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Supplementary information

Ni-electrocatalytic C*sp*–C*sp* doubly decarboxylative coupling

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Ni-Electrocatalytic C(sp^3)–C(sp^3) Doubly Decarboxylative Coupling

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Supplementary information

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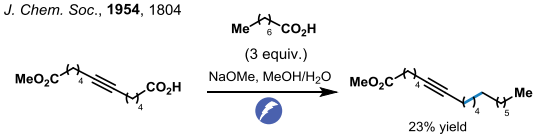
General Experimental

Tetrahydrofuran (THF), acetonitrile (CH_3CN), and dichloromethane (CH_2Cl_2) were obtained by passing the previously degassed solvents through an activated alumina column. All substrates that were purchased (from cheapest supplier), were used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by GC/MS, LC/MS, and thin layer chromatography (TLC). TLC was performed using 0.25 mm E. Merck silica plates (60F-254), using short-wave UV light as the visualizing agent, and phosphomolybdic acid and $Ce(SO_4)_2$, acidic ethanolic anisaldehyde, $KMnO_4$, or iodine absorbed on silica gel was used, and heat as developing agents (not for iodine staining). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and are referenced using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; acetone at 2.05 ppm ^{1}H NMR, 29.84 ppm ^{13}C NMR; CH_3OH at 3.31 ppm ^{1}H NMR, 49.0 ppm ^{13}C NMR; C_6H_6 at 7.16 ppm ^{1}H NMR, 128.06 ppm ^{13}C NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using E. Merck silica (60, particle size 0.043–0.063 mm), and pTLC was performed on Merck silica plates (60F-254). High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Gas chromatography-mass spectrometry (GCMS) were recorded on an Agilent 5975 MSD Series spectrometer.

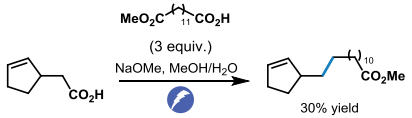
A Survey of *Selected* Kolbe Heterocouplings

Primary carboxylic acids coupling

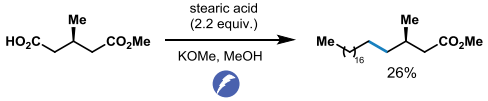
J. Chem. Soc., **1954**, 1804



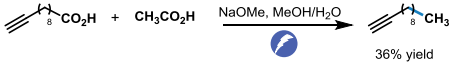
J. Am. Chem. Soc. **1955**, *77*, 3807.



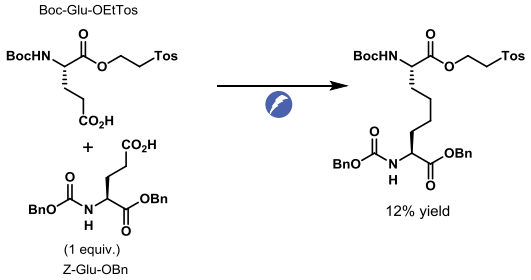
J. Chem. Soc. **1959**, 661.



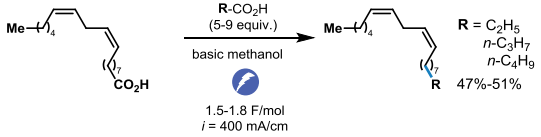
Pak. J. Sci. Ind. Res.,**1976,** *88*, 120537.



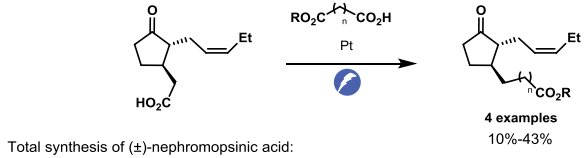
Bio.Med. Chem. Lett. **1997**, *7*, 2963.



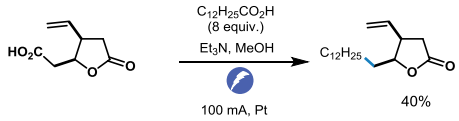
Liebigs Annalen der Chemie **1987**, *5*, 417.



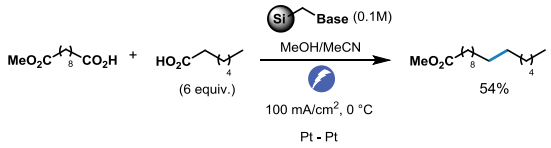
Tetrahedron Letters **1996**, *37*, 8715.



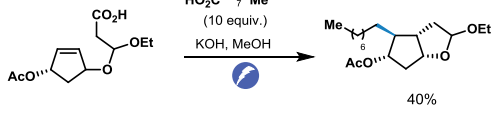
Total synthesis of (±)-nephromopsinic acid:
Helvetica Chimica Acta **2002,** *85*, 3965.



Electrochemistry **2006**, *74*, 615.

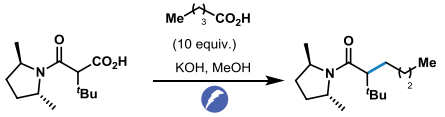


Liebigs Annalen der Chemie **1994**, *11*, 235.

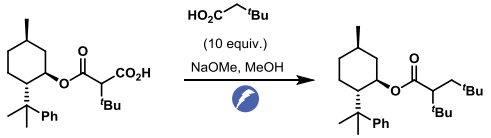


Special secondary and tertiary carboxylic acids coupling

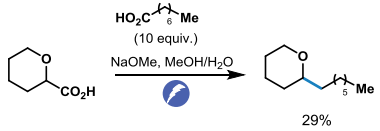
Angew. Chem. Int. Ed. **1995**, 189.

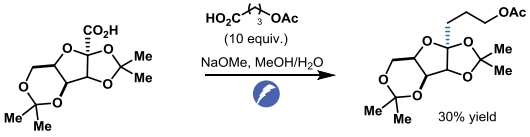


Beilstein J. Org. Chem. **2017**, *13*, 33.



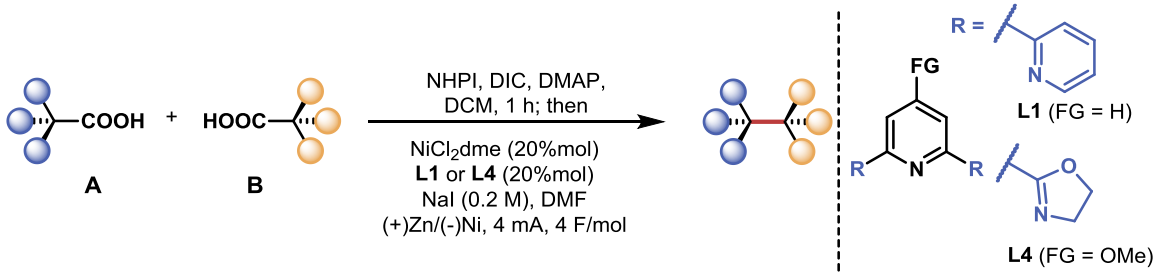
Liebigs Annalen der Chemie **1996**, 13, 55.





Electrochemical Doubly Decarboxylative Coupling Heterocoupling

General procedure for the electrochemical doubly decarboxylative coupling



General procedure **A**: An ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid **A** (0.1 mmol, 1 equiv), carboxylic acid **B** (0.3 mmol, 3 equiv), *N*-hydroxyphthalimide (0.44 mmol, 4.4 equiv) and 4-dimethylaminopyridine (DMAP, 0.04 mmol, 0.4 equiv). Dichloromethane was added (0.2 M). Then *N,N'*-Diisopropylcarbodiimide (DIC, 0.44 mmol, 4.4 equiv) was added dropwise via syringe, and the mixture was allowed to stir until the acid was consumed (determined by TLC, typically 1 h). After consumption of all starting materials, NaI (0.6 mmol, 89.9 mg), $NiCl_2$•dme (20 mol %, 4.4 mg), (4-OMe)-H-PyBox[1] (20 mol %, 5.0 mg) **L4** and anhydrous DMF (3.0 mL) were added. An ElectraSyn vial cap equipped with anode (Zn) and cathode (Ni foam) was inserted into the mixture after which all the contents were degassed via an argon balloon for roughly 60 seconds. The reaction mixture was electrolyzed under a constant current of 4 mA for 4 F/mol. After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 N) was then added [for products containing tertiary amine and pyridine moiety, washing with 0.1 N HCl was omitted]. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography or preparative thin layer chromatography (pTLC) to furnish the desired product.

General procedure **B**: 2,2':6',2''-terpyridine (20 mol %, 4.8 mg) **L1** was used as the ligand.

Graphical guide: electrochemical doubly decarboxylative coupling reaction

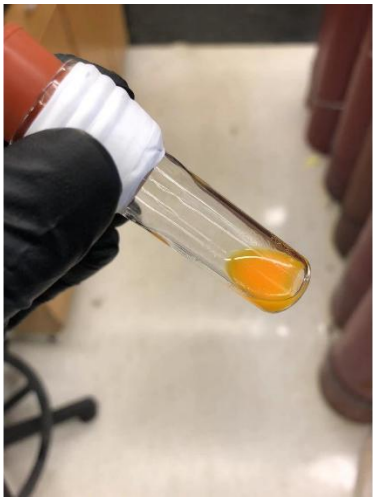
Representative example (0.1 mmol scale)

Photos were taken from the coupling between 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoic acid **4** and cyclobutanecarboxylic acid **3**.

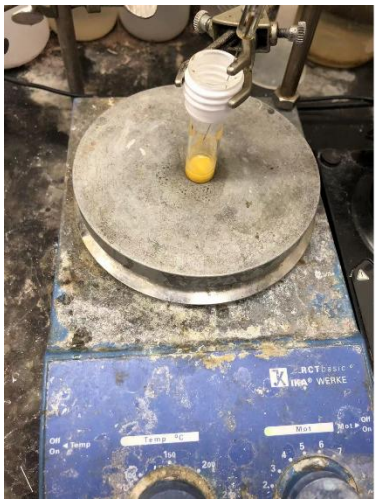


Electrasyn Vial Preparation: **(Left)** Clean 5 mL ElectraSyn 2.0 vial with stir bar. **(Center)** white teflon tape. **(Right)** Teflon tape was wrapped a few times around Electrasyn vial to ensure a good seal.

(Left) Reagents needed. **(Center)** Addition of carboxylic acid 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoic acid (25.1 mg, 0.1 mmol). **(Right)** Addition of NHPI (71.8 mg, 0.44 mmol).




(Left) Addition of DMAP (4.9 mg, 0.04 mmol). **(Center)** CH_2Cl_2 (0.5 mL, 0.2 M) was subsequently added (*no precaution needed*). **(Right)** Addition of cyclobutanecarboxylic acid (28.6 µL, 0.3 mmol) via syringe.

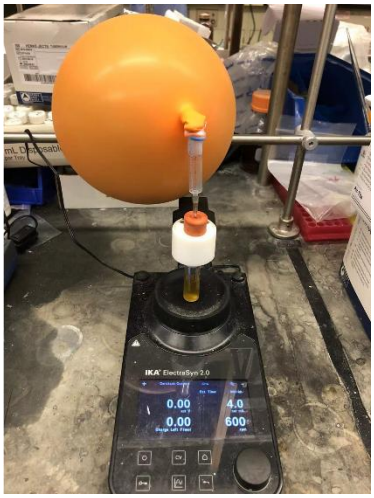


(Left) DIC (68.0 µL, 0.44 mmol) was added. **(Center)** Reaction mixture was stirred at rt for 1h, *t* = 5 min. **(Right)** Reaction mixture, *t* = 60 min.

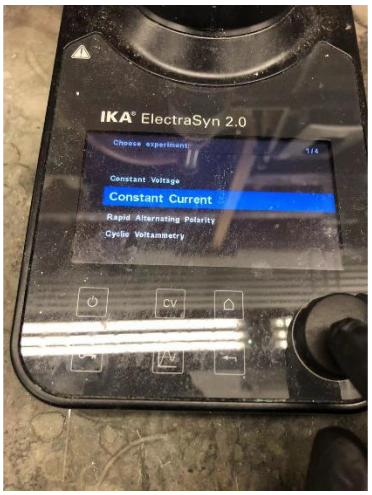
In a separate ElectraSyn 2.0 vial: **(Left)** Addition of $NiCl_2$•dme (4.4 mg, 0.02 mmol). **(Center)** Addition of ligand, (4-OMe)-H-PyBox (5.0 mg, 0.02 mmol). **(Right)** Addition of NaI (90.0 mg, 0.6 mmol).

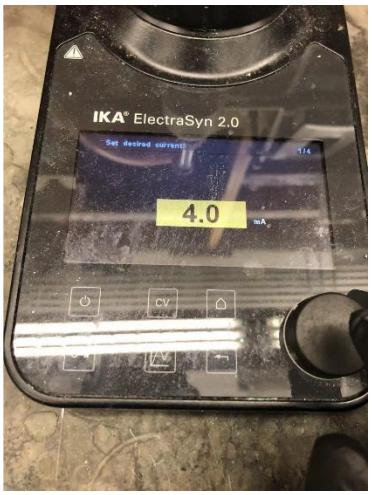


(Left) DMF (3.0 mL) was added. **(Center)** ElectraSyn 2.0 cap equipped with zinc anode and nickel foam cathode (9 mm wide, 40 mm length). **(Right)** ElectraSyn cap was tightly screwed into the reaction vial.

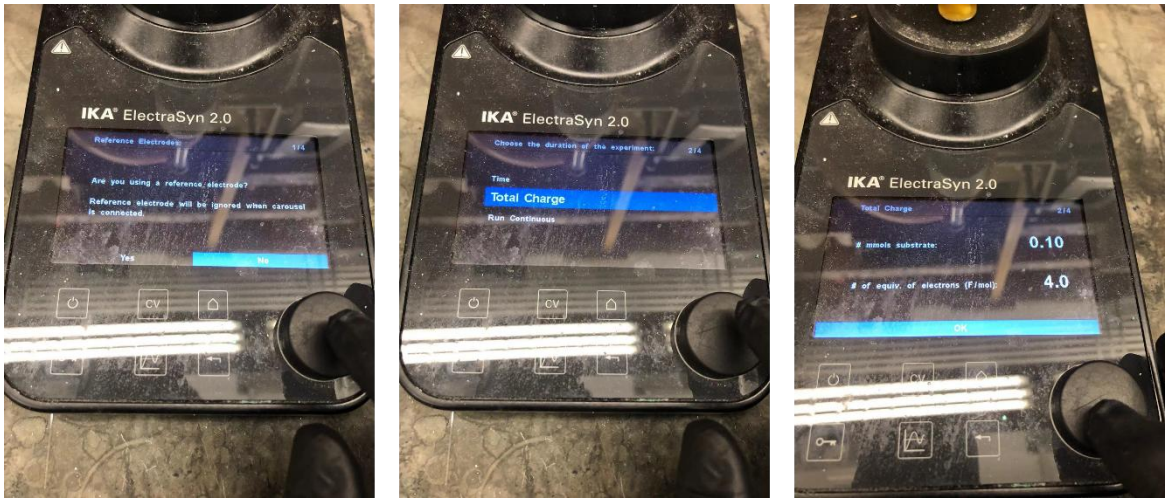


(Left) An argon balloon was attached (a second needle on the septum serves as a vent), and the reaction solution was degassed for roughly 60 seconds. **(Right)** Entire reaction mixture prior to electrolysis.



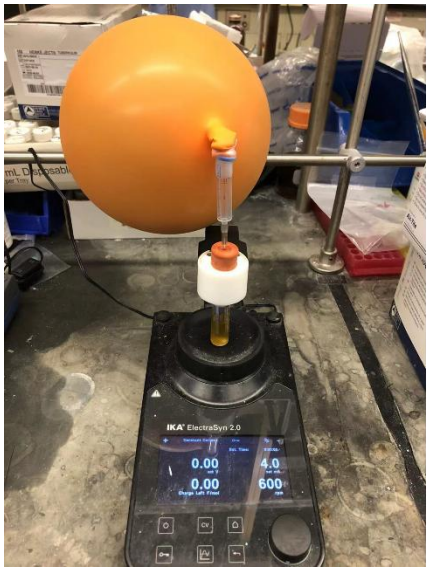


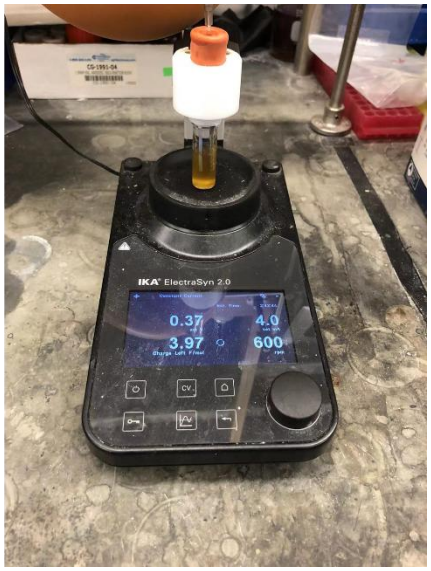
(Left) Select a new experiment. **(Center)** Select constant current. **(Right)** Set the current to 4 mA (for a 0.1 mmol scale).



(Left) No need to use a reference electrode. **(Center)** Select “Total Charge”. **(Right)** Select 0.1 mmol of substrate at 4 F/mol.

(Left) No need to alternate the polarity. **(Center)** Saving reaction parameters is optional. **(Right)** Ready!

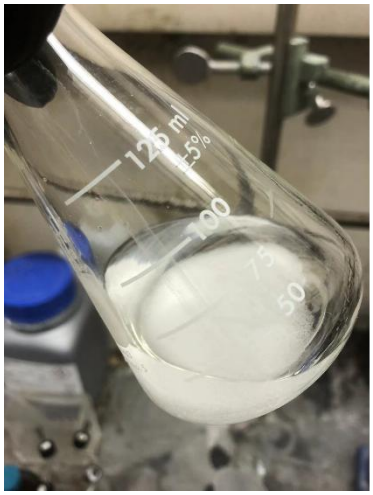


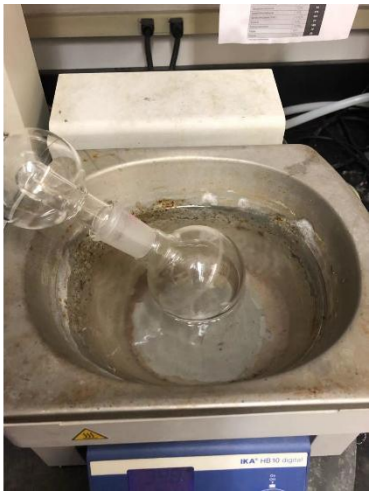


(Left) Complete setup of reaction prior to electrolysis. **(Right)** Reaction setup during electrolysis (*note: 600 rpm stirring*).



(Left) Reaction mixture after electrolysis. **(Center)** Electrodes were rinsed with Et_2O and entire reaction mixture was transferred to a separatory funnel with Et_2O. The organic phase was washed with 0.1N HCl (aq). **(Right)** Combined organic layers were washed with brine (NaCl).





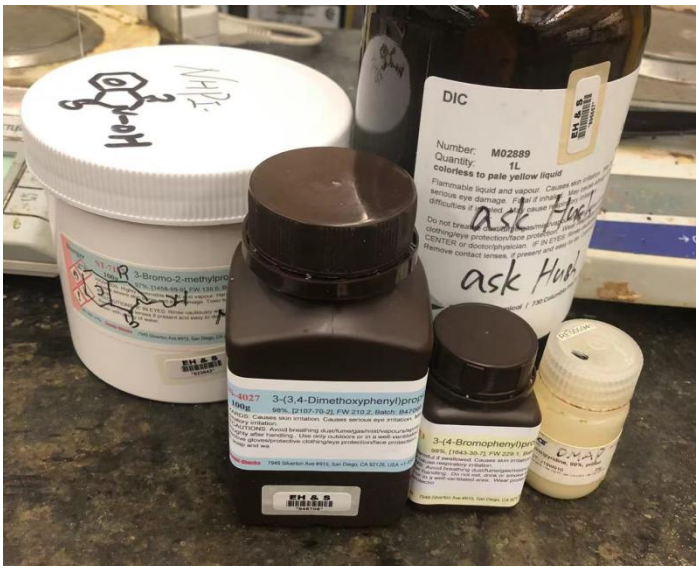
(Left) Combined organic layers were dried over Na_2SO_4. **(Center)** Filtration to remove Na_2SO_4. **(Right)** Solvent removal under reduced pressure.



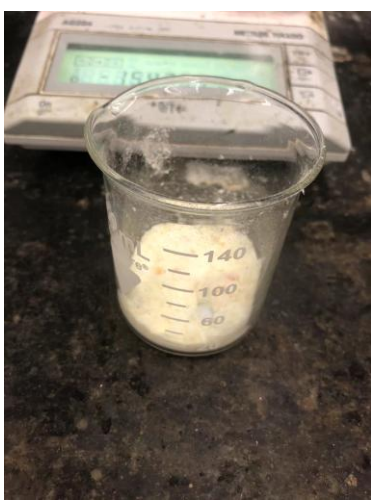
(Left) Crude TLC (10:1 Hexanes: EtOAc). **(Center)** Purification by pTLC (10:1 Hexanes: EtOAc). **(Right)** Tared weight of vial containing desired product (13.3 mg, 51% yield).

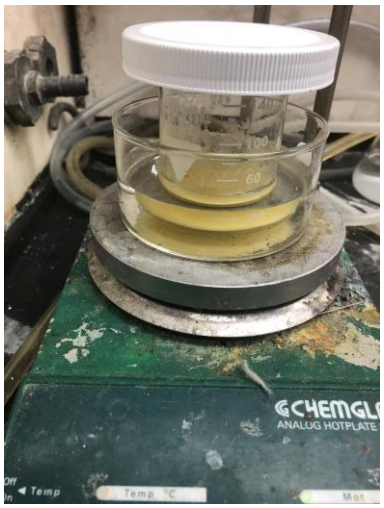
Representative example on 1-gram scale:

Photos were taken from the coupling between 3-(4-bromophenyl)propanoic acid and 3-(3,4-dimethoxyphenyl)propanoic acid.

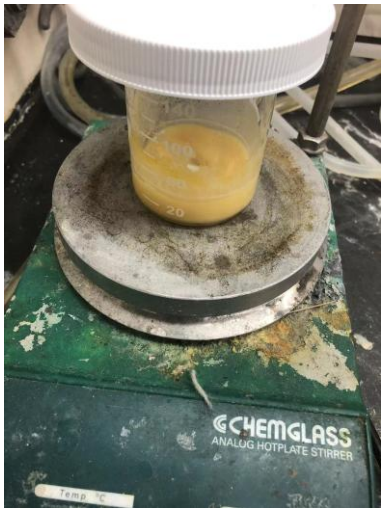


(Center) All reagents required.





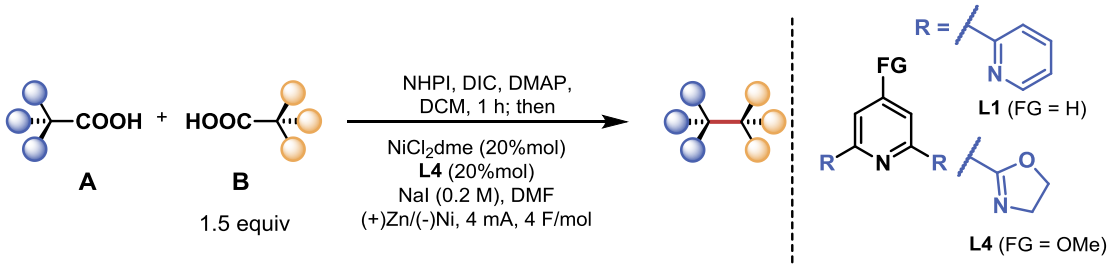
(Left) All solids were weight out: 3-(4-bromophenyl)propanoic acid (1.61 g, 7.0 mmol), 3-(3,4-dimethoxyphenyl)propanoic acid (4.41 g, 21.0 mmol), NHPI (5.04 g, 30.8 mmol), DMAP (0.35 g, 2.8 mmol). **(Center)** CH_2Cl_2 (17.5 ml) was added. **(Right)** Addition of DIC (4.8 ml, 30.8 mmol).

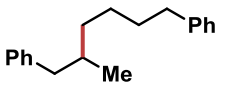


(Left) Reaction mixture after stirring for 1h. **(Center)** Addition of: $NiCl_2$•dme (308 mg, 1.4 mmol), 2,2':6',2"-terpyridine (336 mg, 1.4 mmol), NaI (2.7 g, 18 mmol) and DMF (105 mL). **(Right)** Display of zinc anode and nickel foam cathode (3.5 cm wide, 7.5 cm length).

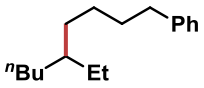

(Left) Electrochemical parameter settings: constant current, 35 mA, 7 mmol, 4 F/mol, no reference electrode, no alternating polarity. The reaction was started. **(Center)** Reaction mixture after electrolysis and the solution eventually turned dark green. After completion of electrolysis, the reaction was worked up and purified as described in general procedure. **(Right)** Weight of product (1.32 g, 54% yield).

Additional substrates with 1.5 equivalent of coupling partner

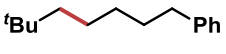




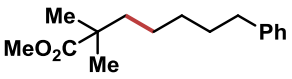
SI-14, 74% (9:1)[a]



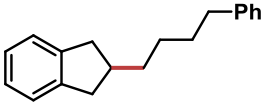
SI-15, 76% (8:1)



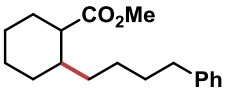
SI-16, 69% (11:1)[b]



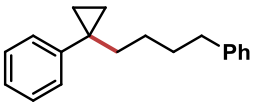
SI-17, 50% (20:1)[b]



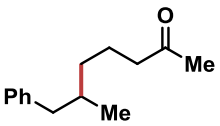
SI-18, 68% (6:1)



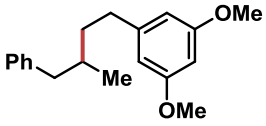
SI-19, 63% (20:1)
dr 5:1



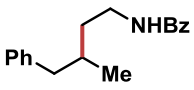
SI-20, 65% (9:1)



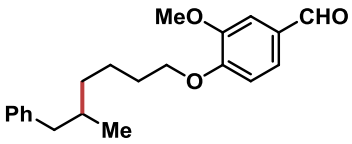
SI-21, 76%



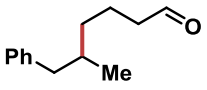
SI-22, 63%



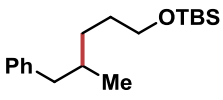
SI-23, 61%



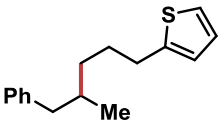
SI-24, 70%



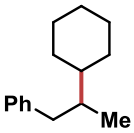
SI-25, 51%



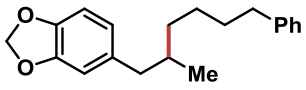
SI-26, 79%



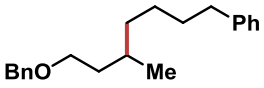
SI-27, 78%



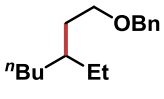
SI-28, 55%



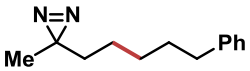
SI-29, 71%



SI-30, 76%



SI-31, 61%

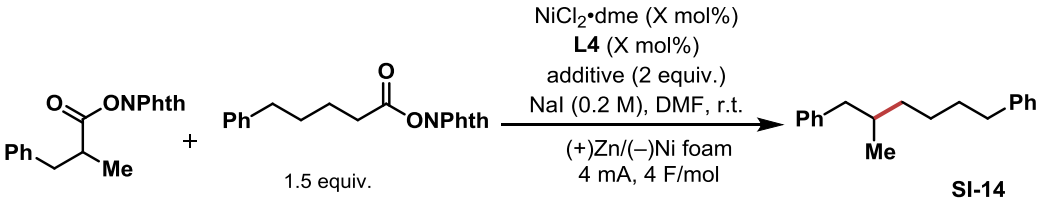


SI-32,
22%[b,c]

Note: the ratio of cross-coupling and homo-coupling from **SI-14** to **SI-20** is indicated in parentheses. [a]The yield was estimated by GC analysis because of an inseparable mixture. [b]**L1** was used as a ligand instead of **L4**. [c]The 1:3 ratio of two acids instead of 1:1.5.

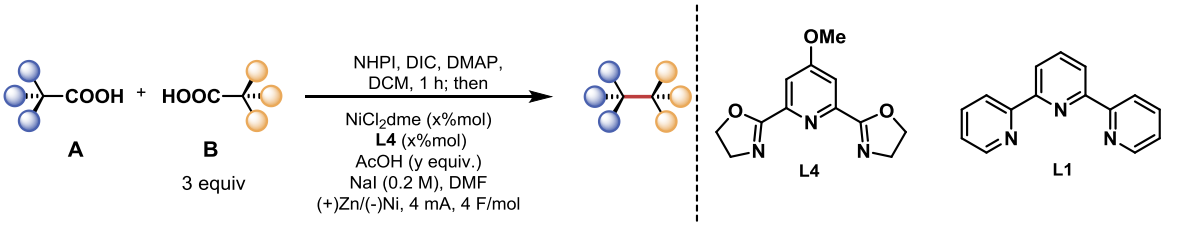
The structure of the carboxylic acid has a strong effect on the selectivity of the reaction, secondary acyclic carboxylic acids and hindered primary carboxylic acids can preferentially afford hetero-coupling products due to the slow dimerization of carbon radicals derived from these acids. Accordingly, this selectivity increase allowed us to reduce the acid stoichiometry to 1:1.5 ratio rather than previous 1:3 ratio (see above).

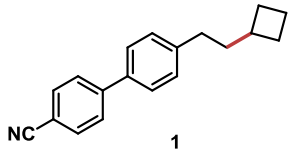
Reduced stoichiometry of nickel and ligand



Entry	X (%)	Additive	x (%)
1	20	/	79
2	10	/	66
3	10	TFA	70
4	10	AcOH	80
5	10	$(BuO)_2P(O)OH$	60
6	10	TsOH	35
7	10	$PhCO_2H$	77
8	10	$^tBuCO_2H$	63
9	10	TFE	53
10	10	HFIP	32
11	**8**	**AcOH**	**79**
12	6	AcOH	68

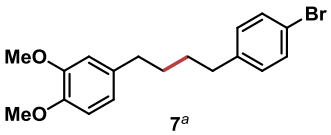
*Note: the yields are based on GC analysis.





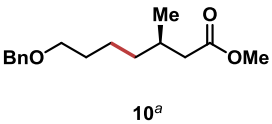
1

x = 20, y = 0, yield 51%
x = 8, y=0, yield 36%
x=8, y=2, yield 49%



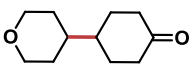
7[a]

x = 20, y = 0, yield 64%
x = 8, y=0, yield 46%
x=8, y=2, yield 61%



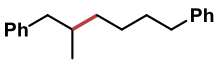
10[a]

x = 20, y = 0, yield 61%
x = 8, y=0, yield 31%
x=8, y=2, yield 54%



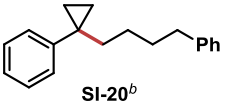
24

x = 20, y = 0, yield 48%
x = 8, y=0, yield 19%
x=8, y=2, yield 30%



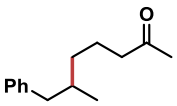
SI-14[b,c]

x = 20, y = 0, yield 79%
x = 8, y=0, yield 62 %
x=8, y=2, yield 79%



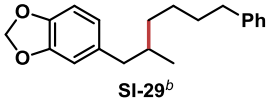
SI-20[b]

x = 20, y = 0, yield 65%
x = 8, y=0, yield 40%
x=8, y=2, yield 57%



SI-21[b]

x = 20, y = 0, yield 76%
x = 8, y=0, yield 53%
x=8, y=2, yield 68%



SI-29[b]

x = 20, y = 0, yield 71%
x = 8, y=0, yield 57%
x=8, y=2, yield 66%

[a]**L1** was used as a ligand instead of **L4**. [b]The 1:1.5 ratio of two acids instead of 1:3. [c]The yield was estimated by GC analysis because of an inseparable mixture.

Unsuccessful or low yielding substrates

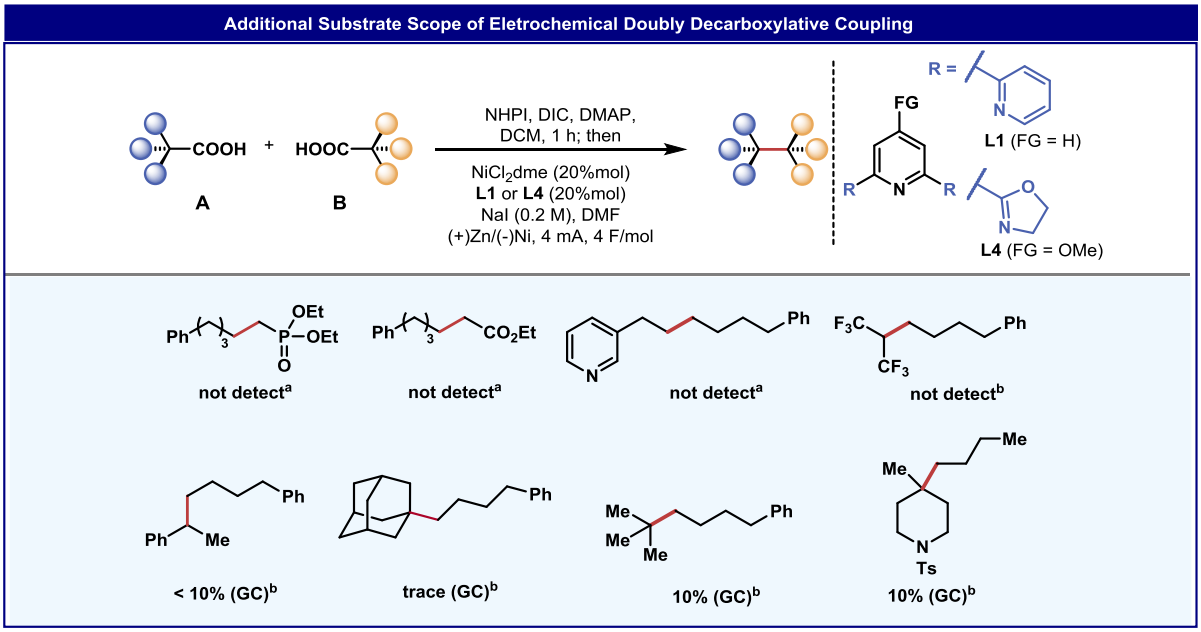


Table S1. Additional Substrate Scope of Eletrochemical Doubly Decarboxylative Coupling. [a]**L1** as the ligand; [b]**L4** as the ligand.

The reaction does not work well in the following three situations:

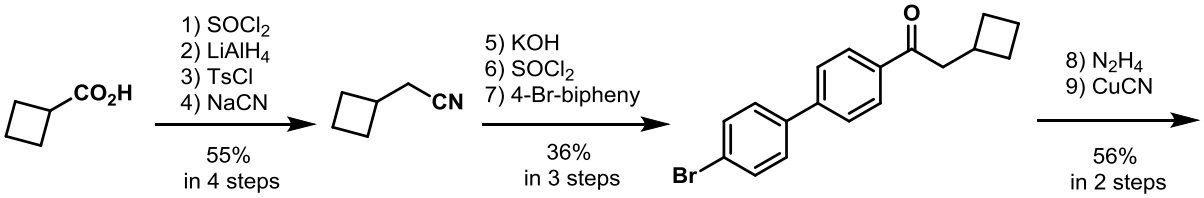
1) A large amount of RAE remained. For instance, the coupling of 3-(pyridin-3-yl)propanoic acid and 5-phenylpentanoic acid. This is presumably due to modulation of nickel catalyst reactivity for RAE reduction via coordination of basic functionality to the nickel center.

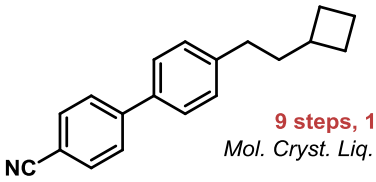
2) RAE is consumed, but a large amount of carboxylic acid remained (no decarboxylation). This case was observed in the coupling of 3,3,3-trifluoro-2-(trifluoromethyl)propanoic acid and 5-phenylpentanoic acid. Probably an acid with low pKa value may be more likely to generate $RCOO^{-}$, instead of RCOO•.

3) Decarboxylation is taking place, but major products are alkanes or alkenes. For instance, the coupling of 4-methyl-1-tosylpiperidine-4-carboxylic acid and 5-phenylpentanoic acid. It may be either due to a mismatch in the consumption rate of RAEs or sluggish radical capture by Ni species owing to steric/electreonic reasons. As a result, unused radicals resulted in the formation of a large amount of alkane and alkene byproducts.

Summary and Comparison with Previous Routes

*Synthesis of **1** (Gray and co-workers)*



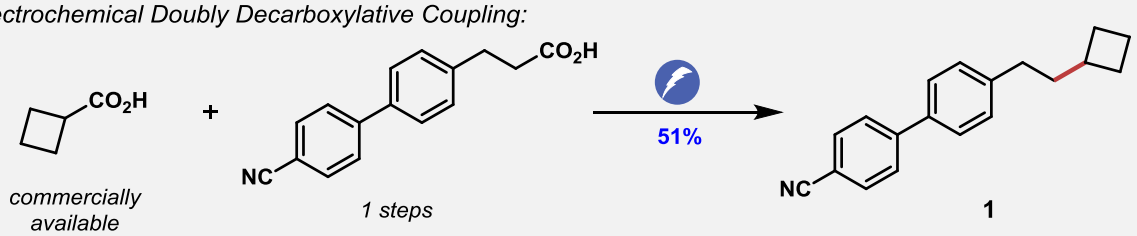


1

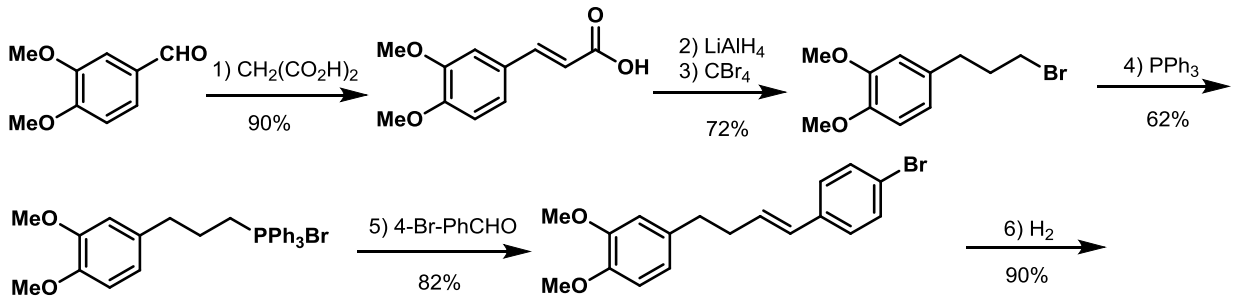
9 steps, 11% overall yield

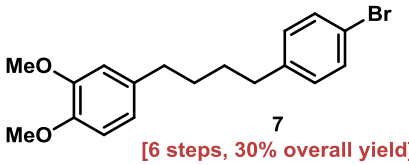
Mol. Cryst. Liq. Cryst. **1989**, *168*, 229

Electrochemical Doubly Decarboxylative Coupling:



*Synthesis of key intermediate **7** towards NDGA analogs by Ma and co-workers*



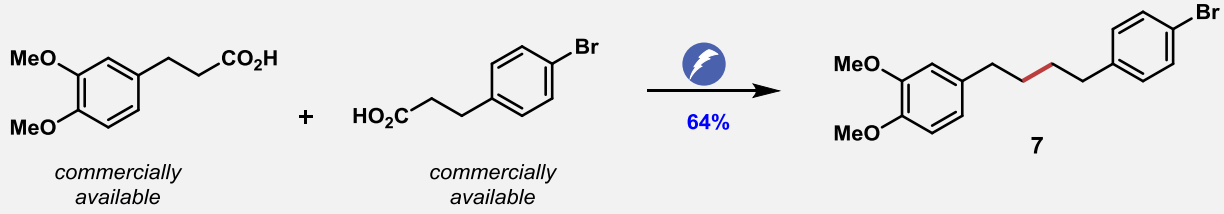


7

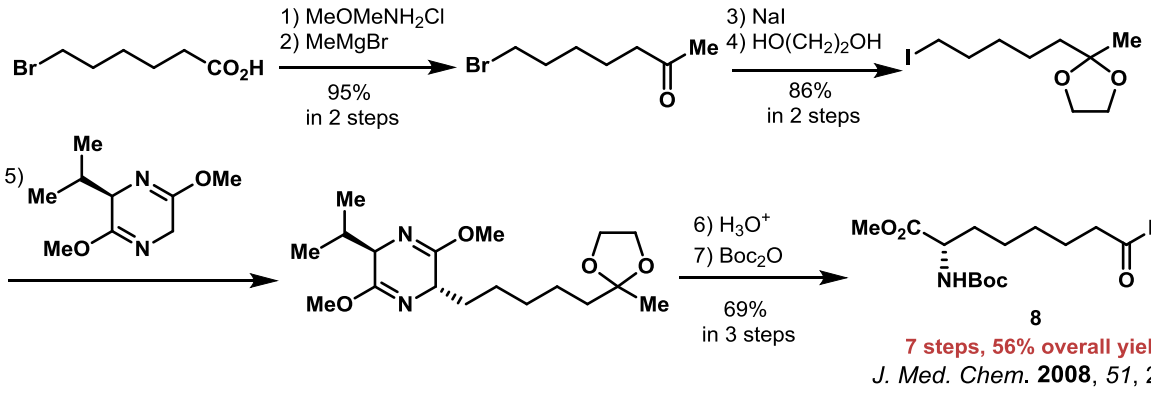
[6 steps, 30% overall yield]

Eur. J. of Med. Chem. **2020**, *186*, 111910

Electrochemical Doubly Decarboxylative Coupling:

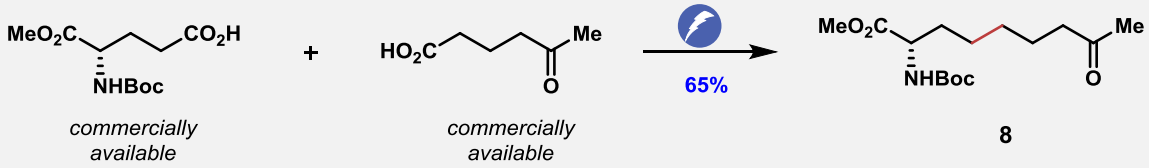


*Previous synthesis of **8** (intermediate of HDAC inhibitor) by Jones and co-workers*

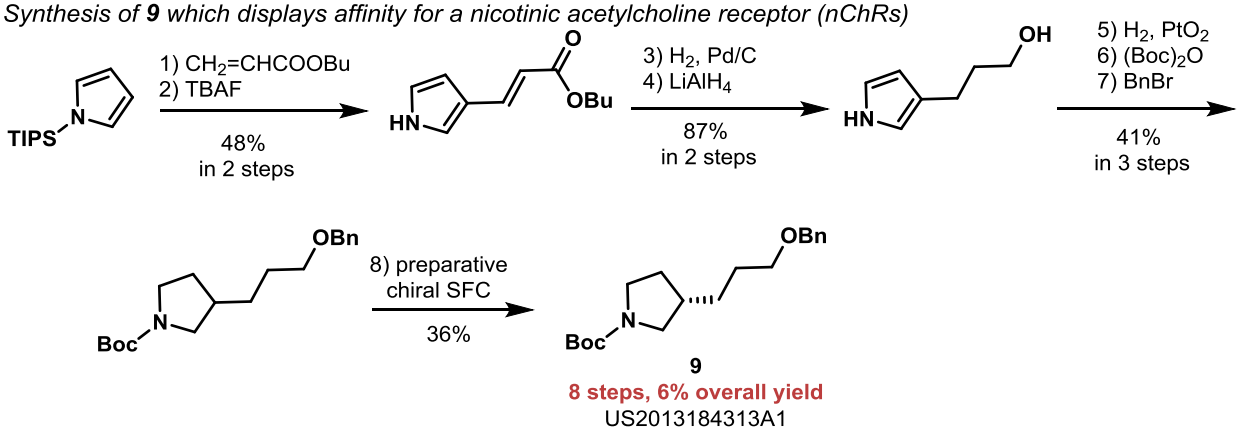


J. Med. Chem. **2008**, *51*, 2350

Electrochemical Doubly Decarboxylative Coupling:

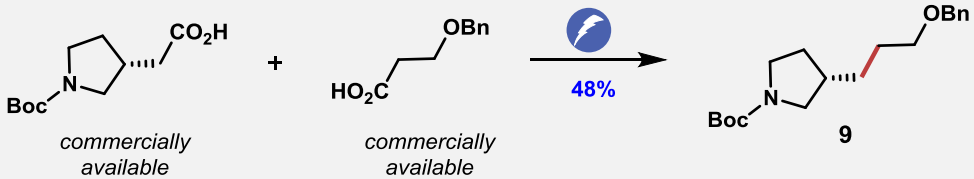


*Synthesis of **9** which displays affinity for a nicotinic acetylcholine receptor (nChRs)*

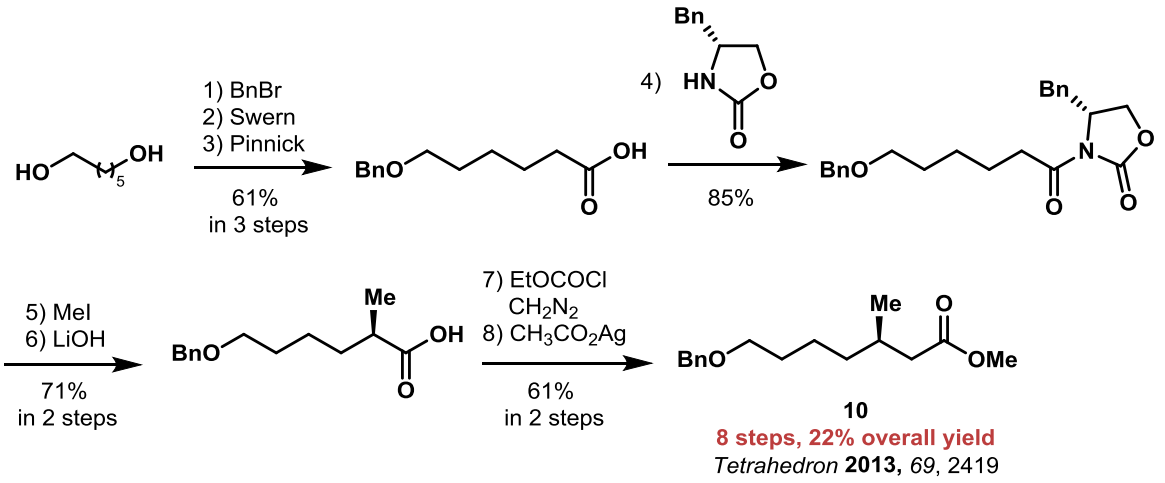


US2013184313A1

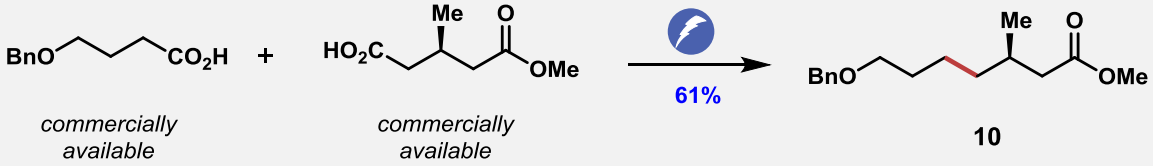
Electrochemical Doubly Decarboxylative Coupling:



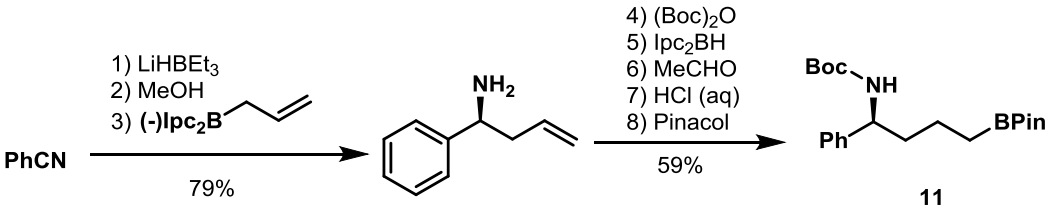
*Synthesis of **10** - intermediate of palmyrolide A by Sudhakar and co-workers*



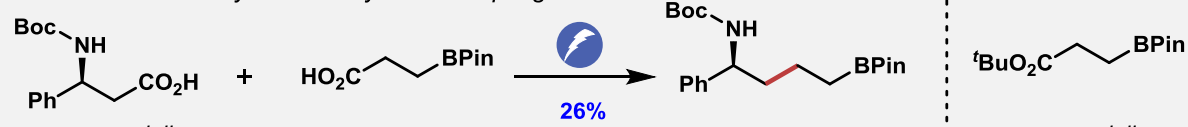
Electrochemical Doubly Decarboxylative Coupling:



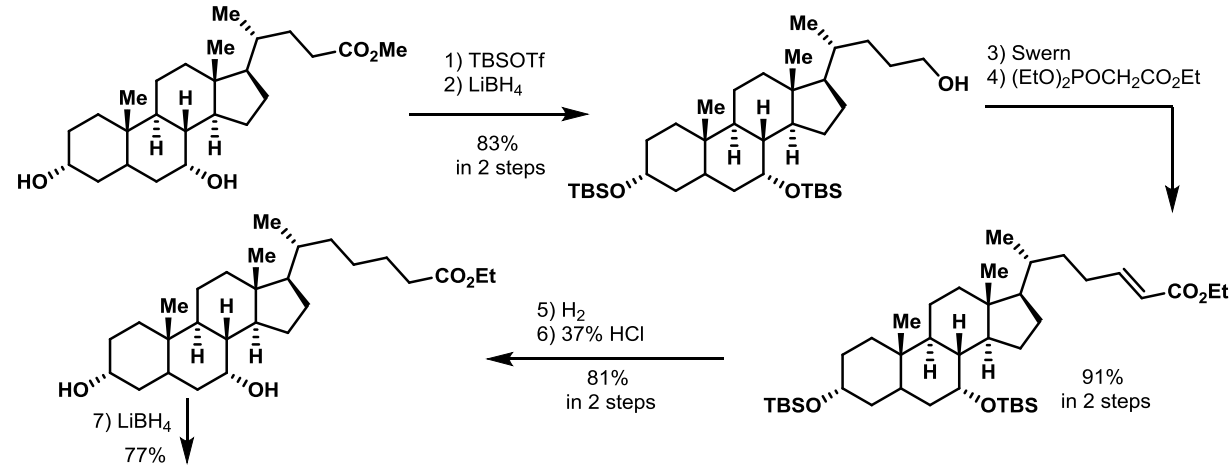
*Synthesis of δ-aminoboronic ester **11** found in Bortezomib by Ramachandran and co-workers*

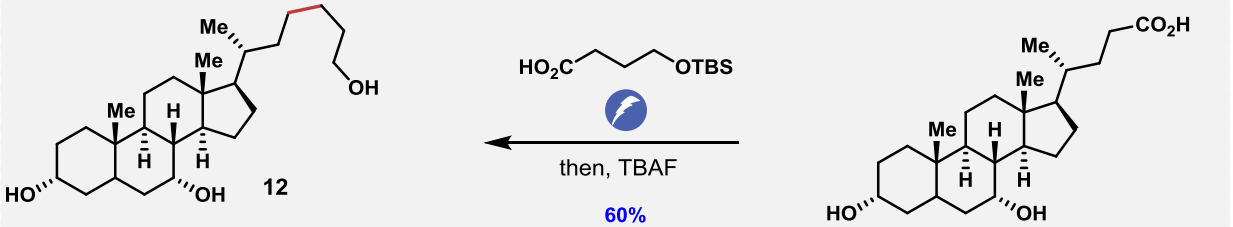


Electrochemical Doubly Decarboxylative Coupling:



*Comparative synthesis of **12**, a GP-BAR1/FXR agonist by Limongelli and co-workers*





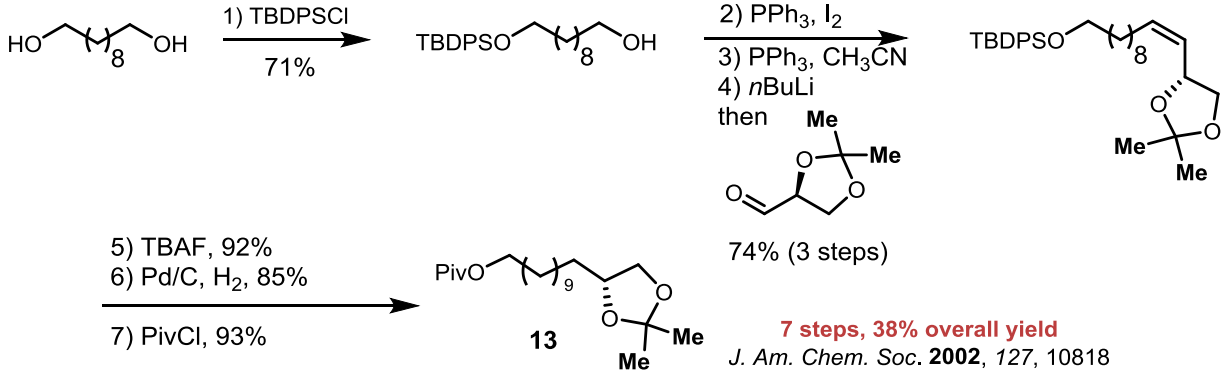
Previous
7 steps, 47% overall yield
J. Med. Chem. **2014**, *57*, 937

TBAF added directly to the reaction solution after electrolysis

commercially available

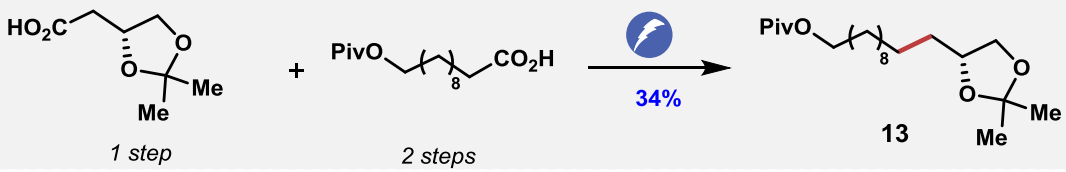
Electrochemical Doubly Decarboxylative Coupling:

*Synthesis of **13**, intermediate used in the total synthesis of Asimicin (Roush and co-workers)*



7 steps, 38% overall yield
J. Am. Chem. Soc. **2002**, *127*, 10818

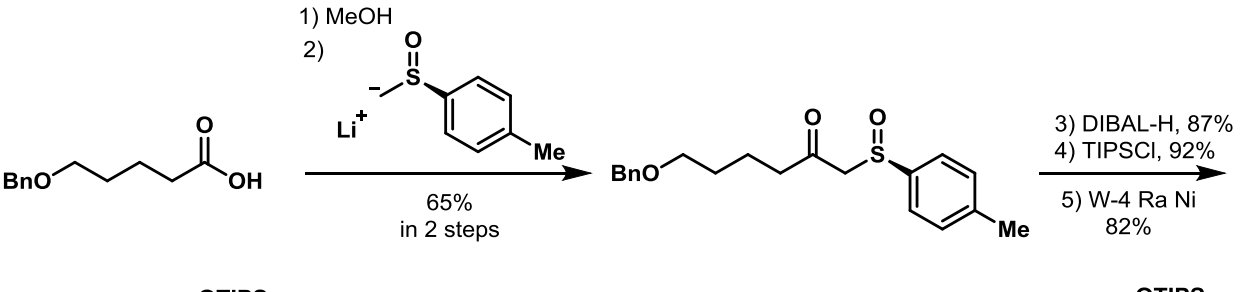
Electrochemical Doubly Decarboxylative Coupling:



1 step

2 steps

*Synthesis of **14**, intermediate used in the total synthesis of (–)-Macrolactin A (Marino and co-workers)*

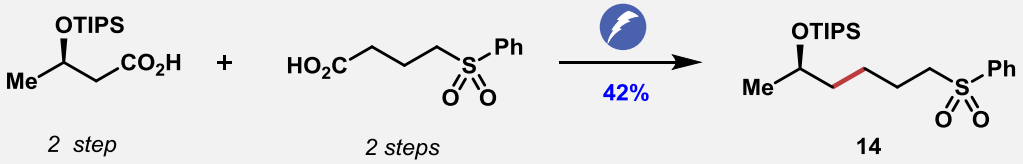


14

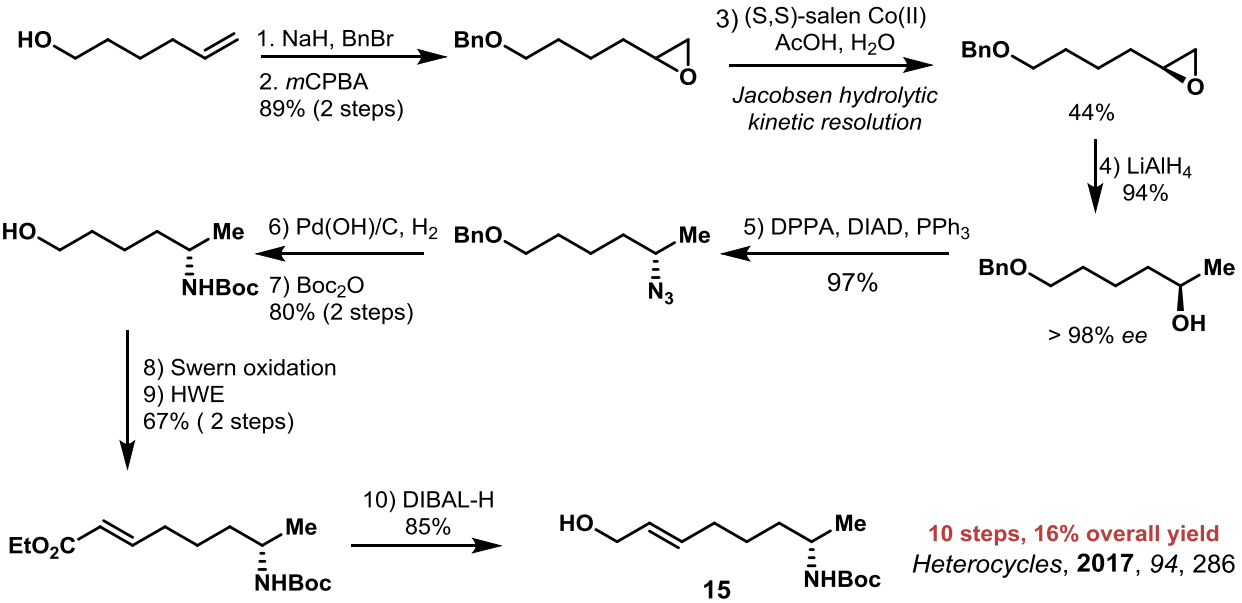
7 steps, 24% overall yield

J. Am. Chem. Soc. **2002,** *124*, 1664

Electrochemical Doubly Decarboxylative Coupling:



*Synthesis of **15**, intermediate used in the total synthesis of (–)-Isosolenopsin (Makabe and co-workers)*

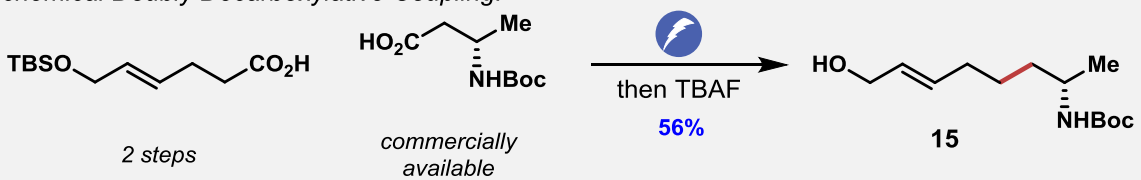


15

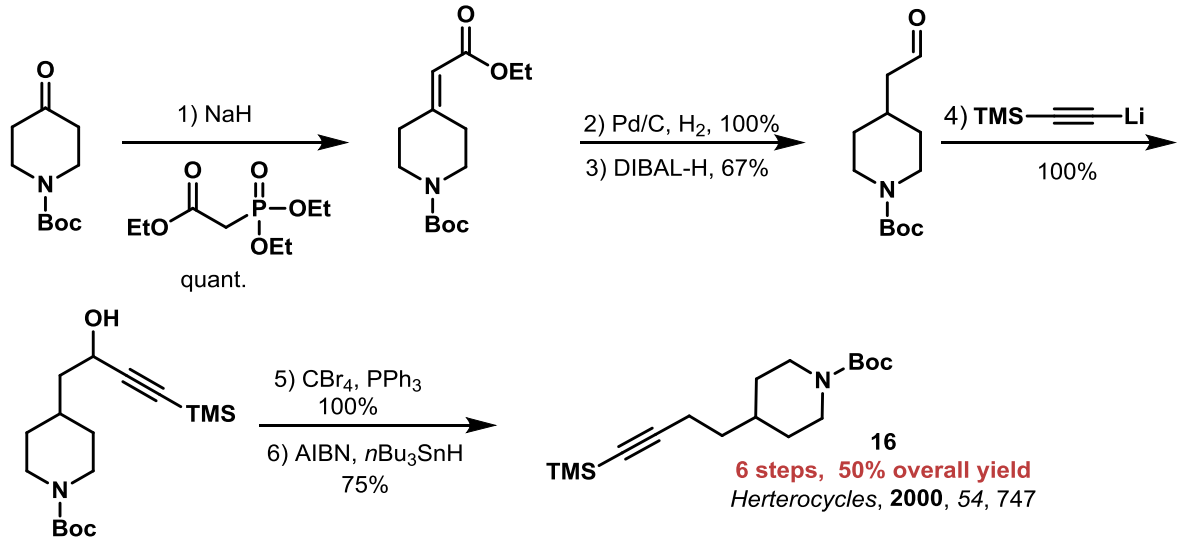
10 steps, 16% overall yield

Heterocycles, **2017**, *94*, 286

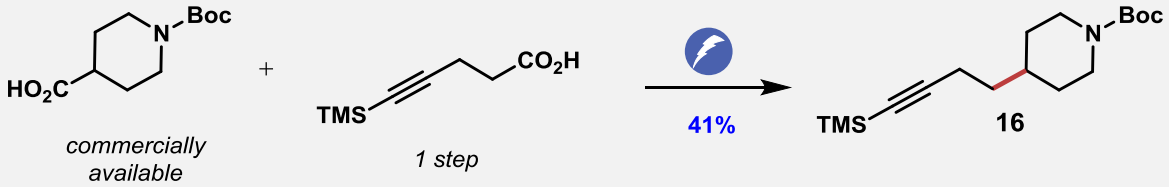
Electrochemical Doubly Decarboxylative Coupling:



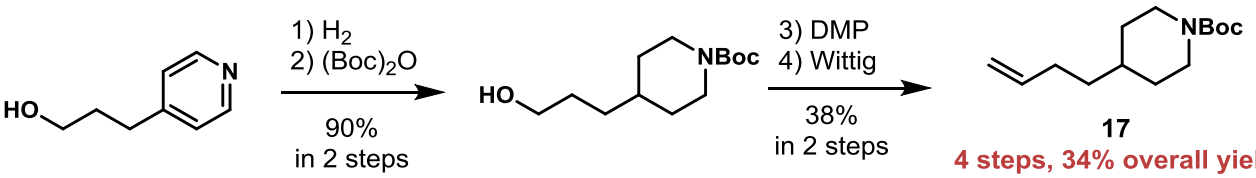
*Synthesis of **16** - used in azabicyclic synthesis by Ikeda and co-workers*



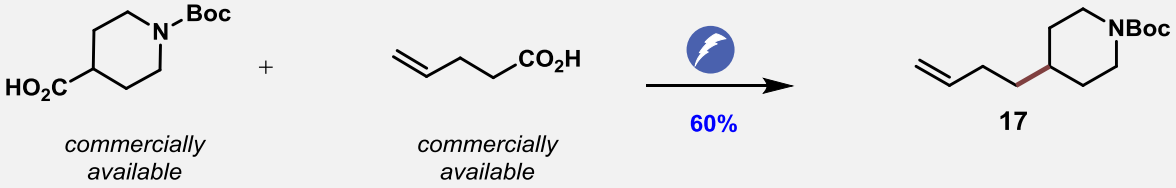
Electrochemical Doubly Decarboxylative Coupling:



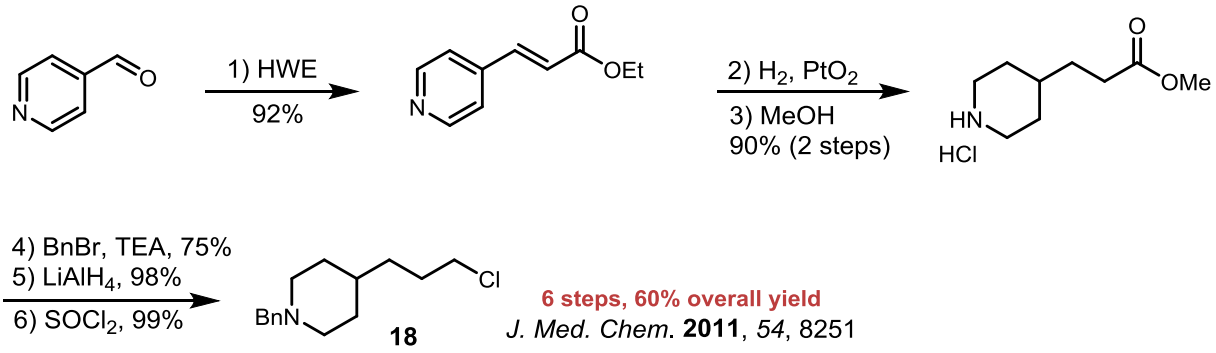
*Synthesis of **17** - used in the synthesis of CNS penetrant compounds*



Electrochemical Doubly Decarboxylative Coupling:



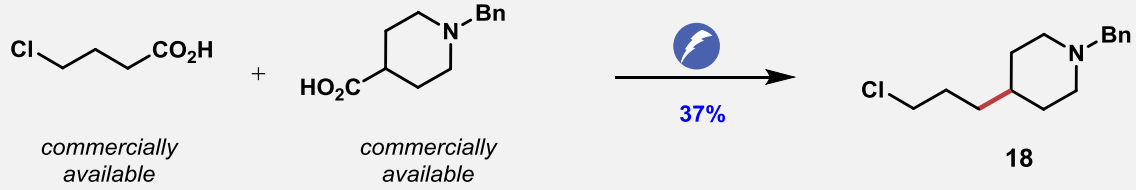
*Synthesis of **18** - used in development towards promising multitarget drug candidates for Alzheimer's*



6 steps, 60% overall yield

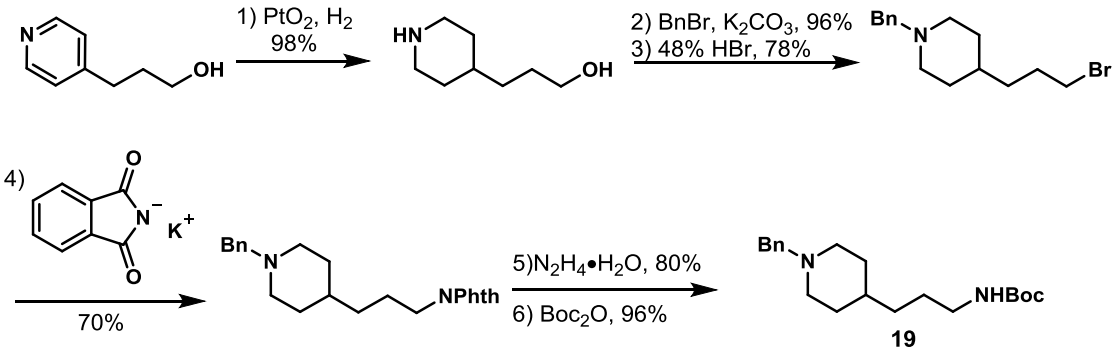
J. Med. Chem. **2011**, *54*, 8251

Electrochemical Doubly Decarboxylative Coupling:



commercially available *commercially available*

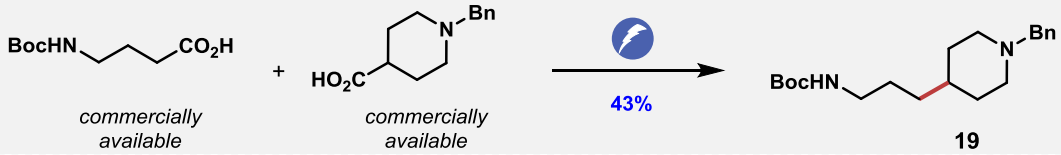
*Synthesis of **19** - intermediate used for evaluation of novel dibenzodiazepinone-type muscarinic receptor ligands*



6 steps, 39% overall yield

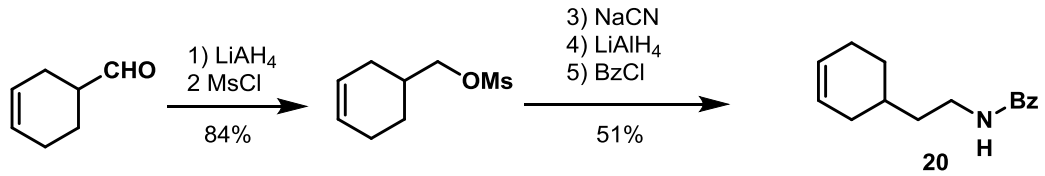
Bioorg. Med. Chem. **2015**, *23*, 3970

Electrochemical Doubly Decarboxylative Coupling:



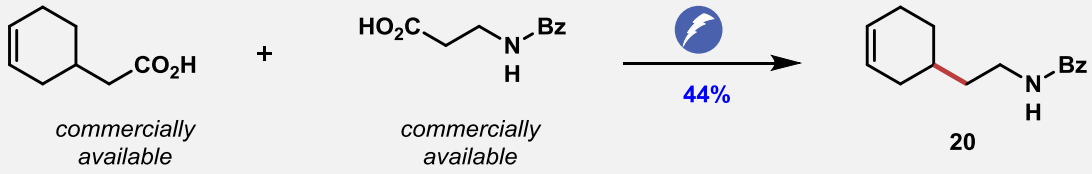
commercially available *commercially available*

*Synthesis of **20**, intermediate used in morphine/morphan derivatives*

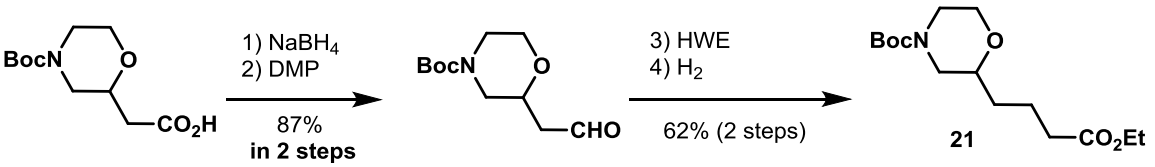


5 steps, 43% overall yield
Z. Naturforsch. **2016**, *71*, 1057

Electrochemical Doubly Decarboxylative Coupling:

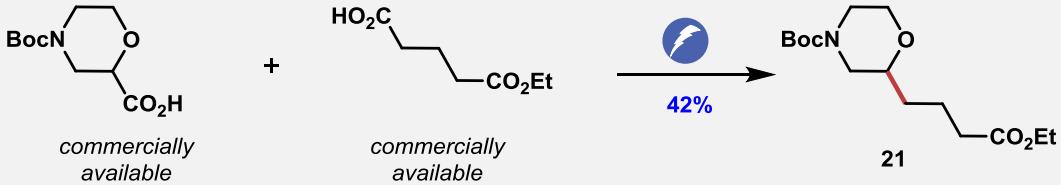


*Synthesis of **21**, intermediate used in the evaluation of having an autotaxin inhibitory action*

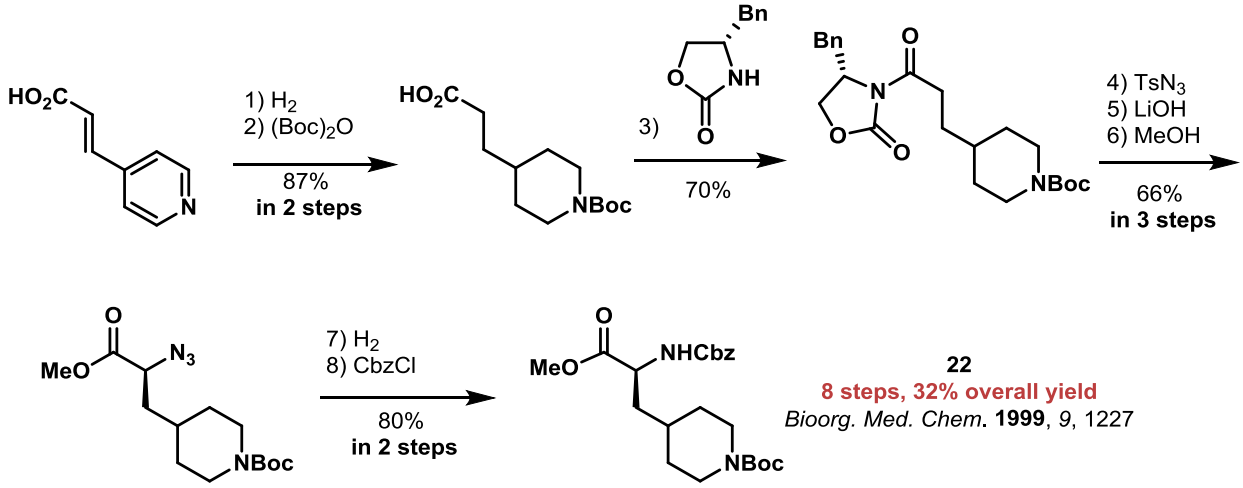


4 steps, 54% overall yield
EP3831812A1

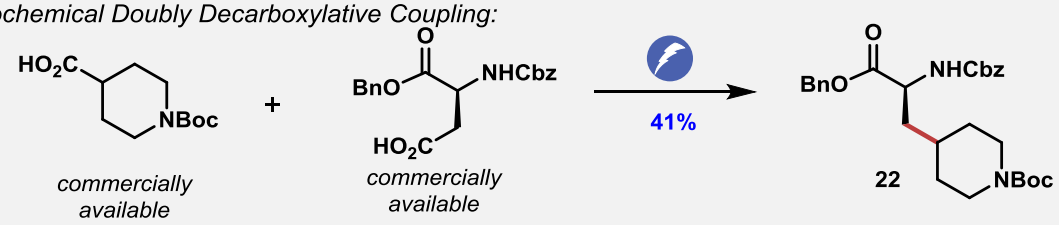
Electrochemical Doubly Decarboxylative Coupling:



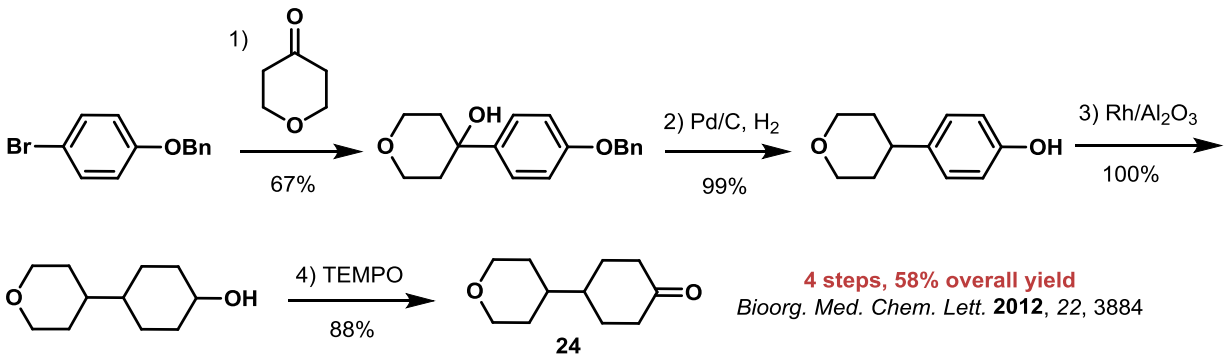
*Synthesis of **22** - used for the evaluation of novel protease inhibitors containing 2-aminopiperidines*



Electrochemical Doubly Decarboxylative Coupling:

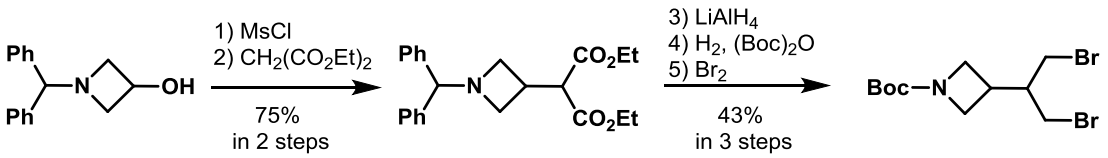


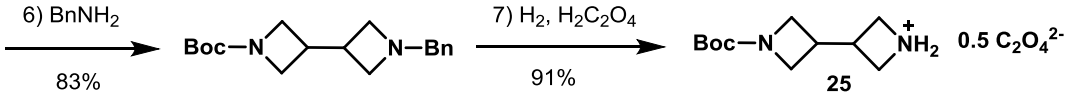
*Synthesis of **24** - intermediate used for evaluation of novel class of cannaboid receptors*



Electrochemical Doubly Decarboxylative Coupling:

*Synthesis of **25** - Evaluation of biazetidines by Enamine*



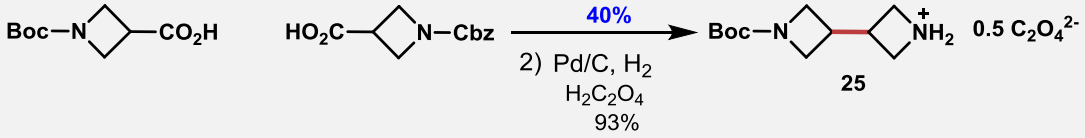


25

7 steps, 24% overall yield

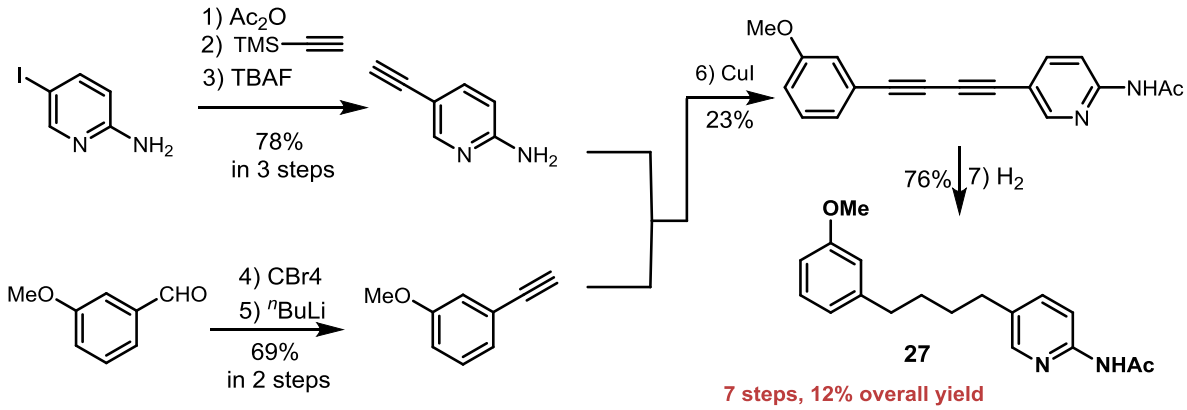
J. Org. Chem. **2019**, *84*, 1363

Electrochemical Doubly Decarboxylative Coupling:



25

*Synthesis of **27** - Evaluation of potential BACE1 inhibitors*

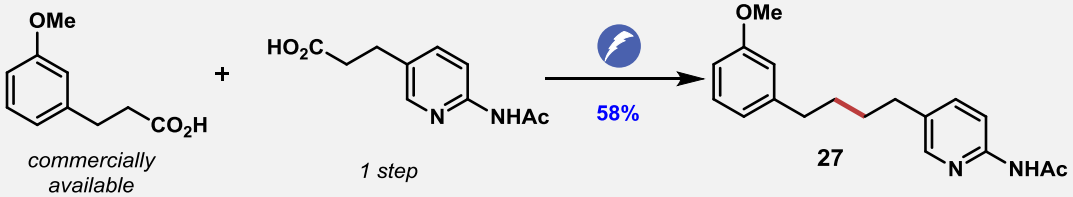


27

7 steps, 12% overall yield

Bioorg. Med. Chem. **2015**, *25*, 5127

Electrochemical Doubly Decarboxylative Coupling:

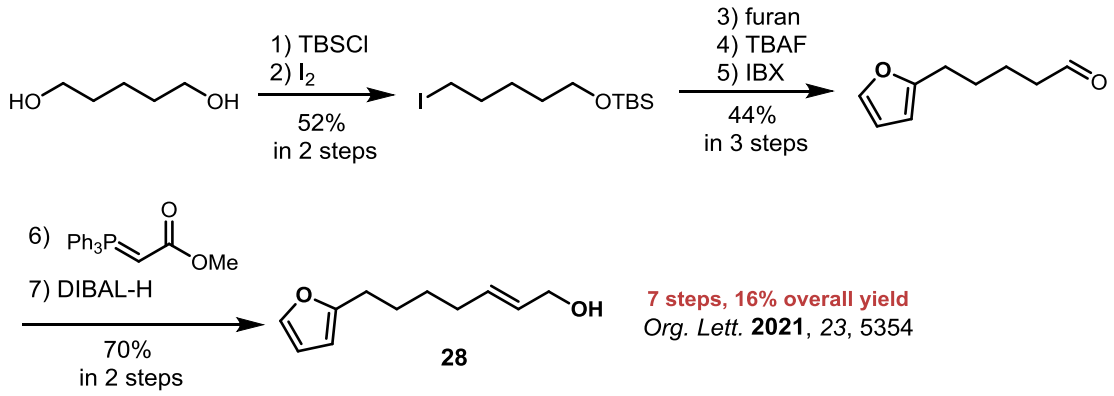


commercially available

1 step

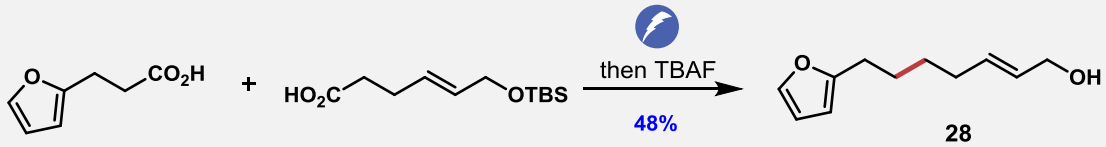
27

*Synthesis of **28** - intermediate used in thel synthesis of 1-Azaspirocyclic Alkaloid Frameworks*



7 steps, 16% overall yield
Org. Lett. **2021**, *23*, 5354

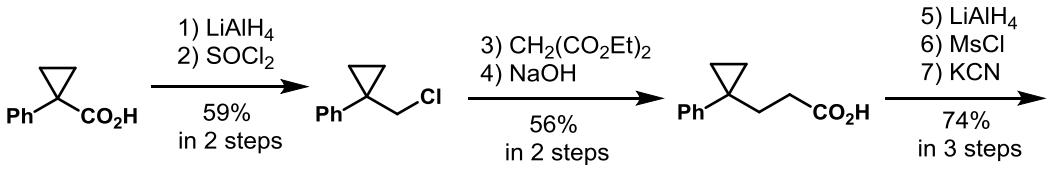
Electrochemical Doubly Decarboxylative Coupling:

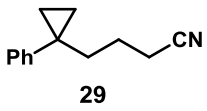


commercially available

2 step

*Synthesis of **29** - intermediate used in thel synthesis of* 4-(1-Phenylcyclopropyl)butanoic acid

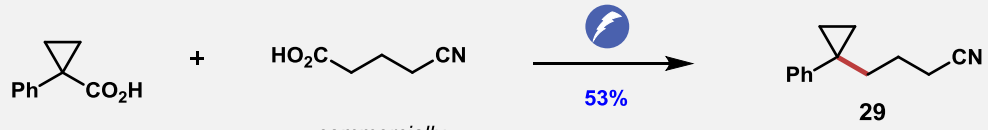




29

7 steps, 24% overall yield
J. Am. Chem. Soc. **1973**, *95*, 5988

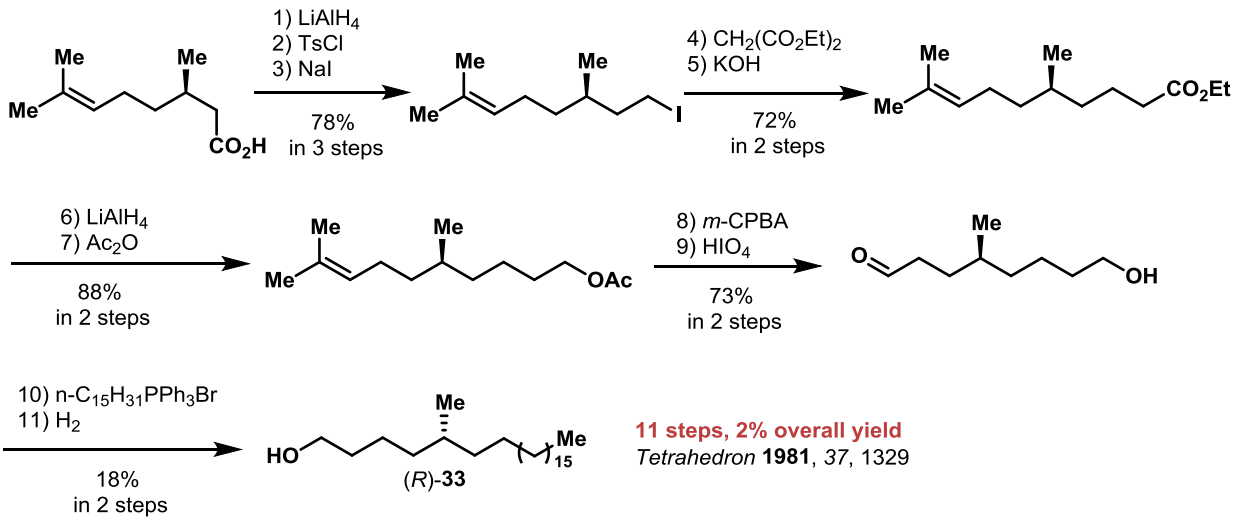
Electrochemical Doubly Decarboxylative Coupling:



commercially available

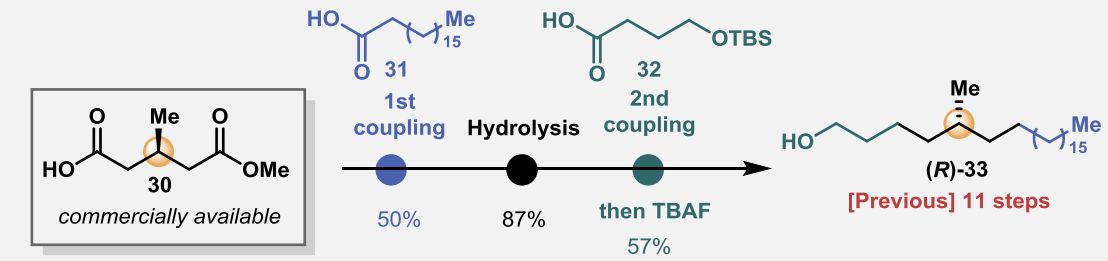
commercially available

*Synthesis of (R)-**33** - intermediate used in the synthesis sinsect pheromones by Mori and co-workers*

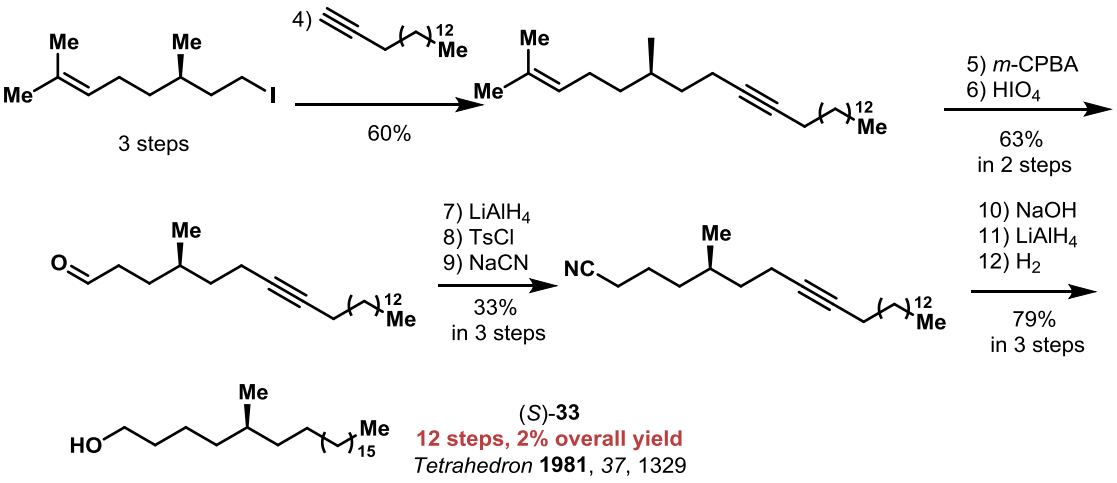


11 steps, 2% overall yield
Tetrahedron **1981**, *37*, 1329

Electrochemical Doubly Decarboxylative Coupling:

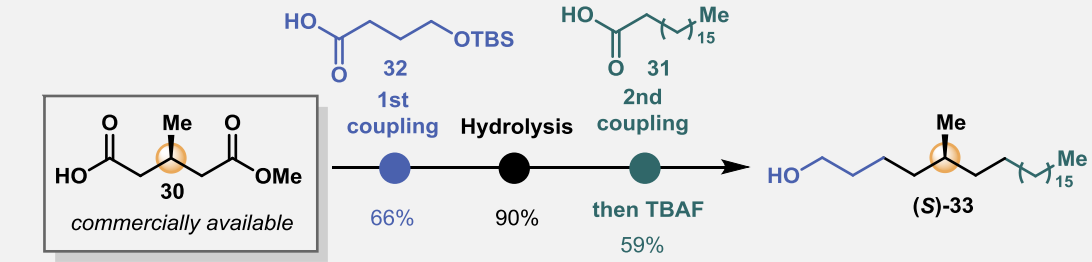


*Synthesis of (S)-**33** - intermediate used in the synthesis sinsect pheromones by Mori and co-workers*

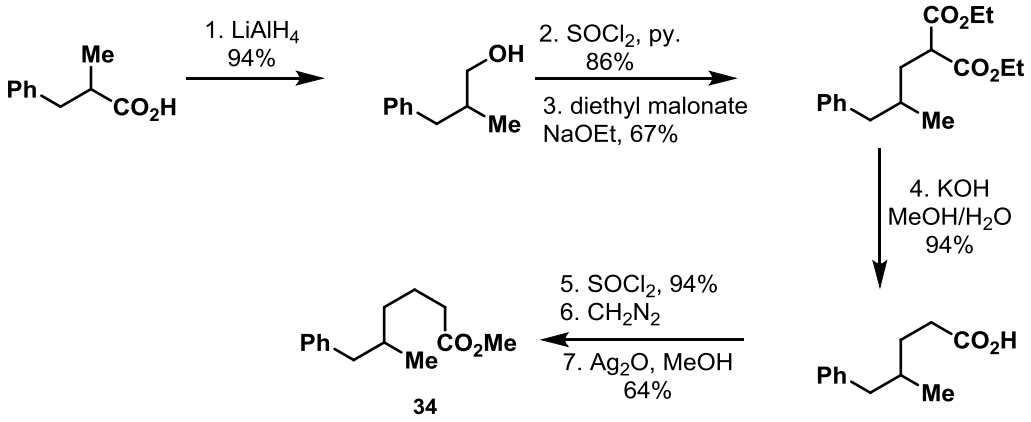


12 steps, 2% overall yield
Tetrahedron **1981**, *37*, 1329

Electrochemical Doubly Decarboxylative Coupling:

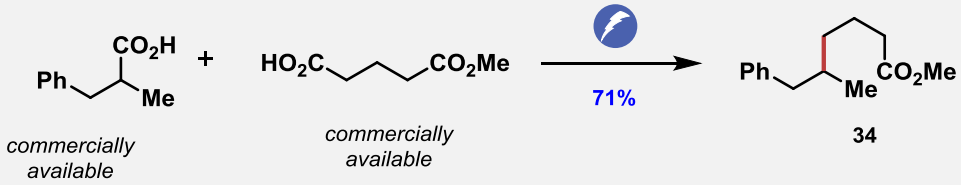


*Synthesis of **34** - intermediate used for intramolecular C-H bond insertion*

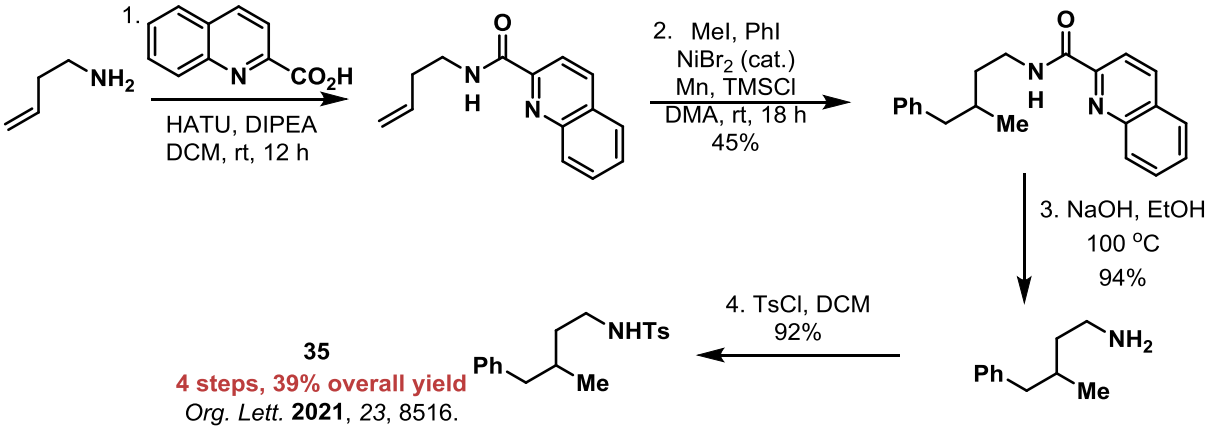


7 steps, 46% overall yield
Chem. Pharm. Bull. **1970**, *18*, 1124.

Electrochemical Doubly Decarboxylative Coupling:

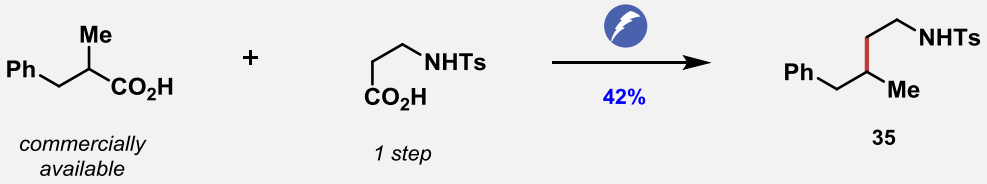


*Synthesis of **35** - intermediate used for C-H amination/cyclization to afford pyrrolidine*

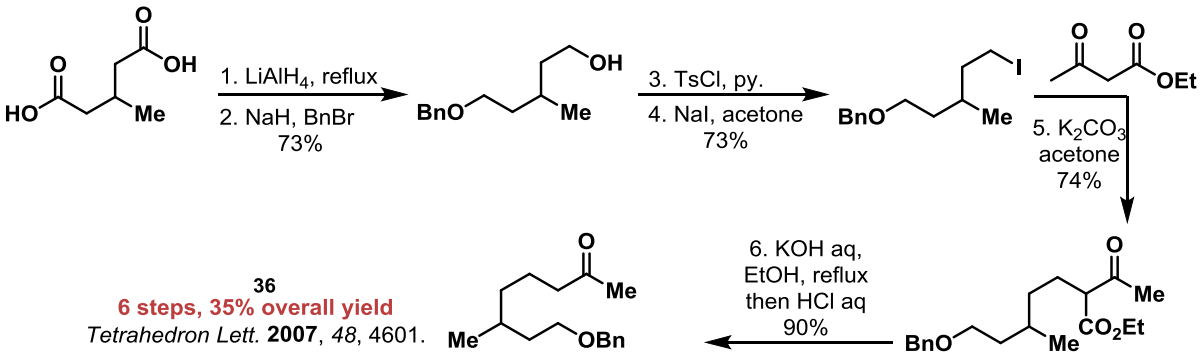


4 steps, 39% overall yield
Org. Lett. **2021**, *23*, 8516.

Electrochemical Doubly Decarboxylative Coupling:

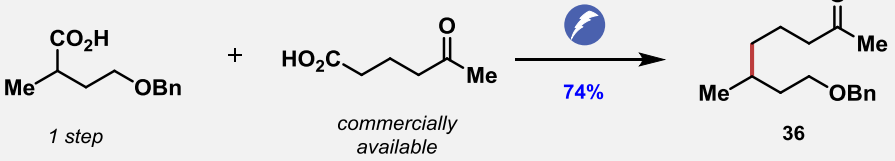


*Synthesis of **36** - intermediate used for synthesis of hormone α1*



36
6 steps, 35% overall yield
Tetrahedron Lett. **2007**, *48*, 4601.

Electrochemical Doubly Decarboxylative Coupling:

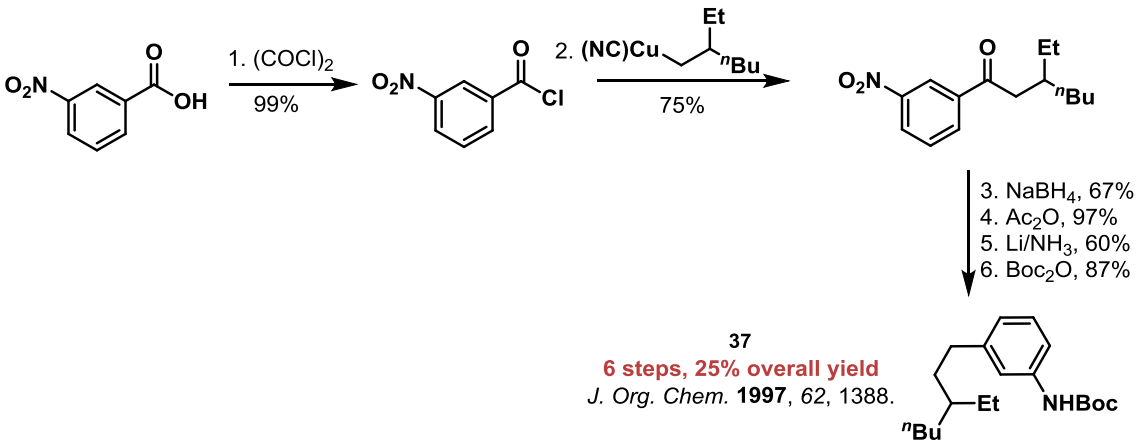


1 step

commercially available

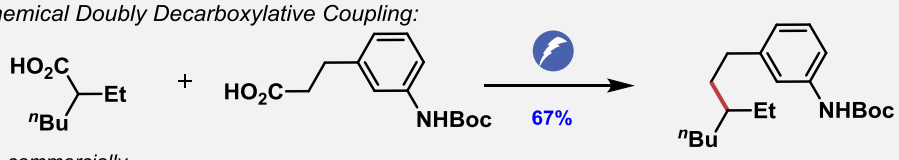
36

*Synthesis of **37** - intermediate used for synthesis of oligo(1,4-phenylenethynylene)s*



37
6 steps, 25% overall yield
J. Org. Chem. **1997**, *62*, 1388.

Electrochemical Doubly Decarboxylative Coupling:

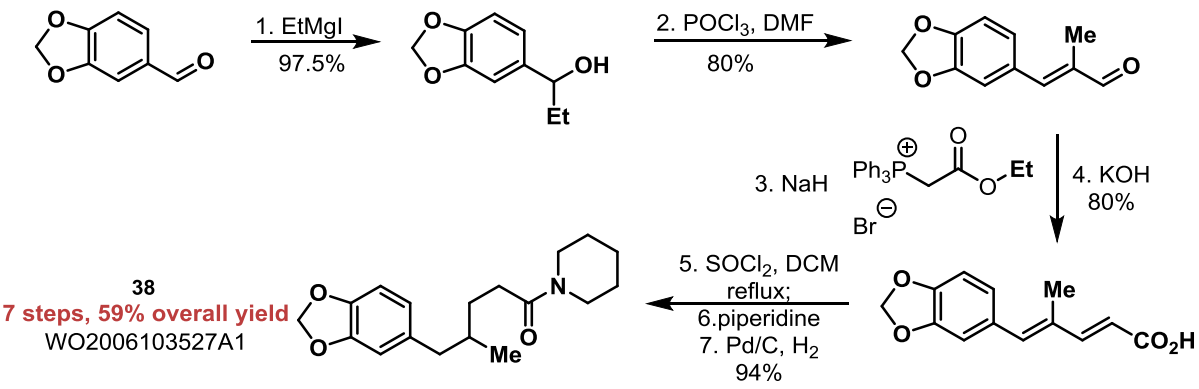


commercially available

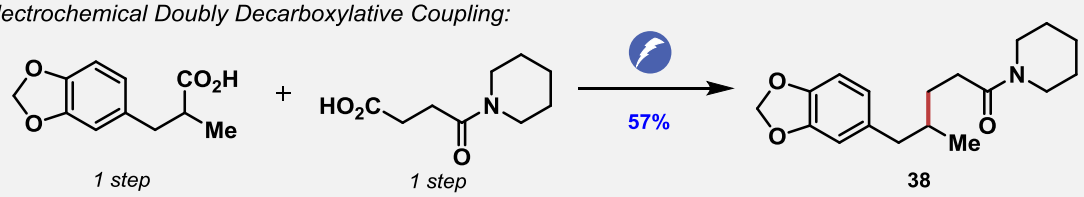
1 step

37

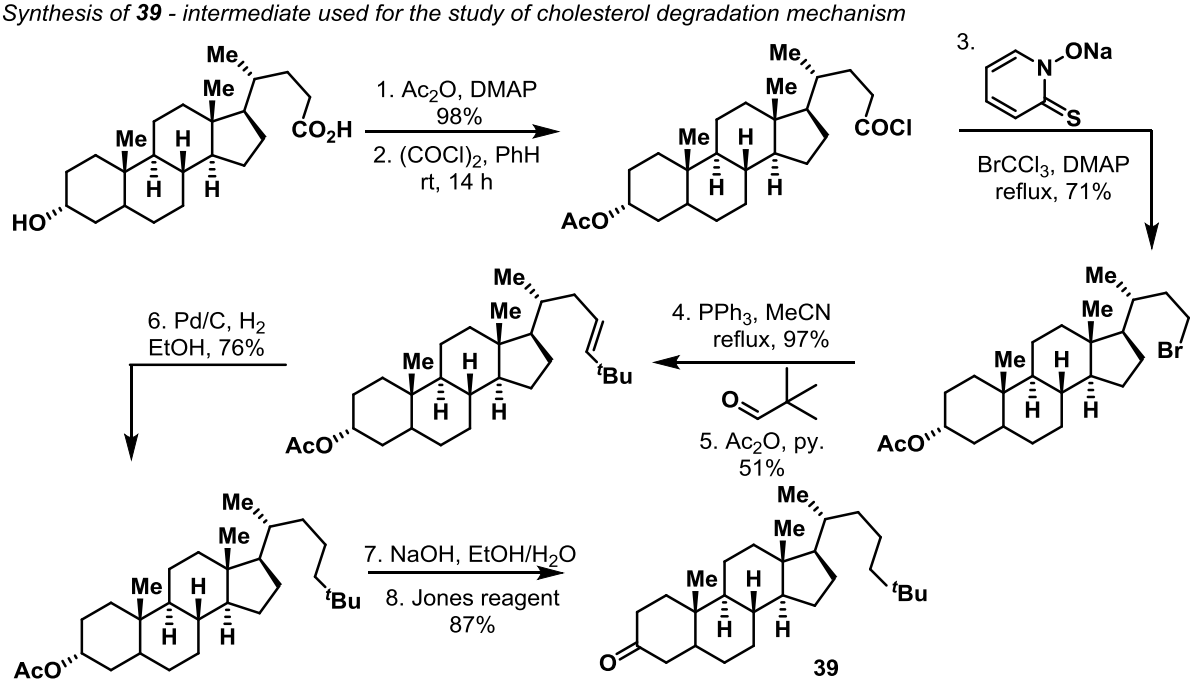
*Synthesis of **38***



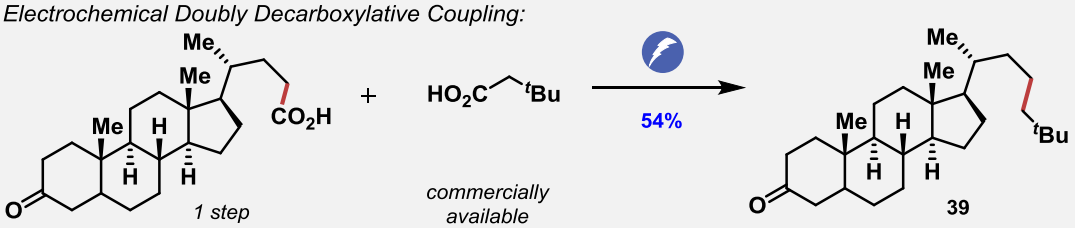
Electrochemical Doubly Decarboxylative Coupling:



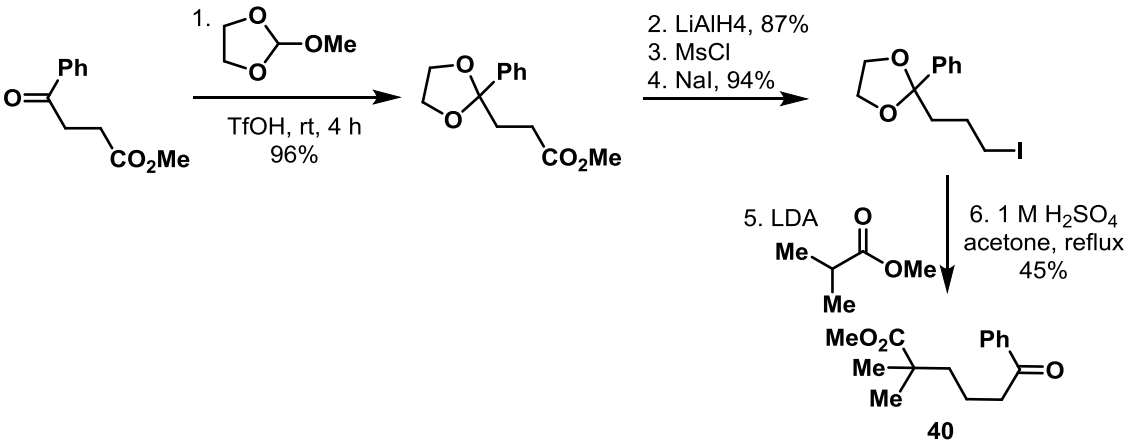
*Synthesis of **39** - intermediate used for the study of cholesterol degradation mechanism*



Electrochemical Doubly Decarboxylative Coupling:



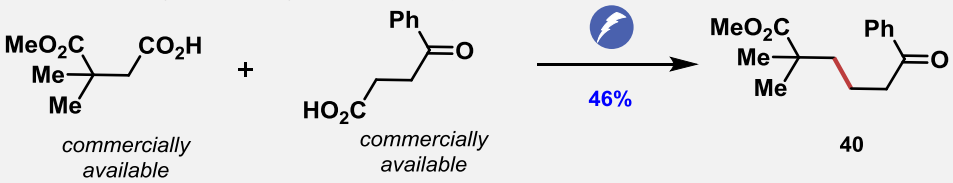
*Synthesis of **40** - intermediate used for the synthesis of* non-thiazolidinedione antidiabetic agents



6 steps, 35% overall yield

Chem. Pharm. Bull. **2003**, *51*, 138.

Electrochemical Doubly Decarboxylative Coupling:



Troubleshooting: Frequently Asked Questions

Question 1:

How do I monitor the reaction?

Answer:

We use TLC analysis with UV visualization (254 nm) to see the starting material (SM). Staining with iodine (absorbed on silica gel) developes a strong deep red spot for the product. The SM is much less responsive to the iodine stain, likewise the product has essentially no absorption at 254 nm. Therefore, even though in many cases the SM and the product coelute, the disappearance of a UV signal (254 nm) and an increasing sensitivity to iodine staining is a positive sign for the progress of the reaction. In addition, ^{1}H NMR aliquot analysis could also be used to monitor reaction progress.

Question 2:

What are the suitable current and voltage values for reactions on different scales?

Answer:

We typically use 4 mA on 0.2 mmol scales. Normal operational voltage range for this reaction is around 0 V - 4.2 V. When a reaction needs to be run on different scale, all the parameters except for substrate concentration (i.e. solvent amount) should follow general procedures. Substrate concentration can be varied from half to double without affecting the reaction efficiency. Accordingly, depending on the amount of solvent used for a reaction, vial size can also be changed to an appropriate size for the reaction.

Question 3:

Is this reaction sensitive to air and water?

Answer:

The reaction is not particularly air- and water-sensitive. Acceptable yields can be still obtained by performing electrolysis under air. The yield was not affected when 2 equiv of H_2O was added to the reaction.

Question 4:

Are the ligands used in this study commercially available?

Answer:

2,2':6',2"-terpyridine **L1** is commercially available. (4-OMe)-H-PyBox[1] **L4** need to be synthesized in 3 steps (column chromatography is not required)**.**

Question 5:

What is the byproduct of this reaction?

Answer: The major side reaction was the dimer of carboxylic acid which was used in 3 equiv.

Question 6:

Will the yield be higher if you use redox-active ester directly?

Answer:

There is nearly no difference between isolated RAEs and in-situ generated RAEs. The yield difference was usually within 5% across the Table 1.

Question 7:

Can you use DMF as a solvent in the RAE synthesis step so that electrolysis can be run in one solvent.

Answer:

DMF could be used for acid-activation step, although the reaction is much slower. Due to this reason, dichloromethane was used for acid-activation step. As described in the main text and general procedure, dichloromethane does not need to be removed and the reaction solution can be directly used for the electrolysis.

Question 9:

How low the catalyst loading can be?

Answer:

20 mol% $NiCl_2$•dme is already the lowest. If the catalyst loading is further reduced, the reaction yield will become much lower.

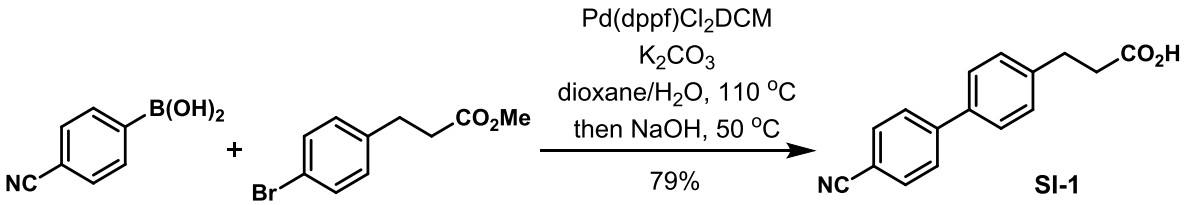
Question 10:

What should we do if acids do not dissolve to DCM or RAEs do not dissolve to DMF. Are these cases also the current limitation?

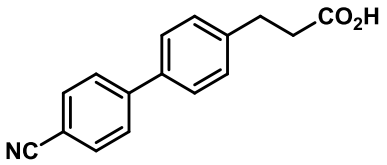
Answer:

Most of the acids we used have relatively good solubility in DCM, and the solubility of the acid has little effect on the generation of RAE. On the other hand, low solubility of RAE could result in low yield of the coupling product. This was observed in the coupling to provide compound **33**. Fortunately, in this case satisfactory reaction yield was obtained by increasing the temperature to 80 ^{o}C. For details, please refer to the synthesis of compound **33**.

Experimental Procedures and Characterization Data for Non-Commercially Available carboxylic Acids



Compound SI-1



3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoic acid (SI-1).

To a solution of methyl 3-(4-bromophenyl)propanoate (1.22 g, 5.0 mmol) in dioxane/H_2O (35 mL/7 mL) was added (4-cyanophenyl)boronic acid (0.81 g, 5.5 mmol), Pd(dppf)Cl_2•DCM (0.41 g, 0.5 mmol) and K_2CO_3 (2.07 g, 15 mmol) under an argon atmosphere. The reaction mixture was stirred at 110 ^oC for 6 h. The solution was diluted with 2 M NaOH (15 mL), and then stirred at 50 ^oC for another 2 h. The mixture was acidified with 1N HCl (pH 2–4). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with MeOH/CH_2Cl_2 (1:20) as the eluent to give **SI-1** (0.99 g, 79%).

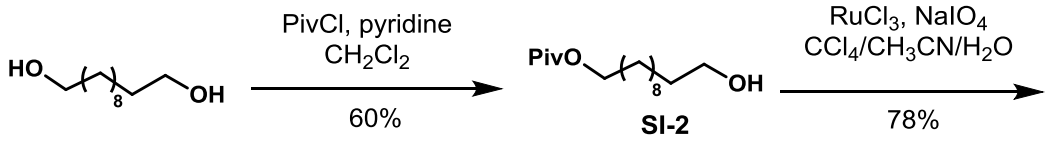
Physical State: white solid.

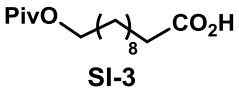
^{1}H NMR (600 MHz, DMSO-d_6): δ 12.16 (s, 1H), 8.05–7.76 (m, 4H), 7.74–7.55 (m, 2H), 7.45–7.25 (m, 2H), 2.96–2.80 (m, 2H), 2.67–2.52 (m, 2H).

^{13}C NMR (151 MHz, DMSO-d_6): δ 173.7, 144.5, 141.8, 136.0, 132.8, 129.1, 127.3, 127.0, 118.9, 109.8, 35.0, 30.0.

HRMS (ESI-TOF): calc'd for $C_{16}H_{14}NO_2$ $[M+H]^+$: 252.1025, found 252.1021.

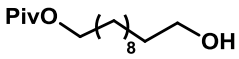
TLC: R_f = 0.3 (20:1 CH_2Cl_2:MeOH).





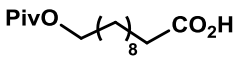
SI-3

Compound SI-3



11-hydroxyundecyl pivalate (SI-2).

To a solution of undecane-1,11-diol (5.65 g, 30 mmol) in CH_2Cl_2 (30 mL) was added pyridine (1.6 mL, 19.5 mmol) and PivCl (1.9 mL, 15 mmol) at 0 ^oC under argon atmosphere. The mixture was then stirred at room temperature for 8 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc/hexane (1:4) as the eluent to give **SI-2** (2.32 g, 78%). The spectroscopic data matched the literature.[2]



11-(pivaloyloxy)undecanoic acid (SI-3).

To a solution 11-hydroxyundecyl isobutyrate (1.42 g, 5.5 mmol) in $CCl_4/CH_3CN/H_2O$ (7.5 mL/7.5 mL/11.5 mL) was added $RuCl_3$ (0.12 g, 0.55 mmol) and $NaIO_4$ (4.7 g, 5.5 mmol) at 0 ^oC. The mixture was then stirred at room temperature for 2 h. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with MeOH/CH_2Cl_2 (1:20) as the eluent to give **SI-3** (1.22 g, 78%).

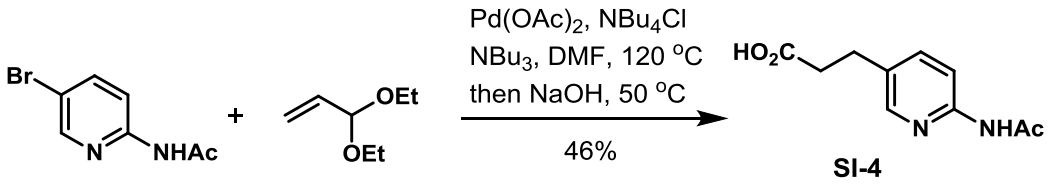
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$):δ 4.04 (t, *J* = 6.6 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.80–1.47 (m, 4H), 1.39 – 1.23 (m, 12H), 1.19 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$):δ 179.8 , 178.7 , 64.4 , 38.7 , 34.0 , 29.4 , 29.3 , 29.2 (2C) , 29.0 , 28.6 , 27.2 , 25.9 , 24.6 .

HRMS (ESI-TOF): calc'd for $C_{16}H_{31}O_4$ $[M+H]^+$: 287.2222, found 287.2231.

TLC: R_f = 0.3 (1:20 MeOH/CH_2Cl_2).



Compound SI-4

3-(6-acetamidopyridin-3-yl)propanoic acid (SI-4).

To a solution of N-(5-bromopyridin-2-yl)acetamide (1.18 g, 5.5 mmol) in DMF (50 mL) was added $Pd(OAc)_2$ (37 mg, 0.17 mmol), NBu_4Cl (1.49 g, 5.5 mmol), NBu_3 (2.6 mL, 11 mmol) and 3,3-diethoxyprop-1-ene (2.5 mL, 16.5 mmol) under an argon atmosphere. The reaction mixture was stirred at 120 °C for 12 h. The solution was diluted with 2 M NaOH (15 mL), and then stirred at 50 °C for another 2 h. The mixture was acidified with 1N HCl (pH 5–6). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with MeOH/CH_2Cl_2 (1:10) as the eluent to give **SI-4** (0.53 g, 46%).

Physical State: yellow solid.

^{1}H NMR (600 MHz, DMSO-d_6): δ 12.15 (s, 1H), 10.39 (s, 1H), 8.16 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 2.77 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.06 (s, 3H).

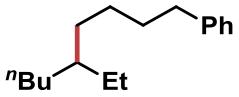
^{13}C NMR (151 MHz, DMSO-d_6):δ 173.6, 169.0, 150.4, 147.4, 137.8, 131.4, 112.9, 34.9, 26.9, 23.8.

HRMS (ESI-TOF): calc'd for $C_{10}H_{13}N_2O_3$ $[M+H]^+$: 209.0926, found 209.0939.

TLC: R_f = 0.2 (1:10 MeOH/CH_2Cl_2).

Experimental Procedures and Characterization Data for Doubly Decarboxylative Coupling Product

Compound SI-15



(5-ethylnonyl)benzene (SI-15).

Following the **General Procedure A** on 0.1 mmol scale 2-ethylhexanoic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 17.6 mg (76%) of the title compound **SI-15**.

Physical State: colorless oil.

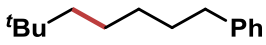
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.19 (m, 3H), 2.61 (d, *J* = 8.0 Hz, 2H), 1.64–1.57 (m, 2H), 1.37–1.11 (m, 13H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.0, 128.4, 128.2, 125.5, 38.8, 36.0, 33.0, 32.9, 32.0, 29.0, 26.5, 25.9, 23.2, 14.2, 10.9.

GC/MS (EI): m/z 232 (10%), 133 (10%), 105 (14%), 91 (100%).

TLC: R_f = 0.9 (hexanes).

Compound SI-16



(6,6-dimethylheptyl)benzene (SI-16).

Following the **General Procedure A** on 0.1 mmol scale 3,3-dimethylbutanoic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 14.1 mg (69%) of the title compound **SI-16**.

Physical State: colorless oil.

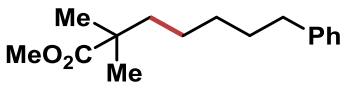
^{1}H NMR (600 MHz, $CDCl_3$): δ ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.29 (td, *J* = 7.2, 1.4 Hz, 2H), 7.22–7.16 (m, 3H), 2.62 (t, *J* = 8.0 Hz, 2H), 1.74–1.59 (m, 2H), 1.44–1.23 (m, 4H), 1.22–1.11 (m, 2H), 0.88 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.9, 128.4, 128.2, 125.5, 44.2, 36.0, 31.6, 30.3, 29.4, 24.4.

GC/MS (EI): m/z 204 (34%), 148 (30%), 91 (100%), 57 (95%).

TLC: R_f = 0.9 (hexanes).

Compound SI-17



methyl 2,2-dimethyl-7-phenylheptanoate (SI-17).

Following the **General Procedure A** on 0.1 mmol scale 4-methoxy-3,3-dimethyl-4-oxobutanoic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (20:1 hexanes:EtOAc) afforded 18.6 mg (76%) of the title compound **SI-17**.

Physical State: colorless oil.

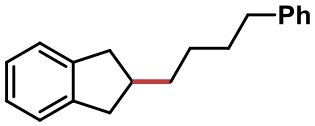
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.26 (m, 2H), 7.19–7.14 (m, 3H), 3.65 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 1.65–1.55 (m, 2H), 1.53–1.46 (m, 2H), 1.35–1.27 (m, 2H), 1.27–1.18 (m, 2H), 1.16 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 178.6, 142.7, 128.4, 128.2, 125.6, 51.6, 42.3, 40.7, 35.9, 31.3, 29.7, 25.2, 24.8.

HRMS (ESI-TOF): calc'd for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1855 , found 249.1854.

TLC: R_f = 0.3 (20:1 hexanes:EtOAc)

Compound SI-18



2-(4-phenylbutyl)-2,3-dihydro-1H-indene (SI-18).

Following the **General Procedure A** on 0.1 mmol scale 2,3-dihydro-1H-indene-2-carboxylic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 16.1 mg (68%) of the title compound **SI-18**.

Physical State: colorless oil.

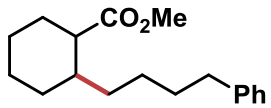
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.1 Hz, 5H), 7.13 (dd, *J* = 5.5, 3.2 Hz, 2H), 3.04 (dd, *J* = 15.5, 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 2.59 (dd, *J* = 15.5, 8.2 Hz, 2H), 2.45 (q, *J* = 7.8 Hz, 1H), 1.68 (p, *J* = 7.7 Hz, 2H), 1.55 (q, *J* = 7.3 Hz, 2H), 1.45 (q, *J* = 8.2 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.6, 142.7, 128.4, 128.2, 126.0, 125.6, 124.3, 40.2, 39.3, 36.0, 35.6, 31.6, 28.1.

GC/MS (EI): m/z 250 (20%), 207 (22%), 117 (100%), 91 (65%).

TLC: R_f = 0.7 (hexanes).

Compound SI-19



methyl 2-(4-phenylbutyl)cyclohexane-1-carboxylate (SI-19).

Following the **General Procedure A** on 0.1 mmol scale 2-(methoxycarbonyl)cyclohexane-1-carboxylic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (20:1 hexanes:EtOAc) afforded **One isomer** 14.5 mg (51%) and **the other isomer** 2.8 mg (10%) of the title compound **SI-19**.

One isomer:

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H), 7.19–7.14 (m, 3H), 3.65 (s, 3H), 2.58 (qdd, *J* = 13.7, 9.0, 6.5 Hz, 2H), 2.05 (ddd, *J* = 12.0, 10.7, 3.5 Hz, 1H), 1.85 (dddd, *J* = 12.5, 7.1, 3.5, 1.5 Hz, 2H), 1.78–1.67 (m, 2H), 1.64–1.50 (m, 4H), 1.49–1.35 (m, 2H), 1.33–1.18 (m, 3H), 1.16–1.06 (m, 1H), 0.97–0.78 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.8, 142.7, 128.4, 128.2, 125.5, 51.3, 50.1, 38.9, 35.8, 34.7, 31.6, 30.8, 30.1, 26.0, 25.7, 25.5.

HRMS (ESI-TOF): calc'd for $C_{18}H_{27}O_2$ $[M+H]^+$: 275.2011 , found 275.2011.

TLC: R_f = 0.3 (20:1 hexanes:EtOAc)

The other isomer:

Physical State: colorless oil.

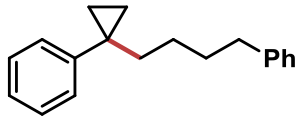
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H), 7.19–7.12 (m, 3H), 3.63 (s, 3H), 2.64–2.53 (m, 3H), 1.84–1.78 (m, 1H), 1.78–1.64 (m, 3H), 1.64–1.56 (m, 3H), 1.56–1.48 (m, 1H), 1.47–1.40 (m, 2H), 1.37–1.29 (m, 3H), 1.28–1.16 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5, 142.7, 128.4, 128.2, 125.6, 51.1, 45.3, 37.2, 35.8, 31.5, 30.0, 28.3, 27.1, 25.6, 23.9, 22.7.

HRMS (ESI-TOF): calc'd for $C_{18}H_{27}O_2$ $[M+H]^+$: 275.2011 , found 275.2012.

TLC: R_f = 0.4 (20:1 hexanes:EtOAc)

Compound SI-20



(1-(4-phenylbutyl)cyclopropyl)benzene (SI-20).

Following the **General Procedure A** on 0.1 mmol scale 1-phenylcyclopropane-1-carboxylic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 16.2mg (76%) of the title compound **SI-20**.

Physical State: colorless oil.

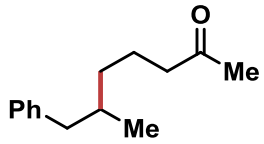
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.22 (m, 6H), 7.21–7.14 (m, 2H), 7.14–7.07 (m, 2H), 2.53 (t, *J* = 7.8 Hz, 2H), 1.64–1.49 (m, 4H), 1.34 (ddt, *J* = 10.4, 6.7, 3.6 Hz, 2H), 0.83–0.76 (m, 2H), 0.69–0.58 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.4, 142.8, 129.0, 128.3, 128.2, 128.0, 125.8, 125.5, 40.2, 35.9, 31.7, 26.9, 25.7, 13.0.

GC/MS (EI): m/z 250 (2%), 132 (19%), 117 (100%), 91 (61%).

TLC: R_f = 0.7 (hexanes).

Compound SI-21



6-methyl-7-phenylheptan-2-one (SI-21).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 5-oxohexanoic acid (1.5 equiv). Purification by PTLC (20:1 hexanes:EtOAc) afforded 15.5 mg (76%) of the title compound **SI-21**.

Physical State: colorless oil.

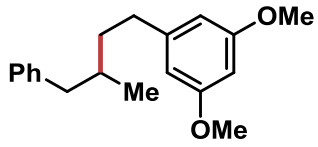
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.6 Hz, 2H), 7.20–7.16 (m, 1H), 7.15–7.11 (m, 2H), 2.62 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.48–2.32 (m, 3H), 2.12 (s, 3H), 1.79–1.63 (m, 2H), 1.60–1.50 (m, 1H), 1.33 (ddt, *J* = 13.3, 10.8, 5.3 Hz, 1H), 1.14 (dddd, *J* = 13.1, 10.8, 7.9, 5.1 Hz, 1H), 0.87 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.1, 141.3, 129.1, 128.1, 125.6, 43.9, 43.5, 36.0, 34.9, 29.9, 21.4, 19.3.

GC/MS (EI): m/z 204 (2%), 186 (19%), 113 (100%), 91 (61%).

TLC: R_f = 0.2 (20:1 hexanes:EtOAc)

Compound SI-22



1,3-dimethoxy-5-(3-methyl-4-phenylbutyl)benzene (SI-22).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 3-(3,5-dimethoxyphenyl)propanoic acid (1.5 equiv). Purification by PTLC (50:1 hexanes:EtOAc) afforded 20.5 mg (63%) of the title compound **SI-22**.

Physical State: colorless oil.

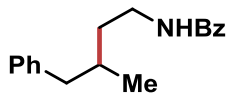
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.25 (m, 2H), 7.21–7.17 (m, 1H), 7.16–7.13 (m, 2H), 6.33 (d, *J* = 2.3 Hz, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 3.78 (s, 6H), 2.74–2.62 (m, 2H), 2.55 (ddd, *J* = 13.6, 10.3, 6.1 Hz, 1H), 2.43 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.80 (dddd, *J* = 8.0, 6.6, 5.1, 1.5 Hz, 1H), 1.70 (dddd, *J* = 13.4, 10.4, 6.1, 5.2 Hz, 1H), 1.48 (dddd, *J* = 13.5, 10.4, 7.8, 5.5 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 160.7 145.2, 141.2, 129.2, 128.1, 125.7, 106.4, 97.6, 55.2, 43.5, 38.1, 34.5, 33.8, 19.4.

HRMS (ESI-TOF): calc'd for $C_{19}H_{25}O_2$ $[M+H]^+$: 285.1855 , found 285.1858.

TLC: R_f = 0.2 (50:1 hexanes:EtOAc)

Compound SI-23



N-(3-methyl-4-phenylbutyl)benzamide (SI-23).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 3-benzamidopropanoic acid (1.5 equiv). Purification by PTLC (4:1 hexanes:EtOAc) afforded 16.3 mg (61%) of the title compound **SI-23**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75–7.69 (m, 2H), 7.51–7.46 (m, 1H), 7.44–7.38 (m, 2H), 7.31–7.24 (m, 2H), 7.22–7.17 (m, 1H), 7.18–7.13 (m, 2H), 6.02 (br, 1H), 3.55 (ddt, *J* = 13.4,

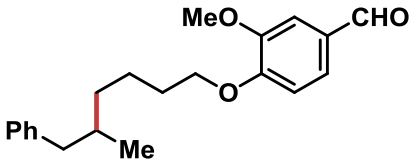
8.9, 5.7 Hz, 1H), 3.50–3.41 (m, 1H), 2.65 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.49 (dd, *J* = 13.4, 7.6 Hz, 1H), 1.86 (ddt, *J* = 13.4, 6.7, 1.6 Hz, 1H), 1.67 (dddd, *J* = 13.8, 8.9, 6.7, 5.0 Hz, 1H), 1.54–1.39 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.4, 140.8, 134.7, 131.3, 129.2, 128.5, 128.2, 126.8, 125.9, 43.5, 38.2, 36.2, 33.0, 19.5.

HRMS (ESI-TOF): calc'd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1701 , found 268.1702.

TLC: R_f = 0.2 (4:1 hexanes:EtOAc)

Compound SI-24



3-methoxy-4-((5-methyl-6-phenylhexyl)oxy)benzaldehyde (SI-24).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 5-(4-formyl-2-methoxyphenoxy)pentanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 22.8 mg (70%) of the title compound **SI-24**.

Physical State: colorless oil.

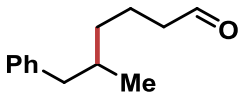
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.46–7.38 (m, 2H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.15–7.12 (m, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 4.08 (t, *J* = 6.9 Hz, 2H), 3.92 (s, 3H), 2.64 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.40 (dd, *J* = 13.4, 8.0 Hz, 1H), 1.86 (td, *J* = 8.7, 4.0 Hz, 2H), 1.82–1.70 (m, 1H), 1.65–1.37 (m, 3H), 1.24 (ddt, *J* = 8.0, 5.1, 3.0 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 190.8, 154.1, 149.8, 141.3, 129.8, 129.1, 128.0, 126.7, 125.6, 111.3, 109.2, 69.0, 55.9, 43.5, 36.1, 34.8, 29.0, 23.3, 19.3.

HRMS (ESI-TOF): calc'd for $C_{21}H_{27}O_3$ $[M+H]^+$: 327.1960 , found 327.1963.

TLC: R_f = 0.2 (10:1 hexanes:EtOAc)

Compound SI-25



5-oxopentanoic acid (SI-25).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 5-oxopentanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 9.7 mg (51%) of the title compound **SI-25**.

Physical State: colorless oil.

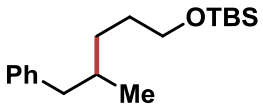
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 2H), 2.63 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.47–2.34 (m, 3H), 1.74 (dt, *J* = 13.1, 7.0 Hz, 2H), 1.62 (dt, *J* = 12.2, 6.4 Hz, 1H), 1.38 (td, *J* = 11.1, 10.2, 5.6 Hz, 1H), 1.23–1.12 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 202.7, 141.1, 129.1, 128.1, 125.7, 44.1, 43.5, 36.0, 34.9, 19.6, 19.3.

GC/MS (EI): m/z 190 (12%), 99 (8%), 91 (100%), 71 (3%), 65 (18%), 55 (38%).

TLC: R_f = 0.4 (10:1 hexanes:EtOAc)

Compound SI-26



Tert-butyldimethyl((4-methyl-5-phenylpentyl)oxy)silane (SI-26).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 4-((tert-butyldimethylsilyl)oxy)butanoic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 23.0 mg (79%) of the title compound **SI-26**.

Physical State: colorless oil.

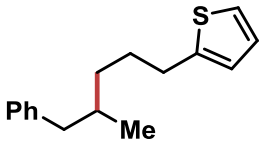
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.20–7.16 (m, 1H), 7.16–7.13 (m, 2H), 3.59 (t, *J* = 6.7 Hz, 2H), 2.64 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.38 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.73 (dddd, *J* = 8.1, 6.7, 5.1, 1.5 Hz, 1H), 1.67–1.57 (m, 1H), 1.56–1.45 (m, 1H), 1.40 (ddt, *J* = 13.3, 10.7, 5.3 Hz, 1H), 1.21 – 1.13 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.5, 129.2, 128.1, 125.6, 63.5, 43.7, 34.9, 32.7, 30.4, 26.0, 19.4, 18.4, -5.3.

GC/MS (EI): m/z 235 (83%), 159 (25%), 117 (26%), 91 (3%), 75 (58%).

TLC: R_f = 0.2 (100:1 hexanes:EtOAc)

Compound SI-27



2-(4-methyl-5-phenylpentyl)thiophene (SI-27).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 4-(thiophen-2-yl)butanoic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 18.9 mg (78%) of the title compound **SI-27**.

Physical State: colorless oil.

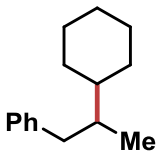
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.25 (m, 2H), 7.24–7.17 (m, 1H), 7.17–7.13 (m, 2H), 7.11 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.77 (dd, *J* = 3.3, 1.3 Hz, 1H), 2.90–2.75 (m, 2H), 2.65 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.38 (dd, *J* = 13.4, 8.2 Hz, 1H), 1.83–1.73 (m, 2H), 1.69 (tddd, *J* = 9.2, 7.2, 3.8, 2.0 Hz, 1H), 1.45 (ddt, *J* = 13.6, 10.8, 5.4 Hz, 1H), 1.25 (dddd, *J* = 15.7, 10.6, 7.2, 5.1 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.7, 141.4, 129.1, 128.1, 126.6, 125.6, 123.9, 122.7, 43.6, 36.1, 34.8, 30.1, 29.4, 19.3.

GC/MS (EI): m/z 244 (27%), 153 (20%), 111 (11%), 97 (100%), 91 (47%).

TLC: R_f = 0.7 (hexanes).

Compound SI-28



(2-cyclohexylpropyl)benzene (SI-28).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with cyclohexanecarboxylic acid (1.5 equiv). Purification by PTLC (hexanes) afforded 11.1mg (55%) of the title compound **SI-28**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.21–7.12 (m, 3H), 2.76 (dd, *J* = 13.3, 5.2 Hz, 1H), 2.29 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.82–1.56 (m, 6H), 1.33–1.00 (m, 6H), 0.78 (d, *J* = 7.0 Hz, 3H).

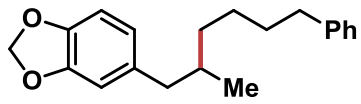
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.3, 129.1, 128.1, 125.4, 42.4, 40.7/40.5, 30.9, 28.6,

26.9/26.8, 26.7, 15.6.

GC/MS (EI): m/z 202 (8%), 111 (64%), 91 (62%), 69 (100%),55 (44%).

TLC: R_f = 0.9 (hexanes).

Compound SI-29



5-(2-methyl-6-phenylhexyl)benzo[d][1,3]dioxole (SI-29).

Following the **General Procedure A** on 0.1 mmol scale 3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanoic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 21.0 mg (71%) of the title compound **SI-29**.

Physical State: colorless oil.

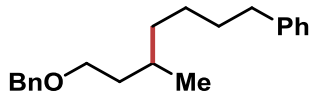
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.21–7.14 (m, 3H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 1.7 Hz, 1H), 6.58 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.92 (s, 2H), 2.65–2.57 (m, 2H), 2.54 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.29 (dd, *J* = 13.5, 8.1 Hz, 1H), 1.74–1.51 (m, 3H), 1.47–1.25 (m, 3H), 1.16 (dtd, *J* = 10.2, 5.7, 5.0, 2.9 Hz, 1H), 0.84 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 147.3, 145.4, 142.8, 135.4, 128.4, 128.2, 125.6, 121.9, 109.4, 107.9, 100.6, 43.4, 36.3, 35.9, 35.1, 31.7, 26.7, 19.3.

GC/MS (EI): m/z 296 (10%), 135 (100%), 91 (27%), 77 (13%).

TLC: R_f = 0.4 (10:1 hexanes:EtOAc)

Compound SI-30



(7-(benzyloxy)-5-methylheptyl)benzene (SI-30).

Following the **General Procedure A** on 0.1 mmol scale 4-(benzyloxy)-2-methylbutanoic acid with 5-phenylpentanoic acid (1.5 equiv). Purification by PTLC (100:1 hexanes:EtOAc) afforded 22.5 mg (76%) of the title compound **SI-30**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (d, *J* = 4.5 Hz, 4H), 7.32–7.27 (m, 3H), 7.22–7.16 (m, 3H), 4.52 (s, 2H), 3.65–3.38 (m, 2H), 2.70–2.47 (m, 2H), 1.72–1.52 (m, 4H), 1.48–1.27 (m,

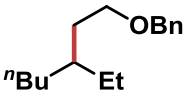
4H), 1.22–1.14 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.8, 138.7, 128.4, 128.3, 128.2, 127.6, 127.4, 125.5, 72.9, 68.7, 36.9, 36.8, 36.0, 31.8, 29.8, 26.6, 19.7.

GC/MS (EI): m/z 296 (1%), 187 (18%), 131 (22%), 117 (16%), 107 (5%), 91 (100%).

TLC: R_f = 0.2 (100:1 hexanes:EtOAc)

Compound SI-31



(((3-ethylheptyl)oxy)methyl)benzene (SI-31).

Following the **General Procedure A** on 0.1 mmol scale 2-ethylhexanoic acid with 3-(benzyloxy)propanoic acid (1.5 equiv). Purification by PTLC (100:1 hexanes:EtOAc) afforded 14.2 mg (61%) of the title compound **SI-31**.

Physical State: colorless oil.

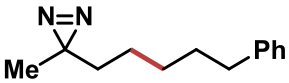
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.32 (m, 4H), 7.30–7.26 (m, 1H), 4.51 (s, 2H), 3.49 (t, *J* = 7.1 Hz, 2H), 1.62–1.53 (m, 2H), 1.43–1.36 (m, 1H), 1.34–1.17 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.7, 128.3, 127.6, 127.4, 72.9, 68.9, 35.9, 33.2, 32.8, 28.8, 26.0, 23.1, 14.1, 10.7.

GC/MS (EI): m/z 234 (1%), 143 (9%), 91 (100%), 83 (21%).

TLC: R_f = 0.2 (100:1 hexanes:EtOAc)

Compound SI-32



3-methyl-3-(5-phenylpentyl)-3H-diazirine (SI-32).

Following the **General Procedure B** on 0.1 mmol scale 3-(3-methyl-3H-diazirin-3-yl)propanoic acid with 4-phenylbutanoic acid (3.0 equiv). Purification by PTLC (hexanes) afforded 4.5 mg (22%) of the title compound **SI-32**.

Physical State: colorless oil.

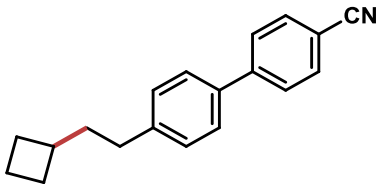
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.25 (m, 2H), 7.20–7.14 (m, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.67–1.53 (m, 2H), 1.37–1.27 (m, 4H), 1.23–1.16 (m, 2H), 0.99 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.5, 128.3, 128.2, 125.6, 35.8, 34.2, 31.2, 28.8, 25.9, 23.9, 19.9.

HRMS (ESI-TOF): calc'd for $C_{13}H_{19}N_2$ $[M+H]^+$: 203.1548 , found 203.1547.

TLC: R_f = 0.5 (hexanes)

Compound 1



4'-(2-Cyclobutylethyl)-[1,1'-biphenyl]-4-carbonitrile (1).

Following the **General Procedure A** on 0.1 mmol scale 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoic acid **SI-1** with cyclobutanecarboxylic acid (3 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 13.3 mg (51%) of the title compound **1**. The NMR Spectrum of compound **1** is not available in the original literature.[3] Accordingly appropriate characterization was conducted and reported below.

Physical State: colorless oil.

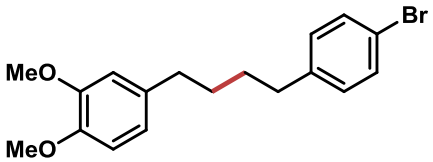
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 2.60–2.52 (m, 2H), 2.31 (dh, *J* = 15.7, 7.7 Hz, 1H), 2.06 (dddd, *J* = 15.6, 6.3, 5.1, 3.1 Hz, 2H), 1.91–1.79 (m, 2H), 1.74 (q, *J* = 7.6 Hz, 2H), 1.64 (pd, *J* = 8.9, 2.5 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.6, 143.7, 136.4, 132.5, 129.1, 127.5, 127.0, 119.0, 110.5, 38.7, 35.6, 33.2, 28.2, 18.4.

HRMS (ESI-TOF): calc'd for $C_{19}H_{20}N$ $[M+H]^+$: 262.1596 , found 262.1602.

TLC: R_f = 0.5 (10:1 hexanes:EtOAc).

Compound 7



4-(4-(4-Bromophenyl)butyl)-1,2-dimethoxybenzene (7).

Following the **General Procedure B** on 0.1 mmol scale 3-(4-bromophenyl)propanoic acid with 3-(3,4-dimethoxyphenyl)propanoic acid (3 equiv). Purification by flash column chromatography (20:1 hexanes:EtOAc) afforded 22.3 mg (64%) of the title compound **7**. The NMR Spectrum is not available in the original literature.[4] Accordingly appropriate characterization was conducted and reported below.

Physical State: colorless oil.

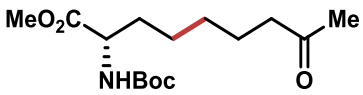
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.73–6.61 (m, 2H), 3.86 (2s, 6H), 2.60–2.51 (m, 4H), 1.75–1.51 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 148.7, 147.1, 141.4, 135.0, 131.3, 130.1, 120.1, 119.3, 111.7, 111.1 , 55.9, 55.8, 35.3, 35.2, 31.1, 30.8.

HRMS (ESI-TOF): calc'd for $C_{18}H_{22}BrO_2$ $[M+H]^+$: 349.0803 , found 349.0804.

TLC: R_f = 0.3 (20:1 hexanes:EtOAc).

Compound 8



Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-8-oxononanoate (8).

Following the **General Procedure B** on 0.1 mmol scale (S)-4-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid with 5-oxohexanoic acid (3 equiv). Purification by flash column chromatography (3:1 hexanes:EtOAc) afforded 19.5 mg (65%) of the title compound **8**. The spectroscopic data matched the literature[5].

Physical State: colorless oil.

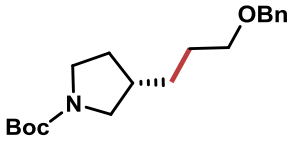
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.99 (d, *J* = 8.5 Hz, 1H), 4.27 (q, *J* = 7.5 Hz, 1H), 3.72 (s, 3H), 2.41 (t, *J* = 7.4 Hz, 2H), 2.12 (s, 3H), 1.82–1.73 (m, 1H), 1.64–1.51 (m, 3H), 1.43 (s, 9H), 1.39–1.23 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 208.9, 173.4, 155.3, 79.8, 53.3, 52.2, 43.5, 32.6, 29.9, 28.6, 28.3, 25.1, 23.4.

TLC: R_f = 0.4 (3:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -10.8 (c = 1.0, MeOH).

Compound 9



***tert*-Butyl (*S*)-3-(3-(benzyloxy)propyl)pyrrolidine-1-carboxylate (9).**

Following the **General Procedure B** on 0.1 mmol scale (R)-2-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)acetic acid with 4-(benzyloxy)butanoic acid (3 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 15.2 mg (48%) of the title compound **9**. The spectroscopic data matched the literature[6].

Physical State: colorless oil.

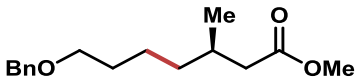
^{1}H NMR (600 MHz, $CDCl_3$): 7.37–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.50 (s, 2H), 3.52 (dd, *J* = 10.6, 7.5 Hz, 1H), 3.49–3.40 (m, 3H), 3.23 (ddd, *J* = 10.8, 9.5, 7.0 Hz, 1H), 2.85 (dd, *J* = 10.6, 8.7 Hz, 1H), 2.09 (ddt, *J* = 16.0, 9.2, 6.9 Hz, 1H), 1.97 (dtd, *J* = 12.8, 6.6, 2.9 Hz, 1H), 1.71–1.58 (m, 2H), 1.50–1.41 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 154.6, 138.5, 128.4, 127.6, 127.5, 78.9, 72.9, 70.2, 51.4, 45.6, 38.6, 31.5, 29.8, 28.5, 28.4.

TLC: R_f = 0.2 (10:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -16.3 (c = 1.0, $CHCl_3$).

Compound 10



Methyl (*R*)-7-(benzyloxy)-3-methylheptanoate (10).

Following the **General Procedure B** on 0.1 mmol scale (R)-5-methoxy-3-methyl-5-oxopentanoic acid with 4-(benzyloxy)butanoic acid (3 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 16.1 mg (61%) of the title compound **10**. The spectroscopic data matched the literature[7].

Physical State: colorless oil.

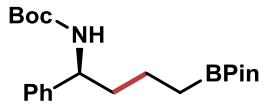
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.50 (s, 2H), 3.66 (s, 3H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.30 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.11 (dd, *J* = 14.8, 8.1 Hz, 1H), 1.95 (dq, *J* = 13.7, 6.8 Hz, 1H), 1.66–1.58 (m, 2H), 1.47–1.29 (m, 3H), 1.24–1.16 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7, 138.6, 128.3, 127.6, 127.5, 72.9, 70.3, 51.4, 41.6, 36.5, 30.3, 29.8, 23.6, 19.7.

TLC: R_f = 0.4 (10:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +4.4 (c = 0.5, $CHCl_3$).

Compound 11



***tert*-Butyl (*S*)-(1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)carbamate (11).**

Following the **General Procedure B** on 0.1 mmol scale 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoic acid[8a] with (S)-3-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid (3 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 9.8 mg (26%) of the title compound **11**. The spectroscopic data matched the literature[8b].

Physical State: colorless oil.

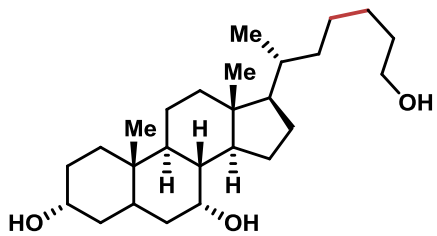
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32–7.27 (m, 2H), 7.27–7.18 (m, 3H), 4.94 (br, 1H), 4.60 (br, 1H), 1.80–1.60 (m, 2H), 1.41 (s, 9H), 1.27–1.16 (m, 14H), 0.83–0.72 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.2, 143.3, 128.4, 126.8, 126.1, 82.9, 79.1, 54.8, 39.5, 28.3, 24.8, 20.5, 10.9.

TLC: R_f = 0.2 (10:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -18.6 (c = 0.5, $CHCl_3$).

Compound 12'



(3*R*,7*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-7-((*tert*-butyldimethylsilyl)oxy)heptan-2-yl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthrene-3,7-diol (12').

Following the **General Procedure B** on 0.1 mmol scale chenodeoxycholic acid with 4-((*tert*-

butyldimethylsilyl)oxy)butanoic acid[9a] (3 equiv). After completion of electrolysis, TBAF (1 N in THF, 1.2 mL) was added and then stir for another 12 h. Purification by flash column chromatography (1:2 hexanes:EtOAc) afforded 24.4 mg (60%) of the title compound **12'**. The spectroscopic data matched the literature[9b].

Physical State: colorless oil.

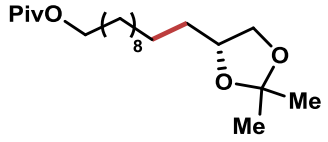
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.84 (q, *J* = 3.1 Hz, 1H), 3.63 (t, *J* = 6.7 Hz, 2H), 3.45 (ddd, *J* = 11.1, 6.7, 4.4 Hz, 1H), 2.20 (dd, *J* = 13.0, 11.2 Hz, 1H), 2.00–1.94 (m, 2H), 1.90–1.77 (m, 3H), 1.74–1.44 (m, 9H), 1.40–1.23 (m, 10H), 1.21–1.08 (m, 3H), 1.07–0.93 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 3H), 0.65 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 72.0, 68.5, 63.0, 56.0, 50.4, 42.6, 41.5, 39.8, 39.6, 39.4, 35.8, 35.7, 35.3, 35.0, 34.5, 32.8 (2C), 30.6, 28.3, 26.2, 25.8, 23.7, 22.8, 20.6, 18.6, 11.7.

TLC: R_f = 0.4 (EtOAc).

$[\alpha]_D^{25}$ = +12.6 (c = 1.0, MeOH).

Compound 13



(*R*)-9-(2,2-Dimethyl-1,3-dioxolan-4-yl)nonyl pivalate (13).

Following the **General Procedure B** on 0.1 mmol scale (R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetic acid[10a] with 10-(pivaloyloxy)decanoic acid **SI-3** (3 equiv). Purification by flash column chromatography (20:1 hexanes:EtOAc) afforded 12.1 mg (34%) of the title compound **13**. The spectroscopic data matched the literature[10b].

Physical State: colorless oil.

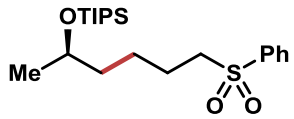
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.09–4.00 (m, 4H), 3.49 (t, *J* = 7.5 Hz, 1H), 1.63–1.58 (m, 3H), 1.51–1.43 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.32–1.24 (m, 16H), 1.19 (s, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 178.6, 108.5, 76.2, 69.5, 64.4, 38.7, 33.6, 29.6, 29.5 (3C), 29.2, 28.6, 27.2, 27.0, 25.9 (2C), 25.8.

TLC: R_f = 0.2 (20:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -2.0 (c = 1.0, $CHCl_3$).

Compound 14



(*R*)-Triisopropyl((6-(phenylsulfonyl)hexan-2-yl)oxy)silane (14).

Following the **General Procedure B** on 0.1 mmol scale (R)-3-((triisopropylsilyl)oxy)butanoic acid[11a] with 4-(phenylsulfonyl)butanoic acid[11b] (3 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 16.6 mg (42%) of the title compound **14**. The spectroscopic data matched the literature[11c].

Physical State: colorless oil.

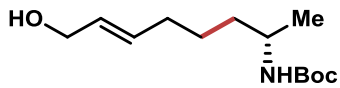
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94–7.87 (m, 2H), 7.69–7.63 (m, 1H), 7.60–7.55 (m, 2H), 3.89 (q, *J* = 5.6 Hz, 1H), 3.14–2.88 (m, 2H), 1.78–1.65 (m, 2H), 1.50–1.34 (m, 4H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.07–0.99 (m, 21H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.2, 133.6, 129.2, 128.0, 67.9, 56.4, 39.2, 23.9, 23.4, 22.9, 18.1, 12.4.

TLC: R_f = 0.3 (10:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -1.1 (c = 0.7, $CHCl_3$).

Compound 15'



***tert*-butyl (*S*,*E*)-(8-hydroxyoct-6-en-2-yl)carbamate (15').**

Following the **General Procedure B** on 0.1 mmol scale (E)-6-((tert-butyldimethylsilyl)oxy)hex-4-enoic acid[12a] with (*S*)-3-((*tert*-butoxycarbonyl)amino)butanoic acid (3 equiv). After completion of electrolysis, TBAF (1 N in THF, 1.2 mL) was added and then stir for another 12 h. Purification by flash column chromatography (3:1 hexanes:EtOAc) afforded 13.5 mg (56%) of the title compound **15'**. The spectroscopic data matched the literature[12b].

Physical State: colorless oil.

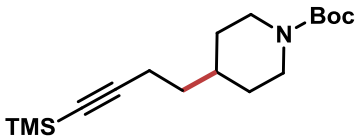
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.69–5.59 (m, 2H), 4.33 (br, 1H), 4.07 (d, *J* = 4.2 Hz, 2H), 3.64 (br, 1H), 2.10–1.98 (m, 2H), 1.72 (br, 1H), 1.47–1.31 (m, 13H), 1.09 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.3, 132.7, 129.4, 79.0, 63.6, 46.2, 36.7, 31.9, 28.4, 25.3, 21.2.

TLC: R_f = 0.3 (3:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +1.0 (c = 0.5, $CHCl_3$).

Compound 16



***tert*-Butyl 4-(4-(trimethylsilyl)but-3-yn-1-yl)piperidine-1-carboxylate (16).**

Following the **General Procedure A** on 0.1 mmol scale 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid[13a] with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (3 equiv). Purification by flash column chromatography (20:1 hexanes:EtOAc) afforded 12.7 mg (41%) of the title compound **16**. The spectroscopic data matched the literature[13b].

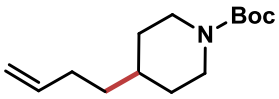
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.07 (br, 2H), 2.67 (t, *J* = 11.8 Hz, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.66 (d, *J* = 13.1 Hz, 2H), 1.55–1.45 (m, 3H), 1.45 (s, 9H), 1.08 (qd, *J* = 12.4, 4.3 Hz, 2H), 0.14 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): 154.9, 107.1, 84.7, 79.2, 43.7, 35.1, 35.0, 31.7, 28.5, 17.2, 0.1.

TLC: R_f = 0.2 (20:1 hexanes:EtOAc).

Compound 17



***tert*-Butyl 4-(but-3-en-1-yl)piperidine-1-carboxylate (17).**

Following the **General Procedure A** on 0.1 mmol scale 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid with pent-4-enoic acid (3 equiv). Purification by flash column chromatography (10:1 hexanes:EtOAc) afforded 14.3 mg (60%) of the title compound **17**. The spectroscopic data matched the literature[14].

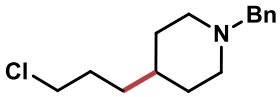
Physical State: colorless oil.

^{1}H NMR (600 MHz, DMSO-d_6): δ 5.79 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06–4.87 (m, 2H), 3.91 (br, 2H), 2.65 (br, 2H), 2.07–1.95 (m, 2H), 1.66–1.50 (m, 2H), 1.38 (s, 10H), 1.33–1.18 (m, 2H), 0.94 (qd, *J* = 12.5, 4.3 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 154.9, 138.8, 114.4, 79.1, 44.0, 35.6, 35.4, 32.1, 30.8, 28.5.

TLC: R_f = 0.4 (10:1 hexanes:EtOAc).

Compound 18



1-Benzyl-4-(3-chloropropyl)piperidine (18).

Following the **General Procedure A** on 0.1 mmol scale 1-benzylpiperidine-4-carboxylic acid with 4-chlorobutanoic acid (3 equiv). Purification by flash column chromatography (3:1 hexanes:EtOAc) afforded 9.4 mg (37%) of the title compound **18**. The spectroscopic data matched the literature[15].

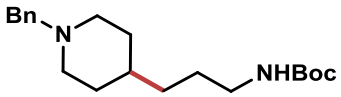
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.30 (m, 4H), 7.28 (t, *J* = 6.9 Hz, 1H), 3.58 (br, 2H), 3.51 (t, *J* = 6.8 Hz, 2H), 2.95 (d, *J* = 11.3 Hz, 2H), 2.03 (t, *J* = 11.7 Hz, 2H), 1.83–1.71 (m, 2H), 1.72–1.63 (m, 2H), 1.47–1.16 (m, 5H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.2, 129.6, 128.3, 127.4, 63.0, 53.5, 45.2, 34.9, 33.5, 31.6, 29.9.

TLC: R_f = 0.2 (3:1 hexanes:EtOAc).

Compound 19



***tert*-Butyl (3-(1-benzylpiperidin-4-yl)propyl)carbamate (19).**

Following the **General Procedure A** on 0.1 mmol scale 1-benzylpiperidine-4-carboxylic acid with 4-((tert-butoxycarbonyl)amino)butanoic acid (3 equiv). Purification by flash column chromatography (1:1 hexanes:EtOAc) afforded 14.2 mg (43%) of the title compound **19**. The spectroscopic data matched the literature[16].

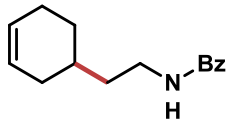
Physical State: colorless oil.

^{1}H NMR (600 MHz, Methanol-d_4):δ 7.35–7.23 (m, 5H), 3.50 (s, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 2.89 (d, *J* = 11.2 Hz, 2H), 2.00 (t, *J* = 11.7 Hz, 2H), 1.69 (d, *J* = 10.3 Hz, 2H), 1.53–1.36 (m, 11H), 1.32–1.17 (m, 5H).

^{13}C NMR (151 MHz, Methanol-d_4):δ 159.4, 139.1, 131.8, 130.1, 129.3, 80.6, 65.3, 55.6, 42.4, 37.4, 35.5, 33.8, 29.6, 29.0.

TLC: R_f = 0.3 (3:1 hexanes:EtOAc).

Compound 20



(*R*)-*N*-(2-(cyclohex-3-en-1-yl)ethyl)benzamide (20).

Following the **General Procedure A** on 0.1 mmol scale cyclohex-3-ene-1-carboxylic acid with 3-benzamidopropanoic acid (3 equiv). Purification by PTLC (4:1 hexanes:EtOAc) afforded 10.0 mg (44%) of the title compound **20**. The spectroscopic data matched the literature[17].

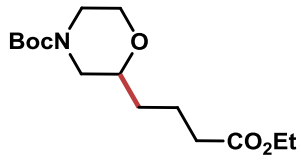
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79–7.68 (m, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 6.22 (s, 1H), 5.72–5.58 (m, 2H), 3.59–3.42 (m, 2H), 2.20–2.12 (m, 1H), 2.09–2.01 (m, 2H), 1.82–1.75 (m, 1H), 1.76–1.53 (m, 4H), 1.33–1.22 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$):δ 167.5, 134.7, 131.3, 128.5, 127.0, 126.8, 126.1, 37.9, 36.2, 31.6, 31.3, 28.7, 25.0.

TLC: R_f = 0.3 (4:1 hexanes:EtOAc).

Compound 21



***tert*-Butyl (*S*)-2-(4-ethoxy-4-oxobutyl)morpholine-4-carboxylate (21).**

Following the **General Procedure A** on 0.1 mmol scale 4-(tert-butoxycarbonyl)morpholine-2-carboxylic acid with 5-ethoxy-5-oxopentanoic acid (3 equiv). Purification by flash column chromatography (6:1 hexanes:EtOAc) afforded 12.6 mg (42%) of the title compound **21**. The NMR Spectrum is not available in the original literature[18]. Accordingly appropriate characterization was conducted and reported below.

Physical State: colorless oil.

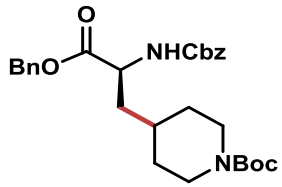
^{1}H NMR (600 MHz, $CDCl_3$):δ 4.12 (q, *J* = 7.1 Hz, 2H), 4.06–3.61 (m, 3H), 3.48 (td, *J* = 11.8, 2.8 Hz, 1H), 3.33 (q, *J* = 10.6, 8.5 Hz, 1H), 2.91 (br, 1H), 2.57 (br, 1H), 2.32 (td, *J* = 7.5, 2.3 Hz, 2H), 1.84–1.74 (m, 1H), 1.73–1.64 (m, 1H), 1.46 (s, 11H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.4, 154.7, 79.9, 75.2, 66.4, 60.3,49.0/47.0, 44.0/42.8, 34.1, 32.4, 28.4, 20.7, 14.2.

HRMS (ESI-TOF): calc'd for $C_{10}H_{20}NO_3$ $[M\text{-}Boc+H]^+$: 202.1443, found 202.1451.

TLC: R_f = 0.2 (6:1 hexanes:EtOAc).

Compound 22



***tert*-Butyl (*S*)-4-(3-(benzyloxy)-2-(((benzyloxy)carbonyl)amino)-3-oxopropyl)piperidine-1-carboxylate (22).**

Following the **General Procedure A** on 0.1 mmol scale (S)-4-(benzyloxy)-3-(((benzyloxy)carbonyl)amino)-4-oxobutanoic acid with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (3 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 20.3 mg (41%) of the title compound **22**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$):δ 7.40–7.247 (m, 10H), 5.32–4.98 (m, 5H), 4.54–4.41 (m, 1H), 4.02 (br, 2H), 2.56 (br, 2H), 1.76–1.65 (m, 2H), 1.58–1.51 (m, 2H), 1.49–1.40 (m, 10H), 1.12–1.00 (m, 2H).

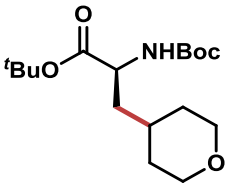
^{13}C NMR (151 MHz, $CDCl_3$):δ 172.6, 155.8, 154.7, 136.1, 135.1, 128.6, 128.5 (2C), 128.4, 128.2, 128.1, 79.3, 67.2, 67.0, 51.7, 43.7/39.6, 32.4, 32.1, 31.4, 28.4.

HRMS (ESI-TOF): calc'd for $C_{23}H_{29}N_2O_4$ $[M\text{-}Boc+H]^+$: 397.2127, found 397.2131.

TLC: R_f = 0.3 (3:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -7.6 (c = 1.0, $CHCl_3$).

Compound 23



***tert*-Butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(tetrahydro-2*H*-pyran-4-yl)propanoate (23).**

Following the **General Procedure A** on 0.1 mmol scale (S)-4-(tert-butoxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoic acid with tetrahydro-2H-pyran-4-carboxylic acid (3 equiv). Purification by flash column chromatography (4:1 hexanes:EtOAc) afforded 14.9 mg (45%) of the title compound **23**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.97–4.88/4.70–4.58 (2m, 1H), 4.26–4.17/4.07–3.98 (2m, 1H), 3.97–3.91 (m, 2H), 3.39–3.30 (m, 2H), 1.77–1.55 (m, 4H), 1.46 (s, 9H), 1.44 (s, 9H), 1.38–1.23 (m, 3H).

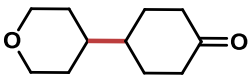
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.5, 155.6, 82.0, 79.9, 68.1/68.0, 51.7/40.4, 33.3, 32.7, 31.9, 28.5, 28.1.

HRMS (ESI-TOF): calc'd for $C_{17}H_{32}NO_5$ $[M+H]^+$: 330.2280, found 330.2275.

TLC: R_f = 0.2 (4:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -0.4 (c = 0.7, $CHCl_3$).

Compound 24



4-(Tetrahydro-2*H*-pyran-4-yl)cyclohexan-1-one (24).

Following the **General Procedure A** on 0.1 mmol scale 4-oxocyclohexane-1-carboxylic acid with tetrahydro-2*H*-pyran-4-carboxylic acid (3 equiv). Purification by flash column chromatography (4:1 hexanes:EtOAc) afforded 8.8 mg (48%) of the title compound **24**. The spectroscopic data matched the literature[19].

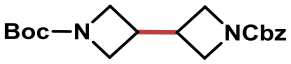
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$):δ 4.01 (dd, *J* = 11.4, 4.0 Hz, 2H), 3.37 (td, *J* = 11.5, 1.9 Hz, 2H), 2.45–2.37 (m, 2H), 2.32 (td, *J* = 13.8, 5.9 Hz, 2H), 2.08 (ddd, *J* = 13.1, 6.2, 3.1 Hz, 2H), 1.67–1.51 (m, 4H), 1.49–1.34 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$):δ 212.0, 68.2, 41.2, 40.8, 39.3, 30.5, 29.5.

TLC: R_f = 0.2 (4:1 hexanes:EtOAc).

Compound 25



***tert*-Butyl [3,3'-biazetidine]-1-carboxylate (25).**

Following the **General Procedure A** on 0.1 mmol scale 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid with 1-((benzyloxy)carbonyl)azetidine-3-carboxylic acid (3 equiv). Purification by PTLC (1:1 hexanes:EtOAc) afforded 13.7 mg (40%) of the title compound **25**.

Physical State: colorless oil.

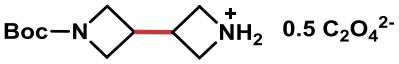
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.32 (m, 4H), 7.33–7.29 (m, 1H), 5.09 (s, 2H), 4.11 (t, *J* = 8.5 Hz, 2H), 4.02 (t, *J* = 8.5 Hz, 2H), 3.68 (dd, *J* = 8.7, 5.0 Hz, 2H), 3.59 (dd, *J* = 8.8, 5.1 Hz, 2H), 2.87–2.73 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.3, 156.2, 136.5, 128.5, 128.0 (2C), 79.6, 66.7, 52.1, 51.7, 31.4, 30.9, 28.3.

HRMS (ESI-TOF): calc'd for $C_{14}H_{19}N_2O_2$ $[M\text{-Boc}+H]^+$: 247.1447, found 247.1458.

TLC: R_f = 0.4 (1:1 hexanes:EtOAc).

Compound 25'



***tert*-Butyl [3,3'-biazetidine]-1-carboxylate (25').**

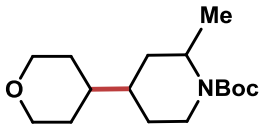
To a solution of *tert*-Butyl [3,3'-biazetidine]-1-carboxylate (**25**) (30 mg, 0.085 mmol) in MeOH (1.5 mL) was added 10% Pd/C (6 mg) and $H_2C_2O_4$ (3.9 mg, 0.043 mmol). The mixture was hydrogenated at 1 atm and rt for 12 h. Then the catalyst was filtered off and washed with MeOH (5 mL); the filtrate was evaporated under reduced pressure to give 21.0 mg (93%) of the title compound **25'**. The spectroscopic data matched the literature[20].

Physical State: white solid.

^{1}H NMR (600 MHz, D_2O): δ 4.25–4.16 (m, 2H), 4.10 (t, *J* = 8.9 Hz, 2H), 3.95–3.86 (m, 2H), 3.64 (t, *J* = 7.2 Hz, 2H) 3.30 (sext, J = 8.2 Hz, 1H), 2.96–2.91 (m, 1H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, D_2O): δ 169.3, 158.0, 81.8, 51.6, 49.2, 34.0, 29.9, 27.6.

Compound 26



***tert*-Butyl (2*S*,4*R*)-2-methyl-4-(tetrahydro-2*H*-pyran-4-yl)piperidine-1-carboxylate (26).**

Following the **General Procedure A** on 0.1 mmol scale 1-(tert-butoxycarbonyl)-2-methylpiperidine-4-carboxylic acid with tetrahydro-2*H*-pyran-4-carboxylic acid (3 equiv). Purification by flash column chromatography (4:1 hexanes:EtOAc) afforded 9.7 mg (34%) of the title compound **26**.

Physical State: colorless oil.

The NMR spectra presented as a mixture of diastereoisomers and rotamers:

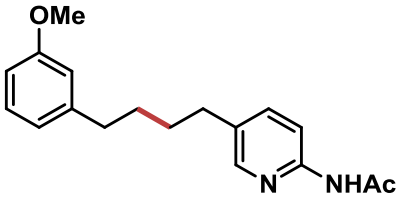
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.55–4.30 (m, *J* = 77.9 Hz, 0.7H), 4.08–3.87 (m, 2.7H), 3.81 (dt, *J* = 10.4, 6.3 Hz, 0.3H), 3.73 (ddd, *J* = 13.8, 7.6, 2.7 Hz, 0.3H), 3.34 (td, *J* = 11.7, 2.2 Hz, 2H), 2.99 (ddd, *J* = 13.9, 10.4, 6.2 Hz, 0.3H), 2.90–2.70 (m, 0.7H), 1.90–1.83 (m, 0.3H), 1.76–1.52 (m, 4.7H), 1.45 (d, *J* = 1.6 Hz, 9H), 1.35–1.22 (m, 5H), 1.16 (d, *J* = 6.3 Hz, 0.9H), 1.11 (d, *J* = 6.9 Hz, 2.1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.4, 79.3, 79.2, 68.4, 68.41, 68.36, 49.9, 46.8, 45.7, 40.3, 40.00, 39.2, 38.3, 37.1, 37.0, 35.3, 34.0, 32.8, 30.7, 30.41, 30.36, 30.3, 29.3, 28.7, 28.6, 26.9, 20.1, 16.5.

HRMS (ESI-TOF): calc'd for $C_{11}H_{22}NO$ $[M\text{-}Boc+H]^+$: 184.1701, found 184.1712.

TLC: R_f = 0.3 (4:1 hexanes:EtOAc).

Compound 27



N-(5-(4-(3-methoxyphenyl)butyl)pyridin-2-yl)acetamide (27).

Following the **General Procedure B** on 0.1 mmol scale 3-(6-acetamidopyridin-3-yl)propanoic acid **SI-4** with 3-(3-methoxyphenyl)propanoic acid (3 equiv). Purification by PTLC (1:1 hexanes:EtOAc) afforded 17.4 mg (58%) of the title compound **27**. The

spectroscopic data matched the literature[21].

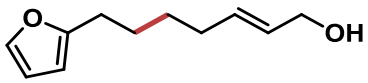
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$):δ 8.42 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.78–6.64 (m, 3H), 3.79 (s, 3H), 2.69–2.51 (m, 4H), 2.18 (s, 3H), 1.70–1.58 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.5, 159.6, 149.5, 147.1, 143.9, 138.3, 133.7, 129.2, 120.8, 114.2, 113.7, 110.9, 55.1, 35.7, 32.2, 30.7 (2C), 24.6.

TLC: R_f = 0.2 (1:1 hexanes:EtOAc).

Compound 28'



(E)-7-(furan-2-yl)hept-2-en-1-ol (28').

Following the **General Procedure B** on 0.1 mmol scale (E)-6-((tert-butyldimethylsilyl)oxy)hex-4-enoic acid[12a] with 3-(furan-2-yl)propanoic acid (3 equiv). After completion of electrolysis, TBAF (1 N in THF, 1.2 mL) was added and then stir for another 12 h. Purification by flash column chromatography (6:1 hexanes:EtOAc) afforded 8.6 mg (48%) of the title compound **28'**. The spectroscopic data matched the literature[22].

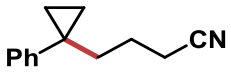
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 1.7 Hz, 1H), 6.27 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.97 (d, *J* = 3.0 Hz, 1H), 5.78–5.56 (m, 2H), 4.08 (d, *J* = 5.4 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.65 (p, *J* = 7.5 Hz, 2H), 1.44 (p, *J* = 7.5 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.2, 140.7, 133.0, 129.1, 110.0, 104.7, 63.8, 31.9 , 28.6, 27.8, 27.5.

TLC: R_f = 0.2 (6:1 hexanes:EtOAc).

Compound 29



4-(1-phenylcyclopropyl)butanenitrile (29).

Following the **General Procedure A** on 0.1 mmol scale 1-phenylcyclopropane-1-carboxylic acid with 4-cyanobutanoic acid (3 equiv). Purification by PTLC (10:1 hexanes:EtOAc)

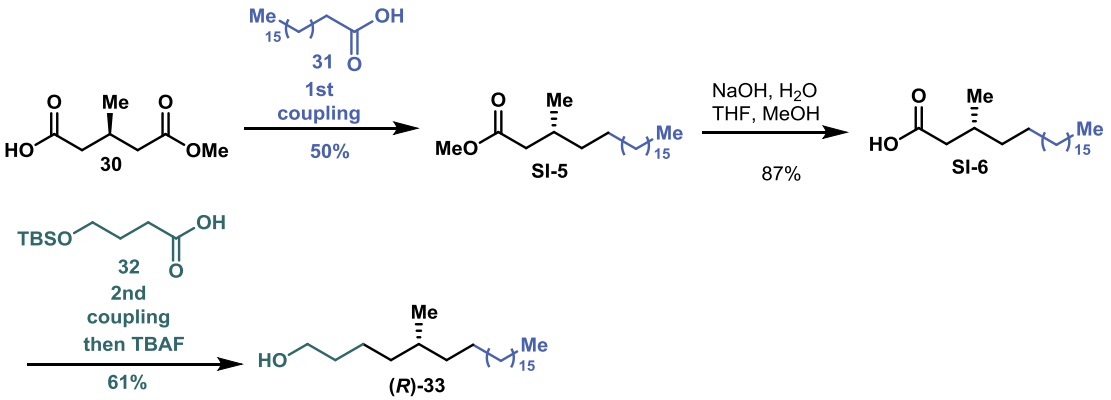
afforded 9.8 mg (53%) of the title compound **29**. The spectroscopic data matched the literature[23].

Physical State: colorless oil.

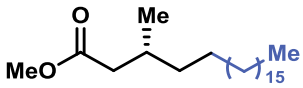
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.26 (m, 4H), 7.23–7.18 (m, 1H), 2.27 (t, *J* = 7.0 Hz, 2H), 1.75–1.67 (m, 2H), 1.68–1.59 (m, 2H), 0.87–0.80 (m, 2H), 0.76–0.65 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.1, 128.9, 128.3, 126.3, 119.7, 39.2, 25.0, 23.3, 17.0, 12.8.

TLC: R_f = 0.5 (10:1 hexanes:EtOAc).



Compound SI-5



4-(1-phenylcyclopropyl)butanenitrile (SI-5).

Following the **General Procedure B** on 0.1 mmol scale (R)-5-methoxy-3-methyl-5-oxopentanoic acid with stearic acid (3 equiv), set the temperature at 80 °C. Purification by flash column chromatography (40:1 hexanes:EtOAc) afforded 17.6 mg (50%) of the title compound **SI-5**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.30 (dd, *J* = 14.7, 6.0 Hz, 1H), 2.10 (dd, *J* = 14.7, 8.2 Hz, 1H), 1.98 – 1.88 (m,1H), 1.25 (m, 34H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H).

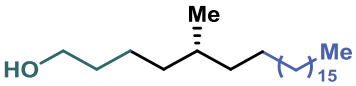
^{13}C NMR (151 MHz, $CDCl_3$): δ ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.8 , 51.3 , 41.7 , 36.7 , 31.9 , 30.3 , 29.7 (4C) 29.6 (2C) , 29.4 , 26.9 , 22.7 , 19.7 , 14.1 .

GC/MS (EI): m/z 354 (0.6%), 323 (0.4%), 157 (7%), 101 (100%), 74 (60%).

TLC: R_f = 0.3 (40:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +2.5 (c = 1.0, $CHCl_3$).

Compound (*R*)-33



5-methyltricosan-1-ol (*R*-33).

To a solution of **SI-10** (53 mg, 0.15 mmol) inTHF/MeOH (0.4 mL/0.25 mL) was added 2 N NaOH (0.25 mL). Then the mixture stir for another 2 h at 50 °C. The mixture was acidified with 1N HCl (pH 2–4). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **SI-6** as a white solid (44.2 mg, 87%) and directly used without further purification.

Following the **General Procedure B** on 0.1 mmol scale **SI-6** with 4-((tert-butyldimethylsilyl)oxy)butanoic acid[9a] (3 equiv), set the temperature at 80 °C. After completion of electrolysis, TBAF (1 N in THF, 1.2 mL) was added and then stir at rt for another 12 h. Purification by flash column chromatography (10:1 hexanes:EtOAc) afforded 20.2 mg (57%) of the title compound **(*R*)-33**. The spectroscopic data matched the literature[24].

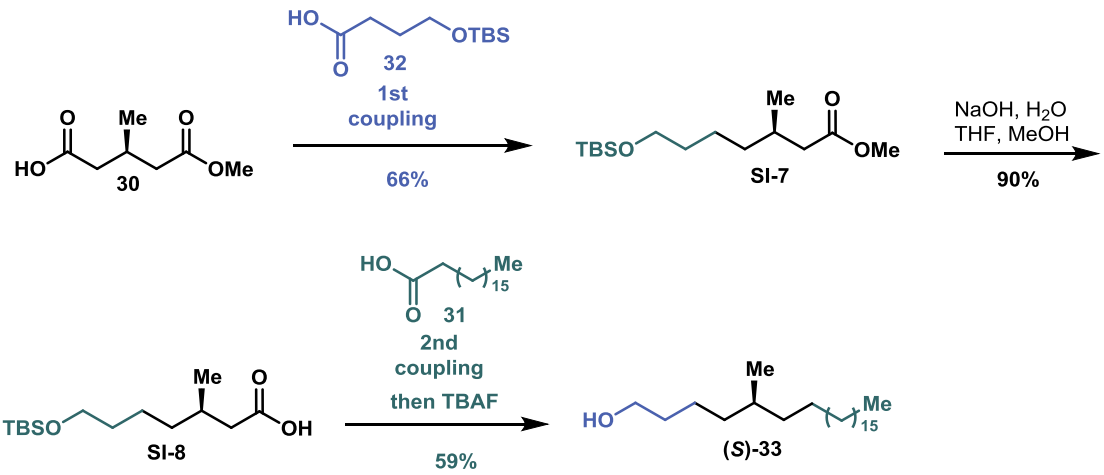
Physical State: White solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.64 (t, *J* = 6.7 Hz, 2H), 1.60–1.50 (m, 2H), 1.45–1.06 (m, 39H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

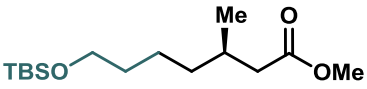
^{13}C NMR (151 MHz, $CDCl_3$): δ 63.1, 37.0, 36.8, 33.2, 32.7, 31.9, 30.0, 29.7 (3C), 29.4, 27.1, 23.2, 22.7, 19.6, 14.1.

TLC: R_f = 0.3 (10:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +1.5 (c = 1.0, ether).



Compound SI-7



4-(1-phenylcyclopropyl)butanenitrile (SI-7).

Following the **General Procedure B** on 0.1 mmol scale (R)-5-methoxy-3-methyl-5-oxopentanoic acid with 4-((tert-butyldimethylsilyl)oxy)butanoic acid[9a] (3 equiv). Purification by flash column chromatography (40:1 hexanes:EtOAc) afforded 19.1 mg (66%) of the title compound **SI-7**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.30 (dd, *J* = 14.7, 6.0 Hz, 1H), 2.11 (dd, *J* = 14.7, 8.2 Hz, 1H), 2.00–1.85 (m, 1H), 1.55–1.45 (m, 2H), 1.41–1.24 (m, 3H), 1.24 – 1.16 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

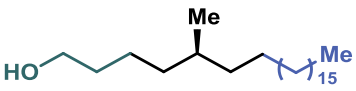
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.8, 63.1, 51.3, 41.6, 36.5, 32.9, 30.3, 26.0, 23.1, 19.7, 18.3, -5.3.

HRMS (ESI-TOF): calc'd for $C_{15}H_{33}O_3Si$ $[M+H]^+$: 289.2199, found 289.2203.

TLC: R_f = 0.2 (3:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +3.1 (c = 1.0, $CHCl_3$).

Compound (*S*)-33



5-methyltricosan-1-ol (*S*)-33

To a solution of **SI-7** (43 mg, 0.15 mmol) inTHF/MeOH (0.4 mL/0.25 mL) was added 2 N

NaOH (0.25 mL). Then the mixture stir for another 2 h at 50 ^{o}C. The mixture was acidified with 1N HCl (pH 2–4). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **SI-8** as a colorless oil (36.6 mg, 90%) and directly used without further purification.

Following the **General Procedure** on 0.1 mmol scale **SI-8** with stearic acid (3 equiv), set the temperature at 80 ^{o}C. After completion of electrolysis, TBAF (1 N in THF, 1.2 mL) was added and then stir at rt for another 12 h. Purification by flash column chromatography (10:1 hexanes:EtOAc) afforded 20.9 mg (59%) of the title compound **(*S*)-33**. The spectroscopic data matched the literature[24].

Physical State: white solid.

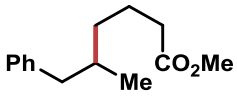
^{1}H NMR (600 MHz, $CDCl_3$): δ ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.64 (t, *J* = 6.6 Hz, 2H), 1.60–1.50 (m, 2H), 1.44–1.05 (m, 39H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 63.1, 37.0, 36.8, 33.2, 32.7, 31.9, 30.0, 29.7 (3C), 29.4, 27.1 , 23.2, 22.7, 19.6, 14.1.

TLC: R_f = 0.3 (10:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = -0.5 (c = 1.0, ether).

Compound 34



Methyl 5-methyl-6-phenylhexanoate (34).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 5-methoxy-5-oxopentanoic acid (1.5 equiv). Purification by PTLC (20:1 hexanes:EtOAc)afforded 15.6 mg (71%) of the title compound **34**. The NMR Spectrum of compound **30** is not available in the original literature.[25] Accordingly appropriate characterization was conducted and reported below.

Physical State: colorless oil.

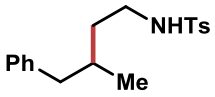
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.21–7.16 (m, 1H), 7.16–7.11 (m, 2H), 3.66 (s, 3H), 2.63 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.38 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.29 (ddd, *J* = 8.2, 6.9, 4.2 Hz, 2H), 1.81–1.66 (m, 2H), 1.69 – 1.55 (m, 1H), 1.40–1.33 (m, 1H), 1.23–1.11 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.2, 141.2, 129.1, 128.1, 125.7, 51.4, 43.5, 36.0, 34.8, 34.3, 22.5, 19.2.

GC/MS (EI): m/z 220 (1%), 129 (50%), 91 (100%), 69 (79%).

TLC: R_f = 0.3 (20:1 hexanes:EtOAc)

Compound 35



4-methyl-N-(3-methyl-4-phenylbutyl)benzenesulfonamide (35).

Following the **General Procedure A** on 0.1 mmol scale 2-methyl-3-phenylpropanoic acid with 3-((4-methylphenyl)sulfonamido)propanoic acid (1.5 equiv). Purification by PTLC (4:1 hexanes:EtOAc) afforded 16.8 mg (53%) of the title compound **35**. The spectroscopic data matched the literature[26].

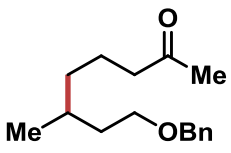
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77–7.65 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.27–7.22 (m, 2H), 7.21–7.15 (m, 1H), 7.09–7.03 (m, 2H), 4.45 (t, *J* = 6.1 Hz, 1H), 3.00 (dq, *J* = 8.5, 6.1 Hz, 1H), 2.93 (ddd, *J* = 12.3, 8.2, 6.3 Hz, 1H), 2.52 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.43 (s, 3H), 2.37 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.76 (dddd, *J* = 8.2, 6.7, 5.2, 1.5 Hz, 1H), 1.56–1.44 (m, 1H), 1.29 (dtd, *J* = 13.8, 8.2, 5.7 Hz, 1H), 0.81 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.3, 140.5, 136.9, 129.7, 129.1, 128.2, 127.1, 125.9, 43.3, 41.2, 36.1, 32.3, 21.5, 19.1.

TLC: R_f = 0.2 (4:1 hexanes:EtOAc)

Compound 36



8-(benzyloxy)-6-methyloctan-2-one (36).

Following the **General Procedure A** on 0.1 mmol scale 4-(benzyloxy)-2-methylbutanoic acid with 5-oxohexanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 18.3 mg (74%) of the title compound **36**. The NMR Spectrum of compound **36** is not

available in the original literature.[27] Accordingly appropriate characterization was conducted and reported below.

Physical State: colorless oil.

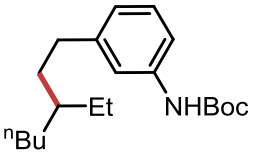
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.30 (m, 4H),, 7.30–7.26 (m, 1H), 4.49 (s, 2H), 3.58–3.38 (m, 2H), 2.39 (ddd, *J* = 8.0, 6.7, 2.9 Hz, 2H), 2.12 (s, 3H), 1.75–1.47 (m, 4H), 1.49–1.37 (m, 1H), 1.29 (ddt, *J* = 13.3, 10.9, 5.4 Hz, 1H), 1.12 (dddd, *J* = 13.2, 10.7, 7.8, 5.3 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.1, 138.6, 128.3, 127.6, 127.4, 72.9, 68.5, 43.9, 36.6, 36.4, 29.8, 29.7, 21.2, 19.4.

HRMS (ESI-TOF): calc'd for $C_{16}H_{24}O_2Na$ $[M+Na]^+$: 271.1674 , found 271.1676.

TLC: R_f = 0.3 (10:1 hexanes:EtOAc)

Compound 37



tert-butyl (S)-(3-(3-ethylheptyl)phenyl)carbamate (37).

Following the **General Procedure A** on 0.1 mmol scale 2-ethylhexanoic acid with 3-(3-((tert-butoxycarbonyl)amino)phenyl)propanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 21.4 mg (67%) of the title compound **37**. The spectroscopic data matched the literature[28]

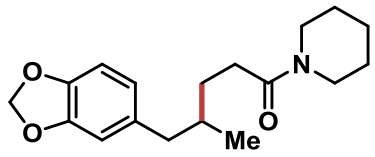
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 (br, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.48 (s, 1H), 2.67–2.40 (m, 2H), 1.60–1.46 (m, 11H), 1.40–1.21 (m, 9H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.7, 144.4, 138.2, 128.8, 123.1, 118.4, 115.8, 80.3, 38.6, 35.2, 33.2, 32.7, 28.9, 28.3, 25.7, 23.1, 14.1, 10.8.

TLC: R_f = 0.2 (10:1 hexanes:EtOAc).

Compound 38



5-(benzo[d][1,3]dioxol-5-yl)-4-methyl-1-(piperidin-1-yl)pentan-1-one (38).

Following the **General Procedure A** on 0.1 mmol scale 3-(benzo[*d*][1,3]dioxol-5-yl)-2-methylpropanoic acid with 4-oxo-4-(piperidin-1-yl)butanoic acid (1.5 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 17.2 mg (57%) of the title compound **38**. The NMR Spectrum of compound **38** is not available in the original literature.[29] Accordingly appropriate characterization was conducted and reported below.

Physical State: colorless oil.

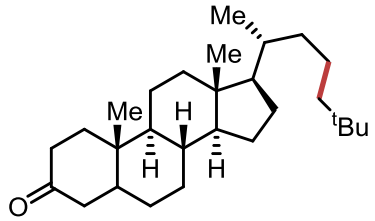
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.70 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.58 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.90 (s, 2H), 3.52 (td, *J* = 5.4, 3.1 Hz, 2H), 3.33 (t, *J* = 5.6 Hz, 2H), 2.55 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.41–2.31 (m, 2H), 2.26 (ddd, *J* = 14.7, 10.5, 5.6 Hz, 1H), 1.76–1.65 (m, 2H), 1.64–1.58 (m, 2H), 1.54–1.47 (m, 4H), 1.46–1.40 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.4, 147.4, 145.5, 134.9, 121.9, 109.4, 107.9, 100.7, 46.7, 43.3, 42.6, 35.0, 32.0/31.3, 26.5/25.5, 24.6, 19.2.

HRMS (ESI-TOF): calc'd for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1913 , found 304.1916.

TLC: R_f = 0.2 (3:1 hexanes:EtOAc)

Compound 39



(8R,9S,10S,13R,14S,17R)-17-((R)-6,6-dimethylheptan-2-yl)-10,13-dimethylhexadecahydro-3H-cyclopenta[a]phenanthren-3-one (39).

Following the **General Procedure A** on 0.1 mmol scale 3,3-dimethylbutanoic acid with (4R)-4-((8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3-oxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 21.6 mg (54%) of the title compound **39**. The spectroscopic data matched the literature[30]

Physical State: white solid.

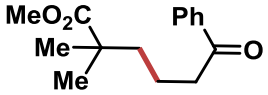
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.69 (t, *J* = 15.0 Hz, 1H), 2.33 (td, *J* = 14.6, 5.4 Hz, 1H), 2.15 (ddt, *J* = 14.6, 4.1, 2.8 Hz, 1H), 2.07–1.97 (m, 3H), 1.94–1.73 (m, 3H), 1.61–1.55 (m, 1H), 1.53–1.03 (m, 19H), 1.01 (s, 3H), 1.00–0.94 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.68 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 213.4, 56.5, 56.4, 44.7, 44.3, 42.7, 42.4, 40.7, 40.1, 37.2, 37.0, 36.8, 35.8, 35.5, 34.9, 30.4, 29.5, 28.3, 26.6, 25.8, 24.2, 22.7, 21.2, 21.0, 18.7, 12.1.

TLC: R_f = 0.5 (10:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = +35.3 (c = 0.45, $CHCl_3$).

Compound 40



Methyl 2,2-dimethyl-6-oxo-6-phenylhexanoate (40).

Following the **General Procedure A** on 0.1 mmol scale 4-methoxy-3,3-dimethyl-4-oxobutanoic acid with 4-oxo-4-phenylbutanoic acid (1.5 equiv). Purification by PTLC (10:1 hexanes:EtOAc) afforded 11.4 mg (46%) of the title compound **40**. The spectroscopic data matched the literature[31]

Physical State: colorless oil.

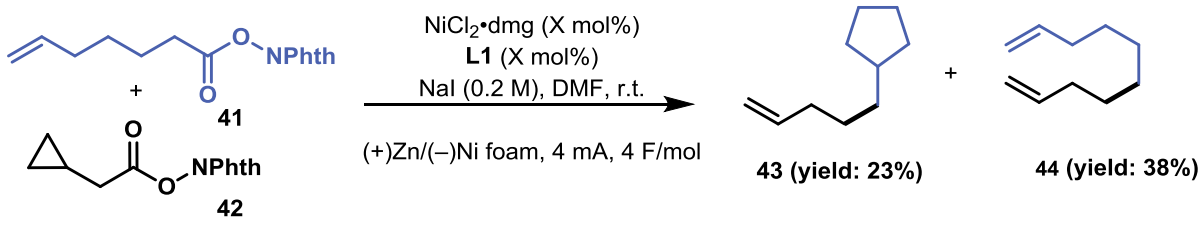
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99–7.89 (m, 2H), 7.59–7.52 (m, 1H), 7.48–7.42 (m, 2H), 3.65 (s, 3H), 2.95 (t, *J* = 7.0 Hz, 2H), 1.73–1.65 (m, 2H), 1.62–1.57 (m, 2H), 1.20 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 199.9, 178.3, 136.9, 132.9, 128.6, 128.0, 51.7, 42.3, 40.2, 38.8, 25.1, 19.8.

TLC: R_f = 0.3 (10:1 hexanes:EtOAc)

Mechanistic Study

A. Experimental procedures and characterization data for radical clock experiments



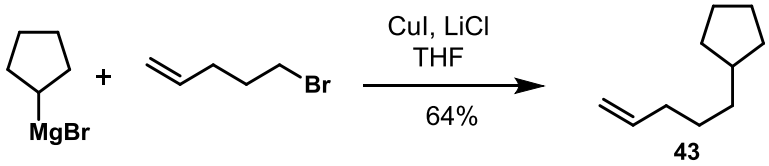
Entry	X	Yield 43	Yield 44
1	5	17%	7%
2	10	25%	41%
3	20	23%	38%
4	30	16%	41%

*Note: the yields are based on GC analysis.

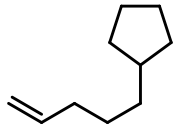
The following experimental procedure was employed for entry 4, and other entries were also performed by following the same procedure by varying Ni and ligand loading.

An ElectraSyn vial (5 mL) with a stir bar was charged with RAE **41**[32] (27.3 mg, 0.1 mmol), RAE **42**[33] (73.5 mg, 0.3 mmol), NaI (0.6 mmol, 89.9 mg), $NiCl_2$•dme (20 mol %, 4.4 mg), 2,2':6',2"-terpyridine **L1** (20 mol %, 4.8 mg), anhydrous DMF (3.0 mL) was then added. An ElectraSyn vial cap equipped with anode (Zn) and cathode (Ni foam) were inserted into the mixture after which all the contents were degassed via an argon balloon for roughly 60 seconds. The reaction mixture was electrolyzed under a constant current of 4 mA for 4 F/mol. The yields of compound **43** and compound **44** were determined by GC-MS, decane as the internal standard

The formation of compound **44** was confirmed by comparing the GC retention time with the same compound obtained from commercial source. The formation of **43** was confirmed by comparing the GC retention time with an authentic sample synthesized as follows;



Compound 43



pent-4-en-1-ylcyclopentane (43).

To a solutiuon of LiCl (1.00 g, 24 mmol) in THF (30 mL) was added :Cyclopentylmagnesium bromide (1.6 M in THF, 7.5 mL, 12 mmol), CuI (0.68g, 3.6 mmol) and 5-bromopent-1-ene (1.5 mL, 12 mmol). The mixture was stirred at rt for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with pentane as the eluent to give **43** (1.06 g, 64%).

Physical State: colorless oil.

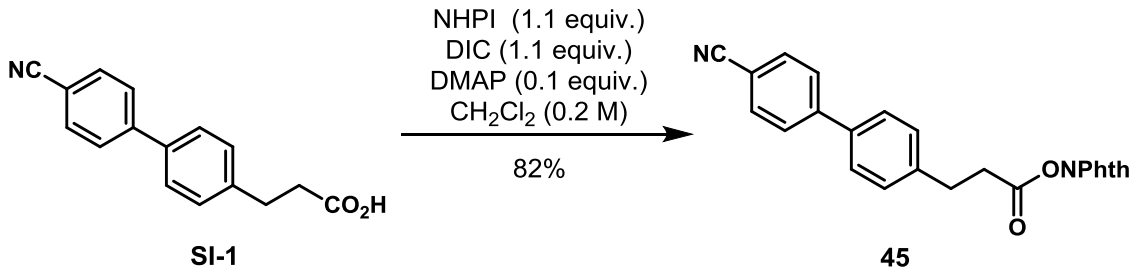
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.90–5.74 (m, 1H), 5.06–4.84 (m, 2H), 2.04 (q, *J* = 7.2 Hz, 2H), 1.78–1.68 (m, 3H), 1.63–1.54 (m, 2H), 151–1.45 (m, 2H), 1.43–1.36 (m, 2H), 1.30 (dt, *J* = 10.9, 6.3 Hz, 2H), 1.18–1.03 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.3, 114.1, 40.1, 35.7, 34.1, 32.7, 28.1, 25.2.

GC/MS (EI): m/z 138 (1%), 95 (50%), 82 (48%), 67 (100%).

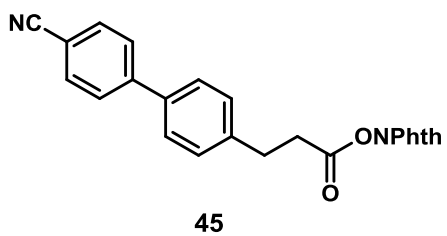
TLC: R_f = 0.9 (pentane).

B. Experimental procedures and characterization data for comparison with photochemical conditions



SI-1 **45**

Compound 45



45

1,3-dioxoisoindolin-2-yl 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoate (45).

To a solution of carboxylic acid **SI-1**, *N*-hydroxyphthalimideor (1.1 equiv) and DMAP (0.1 equiv) in CH_2Cl_2 (0.2 M) was added DIC (1.1 equiv). The mixture was allowed to stir until the acid was totally consumed (determined by TLC). The mixture was filtered and rinsed with additional CH_2Cl_2. Solvents were removed under reduced pressure, and purification of the crude mixture by flash column chromatography on silica gel with EtOAc/hexane (1:4) as the eluent to the title compound **45** (1.17 g, 82%).

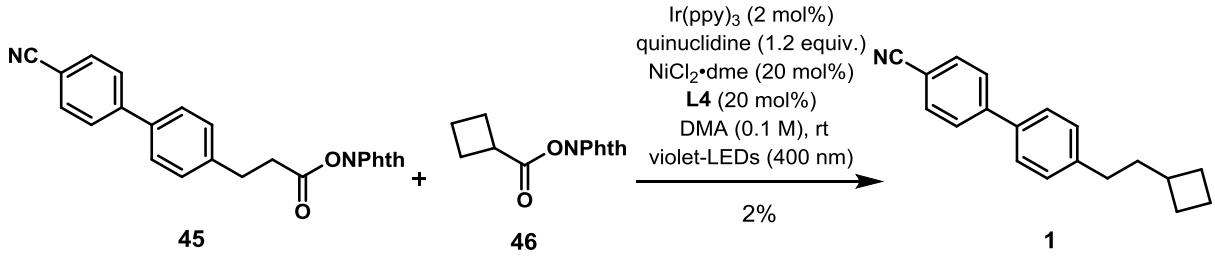
Physical State: white solid.

^{1}H NMR (600 MHz, $CDCl_3$):δ 7.91–7.87 (m, 2H), 7.82–7.77 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 3.16 (t, *J* = 7.7 Hz, 2H), 3.03 (t, *J* = 7.7 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.7, 161.8, 145.3, 139.8, 137.6, 134.8, 132.6, 129.1, 128.8, 127.6, 127.5, 124.0, 118.9, 110.8, 32.5, 30.1 .

HRMS (ESI-TOF): calc'd for $C_{24}H_{17}N_2O_4$ $[M+H]^+$: 397.1188, found 397.1195.

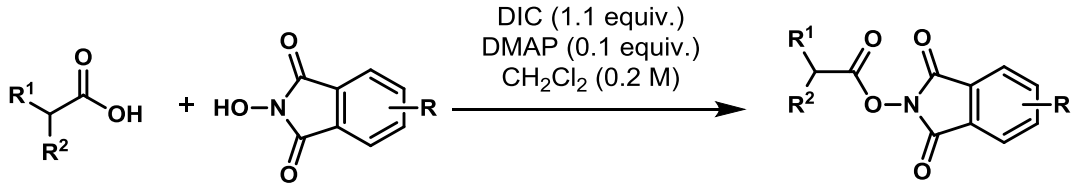
TLC: R_f = 0.2 (4:1 hexanes:EtOAc).



The reaction was prepared inside a nitrogen-filled glove-box (<1 ppm of O_2): An 8 mL borosilicate glass vial was charged with $Ir(ppy)_3$ (1.2 mg, 0.02 equiv), $NiCl_2$ diglyme (1.0 mg, 0.05 equiv), ligand (**L4**) (1.6 mg, 0.06 equiv), **45** (36 mg, 0.09 mmol, 1.0 equiv), **46**[34] (67 mg, 0.27 mmol, 3.0 equiv), quinuclidine (12.20 mg, 1.2 equiv.), and DMA (0.92 mL, 0.1 M). The vial was sealed, wrapped with parafilm tape, taken out of the glove-box and irradiated with a 400 nm (violet LED light, 72 W) photoreactor. The temperature was kept to be below 30 ^oC with cooling fan. The reaction was allowed to stir overnight (18 hours). The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 N) was then added. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by preparative thin layer chromatography (PTLC) to furnish the product **1** (0.5 mg, 2%).

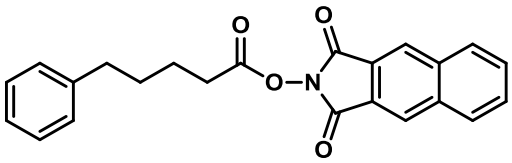
C. Experimental procedures and characterization data for comparison with other electrophiles

General procedure for the synthesis of NHPI Redox-Active Esters



To a solution of carboxylic acid, *N*-hydroxyphthalimideor its analogues (1.1 equiv) and DMAP (0.1 equiv) in CH_2Cl_2 (0.2 M) was added DIC (1.1 equiv). The mixture was allowed to stir until the acid was totally consumed (determined by TLC). The mixture was filtered and rinsed with additional CH_2Cl_2. Solvents were removed under reduced pressure, and purification of the crude mixture by column chromatography afforded the desired NHPI redox-active ester.

Compound SI-9



1,3-dioxoisoindolin-2-yl 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoate (SI-9).

Following the **General Procedure** on a 10 mmol scale with 5-phenylpentanoic acid and 2-hydroxy-1H-benzo[f]isoindole-1,3(2H)-dione[35]. Purification by flash column chromatography on silica gel with hexane/EtOAc/CH_2Cl_2 (5:1:1) as the eluent to the title compound **SI-9** (2.68 g, 72%).

Physical State: white solid.

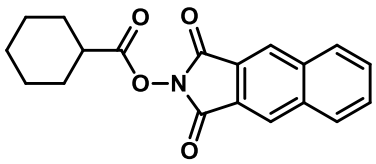
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 (s, 2H), 8.10–8.04 (m, 2H), 7.76–7.71 (m, 2H), 7.32–7.27 (m, 2H), 7.23–7.17 (m, 3H), 2.75–2.65 (m, 4H), 1.89–1.77 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.3, 161.5, 141.7, 135.4, 130.4, 129.7, 128.4, 128.4, 125.9, 125.8, 124.4, 35.4, 30.9, 30.4, 24.2 .

HRMS (ESI-TOF): calc'd for $C_{23}H_{20}NO_4$ $[M+H]^+$: 374.1392, found 374.1390.

TLC: R_f = 0.4 (5:1:1 hexane/EtOAc/CH_2Cl_2).

Compound SI-10



1,3-dioxoisoindolin-2-yl 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoate (SI-10).

Following the **General Procedure** on a 10 mmol scale with cyclohexanecarboxylic acid and 2-hydroxy-1H-benzo[f]isoindole-1,3(2H)-dione[35]. Purification by flash column chromatography on silica gel with hexane/EtOAc/CH_2Cl_2 (5:1:1) as the eluent to the title compound **SI-10** (2.26 g, 70%).

Physical State: white solid.

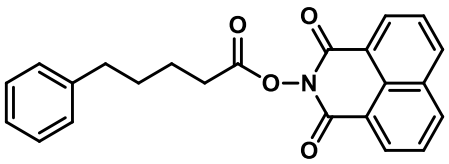
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.34 (s, 2H), 8.11–7.96 (m, 2H), 7.77–7.67 (m, 2H), 2.76 (tt, *J* = 11.0, 3.7 Hz, 1H), 2.20–2.03 (m, 2H), 1.88–1.80 (m, 2H), 1.72–1.65 (m, 3H), 1.52–1.22 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.6, 161.6, 135.4, 130.3, 129.6, 125.6, 124.4, 40.5, 28.8, 25.5, 25.0.

HRMS (ESI-TOF): calc'd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1236, found 324.1243.

TLC: R_f = 0.4 (5:1:1 hexane/EtOAc/CH_2Cl_2).

Compound SI-11



1,3-dioxoisoindolin-2-yl 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoate (SI-11).

Following the **General Procedure** on a 10 mmol scale with 5-phenylpentanoic acid and 2-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione[35]. Purification by flash column chromatography on silica gel with hexane/EtOAc/CH_2Cl_2 (5:1:1) as the eluent to the title compound **SI-11** (2.80 g, 75%).

Physical State: white solid.

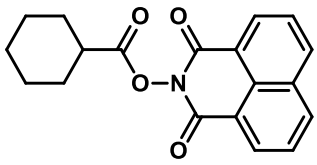
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.25 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.76 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.25–7.16 (m, 3H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 1.99–1.79 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5, 159.5, 141.9, 134.9, 131.9, 131.8, 128.4, 128.3, 127.5, 127.0, 125.8, 122.3, 35.4, 31.1, 30.5, 24.3.

HRMS (ESI-TOF): calc'd for $C_{23}H_{20}NO_4$ $[M+H]^+$: 374.1392, found 374.1396.

TLC: R_f = 0.3 (5:1:1 hexane/EtOAc/CH_2Cl_2).

Compound SI-12



1,3-dioxoisoindolin-2-yl 3-(4'-cyano-[1,1'-biphenyl]-4-yl)propanoate (SI-12).

Following the **General Procedure** on a 10 mmol scale with cyclohexanecarboxylic acid and 2-hydroxy-1H-benzo[de]isoquinoline-1,3(2H)-dione[35]. Purification by flash column chromatography on silica gel with hexane/EtOAc/CH_2Cl_2 (5:1:1) as the eluent to the title compound **SI-12** (2.03 g, 63%).

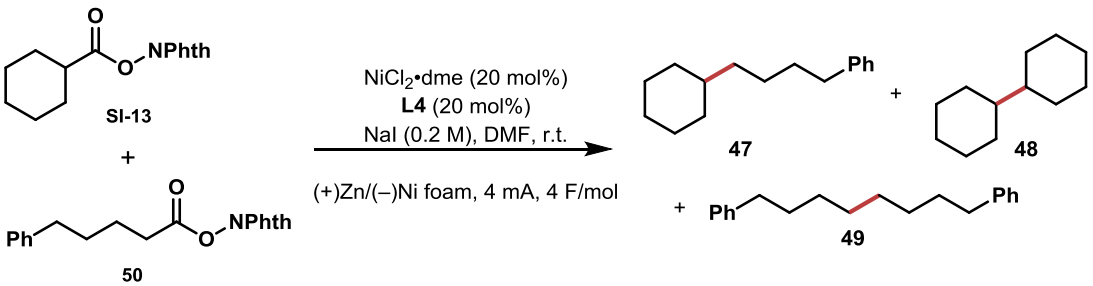
Physical State: white solid.

^{1}H NMR (600 MHz, $CDCl_3$):δ 8.56 (d, *J* = 7.2 Hz, 2H), 8.22 (d, *J* = 8.2 Hz, 2H), 7.74 (t, *J* = 7.8 Hz, 2H), 2.84 (tt, *J* = 11.0, 3.7 Hz, 1H), 1.91–1.82 (m, 2H), 1.77–1.63 (m, 2H), 1.46–1.33 (m, 3H), 1.52–1.22 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.8 , 159.6 , 134.9 , 131.8 , 131.7 , 127.5 , 127.0 , 122.3 , 40.7 , 28.9 , 25.6 , 25.1 .

HRMS (ESI-TOF): calc'd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1236, found 324.1245.

TLC: R_f = 0.3 (5:1:1 hexane/EtOAc/CH_2Cl_2).

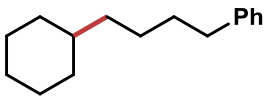


An ElectraSyn vial (5 mL) with a stir bar was charged with RAE **SI-13**[34] (27.3 mg, 0.1 mmol), RAE **50**[27] (95.7 mg, 0.3 mmol), NaI (0.6 mmol, 89.9 mg), $NiCl_2$dme (20 mol %, 4.4

mg), (4-OMe)-H-PyBox (20 mol %, 5.0 mg), anhydrous DMF (3.0 mL) was then added. An ElectraSyn vial cap equipped with anode (Zn) and cathode (Ni foam) were inserted into the mixture after which all the contents were degassed via an argon balloon for roughly 60 seconds. The reaction mixture was electrolyzed under a constant current of 4 mA for 4 F/mol. After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 N) was then added [for products containing tertiary amine moiety, washing with 1 N HCl was omitted]. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography or preparative thin layer chromatography (PTLC) to furnish the product **47** (15.1 mg, 70%, calculated based on the initial amount of **SI-13**), **48** (16%, GC yield) and **49** (22.7 mg, 57%, calculated based on the initial amount of **50**).

The product **47** and **49** were fully characterized, and the formation of **48** was confirmed by matching GC retention time with commertially available 1,1'-bicyclohexane.

Compound 47



(4-cyclohexylbutyl)benzene (47).

Physical State: colorless oil.

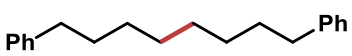
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.26 (m, 2H), 7.21–7.16 (m, 3H), 2.71–2.53 (m, 2H), 1.76–1.56 (m, 7H), 1.41–1.30 (m, 2H), 1.28–1.07 (m, 6H), 0.96–0.73 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.9, 128.4, 128.2, 125.5, 37.6, 37.4, 36.0, 33.4, 31.8, 26.8 , 26.6 , 26.4.

TLC: R_f = 0.9 (hexane).

The spectroscopic data matched the literature[36].

Compound 49



1,8-diphenyloctane (49).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ7.33–7.27 (m, 4H), 7.24–7.17 (m, 6H), 2.65–2.60 (m, 4H), 1.68–1.58 (m, 4H), 1.40–1.30 (m, 8H).

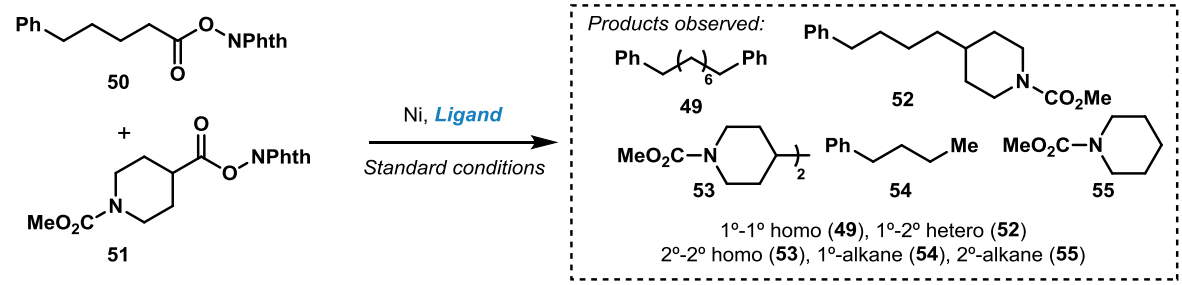
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.9 , 128.4 , 128.2 , 125.5 , 36.0 , 31.5 , 29.4 , 29.3 .

TLC: R_f = 0.7 (hexane).

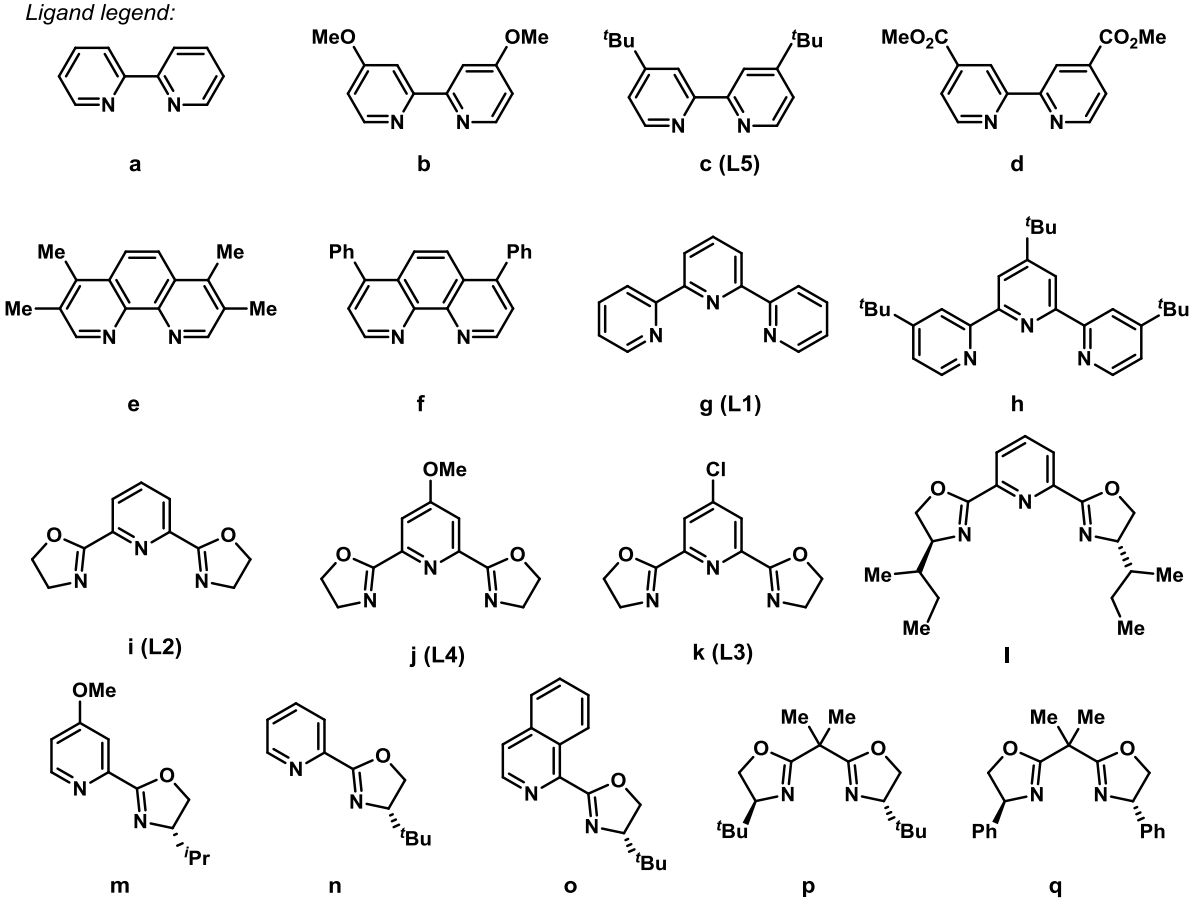
The spectroscopic data matched the literature[37].

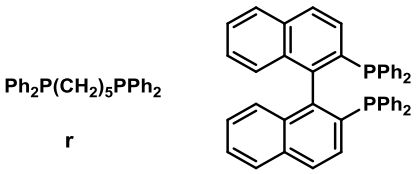
D. Experimental procedures and characterization data for ligand effect: systematic evaluation

Ligand screening:



Ligand legend:





Entry	Ligand	Yield 49	Yield 52	Yield 53	Yield 54	Yield 55
1	**a**	52%	27%	6%	4%	9%
2	**b**	10%	7%	8%	13%	11%
3	**c (L5)**	11%	10%	9%	17%	17%
4	**d**	31%	16%	16%	26%	29%
5	**e**	6%	0%	0%	7%	4%
6	**f**	32%	17%	5%	20%	18%
7	**g (L1)**	71%	50%	10%	2%	11%
8	**h**	71%	49%	6%	6%	16%
9	**i (L2)**	52%	55%	20%	39%	39%
10	**j (L4)**	65%	68%	10%	7%	1%
11	**k (L3)**	33%	34%	13%	20%	13%
12	**l**	39%	33%	9%	22%	12%
13	**m**	22%	14%	0%	16%	13%
14	**n**	22%	13%	6%	11%	8%
15	**o**	6%	12%	9%	41%	23%
16	**p**	16%	11%	9%	36%	24%
17	**q**	16%	12%	16%	32	23%
18	**r**	11%	13%	16%	8%	12%
19	**s**	8%	9%	12%	39%	23%
20	**t**	12%	11%	16%	43%	27%

*Note: the yields are based on GC analysis. The yield of **52**, **53** and **55** was calculated based on the initial amount of **51**. The yield of **49** and **54** was calculated based on the initial amount of **50**.

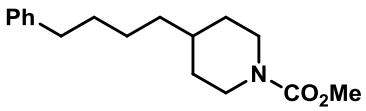
The following experimental procedure was employed for **entry 10**, and other entries were also performed by following the same procedure by varying ligands:

An ElectraSyn vial (5 mL) with a stir bar was charged with RAE **51**[38] (33.2 mg, 0.1 mmol), RAE **50**[34] (95.7 mg, 0.3 mmol), NaI (0.6 mmol, 89.9 mg), $NiCl_2$dme (20 mol %, 4.4 mg), (4-OMe)-H-PyBox (20 mol %, 5.0 mg), anhydrous DMF (3.0 mL) was then added. An ElectraSyn vial cap equipped with anode (Zn) and cathode (Ni foam) were inserted into the mixture after which all the contents were degassed via an argon balloon for roughly 60 seconds. The reaction mixture was electrolyzed under a constant current of 4 mA for 4 F/mol.

After electrolysis, the ElectraSyn vial cap was removed and electrodes were rinsed with Et_2O, which was combined with the crude mixture. The crude mixture was further diluted with Et_2O and aqueous HCl (0.1 N) was then added [for products containing tertiary amine moiety, washing with 1 N HCl was omitted]. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography or preparative thin layer chromatography (pTLC) to furnish the product **49** (23.9 mg, 60%, calculated based on the initial amount of **50**), **52** (17.6 mg, 64%, calculated based on the initial amount of **51**), **53** (2.0 mg, 7%, calculated based on the initial amount of **50**), **54** (7%, GC yield) and **55** (1%, GC yield).

The formation of **54** and **55** was confirmed by matching the GC-MS retention time of the commertially available butylbenzene and methyl piperidine-1-carboxylate[39].

Compound 52



Methyl 4-(4-phenylbutyl)piperidine-1-carboxylate (52).

Physical State: colorless oil.

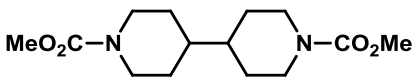
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.20–7.15 (m, 3H), 4.25–3.95 (m, 2H), 3.68 (s, 3H), 2.80–2.65 (m, 2H),, 2.60 (t, *J* = 7.7 Hz, 2H), 1.75–1.53 (m, 4H), 1.41–1.31 (m, 3H), 1.29–1.23 (m, 2H), 1.13–1.02 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.9, 142.6, 128.3, 128.2, 125.6, 52.4, 44.2, 36.3, 35.9, 35.8, 32.1, 31.6, 26.2.

HRMS (ESI-TOF): calc'd for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1964, found 276.1972.

TLC: R_f = 0.3 (6:1 hexane/EtOAc).

Compound 53



Dimethyl [4,4'-bipiperidine]-1,1'-dicarboxylate (53).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.35–3.95 (m, 4H), 3.67 (s, 6H), 2.77–2.60 (m, 4H), 1.77–1.46 (m, 4H), 1.35–0.97 (m, 6H).

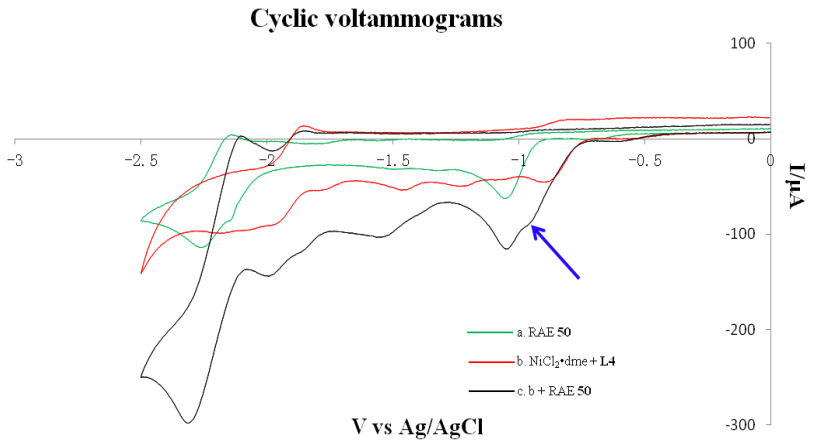
^{13}C NMR (151 MHz, $CDCl_3$): δ 155.8, 52.4, 44.2, 40.9, 29.0.

HRMS (ESI-TOF): calc'd for $C_{24}H_{17}N_2O_4$ $[M+H]^+$: 397.1188, found 397.1195.

TLC: R_f = 0.3 (2:1:1: hexane/EtOAc/CH_2Cl_2).

E. Cyclic voltammetry

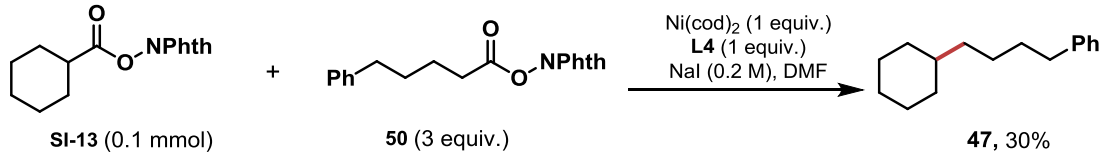
Cyclic voltammograms was recorded with 0.1 M $TBABF_4$ and related compounds in anhydrous DMF (3 mL). Glassy carbon working electrode/Pt counter electrode, Ag/AgCl reference electrode. The scan rate was 100 mV s^{-1}.



a) 5 mM RAE **50**. b) 5 mM ($NiCl_2$•dme + **L4**). c) Solution (b) with 5 mM of RAE **50**.

We have carried out CV experiments to gain more information about the role of Ni catalyst. As demonstrated above, Ni-ligand complex exhibits a complex redox behavior. However, we observed a new peak upon addition of redox active ester **50** (indicated as a blue arrow) together with increase of reduction current. This observation implies that there might be a potential interaction between the RAE and the nickel catalyst, which supports our hypothesis that some degree of the RAE reduction is mediated by low-valent Ni catalyst.

F. Stoichiometric reaction without electric current

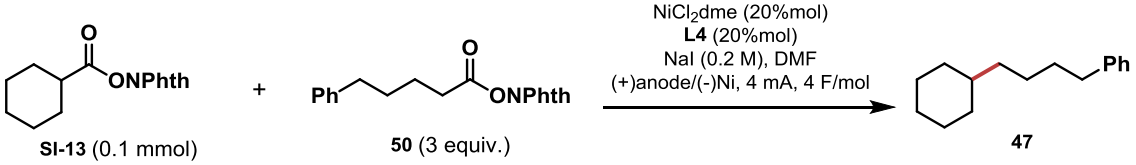


SI-13 (0.1 mmol) **50** (3 equiv.) **47,** 30%

We have carried out a reaction with stoichiometric amount of $Ni(cod)_2$ with no electricity (As shown above). The C-C bond formation was observed in this case, suggesting that this reaction can be initiated with a suitable source of electrons. However, from this experiment it is difficult to conclude that Ni(0) is an active catalytic species since we do not account for the in-situ generation of Ni(I) by various conproportionation and disproportionation pathways commonly observed for low valent Ni chemistry that have not yet fully understood. We believe more rigorous kinetic studies as well as assignment of oxidation state of active Ni species would require much more extensive and precise experiments that forms a basis for follow-up mechanistic analysis.

G. Investigation on the possibility for in-situ formation of zinc reagents

Comparison of Zn and other anodes:



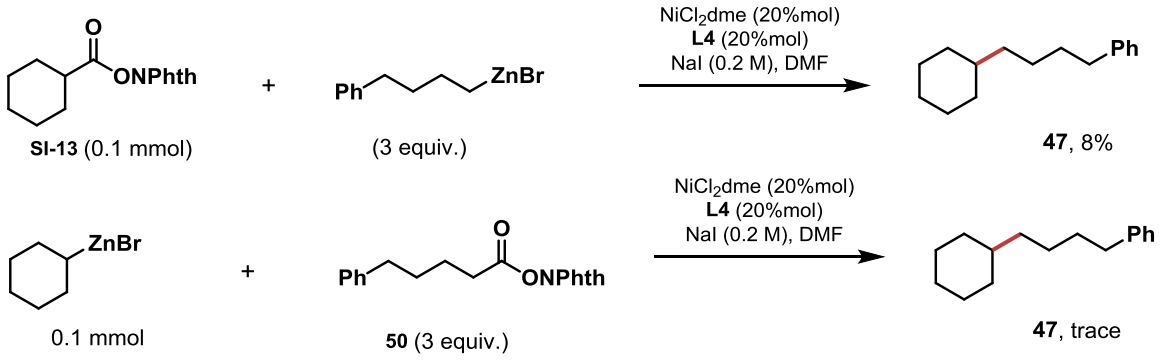
SI-13 (0.1 mmol) **50** (3 equiv.) **47**

Entry	Anode	Yield 47
1	**Zn**	72%
2	**Mg**	58%
3	**Al**	59%
4	**Fe**	38%
5	**Stainless steel**	31%
6	**RVC/DIPEA**	5%

*Note: the yields are based on GC analysis.

To exclude the possibility for the mediation by zinc species, we have carried out the reaction with different anode material. The results shown as above clearly indicate that zinc is not crucial for the reaction.

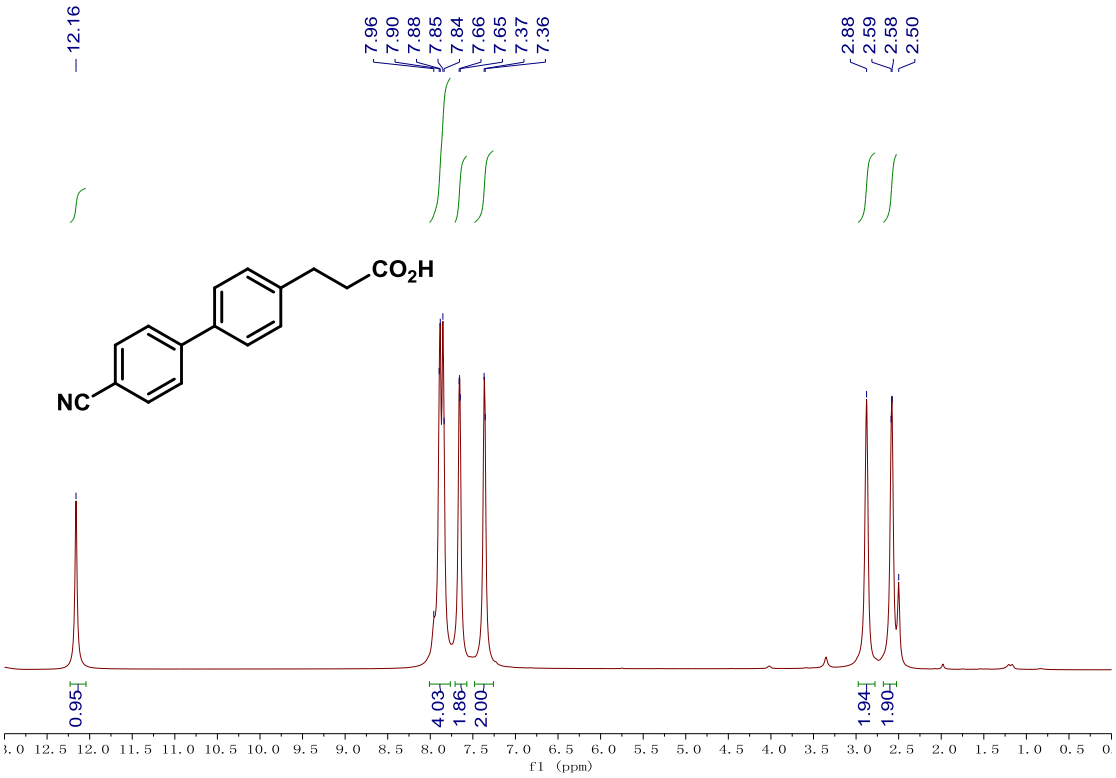
Coupling of RAE with zinc-reagent



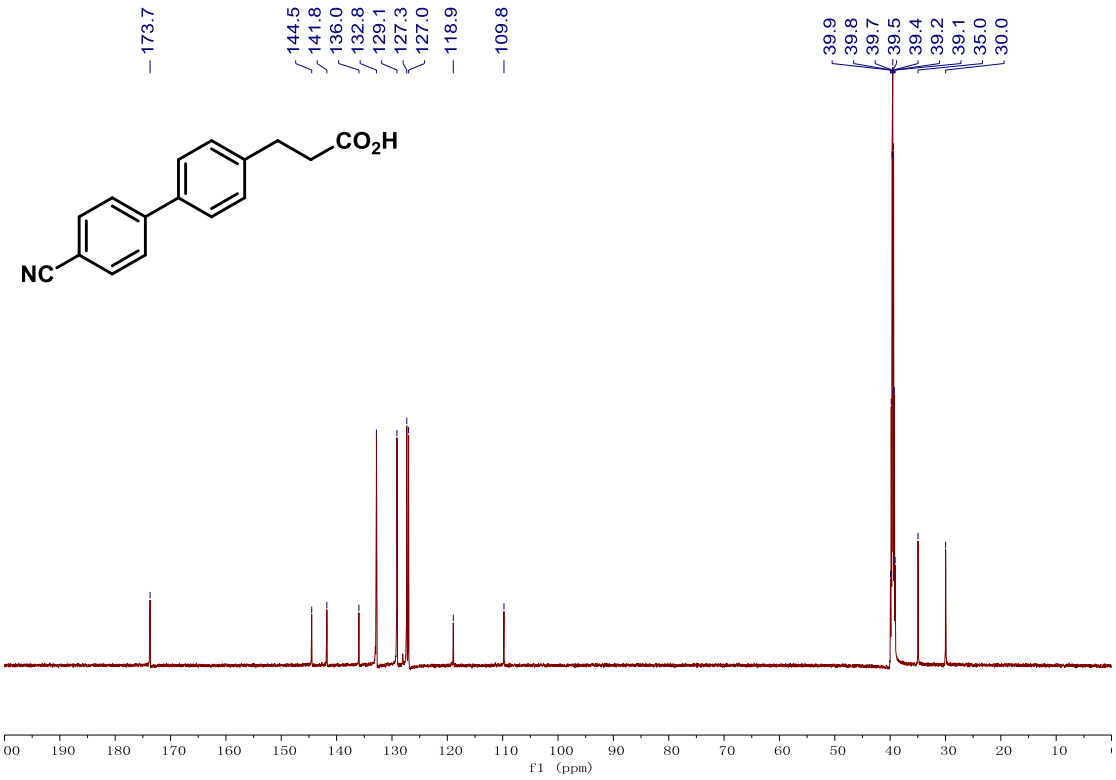
Additionally, we have performed a reaction with pre-generated alkyl zinc reagents. The yield was considerably decreased, which further suggests that alkyl zinc is unlikely to involve in the major reaction pathway.

NMR Spectra

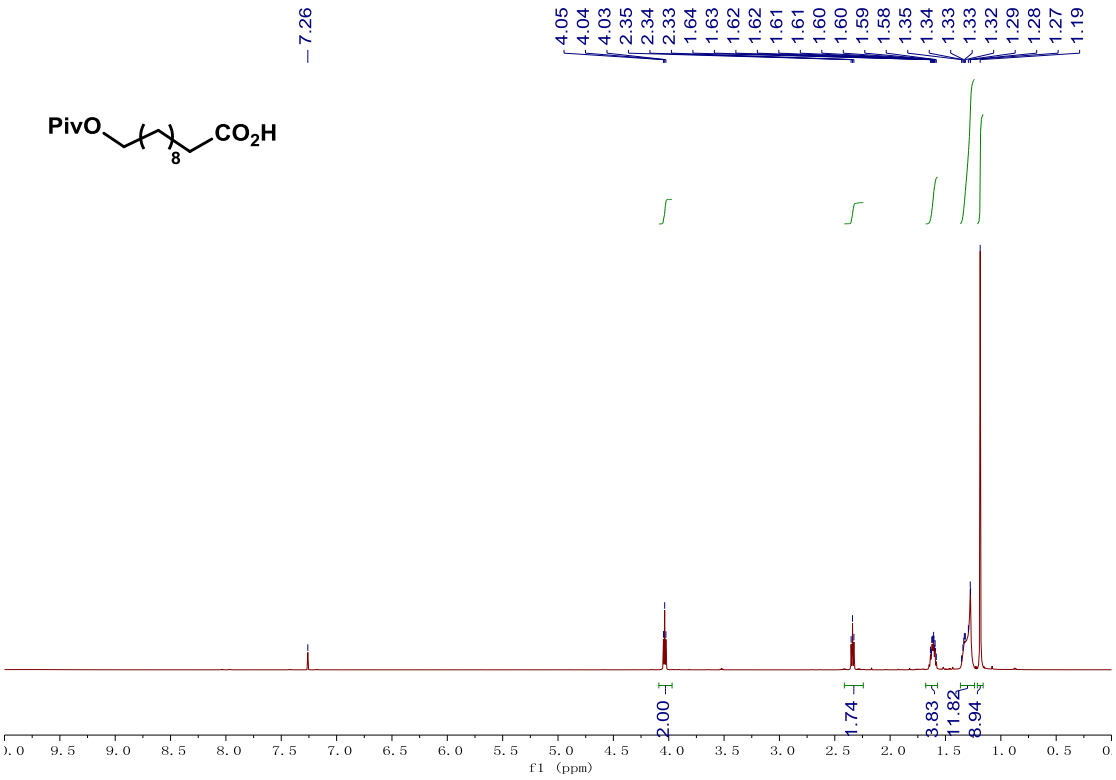
1H NMR of Compound SI-1 (600 MHz, DMSO-d6):



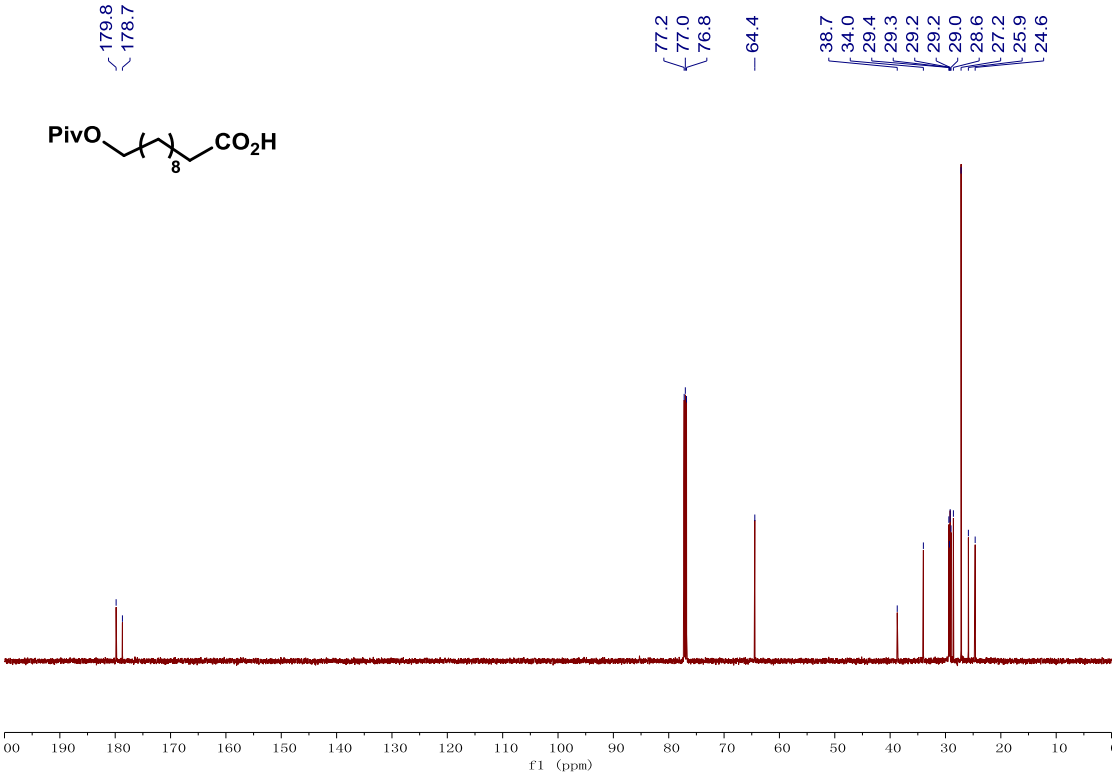
^{13}C NMR of Compound SI-1 (151 MHz, DMSO-d_6):



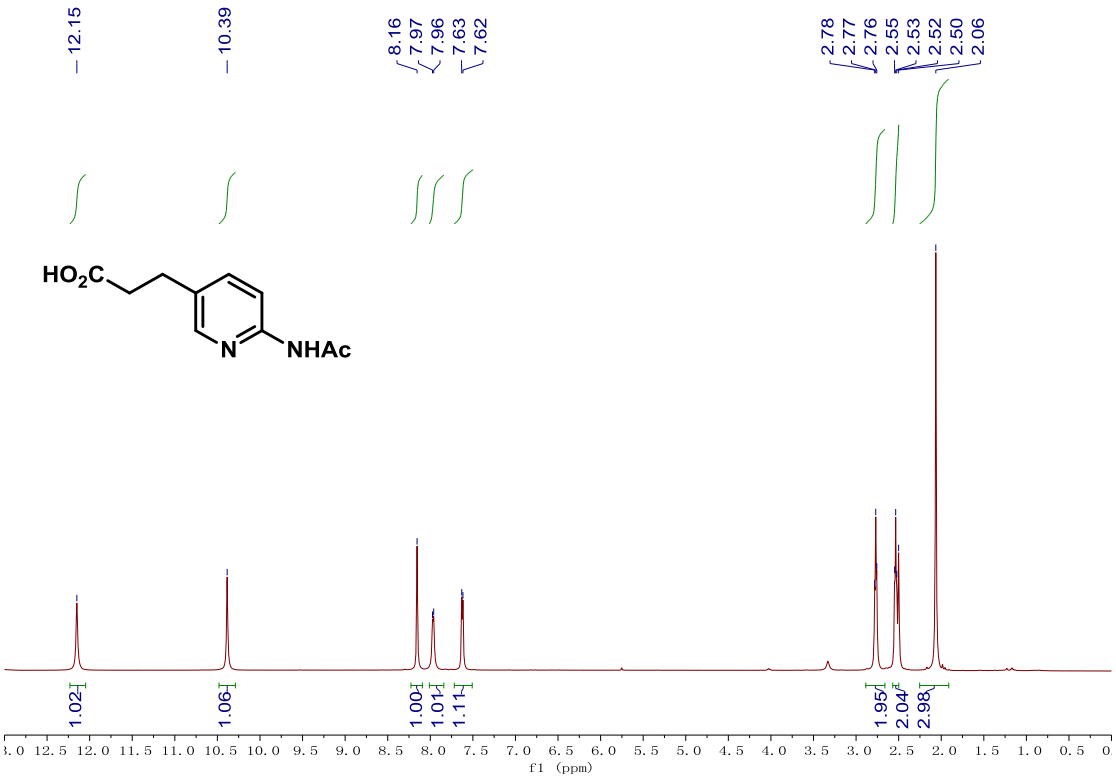
^{1}H NMR of Compound SI-3 (600 MHz, $CDCl_3$):



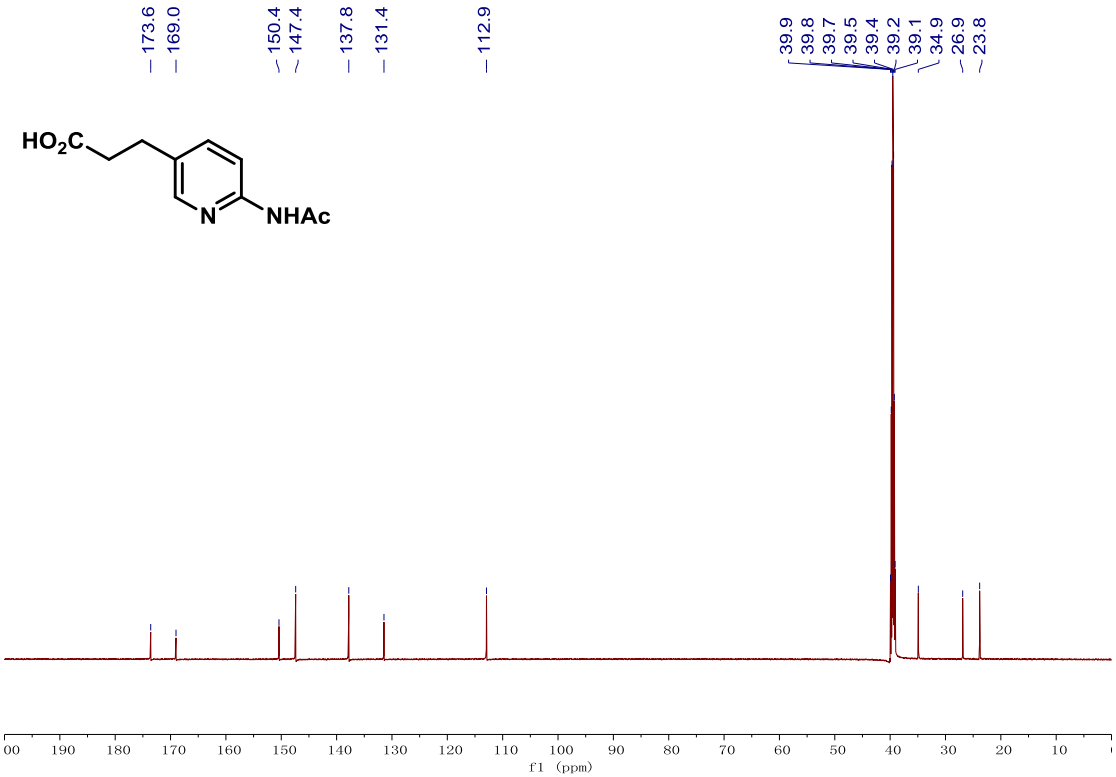
^{13}C NMR of Compound SI-3 (151 MHz, $CDCl_3$):



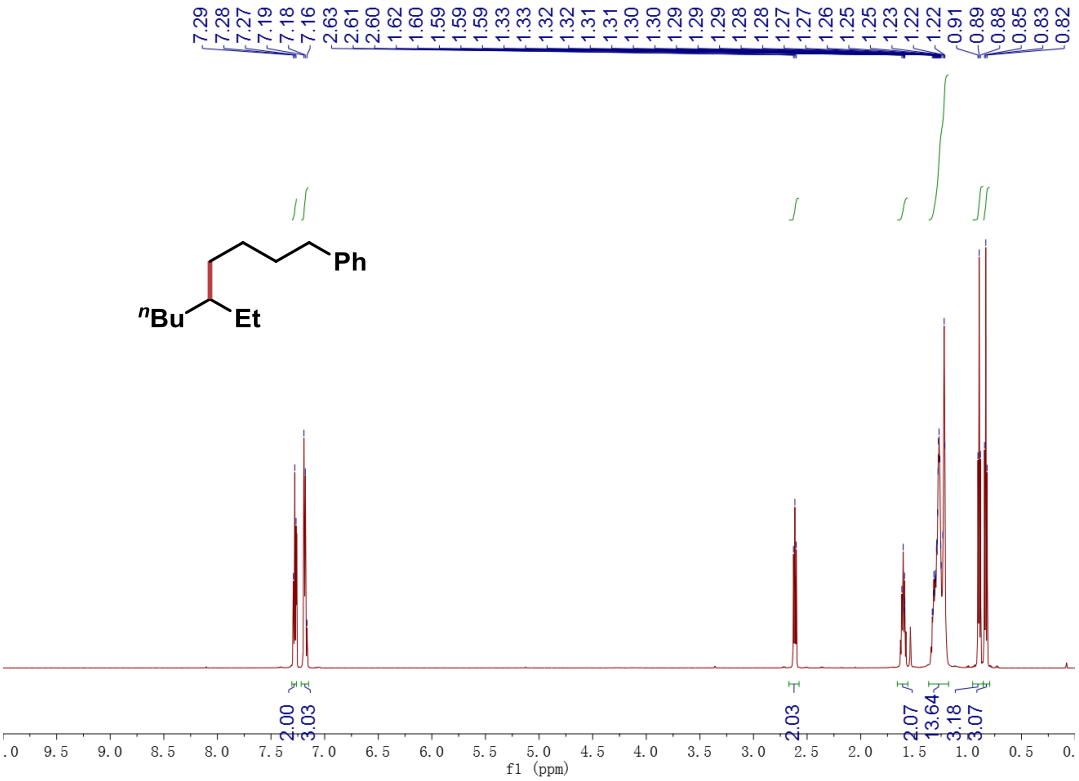
^{1}H NMR of Compound SI-4 (600 MHz, DMSO-d_6):



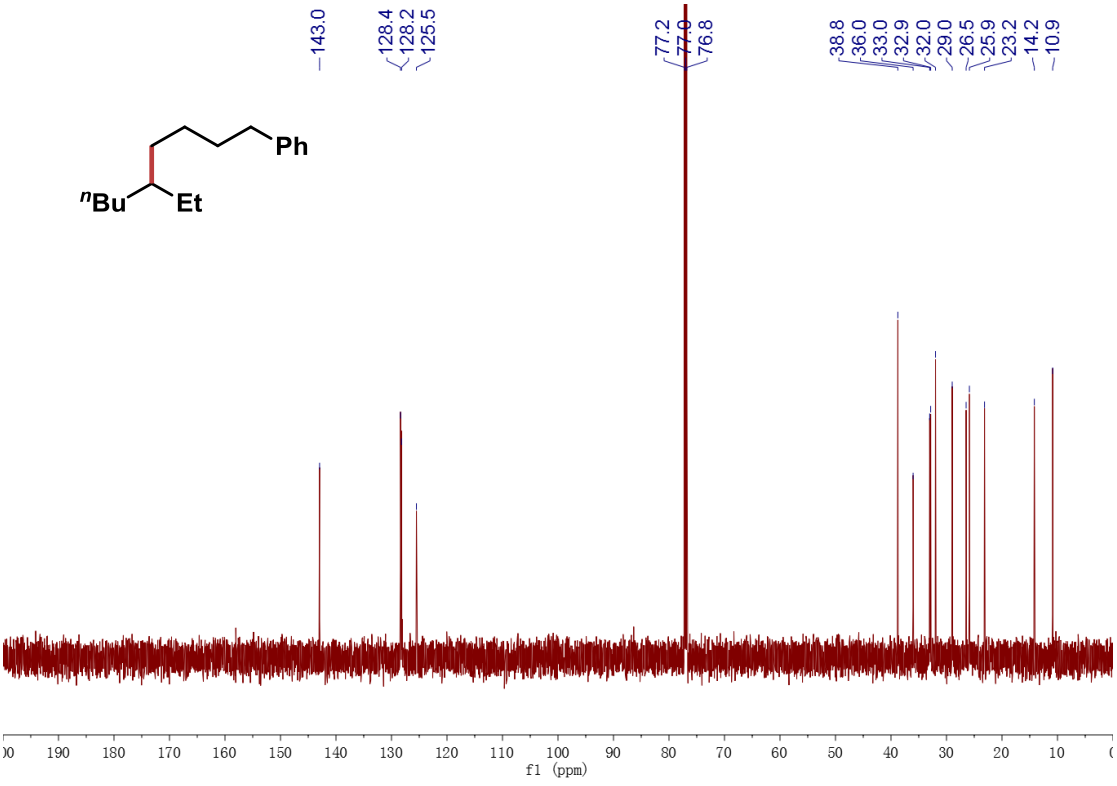
^{13}C NMR of Compound SI-4 (151 MHz, DMSO-d_6):



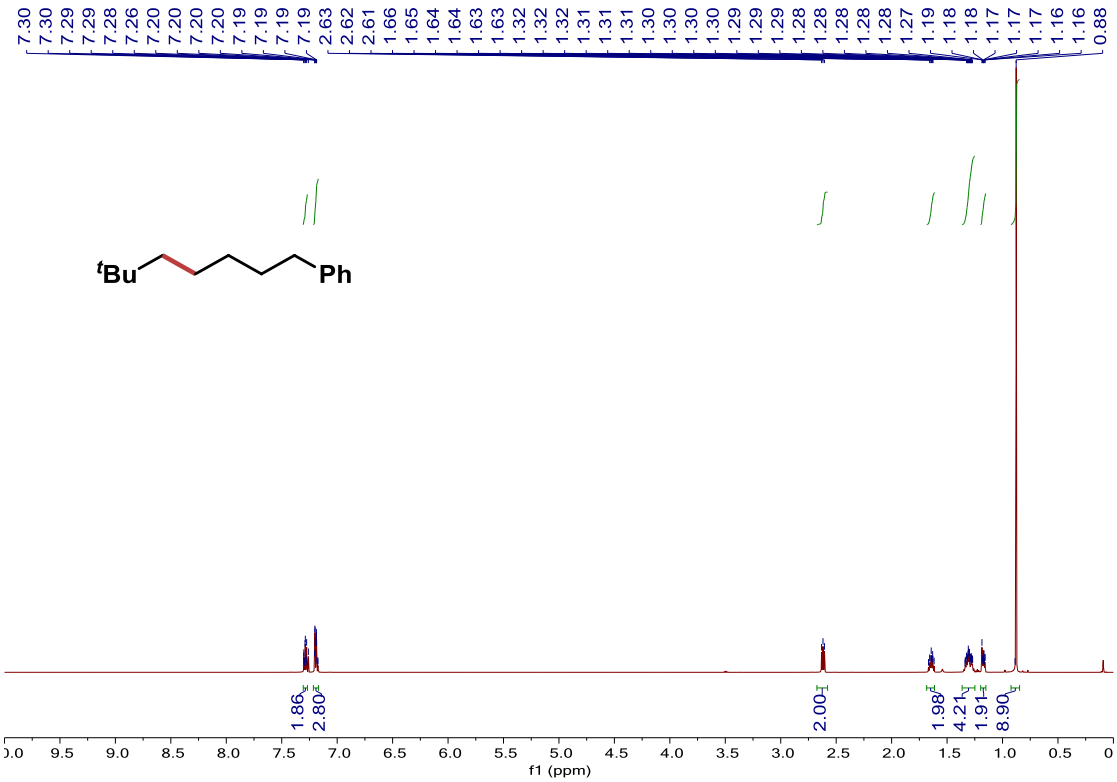
^{1}H NMR of Compound SI-15 (600 MHz, $CDCl_3$):



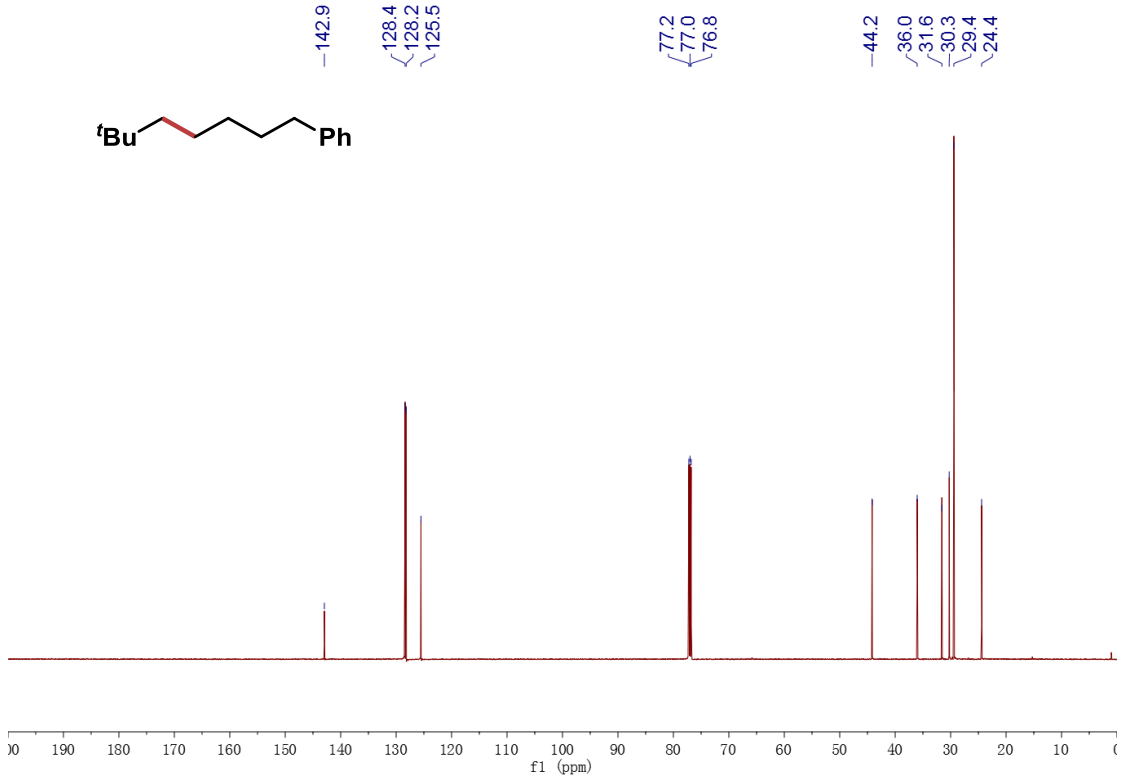
^{13}C NMR of Compound SI-15 (151 MHz, $CDCl_3$):



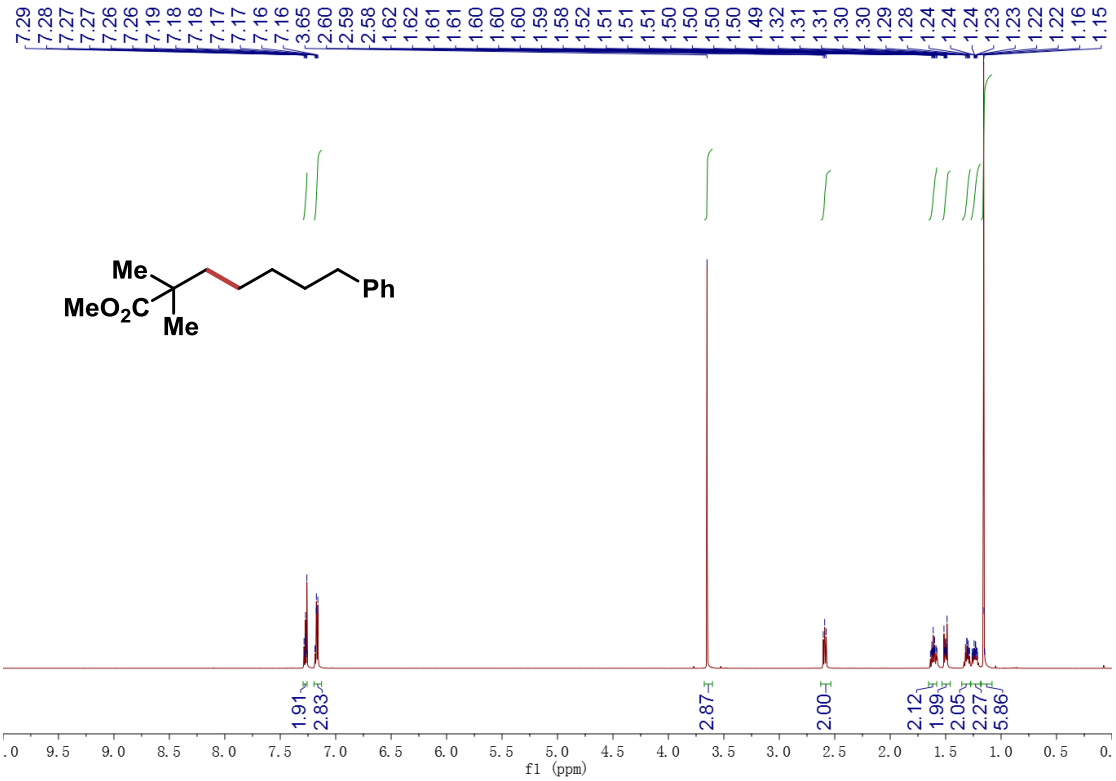
^{1}H NMR of Compound SI-16 (600 MHz, $CDCl_3$):



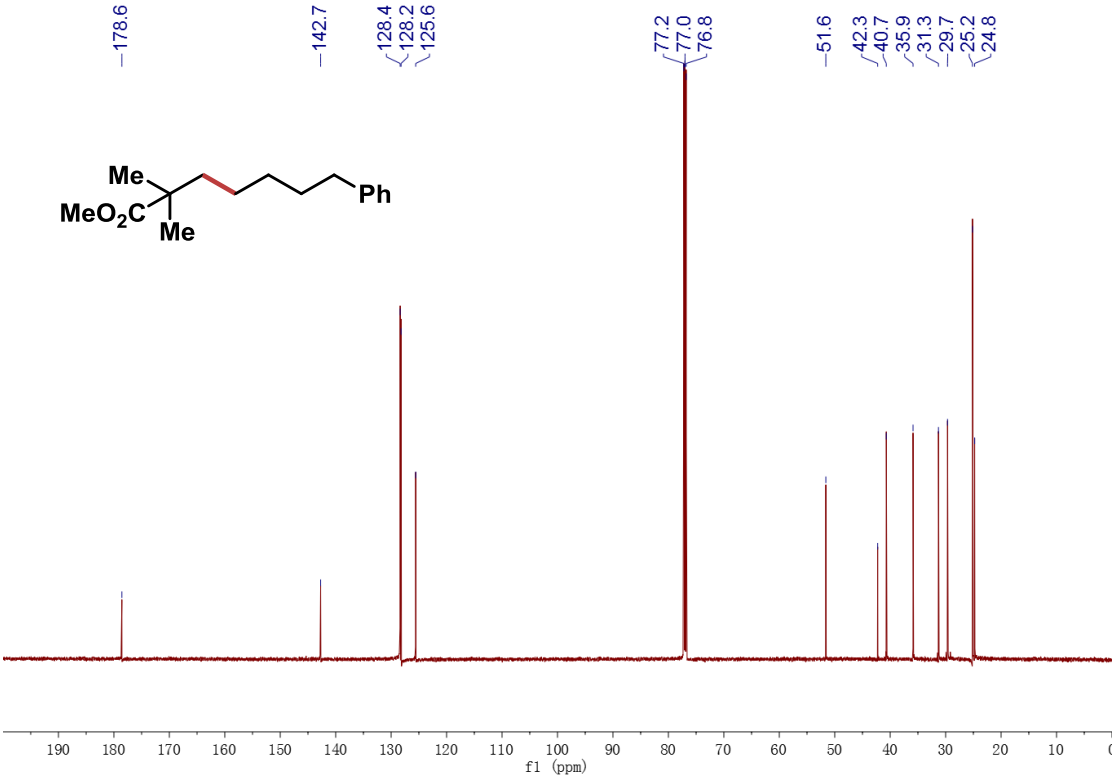
^{13}C NMR of Compound SI-16 (151 MHz, $CDCl_3$):



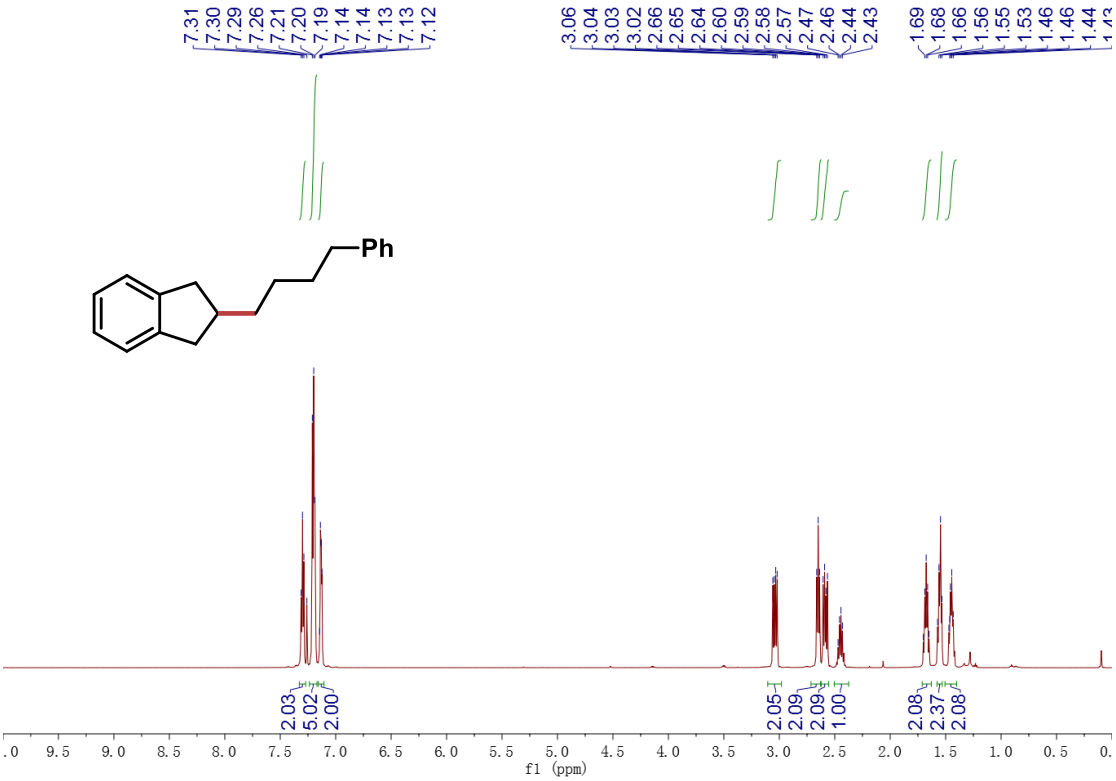
^{1}H NMR of Compound SI-17 (600 MHz, $CDCl_3$):



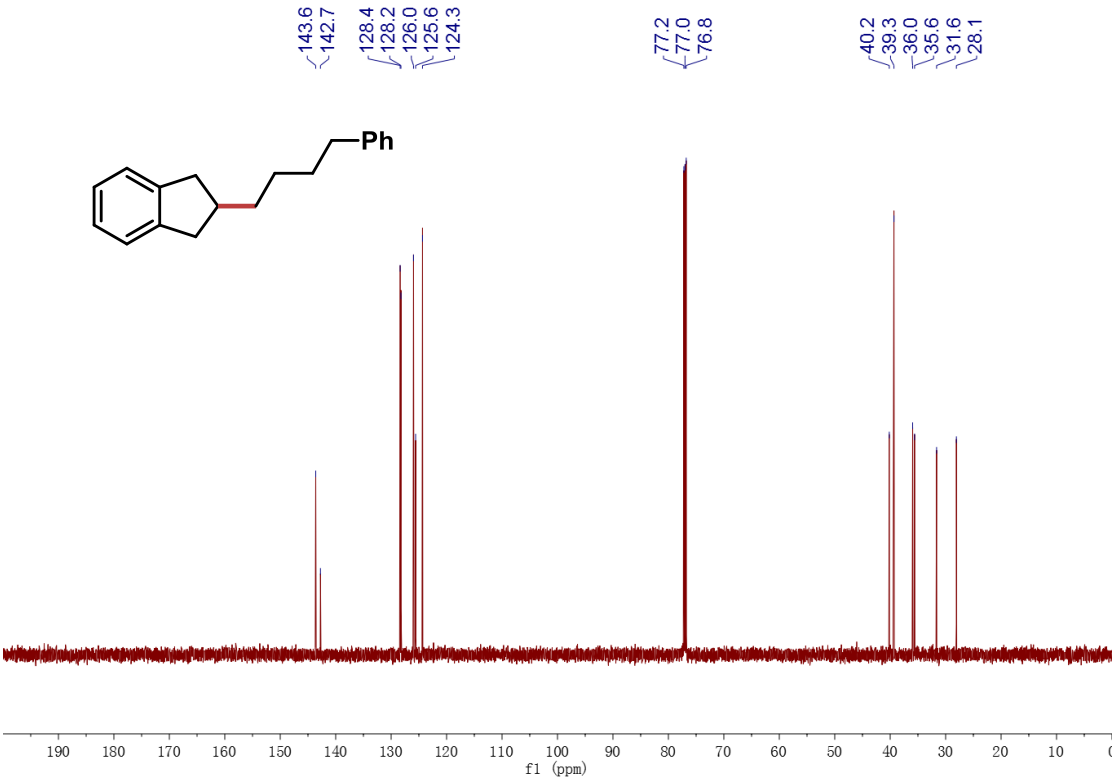
^{13}C NMR of Compound SI-17 (151 MHz, $CDCl_3$):



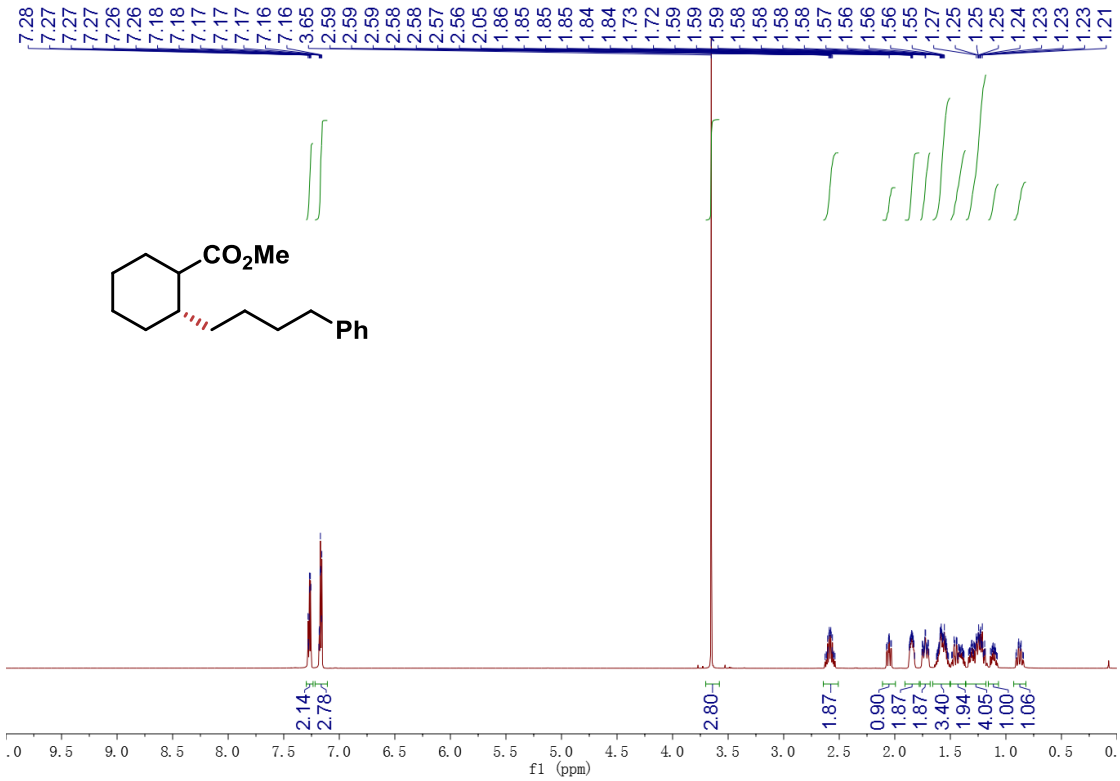
^{1}H NMR of Compound SI-18 (600 MHz, $CDCl_3$):



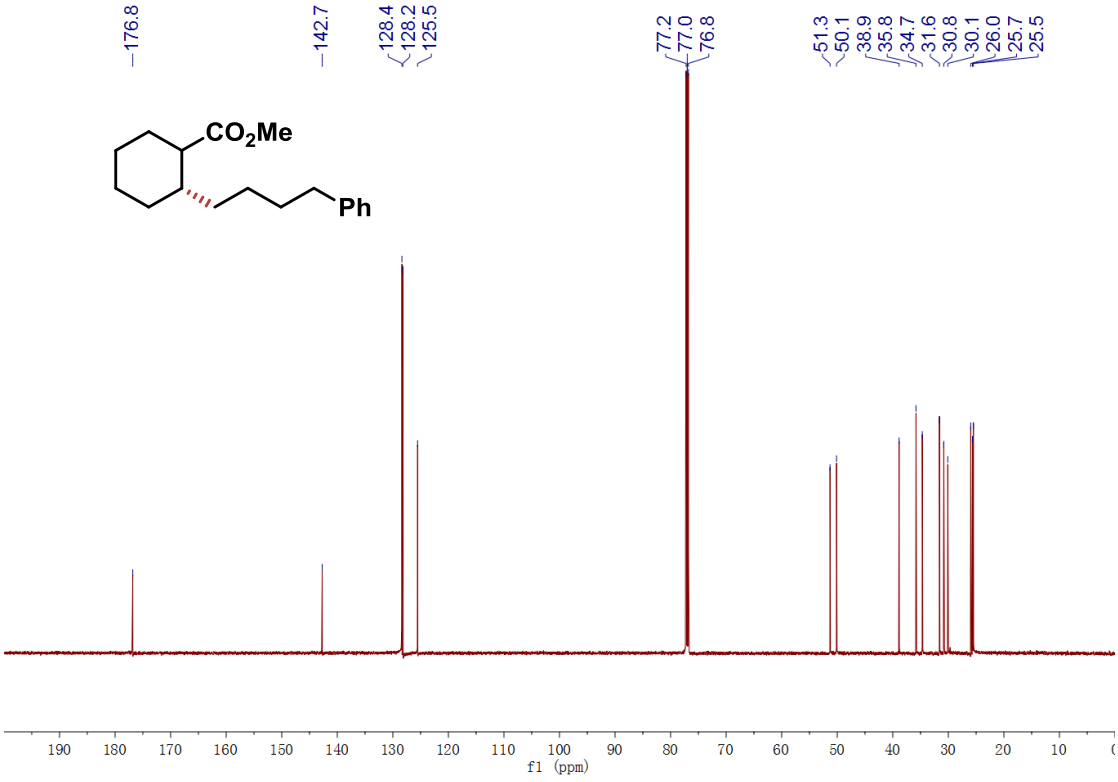
^{13}C NMR of Compound SI-18 (151 MHz, $CDCl_3$):



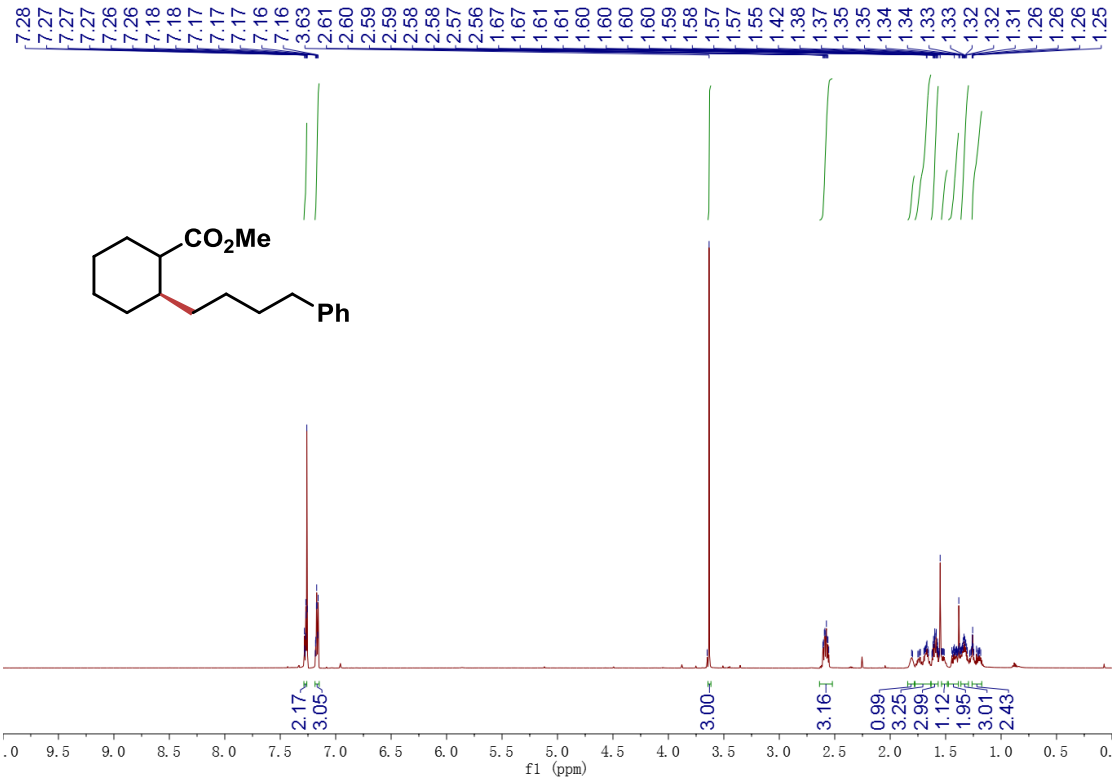
^{1}H NMR of Compound SI-19-one isomer (600 MHz, $CDCl_3$):



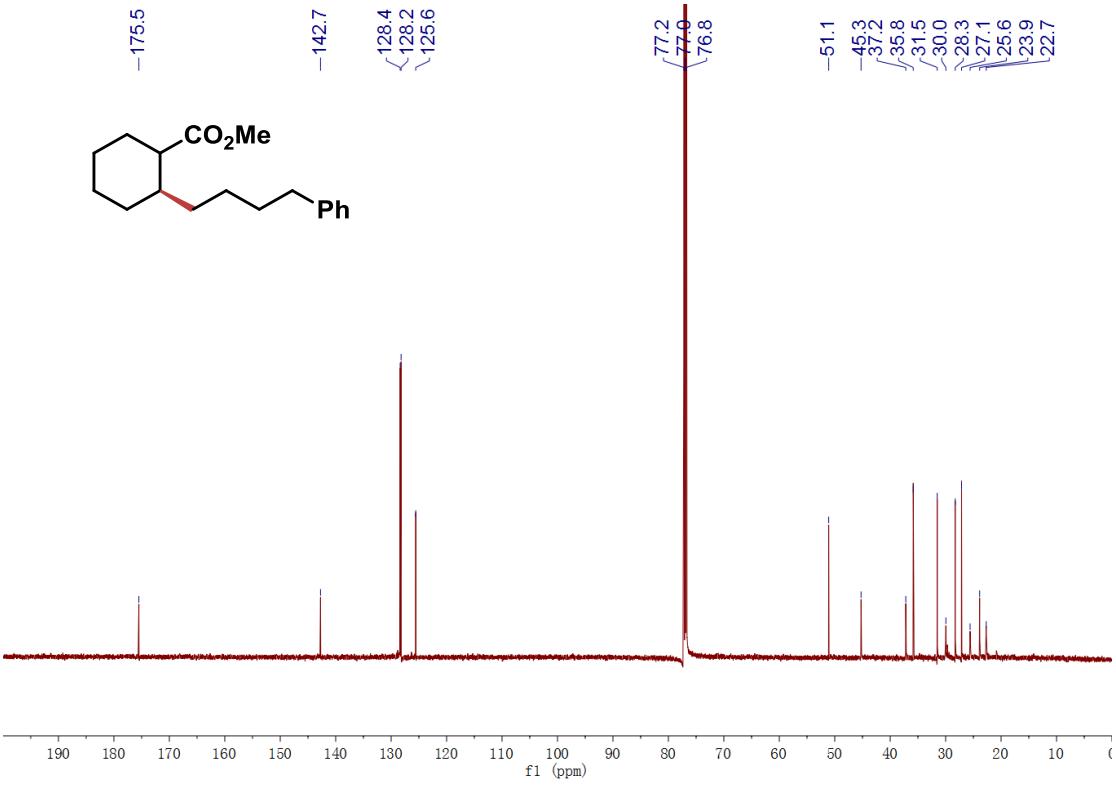
^{13}C NMR of Compound SI-19-one isomer (151 MHz, $CDCl_3$):



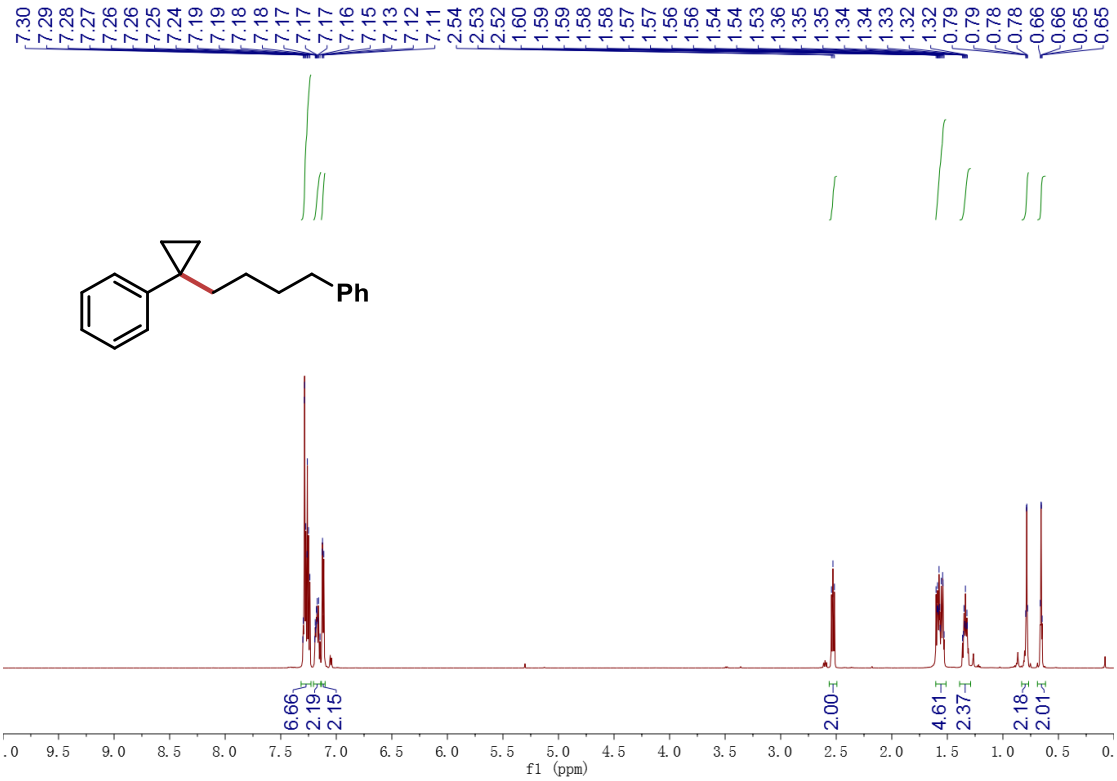
^{1}H NMR of Compound SI-19-the other isomer (600 MHz, $CDCl_3$):



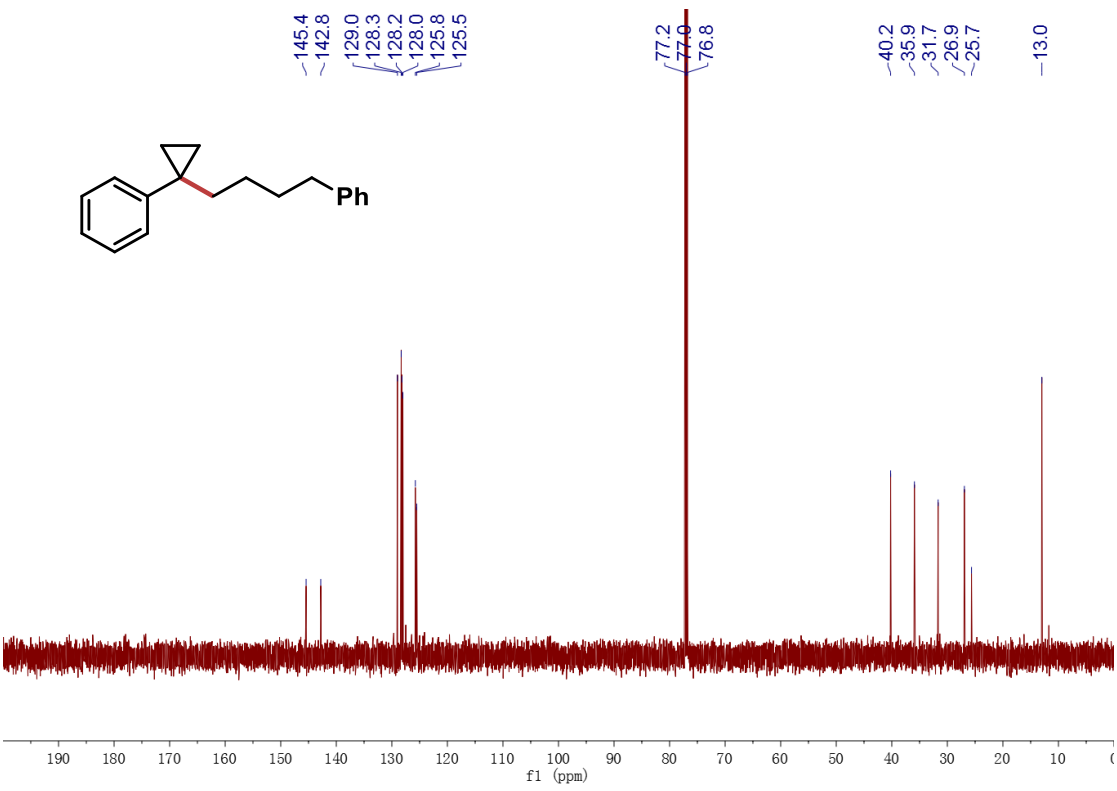
^{13}C NMR of Compound SI-19-the other isomer (151 MHz, $CDCl_3$):



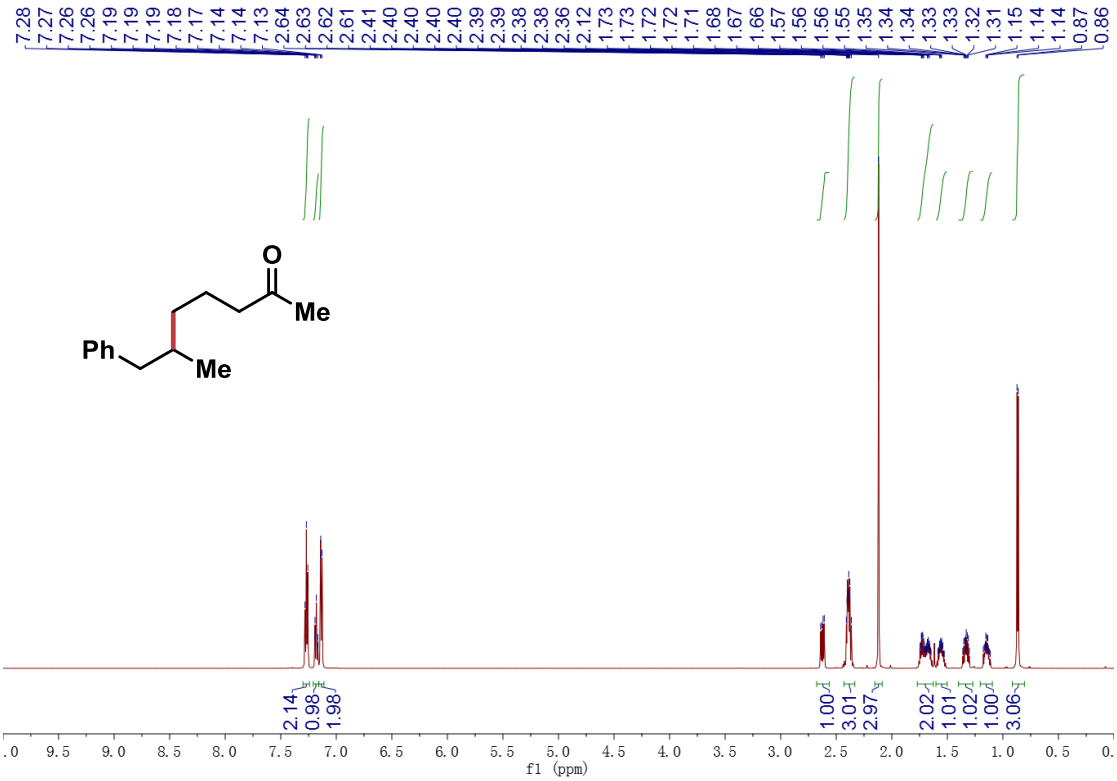
^{1}H NMR of Compound SI-20 (600 MHz, $CDCl_3$):



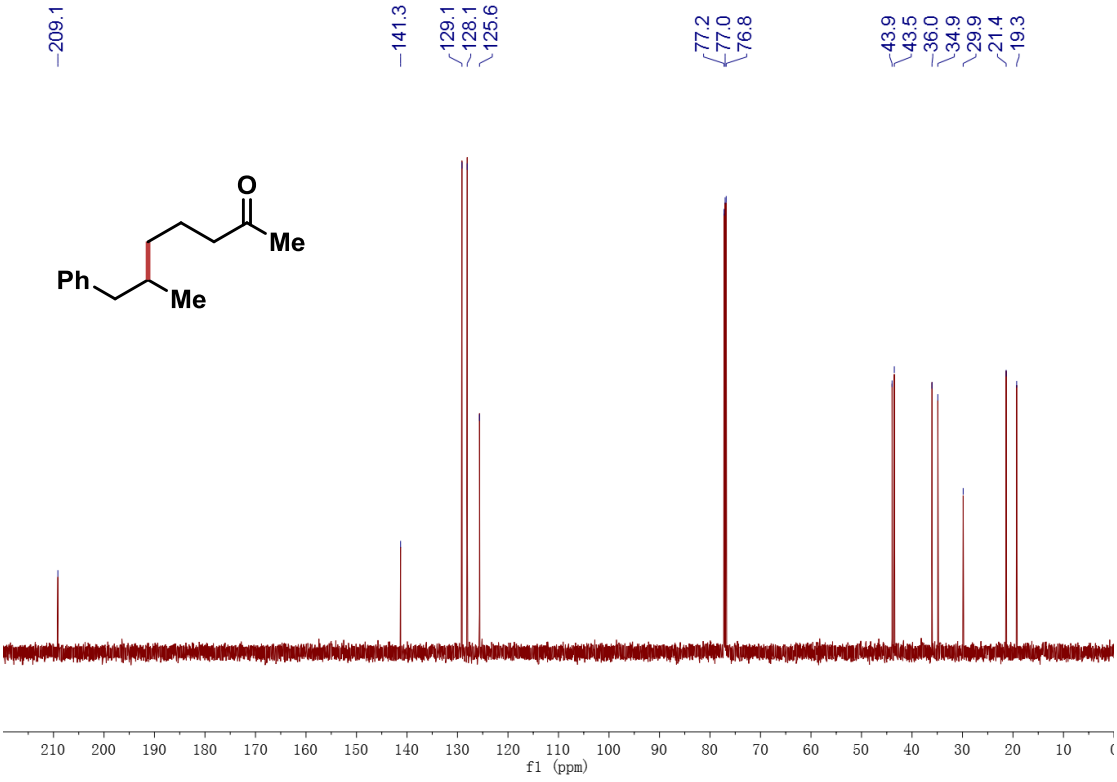
^{13}C NMR of Compound SI-20 (151 MHz, $CDCl_3$):



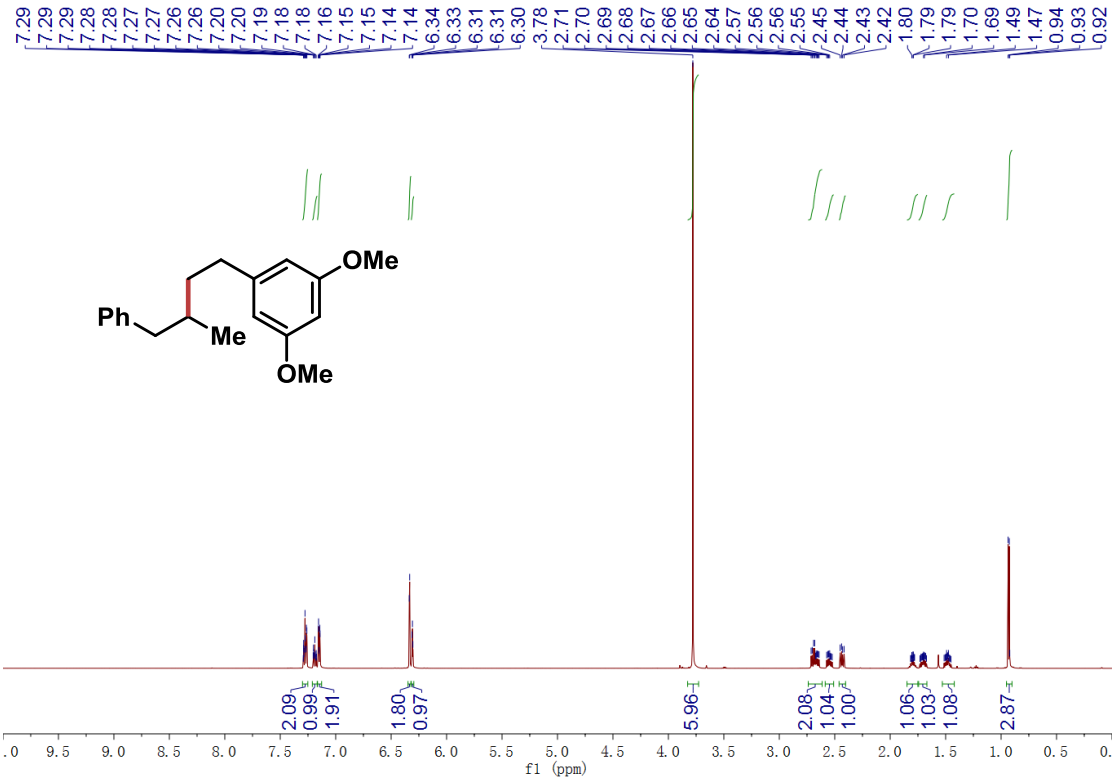
^{1}H NMR of Compound SI-21 (600 MHz, $CDCl_3$):



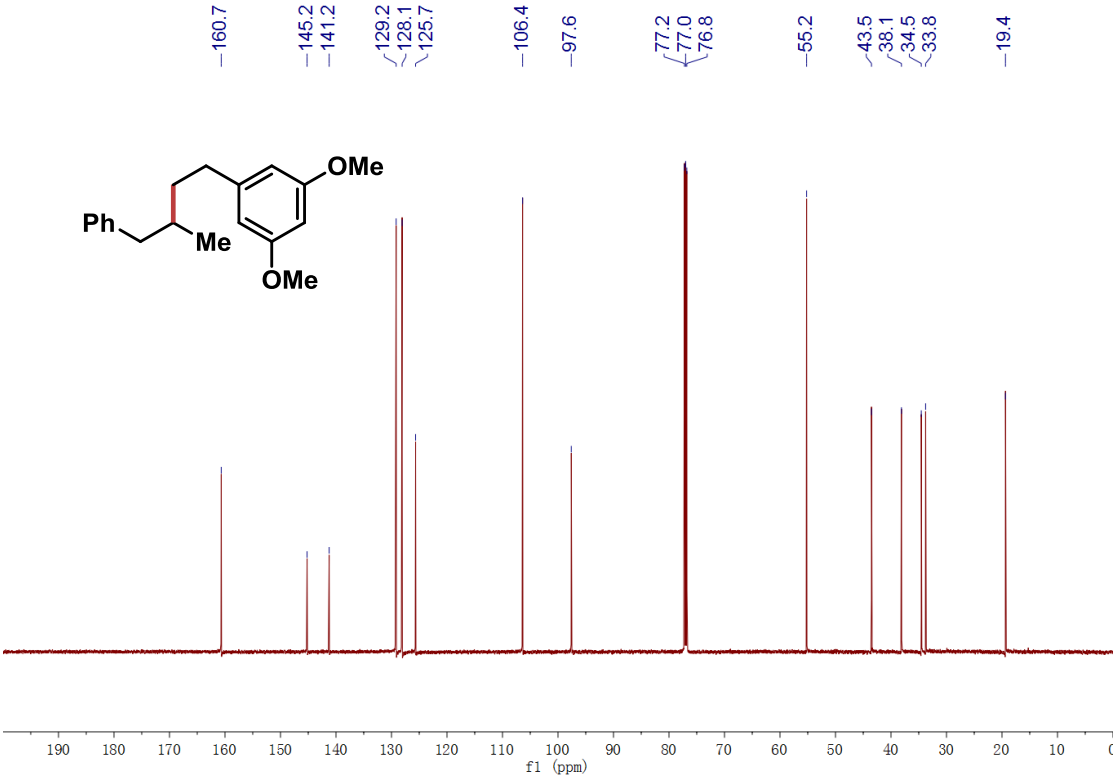
^{13}C NMR of Compound SI-21 (1511 MHz, $CDCl_3$):



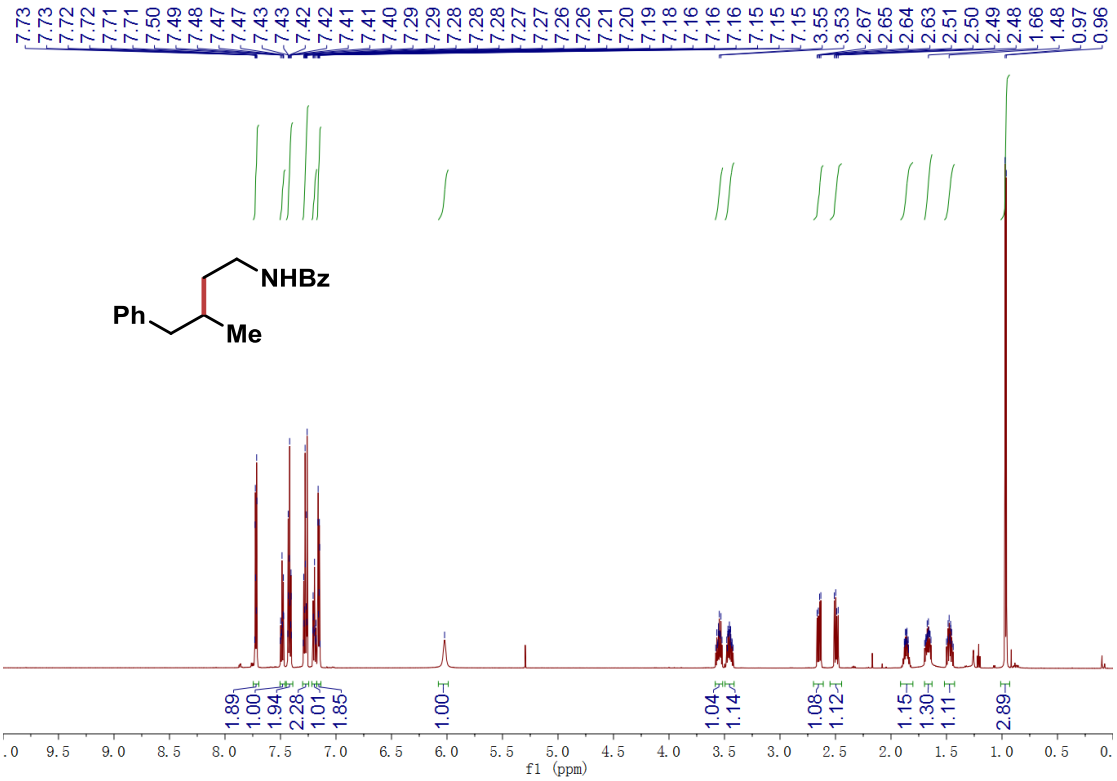
^{1}H NMR of Compound SI-22 (600 MHz, $CDCl_3$):



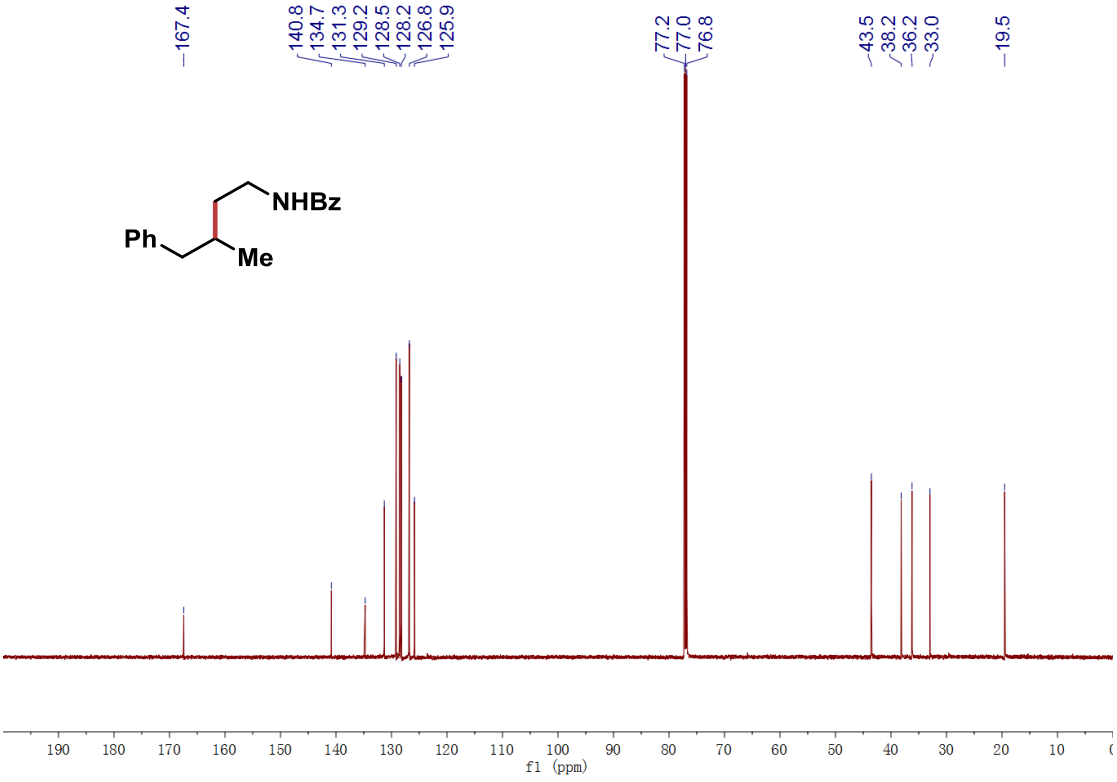
^{13}C NMR of Compound SI-22 (151 MHz, $CDCl_3$):



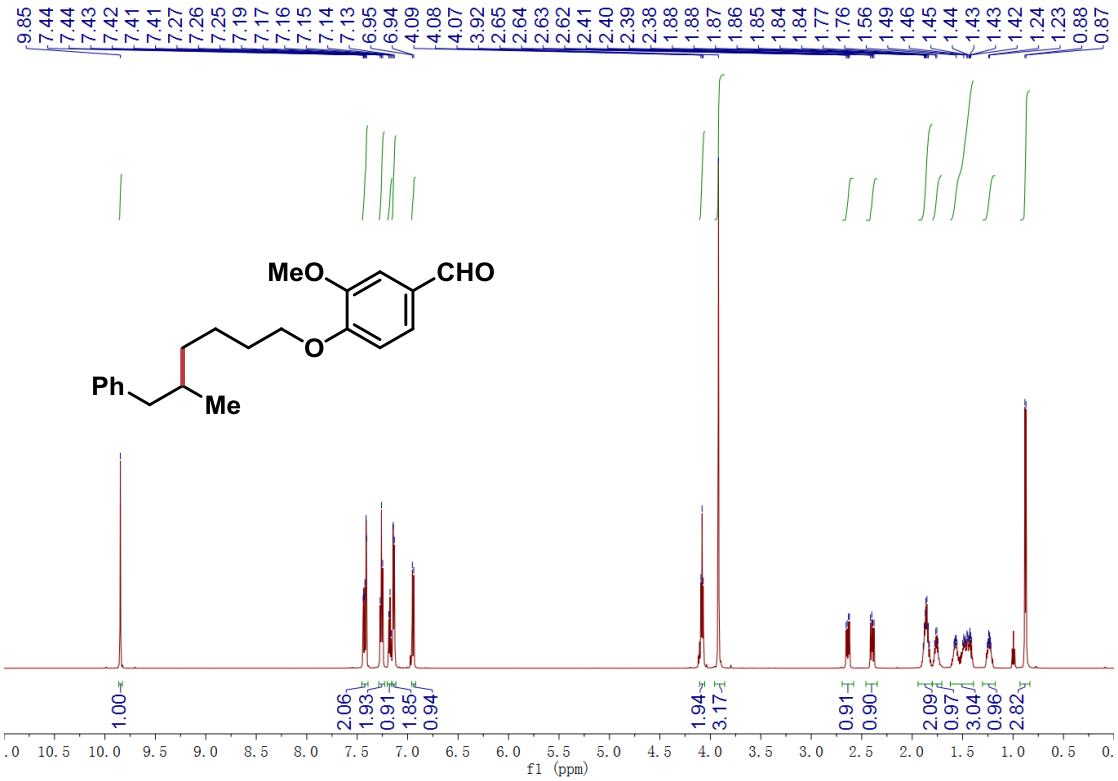
^{1}H NMR of Compound SI-23 (600 MHz, $CDCl_3$):



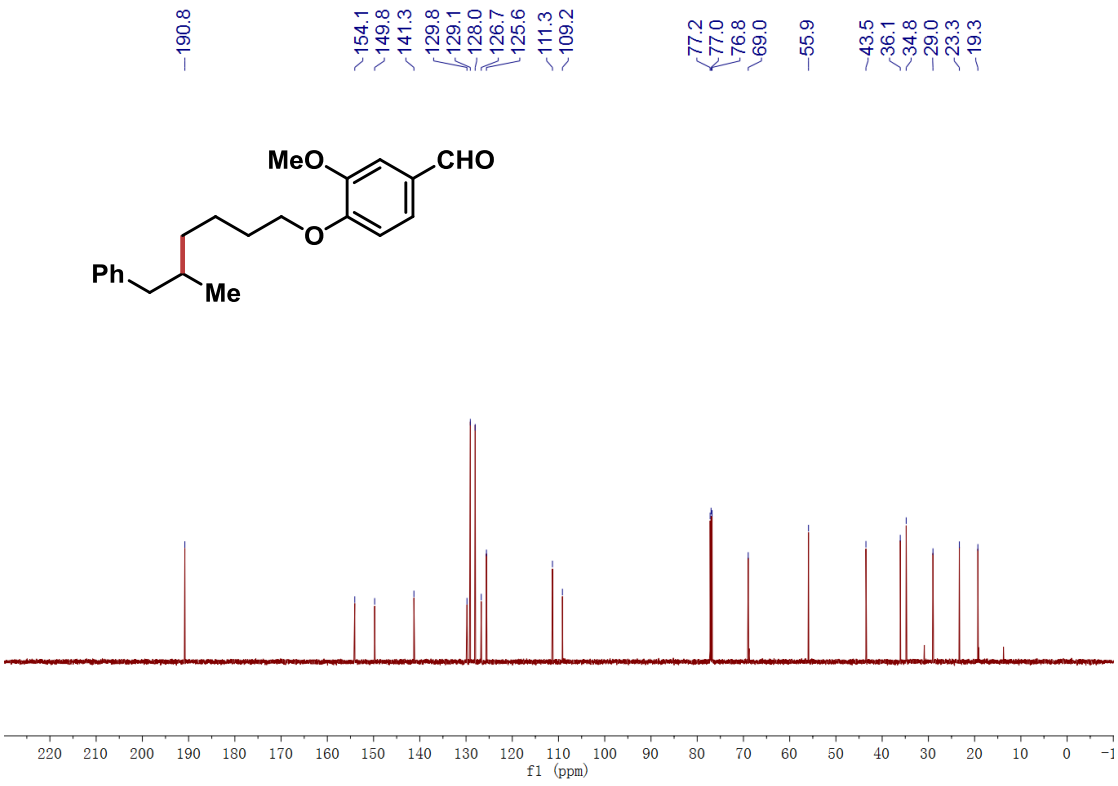
^{13}C NMR of Compound SI-23 (151 MHz, $CDCl_3$):



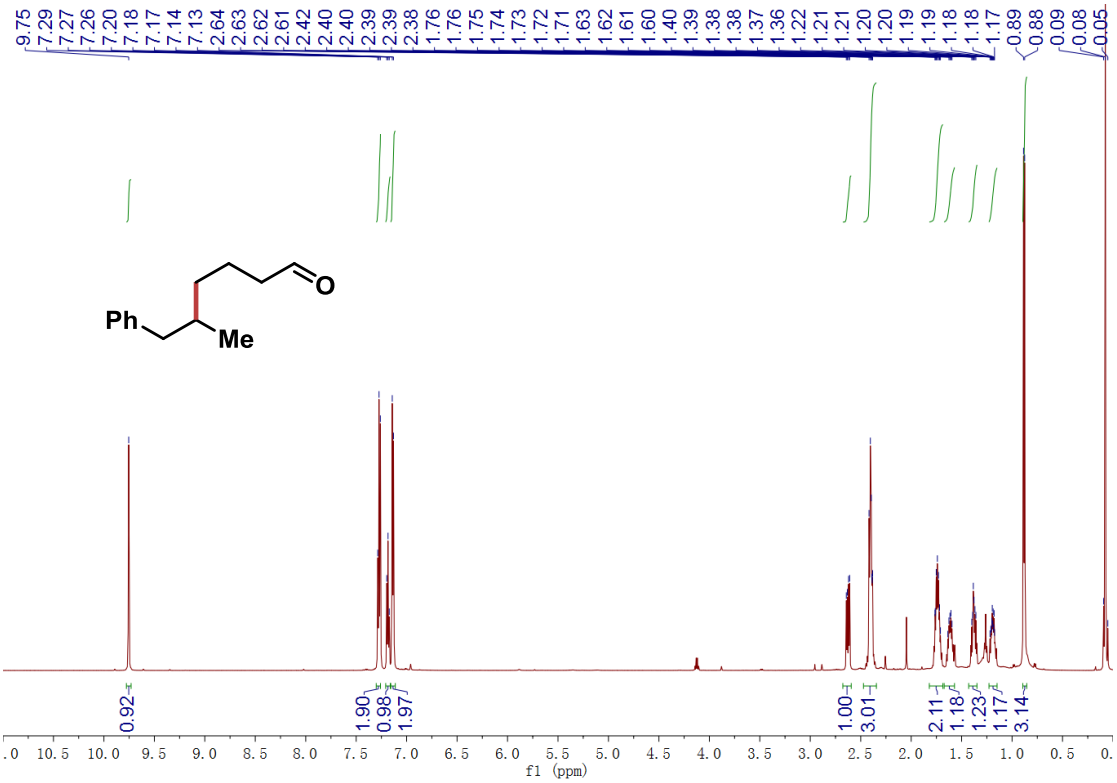
^{1}H NMR of Compound SI-24 (600 MHz, $CDCl_3$):



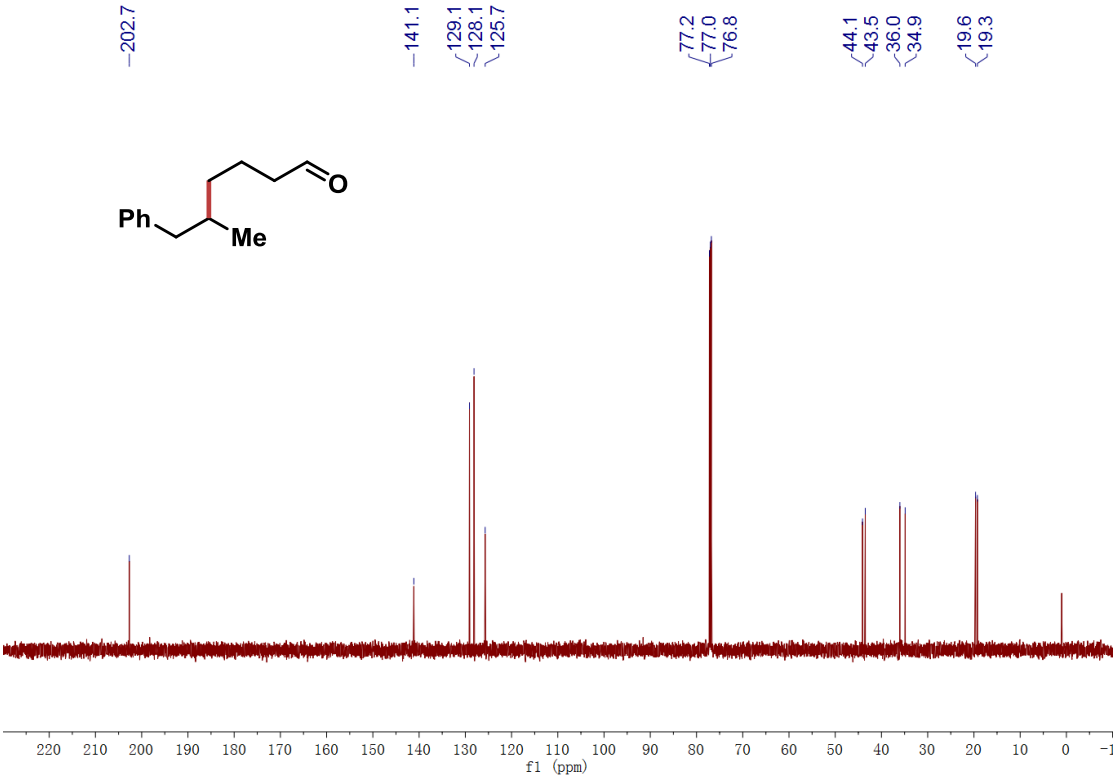
^{13}C NMR of Compound SI-24 (151 MHz, $CDCl_3$):



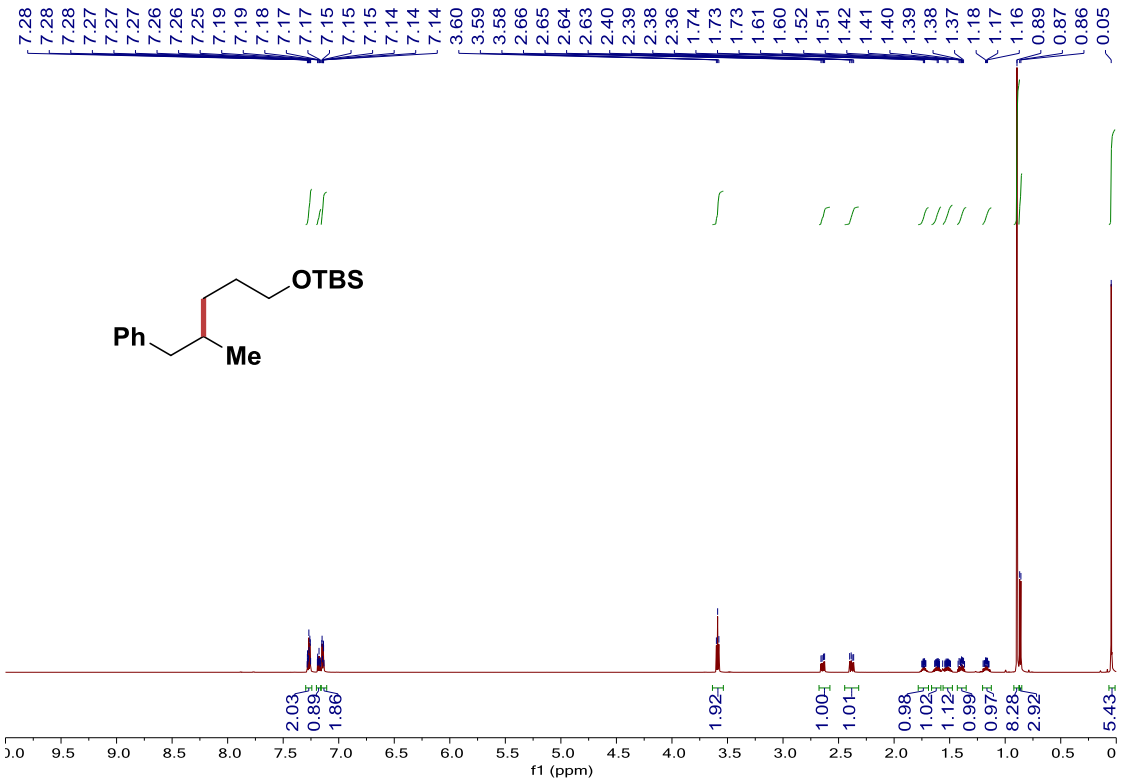
^{1}H NMR of Compound SI-25 (600 MHz, $CDCl_3$):



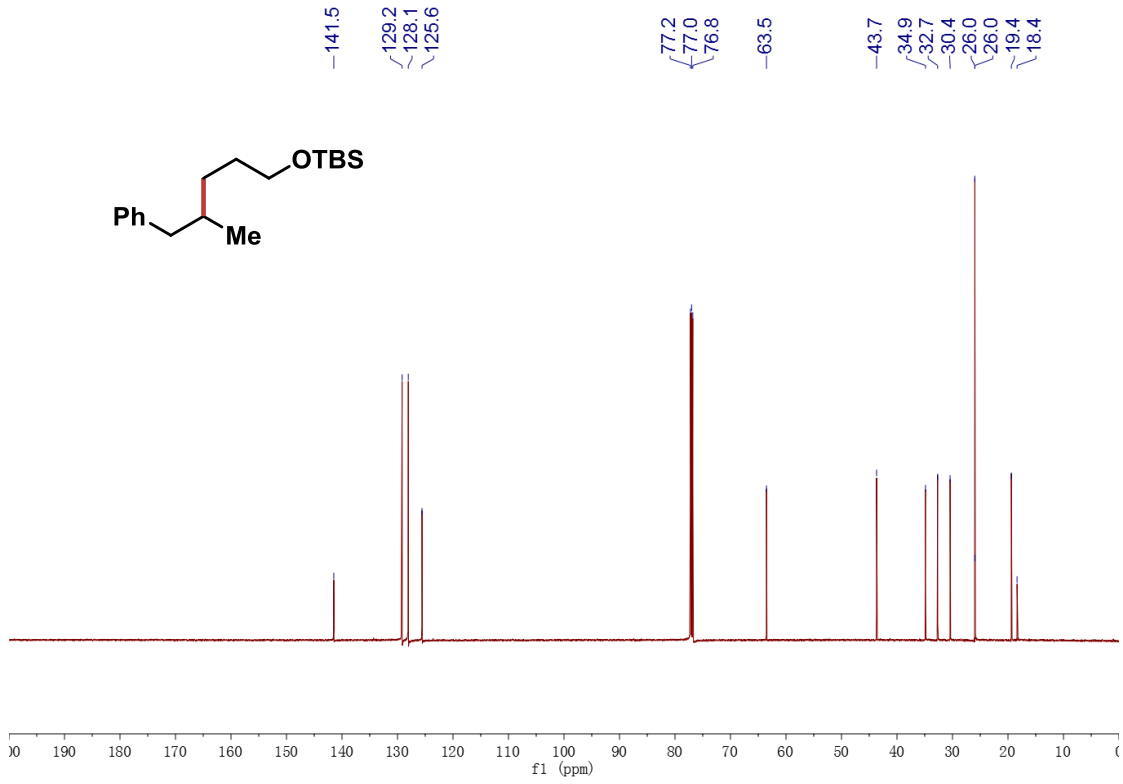
^{13}C NMR of Compound SI-25 (151 MHz, $CDCl_3$):



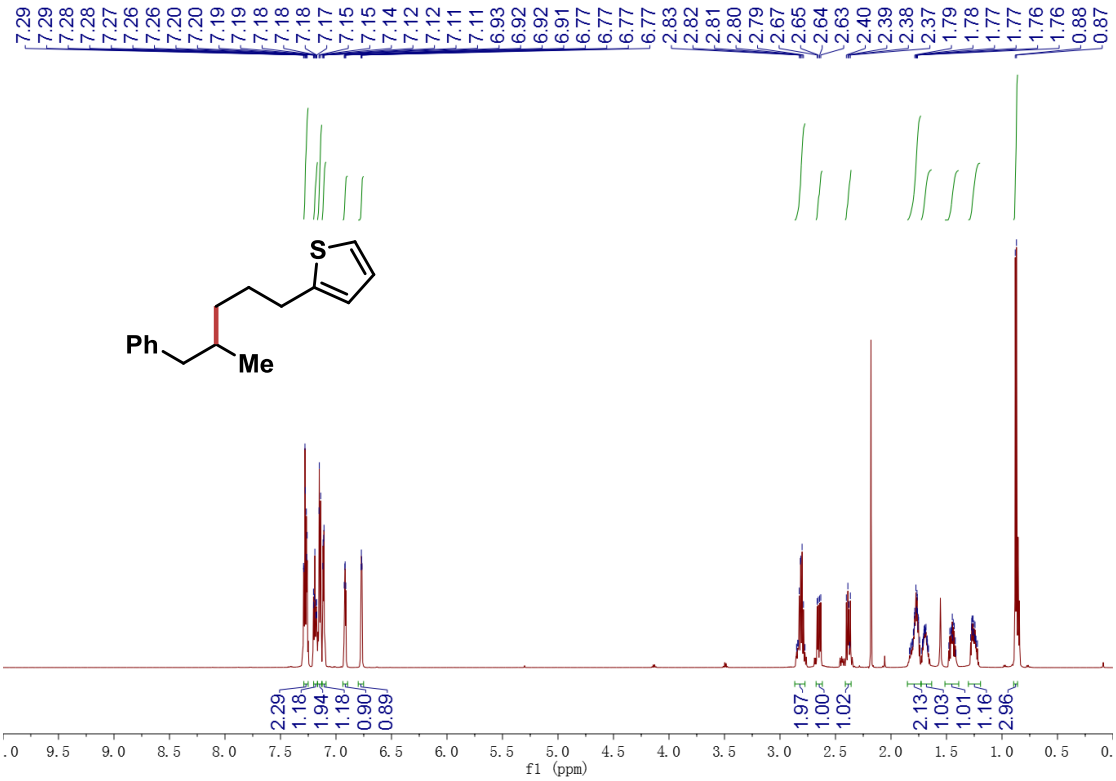
^{1}H NMR of Compound SI-26 (600 MHz, $CDCl_3$):



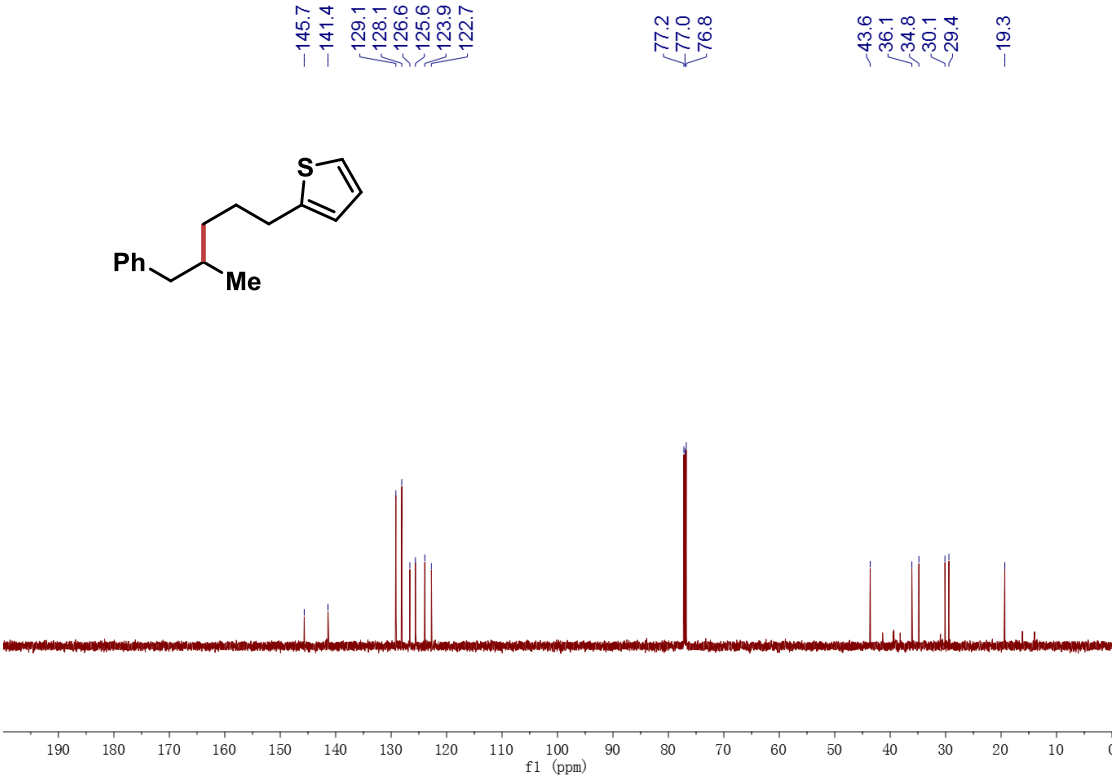
^{13}C NMR of Compound SI-26 (151 MHz, $CDCl_3$):



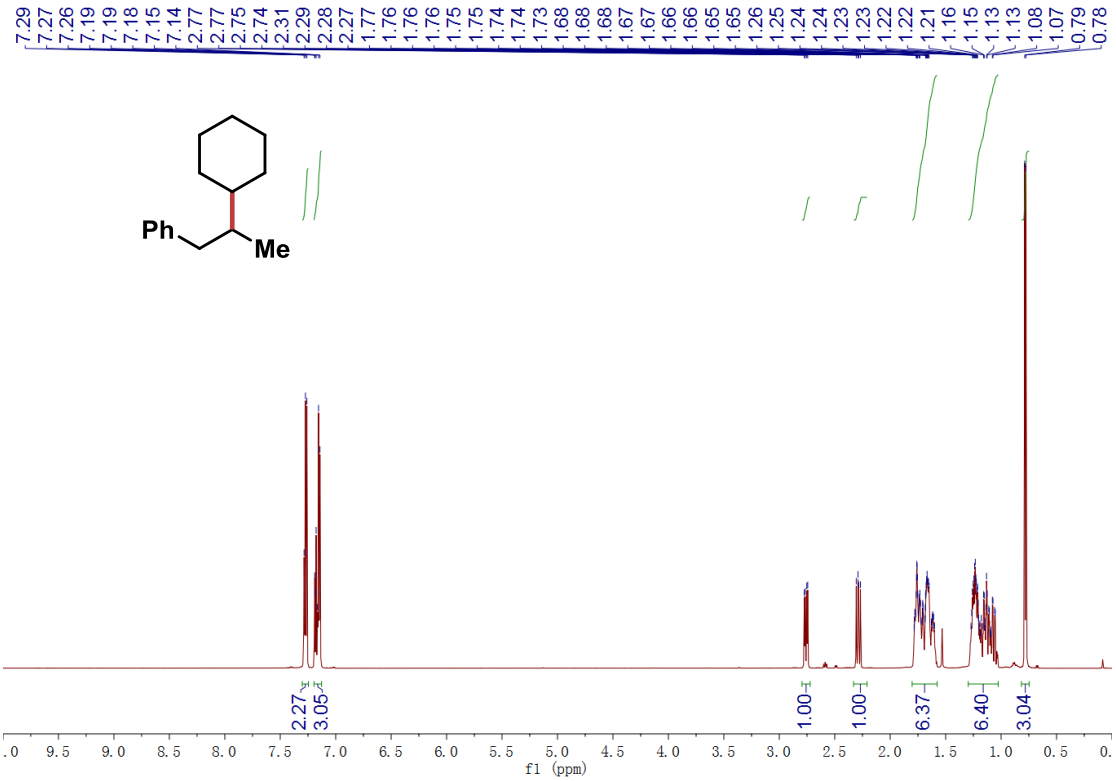
^{1}H NMR of Compound SI-27 (600 MHz, $CDCl_3$):



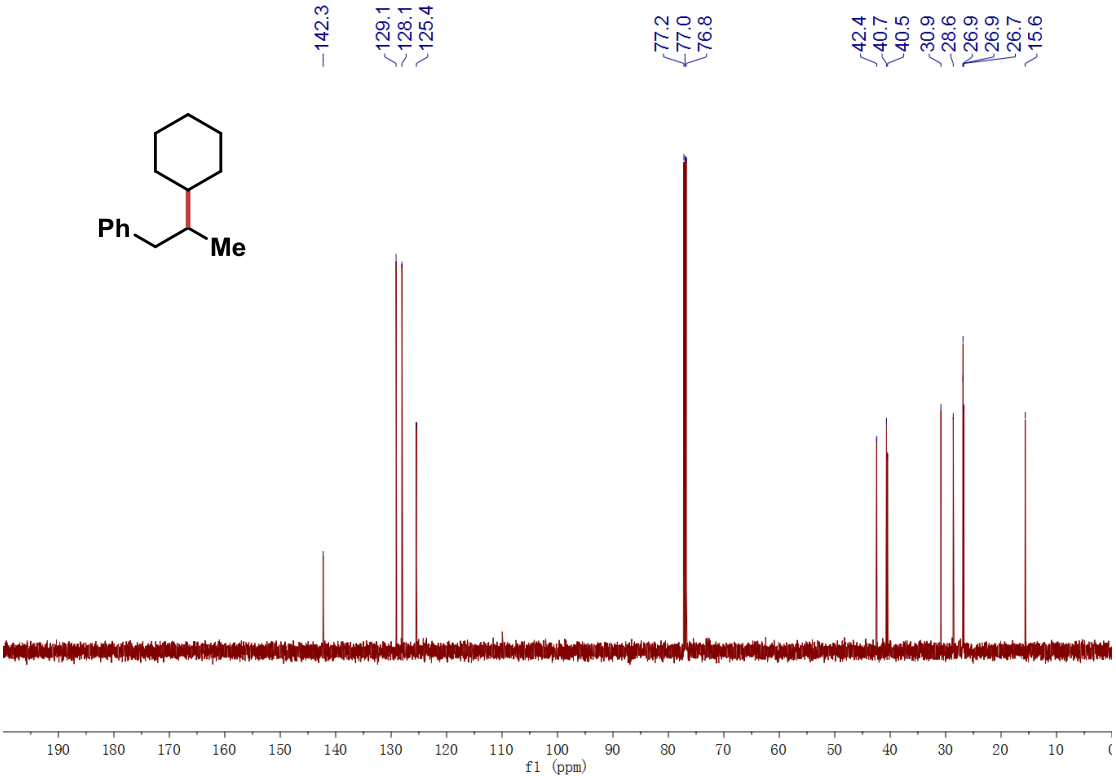
^{13}C NMR of Compound SI-27 (151 MHz, $CDCl_3$):



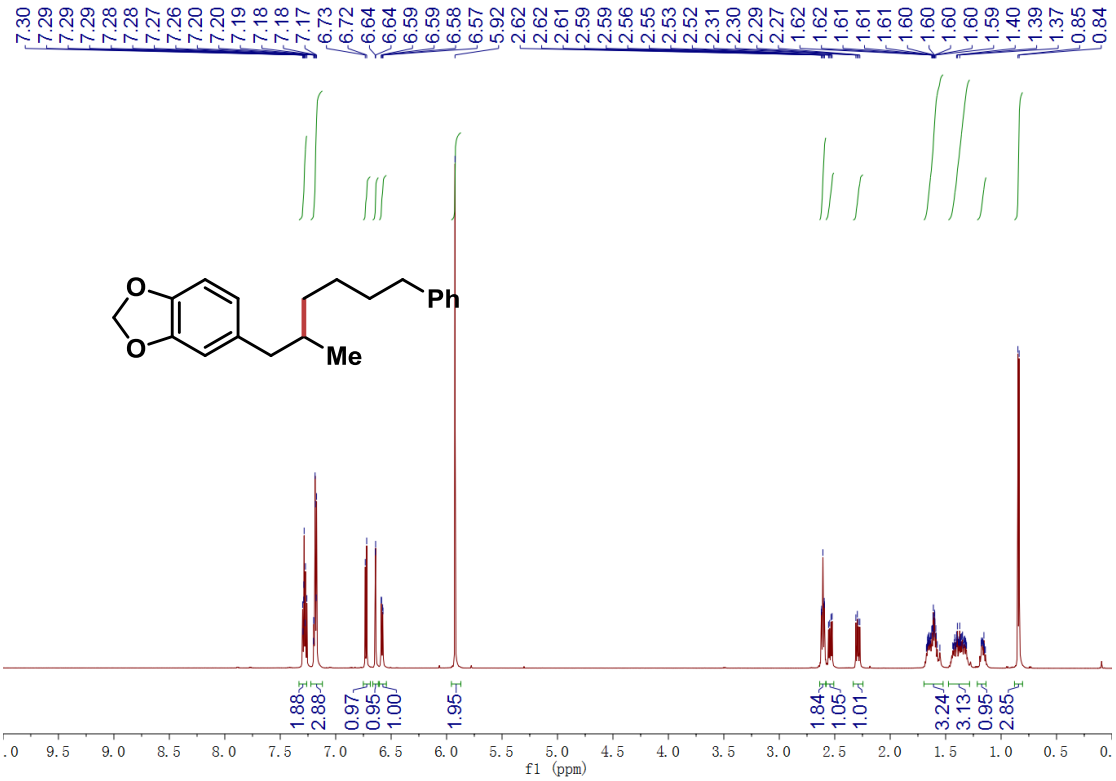
^{1}H NMR of Compound SI-28 (600 MHz, $CDCl_3$):



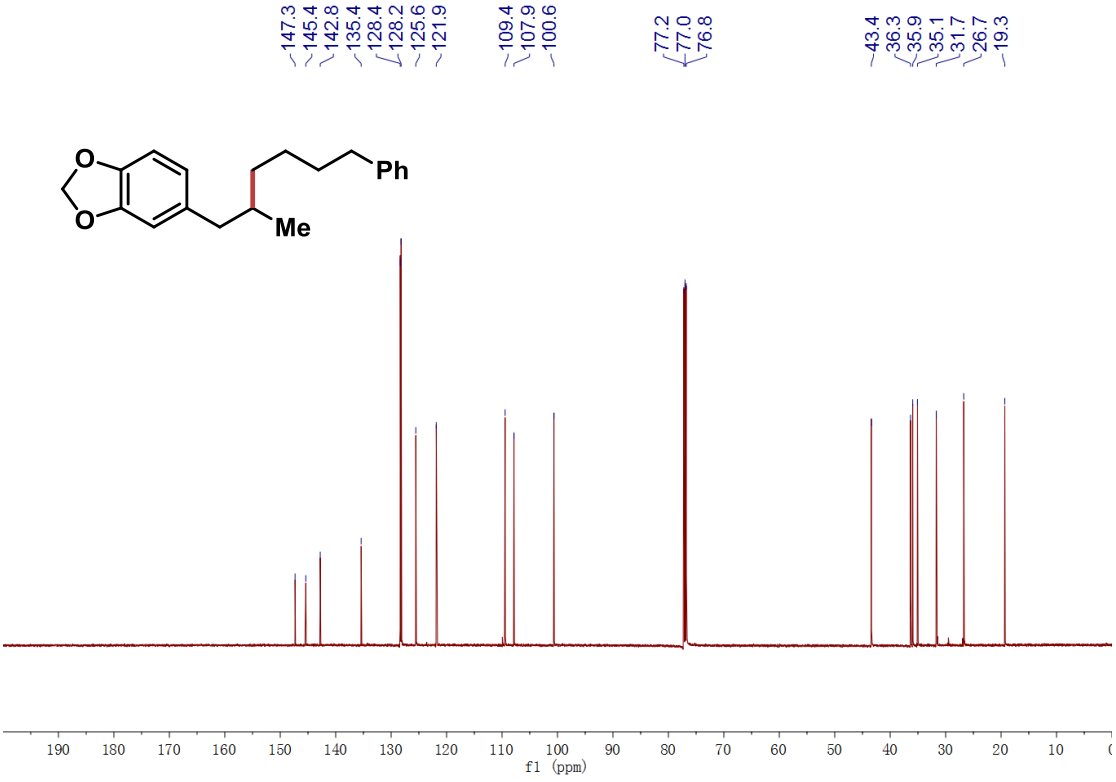
^{13}C NMR of Compound SI-28 (151 MHz, $CDCl_3$):



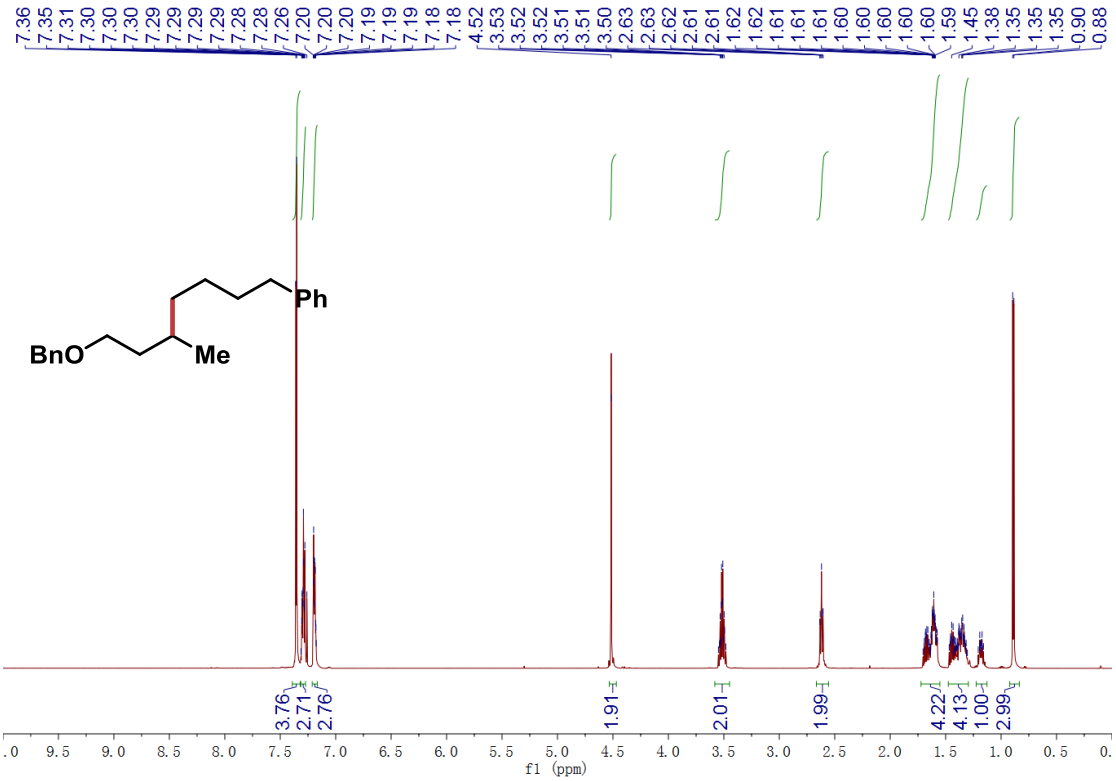
^{1}H NMR of Compound SI-29 (600 MHz, $CDCl_3$):



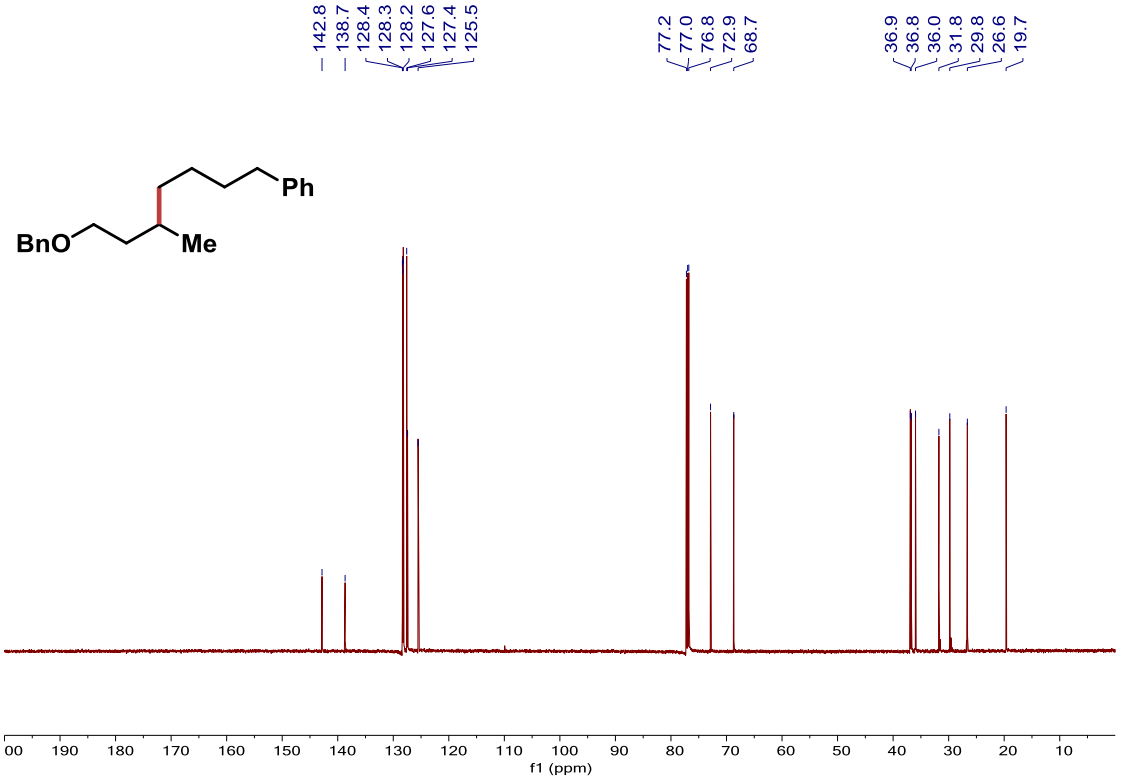
^{13}C NMR of Compound SI-29 (151 MHz, $CDCl_3$):



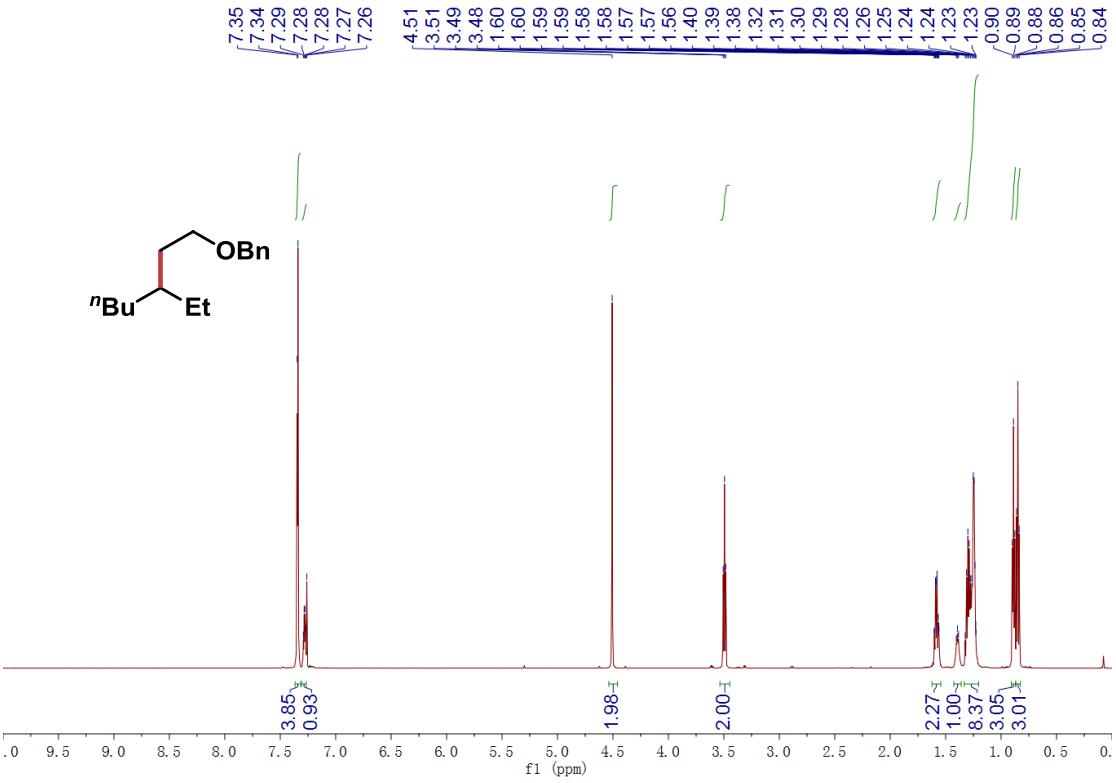
^{1}H NMR of Compound SI-30 (600 MHz, $CDCl_3$):



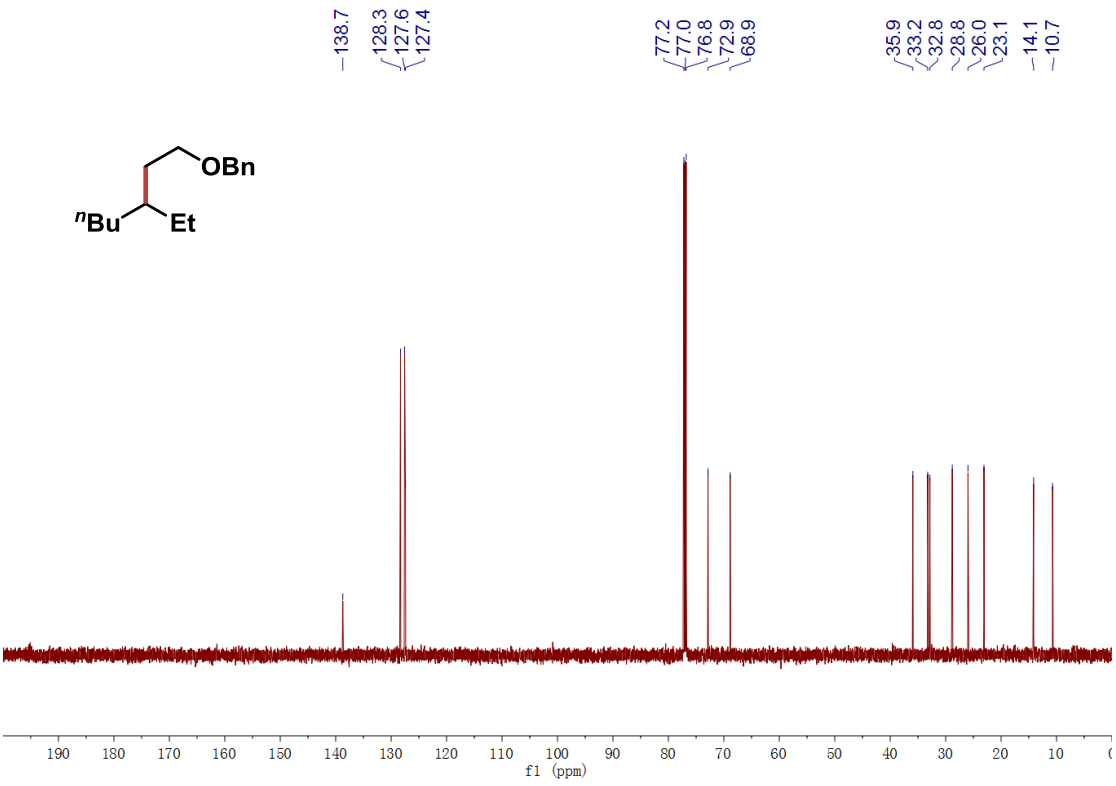
^{13}C NMR of Compound SI-30 (151 MHz, $CDCl_3$):



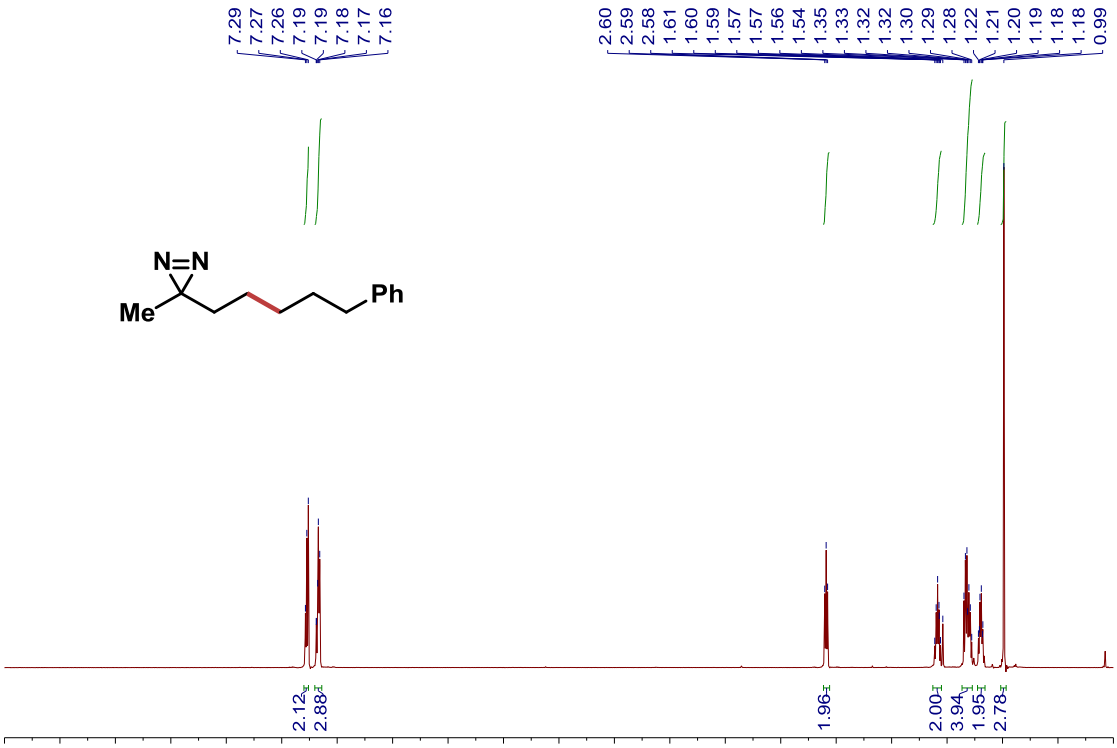
^{1}H NMR of Compound SI-31 (600 MHz, $CDCl_3$):



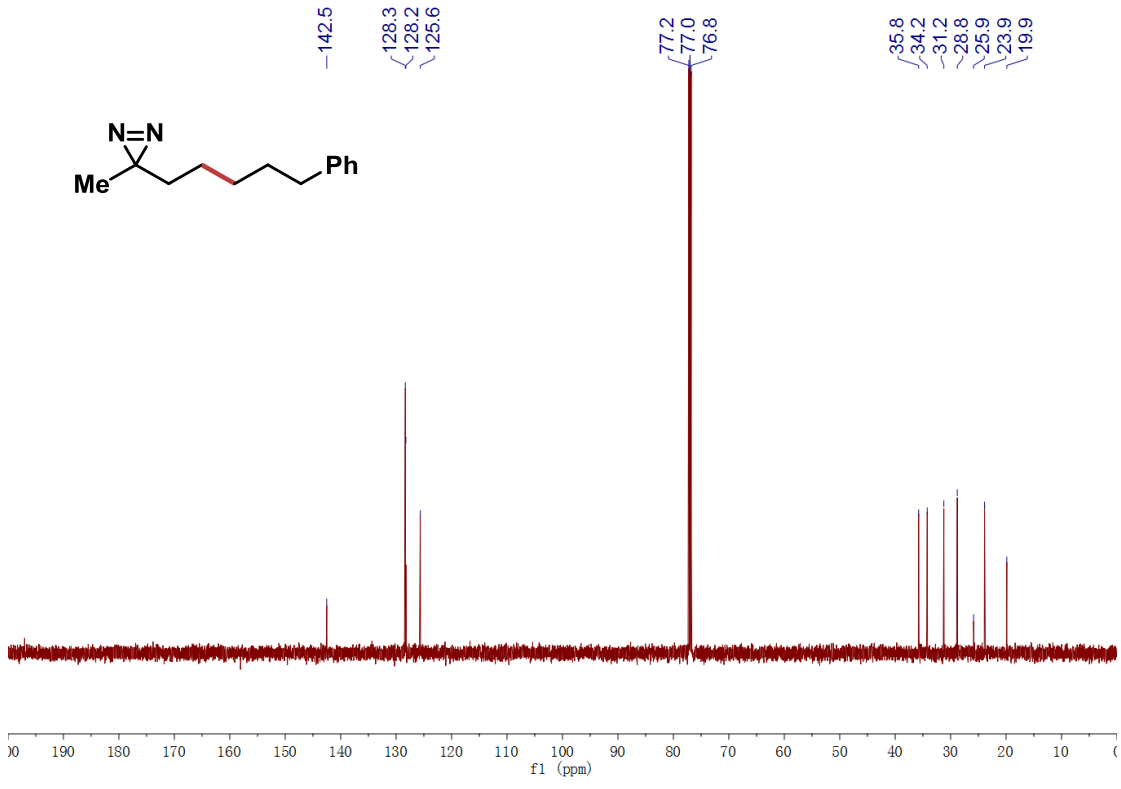
^{13}C NMR of Compound SI-31 (151 MHz, $CDCl_3$):



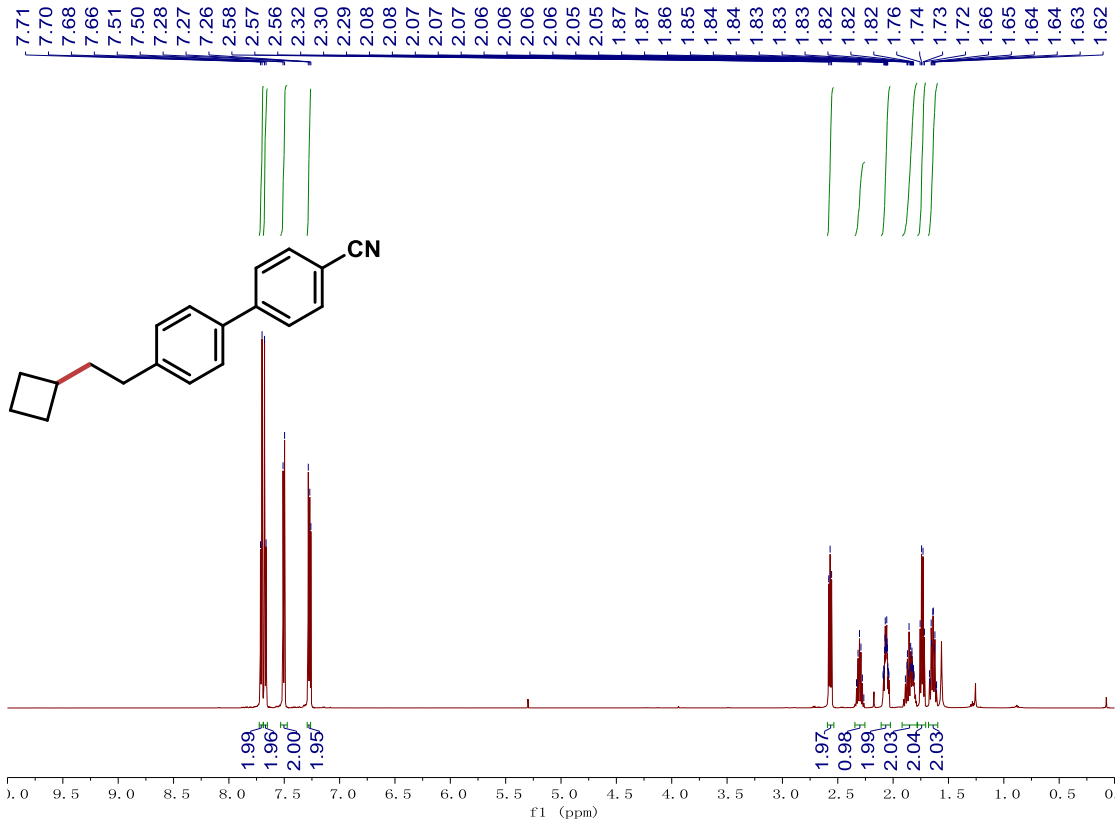
^{1}H NMR of Compound SI-32 (600 MHz, $CDCl_3$):



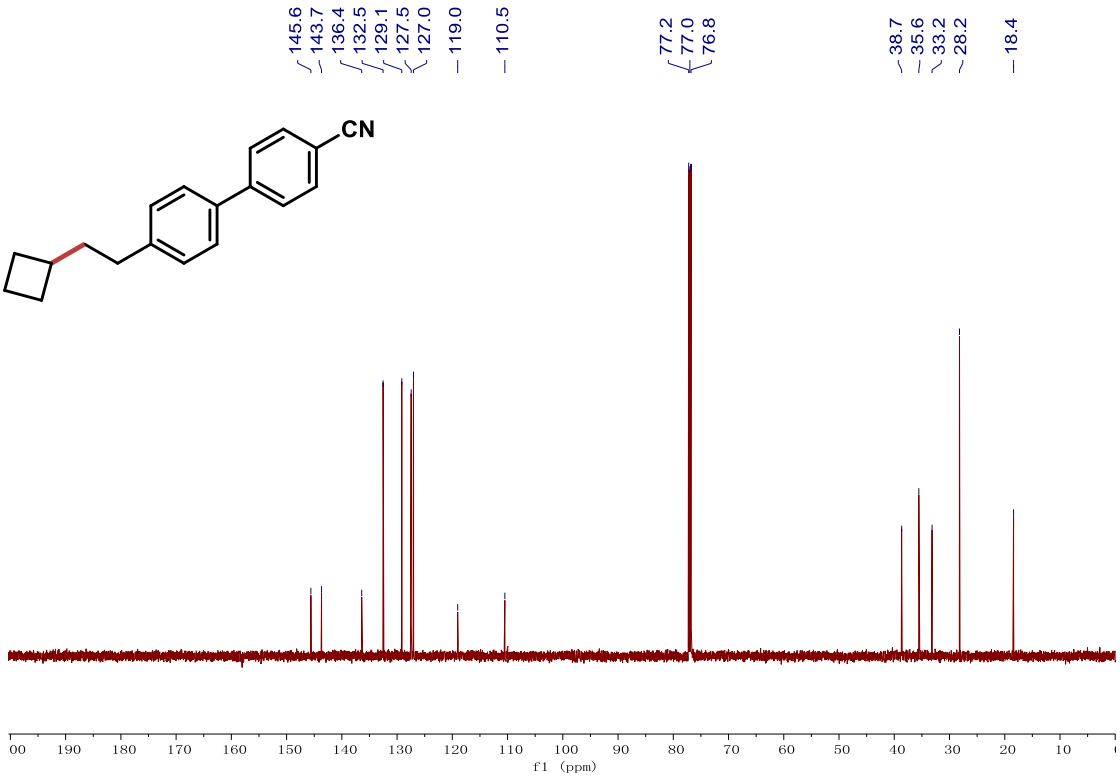
^{13}C NMR of Compound SI-32 (151 MHz, $CDCl_3$):



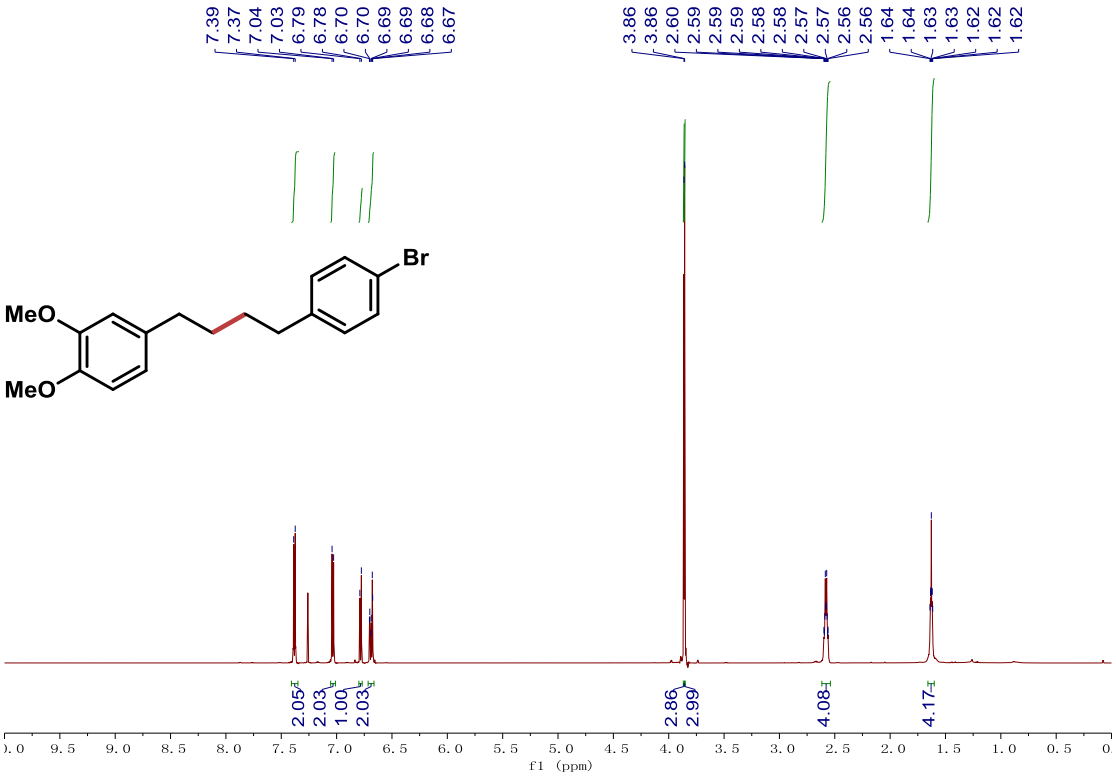
^{1}H NMR of Compound 1 (600 MHz, $CDCl_3$):



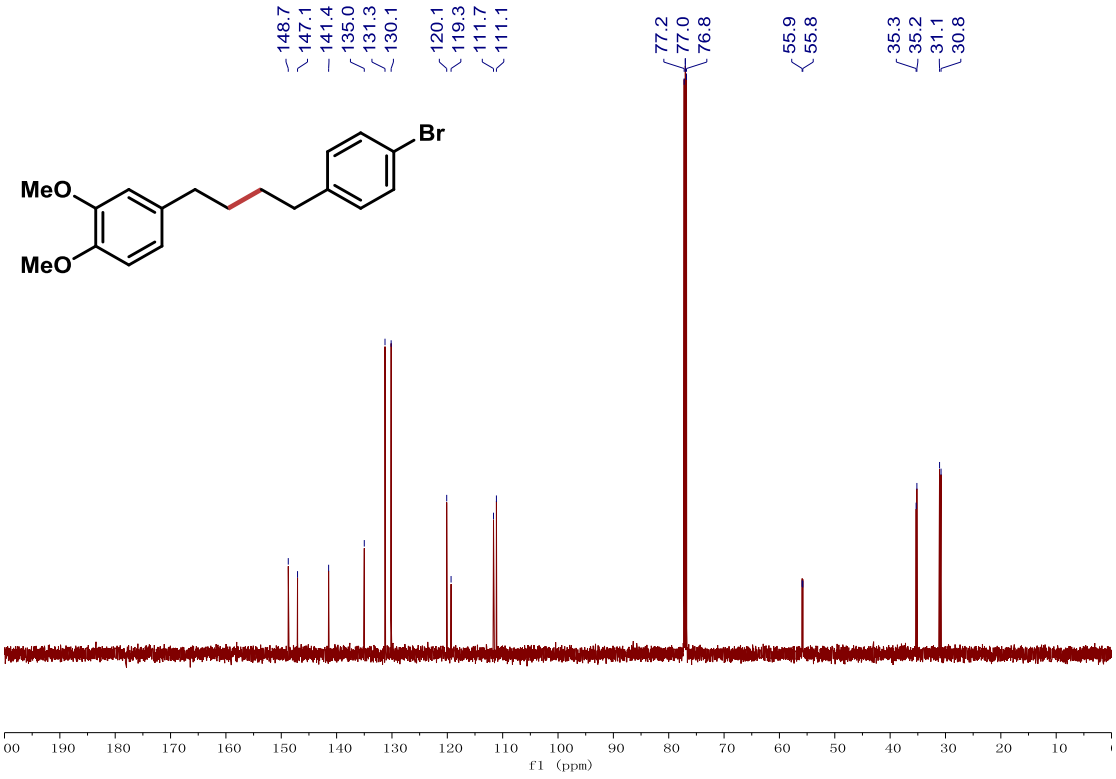
^{13}C NMR of Compound 1 (151 MHz, $CDCl_3$):



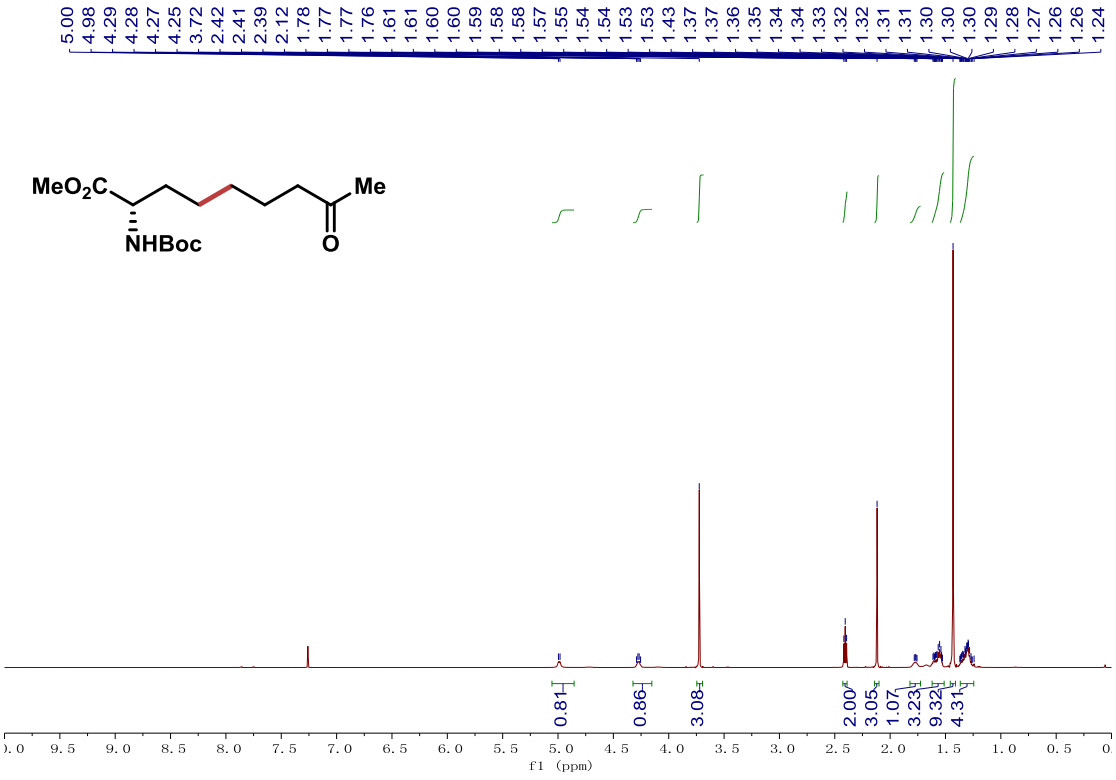
^{1}H NMR of Compound 7 (600 MHz, $CDCl_3$):



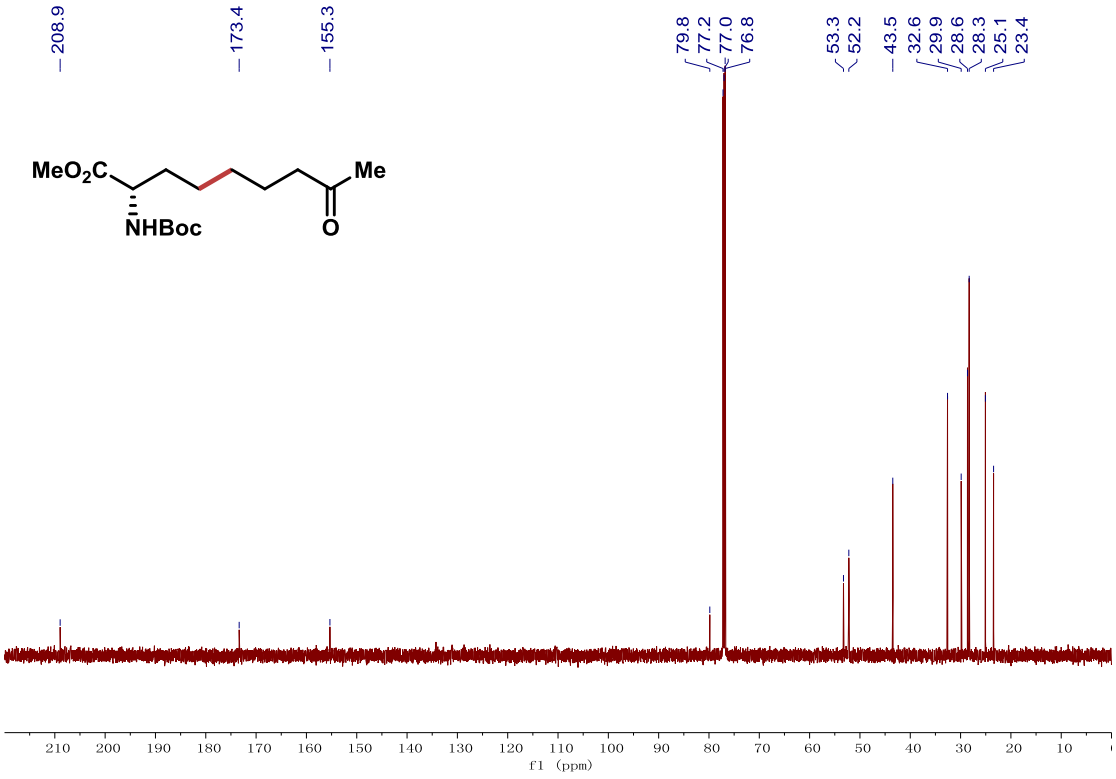
^{13}C NMR of Compound 7 (151 MHz, $CDCl_3$):



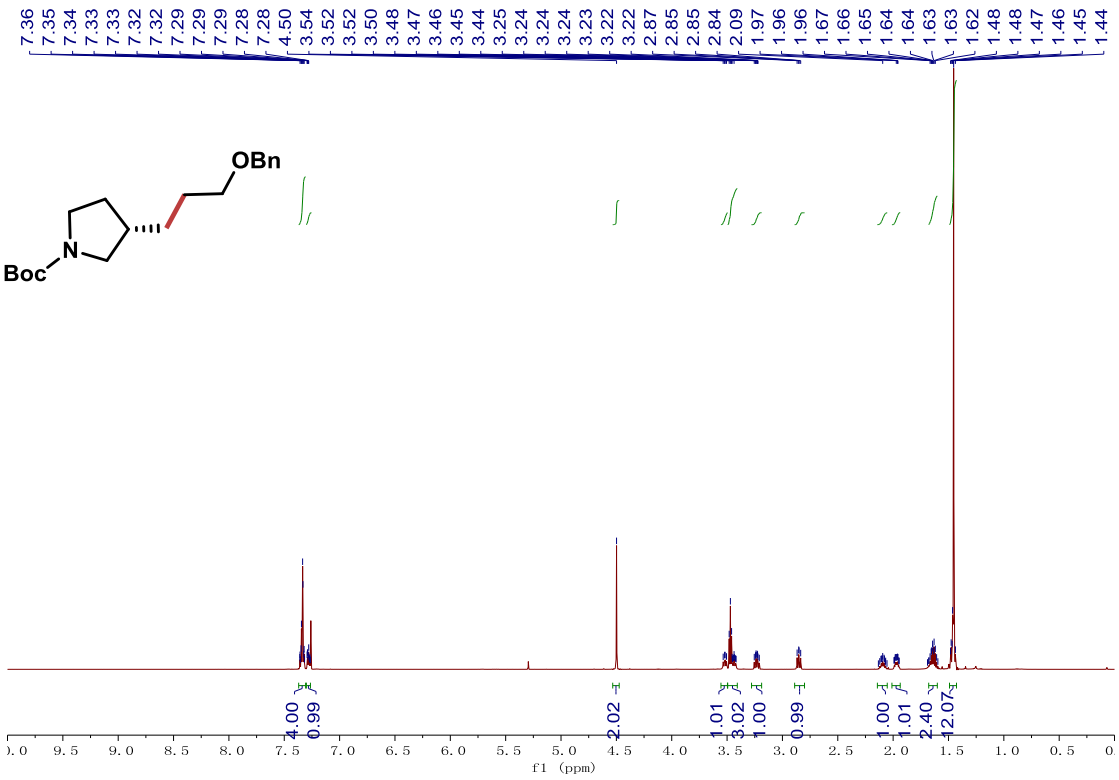
^{1}H NMR of Compound 8 (600 MHz, $CDCl_3$):



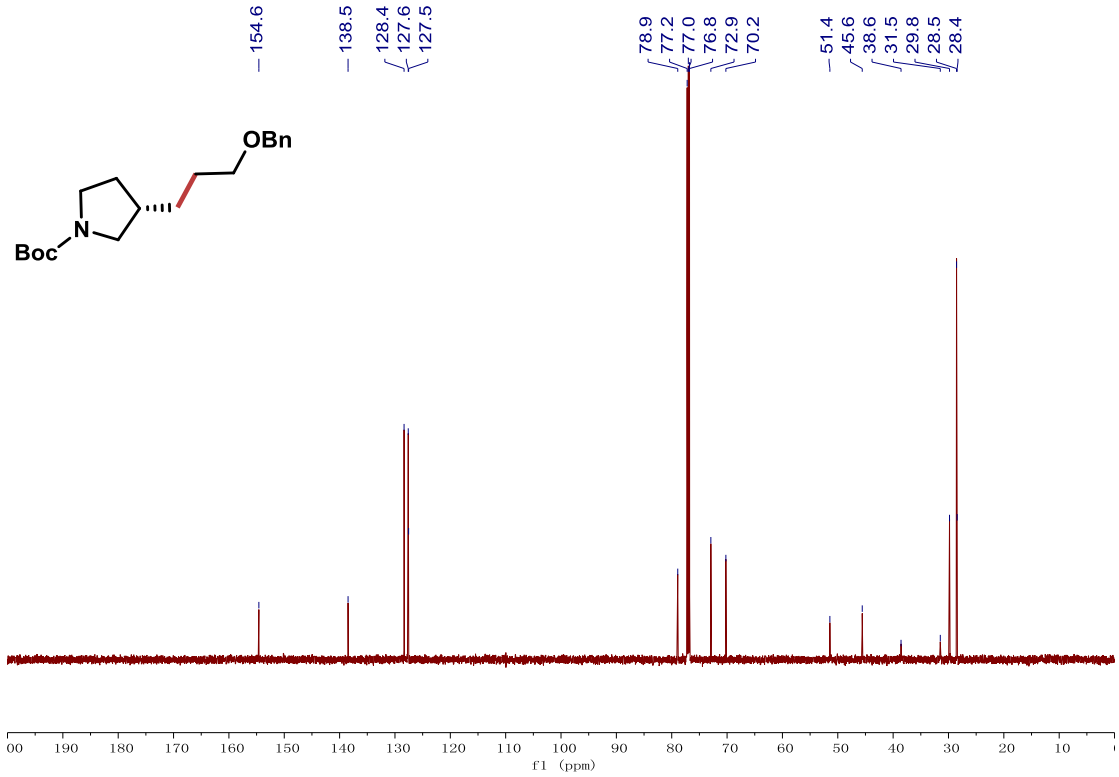
^{13}C NMR of Compound 8 (151 MHz, $CDCl_3$):



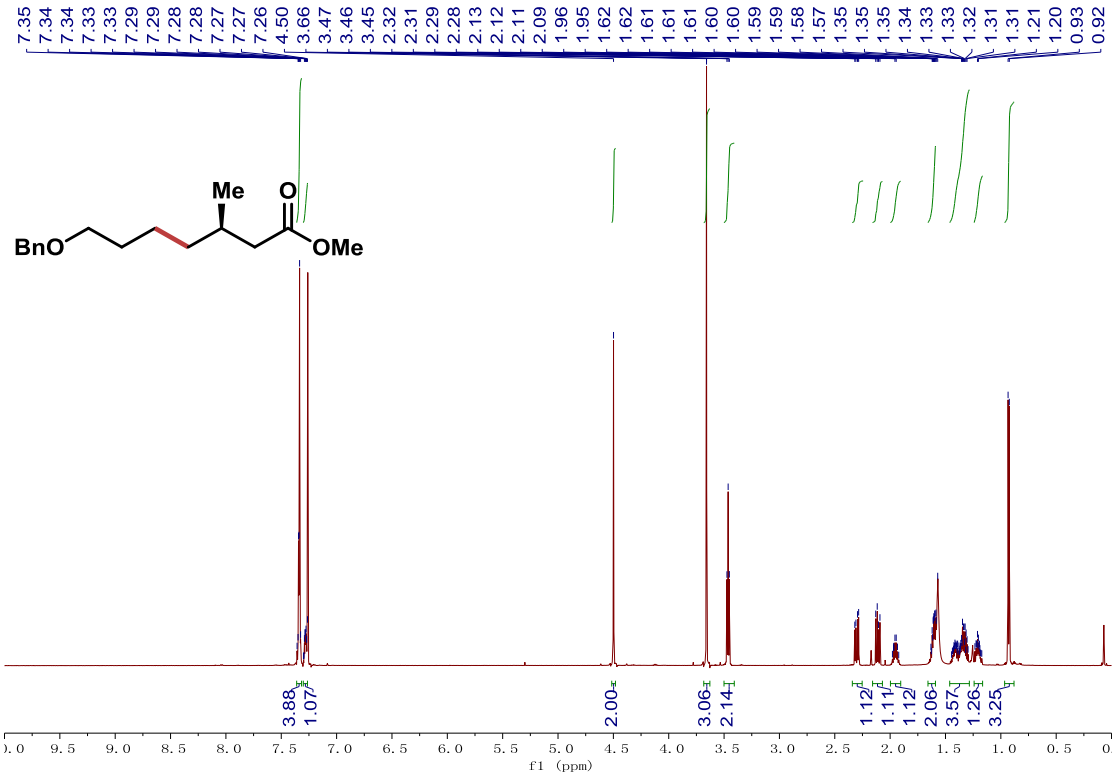
^{1}H NMR of Compound 9 (600 MHz, $CDCl_3$):



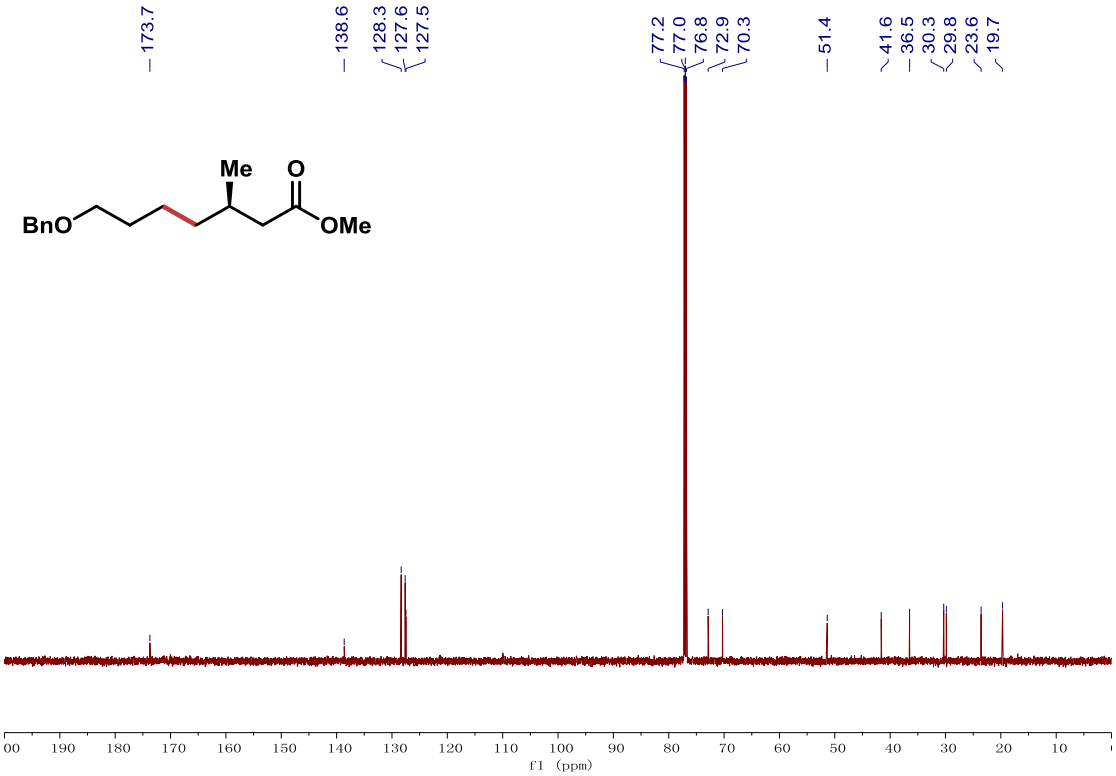
^{13}C NMR of Compound 9 (151 MHz, $CDCl_3$):



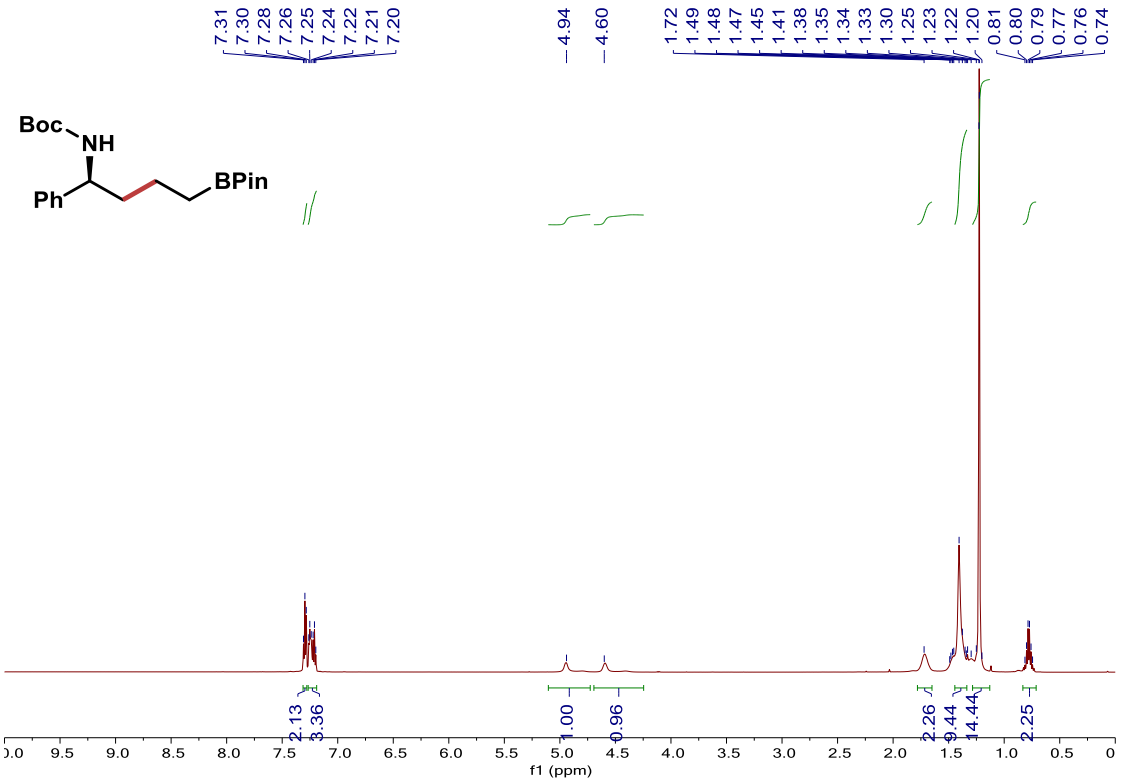
^{1}H NMR of Compound 10 (600 MHz, $CDCl_3$):



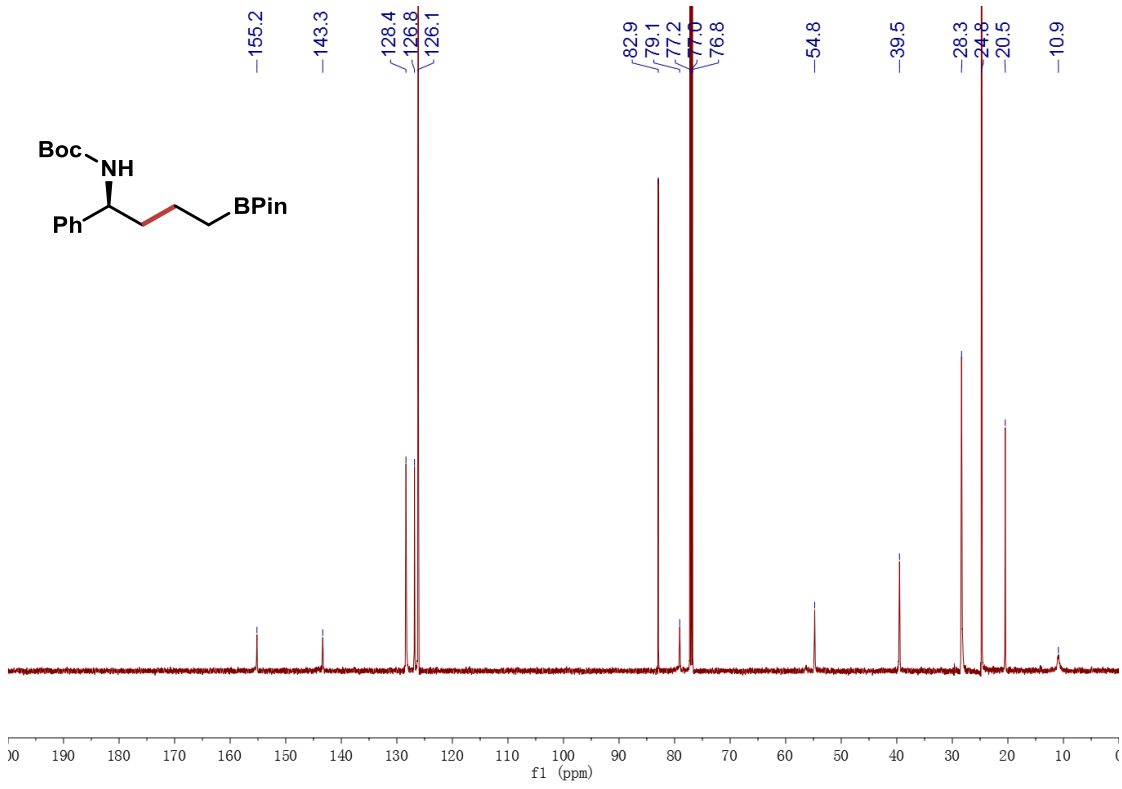
^{13}C NMR of Compound 10 (151 MHz, $CDCl_3$):



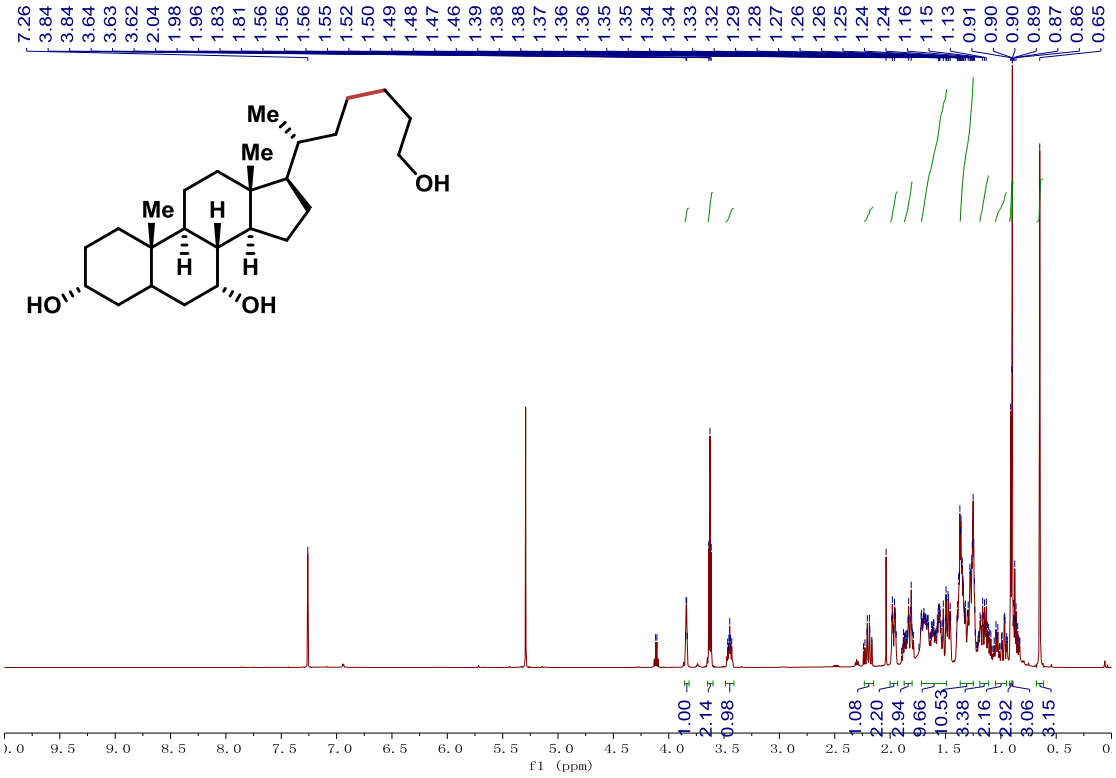
^{1}H NMR of Compound 11 (600 MHz, $CDCl_3$):



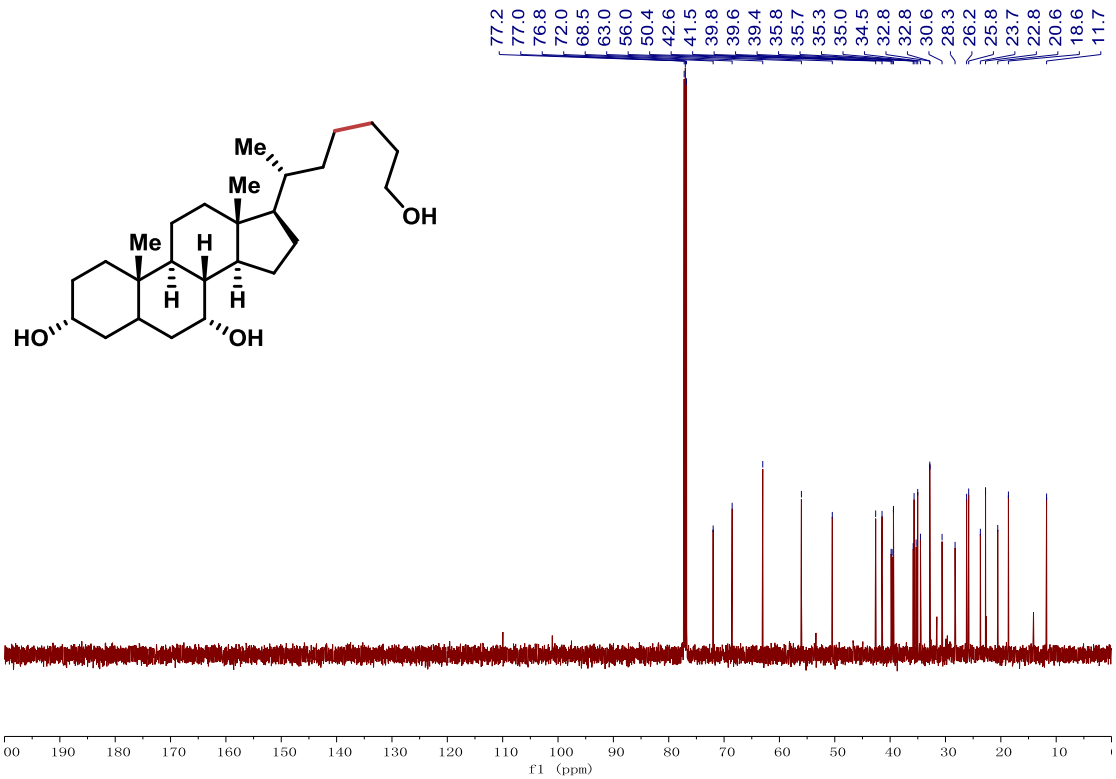
^{13}C NMR of Compound 11 (151 MHz, $CDCl_3$):



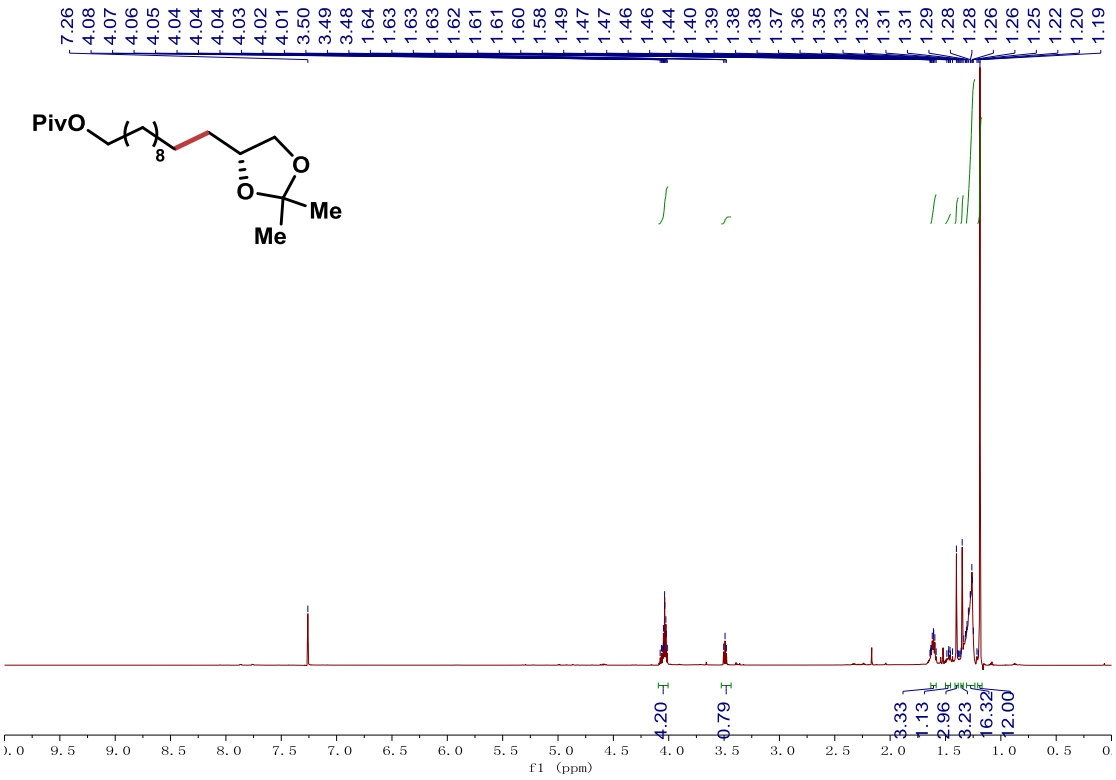
^{1}H NMR of Compound 12' (600 MHz, $CDCl_3$):



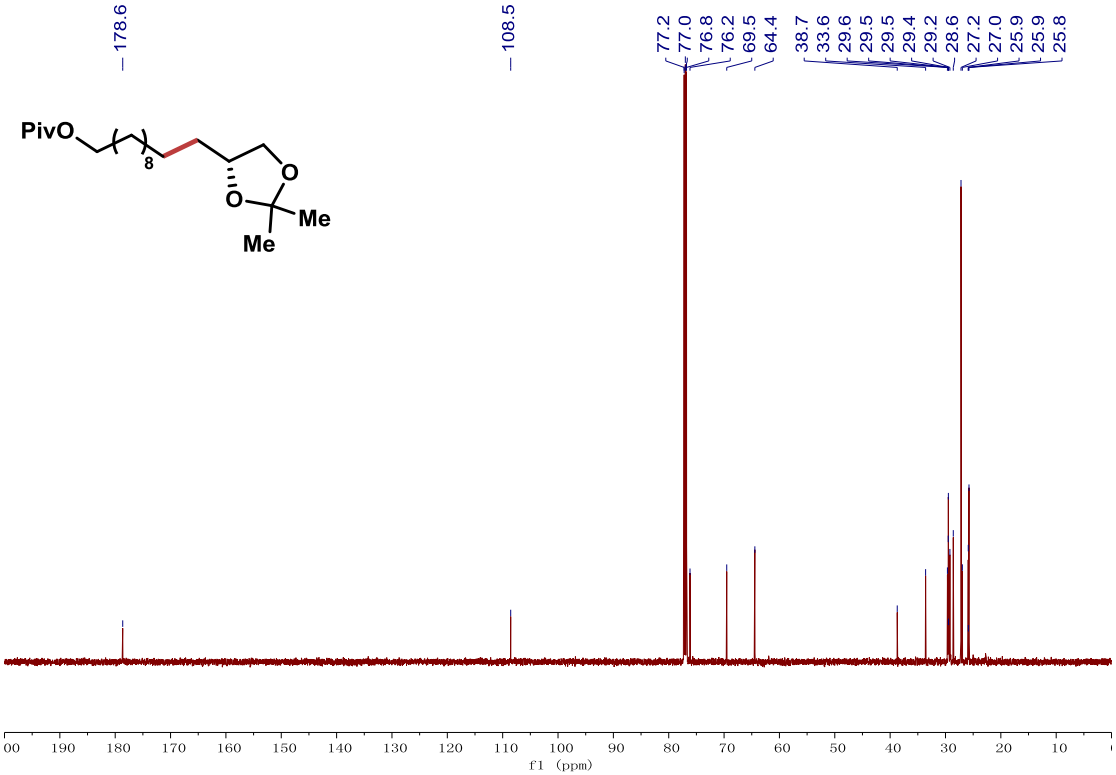
^{13}C NMR of Compound 12' (151 MHz, $CDCl_3$):



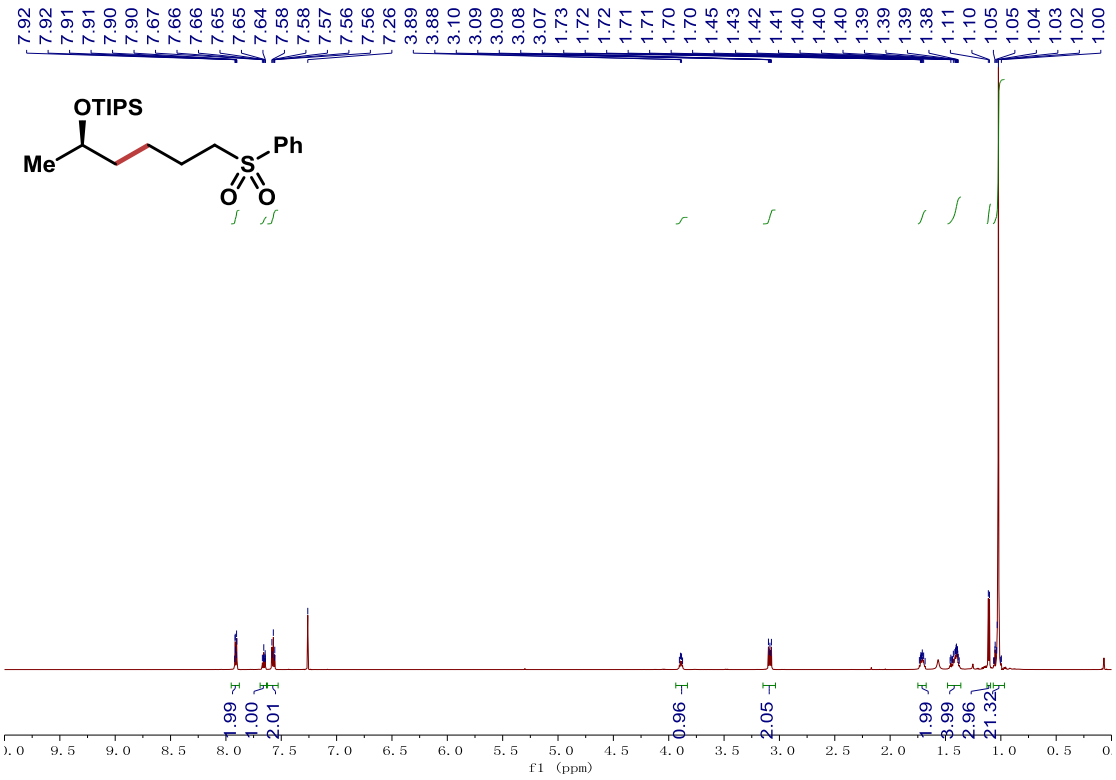
^{1}H NMR of Compound 13 (600 MHz, $CDCl_3$):



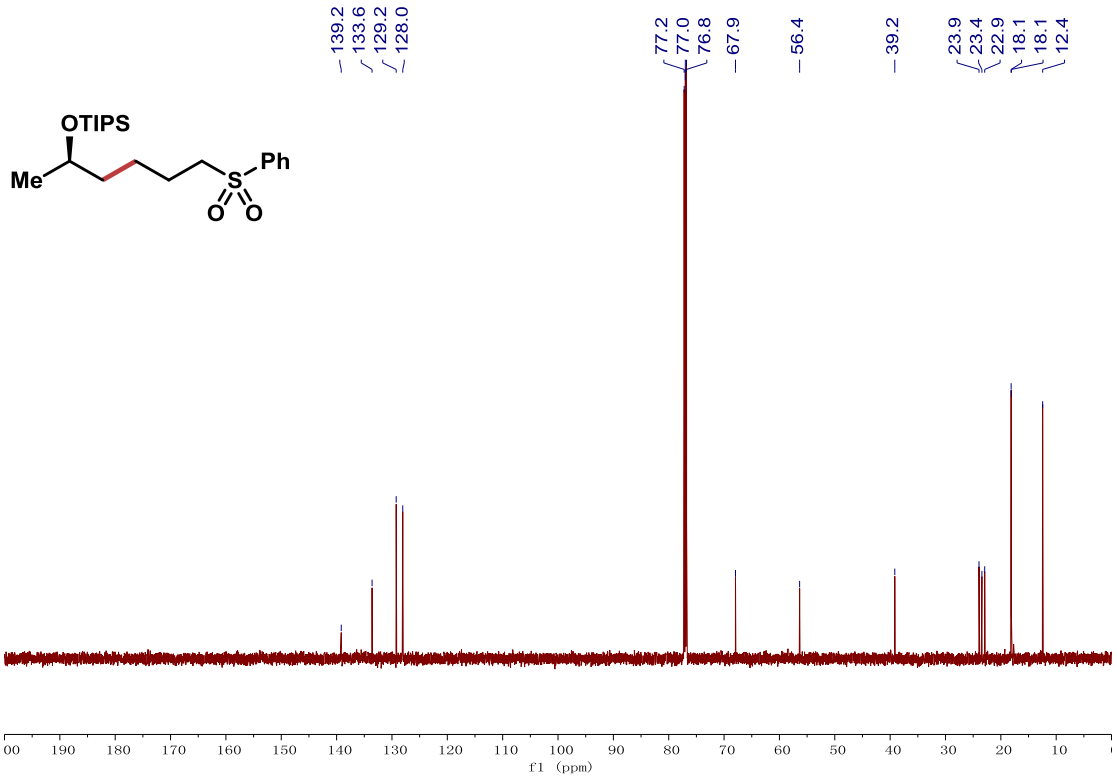
^{13}C NMR of Compound 13 (151 MHz, $CDCl_3$):



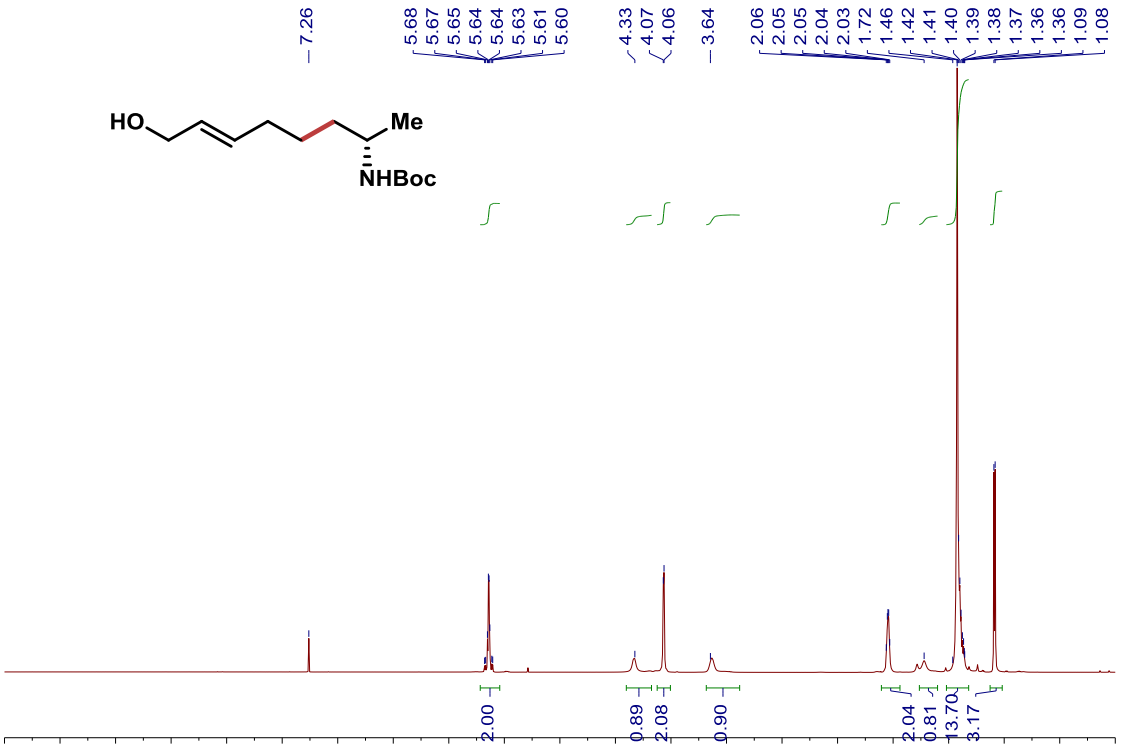
^{1}H NMR of Compound 14 (600 MHz, $CDCl_3$):



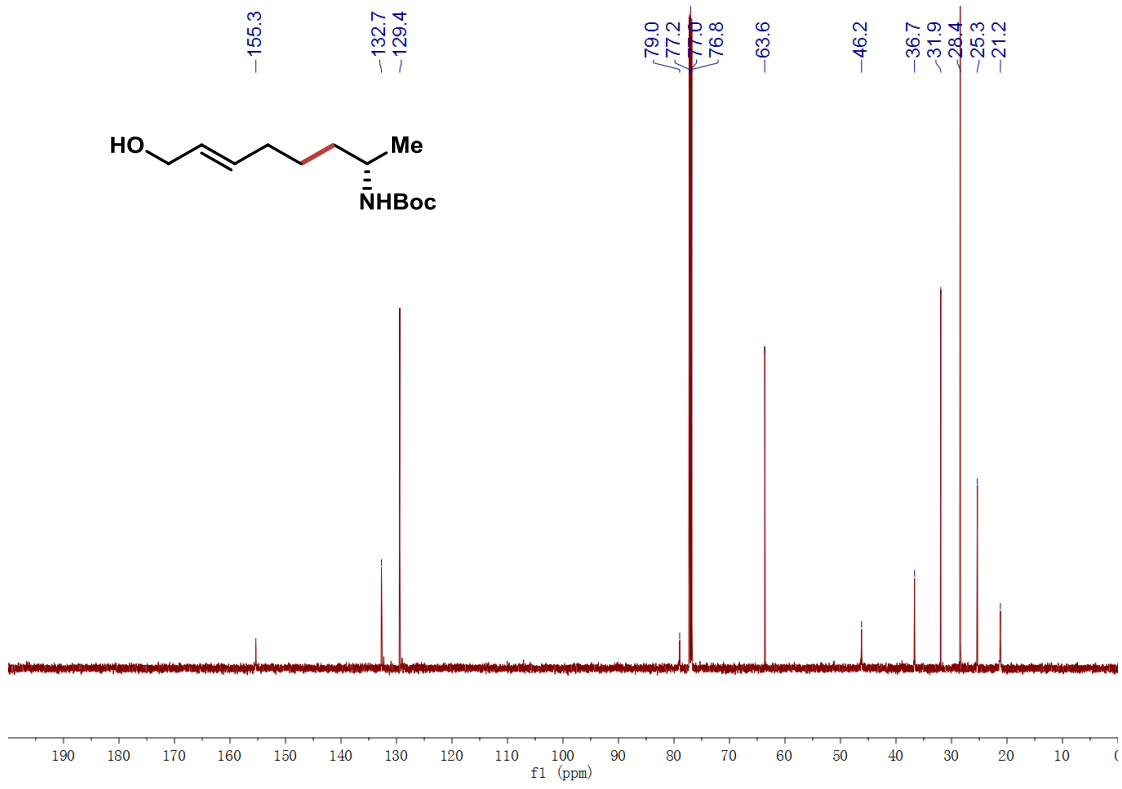
^{13}C NMR of Compound 14 (151 MHz, $CDCl_3$):



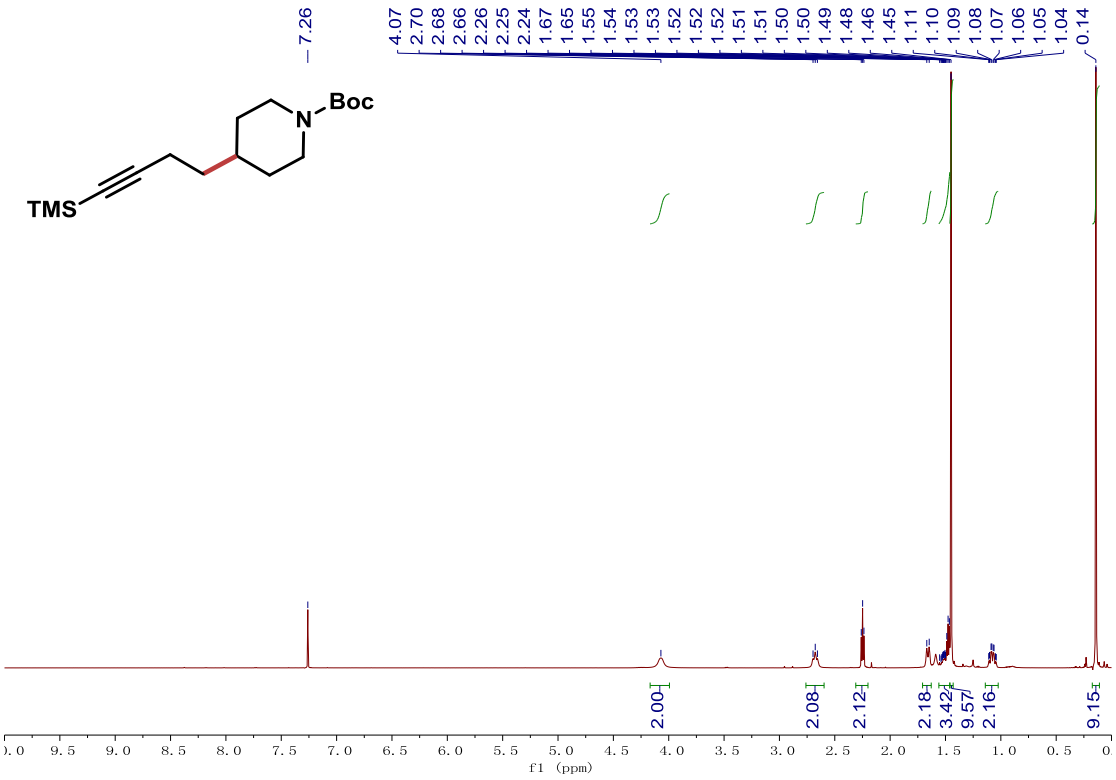
^{1}H NMR of Compound 15' (600 MHz, $CDCl_3$):



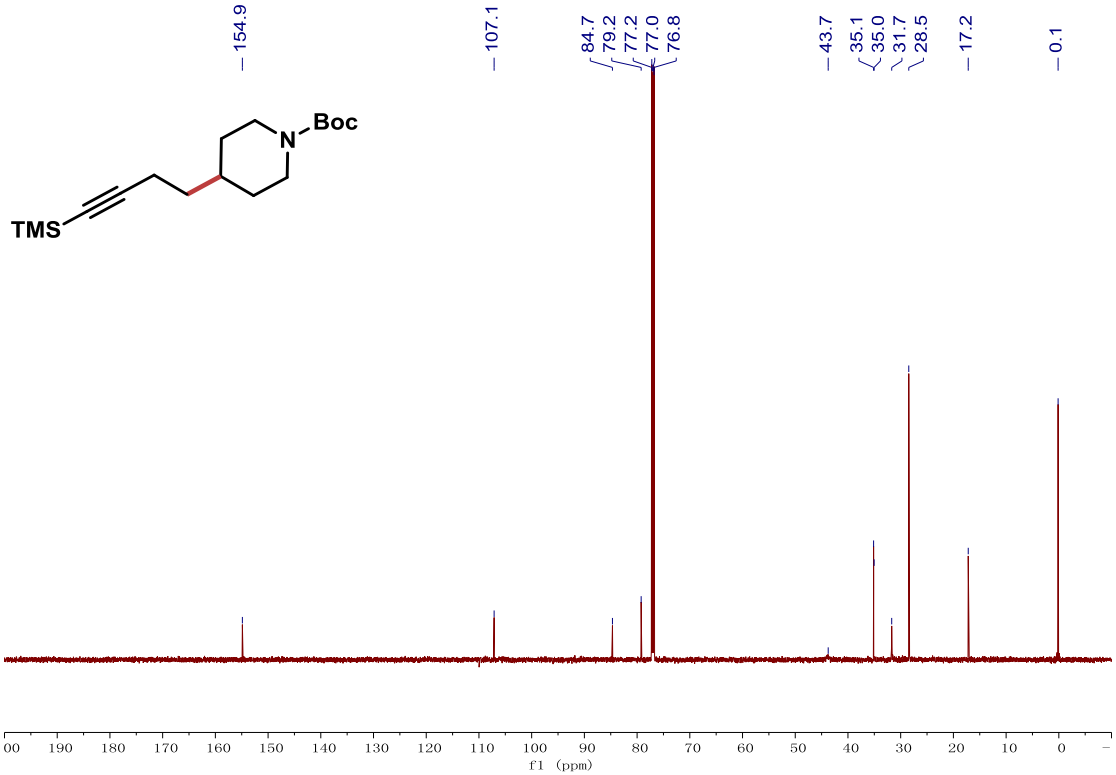
^{13}C NMR of Compound 15' (151 MHz, $CDCl_3$):



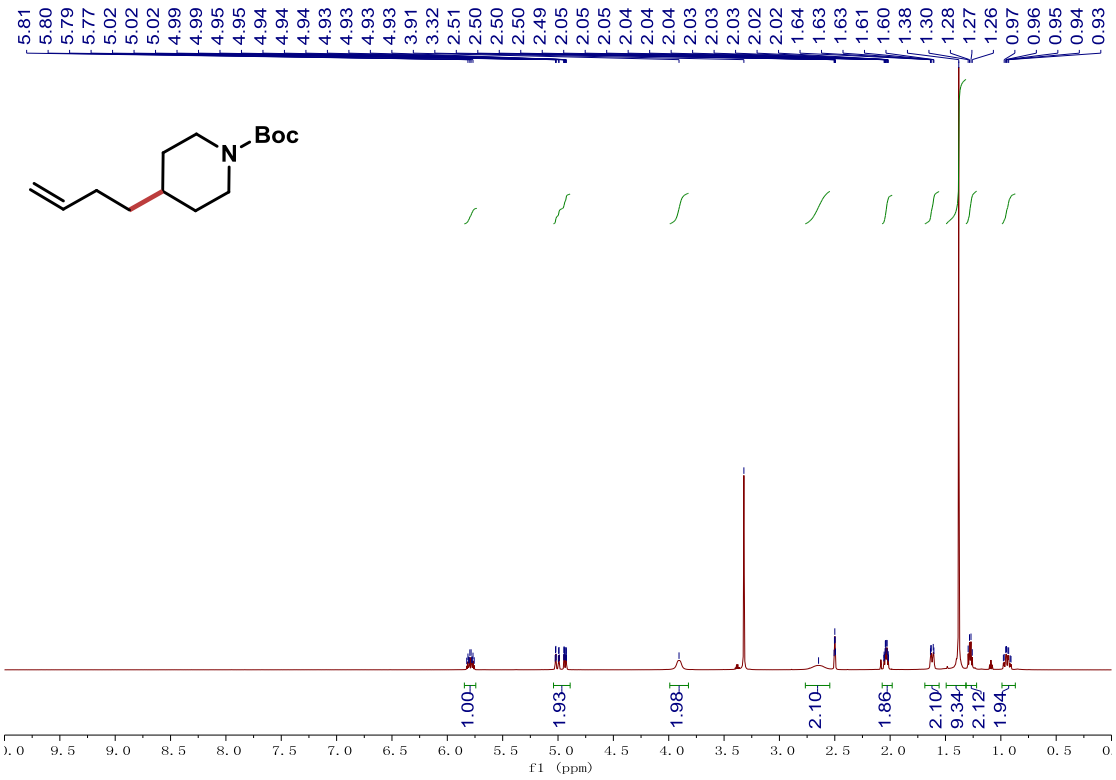
^{1}H NMR of Compound 16 (600 MHz, $CDCl_3$):



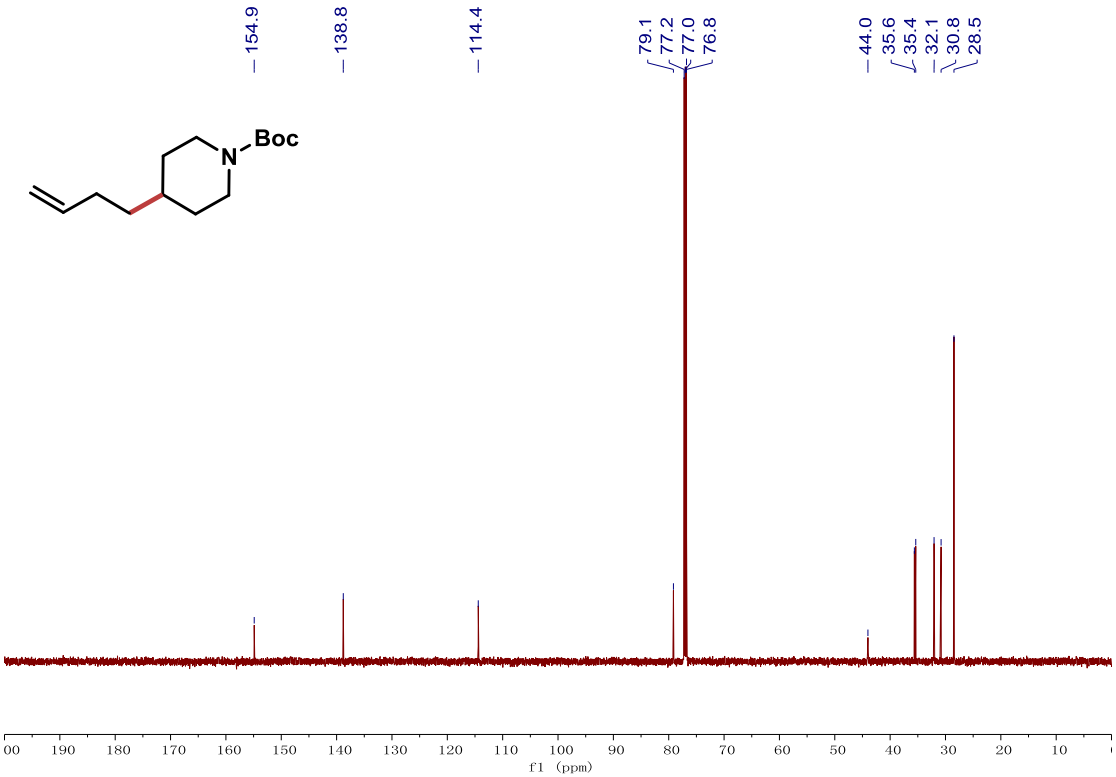
^{13}C NMR of Compound 16 (151 MHz, $CDCl_3$):



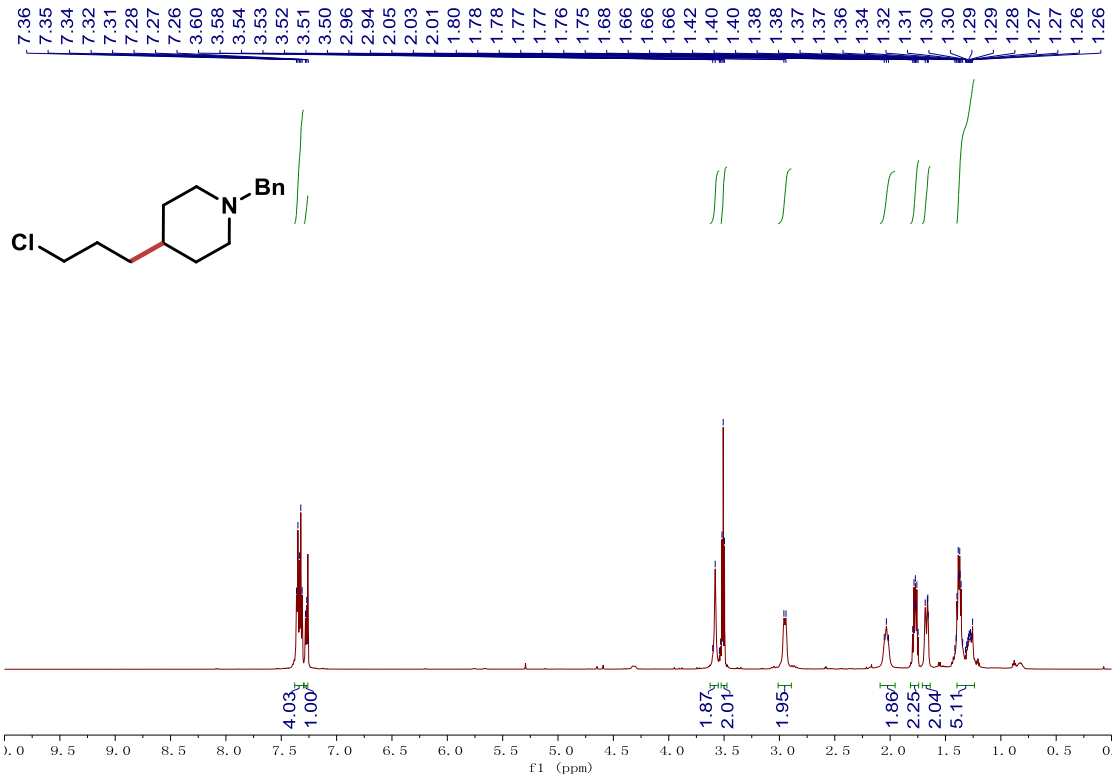
^{1}H NMR of Compound 17 (600 MHz, $CDCl_3$):



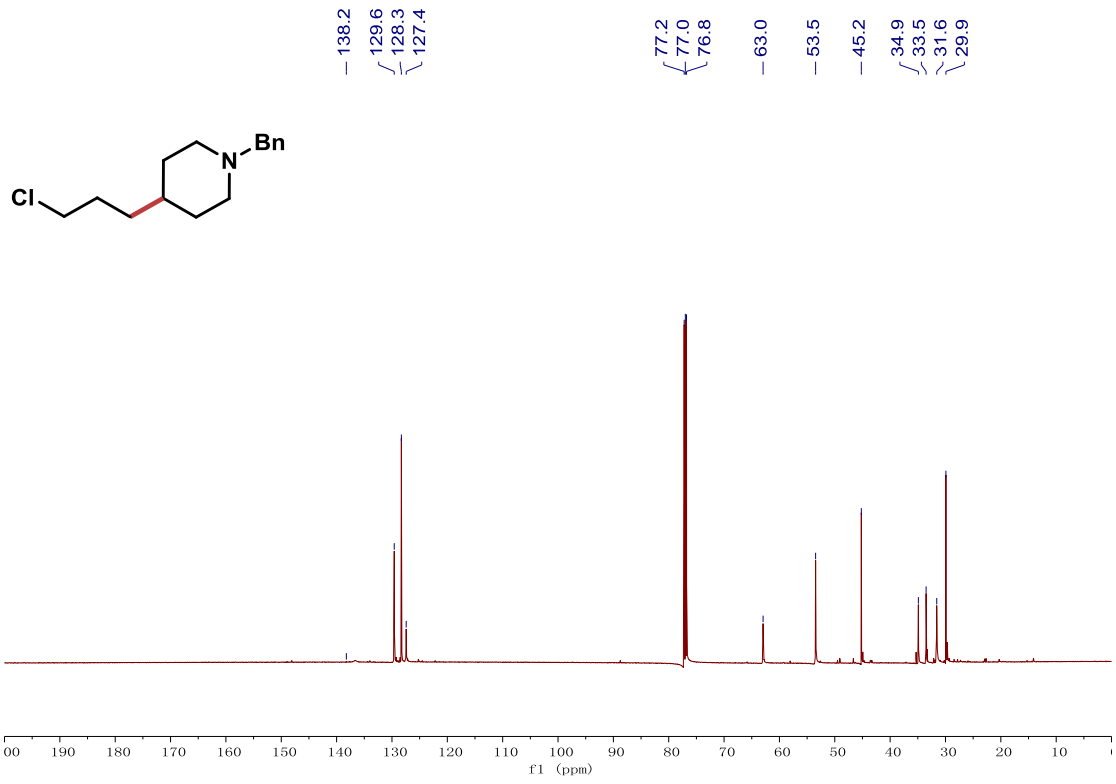
^{13}C NMR of Compound 17 (151 MHz, $CDCl_3$):



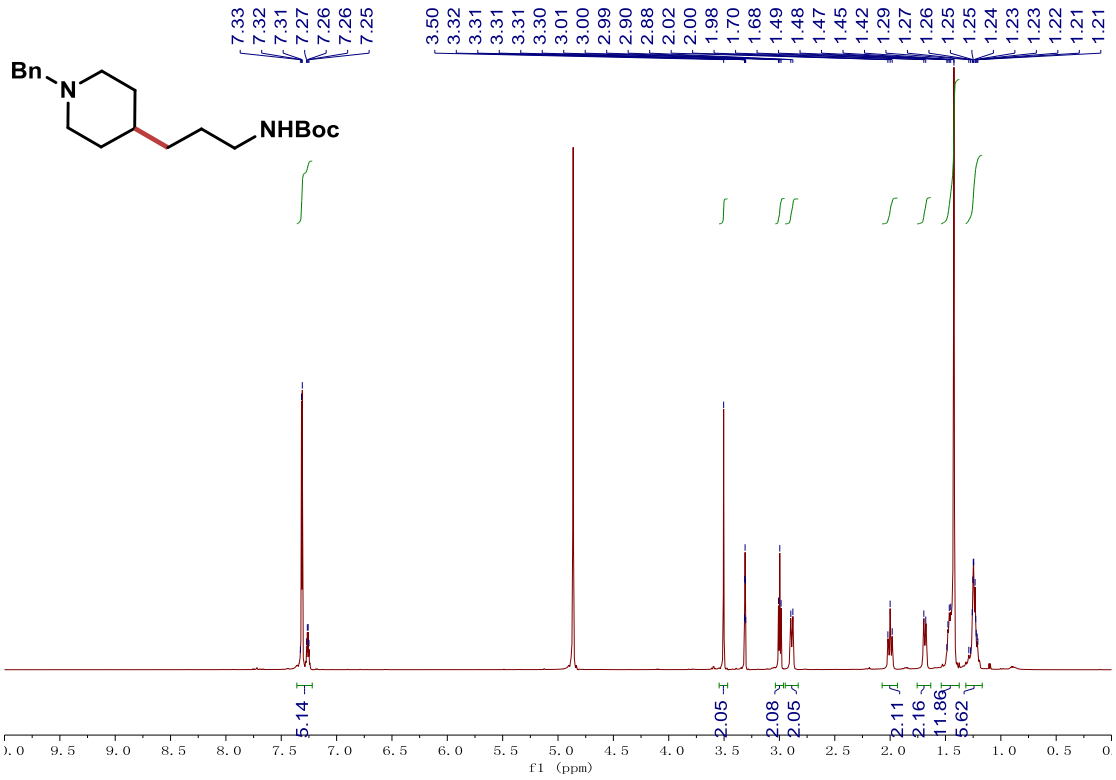
^{1}H NMR of Compound 18 (600 MHz, $CDCl_3$):



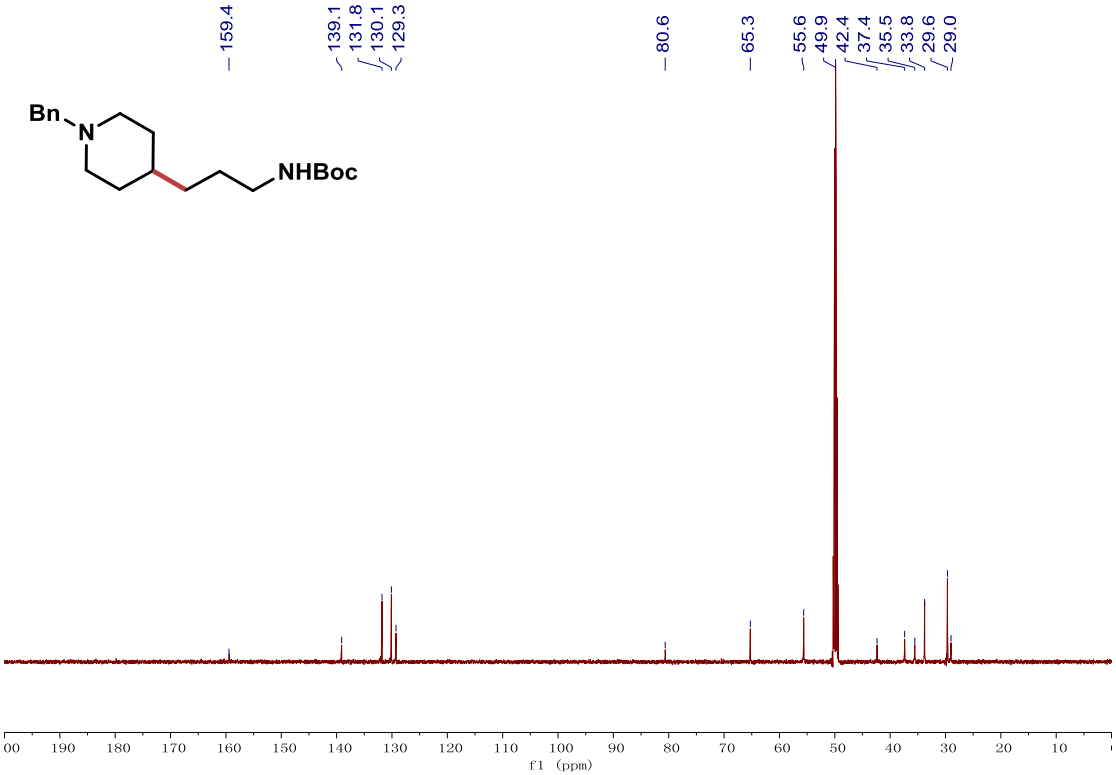
^{13}C NMR of Compound 18 (151 MHz, $CDCl_3$):



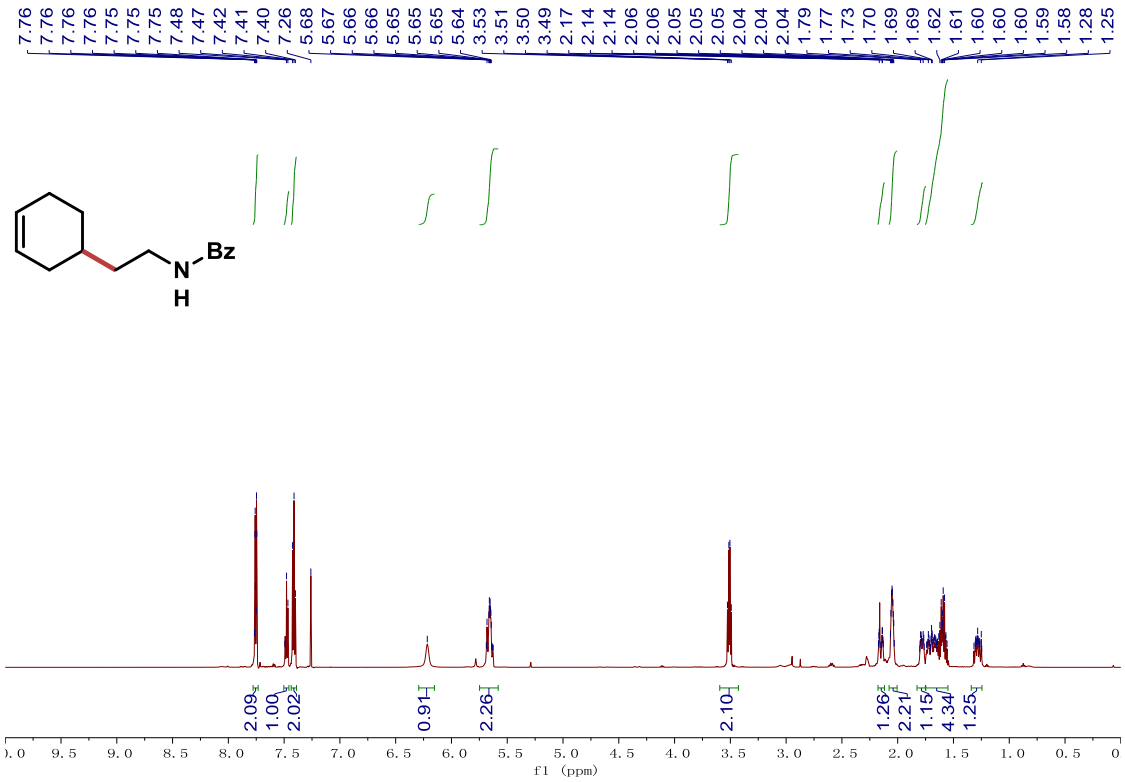
^{1}H NMR of Compound 19 (600 MHz, $CDCl_3$):



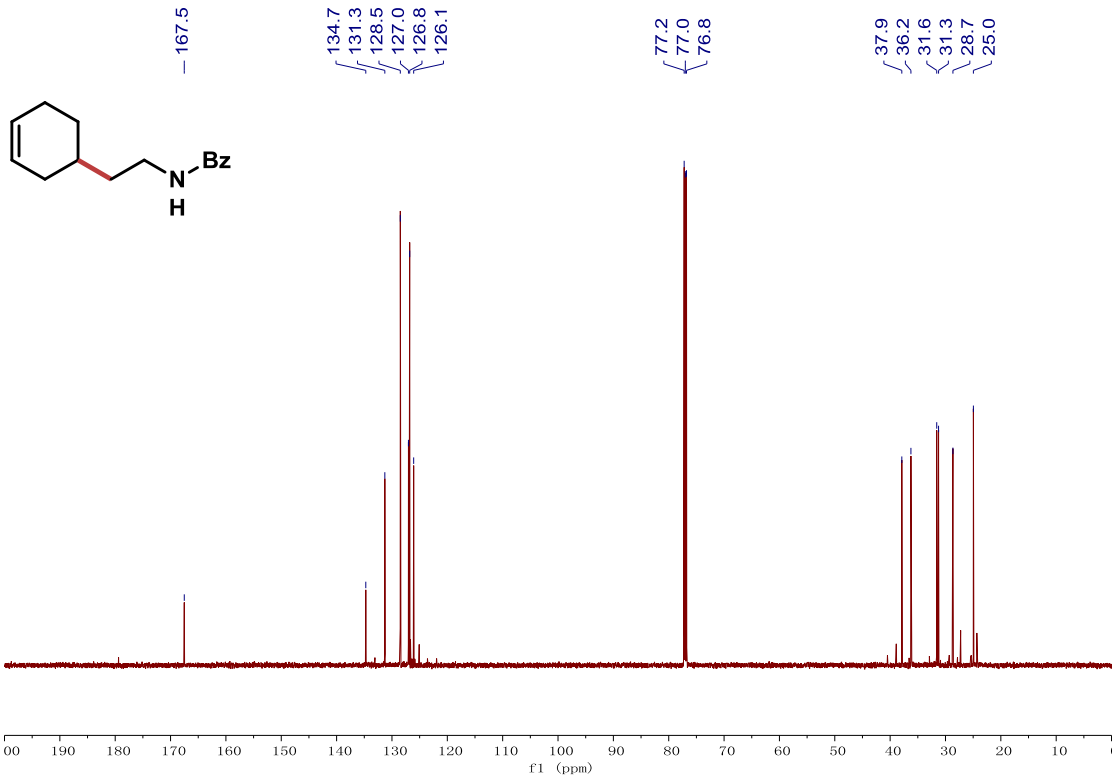
^{13}C NMR of Compound 19 (151 MHz, $CDCl_3$):



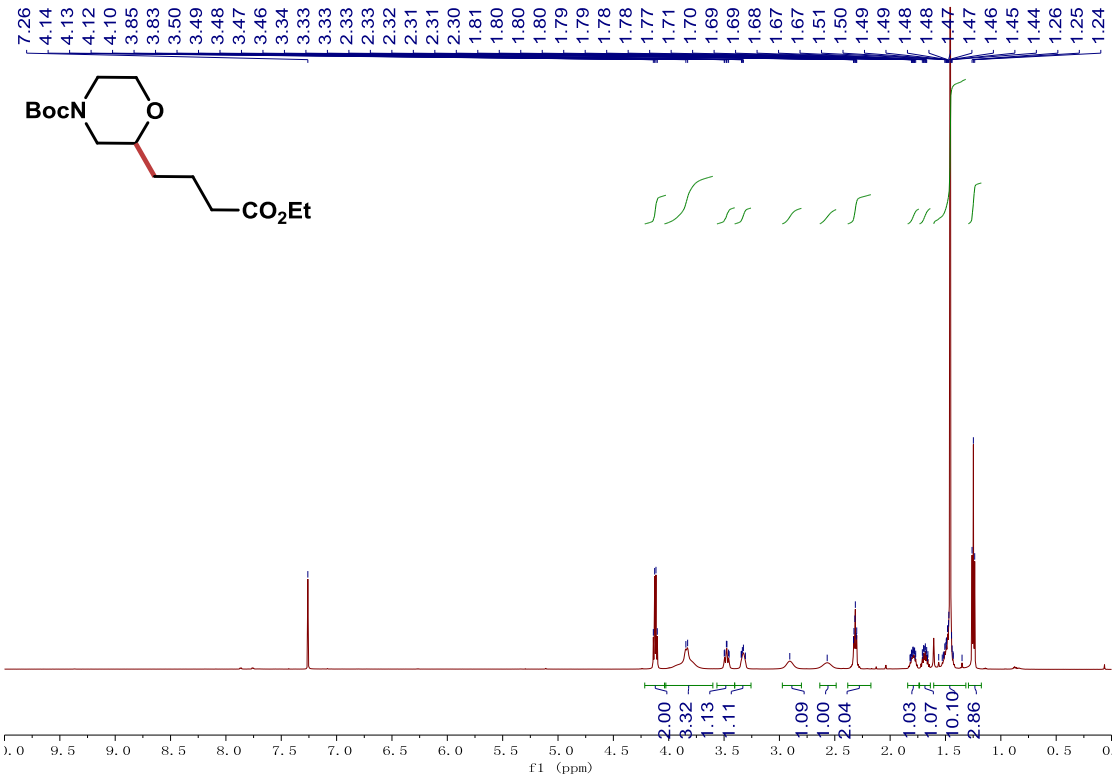
^{1}H NMR of Compound 20 (600 MHz, $CDCl_3$):



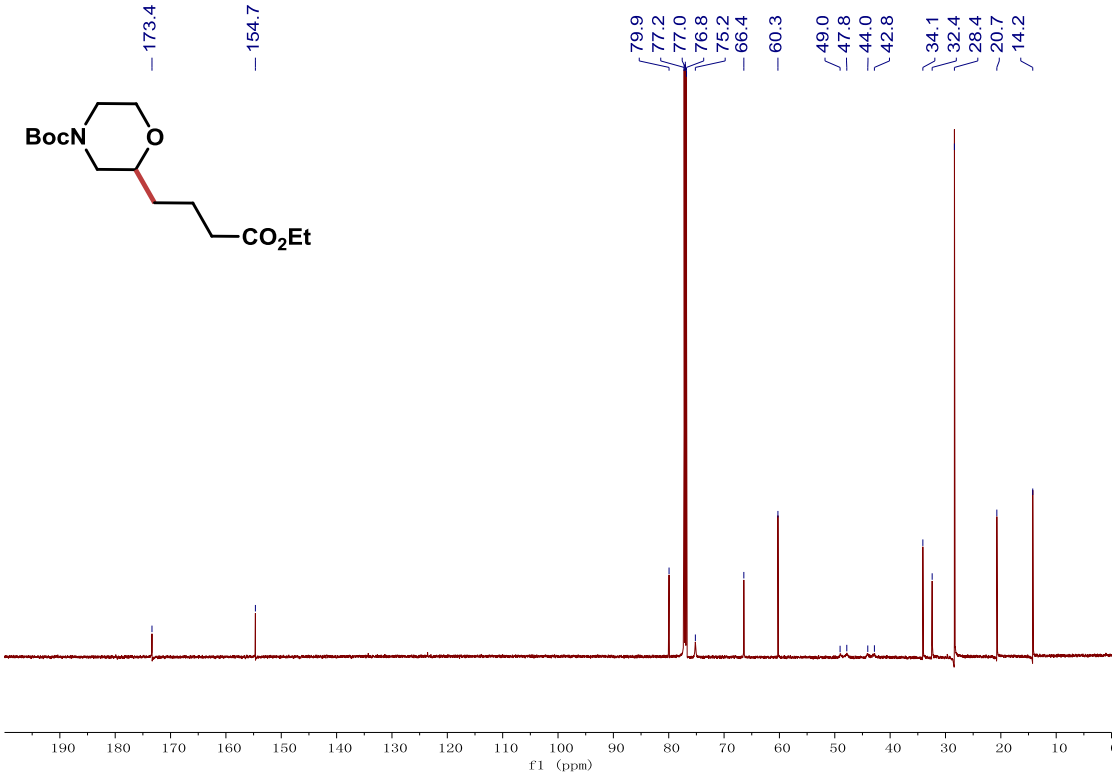
^{13}C NMR of Compound 20 (151 MHz, $CDCl_3$):



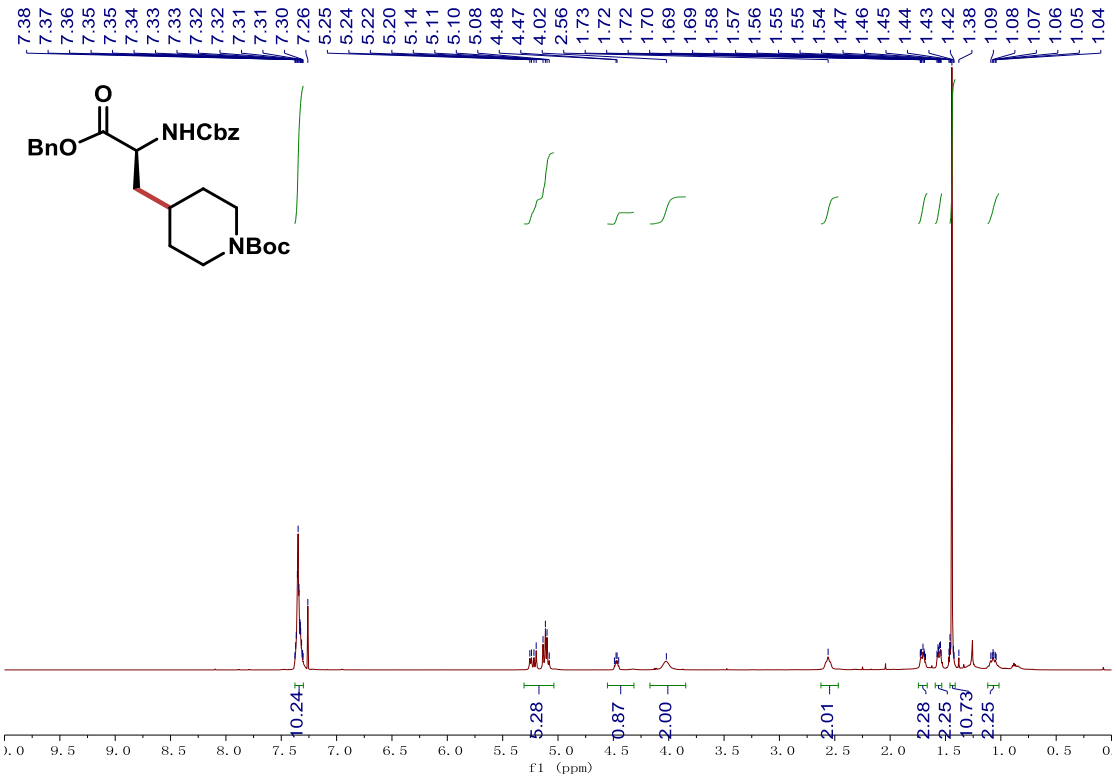
^{1}H NMR of Compound 21 (600 MHz, $CDCl_3$):



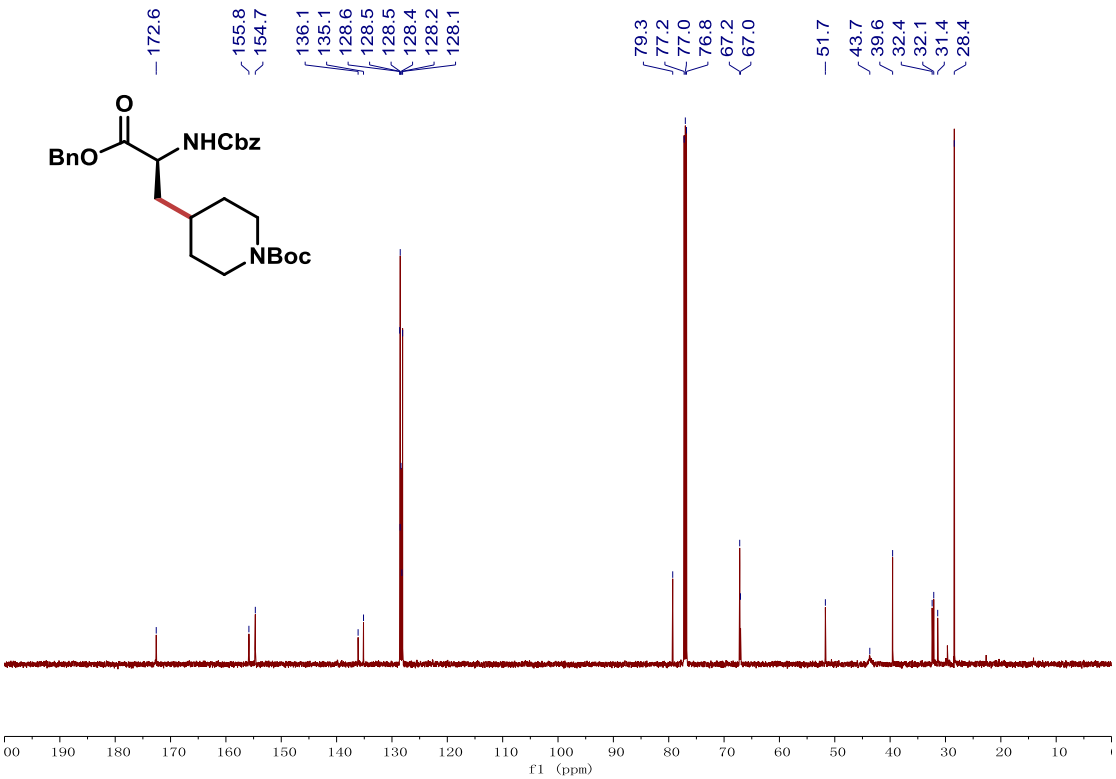
^{13}C NMR of Compound 21 (151 MHz, $CDCl_3$):



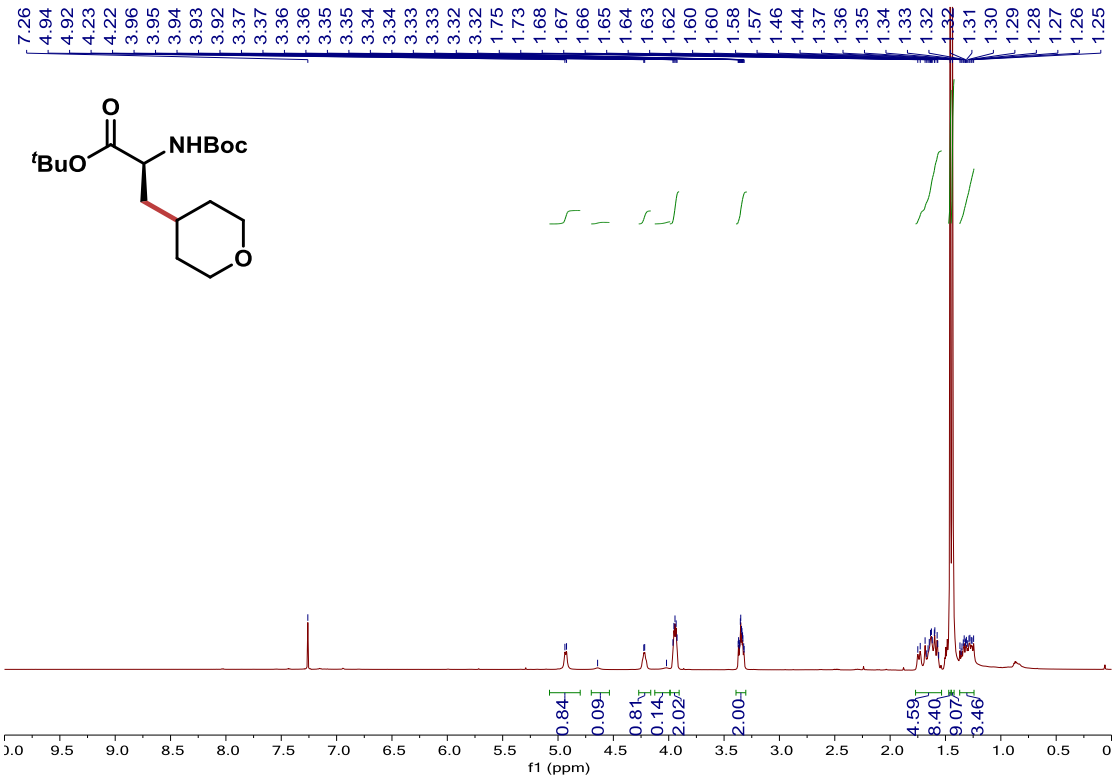
^{1}H NMR of Compound 22 (600 MHz, $CDCl_3$):



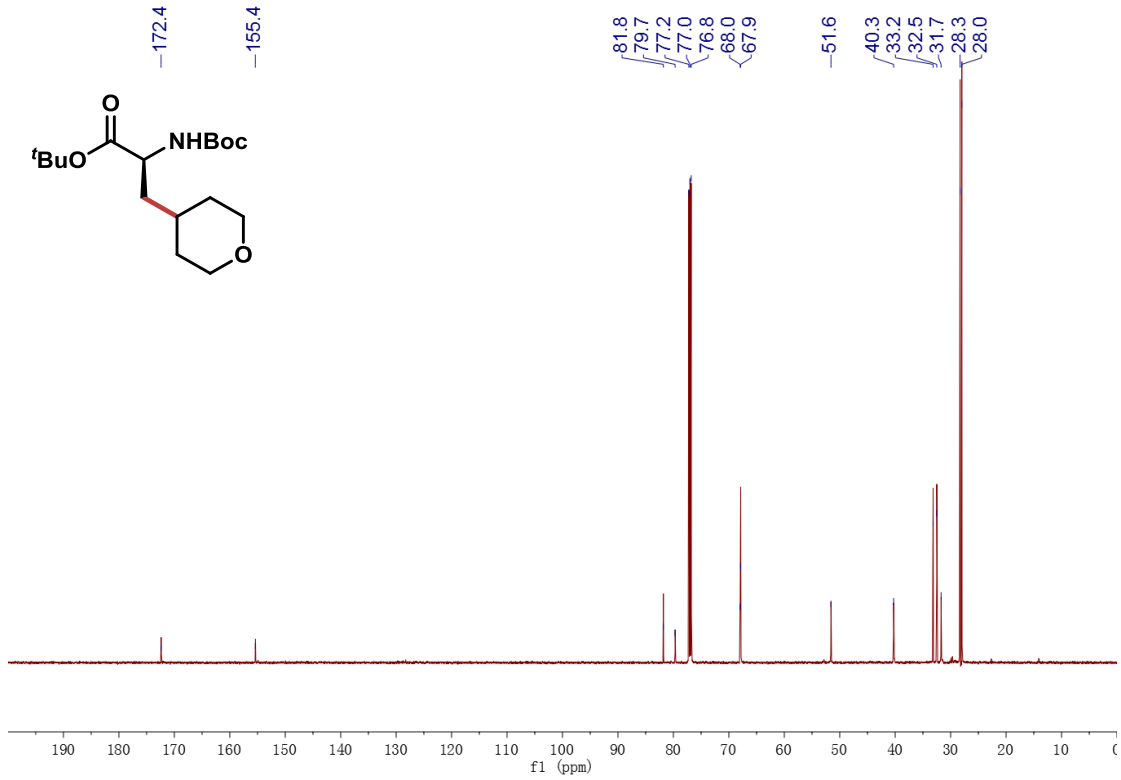
^{13}C NMR of Compound 22 (151 MHz, $CDCl_3$):



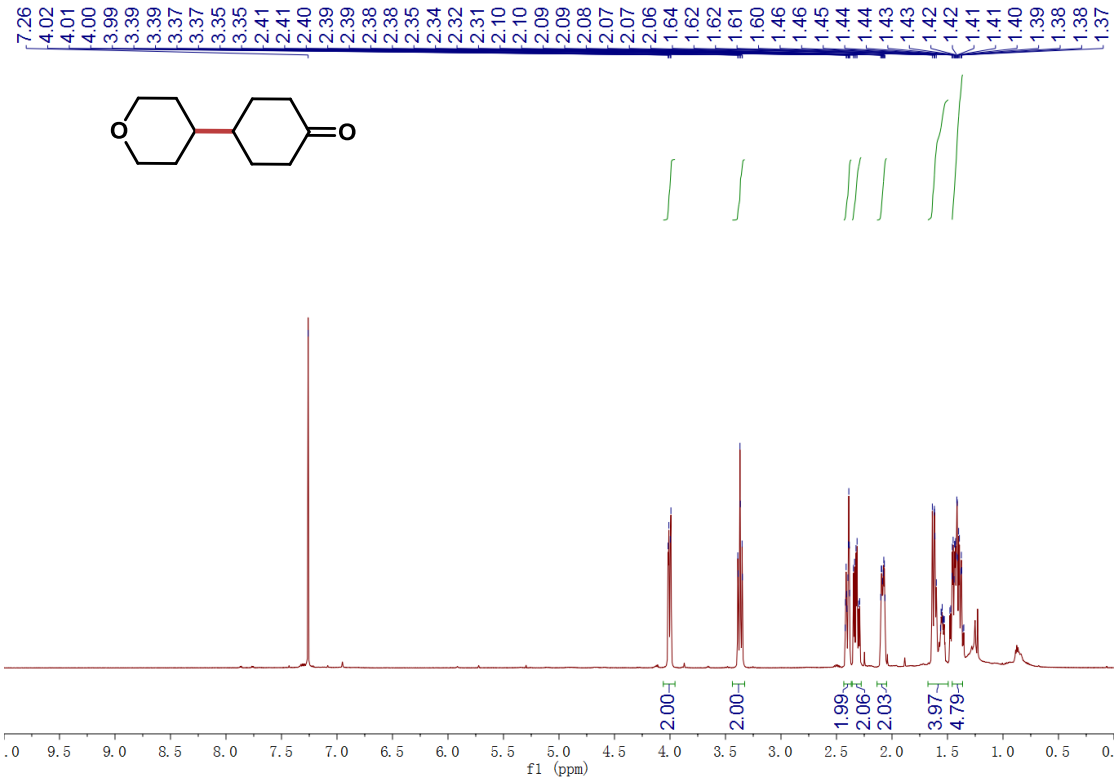
^{1}H NMR of Compound 23 (600 MHz, $CDCl_3$):



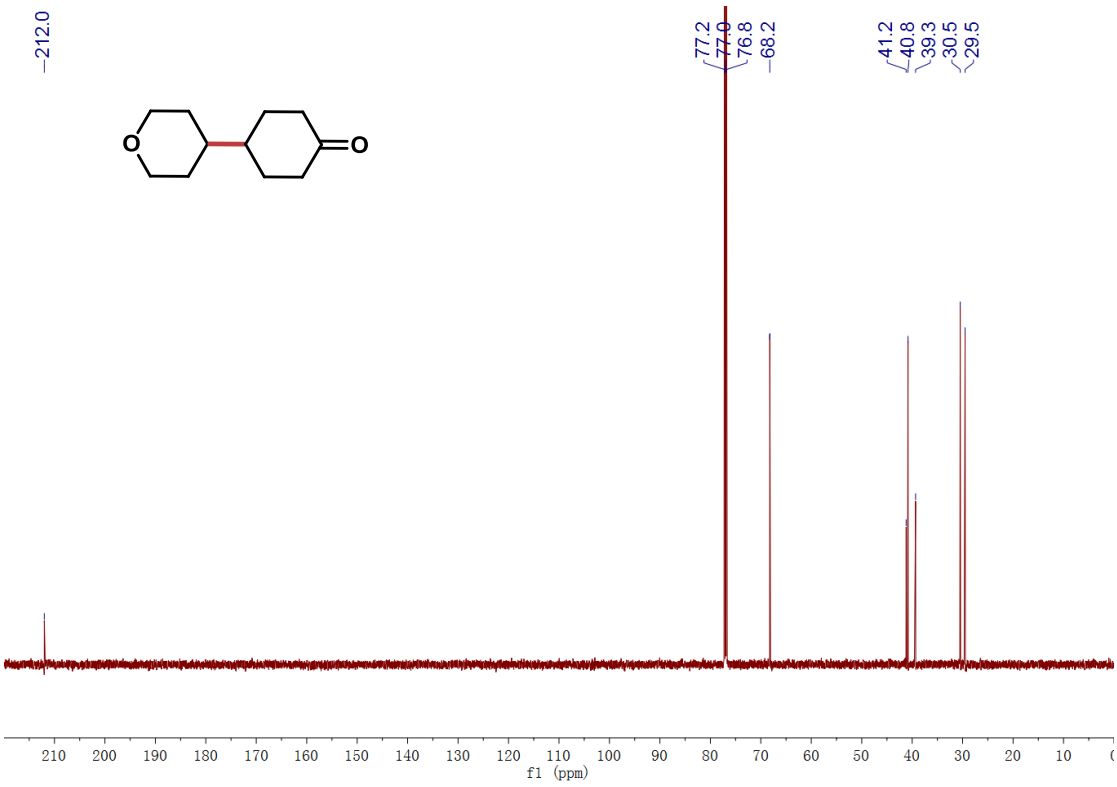
^{13}C NMR of Compound 23 (151 MHz, $CDCl_3$):



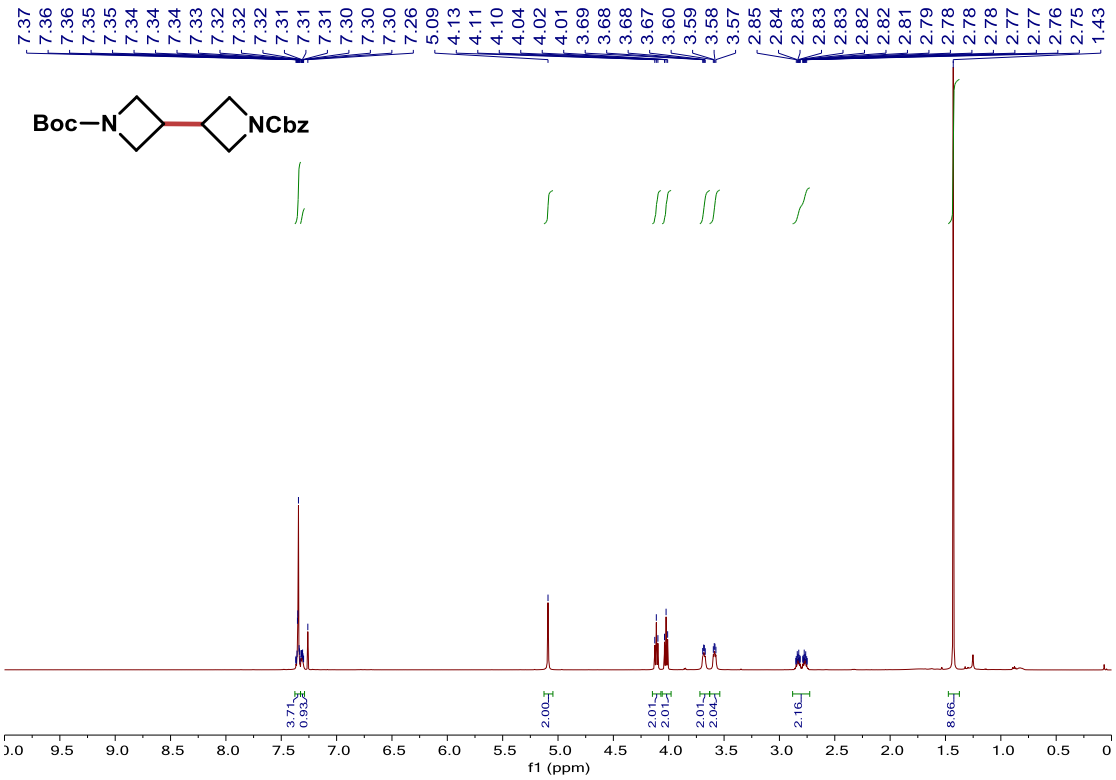
^{1}H NMR of Compound 24 (600 MHz, $CDCl_3$):



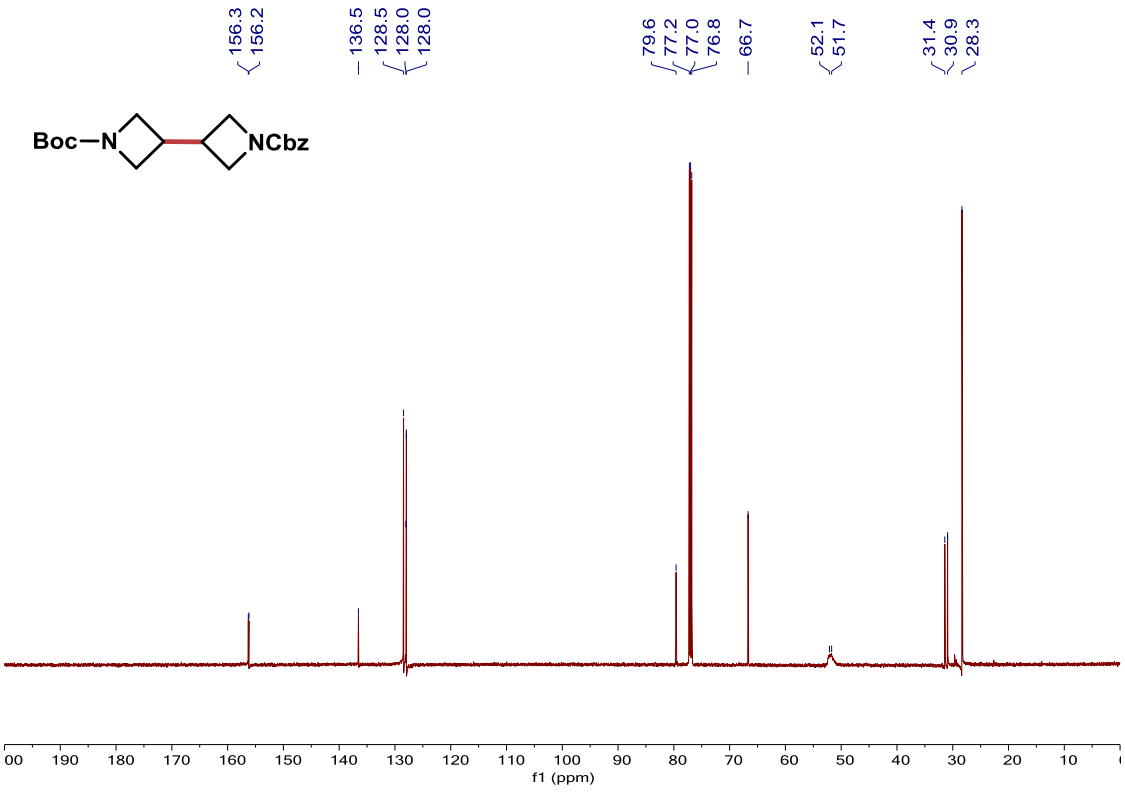
^{13}C NMR of Compound 24 (151 MHz, $CDCl_3$):



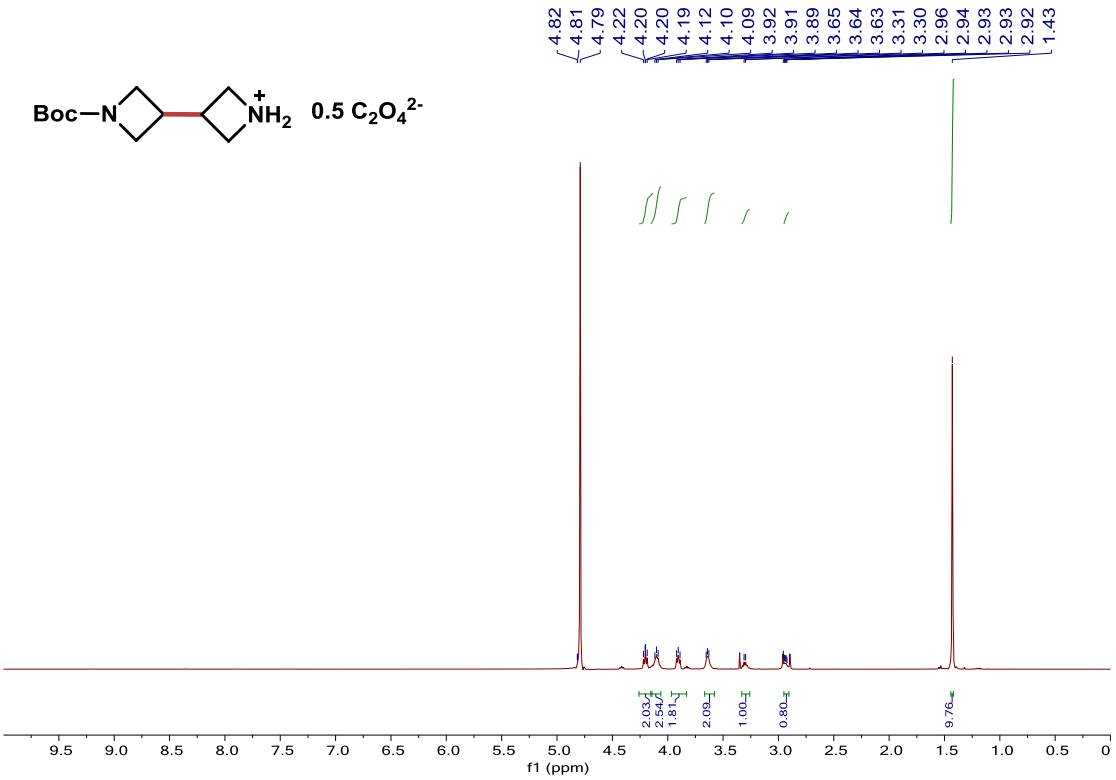
^{1}H NMR of Compound 25 (600 MHz, $CDCl_3$):



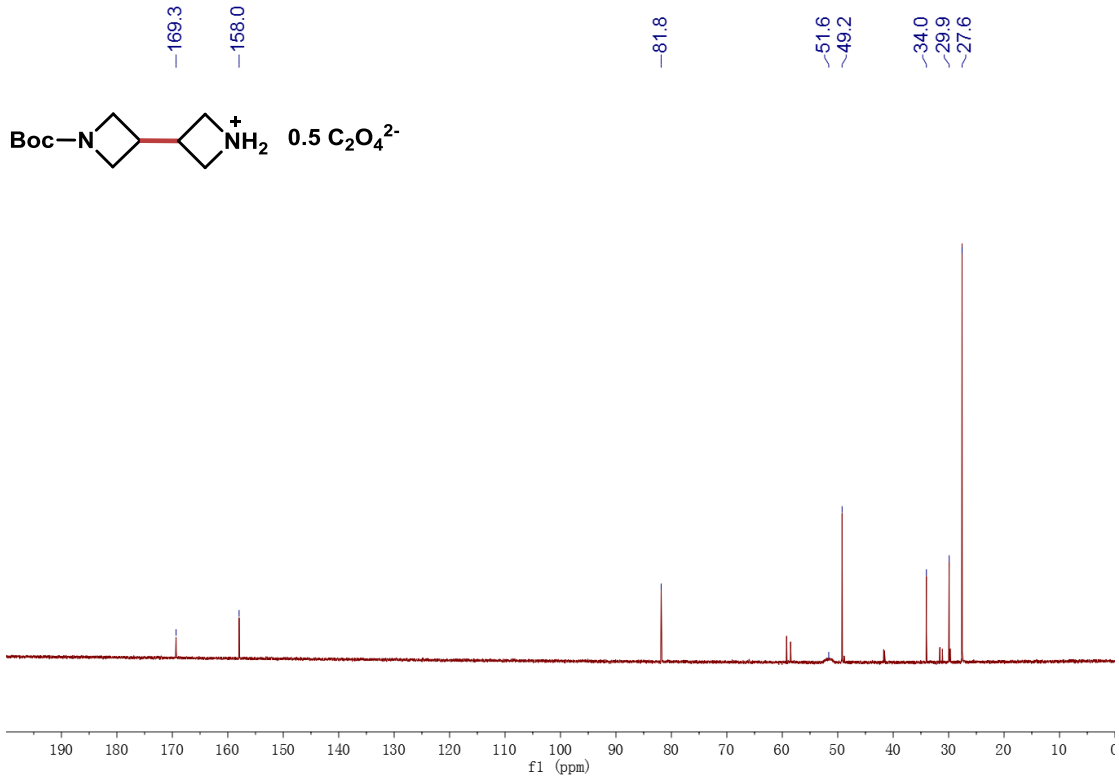
^{13}C NMR of Compound 25 (151 MHz, $CDCl_3$):



^{1}H NMR of Compound 25' (600 MHz, D_2O):

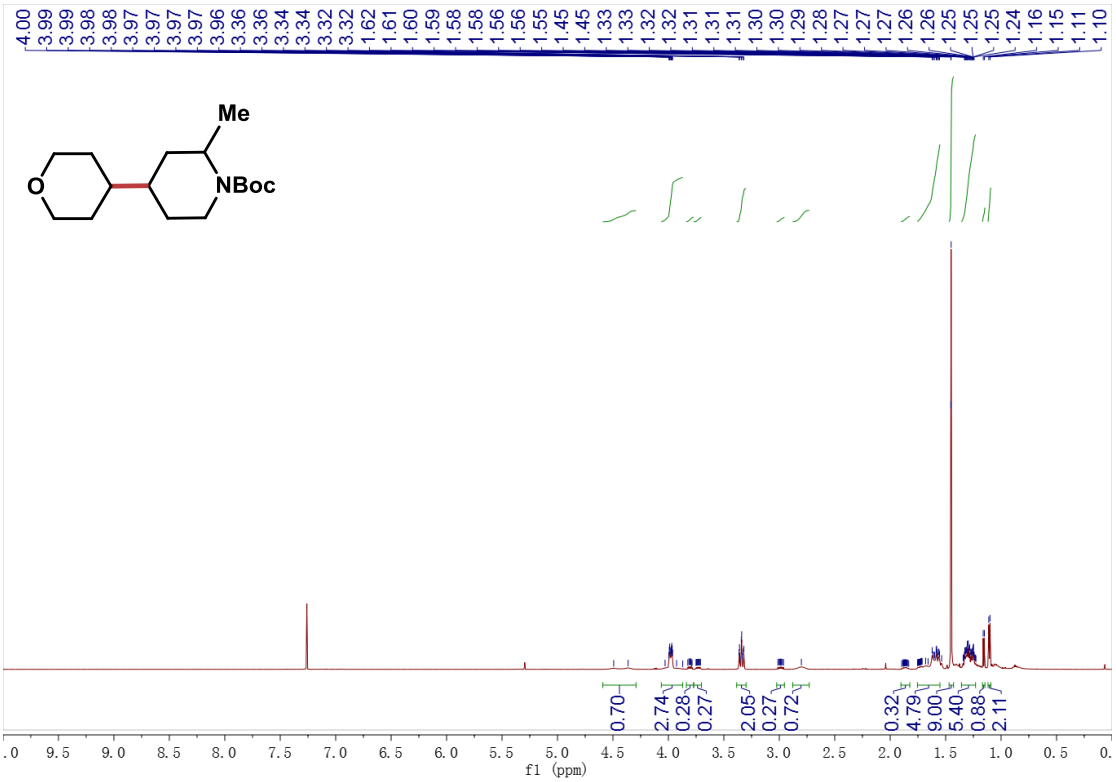


^{13}C NMR of Compound 25' (151 MHz, D_2O):

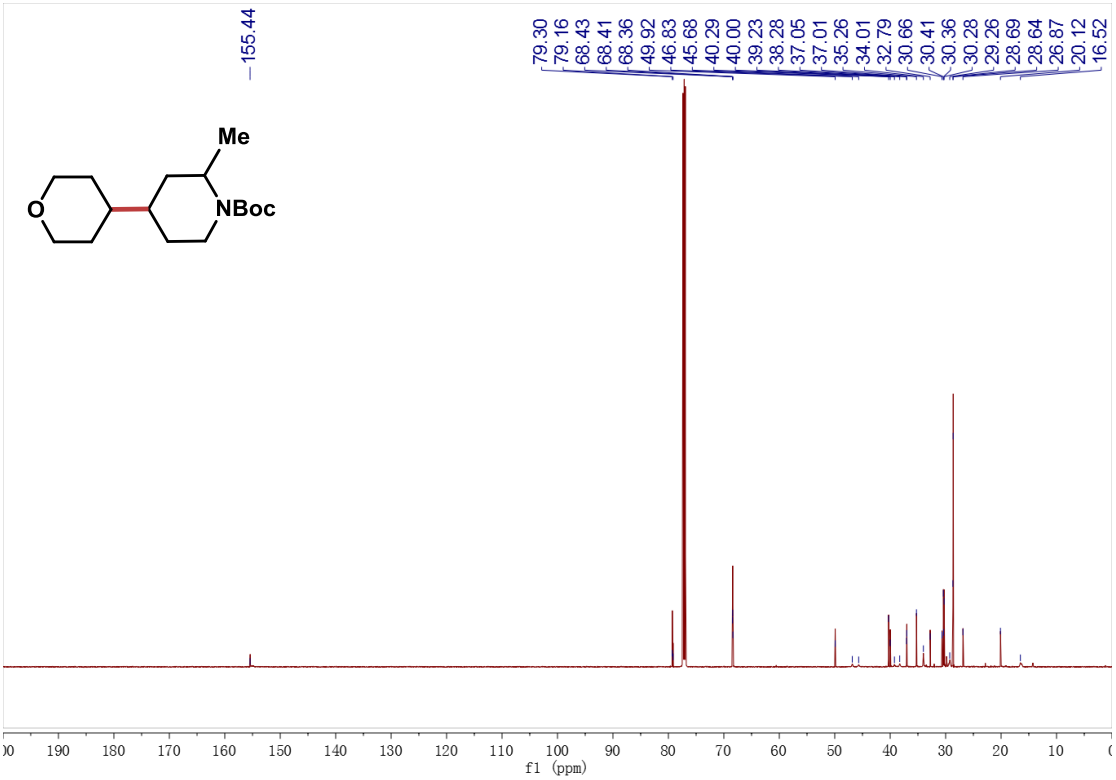


^{1}H NMR of Compound 26 (600 MHz, $CDCl_3$):

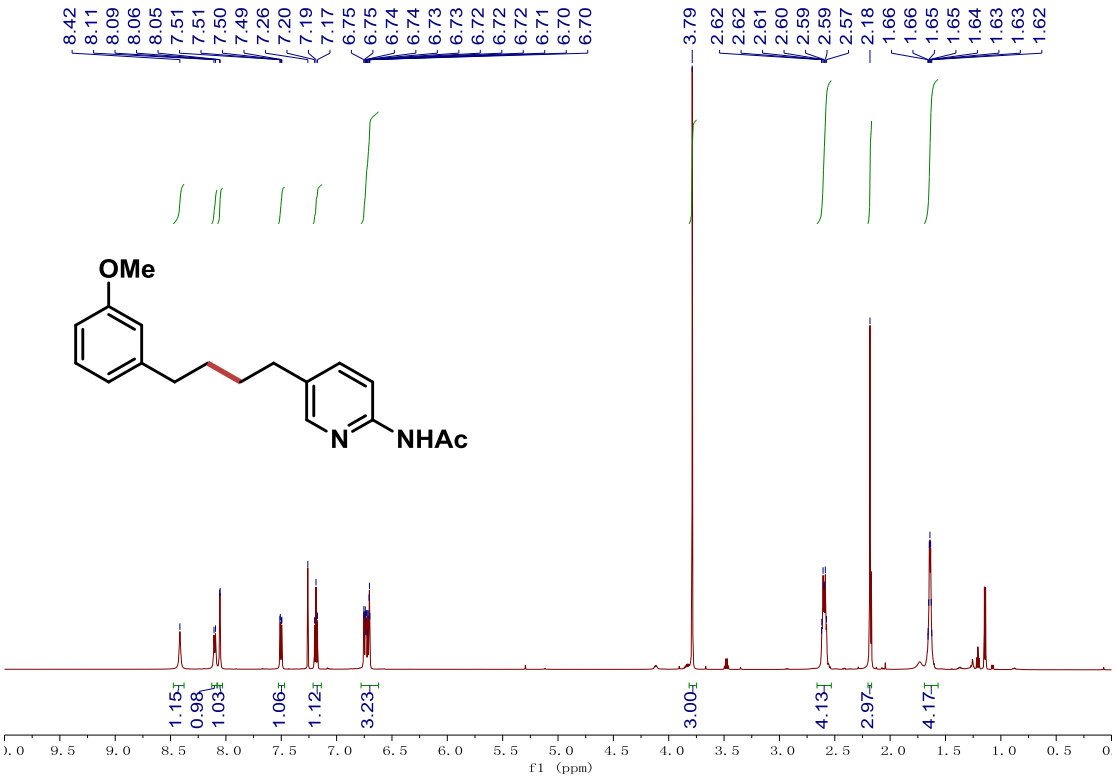
The NMR spectra presented as a mixture of diastereoisomers and rotamers:



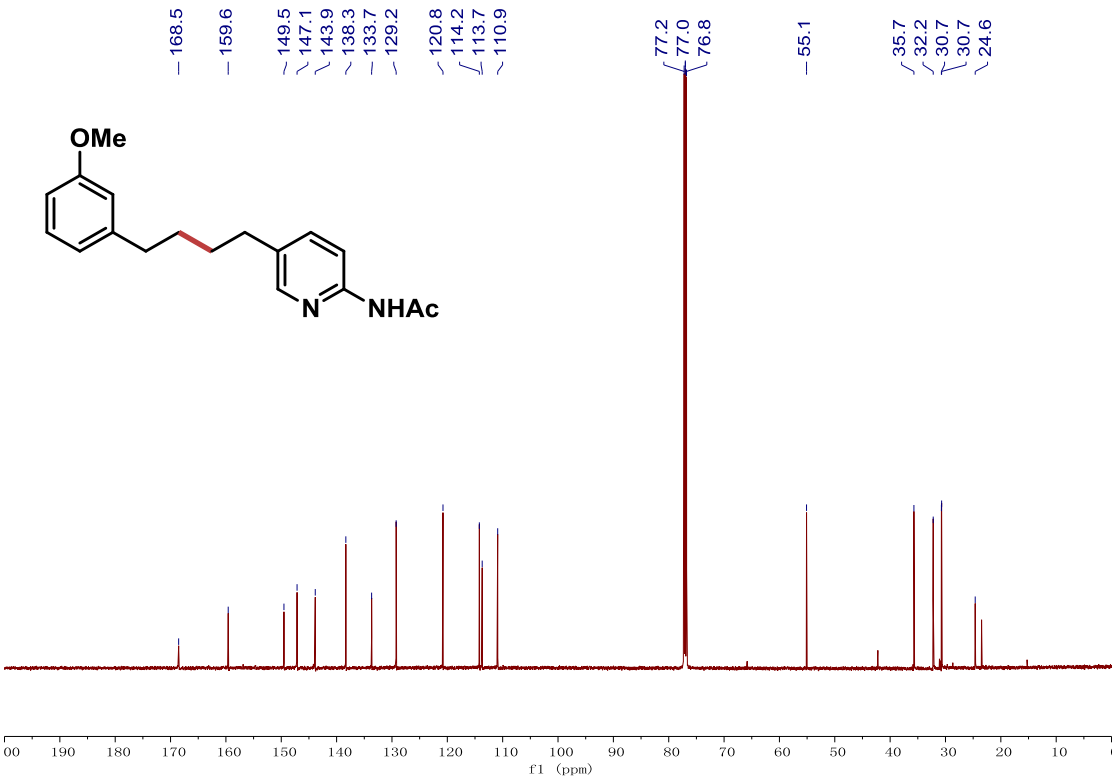
^{13}C NMR of Compound 26 (151 MHz, $CDCl_3$):



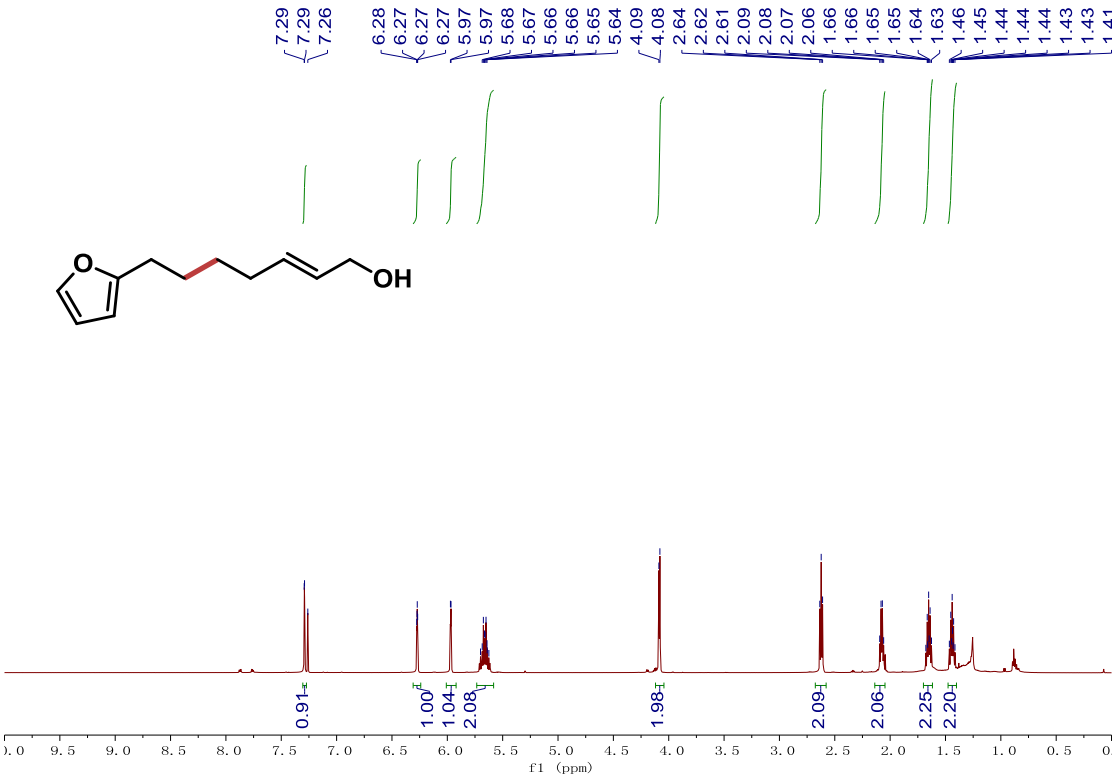
^{1}H NMR of Compound 27 (600 MHz, $CDCl_3$):



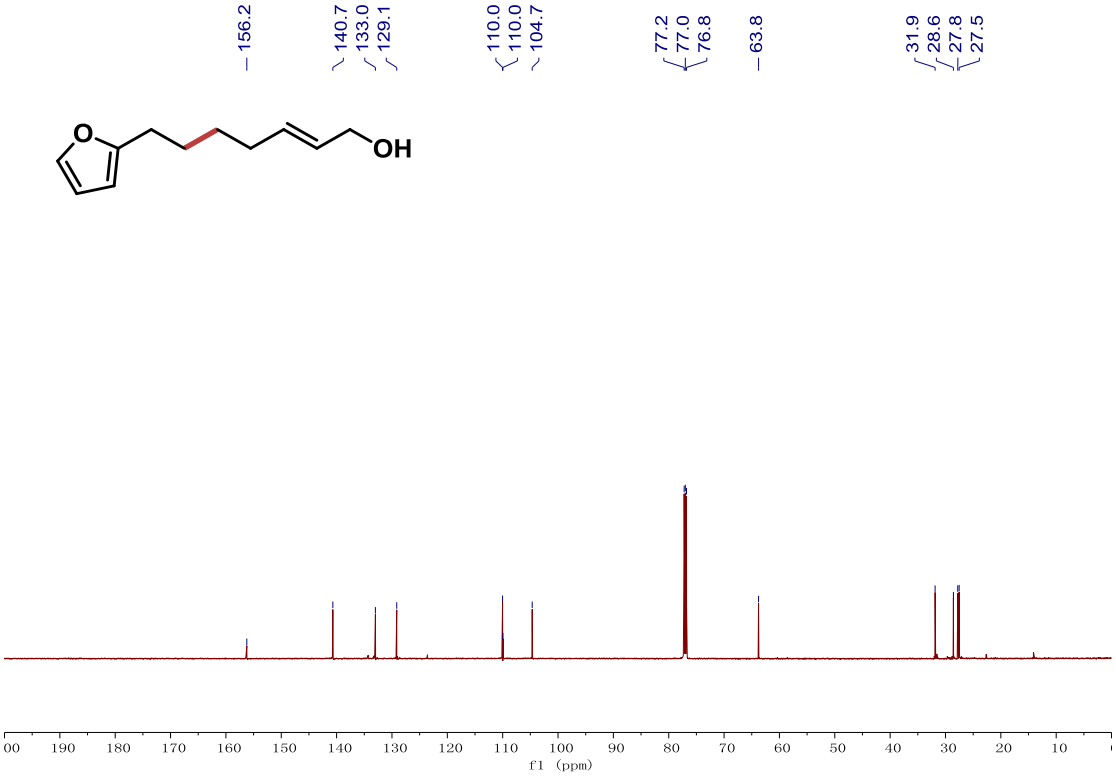
^{13}C NMR of Compound 27 (151 MHz, $CDCl_3$):



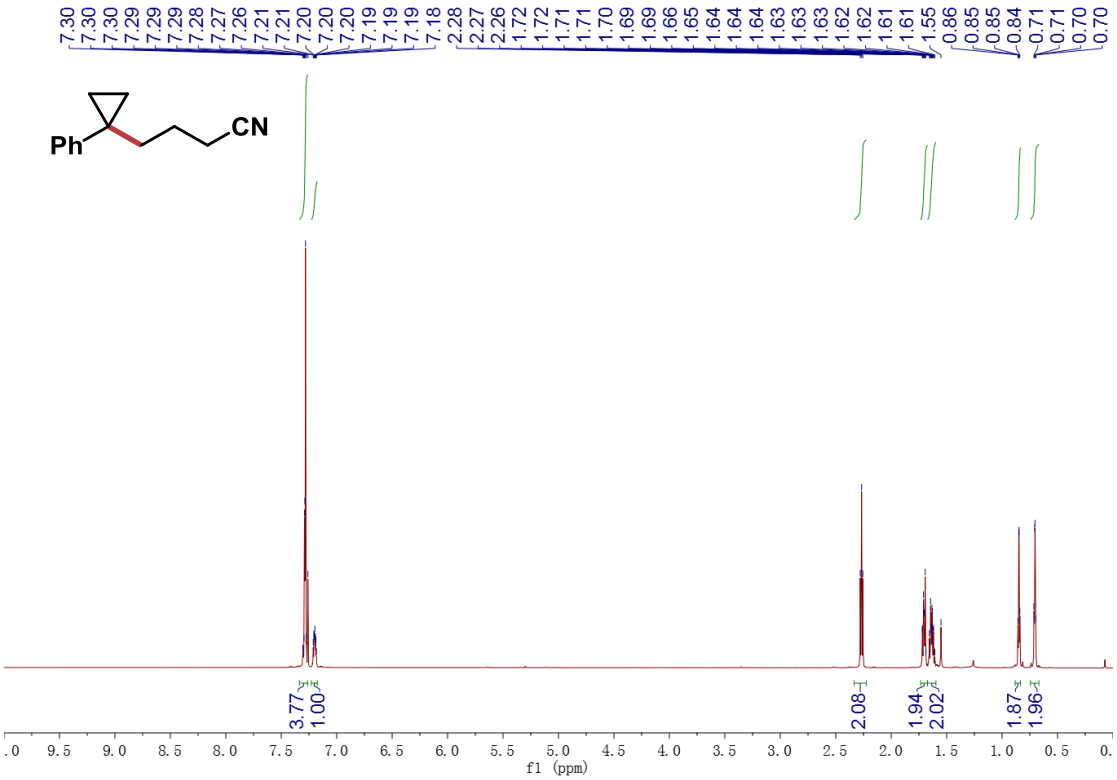
^{1}H NMR of Compound 28' (600 MHz, $CDCl_3$):



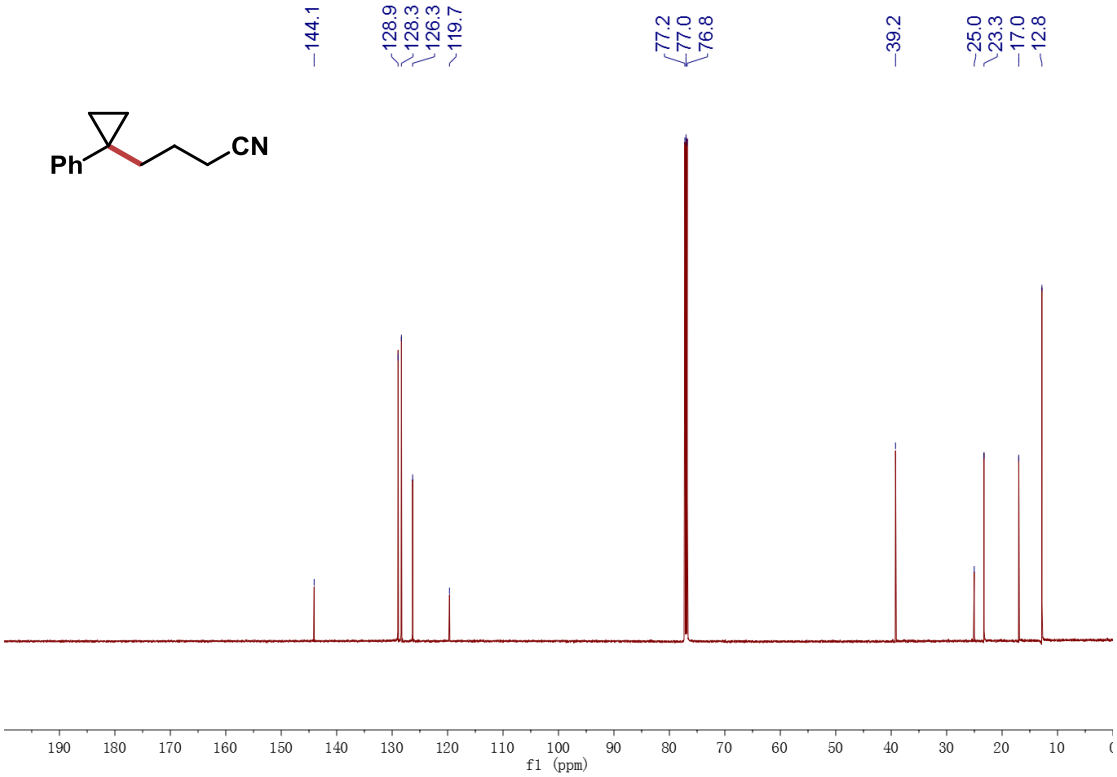
^{13}C NMR of Compound 28' (151 MHz, $CDCl_3$):



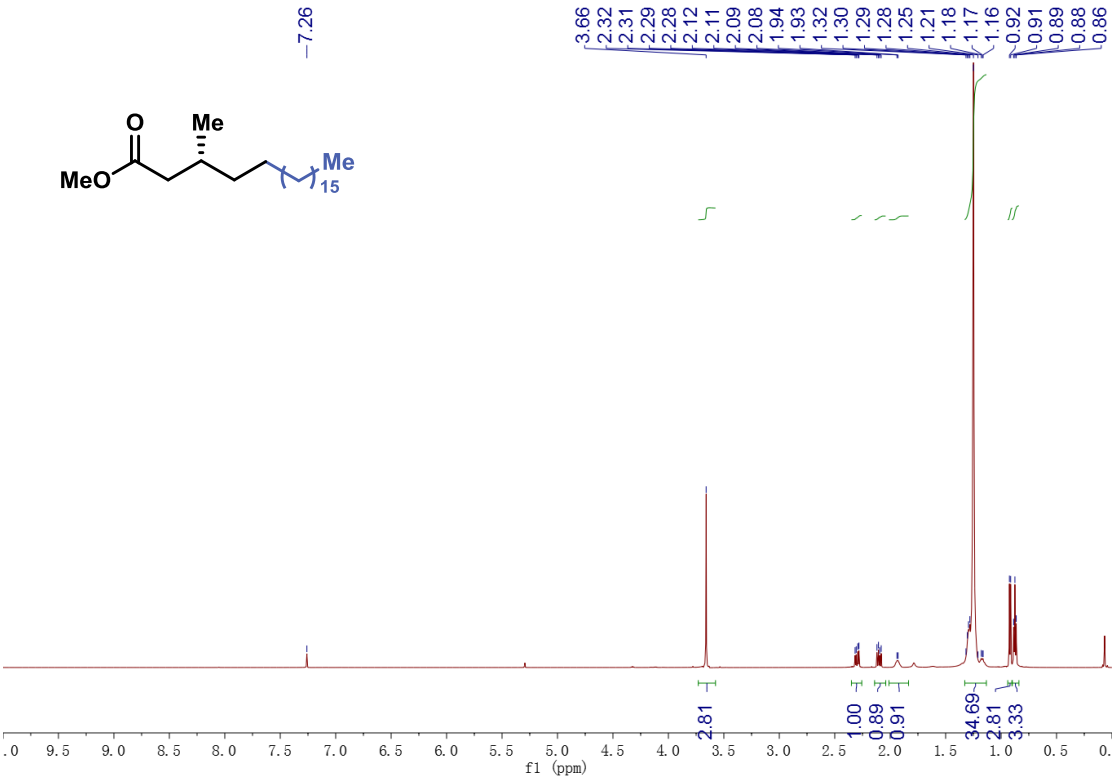
^{1}H NMR of Compound 29 (600 MHz, $CDCl_3$):



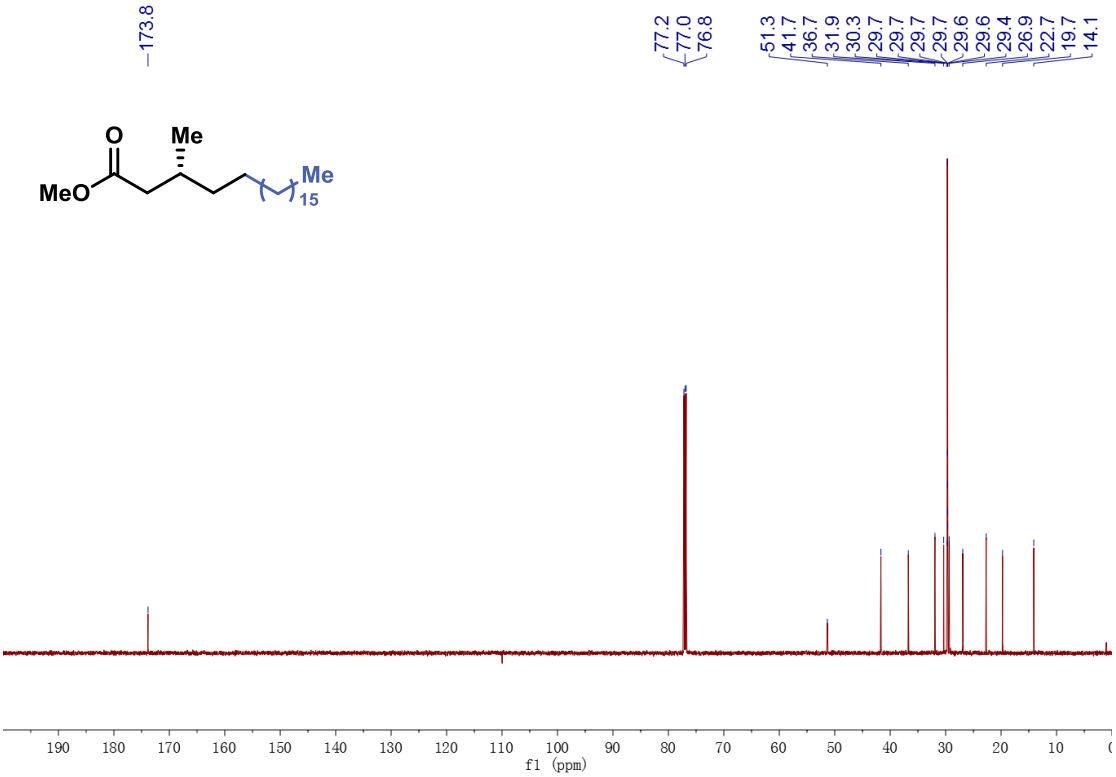
^{13}C NMR of Compound 29 (151 MHz, $CDCl_3$):



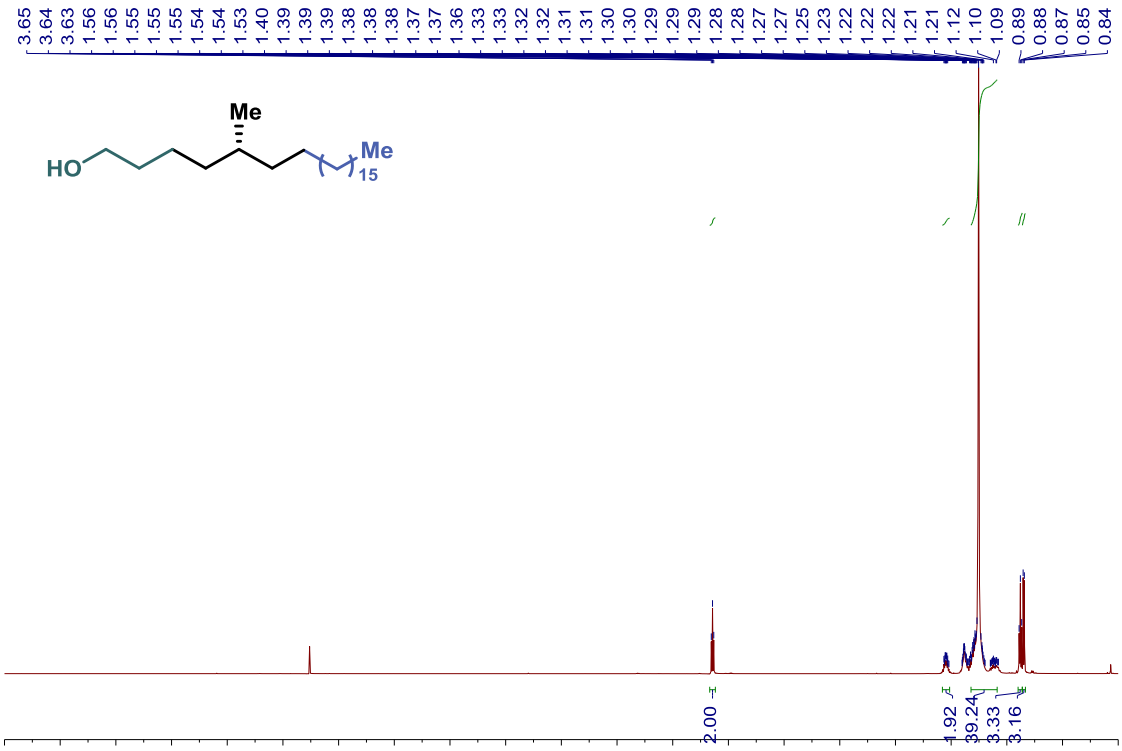
^{1}H NMR of Compound SI-5 (600 MHz, $CDCl_3$):



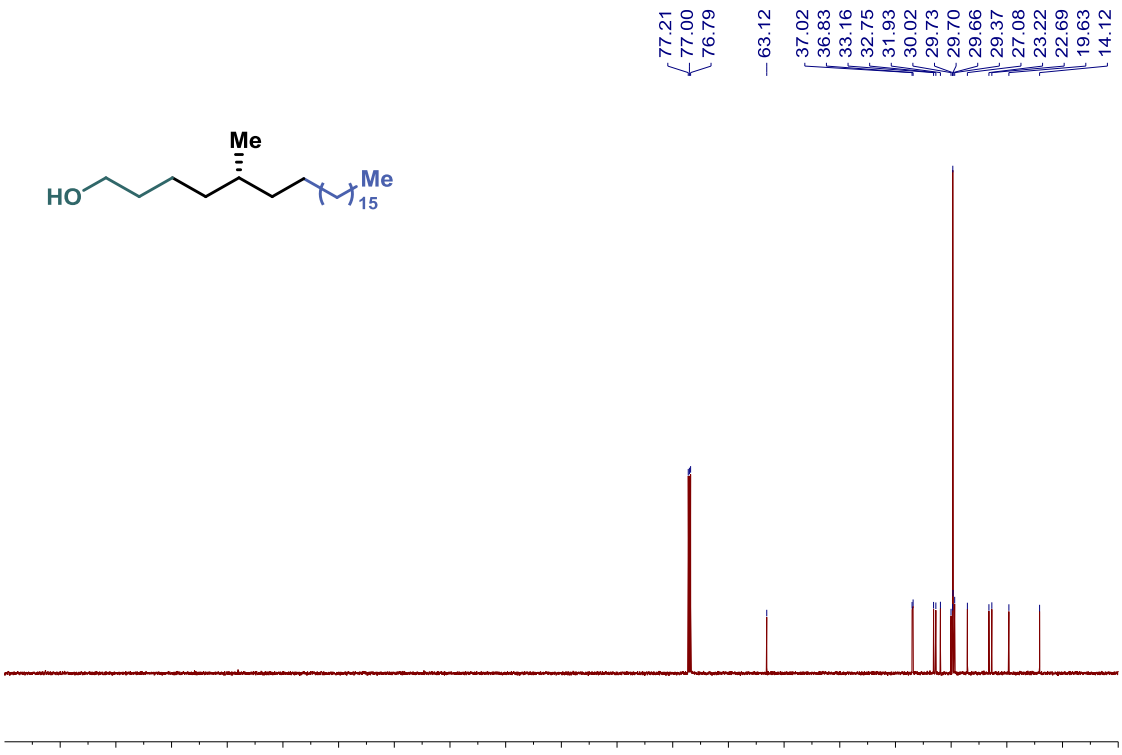
^{13}C NMR of Compound SI-5 (151 MHz, $CDCl_3$):



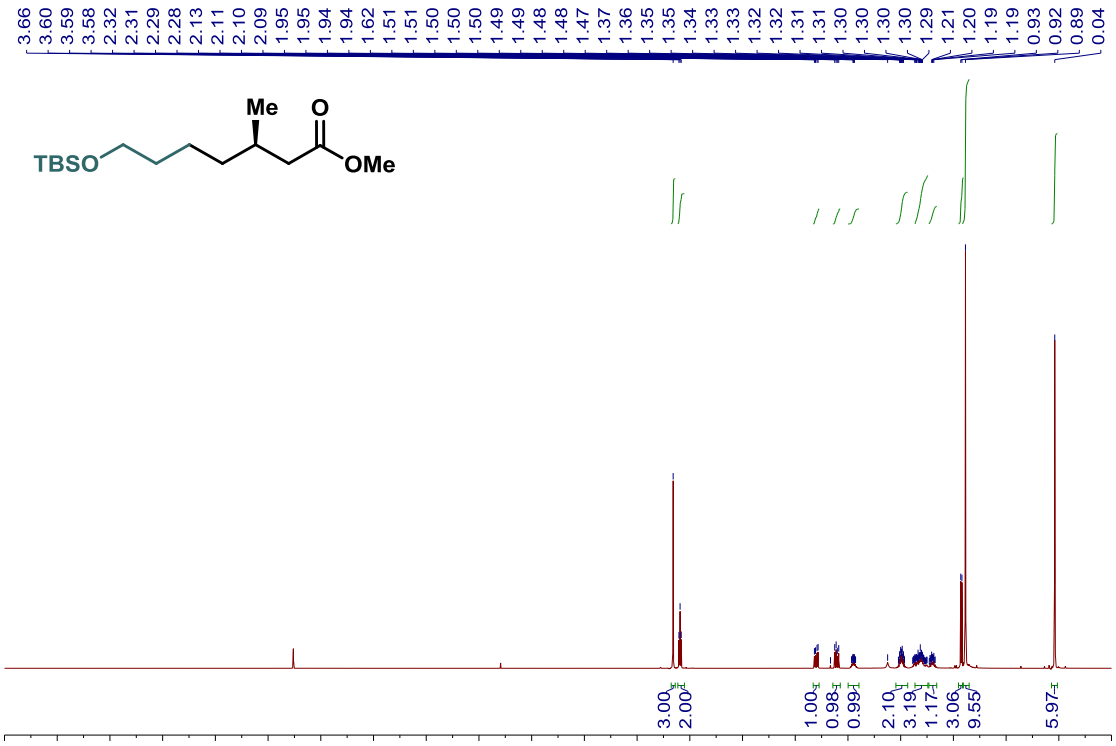
^{1}H NMR of Compound (R)-33 (600 MHz, $CDCl_3$):



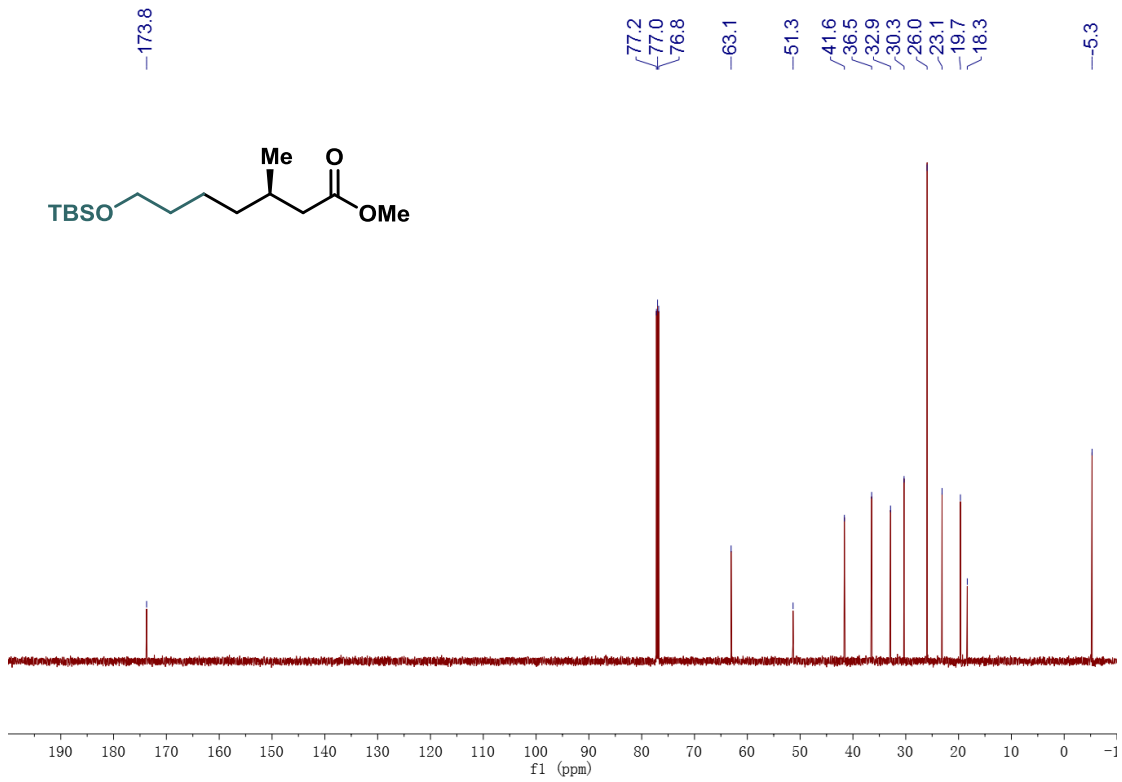
^{13}C NMR of Compound (R)-33 (151 MHz, $CDCl_3$):



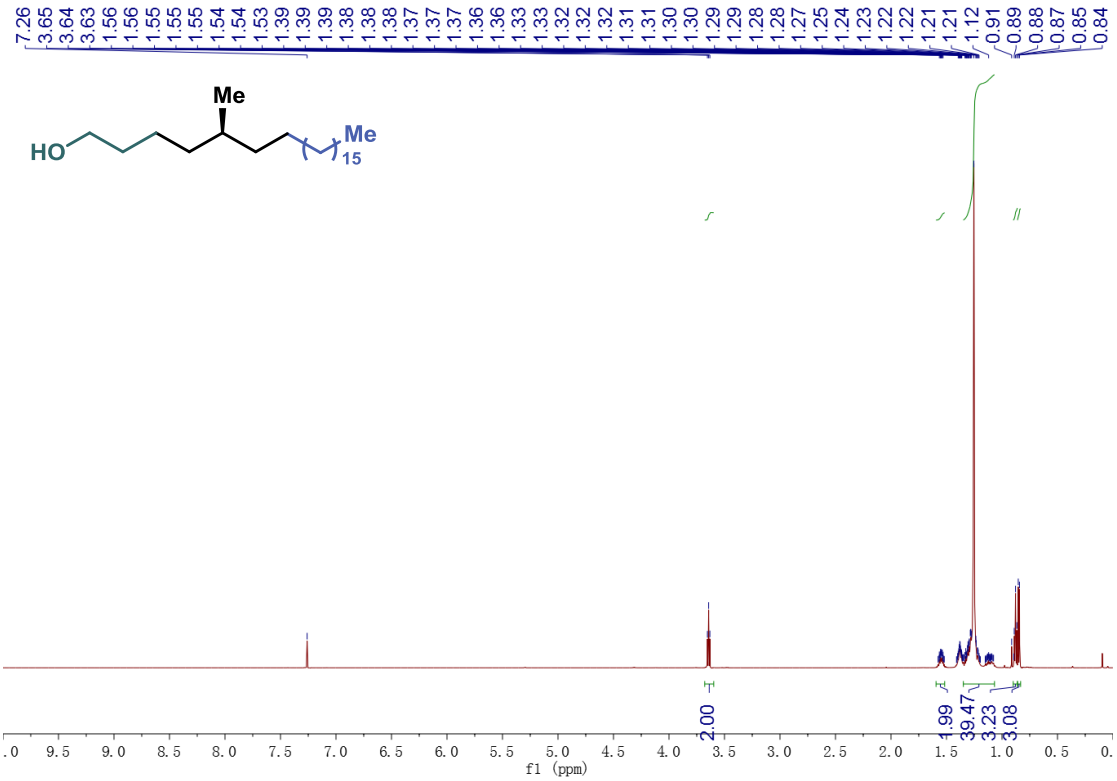
^{1}H NMR of Compound SI-7 (600 MHz, $CDCl_3$):



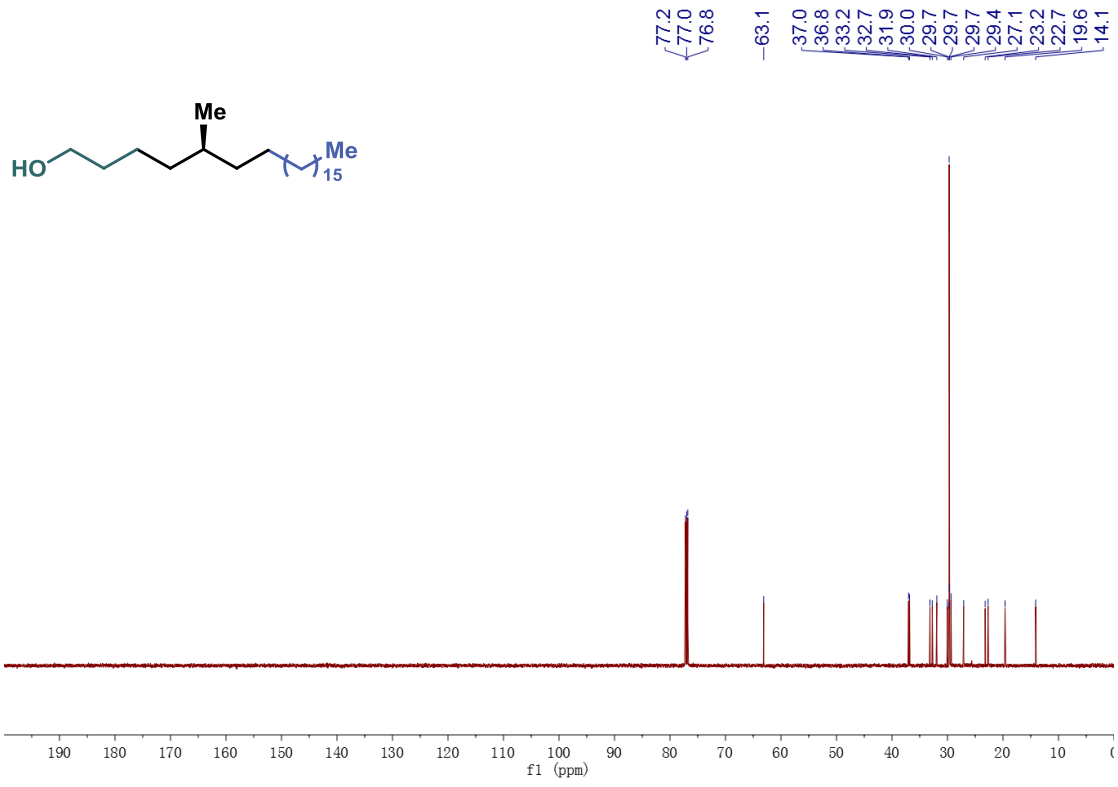
^{13}C NMR of Compound SI-7 (151 MHz, $CDCl_3$):



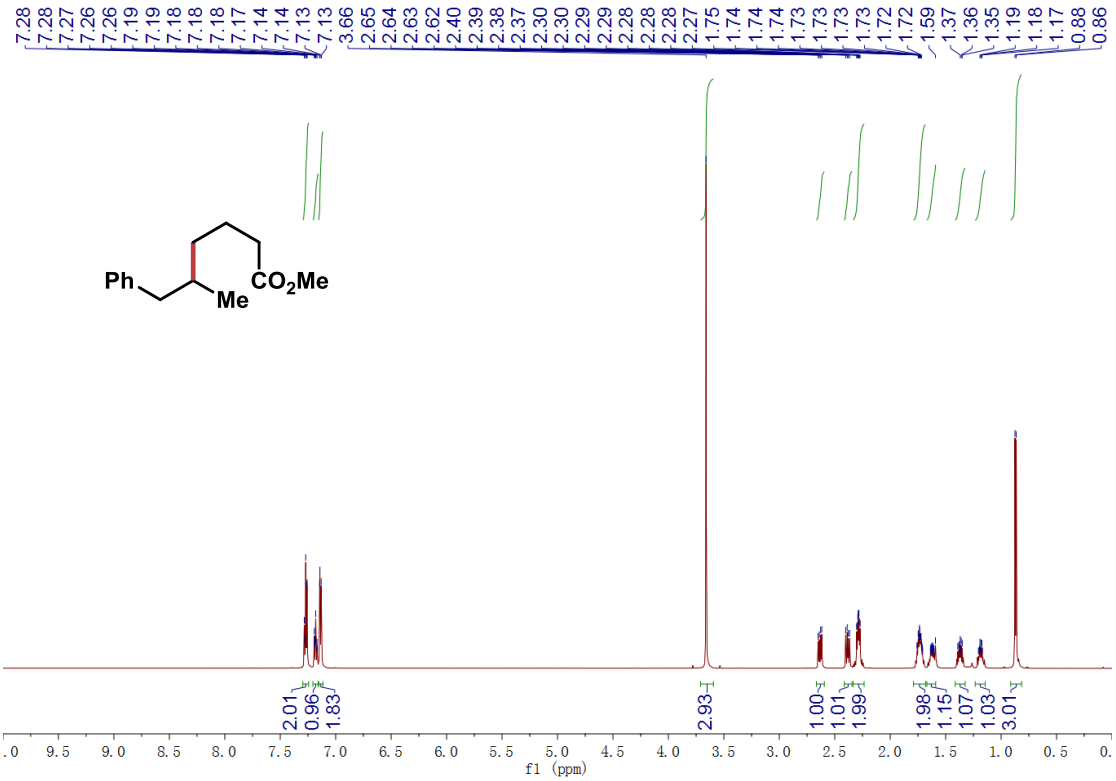
^{1}H NMR of Compound (*S*)-33 (600 MHz, $CDCl_3$):



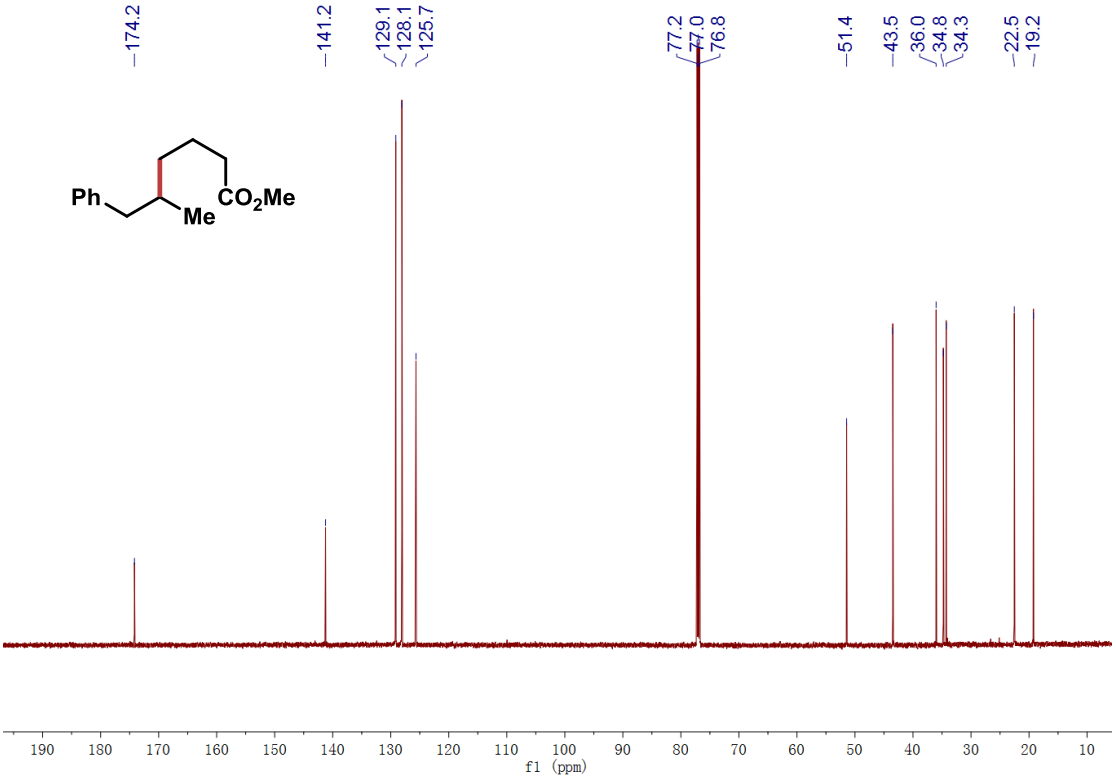
^{13}C NMR of Compound (*S*)-33 (151 MHz, $CDCl_3$):



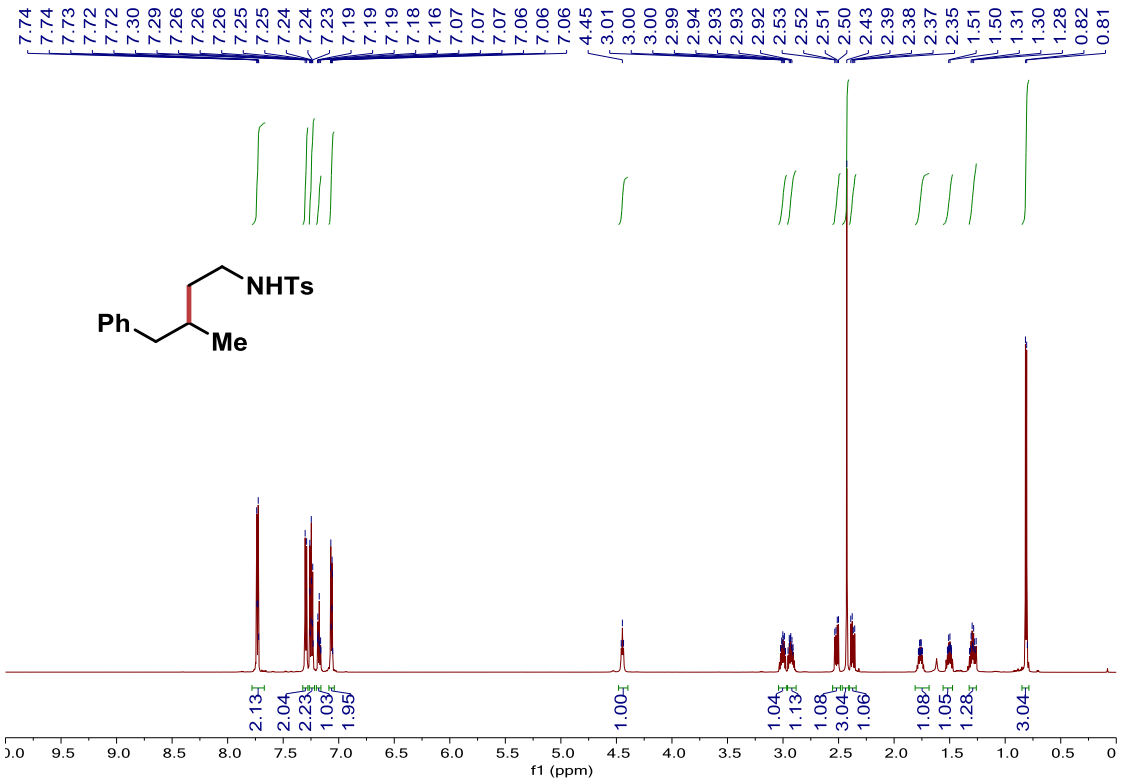
^{1}H NMR of Compound 34 (600 MHz, $CDCl_3$):



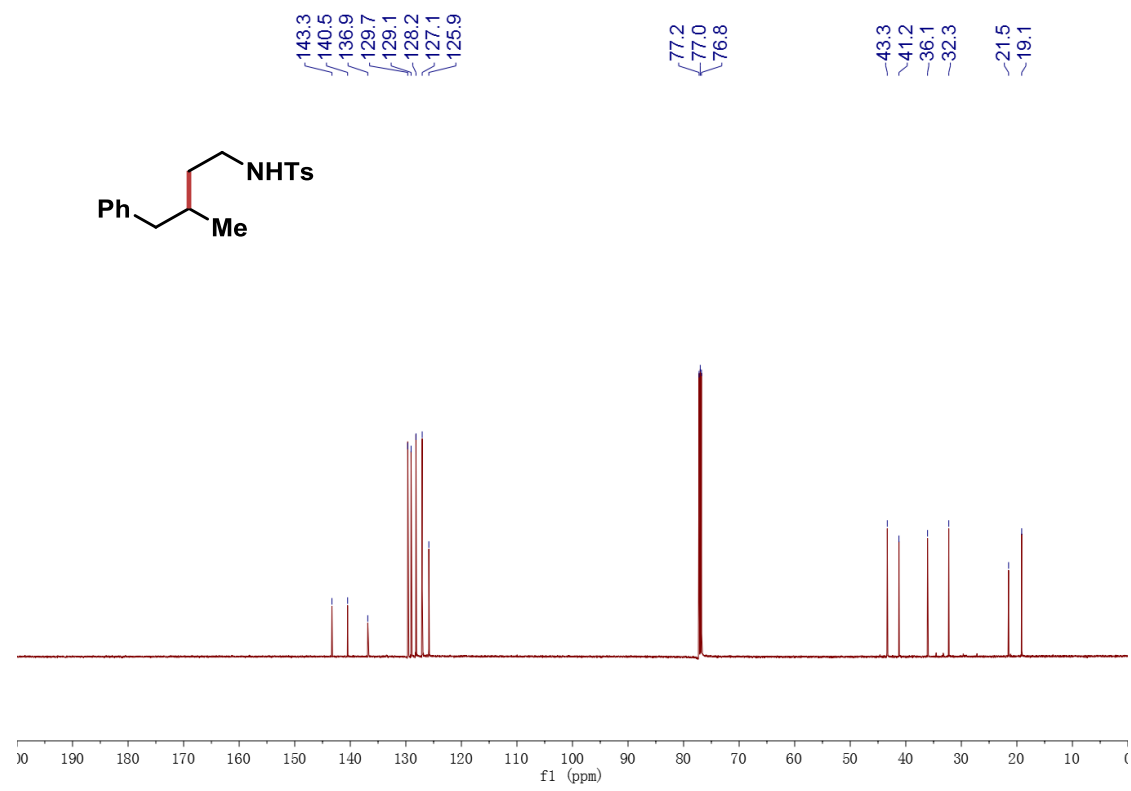
^{13}C NMR of Compound 34 (151 MHz, $CDCl_3$):



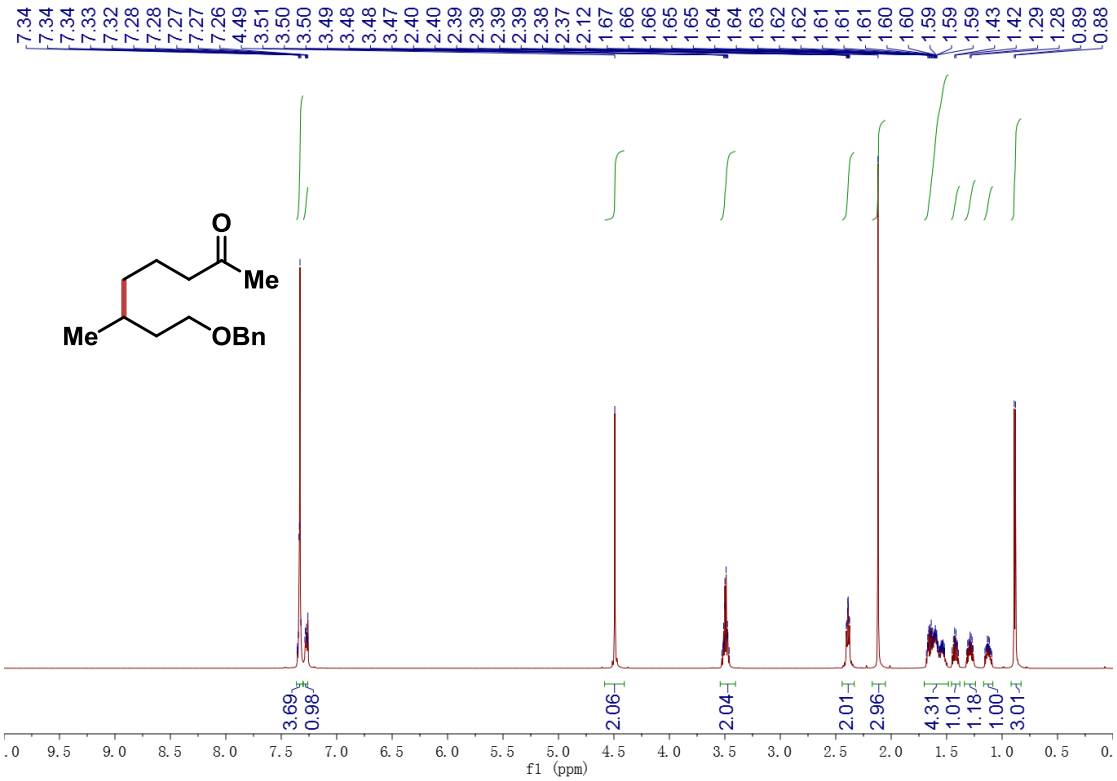
^{1}H NMR of Compound 35 (600 MHz, $CDCl_3$):



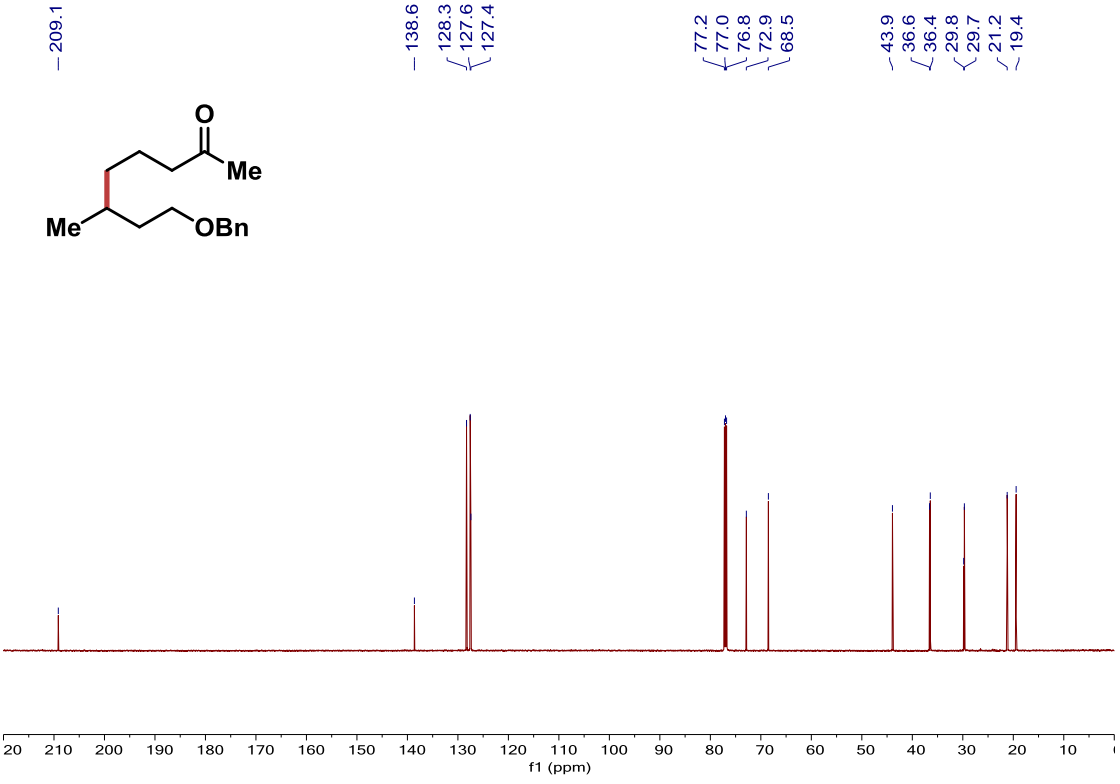
^{13}C NMR of Compound 35 (151 MHz, $CDCl_3$):



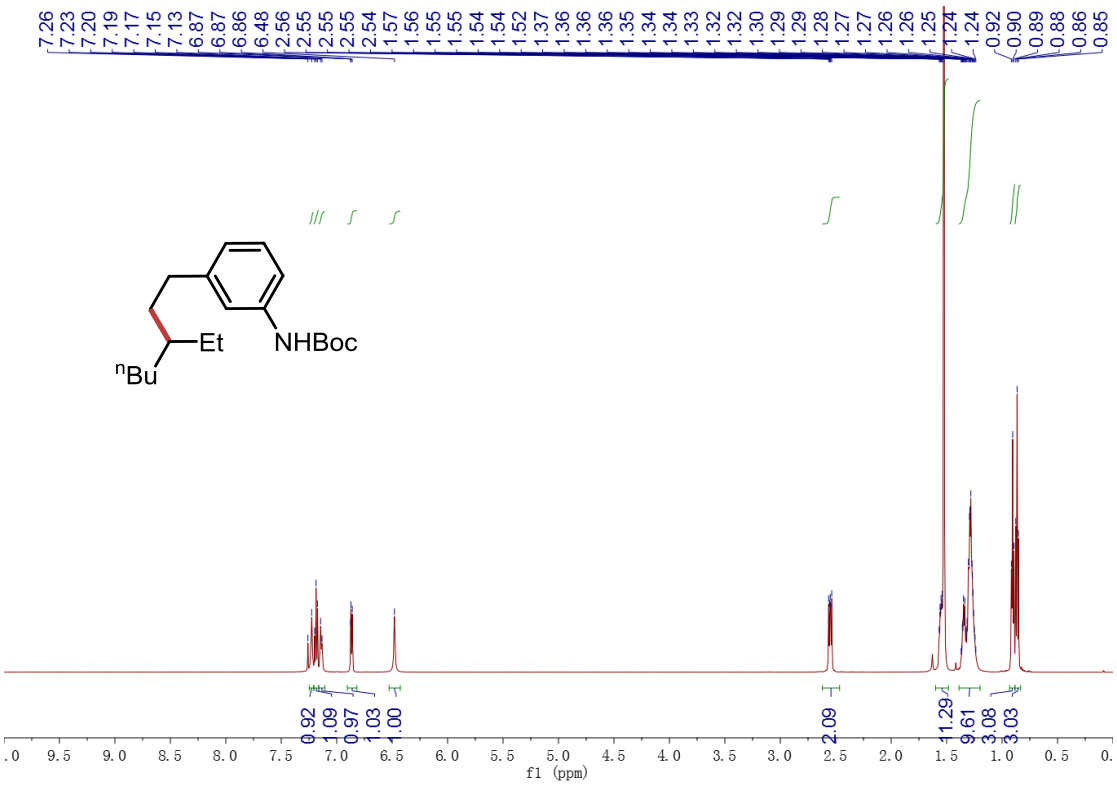
^{1}H NMR of Compound 36 (600 MHz, $CDCl_3$):



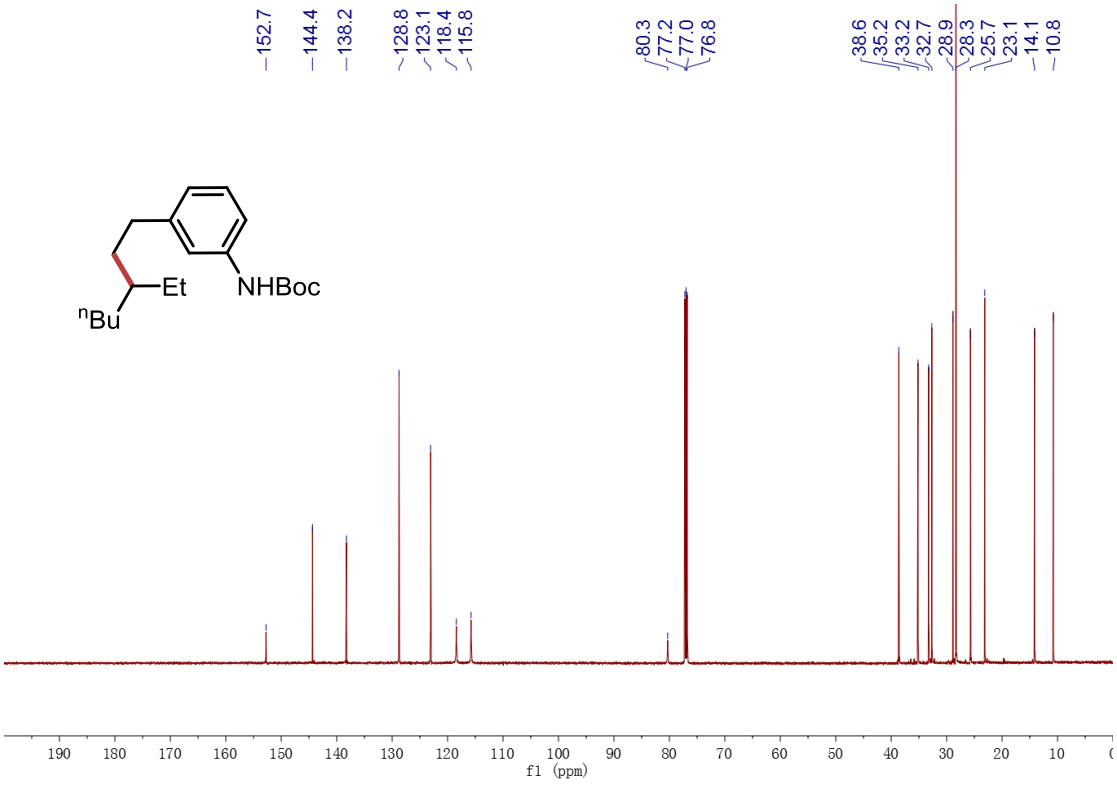
^{13}C NMR of Compound 36 (151 MHz, $CDCl_3$):



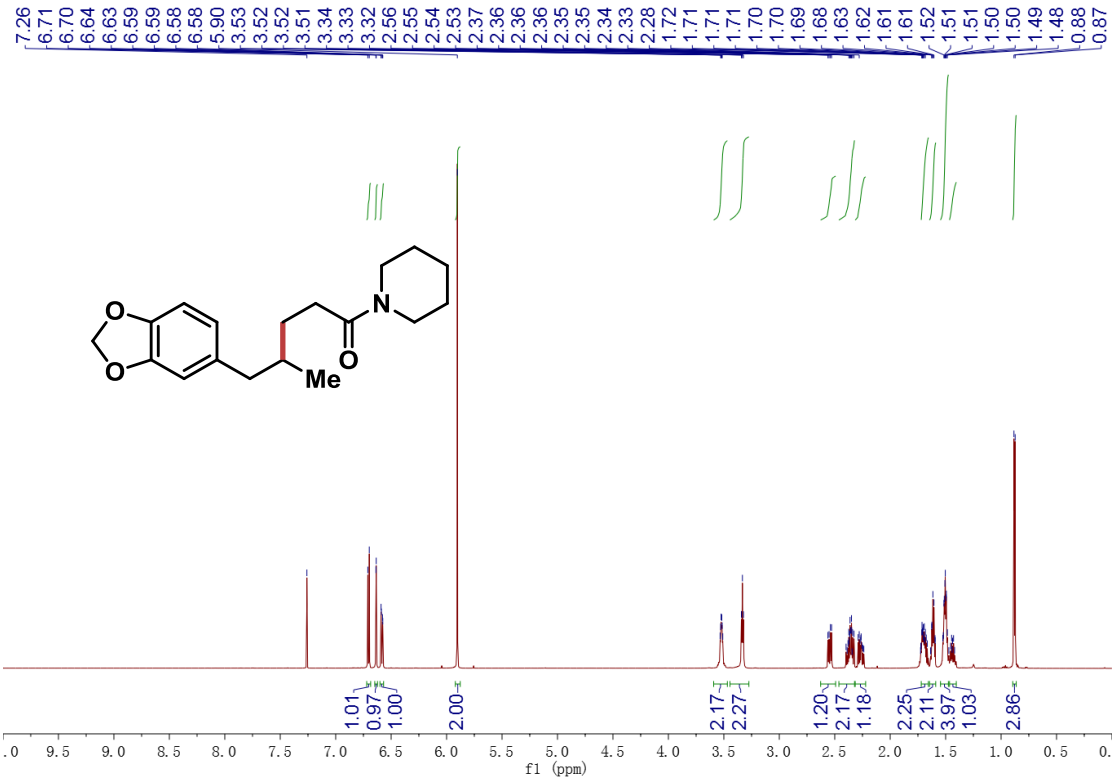
^{1}H NMR of Compound 37 (600 MHz, $CDCl_3$):



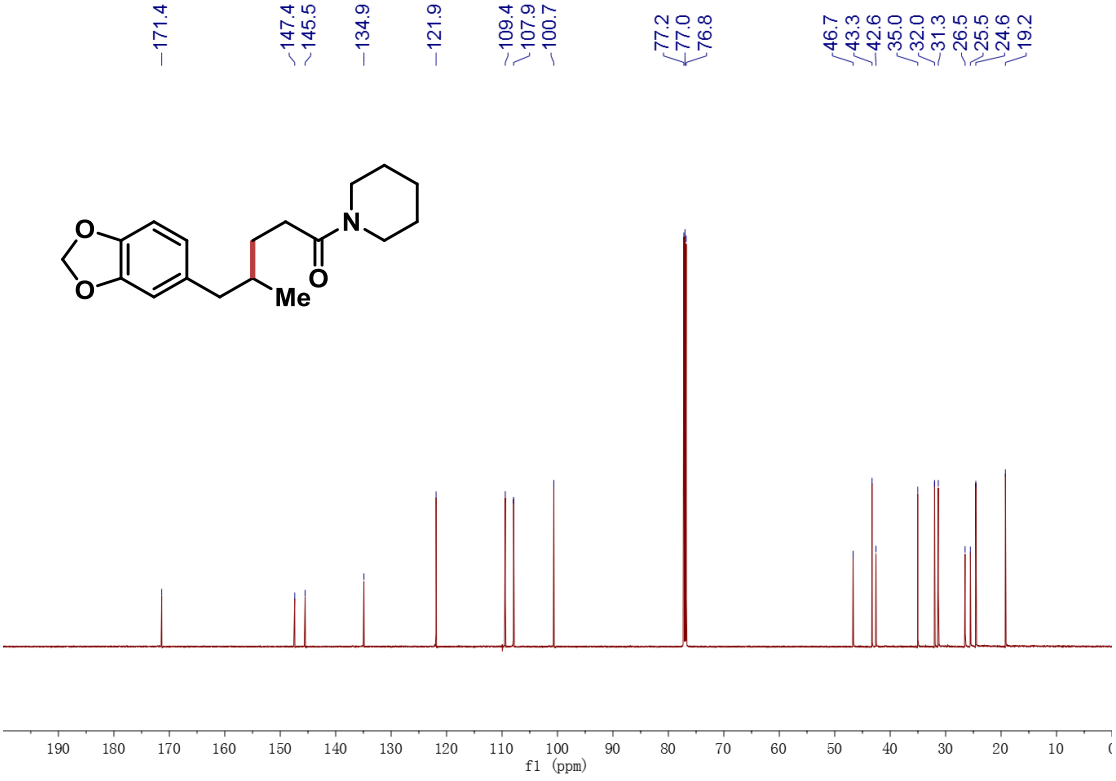
^{13}C NMR of Compound 37 (151 MHz, $CDCl_3$):



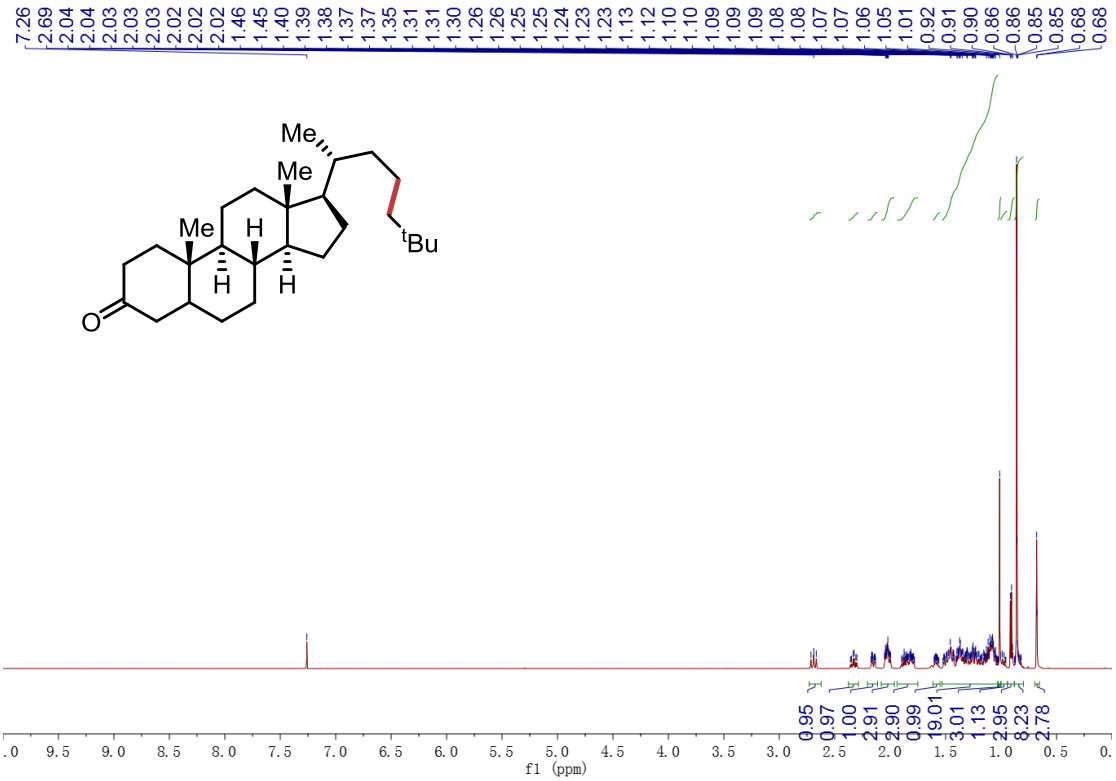
^{1}H NMR of Compound 38 (600 MHz, $CDCl_3$):



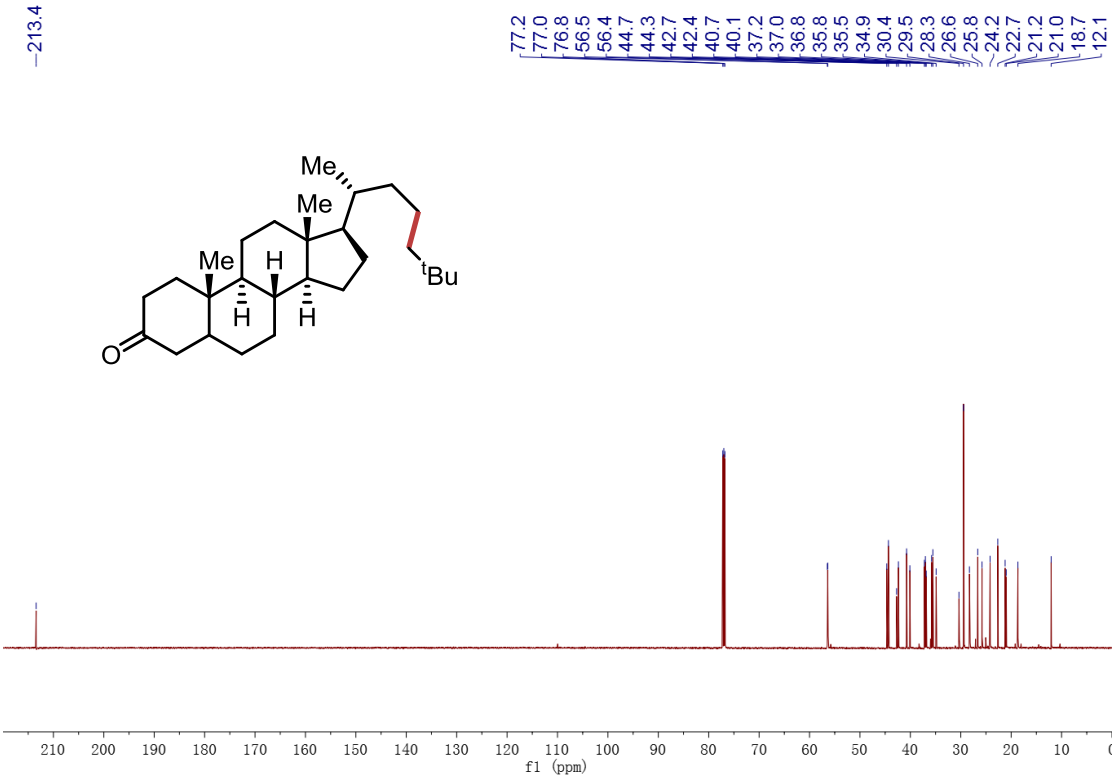
^{13}C NMR of Compound 38 (151 MHz, $CDCl_3$):



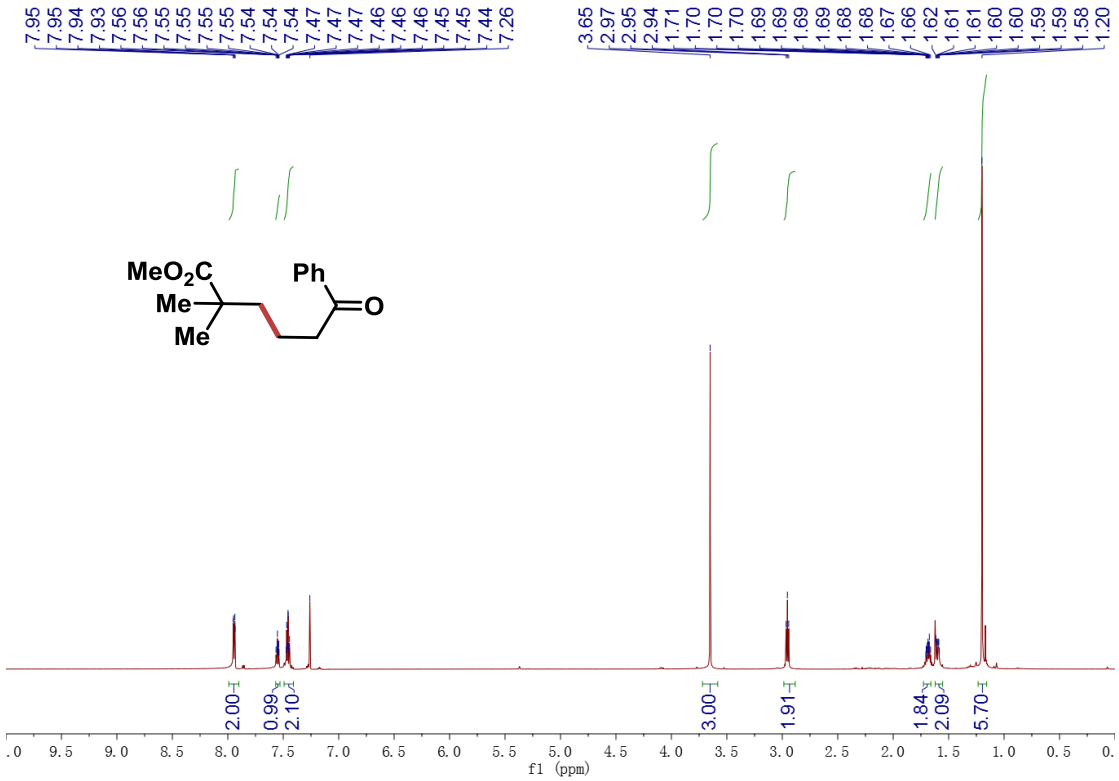
^{1}H NMR of Compound 39 (600 MHz, $CDCl_3$):



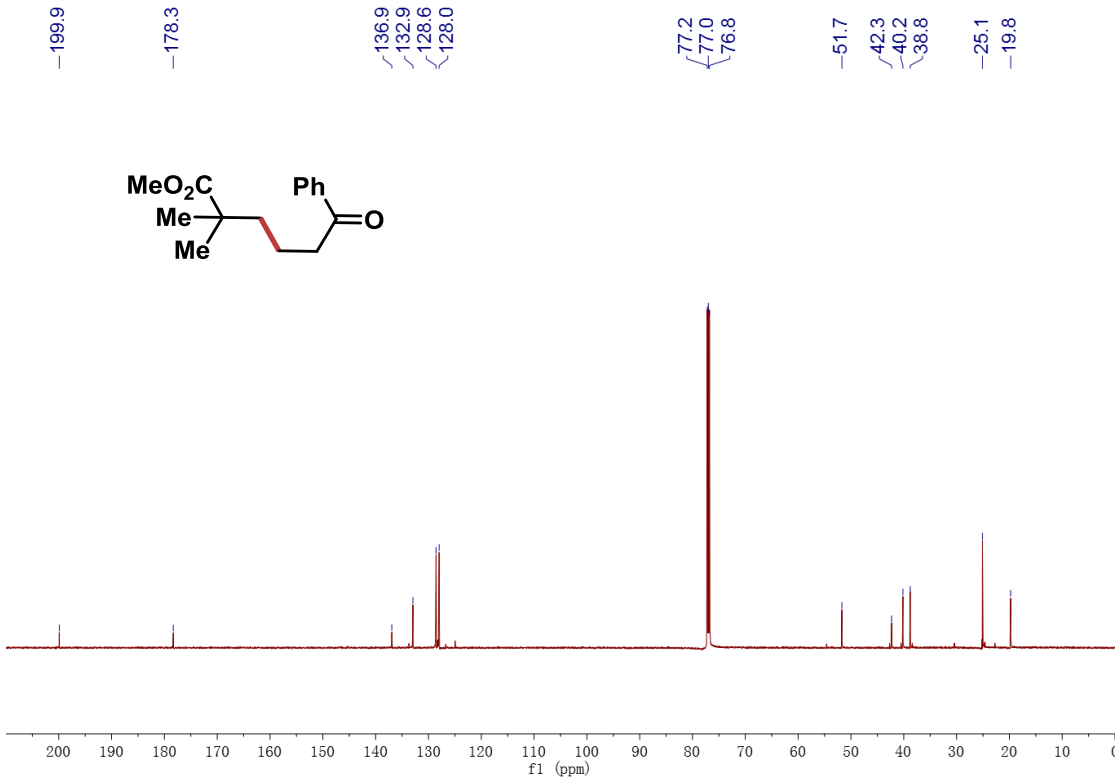
^{13}C NMR of Compound 39 (151 MHz, $CDCl_3$):



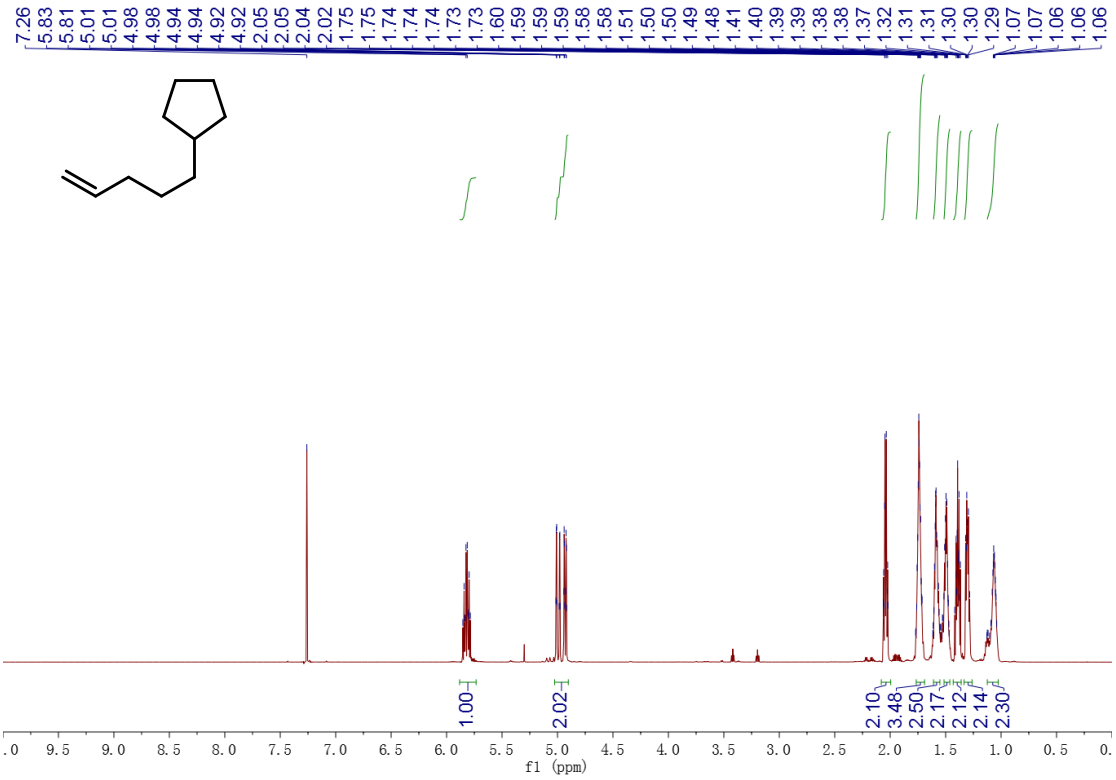
^{1}H NMR of Compound 40 (600 MHz, $CDCl_3$):



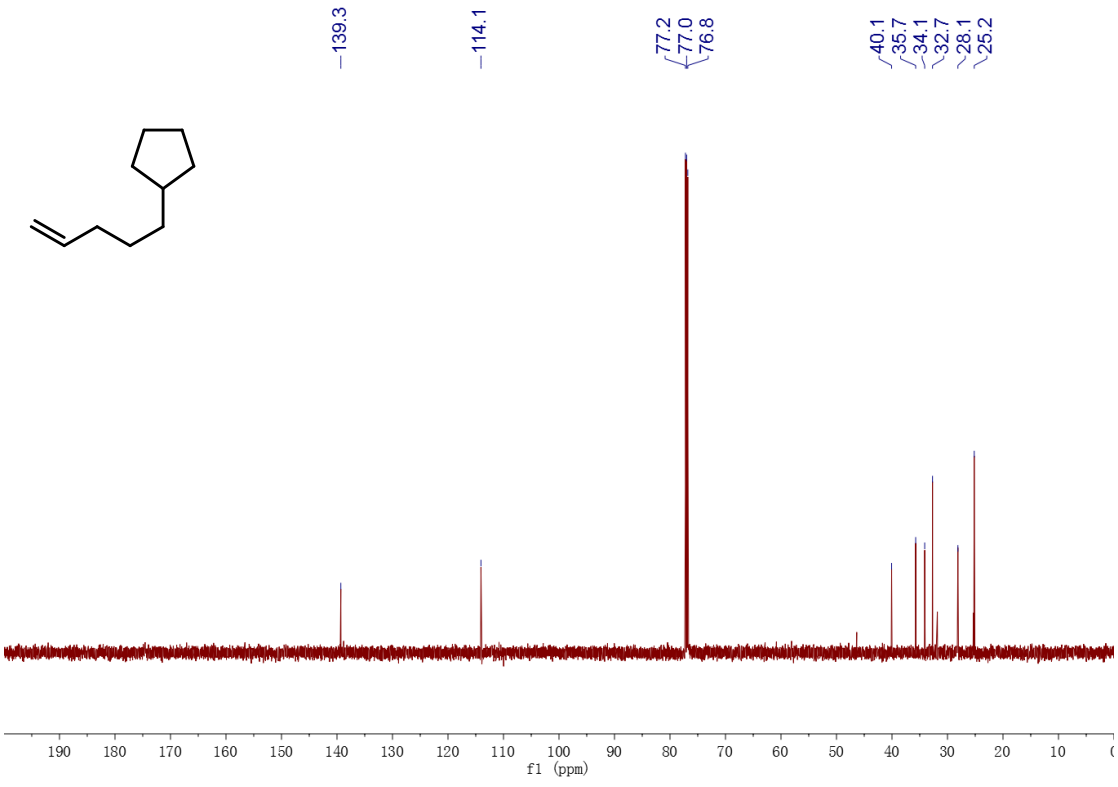
^{13}C NMR of Compound 40 (151 MHz, $CDCl_3$):



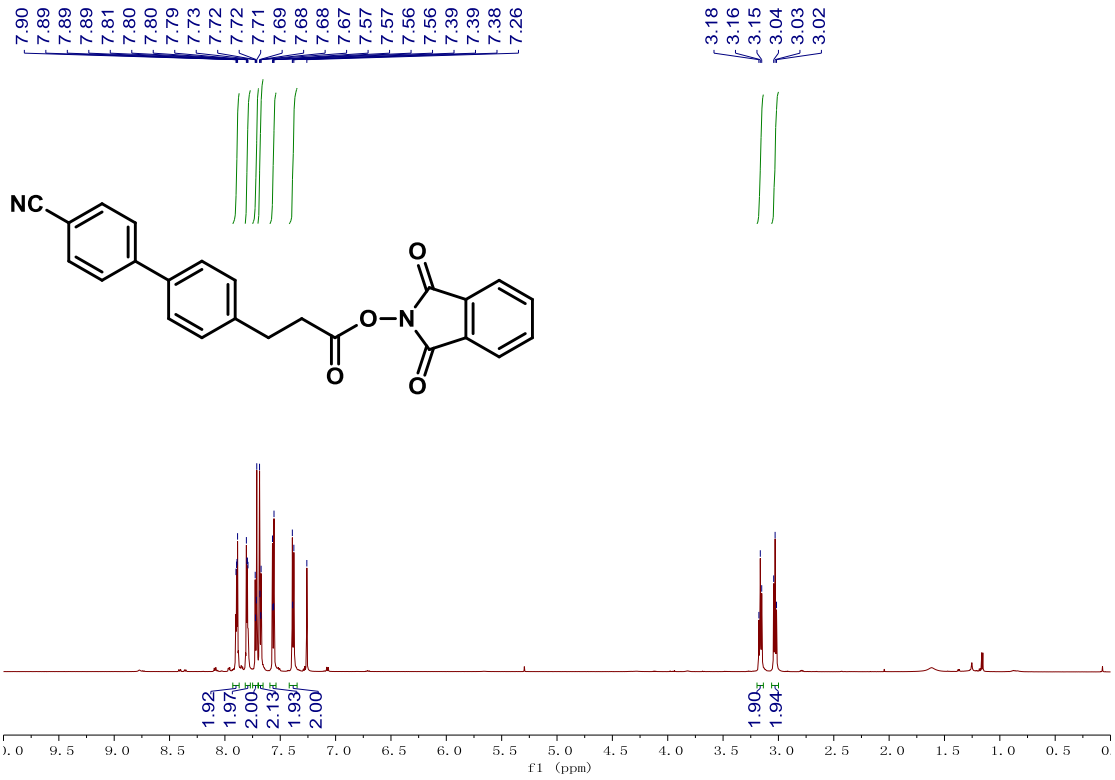
^{1}H NMR of Compound 43 (600 MHz, $CDCl_3$):



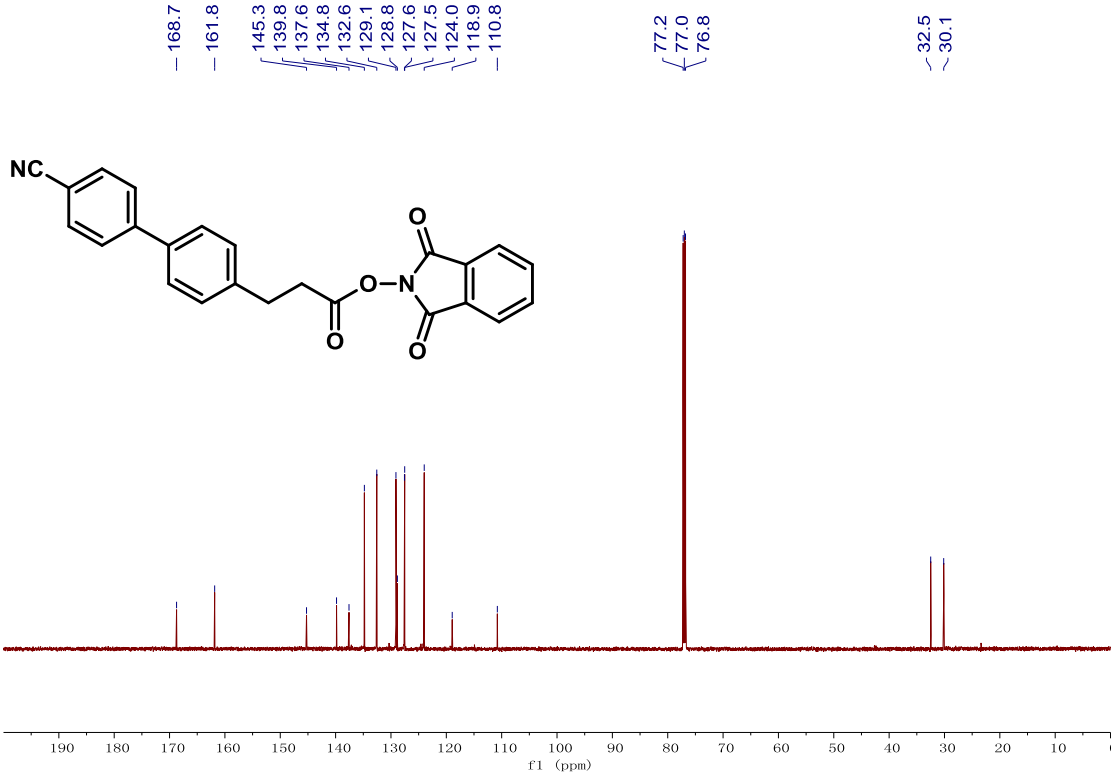
^{13}C NMR of Compound 43 (151 MHz, $CDCl_3$):



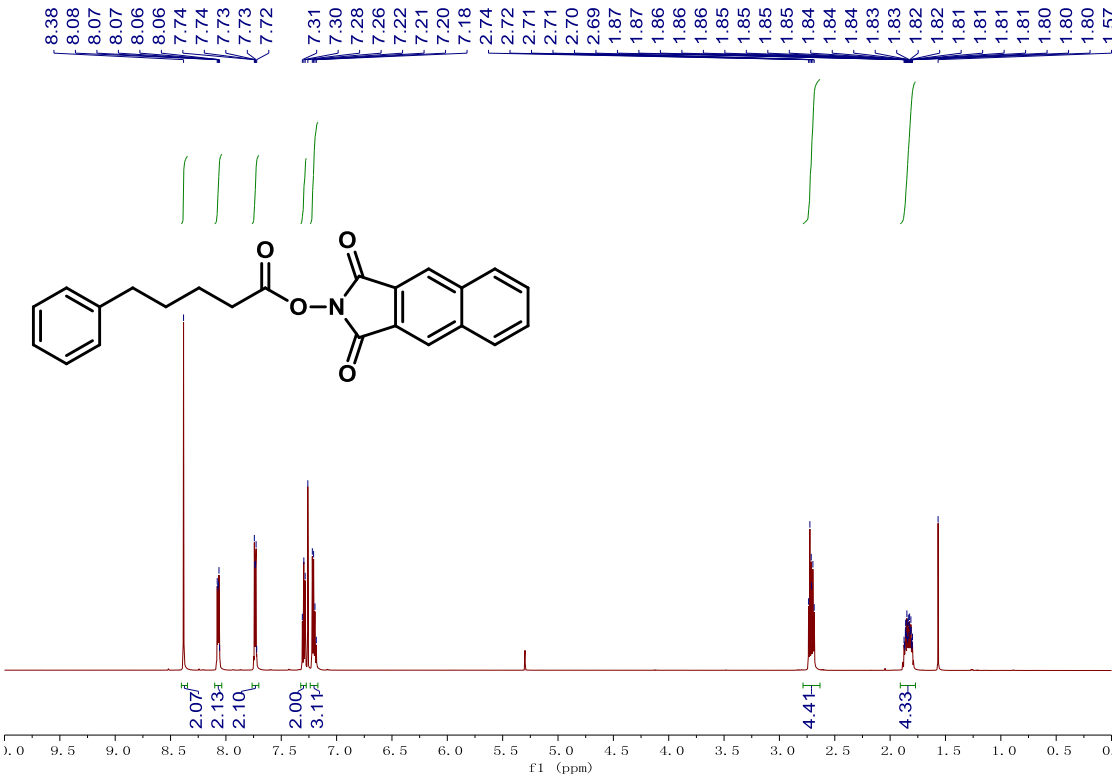
^{1}H NMR of Compound 45 (600 MHz, $CDCl_3$):



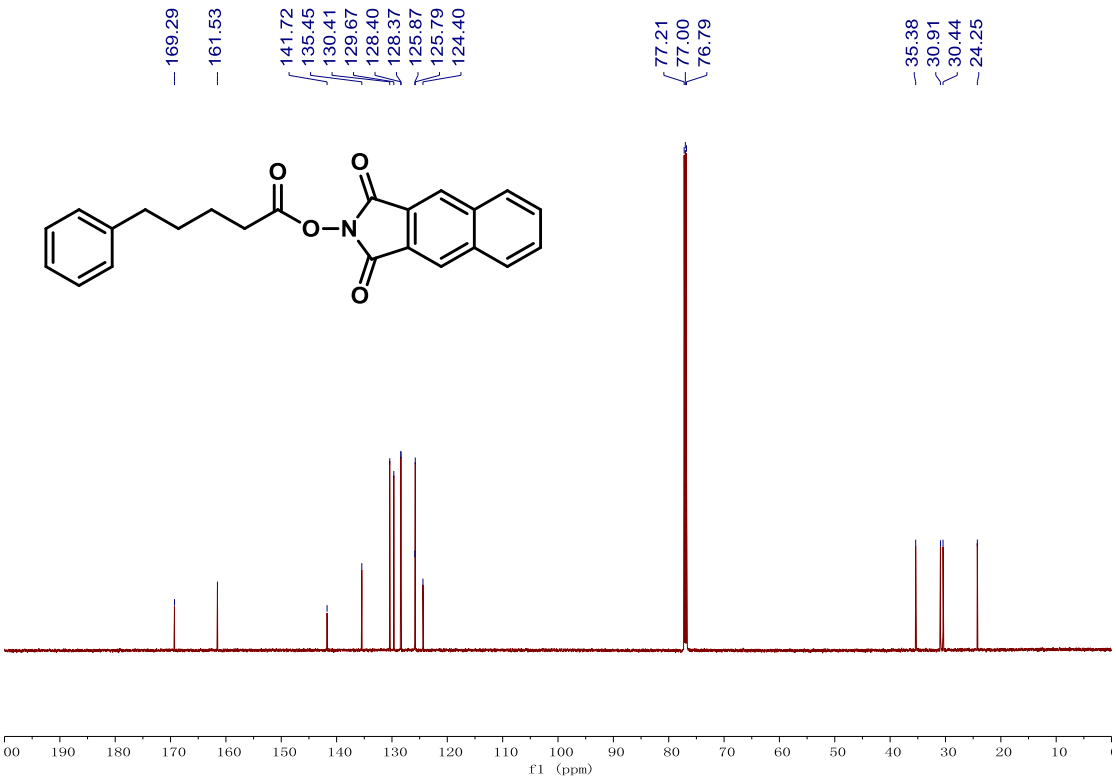
^{13}C NMR of Compound 45 (151 MHz, $CDCl_3$):



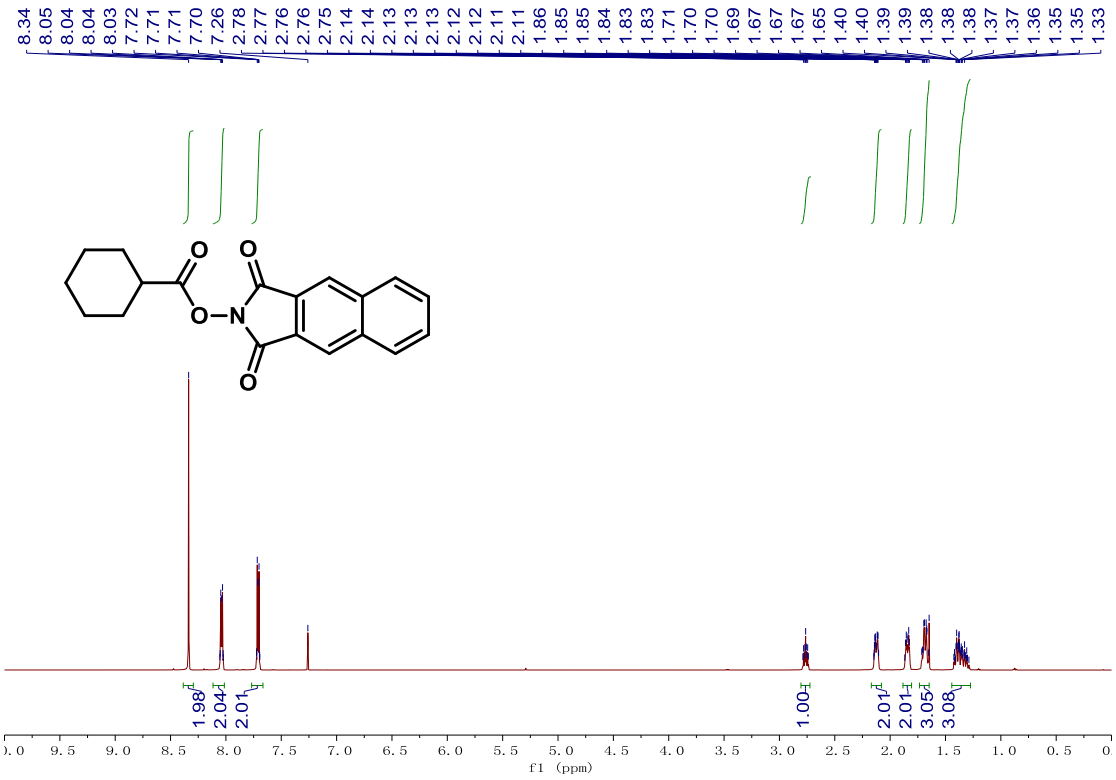
^{1}H NMR of Compound SI-9 (600 MHz, $CDCl_3$):



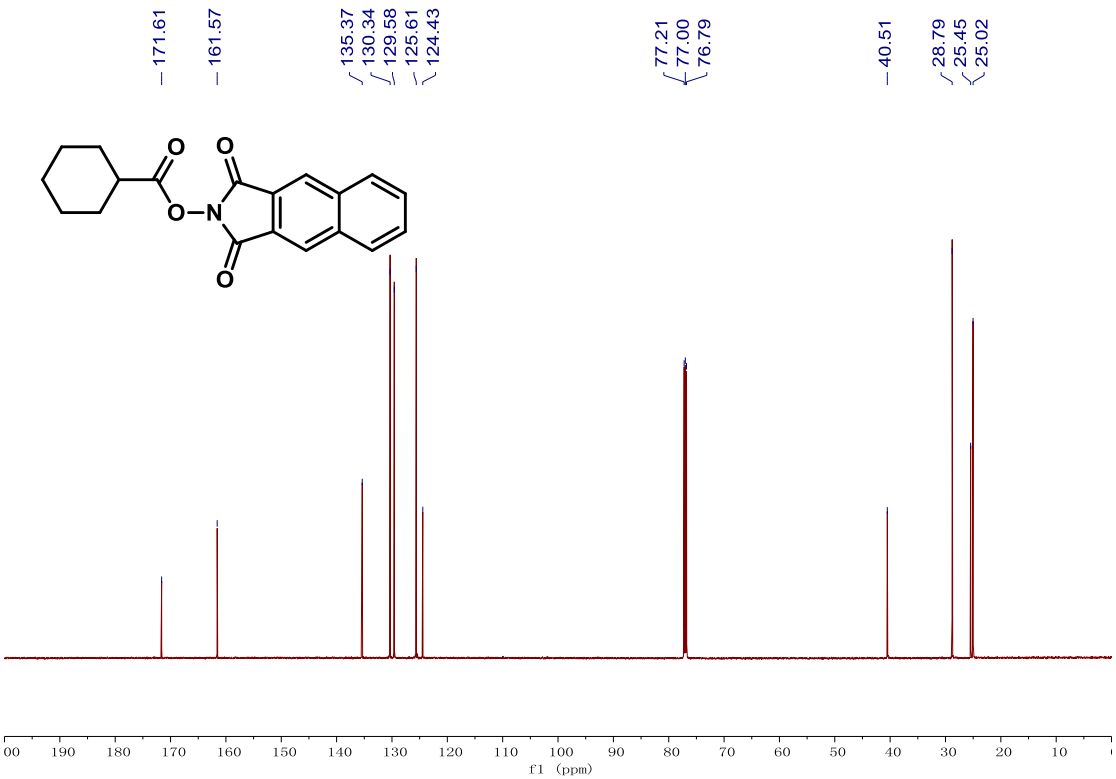
^{13}C NMR of Compound SI-9 (151 MHz, $CDCl_3$):



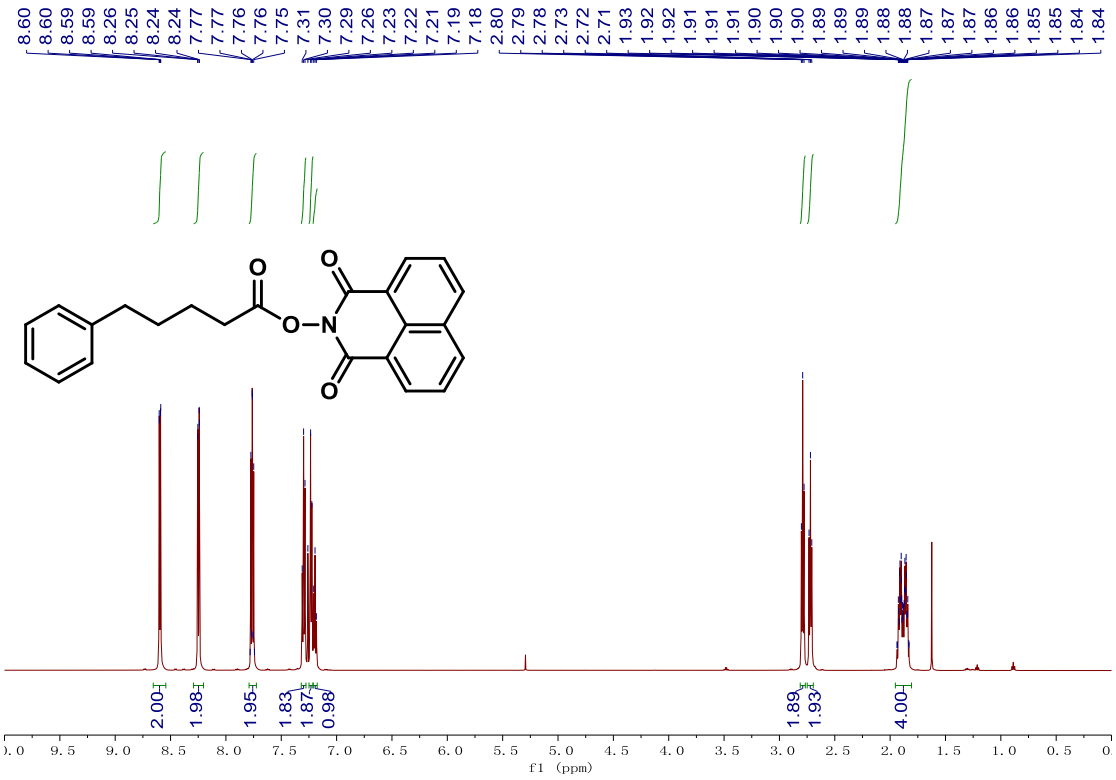
^{1}H NMR of Compound SI-10 (600 MHz, $CDCl_3$):



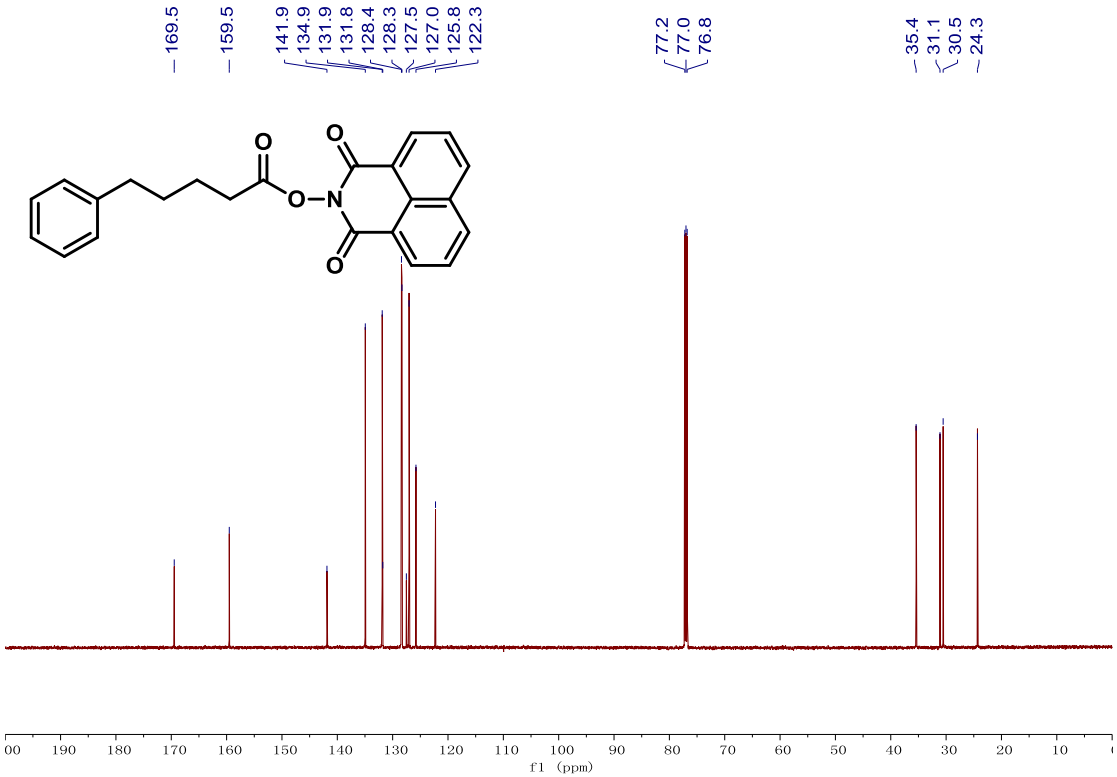
^{13}C NMR of Compound SI-10 (151 MHz, $CDCl_3$):



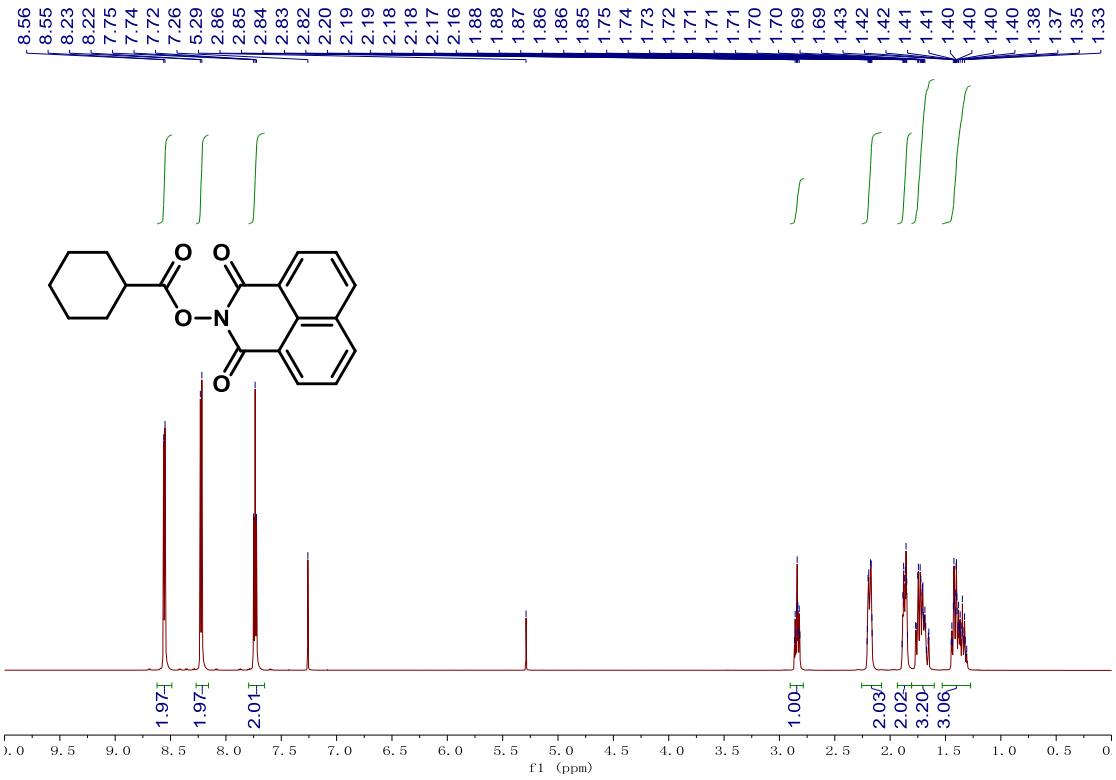
^{1}H NMR of Compound SI-11 (600 MHz, $CDCl_3$):



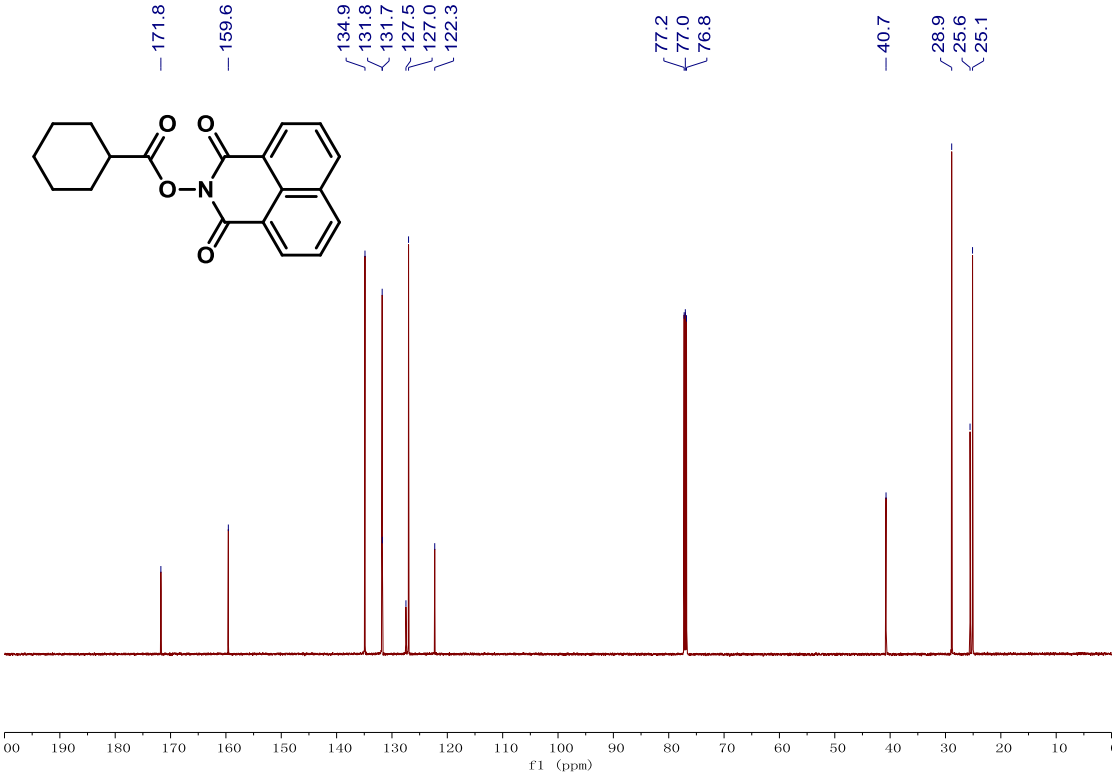
^{13}C NMR of Compound SI-11 (151 MHz, $CDCl_3$):



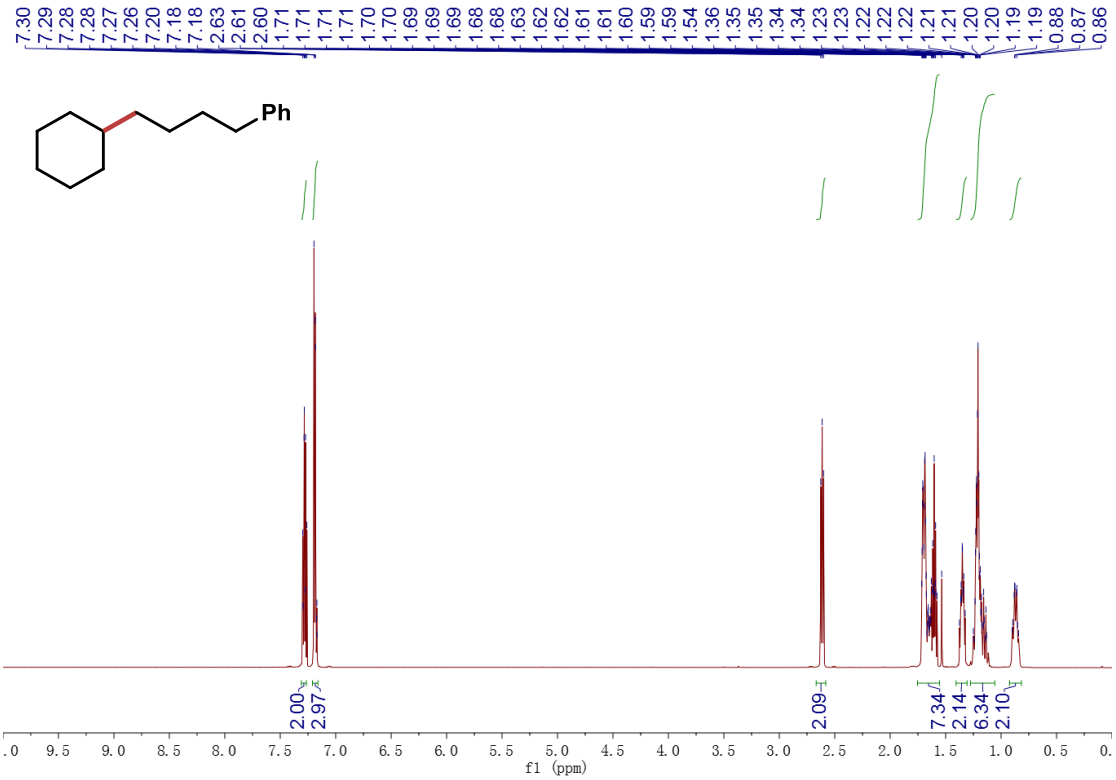
^{1}H NMR of Compound SI-12 (600 MHz, $CDCl_3$):



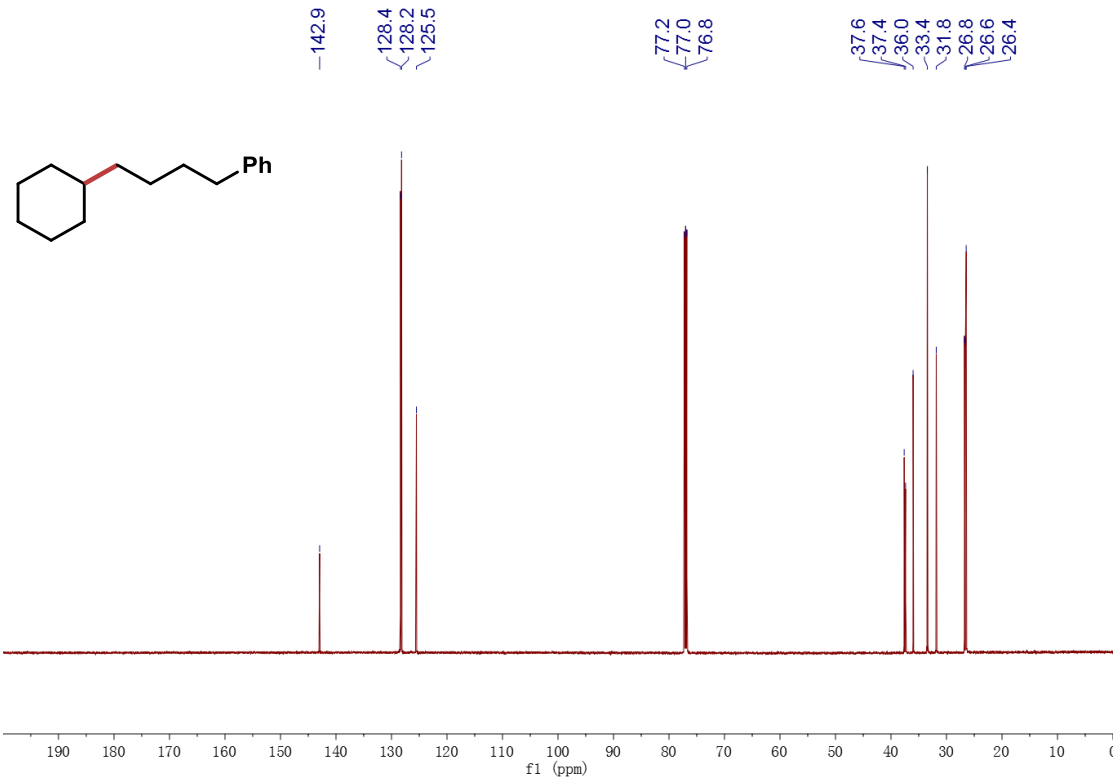
^{13}C NMR of Compound SI-12 (151 MHz, $CDCl_3$):



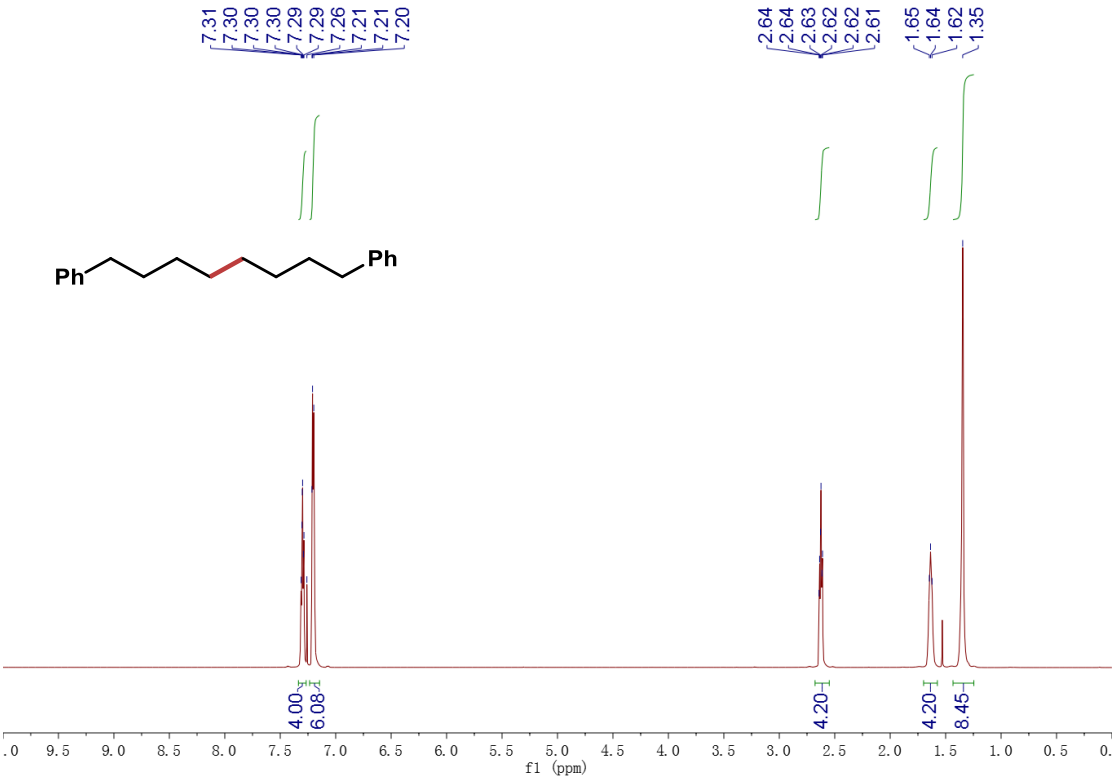
^{1}H NMR of Compound 47 (600 MHz, $CDCl_3$):



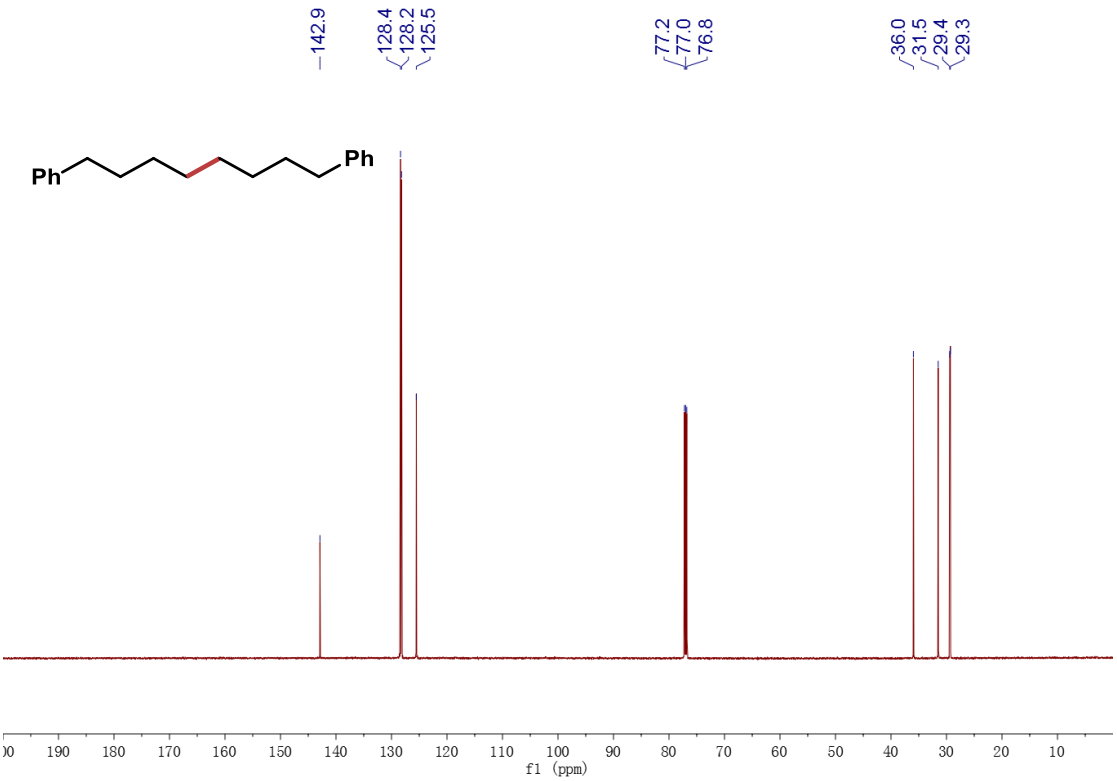
^{13}C NMR of Compound 47 (151 MHz, $CDCl_3$):



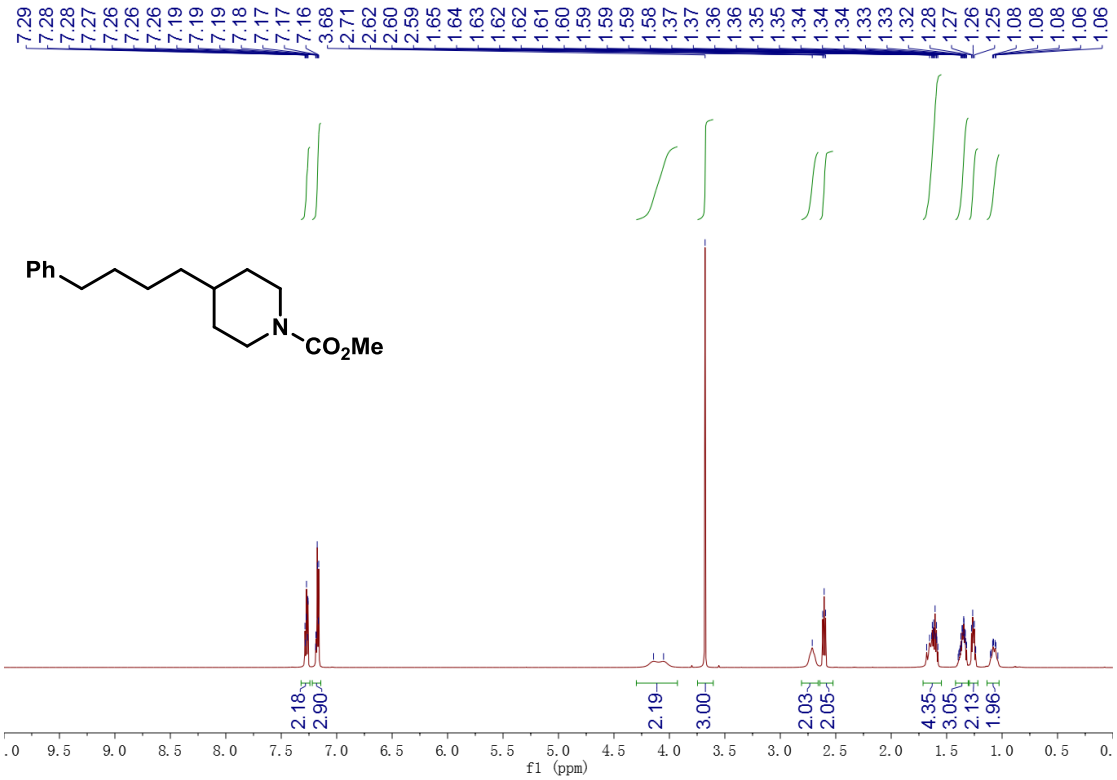
^{1}H NMR of Compound 49 (600 MHz, $CDCl_3$):



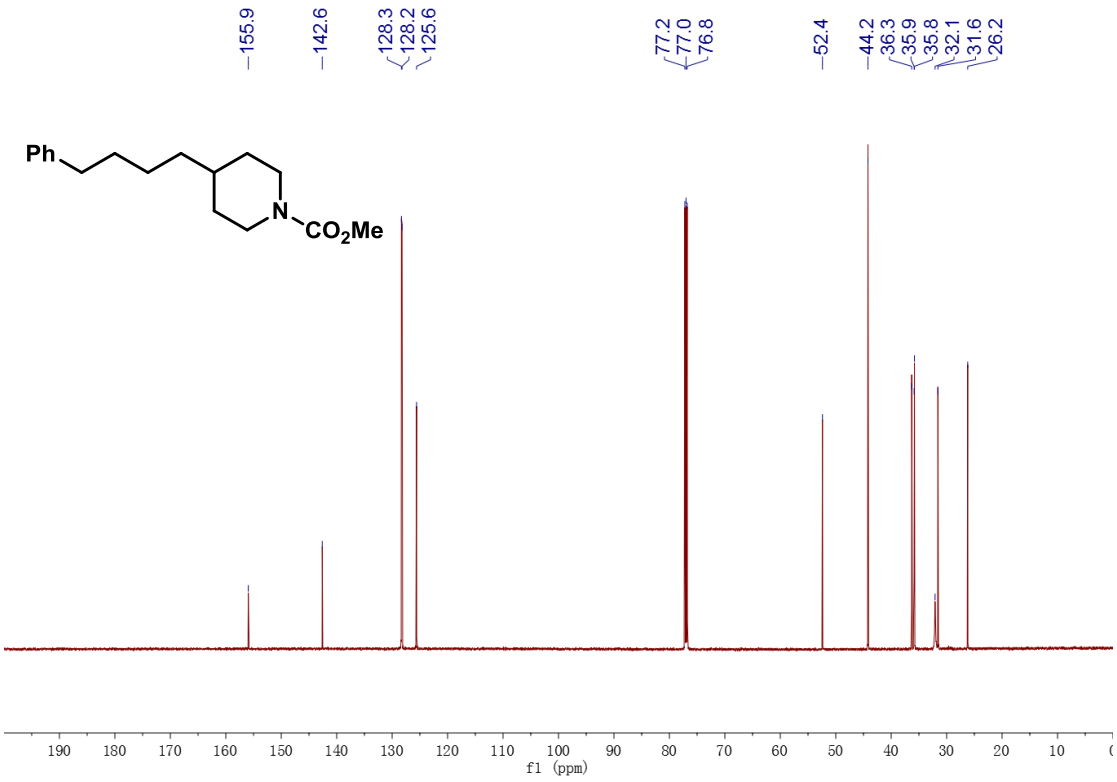
^{13}C NMR of Compound 49 (151 MHz, $CDCl_3$):



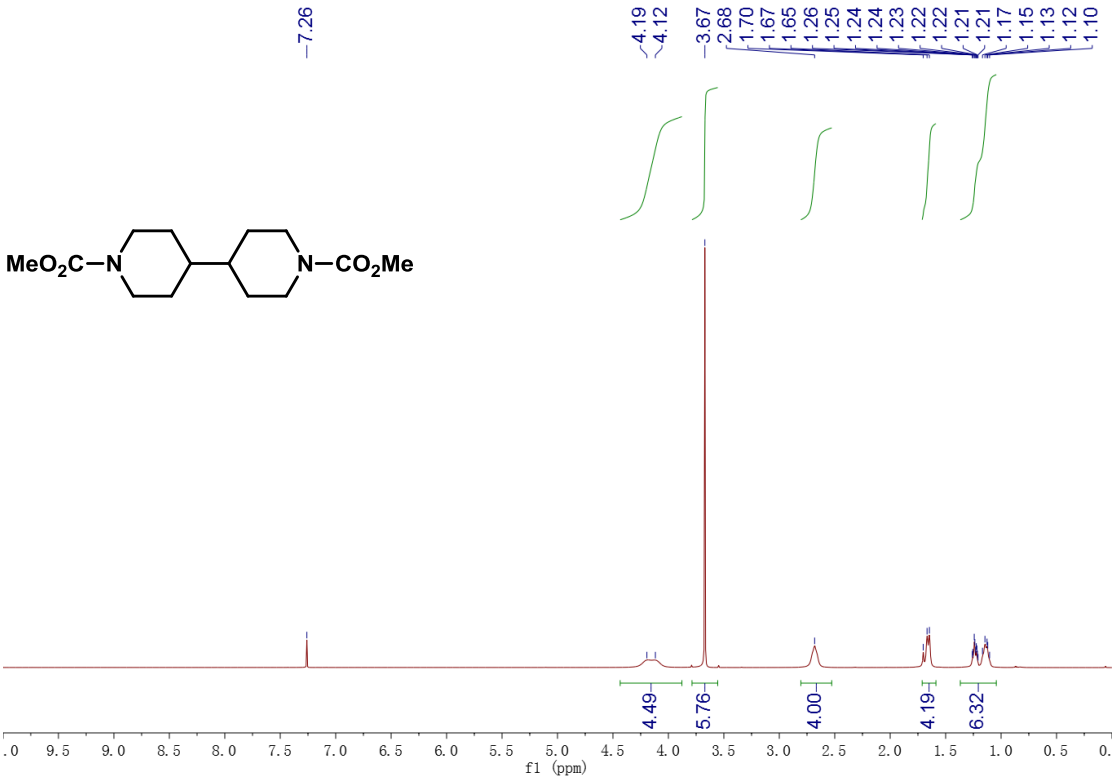
^{1}H NMR of Compound 52 (600 MHz, $CDCl_3$):



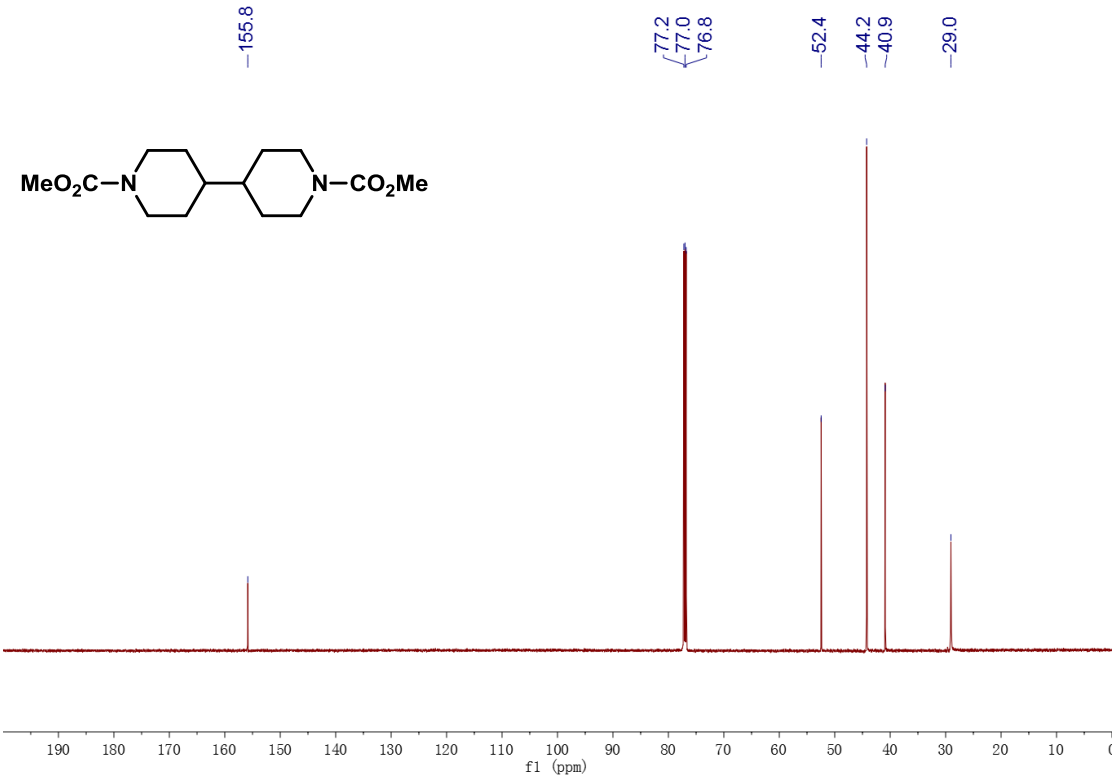
^{13}C NMR of Compound 52 (151 MHz, $CDCl_3$):



^{1}H NMR of Compound 53 (600 MHz, $CDCl_3$):



^{13}C NMR of Compound 53 (151 MHz, $CDCl_3$):



Reference

1. Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* **2011**, *13*, 2138.
2. Fischer, S.; Huwyler, N.; Wolfrum, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 2555.
3. Chan, L K. M.; Gemmell, P. A;. Gray, G. W.; Lacey, D.; Toyne, K. *J. Mol. Cryst. Liq. Cryst.* **1989**, *168*, 229.
4. Wang, Y.; Alenzy, R.; Song, D.; Liu, X.; Teng, Y.; Mowla, R.; Ma, Y.; Polyak, S. W.; Venter, H.; Ma, S. *Eur. J. of Med. Chem.* **2020**, *186*, 111910.
5. Jones, P.; Altamura, S.; De Francesco, R.; Gonzelez Paz, O.; Kinzel, O.; Mesiti, G.; Monteagudo, E.; Pescatore, G.; Rowley, M.; Verdirame, M.; Steinku ̈hler, C. *J. Med. Chem.* **2008**, *51*, 2350.
6. Chandrasekhar, J.; Kozikowski, A. P.; Liu, J.; Tucekmantel, W.; Walker, J. R.; Yuen, P. US2013184313A1
7. Sudhakar, G.; Reddy, K. J.; Nanubolu, J. B. *Tetrahedron* **2013**, *69*, 2419.
8. a) Kemker, I.; Schnepel, C.; Schröder, D. C.; Marion, A.; Sewald, N. *J. Med. Chem.* **2019**, *62*, 7417 b) Ramachandran, P. V.; Mitsuhashi, W.; Biswas, D.; Nicponski, D. R. *Tetrahedron Lett.* **2013**, *54*, 4830.
9. a) Ma, J.-Y.; Huang, W.; Wei, B.-G. *Tetrahedron Lett.* **2011**, *52*, 4598. b) D'Amore, C.; Di Leva, F. S.; Sepe, V.; Renga, B.; Del Gaudio, C.; D'Auria, M. V.; Zampella, A.; Fiorucci, S.; Limongelli, V. *J. Med. Chem.* **2014**, *57*, 937.
10. a) Prepared following known method to its enantiomers, see: Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 4164. b) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818.
11. a) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792. b) Thompson, C. M.; Frick, J. A. *J. Org. Chem.* **1989**, *54*, 890. c) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664.
12. a) Miyata, K.; Kutsuna, H.; Kawakami, S.; Kitamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4649. b) Takemoto,Y.; Hattori, Y.; Makabe, H. *Heterocycles* **2017**, *94*, 286.
13. a) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774. b) Sato, T.; Okamoto, K.; Nakano, Y.; Uenishi, J.; Ikeda, M. *Herterocycles* **2000**, *54*, 747.
14. Song, X.; He, H.; Siahaan, T. J. *Org. Lett.* **2002**, *4*, 549.

15. Bolea, I.; Juárez-Jiménez, J.; de los Ríos, C.; Chioua, M.; Pouplana, R.; Luque, F. J.; Unzeta, M.; Marco-Contelles, J.; Samadi, A. *J. Med. Chem.* **2011**, *54*, 8251.
16. Keller, M.; Trankle, C.; She, X.; Pegoli, A.; Bernhardt, G.;¨ Buschauer, A.; Read, R. W. *Bioorg. Med. Chem.* **2015**, *23*, 3970.
17. Stefaowitz, J.; Schepmann, D.; Daniliuc, C.; Saito, S.; Wünsch, B. *Z. Naturforsch.* **2016**, *71*, 1057.
18. Taichi, T.; Hisayuki, T.; Daisuke, I.; Shuzo, T. EP3831812A1.
19. Wei, Z.; Yang, H.; Liu, Z.; Tremblay, M.; Johnstone, S.; Béha, S.; Yue, S. Y.; Srivastava, S.; Tomaszewski, M. J.; Brown, W.; Walpole, C.; St-Onge, S.; Lessard, E.; Archambault, A.-J.; Groblewski, T.; Pagé, D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3884.
20. Feskov, I. O.; Chernykh, A. V.; Kuchkovska, Y. O.; Daniliuc, C. G.; Kondratov, I. S.; Grygorenko, O. O. *J. Org. Chem.* **2019**, *84*, 1363.
21. Konno, H.; Sato, T.; Saito, Y.; Sakamoto, I.; Akaji, K. *Bioorg. Med. Chem.* **2015**, *25*, 5127.
22. Hoxha, S.; Kalaitzakis, D.; Bosveli, A.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2021**, *23*, 5354.
23. Pomerantz, M.; Witherup, T. H. *J. Am. Chem. Soc.* **1973**, *95*, 5977.
24. Mori, K.; Mastuda, S.; Suguro, T. *Tetrahedron* **1981**, *37*, 1329.
25. Terashima, S.; Nara, M.; Yamada, S.-I. *Chem. Pharm. Bull.* **1970**, *18*, 1124.
26. Zhao, L.; Meng, X.; Zou, Y.; Zhao, J.; Wang, L.; Zhang, L.; Wang, C. *Org. Lett.* **2021**, *23*, 8516.
27. Yajima, A.; Kawanishi, N.; Qi, J.; Asano, T.; Sakagami, Y.; Nukada, T.; Yabuta, G. *Tetrahedron Lett.* **2007**, *48*, 4601.
28. Jones, L.; Schumm, J. S.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1388.
29. Surrinder, K,; Lal, K.; Chandra, T. WO2006103527A1
30. Barton, D. H. R.; Boivin, J.; Crich, D.; Hill, C. H. *J. Chem. Soc., Perkin Trans. 1,* **1986**, 1805.
31. Imoto, H.; Sugayama, Y.; Kimura, H; Momose, Y. *Chem. Pharm. Bull.* **2003**, *51*, 138.
32. Xue, W.; Oestreich, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 11649.
33. Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 260.
34. Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 11132.

35. Xia, H.-D.; Li, Z.-L.; Gu, Q.-S.; Dong, X.-Y.; Fang, J.-H.; Du, X.- Y.; Wang, L.-L.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2020**, *59*, 16926.
36. Shen, Y. Y.; Gu, Y. T.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 12200.
37. Komeyama, K.; Tsunemitsu, R.; Michiyuki, T.; Yoshida, H.; Osaka, I. *Molecules* **2019**, *24*, 1458.
38. Aycock, R. A.; Vogt, D. B.; Jui, N. T. *Chem. Sci.* **2017**, *8*, 7998.
39. Cao, Y.; Yang, J. G.; Deng, Y.; Wang, S.; Liu, Q.; Shen, C.; Lu, W.; Che, C. M.; Chen, Y.; He, L. *Angew. Chem., Int. Ed.* **2020**, *59*, 2080.