nature portfolio

https://doi.org/10.1038/s41586-023-06677-2

Supplementary information

Complex molecule synthesis by electrocatalytic decarboxylative cross-coupling

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Complex Molecule Synthesis by Electrocatalytic Decarboxylative Cross-Coupling

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Supplementary information

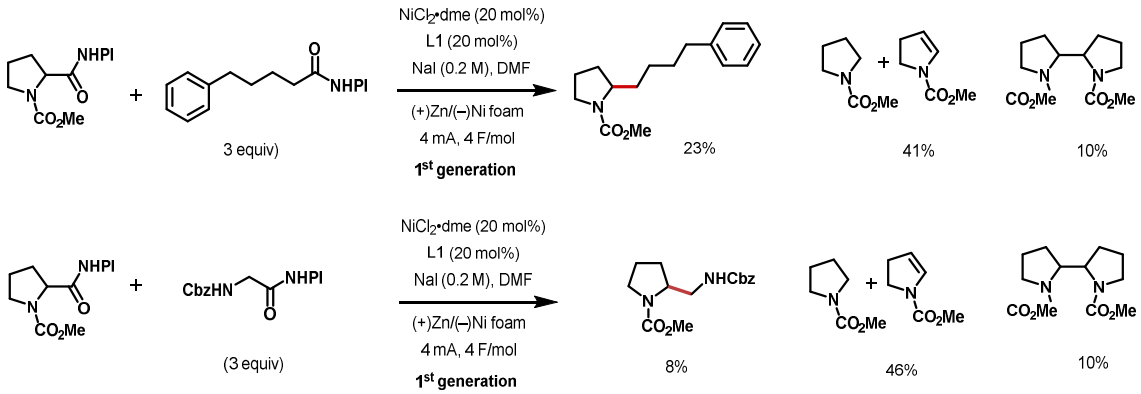
Table of Contents

General Experimental

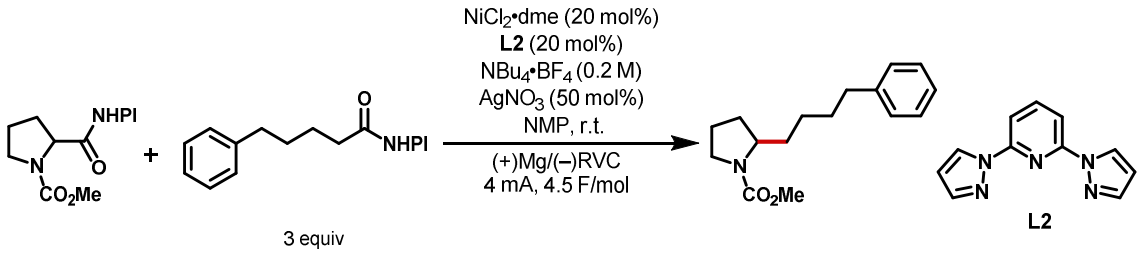
Tetrahydrofuran (THF), acetonitrile (CH_3CN), and dichloromethane (CH_2Cl_2) were obtained by passing the previously degassed solvents through an activated alumina column. All substrates that were purchased (from cheapest supplier), were used without further purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR/GCMS) 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; DMSO at 2.50 ppm ^{1}H NMR, 39.52 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

Optimization of Reaction Parameters for the Ni-Catalyzed Decarboxylative Alkenylation

The coupling of proline derivative was studied by 1st generation dDCC.



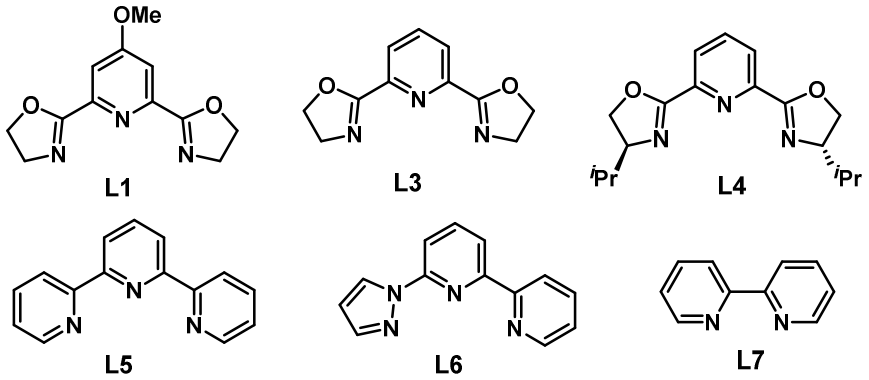
Optimization of reaction parameters

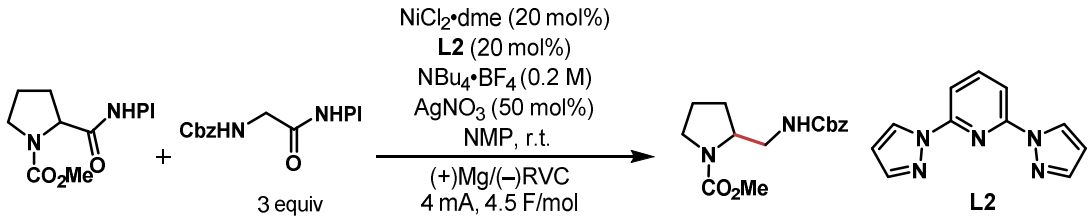


entry	deviation from above	yield[a]/%
1	none	70
2	no $AgNO_3$	32
3	Zn instead of Mg	40
4	Fe instead of Mg	16
5	stainless steel instead of Mg	trace
6	Ni foam instead of RVC	55
7	C instead of RVC	35
8	DMF instead of NMP	34
9	DMA instead of NMP	57
10	CH_3CN instead of NMP	29
11	DMSO instead of NMP	62
12	**L1** instead of **L2**	60
13	**L3** instead of **L2**	44
14	**L4** instead of **L2**	39

15	**L5** instead of **L2**	10
16	**L6** instead of **L2**	14
17	**L7** instead of **L2**	49
19	$NiBr_2$•dme instead of $NiCl_2$•dme	34
20	$NiCl_2$•$6H_2O$ instead of $NiCl_2$•dme	58
21	$Ni(acac)_2$ instead of $NiCl_2$•dme	31
22	no NBu_4•BF_4	62
23	NaI instead of NBu_4•BF_4	45
24	NBu_4•Br instead of NBu_4•BF_4	44
25	NBu_4•PF_6 instead of NBu_4•BF_4	63

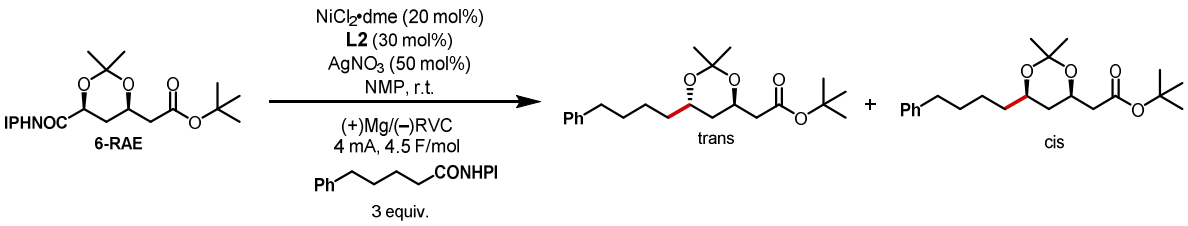
[a] The yields are based on GC analysis.





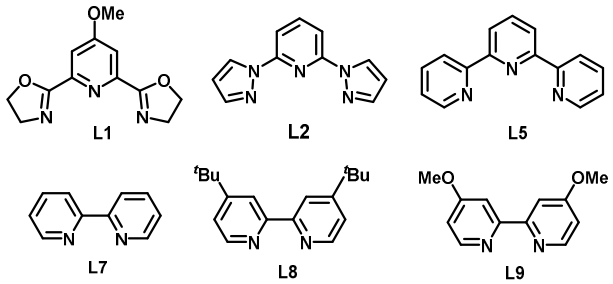
entry	deviation from above	yield[a]/%
1	none	67
2	no $AgNO_3$	29
3	Zn instead of Mg	12
4	Ni foam instead of RVC	40
5	DMF instead of NMP	29
6	**L1** instead of **L2**	41
7	**L5** instead of **L2**	30

[a] Isolated yield.



entry	deviation from above	yield[a]/%	trans/cis
1	none	49	2:3
2	**L1** instead of **L2**	63	2:3
3	**L5** instead of **L2**	58	<1:20
4	**L7** instead of **L2**	41	1:10
5	**L8** instead of **L2**	34	1:3
6	**L9** instead of **L2**	38	1:4
7	**L5** instead of **L2**, add $MgCl_2$ (2 eq.)	66 (68)	<1:20
8	no ligand, add $MgCl_2$ (2 eq.)	60 (54)	>20:1
9[b]	$NiCl_2$•dme (20 mol%), **L5** (30 mol%) $MgCl_2$ (2 eq.), Zn power (3 eq), NMP	trace	/
10[c]	$NiBr_2$•dme (10 mol%), **L5** (15 mol%) (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6 (2 mol%) DIPEA (3 eq), NMP, blue LED	0	/

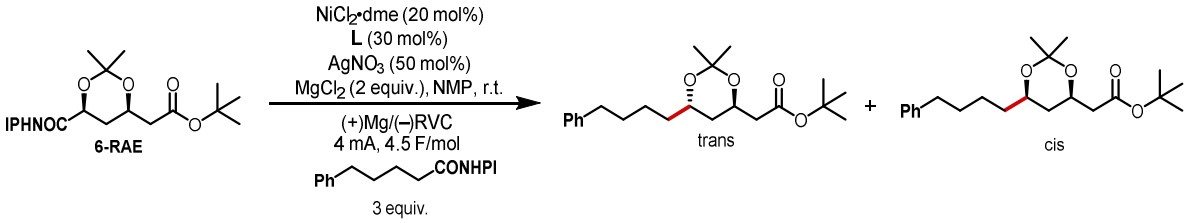
[a]The yields are based on ^{1}H NMR; The results in parentheses are isolated yields. [b]Comparison with Zn powder condition. [c]Comparison with photochemical condition.



Effect of solvent and ligand in stereochemical control

In the case of ligand free system, diastereoselectivity highly solvent dependent as solvent is the ligand. For a ligated Ni-complex, solvent plays little to no role. Between similar imine-type ligands such as **L1** and **L5**, **L5** shows better diastereoselectivity which can be attributed to more steric encumbrance in the latter case. This is also indicative that stereocontrol in a ligated Ni complex is dictated by steric effects. Though the change from a 5- to 6-membered ring in the ligand seems trivial, it is worth pointing out that Ni-catalysis is very sensitive to structural

changes particularly around the Ni center (J. Am. Chem. Soc. **2023**, *145*, 11518. This work illustrates how a subtle change of ligand structure affects stereochemical outcome).

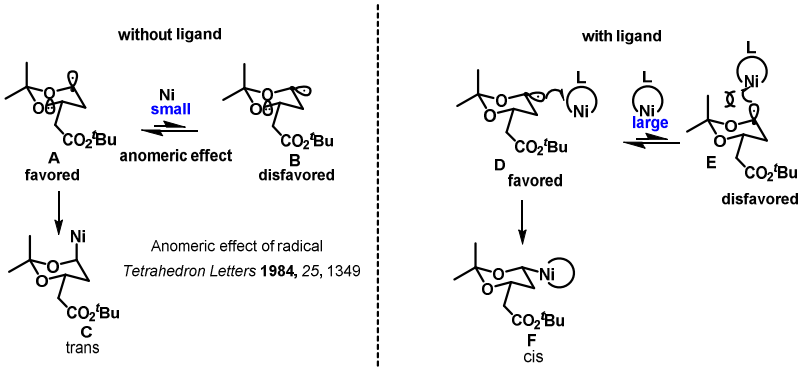


entry	solvent	ligand free yield/% (trans/cis)	terpyridine (L5) yield/% (trans/cis)	(4-OMe)-Pybox (L1) yield/% (trans/cis)
1	NMP	60 (>20:1)	66 (<1:20)	63 (1:1.5)
2	DMF	44 (10:1)	57 (<1:20)	55 (1:1.3)
3	DMA	49 (16:1)	47 (<1:20)	47 (1:1.4)
4	DMI	41 (12:1)	36 (1:7)	40 (1:1.5)
5	DMSO	28 (2:1)	58 (<1:20)	37 (1:1.3)
6	CH_3CN	14 (1:1)	24 (1:2.5)	11 (1:1.4)
7	THF	<5 (/)	<5 (/)	<5 (/)

Tentative rationale for the selectivity

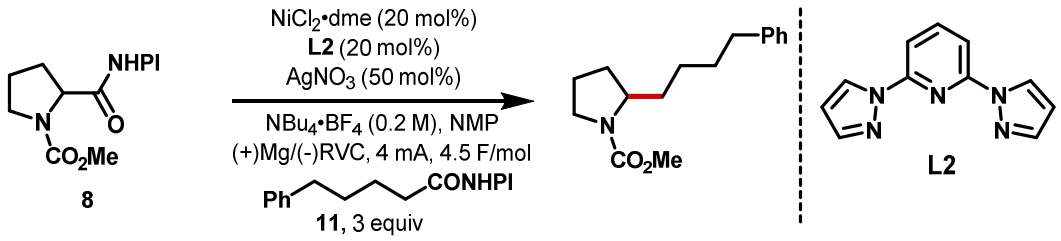
In the dDCC reaction of **6-RAE**, only *cis*-diol product was obtained when **L5** was used as the ligand. In contrast, the omission of the ligand led to the formation of *trans*-diol product. A working hypothesis is proposed as follows:

Single electron transfer to **6-RAE** gives alkyl radical **A**, which is thermodynamically more favorable than **B** due to the anomeric effect of carbon radicals. If there is no ligand in the reaction, the less hindered Ni catalyst would rather combine with the radical **A**, and then afforded the trans-coupled intermediate **C**. By contrast, when there is a ligand to coordinate with Ni, the increased steric hinderance of the catalyst will preferentially generate radical **D** to avoid the 1,3-diaxial interactions, leading to cis-coupled intermediate **F**.



Effect of Ag nanoparticles in dDCC

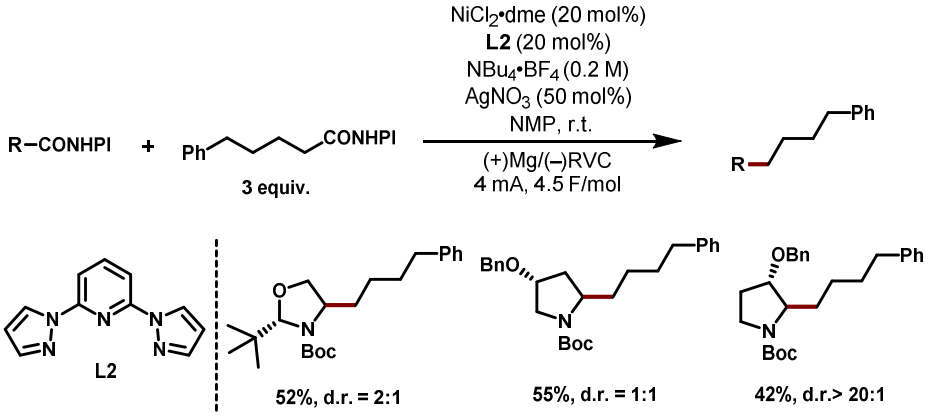
Based on our previous research (Science **2022**, *375*, 745) on the in situ formation of electrode-deposited Ag nanoparticles (AgNP), 1) this AgNP layer effectively preventing catalyst deactivation. To test this hypothesis, we increased the amount of catalyst and ligand to 30% mol which resulted in a modest 12% increase in yield in the absence of the silver salt (entry 3). 2) The AgNP actively modulates diffusion rate of RAEs at the electrode surface due to the adsorptive behavior, thus overcoming consumption rate difference between to RAEs. To investigate this conjecture, we slowly added either of the RAEs to the reaction system to see how much it will affect coupling yield (entry 4 and 5). The results showed that there was only marginal increase in yield, meaning that AgNP is unlikely to equalize the consumption rate of the two RAEs. Interestingly, when both RAEs are slowly-injected, the yield improves to the extent that higher catalyst loading was employed (entry 6). Since this experiment does not address consumption rate difference but changes initial ratio of catalyst and RAE, it also implies that concentration of active catalyst loading is an important factor for the coupling.



entry	deviation from above	yield[a]/%
1	none	70
2	no $AgNO_3$	32
3	no $AgNO_3$, $NiCl_2$•dme (30 mol%), **L2** (30 mol%)	44
4	no $AgNO_3$, **8** was added by syringe pump in 1.5 h	39
5	no $AgNO_3$, **9** was added by syringe pump in 1.5 h	37
6	no $AgNO_3$, **8** and **9** was added by syringe pump in 1.5 h	45

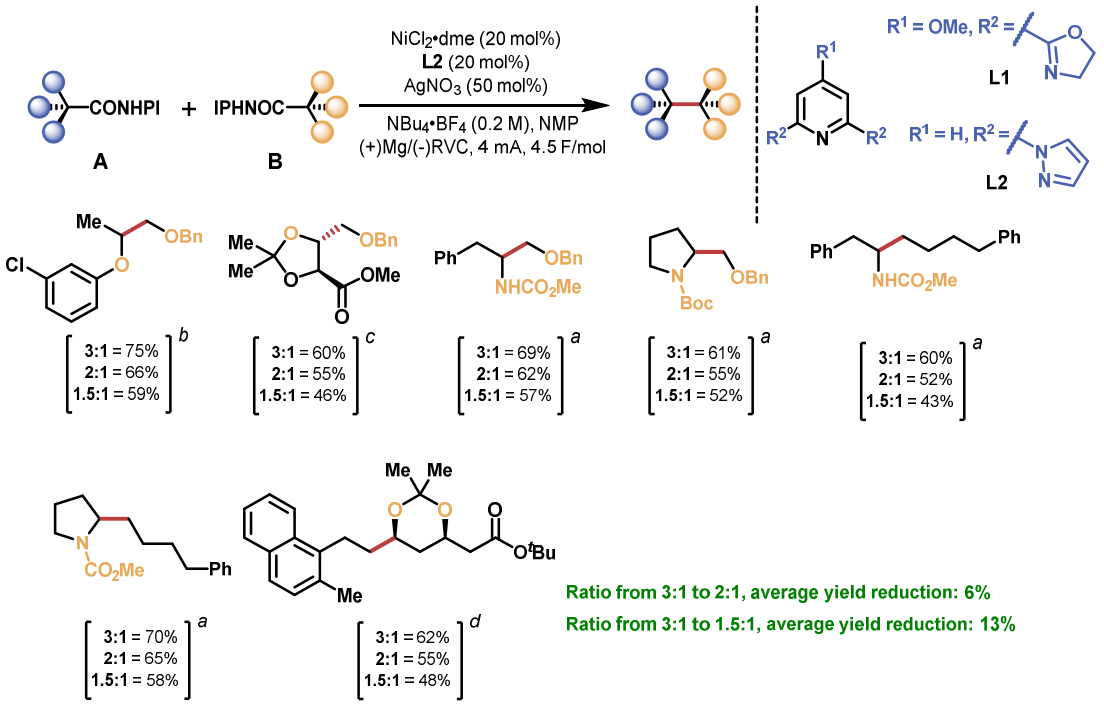
Effect of substrate structures in stereochemical control

The diastereoselectivity of *gem*-nitrogen substituted alkyl radicals in dDCC could be highly substrate-dependent as shown below:



Effect of RAEs' ratio in coupling efficiency

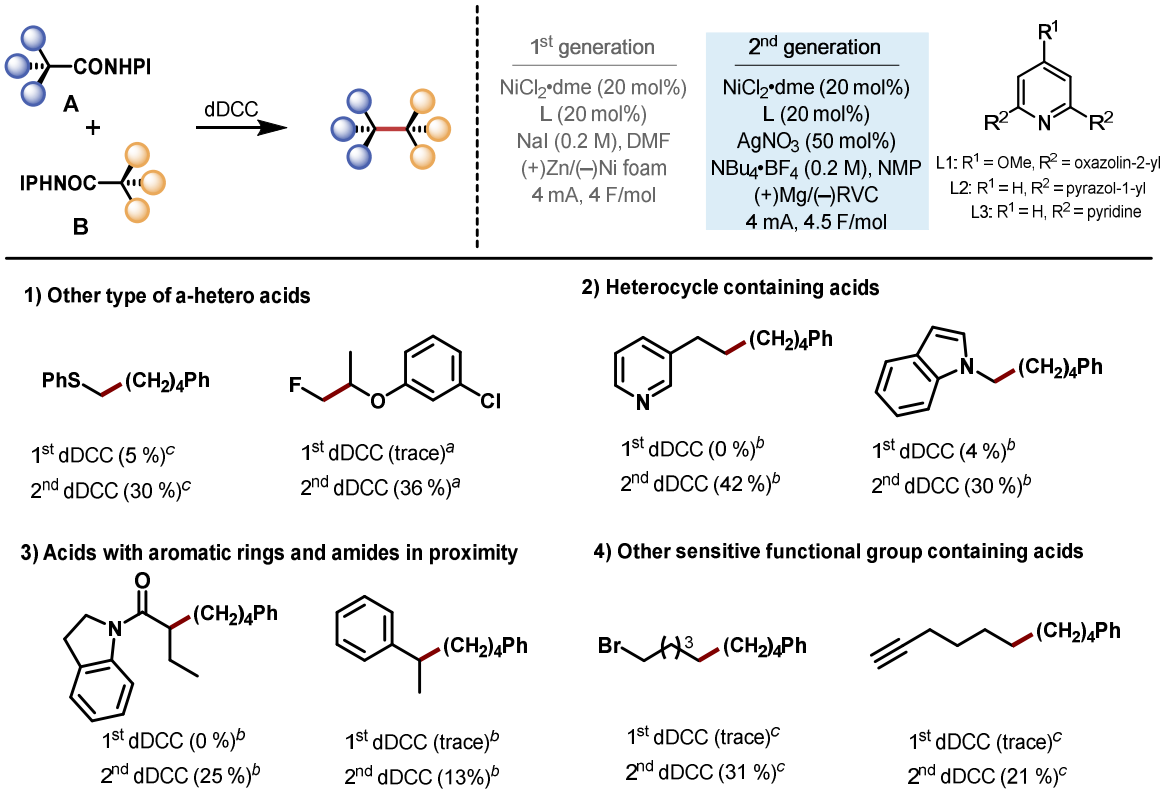
To further understand the impact of carboxylic acid molar ratios on the reaction yield, we investigated seven different substrates (as shown in the figure below). Interestingly, we found that reducing the ratio from 3:1 to 2:1 only resulted in a modest 6% decrease in the average yield. Nevertheless, reducing the molar ratio from 3:1 to 1.5:1 led to a 13% decrease in the average yield.



[a]Reactions were performed on 0.1 mmol scale (2[o] RAEs were used as the limiting reagents), 20 mol% $NiCl_2$•dme, 20 mol% **L2**, 50 mol% $AgNO_3$ and NBu_4•BF_4 (0.2 M) in NMP. [b]**L1** was used as a ligand instead of **L2**, [c]Reaction was performed without a ligand, [d]terpyridine was used as a ligand instead of **L2**

Additional substrates enhanced by Ag nanoparticles

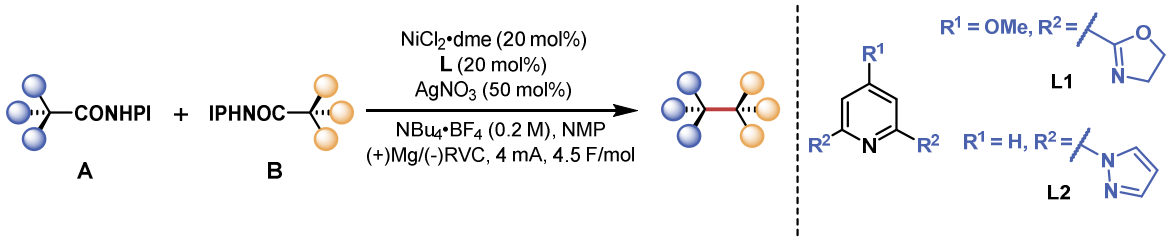
To further explore the potential of this Ag nanoparticles, investigations involving several different substrate classes were conducted. We have found that, in the presence of AgNP, α-S and α-F substituted RAEs also exhibit a significant increase in yield compared to the 1st gen. dDCC (without AgNP). Furthermore, for RAEs containing heterocycles, especially those with pyridine, the difference between the 1st gen. dDCC and the 2nd gen. dDCC (with AgNP) is particularly remarkable, resulting in a significant increase in yield from 0% to 42%. In our previous discussions about the limitations of the 1st gen. dDCC, we pointed out that the reaction is not applicable to alkyl acids adjacent to acyl or aromatic rings. However, by introducing in-situ formed AgNP, we observed this reaction can be applied to such substrates. Finally, we explored more sensitive functional groups, such as bromides and terminal alkynes. The yield improvements were also substantial compared to the 1st gen. dDCC, demonstrating that AgNP can enhance the compatibility of functional groups in the reaction.



[a]**L1** was used as a ligand, [b]**L2** was used as a ligand, [c]**L3** was used as a ligand

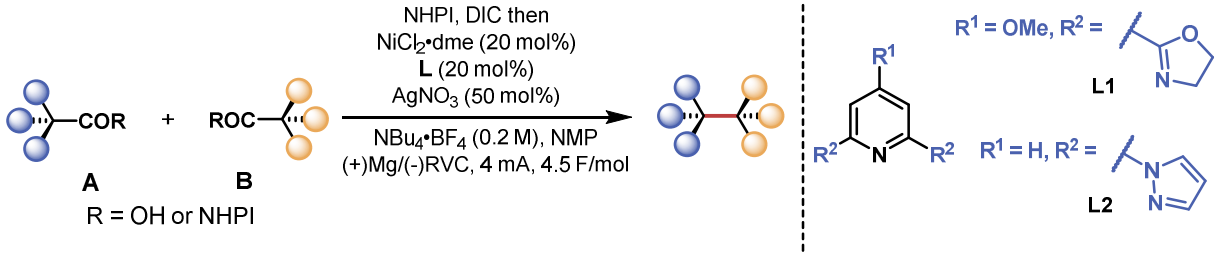
Electrochemical Doubly Decarboxylative Coupling

General procedure A: isolated RAE for electrocatalytic cross-coupling of α-substituted carboxylic acids



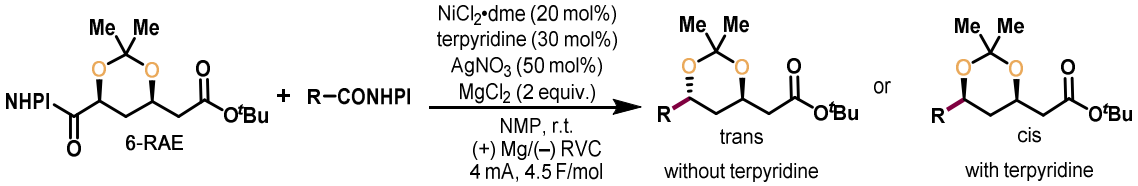
General procedure **A**: An ElectraSyn vial (5 mL) with a stir bar was charged with RAE **A** (0.1 mmol, 1 equiv.), RAE **B** (0.3 mmol, 3 equiv.), $NiCl_2$•dme (4.4 mg, 0.02 mmol, 0.2 equiv.), ligand as indicated (**L1** (,5.0 mg, 0.02 mol, 0.2 equiv.), **L2** (4.3 mg, 0.02 mmol, 0.2 equiv.) or without ligand), $AgNO_3$ (8.1 mg, 0.05 mmol, 0.5 equiv.), $TBABF_4$ (197.6 mg, 0.6 mmol, 6 equiv.), and anhydrous NMP (3.0 mL) were added, the solution was then stirred for 2 mins. An ElectraSyn vial cap equipped with anode (Mg) and cathode (RVC) 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 4.5 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 (5 ml) and aqueous 0.1 N HCl (5 mL) was then added [for products containing tertiary amine and pyridine moiety, washing with 0.1 N HCl was omitted]. The resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography or preparative thin layer chromatography (pTLC) to furnish the desired product.

General procedure B: *in situ* generated RAE for electrocatalytic cross-coupling of α-substituted carboxylic acids (one-pot)



General procedure **B**: 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 (68 mg, 0.44 mmol, 4.4 equiv) and DCM (2 mL) was added to the vial followed by the addition of *N,N'*-Diisopropylcarbodiimide (72 µL, 0.44 mmol, 4.4 equiv). The mixture was allowed to stir until the acid was consumed (typically 1-2 h). After consumption of all starting materials, DCM was removed under a stream of air. $NiCl_2$•dme (4.4 mg, 0.02 mmol, 0.2 equiv.), ligand as indicated (**L1** (5.0 mg, 0.02 mmol, 0.2 equiv.), **L2** (4.3 mg, 0.02 mmol, 0.2 equiv.) or without ligand)), $AgNO_3$ (8.1 mg, 0.05 mmol, 0.5 equiv.), $TBABF_4$ (197.6 mg, 0.6 mmol, 5.0 equiv.) were added (One of the coupling partner can be an isolated RAE, which was added at this point), the solution was then stirred for 2 mins. An ElectraSyn vial cap equipped with anode (Mg) and cathode (RVC) 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 4.5 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 (5 ml) and aqueous 0.1 N HCl (5 mL) was then added [for products containing tertiary amine and pyridine moiety, washing with 0.1 N HCl was omitted]. The resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography or preparative thin layer chromatography (pTLC) to furnish the desired product.

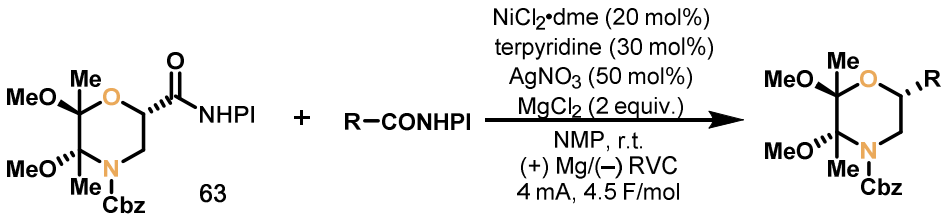
General procedure C: electrochemical decarboxylative cross-coupling of 6-RAE



General procedure **C**: An ElectraSyn vial (5 mL) with a stir bar was charged with **6-RAE** (0.1 mmol, 1 equiv), coupling partner RAE (0.3 mmol, 3 equiv), $NiCl_2$•dme (4.4 mg, 0.02 mmol, 0.2 equiv.), ligand as indicated (without or with terpyridine (7.5 mg, 0.03 mmol, 0.3 equiv.)), $AgNO_3$ (8.1 mg, 0.05 mmol, 0.5 equiv.), $MgCl_2$ (19.1 mg, 0.2 mmol, 2 equiv.), and anhydrous NMP (3.0 mL) were added, the solution was then stirred for 2 mins. An ElectraSyn vial cap equipped with anode (Mg) and cathode (RVC) 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 4.5 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 (5 ml) and aqueous 0.1 N HCl (5 mL) was then added [for products containing tertiary amine and pyridine moiety, washing with 0.1 N HCl was omitted]. The resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography or preparative thin layer chromatography (pTLC) to furnish the desired product.

General procedure D: electrochemical decarboxylative cross-coupling of 63



General procedure **D**: An ElectraSyn vial (5 mL) with a stir bar was charged with **63** (0.1 mmol, 1 equiv), coupling partner RAE (0.3 mmol, 3 equiv), $NiCl_2$•dme (4.4 mg, .0.02 mmol, 0.2 equiv.), terpyridine (7.5 mg, 0.03 mmol, 0.3 equiv.), $AgNO_3$ (8.1 mg, 0.05 mmol, 0.5 equiv.), $MgCl_2$ (19.1 mg, 0.2 mmol, 2 equiv.), and anhydrous NMP (3.0 mL) were added, the solution was then stirred for 2 mins. An ElectraSyn vial cap equipped with anode (Mg) and cathode (RVC) 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 4.5 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 (5 ml) and aqueous 0.1 N HCl (5 mL) was then added [for products containing tertiary amine and pyridine moiety, washing with 0.1 N HCl was omitted]. The resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography or preparative thin layer chromatography (pTLC) to furnish the desired product.

Graphical guide: isolated RAE for electrocatalytic cross-coupling of α-substituted carboxylic acids

Representative example (0.1 mmol scale)

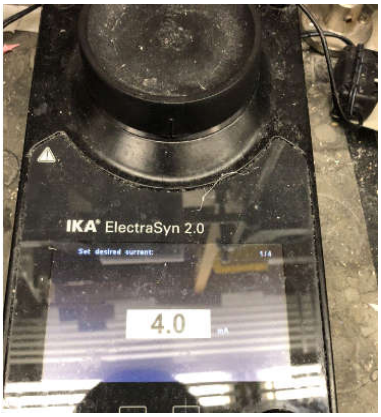
Photos were taken from the coupling between 2-(1,3-dioxoisoindolin-2-yl) 1-methyl pyrrolidine-1,2-dicarboxylate **8** and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **49** (3 equiv.)

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.

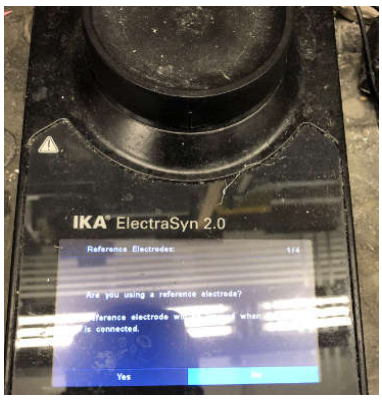
(Left) Reagents needed. **(Center)** All solids were weight out: RAE **8** (0.1 mmol, 31.8 mg), RAE **49** (0.3 mmol, 93.3 mg), $NiCl_2$•dme (20 mol %, 4.4 mg), **L2** (20 mol %, 4.3 mg), $AgNO_3$ (50 mol %, 8.1 mg), $TBABF_4$ (0.6 mmol, 197.6 mg). **(Right)** NMP (3.0 mL) was subsequently added and stirred for 2 min.

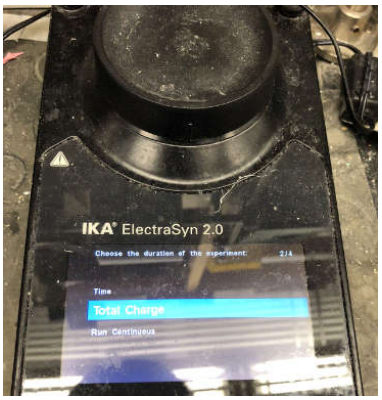


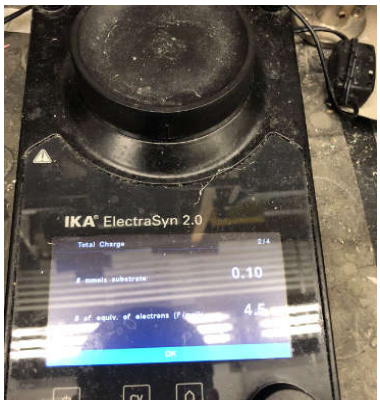
(Left) ElectraSyn 2.0 cap equipped with Mg anode and RVC cathode (9 mm wide, 40 mm length). **(Center)** ElectraSyn cap was tightly screwed into the reaction vial. **(Right)** An argon balloon was attached (a second needle on the septum serves as a vent), and the reaction solution was degassed for roughly 60 seconds.



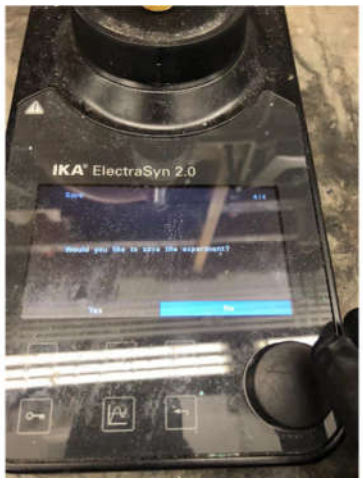
(Left) Select a new experiment. **(Center)** Select constant current. **(Right)** Set the current to 4 mA (for a 0.1 mmol scale).







(Left) No need to use a reference electrode. **(Center)** Select “Total Charge”. **(Right)** Select 0.1 mmol of substrate at 4.5 F/mol.

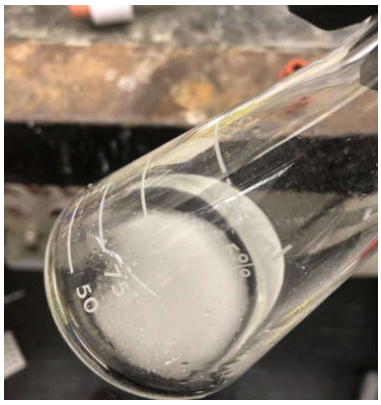


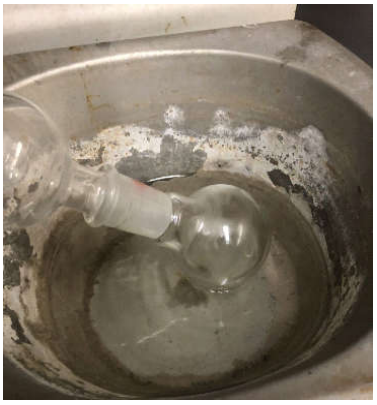
(Left) No need to alternate the polarity. **(Center)** Saving reaction parameters is optional. **(Right)** Ready!


(Left) Complete setup of reaction prior to electrolysis. **(Right)** Reaction setup during electrolysis (*note: 800 rpm stirring*).

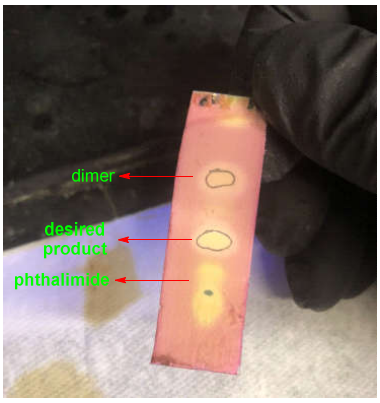


(Left) Reaction mixture after electrolysis. **(Center)** Electrodes were rinsed with Et_2O and entire reaction mixture was transferred to a separatory funnel with Et_2O. The organic phase was washed with 0.1N HCl (aq). **(Right)** Combined organic layers were washed with brine (NaCl).





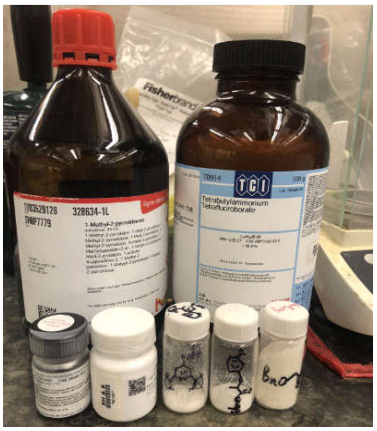
(Left) Combined organic layers were dried over Na_2SO_4. **(Center)** Filtration to remove Na_2SO_4. **(Right)** Solvent removal under reduced pressure.




(Left) Crude TLC (4:1 Hexanes: EtOAc). **(Center)** Purification by pTLC (4:1 Hexanes: EtOAc). **(Right)** Tared weight of vial containing desired product (16.8 mg, 68% yield).

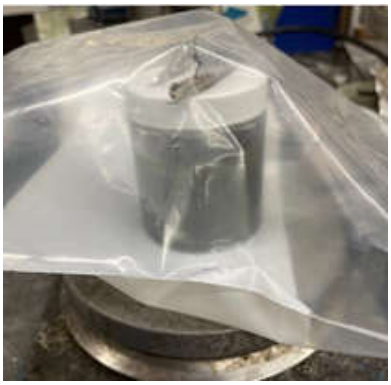
Representative example on 5 mmol scale:

Photos were taken from the coupling between1,3-dioxoisoindolin-2-yl 2-(3-chlorophenoxy)propanoate **SI-13** and 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate **49** (3 equiv.)

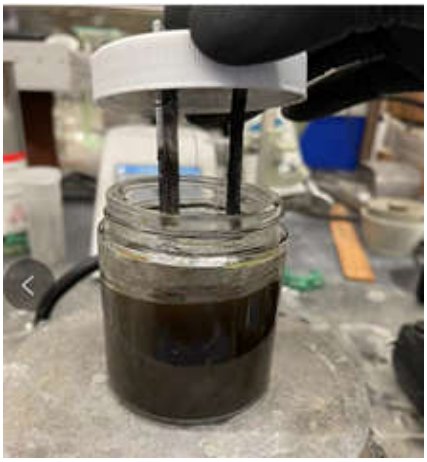


(Left) All reagents required. **(Center)** Starting materials were weight out: 1,3-dioxoisoindolin-2-yl 2-(3-chlorophenoxy)propanoate (1.73 g, 5.0 mmol), 1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate (4.67 g, 15.0 mmol), $NiCl_2$•dme (220 mg, 1.0 mmol), (4-OMe)-H-PyBox **L1** (250 mg, 1.0 mmol), $AgNO_3$ (425 mg, 2.5 mmol) and NBu_4BF_4 (4.93 g, 15 mmol). **(Right)** Hand-made electrochemical cap equipped with Mg anode and RVC cathode (3.2 cm wide, 5.0 cm length).



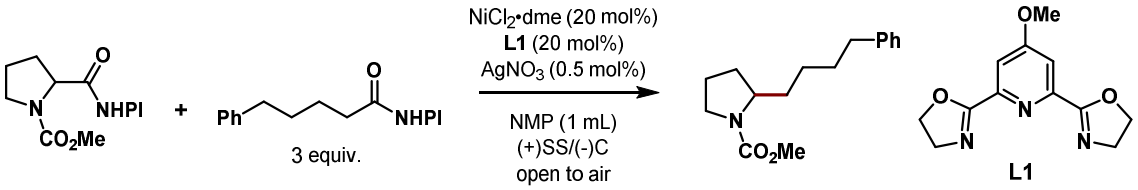


(Left) NMP (75 mL) was added and hand-made cap was tightly screwed into the reaction vial. **(Center)** The reaction solution was degassed for roughly 3 min. **(Right)** Electrochemical parameter settings: constant current, 25 mA, 5 mmol, 4.5 F/mol, no reference electrode, no alternating polarity. The reaction was started under Argon protection.



(Left) Reaction mixture after electrolysis and the solution eventually turned dark brown. After completion of electrolysis, the reaction was worked up and purified as described in general procedure. **(Right)** Weight of product (886 mg, 64% yield).

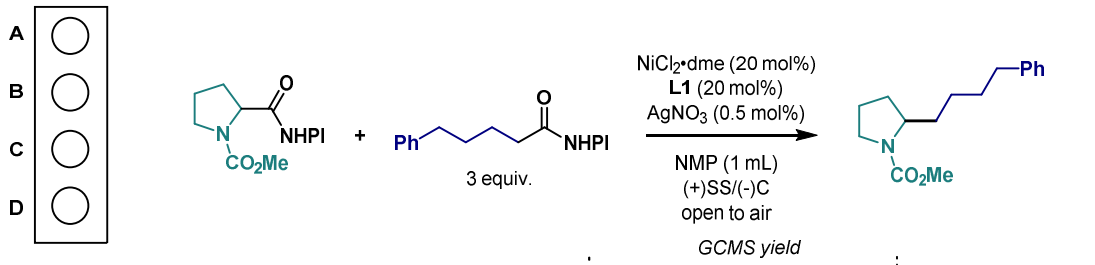
Preliminary Study of Parallel Synthesisin IKA E-Hive



To four stainless stee IKA E-hive vial were each added silver nitrate (4.25 mg, 0.025 mmol, 0.5 equiv.), 2-(1,3-dioxoisoindolin-2-yl) 1-methyl pyrrolidine-1,2-dicarboxylate (15.9 mg, 0.050 mmol, 1.0 equiv.), 1,3-dioxoisoindolin-2-yl 5-phenylpentanoate (48.5 mg, 0.15 mmol, 3 equiv.), **L1** (2.5 mg, 0.01 mmol, 0.2 equiv.), and $NiCl_2$•dme (2.2 mg, 0.01 mmol, 0.2 equiv.). The contents were diluted in NMP (1 mL) and the vials were sealed with an IKA E-hive cap equipped with a graphite cathode. The vials were placed in a 1X4 IKA e-hive vial holder and placed in the E-hive. The E-hive was closed, and the 4 vials were allowed to undergo electrolysis at constant voltage (-6V) for 12 hours. Upon completion, the reaction mixtures were evaluated by GC-MS using dodecane as an internal standard. The four vials were shown to give an average yield of 29% with a deviation of 1% (see table in note 3). Work up and isolation of the products was carried out according to **general procedure A**.

Notes:

1. The graphite cathode can be cleaned by simply scraping the rod with a razor blade and rinsing with acetone.
2. The stainless steel casing itselfs acts as a sacrificial material and some discoloration is observerd on the interior which does not affect subsequent runs.
3. The reaction appears to run much slower in the e-hive and thus 12 hours are needed to ensure full consumption of starting material (see below).



					GCMS yield					
Entry	**Scale**	**[rxn]**	**Conditions**	**Time**	**A**	**B**	**C**	**D**	**Avg.**	**Spread**
1	0.025 mmol	0.025 M	-6V	3.5 h	16%	16%	16%	15%	15.75%	1%
2	0.025 mmol	0.025 M	-6V	12 h	24%	26%	24%	27%	25.25%	3%
3	0.050 mmol	0.050 M	-6V	12 h	28%	29%	28%	29%	**28.5%**	**1%**
4	0.050 mmol	0.050 M	-8V	12 h	31%	29%	26%	31%	29.25%	**5%**
5	0.100 mmol	0.100 M	-6V	12 h	26%	26%	21%	28%	25.25%	**7%**

Troubleshooting: Frequently Asked Questions

Question 1:

How do I monitor the reaction?

Answer:

We use TLC analysis with iodine (absorbed on silica gel) stain or UV visualization (254 nm) to monitor the reaction. ^{1}H NMR, GCMS, or LCMS can also be used to obtain more information on the reaction progress.

Question 2:

How do I choose ligand for different substrates?

Answer:

If the newly formed C-C bond does not result in the generation of diastereomers, we recommend choosing **L2** (suitable for α-amino acid-derived RAE) or **L1** (suitable for α-hydroxy acid-derived RAE) as the ligand. When diastereomers are formed after the coupling (such as **6-RAE** and compound **63**), using terpyridine or ligand free would afford either of the diastereomer respectively.

Question 3:

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

Answer:

We typically use 4 mA on 0.1 mmol scales in 3.0 mL NMP solvent with ElectraSyn 5mL vial. Normal operational voltage range for this reaction is around 0 V - 8 V, and the voltage slowly increases as RAE is consumed.

Question 4:

Why does the ligand need to be increased to 0.3 equivalent when 6-RAE is used as a coupling partner? What role does $MgCl_2$ play in the reaction?

Answer:

The diastereoselectivity in the dDCC reaction with 6-RAE is completely different when ligand is used or not. In the cis-coupling reaction (with ligand), 0.1 more equivalent terpyridine was requied to ensure that there was enough ligand to coordinate with the nickel, which gave a better reproducibility of the reaction. The addition of $MgCl_2$ can prevent the hydrolysis of RAE.

Question 5:

Is this reaction sensitive to air and water?

Answer:

The reaction is not particularly air- and water-sensitive. Acceptable yields (around 10% lower) 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 6:

What is the byproduct of this reaction?

Answer: The major byproduct was the dimer of carboxylic acid which was used in 3 equiv. Sometimes, alkane and alkenes are also formed from carbon radicals.

Question 7:

How can the electrodes be recycled?

Answer: The Mg electrodes can be washed with 1 N HCl, water, and acetone. The stains and insoluble salts in the surface can be removed with a razor blade. Since the Ag-deposition on the RVC might affect the reaction reproducibility, we do not recommend repeated use of RVC.

Question 8:

Can NMP be used as solvent in the RAE synthesis step in *in situ* protocol?

Answer:

NMP could be used for acid-activation step, but the yield would be slightly lower and the reaction would be much solwer.

Question 9:

Can the reaction be run more concentrated or diluted?

Answer:

The reaction is not particularly sensitive to concentration.

Ideality Calculation

The calculation method for ideality is as follows:

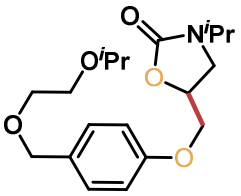
$$\%\text{ideality} = \frac{[(\text{no. of construction rxn}) + (\text{no. of strategic redox rxn})}{(\text{total no. of steps})} \times 100$$

The ideality is determined by the proportion of construction reactions and strategic redox reactions within the entire synthetic route. Construction reactions, as defined by Hendrickson, involve the formation of skeletal bonds (C-C and C-heteroatom). Strategic redox reactions, another type of construction reaction, directly establish the correct functionality found in the final product, such as asymmetric oxidations and reductions or C-H oxidations. All other types of reactions fall into the category of concession steps: (1) Nonstrategic redox manipulations (e.g., reduction of ester to alcohol), (2) functional group interconversions (i.e., alcohol to mesylate to azide), and (3) protecting group manipulations. (*J. Org. Chem.* **2010**, *75*, 4657)

We used green spot to highlight the ideal steps in the following route comparison.

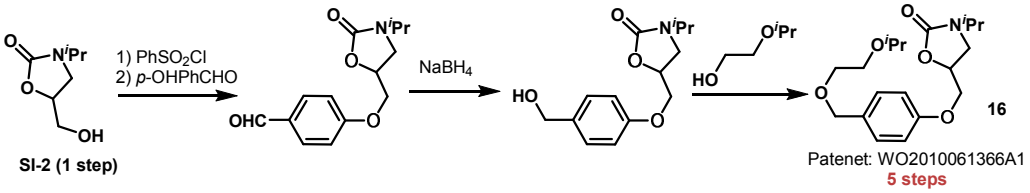
Summary and Comparison with Previous Routes

Compound 16

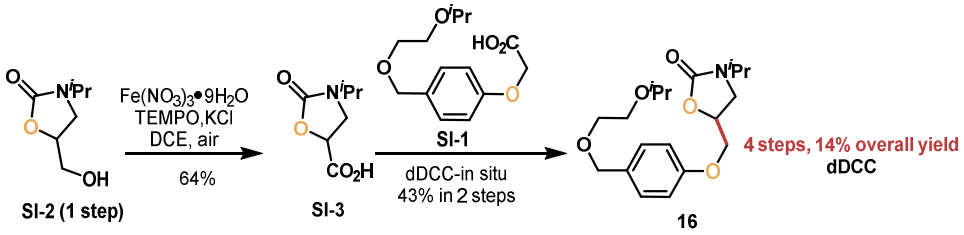


16

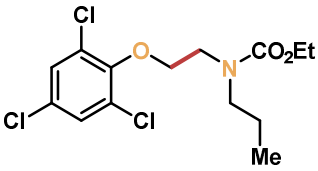
Route from literature (yield is not available)



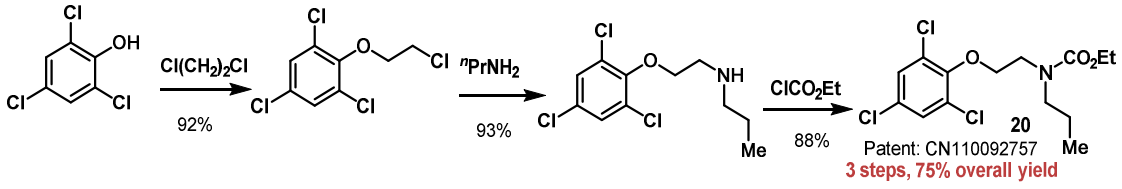
Route from dDCC



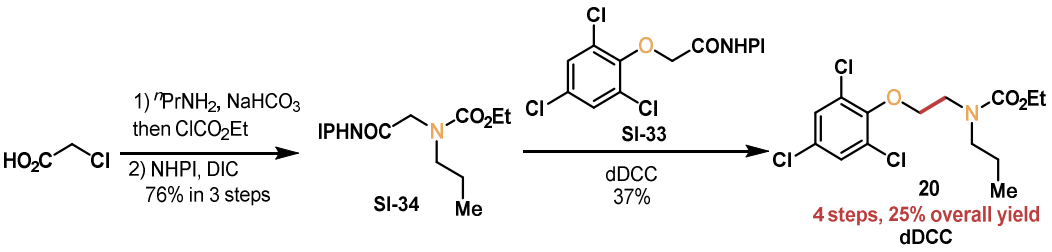
Compound 20



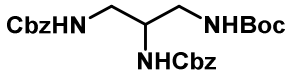
Route from literature



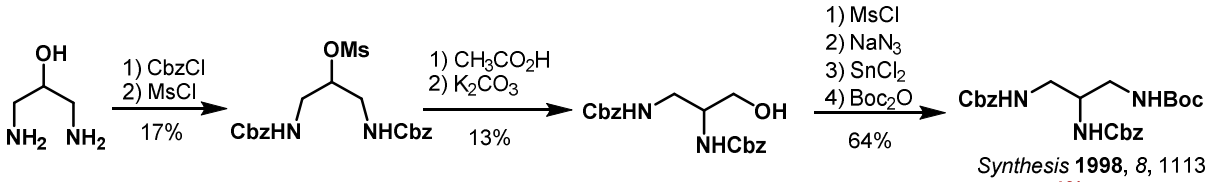
Route from dDCC



Compound 23



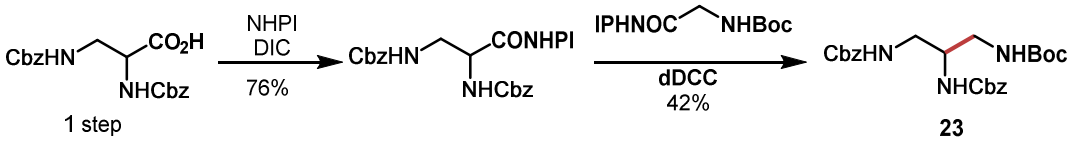
Route from literature



Synthesis **1998**, *8*, 1113

8 steps, 1% overall yield

Route from dDCC

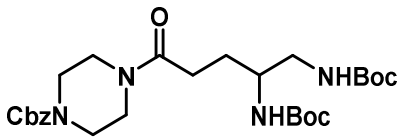


23

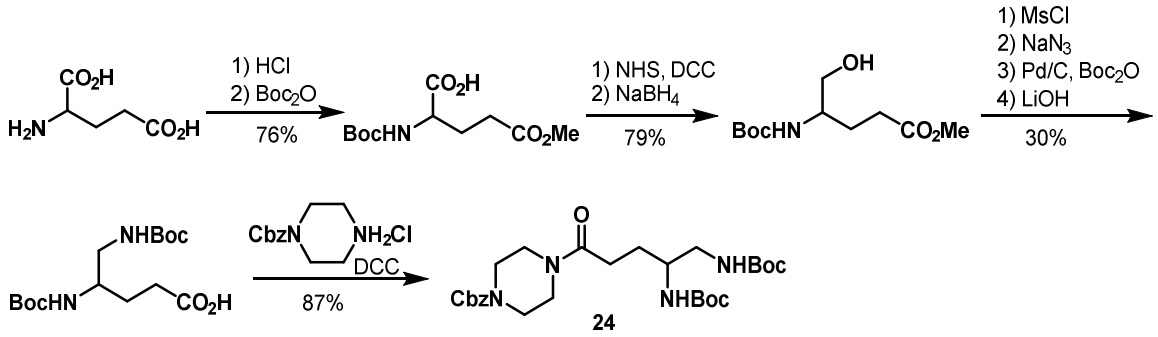
3 steps, 30% overall yield

dDCC

Compound 24



Route from literature

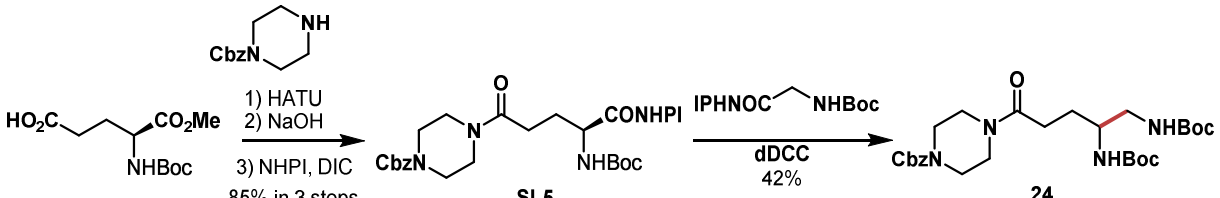


24

European Journal of Medicinal Chemistry **2016**, *122*, 702

9 steps, 16% overall yield

Route from dDCC



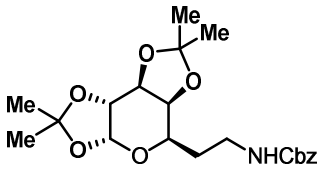
SI-5

24

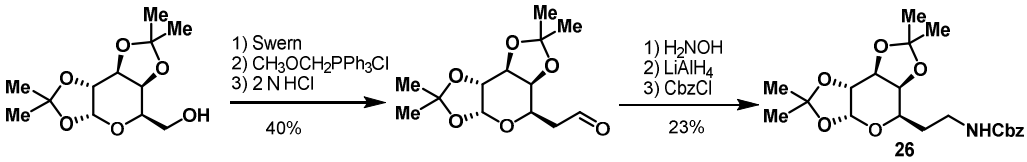
4 steps, 36% overall yield

dDCC

Compound 26

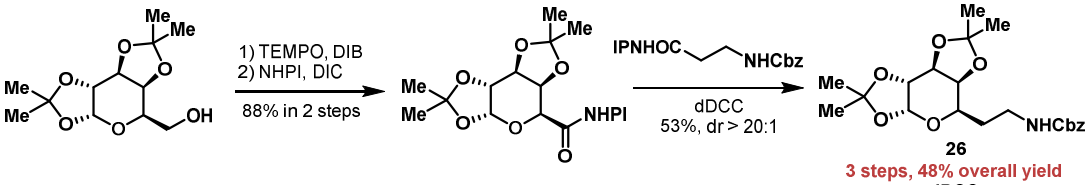


Route from literature



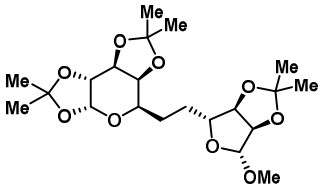
Carbohydrate Research **2003**, *338*, 2375
6 steps, 9% overall yield

Route from dDCC

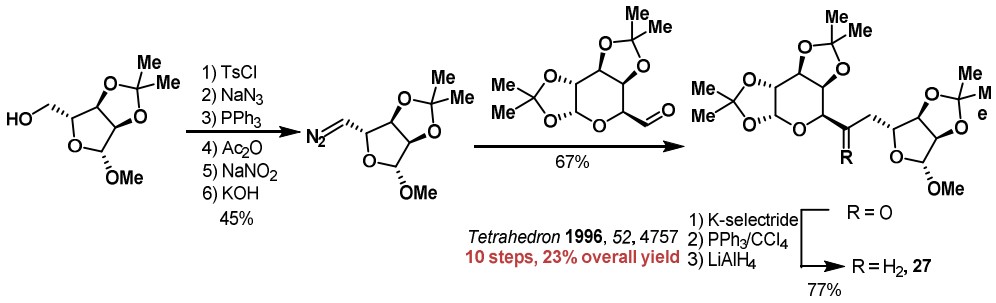


3 steps, 48% overall yield
dDCC

Compound 27

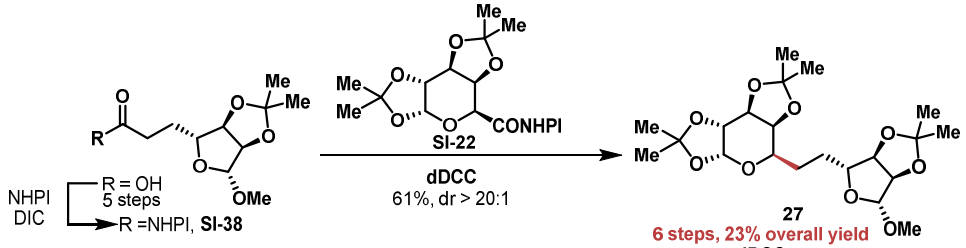


Route from literature



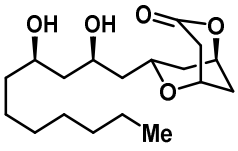
Tetrahedron **1996**, *52*, 4757
10 steps, 23% overall yield

Route from dDCC



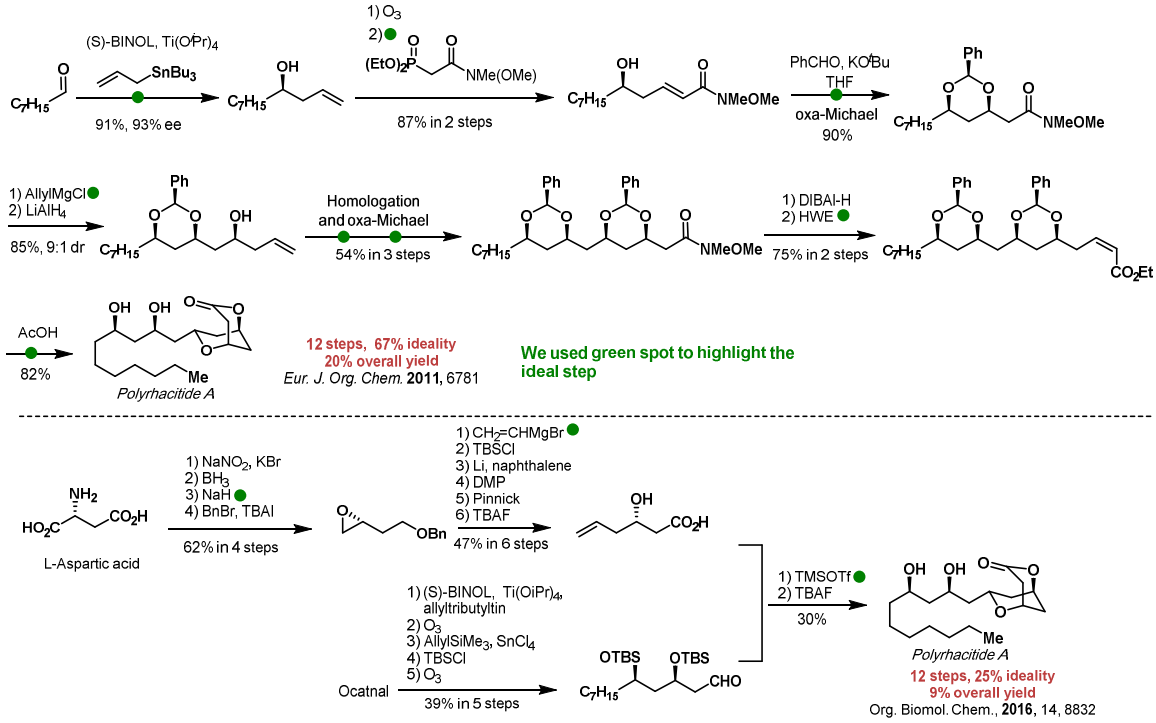
6 steps, 23% overall yield
dDCC

Polyrhacitide A

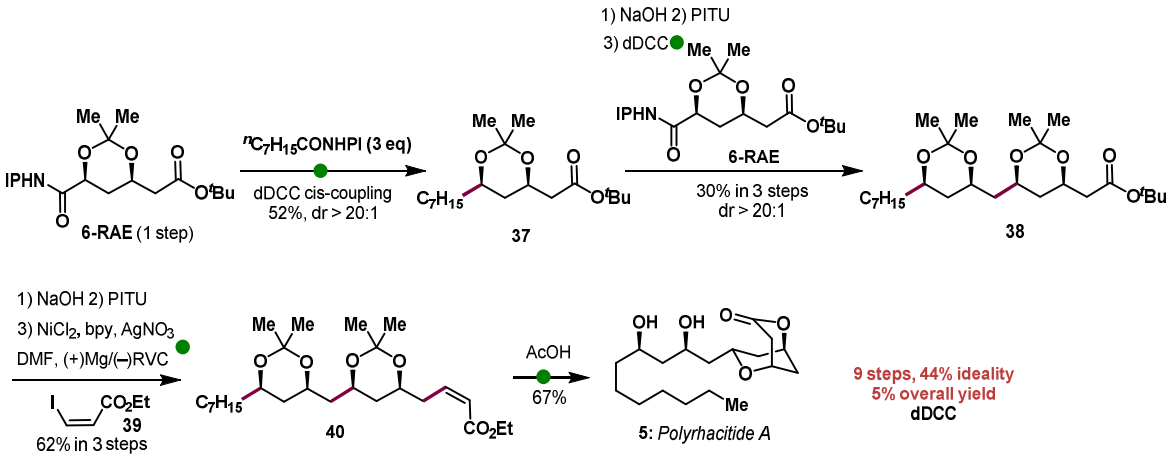


5: *Polyrhacitide A*

Selected route from literature



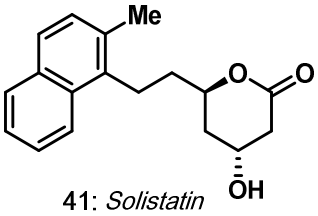
Route from dDCC



Other reference about polyrhacitide A synthesis (9-28 steps, 2-16% overall yield)

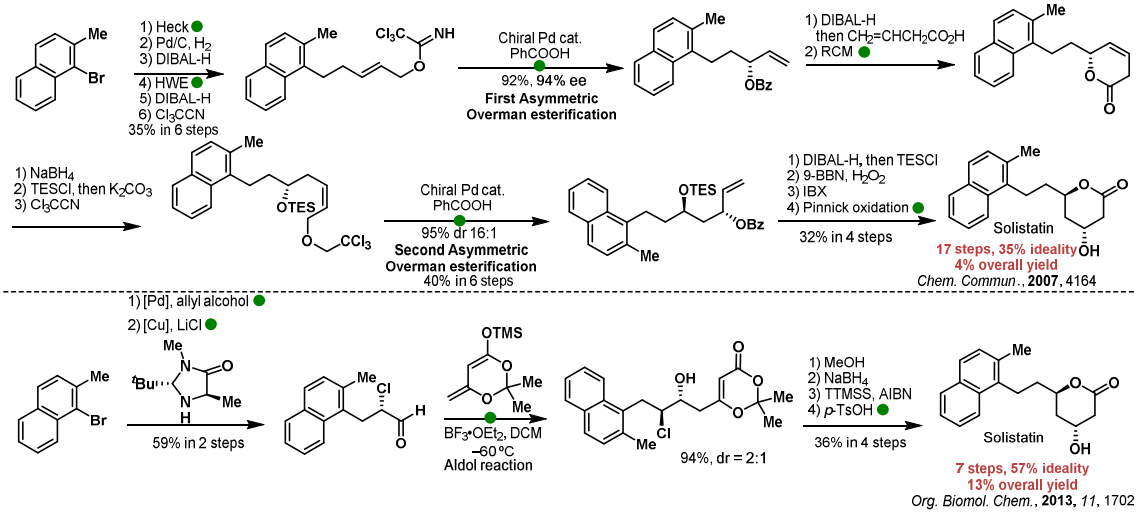
a) *Org. Lett.* **2009**, 11, 5634. b) *Org. Lett*. **2011**, *13*, 744. c) *Tetrahedron Letters* **2010**, *51*, 2154. d) *Org. Lett.* **2013**, 15, 2282. e) *Tetrahedron Letters* **2010**, *51*, 2052. f) *Tetrahedron* **2012**, *68*, 3179.

Solistatin

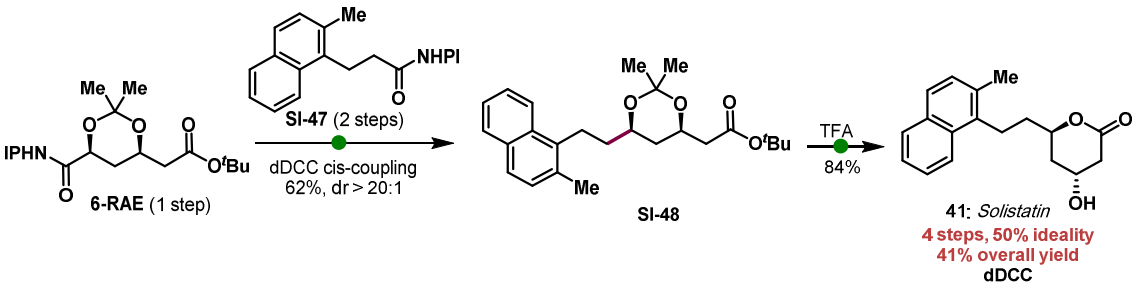


41: *Solistatin*

Selected route from literature



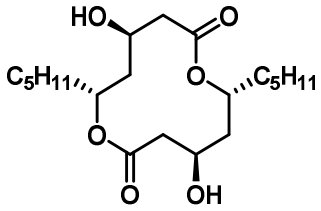
Route from dDCC



Other reference about Solistatin 41 synthesis:

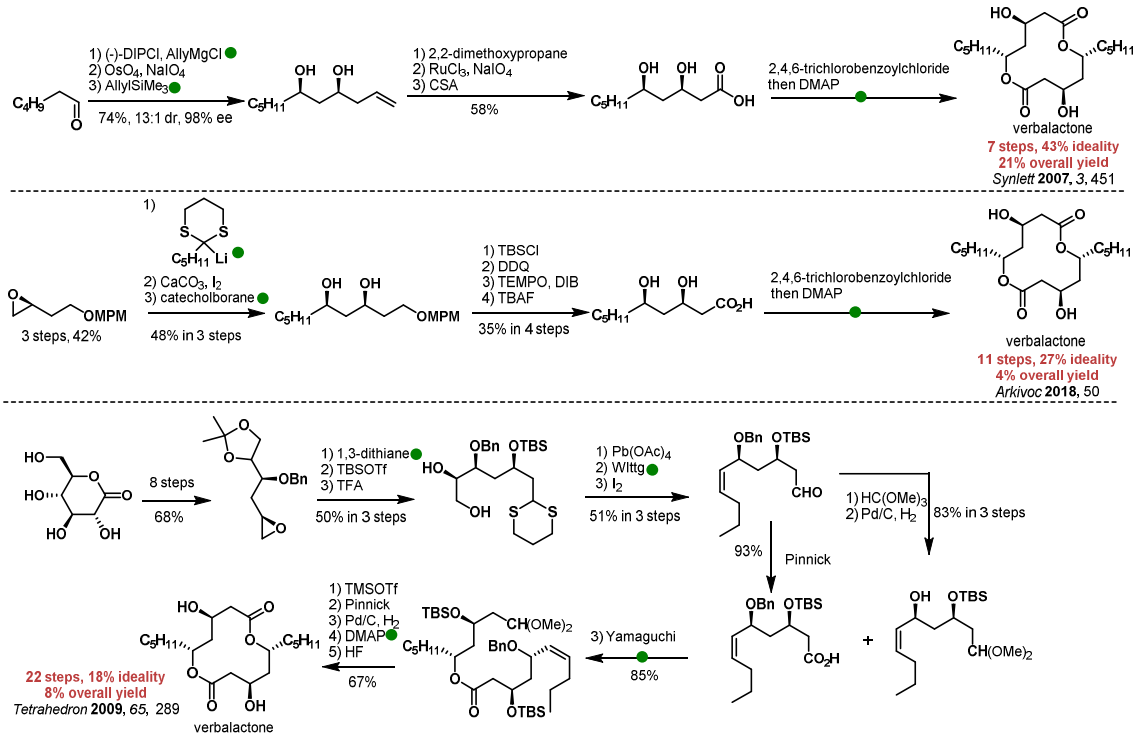
Journal of Biotechnology **2017**, *258*, 171 (11steps, 9%).

Verbalactone

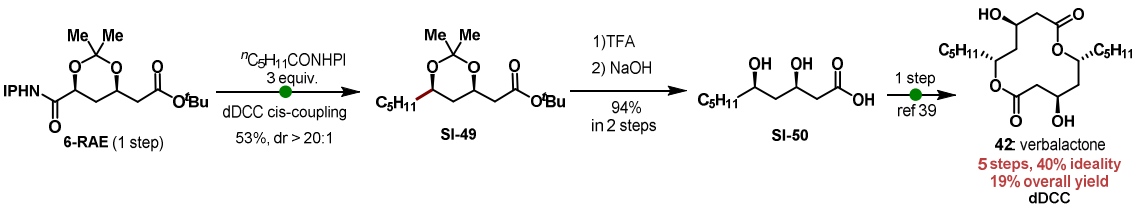


42: verbalactone

Selected route from literature



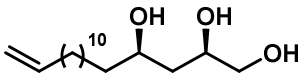
Route from dDCC



Other reference about verbalactone 42 synthesis (8-22 steps, 0.6%-13% overall yield)

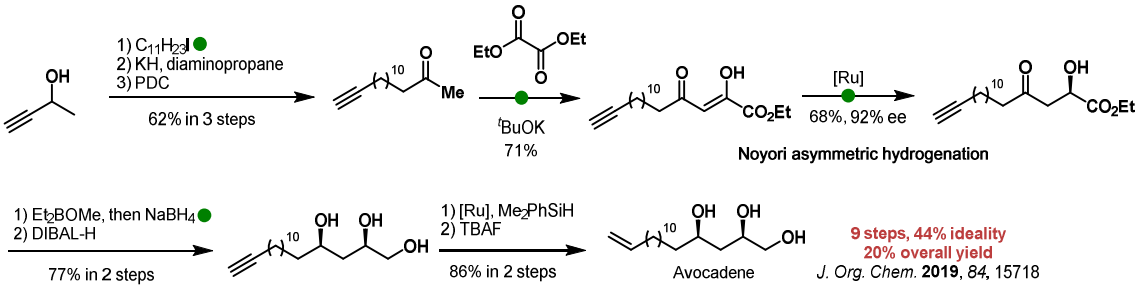
a) *Tetrahedron Letters* **2004**, *45*, 7483. b) *Tetrahedron Letters* **2004**, *45*, 5577. c) *Synthetic Communications* **2008**, *38*, 3129. d) *Tetrahedron Letters* **2009**, *50*, 2048. e) *Tetrahedron* **2009**, *65*, 8677. f) *Helvetica Chimica Acta.* **2009**, *92*, 1840. g) *Synthesis* **2011**, *2011*, 1954. h) *Tetrahedron: Asymmetry* **2012**, *23*, 381. i) *Russ J Org Chem* **2012**, *48*, 977. j) *Monatsh Chem* **2014**, *145*, 2019. k) *Monatsh Chem* **2016**, *147*, 1985.

Avocadene

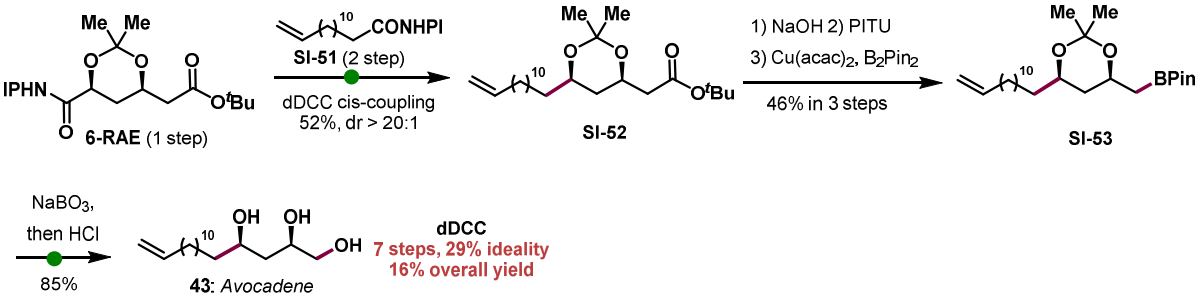


43: *Avocadene*

Selected route from literature



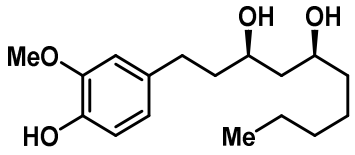
Route from dDCC



Other reference about avocadene 43 synthesis (8-9 steps, 14%-17% overall yield)

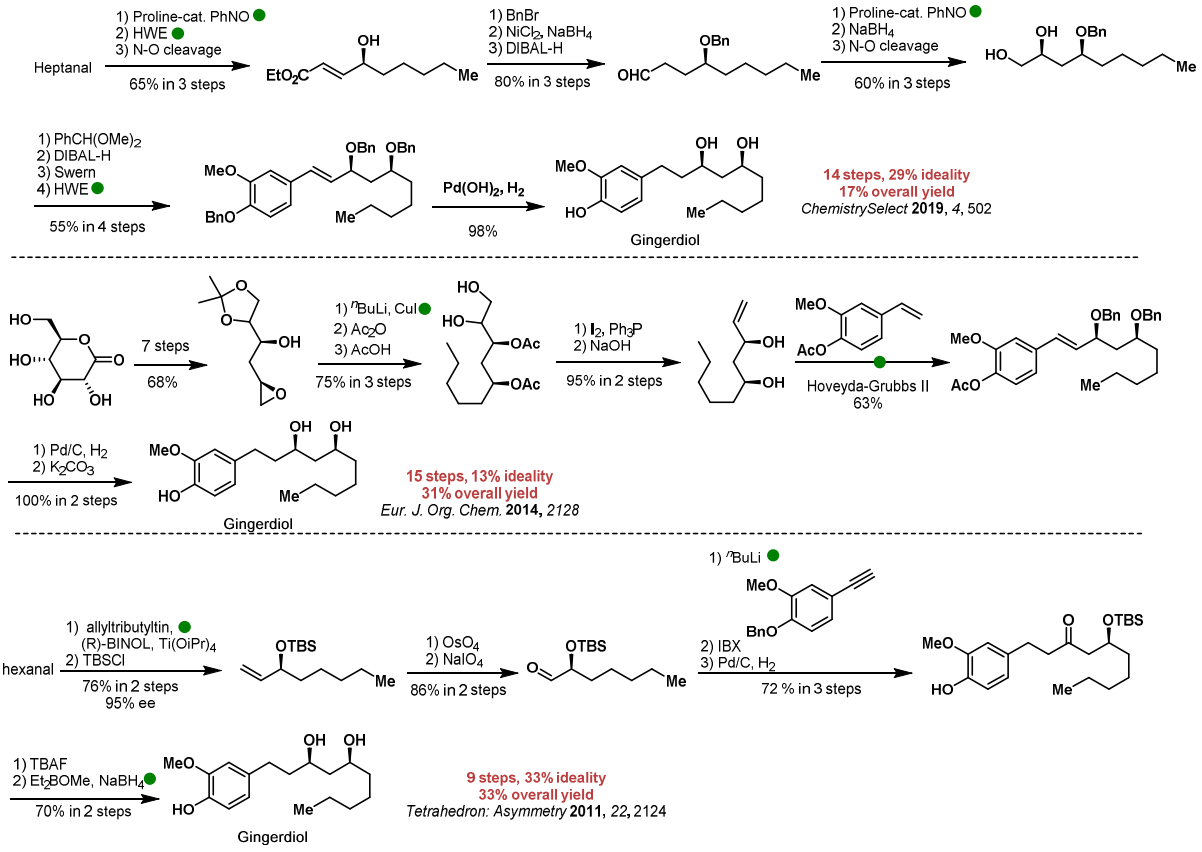
a) *Agric. Biol. Chem.* **1982**, *46*, 481*;* b) *Tetrahedron* **2008**, *64*, 9377 (enantiomer);

Gingerdiol

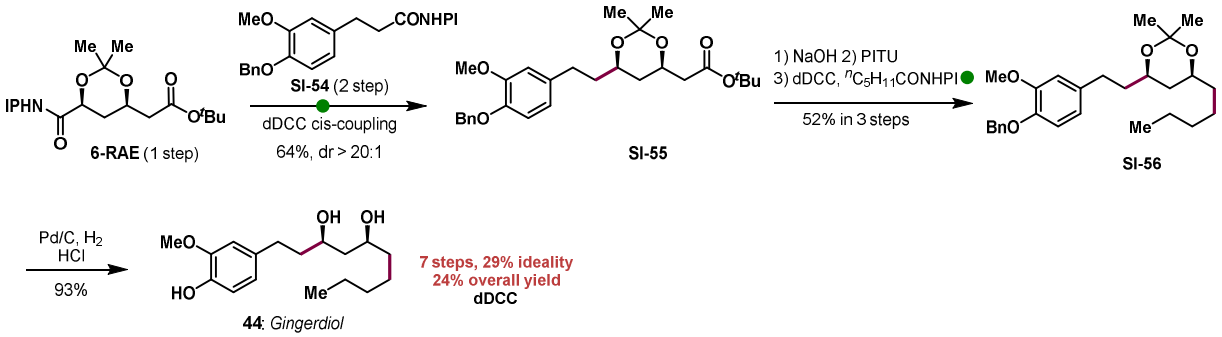


44:Gingerdiol

Selected route from literature



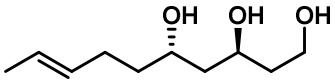
Route from dDCC



Other reference about gingerdiol 44 synthesis (8-11 steps, 8-20%)

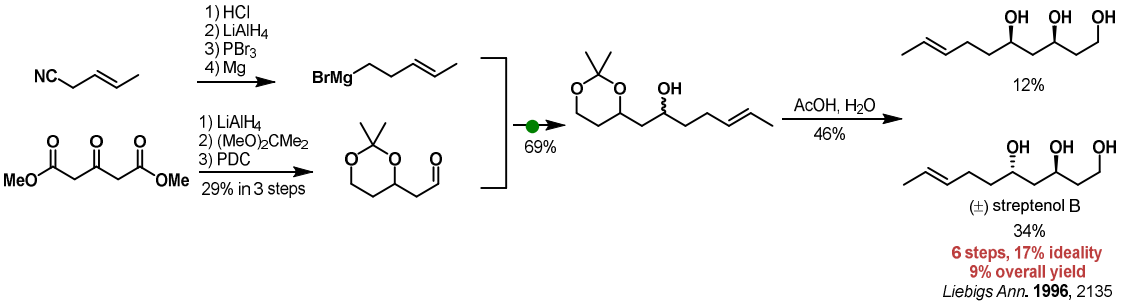
a) Tetrahedron Lett. ***2001****, 42,* 6401*; b) Eur. J. C.* **2013**, *4*, 191.

Streptenol B

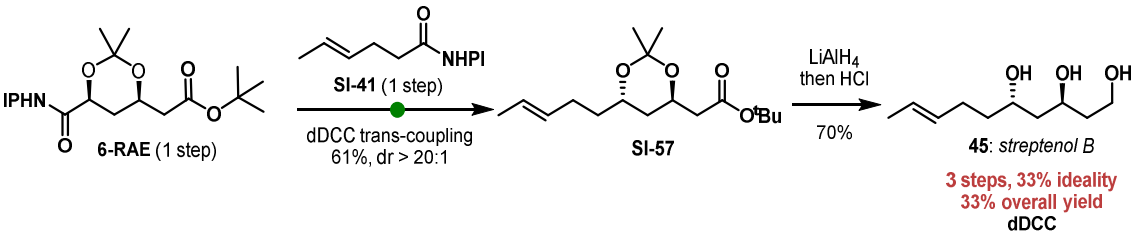


45: *streptenol B*

Selected route from literature



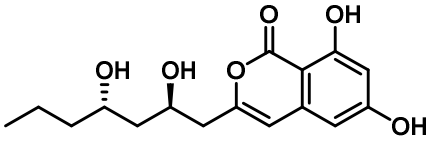
Route from dDCC



Other reference about streptenol B 45 synthesis:

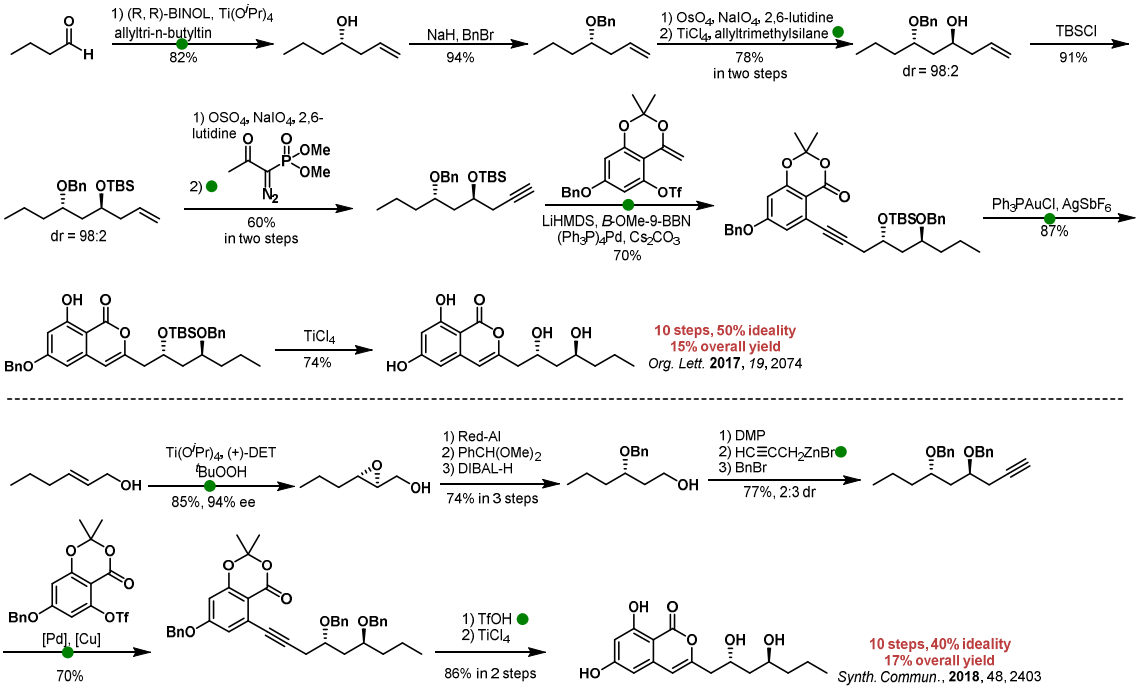
Tetrahedron, **1991**, *47,* 3335 (5 steps, 60%, start from streptenol A).

Exserolide F

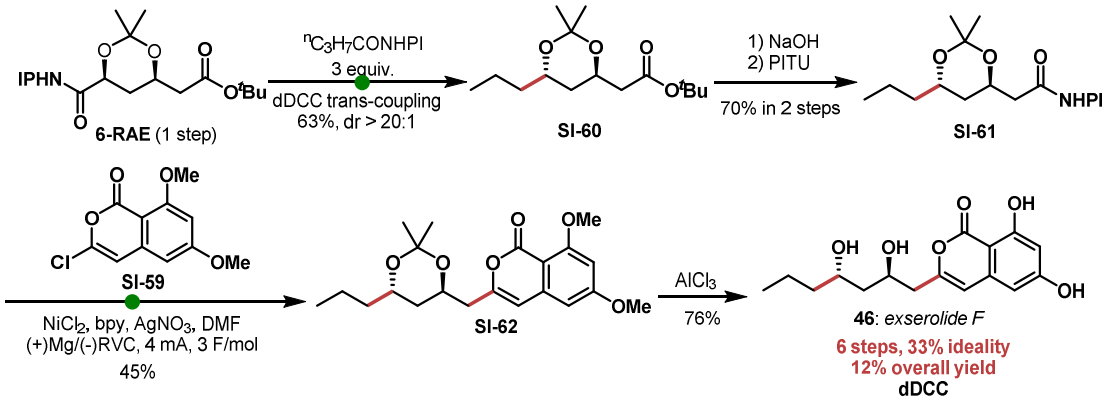


46: *exserolide F*

Selected route from literature



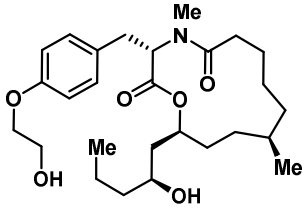
Route from dDCC



Other reference about exserolide F 46 synthesis:

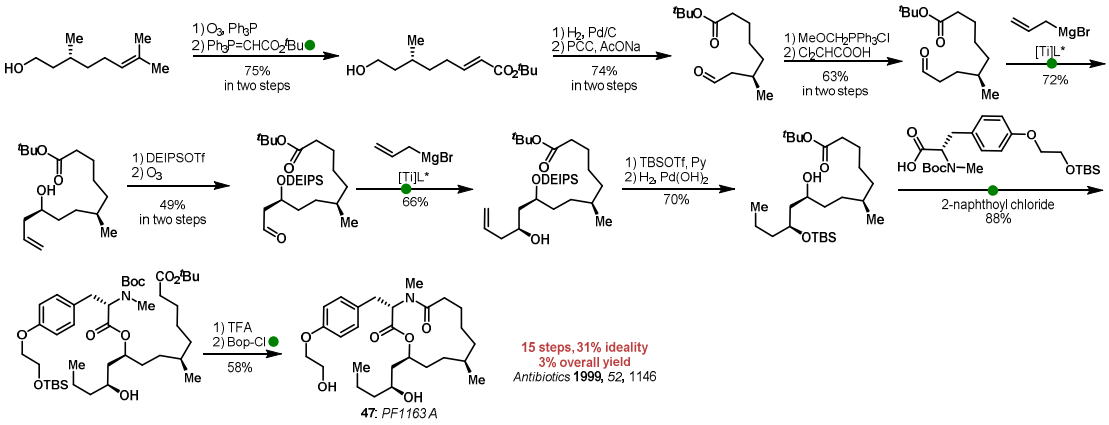
Note: Exserolide F had been synthesized only twice.

PF1163 A

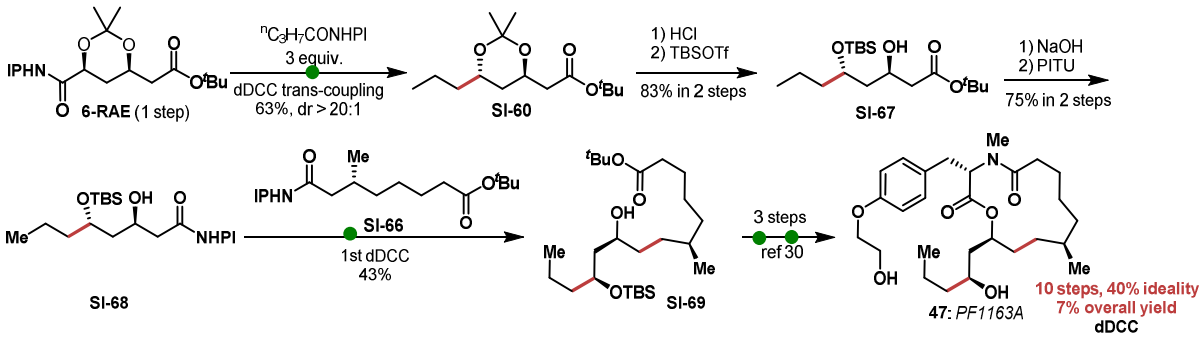


47: *PF1163 A*

Selected route from literature



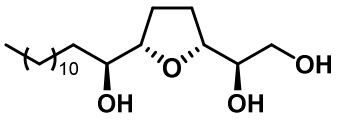
Route from dDCC



Other reference about PF1163A 47 synthesis:(13-17 stesp, 2-3% overall yield)

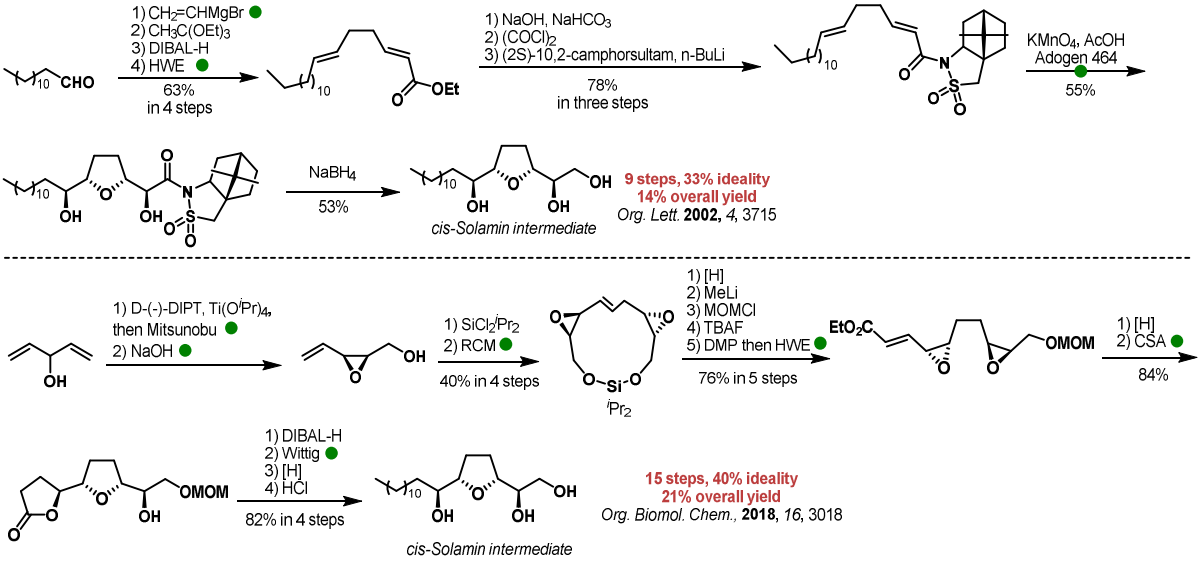
a) *Synlett* **2010**, *08*, 1255. b) *Tetrahedron Asymmetry* **2012**, *23*, 769.

cis-Solamin intermediate

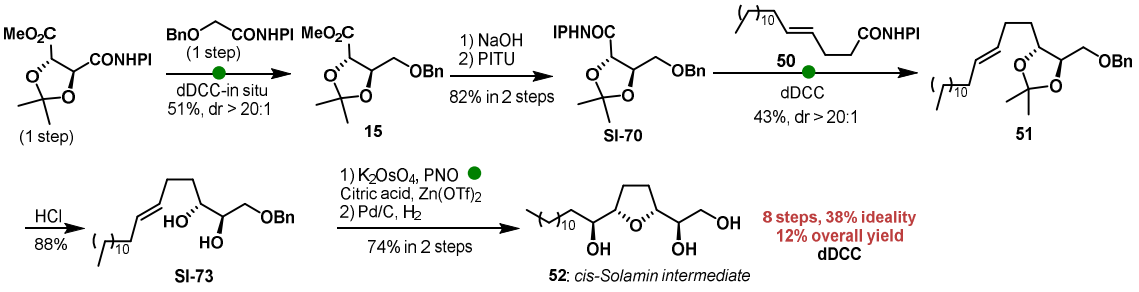


52: *cis-Solamin intermediate*

Selected route from literature



Route from dDCC

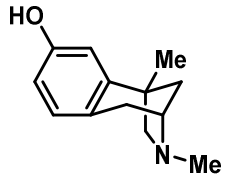


Other reference about cis-solamin 52 intermediate synthesis (6-10 steps, 15-52% overall yield)

a) *J. Org. Chem.* **2004**, *69*, 3368. b) *Angew. Chem. Int. Ed.* **2005**, *44*, 4766. c) *Org. Lett.* **2020**, *22*, 1618.

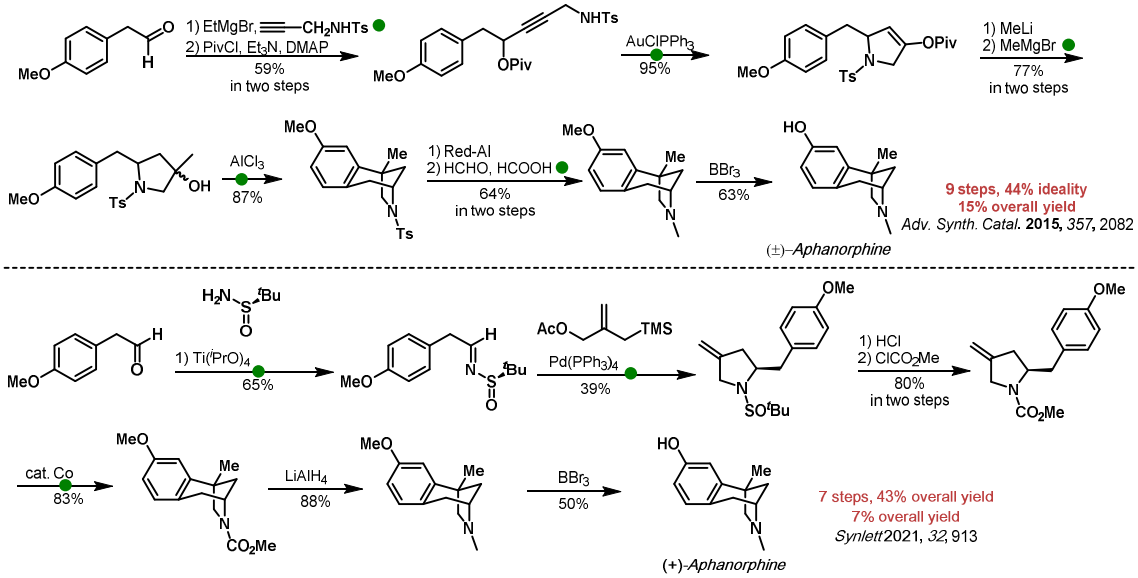
.

Aphanorphine

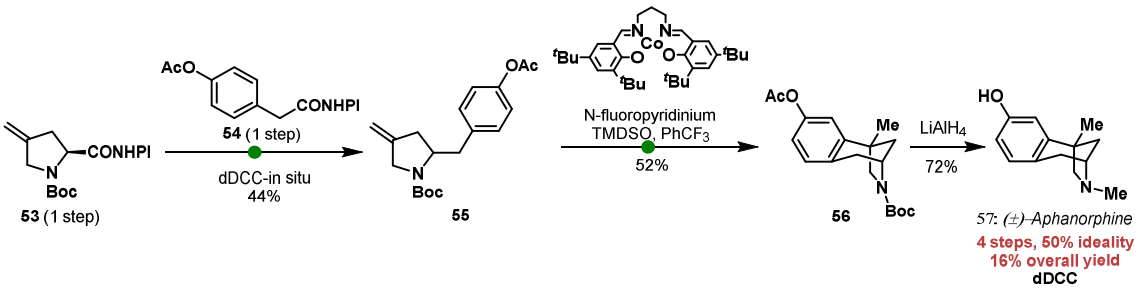


57: *Aphanorphine*

Selected route from literature



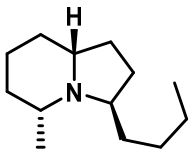
Route from dDCC



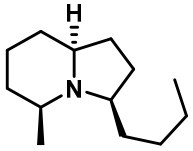
Other reference about aphanorphine 57 synthesis (8-21 steps, 0.5-25% overall yield)

Note: Other aphanorphine synthesis routes, more than 20, can be found in the reference of Synlett ***2021****, 32, 913.*

Indolizidine 195B and monomorine I

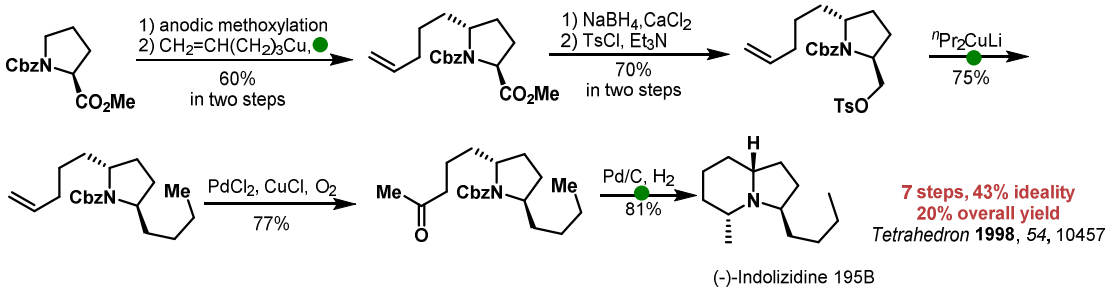


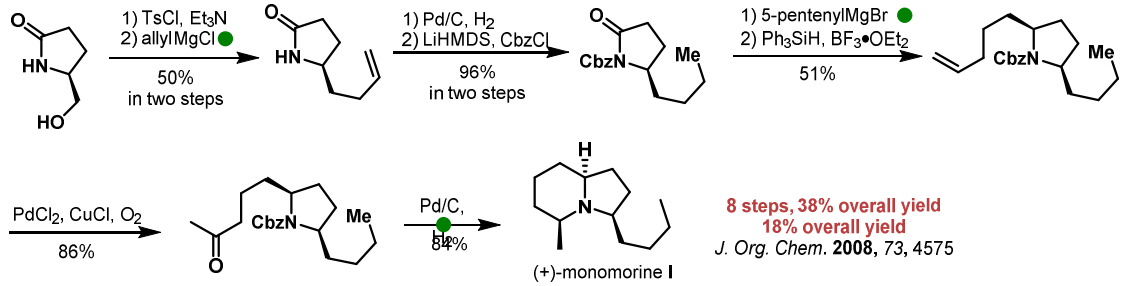
61: *(-)-Indolizidine 195B*



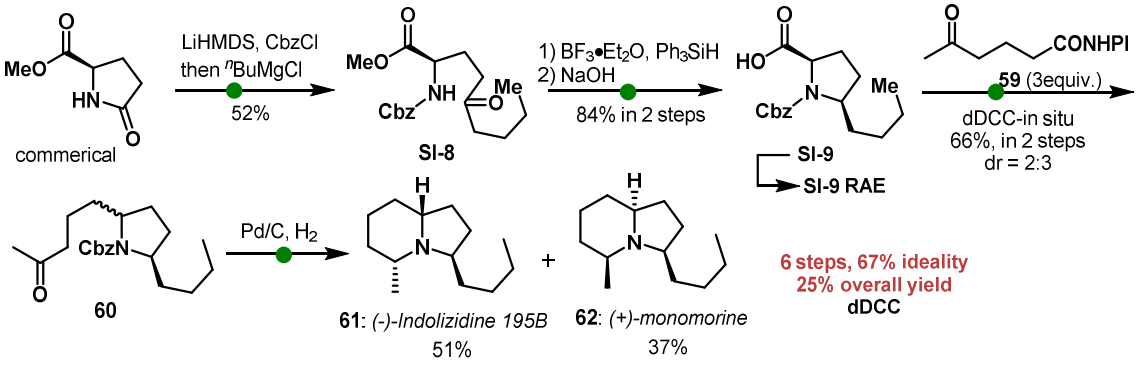
62: *(+)-monomorine I*

Selected route from literature





Route from dDCC

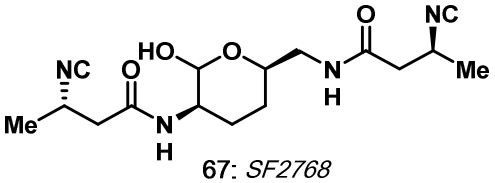


Other reference about indolizidine 195B 61 (7-18 steps, 2-20% overall yield) and monomorine I 62 (7-25 steps, 1-26% overall yield) synthesis:

Indolizidine 195B: *Curr. Org. Synth.* **2020**, *17*, 82 (review).

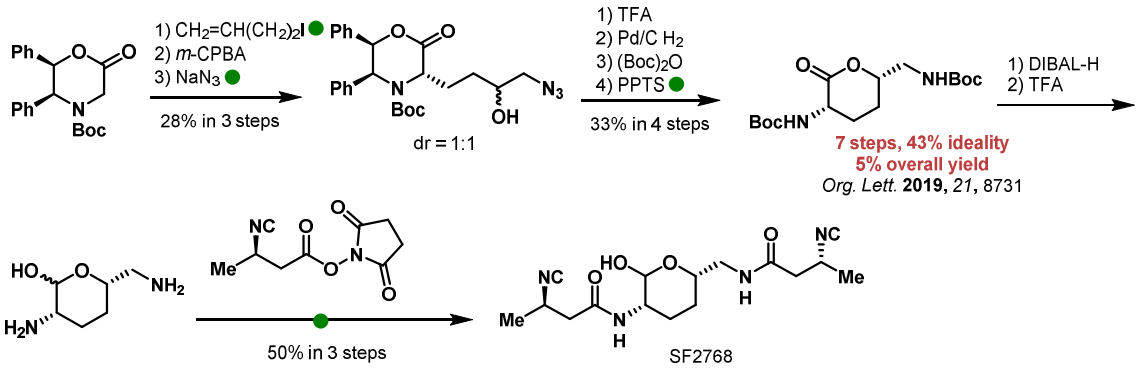
Monomorine I: a) *Eur. J. Org. Chem.* **2021**, 3850. b) *Other* monomorine *synthesis routes can be found in the reference of Tetrahedron Asymmetry* ***2017****, 28,* 1582.

SF2768

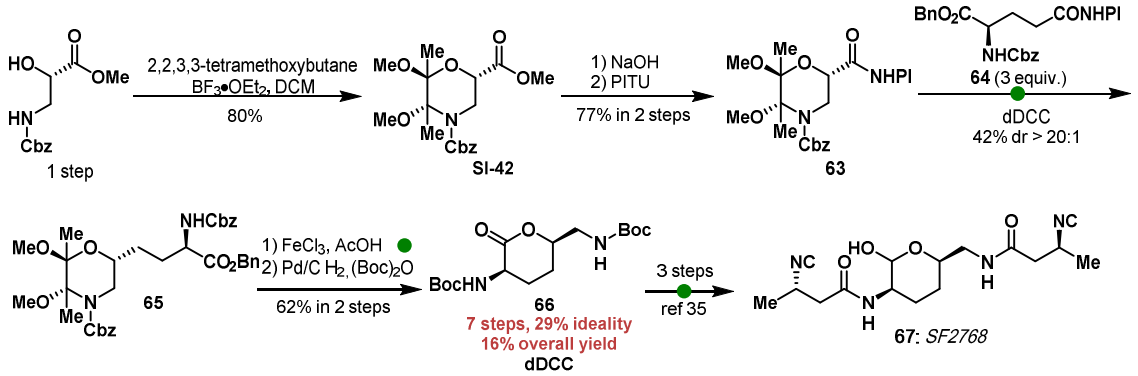


67: *SF2768*

Selected route from literature



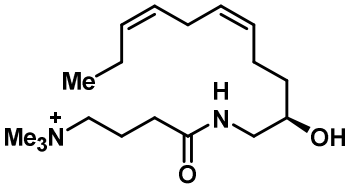
Route from dDCC



Other reference about SF2768 67 synthesis:

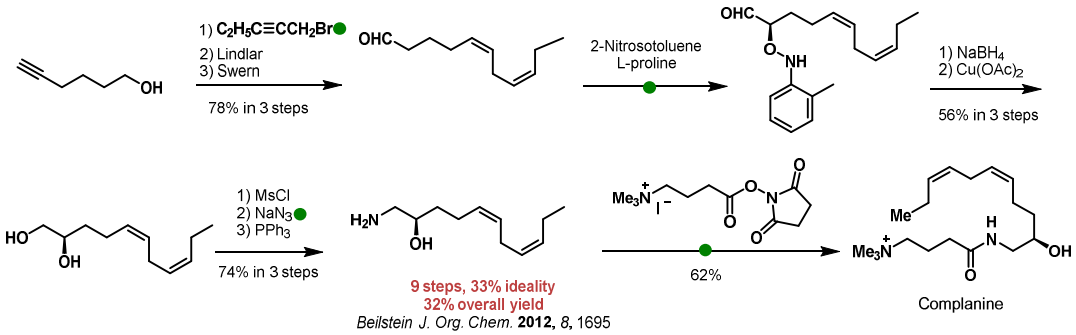
Note: SF2768 had been synthesized only once.

Complanine

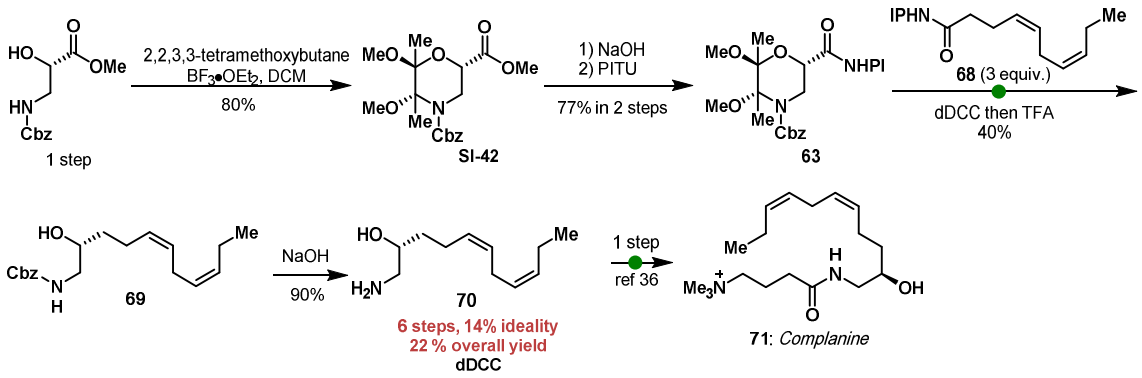


Complanine

Selected route from literature



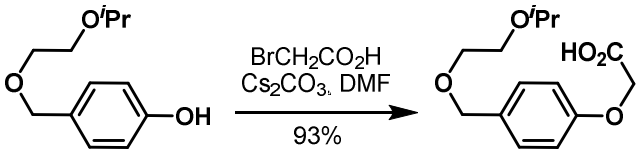
Route from dDCC



Other reference about complanine 71 synthesis:

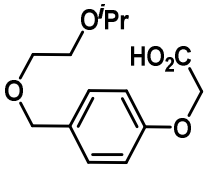
Beilstein J. Org. Chem. **2009**, *5* (10 steps, 2%).

Experimental Procedures and Characterization Data for Non-Commercially Carboxylic acids



SI-1

Compound SI-1



2-(4-((2-isopropoxyethoxy)methyl)phenoxy)acetic acid (SI-1)

To a solution of 4-((2-isopropoxyethoxy)methyl)phenol (525 mg, 2.5 mmol, 1.0 equiv.) in DMF (10 mL) was added Cs_2CO_3 (4.07 g; 12.5 mmol, 5.0 equiv.) and $BrCH_2CO_2H$ (345 mg, 2.5 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with additional H_2O (20 mL) and washed with Et_2O (3 × 10 mL). The aqueous layer was then acidified to pH = 1 by 1N HCl and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give acid **SI-1** 623 mg (93%) which can be used without further purification.

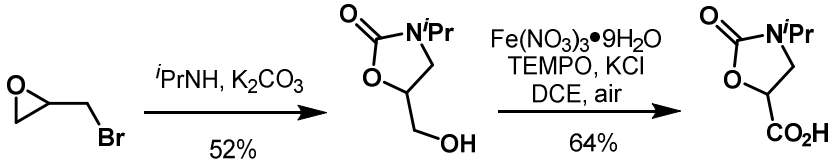
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.62 (s, 2H), 4.51 (s, 2H), 3.69–3.53 (m, 5H), 1.17 (d, J = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.8, 157.0, 131.7, 129.4, 114.5, 72.7, 72.2, 69.4, 67.3, 64.8, 21.9.

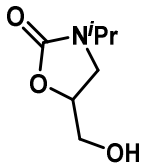
HRMS (ESI-TOF): calc'd for $C_{14}H_{20}O_5Na$ $[M+Na]^+$: 291.1208, found 291.1218

TLC: R_f = 0.3 (20:1 DCM:MeOH)



SI-2 SI-3

Compound SI-2



5-(hydroxymethyl)-3-isopropyloxazolidin-2-one (SI-2)

To a suspension of K_2CO_3 (1.38 g, 10 mmol, 1.0 equiv.) in anhydrous methanol (10 ml) was added epibromohydrin (0.99 mL, 10 mmol, 1.0 equiv.), Et_3N (1.4 mL, 10 mmol, 1.0 equiv.) and ^{i}PrNH$_2$ (0.21 mL, 2 mmol, 0.2 equiv.). The reaction was stirred in an oil bath at 70 ºC for 12 h. The reaction mixture was then filtered, and the organic solvent was removed under reduced pressure. The residue was purified by column chromatography with acetone/hexane (1:2) as the eluent to give **SI-2** (165 mg, 52%).

Physical State: white solid.

m.p.: 56-58 ºC.

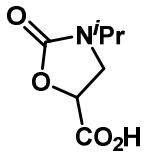
^{1}H NMR (600 MHz, $CDCl_3$):δ 4.64–4.53 (m, 1H), 4.08 (td, *J* = 6.8, 2.7 Hz, 1H), 3.91–3.78 (m, 1H), 3.71–3.58 (m, 1H), 3.50 (dd, *J* = 8.8, 1.4 Hz, 1H), 3.41 (dd, *J* = 8.4, 6.7 Hz, 1H), 2.77 (br, 1H), 1.17 (ddd, *J* = 6.6, 4.7, 1.6 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.1, 73.4, 63.1, 44.8, 40.7, 19.8, 19.5.

HRMS (ESI-TOF): calc'd for $C_7H_{14}NO_3$ $[M+H]^+$: 160.0974, found 160.0975.

TLC: R_f = 0.3 (2:1 hexanes:acetone)

Compound SI-3



3-isopropyl-2-oxooxazolidine-5-carboxylic acid (SI-3)

To a solution of 5-(hydroxymethyl)-3-isopropyloxazolidin-2-one **SI-2** (159 mg, 1.0 mmol, 1.0 equiv.) in DMF (10 mL) was added $Fe(NO_3)_3$•$9H_2O$ (40.5 mg, 0.1 mmol, 0.1 equiv.), TEMPO (15.6 mg, 0.1 mmol, 0.1 equiv.) and KCl (7.5 mg, 0.1 mmol, 0.1 equiv.) under air. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography with acetone/hexane (1:2→1:0) as the eluent to give **SI-3** (111 mg, 64%).

Physical State: colorless oil.

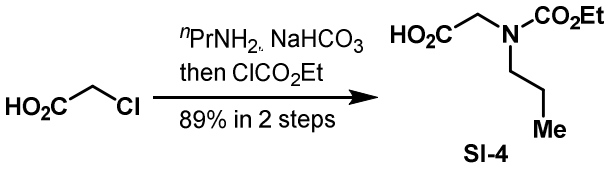
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (br, 1H), 4.96 (dd, *J* = 9.8, 5.5 Hz, 1H), 4.10 (p, *J* = 6.8 Hz, 1H), 3.82 (t, *J* = 9.5 Hz, 1H), 3.66 (dd, *J* = 9.1, 5.4 Hz, 1H), 1.19 (d, *J* = 3.8 Hz, 3H), 1.18 (d, *J* = 3.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 156.4, 69.9, 45.3, 42.9, 19.8, 19.6.

HRMS (ESI-TOF): calc'd for $C_7H_{12}NO_4$ $[M+H]^+$: 174.0766, found 174.0770.

TLC: R_f = 0.2 (acetone)

Compound SI-4



***N*-(ethoxycarbonyl)-*N*-propylglycine (SI-4)**

To a solution of 2-chloroacetic acid (945 mg, 10 mmol, 1 equiv.) in H_2O (8 mL) was added $NaHCO_3$ (840mg, 10 mmol, 1.0 equiv.) and ^{n}PrNH$_2$ (8.2 mL, 100 mmol, 10.0 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 6 h. The solvent of the mixture was removed under vacuum. The residue was dissolved in THF/H_2O (10 mL/20 mL), K_2CO_3 (2.1 g, 15 mmol, 1.5 equiv.) and $ClCO_2Et$ (1.1 mL, 11 mmol, 1.1 equiv.) were then added. The reaction mixture was stirred at room temperature for another 6 h. The reaction was quenched with 1 N HCl (40 mL). The resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give acid **SI-4** 1.68 g (89%) which can be used without further purification.

Physical State: Colorless oil.

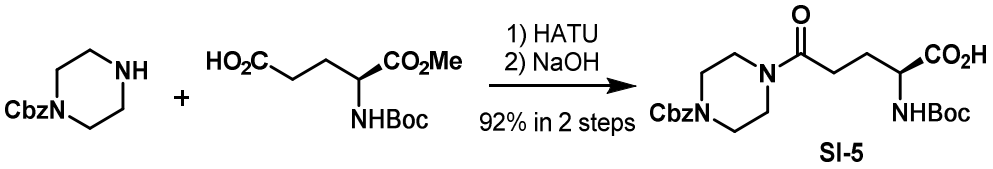
^{1}H NMR (600 MHz, $CDCl_3$): δ 11.20 (s, 1H), 4.22–4.08 (m, 2H), 4.06–2.94 (m, 2H), 3.34–3.18 (m, 2H), 1.62–1.45 (m, 2H), 1.24 (dt, *J* = 31.3, 7.3 Hz, 3H), 0.89 (dt, *J* = 9.7, 5.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.3, 174.9, 157.1, 156.1, 62.0, 61.7, 50.2, 49.9, 48.9, 48.4, 21.5, 21.1, 14.5, 11.1.

HRMS (ESI-TOF): calc'd for $C_8H_{16}NO_4$ $[M+H]^+$: 190.1079, found 190.1077.

TLC: R_f = 0.3 (20:1 DCM:MeOH)

Compound SI-5



(*S*)-5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*tert*-butoxycarbonyl)amino)-5-oxopentanoic acid (SI-5)

To a solution of (*S*)-4-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid (261 mg, 1 mmol, 1.0 equiv.) in CH_3CN (5 mL) was added benzyl piperazine-1-carboxylate (0.22 mL, 1.1 mmol, 1.1 equiv.), DIPEA (0.25 mL, 1.4 mmol, 1.4 equiv.), HATU (418 mg, 1.1 mmol, 1.1 equiv.) at room temperature and stirred at room temperature for 2 h. At this time, the reaction mixture was added 1 M NaOH (3 mL), MeOH (3 mL) and stirred at room temperature for 12 h. The reaction was transferred to a separatory funnel, diluted with H_2O (10 mL) and washed with CH_2Cl_2 (3 × 10 mL). The aqueous layer was adjusted to pH 1 via the addition of aqueous 1 N HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give acid **SI-5** 413 mg (92%) which can be used without further purification.

Physical State: White foam.

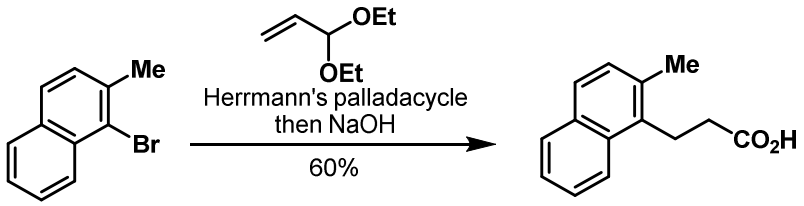
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5H), 5.73 (d, *J* = 6.6 Hz, 1H), 5.14 (s, 2H), 4.14 (q, *J* = 5.8 Hz, 1H), 3.70–3.30 (m, 8H), 2.70–2.60 (m, 1H), 2.49–2.38 (m, 1H), 2.26–2.18 (m, 1H), 2.00–1.89 (m, 1H), 1.40 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4, 172.1, 155.9, 155.1, 136.3, 128.5, 128.2, 128.0, 79.7, 67.5, 53.7, 45.3, 43.5, 41.6, 29.8, 28.8, 28.3.

HRMS (ESI-TOF): calc'd for $C_{22}H_{32}N_3O_7$ $[M+H]^+$: 450.2240, found 450.2253.

TLC: R_f = 0.3 (10:1 DCM:MeO)

Compound SI-6



3-(2-methylnaphthalen-1-yl)propanoic acid (SI-6)

To a solution of 1-bromo-2-methylnaphthalene (266 mg, 1.2 mmol, 1.0 equiv.) in NMP (4 mL) was added NaOAc (148 mg, 1.8 mmol, 1.5 equiv.), Herrmann's palladacycle (114 mg, 0.12 , 0.1 equiv.mmol) and acrolein diethyl acetal (0.56 mL, 3.6 mmol, 3.0 equiv.) at room temperature. The reaction mixture was stirred at 160 ºC for 48 h and then cool to 50 ºC. The solution was diluted with 2 M NaOH (4 mL), and then stirred at 50 ºC for another 2 h. The mixture was acidified with 1 N HCl (pH 1–2). The resulting mixture was extracted with EtOAc (3 × 10 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 acetone/hexane (1:2) as the eluent to give **SI-6** 160 mg (60%) as a white solid. The spectroscopic data matched the literature[1].

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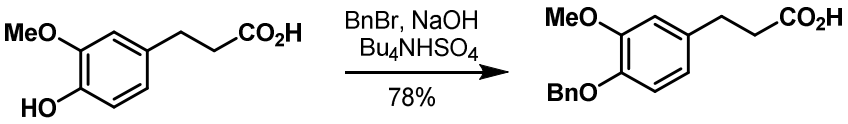
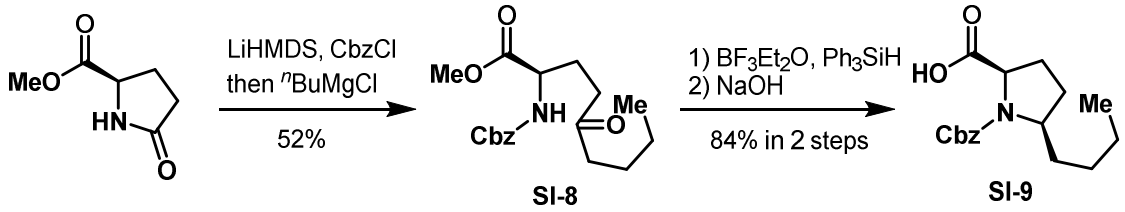
Compound SI-7

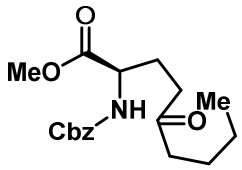


3-(4-(benzyloxy)-3-methoxyphenyl)propanoic acid (**SI-7**)

To a solution of 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (196 mg, 1 mmol, 1.0 equiv.) in 1 N NaOH/THF (2.5/1.25 mL) was added Bu_4NHSO_4 (13.6 mg, 0.04 mmol, 0.04 equiv.) and BnBr (0.18 mL, 1.5 mol, 1.5 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 16 h and 80 ºC for 1 h. The reaction was quenched with 1 N HCl (5 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 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 acetone/hexane (1:3) as the eluent to give **SI-7** 223 mg (78%) as a white solid. The spectroscopic data matched the literature[2].



Compound SI-8



Methyl (*R*)-2-(((benzyloxy)carbonyl)amino)-5-oxononanoate (SI-8)

To a solution of methyl (R)-5-oxopyrrolidine-2-carboxylate (143 mg, 1 mmol, 1.0 equiv.) in THF (4 mL) was added LiHMDS (1.1 mL, 1.0 M in THF, 1.1 equiv.) at –78 ºC under argon, and the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture then was added CbzCl (0.16 mL, 1.1 mmol, 1.1 equiv.) at –78 ºC, and the reaction mixture was stirred at –78 ºC ~0 ºC for 1 h. To the reaction mixture was then added TMEDA (0.45 mL, 3.3 mmol, 3.3 equiv.) and ^{n}BuMgCl (0.17 mL, 2.0 M in THF, 3.4 equiv.) at –78 ºC, and the reaction mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with ^{i}PrOH (0.35 mL) and 10% HCl (3 mL), and the aqueous mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (2 × 10 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 acetone/hexane (1:4) as the eluent to give **SI-8** 174 mg (52%).

Physical State: white solid.

m.p.: 45-47 ºC.

^{1}H NMR (600 MHz, $CDCl_3$):δ 7.39–7.28 (m, 5H), 5.40 (br, 1H), 5.23–5.01 (m, 2H), 4.39–4.27 (m, 1H), 3.74 (s, 3H), 2.58–2.42 (m, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.21–2.07 (m, 1H), 1.99–1.84 (m, 1H), 1.53 (p, *J* = 7.5 Hz, 2H), 1.29 (h, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

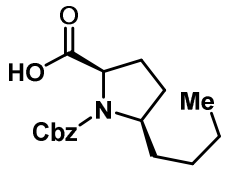
^{13}C NMR (151 MHz, Chloroform-*d*): δ 209.8, 172.5, 155.9, 136.2, 128.5, 128.2, 128.1, 67.0, 53.4, 52.5, 42.6, 38.3, 26.3, 25.8, 22.3, 13.8.

HRMS (ESI-TOF): calc'd for $C_{18}H_{26}NO_5$ $[M+H]^+$: 336.1811, found 336.1813.

TLC: R_f = 0.3 (4:1 hexanes: acetone)

$[\alpha]_D^{25}$ = –7.9 (c = 0.73, $CHCl_3$)

Compound SI-9



(2*R*,5*R*)-1-((benzyloxy)carbonyl)-5-butylpyrrolidine-2-carboxylic acid (SI-9)

To a solution of Ph_3SiH (140 mg, 0.54 mmol, 2.0 equiv.) in DCM (0.8 mL) was added BF_3•Et_2O (0.14 mL, 1.08 mmol, 4.0 equiv.) at room temperature under argon. The solution was stirred for 10 min at the same temperature, and then transferred via a cannula to a stirred solution of **SI-8** (90 mg, 0.27 mmol, 1.0 equiv.) in DCM (1 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, and then at room temperature for 2 h. The solvent of the mixture was removed under vacuum. The residue was dissolved in 4 M NaOH (1.2 mL)/MeOH (2.4 mL)/THF (1.2 mL) at room temperature, and the reaction mixture was stirred at the same temperature for 12 h. The reaction was quenched with 1 N HCl (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 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/DCM (1:20) as the eluent to give **SI-9** 69 mg (84%).

Physical State: colorless oil.

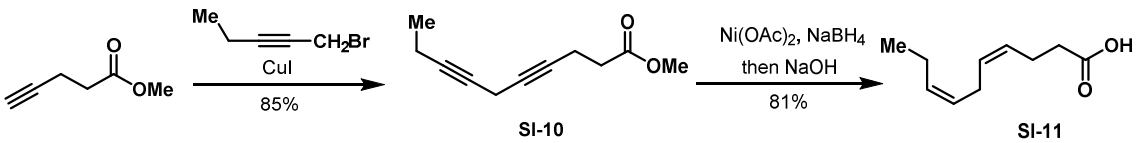
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57–7.26 (m, 5H), 5.56–5.05 (m, 2H), 4.41 (q, *J* = 7.6 Hz, 1H), 4.13–3.81 (m, 1H), 2.36–2.09 (m, 2H), 2.03–1.93 (m, 1H), 1.83–1.59 (m, 1H), 1.45–1.14 (m, 6H), 0.94–0.76 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5, 157.1, 135.9, 128.5, 128.3, 128.1, 68.0, 67.0, 60.3, 59.5, 59.1, 34.0, 29.7, 28.2, 26.7, 22.5, 14.0.

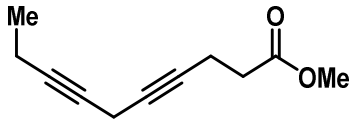
HRMS (ESI-TOF): calc'd for $C_{17}H_{24}NO_4$ $[M+H]^+$: 306.1705, found 306.1706.

TLC: R_f = 0.4 (20:1 DCM:MeOH)

$[\alpha]_D^{25}$ = +35.8 (c = 0.40, $CHCl_3$)



Compound SI-10



Methyl deca-4,7-diynoate (SI-10)

To a solution of methyl pent-4-ynoate (0.28 mL, 2.4 mmol, 1.3 equiv.) in DMF (3 mL) was added CuI (458 mg, 2.4 mmol, 1.3 equiv.), NaI (360 mg, 2.4 mmol, 1.3 equiv.), Cs_2CO_3 (784 mg, 2.4 mmol, 1.3 equiv.) and 1-bromopent-2-yne (0.19 mL, 1.9 mmol, 1.0 equiv.) at room temperature, and the solution was stirred for 18 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with Et_2O (3 × 10 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 (1:20) as the eluent to give **SI-10** 280 mg (85%).

Physical State: colorless oil.

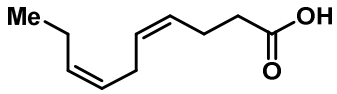
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.08 (t, J = 2.3 Hz, 2H), 2.55–2.37 (m, 4H), 2.22–2.04 (m, 2H), 1.09 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4, 81.9, 78.3, 75.4, 73.4, 51.7, 33.3, 14.6, 13.8, 12.3, 9.6.

HRMS (ESI-TOF): calc'd for $C_{11}H_{15}O_2$ $[M+H]^+$: 179.1072, found 179.1077.

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

Compound SI-11



(4*Z*,7*Z*)-deca-4,7-dienoic acid (SI-11)

To a solution of $Ni(OAc)_2$•$4H_2O$ (283 mg, 1.14 mmol, 1.0 equiv.) in EtOH (5 mL) was added and $NaBH_4$ (48 mg, 1.14 mmol) at 0 °C. The mixture was stirred under a hydrogen atmosphere at ambient temperature for 30 min. Ethylene diamine (305 μL, 4.56 mmol, 4.0 equiv.) and **SI-10** (203 mg, 1.14 mmol, 1.0 equiv.) were added, and stirring under a hydrogen atmosphere at room temperature was continued for 3 h. The solution was diluted with 2 M NaOH (2 mL), and then stirred at room temperature for another 12 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with Et_2O (3 × 10 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 (1:3) as the eluent to give **SI-11** 155 mg (81%).

Physical State: colorless oil.

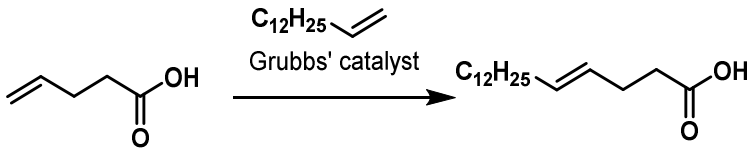
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.49–5.23 (m, 4H), 2.80 (t, *J* = 7.1 Hz, 2H), 2.47–2.34 (m, 4H), 2.11–1.93 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 179.4, 132.2, 130.0, 127.2, 126.8, 34.0, 25.5, 22.5, 20.5, 14.2.

HRMS (ESI-TOF): calc'd for $C_{11}H_{14}O_2$ $[M-H]^+$: 167.1077, found 167.1077.

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

Compound SI-12

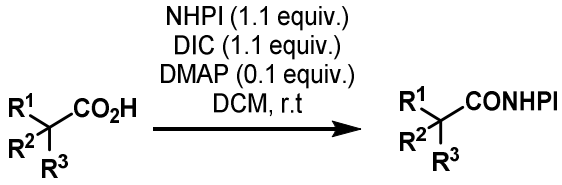


(*E*)-heptadec-4-enoic acid (SI-12)

To a solution of tetradec-1-ene (9.8 g, 50 mmol) and 4-pentenoic acid (1.0 g, 10 mmol, 1.0 equiv.) in dry CH_2Cl_2 (1000 mL) was added Grubbs' second generation catalyst (424.5 mg, 0.5 mmol, 0.05 equiv.). The mixture was stirred at 40 ^{o}C for 12 h under argon atmosphere. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10:1 hexanes:EtOAc) to give the title compound **SI-12** 1.62 g (62%) as a white solid. The spectroscopic data matched the literature[3].

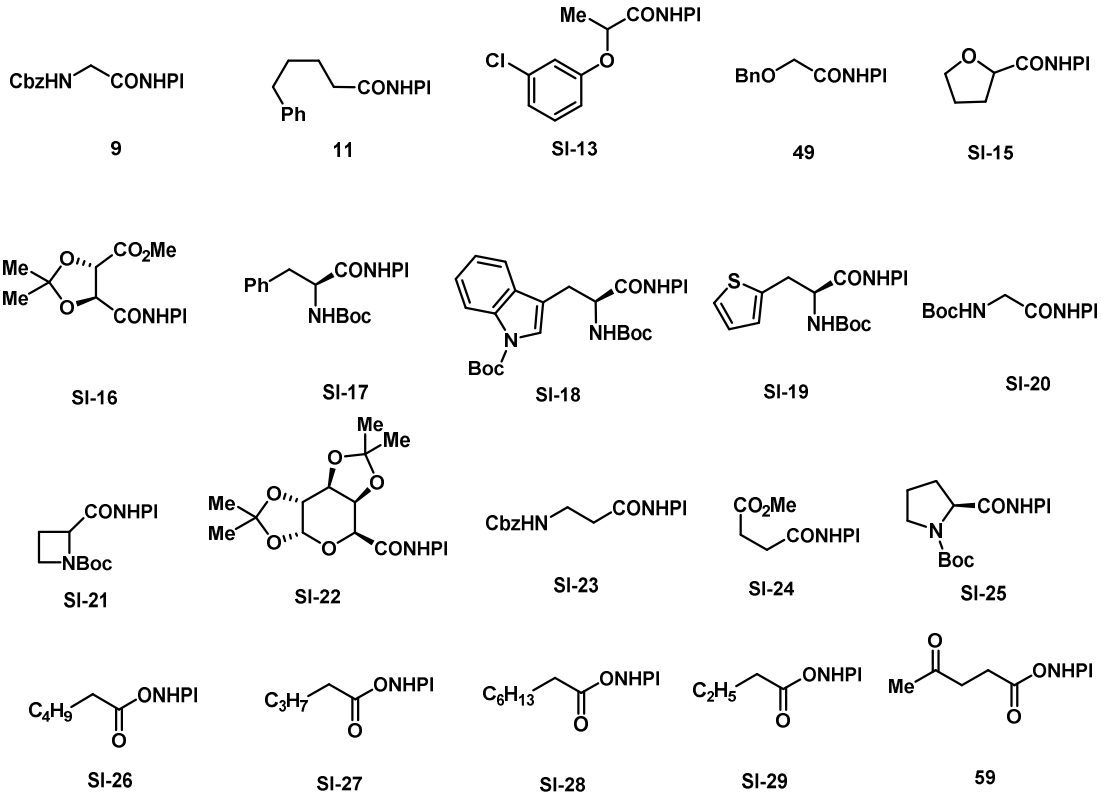
Experimental Procedures and Characterization Data for Redox Active Esters

General procedure E: synthesis of redox active esters

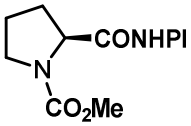


To a stirring solution of carboxylic acid (1.0 equiv.) in anhydrous DCM (0.2 M) was added N-hydroxyphthalimide (1.1 equiv.), 4-dimethylaminopyridine (0.1 equiv.) and DIC (1.1 equiv.) was added via syringe. The reaction mixture was vigorously stirred until complete (monitored by TLC, 0.5 h – 2 h). Upon completion, the mixture was filtered over Celite® and rinsed with additional CH_2Cl_2/Et_2O. The solvent was removed under reduced pressure, and and purification by column chromatography afforded the desired redox-activated ester. Redox-active esters shown below **9**[4], **11**[5], **S-13**[6], **S-142**[7], **S-15**[8], **S-16**[9], **S-17**[10], **S-18**[11], **S-19**[12], **S-20**[13], **S-21**[13], **S-22**[14], **S-23**[15], **S-24**[16], **S-25**[10], **S-26**[17], **S-27**[17], **S-28**[17], **S-29**[17], **59**[11] have previously been reported in the literature. Please see these references for characterization. For newly reported redox active esters, HRMS usually failed to detect the target mass due to instability of the NHPI ester motif.

Known redox active esters



Compound 8



2-(1,3-dioxoisoindolin-2-yl) 1-methyl (*S*)-pyrrolidine-1,2-dicarboxylate (8)

Prepared according to **general procedure E** from (methoxycarbonyl)-L-proline on 20 mmol scale. Purification by column chromatography (3:1 hexanes:EtOAc) afforded 5.0 g (79%) of the title compound **8**.

Physical State: white solid.

m.p.: 126-128 ºC.

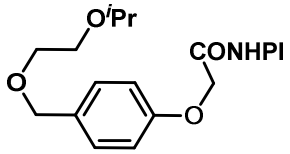
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88–7.84 (m, 2H), 7.80–7.74 (m, 2H), 4.75/4.63 (2dd, *J* = 7.8, 4.5 Hz/*J* = 8.7, 4.0 Hz, 1H), 3.77/3.73 (2s, 3H), 3.69–3.62/3.49–3.43 (2m, 1H), 3.61–3.51 (m, 1H) 2.53–2.29 (m, 2H), 2.13–2.04 (m, 1H), 2.03–1.93 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.3, 169.1, 161.6, 155.2, 154.6, 134.8, 134.7, 128.8 (2C), 123.9, 57.3 (2C), 57.0, 56.9, 52.9, 52.8, 52.7, 46.8, 46.3, 31.3, 30.2, 24.4, 23.6.

TLC: R_f = 0.3 (2:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = –72.6 (c = 1.0, $CHCl_3$)

Compound SI-31



1,3-dioxoisoindolin-2-yl 2-(4-((2-isopropoxyethoxy)methyl)phenoxy)acetate (SI-31)

Prepared according to general **general procedure E** from **SI-1** on 2.5 mmol scale. Purification by column chromatography (5:1 hexanes:EtOAc) afforded 708 mg (67%) of the title compound **SI-31**.

Physical State: white solid.

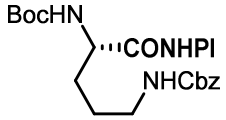
m.p.: 73-75 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 5.03 (s, 2H), 4.52 (s, 2H), 3.79–3.39 (m, 5H), 1.17 (d, *J* = 6.1 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.5, 161.5, 156.8, 134.9, 132.4, 129.4, 128.8, 124.1, 114.7, 72.6, 71.9, 69.6, 67.4, 63.5, 22.0.

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

Compound SI-32



1,3-dioxoisoindolin-2-yl (*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoate (SI-32)

Prepared according to **general procedure E** from (*S*)-5-(((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)pentanoic acid on 5.0 mmol scale. Purification by column chromatography (3:1 hexanes:EtOAc) afforded 2.02 g (79%) of the title compound **SI-32**.

Physical State: white solid.

m.p.: 130-132 ºC.

^{1}H NMR (600 MHz, $CDCl_3$):δ 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.38–7.27 (m, 5H), 5.22–4.93 (m, 4H), 4.76/4.47 (2br, 1H), 3.35–3.20 (m, 2H), 2.09–1.99 (m,

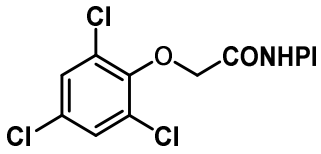
1H), 1.99–1.86 (m, 1H), 1.80–1.65 (m, 2H), 1.51/1.46 (2s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.2, 161.5, 156.5, 154.8, 136.6, 134.8, 128.7, 128.4, 128.0, 124.0, 80.6, 66.6, 51.6, 40.3, 30.0, 28.2, 25.3.

TLC: R_f = 0.3 (2:1 hexanes:acetone)

[α]$_D^{25}$ = –4.9 (c = 1.0, $CHCl_3$)

Compound SI-33



1,3-dioxoisoindolin-2-yl 2-(2,4,6-trichlorophenoxy)acetate (SI-33)

Prepared according to **general procedure E** from 2-(2,4,6-trichlorophenoxy)acetic acid on 2.0 mmol scale. Purification by column chromatography (5:1 hexanes:EtOAc) afforded 709 mg (89%) of the title compound **SI-33**.

Physical State: white solid.

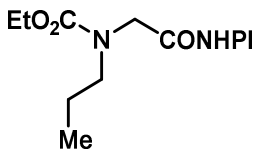
m.p.: 156-158 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.35 (s, 2H), 5.04 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.2, 161.4, 149.1, 135.0, 130.9, 129.8, 129.0, 128.7, 124.1, 67.2.

TLC: R_f = 0.4 (4:1 hexanes:EtOAc)

Compound SI-34



1,3-dioxoisoindolin-2-yl *N*-(ethoxycarbonyl)-*N*-propylglycinate (SI-34)

Prepared according to **general procedure E** from **SI-4** on 5.0 mmol scale. Purification by column chromatography (5:1 hexanes:EtOAc) afforded 1.29 g (77%) of the title compound **SI-34**.

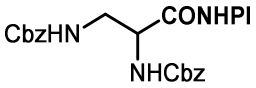
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.9–7.85 (m, 2H), 7.82–7.75 (m, 2H), 4.43/4.32 (2s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.36/3.32 (2t, *J* = 7.4 Hz, 1H), 1.59 (qd, *J* = 7.7, 2.7 Hz, 2H), 1.28 (dt, *J* = 14.8, 7.1 Hz, 3H), 1.03–0.85 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.6, 161.5, 156.5, 155.7, 134.8 (2C), 128.8, 124.0, 62.1, 62.0, 50.4, 49.7, 46.8, 21.4, 21.2, 14.5, 14.3, 11.0.

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

Compound SI-35



1,3-dioxoisoindolin-2-yl 2,3-bis(((benzyloxy)carbonyl)amino)propanoate (SI-35)

Prepared according to **general procedure E** from 2,3-bis(((benzyloxy)carbonyl)amino)propanoic acid[18] on 3 mmol scale. Purification by column chromatography (5:1 hexanes:EtOAc) afforded 1.15 g (74%) of the title compound **SI-35**.

Physical State: white solid.

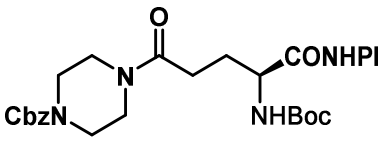
m.p.: 150-152 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.42–7.28 (m, 10H), 6.20 (d, *J* = 7.6 Hz, 1H), 5.79 (t, *J* = 6.6 Hz, 1H), 5.23–5.03 (m, 4H), 4.94–4.86 (m, 1H), 3.98 (ddd, *J* = 14.9, 7.6, 3.3 Hz, 1H), 3.75 (dt, *J* = 14.7, 5.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.3, 161.8, 157.7, 155.7, 136.1, 136.0, 135.0, 128.7, 128.5 (two peaks), 128.2(three peaks) 128.0, 124.2, 67.4, 67.3, 54.4, 43.1.

TLC: R_f = 0.3 (2:1 hexanes:acetone)

Compound SI-36



benzyl (S)-4-(4-((tert-butoxycarbonyl)amino)-5-((1,3-dioxoisoindolin-2-yl)oxy)-5-oxopentanoyl)piperazine-1-carboxylate(SI-36)

Prepared according to **general procedure E** from **SI-5** on 1.0 mmol scale. Purification by column chromatography (2:1 hexanes:EtOAc) afforded 547 mg (92%) of the title compound **SI-36**.

Physical State: white foam.

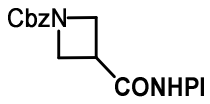
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.39–7.30 (m, 5H), 5.65 (d, *J* = 7.9 Hz, 1H), 5.15 (s, 2H), 4.77/4.58 (2br, 1H), 3.74–3.38 (m, 8H), 2.73–2.57 (m, 2H), 2.38–2.28 (m, 2H), 1.51/145 (2s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.2, 169.1, 161.5, 155.1, 154.9, 136.3, 134.8, 128.7, 128.5, 128.1, 128.0, 124.0, 81.5, 80.4, 67.4, 53.1, 51.8, 45.1, 43.7, 41.5, 28.6, 28.2, 28.0, 27.5, 26.6.

TLC: R_f = 0.2 (2:1 hexanes:acetone)

$[\alpha]_D^{25}$ = –4.4 (c = 1.0, $CHCl_3$)

Compound SI-37



1-benzyl 3-(1,3-dioxoisoindolin-2-yl) azetidine-1,3-dicarboxylate (SI-37)

Prepared according to **general procedure E** from 1-((benzyloxy)carbonyl)azetidine-3-carboxylic acid on 2.0 mmol scale. Purification by column chromatography (3:1 hexanes:EtOAc) afforded 669 mg (88%) of the title compound **SI-37**.

Physical State: white solid.

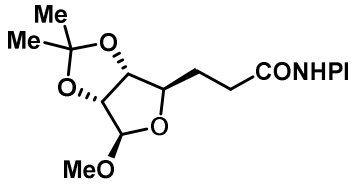
m.p.: 107-109 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.41–7.29 (m, 5H), 5.12 (s, 2H), 4.44–4.28 (m, 4H), 3.77 (tt, *J* = 8.8, 6.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.8, 161.6, 158.0, 155.9, 136.2, 134.9, 128.7, 128.5, 128.2, 128.0, 124.1, 67.0, 51.4, 30.0 (2C)

TLC: R_f = 0.4 (2:1 hexanes:EtOAc)

Compound SI-38



1,3-dioxoisoindolin-2-yl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)propanoate (SI-38)

Prepared according to **general procedure E** from 3-((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)propanoic acid[19] on 4.0 mmol scale. Purification by column chromatography (3:1 hexanes:EtOAc) afforded 1.14 g (73%) of the title compound **SI-38**.

Physical State: white solid.

m.p.: 88-90 ºC

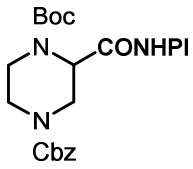
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 4.98 (s, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.25 (t, *J* = 7.8 Hz, 1H), 3.38 (s, 3H), 2.94–2.83 (m, 1H), 2.78 (dt, *J* = 16.5, 8.0 Hz, 1H), 2.02 (q, *J* = 7.7 Hz, 2H), 1.48 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.1, 161.8, 134.7, 128.9, 124.0, 112.5, 109.9, 109.8, 88.6, 88.4, 83.9, 55.3 (two peaks), 30.0, 27.9, 26.5, 25.0.

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

$[\alpha]_D^{25}$ = –10.3 (c = 1.0, $CHCl_3$)

Compound SI-39



4-benzyl 1-(*tert*-butyl) 2-(1,3-dioxoisoindolin-2-yl) piperazine-1,2,4-tricarboxylate (SI-39)

Prepared according to **general procedure E** from 4-((benzyloxy)carbonyl)-1-(tert-butoxycarbonyl)piperazine-2-carboxylic acid on 2.0 mmol scale. Purification by column chromatography (3:1 hexanes:EtOAc) afforded 672 mg (66%) of the title compound **SI-39**.

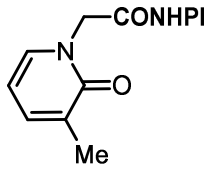
Physical State: white foam.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.9, 3.2 Hz, 2H), 7.79 (dd, *J* = 6.0, 3.1 Hz, 2H), 7.43–7.26 (m, 5H), 5.41–5.12 (m, 2H), 5.11–4.92 (m, 1H), 4.90–4.60 (m, 1H), 4.30–4.03 (m, 1H), 4.02–3.78 (m, 1H), 3.47–3.22 (m, 2H), 3.15–2.88 (m, 1H), 1.51/1.49 (2s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.0, 161.3, 154.9, 154.5, 136.5, 134.8, 128.9, 128.4, 128.0, 124.0, 82.0, 81.5, 67.6, 53.7, 52.3, 44.0, 42.8, 41.4, 40.1, 28.2, 28.0.

TLC: R_f = 0.4 (2:1 hexanes:EtOAc)

Compound SI-40



1,3-dioxoisoindolin-2-yl 2-(3-methyl-2-oxopyridin-1(2H)-yl)acetate (SI-40)

Prepared according to **general procedure E** from 2-(3-methyl-2-oxopyridin-1(2H)-yl)acetic acid on 1.0 mmol scale. Purification by column chromatography (2:1 hexanes:EtOAc) afforded 243 mg (66%) of the title compound **SI-39**.

Physical State: white solid.

m.p.: 176-178 ºC.

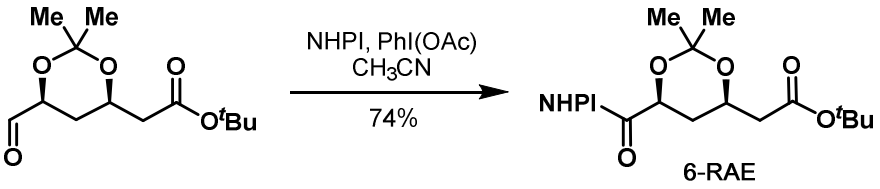
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.4, 2.3 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.23 (d, *J* = 6.8 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 6.16 (t, *J* = 6.8 Hz, 1H), 5.07 (s, 2H), 2.17 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.7, 162.6, 161.3, 137.4, 134.9, 134.5, 130.4, 128.7, 124.1, 106.4, 47.8, 17.1.

TLC: R_f = 0.2 (2:1 hexanes:EtOAc)

Compound 6-RAE

One step procedure:

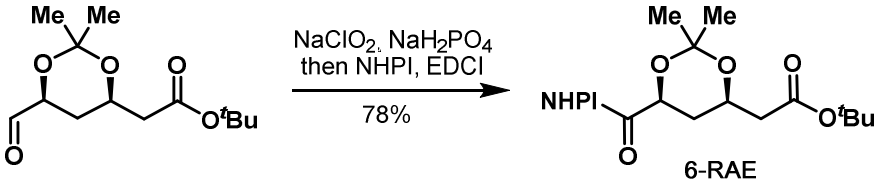


1,3-dioxoisoindolin-2-yl (4*S*,6*R*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxane-

4-carboxylate (6-RAE).

The following procedure was modified from the literature[40].To a solution of *tert*-butyl 2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1.29 g, 5.0 mmol, 1.0 equiv.) and NHPI (927 mg, 6.0 mmol, 1.2 equiv.) in CH_3CN (20 ml) was added $PhI(OAc)_2$ (1.93 g, 6.0 mmol, 1.2 equiv.) at 0 ºC under argon, and then the mixture was stirred at 0 ºC for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (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 (4:1 hexanes:EtOAc) to give **6-RAE** (1.55 g, 74%).

One pot procedure:



1,3-dioxoisoindolin-2-yl (4*S*,6*R*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxane-4-carboxylate (6-RAE).

To a solution of tert-butyl 2-((4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1.0 g, 3.9 mmol, 1.0 equiv.) in ^{t}BuOH/H_2O (5 ml/2.5 ml) was added 2-methyl-2-butene (2.1 ml, 19.5 mmol, 5.0 equiv.), NaH_2PO_4 (1.40 g, 11.7 mmol, 3.0 equiv.) and $NaClO_2$ (1.05 g, 11.7 mmol, 3.0 equiv.) at 0 ºC. The mixture was stirred at room temperature for 2 h and the solvent of the mixture was removed under vacuum. At this time, the reaction mixture was dissolved in DCM (20 ml) and NHPI (694 mg, 4.3 mmol, 1.1 equiv.), EDCI (816 mg, 4.3 mmol, 1.1 equiv.) were added. The mixture was then stirred at room temperature for 2 h. The reaction was quenched with 1N HCl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 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 column chromatography with EtOAc/hexane (3:7) as the eluent to give **6-RAE** (1.26 g, 78%).

Physical State: white solid.

m.p.: 116-118 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.94 (dd, *J* = 12.1, 2.8 Hz, 1H), 4.46–4.36 (m, 1H), 2.50 (dd, *J* = 15.5, 7.1 Hz, 1H), 2.40 (dd, *J* = 15.6, 5.8 Hz, 1H), 2.13 (dt, *J* = 12.8, 2.6 Hz, 1H), 1.79 (q, *J* = 12.2 Hz, 1H), 1.53 (s, 3H),

1.48 (s, 3H), 1.45 (s, 9H).

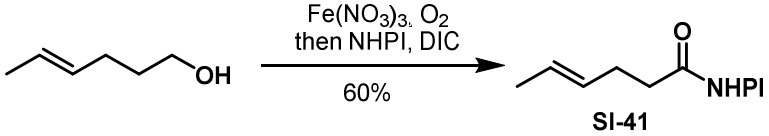
^{13}C NMR (151 MHz, $CDCl_3$): δ 169.7, 167.0, 161.5, 134.8, 128.8, 124.0, 100.0, 81.0, 67.4, 65.6, 42.2, 33.0, 29.6, 28.1, 19.3.

TLC: R_f = 0.4 (7:3 hexanes:EtOAc)

[α]$_D^{25}$ = +16.2 (c = 1.0, $CHCl_3$)

Compound SI-41

1,3-dioxoisoindolin-2-yl (*E*)-hex-4-enoate (SI-41)



SI-41

To a solution of (E)-hex-4-en-1-ol (1 g, 10 mmol, 1.0 equiv.) in DCE (40 mL) was added $Fe(NO_3)_3 \cdot 9H_2O$ (404 mg, 1 mmol, 0.1 equiv.), TEMPO (155 mg, 1 mmol, 0.1 equiv.), KCl (75 mg, 1 mmol, 0.1 equiv.), and sequentially under the atmosphere of oxygen from a gas bag. The mixture was then stirred at room temperature for 12 h. At this time, the crude reaction mixture was added N-hydroxyphthalimide (1.8 g, 11 mmol, 1.1 equiv.) and DIC (1.7 mL, 11 mmol, 1.1 equiv.). After stirred at room temperature for further 2 hours, the mixture was filtered through a pad of Celite, washed with dichloromethane. The solution was then concentrated in vacuum and purified by flash column chromatography on silica gel (10:1 hexanes: EtOAc) to give the title compound **SI-41** 1.6g (60%).

Physical State: white solid.

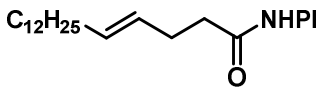
m.p.: 75-77 ºC

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89–7.86 (m, 2H), 7.80–7.76 (m, 2H), 5.63–5.54 (m, 1H), 5.52–5.44 (m, 1H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.50–2.41 (m, 2H), 1.68 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.1, 161.9, 134.7, 128.9, 127.7, 127.5, 123.9, 31.1, 27.51, 17.9.

TLC: R_f = 0.3 (6:1 hexanes:EtOAc)

Compound 50



1,3-dioxoisoindolin-2-yl (E)-heptadec-4-enoate (50)

Prepared according to **general procedure E** from **SI-12**

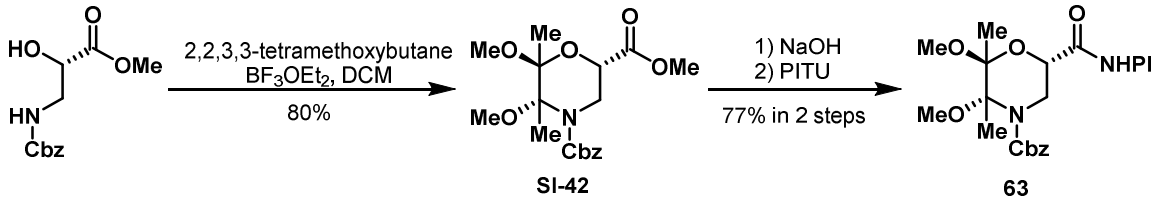
Physical State: faint yellow solid.

m.p.: 48-50 ºC.

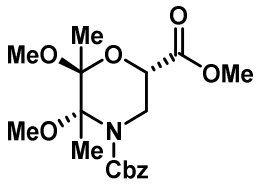
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94–7.84 (m, 2H), 7.82–7.71 (m, 2H), 5.56 (dt, *J* = 14.2, 6.7 Hz, 1H), 5.46 (dt, *J* = 14.8, 6.5 Hz, 1H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.46 (q, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.1 Hz, 2H), 1.44–1.13 (m, 20H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 161.9, 134.7, 133.1, 129.0, 126.4, 123.9, 32.5, 31.9, 31.2, 29.7, 29.6 (2C), 29.5, 29.4, 29.3, 29.2, 27.5, 22.7, 14.1.

TLC: R_f = 0.3 (6:1 hexanes:EtOAc)



Compound SI-42



4-benzyl 2-methyl (2*S*,5*R*,6*S*)-5,6-dimethoxy-5,6-dimethylmorpholine-2,4-dicarboxylate (SI-42)

To a solution of methyl (*S*)-3-(((benzyloxy)carbonyl)amino)-2-hydroxypropanoate[20] (1.01 g, 4 mmol, 1.0 equiv.) in DCM (12 mL) was added 2,2,3,3-tetramethoxybutane (3.56 g, 20 mmol, 5.0 equiv.) and BF_3•OEt_2 (56 µL, 0.48 mol), at room temperature. After 4 h, triethylamine (0.3 mL) was added to quench the reaction and the resulting solution was stirred for 1 h. The solution was then diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (50 mL), brine (50 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-42** 1.18 g (80%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.29 (m, 5H), 5.22–5.07 (m, 2H), 4.44 (dd, *J* = 11.5, 3.2 Hz, 1H), 4.22 (dd, *J* = 13.5, 3.2 Hz, 1H), 3.75 (s, 3H), 3.33 (dd, *J* = 13.5, 11.5 Hz, 1H), 3.25 (s,

3H), 3.18 (s, 3H), 1.71 (s, 3H), 1.40 (s, 3H).

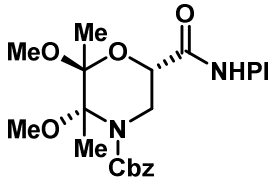
^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5, 156.1, 136.5, 128.5, 127.9, 127.7, 101.4, 90.1, 67.6, 67.1, 52.2, 48.5, 48.4, 42.3, 18.9, 17.7.

HRMS (ESI-TOF): calc'd for $C_{18}H_{25}NO_7Na$ $[M+Na]^+$: 390.1529, found 390.1537.

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

$[\alpha]_D^{25}$ = +46.0 (c = 0.8, $CHCl_3$)

Compound 63



4-benzyl 2-(1,3-dioxoisoindolin-2-yl) (2*S*,5*R*,6*S*)-5,6-dimethoxy-5,6-dimethylmorpholine-2,4-dicarboxylate (63)

To a solution of **SI-42** (734 mg, 2 mmol) in MeOH (6 mL) was 2M NaOH (2 mL) and the mixture was then stirred at room temperature for 12 h. 1 N HCl (1.8 mL) was added, and the solvent of the mixture was removed under vacuum. At this time, the reaction mixture was dissolved in CH_3CN (10 ml) and PITU (1.22 g, 3.0 mmol, 1.5 equiv.), DIPEA (0.18 mL, 1.0 mmol, 1.5 equiv.) were added. The mixture was then stirred at room temperature for 4 h. The mixture was filtered over Celite® and rinsed with additional CH_2Cl_2 (10 ml) and Et_2O (10 ml). The solvent was removed under reduced pressure, and and purification by column chromatography with EtOAc/hexane (1:2) as the eluent to give **63** 767 mg (77%).

Physical State: white solid.

m.p.: 53-55 ºC.

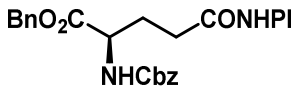
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dt, *J* = 5.5, 2.5 Hz, 2H), 7.80 (ddd, *J* = 5.5, 3.1, 1.6 Hz, 2H), 7.41–7.29 (m, 5H), 5.30–5.08 (m, 2H), 4.86 (dd, *J* = 11.1, 3.1 Hz, 1H), 4.40 (dd, *J* = 13.4, 3.1 Hz, 1H), 3.59 (dd, *J* = 13.4, 11.2 Hz, 1H), 3.29 (s, 3H), 3.22 (s, 3H), 1.73 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.6, 161.4, 156.1, 136.4, 134.8, 128.8, 128.5, 128.0, 127.8, 124.0, 101.8, 90.3, 67.3, 66.4, 48.8, 48.7, 42.4, 19.0, 17.6.

TLC: R_f = 0.3 (2:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = +58.5 (c = 1.0, $CHCl_3$)

Compound SI-43



1-benzyl 5-(1,3-dioxoisoindolin-2-yl) ((benzyloxy)carbonyl)-*D*-glutamate (SI-43)

Prepared according to **general procedure E** from (R)-5-(benzyloxy)-4-(((benzyloxy)carbonyl)amino)-5-oxopentanoic acid on 5.0 mmol scale. Purification by column chromatography (4:1 hexanes:EtOAc) afforded 2.17 g (84%) of the title compound **SI-43**.

Physical State: white foam.

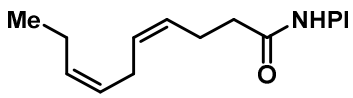
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dt, *J* = 5.5, 2.6 Hz, 2H), 7.41–7.27 (m, 10H), 5.67–5.52 (m, 1H), 5.20 (s, 2H), 5.13 (s, 2H), 4.74–4.33 (m, 1H), 2.88–2.58 (m, 2H), 2.46–2.33 (m, 1H), 2.27–2.09 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.1, 168.7, 161.7, 155.9, 136.0, 134.9, 134.7, 128.8, 128.6 (2C), 128.5, 128.3, 128.1 (2C), 123.9, 67.6, 67.2, 53.1, 27.5, 27.2.

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

$[\alpha]_D^{25}$ = –4.4 (c = 1.0, $CHCl_3$)

Compound 68



1,3-dioxoisoindolin-2-yl (4*Z*,7*Z*)-deca-4,7-dienoate (68)

Prepared according to **general procedure E** from **SI-11** on 1.2 mmol scale. Purification by column chromatography (10:1 hexanes:EtOAc) afforded 289 mg (77%) of the title compound **68**.

Physical State: colorless oil

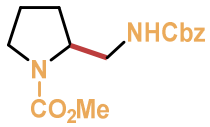
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91–7.85 (m, 2H), 7.83–7.75 (m, 2H), 5.54–5.37 (m, 3H), 5.34–5.26 (m, 1H), 2.83 (td, *J* = 7.2, 1.7 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.58–2.47 (m, 2H), 2.13–2.01 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.0, 161.9, 134.7, 132.3, 130.7, 128.9, 126.6, 126.2, 123.9, 31.0, 25.5, 22.4, 20.5, 14.2.

TLC: R_f = 0.3 (6:1 hexanes:EtOAc)

Experimental Procedures and Characterization Data for Doubly Decarboxylative Coupling Product

Compound 10



Methyl (*S*)-2-((((benzyloxy)carbonyl)amino)methyl)pyrrolidine-1-carboxylate (10). Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **8** with RAE **49** (3.0 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 19.5 mg (67%) of the title compound **10**.

Physical State: colorless oil.

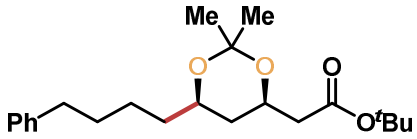
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 5.92/4.94 (2br, 1H), 5.09 (s, 2H), 4.03–3.86 (m, 1H), 3.69 (s, 3H), 3.52–3.08 (m, 4H), 2.02–1.69 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.0, 156.7, 136.8, 128.4, 128.1, 127.9, 66.8, 66.5, 57.7, 57.0, 52.5, 46.9, 45.6, 44.0, 29.2, 23.9, 23.0.

HRMS (ESI-TOF): calc'd for $C_{15}H_{21}N_2O_4$ $[M+H]^+$: 293.1501, found 293.1510.

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

Compound 12-(6*R*)



Tert-butyl 2-((4*R*,6*R*)-2,2-dimethyl-6-(4-phenylbutyl)-1,3-dioxan-4-yl)acetate (12-(6*R*)). Following the **General Procedure C (**with terpyridine**)** on 0.1 mmol scale **6-RAE** with RAE **11** (3.0 equiv). Purification by PTLC (16:1 hexanes:EtOAc) afforded 24.6 mg (68%) of the title compound **12-(6*R*)**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.23 (m, 2H), 7.20–7.14 (m, 3H), 4.31–4.17 (m, 1H), 3.86–3.78 (m, 1H), 2.61 (t, J = 12.0 Hz, 2H), 2.43 (dd, J = 15.1, 7.0 Hz, 1H), 2.29 (dd, J = 15.1, 6.2 Hz, 1H), 1.68–1.49 (m, 4H), 1.45 (s, 9H), 1.44 (s, 3H), 1.43–1.38 (m, 3H), 1.37 (s, 3H), 1.15 (dt, J = 12.7, 11.5 Hz, 1H).

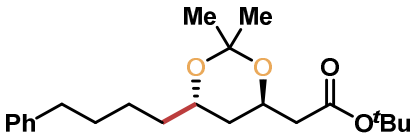
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.4, 142.6, 128.4, 128.2, 125.6, 98.6, 80.5, 68.8, 66.3, 42.8, 36.5, 36.2, 35.9, 31.4, 30.1, 28.1, 24.6, 19.7.

HRMS (ESI-TOF): calc'd for $C_{22}H_{34}O_4Na$ $[M+Na]^+$: 385.2355, found 385.2352.

TLC: R_f = 0.3 (16:1 hexanes:EtOAc)

[α]$_D^{25}$ = +3.4 (c = 1.0, $CHCl_3$)

Compound 12-(6*S*)



Tert-butyl 2-((4*R*,6*S*)-2,2-dimethyl-6-(4-phenylbutyl)-1,3-dioxan-4-yl)acetate (12-(6*S*)).

Following the **general procedure C** (without ligand) on 0.1 mmol scale **6-RAE** with RAE **11** (3.0 equiv). Purification by PTLC (16:1 hexanes:EtOAc) afforded 19.5 mg (54%) of the title compound **12-(6*S*)**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.24 (m, 2H), 7.21–7.08 (m, 3H), 4.33–4.12 (m, 1H), 3.83–3.63 (m, 1H), 2.61 (t, *J* = 12.0 Hz, 2H), 2.41 (dd, *J* = 15.0, 8.2 Hz, 1H), 2.35 (dd, *J* = 15.0, 5.5 Hz, 1H), 1.67–1.52 (m, 4H), 1.50–1.40 (m, 12H), 1.39–1.33 (m, 4H), 1.32 (s, 3H).

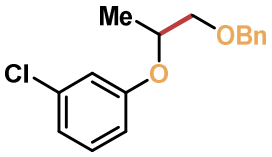
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 142.6, 128.3, 128.2, 125.6, 100.4, 80.5, 66.4, 63.8, 42.3, 38.0, 35.9, 35.6, 31.4, 28.1, 25.0, 24.8, 24.5.

HRMS (ESI-TOF): calc'd for $C_{22}H_{34}O_4Na$ $[M+H]^+$: 385.2355 , found 385.2343.

TLC: R_f = 0.3 (16:1 hexanes:EtOAc)

[α]$_D^{25}$ = +23.5 (c = 1.0, $CHCl_3$)

Compound 13



1-((1-(benzyloxy)propan-2-yl)oxy)-3-chlorobenzene (13).

Following the **general procedure A** (with **L1**) on 0.1 mmol scale RAE **SI-13** with RAE **49** (3.0 equiv). Purification by PTLC (20:1 hexanes:EtOAc) afforded 20.7 mg (75%) of the title compound **13**.

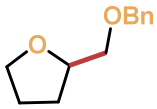
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 2.2 Hz, 1H), 6.92 (ddd, *J* = 7.9, 2.1, 0.9 Hz, 1H), 6.82 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 4.59 (s, 2H), 4.58–4.52 (m, 1H), 3.65 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.56 (dd, *J* = 10.2, 4.5 Hz, 1H), 1.33 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 158.7, 138.0, 134.8, 130.2, 128.4, 127.7, 127.6, 121.0, 116.4, 114.3, 73.6, 73.4, 73.1, 17.0.

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

Compound 14



2-((benzyloxy)methyl)tetrahydrofuran (14).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-15** with RAE **49** (3.0 equiv). Purification by PTLC (16:1 hexanes:EtOAc) afforded 13.1 mg (68%) of the title compound **14**.

Physical State: colorless oil.

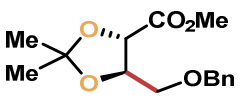
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.14–4.04 (m, 1H), 3.89 (dt, *J* = 8.4, 6.5 Hz, 1H), 3.84–3.74 (m, 1H), 3.51–3.44 (m, 2H), 1.99–1.82 (m, 3H), 1.68–1.61 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.3, 128.3, 127.7, 127.5, 77.9, 73.3, 72.7, 68.3, 28.1, 25.6.

HRMS (ESI-TOF): calc'd for $C_{12}H_{16}O_2Na$ $[M+Na]^+$: 215.1048, found 215.1051.

TLC: R_f = 0.3 (16:1 hexanes:EtOAc)

Compound 15



Methyl (4*S*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate.

Following the **general procedure A** (without ligand) on 0.1 mmol scale RAE **SI-16** with RAE **49** (3.0 equiv). Purification by flash column chromatography on silica gel (10:1 hexanes:EtOAc) afforded 16.9 mg (60%) of the title compound **15**. (The reacton was also examined by in situ generated RAE, 51% yield in 1 mmol scale) The spectroscopic data matched the literature[38].

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, J = 4.4 Hz, 4H), 7.29 (ddd, J = 8.7, 4.9, 3.9 Hz, 1H), 4.67–4.59 (m, 2H), 4.40 (d, J = 7.6 Hz, 1H), 4.36 (ddd, J = 7.8, 5.3, 3.2 Hz, 1H), 3.79–3.75 (m, 4H), 3.68 (dd, J = 10.7, 5.3 Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H).

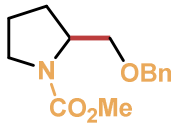
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.1, 137.8, 128.4, 127.7 (2C), 111.7, 78.3, 75.6, 73.6, 69.8, 52.4, 26.9, 25.7.

GC/MS (EI): m/z 280 (1%), 265 (11%), 159 (3%), 117 (12%), 91 (100%).

TLC: R_f = 0.35 (10:1 hexanes:EtOAc)

$[\alpha]_D^{20}$ = 19.1 (c = 0.67, $CHCl_3$) (lit. $[\alpha]_D^{21}$ = 19.0 (*c* = 1.3, $CHCl_3$))

Compound 17



Methyl 2-((benzyloxy)methyl)pyrrolidine-1-carboxylate (17).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **8** with RAE **49** (3.0 equiv). Purification by PTLC (85:15 hexanes:acetone) afforded 16.9 mg (68%) of the title compound **17**.

Physical State: colorless oil.

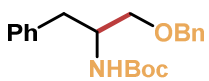
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–7.26 (m, 5H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.16–3.89 (m, 1H), 3.67 (s, 3H), 3.67–3.22 (m, 4H), 2.08–1.72 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.6, 138.5, 128.3, 127.5, 73.2, 70.9, 70.5, 57.1, 56.4, 52.2, 46.9, 46.6, 28.8, 28.0, 23.9, 22.9.

HRMS (ESI-TOF): calc'd for $C_{14}H_{20}NO_3$ $[M+H]^+$: 250.1443, found 250.1453.

TLC: R_f = 0.4 (4:1 hexanes: EtOAc)

Compound 18



***Tert*-butyl-(1-(benzyloxy)-3-phenylpropan-2-yl)carbamate (18).**

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-17** with RAE **49** (3.0 equiv). Purification by PTLC (6:1 hexanes:EtOAc) afforded 23.2 mg (68%) of the title compound **18**.

Physical State: colorless oil.

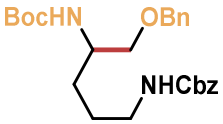
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–7.29 (m, 5H), 7.28–7.23 (m, 2H), 7.23–7.15 (m, 3H), 4.89 (br, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 3.96 (br, 1H), 3.45–3.35 (m, 2H), 2.96–2.82 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.3, 138.2, 138.1, 129.4, 128.4, 128.3, 127.7, 126.3, 79.2, 73.2, 70.1, 51.6, 37.9, 28.4.

HRMS (ESI-TOF): calc'd for $C_{21}H_{27}NO_3Na$ $[M+Na]^+$: 364.1889, found 364.1897.

TLC: R_f = 0.3 (6:1 hexanes:EtOAc)

Compound 19



Benzyl *tert*-butyl (5-(benzyloxy)pentane-1,4-diyl)dicarbamate (19).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-32** with RAE **49** (3.0 equiv). Purification by PTLC 0.3 (3:1 hexanes:EtOAc) afforded 25.6 mg (58%) of the title compound **19**.

Physical State: colorless oil.

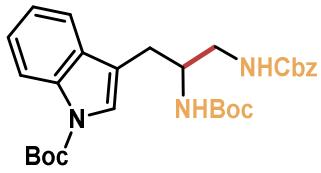
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.27 (m, 10H), 5.09 (s, 2H), 4.88 (br, 1H), 4.76 (d, *J* = 9.3 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.73 (br, 1H), 3.50–3.38 (m, 2H), 3.26–3.14 (m, 2H), 1.61–1.47 (m, 4H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.4, 155.7, 138.0, 136.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.6, 79.3, 73.2, 71.9, 66.6, 50.0, 40.9, 29.5, 28.4, 26.5.

HRMS (ESI-TOF): calc'd for $C_{25}H_{35}N_2O_5$ $[M+H]^+$: 443.2546, found 443.2545.

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

Compound 21



***Tert*-butyl-3-(3-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)propyl)-1H-indole-1-carboxylate (21).**

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-18** with RAE **9** (3.0 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 32.4 mg (62%) of the title compound **21**.

Physical State: colorless oil.

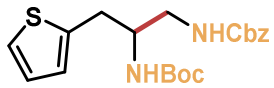
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (br, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.47–7.40 (m, 1H), 7.39–7.29 (m, 6H), 7.26–7.23 (m, 1H), 5.21–4.99 (m, 3H), 4.85 (br, 1H), 4.02 (br, 1H), 3.38 (d, *J* = 13.9 Hz, 1H), 3.26 (br, 1H), 2.96 (br, 1H), 2.84 (dd, *J* = 14.6, 7.2 Hz, 1H), 1.66 (s, 9H), 1.41 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.0, 155.9, 149.6, 136.4, 135.5, 130.4, 128.5, 128.1 (2C), 124.5, 123.8, 122.6, 119.1, 116.2, 115.3, 83.6, 79.6, 66.9, 51.2, 44.6, 28.3, 28.2.

HRMS (ESI-TOF): calc'd for $C_{29}H_{38}N_3O_6$ $[M+H]^+$: 524.2761, found 524.2756.

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

Compound 22



Benzyl *tert*-butyl (3-(thiophen-2-yl)propane-1,2-diyl)dicarbamate (22).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-19** with RAE **9** (3.0 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 21.8 mg (56%) of the title compound **22**.

Physical State: colorless oil.

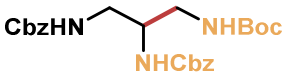
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.96–6.91 (m, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 5.23–4.97 (m, 3H), 4.83 (br, 1H), 3.90 (br, 1H), 3.45–3.28 (m, 1H), 3.25 (br, 1H), 3.10–2.96 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.0, 155.8, 139.1, 136.4, 128.5, 128.1 (2C), 127.0, 126.2, 124.3, 79.7, 66.9, 52.2, 44.3, 32.6, 28.3.

HRMS (ESI-TOF): calc'd for $C_{20}H_{26}N_2O_4SNa$ $[M+Na]^+$: 413.1511, found 413.1514.

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

Compound 23



Dibenzyl *tert*-butyl propane-1,2,3-triyltricarbamate (23).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-35** with RAE **SI-20** (3.0 equiv). Purification by PTLC (3:1 hexanes:acetone) afforded 19.2 mg (42%) of the title compound **23**.

Physical State: colorless oil.

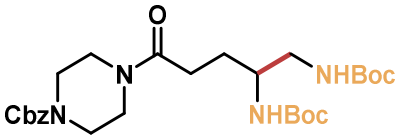
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7.30 (m, 10H), 5.80 (br, 1H), 5.64 (br, 1H), 5.23–4.96 (m, 5H), 3.74–3.61 (m, 1H), 3.52–3.42 (m, 1H), 3.41–3.31 (m, 1H), 3.31–3.15 (m, 2H).1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.6, 157.2, 156.4, 136.4, 136.3, 128.5 (2C), 128.2, 128.1 (2C), 80.0, 67.0, 66.7, 53.2, 41.5, 40.8, 28.3.

HRMS (ESI-TOF): calc'd for $C_{24}H_{31}N_3O_6Na$ $[M+Na]^+$: 480.2111, found 480.2115.

TLC: R_f = 0.3 (3:1 hexanes:acetone)

Compound 24



Benzyl 4-(4,5-bis((*tert*-butoxycarbonyl)amino)pentanoyl)piperazine-1-carboxylate (24).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-36** with RAE **SI-20** (3.0 equiv). Purification by PTLC (3:1 hexanes:acetone) afforded 25.1 mg (47%) of the title compound **24**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5H), 5.15 (s, 2H), 4.88 (br, 2H), 3.67–3.55 (m, 3H), 3.56–3.38 (m, 6H), 3.25–3.10 (m, 2H), 2.53–2.31 (m, 2H), 1.86 (dtt, J = 13.8, 6.6, 3.5 Hz, 1H), 1.78–1.64 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H).

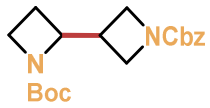
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.1, 156.6, 156.4, 155.1, 136.3, 128.6, 128.2, 128.0, 79.5,

79.3, 67.5, 51.5, 45.2, 44.6, 43.7, 41.5, 29.6, 28.4, 27.9.

HRMS (ESI-TOF): calc'd for $C_{27}H_{43}N_4O_7$ $[M+H]^+$: 535.3132, found 535.3146.

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

Compound 25



1'-benzyl 1-(*tert*-butyl) [2,3'-biazetidine]-1,1'-dicarboxylate (25).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-21** with RAE **SI-37** (3.0 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 14.9 mg (43%) of the title compound **25**.

Physical State: colorless oil.

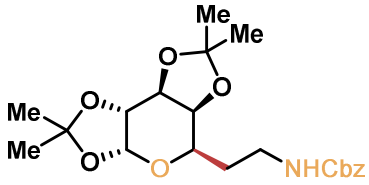
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.27 (m, 5H), 5.08 (s, 2H), 4.39 (dt, *J* = 8.6, 6.4 Hz, 1H), 4.07 (t, *J* = 8.6 Hz, 1H), 4.03 (t, *J* = 8.8 Hz, 1H), 3.96–3.82 (m, 3H), 3.77 (td, *J* = 9.0, 5.4 Hz, 1H), 3.02–2.76 (m, 1H), 2.28 (ddt, *J* = 12.2, 8.9, 3.8 Hz, 1H), 1.94–1.83 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.6, 156.3, 136.7, 128.4, 127.9, 127.9, 79.8, 66.5, 62.8, 52.1, 50.5, 49.9, 46.1, 33.0, 28.3, 18.8.

HRMS (ESI-TOF): calc'd for $C_{19}H_{26}N_2O_4Na$ $[M+Na]^+$: 369.1790, found 369.1798.

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

Compound 26



Benzyl (2-((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)ethyl)carbamate (26).

Following the **general procedure A** (with **L1**) on 0.1 mmol scale RAE **SI-22** with RAE **SI-23** (3.0 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 21.6 mg (53%) of the title compound **26**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 5.51 (d, *J* = 4.8 Hz, 1H), 5.16–5.04 (m, 3H), 4.58 (d, *J* = 7.7 Hz, 1H), 4.29 (dd, *J* = 5.4, 2.5 Hz, 1H), 4.11 (d, *J* = 7.9 Hz, 1H), 3.81 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.44–3.36 (m, 1H), 3.35–3.26 (m, 1H), 1.95–1.69 (m, 2H), 1.47 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H).

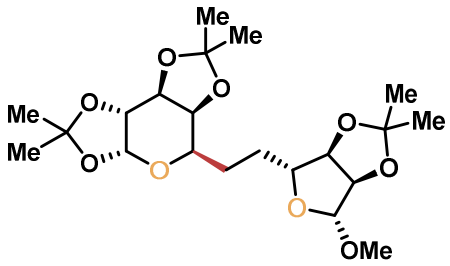
^{13}C NMR (151 MHz, $CDCl_3$) δ 156.4, 136.7, 128.4, 128.1, 128.0, 109.2, 108.4, 96.5, 72.8, 70.9, 70.4, 66.5, 65.5, 37.9, 29.4, 26.0, 25.9, 24.9, 24.3.

HRMS (ESI-TOF): calc'd for $C_{21}H_{30}NO_7$ $[M+H]^+$: 408.2022, found 408.2028.

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

$[\alpha]_D^{25}$ = –20.0 (c = 0.4, $CHCl_3$)

Compound 27



(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-5-(2-((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (27).

Following the **general procedure A** (with **L1**) on 0.1 mmol scale RAE **SI-22** with RAE **SI-38** (3.0 equiv). Purification by PTLC (6:1 hexanes:EtOAc) afforded 26.2 mg (61%) of the title compound **27**.

Physical State: white solid

m.p.: 94-96 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.52 (d, *J* = 5.1 Hz, 1H), 4.93 (s, 1H), 4.60–4.57 (m, 2H), 4.54 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.29 (dd, *J* = 5.1, 2.3 Hz, 1H), 4.21 (ddd, *J* = 9.5, 5.5, 1.0 Hz, 1H), 4.12 (dd, *J* = 7.9, 1.9 Hz, 1H), 3.76 (ddd, *J* = 9.1, 4.5, 1.8 Hz, 1H), 3.34 (s, 3H), 1.89–1.80 (m, 1H), 1.78–1.69 (m, 1H), 1.68–1.57 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H).

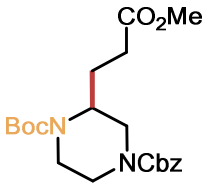
^{13}C NMR (151 MHz, $CDCl_3$): δ 112.1, 109.5, 109.0, 108.3, 96.6, 86.4, 85.6, 84.2, 72.8, 71.0, 70.5, 66.3, 55.0, 30.5, 26.5, 26.4, 26.0 (2C), 25.1, 24.9, 24.5.

HRMS (ESI-TOF): calc'd for $C_{21}H_{34}O_9Na$ $[M+Na]^+$: 453.2101, found 453.2105.

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

[α]$_D^{25}$ = –53.2 (c = 1.0, $CHCl_3$)

Compound 28



4-benzyl 1-(*tert*-butyl) 2-(3-methoxy-3-oxopropyl)piperazine-1,4-dicarboxylate (28).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-39** with RAE **SI-24** (3.0 equiv). Purification by PTLC (4:1 hexanes:EtOAc) afforded 13.8 mg (34%) of the title compound **28**.

Physical State: colorless oil.

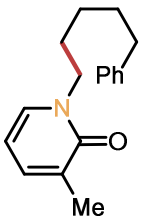
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5H), 5.16 (d, *J* = 12.6 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 4.36–3.81 (m, 4H), 3.66 (s, 3H), 3.16–2.67 (m, 3H), 2.42–2.15 (m, 2H), 2.04–1.88 (m, 1H), 1.87–1.68 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.3, 155.5, 154.5, 136.4, 128.5, 128.1, 128.0, 80.3, 67.4, 51.6, 50.4, 49.6, 46.8, 46.4, 43.7, 43.5, 38.8, 37.6, 30.3, 28.3, 24.1.

HRMS (ESI-TOF): calc'd for $C_{21}H_{31}N_2O_6$ $[M+H]^+$: 407.2182, found 407.2180.

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

Compound 29



3-methyl-1-(5-phenylpentyl)pyridin-2(1H)-one (29).

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE **SI-40** with RAE **11** (3.0 equiv). Purification by PTLC (3:1 hexanes:EtOAc) afforded 10.2 mg (40%) of the title compound **29**.

Physical State: colorless oil.

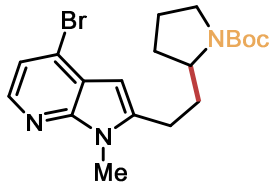
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.5 Hz, 2H), 7.19–7.13 (m, 4H), 7.08 (dd, *J* = 6.9, 1.9 Hz, 1H), 6.05 (t, *J* = 6.7 Hz, 1H), 3.90 (t, *J* = 7.2 Hz, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.14 (s, 3H), 1.77 (p, *J* = 7.6 Hz, 2H), 1.66 (p, *J* = 7.7 Hz, 2H), 1.39 (p, *J* = 7.8 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.8, 142.3, 136.4, 134.8, 129.9, 128.3, 128.2, 125.7, 105.4, 50.0, 35.7, 31.0, 29.0, 26.3, 17.2.

HRMS (ESI-TOF): calc'd for $C_{17}H_{21}NONa$ $[M+H]^+$: 278.1521, found 278.1526.

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

Compound 30



***Tert*-butyl 2-(2-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (30).**

Following the **general procedure A** (with **L2**) on 0.1 mmol scale RAE derived from 3-(4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)propanoic acid with RAE **SI-25** (3.0 equiv). Purification by PTLC (3:1 hexanes:acetone) afforded 15.0 mg (37%) of the title compound **30**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 5.2 Hz, 1H), 7.21–7.16 (m, 1H), 6.26 (s, 1H), 4.09–3.87 (m, 1H), 3.79 (s, 3H), 3.55–3.30 (m, 2H), 2.86–2.68 (m, 2H), 2.30–2.09 (m, 1H), 2.08–1.98 (m, 1H), 1.97–1.67 (m, 4H), 1.45 (s, 9H).

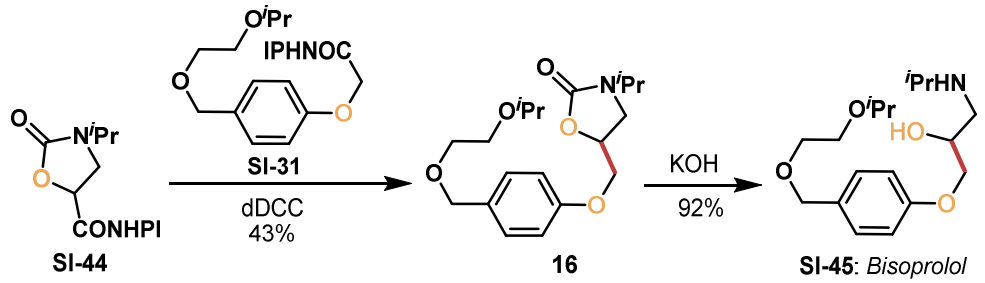
^{13}C NMR (151 MHz, $CDCl_3$): δ 154.7, 148.2, 142.8, 142.3, 141.6, 141.4, 123.6, 122.0, 118.8, 118.6, 96.8, 79.4, 79.1, 56.9 , 56.7 , 46.6, 46.2, 33.0, 32.8, 30.8, 30.3, 28.5, 28.4, 24.1, 24.0, 23.9, 23.1.

HRMS (ESI-TOF): calc'd for $C_{19}H_{27}BrN_3O_2$ $[M+H]^+$: 408.1287, found 408.1283.

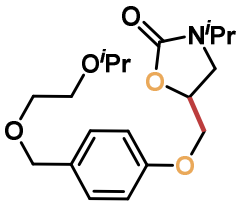
TLC: R_f = 0.5 (3:1 hexanes:acetone)

Complex Molecules Synthesis

Synthesis of bisoprolol



Compound 16



5-((4-((2-isopropoxyethoxy)methyl)phenoxy)methyl)-3-isopropyloxazolidin-2-one (16). Following the **general procedure A** (with **L1**) on 0.1 mmol RAE **SI-44** RAE (prepared in situ from **SI-3**, 3.0 equiv) with RAE **SI-31** (3.0 equiv). Purification by PTLC (3:1 hexanes:acetone) afforded 15.1 mg (43%) of the title compound **16**.

Physical State: colorless oil.

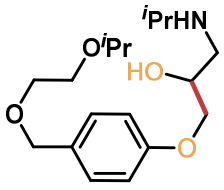
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.87–4.71 (m, 1H), 4.50 (s, 2H), 4.24–3.99 (m, 3H), 3.72–3.53 (m, 6H), 3.48 (dd, J = 8.7, 5.7 Hz, 1H), 1.20 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.7, 156.7, 131.5, 129.4, 114.4, 72.7, 71.9, 70.7, 69.5, 68.2, 67.4, 44.8, 41.9, 22.0, 19.8, 19.7.

HRMS (ESI-TOF): calc'd for $C_{19}H_{29}NO_5Na$ $[M+Na]^+$: 374.1943, found 374.1950

TLC: R_f = 0.3 (3:1 hexanes:acetone)

Compound SI-45



Bisoprolol (SI-45)

A solution of **16** (10 mg, 0.028 mmol, 1.0 equiv.) in EtOH/4N KOH (0.25 mL/0.25 mL) was refluxed for 12 h. The reaction was quenched with H_2O (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 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 (DCM:MeOH:Et_3N 40:1) to give **SI-45** (8.5 mg, 92%).

Physical State: colorless oil.

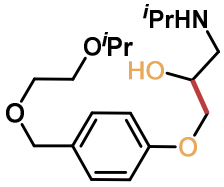
^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.39 (s, 2H), 3.96–3.91 (m, 1H), 3.89–3.83 (m, 2H), 3.54 (p, *J* = 6.1 Hz, 1H), 3.50–3.45 (m, 4H), 2.77 (p, *J* = 6.2 Hz, 1H), 2.72 (dd, *J* = 11.8, 3.9 Hz, 1H), 2.60 (dt, *J* = 13.9, 5.1 Hz, 1H), 1.07 (d, *J* = 6.1 Hz, 6H), 1.00 (dd, *J* = 6.3, 1.7 Hz, 6H).

^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ 158.1, 130.4, 129.2, 114.2, 71.7, 70.8, 70.7, 69.1, 68.0, 66.7, 49.6, 48.4, 22.4, 22.0.

HRMS (ESI-TOF): calc'd for $C_{18}H_{32}NO_4$ $[M+H]^+$: 326.2331 , found 326.2340.

TLC: R_f = 0.3 (20:1 DCM:MeOH)

Comparison of NMR data of synthetic bisoprolol (SI-45) with literature



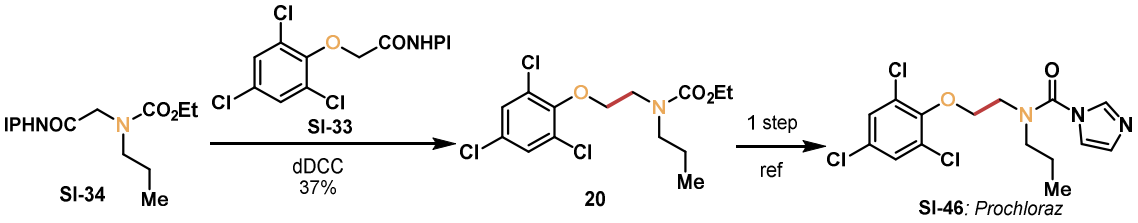
^{1}H NMR Data

Literature **SI-45**[21] ($CDCl_3$)	Synthetic **SI-45** (600 MHz, $CDCl_3$)	Δδ
7.06 (m, 4H);	7.23 (d, *J* = 8.6 Hz, 2H) 6.90 (d, *J* = 8.6 Hz, 2H)	-
4.50 (s, 2H),	4.39 (s, 2H)	-0.11
4.29 (m, IH),	3.96–3.91 (m, 1H)	-
3.99 (m, 2H)	3.89–3.83 (m, 2H)	-
3.61 (m, 5H)	3.54 (p, *J* = 6.1 Hz, 1H) 3.50–3.45 (m, 4H)	-
3.05 (m, 3H)	2.77 (p, *J* = 6.2 Hz, 1H)	-

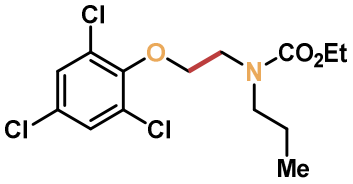
	2.72 (dd, J = 11.8, 3.9 Hz, 1H) 2.60 (dt, J = 13.9, 5.1 Hz, 1H)	
1.28 (d, 6H, J = 2.3 Hz), 1.17 (d, 6H, J = 6.3 Hz),	1.07 (d, J = 6.1 Hz, 6H) 1.00 (dd, J = 6.3, 1.7 Hz, 6H)	-0.19 -0.17

The ^{13}C NMR of **SI-45** bisoprolol is not available in the Literature.

Formal synthesis of prochloraz



Compound 20



Ethyl propyl(2-(2,4,6-trichlorophenoxy)ethyl)carbamate (20).

Following the **general procedure A** (with **L1**) on 0.1 mmol RAE **SI-34** with RAE **SI-33** (3.0 equiv). Purification by PTLC (6:1 hexanes:EtOAc) afforded 13.1 mg (37%) of the title compound **20**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 (d, J = 5.9 Hz, 2H), 4.25–4.00 (m, 4H), 3.73–3.60 (m, 2H), 3.36 (t, J = 7.5 Hz, 2H), 1.66–1.54 (m, 2H), 1.32–1.15 (m, 3H), 0.90 (t, J = 7.7 Hz, 3H).

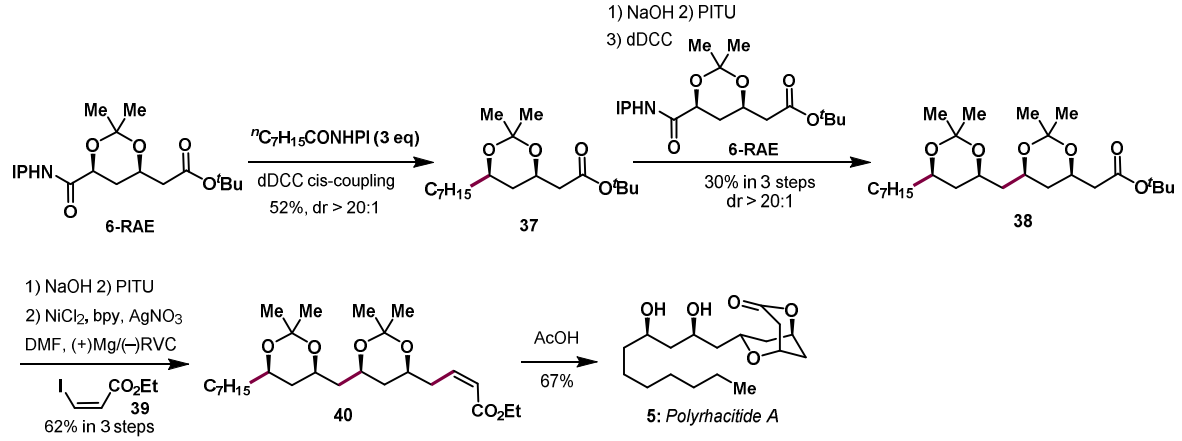
^{13}C NMR (151 MHz, $CDCl_3$): δ 156.6, 156.2, 150.4, 150.2, 130.0, 129.7, 129.6, 128.8, 72.1, 72.0, 61.2, 50.5, 50.3, 47.6, 46.7, 21.8, 21.4, 14.7, 11.2.

HRMS (ESI-TOF): calc'd for $C_{14}H_{19}Cl_3NO_3$ $[M+H]^+$: 354.0431, found 354.0438.

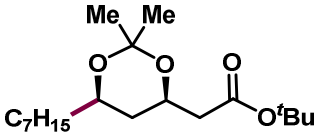
TLC: R_f = 0.3 (6:1 hexanes:EtOAc)

*Note: The ^{1}H NMR and ^{13}C NMR of **20** is not available in the Literature.*

Synthesis of polyrhacitide A



Compound 37



***Tert*-butyl 2-((4*R*,6*R*)-6-heptyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate (37).**

Following the **general procedure C** (with terpyridine) on 0.1 mmol scale **6-RAE** with **SI-28** (3.0 equiv). Purification by flash column chromatography on silica gel (16:1 hexanes:EtOAc) afforded 19.0 mg (58%) of the title compound **37**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29–4.15 (m, 1H), 3.89–3.73 (m, 1H), 2.42 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.29 (dd, *J* = 15.0, 6.2 Hz, 1H), 1.62–1.53 (m, 1H), 1.53–1.47 (m, 1H), 1.47–1.41 (m, 12H), 1.36 (s, 3H), 1.35–1.32 (m, 1H), 1.31–1.20 (m, 10H), 1.14 (q, *J* = 11.9 Hz, 1H), 0.87 (t, *J* = 6.8 Hz, 3H).

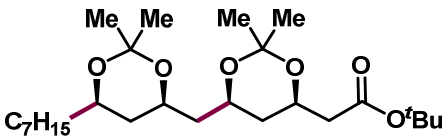
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.4, 98.5, 80.5, 68.9, 66.3, 42.8, 36.5, 36.4, 31.8, 30.2, 29.5, 29.2, 28.1, 24.9, 22.6, 19.7, 14.1.

HRMS (ESI-TOF): calc'd for $C_{19}H_{36}O_4Na$ $[M+Na]^+$: 351.2511, found 351.2512.

TLC: R_f = 0.4 (16:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +5.4 (c = 1.0, $CHCl_3$).

Compound 38



***Tert*-butyl 2-((4*R*,6*R*)-6-(((4*R*,6*R*)-6-heptyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (38).**

To a solution of **37** (32.8 mg, 0.1 mmol, 1.0 equiv) in MeOH (0.3 mL) was 2 M NaOH (0.1 mL) and the mixture was then stirred at 60 ºC for 12 h. 1 N HCl (90 µL) was added, and the solvent of the mixture was removed under vacuum. Traces of MeOH and H_2O were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in CH_3CN (0.5 ml), PITU (44.8 mg, 0.11 mmol, 1.1 equiv) and DIPEA (8.7 µL, 0.05 mmol, 0.5 equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **RAE** as a colorless oil and directly used for the next reaction.

Following the **general procedure C** (with terpyridine) on the crude **RAE** (from last step) with **6-RAE** (3.0 equiv). Purification by flash column chromatography on silica gel (9:1 hexanes:EtOAc) afforded 13.7 mg (30% in 2 steps) of the title compound **38**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.34–4.18 (m, 1H), 4.10–3.89 (m, 2H), 3.85–3.72 (m, 1H), 2.43 (dd, *J* = 15.0, 7.1 Hz, 1H), 2.30 (dd, *J* = 14.9, 6.0 Hz, 1H), 1.80 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.61–1.57 (m, 1H), 1.53–1.42 (m, 15H), 1.41 (s, 3H), 1.37 (s, 3H), 1.37–1.33 (m, 4H), 1.34–1.05 (m, 12H), 0.88 (t, *J* = 6.6 Hz, 3H).

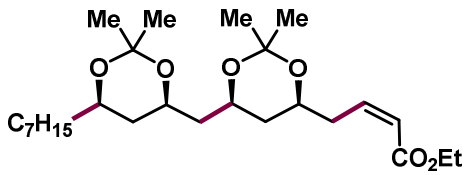
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 98.6, 98.3, 80.6, 69.0, 66.3, 65.2 (2C), 42.8, 42.7, 36.8, 36.5, 36.2, 31.8, 30.3, 30.1, 29.6, 29.2, 28.1, 25.0, 22.6, 19.8, 19.7, 14.1.

HRMS (ESI-TOF): calc'd for $C_{26}H_{48}O_6Na$ $[M+Na]^+$: 479.3349, found 479.3355.

TLC: R_f = 0.3 (9:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +2.0 (c = 0.28, $CHCl_3$).

Compound 40



Ethyl (*Z*)-4-((4*S*,6*S*)-6-(((4*R*,6*R*)-6-heptyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)but-2-enoate (40).

To a solution of **38** (9.1 mg, 0.02 mmol, 1.0 equiv) in MeOH (0.4 mL) was 1 M NaOH (0.3 mL) and the mixture was then stirred at 60 ºC for 12 h. 1 N HCl (0.275 mL) was added, and the solvent of the mixture was removed under vacuum. At this time, the reaction mixture was dissolved in CH_3CN (0.25 ml), PITU (12.2 mg, 0.03 mmol, 1.5 equiv) and DIPEA (1.8 µL, 0.01 mmol, 0.5 equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **RAE** as a colorless oil and directly used for the next reaction.

An ElectraSyn vial (5 mL) with a stir bar was charged with the crude **RAE** (from last step) and $AgNO_3$ (0.01 mmol, 1.7 mg, 0.5 equiv), $NiCl_2 \cdot 6H_2O$ (0.004 mmol, 0.95 mg, 0.2 equiv) and bpy (0.004 mmol, 0.63 mg, 0.2 equiv) in DMF (0.3 mL), anhydrous DMF (2.7 mL) were added. An ElectraSyn vial cap equipped with anode (Mg) and cathode (RVC) 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 6 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 The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (9:1 hexanes:EtOAc) to give **40** (6.2 mg, 62% in 2 steps).

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.36 (dt, *J* = 11.6, 7.1 Hz, 1H), 5.84 (d, *J* = 11.6 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.06–3.91 (m, 3H), 3.84–3.68 (m, 1H), 2.98–2.88 (m, 1H), 2.82– 2.58(m, 1H), 1.79 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.52–1.44 (m, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.36–1.33 (m, 1H), 1.32–1.19 (m, 12H), 1.18–1.07 (m, 1H), 0.87 (t, *J* = 6.8 Hz, 3H).

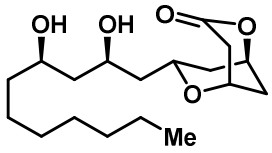
^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4, 145.8, 121.0, 98.5, 98.3, 69.0, 68.4, 65.2, 59.8, 42.7, 36.8, 36.5, 36.3, 35.6, 31.8, 30.3, 30.2, 29.5, 29.2, 25.0, 22.6, 19.8, 14.3.

HRMS (ESI-TOF): calc'd for $C_{26}H_{46}O_6Na$ $[M+Na]^+$: 477.3192, found 477.3200.

TLC: R_f = 0.5 (9:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = –16.1 (c = 0.36, $CHCl_3$).

Compound 5



Polyrhacitide A (5).

A solution of **40** (8.0 mg, 0.018 mmol, 1.0 equiv) in AcOH/H_2O (0.4 mL/0.1 mL) was heated at 100 °C and stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 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 (DCM:MeOH 40:1) to give **5** (3.9 mg, 67%).

Physical State: white solid.

m.p.: 70-72 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.90–4.86 (m, 1H), 4.41 (br, 1H), 4.12–4.01 (m, 2H), 3.88–3.79 (m, 1H), 2.91 (d, *J* = 19.3 Hz, 1H), 2.81 (dd, *J* = 19.0, 5.5 Hz, 1H), 2.07–1.92 (m, 3H), 1.77–1.36 (m, 8H), 1.35–1.20 (m, 9H), 0.87 (t, *J* = 7.0 Hz, 3H).

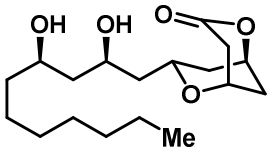
^{13}C NMR (151 MHz, $CDCl_3$): δ 169.2, 72.7, 72.5, 72.2, 67.0, 66.0, 43.3, 43.0, 37.8, 37.2, 36.4, 31.8, 29.6, 29.5, 29.3, 25.4, 22.6, 14.1.

HRMS (ESI-TOF): calc'd for $C_{18}H_{33}O_5$ $[M+H]^+$: 329.2328, found 329.2334.

TLC: R_f = 0.3 (DCM:MeOH 40:1).

$[\alpha]_D^{25}$ = +7.0 (c = 0.2, MeOH). (lit. $[\alpha]_D^{30}$ = +7.8 (*c* = 0.4, MeOH))[22].

Comparison of NMR data of synthetic polyrhacitide A (5) with literature



^{1}H NMR Data

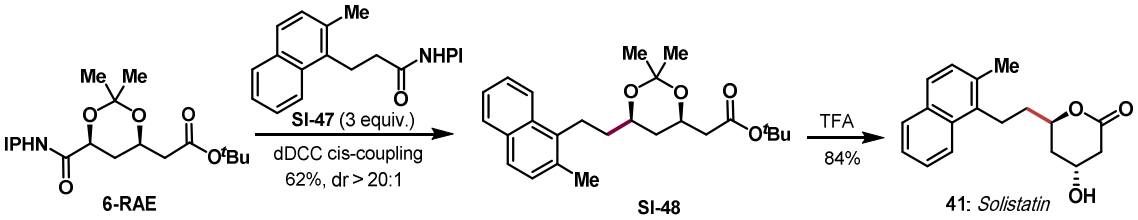
Literature **5**[22] (300 MHz, $CDCl_3$)	Synthetic **5** (600 MHz, $CDCl_3$)	Δδ
4.86–4.83 (m, 1H)	4.90–4.86 (m, 1H)	-
4.38 (br, 1H)	4.41 (br, 1H)	0.03
4.07–4.00 (m, 2H)	4.12–4.01 (m, 2H)	-

3.82–3.76 (m, 1H)	3.88–3.79 (m, 1H)	-
2.88 (d, *J* = 19.2 Hz, 1H)	2.91 (d, *J* = 19.3 Hz, 1H)	0.03
2.77 (d, *J* = 19.2 Hz, 1H)	2.81 (dd, *J* = 19.0, 5.5 Hz, 1H)	0.04
2.07–1.99 (m, 3H)	2.07–1.92 (m, 3H)	-
1.76–1.44 (m, 8H)	1.77–1.36 (m, 8H)	-
1.42–1.24 (m, 9H)	1.35–1.20 (m, 9H)	-
0.88 (t, *J* = 6.7 Hz, 3 H)	0.87 (t, *J* = 7.0 Hz, 3H)	-0.01

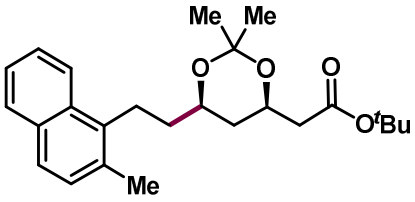
^{13}C NMR Data

Literature **5**[22] (75 MHz, $CDCl_3$)	Synthetic **5** (151 MHz, $CDCl_3$)	Δδ
168.2	169.2	1.0
72.6	72.7	0.1
72.1	72.5,	0.4
72.0	72.2	0.2
67.0	67.0	0
66.1	66.0	-0.1
43.5	43.3	-0.2
43.1	43.0	-0.1
37.9	37.8	-0.1
37.4	37.2	-0.2
36.5	36.4	-0.1
31.9	31.8	-0.1
29.7	29.6	-0.1
29.7	29.5	-0.2
29.4	29.3	-0.1
25.5	25.4	-0.1
22.8	22.6	-0.2
14.3	14.1.	-0.2

Synthesis of solistatin



Compound SI-48



***Tert*-butyl 2-((4*R*,6*R*)-2,2-dimethyl-6-(2-(2-methylnaphthalen-1-yl)ethyl)-1,3-dioxan-4-yl)acetate (SI-48).**

Following the **general procedure C** (with terpyridine) on 0.1 mmol scale **6-RAE** with **SI-47** (prepared in situ from **SI-6**, 3.0 equiv). Purification by PTLC (9:1 hexanes:EtOAc) afforded 24.6 mg (62%) of the title compound **SI-48**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 4.33–4.17 (m, 1H), 4.00–3.85 (m, 1H), 3.26–3.16 (m, 1H), 3.15–3.05 (m, 1H), 2.50 (s, 3H), 2.45 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.31 (dd, *J* = 15.2, 6.3 Hz, 1H), 1.87–1.67 (m, 2H), 1.59 (d, *J* = 11.0 Hz, 1H), 1.48 (s, 3H), 1.48–1.41 (m, 12H), 1.32–1.21 (m, 1H)..

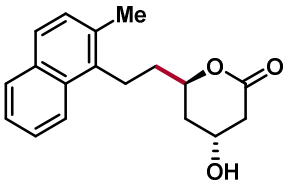
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 135.3, 132.9, 132.5, 132.1, 129.2, 128.5, 126.0, 125.8, 124.4, 123.8, 98.7, 80.6, 68.4, 66.2, 42.7, 36.5 (2C), 30.2, 28.1, 23.8, 20.1, 19.8.

HRMS (ESI-TOF): calc'd for $C_{25}H_{34}O_4Na$ $[M+Na]^+$: 421.2355, found 421.2351.

TLC: R_f = 0.5 (9:1 hexanes:EtOAc).

$[\alpha]_D^{25}$ = +6.8 (c = 0.5, $CHCl_3$).

Compound 41



Solistatin (41).

To a solution of **SI-48** (11 mg, 0.028 mmol, 1.0 equiv) in DCM (2 mL) was added TFA (0.4 mL) at 0 °C. The mixture was then stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 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 PTLC with acetone/hexane (1:3) as the eluent to give **41** (6.5 mg, 84%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.50 (td, *J* = 8.4, 1.4 Hz, 1H), 7.41 (td, *J* = 8.0, 1.1 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 4.88–4.81 (m, 1H), 4.45–4.38 (m, 1H), 3.45–3.35 (m, 1H), 3.23–3.12 (m, 1H), 2.79 (dd, *J* = 17.6, 5.0 Hz, 1H), 2.68 (ddd, *J* = 17.6, 3.7, 1.7 Hz, 1H), 2.52 (s, 3H), 2.05–1.97 (m, 2H), 1.96–1.88 (m, 1H), 1.88–1.80 (m, 1H).

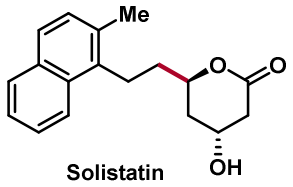
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 134.2, 133.1, 132.6, 131.9, 129.2, 128.6, 126.4, 126.1, 124.6, 123.3, 75.5, 62.9, 38.7, 36.1, 35.6, 24.0, 20.1.

HRMS (ESI-TOF): calc'd for $C_{18}H_{20}O_3Na$ $[M+Na]^+$: 307.1310, found 307.1313.

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

$[\alpha]_D^{25}$ = +26.0 (c = 0.35, $CHCl_3$). (lit. $[\alpha]_D^{20}$ = +29.1 (*c* = 0.17, $CHCl_3$))[23]

Comparison of NMR data of synthetic solistatin (41) with literature



Solistatin

^{1}H NMR Data

Literature **41**[23] (400 MHz, $CDCl_3$)	Synthetic **41** (600 MHz, $CDCl_3$)	Δδ
8.04 (d, *J* = 8.6 Hz, 1H)	8.03 (d, *J* = 8.5 Hz, 1H)	-0.01
7.81 (d, *J* = 7.9 Hz, 1H)	7.80 (dd, *J* = 8.1, 1.3 Hz, 1H)	-0.01
7.64 (d, *J* = 8.3 Hz, 1H)	7.64 (d, *J* = 8.3 Hz, 1H)	0
7.5 (dt, *J* = 7.6, 1.3 Hz, 1H)	7.50 (td, *J* = 8.4, 1.4 Hz, 1H)	0

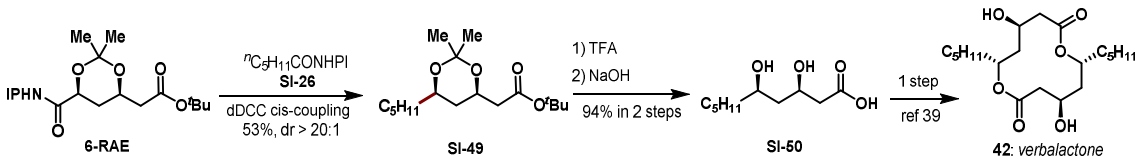
7.41 (t, *J* = 7.6 Hz, 1H)	7.41 (td, *J* = 8.0, 1.1 Hz, 1H)	0
7.30 (d, *J* = 8.3 Hz, 1H)	7.30 (d, *J* = 8.4 Hz, 1H)	0
4.85 (m, 1H)	4.88–4.81 (m, 1H)	-
4.42 (m, 1H)	4.45–4.38 (m, 1H)	-
3.41 (m, 1H)	3.45–3.35 (m, 1H)	-
3.19 (m, 1H)	3.23–3.12 (m, 1H)	-
2.80 (dd, *J* = 17.0, 5.0 Hz, 1H)	2.79 (dd, *J* = 17.6, 5.0 Hz, 1H)	-0.01
2.67 (ddd, *J* = 17.0, 3.6, 1.6 Hz,1H)	2.68 (ddd, *J* = 17.6, 3.7, 1.7 Hz, 1H)	-0.01
2.52 (s, 3H)	2.52 (s, 3H)	0
2.03-1.98 (m, 2H)	2.05–1.97 (m, 2H)	-
1.93 (m, 1H)	1.96–1.88 (m, 1H)	-
1.86 (dt, *J* = 12.9, 3.3 Hz, 1H)	1.88–1.80 (m, 1H)	-

^{13}C NMR Data

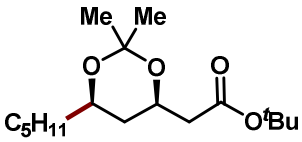
Literature **41**[23] (101 MHz, $CDCl_3$)	Synthetic **41** (151 MHz, $CDCl_3$)	Δδ
170.1	170.3	0.2
134.2	134.2	0
133.2	133.1	-0.1
132.6	132.6	0
132.0	131.9	-0.1
129.3	129.2	-0.1
128.7	128.6	-0.1
126.5	126.4	-0.1-
126.2	126.1	-0.1
124.6	124.6	-0
123.4	123.3	-0.1
75.5	75.5	0
63.0	62.9	-0.1
38.8	38.7	-0.1
36.2	36.1	-0.1
35.7	35.6	-0.1
24.1	24.0	-0.1

20.2	20.1	-0.1

Formal synthesis of verbalactone



Compound SI-49



***Tert*-butyl 2-((4*R*,6*R*)-2,2-dimethyl-6-pentyl-1,3-dioxan-4-yl)acetate (SI-49).**

Following the **general procedure C** (with terpyridine) on 0.1 mmol scale **6-RAE** with RAE **SI-26** (3.0 equiv). Purification by flash column chromatography on silica gel (16:1 hexanes:EtOAc) afforded 15.9 mg (53%) of the title compound **SI-49**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29–4.16 (m, 1H), 3.87–3.74 (m, 1H), 2.42 (dd, *J* = 15.0, 7.1 Hz, 1H), 2.29 (dd, *J* = 15.1, 6.2 Hz, 1H), 1.56 (dt, *J* = 12.9, 2.6 Hz, 1H), 1.52–1.47 (m, 1H), 1.46–1.42 (m, 12H), 1.40–1.32 (m, 5H), 1.34–1.22 (m, 5H), 1.19–1.10 (m, 1H), 0.88 (t, *J* = 7.0 Hz, 3H).

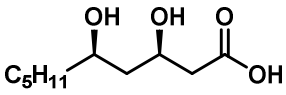
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.4, 98.6, 80.5, 68.9, 66.3, 42.8, 36.5, 36.4, 31.8, 30.2, 28.1, 24.6, 22.6, 19.7, 14.0.

HRMS (ESI-TOF): calc'd for $C_{17}H_{32}O_4Na$ $[M+Na]^+$: 323.2198, found 323.2204.

TLC: R_f = 0.4 (16:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = +7.1 (c = 1.0, $CHCl_3$).

Compound SI-50



(3*R*,5*R*)-3,5-dihydroxydecanoic acid (SI-50).

To a solution of **SI-49** (30.0 mg, 0.1 mmol, 1.0 equiv) in DCM (0.25 mL) was added TFA (50 μL) at 0 °C. The mixture was then stirred at room temperature for 4 h. The solvent was removed

under vacuum. At this time, the reaction mixture was dissolved in THF/H_2O (0.4 ml/0.1mL) and NaOH (13μL, 8 M in MeOH) was added. The mixture was then stirred at room temperature for 12 h. A citric acid–sodium hydroxide buffer (pH 6, 1 ml) was added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **SI-50** (19.2 mg, 94%). (Since **SI-50** was found to be unstable, the NMR was done in CD_3OD with Na_2CO_3)

Physical State: colorless oil.

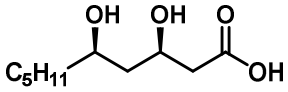
^{1}H NMR (600 MHz, CD_3OD): δ 4.13–4.06 (m, 1H), 3.80–3.71 (m, 1H), 2.36 (dd, *J* = 15.0, 4.9 Hz, 1H), 2.28 (dd, *J* = 15.0, 7.7 Hz, 1H), 1.59 (t, *J* = 6.5 Hz, 2H), 1.51–1.39 (m, 3H), 1.38–1.25 (m, 5H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, CD_3OD): δ 180.5, 71.2, 69.4, 45.5, 44.8, 38.5, 33.1, 26.3, 23.7, 14.4.

HRMS (ESI-TOF): calc'd for $C_{10}H_{20}O_4Na$ $[M+Na]^+$: 227.1259, found 227.1261.

$[\alpha]_D^{25}$ = +13.3 (c = 0.15, $CHCl_3$). (lit. $[\alpha]_D^{25}$ = +15.0 (*c* = 0.23, $CHCl_3$))[24].

Comparison of NMR data of synthetic SI-50 with literature



^{1}H NMR Data

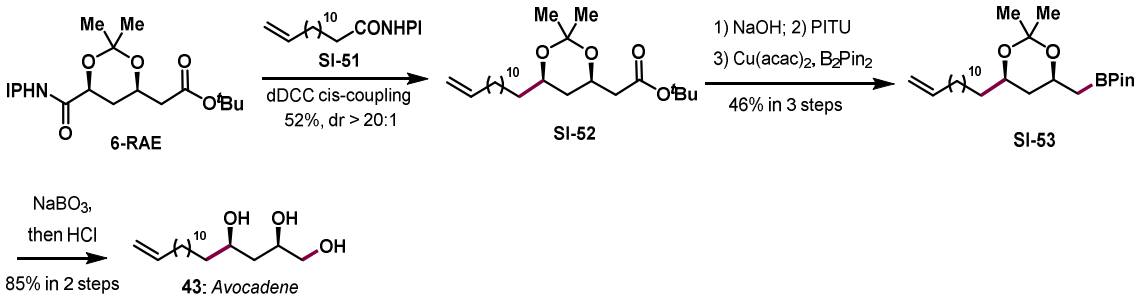
Literature **SI-50**[24] (CD_3OD, 300 MHz)	Synthetic **SI-50** (CD_3OD, 600 MHz)	Δδ
4.19–4.06 (m, 1H)	4.13–4.06 (m, 1H)	-
3.81–3.69 (m, 1H)	3.80–3.71 (m, 1H)	-
2.38 (dd, *J* = 15.0, 6.0 Hz, 1H)	2.36 (dd, *J* = 15.0, 4.9 Hz, 1H)	-0.02
2.28 (dd, *J* = 15.0, 9.0 Hz, 1H)	2.28 (dd, *J* = 15.0, 7.7 Hz, 1H)	0
1.59 (t, *J* = 6.0 Hz, 2H)	1.59 (t, *J* = 6.5 Hz, 2H)	0
1.52–1.38 (m, 3H)	1.51–1.39 (m, 3H)	-
1.40–1.20 (m, 5H)	1.38–1.25 (m, 5H)	-
0.91 (t, *J* = 6.0 Hz, 3H)	0.91 (t, *J* = 7.0 Hz, 3H)	0

^{13}C NMR Data

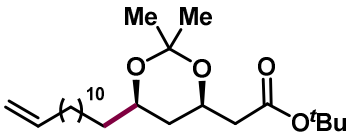
Literature **SI-50**[24]	Synthetic **SI-50**	Δδ

(400 MHz)	(600 MHz)	
180.1	180.5	0.4
71.3	71.2	-0.1
69.4	69.4	0
45.3	45.5	0.2
44.8	44.8	0
38.6	38.5	-0.1
33.1	33.1	0
26.2	26.3	0.1
23.7	23.7	0
14.3	14.4	0.1

Synthesis of avocadene



Compound SI-52



***Tert*-butyl 2-((4*R*,6*R*)-2,2-dimethyl-6-(tridec-12-en-1-yl)-1,3-dioxan-4-yl)acetate (SI-52).** Following the **general procedure C** (with terpyridine) on 0.1 mmol scale **6-RAE** with **SI-51** (prepared in situ from tetradec-13-enoic acid[37], 3.0 equiv) Purification by flash column chromatography on silica gel (16:1 hexanes:EtOAc) afforded 21.3 mg (52%) of the title compound **SI-52**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.95–5.65 (m, 1H), 4.95 (dd, *J* = 38.6, 13.7 Hz, 2H), 4.38–4.06 (m, 1H), 3.92–3.69 (m, 1H), 2.42 (dd, *J* = 15.7, 7.2 Hz, 1H), 2.29 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.56 (dd, *J* = 12.9, 2.4 Hz, 1H), 1.47–1.41 (m, 12H), 1.40–1.31 (m, 7H), 1.30–1.21 (m, 18H), 1.14 (q, *J* = 11.6 Hz, 1H).

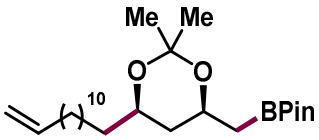
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.4, 139.2, 114.1, 98.6, 80.5, 68.9, 66.3, 42.8, 36.5, 36.4, 33.8, 30.2, 29.6 (three peaks), 29.5, 29.1, 28.9, 28.1, 24.9, 19.7.

HRMS (ESI-TOF): not found

TLC: R_f = 0.4 (16:1 hexanes:EtOAc)

[α]$_D^{25}$ = -0.6 (c = 0.67, $CHCl_3$).

Compound SI-53



2-(((4*S*,6*R*)-2,2-dimethyl-6-(tridec-12-en-1-yl)-1,3-dioxan-4-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (SI-53).

To a solution of **SI-52** (39.5 mg, 0.1 mmol, 1.0 equiv) in MeOH (0.3 mL) was 2 M NaOH (0.1 mL) and the mixture was then stirred at 60 °C for 12 h. 1 N HCl (90 μL) was added, and the solvent of the mixture was removed under vacuum. At this time, the reaction mixture was dissolved in CH_3CN (0.5 ml), PITU (44.8 mg, 0.11 mmol, 1.1 equiv) and DIPEA (8.7 μL, 0.05 mmol, 0.5 equiv) were added The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **RAE** as a colorless oil and directly used for the next reaction.

To a 5 mL culture tube equipped with a stir bar were added crude **RAE** (from last step), B_2pin_2 (77 mg, 0.3 mmol, 3.0 equiv), LiOH•H_2O (60 mg, 1.5 mmol, 15.0 equiv), $Cu(acac)_2$ (8.0 mg, 0.03 mol, 0.3 equiv) and $MgCl_2$ (14.5 mg, 0.15 mmol, 1.5 equiv). The tube was evacuated and backfilled with argon for 3 times. Degassed dioxane/DMF (4/1, 0.7 ml) was added, and the resulting mixture was stirred at RT until dark brown color was observed. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with (9:1 hexanes:EtOAc) as the eluent to give **SI-53** (20.5 mg, 46%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.08–4.83 (m, 2H), 4.09–3.98 (m, 1H), 3.86–3.69 (m, 1H), 2.08–1.98 (m, 2H), 1.57–1.53 (m, 1H), 1.42 (s, 3H), 1.39–1.33 (m, 6H), 1.30–1.22 (m, 30H), 1.11–1.08 (m, 1H), 1.01 (dd, *J* = 15.1, 8.1 Hz, 1H).

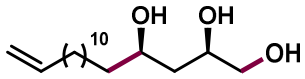
^{13}C NMR (151 MHz, $CDCl_3$): δ 139.3, 114.1, 98.3, 83.1, 69.2, 66.9, 38.9, 36.4, 33.8, 30.4, 29.6 (four peaks), 29.5, 29.2, 28.9, 25.0, 24.8, 24.7, 19.9.

HRMS (ESI-TOF): calc'd for $C_{26}H_{49}BO_4Na$ $[M+Na]^+$: 459.3616, found 459.3597.

TLC: R_f = 0.5 (9:1 hexanes:EtOAc)

[α]$_D^{25}$ = +4.6 (c = 0.9, $CHCl_3$).

Compound 43



Avocadene (43).

To a solution of **SI-53** (10 mg, 0.024 mmol, 1.0 equiv) in THF/H_2O (1:1, 1 mL) was added $NaBO_3 \cdot 4H_2O$ (22 mg, 0.144 mmol, 6.0 equiv) at room temperature. The mixture was stirred for 10 min before 1 N HCl (0.1 mL) was added. The resulting solution was stirred for another 10 min. The reaction was quenched with H_2O (5 mL). The resulting mixture was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with (20:1 DCM:MeOH) as the eluent to give **43** (5.6 mg, 85%).

Physical State: white solid.

m.p.: 61-63 ºC.

^{1}H NMR (600 MHz, CD_3OD): δ 5.93–5.72 (m, 1H), 4.98 (d, *J* = 17.1 Hz, 1H), 4.91 (d, *J* = 10.3 Hz, 1H), 3.86–3.70 (m, 2H), 3.50 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.46 (dd, *J* = 11.2, 5.7 Hz, 1H), 2.14–1.97 (m, 2H), 1.66 (dt, *J* = 13.9, 4.1 Hz, 1H), 1.57–1.22 (m, 21H).

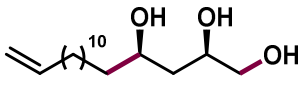
^{13}C NMR (151 MHz, CD_3OD): δ 140.1, 114.7, 72.1, 71.2, 67.2, 41.2, 38.6, 34.9, 30.9, 30.8, 30.7 (two peaks), 30.6, 30.2, 30.1, 26.6.

HRMS (ESI-TOF): calc'd for $C_{17}H_{34}O_3Na$ $[M+Na]^+$: 309.2406, found 309.2418.

TLC: R_f = 0.3 (20:1 DCM:MeOH)

[α]$_D^{25}$ = –2.4 (c = 0.3, $CHCl_3$). (lit. $[\alpha]_D$ = -5.4 (*c* = 1.1, $CHCl_3$))[25].

Comparison of NMR data of synthetic avocadene (43) with literature



Avocadene

^{1}H NMR Data

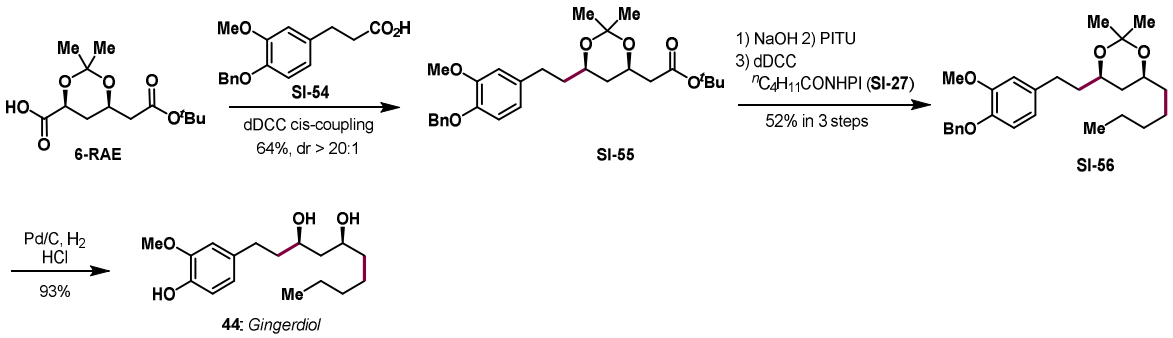
Literature **43**[25] (700 MHz, CD_3OD)	Synthetic **43** (600 MHz, CD_3OD)	Δδ
5.80 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H)	5.93–5.72 (m, 1H)	-
4.99-4.95 (m, 1H)	4.98 (d, *J* = 17.1 Hz, 1H)	-
4.90 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H)	4.91 (d, *J* = 10.3 Hz, 1H)	0.01
3.83-3.72 (m, 2H)	3.86–3.70 (m, 2H)	-
3.49 (dd, *J* = 11.2, 4.6 Hz, 1H)	3.50 (dd, *J* = 11.2, 4.1 Hz, 1H)	0.01
3.45 (dd, *J* = 11.2, 6.0 Hz, 1H)	3.46 (dd, *J* = 11.2, 5.7 Hz, 1H)	0.01
2.07-2.00 (m, 2H)	2.14–1.97 (m, 2H)	-
1.65 (app dt, *J* = 14.1, 4.5 Hz, 1H)	1.66 (dt, *J* = 13.9, 4.1 Hz, 1H)	0.01
1.56-1.20 (m, 21H)	1.57–1.22 (m, 21H)	-

^{13}C NMR Data

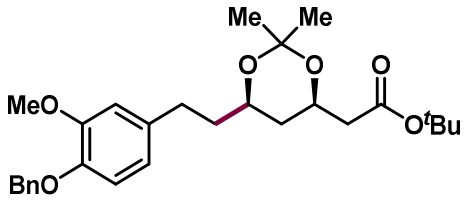
Literature **43**[25] (176 MHz, CD_3OD)	Synthetic **43** (151 MHz, CD_3OD)	Δδ
140.2	140.1	-0.1
114.7	114.7	0
72.2	72.1	-0.1
71.2	71.2	0
67.3	67.2	-0.1
41.2	41.2	0
38.7	38.6	-0.1
34.9	34.9	0
30.8 (3C)	30.9	-
30.7	30.8	-
	30.7 (2C)	-
30.6	30.6	0
30.2	30.2	0

30.1	30.1	0
26.6	26.6	0

Synthesis of gingerdiol



Compound SI-55



***Tert*-butyl 2-((4*R*,6*R*)-6-(4-(benzyloxy)-3-methoxyphenethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (SI-55).**

Following the **general procedure C** (with terpyridine) on 0.1 mmol scale **6-RAE** with **SI-54** (prepared in situ from **SI-7**, 3.0 equiv). Purification by PTLC (9:1 hexanes:EtOAc) afforded 30.1 mg (64%) of the title compound **SI-55**.

Physical State: white solid.

m.p.: 53-55 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 6.64 (dd, *J* = 8.1, 1.9 Hz, 1H), 5.12 (s, 2H), 4.25–4.16 (m, 1H), 3.87 (s, 3H), 3.85–3.77 (m, 1H), 2.71–2.63 (m, 1H), 2.62–2.54 (m, 1H), 2.43 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.29 (dd, *J* = 15.1, 6.2 Hz, 1H), 1.85–1.75 (m, 1H), 1.70–1.61 (m, 1H), 1.54 (dt, *J* = 12.7, 2.5 Hz, 1H), 1.44 (s, 9H), 1.43 (s, 3H), 1.40 (s, 3H), 1.21 (q, *J* = 11.9 Hz, 1H).

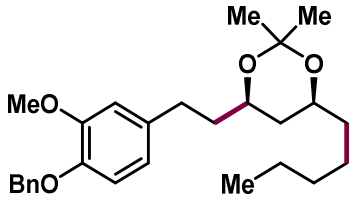
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 149.5, 146.3, 137.4, 135.3, 128.5, 127.7, 127.3, 120.3, 114.2, 112.4, 98.7, 80.6, 71.2, 67.7, 66.2, 56.0, 42.7, 38.0, 36.6, 30.7, 30.2, 28.1, 19.8.

HRMS (ESI-TOF): calc'd for $C_{28}H_{38}O_6Na$ $[M+Na]^+$: xx 493.2566, found 493.2569.

TLC: R_f = +0.3 (9:1 hexanes:EtOAc)

[α]D^{25} = +17.6 (c = 1.0, $CHCl_3$).

Compound SI-56



(4*R*,6*S*)-4-(4-(benzyloxy)-3-methoxyphenethyl)-2,2-dimethyl-6-pentyl-1,3-dioxane (SI-56).

To a solution of **SI-55** (47.0 mg, 0.1 mmol, 1.0 equiv) in MeOH (0.3 mL) was 2 M NaOH (0.1 mL) and the mixture was then stirred at 60 ºC for 12 h. 1 N HCl (90 µL) was added, and the solvent of the mixture was removed under vacuum. Traces of MeOH and H_2O were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in CH_3CN (0.5 ml), PITU (44.8 mg, 0.11 mmol, 1.1 equiv) and DIPEA (8.7 µL, 0.05 mmol, 0.5 equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **RAE** as a white foam and directly used for the next reaction.

An ElectraSyn vial (5 mL) with a stir bar was charged with the crude **RAE** (from last step), RAE **SI-27** (74.1 mg, 0.3 mmol, 3.0 equiv), $NiCl_2$dme (4.4 mg, 0.02 mmol, 0.2 equiv.), terpyridine (4.7 mg, 0.02 mmol, 0.2 equiv.), NaI (89.9 mg, 0.6 mmol, 6 equiv.), and anhydrous DMF (3.0 mL) were 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. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by PTLC EtOAc/hexane (1:20) as the eluent to give **SI-56** (22.1 mg, 52%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 6.8 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.65 (dd, *J* = 8.1, 2.0 Hz, 1H), 5.12 (s, 2H), 3.87 (s, 3H), 3.83–3.72 (m, 2H), 2.71–2.63 (m, 1H), 2.63–2.55 (m, 1H), 1.85–1.76 (m, 1H), 1.71–1.61 (m, 1H), 1.53–1.44 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.39–1.33 (m, 2H), 1.33–1.23 (m, 5H), 1.19–1.11 (m, 1H), 0.88 (t, *J* = 7.0 Hz, 3H).

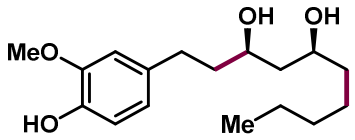
^{13}C NMR (151 MHz, $CDCl_3$): δ 149.5, 146.2, 137.4, 135.4, 128.5, 127.7, 127.3, 120.3, 114.2, 112.4, 98.4, 71.2, 69.0, 67.9, 55.9, 38.1, 37.0, 36.4, 31.8, 30.7, 30.3, 24.6, 22.6, 19.9, 14.0.

HRMS (ESI-TOF): calc'd for $C_{27}H_{38}O_4Na$ $[M+Na]^+$: 449.2668, found 449.2659.

TLC: R_f = 0.5 (9:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = +15.0 (c = 1.0, $CHCl_3$).

Compound 44



Gingerdiol (44).

To a solution of **SI-56** (10.0 mg, 0.023 mmol, 1.0 equiv) in MeOH (0.8 mL) was added 3 N HCl (0.4 ml). The mixture was then stirred at room temperature for 1 h. At this time, 10% Pd/C (2 mg) was added. The resulting heterogeneous suspension was flushed with hydrogen for 5 minutes and then left under a hydrogen atmosphere for 5 h. The resulting suspension was diluted with ethyl acetate (5 mL) and filtered through a short pad of celite which was then washed with ethyl acetate (5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by PTLC with (1:1 hexanes:EtOAc) as the eluent to give **44** (8.4 mg, 93%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.47 (br, 1H), 3.88 (s, 3H), 3.92–3.81 (m, 2H), 2.70 (ddd, *J* = 14.8, 9.6, 5.9 Hz, 1H), 2.62 (ddd, *J* = 13.9, 9.3, 6.8 Hz, 1H), 2.41 (br, 2H), 1.84–1.69 (m, 2H), 1.62 (dt, *J* = 14.5, 2.3 Hz, 1H), 1.56–1.23 (m, 9H), 0.89 (t, *J* = 6.6 Hz, 3H).

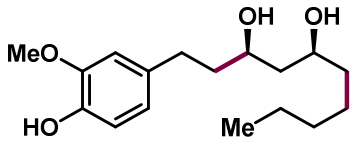
^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 143.7, 133.9, 120.9, 114.2, 111.0, 73.3, 72.3, 55.9, 43.0, 40.0, 38.3, 31.8, 31.4, 25.0, 22.6, 14.0.

HRMS (ESI-TOF): calc'd for $C_{17}H_{28}O_4Na$ $[M+Na]^+$: 319.1885, found 319.1897.

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

$[\alpha]_D^{25}$ = +7.1 (c = 0.28, $CHCl_3$). (lit. $[\alpha]_D^{20}$ = +8.2 (*c* = 2.0, $CHCl_3$))[26]

Comparison of NMR data of synthetic gingerdiol (44) with literature



Gingerdiol

^{1}H NMR Data

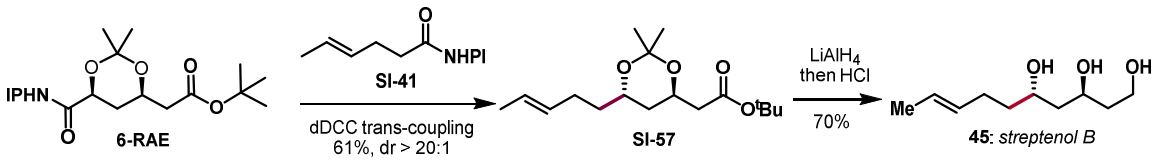
Literature **44**[26] (400 MHz, $CDCl_3$)	Synthetic **44** (600 MHz, $CDCl_3$)	Δδ
6.82 (d, *J* = 8.0 Hz, 1 H)	6.83 (d, *J* = 8.0 Hz, 1H)	0.01
6.69 (dd, *J* = 11.3, 3.3 Hz, 2H)	6.71 (d, *J* = 2.0 Hz, 1H)	-
	6.69 (dd, *J* = 8.0, 1.9 Hz, 1H)	-
5.62 (s, 1H)	5.47 (br, 1H)	-0.15
3.86 (s, 3H)	3.88 (s, 3H)	0.02
3.90–3.81 (m, 2H),	3.92–3.81 (m, 2H)	-
3.24 (s, 2H)	2.41 (br, 2H)	-0.83
2.70 (ddd, *J* = 15.2, 9.5, 6.0 Hz, 1H),	2.70 (ddd, *J* = 14.8, 9.6, 5.9 Hz, 1H)	0
2.61 (ddd, *J* = 13.9, 10.9, 6.3 Hz, 1H)	2.62 (ddd, *J* = 13.9, 9.3, 6.8 Hz, 1H)	0.1
1.83–1.66 (m, 2H)	1.84–1.69 (m, 2H)	-
1.51 (d, *J* = 17.3 Hz, 1H)	1.62 (dt, *J* = 14.5, 2.3 Hz, 1H)	0.11
1.46–1.25 (m, 9H)	1.56–1.23 (m, 9H)	-
0.89 (t, *J* = 6.7 Hz, 3H)	0.89 (t, *J* = 6.6 Hz, 3H)	0

^{13}C NMR Data

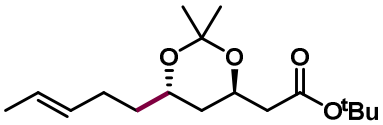
Literature **44**[26] (101 MHz, $CDCl_3$)	Synthetic **44** (126 MHz, $CDCl_3$)	Δδ
146.4	146.4	0
143.7	143.7	0
133.9	133.9	0
120.8	120.9	0.1
114.3	114.2	-0.1
111.0	111.0	0

73.2	73.3	0.1
72.3	72.3	0
55.8	55.9	0.1
42.9	43.0	0.1
40.0	40.0	0
38.2	38.3	0.1
31.8	31.8	0
31.4	31.4	0
25.0	25.0	0
22.6	22.6	0
14.0	14.0	0

Synthesis of streptenol B



Compound SI-57



***Tert*-butyl 2-((4*R*,6*S*)-2,2-dimethyl-6-((*E*)-pent-3-en-1-yl)-1,3-dioxan-4-yl)acetate (SI-57).** Following the **general procedure C** (without ligand) on 0.1 mmol scale **6-RAE** with RAE **SI-41**. Purification by flash column chromatography on silica gel (30:1 hexanes:EtOAc) afforded 18.2 mg (61%) of the title compound **SI-57**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50–5.29 (m, 2H), 4.25–4.15 (m, 1H), 3.84–3.73 (m, 1H), 2.41 (dd, *J* = 14.9, 8.2 Hz, 1H), 2.34 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.13–1.96 (m, 2H), 1.67–1.54 (m, 7H), 1.44 (s, 9H), 1.35 (s, 3H), 1.31 (s, 3H).

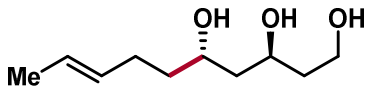
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 130.6, 125.3, 100.5, 80.5, 65.7, 63.8, 42.3, 38.0, 35.5, 28.4, 28.1, 24.7, 24.6, 17.9.

GC/MS (EI): m/z 283 (30%), 241 (5%), 225 (10%), 184 (25%), 167 (35%), 149 (30%), 125 (40%), 107 (65%), 98 (20%), 81 (35%), 69 (20%), 57 (100%).

TLC: R_f = 0.45 (10:1 hexanes:EtOAc)

[α]D^{25} = +19.6 (c = 1.0, $CHCl_3$)

Compound 45



Streptenol B (45)

To a solution of **SI-57** (30 mg, 0.1 mmol, 1.0 equiv) in THF (1 mL) was added $LiAlH_4$ (60 µL, 2 M in THF, 1.2 equiv) at 0 °C under argon. The reaction was then stirred at room temperature for 8 hours. After the mixture was cooled to 0 °C, the reaction was quenched by carefully adding 1N HCl (0.5 mL). The mixture was stirred at room temperature for 3 hours. Then the resulting mixture was extracted with ethyl acetate (5 × 3 mL) and the separated organic layer was washed with water (1 × 15 mL) and brine (1 × 15 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo and then the residue was purified by PTLC (1:2 hexanes:actone) to afforded 13.2 mg (70%) of the title compound **45**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.54–5.37 (m, 2H), 4.29–4.19 (m, 1H), 4.04–3.96 (m, 1H), 3.95–3.83 (m, 2H), 2.15–2.04 (m, 2H), 1.88–1.69 (m, 2H), 1.69–1.63 (m, 3H), 1.64–1.49 (m, 4H).

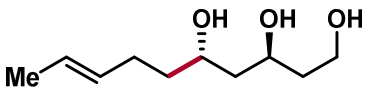
^{13}C NMR (126 MHz, $CDCl_3$): δ 130.7, 125.6, 69.7, 69.1, 61.9, 42.6, 38.2, 37.0, 29.0, 17.9.

HRMS (ESI-TOF): calc'd for: $C_{10}H_{19}O_2$ $[M - OH]^+$: 171.1385, found 171.1384.

TLC: R_f = 0.40 (1:2 hexanes:acetone)

[α]D^{20} = +5.6 (c = 0.7, CH_2Cl_2) (lit. $[\alpha]_D^{20}$ = +9.5 (*c* = 1.0, CH_2Cl_2))[27]

Comparison of NMR data of synthetic streptenol B (45) with literature



^{1}H NMR Data

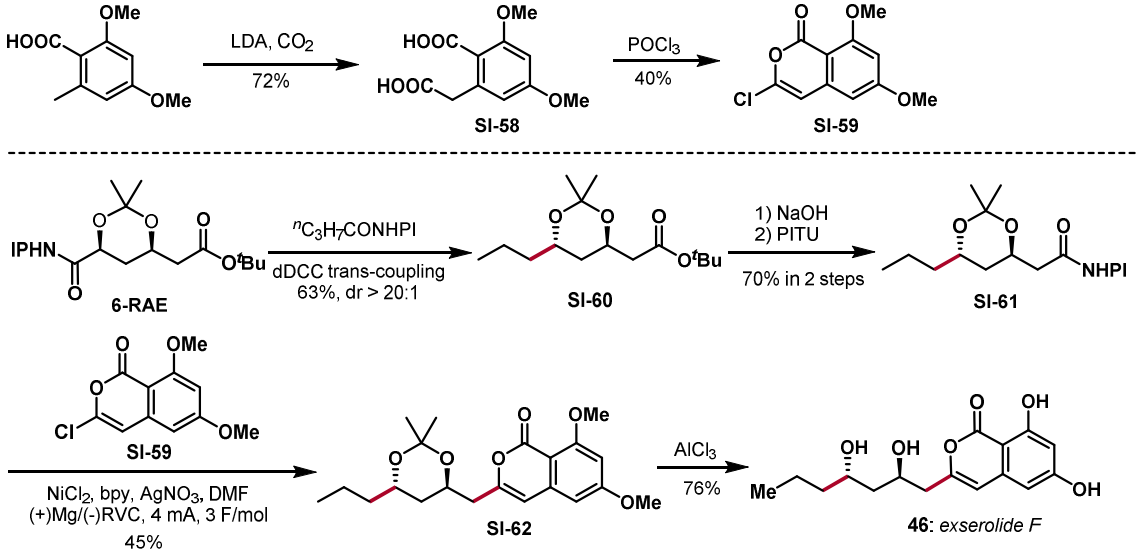
Literature **45**[27.] (unknown)	Synthetic **45** (600 MHz, $CDCl_3$)	Δδ
5.44, 5,48 (m, 2H)	5.54–5.37 (m, 2H)	-
4.22 (m, 1H)	4.29–4.19 (m, 1H)	-
3.98 (m, 1H)	4.04–3.96 (m, 1H)	-

3.86, 3.91 (m, 2H)	3.95–3.83 (m, 2H)	-
2.09,2.11 (m, 2H)	2.15–2.04 (m, 2H)	-
1.68, 1.82 (m, 2H)	1.88–1.69 (m, 2H)	-
1.66 (m, 3H)	1.69–1.63 (m, 3H)	-
1.64 (m, 2H) 1.54, 1.62 (m, 2H)	1.64–1.49 (m, 4H)	-

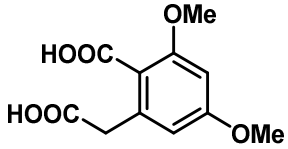
^{13}C NMR Data

Literature **45**[27.] (unknown)	Synthetic **45** (126 MHz, $CDCl_3$)	Δδ
130.7	130.7	0
125.6	125.6	0
69.8	69.7	-0.1
69.1	69.1	0
61.9	61.9	0
42.6	42.6	0
38.3	38.2	-0.1
37.0	37.0	0
29.0	29.0	0
17.9	17.9	0

Synthesis of exserolide F



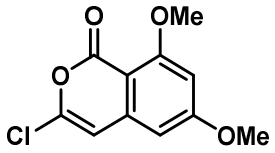
Compound SI-58



2-(carboxymethyl)-4,6-dimethoxybenzoic acid (SI-58)

To a stirring solution of 2-methyl-4,6-dimethoxybenzoic acid (1.96 g, 10 mmol, 1.0 equiv) in THF (20 mL) at –78 °C was added LDA (2 M, 11 mL, 22 mmol, 2.0 equiv) dropwise. After the mixture was stirred at –78 °C for 1 h, CO_2 was bubbled into the mixture for 10 mins. The reaction mixture was allowed to reach room temperature, and the reaction was quenched with a saturated solution of NH_4Cl (20 mL) and acidified with 1 N HCl to pH = 2. The resulting mixture was extracted with ethyl acetate (3 × 50 mL) and the separated organic layer was washed with water (50 mL) and brine (2 × 50 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo and then the residue was purified by recrystallization with methanol to give the title compound **SI-58** (1.7 g, 72%). The spectroscopic data matched the literature[28].

Compound SI-59



3-chloro-6,8-dimethoxy-1H-isochromen-1-one (SI-59)

A mixture of **SI-58** (1.2 g, 5 mmol, 1.0 equiv) and phosphorus oxychloride (5 mL) is taken in a round bottom flask. The reaction mixture was stirred at 80 ºC and monitored by TLC once an hour until it was completed (3 h) and then the mixture was cooled to room temperature. The phosphorus oxychloride was removed in vacuum. The residue was then purified by flash column chromatography on silica gel (5:1 hexanes:EtOAc) afforded (480 mg, 40%) of the title compound **SI-59**.

Physical State: faint yellow solid.

m.p.: 180-182 ºC.

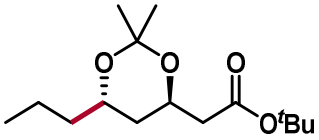
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.44 (s, 1H), 6.32 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.9, 163.6, 157.2, 143.7, 141.9, 104.4, 101.8, 100.0, 98.7, 56.3, 55.7.

HRMS (ESI-TOF): calc'd for : $C_{11}H_{10}ClO_4$ $[M + H]^+$: 241,0268, found 241.0269.

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

Compound SI-60



***Tert*-butyl 2-((4*R*,6*S*)-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)acetate (SI-60)**

Following the **general procedure C** (without ligand) on 1 mmol scale **6-RAE** with RAE **SI-29** (3 equiv.) Purification by flash column chromatography on silica gel (30:1 hexanes:EtOAc) afforded (170.4 mg, 63%) of the title compound **SI-60**

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.24–4.17 (m, 1H), 3.84–3.74 (m, 1H), 2.41 (dd, *J* = 15.0, 8.3 Hz, 1H), 2.34 (dd, *J* = 15.0, 5.4 Hz, 1H), 1.66–1.58 (m, 2H), 1.56–1.47 (m, 1H), 1.48–1.41 (m, 10H), 1.41–1.37 (m, 1H), 1.35 (s, 3H), 1.34–1.27 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H).

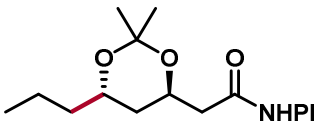
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 100.4, 80.5, 66.2, 63.8, 42.3, 38.0, 37.9, 28.1, 24.8, 24.6, 18.6, 13.9.

GC/MS (EI): m/z 257 (48%), 201 (18%), 173 (10%), 159 (20%), 141 (100%), 123 (60%), 99 (40%), 81 (45%), 57 (95%).

TLC: R_f = 0.4 (15:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = +28.5 (c = 1.0, $CHCl_3$).

Compound SI-61



1,3-dioxoisoindolin-2-yl 2-((4*R*,6*S*)-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)acetate (SI-61)

To a solution of **SI-60** (136.1 mg, 0.5 mmol, 1.0 equiv) in MeOH (1.5 mL) was 2 M NaOH (0.5 mL) and the mixture was then stirred at 60 °C for 12 h. 1 N HCl (450 µL) was added, and the solvent of the mixture was removed under vacuum. Traces of MeOH and H_2O were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in CH_3CN (2.5 ml), PITU (306 mg, 0.75 mmol, 1.5 equiv) and DIPEA (43.5 µL, 0.25 mmol, 0.5 equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction

was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered. The filtrate was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (5:1 hexanes:EtOAc) to give the title compound **SI-61** (126.2 mg, 70%).

Physical State: white solid.

m.p.: 120-122 ºC.

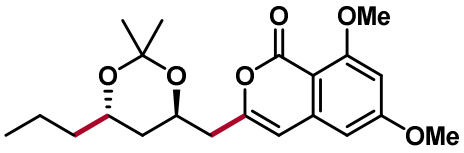
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.40–4.30 (m, 1H), 3.93–3.79 (m, 1H), 2.88 (dd, *J* = 15.5, 8.1 Hz, 1H), 2.79 (dd, *J* = 15.5, 5.3 Hz, 1H), 1.75 (td, *J* = 9.0, 6.3 Hz, 2H), 1.59–1.50 (m, 1H), 1.45‑1.34 (m, 9H), 0.92 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ167.0, 161.8, 134.7, 128.9, 124.0, 100.9, 66.2, 63.2, 37.8, 37.7, 24.6, 24.4, 18.5, 13.9.

TLC: R_f = 0.3 (5:1 hexanes:EtOAc)

[α]$_D^{25}$ = +28.5 (c = 1.0, $CHCl_3$).

Compound SI-62



3-(((4*R*,6S)-2,2-dimethyl-6-propyl-1,3-dioxan-4-yl)methyl)-6,8-dimethoxy-1H-isochromen-1-one (SI-62)

An ElectraSyn vial (5 mL) with a stir bar was charged with **SI-61** (36.1 mg, 0.1 mmol, 1.0 equiv), **SI-59** (36.0 mg, 0.15 mmol, 1.5 equiv), $AgNO_3$ (8.5 mg, 0.05 mmol, 0.05 equiv), $NiCl_2$•$6H_2O$ (4.8 mg, 0.02 mol, 0.2 equiv.), 2,2'-Bipyridine (3.1 mg, 0.02 mol, 0.2 equiv.) and anhydrous DMF (3 mL). An ElectraSyn vial cap equipped with anode (Mg) and cathode (RVC) 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 3 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. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude

material was purified by PTLC (1:1 hexanes:EtOAc) to furnish the title compound **SI-62** (16.8 mg, 45%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.43 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 6.18 (s, 1H), 4.30–4.23 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.85–3.77 (m, 1H), 2.68 (dd, *J* = 14.8, 8.2 Hz, 1H), 2.57 (dd, *J* = 14.8, 5.3 Hz, 1H), 1.69–1.58 (m, 2H), 1.54–1.46 (m, 1H), 1.45–1.36 (m, 3H), 1.33 (s, 6H), 0.90 (t, *J* = 7.1 Hz, 3H).

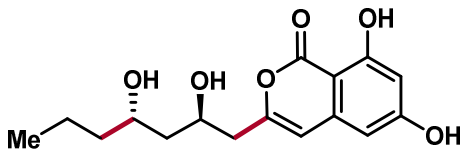
^{13}C NMR (151 MHz, $CDCl_3$): δ 165.4, 163.3, 159.5, 155.4, 142.2, 104.8, 103.1, 100.5, 99.7, 98.3, 66.3, 64.0, 56.3, 55.6, 39.6, 38.1, 37.9, 24.8, 24.6, 18.5, 13.9.

HRMS (ESI-TOF): calc'd for : $C_{21}H_{29}O_6$ $[M + H]^+$: 377.1964, 377.1958.

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

$[\alpha]_D^{25}$ = –4.6 (c = 1.0, $CHCl_3$)

Compound 46



Exserolide F (46)

To a stirring mixture of $AlCl_3$ (60 mg, 0.45 mmol, 1.5 equiv) in benzene (0.2 mL) at 0 °C was added a solution of **SI-62** (11.3 mg, 0.03 mmol, 1.0 equiv) in benzene (0.4 mL) dropwise. The reaction mixture was allowed to reach room temperature and stirred for a further 12 h. After the mixture was cooled to 0 ºC, the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL) and the separated organic layer was washed with water (5 mL) and brine (2 × 5 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo and then the residue was purified by PTLC (1:3 hexanes:EtOAc) to afforded 7.1 mg (76%) of the title compound **46**. The spectroscopic data matched the literature.

Physical State: white solid.

m.p.: 85-87 ºC.

^{1}H NMR (600 MHz, $(CD_3)_2CO$): δ 11.17 (s, 1H), 9.59 (br, 1H), 6.44 (s, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 4.32 (tt, *J* = 8.5, 4.4 Hz, 1H), 4.13 (s, 1H), 3.95–3.86 (m,

1H), 3.63 (s, 1H), 2.67 (dd, *J* = 14.3, 4.6 Hz, 1H), 2.60 (dd, *J* = 14.5, 8.3 Hz, 1H), 1.65–1.55 (m, 2H), 1.51–1.34 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H).

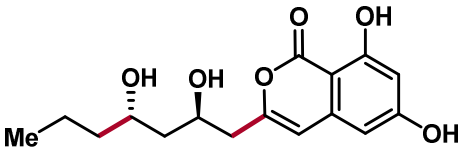
^{13}C NMR (151 MHz, $(CD_3)_2CO$): δ 167.1, 166.3, 164.5, 156.5, 141.0, 106.4, 103.3, 102.2, 99.9, 68.3, 66.7, 44.9, 42.8, 41.2, 19.6, 14.4.

HRMS (ESI-TOF): calc'd for: $C_{16}H_{20}O_6$ $[M+H]^+$: 309.1338, found 309.1349.

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

$[\alpha]_D^{25}$ = –10.0 (c = 0.15, MeOH) (lit. $[\alpha]_D^{25}$ = –15.6 (*c* = 0.09, MeOH))[29]

Comparison of NMR data of synthetic exserolide F (46) with literature



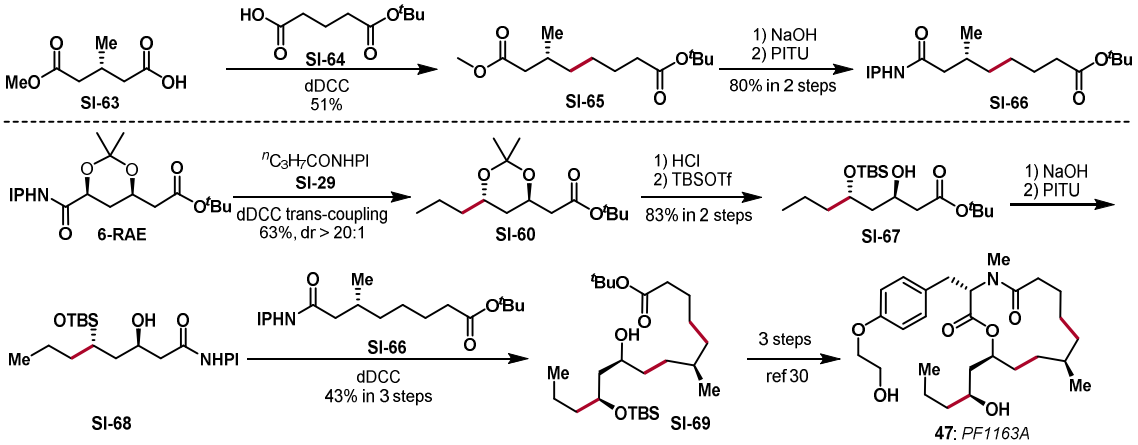
^{1}H NMR Data

Literature **46**[29] (600 MHz, $(CD_3)_2CO$)	Synthetic **46** (600 MHz, $(CD_3)_2CO$)	Δδ
11.16 (s, 1H)	11.17 (s, 1H)	0.01
9.63 (s, 1H)	9.59 (br, 1H)	0.04
6.44 (s, 1H)	6.44 (s, 1H)	0
6.41 (d, *J* = 1.8 Hz, 1H)	6.42 (d, *J* = 2.2 Hz, 1H)	0.01
6.37 (d, *J* = 1.8 Hz, 1H)	6.37 (d, *J* = 2.3 Hz, 1H)	0
4.32 (m, 1H)	4.32 (tt, *J* = 8.5, 4.4 Hz, 1H)	-
4.12 (d, *J* = 4.8, 1H)	4.13 (s, 1H)	-
3.90 (m, 1H)	3.95–3.86 (m, 1H)	-
3.63 (d, *J* = 5.4 Hz, 1H)	3.63 (s, 1H)	-
2.67 (dd, *J* = 14.4, 4.8 Hz, 1H)	2.67 (dd, *J* = 14.3, 4.6 Hz, 1H)	0
2.60 (dd, *J* = 14.4, 8.4 Hz, 1H)	2.60 (dd, *J* = 14.5, 8.3 Hz, 1H)	0
1.60 (m, 2H)	1.65–1.55 (m, 2H)	-
1.45 (m, 4H)	1.51–1.34 (m, 4H)	-
0.90 (t, *J* = 7.2 Hz, 3H)	0.90 (t, *J* = 7.1 Hz, 3H)	0

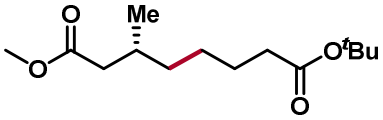
^{13}C NMR Data

Literature **46**[29] (151 MHz, $(CD_3)_2CO$)	Synthetic **46** (151 MHz, $(CD_3)_2CO$)	Δδ
167.0	167.1	0.1
166.3	166.3	0
164.3	164.5	0.2
156.5	156.5	0
140.9	141.0	0.1
106.4	106.4	0
103.2	103.3	0.1
102.1	102.2	0.1
99.8	99.9	0.1
68.2	68.3	0.1
66.6	66.7	0.1
44.8	44.9	0.1
42.8	42.8	0
41.2	41.2	0
19.5	19.6	0.1
14.4	14.4	0

Formal synthesis of PF1163



Compound SI-65



8-(*tert*-butyl) 1-methyl (*R*)-3-methyloctanedioate (SI-65)

An ElectraSyn vial (30 mL) with a stir bar were charged with **SI-63** (160 mg, 1 mmol, 1.0 equiv), **SI-64** (564 mg, 3 mmol, 3.0 equiv), N-hydroxyphthalimide (718 mg, 4.4 mmol, 4.4 equiv) and 4-dimethylaminopyridine (49 mg, 0.4 mmol, 0.4 equiv). Dichloromethane was added (15 mL). Then N,N′-Diisopropylcarbodiimide (0.68 mL, 4.4 mmol, 4.4 equiv) was added dropwise via syringe, and the mixture was allowed to stir until the acid was consumed. After consumption of all starting materials, NaI (450 mg, 3 mmol, 3.0 equiv), $NiCl_2$•dme (44 mg, 0.2 mmol, 0.2 equiv.), (4-OMe)-H-PyBox (50 mg, 0.2 mmol, 0.2 equiv.) and anhydrous DMF (15 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 8 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. 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 (50:1 hexanes:EtOAc) to furnish the title compound **SI-65** (131.8 mg, 51%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.29 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.20 (t, *J* = 7.5 Hz, 2H), 2.11 (dd, *J* = 14.8, 8.1 Hz, 1H), 1.98–1.90 (m, 1H), 1.61–1.53 (m, 2H), 1.43 (s, 9H), 1.36–1.26 (m, 3H), 1.23–1.16 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H).

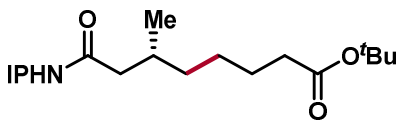
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7, 173.1, 80.0, 51.3, 41.6, 36.3, 35.5, 30.2, 28.1, 26.3, 25.2, 19.6.

GC/MS (EI): m/z 227 (2%), 185 (50%), 171 (23%), 152, (17%), 143 (15%), 125 (23%), 101 (25%), 83 (20%), 69 (15%), 57 (100%).

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

$[\alpha]_D^{25}$ = +4.1 (c = 1.0, $CHCl_3$).

Compound SI-66



8-(*tert*-butyl) 1-(1,3-dioxoisoindolin-2-yl) (*R*)-3-methyloctanedioate (SI-66)

To a solution of **SI-65** (129.6 mg, 0.5 mmol, 1.0 equiv) in MeOH (1.5 mL) was 2 M NaOH (0.5 mL) and the mixture was then stirred at 60 °C for 12 h. 1 N HCl (450 µL) was added, and the solvent of the mixture was removed under vacuum. Traces of MeOH and H_2O were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in CH_3CN (2.5 ml), PITU (306 mg, 0.75 mmol, 1.5 equiv) and DIPEA (43.5 µL, 0.25 mmol, 0.5 equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, filtered. The filtrate was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (10:1 hexanes: EtOAc) to give the title compound **SI-66** (155.6 mg, 80%).

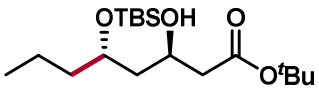
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 2.64 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.53–2.45 (m, 1H), 2.23 (t, *J* = 7.4 Hz, 2H), 2.10 (h, *J* = 6.4 Hz, 1H), 1.66–1.55 (m, 2H), 1.51–1.45 (m, 1H), 1.44 (s, 9H), 1.41–1.29 (m, 3H), 1.08 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1, 168.9, 162.0, 134.7, 129.0, 123.9, 80.0, 38.2, 36.1, 35.5, 30.5, 28.1, 26.3, 25.1, 19.4.

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

Compound SI-67



***Tert*-butyl (3*R*,5*S*)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxyoctanoate (SI-67)**

To a solution of **SI-60** (136 mg, 0.5 mmol, 1.0 equiv) in acetonitrile (2 mL) at 0 °C, 0.02 M HCl (0.5 mL) was added dropwise. The mixture was then stirred at room temperature for 6 h. The solvent was concentrated, and the residue was dried in vacuo for 1 h. Then CH_2Cl_2 (5 mL) and 2,6-lutidine (174 µL, 1.5 mmol, 3.0 equiv) were added to the residue. After the mixture cooling to -78 °C, TBSOTf (118 µL, 0.525 mmol, 1.05 equiv) was added to the solution over 5 min. The reaction mixture was stirred at this temperature for 4 h before it was quenched with a saturated aqueous $KHSO_4$ solution (3 mL). The mixture was then diluted with diethyl ether (5 mL), warmed to room temperature, and extracted with diethyl ether (3 × 5 mL). The

combined organic layers were washed sequentially with H_2O (5 mL), a saturated aqueous $NaHCO_3$ solution (5 mL), and brine (5 mL). The washed organic phase was then dried over Na_2SO_4, filtered, and evaporated to provide crude material, which was purified by flash chromatography (20:1 hexanes:EtOAc) on silica gel to afford title compound **SI-67** (144.3 mg, 83%)

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29–4.22 (m, 1H), 4.00–3.96 (m, 1H), 3.57 (d, *J* = 2.5 Hz, 1H), 2.41 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.34 (dd, *J* = 15.8, 4.8 Hz, 1H), 1.66–1.56 (m, 2H), 1.55–1.50 (m, 2H), 1.45 (s, 9H), 1.35–1.26 (m, 2H), 0.93–0.87 (m, 12H), 0.09 (s, 3H), 0.07 (s, 3H).

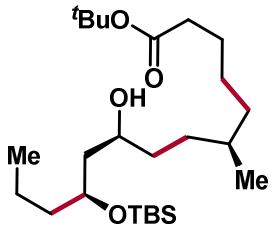
^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7, 80.8, 70.3, 65.2, 43.4, 41.7, 39.1, 28.1, 25.9, 18.6, 18.0, 14.2, -4.5, -4.7.

HRMS (ESI-TOF): calc'd for: $C_{18}H_{38}O_4SiNa$ $[M+Na]^+$: 369.2437, found 69.2440.

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

$[\alpha]_D^{25}$ = +3.4 (c = 0.5, $CHCl_3$).

Compound SI-69



***Tert*-butyl (6*R*,9*S*,11*S*)-11-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-6-methyltetradecanoate (SI-69)**

To a solution of **SI-67** (34.6 mg, 0.1 mmol, 1.0 equiv) in MeOH (0.3 mL) was 2 M NaOH (0.1 mL) and the mixture was then stirred at 60 ºC for 12 h. 1 N HCl (90 µL) was added and the solvent of the mixture was removed under vacuum. Traces of MeOH and H_2O were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in CH_3CN (0.5 ml), PITU (44.8 mg, 0.11 mmol, 1.1 equiv) and DIPEA (8.7 µL, 0.05 mmol, 0.05 equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **crude RAE** as a colorless oil and directly used for the next reaction.

An ElectraSyn vial (5 mL) with a stir bar was charged with **crude RAE** (from last step), **SI-66** (117.1 mg, 0.3 mmol, 3.0 equiv), NaI (89.9 mg, 0.6 mmol, 6.0 equiv), $NiCl_2$•dme (4.4 mg, 0.02 mmol, 0.2 equiv.), (4-OMe)-H-PyBox (5.0 mg, 0.02 mmol, 0.2 equiv.) and anhydrous DMF (3 mL). 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. The organic layers were further washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by PTLC (15:1 hexanes:EtOAc) to furnish the title compound **SI-69** (19.1 mg, 43% in two steps).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.02–3.96 (m, 1H), 3.96–3.87 (m, 1H), 3.49 (br, 1H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.62–1.51 (m, 6H), 1.48–1.41 (m, 11H)., 1.34–1.25 (m, 8H), 1.14–1.07 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H).

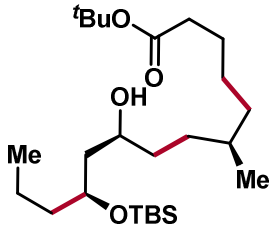
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.3, 79.9, 71.8, 68.7, 41.2, 38.3, 36.6, 35.6, 35.5, 32.8, 32.7, 28.1, 26.5, 25.8, 25.4, 19.6, 19.1, 17.9, 14.2, -4.6, -4.7.

HRMS (ESI-TOF): calc'd for : $C_{25}H_{53}O_4Si$ $[M + H]^+$: 445.3713, 445.3708.

TLC: R_f = 0.4 (15:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = +13.3 (c = 0.15, MeOH). (lit. $[\alpha]_D^{25}$ = +18 (*c* = 1.2, MeOH))[30]

Comparison of NMR data of synthetic SI-69 with literature



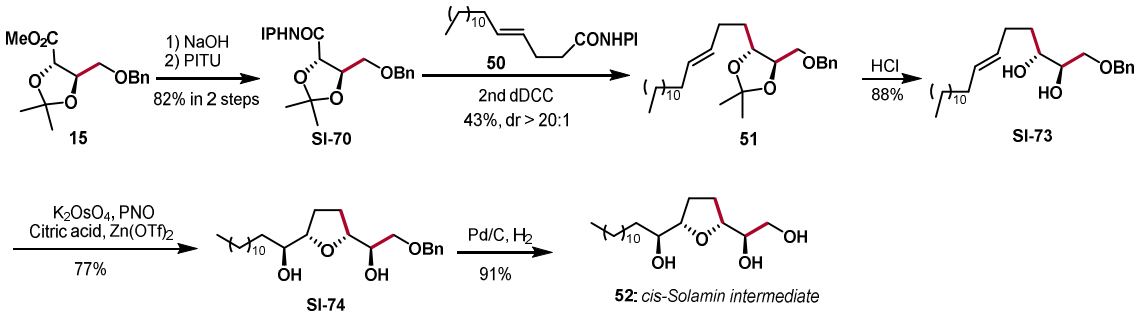
^{1}H NMR Data

Literature **SI-69**[30] (unknown, $CDCl_3$)	Synthetic **SI-69** (600 MHz, $CDCl_3$)	Δδ
3.99 (m, 1H)	4.02–3.96 (m, 1H)	-
3.86–3.93 (m, 1H)	3.96–3.87 (m, 1H)	-

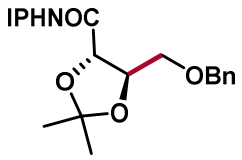
3.40–3.60 (br, 1H)	3.49 (br, 1H)	-
2.20 (t, *J* = 7.5 Hz, 2H)	2.20 (t, *J* = 7.5 Hz, 2H)	0
1.44 (s, 9H)	1.44 (s, 9H)	-
	1.62–1.51 (m, 8H)	
1.00–1.64 (m, 17H)	1.34–1.25 (m, 8H)	-
	1.14–1.07 (m, 1H)	
0.93 (t, *J* = 7.0Hz, 3H)	0.92 (t, *J* = 7.3 Hz, 3H)	-0.01
0.89 (s, 9H)	0.89 (s, 9H)	0
0.85 (d, *J* = 7.0 Hz, 3 H)	0.86 (d, *J* = 6.5 Hz, 3H)	0.01
0.10 (s, 3H)	0.10 (s, 3H)	0
0.07 (s, 3H)	0.08 (s, 3H)	0.01

*Note: the ^{13}C NMR of **SI-69** is not available in the Literature.*

Formal synthesis of cis-solamin intermediate



Compound SI-70



1,3-dioxoisoindolin-2-yl (4*S*,5*R*)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (SI-70)

To a solution of **15** (140 mg, 0.5 mmol, 1.0 equiv) in MeOH (1.5 mL) was added 2 M NaOH (0.5 mL) and the mixture was then stirred at 60 °C for 12 h. 1 N HCl (450 µL) was added, and the solvent of the mixture was removed under vacuum. Traces of MeOH and H_2O were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in CH_3CN (2.5 ml), PITU (306 mg, 0.75 mmol, 1.5 equiv) and DIPEA (43.5 µL, 0.25 mmol, 0.5

equiv) were added. The mixture was then stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered. The filtrate was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (5:1 hexanes:EtOAc) to give the title compound **SI-70** (160.7 mg, 78%).

Physical State: white solid.

m.p.: 220 ºC (decomposed).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.39–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.86 (d, *J* = 7.2 Hz, 1H), 4.73–4.61 (m, 3H), 3.86 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.79 (dd, *J* = 11.1, 4.7 Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H).

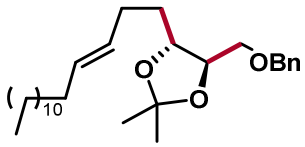
^{13}C NMR (126 MHz, $CDCl_3$): δ 167.9, 161.4, 137.7, 134.9, 128.8, 128.4, 127.7, 127.6, 124.1, 112.8, 78.8, 73.8, 73.6, 68.8, 26.8, 25.3.

HRMS (ESI-TOF): calc'd for: $C_{22}H_{22}NO_7$ $[M + H]^+$: 412.1396, found 412.1388.

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

$[\alpha]_D^{25}$ = +39.5 (c =1.0, $CHCl_3$).

Compound 51



(4*R*,5*R*)-4-((benzyloxy)methyl)-5-((*E*)-hexadec-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (51)

Following the **general procedure A** (with **L1**) on 0.1 mmol scale RAE **70** with RAE **50** Purification by PTLC (25:1 hexanes:EtOAc) afforded 19.2 mg (43%) of the title compound **51**.

Physical State: colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.31 (m, 4H), 7.31–7.27 (m, 1H), 5.48–5.32 (m, 2H), 4.64–4.54 (m, 2H), 3.89–3.77 (m, 2H), 3.56 (d, *J* = 5.1 Hz, 2H), 2.22–2.01 (m, 2H), 1.96 (q, *J* = 6.6 Hz, 2H), 1.68–1.58 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.33–1.20 (m, 20H), 0.89 (t, *J* = 6.5 Hz, 3H).

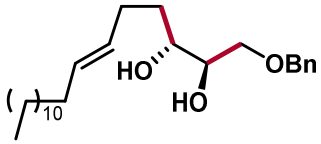
^{13}C NMR (151 MHz, $CDCl_3$): δ 138.0, 131.2, 129.0, 128.4, 127.6, 108.7, 80.0, 77.8, 73.5, 70.7, 33.2, 32.6, 31.9, 29.7, 29.6 (2C), 29.5, 29.4, 29.2, 28.9, 27.3, 27.0, 22.7, 14.1.

GC/MS (EI): m/z 444 (3%), 429 (3%), 386 (3%), 369 (3%), 281 (10%), 207 (45%), 91 (100%).

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

[α]D25 = +4.8 (c = 1.0, $CHCl_3$).

Compound SI-73



(2*R*,3*R*,*E*)-1-(benzyloxy)nonadec-6-ene-2,3-diol (SI-73)

To a solution of **SI-72** (44.5 mg, 0.1 mmol) in acetonitrile (1 mL) at 0 °C, 0.2 M HCl (0.1 mL) was added dropwise. The mixture was then stirred at room temperature for 6 h. The solvent was concentrated in vacuo and the residue was purified by PTLC (3:1 hexanes:EtOAc) to give the title compound **SI-73** (35.6 mg, 88%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.29 (m, 5H), 5.42 (dtd, *J* = 21.8, 15.3, 6.4 Hz, 2H), 4.61–4.50 (m, 2H), 3.68–3.55 (m, 4H), 2.21–2.12 (m, 1H), 2.12–2.03 (m, 1H), 1.97 (q, *J* = 6.9 Hz, 2H), 1.67–1.58 (m, 1H), 1.57–1.49 (m, 1H), 1.35–1.30 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H).

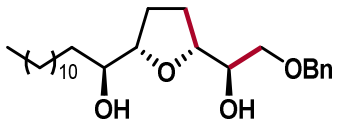
^{13}C NMR (151 MHz, $CDCl_3$): δ 137.6, 131.3, 129.3, 128.5, 127.9, 127.8, 73.6, 72.8, 72.3, 71.7, 33.3, 32.6, 31.9, 29.7, 29.6 (3C), 29.5, 29.3, 29.2, 28.6, 22.7, 14.1.

HRMS (ESI-TOF): calc'd for: $C_{26}H_{45}O_3$ $[M + H]^+$: 405.3369, found 405.3362.

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

[α]D25 = +9.2 (c = 1.0, $CHCl_3$).

Compound SI-74



(*S*)-1-((2*S*,5*R*)-5-((*R*)-2-(benzyloxy)-1-hydroxyethyl)tetrahydrofuran-2-yl)tridecan-1-ol (SI-74)

To a solution of **SI-73** (20.2 mg, 0.05 mmol, 1.0 equiv) in acetonitrile (0.6 mL) and water (0.4 mL) was added pyridine N-oxide (9.5 mg, 0.1 mmol, 2.0 equiv), citric acid (7.2 mg, 0.0375 mmol, 0.75 equiv), potassium osmate dihydrate (0.15 mg, 0.0005 mmol, 0.01 equiv.) and the zinc trifluoromethansulfonate (9.1 mg, 0.025 mmol). The resulting solution was warmed to 60

°C and the mixture was left to stir at same temperature for 12 h. Sodium sulfite (1 mg) and water (0.5 mL) were added, and the reaction was cooled to room temperature. The mixture was extracted with ethyl acetate (3 × 2 mL) and the combined organic layers were washed with 2 M HCl (2 mL), 3 M NaOH (2 mL), and brine (2 mL), dried over sodium sulfate, and filtered, then the solvent was removed in vacuo. The residue was purified by PTLC (2:1 hexanes:EtOAc) to give the title compound **SI-74** (16.2 mg, 77%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5H), 4.57 (s, 2H), 4.03–3.98 (m, 1H), 3.89–3.84 (m, 1H), 3.76–3.71 (m, 1H), 3.57 (d, *J* = 5.0 Hz, 2H), 3.44–3.38 (m, 1H), 2.05–1.71 (m, br, 6H), 1.52–1.41 (m, 2H), 1.36–1.20 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H).

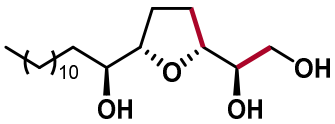
^{13}C NMR (151 MHz, $CDCl_3$): δ 137.9, 128.4, 127.8, 82.6, 79.4, 74.3, 73.4, 72.7, 72.3, 34.5, 31.9, 29.7 (2C), 29.6, 29.3, 28.2, 27.9, 25.8, 22.7, 14.1.

HRMS (ESI-TOF): calc'd for: $C_{26}H_{45}O_4$ $[M + H]^+$: 421.3318, found 421.3317.

TLC: R_f = 0.3 (2:1 hexanes:EtOAc)

$[\alpha]_D^{25}$ = –5.7 (c = 1.0, $CHCl_3$)

Compound 52



(*R*)-1-((2*R*,5*S*)-5-((*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl)ethane-1,2-diol (52)

To a solution of **SI-74** (10.5 mg, 0.025 mmol) in anhydrous methanol (1.5 mL) was added 20% Pd/C (2 mg). The resultant mixture was stirred under 1 atm of hydrogen for 8 h at room temperature. The mixture was filtered over Celite and rinsed with methanol. The solvent was then evaporated in vacuo. The crude product was purified by PTLC (1:1 hexanes:acetone) to afford 7.5 mg (91%) of title compound **52**.

Physical State: colorless oil.

^{1}H NMR (400 MHz, CD_3OD): δ 3.97 (td, *J* = 6.9, 3.8 Hz, 1H), 3.80 (td, *J* = 6.6, 3.8 Hz, 1H), 3.62 (dd, *J* = 11.1, 5.4 Hz, 1H), 3.57 (dd, *J* = 11.1, 6.2 Hz, 1H), 3.50 (ddd, *J* = 6.2, 5.3, 3.9 Hz, 1H), 3.45–3.36 (m, 1H), 1.99–1.76 (m, 4H), 1.52–1.44 (m, 3H), 1.39–1.21 (m, 19H), 0.90 (t, *J* = 6.9 Hz, 3H).

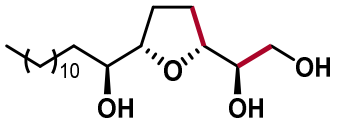
^{13}C NMR (151 MHz, CD_3OD): δ 83.8, 80.8, 75.3, 74.9, 65.1, 35.2, 33.1, 30.8 (5C), 30.7, 30.5, 28.9, 28.6, 26.9, 23.7, 14.4.

HRMS (ESI-TOF): calc'd for: $C_{19}H_{38}O_4Na$ $[M + Na]^+$: 353.2668, found 353.2661.

TLC: R_f = 0.3 (1:1 hexanes:acetone)

$[\alpha]_D^{25}$ = –14.4 (c = 0.25, $CHCl_3$). (lit. $[\alpha]_D^{25}$ = –12.9 (*c* = 0.70, $CHCl_3$))[31]

Comparison of NMR data of synthetic 52 with literature



^{1}H NMR Data

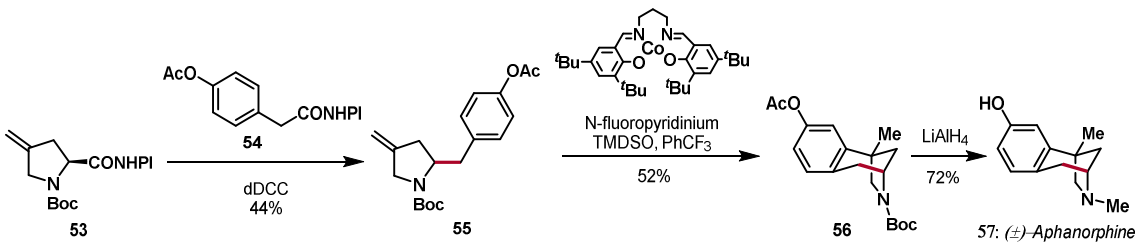
Literature **52**[31] (400 MHz, CD_3OD)	Synthetic **52** (400 MHz, CD_3OD)	Δδ
3.96 (dt, *J* = 3.8, 7.1 Hz, 1H)	3.97 (td, *J* = 6.9, 3.8 Hz, 1H)	0.01
3.80 (dt, *J* = 4.5, 7.1 Hz, 1H)	3.80 (td, *J* = 6.6, 3.8 Hz, 1H)	0
3.62 (dd, *J* = 5.5, 11.1 Hz, 1H)	3.62 (dd, *J* = 11.1, 5.4 Hz, 1H)	0
3.57 (dd, *J* = 6.2, 11.1 Hz, 1H)	3.57 (dd, *J* = 11.1, 6.2 Hz, 1H)	0
3.50 (dt, *J* = 4.5, 5.5 Hz, 1H)	3.50 (ddd, *J* = 6.2, 5.3, 3.9 Hz,1H)	0
3.40 (dt, *J* = 7.1, 4.5 Hz, 1H)	3.45–3.36 (m, 1H)	-
1.97–1.74 (m, 4H)	1.99–1.76 (m, 4H)	0
1.54–1.43 (m, 3H)	1.52–1.44 (m, 3H)	0
1.41–1.20 (m, 19H)	1.39–1.21 (m, 19H)	-
0.90 (t, *J* = 7.1 Hz, 3H)	0.90 (t, *J* = 6.9 Hz, 3H)	0

^{13}C NMR Data

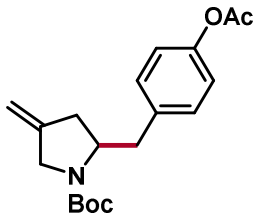
Literature **52**[31] (101 MHz, CD_3OD)	Synthetic **52** (151 MHz, CD_3OD)	Δδ
83.8	83.8	0
80.8	80.8	0
75.3	75.3	0
74.9	74.9	0
65.1	65.1	0
35.2	35.2	0
33.1	33.1	0

30.8 (3C)	30.8 (5C)	-
30.7 (3C)	30.7	-
30.5	30.5	0
28.8	28.9	0.1
28.6	28.6	0
26.9	26.9	0
23.7	23.7	0
14.4	14.4	0

Synthesis of aphanorphine



Compound 55



***Tert*-butyl 2-(4-acetoxybenzyl)-4-methylenepyrrolidine-1-carboxylate (55)**

Following the **general procedure A** (without ligand) on 0.1 mmol scale **53** (prepared in situ from (S)-1-(tert-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid) with **54** (prepared in situ from 2-(4-acetoxyphenyl)acetic acid, 3.0 equiv), set the temperature at 60 °C. Purification by flash column chromatography on silica gel (20:1 hexanes:EtOAc) afforded 146.7 mg (44%) of the title compound **55**.

Physical State: colorless oil

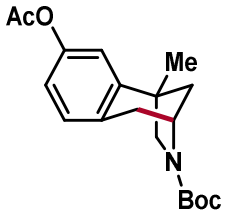
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (d, *J* = 30.7 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 5.05–4.89 (m, 2H), 4.27–3.96 (m, 2H), 3.90–3.77 (m, 1H), 3.15–2.86 (m, 1H), 2.58 (br, 1H), 2.49 (dd, *J* = 13.1, 9.5 Hz, 1H), 2.31–2.24 (m, 4H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5, 154.0, 149.1, 144.9, 144.0, 136.2, 130.4, 130.2, 121.5, 107.9, 107.5, 79.5, 58.7, 58.2, 50.5, 49.9, 39.8, 38.8, 36.8, 35.8, 28.5, 21.1.

HRMS (ESI-TOF): calc'd for $C_{14}H_{18}NO_2$ $[M - Boc + 2H]^+$: 232.1338, found 232.1349.

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

Compound 56



***Tert*-butyl 8-acetoxy-1-methyl-1,2,4,5-tetrahydro-3H-1,4-methanobenzo[d]azepine-3-carboxylate (56)**

A 4 mL vial was charged with **55** (33 mg, 0.1 mmol, 1.0 equiv), Co catalyst (2.8 mg, 0.005 mmol, 0.05 equiv) and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (45 mg, 0.2 mmol, 2.0 equiv). After being dried in vacuo for 0.5 h, $PhCF_3$ (1 mL) was added. The solution was bubbled with Ar for 10 min before poly(methylhydrosiloxane) (44 μL, 0.2 mmol, 2.0 equiv) was added. The resulting mixture was stirred at room temperature for 20 hours before diluted with ethyl acetate (4 mL). The solution was washed with water (1 mL) and brine (3 × 1 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by PTLC (10:1 hexanes:EtOAc) to give the title compound **56** (17.4 mg, 52%).

Physical State: White solid.

m.p.: 125-127 ºC.

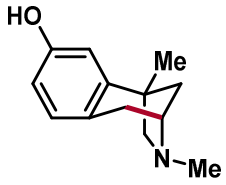
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 12.6, 8.3 Hz, 1H), 6.96 (t, *J* = 2.4 Hz, 1H), 6.89 (dt, *J* = 8.2, 2.4 Hz, 1H), 4.44 (dt, *J* = 5.7, 2.7 Hz, 0.5H), 4.31 (dt, *J* = 5.8, 2.8 Hz, 0.5H), 3.35 (ddd, *J* = 29.8, 10.0, 1.5 Hz, 1H), 3.24–3.16 (m, 1.5H), 3.08 (d, *J* = 16.9 Hz, 0.5H), 2.92 (dt, *J* = 16.9, 3.1 Hz, 1H), 2.29/2.30 (2s, 3H), 2.02–1.91 (m, 1H), 1.88 (t, *J* = 10.1 Hz, 1H), 1.50/1.49 (2s, 3H), 1.46/1.40 (2s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.9, 169.8, 153.9 (2C), 148.8, 148.7, 146.3, 146.1, 131.7, 131.3, 130.6, 130.3, 119.8, 119.7, 116.8, 116.6, 79.2 (2C), 61.3, 60.9, 54.4, 54.0, 41.9, 41.7, 41.3, 40.8, 36.8, 36.3, 28.6, 28.5, 21.1, 20.9, 20.8.

HRMS (ESI-TOF): calc'd for $C_{14}H_{18}NO_2$ $[M - Boc + 2H]^+$: 232.1338, found 232.1340.

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

Compound 57



1,3-dimethyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[d]azepin-8-ol (57)

To a solution of **SI-78** (16.5 mg, 0.05 mmol, 1.0 equiv) in THF (0.5 mL) was added 2 M $LiAlH_4$ in THF (0.15 mL, 0.3 mmol, 6.0 equiv) at 0 ºC. The reaction was then heated at 60 ºC for 18 hours. After the mixture was cooled to 0 ºC, the reaction was quenched by carefully adding 1 mL 15% potassium sodium tartrate solution. The aqueous layer was extracted with ethyl acetate (2 mL x 3). The combined organic layers were passed through a plug of celite, which was then washed with ethyl acetate (5 ml). The filtrate dried over sodium sulfate and concentrated in vacuo. The crude product was placed on a filter and then rinsed with Et_2O (0.5 mL x 2) to give the titled compound **57** (7.4 mg, 72%).

Physical State: white solid.

m.p.: 210-212 ºC.

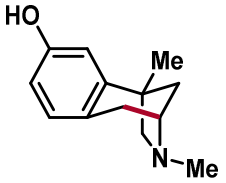
^{1}H NMR (500 MHz, CD_3OD): δ 6.91 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 6.57 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.41 (dt, *J* = 6.0, 3.0 Hz, 1H), 2.98 (d, *J* = 16.3 Hz, 1H), 2.91–2.82 (m, 1H), 2.65 (d, *J* = 9.5 Hz, 1H), 2.43 (s, 3H), 2.04 (ddd, *J* = 11.2, 5.9, 1.2 Hz, 1H), 1.85 (d, *J* = 11.1 Hz, 1H), 1.46 (s, 3H).

^{13}C NMR (151 MHz, CD_3OD): δ 156.7, 148.6, 131.2, 125.2, 114.5, 110.9, 72.7, 63.4, 44.3, 42.8, 42.1, 36.7, 21.7.

HRMS (ESI-TOF): calc'd for : $C_{13}H_{17}NO$ $[M+H]^+$: 204.1388, found 204,1391.

TLC: R_f = 0.3 (100:2:1 CH_2Cl_2:MeOH:Et_3N)

Comparison of NMR data of synthetic aphanorphine (57) with literature



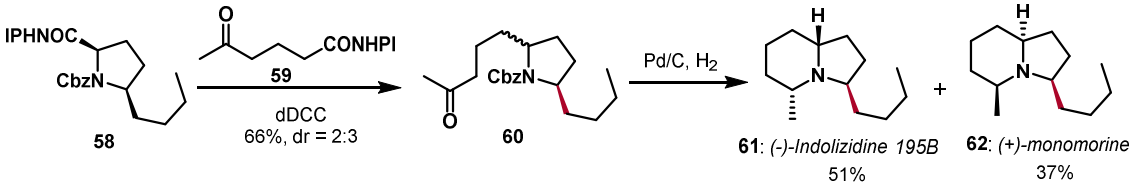
^{1}H NMR Data

Literature **57**[32] (200 MHz, CD_3OD)	Synthetic **57** (500 MHz, CD_3OD)	Δδ
6.90 (d, *J* = 8.2 Hz, 1H)	6.91 (d, *J* = 8.2 Hz, 1H)	0.01
6.68 (d, *J* = 2.5 Hz, 1H)	6.68 (d, *J* = 2.6 Hz, 1H)	0
6.56 (dd, *J* = 2.5, 8.2 Hz, 1H)	6.57 (dd, *J* = 8.2, 2.6 Hz, 1H)	0.01
3.42 (quin, *J* = 2.7 Hz, 1H)	3.41 (dt, *J* = 6.0, 3.0 Hz, 1H)	-0.01
3.00 (br d, *J* = 16.5 Hz, 1H)	2.98 (d, *J* = 16.3 Hz, 1H)	-0.02
2.84–2.89 (m, 2H)	2.91–2.82 (m, 1H)	-
2.65 (d, *J* = 9.5 Hz, 1H)	2.65 (d, *J* = 9.5 Hz, 1H)	0
2.43 (s, 3H)	2.43 (s, 3H)	0
2.04 (ddd, *J* = 1.1, 5.8, 11.0 Hz, 1H)	2.04 (ddd, *J* = 11.2, 5.9, 1.2 Hz, 1H)	0
1.85 (d, *J* = 11.0 Hz,1H)	1.85 (d, *J* = 11.1 Hz, 1H)	0
1.45 (s, 3H)	1.46 (s, 3H).	0.01

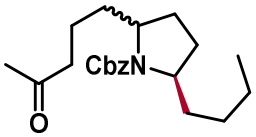
^{13}C NMR Data

Literature[32] (50 MHz, CD_3OD)	Synthetic **57** (151 MHz, CD_3OD)	Δδ
156.6	156.7	0.1
148.4	148.6	0.2
131.3	131.2	-.01
125.2	125.2	0
114.6	114.5	-0.1
110.9	110.9	0
72.7	72.7	0
63.7	63.4	-0.3
44.3	44.3	0
42.8	42.8	0
42.0	42.1	0.1
36.6	36.1	-0.5
21.6	21.7	0.1

Synthesis of indolizidine 195B and monomorine



Compound 60



Benzyl (2*R*)-2-butyl-5-(4-oxopentyl)pyrrolidine-1-carboxylate (60).

Following the **general procedure A** (with **L2**) on 1 mmol scale **58** ((prepared in situ from **SI-9**) with **59** (3 equiv.). Purification by flash column chromatography on silica gel (30:1 hexanes:acetone) afforded 227.4 mg (66%) of the title compound **60**.

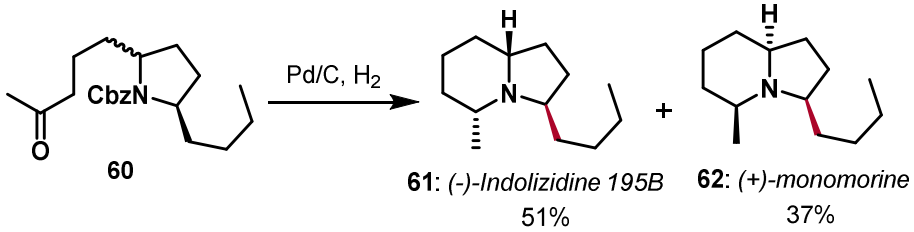
Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.32 (m, 4H), 7.32–7.28 (m, 1H), 5.20–5.03 (m, 2H), 3.87–3.68 (m, 2H), 2.56–2.21 (m, 2H), 2.13/2.03 (s, 3H), 2.00–1.78 (m, 3H), 1.71–1.46 (m, 5H), 1.36–1.12 (m, 6H), 0.92–0.79 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.0, 208.6, 154.3, 154.1, 137.0 (2C), 128.4 (3C), 128.1, 127.9, 127.8, 66.5, 66.4 (2C), 58.2, 57.7, 57.2, 43.4, 43.2, 33.6, 33.5, 32.2, 32.0, 29.8, 29.7, 28.8, 28.7, 28.5, 27.6, 26.6 (2C), 22.6, 22.5, 20.6, 20.4, 14.1, 14.0 (2C).

HRMS (ESI-TOF): calc'd for $C_{21}H_{32}NO_3$ $[M + H]^+$: 346.2382, found 346.2377.

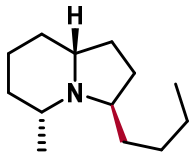
TLC: R_f = 0.4 (15:1 hexanes:acetone)



To a solution of **60** (104 mg, 0.3 mmol, 1.0 equiv.) in anhydrous methanol (15 mL) was added 20% Pd/C (10 mg). The resultant mixture was stirred under 1 atm of hydrogen for 5 h at room temperature. The mixture was filtered over Celite and rinsed with methanol. The solvent was then evaporated in vacuo. The crude product was purified by flash chromatography on Al_2O_3

(200:1 hexanes:EtOAc) to afford 29.7 mg (51%) **61** indolizidine 195B and 21.5 mg (37%) **62** monomorine.

Compound 61



Indolizidine 195B

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.30–3.25 (m, 1H), 2.56–2.47 (m, 1H), 2.43–2.34 (m, 1H), 1.92–1.84 (m, 2H), 1.81–1.75 (m, 1H), 1.73–1.67 (m, 1H), 1.62–1.57 (m, 1H), 1.55–1.49 (m, 1H), 1.48–1.41 (m, 2H), 1.37–1.16 (m, 5H), 1.14–0.99 (m, 3H), 1.09 (d, J = 6.2 Hz, 1H), 0.89 (t, J = 7.2 Hz, 3H).

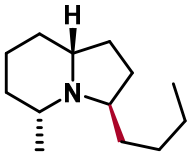
^{13}C NMR (151 MHz, $CDCl_3$): δ 58.9, 58.8, 52.0, 34.5, 32.4, 30.0, 29.1, 26.3, 24.9, 24.7, 23.0, 20.4, 14.2.

HRMS (ESI-TOF): calc'd for $C_{13}H_{26}N$ $[M + H]^+$: 196.2065, found 196.2060.

TLC: R_f = 0.4 (10:1 hexanes:EtOAc on Al_2O_3)

$[\alpha]_D^{25}$ = –96.4 (c = 0.14, MeOH) (lit. $[\alpha]_D^{23}$ = –96 (c = 0.19, MeOH))[33]

Comparison of NMR data of synthetic indolizidine 195B (61) with literature



^{1}H NMR Data

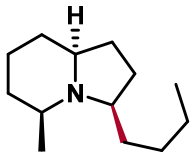
Literature **61**[33] ($CDCl_3$)	Synthetic **61** ($CDCl_3$)	Δδ
3.37–3.25 (m, 1H)	3.30–3.25 (m, 1H)	-
2.61–2.36 (m, 2H)	2.56–2.47 (m, 1H),	-
	2.43–2.34 (m, 1H)	-
1.94–1.02 (m, 16H)	1.92–1.84 (m, 2H)	-
	1.81–1.75 (m, 1H)	-
	1.73–1.67 (m, 1H)	-
	1.62–1.57 (m, 1H)	-

	1.55–1.49 (m, 1H)	-
	1.48–1.41 (m, 2H)	-
	1.37–1.16 (m, 5H)	-
	1.14–0.99 (m, 3H)	
1.12 (d, J = 5.7 Hz, 3H)	1.09 (d, J = 6.2 Hz, 1H)	-0.3
0.90 (t, J = 7.0 Hz, 3H)	0.89 (t, J = 7.2 Hz, 3H)	-0.1

^{13}C NMR Data

Literature **61**[33] (75 MHz, $CDCl_3$)	Synthetic **61** (151 MHz, $CDCl_3$)	Δδ
60.2	58.9	-1.3
58.9	58.8	0.1
51.9	52	0
34.5	34.5	0
32.4	32.4	0
30.0	30.0	0
29.4	29.1	0
26.3	26.3	-0.1
24.9	24.9	0
24.8	24.7	0
23.0	23.0	0
20.4	20.4	0
14.2	14.2	0.1

Compound 62



Monomorin (62)

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.50–2.42 (m, 1H), 2.24–2.15 (m, 1H), 2.10–2.02 (m, 1H), 1.86–1.77 (m, 1H), 1.76–1.60 (m, 4H), 1.55–1.48 (m, 1H), 1.47–1.36 (m, 2H), 1.36–1.16 (m, 8H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H).

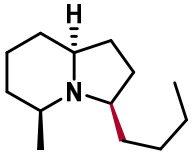
^{13}C NMR (151 MHz, $CDCl_3$): δ 67.1, 62.9, 60.2, 39.7, 35.8, 30.9, 30.3, 29.7, 29.4, 24.9, 22.9 (2C), 14.1.

HRMS (ESI-TOF): calc'd for $C_{13}H_{26}N$ $[M + H]^+$: 196.2065, found 196.2068.

TLC: R_f = 0.5 (10:1 hexanes:EtOAc on Al_2O_3)

$[\alpha]_D^{20}$ = +26 (*c* = 0.1, n-hexane) (lit. $[\alpha]_D^{20}$ = +32 (*c* = 0.14, n-hexane))[34]

Comparison of NMR data of synthetic monomorin (62) with literature



^{1}H NMR Data

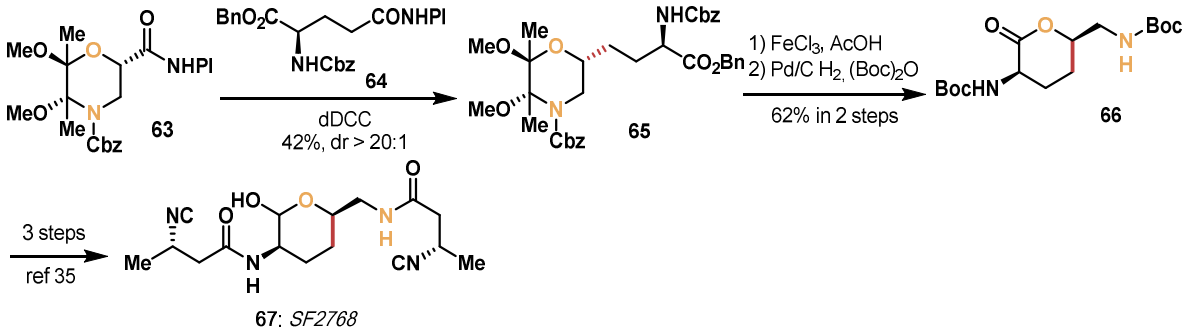
Literature **62**[34] (500 MHz, $CDCl_3$)	Synthetic **62** (600 MHz, $CDCl_3$)	Δδ
2.48 (brt, *J* = 8.3 Hz, 1H)	2.50–2.42 (m, 1H)	-
2.29–2.17 (m, 1H),	2.24–2.15 (m, 1H)	-
2.11–2.05 (m, 1H)	2.10–2.02 (m, 1H)	-
1.90–1.50 (m, 6H)	1.86–1.77 (m, 1H)	-
	1.76–1.60 (m, 4H)	-
1.49–1.15 (m, 10H)	1.55–1.48 (m, 1H)	-
	1.47–1.36 (m, 2H)	-
	1.36–1.16 (m, 8H)	-
1.14 (d, *J* = 6.0 Hz, 3H)	1.12 (d, *J* = 6.4 Hz, 3H)	-0.02
0.89 (t, *J* = 7.0 Hz, 3H);	0.88 (t, *J* = 7.1 Hz, 3H)	-0.01

^{13}C NMR Data

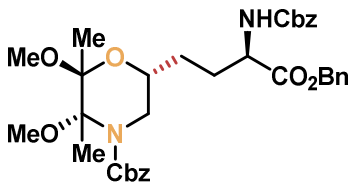
Literature **62**[34] (126 MHz, $CDCl_3$)	Synthetic **62** (151 MHz, $CDCl_3$)	Δδ
67.1	67.1	0

62.9	62.9	0
60.2	60.2	0
39.7	39.7	0
35.8	35.8	0
30.9	30.9	0
30.3	30.3	0
29.8	29.7	-0.1
29.4	29.4	0
24.9	24.9	0
22.9 (2C)	22.9 (2C)	-
14.0	14.1	0.1

Formal synthesis of SF2768



Compound 65



Benzyl (2*S*,3*R*,6*R*)-6-((*R*)-4-(benzyloxy)-3-(((benzyloxy)carbonyl)amino)-4-oxobutyl)-2,3-dimethoxy-2,3-dimethylmorpholine-4-carboxylate (65).

Following the **general procedure D** on 0.1 mmol scale RAE **63** with RAE **64** (3.0 equiv) Purification by PTLC (4:1 hexanes:acetone) afforded 26.6 mg (42%) of the title compound **65**.

Physical State: colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 15H), 5.38 (d, *J* = 8.2 Hz, 1H), 5.25–4.98 (m, 6H), 4.41 (td, *J* = 8.0, 5.2 Hz, 1H), 3.83 (dd, *J* = 13.3, 2.7 Hz, 1H), 3.76–3.65 (m, 1H), 3.16 (s,

3H), 3.14 (s, 3H), 2.93 (dd, J = 13.3, 11.1 Hz, 1H), 1.96–1.81 (m, 2H), 1.71 (s, 3H), 1.50–1.40 (m, 2H), 1.30 (s, 3H).

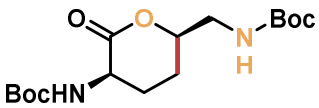
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 155.9, 155.8, 136.6, 136.2, 135.2, 128.5 (2C), 128.4 (2C), 128.1 (3C), 127.9, 127.7, 100.7, 90.2, 67.1 (2C), 67.0, 53.7, 48.4, 47.9, 45.3, 28.5, 28.0, 18.9, 18.0.

HRMS (ESI-TOF): calc'd for $C_{35}H_{42}N_2O_9Na$ $[M+Na]^+$: 657.2788, found 657.2805.

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

$[\alpha]_D^{25}$ = + 17.9 (c = 1.0, $CHCl_3$).

Compound 66



***Tert*-butyl ((3*R*,6*R*)-6-(((*tert*-butoxycarbonyl)amino)methyl)-2-oxotetrahydro-2H-pyran-3-yl)carbamate (66)**

To a solution of **65** (10 mg, 0.016 mmol, 1.0 equiv) in toluene/AcOH/H_2O (2.5 mL/0.25 mL/ 12.5 µL) was added $FeCl_3$ (50 µL, 0.02 M in AcOH) at room temperature. The mixture was stirred at 80 ºC for 10 h. The solvent was then removed under reduced pressure and traces of acetic acid were removed azeotropically with toluene. At this time, the reaction mixture was dissolved in EtOAc (1.5 ml), 10% Pd/C (5 mg) and Boc_2O (20.9 mg, 0.096 mmol, 6 equiv) were added. The resulting heterogeneous suspension was flushed with hydrogen for 5 minutes and then left under a hydrogen atmosphere for 48 h. The resulting suspension was filtered through a short pad of celite with the aid of ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with (3:1 hexanes:acetone) as the eluent to give **66** (3.4 mg, 62%).

Physical State: white solid.

m.p.: 77-79 ºC.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.31 (br, 1H), 4.97 (br, 1H), 4.54–4.34 (m, 2H), 3.65–3.44 (m, 1H), 3.19 (td, J = 14.4, 6.6 Hz, 1H), 2.67–2.48 (m, 1H), 2.01 (ddt, J = 14.8, 10.8, 4.6 Hz, 1H), 1.75 (dtd, J = 14.1, 11.3, 5.5 Hz, 1H), 1.59–1.51 (m, 1H), 1.45 (s, 9H), 1.44 (s, 9H).

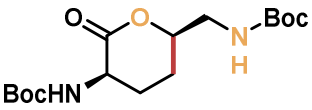
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7, 155.9, 155.2, 80.3, 79.9, 48.5, 43.9, 28.3 (2C), 24.6, 23.2.

HRMS (ESI-TOF): calc'd for $C_{16}H_{28}N_2O_6Na$ $[M+H]^+$: 367.1845, found 367.1844.

TLC: R_f = 0.3 (3:1 hexanes:acetone)

$[\alpha]_D^{25}$ = –65.7 (c = 0.3, $CHCl_3$). (enantiomer, lit. $[\alpha]_D^{20}$ = +70.6 (*c* = 1.0, $CHCl_3$))[35]

Comparison of NMR data of synthetic 66 with literature



^{1}H NMR Data

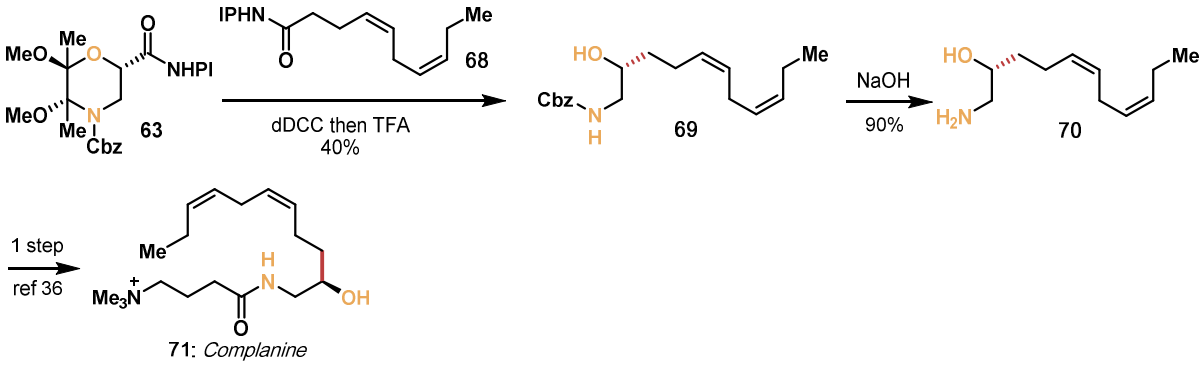
Literature (+) **66**[35] (600 MHz, $CDCl_3$)	Synthetic (-) **66** (600 MHz, $CDCl_3$)	Δδ
5.33 (d, *J* = 6.6 Hz, 1H)	5.31 (br, 1H)	-0.02
4.99 (t, *J* = 6.1 Hz, 1H)	4.97 (br, 1H)	-0.02
4.53–4.35 (m, 2H)	4.54–4.34 (m, 2H)	-
3.54–3.45 (m, 1H)	3.65–3.44 (m, 1H)	-
3.18 (dt, *J* = 13.9, 6.3 Hz, 1H)	3.19 (td, *J* = 14.4, 6.6 Hz, 1H)	0.01
2.67–2.50 (m, 1H)	2.67–2.48 (m, 1H)	-
2.00 (ddt, *J* = 15.0, 10.2, 4.3 Hz, 1H)	2.01 (ddt, *J* = 14.8, 10.8, 4.6 Hz, 1H)	0.01
1.74 (dtd, *J* = 16.5, 11.6, 5.4 Hz, 1H)	1.75 (dtd, *J* = 14.1, 11.3, 5.5 Hz, 1H)	0.01
1.55 (ddt, *J* = 16.8, 12.0, 5.0 Hz, 1H)	1.59–1.51 (m, 1H)	-
1.43 (s, 9H)	1.45 (s, 9H)	0.02
1.42 (s, 9H)	1.44 (s, 9H)	0.02

^{13}C NMR Data

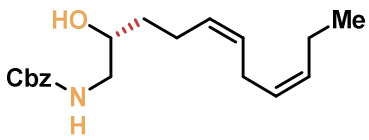
Literature (+) **66**[35] (151 MHz, $CDCl_3$)	Synthetic (-) **66** (151 MHz, $CDCl_3$)	Δδ
172.9	172.7	-0.2
156.0	155.9	-0.1
155.3	155.2	-0.1
80.4	80.3	-0.1
80.0	79.9	-0.1
76.9	obscured by $CDCl_3$	-

48.6	48.5	-0.1
44.0	43.9	-0.1
28.5 28.4	28.3 (2C)	-
24.7	24.6	-0.1
23.3	23.2	-0.1

Formal synthesis of complanine



Compound 69



Benzyl ((*R*,5*Z*,8*Z*)-2-hydroxyundeca-5,8-dien-1-yl)carbamate (69).

Following the **general procedure D** on 0.1 mmol scale **63** with **68** (3.0 equiv). After completion of electrolysis, TFA (1.5 mL) was added, and then the reaction was stirred at rt for another 12 h. Purification by PTLC (3:1 hexanes:acetone) afforded 12.7 mg (40%) of the title compound **69**.

Physical State: colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.29 (m, 5H), 5.47–5.26 (m, 4H), 5.19 (br, 1H), 5.10 (s, 2H), 3.75–3.68 (m, 1H), 3.42–3.33 (m, 1H), 3.14–3.03 (m, 1H), 2.85–2.69 (m, 2H), 2.26–1.90 (m, 4H), 1.58–1.46 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H).

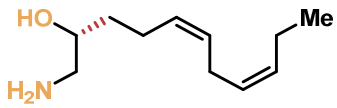
^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.1, 136.4, 132.1, 129.2, 128.9, 128.5, 128.1 (2C), 127.0, 70.9, 66.9, 47.0, 34.4, 25.5, 23.3, 20.5, 14.2.

HRMS (ESI-TOF): calc'd for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2069, found 318.2079.

TLC: R_f = 0.4 (3:1 hexanes:acetone)

$[\alpha]_D^{25}$ = –9.1 (c = 1.0, $CHCl_3$).

Compound 70



(*R*,5*Z*,8*Z*)-1-aminoundeca-5,8-dien-2-ol (70)

A solution of **69** (10 mg, 0.03 mmol, 1.0 equiv) in MeOH/2 M KOH (0.25 mL/0.25 mL) was heated at 100 °C and stirred for 12 h. The reaction was quenched with H_2O (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 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 (DCM:MeOH:Et_3N 200:5:1) to give **70** (5.2 mg, 90%).

Physical State: colorless oil.

^{1}H NMR (600 MHz, CD_3OD): 5.45–5.21 (m, 4H), 3.76 (br, 1H), 3.01 (d, J = 12.2 Hz, 1H), 2.81 (t, J = 6.3 Hz, 2H), 2.76 (t, J = 11.0 Hz, 1H), 2.30–2.22 (m, 1H), 2.21–2.13 (m, 1H), 2.12–2.04 (m, 2H), 1.57–1.47 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). (^{1}H NMR of **70** matched with the literature[36])

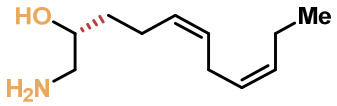
^{13}C NMR (151 MHz, CD_3OD) δ 131.4, 129.0, 128.4, 127.1, 71.1, 46.8, 34.6, 25.1, 23.1, 20.2, 13.4. (^{13}C NMR of **70**•HCl matched with the literature[36])

HRMS (ESI-TOF): calc'd for $C_{11}H_{22}NO$ $[M+H]^+$: 184.1701, found 184.1702.

TLC: R_f = 0.2 (40:1 DCM:MeOH)

$[\alpha]_D^{25}$ = –2.3 (c = 0.25, MeOH).

Comparison of NMR data of synthetic 70 with literature



^{1}H NMR Data

Literature **70**[36] (600 MHz, CD_3OD)	Synthetic **70** (600 MHz, CD_3OD)	Δδ
5.37–5.25 (m, 4H)	5.45–5.21 (m, 4H)	-
3.75 (br, 1H)	3.76 (br, 1H)	0.01

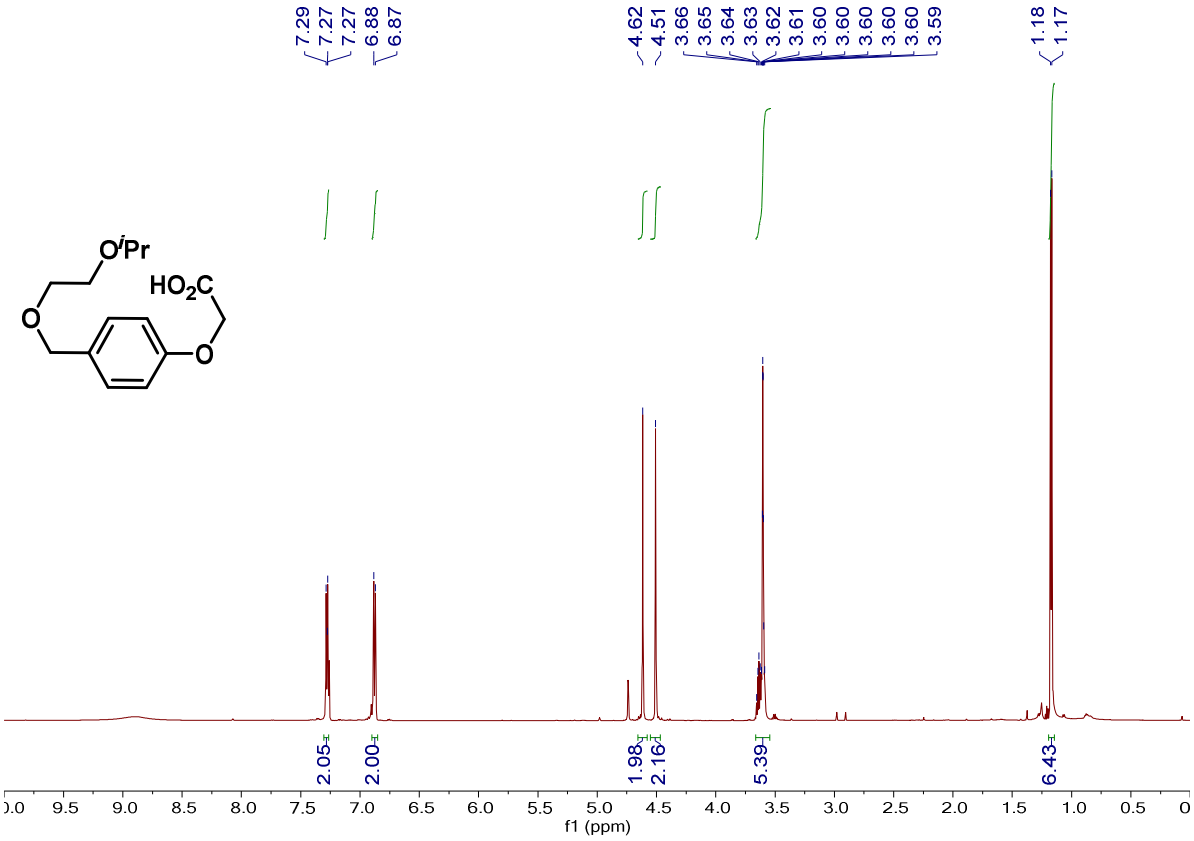
2.96 (dd, *J* = 12.4, 3.1 Hz, 1H)	3.01 (d, *J* = 12.2 Hz, 1H)	0.05
2.79 (t, *J* = 6.6 Hz, 2H)	2.81 (t, *J* = 6.3 Hz, 2H)	0.02
2.73 (dd, *J* = 12.4, 9.6 Hz, 1H)	2.76 (t, *J* = 11.0 Hz, 1H)	0.03
2.23 (m, 1H)	2.30–2.22 (m, 1H)	-
2.16 (m, 1H)	2.21–2.13 (m, 1H)	-
2.06 (m, 2H)	2.12–2.04 (m, 2H)	-
1.49 (m, 2H)	1.57–1.47 (m, 2H)	-
0.95 (t, *J* = 7.6 Hz, 3H)	0.96 (t, *J* = 7.4 Hz, 3H)	0.01

^{13}C NMR Data

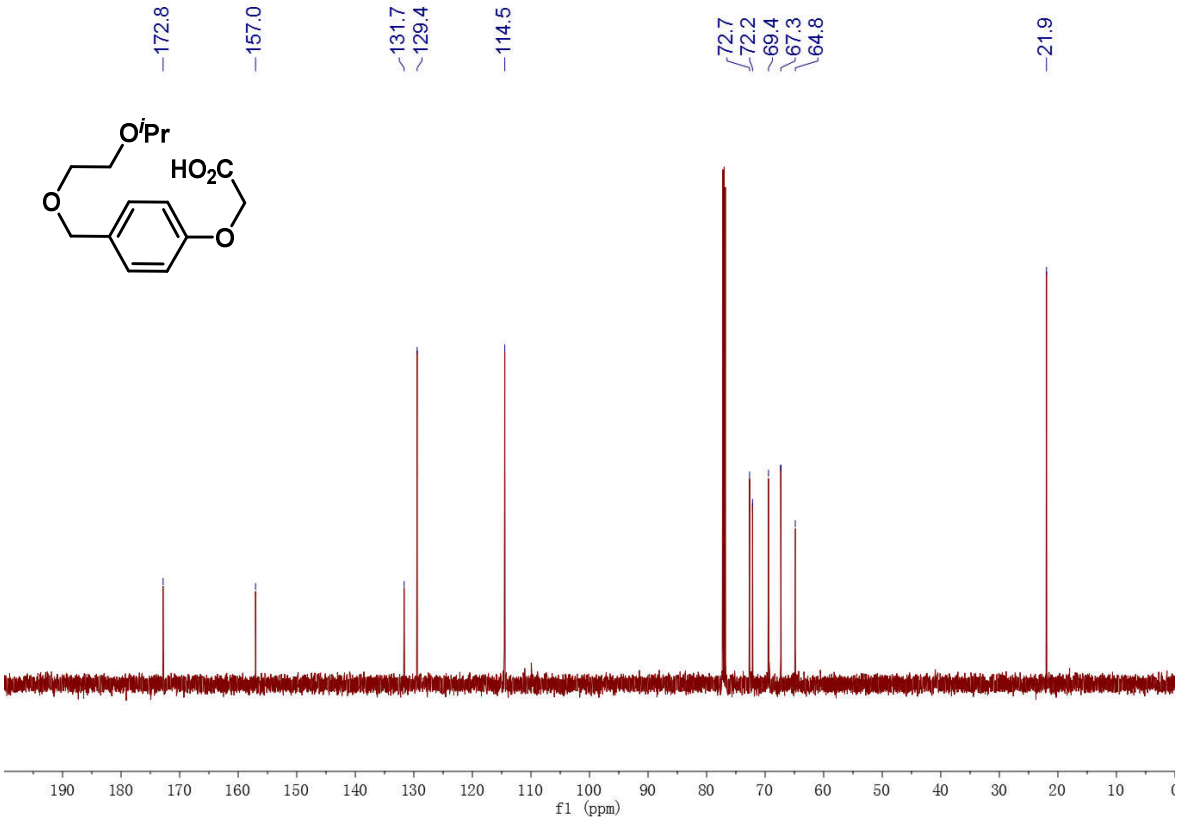
Literature (+) **70** (not clarified)[36] (600 MHz, CD_3OD)	Synthetic (-) **70•HCl** (600 MHz, CD_3OD)	Δδ
131.4	131.4	0
129.0	129.0	0
128.3	128.4	0.1
127.0	127.1	0.1
71.4	71.1	-0.3
46.9	46.8	-0.1
34.5	34.6	0.1
25.0	25.1	0.1
23.0	23.1	0.1
20.1	20.2	0.1
13.3	13.4	0.1

NMR Spectra

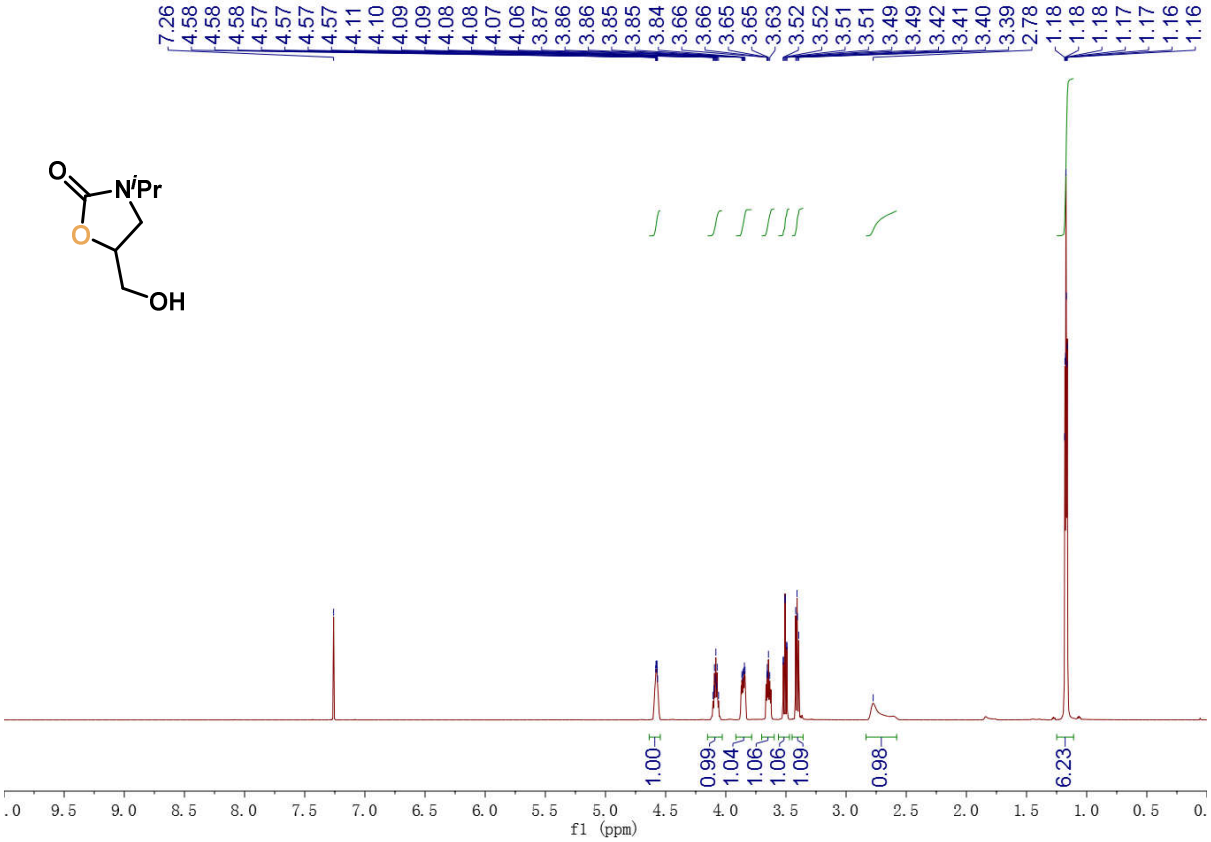
^{1}H NMR of Compound SI-1 (600 MHz, $CDCl_3$):



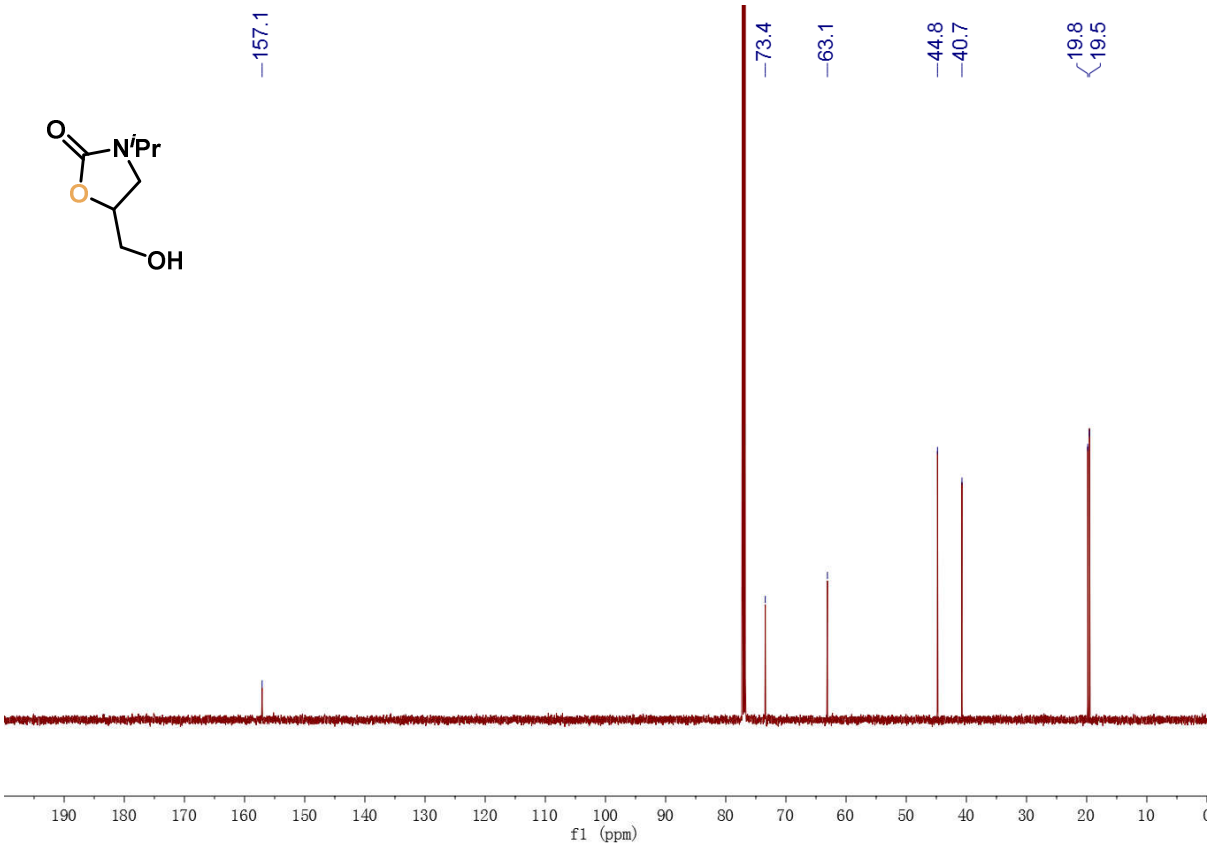
^{13}C NMR of Compound SI-1 (151 MHz, $CDCl_3$):



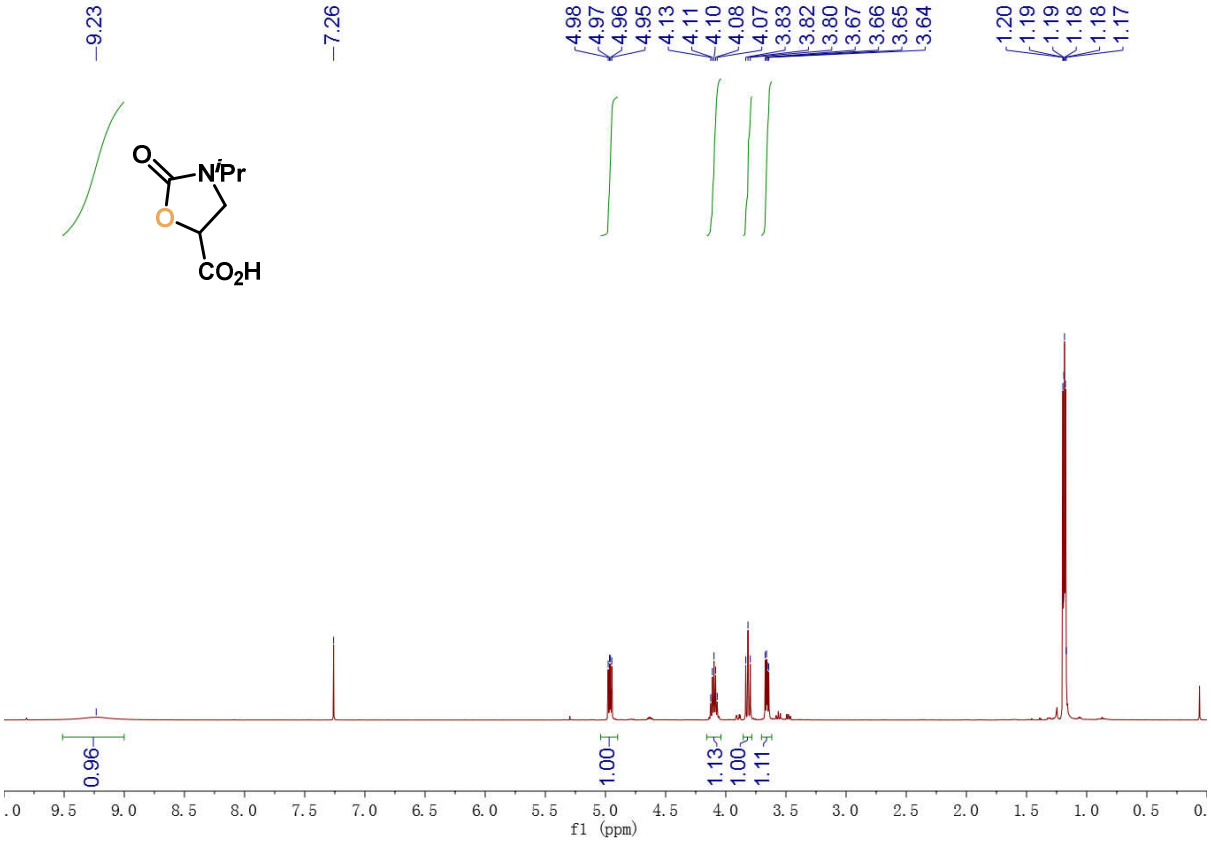
^{1}H NMR of Compound SI-2 (600 MHz, $CDCl_3$):



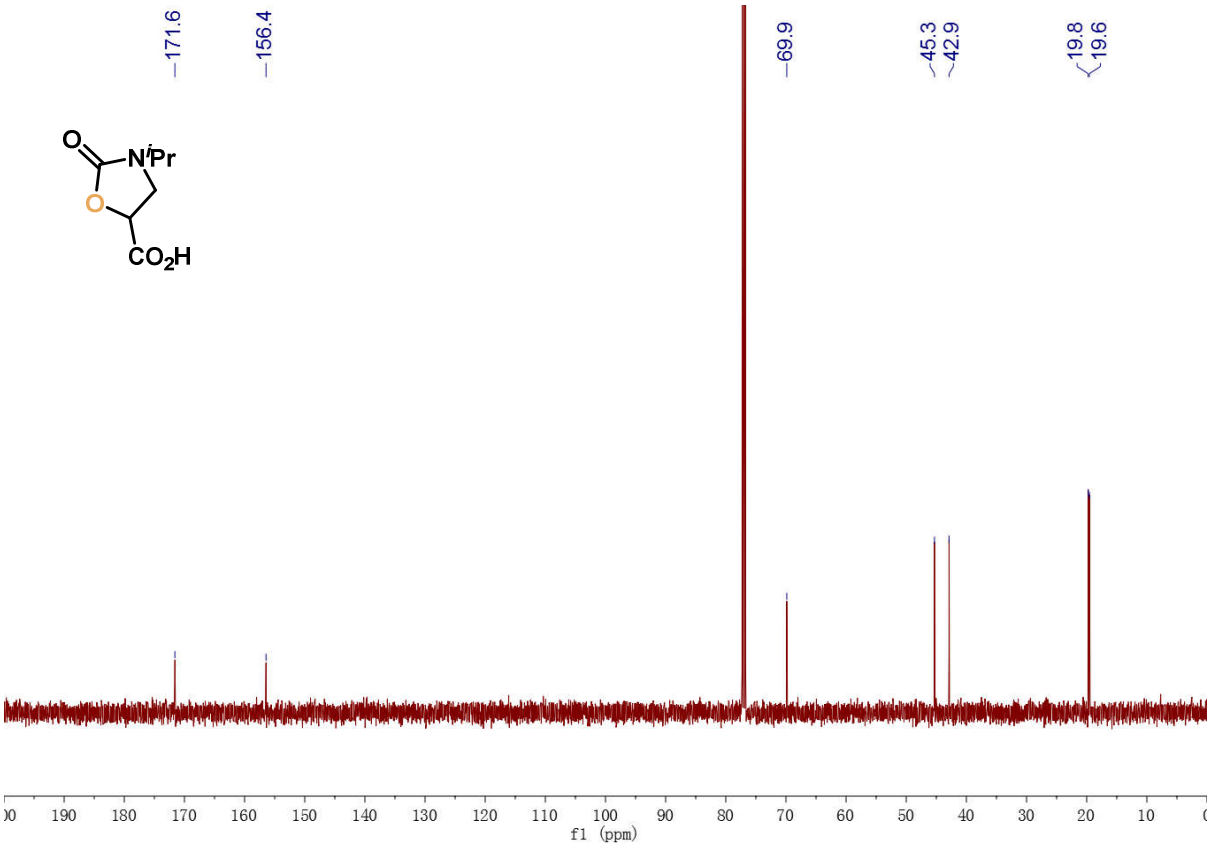
^{13}C NMR of Compound SI-2 (151 MHz, $CDCl_3$):



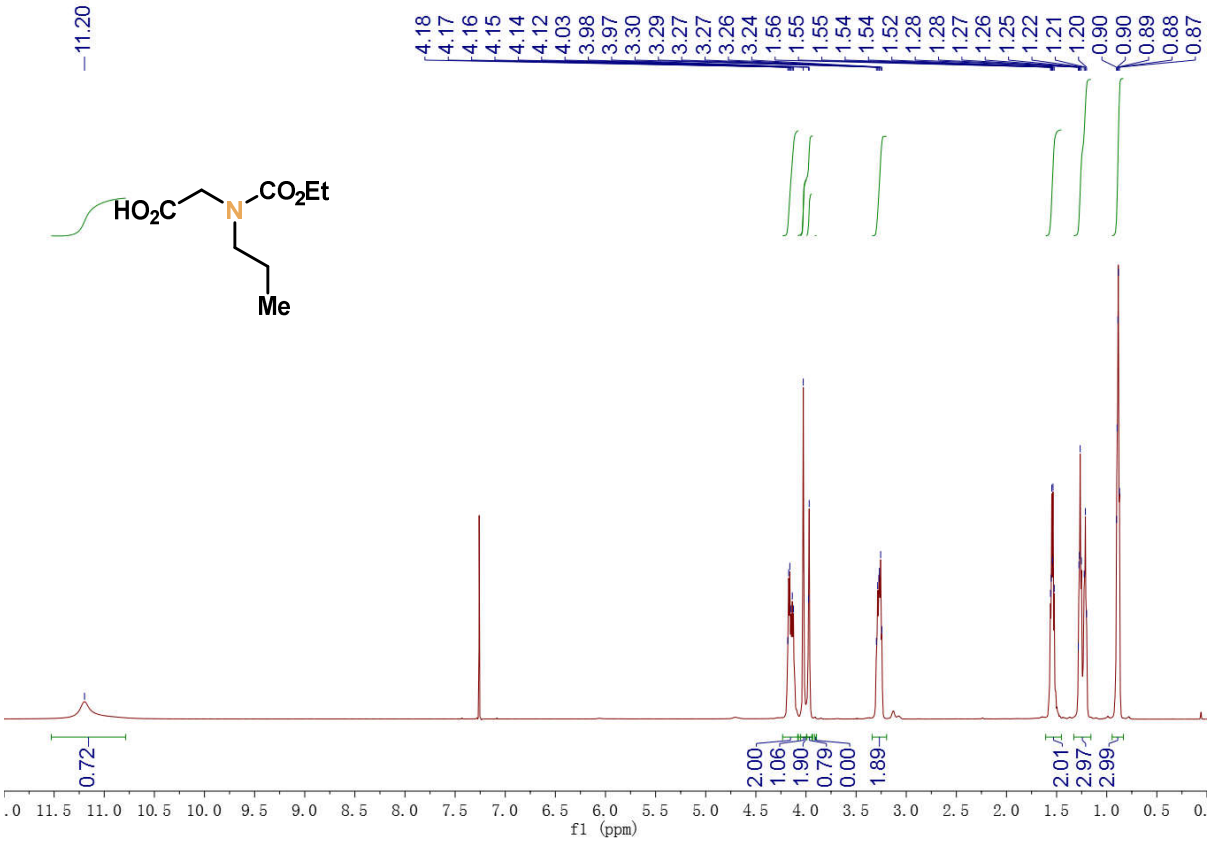
^{1}H NMR of Compound SI-3 (500 MHz, $CDCl_3$):



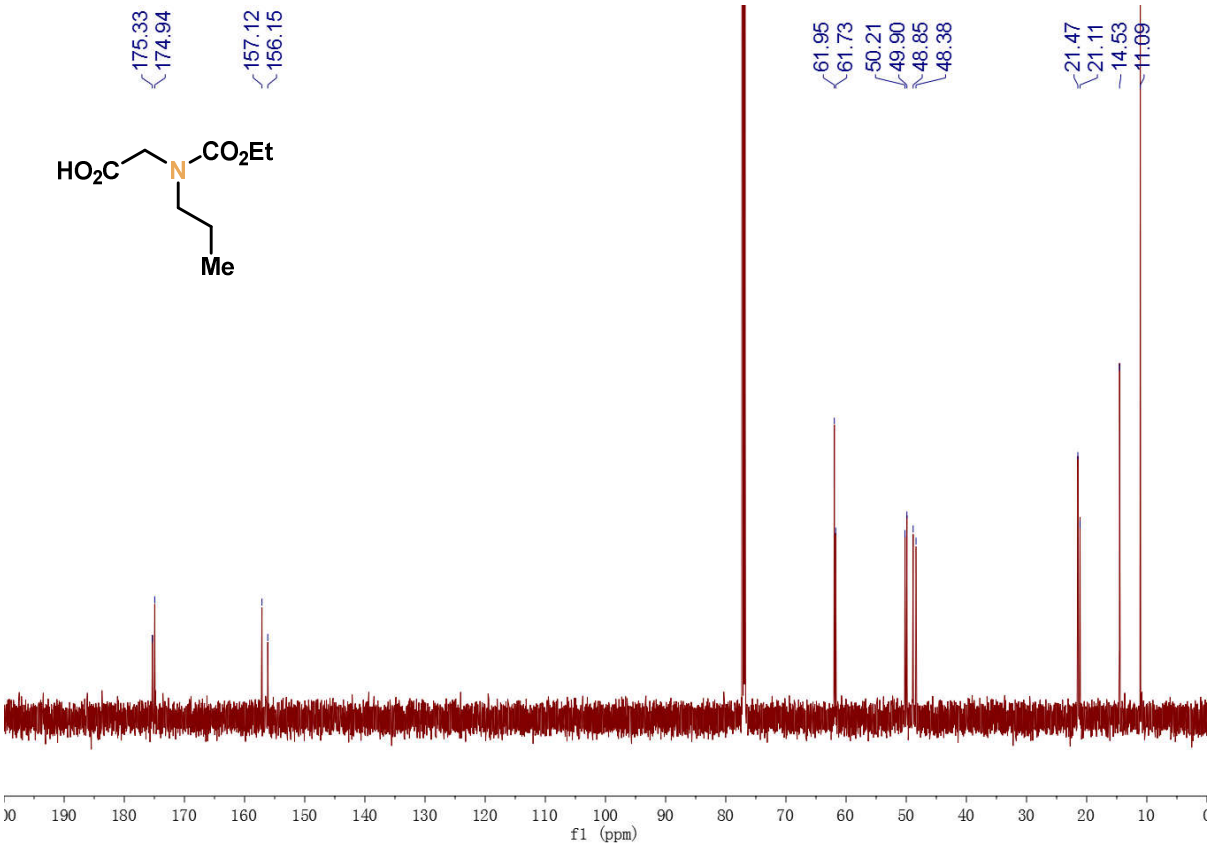
^{13}C NMR of Compound SI-3 (126 MHz, $CDCl_3$):



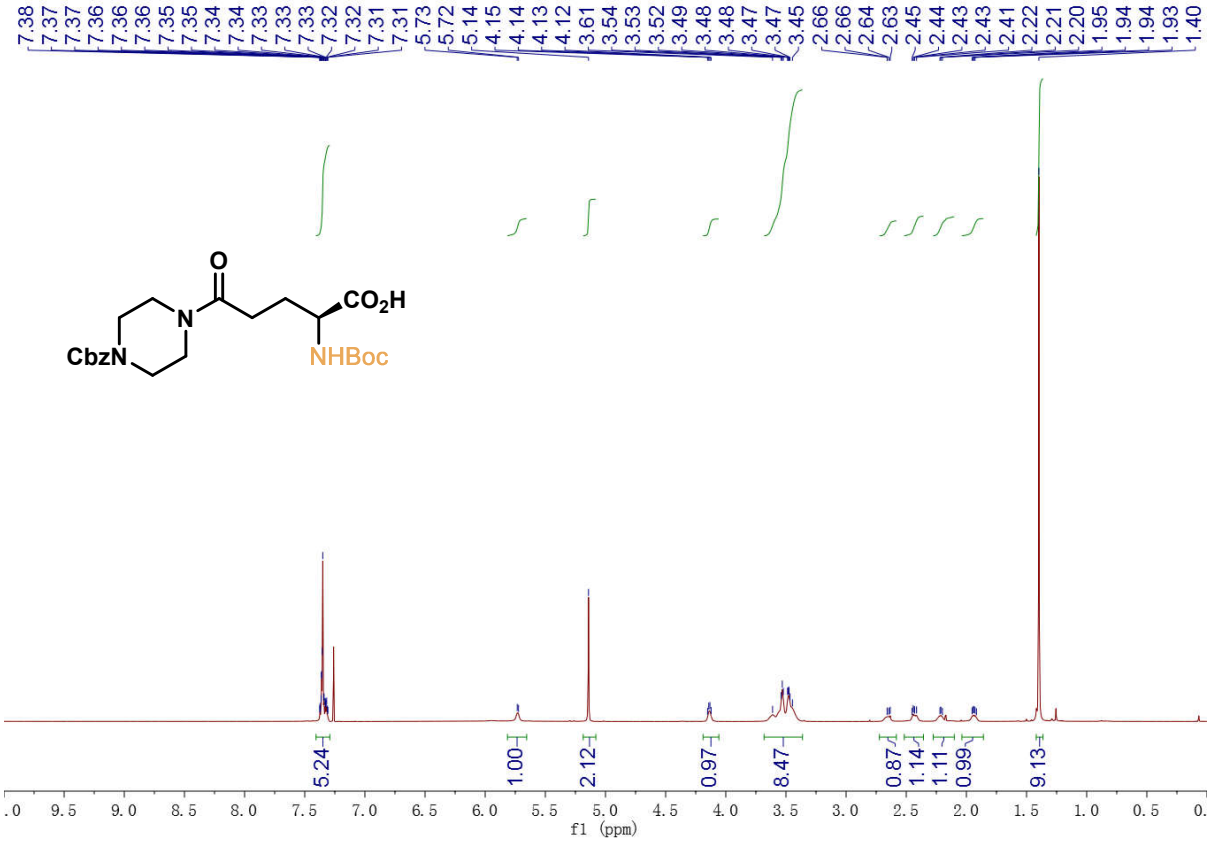
^{1}H NMR of Compound SI-4 (600 MHz, $CDCl_3$):



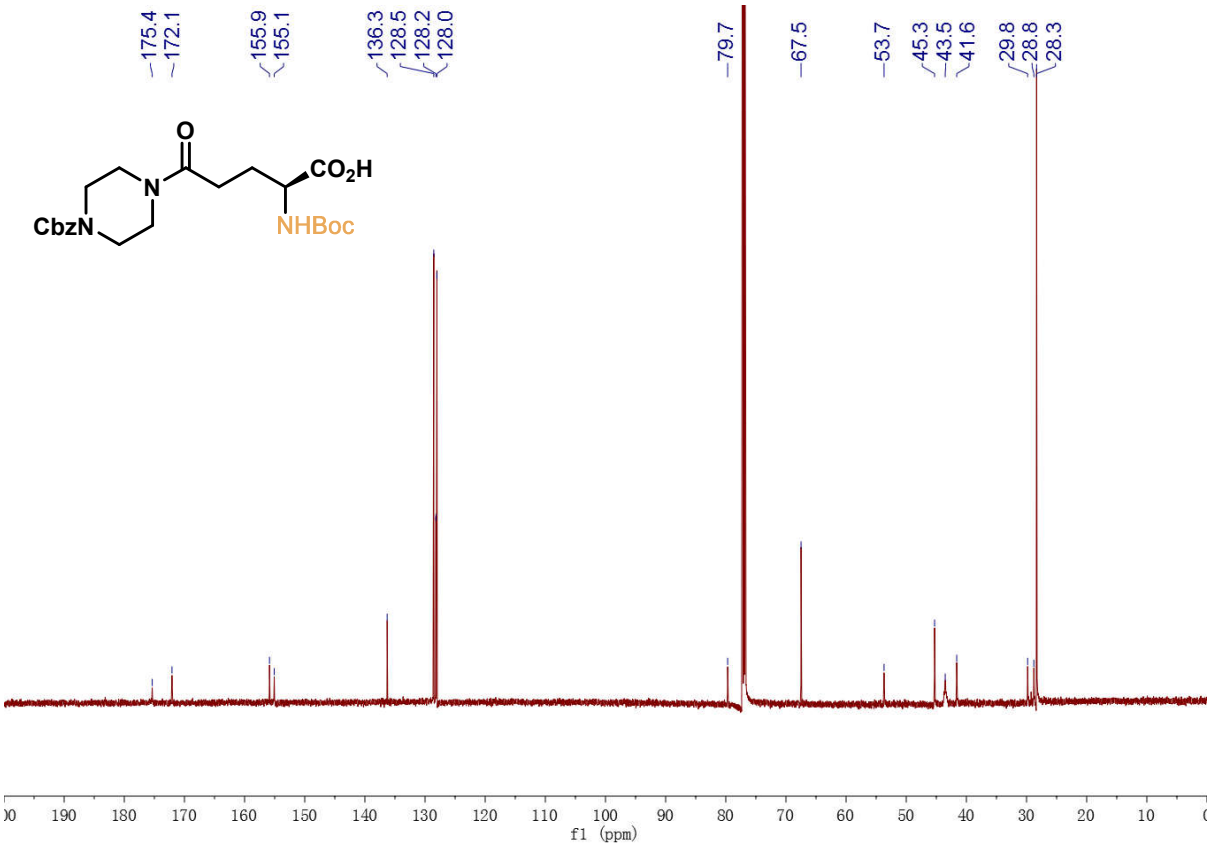
^{13}C NMR of Compound SI-4 (151 MHz, $CDCl_3$):



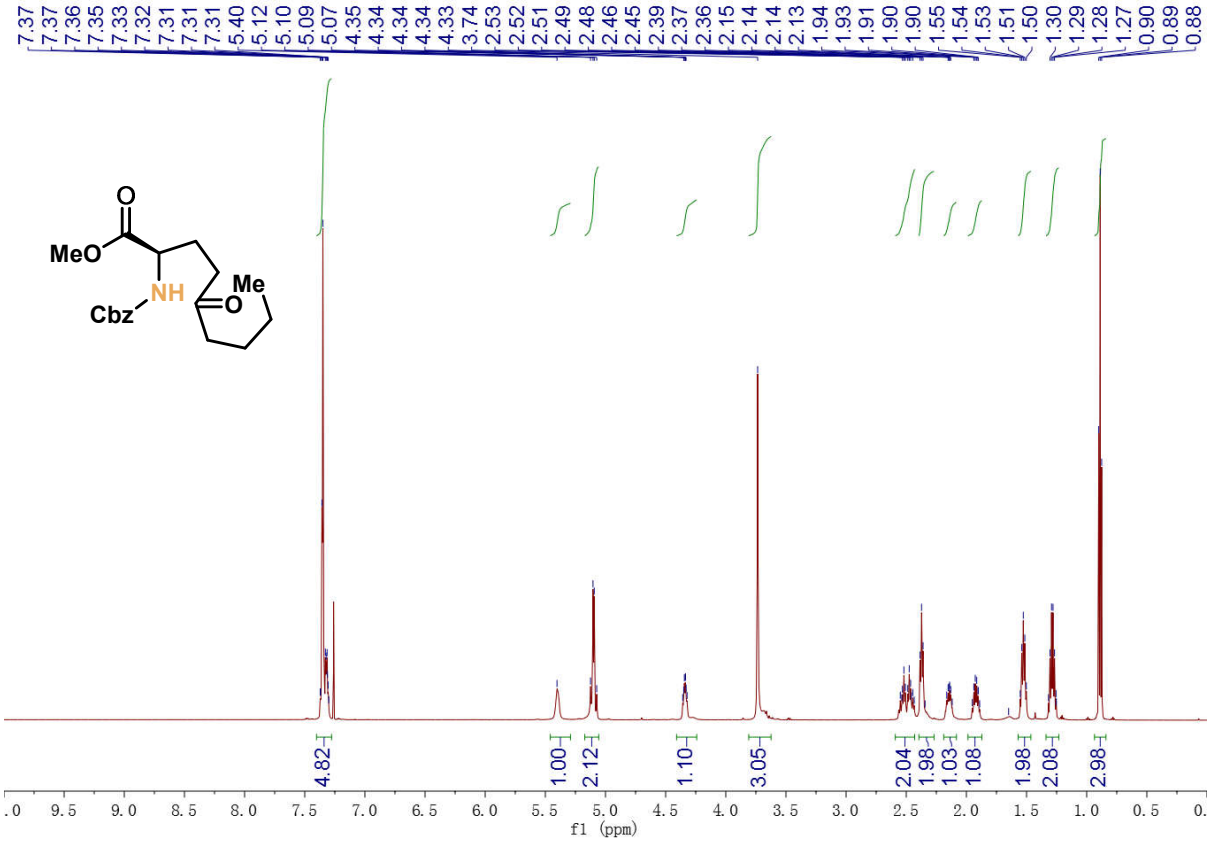
^{1}H NMR of Compound SI-5 (600 MHz, $CDCl_3$):



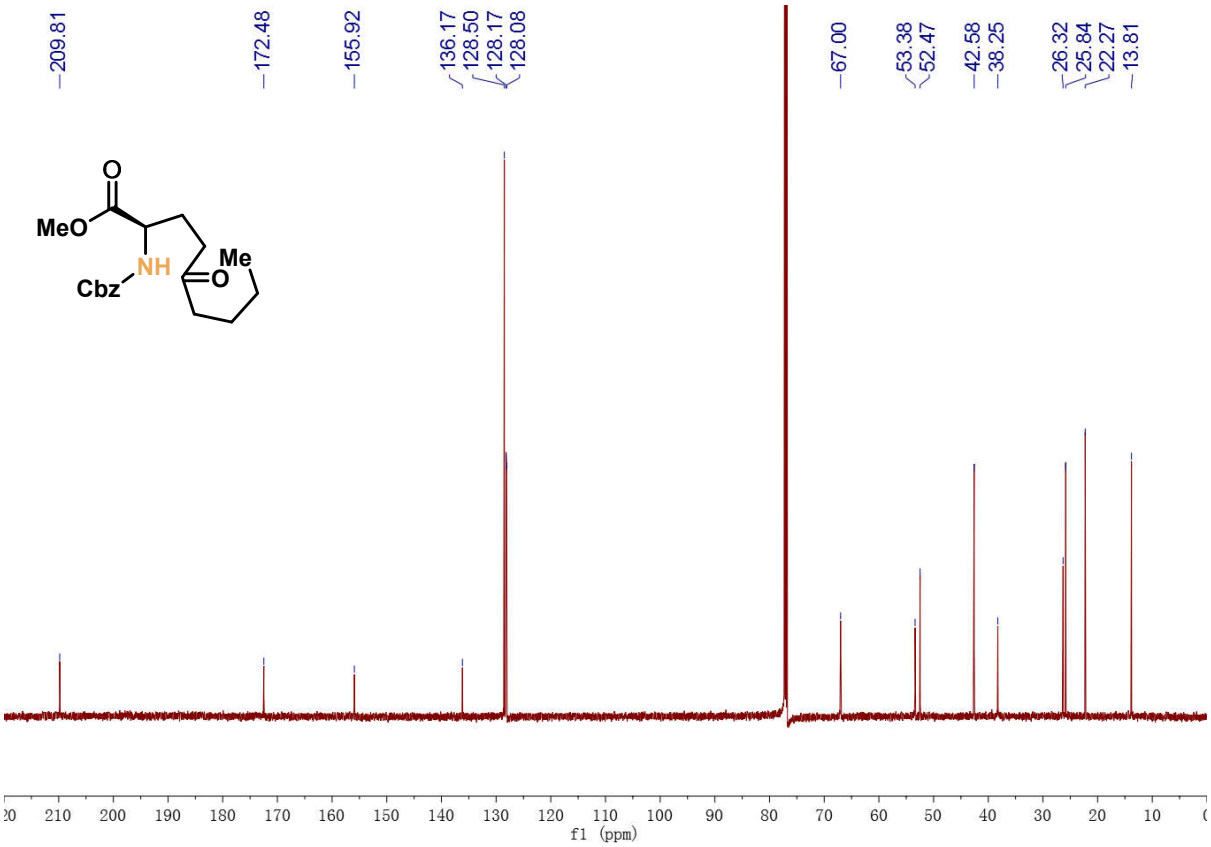
^{13}C NMR of Compound SI-5 (151 MHz, $CDCl_3$):



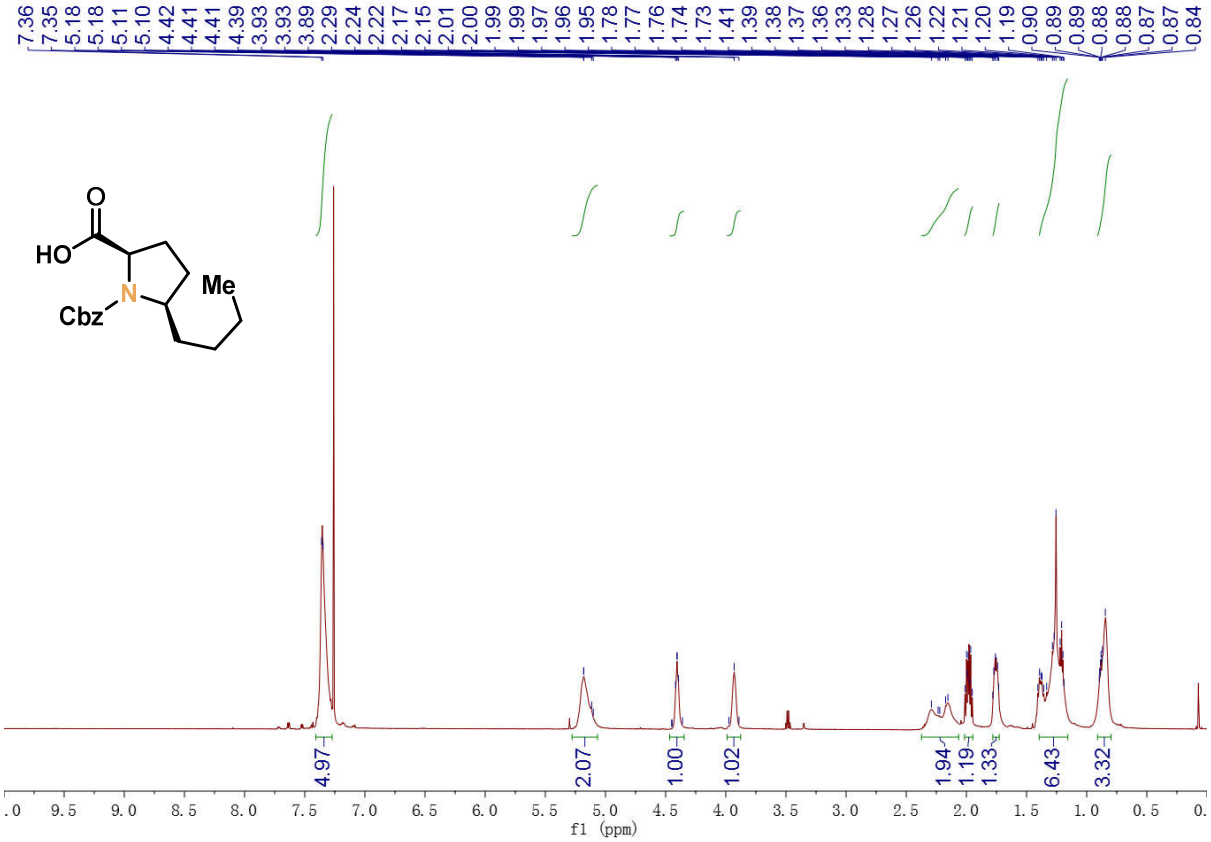
^{1}H NMR of Compound SI-8 (600 MHz, $CDCl_3$):



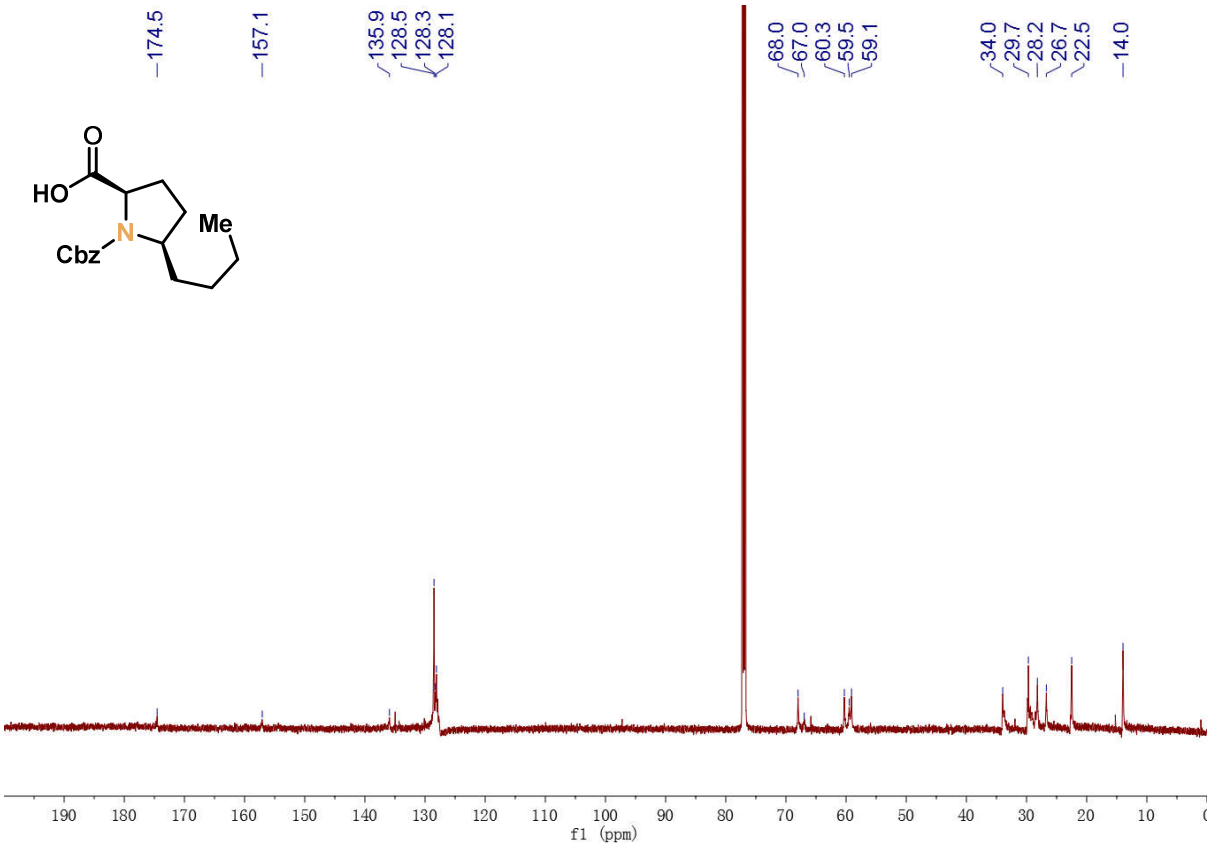
^{13}C NMR of Compound SI-8 (151 MHz, $CDCl_3$):



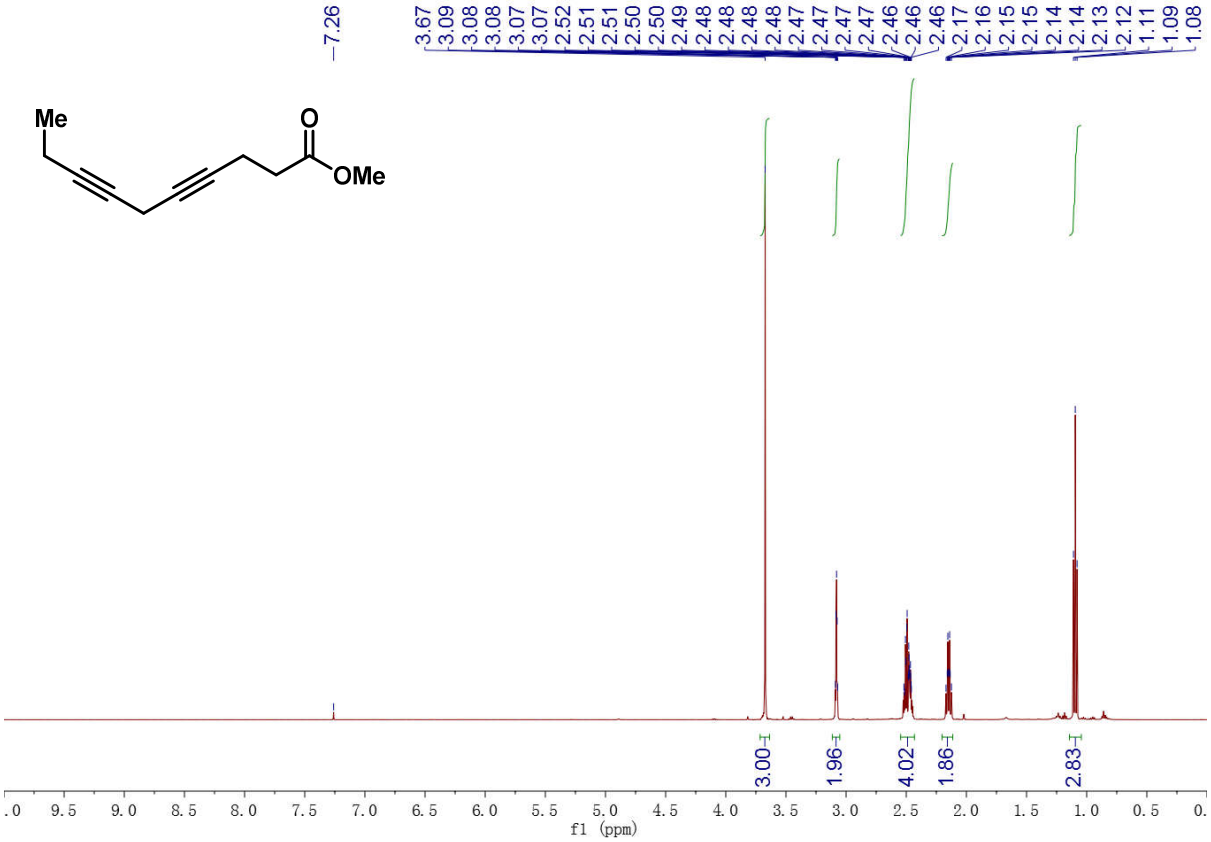
^{1}H NMR of Compound SI-9 (600 MHz, $CDCl_3$):



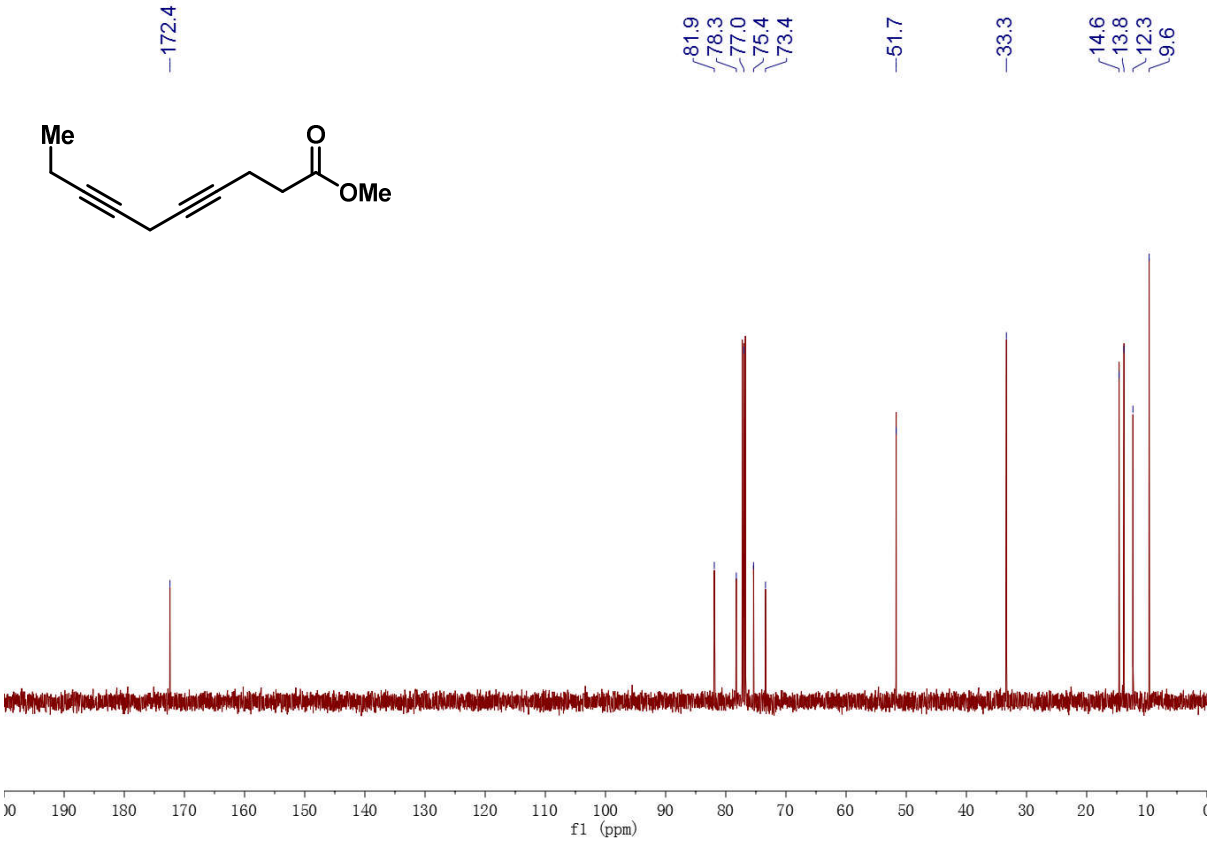
^{13}C NMR of Compound SI-9 (151 MHz, $CDCl_3$):



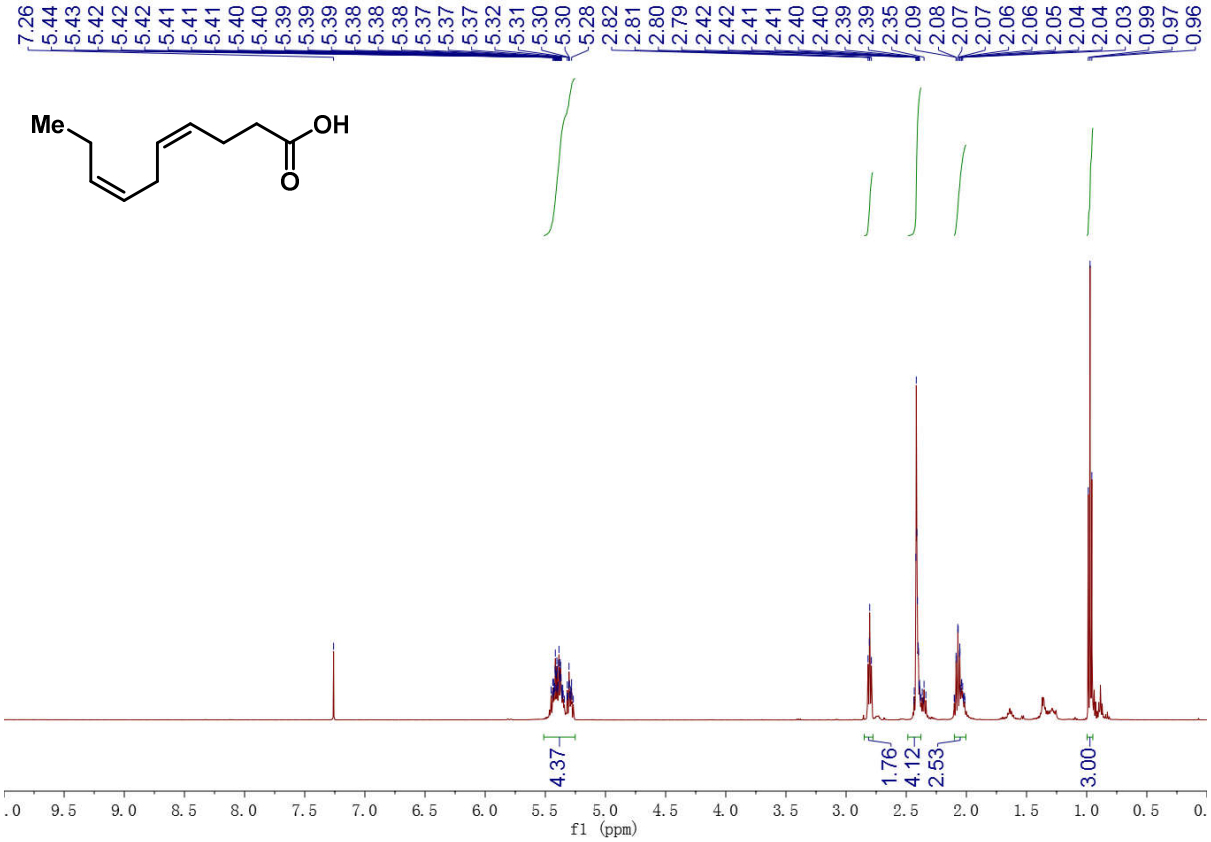
^{1}H NMR of Compound SI-10 (600 MHz, $CDCl_3$):



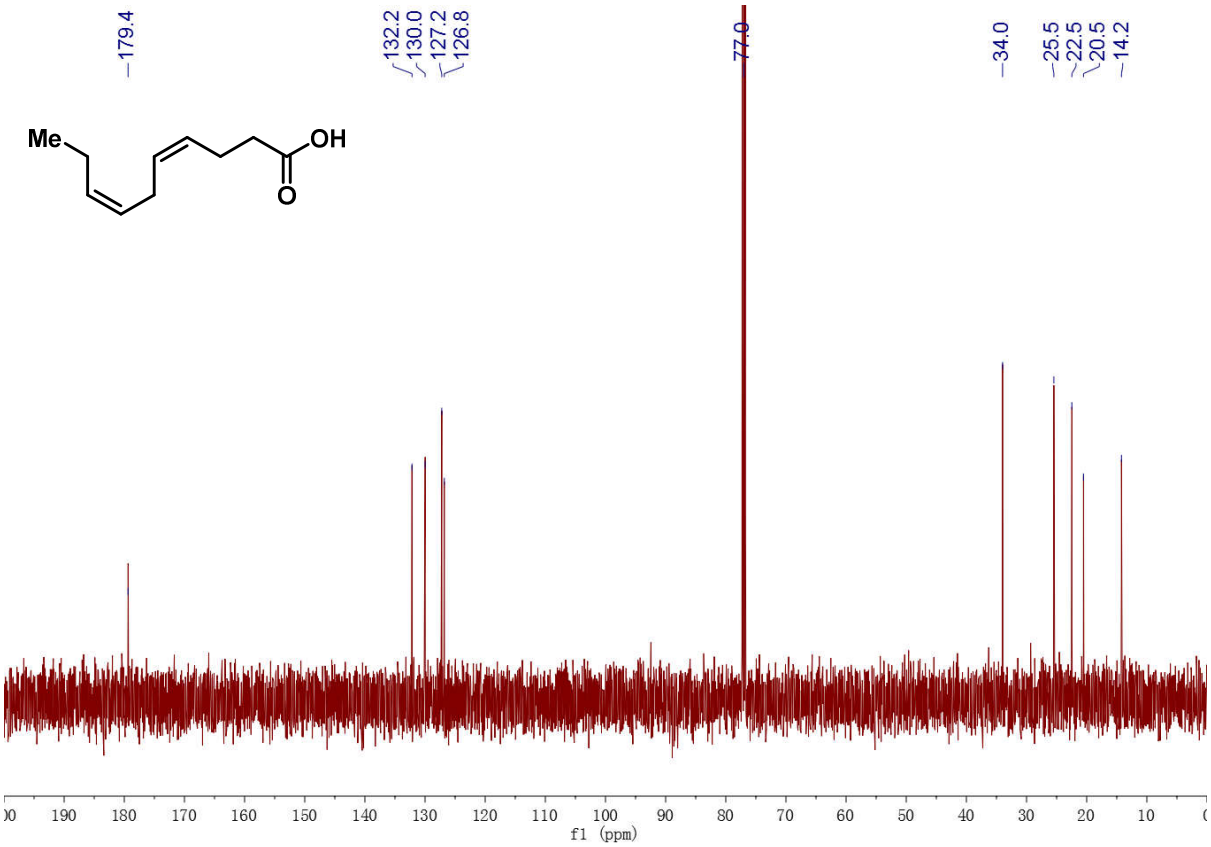
^{13}C NMR of Compound SI-10 (151 MHz, $CDCl_3$):



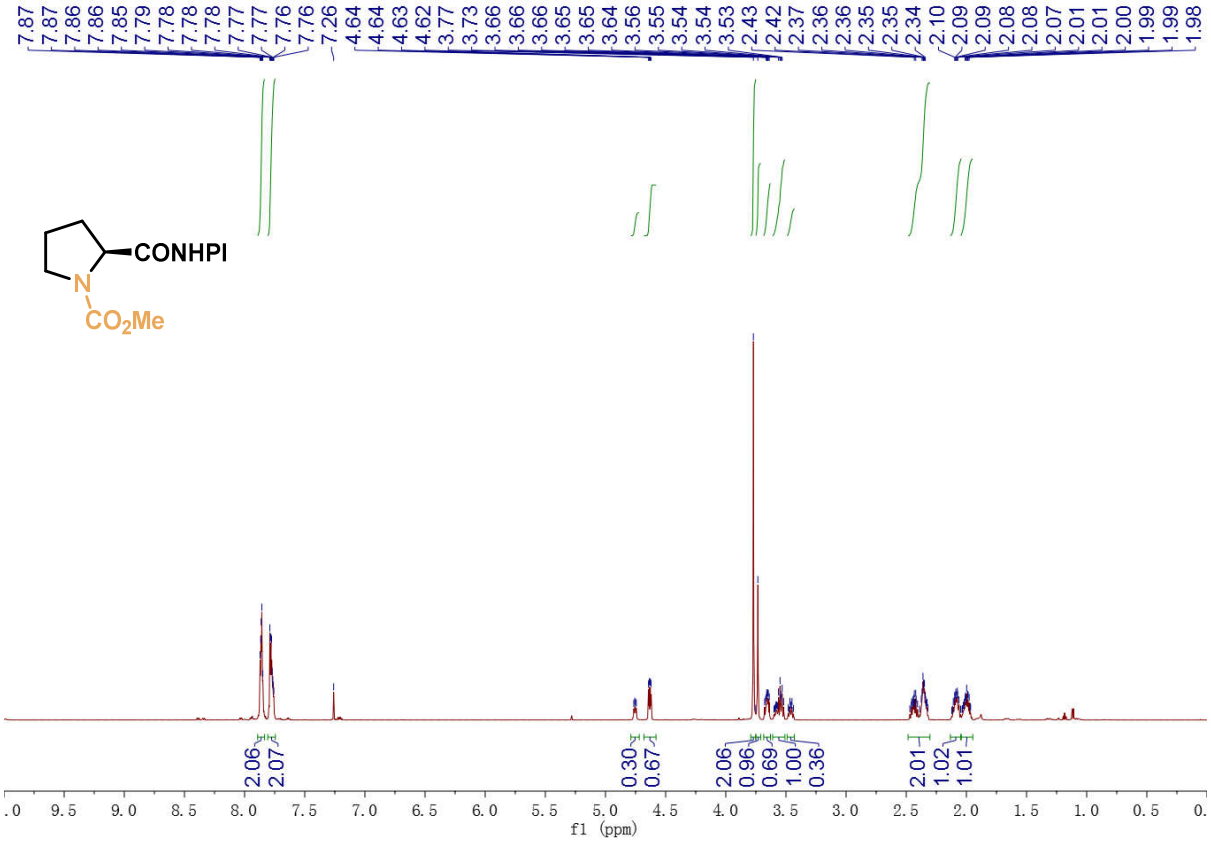
^{1}H NMR of Compound SI-11 (600 MHz, $CDCl_3$):



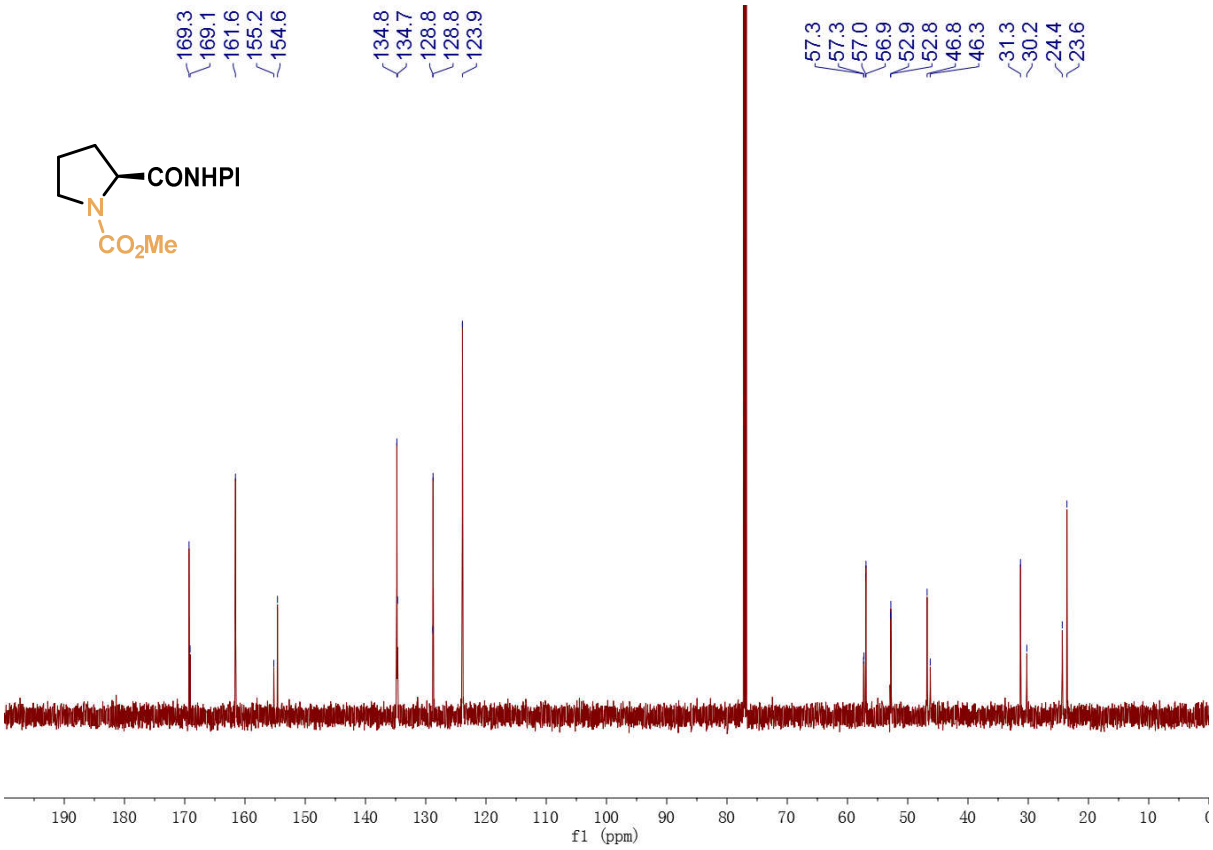
^{13}C NMR of Compound SI-11 (151 MHz, $CDCl_3$):



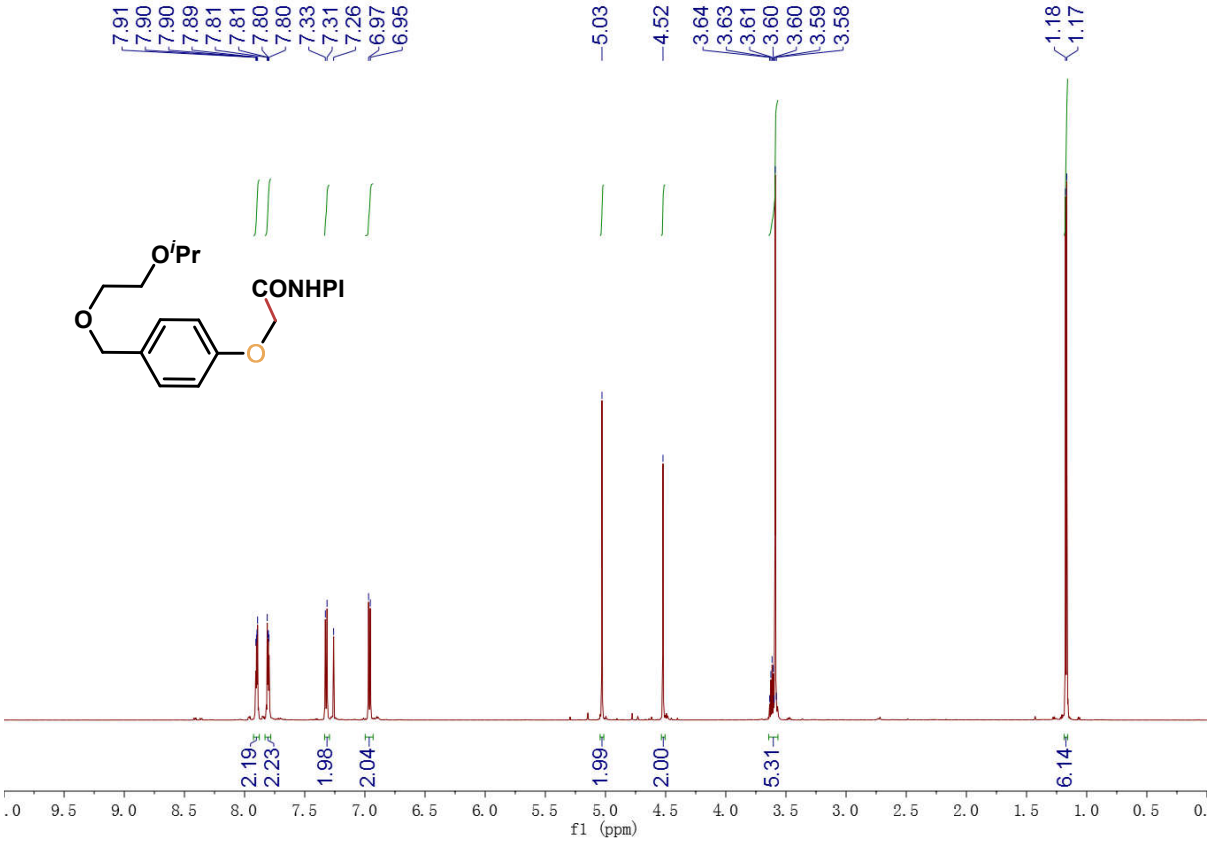
^{1}H NMR of Compound 8 (600 MHz, $CDCl_3$):



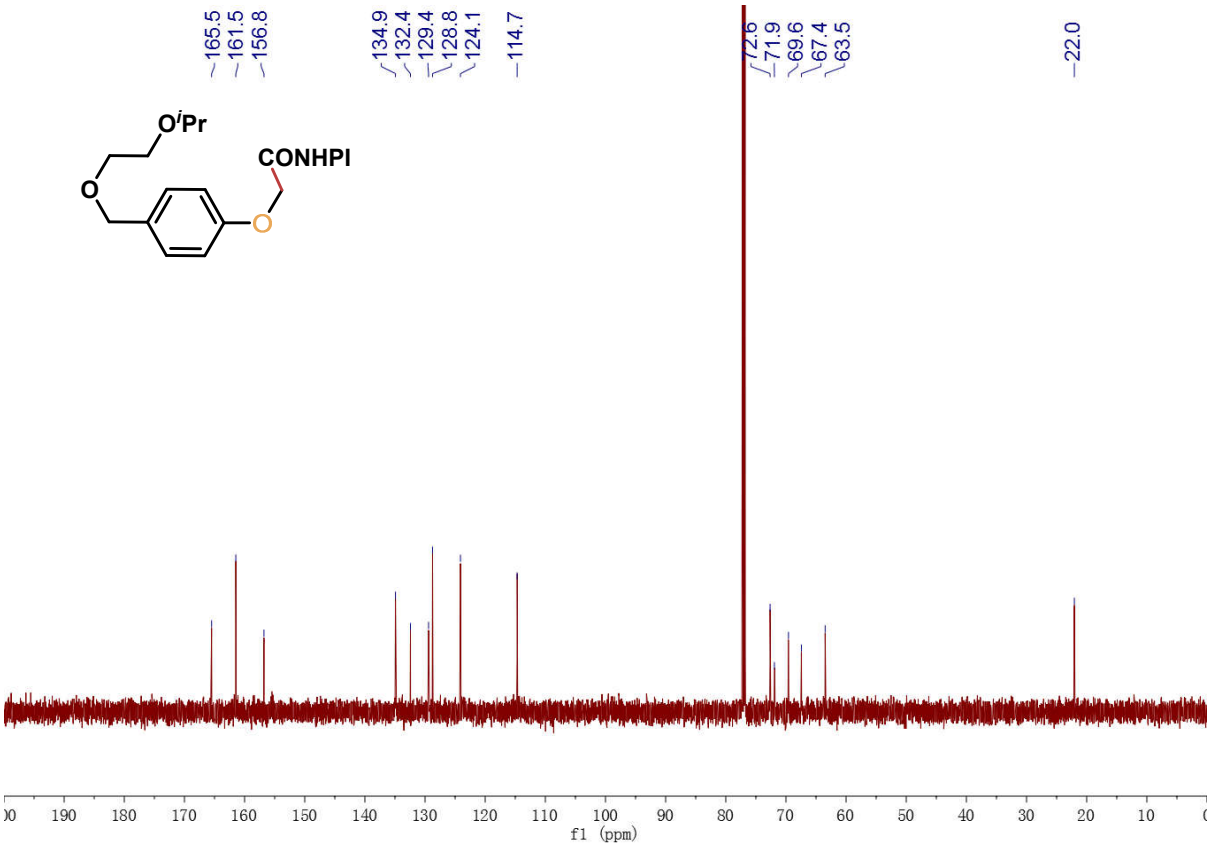
^{13}C NMR of Compound 8 (151 MHz, $CDCl_3$):



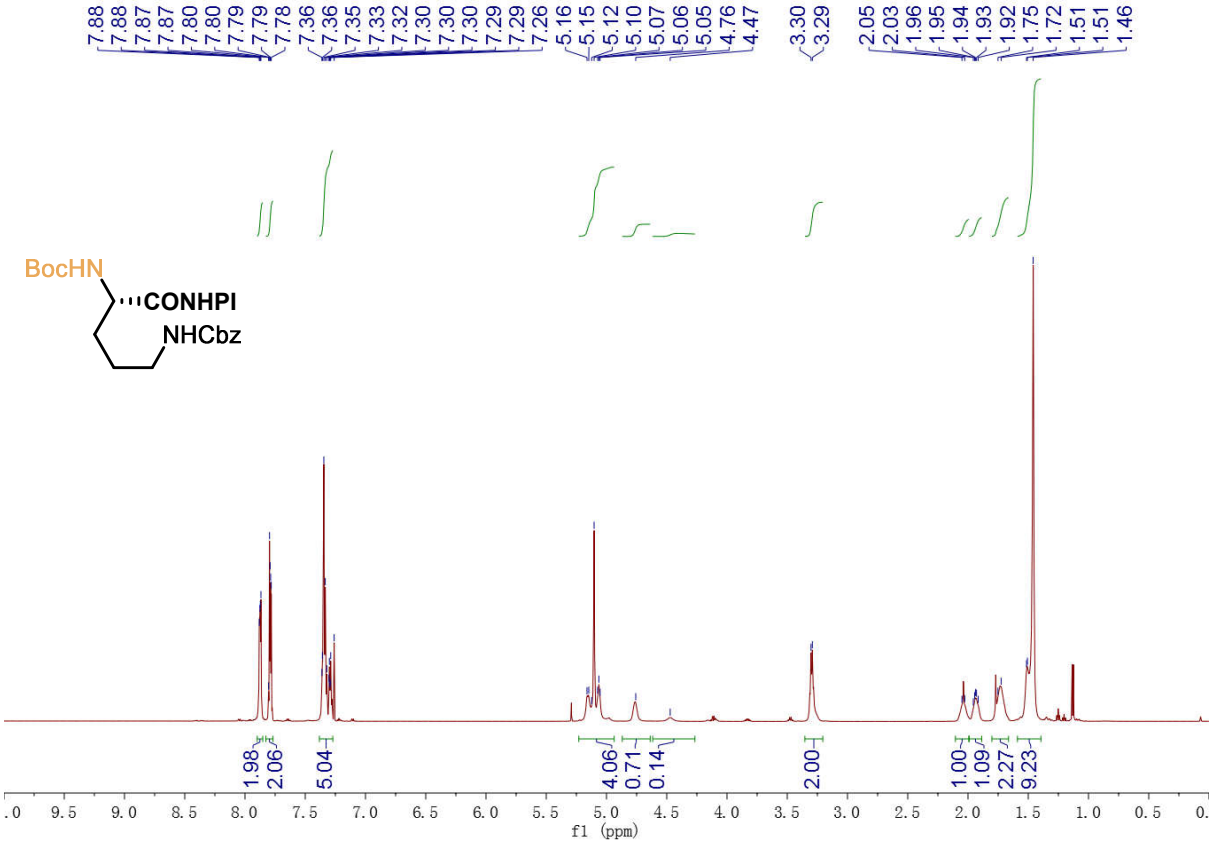
^{1}H NMR of Compound SI-31 (600 MHz, $CDCl_3$):



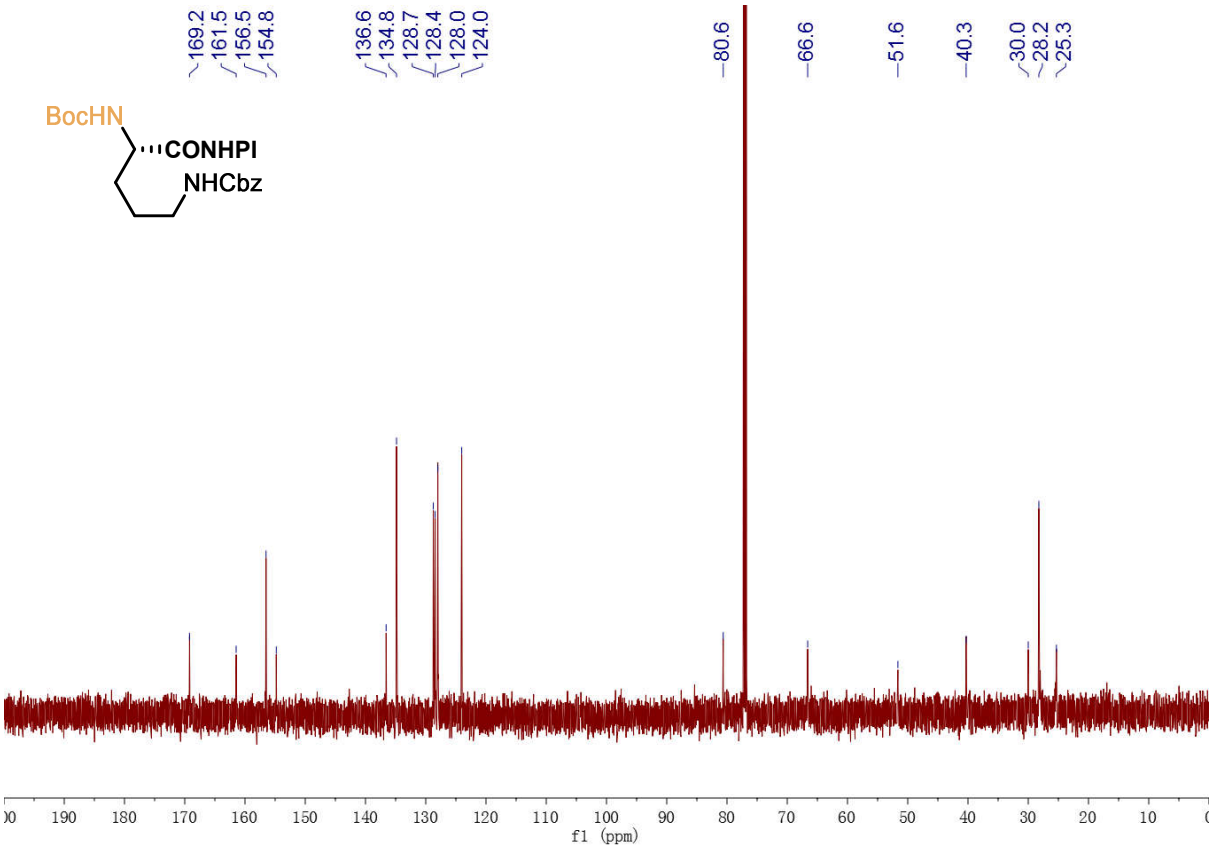
^{13}C NMR of Compound SI-31 (151 MHz, $CDCl_3$):



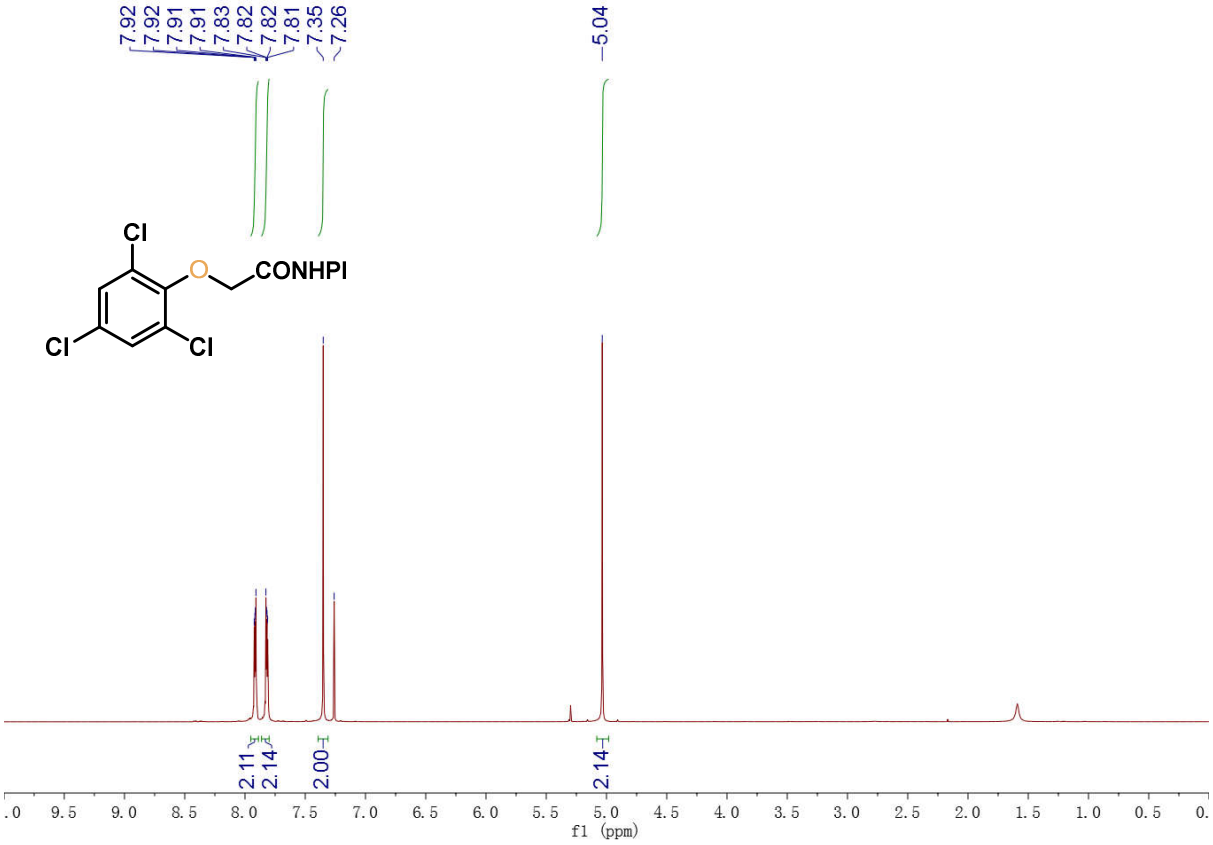
^{1}H NMR of Compound SI-32 (600 MHz, $CDCl_3$):



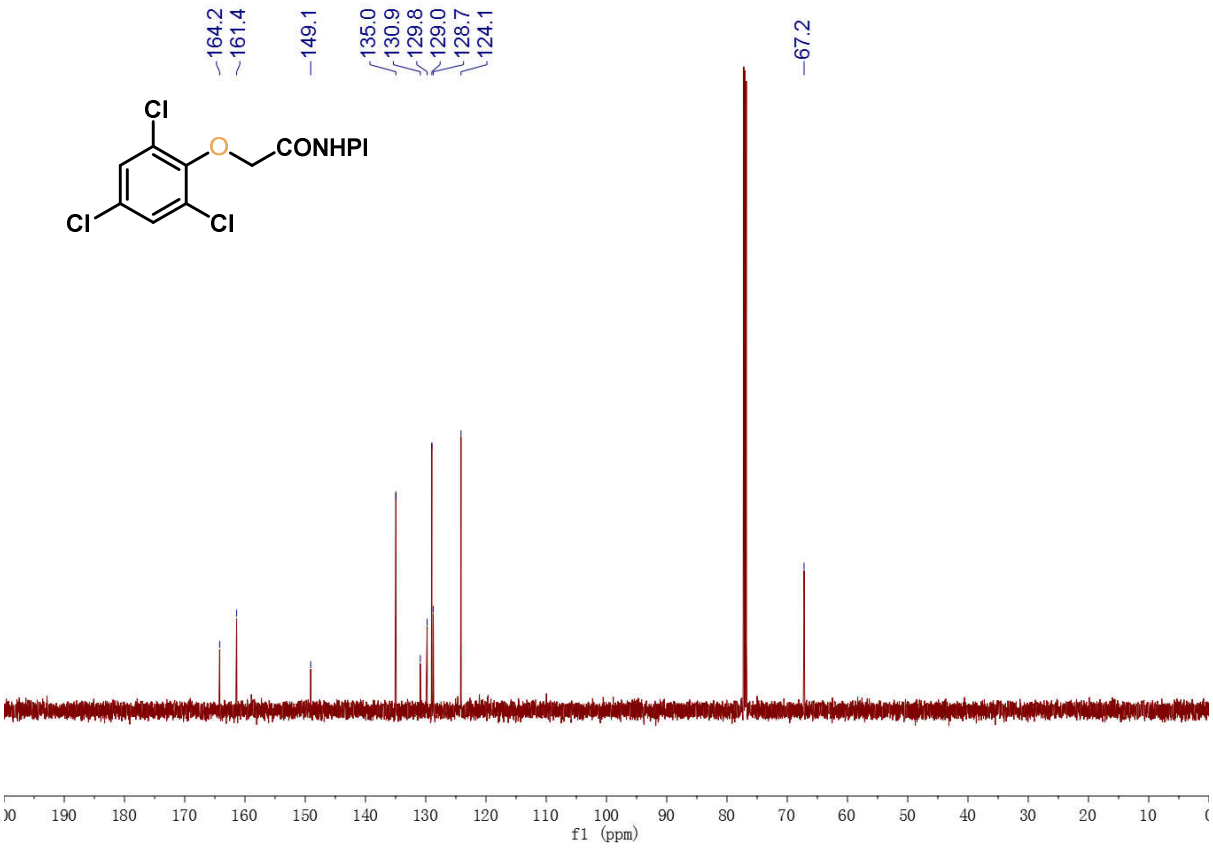
^{13}C NMR of Compound SI-32 (151 MHz, $CDCl_3$):



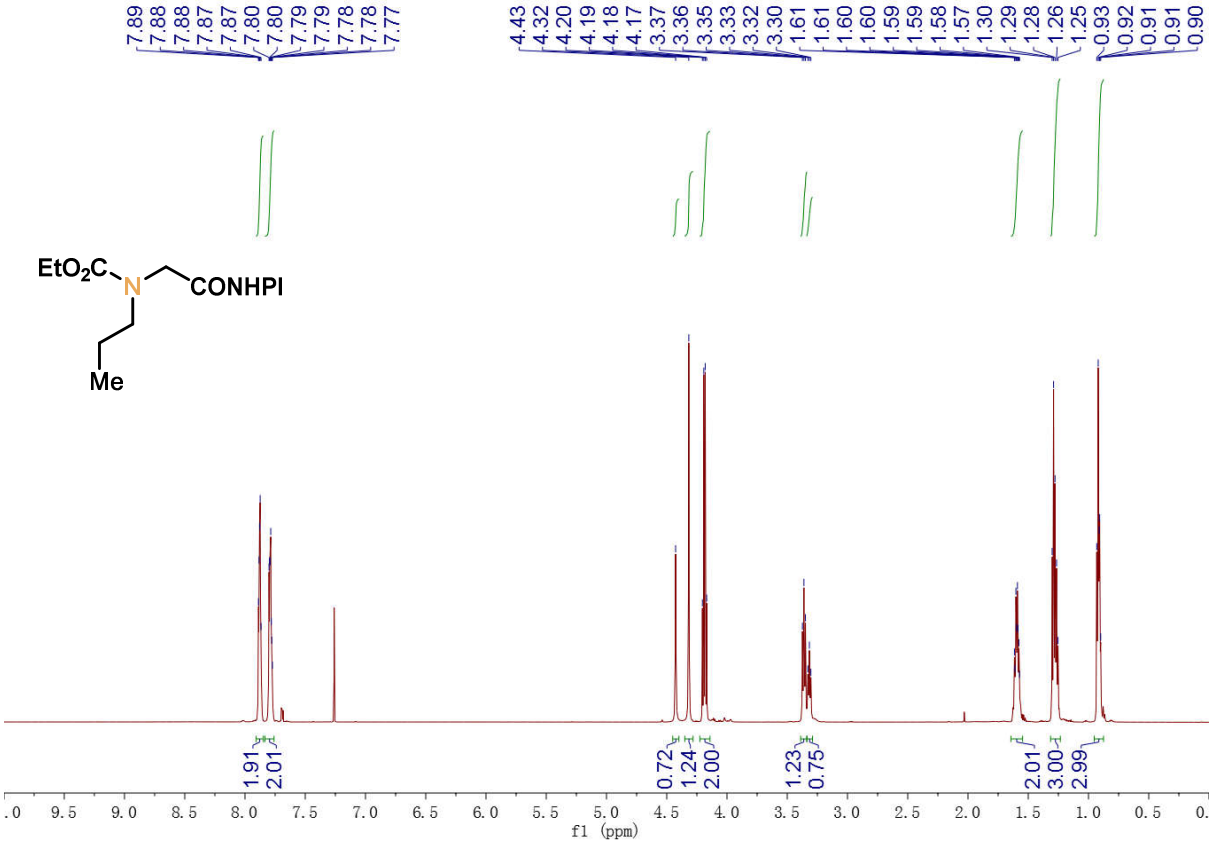
^{1}H NMR of Compound SI-33 (600 MHz, $CDCl_3$):



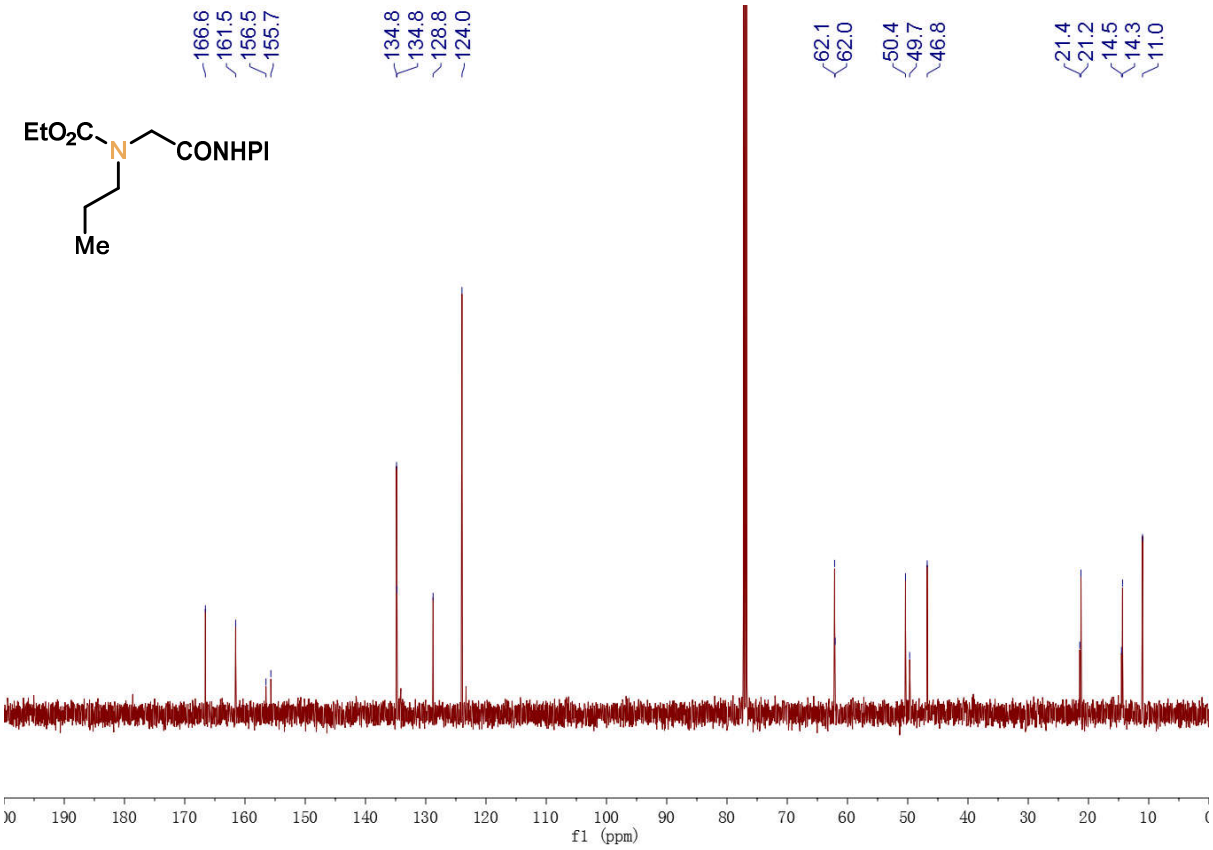
^{13}C NMR of Compound SI-33 (151 MHz, $CDCl_3$):



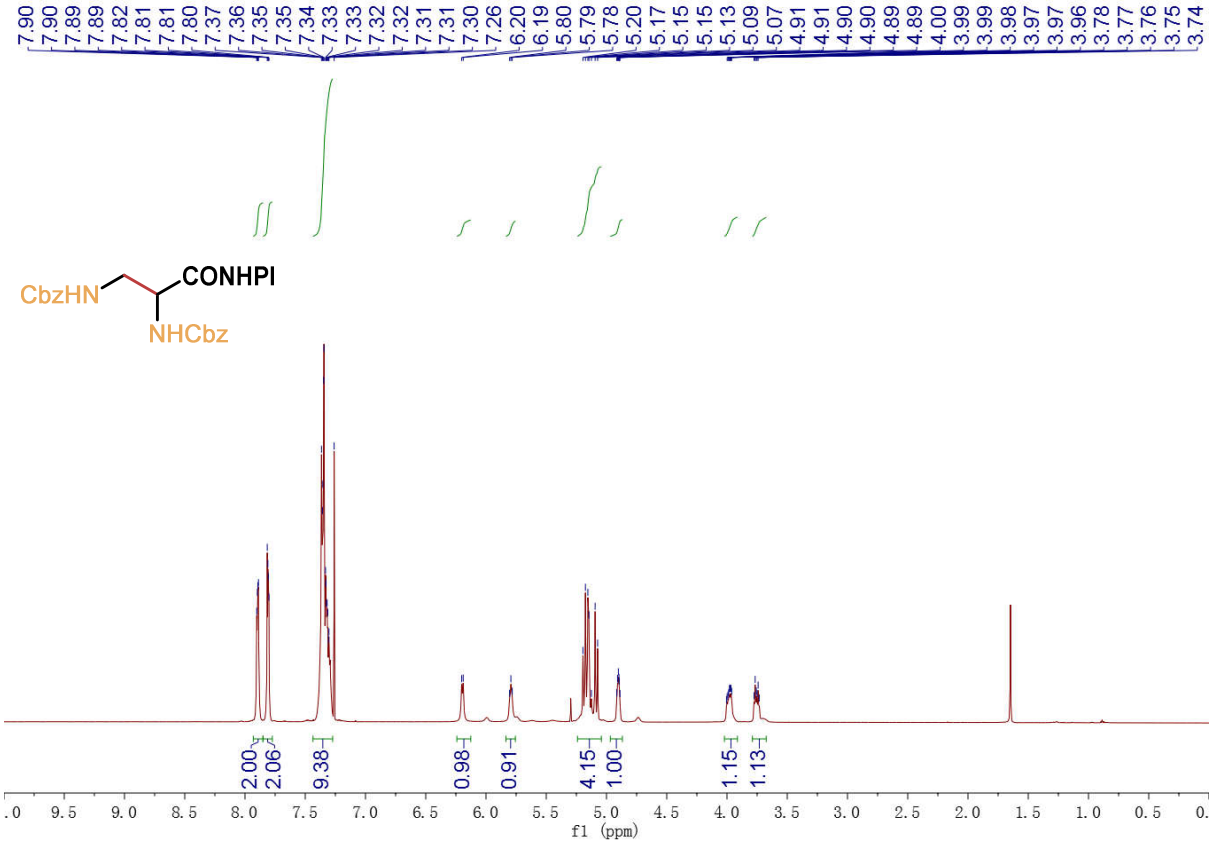
^{1}H NMR of Compound SI-34 (600 MHz, $CDCl_3$):



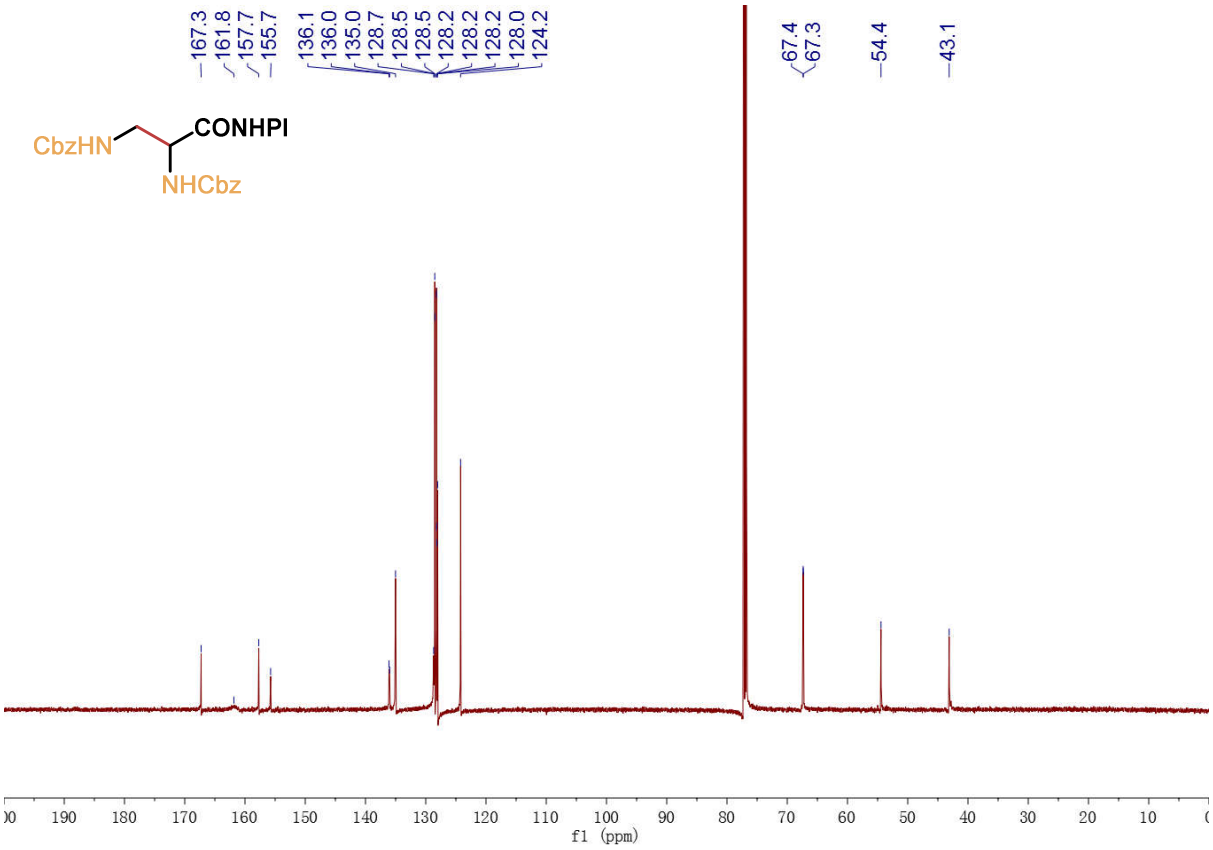
^{13}C NMR of Compound SI-34 (151 MHz, $CDCl_3$):



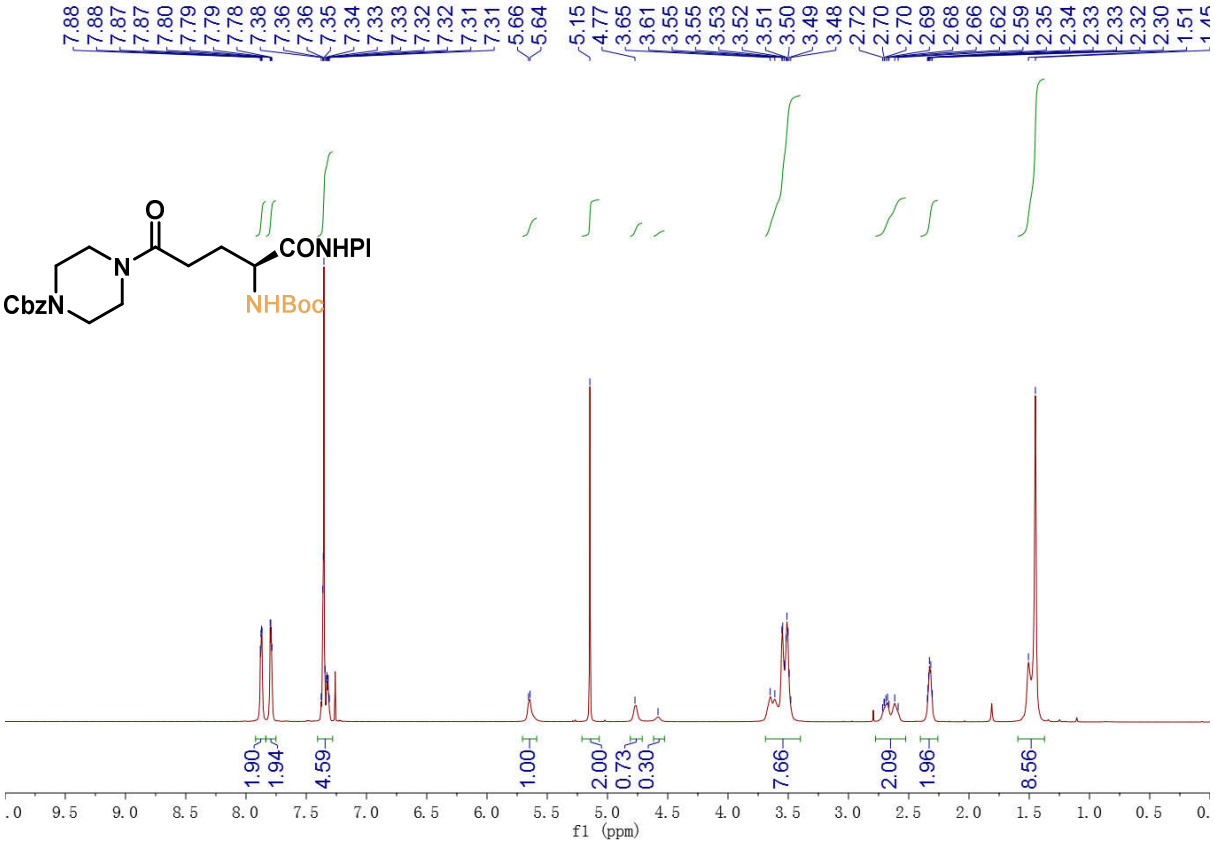
^{1}H NMR of Compound SI-35 (600 MHz, $CDCl_3$):



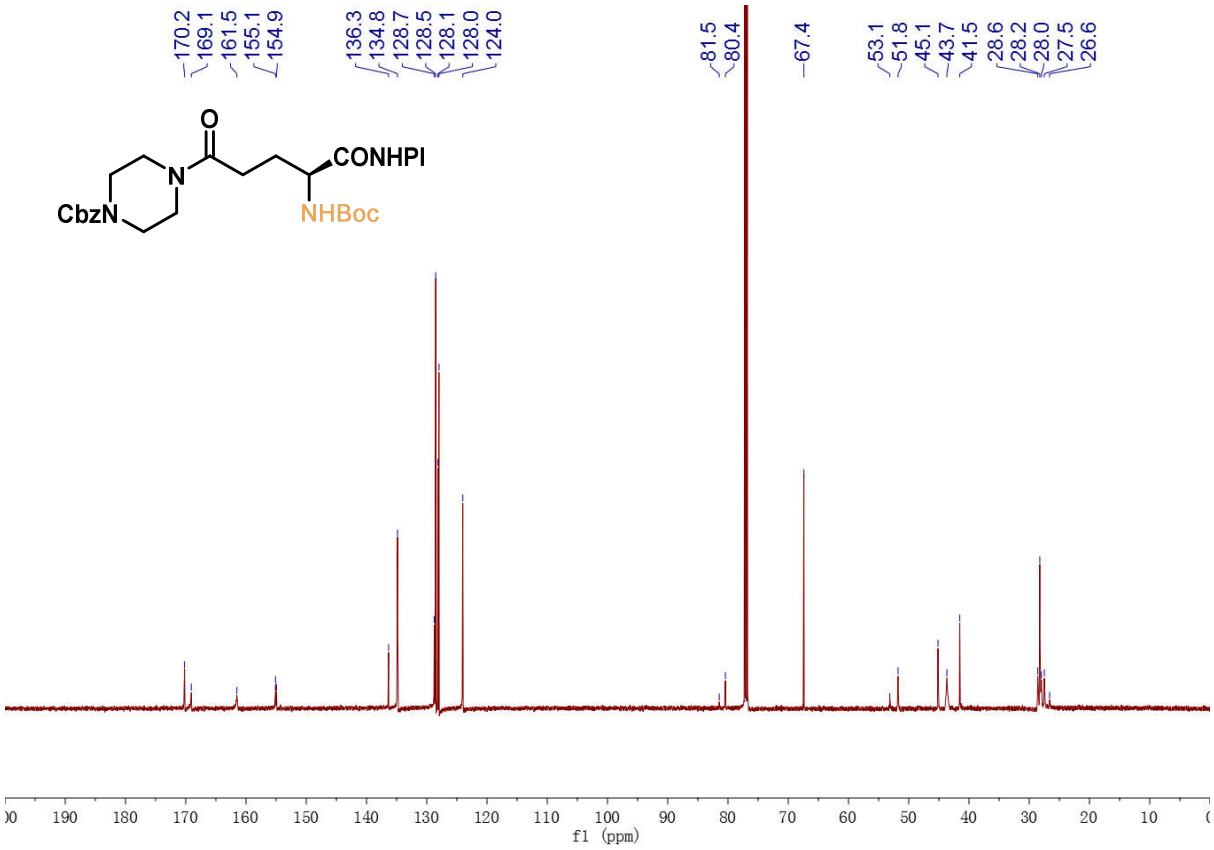
^{13}C NMR of Compound SI-35 (151 MHz, $CDCl_3$):



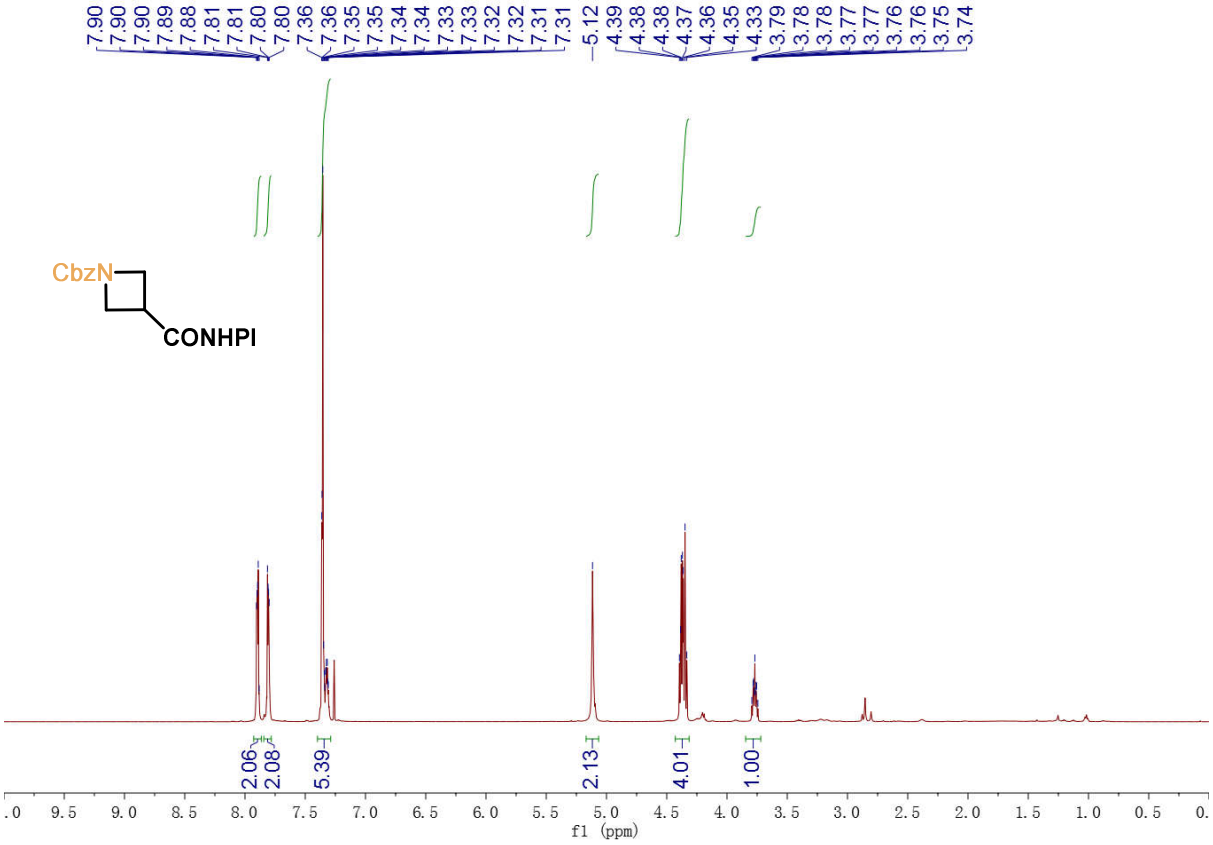
^{1}H NMR of Compound SI-36 (600 MHz, $CDCl_3$):



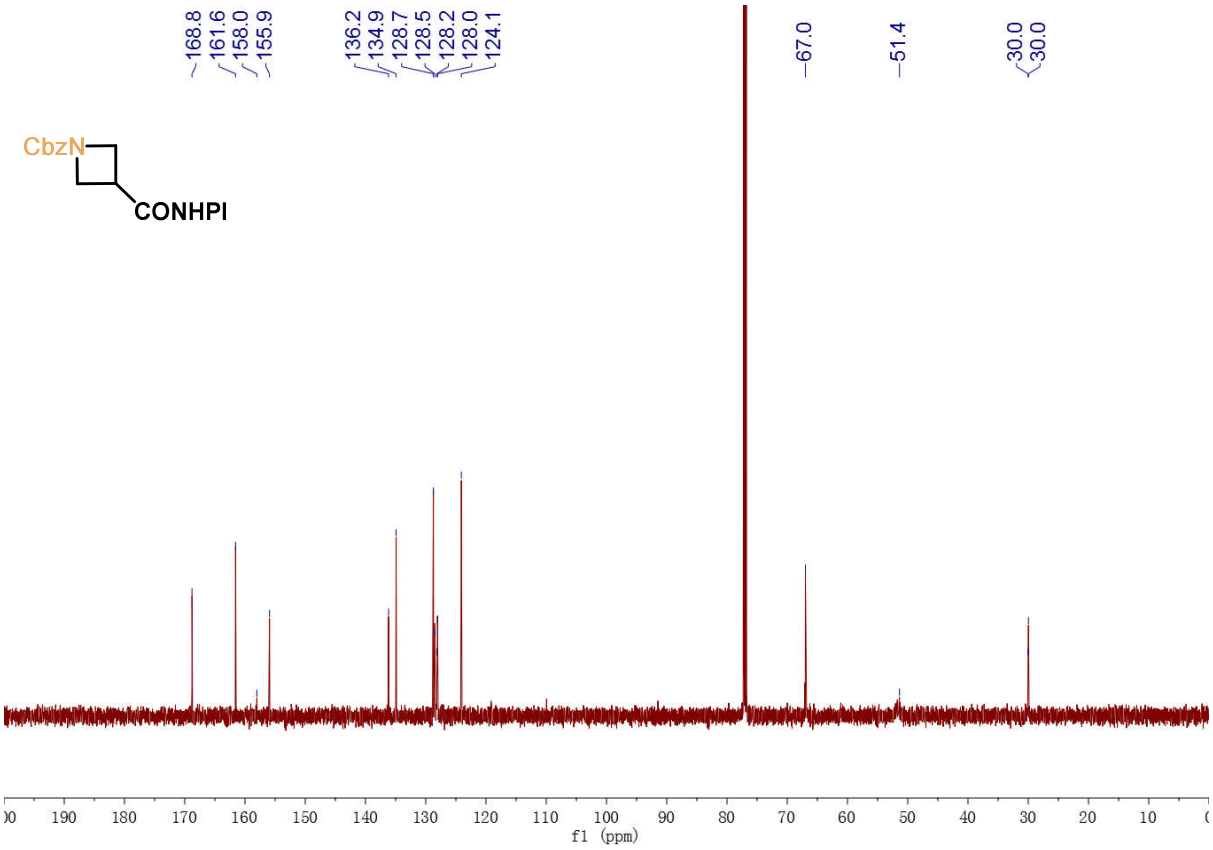
^{13}C NMR of Compound SI-36 (151 MHz, $CDCl_3$):



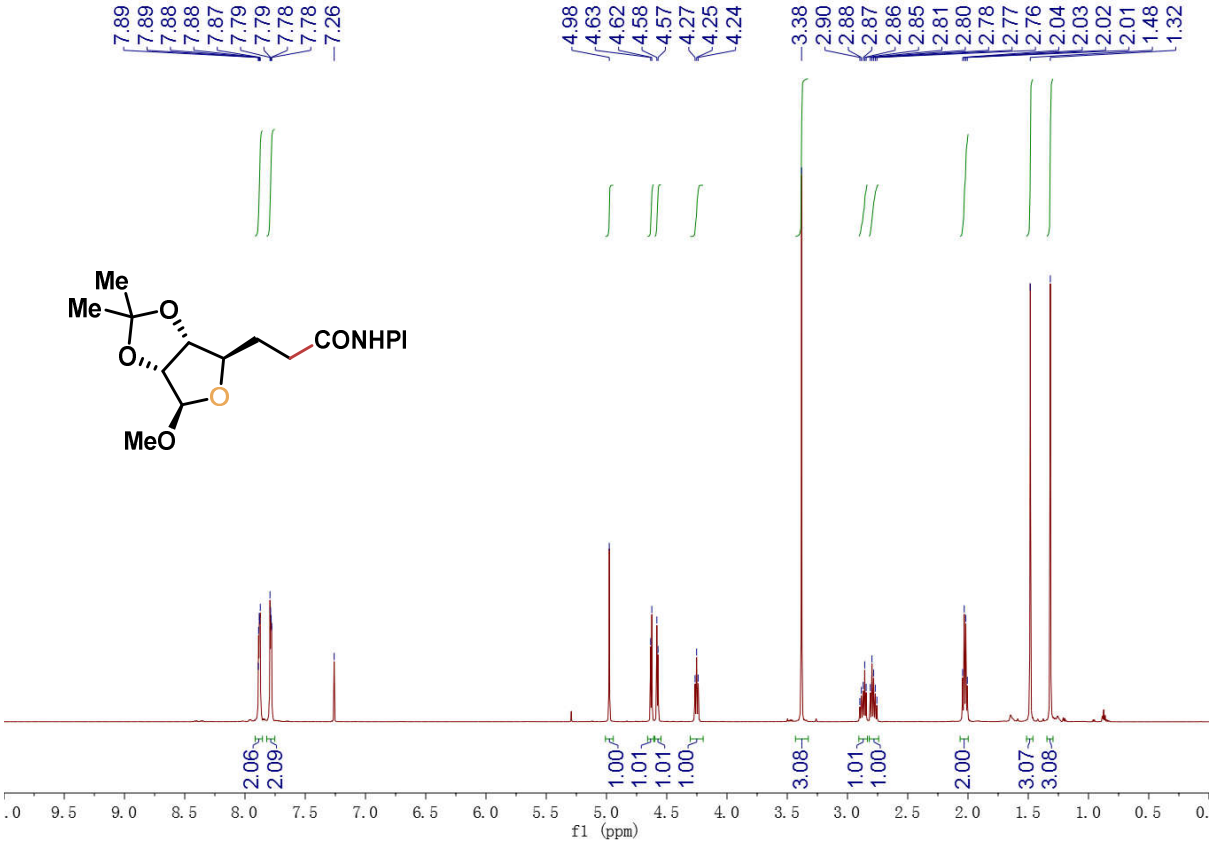
^{1}H NMR of Compound SI-37 (600 MHz, $CDCl_3$):



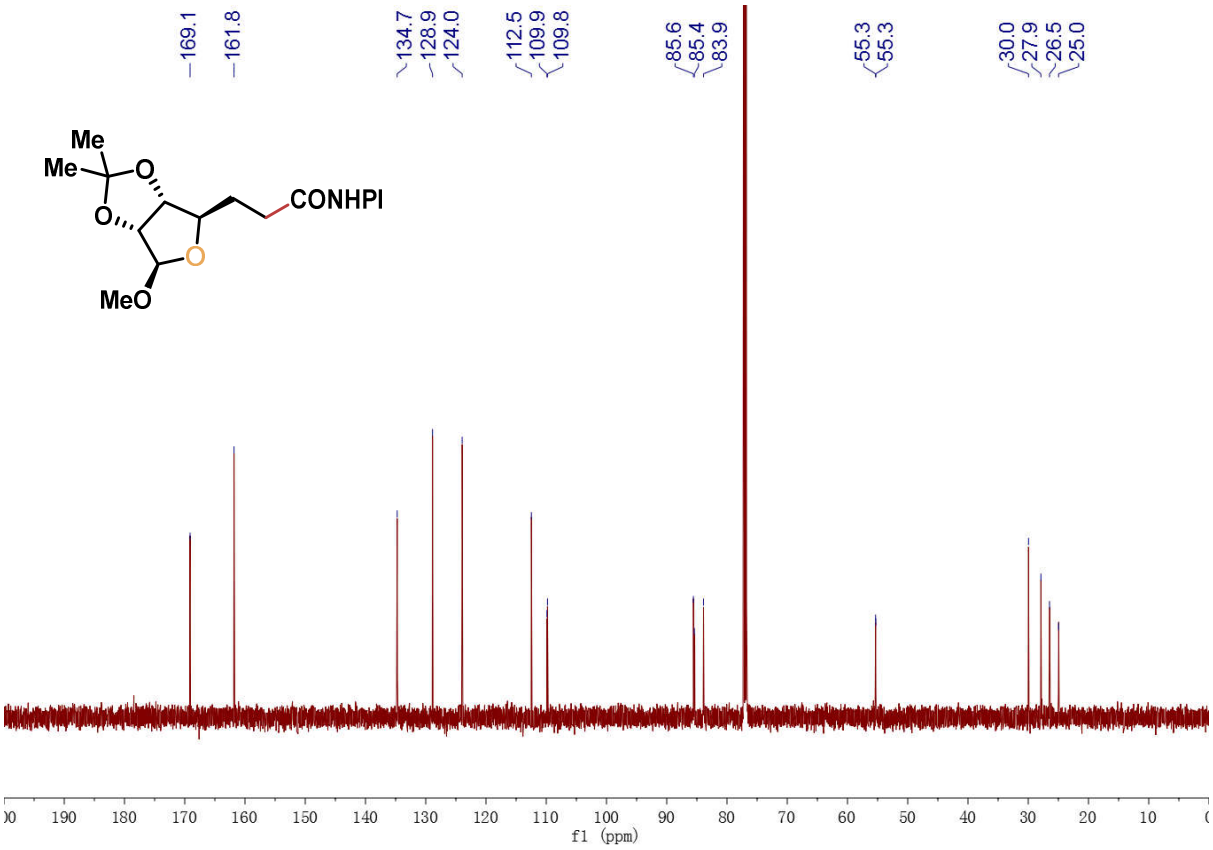
^{13}C NMR of Compound SI-37 (151 MHz, $CDCl_3$):



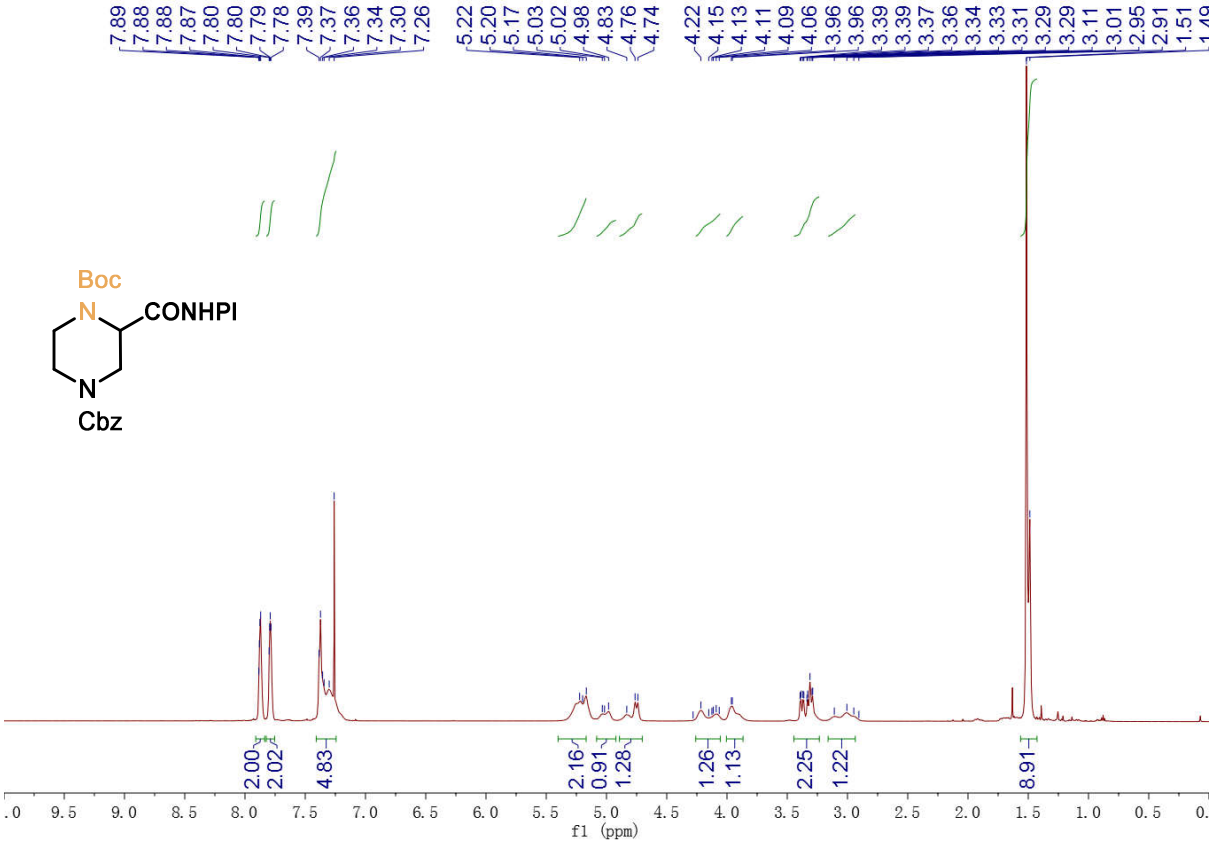
^{1}H NMR of Compound SI-38 (600 MHz, $CDCl_3$):



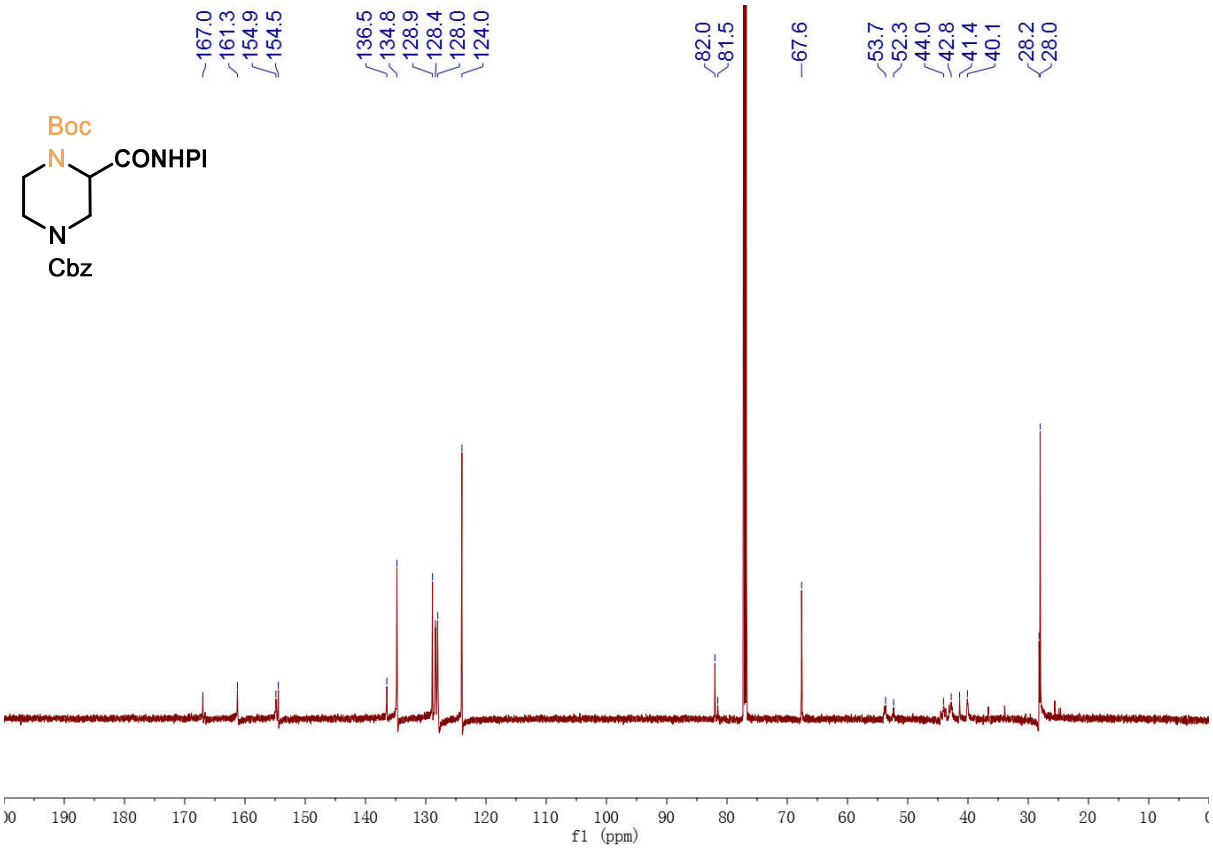
^{13}C NMR of Compound SI-38 (151 MHz, $CDCl_3$):



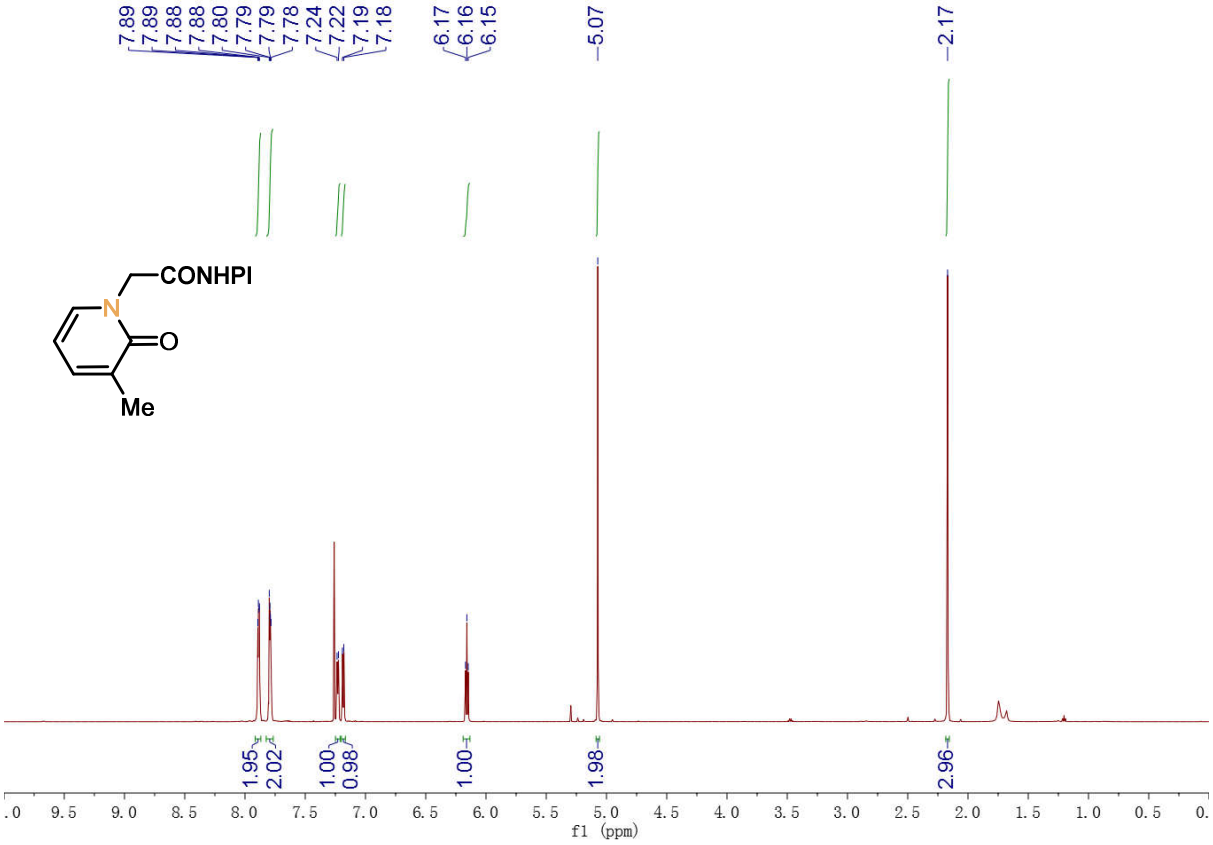
^{1}H NMR of Compound SI-39 (600 MHz, $CDCl_3$):



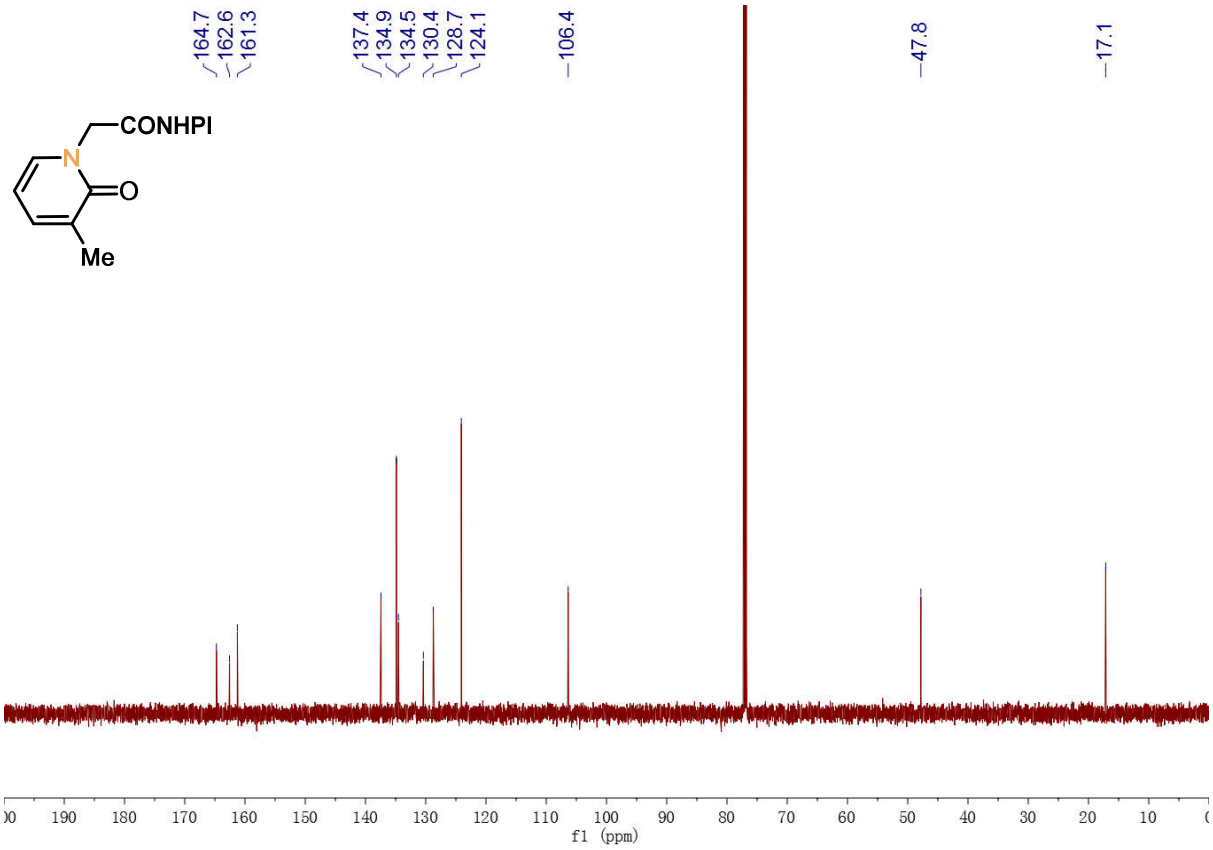
^{13}C NMR of Compound SI-39 (151 MHz, $CDCl_3$):



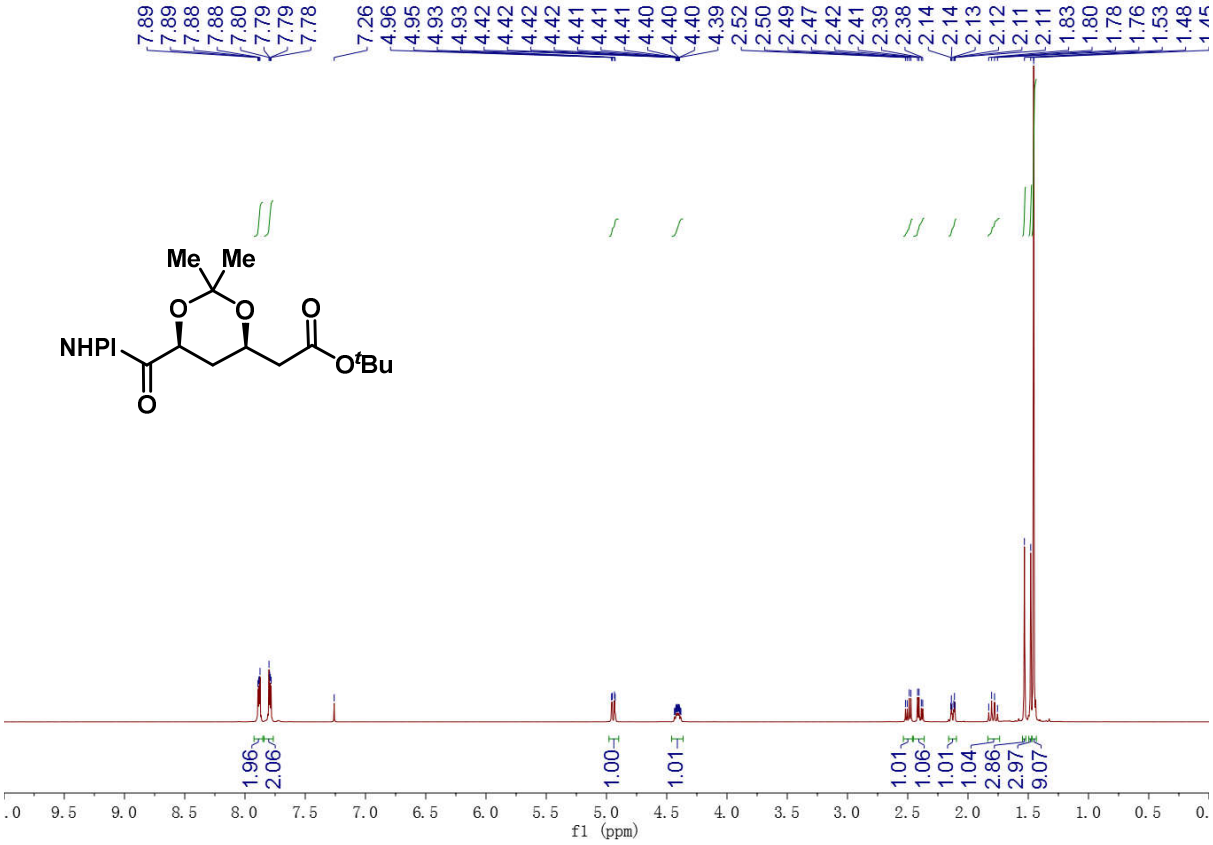
^{1}H NMR of Compound SI-40 (600 MHz, $CDCl_3$):



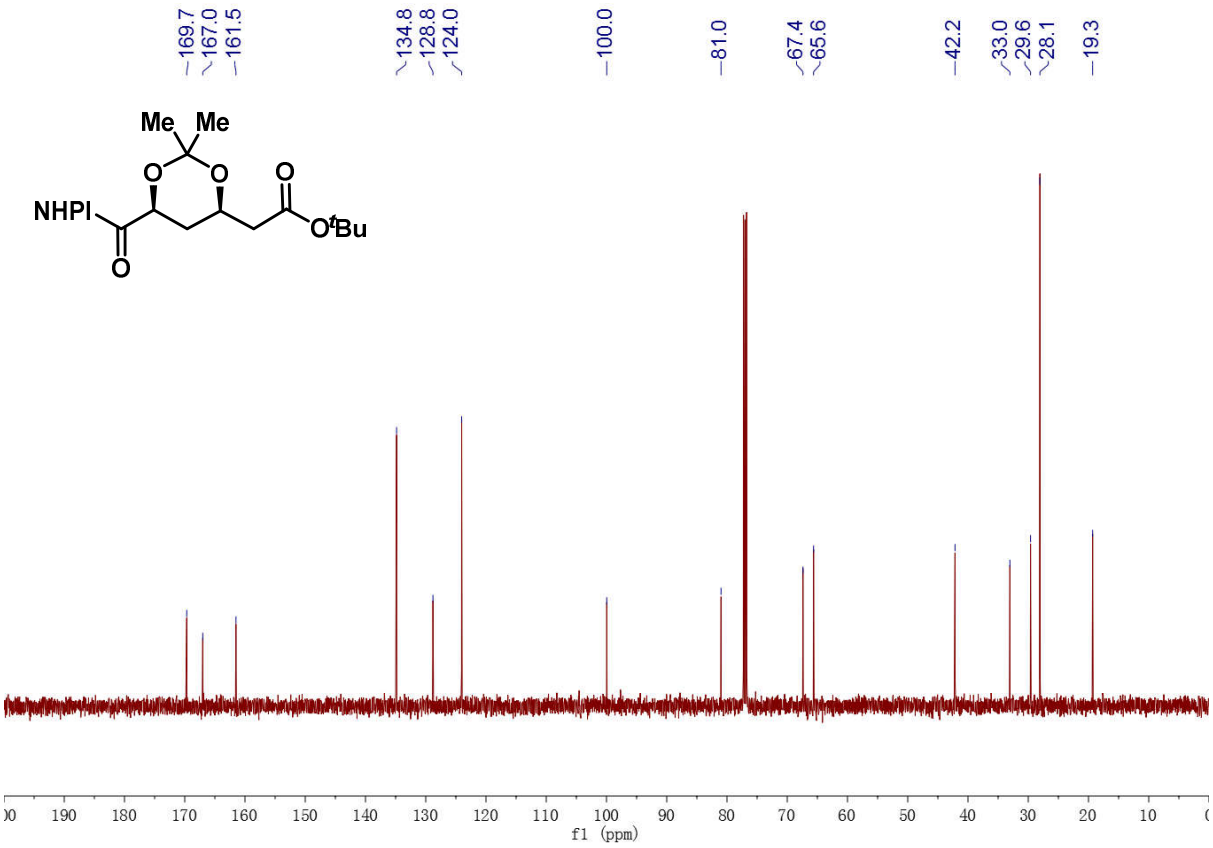
^{13}C NMR of Compound SI-40 (151 MHz, $CDCl_3$):



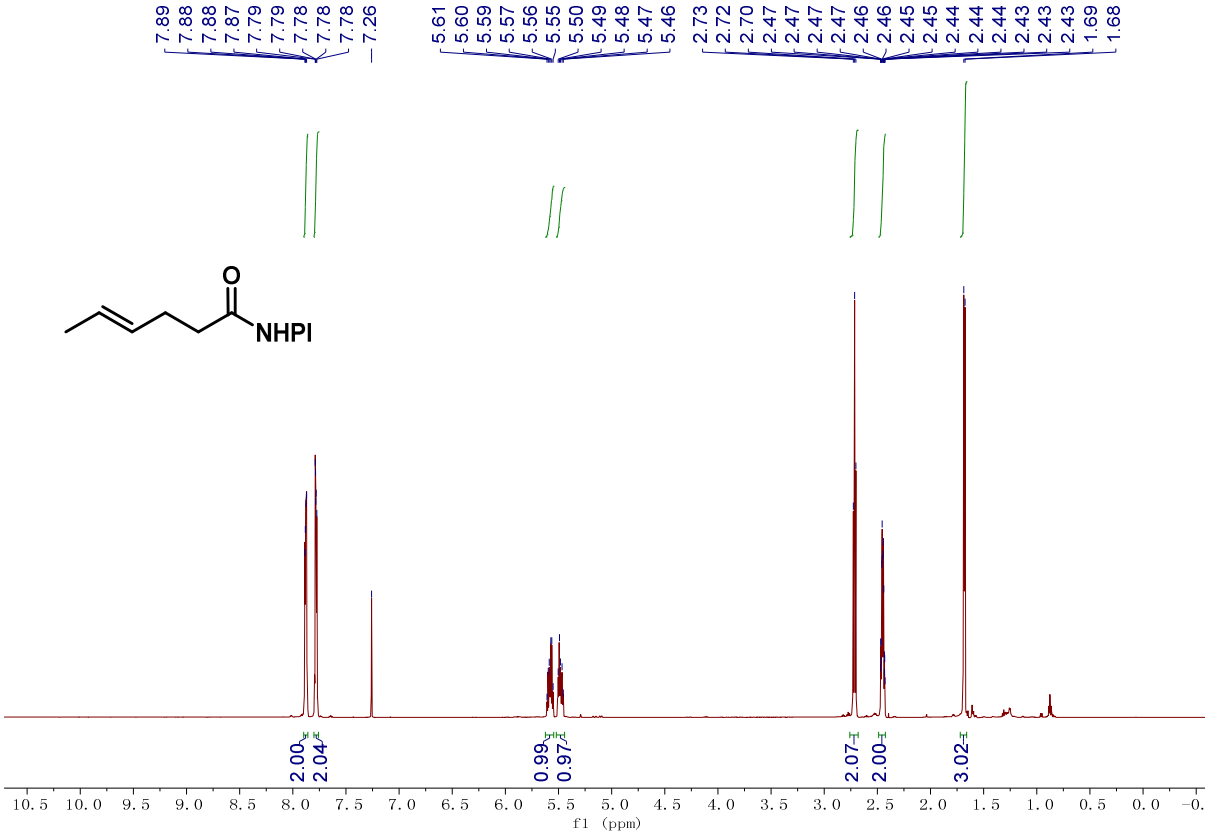
^{1}H NMR of Compound 6-RAE (600 MHz, $CDCl_3$):



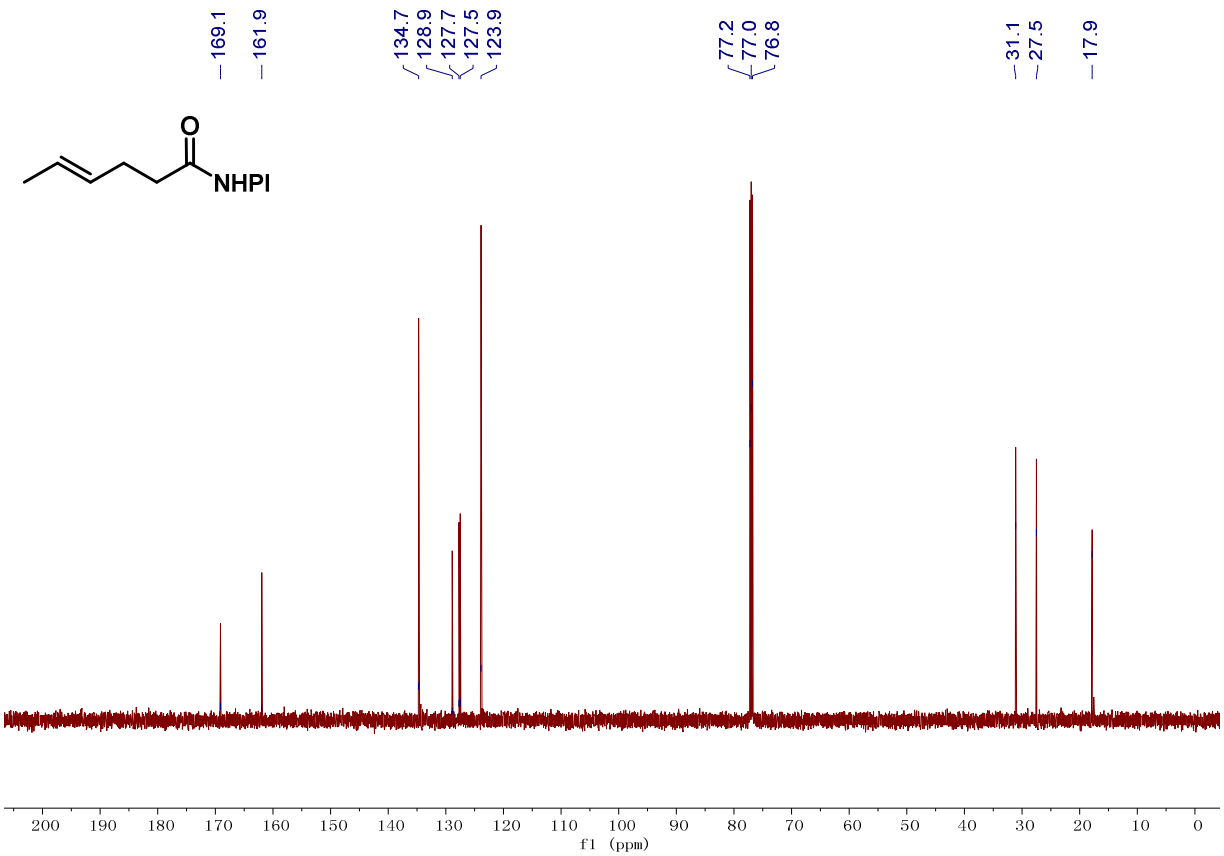
^{13}C NMR of Compound 6-RAE (151 MHz, $CDCl_3$):



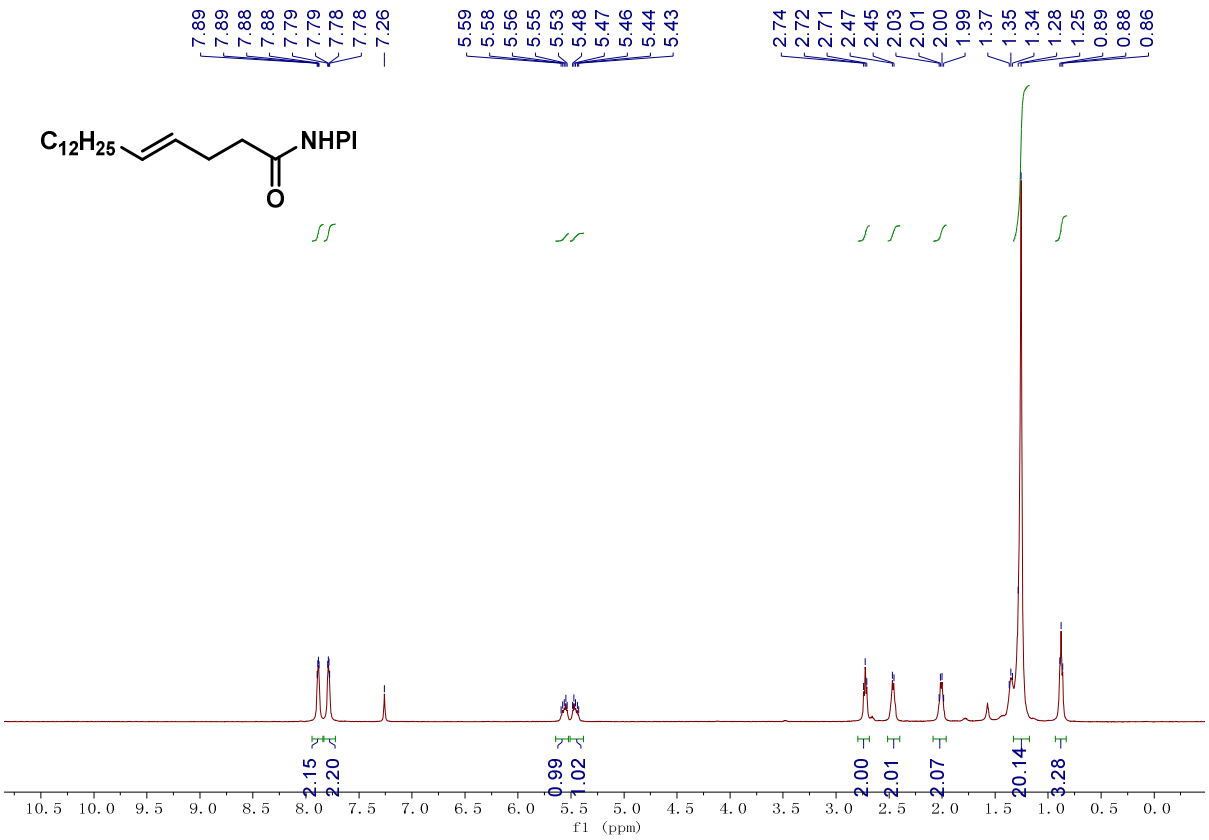
^{1}H NMR of Compound SI-41 (600 MHz, $CDCl_3$):



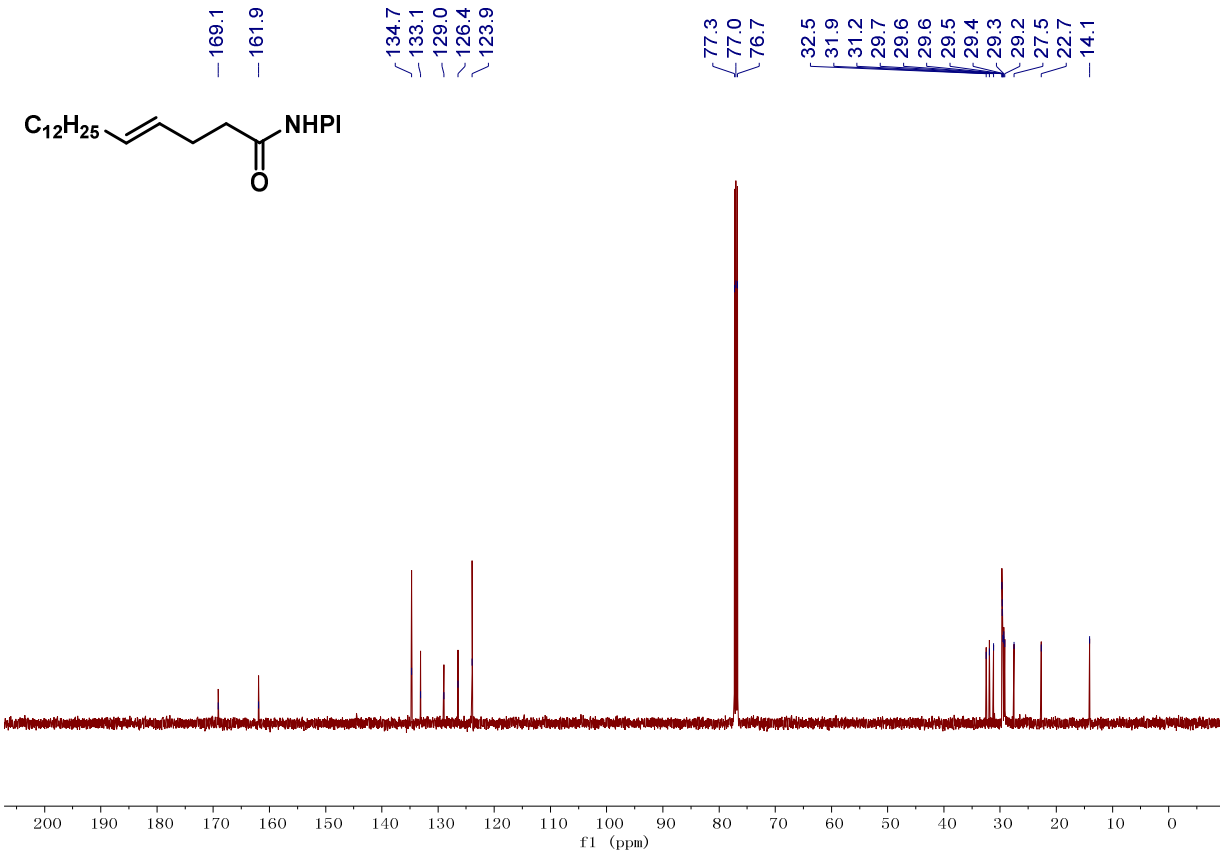
^{13}C NMR of Compound SI-41 (151 MHz, $CDCl_3$):



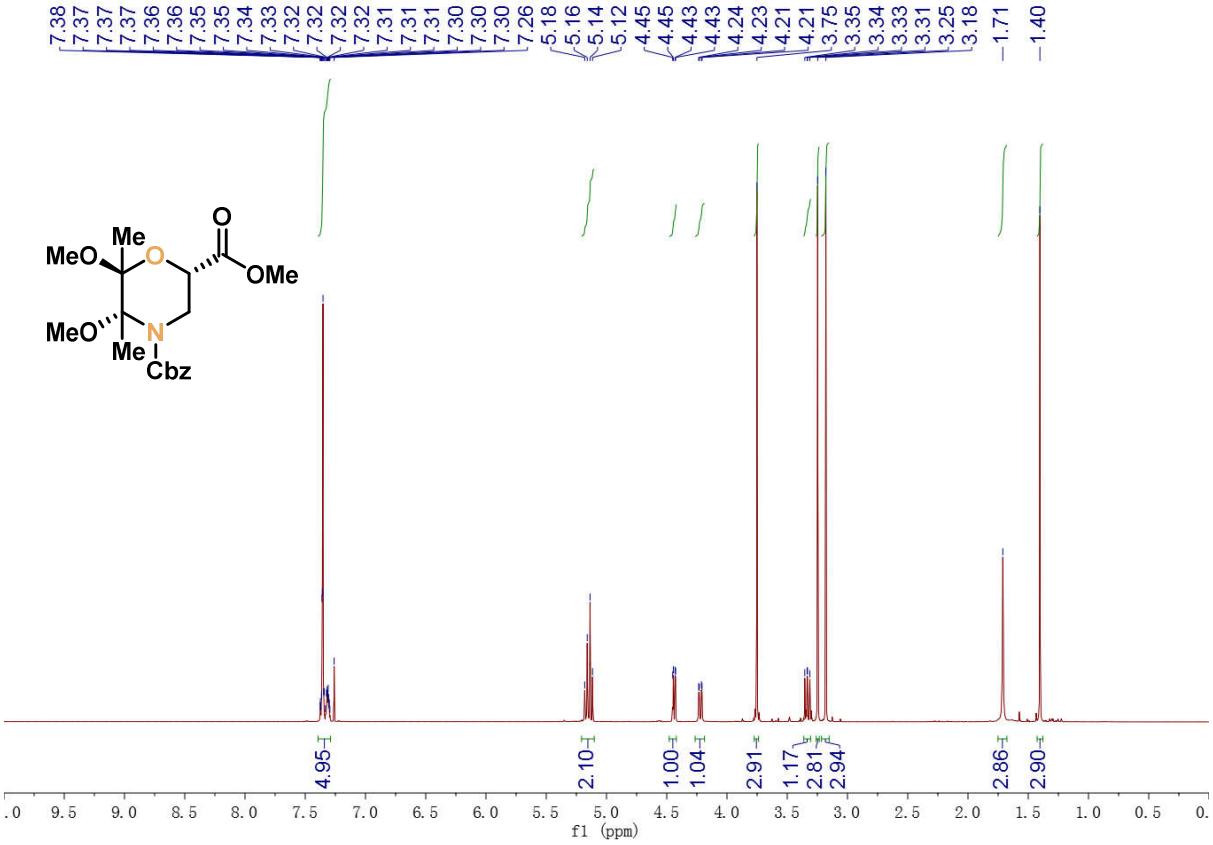
^{1}H NMR of Compound 50 (600 MHz, $CDCl_3$):



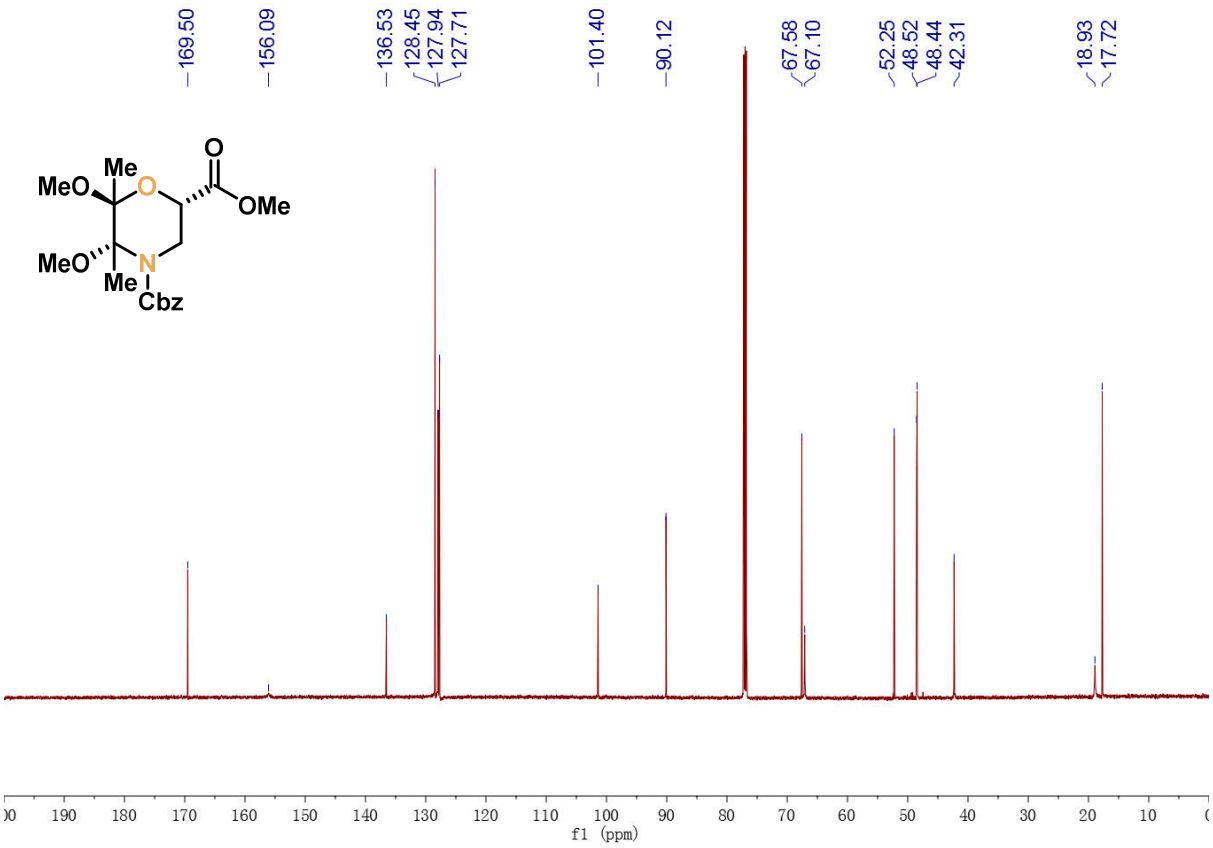
^{13}C NMR of Compound 50 (151 MHz, $CDCl_3$):



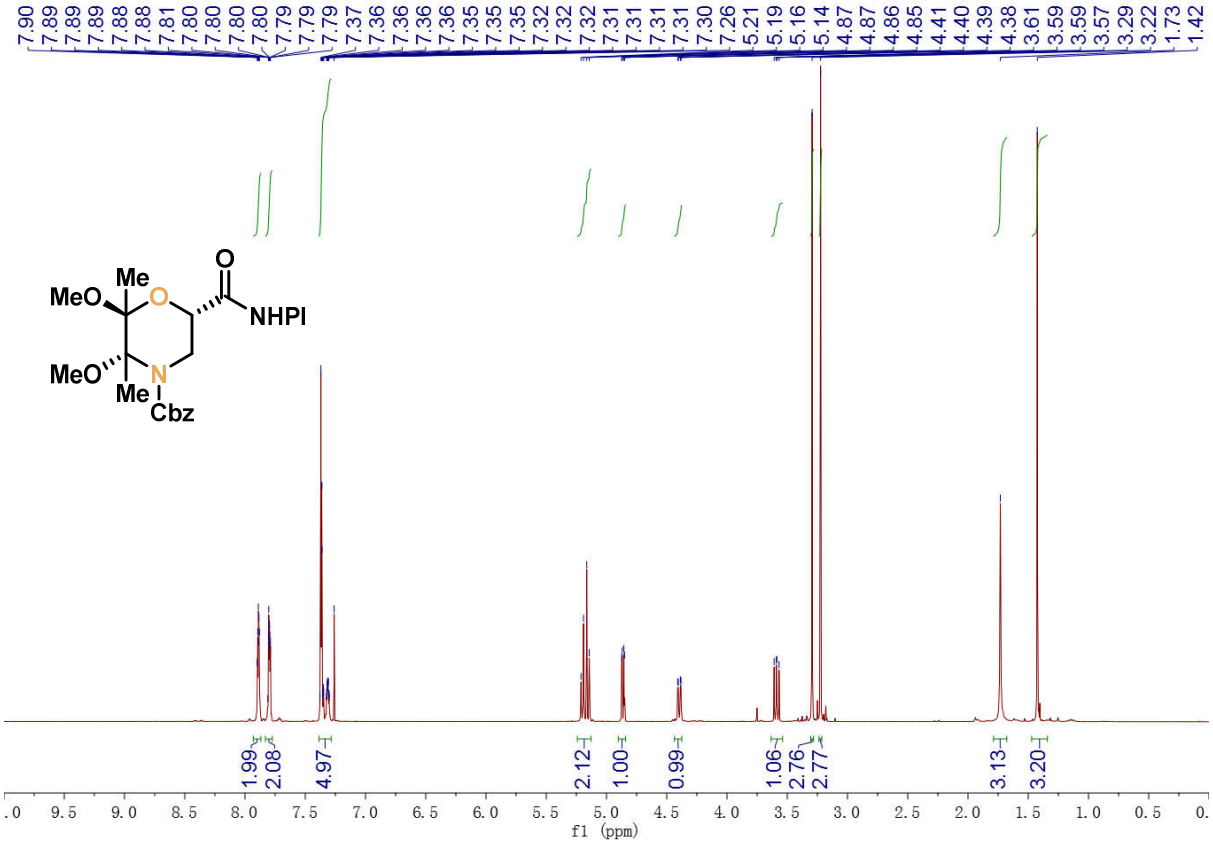
^{1}H NMR of Compound SI-42 (600 MHz, $CDCl_3$):



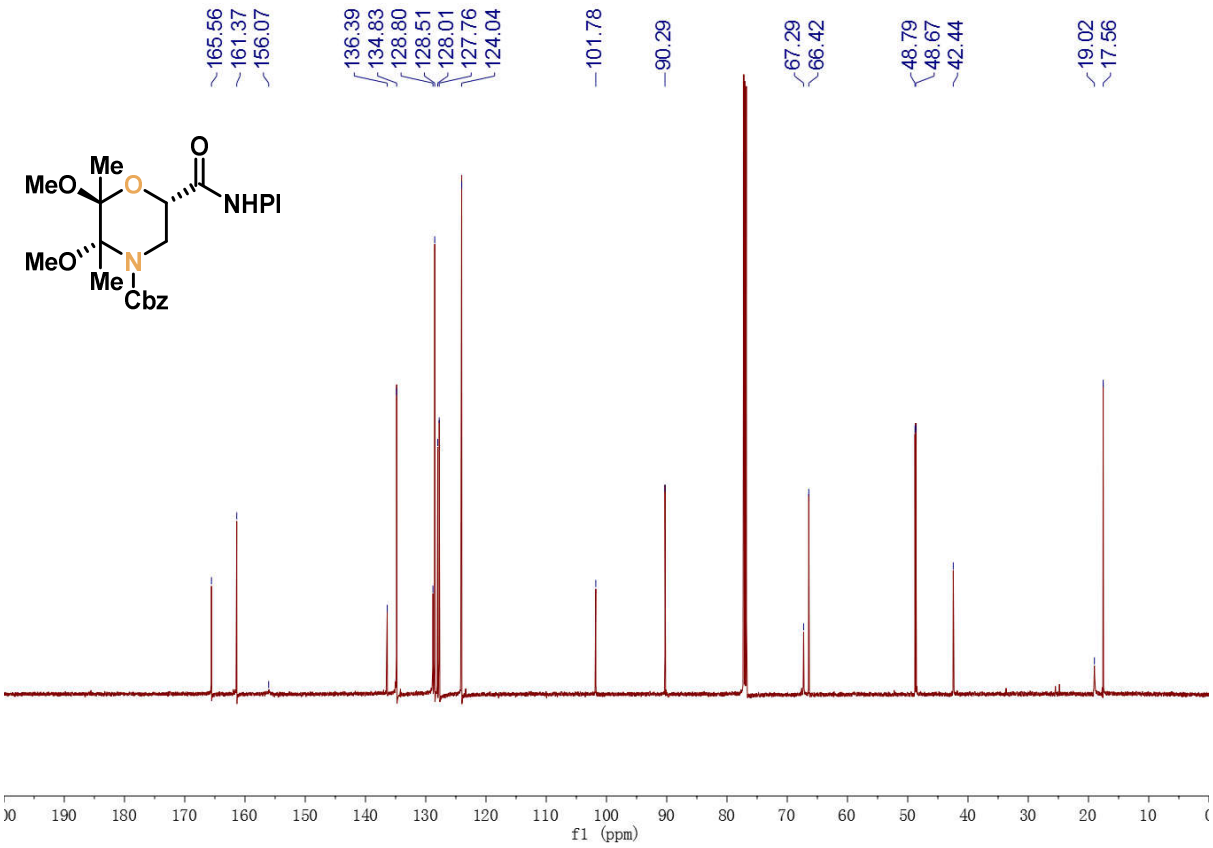
^{13}C NMR of Compound SI-42 (151 MHz, $CDCl_3$):



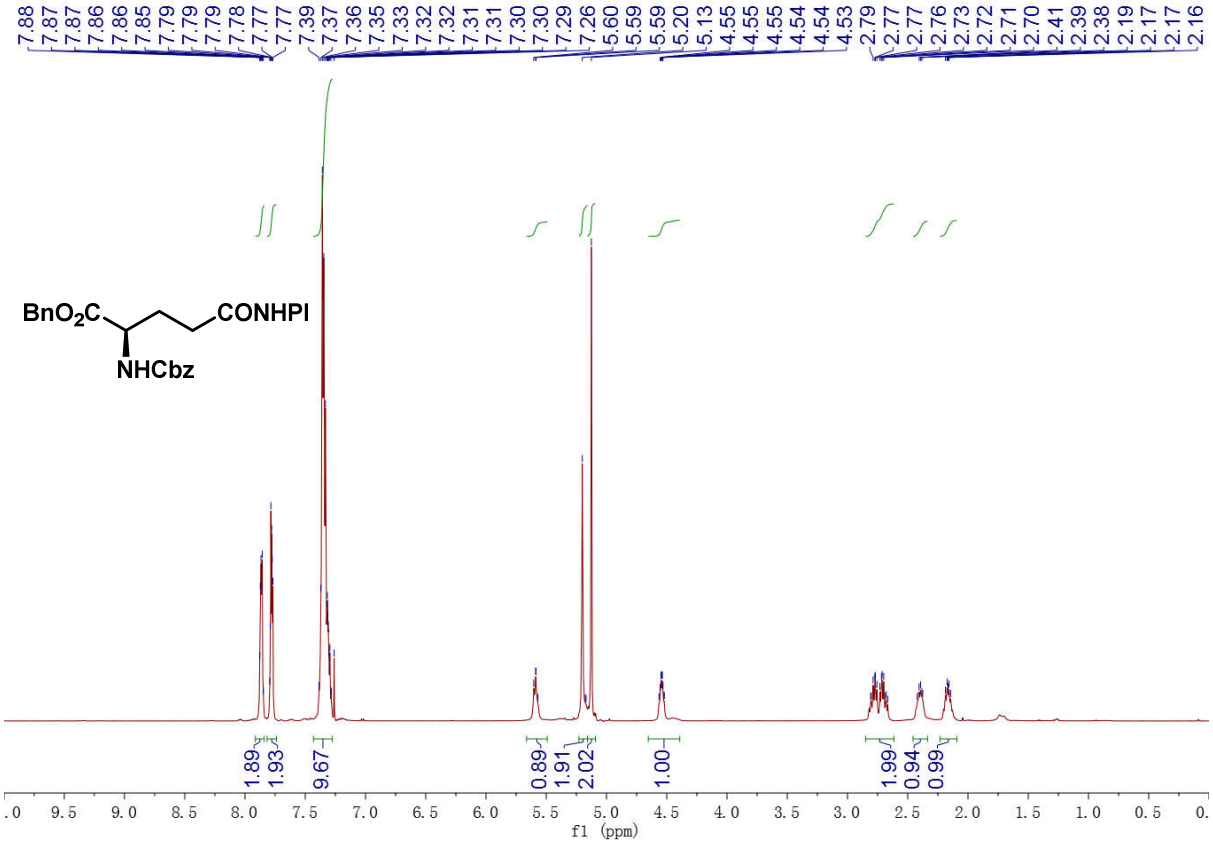
^{1}H NMR of Compound 63 (600 MHz, $CDCl_3$):



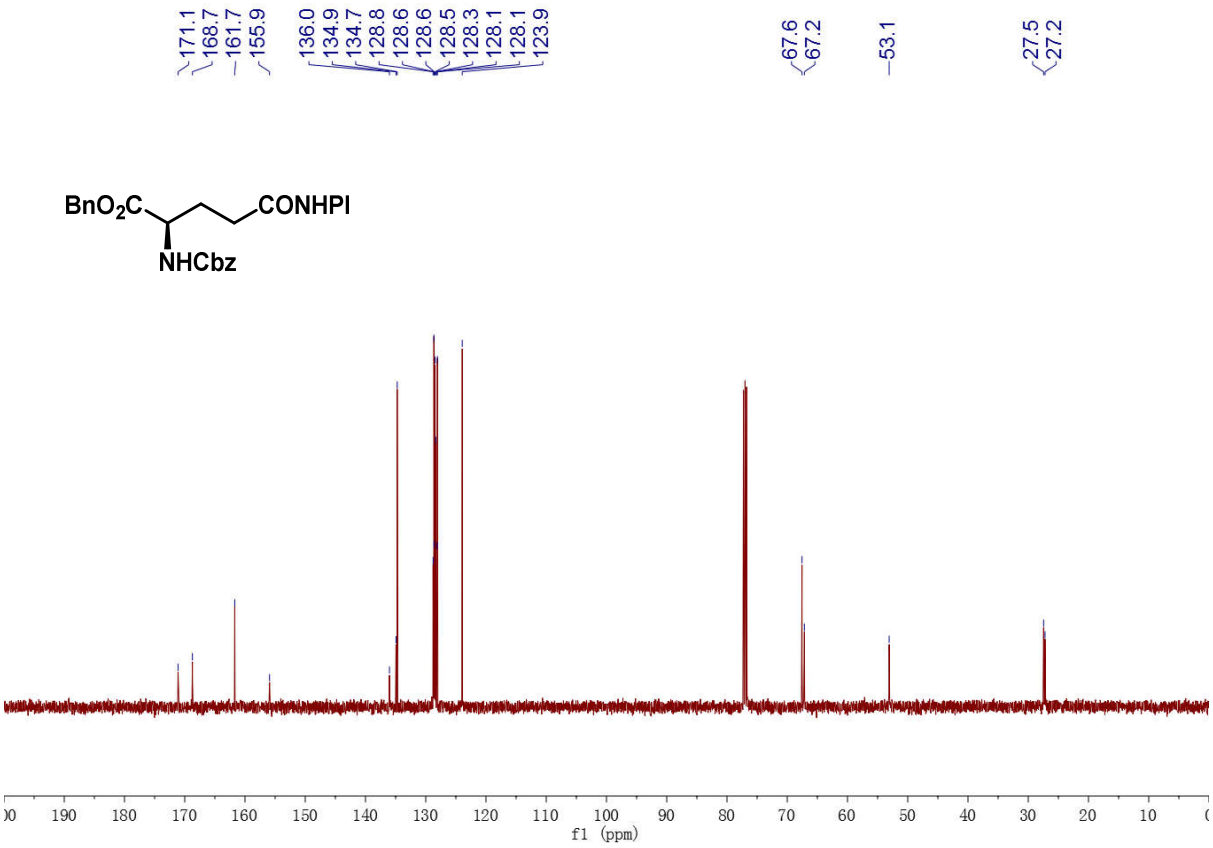
^{13}C NMR of Compound 63 (151 MHz, $CDCl_3$):



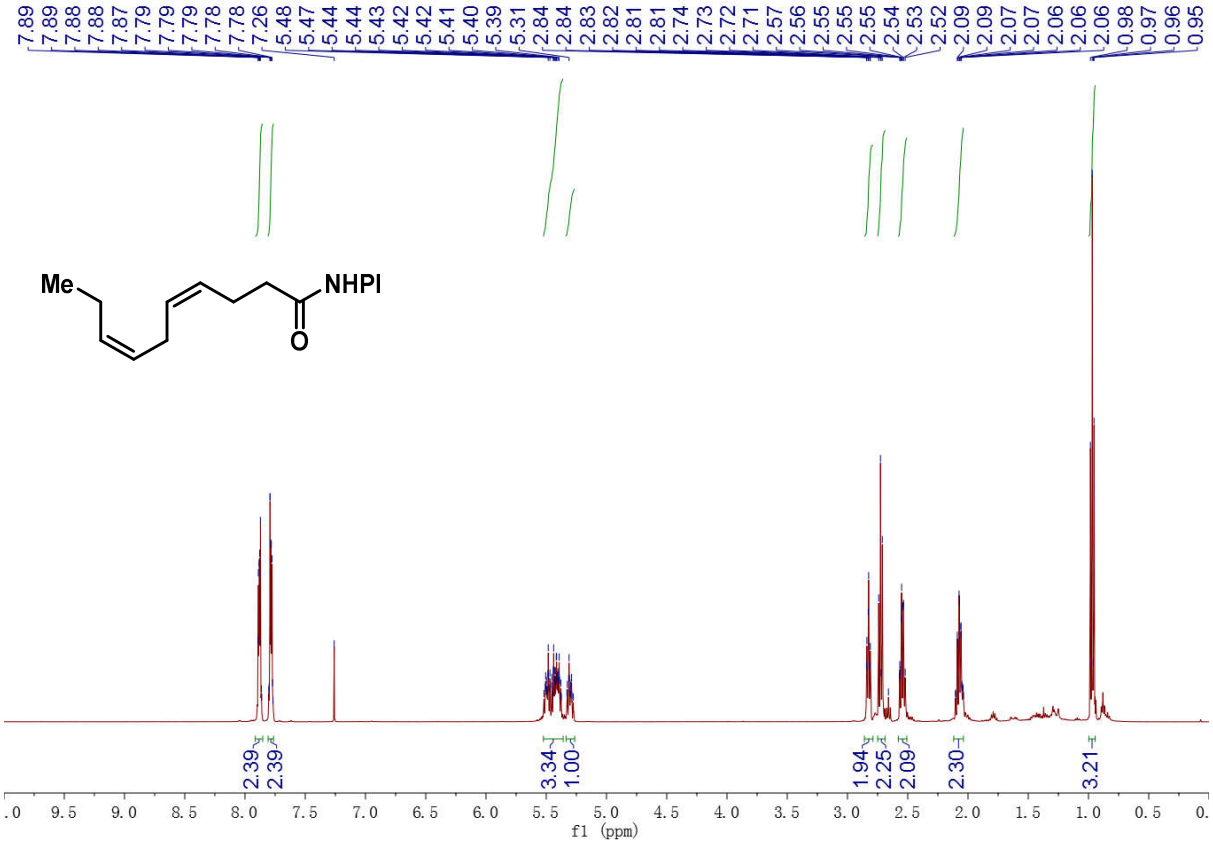
^{1}H NMR of Compound SI-43 (500 MHz, $CDCl_3$):



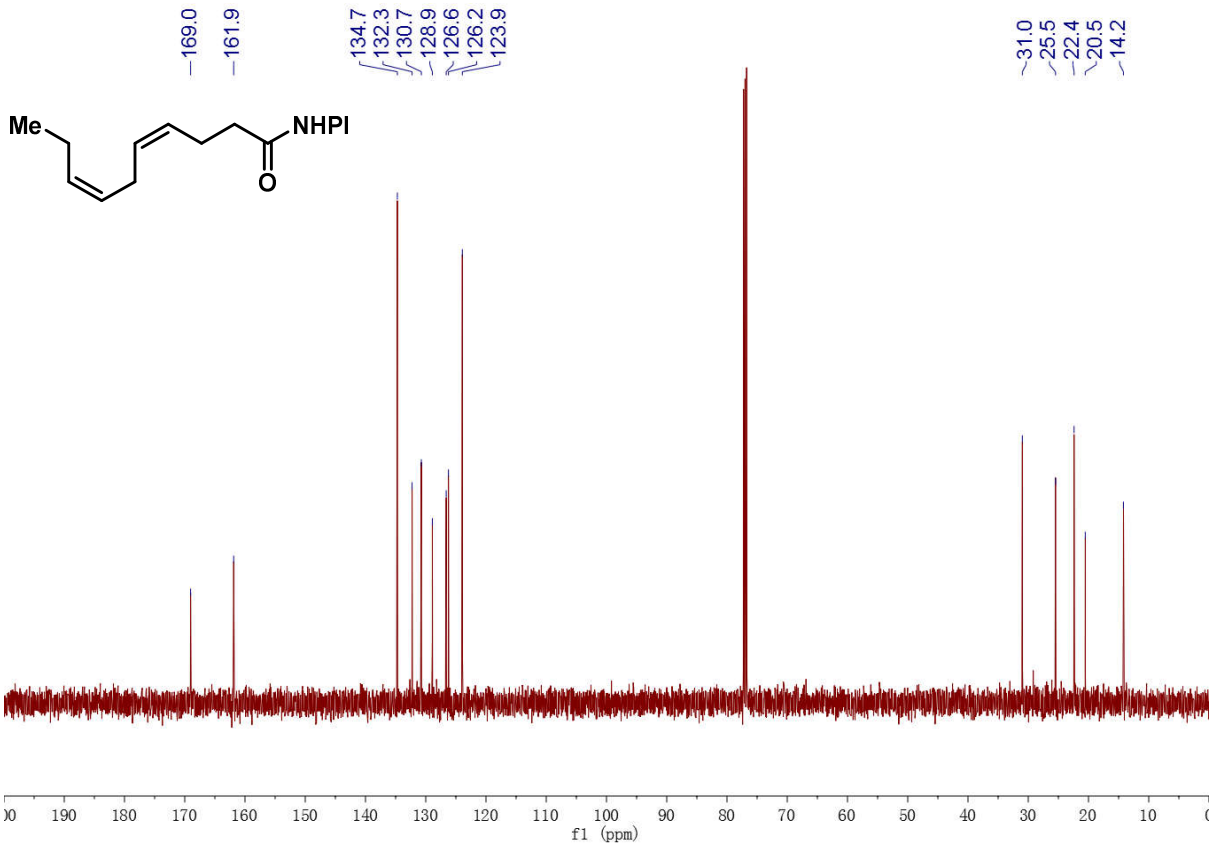
^{13}C NMR of Compound SI-43 (126 MHz, $CDCl_3$):



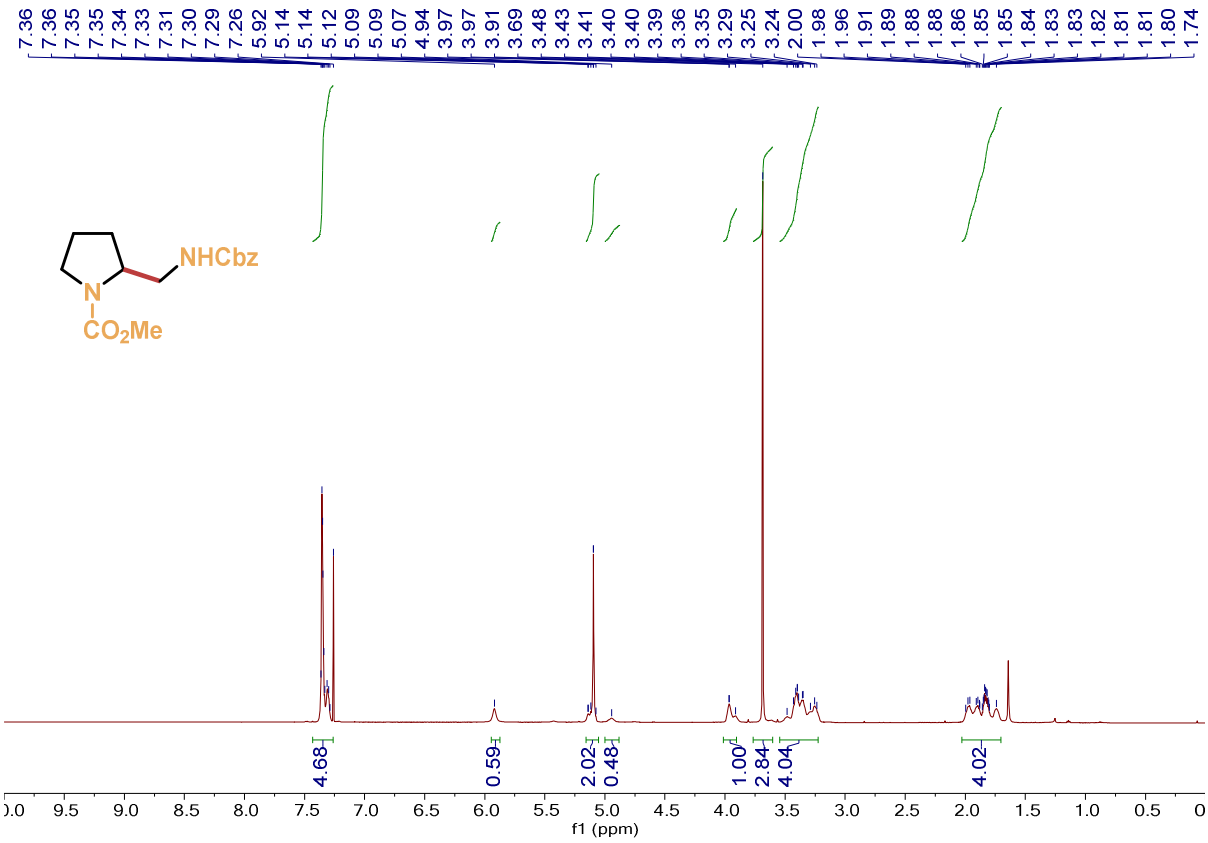
^{1}H NMR of Compound 68 (500 MHz, $CDCl_3$):



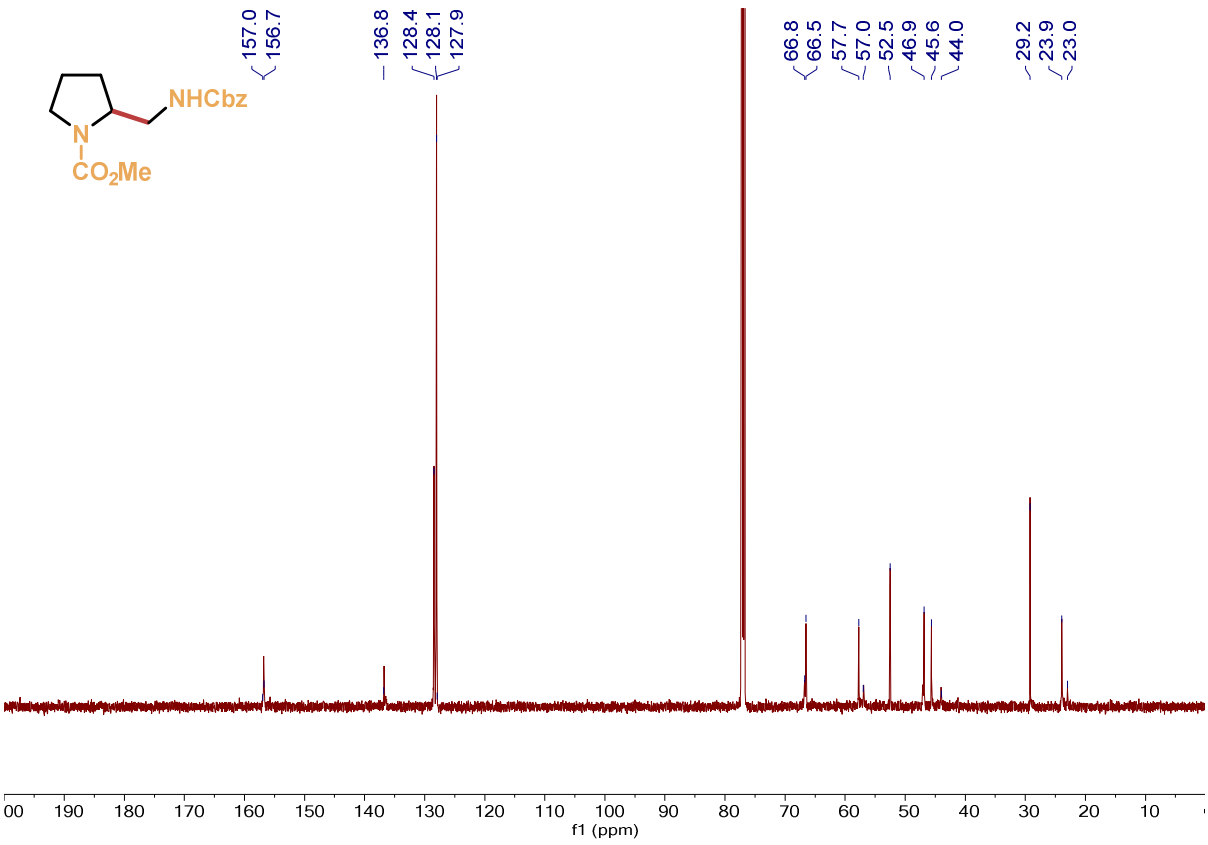
^{13}C NMR of Compound 68 (126 MHz, $CDCl_3$):



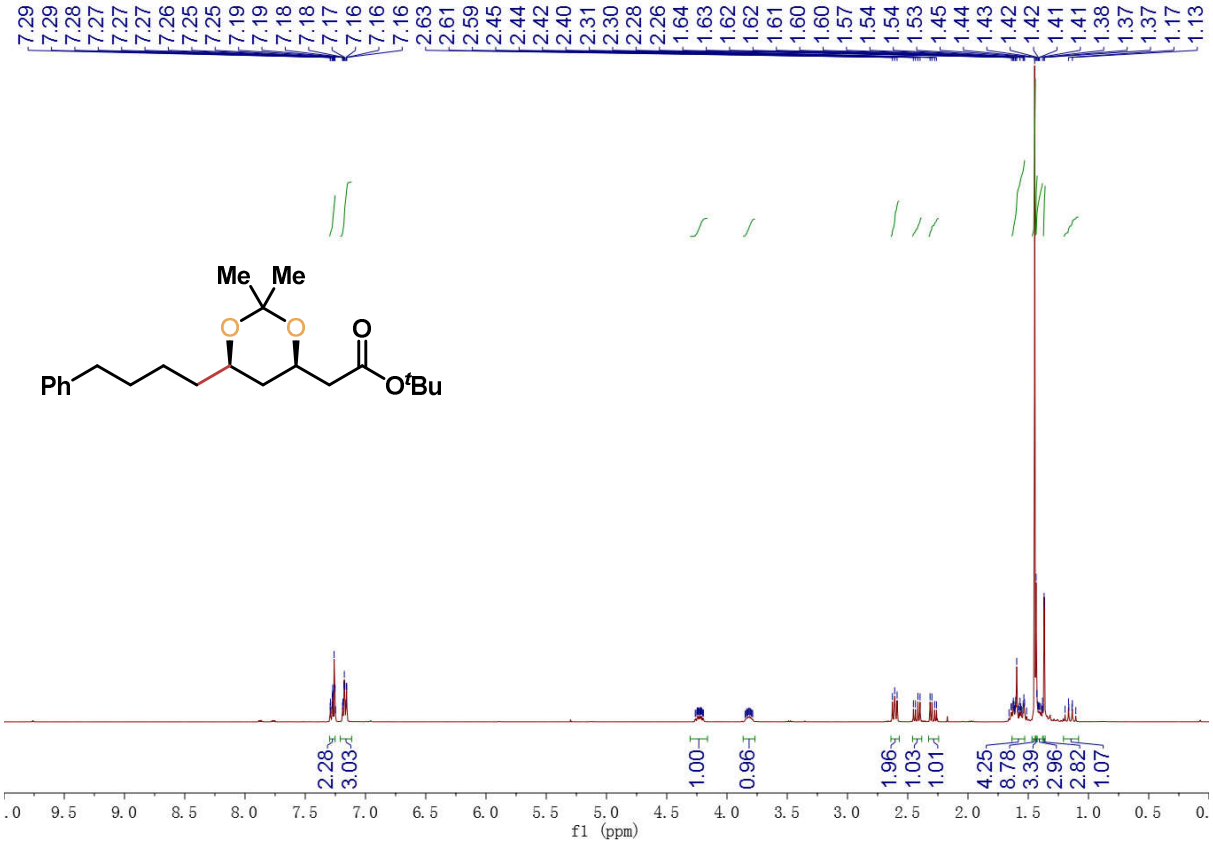
^{1}H NMR of Compound 10 (600 MHz, $CDCl_3$):



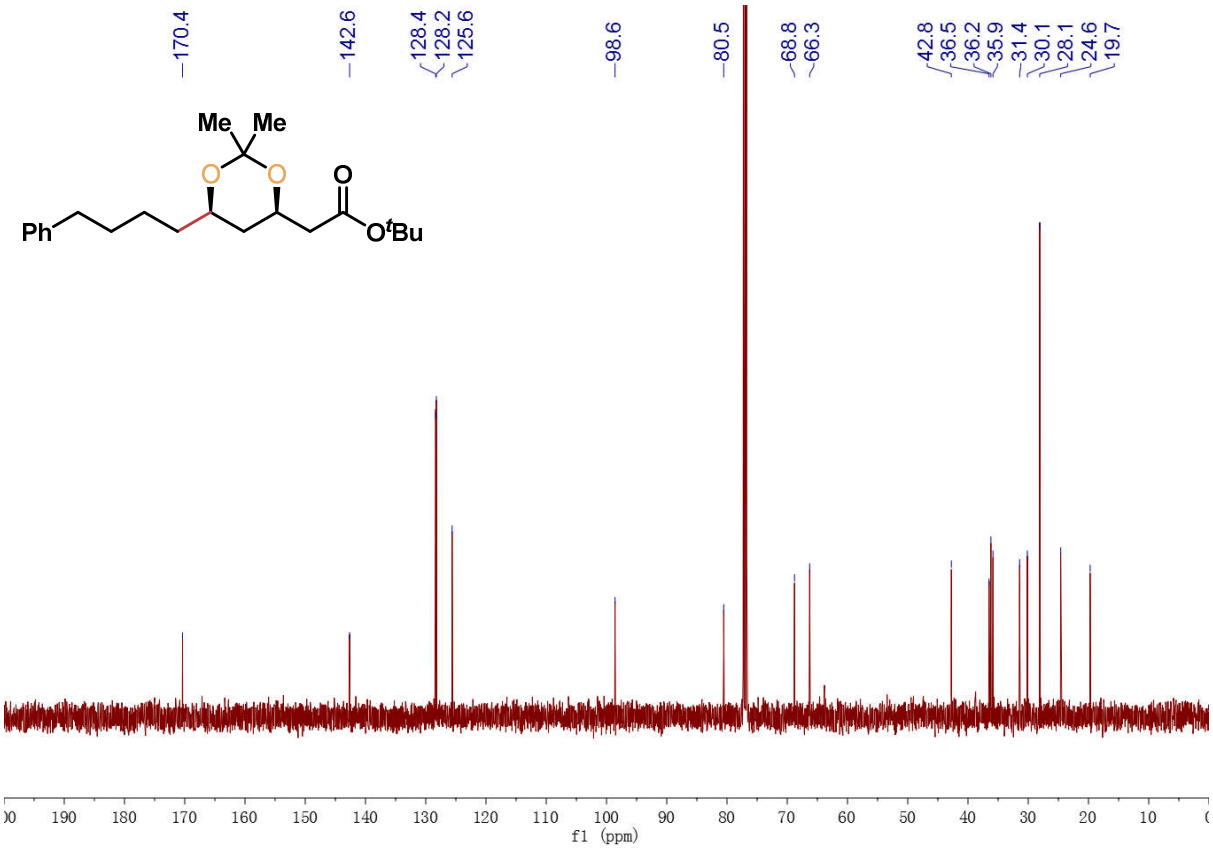
^{13}C NMR of Compound 10 (151 MHz, $CDCl_3$):



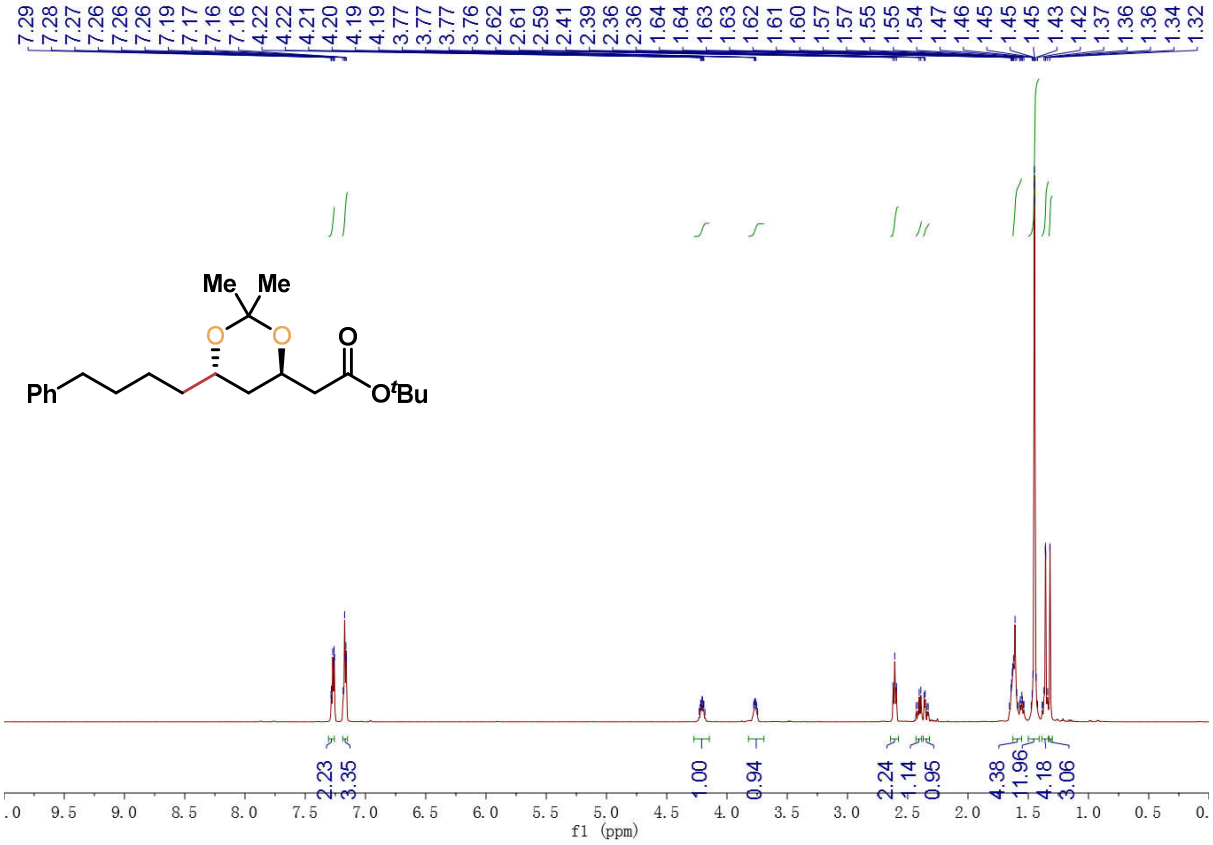
^{1}H NMR of Compound 12-(6R) (600 MHz, $CDCl_3$):



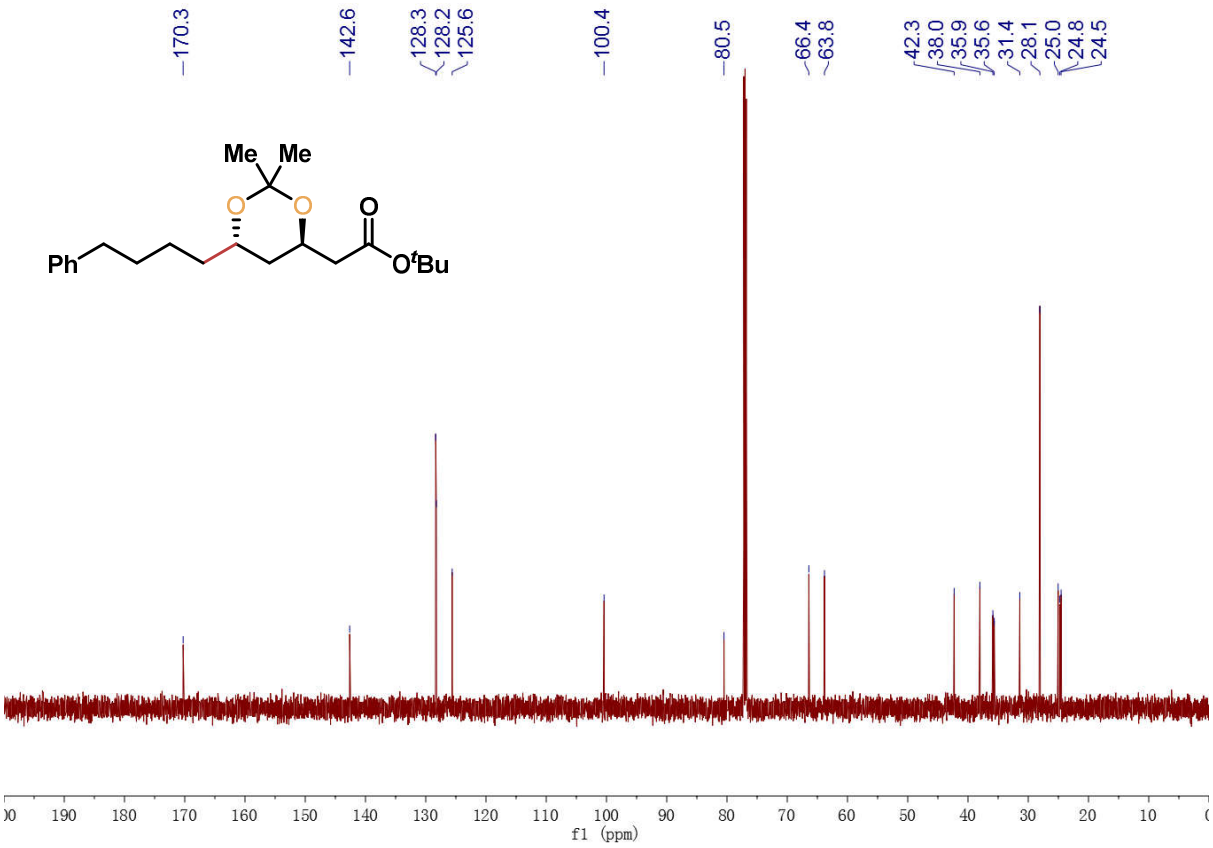
^{13}C NMR of Compound 12-(6R) (151 MHz, $CDCl_3$):



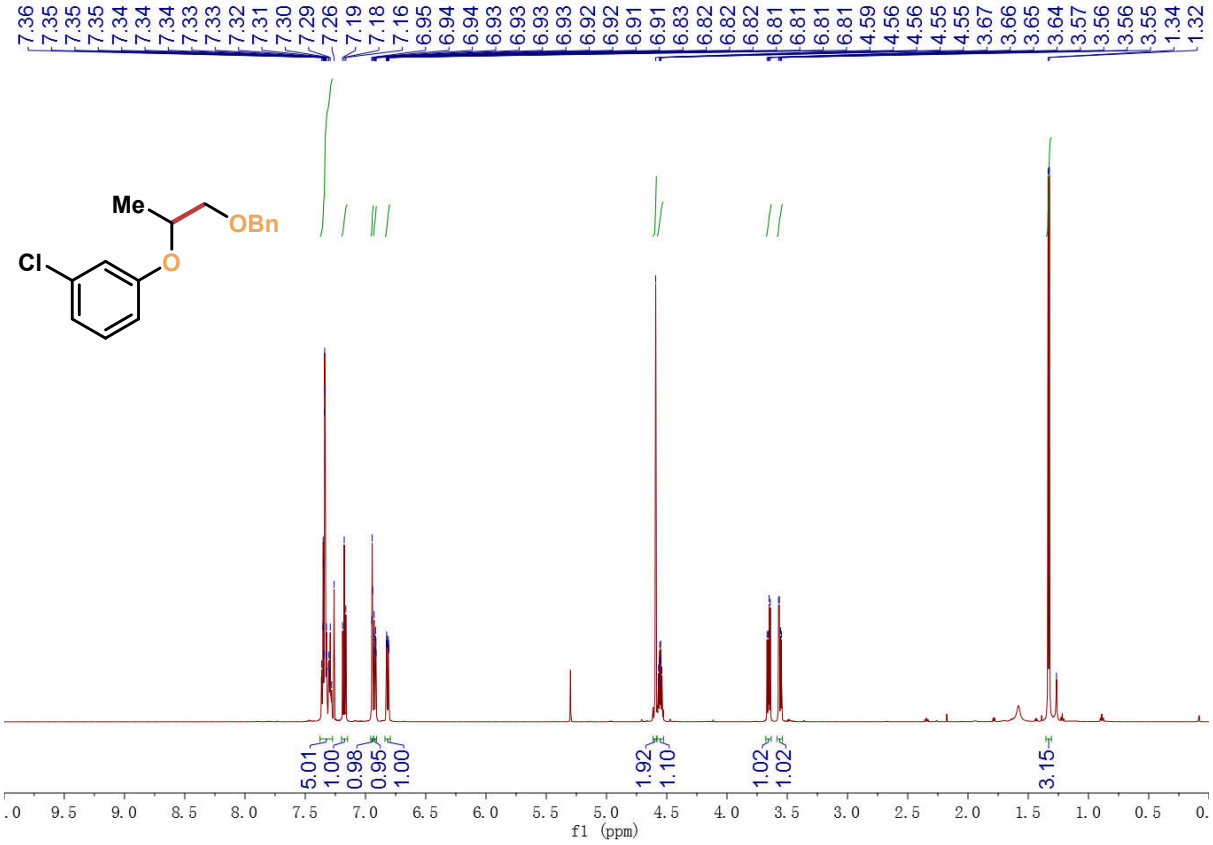
^{1}H NMR of Compound 12-(6S) (600 MHz, $CDCl_3$):



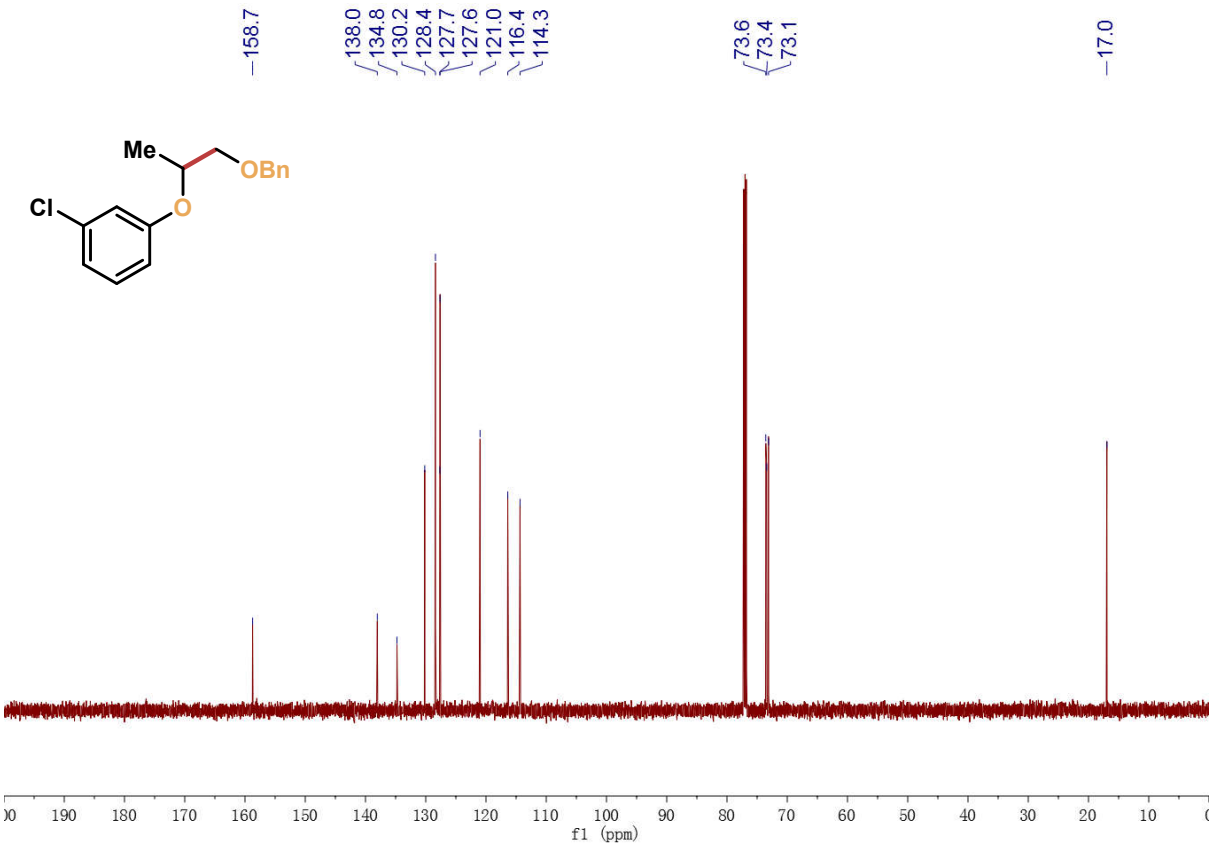
^{13}C NMR of Compound 12-(6S) (151 MHz, $CDCl_3$):



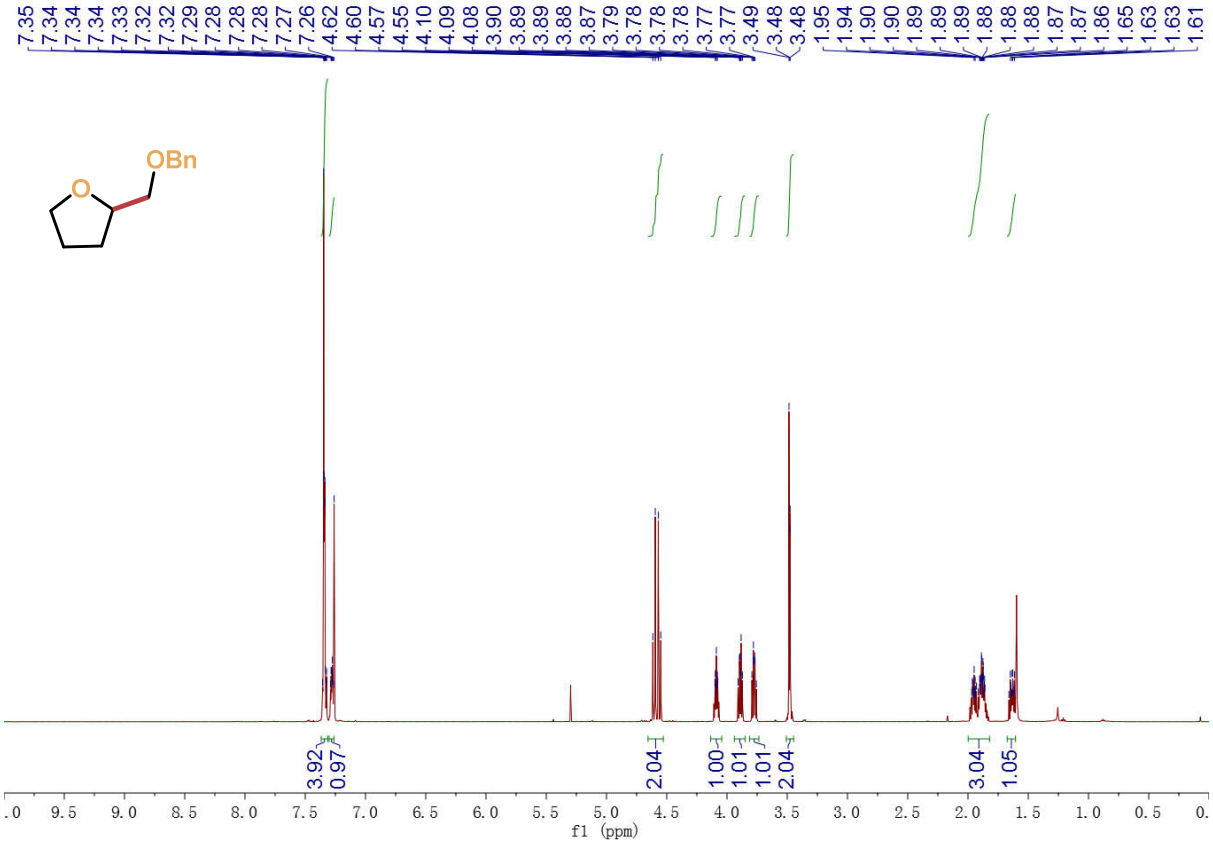
^{1}H NMR of Compound 13 (600 MHz, $CDCl_3$):



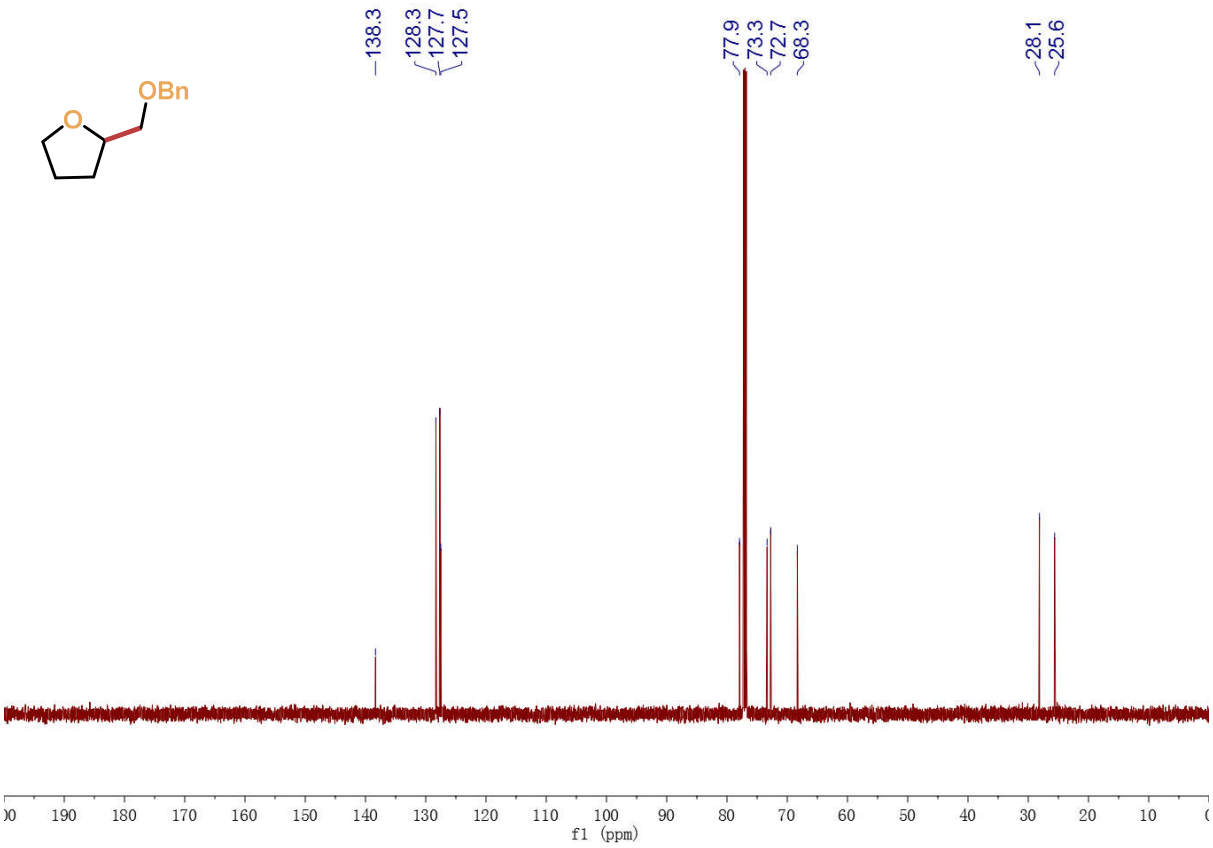
^{13}C NMR of Compound 13 (151 MHz, $CDCl_3$):



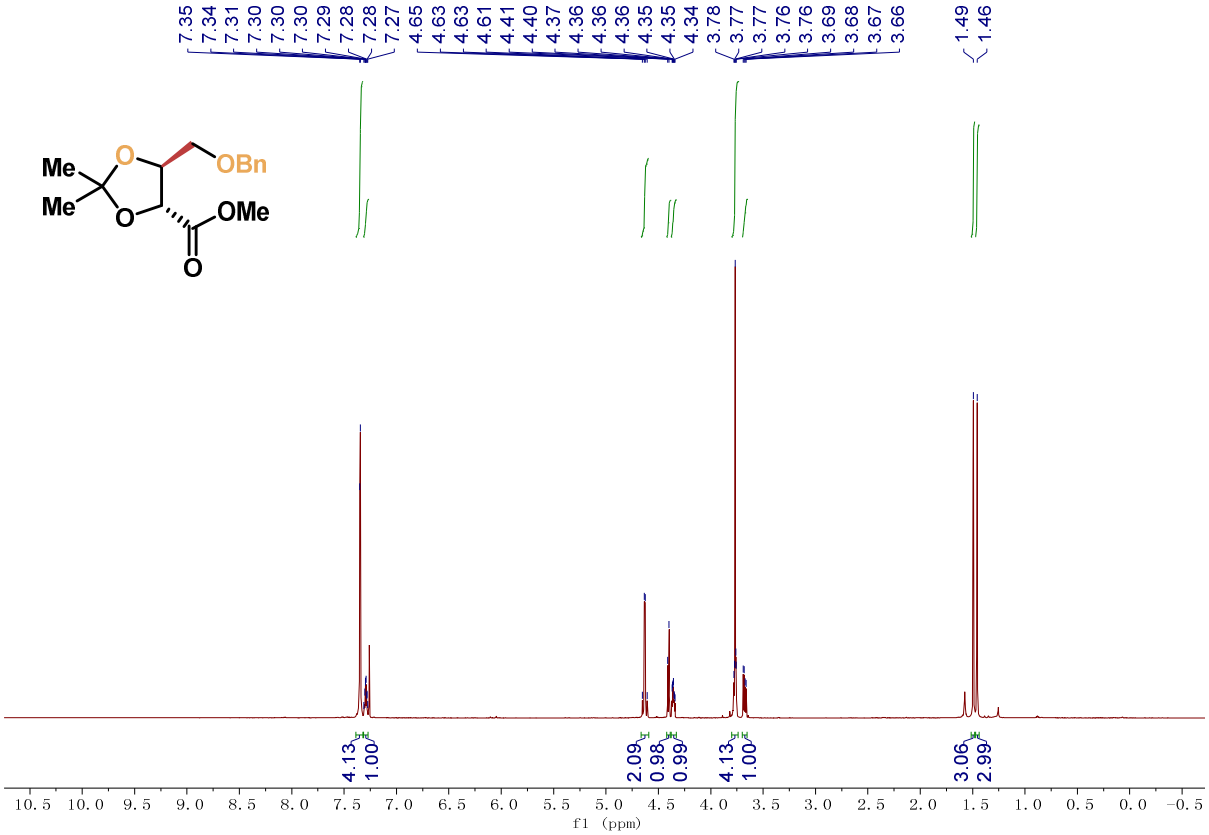
^{1}H NMR of Compound 14 (600 MHz, $CDCl_3$):



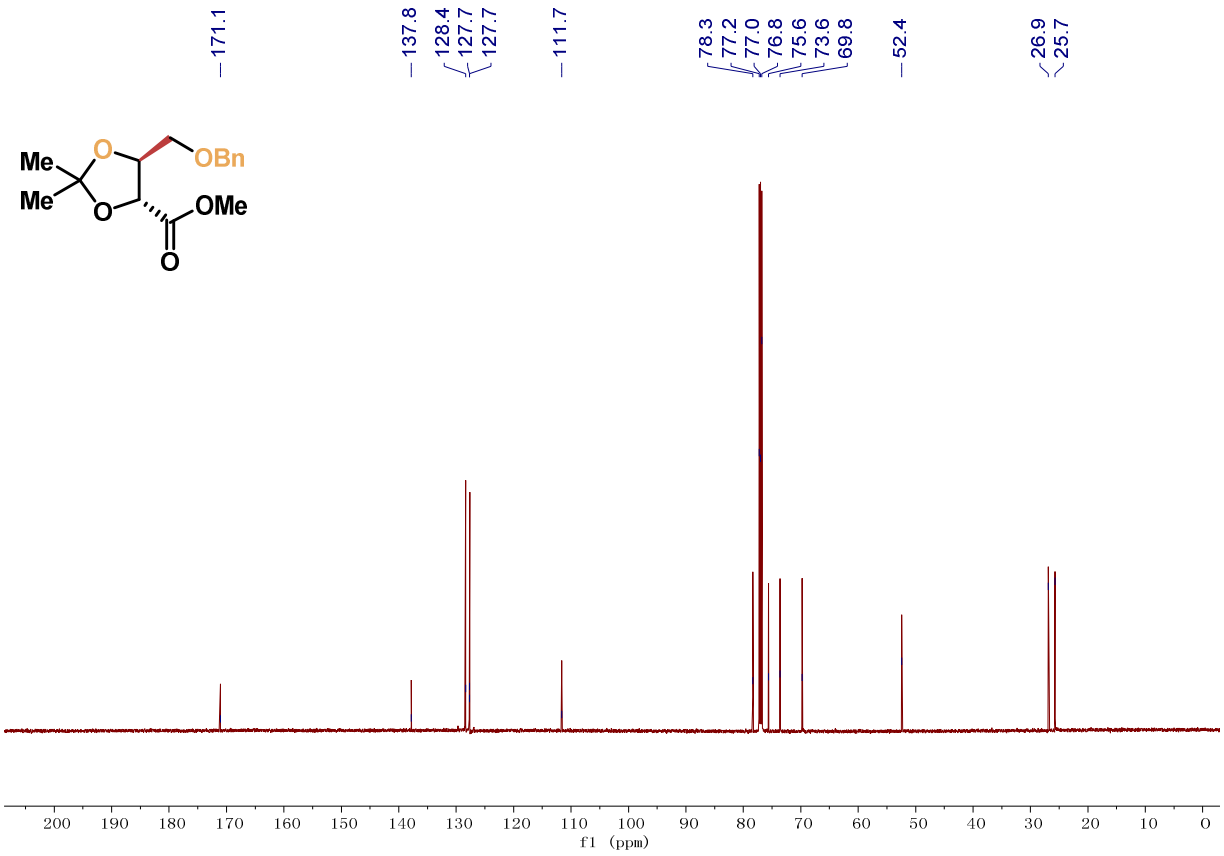
^{13}C NMR of Compound 14 (151 MHz, $CDCl_3$):



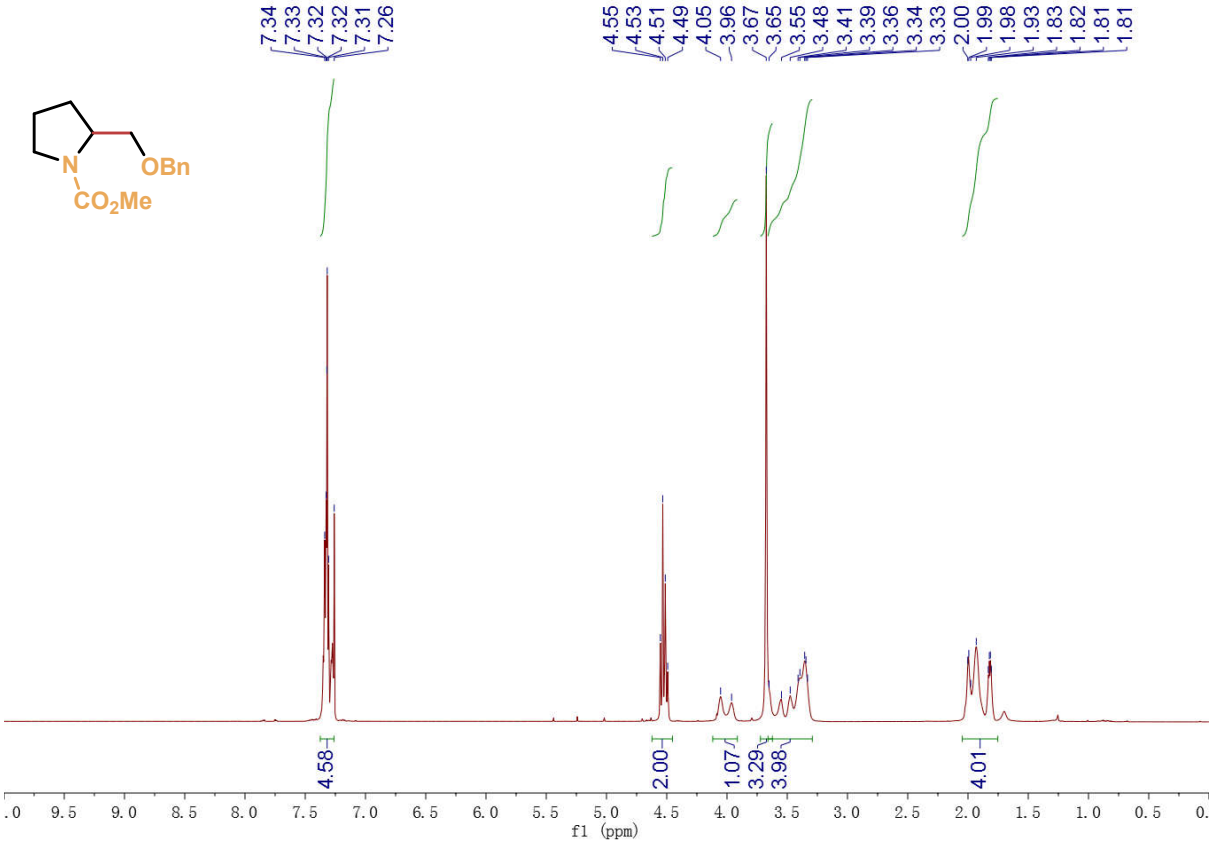
^{1}H NMR of Compound 15 (600 MHz, $CDCl_3$):



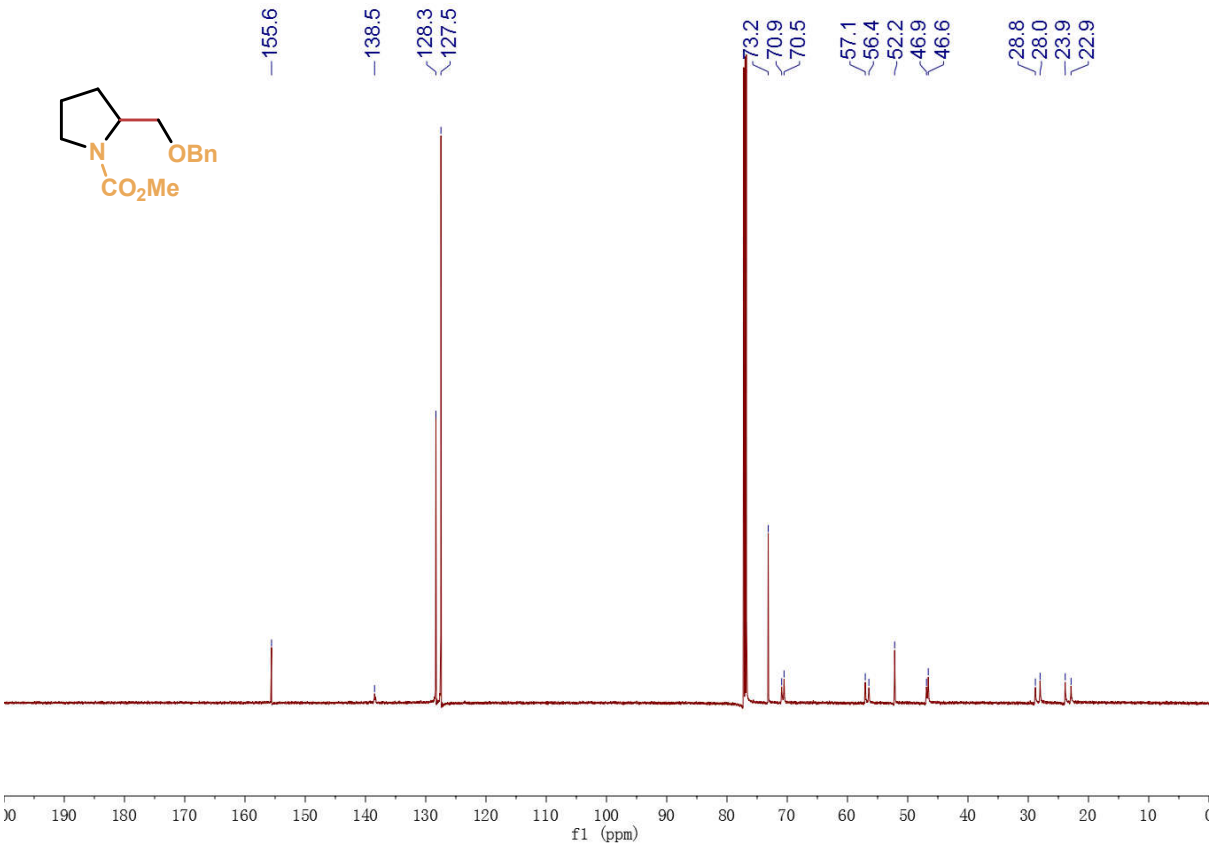
^{13}C NMR of Compound 15 (151 MHz, $CDCl_3$):



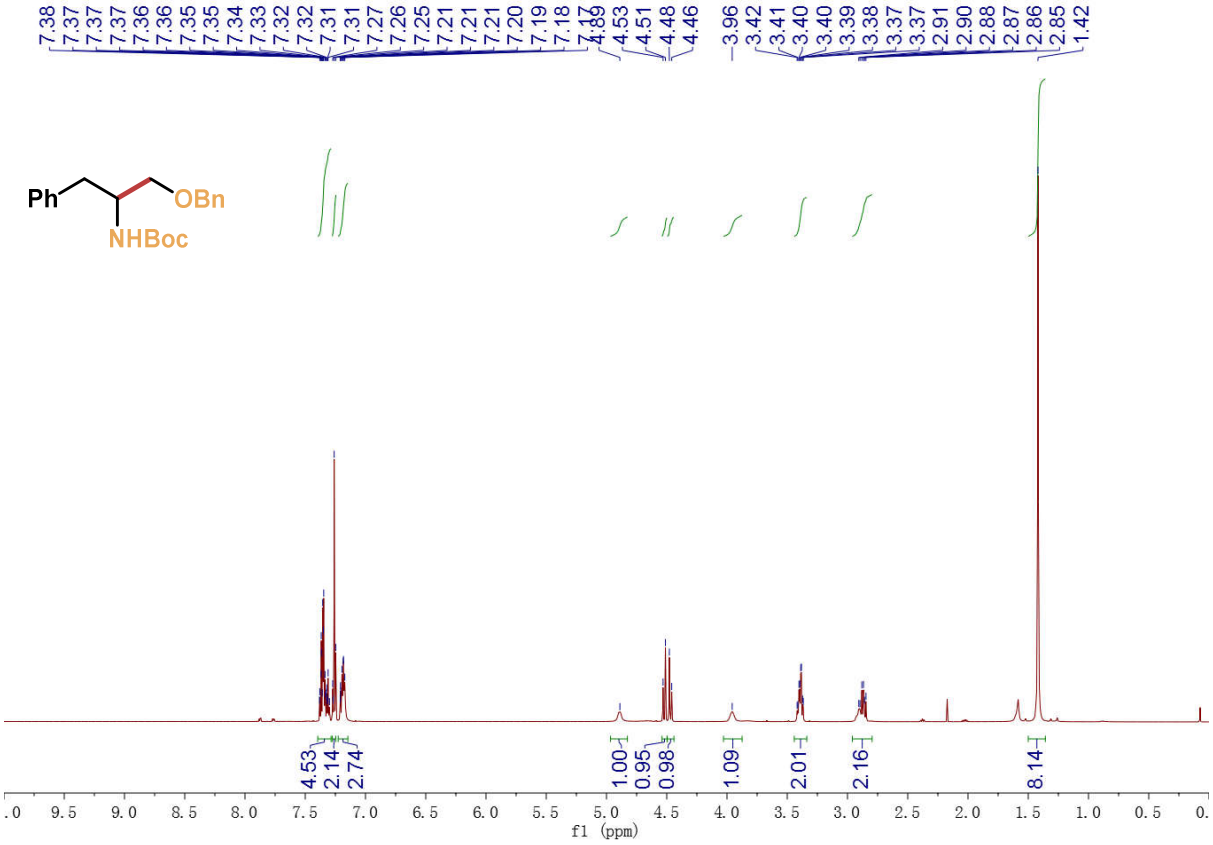
^{1}H NMR of Compound 17 (600 MHz, $CDCl_3$):



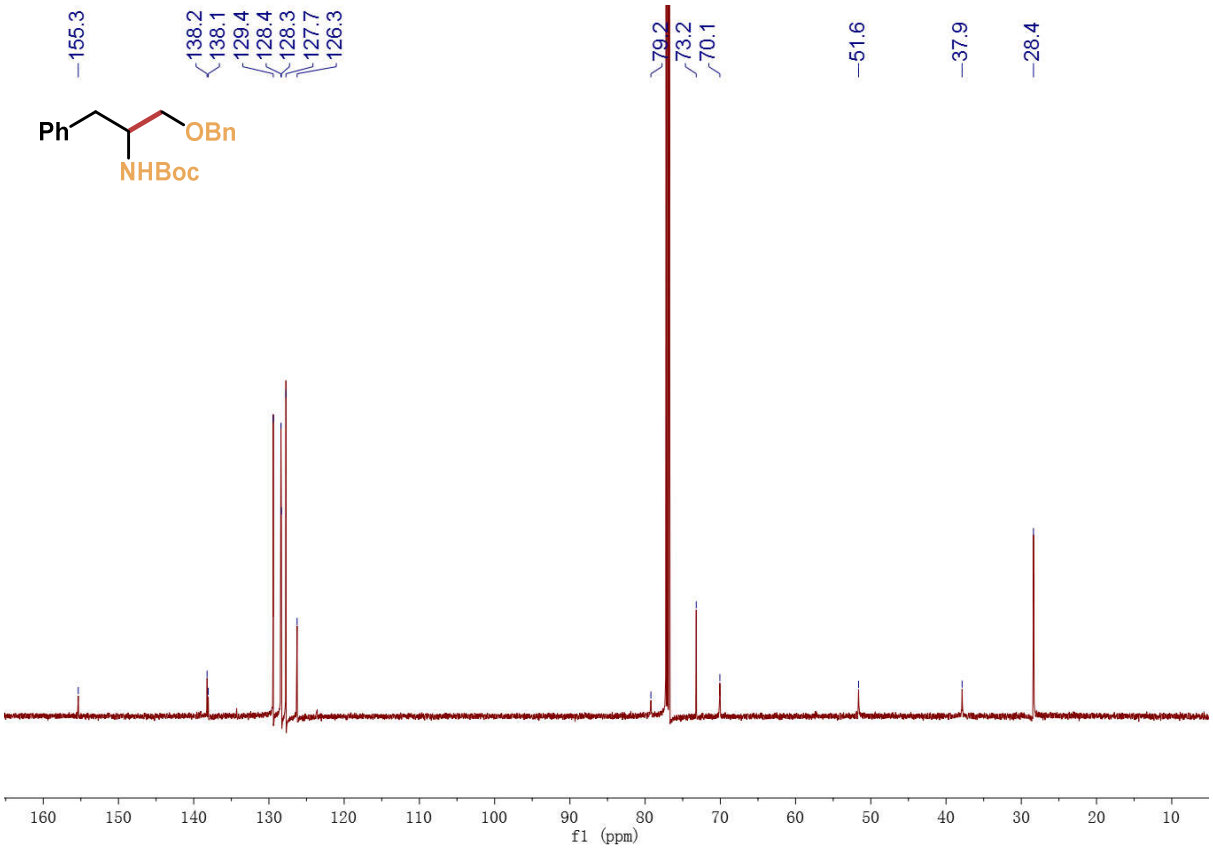
^{13}C NMR of Compound 17 (151 MHz, $CDCl_3$):



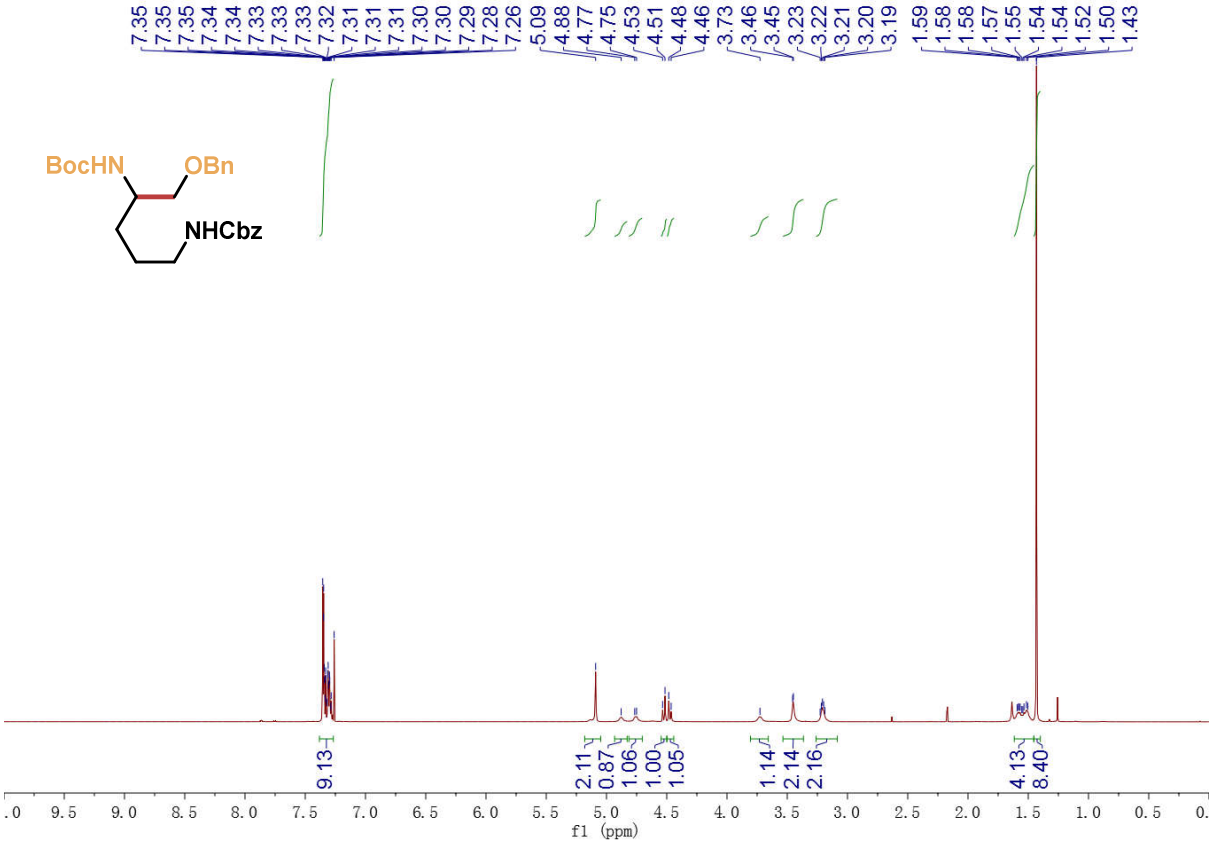
^{1}H NMR of Compound 18 (600 MHz, $CDCl_3$):



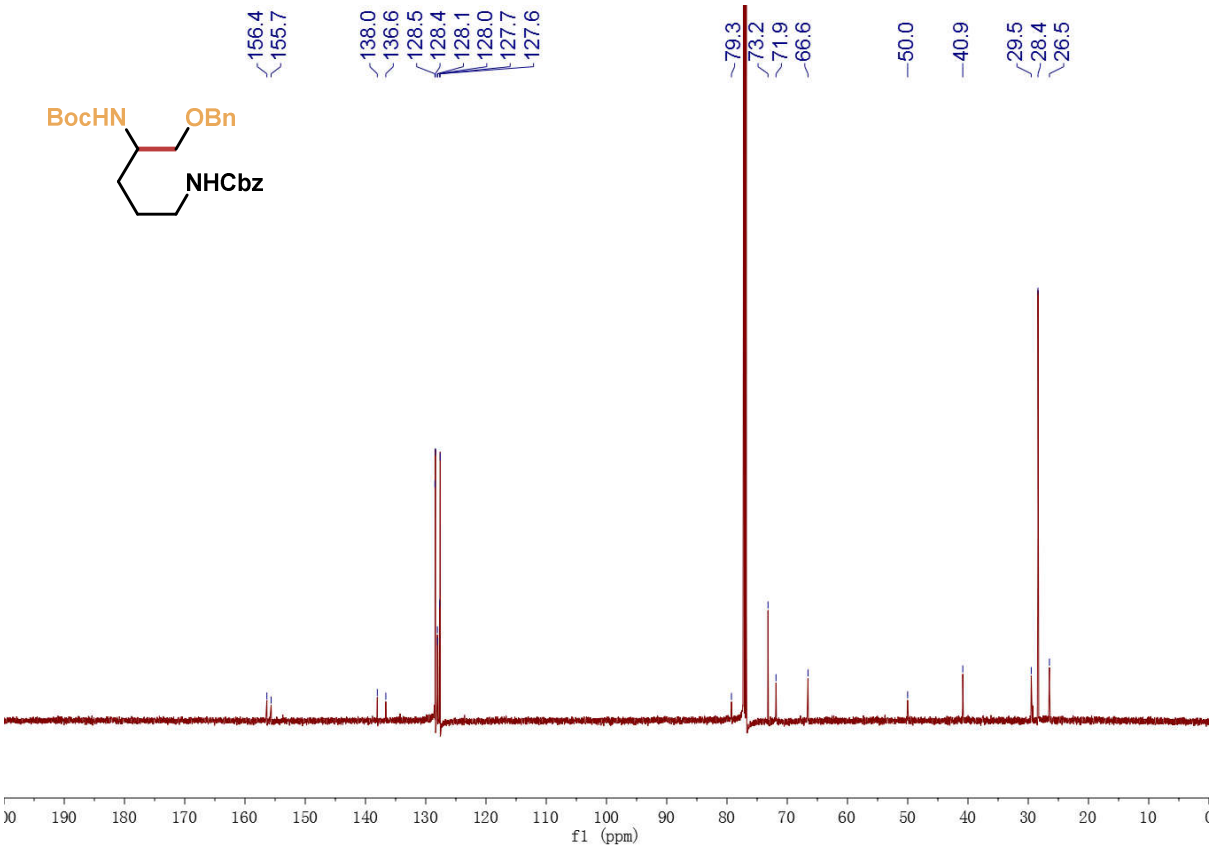
^{13}C NMR of Compound 18 (151 MHz, $CDCl_3$):



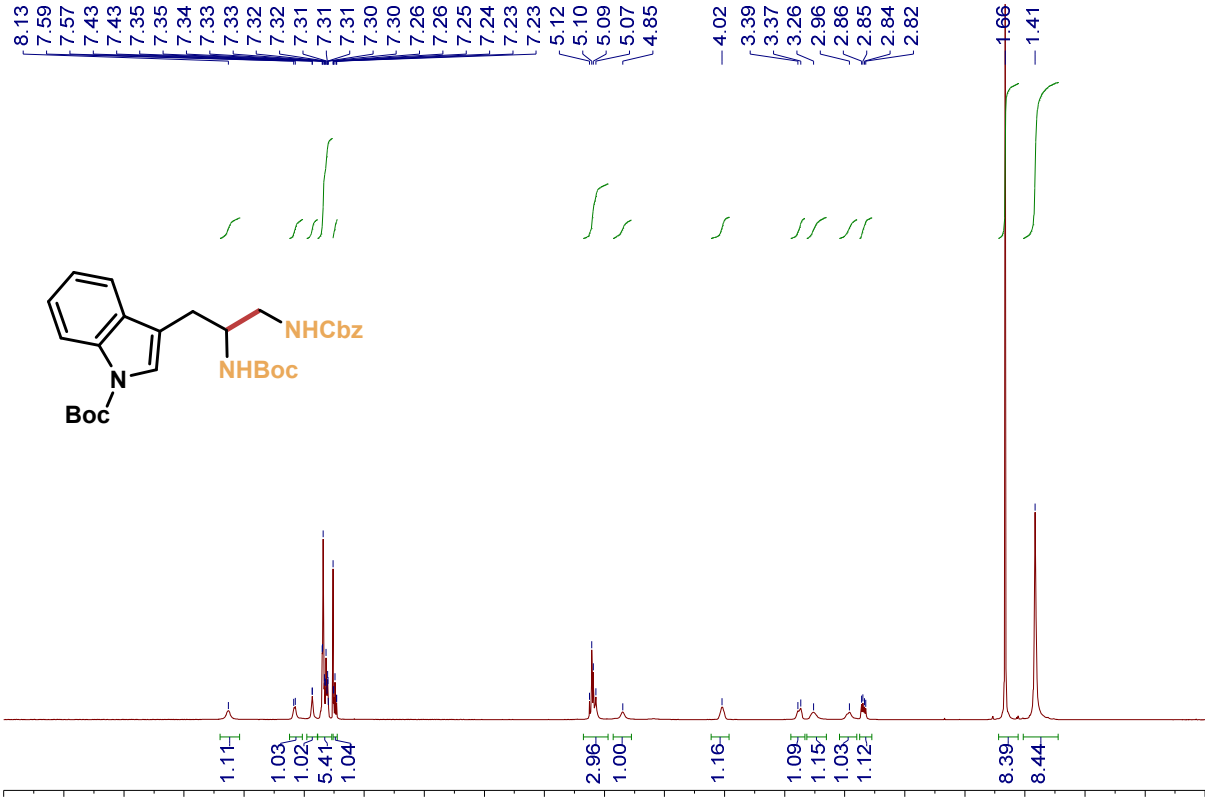
^{1}H NMR of Compound 19 (600 MHz, $CDCl_3$):



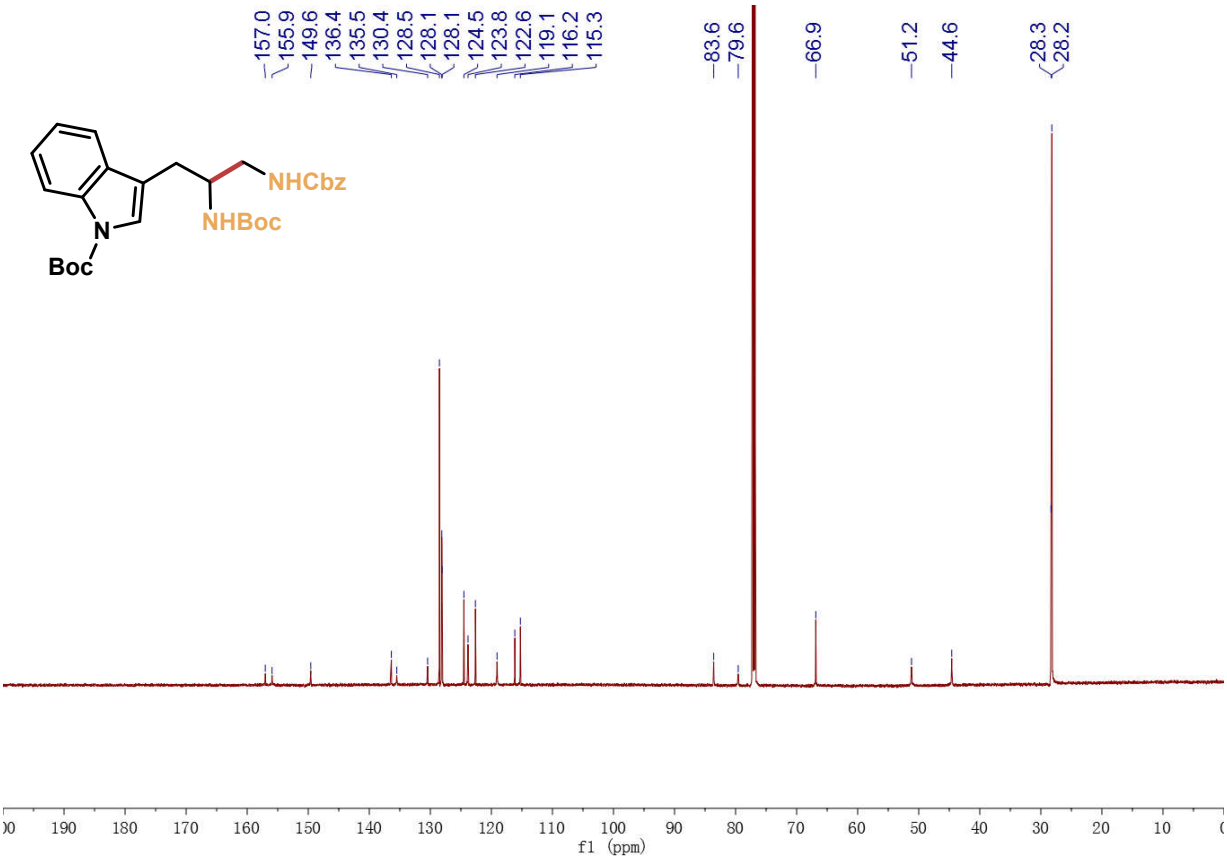
^{13}C NMR of Compound 19 (151 MHz, $CDCl_3$):



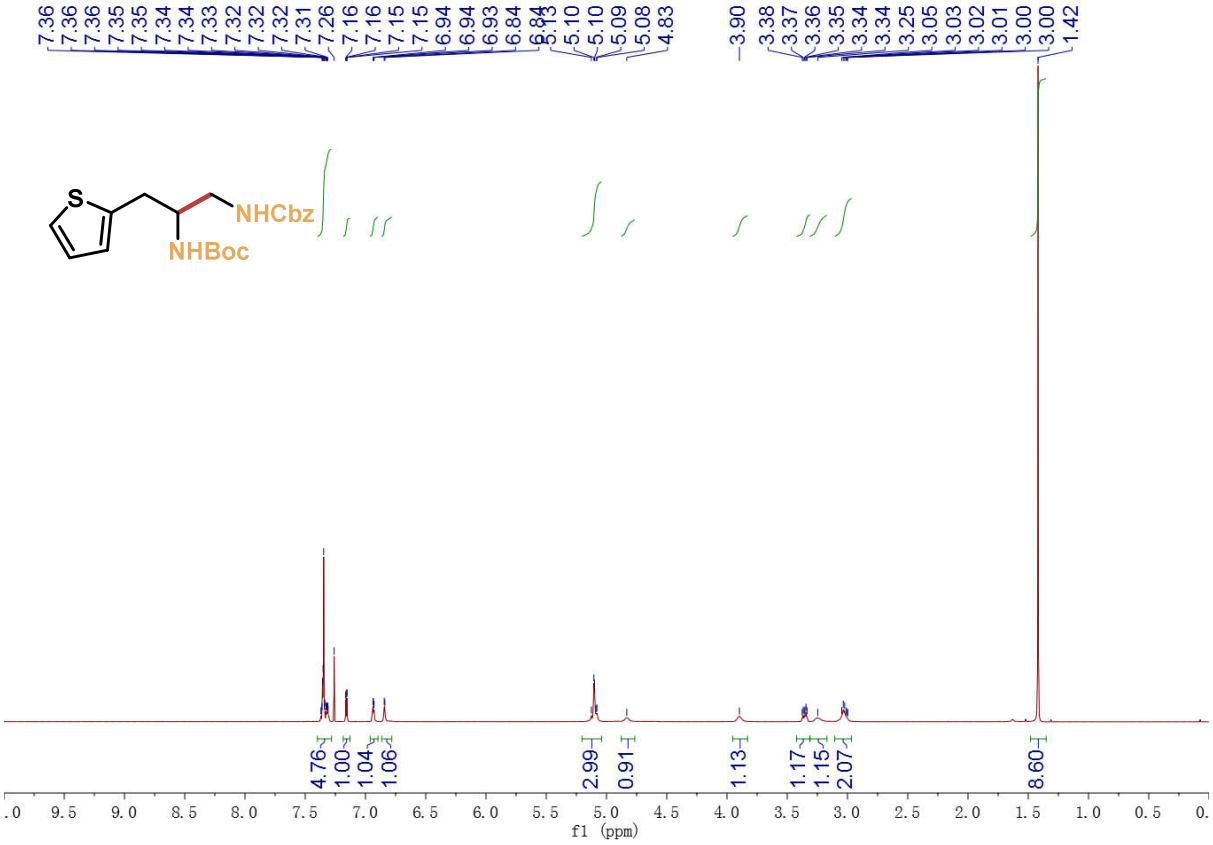
^{1}H NMR of Compound 21 (600 MHz, $CDCl_3$):



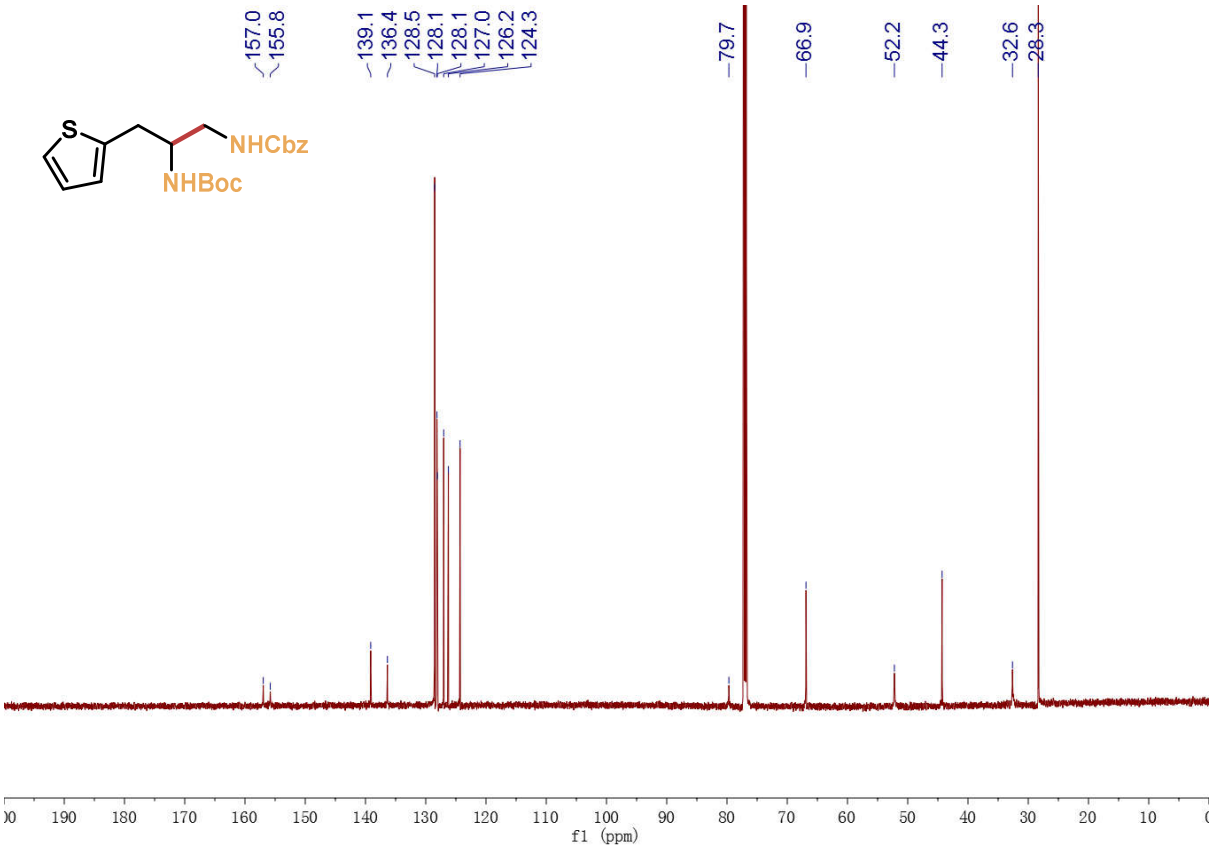
^{13}C NMR of Compound 21 (151 MHz, $CDCl_3$):



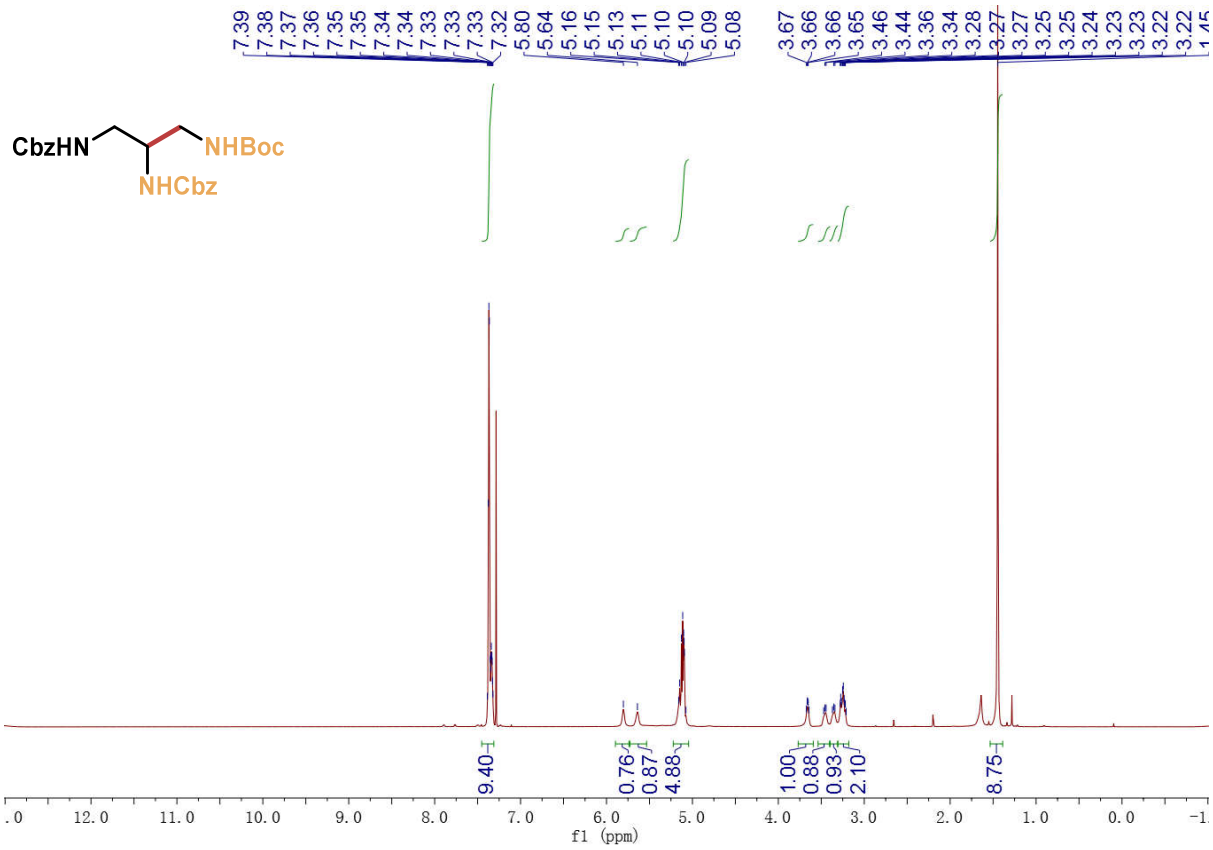
^{1}H NMR of Compound 22 (600 MHz, $CDCl_3$):



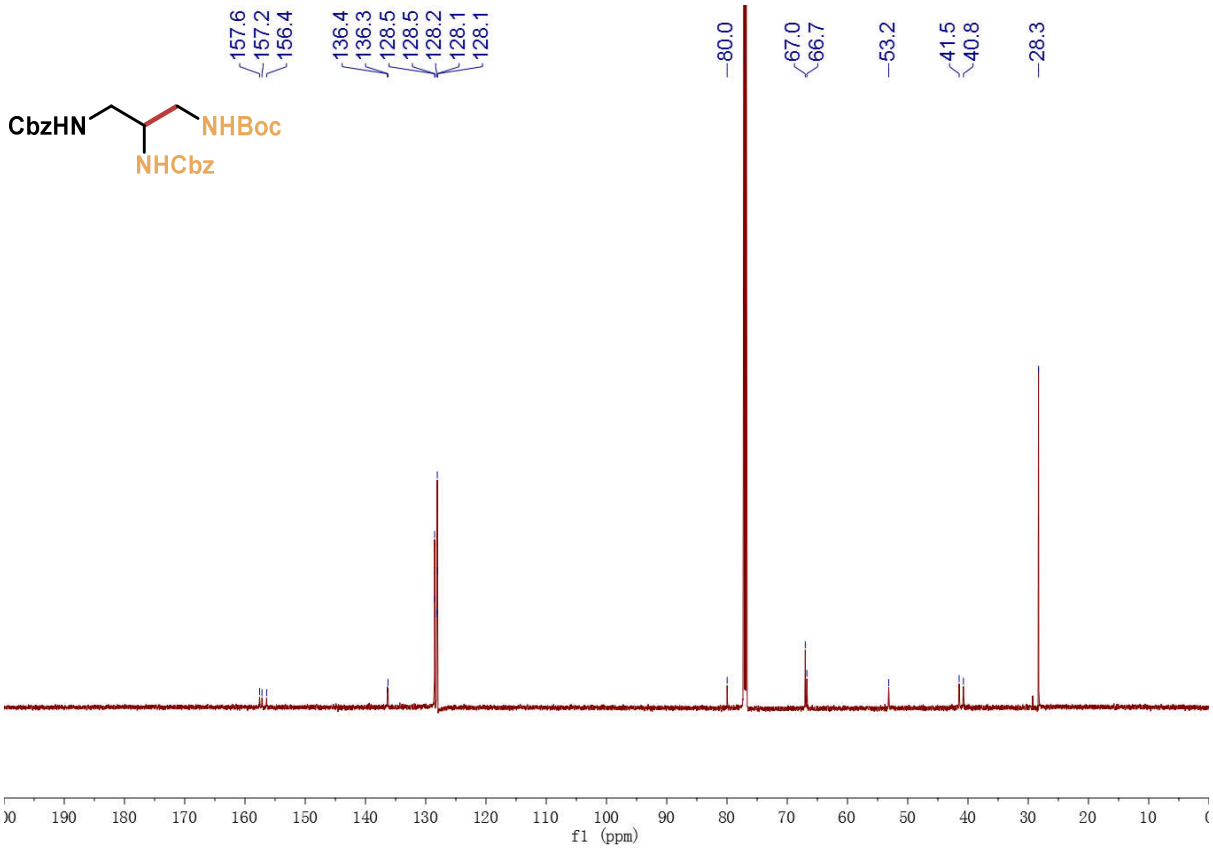
^{13}C NMR of Compound 22 (151 MHz, $CDCl_3$):



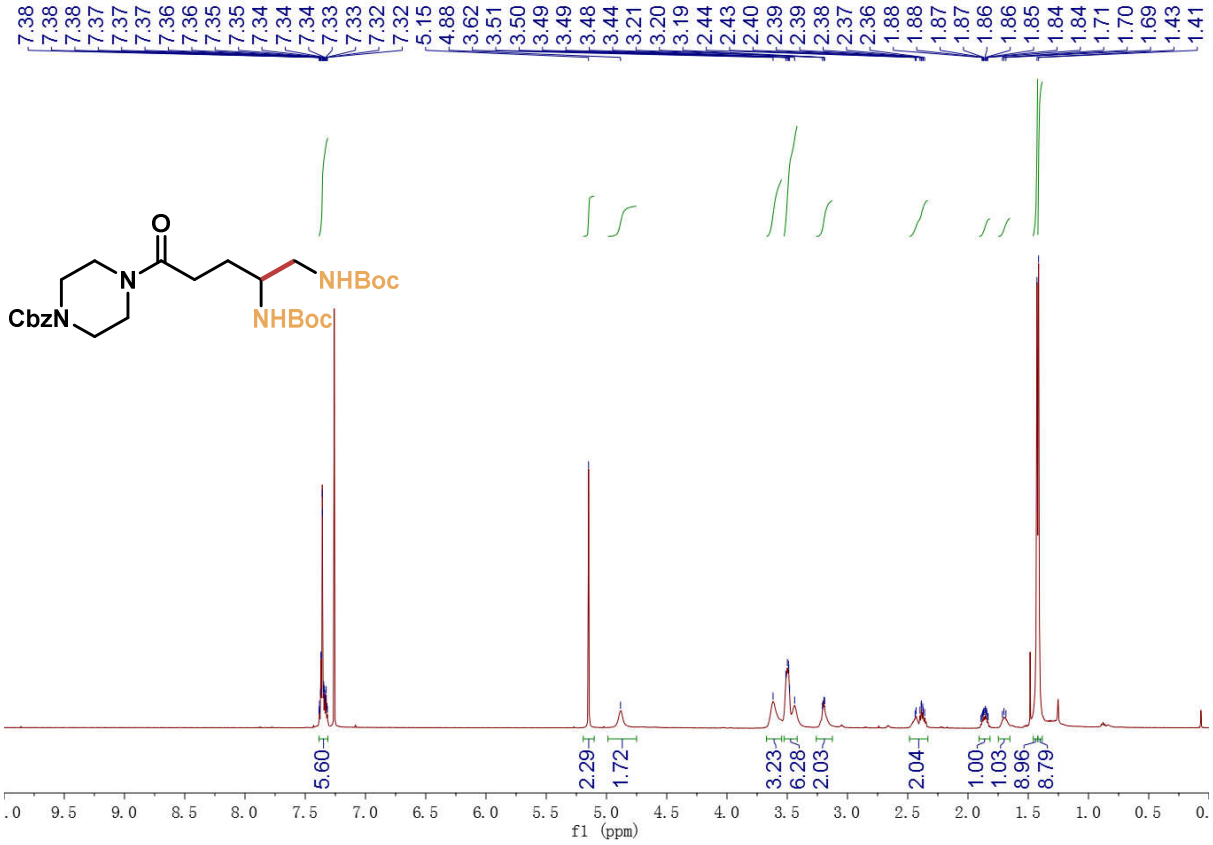
^{1}H NMR of Compound 23 (600 MHz, $CDCl_3$):



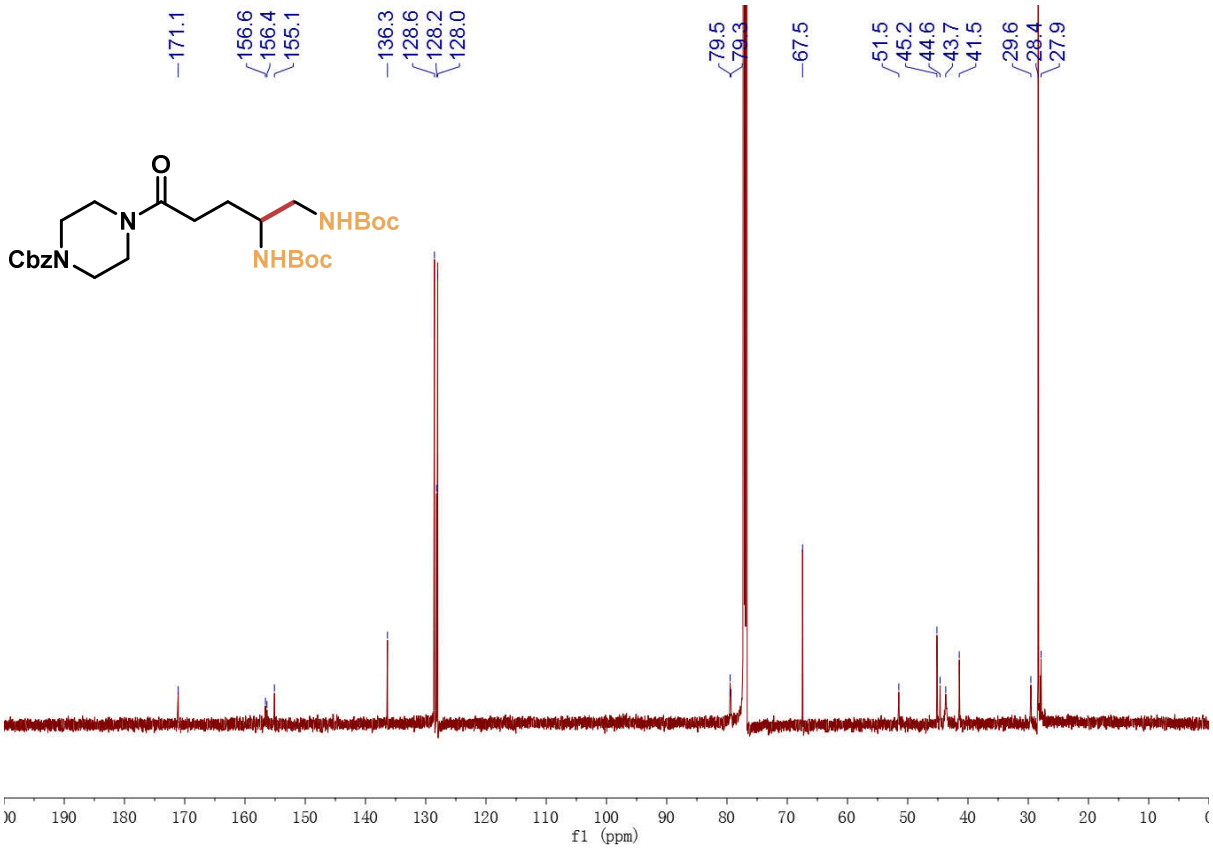
^{13}C NMR of Compound 23 (151 MHz, $CDCl_3$):



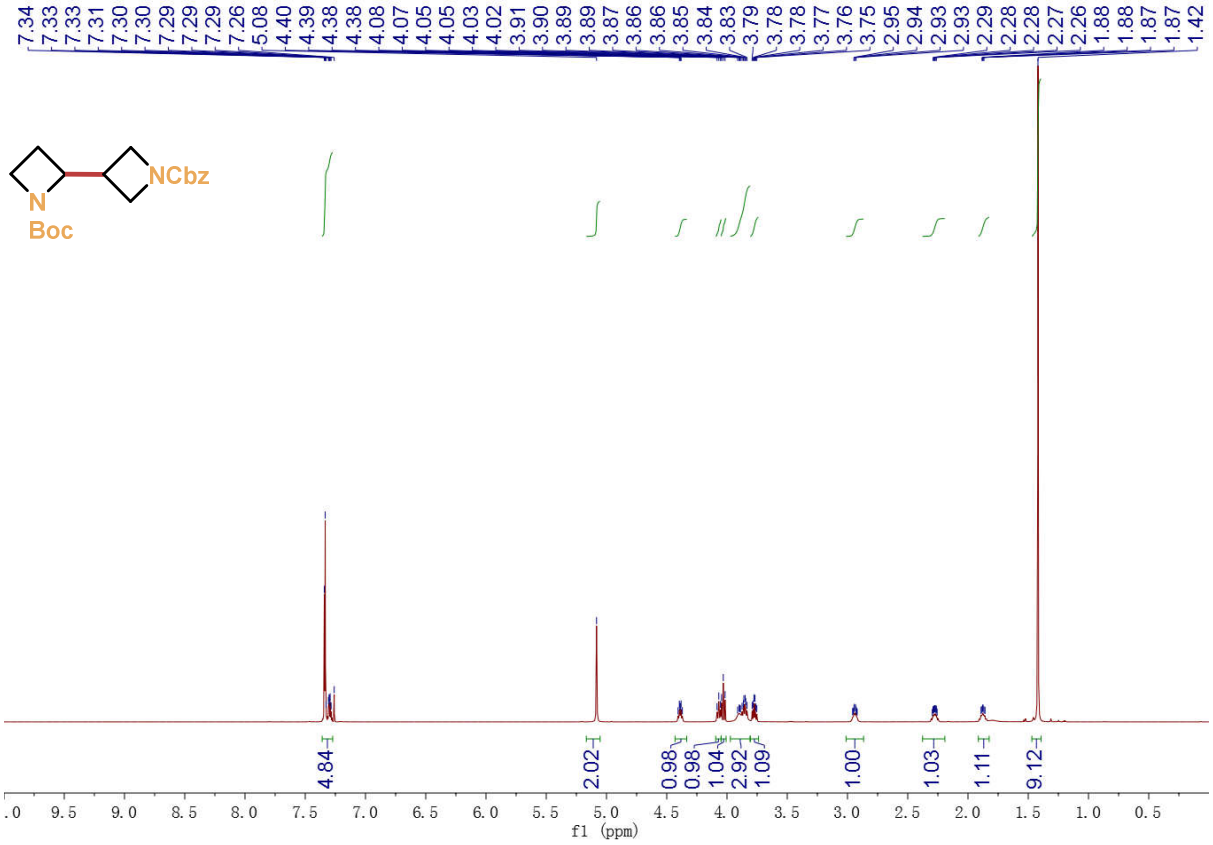
^{1}H NMR of Compound 24 (600 MHz, $CDCl_3$):



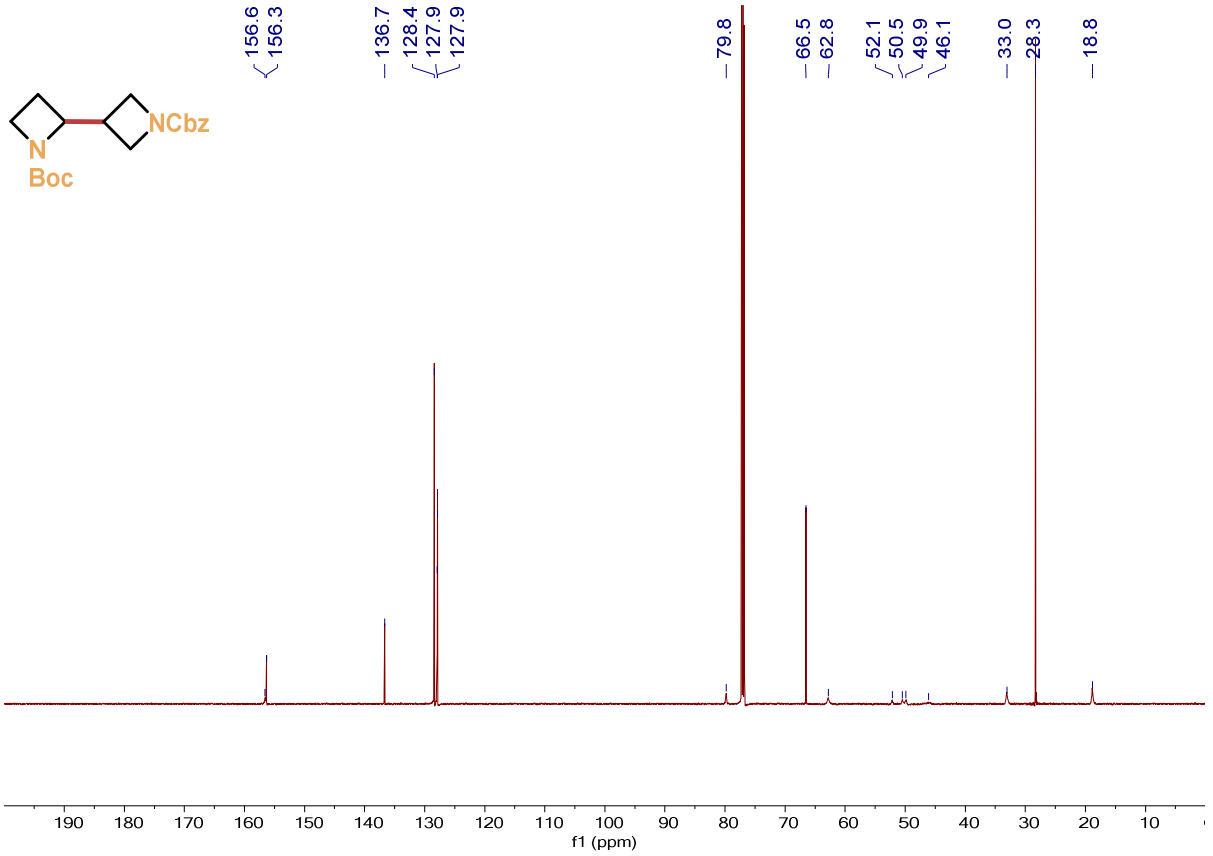
^{13}C NMR of Compound 24 (151 MHz, $CDCl_3$):



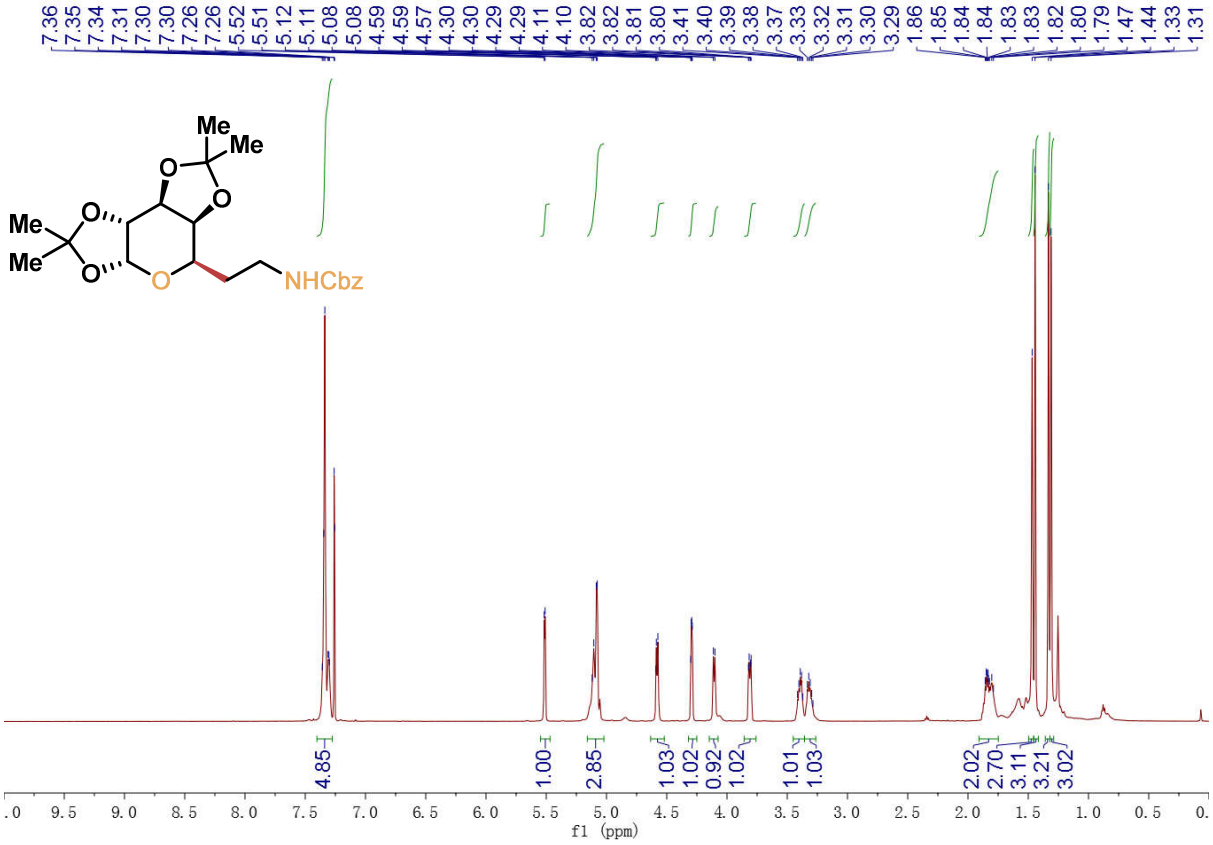
^{1}H NMR of Compound 25 (600 MHz, $CDCl_3$):



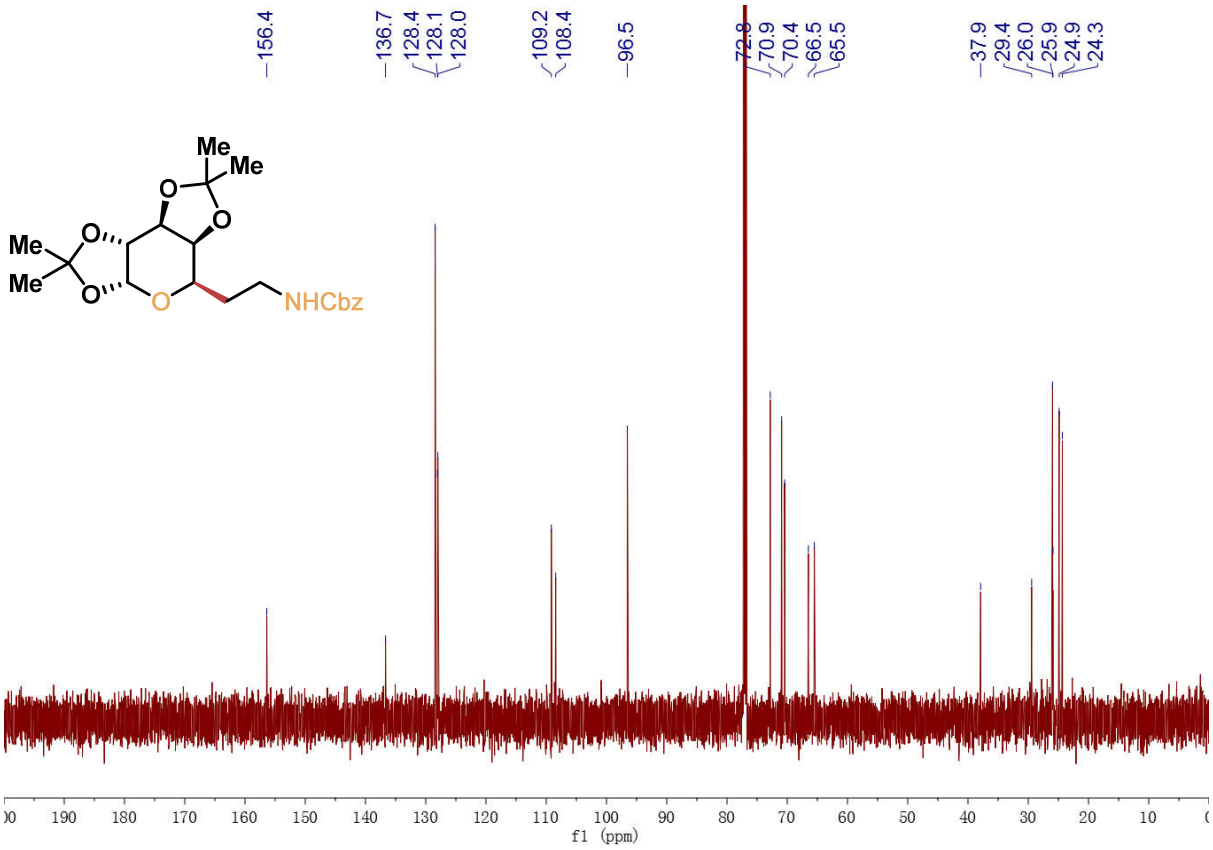
^{13}C NMR of Compound 25 (151 MHz, $CDCl_3$):



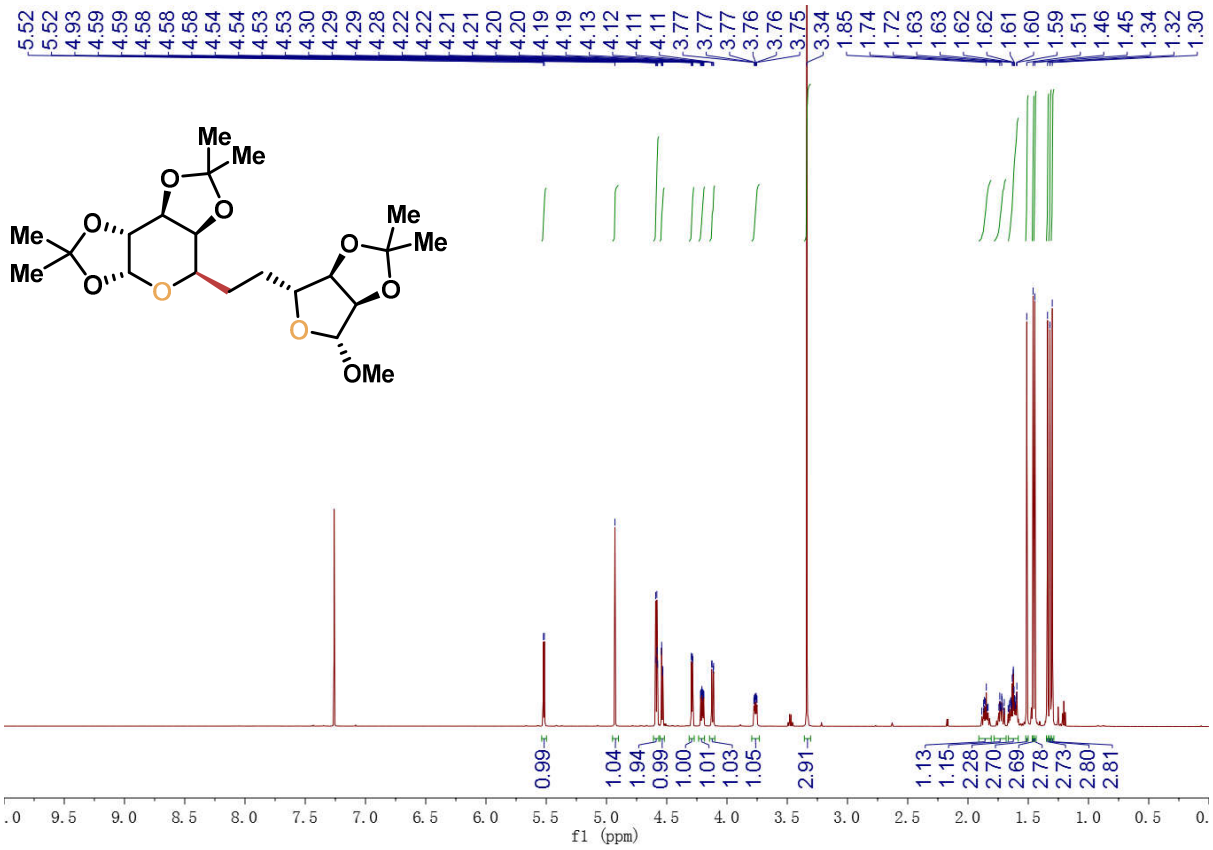
^{1}H NMR of Compound 26 (600 MHz, $CDCl_3$):



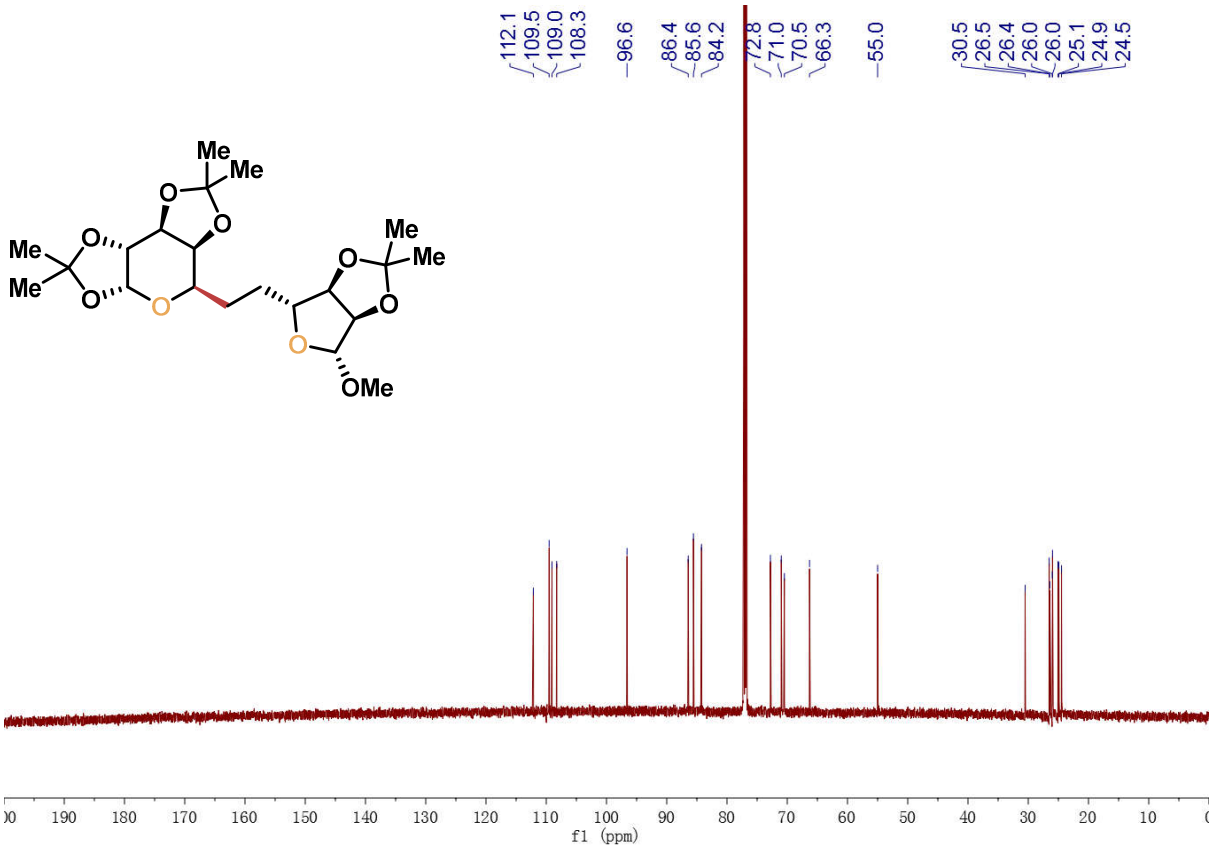
^{13}C NMR of Compound 26 (151 MHz, $CDCl_3$):



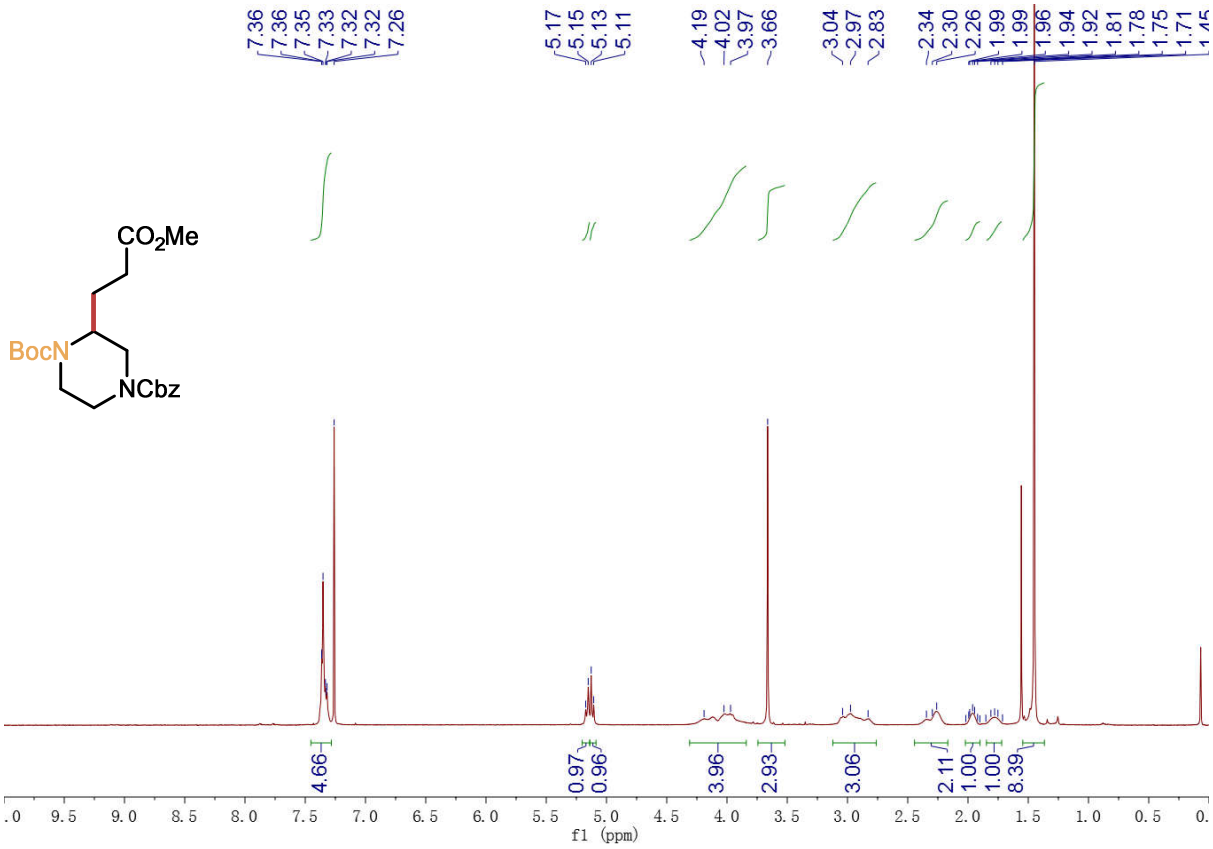
^{1}H NMR of Compound 27 (600 MHz, $CDCl_3$):



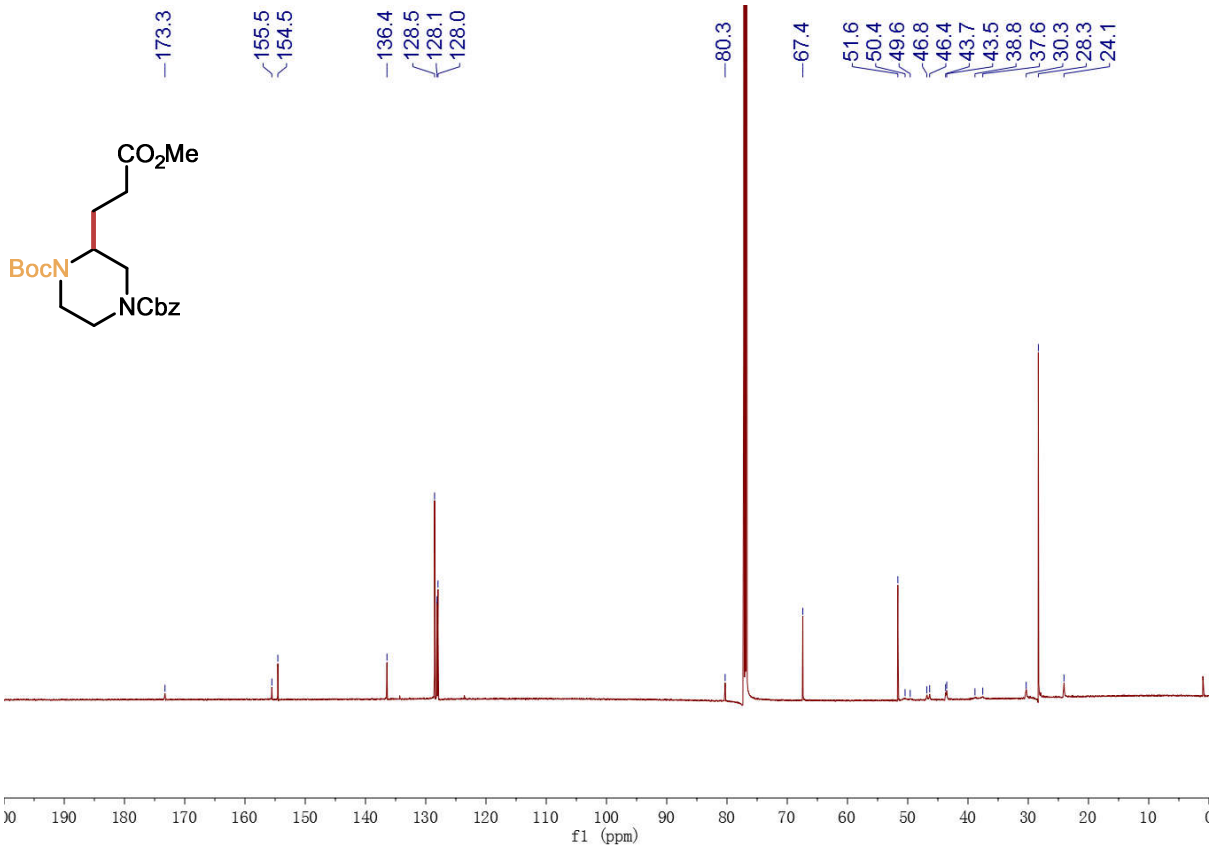
^{13}C NMR of Compound 27 (151 MHz, $CDCl_3$):



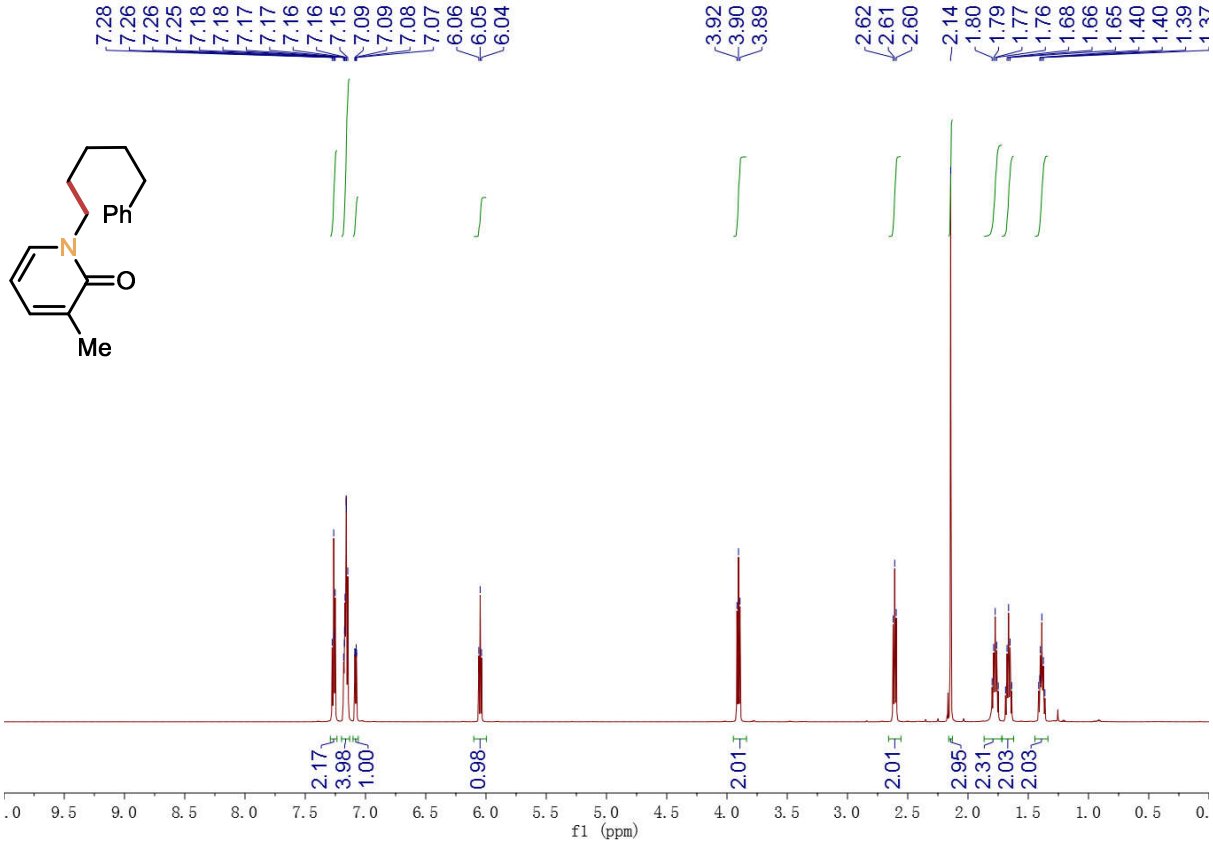
^{1}H NMR of Compound 28 (600 MHz, $CDCl_3$):



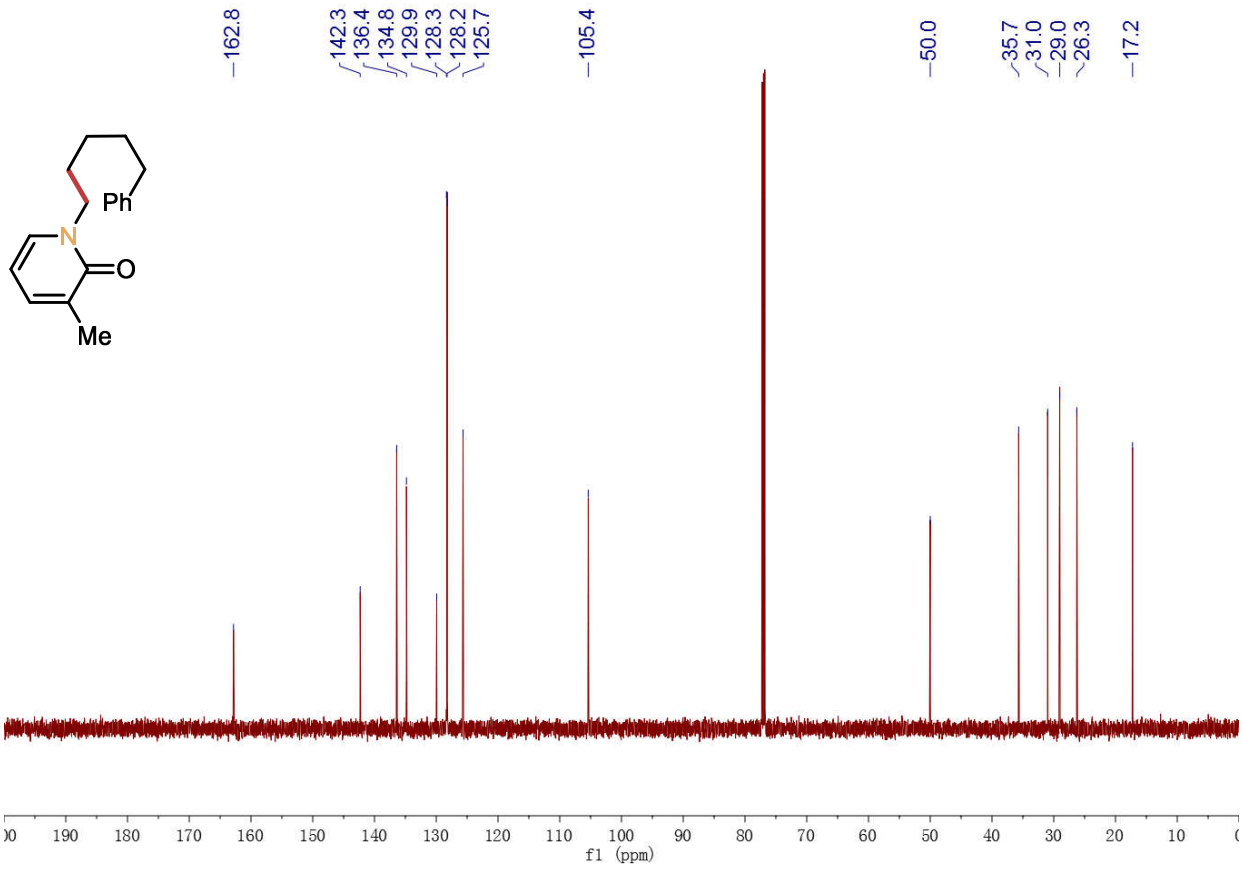
^{13}C NMR of Compound 28 (151 MHz, $CDCl_3$):



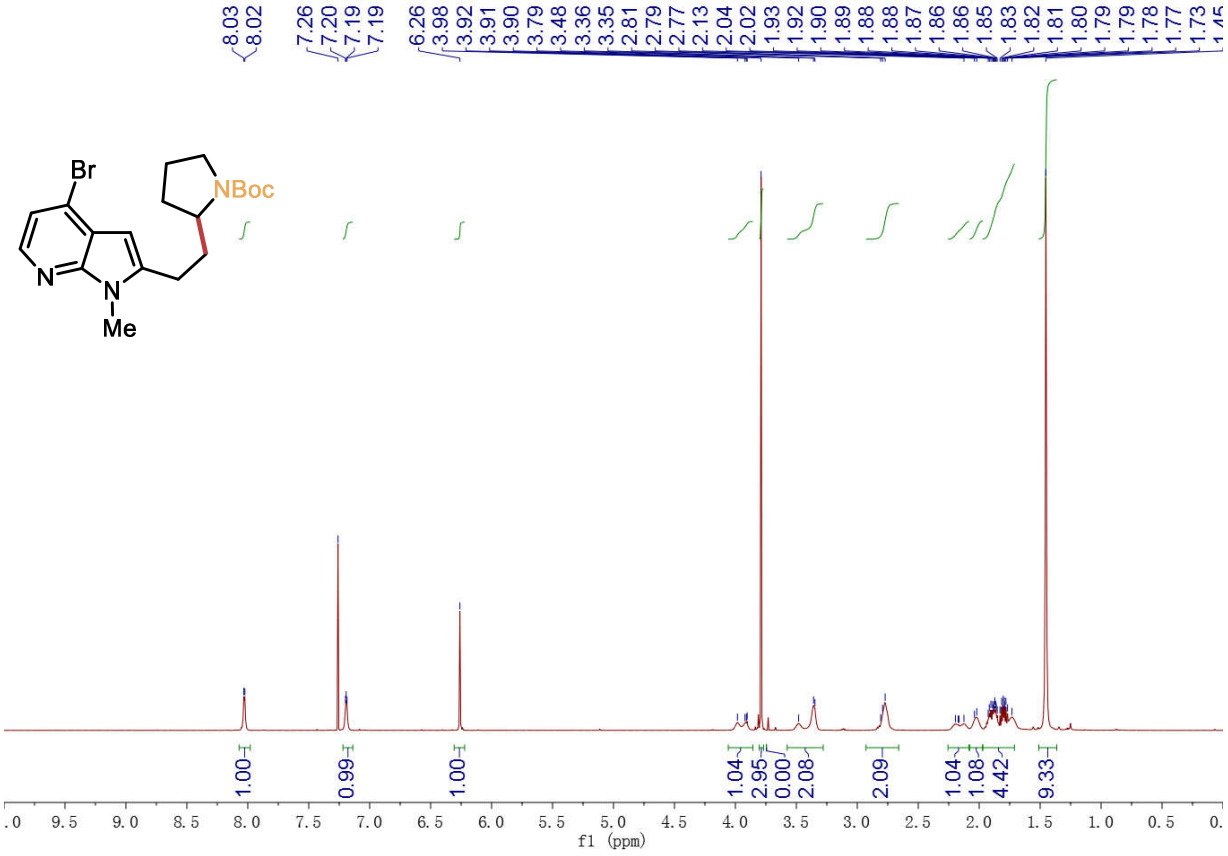
^{1}H NMR of Compound 29 (600 MHz, $CDCl_3$):



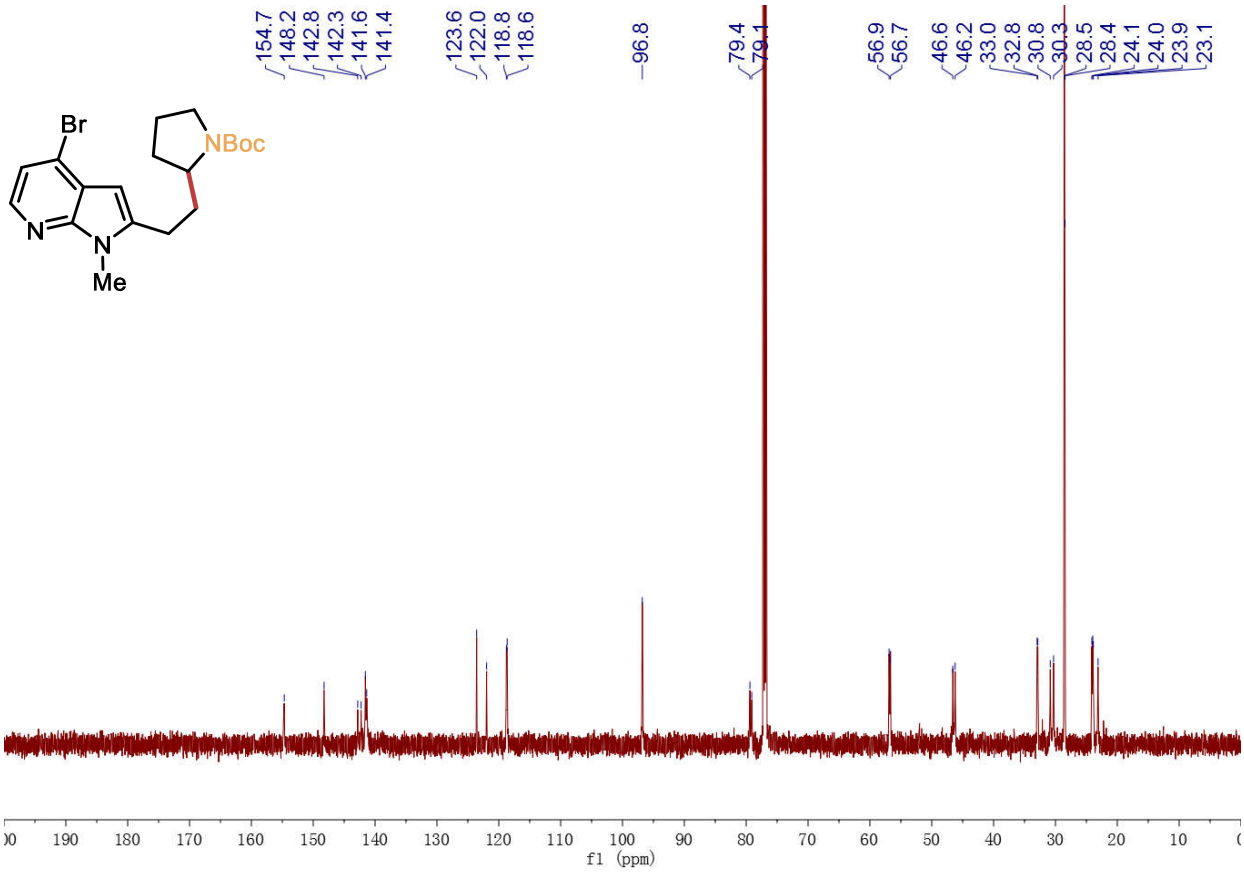
^{13}C NMR of Compound 29 (151 MHz, $CDCl_3$):



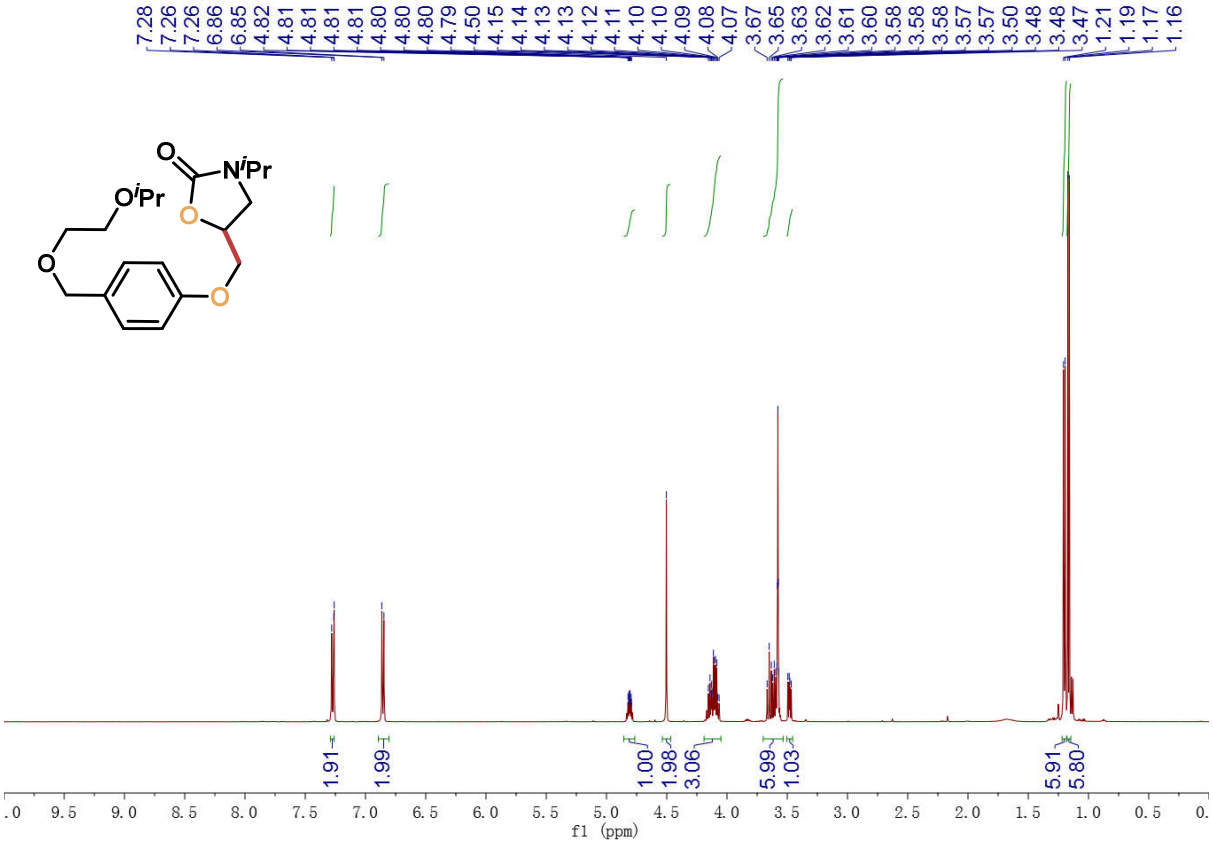
^{1}H NMR of Compound 30 (600 MHz, $CDCl_3$):



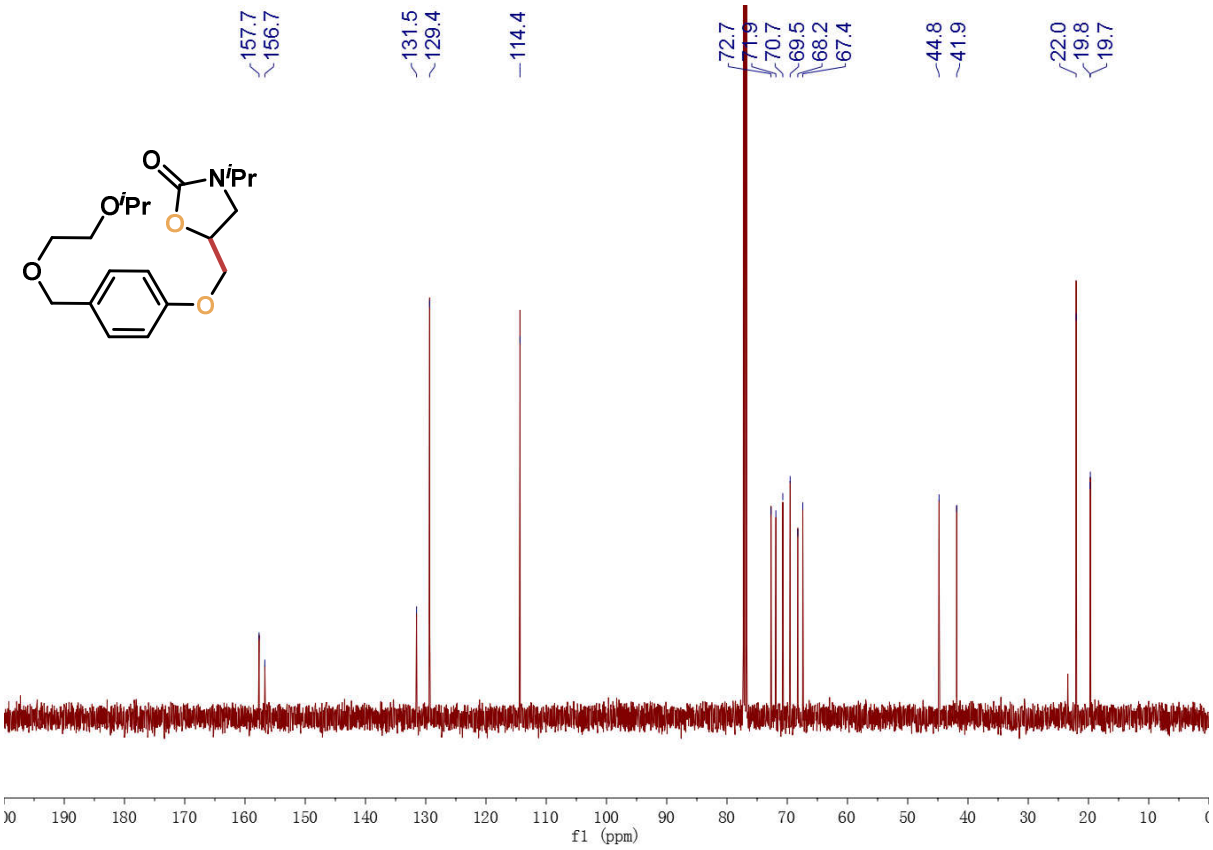
^{13}C NMR of Compound 30 (151 MHz, $CDCl_3$):



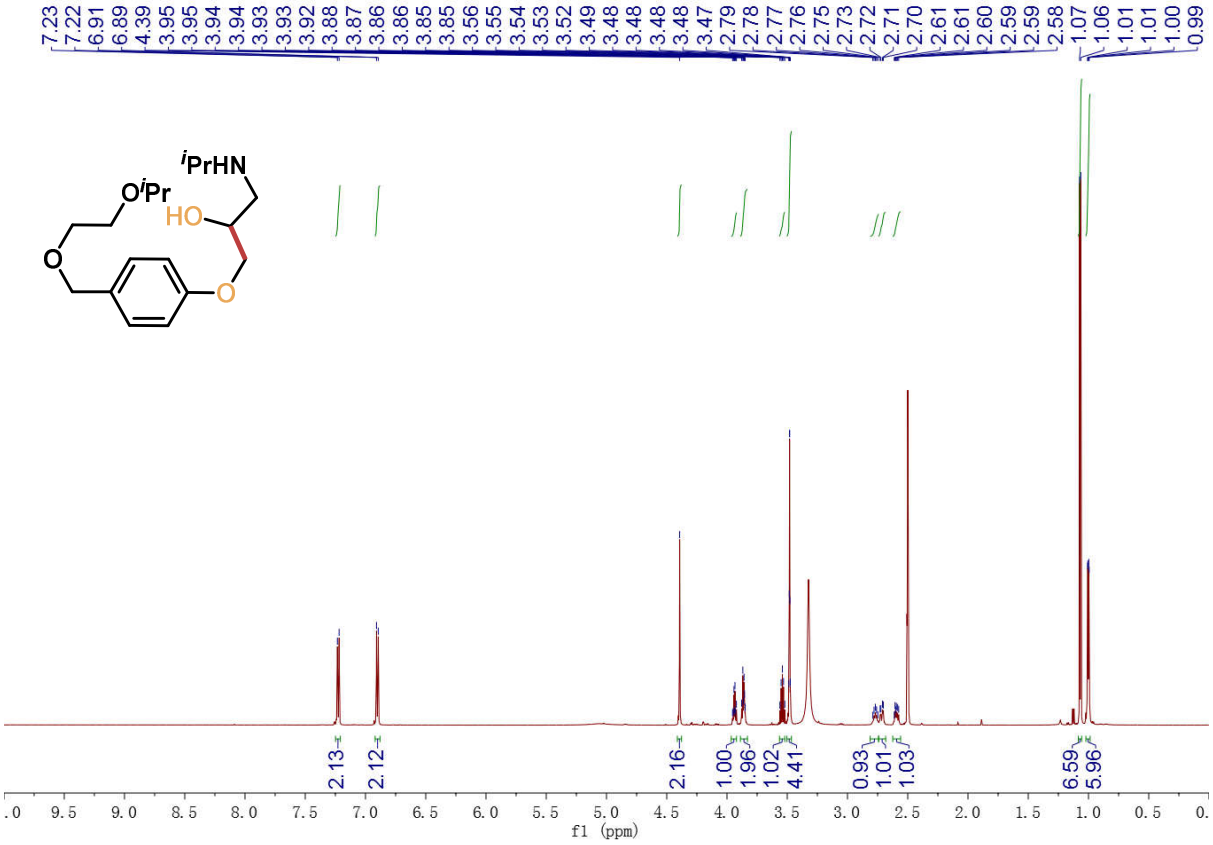
^{1}H NMR of Compound 16 (500 MHz, $CDCl_3$):



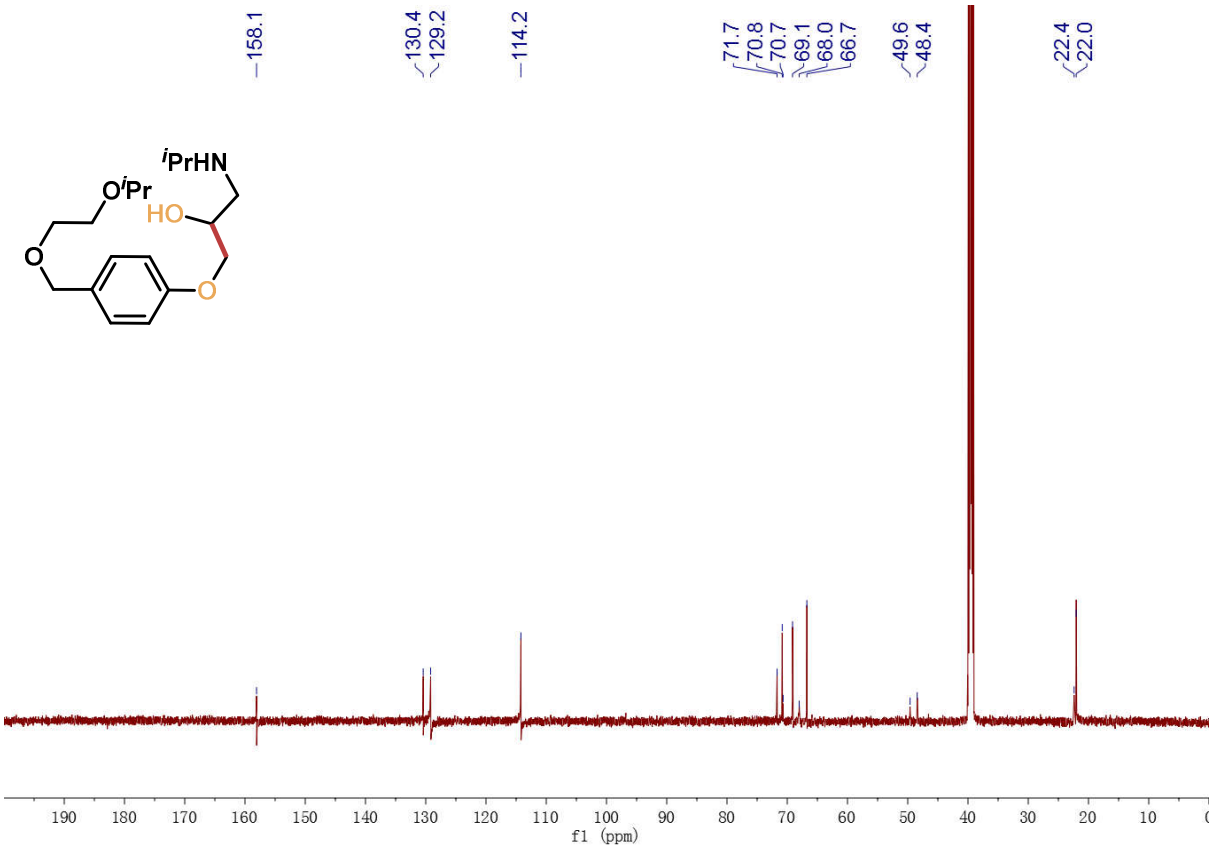
^{13}C NMR of Compound 16 (126 MHz, $CDCl_3$):



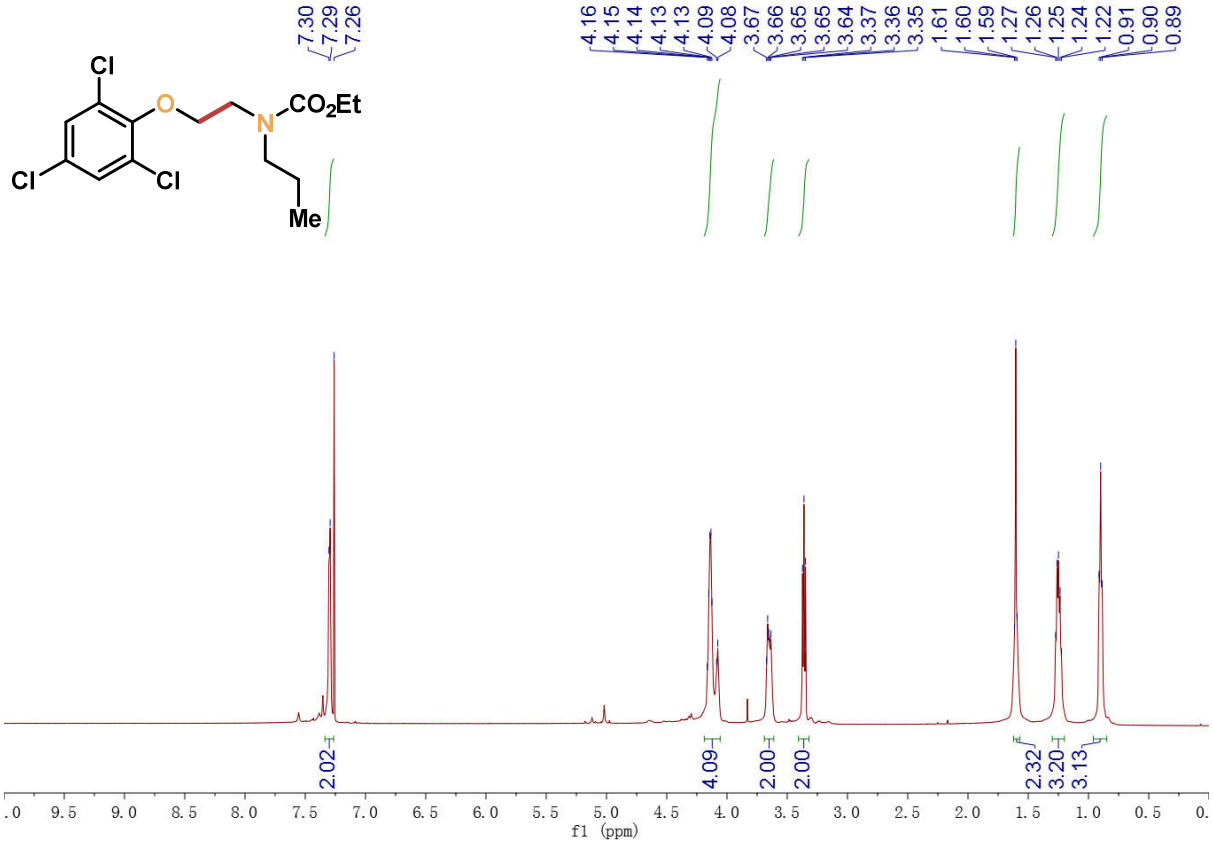
^{1}H NMR of Compound SI-45 (600 MHz, $(CD_3)_2SO$):



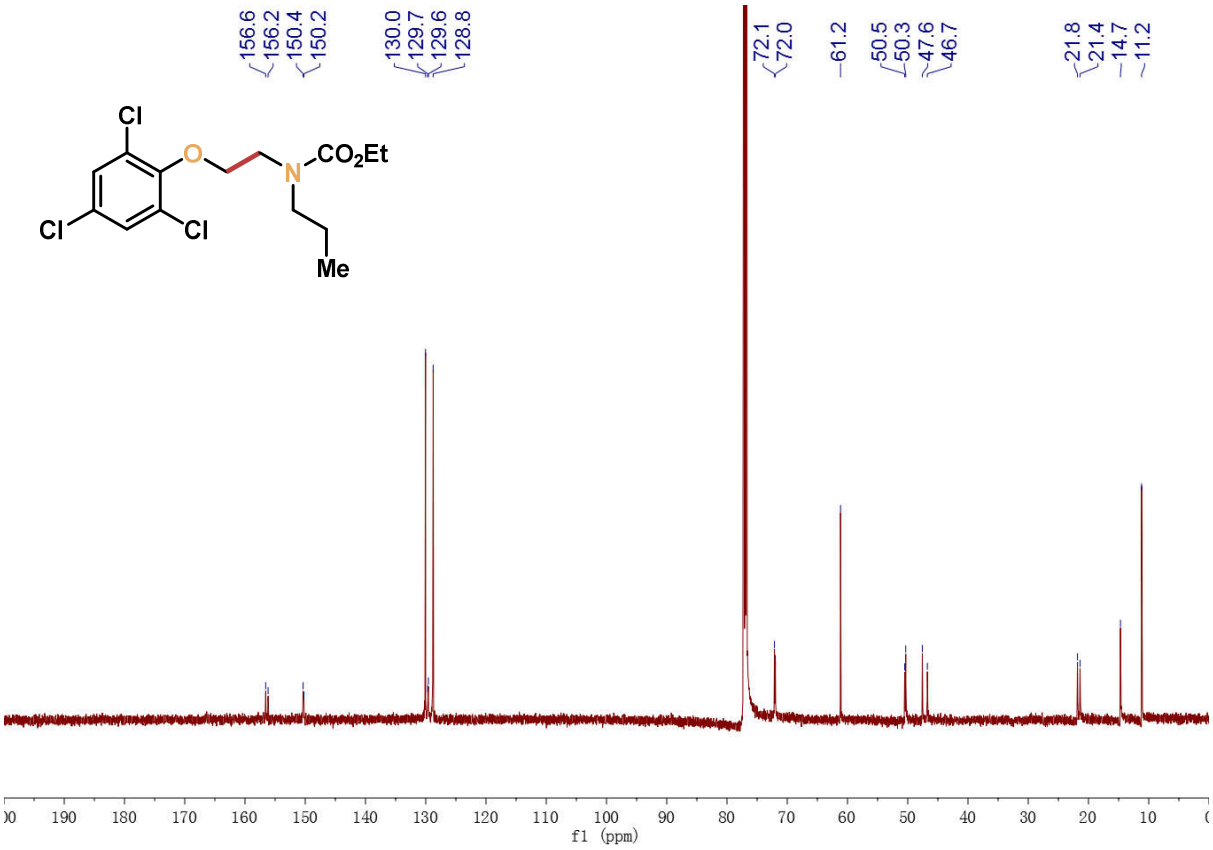
^{13}C NMR of Compound SI-45 (126 MHz, $(CD_3)_2SO$):



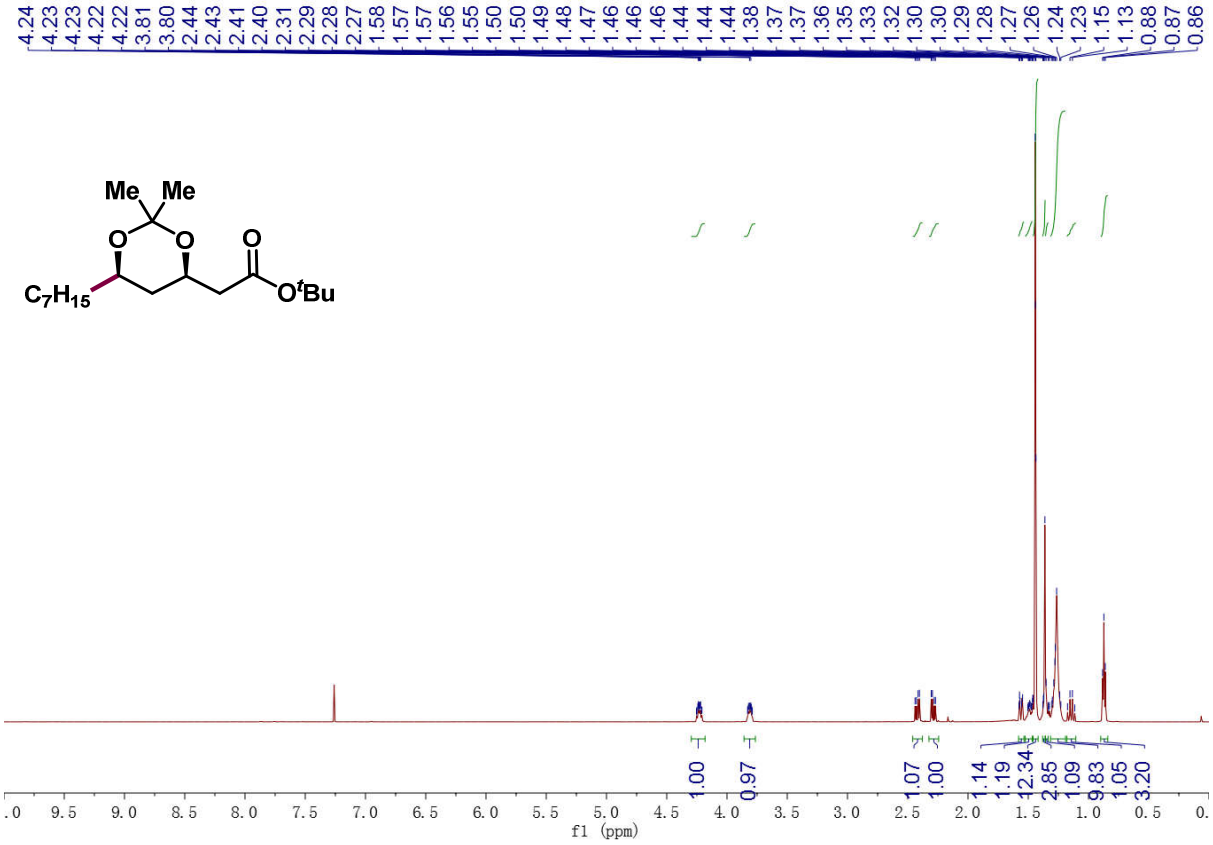
^{1}H NMR of Compound 20 (600 MHz, $CDCl_3$):



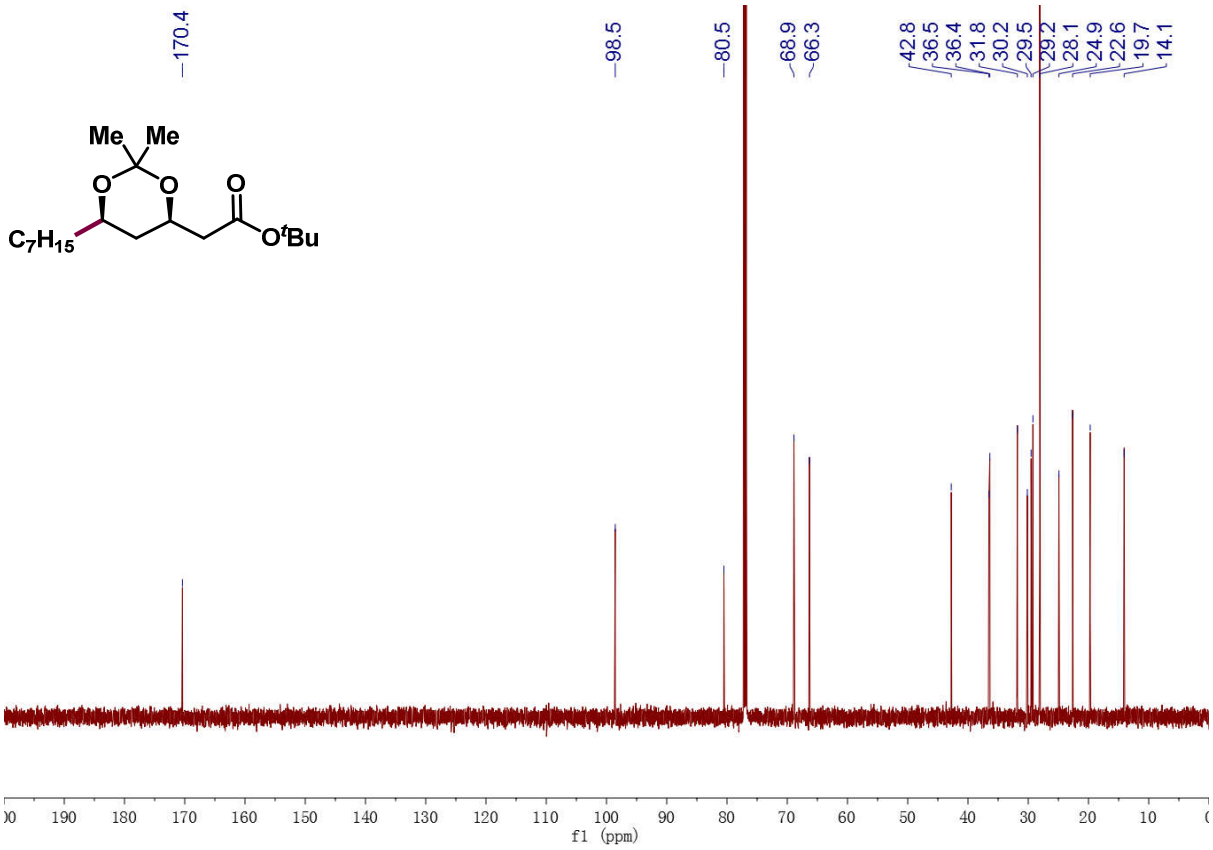
^{13}C NMR of Compound 20 (151 MHz, $CDCl_3$):



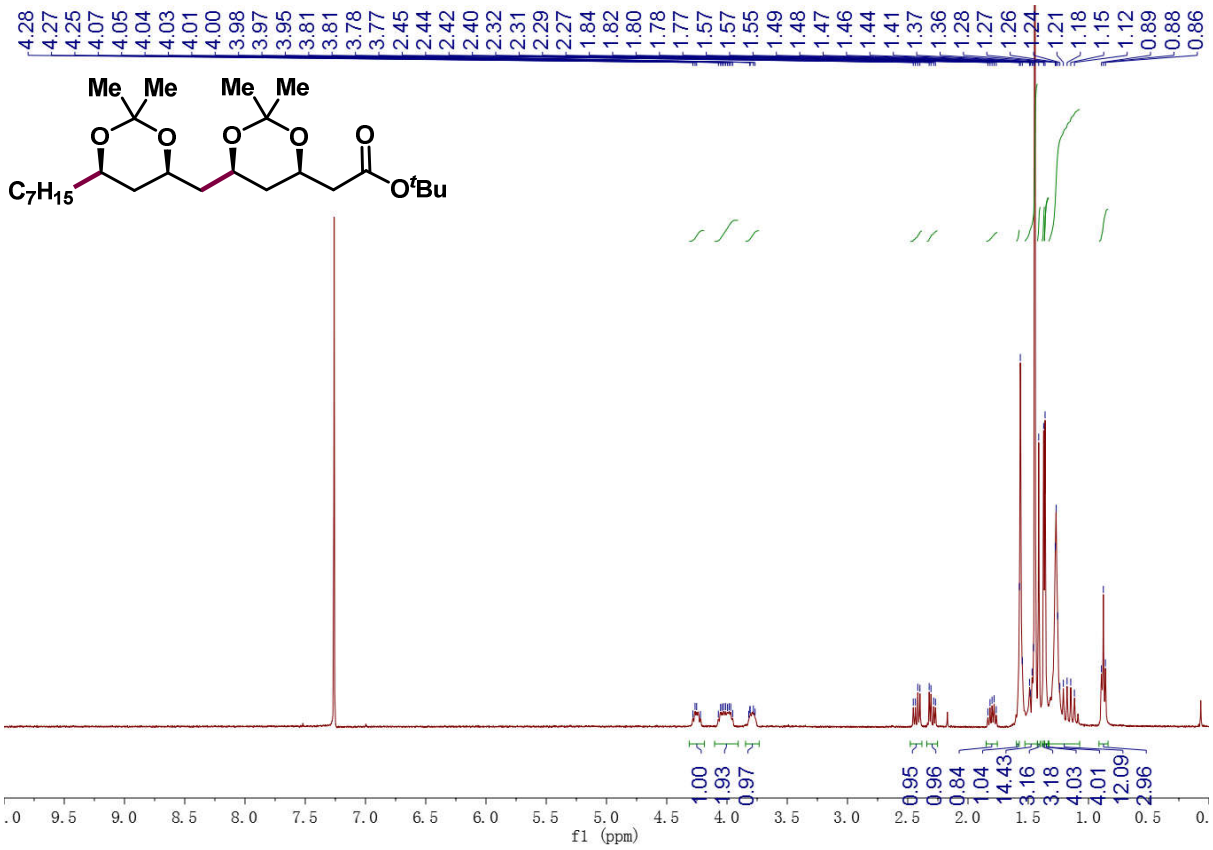
^{1}H NMR of Compound 37 (600 MHz, $CDCl_3$):



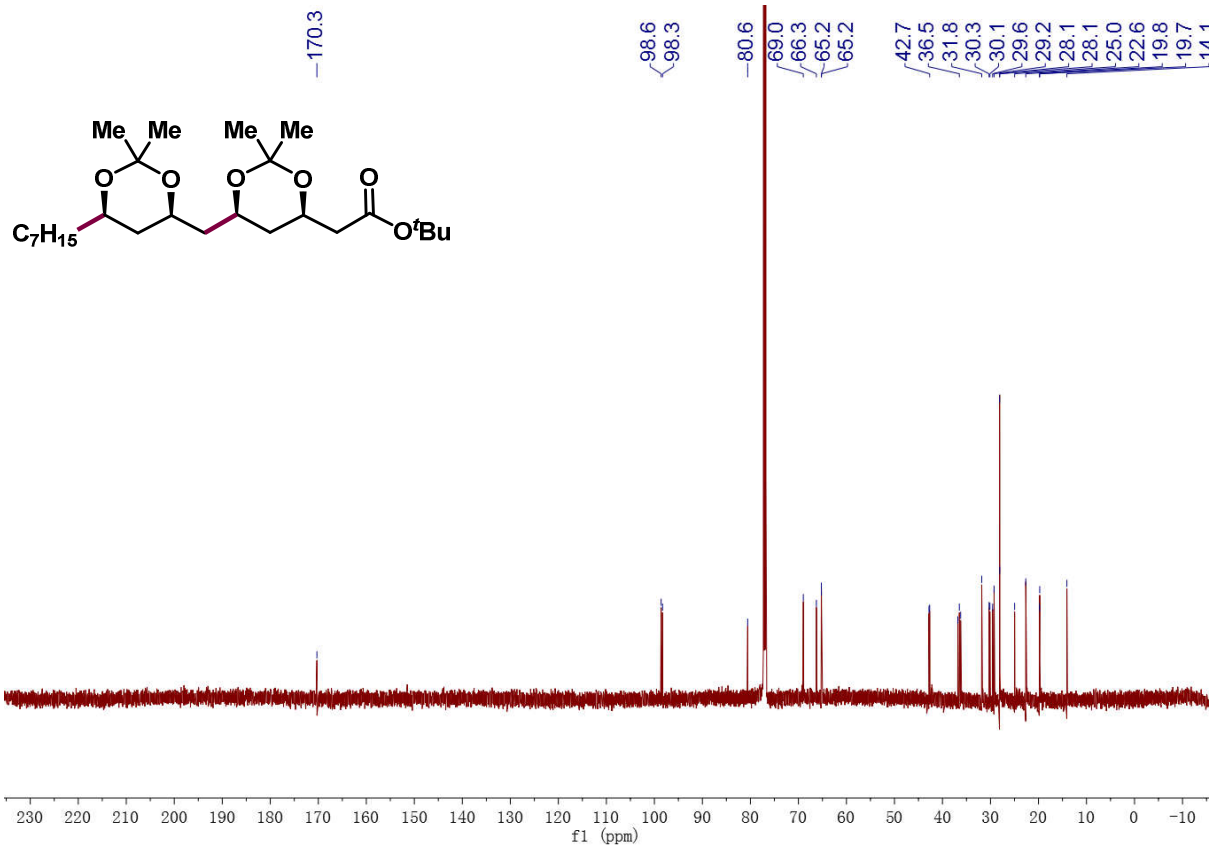
^{13}C NMR of Compound 37 (151 MHz, $CDCl_3$):



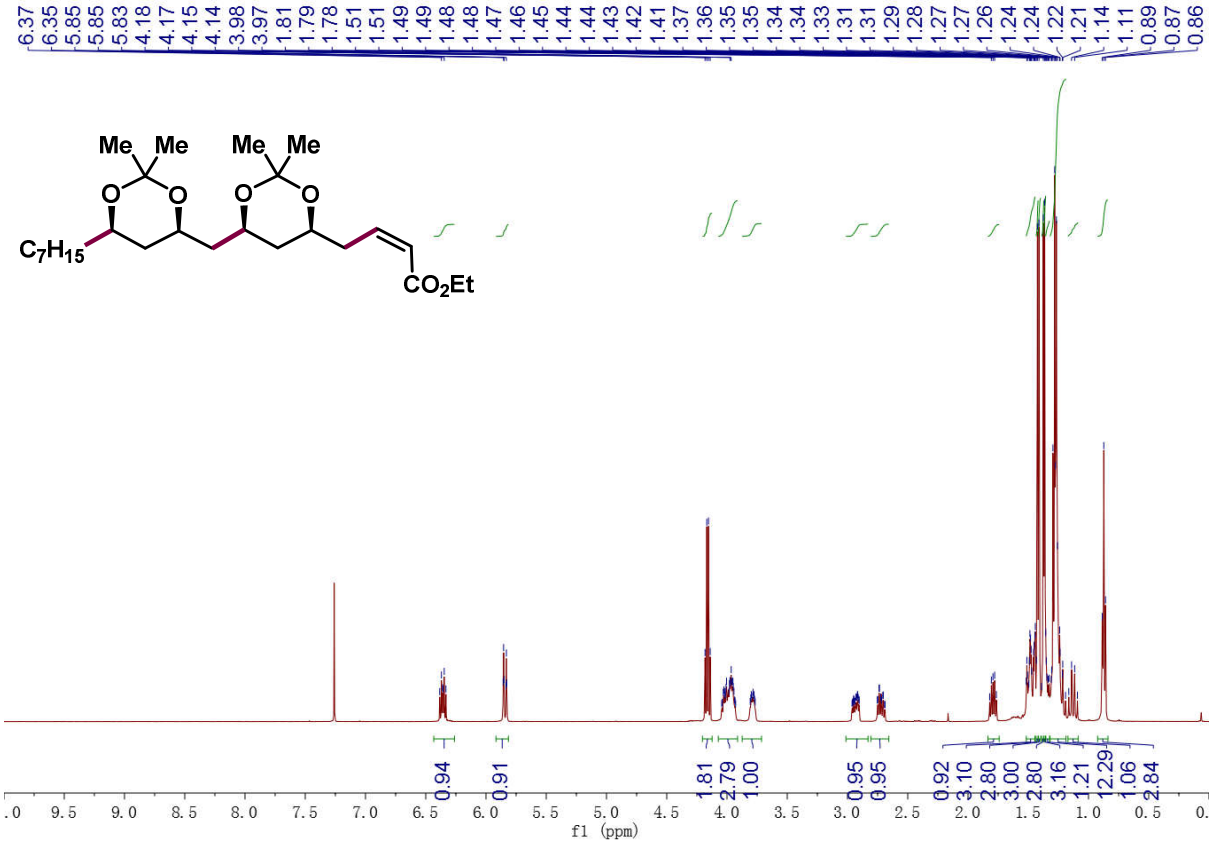
^{1}H NMR of Compound 38 (600 MHz, $CDCl_3$):



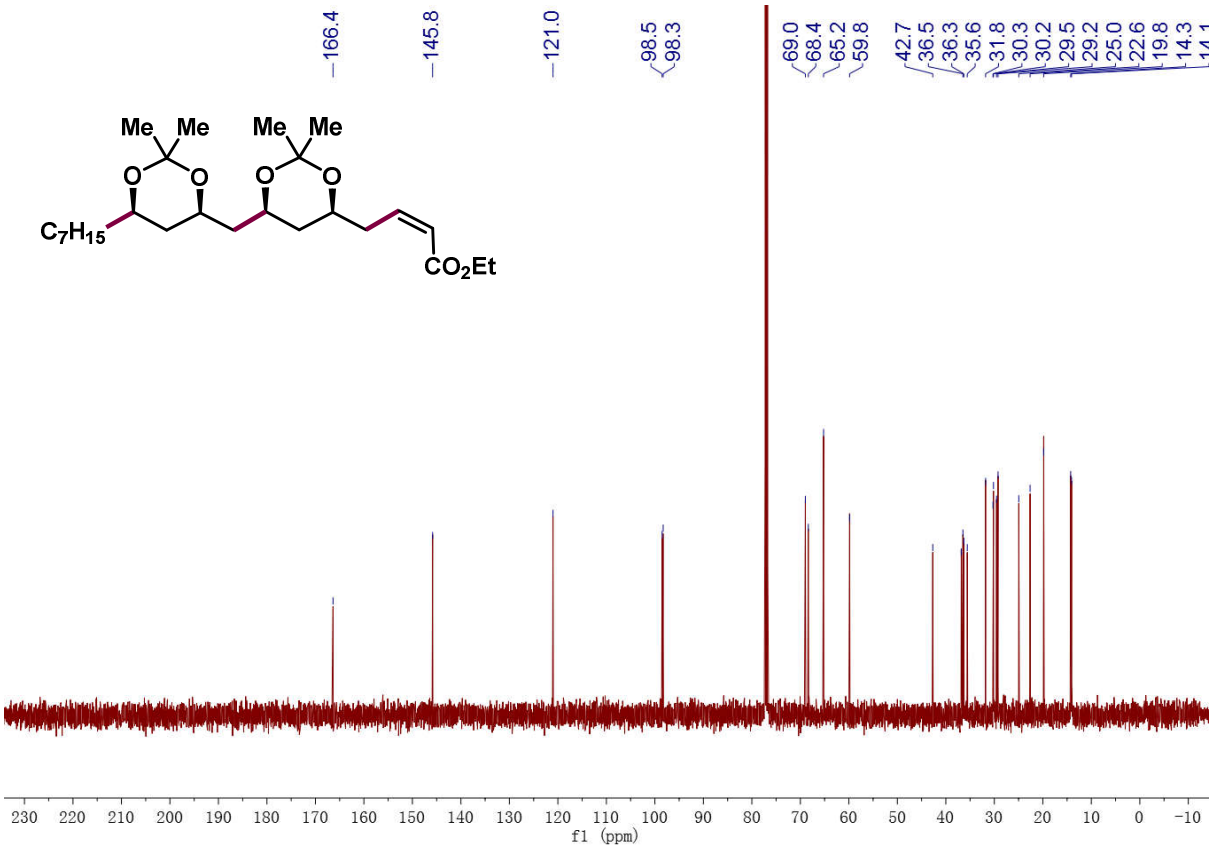
^{13}C NMR of Compound 38 (151 MHz, $CDCl_3$):



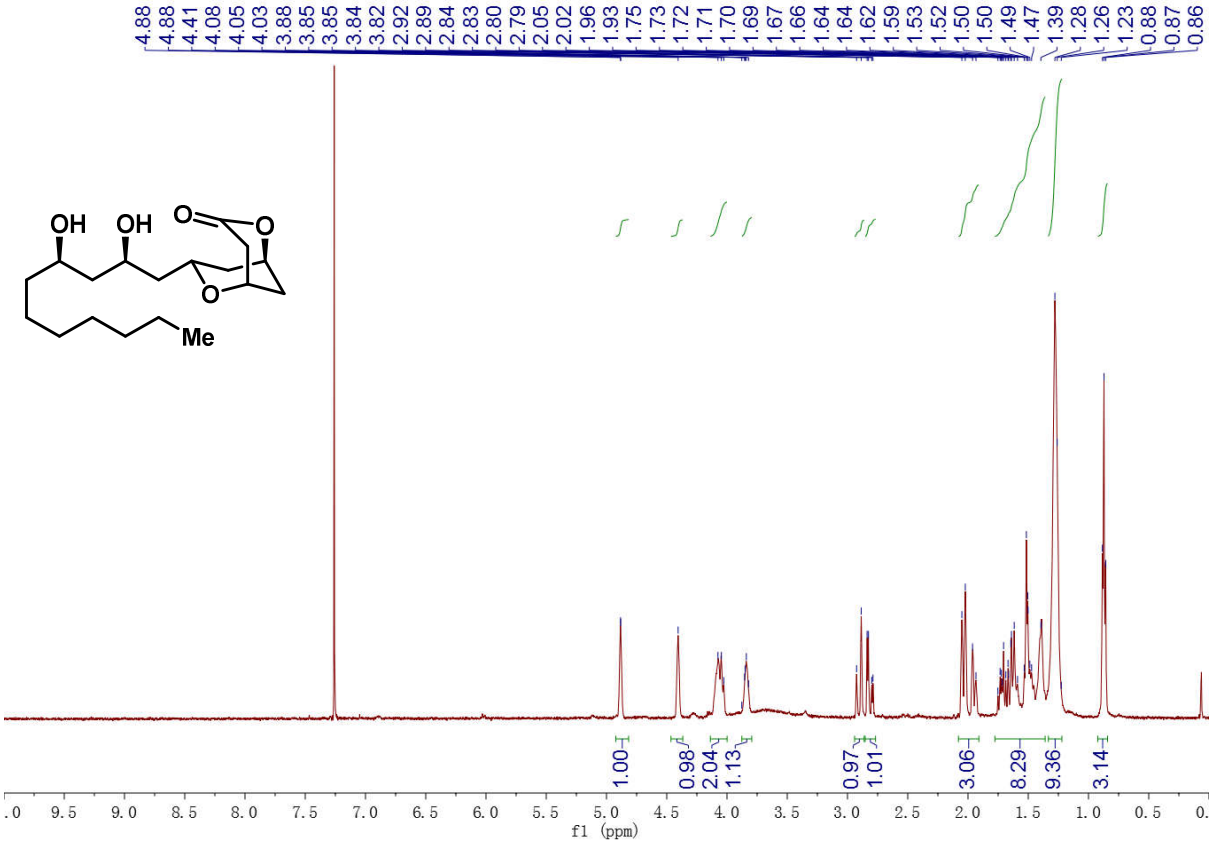
^{1}H NMR of Compound 40 (500 MHz, $CDCl_3$):



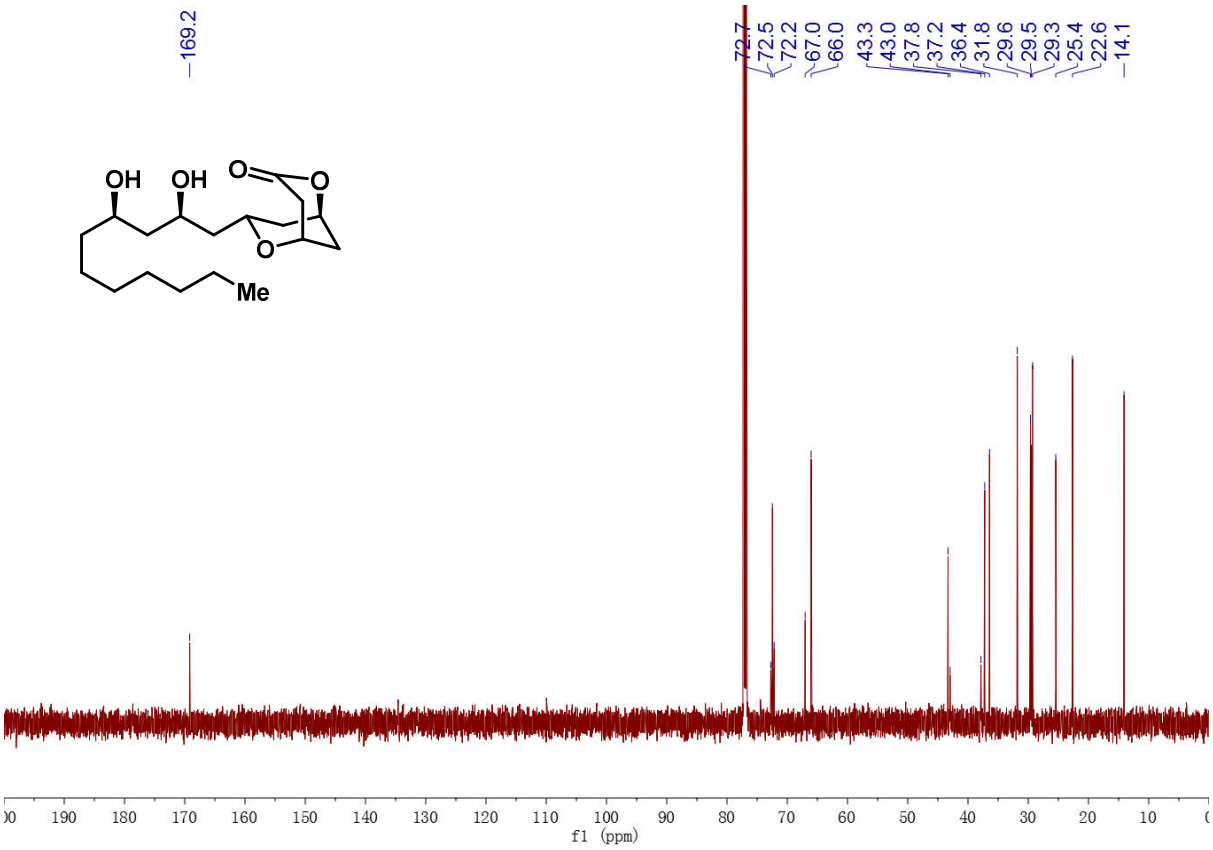
^{13}C NMR of Compound 40 (126 MHz, $CDCl_3$):



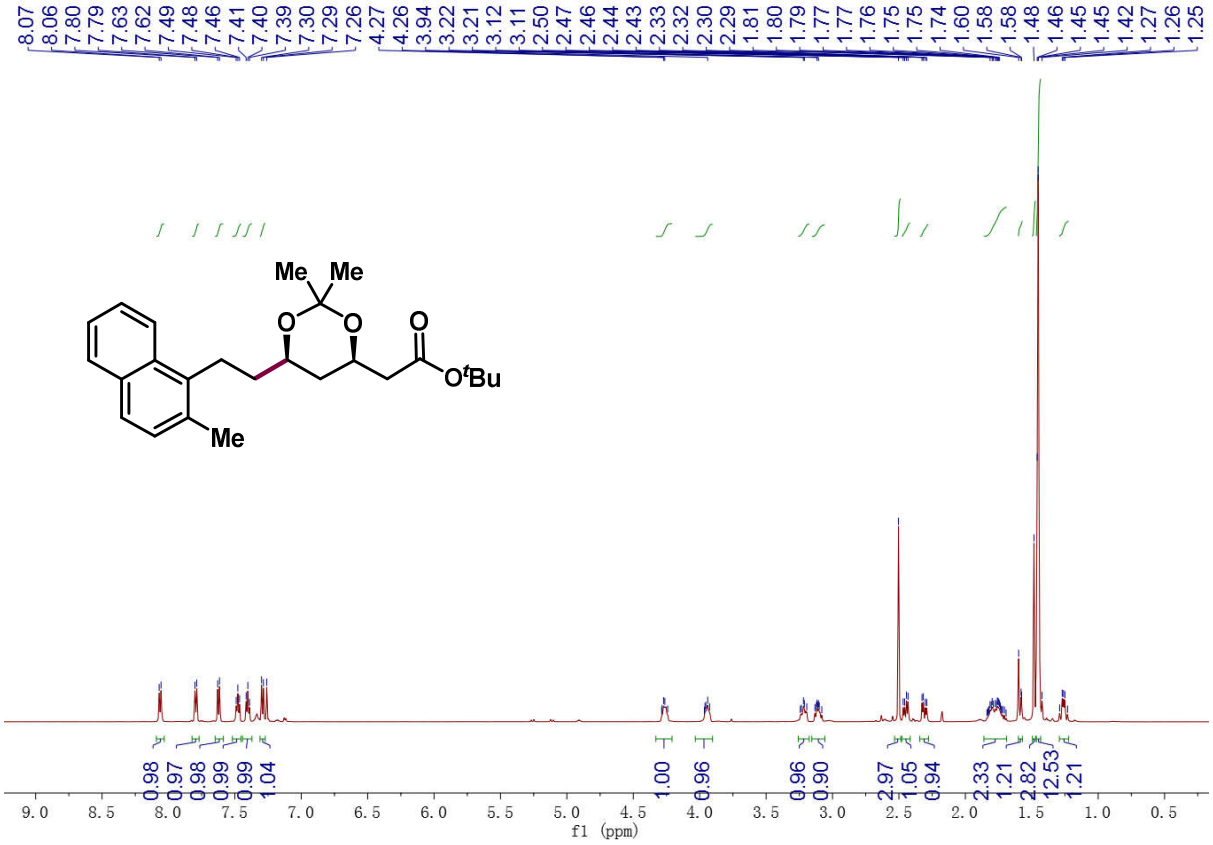
^{1}H NMR of Compound 5 (600 MHz, $CDCl_3$):



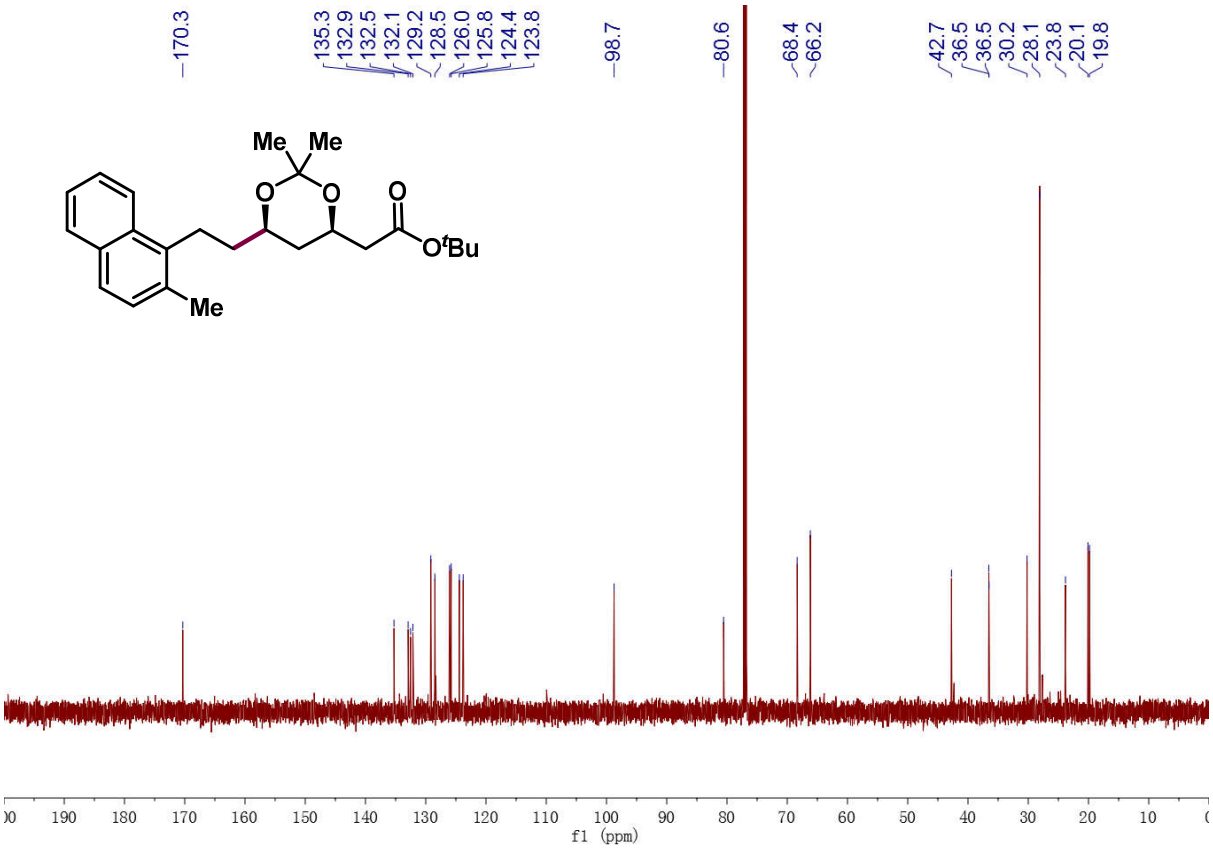
^{13}C NMR of Compound 5 (151 MHz, $CDCl_3$):



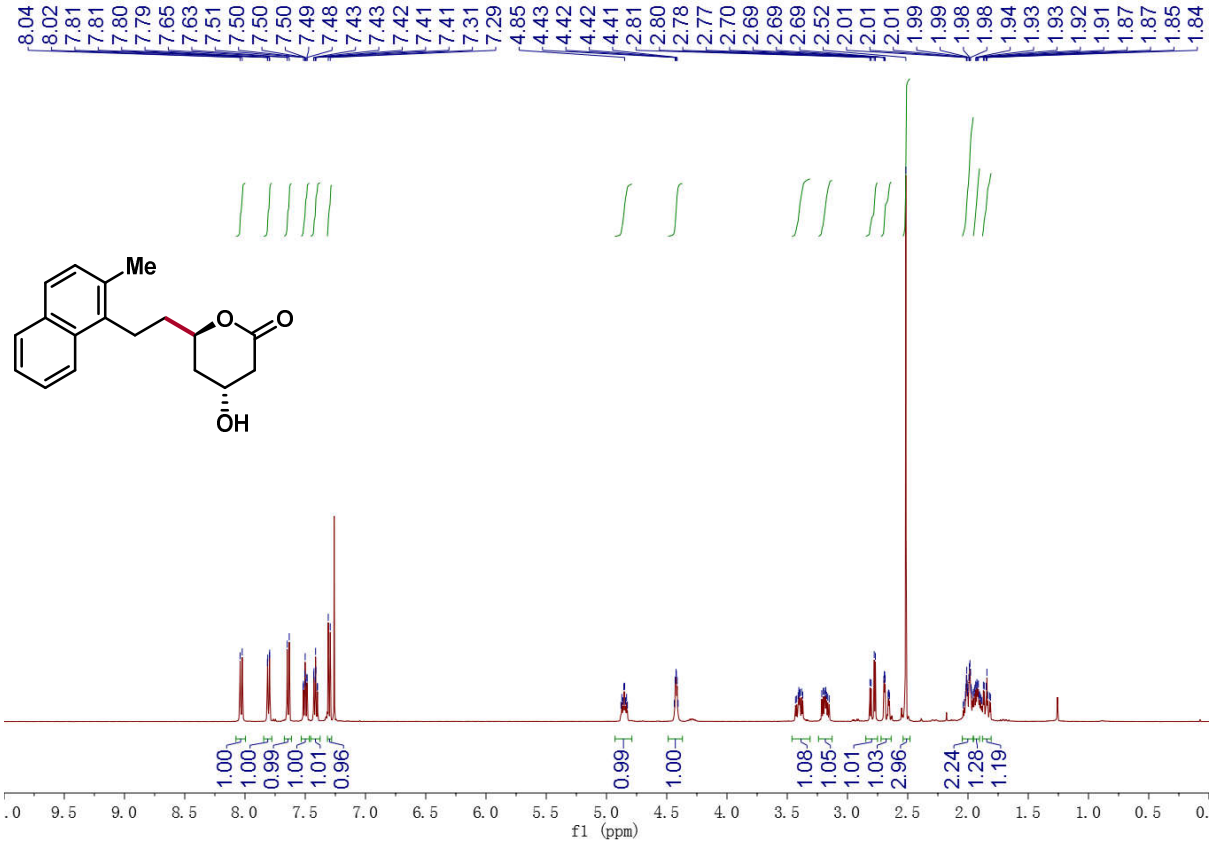
^{1}H NMR of Compound SI-48 (600 MHz, $CDCl_3$):



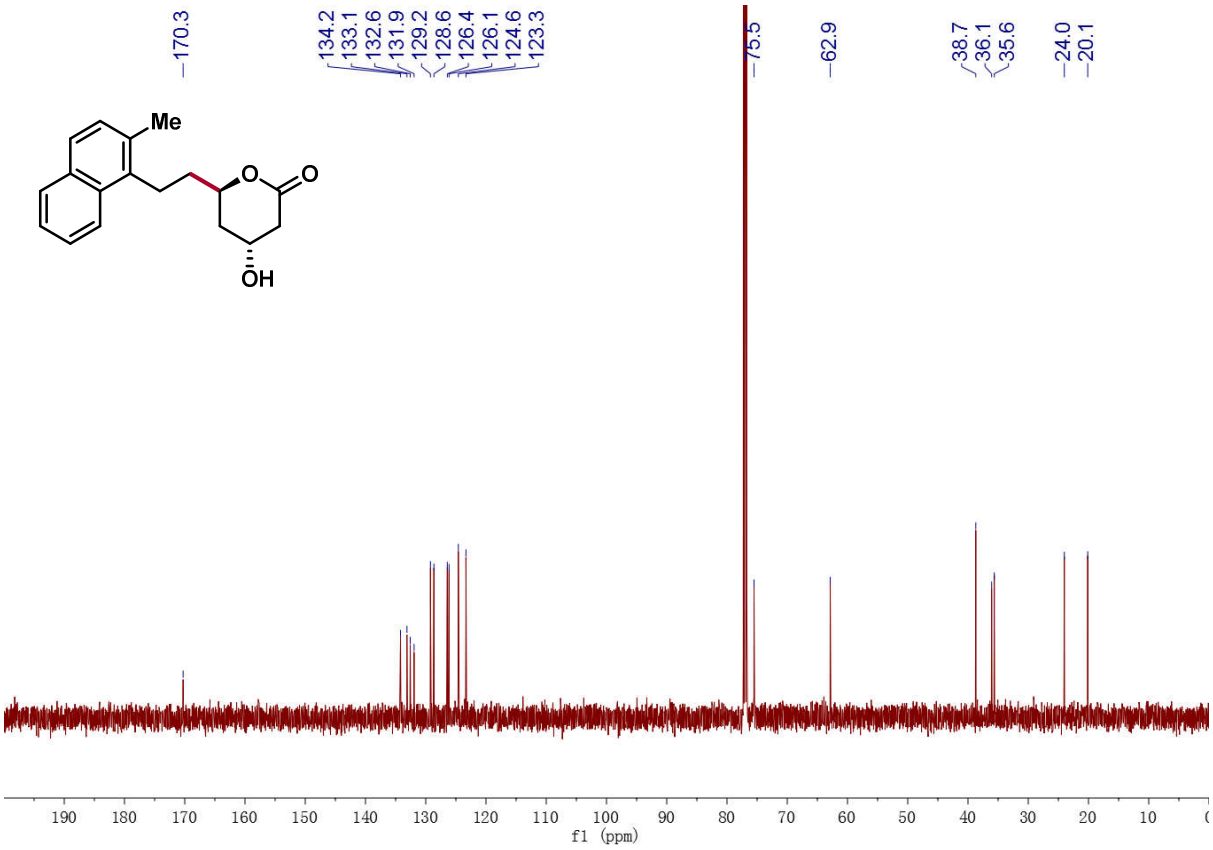
^{13}C NMR of Compound SI-48 (151 MHz, $CDCl_3$):



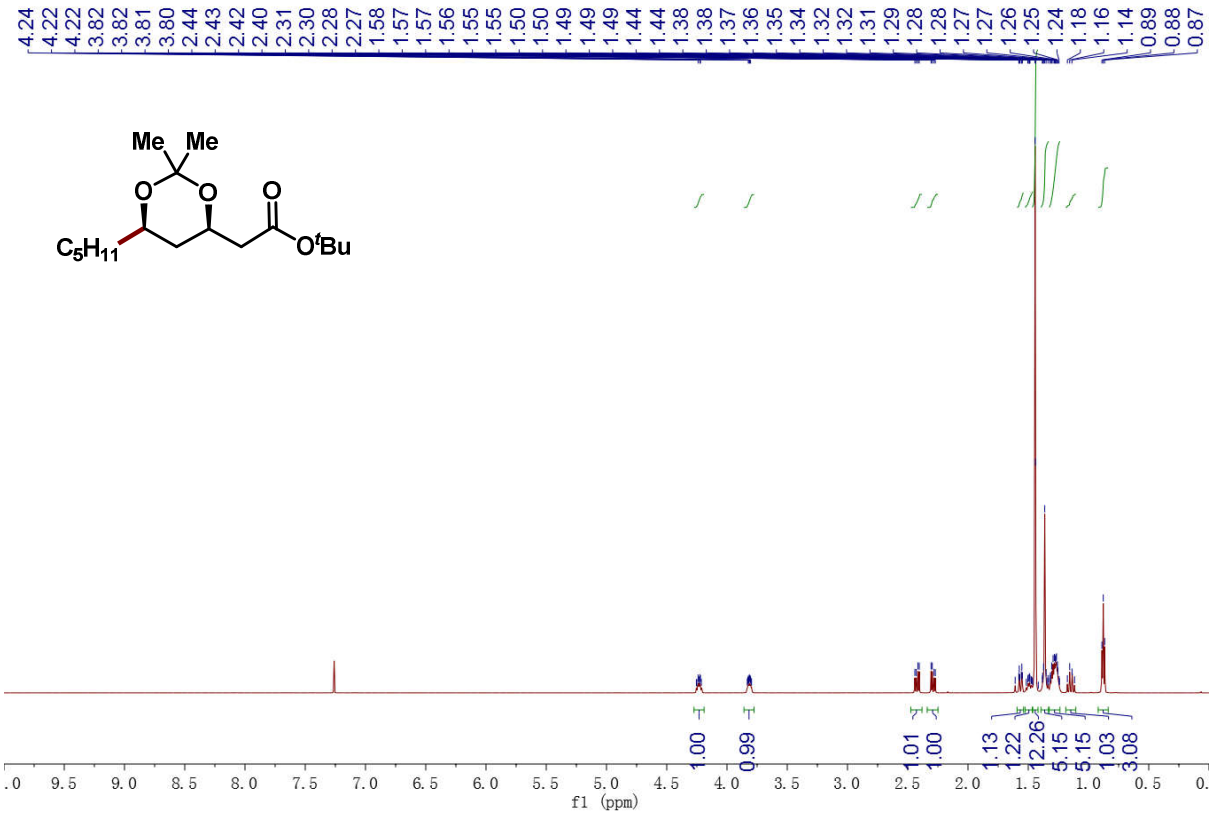
^{1}H NMR of Compound 41 (600 MHz, $CDCl_3$):



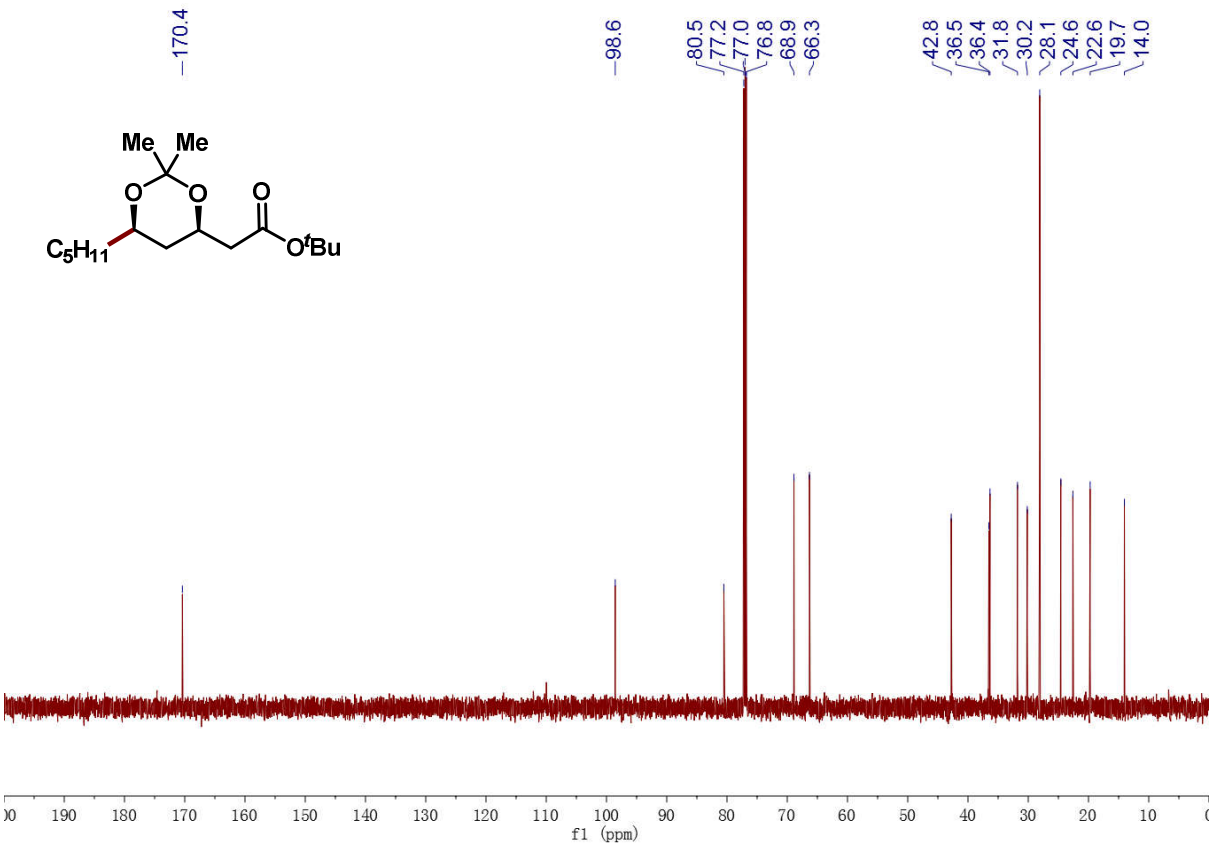
^{13}C NMR of Compound 41 (151 MHz, $CDCl_3$):



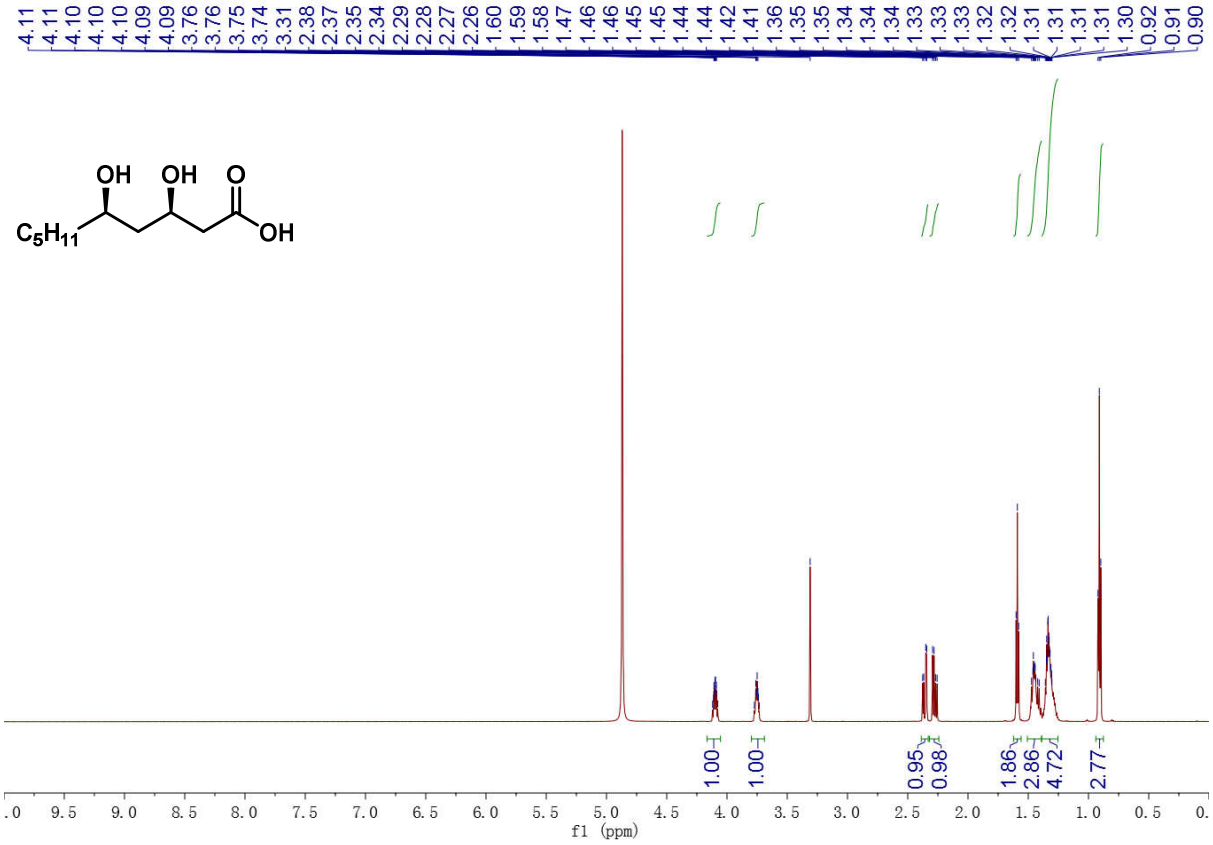
^{1}H NMR of Compound SI-49 (600 MHz, $CDCl_3$):



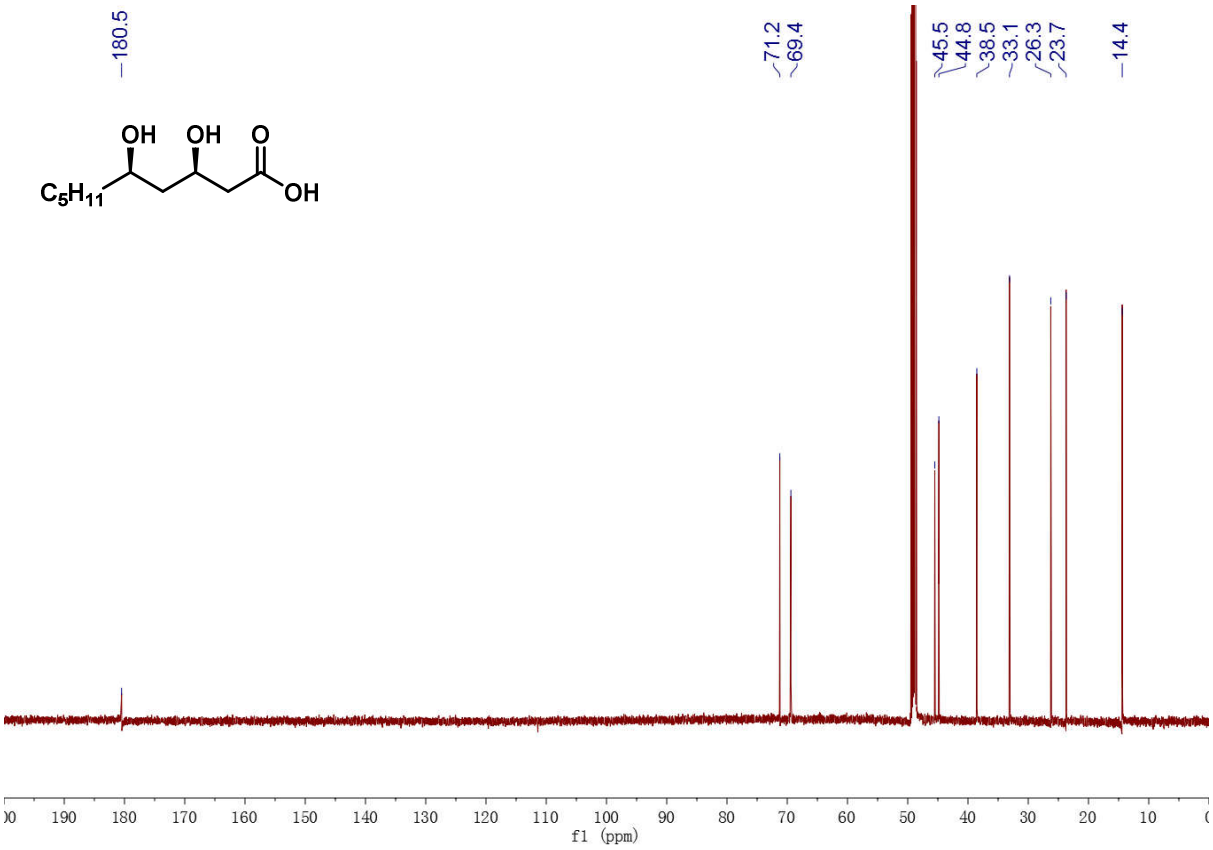
^{13}C NMR of Compound SI-2 (151 MHz, $CDCl_3$):



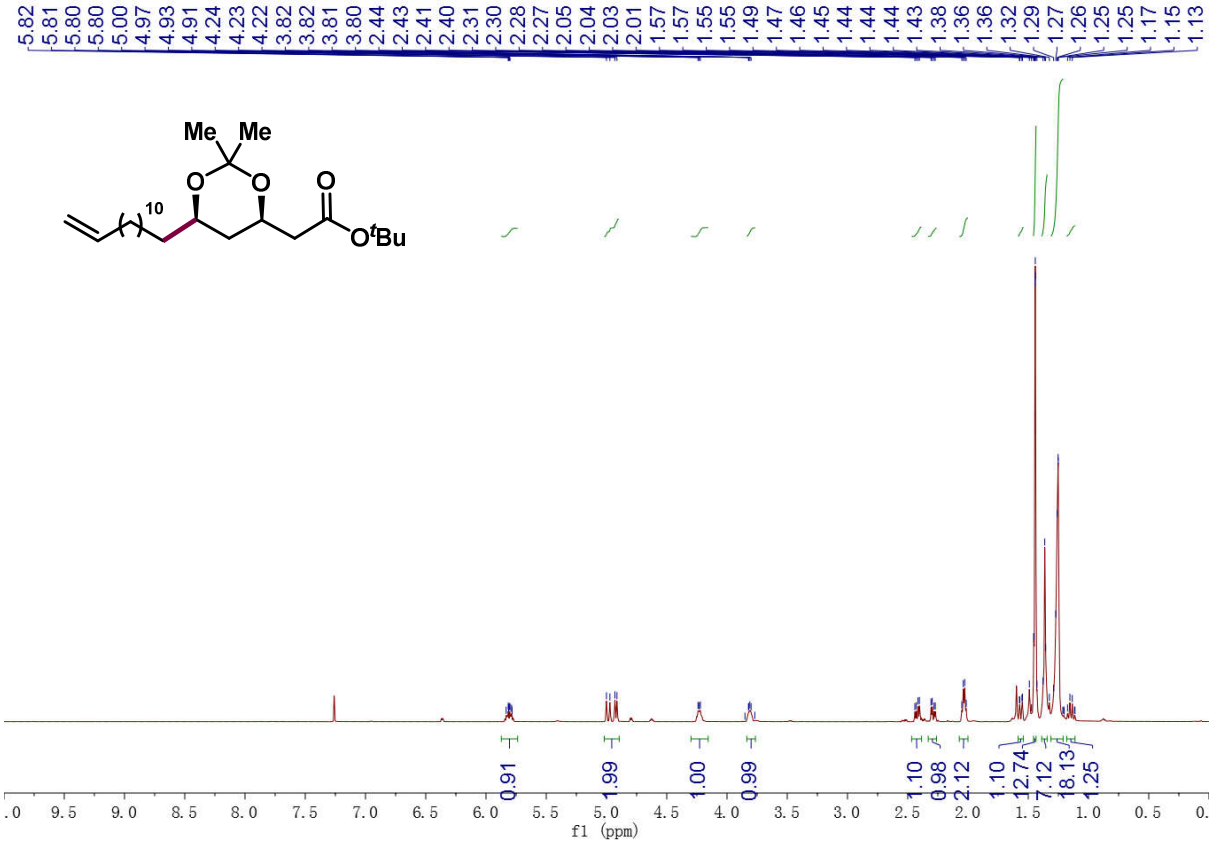
[1]H NMR of Compound SI-50 (600 MHz, CD_3OD):



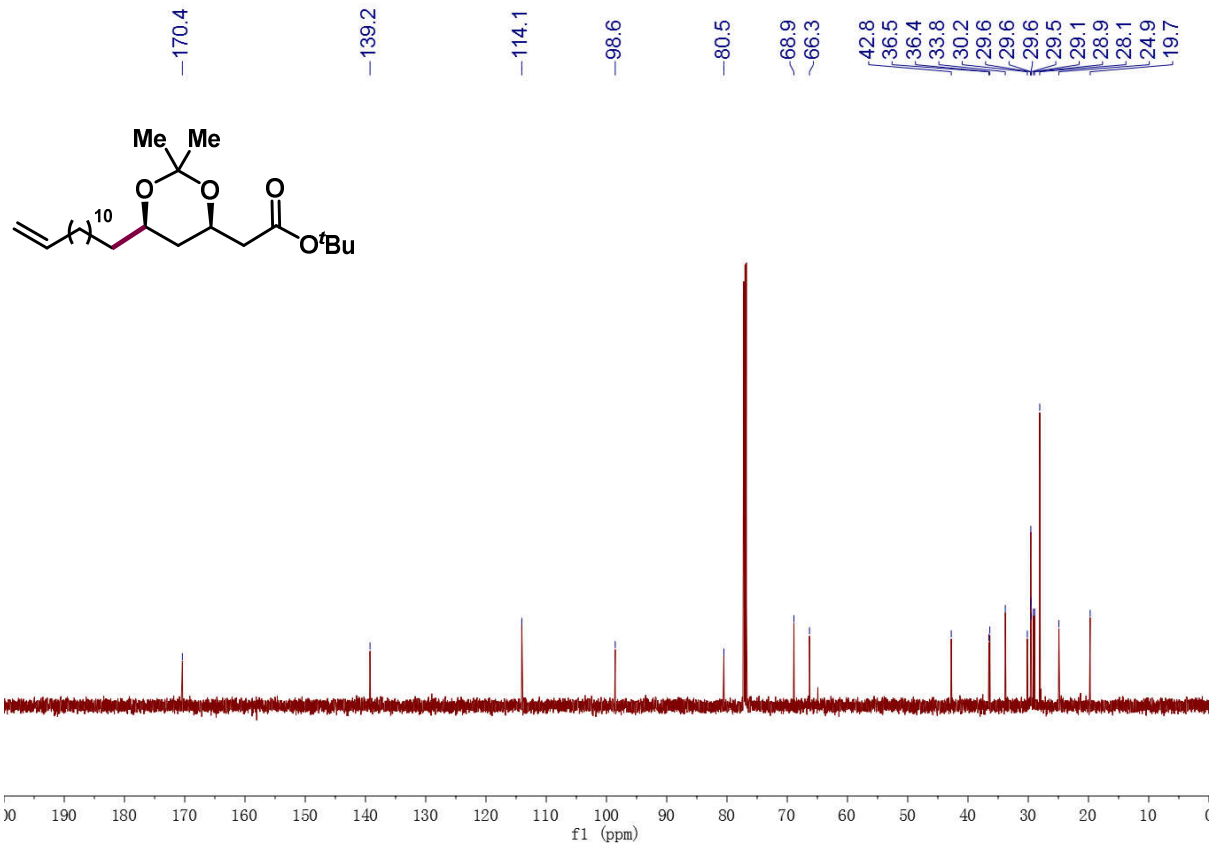
[13]C NMR of Compound SI-2 (151 MHz, CD_3OD):



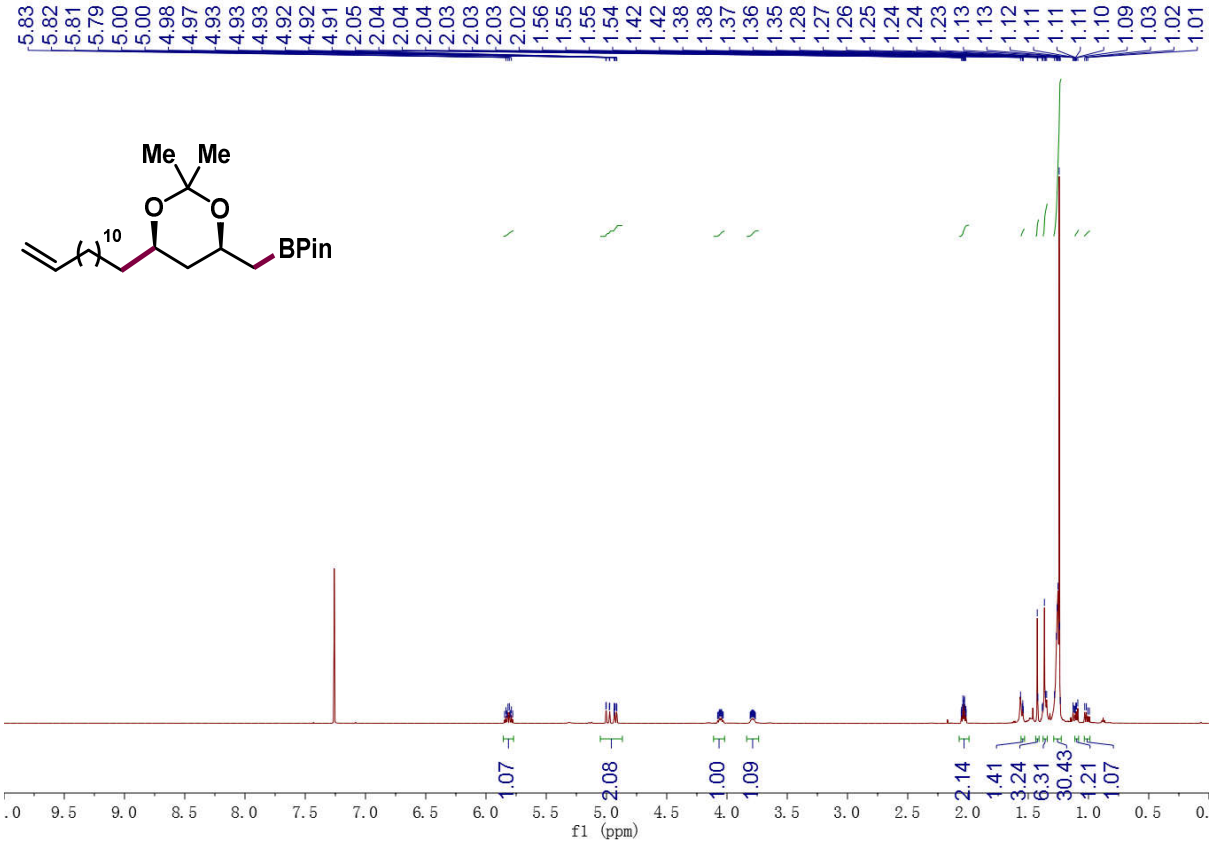
^{1}H NMR of Compound SI-52 (600 MHz, $CDCl_3$):



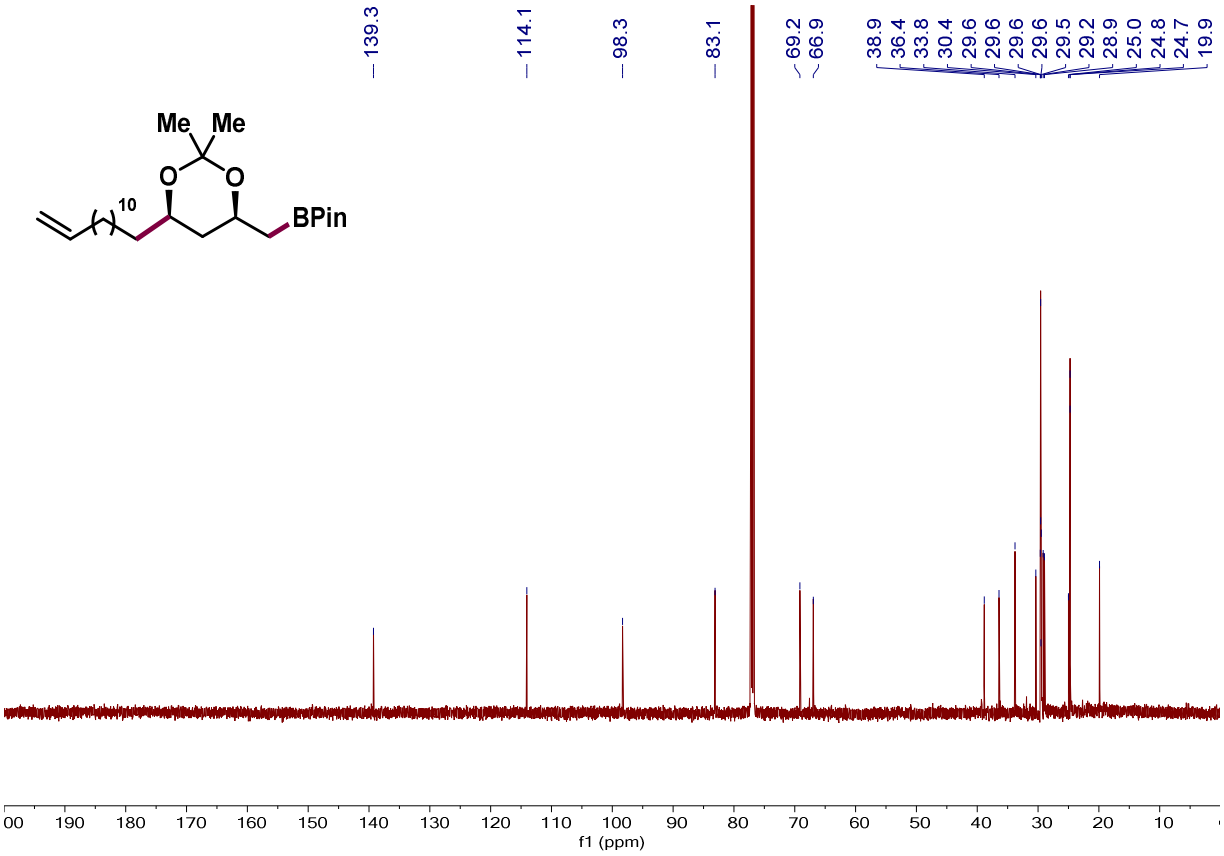
^{13}C NMR of Compound SI-52 (151 MHz, $CDCl_3$):



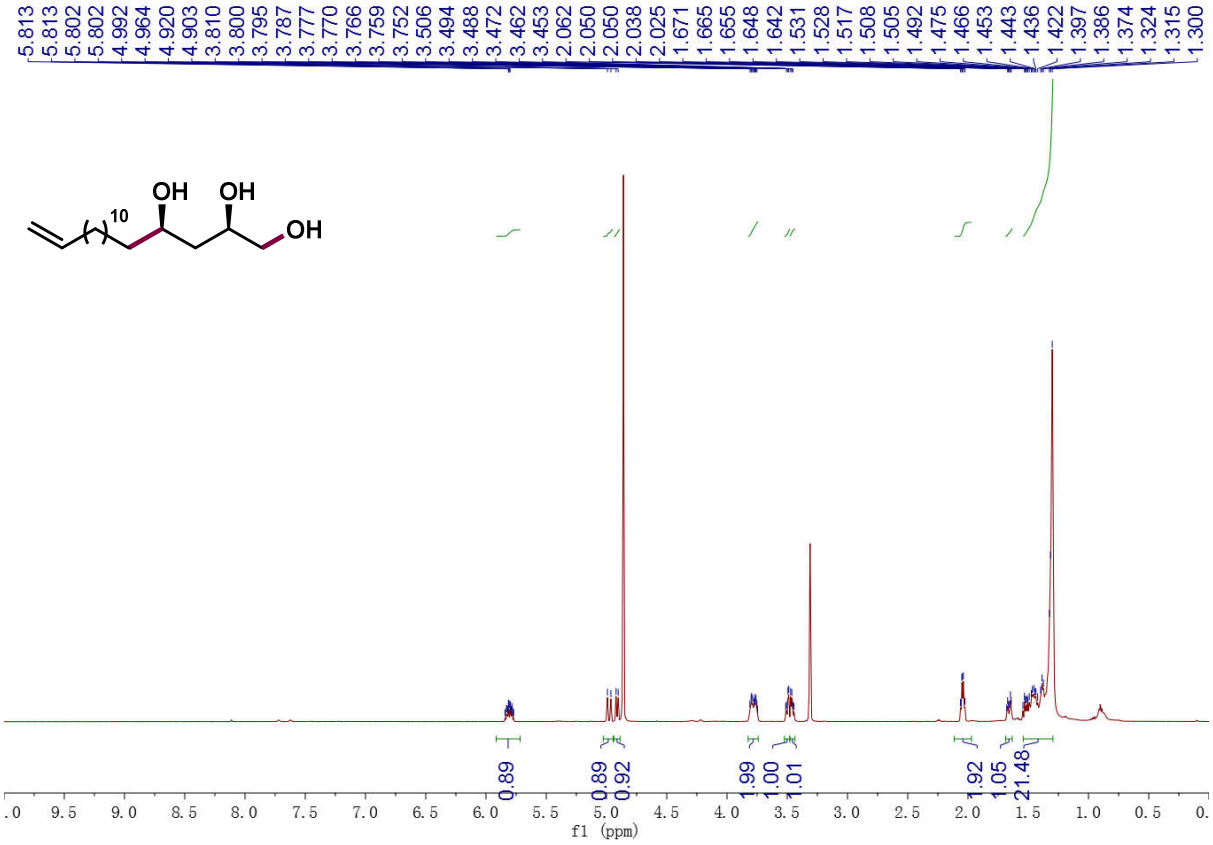
^{1}H NMR of Compound SI-53 (600 MHz, $CDCl_3$):



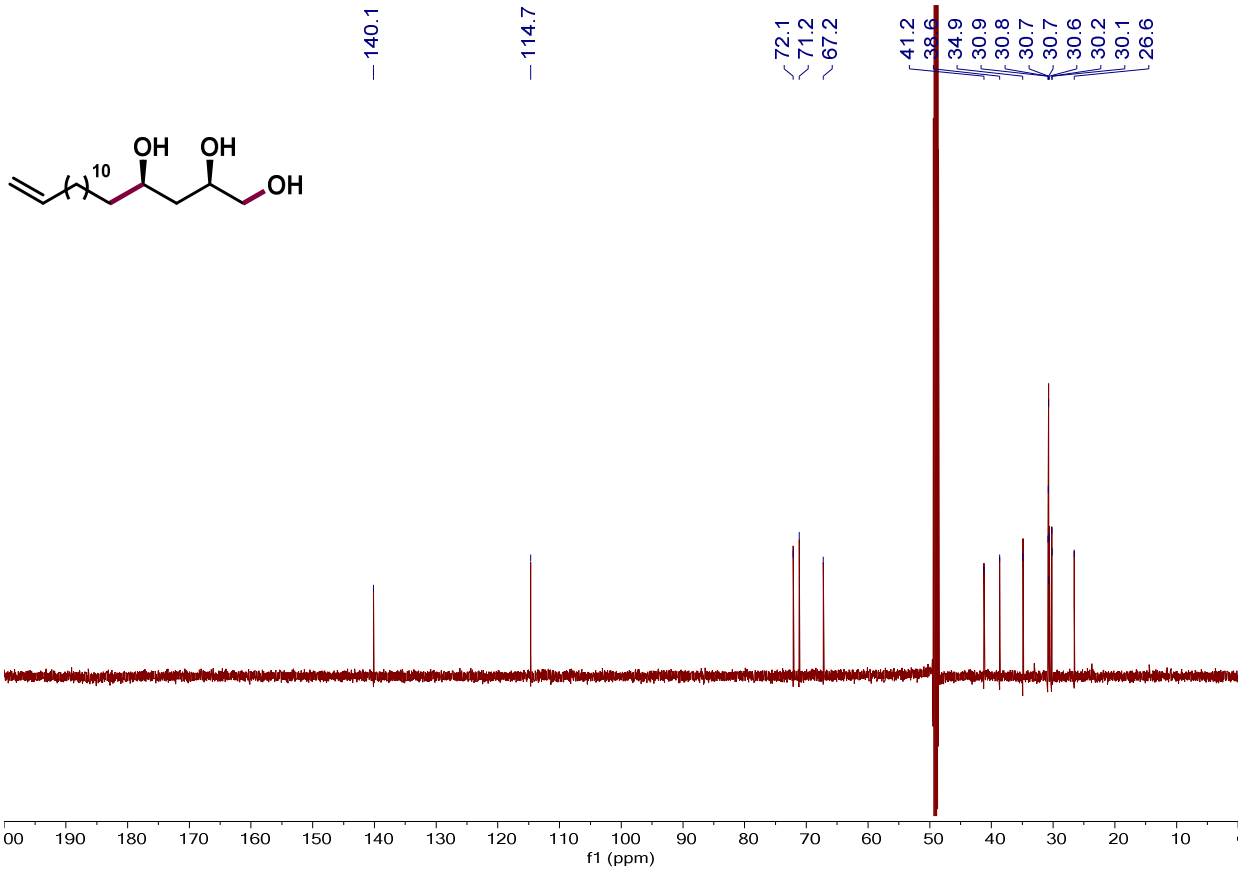
^{13}C NMR of Compound SI-53 (151 MHz, $CDCl_3$):



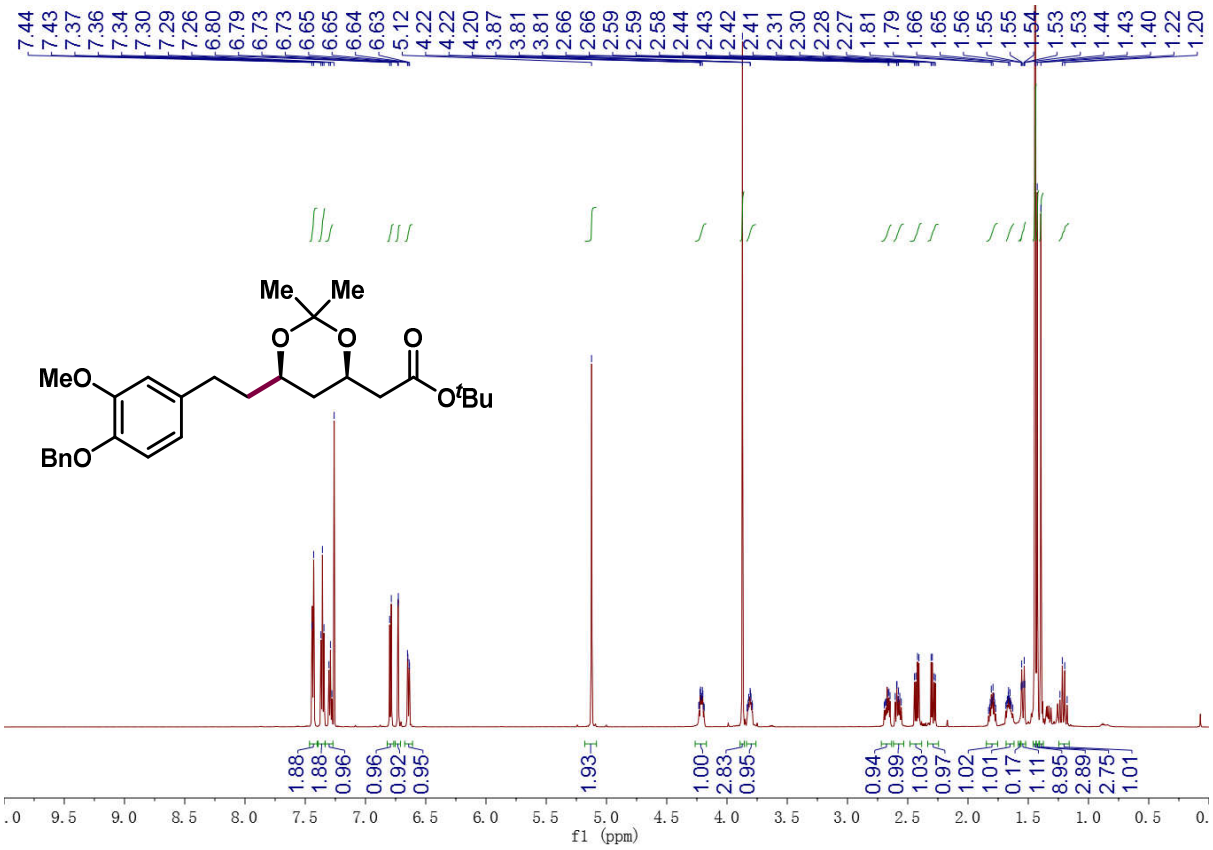
^{1}H NMR of Compound 43 (600 MHz, CD_3OD):



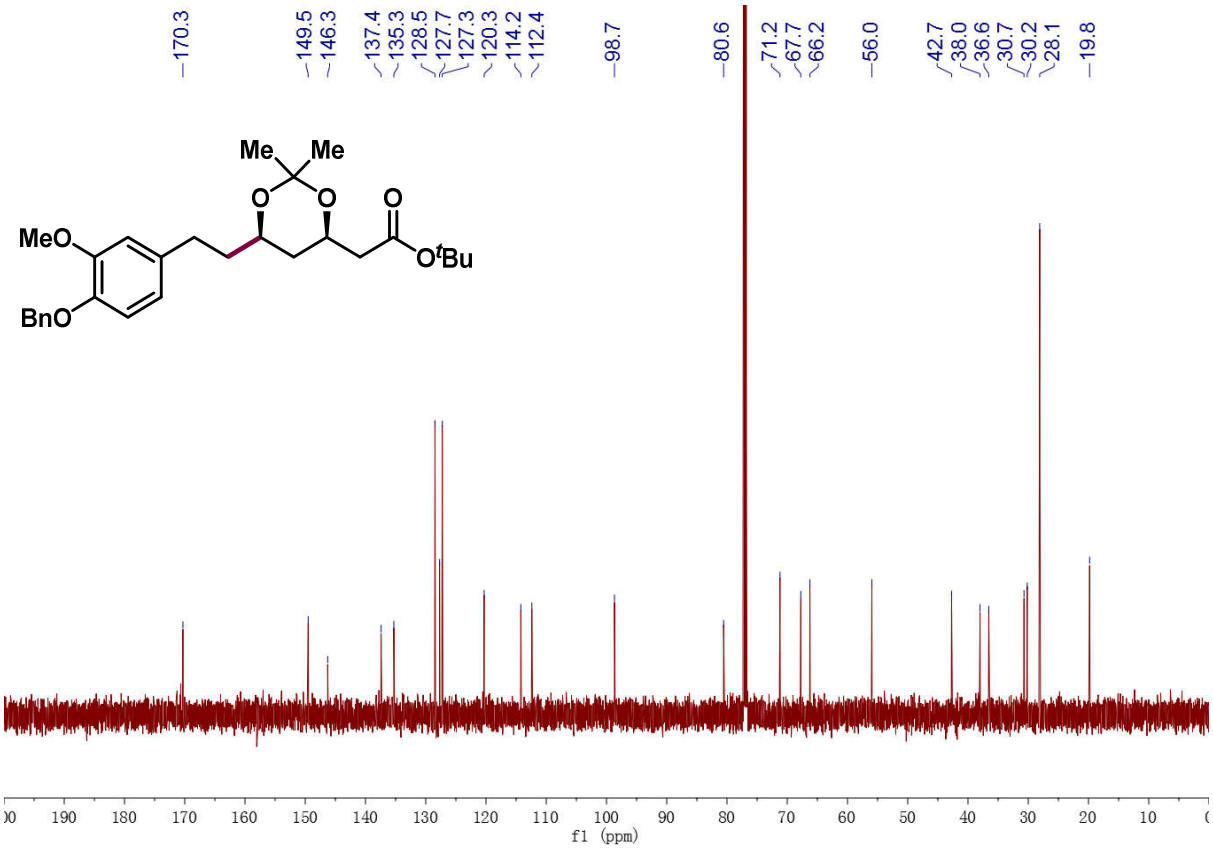
^{13}C NMR of Compound 43 (151 MHz, CD_3OD):



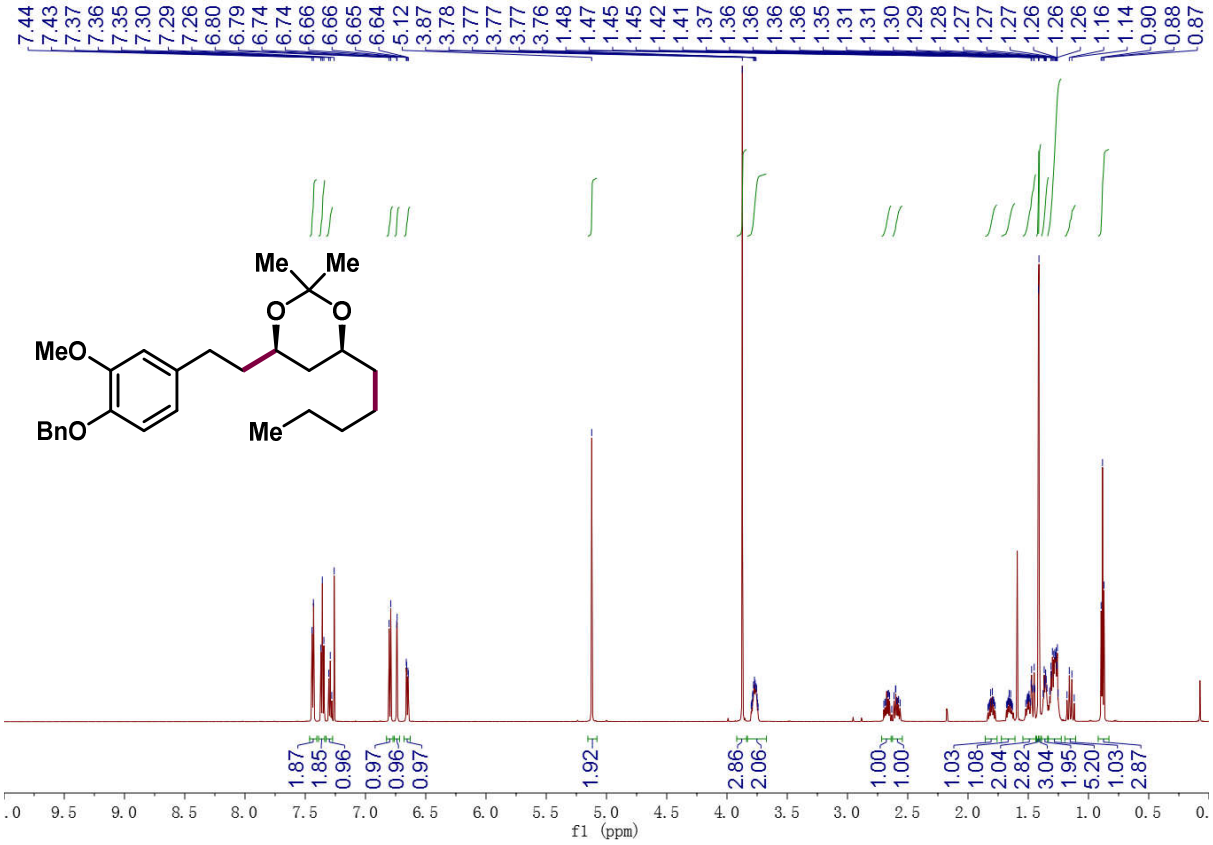
^{1}H NMR of Compound SI-55 (600 MHz, $CDCl_3$):



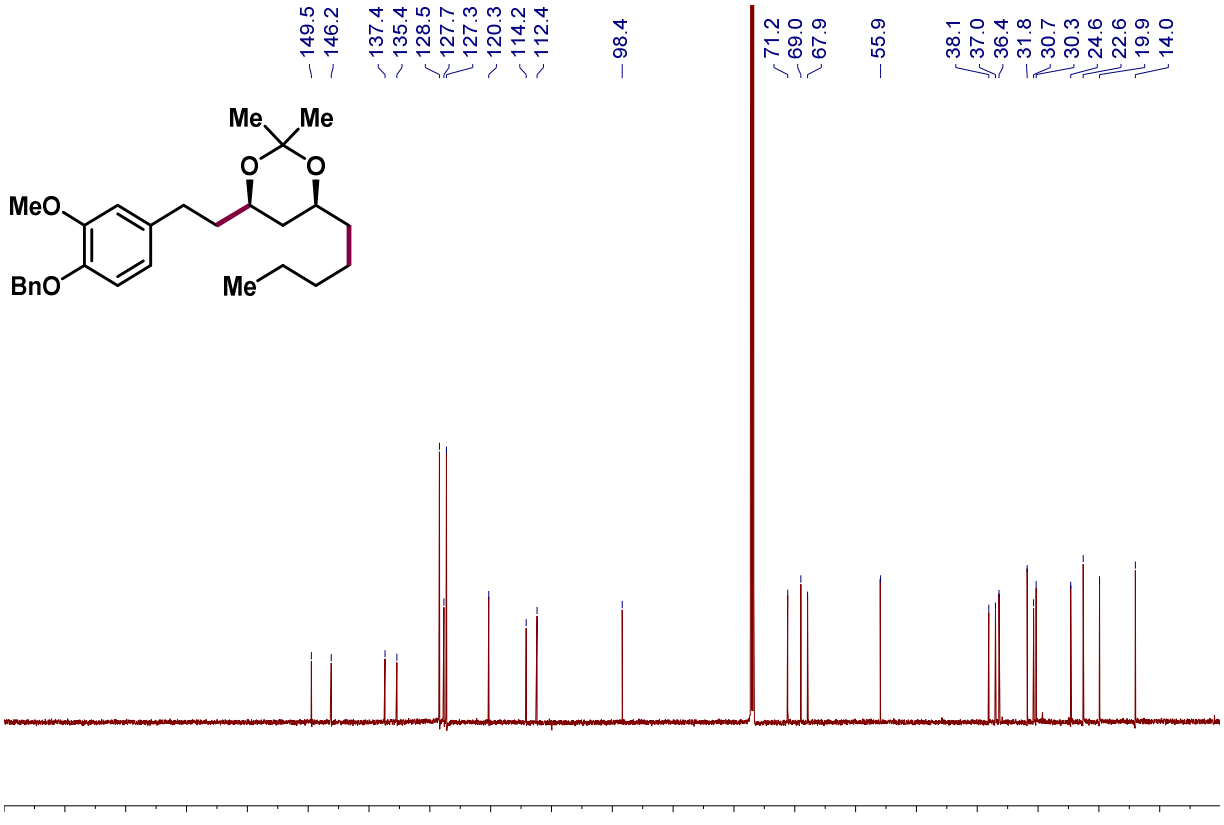
^{13}C NMR of Compound SI-55 (151 MHz, $CDCl_3$):



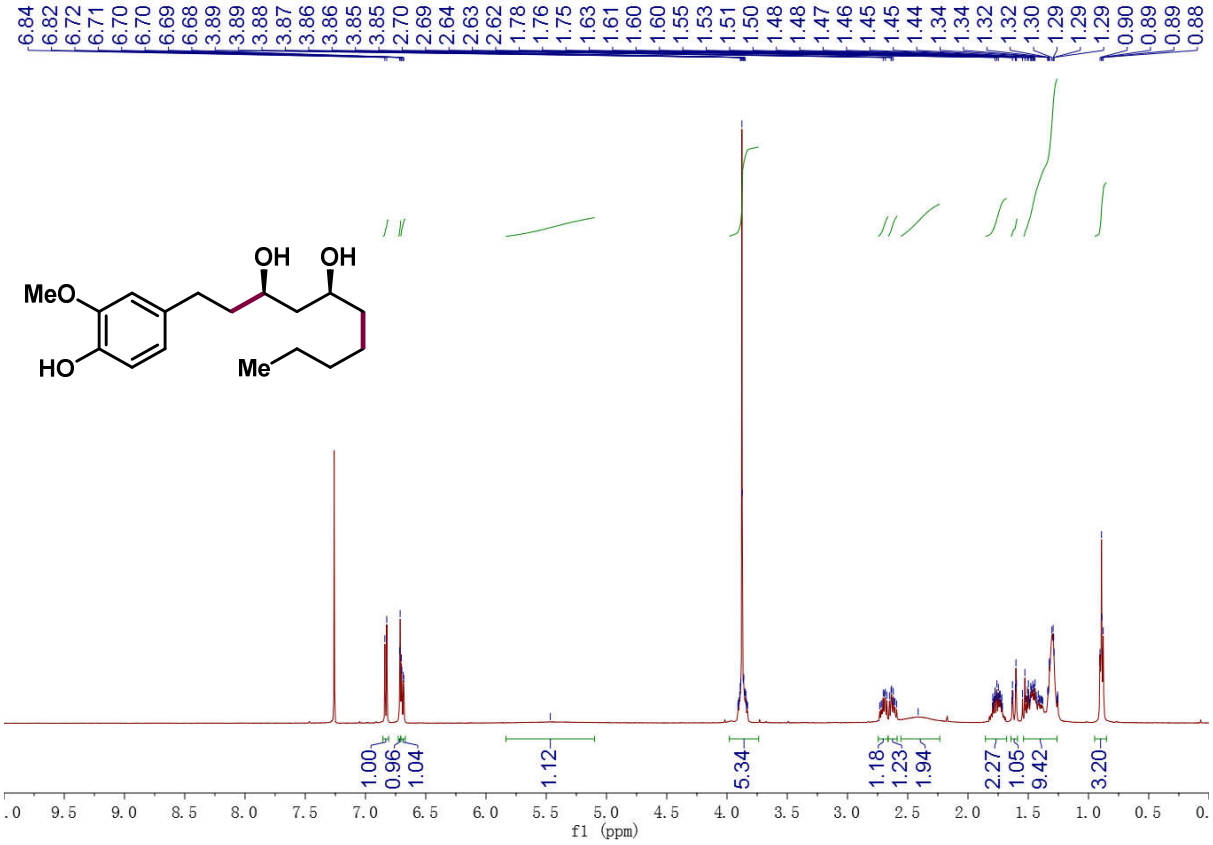
^{1}H NMR of Compound SI-56 (600 MHz, $CDCl_3$):



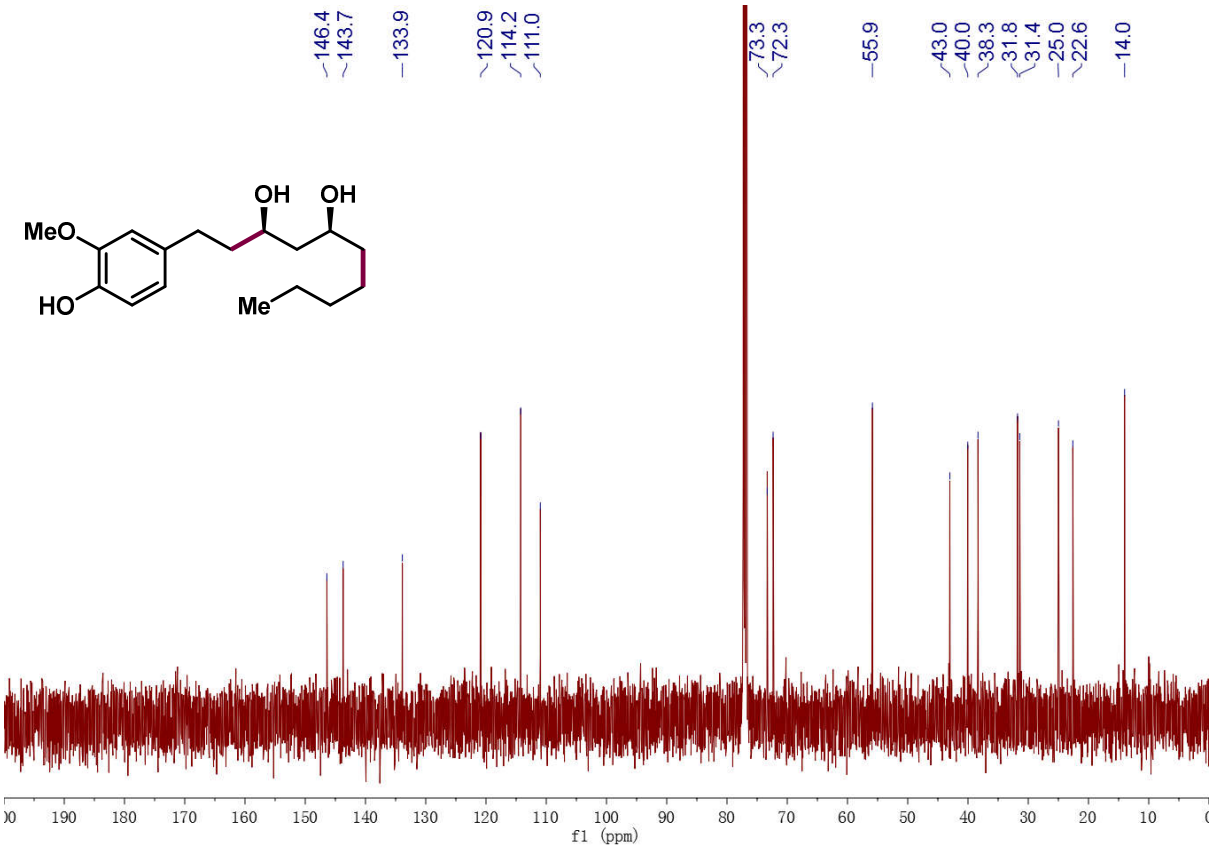
^{13}C NMR of Compound SI-56 (151 MHz, $CDCl_3$):



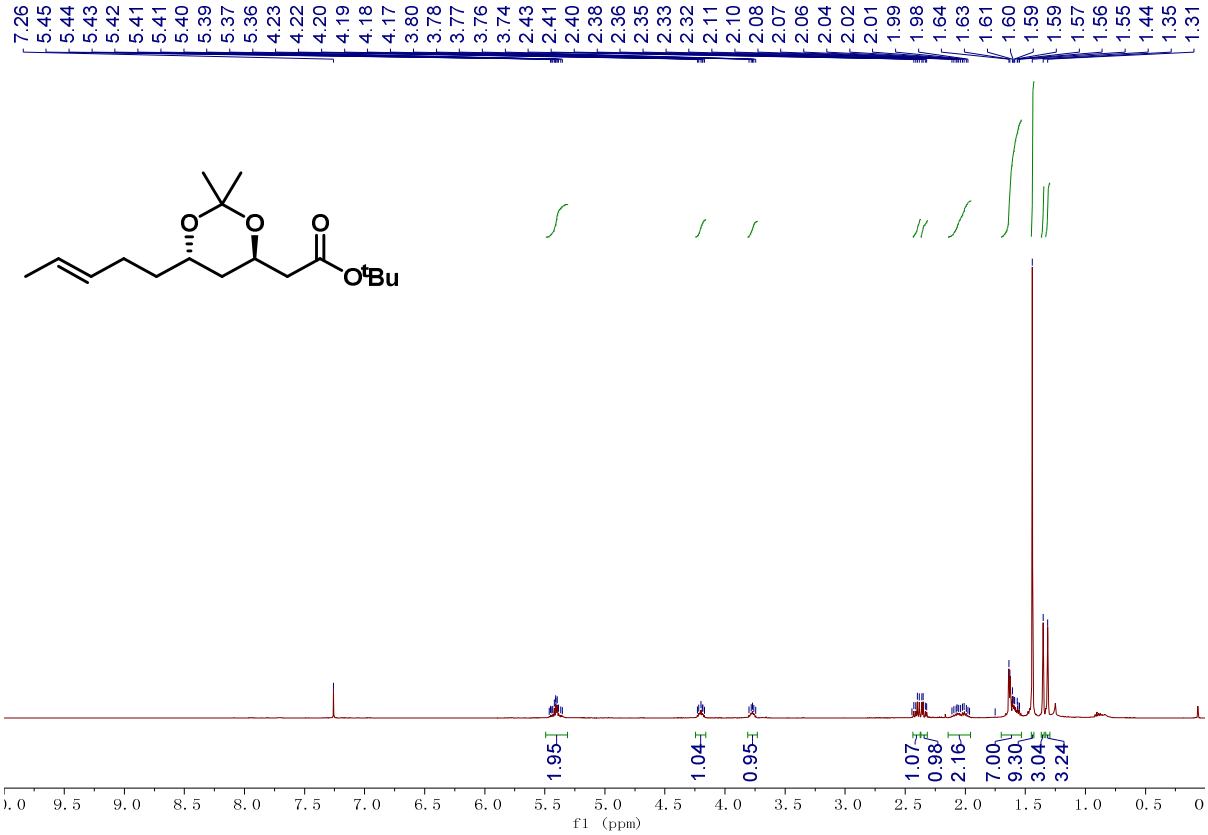
^{1}H NMR of Compound 44 (600 MHz, $CDCl_3$):



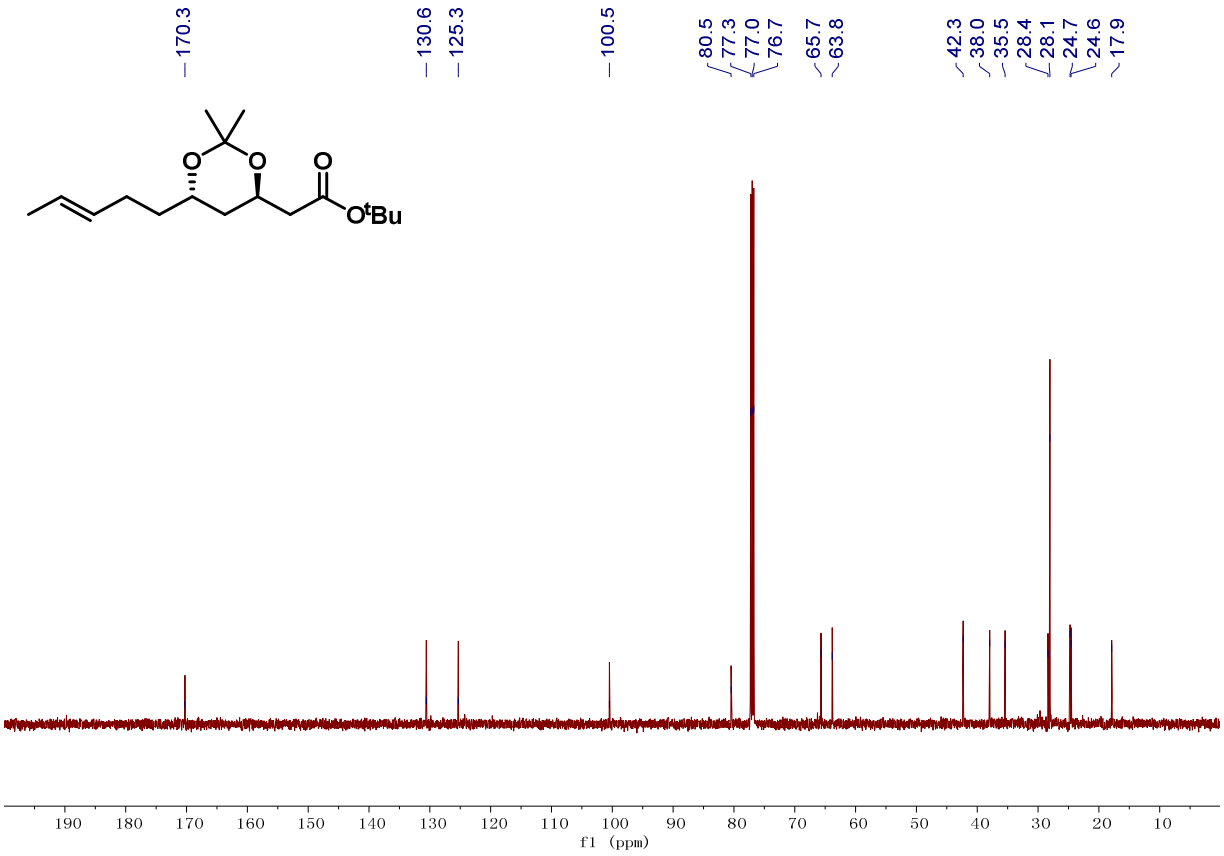
^{13}C NMR of Compound 44 (151 MHz, $CDCl_3$):



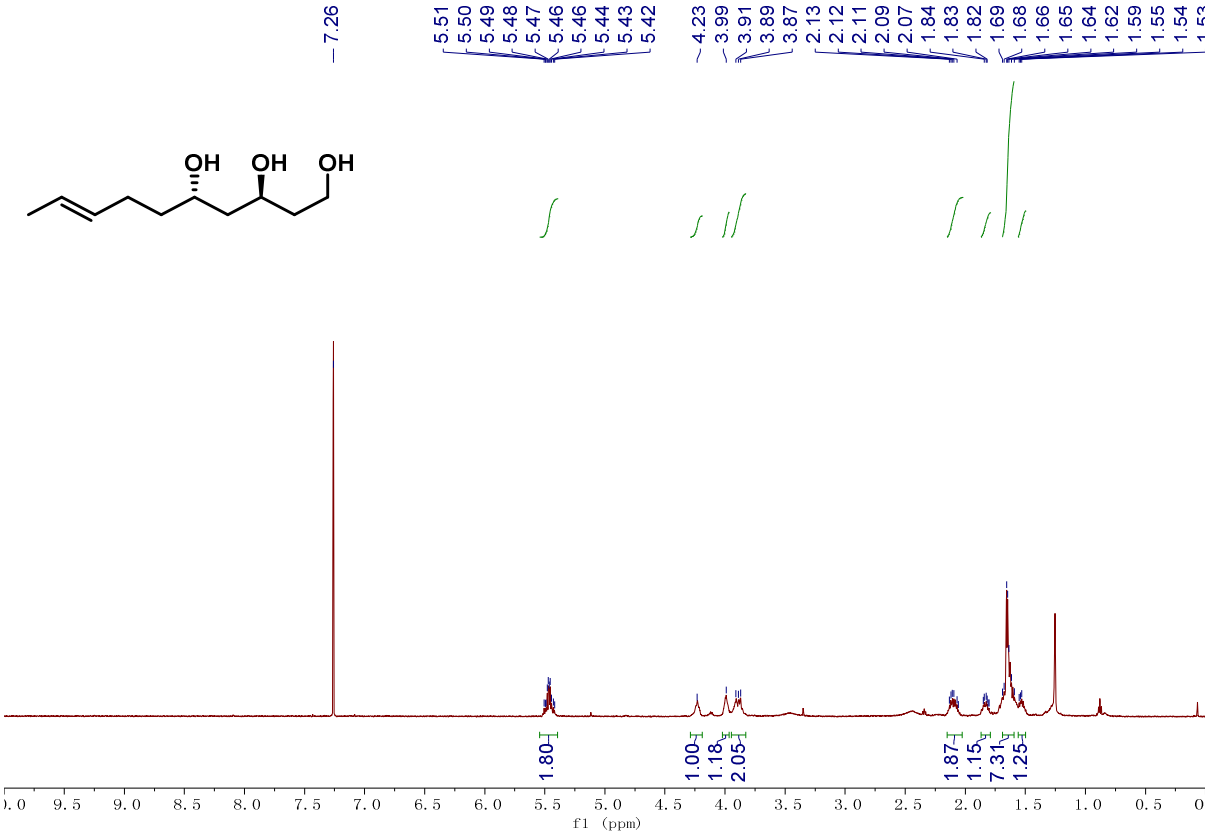
^{1}H NMR of Compound SI-57 (500 MHz, $CDCl_3$):



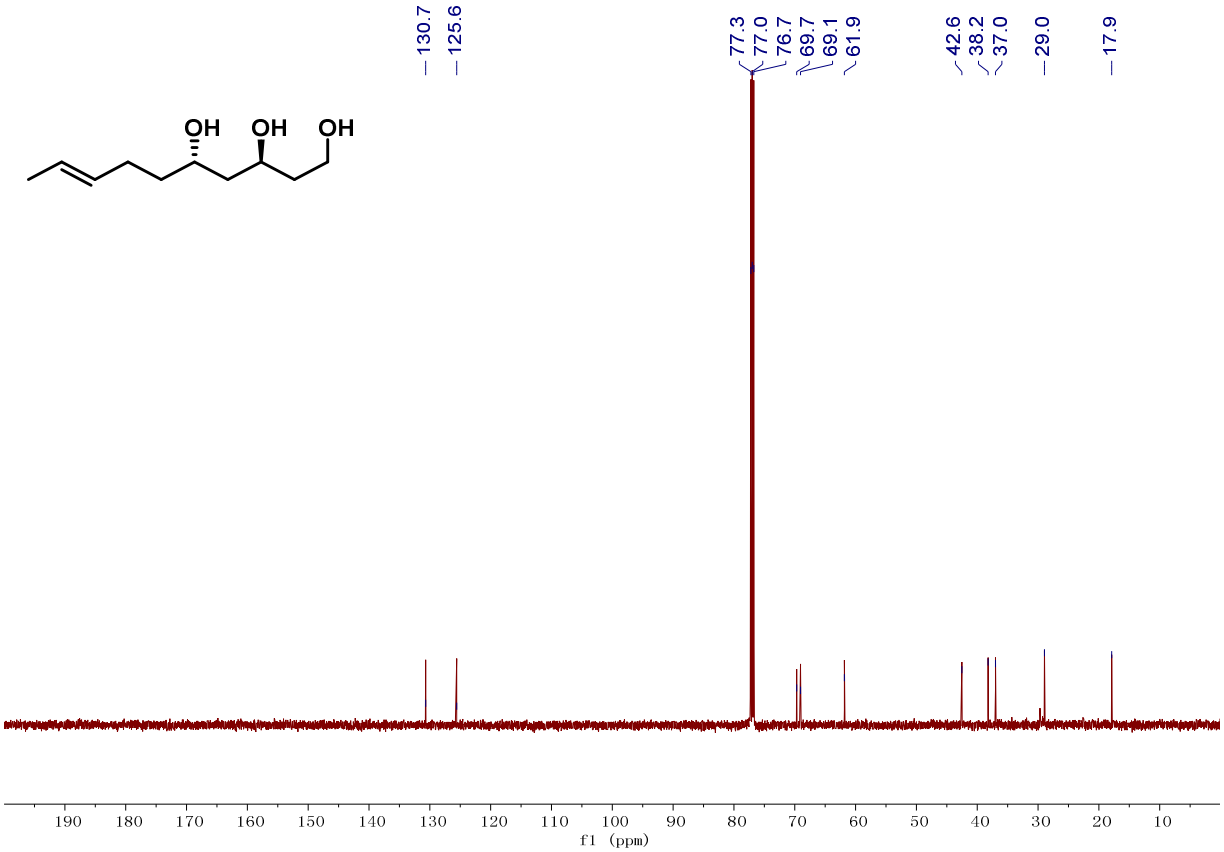
^{13}C NMR of Compound SI-57 (126 MHz, $CDCl_3$):



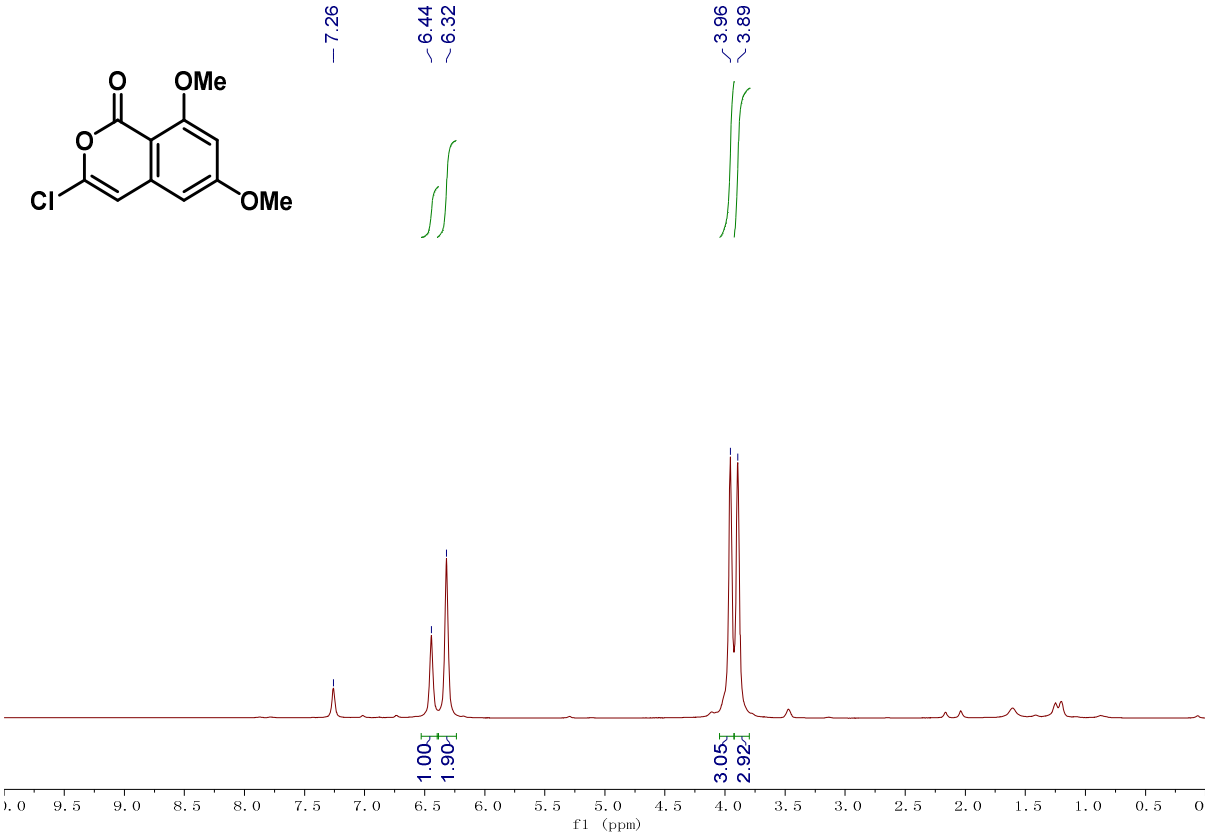
^{1}H NMR of Compound 45 (600 MHz, $CDCl_3$):



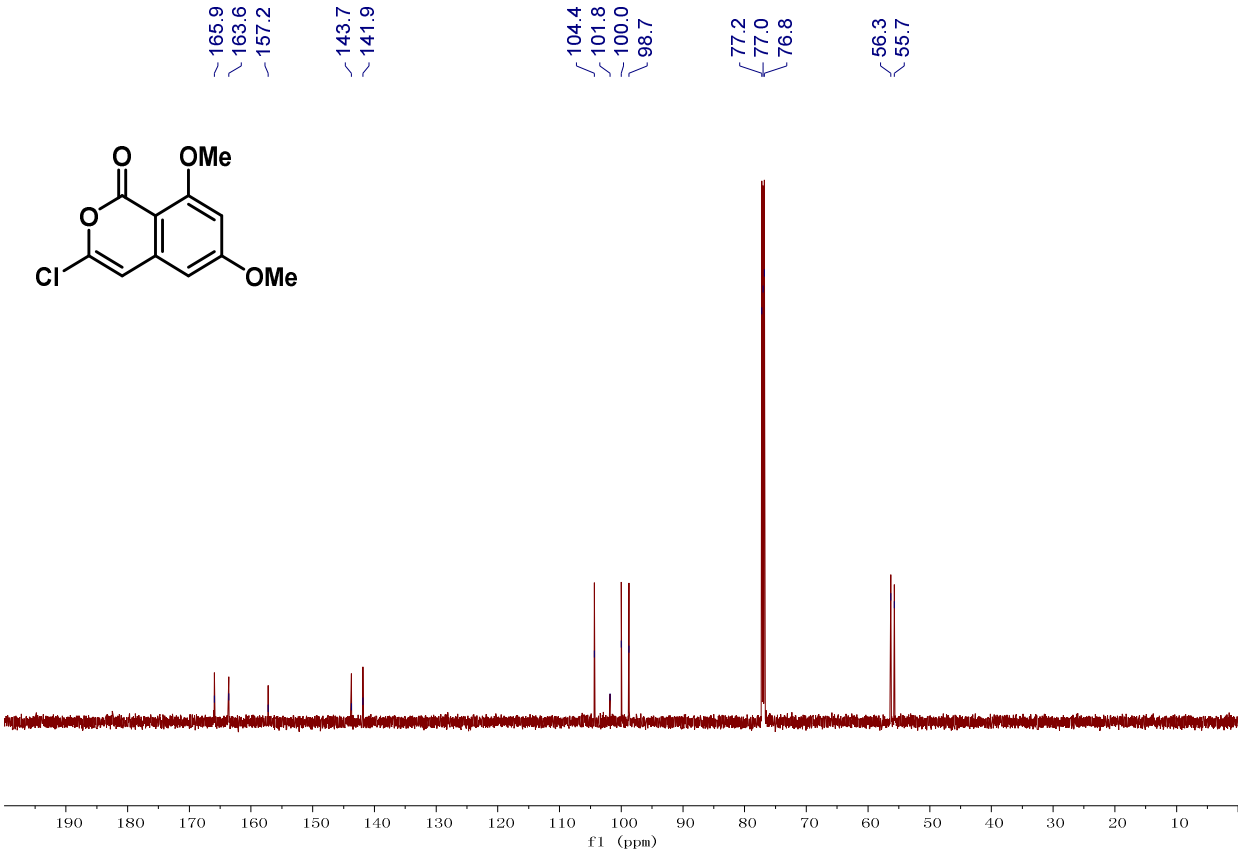
^{13}C NMR of Compound 45 (151 MHz, $CDCl_3$):



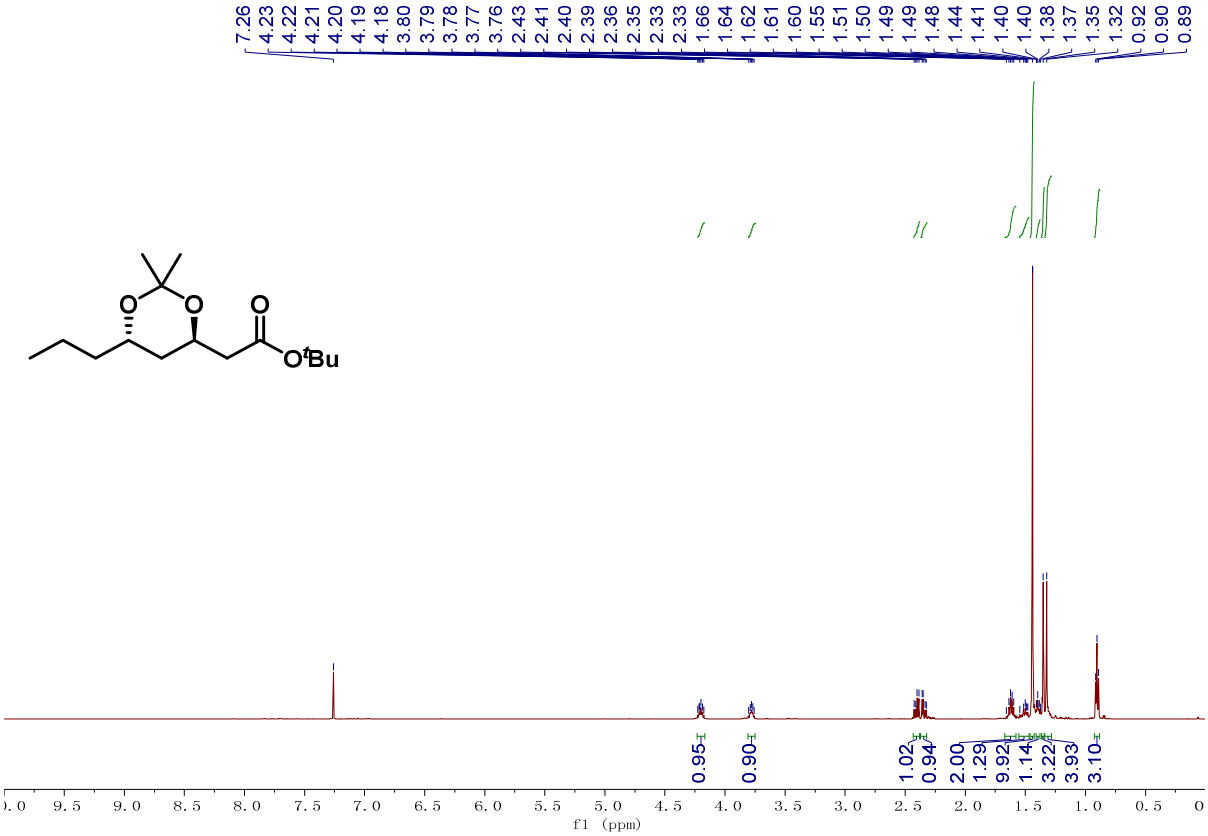
^{1}H NMR of Compound SI-59 (600 MHz, $CDCl_3$):



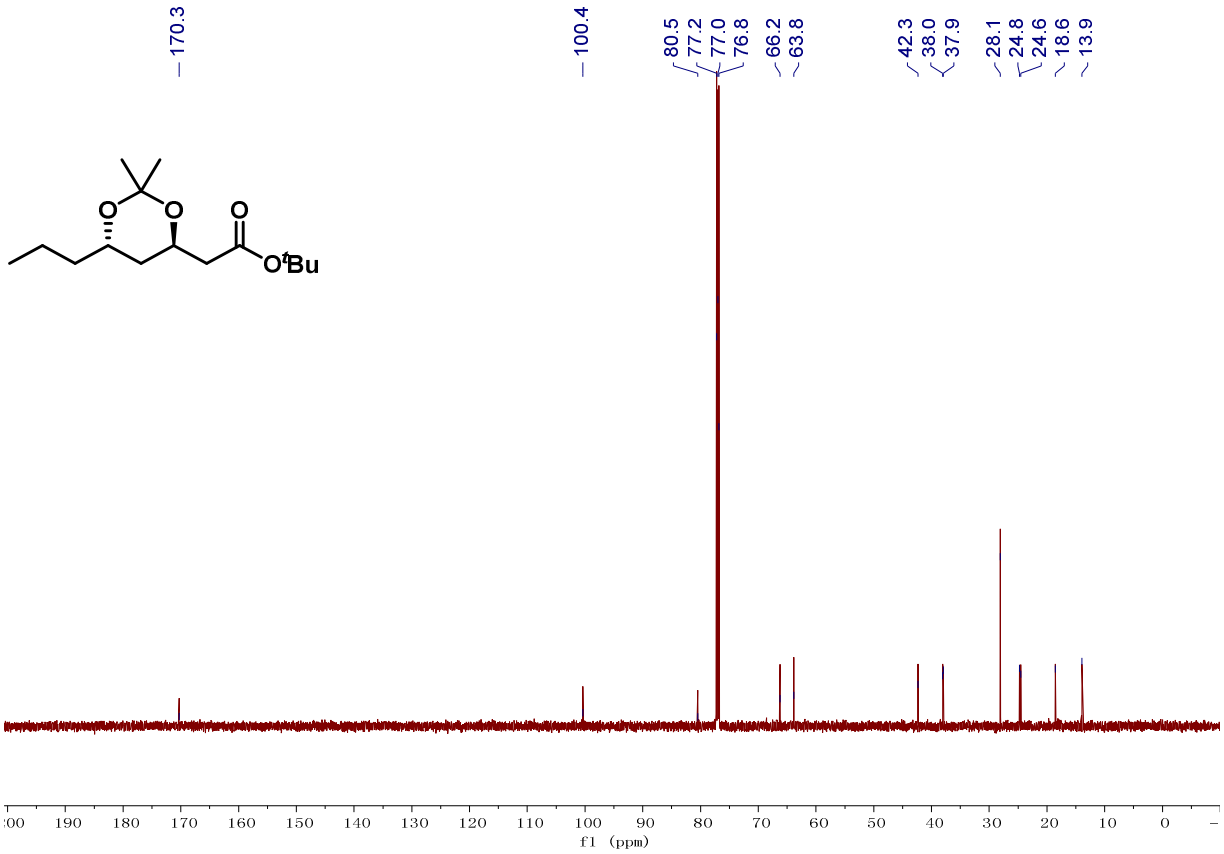
^{13}C NMR of Compound SI-59 (151 MHz, $CDCl_3$):



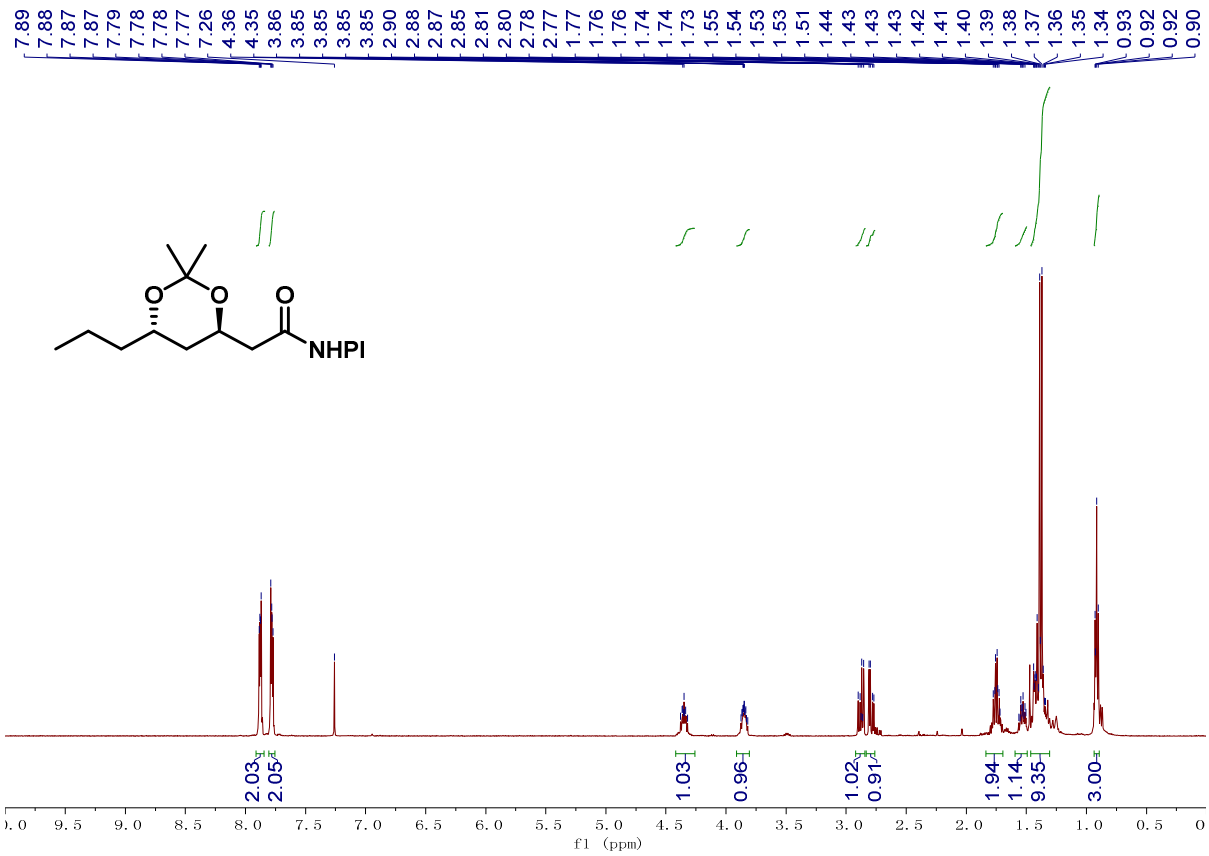
^{1}H NMR of Compound SI-60 (600 MHz, $CDCl_3$):



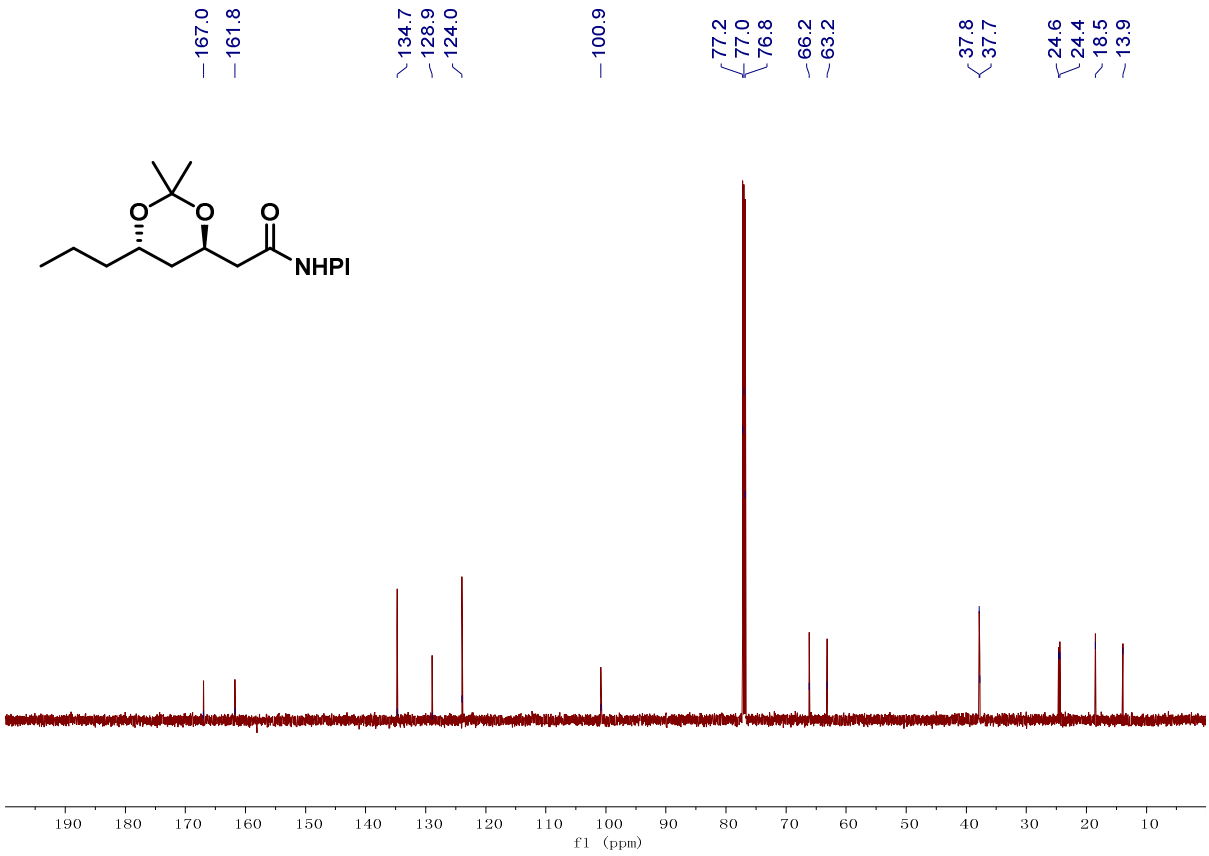
^{13}C NMR of Compound SI-60 (151 MHz, $CDCl_3$):



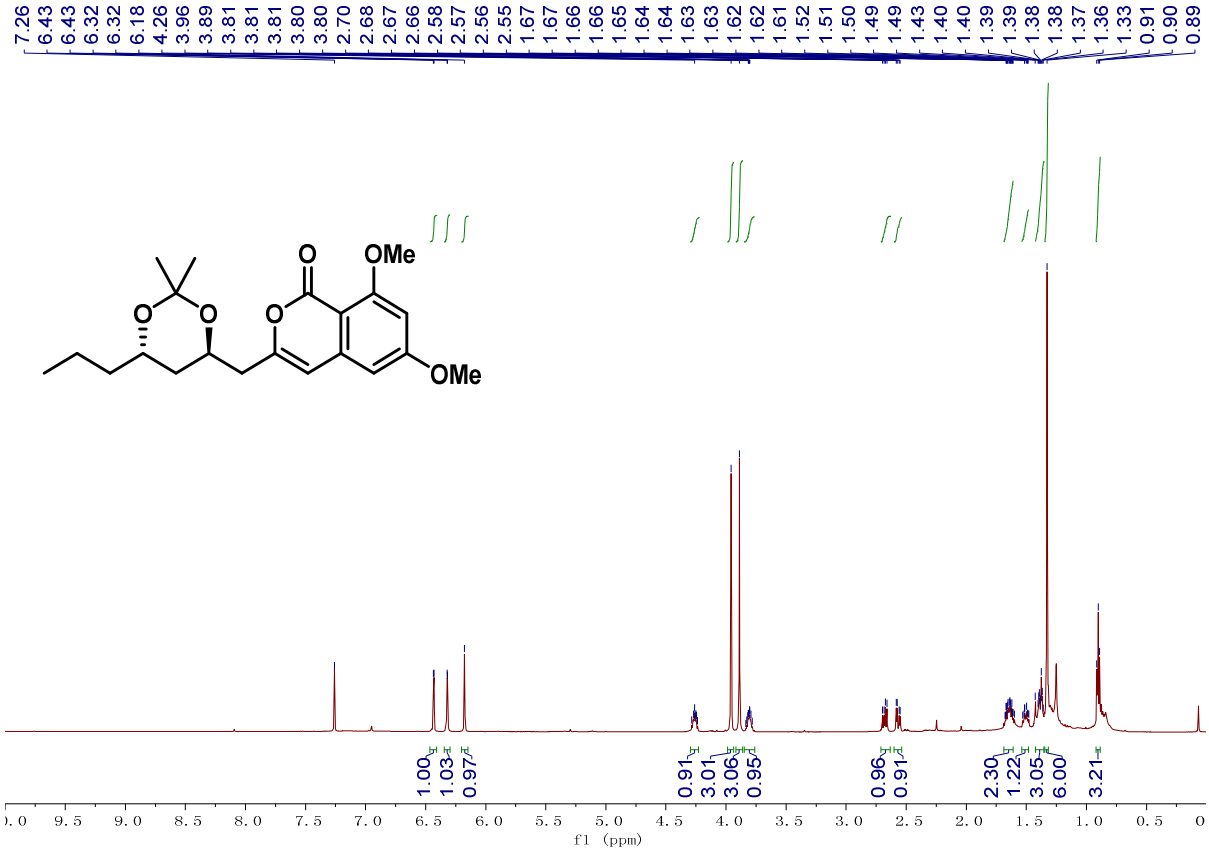
^{1}H NMR of Compound SI-61 (600 MHz, $CDCl_3$):



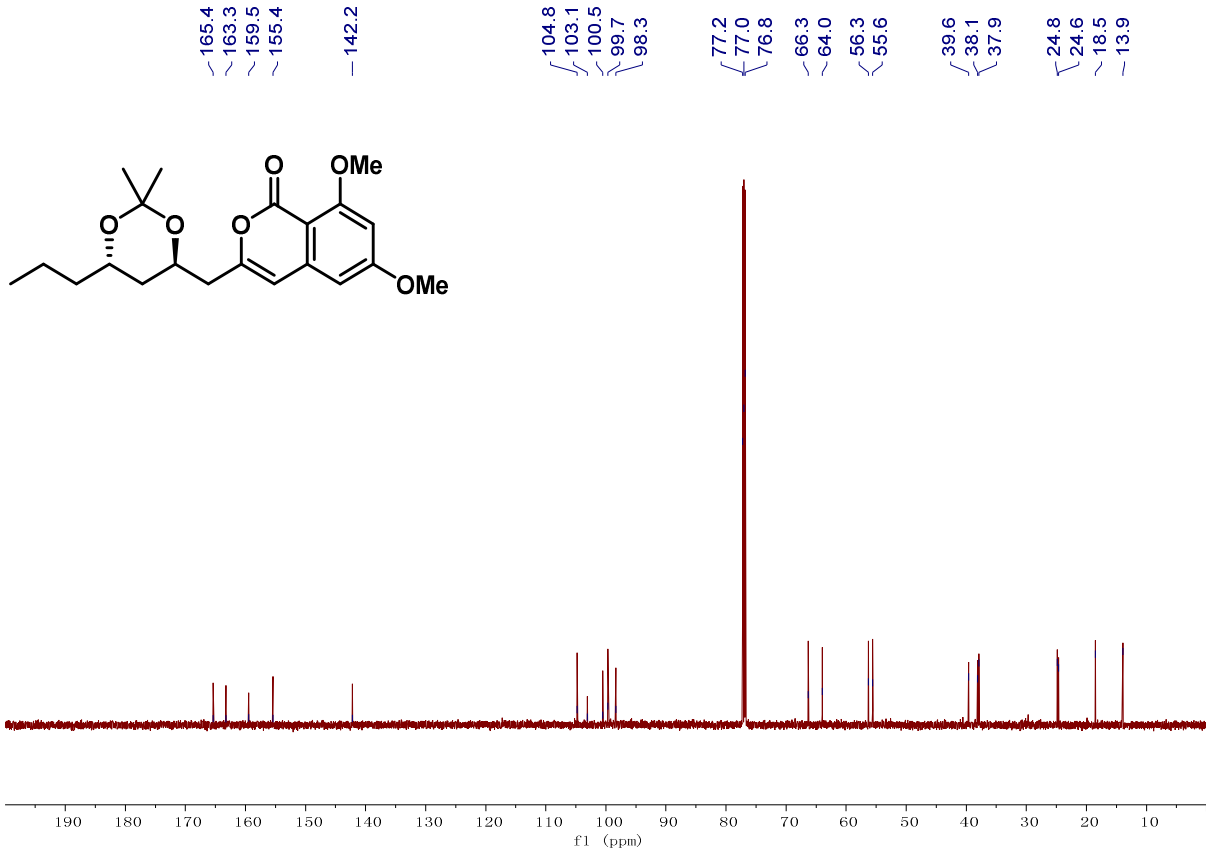
^{13}C NMR of Compound SI-61 (151 MHz, $CDCl_3$):



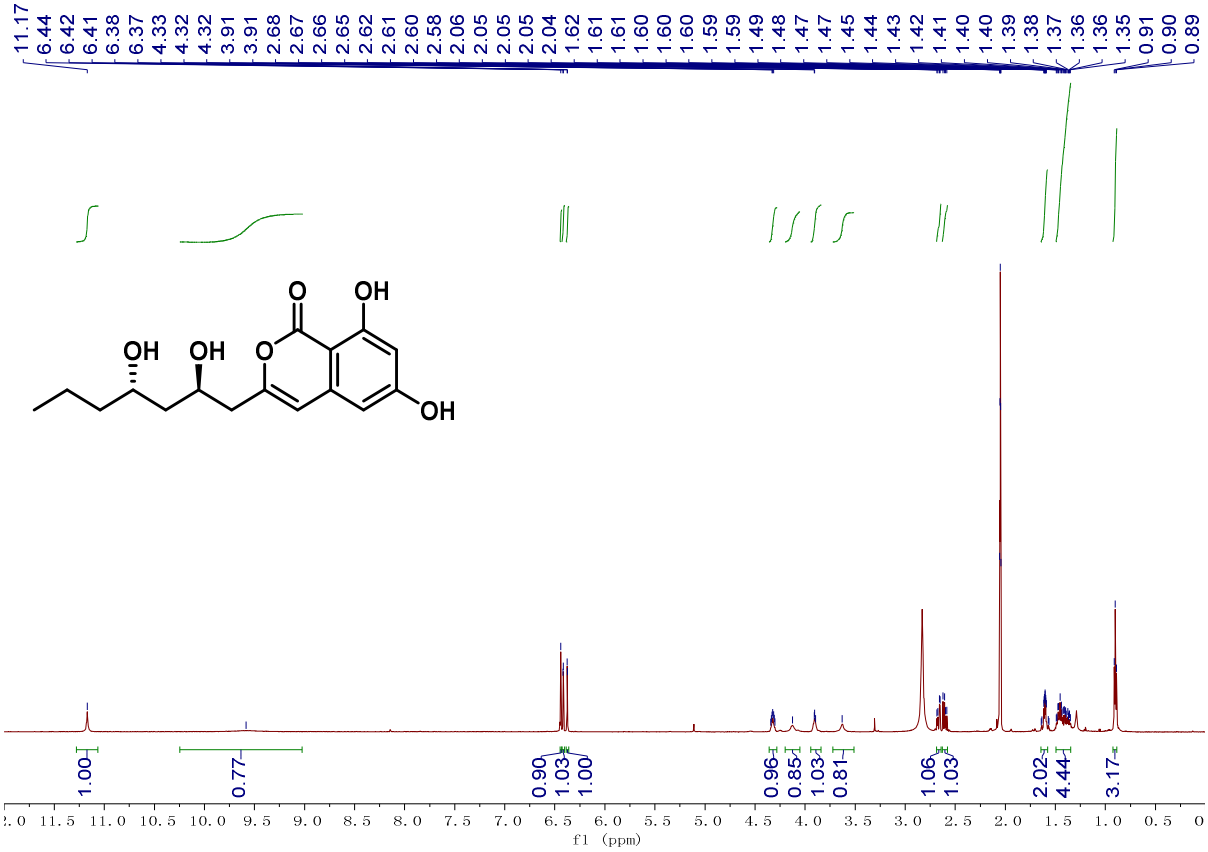
^{1}H NMR of Compound SI-62 (600 MHz, $CDCl_3$):



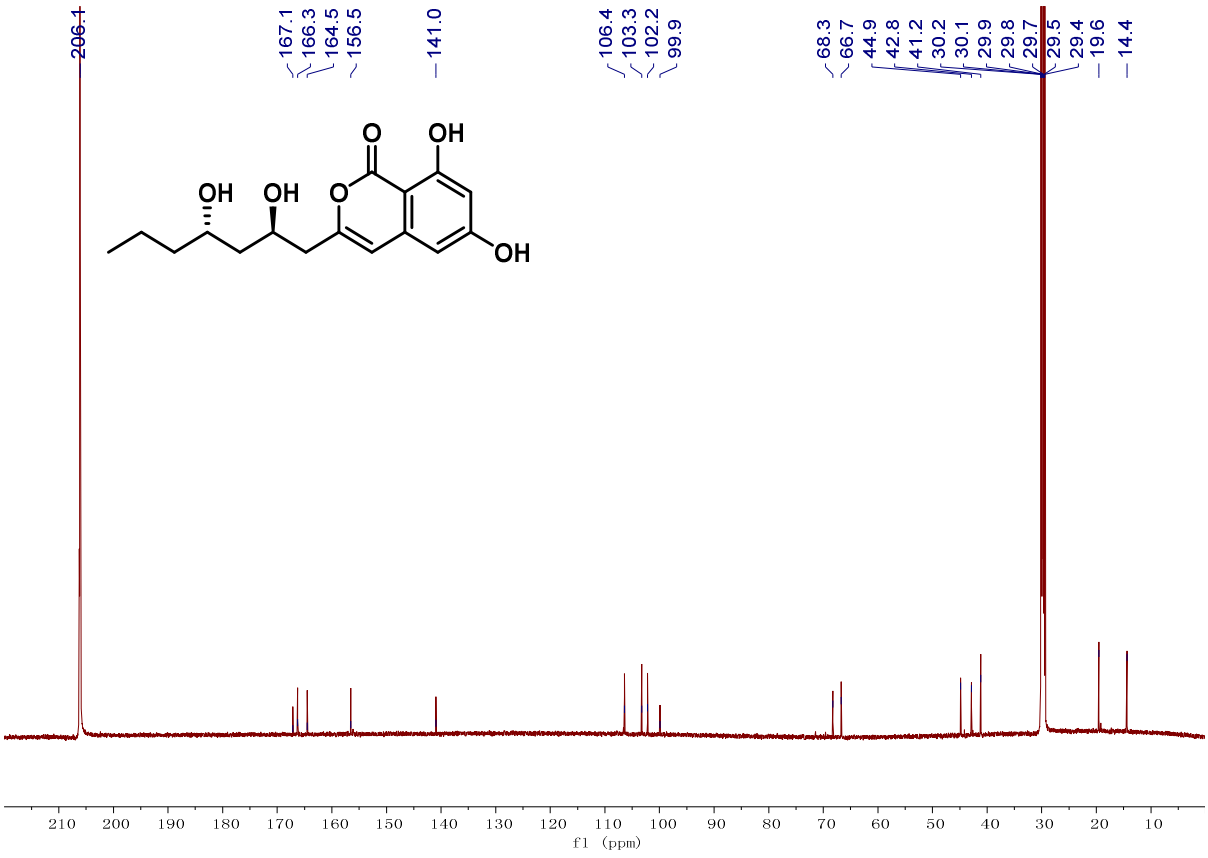
^{13}C NMR of Compound SI-62 (151 MHz, $CDCl_3$):



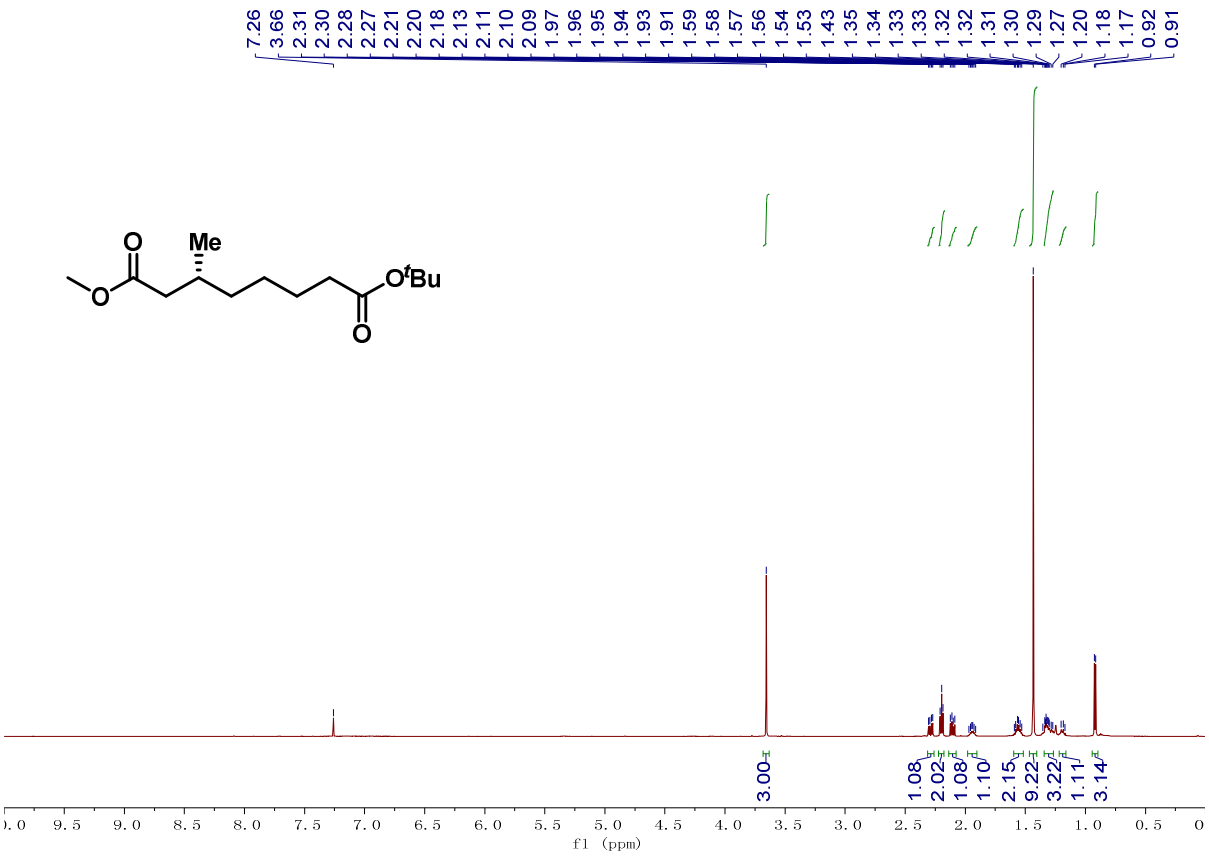
^{1}H NMR of Compound 46 (600 MHz, $(CD_3)_2CO$):



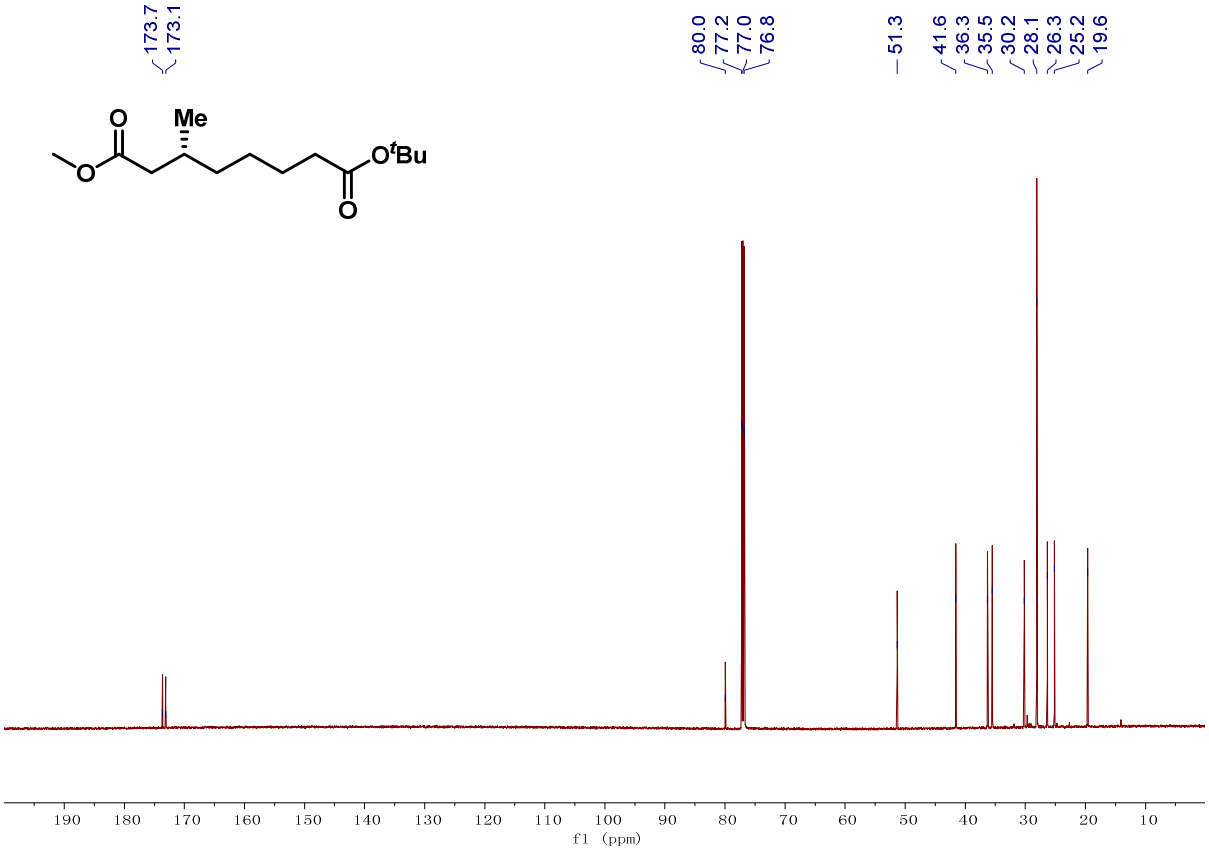
^{13}C NMR of Compound 46 (151 MHz, $(CD_3)_2CO$):



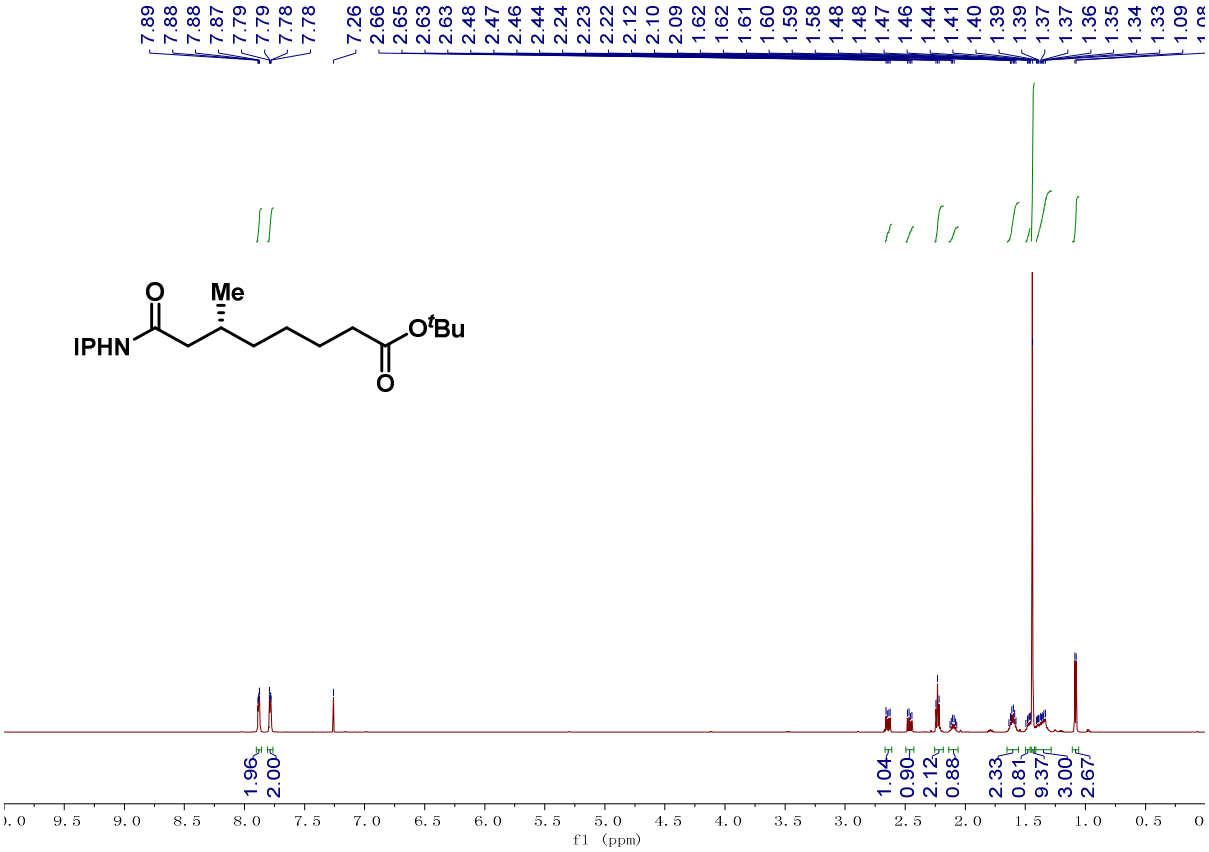
^{1}H NMR of Compound SI-65 (600 MHz, $CDCl_3$):



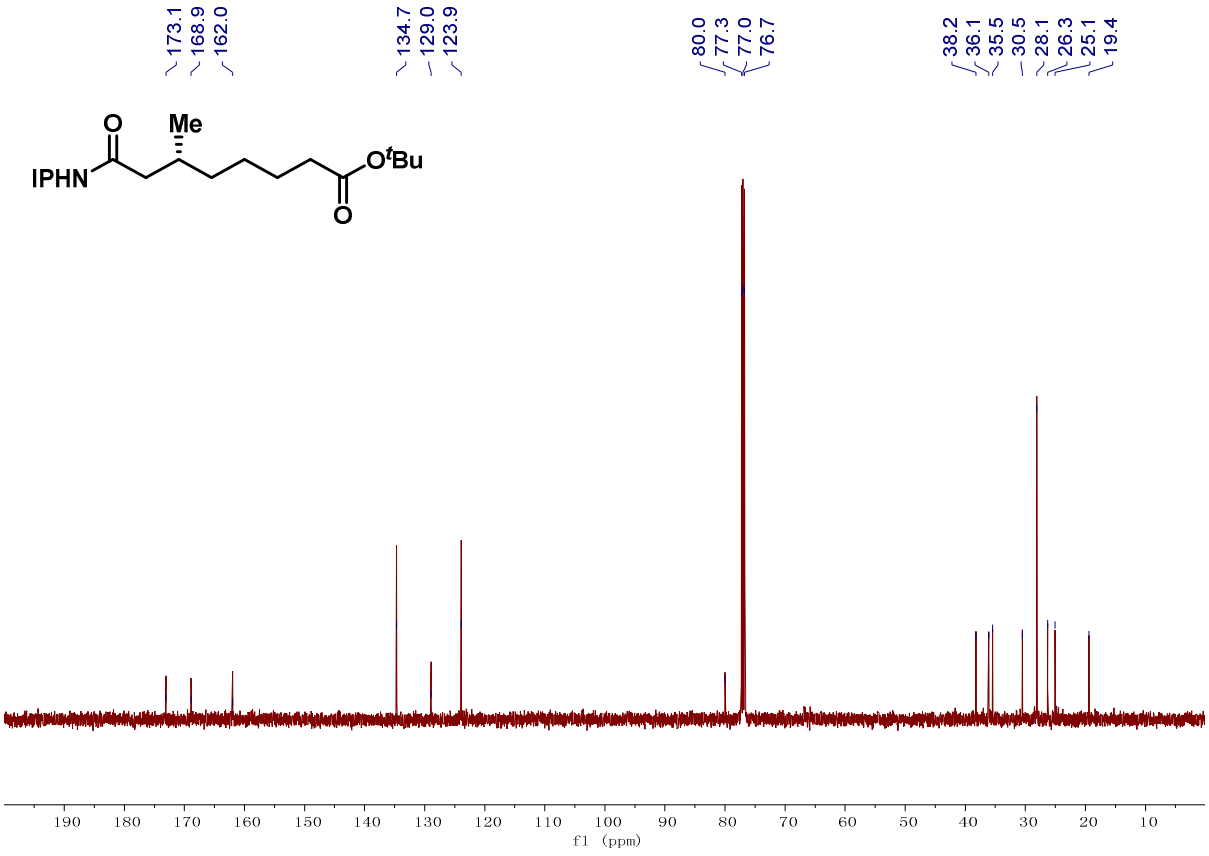
^{13}C NMR of Compound SI-65 (151 MHz, $CDCl_3$):



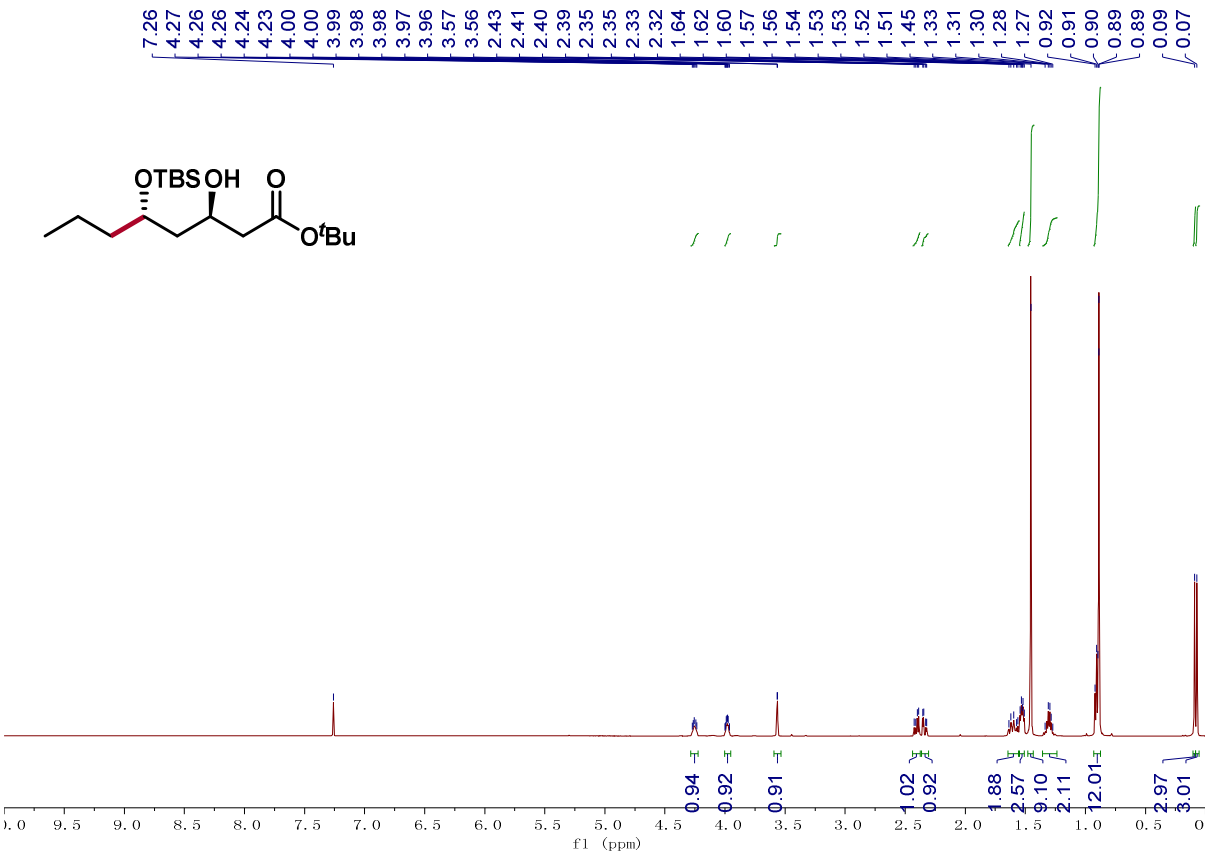
^{1}H NMR of Compound SI-66 (600 MHz, $CDCl_3$):



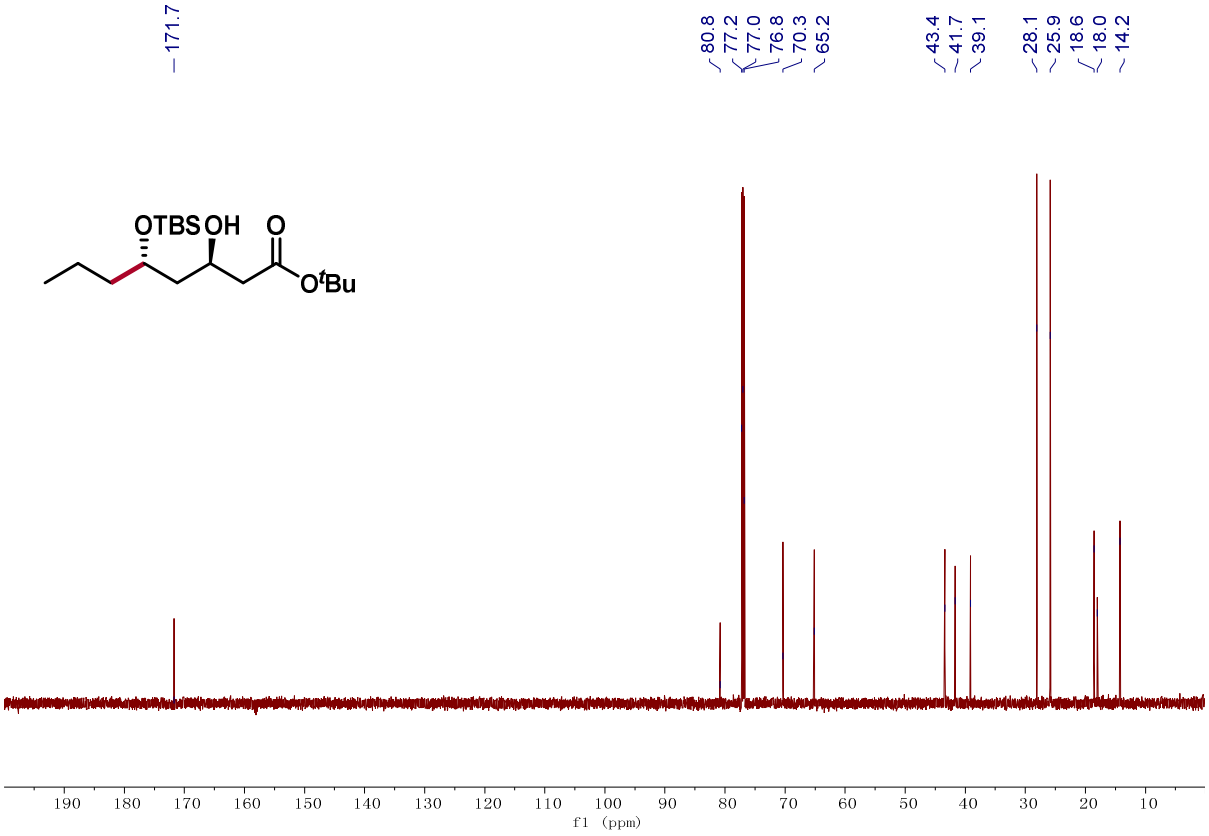
^{13}C NMR of Compound SI-66 (151 MHz, $CDCl_3$):



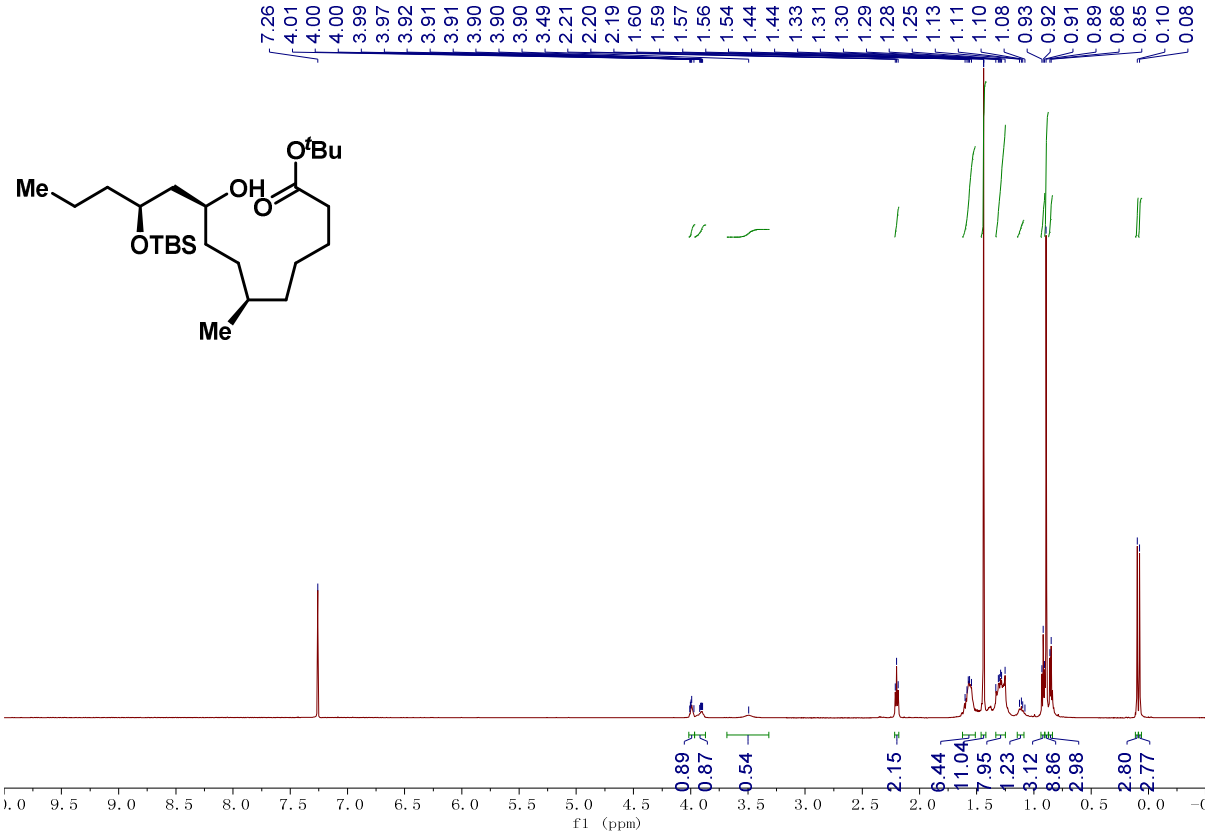
^{1}H NMR of Compound SI-67 (600 MHz, $CDCl_3$):



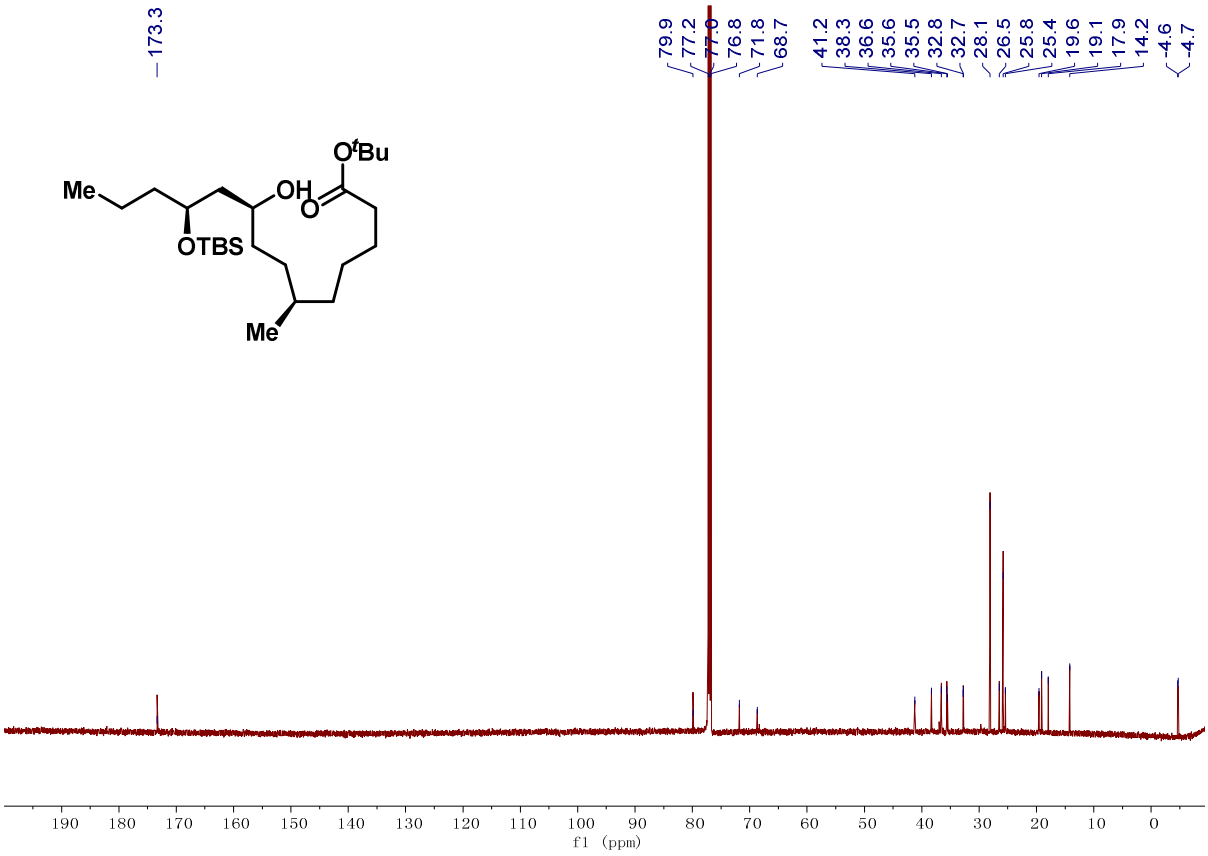
^{13}C NMR of Compound SI-67 (151 MHz, $CDCl_3$):



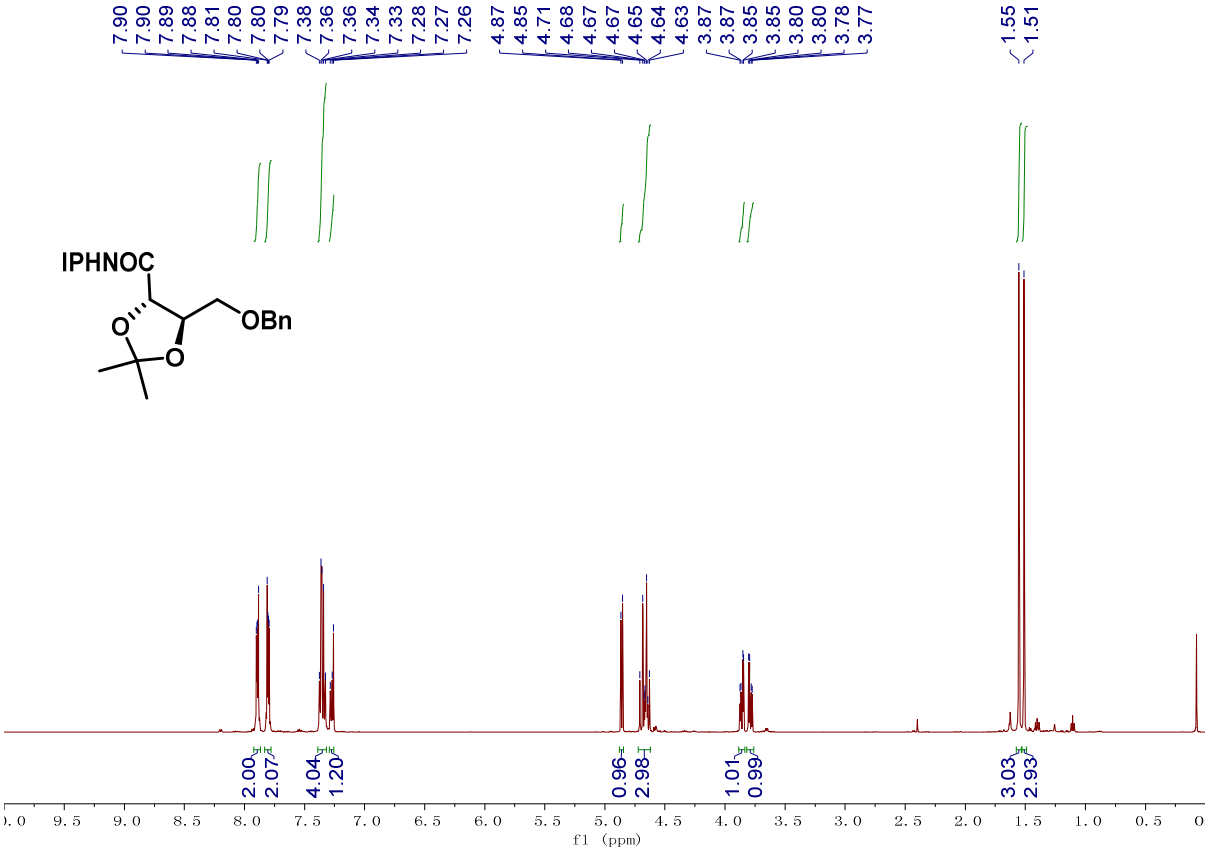
^{1}H NMR of Compound SI-69 (600 MHz, $CDCl_3$):



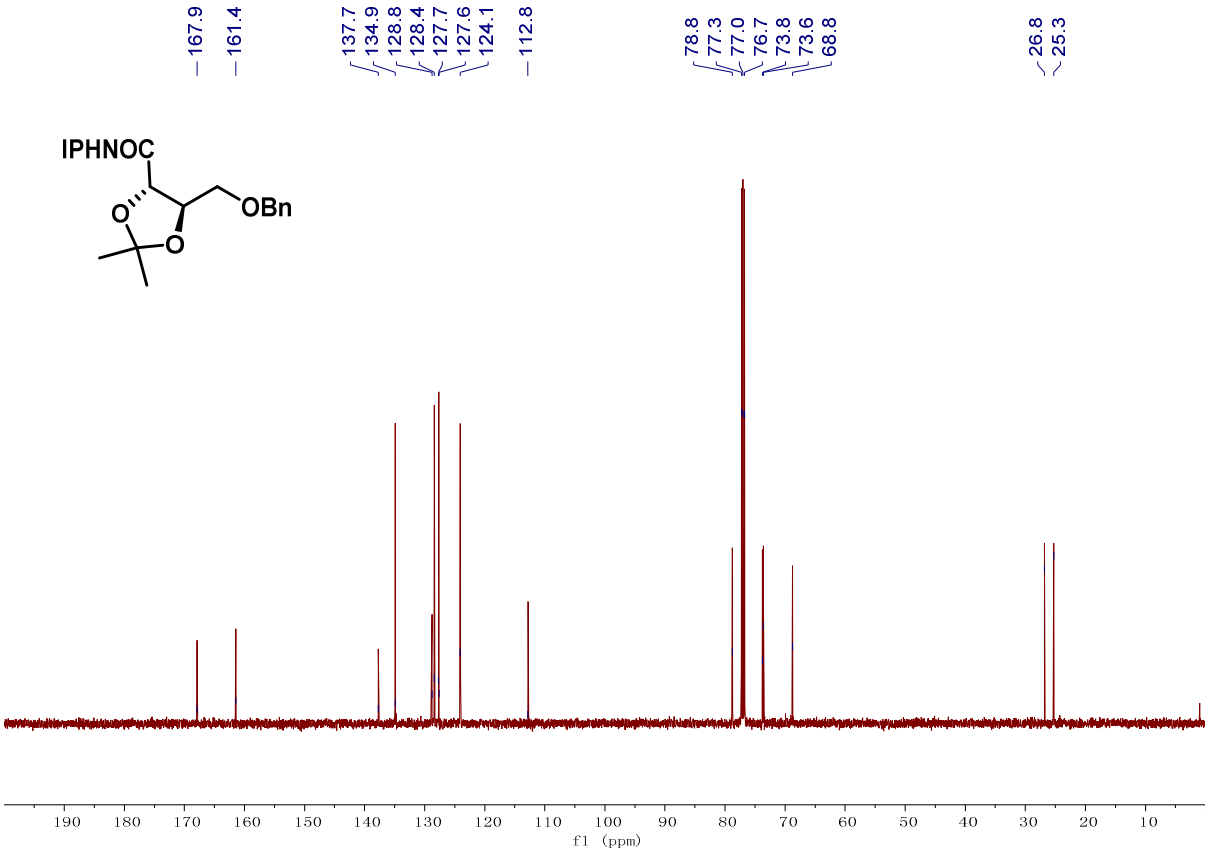
^{13}C NMR of Compound SI-69 (151 MHz, $CDCl_3$):



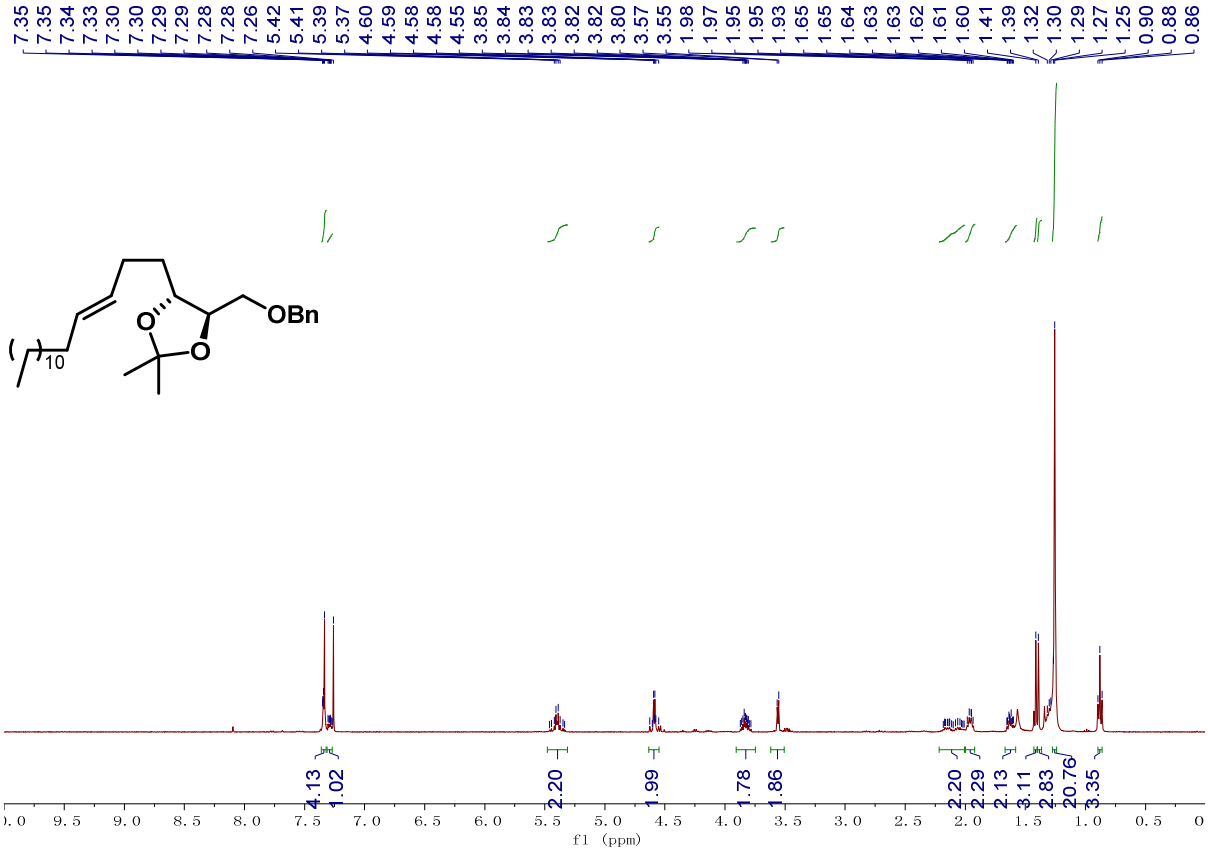
^{1}H NMR of Compound SI-70 (500 MHz, $CDCl_3$):



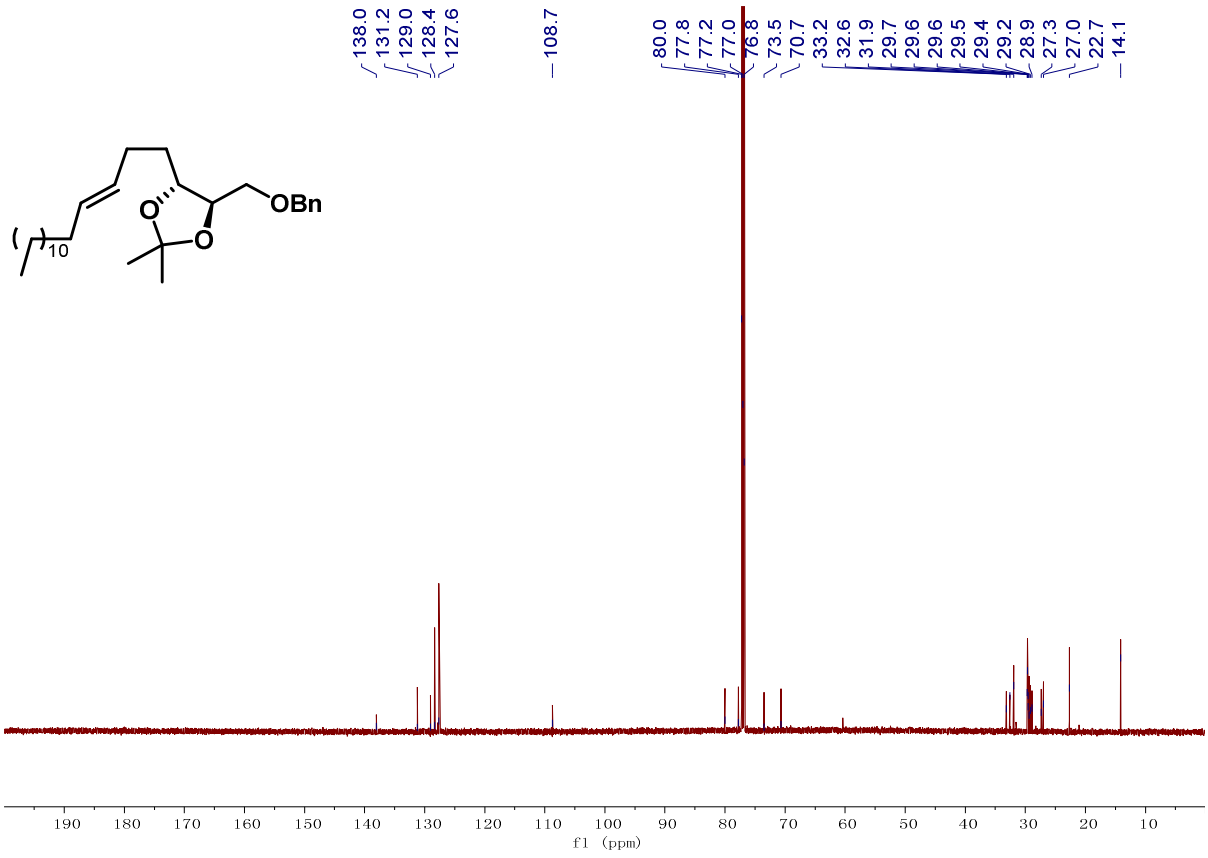
^{13}C NMR of Compound SI-70 (126 MHz, $CDCl_3$):



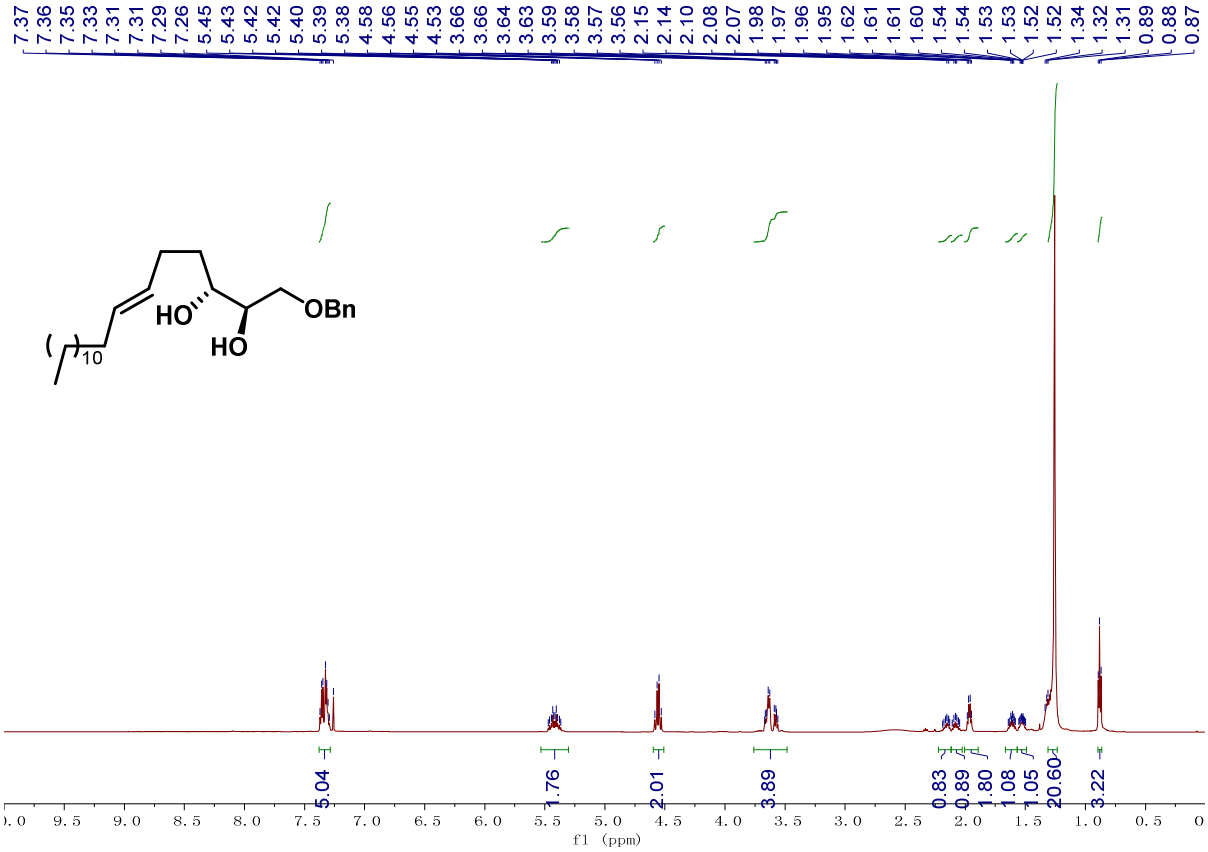
^{1}H NMR of Compound 51 (400 MHz, $CDCl_3$):



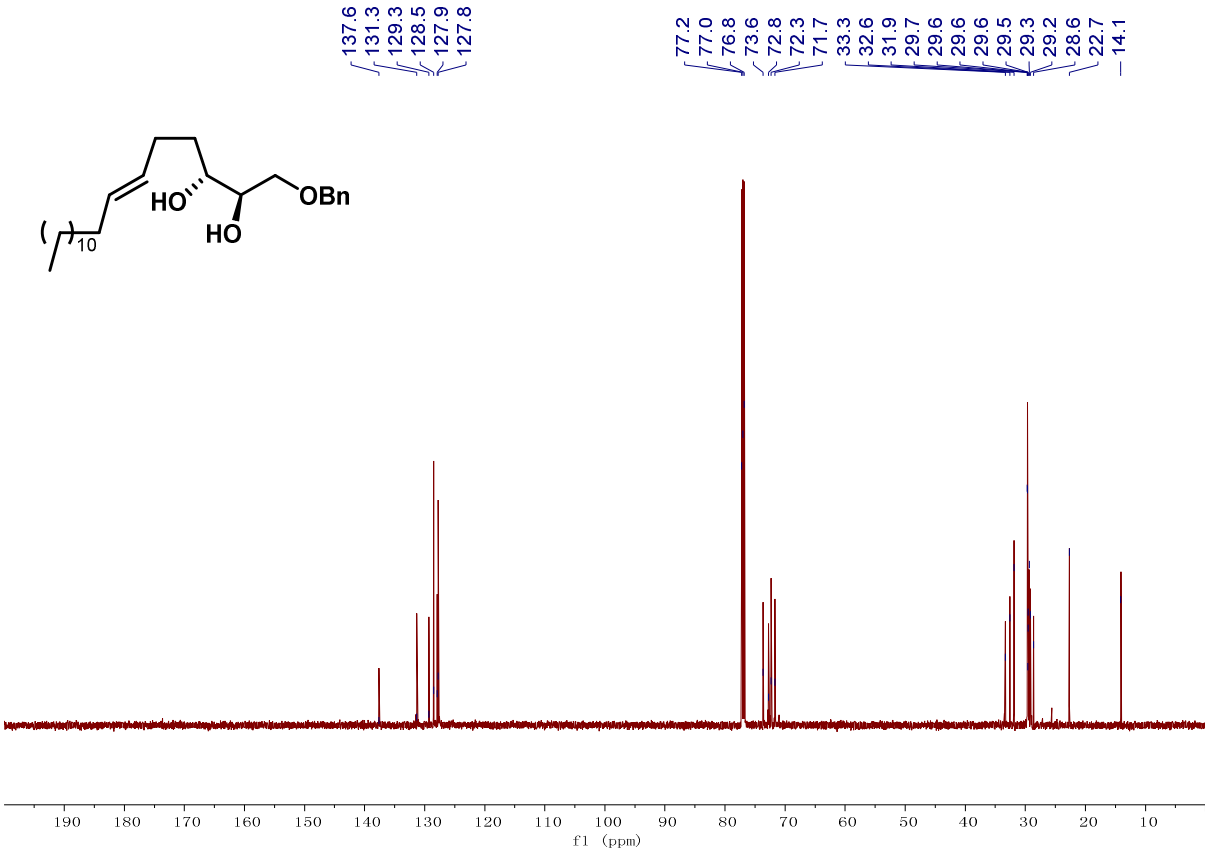
^{13}C NMR of Compound 51 (151 MHz, $CDCl_3$):



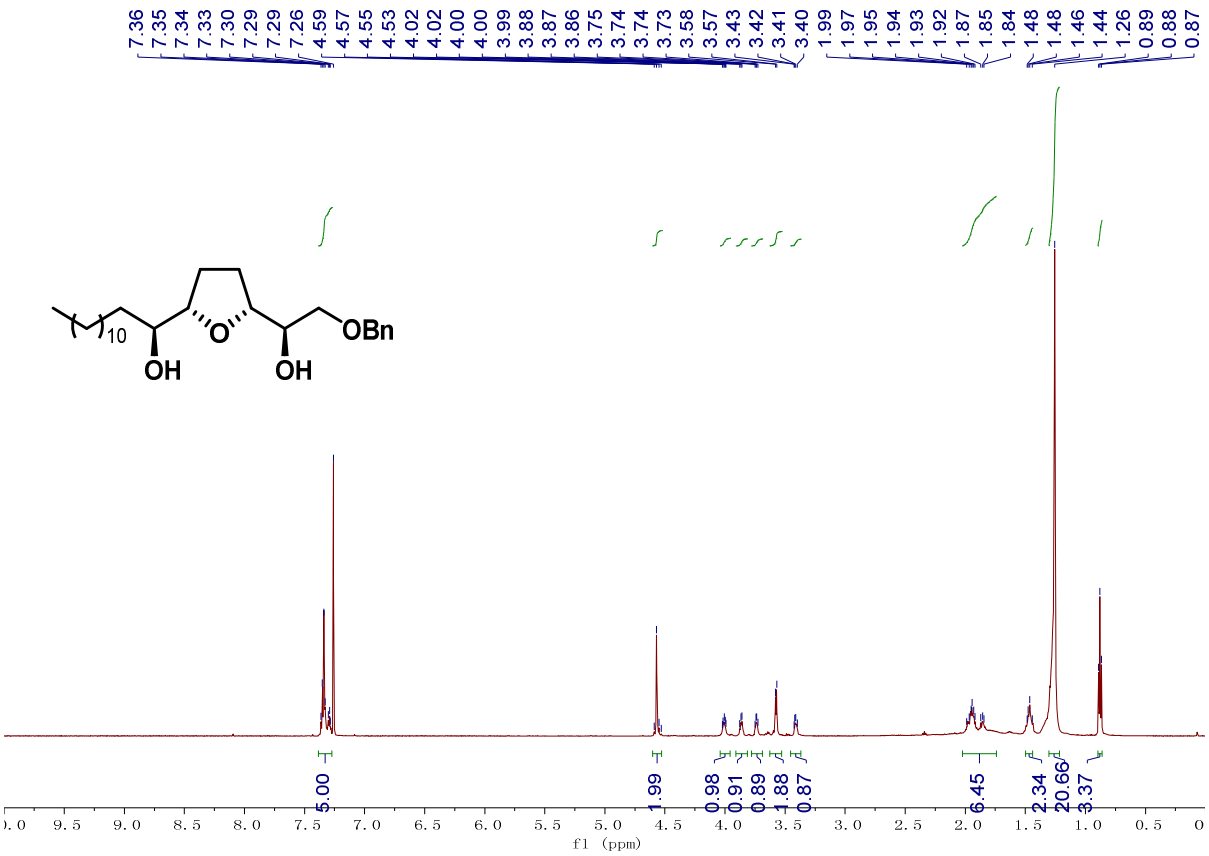
^{1}H NMR of Compound SI-73 (600 MHz, $CDCl_3$):



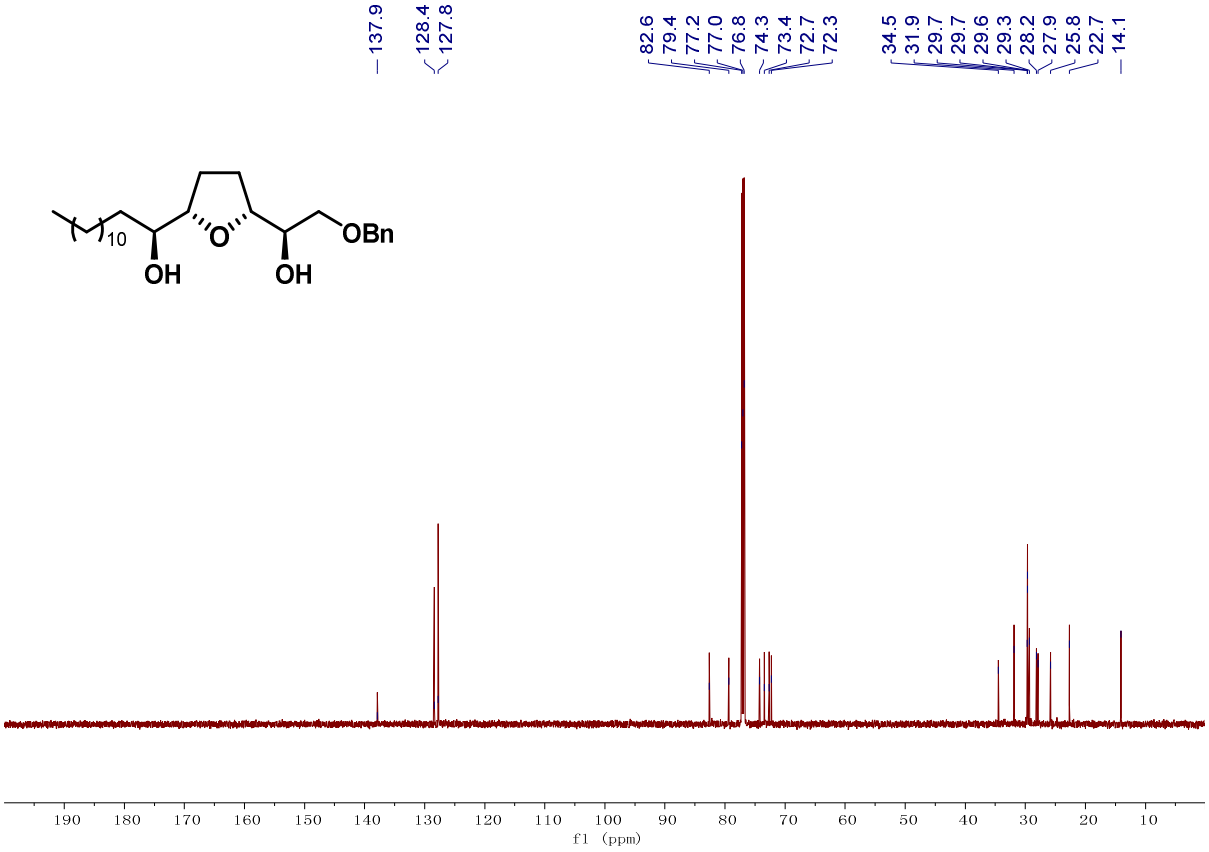
^{13}C NMR of Compound SI-73 (151 MHz, $CDCl_3$):



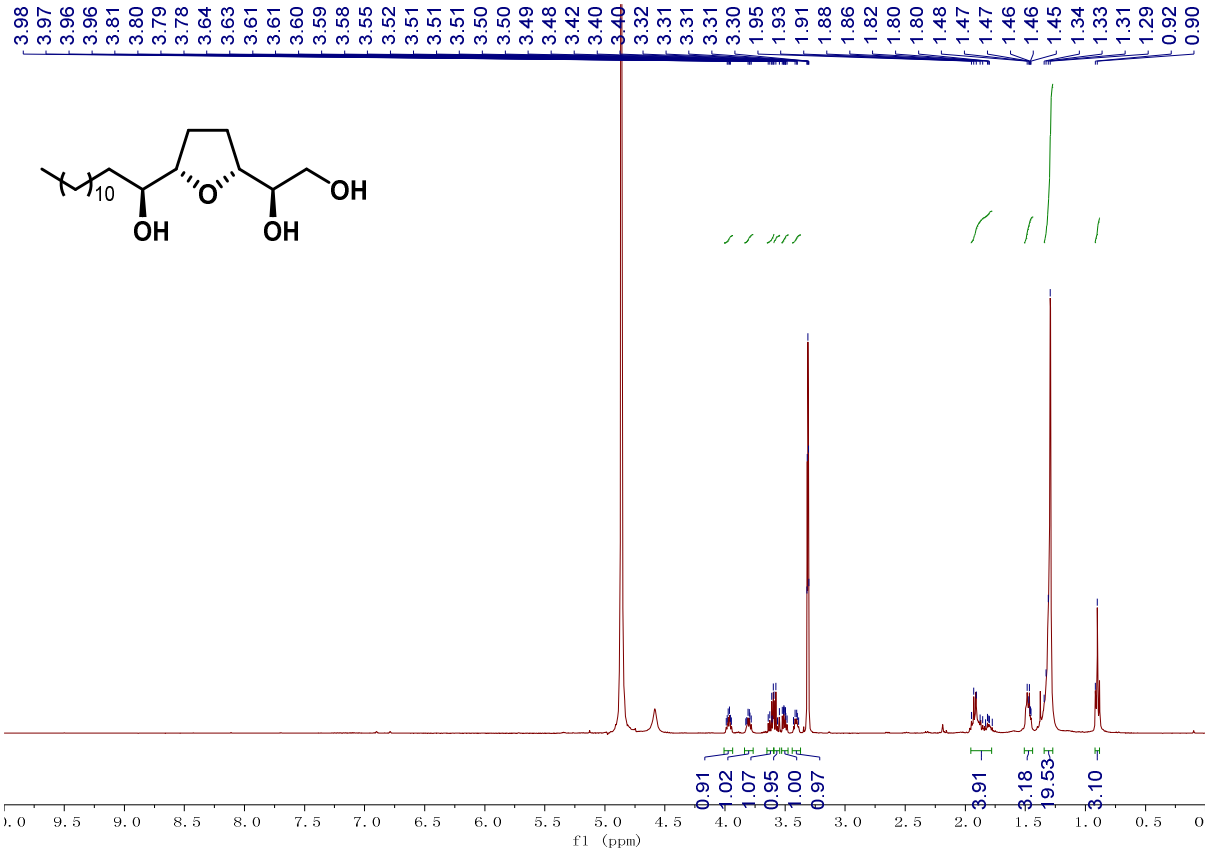
^{1}H NMR of Compound SI-74 (600 MHz, $CDCl_3$):



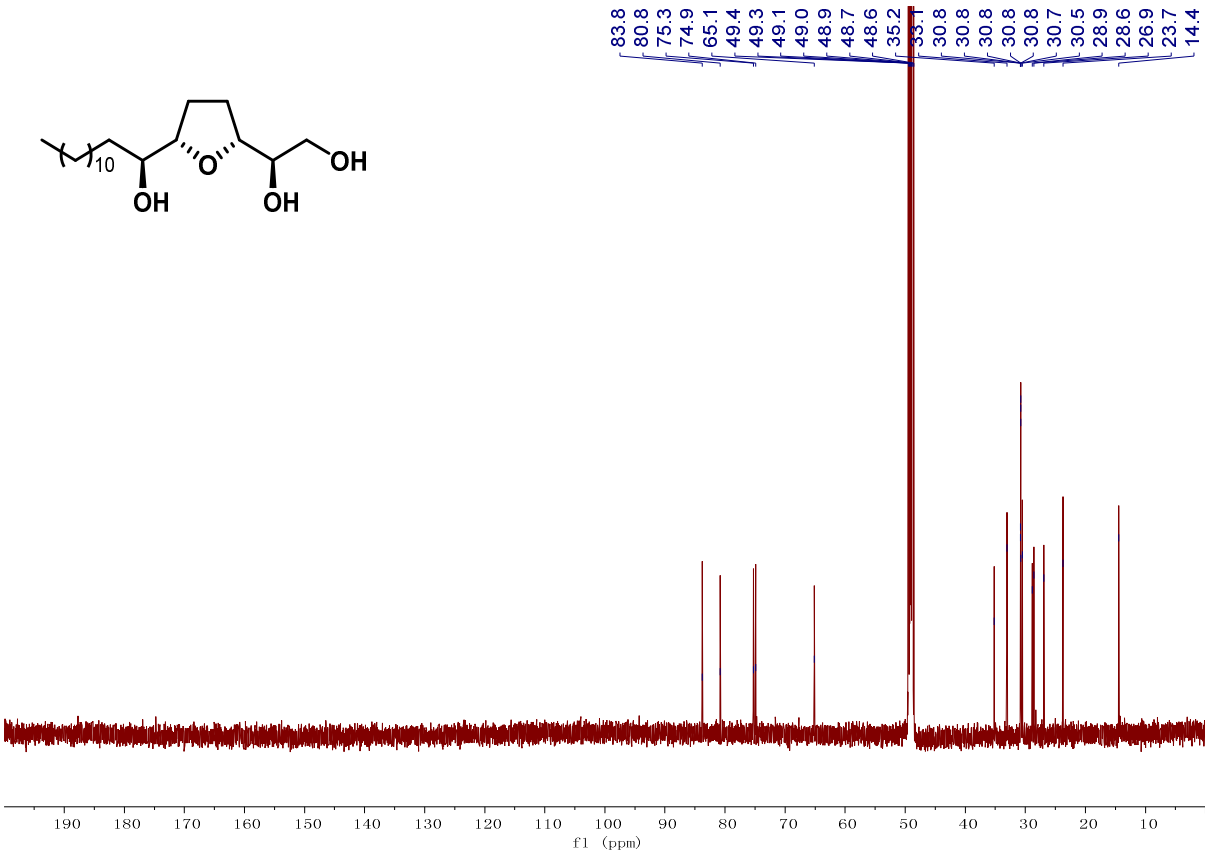
^{13}C NMR of Compound SI-74 (151 MHz, $CDCl_3$):



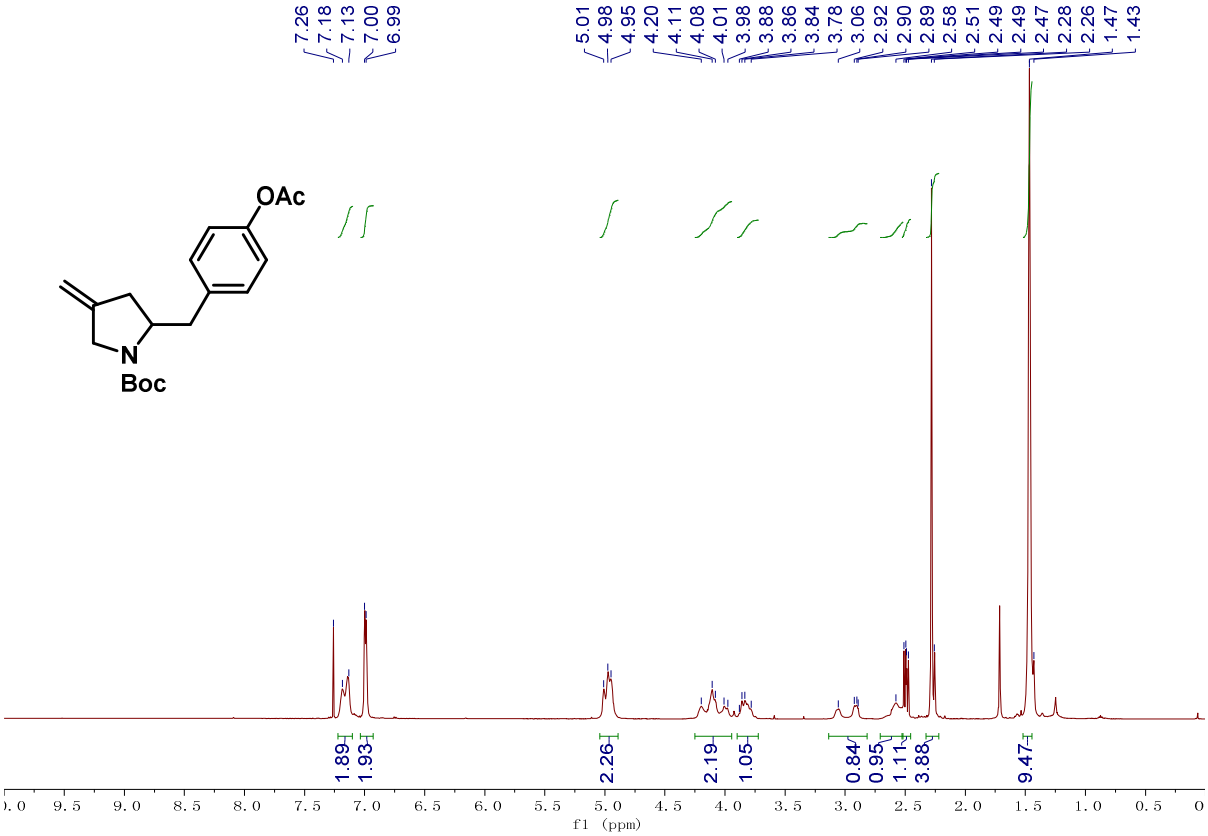
^{1}H NMR of Compound 52 (400 MHz, CD_3OD):



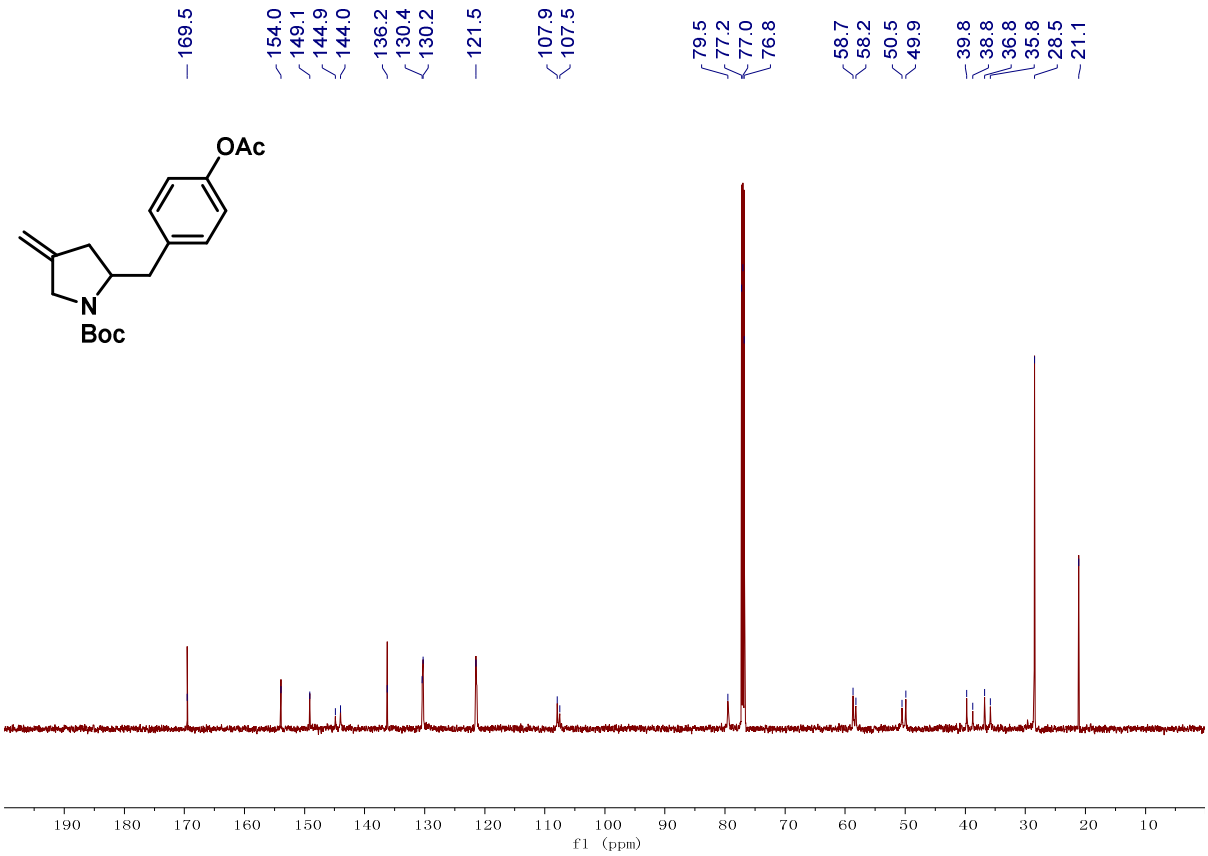
^{13}C NMR of Compound 52 (151 MHz, CD_3OD):



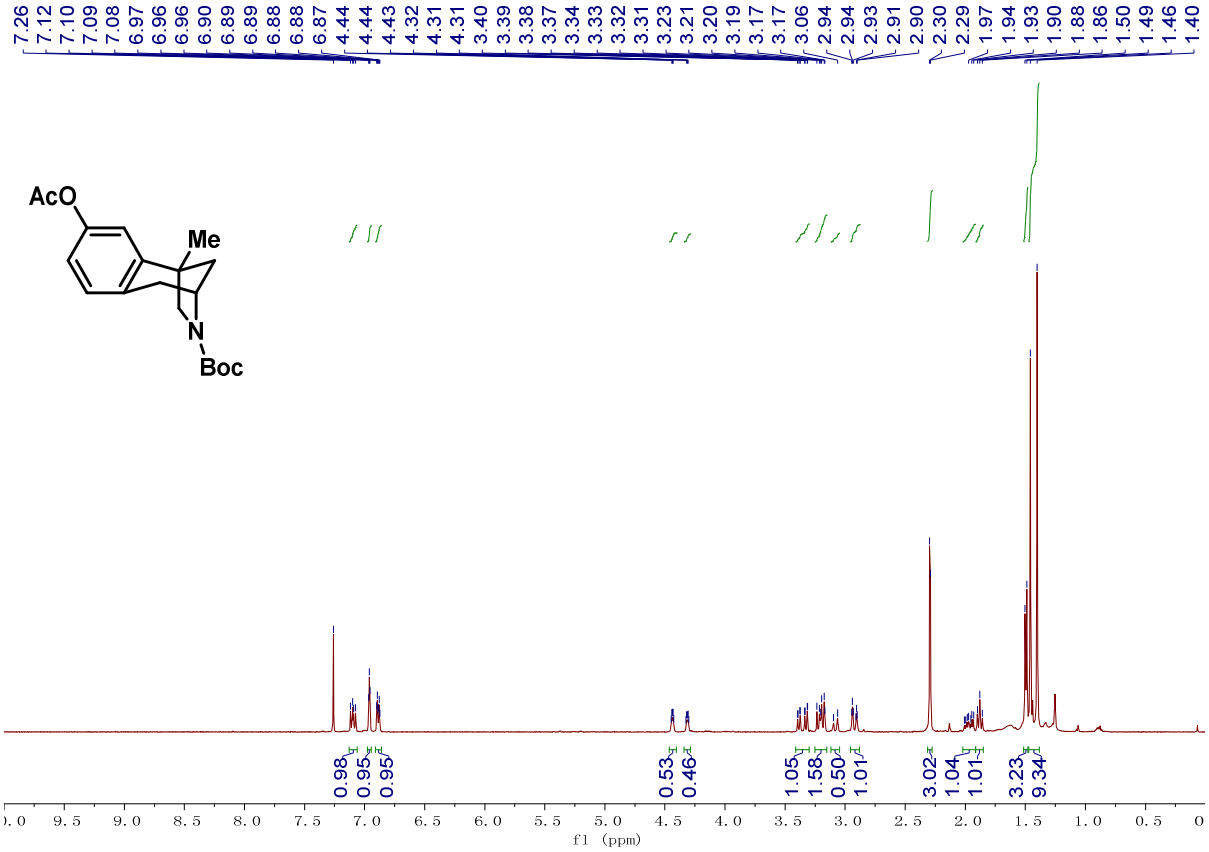
^{1}H NMR of Compound 55 (600 MHz, $CDCl_3$):



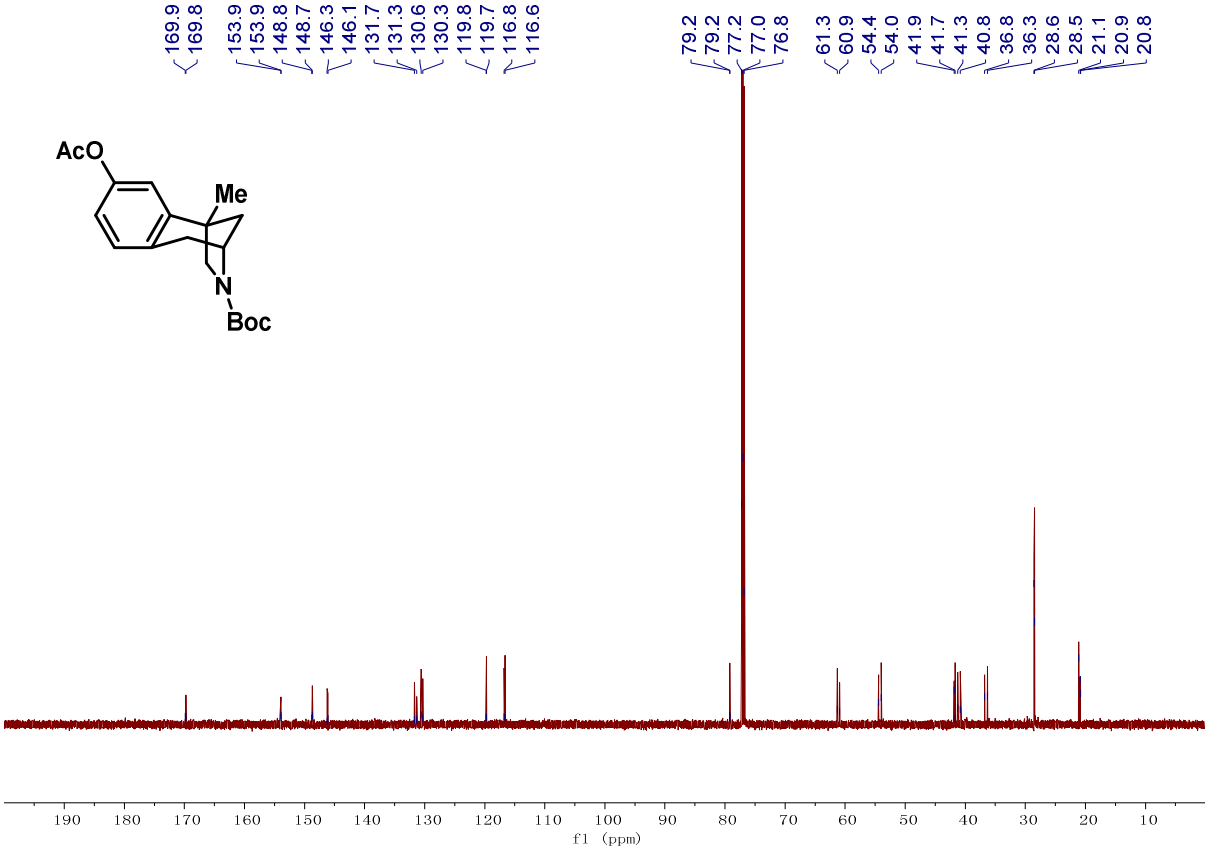
^{13}C NMR of Compound 55 (151 MHz, $CDCl_3$):



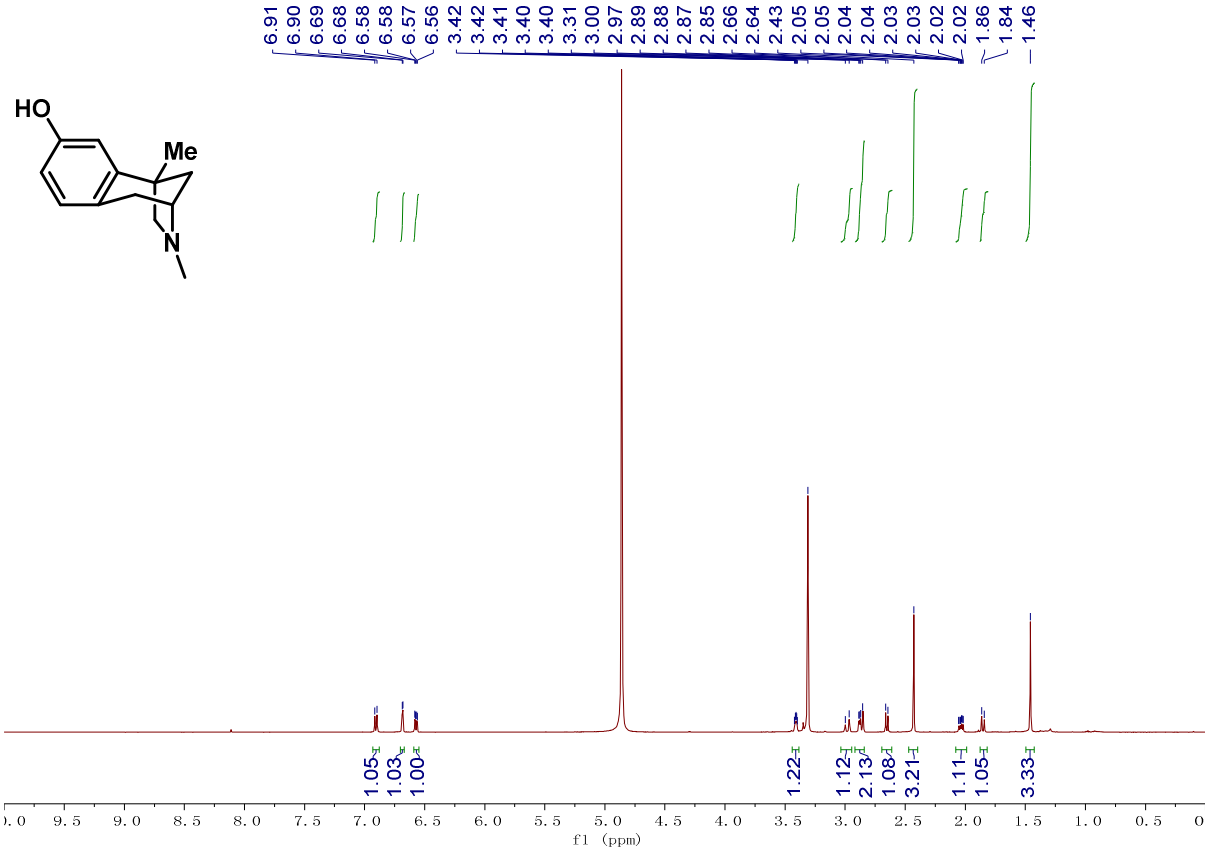
^{1}H NMR of Compound 56 (600 MHz, $CDCl_3$):



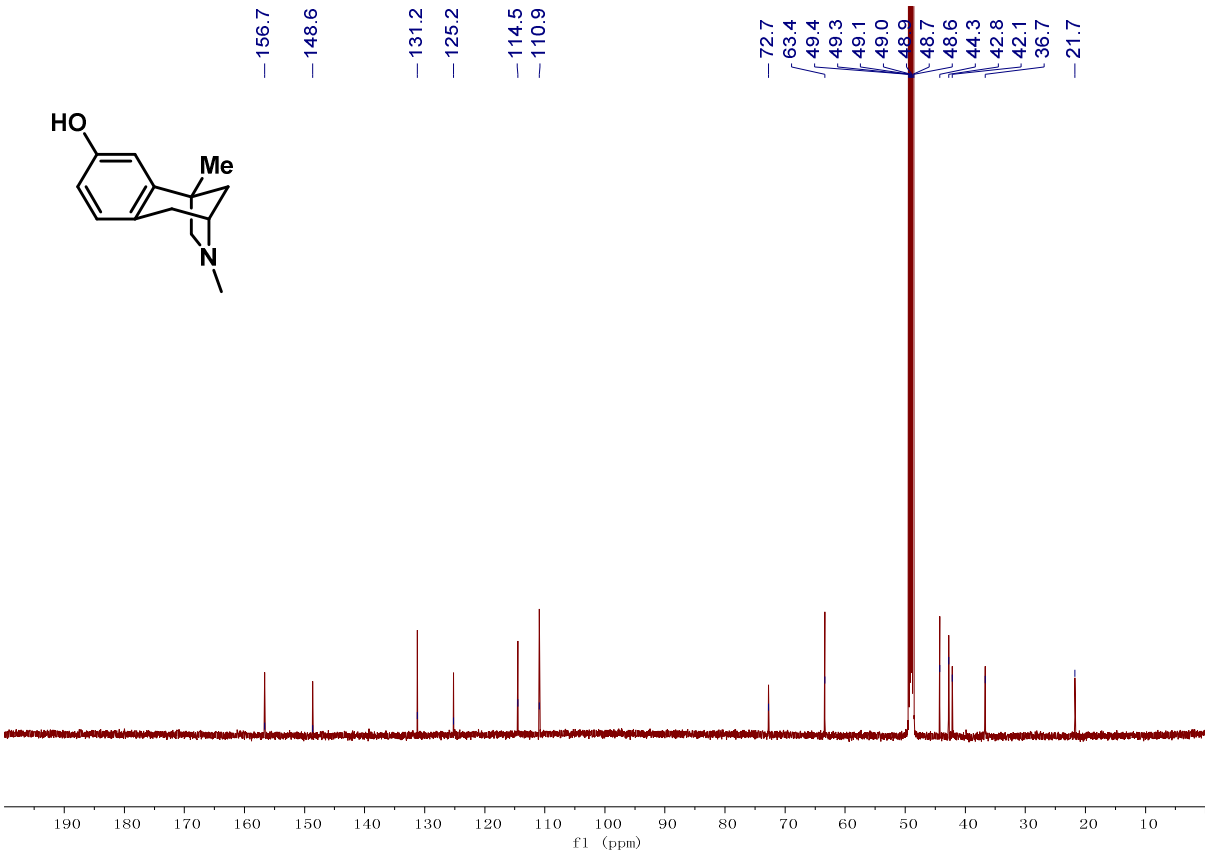
^{13}C NMR of Compound 56 (151 MHz, $CDCl_3$):



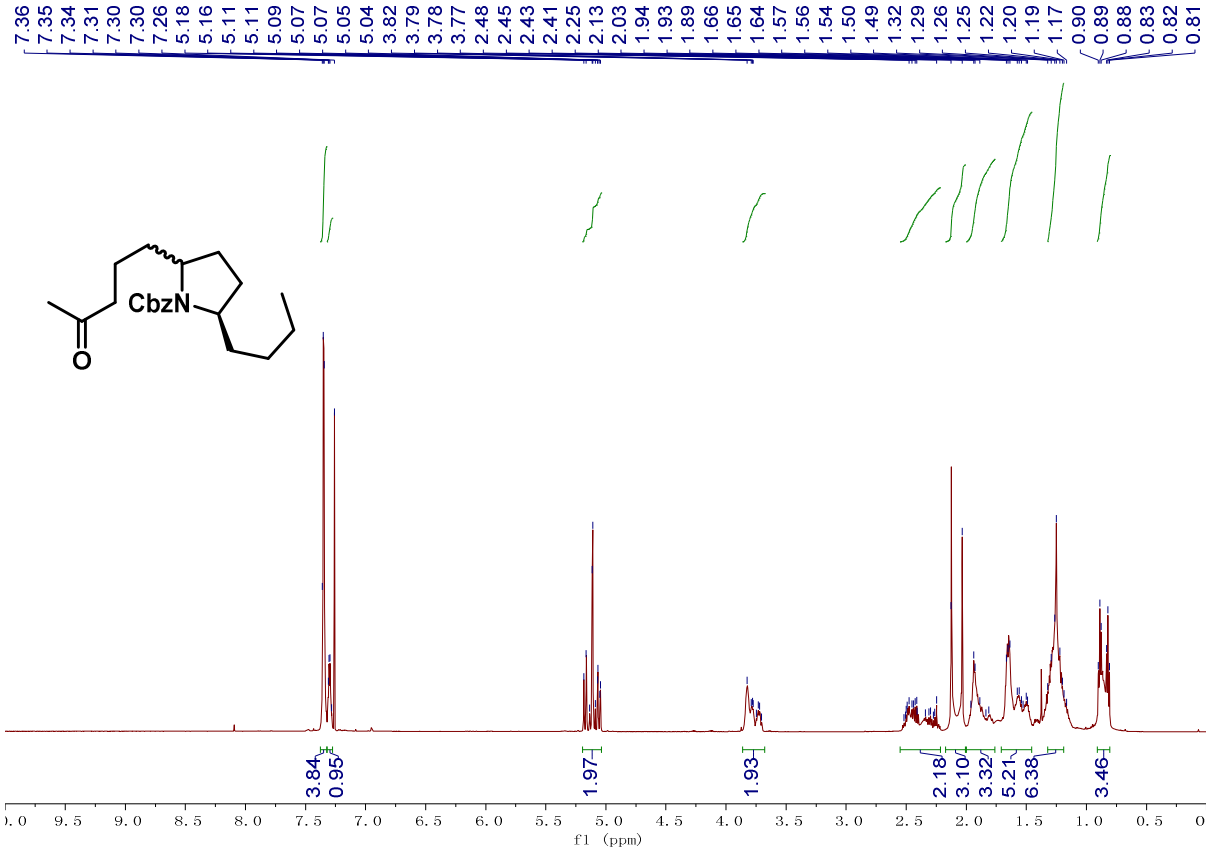
^{1}H NMR of Compound 57 (500 MHz, CD_3OD):



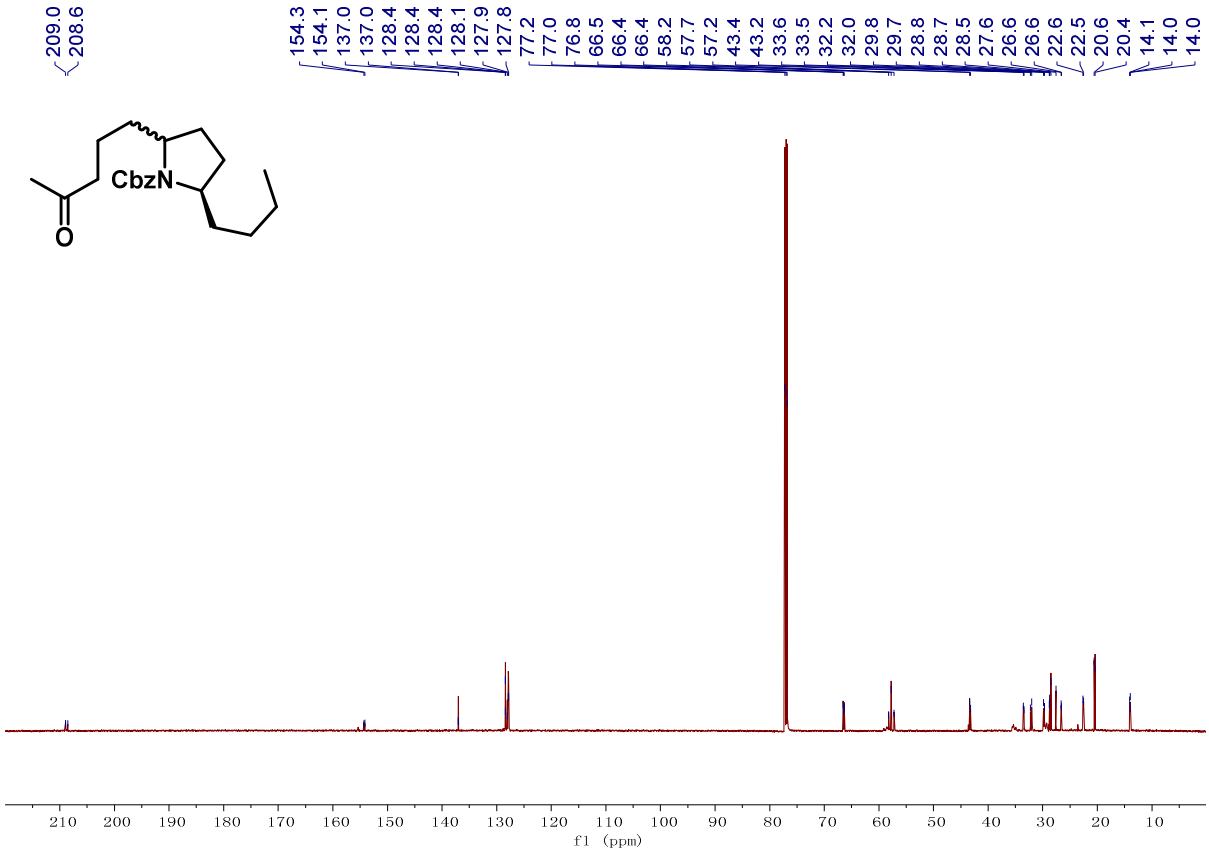
^{13}C NMR of Compound 57 (151 MHz, CD_3OD):



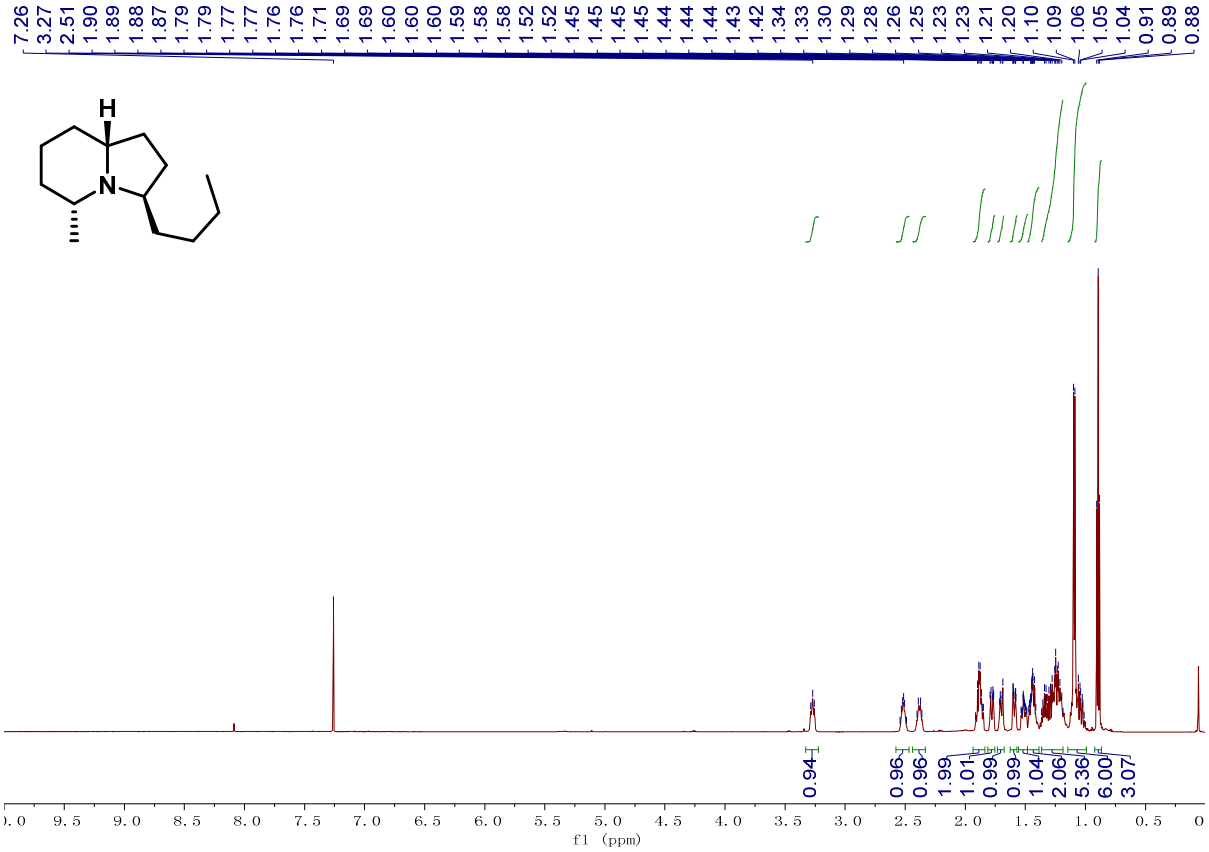
^{1}H NMR of Compound 60 (600 MHz, $CDCl_3$):



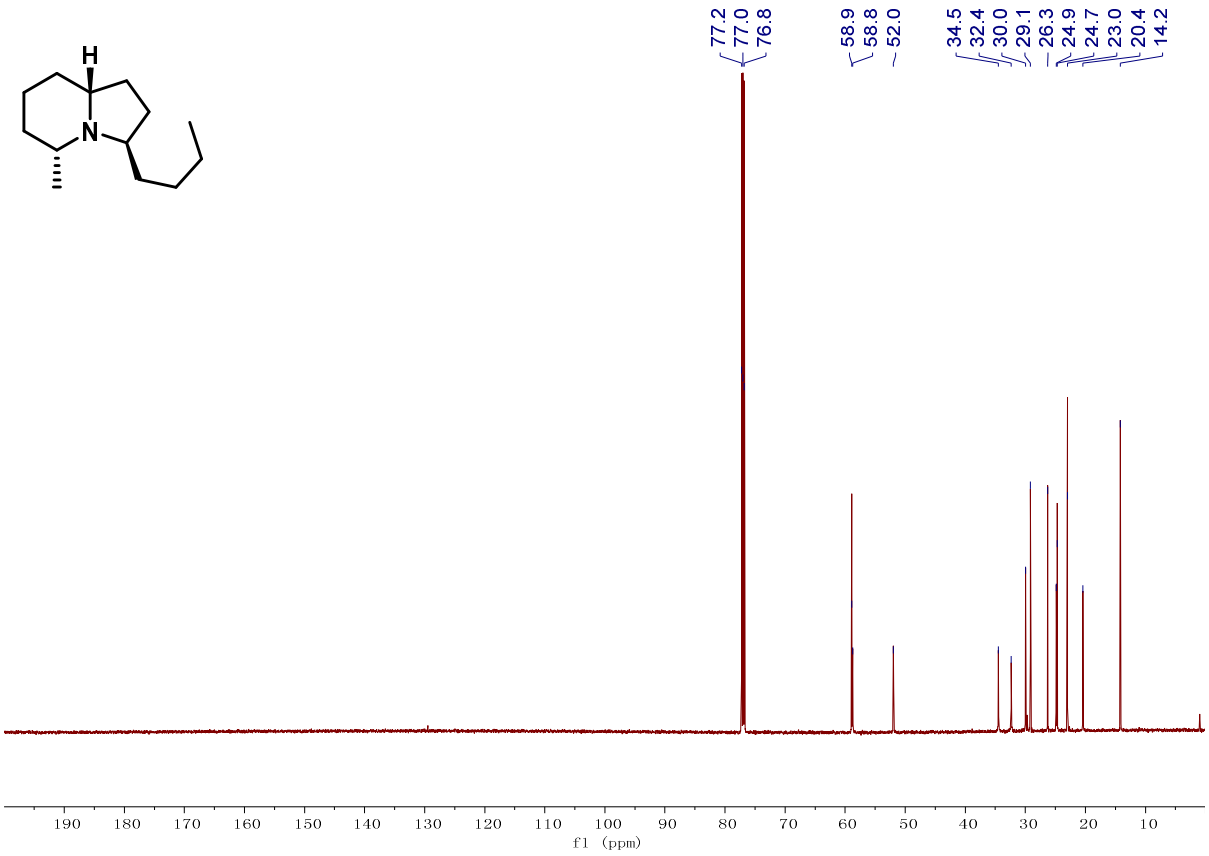
^{13}C NMR of Compound 60 (151 MHz, $CDCl_3$):



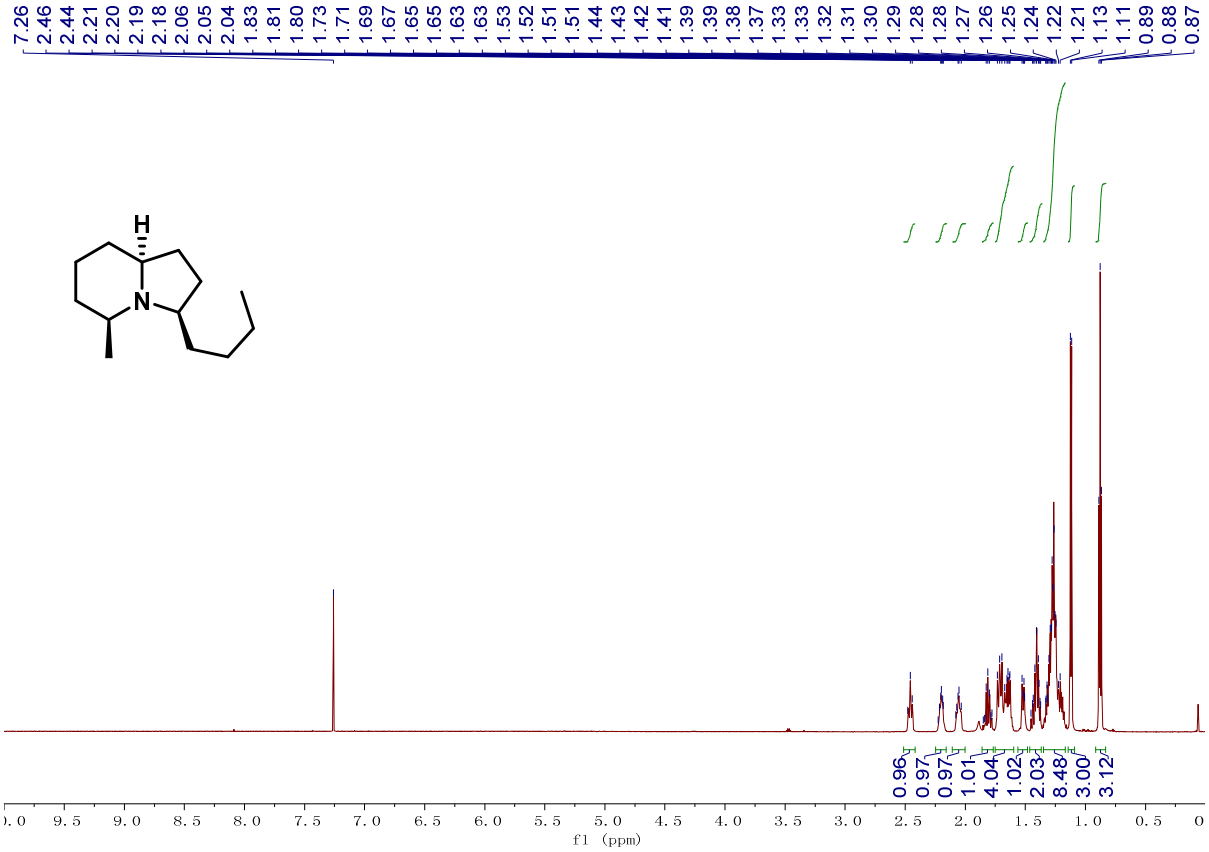
^{1}H NMR of Compound 61 (600 MHz, $CDCl_3$):



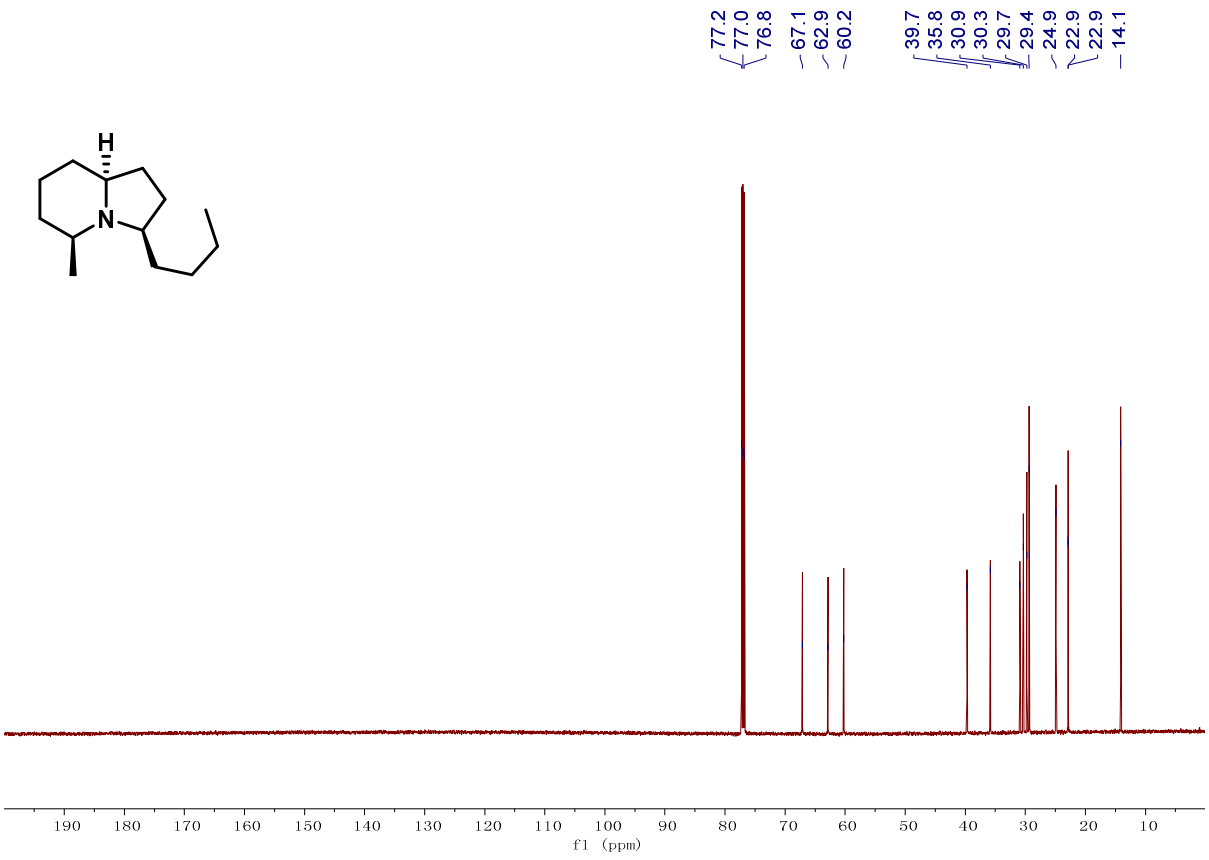
^{13}C NMR of Compound 61 (151 MHz, $CDCl_3$):



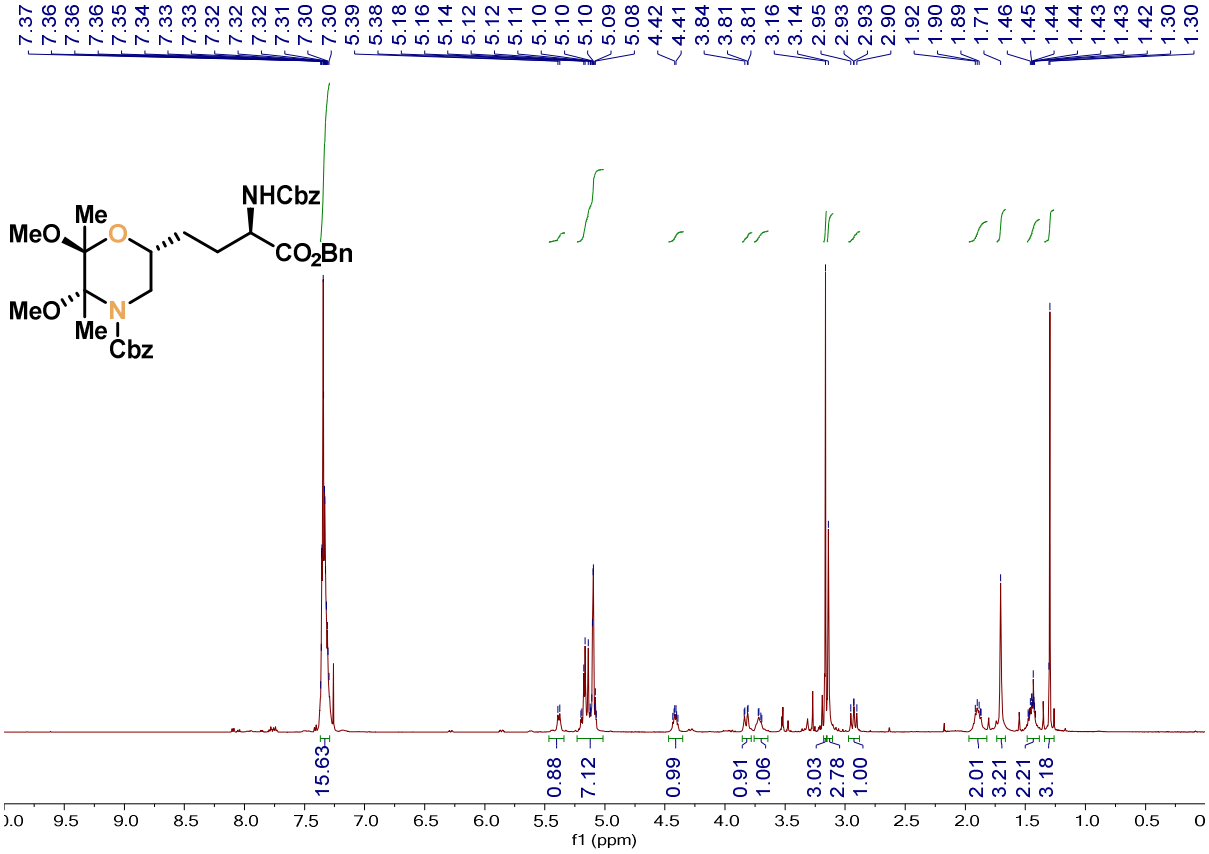
^{1}H NMR of Compound 62 (600 MHz, $CDCl_3$):



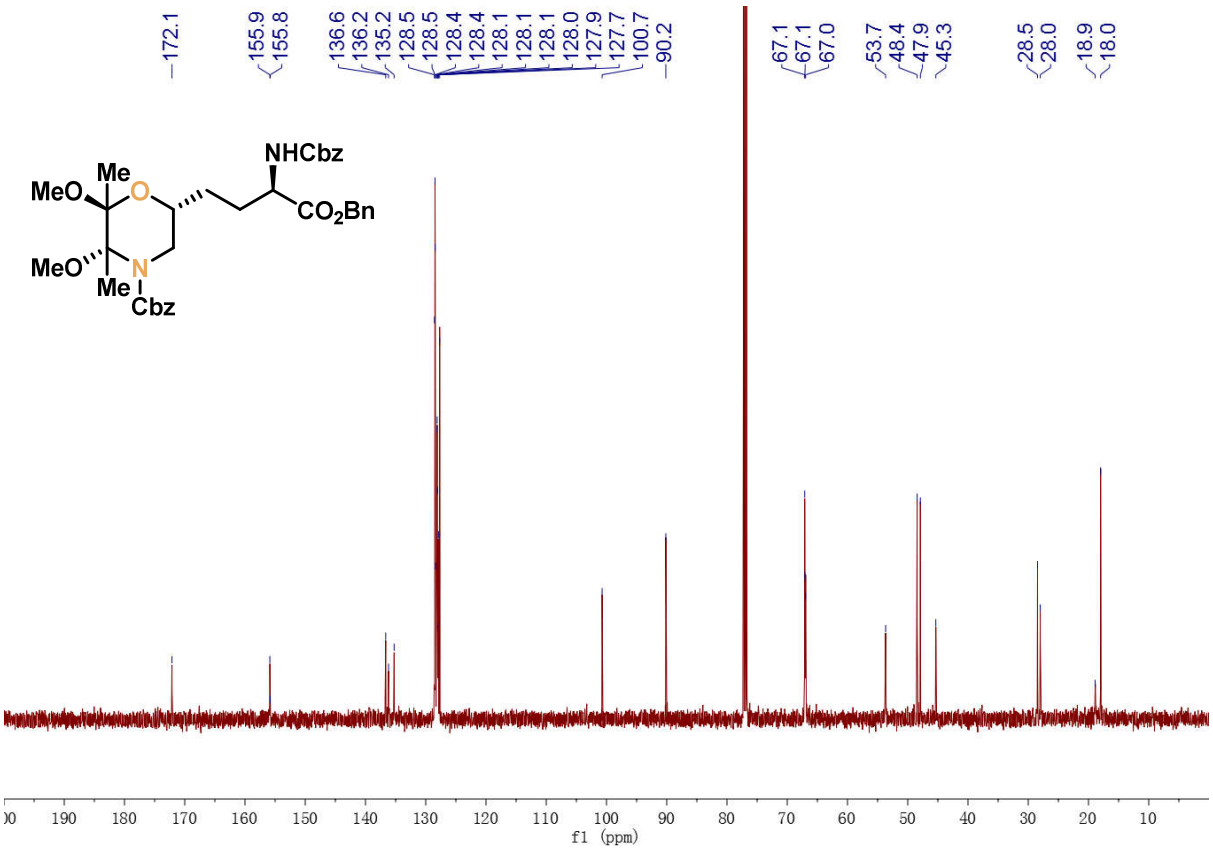
^{13}C NMR of Compound 62 (151 MHz, $CDCl_3$):



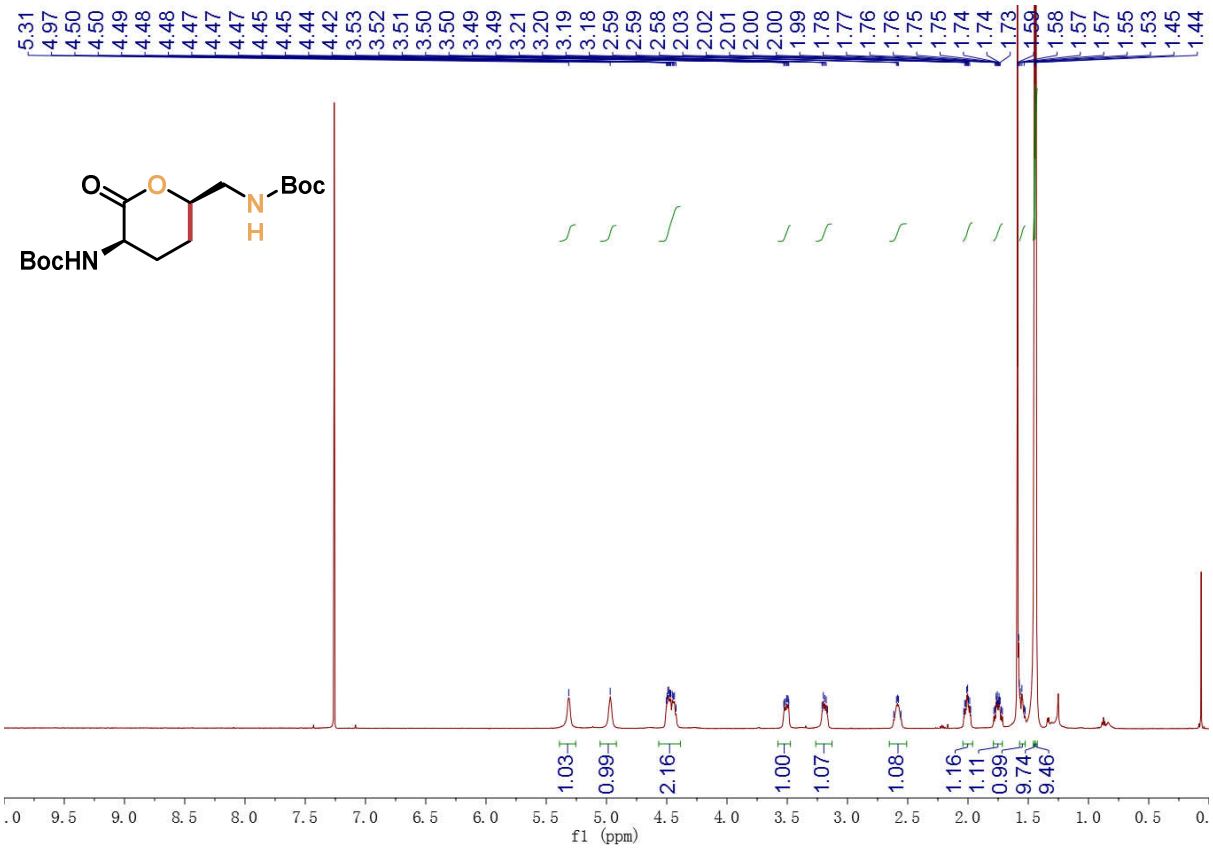
^{1}H NMR of Compound 65 (600 MHz, $CDCl_3$):



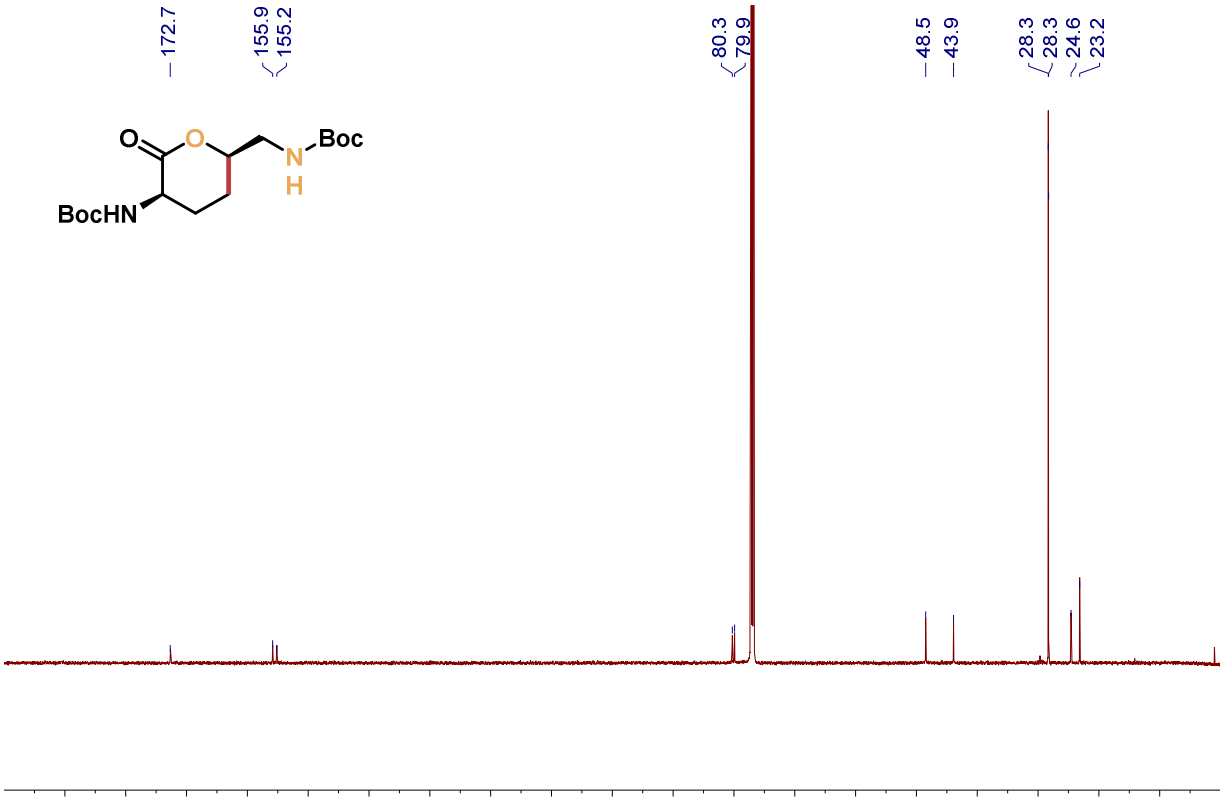
^{13}C NMR of Compound 65 (151 MHz, $CDCl_3$):



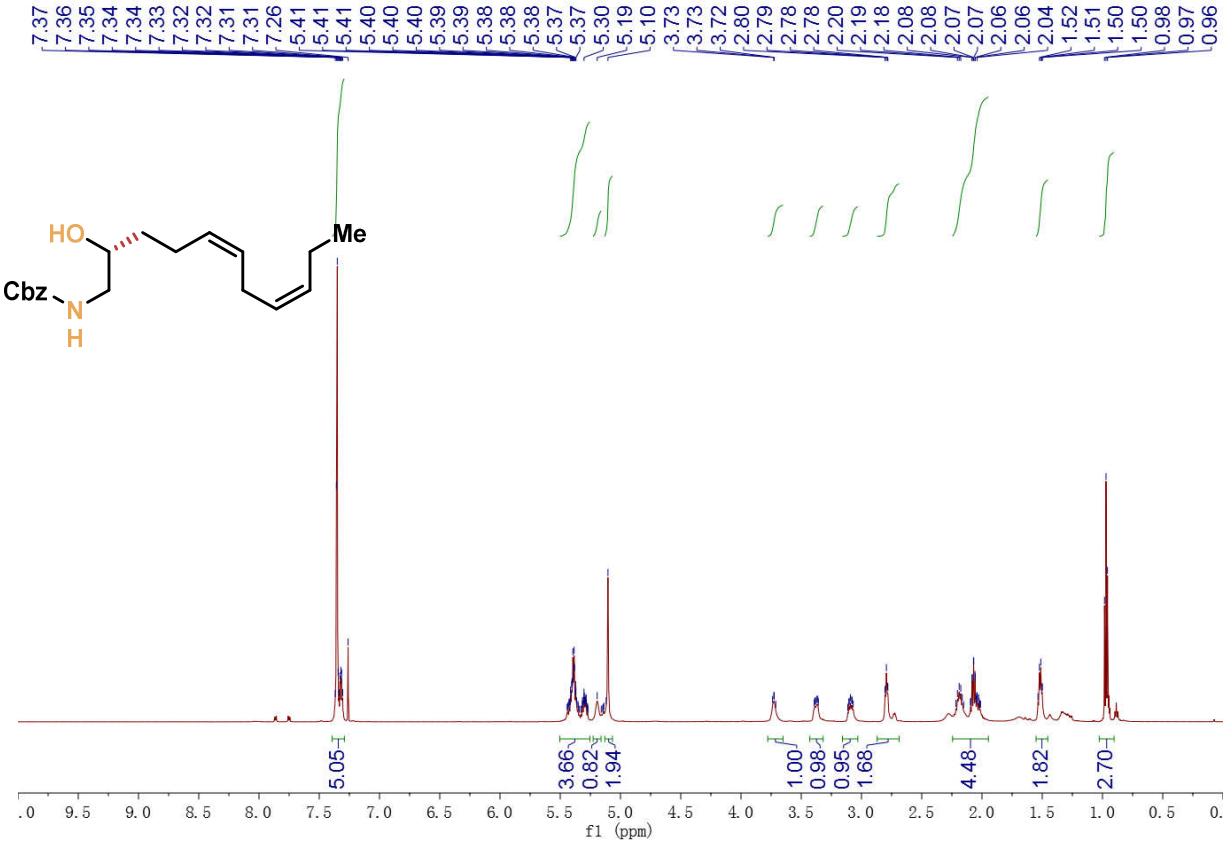
^{1}H NMR of Compound 66 (600 MHz, $CDCl_3$):



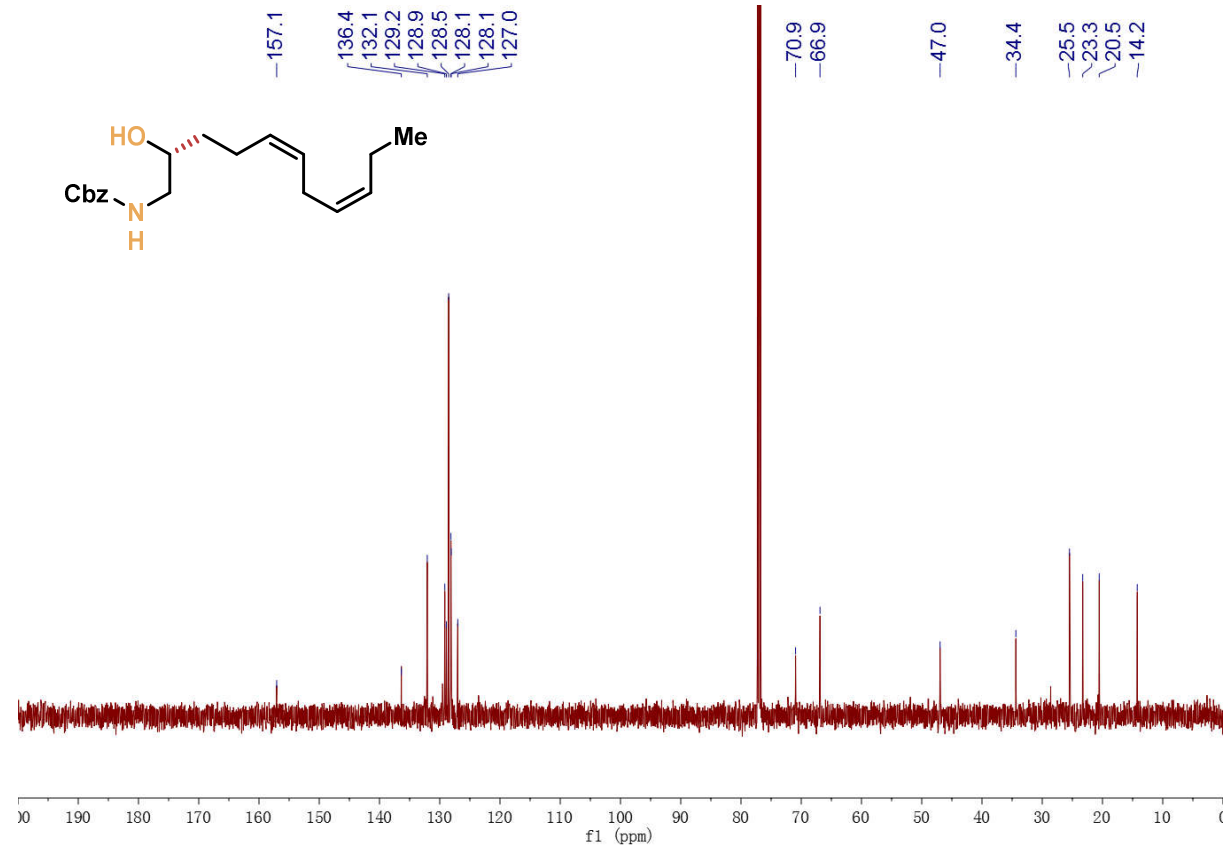
^{13}C NMR of Compound 66 (151 MHz, $CDCl_3$):



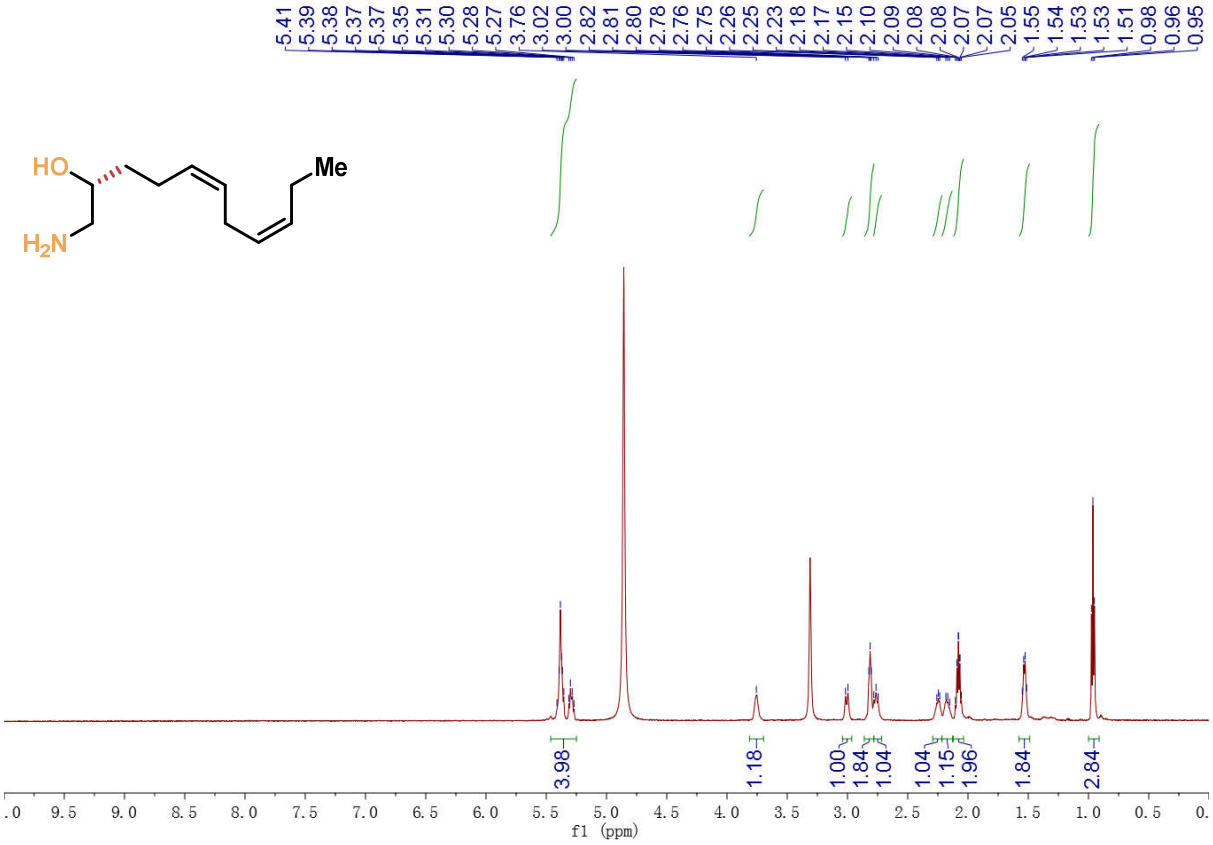
^{1}H NMR of Compound 69 (600 MHz, $CDCl_3$):



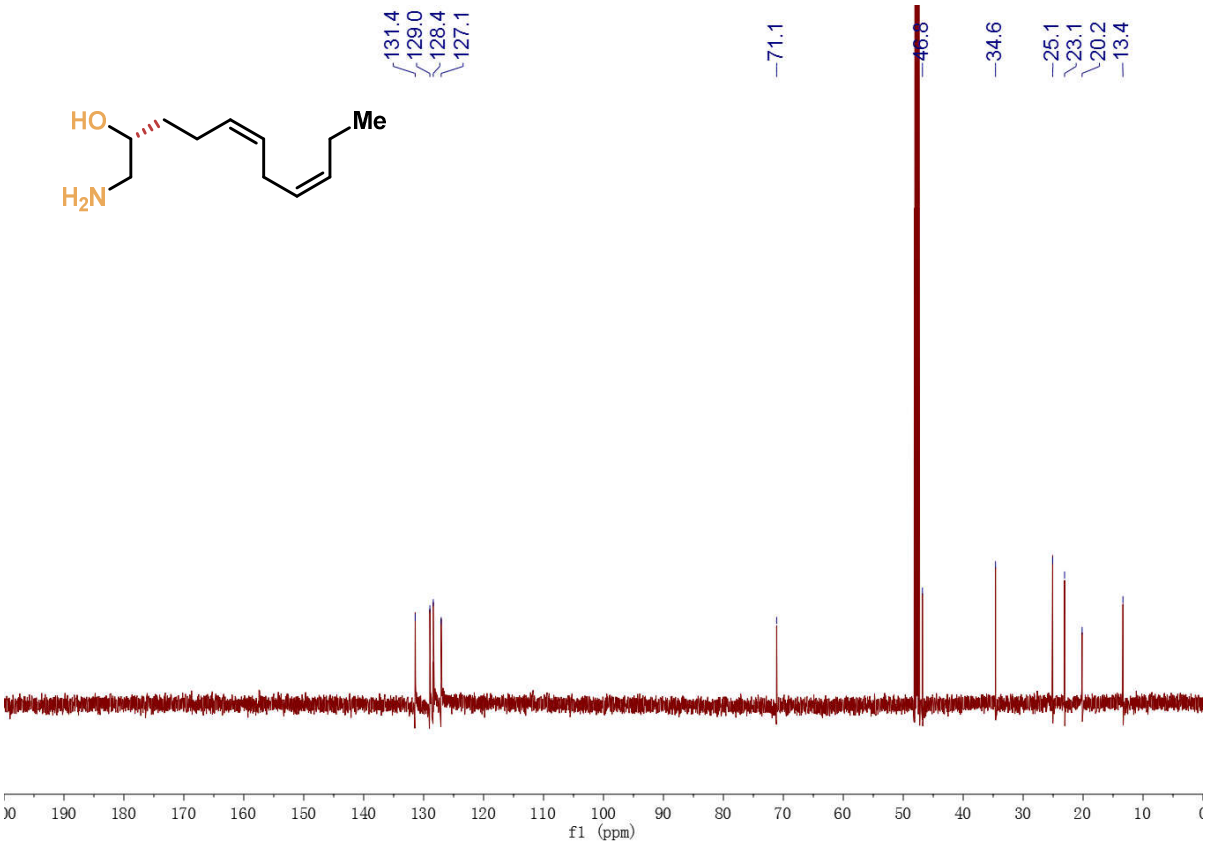
^{13}C NMR of Compound 69 (151 MHz, $CDCl_3$):



^{1}H NMR of Compound 70 (600 MHz, CD_3OD):



^{13}C NMR of Compound 70•HCl(151 MHz, CD_3OD):



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