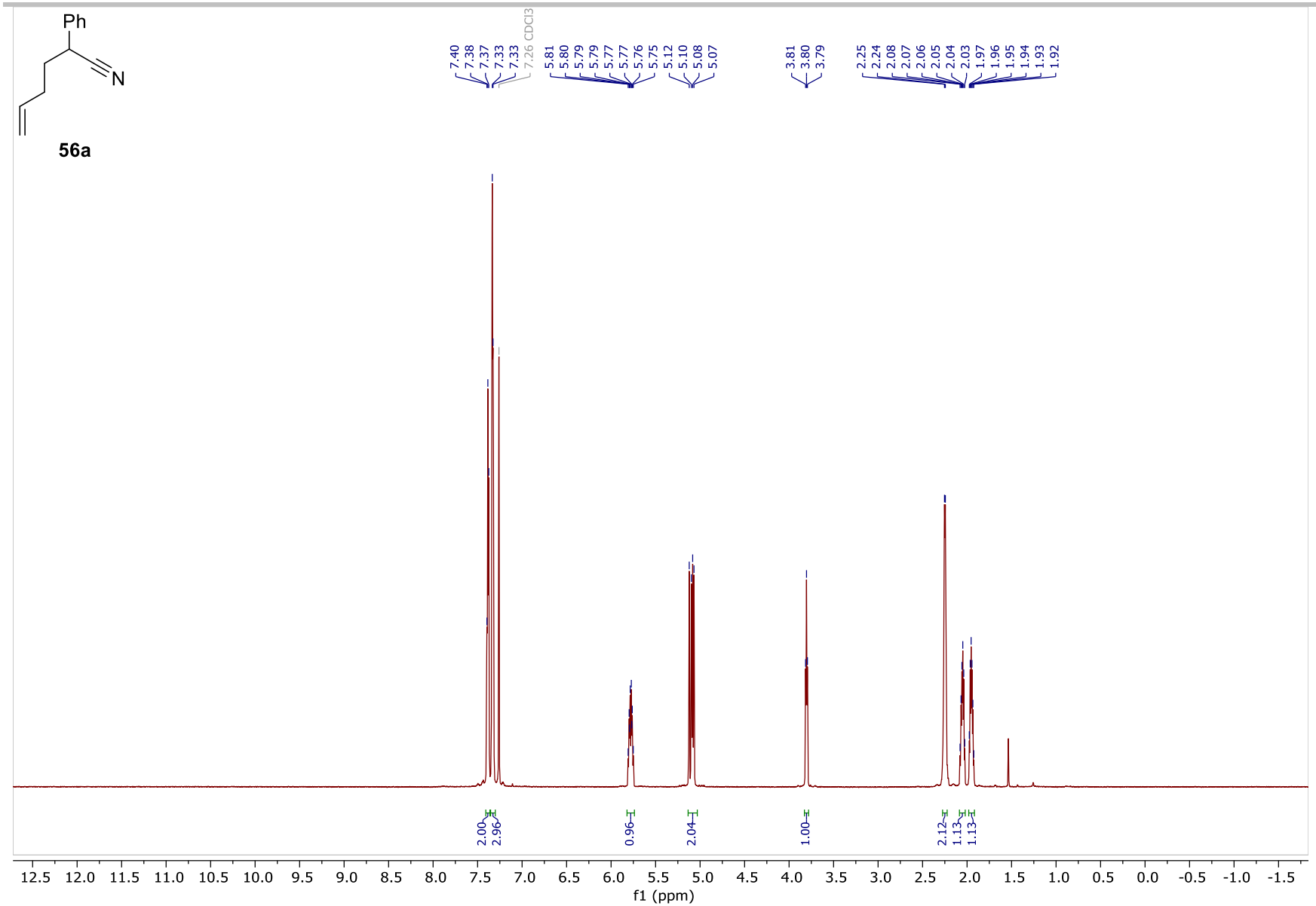

Figure S130. ^{1}H NMR (700 MHz, $CDCl_3$) of **56a**.

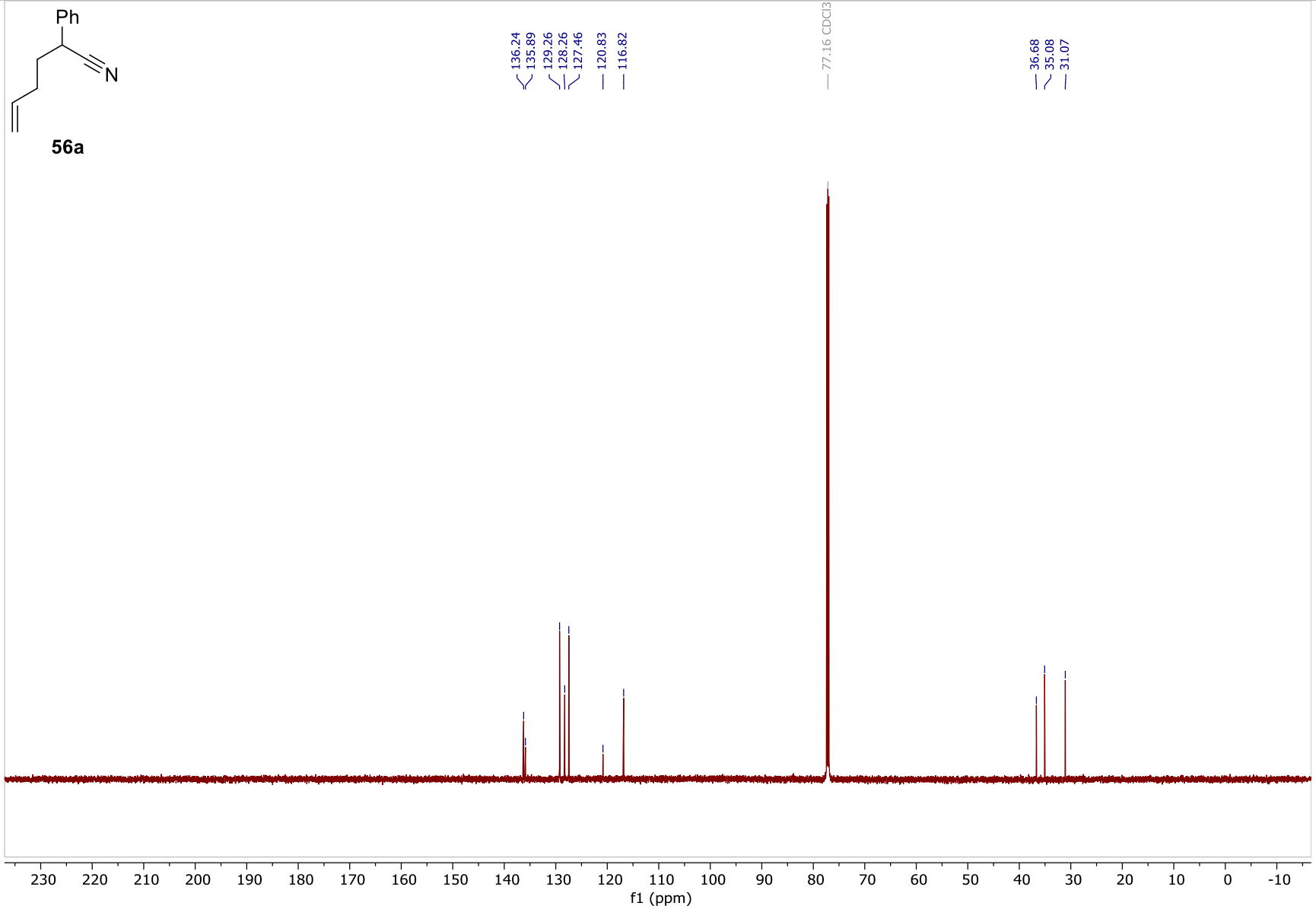

Figure S131. ^{13}C NMR (175 MHz, $CDCl_3$) of **56a**.

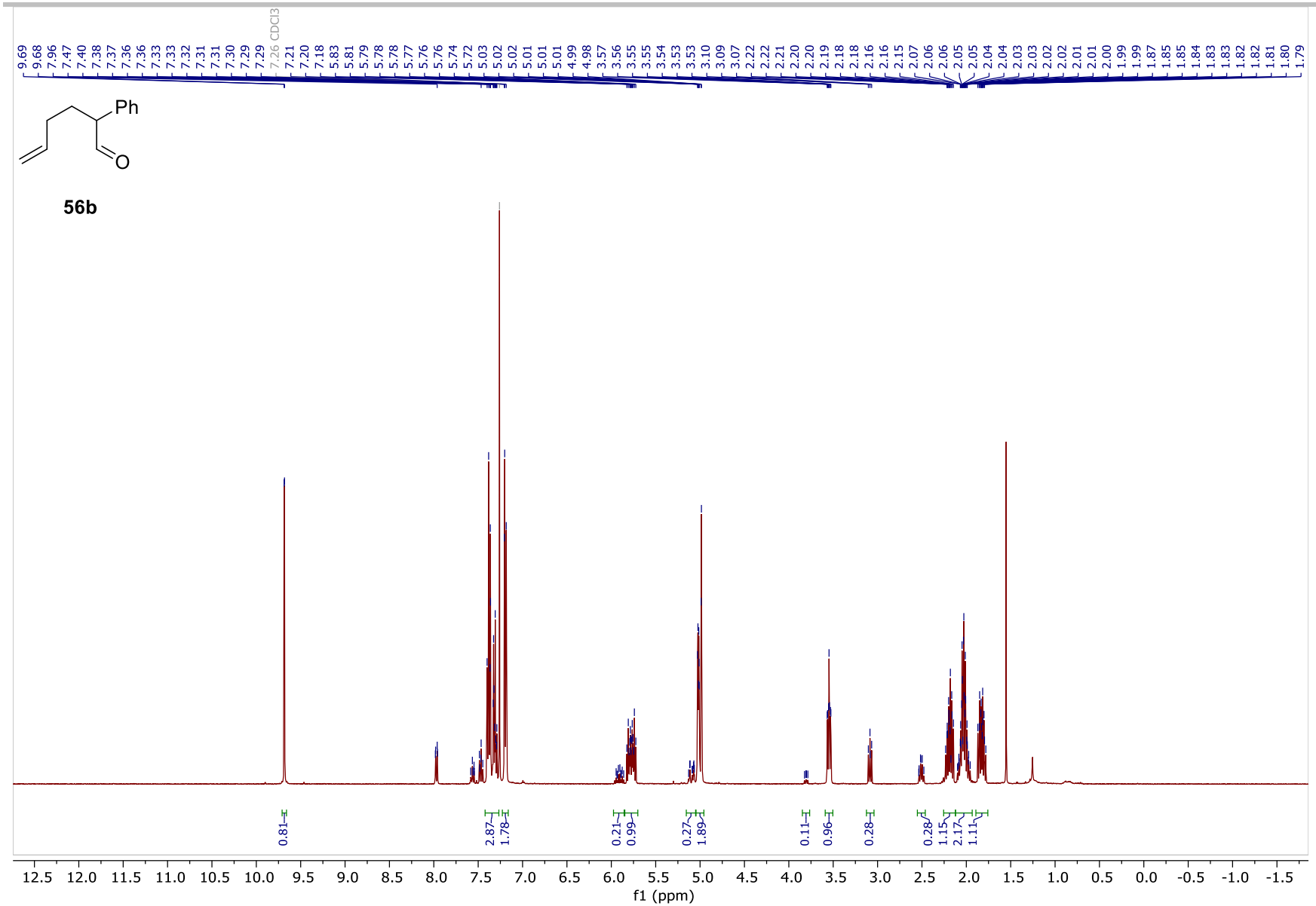

Figure S132. ^{1}H NMR (400 MHz, $CDCl_3$) of **56b**.

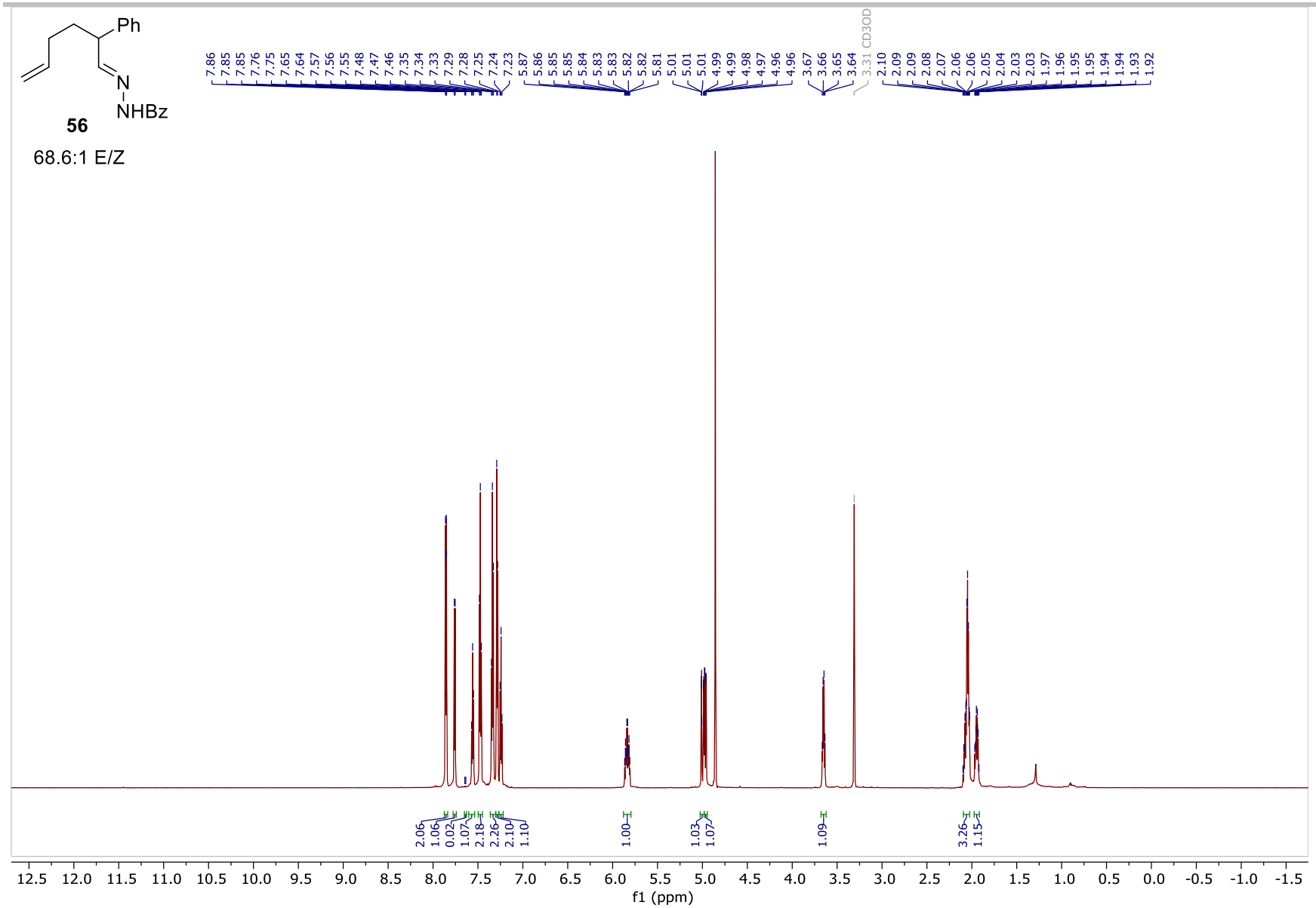

Figure S133. ^{1}H NMR (700 MHz, CD_3OD) of **56**.

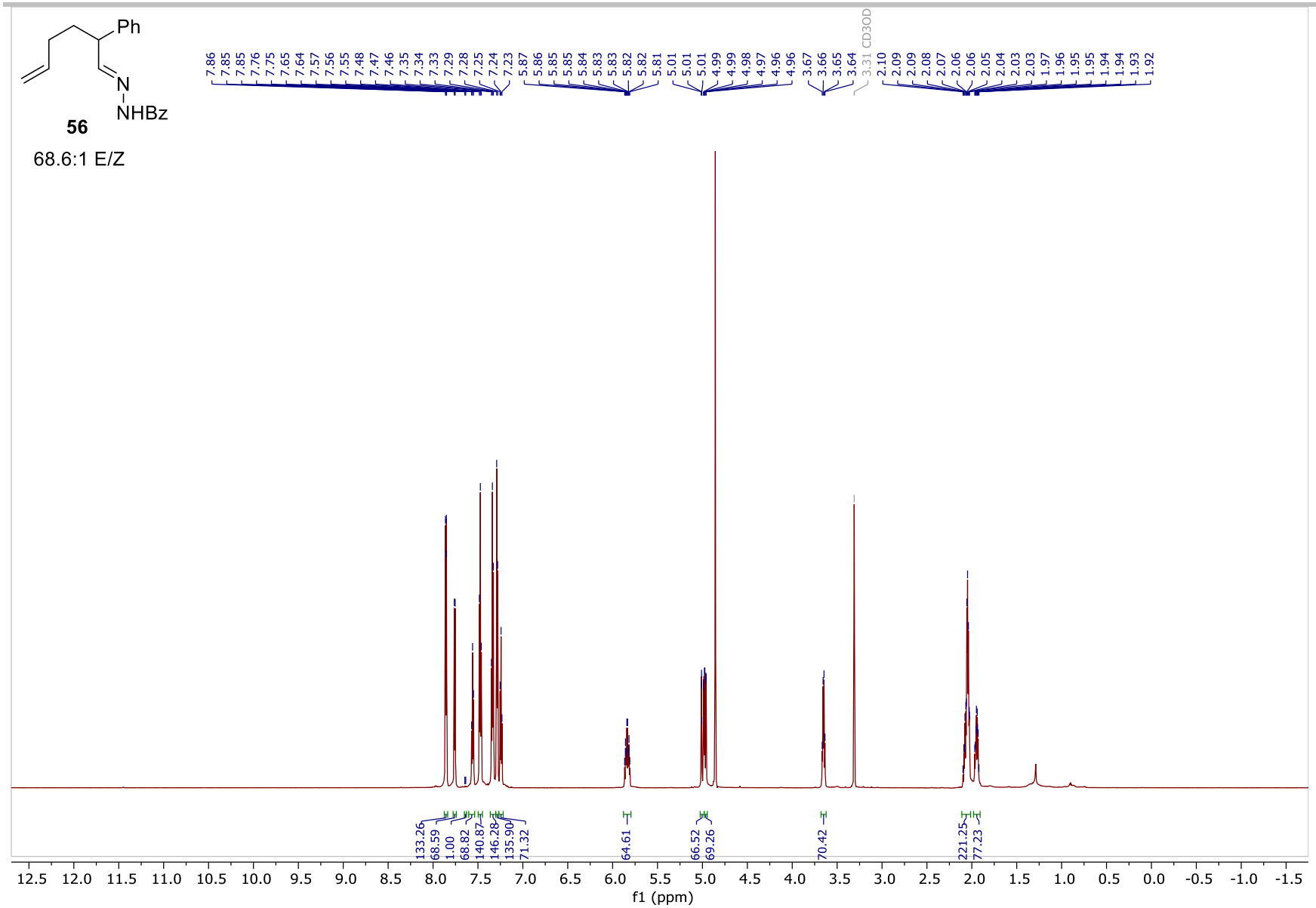

Figure S134. ^{1}H NMR (700 MHz, CD_3OD) of **56** showing 68.6 E:Z ratio of hydrazone isomers.

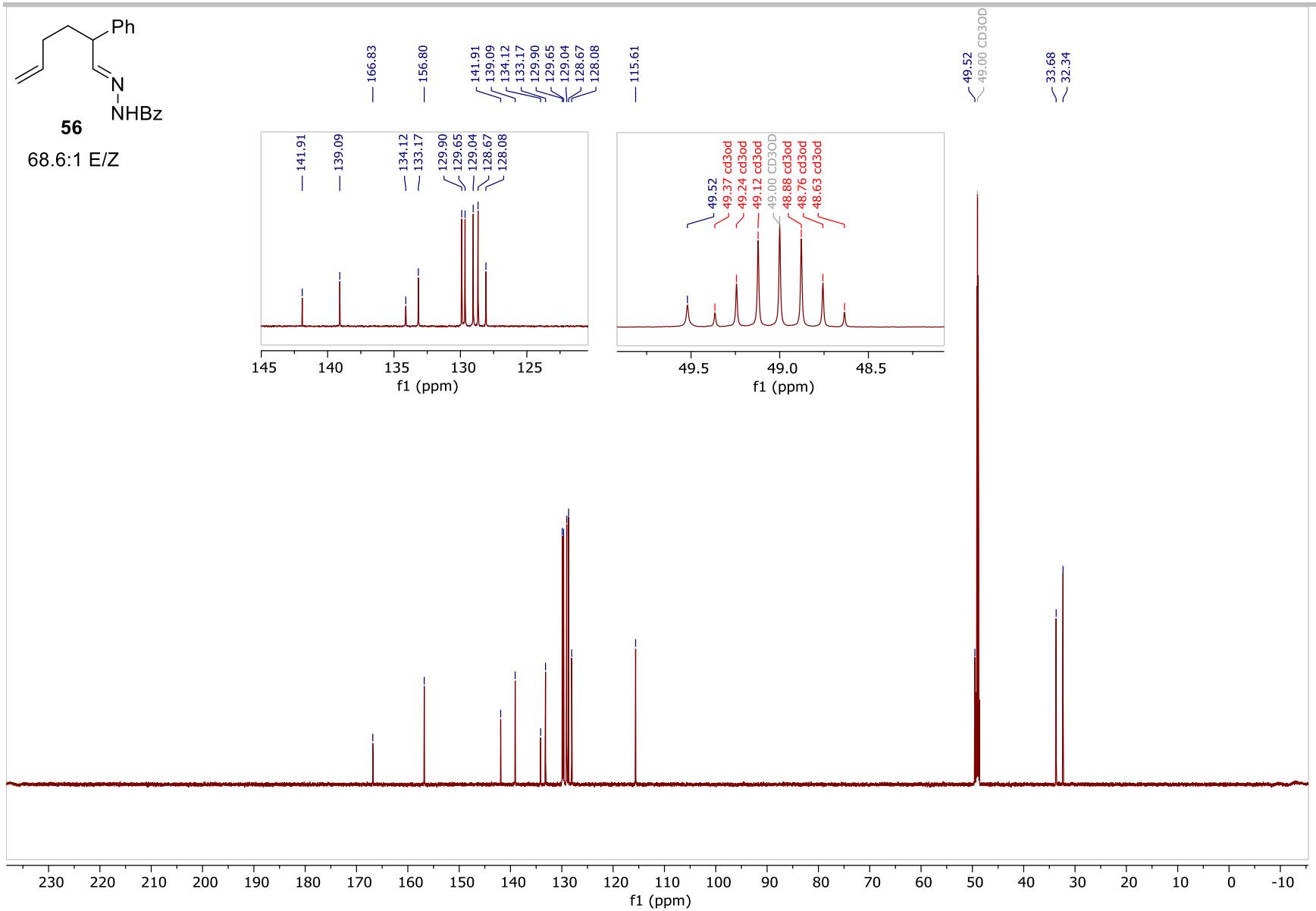

Figure S135. ^{13}C NMR (175 MHz, CD_3OD) of **56**.

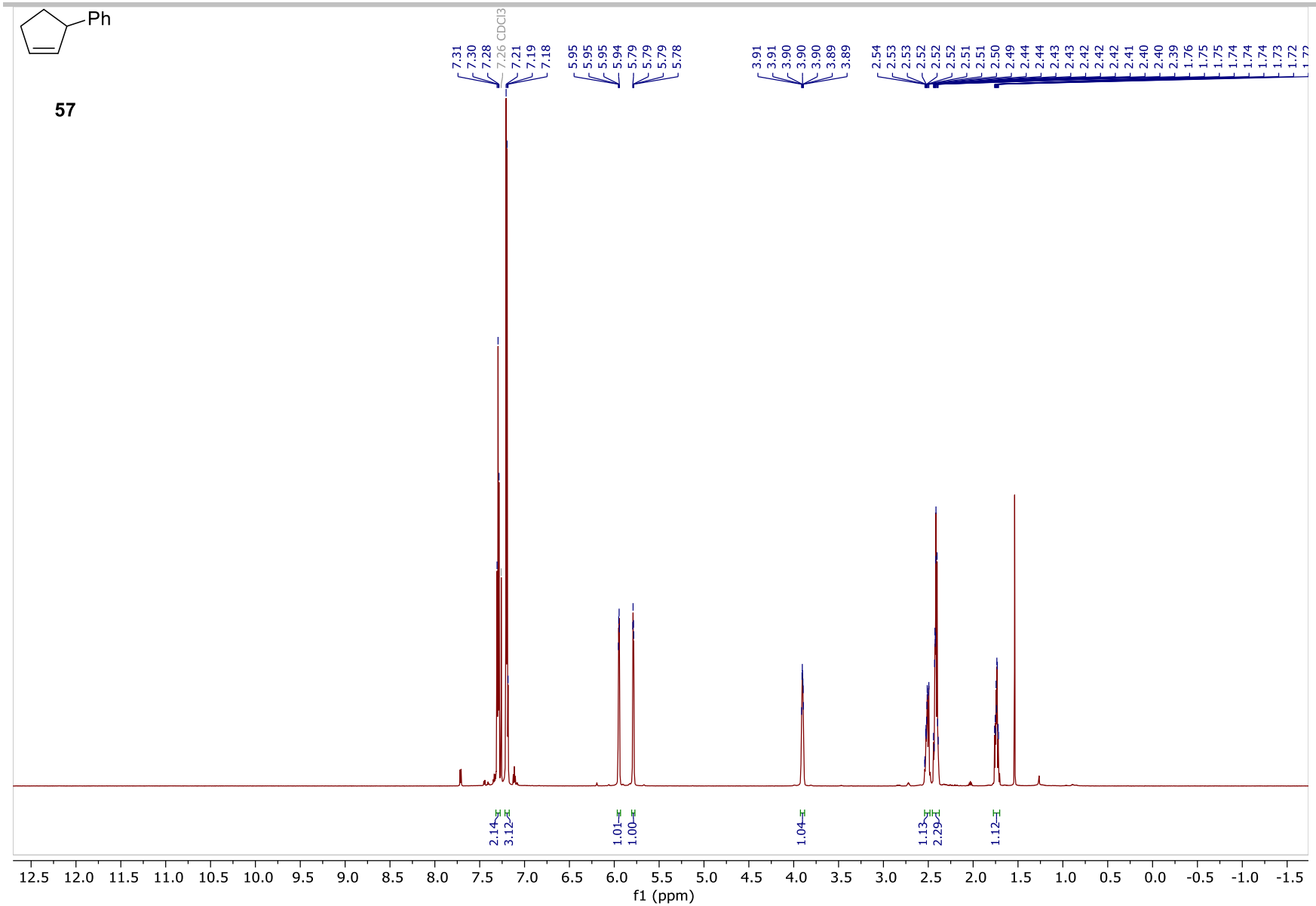

Figure S136. ^{1}H NMR (700 MHz, $CDCl_3$) of **57**.

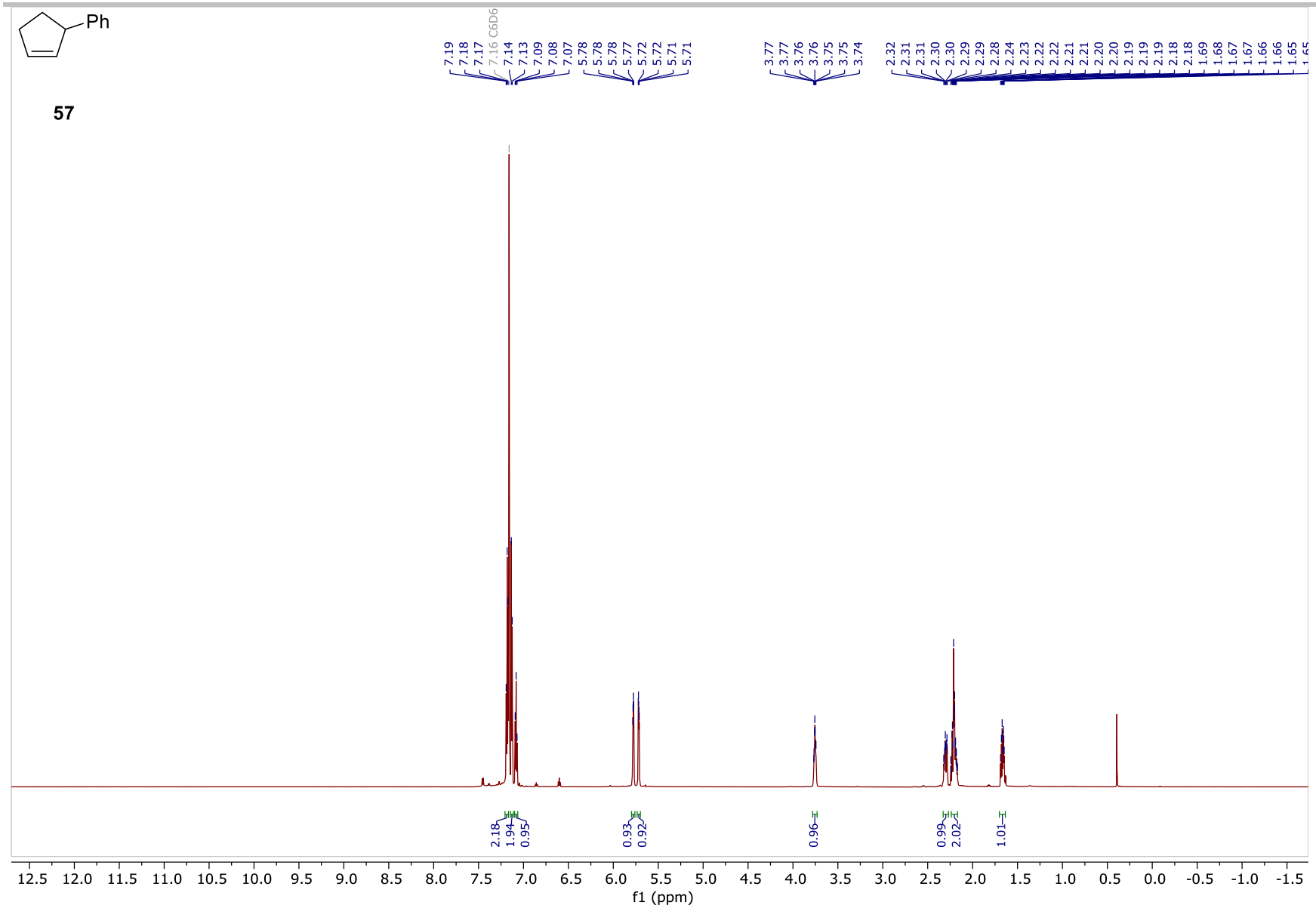

Figure S137. ^{1}H NMR (700 MHz, C_6D_6) of **57.**

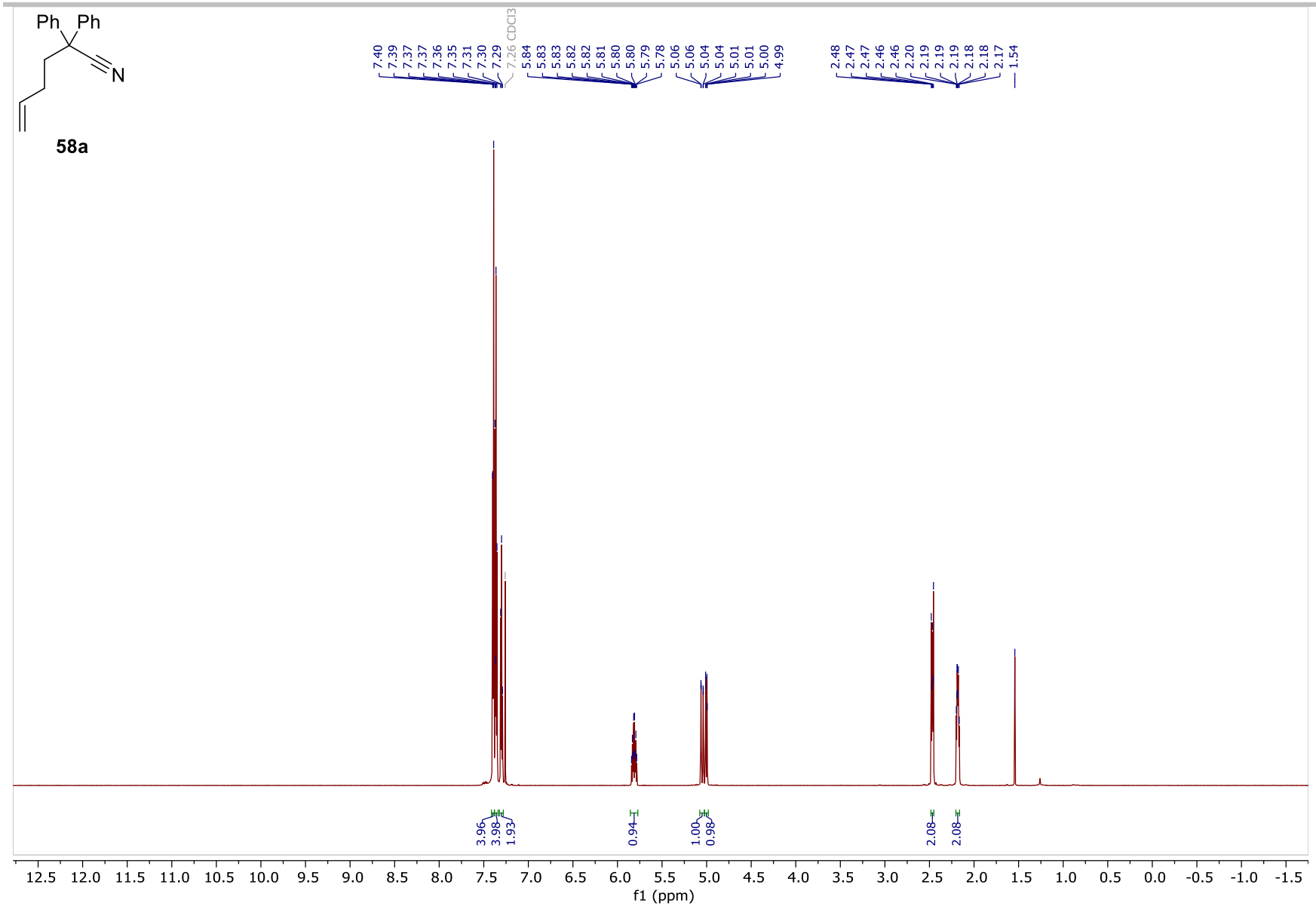

Figure S138. ^{1}H NMR (700 MHz, $CDCl_3$) of **58a**.

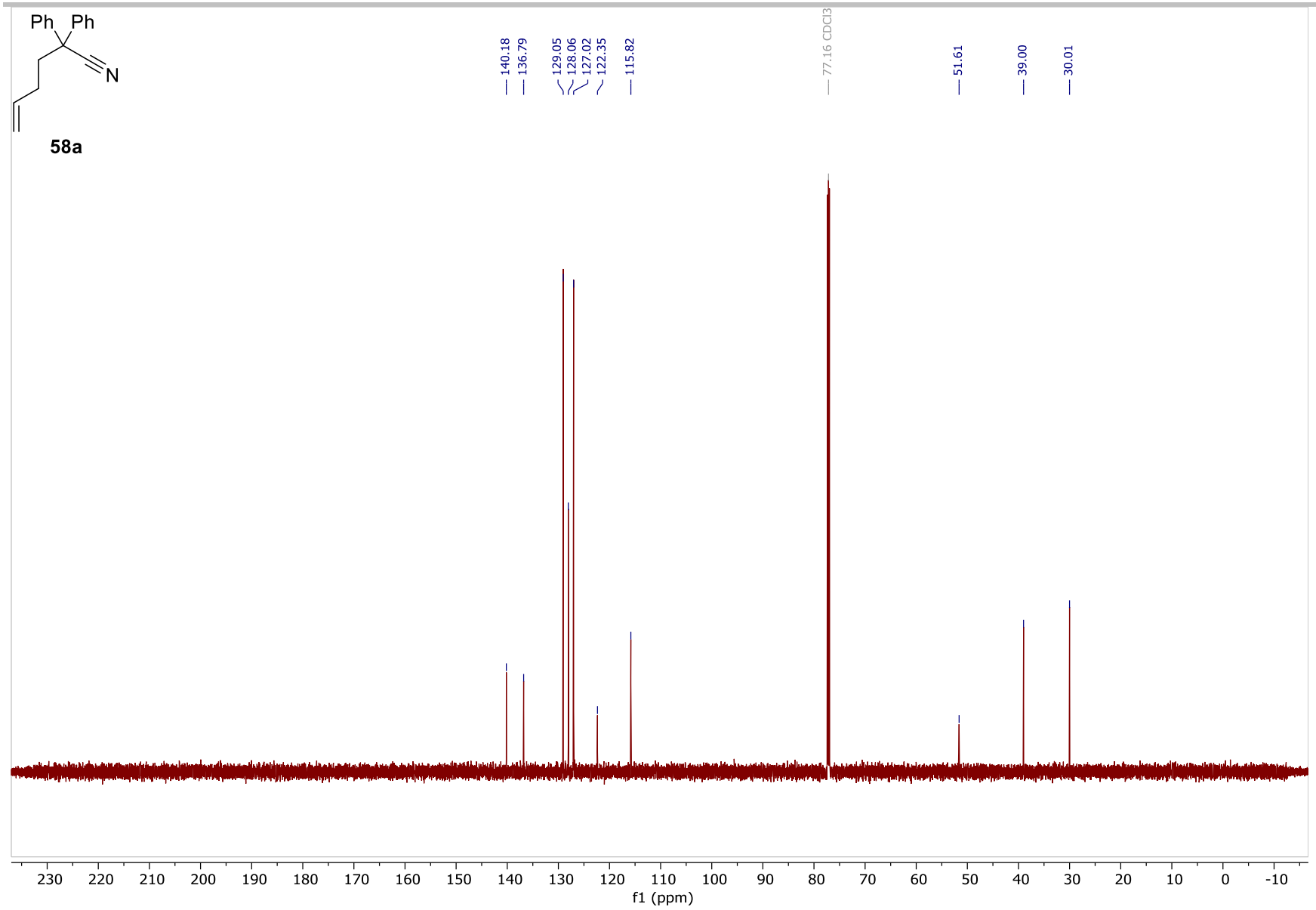

Figure S139. ^{13}C NMR (175 MHz, $CDCl_3$) of **58a**.

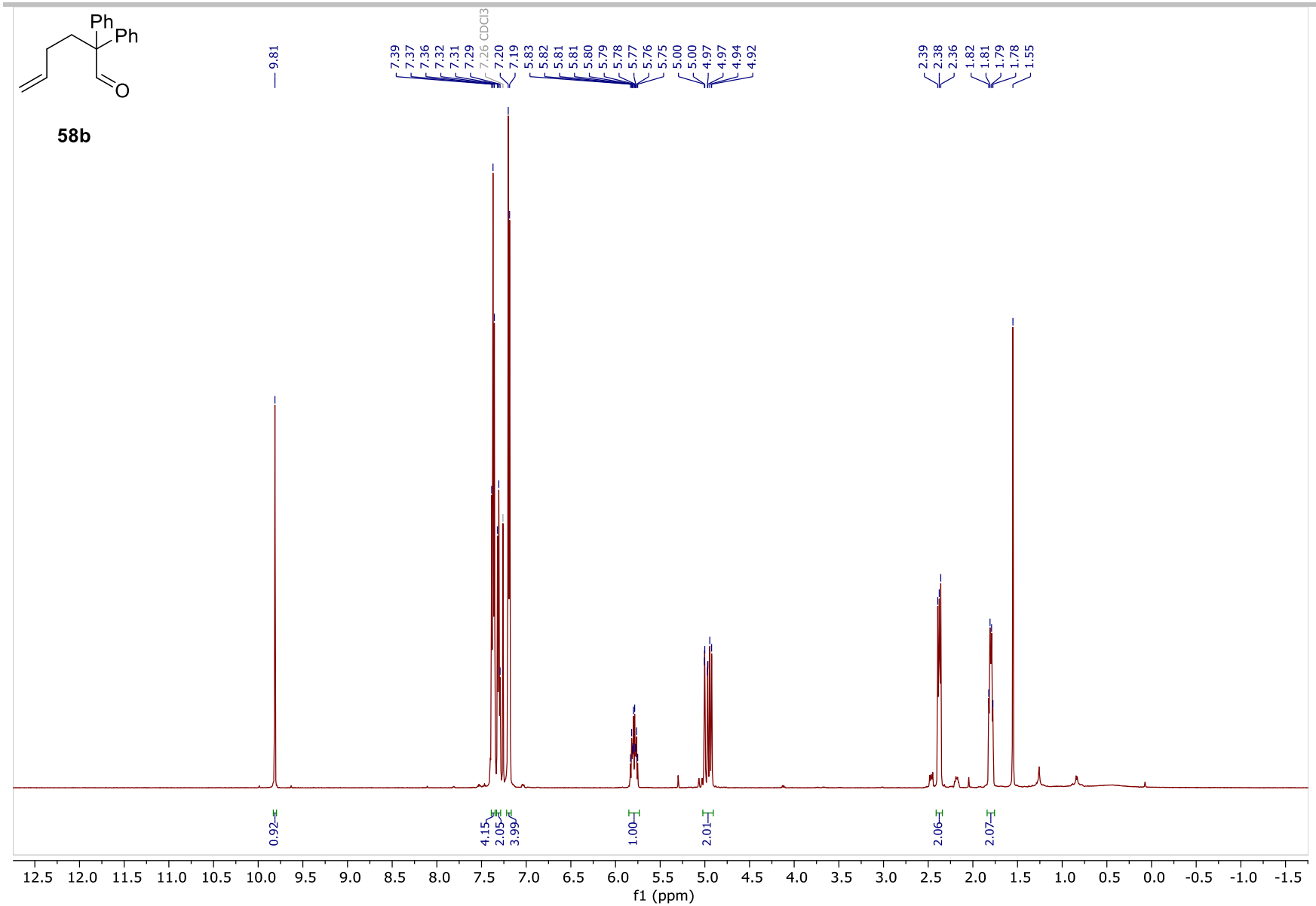

Figure S140. ^{1}H NMR (700 MHz, $CDCl_3$) of **58b**.

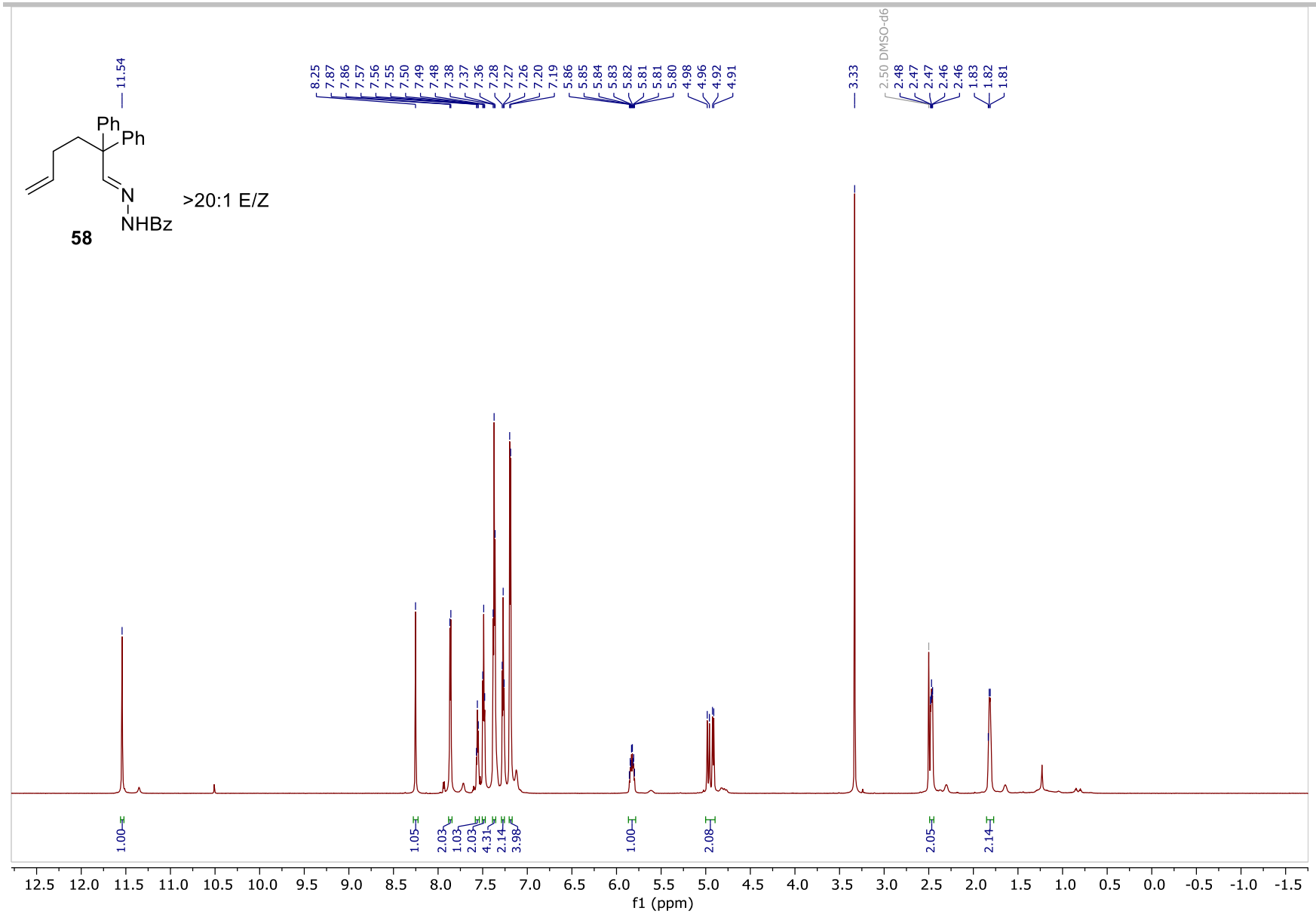

Figure S141. ^{1}H NMR (700 MHz, DMSO-d_6) of **58**.

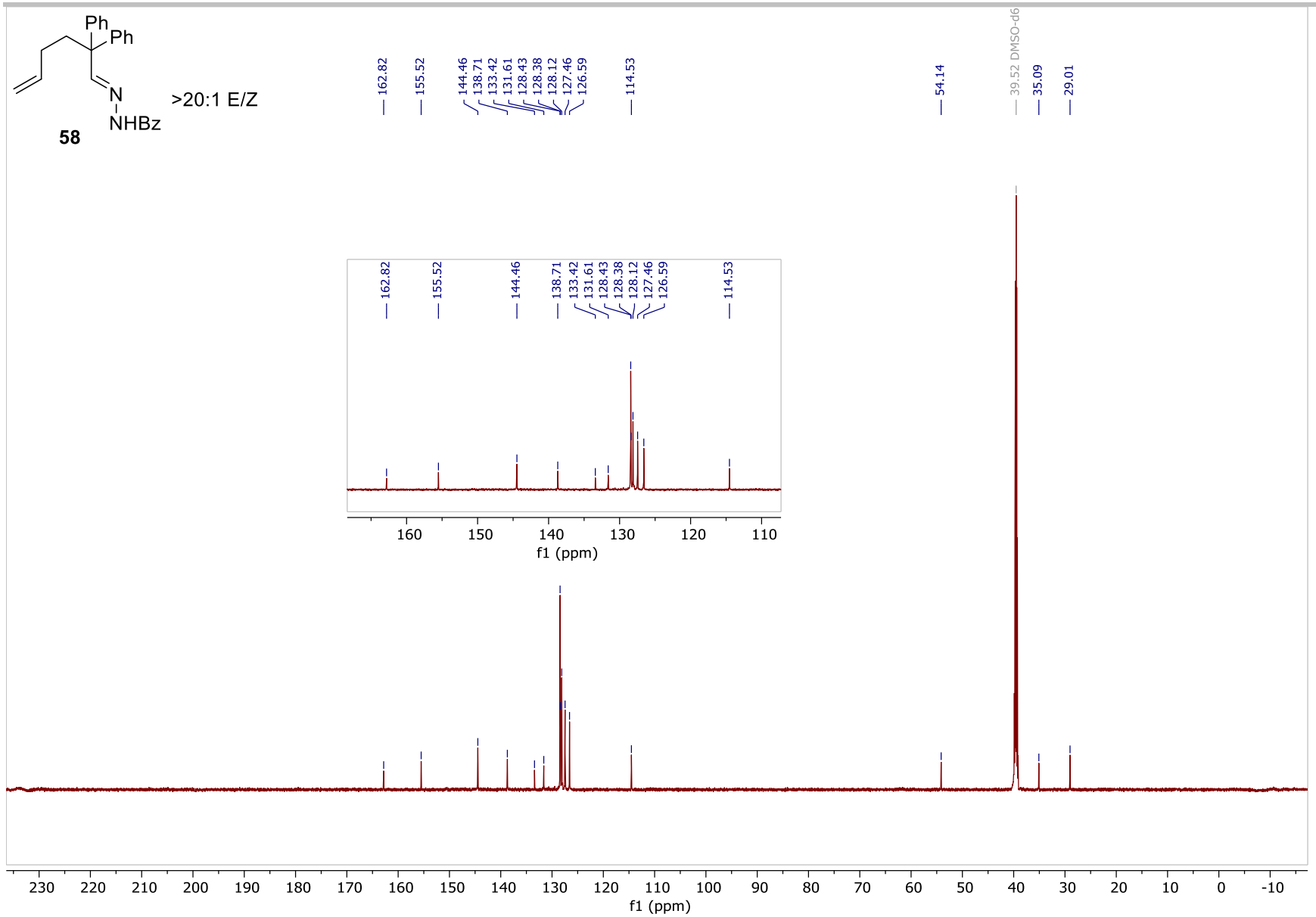

Figure S142. ^{13}C NMR (175 MHz, DMSO-d_6) of **58**.

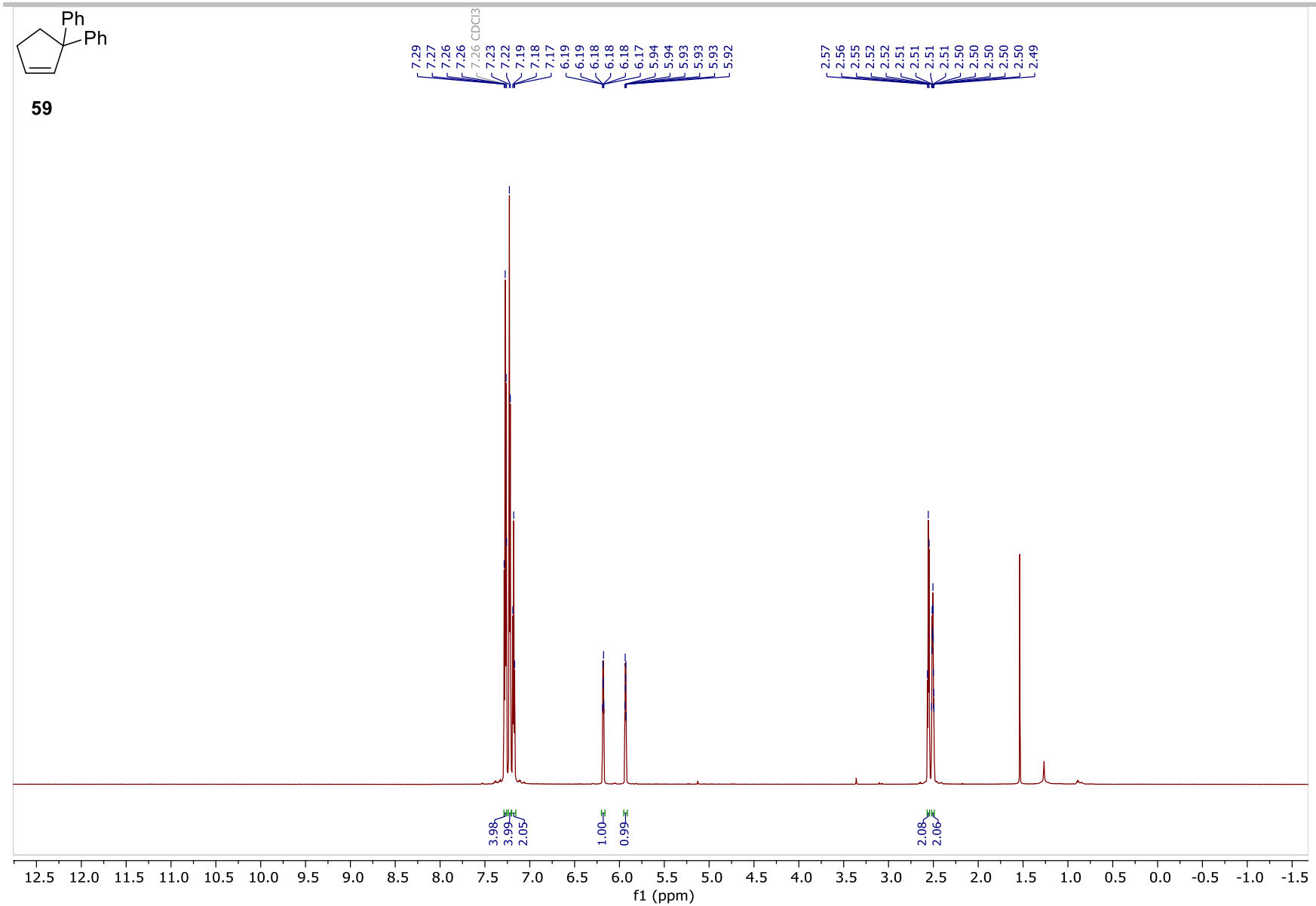

Figure S143. ^{1}H NMR (700 MHz, $CDCl_3$) of **59**.

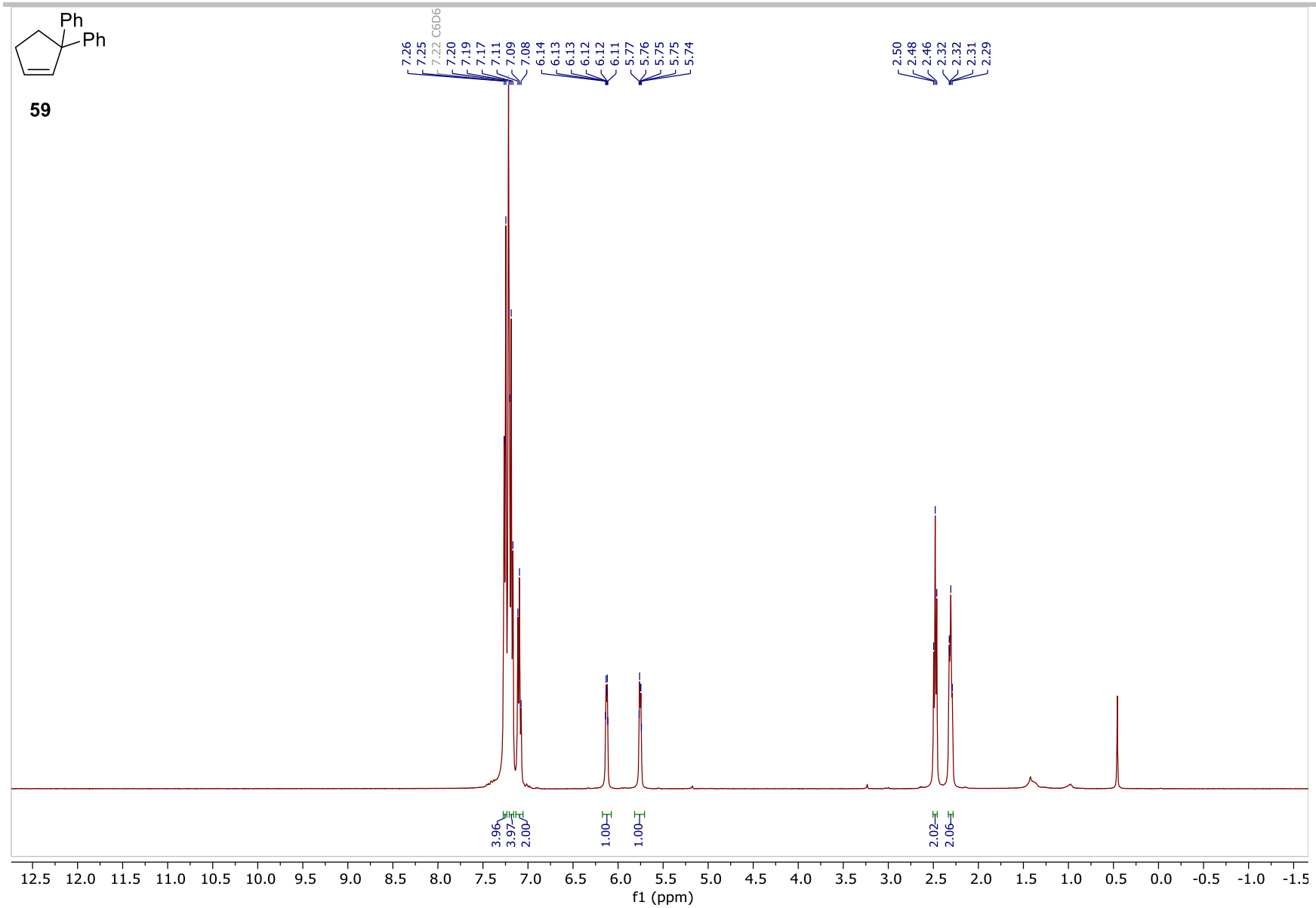

Figure S144. ^{1}H NMR (400 MHz, C_6D_6) of **59.**

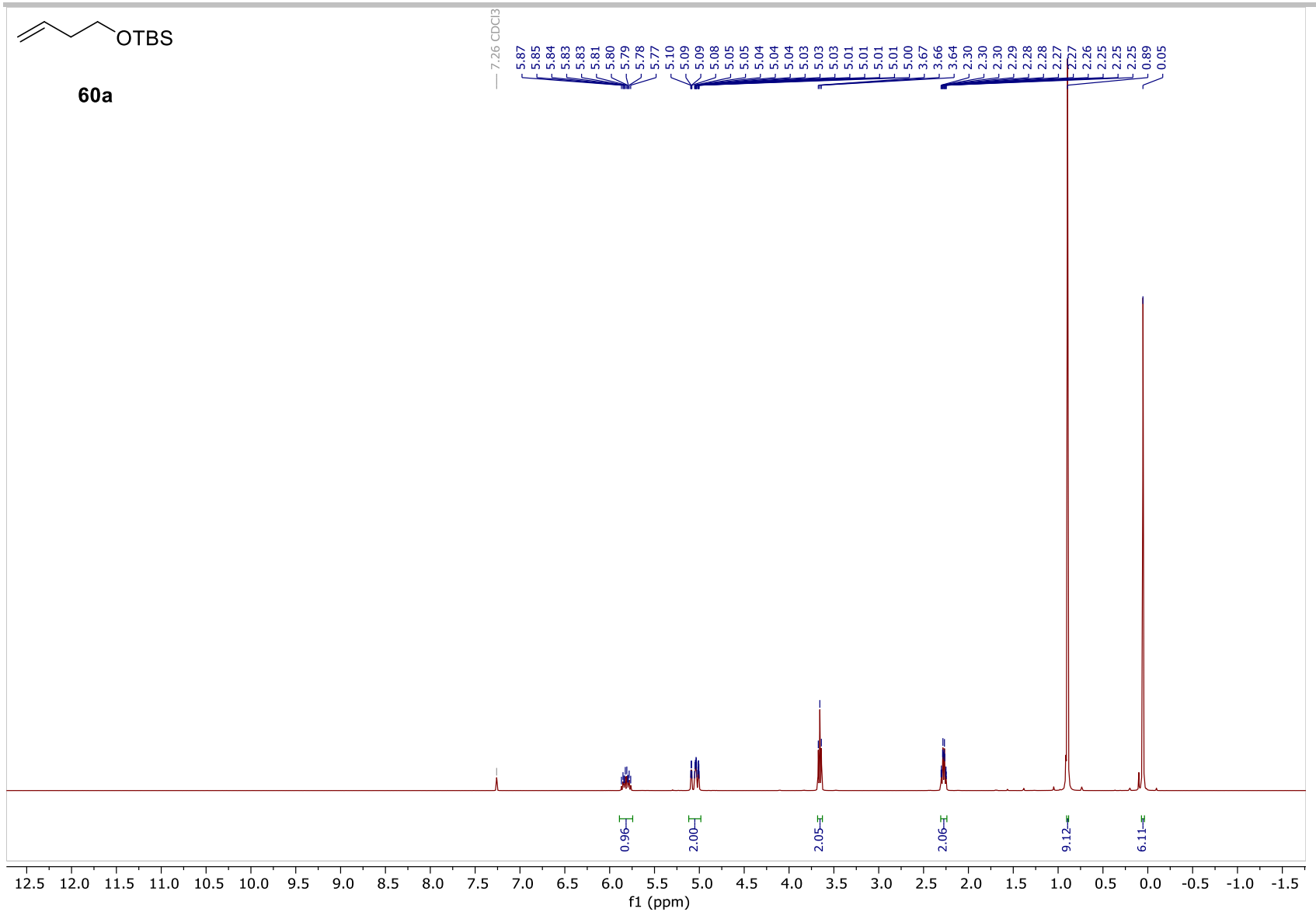

Figure S145. ^{1}H NMR (400 MHz, $CDCl_3$) of **60a**.

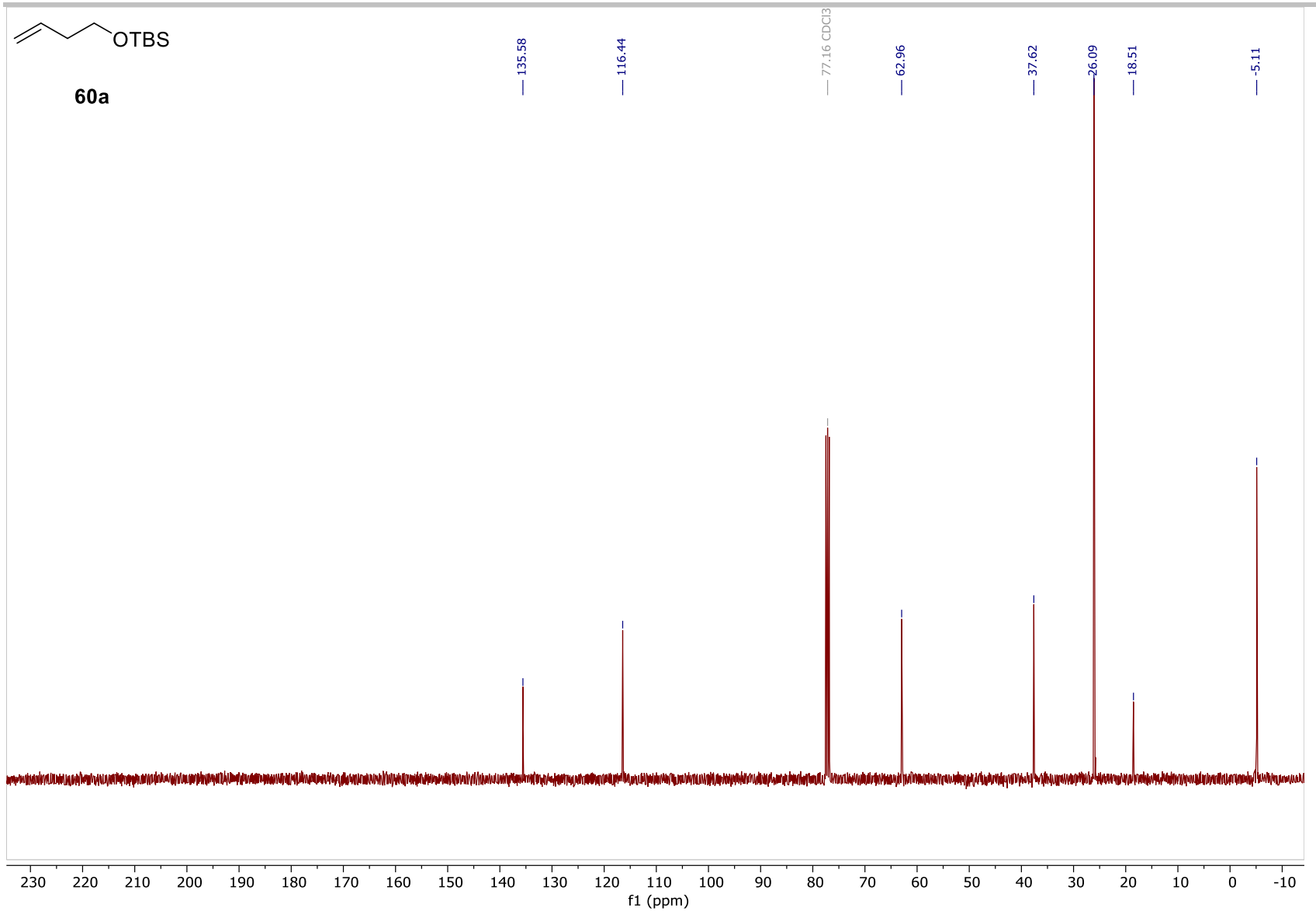

Figure S146. ^{13}C NMR (100 MHz, $CDCl_3$) of **60a**.

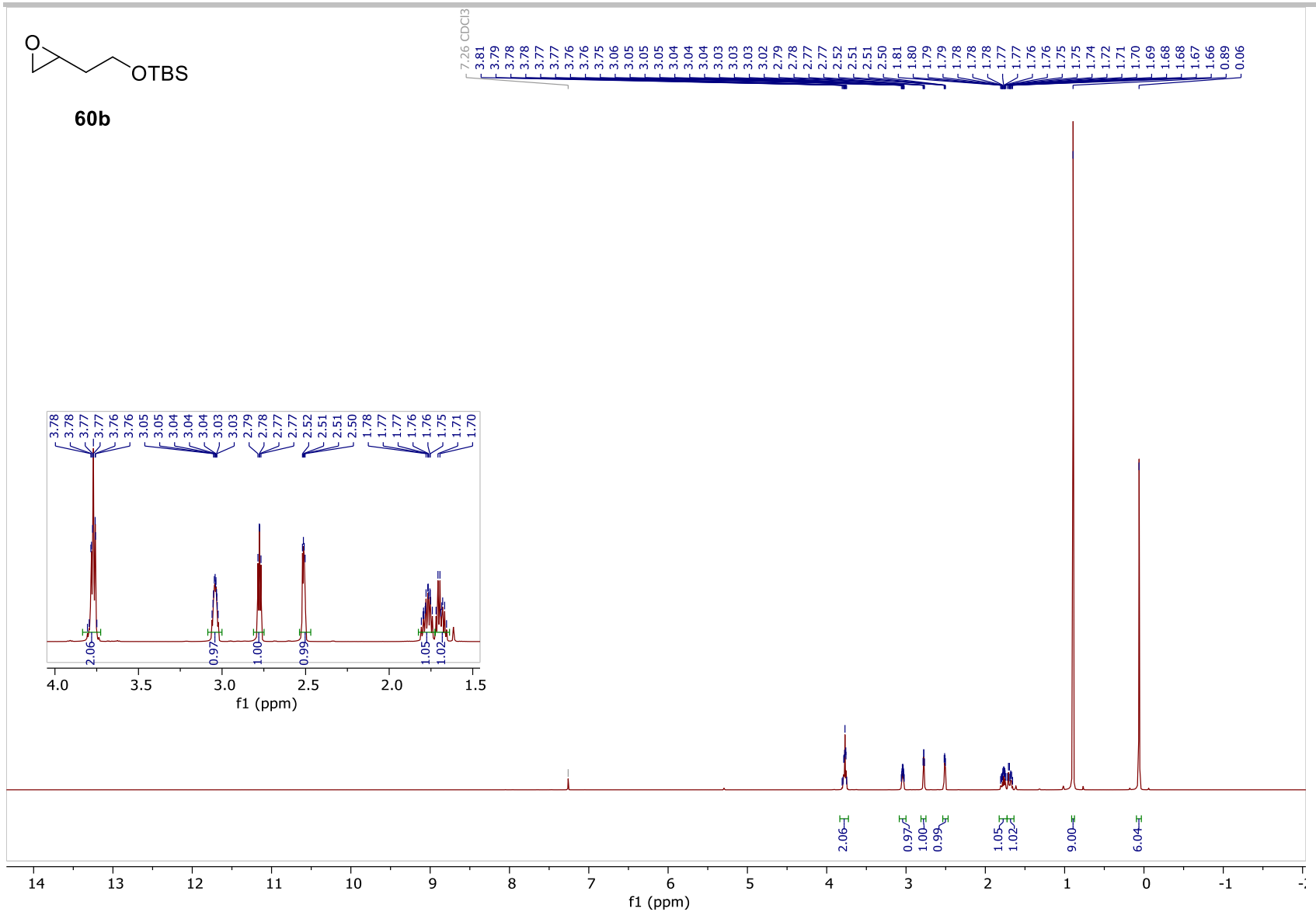

Figure S147. ^{1}H NMR (500 MHz, $CDCl_3$) of **60b**.

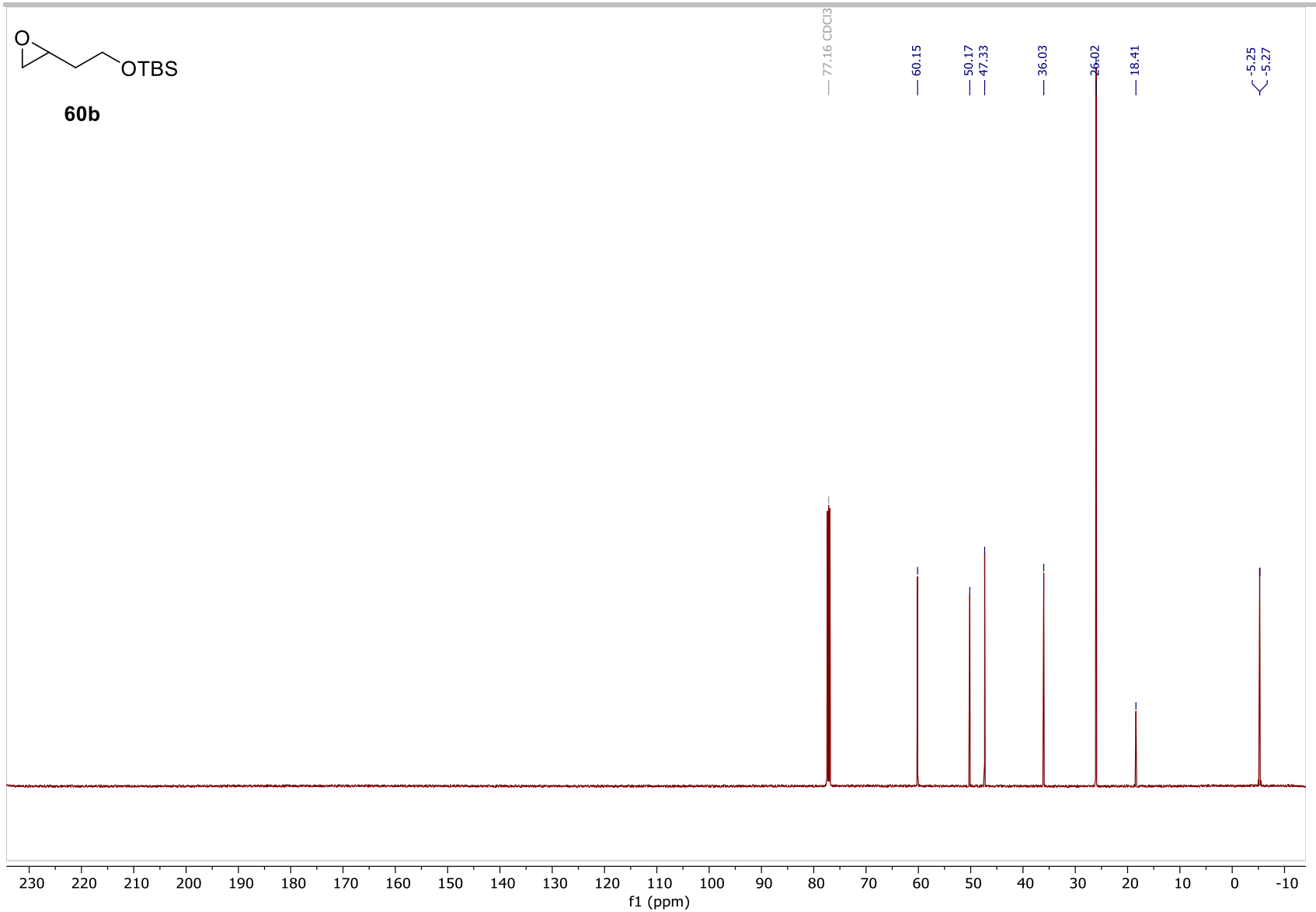

Figure S148. ^{13}C NMR (125 MHz, $CDCl_3$) of **60b**.

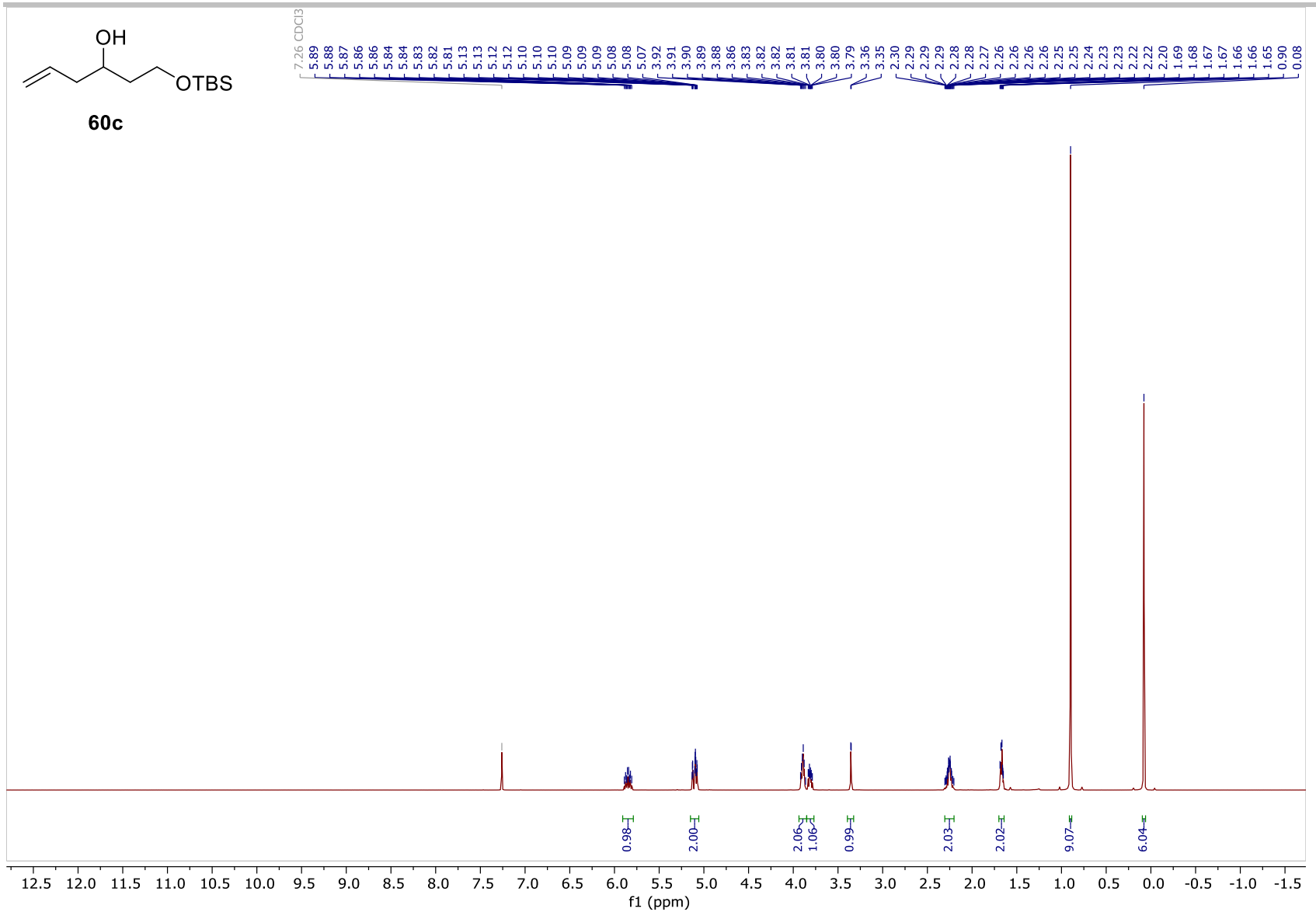

Figure S149. ^{1}H NMR (500 MHz, $CDCl_3$) of **60c**.

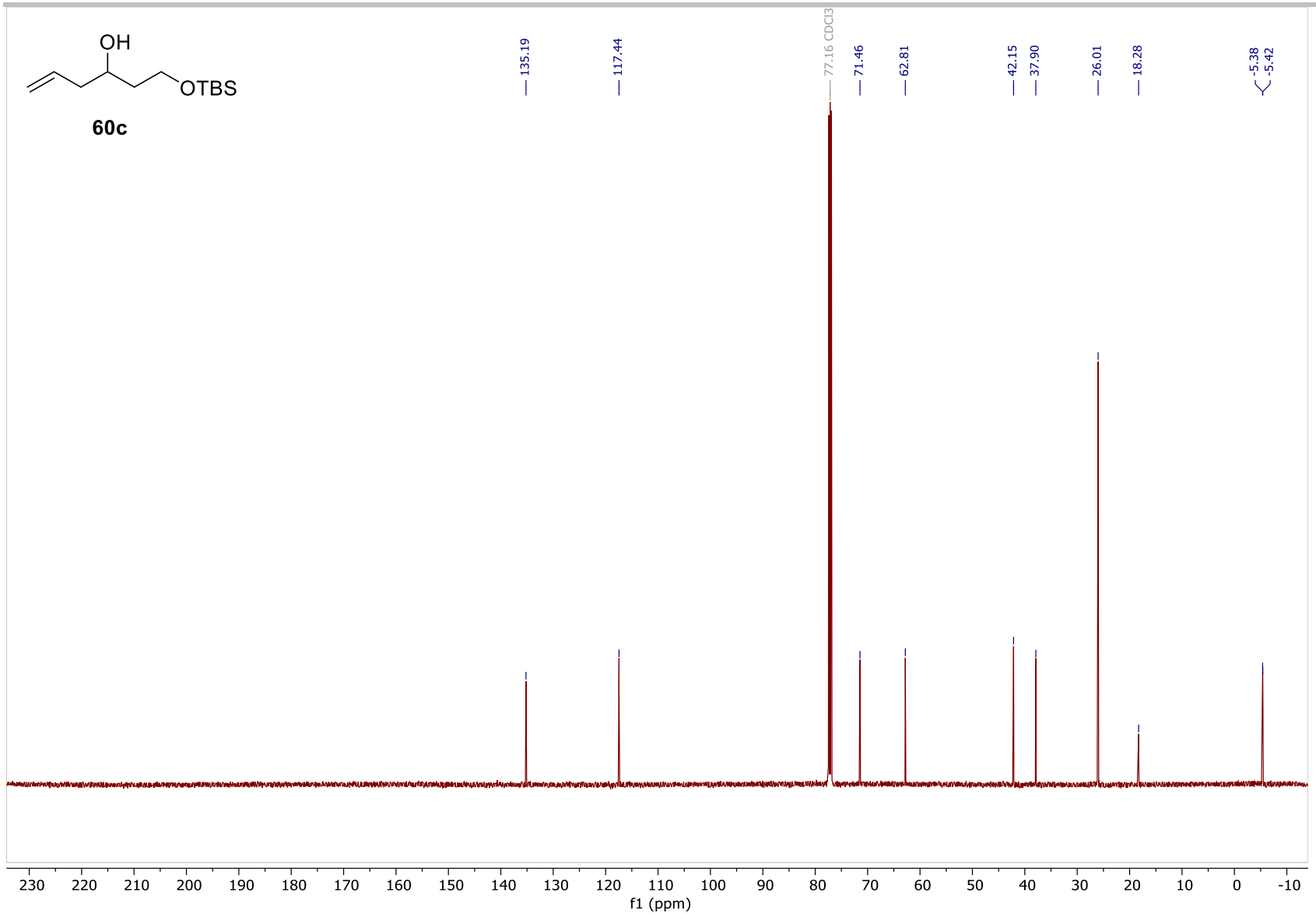

Figure S150. ^{13}C NMR (125 MHz, $CDCl_3$) of **60c**.

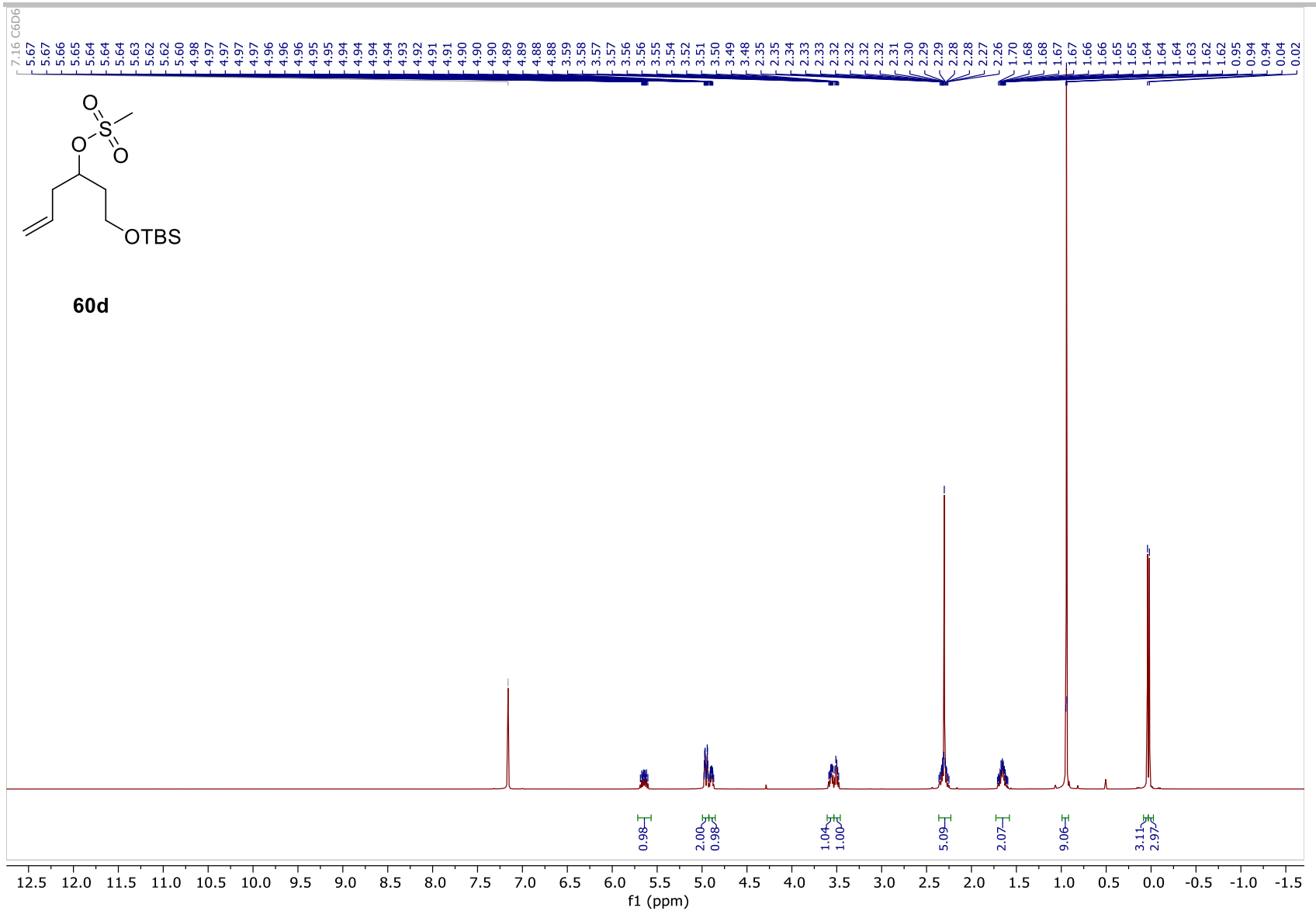

Figure S151. ^{1}H NMR (500 MHz, C_6D_6) of **60d**.

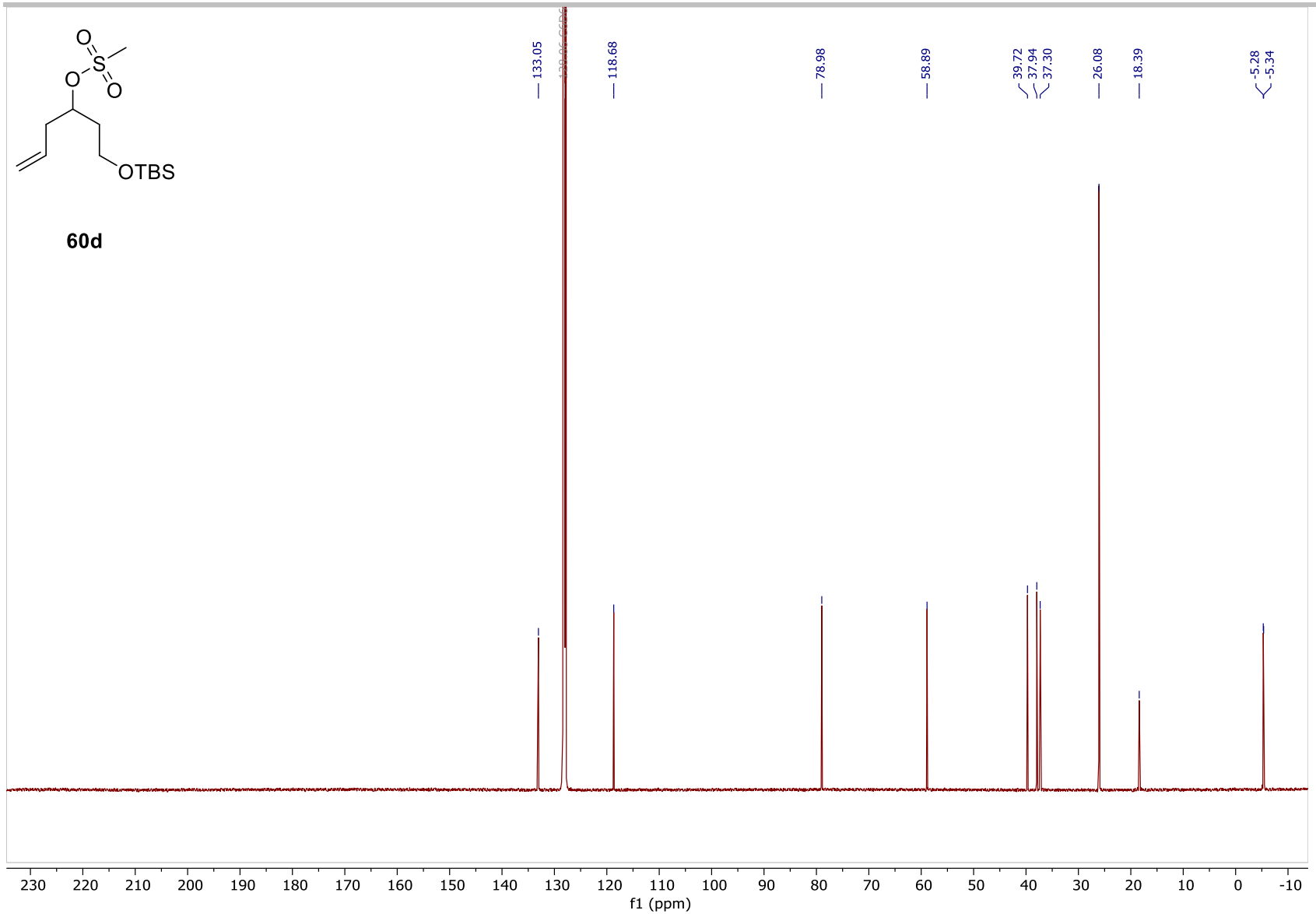

Figure S152. ^{13}C NMR (125 MHz, C_6D_6) of **60d**.

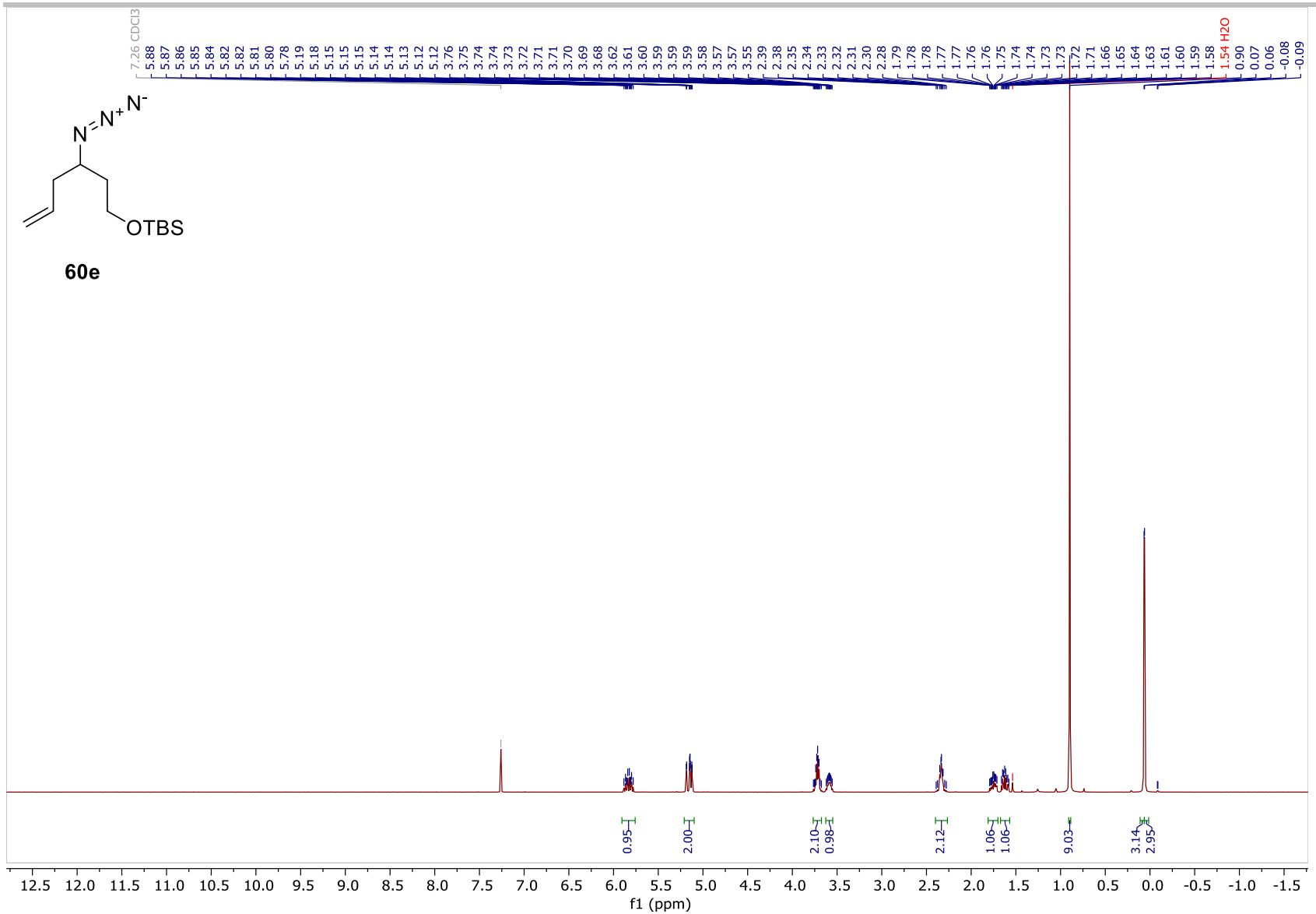

Figure S153. ^{1}H NMR (400 MHz, $CDCl_3$) of **60e**.

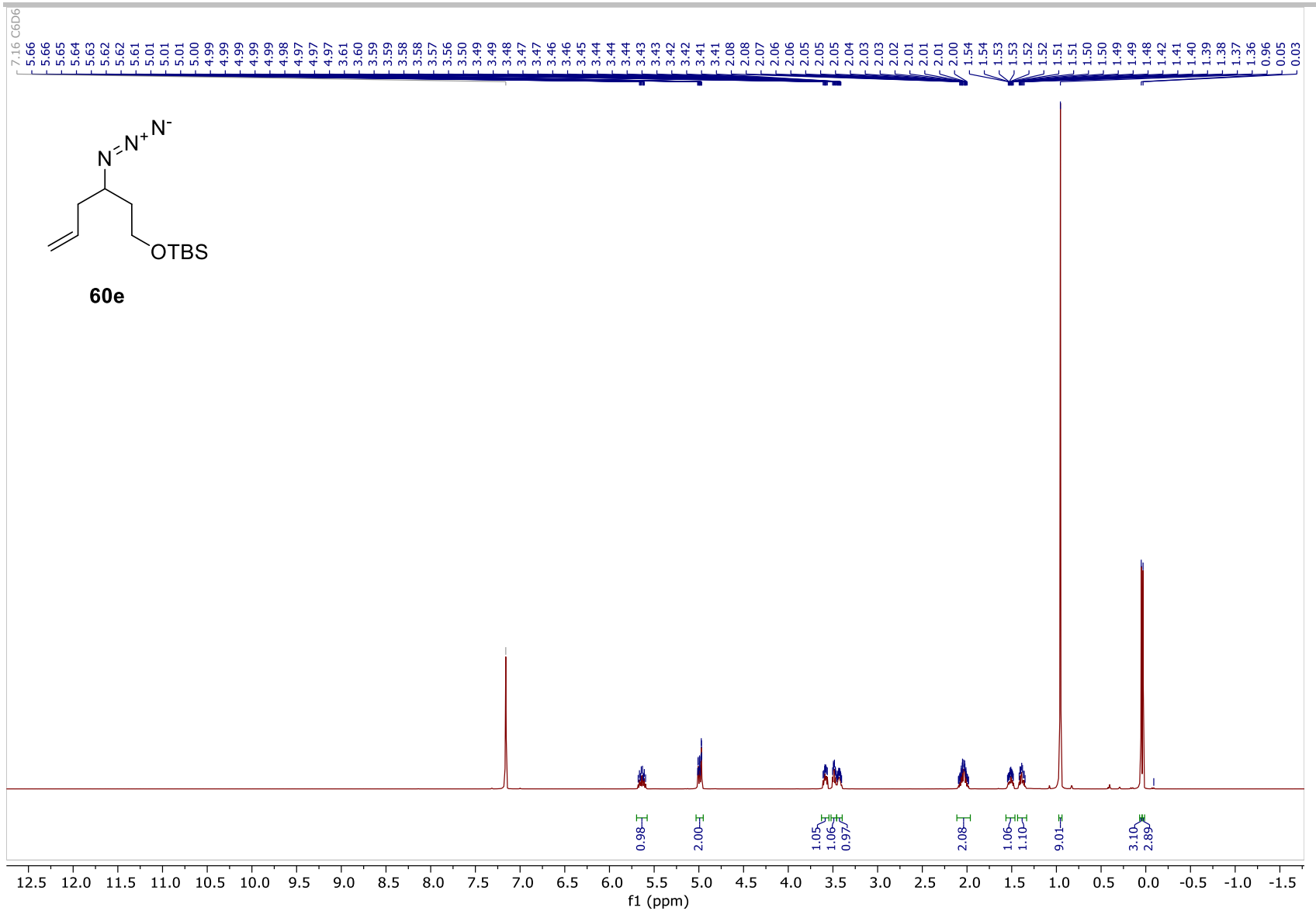

Figure S154. ^{1}H NMR (500 MHz, C_6D_6) of **60e**.

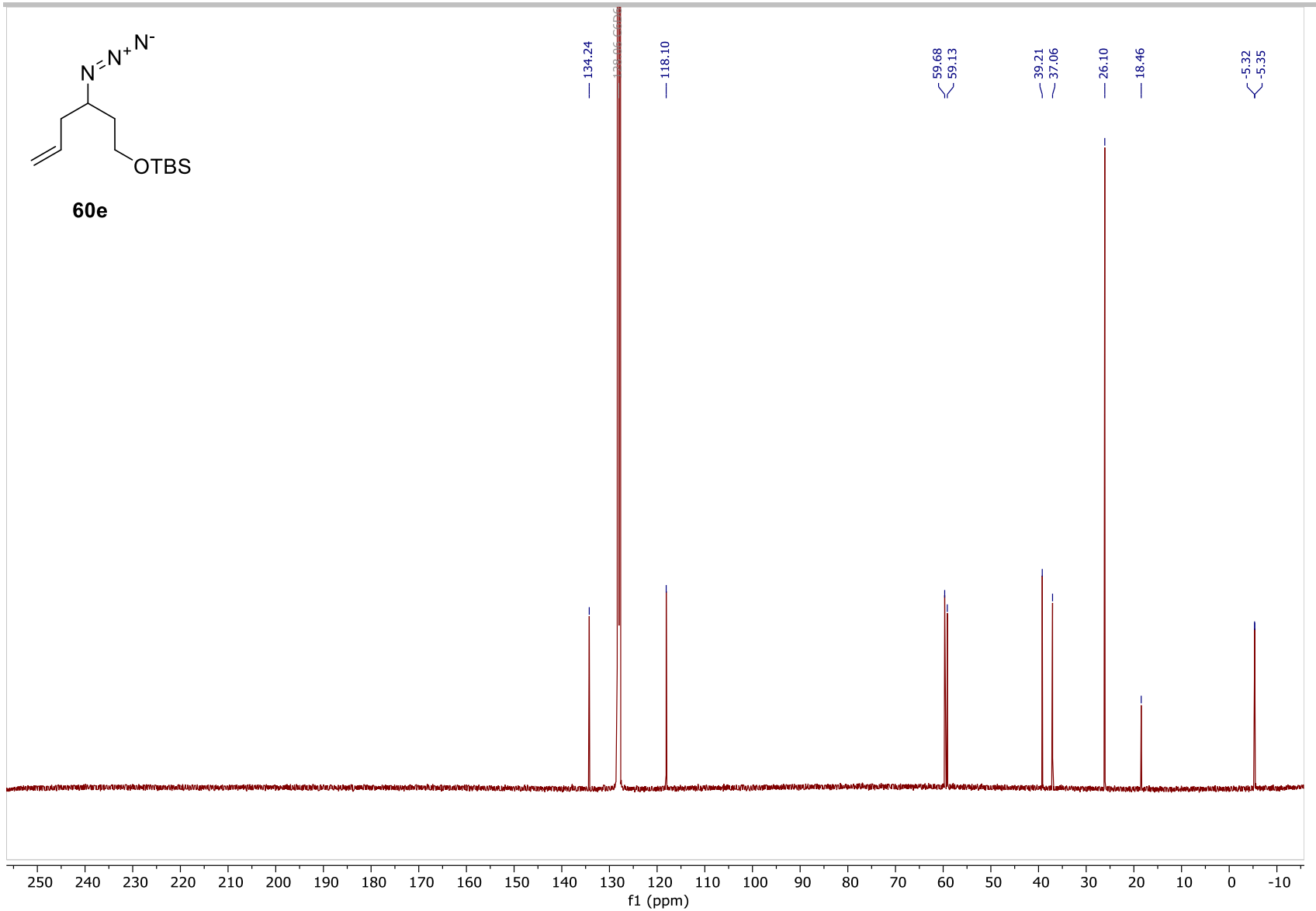

Figure S155. ^{13}C NMR (125 MHz, C_6D_6) of **60e**.

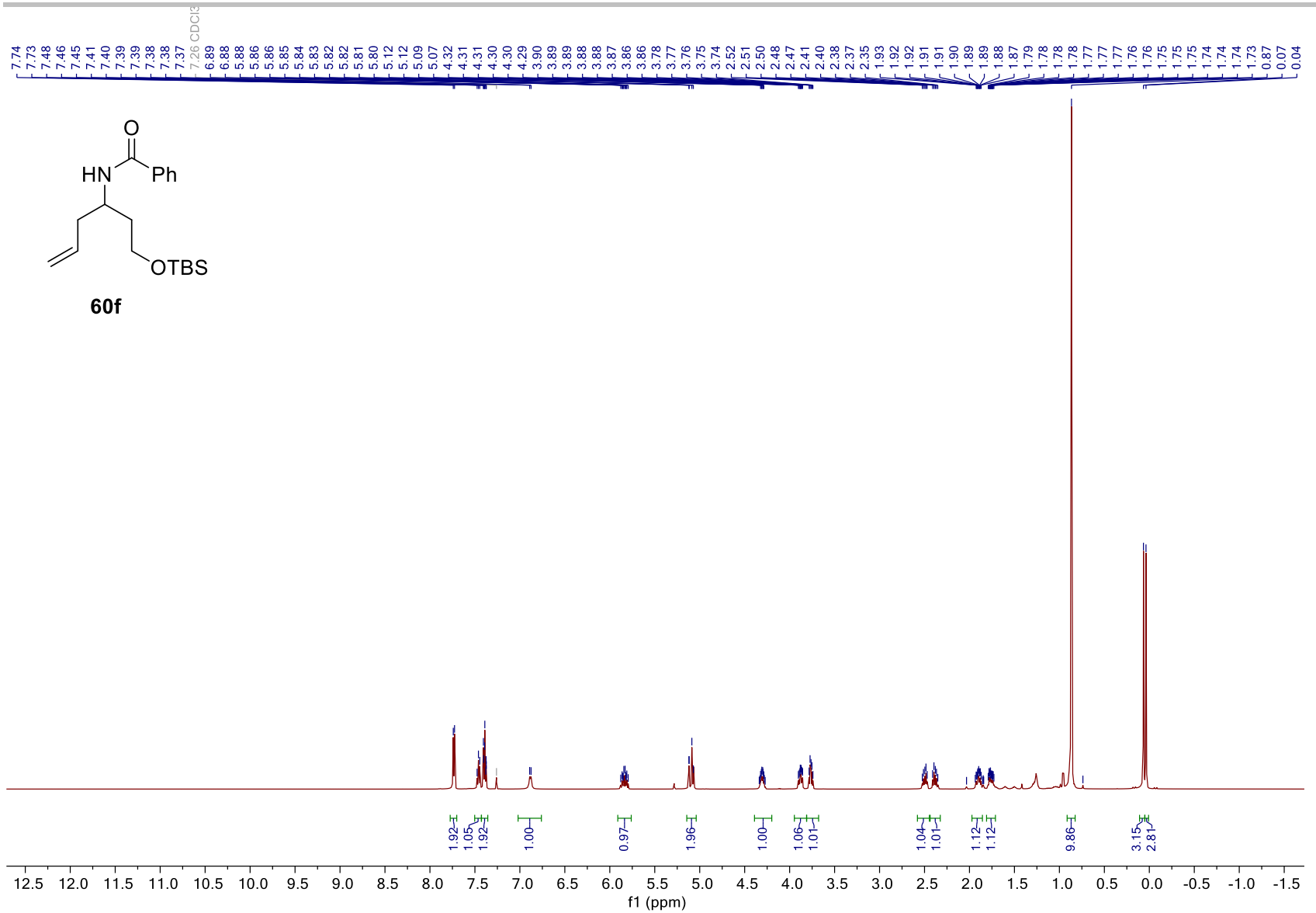

Figure S156. ^{1}H NMR (500 MHz, $CDCl_3$) of **60f**.

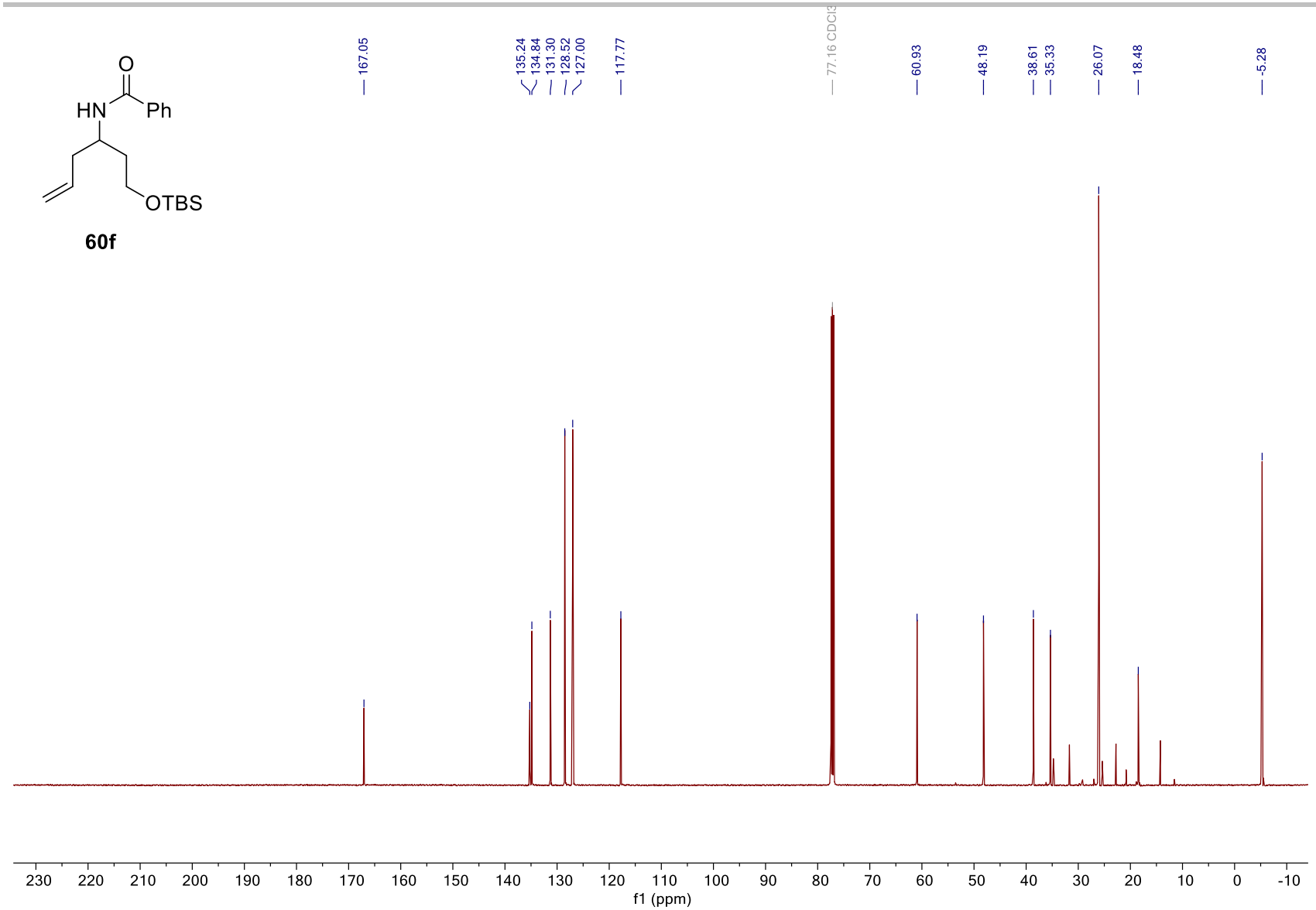

Figure S157. ^{13}C NMR (125 MHz, $CDCl_3$) of **60f**.

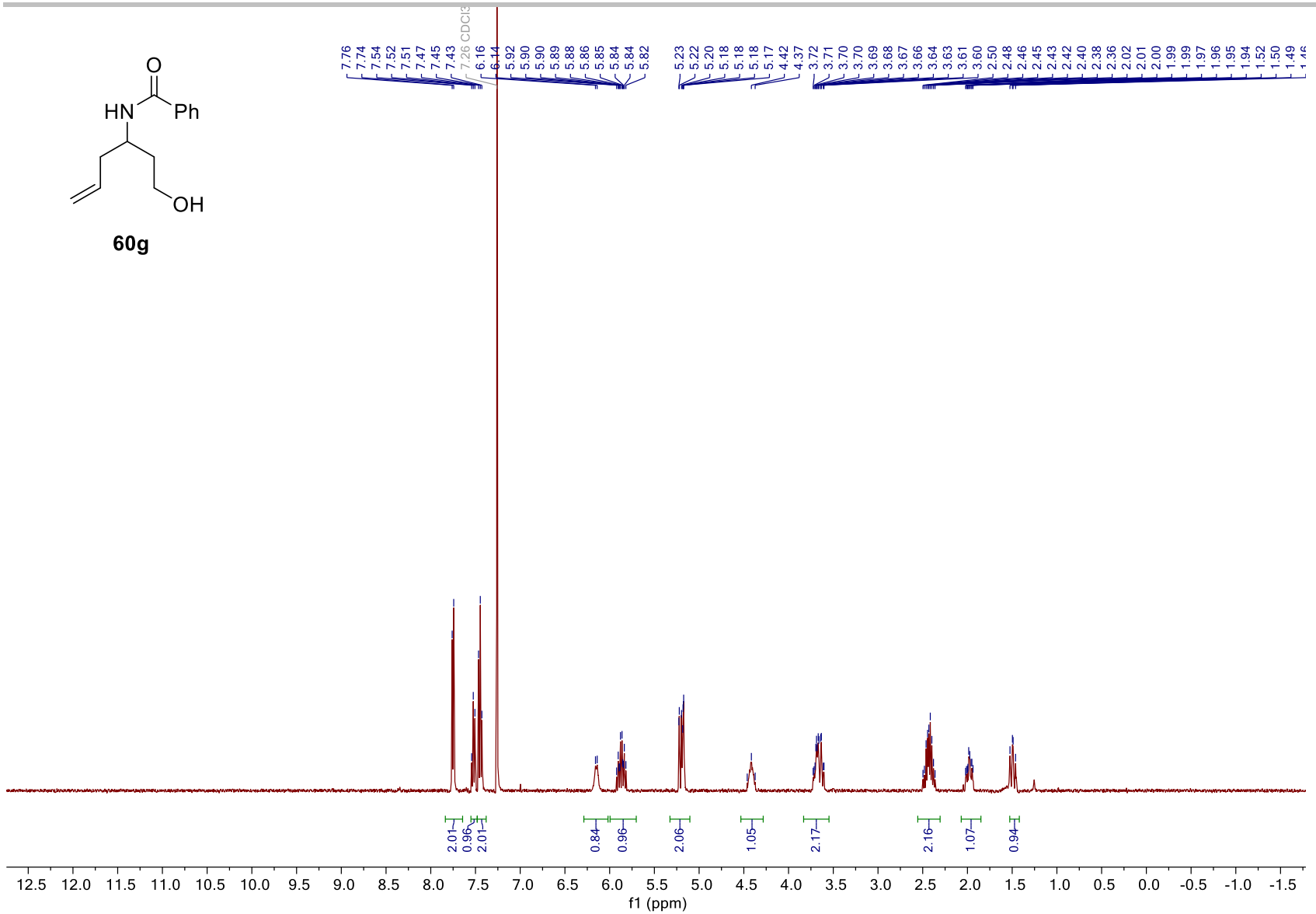

Figure S158. ^{1}H NMR (400 MHz, $CDCl_3$) of **60g**.

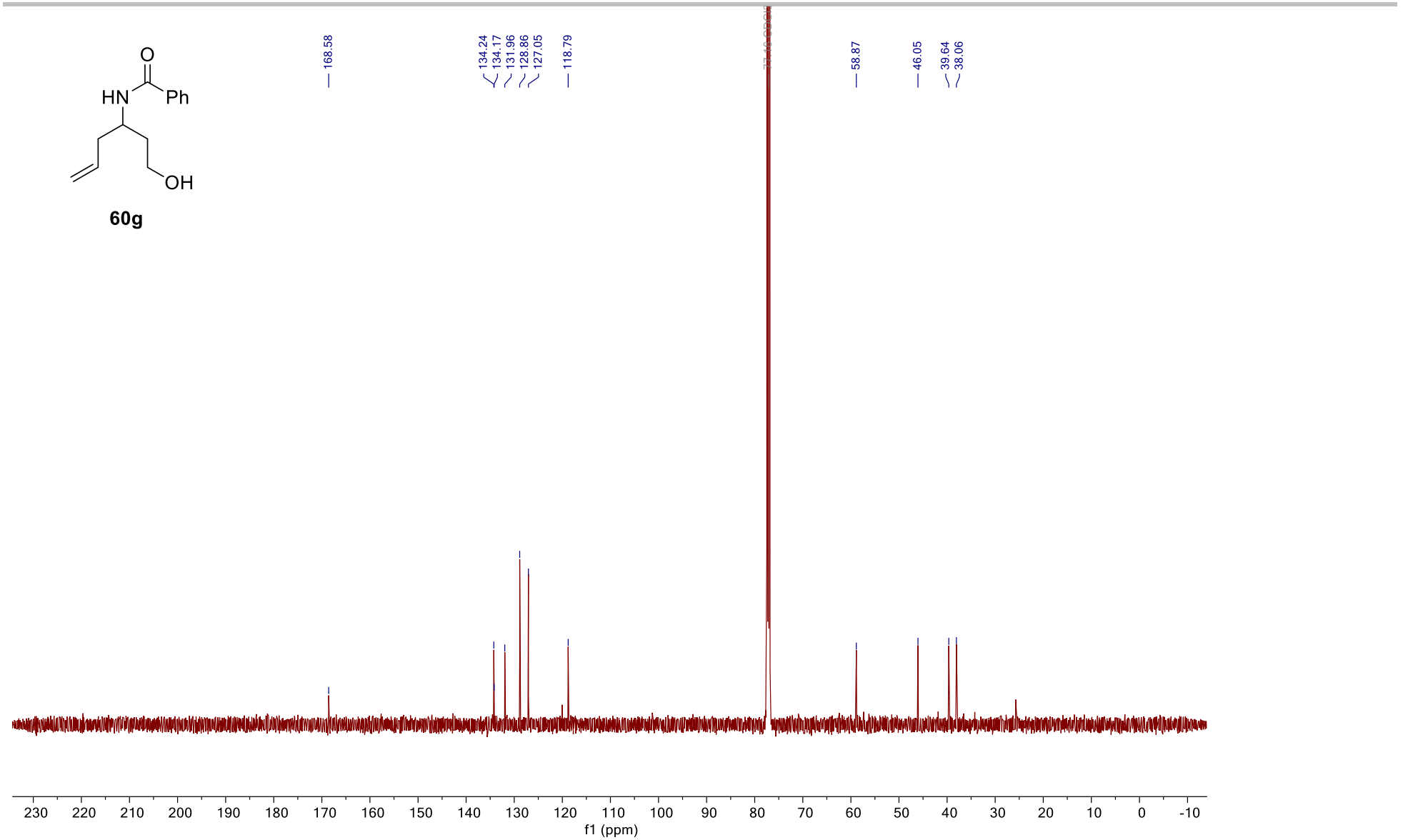

Figure S159. ^{13}C NMR (125 MHz, $CDCl_3$) of **60g**.

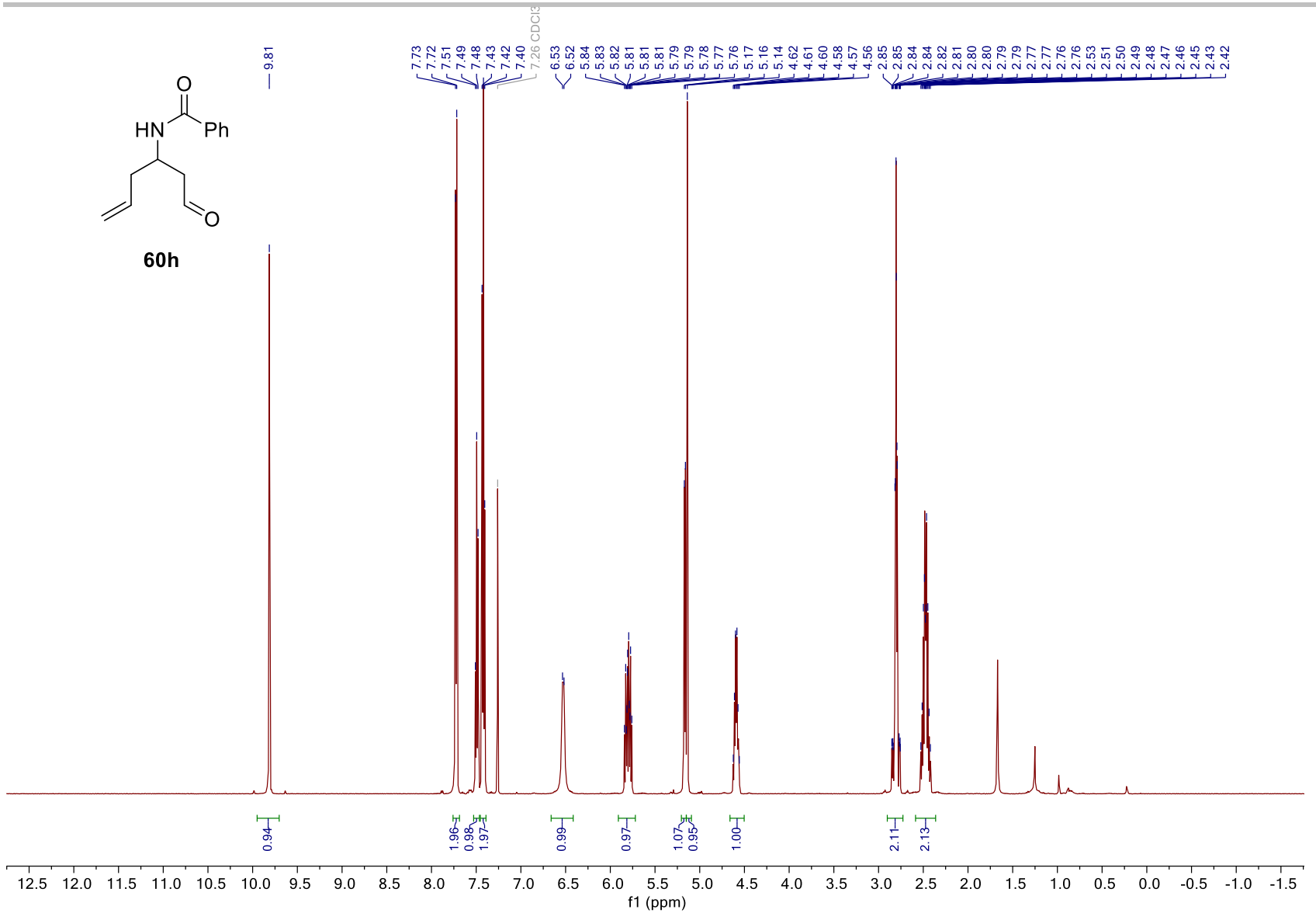

Figure S160. ^{1}H NMR (400 MHz, $CDCl_3$) of **60h**.

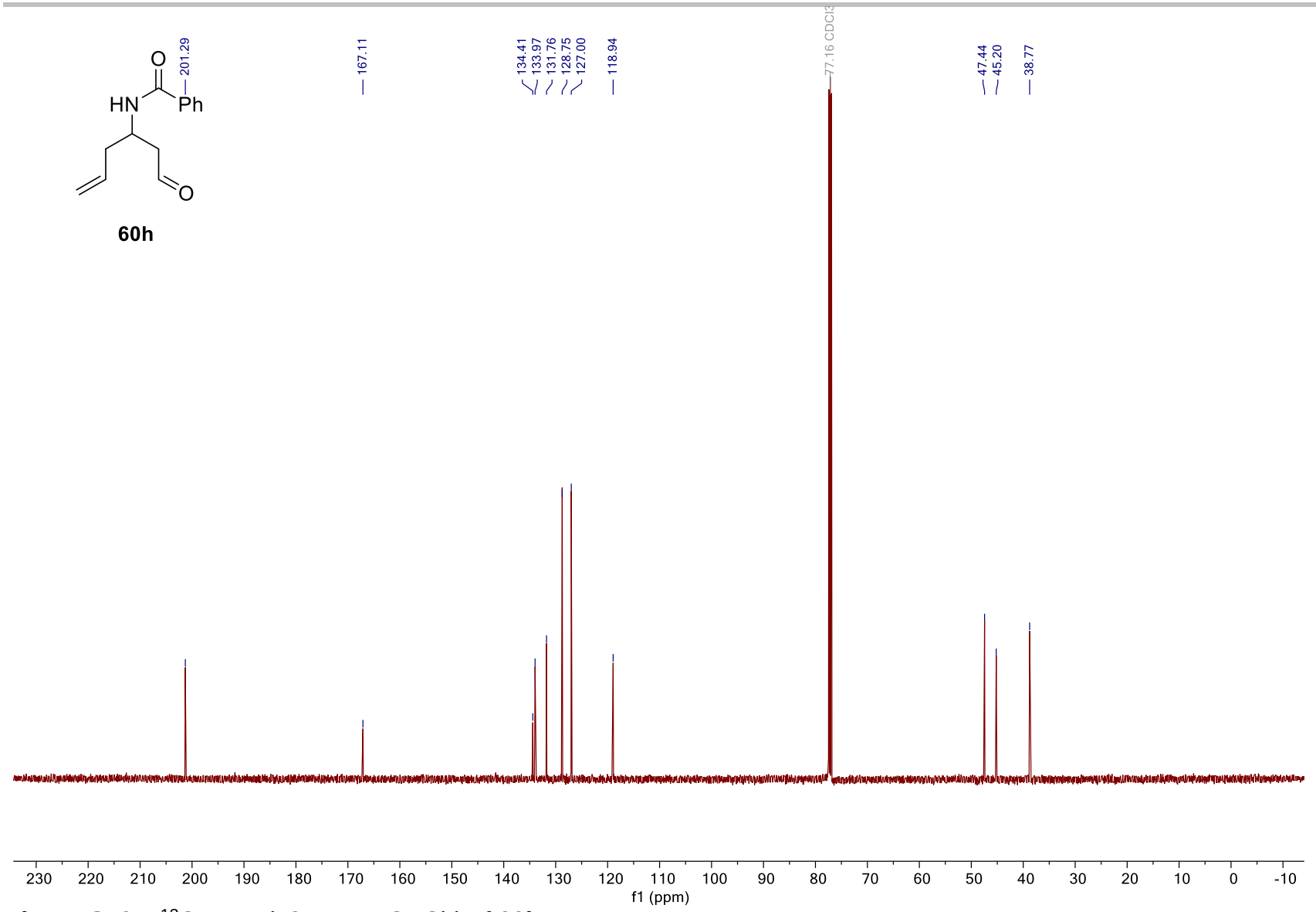

Figure S161. ^{13}C NMR (125 MHz, $CDCl_3$) of **60h**.

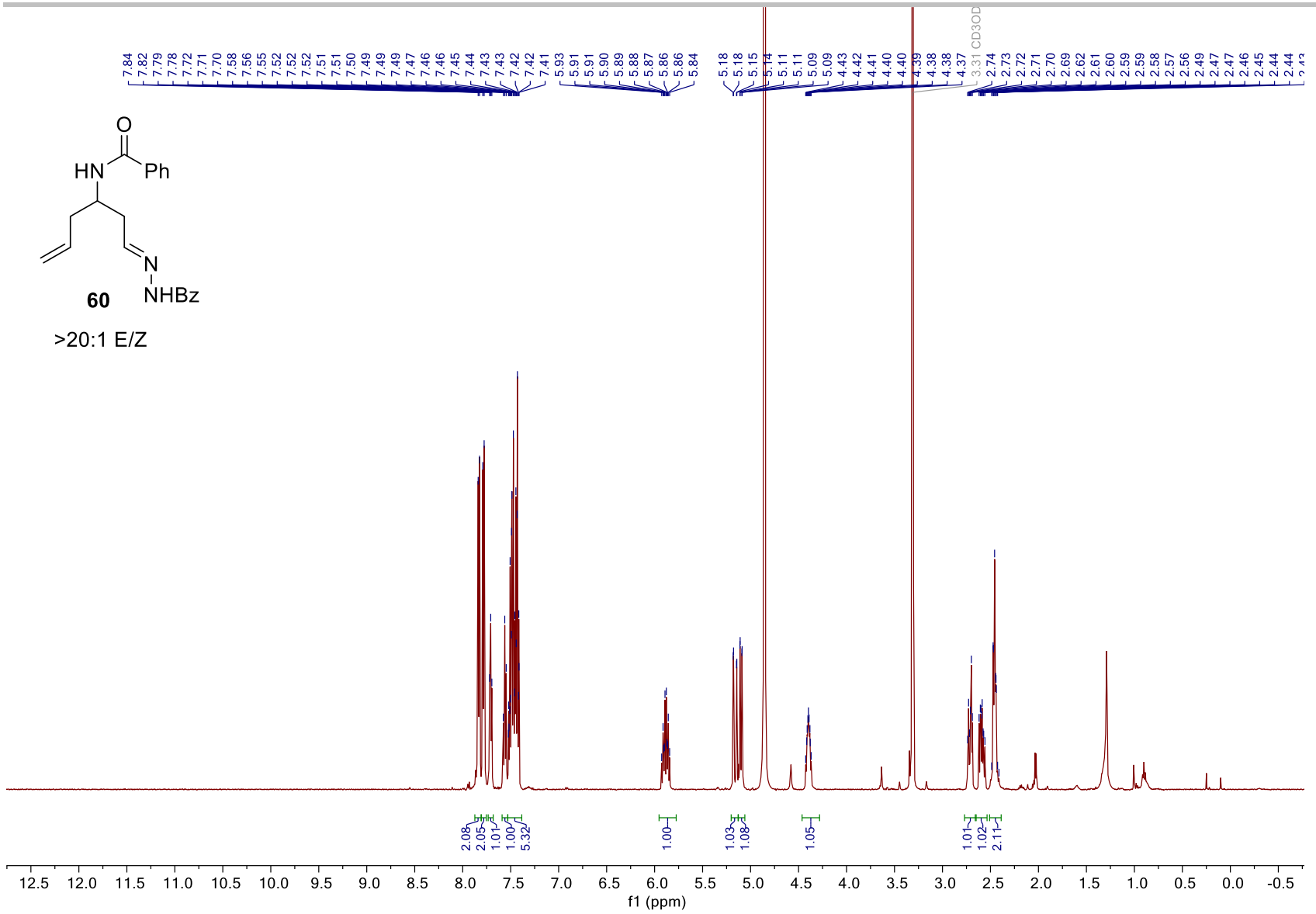

Figure S162. ^{1}H NMR (500 MHz, CD_3OD) of **60**.

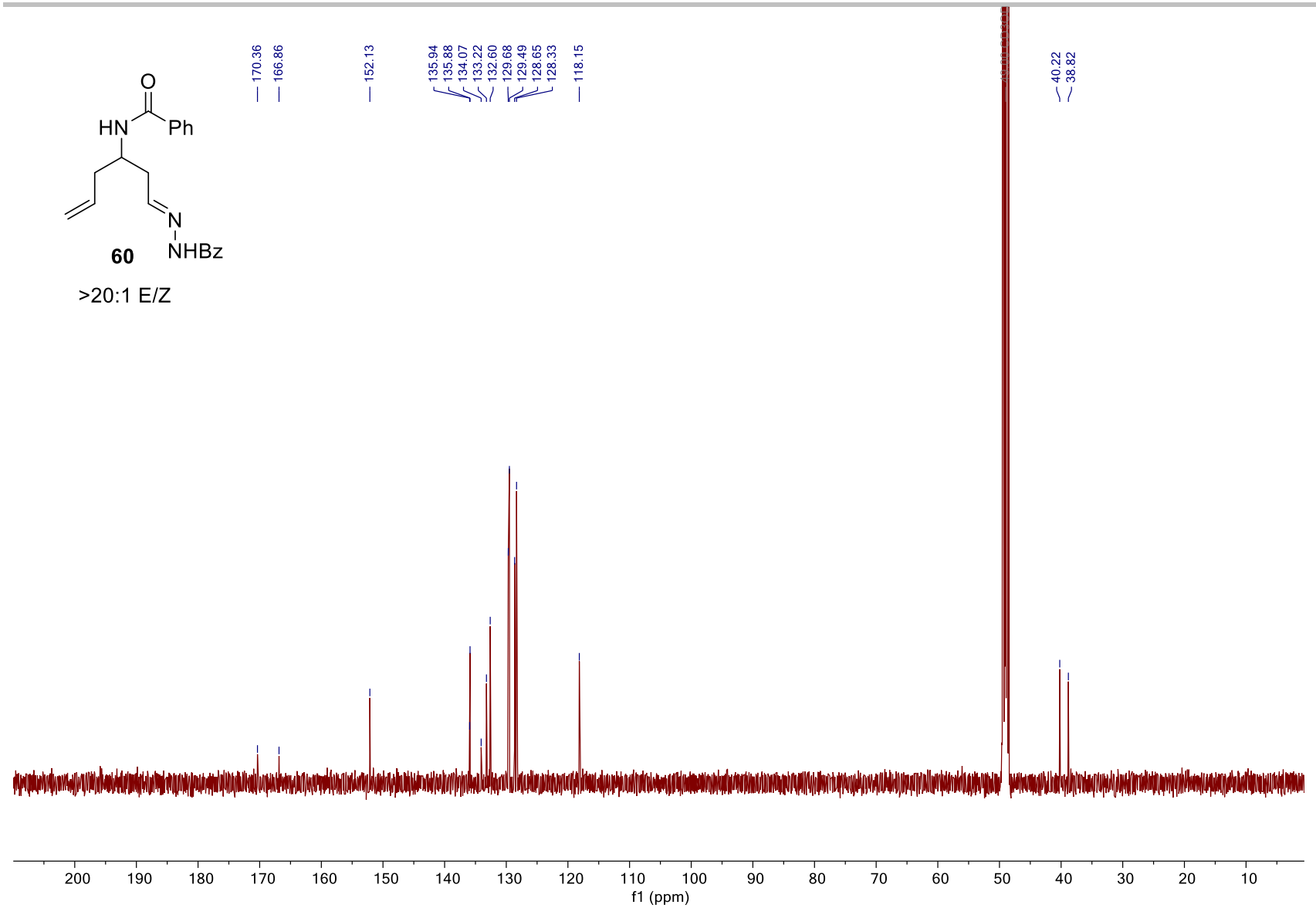

Figure S163. ^{13}C NMR (125 MHz, CD_3OD) of **60**.

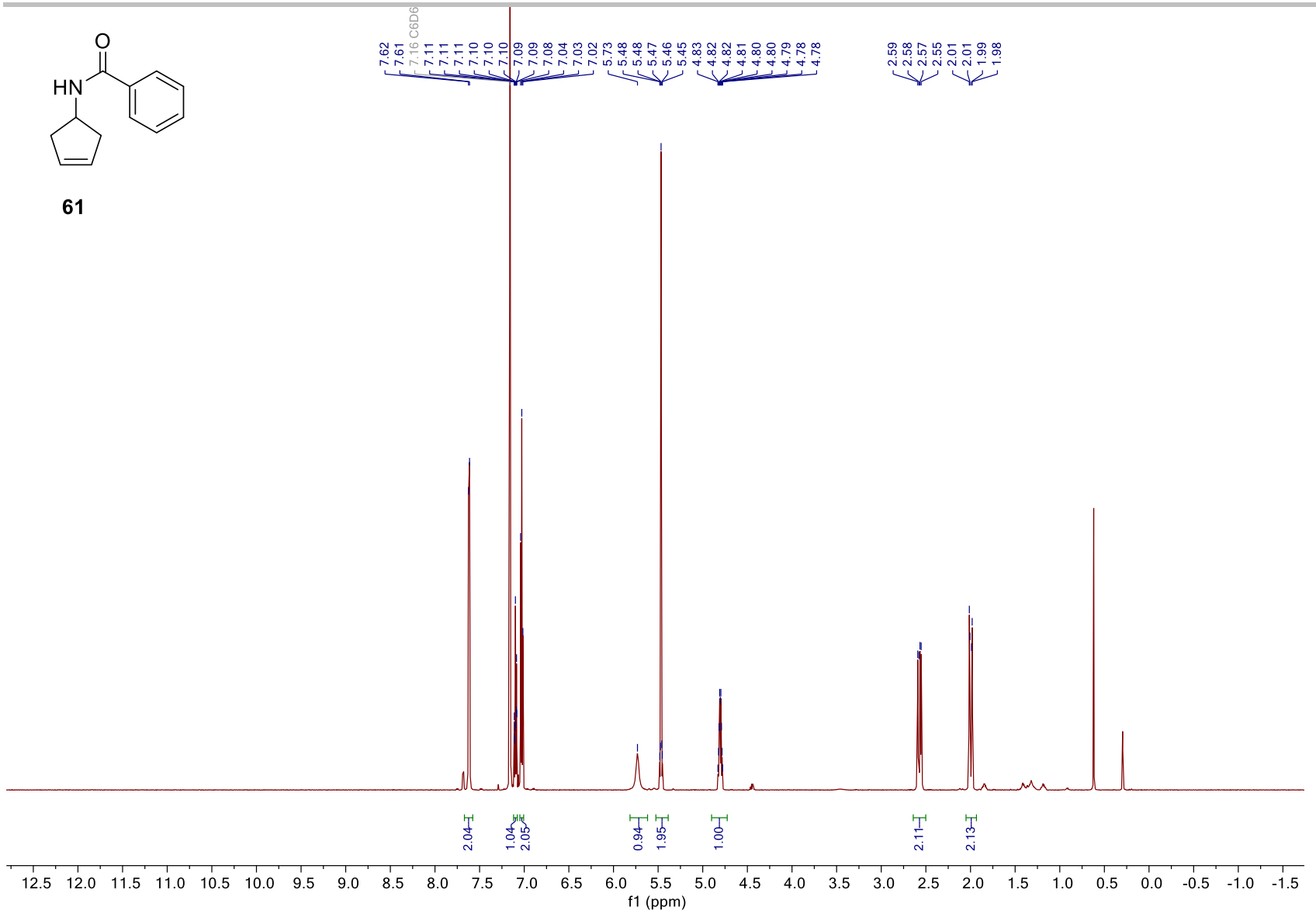

Figure S164. ^{1}H NMR (600 MHz, C_6D_6) of **61**.

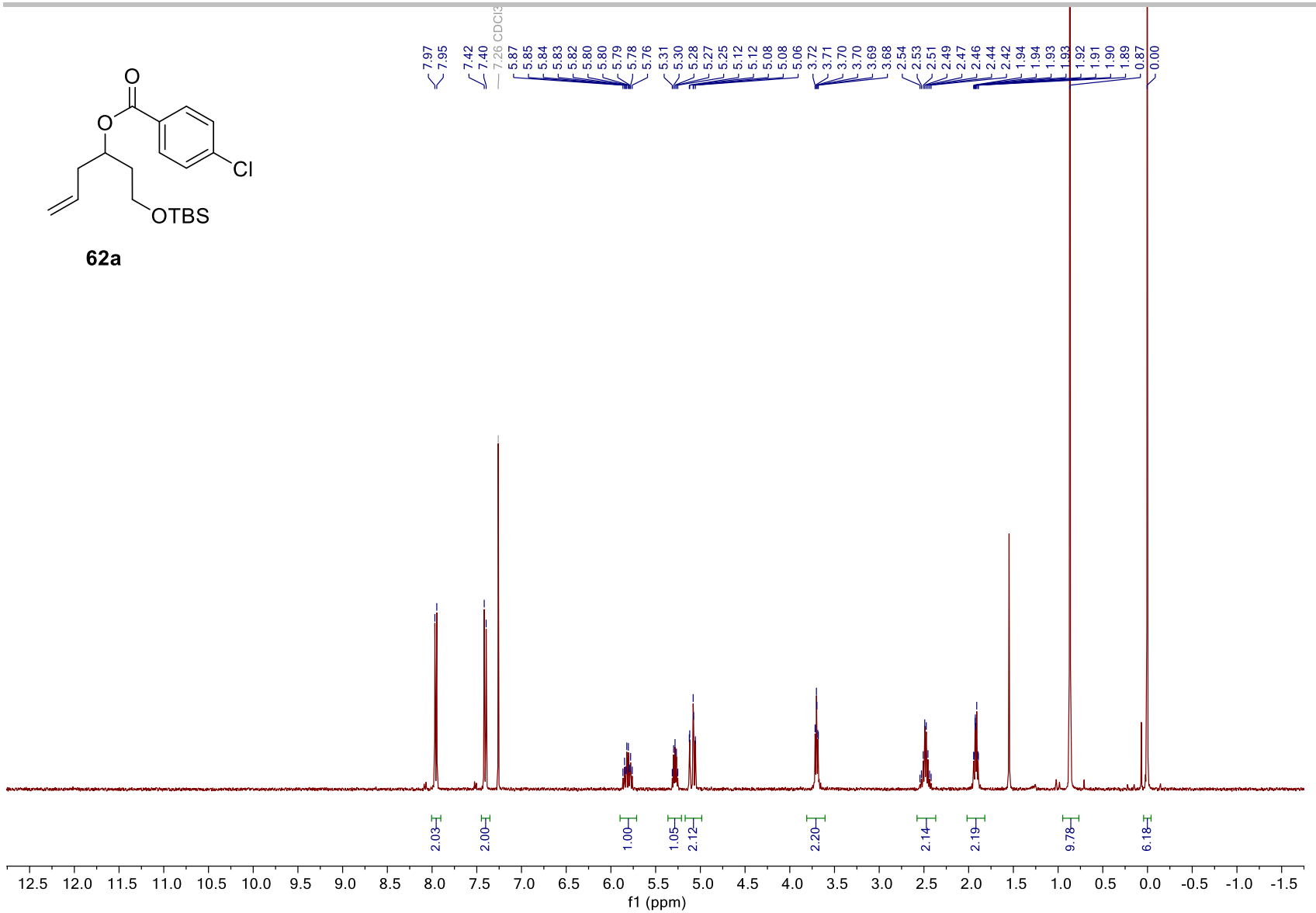

Figure S165. ^{1}H NMR (400 MHz, $CDCl_3$) of **62a**.

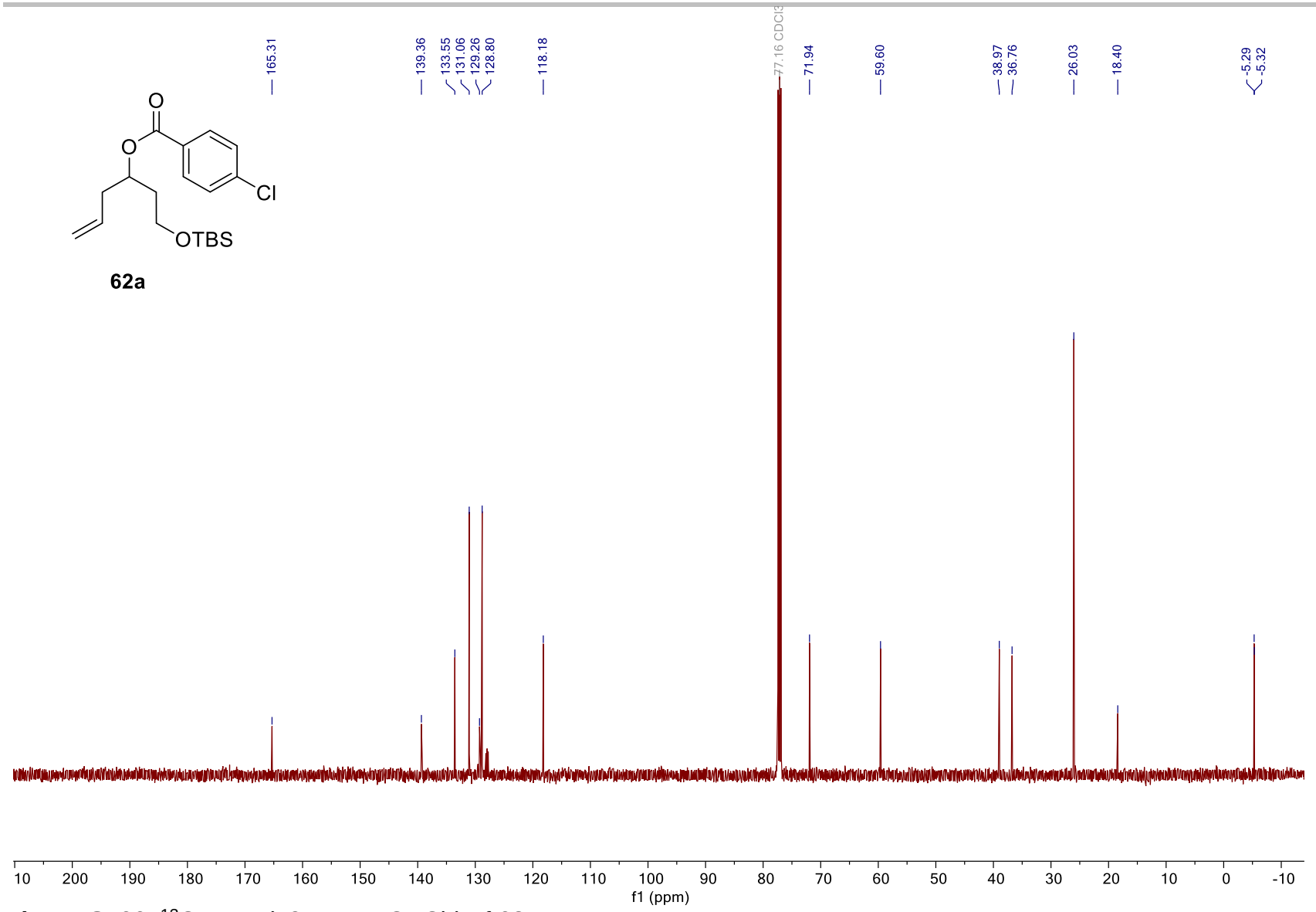

Figure S166. ^{13}C NMR (125 MHz, $CDCl_3$) of **62a**.

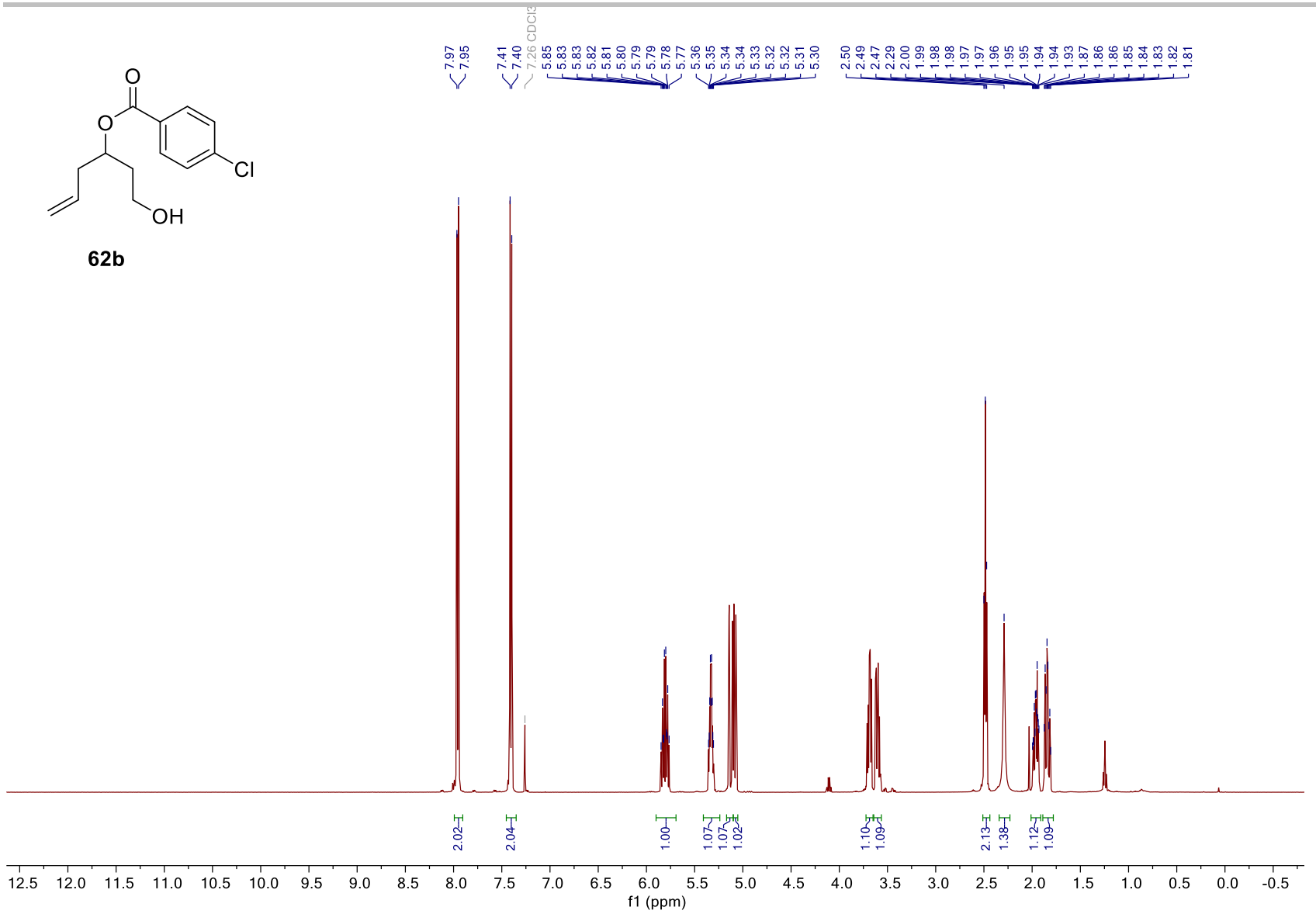

Figure S167. ^{1}H NMR (500 MHz, $CDCl_3$) of **62b**.

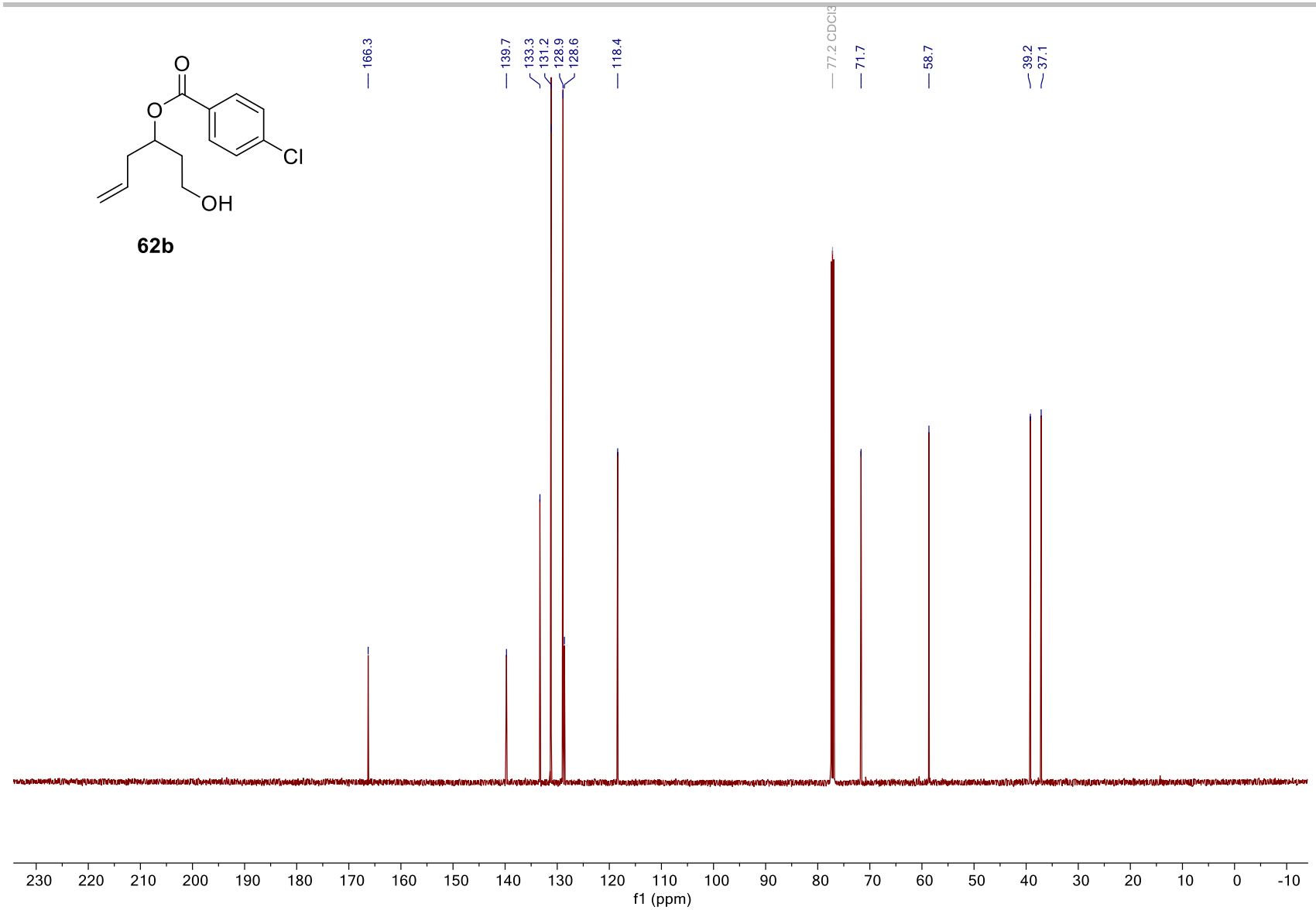

Figure S168. ^{13}C NMR (125 MHz, $CDCl_3$) of **62b**.

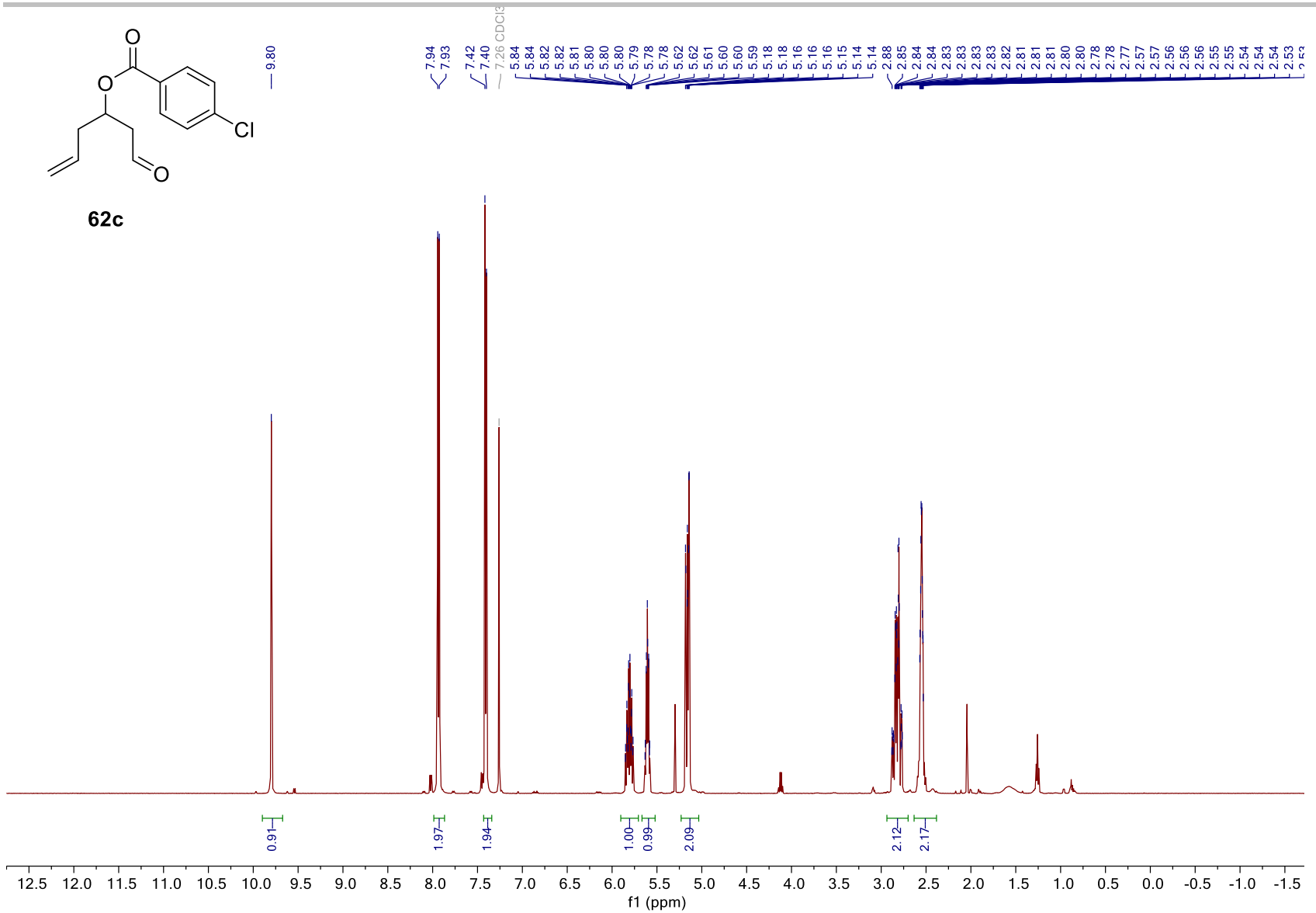

Figure S169. ^{1}H NMR (500 MHz, $CDCl_3$) of **62c**.

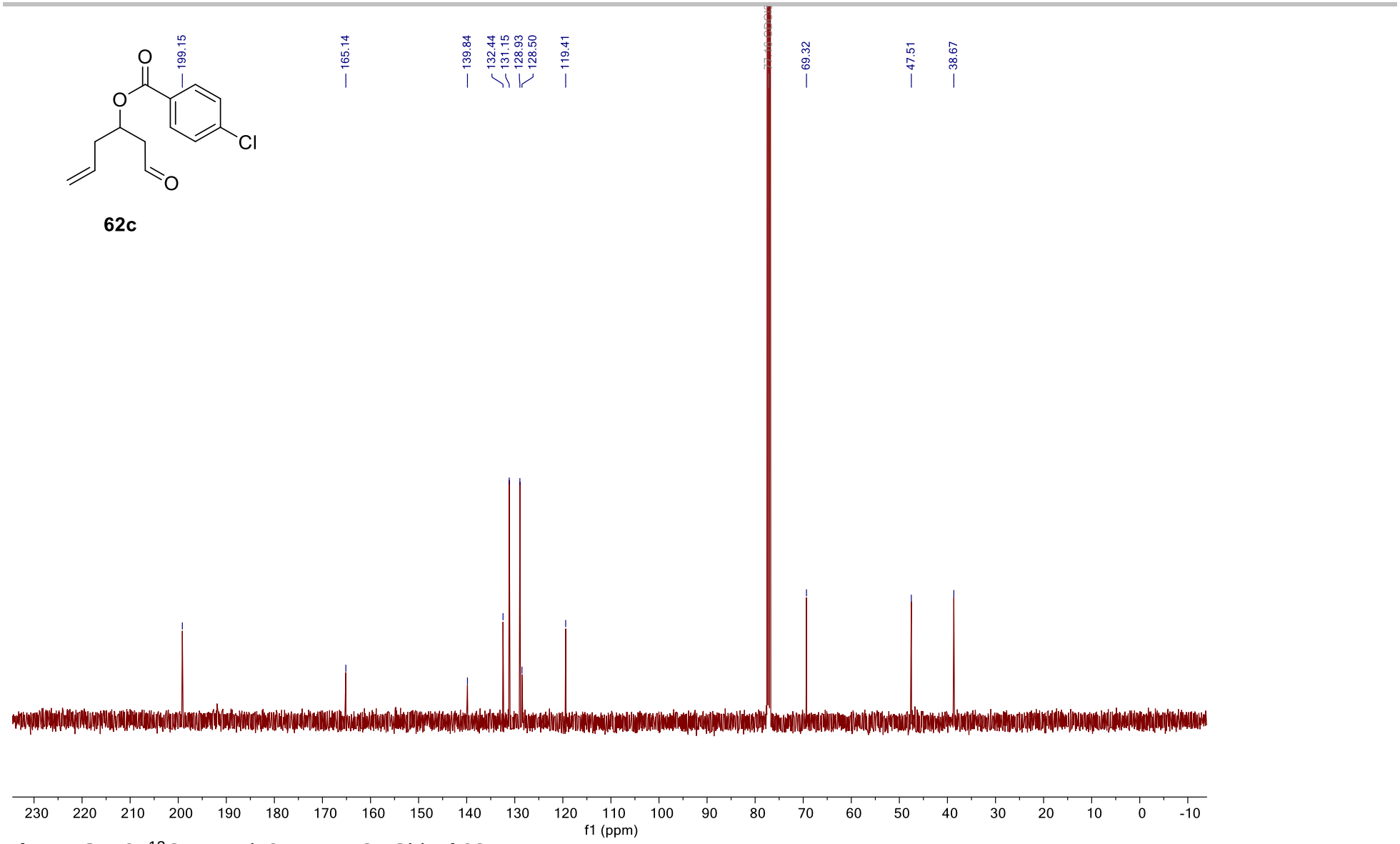

Figure S170. ^{13}C NMR (125 MHz, $CDCl_3$) of **62c**.

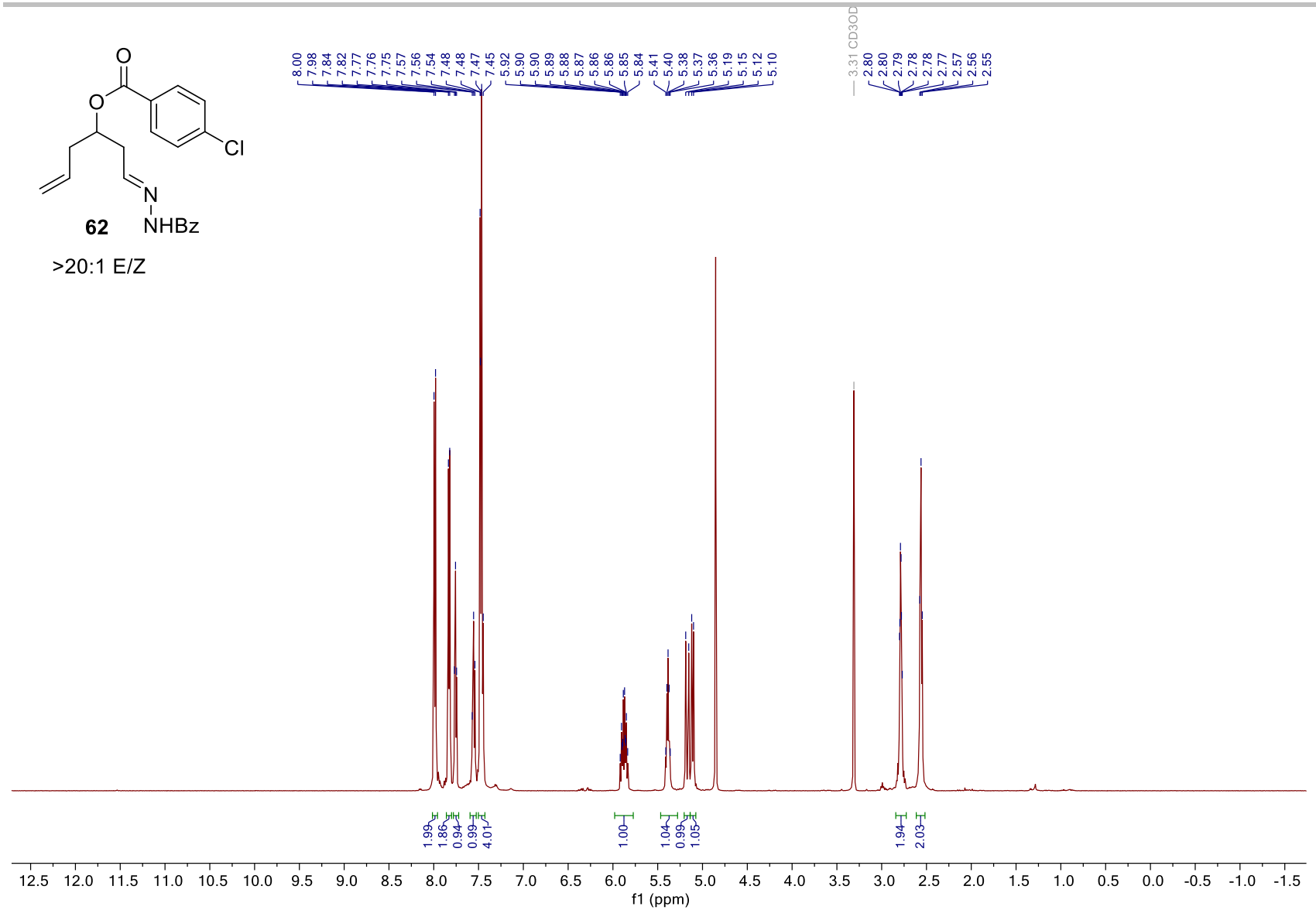

Figure S171. ^{1}H NMR (500 MHz, CD_3OD) of **62**.

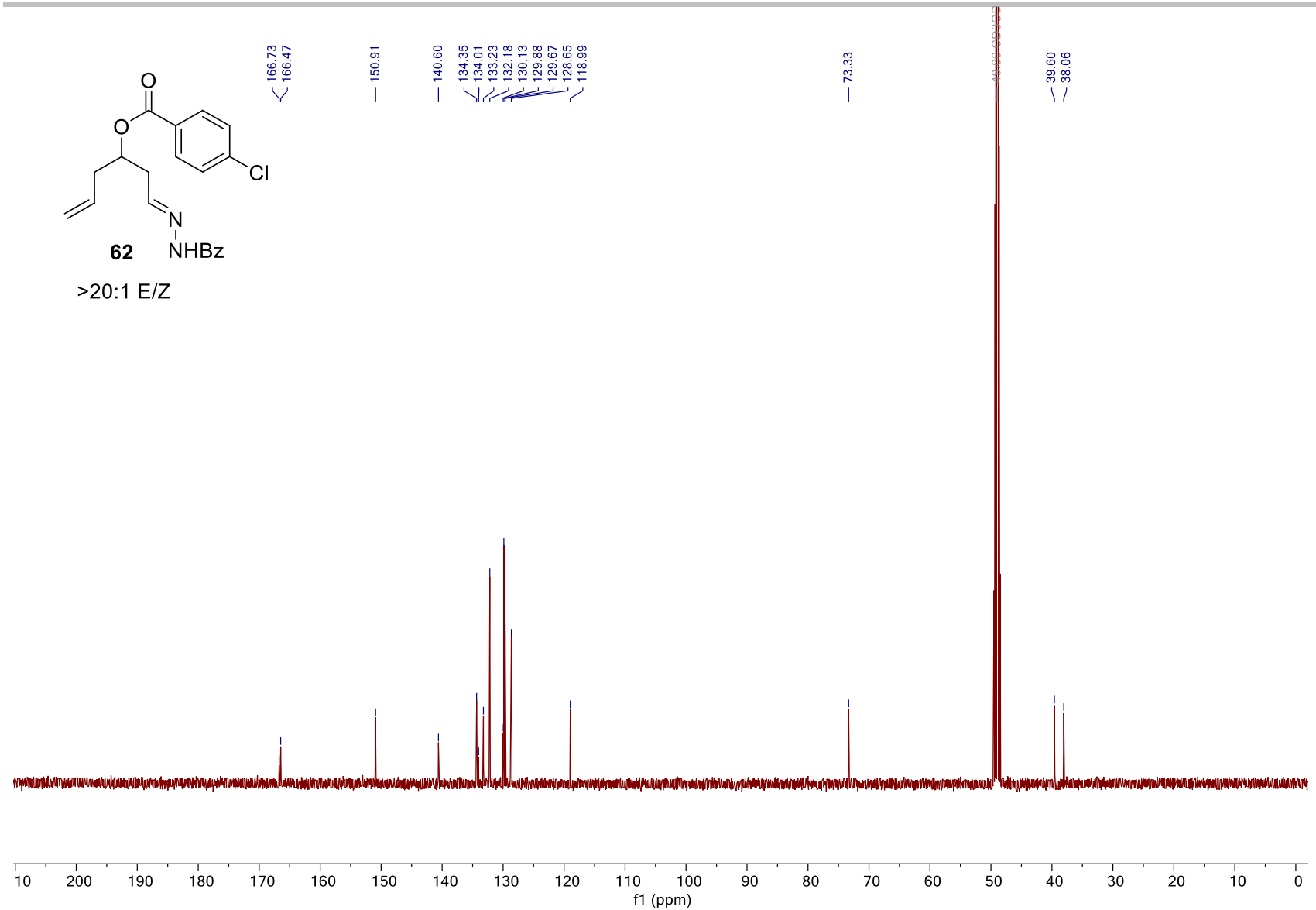

Figure S172. ^{13}C NMR (125 MHz, CD_3OD) of **62**.

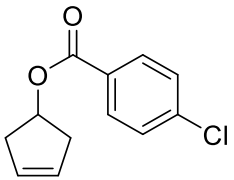

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Figure S173. ^{1}H NMR (500 MHz, C_6D_6) of **63**.

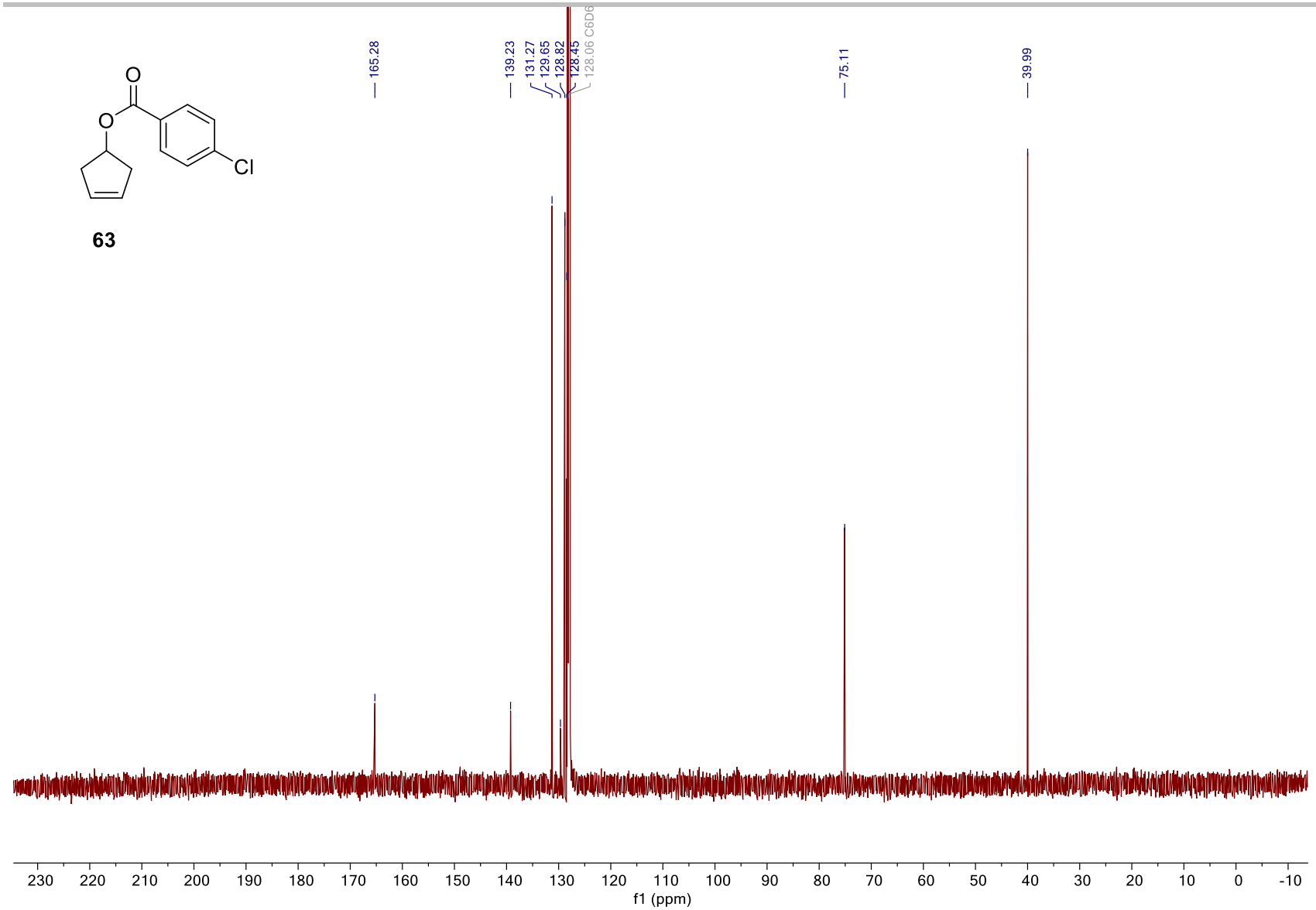


Figure S174. ^{13}C NMR (125 MHz, C_6D_6) of **63**.

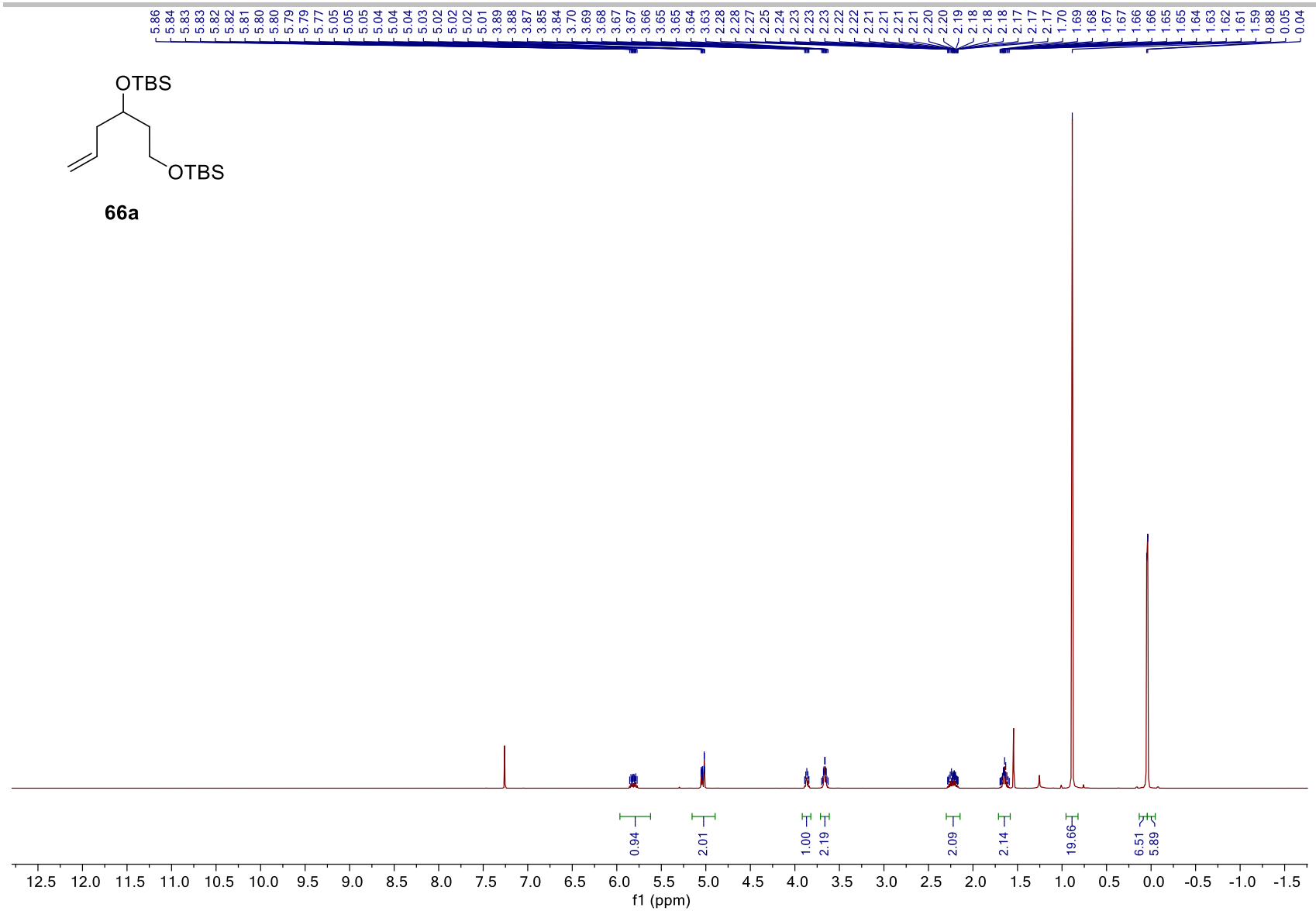


Figure S175. ^{1}H NMR (500 MHz, $CDCl_3$) of **66a**.

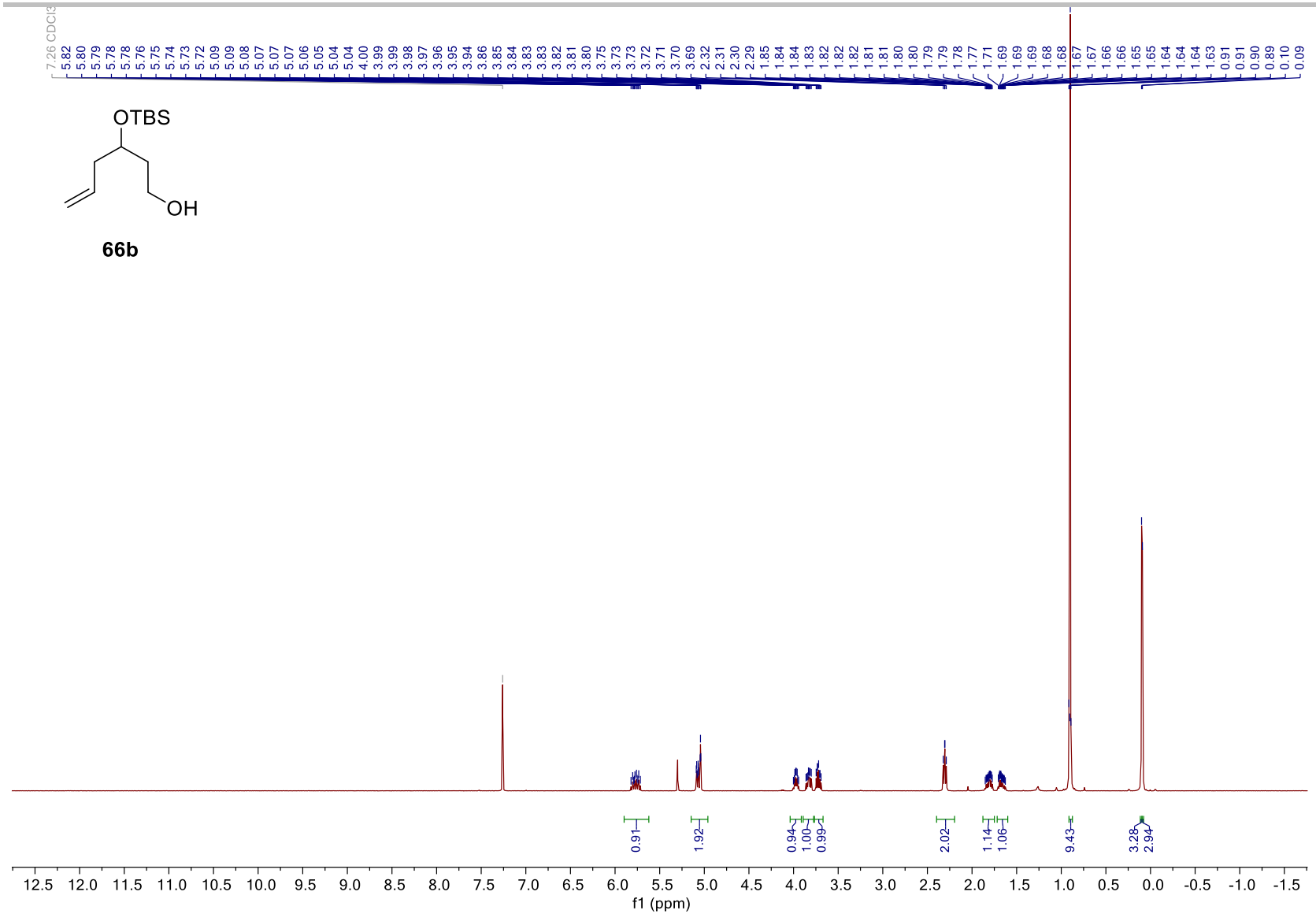


Figure S176. ^{1}H NMR (500 MHz, $CDCl_3$) of **66b**.

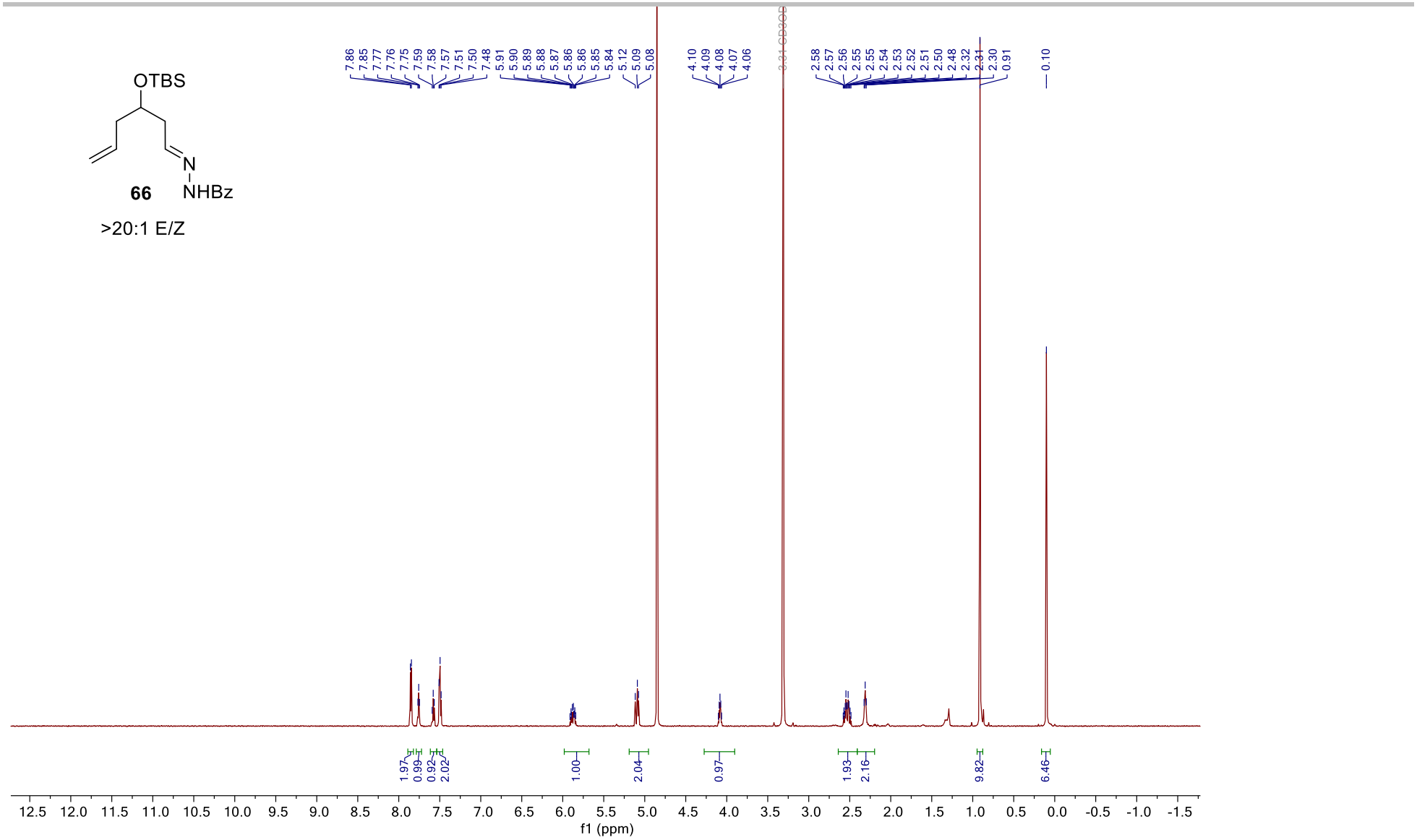


Figure S177. ^{1}H NMR (600 MHz, CD_3OD) of **66**.

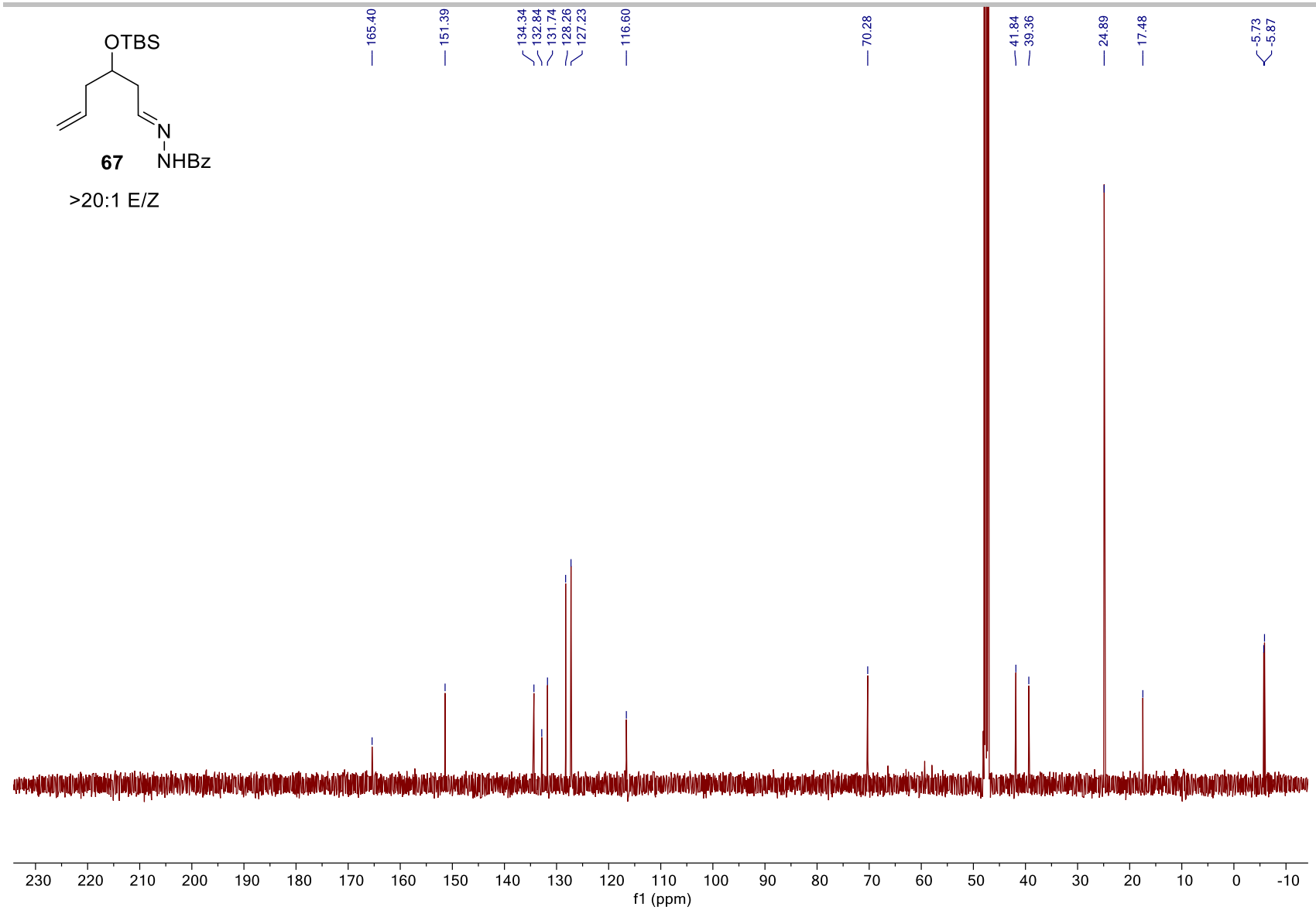


Figure S178. ^{13}C NMR (125 MHz, CD_3OD) of **66**.

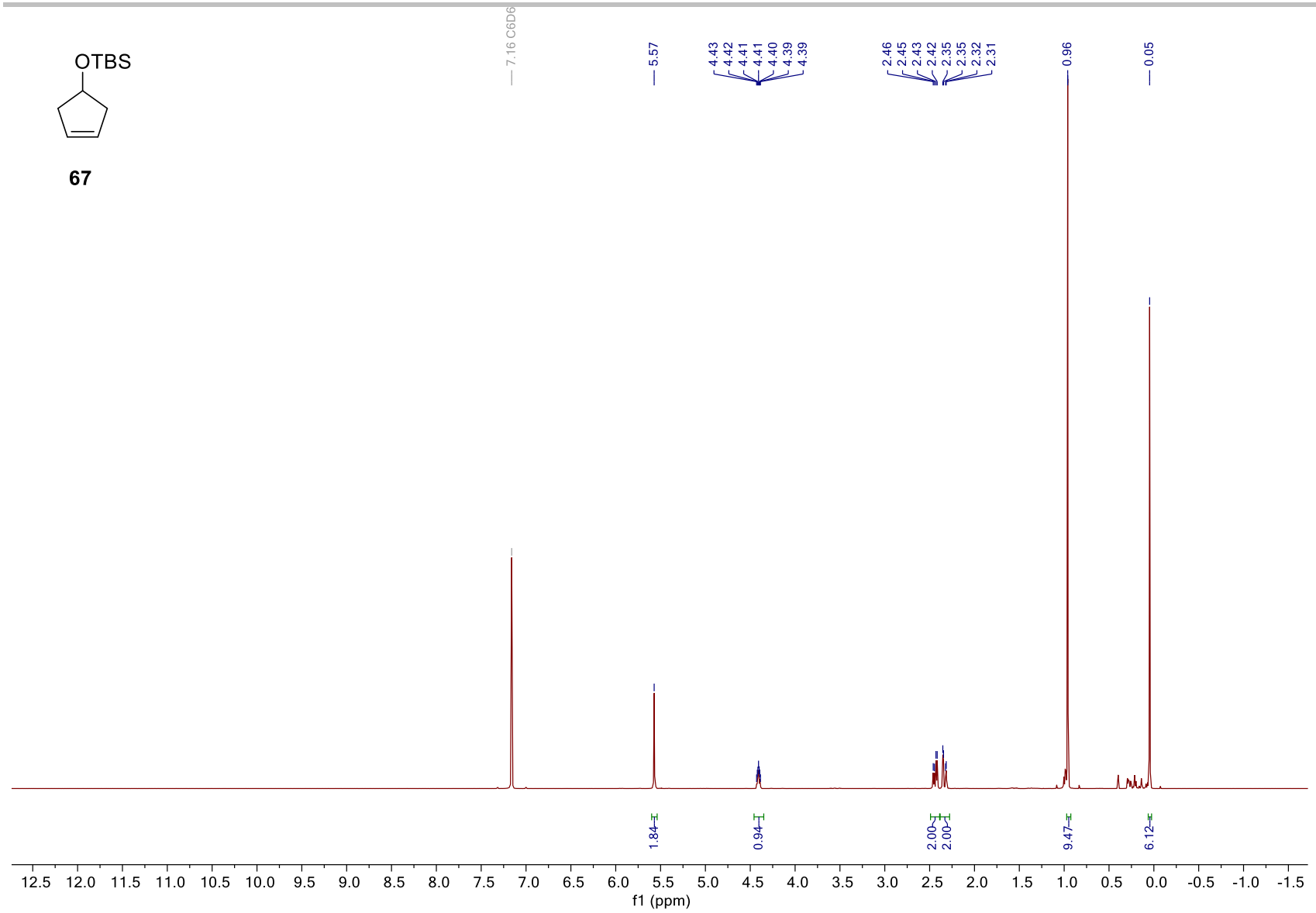


Figure S179. ^{1}H NMR (500 MHz, C_6D_6) of **67**.

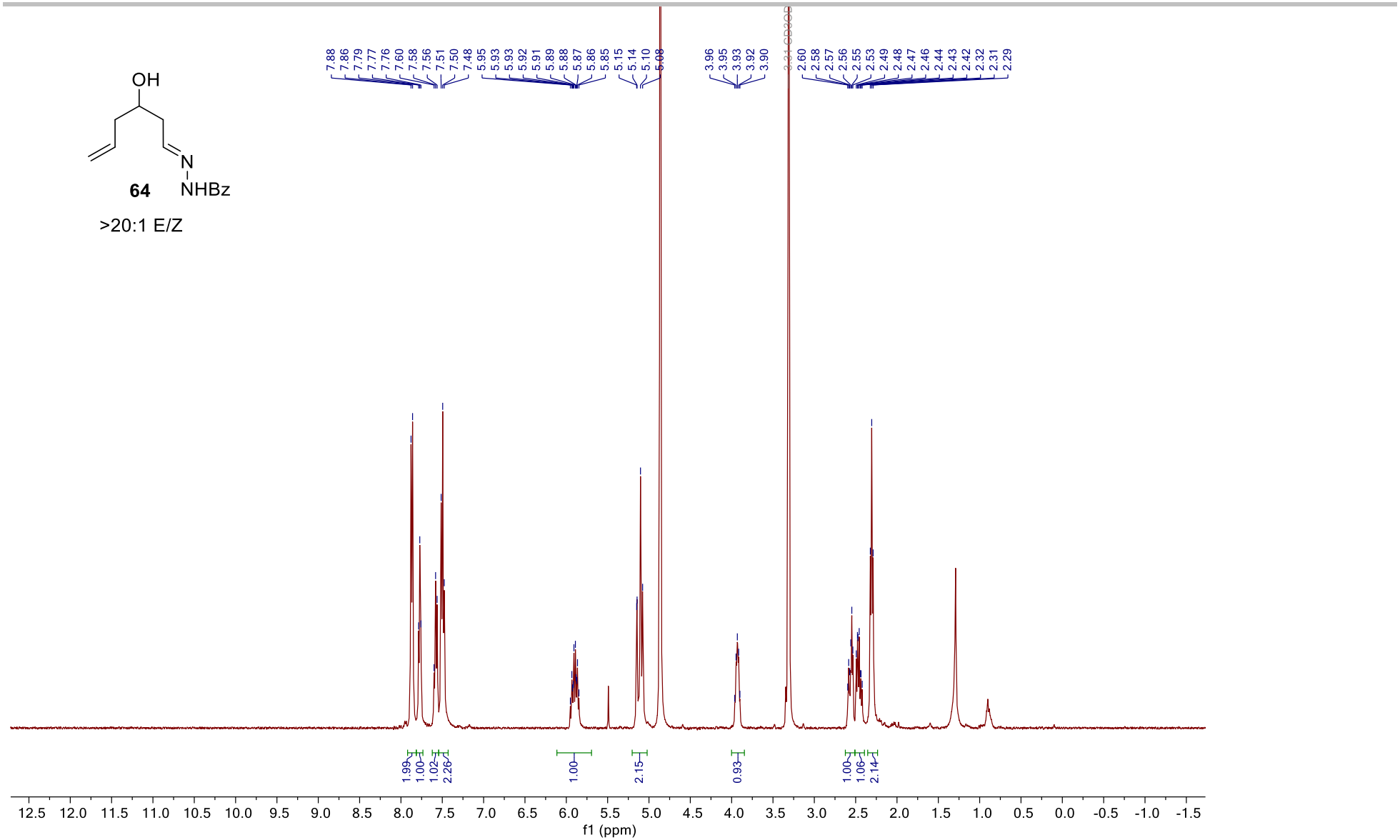


Figure S180. ^{1}H NMR (400 MHz, CD_3OD) of **64**.

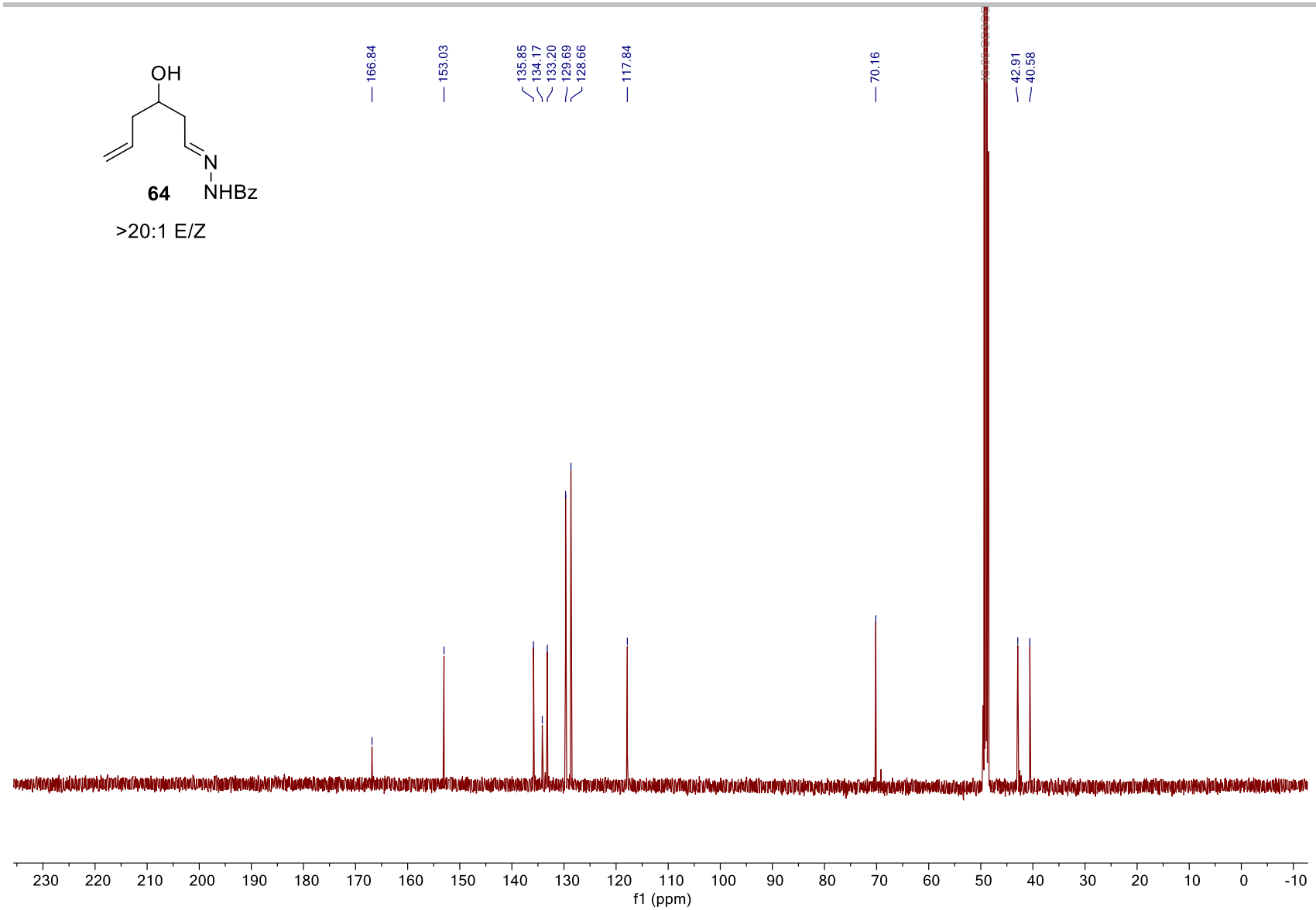
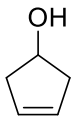


Figure S181. ^{13}C NMR (125 MHz, CD_3OD) of **64**.



65

Figure S182. ^{1}H NMR (400 MHz, $CDCl_3$) of **65**.

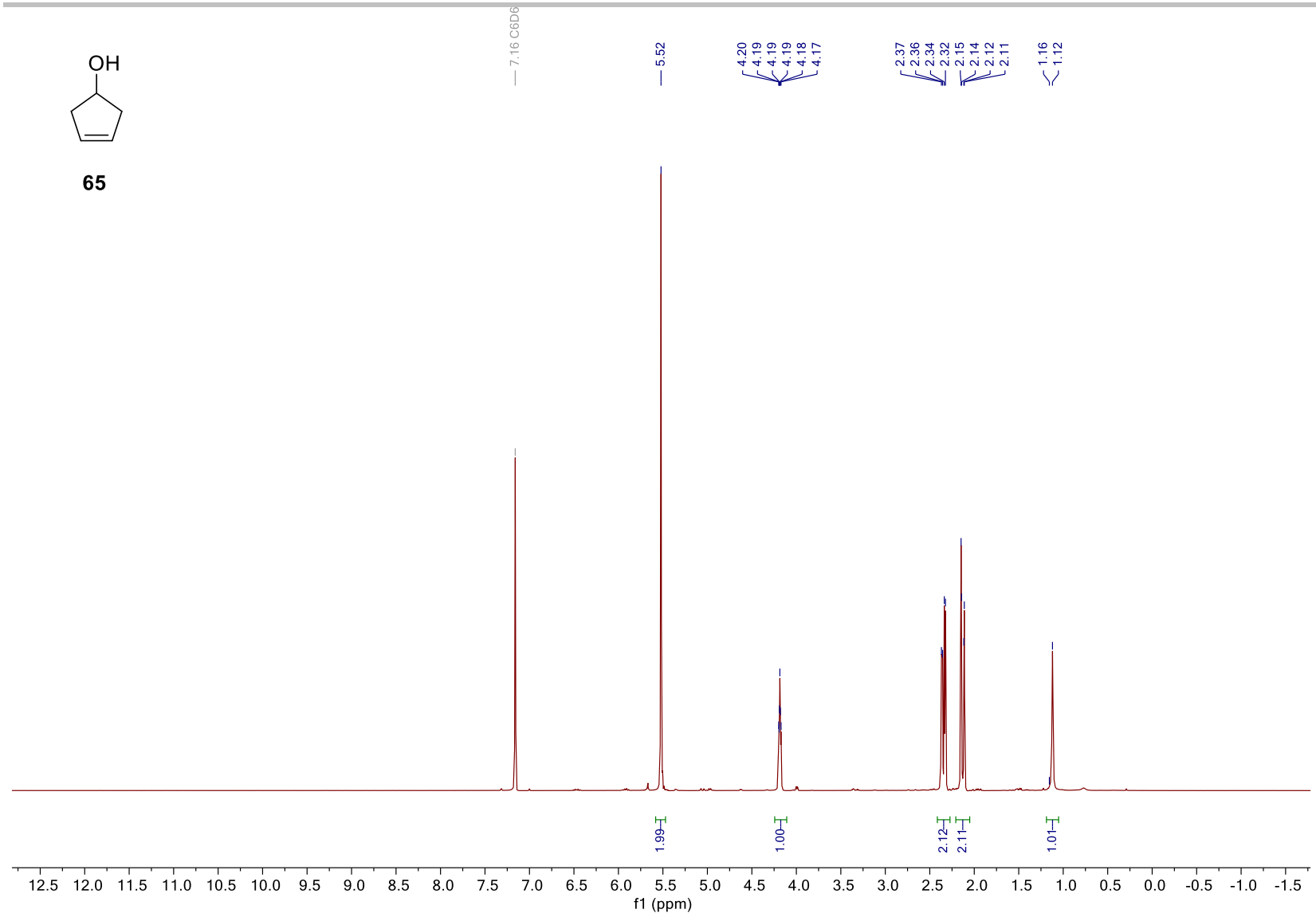


Figure S183. ^{1}H NMR (500 MHz, C_6D_6) of **65**.

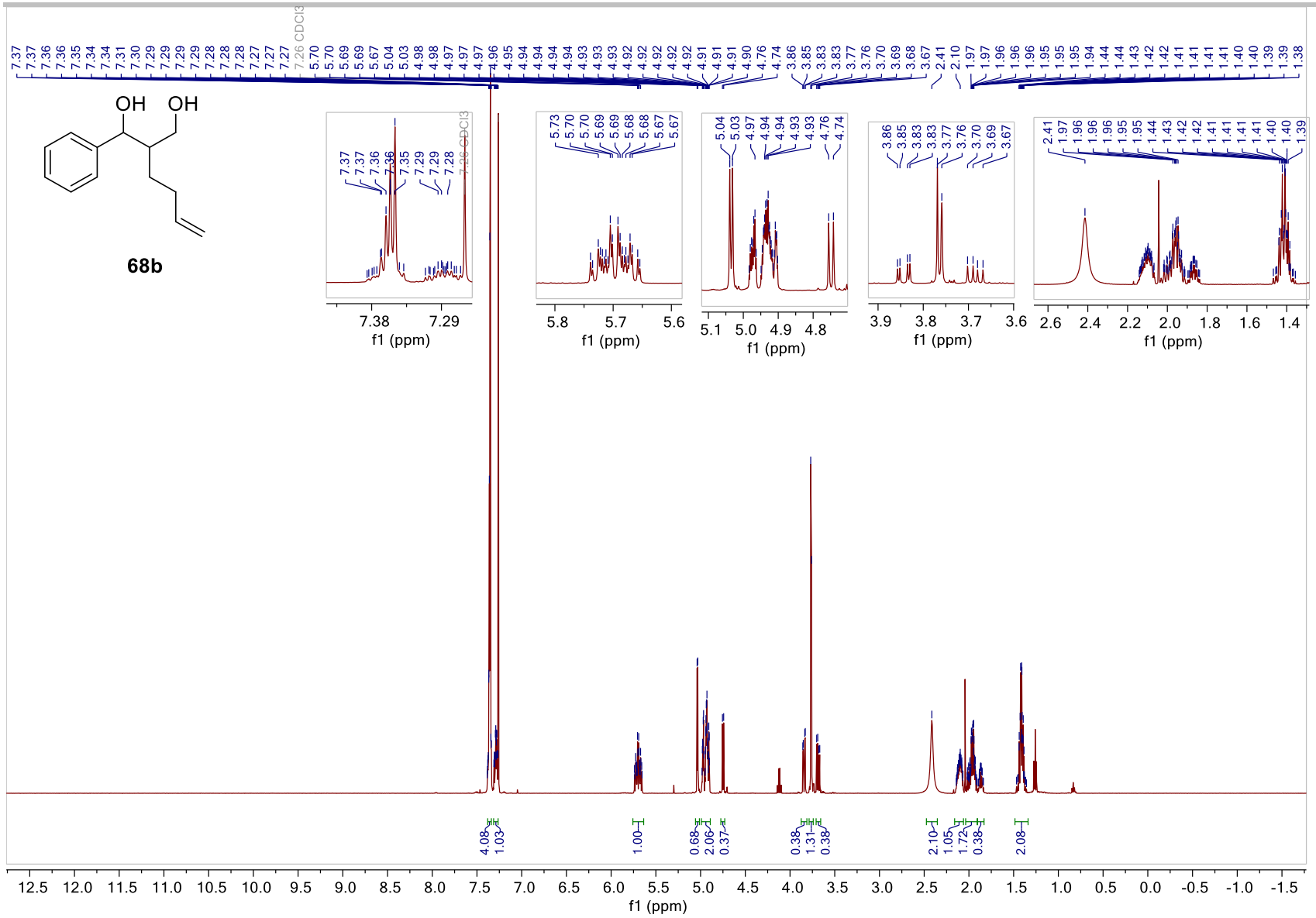


Figure S184. ^{1}H NMR (500 MHz, $CDCl_3$) of **68b**.

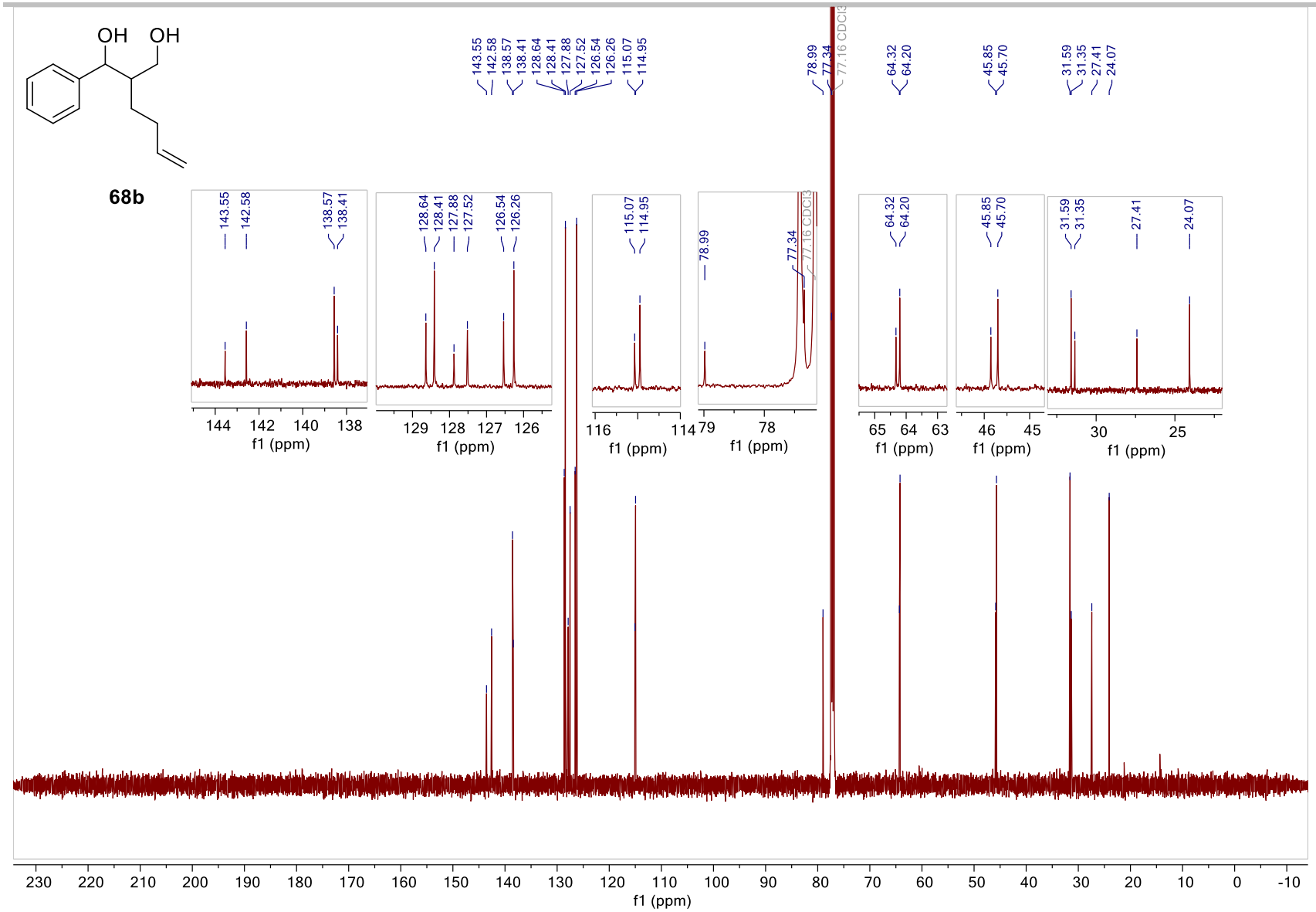


Figure S185. ^{13}C NMR (125 MHz, $CDCl_3$) of **68b**.

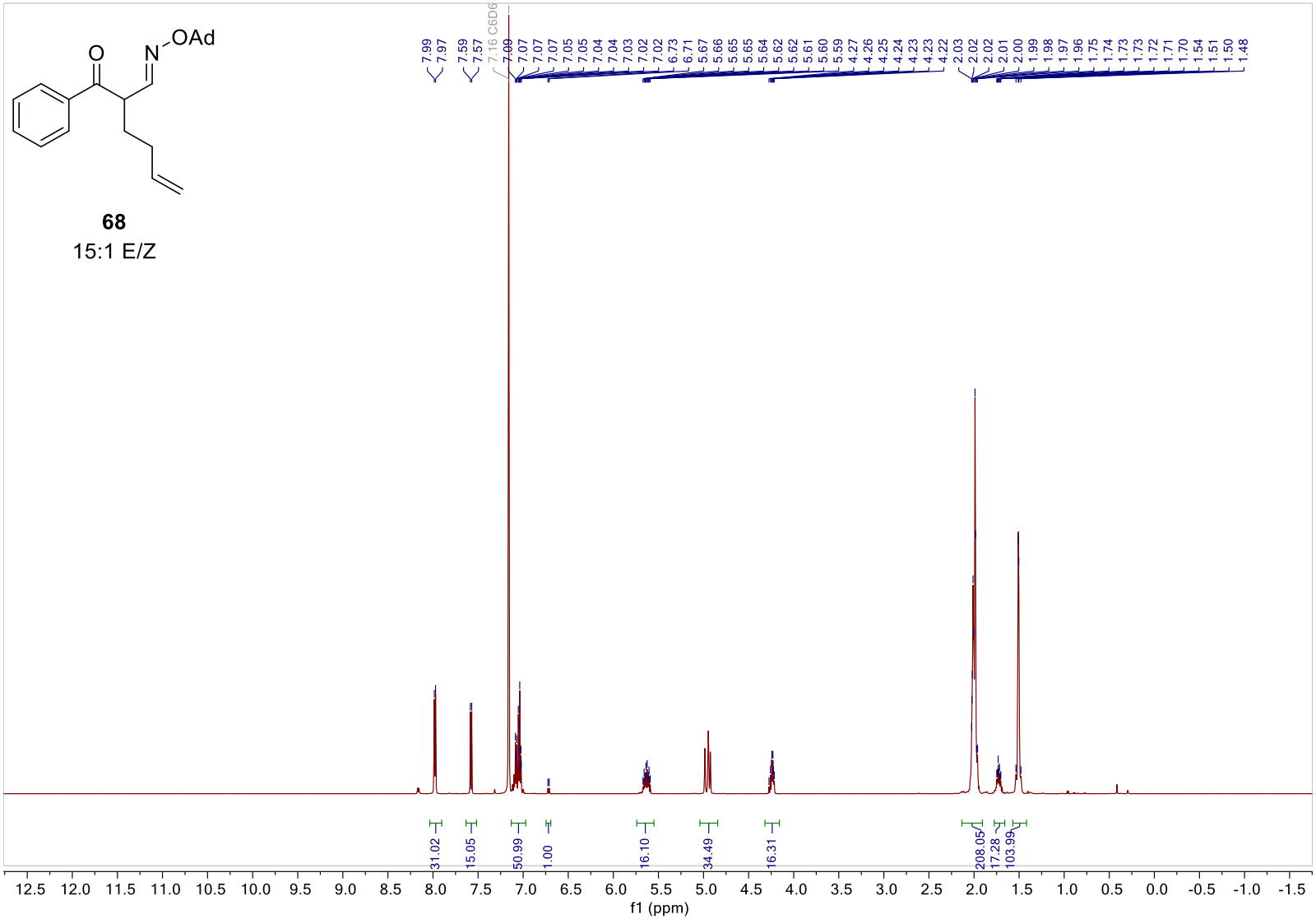


Figure S186. ^{1}H NMR (500 MHz, C_6D_6) of **68**.

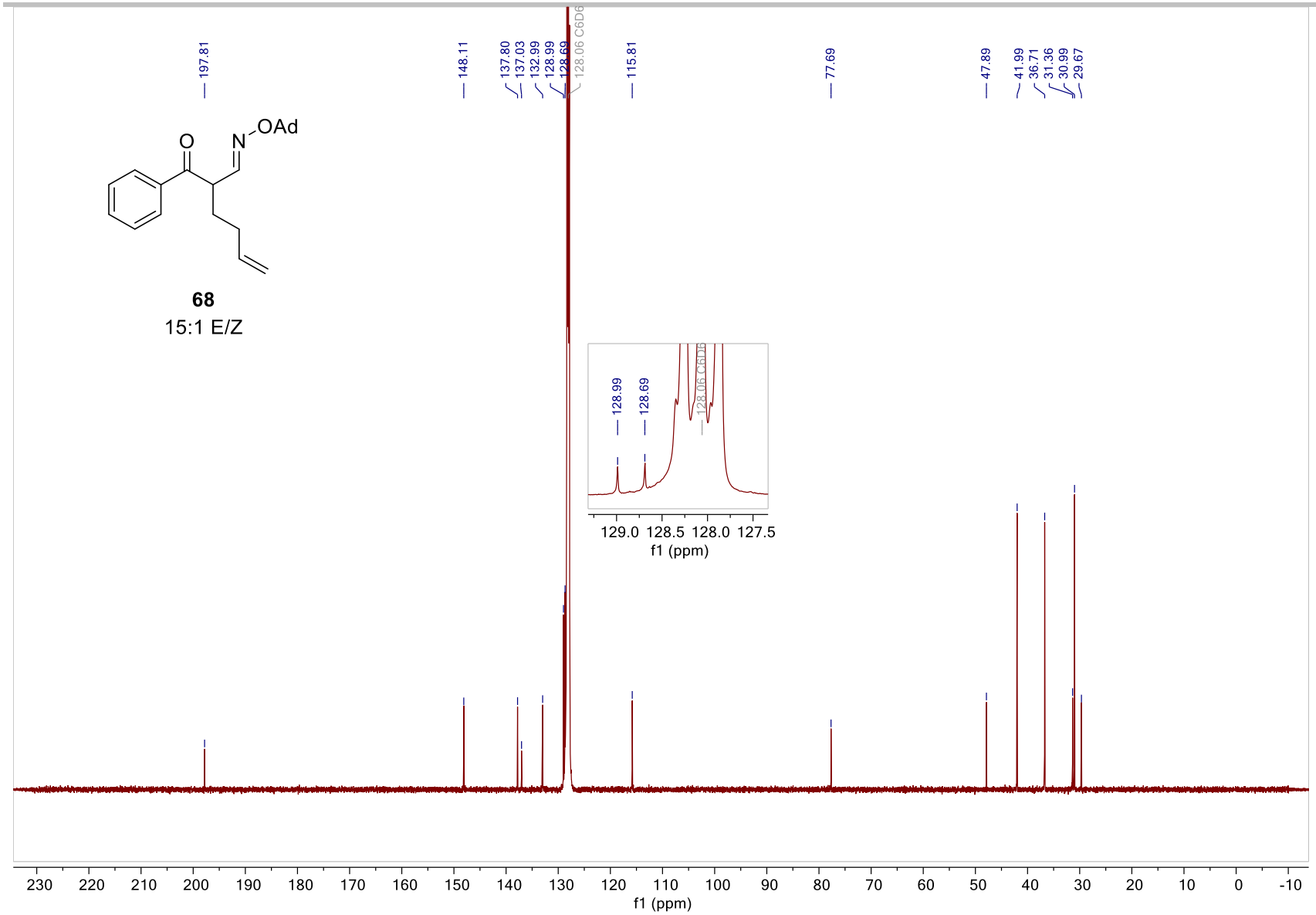


Figure S187. ^{13}C NMR (125 MHz, C_6D_6) of **68**.

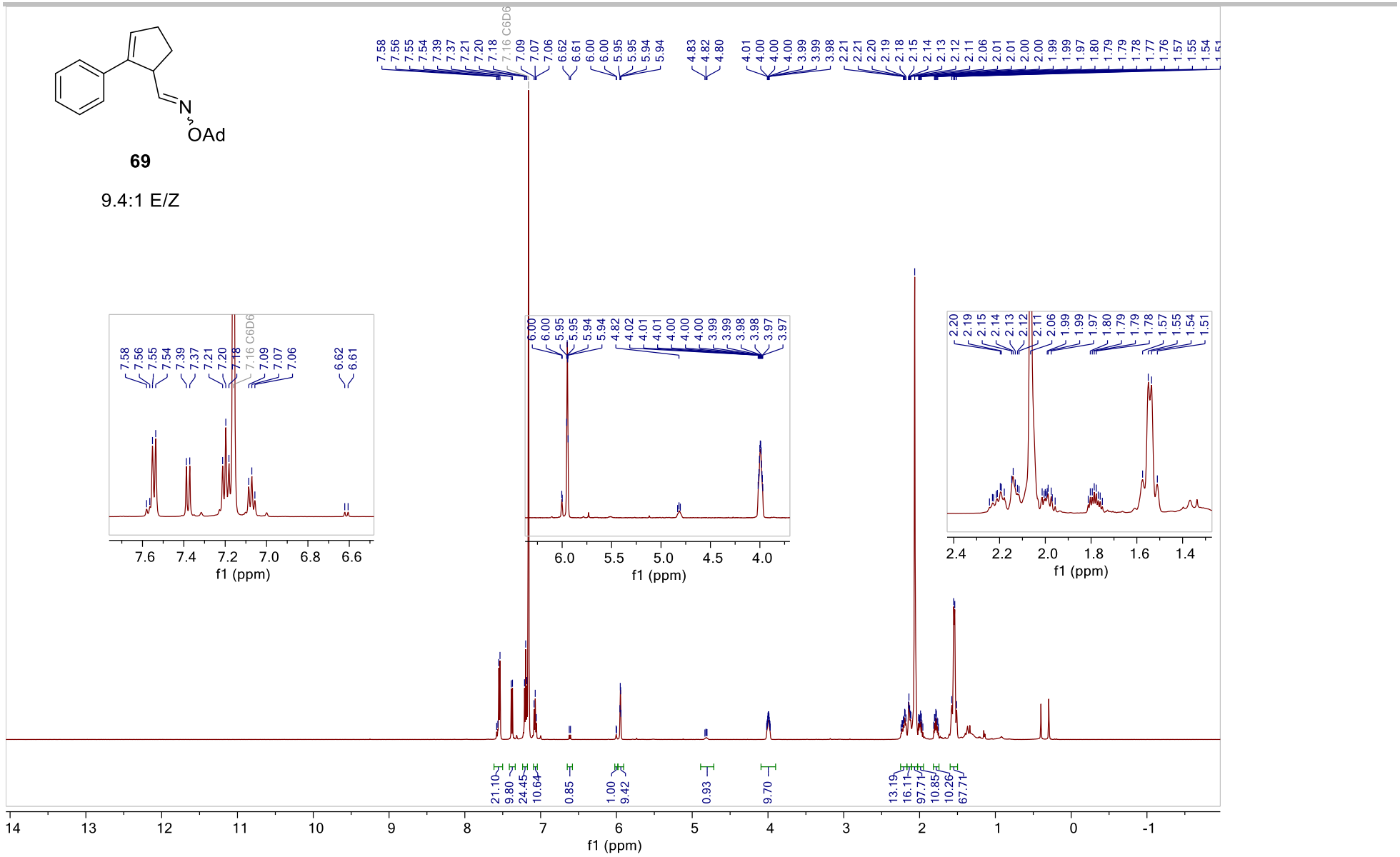


Figure S188. ^{1}H NMR (500 MHz, C_6D_6) of **69**.

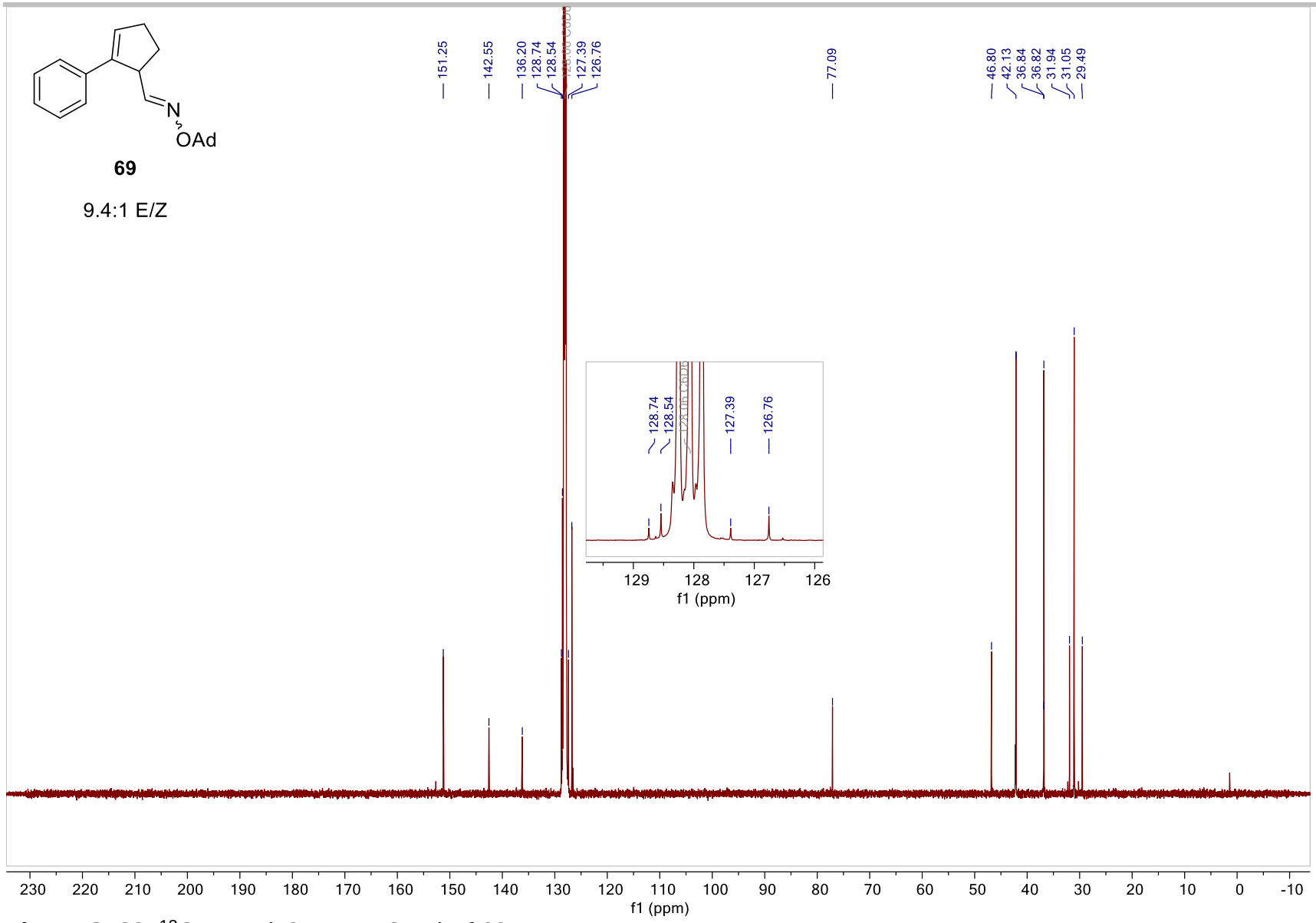


Figure S189. ^{13}C NMR (125 MHz, C_6D_6) of **69**.

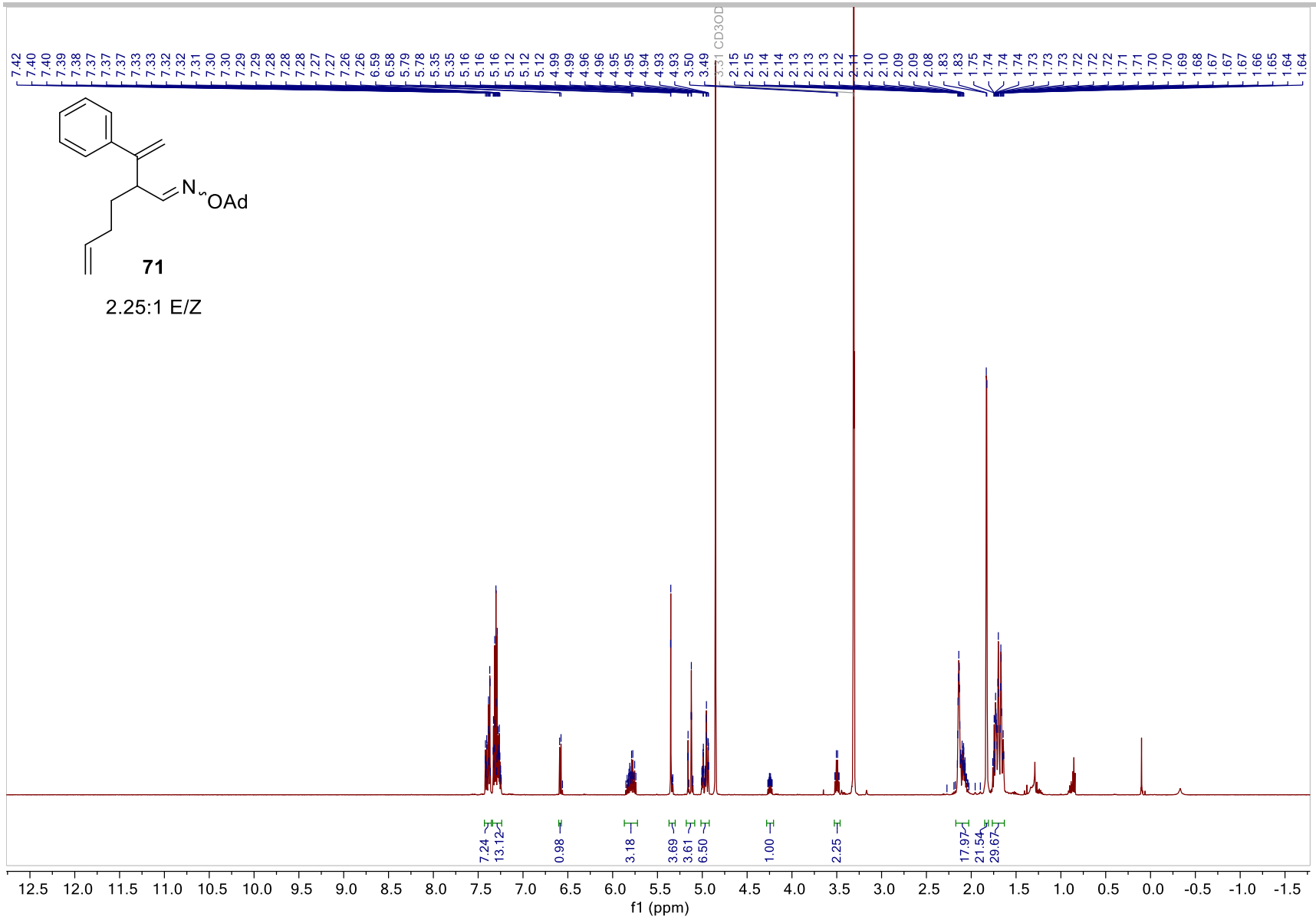


Figure S190. ^{1}H NMR (500 MHz, CD_3OD) of **71**.

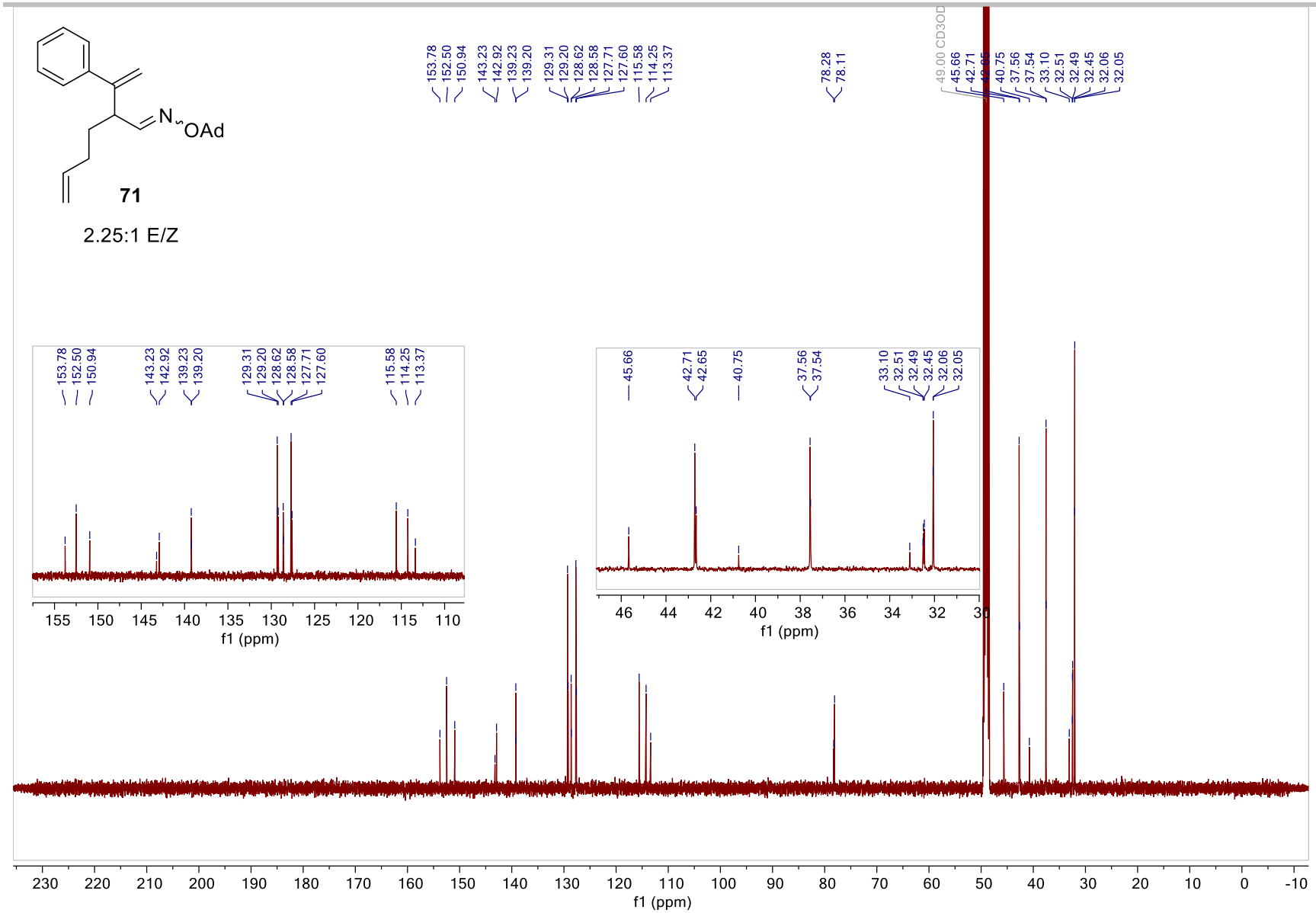


Figure S191. ^{13}C NMR (125 MHz, CD_3OD) of **71**.

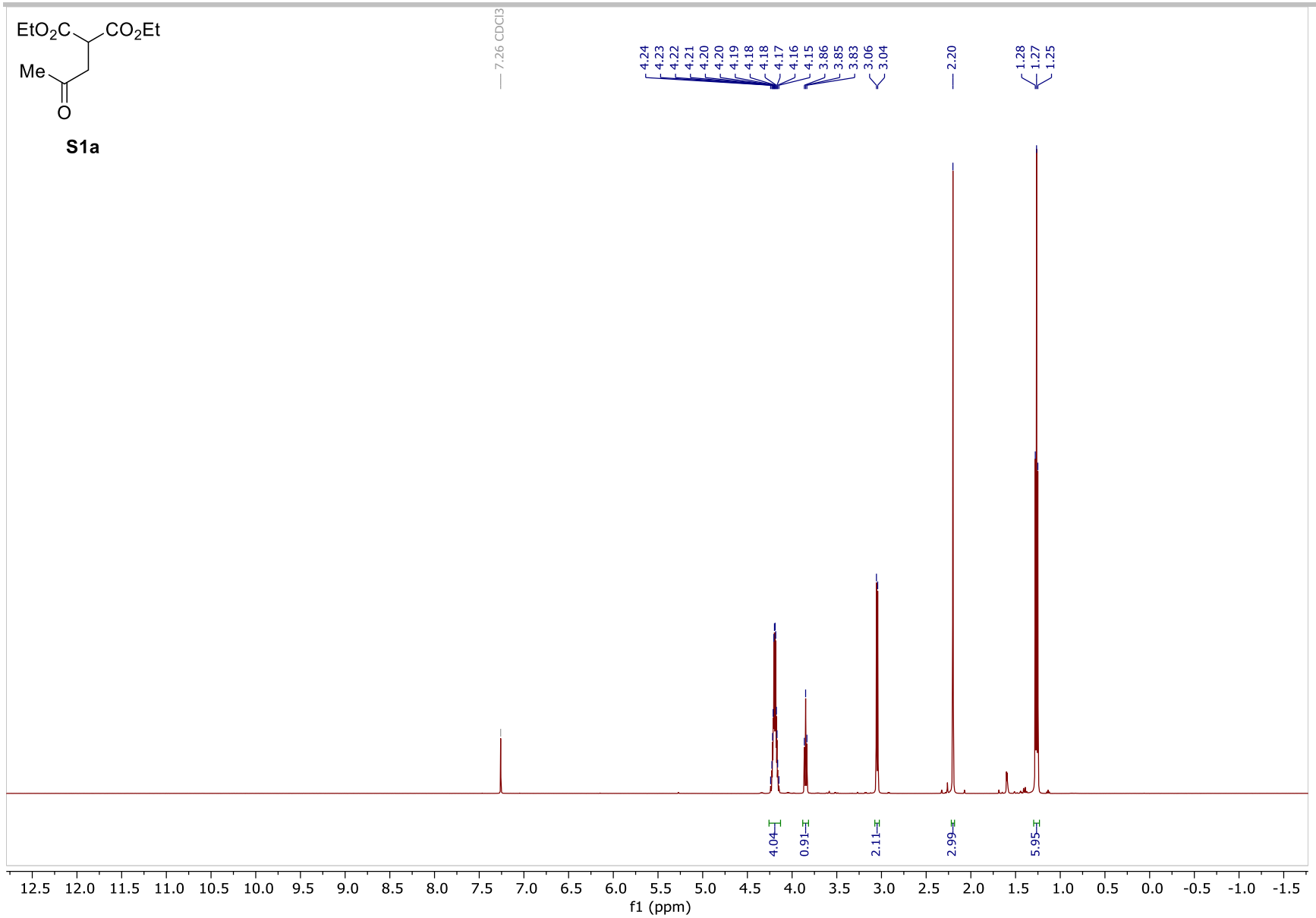


Figure S192. ^{1}H NMR (500 MHz, $CDCl_3$) of **S1a**.

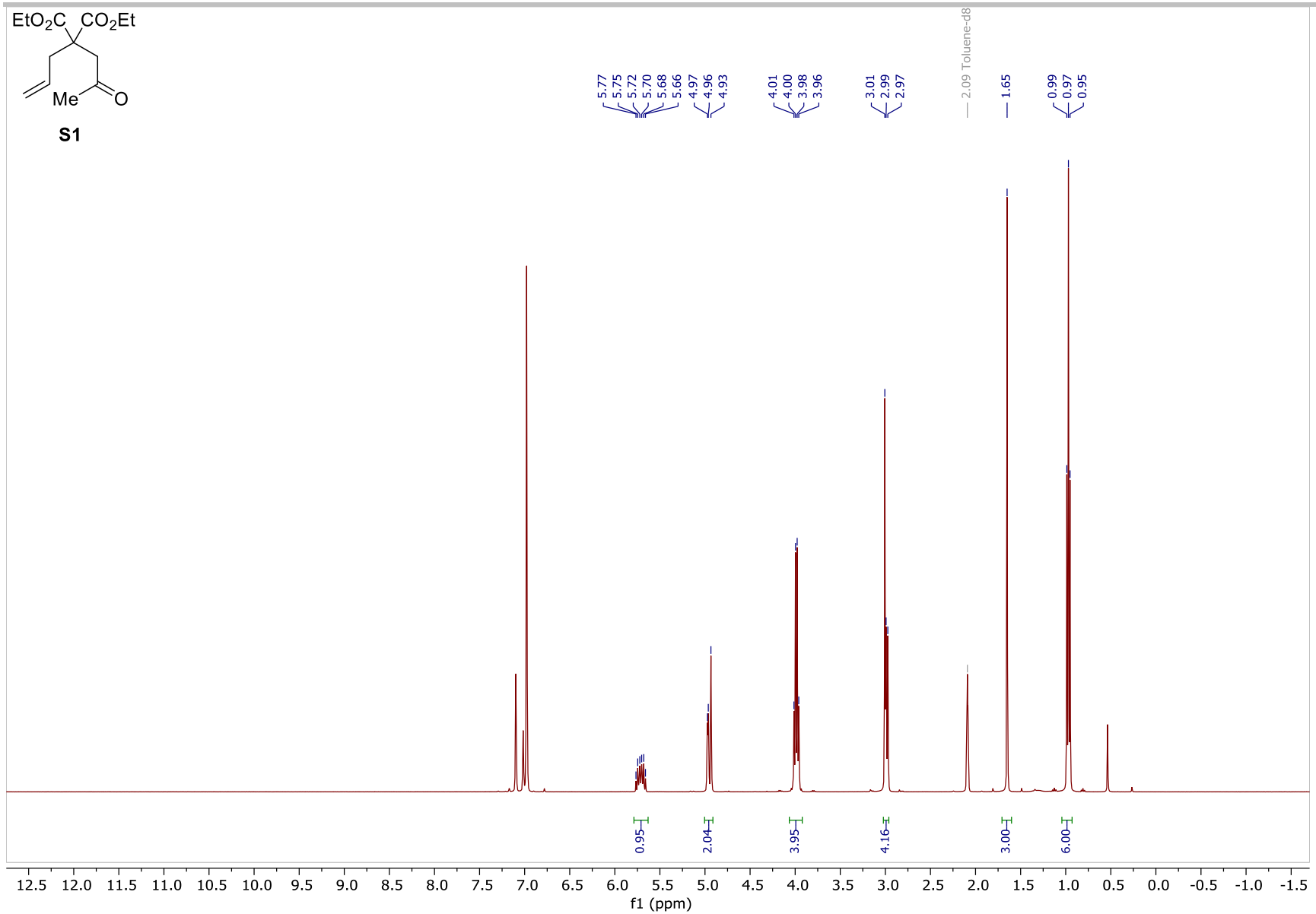


Figure S193. ^{1}H NMR (400 MHz, toluene-d_8) of **S1**.

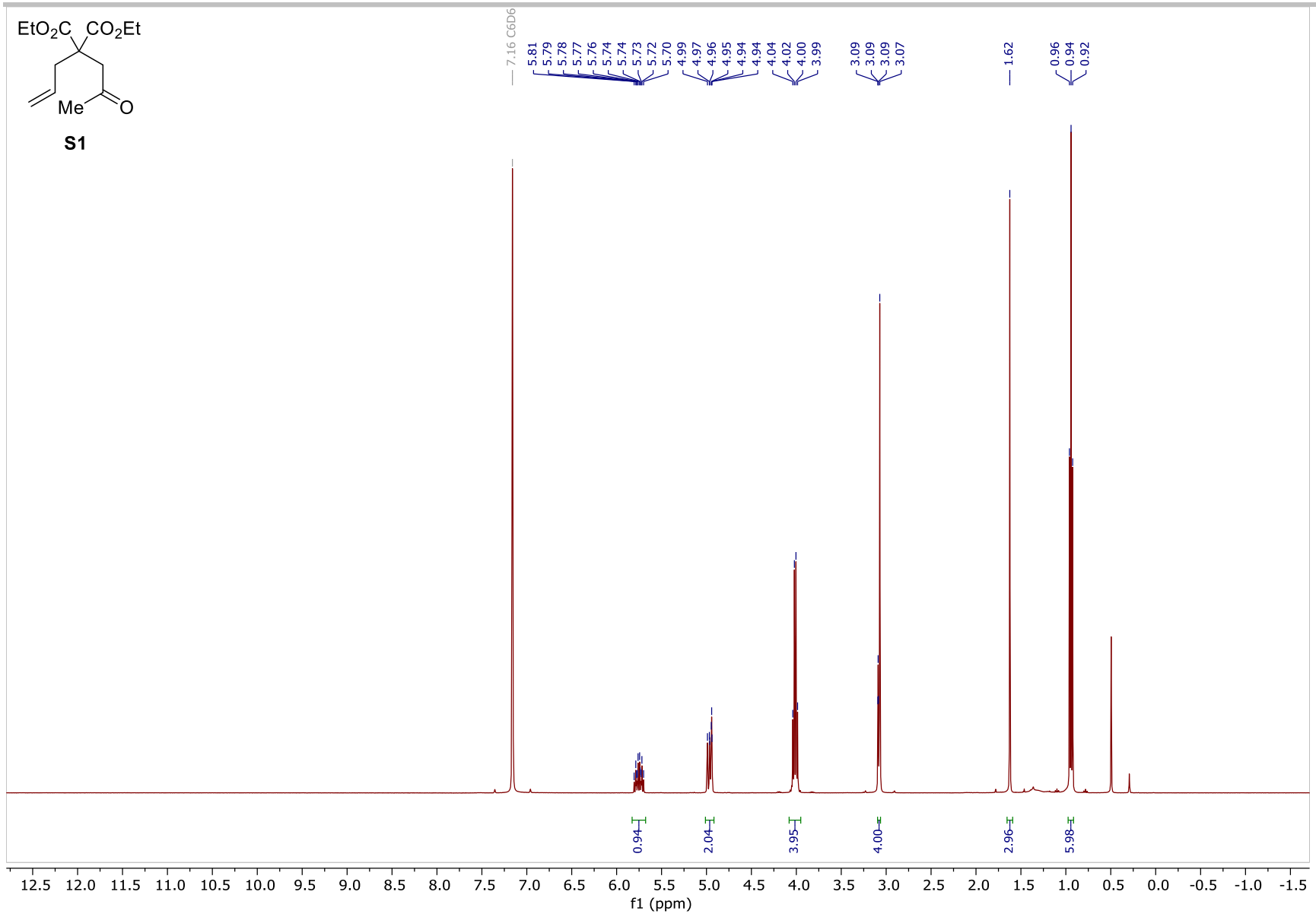


Figure S194. ^{1}H NMR (400 MHz, C_6D_6) of **S1**.

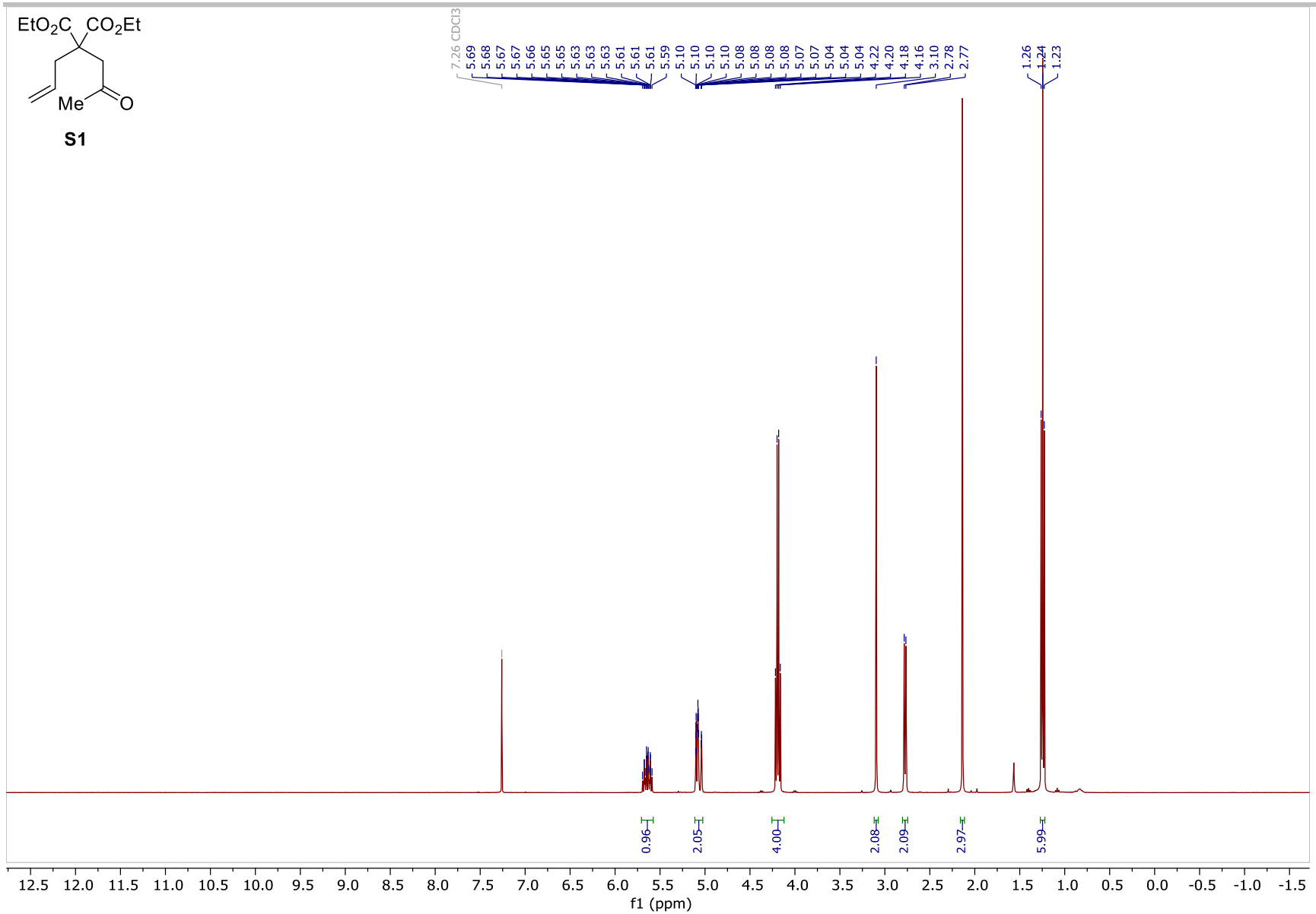


Figure S195. ^{1}H NMR (400 MHz, $CDCl_3$) of **S1**.

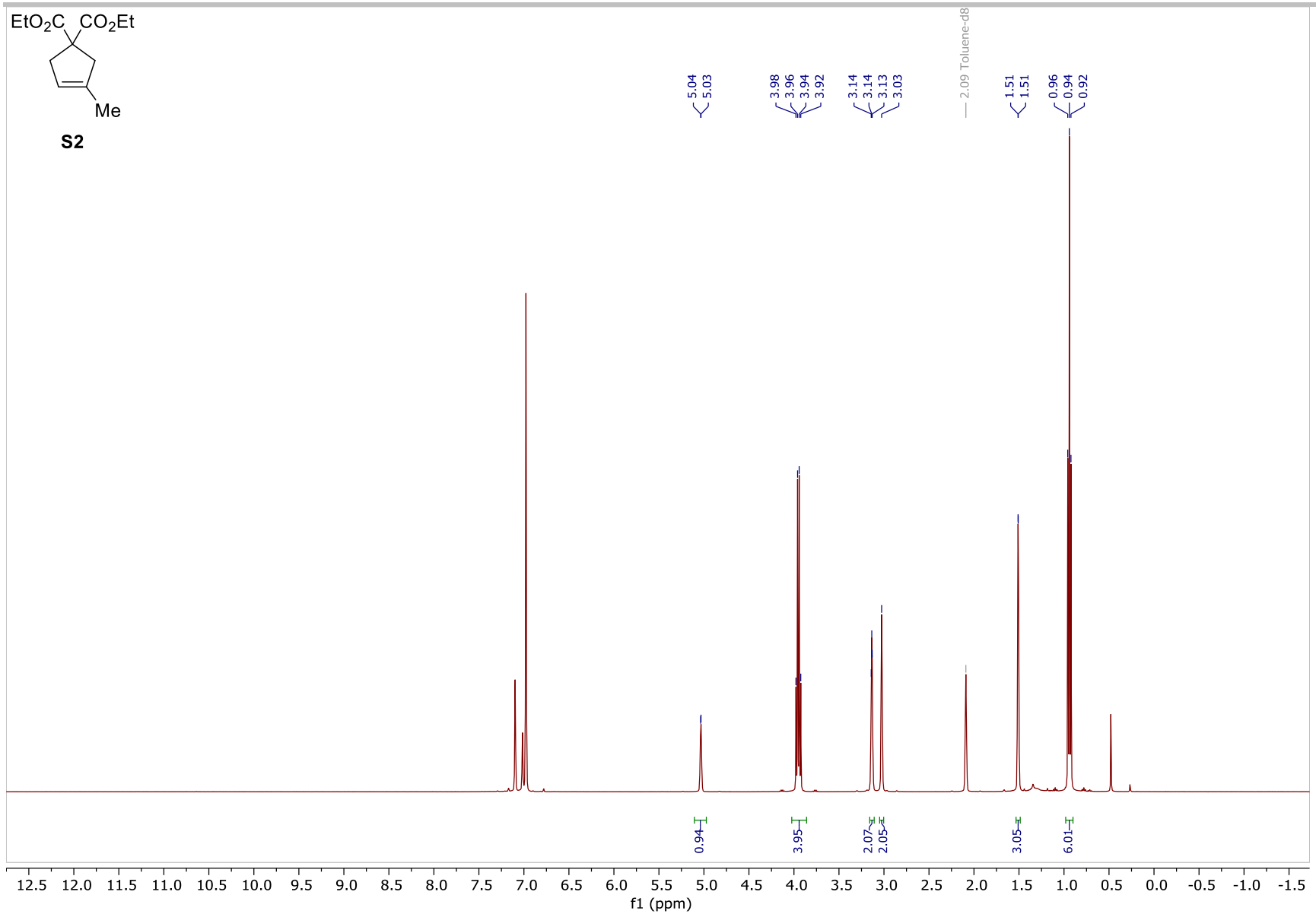


Figure S196. ^{1}H NMR (400 MHz, toluene-d_8) of **S2**.

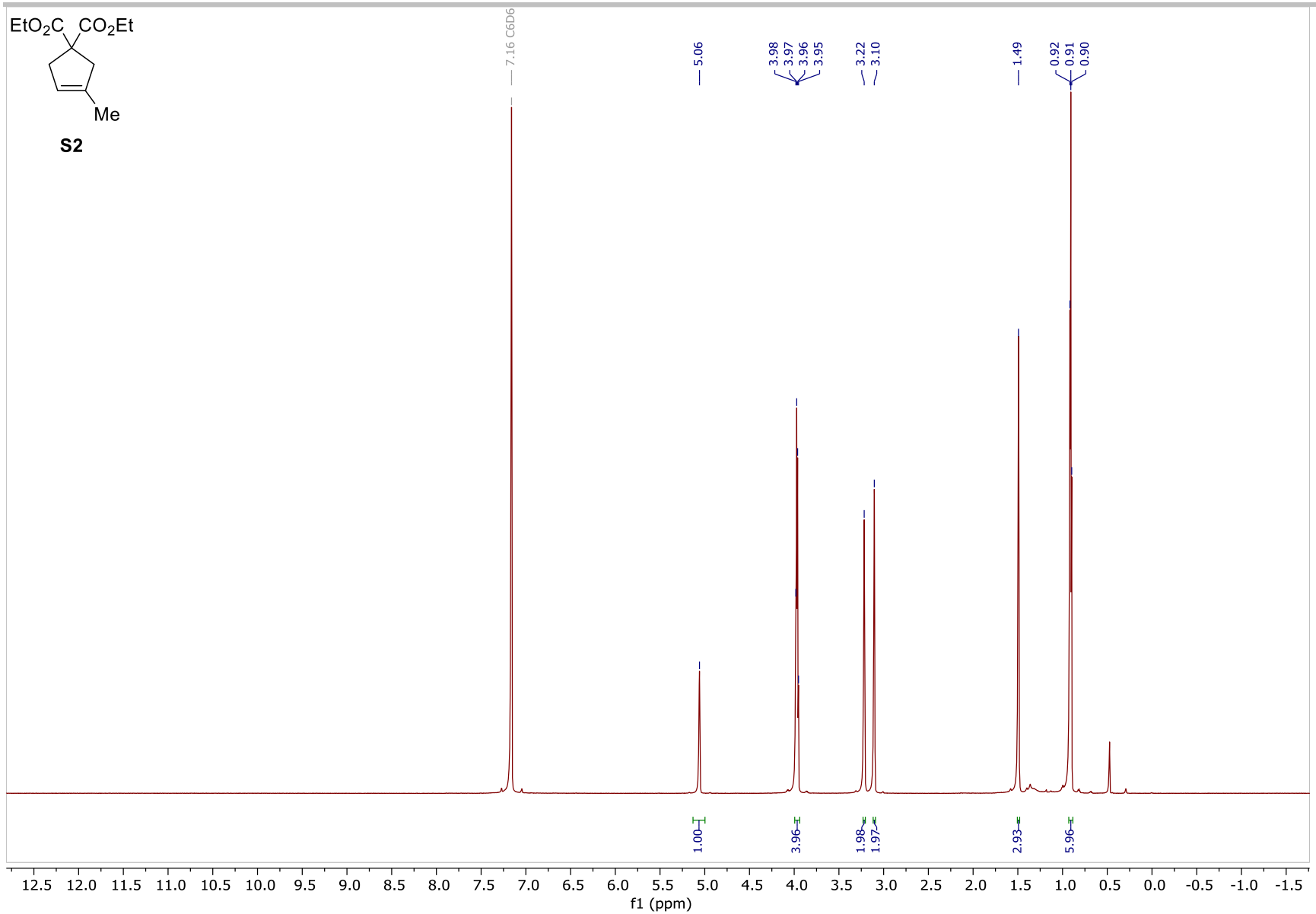


Figure S197. ^{1}H NMR (700 MHz, C_6D_6) of **S2**.

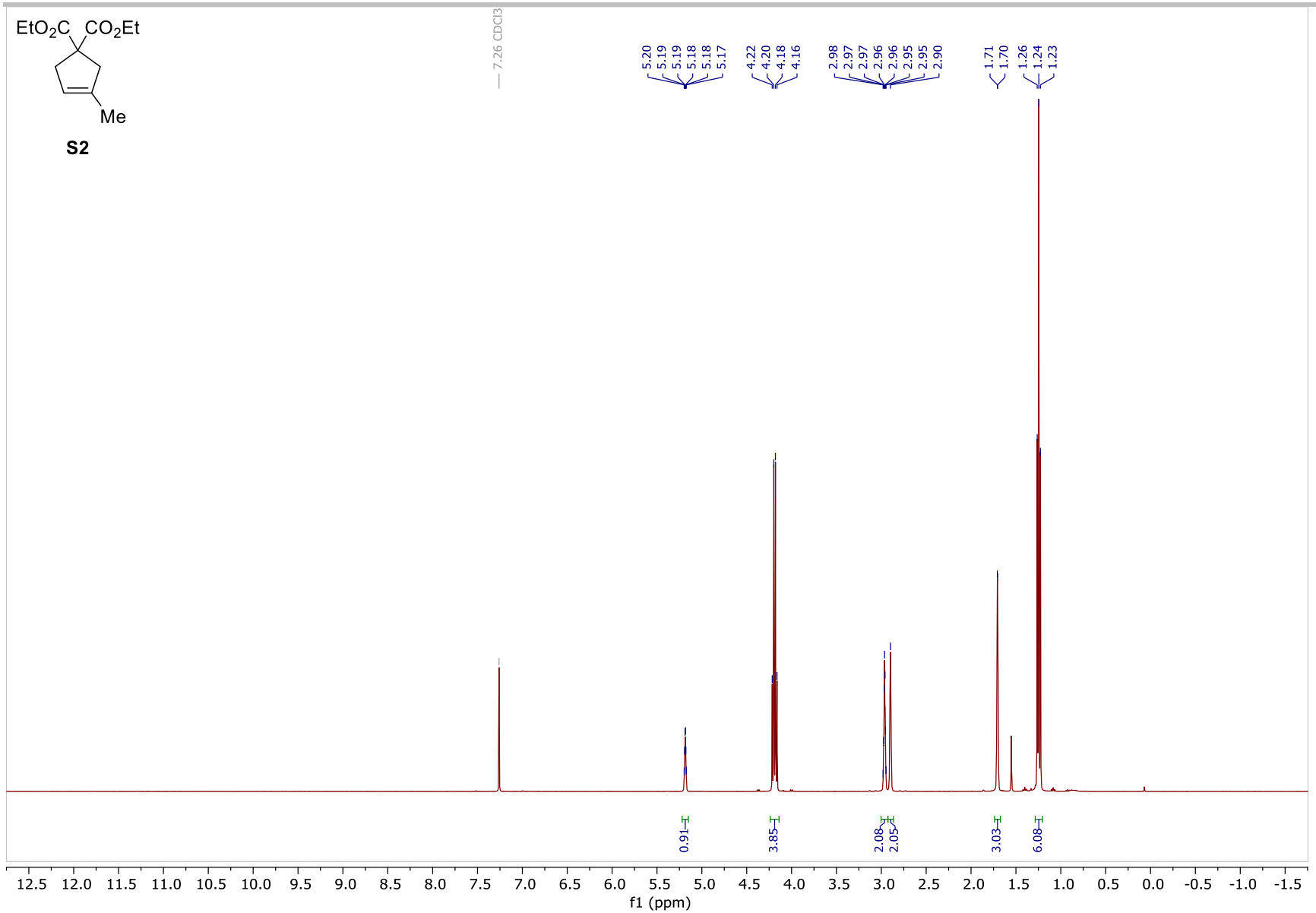


Figure S198. ^{1}H NMR (400 MHz, $CDCl_3$) of **S2**.

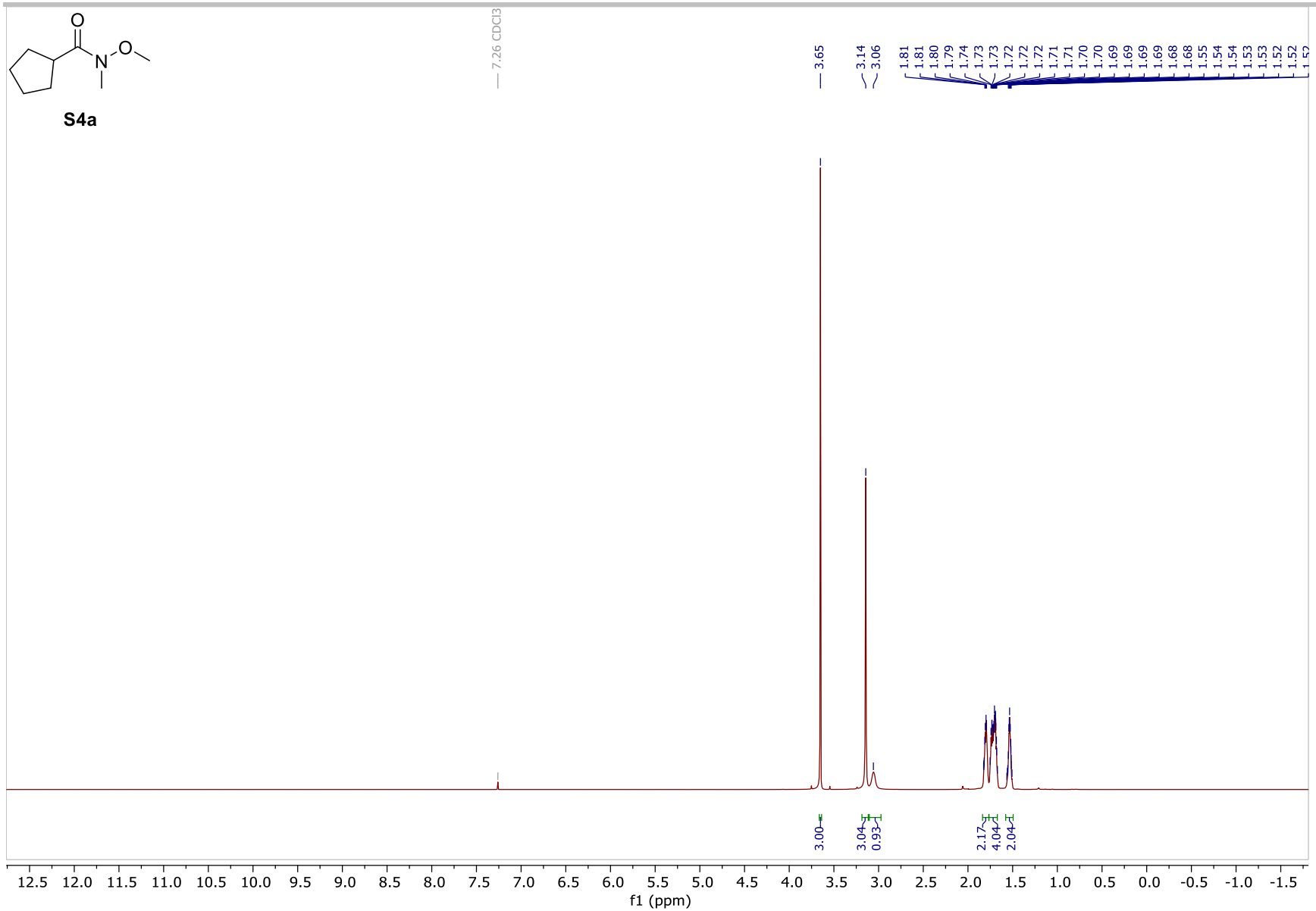


Figure S199. ^{1}H NMR (700 MHz, $CDCl_3$) of **S4a**.

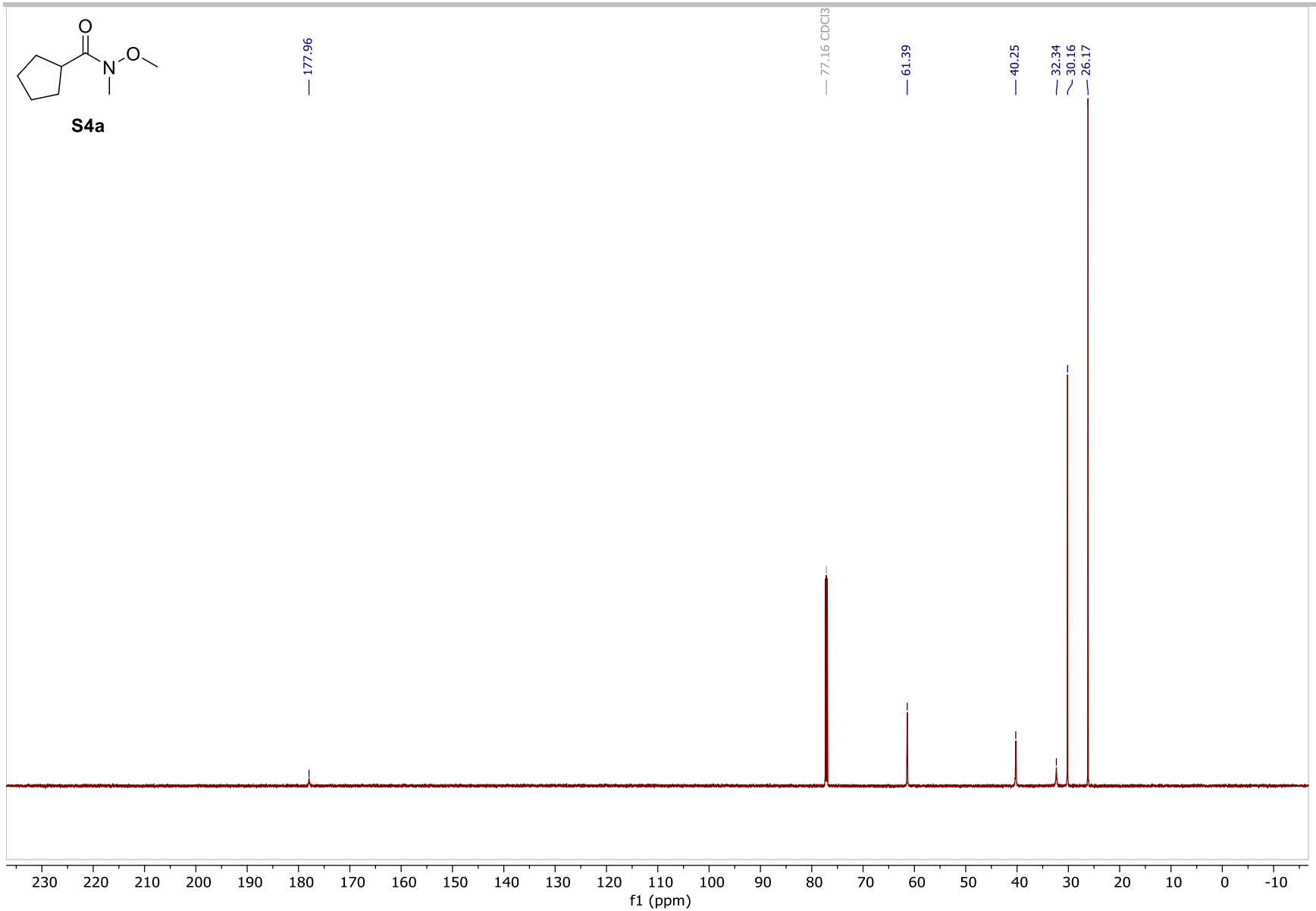


Figure S200. ^{13}C NMR (175 MHz, $CDCl_3$) of **S4a**.

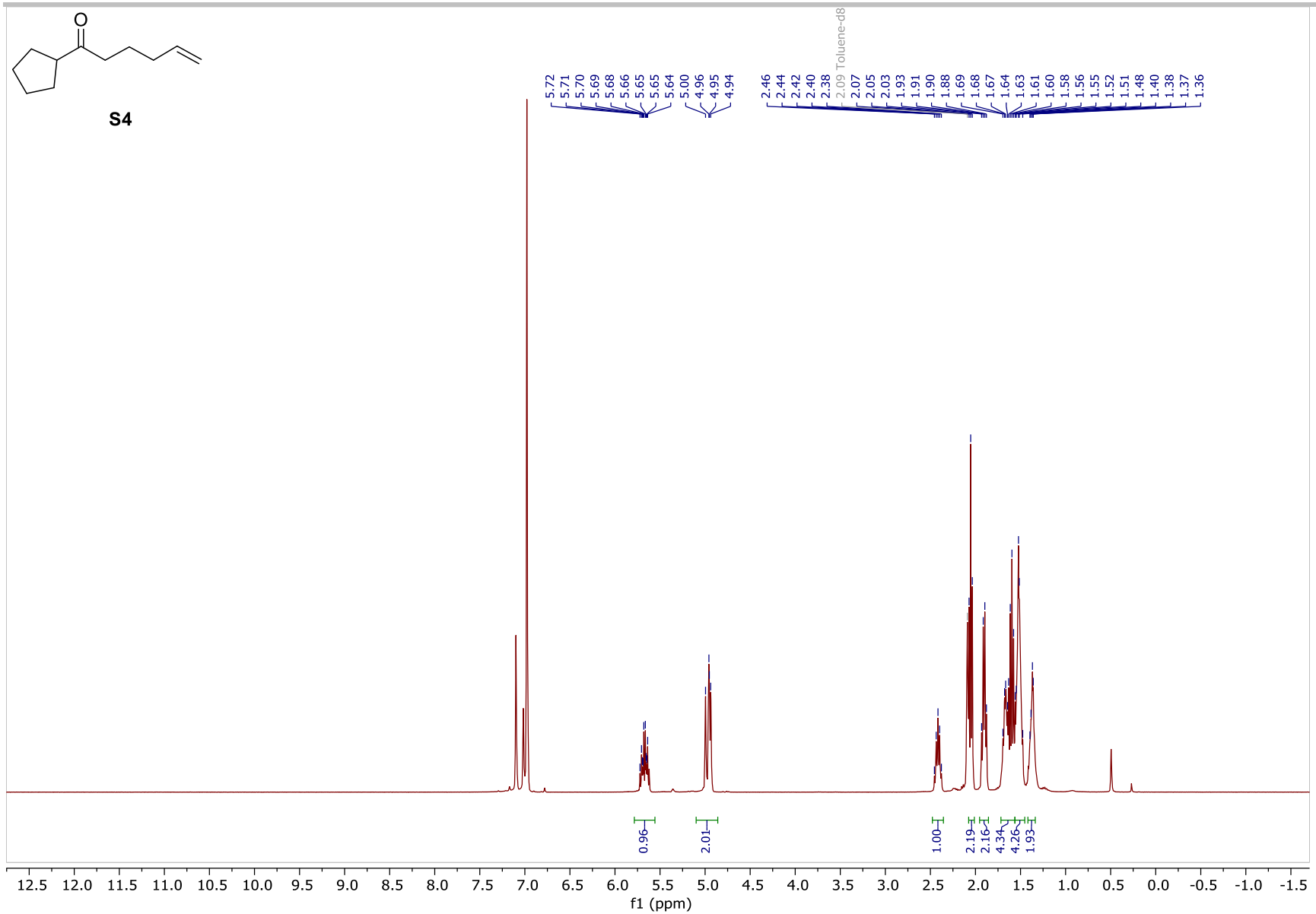


Figure S201. ^{1}H NMR (400 MHz, toluene-d_8) of **S4**.

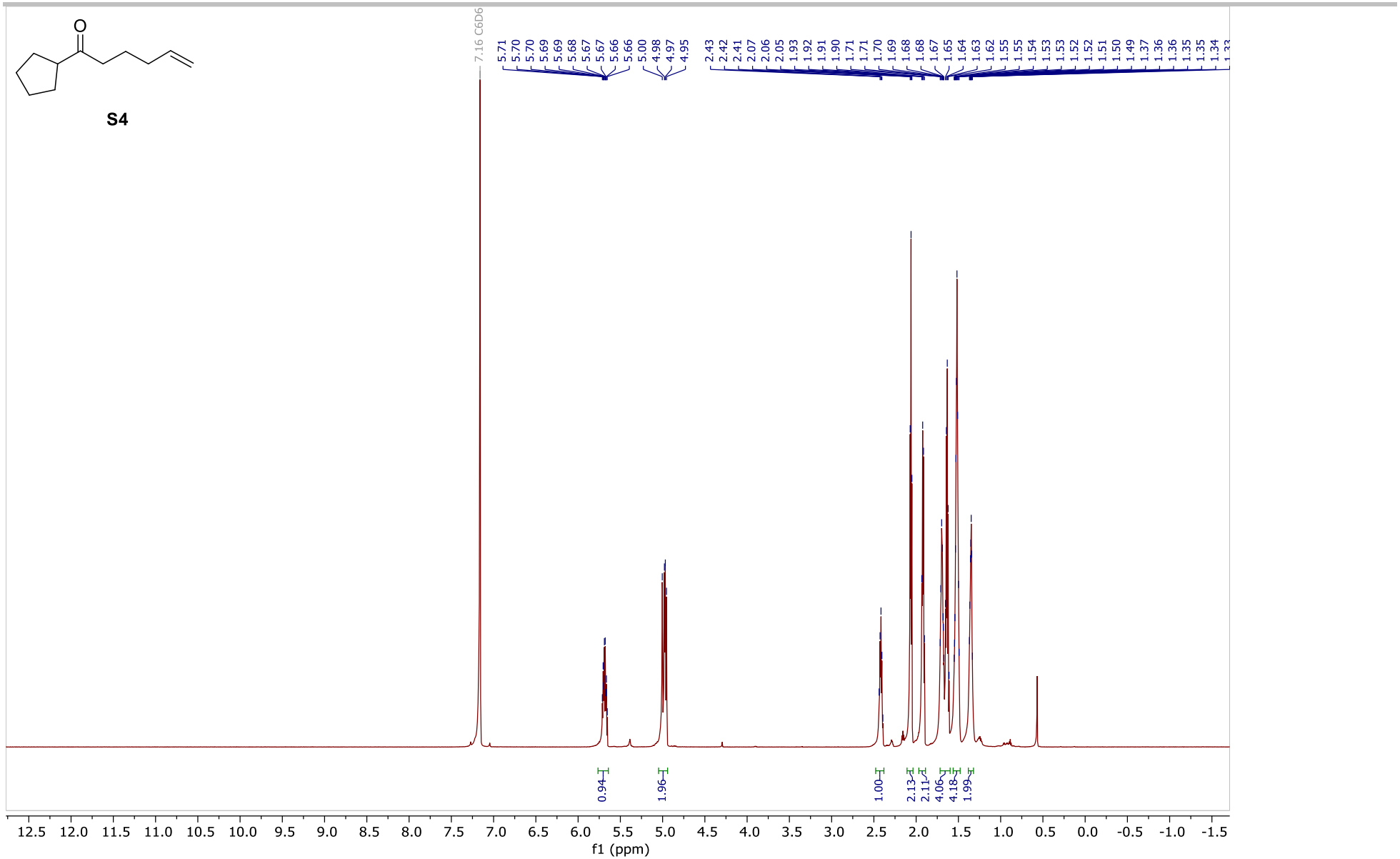


Figure S202. ^{1}H NMR (700 MHz, C_6D_6) of **S4**.

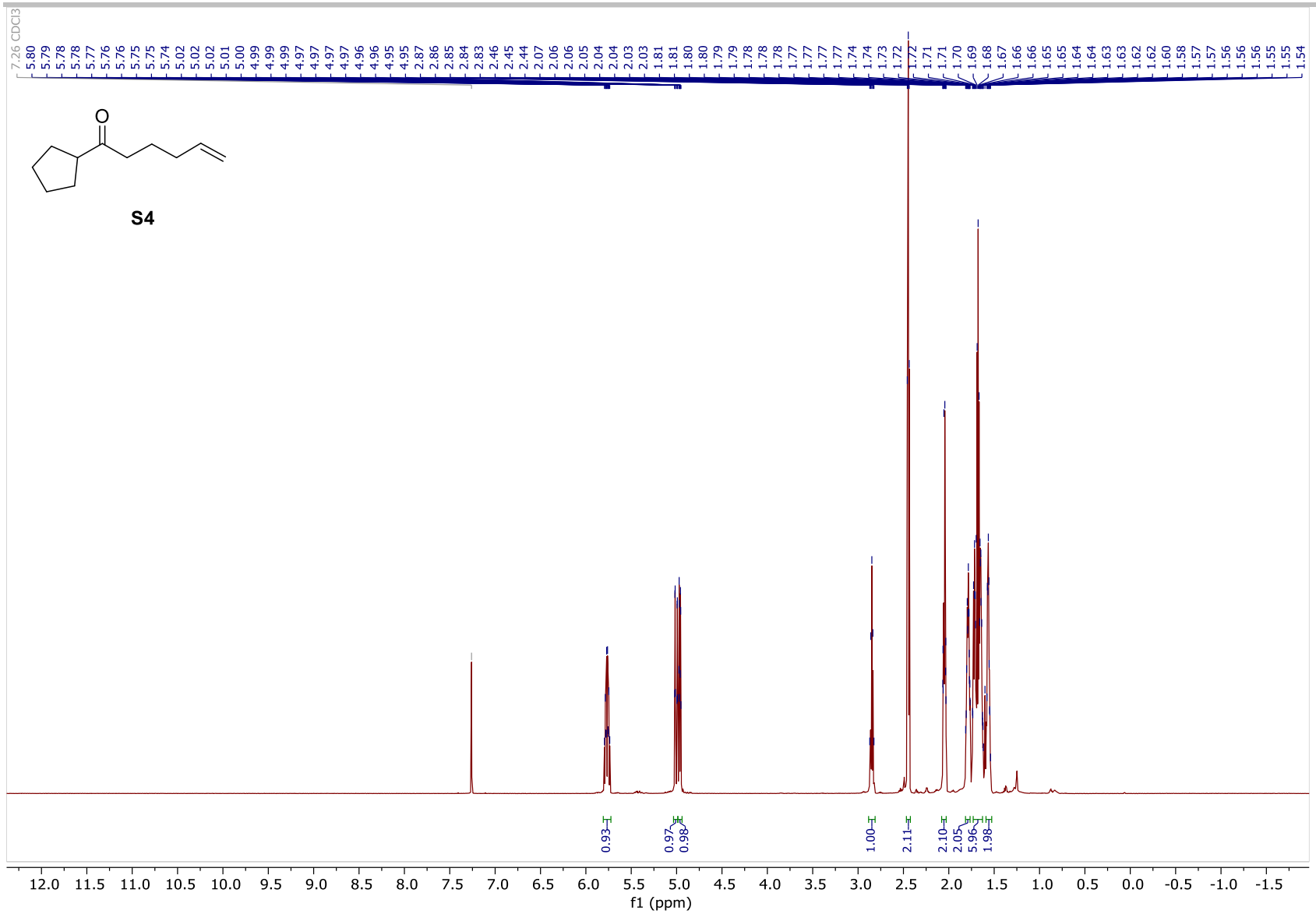


Figure S203. ^{1}H NMR (700 MHz, $CDCl_3$) of **S4**.

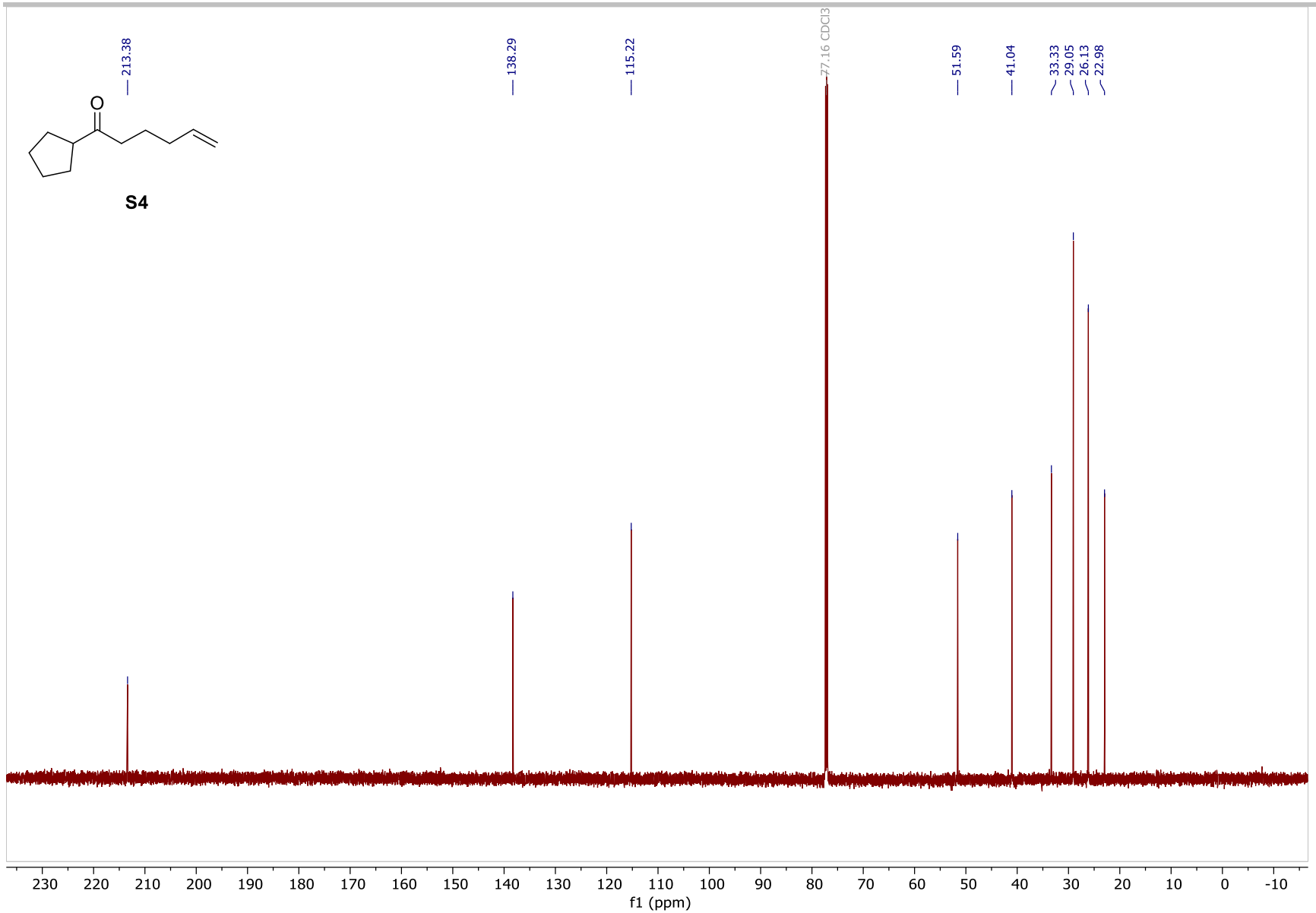


Figure S204. ^{13}C NMR (175 MHz, $CDCl_3$) of **S4**.

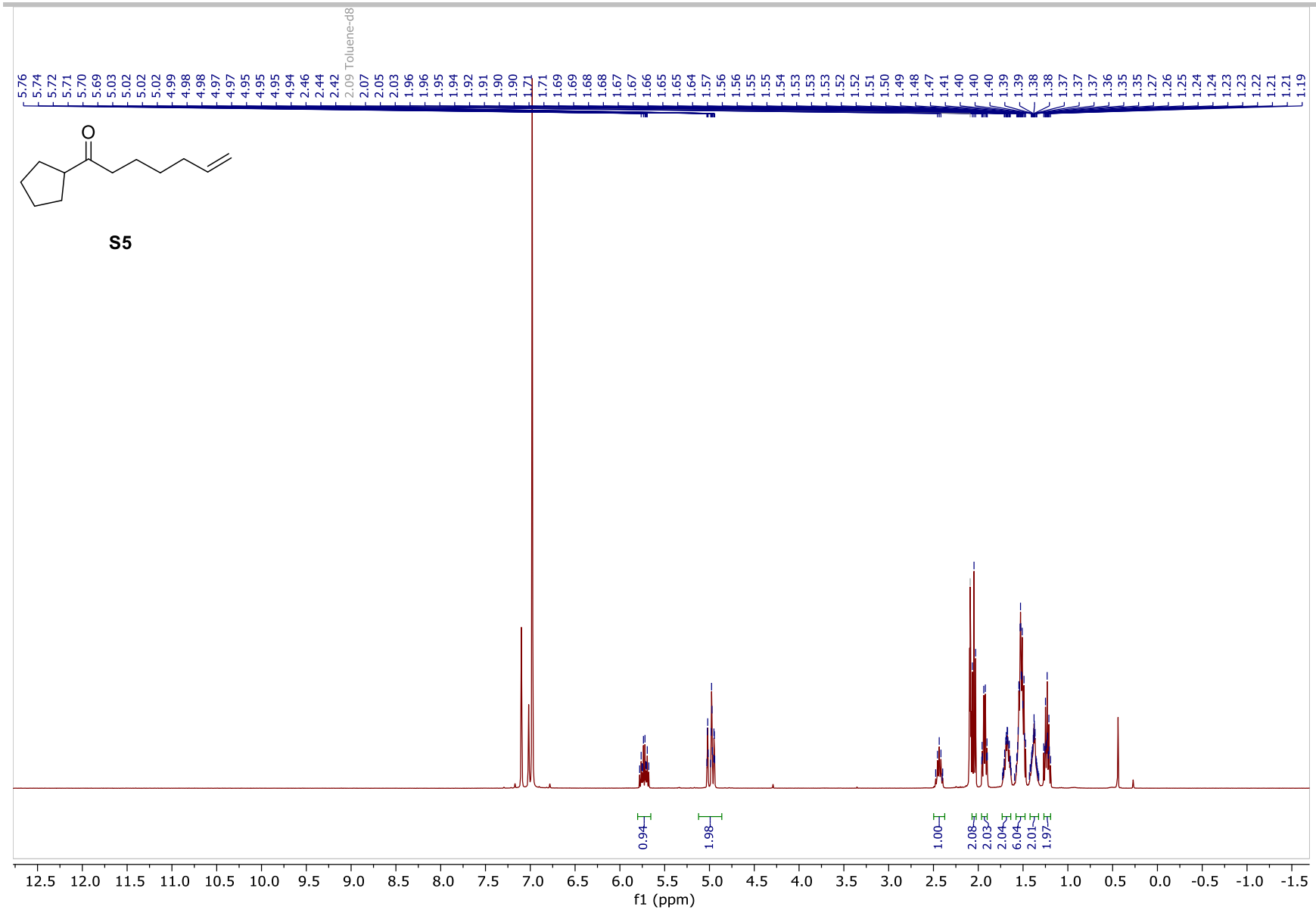


Figure S205. ^{1}H NMR (400 MHz, toluene-d$_8$) of **S5**.

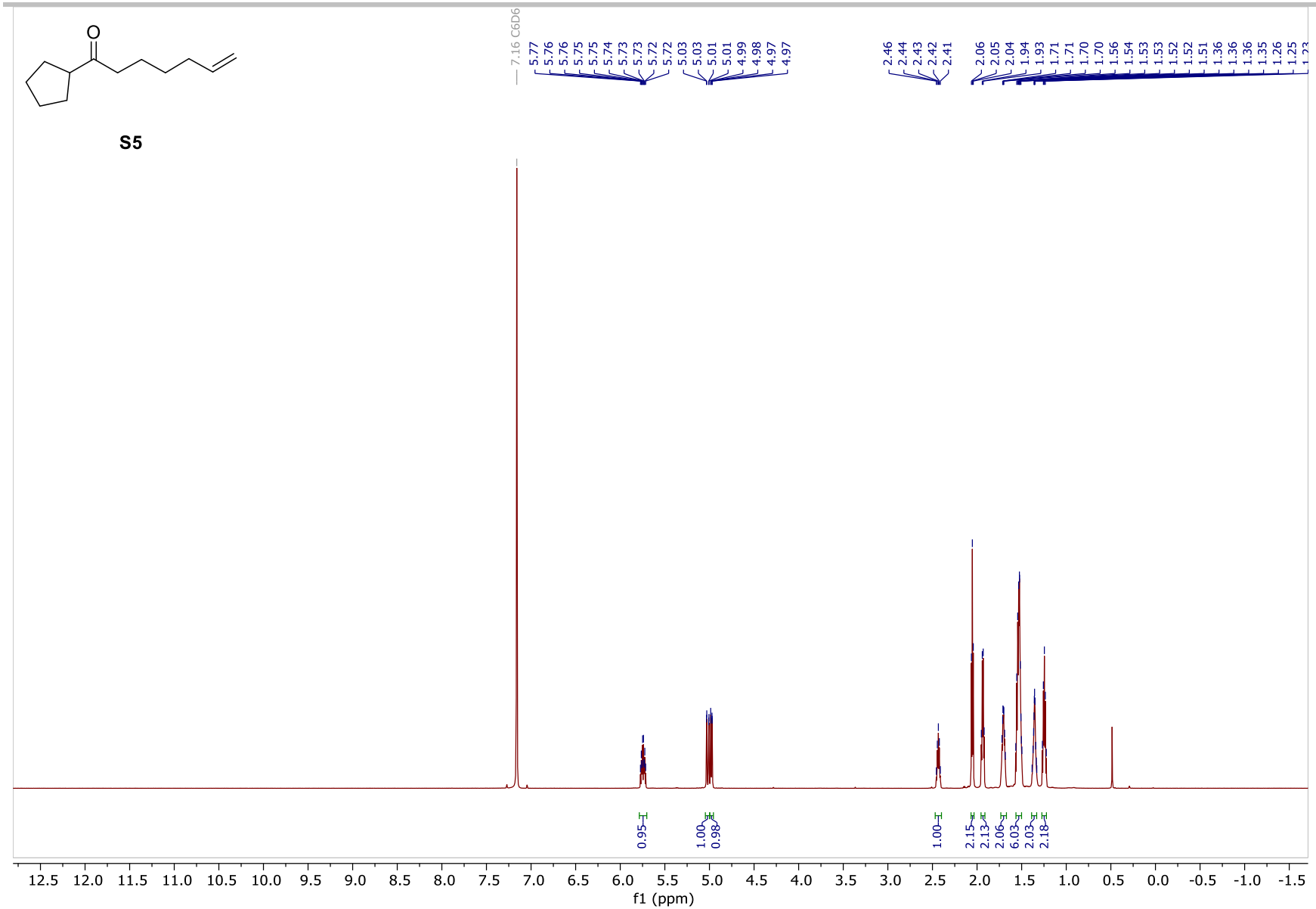


Figure S206. ^{1}H NMR (700 MHz, C_6D_6) of **S5**.

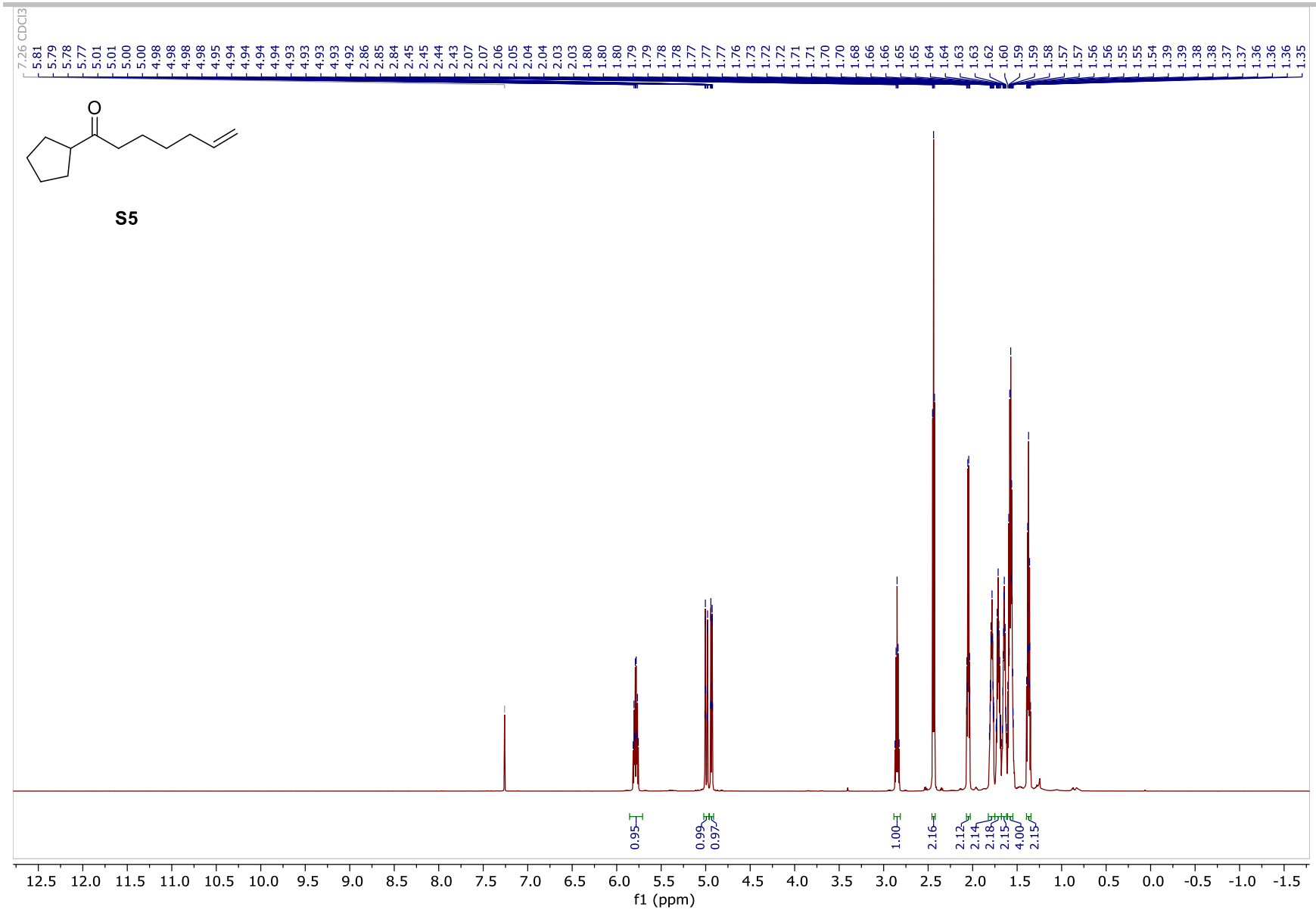


Figure S207. ^{1}H NMR (700 MHz, $CDCl_3$) of **S5**.

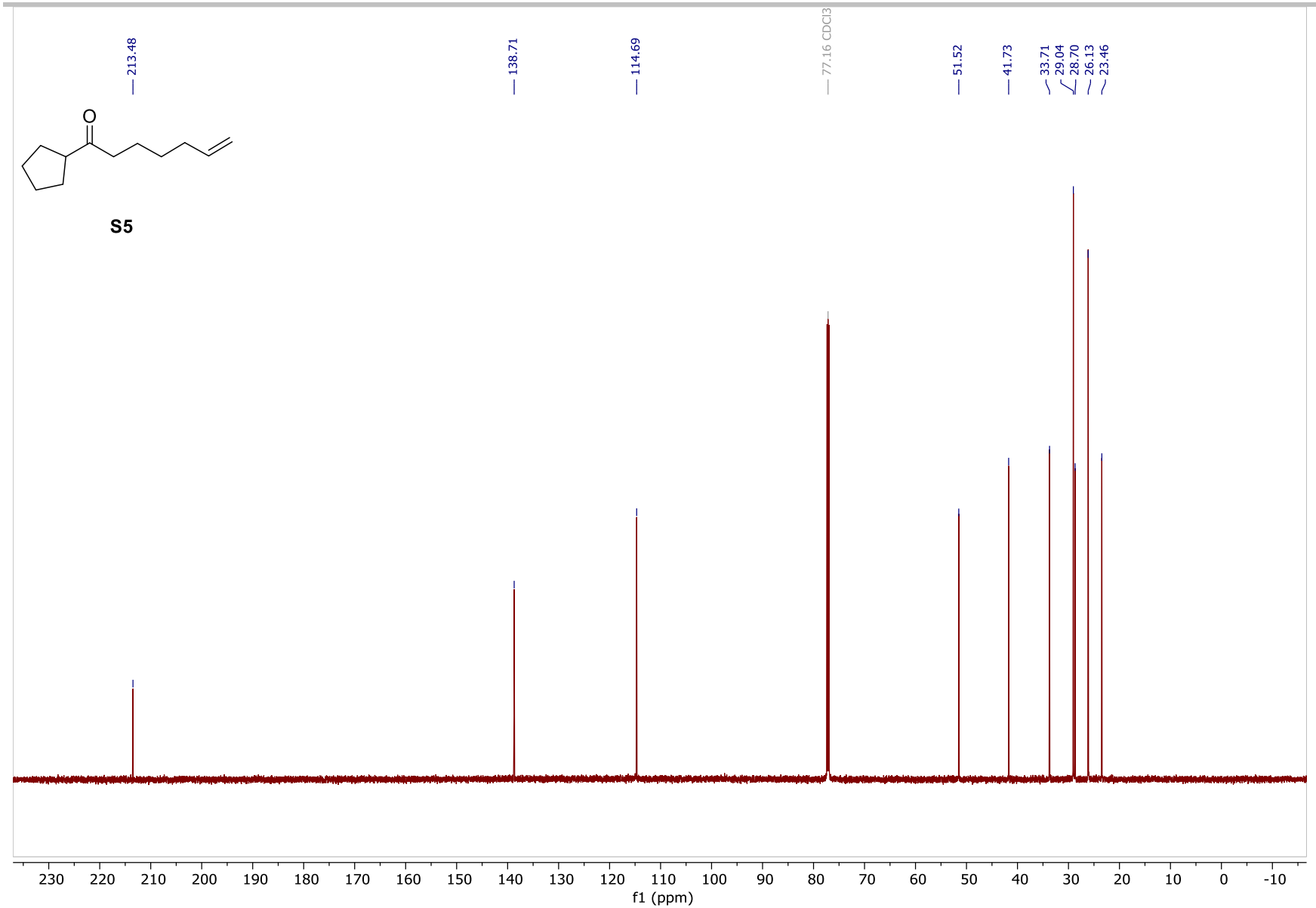


Figure S208. ^{13}C NMR (175 MHz, $CDCl_3$) of **S5**.

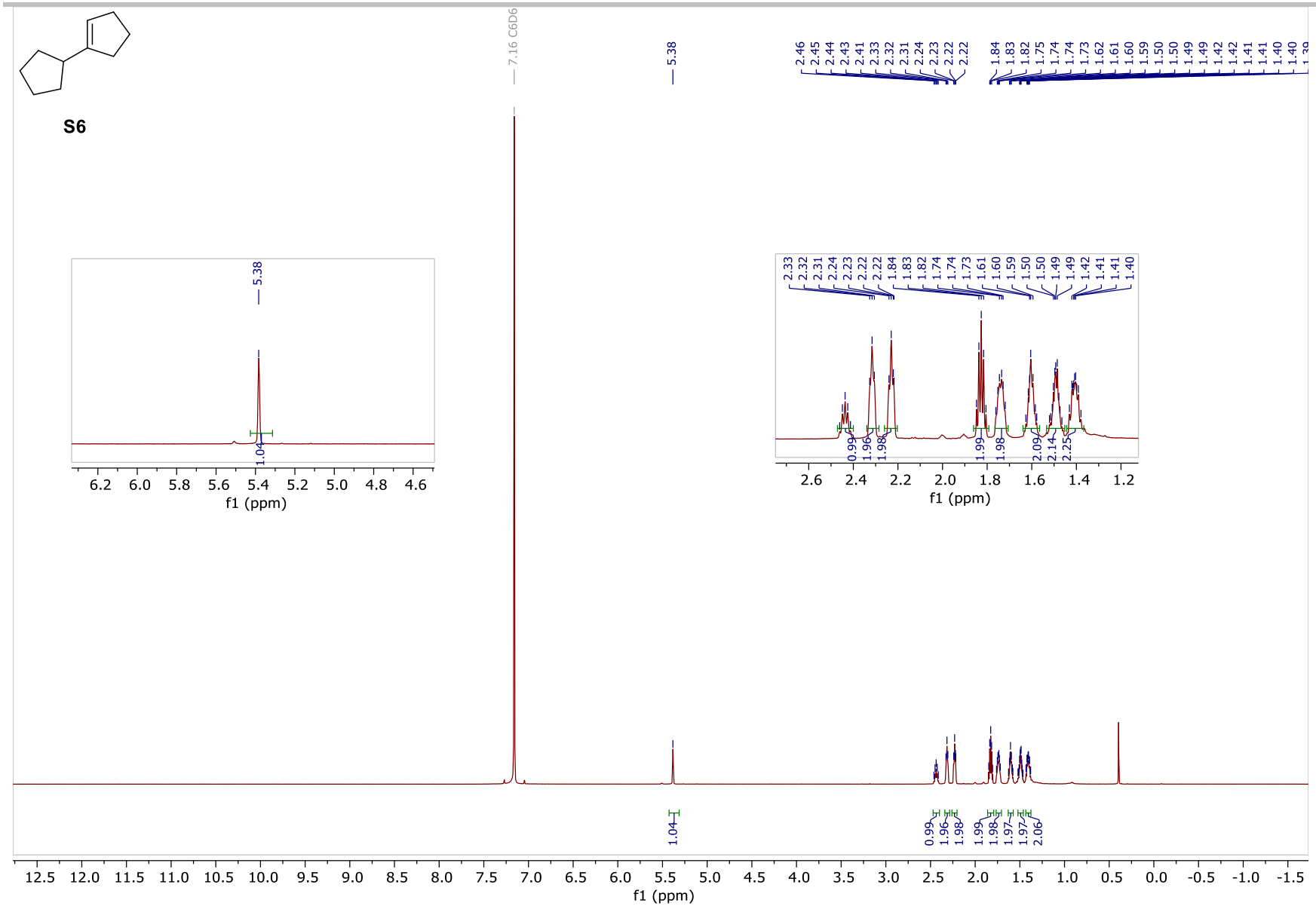


Figure S209. ^{1}H NMR (700 MHz, C_6D_6) of **S6**.

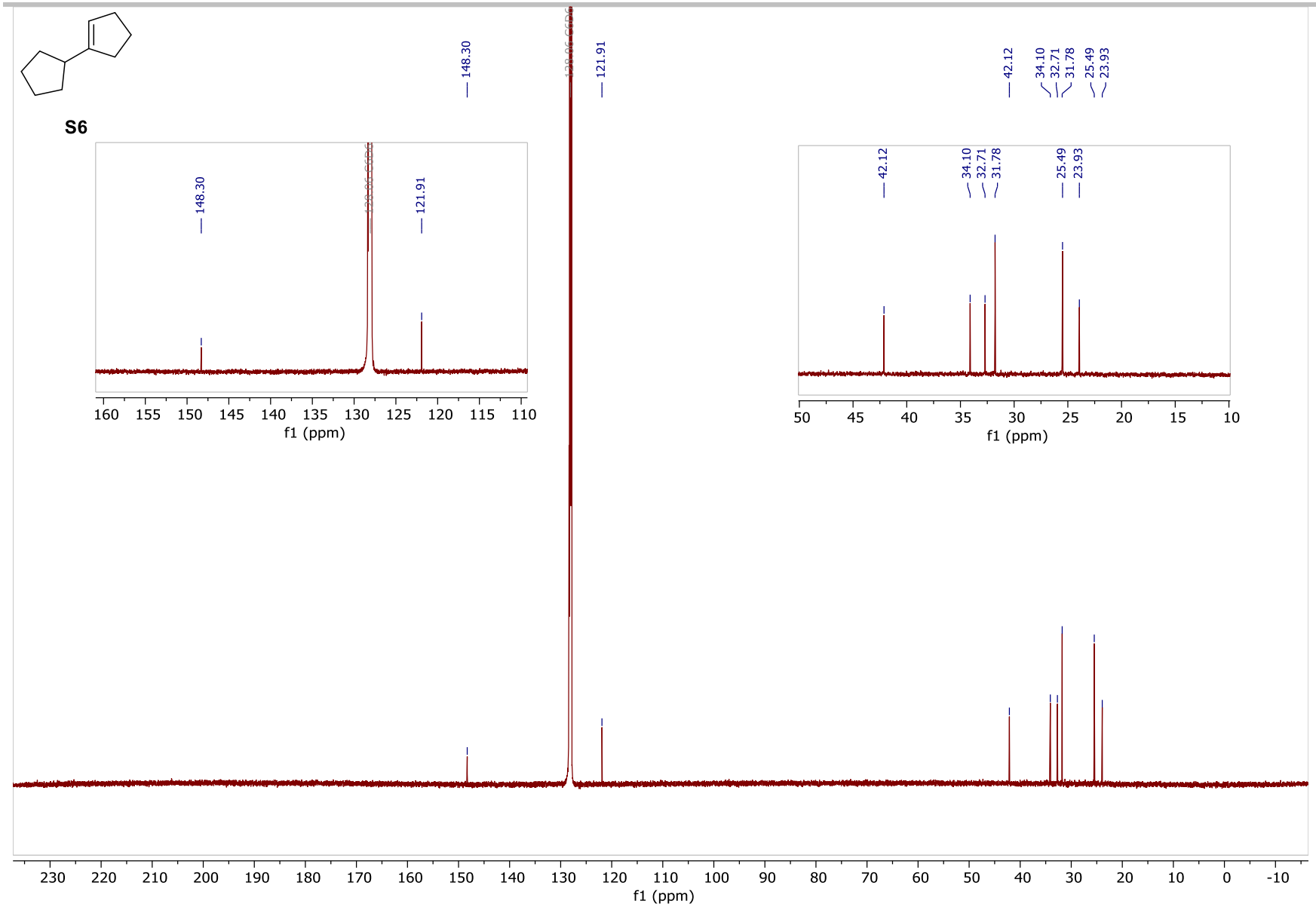


Figure S210. ^{13}C NMR (175 MHz, C_6D_6) of **S6**.

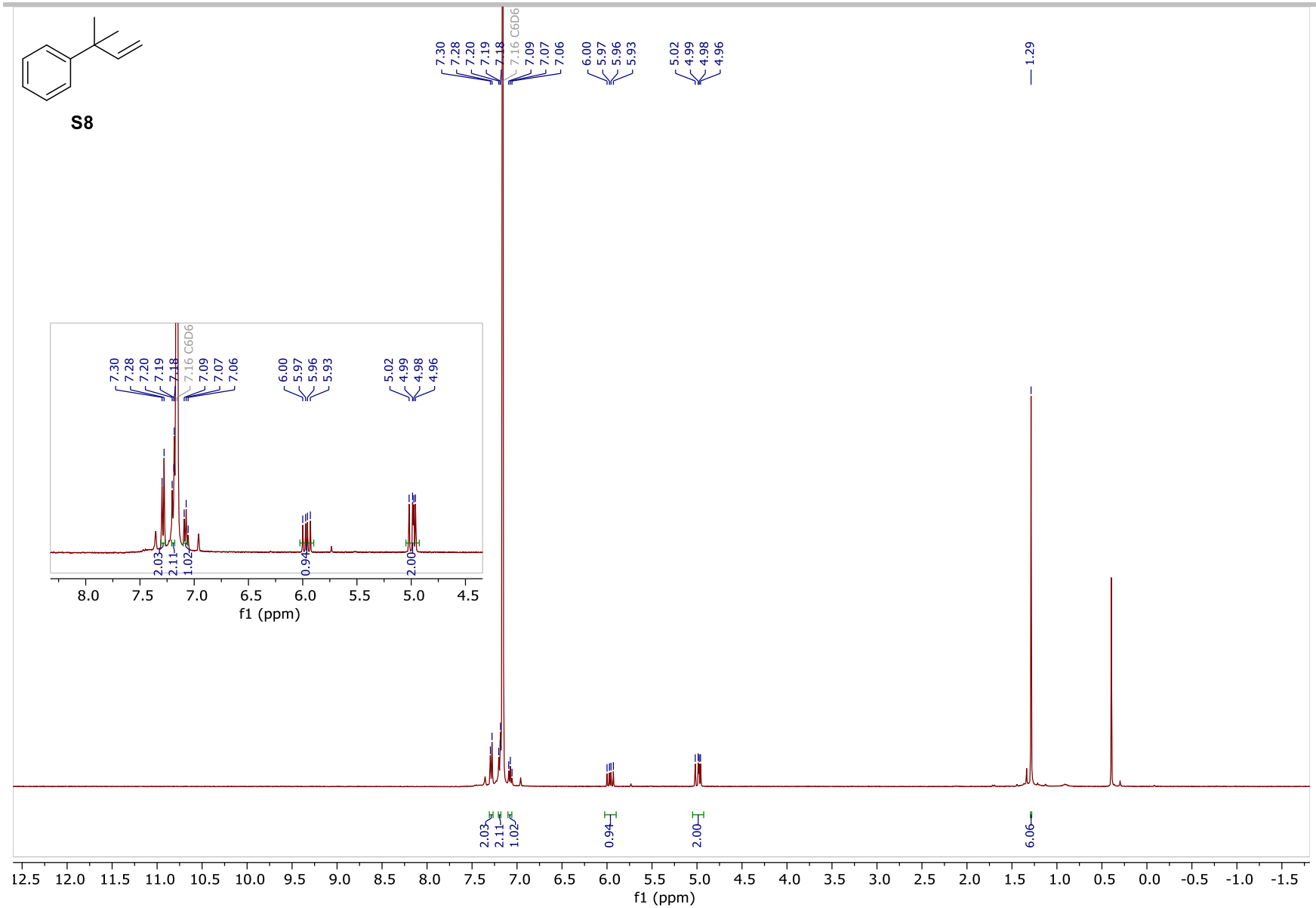


Figure S211. ^{1}H NMR (400 MHz, C_6D_6) of **S8**.

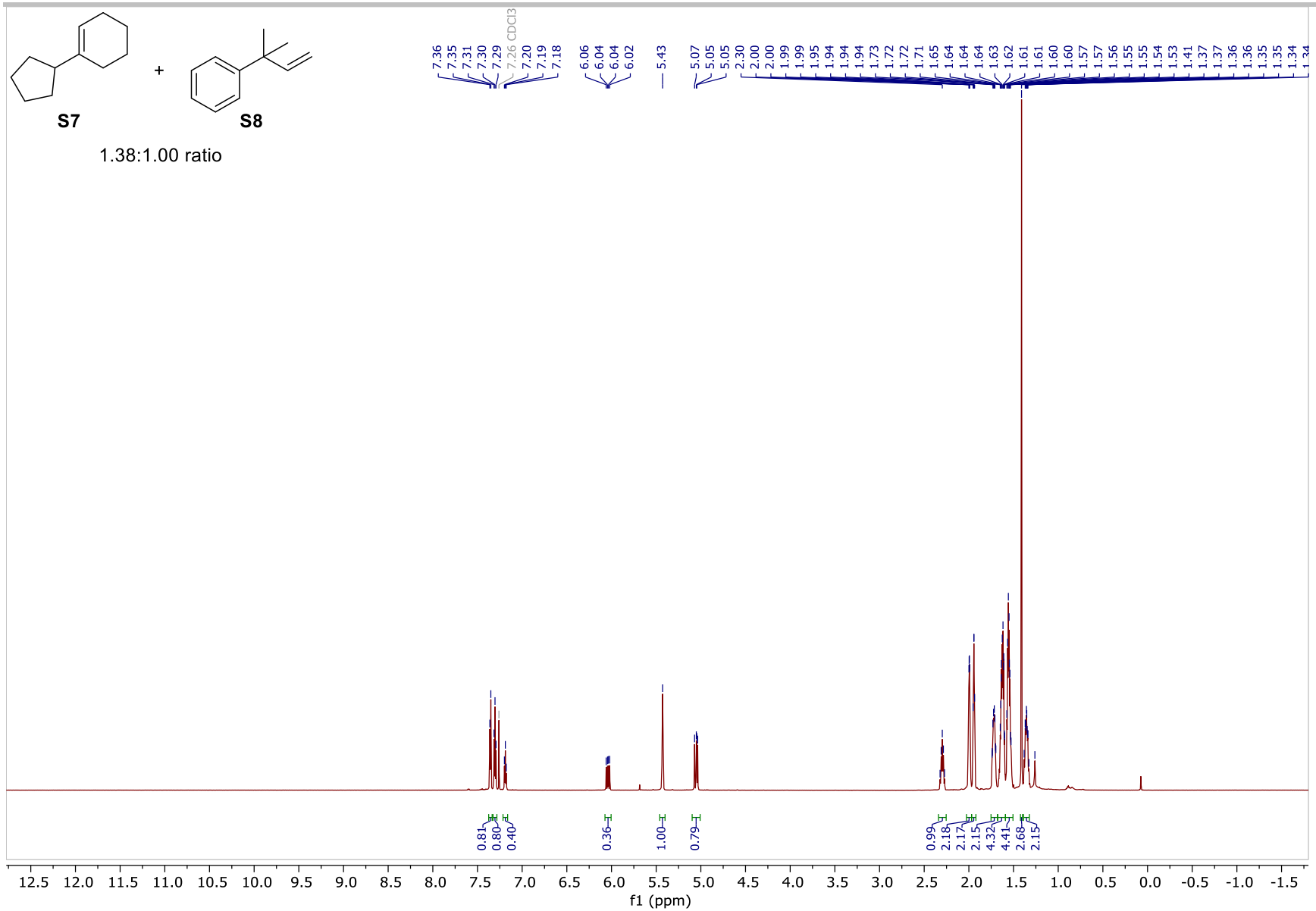


Figure S212. ^{1}H NMR (700 MHz, $CDCl_3$) of the mixture of **S7** and **S8**.

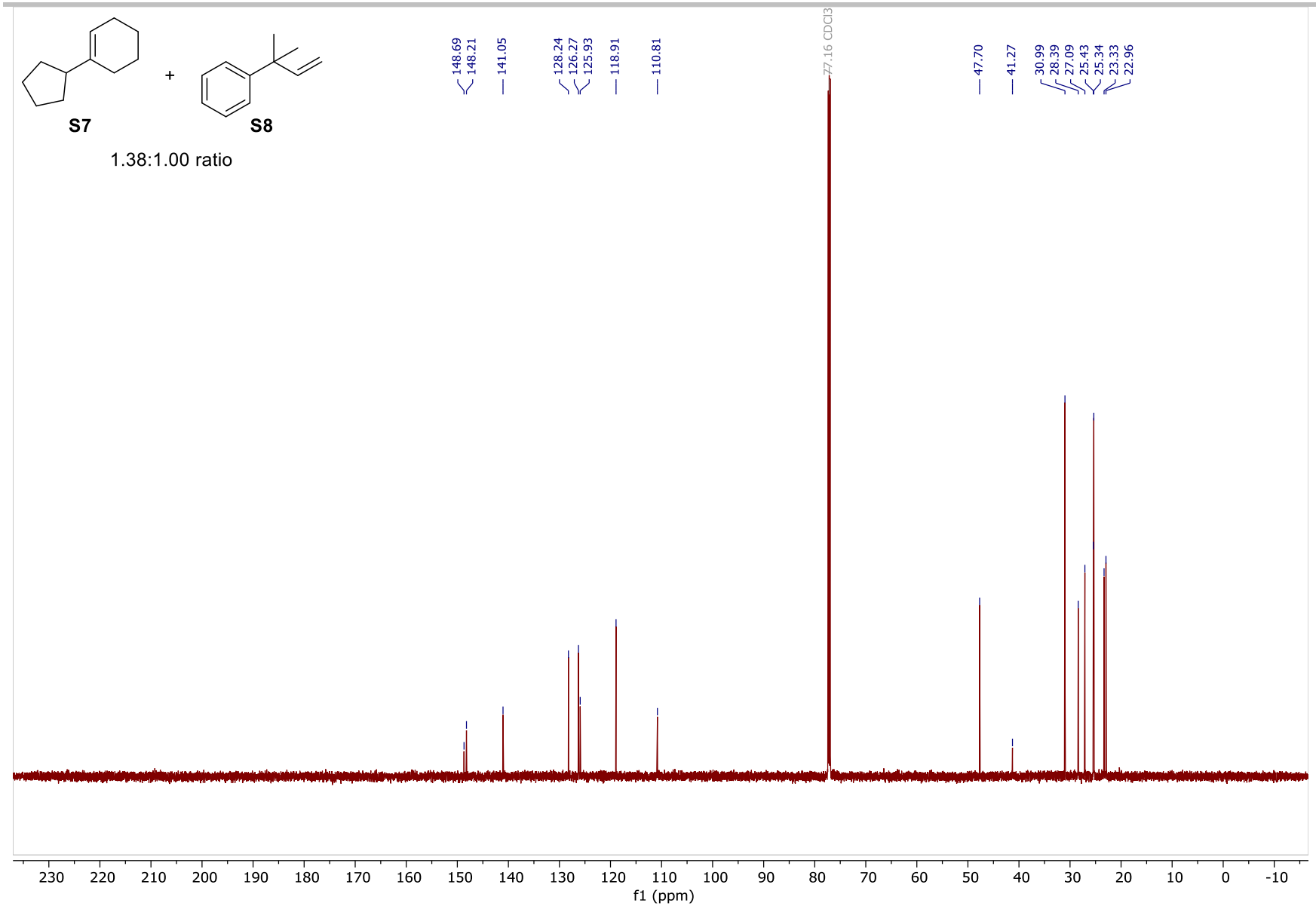


Figure S213. ^{13}C NMR (175 MHz, $CDCl_3$) of the mixture of **S7** and **S8**.

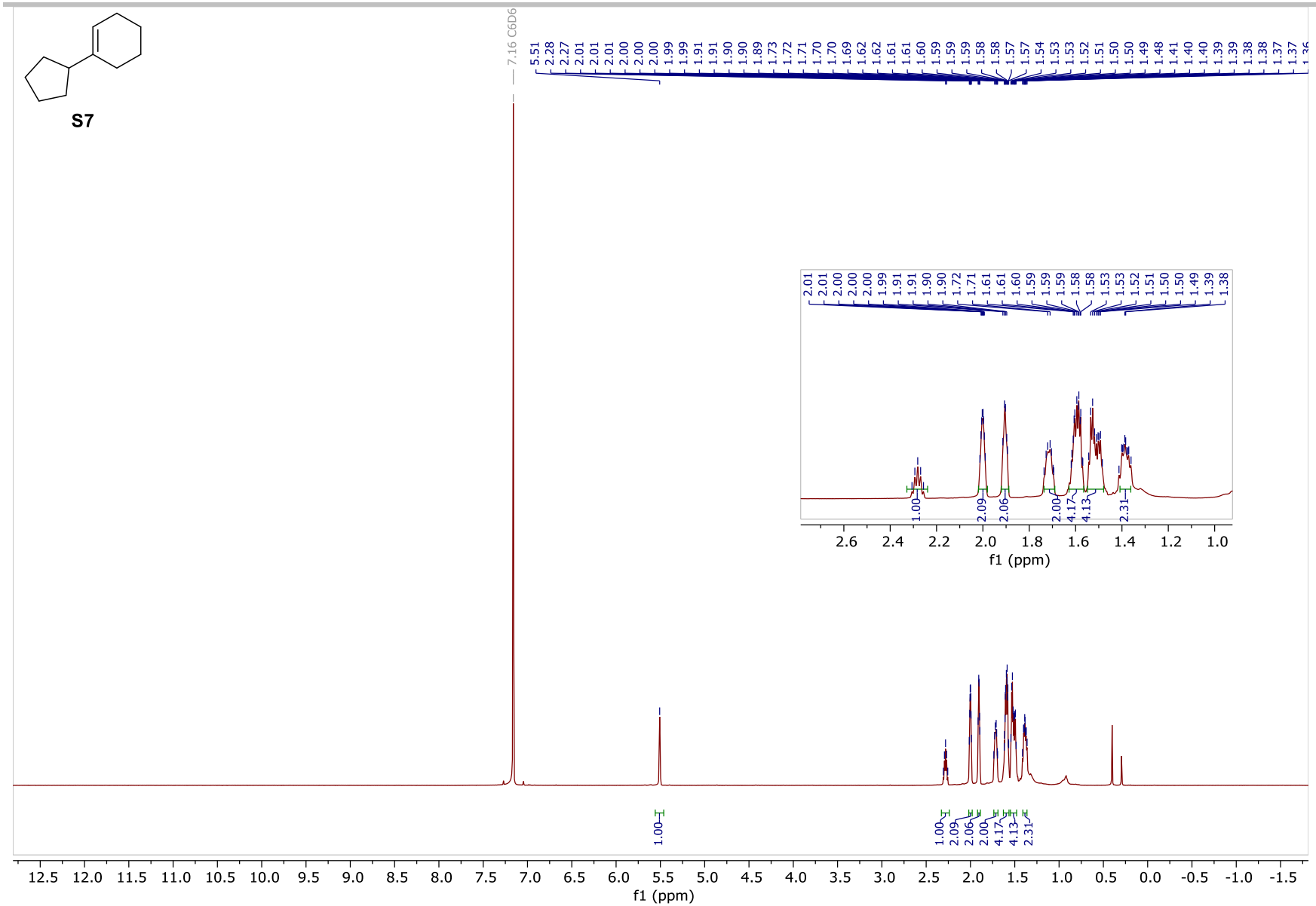


Figure S214. ^{1}H NMR (700 MHz, C_6D_6) of **S7**.

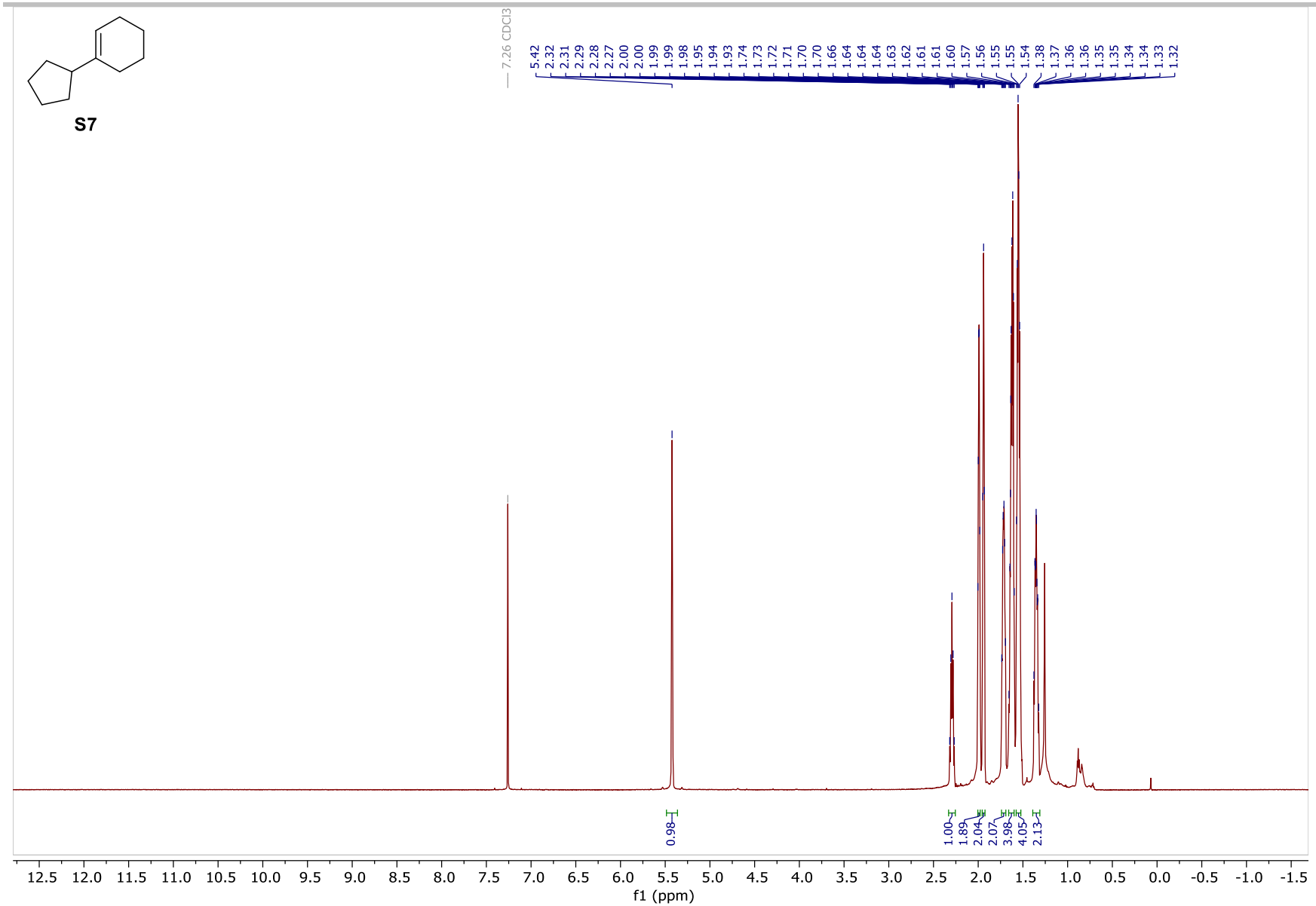


Figure S215. ^{1}H NMR (700 MHz, $CDCl_3$) of **S7**.

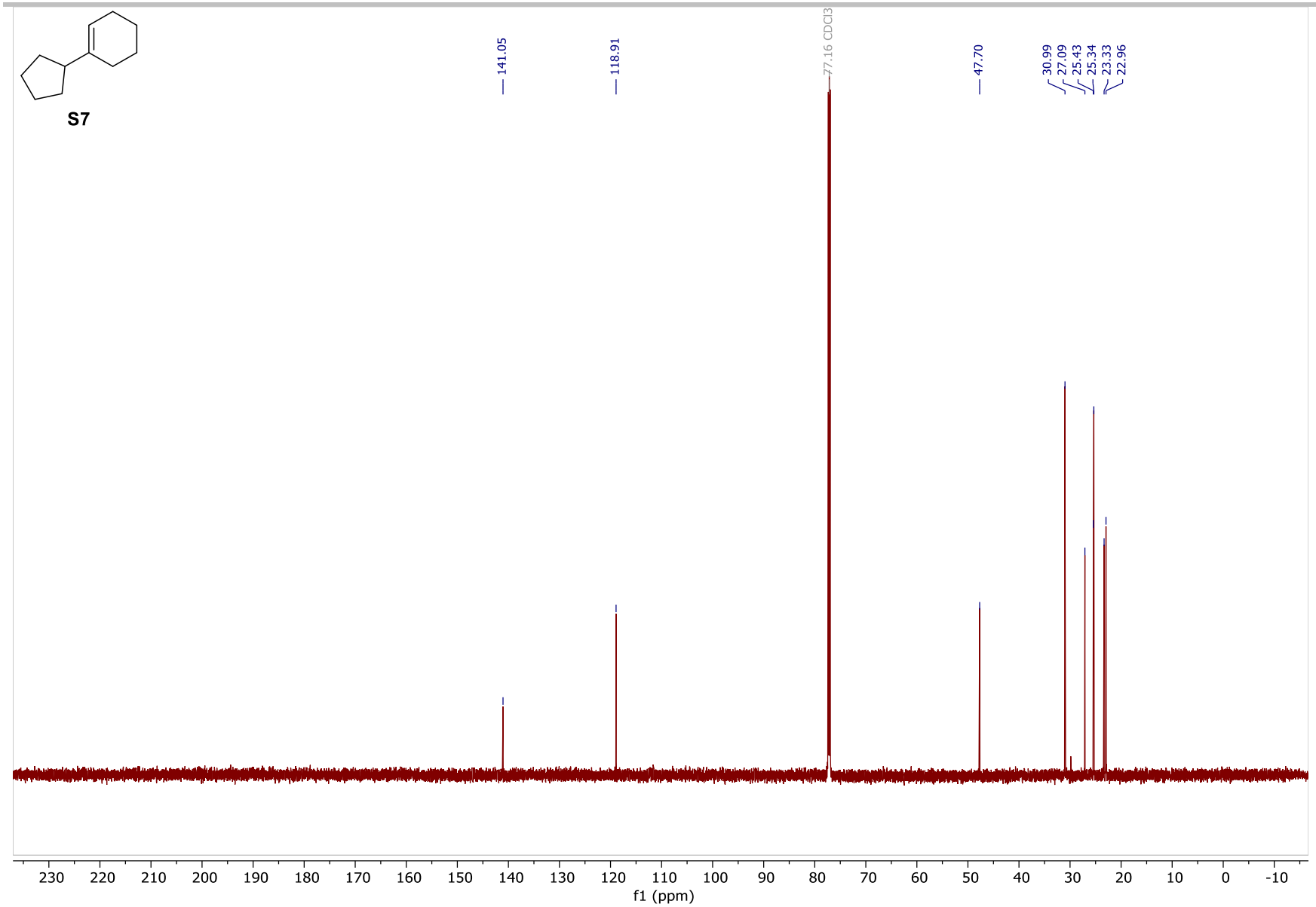


Figure S216. ^{1}H NMR (175 MHz, $CDCl_3$) of **S7**.