Supporting Information

Biocompatible Photo-induced Alkylation of Dehydroalanine for the Synthesis of Unnatural α-Amino Acids

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1. General Information

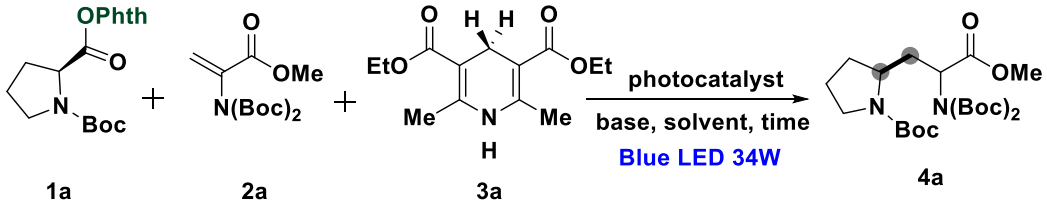
All solvents were dried and distilled before use by standard procedures and reagents were of the highest commercially available grade purchased from Sigma-Aldrich, Oakwood Chemicals, and Stream Chemicals and used as received or purified according to the procedures outlined in *Purification of Common Laboratory Chemicals*[1]. Glassware used was dried in oven or flame dried under vacuum and cooled under an inert atmosphere. The photochemical experiments were performed using a 34 W Kessil H150 blue LED (emission: 380 – 525 nm) as the visible light source, in Schlencks flasks. Column flash chromatography was performed using silica gel 60 (230−400 mesh), and analytical thin-layer chromatography (TLC) was performed using silica gel aluminum sheets. Compounds were visualized on TLC by UV-light, $KMnO_4$, I_2, $H_3[P(Mo_3O_{10})_4]$ x H_2O (PMA) and Vanillin. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million relative to the residual solvent signals[2], and coupling constants (J) are reported in hertz. The following abbreviations indicate the multiplicity of each signal: (s), singlet; (d), doublet; (t), triplet; (q), quartet; (hept), heptet; (m), multiplet; (dd), doublet of doublets; (dt), doublet of triplets; (dq), doublet of quartet; (dp), doublet of pentet; (ddd), doublet of doublet of doublets; (ddt), doublet of doublet of triplets (dtt), doublet of triplet of triplets; (ttd), triplet of triplets of doublets; (qq), quartet of quartets. High-resolution ESI mass spectra were obtained using a Waters Acquity UPLC H-class liquid chromatograph coupled with a Waters Xevo G2-XS QToF mass spectrometer with an electrospray interface (ESI).

2. General procedure for reaction optimization screening

An oven-dried 10 mL Schlenk tube was charged with $[Ru(bpy)_3](PF_6)_2$ (0.002 mmol, 1 mol%), *N*-(acyloxy)-phthalimide **1a** (72.1 mg, 0.2 mmol),

dehydroalanine **2a** (90.4 mg, 0.3 mmol), Hantzsch ester **3a** (76 mg, 0.3 mmol), diisopropylethylamine (76.6 μL, 0,44 mmol) and a magnetic stir bar. After the addition of a solvent (1.4 mL), the tube was capped with a septum and the mixture was stirred and bubbled with Argon for 5 min. Then, the tube was placed in front of a Blue LED lamp (Kessil ~456 nm – 3 cm distance) and the reaction mixture was stirred for twenty hours. Once the time has passed, the reaction mixture was diluted with ethyl acetate and washed with 10% HCl (3 x 25 mL), NaOH 1M (3 x 25 mL), Brine (1 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10% EtOAc/hexanes) to provide the title compound **4a** as a very viscous colorless oil.

3. Optimization table



1a 0.2 mmol | **2a** 0.3 mmol | **3a** 0.3 mmol | **4a**

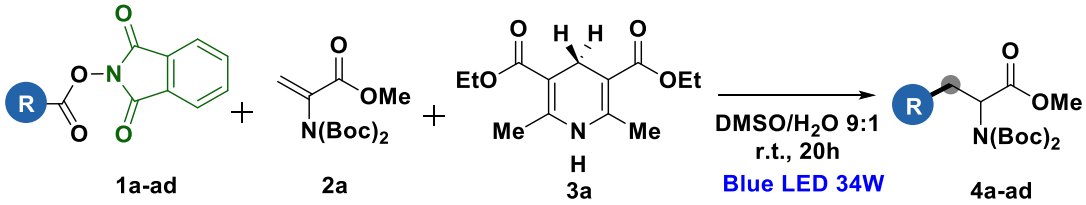
Entry	Catalyst	Base	Solvent	Time	Ligth	Yield (%)[a]
1	$[Ru(bpy)_3](PF6)_2$	DIPEA	DMSO dry	20h	blue LED	70
2	$[Ru(bpy)_3](PF6)_2$	DIPEA	ACN	20h	blue LED	87
3	$[Ru(bpy)_3](PF6)_2$	DIPEA	DMF	20h	blue LED	64
4	$[Ru(bpy)_3](PF6)_2$	DIPEA	DCM	20h	blue LED	77
5	$[Ru(bpy)_3](PF6)_2$	DIPEA	DMSO/H_2O[b]	20h	blue LED	80
6	$[Ru(bpy)_3](PF6)_2$	DIPEA	DMSO/H_2O[c]	20h	blue LED	77
7	$[Ru(bpy)_3](PF6)_2$	K_2CO_3	DMSO/H_2O[b]	20h	blue LED	54
8	$[Ru(bpy)_3](PF6)_2$	DIPEA	ACN/H_2O[b]	20h	blue LED	64
9	-	DIPEA	ACN	20h	blue LED	67
10	-	DIPEA	DMSO/H_2O[c]	20h	blue LED	38
11	-	DIPEA	DMF	20h	blue LED	72
12	-	DIPEA	DCM	20h	blue LED	60
13	-	DIPEA	DMSO dry	20h	blue LED	70
14	-	DIPEA	DMSO/H_2O[b]	20h	blue LED	65
15	-	DABCO	DMSO dry	20h	blue LED	28
16	-	TEA	DMSO dry	20h	blue LED	70
17	-	K_2CO_3	DMSO dry	20h	blue LED	41
18	-	-	DMSO dry	20h	blue LED	76
19[d]	-	DIPEA	DMSO dry	20h	blue LED	32

20[d]	-	-	DMSO dry	20h	blue LED	traces
21	-	DIPEA	DMSO dry	20h	-	-
22	-	-	DMSO dry	10h	blue LED	77
23[e]	-	-	DMSO dry	10h	blue LED	95
24[e,f]	-	-	DMSO/H_2O[b]	10h	blue LED	64
25[e,f,g]	-	-	DMSO/H_2O[b]	10h	blue LED	40
26[e]	-	-	DMSO/H_2O[b]	20h	blue LED	90

a) Isolated yield; b) Mixture 9:1; c) Mixture 2:1; d) Without Hantzsch ester; e) Reaction carry out using 2.1 equivalents of Hantzsch ester (**3a**); f) Reaction carry out in a common vial without inert atmosphere; g) Reaction carry out changing the equivalents between compounds **1a** and **2a**.

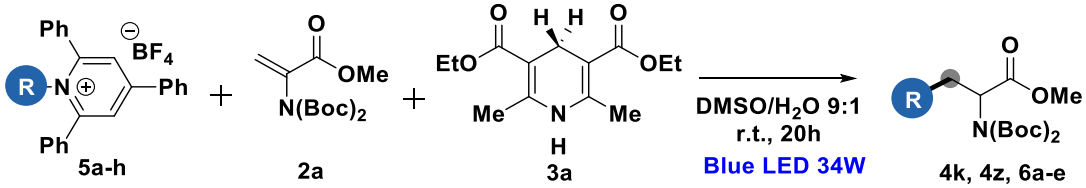
4. General procedures for photo-induced non-natural amino acid synthesis

General Procedure **4A** – decarboxylative process



An oven-dried 10 mL Schlenk tube was charged with *N*-(acyloxy)-phthalimides **1a-ad** (0.2 mmol), dehydroalanine **2a** (0.3 mmol), Hantzsch ester **3a** (106.4 mg, 0.42 mmol), and a magnetic stir bar. After the addition of a mixture of DMSO/H_2O 9:1 (1.4 mL), the tube was capped and placed in front of a LED bulb (Kessil ~456 nm) and the reaction mixture was stirred for twenty hours. Once the time has passed, the reaction mixture was diluted with ethyl acetate and washed with 10% HCl (3 x 25 mL), NaOH 1M (3 x 25 mL), Brine (1 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc/hexanes) to provide pure compounds **4a-ad**.

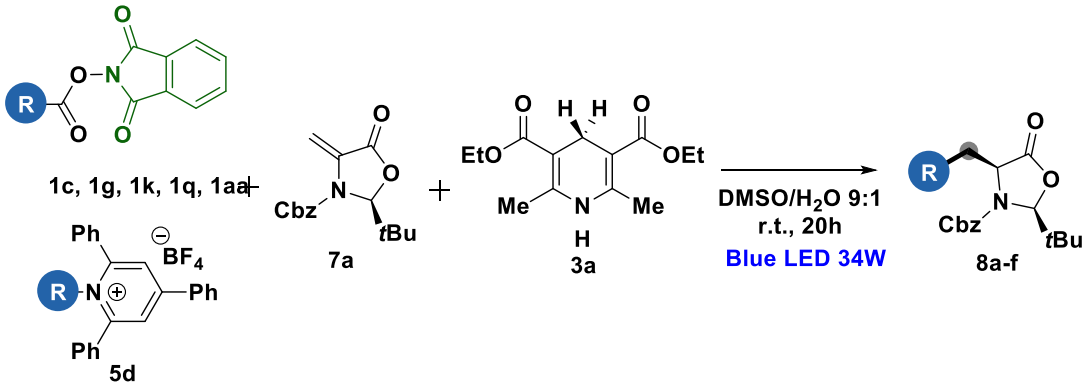
General Procedure **4B** – deaminative process:



An oven-dried 10 mL Schlenk tube was charged with *N*-Alkylpyridinium salts **5a-h** (0.2 mmol), dehydroalanine **2a** (0.3 mmol), Hantzsch ester **3a** (106.4

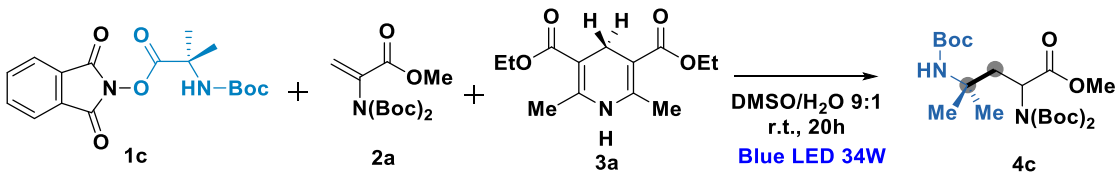
mg, 0.42 mmol), and a magnetic stir bar. After the addition of a mixture of DMSO/H_2O 9:1 (1.4 mL), the tube was capped and placed in front of a LED bulb (Kessil ~456 nm) and the reaction mixture was stirred for twenty hours. Once the time has passed, the reaction mixture was diluted with ethyl acetate and washed with 10% HCl (3 x 25 mL), Brine (1 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc/hexanes) to provide pure compounds **4k, 4z, 6a-e.**

General Procedure **4C** – Karaday-Beckwith acceptor:



An oven-dried 10 mL Schlenk tube was charged with *N*-(Acyloxy)-Phthalimides **1c, 1g, 1k, 1q, 1aa** and *N*-Alkylpyridinium salts **5d** (0.1 mmol), Karady-Beckwith alkene **7a** (0.15 mmol), Hantzsch ester **3a** (53.2 mg, 0.21 mmol), and a magnetic stir bar. After the addition of a mixture of DMSO/H_2O 9:1 (0.7 mL), the tube was capped and placed in front of a LED bulb (Kessil ~456 nm) and the reaction mixture was stirred for twenty hours. Once the time has passed, the reaction mixture was diluted with ethyl acetate and washed with 10% HCl (3 x 25 mL), NaOH 1M (3 x 25 mL), Brine (1 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc/hexanes) to provide pure compounds **8a-f**.

5. Procedure for scale-up reaction



An oven-dried 50 mL Schlenk tube was charged with *N*-(Acyloxy)-Phthalimides **1c** (2 mmol), dehydroalanine **2a** (3 mmol), Hantzsch ester **3a** (1.06 g, 4.2 mmol), and a magnetic stir bar. After the addition of a mixture of DMSO/H_2O 9:1 (14 mL), the tube was capped and placed between two LED bulbs (Kessil ~456 nm) at 3 cm in length from each. The reaction mixture was stirred for twenty hours. Once the time has passed, the reaction was diluted with ethyl acetate (100 mL) and washed with 10% HCl (3 x 150 mL), NaOH 1M (3 x 150 mL), Brine (1 x 150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (EtOAc/hexanes) to provide pure compound **4c** in 82% (755 mg) as a colorless oil. $\boldsymbol{R_f}$ = 0.5 (hexanes/EtOAc 9:1).

Experimental set-up

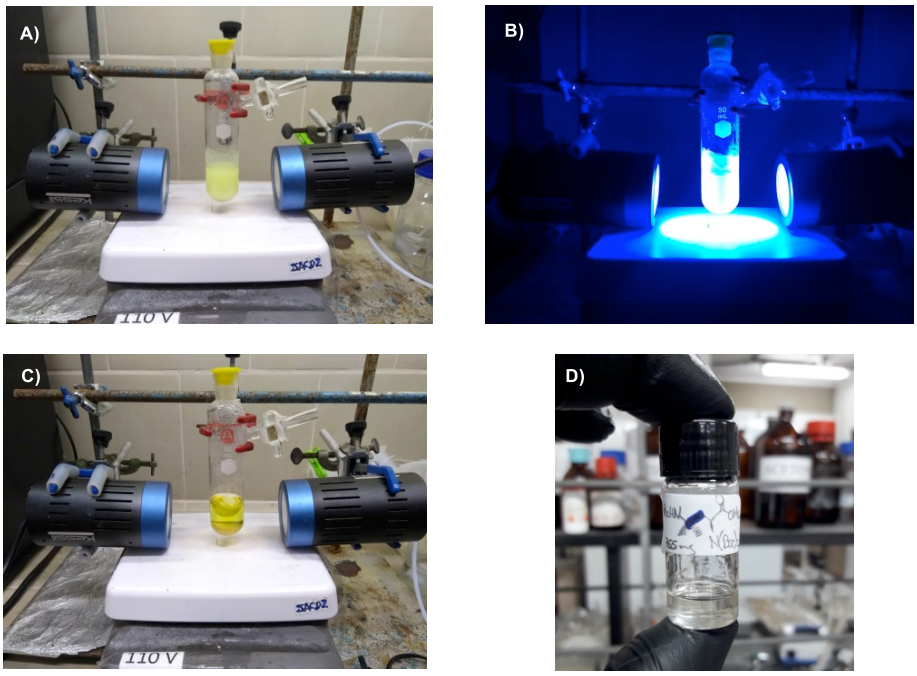


FIGURE S1. (A) Heterogeneous reaction mixture prior to switch-on the LED bulbs; (B) Reaction mixture when the LED bulbs are switch-on; (C) Homogeneous reaction mixture after 20 hours of reaction; (D) Isolated product. All the photographs were taken during the experiments performed by the authors.

6. Mechanistic considerations

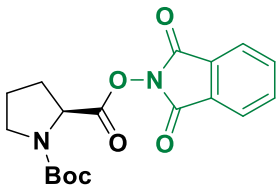
The lack of reactivity in the absence of Hantzsch ester is a good indicative of the formation of the EDA complex. Additionally, the formation of both EDA complexes suggested in this work is well supported by literature. Studies regarding NHPI

ester-Hantzsch ester EDA-complex were reported first by Chen[9c] and later by our group[9a] In the other hand, Aggarwall and Glorius studied the TPPsalt-Hantzsch ester EDA-complex also very recently.

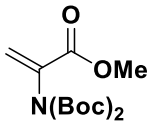
However, in order to verify the possibility of a ternary EDA-complex, we performed again UV-Vis experiments and NMR studies.

7. Spectroscopic and visual evidencies of EDA complex formation

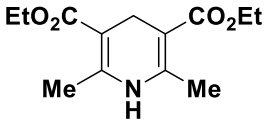
Spectroscopic evidence: To identify light-absorbing species of the photo-induced alkylation reaction, the optical absorption spectra of a series of solutions were recorded (figure S1). The solutions of **1a** (0.1 molL^{-1}), **2a** (0.1 molL^{-1}), **3a** (0.1 molL^{-1}), **1a** + **2a** (0.1 molL^{-1}), **1a** + **3a** (0.1 molL^{-1}), and **1a** + **2a** + **3a** (0.1 molL^{-1}) in DMSO were prepared. No obvious change of the absorption was observed for the solutions of **1a** and **2a** in DMSO. In contrast, Hantzsch ester **3a** solution showed a shift absorption spectrum to the lower energy region, and when the mixture **1a** + **3a** was analyzed, a clear bathochromic displacement in the visible region could be observed, corresponding to a charge transference, which is diagnostic of an EDA complex.



1a



2a



3a

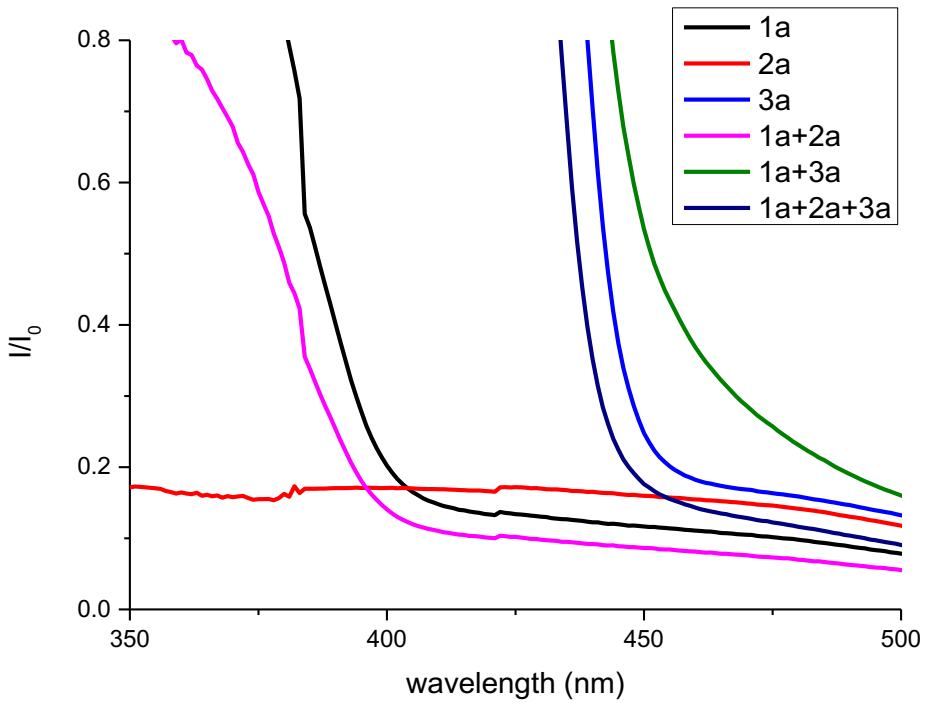


FIGURE S2. UV-Visible spectras.

Visual evidence: 0.1 M solutions of 1-(tert-butyl) 2-(1,3-dioxoisoindolin-2-yl) (S)-pyrrolidine-1,2-dicarboxylate (**1a**), methyl 2-(di-(tert-butoxycarbonyl) amino) acrylate (**2a**), diethyl 2,6- dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3a**), and the equimolar mixtures of **1a** + **3a** and **1a** + **2a** + **3a** were prepared (sonication and slightly heating were required to solubilize completely the compound **1a**), as shown by figure S2. The intensification of the color observed in the solution containing the mixture **1a** + **3a** can be attributed to the formation of an EDA complex between the reactants.

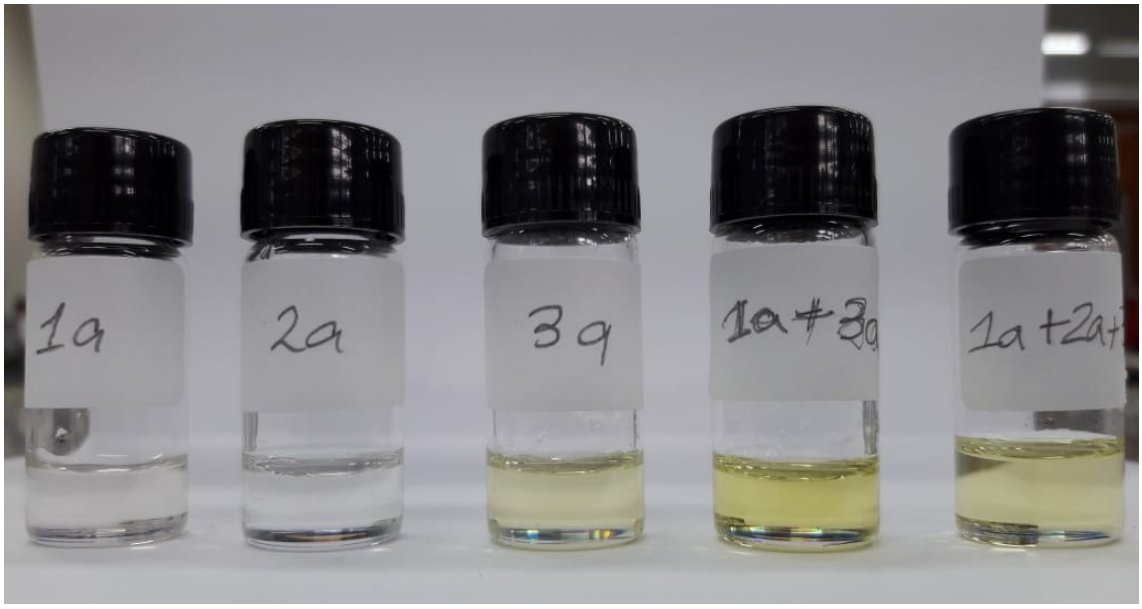
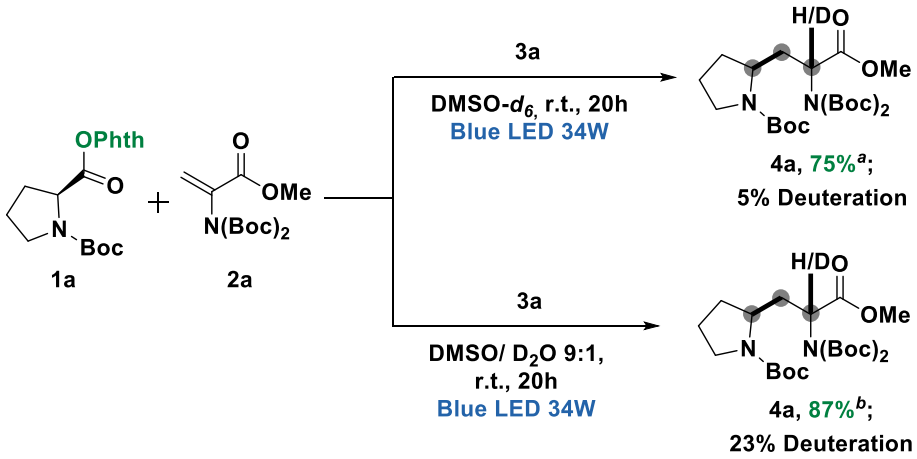


FIGURE S3. DMSO 0.1 M solutions of **1a**, **2a**, **3a**, and the respective mixtures (1a + 3a) and (1a + 2a + 3a). Photographs were taken by the authors.

8. Deuterium labelling experiments.

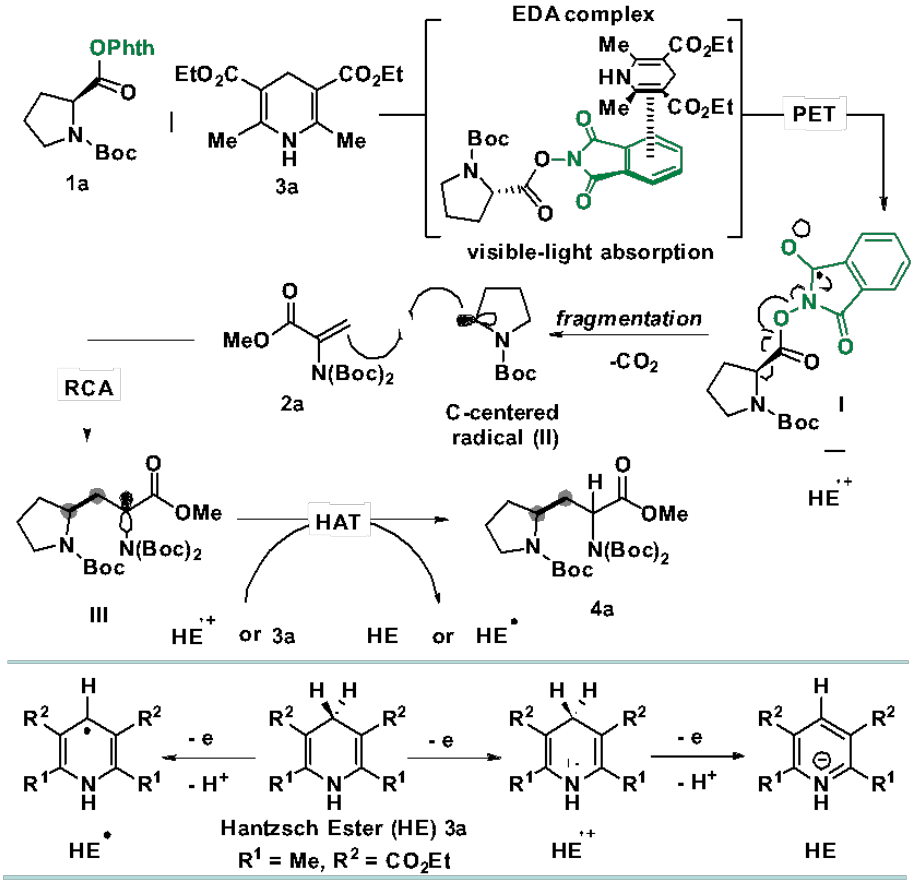
In order to unveil the proton source involved in the last step of the proposed mechanism.



Scheme S1. Deuterium labelling experiments.

By carrying out experiments with deuterium labelled solvents product **4a** did not afford high levels of deuterium incorporation, indicating that the Hantzsch ester should acts as the main proton source (Scheme 1). Based on these observations and previous literature reports,[9b] a plausible reaction mechanism is outlined in Scheme 2. Upon light absorption by the EDA complex formed between **1a** and **3a**, a PET process takes place affording

the reduced NHPI ester (**I**) and the oxidized Hantzsch ester (radical-cation). The reduced NHPI ester (**I**) undergoes fragmentation to release carbon dioxide and the *C*-centered radical (**II**). Subsequently, radical conjugated addition to **2a** affords tertiary radical intermediate **III**, which lastly is protonated through a hydrogen atom transfer from Hantzsch ester radical cation (BDFE = 31.4 kcal/mol)[10] or by **3a** (BDFE = 69.4 kcal/mol)[10] to give the desired compound **4a** (BDFE = ~ 84.3 kcal/mol).[11] However, we cannot rule-out an alternative single-electron transfer process occurring simultaneously in which intermediate **III** would be reduced by Hantzsch ester radical to afford an anion that subsequently is protonated by the water, like suggest experiments shown in Scheme 1.



Scheme S2. Plausible reaction mechanism.

9. NMR Studies as evidences of the EDA-Complex formation

^{1}H NMR experiments were performed by the preparation of DMSO-d_6 solutions containing Hantzsch ester (**HE**) and NHPI ester (**2a**) in three different ratios,

keeping constant the amount of **HE** (0.05 molL^{-1}) and increasing the amount of **2a** (**HE : 1a** = 1:1, 1:1.5 and 1:2). The figure S4 shows the expansion of the spectras collected, on which the Hantzsch ester methylenic protons shift were monitored. From this set of experiments it is possible to observe the change in the chemical shifts of the monitored hydrogens with the addition of increasing amounts of **2a**. In presence of **2a**, the shift is also observed and was almost the same of the observed when the **HE** : **1a** rate is 1:1.5, ruling out the possibility of a ternary EDA-complex system.

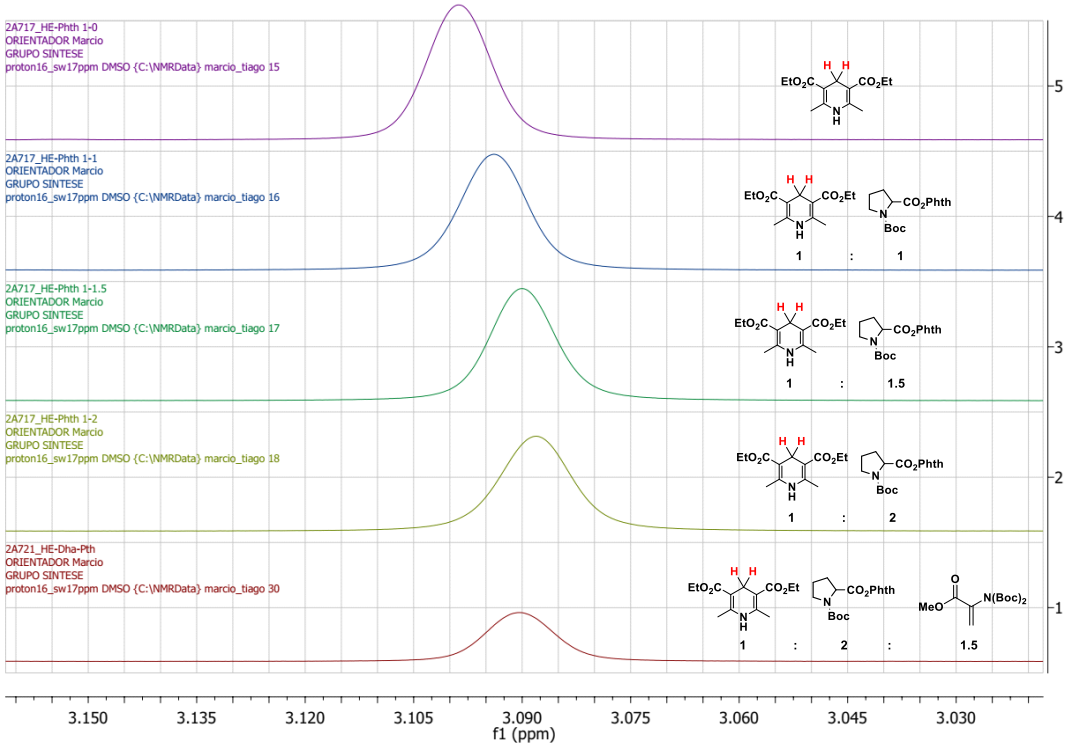


FIGURE S4.

The same NMR experiments were done replacing the NHPI ester **2a** by the pyridinium salt **5d** (Figure S5). From this second set of experiments it is also possible to observe a variation in the chemical shifts of the monitored HE methylenic proton with the addition of increasing amounts of **5d**. Again, in the presence of **2a**, the shifting is also observed and is almost the same of the observed when the **HE** : **5a** rate is 1:1.5, which also ruling out the possibility of a ternary EDA-complex system.

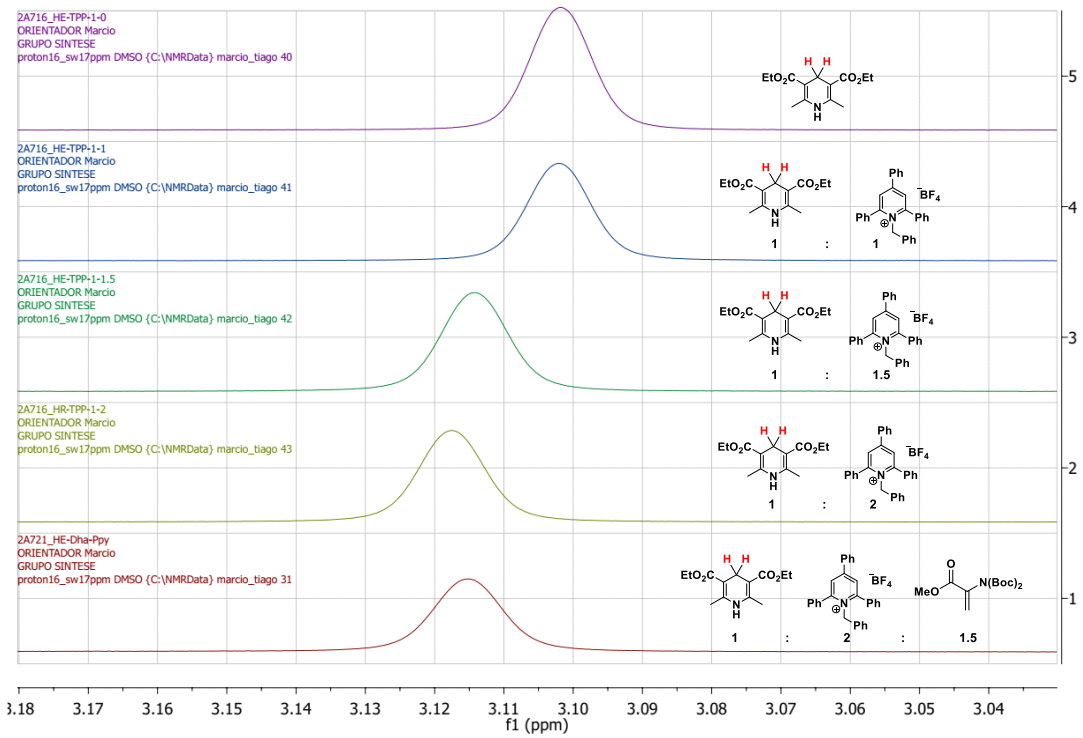
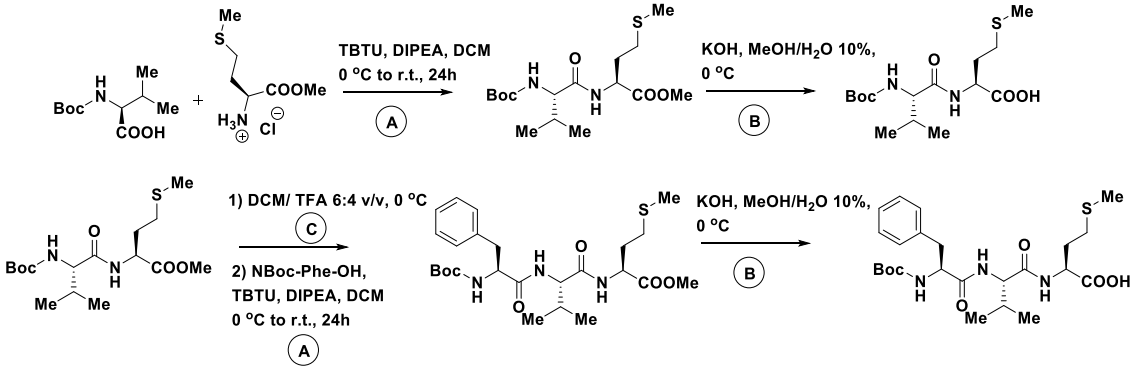


FIGURE S5.

10. General procedures for Peptide-Coupling and Deprotection

General procedures **6A – 6C**



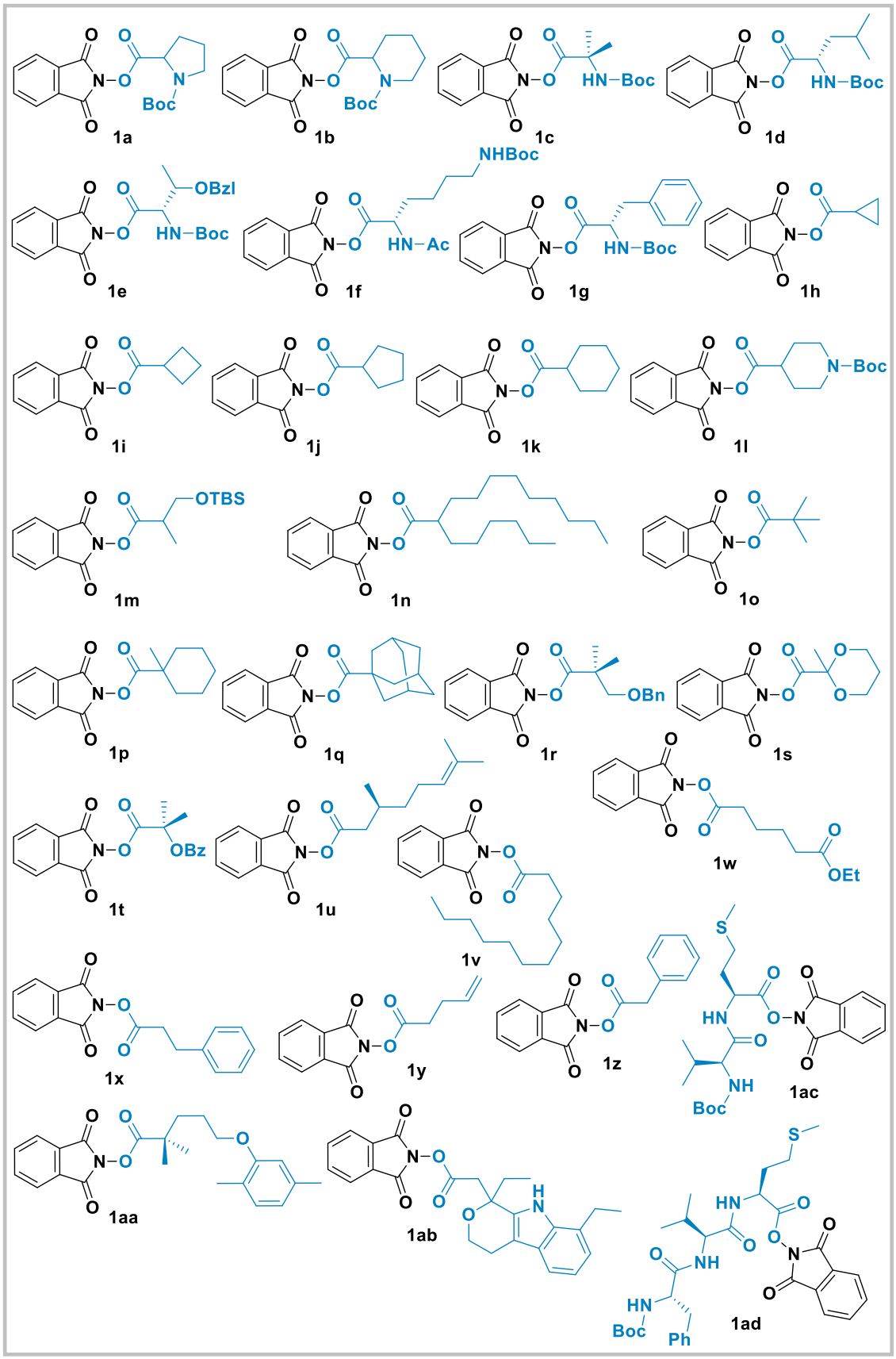
Procedure 6A: A round-bottom flask equipped with magnetic stir bar was charged with *N*-protected free carboxylic acid (1.2 equiv) and DCM (0.5 M) and was cooled to 0 ºC. TBTU (1.5 equiv) was added in a single portion, followed by DIPEA (3.5 equiv) and stirred for 30 min. Then, the amine coupling partner (1 equiv.) was added to the reaction mixture. After stirring 10 minutes, the reaction mixture was allowed to warm to room temperature and stirred for additional 24

hours. Passed that time, the mixture was partitioned between a 10% HCl solution and DCM. The organic phase was washed with HCl 10% (2x), $NaHCO_3$ (2x), and brine (1x). Next, it was dried over anhydrous Na_2SO_4. and concentrated by rotary evaporation. The resultant white solid was taken forward without further purification.

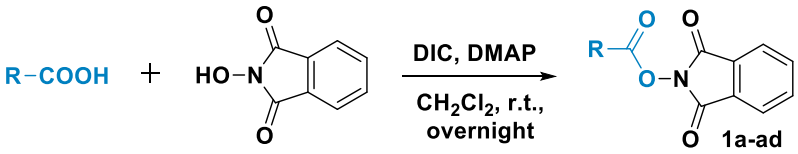
Procedure 6B: The crude protected peptide was dissolved in a mixture of MeOH/ H_2O 10% at 0 °C. After stirring 10 min, KOH (3 equiv.) was added and the reaction mixture was checked by Thin Layer Chromatography until consumption of the starting material. Then, a 10% HCl solution was added until pH = 2-3 be reached and the aqueous layer was extracted with ethyl acetates (2x). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The resultant white solid was taken forward without further purification.

Procedure 6C: The crude protected peptide was dissolved in a mixture of DCM/ TFA/ 6:4 v/v (10 ml/g) at 0 °C. The reaction mixture was allowed to stir and checked by thin layer chromatography until consumption of the starting material. Then the reaction was concentrated under reduced pressure and the TFA was entirely removed by repetitive addition and evaporation of further DCM.

11. General procedure for preparation of *N*-(Acyloxy)-Phthalimides (NHPI) redox active esters

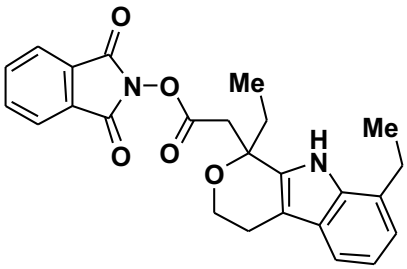


NHPI esters **1a-ad** were prepared according to the previously reported procedure.[3]

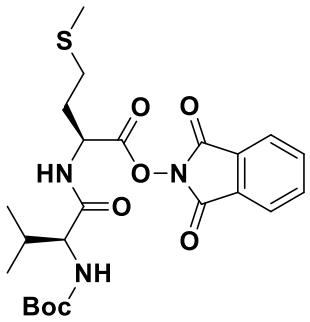


A round-bottom flask was charged with (if solid) carboxylic acid (1.0 equiv), *N*-hydroxyphthalimide (1.0 equiv) and DMAP (0.1 equiv). Dichloromethane was added (0.15 M), and the mixture was stirred vigorously. Carboxylic acid (1.0 equiv) was added via syringe (if liquid). DIC (1.1 equiv) was then added dropwise via syringe, and the mixture was allowed to stir until the acid was consumed (determined by TLC). Typical reaction times were between 0.5 h and 12 h. The mixture was filtered (over Celite, SiO_2, or through a fritted funnel) and rinsed with additional CH_2Cl_2. The solvent was removed under reduced pressure, and purification by column chromatography afforded the corresponding *N*-(Acyloxy)-Phthalimides.

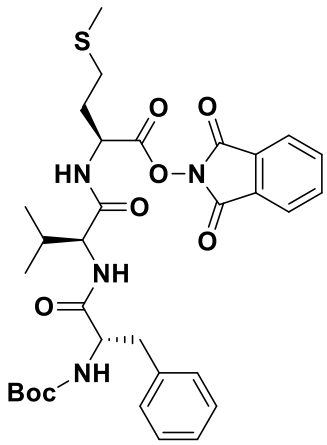
Note: Some esters are prone to hydrolysis on silica gel during column chromatography and should be purified as quickly as possible to obtain reasonable separation.



1,3-dioxoisoindolin-2-yl 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetate (**1ab**) was synthesized according to the general procedure before mentioned. Flash column chromatography purification 0-20% of EtOAc in hexanes afforded the title compound in 57% (485.0 mg) as a white solid. R_f = 0.5-0.6 (hexanes/EtOAc 8:2). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 8.87 (s, 1H), 7.98 – 7.91 (m, 2H), 7.88 – 7.81 (m, 2H), 7.38 (d, J = 7.7 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.1 Hz, 1H), 4.19 – 4.11 (m, 1H), 4.07 – 3.98 (m, 1H), 3.38 (d, J = 13.8 Hz, 1H), 3.19 (d, J = 13.8 Hz, 1H), 2.99 – 2.75 (m, 4H), 2.27 – 2.08 (m, 2H), 1.28 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 167.5, 162.4, 135.2, 134.9, 134.3, 128.9, 127.2, 126.2, 124.3, 121.0, 119.9, 116.2, 109.3, 75.5, 61.1, 41.0, 31.6, 24.3, 22.5, 14.3, 7.7. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd. for $C_{25}H_{24}N_2O_5H$ 433.1758; Found: 433.1759.



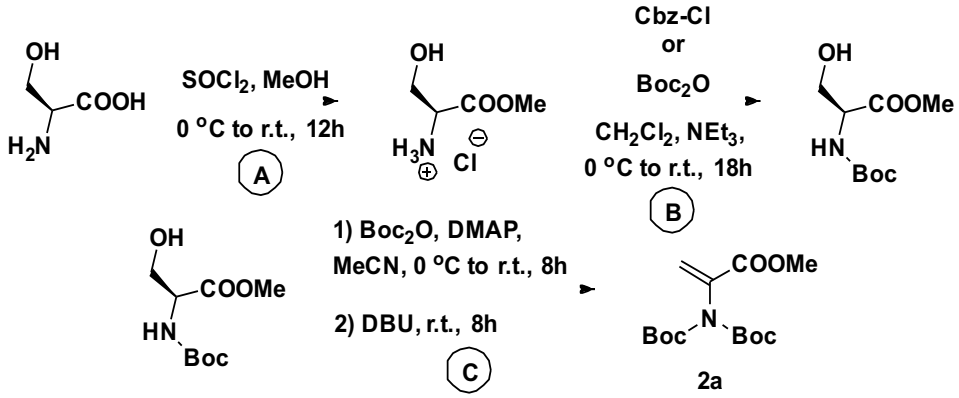
1,3-dioxoisoindolin-2-yl (tert-butoxycarbonyl)-L-valyl-L-methioninate (**1ac**) was synthesized according to the general procedure before mentioned. Flash column chromatography purification 0-40% of EtOAc in hexanes afforded the title compound in 57% (485.0 mg) as a white solid. R_f = 0.4-0.5 (hexanes/EtOAc 7:3). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.91 – 7.85 (m, 2H), 7.79 (dd, J = 5.6, 3.2 Hz, 2H), 7.12 – 6.86 (m, 1H), 5.24 – 5.00 (m, 2H), 4.06 – 3.89 (m, 1H), 2.74 – 2.65 (m, 2H), 2.39 – 2.21 (m, 2H), 2.20 – 2.02 (m, 4H), 1.42 (s, 9H), 1.00 – 0.91 (m, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.9, 168.6, 161.5, 156.1, 135.0, 128.9, 124.2, 80.3, 60.1, 50.0, 31.6, 29.7, 28.4, 19.3, 15.5. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{31}N_3O_7SNa$ 516.1775; Found: 516.1783.



1,3-dioxoisoindolin-2-yl (tert-butoxycarbonyl)-L-phenylalanyl-L-valyl-L-methioninate (**1ad**) was synthesized according to the general procedure before mentioned. Flash column chromatography purification 0-60% of EtOAc in hexanes afforded the title compound in 53% (900.0 mg) as a white solid. R_f = 0.3 (hexanes/EtOAc 6:4). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.83 – 7.77 (m, 2H), 7.75 – 7.69 (m, 2H), 7.35 – 7.23 (m, 1H), 7.21 – 7.15 (m, 3H), 7.14 – 7.10 (m, 2H), 6.82 – 6.36 (m, 1H), 5.08 – 4.91 (m, 2H), 4.38 – 4.20 (m, 2H), 3.08 – 2.91 (m, 2H), 2.69 – 2.55 (m, 2H), 2.33 – 2.21 (m, 2H), 2.19 – 2.05 (m, 4H), 1.33 – 1.28 (m, 9H), 0.87 – 0.77 (m, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.0, 171.0, 168.4, 161.6, 156.4, 136.5, 135.0, 129.4, 129.1, 128.9, 127.2, 124.2, 81.5, 58.6, 56.1, 50.1, 37.8, 31.2, 29.9, 29.8, 28.3, 19.2, 15.5. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{32}H_{40}N_4O_8SNa$ 663.2459; Found: 663.2479.

12. Preparation of dehydrated amino acid 2a.

General procedures **8A – 8C**



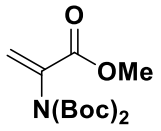
Procedure 8A: To a stirring solution of *L*-Serine in methanol at 0 °C was added thionyl chloride drop by drop. After the addition of thionyl chloride, the solution was warmed to room temperature and stirred for 12 hours. The reaction mixture was concentrated by reduced pressure and the residue was triturated and concentrated by reduced pressure in three cycles employing toluene, methanol, and diethyl ether (for the entire removal of dimethyl sulphite), to afford the product as a white solid.

Dehydrated amino acid **2a** were prepared according to the previously reported procedure.[4]

Procedure 8B: To a stirring solution of *L*-serine methyl ester hydrochloride (1 equiv) in dichloromethane (1 M) at 0 °C was added triethylamine (2.2 equiv) and di-*tert*-butyl dicarbonate (1.1 equiv). After stirring for 30 minutes, the solution was warmed to room temperature, and stirred for an additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was passed through a silica plug (50% ethyl acetate in hexanes) to afford the product as a clear, colorless oil. The physical properties and spectral data are consistent with the reported values.[5]

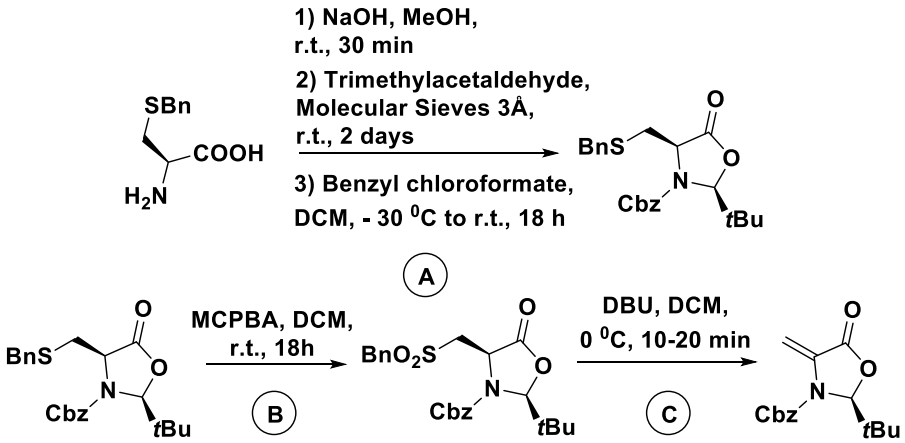
Procedure 8C To a stirring solution of methyl (*tert*-butoxycarbonyl)-*L*-serinate (1.0 equiv) in acetonitrile (6 M) at 0 °C was added di-*tert*-butyl dicarbonate (2.2 equiv) and 4-dimethylaminopyridine (0.20 equiv). The resulting solution was warmed to room temperature and stirred for 8 hours. DBU (0.10 equiv) was added, and the resulting mixture was stirred for an additional 8 hours. The reaction was concentrated by rotary evaporation then diluted in ethyl acetate. The mixture was washed with 1M HCl and saturated aqueous $NaHCO_3$, dried over

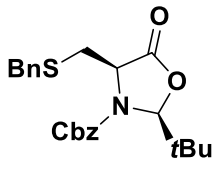
Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by passing through a short plug of silica (5% – 15% ethyl acetate/hexanes) to afford the product **2a** as a white solid. The physical properties and spectral data are consistent with the reported values.[6]



Methyl 2-(di-(*tert*-butoxycarbonyl) amino) acrylate (**2a**) was synthesized according to the general procedures **8A-C** using *L*-Serine (4.0 g, 38.06 mmol). Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 75,4% (5.26g) as a colorless oil which precipitate into a white solid overnight inside of freezer. R_f = 0.4 (hexanes/EtOAc 9:1). The spectral data are consistent with the reported values.[6] **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 6.29 (s, 1H), 5.60 (s, 1H), 3.74 (s, 3H), 1.41 (s, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 164.0, 150.7, 136.1, 124.7, 83.2, 52.4, 27.9.

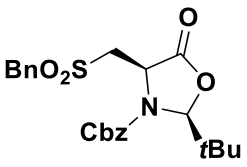
13. Preparation of Karady-Beckwith alkene 7a





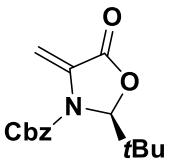
Procedure 9A – Benzyl (2S,4R)-4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate: To a round bottom flask equipped with a stir bar was added *S*-benzyl-*L*-cysteine (10 g, 47 mmol, 1 equiv.), NaOH (1.8 g, 45 mmol, 0.95 equiv), and anhydrous MeOH (500 mL). The reaction was stirred at room temperature for 30 minutes. Trimethylacetaldehyde (6.18 ml, 57 mmol, 1.2 equiv) and activated 3 Å molecular sieves (50 g) were added to the reaction flask, each

in one portion. The reaction was placed under nitrogen atmosphere and stirred at room temperature until the starting material had been consumed (determined by ^{1}H NMR of a filtered and concentrated aliquot of the reaction solution dissolved in CD_3OD). The reaction was quickly filtered through celite and concentrated by rotary evaporation. The residue was dried under high vacuum for 24 hours to afford the imine as a white solid. The imine was dissolved in anhydrous DCM (500 mL) and cooled to -30 °C. Benzyl chloroformate (10.1 mL, 71 mmol, 1.5 equiv) was added to the reaction dropwise via syringe. The reaction was allowed to reach 0 °C. The reaction was stirred for a full 18 hours then warmed to room temperature and stirred for an additional 6 hours. The mixture was washed with 1 M aqueous NaOH (1x 250 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (0%–10% ethyl acetate/hexanes) to afford the product (8.3 g, 41% yield) as a colorless oil. The physical properties and spectral data were consistent with the reported values.[4] **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.40 – 7.35 (m, 5H), 7.31 – 7.22 (m, 5H), 5.54 (s, 1H), 5.27 – 5.14 (m, 2H), 4.54 (t, J = 7.0 Hz, 1H), 3.84 – 3.69 (m, 2H), 2.97 – 2.74 (m, 2H), 0.92 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.4, 156.0, 137.8, 135.2, 129.2, 128.8, 128.7, 128.6, 127.3, 96.4, 68.7, 57.7, 37.0, 36.6, 33.4, 24.9.



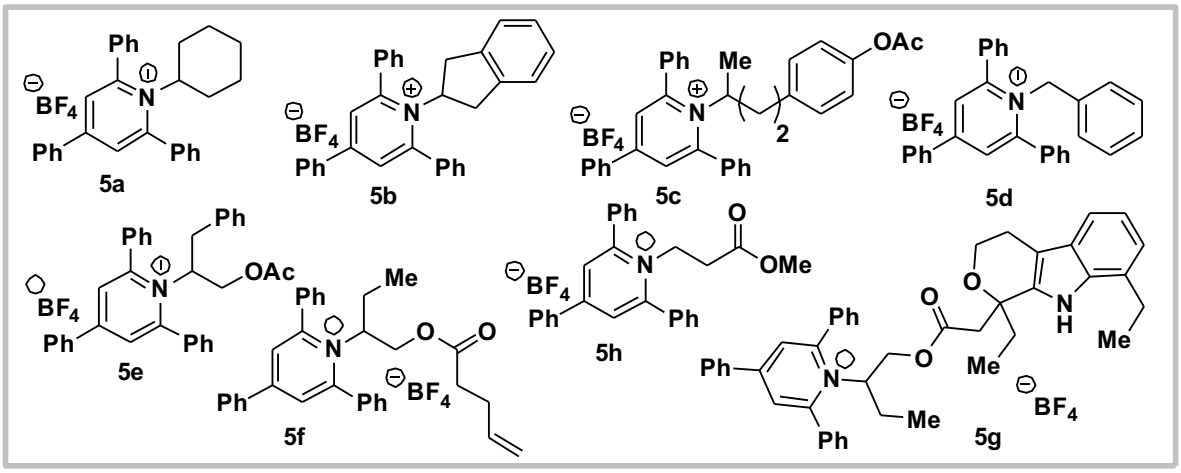
Procedure 9B – Benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate: To a round bottom flask equipped with a stir bar was added benzyl (2S,4R)- 4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (6.3 g, 15.25 mmol, 1 equiv), meta-chloroperoxybenzoic acid (6.6 g, 38.12 mmol, 2.5 equiv), and DCM (205 mL). The reaction was stirred at room temperature for 18 hours. The reaction mixture was washed with 1 M aqueous sodium hydroxide (3 x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (10%–30% ethyl acetate/hexanes) to afford the product (5.5 g, 81% yield) as a white foam. The physical properties and spectral data were consistent with the reported values.[4] **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.44 – 7.33 (m, 10H), 5.62 (s, 1H), 5.30 – 5.18 (m, 2H), 5.09 (dd, J = 8.1, 4.1 Hz, 1H), 4.71 – 4.37 (m, 2H), 3.48 – 3.08 (m, 2H), 0.89

(s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 170.8, 155.4, 135.0, 131.0, 129.3, 129.1, 129.0, 128.9, 128.0, 97.0, 69.0, 60.5, 53.7, 52.7, 37.2, 24.6.

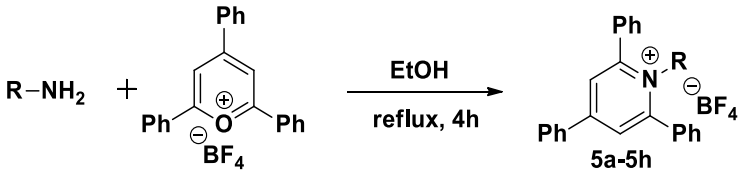


Procedure 9C – Benzyl (S)-2-(*tert*-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (7a): To a round bottom flask equipped with a stir bar was added (benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate) (5.5g, 12.4 mmol, 1 equiv), and DCM (155 mL).The flask was chilled to 0 °C in an ice bath, and DBU (2.1 mL, 13.6 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred at 0 °C until the starting material had been consumed (determined by TLC, about 10 minutes). While still at 0 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL), the layers were separated, and the organic phase was washed with saturated aqueous ammonium chloride (3x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5%–10% ethyl acetate/ hexanes) to afford the product (3.4 g, 98% yield) as a white solid. The physical properties and spectral data are consistent with the reported values.[4] **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.31 (s, 5H), 5.64 (s, 1H), 5.61 (s, 2H), 5.18 (s, 2H), 0.86 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 164.7, 152.5, 134.8, 130.2, 129.0, 128.9, 128.8, 104.5, 94.1, 68.9, 38.8, 24.4.

14. Preparation of *N*-Alkylpyridinium salts



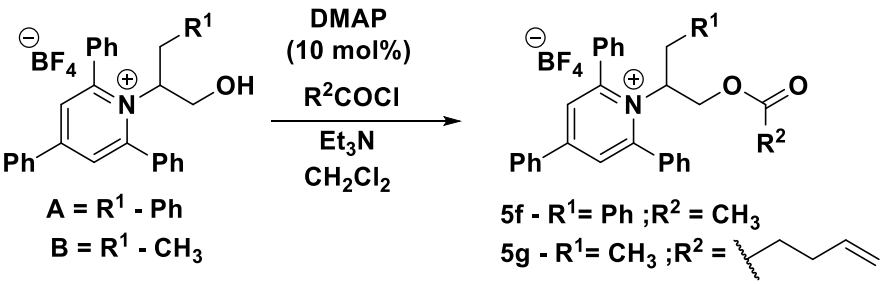
N-Alkylpyridinium salts **5a-h** were prepared according to the previously reported procedure[8].



General procedure 10A:

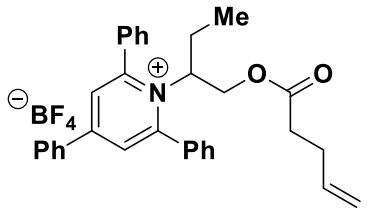
Primary amine (1.2 equiv) was added to a suspension of 2,4,6-triphenylpyrylium tetrafluoroborate (1.0 equiv) and EtOH (1.0 M) in a round-bottomflask. The flask was fitted with a reflux condenser. The mixture was stirred and heated at reflux in an oil bath at 80-85 ^{o}C for 4 h. The mixture was then allowed to cool to room temperature. If product precipitation occurred, the solid was filtered, washed with EtOH (3 x 25 mL) and then Et_2O (3 x 25 mL), and dried under high vacuum. If product precipitation did not occur, the solution was diluted with Et_2O (2-3x volume of EtOH used) and vigorously stirred for 1 h to induce trituration. The resulting solid pyridinium salt was filtered and washed with Et_2O (3 x 25 mL). If the pyridinium salt failed to precipitate at this point, the flask containing the reaction mixture and Et_2O was sealed with parafilm and stored in a -27 °C freezer for 1-3 days (or until precipitation occurred). The cold mixture was quickly filtered and washed with Et_2O (3 x 25 mL) to give the corresponding analytically pure pyridinium salt. If the salt still did not precipitate, it was subjected to silica gel chromatography using acetone/CH_2Cl_2 as the eluent.

General Procedure 10B – *O*-acylated - *N*-alkyl-pyridinium salts 5e and 5f



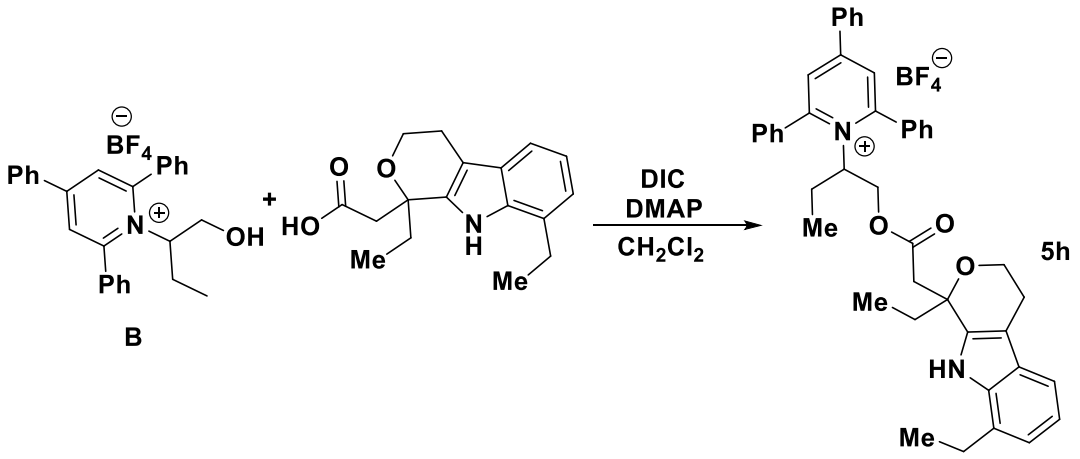
To a solution of respective salt **A**/salt **B** (1 eq.) – prepared according the general procedure 9A – and DMAP (10 mol%) in anhydrous CH_2Cl_2 was added Et_3N (2 equiv.). The reaction mixture was then cooled to 0ºC. Corresponding acyl chloride (2 equiv.) was added dropwise to the mixture. The reaction was allowed to warm to rt and stirred overnight, before being quenched with H_2O and extracted with

CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentration in vacuum. Purification by flashcolumn chromatography (2–10% acetone/CH_2Cl_2) provided the desired product **5e/5f**.



1-(1-(pent-4-enoyloxy)butan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**5f**) was synthesized according to the general procedure 9B: Flash column chromatography purification 0-60% of Acetone in hexanes afforded the title compound in 92% (500 mg) as a light yellow oil. R_f = 0.6-0.7 (hexanes/Acetone 1:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 8.29 (s, 2H), 8.06 (dt, *J* = 8.2, 1.5 Hz, 2H), 7.77 – 7.56 (m, 13H), 5.79 – 5.67 (m, 1H), 5.09 – 5.00 (m, 1H), 4.99 – 4.88 (m, 2H), 4.26 – 3.93 (m, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 2.25 (q, *J* = 7.3, 6.6 Hz, 2H), 2.14 – 1.53 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.4, 157.0, 137.8, 134.6, 133.8, 132.5, 130.9, 130.6, 129.7, 116.2, 71.8, 65.4, 33.8, 29.6, 28.0, 11.3. **HRMS (ESI)** m/z: $[M]^+$ Calcd. for $C_{32}H_{32}NO_2$ 462.2428; Found:462.2430

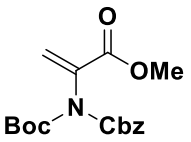
General procedure 10C – O-acylated N-alkyl-pyridinium salt 5g



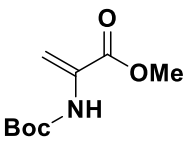
To a solution of Etodolac (284.7 mg; 0.99 mmol), **B** (476 mg; 0.99 mmol,) – prepared according the general procedure 9A – and DMAP (6 mg; 0,05 mmol) in DCM (10 mL) was added DIC (145 µL; 0.99 mmol). The reaction mixture was stirred at rt for 24 h, then solid was removed by filtration in a pad of silica. The residue was purified by flash column chromatography (DCM/acetone = 10:1) to provide 1-(1-(2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetoxy)butan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **5g** (530 mg,

0.72 mmol, 73% yield) as a yellowish solid. R_f = 0.6-0.7 (hexanes/Acetone 1:1). **NMR ^{1}H (400 MHz, CD_3OD)** δ 8.46 – 8.00 (m, 4H), 7.80 – 7.39 (m, 13H), 7.20 – 6.77 (m, 3H), 5.12 – 4.95 (m, 1H), 4.03 – 3.85 (m, 2H), 3.83 – 3.74 (m, 2H), 3.08 – 2.68 (m, 4H), 2.67 – 2.44 (m, 2H), 2.06 – 1.87 (m, 2H), 1.85 – 1.37 (m, 2H), 1.29 – 1.16 (m, 3H), 0.74 – 0.56 (m, 6H). **NMR ^{13}C (100 MHz, CD_3OD)** δ 170.7, 156.7, 136.4, 134.4, 133.9, 132.5, 131.0, 130.7, 129.7, 129.6, 128.1, 128.0, 127.7, 121.3, 120.4, 120.3, 116.6, 116.6, 109.1, 77.1, 71.3, 65.1, 61.9, 43.9, 32.5, 27.5, 25.0, 23.1, 14.8, 11.1, 8.1. **HRMS (ESI)** m/z: $[M]^+$ Calcd. for $C_{44}H_{45}N_2O_3$ 649.3425; Found: 649.3451.

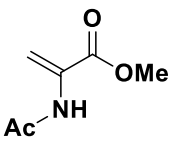
15. Reactivity experiments against others Dha's.



2a': 82% yield

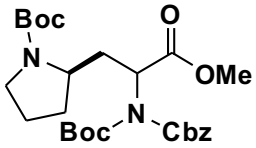


2a'': traces

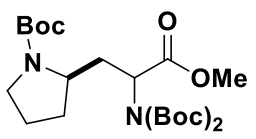


2a''': traces

16. Characterization data of compounds 4a', 4a-ad.

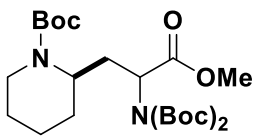


***Tert*-butyl 2-(2-(((benzyloxy)carbonyl)((*tert*-butyloxy)carbonyl)amino)-3-methoxy-3-oxopropyl)pyrrolidine-1-carboxylate** (**2a'**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-30% of EtOAc in hexanes afforded the title compound in 82% (83.3 mg) as a colorless oil. R_f = 0.4-0.5 (hexanes/EtOAc 8:2). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.42 – 7.30 (m, 5H), 5.29 – 5.18 (m, 2H), 4.96 (s, 1H), 3.83 (s, 1H), 3.69 – 3.59 (m, 3H), 3.45 – 3.20 (m, 2H), 2.75 – 2.12 (m, 1H), 2.08 – 1.64 (m, 5H), 1.47 – 1.37 (m, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 170.8, 154.6, 153.8, 151.4, 135.3, 128.7, 128.5, 84.0, 79.5, 69.1, 57.2, 56.1, 52.4, 46.1, 35.7, 30.8, 28.6, 28.0, 23.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{26}H_{38}N_2NaO_8$ 529.2520; Found: 529.2535.

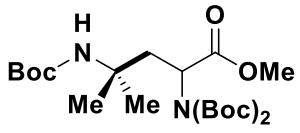


Tert-butyl 2-(2-(di-(tert-butoxycarbonyl) amino)-3-methoxy-3-oxopropyl) pyrrolidine-1-carboxylate (**4a**) was

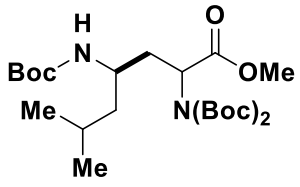
synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 90% (85.4 mg) as a colorless oil. R_f = 0.3-0.4 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.15 – 4.76 (m, 1H), 3.95 – 3.83 (m, 1H), 3.71 (s, 3H), 3.45 – 3.24 (m, 2H), 2.74 – 2.64 (m, 1H), 2.00 – 1.87 (m, 1H), 1.86 – 1.74 (m, 2H), 1.74 – 1.60 (m, 2H), 1.49 (s, 18H), 1.47 – 1.41 (m, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.2, 154.6, 152.1, 83.3, 79.4, 56.9, 56.2, 52.4, 46.2, 35.5, 31.1, 28.7, 28.2, 23.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{40}N_2O_8Na$ 495.2677; Found: 495.2684.



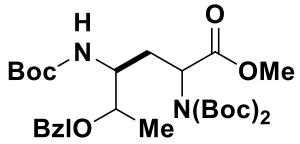
***Tert*-butyl 2-(2-(di-(*tert*-butoxycarbonyl) amino)-3-methoxy-3-oxopropyl) piperidine-1-carboxylate** (**4b**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 76% (73.5 mg) as a colorless oil. R_f = 0.3-0.4 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.89 (t, J = 6.6 Hz, 1H), 4.33 (s, 1H), 4.00 – 3.88 (m, 1H), 3.69 (s, 3H), 2.85 (t, J = 13.3 Hz, 1H), 2.67 – 2.53 (m, 1H), 1.93 (dt, J = 14.5, 7.0 Hz, 1H), 1.61 – 1.54 (m, 4H), 1.52 – 1.45 (m, 20H), 1.44 – 1.39 (m, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.6, 155.2, 152.3, 83.1, 79.4, 56.5, 55.7, 52.4, 52.3, 30.8, 28.8, 28.6, 28.1, 25.6, 19.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{42}N_2O_8Na$ 509.2833; Found: 509.2837.



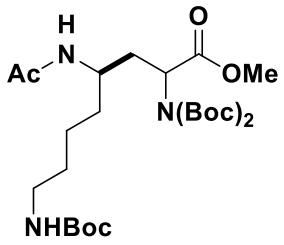
Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-((*tert*-butoxycarbonyl) amino)-4-methylpentanoate (**4c**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 96% (88.8 mg) as a colorless oil. R_f = 0.5 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.01 (dd, J = 6.8, 3.7 Hz, 1H), 4.79 (s, 1H), 3.71 (s, 3H), 2.53 (d, J = 16.1 Hz, 1H), 2.14 (dd, J = 14.8, 6.5 Hz, 1H), 1.49 (s, 18H), 1.41 (s, 9H), 1.33 (s, 3H), 1.29 (s, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.4, 154.6, 152.1, 83.3, 78.8, 55.2, 52.7, 51.9, 41.5, 28.6, 28.1, 27.6, 27.2. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{40}N_2O_8Na$ 483.2677; Found: 483.2678.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-((*tert*-butoxycarbonyl) amino)-6-methylheptanoate (**4d**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 67% (65.0 mg) as a colorless oil. R_f = 0.3-0.4 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.96 (dt, J = 13.8, 5.8 Hz, 1H), 4.43 (dd, J = 23.2, 9.2 Hz, 1H), 3.87 – 3.56 (m, 4H), 2.46 – 2.14 (m, 1H), 2.13 – 1.64 (m, 1H), 1.64 – 1.54 (m, 1H), 1.48 (s, 18H), 1.43 – 1.38 (m, 9H), 1.33 – 1.17 (m, 2H), 0.89 (dd, J = 6.5, 5.8 Hz, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.9, 155.6, 152.2, 83.3, 79.1, 55.4, 52.5, 47.2, 44.9, 37.1, 28.5, 28.1, 25.1, 23.0, 22.7. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{44}N_2O_8Na$ 511.2990; Found: 511.2999.

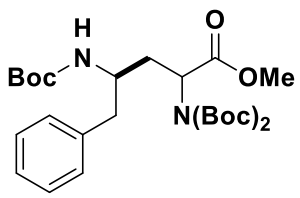


Methyl 5-(benzyloxy)-2-(di-(*tert*-butoxycarbonyl) amino)-4-((*tert*-butoxycarbonyl) amino) hexanoate (**4e**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 51% (57.6 mg) as a colorless oil. R_f = 0.3-0.4 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.39 – 7.23 (m, 5H), 5.11 – 4.93 (m, 1H), 4.90 – 4.72 (m, 1H), 4.65 – 4.37 (m, 2H), 3.80 – 3.66 (m, 4H), 3.65 – 3.45 (m, 1H), 2.68 – 2.23 (m, 1H), 2.17 – 1.74 (m, 1H), 1.50 – 1.45 (m, 18H), 1.44 – 1.38 (m, 9H), 1.26 – 1.14 (m, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.3, 155.8, 152.2, 138.6, 128.5, 127.8, 127.8, 83.2, 79.1, 75.4, 71.1, 55.9, 52.4, 52.3, 32.8, 28.5, 28.1, 16.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{46}N_2O_9Na$ 589.3096; Found: 589.3094.

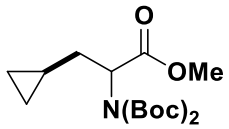


Methyl 4-acetamido-2-(di-(*tert*-butoxycarbonyl) amino)-8-((*tert*-butoxycarbonyl) amino) octanoate (**4f**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-20% of hexanes in EtOAc afforded the title compound in 48% (52.9 mg) as a colorless oil. R_f = 0.35-0.45 (EtOAc/hexanes 8:2). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.71 (d, J = 8.7 Hz, 1H), 4.94 – 4.83 (m, 1H), 4.67 – 4.56 (m, 1H), 4.11 – 3.84 (m, 1H), 3.69 (s, 3H), 3.12 – 2.99 (m, 2H), 2.48 – 2.22 (m, 1H), 2.08 – 2.01

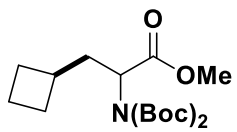
(m, 1H), 1.97 – 1.88 (m, 3H), 1.51 – 1.43 (m, 22H), 1.41 (s, 9H), 1.35 – 1.28 (m, 2H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.2, 169.8, 156.2, 152.3, 83.6, 79.1, 55.4, 52.5, 47.5, 40.4, 36.4, 35.0, 29.8, 28.5, 28.1, 23.6, 23.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{26}H_{47}N_3O_9Na$ 568.3205; Found: 568.3212.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-((*tert*-butoxycarbonyl) amino)-5-phenylpentanoate (**4g**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-30% of EtOAc in hexanes afforded the title compound in 74% (77.5 mg) as a colorless oil. R_f = 0.3-0.40 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.23 – 7.19 (m, 2H), 7.11 (t, J = 6.7 Hz, 3H), 5.01 – 4.86 (m, 1H), 4.58 – 4.35 (m, 1H), 3.99 – 3.65 (m, 1H), 3.61 (s, 3H), 2.94 – 2.58 (m, 2H), 2.43 – 2.06 (m, 1H), 2.07 – 1.53 (m, 1H), 1.40 (s, 9H), 1.36 – 1.30 (m, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.8, 155.4, 151.8, 138.1, 129.6, 128.5, 126.4, 55.5, 52.5, 49.9, 41.7, 33.8, 28.5, 28.0. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{27}H_{42}N_2O_8Na$ 545.2833; Found: 545.2838.

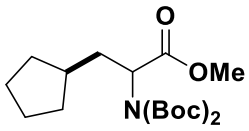


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-cyclopropylpropanoate (**4h**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 11% (7.8 mg) as a colorless oil. R_f = 0.5 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.01 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.70 (s, 3H), 2.07 – 1.98 (m, 1H), 1.82 – 1.72 (m, 1H), 1.49 (s, 18H), 0.73 (qq, *J* = 7.6, 5.0, 3.8 Hz, 1H), 0.44 (ttd, *J* = 13.1, 8.7, 4.3 Hz, 2H), 0.15 – 0.03 (m, 2H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.5, 152.2, 83.1, 58.8, 52.2, 35.2, 28.2, 8.2, 5.0, 4.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{29}NO_6Na$ 366.1887; Found: 366.1885.

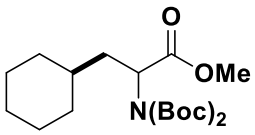


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-cyclobutylpropanoate (**4i**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 56% (40.2 mg) as a colorless oil. R_f = 0.5-0.55 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.80 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.68 (s, 3H), 2.32 (hept, *J* = 8.0 Hz, 1H),

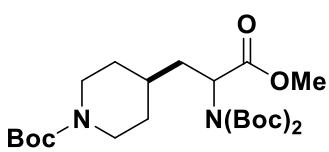
2.20 – 2.11 (m, 1H), 2.09 – 1.92 (m, 3H), 1.90 – 1.74 (m, 2H), 1.69 – 1.61 (m, 2H), 1.48 (s, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.7, 152.1, 83.0, 57.0, 52.2, 36.9, 33.3, 28.4, 28.3, 28.1, 18.6. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{31}NO_6Na$ 380.2044; Found: 380.2041.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-cyclopentylpropanoate (**4j**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 62% (46.2 mg) as a colorless oil. R_f = 0.6 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.89 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.69 (s, 3H), 2.05 (ddd, *J* = 13.5, 8.1, 5.1 Hz, 1H), 1.93 (ddd, *J* = 14.5, 9.8, 4.9 Hz, 1H), 1.84 – 1.70 (m, 4H), 1.51 – 1.46 (m, 21H), 1.17 – 1.04 (m, 2H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.9, 152.3, 83.1, 57.8, 52.2, 37.1, 36.1, 33.0, 32.6, 28.1, 25.3, 25.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{33}NO_6Na$ 394.2200; Found: 394.2203.

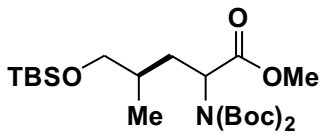


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-cyclohexylpropanoate (**4k**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 70% (53.7 mg) and in 80% (61.8 mg) according to the general procedure B. Colorless oil. R_f = 0.5 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.95 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.70 (s, 3H), 1.95 (ddd, *J* = 14.1, 9.0, 4.9 Hz, 1H), 1.79 (ddd, *J* = 14.3, 11.7, 7.0 Hz, 2H), 1.73 – 1.58 (m, 4H), 1.49 (s, 18H), 1.30 – 1.09 (m, 4H), 1.04 – 0.79 (m, 2H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.0, 152.2, 83.1, 56.1, 52.3, 37.8, 34.6, 34.1, 32.8, 28.1, 26.6, 26.5, 26.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{20}H_{35}NO_6Na$ 408.2357; Found: 408.2358.

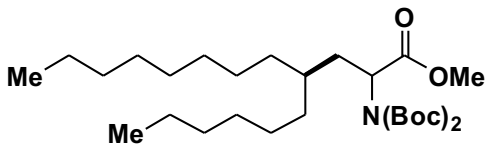


***Tert*-butyl 4-(2-(di-(*tert*-butoxycarbonyl) amino)-3-methoxy-3-oxopropyl) piperidine-1-carboxylate** (**4l**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-20% of EtOAc in hexanes afforded the title compound in 47% (45.7 mg) as a colorless oil. R_f = 0.2 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.94 (dd, *J* = 9.4,

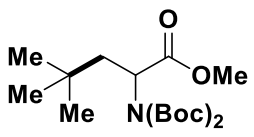
5.1 Hz, 1H), 4.20 – 3.92 (m, 2H), 3.69 (s, 3H), 2.63 (q, *J* = 14.0 Hz, 2H), 2.00 (ddd, *J* = 14.2, 8.9, 5.2 Hz, 1H), 1.87 – 1.72 (m, 3H), 1.62 – 1.53 (m, 1H), 1.47 (s, 18H), 1.43 (s, 9H), 1.28 – 0.99 (m, 2H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.6, 155.0, 152.2, 83.3, 79.4, 55.7, 52.3, 36.9, 33.1, 32.7, 31.7, 28.6, 28.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{42}N_2O_8Na$ 509.2833; Found: 509.2847.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-5-((*tert*-butyldimethylsilyl) oxy)-4-methylpentanoate (**4m**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 70% (66.4 mg) as a colorless oil. R_f = 0.7-0.8 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.99 – 4.87 (m, 1H), 3.74 – 3.66 (m, 3H), 3.56 – 3.36 (m, 2H), 2.29 – 2.02 (m, 1H), 1.79 – 1.59 (m, 2H), 1.49 – 1.44 (m, 18H), 0.93 – 0.88 (m, 3H), 0.86 (s, 9H), 0.01 (s, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.7, 152.2, 83.1, 68.7, 56.6, 52.2, 33.6, 33.0, 28.1, 26.1, 18.4, 17.6, -5.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{45}NNaO_7Si$ 498.2858; Found: 498.2866.

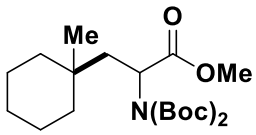


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-hexyldodecanoate (4n) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 48% (50.3 mg) as a colorless oil. R_f = 0.75 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.93 (dd, *J* = 9.3, 5.2 Hz, 1H), 3.69 (s, 3H), 1.99 – 1.81 (m, 2H), 1.48 (s, 18H), 1.32 – 1.15 (m, 25H), 0.86 (t, *J* = 6.6 Hz, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.1, 152.3, 83.0, 56.5, 52.2, 34.6, 34.1, 33.9, 33.3, 32.0, 30.2, 30.1, 29.9, 29.8, 29.5, 28.1, 26.9, 26.8, 26.4, 26.4, 22.8, 14.2. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{55}NO_6Na$ 536.3922; Found: 536.3930.

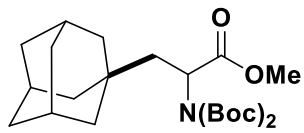


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4,4-dimethylpentanoate (4o) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 73% (52.5

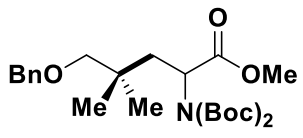
mg) as a colorless oil. R_f = 0.4-0.55 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.92 (dd, *J* = 7.9, 3.3 Hz, 1H), 3.69 (s, 3H), 2.21 (ddd, *J* = 15.1, 3.3, 1.0 Hz, 1H), 1.51 – 0.90 (m, 18H), 1.71 – 1.63 (m, 1H), 1.49 (s, 18H), 0.92 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.4, 152.3, 83.1, 55.8, 52.5, 43.7, 30.4, 29.5, 28.2. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{33}NO_6Na$ 382.2200; Found: 382.2201.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-(1-methylcyclohexyl) propanoate (**4p**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 46% (36.4 mg) as a colorless oil. R_f = 0.6-0.7 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.93 (dd, J = 7.5, 3.1 Hz, 1H), 3.69 (s, 3H), 2.25 (dd, J = 15.2, 3.2 Hz, 1H), 1.71 (dd, J = 15.2, 7.5 Hz, 1H), 1.49 (s, 18H), 1.46 – 1.38 (m, 5H), 1.32 – 1.23 (m, 5H), 0.89 (s, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.5, 152.3, 83.1, 55.1, 52.5, 42.3, 37.8, 32.8, 28.2, 26.5, 24.7, 22.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{37}NO_6Na$ 422.2513; Found: 422.2511.

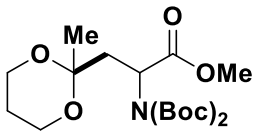


Methyl 3-((3r,5r,7r)-adamantan-1-yl)-2-(di-(*tert*-butoxycarbonyl) amino) propanoate (**4q**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 95% (83.1 mg) as a colorless oil. R_f = 0.45-0.6 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.97 (dd, *J* = 7.4, 3.6 Hz, 1H), 3.69 (s, 3H), 2.10 (dd, *J* = 15.2, 3.5 Hz, 1H), 1.98 – 1.91 (m, 3H), 1.69 (d, *J* = 12.5 Hz, 3H), 1.61 (d, *J* = 12.1 Hz, 4H), 1.57 – 1.44 (m, 24H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.5, 152.2, 83.1, 54.2, 52.4, 44.9, 42.3, 37.1, 32.3, 28.7, 28.2. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{39}NO_6Na$ 460.2670; Found: 460.2670.

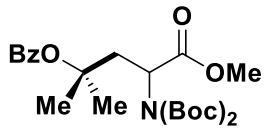


Methyl 5-(benzyloxy)-2-(di-(*tert*-butoxycarbonyl) amino)-4,4-dimethylpentanoate (4r) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 63% (57.1 mg) as a colorless oil. R_f = 0.6 (hexanes/EtOAc 9:1).

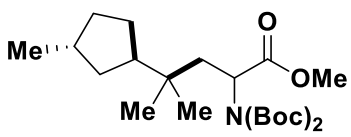
NMR ^{1}H (400 MHz, $CDCl_3$) δ 7.53 – 7.13 (m, 5H), 5.05 (dt, J = 7.9, 4.1 Hz, 1H), 4.60 – 4.38 (m, 2H), 3.68 (s, 3H), 3.33 – 3.11 (m, 2H), 2.39 – 2.27 (m, 1H), 1.85 (tdd, J = 15.0, 7.5, 1.4 Hz, 1H), 1.48 (s, 18H), 1.03 – 0.92 (m, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.3, 152.2, 139.1, 128.4, 128.3, 127.3, 83.0, 79.2, 73.2, 55.4, 52.4, 39.4, 34.5, 28.1, 24.9, 24.7. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{39}NO_7Na$ 488.2619; Found: 488.2624.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-(2-methyl-1,3-dioxan-2-yl) propanoate (**4s**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-20% of EtOAc in hexanes afforded the title compound in 39% (31.8 mg) as a colorless oil. R_f = 0.3-0.45 (hexanes/EtOAc 8:2). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.32 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.95 – 3.77 (m, 4H), 3.70 (s, 3H), 2.65 (dd, *J* = 15.6, 2.9 Hz, 1H), 2.30 – 2.19 (m, 1H), 1.85 (dtt, *J* = 13.7, 9.2, 4.6 Hz, 1H), 1.48 (s, 19H), 1.42 (s, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.1, 152.3, 98.4, 82.7, 60.0, 59.9, 54.4, 52.5, 39.9, 28.2, 25.2, 20.7. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{33}NO_8Na$ 426.2098; Found: 426.2101.

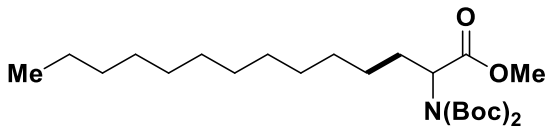


4-(di-(*tert*-butoxycarbonyl) amino)-5-methoxy-2-methyl-5-oxopentan-2-yl benzoate (4t) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-20% of EtOAc in hexanes afforded the title compound in 89% (82.8 mg) as a colorless oil. R_f = 0.5-0.6 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.96 (d, J = 7.9 Hz, 2H), 7.54 – 7.46 (m, 1H), 7.39 (t, J = 7.3 Hz, 2H), 5.26 (dd, J = 7.4, 4.2 Hz, 3H), 3.72 (s, 1H), 2.71 – 2.59 (m, 2H), 1.65 (d, J = 3.2 Hz, 6H), 1.47 – 1.38 (m, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.9, 165.9, 152.3, 132.6, 131.9, 129.8, 128.2, 83.3, 81.9, 54.9, 52.7, 41.2, 28.0, 26.6, 26.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{35}NO_8Na$ 488.2255; Found: 488.2267.

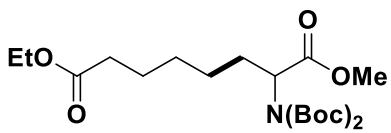


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-methyl-4-((3R)-3-methylcyclopentyl) pentanoate (4u) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 61% (52,4 mg) as a colorless oil. R_f =

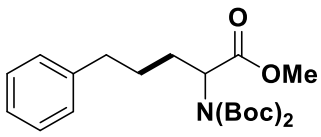
0.65 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.94 (dt, *J* = 7.6, 3.6 Hz, 1H), 3.68 (s, 3H), 2.22 (dt, *J* = 15.3, 3.7 Hz, 1H), 1.94 – 1.79 (m, 2H), 1.77 – 1.61 (m, 3H), 1.54 – 1.43 (m, 20H), 1.31 – 1.18 (m, 1H), 1.15 – 0.99 (m, 1H), 0.97 – 0.91 (m, 3H), 0.87 – 0.79 (m, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.5, 152.3, 83.0, 55.3, 52.4, 48.1, 41.3, 36.8, 35.6, 34.8, 34.2, 28.1, 27.8, 24.2, 24.1, 21.3. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{41}NO_6Na$ 450.2826; Found: 450.2829.



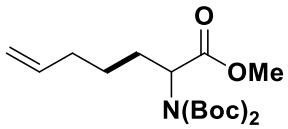
Methyl 2-(di-(*tert*-butoxycarbonyl) amino) tetradecanoate (4v) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 47% (42.6 mg) as a colorless oil. R_f = 0.7 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.84 (dd, *J* = 9.7, 5.0 Hz, 1H), 3.69 (s, 3H), 2.07 (dq, *J* = 15.2, 5.7, 4.9 Hz, 1H), 1.86 (dq, *J* = 17.7, 11.4, 6.4 Hz, 1H), 1.48 (s, 18H), 1.24 (s, 20H), 0.86 (t, *J* = 6.7 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.7, 152.3, 83.0, 58.3, 52.2, 32.0, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 28.1, 26.3, 22.8, 14.2. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{47}NO_6Na$ 480.3296; Found: 480.3297.



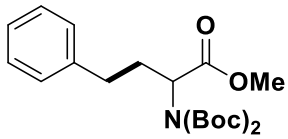
8-ethyl 1-methyl 2-(di-(*tert*-butoxycarbonyl) amino) octanedioate (4w) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 66% (57.3 mg) as a colorless oil. R_f = 0.3-0.4 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.83 (dd, *J* = 9.6, 5.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.08 (ddd, *J* = 14.4, 5.8, 5.0 Hz, 1H), 1.88 (ddd, *J* = 14.2, 9.4, 5.1 Hz, 1H), 1.67 – 1.57 (m, 2H), 1.48 (s, 18H), 1.39 – 1.29 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.8, 171.6, 152.3, 83.2, 60.3, 58.2, 52.3, 34.4, 29.9, 28.9, 28.1, 26.0, 24.9, 14.4. **HRMS (ESI)** m/z: [M+Na]+ Calcd. for $C_{21}H_{37}NO_8Na$ 454.2411; Found: 454.2415.



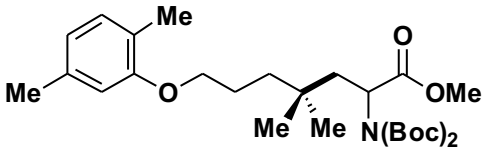
Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-5-phenylpentanoate (**4x**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 40% (36.1 mg) as a colorless oil. R_f = 0.75 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.19 (t, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 3H), 4.84 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.63 (s, 3H), 2.68 – 2.48 (m, 2H), 2.06 (ddt, *J* = 15.4, 10.9, 5.8 Hz, 1H), 1.86 (ddt, *J* = 13.8, 9.0, 4.7 Hz, 1H), 1.70 – 1.50 (m, 2H), 1.40 (s, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.5, 152.2, 142.1, 128.5, 128.4, 125.9, 83.2, 58.0, 52.3, 35.5, 29.5, 28.1, 28.0. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{22}H_{33}NO_6Na$ 430.2200; Found: 430.2202.



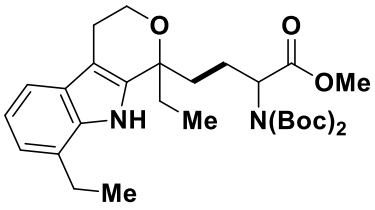
Methyl 2-(di-(*tert*-butoxycarbonyl) amino) hept-6-enoate (**4y**) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 28% (20.1 mg) as a colorless oil. R_f = 0.4-0.5 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.78 (ddt, *J* = 16.9, 10.4, 6.5 Hz, 1H), 5.05 – 4.91 (m, 2H), 4.86 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.70 (s, 3H), 2.16 – 2.01 (m, 3H), 1.95 – 1.84 (m, 1H), 1.49 (s, 20H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.6, 152.3, 138.4, 115.0, 83.2, 58.1, 52.3, 33.4, 29.4, 28.1, 25.6. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{31}NO_6Na$ 380.2044; Found: 380.2043.



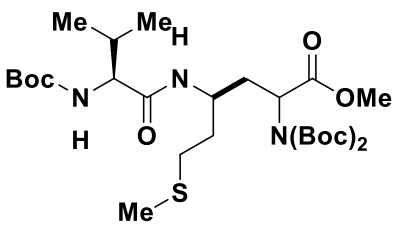
Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-phenylbutanoate (4z) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 31% (24.3 mg) and in 72% (58.4 mg) according to the general procedure 4B. Colorless oil. R_f = 0.55-0.6 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 6.5 Hz, 2H), 7.18 – 7.12 (m, 3H), 4.87 (dd, *J* = 9.3, 5.2 Hz, 1H), 3.68 (s, 3H), 2.65 (t, *J* = 8.0 Hz, 2H), 2.49 – 2.38 (m, 1H), 2.24 – 2.10 (m, 1H), 1.46 (s, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.4, 152.2, 141.4, 128.5, 128.5, 126.1, 83.2, 57.9, 52.3, 32.7, 31.9, 28.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{31}NO_6Na$ 416.2044; Found: 416.2041.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-7-(2,5-dimethylphenoxy)-4,4-dimethylheptanoate (4aa) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 77% (78.5 mg) as a colorless oil. R_f = 0.6-0.7 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 6.99 (d, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.61 (s, 1H), 4.97 (dd, *J* = 7.7, 3.0 Hz, 1H), 3.90 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 3H), 2.33 – 2.26 (m, 4H), 2.17 (s, 3H), 1.80 – 1.69 (m, 3H), 1.50 (s, 18H), 1.44 – 1.37 (m, 2H), 0.95 (s, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.3, 157.2, 152.3, 136.5, 130.3, 123.7, 120.6, 112.0, 83.1, 68.6, 55.4, 52.5, 41.5, 38.4, 32.7, 28.1, 27.2, 26.9, 24.4, 21.5, 15.9. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{28}H_{45}NNaO_7$ 530.3088; Found: 530.3096.

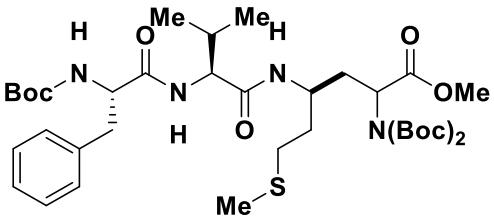


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)butanoate (4ab) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-30% of EtOAc in hexanes afforded the title compound in 15% (16.1 mg) as a colorless oil. R_f = 0.4-0.5 (hexanes/EtOAc 8:2). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.94 (s, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.08 – 7.02 (m, 1H), 7.00 – 6.96 (m, 1H), 4.85 – 4.74 (m, 1H), 4.05 – 3.96 (m, 2H), 3.65 (s, 3H), 2.92 – 2.68 (m, 4H), 1.99 – 1.85 (m, 4H), 1.52 – 1.48 (m, 2H), 1.39 (s, 18H), 1.37 – 1.34 (m, 3H), 0.92 – 0.87 (m, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.6, 152.1, 136.8, 134.9, 126.9, 126.6, 120.3, 119.8, 115.9, 109.3, 83.4, 76.8, 60.5, 58.0, 52.2, 34.7, 31.9, 28.0, 25.1, 24.1, 22.5, 14.0, 8.2. **HRMS (ESI) 4ab**, m/z: $[M+Na]^+$ Calcd. for $C_{30}H_{44}N_2O_7Na$ 567.3041; Found: 567.3051.



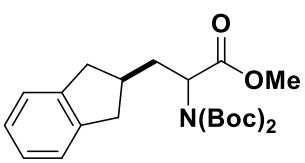
Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-((*S*)-2-((*tert*-butoxycarbonyl) amino)-3-methylbutanamido)-6-(methylthio) hexanoate (4ac) was synthesized according to the general procedure 4A. Flash column chromatography

purification 0-40% of EtOAc in hexanes afforded the title compound in 65% (78.2 mg) as a colorless oil. R_f = 0.2-0.3 (hexanes/EtOAc 8:2). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 6.55 – 6.18 (m, 1H), 5.39 – 4.92 (m, 1H), 4.88 – 4.72 (m, 1H), 4.21 – 3.76 (m, 2H), 3.73 – 3.66 (m, 3H), 2.61 – 2.36 (m, 3H), 2.17 – 1.92 (m, 5H), 1.88 – 1.69 (m, 2H), 1.52 – 1.45 (m, 18H), 1.45 – 1.40 (m, 9H), 0.96 – 0.80 (m, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.6, 171.3, 156.0, 152.1, 83.7, 79.9, 60.4, 55.9, 52.7, 47.5, 35.3, 34.7, 30.7, 30.5, 28.4, 28.1, 19.5, 15.6. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{28}H_{51}N3O_9SNa$ 628.3238; Found: 628.3245.



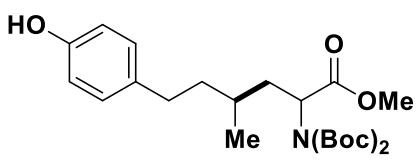
Methyl (6*S*,9*S*,12*S*)-6-benzyl-14-(di-(*tert*-butoxycarbonyl) amino)-9-isopropyl-2,2-dimethyl-12-(2-(methylthio) ethyl)-4,7,10-trioxo-3-oxa-5,8,11-triazapentadecan-15-oate (4ad) was synthesized according to the general procedure 4A. Flash column chromatography purification 0-40% of EtOAc in hexanes afforded the title compound in 76% (114.9 mg) as a colorless oil. R_f = 0.4-0.5 (hexanes/EtOAc 7:3). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.34 – 7.16 (m, 5H), 6.71 – 6.58 (m, 1H), 6.56 – 6.44 (m, 1H), 5.15 – 4.96 (m, 1H), 4.91 – 4.77 (m, 1H), 4.44 – 4.27 (m, 1H), 4.24 – 3.93 (m, 2H), 3.73 – 3.67 (m, 3H), 3.19 – 2.97 (m, 2H), 2.51 – 2.41 (m, 2H), 2.40 – 2.13 (m, 2H), 2.11 – 1.97 (m, 4H), 1.88 – 1.69 (m, 2H), 1.50 (s, 18H), 1.42 – 1.36 (m, 9H), 0.92 – 0.77 (m, 6H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.5, 171.1, 170.5, 155.7, 152.2, 136.6, 129.4, 128.7, 127.0, 83.6, 80.5, 58.7, 55.9, 55.1, 52.6, 47.1, 37.6, 35.1, 33.9, 30.6, 30.5, 28.3, 28.1, 19.4, 15.5. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{37}H_{60}N_4O_{10}SNa$ 775.3922; Found: 775.3929.

17. Characterization data of compounds 6a-f.

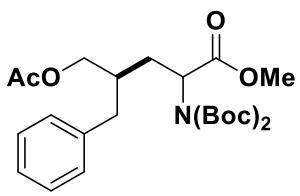


Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-3-(2,3-dihydro-1H-inden-2-yl) propanoate (6a) was synthesized according to the general procedure 4B. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 67% (56.1 mg) as a colorless oil. R_f = 0.55-0.6 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.21 – 7.15

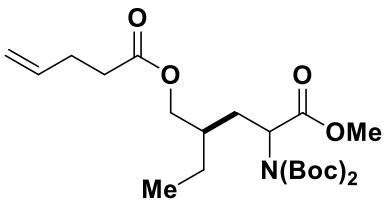
(m, 2H), 7.14 – 7.09 (m, 2H), 5.01 (dd, *J* = 9.7, 4.9 Hz, 1H), 3.73 (s, 3H), 3.08 (ddd, *J* = 15.4, 13.0, 7.6 Hz, 2H), 2.64 (ddd, *J* = 15.4, 8.1, 4.5 Hz, 2H), 2.51 (dp, *J* = 16.0, 7.9 Hz, 1H), 2.30 (ddd, *J* = 13.9, 8.7, 4.9 Hz, 1H), 2.15 (ddd, *J* = 13.6, 9.6, 5.9 Hz, 1H), 1.51 (s, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 171.6, 152.3, 143.2, 143.1, 126.3, 126.3, 124.5, 124.4, 83.2, 57.4, 52.3, 39.5, 39.1, 37.2, 35.7, 28.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{33}NO_6Na$ 442.2200; Found: 442.2207.



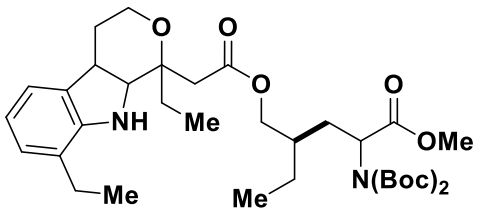
Methyl 2-(di-(tert-butoxycarbonyl) amino)-6-(4-hydroxyphenyl)-4-methylhexanoate (6b) was synthesized according to the general procedure 4B. Flash column chromatography purification 0-25% of EtOAc in hexanes afforded the title compound in 68% (33.6 mg) as a colorless oil. R_f = 0.2-0.3 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 6.94 (dd, J = 10.8, 8.1 Hz, 2H), 6.67 (d, J = 8.1 Hz, 2H), 5.29 (s, 1H), 4.89 (dt, J = 8.4, 4.9 Hz, 1H), 3.64 (d, J = 5.6 Hz, 3H), 2.57 – 2.34 (m, 2H), 2.16 – 1.97 (m, 1H), 1.83 – 1.56 (m, 2H), 1.54 – 1.45 (m, 1H), 1.41 (d, J = 2.9 Hz, 18H), 1.33 – 1.23 (m, 1H), 0.90 (t, J = 6.0 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.0, 153.8, 152.3, 134.8, 129.4, 115.3, 83.3, 56.5, 52.4, 38.5, 37.6, 32.5, 30.2, 28.1, 20.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{37}NO_7Na$ 474.2462; Found: 474.2458.



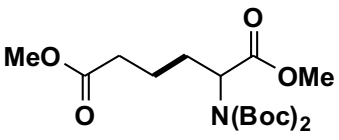
Methyl 5-acetoxy-4-benzyl-2-(di-(*tert*-butoxycarbonyl) amino) pentanoate (6c) was synthesized according to the general procedure 4B. Flash column chromatography purification 0-15% of EtOAc in hexanes afforded the title compound in 63% (30.4 mg) as a colorless oil. R_f = 0.3 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.22 – 7.16 (m, 2H), 7.14 – 7.04 (m, 3H), 5.08 – 4.91 (m, 1H), 4.09 – 3.75 (m, 2H), 3.67 – 3.60 (m, 3H), 2.85 – 2.62 (m, 1H), 2.56 – 2.38 (m, 1H), 2.14 – 1.83 (m, 6H), 1.43 (s, 9H), 1.36 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** 171.5, 171.2, 152.3, 139.5, 129.3, 128.5, 126.3, 83.5, 66.4, 55.9, 52.4, 36.9, 36.5, 32.1, 28.1, 21.0. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{37}NO_8Na$ 502.2411; Found: 502.2405.



Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-((pent-4-enoyloxy) methyl) hexanoate (6d) was synthesized according to the general procedure 4B. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 68% (31.2 mg) as a colorless oil. R_f = 0.5-0.6 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 5.86 – 5.74 (m, 1H), 5.03 – 4.92 (m, 2H), 4.39 (dt, J = 7.1, 1.1 Hz, 1H), 4.16 – 3.92 (m, 2H), 3.70 (s, 3H), 2.44 – 2.30 (m, 4H), 2.16 – 2.03 (m, 1H), 1.98 – 1.85 (m, 1H), 1.68 – 1.55 (m, 1H), 1.48 (s, 18H), 1.43 – 1.37 (m, 2H), 0.89 (td, J = 7.5, 5.2 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.2, 171.6, 152.2, 136.8, 115.6, 83.3, 66.7, 56.1, 52.4, 36.0, 33.6, 31.9, 29.0, 28.1, 23.2, 11.0. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{25}H_{39}NO_8Na$ 480.2568; Found: 480.2572.



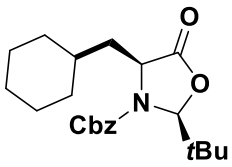
Methyl 2-(di-(*tert*-butoxycarbonyl) amino)-4-((2-(1,8-diethyl-1,3,4,4a,9,9a-hexahydropyrano[3,4-b]indol-1-yl)acetoxy) methyl) hexanoate (6e) was synthesized according to the general procedure 4B. Flash column chromatography purification 0-15% of EtOAc in hexanes afforded the title compound in 78% (50.6 mg) as a colorless oil. R_f = 0.3-0.4 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 9.14 (s, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 7.1 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.17 – 3.89 (m, 4H), 3.73 – 3.67 (m, 3H), 3.08 – 2.70 (m, 6H), 2.19 – 2.07 (m, 2H), 2.06 – 1.86 (m, 2H), 1.72 – 1.60 (m, 1H), 1.51 – 1.47 (m, 20H), 1.40 – 1.34 (m, 3H), 0.94 – 0.86 (m, 3H), 0.83 (t, J = 7.4 Hz, 3H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.1, 171.5, 152.2, 136.1, 134.6, 126.7, 126.3, 120.4, 119.7, 116.0, 108.5, 83.4, 74.7, 67.3, 60.7, 56.1, 52.4, 43.1, 36.0, 31.9, 30.8, 28.1, 24.3, 23.2, 22.5, 13.9, 10.9, 7.7. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{35}H_{52}N_2O_9Na$ 667.3565; Found: 667.3582.



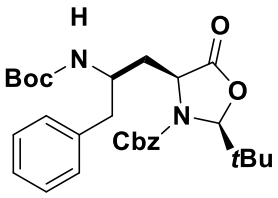
Dimethyl 2-(di-(*tert*-butoxycarbonyl) amino) hexanedioate (6f) was synthesized according to the general procedure 4B. Flash column chromatography purification 0-25% of EtOAc in hexanes afforded the title compound in 25% (19.8

mg) as a colorless oil. R_f = 0.2-0.3 (hexanes/EtOAc 9:1). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 4.87 (dd, J = 9.7, 5.1 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.44 – 2.27 (m, 2H), 2.18 – 2.07 (m, 1H), 1.99 – 1.86 (m, 1H), 1.68 (p, J = 6.9, 6.1 Hz, 2H), 1.49 (s, 18H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.8, 171.3, 152.2, 83.4, 57.9, 52.4, 51.7, 33.7, 29.5, 28.1, 21.8. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{31}NNaO_8$ 412.1942; Found: 412.1941.

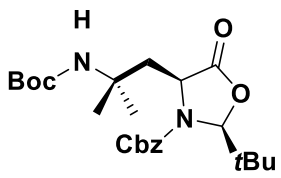
18. Characterization data of compounds 8a-f.



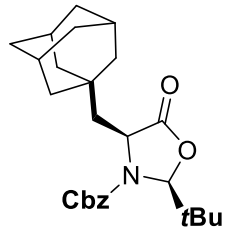
Benzyl (2*S*,4*S*)-2-(*tert*-butyl)-4-(cyclohexylmethyl)-5-oxooxazolidine-3-carboxylate (8a) was synthesized according to the general procedure 4C. Flash column chromatography purification 0-15% of EtOAc in hexanes afforded the title compound in 74% (27.5 mg) as a colorless oil. R_f = 0.6-0.7 (hexanes/EtOAc 85:15). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.40 – 7.31 (m, 5H), 5.55 (s, 1H), 5.22 – 5.10 (m, 2H), 4.45 – 4.33 (m, 1H), 1.81 – 1.70 (m, 2H), 1.67 – 1.51 (m, 6H), 1.10 (d, J = 31.4 Hz, 5H), 0.98 – 0.93 (m, 7H), 0.92 – 0.82 (m, 2H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.3, 156.2, 135.4, 129.4, 128.8, 128.6, 96.4, 68.5, 55.1, 41.3, 37.1, 34.4, 33.6, 33.0, 27.0, 26.6, 26.1, 25.1. **HRMS (ESI)** m/z: $[M+H]^+$ Calcd. for $C_{22}H_{31}NO_4Na$ 396.2145; Found: 396.2144.



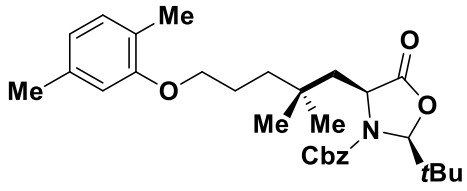
Benzyl (2*S*,4*S*)-4-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (8b) was synthesized according to the general procedure 4C. Flash column chromatography purification 0-20% of EtOAc in hexanes afforded the title compound in 78% (40.0 mg) as a colorless oil. R_f = 0.4-0.5 (hexanes/EtOAc 85:15). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.28 (s, 5H), 7.22 – 7.13 (m, 3H), 7.06 (t, J = 8.2 Hz, 2H), 5.45 (s, 1H), 5.17 – 5.02 (m, 2H), 4.44 – 4.32 (m, 1H), 4.19 – 3.87 (m, 1H), 3.00 – 2.59 (m, 2H), 2.28 – 1.79 (m, 2H), 1.39 – 1.25 (m, 9H), 0.87 – 0.71 (m, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.4, 156.1, 155.5, 138.1, 135.5, 129.6, 129.5, 128.8, 128.8, 128.6, 126.6, 96.7, 79.4, 68.6, 55.2, 50.7, 41.4, 37.5, 36.9, 28.5, 24.8. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{38}N_2O_6Na$ 533.2622; Found: 533.2625.



Benzyl (2S,4S)-4-(2-((*tert*-butoxycarbonyl)amino)-2-methylpropyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (8c) was synthesized according to the general procedure 4C. Flash column chromatography purification 0-15% of EtOAc in hexanes afforded the title compound in 56% (25.2 mg) as a colorless oil. R_f = 0.4-0.5 (hexanes/EtOAc 85:15). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.37 (s, 5H), 5.70 (s, 1H), 5.56 (s, 1H), 5.19 (s, 2H), 4.51 – 4.44 (m, 1H), 2.20 – 2.02 (m, 2H), 1.43 (s, 9H), 1.38 (s, 6H), 0.94 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.7, 156.0, 154.9, 135.1, 129.1, 129.0, 128.9, 96.7, 78.8, 68.8, 54.1, 51.7, 45.5, 37.1, 28.6, 27.2, 25.0. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{36}N_2O_6Na$ 471.2466; Found: 471.2462.

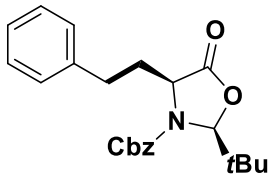


Benzyl (2S,4S)-4-(((3S,5S,7S)-adamantan-1-yl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (**8d**) was synthesized according to the general procedure 4C. Flash column chromatography purification 0-10% of EtOAc in hexanes afforded the title compound in 50% (21.3 mg) as a colorless oil. R_f = 0.7-0.8 (hexanes/EtOAc 85:15). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.37 (s, 5H), 5.54 (s, 1H), 5.22 – 5.10 (m, 2H), 4.46 – 4.38 (m, 1H), 1.90 (s, 3H), 1.79 – 1.56 (m, 9H), 1.55 – 1.43 (m, 5H), 0.95 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.7, 155.8, 135.3, 129.1, 128.9, 128.8, 96.1, 68.5, 52.7, 49.4, 42.5, 37.1, 36.9, 32.9, 28.6, 25.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{26}H_{35}NO_4Na$ 448.2458; Found: 448.2464.



Benzyl (2S,4S)-2-(*tert*-butyl)-4-(5-(2,5-dimethylphenoxy)-2,2-dimethylpentyl)-5-oxooxazolidine-3-carboxylate (8e) was synthesized according to the general procedure 4C. Flash column chromatography purification 0-20% of EtOAc in hexanes afforded the title compound in 54% (26.7 mg) as a colorless oil. R_f = 0.8-0.9 (hexanes/EtOAc 80:20). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.37 – 7.33 (m, 5H), 7.00 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.62 (s, 1H), 5.56 (s, 1H), 5.21 – 5.12 (m, 2H), 4.44 – 4.40 (m, 1H), 3.92 – 3.84 (m, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 1.99 – 1.92 (m, 1H), 1.78 – 1.67 (m, 3H), 1.51 – 1.43 (m, 2H), 1.05 – 0.93

(m, 15H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 173.4, 157.2, 155.9, 136.6, 135.3, 130.4, 129.0, 128.84, 128.80, 123.6, 120.7, 112.2, 96.2, 68.5, 61.9, 54.2, 46.6, 38.7, 37.0, 33.3, 27.2, 26.9, 25.1, 24.4, 21.5, 15.94. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{30}H_{41}NNaO_5$ 518.2877; Found: 518.2880.



Benzyl (2S,4S)-2-(*tert*-butyl)-5-oxo-4-phenethyloxazolidine-3-carboxylate (8f) was synthesized according to the general procedure 4C. Flash column chromatography purification 0-15% of EtOAc in hexanes afforded the title compound in 72% (27.5 mg) as a colorless oil. R_f = 0.7-0.8 (hexanes/EtOAc 85:15). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.32 – 7.28 (m, 3H), 7.25 – 7.20 (m, 2H), 7.20 – 7.17 (m, 2H), 7.13 – 7.08 (m, 3H), 5.48 (d, J = 1.1 Hz, 1H), 5.06 (s, 2H), 4.22 (t, J = 7.5 Hz, 1H), 2.95 – 2.86 (m, 1H), 2.83 – 2.73 (m, 1H), 2.18 – 2.12 (m, 1H), 2.11 – 2.04 (m, 1H), 0.89 (s, 9H). **NMR ^{13}C (100 MHz, $CDCl_3$)** δ 172.7, 156.1, 140.7, 135.4, 128.9, 128.8, 128.6, 126.3, 96.4, 68.4, 56.6, 37.2, 34.9, 32.4, 25.1. **HRMS (ESI)** m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{27}NO_4Na$ 404.1832; Found:404.1829.

19. NMR spectra. Compounds 2a and 7a.

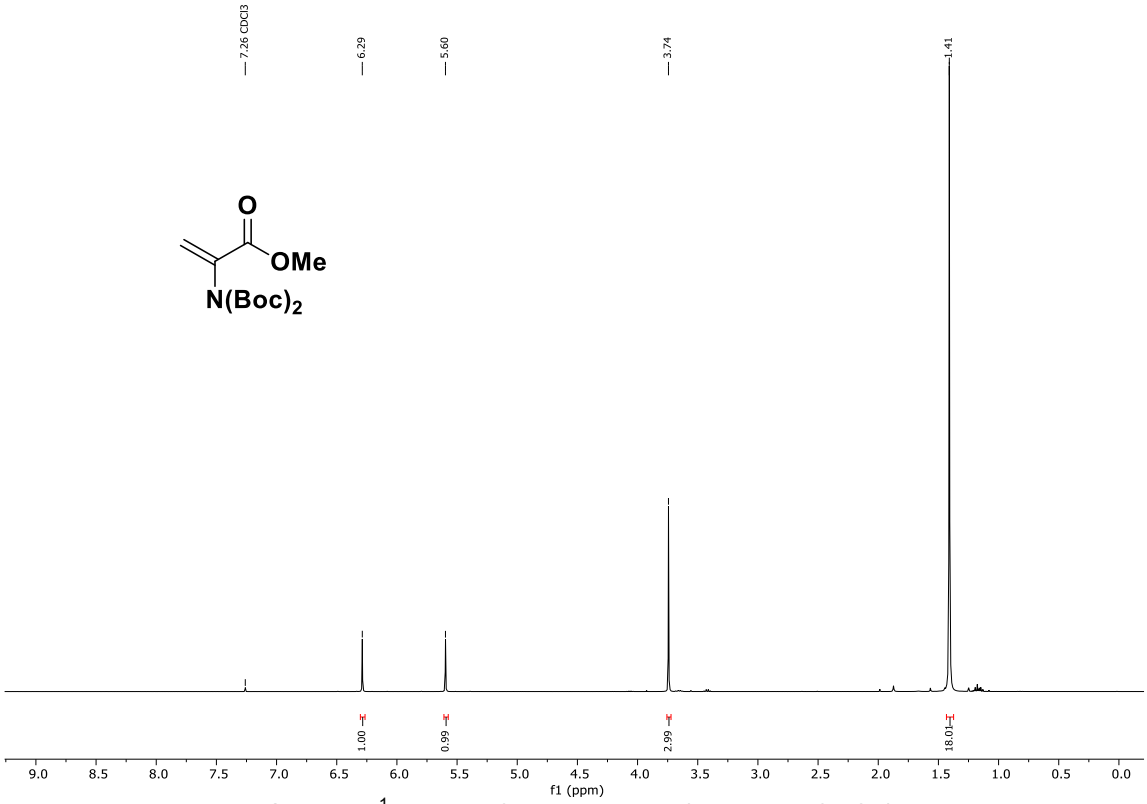


FIGURE 2. ^{1}H NMR of compound **2a** (400 MHz, $CDCl_3$).

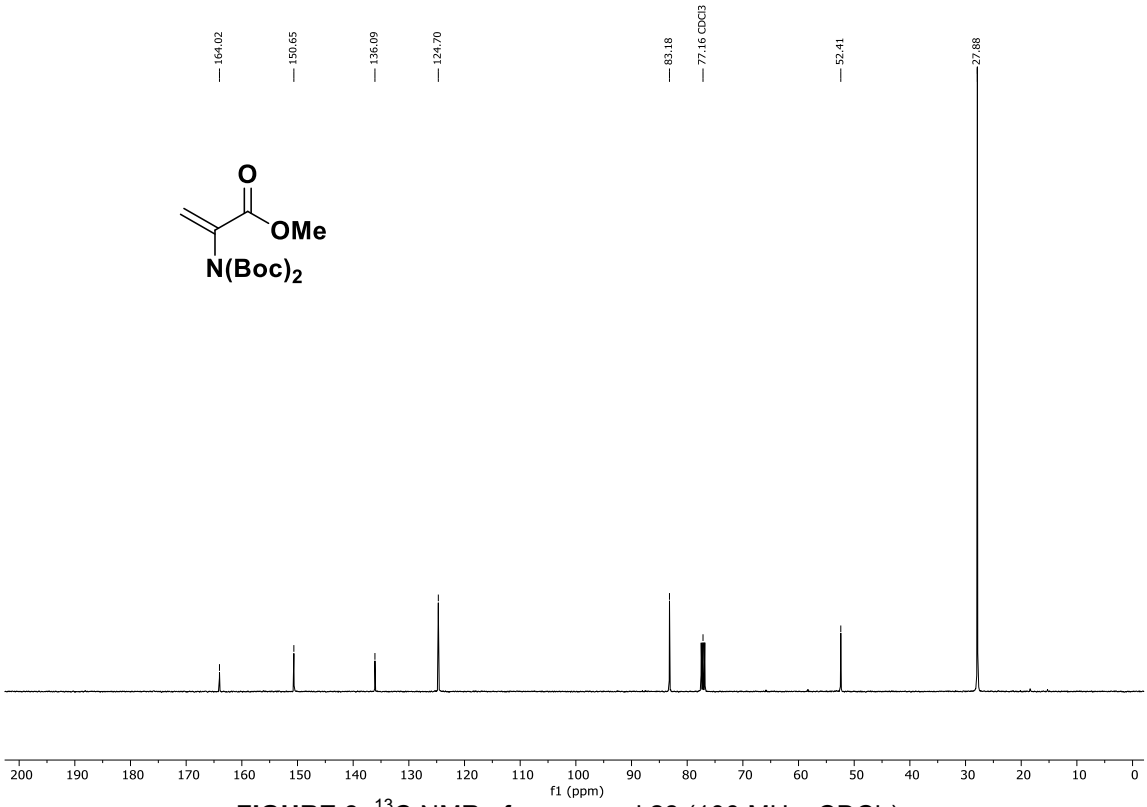


FIGURE 3. ^{13}C NMR of compound **23** (100 MHz, $CDCl_3$).

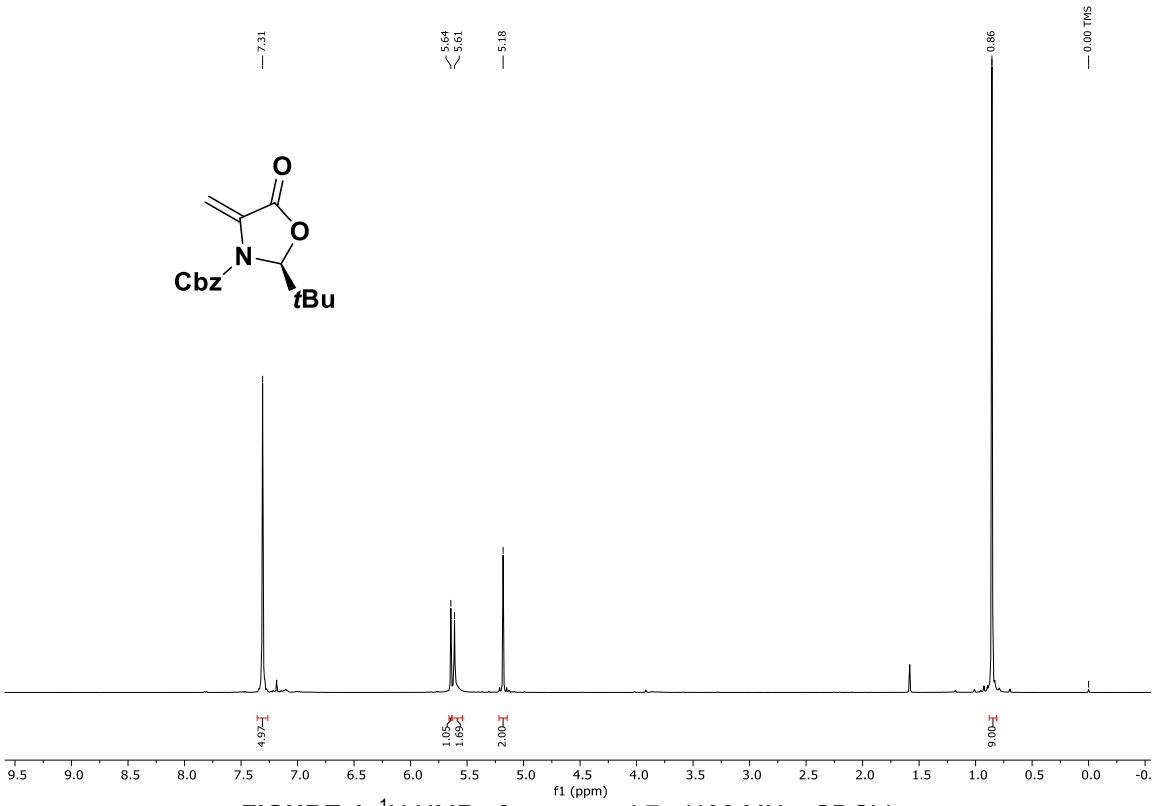


FIGURE 4. ^{1}H NMR of compound **7a** (400 MHz, $CDCl_3$).

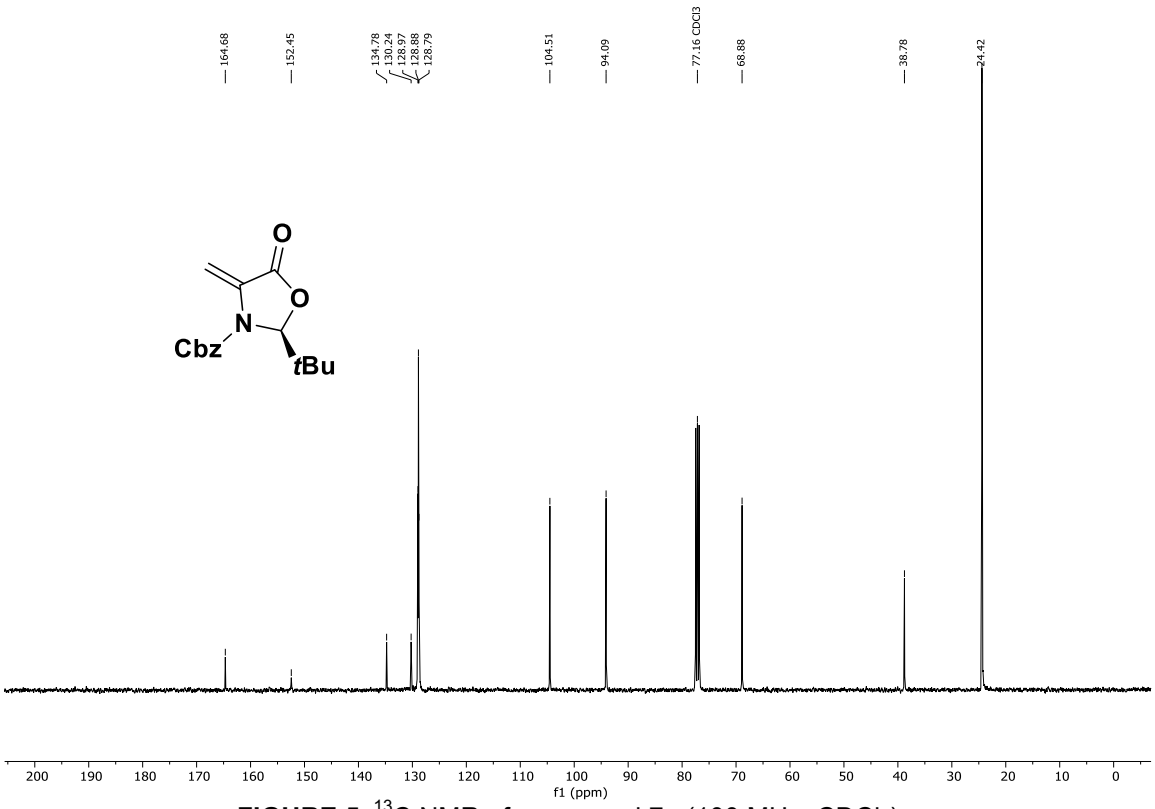


FIGURE 5. ^{13}C NMR of compound **7a** (100 MHz, $CDCl_3$).

20. NMR spectra. Compounds 4a', 4a-ad.

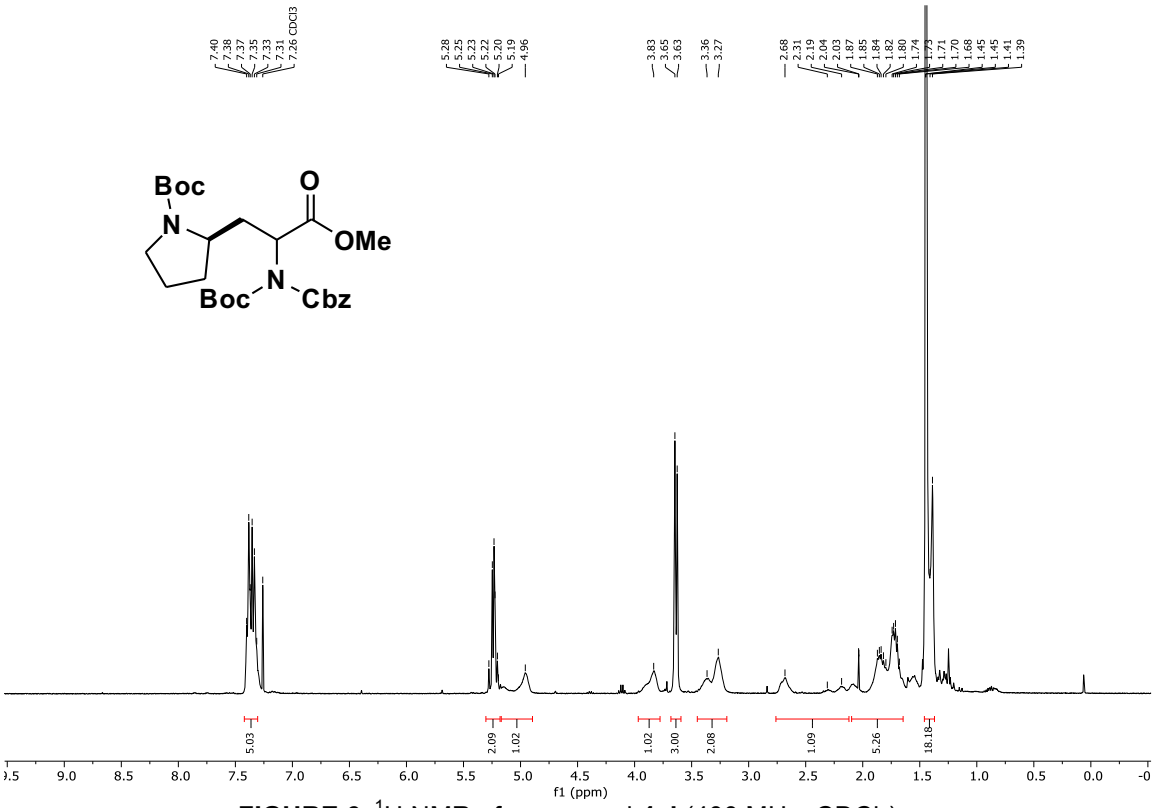


FIGURE 6. ^{1}H NMR of compound **4a'** (400 MHz, $CDCl_3$).

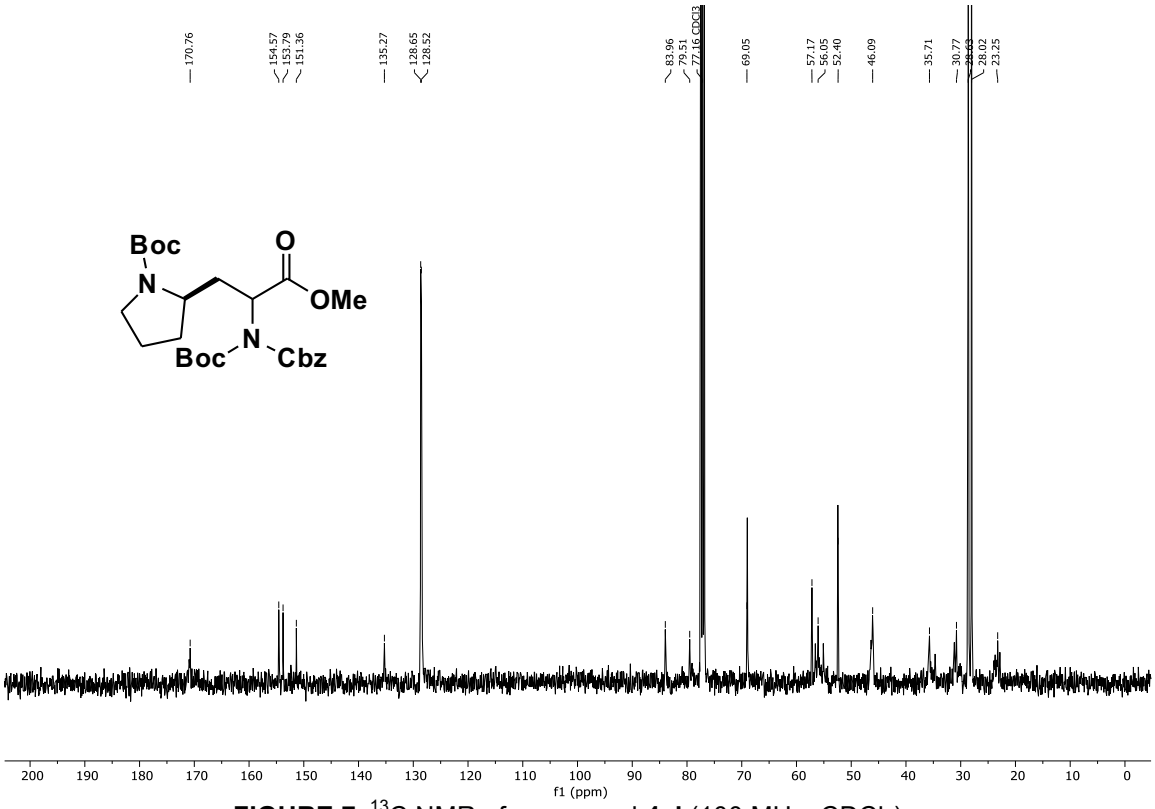


FIGURE 7. ^{13}C NMR of compound **4a'** (100 MHz, $CDCl_3$).

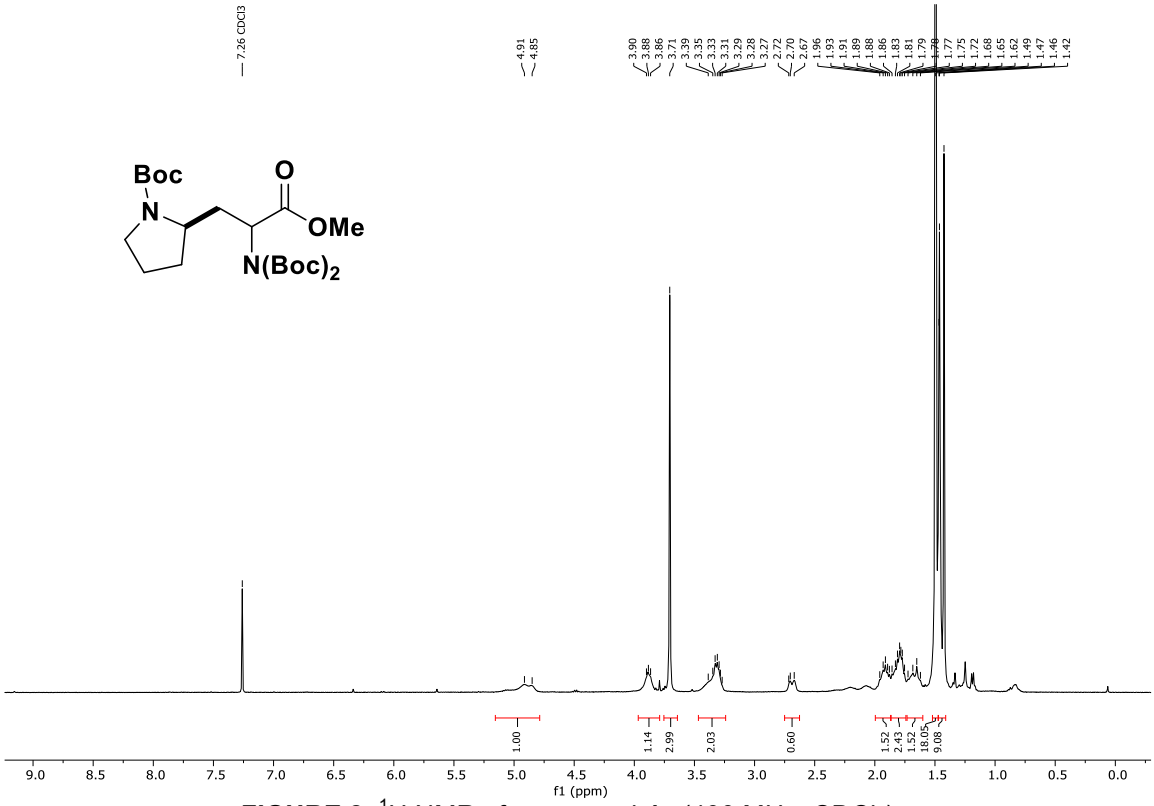


FIGURE 8. ^{1}H NMR of compound **4a** (400 MHz, $CDCl_3$).

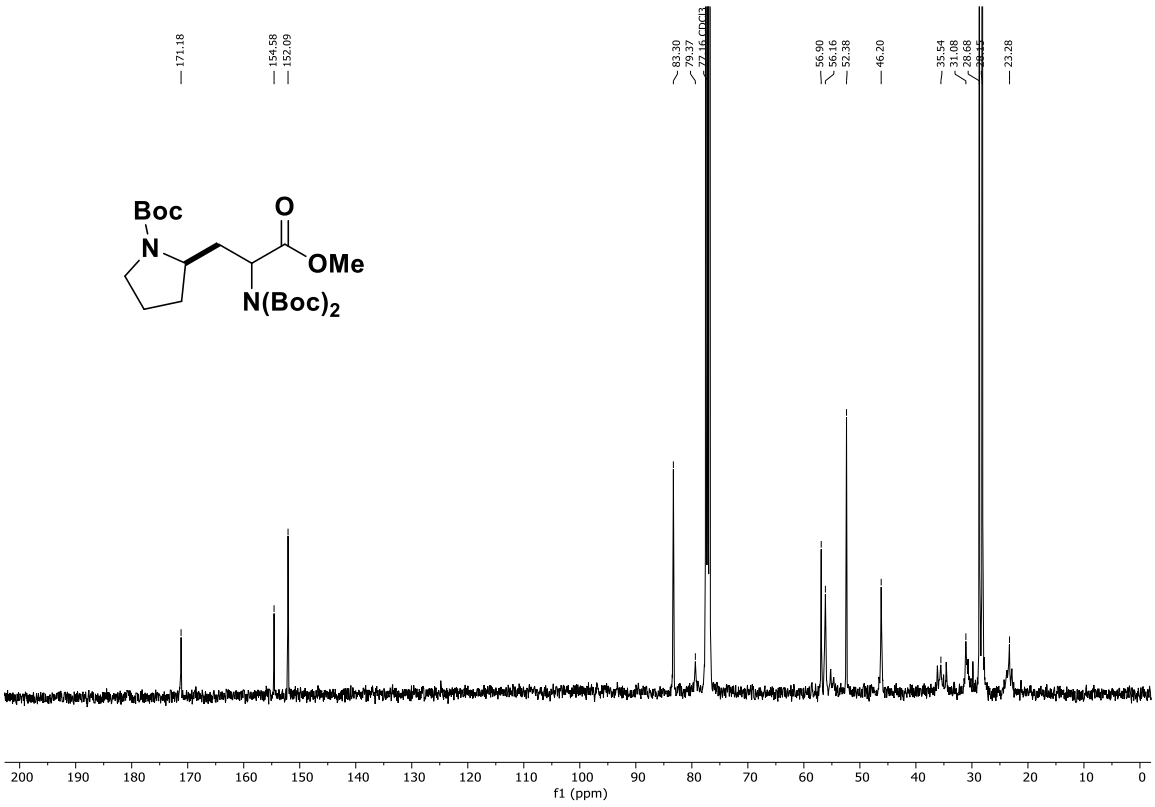


FIGURE 9. ^{13}C NMR of compound **4a** (100 MHz, $CDCl_3$).

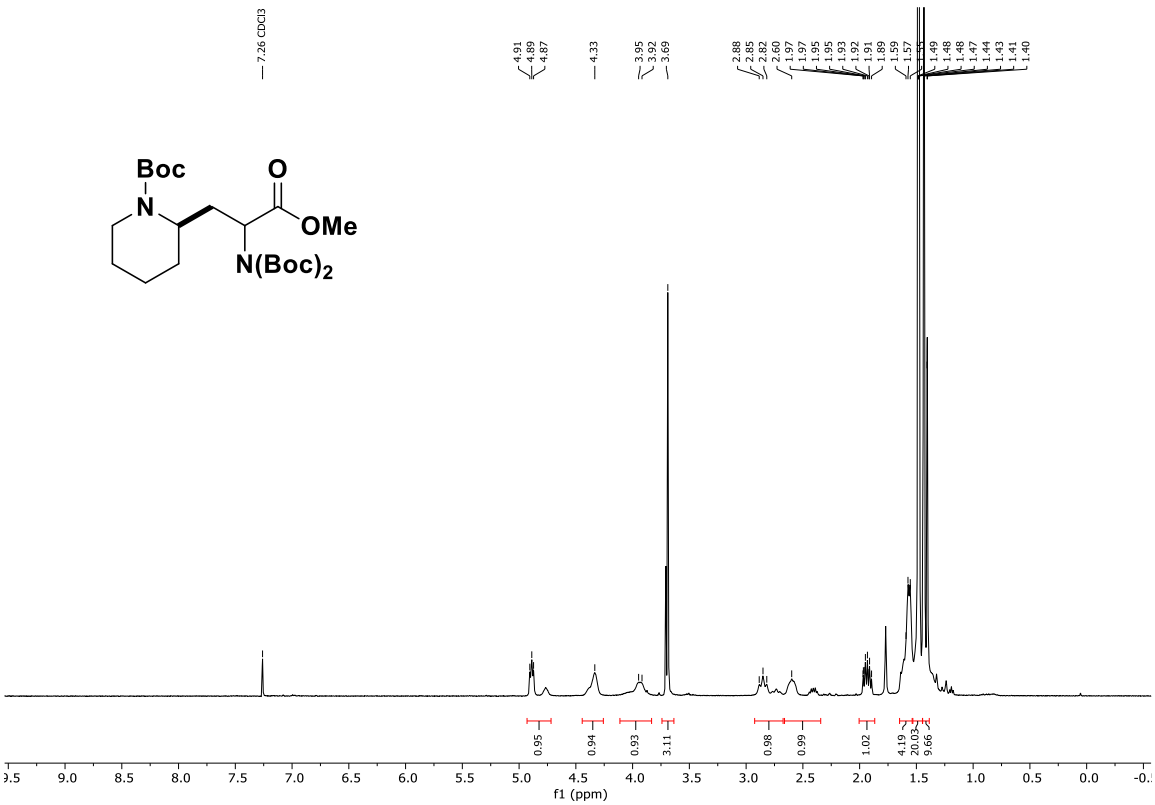


FIGURE 10. ^{1}H NMR of compound **4b** (400 MHz, $CDCl_3$).

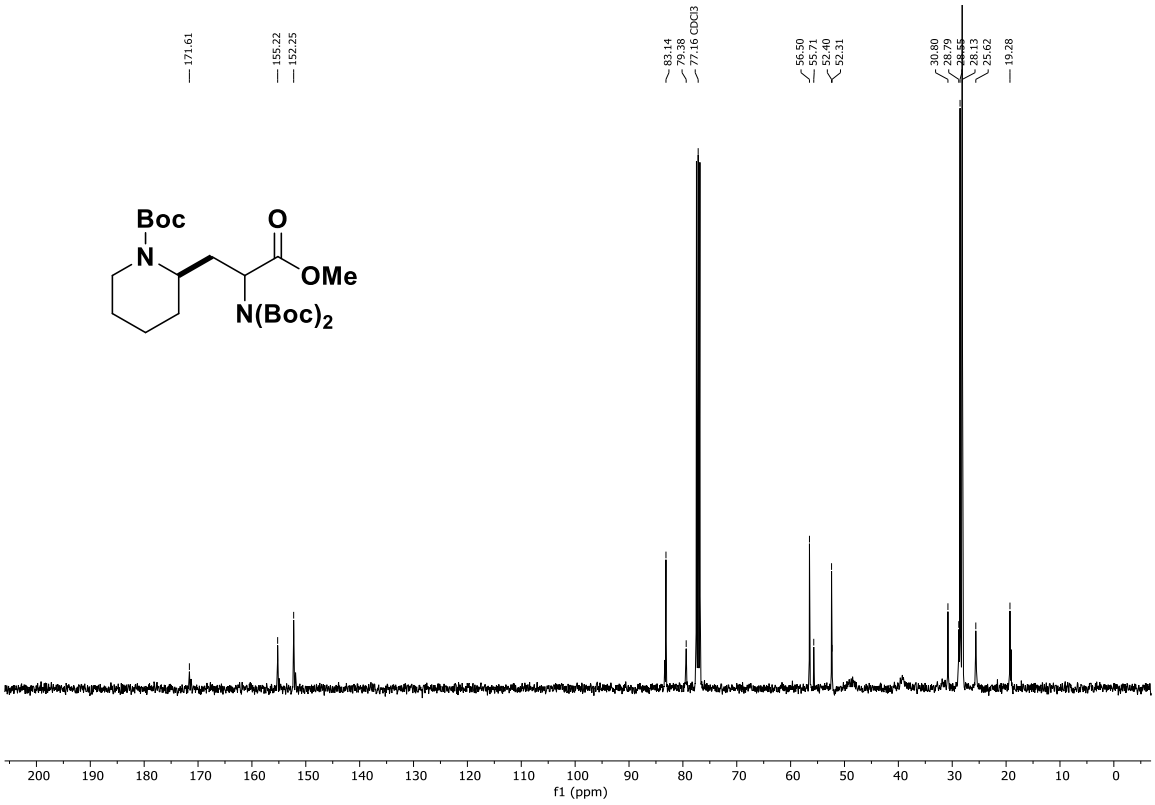


FIGURE 11. ^{13}C NMR of compound **4b** (100 MHz, $CDCl_3$).

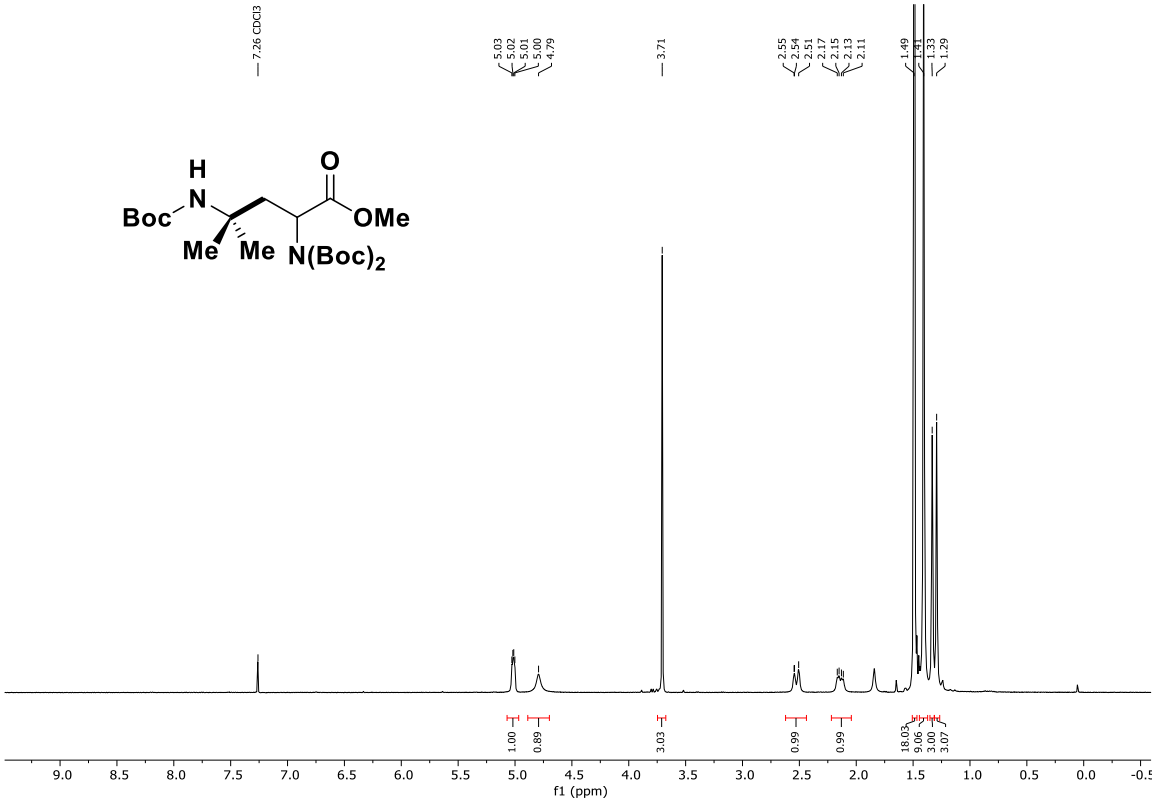


FIGURE 12. ^{1}H NMR of compound **4c** (400 MHz, $CDCl_3$).

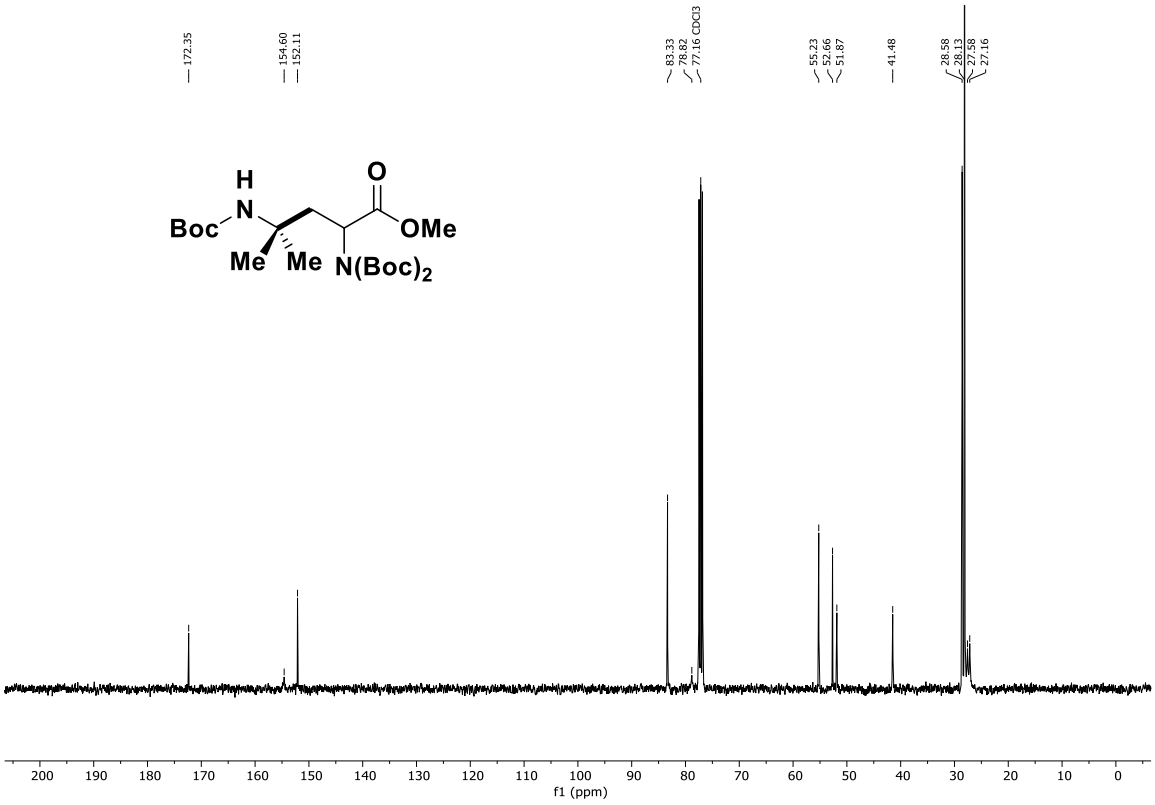


FIGURE 13. ^{13}C NMR of compound **4c** (100 MHz, $CDCl_3$).

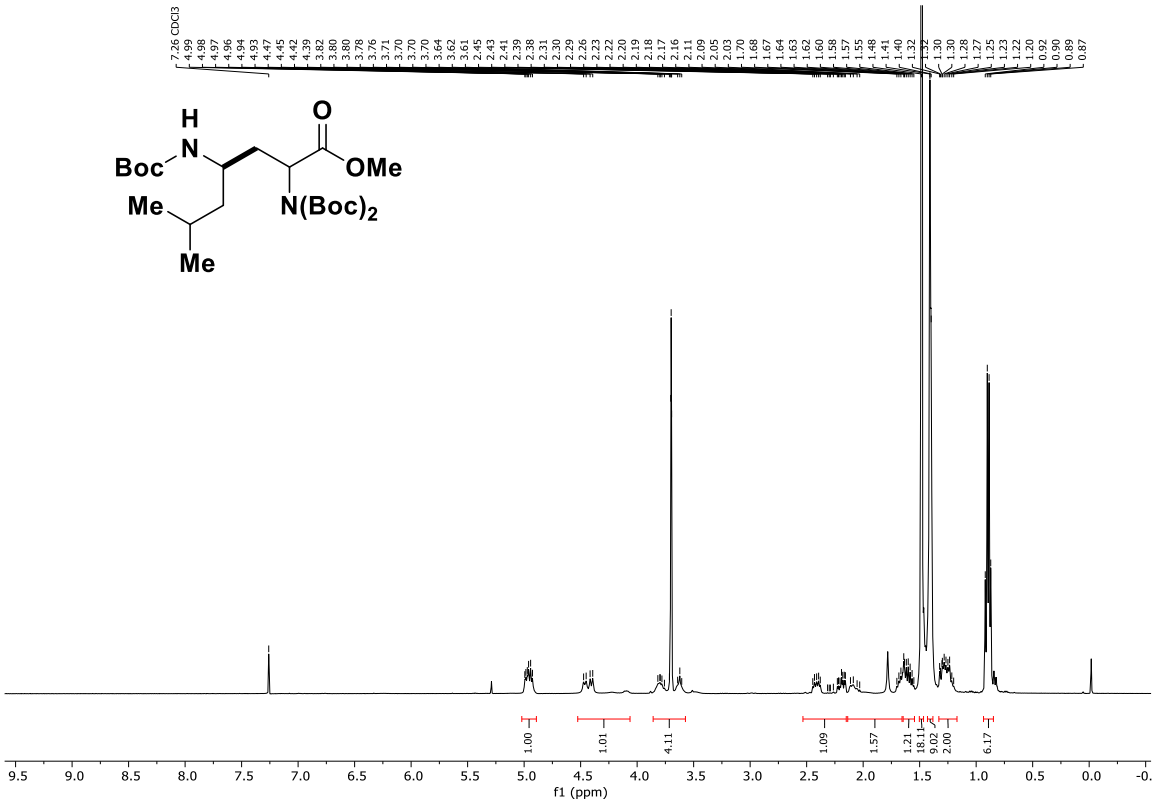


FIGURE 14. ^{1}H NMR of compound **4d** (400 MHz, $CDCl_3$).

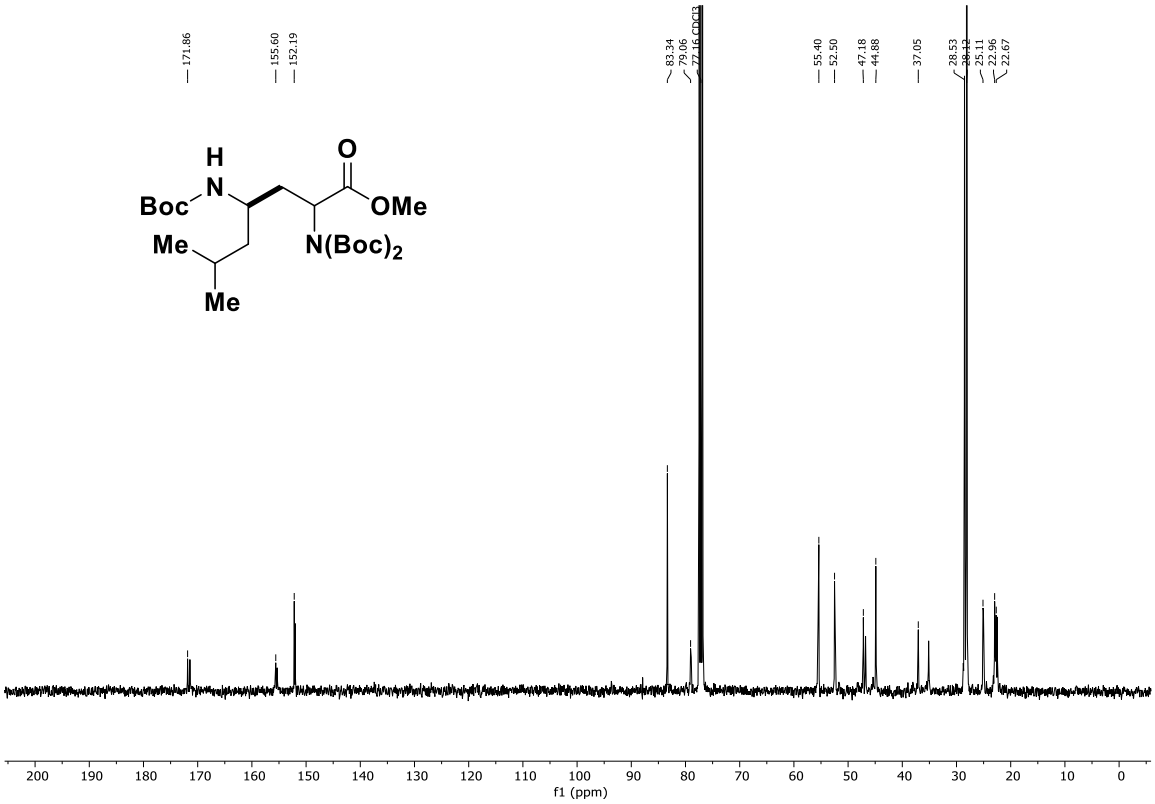


FIGURE 15. ^{13}C NMR of compound **4d** (100 MHz, $CDCl_3$).

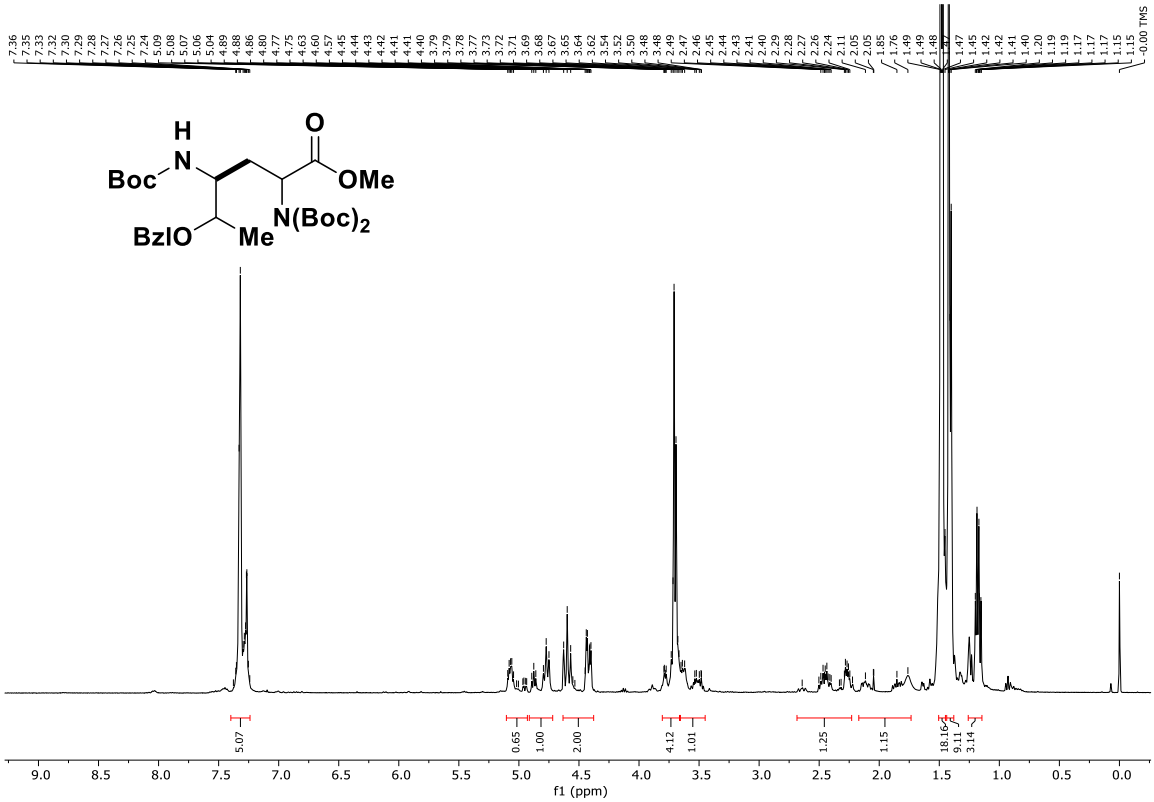


FIGURE 16. ^{1}H NMR of compound **4e** (400 MHz, $CDCl_3$).

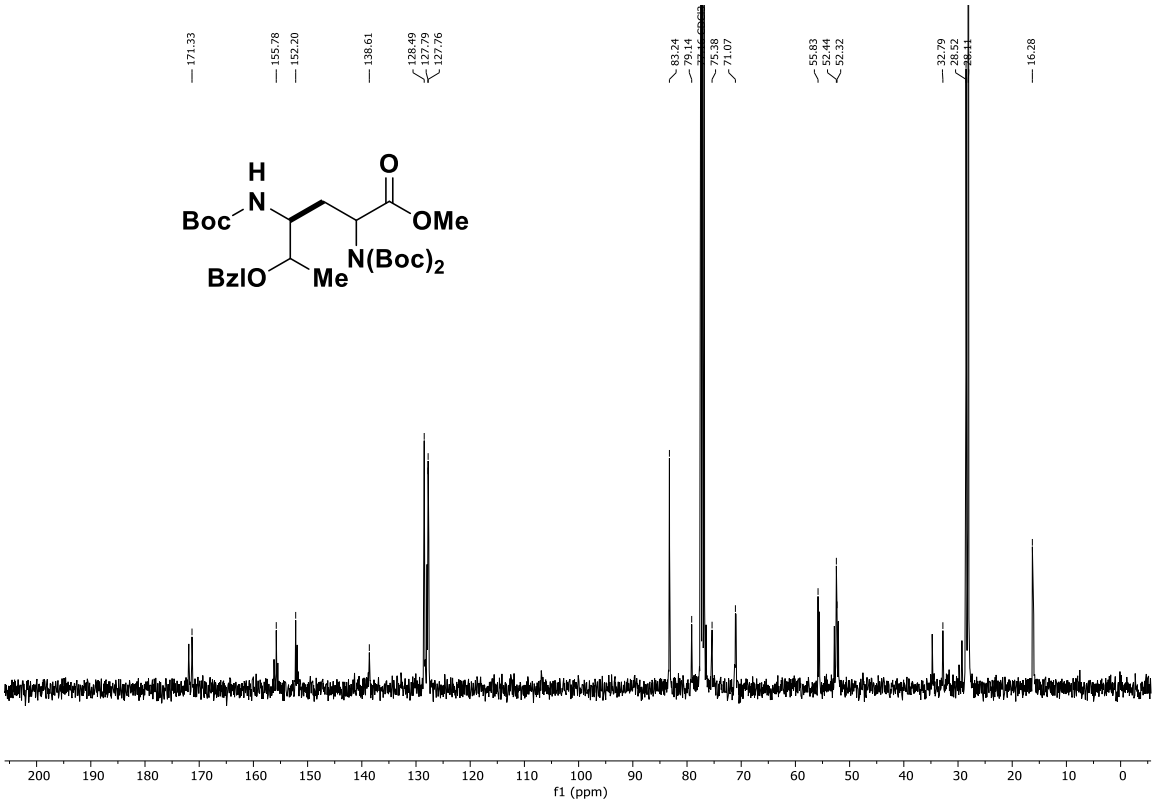


FIGURE 17. ^{13}C NMR of compound **4e** (100 MHz, $CDCl_3$).

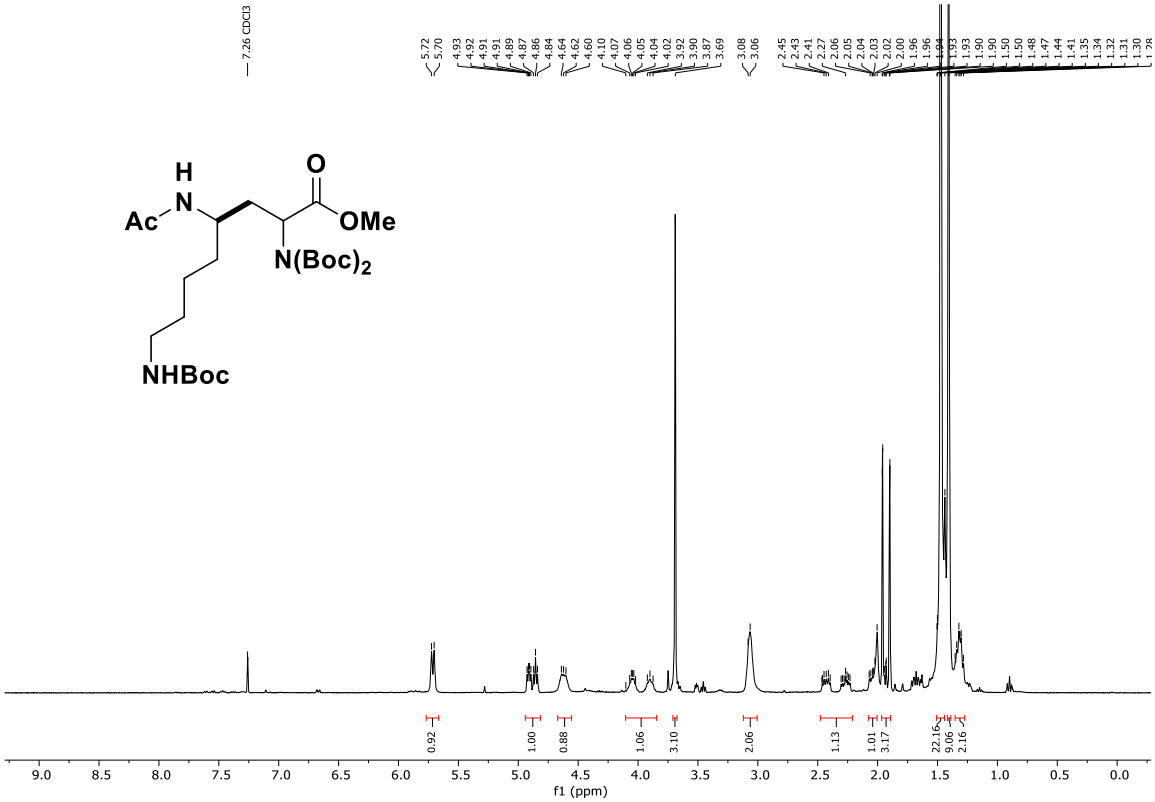


FIGURE 18. ^{1}H NMR of compound **4f** (400 MHz, $CDCl_3$).

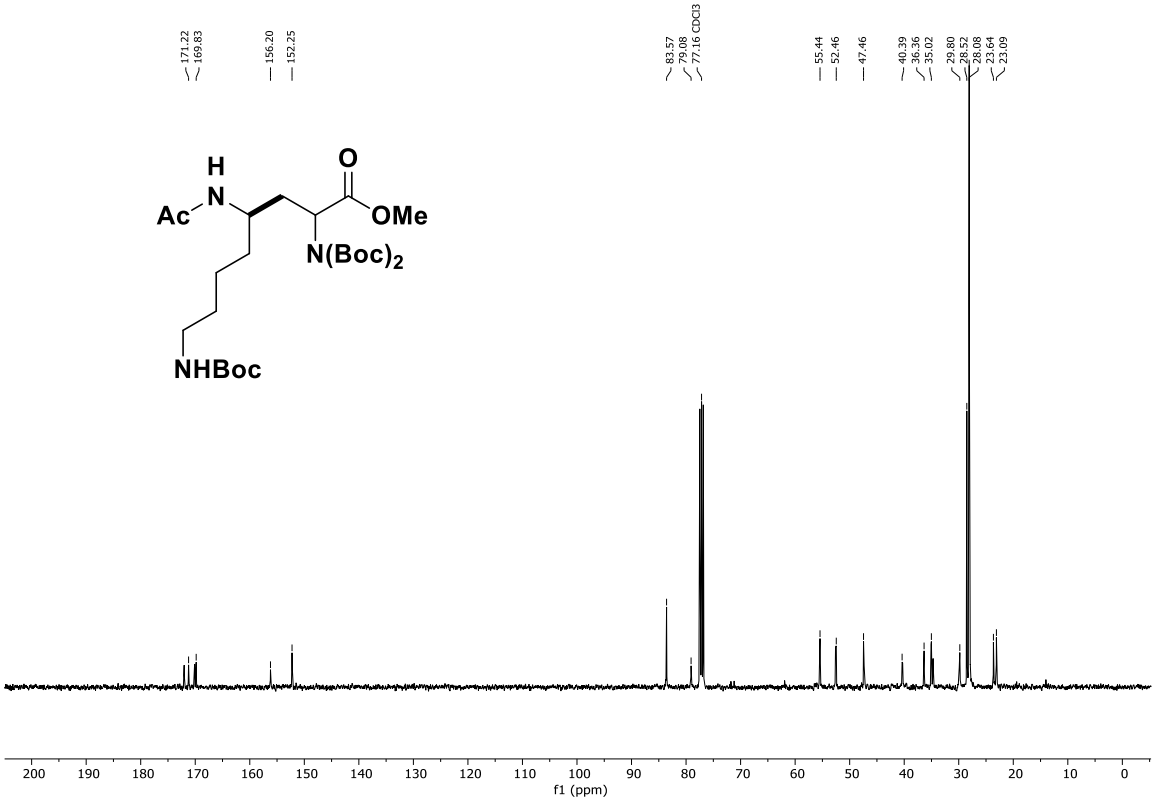


FIGURE 19. ^{13}C NMR of compound **4f** (100 MHz, $CDCl_3$).

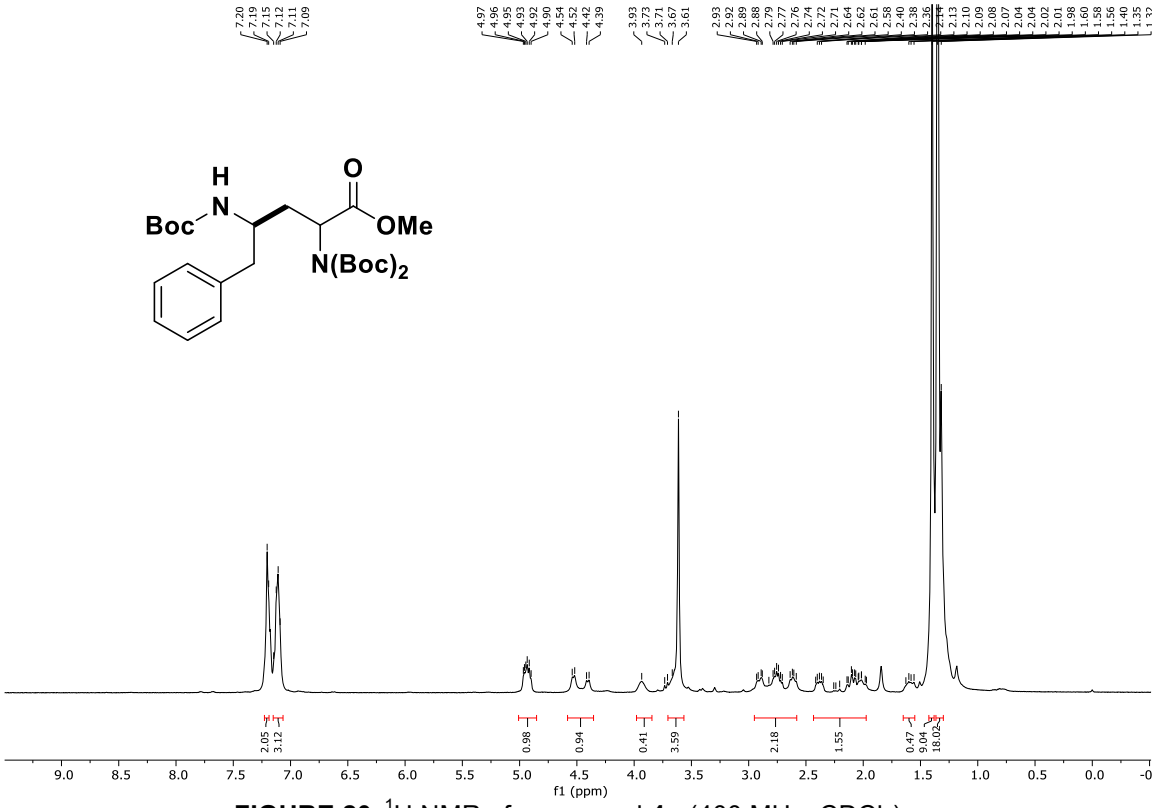


FIGURE 20. ^{1}H NMR of compound **4g** (400 MHz, $CDCl_3$).

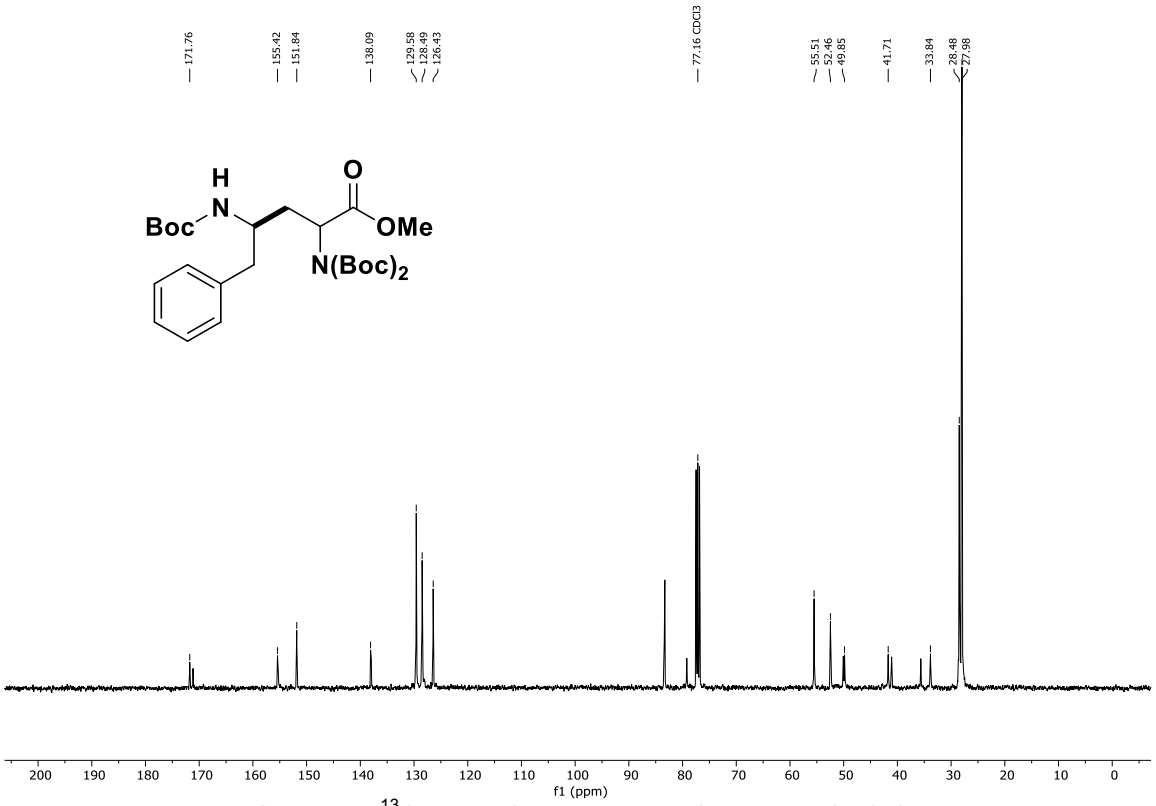


FIGURE 21. ^{13}C NMR of compound **4g** (100 MHz, $CDCl_3$).

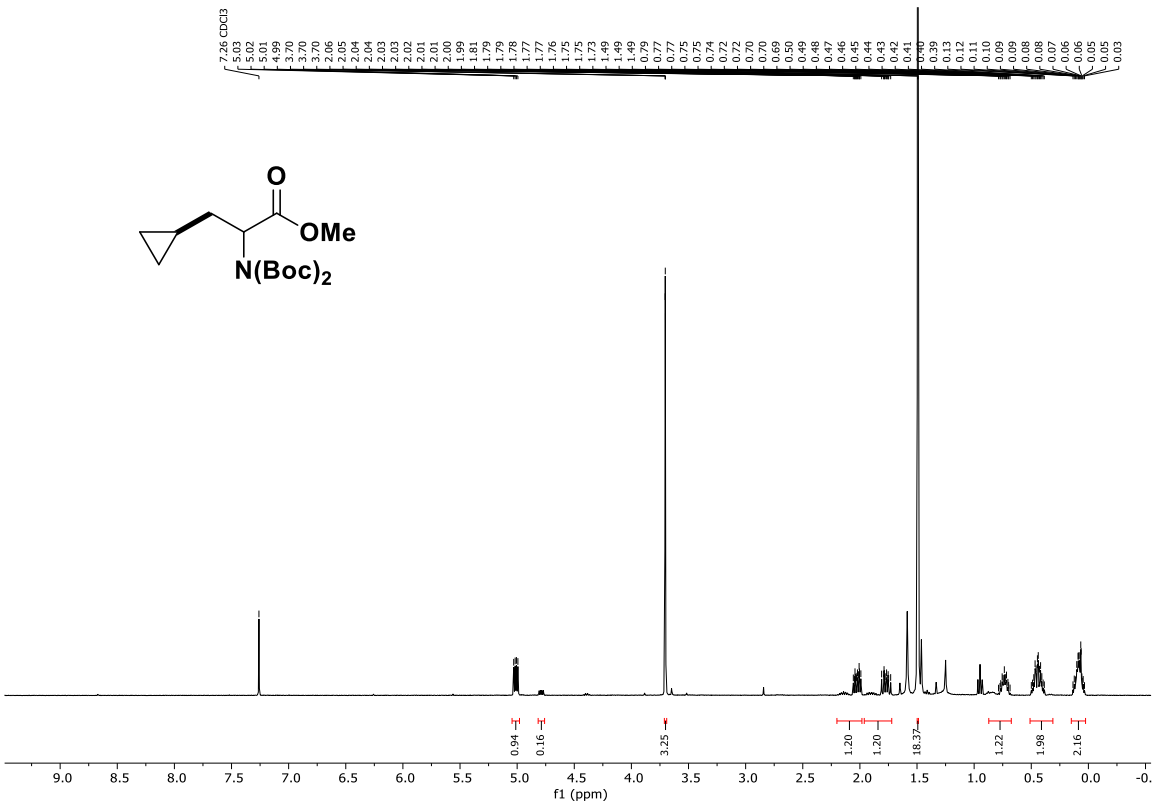


FIGURE 22. ^{1}H NMR of compound **4h** (400 MHz, $CDCl_3$).

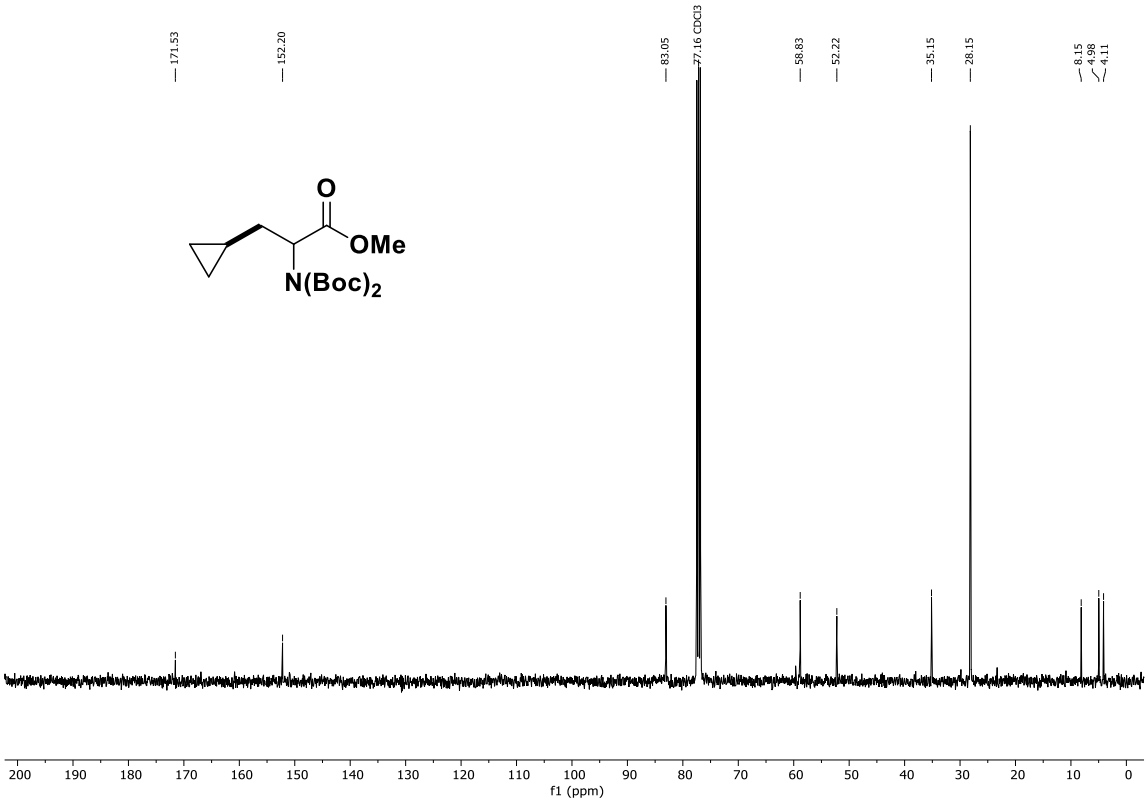


FIGURE 23. ^{13}C NMR of compound **4h** (100 MHz, $CDCl_3$).

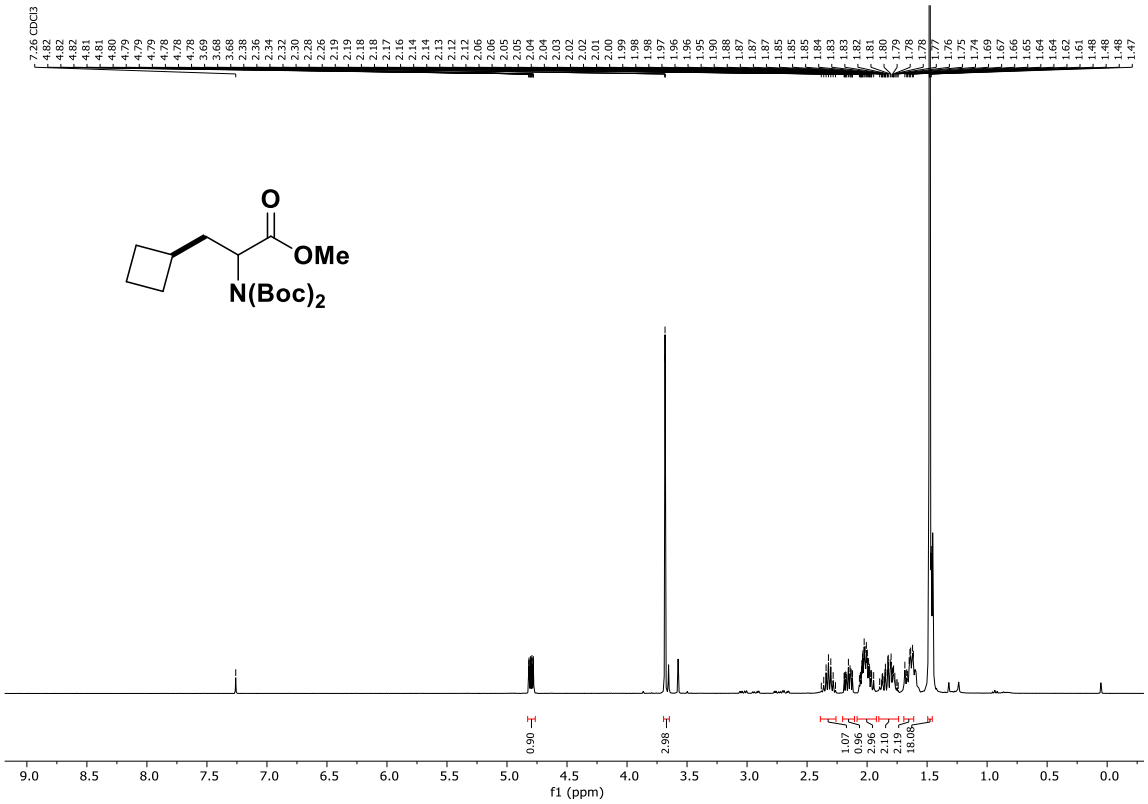


FIGURE 24. ^{1}H NMR of compound **4i** (400 MHz, $CDCl_3$).

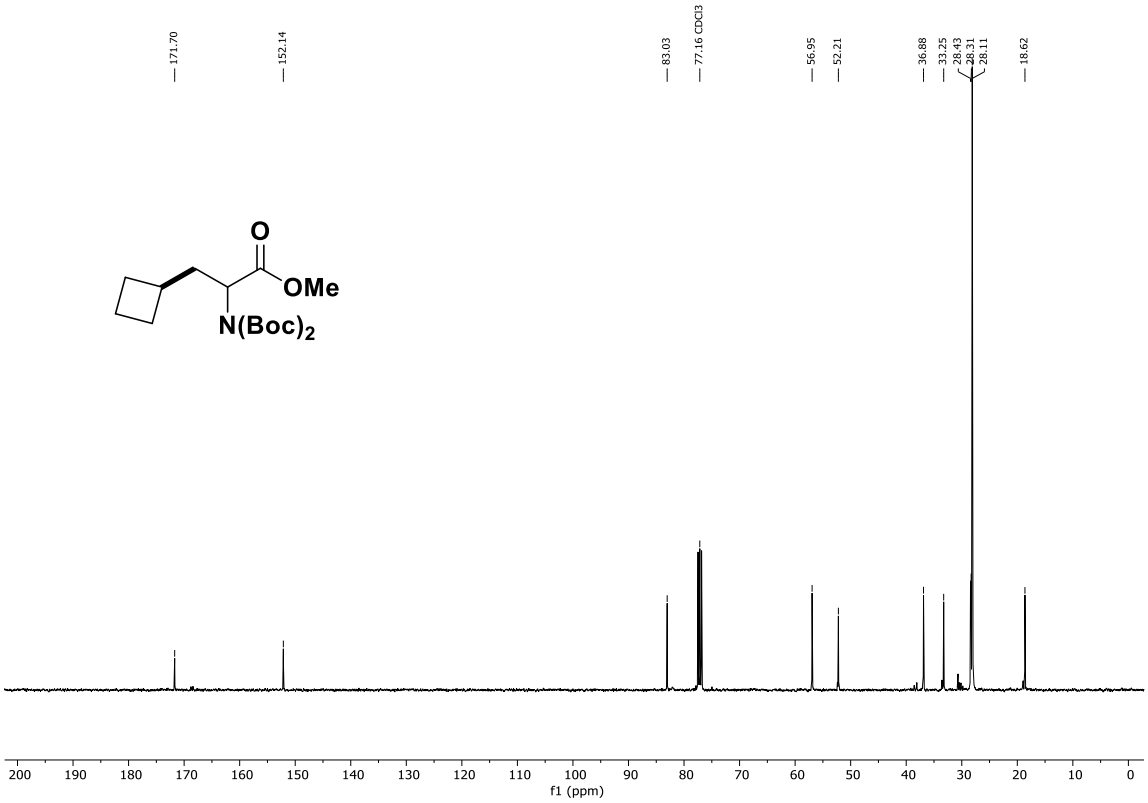


FIGURE 25. ^{13}C NMR of compound **4i** (100 MHz, $CDCl_3$).

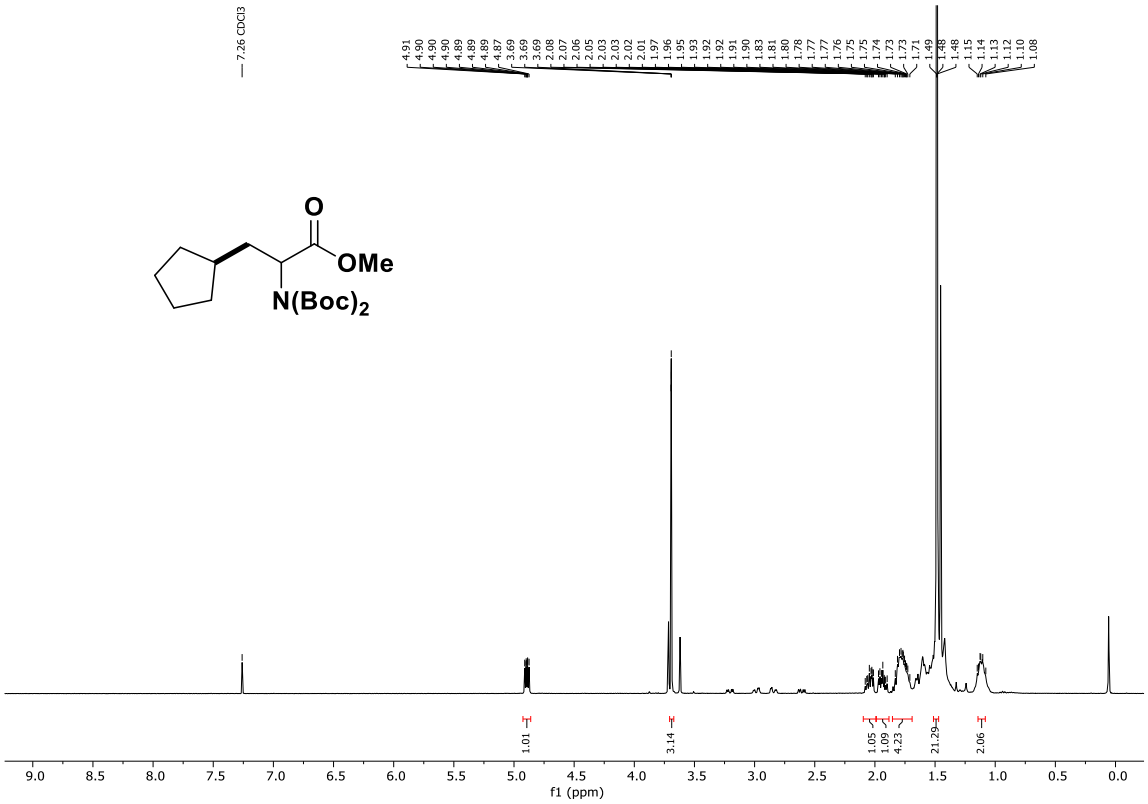


FIGURE 26. ^{1}H NMR of compound **4j** (400 MHz, $CDCl_3$).

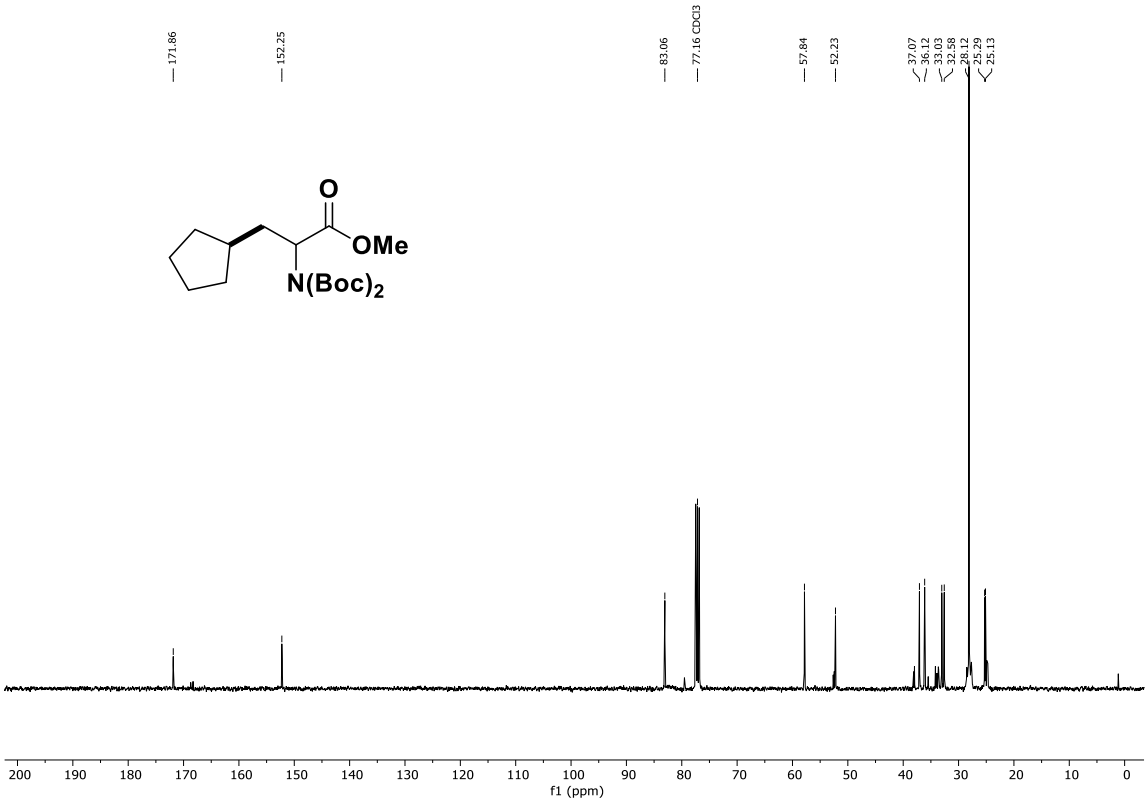


FIGURE 27. ^{13}C NMR of compound **4j** (100 MHz, $CDCl_3$).

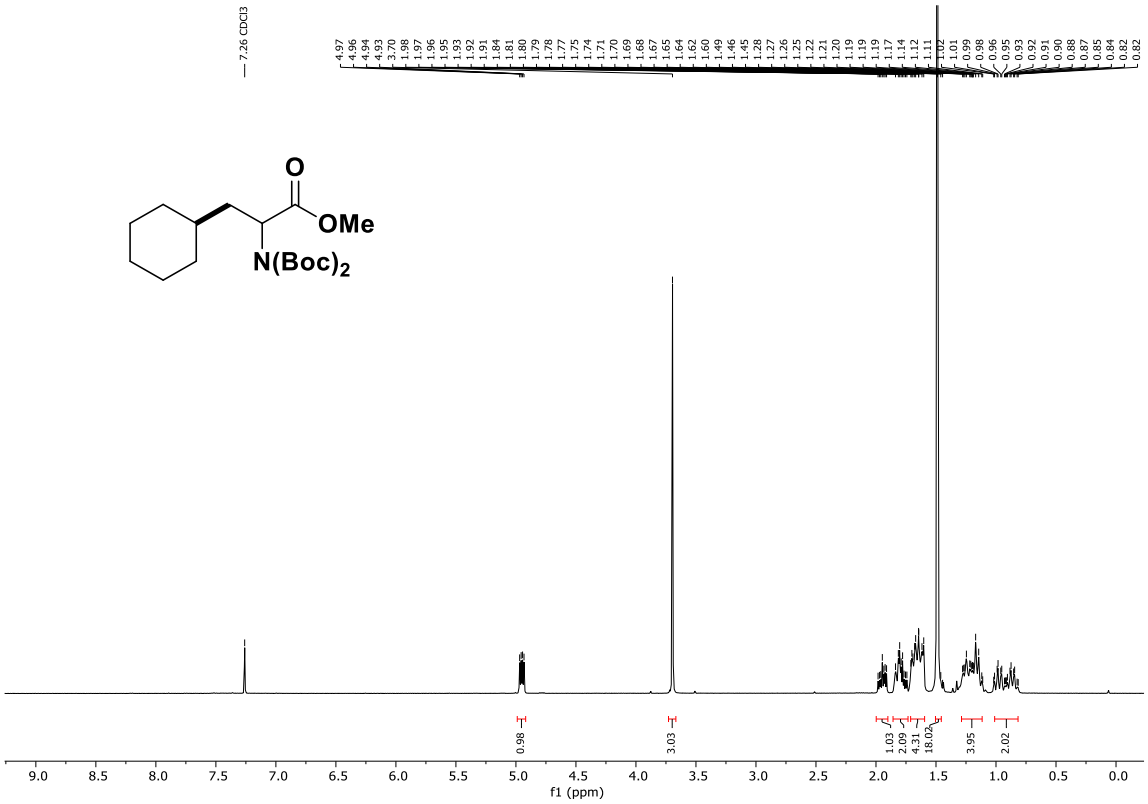


FIGURE 28. ^{1}H NMR of compound **4k** (400 MHz, $CDCl_3$).

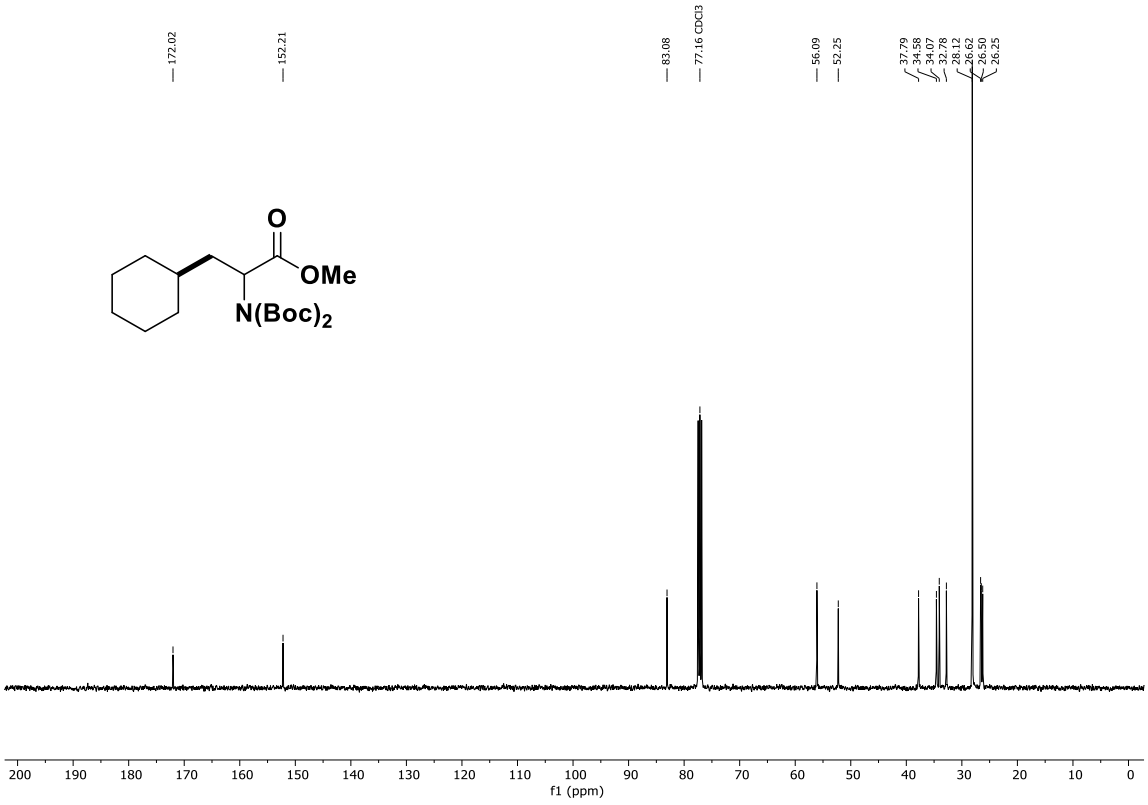


FIGURE 29. ^{13}C NMR of compound **4k** (100 MHz, $CDCl_3$).

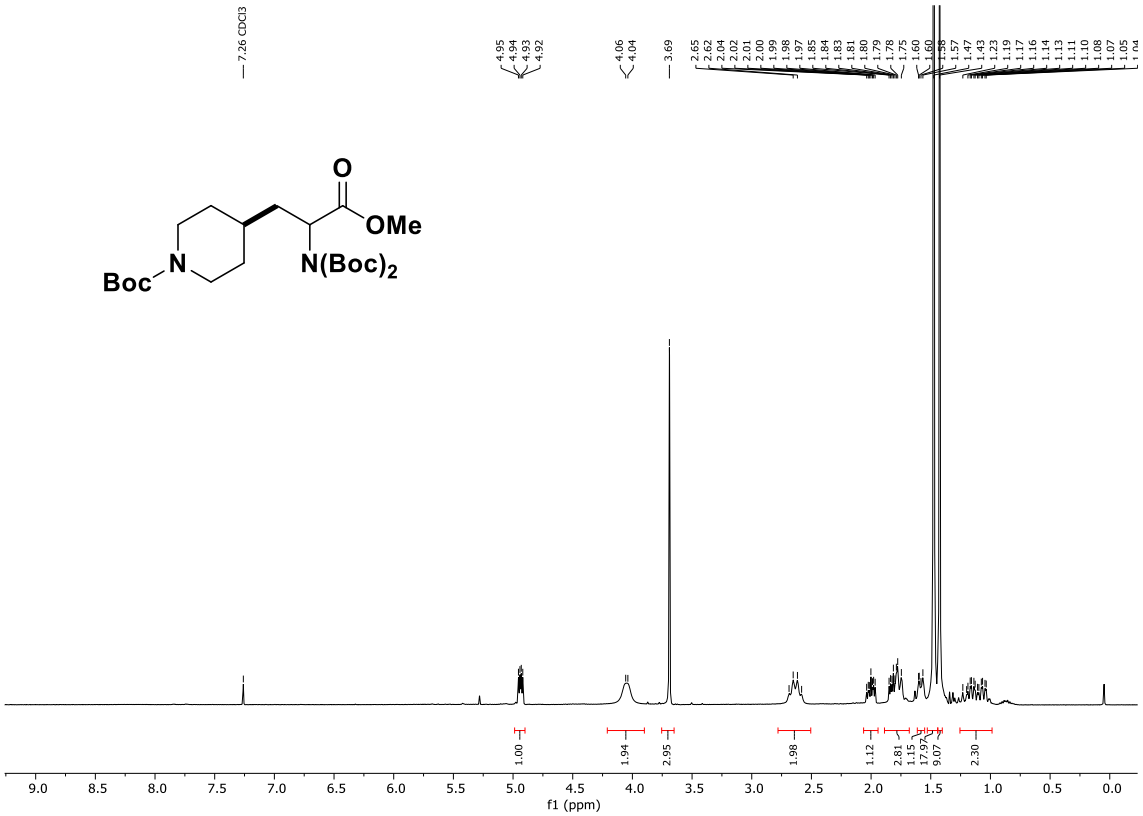


FIGURE 30. ^{1}H NMR of compound **4l** (400 MHz, $CDCl_3$).

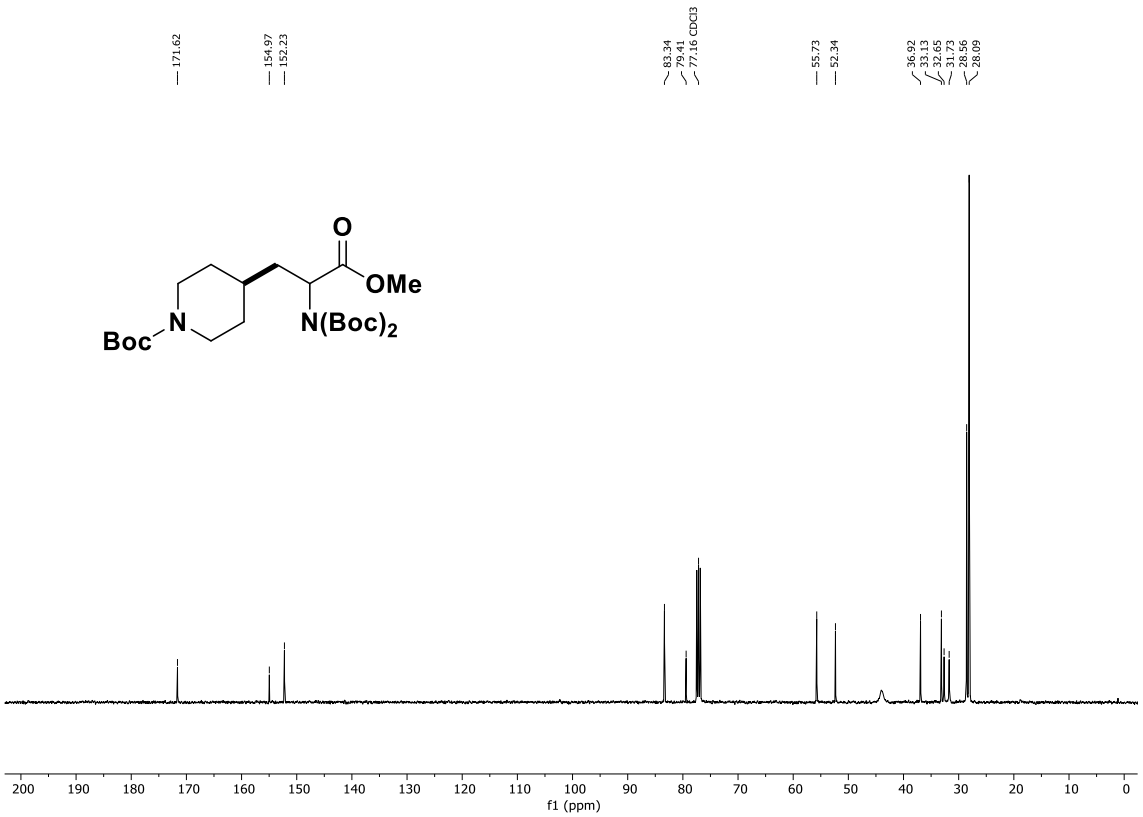


FIGURE 31. ^{13}C NMR of compound **4l** (100 MHz, $CDCl_3$).

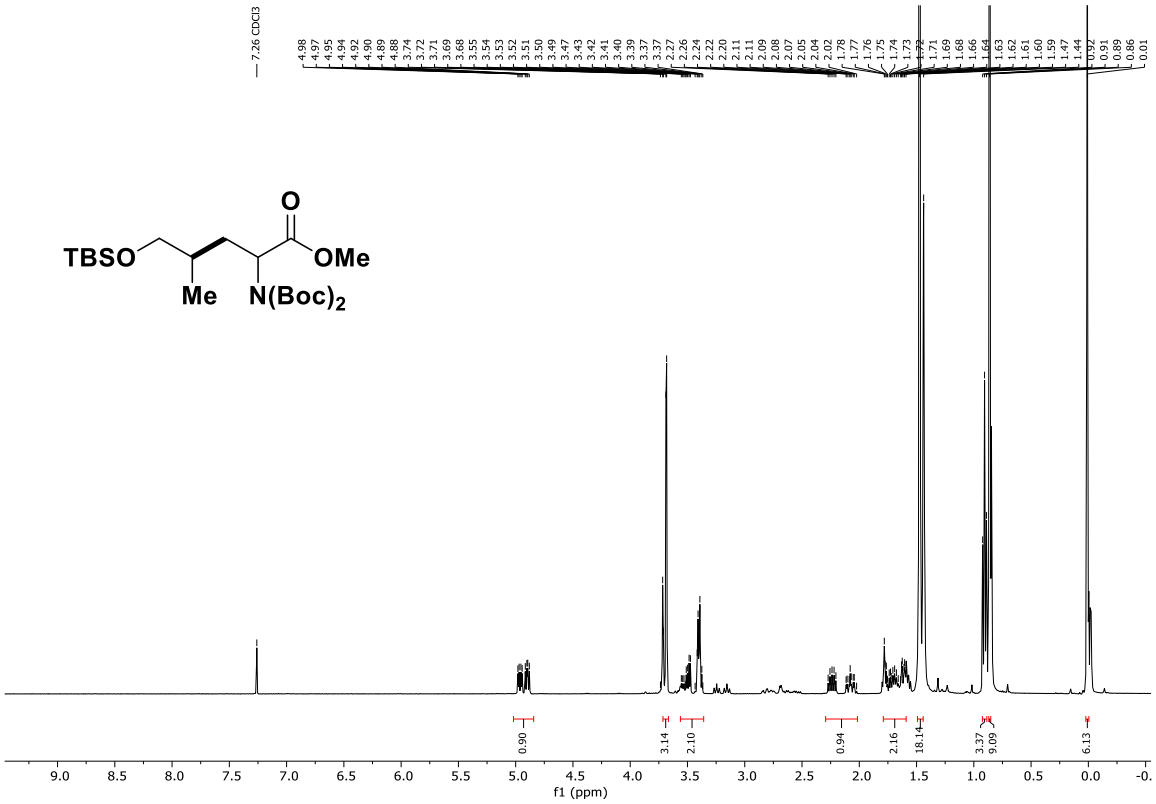


FIGURE 32. ^{1}H NMR of compound **4m** (400 MHz, $CDCl_3$).

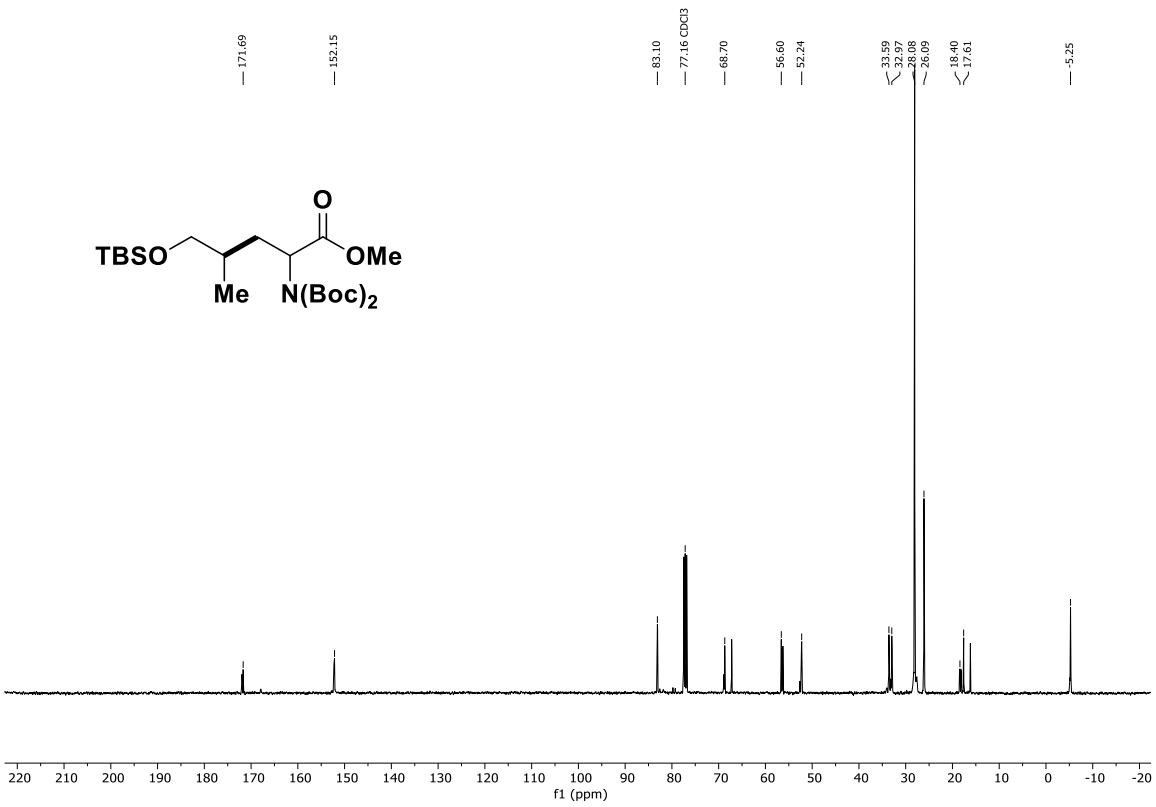


FIGURE 33. ^{13}C NMR of compound **4m** (100 MHz, $CDCl_3$).

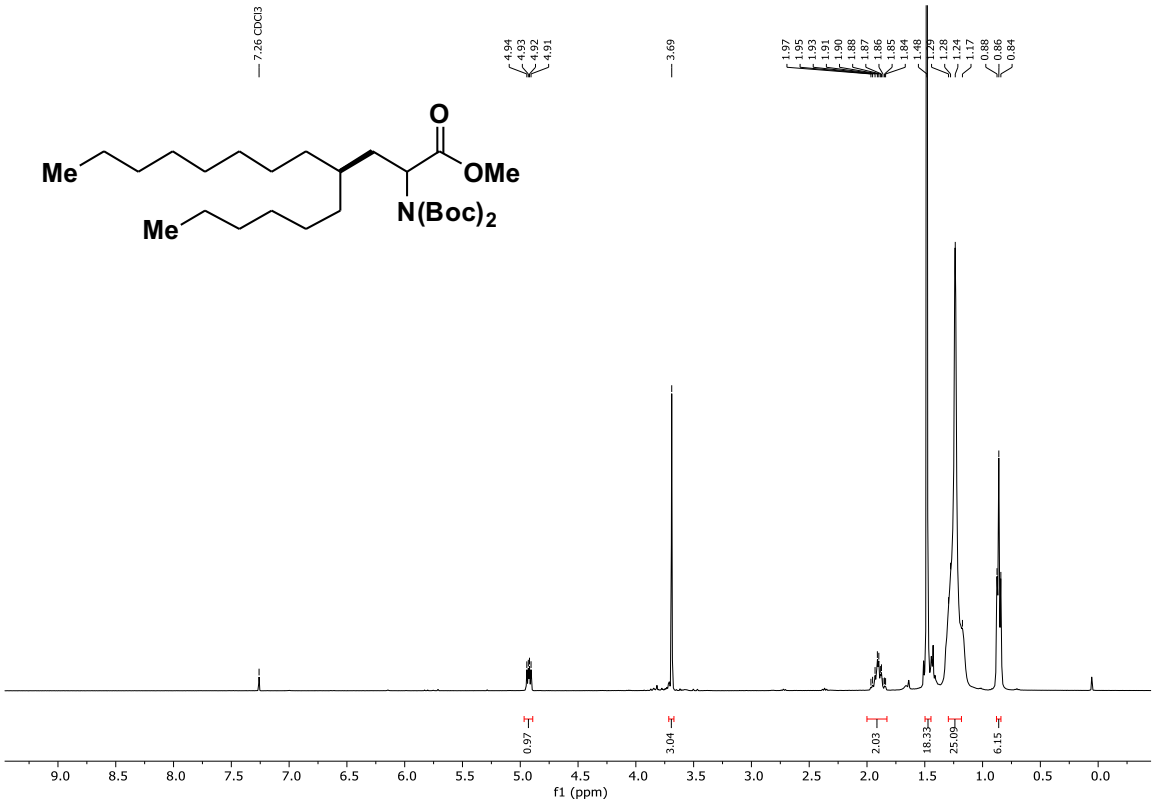


FIGURE 34. ^{1}H NMR of compound **4n** (400 MHz, $CDCl_3$).

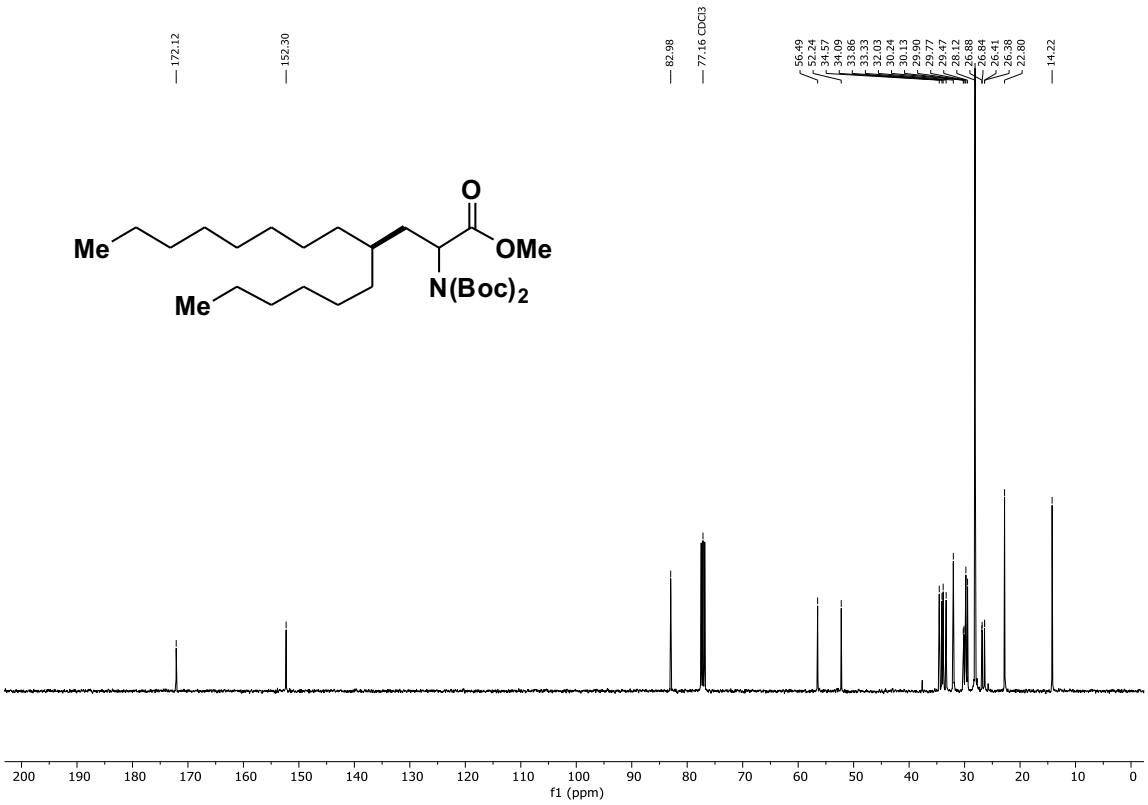


FIGURE 35. ^{13}C NMR of compound **4n** (100 MHz, $CDCl_3$).

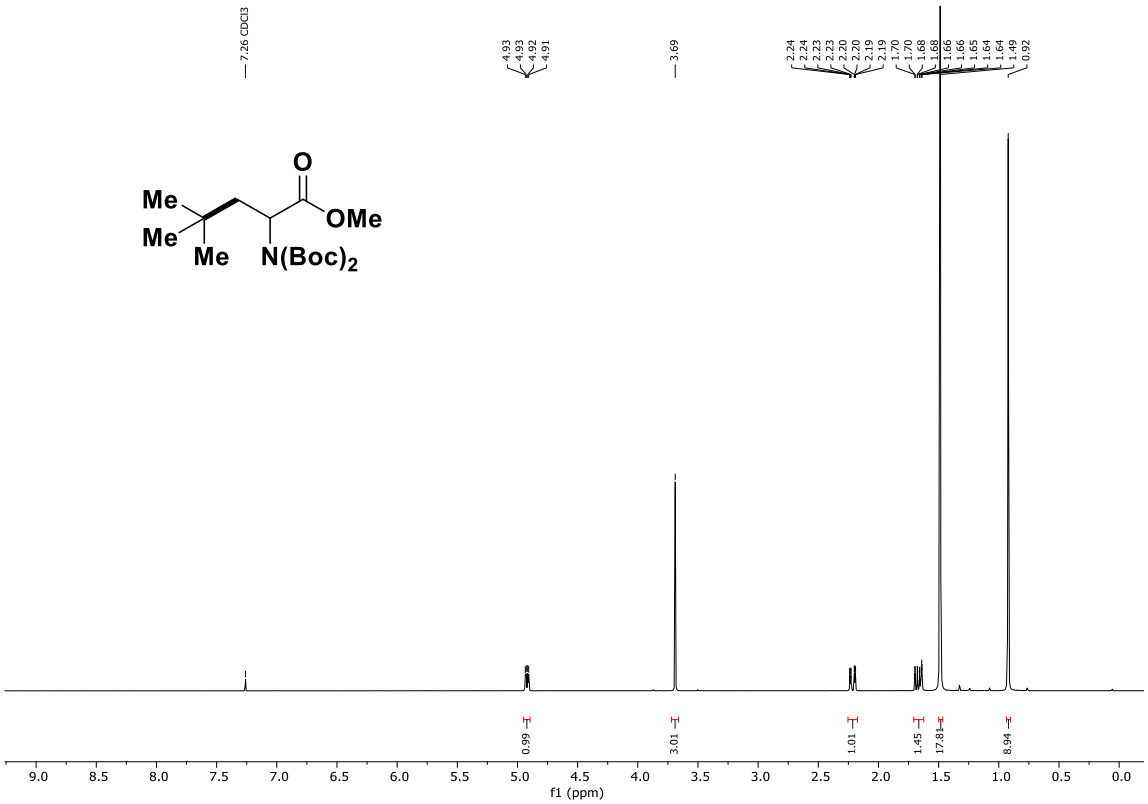


FIGURE 36. ^{1}H NMR of compound **4o** (400 MHz, $CDCl_3$).

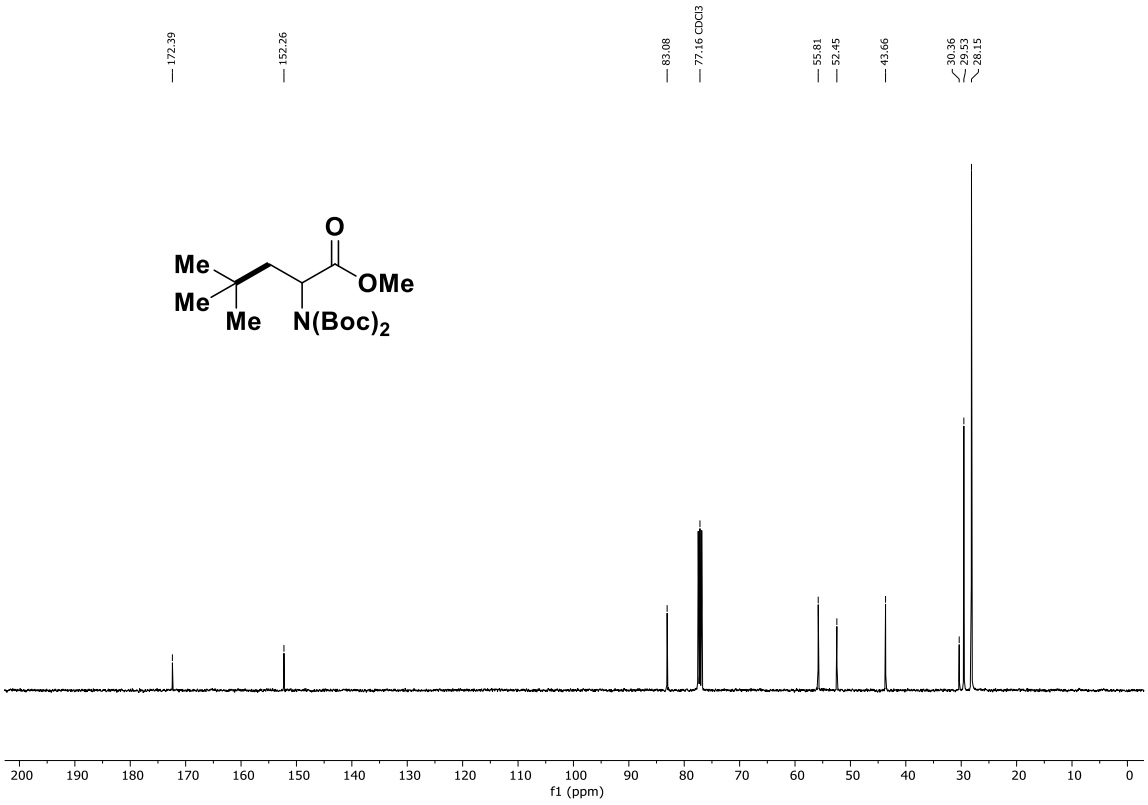


FIGURE 37. ^{13}C NMR of compound **4o** (100 MHz, $CDCl_3$).

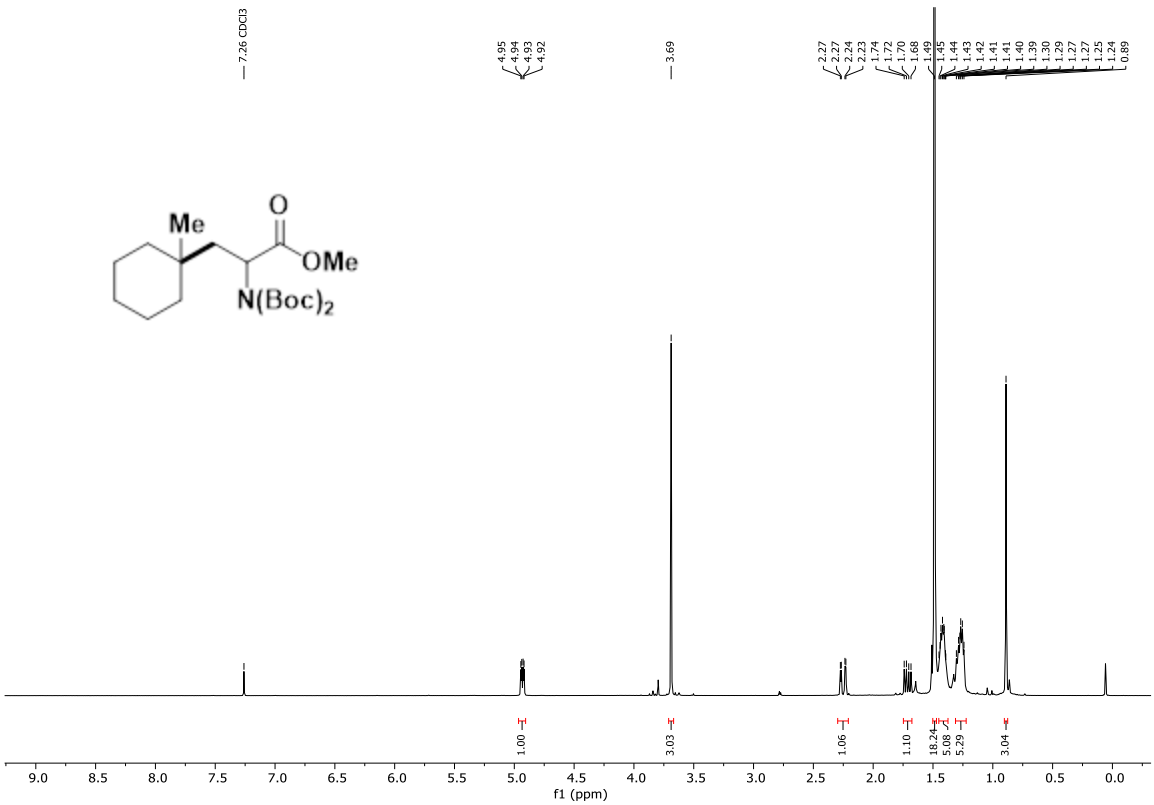


FIGURE 38. ^{1}H NMR of compound **4p** (400 MHz, $CDCl_3$).

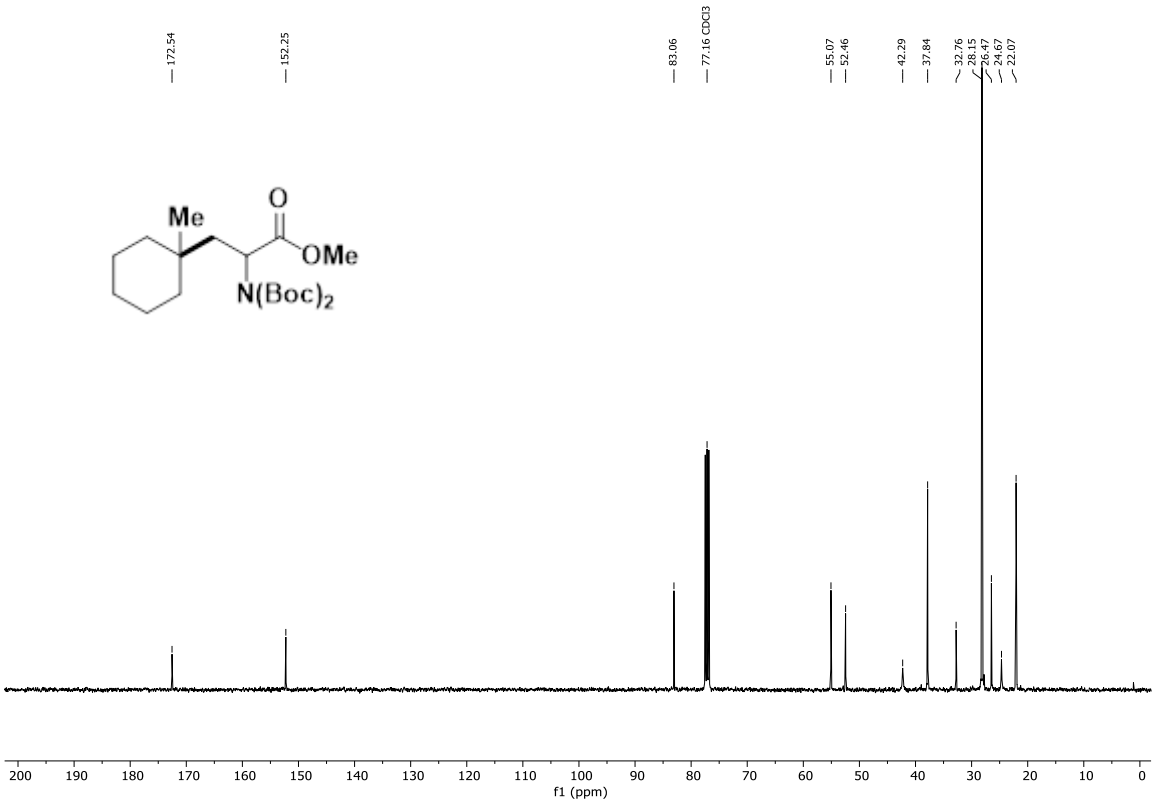


FIGURE 39. ^{13}C NMR of compound **4p** (100 MHz, $CDCl_3$).

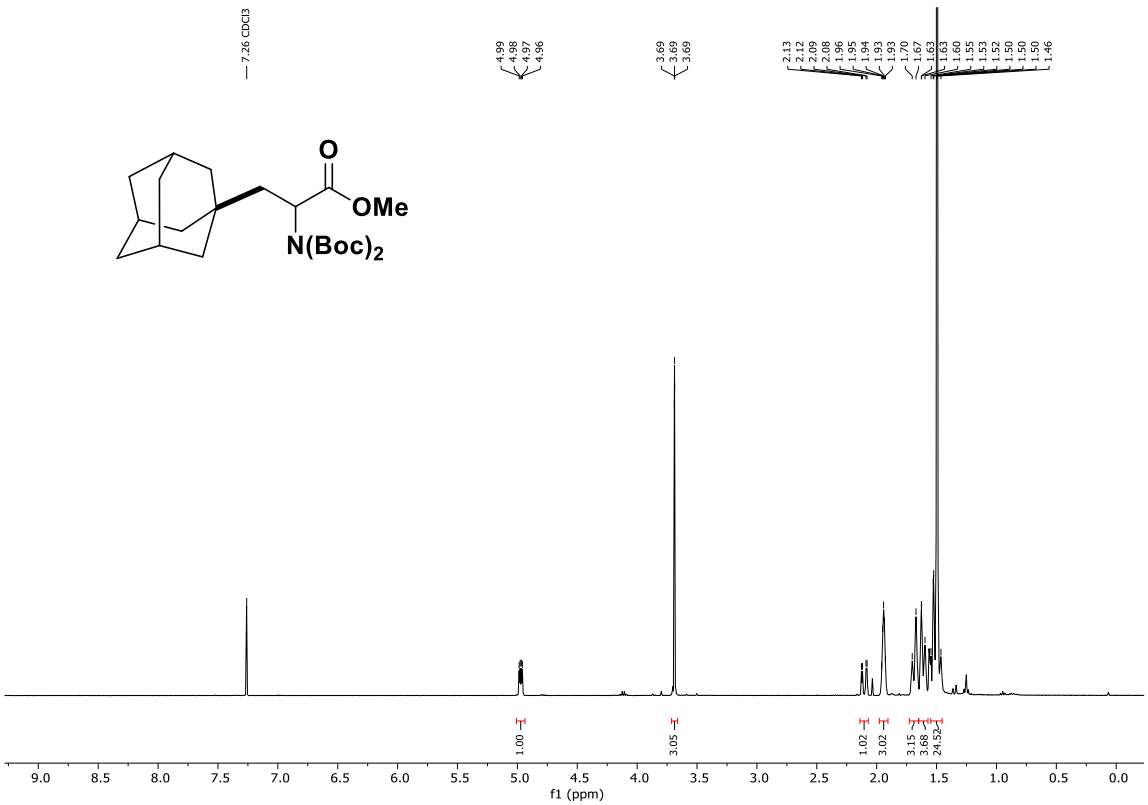


FIGURE 40. ^{1}H NMR of compound **4q** (400 MHz, $CDCl_3$).

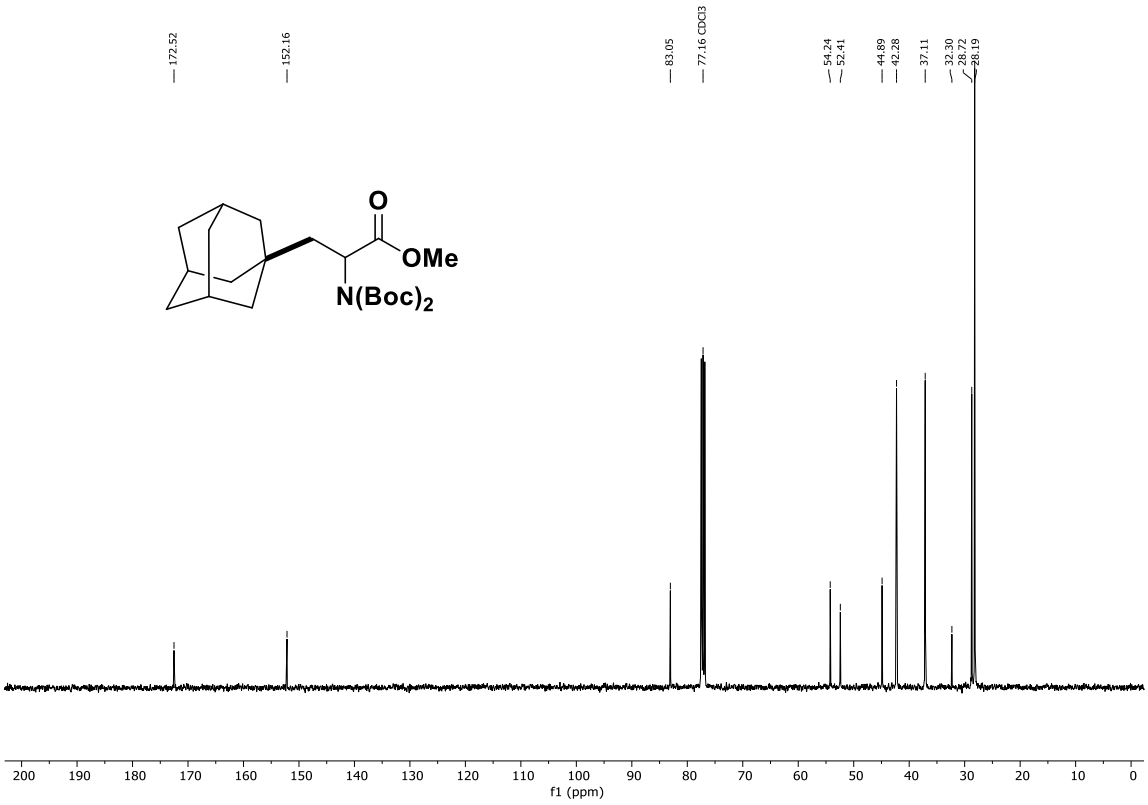


FIGURE 41. ^{13}C NMR of compound **4q** (100 MHz, $CDCl_3$).

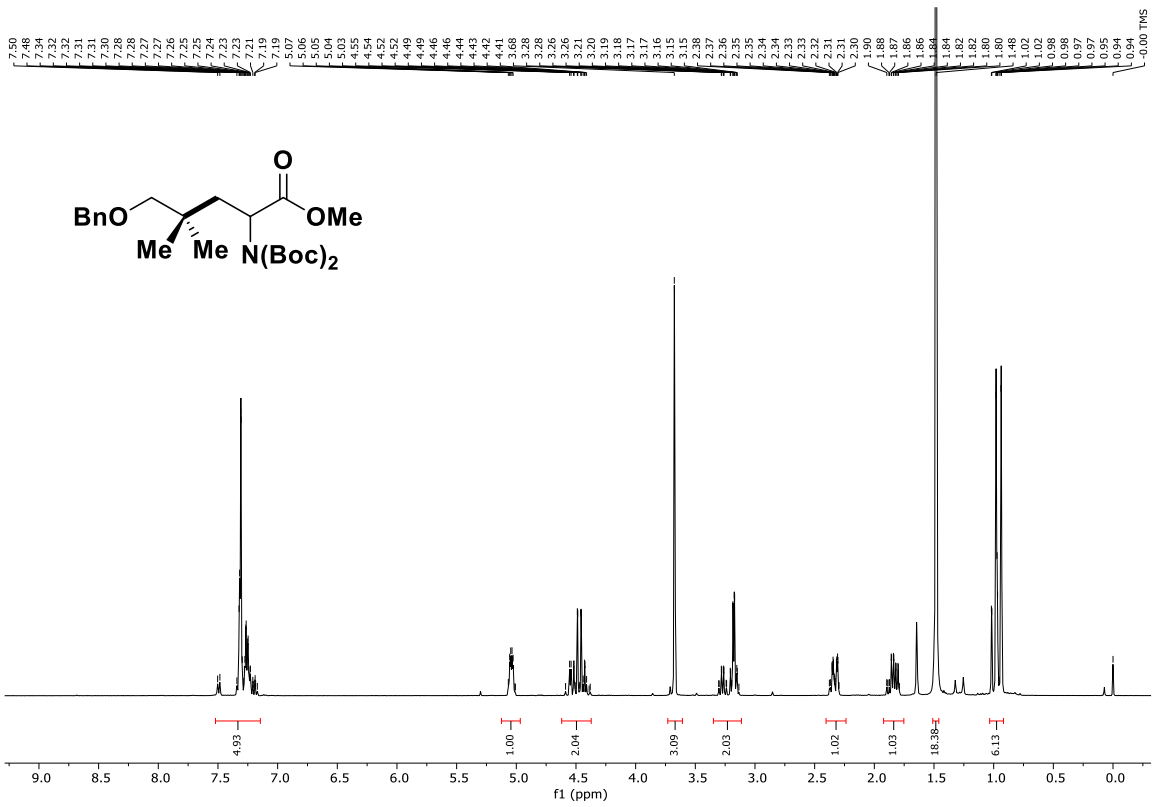


FIGURE 42. ^{1}H NMR of compound **4r** (400 MHz, $CDCl_3$).

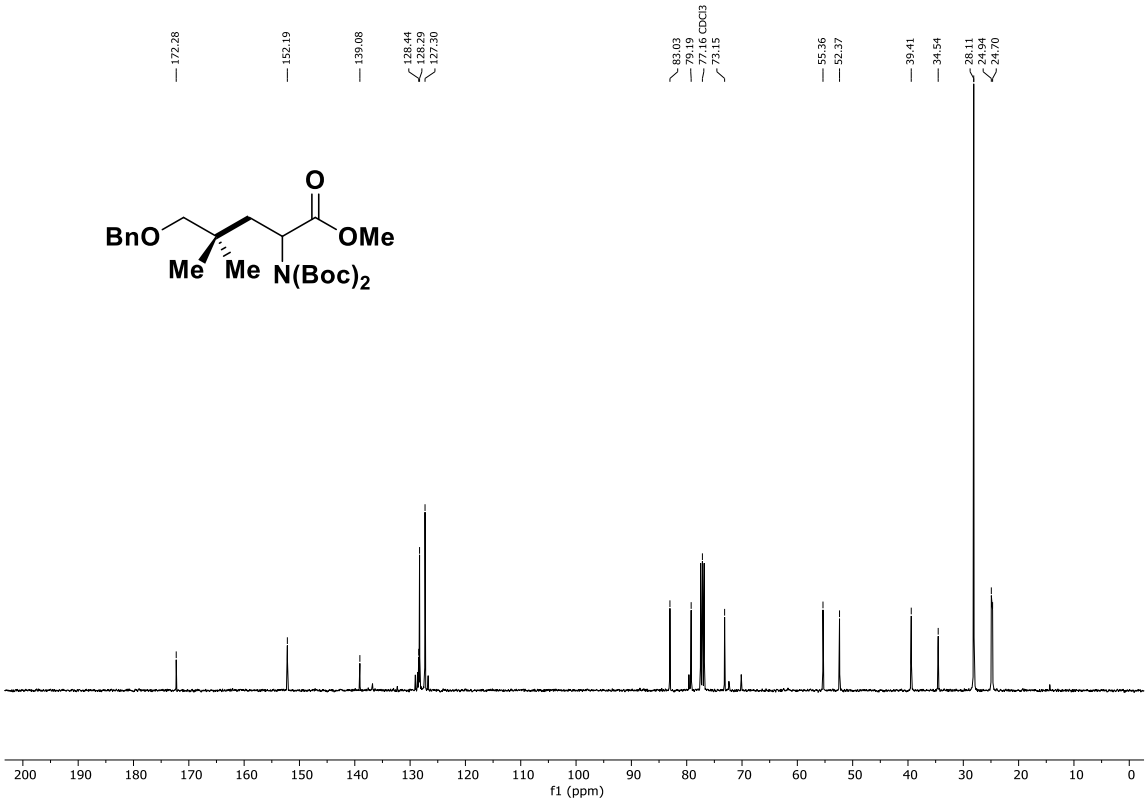


FIGURE 43. ^{13}C NMR of compound **4r** (100 MHz, $CDCl_3$).

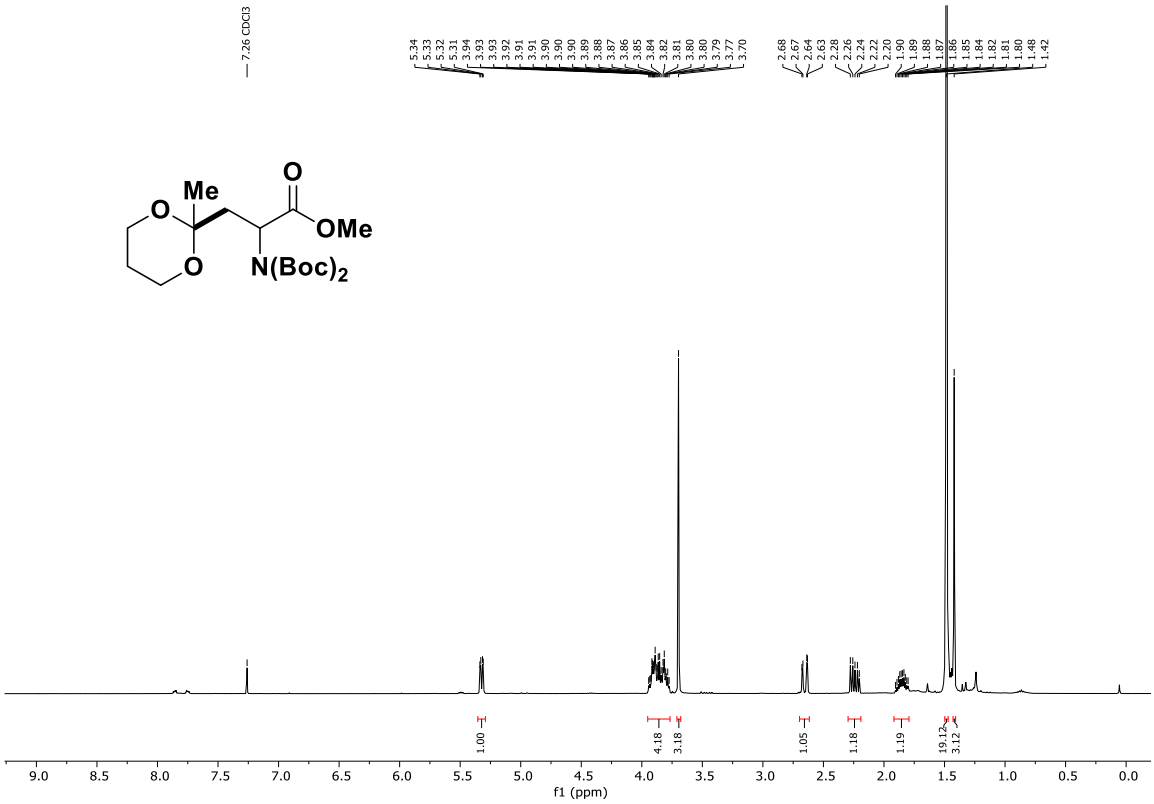


FIGURE 44. ^{1}H NMR of compound **4s** (400 MHz, $CDCl_3$).

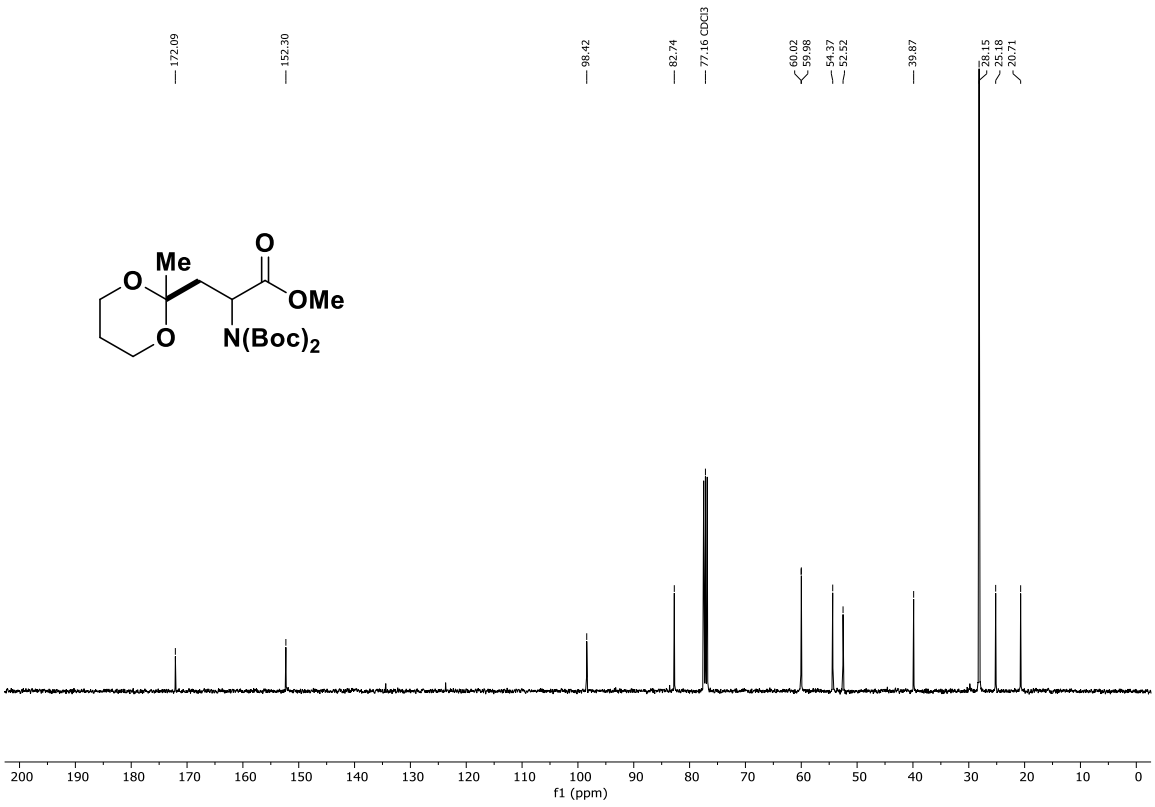


FIGURE 45. ^{13}C NMR of compound **4s** (100 MHz, $CDCl_3$).

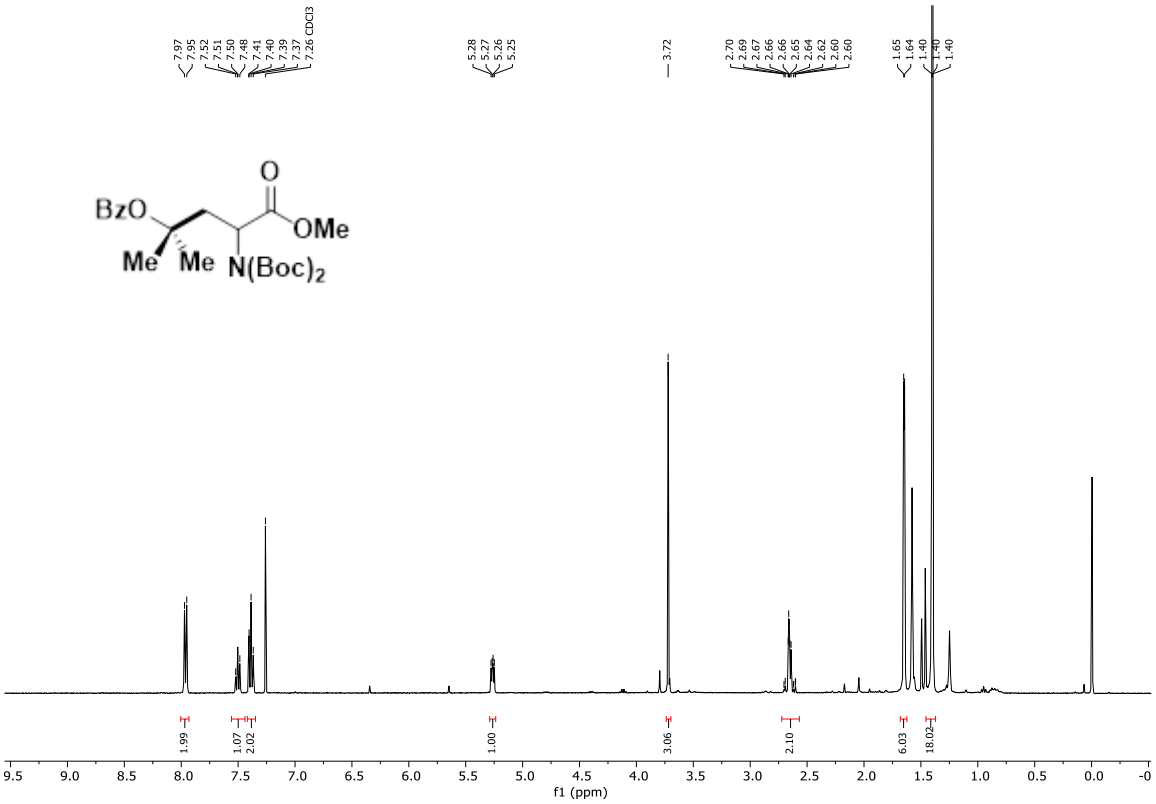


FIGURE 46. ^{1}H NMR of compound **4t** (400 MHz, $CDCl_3$).

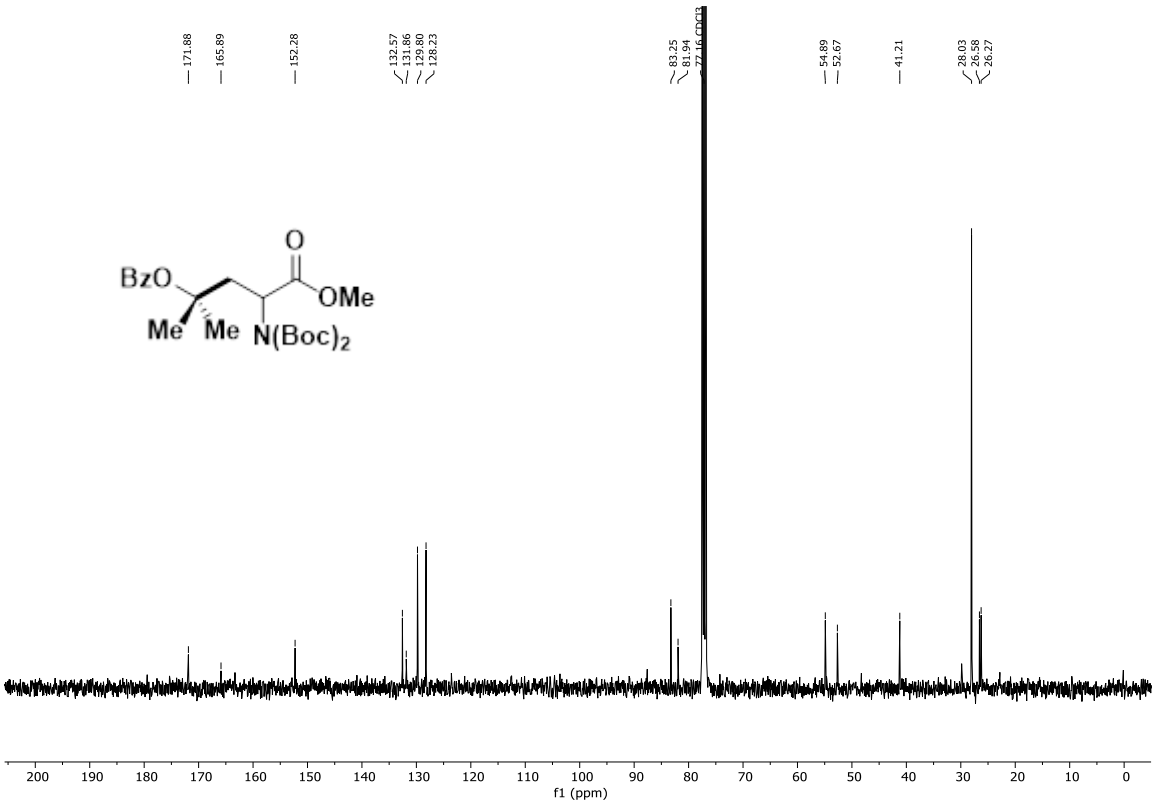


FIGURE 47. ^{13}C NMR of compound **4t** (100 MHz, $CDCl_3$).

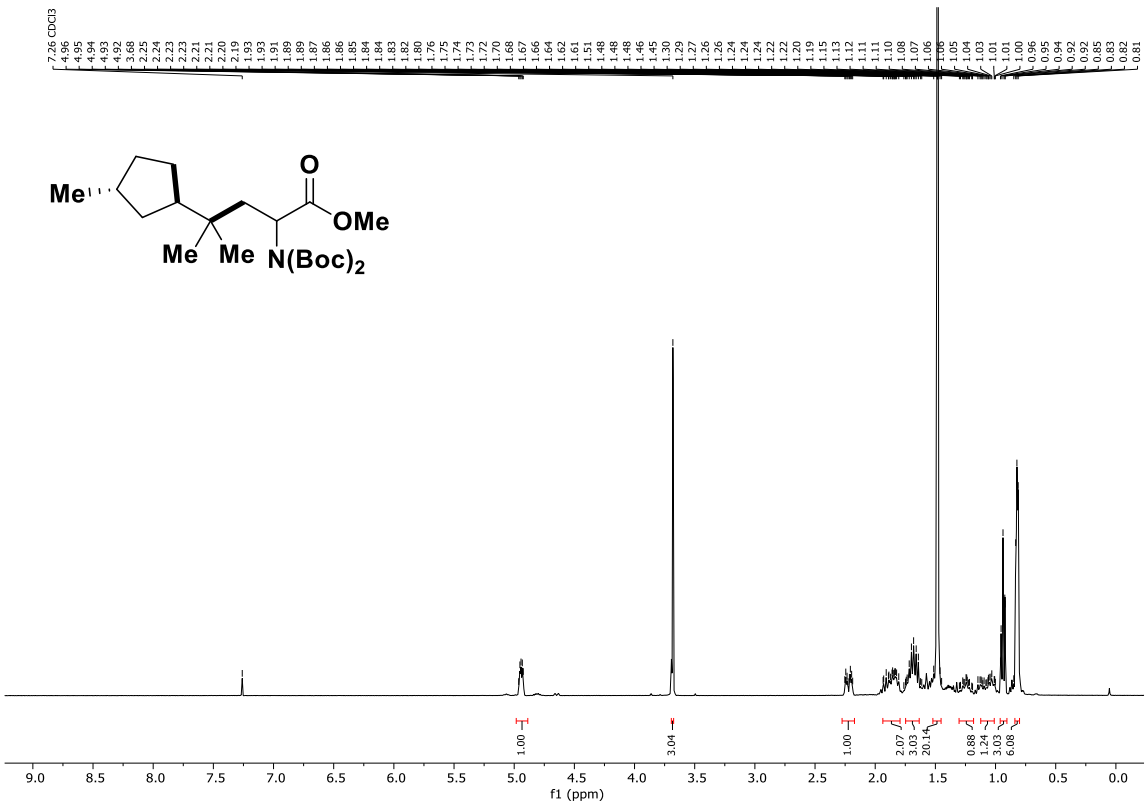


FIGURE 48. ^{1}H NMR of compound **4u** (400 MHz, $CDCl_3$).

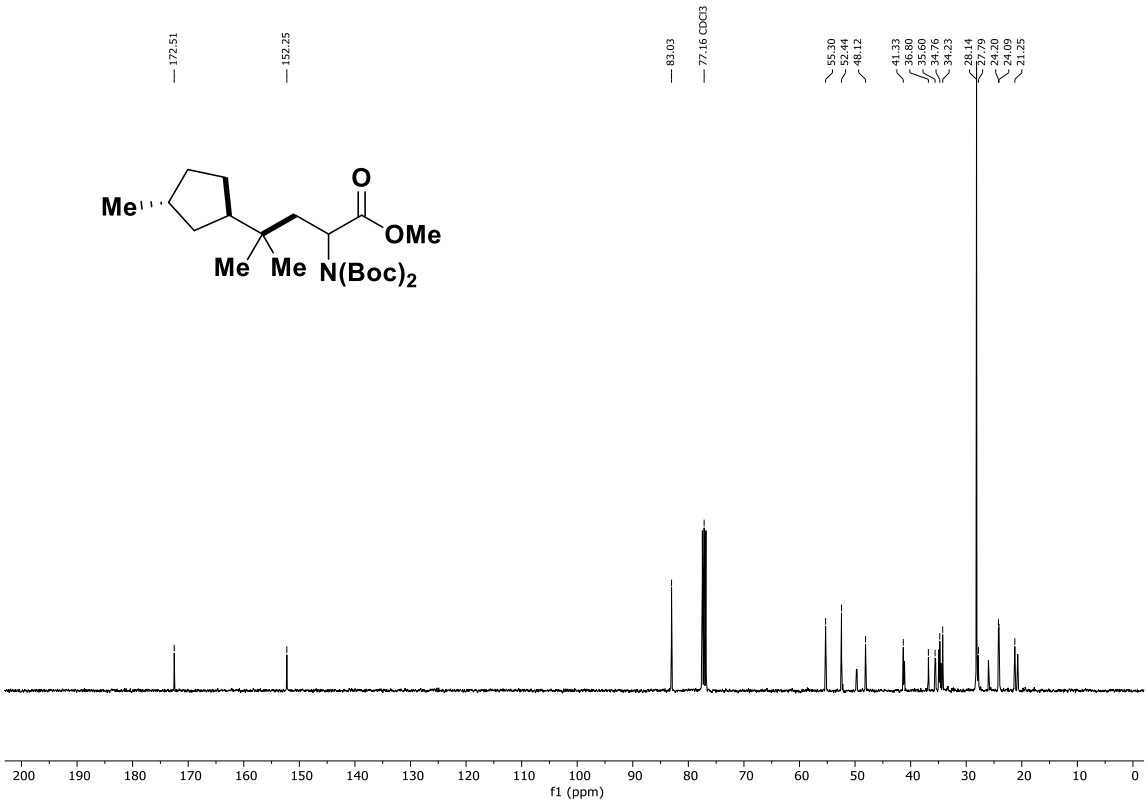


FIGURE 49. ^{13}C NMR of compound **4u** (100 MHz, $CDCl_3$).

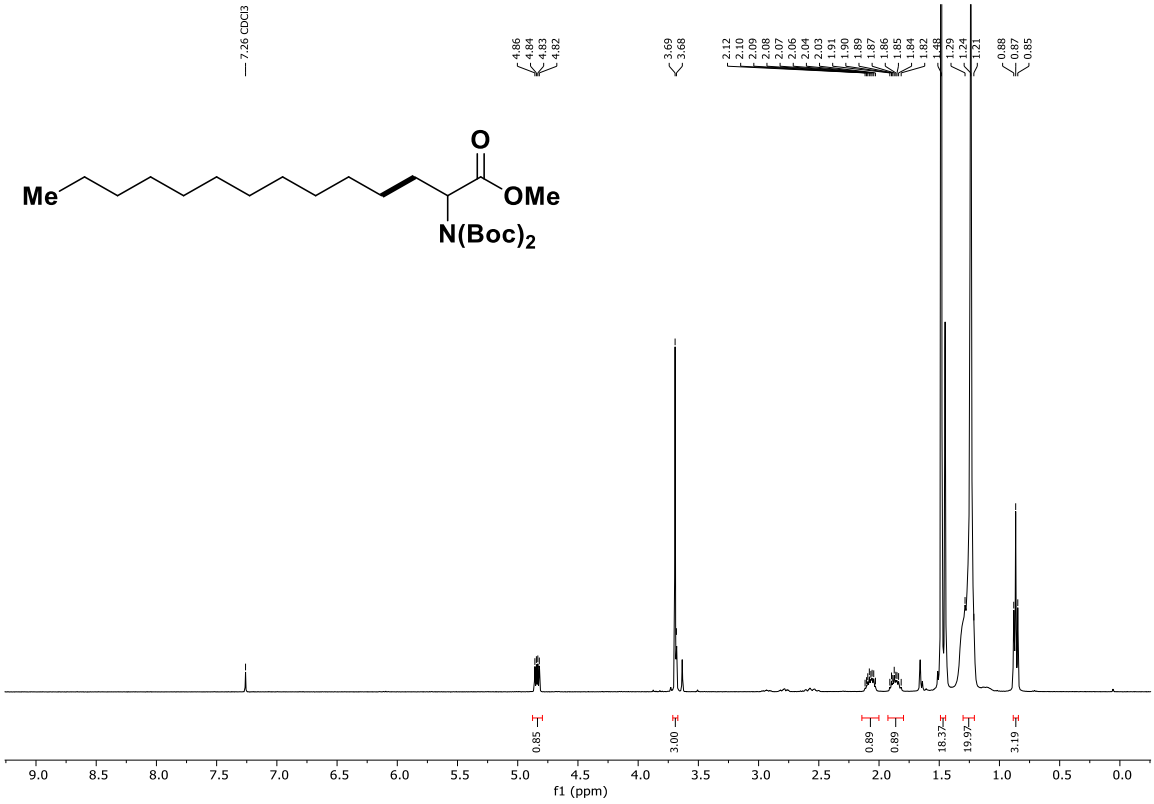


FIGURE 50. ^{1}H NMR of compound **4v** (400 MHz, $CDCl_3$).

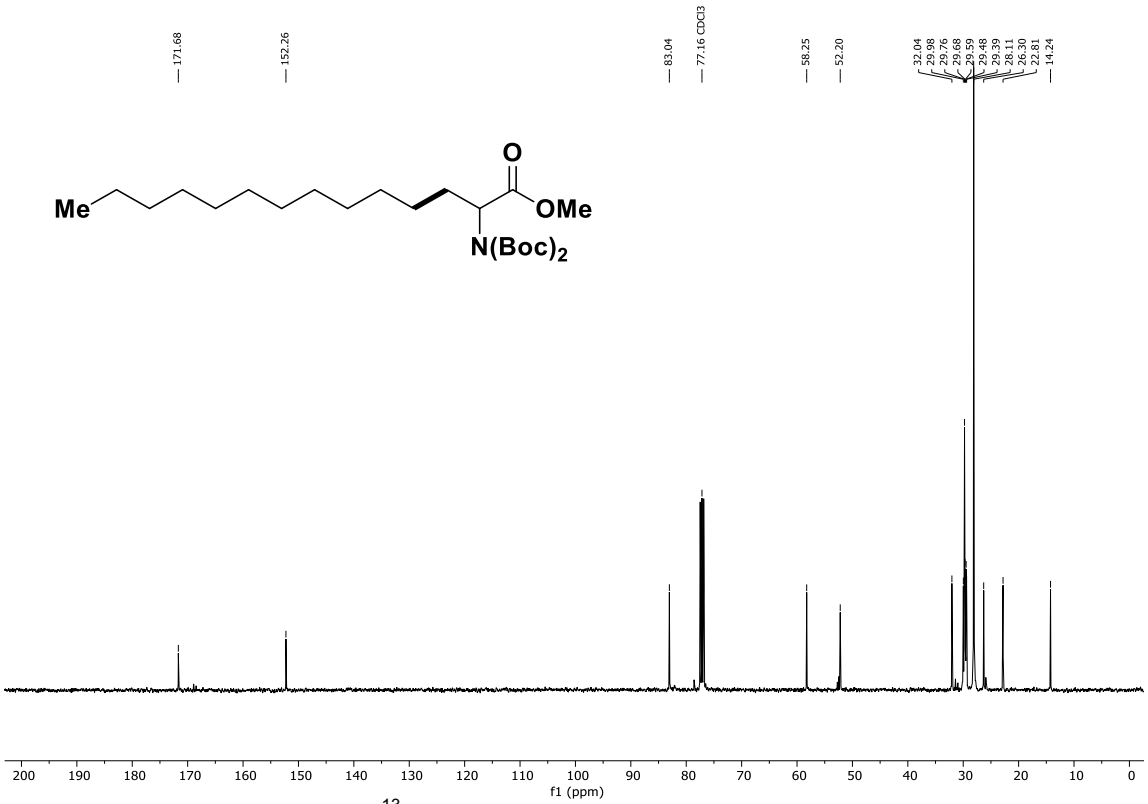


FIGURE 51. ^{13}C NMR of compound **4v** (100 MHz, $CDCl_3$).

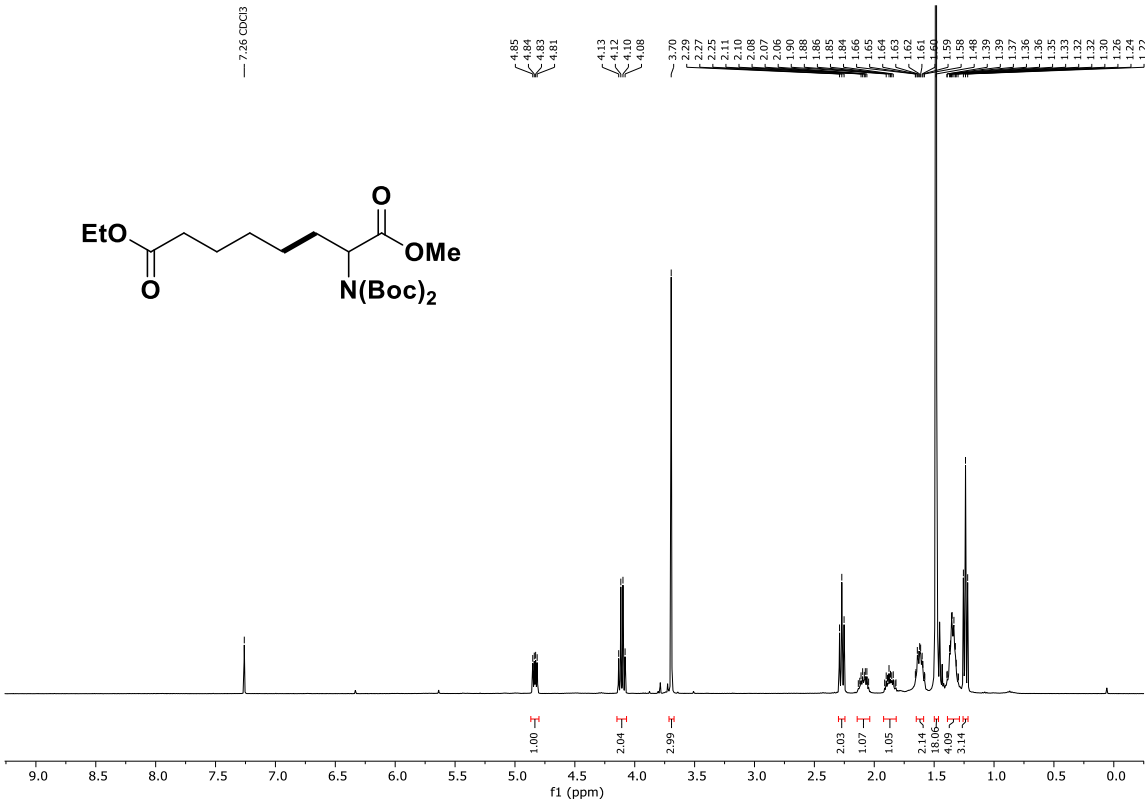


FIGURE 52. ^{1}H NMR of compound **4w** (400 MHz, $CDCl_3$).

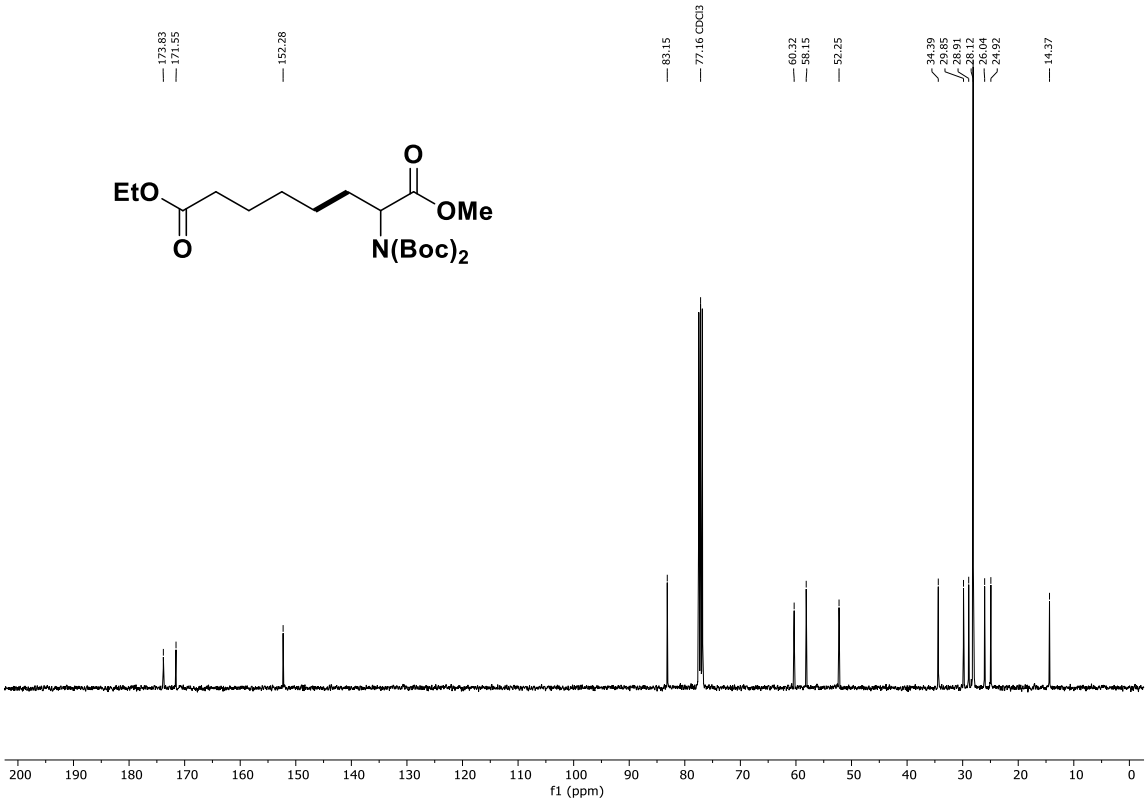


FIGURE 53. ^{13}C NMR of compound **4w** (100 MHz, $CDCl_3$).

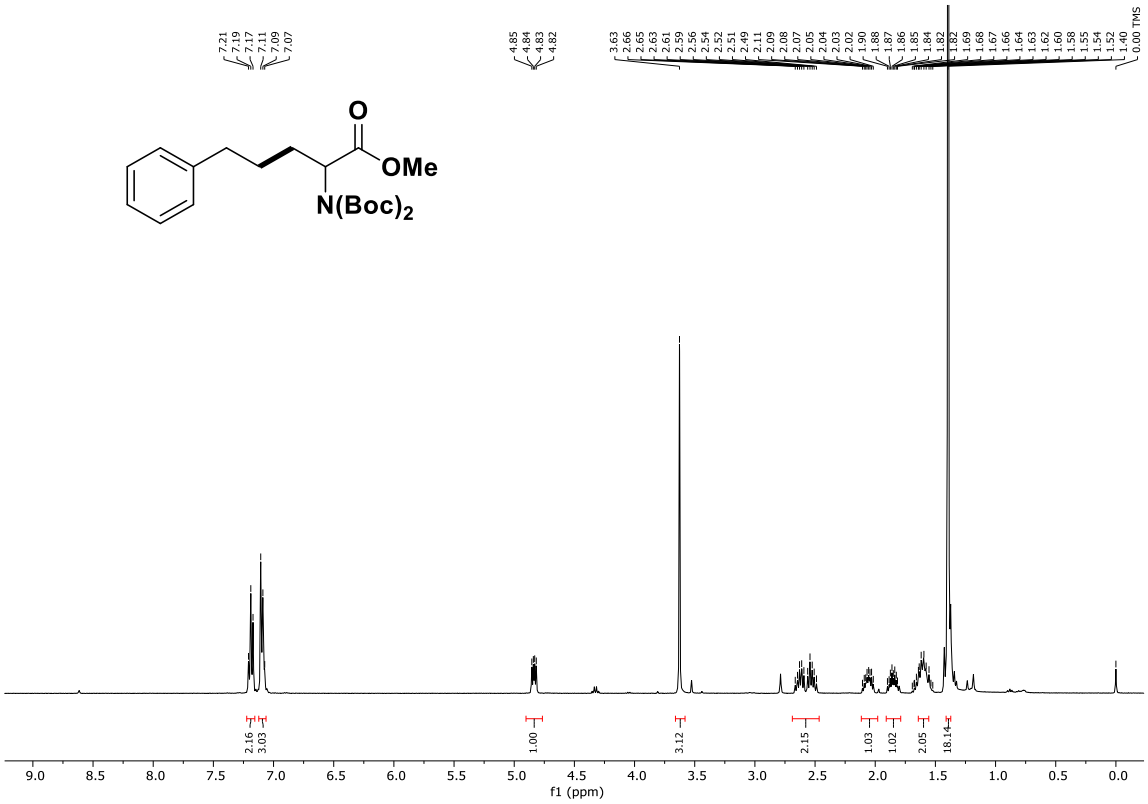


FIGURE 54. ^{1}H NMR of compound **4x** (400 MHz, $CDCl_3$).

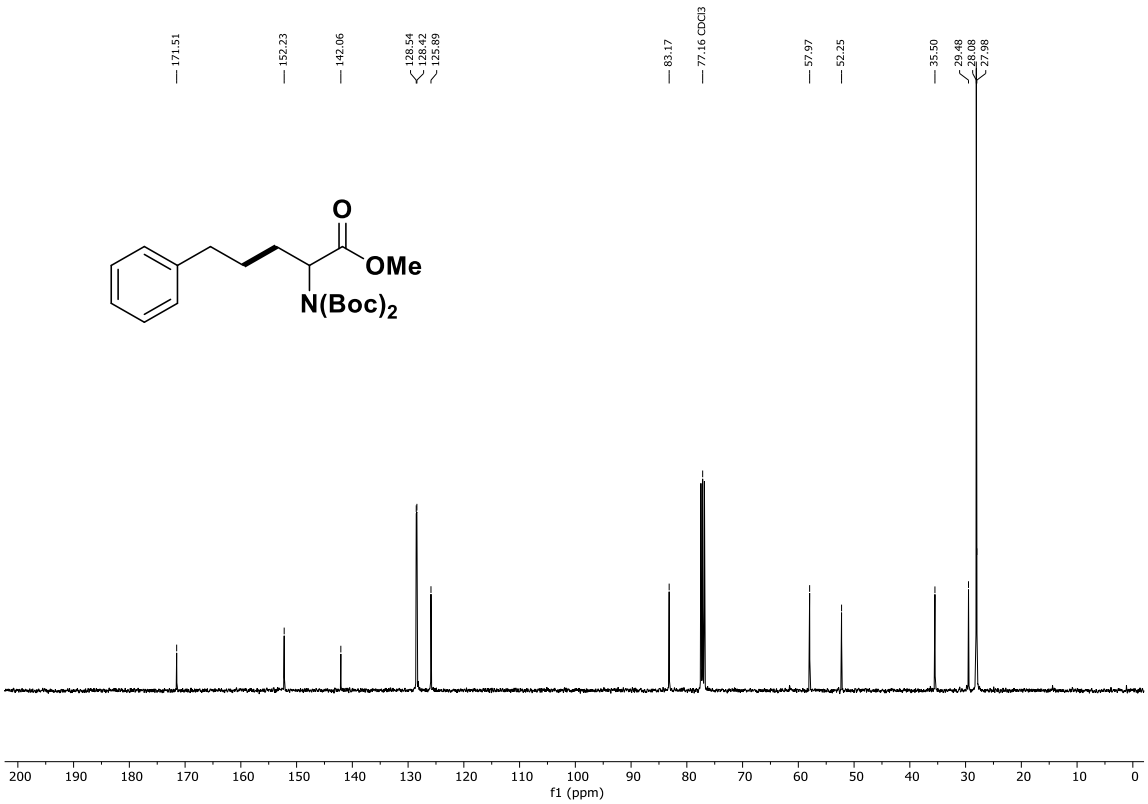


FIGURE 55. ^{13}C NMR of compound **4x** (100 MHz, $CDCl_3$).

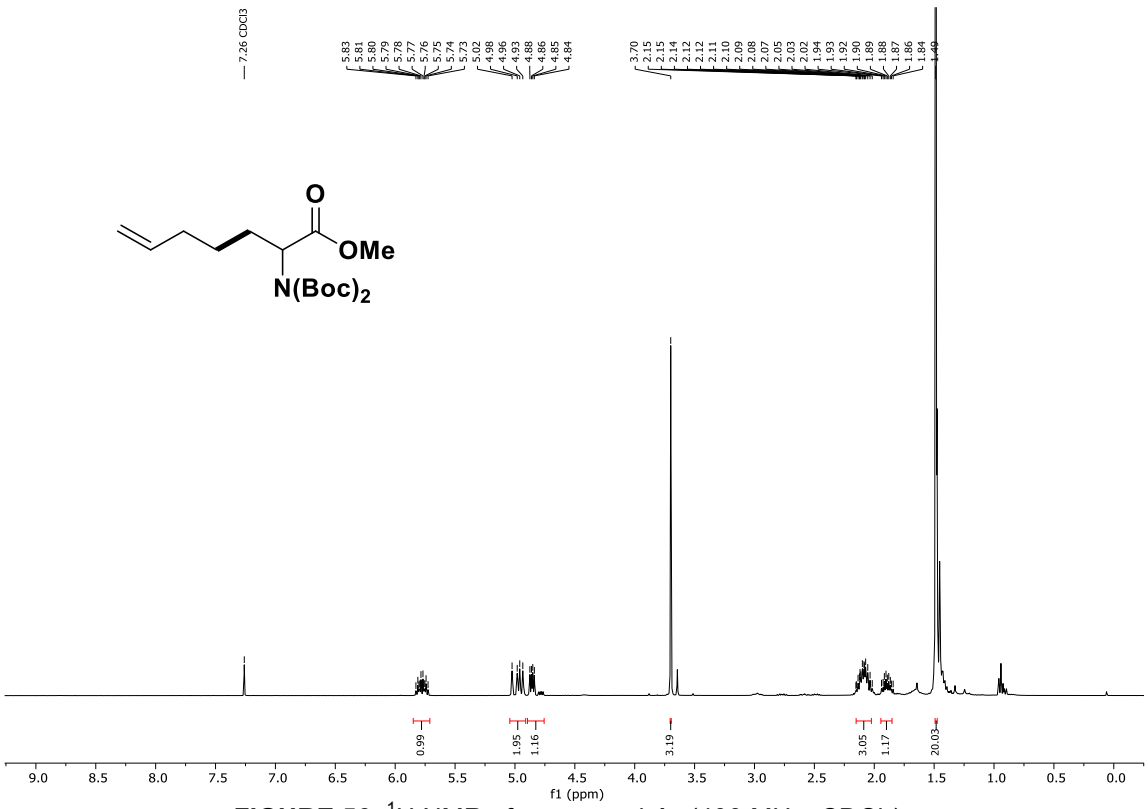


FIGURE 56. ^{1}H NMR of compound **4y** (400 MHz, $CDCl_3$).

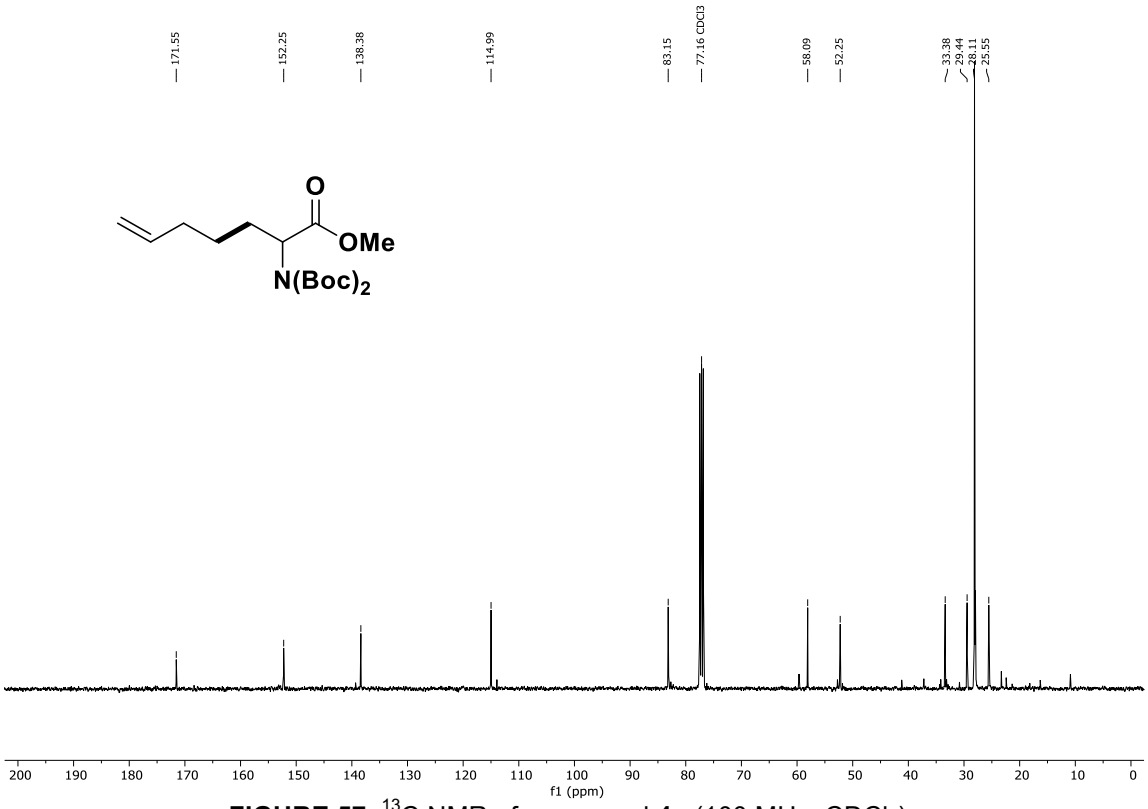


FIGURE 57. ^{13}C NMR of compound **4y** (100 MHz, $CDCl_3$).

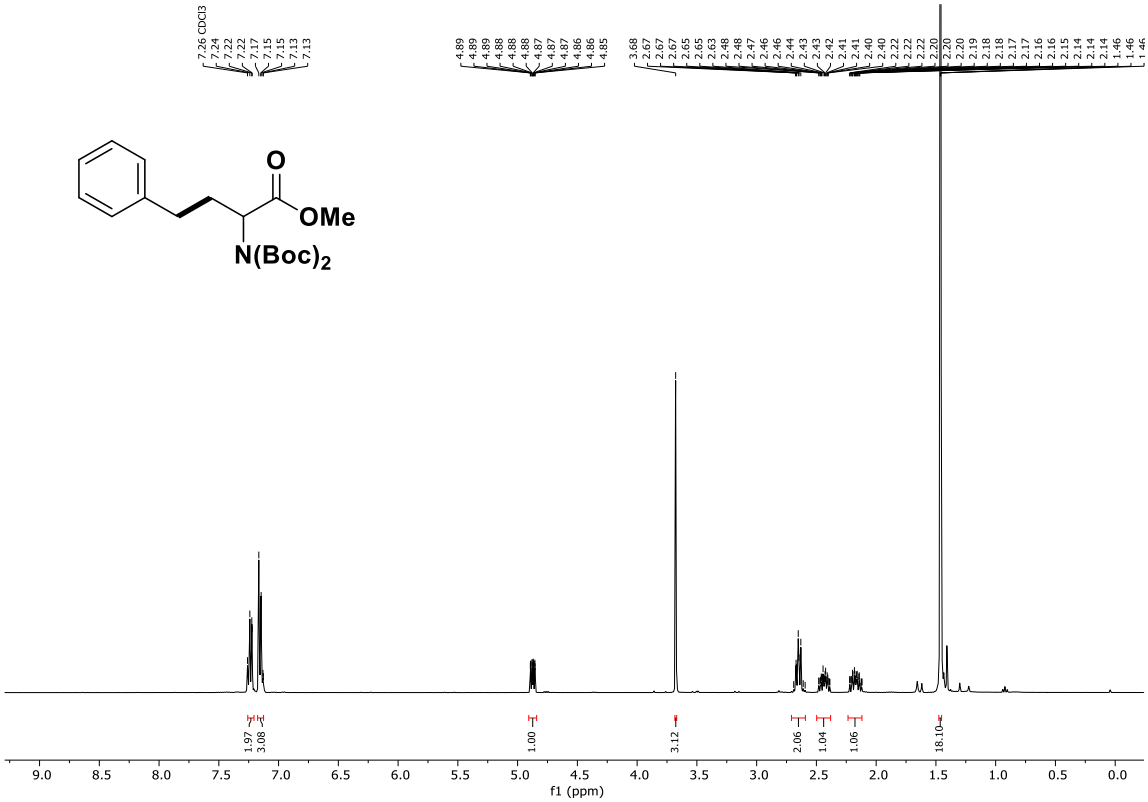


FIGURE 58. ^{1}H NMR of compound **4z** (400 MHz, $CDCl_3$).

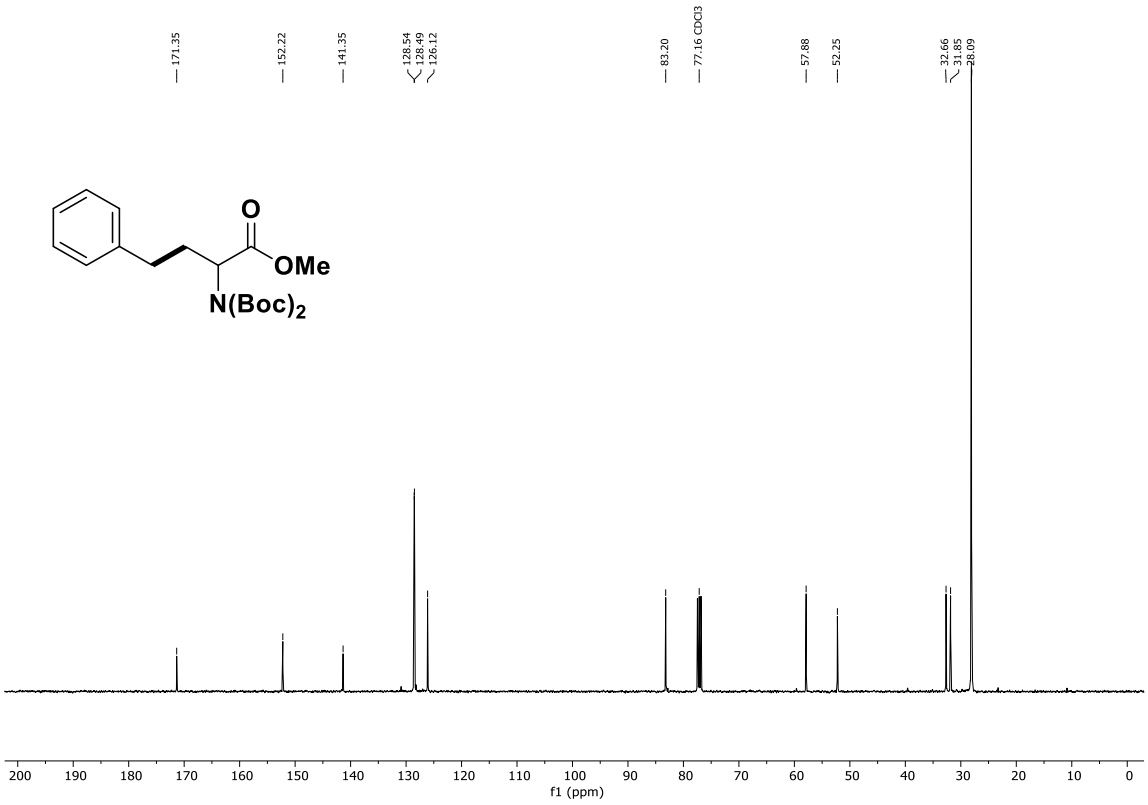


FIGURE 59. ^{13}C NMR of compound **4z** (100 MHz, $CDCl_3$).

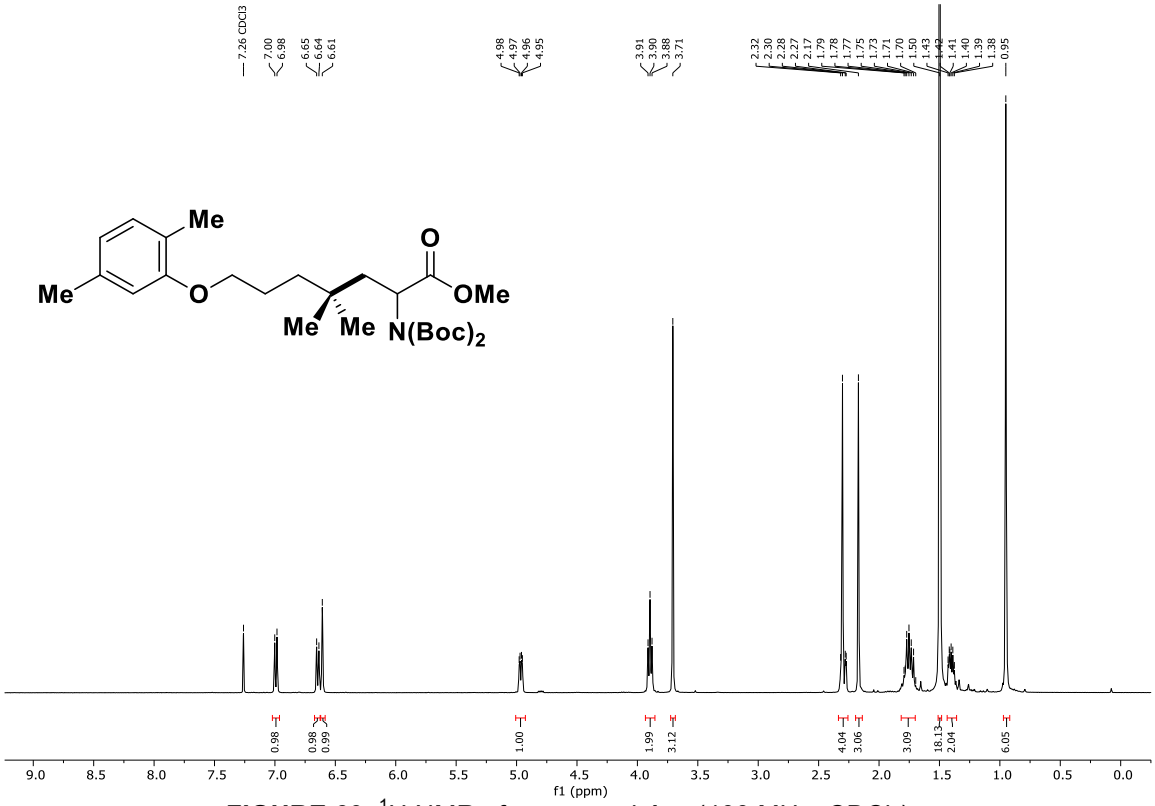


FIGURE 60. ^{1}H NMR of compound **4aa** (400 MHz, $CDCl_3$).

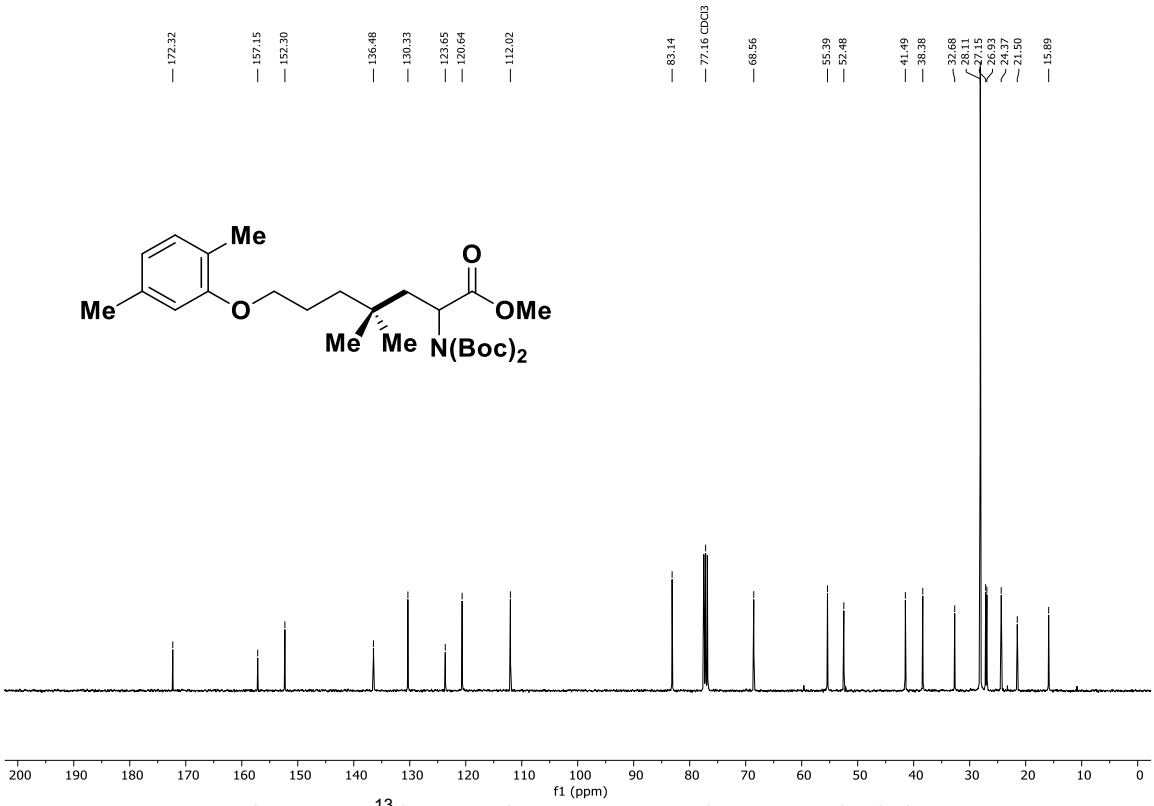


FIGURE 61. ^{13}C NMR of compound **4aa** (100 MHz, $CDCl_3$).

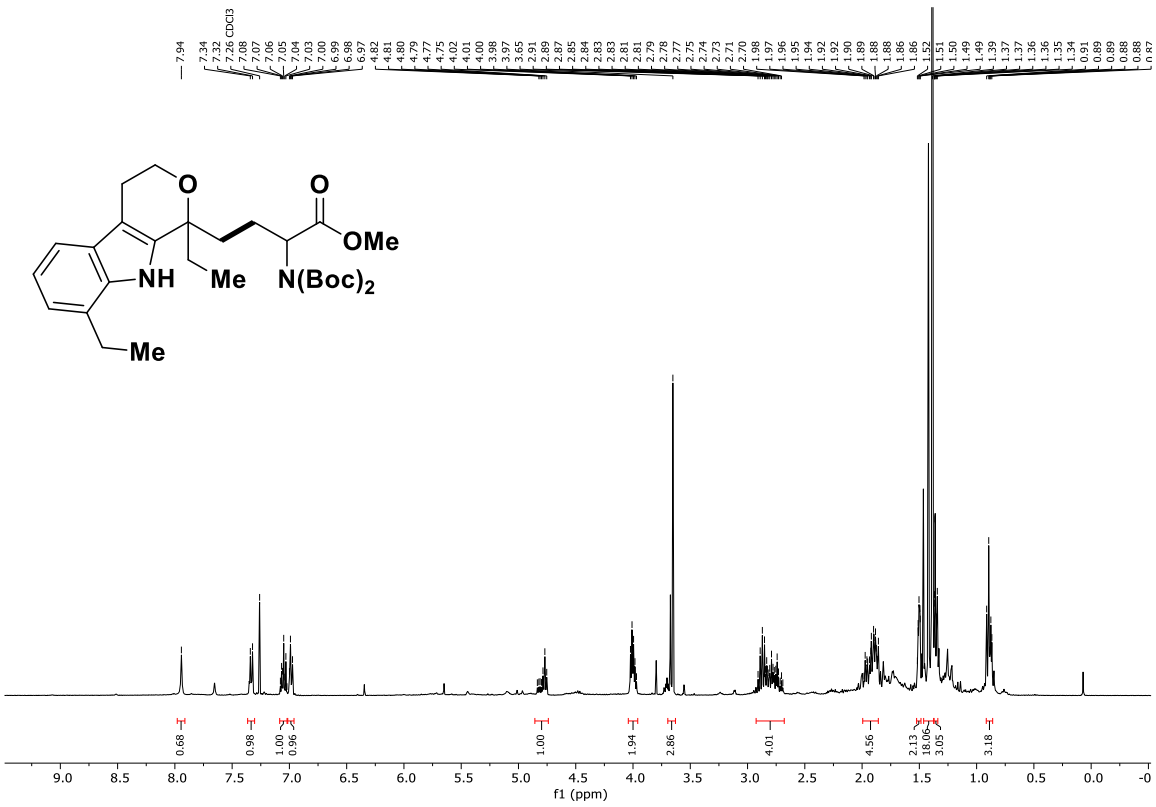


FIGURE 62. ^{1}H NMR of compound **4ab** (400 MHz, $CDCl_3$).

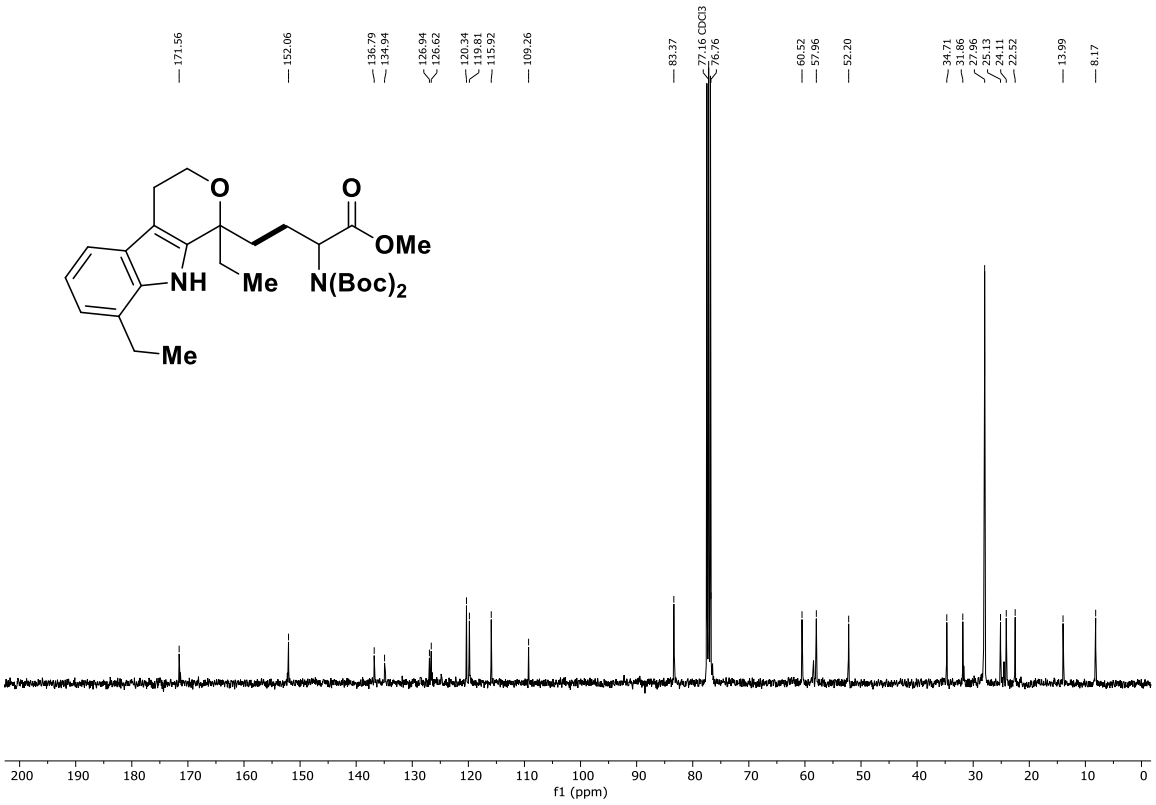


FIGURE 63. ^{13}C NMR of compound **4ab** (100 MHz, $CDCl_3$).

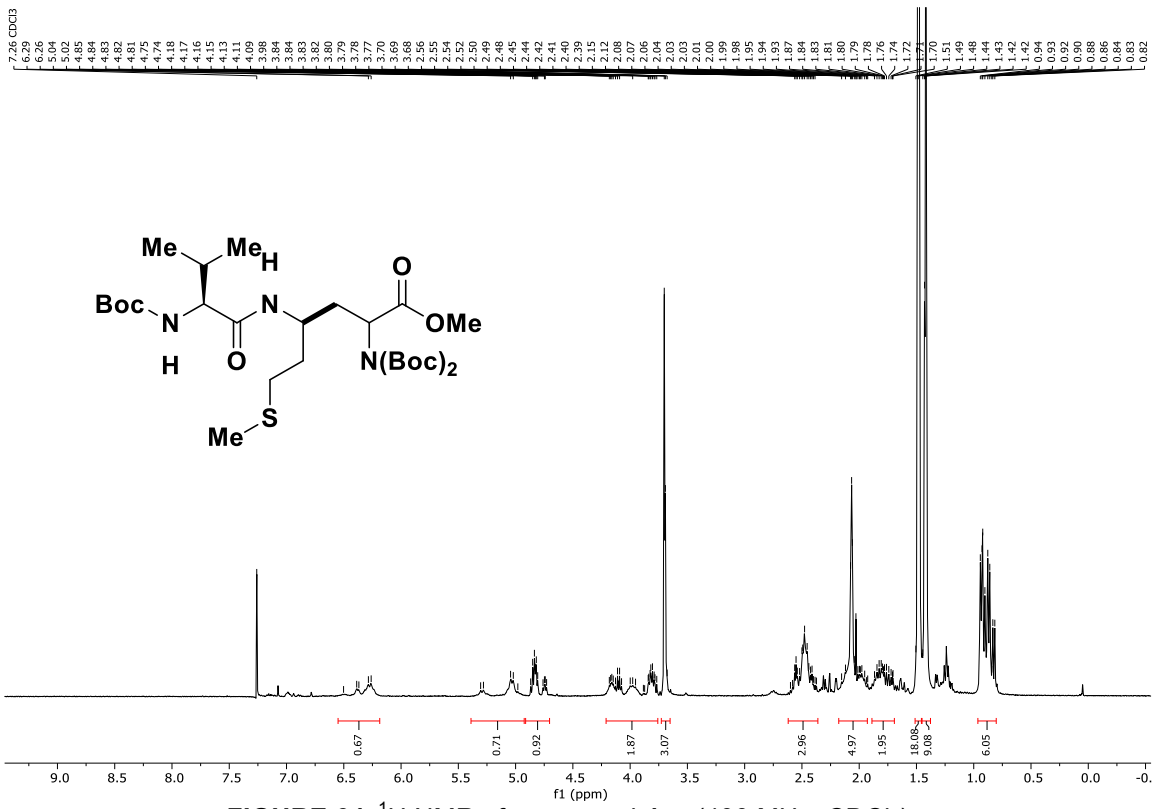


FIGURE 64. ^{1}H NMR of compound **4ac** (400 MHz, $CDCl_3$).

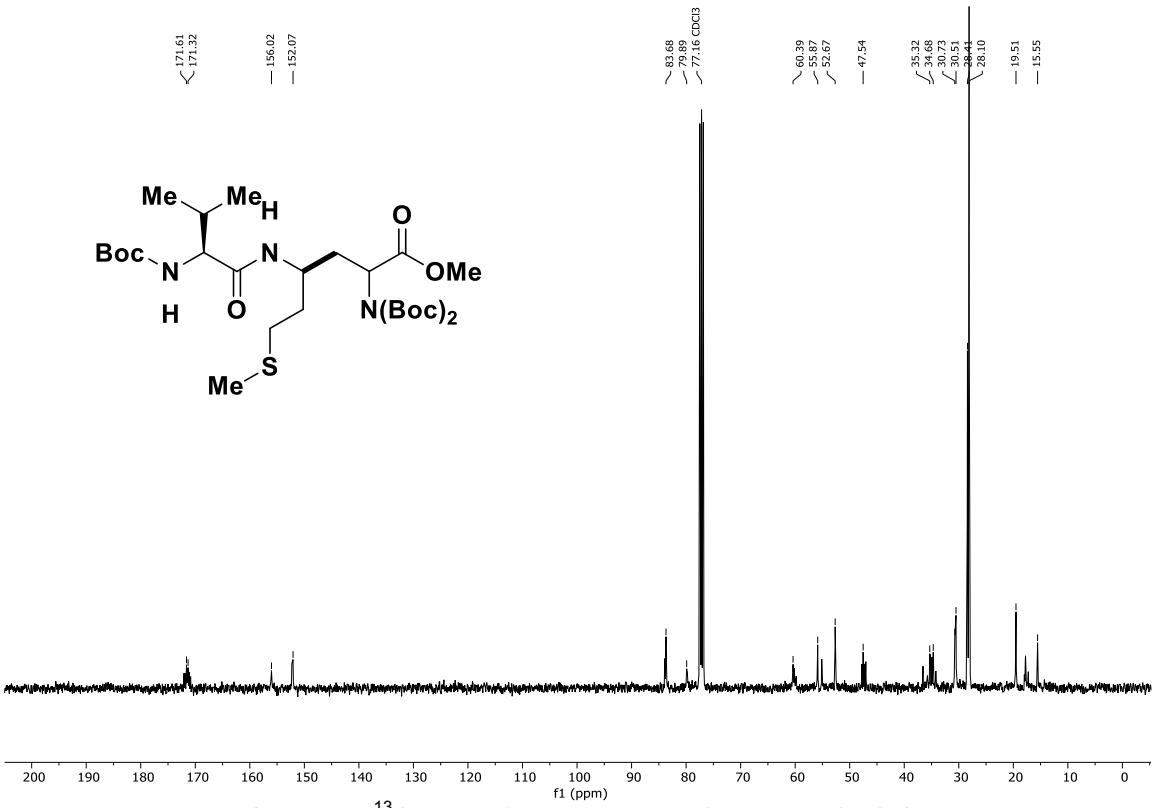


FIGURE 65. ^{13}C NMR of compound **4ac** (100 MHz, $CDCl_3$).

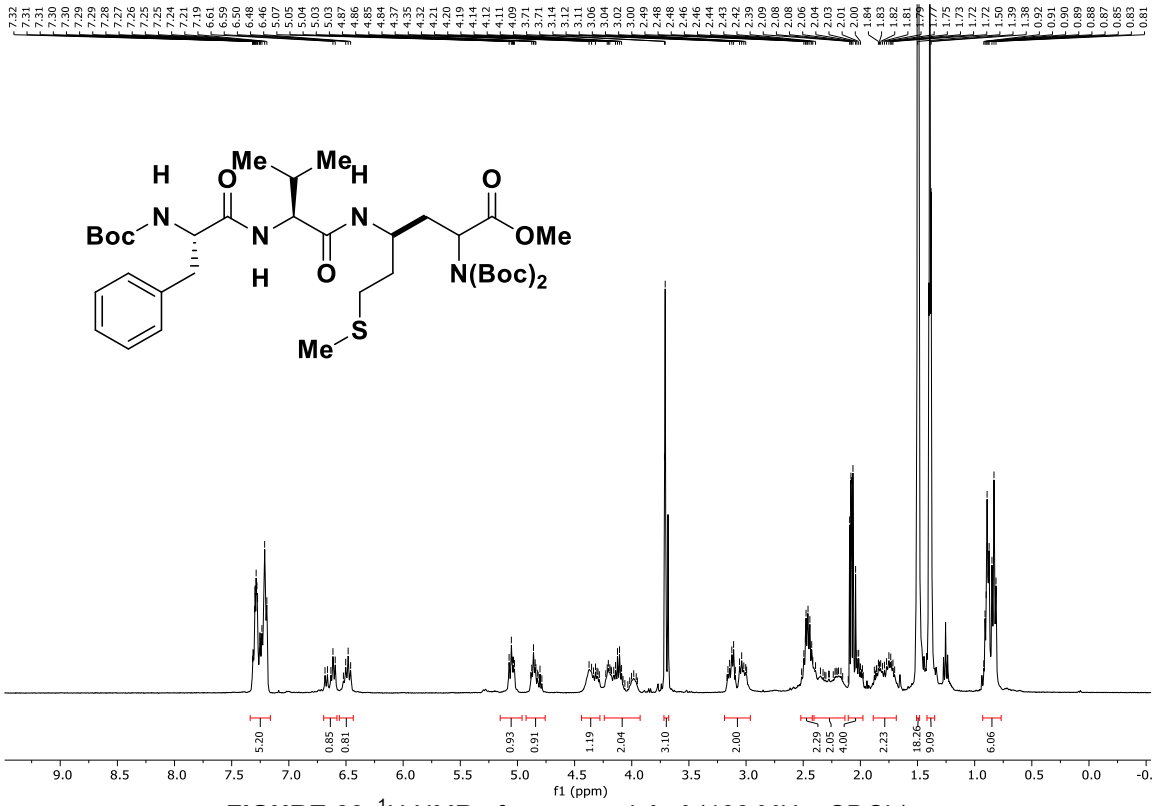


FIGURE 66. ^{1}H NMR of compound **4ad** (400 MHz, $CDCl_3$).

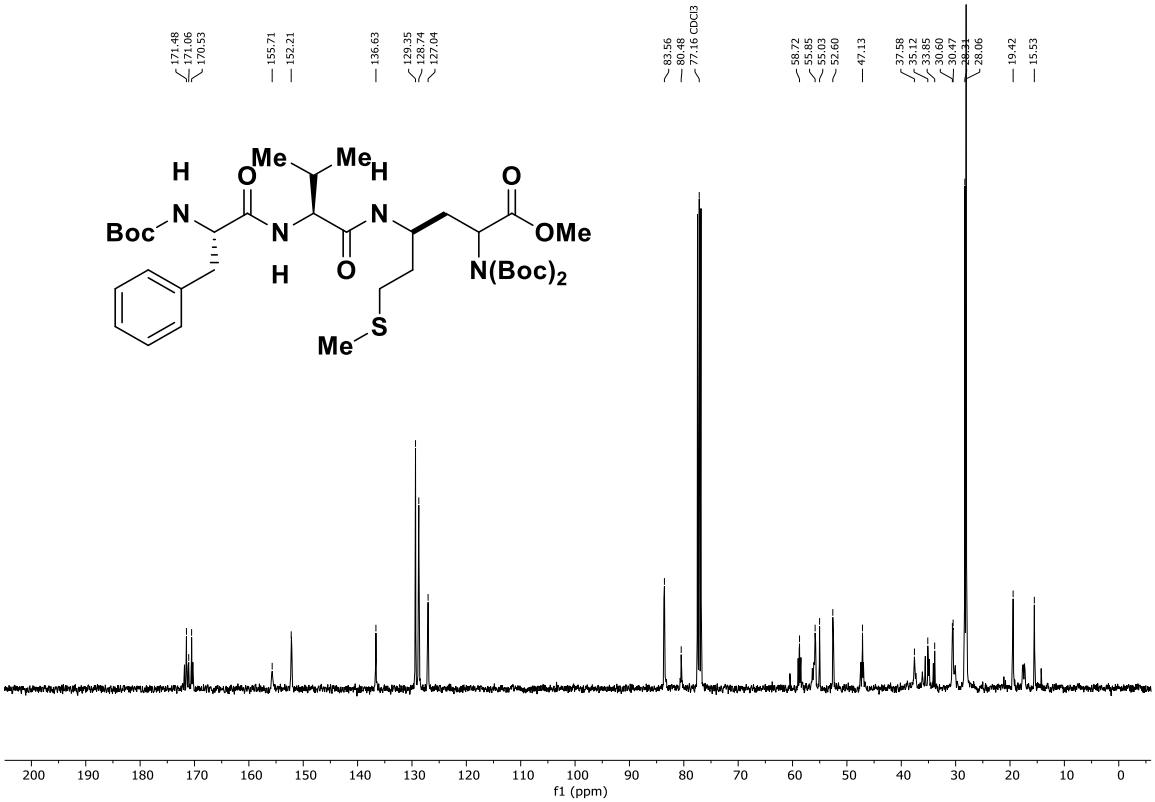


FIGURE 67. ^{13}C NMR of compound **4ad** (100 MHz, $CDCl_3$).

21. NMR spectra. Compounds 6a-f.

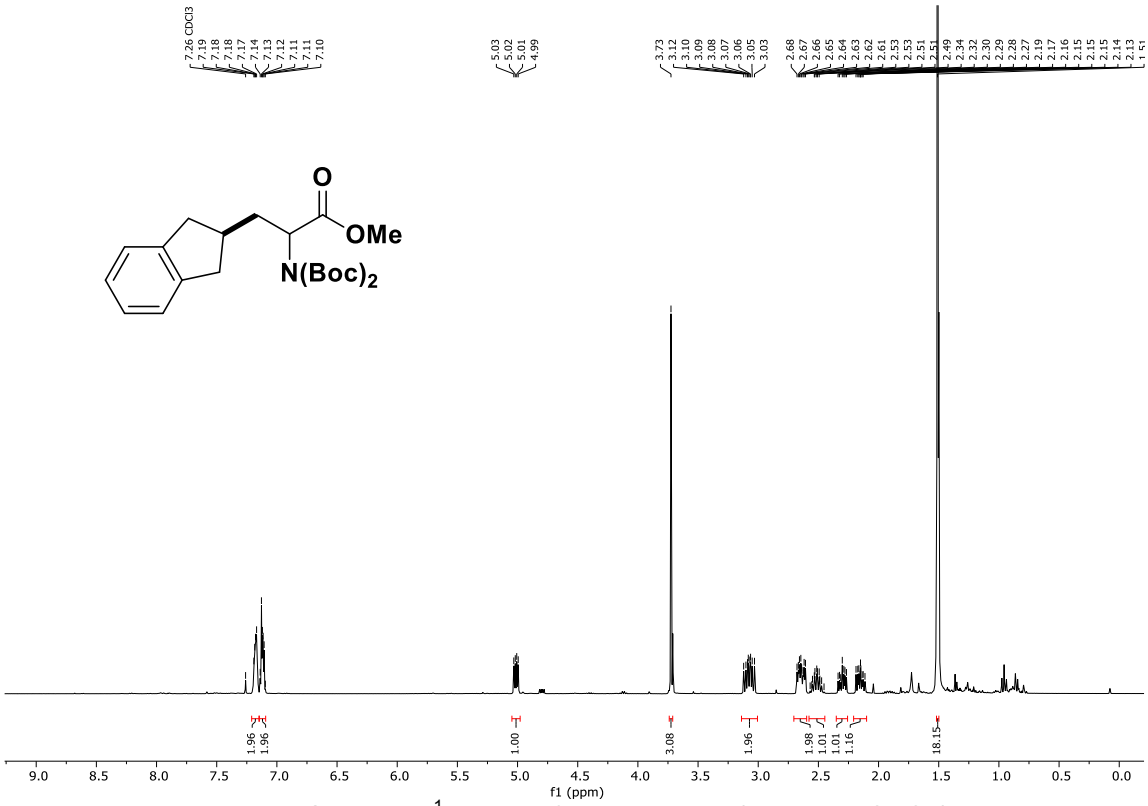


FIGURE 68. ^{1}H NMR of compound **6a** (400 MHz, $CDCl_3$).

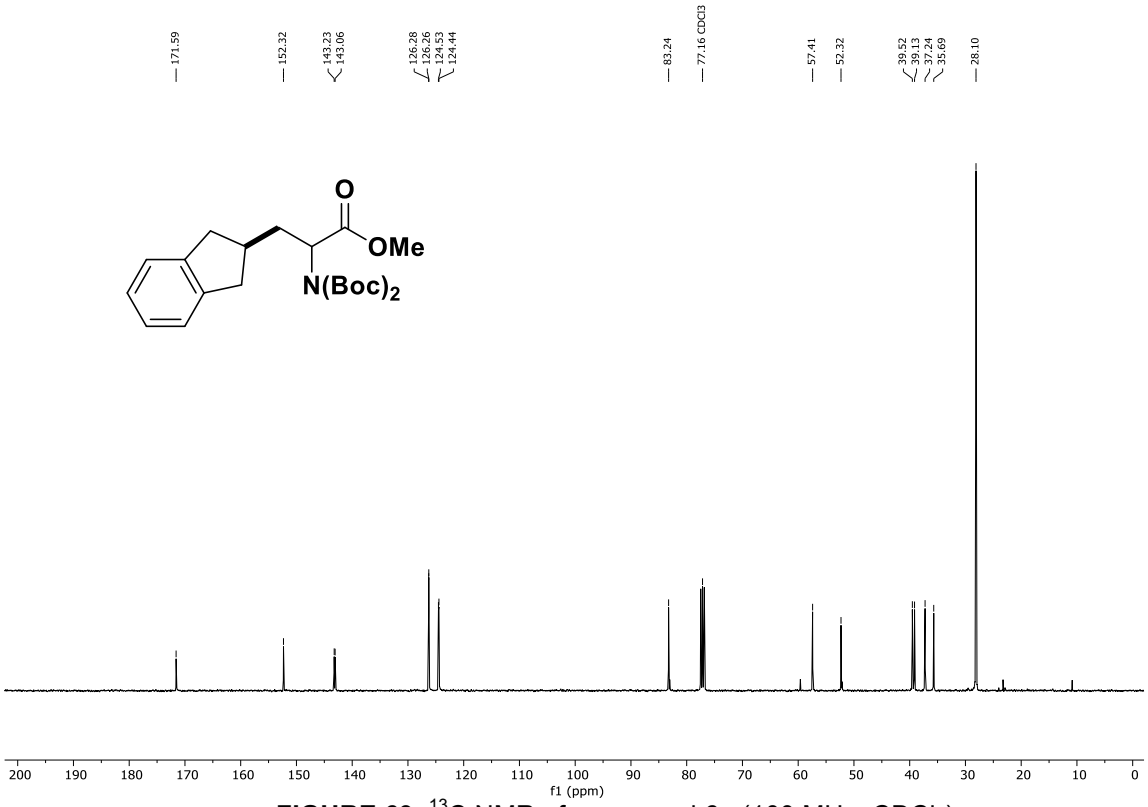


FIGURE 69. ^{13}C NMR of compound **6a** (100 MHz, $CDCl_3$).

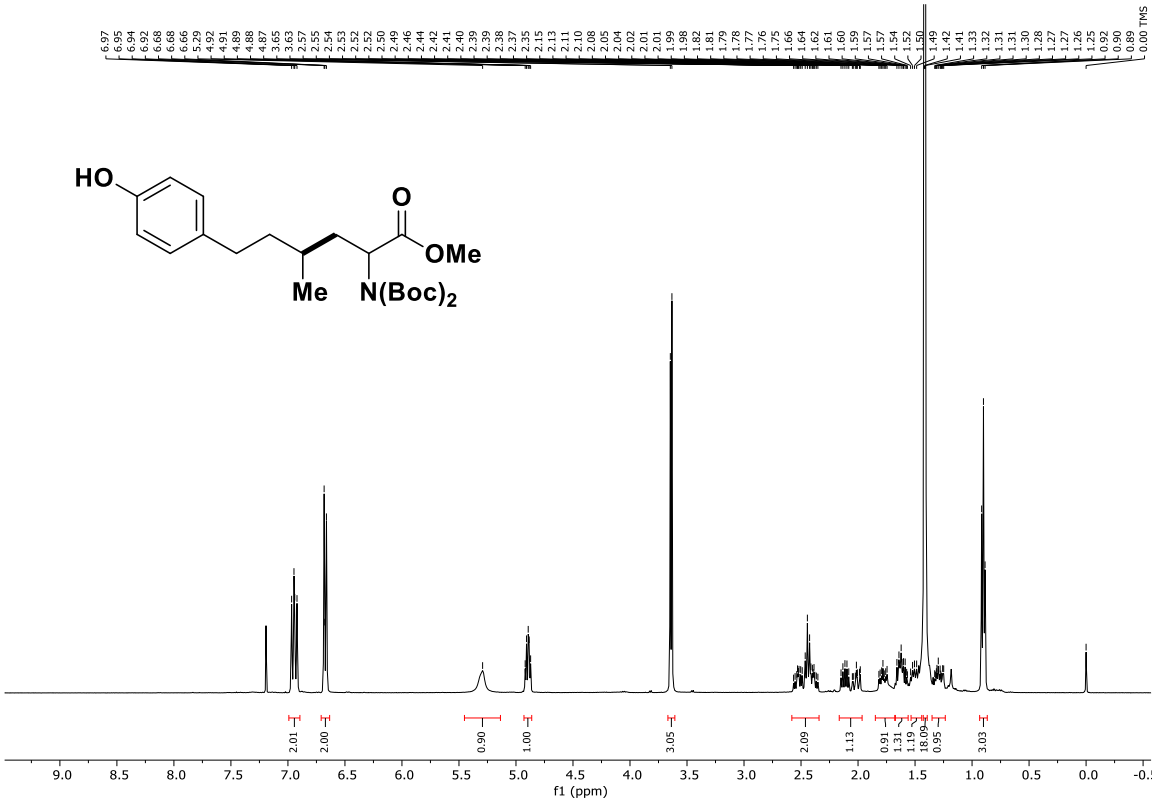


FIGURE 70. ^{1}H NMR of compound **6b** (400 MHz, $CDCl_3$).

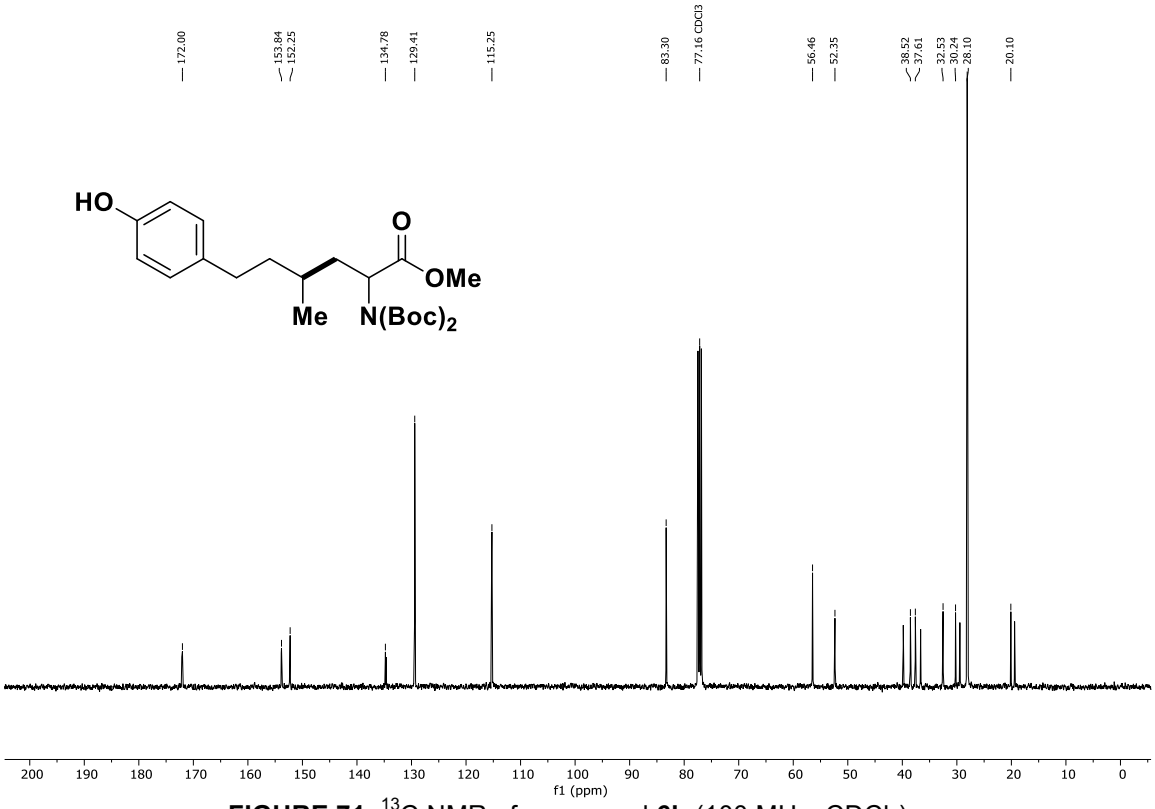


FIGURE 71. ^{13}C NMR of compound **6b** (100 MHz, $CDCl_3$).

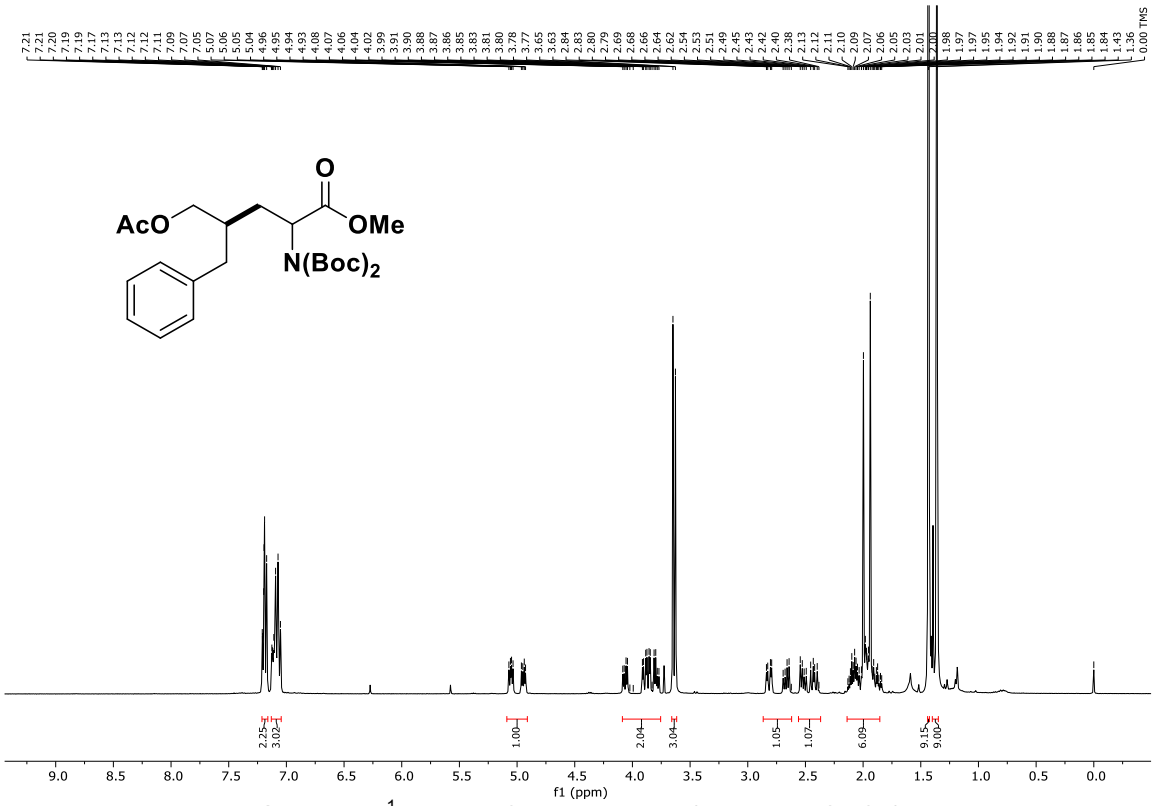


FIGURE 72. ^{1}H NMR of compound **6c** (400 MHz, $CDCl_3$).

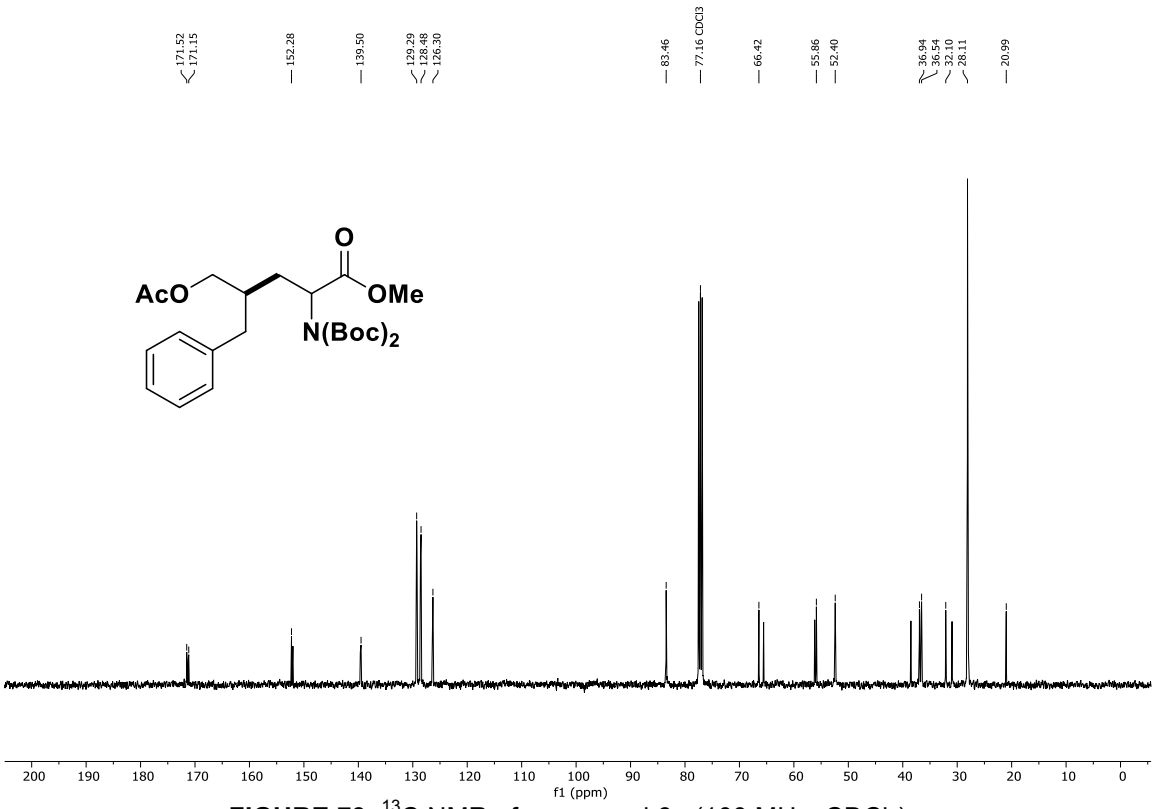


FIGURE 73. ^{13}C NMR of compound **6c** (100 MHz, $CDCl_3$).

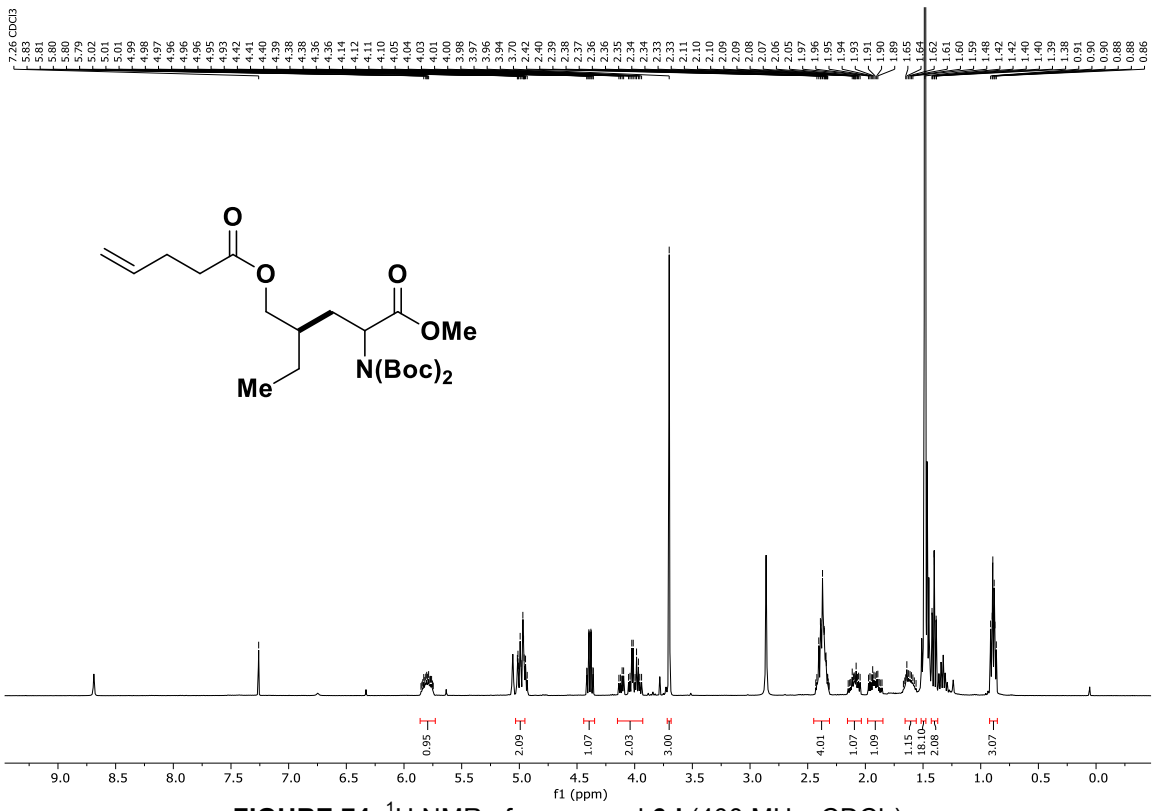


FIGURE 74. ^{1}H NMR of compound **6d** (400 MHz, $CDCl_3$).

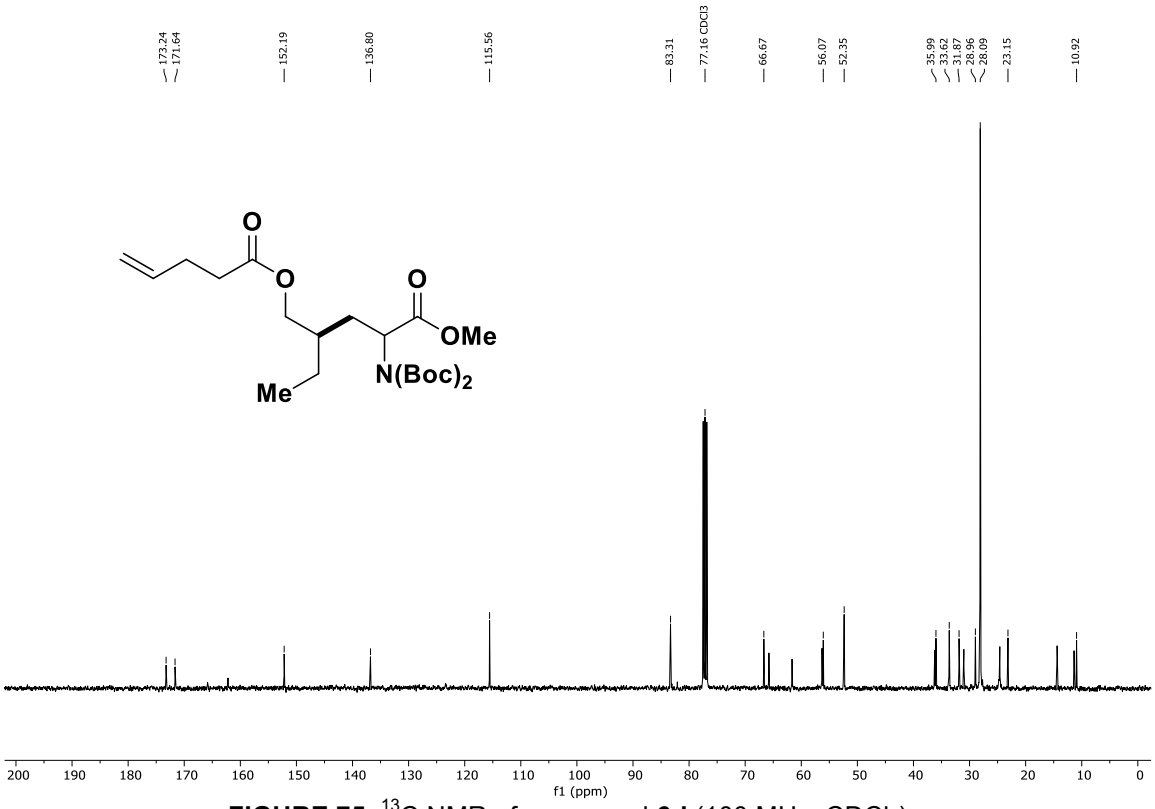


FIGURE 75. ^{13}C NMR of compound **6d** (100 MHz, $CDCl_3$).

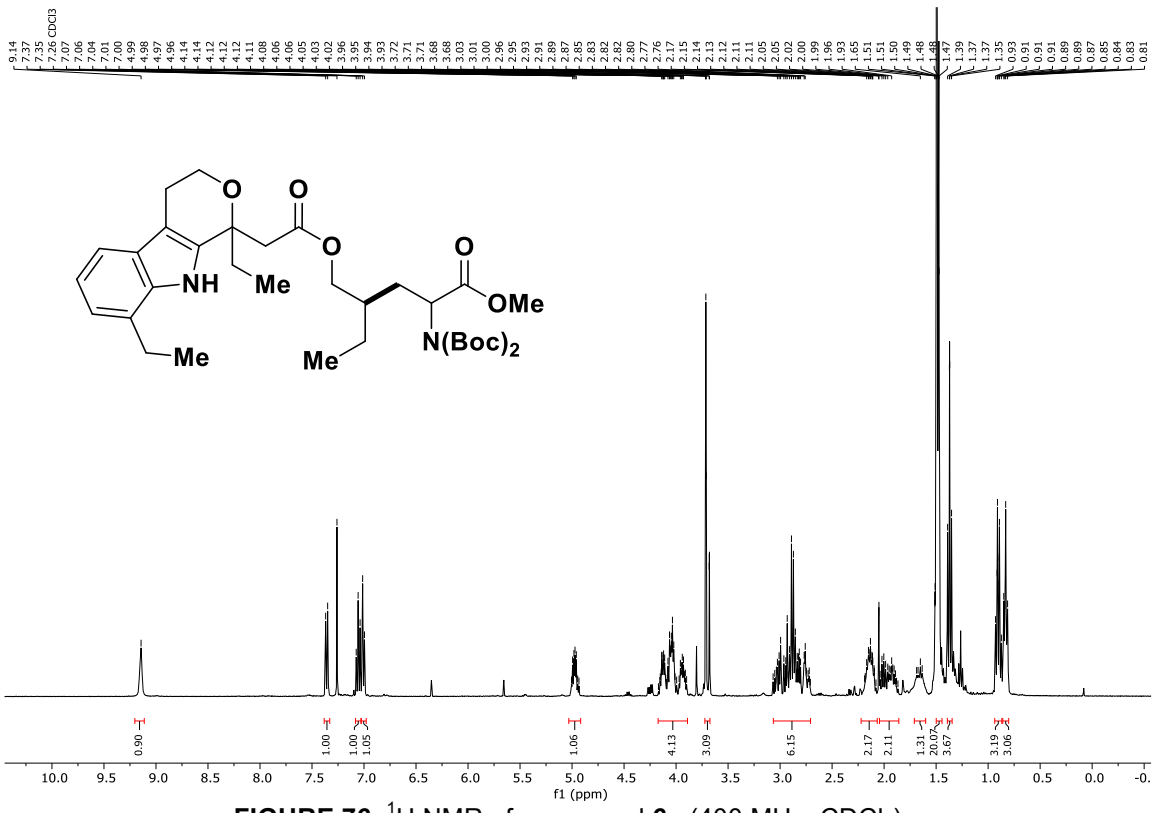


FIGURE 76. ^{1}H NMR of compound **6e** (400 MHz, $CDCl_3$).

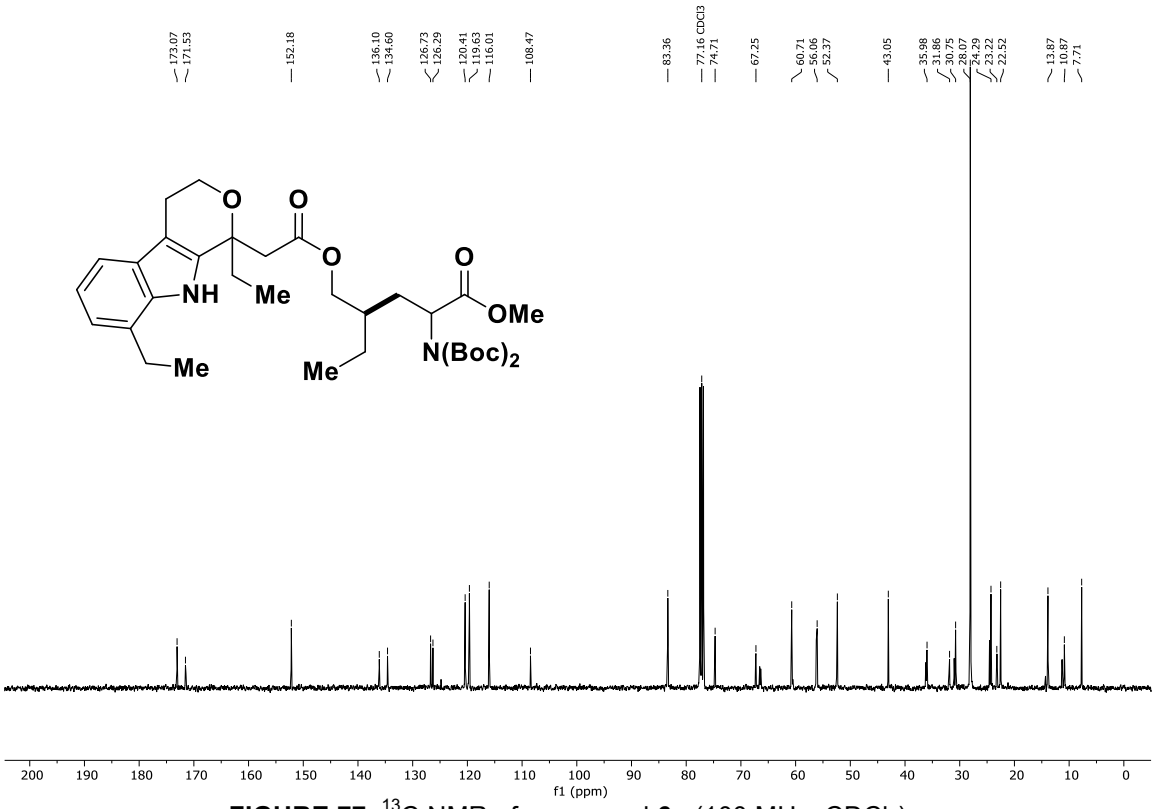


FIGURE 77. ^{13}C NMR of compound **6e** (100 MHz, $CDCl_3$).

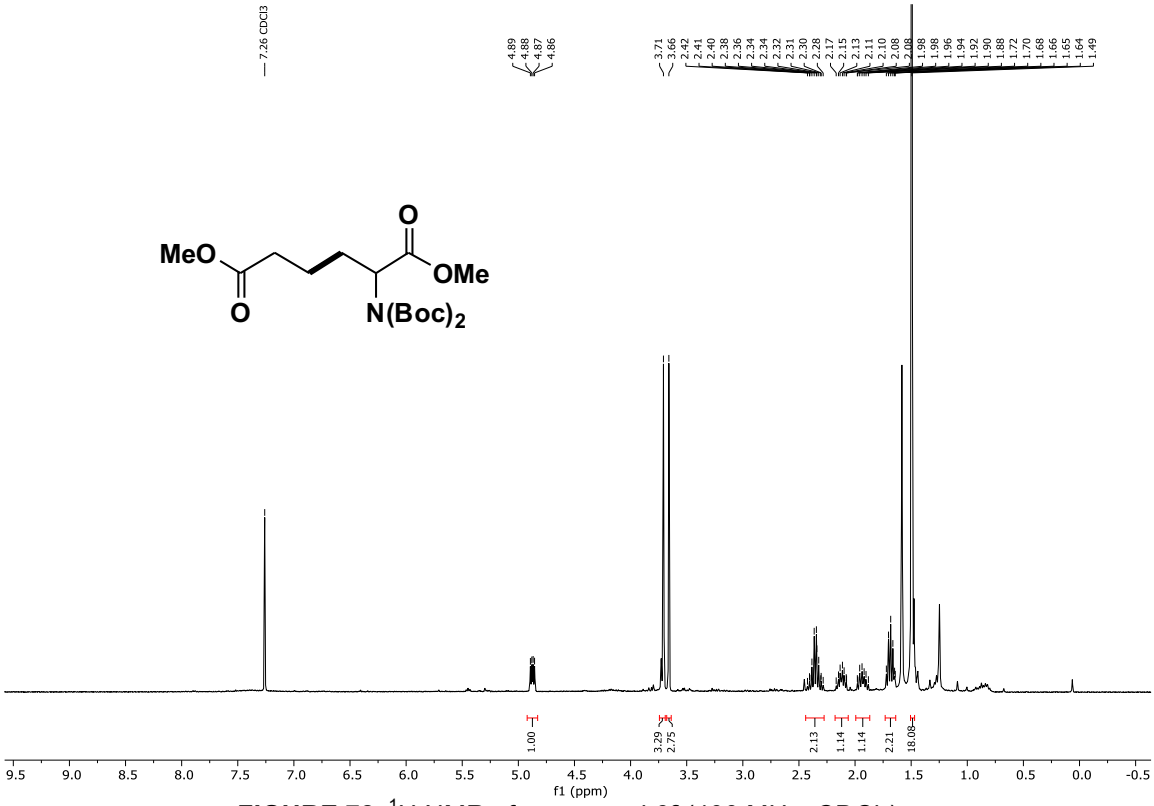


FIGURE 78. ^{1}H NMR of compound **6f** (400 MHz, $CDCl_3$).

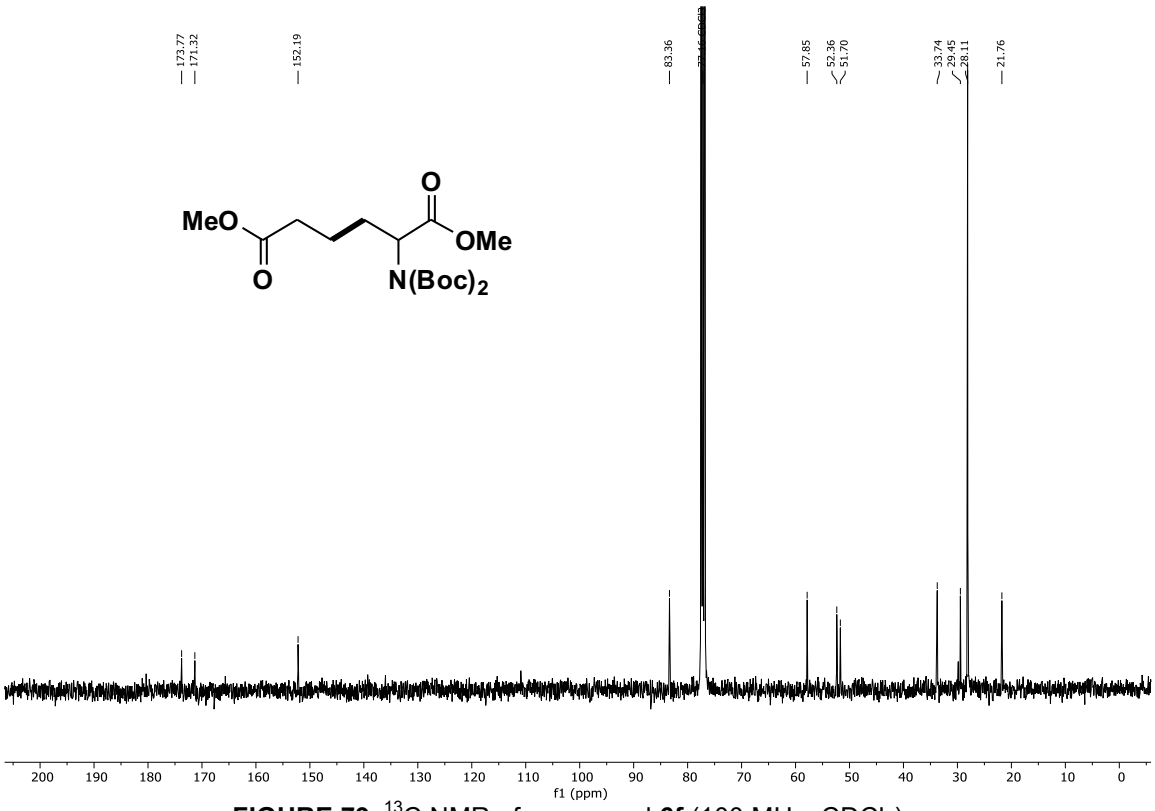


FIGURE 79. ^{13}C NMR of compound **6f** (100 MHz, $CDCl_3$).

22. NMR spectra. Compounds 8a-f.

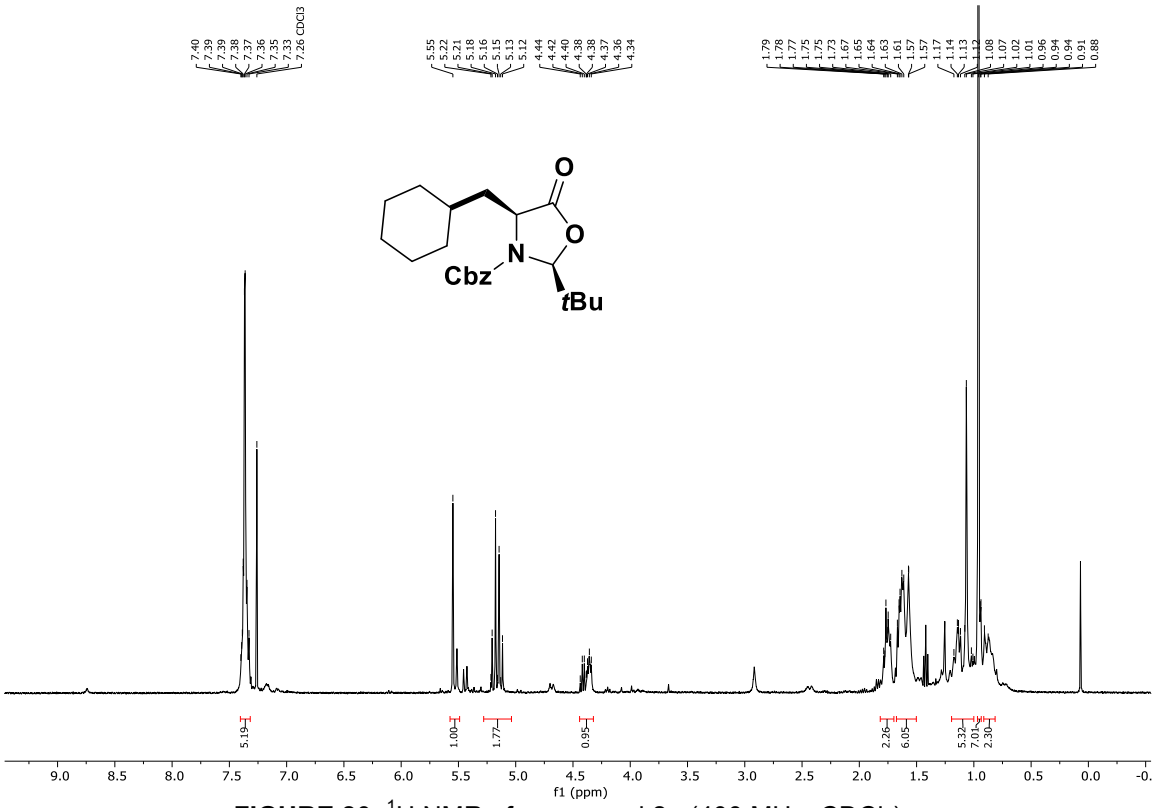


FIGURE 80. ^{1}H NMR of compound **8a** (400 MHz, $CDCl_3$).

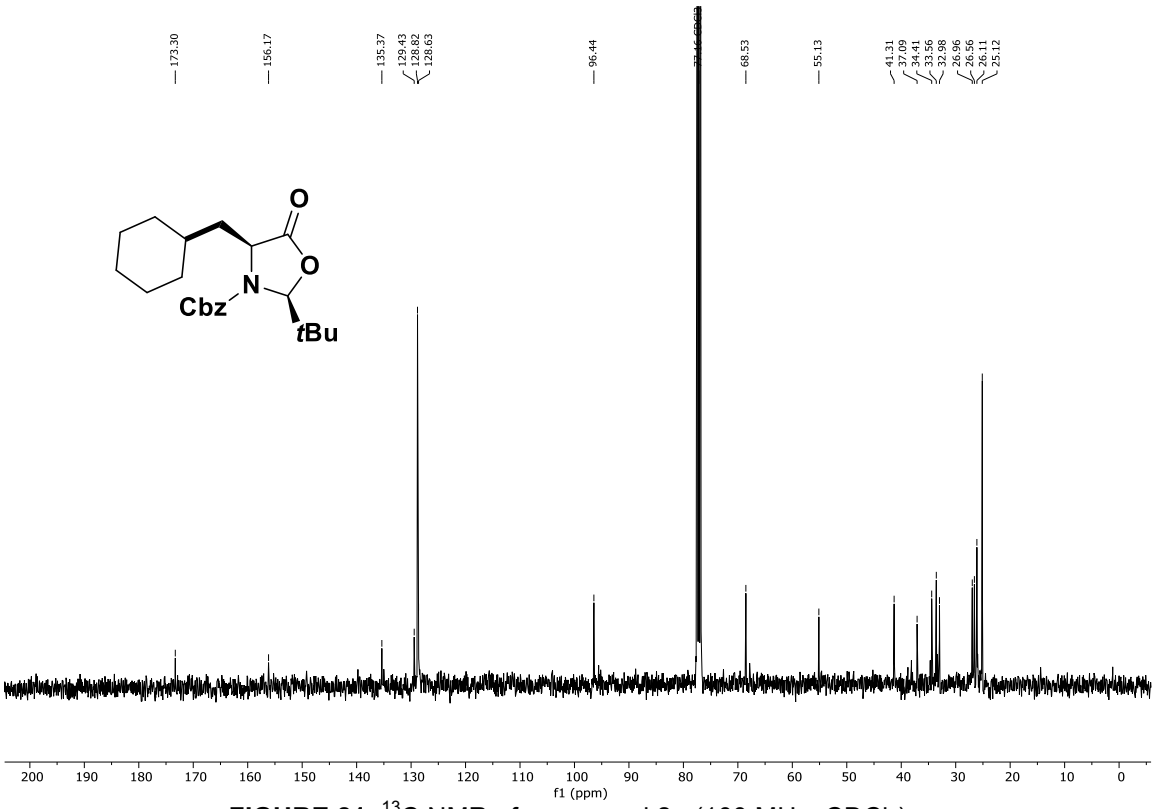


FIGURE 81. ^{13}C NMR of compound **8a** (100 MHz, $CDCl_3$).

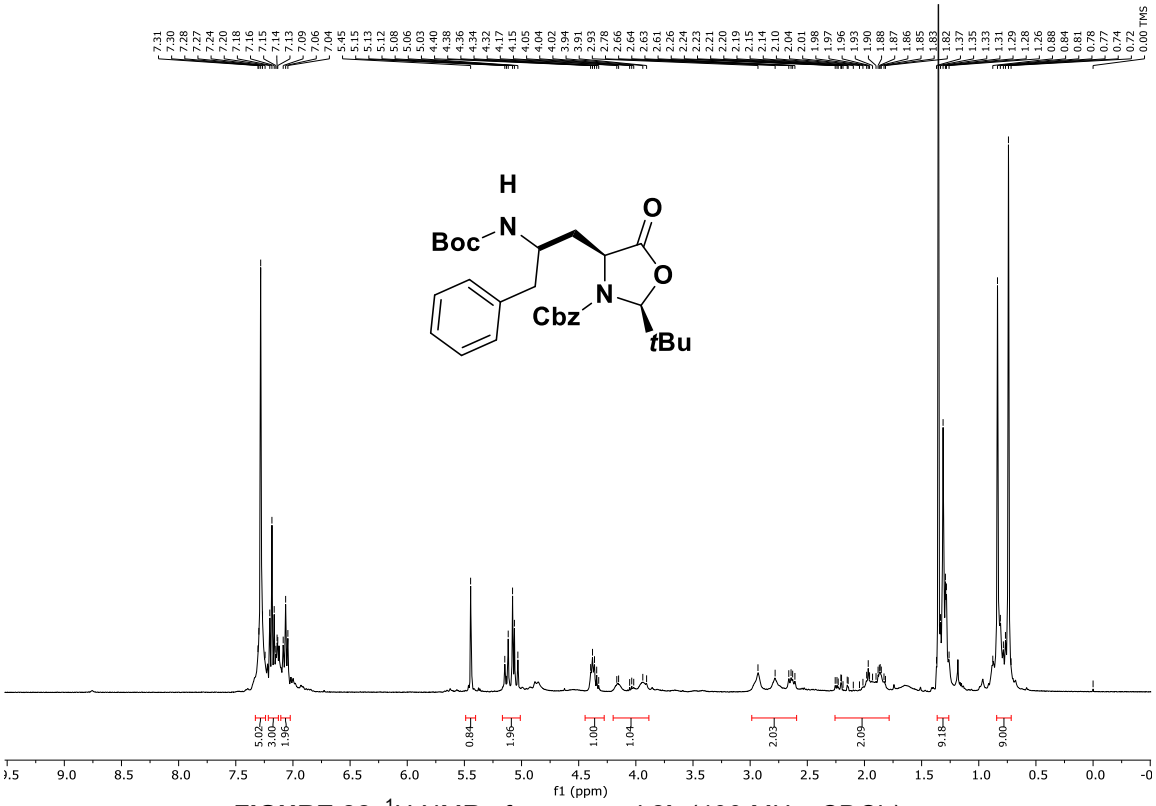


FIGURE 82. ^{1}H NMR of compound **8b** (400 MHz, $CDCl_3$).

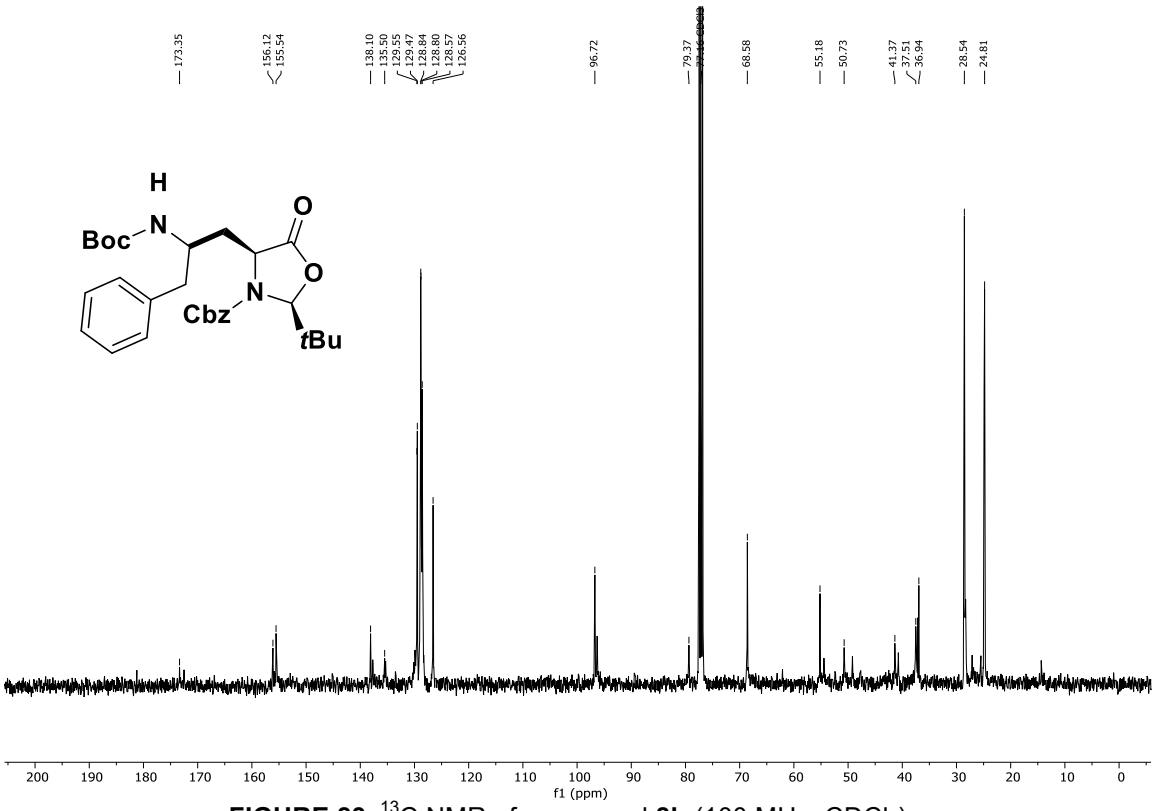


FIGURE 83. ^{13}C NMR of compound **8b** (100 MHz, $CDCl_3$).

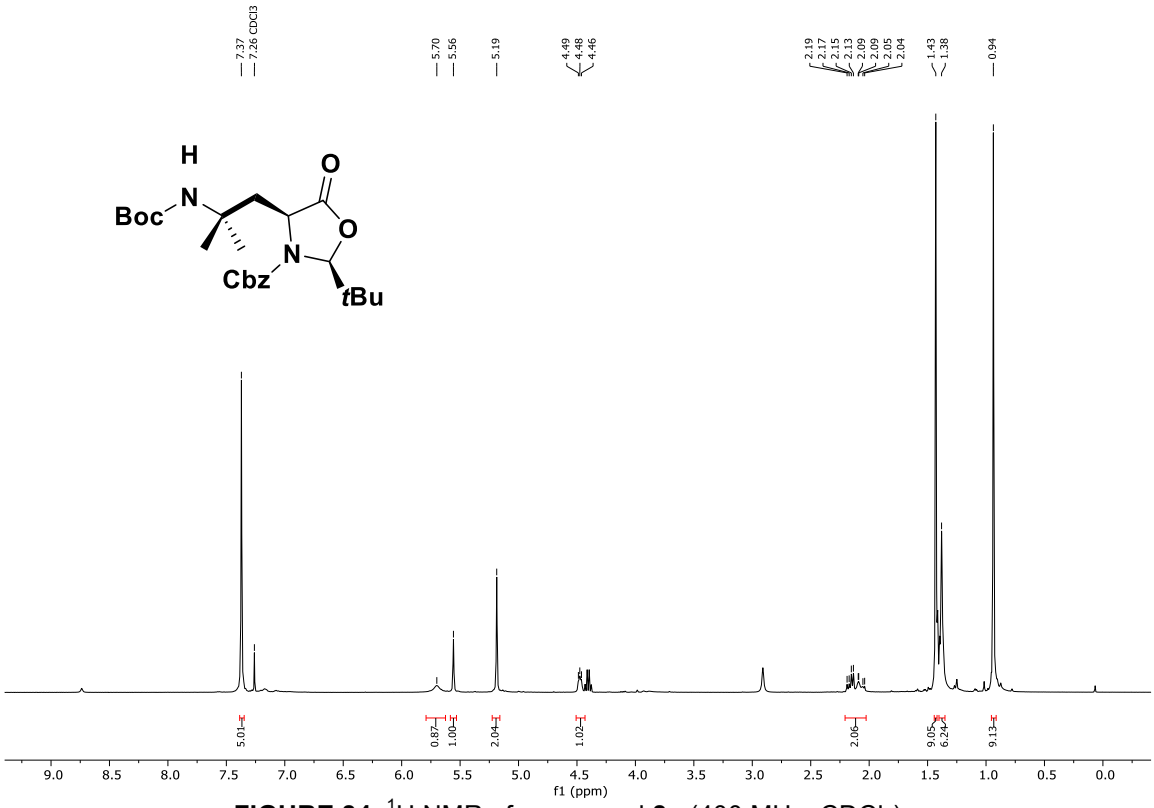


FIGURE 84. ^{1}H NMR of compound **8c** (400 MHz, $CDCl_3$).

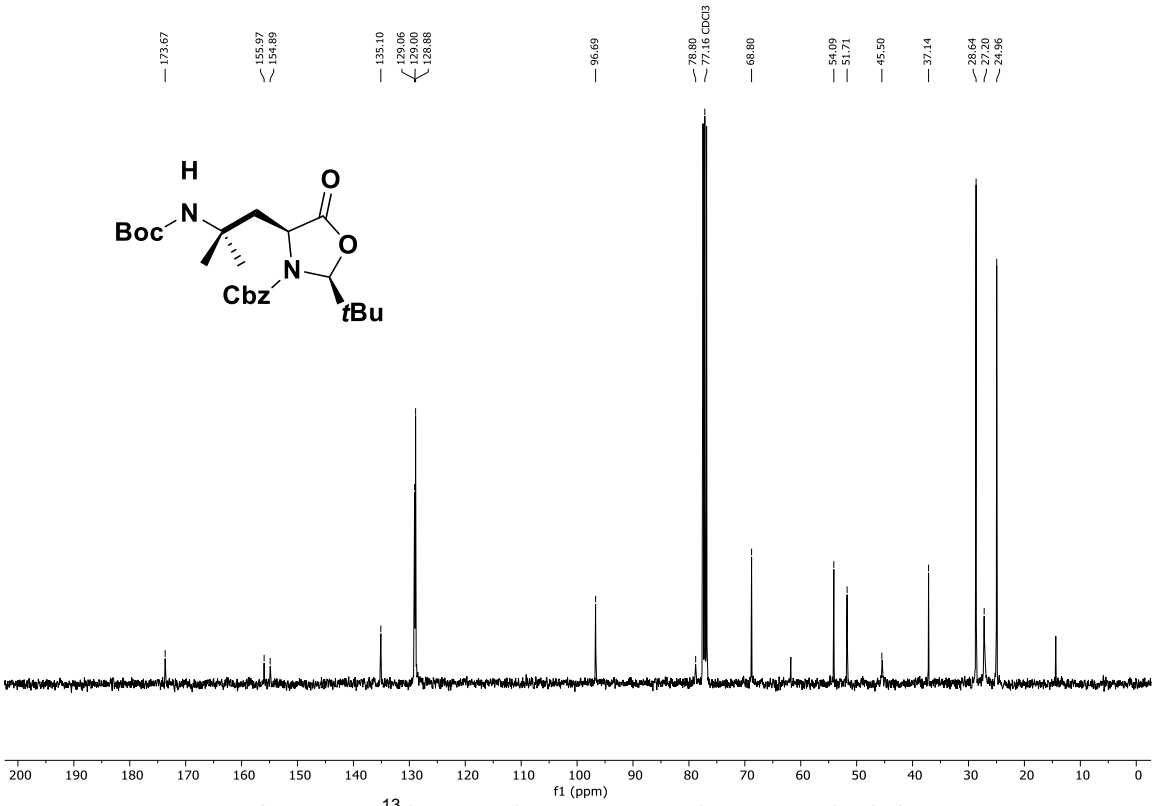


FIGURE 85. ^{13}C NMR of compound **8c** (100 MHz, $CDCl_3$).

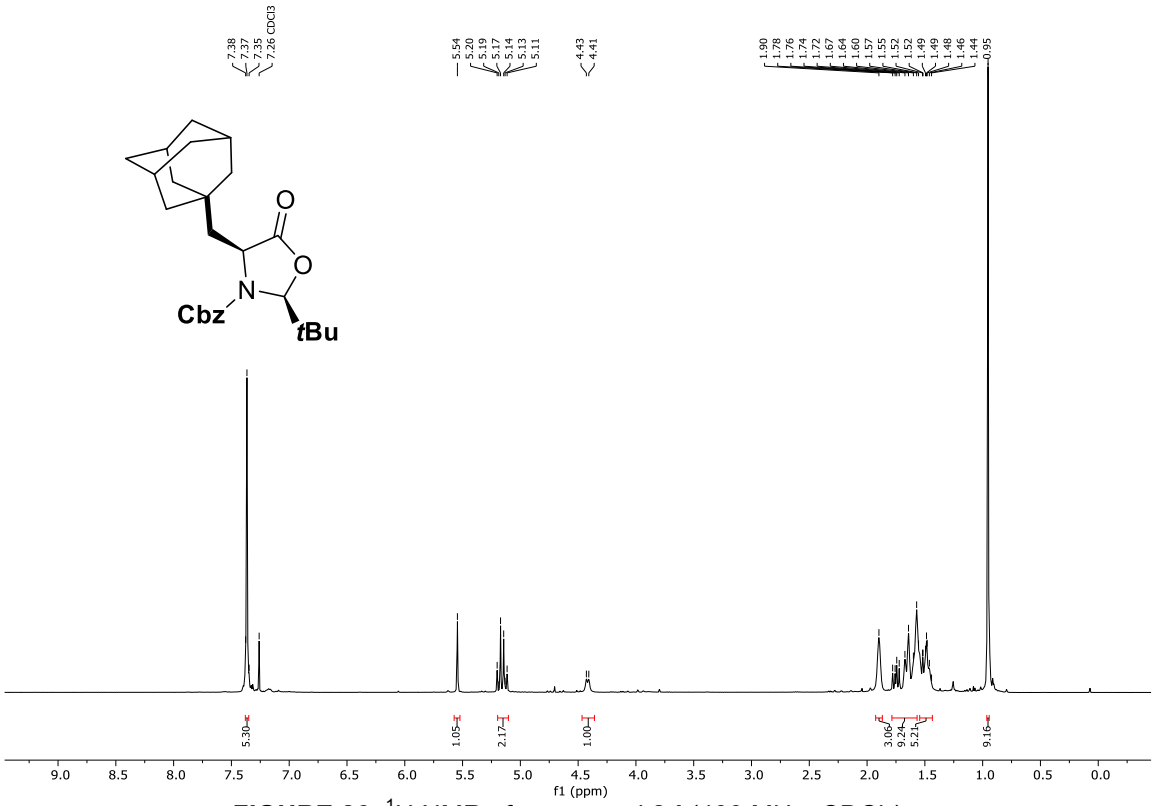


FIGURE 86. ^{1}H NMR of compound **8d** (400 MHz, $CDCl_3$).

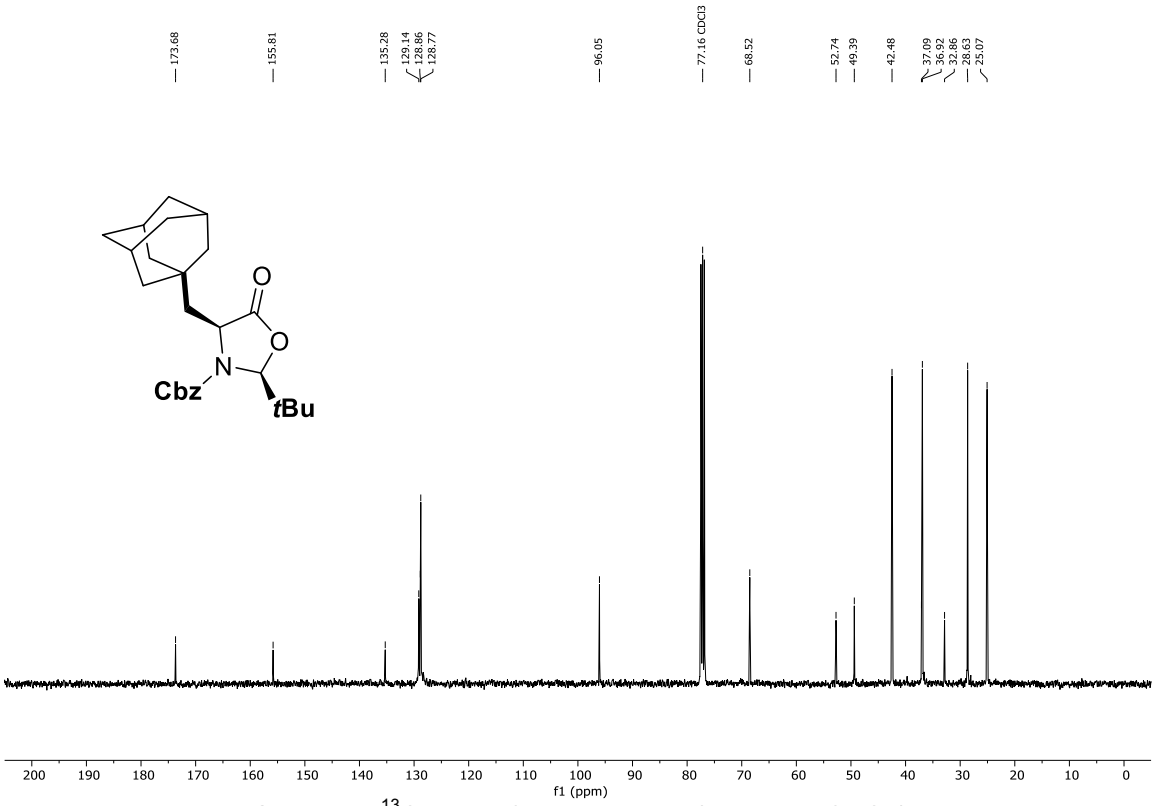


FIGURE 87. ^{13}C NMR of compound **8d** (100 MHz, $CDCl_3$).

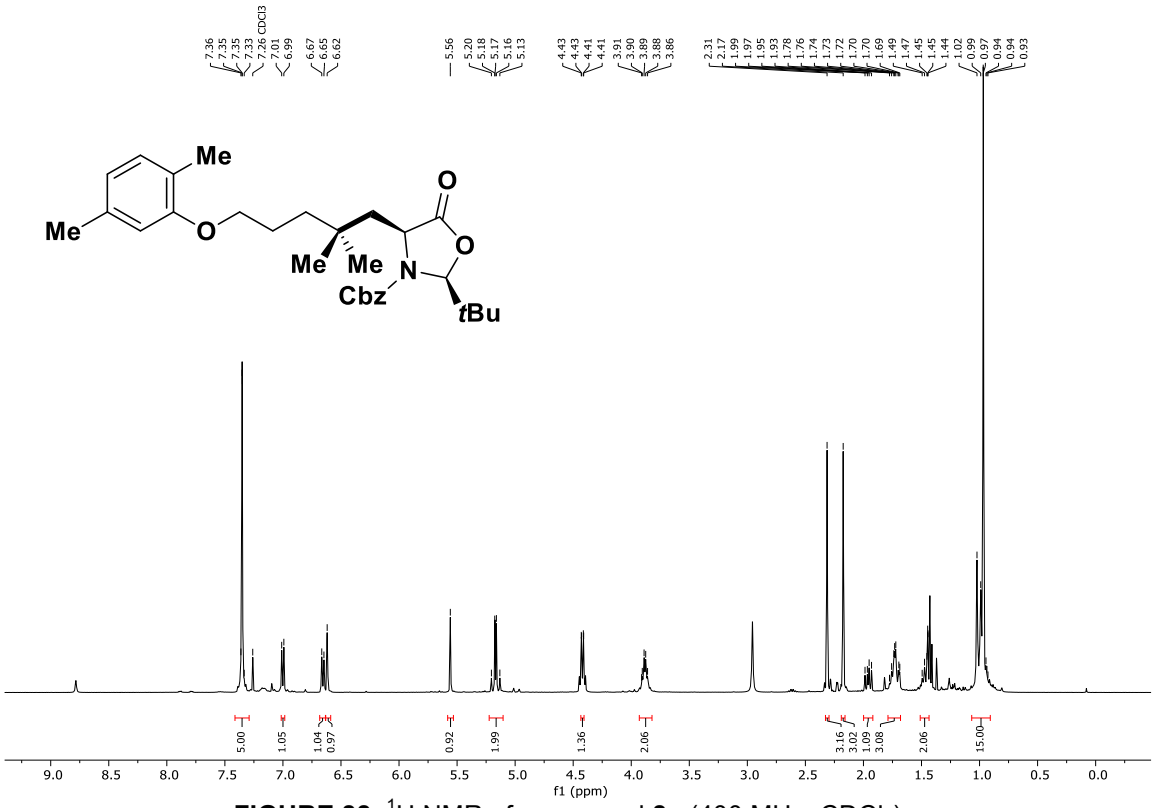


FIGURE 88. ^{1}H NMR of compound **8e** (400 MHz, $CDCl_3$).

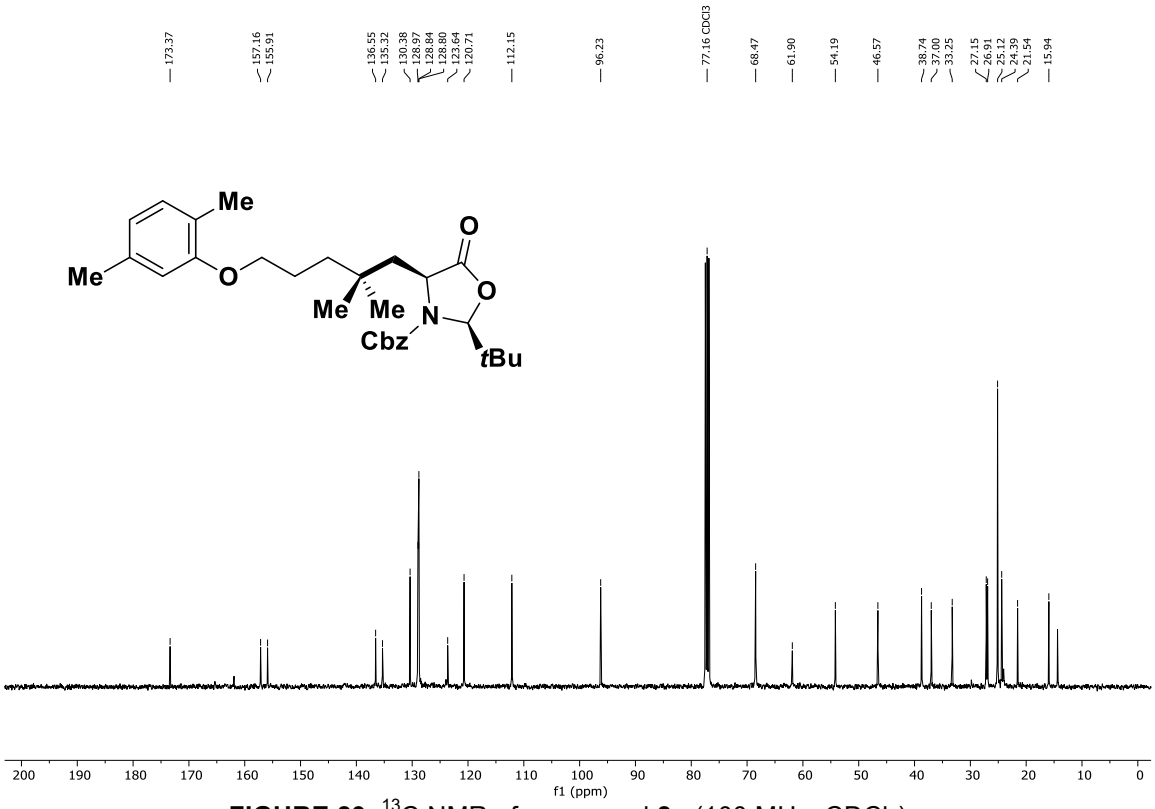


FIGURE 89. ^{13}C NMR of compound **8e** (100 MHz, $CDCl_3$).

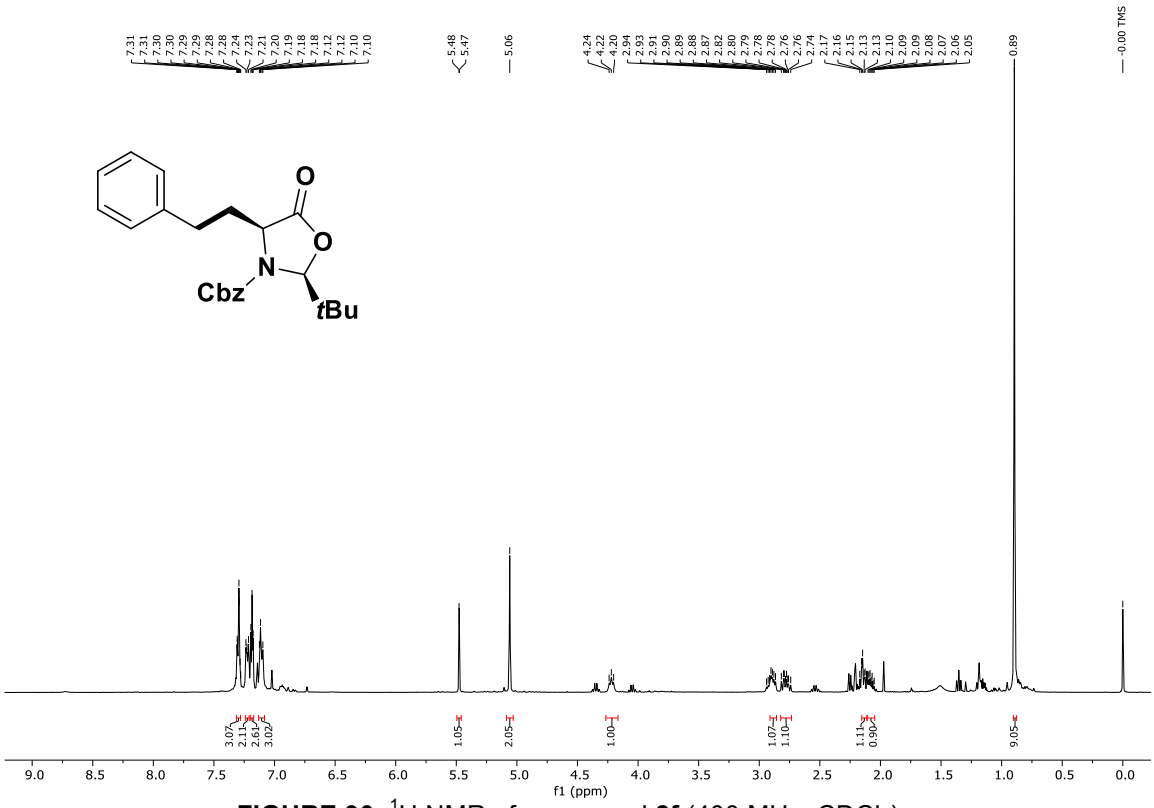


FIGURE 90. ^{1}H NMR of compound **8f** (400 MHz, $CDCl_3$).

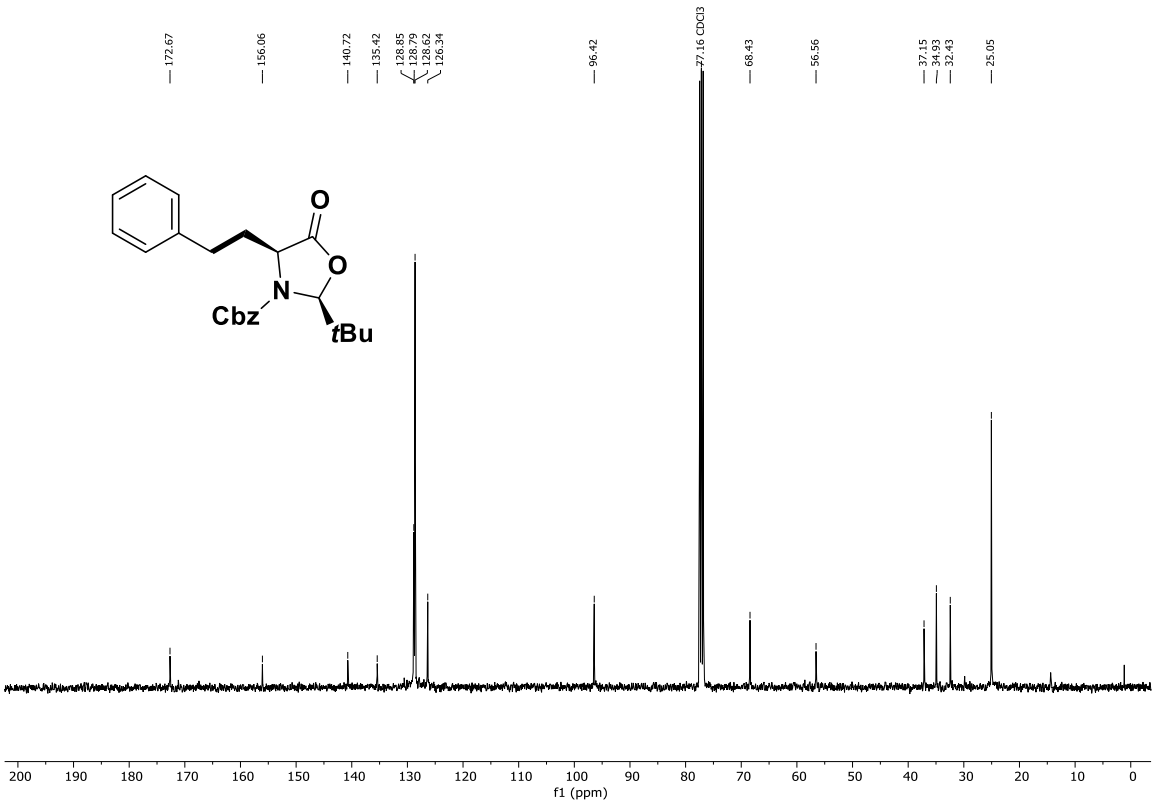


FIGURE 91. ^{13}C NMR of compound **8f** (100 MHz, $CDCl_3$).

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