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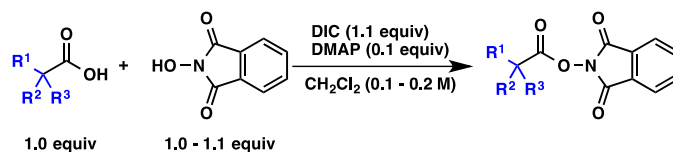
General Experimental

Tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), dichloromethane (CH₂Cl₂), and acetonitrile (MeCN) were obtained by passing the previously degassed solvents through an activated alumina column. Isopropanol (*i*-PrOH, from Fisher chemical, HPLC grade, not anhydrous) was used as received. DIC (*N,N'*-diisopropylcarbodiimide) was purchased from Chem-Impex. NiCl₂•6H₂O was purchased from Sigma-Aldrich (lot # MKBV1320V). Ni(ClO₄)₂•6H₂O was purchased from Strem Chemicals, Inc (lot # 25024400). Di-*t*BuBipy was purchased from Sigma-Aldrich. Zinc powder was purchased from Alfa Aesar (lot # H22X003). PhSiH₃ was purchased from Oakwood Chemical. All reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC), GC/MS, GC/FID, or LC/MS. 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, *p*-anisaldehyde, or KMnO₄ and heat as developing agents. NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and are calibrated using residual undeuterated solvent (CHCl₃ at 7.26 ppm ¹H NMR, 77.16 ppm ¹³C 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 gel (60, particle size 0.043–0.063 mm), and preparative TLC 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. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

Handling of [Ni] Catalysts

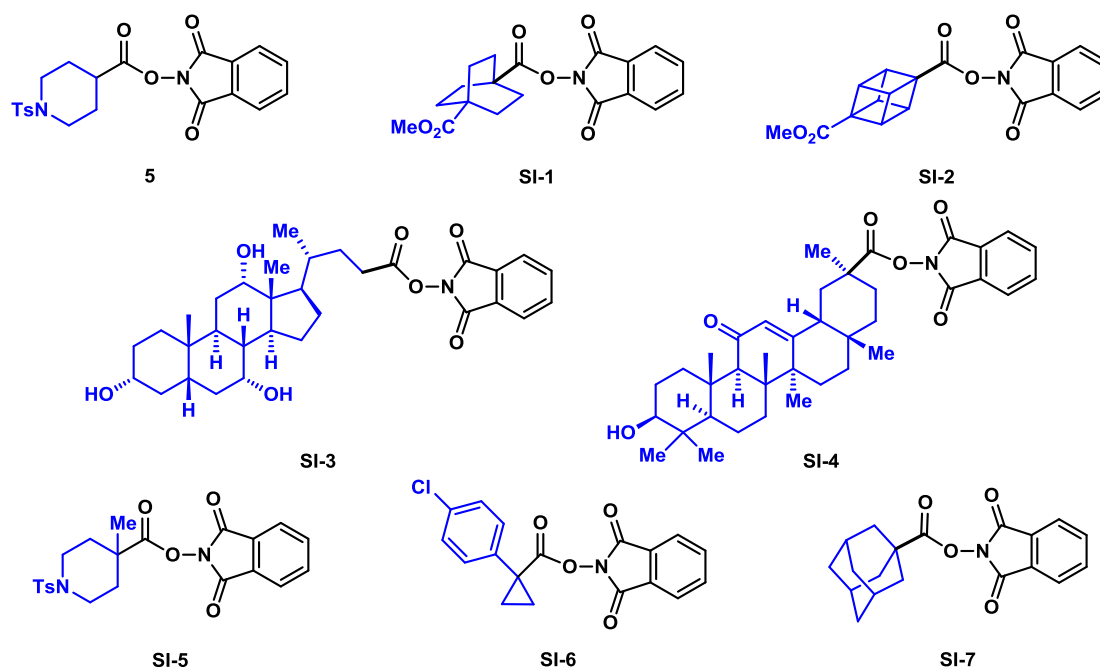
All nickel catalysts were handled open to air on the bench top, and the bottles were not stored under inert atmosphere.

General Procedure for the Synthesis of NHPI Redox-active Esters (General Procedure A)



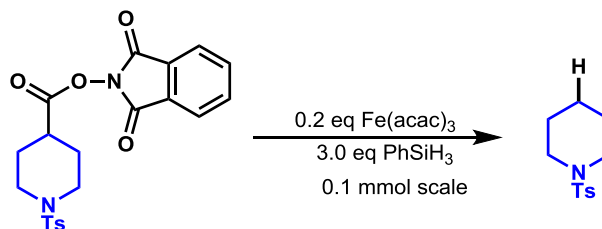
NHPI esters were prepared according to the previously reported procedure.^{1,2} In short, a round-bottom flask or culture tube was charged with (if solid) carboxylic acid (1.0 equiv), *N*-hydroxyphthalimide, 1.0 – 1.1 equiv.) and DMAP (0.1 equiv.). Dichloromethane was added (0.1 – 0.2 M), and the mixture was stirred vigorously. Carboxylic acid (1.0 equiv.) was added via syringe (if liquid). DIC (1.1 equiv.) was then added dropwise via syringe, and the mixture was allowed to stir until the acid was consumed (determined by TLC). Typical reaction times were between 0.5 h and 12 h. The mixture was filtered (through thin pads of Celite, SiO_2 , or through a fritted funnel) and rinsed with additional $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$. The solvent was removed under reduced pressure, and purification of the resulting residue by column chromatography afforded the desired NHPI redox-active ester.

We and others^{3,4} have previously reported the synthesis of redox-active esters shown below. Please see ref. 1-2 for graphical supporting information on the synthesis of NHPI RAEs.



Optimization Details for Decarboxylation

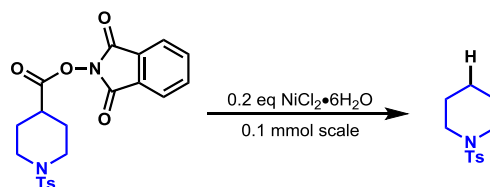
1. Using Fe(acac)₃ as catalyst



Ligand (0.3 equiv)	Solvent (0.5 mL)	Reductant (equiv)	Activation (equiv)	T (°C)	Time (h)	Yield(%) ^a
-	NMP	Zn (3.0)	TMSCI (3.0)	60	1	53
-	NMP	Zn (3.0)	TMSCI (3.0)	60	2	52
dppbz	NMP	Zn (3.0)	TMSCI (3.0)	60	1	56
-	NMP	Zn (3.0)	TMSCI/1,2-dibromoethane (1 drop)	60	1	trace
-	NMP	Mn(3.0)	TMSCI (3.0)	60	1	52
dppbz	NMP	Zn (3.0)	TMSCI (3.0)	rt	1	57
dppbz	MeCN	Zn (3.0)	TMSCI (3.0)	60	1	54
dppbz	THF	Zn (3.0)	TMSCI (3.0)	60	1	14
dppbz	1,4-dioxane	Zn (3.0)	TMSCI (3.0)	60	1	18
dppbz	DMA	Zn (3.0)	TMSCI (3.0)	60	1	53
dppbz	DMF	Zn (3.0)	TMSCI (3.0)	60	1	53
dppbz	DMF	Zn (3.0)	TMSCI (3.0)	rt	1	59
dppbz	DMF	Zn (3.0)	TMSCI (3.0)	40	1	57
-	DMF	Zn (3.0)	TMSCI (3.0)	60	1	29
dppbz	DMF	Zn (3.0)	TMSCI (3.0)/1,2-dibromoethane (0.3)	60	1	16
-	DMF	Zn (3.0)	-	rt	1	0

^a. Yield was determined by GC using dodecane as standard

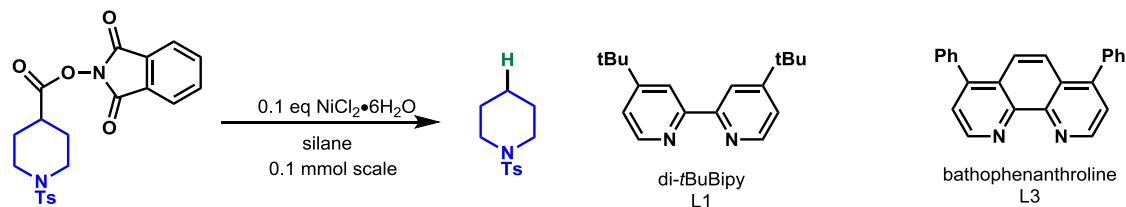
2. Using NiCl₂•6H₂O as catalyst (activated Zn)



Ligand	Solvent	Zn	Activation	PhSiH ₃	Temperature	Time	Yield ^a
–	0.5 mL NMP	3 eq	3 eq TMSCl	3 eq	60°C	1 h	50%
–	0.5 mL MeCN	3 eq	3 eq TMSCl	3 eq	60°C	1 h	0%
–	0.5 mL THF	3 eq	3 eq TMSCl	3 eq	60°C	1 h	0%
–	0.5 mL dioxane	3 eq	3 eq TMSCl	3 eq	60°C	1 h	0%
–	0.5 mL DMA	3 eq	3 eq TMSCl	3 eq	60°C	1 h	0%
–	0.5 mL DMF	3 eq	3 eq TMSCl	3 eq	60°C	1 h	0%
0.2 eq bitByPy	0.5 mL DMF	3 eq	3 eq TMSCl	3 eq	RT	1 h	23%
0.4 eq bitByPy	0.5 mL DMF	3 eq	3 eq TMSCl	3 eq	RT	1 h	47%
0.2 eq batho	0.5 mL DMF	3 eq	3 eq TMSCl	3 eq	RT	1 h	51%
0.4 eq batho	0.5 mL DMF	3 eq	3 eq TMSCl	3 eq	RT	1 h	55%
0.4 eq batho	0.5 mL DMF	3 eq	1 eq TMSCl	3 eq	RT	1 h	63%
0.4 eq batho	0.5 mL DMF	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	65%
0.4 eq batho	0.5 mL DMF	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	4 h	64%
0.4 eq batho	0.5 mL DMF	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq PMHS	RT	1 h	46%
0.4 eq batho	0.5 mL DMF	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	20% (substrate added later)
0.4 eq batho	0.5 mL DMF	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	8% (tetrachloro substrate)
0.4 eq batho	0.5 mL THF	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	79%
0.4 eq batho	0.5 mL NMP	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	66%
0.4 eq batho	0.5 mL DMA	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	66%
0.4 eq batho	0.5 mL dioxane	3 eq	0.3 eq TMSCl and 0.3 eq (BrCH ₂) ₂	3 eq	RT	1 h	64%
0.4 eq batho	0.5 mL DMF	1.5 eq	0.3 eq TMSCl and 0.15 eq (BrCH ₂) ₂	3 eq	RT	1 h	64%
0.4 eq batho	1 mL DMF	1.5 eq	0.3 eq TMSCl and 0.15 eq (BrCH ₂) ₂	3 eq	RT	1 h	58%
0.4 eq batho	2 mL DMF	1.5 eq	0.3 eq TMSCl and 0.15 eq (BrCH ₂) ₂	3 eq	RT	1 h	55%

^a Yield was determined by GC using dodecane as standard

3. Using NiCl₂•6H₂O as catalyst (unactivated Zn)

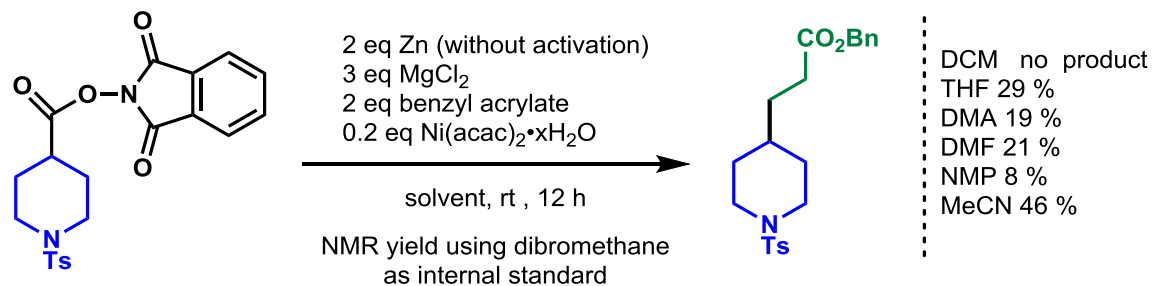


Ligand (0.2 equiv)	Solvent (0.5 mL)	Reductant (equiv)	Additive (equiv)	Silane (equiv)	T (°C)	Time (h)	Yield(%) ^a
L3	MeCN	Zn (3.0)	-	PhSiH ₃ (1.5)	rt	1	62
L3	DMA	Zn (3.0)	-	PhSiH ₃ (1.5)	rt	1	45
L3	MeCN	Zn (3.0)	LiCl (3 equiv)	PhSiH ₃ (1.5)	rt	1	49
L3	MeCN	Zn (3.0)	LiCl (3 equiv) TMSCl/1,2-dibromoethane (1 drop)	PhSiH ₃ (1.5)	rt	1	0
L3	THF	Zn (3.0)	LiCl (3 equiv) TMSCl/1,2-dibromoethane (1 drop)	PhSiH ₃ (1.5)	rt	1	0
L3	MeCN	Mn (3.0)	-	PhSiH ₃ (1.5)	rt	1	64
L3	MeCN	Zn (3.0)	K ₂ CO ₃ (1 equiv)	PhSiH ₃ (1.5)	rt	1	33
L3	MeCN	Zn (0.5)	-	PhSiH ₃ (1.5)	rt	1	65
L3	THF	Mn (0.5)	-	PhSiH ₃ (1.5)	rt	1	47
L3	THF	Zn (0.2)	-	PhSiH ₃ (1.5)	rt	1	trace
L3	MeCN	Zn (0.5)	-	iPr ₃ SiH (1.5)	rt	1	0
L1	THF	Zn (0.2)	-	PhSiH ₃ (2.0)	rt	2.5	65
L1	THF	Zn (0.2)	-	PhSiH ₃ (1.5)	rt	1	61
L1	THF	Zn (0.2)	iPrOH (15 μL)	PhSiH ₃ (1.5)	rt	2.5	65
L1	THF	Zn (0.2)	iPrOH (15 μL)	PhSiH ₃ (1.5)	40	1	72
L1	THF	Zn (0.2)	EtOH (15 μL)	PhSiH ₃ (1.5)	40	1	69
L1	THF	Zn (0.2)	4-OMe phenol (2 equiv)	PhSiH ₃ (1.5)	40	1	73
L1	THF	Zn (0.2)	-	PhSiH ₃ (1.5)	40	1	65
L1	iPrOH	Zn (0.2)	-	PhSiH ₃ (1.5)	rt	2.5	25
L1	DMF	Zn (0.2)	tBusH (23 μL)	PhSiH ₃ (1.5)	rt	1	46
L1	DMF	Zn (0.2)	tBusH (23 μL)	-	rt	1	21
L1	DMF	Zn (0.2)	Hantzsch Ester (0.2 equiv)	PhSiH ₃ (1.5)	rt	1	67

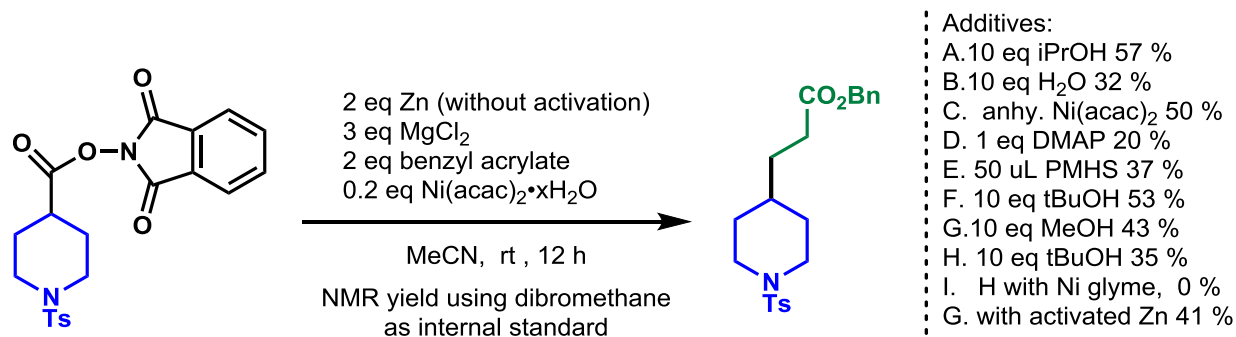
^a. Yield was determined by GC using dodecane as standard

Optimization Details for Conjugate Addition

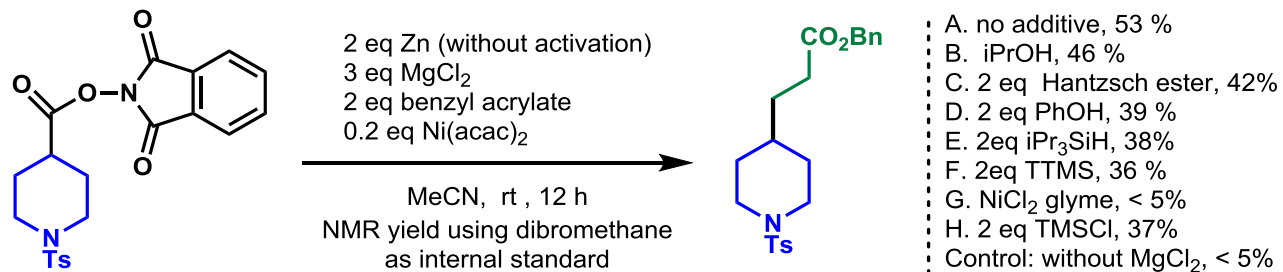
1. Solvent Screening Using Ni(acac)₂·xH₂O/MgCl₂



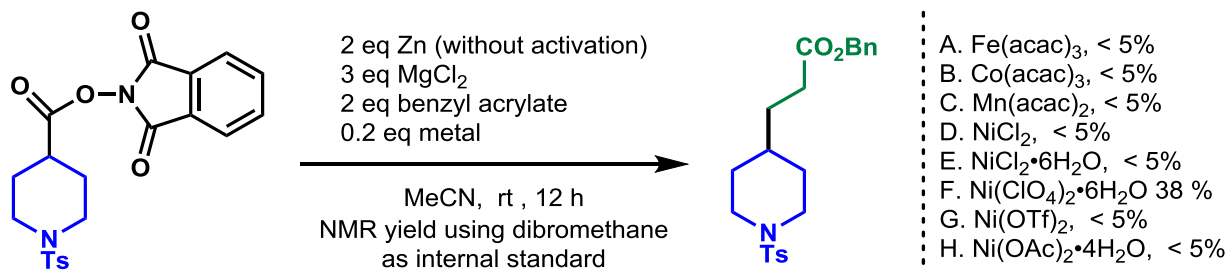
2. Additives Screening Using Ni(acac)₂·xH₂O/MgCl₂



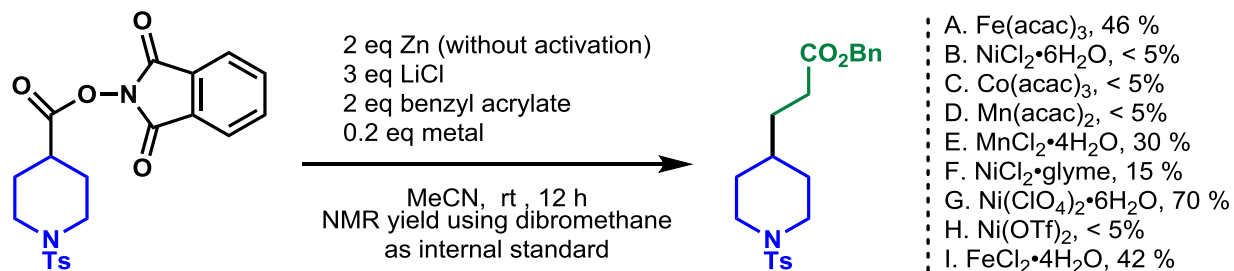
3. Additives Screening Using Ni(acac)₂/MgCl₂



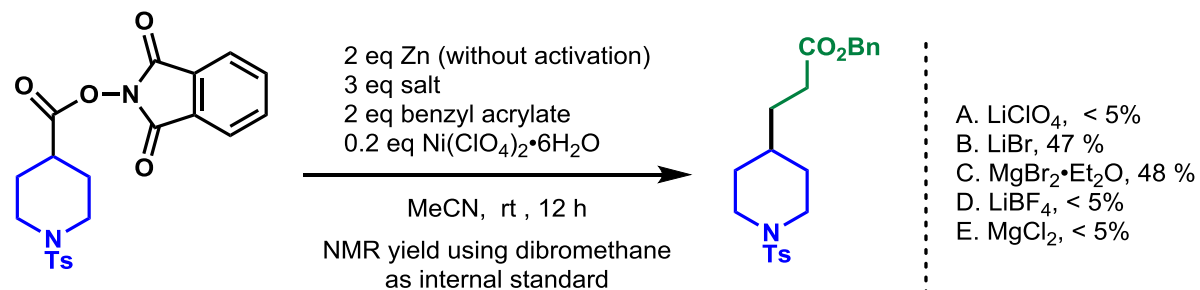
4. Metal Screening using MgCl₂ salt



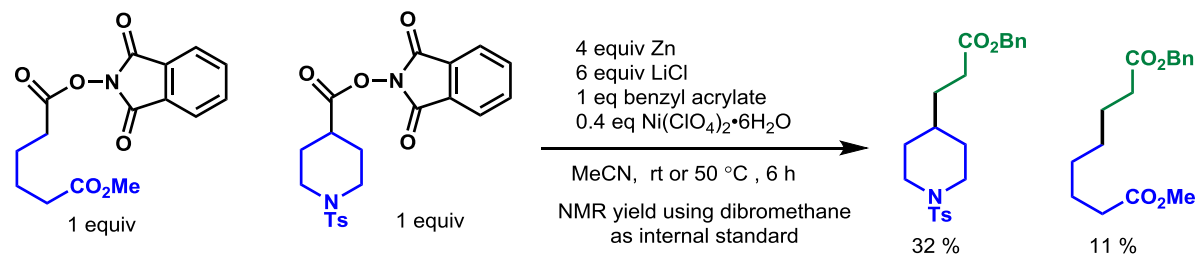
5. Metal Screening using LiCl salt



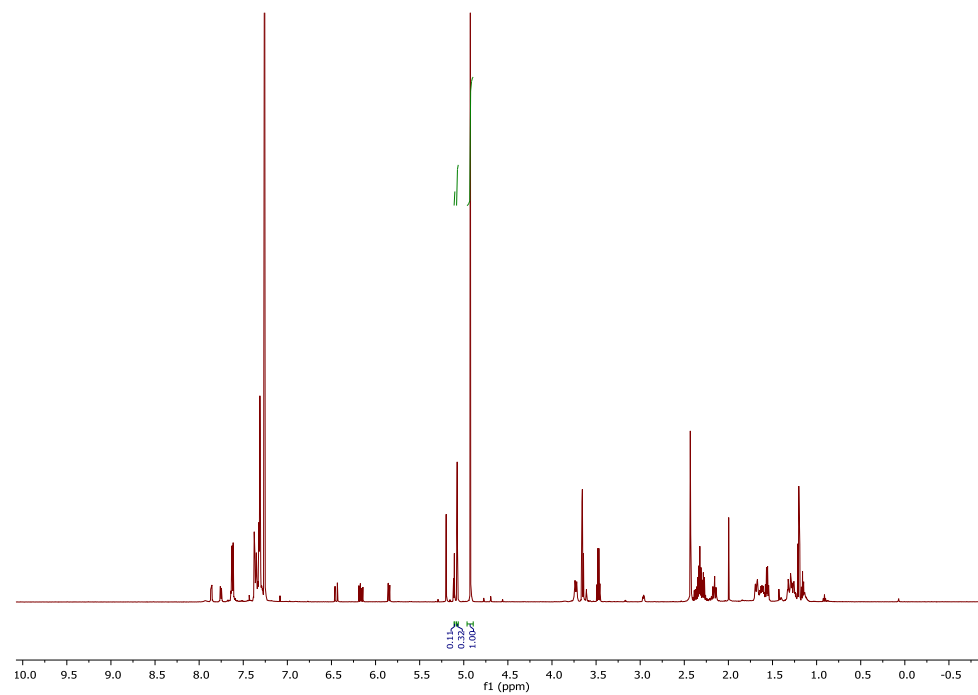
6. Salt Screening using Ni(ClO₄)₂·6H₂O catalyst



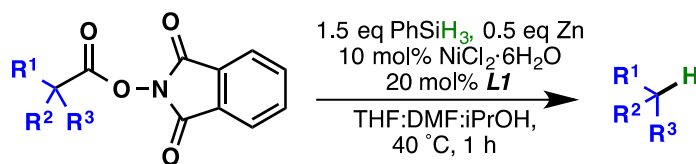
Competition Experiments:



Crude ¹H NMR using CH₂Br₂ as internal standard



General Procedure for the Ni-Catalyzed Decarboxylation of NHPI Redox-active Esters (General Procedure B).



Procedure for 0.1 mmol scale:

A culture tube was charged with NHPI redox-active ester (0.1 mmol, 1.0 equiv.), Zn metal (3.2 mg, 0.05 mmol, 0.5 equiv.) and a stir bar. The tube was then evacuated and backfilled with argon from a balloon. THF (0.5 mL, anhydrous) and *i*-PrOH (0.05 mL) were added. A solution of NiCl₂·6H₂O/**L1** (1.0 M in DMF, 0.1 mL, 10 mol% NiCl₂·6H₂O, 20 mol% **L1**) and PhSiH₃ (18 μL, neat, 1.5 equiv) were added in quick succession. *NOTE: It is important to add the PhSiH₃ quickly after addition of the [Ni] stock solution. Diminished yields were observed when this procedure is not followed.* The culture tube was then placed in a preheated 40 °C oil bath and stirred for 1 hour. The mixture was then removed from the oil bath, allowed to cool to ambient temperature, and quenched with H₂O (distilled) and sat. aq. NH₄Cl solution (1:1 v/v). The mixture was extracted with EtOAc or Et₂O three times, and the organic layer was dried over MgSO₄. The organic layer was concentrated on a rotary evaporator under reduced pressure at 40 °C. The crude product was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

Procedure for gram-scale: synthesis of 6

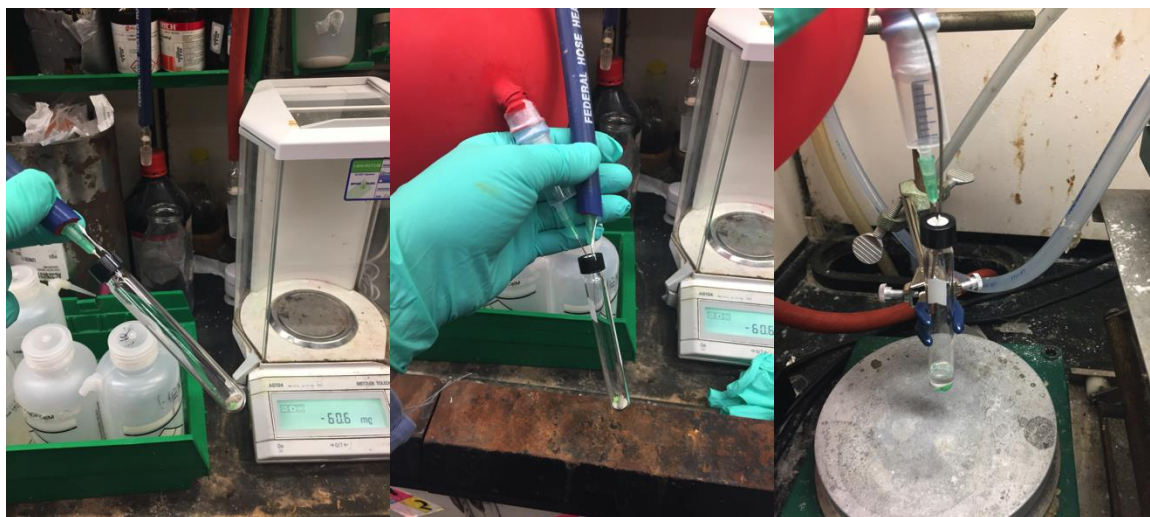
The Ni-catalyzed decarboxylation procedure for gram-scale was slightly modified from the 0.1 mmol scale procedure. A two-neck round bottom flask was charged with NiCl₂·6H₂O (0.055 g, 0.233 mmol, 10 mol %) and **L1** (0.125 g, 0.467 mmol, 20 mol %). The flask was equipped with a reflux condenser and rubber septum, and the apparatus was purged with Ar from a balloon for 5 min. DMF (2.3 mL, anhydrous) was added, and the mixture was stirred for 10 minutes. THF (10 mL) and *i*-PrOH (1.2 mL) were then added, followed by **5** (1.00 g, 2.334 mmol, 1.0 equiv) and Zn powder (0.076 g, 1.167

mmol, 0.5 equiv). Immediately following the addition of the Zn powder, PhSiH₃ (neat, 0.431 mL, 3.50 mmol, 1.5 equiv) was added dropwise. Upon completion of the addition of PhSiH₃, the reaction mixture was placed in a preheated 40 °C oil bath and stirred for 1 hour. After placing the flask in the oil bath, an additional 2 mL of THF was used to rinse the sides of the flask to ensure all **5** and Zn powder were in the mixture. After 1 hour the mixture was allowed to cool to ambient temperature. H₂O (distilled) and sat. aq. NH₄Cl were added (1:1 v/v), and the mixture was transferred to a separatory funnel. The mixture was extracted with EtOAc, and the organic extracts were filtered over a small plug of silica gel. The filtrate was concentrated on a rotary evaporator under reduced pressure at 40 °C, and the crude product was purified by flash column chromatography (silica gel, gradient elution, 1:1 hexanes:CH₂Cl₂ to CH₂Cl₂ to 19:1 CH₂Cl₂:Et₂O) to afford pure **6** (470 mg, 84%) as a white solid.

Graphical Supporting Information for decarboxylation of NHPI RAEs (0.1 mmol scale)



(Left) Solid materials for Ni-catalyzed decarboxylation. **(Center)** $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (24 mg, green solid) and di-*t*BuBipy **L1** (54 mg, white solid) were weighed on the bench top. **(Right)** $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and di-*t*BuBipy **L1** were added to a culture tube.



(Left) The tube was evacuated. **(Center)** The tube was refilled with Ar from a balloon. **(Right)** After addition of DMF (1 mL, anhydrous).



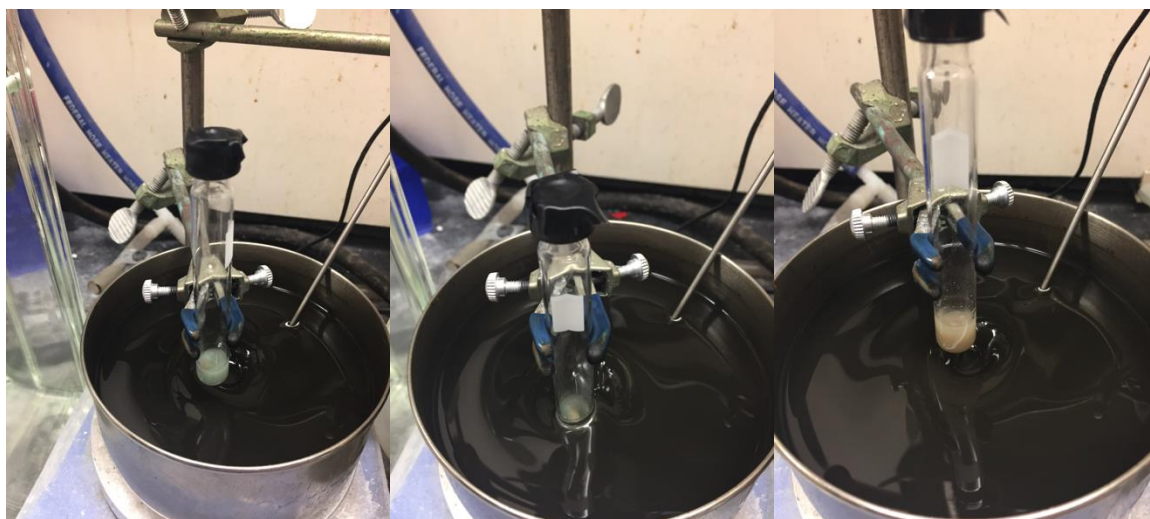
(Left) Stock solution of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and di-*t*BuBipy **L1** (1.0 M of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ in DMF) after 10 minutes of stirring. For a 0.1 mmol scale reaction, 0.1 mL of this solution is used. **(Center)** Redox-active ester **5** (43 mg) and Zn powder (3.2 mg). **(Right)** **5** and Zn powder were added to a culture tube, and the tube was evacuated.



(Left) The tube was refilled with Ar from a balloon. **(Center)** THF (0.5 mL, anhydrous) was added. **(Right)** *i*-PrOH (0.05 mL) was added.



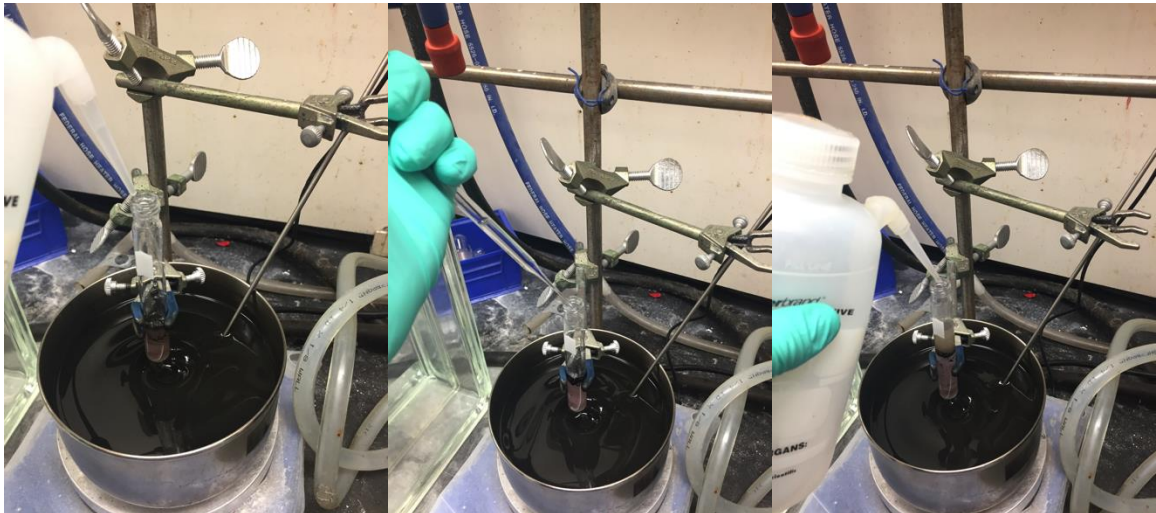
(Left) Addition of 0.1 mL of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and di-*t*BuBipy **L1** stock solution (1.0 M in DMF). **(Center)** After addition of [Ni] stock solution. The reaction mixture was not stirred at this time. **(Right)** Addition of PhSiH_3 (18 μL) via microliter syringe. It is important to add the PhSiH_3 quickly after addition of the [Ni] stock solution.



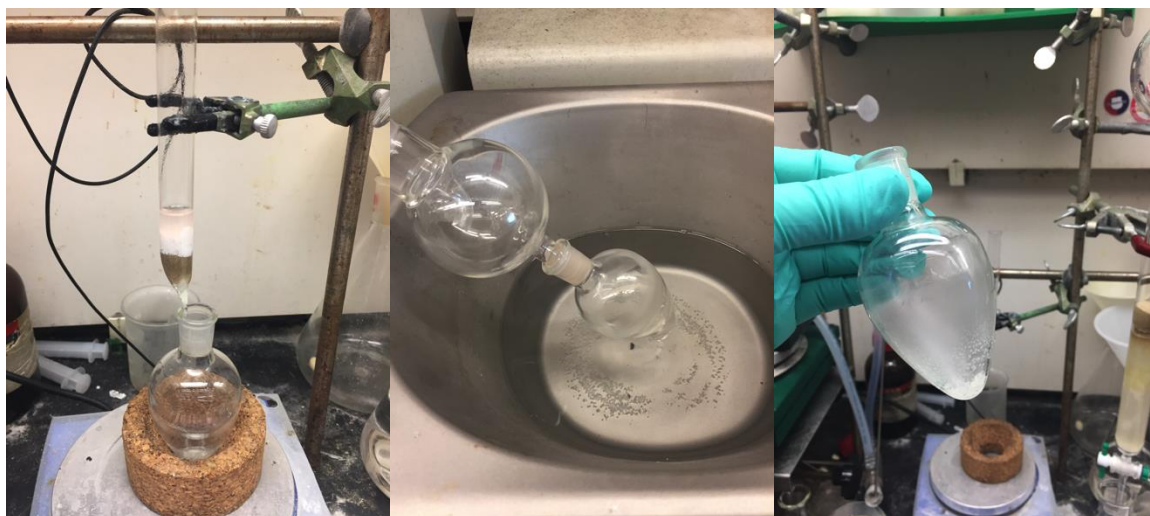
(Left) The Ar balloon was removed, and the culture tube septum was sealed with electrical tape. **(Center)** The reaction mixture is placed in an oil bath preheated to 40 °C and vigorously stirred (> 1000 RPM). **(Right)** The green/blue color disappeared quickly (< 3 min) upon heating. The reaction mixture was removed from the oil bath for the clarity for this photo.



(Left) Reaction mixture after 45 minutes. **(Center)** TLC of the reaction (2:1 hexanes/EtOAc, UV). Lane 1: starting material **5**. Lane 2: co-spot. Lane 3: reaction mixture. **(Right)** TLC of the reaction (2:1 hexanes/EtOAc, KMnO_4). Lane 1: starting material **5**. Lane 2: co-spot. Lane 3: reaction mixture. The back of the plate is shown.



(Left) The reaction mixture was diluted with H_2O (distilled). **(Center)** Sat. aq. NH_4Cl solution is added (approx. 1:1 v/v with distilled H_2O). **(Right)** Et_2O was added. The mixture was extracted 3 times with Et_2O or EtOAc.



(Left) The organic extracts were filtered over a plug of MgSO_4 (anhydrous). **(Center)** Concentration of the organic layer. **(Right)** Crude product to be purified by PTLC or flash column chromatography.

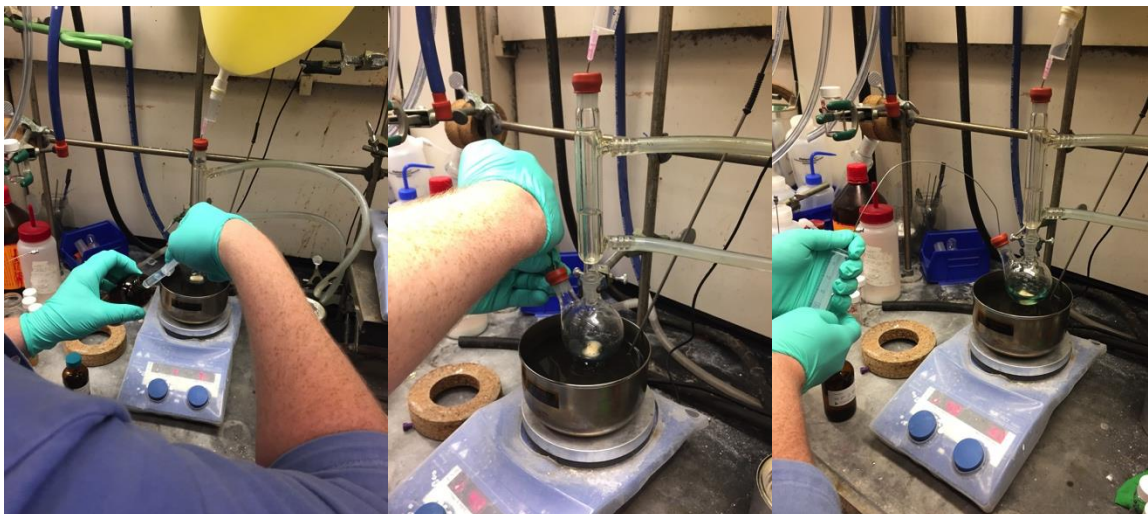
Graphical Supporting Information for Gram-scale decarboxylation of NHPI RAEs
Gram-scale synthesis of 6



(Left) Materials for Ni-catalyzed decarboxylation: di-*t*BuBipy **L1**, NiCl₂•6H₂O, **5**, Zn powder. **(Center)** NiCl₂•6H₂O (0.055 g) in two-neck flask. **(Right)** di-*t*BuBipy **L1** (0.125 g) and NiCl₂•6H₂O.



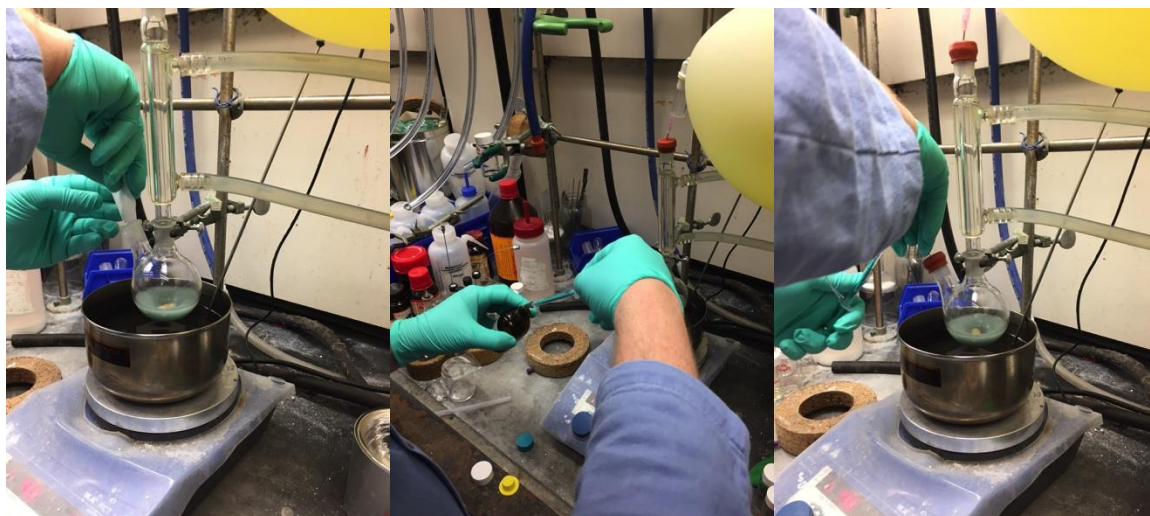
(Left) The flask was fitted with a reflux condenser, and the apparatus was purged with Ar from a balloon for 5 min through a vent needle. **(Center)** DMF (2.3 mL) was added **(Right)** The solution of NiCl₂•6H₂O and di-*t*BuBipy **L1** was stirred for 10 minutes prior to further addition of reagents.



(Left) *i*-PrOH (1.2 mL) was taken up into a syringe. **(Center)** Addition of *i*-PrOH. **(Right)** Addition of THF (12 mL, anhydrous).



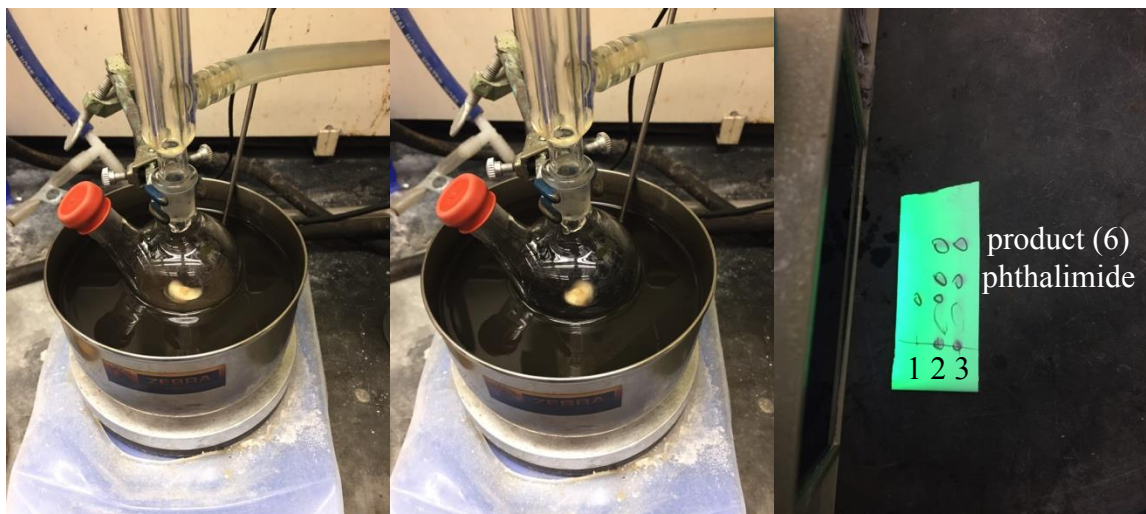
(Left) Compound **5**. **(Center)** Zn powder (0.076 g). **(Right)** The septum was removed, and **5** (1.00 g) was quickly added.



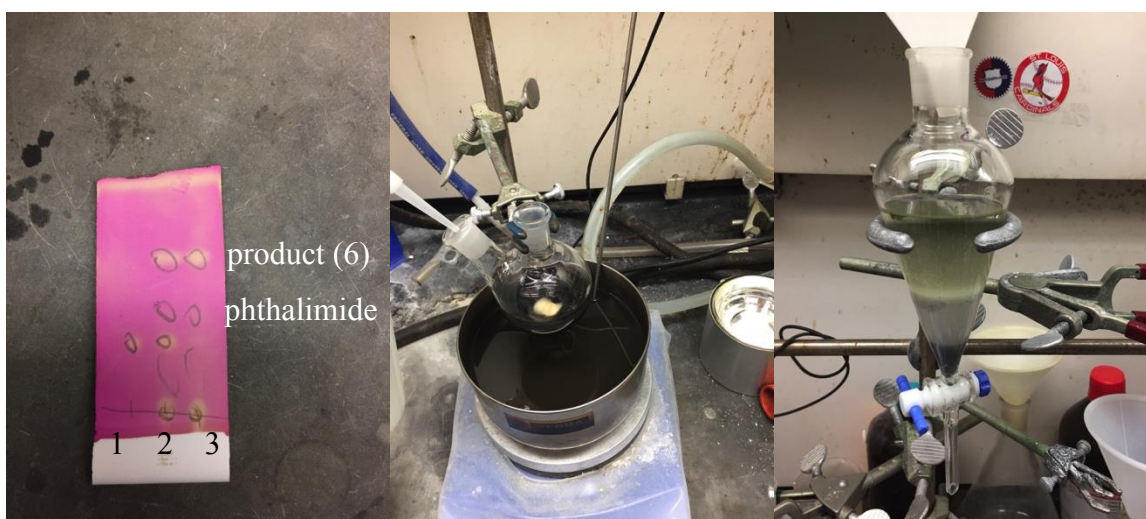
(Left) Addition of Zn powder (0.076 g). **(Center)** PhSiH₃ (0.431 mL) was taken up into a syringe. **(Right)** PhSiH₃ was added dropwise.



(Left) After addition of PhSiH₃, the flask was placed into an oil bath preheated to 40 °C. **(Center)** An additional small amount of THF (< 2 mL) was used to rinse the sides of the flask to ensure all of compound **5**, Zn, and PhSiH₃ are in the reaction mixture. **(Right)** Close-up of reaction mixture shortly after (< 1 min) heating.



(Left) After approximately 10 minutes of heating. **(Center)** After 1 hour of heating. **(Right)** TLC of reaction mixture (2:1 hexanes/EtOAc). Lane 1: Starting material **5**. Lane 2: co-spot. Lane 3: reaction mixture.



(Left) TLC of reaction mixture (2:1 hexanes/EtOAc, KMnO_4). Lane 1: Starting material **5**. Lane 2: co-spot. Lane 3: reaction mixture. **(Center)** The reaction was removed from the oil bath, and water (distilled) was added. **(Right)** The mixture was transferred to a separatory funnel, and EtOAc was added.

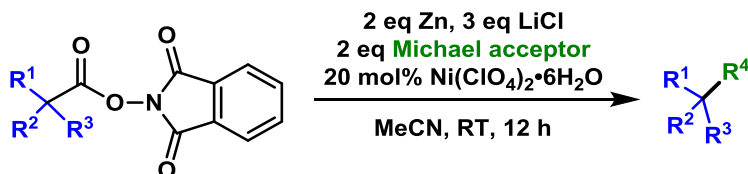


(Left) Sat. aq. NH_4Cl was added, and the organic layer was washed. Subsequent, washes with H_2O and brine were performed. **(Center)** Filtration of the organic layer over a thin pad of silica gel. **(Right)** Evaporation of the volatile organics under reduced pressure.



(Above) Isolated product **6** (purified by flash column chromatography, gradient elution of 1:1 hexanes/ CH_2Cl_2 to CH_2Cl_2 to 19:1 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$).

General Procedure for the Ni-catalyzed Giese Conjugate Addition (General Procedure C).



Procedure for 0.1 mmol scale:

A culture tube was charged with LiCl (13 mg, 0.3 mmol, 3.0 equiv). *Note: Due to its hygroscopic nature, LiCl can be difficult to weigh on small scale. In our experience excess LiCl is not detrimental to the success of the reaction.* Next, NHPI RAE (0.1 mmol, 1.0 equiv), Zn powder (13 mg, 0.2 mmol, 2.0 equiv), and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (7.4 mg, 0.04 mmol, 0.2 equiv) were added. A stir bar was added, and the culture tube was evacuated. The tube was backfilled with Ar from a balloon, and Michael acceptor (0.2 mmol, 2.0 equiv) was added *via* syringe. To the reaction mixture was added 0.25 mL MeCN (0.4 M), and the mixture was stirred overnight at ambient temperature. After at least 12 hours, H_2O (distilled) and sat. aq. NH_4Cl solution (1:1 v/v) were added. The mixture was extracted with EtOAc or Et_2O three times, and the organic layer was dried over MgSO_4 . The crude product was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield pure compound.

Procedure for gram-scale: synthesis of 7

The gram-scale procedure was slightly modified from the 0.1 mmol procedure. A culture tube was charged with LiCl (297 mg, 7.0 mmol, 3.0 equiv). Next, NHPI RAE **5** (1.00 g, 2.334 mmol, 1.0 equiv), Zn powder (303 mg, 4.668 mmol, 2.0 equiv), and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (86.4 mg, 0.1 equiv) were added. A stir bar was added, and the culture tube was evacuated. The tube was backfilled with Ar from a balloon, and MeCN (4 mL) was added. To the reaction mixture was added benzyl acrylate (2.0 equiv, 4.7 mmol) *via* syringe. The sides of the tube were washed with additional MeCN (1.8 mL). The

heterogenous mixture was stirred uniformly and the mixture was stirred overnight at ambient temperature. After at least 12 hours, H₂O (distilled) and sat. aq. NH₄Cl solution (1:1 v/v) were added. The mixture was transferred to a separatory funnel and was extracted with Et₂O three times, and the organic layer was dried over MgSO₄. The organic layer was concentrated on a rotary evaporator under reduced pressure at 40 °C. The crude product was purified by silica gel flash column chromatography (hexanes:EtOAc 10:1) to afford pure **7** (836 mg, 89 % yield).

Graphical Supporting Information for Giese Conjugate Addition Reaction.



(Above) Starting materials for Giese decarboxylative conjugate addition: Zn powder, benzyl acrylate, RAE 5, $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, and LiCl.



(Left) Zn powder. (Center) LiCl was weighted directly into the culture tube. (Right) Sealed culture tube containing LiCl, Zn powder, and a stir bar.



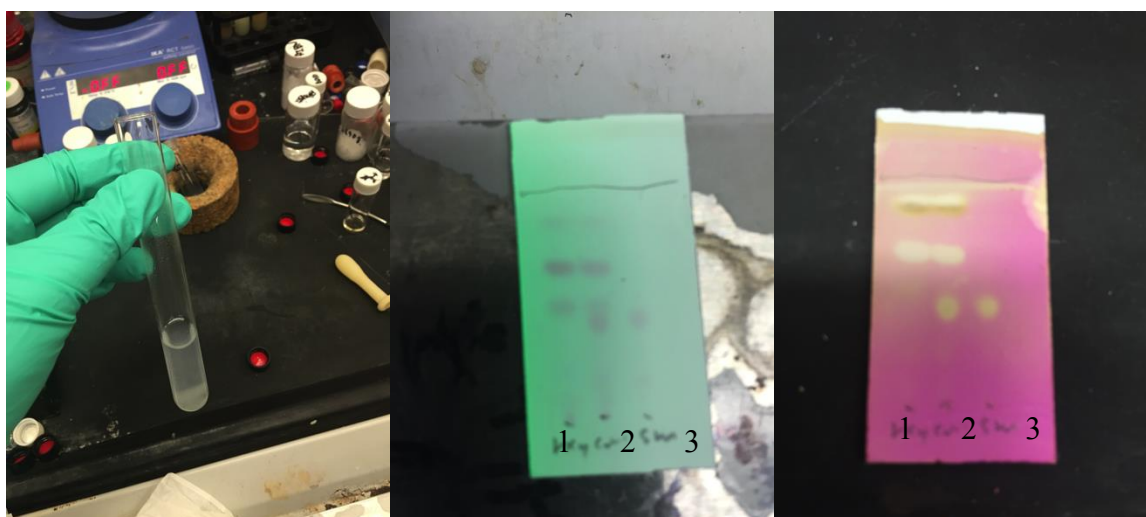
(Left) compound **5** **(Center)** $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. **(Right)** After addition of **5** and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, the tube was placed under vacuum.



(Left) The culture tube was placed under Ar atmosphere from a balloon. **(Center)** Addition of benzyl acrylate. **(Right)** Addition of 0.25 mL MeCN.

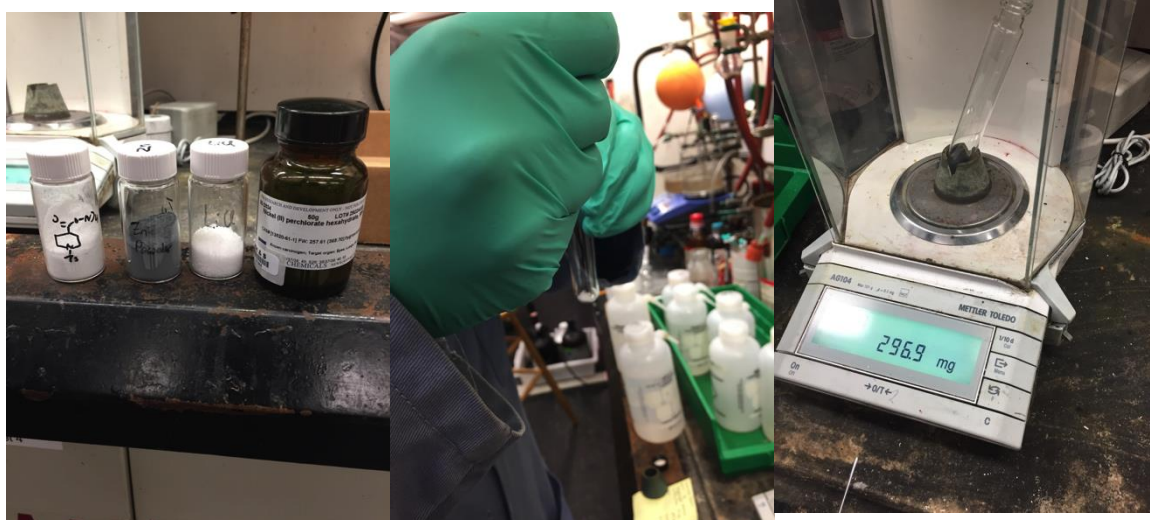


(Left) The reaction was stirred. Care was taken to ensure that no Zn powder accumulated on the sides of the culture tube. **(Center)** After 12 hr of stirring. **(Right)** The reaction was diluted with H₂O (distilled) and extracted.

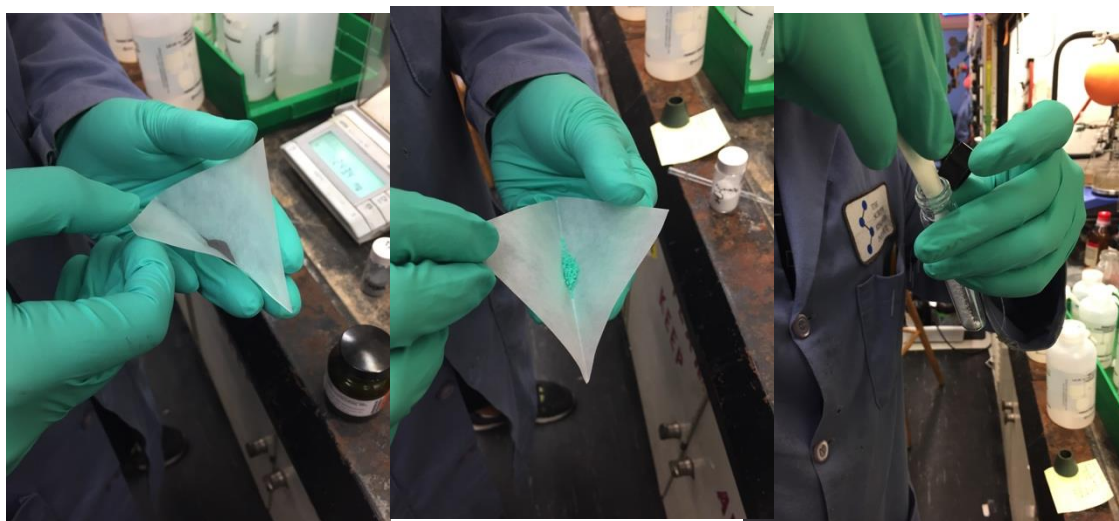


(Left) The organic layer (shown above) was concentrated and purified to afford product. **(Center)** TLC (UV). Lane 1: reaction mixture. Lane 2: co-spot. Lane 3: starting material **5** **(Right)** TLC (KMnO₄ stain). Lane 1: reaction mixture. Lane 2: co-spot. Lane 3: starting material **5**.

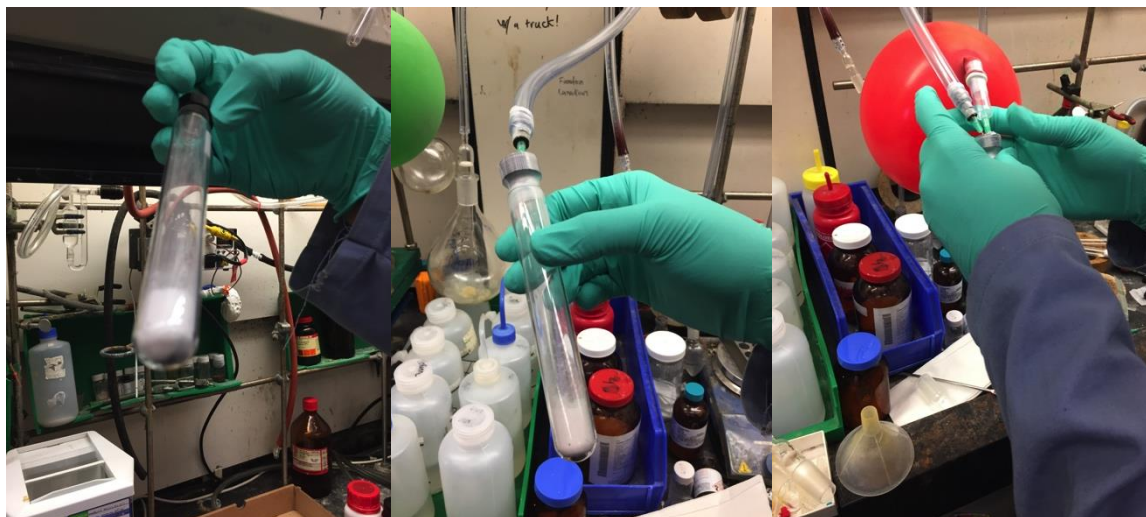
Graphical Supporting Information for Gram-scale Giese Conjugate Addition Reaction.



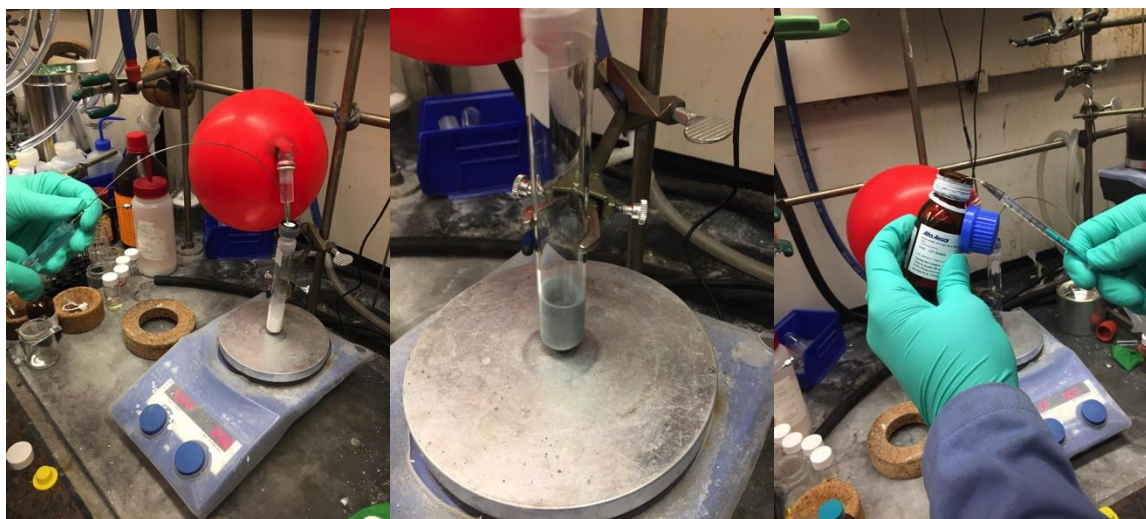
(Left) Materials for Giese-type Conjugate addition: compound **5**, Zn powder, LiCl, and Ni(ClO₄)₂•6H₂O. (Center) LiCl was weighed directly into reaction vessel. (Right) Mass of LiCl added to a tared culture tube.



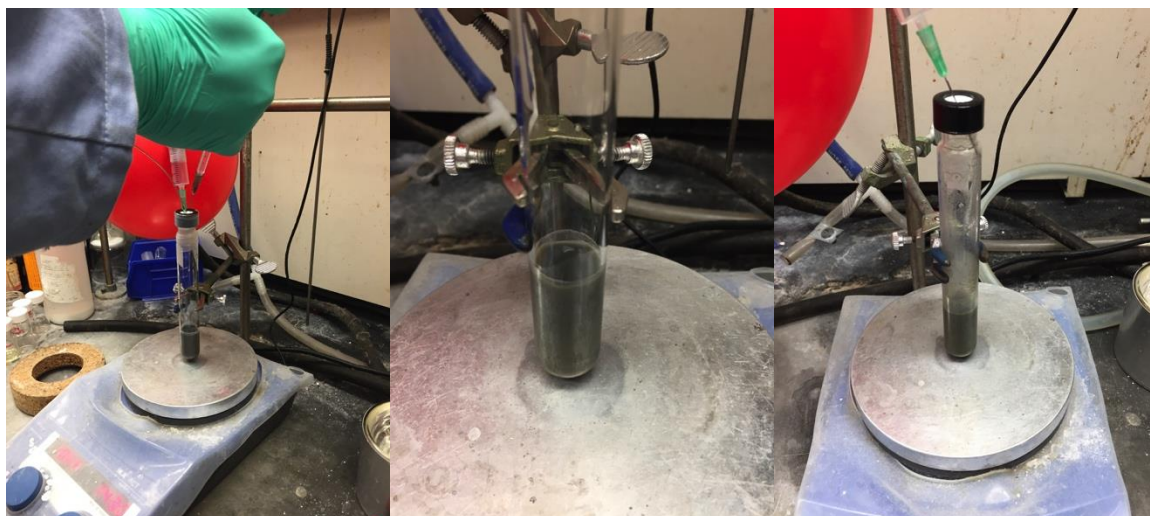
(Left) Zn powder (Center) Ni(ClO₄)₂•6H₂O. (Right) Addition of **5** to culture tube.



(Left) Capped culture tube containing **5**, $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, and Zn. **(Center)** The tube was placed under vacuum. **(Right)** The tube was backfilled with Ar from a balloon.



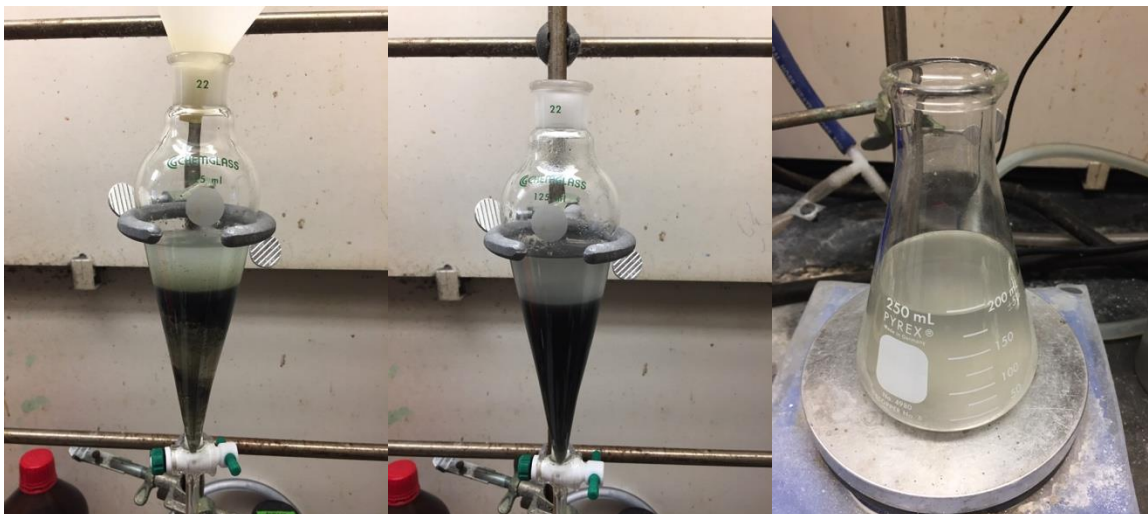
(Left) Addition of MeCN (anhydrous). **(Center)** Reaction mixture prior to addition of Michael acceptor. **(Right)** Michael acceptor (benzyl acrylate) was taken up into a syringe.



(Left) Addition of benzyl acrylate. **(Center)** Reaction mixture after addition of benzyl acrylate. A slight change in color from grey to greenish-grey was often observed. **(Right)** After 24 hours of stirring.



(Left) The mixture is diluted with H₂O (distilled). **(Center)** Addition of sat. aq. NH₄Cl (approx. 1:1 v/v with H₂O). **(Right)** After quenching.

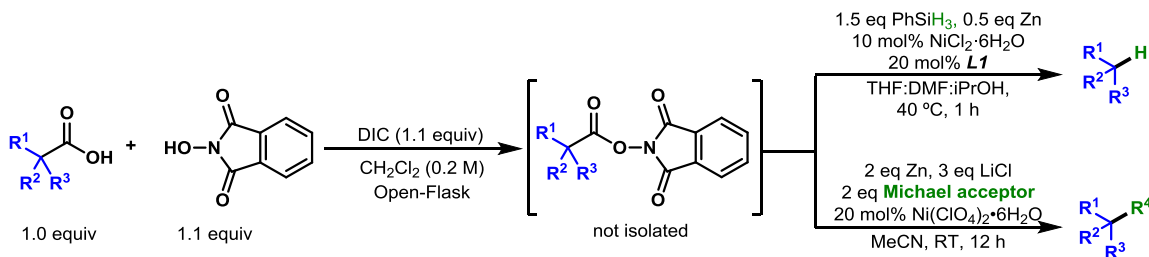


(Left) The mixture is transferred to a separatory funnel, and Et_2O is added. Additional Et_2O is used to rinse the reaction vessel. **(Center)** After first extraction. The mixture is extracted two more times with additional Et_2O . **(Right)** The organic extracts are dried with MgSO_4 (anhydrous).



(Left) The MgSO_4 was removed through filtration. **(Center)** Concentration of the organic extracts. **(Right)** Pure product **7** after purification by column chromatography.

**One-pot Activation for Decarboxylation and Giese Conjugate Addition Reactions
(General Procedure D).**



Procedure on 0.1 mmol scale:

A culture tube was charged with carboxylic acid (0.1 mmol, 1.0 equiv) and NHPI (0.11 mmol, 1.1 equiv). CH₂Cl₂ (0.5 mL, anhydrous, 0.2 M) was added, and DIC (0.11 mmol, 17 μL) was added dropwise. The reactions were monitored by TLC (typical time was 1 hr). After consumption of all starting material, the solvent was removed on a rotary evaporator at 40 °C under reduced pressure and dried on a high-vacuum line for at least 5 minutes to remove residue of CH₂Cl₂. The resulting crude RAEs were then used in decarboxylation (**General Procedure B**) or Giese conjugate addition reactions (**General Procedure C**) in the same reaction vessel without further purification or isolation of the RAE.

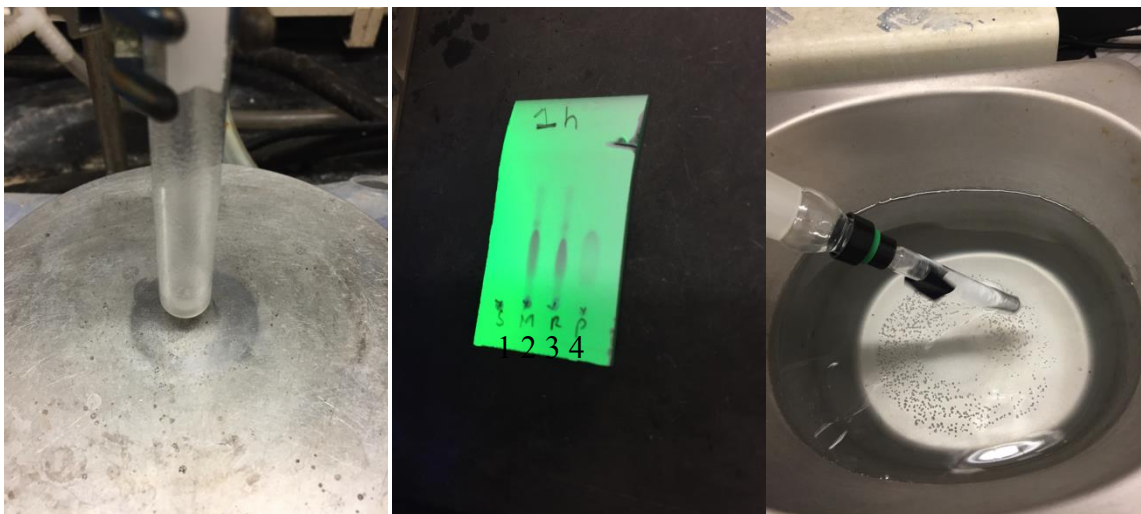
Graphical Supporting Information for One-pot Activation for Decarboxylation and Giese Conjugate Addition Reactions.



(Left) **45**, *N*-hydroxyphthalimide, and DIC. **(Center)** **45** and *N*-hydroxyphthalimide were added to a culture tube. **(Right)** CH_2Cl_2 was added.



(Left) The mixture was stirred. **(Center)** DIC was added dropwise at RT. **(Right)** Reaction mixture 1 minute after completion of DIC addition.



(Left) After 1 h of stirring. (Center) TLC (DCM, UV) Lane 1: starting material **45**. Lane 2: co-spot. Lane 3: reaction mixture. Lane 4: authentic sample of **5** (Right) CH_2Cl_2 was removed via rotary evaporator.



(Above) Redox-active ester **5** prepared via one-pot activation. Following this one-pot activation protocol, the RAEs were used directly in decarboxylation or Giese conjugate addition reactions in the same reaction vessel without further purification.

Methods for peptide synthesis:

Analytical reverse-phase HPLC was performed on a Hitachi D-7000 separations module equipped with a L-4500A photodiode array detector. Peptides were analyzed using a Vydac 218TP54 Protein & Peptide C18 column (5 μm , 4.6 mm x 250 mm) at a flow rate of 1.5 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B). Results were analyzed using Hitachi Model D-7000 Chromatography Data Station Software.

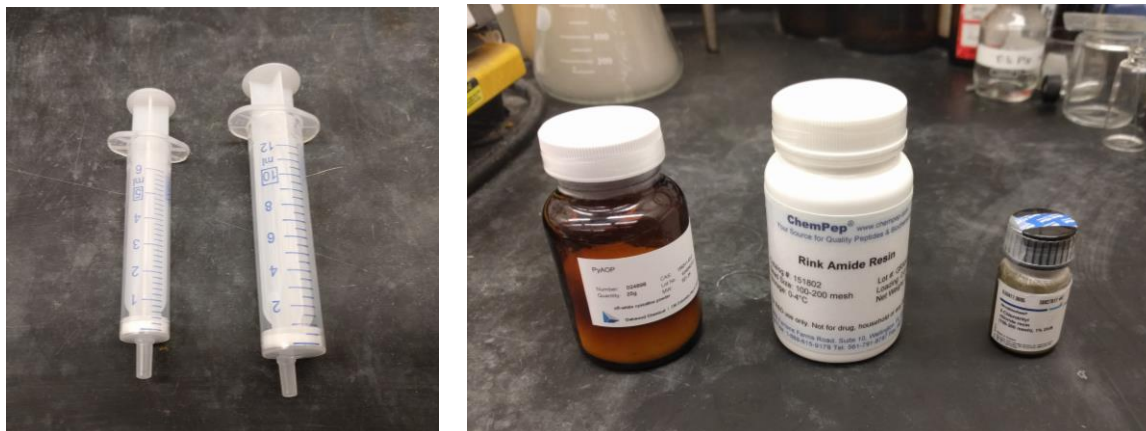
Preparative reverse-phase HPLC was performed using a Hitachi system comprised of an L-7150 pump and L-4000 programmable UV detector operating at a wavelength of 230 nm coupled to a Hitachi D-2500 Chromato-Integrator. Peptides were purified on a Thermo Scientific Bio-basic C18 10 μm preparative column operating at a flow rate of 12 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B) and a linear gradient as specified. Peptides were isolated as white solids (unless otherwise noted) following lyophilization.

An Innova 2000 portable platform shaker (operating at 145-170 rpm) was used for the general mixing and agitation of solid-phase reactions (including SPPS and on-resin 1,4-addition reactions).

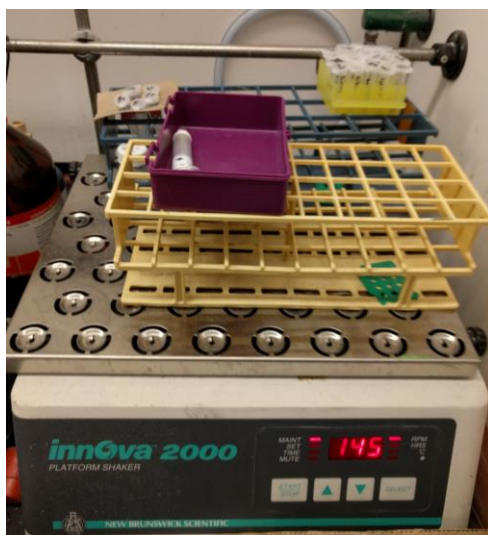
Materials

Commercial materials were used as received unless otherwise noted. Amino acids and coupling reagents were obtained from Novabiochem or Combi-blocks. Rink amide resin (0.8 mmol/g) was purchased from Chempep and 2-chlorotriyl chloride resin (1.51 mmol/g) was purchased from Novabiochem. Solid-phase reaction vessels and pressure

caps were purchased from Torviq. Reagents that were not commercially available were synthesized following literature procedures.



(Left) Solid-phase reaction vessels purchased from Torviq. **(Right)** PyAOP coupling reagent and commercially available resins (Chempep Rink amide resin and Novabiochem 2-chlorotriyl chloride resin).



(Above) Orbital shaker for solid-phase peptide synthesis (SPPS).

Solid-phase peptide synthesis

Preloading Rink amide resin

Rink amide resin (1.0 equiv., substitution = 0.8 mmol/g) was swollen in dry DCM for 30 min then washed with DCM (5 x 3 mL) and DMF (5 x 3 mL). A solution of Fmoc-AA-OH (4.0 equiv.) and *N*-methylmorpholine (NMM) (8.0 equiv.) in DMF (final concentration of 0.1 M with respect to the resin) was added and the resin agitated on an orbital shaker at rt for 2-3 h. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and capped with a solution of acetic anhydride/pyridine (1:9 v/v, 3 mL) for 10 min. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS).

Preloading 2-chlorotriyl chloride resin

2-chlorotriyl chloride resin (1.0 equiv., substitution = 1.51 mmol/g) was swollen in dry DCM for 30 min then washed with DCM (5 x 3 mL) and DMF (5 x 3 mL). A solution of Fmoc-AA-OH (4.0 equiv.) and *N,N*-diisopropylethylamine (DIEA) (8.0 equiv.) in DMF (final concentration of 0.1 M with respect to the resin) was added and the resin agitated on an orbital shaker at rt for 16 h. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and capped with a solution of DCM/MeOH/DIEA (17:2:1 v/v/v, 3 mL) for 30 min. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS).

Estimation of amino acid loading

The loading efficiency was evaluated through treatment of the resin with 20% piperidine/DMF (3 mL, 2 x 3 min) to deprotect the Fmoc group. The combined

deprotection solutions were diluted to 10 mL with 20% piperidine/DMF. An aliquot of this mixture (50 μ L) was diluted 200-fold with 20% piperidine/DMF and the UV absorbance of the piperidine-fulvene adduct was measured ($\lambda = 301$ nm, $\epsilon = 7800$ M⁻¹ cm⁻¹) to quantify the amount of amino acid loaded onto the resin. The theoretical maximum for the reported yields of all isolated peptides is based on the numerical value obtained from the resin loading.

General iterative peptide assembly (Fmoc-SPPS)

Peptides were elongated using iterative Fmoc-solid-phase peptide synthesis (Fmoc-SPPS), according to the following general protocols:

Deprotection: The resin was treated with 20% piperidine/DMF (3 mL, 2 x 3 min) and washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

General amino acid coupling: A preactivated solution of protected amino acid (4 equiv.), PyBOP (4 equiv.) and *N*-methylmorpholine (NMM) (8 equiv.) in DMF (final concentration 0.1 M) was added to the resin. After 1 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

Capping: Acetic anhydride/pyridine (1:9 v/v) was added to the resin (3 mL). After 3 min the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

Cleavage: A mixture of TFA and water (95:5 v/v) was added to the resin. After 2 h, the resin was washed with TFA (3 x 2 mL) and DCM (3 x 2 mL). Note: The scavenger triisopropylsilane (TIS) was excluded from the cleavage mixture to prevent unwanted reduction of alkene-containing peptides.

Work-up: The combined cleavage solution and TFA and DCM washes were concentrated under a stream of nitrogen. The residue was treated with cold Et₂O to precipitate the crude peptide, which was subsequently dissolved in water/acetonitrile containing 0.1% TFA, filtered and purified by reverse-phase HPLC.

Coupling of Fmoc-Glu(OAllyl)-OH

A solution of the Fmoc-Glu(OAllyl)-OH (4.0 equiv.), PyAOP (4.0 equiv.) and DIEA (8.0 equiv.) in DMF (final concentration 0.1 M) was added to the resin (1.0 equiv.) and shaken. After 16 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL). A capping step was performed as described above before proceeding with subsequent solid-phase transformations.

Coupling of H-Pro-OAllyl·TFA

A solution of H-Pro-OAllyl·TFA (10.0 equiv.), PyAOP (10.0 equiv.) and DIEA (20.0 equiv.) in DMF (final concentration 0.1 M) was added to the resin (1.0 equiv.) and shaken. After 3 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL).

On-resin deallylation

A solution of Pd(PPh₃)₄ (25 mg, 22 μmol) and PhSiH₃ (123 μL, 1 mmol) in dry DCM (2 mL) was added to the resin (25 μmol). The resin was shaken for 1 h then washed with DCM (10 x 3 mL). The progress of the reaction was checked by cleavage of a small portion of resin beads followed by LC-MS analysis. The procedure was repeated if necessary, and upon completion, the resin was washed with DCM (10 x 3 mL) and DMF (10 x 3 mL).

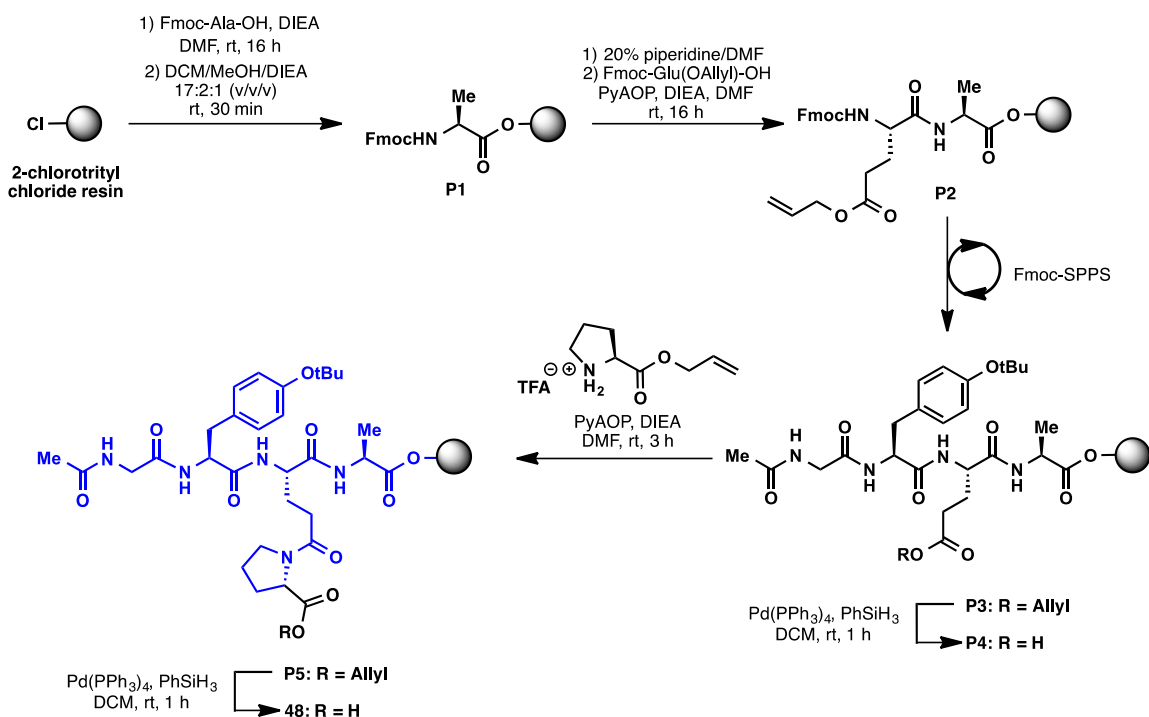
On-resin acryloyl chloride coupling

Acryloyl chloride was used to install Michael acceptors onto resin-bound peptide substrates. The resin-bound substrate (25 μmol) bearing a free amine was washed with DCM (5 x 3 mL). A solution of Et_3N (5.0 equiv.) in DCM (0.2 mL) was cooled to 0 $^\circ\text{C}$ and added to the resin. Immediately thereafter, a solution of acryloyl chloride (5.0 equiv.) in DCM (0.2 mL) at 0 $^\circ\text{C}$ was added to the resin (note that the addition of acryloyl chloride causes the reaction solution to turn yellow in color and is accompanied by a slight exotherm). The resin was agitated at rt for 1 h and washed with DCM (10 x 3 mL) and DMF (5 x 3 mL).

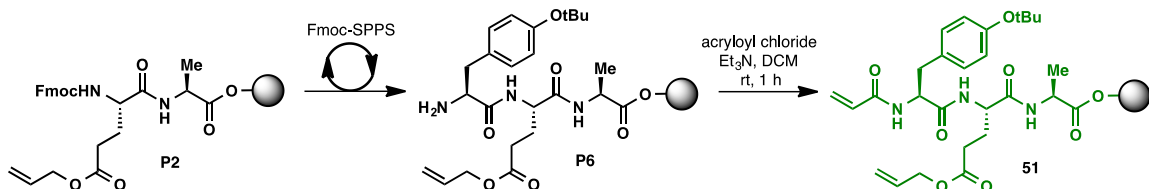
Preparation of substrates for on-resin couplings

Resin-bound peptides for solid-phase 1,4-additions were prepared using Fmoc-SPPS as described in the general methods. Overall synthetic strategies for the preparation of resin-bound substrates **48** and **51** are outlined below:

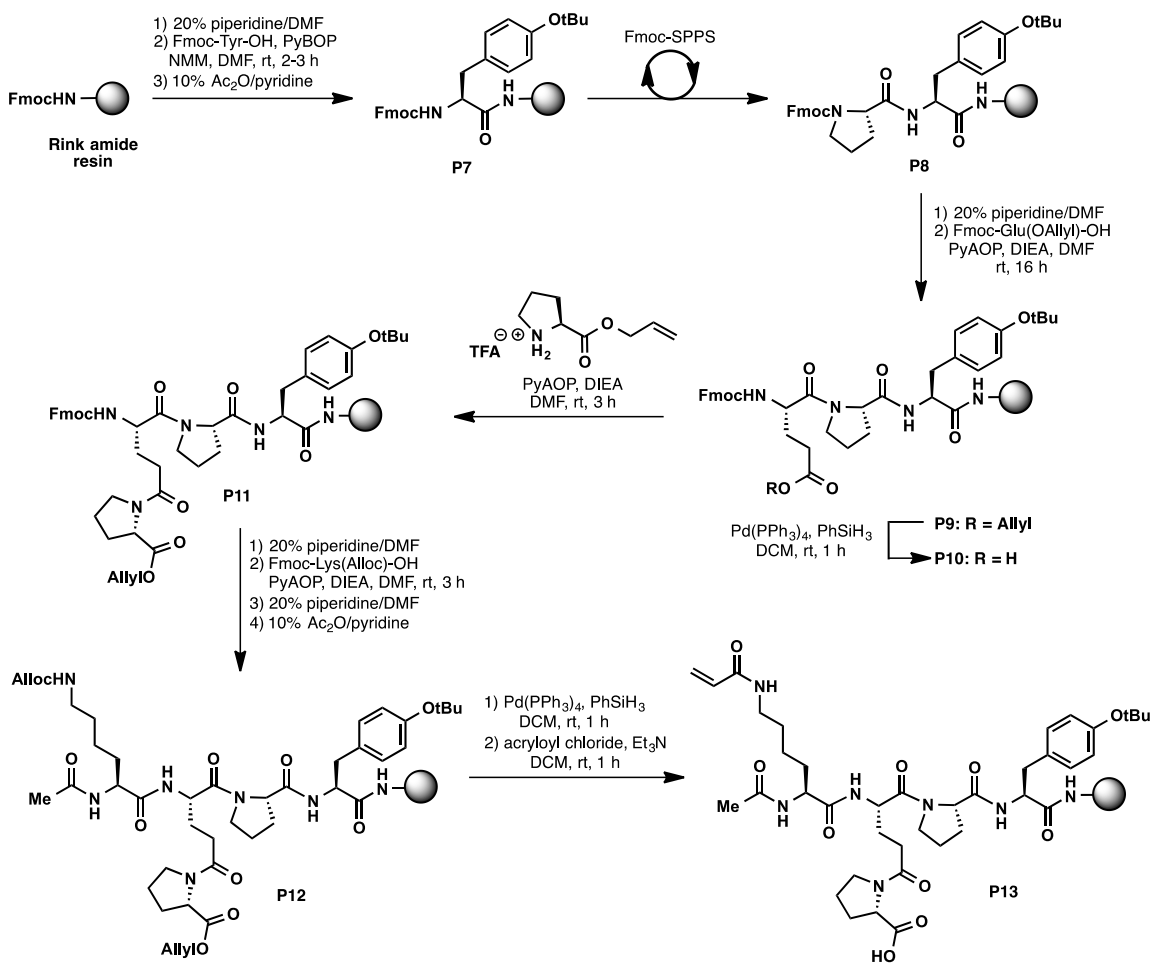
Preparation of **48**:



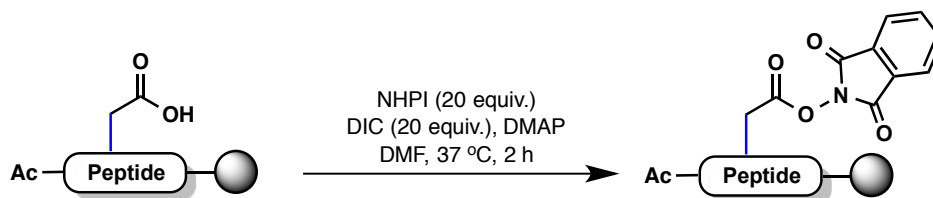
Preparation of **51**:



Preparation of P13 (resin-bound precursor to macrocyclization substrate 53):



General procedures for on-resin activation:

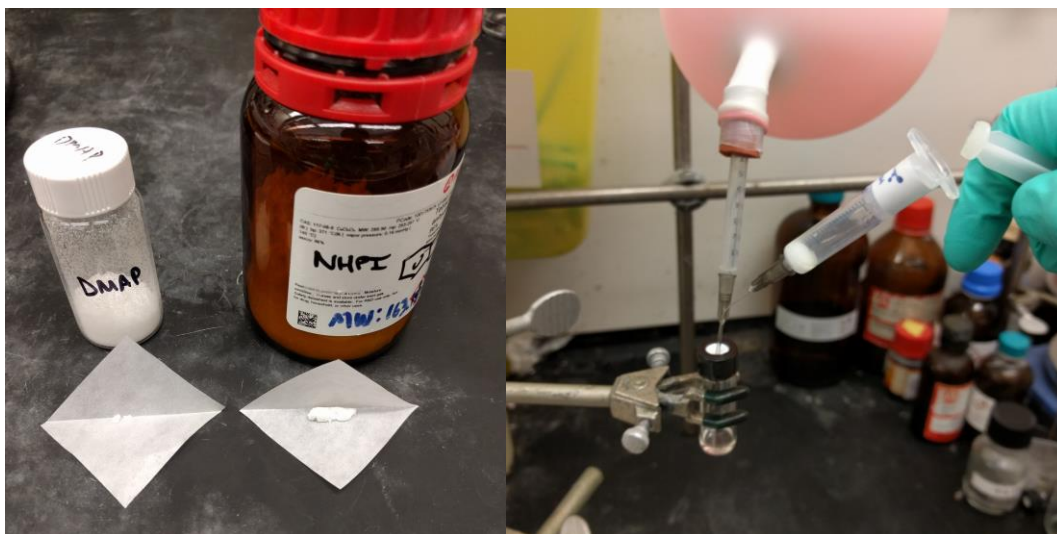


The resin-bound peptide (12.5 – 25 μmol) was washed with dry DMF (5 x 3 mL) under an argon atmosphere. *N*-hydroxyphthalimide (NHPI) (20.0 equiv.) and DMAP (2.0 equiv.) were added as solids to the reaction vessel by removing the plunger of the fritted syringe. Following addition, the plunger was replaced and a solution of DIC (20.0 equiv.) in dry DMF (40-60 mM concentration with respect to the resin-bound peptide) was added to the resin. The resin was capped, sealed with Teflon tape, and agitated at 37 °C for 2 h on a rotary evaporator (see graphical representation below for additional details). The activation solution was then expelled and the resin washed under an argon atmosphere with dry DMF (5 x 3 mL).

Graphical Supporting Information for activation of resin-bound carboxylic acids with NHPI



(Left) A flame-dried round bottom flask under an argon atmosphere is charged with dry DMF. **(Center)** The resin-bound peptide (contained in the fritted solid-phase reaction vessel) is washed 5 times with dry DMF. **(Right)** A small, flame-dried reaction vial is charged with DMF and DIC.



(Left) *N*-hydroxyphthalimide (NHPI) (20.0 equiv.) and DMAP are weighed out. **(Right)** The plunger of the solid-phase reaction vessel is carefully removed.



(Left) NHPI is added as a solid to the reaction vessel followed by DMAP. **(Right)** After

replacing the syringe plunger, the solution of DIC and DMF in the small reaction vial is drawn up into the syringe; note the emergence of a yellow-orange color.

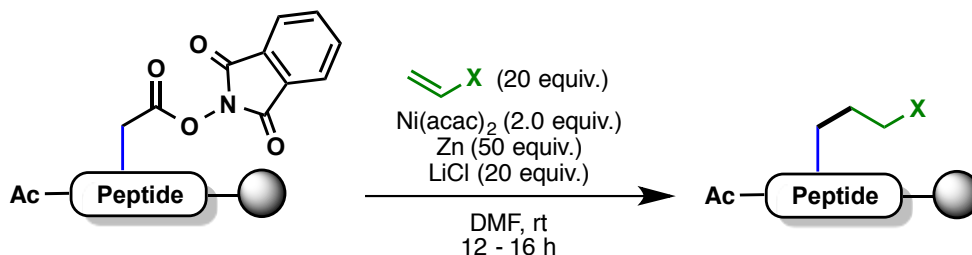


(Left) The reaction vessel is capped with a pressure cap (Torviq) and thoroughly sealed with Teflon tape and parafilm. **(Right)** The resin-bound peptide is attached to a rotovap, lowered into the water bath (37 °C) and agitated at 90 rpm for 2 h.



(Left) The activation solution is expelled. **(Right)** The resin-bound peptide is washed with dry DMF (5 x 3 mL).

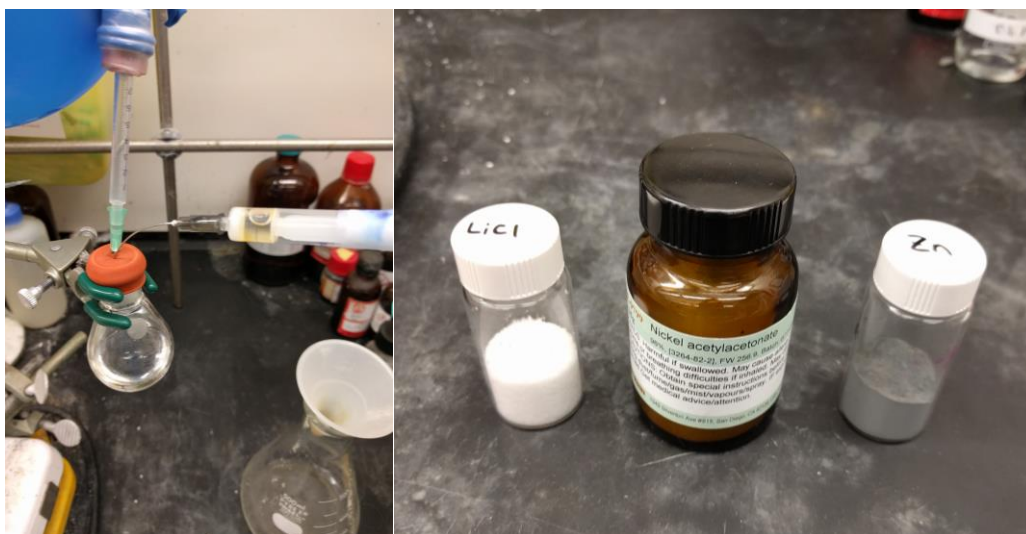
General procedure for on-resin 1,4-addition (resin-bound acid):



Following on-resin activation, the resin-bound peptide was immediately subjected to on-resin 1,4-addition. Under an argon atmosphere, the resin was washed with dry DMF (5 x 3 mL). Ni(acac)₂ (2.0 equiv.), Zn powder (50 equiv.), and LiCl (20 equiv.) were added as solids to the reaction vessel by removing the plunger of the fritted syringe. Following addition, the plunger was replaced and a solution of Michael acceptor (20.0 equiv.) in dry DMF (60-85 mM concentration with respect to the resin-bound peptide) was added to the resin, affording a heterogeneous green-gray suspension. The resin was capped and agitated (170 rpm) at rt for 12-16 h. The reaction mixture (now yellow-orange in color with suspended zinc powder) was then expelled and the resin washed thoroughly with DMF (10 x 3 mL), DCM (10 x 3 mL) and DMF (10 x 3 mL). Note that some zinc powder remains trapped in the syringe frit even after repeated washing steps. Prior to cleavage of the resin-bound peptide, the resin beads were transferred to a fresh fritted syringe and washed with DCM (10 x 3 mL).

Note: On-resin 1,4-additions were found to proceed more efficiently at higher concentrations. As a consequence of the heterogeneous nature of the reaction (due to the presence of Zn powder), high substrate concentrations should be preferentially employed.

Graphical Supporting Information for on-resin 1,4-additions



(Left) Following on-resin activation, the reaction is washed with dry DMF (5 x 3 mL). Following the washing steps, the remaining solvent is expelled from the syringe. **(Right)** Reagents employed in the on-resin 1,4-addition (LiCl , $\text{Ni}(\text{acac})_2$, Zn powder).



(Left) Appropriate amounts of $\text{Ni}(\text{acac})_2$ (2.0 equiv.) and Zn powder (50.0 equiv.) are weighed out together. **(Right)** A solution of Michael acceptor (e.g. phenylvinyl sulfone) is prepared in DMF (83 mM final concentration with respect to the resin-bound peptide

substrate).



(Left) After careful removal of the syringe plunger, $\text{Ni}(\text{acac})_2$ and Zn powder are added together to the back of the syringe. **(Right)** LiCl is quickly added to the syringe; note that LiCl is very hygroscopic, so addition is done as quickly as possible to avoid the introduction of excess moisture.

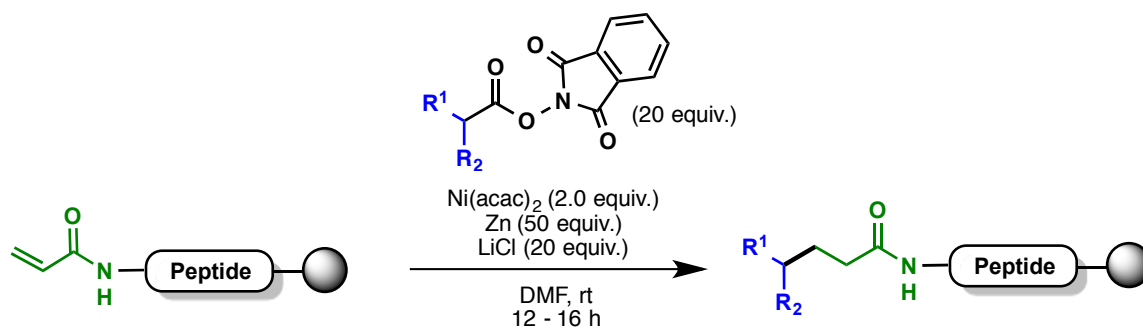


(Left) The syringe plunger is replaced and pushed down toward the frit **(Right)** The syringe is now poised for addition of the Michael acceptor in DMF.



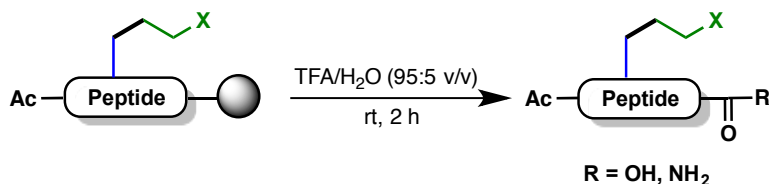
(Left) The DMF solution containing the Michael acceptor is added to the syringe. **(Right)** The syringe is capped and the resulting heterogeneous green-gray solution is agitated on an orbital shaker at room temperature for 12 – 16 h.

General procedure for on-resin 1,4-addition (resin-bound acceptor):



Following installation of the on-resin Michael acceptor using acryloyl chloride, the resin-bound peptide was subjected to on-resin 1,4-addition with a preformed NHPI ester. Under an argon atmosphere, the resin was first washed with dry DMF (5 x 3 mL). Ni(acac)₂ (2.0 equiv.), Zn powder (50.0 equiv.), and LiCl (20 equiv.) were added as solids to the reaction vessel by removing the plunger of the fritted syringe. Following addition, the plunger was replaced and a solution of NHPI ester (20.0 equiv.) in dry DMF (60-85 mM concentration with respect to the resin-bound peptide) was added to the resin, affording a heterogeneous green-gray suspension. The resin was capped and agitated (170 rpm) at rt for 12-16 h. The reaction mixture (now dark brown in color with suspended zinc powder) was then expelled and the resin washed thoroughly with DMF (10 x 3 mL), DCM (10 x 3 mL) and DMF (10 x 3 mL). The progress of the reaction was monitored by removing a few beads from the syringe and cleaving the resin-bound peptide with a solution of TFA/H₂O (95:5 v/v) at rt for 1 h. The cleavage solution was analyzed by LC-MS analysis, and the 1,4-addition reaction repeated with a fresh batch of NHPI ester (20.0 equiv.) if substantial unreacted peptide was observed. Following the second 1,4-addition reaction, the resin beads were transferred to a fresh fritted syringe and washed with DCM (10 x 3 mL).

Resin cleavage and product purification:

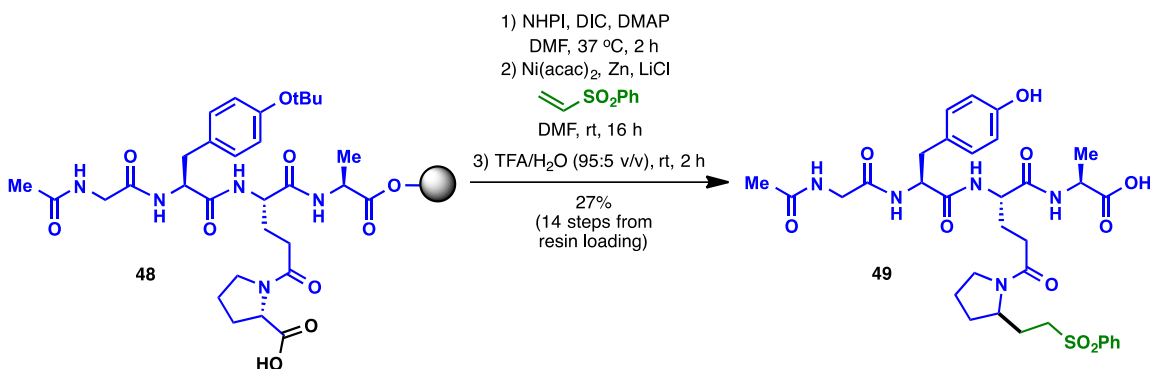


To isolate the peptide product, the resin was first washed with DCM (15 x 3 mL) then cleaved from the resin using TFA/H₂O (95:5 v/v, 3 mL, rt, 2 h). The cleavage mixture was expelled into a 50 mL centrifuge tube and the resin washed with TFA (3 x 2 mL) and DCM (3 x 2 mL). The combined washings were added to the centrifuge tube, and the resulting solution was concentrated under a stream of nitrogen. The crude residue was treated with cold Et₂O and sonicated to precipitate the peptide. The mixture was centrifuged (5 min, 3000 x g), the supernatant was discarded, and the crude peptide product was collected as a solid pellet. The crude product was resuspended in a mixture of H₂O/acetonitrile containing 0.1% TFA and immediately purified by preparative reverse-phase HPLC using a linear gradient as specified. Fractions containing the desired product were concentrated on a rotary evaporator to remove acetonitrile and then lyophilized to afford the target compound as a fluffy white solid.

Note on overall yield calculations and step counts: Yields are based on the amount of isolated material relative to the theoretical maximum based on the original loading of the solid-support. Upon attachment of the first amino acid to the resin, an Fmoc deprotection step is performed to quantify the loading of the resin (see general SPPS methods for details). In the step counts given below, this deprotection step is considered to be step #1 in the overall peptide synthesis protocol, as it is the first step following the resin loading. The summation of all subsequent steps allows for the calculation of percent yield over a given number of steps from the original resin loading.

Compound preparation and characterization data:

Peptide 49

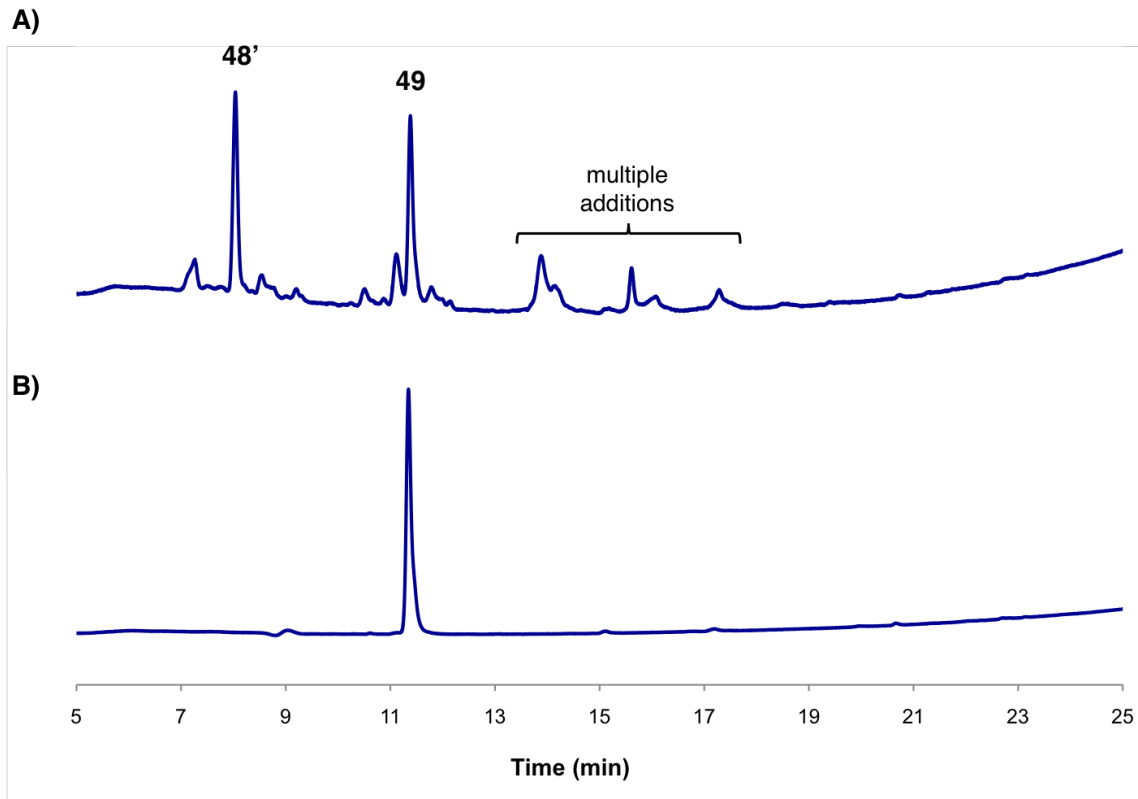


Peptide **49** was prepared on a 12.5 μmol scale from resin-bound substrate **48** through activation as the corresponding NHPI ester and subsequent addition of Ni(acac)₂ (2.0 equiv.), Zn (50.0 equiv.), and LiCl (20.0 equiv.) followed by a solution of phenyl vinylsulfone (20.0 equiv.) in DMF (0.15 mL, 83 mM with respect to the resin-bound peptide). After cleavage from the resin and ether precipitation, the crude peptide was purified by reverse-phase HPLC (10% B for 5 min, 10% to 50% B over 30 min, then 50% to 70% B over 5 min) and lyophilized to afford peptide **49** as a fluffy white solid (2.4 mg, 27% yield based on the original resin loading).

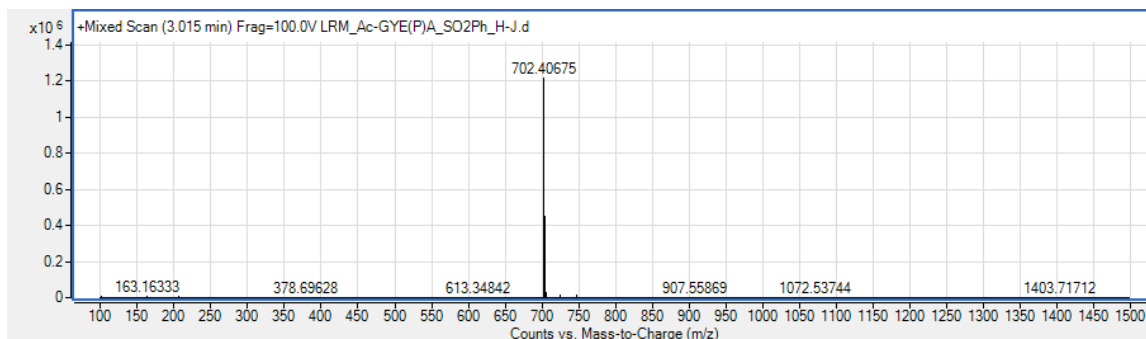
Isolated as an ~8:1 mixture of diastereomers;

¹H NMR (600 MHz, DMSO-*d*₆, major diastereomer) δ 12.56 (br s, 1H), 9.16 (s, 1H), 8.13 (dd, $J = 7.0, 2.0$ Hz, 1H), 8.11 – 8.00 (m, 2H), 7.94 – 7.85 (m, 3H), 7.79 – 7.71 (m, 1H), 7.68 – 7.62 (m, 2H), 6.99 (d, $J = 8.4$ Hz, 2H), 6.61 (d, $J = 8.4$ Hz, 2H), 4.45 – 4.38 (m, 1H), 4.29 – 4.22 (m, 1H), 4.22 – 4.14 (m, 1H), 3.98 – 3.90 (m, 1H), 3.69 (dt, $J = 16.6, 5.4$ Hz, 1H), 3.54 (dd, $J = 16.5, 5.6$ Hz, 1H), 3.35 – 3.25 (m, 3H, partially obscured by water peak), 2.87 (dd, $J = 14.0, 4.4$ Hz, 1H), 2.65 (dd, $J = 14.0, 9.3$ Hz, 1H), 2.24 (t, $J = 8.0$ Hz, 2H), 1.98 – 1.90 (m, 1H), 1.90 – 1.82 (m, 1H), 1.81 (s, 3H), 1.80 – 1.66 (m, 4H), 1.64 – 1.49 (m, 2H), 1.28 (d, $J = 7.3$ Hz, 3H) ppm; (Note: one H obscured by water peak).

^{13}C NMR (151 MHz, DMSO, major diastereomer) δ 174.0, 170.9, 170.8, 170.4, 169.6, 168.8, 155.8, 138.9, 133.8, 130.1, 129.4, 127.7, 127.6, 114.8, 55.0, 54.1, 52.1, 51.7, 47.5, 46.2, 42.0, 36.6, 30.2, 28.7, 27.5, 25.9, 23.4, 22.4, 17.0 ppm.

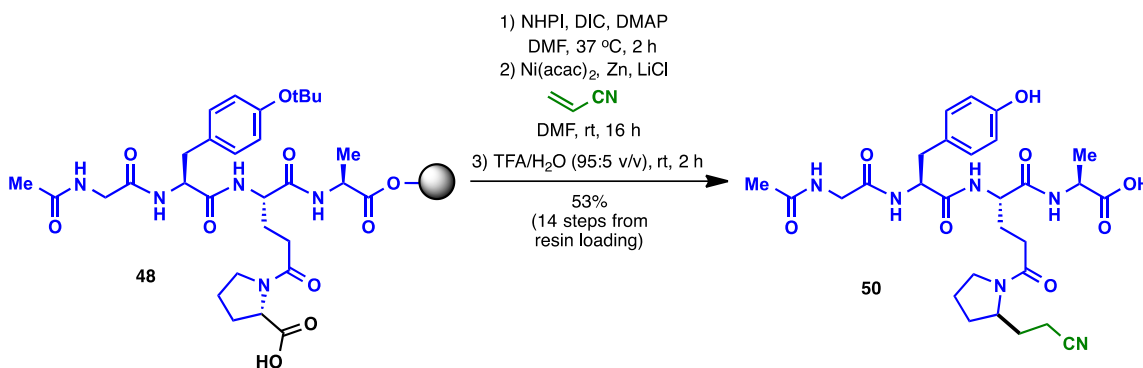


A) Crude analytical HPLC trace of the formation of peptide **49** from resin-bound peptide **48** following on-resin activation, 1,4-addition, and TFA cleavage (5 to 100% B over 25 min, $\lambda = 230$ nm) [note that **48'** designates the TFA-cleaved peptide, accompanied by loss of side-chain protecting groups]; **B)** Purified peptide **49** ($R_t = 11.3$ min, 5 to 100% B over 25 min, $\lambda = 230$ nm).



LRMS (ESI-TOF): calc'd for $C_{33}H_{44}N_5O_{10}S$ $[M+H]^+$ 702.28; found 702.41

Peptide 50

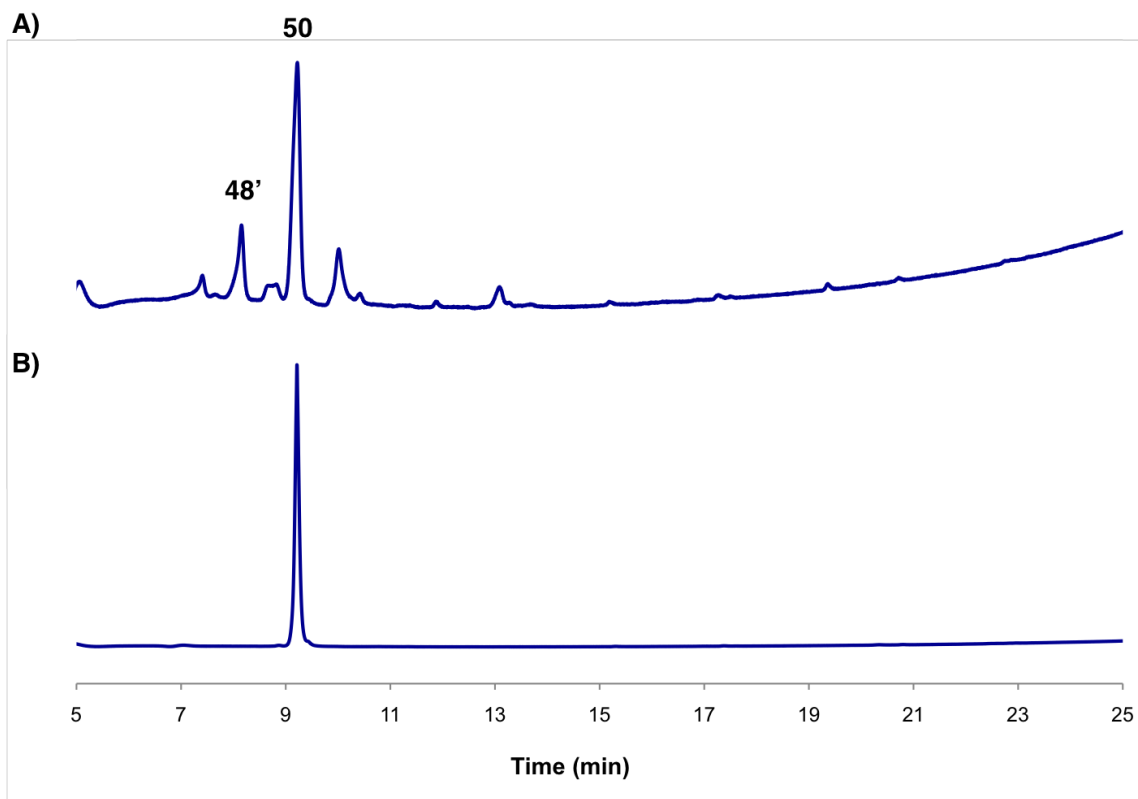


Peptide **50** was prepared on a 12.5 μmol scale from resin-bound substrate **48** through activation as the corresponding NHPI ester and subsequent addition of $\text{Ni}(\text{acac})_2$ (2.0 equiv.), Zn (50.0 equiv.), and LiCl (20.0 equiv.) followed by a solution of acrylonitrile (20.0 equiv.) in DMF (0.15 mL, 83 mM with respect to the resin-bound peptide). After cleavage from the resin and ether precipitation, the crude peptide was purified by reverse-phase HPLC (5% B for 5 min, 5% to 40% B over 30 min) and lyophilized to afford peptide **50** as a fluffy white solid (3.9 mg, 53% yield based on the original resin loading).

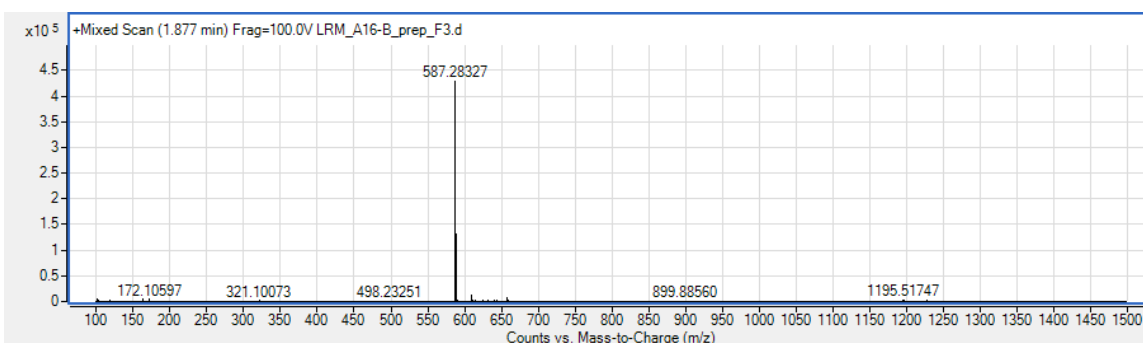
Isolated as an $\sim 10:1$ mixture of diastereomers;

¹H NMR (600 MHz, DMSO-*d*₆, major diastereomer) δ 9.14 (s, 1H), 8.15 (td, *J* = 6.7, 2.5 Hz, 1H), 8.09 (t, *J* = 7.8 Hz, 1H), 8.03 (t, *J* = 5.8 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.04 – 6.95 (m, 2H), 6.64 – 6.57 (m, 2H), 4.46 – 4.38 (m, 1H), 4.32 – 4.24 (m, 1H), 4.26 (br s, 1H), 4.23 – 4.13 (m, 1H), 4.02 – 3.93 (m, 1H), 3.73 – 3.66 (m, 1H), 3.55 (ddd, *J* = 16.6, 5.6, 2.8 Hz, 1H), 3.42 – 3.29 (m, 2H), 2.87 (dd, *J* = 13.9, 4.3 Hz, 1H), 2.65 (dd, *J* = 13.9, 9.3 Hz, 1H), 2.49 – 2.42 (m, 2H), 2.33 – 2.22 (m, 2H), 1.95 – 1.83 (m, 3H), 1.84 – 1.74 (m, 3H), 1.81 (s, 3H), 1.72 – 1.64 (m, 1H), 1.64 – 1.56 (m, 1H), 1.28 (d, *J* = 7.3 Hz, 3H) ppm;

¹³C NMR (151 MHz, DMSO, major diastereomer) δ 174.0, 170.8, 170.8, 170.5, 169.5, 168.8, 155.7, 130.1, 127.7, 120.6, 114.8, 55.4, 54.1, 51.7, 47.5, 46.2, 41.9, 36.7, 30.1, 28.5, 28.4, 27.4, 23.4, 22.4, 17.0, 13.5 ppm. (Note: residual TFA is observed following lyophilization: δ 158.1 - quartet).

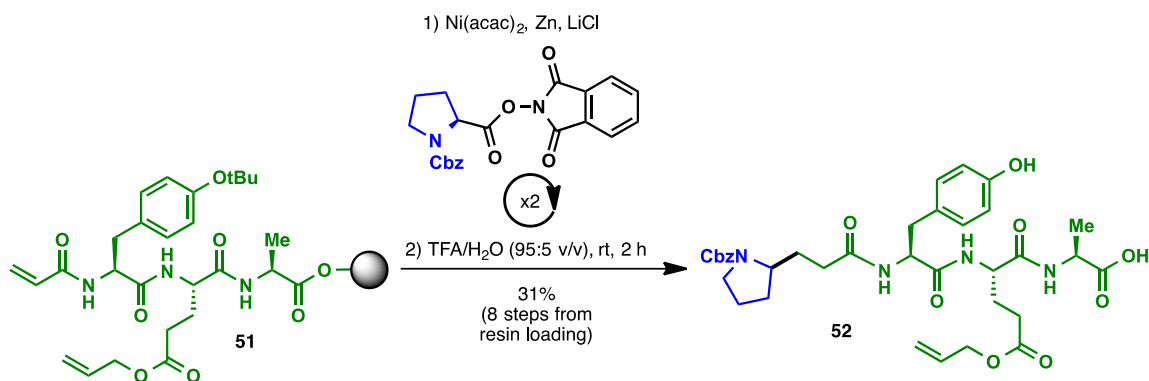


A) Crude analytical HPLC trace of the formation of peptide **50** from resin-bound peptide **48** following on-resin activation, 1,4-addition, and TFA cleavage (5 to 100% B over 25 min, $\lambda = 230$ nm) [note that **48'** designates the TFA-cleaved peptide, accompanied by loss of side-chain protecting groups]; **B)** Purified peptide **50** ($R_t = 9.2$ min, 5 to 100% B over 25 min, $\lambda = 230$ nm).



LRMS (ESI-TOF): calc'd for $C_{28}H_{39}N_6O_8$ $[M+H]^+$ 587.28; found 587.28

Peptide 52

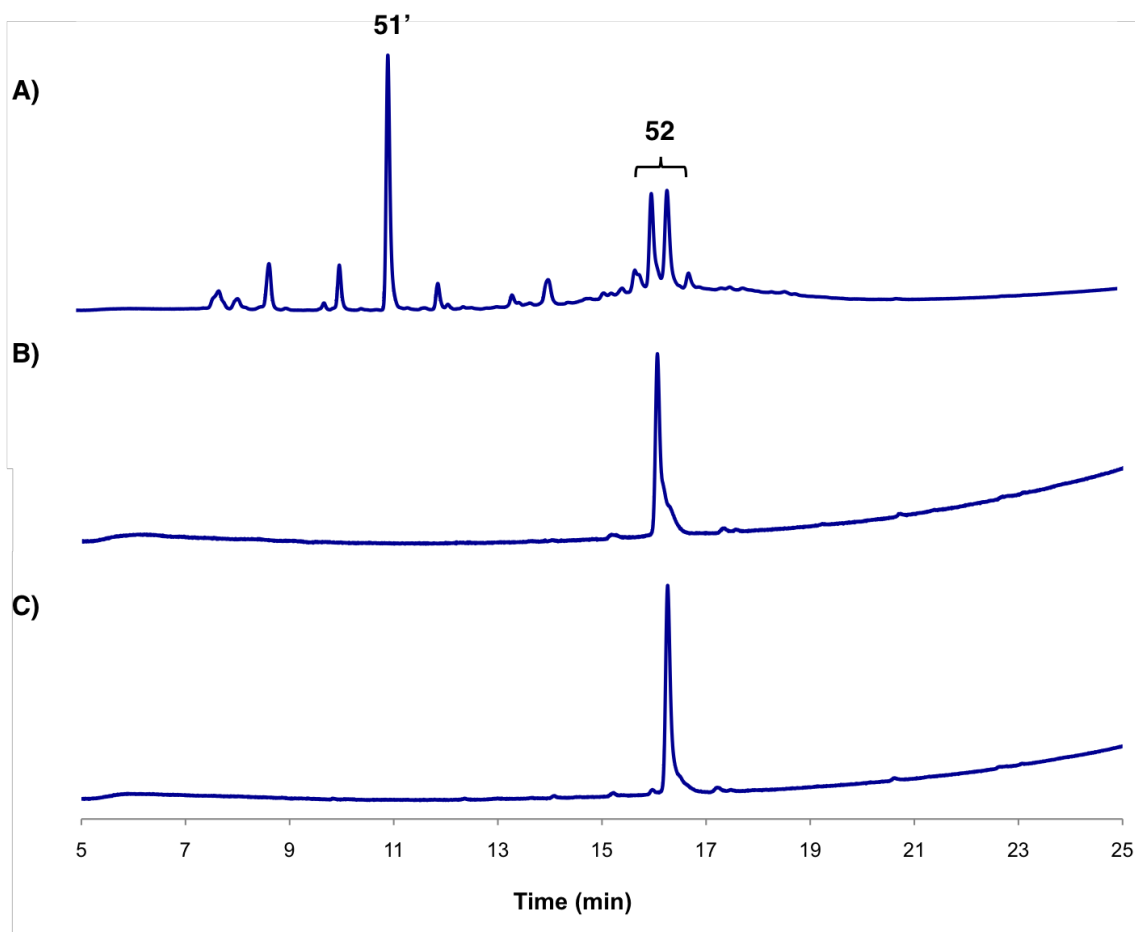


Peptide **52** was prepared on a 12.5 μmol scale from resin-bound substrate **51** through treatment with $\text{Ni}(\text{acac})_2$ (2.0 equiv.), Zn (50.0 equiv.), and LiCl (20.0 equiv.) followed by addition of a solution of Cbz-Pro-NHPI ester (20.0 equiv.) in DMF (0.2 mL, 63 mM with respect to the resin-bound peptide). The 1,4-addition reaction was repeated once more prior to cleavage of the peptide from the resin. The crude residue was precipitated in cold ether and purified by reverse-phase HPLC (20% B for 5 min, 20% to 50% B over 25 min, then 70% for 10 min) and lyophilized to afford peptide **52** as separable diastereomers (1:1 ratio), each as a fluffy white solid (2.6 mg combined weight, 31% yield based on the original resin loading).

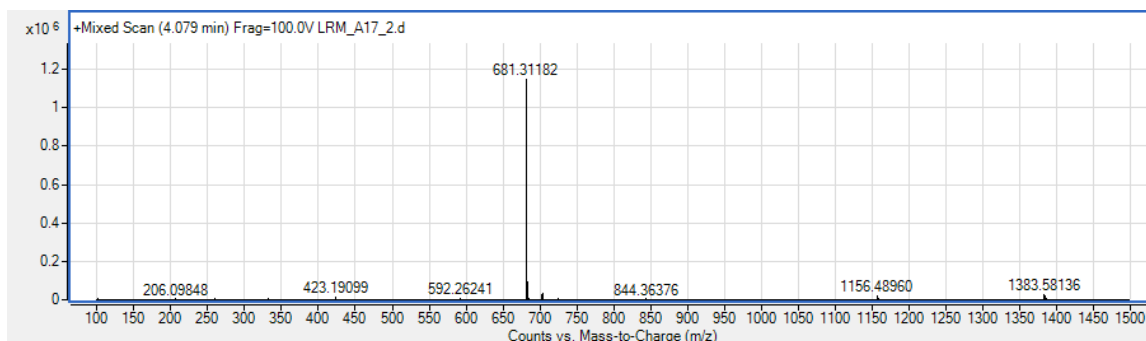
¹H NMR (600 MHz, DMSO-*d*₆, **52a)** δ 12.53 (br s, 1H), 9.16 (s, 1H), 8.20 (d, $J = 7.1$ Hz, 1H), 8.05 – 7.94 (m, 2H), 7.44 – 7.25 (m, 5H), 7.02 (d, $J = 8.2$ Hz, 2H), 6.62 (d, $J = 8.0$ Hz, 2H), 5.91 (ddt, $J = 16.3, 10.6, 5.4$ Hz, 1H), 5.29 (dd, $J = 17.2, 1.7$ Hz, 1H), 5.20 (dd, $J = 10.5, 1.5$ Hz, 1H), 5.09 – 5.00 (m, 2H), 4.63 – 4.47 (m, 2H), 4.46 – 4.37 (m, 1H), 4.34 – 4.27 (m, 1H), 4.22 – 4.12 (m, 1H), 3.76 – 3.61 (m, 1H), 3.26 – 3.16 (m, 1H), 2.87 (dd, $J = 14.1, 4.4$ Hz, 1H), 2.69 – 2.57 (m, 1H), 2.56 – 2.52 (m, 1H), 2.43 – 2.30 (m, 2H), 2.10 – 1.88 (m, 3H), 1.88 – 1.67 (m, 4H), 1.61 – 1.49 (m, 1H), 1.49 – 1.35 (m, 1H), 1.28 (d, $J = 7.3$ Hz, 3H) ppm; (Note: one H obscured by water peak).

¹H NMR (600 MHz, DMSO-*d*₆, **52b)** δ 12.57 (br s, 1H), 9.28 – 9.03 (m, 1H), 8.25 – 8.11 (m, 1H), 8.07 – 7.90 (m, 2H), 7.41 – 7.24 (m, 5H), 7.05 – 6.93 (m, 2H), 6.62 (d, $J =$

9.0 Hz, 2H), 5.90 (ddt, $J = 17.3, 10.7, 5.4$ Hz, 1H), 5.28 (dd, $J = 17.2, 1.7$ Hz, 1H), 5.19 (dd, $J = 10.5, 1.4$ Hz, 1H), 5.06 – 5.03 (m, 2H), 4.53 (d, $J = 5.4$ Hz, 2H), 4.47 – 4.36 (m, 1H), 4.33 – 4.26 (m, 1H), 4.21 – 4.12 (m, 1H), 3.73 – 3.60 (m, 1H), 2.86 (dd, $J = 13.9, 4.3$ Hz, 1H), 2.65 – 2.57 (m, 1H), 2.53 – 2.51 (m, 1H), 2.41 – 2.33 (m, 2H), 2.08 – 1.88 (m, 3H), 1.87 – 1.66 (m, 4H), 1.60 – 1.48 (m, 1H), 1.48 – 1.39 (m, 1H), 1.27 (d, $J = 7.3$ Hz, 3H) ppm. (Note: two H's obscured by water peak)

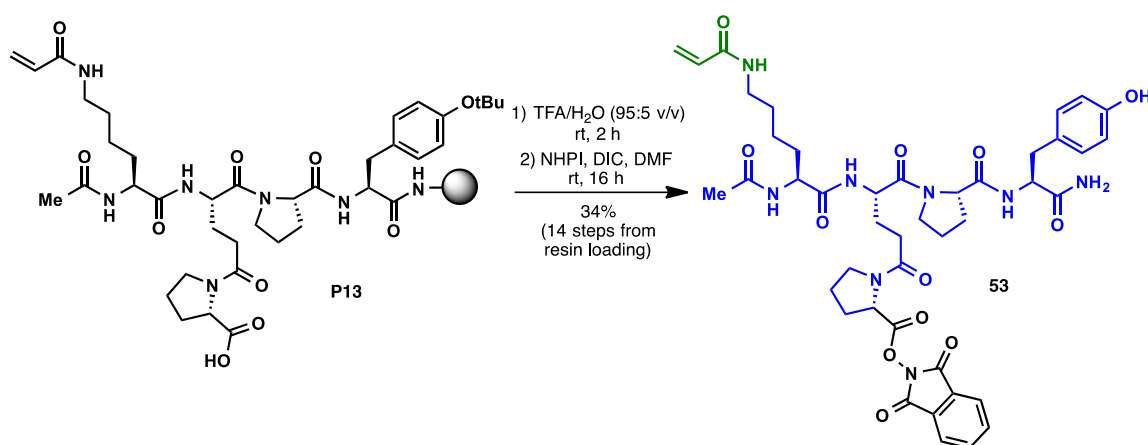


A) Crude analytical HPLC trace of the formation of peptide **52** from resin-bound peptide **51** following 1,4-addition and TFA cleavage (5 to 100% B over 25 min, $\lambda = 230$ nm) [note that **51'** designates the TFA-cleaved peptide, accompanied by loss of acid-labile side-chain protecting groups]; **B)** Purified peptide **52a** ($R_t = 16.1$ min, 5 to 100% B over 25 min, $\lambda = 230$ nm); **C)** Purified peptide **52b** ($R_t = 16.3$ min, 5 to 100% B over 25 min, $\lambda = 230$ nm).



LRMS (ESI-TOF): calc'd for $C_{35}H_{45}N_4O_{10}$ $[M+H]^+$ 681.31; found 681.31

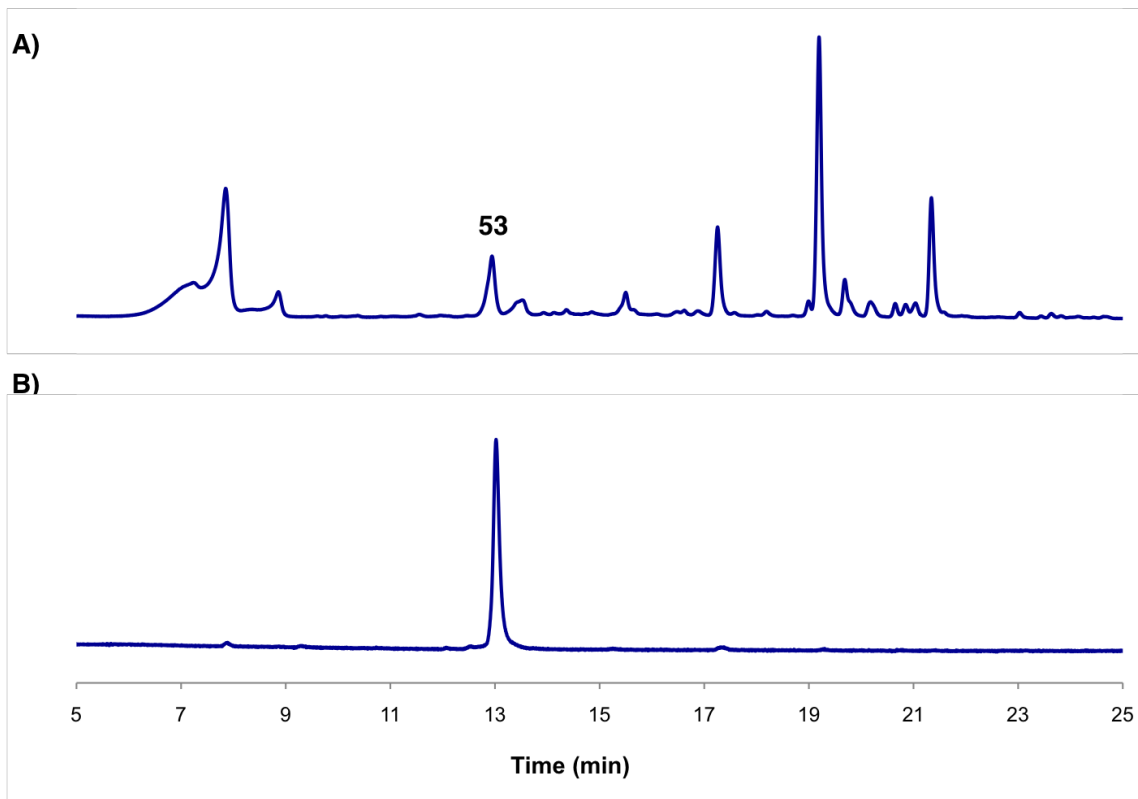
Preparation of peptide **53** for macrocyclization:



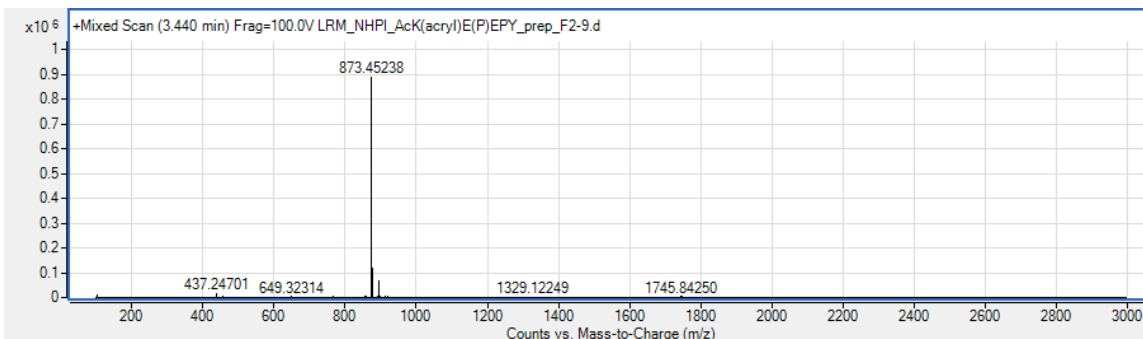
Peptide **53** was prepared on a 50 μ mol scale from resin-bound substrate **P13** using standard SPPS protocols, followed by on-resin deallylation and acryloyl chloride coupling (outlined in the general methods section). The crude peptide was then cleaved from the resin using TFA/H₂O (95:5 v/v, rt, 2 h), concentrated under a stream of nitrogen, and ether precipitated. The crude precipitated peptide was then dissolved in DMF (0.8 mL) and treated with NHPI (5.0 equiv.) followed by DIC (5.0 equiv.). After stirring at rt for 16 h, the reaction was deemed complete by LC-MS analysis. The crude mixture was purified by preparative reverse-phase HPLC (25% B for 10 min, 25% to 55% B over 25 min) and immediately lyophilized to afford the target NHPI ester **53** as a fluffy white

solid (14.7 mg, 34% yield based on the original resin loading).

^1H NMR (600 MHz, DMSO- d_6) δ 9.14 (s, 1H), 8.13 (d, $J = 7.6$ Hz, 1H), 8.05 (t, $J = 5.7$ Hz, 1H), 8.00 – 7.89 (m, 5H), 7.76 (d, $J = 8.2$ Hz, 1H), 7.18 – 7.13 (m, 1H), 7.04 – 7.01 (m, 1H), 6.99 (d, $J = 8.5$ Hz, 2H), 6.62 (d, $J = 8.4$ Hz, 2H), 6.19 (dd, $J = 17.1, 10.2$ Hz, 1H), 6.05 (dd, $J = 17.1, 2.3$ Hz, 1H), 5.55 (dd, $J = 10.2, 2.3$ Hz, 1H), 4.77 (dd, $J = 9.0, 3.7$ Hz, 1H), 4.55 – 4.48 (m, 1H), 4.31 – 4.16 (m, 3H), 3.67 – 3.47 (m, 4H, partially obscured by H₂O peak), 3.15 – 3.04 (m, 2H), 2.89 (dd, $J = 13.9, 5.4$ Hz, 1H), 2.72 (dd, $J = 13.9, 8.6$ Hz, 1H), 2.45 – 2.33 (m, 3H), 2.17 – 2.07 (m, 1H), 2.07 – 1.99 (m, 1H), 1.99 – 1.62 (m, 9H), 1.61 – 1.52 (m, 1H), 1.53 – 1.35 (m, 3H), 1.34 – 1.15 (m, 3H) ppm.

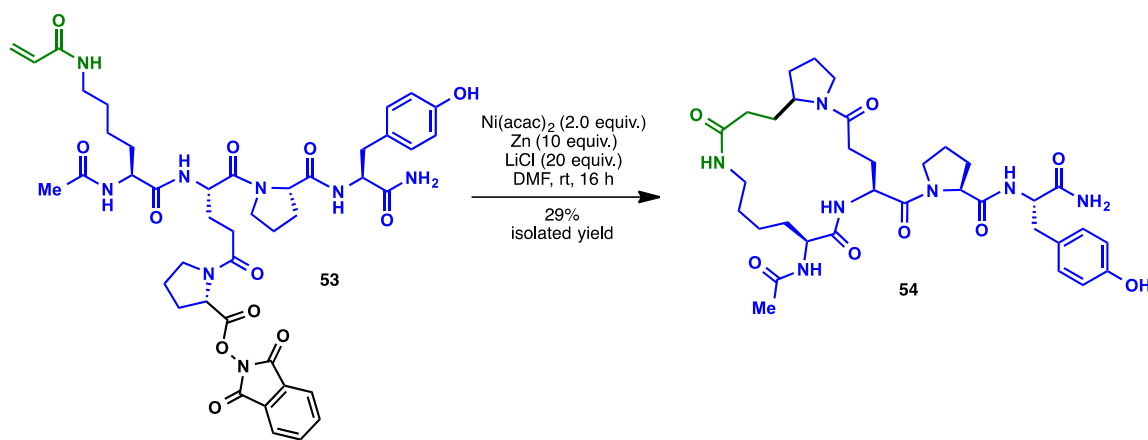


A) Crude analytical HPLC trace of the formation of peptide **53** following SPPS and NHPI activation (5 to 100% B over 25 min, $\lambda = 280$ nm); **B)** Purified peptide **53** ($R_t = 13.0$ min, 5 to 100% B over 25 min, $\lambda = 280$ nm).



LRMS (ESI-TOF): calc'd for $C_{43}H_{53}N_8O_{12}$ $[M+H]^+$ 873.38; found 873.45

Peptide 54



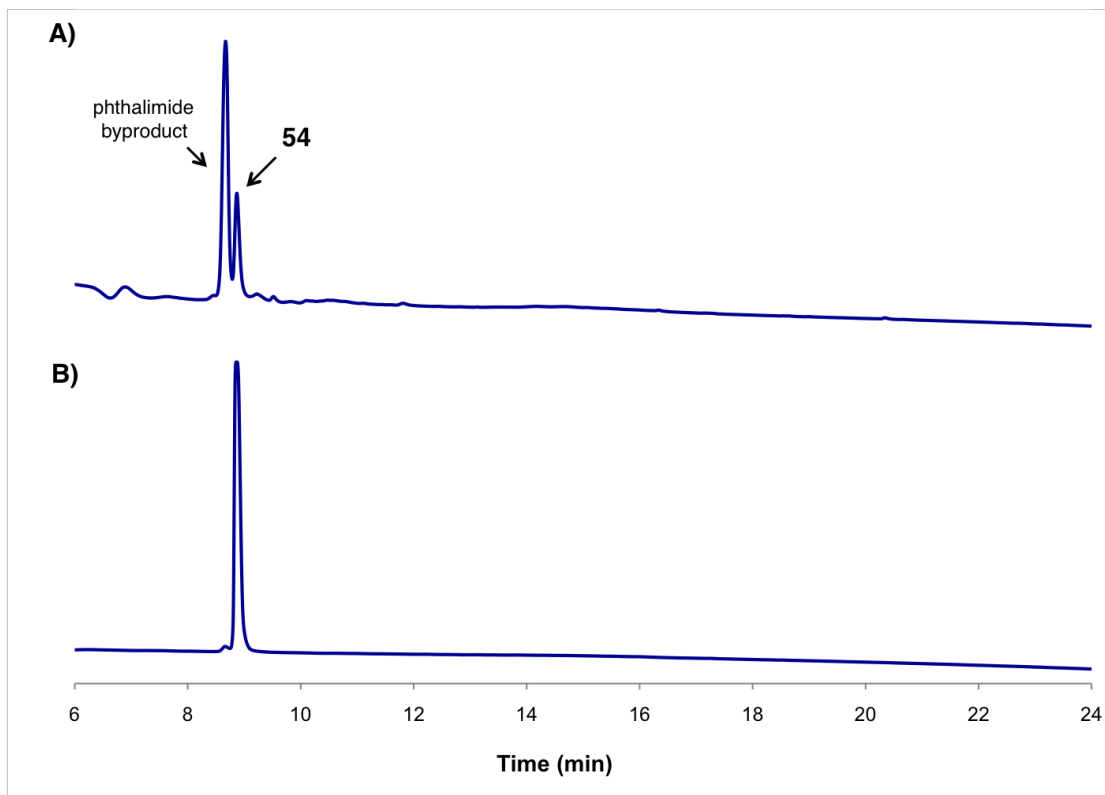
Peptide **54** was prepared from peptide **53** using a modification of the on-resin 1,4-addition protocol. Peptide **53** (7.6 mg, 8.7 μmol) was dissolved in dry DMF (0.87 mL, 10 mM with respect to peptide **53**) and treated with $\text{Ni}(\text{acac})_2$ (2.0 equiv.), Zn powder (10 equiv.), and LiCl (20 equiv.). The resulting heterogeneous mixture was stirred vigorously at rt for 16 h, at which point LC-MS analysis indicated formation of the target peptide macrocycle **54**. The reaction was diluted with a mixture of water/MeCN (10:1 v/v) and passed through a micropore filter to remove excess zinc powder. The resulting solution was purified by preparative reverse-phase HPLC (10% B for 15 min, 10% to 50% B over

40 min) to afford **54** as a fluffy white solid following lyophilization and as a mixture of diastereomers (1.7 mg, 29%).

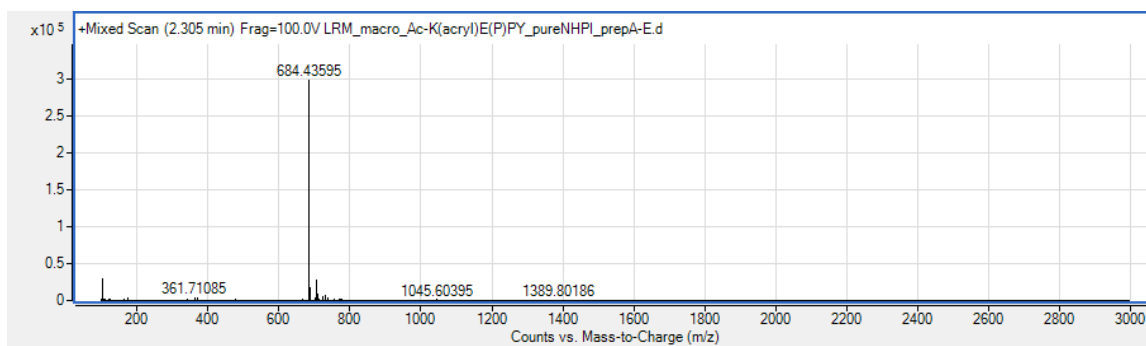
Isolated as an ~1.2:1 mixture of diastereomers;

¹H NMR (600 MHz, DMSO-*d*₆, diastereomers) δ 9.15 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 0.55H, *NH*), 7.98 (d, *J* = 8.1 Hz, 0.45H, *NH*), 7.88 – 7.81 (m, 0.55H, *NH*), 7.79 (t, *J* = 5.5 Hz, 0.45H, *NH*), 7.74 (d, *J* = 7.5 Hz, 1H, *NH*), 7.67 (d, *J* = 8.1 Hz, 0.45H, *NH*), 7.35 (d, *J* = 8.2 Hz, 0.4H, *NH*), 7.24 – 7.08 (m, 1H, *NH*), 7.06 – 6.94 (m, 3H), 6.69 – 6.56 (m, 2H), 4.60 – 4.49 (m, 0.45H), 4.40 – 4.33 (m, 0.55H), 4.32 – 4.20 (m, 2H), 4.18 – 4.09 (m, 1H), 3.86 – 3.74 (m, 1H), 3.70 – 3.53 (m, 1H), 3.52 – 3.21 (m, 3H, partially obscured by H₂O peak), 3.15 – 2.96 (m, 1.45H), 2.94 – 2.85 (m, 1H), 2.85 – 2.79 (m, 0.55H), 2.78 – 2.69 (m, 1H), 2.42 – 2.36 (m, 2H), 2.22 – 2.12 (m, 1H), 2.12 – 1.64 (m, 15H), 1.64 – 1.48 (m, 2H), 1.48 – 1.39 (m, 2H), 1.38 – 1.19 (m, 3H) ppm.

¹³C NMR (151 MHz, DMSO, diastereomers) δ 172.8, 172.7, 171.7, 171.2, 171.1, 171.1, 170.9, 170.3, 170.3, 170.0, 169.8, 169.3, 169.2, 155.7, 130.1, 130.0, 127.9, 127.9, 114.8, 59.7, 59.6, 56.5, 55.9, 54.1, 54.1, 53.3, 52.9, 49.9, 49.3, 46.9, 46.6, 45.5, 45.2, 38.2, 37.3, 36.4, 36.3, 32.7, 32.2, 31.9, 31.7, 30.8, 30.7, 30.0, 29.5, 29.2, 29.0, 29.0, 28.9, 28.8, 28.8, 28.7, 28.6, 28.6, 28.5, 28.0, 27.5, 26.5, 24.3, 24.2, 22.9, 22.6, 22.5, 22.3, 21.6, 21.4 ppm. (Note: diastereomeric mixture gives rise to complex ¹³C spectrum; residual TFA is observed following lyophilization: δ 158.0 – quartet, *J* = 34.5 Hz).

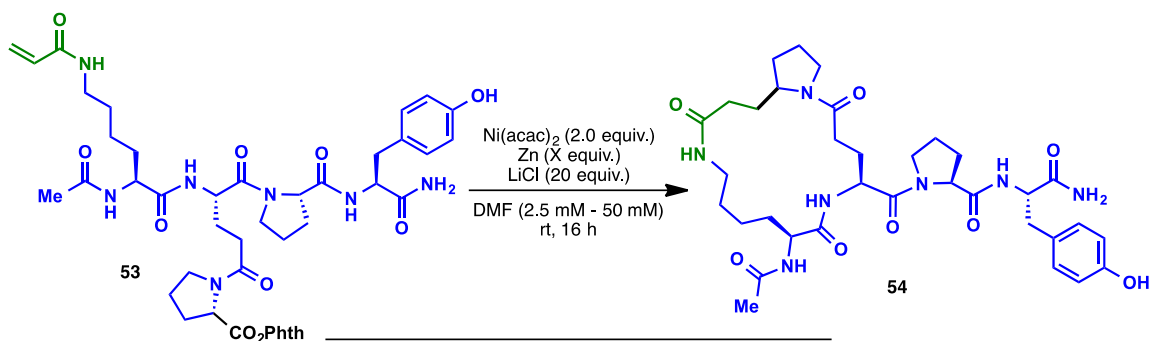


A) Representative crude analytical HPLC trace of the formation of peptide **54** from linear precursor **53** (5 to 100% B over 25 min, $\lambda = 210$ nm); **B)** Purified peptide **54** (Rt = 8.9 min, 5 to 100% B over 25 min, $\lambda = 210$ nm).



LRMS (ESI-TOF): calc'd for $C_{34}H_{50}N_7O_8$ $[M+H]^+$ 684.37; found 684.44

Macrocyclization screen – reaction concentration and zinc loading



entry	Concentration ^a	Zn (X equiv.)	yield (%) ^b
1	50 mM	50 equiv.	18
2	50 mM	10 equiv.	17
3	10 mM	10 equiv.	29
4	2.5 mM	10 equiv.	0 ^c

^a Concentration with respect to peptide 53; ^b isolated yield following HPLC purification; ^c No product observed, major byproducts include ester hydrolysis and a dehydration byproduct (loss of H₂O).

Note on macrocyclization reactions: At higher concentrations (50 mM, entries 1-2), the major byproducts of the macrocyclization reaction were derived from oligomerization of the starting linear peptide. Reducing the concentration of the cyclization reaction to 10 mM (entry 3) served to decrease the amount of oligomerization byproducts while leading to a slight increase in hydrolysis of the active ester and reduction of the acryloyl group (to form the saturated, lysine-linked propionamide). At even lower concentrations (2.5 mM) in combination with decreased zinc loading (entry 4), however, hydrolysis of the activated ester and formation of a dehydration byproduct predominated.

Troubleshooting: Frequently Asked Questions

Part I. Redox-Active Ester Synthesis

Question 1:

I am trying to get high-resolution spectrometry (HRMS) data for my redox-active ester, but I am having trouble. What do I do?

Answer:

For these types of compounds, obtaining HRMS data by ESI can be difficult. We normally rely heavily on ^1H and ^{13}C NMR data to determine if we have the correct compound. If necessary, a crystal structure can typically be obtained for most redox-active esters.

For other questions regarding the synthesis, purification, characterization, stability and storage of redox-active esters, please see our previous papers^{1,2} for fully-detailed answers.

Part II. Nickel-Catalyzed Reductive Decarboxylation

Question 1:

Have you tried any other nickel sources for this reaction? What about other metal catalysts?

Answer:

We tried other nickel sources, but $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ performed best while also being very cost efficient. Fe salts are also competent at catalyzing this reaction. For an unoptimized procedure using $\text{Fe}(\text{acac})_3$, see the synthesis of **19b**.

Question 2:

How do you monitor the reactions?

Answer:

We monitor the reactions by a combination of TLC (and appropriate staining or UV visualization), GC/MS, and LC/MS. For smaller molecules, formation of products can be observed on GC/MS. For compounds containing basic nitrogen atoms, LC/MS works well.

Question 3:

Do I need a glovebox to run this reaction?

Answer:

We do not set up or run the reaction in a glovebox. A glovebox is not necessary to run this reaction. We evacuate the air from the tube via vacuum manifold though.

Question 4:

Do I need to activate the zinc for this reaction?

Answer:

We do not activate the zinc. During the course of optimization we found that activation of the zinc with TMSCl and 1,2-dibromoethane did not improve or hurt the yield of the reaction.

Question 5:

Is it necessary to run the reaction for a one hour period, or can I quench it sooner or later?

Answer:

The reaction can be stopped sooner if there is complete consumption of the redox-active ester starting material. The best way to determine if the starting material has been completely consumed is by TLC analysis with a co-spot of the reaction mixture and starting material. Similarly, the reaction time can be extended if there is still redox-active ester present after 1 hour. In general, we saw complete consumption of starting material

within a one hour period. We also found that leaving the reaction longer even after complete consumption of starting material was not detrimental to the yield.

Question 6:

Are there any indicative color changes during the reaction?

Answer:

We often observe that the reaction mixture quickly changes from the green-blue color of the Ni stock solution to a light gray/brown (within 5 minutes of heating). After 30 minutes to 1 hour, the reaction typically turns a dark brown/black color. The initial color change from green-blue to a light gray/brown color typically occurs for successful reactions. The second color change (from light gray/brown to dark brown/black) is not always observed and does not seem to be indicative of the yield or success of the reaction.

Question 7:

How do I work up the reaction?

Answer:

We quench the reaction with 1:1 H₂O/sat. aq. NH₄Cl solution. The mixture is then extracted with Et₂O or EtOAc for three to four times. The organic extracts are dried over MgSO₄, Na₂SO₄, or a plug of silica gel and then concentrated to yield the crude product.

Question 8:

How do I purify my product?

Answer:

We use both silica gel flash column chromatography and PTLC. Reverse-phase HPLC can be used for very polar compounds.

Question 9:

How do I determine which redox-active ester to use?

Answer:

For the Ni-catalyzed reductive decarboxylation, use of NHPI RAEs is preferred over other RAEs (TCNHPI or –OAt) due to higher obtained yields in the optimization process.

Question 10:

What other possible byproducts could be observed in this reaction?

Answer:

We observe hydrolysis of the NHPI RAE to the corresponding carboxylic acid.

Question 11:

I obtained the product, but the yield is not satisfactory for my purposes. What do you recommend I try to optimize the reaction?

Answer:

For optimization, we recommend the following:

1. Try heating the reaction at temperatures higher than 40 °C, such as 60 °C
2. Adding larger amounts of PhSiH₃ and Zn.
3. If the NHPI RAE seems prone to hydrolysis, consider removing *i*-PrOH from the reaction mixture.
4. Consider running the reaction on larger scale. We observed that reaction tends to work better on larger scale.
5. Try activating the Zn with TMSCl and 1,2-dibromoethane or aqueous HCl.

Part III. Nickel-Catalyzed Giese-type Conjugate Addition

Question 1:

Have you tried any other nickel sources for this reaction? What about other metal catalysts?

Answer:

We tried other nickel sources, but $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ performed best. Other salts such as Fe and Mn salts also delivered the product, albeit in reduced yields.

Question 2:

Is LiCl essential for the reaction? Does the LiCl need to be rigorously dried? Can I use a different salt?

Answer:

If the reaction is run without any salt additives, it does not work. LiCl proved to be the best additive during the optimization process. We do not rigorously dry the LiCl. Due to its hygroscopic nature, we weigh the LiCl directly into the reaction flask, and the flask is not subsequently flame-dried. Excess LiCl does not hurt the yield. Other salts such as MgCl_2 , LiBr, and $\text{MgBr}_2 \cdot \text{OEt}_2$ also gave the desired product but in lower yield. Reactions with additives such as LiBF_4 and LiClO_4 did not afford the desired product.

Question 3:

Do I need a ligand for this reaction?

Answer:

We do not add any additional ligand to the reaction mixture. Screening of bipyridine-type ligands showed that including these ligands in the reaction mixture was detrimental to the yield of the desired product.

Question 4:

Are there limitations on the type of Michael acceptors that can be used?

Answer:

For most Michael acceptors we observed the desired product in isolable quantities (> 20%). To date, the only acceptors that failed to give any product were unprotected

maleimide and acrylic acid. We anticipate that acceptors similar to maleimide and acrylic acid with acidic protons could be problematic.

Question 5:

I'm working on small scales, and the general procedure requires relatively high concentration (0.4 M). Can I dilute the reaction?

Answer:

The reaction can be diluted to 0.2 M with no significant ill effect. Further dilution will likely be detrimental. We found that barely any product formation occurs at 0.05 M reaction concentration for the substrate used for optimization.

Question 6:

How does stirring affect the reaction?

Answer:

We recommend smooth, uniform stirring that prevents accumulation of zinc on the sides of the reaction flask. An accumulation of zinc can occur if the stirring is too slow or if the reaction vessel is too far removed from the center of the stir plate. These potential detriments are particularly pronounced on smaller scale.

Question 7:

How do you monitor the reactions?

Answer:

We monitor the reactions by a combination of TLC (and appropriate staining or UV visualization), GC/MS, and LC/MS. For smaller molecules, GC/MS typically shows the formation of the product. For compounds containing basic nitrogen atoms, LC/MS works well.

Question 8:

Do I need a glovebox to run this reaction?

Answer:

We do not set up or run the reaction in a glovebox. A glovebox is not necessary to run this reaction. We evacuate the air from the tube via vacuum manifold

Question 9:

Do I need to activate the zinc for this reaction?

Answer:

We do not activate the zinc. During the course of optimization we found that activation of the zinc with TMSCl and 1,2-dibromoethane did not improve or hurt the yield of the reaction.

Question 10:

Is it necessary to run the reaction for a 12 hour period, or can I quench it sooner or later?

Answer:

The reaction can be stopped sooner if there is complete consumption of the redox-active ester starting material. The best way to determine if the starting material has been completely consumed is by TLC analysis with a co-spot of the reaction mixture and starting material. Similarly, the reaction time can be extended if there is still redox-active ester present after 12 hours. In general, we saw complete consumption of starting material within a 12 hour period. We also found that leaving the reaction longer even after complete consumption of starting material was not detrimental to the yield.

Question 11:

Are there any indicative color changes during the reaction?

Answer:

Upon addition of the Michael acceptor, the reaction mixture often changes from a gray color to a green or black color (depending on the Michael acceptor) slowly over 20 to 30 minutes.

Question 12:

How do I work up the reaction?

Answer:

We quench the reaction with 1:1 H₂O/sat. aq. NH₄Cl solution. The mixture is then extracted with Et₂O or EtOAc three to four times. The organic extracts are dried over MgSO₄, Na₂SO₄, or a plug of silica gel and then concentrated to yield the crude product.

Question 13:

How do I purify my product?

Answer:

We use both silica gel flash column chromatography and PTLC. Reverse-phase HPLC can be used for very polar compounds.

Question 14:

How do I determine which redox-active ester to use?

Answer:

For the Ni-catalyzed 1,4 conjugate addition, use of NHPI RAEs is preferred over other RAEs (TCNHPI or -OAt) due to higher obtained yields in the optimization process.

Question 15:

What other possible byproducts could be observed in this reaction?

Answer:

We observe hydrolysis of the NHPI RAE to the corresponding carboxylic acid as well as small amounts of decarboxylation (depending on the substrate).

Question 16:

I obtained the product, but the yield is not satisfactory for my purposes. What do you recommend I try to optimize the reaction?

Answer:

For optimization, we recommend the following:

1. Try heating the reaction at 50 °C. We found empirically that primary carboxylic acid derived NHPI RAEs benefited from being heated in an oil bath at 50 °C for the duration of the reaction.
2. Try more Zn or more Michael acceptor.
3. Try activating the Zn with TMSCl and 1,2-dibromoethane or aqueous HCl.
4. Consider running the reaction on a larger scale. We observed that the reaction tends to work better on larger scales.

Part IV. One-pot Activation of Carboxylic Acids for Reductive Decarboxylation and Giese-type Conjugate Addition Reactions**Question 1:**

Do I have to use DIC?

Answer:

We prefer DIC since it is a liquid and is therefore easier to handle. DCC works equally well.

Question 2:

What solvents are best for the one-pot activation procedure?

Answer:

Dichloromethane was found to be the optimal solvent for the one-pot activation procedure. DMF afforded inferior results.

Question 3:

Do I need to remove CH₂Cl₂ before running either the decarboxylation or Giese conjugate addition reaction?

Answer:

Significant (solvent) quantities of CH₂Cl₂ inhibit product formation in both reductive decarboxylation or Giese-type conjugate addition reaction. The majority of the solvent was removed on a rotary evaporator before conducting the second operation (decarboxylation or Giese conjugate addition). We did not check for the complete removal of CH₂Cl₂ by ¹H NMR before performing the second operation in the same reaction flask.

Part V. On-Resin Peptide Giese Conjugate Addition and Peptide Macrocyclization**Question 1:**

How do you monitor the reactions?

Answer:

Monitoring the progress of reactions directly on-resin can be difficult and generally requires cleavage of the peptide from the solid-support prior to analysis using conventional methods (for Rink amide resin, cleavage requires treatment with TFA). As such, the on-resin activation of the carboxylic acid generally cannot be monitored without hydrolyzing the active ester. Excess equivalents of activating agents are therefore utilized

to ensure complete activation of the acid. Following the 1,4-addition, however, the outcome of the activation-coupling sequence can be evaluated by performing a “test cleavage,” whereby a small number of resin beads are treated with TFA to cleave the peptide and the resultant peptide-containing residue is analyzed by LC-MS and analytical HPLC (210 nm, 230 nm and 280 nm are generally the most useful for reaction monitoring).

Question 2:

What if the reaction does not proceed to completion?

Answer:

If there is still starting material bearing a free carboxylic acid after a single activation-1,4-addition procedure, the activation-addition protocol may be repeated additional times without issue. In the case of on-resin acid derivatization, repeating the activation-addition protocol was generally not necessary to provide satisfactory yields of the target products. However, repeated 1,4-additions were found to be particularly useful in the case of the reaction of resin-bound acceptors (e.g. reaction of **51** to **52**), with preformed NHPI esters. These processes do not require on-resin activation, and as such, can be repeated in a simple and rapid manner. In the event of repeated couplings, we suggest replacing the fritted syringe, as the excess Zn powder employed in the reaction may clog the frit after repeated treatments.

Question 3:

What major byproducts should I look out for?

Answer:

Incomplete reactions (recovered starting material) and decarboxylation accompanied by reduction (net loss of 44 mass units from the starting peptide) are potential byproducts

from the on-resin 1,4-addition protocol. In some cases of resin-bound acid derivatization, we also observed products consistent with the addition of multiple equivalents of Michael acceptor (see for instance the crude HPLC of the reaction of **48** to **49**, which was accompanied by some multiple addition products). The extent of multiple additions was found to be highly dependent on the nature of the acceptor employed and was not observed in reactions with resin-bound acceptors (e.g. **51** to **52**). In some preliminary studies on the activation of the side-chain carboxylic acids of Asp and Glu, we also observed cyclization of the amide backbone onto the activated acid resulting in a byproduct consistent with the mass of the starting peptide-H₂O. Backbone amide protection (e.g. with a Dmb group) can help resolve this issue.

Question 4:

How anhydrous does the reaction need to be? Is moisture tolerated at all?

Answer:

While reactions were not performed strictly anhydrously (activations and 1,4-additions were carried out in solid-phase reaction vessels which were capped and placed on an orbital shaker rather than in round bottom flasks under an inert atmosphere), we did make an effort to exclude water and oxygen from both the solvents used in the reaction steps as well as the solvents used to wash the peptide immediately before the reaction and in-between the activation and conjugate addition steps. To wash the resin “anhydrously,” we simply charged a round bottom flask with dry DMF under an inert atmosphere and syringed out portions of this solution to perform the wash steps (see photos for more details). Care was taken specifically to wash the activated ester (e.g. the on-resin NHPI ester) with dry solvent to minimize hydrolysis. In the 1,4-addition reaction, dry solvents were also employed to exclude excess moisture. Nevertheless, the reaction proved tolerant to some moisture (e.g. the hygroscopic nature of LiCl means that the reaction is carried out without issue in the presence of some moisture).

Question 5:

How important is the concentration of reagents to the success of the on-resin 1,4-addition?

Answer:

In general, the higher the concentration, the better for on-resin reactions. Since the reaction mixture is heterogeneous (due to the insoluble Zn powder), high concentration and efficient mixing is very important to reaction success, particularly when the substrate is also heterogeneous (e.g. a resin-bound peptide). We found that concentrations of 80 mM with respect to the resin-bound substrate were suitable. In addition, a large excess of Michael acceptor or activated ester (20.0 equiv.) was typically employed. These factors help overcome the “pseudo-dilution” effect generally exhibited by resin-bound substrates.

Question 6:

How does the solid-phase 1,4-addition differ than the general reaction protocol for small molecules?

Answer:

One of the main differences between the resin-bound 1,4-addition method and the solution-phase approach for small molecules is the amount of catalyst, Zn, and LiCl employed. As noted above, the “pseudo-dilution” effect and challenges associated with a heterogeneous substrate tend to mandate higher catalyst loadings (2 equiv. in this case versus 20 mol% for the solution-phase approach) and larger reagent excesses. In addition, we found that Ni(acac)₂ (rather than Ni(ClO₄)₂ hexahydrate) proved to be an optimal catalyst for overall yields and conversions. Another crucial factor for the success of the on-resin protocol is the use of DMF as a solvent. Application of MeCN, as in the solution-phase approach, resulted in minimal product formation and was accompanied by the recovery of unreacted carboxylic acid (presumably following hydrolysis of the active

ester during TFA cleavage from the resin). We attribute the lack of success with MeCN to insufficient resin swelling in this solvent. As noted above, efficient mixing of the heterogeneous reaction solution and accessibility of the substrate on the solid-phase are vital to reaction success. Solvents in which the resin exhibits suitable swelling properties should therefore be employed.

Question 7:

Are there any additional issues that need to be addressed when performing an intra-molecular 1,4-addition (e.g. macrocyclization reaction)?

Answer:

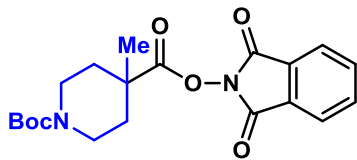
There are a few key differences between the protocol for intermolecular, on-resin 1,4-addition and the intramolecular, solution-phase macrocyclization protocol. First, additional time (~16 h) is required for NHPI ester formation in solution as opposed to on-resin (where large excesses of reagents may be readily employed). Reaction concentration also proved to be crucial to the success of the intramolecular, solution-phase reaction. While higher concentrations are generally preferable on-resin, the macrocyclization reaction was more effective at slightly higher dilution (e.g. 10 mM), where oligomerization byproducts could be minimized. At this concentration, we also found that we could reduce the amount of zinc (10 equiv.) in solution versus the on-resin protocol (50 equiv. zinc). However, lower zinc loadings (10 equiv.) at even higher dilutions (2.5 mM) shut down the desired macrocyclization pathway, with ester hydrolysis and a byproduct consistent with dehydration of the starting carboxylic acid predominating. We speculate that the relative concentration of zinc is crucial to the success of the reaction, and that lower reaction concentrations may be feasible with higher zinc loadings.

In addition to the above observations, it is also of note that while the intramolecular

1,4-addition proceeded well in solution, attempted on-resin cyclization of the same substrate was unsuccessful. We suspect that the presence of side-chain protecting groups and the bulky resin/resin-linker may conformationally restrict the peptide substrate, hindering preorganization of the linear chain.

Experimental Procedures and Characterization Data for Redox-Active Esters

Compound SI-8



SI-8

1-(tert-butyl) 4-(1,3-dioxoisindolin-2-yl) 4-methylpiperidine-1,4-dicarboxylate (SI-8)

Following **General Procedure A** on a 5.0 mmol scale. Purification by chromatography (silica gel, 4:1 hexanes:EtOAc) afforded 1.76g (91%) of the title compound SI-8.

Physical State: white solid.

m.p. 110-115 °C.

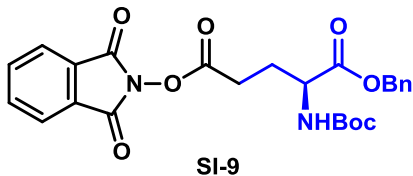
R_f = 0.67 (2:1 hexanes:EtOAc).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.85 (dd, J = 5.4, 3.1 Hz, 2H), 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 3.90 (s, 2H), 3.10 (s, 2H), 2.27 – 2.19 (m, 2H), 1.56 – 1.47 (m, 2H), 1.45 (s, 3H), 1.43 (s, 9H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 172.71, 162.05, 154.74, 134.85, 129.00, 128.99, 124.00, 79.70, 79.48, 41.84, 41.03, 34.83, 28.49, 26.22 ppm.

MS (ESI-TOF, m/z): calc'd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ 389.1707; found 389.1708.

Compound SI-9



SI-9

1-benzyl 5-(1,3-dioxoisindolin-2-yl) (tert-butoxycarbonyl)-L-glutamate (SI-9)

Following **General Procedure A** on 5.0 mmol scale. Purification by chromatography (silica gel, 4:1 hexanes:EtOAc) afforded 2.21g (92%) of the title compound **SI-9**.

Physical State: white solid.

m.p. 129-131 °C.

R_f = 0.47 (2:1 hexanes:EtOAc).

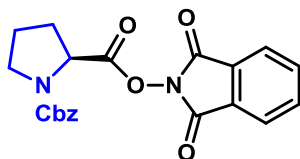
¹H NMR (600 MHz, CDCl₃): δ 7.89 (dd, J = 5.5, 3.1 Hz, 2H), 7.79 (dd, J = 5.5, 3.1 Hz, 2H), 7.39 – 7.32 (m, 5H), 5.22 (d, J = 9.4 Hz, 1H), 5.20 (s, 2H), 4.46 (d, J = 7.4 Hz, 1H), 2.79 (ddd, J = 17.0, 9.5, 6.3 Hz, 1H), 2.70 (ddd, J = 17.0, 9.5, 5.9 Hz, 1H), 2.42-2.34 (m, 1H), 2.17 – 2.08 (m, 1H), 1.44 (s, 9H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 171.07, 168.36, 161.30, 154.89, 134.63, 134.33, 128.41, 128.22, 128.12, 127.92, 123.54, 79.83, 67.04, 52.20, 27.82, 27.15, 26.87 ppm.

HRMS (ESI-TOF): calc'd for C₂₅H₂₇N₂O₈ [M+H]⁺ 483.1762; found 483.1761.

$[\alpha]_D^{20}$ = +3.6 (c 1.0, CHCl₃).

Compound SI-10



SI-10

1-benzyl 2-(1,3-dioxoisindolin-2-yl) (S)-pyrrolidine-1,2-dicarboxylate (SI-10)

Following **General Procedure A** on a 5.0 mmol scale. Purification by chromatography (silica gel, 4:1 hexanes:EtOAc) afforded 1.76g (91%) of the title compound **SI-10**. A mixture of rotomers was observed in CDCl₃ NMR at a ratio of 1.8:1.

Physical State: thick colorless oil.

R_f = 0.31 (2:1 hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.84 (ddd, J = 8.3, 5.4, 3.1 Hz, 5.6H), 7.74 (ddd, J = 11.8, 5.5, 3.1 Hz, 5.6H), 7.44 – 7.27 (m, 14H), 5.29 (d, J = 12.3 Hz, 1.8H), 5.21 (d, J =

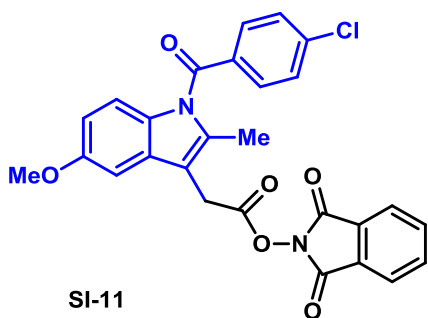
12.4 Hz, 1H), 5.13 (dd, $J = 12.4, 4.3$ Hz, 2.8H), 4.78 (dd, $J = 7.4, 4.9$ Hz, 1H), 4.70 (dd, $J = 8.6, 3.8$ Hz, 1.8H), 3.70 – 3.60 (m, 2.8H), 3.52 (ddt, $J = 26.1, 10.3, 7.6$ Hz, 2.8H), 2.46 – 2.32 (m, 5.6H), 2.12 – 2.04 (m, 2.8H), 2.03 – 1.94 (m, 2.8H) ppm. Complex ^1H spectrum was observed due to rotamers.

^{13}C NMR (151 MHz, CDCl_3): δ 169.30, 169.11, 161.53, 154.59, 153.94, 136.43, 136.34, 136.33, 134.84, 134.75, 128.77, 128.74, 128.41, 128.39, 128.05, 128.05, 127.97, 127.90, 127.87, 123.90, 123.87, 67.36, 67.23, 57.37, 56.98, 46.82, 46.36, 31.31, 30.24, 24.31, 23.45 ppm. Complexity ^{13}C spectrum was observed due to rotamers.

MS (ESI-TOF, m/z): calc'd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ 395.1238; found 395.1237.

$[\alpha]_{\text{D}}^{20} = -68.2$ (c 1.0, CH_2Cl_2).

Compound SI-11



1,3-dioxoisindolin-2-yl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (SI-11)

Following **General Procedure A** on a 5.0 mmol scale. Purification by chromatography (silica gel, CH_2Cl_2), followed by trituration of CH_2Cl_2 /hexanes afforded 0.98g (64%) of the title compound **SI-11**.

Physical State: white solid.

m.p. 170-172 °C.

$R_f = 0.37$ (2:1 hexanes:EtOAc).

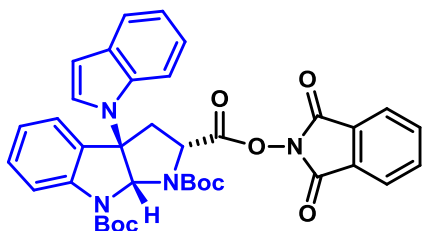
^1H NMR (600 MHz, CDCl_3): δ 7.91 – 7.86 (m, 2H), 7.81 – 7.76 (m, 2H), 7.71 – 7.67 (m, 2H), 7.50 – 7.45 (m, 2H), 7.03 (d, $J = 2.4$ Hz, 1H), 6.93 (dd, $J = 9.0, 0.5$ Hz, 1H), 6.71

(dd, $J = 9.0, 2.5$ Hz, 1H), 4.04 (s, 2H), 3.89 (s, 3H), 2.42 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 168.43, 167.15, 161.92, 156.38, 139.56, 136.59, 134.96, 133.83, 131.44, 130.90, 130.09, 129.31, 129.02, 124.15, 115.17, 112.61, 110.32, 100.79, 55.90, 27.28, 13.60 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{27}\text{H}_{20}\text{N}_2\text{ClO}_6$ $[\text{M}+\text{H}]^+$ 503.1004; found 503.1001.

Compound SI-12



SI-12

1,8-di-tert-butyl-2-(1,3-dioxoisindolin-2-yl)-(2R,3aR)-3a-(1H-indol-1-yl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,2,8-tricarboxylate (SI-12)

The corresponding methyl ester⁵ (360 mg, 0.675 mmol) was treated with 5 equiv NaOH (dissolve in 1 mL H_2O) in 5 mL THF/MeOH (2:1). The reaction was heated up to 40 °C for 5 h. After cooling, this reaction was acidified with 1M HCl, and extracted with EtOAc for three times. The organic extracts were washed with brine, dried, and concentrated *in vacuum*. The resulting acid was used in next step without further purification.

Following **General Procedure A** on a 0.675 mmol scale. Purification by chromatography (silica gel, 4:1 hexanes:EtOAc) afforded 224 mg (50%, over 2 steps) of the title compound **SI-12**.

Physical State: white solid.

m.p. 54-55 °C.

R_f = 0.19 (4:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.79 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.77 – 7.74 (br, 1H), 7.71 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.40 (d, $J =$

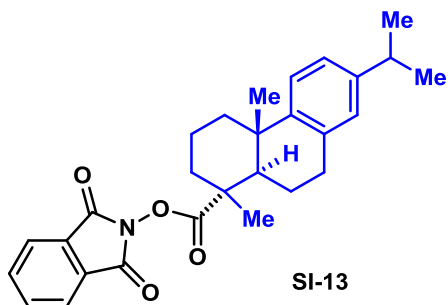
8.3 Hz, 1H), 7.36 (td, $J = 7.9, 1.3$ Hz, 1H), 7.25 (t, $J = 8.4$ Hz, 1H), 7.16 (t, $J = 7.5$ Hz, 2H), 6.97 (d, $J = 3.4$ Hz, 1H), 6.87 (s, 1H), 6.44 (d, $J = 3.3$ Hz, 1H), 5.23 (br, 1H), 3.83 (dd, $J = 13.9, 10.2$ Hz, 1H), 3.25 (d, $J = 13.9$ Hz, 1H), 1.54 (s, 9H), 1.52 (s, 9H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ ^{13}C NMR (151 MHz, CDCl_3) δ 171.08, 168.36, 161.30, 154.89, 134.63, 134.33, 128.41, 128.22, 128.12, 127.92, 123.54, 79.83, 67.04, 52.20, 27.82, 27.15, 26.87 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{37}\text{H}_{37}\text{N}_4\text{O}_8$ $[\text{M}+\text{H}]^+$ 665.2606; found 665.2605.

$[\alpha]_{\text{D}}^{20} = +123.0$ (c 1.0, CH_2Cl_2).

Compound SI-13



1,3-dioxoisindolin-2-yl

(1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate (SI-13)

Following **General Procedure A** on a 5.0 mmol scale. Purification by chromatography (silica gel, 10:1 hexanes:Et₂O), afforded 804 mg (65%) of the title compound **SI-13**. Note: the starting material dehydroabietic acid is in 55% purity from TCI America.

Physical State: white solid.

m.p. 62-63 °C.

$R_f = 0.51$ (4:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.88 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.81 – 7.75 (m, 2H), 7.19 (d, $J = 8.2$ Hz, 1H), 7.02 (dd, $J = 8.2, 2.0$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 3.10 (ddd, $J = 18.4, 11.5, 7.5$ Hz, 1H), 3.02 – 2.94 (m, 1H), 2.84 (p, $J = 6.9$ Hz, 1H), 2.44 (dd, $J =$

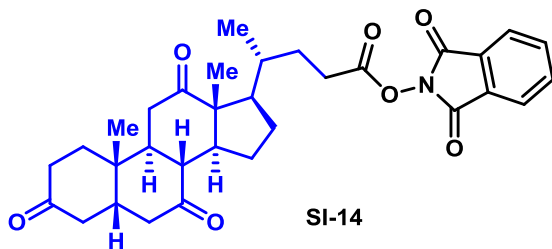
12.5, 2.2 Hz, 1H), 2.37 (dq, $J = 13.1, 2.9$ Hz, 1H), 2.12 (td, $J = 12.8, 5.4$ Hz, 1H), 2.02 – 1.91 (m, 2H), 1.90 – 1.78 (m, 3H), 1.58 (td, $J = 12.8, 4.9$ Hz, 1H), 1.46 (s, 3H), 1.28 (s, 3H), 1.23 (d, $J = 6.9$ Hz, 6H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 174.71, 162.28, 146.48, 146.02, 134.90, 134.77, 129.21, 127.14, 124.24, 124.07, 123.96, 47.87, 45.22, 37.92, 37.17, 36.42, 33.60, 30.05, 25.36, 24.13, 24.09, 21.86, 18.47, 16.67 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{28}\text{H}_{32}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 446.2326; found 446.2327.

$[\alpha]_{\text{D}}^{20} = +76.4$ (c 1.0, CH_2Cl_2).

Compound SI-14



1,3-dioxoisindolin-2-yl-(4R)-4-((5S,8R,9S,10S,13R,14S)-10,13-dimethyl-3,7,12-trioxo hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (SI-14)

Following **General Procedure A** on a 5.0 mmol scale. Purification by chromatography (silica gel, 2:1 hexanes:EtOAc), afforded 2.02 g (74%) of the title compound **SI-14**.

Physical State: white solid.

m.p. 195-200 °C.

$R_f = 0.18$ (1:1 hexanes/EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.88 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.81 – 7.77 (m, 2H), 2.94 – 2.82 (m, 3H), 2.76 (ddd, $J = 16.0, 8.6, 5.1$ Hz, 1H), 2.64 (dt, $J = 16.1, 8.2$ Hz, 1H), 2.38 – 2.18 (m, 6H), 2.18 – 2.09 (m, 2H), 2.09 – 1.94 (m, 5H), 1.90 – 1.83 (m, 1H), 1.62 (td, $J = 14.5, 4.6$ Hz, 1H), 1.58 – 1.50 (m, 1H), 1.46 – 1.38 (m, 2H), 1.41 (s, 3H), 1.29 (qd, $J = 12.0, 5.7$ Hz, 1H), 1.12 (s, 3H), 0.93 (d, $J = 6.6$ Hz, 3H) ppm.

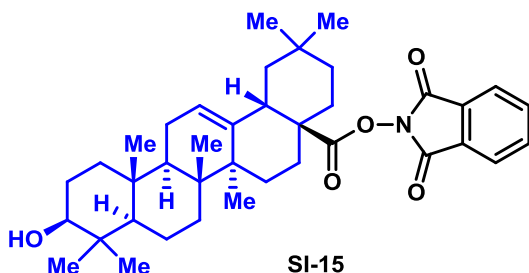
^{13}C NMR (151 MHz, CDCl_3): δ 212.02, 209.16, 208.78, 170.00, 162.12, 134.88, 129.10,

124.10, 57.10, 51.93, 49.16, 47.02, 45.79, 45.69, 45.14, 42.96, 38.79, 36.66, 36.18, 35.46, 35.44, 30.47, 28.65, 27.79, 25.31, 22.07, 18.69, 12.02 ppm.

MS (ESI-TOF, m/z): calc'd for $C_{32}H_{38}NO_7$ $[M+H]^+$ 548.2643; found 548.2645.

$[\alpha]_D^{20} = +16.5^\circ$ (c 1.0, CH_2Cl_2).

Compound SI-15



*1,3-dioxoisindolin-2-yl-(4a*S*,6a*S*,6b*R*,8a*R*,10*S*,12a*R*,12b*R*,14b*S*)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydricene-4a(2*H*)-carboxylate (SI-15)*

Following **General Procedure A** on a 5.0 mmol scale with oleanolic acid afforded 2.25 g (75%) of **SI-15** following purification by column chromatography (7:3 hexanes/EtOAc to 1:1 hexanes/EtOAc).

Physical State: white solid.

m.p. 160-171 °C.

$R_f = 0.36$ (7:3 hexanes/EtOAc).

1H NMR (600 MHz, $CDCl_3$) δ 7.86 (dd, $J = 5.5, 3.0$ Hz, 2H), 7.76 (dd, $J = 5.5, 3.1$ Hz, 2H), 5.32 (t, $J = 3.7$ Hz, 1H), 3.24 – 3.18 (m, 1H), 2.92 – 2.86 (m, 1H), 2.18 (td, $J = 13.9, 3.7$ Hz, 1H), 2.01 (tt, $J = 14.1, 4.8$ Hz, 2H), 1.94 (ddd, $J = 14.0, 4.4, 2.6$ Hz, 1H), 1.92 – 1.81 (m, 3H), 1.72 (t, $J = 13.7$ Hz, 1H), 1.66 – 1.38 (m, 9H), 1.36 – 1.17 (m, 4H), 1.19 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.91 – 0.87 (m, 1H), 0.86 (s, 3H), 0.78 (s, 3H), 0.74 (dd, $J = 11.4, 2.0$ Hz, 1H) ppm.

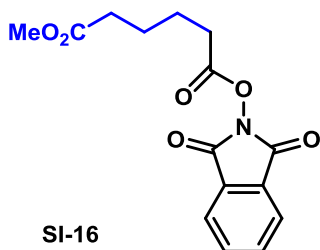
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.89, 162.38, 142.69, 134.72, 129.23, 123.93, 123.45, 79.20, 55.42, 47.81, 47.33, 45.97, 42.15, 41.72, 39.56, 38.92, 38.71, 37.19, 33.98, 33.12,

32.99, 32.66, 30.76, 28.27, 28.15, 27.36, 25.75, 23.66, 23.64, 23.37, 18.51, 17.09, 15.73, 15.56 ppm.

MS (ESI-TOF, m/z): calc'd for $C_{38}H_{52}NO_5$ $[M+H]^+$ 602.3840; found 602.3840.

$[\alpha]_D^{20} = +54.9^\circ$ (c 1.0, CH_2Cl_2).

Compound SI-16



1,3-dioxoisindolin-2-yl methyl adipate (SI-16)

Following **General Procedure A** on a 10.0 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 2.28g (75%) of the title compound **SI-16**.

Physical State: white solid.

m.p. 63-65 °C.

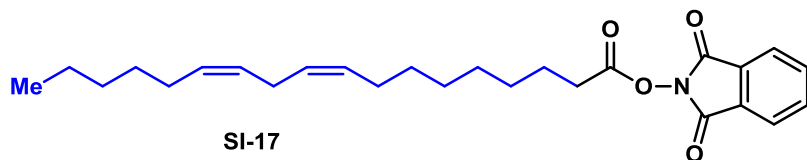
$R_f = 0.45$ (2:1 hexanes:EtOAc).

1H NMR (600 MHz, $CDCl_3$): δ 7.83 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.75 (dd, $J = 5.5, 3.1$ Hz, 2H), 3.64 (s, 3H), 2.66 (t, $J = 7.0$ Hz, 2H), 2.35 (t, $J = 7.0$ Hz, 2H), 1.82 – 1.72 (m, 4H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.54, 169.26, 161.94, 134.82, 128.89, 123.97, 51.64, 33.46, 30.67, 24.09, 24.04 ppm.

HRMS (ESI-TOF): calc'd for $C_{15}H_{16}NO_6$ $[M+H]^+$ 306.0972; found 306.0974.

Compound SI-17



1,3-dioxoisindolin-2-yl (9Z,12Z)-octadeca-9,12-dienoate (SI-17)

Following **General Procedure A** on a 5.0 mmol scale with linoleic acid afforded 1.63 g (77%) of **SI-17** following purification by column chromatography (4:1 hexanes/EtOAc).

Physical State: colorless oil.

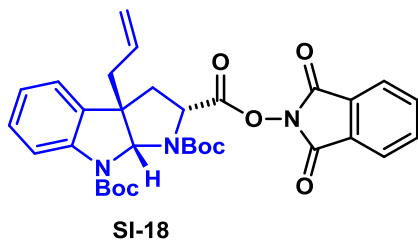
R_f = 0.33 (4:1 hexanes/EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.89 (dd, J = 5.4, 3.1 Hz, 2H), 7.84 – 7.70 (m, 2H), 5.42 – 5.28 (m, 4H), 2.80 – 2.75 (m, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.09 – 2.02 (m, 4H), 1.79 (p, J = 7.5 Hz, 2H), 1.48 – 1.41 (m, 2H), 1.40 – 1.24 (m, 12H), 0.89 (t, J = 6.9 Hz, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 169.76, 162.14, 134.86, 130.37, 130.17, 129.12, 128.23, 128.06, 124.09, 31.68, 31.14, 29.72, 29.50, 29.18 (2C), 28.95, 27.36, 27.34, 25.79, 24.81, 22.73, 14.23 ppm.

MS (ESI-TOF, m/z): calc'd for $\text{C}_{26}\text{H}_{36}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 426.2639; found 426.2641.

Compound SI-18



1,8-di-tert-butyl-2-(1,3-dioxoisindolin-2-yl)-(2S,3aS,8aR)-3a-allyl-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,2,8-tricarboxylate (SI-18)

The corresponding methyl ester⁷ (879 mg, 1.917 mmol) was treated with 5 equiv NaOH (in 5 mL H_2O) in 20 mL THF/MeOH (2:1). The reaction was heated up to 40 °C for 5 h.

After cooling, this mixture was acidified with 1M HCl, and was extracted with EtOAc for three times. The combined organic phase was washed with brine, dried over anhydrous MgSO₄, and concentrated *in vacuo*. The resulting acid was used in next step without further purification.

Following **General Procedure A** on a 1.9 mmol scale. Purification by chromatography (silica gel, 4:1 hexanes:EtOAc) afforded 726 mg (85% over 2 steps) of the title compound **SI-18**.

Physical State: clear yellow oil.

$R_f = 0.4$ (1:1 hexanes:Et₂O).

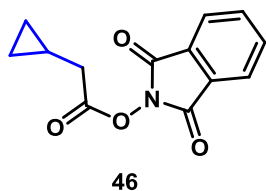
¹H NMR (600 MHz, CDCl₃): δ 7.84 (td, $J = 6.5, 5.5, 2.8$ Hz, 2H), 7.76 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.67 – 7.55 (m, 1H), 7.24 (t, $J = 7.7$ Hz, 1H), 7.21 – 7.15 (m, 1H), 7.07 (t, $J = 7.4$ Hz, 1H), 6.03 (s, 1H), 5.62 – 5.44 (m, 1H), 5.09 – 4.98 (m, 2H), 4.33 – 4.25 (m, 1H), 2.83 (dd, $J = 13.0, 7.1$ Hz, 1H), 2.49 – 2.38 (m, 3H), 1.55 (s, 9H), 1.44 (brs, 9H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 166.54, 161.85, 161.56, 152.28, 142.11, 134.83, 134.52 (br), 132.04, 128.83, 128.75, 123.96, 123.95, 122.84, 119.42, 117.39, 81.79, 81.53, 80.47 (br), 57.45, 41.97, 28.32, 28.04 (br), 23.38, 17.61 ppm.

HRMS (ESI-TOF): calc'd for C₃₂H₃₆N₃O₈ [M+H]⁺ 590.2497; found 590.2500.

$[\alpha]_D^{20} = -18.9$ (c 1.0, CH₂Cl₂).

Compound 46



1,3-dioxoisindolin-2-yl 2-cyclopropylacetate (46)

Following **General Procedure A** on a 10.0 mmol scale. Purification by flash column chromatography (silica gel, 10:1 CH₂Cl₂:Et₂O), followed by trituration from

CH₂Cl₂/hexanes afforded 1.39g (57%) of the title compound **46**.

Physical State: white solid.

m.p. 76-77 °C.

R_f = 0.84 (4:1 hexanes:Et₂O).

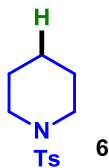
¹H NMR (600 MHz, CDCl₃): δ 7.90 – 7.86 (m, 2H), 7.80 – 7.76 (m, 2H), 2.58 (d, *J* = 7.1 Hz, 2H), 1.22 – 1.13 (m, 1H), 0.70 – 0.63 (m, 2H), 0.36 – 0.28 (m, 2H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 169.04, 162.08, 134.86, 129.07, 124.06, 36.12, 6.66, 4.77 ppm.

HRMS (ESI-TOF): calc'd for C₁₃H₁₂NO₄ [M+H]⁺ 246.0761; found 246.0763.

Experimental Procedures and Characterization Data for Decarboxylation Products

Compound 6



1-tosylpiperidine (6)

0.1 mmol Scale: Following **General Procedure B** on a 0.1 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 17.0 mg (71%) of the title compound **6**.

Gram-Scale Synthesis: Following gram-scale **General Procedure B** on a 2.3 mmol scale. Purification by column chromatography (silica gel, 19:1 CH₂Cl₂:Et₂O) afforded 470 mg (84%) of the title compound **6**.

Physical State: white solid.

m.p. 60-65 °C.

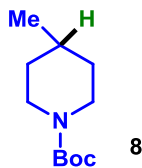
R_f = 0.64 (4:1 hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.65 – 7.62 (m, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 3.01 – 2.92 (m, 4H), 2.43 (s, 3H), 1.67 – 1.59 (m, 4H), 1.44 – 1.37 (m, 2H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 143.40, 133.41, 129.65, 127.84, 47.07, 25.30, 23.66, 21.65 ppm.

Spectroscopic data matches that reported in the literature.⁶

Compound 8



tert-butyl 4-methylpiperidine-1-carboxylate (8)

Following **General Procedure A** on a 0.1 mmol scale. Purification by PTLC (silica gel,

10:1 hexanes:Et₂O) afforded 15.7 mg (79%) of the title compound **8**.

Physical State: colorless oil.

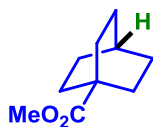
R_f = 0.57 (10:1 hexanes:Et₂O).

¹H NMR (600 MHz, CDCl₃): δ 4.04 (s, br, 2H), 2.67 (s, br, 2H), 1.59 (d, J = 12.8 Hz, 2H), 1.52 – 1.47 (m, 1H), 1.45 (s, 9H), 1.13 – 1.02 (m, 2H), 0.93 (d, J = 6.5 Hz, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 155.08, 79.26, 44.41 (br), 34.19, 31.13, 28.63, 22.05 ppm.

Spectroscopic data matches that reported in the literature.⁸

Compound 9



9

methyl bicyclo[2.2.2]octane-1-carboxylate (9)

Following **General Procedure A** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:Et₂O) afforded 8.2 mg (49%) of the title compound **9**.

Physical State: colorless oil.

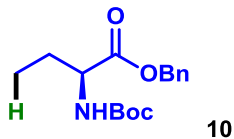
R_f = 0.51 (10:1 hexanes:Et₂O).

¹H NMR (600 MHz, CDCl₃): δ 3.63 (s, 3H), 1.75 – 1.70 (m, 6H), 1.62 (h, J = 3.0 Hz, 1H), 1.60 – 1.55 (m, 6H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 178.85, 51.71, 38.46, 28.22, 25.53, 23.88 ppm.

MS (GCMS, EI): m/z = 168 (90%), 139 (88%), 109 (100%), 79 (42%), 67 (85%).

Compound 10



benzyl (S)-2-((tert-butoxycarbonyl)amino)butanoate (10)

Following **General Procedure B** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 19.1 mg (65%) of the title compound **10**.

Physical State: colorless oil.

R_f = 0.40 (10:1 hexanes:EtOAc).

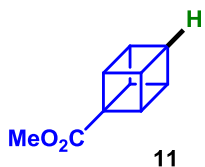
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.39 – 7.30 (m, 5H), 5.21 (d, J = 12.5 Hz, 1H), 5.14 (d, J = 12.5 Hz, 1H), 5.09 – 4.98 (m, 1H), 4.31 (q, J = 7.1 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.74 – 1.65 (m, 1H), 1.44 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 172.78, 155.51, 135.61, 128.72, 128.51, 128.37, 79.93, 67.07, 54.75, 28.47, 26.06, 9.69 ppm.

$[\alpha]_D^{20}$ = -8.8 (c 1.0, CH_2Cl_2).

Spectroscopic data matches that reported in the literature.⁹

Compound 11



methyl cubane-1-carboxylate (11)

Following **General Procedure A** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:Et₂O) afforded 12.5 mg (77%) of the title compound **11**.

Physical State: colorless oil.

R_f = 0.57 (10:1 hexanes:Et₂O).

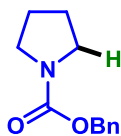
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 4.25 (dtd, J = 6.5, 2.3, 1.5 Hz, 3H), 4.03 – 3.97 (m, 4H),

3.70 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 172.98, 55.80, 51.58, 49.62, 47.99, 45.31 ppm.

MS (GCMS, EI): m/z = 162 (9%), 103 (100%), 77 (81%).

Compound 12



12

benzyl pyrrolidine-1-carboxylate (12)

Following **General Procedure A** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 13.2 mg (65%) of the title compound **12**.

Physical State: colorless oil.

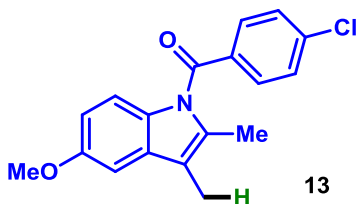
R_f = 0.45 (10:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.40 – 7.28 (m, 5H), 5.14 (s, 2H), 3.40 (dt, J = 20.3, 6.6 Hz, 4H), 1.86 (dt, J = 11.2, 5.7 Hz, 4H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 155.07, 137.28, 128.55, 127.96 (2C), 66.70, 46.37, 45.93, 25.88, 25.09 ppm.

Spectroscopic data matches that reported in the literature.¹⁰

Compound 13



13

(4-chlorophenyl)(5-methoxy-2,3-dimethyl-1H-indol-1-yl)methanone (13)

Following **General Procedure B** on a 0.1 mmol scale at 60°C with 3 equiv PhSiH_3 . Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 16.0 mg (51%) of the title

compound **13**.

Physical State: yellow oil.

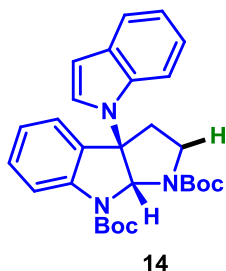
R_f = 0.73 (10:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.66 – 7.62 (m, 2H), 7.49 – 7.44 (m, 2H), 6.91 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.66 (dd, J = 9.0, 2.5 Hz, 1H), 3.85 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 168.36, 156.09, 139.00, 134.53, 133.92, 132.09, 131.17, 131.01, 129.16, 115.56, 115.07, 111.29, 101.42, 55.86, 13.46, 8.92 ppm.

MS (GCMS, EI): m/z = 315 (4%), 313 (12%), 141 (33%), 139 (100%).

Compound 14



di-tert-butyl-(3aR,8aR)-3a-(1H-indol-1-yl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate (14)

Following **General Procedure B** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 41.2 mg (87%) of the title compound **14**.

Physical State: colorless oil.

R_f = 0.56 (10:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.79 (s, br, 1H), 7.64 – 7.59 (m, 1H), 7.36 (ddd, J = 8.4, 7.4, 1.4 Hz, 1H), 7.27 (s, br, 1H), 7.22 – 7.05 (m, 5H), 6.78 (s, 1H), 6.46 (d, J = 3.4 Hz, 1H), 4.12 (dd, J = 11.7, 7.5 Hz, 1H), 3.15 (t, J = 10.6 Hz, 1H), 2.99 (td, J = 11.9, 4.9 Hz, 1H), 2.52 (dd, J = 11.9, 4.8 Hz, 1H), 1.54 (s, 9H), 1.52 (s, 9H) ppm.

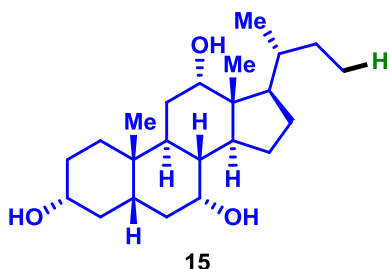
^{13}C NMR (151 MHz, CDCl_3): δ 153.69 (br), 152.23, 143.43, 135.09, 130.62, 130.54, 129.81 (br), 126.26, 124.93 (br), 123.64, 122.09, 121.51, 120.12, 116.77 (br), 111.64 (br),

101.94, 82.30, 80.79, 79.90, 74.24, 45.55, 29.84, 28.48, 28.43 ppm.

HRMS (ESI-TOF): calc'd for C₂₈H₃₄N₃O₄ [M+H]⁺ 476.2544; found 476.2547.

[α]_D²⁰ = -75.8 (c 1.0, CH₂Cl₂).

Compound 15



(3R,5S,7R,8R,9S,10S,12S,13R,14S,17R)-17-((R)-sec-butyl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-3,7,12-triol (15)

Following **General Procedure B** on a 0.1 mmol scale. Purification by flash column chromatography (silica gel, 4:1 EtOAc/CH₂Cl₂) afforded 16 mg (44%) of the title compound **15**.

Physical State: white amorphous solid.

R_f = 0.29 (4:1 EtOAc/CH₂Cl₂).

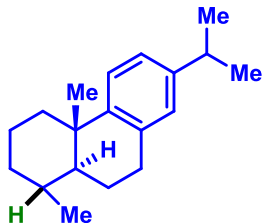
¹H NMR (600 MHz, CDCl₃): δ 3.99 (t, *J* = 3.1 Hz, 1H), 3.87 – 3.82 (m, 1H), 3.49 – 3.40 (m, 1H), 2.26 – 2.16 (m, 2H), 2.03 – 1.83 (m, 6H), 1.81 – 1.58 (m, 5H), 1.57 – 1.48 (m, 3H), 1.48 – 1.35 (m, 3H), 1.34 – 1.21 (m, 2H), 1.16 – 1.03 (m, 2H), 1.00 – 0.95 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 3H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.68 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 73.25, 72.12, 68.62, 47.28, 46.57, 41.99, 41.62, 39.84, 39.76, 36.98, 35.41, 34.86, 34.71, 30.65, 28.38, 28.30, 27.60, 26.74, 23.36, 22.67, 17.29, 12.69, 10.61 ppm.

MS (ESI-TOF, *m/z*): calc'd for C₂₃H₄₁O₃ [M+H]⁺ 365.3050; found 365.3052.

[α]_D²⁰ = + 23.4 ° (c 1.0, CH₂Cl₂).

Compound 16



7-isopropyl-1,4a-dimethyl-1,2,3,4,9,10,10a-octahydrophenanthrene (16)

Following **General Procedure B** on a 0.1 mmol scale. Purification by PTLC (silica gel, hexanes) afforded 17.2 mg (65%) of the title compound **16** as an inseparable mixture of diastereomers (1.7:1 *dr*).

Physical State: colorless oil.

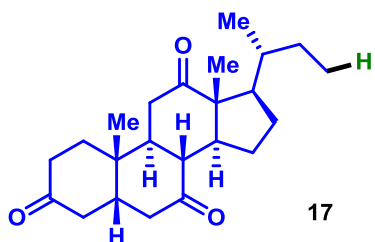
R_f = 0.89 (hexanes).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.22 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1.7H), 7.01 – 6.98 (m, 2.7H), 6.92 – 6.88 (m, 2.7H), 2.93 – 2.78 (m, 8.1H), 2.29 – 2.22 (m, 2.7H), 2.01 – 1.92 (m, 3.8H), 1.84 – 1.64 (m, 7.1H), 1.63 – 1.55 (m, 5.1H), 1.53 – 1.46 (m, 2.7H), 1.44 – 1.35 (m, 2.7H), 1.24 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.9 Hz, 5.1H), 1.18 (d, J = 0.9 Hz, 5.1H), 1.10 (d, J = 0.8 Hz, 3H), 1.01 (d, J = 7.6 Hz, 5.1H), 0.93 (d, J = 6.4 Hz, 3H) ppm. (mixtures of diastereomers).

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 147.30, 145.91, 145.60, 145.55, 135.39, 135.20, 127.10, 127.05, 124.76, 124.42, 123.93, 123.80, 49.14, 44.58, 38.76, 38.34, 37.43, 37.19, 36.34, 34.07, 33.60, 33.23, 31.73, 30.50, 29.84, 25.70, 24.71, 24.16, 24.14, 22.92, 22.27, 21.46, 20.64, 18.21, 15.28 ppm. (mixture of diastereomers).

HRMS (ESI-TOF): calc'd for $\text{C}_{19}\text{H}_{29}$ $[\text{M}+\text{H}]^+$ 257.2264; found 257.2264.

Compound 17



(5S,8R,9S,10S,13R,14S)-17-((R)-sec-butyl)-10,13-dimethyldodecahydro-3H-cyclopenta[a]phenanthrene-3,7,12(2H,4H)-trione (17)

Following **General Procedure B** on a 0.1 mmol scale. Purification by PTLC (silica gel, 1:1 hexanes:EtOAc) afforded 16 mg (45%) of the title compound **17**.

Physical State: white amorphous solid.

$R_f = 0.5$ (1:1 hexanes/EtOAc).

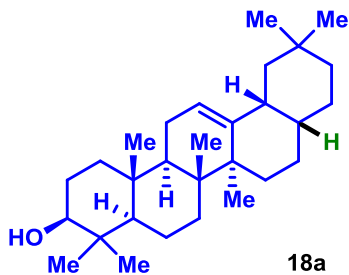
$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 2.95 – 2.79 (m, 3H), 2.38 – 2.18 (m, 6H), 2.16 – 2.09 (m, 2H), 2.08 – 1.93 (m, 4H), 1.85 (td, $J = 11.3, 7.2$ Hz, 1H), 1.61 (td, $J = 14.5, 4.6$ Hz, 1H), 1.53 – 1.45 (m, 1H), 1.40 (s, 3H), 1.34 – 1.21 (m, 3H), 1.20 – 1.08 (m, 1H), 1.07 (s, 3H), 0.86 (t, $J = 7.3$ Hz, 3H), 0.83 (d, $J = 6.5$ Hz, 3H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 212.21, 209.22, 208.95, 57.05, 51.96, 49.21, 47.03, 45.75, 45.64, 45.15, 42.96, 38.83, 37.56, 36.65, 36.17, 35.45, 28.01, 27.85, 25.37, 22.07, 18.59, 12.02, 11.01 ppm.

MS (ESI-TOF, m/z): calc'd for $\text{C}_{23}\text{H}_{35}\text{O}_3$ $[\text{M}+\text{H}]^+$ 359.2581; found 359.2581.

$[\alpha]_D^{20} = +15.0^\circ$ (c 1.0, CH_2Cl_2).

Compound 18a



(3*S*,4*aR*,6*aR*,6*bS*,12*aR*,14*aR*,14*bR*)-4,4,6*a*,6*b*,11,11,14*b*-heptamethyl-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,14,14*a*,14*b*-icosahydropicen-3-ol (18*a*)

Following **General Procedure B** on a 0.1 mmol scale. Purification by column chromatography (silica gel, 7:3 hexanes:EtOAc) afforded 22 mg (53%) of the title compound **18a** (>20:1 *dr*).

Physical State: white amorphous solid.

R_f = 0.6 (7:3 hexanes/EtOAc).

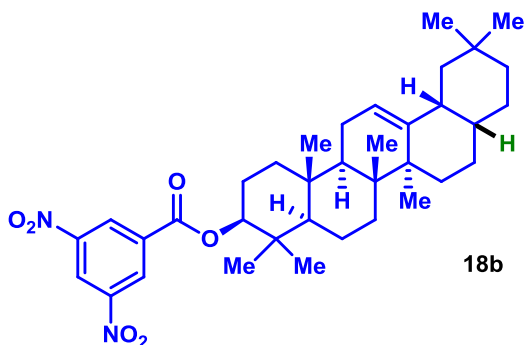
$^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.20 (t, J = 3.7 Hz, 1H), 3.22 (dd, J = 11.3, 4.5 Hz, 1H), 2.34 (dt, J = 13.8, 4.8 Hz, 1H), 1.88 – 1.87 (m, 1H), 1.86 (d, J = 3.7 Hz, 1H), 1.80 (qd, J = 13.1, 3.5 Hz, 1H), 1.70 (tt, J = 14.2, 4.8 Hz, 1H), 1.64 – 1.51 (m, 7H), 1.51 – 1.33 (m, 4H), 1.28 – 1.18 (m, 2H), 1.14 – 1.03 (m, 2H), 1.11 (s, 3H), 1.03 – 0.95 (m, 3H), 1.00 (s, 3H), 0.93 (d, J = 0.8 Hz, 3H), 0.89 (s, 3H), 0.87 (s, 6H), 0.79 (s, 3H), 0.75 (dd, J = 11.7, 1.9 Hz, 1H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 146.10, 121.22, 79.19, 55.39, 47.88, 45.11, 42.60, 41.05, 39.27, 38.91, 38.61, 37.26, 35.88, 33.83, 33.80, 33.22, 31.34, 31.24, 28.29, 28.14, 27.38, 25.22, 23.99, 23.49, 22.41, 18.56, 17.62, 15.76, 15.51 ppm.

MS (ESI-TOF, m/z): High resolution mass spec data could not be obtained for this compound.

$[\alpha]_D^{20} = +61.5^\circ$ (c 1.0, CH_2Cl_2).

Compound 18b



(3*S*,4*aR*,6*a**R*,6*b**S*,8*a**R*,12*a**R*,14*a**R*,14*b**R*)-4,4,6*a*,6*b*,11,11,14*b*-heptamethyl-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,14,14*a*,14*b*-icosahydricen-3-yl 3,5-dinitrobenzoate (18*b*)**

A culture tube was charged with **18a** (0.015 g, 0.036 mmol), 3,5-dinitrobenzoyl chloride (0.084 g, 0.36 mmol), and DMAP (4.4 mg, 0.036 mmol). Dichloromethane (0.1 mL) and Et₃N (0.05 mL) were added, and the mixture was stirred for 1 hr. The mixture was loaded directly onto a silica gel column for purification (4:1 hexanes:EtOAc). The pure product was recrystallized from hexanes/Et₂O.

Physical State: white needles.

m.p. > 200 °C

R_f = 0.6 (4:1 hexanes/EtOAc).

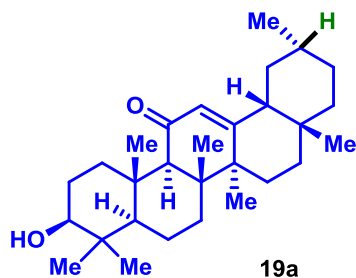
¹H NMR (600 MHz, CDCl₃) δ 9.22 (t, *J* = 2.1 Hz, 1H), 9.14 (d, *J* = 2.1 Hz, 2H), 5.21 (t, *J* = 3.7 Hz, 1H), 4.88 (dd, *J* = 11.5, 5.1 Hz, 1H), 2.36 (dt, *J* = 13.8, 4.8 Hz, 1H), 1.91 (t, *J* = 2.9 Hz, 1H), 1.90 (d, *J* = 3.6 Hz, 1H), 1.87 – 1.76 (m, 3H), 1.76 – 1.67 (m, 2H), 1.68 – 1.42 (m, 9H), 1.41 – 1.35 (m, 2H), 1.24 – 1.16 (m, 3H), 1.14 (d, *J* = 0.9 Hz, 3H), 1.12 – 1.09 (m, 1H), 1.07 (s, 3H), 1.03 (d, *J* = 0.7 Hz, 3H), 1.02 – 0.99 (m, 1H), 0.97 (s, 3H), 0.90 (s, 6H), 0.88 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃) δ 162.32, 148.82, 146.18, 134.78, 129.47, 122.33, 121.01, 84.50, 55.51, 47.83, 45.10, 42.62, 41.04, 39.31, 38.32, 38.24, 37.19, 35.86, 33.82, 33.79, 33.11, 31.35, 31.22, 28.49, 28.12, 25.20, 23.99, 23.78, 23.51, 22.38, 18.47, 17.62, 17.23, 15.58 ppm.

MS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.

[α]_D²⁰ = + 56.0 ° (c = 0.5, CH₂Cl₂).

Compound 19a



(2R,4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydronicen-13(2H)-one
(19a)

Following **General Procedure B** on a 0.1 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 34.4 mg (81%) of the title compound **19a** as an inseparable mixture of diastereomers (4:1 *dr*).

Physical State: colorless oil.

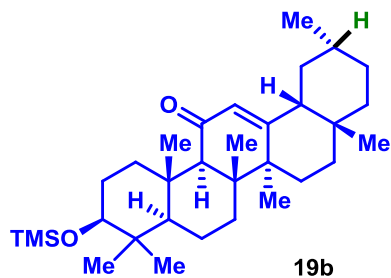
R_f = 0.37 (4:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 5.60 (s, 0.8H), 5.58 (s, 0.2H), 3.21 (ddd, J = 11.3, 5.0, 3.2 Hz, 1H), 2.78 (dt, J = 13.5, 3.6 Hz, 1H), 2.33 (s, 1H), 2.17 – 1.96 (m, 2H), 1.87 – 1.77 (m, 1H), 1.73 – 1.55 (m, 3H), 1.52 – 1.38 (m, 4H), 1.35 (s, 3H), 1.32 – 1.15 (m, 3H), 1.15 – 1.11 (m, 6H), 0.99 (d, J = 1.8 Hz, 3H), 0.88 (d, J = 6.5 Hz, 2H), 0.81 (d, J = 15.9 Hz, 5H), 0.73 – 0.65 (m, 1H) ppm. (mixture of diastereomers).

^{13}C NMR (151 MHz, CDCl_3): δ 200.51, 200.47, 171.01, 170.53, 134.40, 128.13, 128.10, 123.69, 78.90, 61.91, 55.10, 55.08, 51.84, 45.59, 45.54, 45.51, 43.54, 43.47, 41.53, 40.97, 39.28, 39.27, 37.89, 37.21, 34.45, 33.50, 32.95, 32.92, 32.54, 30.76, 29.84, 29.08, 28.87, 28.24, 27.77, 27.45, 26.92, 26.79, 26.77, 26.65, 26.58, 23.49, 23.47, 22.52, 18.85, 18.82, 17.64, 17.05, 16.52, 15.72 ppm. (mixture of diastereomers).

Spectroscopic data matches that reported in the literature.¹⁰

Compound 19b



(2R,4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-2,4a,6a,6b,9,9,12a-heptamethyl-10-((trimethylsilyl)oxy)-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2H)-one (19b)

Note: The following experiment to obtain 19b was done during the optimization process.

A 20 mL vial was charged with **SI-4** (127.3 mg, 0.21 mmol, 1.0 equiv.), zinc (40.5 mg, 0.62 mmol, 3 equiv.), and Fe(acac)₃ (7.3mg, 0.021 mmol, 0.1 equiv.). NMP (1 mL) was added and the mixture was stirred at 20 °C for 5 min when TMSCl (0.077mL, 1 mol/L, 3 equiv.) and PhSiH₃ (0.077mL, 0.62 mmol, 3 equiv.) were added sequentially. The reaction mixture was heated to 60 °C for 4 hours and was diluted with sat. NH₄Cl (3 mL) after cooling to rt. The resulting mixture was extracted with MTBE (10 mL×2); the combined organic layers was washed with brine (5 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (Silica gel, gradient elution: hexanes:MTBE, 100:0 to 70:30) to give **19b** (43.1 mg, 41%) as a crystalline mixture of diastereomers (*d.r.* = ~3:1).

Physical State: white solid.

R_f = 0.56 (5:1 hexanes:EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 5.59 (s, 0.7 H), 5.58 (s, 0.2H), 3.20 (d, *J* = 12.0 Hz, 1H), 2.74 (d, *J* = 12.0 Hz, 1H), 2.33 (s, 1H), 1.99-2.11 (m, 2H), 1.80-1.84 (m, 1H), 1.56-1.74 (m, 4H), 1.37-1.50 (m, 6H), 1.36 (s, 3H), 1.26-1.31 (m, 2H), 1.08-1.17 (m, 8H), 0.94-1.00 (m, 2H), 0.88-0.90 (m, 6H), 0.83 (s, 3H), 0.77, (s, 3H), 0.67 (*J* = 8.0 Hz, 1H) ppm. (mixture of diastereomers).

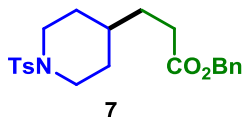
¹³C NMR (100 MHz, CDCl₃): δ 200.67, 170.96, 170.48, 128.15, 79.60, 62.02, 55.18,

51.83, 45.58, 45.55, 43.46, 41.53, 40.98, 40.62, 39.65, 39.35, 37.89, 37.19, 34.45, 33.51, 32.99, 32.96, 32.55, 31.74, 30.78, 29.09, 28.87, 28.62, 27.77, 26.93, 26.80, 26.77, 26.66, 26.57, 23.63, 23.49, 22.81, 22.54, 18.86, 18.83, 17.87, 17.06, 16.62, 16.20, 14.28, 0.65 ppm. (mixture of diastereomers).

HRMS (ESI-TOF): calc'd for $C_{32}H_{55}SiO_5$ $[M+H]^+$ 499.3971; found 499.3977.

Experimental Procedures and Characterization Data for Giese Conjugate Addition Reaction

Compound 7



benzyl 3-(1-tosylpiperidin-4-yl)propanoate (7)

0.1 mmol Scale: Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 27.3 mg (68%) of the title compound **7**.

Gram-scale Synthesis: Following gram-scale **General Procedure C** on a 2.3 mmol scale. Purification by column chromatography (silica gel, 10:1 hexanes:EtOAc) afforded 836 mg (89%) of the title compound **7**.

Physical State: colorless oil

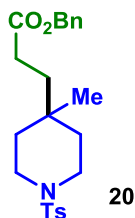
$R_f = 0.50$ (7:3 hexanes:EtOAc).

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.63 (d, $J = 8.0$ Hz, 2 H), 7.38 – 7.27 (m, 7 H), 5.08 (s, 2 H), 3.73 (dt, $J = 11.8, 3.3$ Hz, 2 H), 2.44 (s, 3 H), 2.33 (t, $J = 7.6$ Hz, 2 H), 2.16 (td, $J = 11.9, 2.6$ Hz, 2 H), 1.73 – 1.64 (m, 2 H), 1.57 (q, $J = 7.3$ Hz, 2 H), 1.28 (qd, $J = 11.8, 7.0$ Hz, 2 H), 1.14 (ddq, $J = 15.0, 7.9, 3.5$ Hz, 1 H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 173.34, 143.52, 136.03, 133.26, 129.69, 128.69, 128.43, 128.40, 127.88, 66.39, 46.42, 34.61, 31.55, 31.25, 31.05, 21.67 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{22}\text{H}_{28}\text{NSO}_4$ $[\text{M}+\text{H}]^+$ 402.1734; found 402.1739.

Compound 20



benzyl 3-(4-methyl-1-tosylpiperidin-4-yl)propanoate (20)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 31.1 mg (75%) of the title compound **20**.

Physical State: colorless oil.

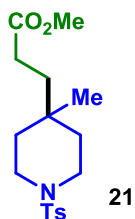
R_f = 0.45 (3:1 hexanes:EtOAc).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.65 – 7.61 (m, 2H), 7.39 – 7.29 (m, 7H), 5.08 (s, 2H), 3.23 – 3.15 (m, 2H), 2.79 (ddd, J = 12.3, 9.2, 3.4 Hz, 2H), 2.43 (s, 3H), 2.31 – 2.22 (m, 2H), 1.58 – 1.52 (m, 2H), 1.49 (ddd, J = 13.4, 9.2, 4.0 Hz, 2H), 1.40 (ddd, J = 13.5, 6.2, 3.4 Hz, 2H), 0.78 (s, 2H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 173.73, 143.53, 135.93, 133.52, 129.77, 128.70, 128.68, 128.42, 128.39, 128.37, 127.74, 66.49, 42.25, 42.23, 36.06, 35.95, 30.57, 28.73, 23.00, 21.66 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{23}\text{H}_{29}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 416.1890; found 416.1892.

Compound 21



methyl 3-(4-methyl-1-tosylpiperidin-4-yl)propanoate (21)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 26.4 mg (78%) of the title compound **21**.

Physical State: colorless oil.

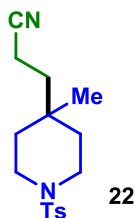
$R_f = 0.41$ (3:1 hexanes:EtOAc).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.66 – 7.62 (m, 2H), 7.34 – 7.29 (m, 2H), 3.64 (s, 3H), 3.24 – 3.14 (m, 2H), 2.80 (ddd, $J = 12.3, 9.2, 3.4$ Hz, 2H), 2.43 (s, 3H), 2.26 – 2.18 (m, 2H), 1.57 – 1.46 (m, 4H), 1.45 – 1.36 (m, 2H), 0.78 (s, 3H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 174.37, 143.55, 133.54, 129.78, 127.76, 51.80, 42.26, 36.06, 36.02, 30.58, 28.51, 23.01, 21.68 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{17}\text{H}_{26}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 340.1577; found 340.1575.

Compound 22



methyl 3-(4-methyl-1-tosylpiperidin-4-yl)propanoate (22)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 CH_2Cl_2 : Et_2O) afforded 23.5 mg (77%) of the title compound **22**.

Physical State: colorless oil.

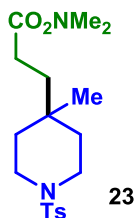
$R_f = 0.71$ (1:1 hexanes:EtOAc).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.66 – 7.61 (m, 2H), 7.36 – 7.31 (m, 2H), 3.25 – 3.17 (m, 2H), 2.80 (ddd, $J = 12.4, 9.3, 3.4$ Hz, 2H), 2.44 (s, 3H), 2.29 – 2.21 (m, 2H), 1.64 – 1.56 (m, 2H), 1.52 (ddd, $J = 13.4, 9.3, 4.1$ Hz, 2H), 1.44 (dddd, $J = 13.5, 6.1, 3.6, 1.1$ Hz, 2H), 0.83 (s, 3H) ppm.

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 143.76, 133.31, 129.87, 127.75, 120.08, 42.08, 36.93, 35.78, 30.93, 22.58, 21.69, 11.77 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 307.1475; found 307.1479.

Compound 23



N,N-dimethyl-*O*-(3-(4-methyl-1-tosylpiperidin-4-yl)propanoyl)hydroxylamine (**23**)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 1:1 CH₂Cl₂:EtOAc) afforded 31.2 mg (88%) of the title compound **23**.

Physical State: colorless oil.

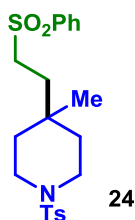
R_f = 0.31 (1:1 CH₂Cl₂:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.64 – 7.60 (m, 2H), 7.32 – 7.29 (m, 2H), 3.13 (ddd, *J* = 11.2, 6.7, 3.9 Hz, 2H), 2.96 (s, 3H), 2.90 (s, 3H), 2.86 (td, *J* = 8.7, 4.4 Hz, 2H), 2.42 (s, 3H), 2.22 – 2.15 (m, 2H), 1.52 (ddt, *J* = 11.2, 8.7, 3.7 Hz, 4H), 1.46 – 1.39 (m, 2H), 0.81 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 172.97, 143.54, 133.49, 129.78, 127.70, 42.30, 37.35, 36.16, 35.66, 35.60, 30.54, 27.44, 23.73, 21.65 ppm.

HRMS (ESI-TOF): calc'd for C₁₈H₂₉N₂O₃S [M+H]⁺ 353.1893; found 353.1895.

Compound 24



N,N-dimethyl-*O*-(3-(4-methyl-1-tosylpiperidin-4-yl)propanoyl)hydroxylamine (**24**)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 CH₂Cl₂:Et₂O) afforded 23.2 mg (54%) of the title compound **24**.

Physical State: colorless oil.

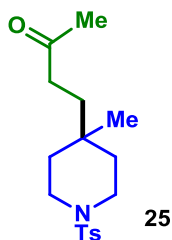
$R_f = 0.59$ (1:1 CH₂Cl₂:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.89 – 7.85 (m, 2H), 7.68 – 7.64 (m, 1H), 7.63 – 7.60 (m, 2H), 7.58 – 7.53 (m, 2H), 7.34 – 7.30 (m, 2H), 3.17 (dt, $J = 11.0, 4.9$ Hz, 2H), 3.03 – 2.93 (m, 2H), 2.74 (ddd, $J = 12.4, 9.3, 3.4$ Hz, 2H), 2.44 (s, 3H), 1.65 – 1.55 (m, 2H), 1.44 (ddd, $J = 13.5, 9.4, 4.1$ Hz, 2H), 1.41 – 1.32 (m, 2H), 0.75 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 143.70, 139.04, 133.95, 133.46, 129.85, 129.48, 128.08, 127.71, 51.61, 42.06, 35.99, 33.48, 30.66, 22.87, 21.70 ppm.

HRMS (ESI-TOF): calc'd for C₂₁H₂₈NO₄S₂ [M+H]⁺ 422.1454; found 422.1458.

Compound 25



4-(4-methyl-1-tosylpiperidin-4-yl)butan-2-one (25)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 CH₂Cl₂:Et₂O) afforded 25.5 mg (79%) of the title compound **25**.

Physical State: colorless oil.

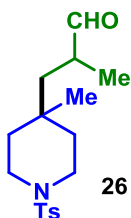
$R_f = 0.37$ (2:1 hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.63 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 7.9$ Hz, 2H), 3.20 – 3.12 (m, 2H), 2.81 (ddd, $J = 12.3, 9.1, 3.4$ Hz, 2H), 2.43 (s, 3H), 2.37 – 2.31 (m, 2H), 2.12 (s, 3H), 1.53 – 1.43 (m, 4H), 1.40 (ddd, $J = 13.4, 6.4, 3.6$ Hz, 2H), 0.77 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 208.79, 143.56, 133.51, 129.79, 127.75, 42.29, 37.87, 36.14, 34.41, 30.39, 30.15, 23.39, 21.68 ppm.

HRMS (ESI-TOF): calc'd for C₁₇H₂₆NO₃S [M+H]⁺ 324.1628; found 324.1627.

Compound 26



2-methyl-3-(4-methyl-1-tosylpiperidin-4-yl)propanal (26)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 CH₂Cl₂:Et₂O) afforded 23.6 mg (73%) of the title compound **26**.

Physical State: colorless oil.

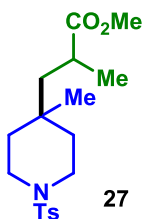
R_f = 0.56 (2:1 hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 9.51 (d, J = 2.7 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.35 – 7.30 (m, 2H), 3.36 – 3.26 (m, 2H), 2.69 (dddd, J = 11.7, 10.0, 8.0, 3.3 Hz, 2H), 2.43 (s, 3H), 2.38 (tdd, J = 7.4, 3.8, 2.8 Hz, 1H), 1.84 (dd, J = 14.5, 7.5 Hz, 1H), 1.50 (dddd, J = 15.8, 14.0, 10.1, 4.2 Hz, 2H), 1.42 (dddd, J = 13.4, 5.3, 3.3, 1.9 Hz, 1H), 1.37 (dddd, J = 13.4, 5.2, 3.2, 1.7 Hz, 1H), 1.08 (d, J = 7.2 Hz, 3H), 0.78 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 204.65, 143.57, 133.52, 129.77, 127.77, 43.04, 42.24, 42.23, 42.16, 36.64, 36.55, 31.39, 23.04, 21.68, 16.65 ppm.

HRMS (ESI-TOF): calc'd for C₁₇H₂₆NO₃S [M+H]⁺ 324.1628; found 324.1629.

Compound 27



methyl 2-methyl-3-(4-methyl-1-tosylpiperidin-4-yl)propanoate (27)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 CH₂Cl₂:Et₂O) afforded 27.8 mg (79%) of the title compound **27**.

Physical State: colorless oil.

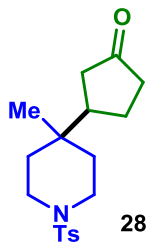
$R_f = 0.60$ (2:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.65 – 7.62 (m, 2H), 7.33 – 7.30 (m, 2H), 3.62 (s, 3H), 3.28 – 3.20 (m, 2H), 2.70 (tdd, $J = 12.8, 9.8, 3.4$ Hz, 2H), 2.52 – 2.45 (m, 1H), 2.43 (s, 3H), 1.85 (dd, $J = 14.3, 9.2$ Hz, 1H), 1.51 – 1.45 (m, 2H), 1.44 – 1.38 (m, 1H), 1.32 (dddd, $J = 13.5, 5.7, 3.3, 1.5$ Hz, 1H), 1.13 – 1.09 (m, 1H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.75 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 177.97, 143.49, 133.55, 129.73, 127.76, 51.81, 46.06, 42.23, 42.22, 36.61, 35.99, 35.03, 31.28, 22.65, 21.67, 20.47 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{18}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 354.1733; found 354.1734.

Compound 28



3-(4-methyl-1-tosylpiperidin-4-yl)cyclopentan-1-one (28)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) afforded 16.1 mg (48%) of the title compound **28**.

Physical State: colorless oil.

$R_f = 0.60$ (2:1 hexanes:EtOAc).

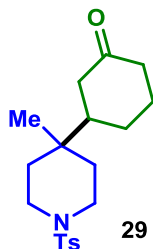
^1H NMR (600 MHz, CDCl_3): δ 7.67 – 7.63 (m, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 3.48 (dddd, $J = 16.3, 11.4, 4.4, 2.2$ Hz, 2H), 2.61 (tdd, $J = 11.6, 6.3, 3.1$ Hz, 2H), 2.44 (s, 3H), 2.32 (dd, $J = 18.7, 8.3$ Hz, 1H), 2.21 – 2.08 (m, 2H), 2.05 – 1.85 (m, 2H), 1.66 – 1.53 (m, 4H), 1.48 – 1.42 (m, 1H), 1.36 (ddt, $J = 13.3, 4.9, 2.6$ Hz, 1H), 0.77 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 218.50, 143.63, 133.48, 129.81, 127.79, 47.54, 42.19,

42.11, 39.31, 39.02, 35.15, 34.54, 32.43, 23.19, 21.70, 18.38 ppm.

HRMS (ESI-TOF): calc'd for C₁₈H₂₆NO₃S [M+H]⁺ 336.1628; found 336.1628.

Compound 29



3-(4-methyl-1-tosylpiperidin-4-yl)cyclohexan-1-one (29)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 8:1 CH₂Cl₂:Et₂O) afforded 16.3 mg (47%) of the title compound **29**.

Physical State: clear colorless oil.

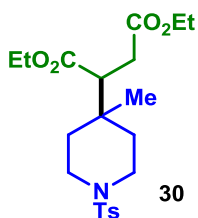
R_f = 0.6 (8:1 CH₂Cl₂:Et₂O).

¹H NMR (600 MHz, CDCl₃): δ 7.65 – 7.63 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.47 – 3.41 (m, 2H), 2.61 – 2.54 (m, 2H), 2.44 (s, 3H), 2.35 (tdt, *J* = 13.8, 4.2, 2.2 Hz, 2H), 2.21 (td, *J* = 14.0, 6.7 Hz, 1H), 2.12 – 2.06 (m, 1H), 2.05 – 1.98 (m, 1H), 1.89 – 1.83 (m, 1H), 1.51 (dddd, *J* = 24.9, 12.9, 9.2, 3.9 Hz, 5H), 1.42 – 1.36 (m, 1H), 1.30 (qd, *J* = 12.8, 3.6 Hz, 1H), 0.74 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 212.08, 143.63, 133.39, 129.81, 127.82, 48.54, 42.45, 42.28, 42.19, 41.49, 34.87, 34.60, 33.34, 25.44, 25.08, 21.71, 17.73.

MS (EI): calc'd for C₁₉H₂₈NO₃S [M+H]⁺ 350.1784; found 350.1784.

Compound 30



diethyl 2-(4-methyl-1-tosylpiperidin-4-yl)succinate (30)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 CH₂Cl₂:Et₂O) afforded 27.7 mg (65%) of the title compound **30**.

Physical State: colorless oil.

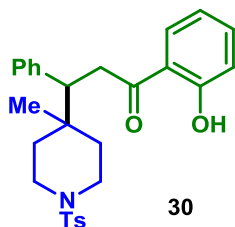
R_f = 0.59 (2:1 hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.63 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 4.17 – 4.03 (m, 4H), 3.42 (dt, J = 11.2, 4.8 Hz, 1H), 3.34 (dt, J = 11.0, 4.8 Hz, 1H), 2.68 (dddd, J = 18.8, 14.6, 10.4, 3.5 Hz, 4H), 2.43 (s, 3H), 2.35 (dd, J = 16.2, 2.6 Hz, 1H), 1.77 (ddd, J = 14.4, 10.3, 4.3 Hz, 1H), 1.58 (ddd, J = 14.3, 10.2, 4.2 Hz, 1H), 1.51 – 1.44 (m, 1H), 1.38 (dd, J = 11.0, 7.0 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 0.82 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 173.24, 172.30, 143.68, 133.48, 129.84, 127.74, 60.89, 60.64, 50.00, 42.02, 41.98, 35.00, 34.88, 33.30, 31.84, 21.67, 19.48, 14.33, 14.24 ppm.

HRMS (ESI-TOF): calc'd for C₂₁H₃₂NO₆S [M+H]⁺ 426.1945; found 426.1946.

Compound 31



1-(2-hydroxyphenyl)-3-(4-methyl-1-tosylpiperidin-4-yl)-3-phenylpropan-1-one (30)

Following **General Procedure C** on a 0.1 mmol scale using 4 equiv of hydroxychalcone. Purification by PTLC (silica gel, 20:1 CH₂Cl₂:Et₂O) afforded 25.6 mg (54%) of the title compound **30**.

Physical State: colorless oil.

R_f = 0.42 (2:1 hexanes:EtOAc).

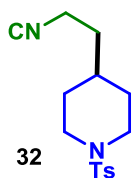
¹H NMR (600 MHz, CDCl₃): δ 12.03 (s, 1H), 7.75 (dd, J = 8.1, 1.6 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.43 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.25 – 7.21 (m, 2H),

7.20 – 7.16 (m, 1H), 7.15 – 7.12 (m, 2H), 6.91 (dd, $J = 8.4, 1.1$ Hz, 1H), 6.88 (ddd, $J = 8.2, 7.3, 1.1$ Hz, 1H), 3.60 – 3.48 (m, 3H), 3.28 (dd, $J = 16.7, 3.6$ Hz, 1H), 3.23 (dd, $J = 10.0, 3.6$ Hz, 1H), 2.55 (td, $J = 11.9, 3.1$ Hz, 1H), 2.47 (td, $J = 11.9, 2.9$ Hz, 1H), 2.44 (s, 3H), 1.69 (dtd, $J = 13.3, 11.3, 4.6$ Hz, 2H), 1.59 – 1.53 (m, 1H), 1.16 – 1.12 (m, 1H), 0.83 (s, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 204.83, 162.48, 143.61, 140.34, 136.45, 133.50, 129.79, 129.68, 129.50 (br), 128.12, 127.77, 126.93, 119.59, 118.96, 118.74, 50.96, 42.27, 42.23, 38.24, 35.24, 34.99, 34.54, 21.70, 18.79 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{28}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 478.2046; found 478.2043.

Compound 32



3-(1-tosylpiperidin-4-yl)propanenitrile (32)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 1:1 hexanes:EtOAc) afforded 18.4 mg (63%) of the title compound **32**.

Physical State: white solid.

m.p. 193-196 °C.

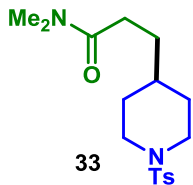
$R_f = 0.53$ (1:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.62 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 3.82 – 3.74 (m, 2H), 2.43 (s, 3H), 2.35 (t, $J = 7.1$ Hz, 2H), 2.23 (td, $J = 11.7, 2.4$ Hz, 2H), 1.76 – 1.72 (m, 2H), 1.58 (q, $J = 6.9$ Hz, 2H), 1.35 – 1.27 (m, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 143.74, 132.99, 129.78, 127.82, 119.34, 46.26, 34.10, 31.25, 30.90, 21.66, 14.68 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{NaO}_2\text{S}$ $[\text{M}+\text{Na}]^+$ 315.1138; found 315.1126.

Compound 33



N,N-dimethyl-3-(1-tosylpiperidin-4-yl)propanamide (**33**)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 1:1 hexanes:EtOAc) afforded 14.9 mg (43%) of the title compound **33**.

Physical State: clear colorless oil.

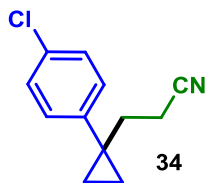
R_f = 0.11 (1:1 hexanes:EtOAc).

^1H NMR (600 MHz, CDCl_3): δ 7.64–7.61 (m, 2 H), 7.32–7.29 (m, 2 H), 3.73 (dd, J = 11.9, 4.0 Hz, 2 H), 2.97 (s, 3 H), 2.91 (s, 3 H), 2.43 (s, 3 H) 2.27 (t, J = 7.6 Hz, 2 H), 2.23 (td, J = 11.6, 2.4 Hz, 2 H), 1.77–1.69 (m, 2 H), 1.65–1.49 (m, 2 H), 1.36–1.20 (m, 3 H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 172.72, 143.52, 133.24, 129.69, 127.87, 46.48, 37.35, 35.55, 34.67, 31.40, 31.11, 30.22, 21.66 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 339.17369; found 339.17354.

Compound 34



3-(1-(4-chlorophenyl)cyclopropyl)propanenitrile (**34**)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 9.7 mg (47%) of the title compound **34**.

Physical State: clear colorless oil.

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

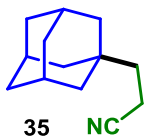
^1H NMR (600 MHz, CDCl_3): δ 7.30 – 7.23 (m, 4H), 2.23 (t, J = 7.4 Hz, 2H), 1.89 (t, J =

7.4 Hz, 2H), 0.90 – 0.86 (m, 2H), 0.85 – 0.81 (m, 2H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 141.25, 132.78, 130.70, 128.89, 119.63, 36.09, 24.63, 15.24, 12.84 ppm

HRMS (ESI-TOF): calc'd for C₁₂H₁₃CIN [M+H]⁺ 206.0731; found 206.0731.

Compound 35



3-(adamantan-1-yl)propanenitrile (35)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 18.4 mg (86%) of the title compound **35**.

Physical State: colorless oil.

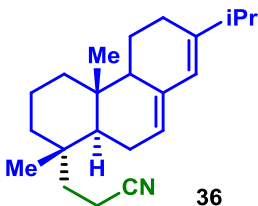
R_f = 0.5 (10:1hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 2.28 – 2.25 (m, 2H), 1.98 (p, *J* = 3.1 Hz, 3H), 1.75 – 1.69 (m, 3H), 1.62 (dddt, *J* = 12.7, 4.0, 2.7, 1.5 Hz, 3H), 1.50 – 1.46 (m, 8H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 121.05, 41.78, 39.60, 36.96, 32.26, 28.51, 11.11 ppm.

HRMS (ESI-TOF): calc'd for C₁₃H₂₀N [M+H]⁺ 190.1590; found 190.1590.

Compound 36



3-((1S,4aS,10aS)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,4b,5,6,10,10a-decahydrophenanthren-1-yl)propanenitrile (36)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel,

10:1 CH₂Cl₂:Et₂O) afforded 17.6 mg (56%) of the title compound **36**.

Physical State: colorless oil.

R_f = 0.42 (10:1 hexanes:Et₂O).

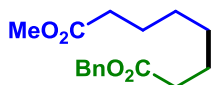
¹H NMR (600 MHz, CDCl₃): δ 5.79 – 5.76 (m, 1H), 5.40 (dt, J = 5.3, 2.6 Hz, 1H), 2.26 – 2.18 (m, 3H), 2.12 – 1.94 (m, 4H), 1.86 (dddd, J = 14.0, 10.4, 4.9, 2.4 Hz, 2H), 1.82 – 1.77 (m, 1H), 1.72 – 1.65 (m, 1H), 1.60 – 1.50 (m, 3H), 1.39 (dtd, J = 12.8, 3.3, 1.7 Hz, 1H), 1.29 – 1.13 (m, 4H), 1.02 (d, J = 5.5 Hz, 3H), 1.00 (d, J = 5.6 Hz, 3H), 0.95 (d, J = 0.7 Hz, 3H), 0.82 (d, J = 0.7 Hz, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 145.69, 135.70, 122.38, 120.83, 120.60, 51.18, 48.06, 39.47, 38.91, 37.53, 35.43, 35.11, 35.02, 27.62, 23.78, 22.75, 21.54, 20.97, 20.26, 18.41, 14.22, 11.78 ppm.

MS (GCMS, EI): m/z = 311 (29%), 296 (25%), 281 (15%), 268 (15%), 207 (100%).

$[\alpha]_D^{20}$ = -14.2 (c 1.0, CH₂Cl₂).

Compound 37



37

1-benzyl 8-methyl octanedioate (37)

Following **General Procedure C** on a 0.1 mmol scale at 50 °C. Purification by PTLC (silica gel, 10:1 toluene:Et₂O) afforded 21.0 mg (76%) of the title compound **37**.

Physical State: clear colorless oil.

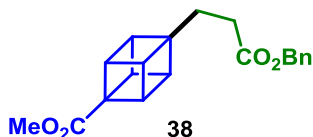
R_f = 0.68 (7:3 hexanes:EtOAc).

¹H NMR (600 MHz, CDCl₃): δ 7.39–7.29 (m, 5 H), 5.11 (s, 2 H), 3.66 (s, 3 H), 2.35 (t, J = 7.5 Hz, 2 H), 2.29 (t, J = 7.5 Hz, 2 H), 1.71–1.58 (m, 4 H), 1.33 (p, J = 3.6 Hz, 4 H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 174.29, 173.66, 136.23, 128.69, 128.33 (2C), 66.25, 51.62, 34.36, 34.12, 28.88, 28.87, 24.88 (2C) ppm.

HRMS (ESI-TOF): calc'd for C₁₆H₂₃O₄ [M+H]⁺ 279.1591; found 279.1589.

Compound 38



methyl 4-(3-(benzyloxy)-3-oxopropyl)cubane-1-carboxylate (38)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, CH₂Cl₂) afforded 18.0 mg (56%) of the title compound **38**.

Physical State: clear colorless oil.

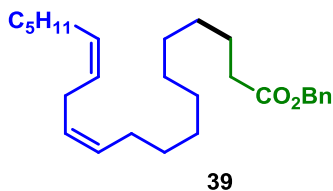
R_f = 0.5 (CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ 7.38 – 7.30 (m, 5H), 5.11 (s, 2H), 4.07 (dd, *J* = 5.7, 4.2 Hz, 3H), 3.71 (dd, *J* = 5.6, 4.3 Hz, 3H), 3.69 (s, 3H), 2.36 – 2.31 (m, 2H), 1.97 (dd, *J* = 8.5, 6.8 Hz, 2H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 173.64, 172.95, 136.01, 128.71, 128.40, 128.37, 66.46, 58.85, 56.45, 51.61, 46.13, 45.77, 29.37, 28.12 ppm.

HRMS (ESI-TOF): calc'd for C₂₀H₂₁O₄ [M+H]⁺ 325.1434; found 325.1433.

Compound 39



Benzyl (11Z,14Z)-icosa-11,14-dienoate (39)

Following **General Procedure C** on a 0.1 mmol scale at 50 °C. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) afforded 17.4 mg (44%) of the title compound **39**.

Physical State: clear colorless oil.

R_f = 0.6 (10:1 hexanes:EtOAc).

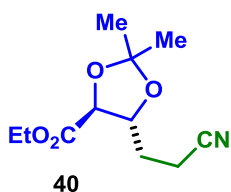
¹H NMR (600 MHz, CDCl₃): δ 7.38 – 7.31 (m, 5H), 5.41 – 5.30 (m, 4H), 5.12 (s, 2H),

2.78 (t, $J = 7.0$ Hz, 2H), 2.35 (t, $J = 7.5$ Hz, 2H), 2.05 (dtt, $J = 7.9, 3.7, 2.1$ Hz, 4H), 1.64 (p, $J = 7.5$ Hz, 2H), 1.40 – 1.24 (m, 18H), 0.89 (t, $J = 6.9$ Hz, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3): δ 173.84, 136.28, 130.34, 130.29, 128.67, 128.30 (2C), 128.11, 128.08, 66.20, 34.49, 31.68, 29.81, 29.62, 29.57, 29.50, 29.43, 29.39, 29.28, 27.38, 27.35, 25.78, 25.10, 22.73, 14.23 ppm.

HRMS (ESI-TOF): calc'd for $\text{C}_{27}\text{H}_{43}\text{O}_2$ $[\text{M}+\text{H}]^+$ 399.3258; found 399.3258.

Compound 40



Ethyl (4S,5R)-5-(2-cyanoethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (40)

Following one-pot **General Procedure D** on a 0.1 mmol scale. Purification by PTLC (silica gel, CH_2Cl_2) afforded 10.2 mg (45%) of the title compound **40** as an inseparable mixture of diastereomers (6:1 *dr*).

Physical State: clear colorless oil.

$R_f = 0.6$ (CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3): δ 4.63 (d, $J = 6.8$ Hz, 0.17 H_{min}), 4.43 (ddd, $J = 10.2, 6.8, 3.3$ Hz, 0.17 H_{min}), 4.31 – 4.21 (m, 2.37H), 4.19 (ddd, $J = 8.3, 7.6, 3.5$ Hz, 1 H_{maj}), 4.15 (d, $J = 6.9$ Hz, 1 H_{maj}), 2.60 – 2.48 (m, 2.38H), 2.19 (dtd, $J = 14.0, 8.0, 3.5$ Hz, 1 H_{maj}), 2.03 – 1.95 (m, 1 H_{maj}), 1.93 (dddd, $J = 13.8, 8.5, 7.7, 3.3$ Hz, 0.17 H_{min}), 1.73 (dddd, $J = 13.8, 10.3, 7.3, 5.4$ Hz, 0.17 H_{min}), 1.58 (d, $J = 0.7$ Hz, 1 H_{min}), 1.46 (d, $J = 0.7$ Hz, 3 H_{maj}), 1.43 (d, $J = 0.8$ Hz, 3 H_{maj}), 1.38 (d, $J = 0.7$ Hz, 1 H_{min}), 1.32 – 1.30 (m, 3.5H) ppm.

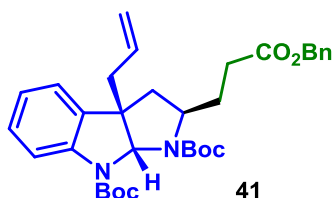
^{13}C NMR (151 MHz, CDCl_3): δ 170.19 (maj), 169.62 (min), 119.05 (maj), 118.99 (min), 111.68 (maj), 111.22 (min), 78.65 (maj), 76.98 (maj), 76.81 (min), 75.45 (min), 61.87 (maj), 61.58 (min), 29.84 (min), 29.66 (maj), 27.16 (maj), 26.78 (min), 25.73 (maj),

25.68 (min), 14.46 (min), 14.36 (min), 14.32 (maj), 14.03 (maj) ppm.

HRMS (ESI-TOF): calc'd for C₁₁H₁₈NO₄ [M+H]⁺ 228.1230; found 228.1232.

[α]_D²⁰ = +10.5 (c 1.0, CH₂Cl₂)

Compound 41



Di-tert-butyl

(2R,3aS,8aR)-3a-allyl-2-(3-(benzyloxy)-3-oxopropyl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-1,8-dicarboxylate (41)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, CH₂Cl₂) afforded 36.6 mg (65%) of the title compound **41** (>20:1 dr).

Physical State: clear yellow oil.

R_f = 0.3 (CH₂Cl₂).

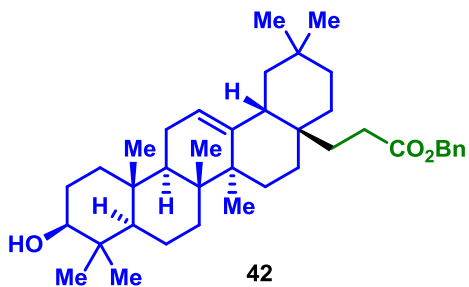
¹H NMR (600 MHz, CDCl₃): δ 7.63 (brs, 1H), 7.36 – 7.26 (m, 5H), 7.21 – 7.16 (m, 1H), 7.10 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.99 (td, *J* = 7.4, 1.1 Hz, 1H), 6.13 (s, 1H), 5.57 (dddd, *J* = 16.6, 10.1, 8.3, 6.3 Hz, 1H), 5.11 – 4.99 (m, 4H), 4.12 (tdd, *J* = 8.5, 6.6, 1.4 Hz, 1H), 2.51 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.39 (dd, *J* = 13.8, 8.3 Hz, 1H), 2.31 – 2.18 (m, 3H), 1.96 (d, *J* = 13.0 Hz, 1H), 1.55 (s, 9H), 1.47 (s, 9H), 1.45 – 1.35 (m, 2H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 173.03, 154.59, 152.63, 142.05, 126.52, 136.12, 133.17, 128.58, 128.29, 128.20, 128.17, 123.21, 122.77, 119.14, 116.70 (br), 81.54, 81.46, 80.39, 66.13, 58.89, 55.18, 43.28, 31.69, 30.61, 28.57, 28.54, 28.51 ppm.

HRMS (ESI-TOF): calc'd for C₃₃H₄₃N₂O₆ [M+H]⁺ 563.3116; found 563.3115.

[α]_D²⁰ = –53.9 (c 1.0, CH₂Cl₂)

Compound 42



Benzyl

3-((4aR,6aS,6bR,8aR,10S,12aR,12bR,14bR)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydronicen-4a(2H)-yl)propanoate (42)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, CH₂Cl₂) afforded 31.7 mg (55%) of the title compound **42**.

Physical State: white solid.

m.p. 144–147°C.

R_f = 0.3 (CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃): δ 7.38 – 7.30 (m, 5H), 5.18 (t, *J* = 3.7 Hz, 1H), 5.09 (d, *J* = 2.2 Hz, 2H), 3.22 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.25 (dddd, *J* = 41.1, 14.8, 11.8, 5.0 Hz, 2H), 1.98 – 1.81 (m, 6H), 1.71 (t, *J* = 13.6 Hz, 1H), 1.67 – 1.57 (m, 3H), 1.57 – 1.46 (m, 3H), 1.43 – 1.22 (m, 7H), 1.14 (s, 3H), 1.13 – 1.10 (m, 1H), 1.04 (ddd, *J* = 13.4, 4.6, 2.5 Hz, 1H), 0.99 (s, 3H), 0.97 – 0.89 (m, 9H), 0.87 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H), 0.73 (dd, *J* = 11.8, 1.9 Hz, 1H) ppm.

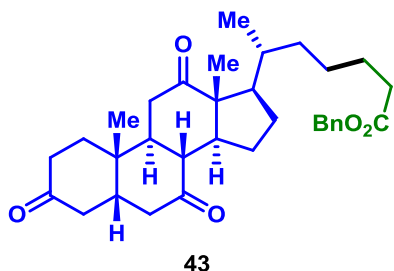
¹³C NMR (151 MHz, CDCl₃): δ 174.53, 144.45, 136.21, 128.63, 128.35, 128.26, 122.59, 79.13, 66.30, 55.30, 47.75, 47.11, 46.70, 41.66, 39.92, 38.91, 38.72, 37.04, 34.90, 34.50, 34.49, 33.38, 32.91, 32.61, 31.06, 28.56, 28.22, 27.35, 26.23, 25.77, 23.71, 23.69, 23.08, 18.45, 16.78, 15.73, 15.63 ppm

Note: The stereochemistry was determined when the benzyl ester was hydrolyzed to its corresponding acid and the spectrum was found to match with that of the literature.¹¹

HRMS (ESI-TOF): calc'd for C₃₉H₅₉O₃ [M+H]⁺ 575.4459; found 575.4457.

[α]_D²⁰ = +43.1 (c 1.0, CH₂Cl₂).

Compound 43



benzyl (R)-6-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexa-decahydro-1H-cyclopenta[a]phenanthren-17-yl)heptanoate (43)

Following **General Procedure C** on a 0.1 mmol scale at 50 °C. Purification by PTLC (silica gel, 1:1 hexanes:EtOAc) afforded 24.0 mg (46%) of the title compound **43**.

Physical State: white solid.

m.p. 126–128 °C.

R_f = 0.42 (1:1hexanes:EtOAc).

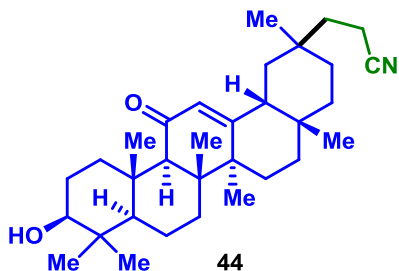
¹H NMR (600 MHz, CDCl₃): δ 7.37 – 7.30 (m, 5H), 5.11 (s, 2H), 2.93 – 2.81 (m, 4H), 2.38 – 2.18 (m, 8H), 2.16 – 2.08 (m, 2H), 2.04 – 1.93 (m, 4H), 1.83 (td, J = 11.1, 7.0 Hz, 1H), 1.68 – 1.54 (m, 3H), 1.42 – 1.38 (m, 5H), 1.24 (dddd, J = 17.6, 14.4, 10.7, 4.4 Hz, 3H), 1.07 – 1.02 (m, 4H), 0.81 (d, J = 6.6 Hz, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 212.18, 209.23, 208.91, 173.77, 136.23, 128.66, 128.30, 128.29, 66.21, 57.03, 51.92, 49.15, 46.98, 45.94, 45.70, 45.12, 42.93, 38.78, 36.62, 36.14, 35.98, 35.41, 35.12, 34.48, 27.92, 26.19, 25.43, 25.31, 22.04, 19.08, 11.98 ppm.

HRMS (ESI-TOF): calc'd for C₃₃H₄₅O₅ [M+H]⁺ 521.3262; found 521.3259.

[α]_D²⁰ = +6.3 (c 1.0, CH₂Cl₂).

Compound 44



3-((2R,4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicen-2-yl)propanenitrile (44)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 1:1 hexanes:EtOAc) afforded 36.5 mg (76%) of the title compound **44** as an inseparable mixture of diastereomers (1.2:1 *dr*).

Physical State: white solid.

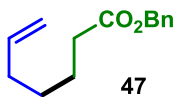
R_f = 0.5 (1:1 hexanes:EtOAc).

$^1\text{H NMR}$ (600 MHz, CDCl_3): δ 5.58 (s, 1H), 5.56 (s, 0.8H), 3.21 (ddd, J = 11.3, 5.1, 2.8 Hz, 1.8H), 2.77 (dq, J = 13.4, 3.8 Hz, 1.8H), 2.31 (d, J = 4.7 Hz, 1.8H), 2.28 (td, J = 7.5, 1.5 Hz, 2H), 2.20 (t, J = 8.1 Hz, 1.6H), 2.14 – 2.10 (m, 1H), 2.08 – 1.96 (m, 2.6H), 1.81 (tt, J = 13.1, 3.9 Hz, 2H), 1.77 – 1.56 (m, 13.8H), 1.50 – 1.26 (m, 16.8H), 1.24 – 1.06 (m, 15.8H), 1.02 – 0.91 (m, 9.2H), 0.90 (s, 3H), 0.88 (s, 2.4H), 0.87 (s, 2.4H), 0.86 (s, 3H), 0.79 (s, 5.4H), 0.68 (dt, J = 11.6, 2.2 Hz, 1.8H) ppm. (mixture of diastereomers).

$^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 200.28, 200.16, 169.58, 169.33, 128.53, 120.54, 120.40, 78.83, 78.81, 61.91, 55.04, 55.01, 47.00, 46.94, 45.54, 45.49, 43.46, 43.43, 43.00, 42.87, 41.03, 39.24, 39.22, 37.21, 37.20, 35.83, 35.81, 33.68, 33.36, 32.85, 32.84, 32.68, 32.35, 32.17, 32.12, 30.92, 28.75, 28.72, 28.21, 27.39, 27.38, 26.66, 26.43, 26.42, 23.63, 23.52, 20.31, 18.82, 17.59, 16.47, 15.70, 11.98, 11.80 ppm. (mixture of diastereomers).

HRMS (ESI-TOF): calc'd for $\text{C}_{32}\text{H}_{50}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 480.3836; found 480.3837.

Compound 47



benzyl hept-6-enoate (47)

Following **General Procedure C** on a 0.1 mmol scale. Purification by PTLC (silica gel, 10:1 hexanes:Et₂O) afforded 9.4 mg (43%) of the title compound **47**.

Physical State: colorless oil.

R_f = 0.64 (10:1 hexanes:Et₂O).

¹H NMR (600 MHz, CDCl₃): δ 7.40 – 7.30 (m, 5H), 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00 (ddt, J = 17.1, 3.0, 1.4 Hz, 1H), 4.95 (ddt, J = 10.2, 2.3, 1.2 Hz, 1H), 2.39 – 2.34 (m, 2H), 2.06 (tdt, J = 7.9, 6.6, 1.4 Hz, 2H), 1.72 – 1.63 (m, 2H), 1.42 (tt, J = 9.8, 6.5 Hz, 2H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ 173.65, 138.53, 136.24, 128.69, 128.32 (2C), 114.84, 66.25, 34.29, 33.49, 28.47, 24.55 ppm.

Spectroscopic data matches that reported in the literature.¹²

X-Ray Crystallographic Data for Compound **18b**

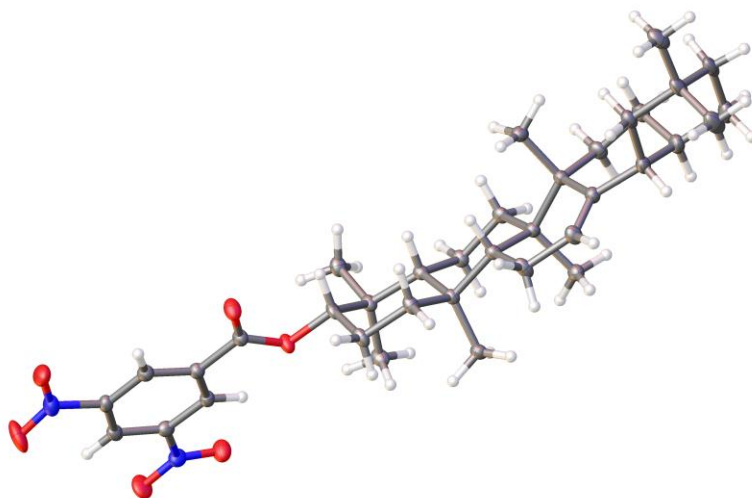


Table 1. Crystal data and structure refinement for **18b**.

Empirical formula	C ₃₆ H ₅₀ N ₂ O ₆	
Molecular formula	C ₃₆ H ₅₀ N ₂ O ₆	
Formula weight	606.78	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 14.3817(4) Å	α = 90°.
	b = 7.2036(2) Å	β = 93.3070(10)°.
	c = 15.6304(5) Å	γ = 90°.
Volume	1616.61(8) Å ³	
Z	2	
Density (calculated)	1.247 Mg/m ³	
Absorption coefficient	0.673 mm ⁻¹	
F(000)	656	
Crystal size	0.28 x 0.15 x 0.1 mm ³	
Crystal color, habit	colorless block	
Theta range for data collection	2.832 to 70.289°.	
Index ranges	-17 ≤ h ≤ 17, -8 ≤ k ≤ 8, -18 ≤ l ≤ 19	
Reflections collected	27383	

Independent reflections	6109 [R(int) = 0.0463]
Completeness to theta = 67.500°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5220 and 0.3790
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6109 / 1 / 404
Goodness-of-fit on F ²	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0294, wR2 = 0.0785
R indices (all data)	R1 = 0.0298, wR2 = 0.0789
Absolute structure parameter	0.04(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.218 and -0.166 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Baran606. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1147(1)	5318(2)	6426(1)	21(1)
O(2)	1671(1)	2548(2)	6930(1)	26(1)
O(3)	4(1)	-4(2)	9384(1)	33(1)
O(4)	-1188(1)	1459(2)	9836(1)	44(1)
O(5)	-1920(1)	7630(2)	8777(1)	34(1)
O(6)	-1085(1)	8833(2)	7809(1)	30(1)
N(1)	-537(1)	1313(2)	9371(1)	26(1)
N(2)	-1296(1)	7556(2)	8277(1)	23(1)
C(1)	7680(1)	4495(3)	1172(1)	32(1)
C(2)	6428(2)	5099(4)	39(1)	38(1)
C(3)	6868(1)	5769(3)	905(1)	27(1)
C(4)	7221(1)	7783(3)	834(1)	30(1)
C(5)	6441(2)	9192(3)	685(1)	32(1)
C(6)	5725(1)	9116(3)	1377(1)	26(1)
C(7)	5353(1)	7133(3)	1473(1)	22(1)
C(8)	6150(1)	5711(3)	1600(1)	23(1)
C(9)	4668(1)	6976(2)	2180(1)	19(1)

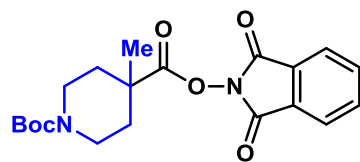
C(10)	4792(1)	8142(2)	3000(1)	18(1)
C(11)	5289(1)	10015(3)	2851(1)	24(1)
C(12)	6088(1)	9867(3)	2244(1)	26(1)
C(13)	5442(1)	7023(3)	3638(1)	22(1)
C(14)	3164(1)	9532(3)	2666(1)	21(1)
C(15)	3785(1)	8485(2)	3349(1)	17(1)
C(16)	3367(1)	6551(2)	3550(1)	17(1)
C(17)	3274(1)	5342(3)	2738(1)	23(1)
C(18)	3990(1)	5715(3)	2099(1)	22(1)
C(19)	3863(1)	9674(2)	4173(1)	19(1)
C(20)	2981(1)	9649(2)	4684(1)	18(1)
C(21)	2710(1)	7654(2)	4903(1)	16(1)
C(22)	1592(1)	7272(3)	3557(1)	20(1)
C(23)	2465(1)	6535(2)	4070(1)	16(1)
C(24)	2284(1)	4498(2)	4328(1)	19(1)
C(25)	1565(1)	4318(2)	5008(1)	20(1)
C(26)	1866(1)	5431(2)	5796(1)	19(1)
C(27)	2012(1)	7517(2)	5630(1)	18(1)
C(28)	1077(1)	8514(3)	5438(1)	22(1)
C(29)	2475(1)	8369(3)	6453(1)	23(1)
C(30)	1154(1)	3863(2)	6949(1)	18(1)
C(31)	425(1)	4067(2)	7595(1)	18(1)
C(32)	279(1)	2612(3)	8162(1)	20(1)
C(33)	-392(1)	2827(3)	8755(1)	20(1)
C(34)	-929(1)	4412(3)	8807(1)	20(1)
C(35)	-757(1)	5818(3)	8239(1)	20(1)
C(36)	-92(1)	5697(3)	7634(1)	18(1)

References

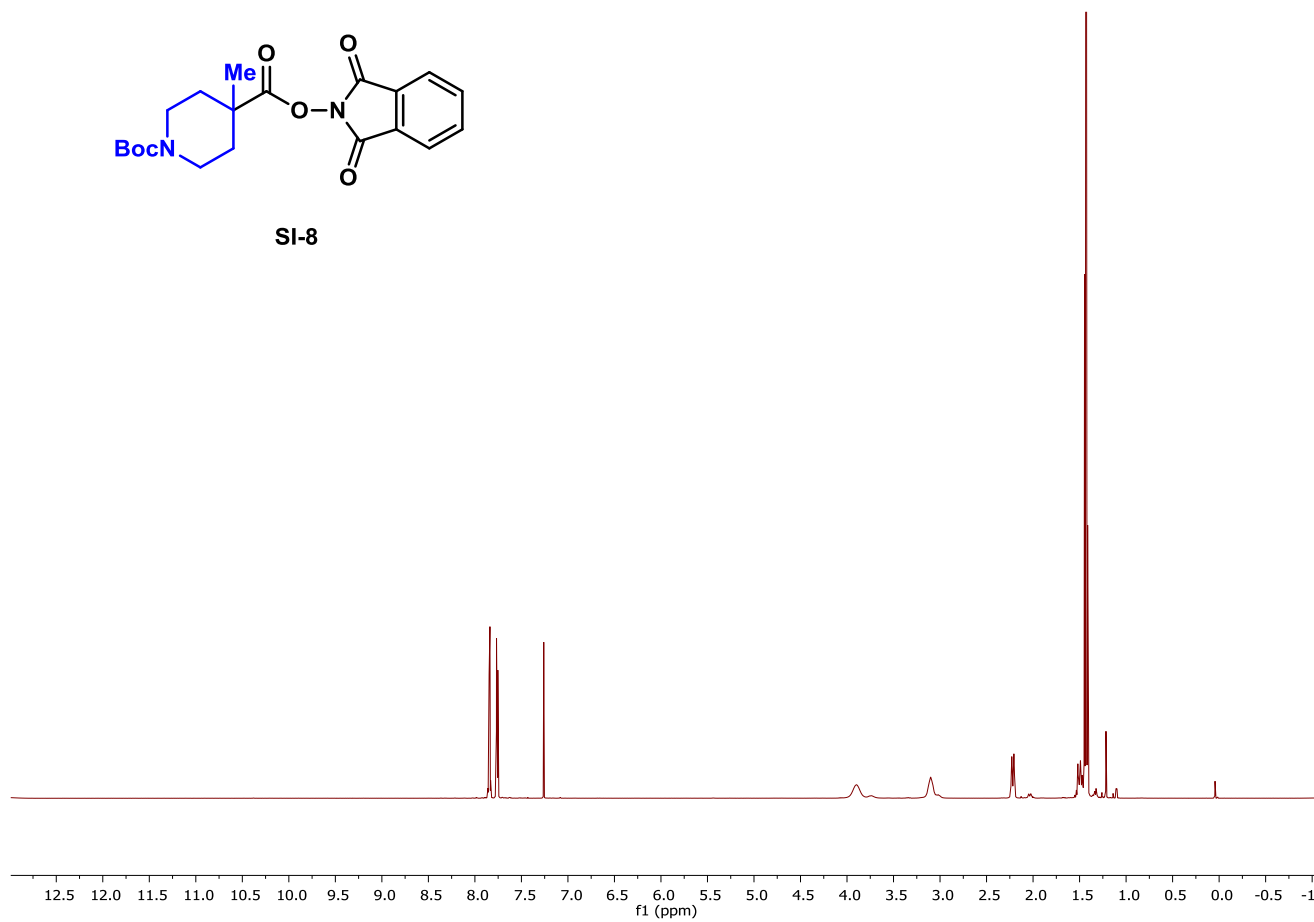
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Spectra for Redox-Active Ester Compounds

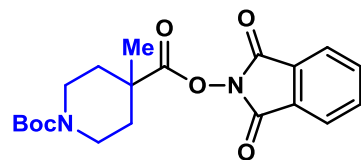
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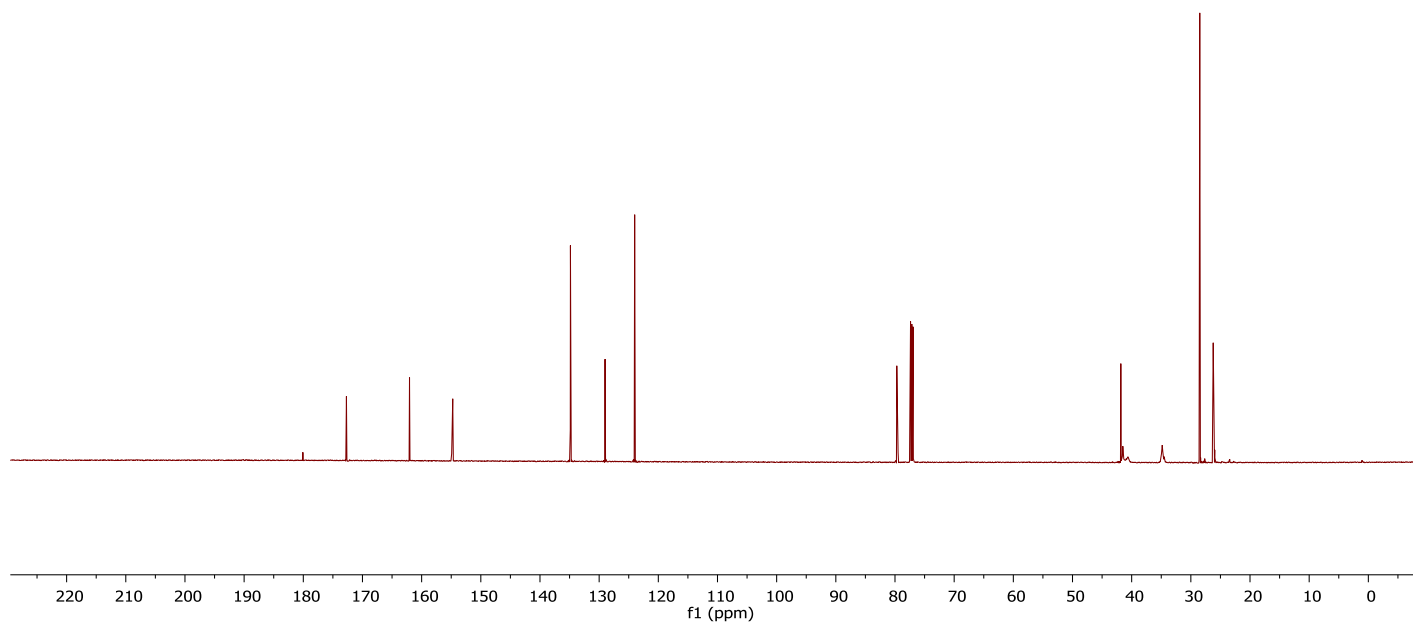
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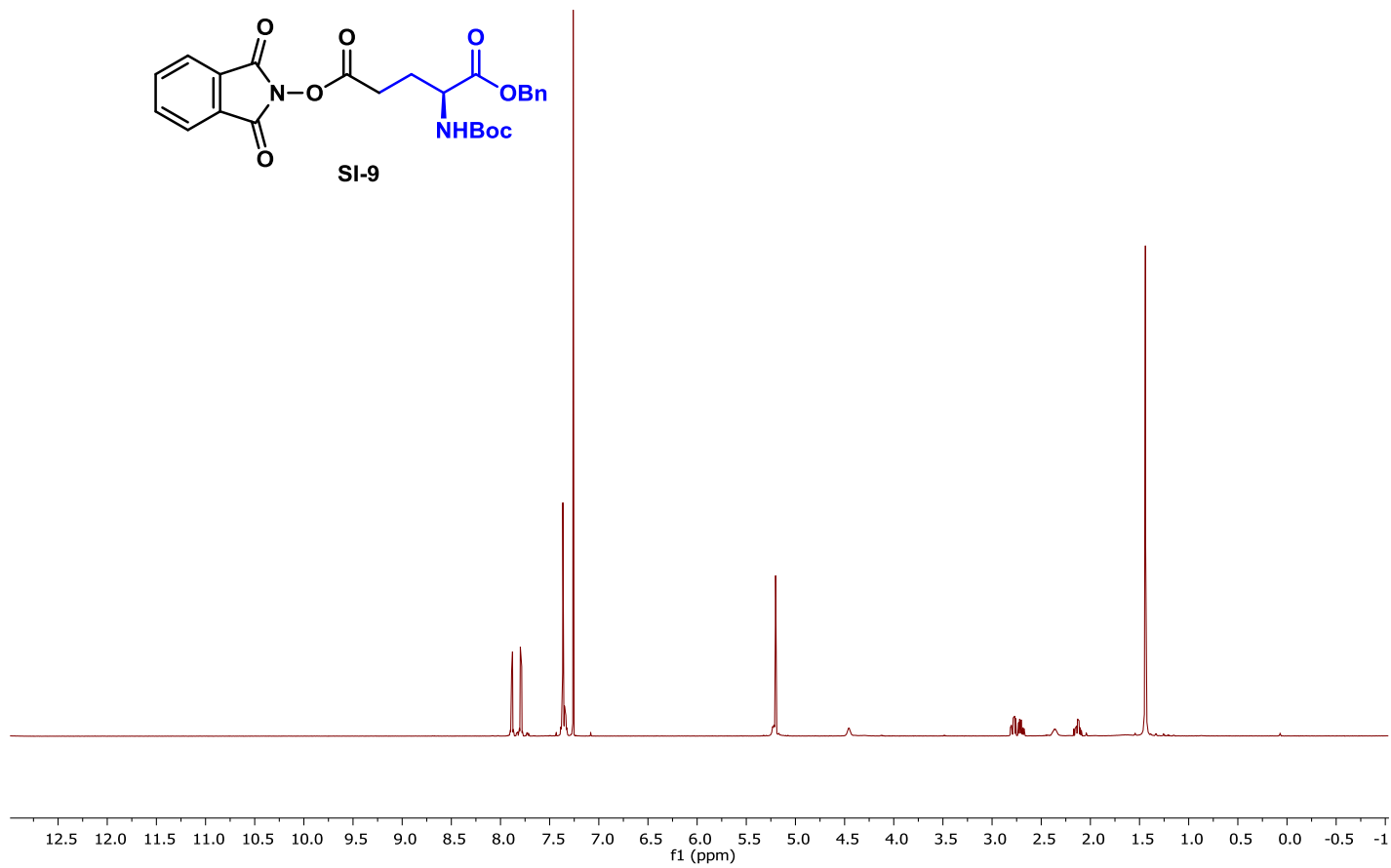
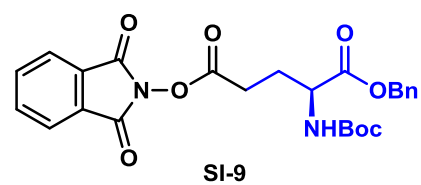
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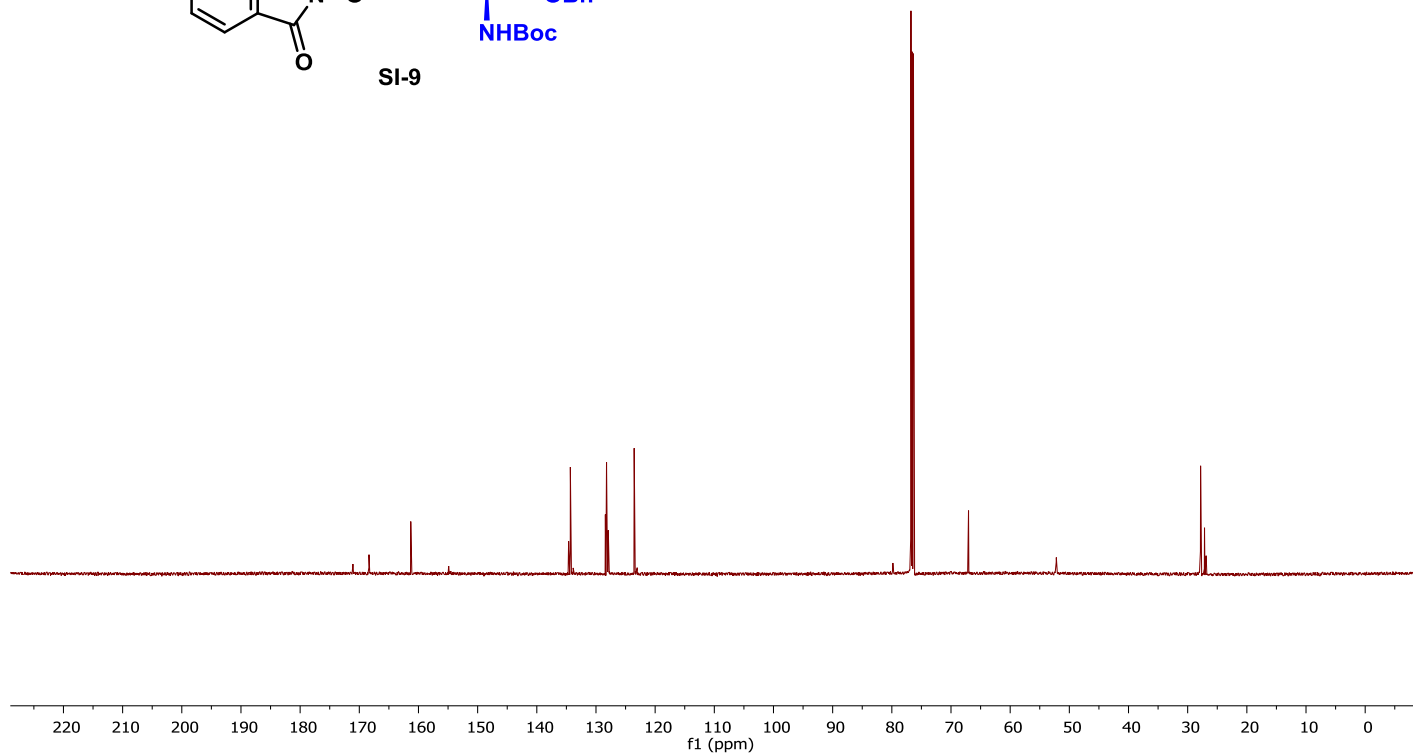
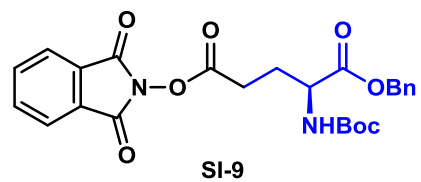
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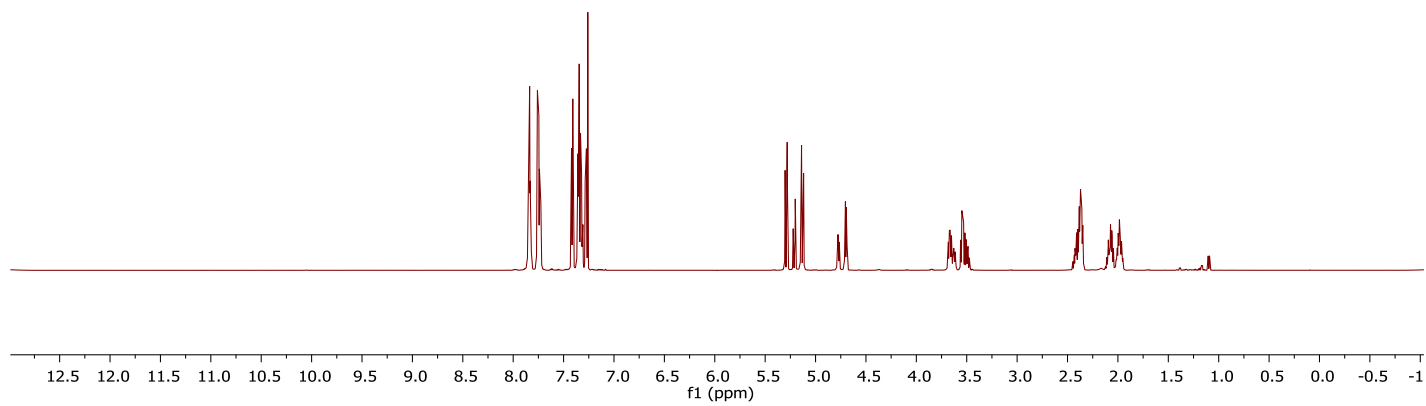
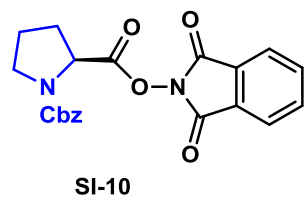
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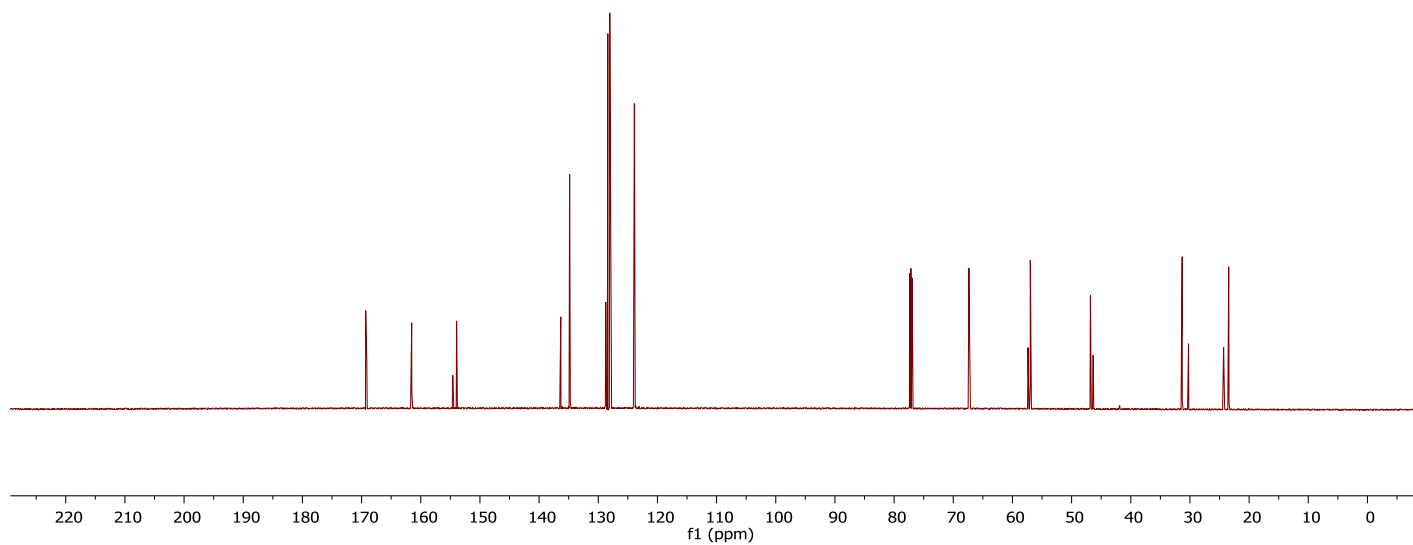
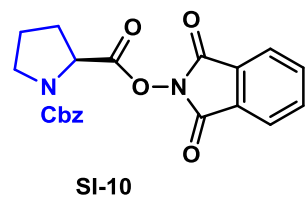
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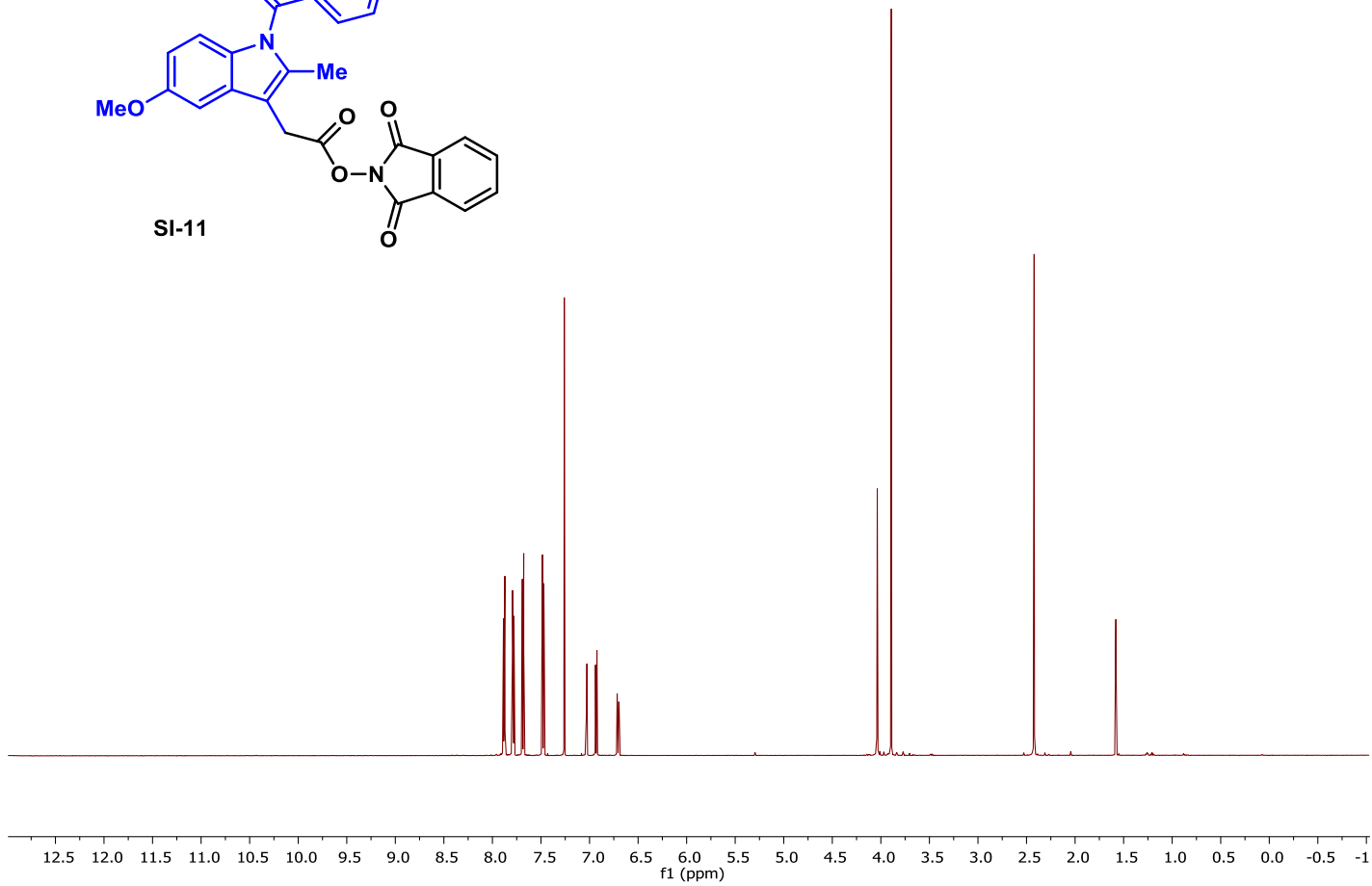
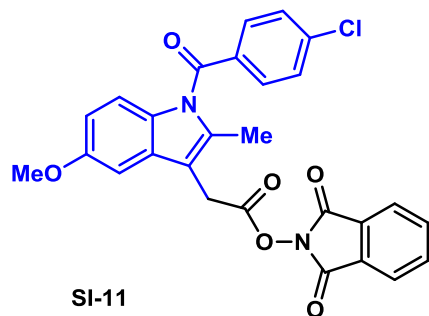
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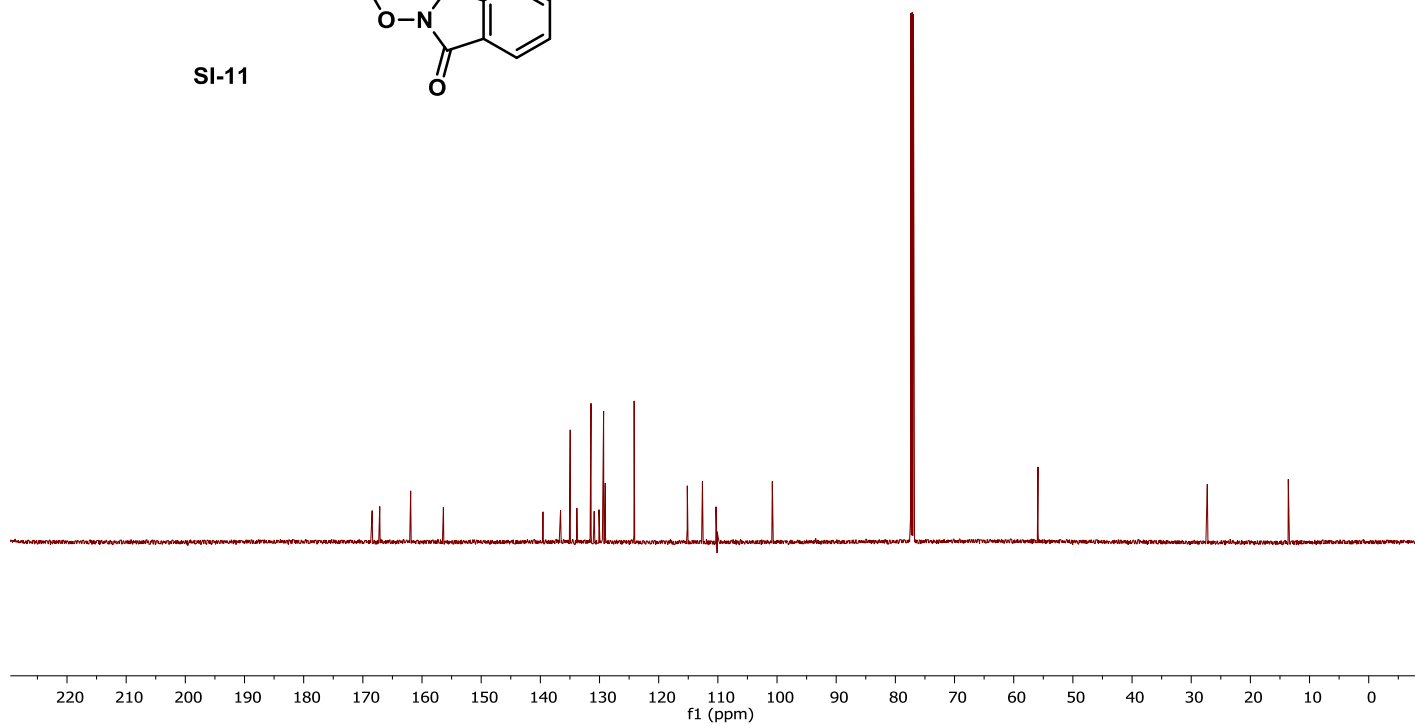
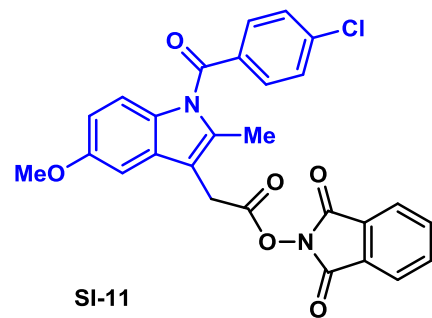
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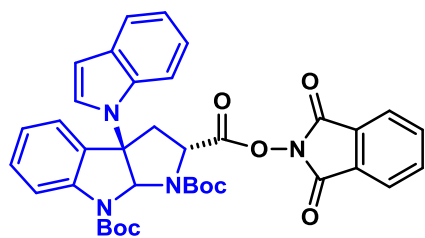
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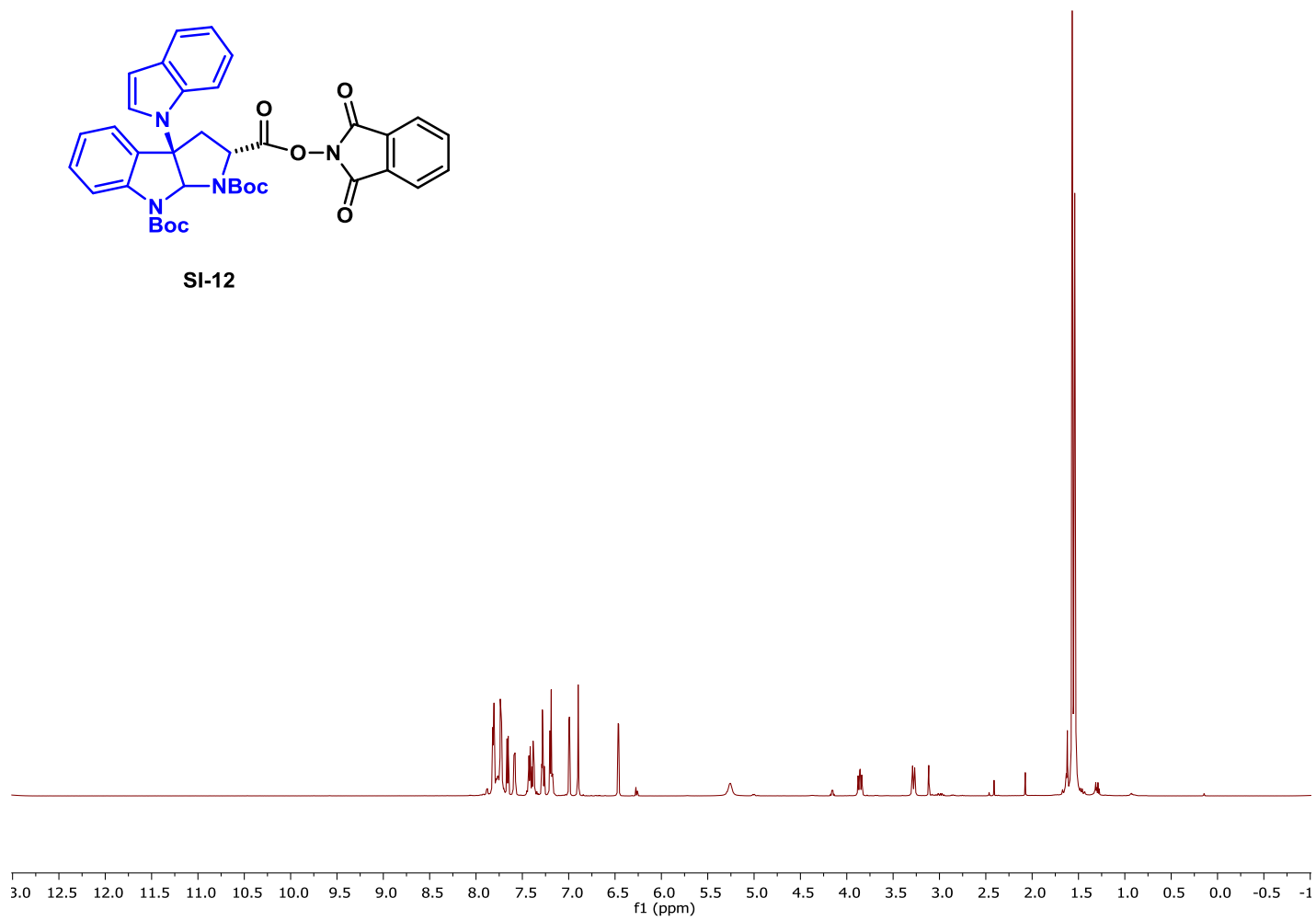
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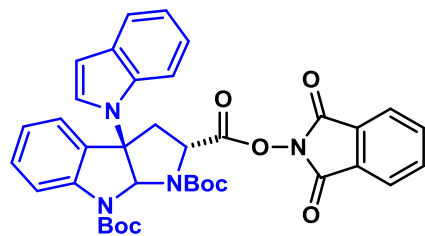
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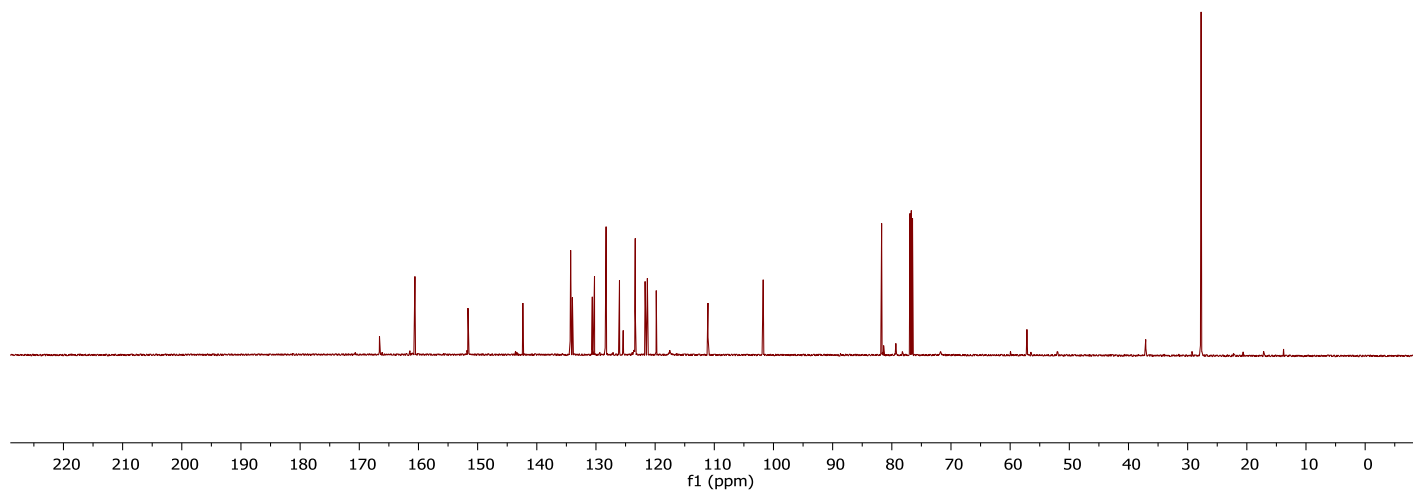
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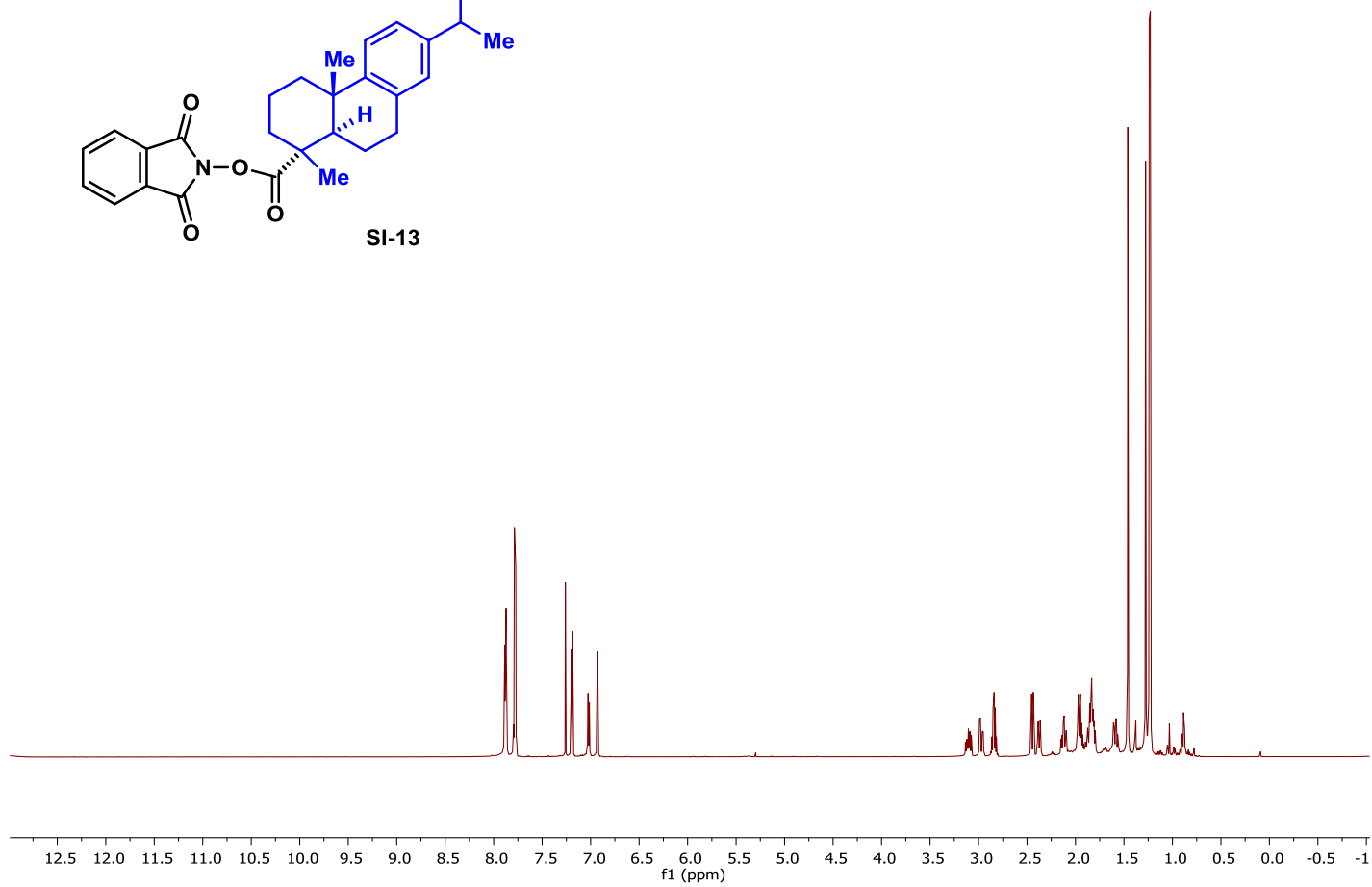
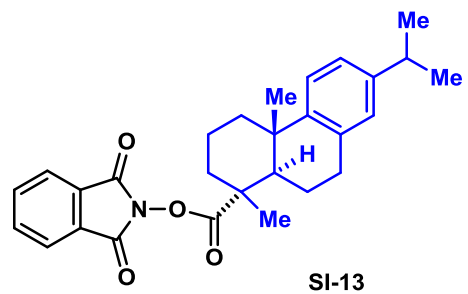
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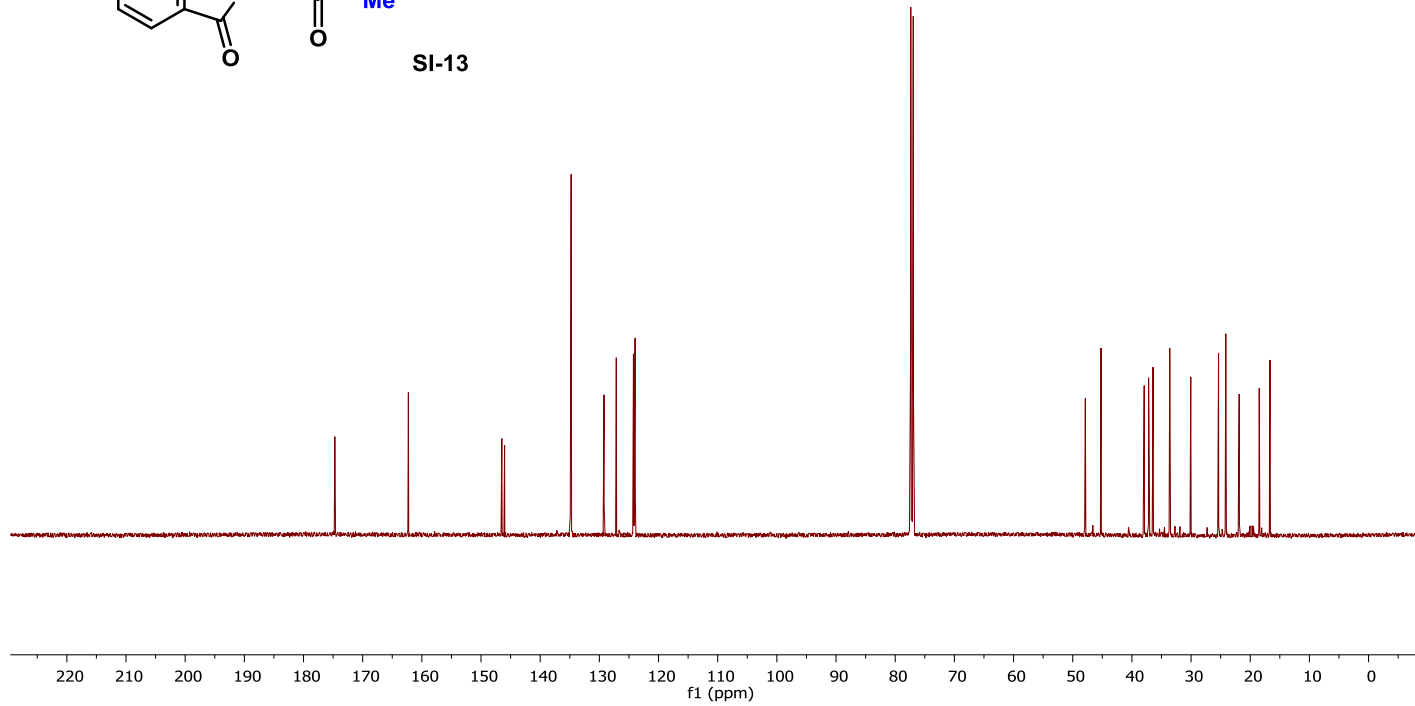
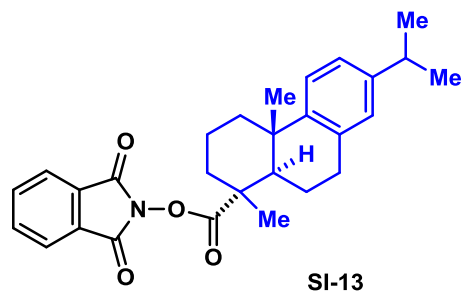
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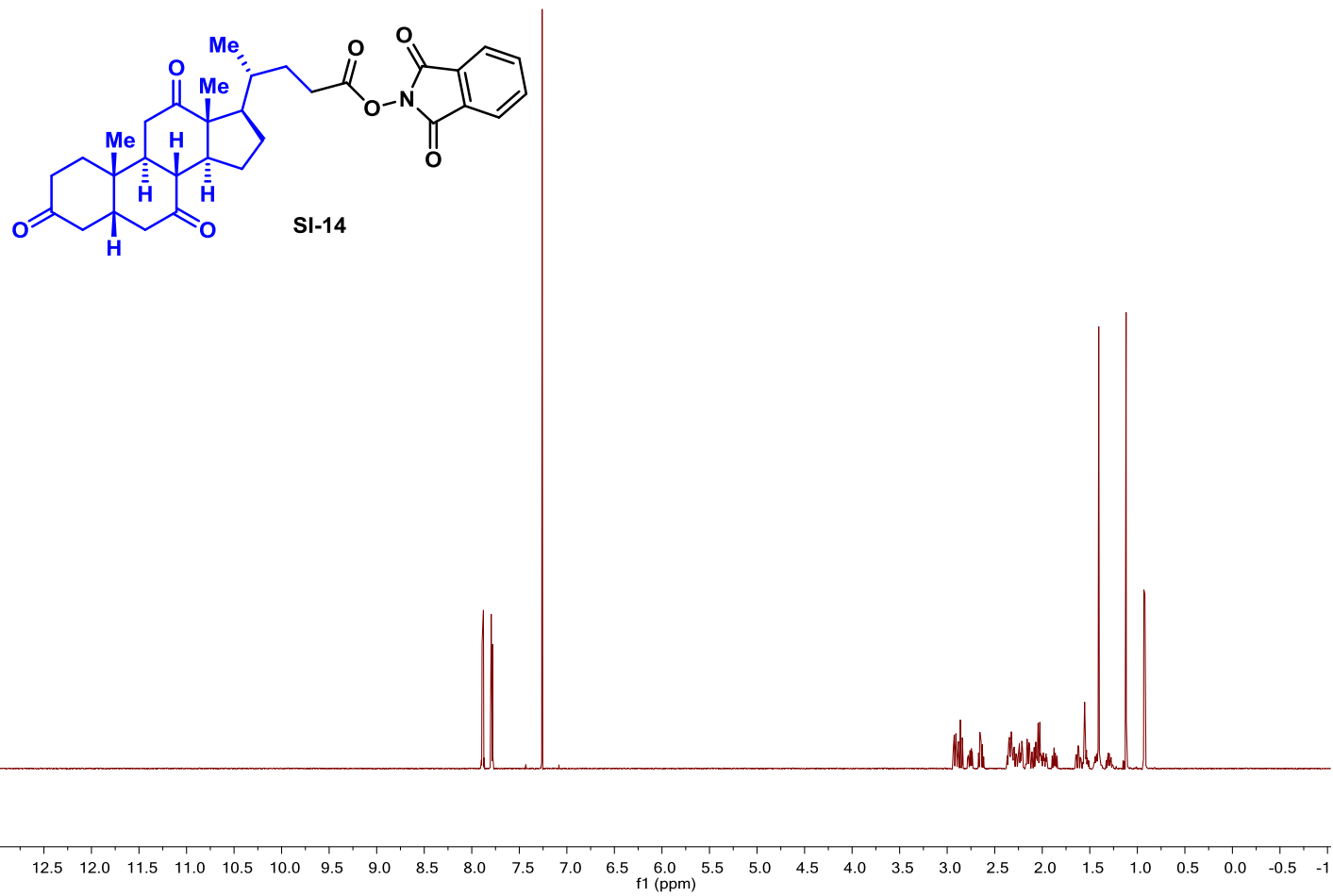
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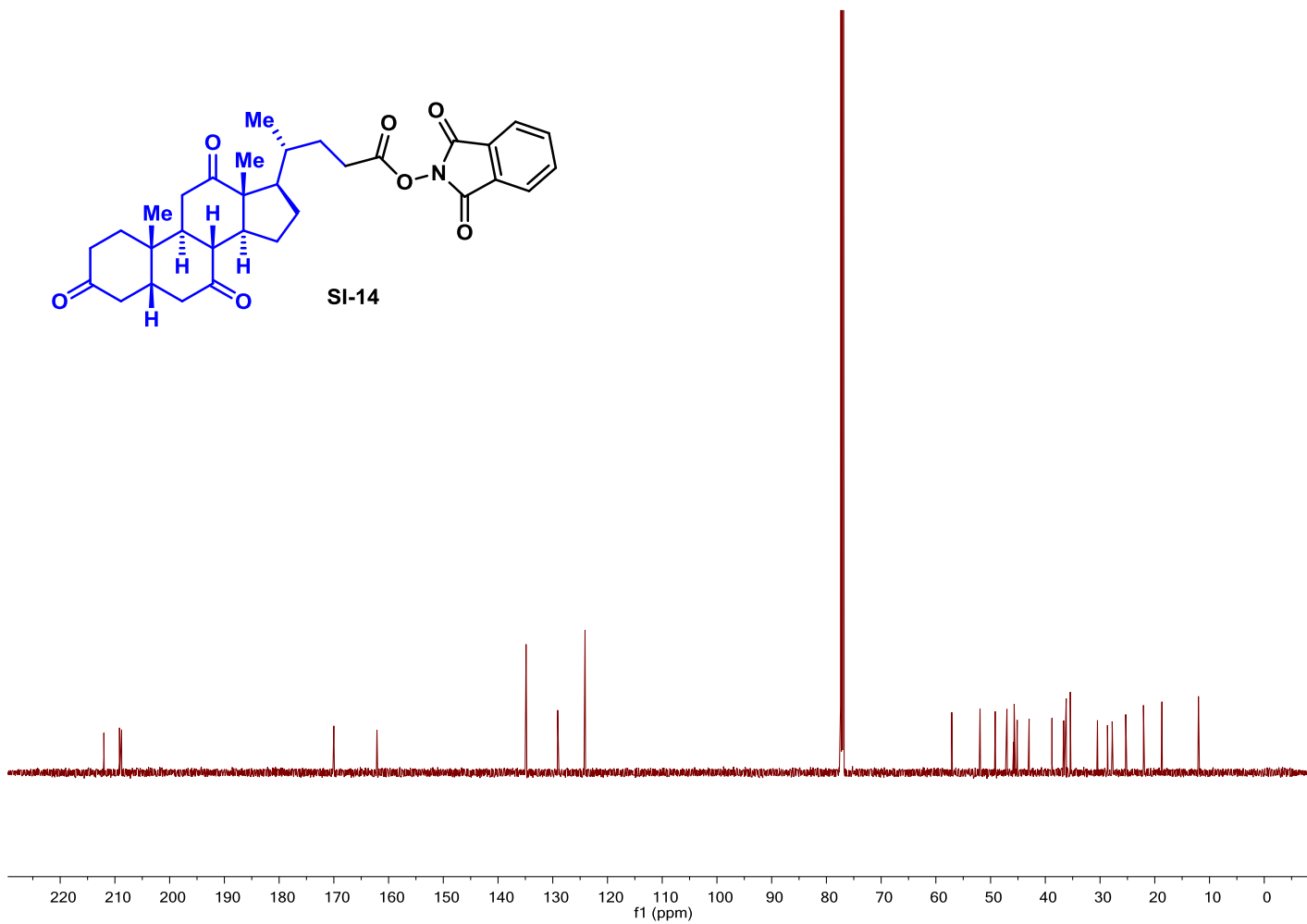
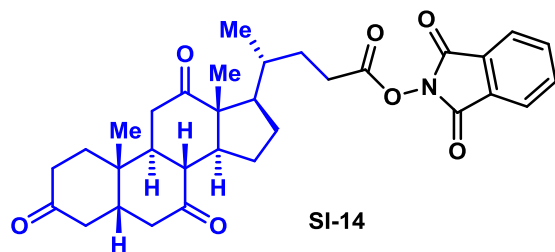
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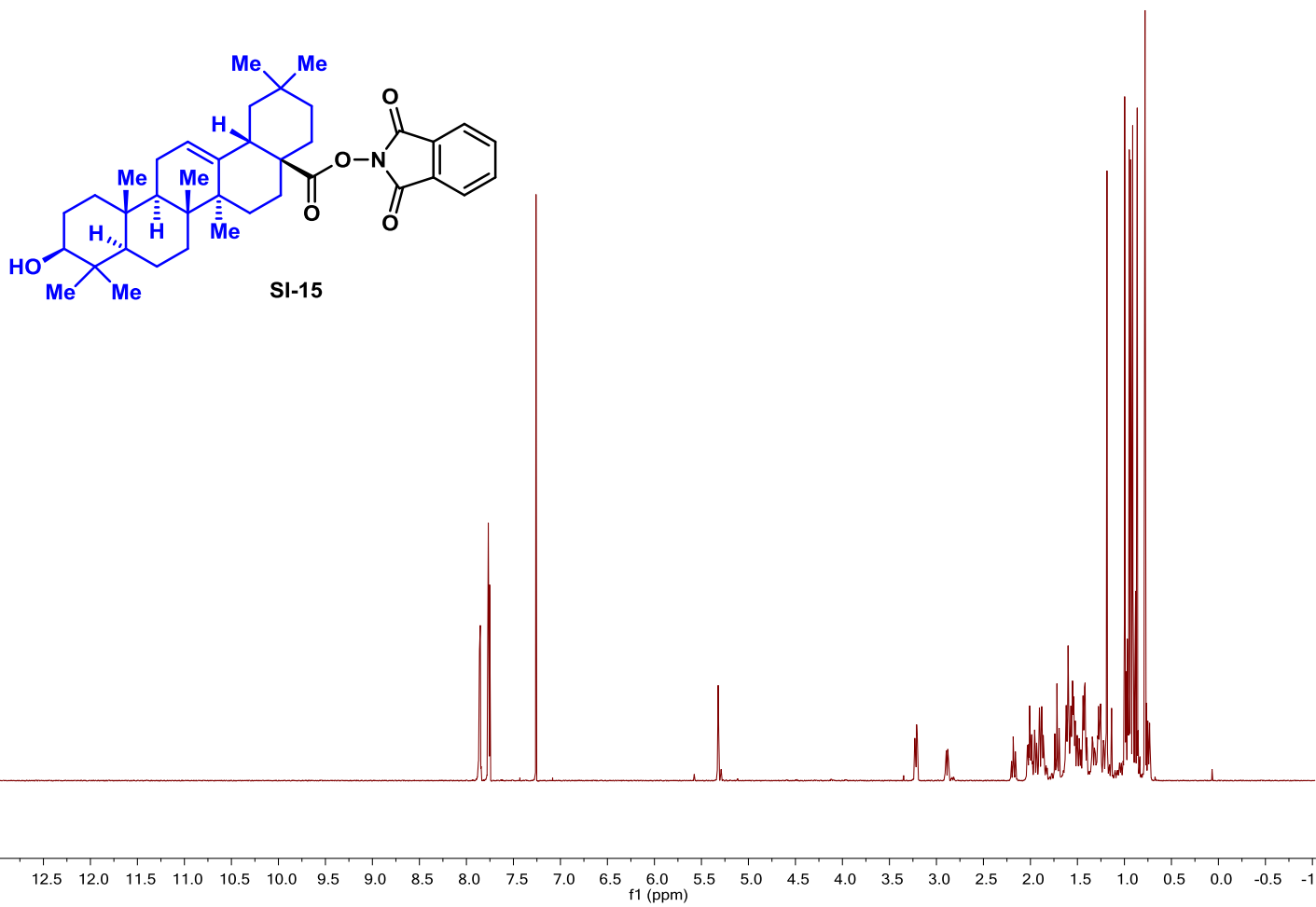
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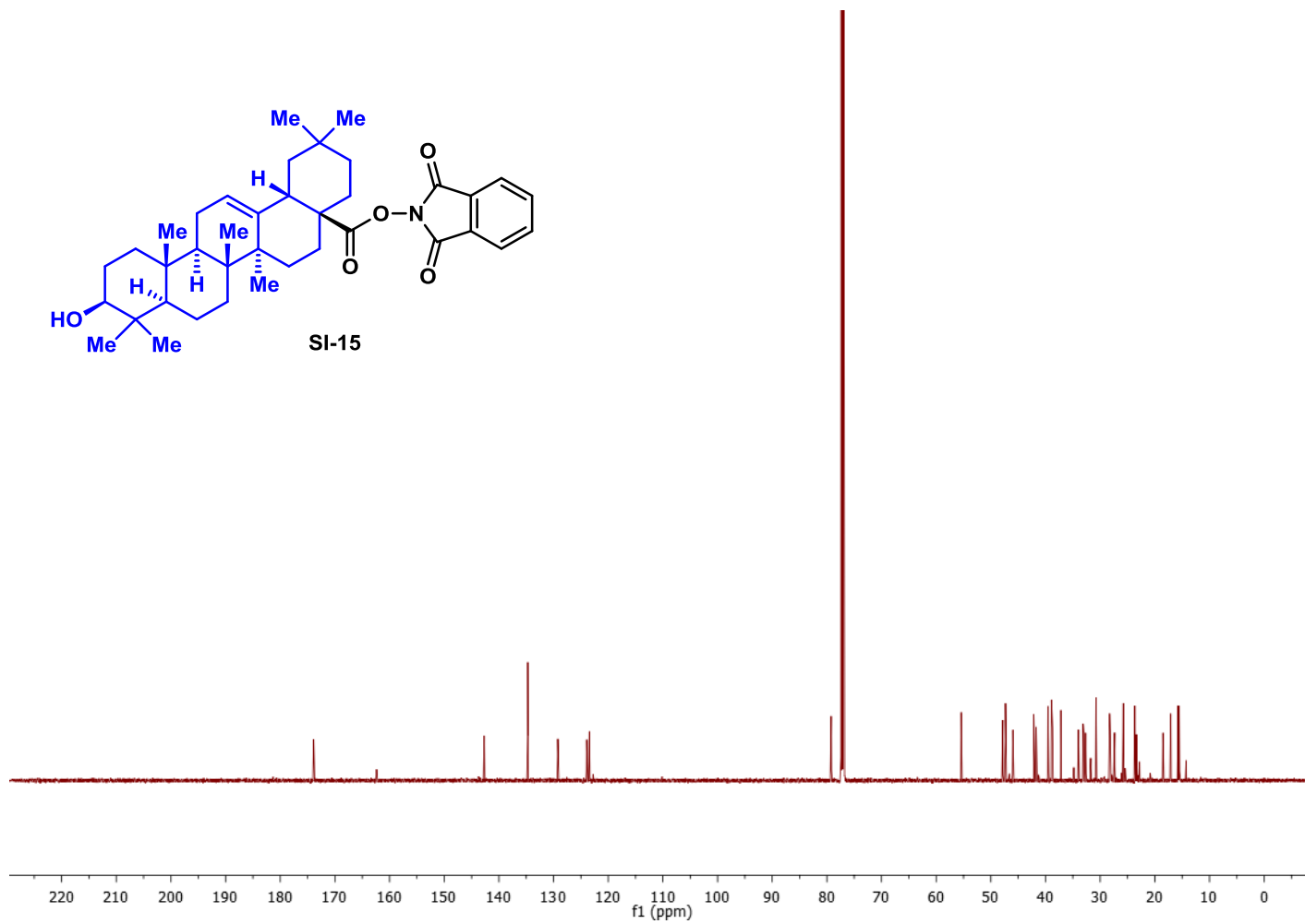
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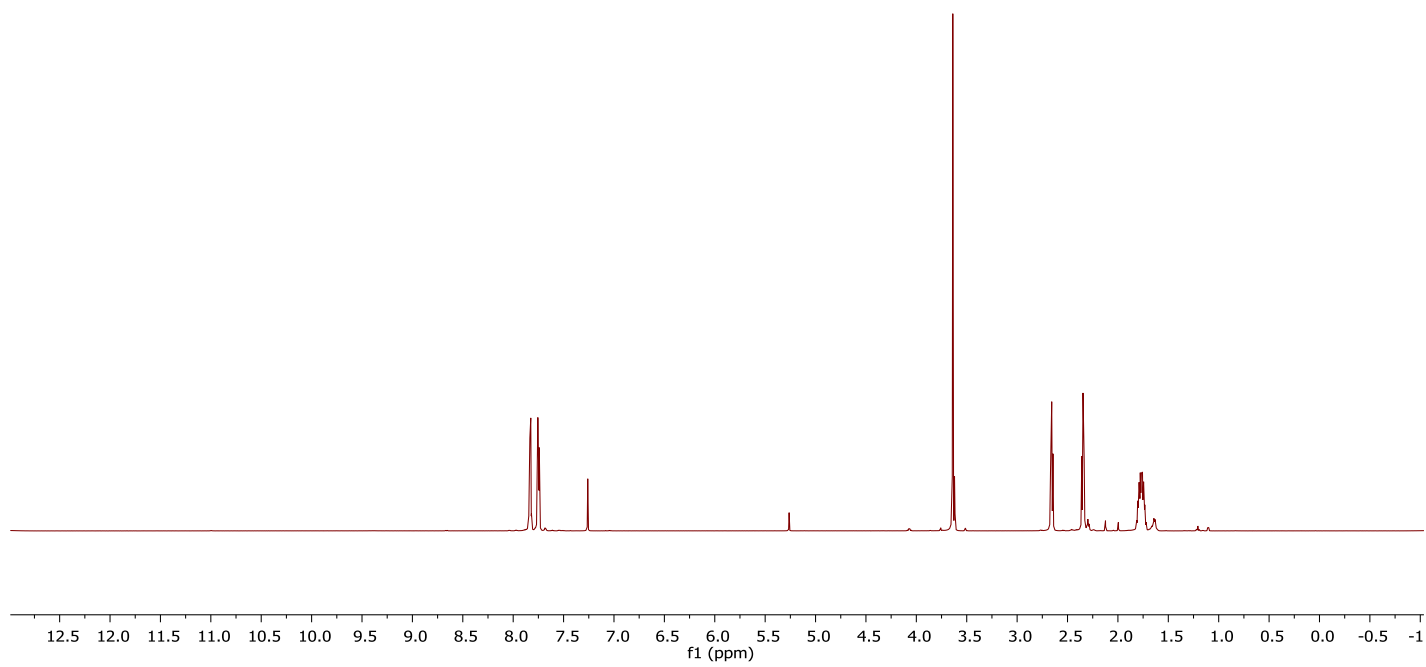
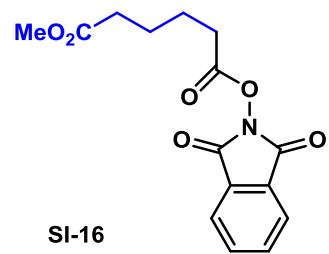
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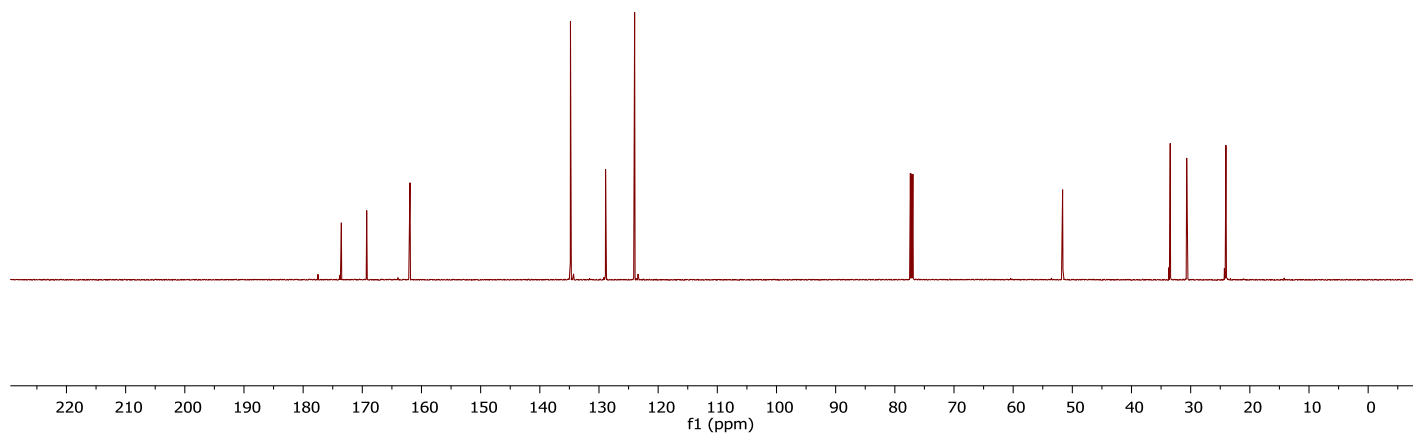
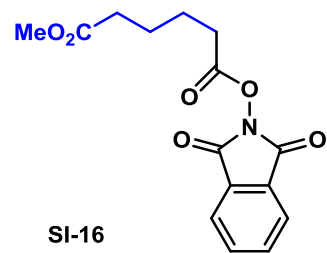
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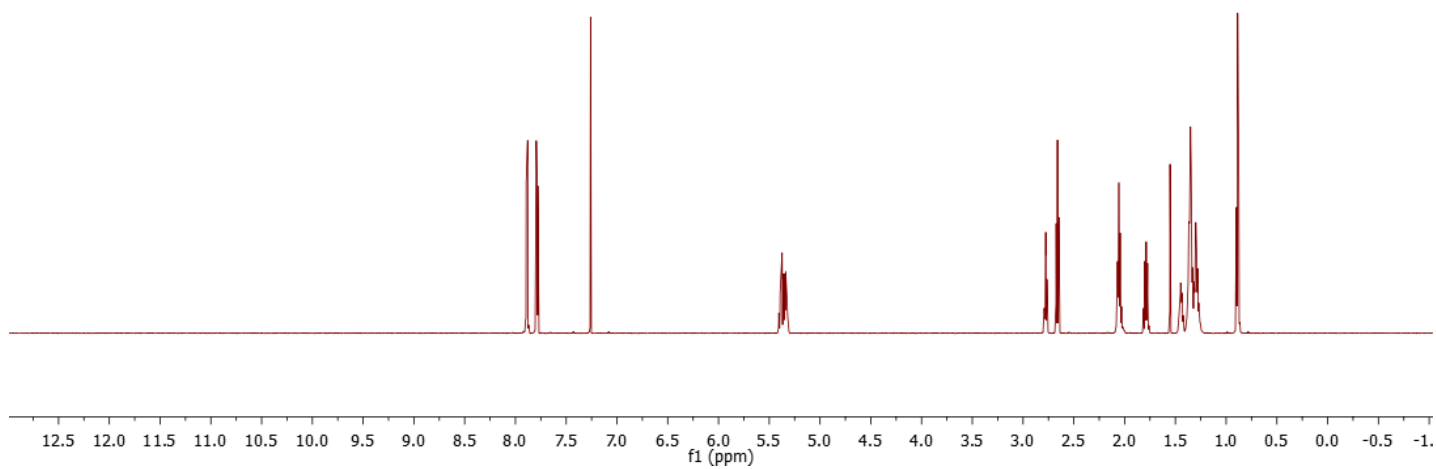
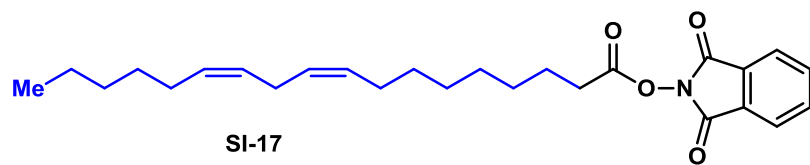
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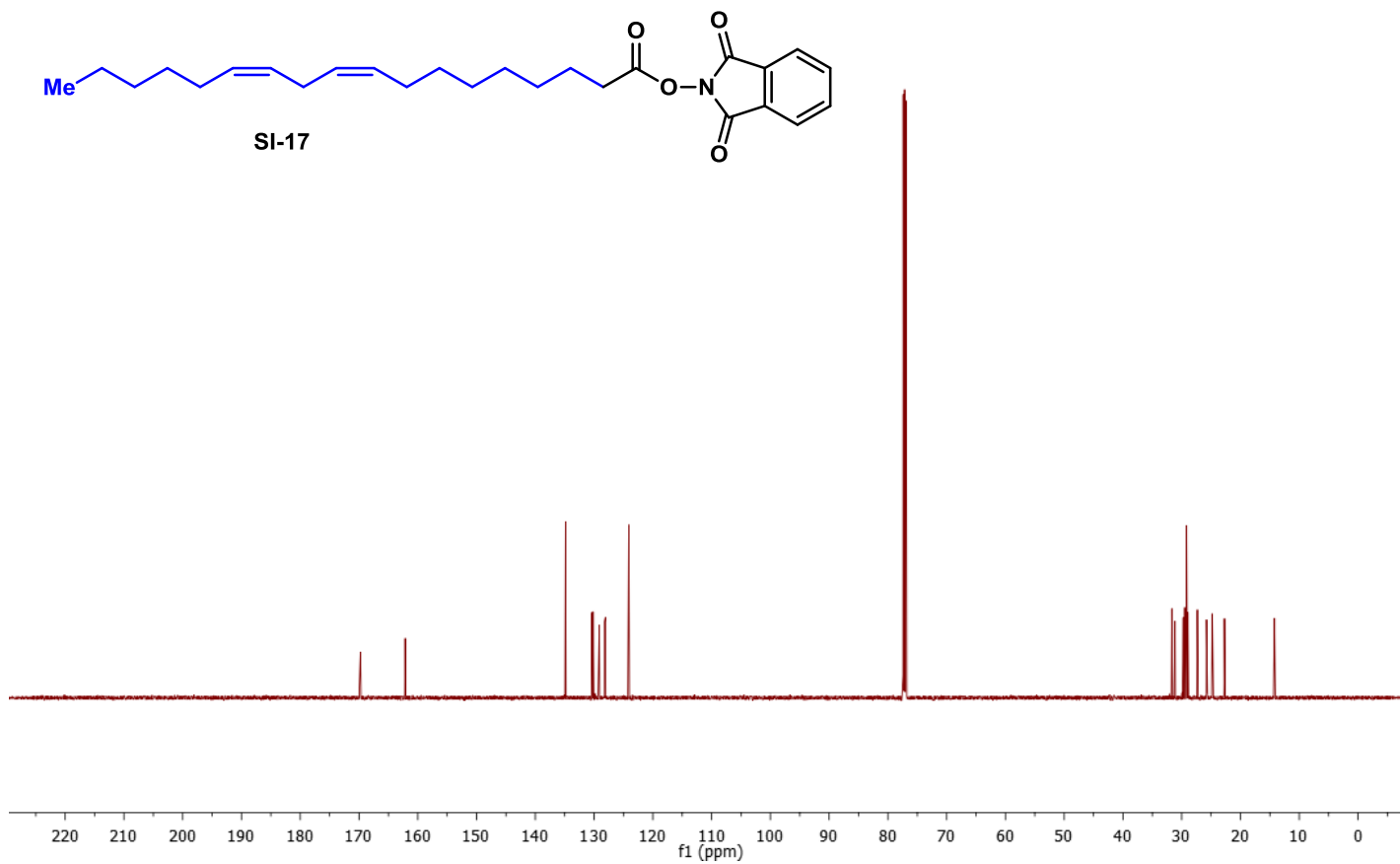
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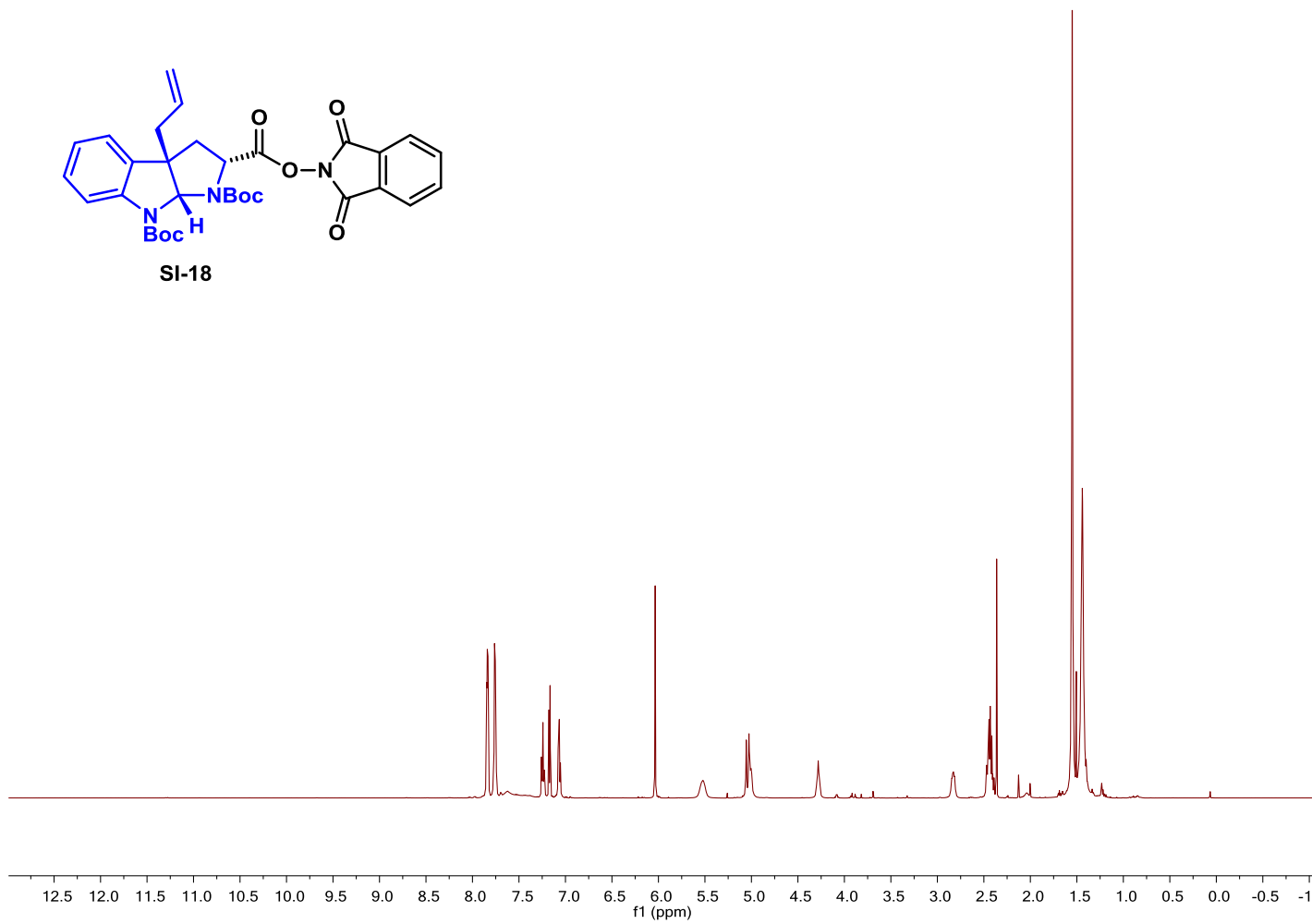
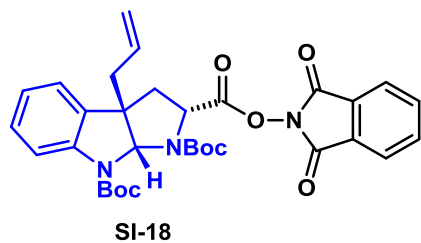
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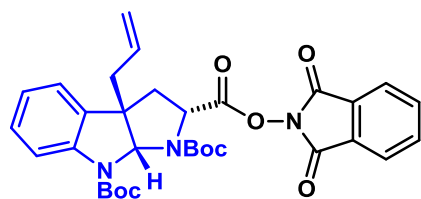
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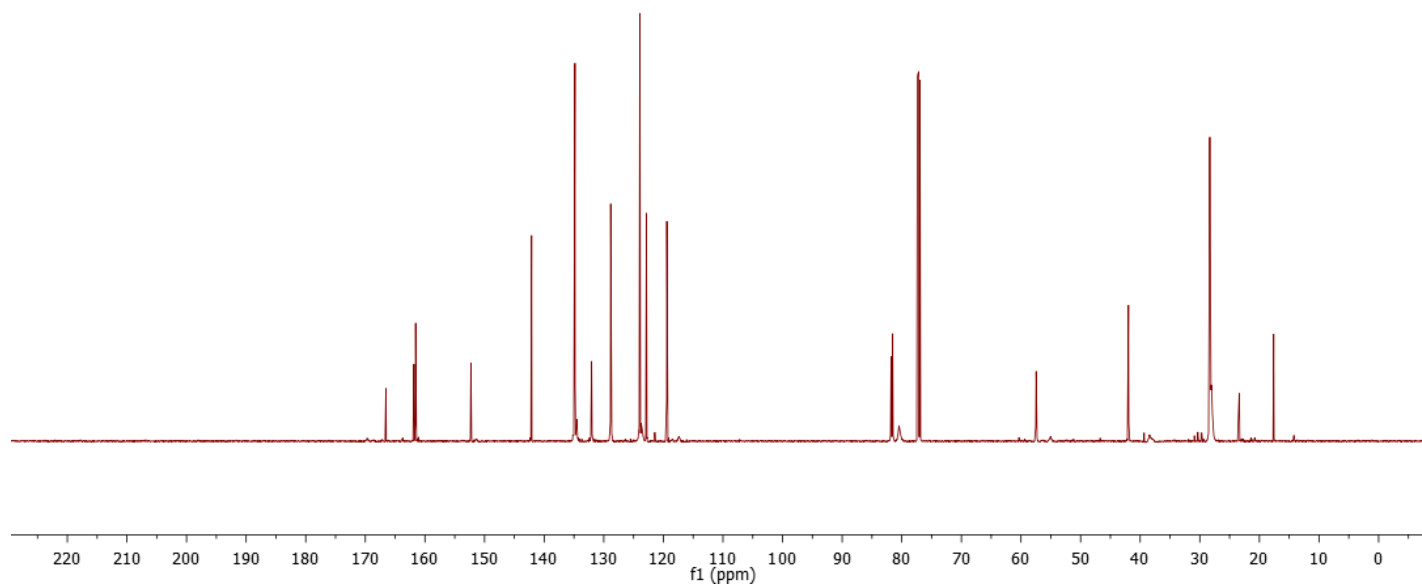
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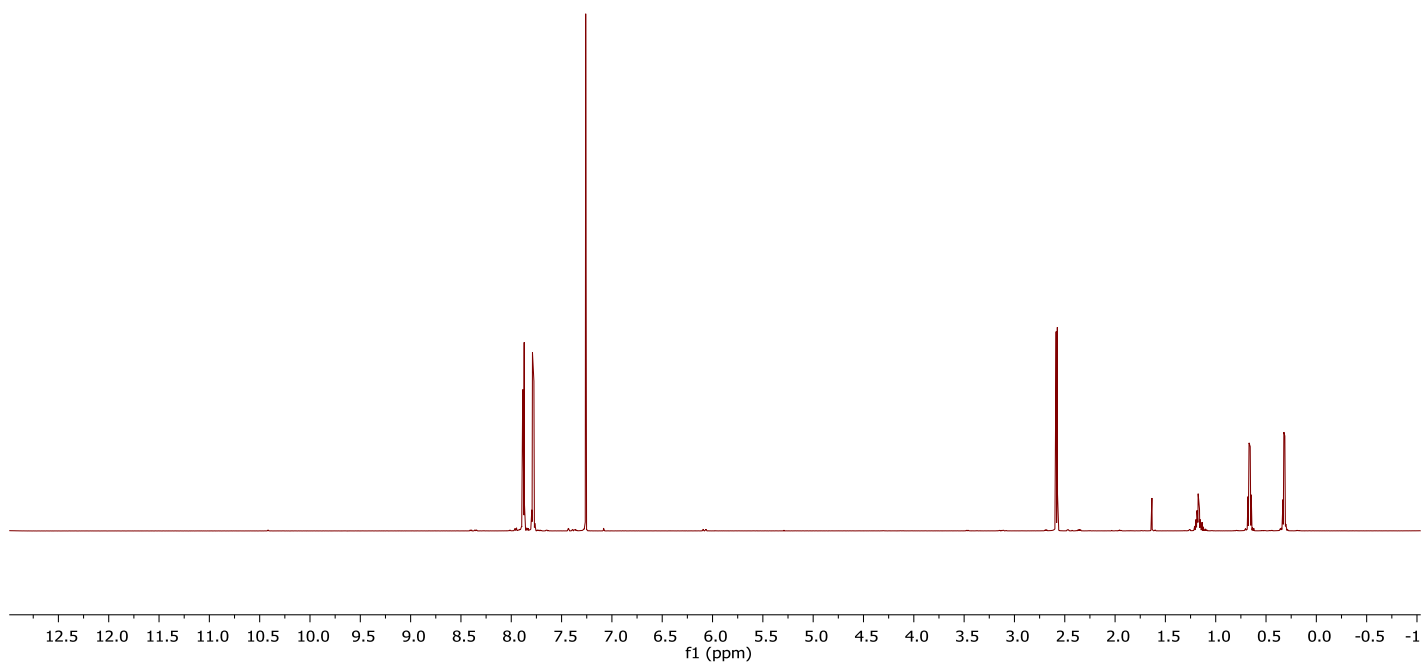
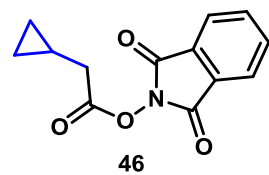
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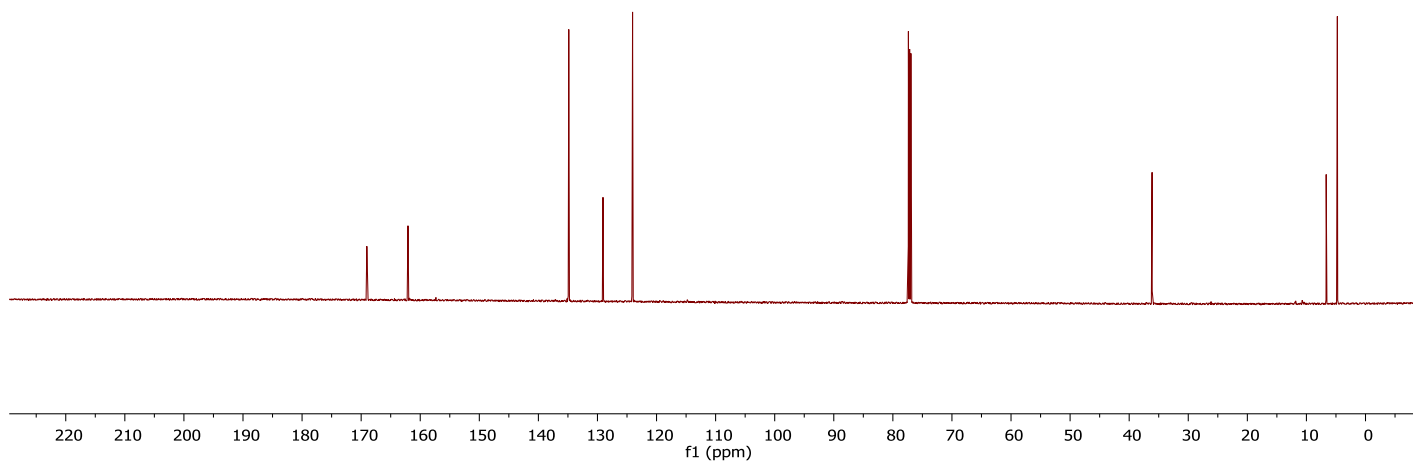
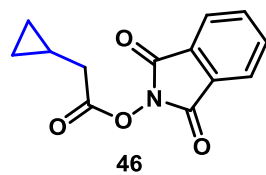
SI-18



Compound 46 ^1H NMR

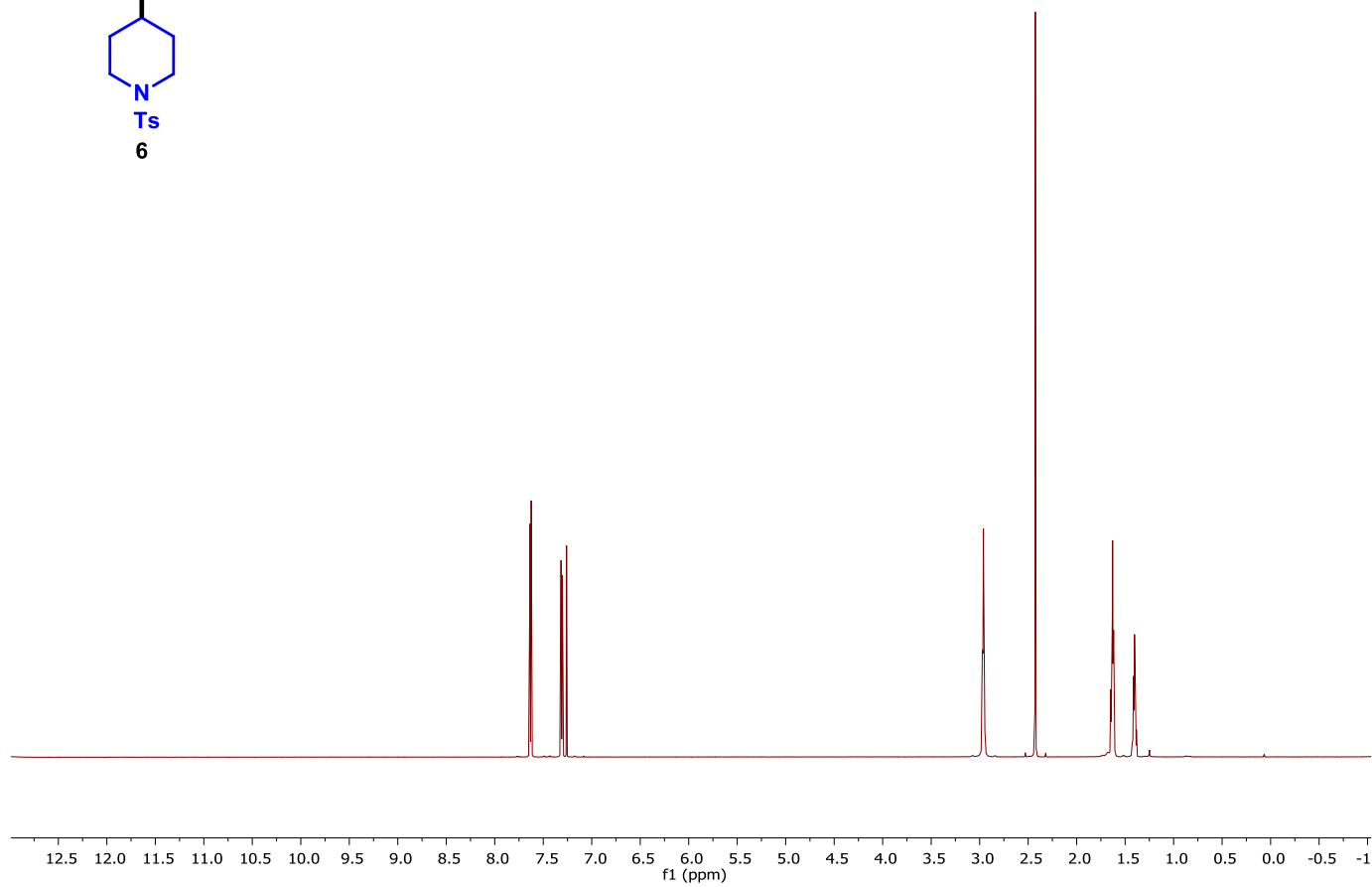
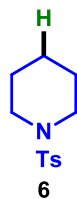


Compound 46 ^{13}C NMR

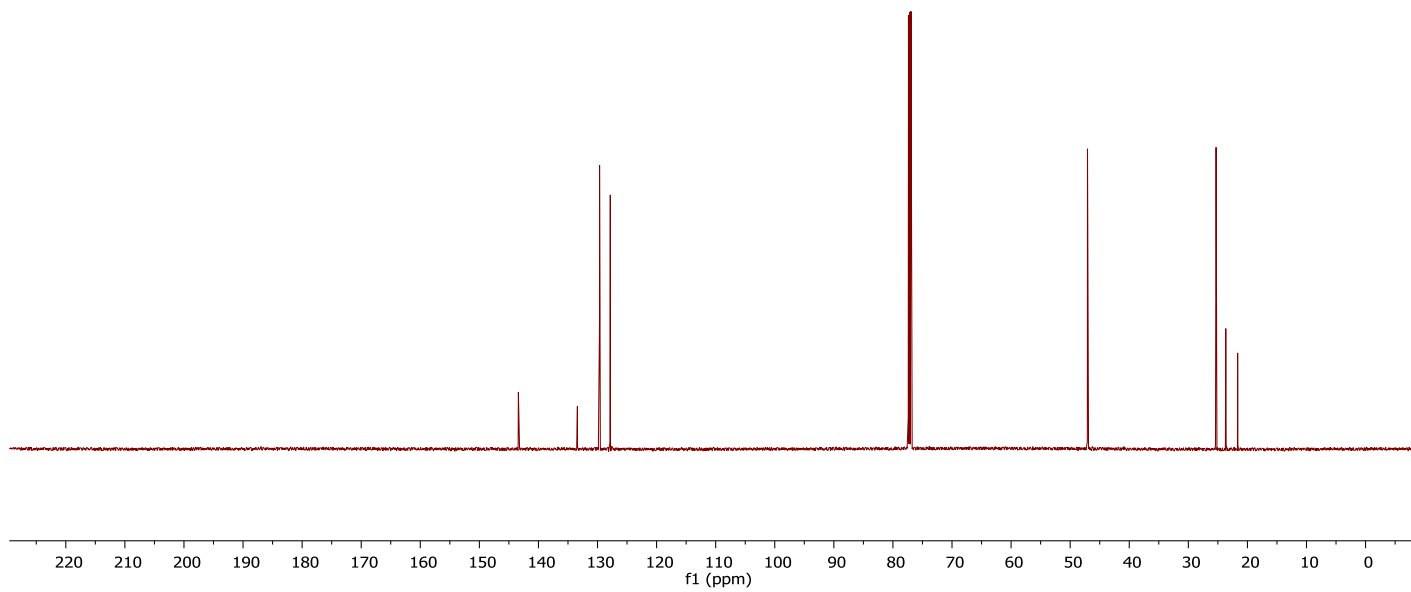
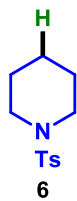


Spectra for Decarboxylation Compounds

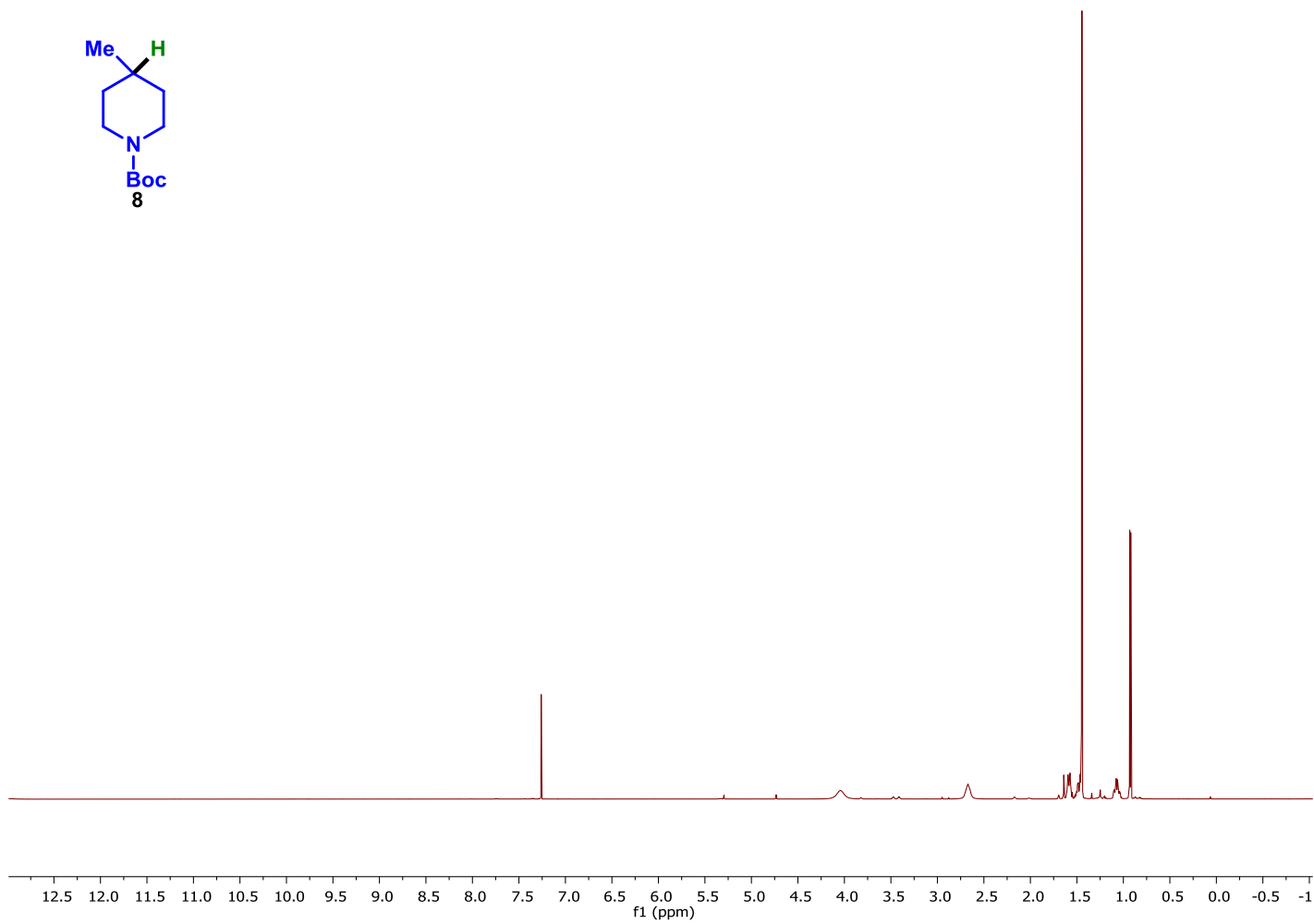
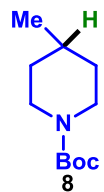
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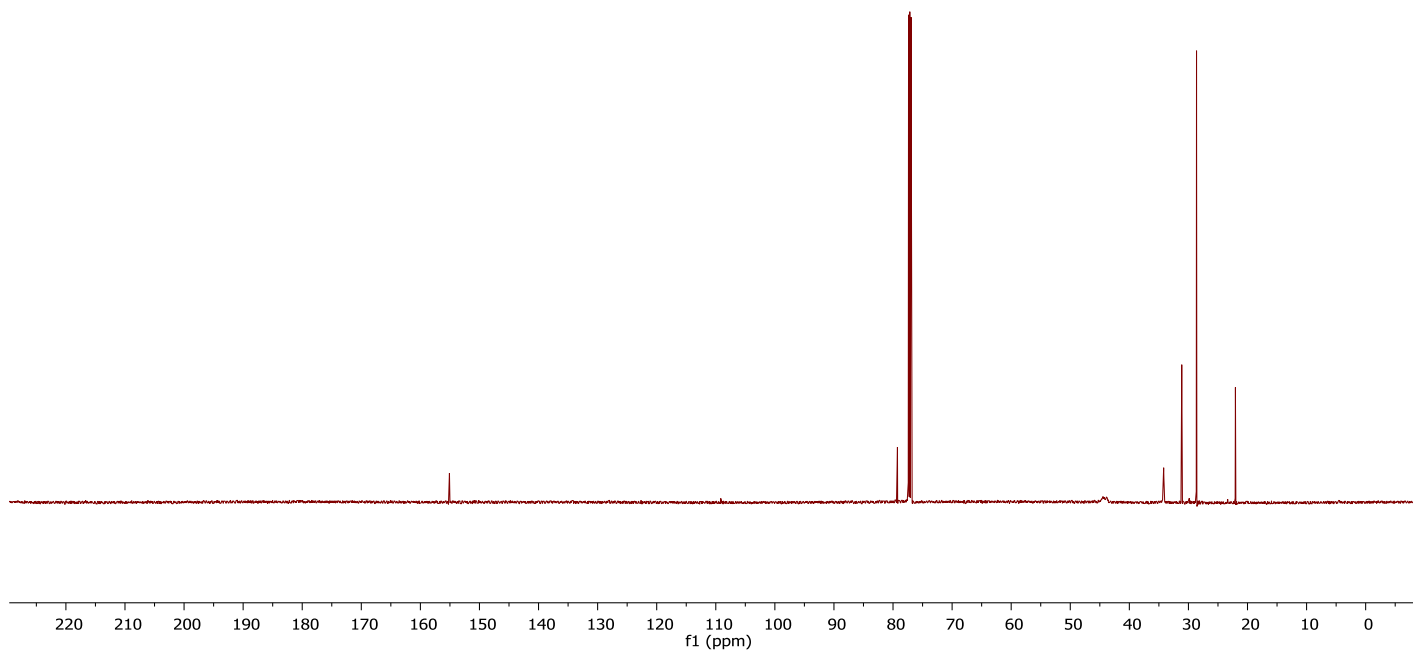
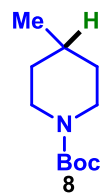
Compound 6 ^{13}C NMR



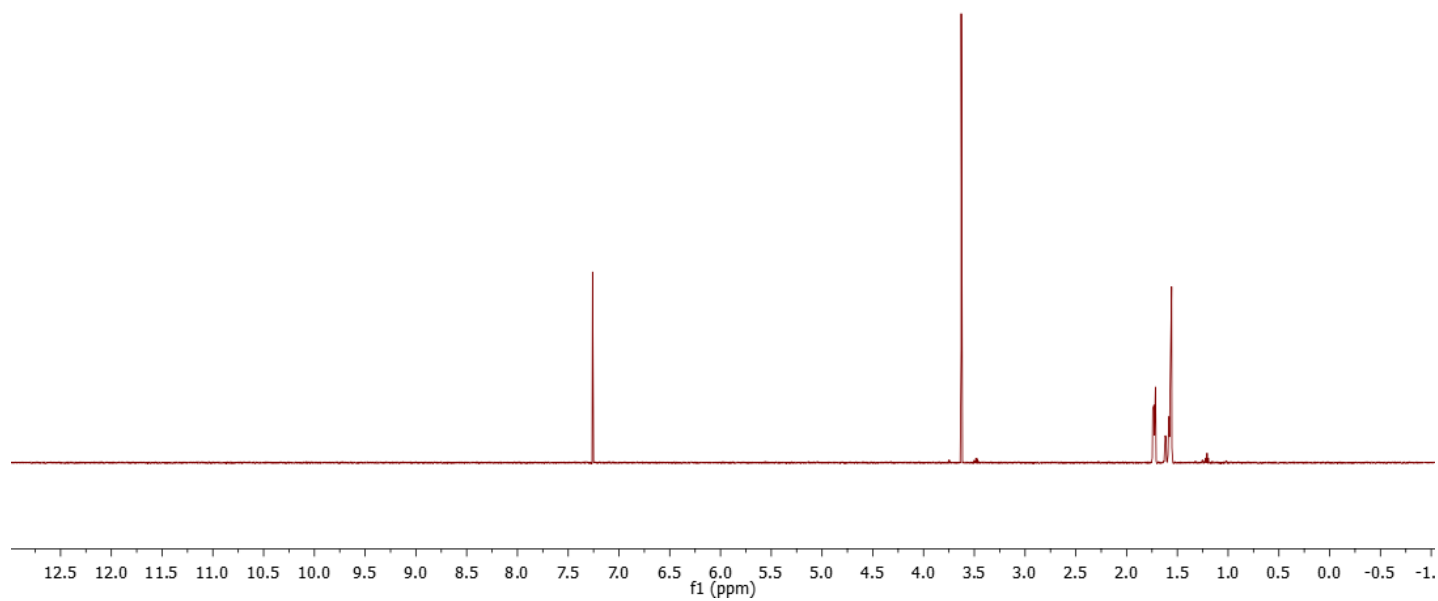
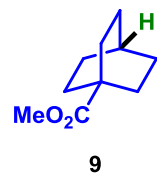
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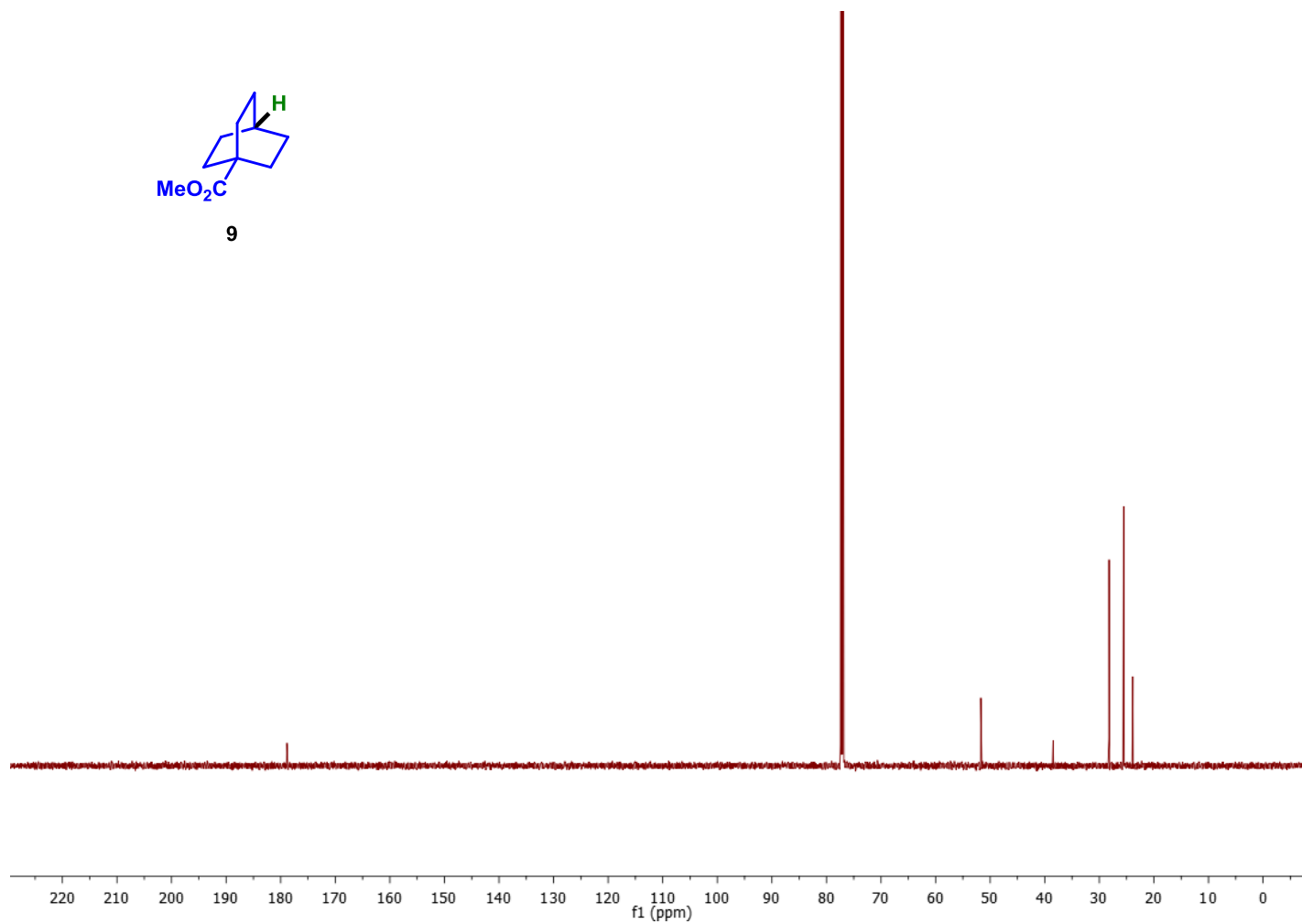
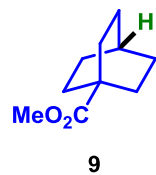
Compound 8 ^{13}C NMR



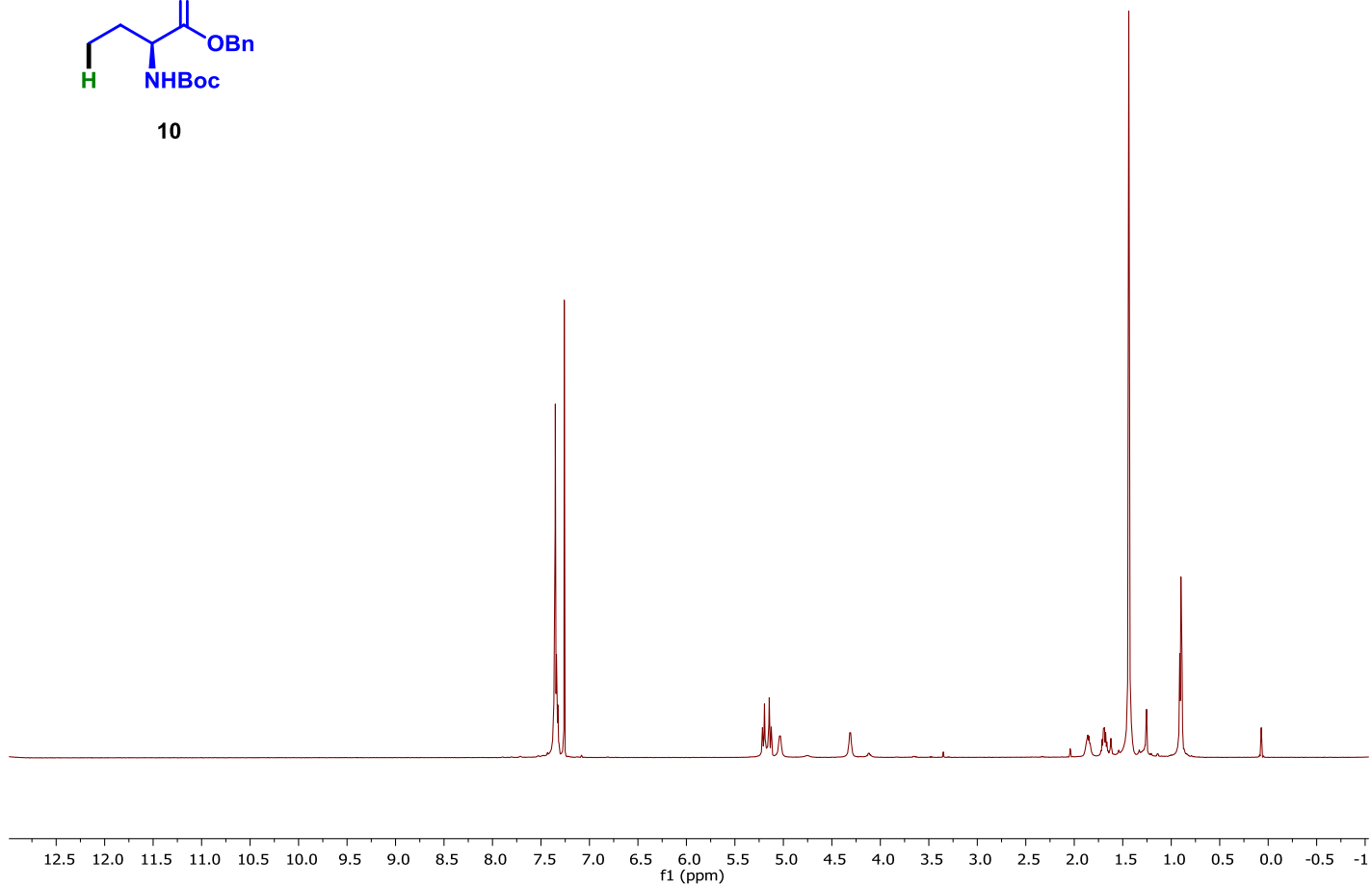
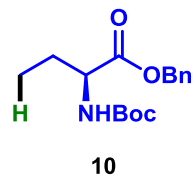
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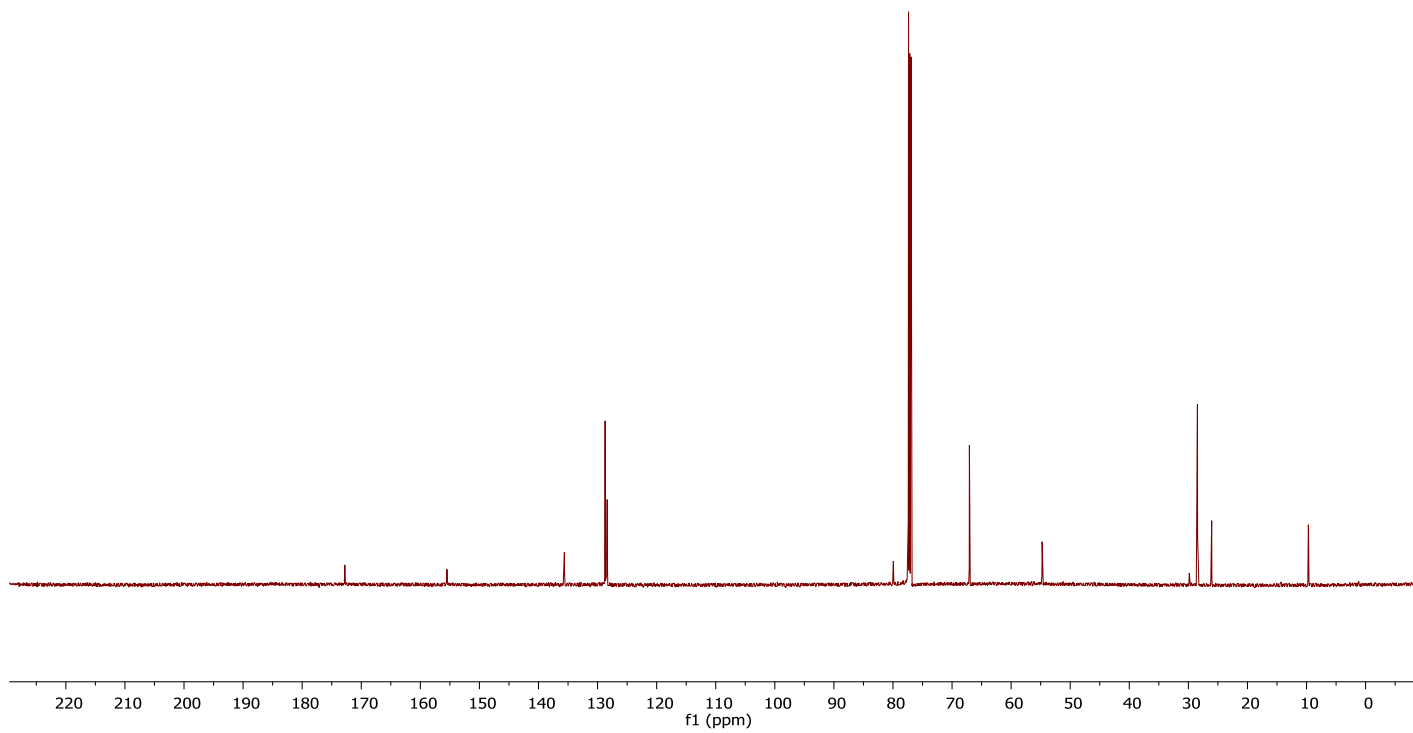
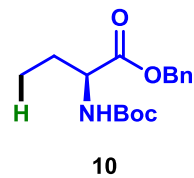
Compound 9 ^{13}C NMR



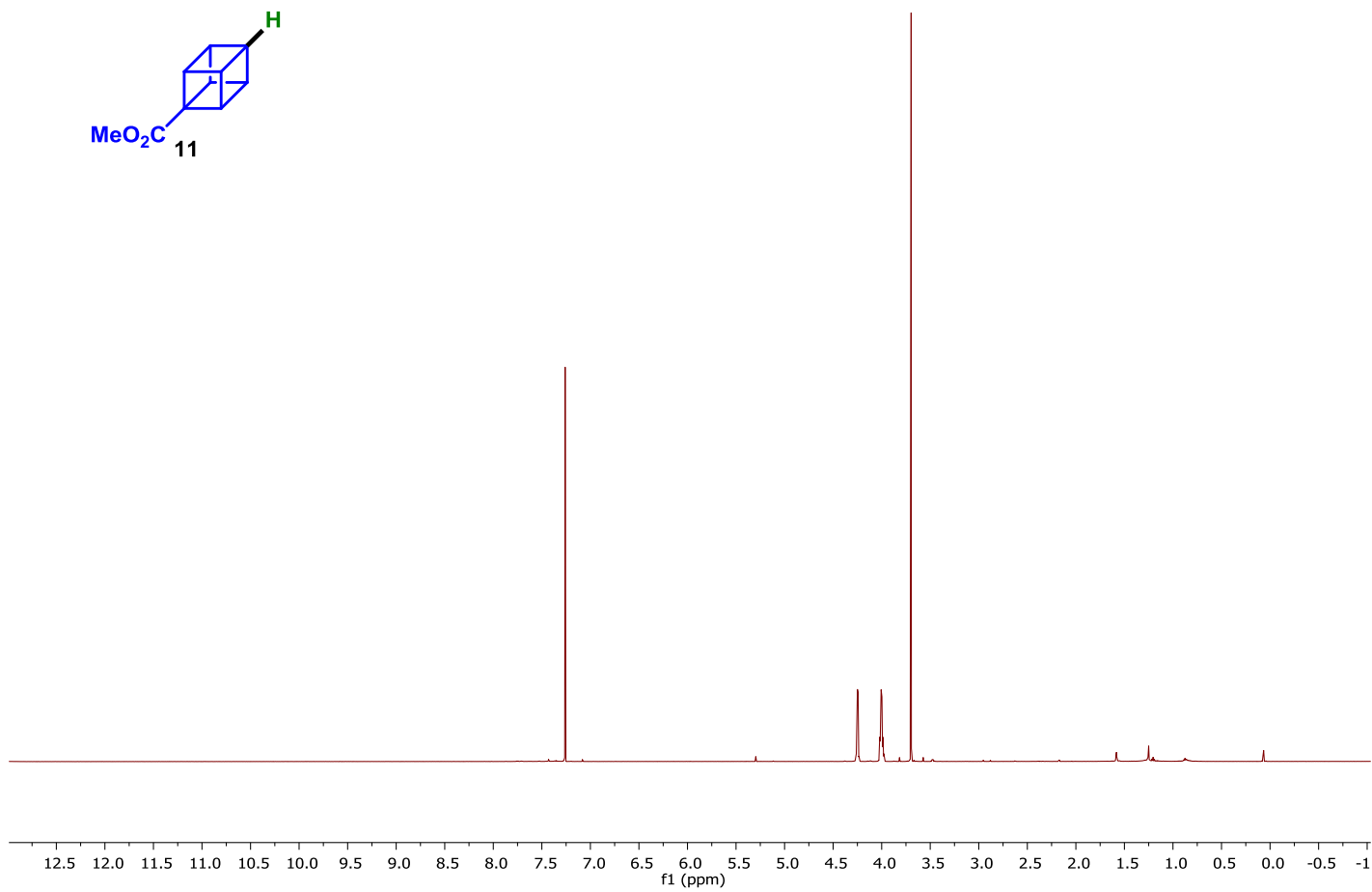
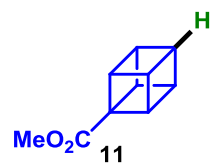
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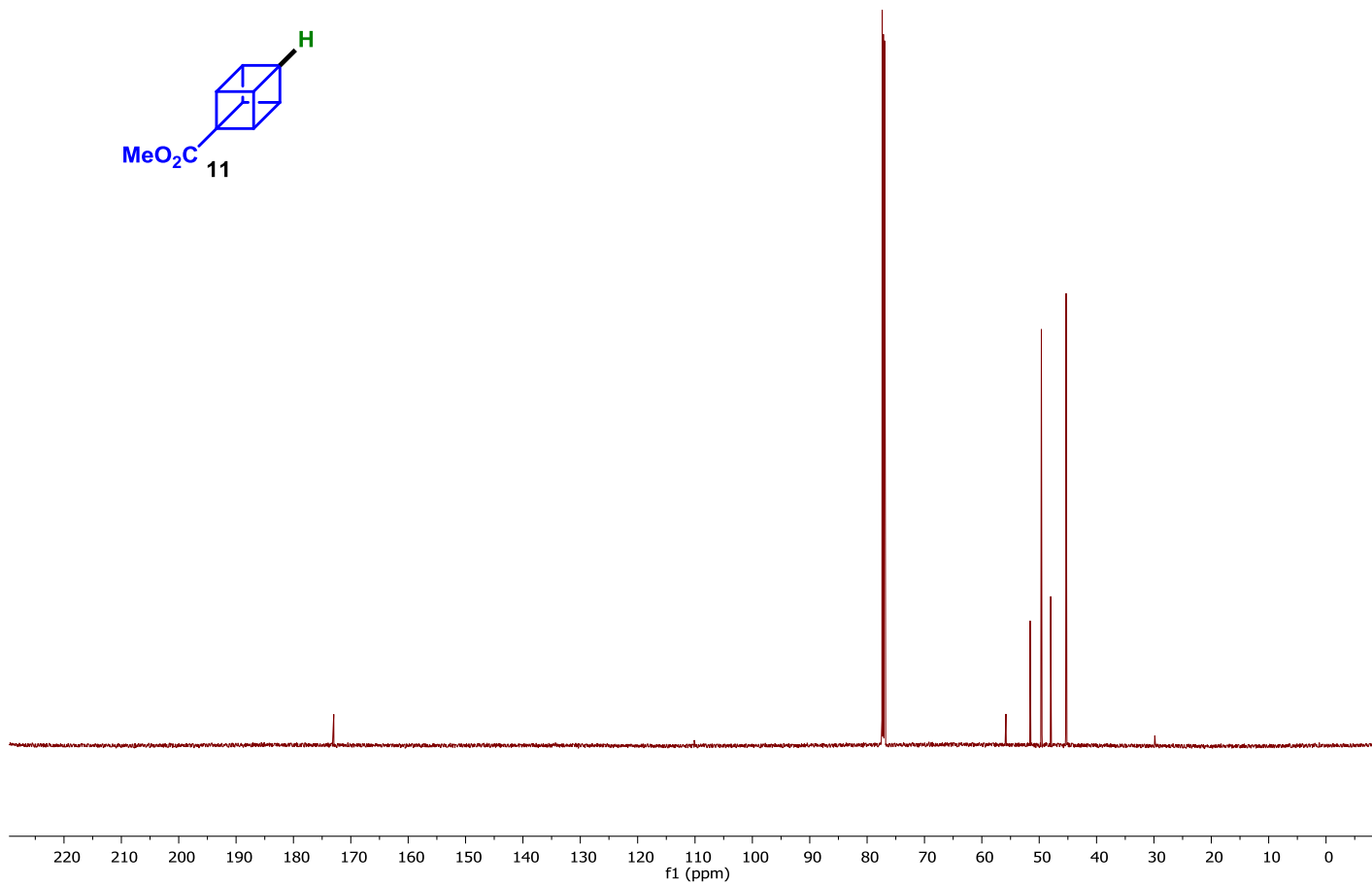
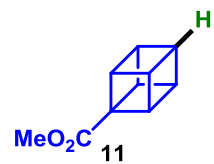
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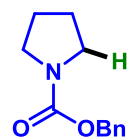
Compound 11 ^1H NMR



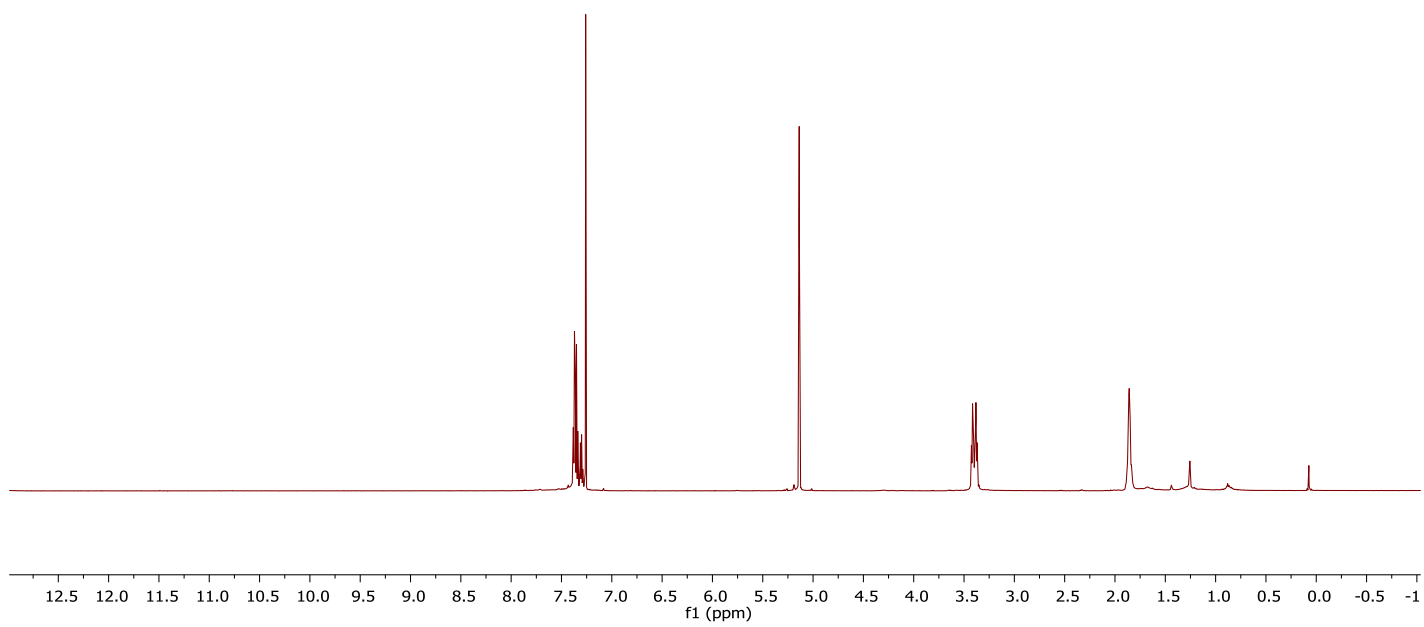
Compound 11 ^{13}C NMR



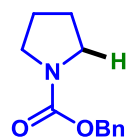
Compound 12 ^1H NMR



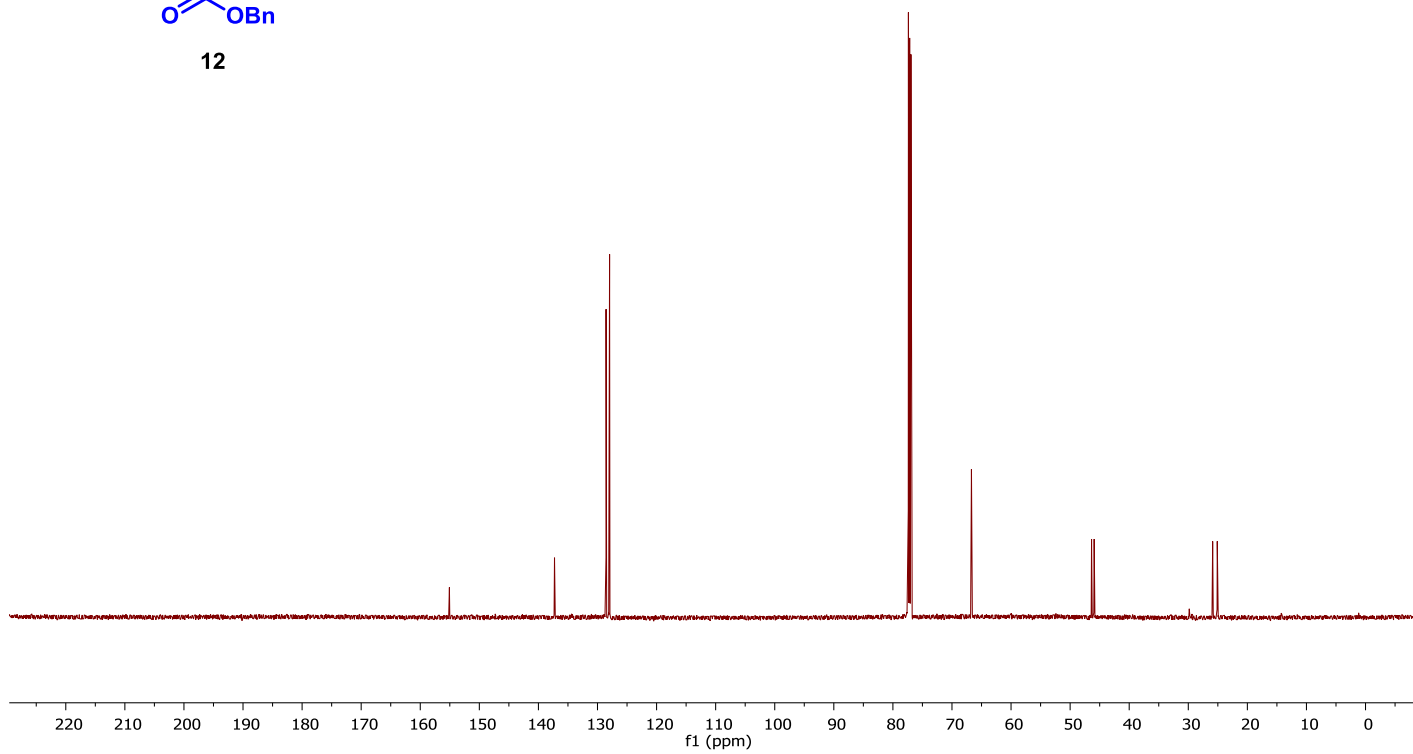
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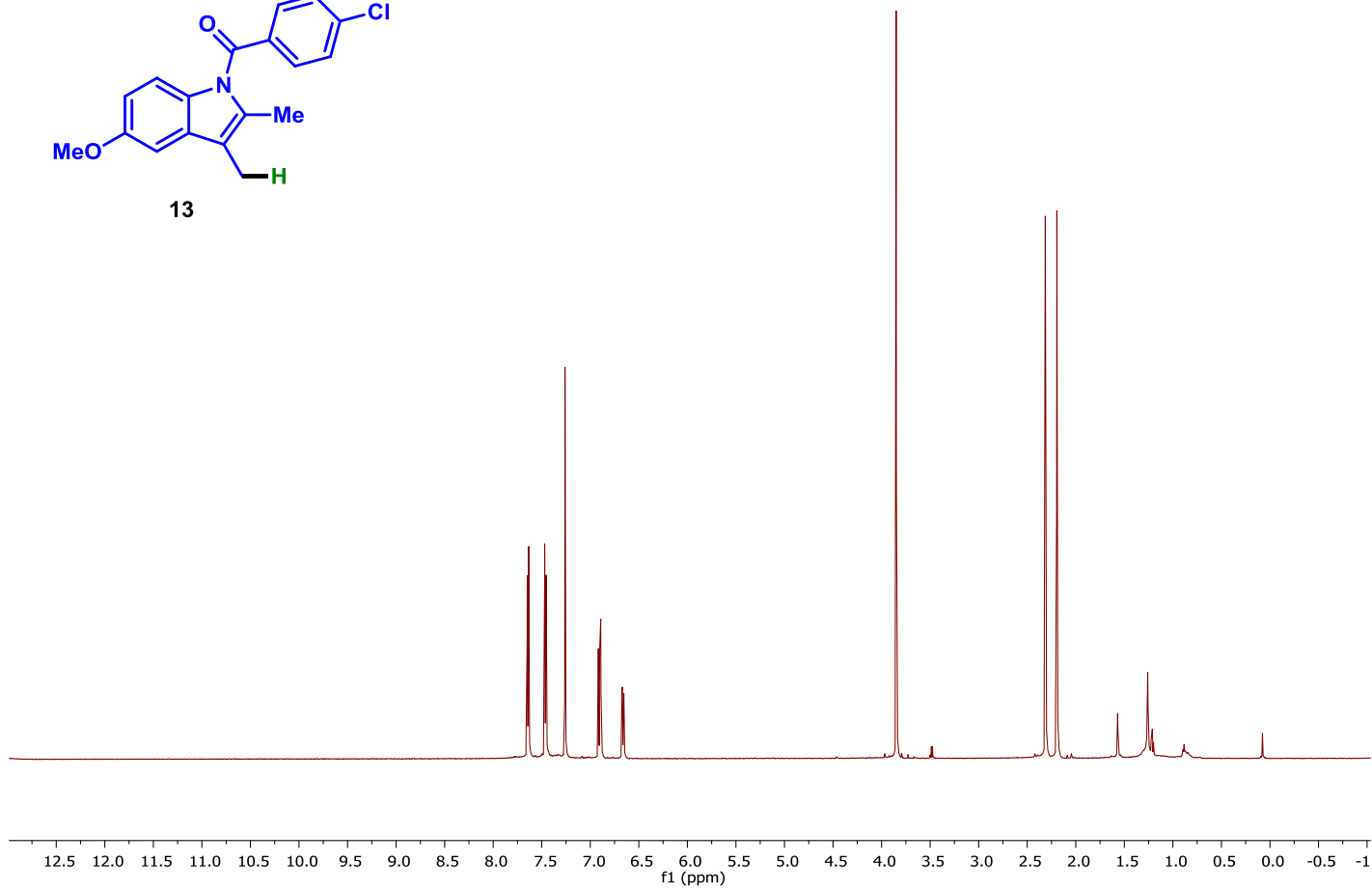
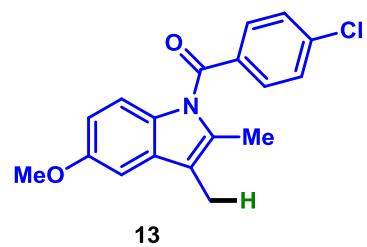
Compound 12 ^{13}C NMR



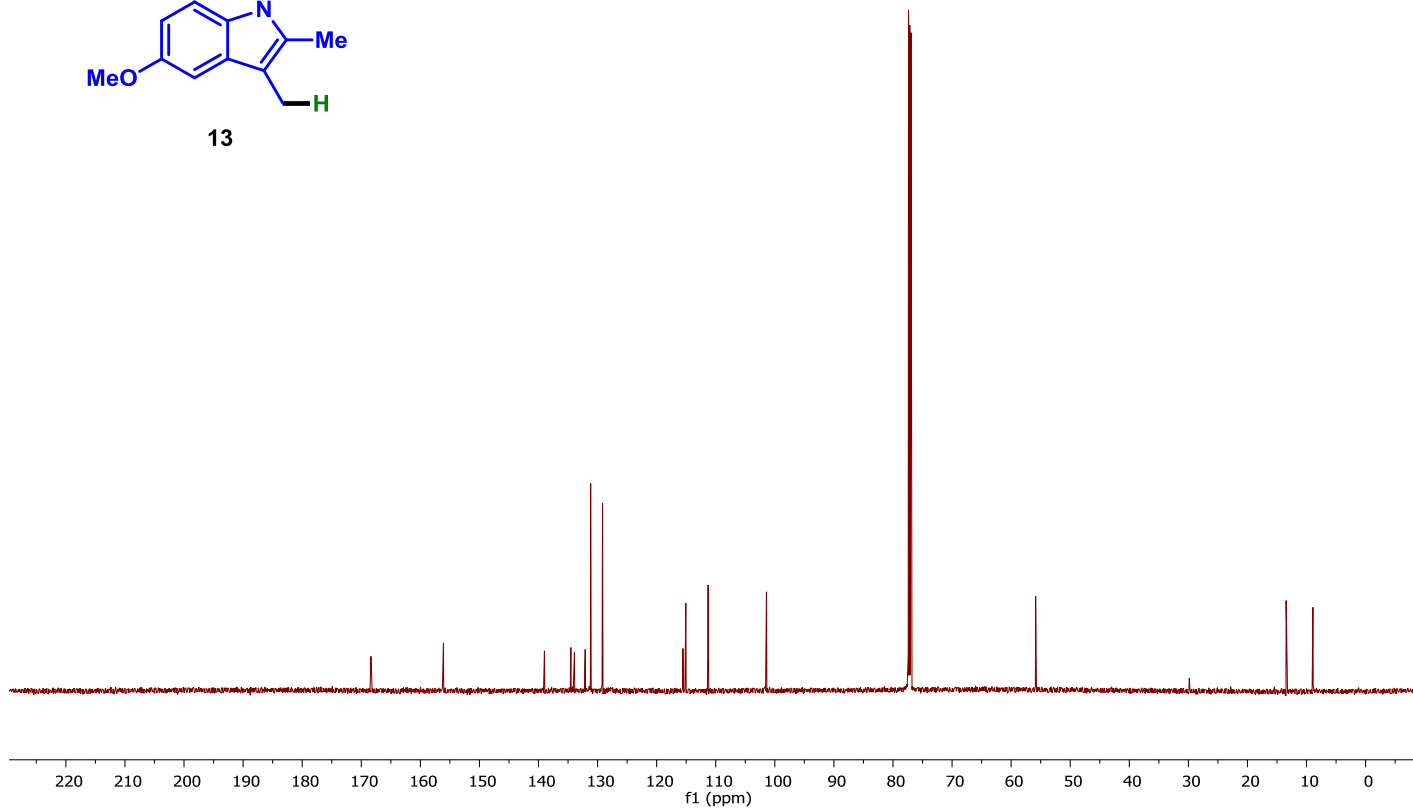
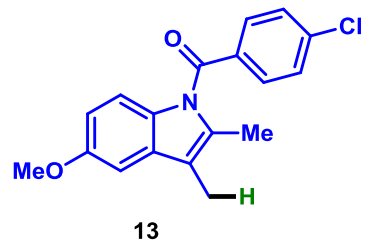
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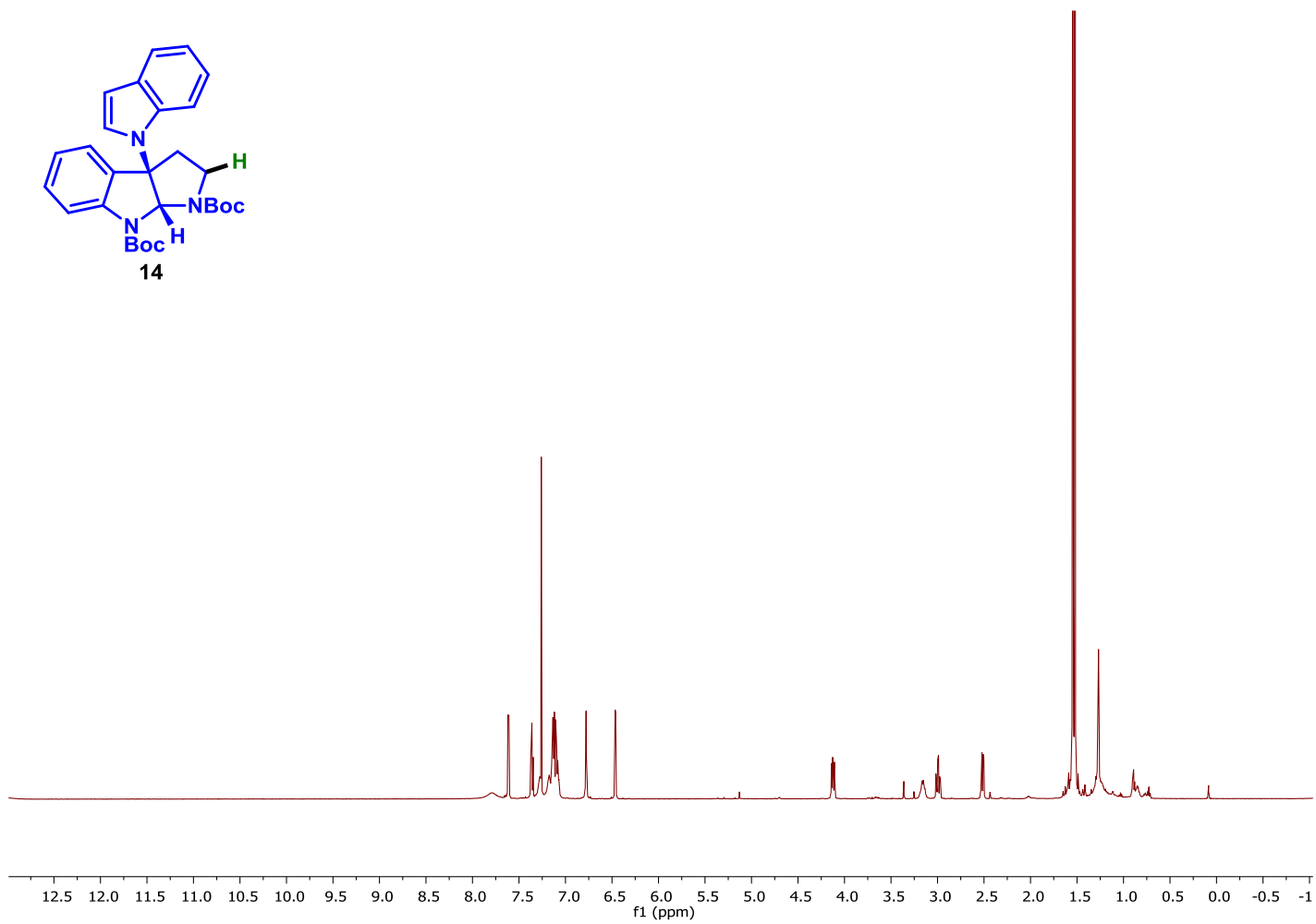
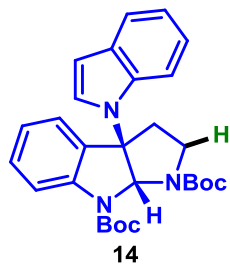
Compound 13 ¹H NMR



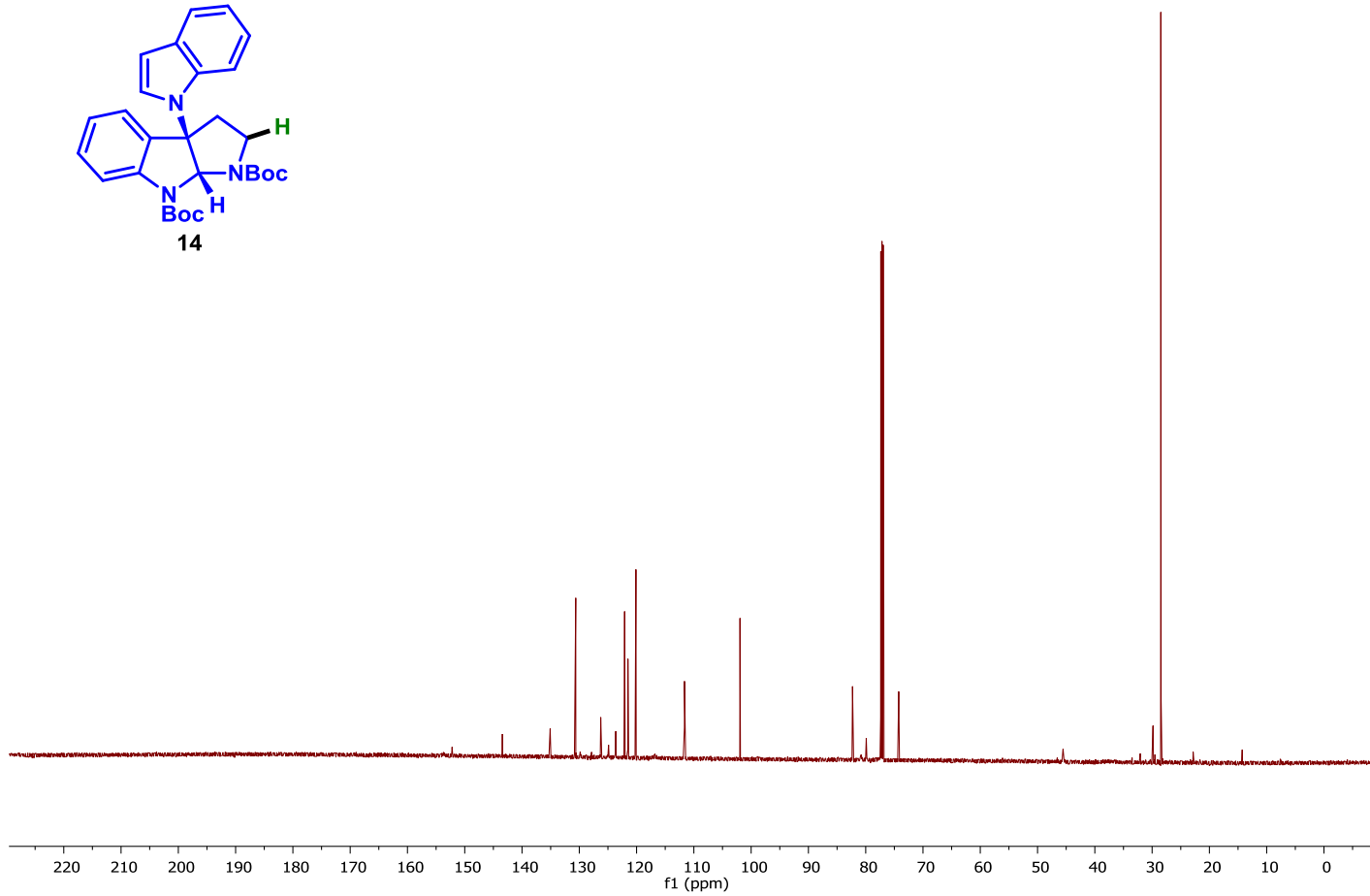
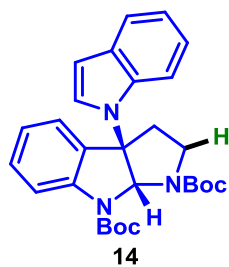
Compound 13 ^{13}C NMR



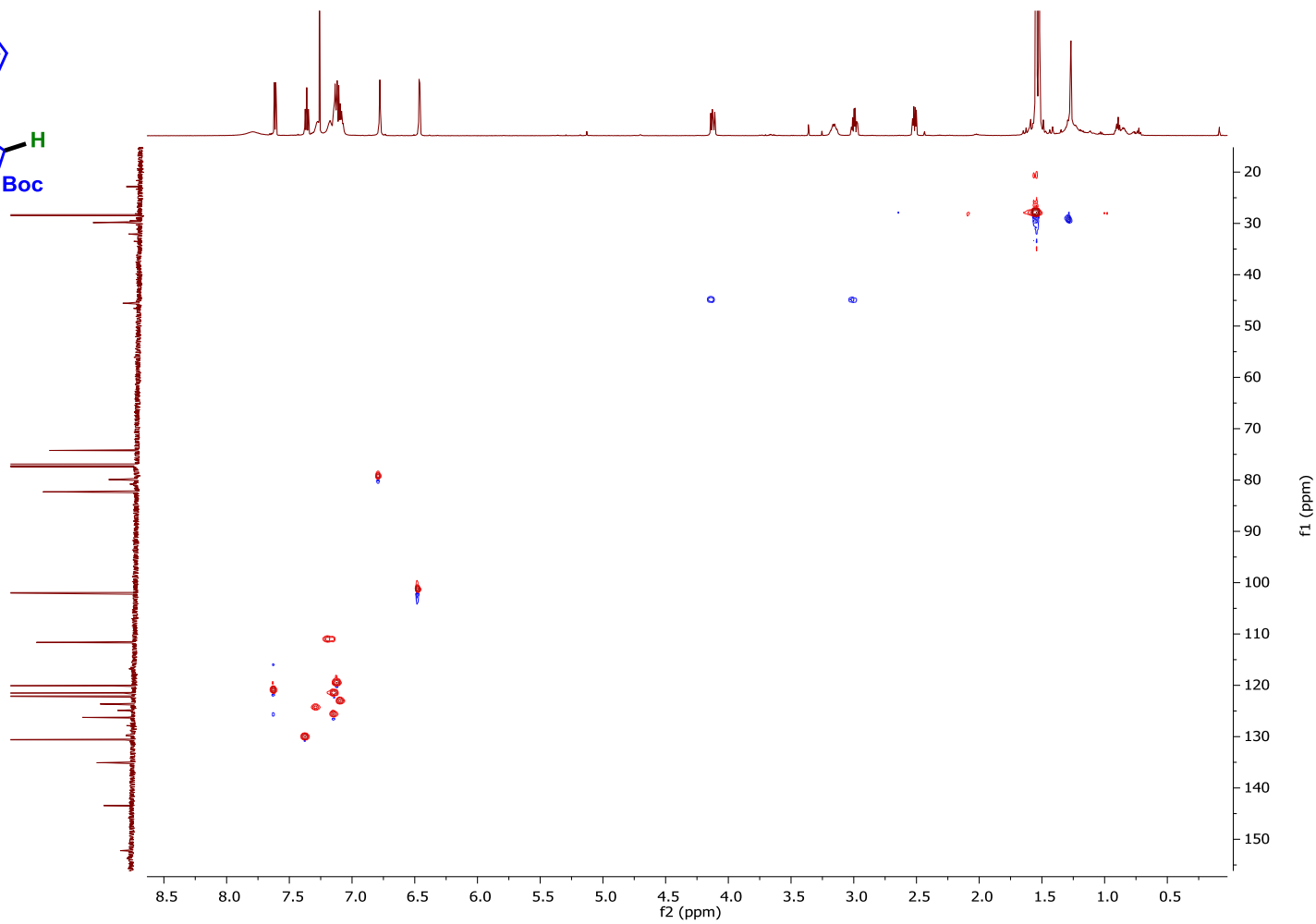
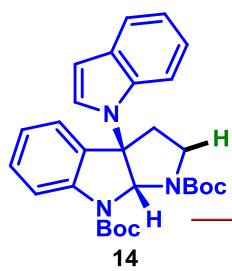
Compound 14 ^1H NMR



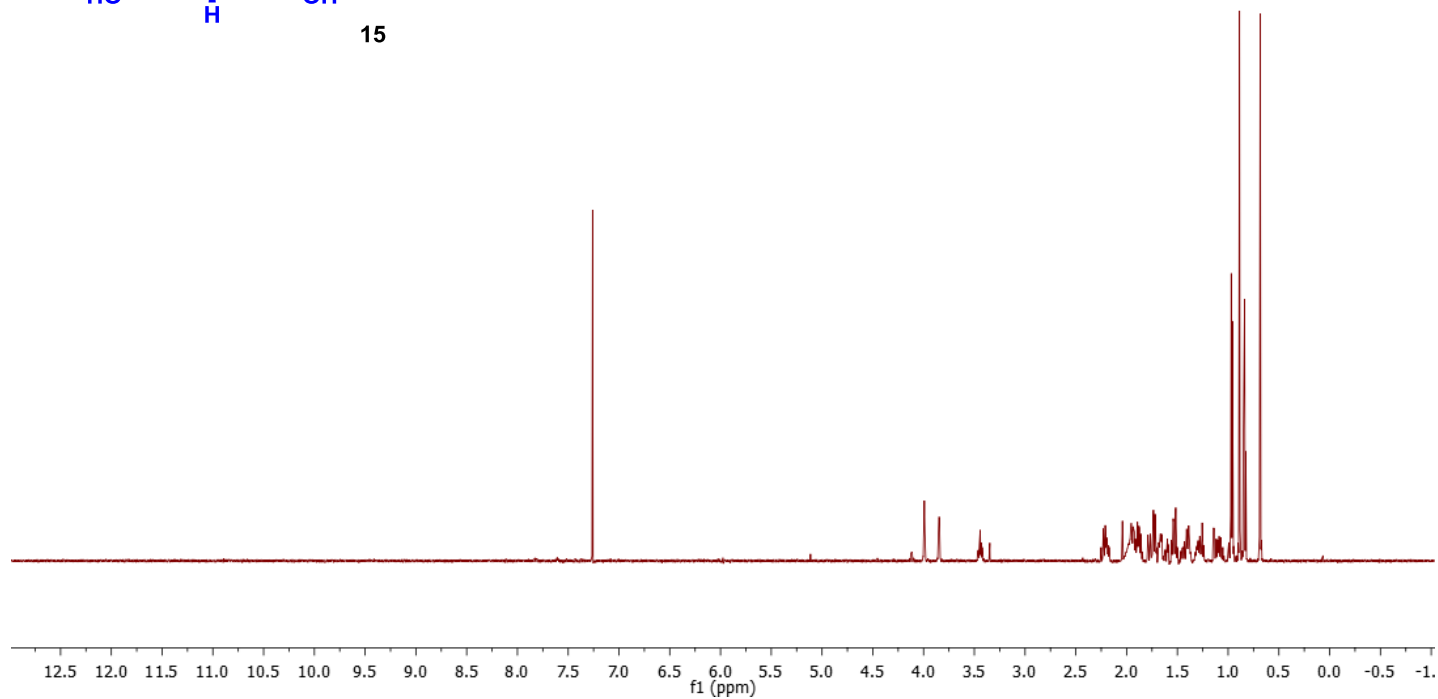
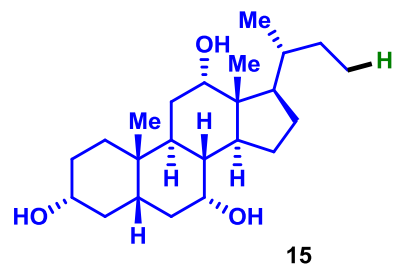
Compound 14 ^{13}C NMR



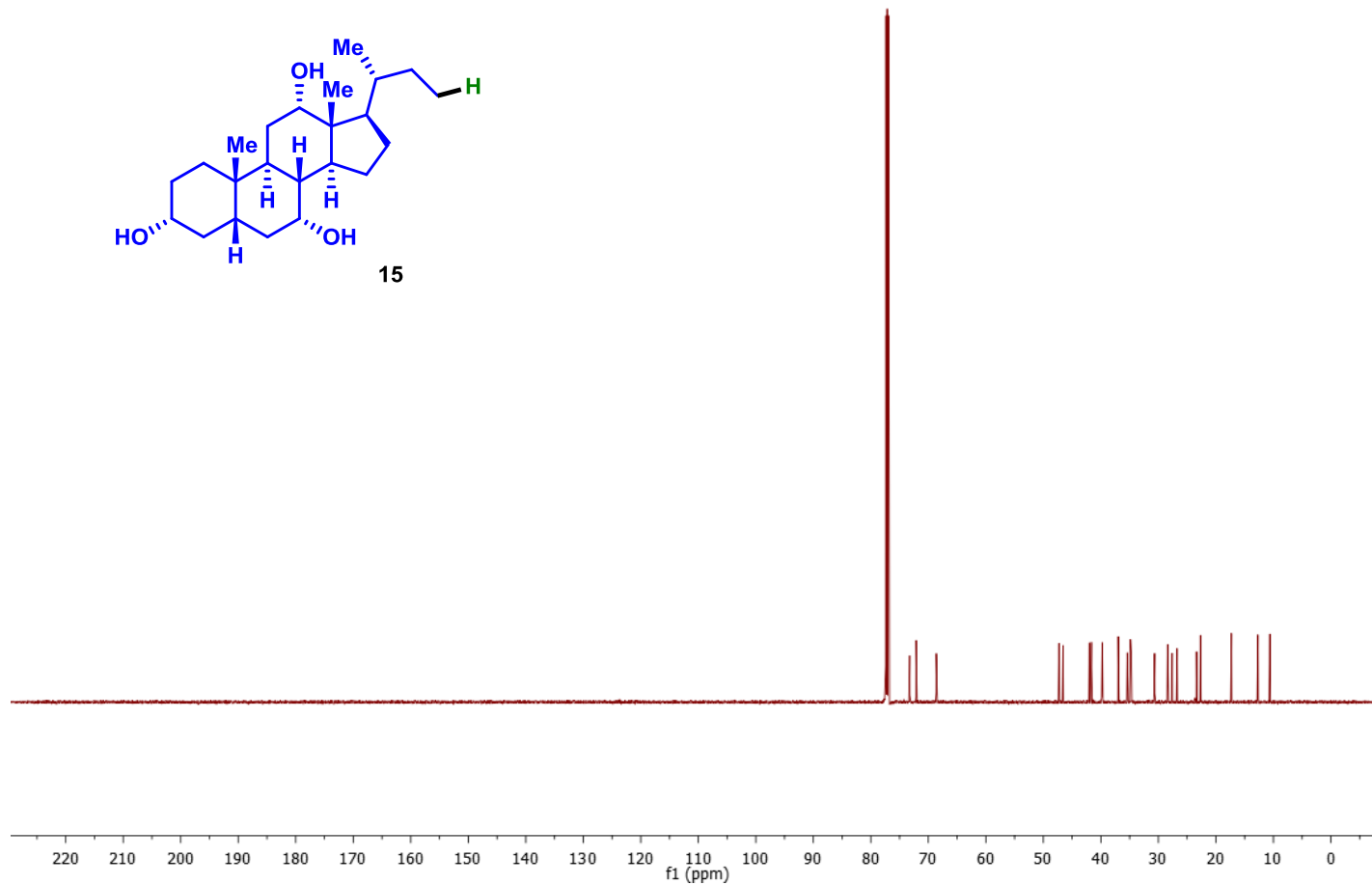
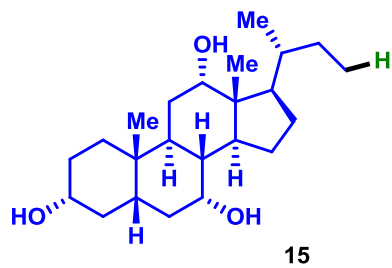
Compound 14 HSQC



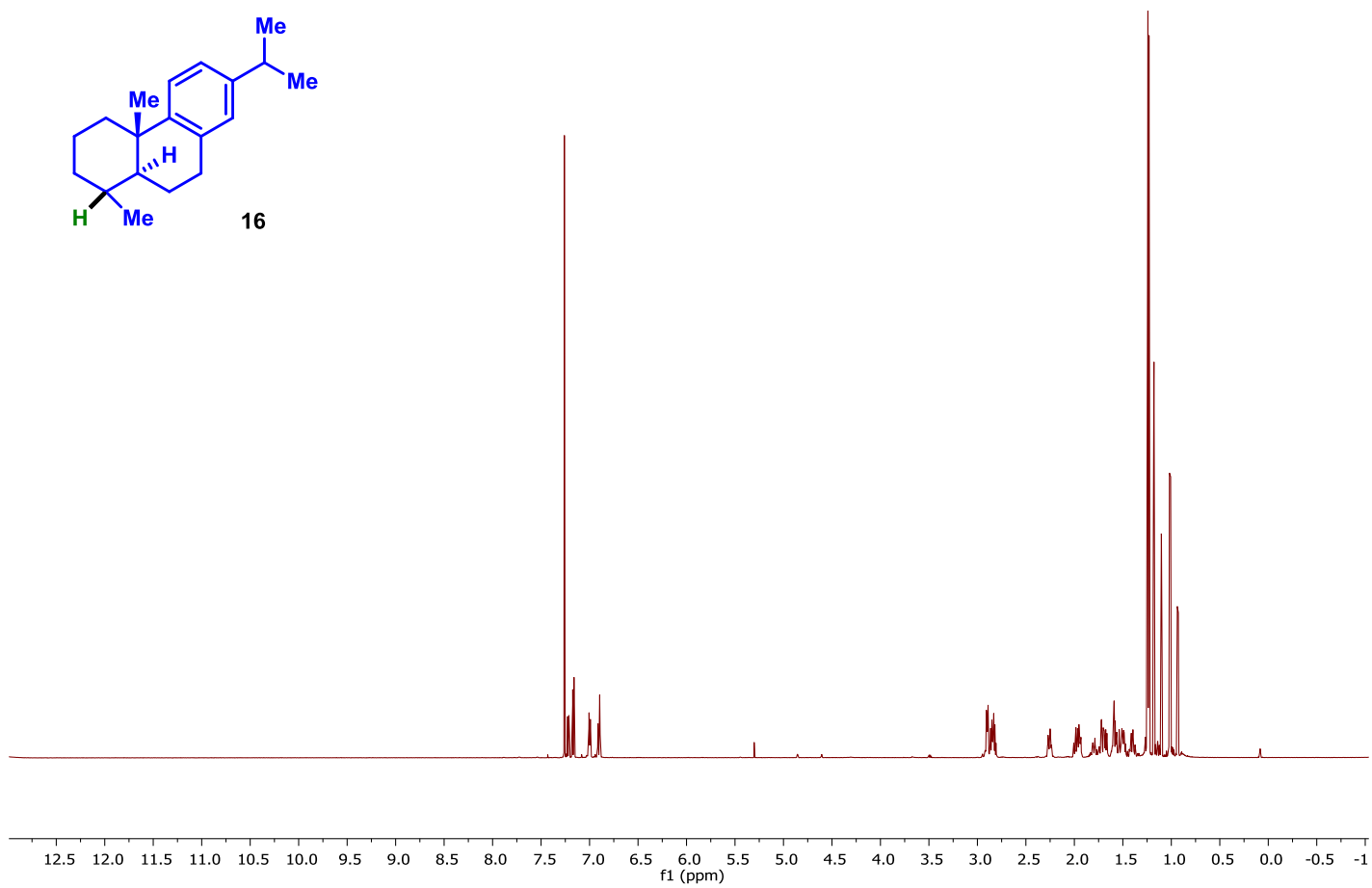
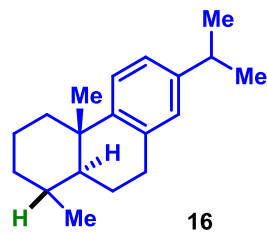
Compound 15 ^1H NMR



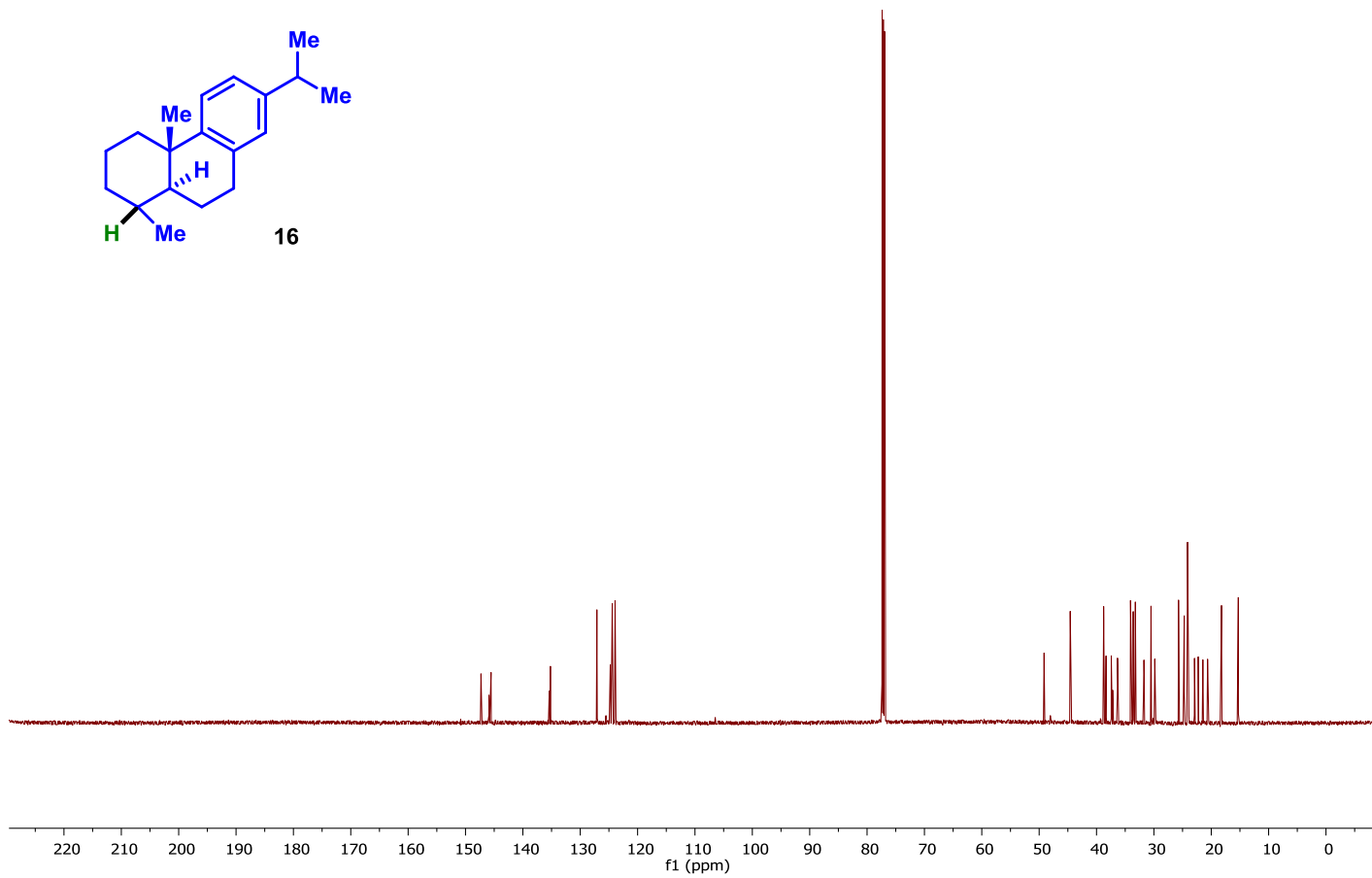
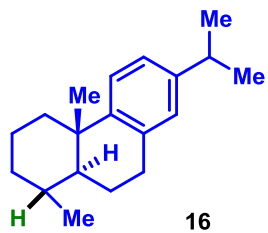
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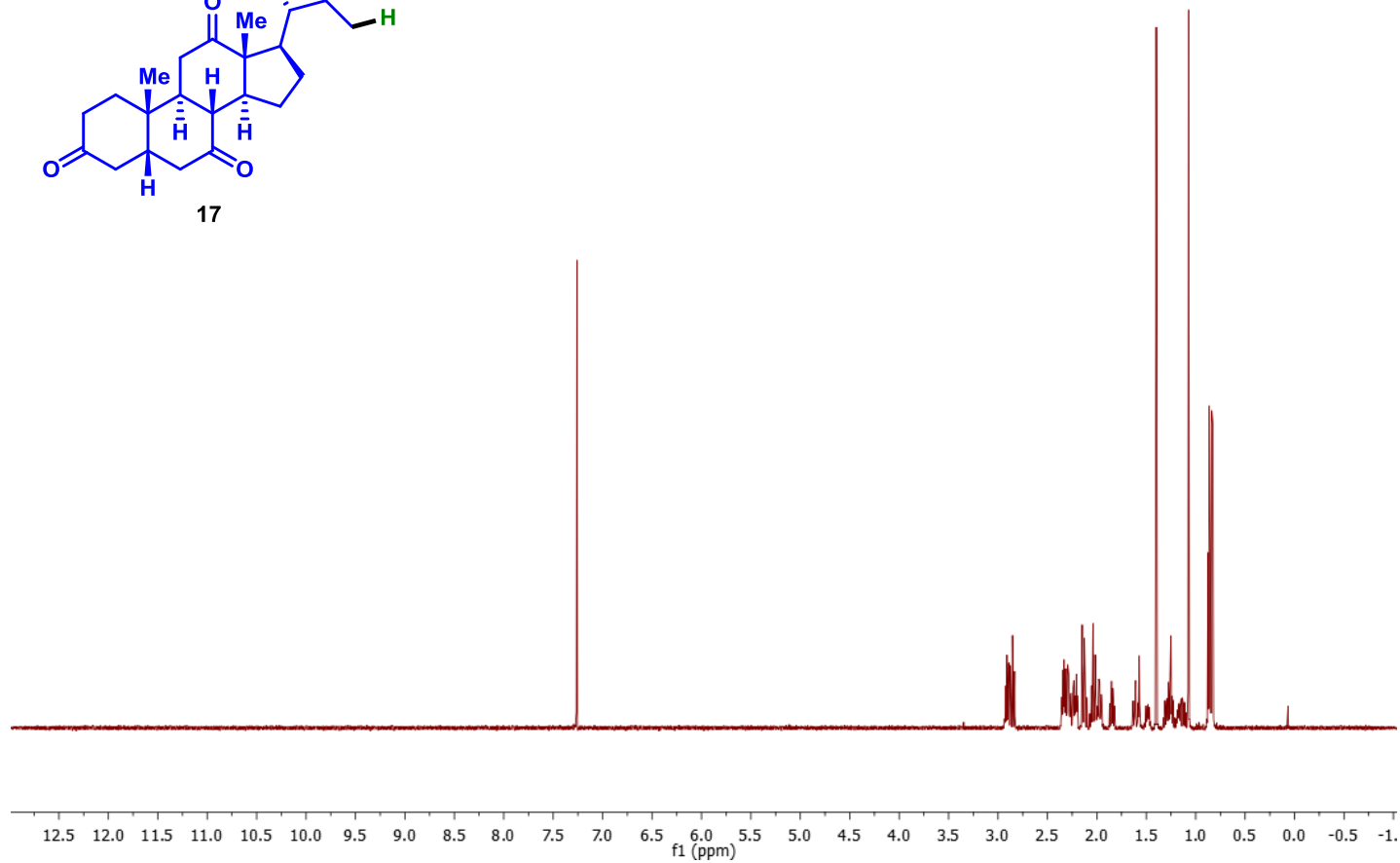
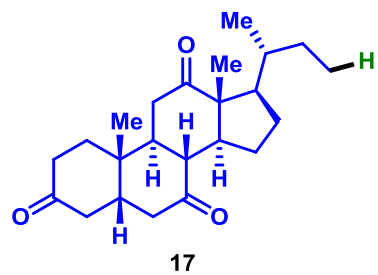
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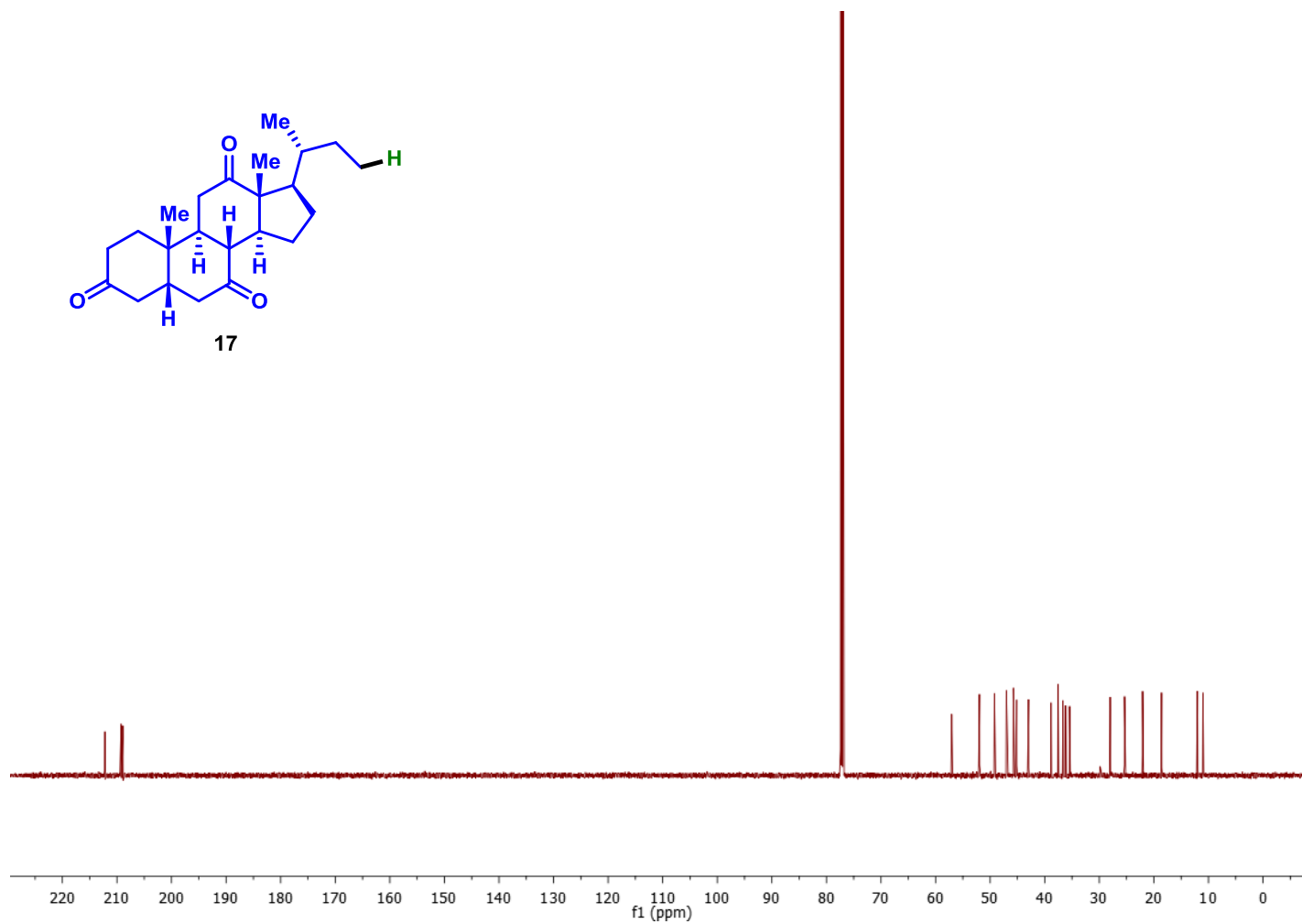
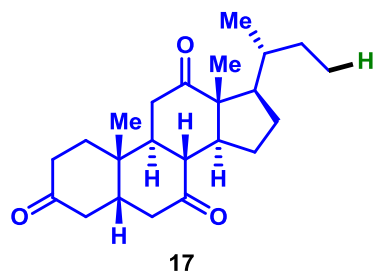
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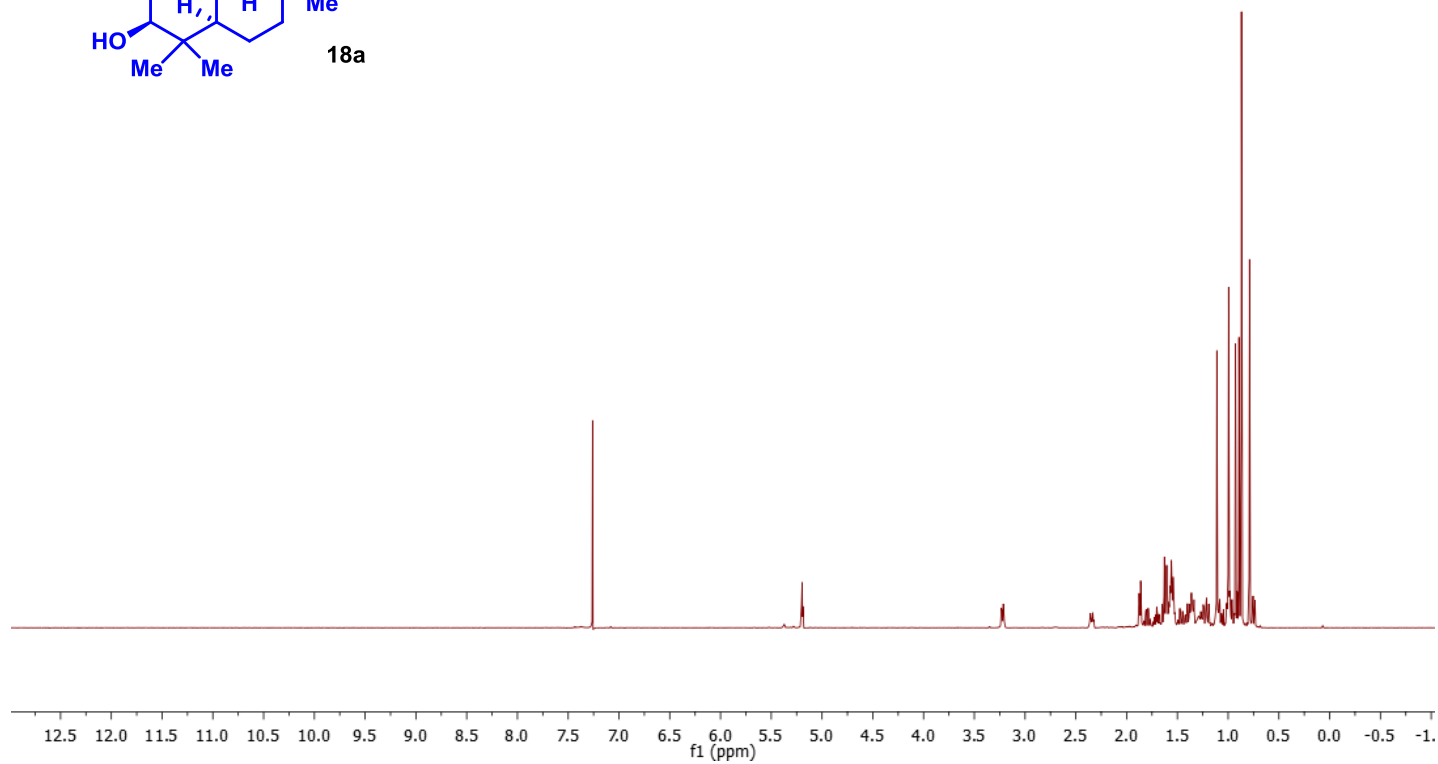
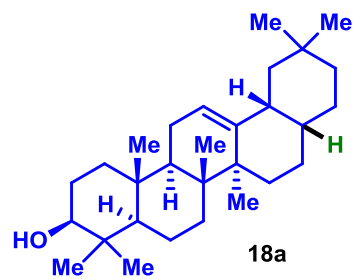
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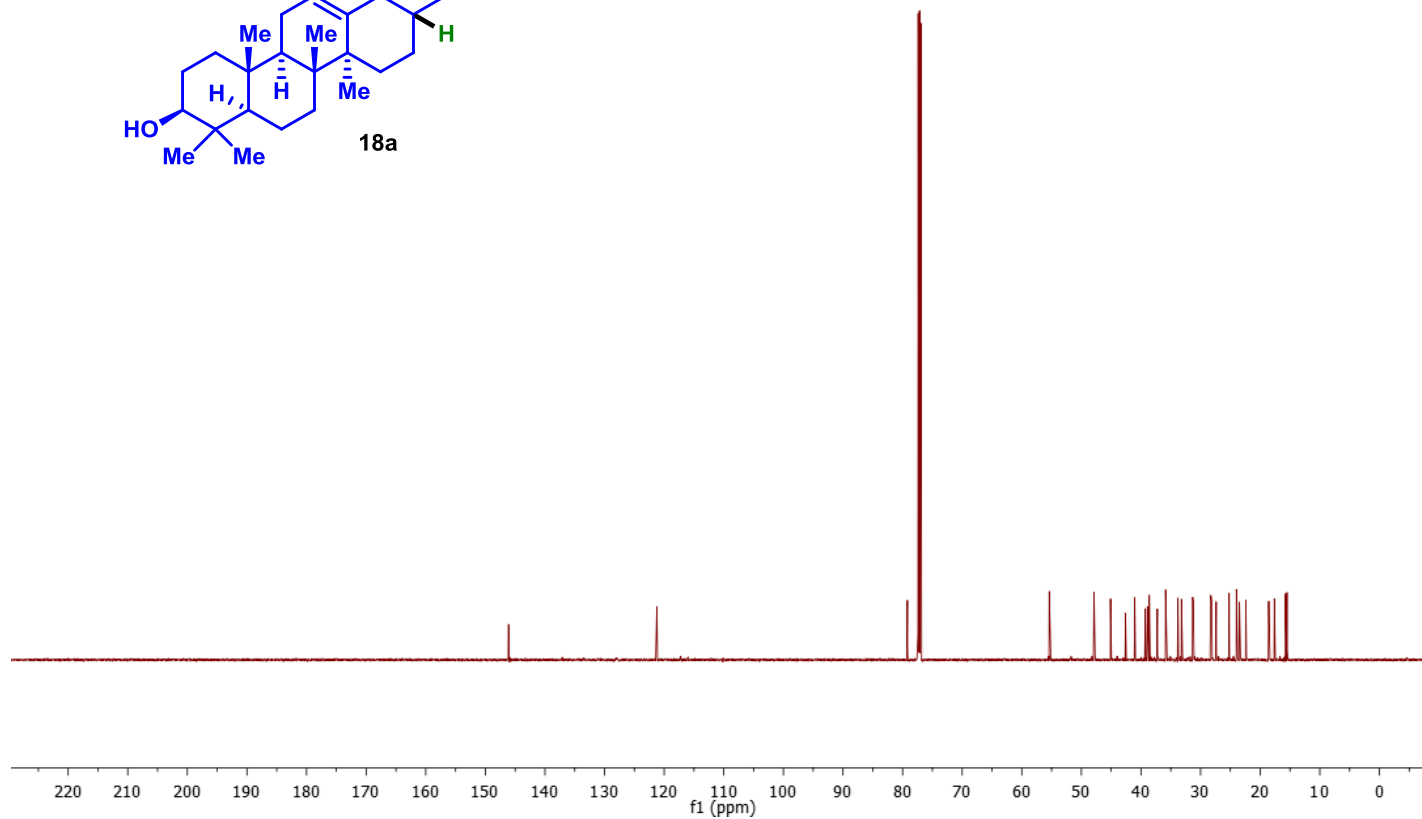
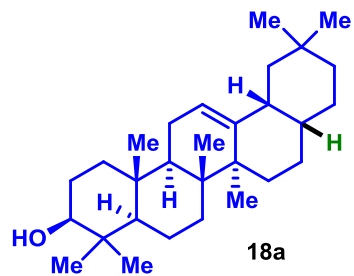
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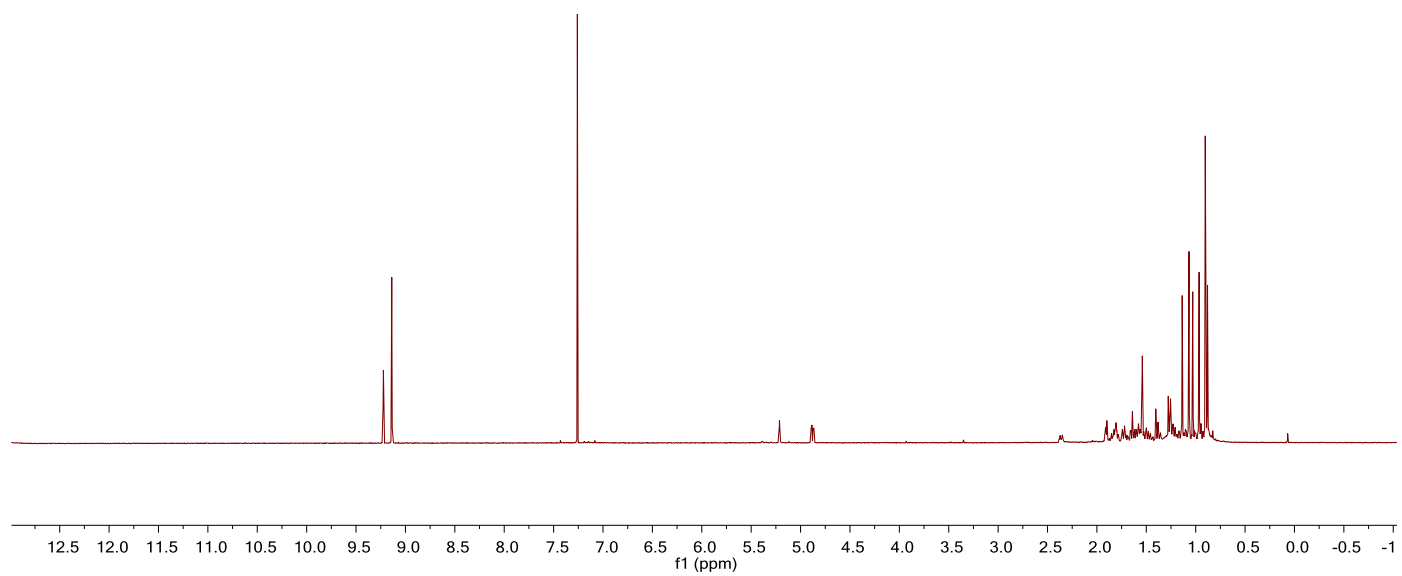
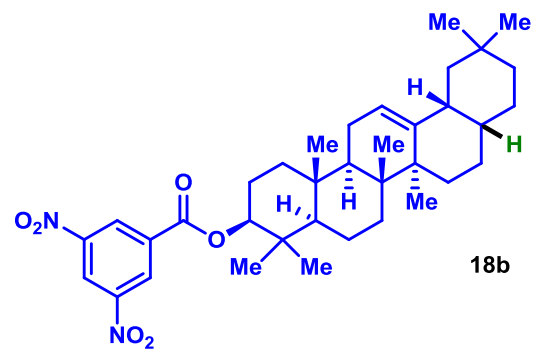
Compound 18a ^1H NMR



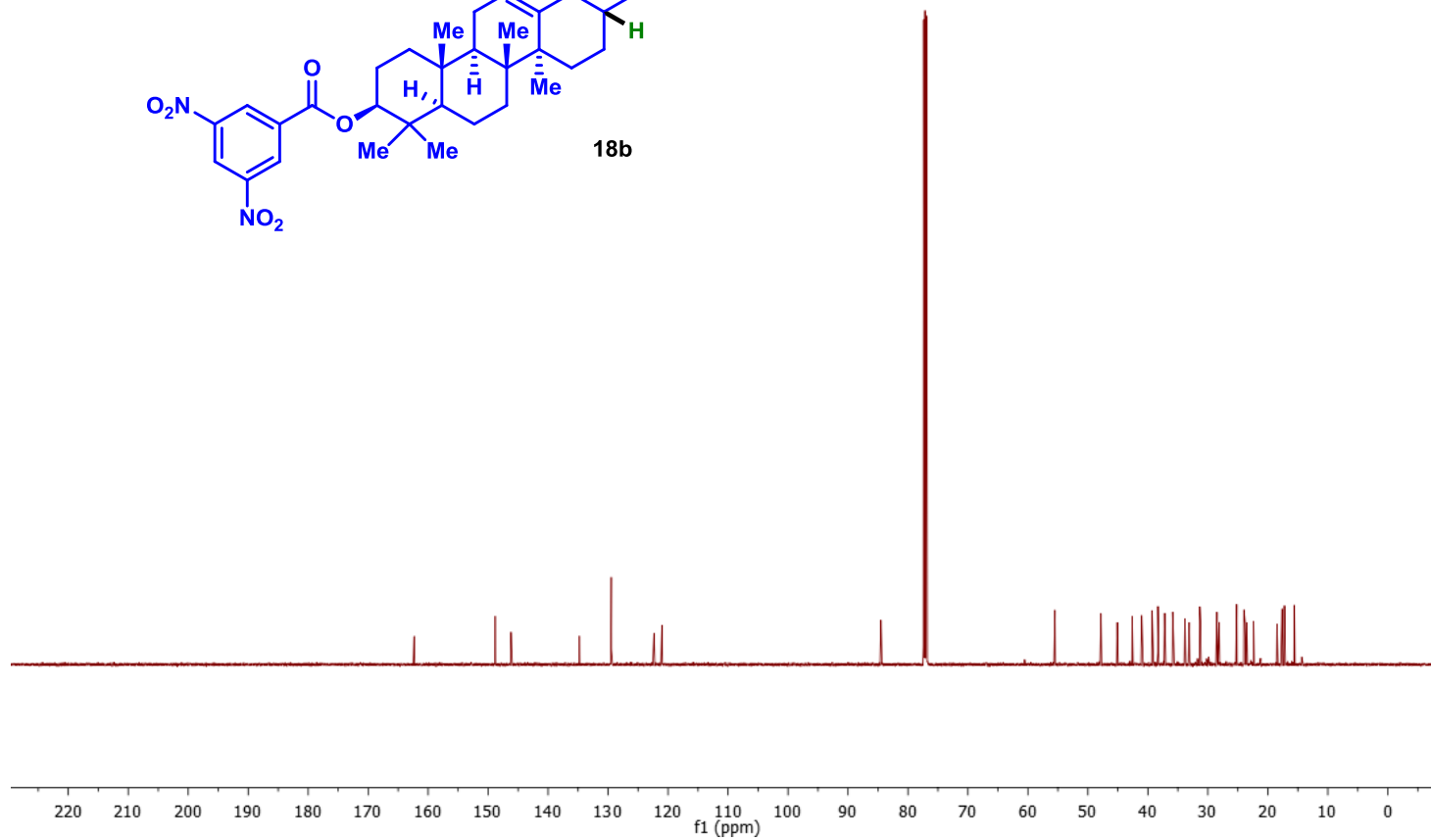
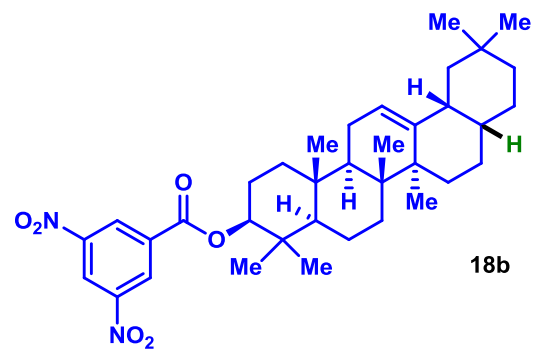
Compound 18a ¹³C NMR



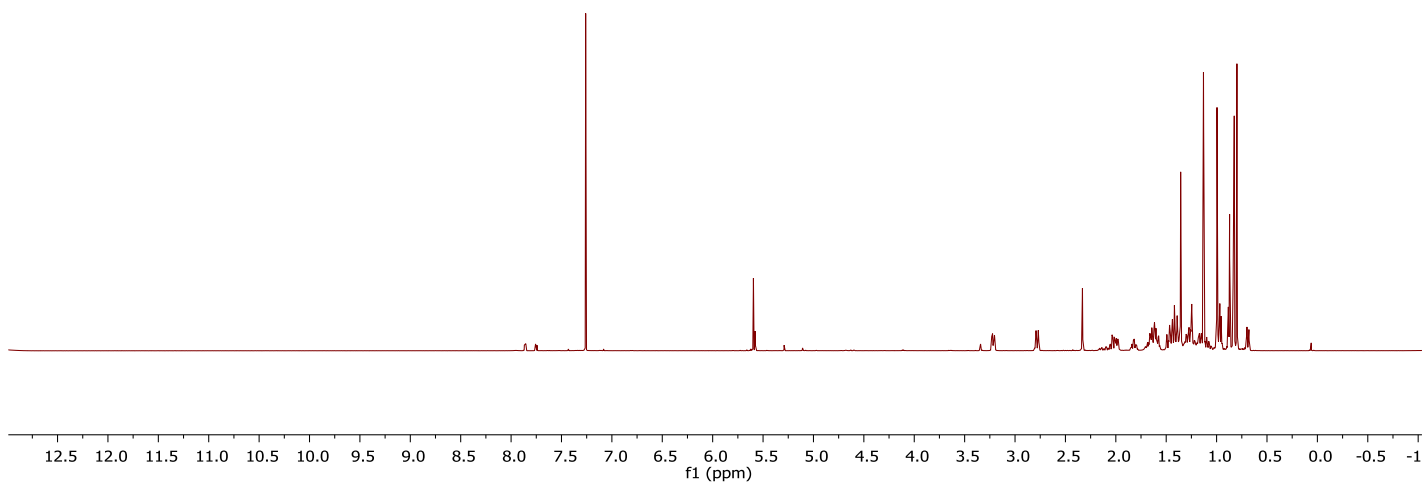
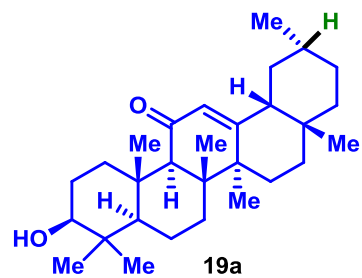
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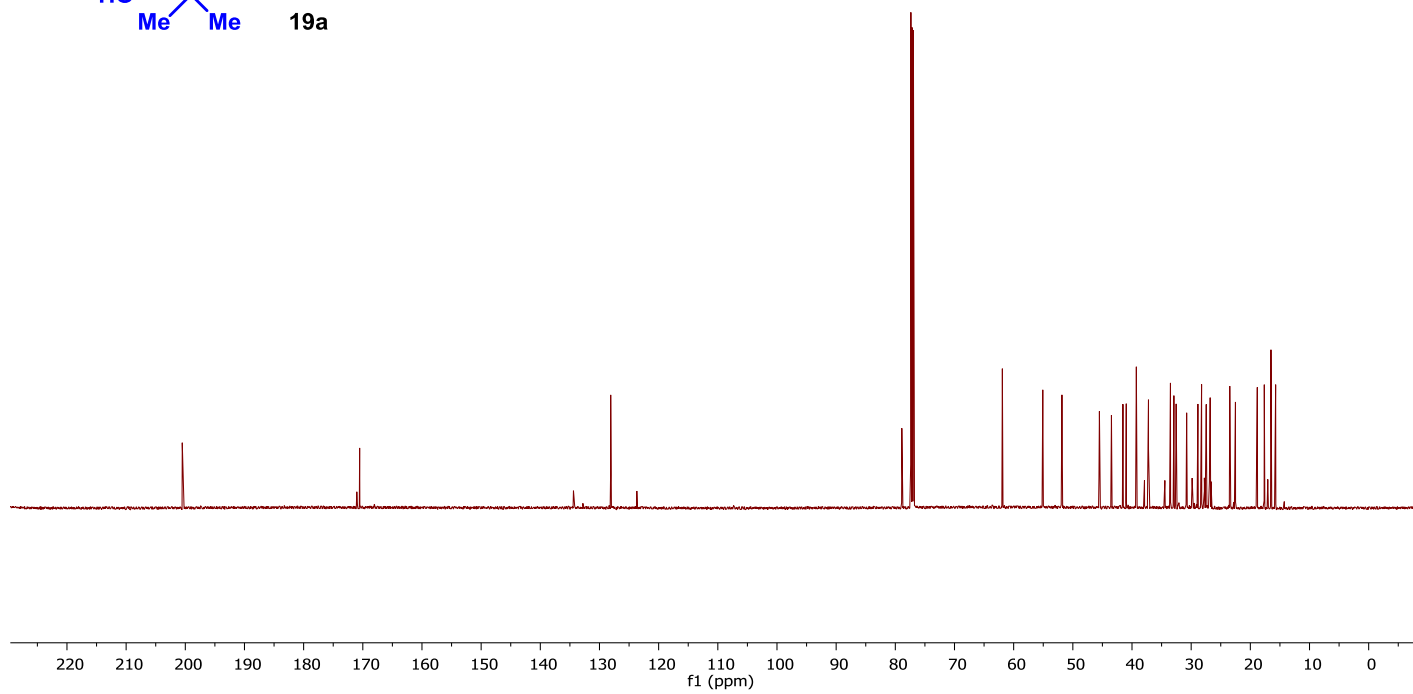
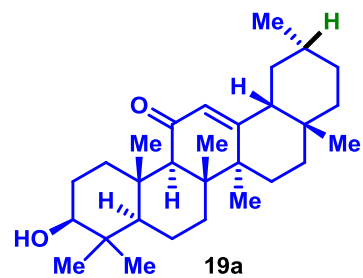
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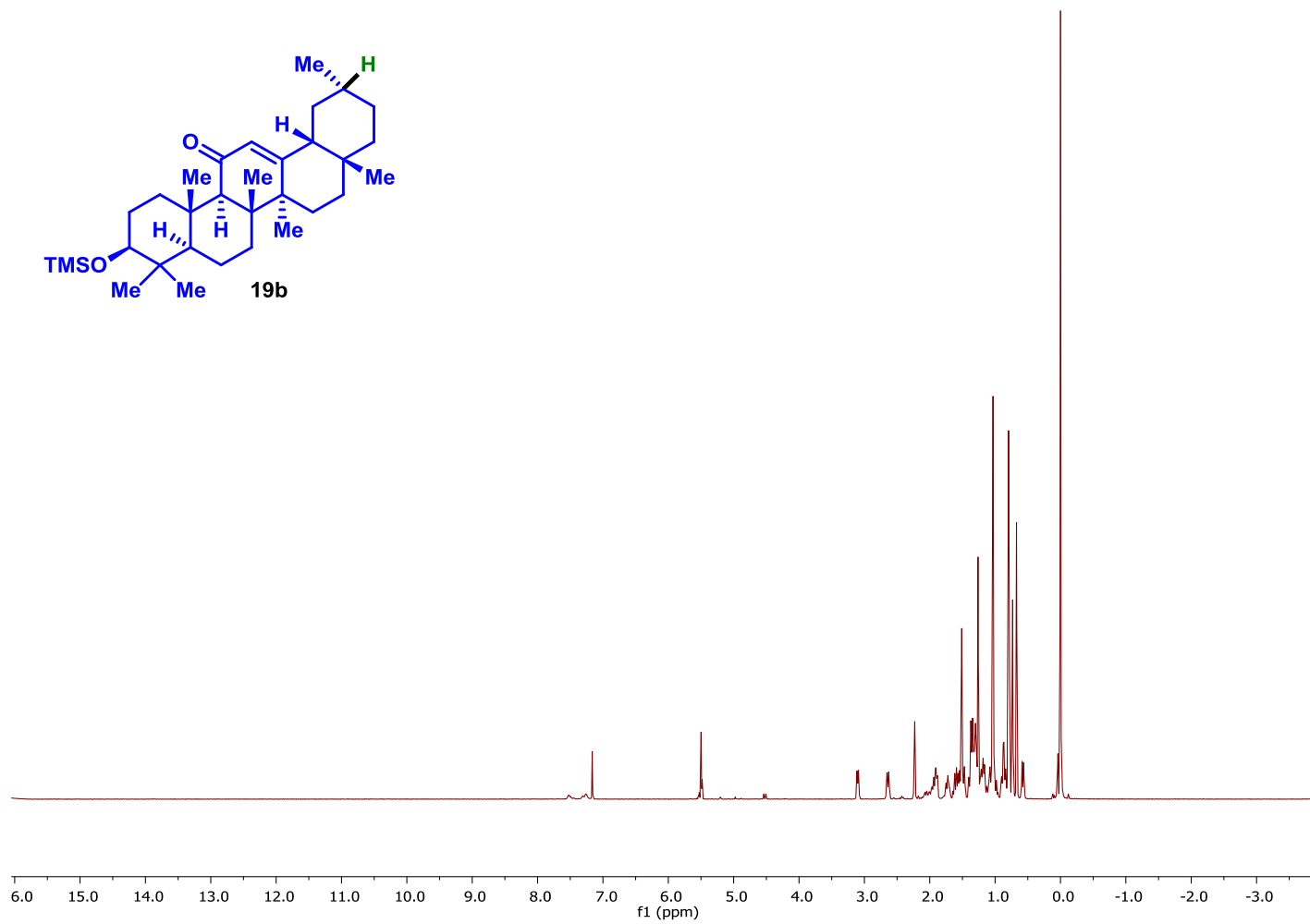
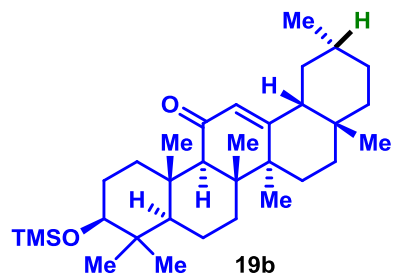
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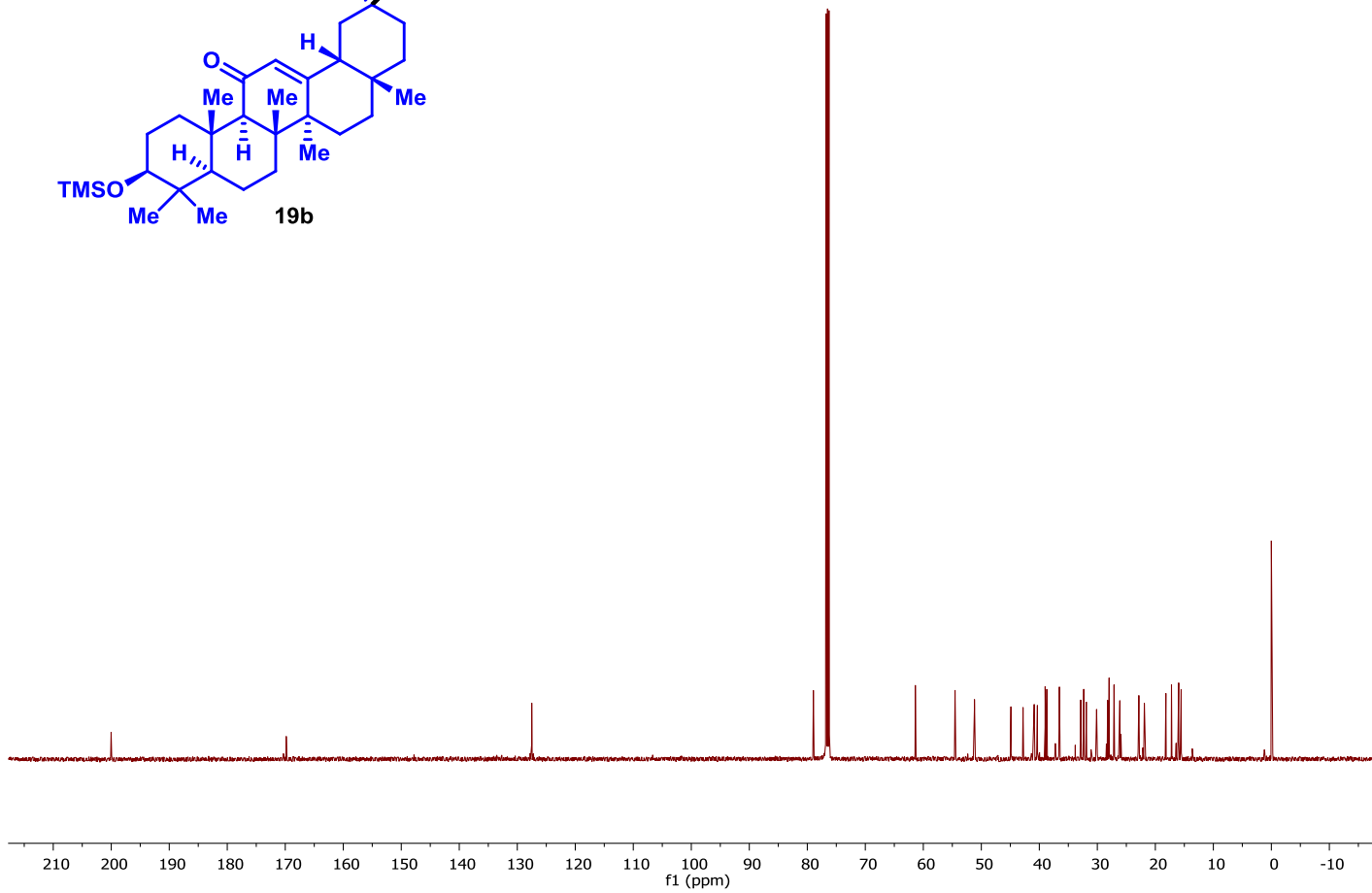
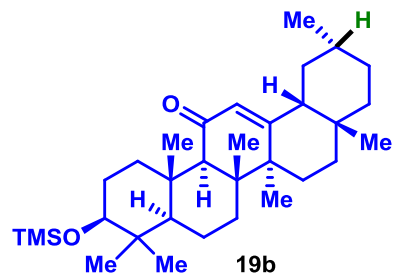
Compound 19a ^{13}C NMR



Compound 19b ^1H NMR

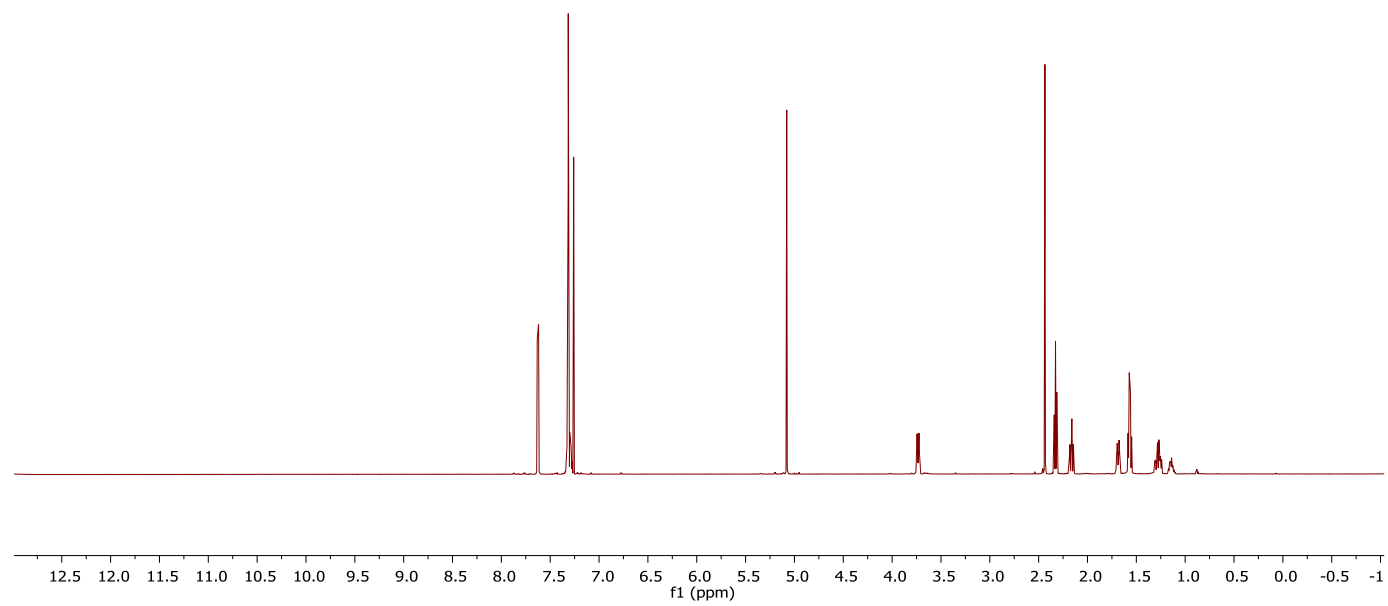
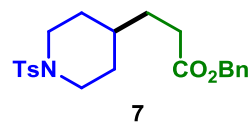


Compound 19b ¹³C NMR

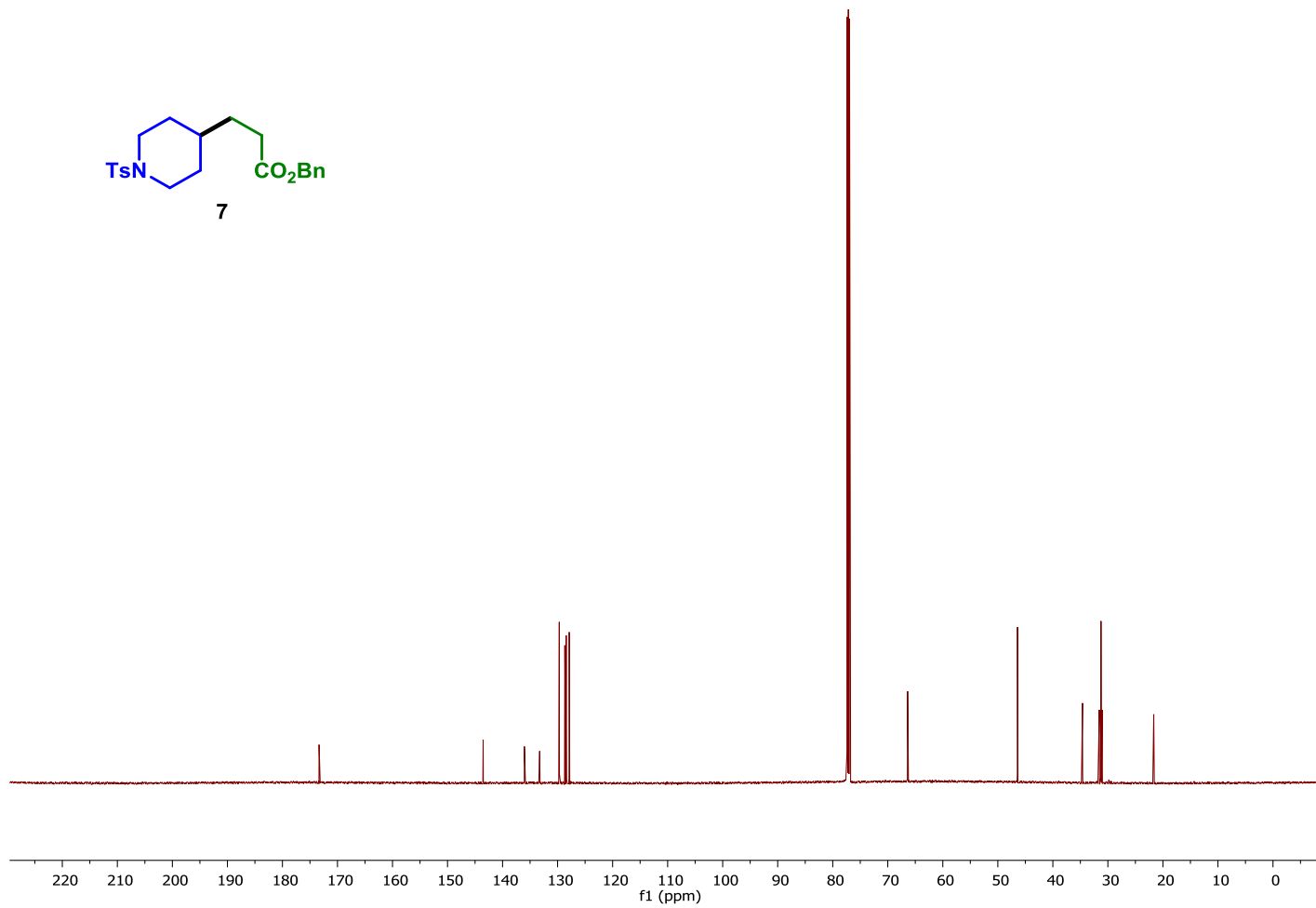
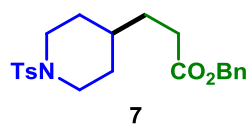


Spectra for Giese Conjugate Addition Compounds

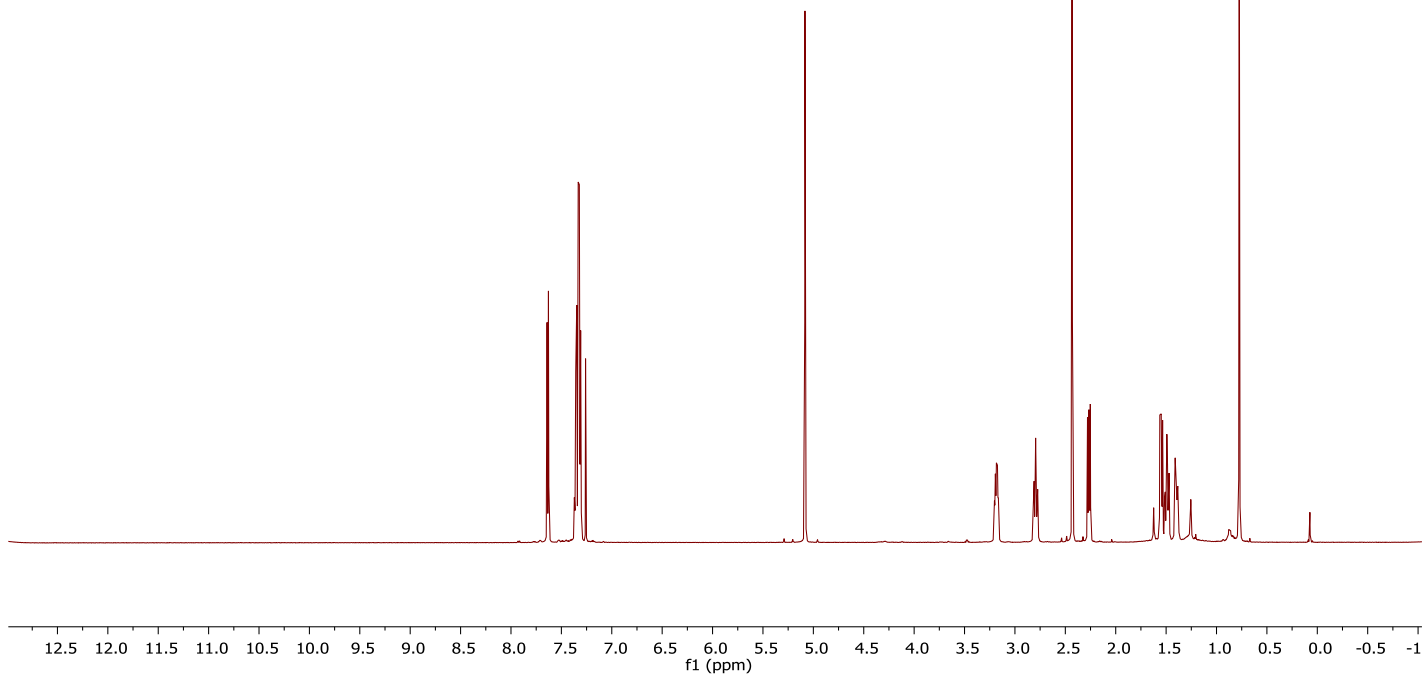
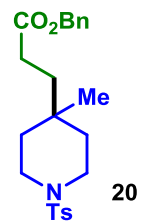
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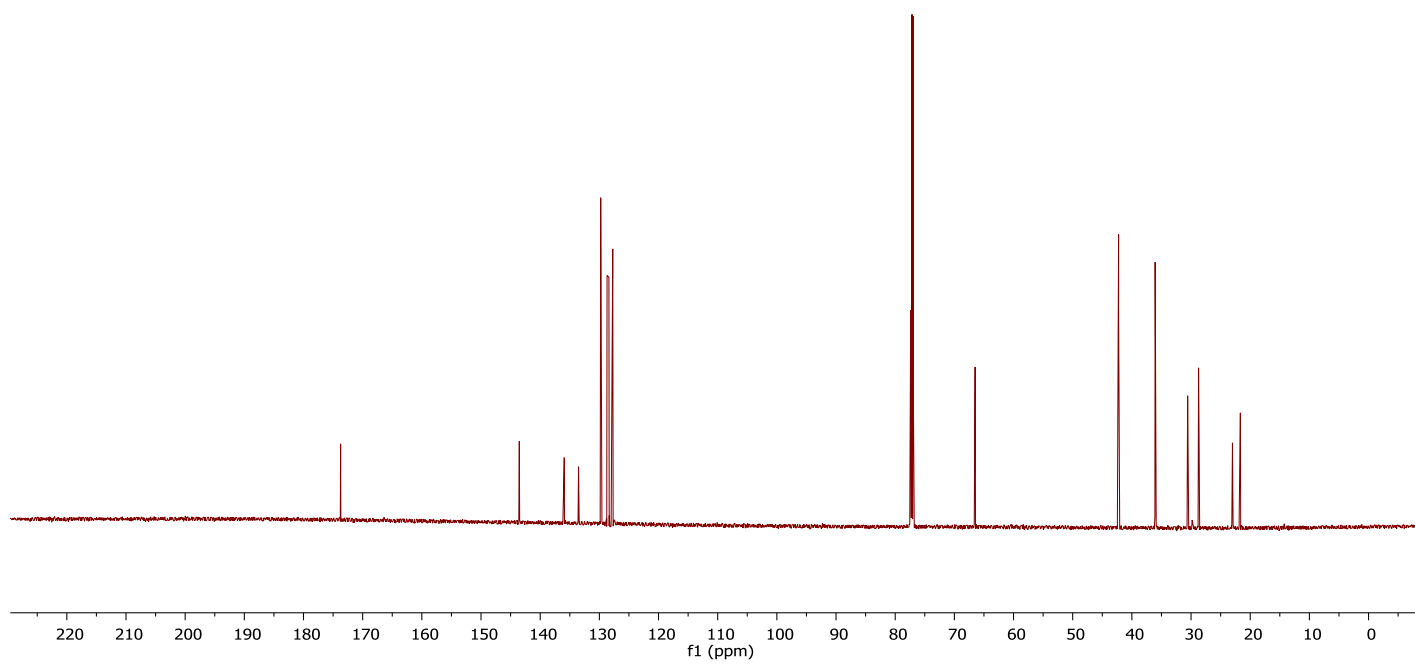
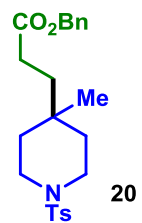
Compound 7 ¹³C NMR



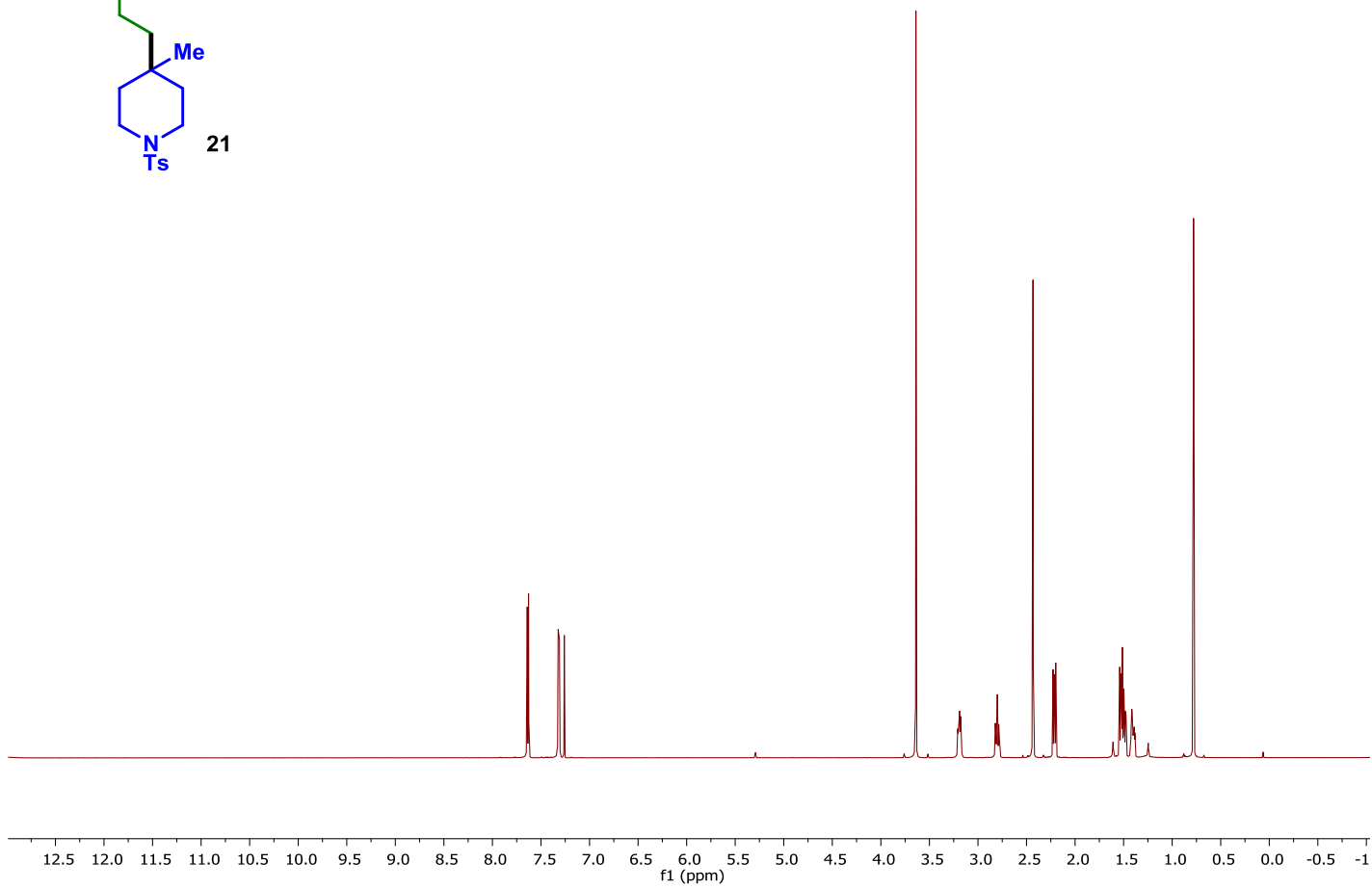
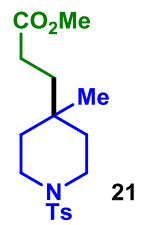
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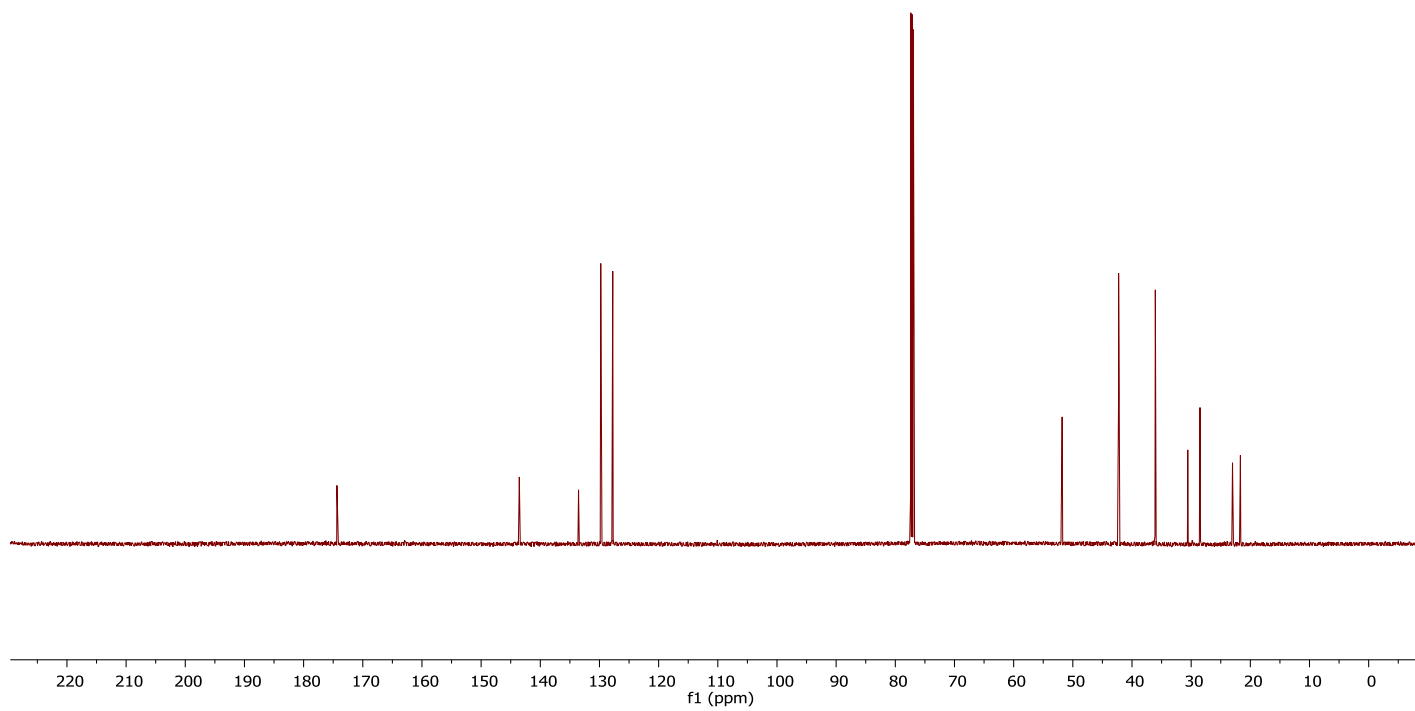
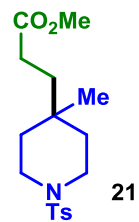
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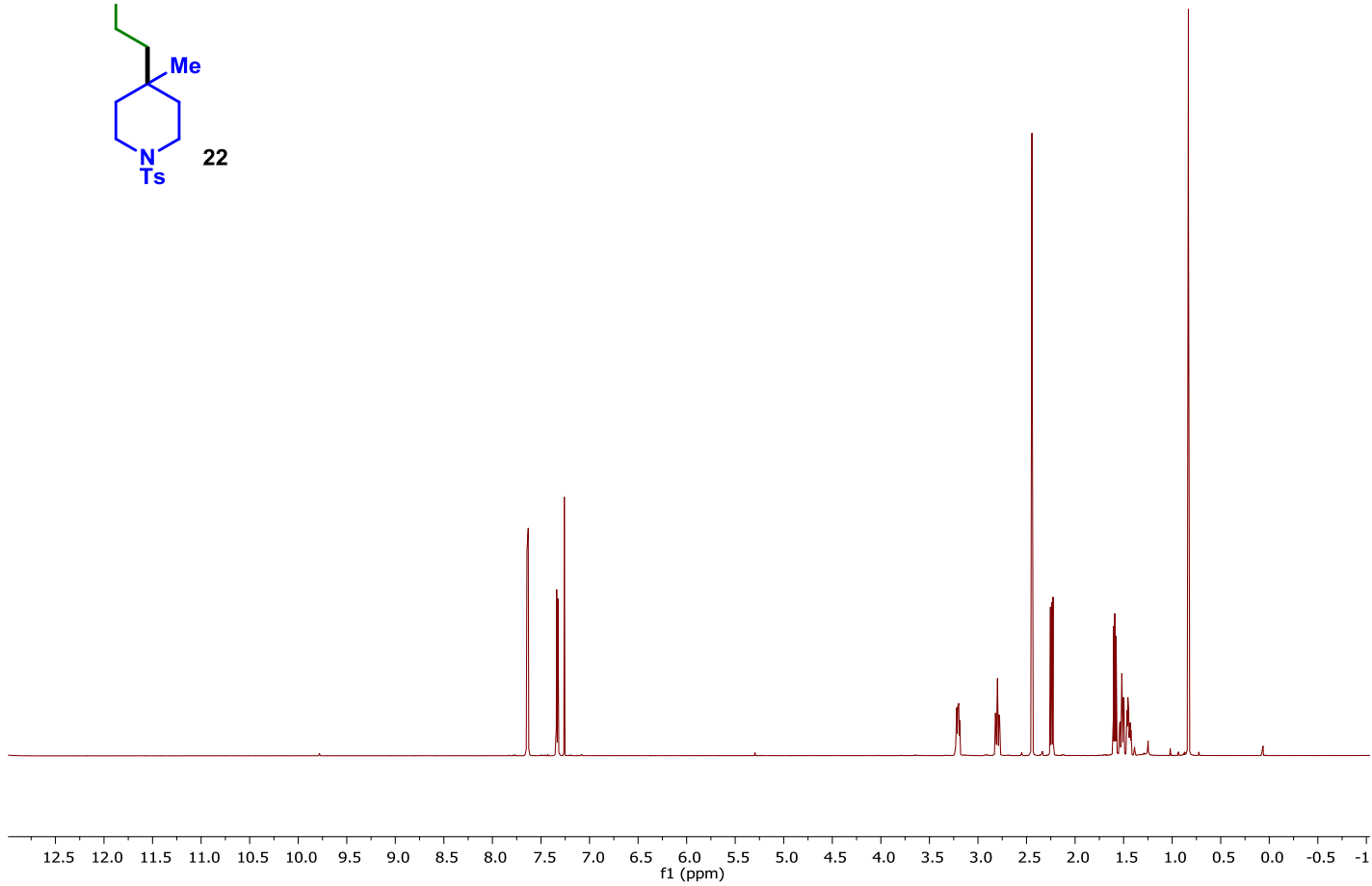
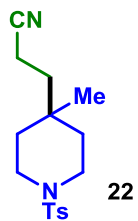
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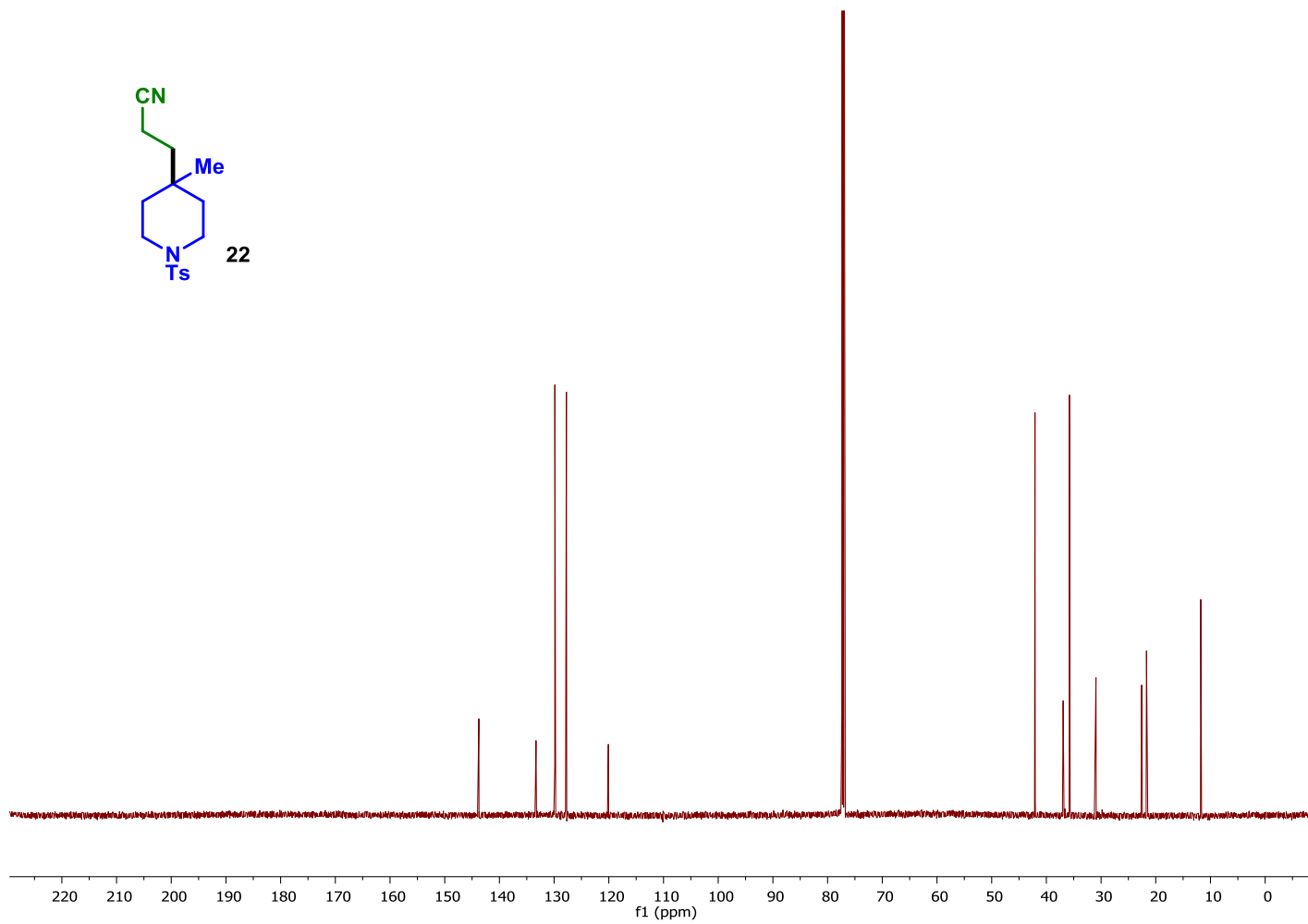
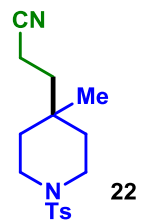
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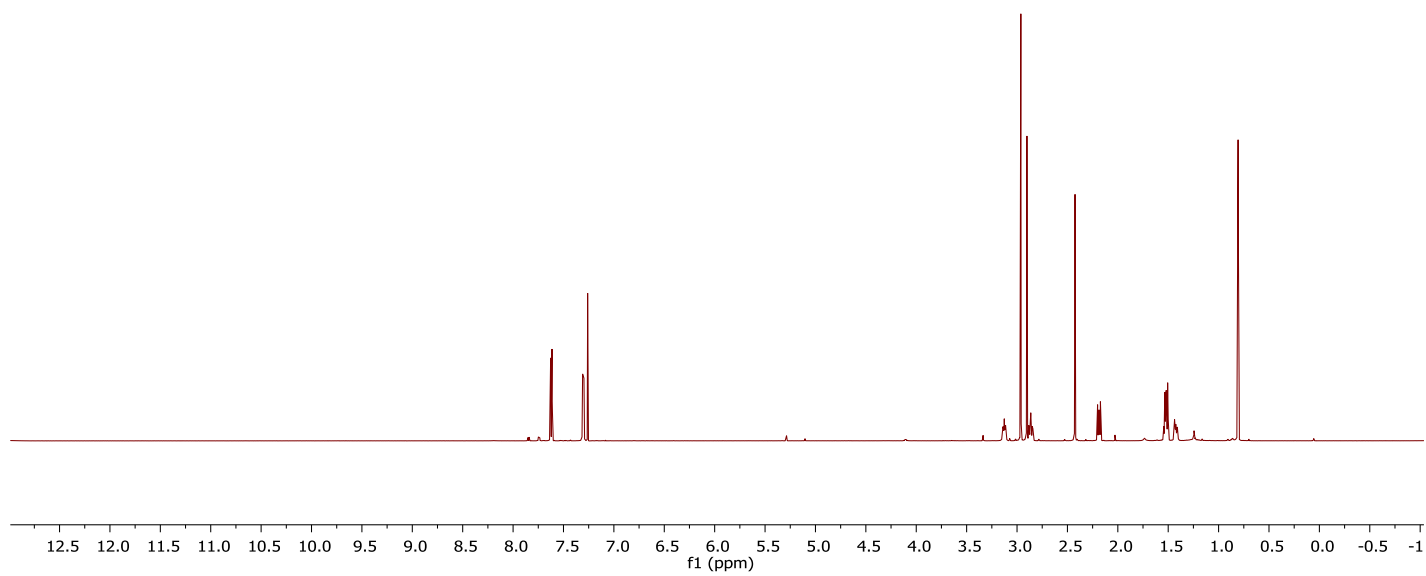
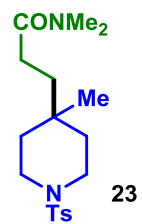
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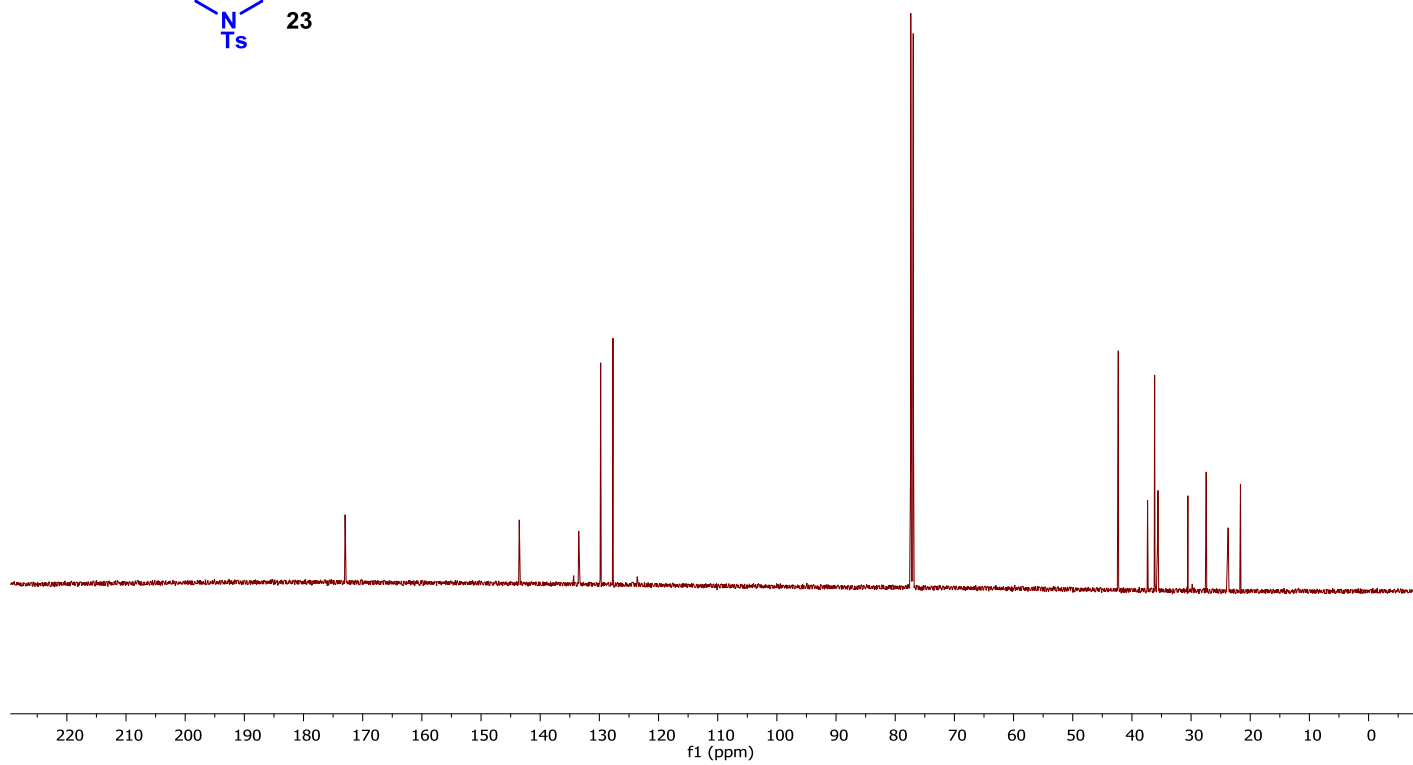
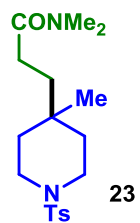
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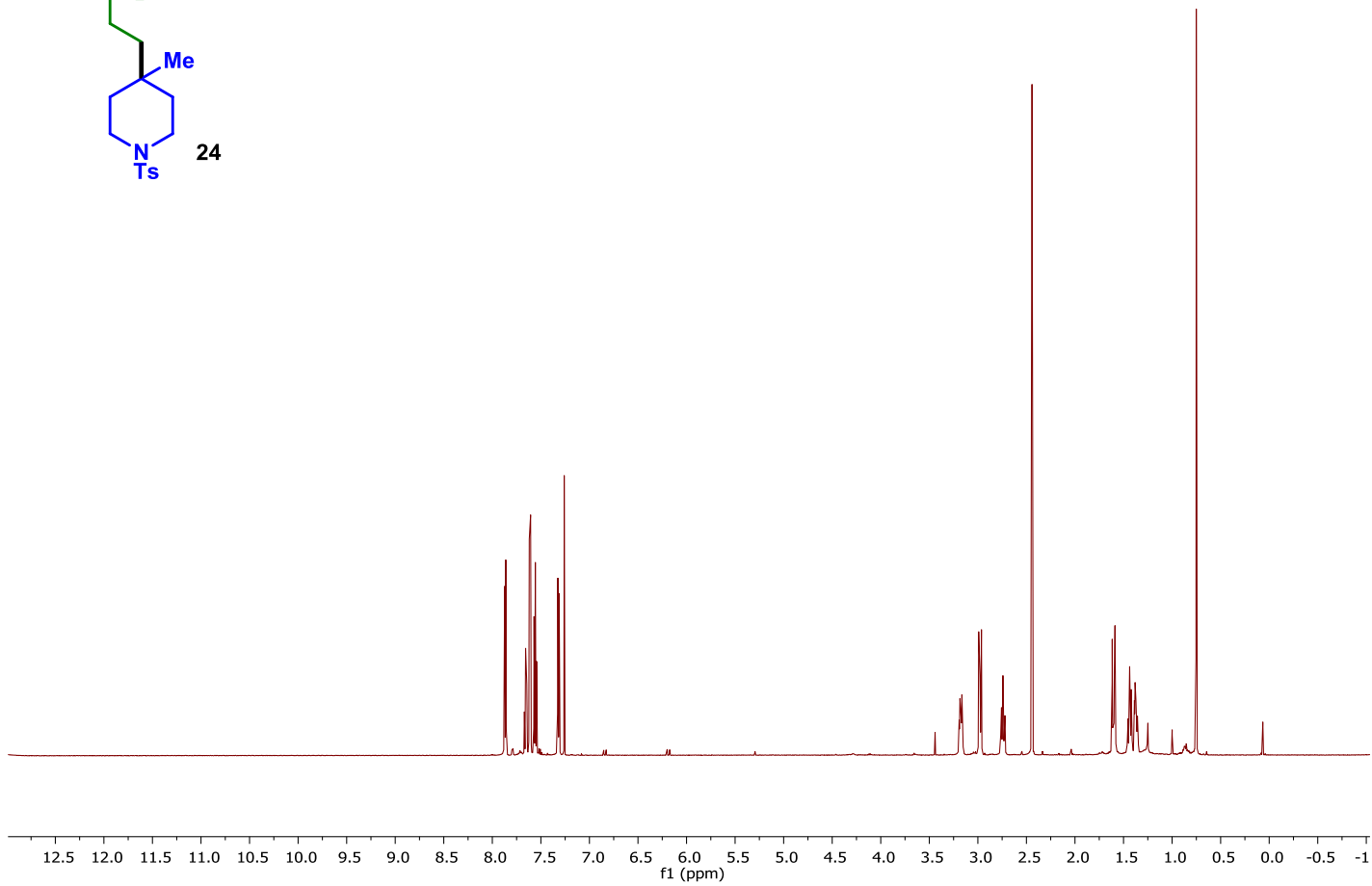
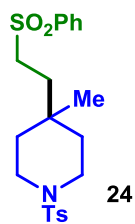
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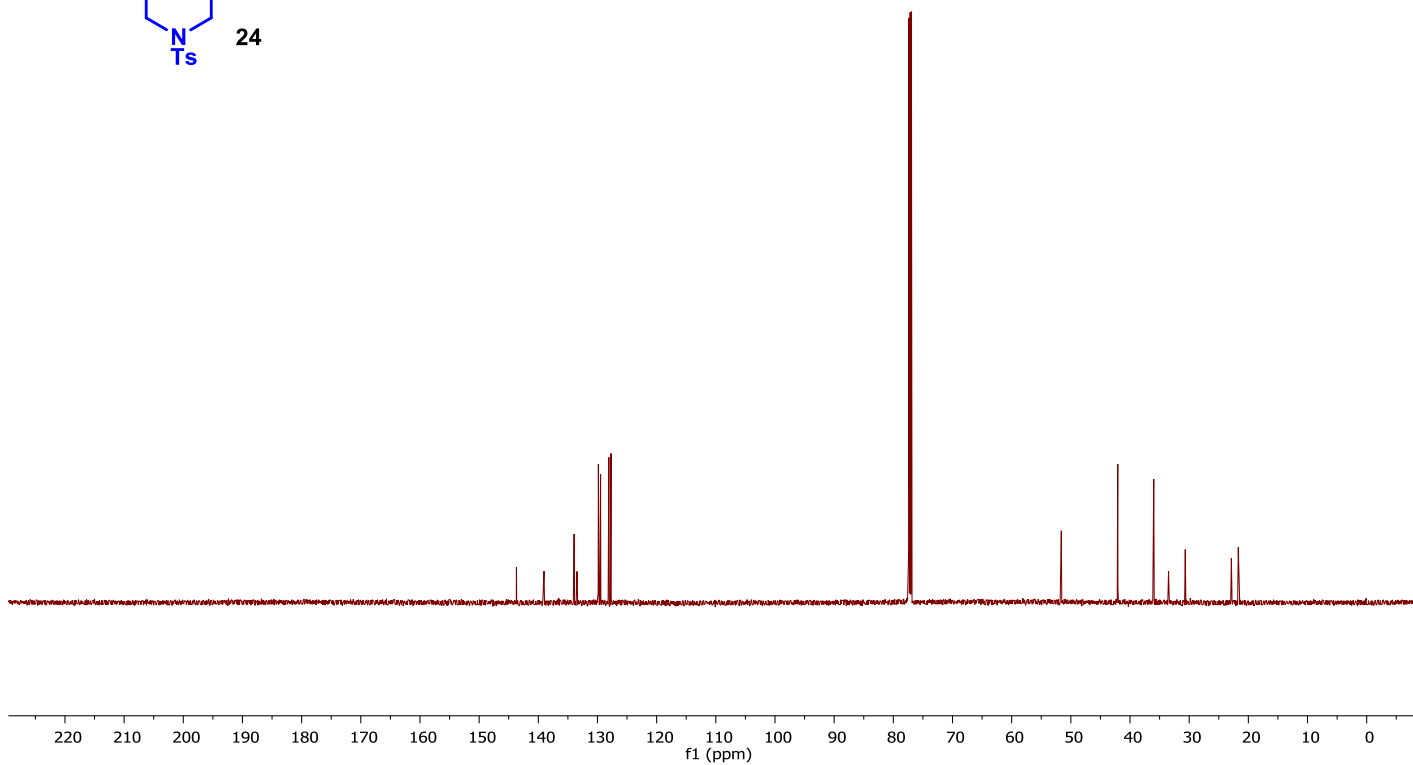
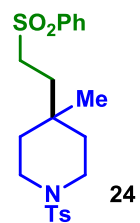
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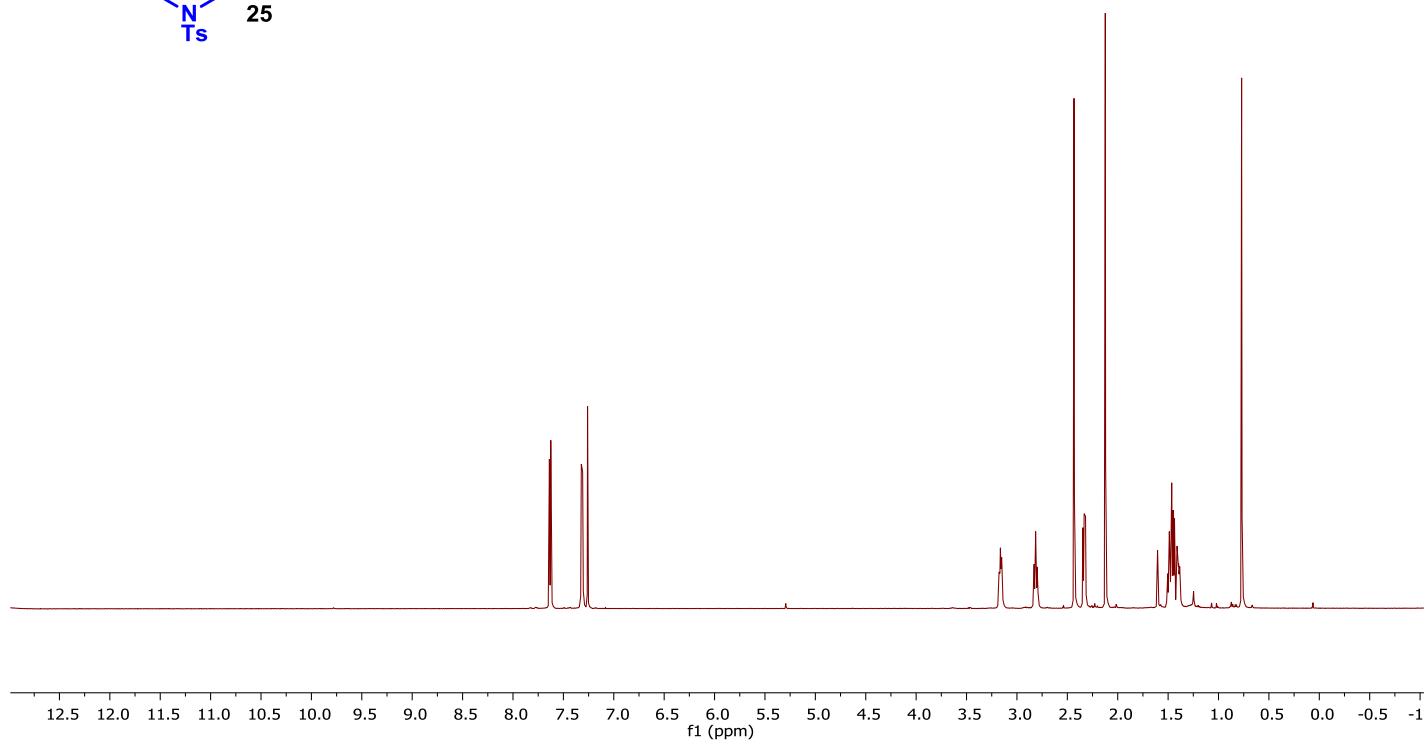
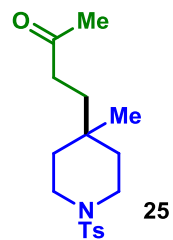
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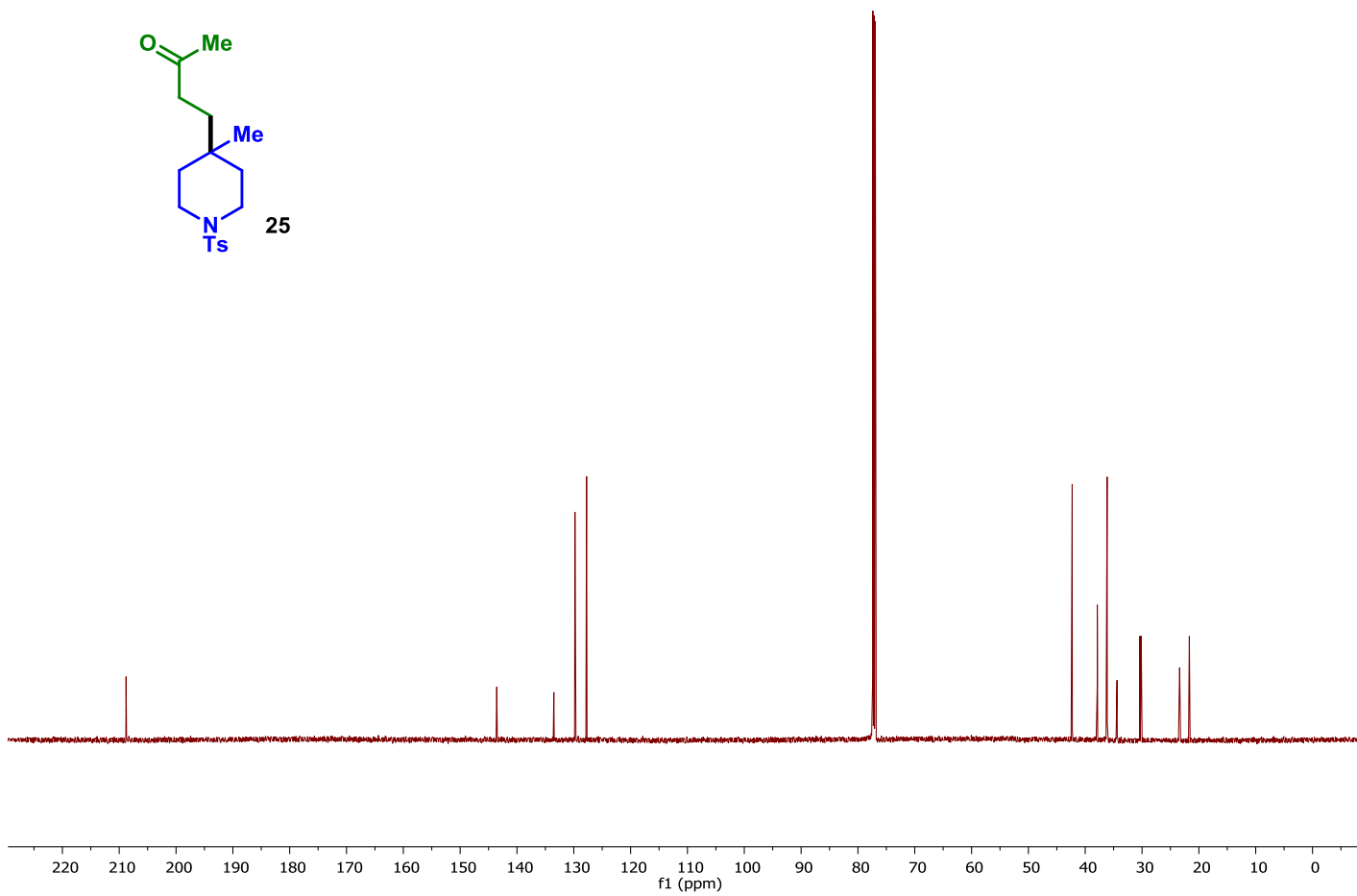
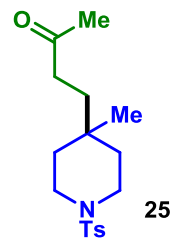
Compound 24 ^{13}C NMR



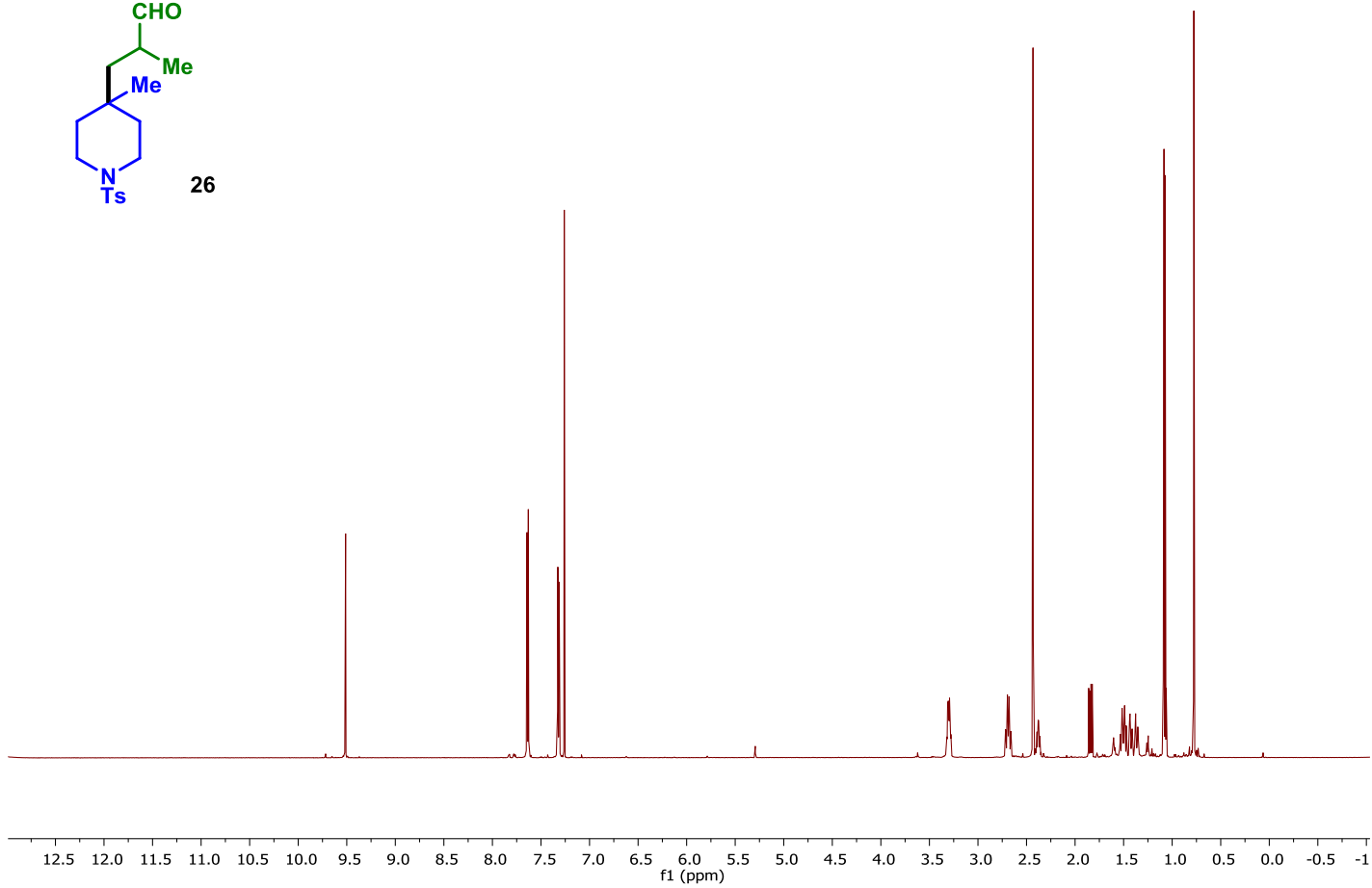
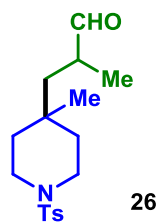
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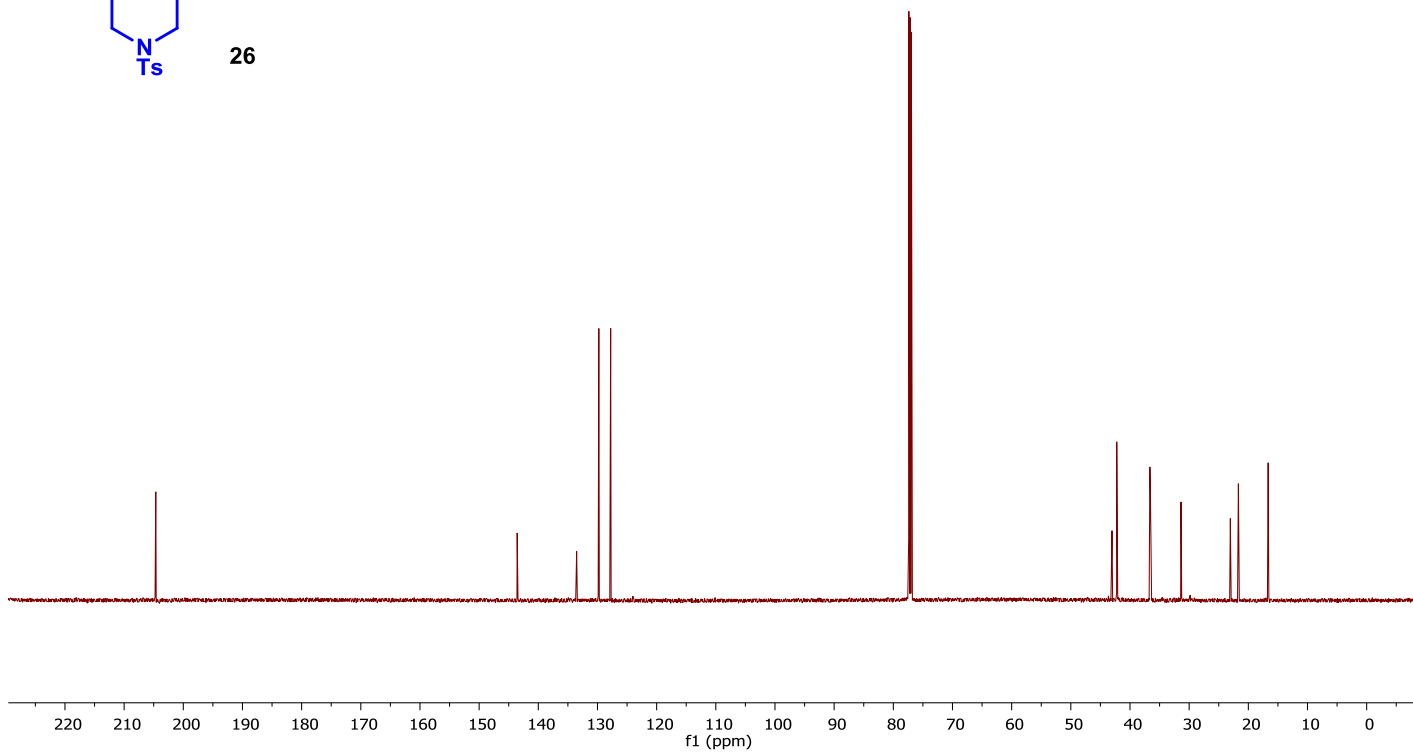
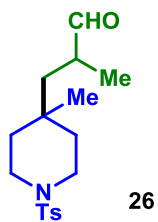
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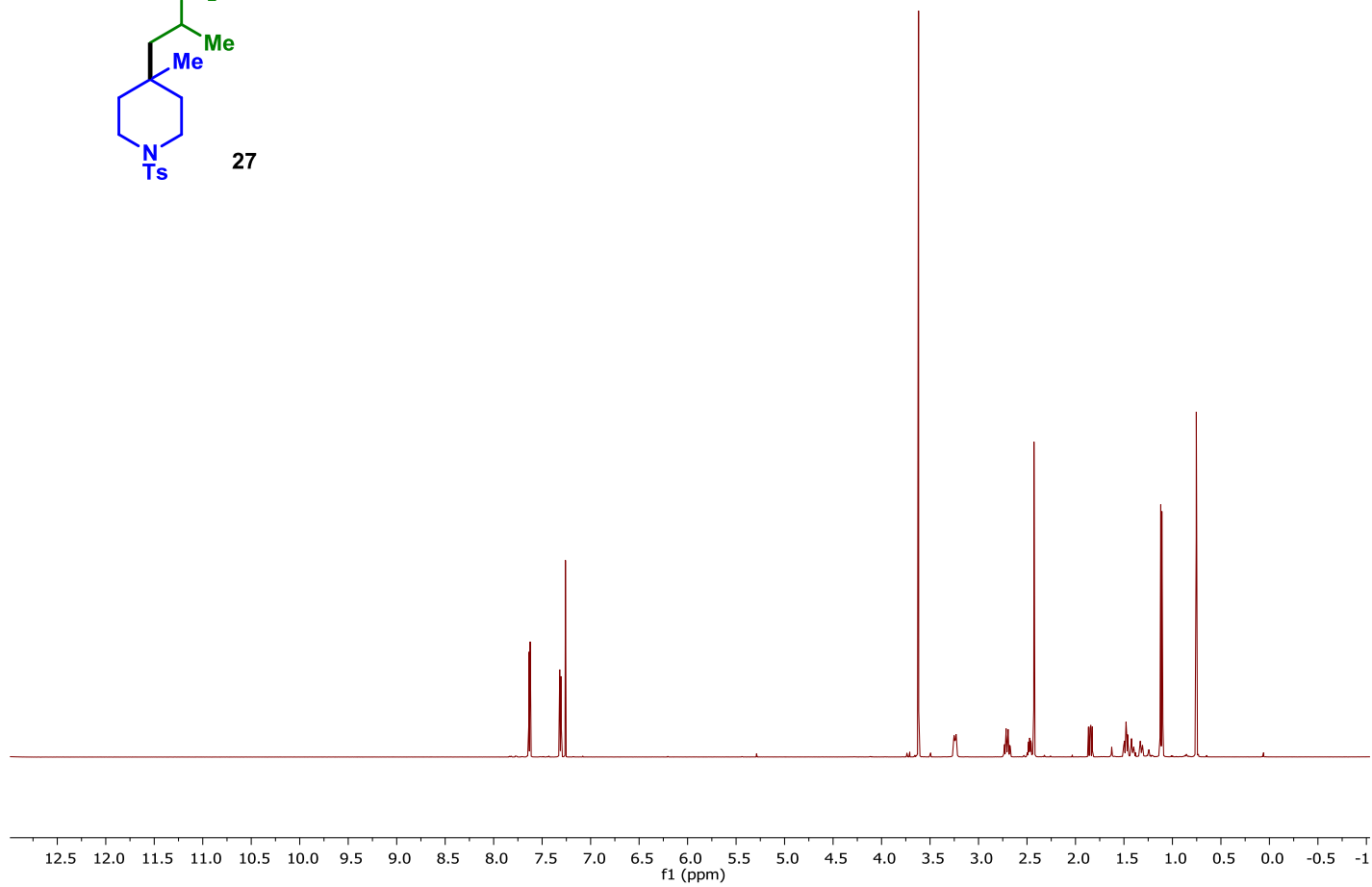
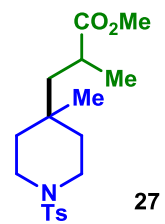
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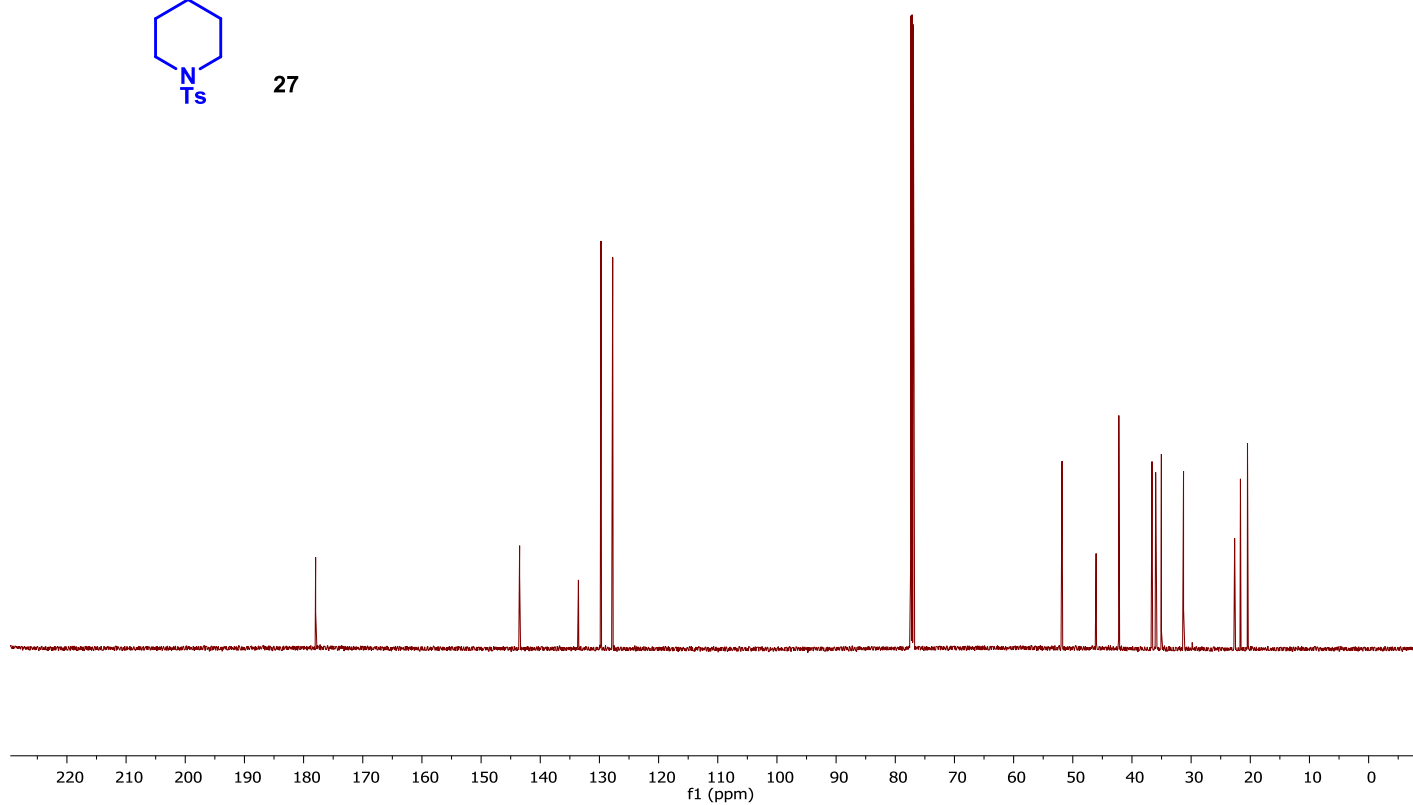
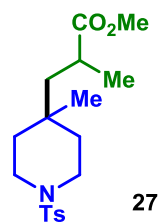
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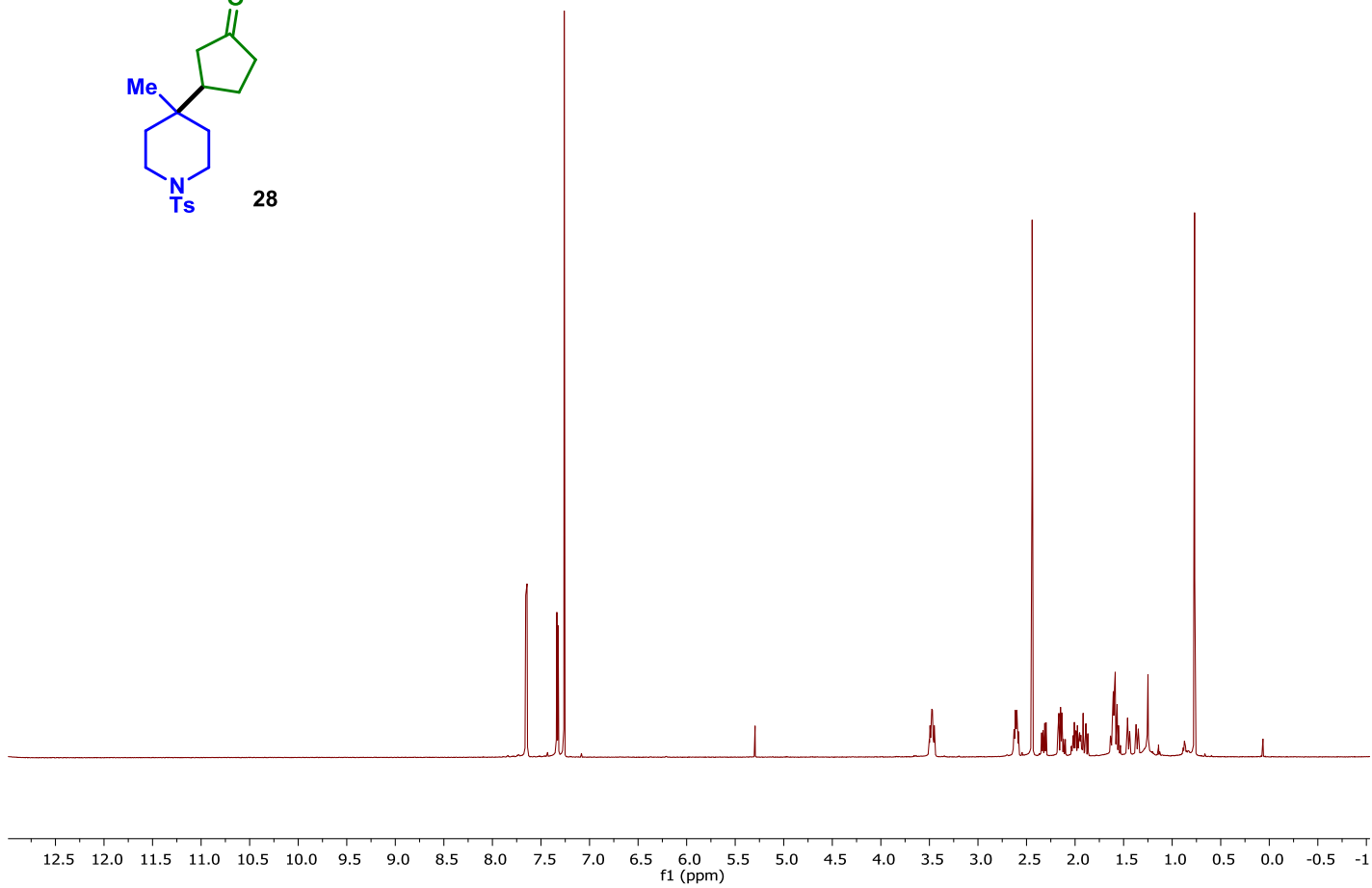
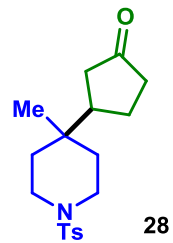
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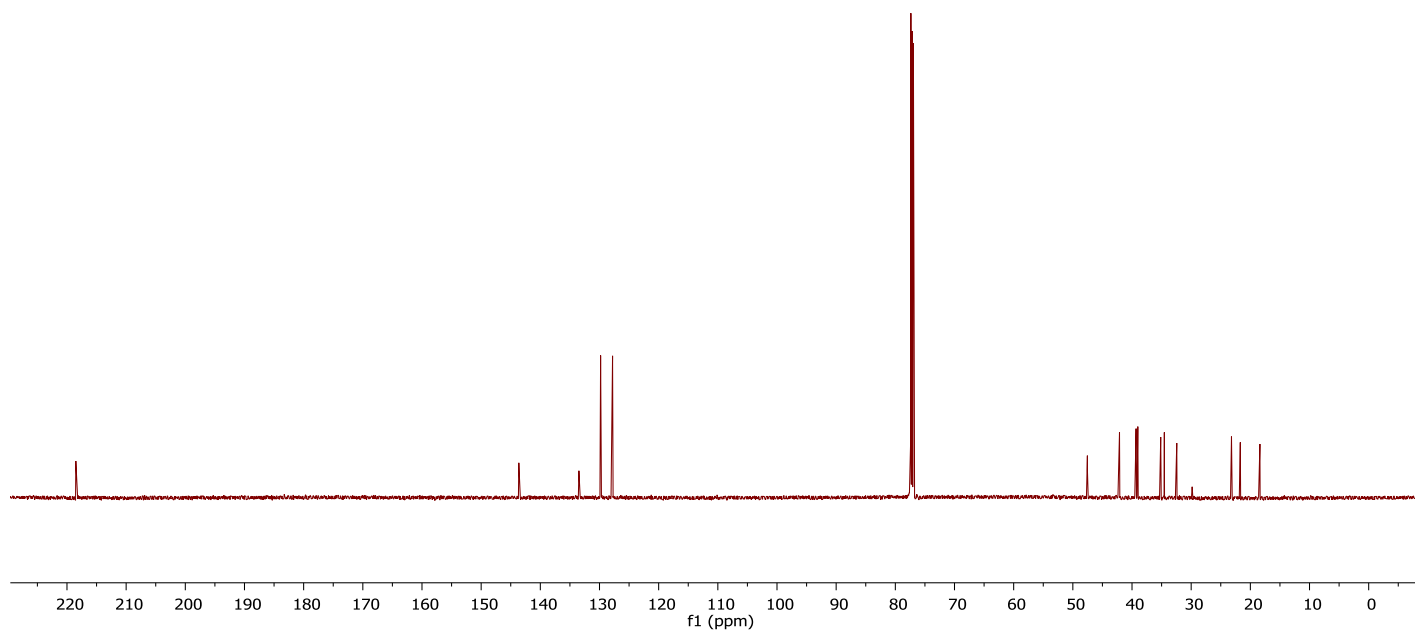
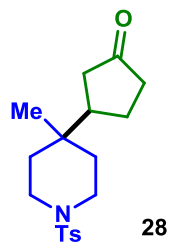
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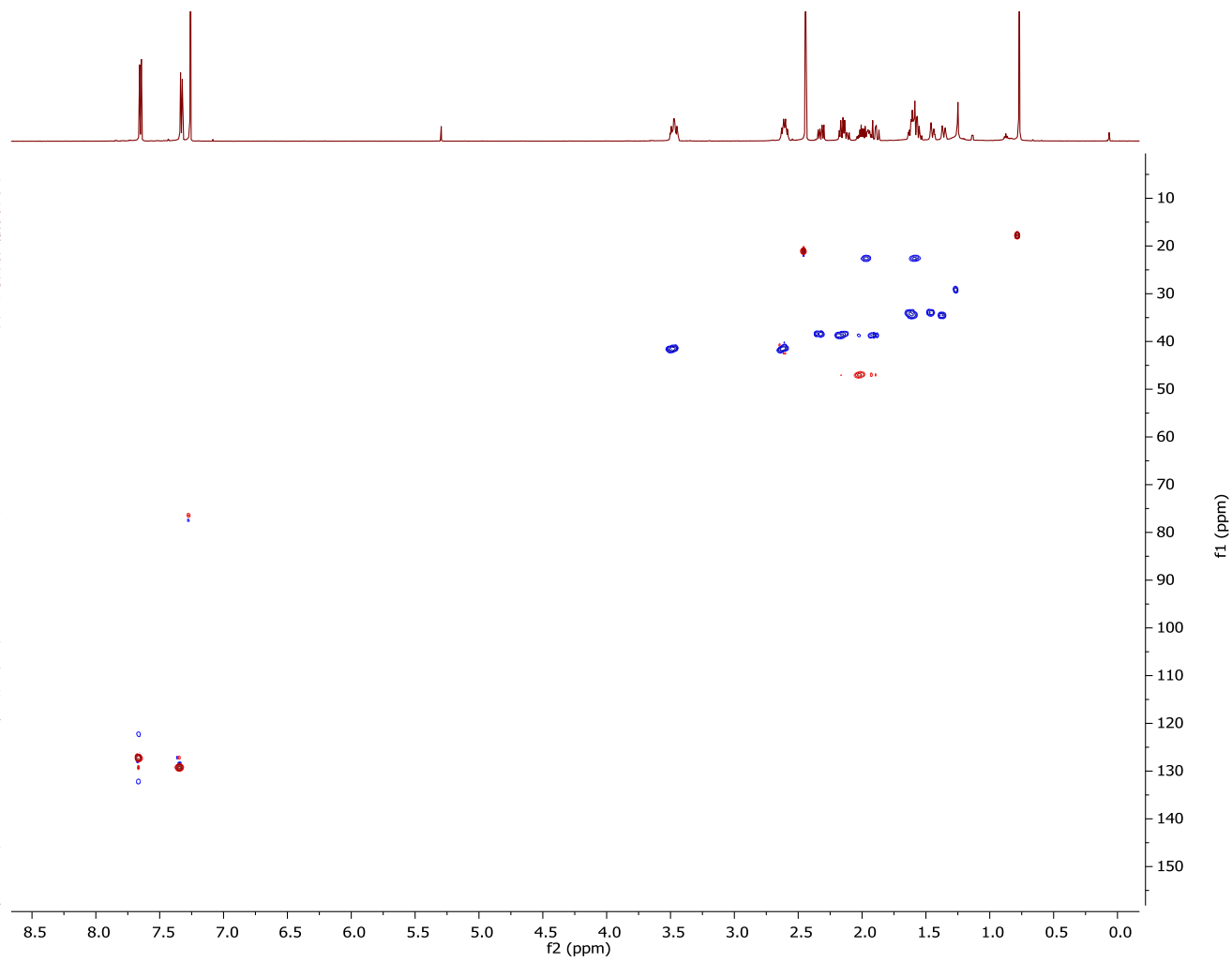
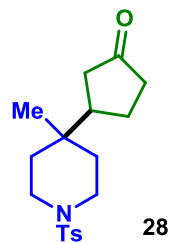
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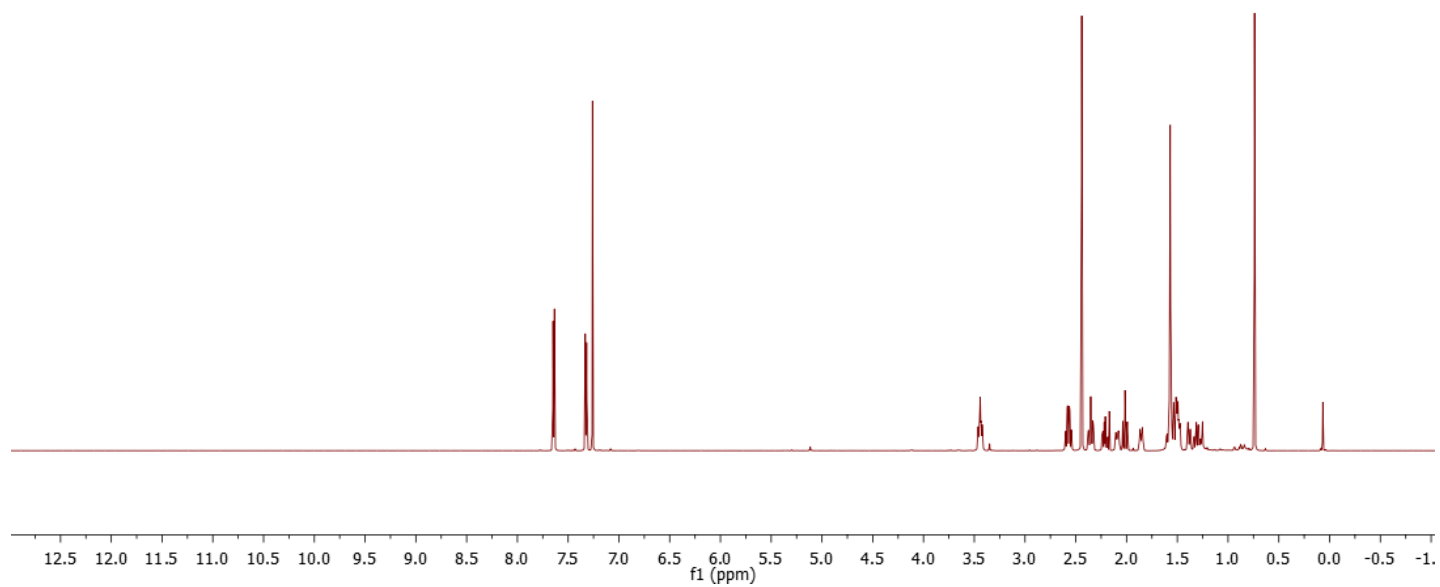
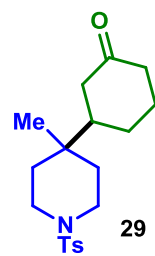
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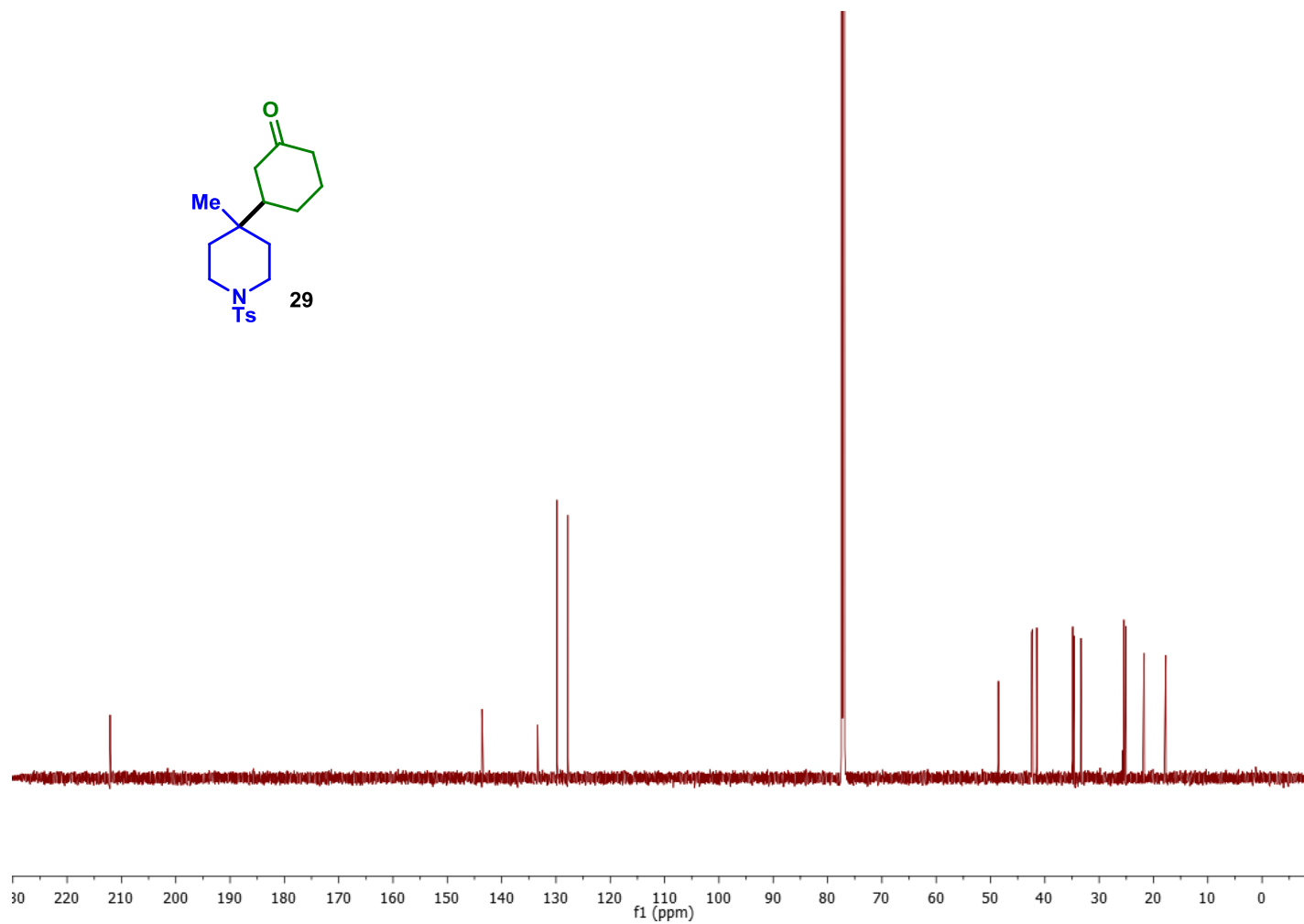
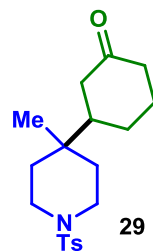
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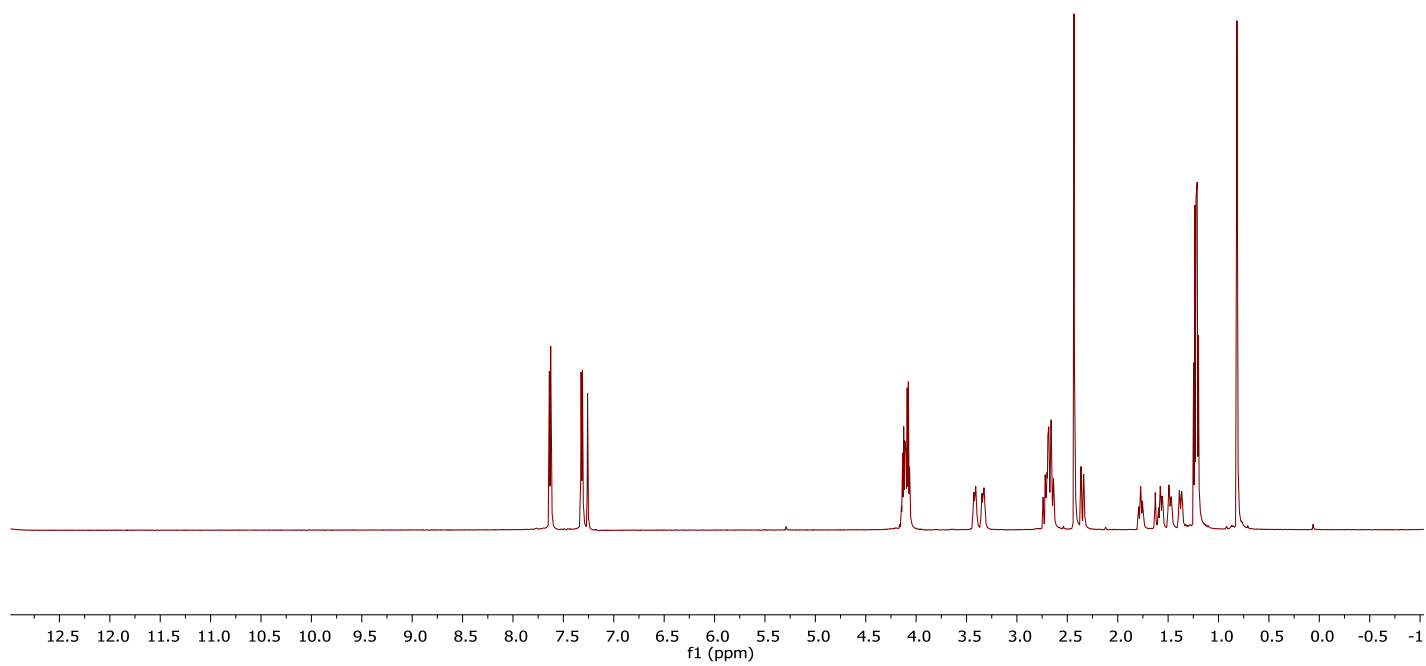
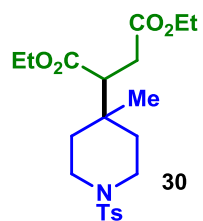
Compound 29 ¹H NMR



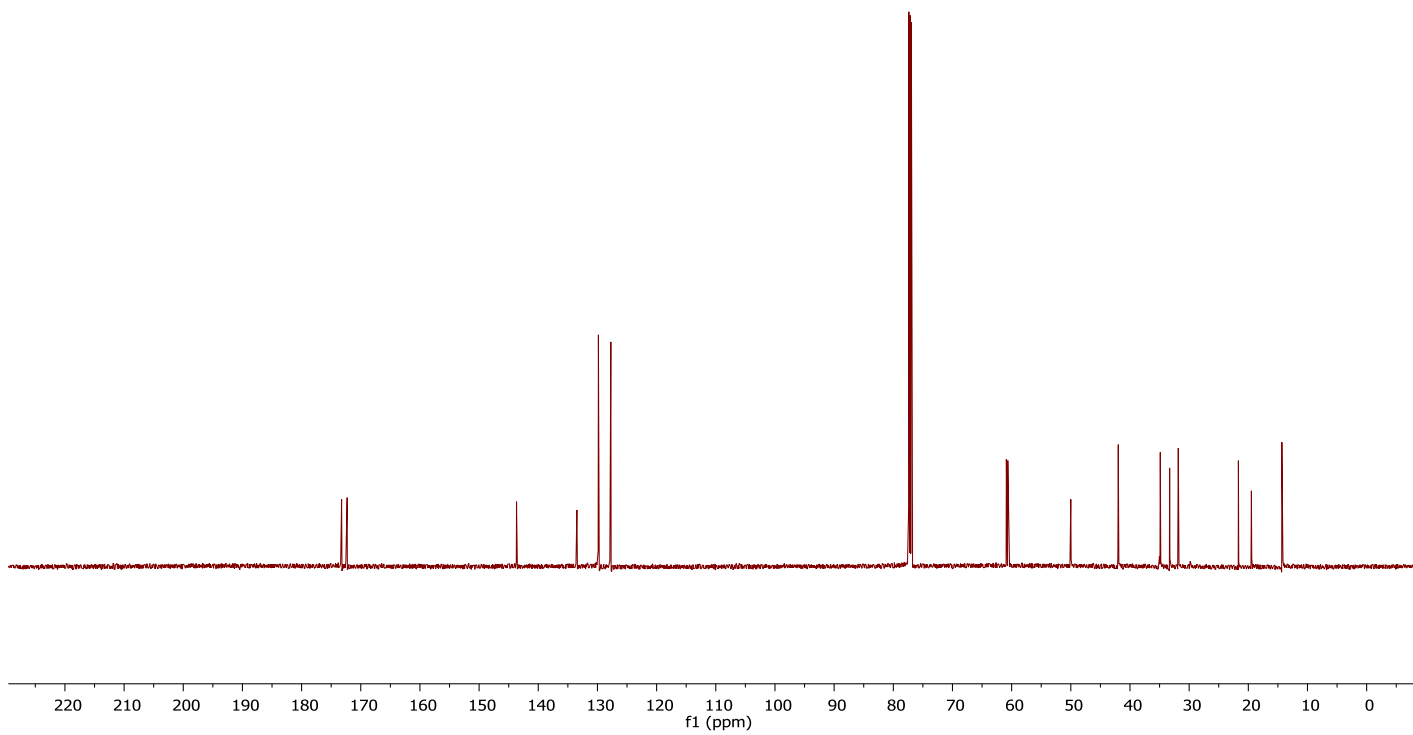
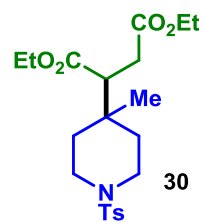
Compound 29 ^{13}C NMR



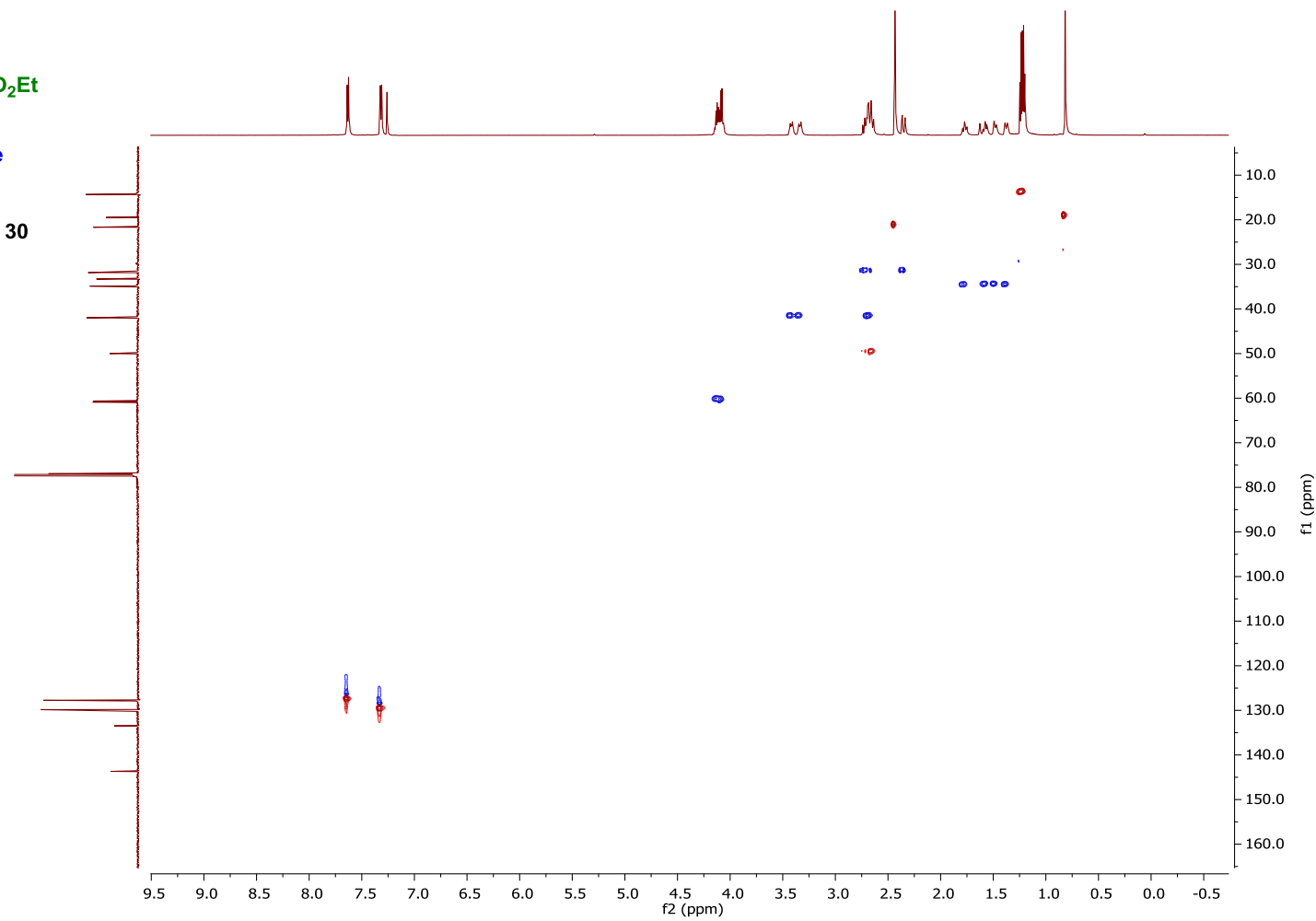
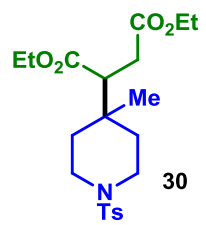
Compound 30 ¹H NMR



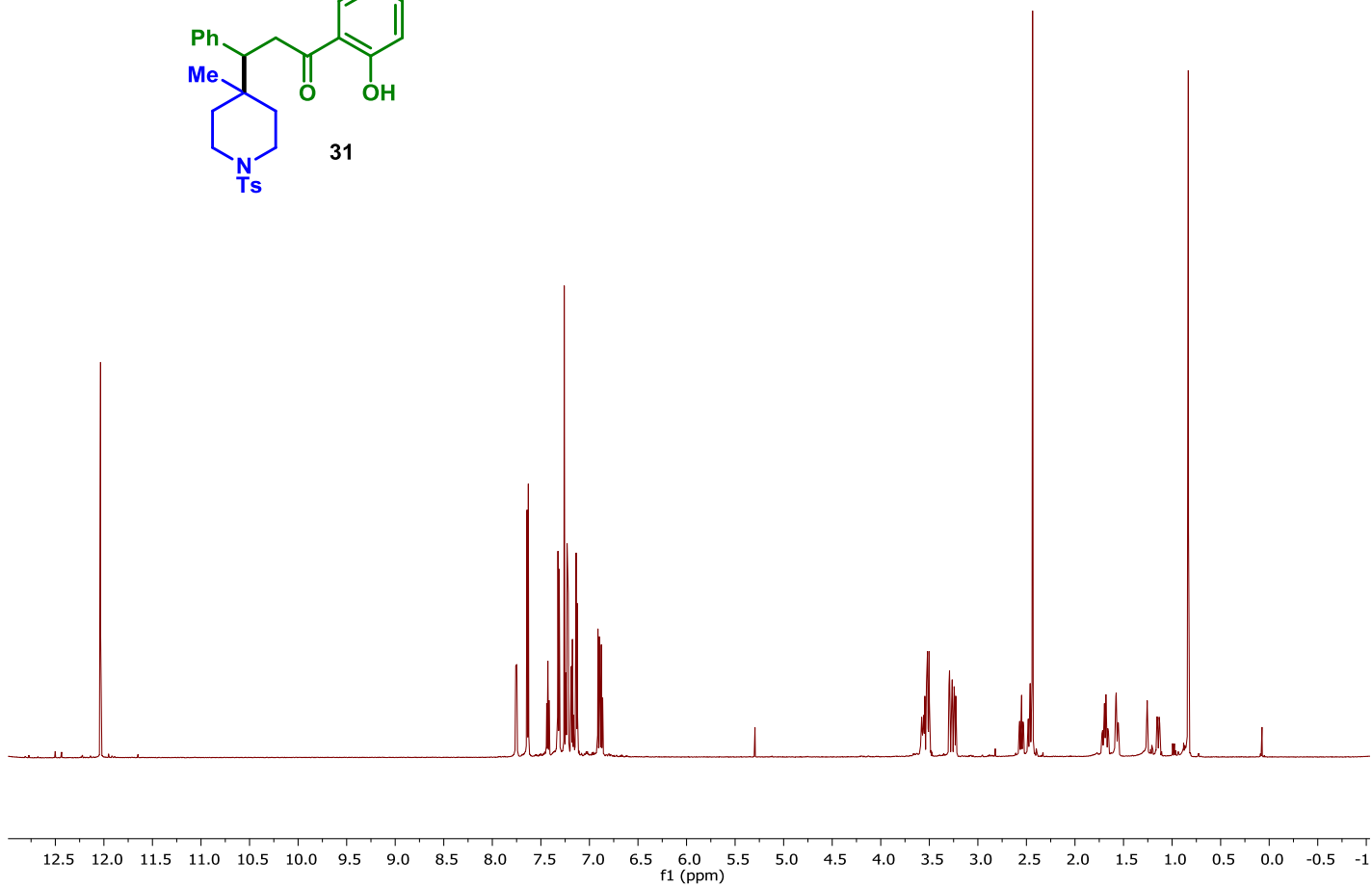
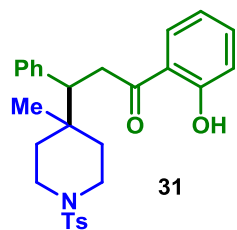
Compound 30 ¹³C NMR



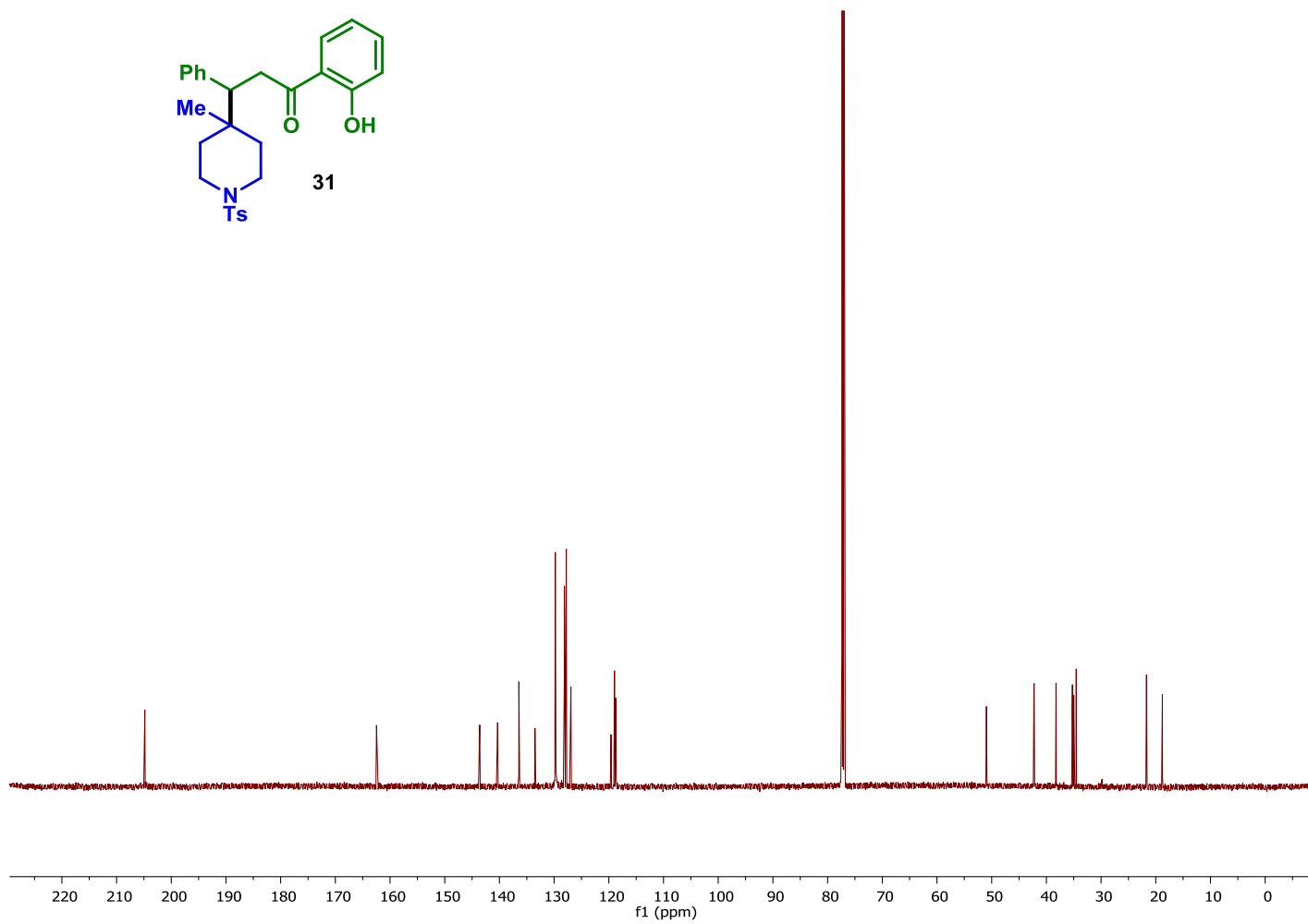
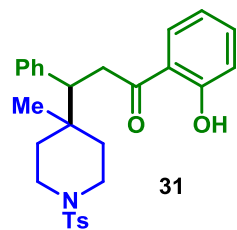
Compound 30 HSQC



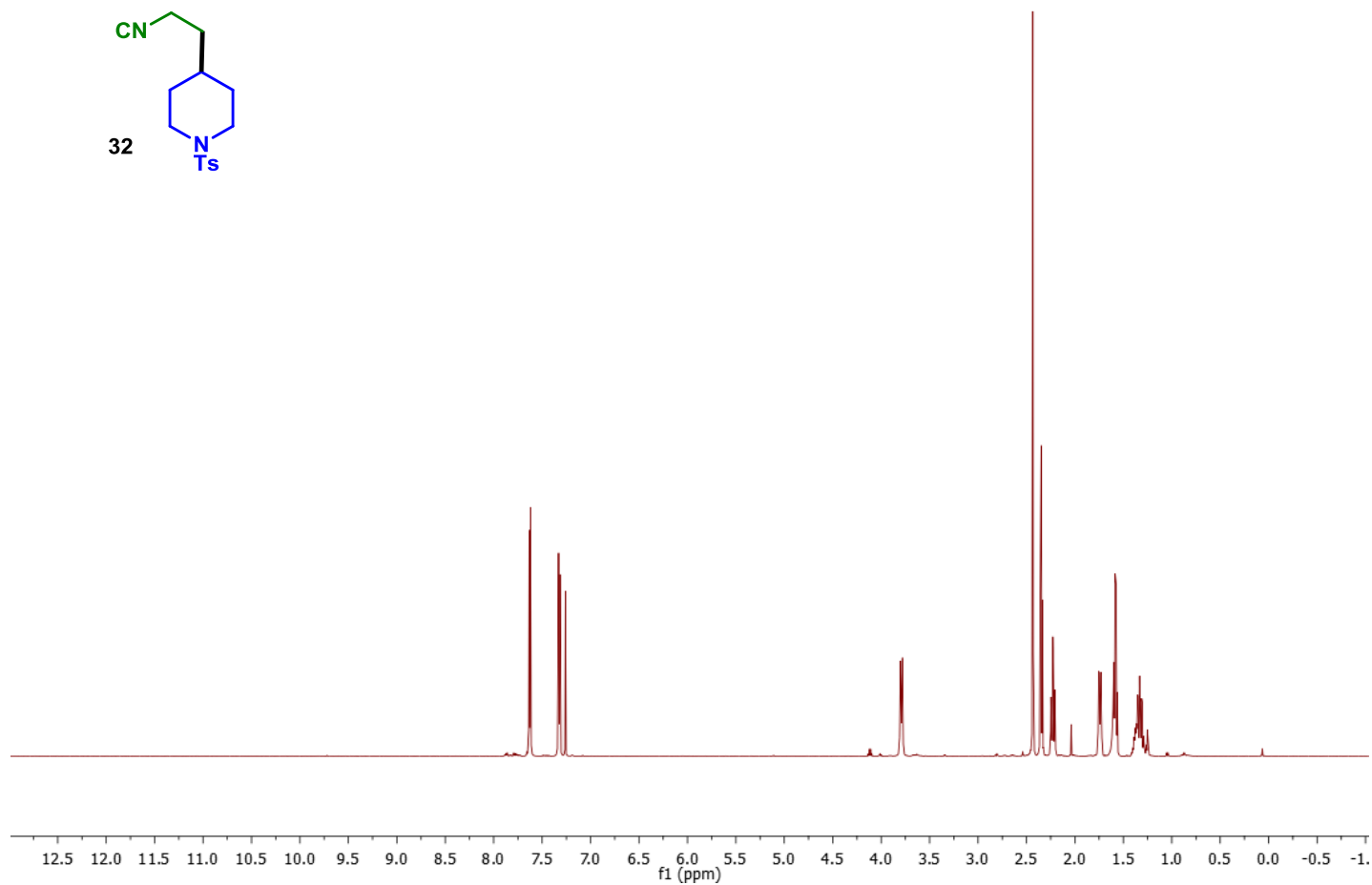
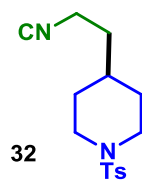
Compound 31 ^1H NMR



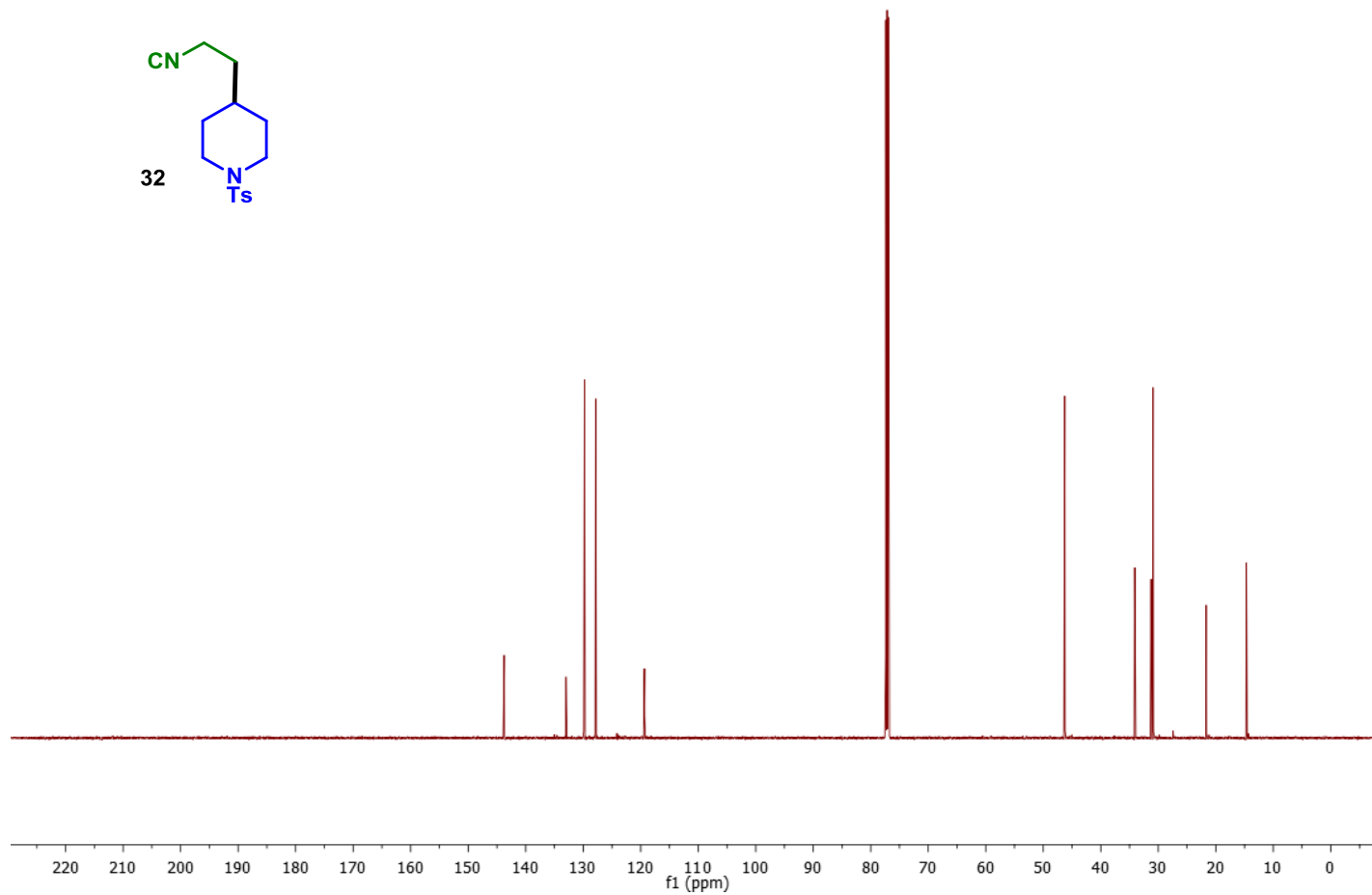
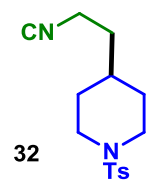
Compound 31 ^{13}C NMR



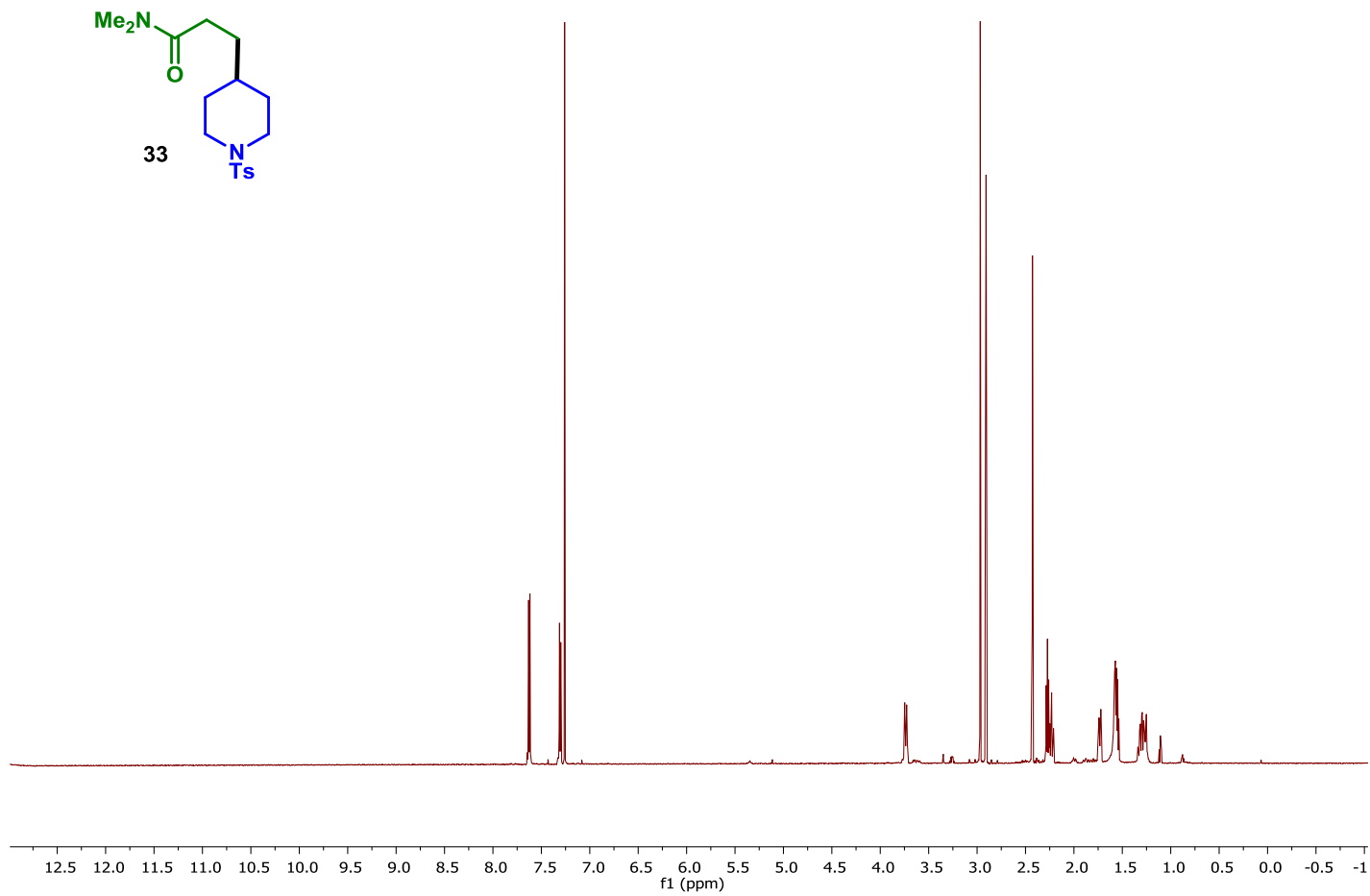
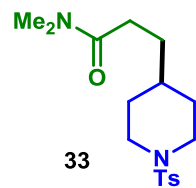
Compound 32 ^1H NMR



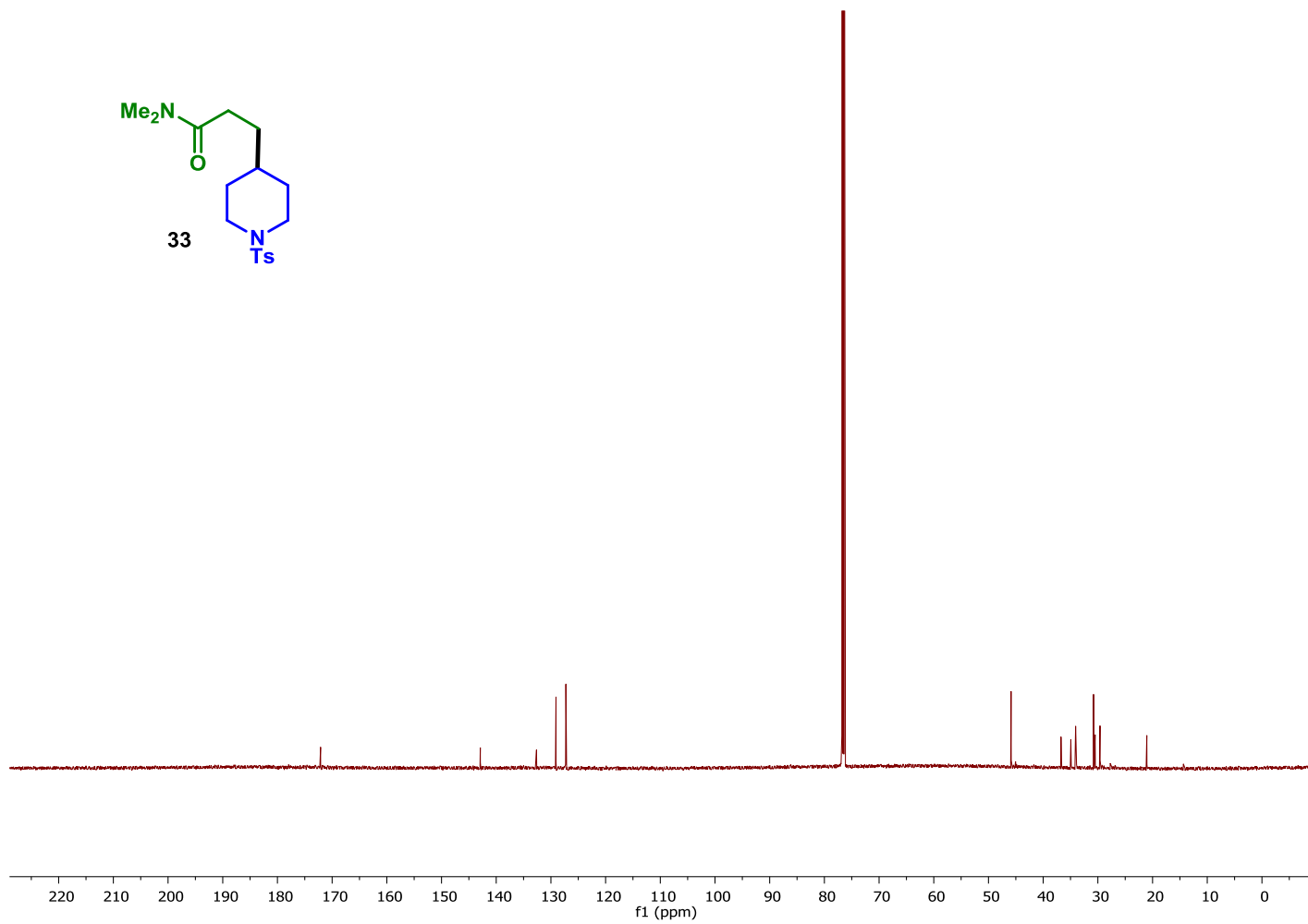
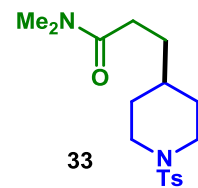
Compound 32 ^{13}C NMR



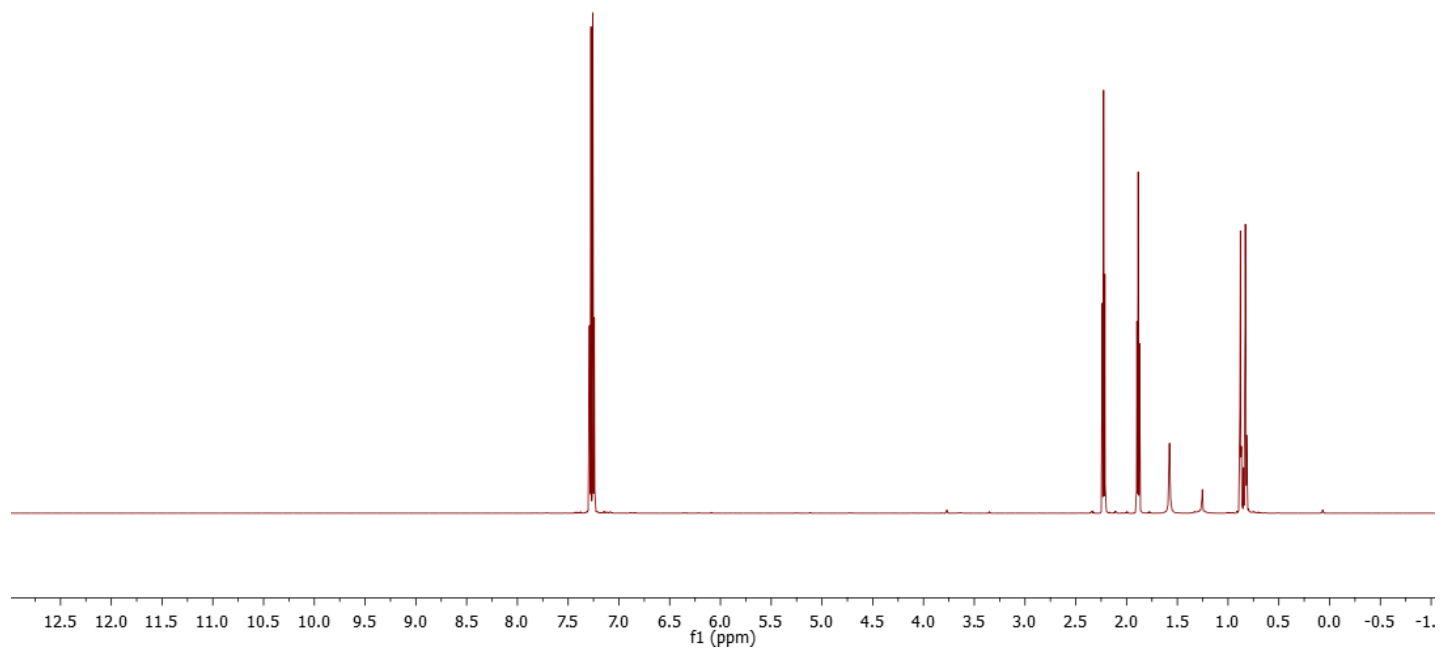
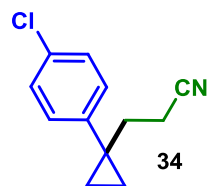
Compound 33 ^1H NMR



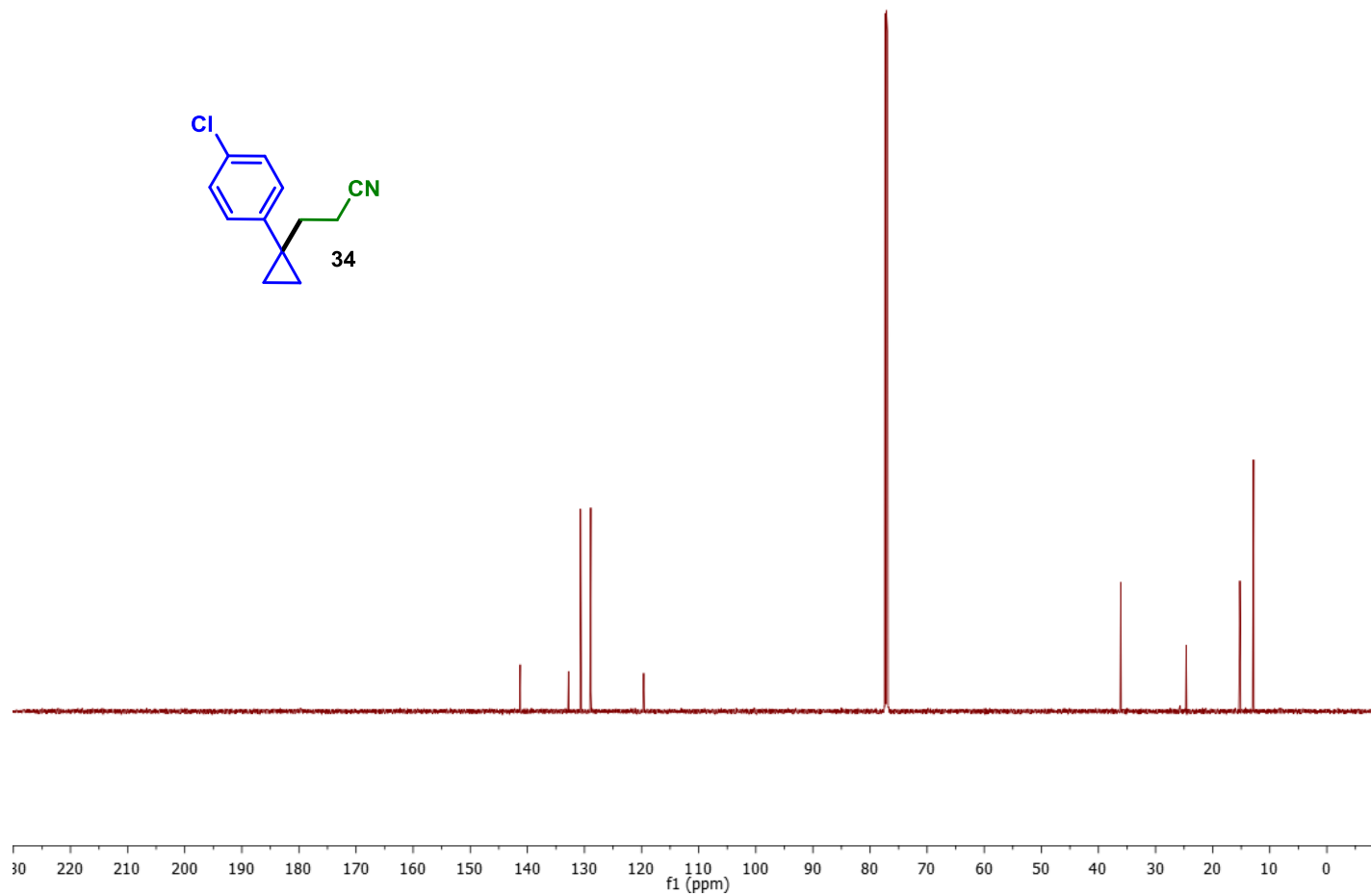
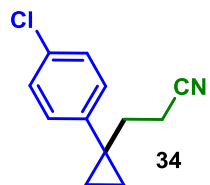
Compound 33 ¹³C NMR



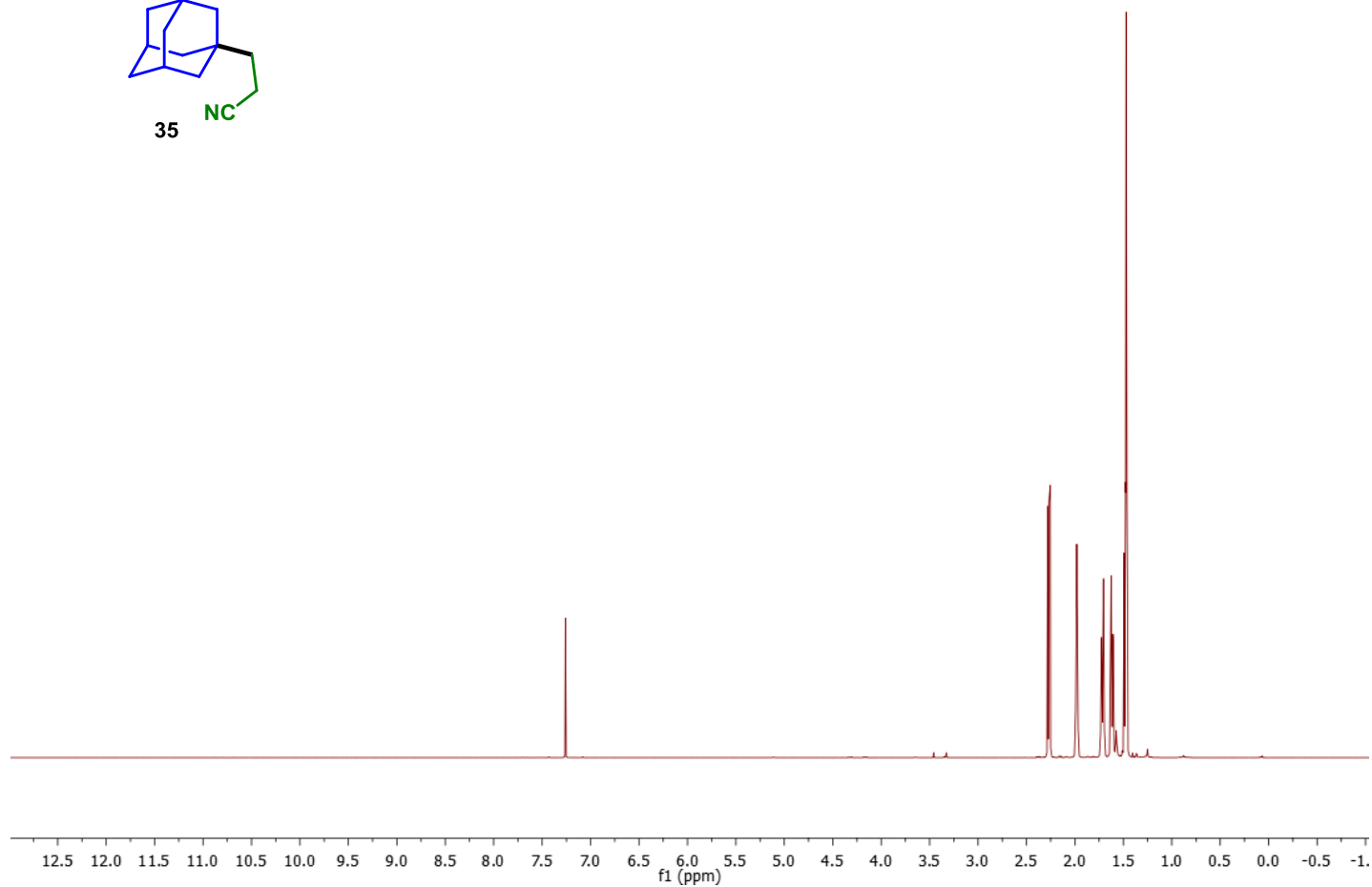
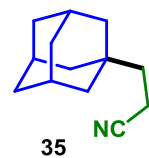
Compound 34 ^1H NMR



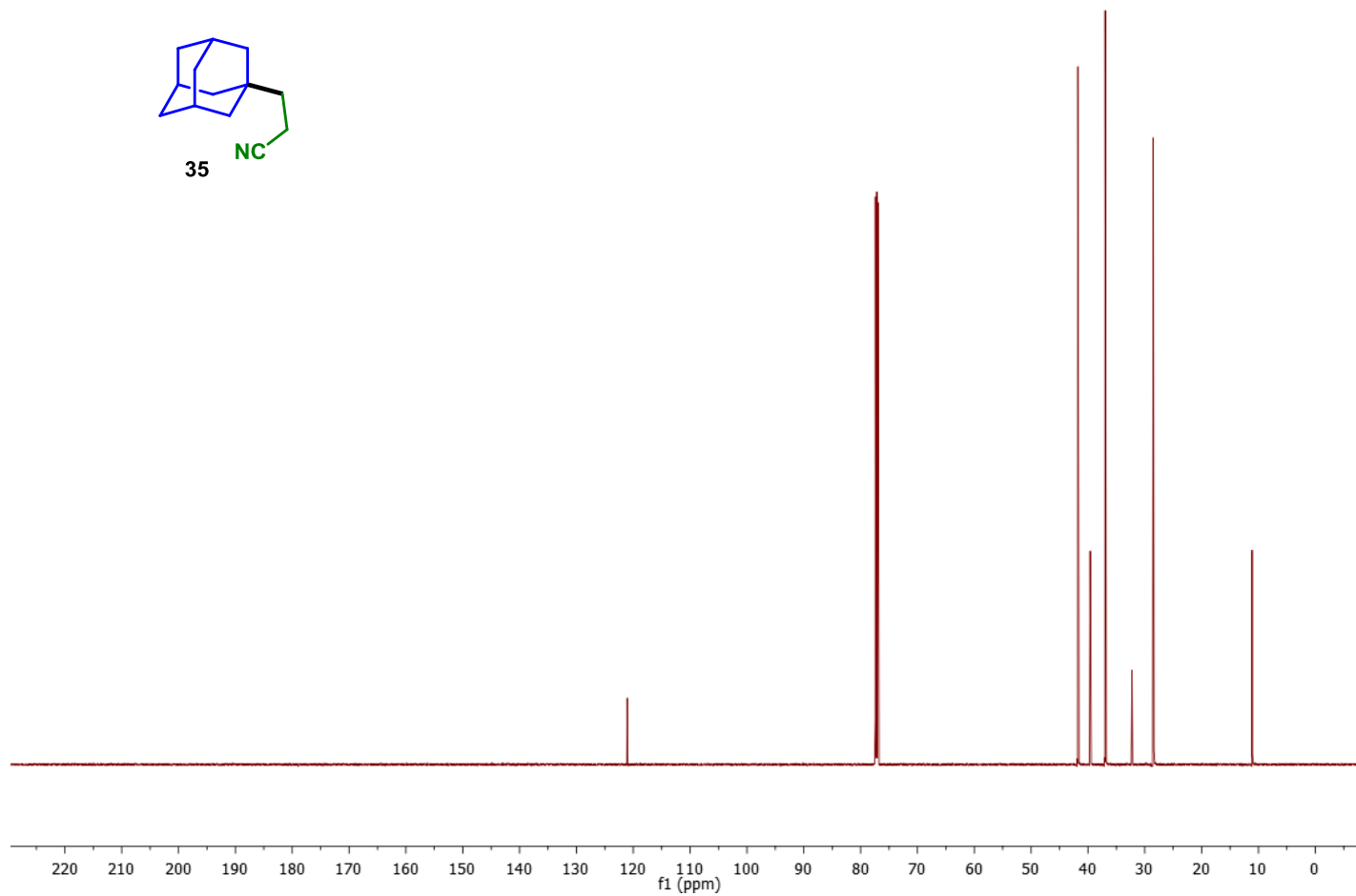
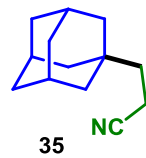
Compound 34 ^{13}C NMR



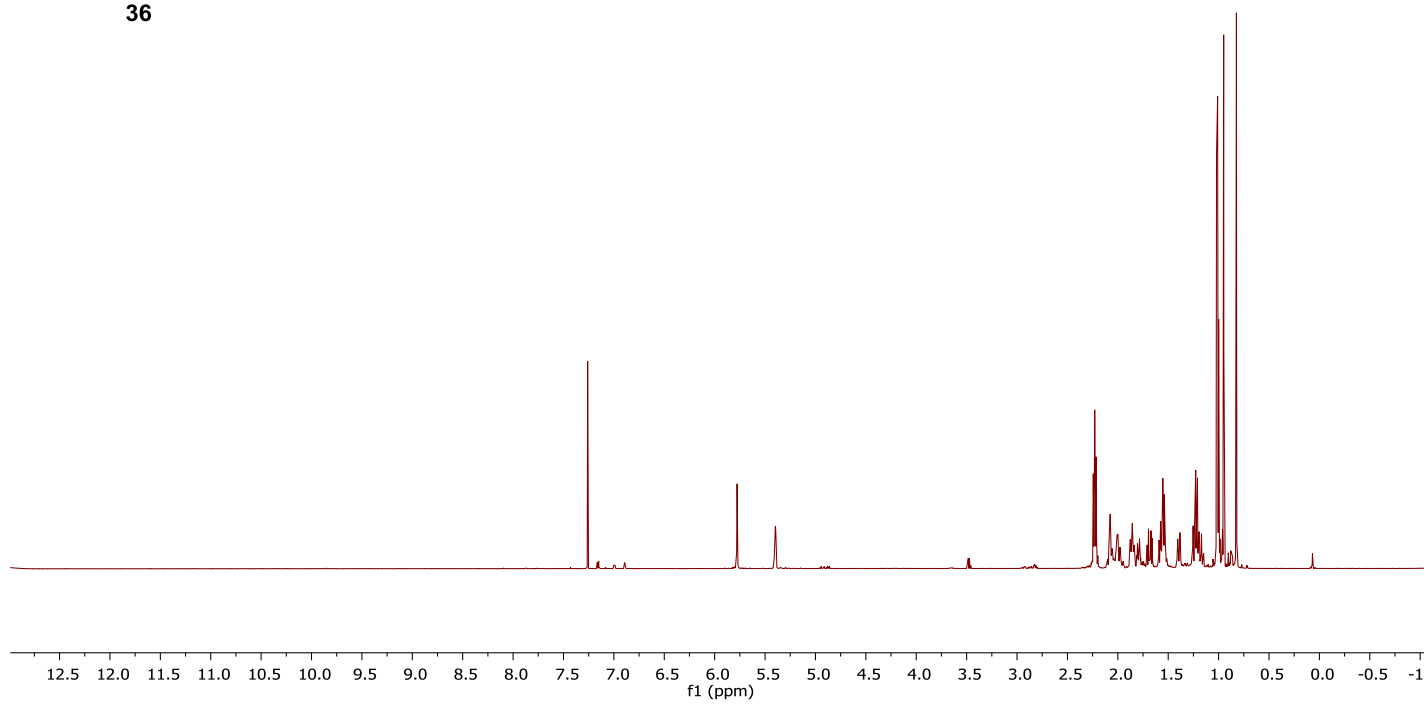
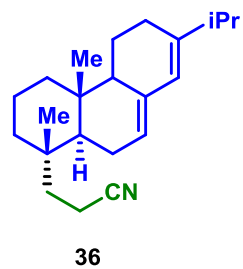
Compound 35 ^1H NMR



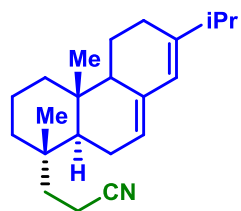
Compound 35 ^{13}C NMR



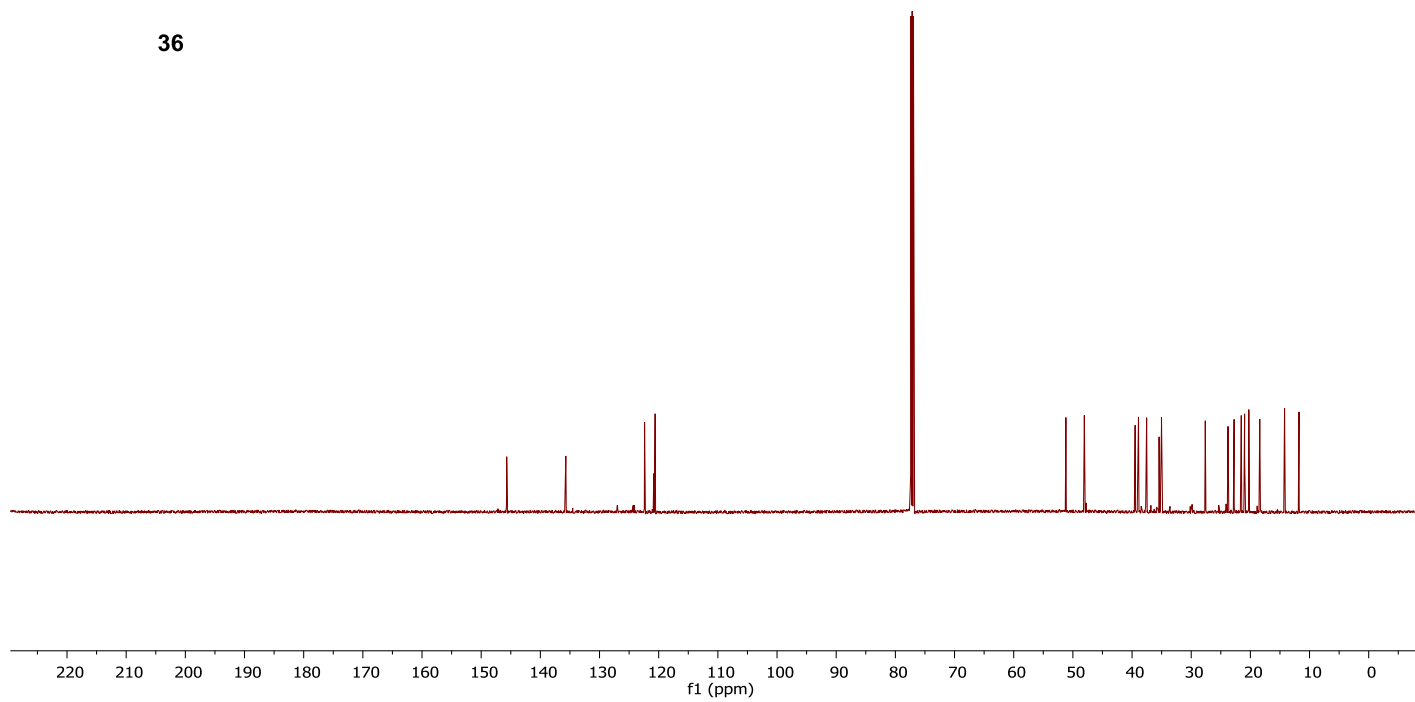
Compound 36 ^1H NMR



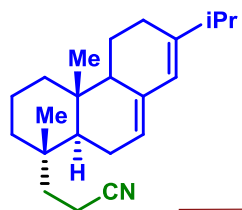
Compound 36 ^{13}C NMR



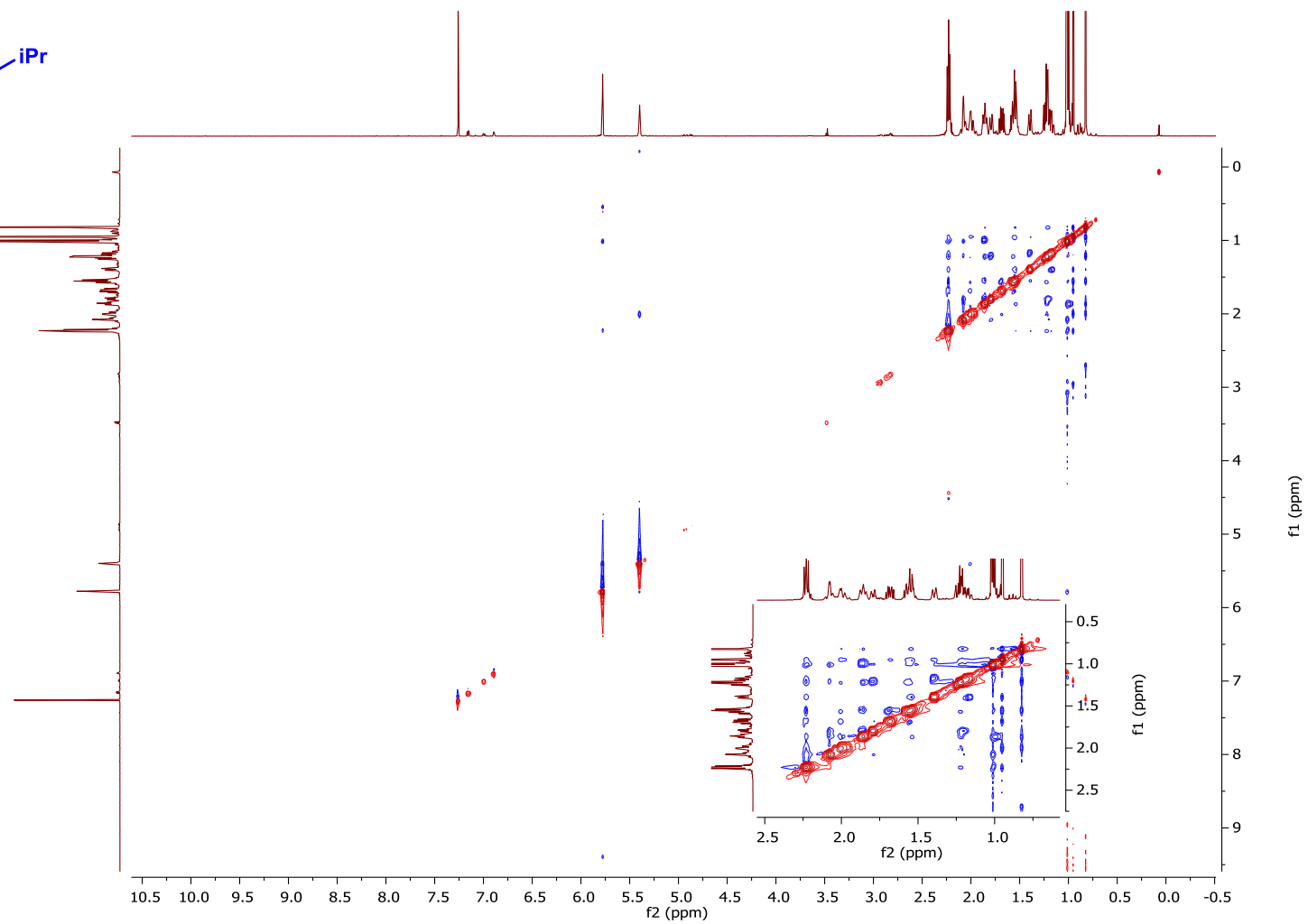
36



Compound 36 NOESY



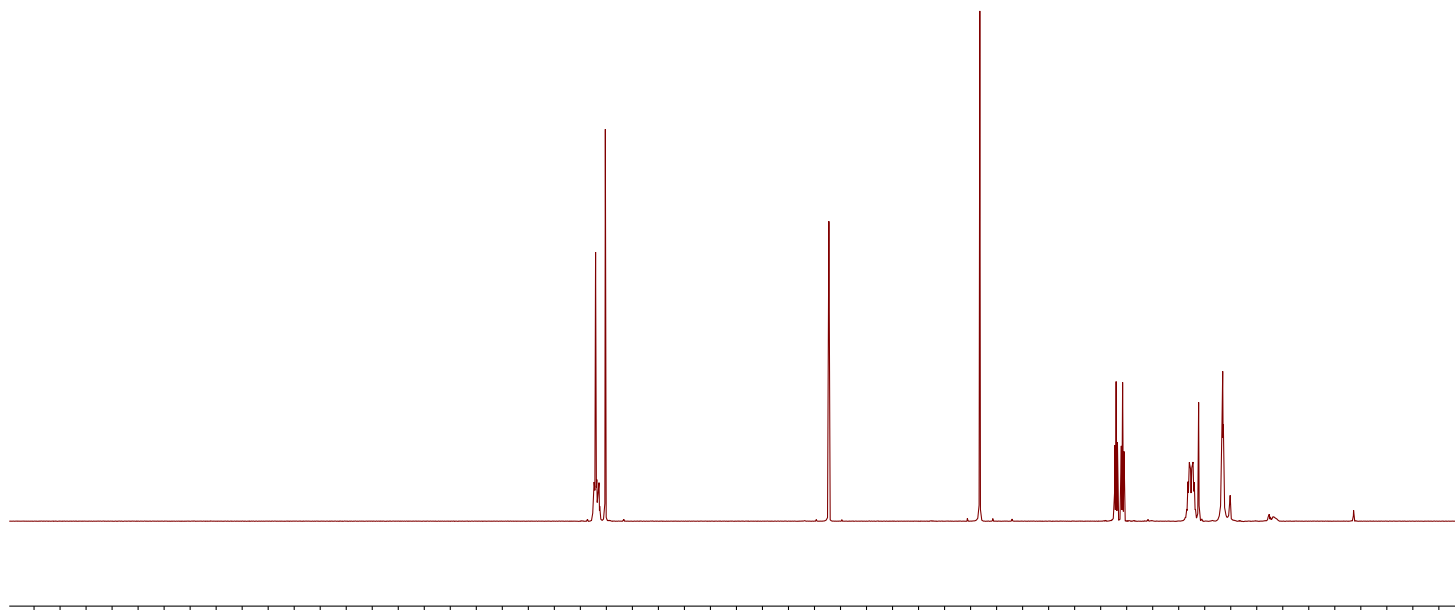
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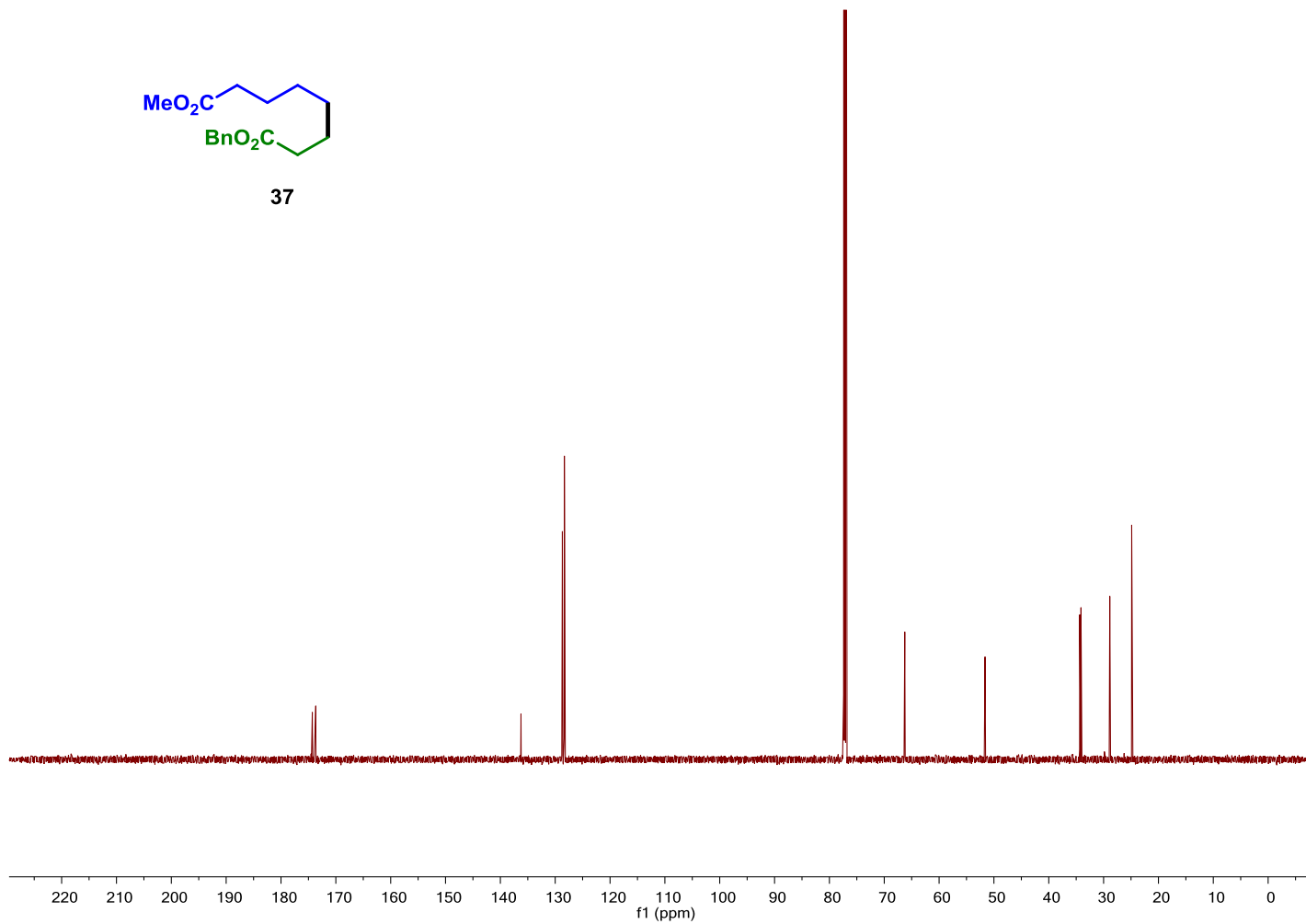
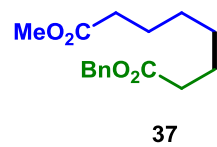
Compound 37 ^1H NMR



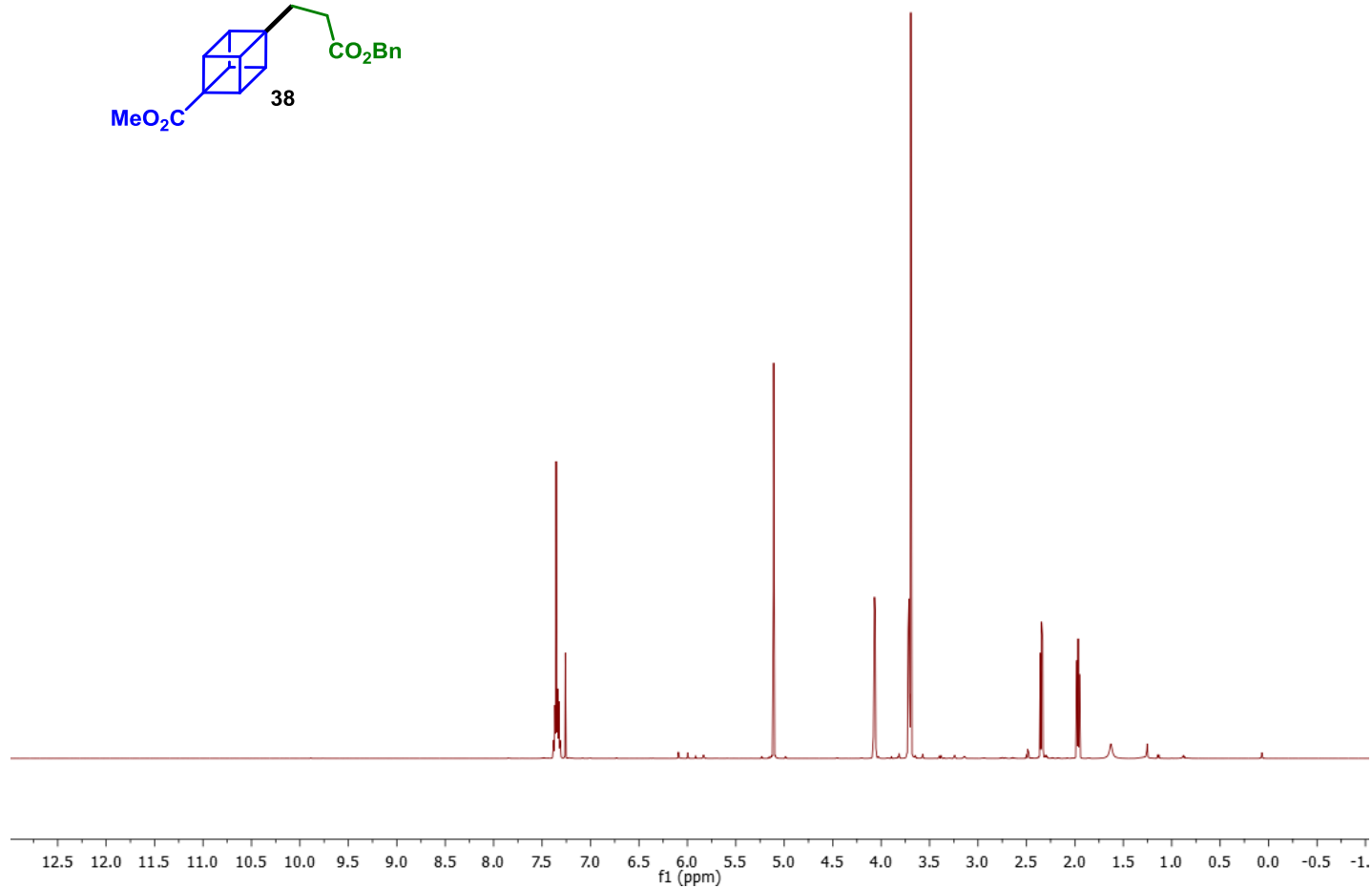
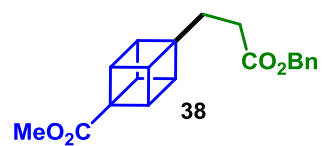
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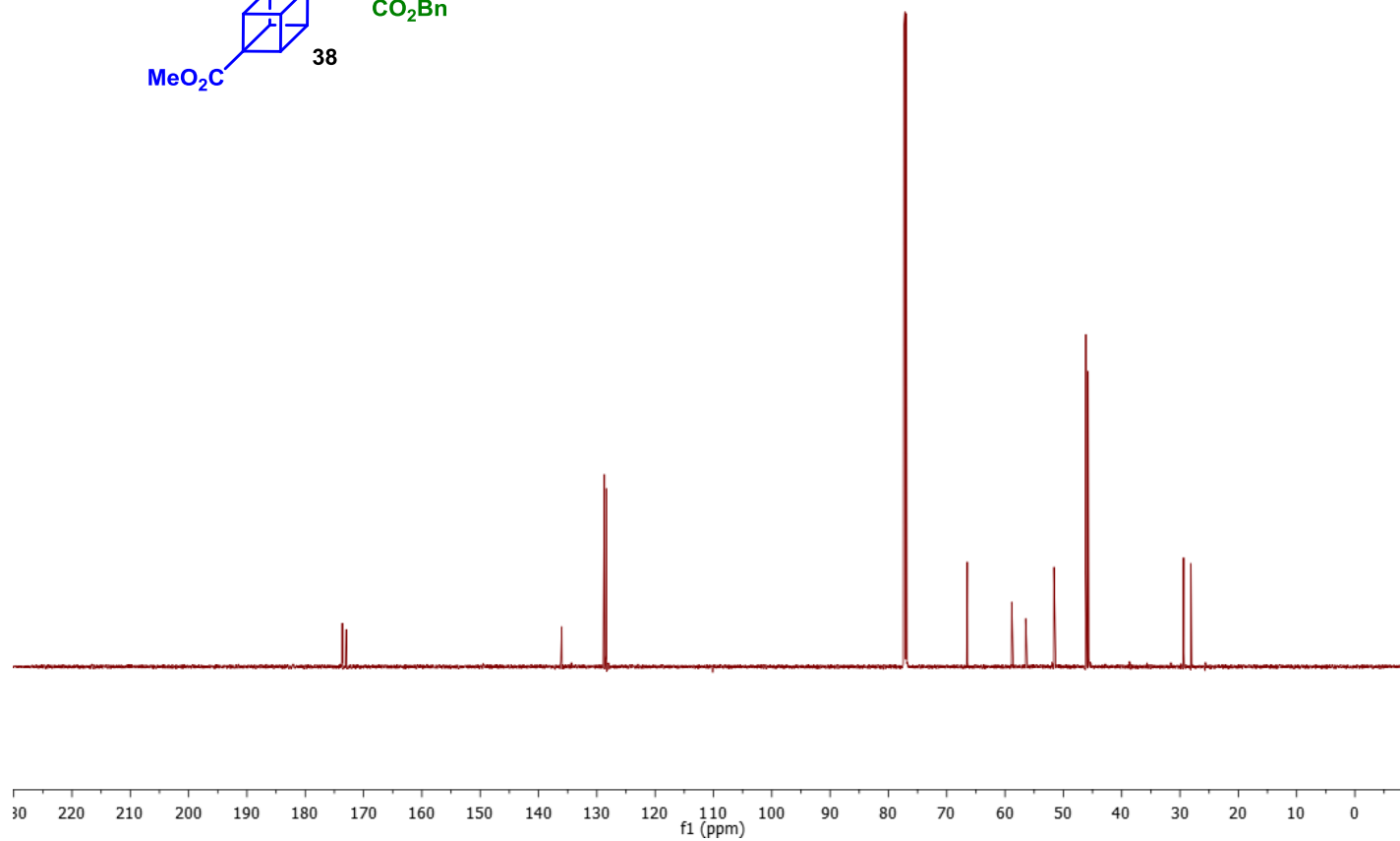
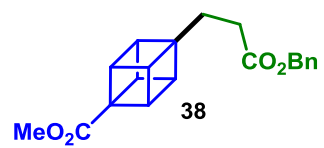
Compound 37 ^{13}C NMR



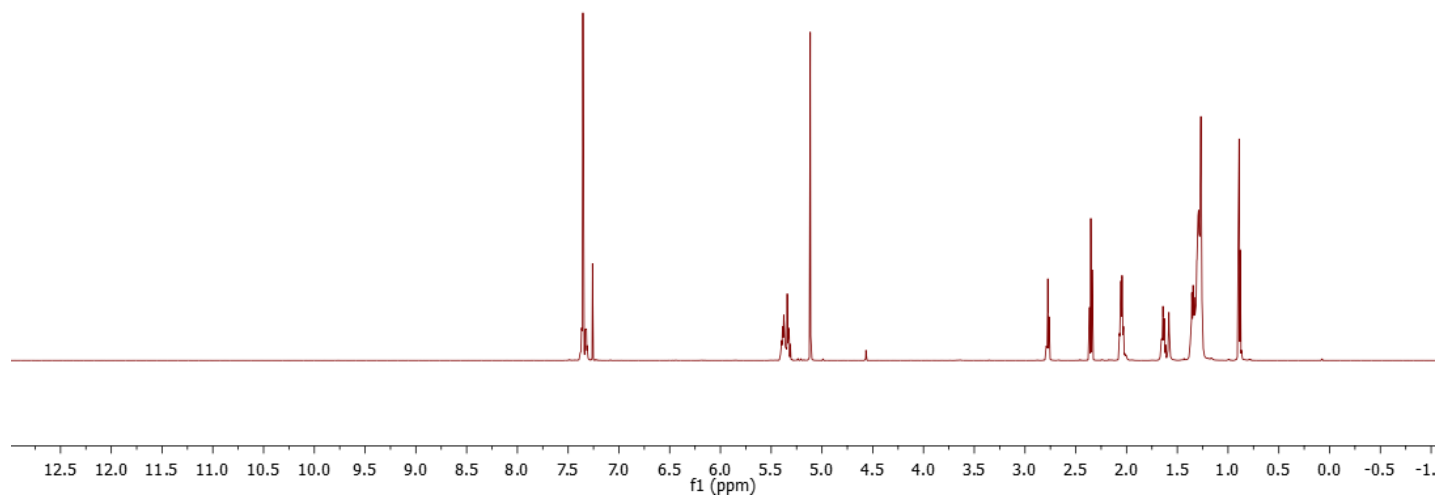
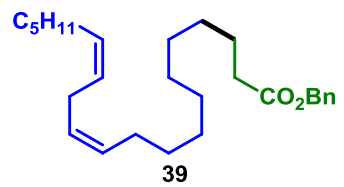
Compound 38 ^1H NMR



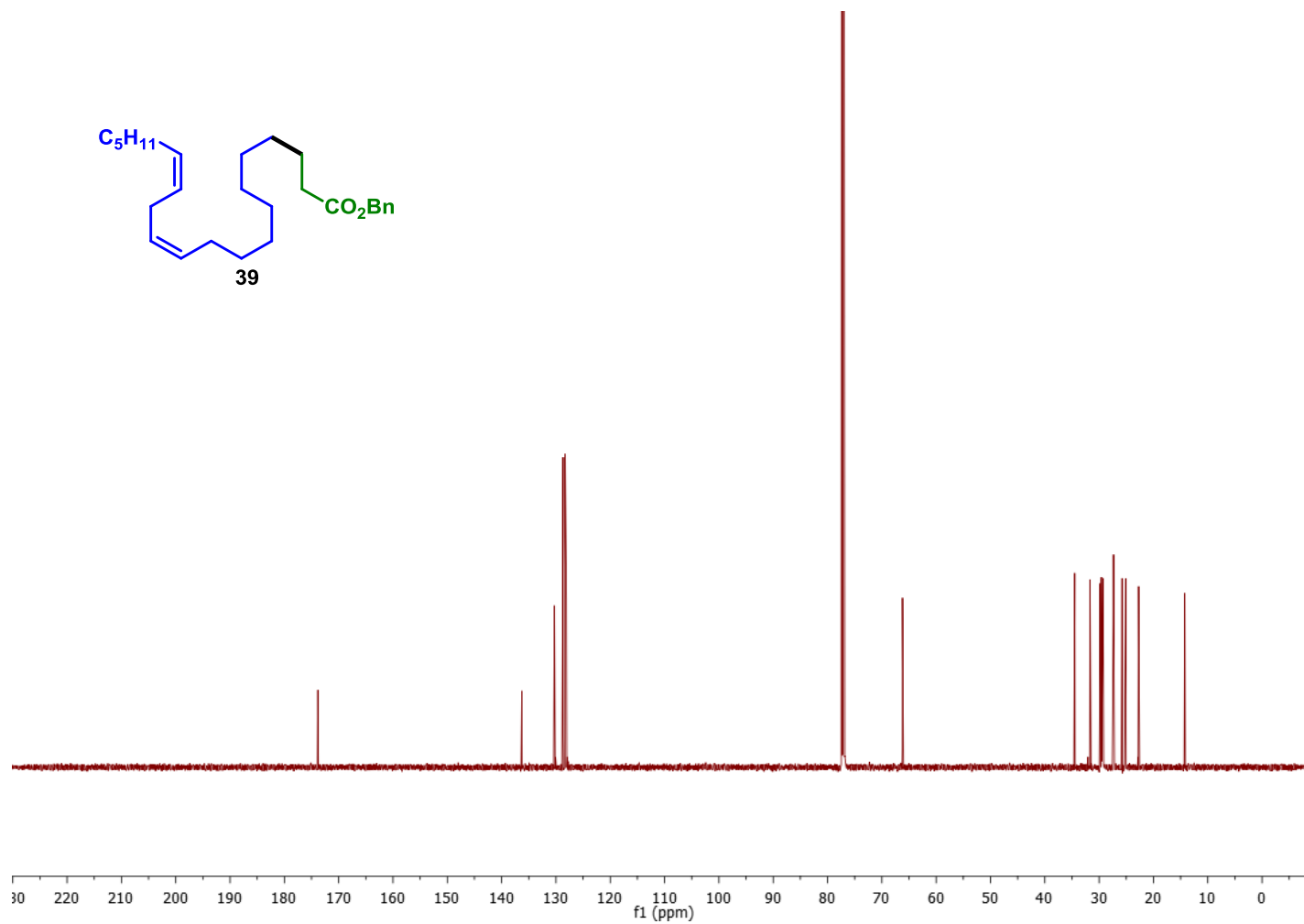
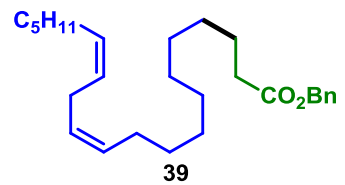
Compound 38 ^{13}C NMR



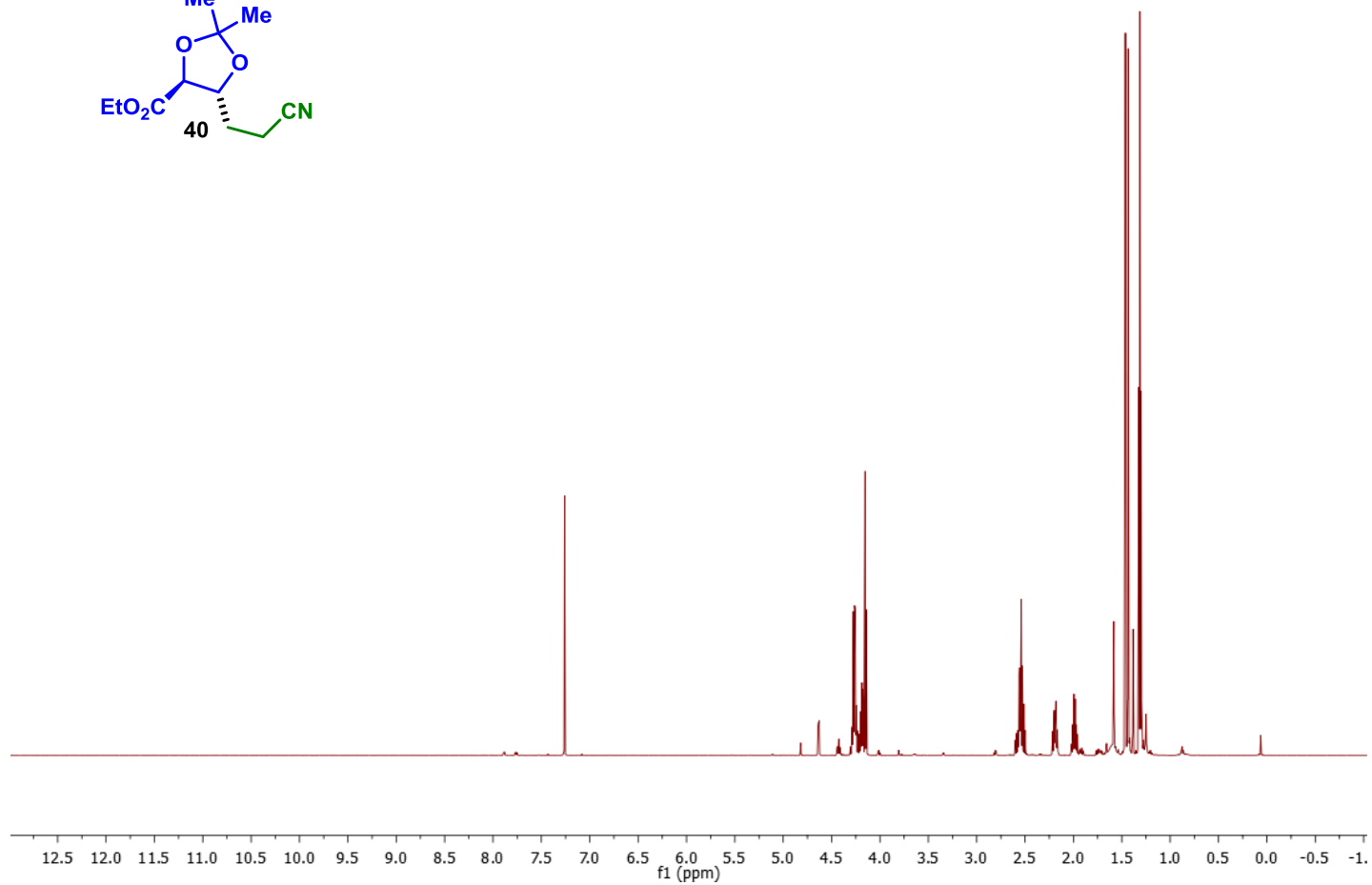
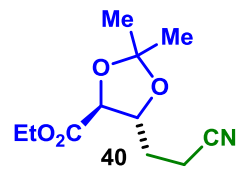
Compound 39 ^1H NMR



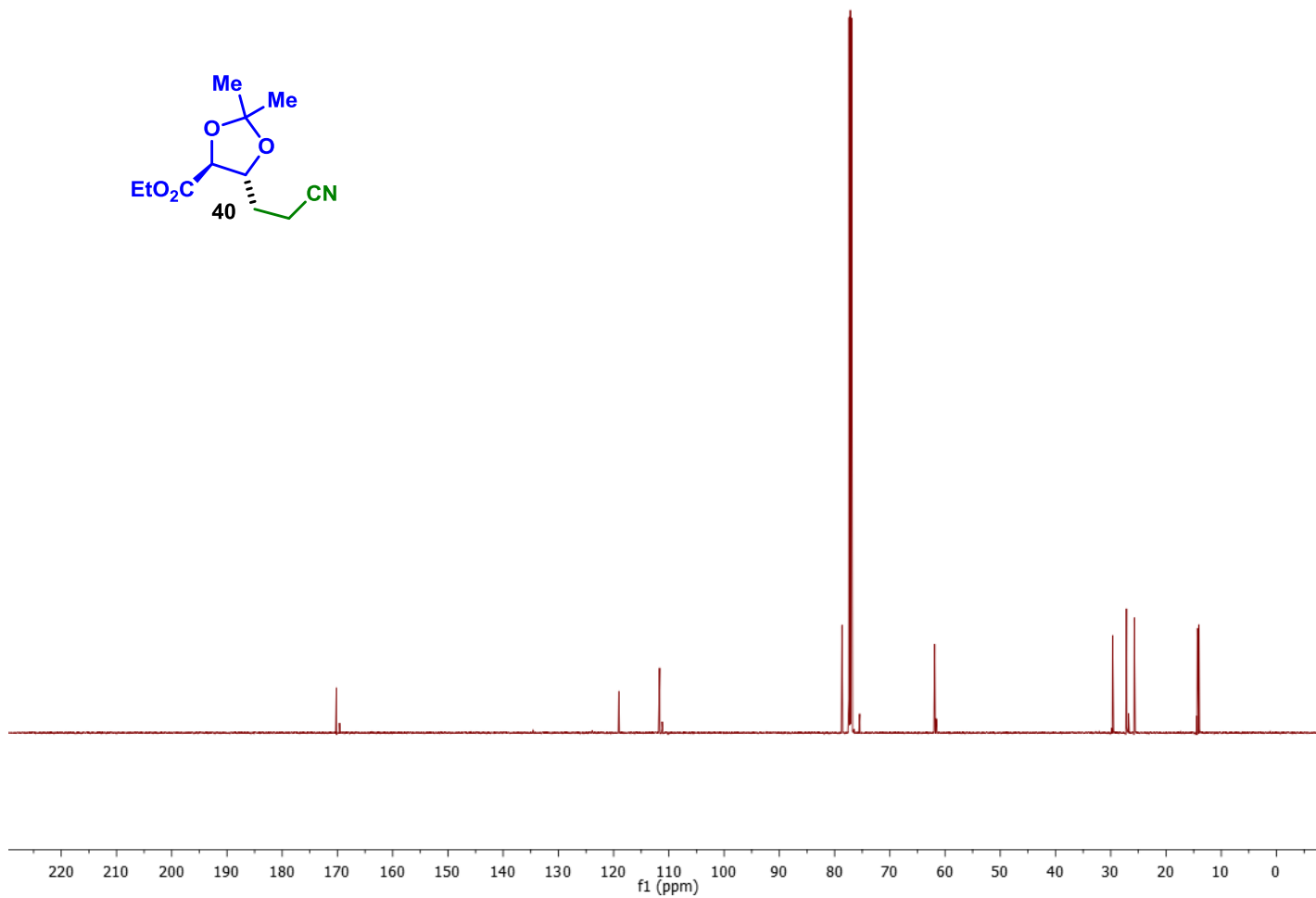
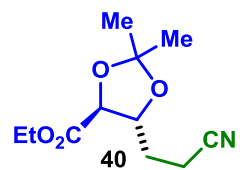
Compound 39 ^{13}C NMR



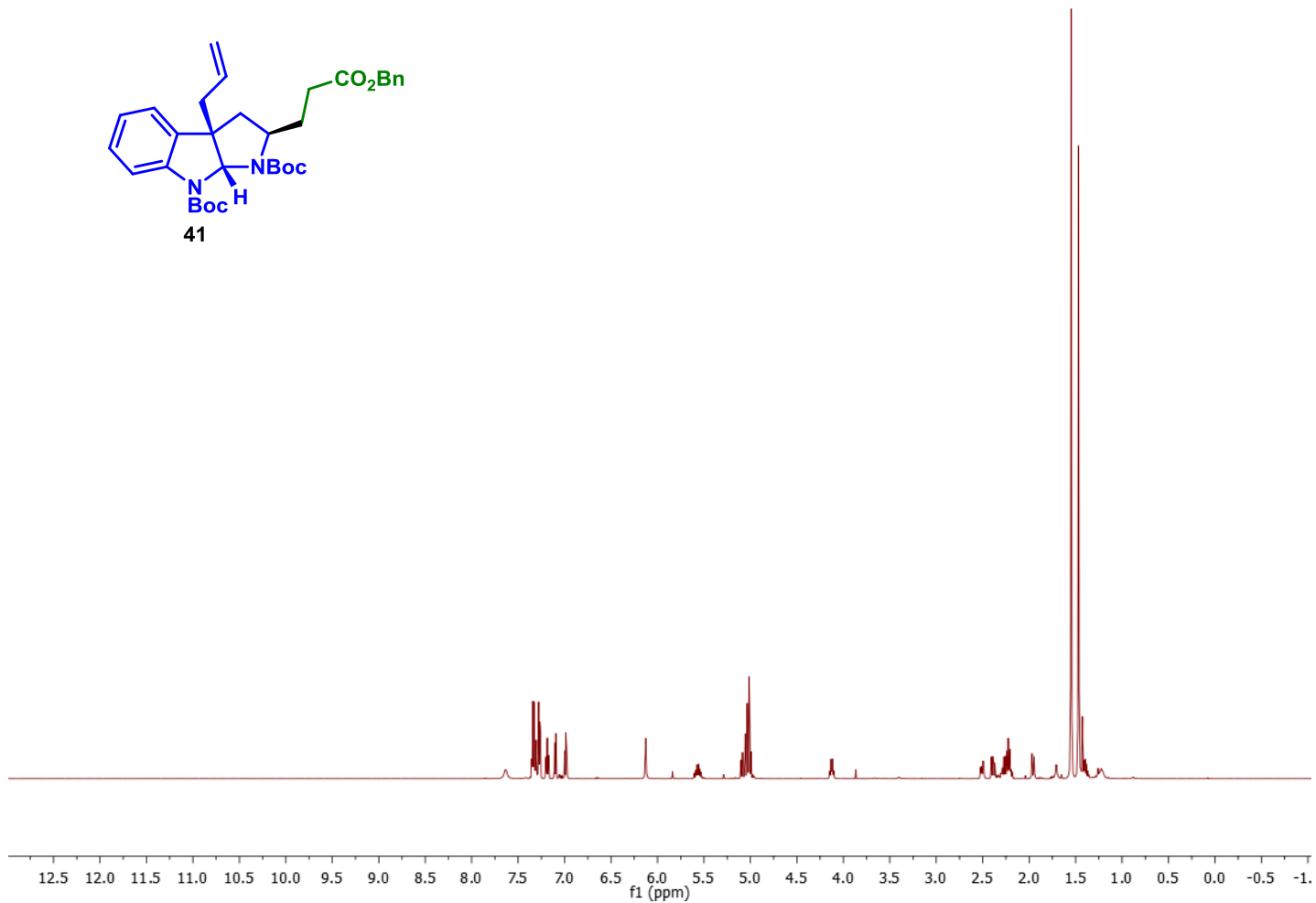
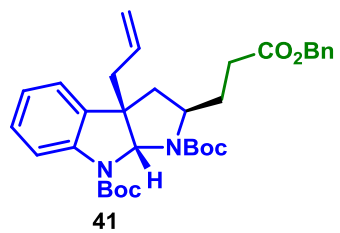
Compound 40 ¹H NMR



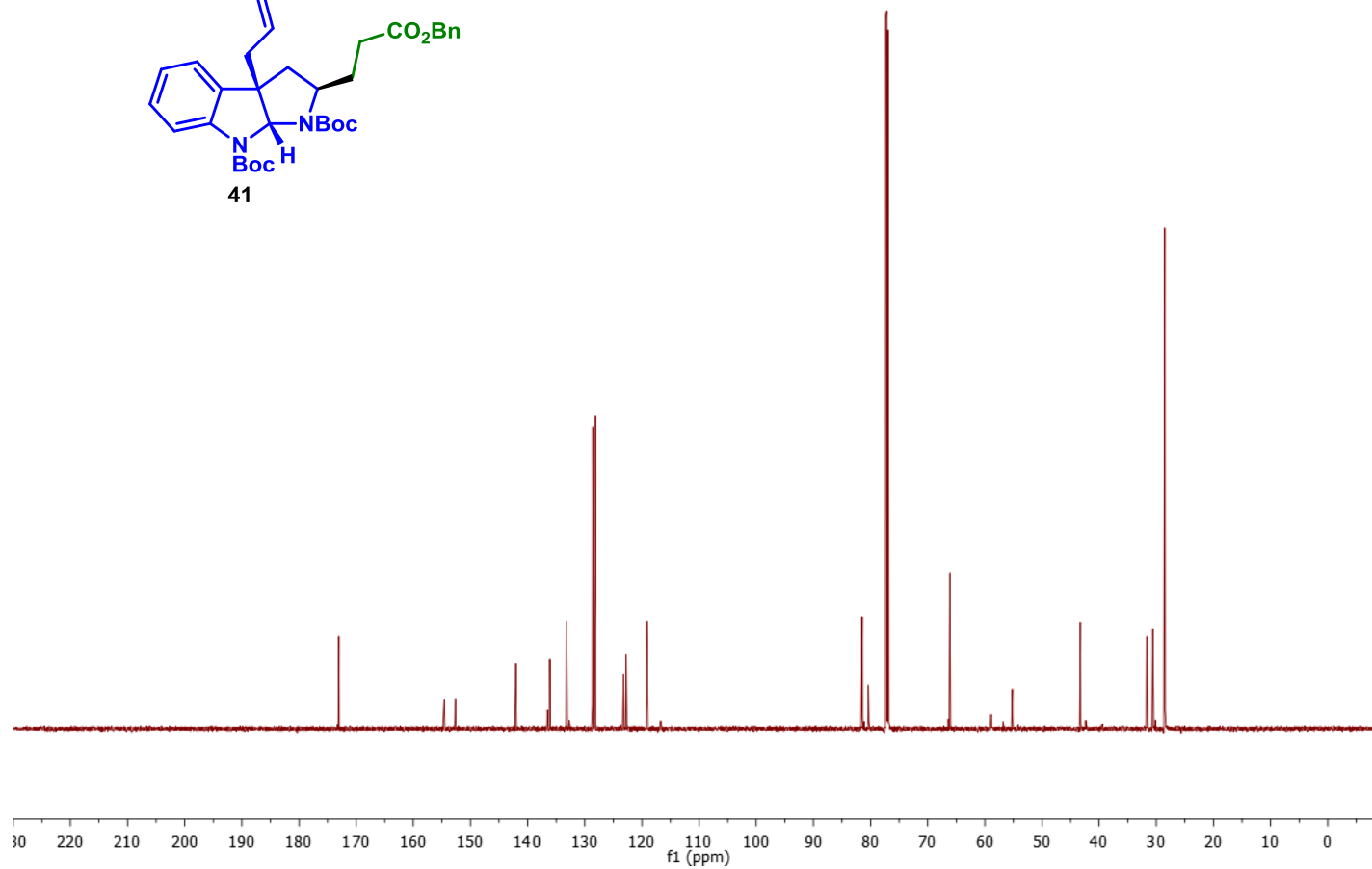
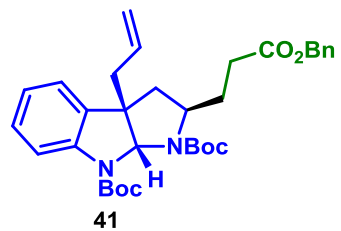
Compound 40 ^{13}C NMR



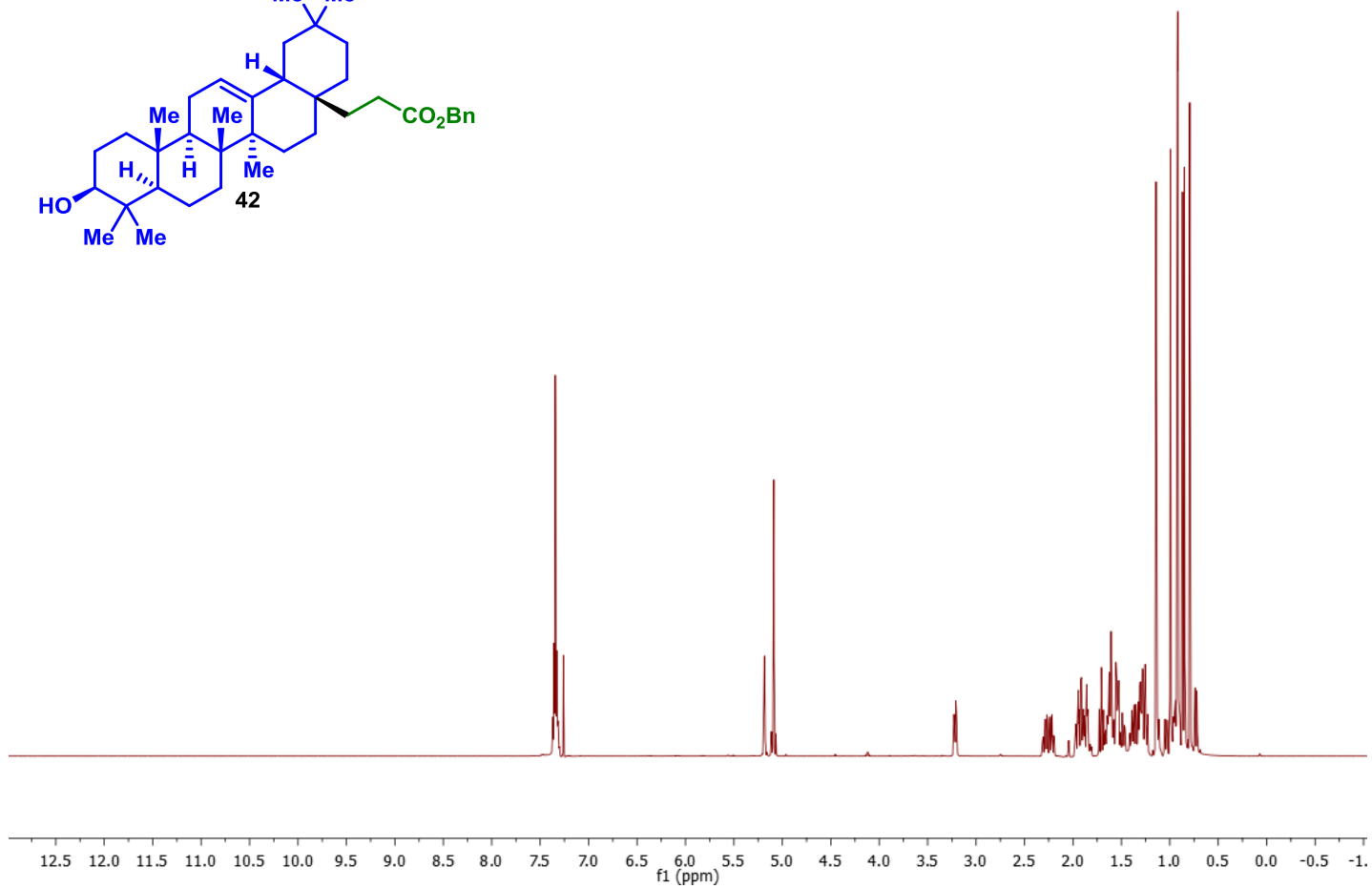
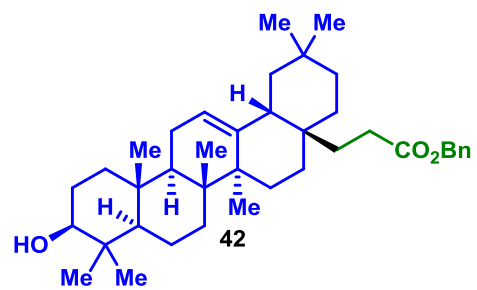
Compound 41 ¹H NMR



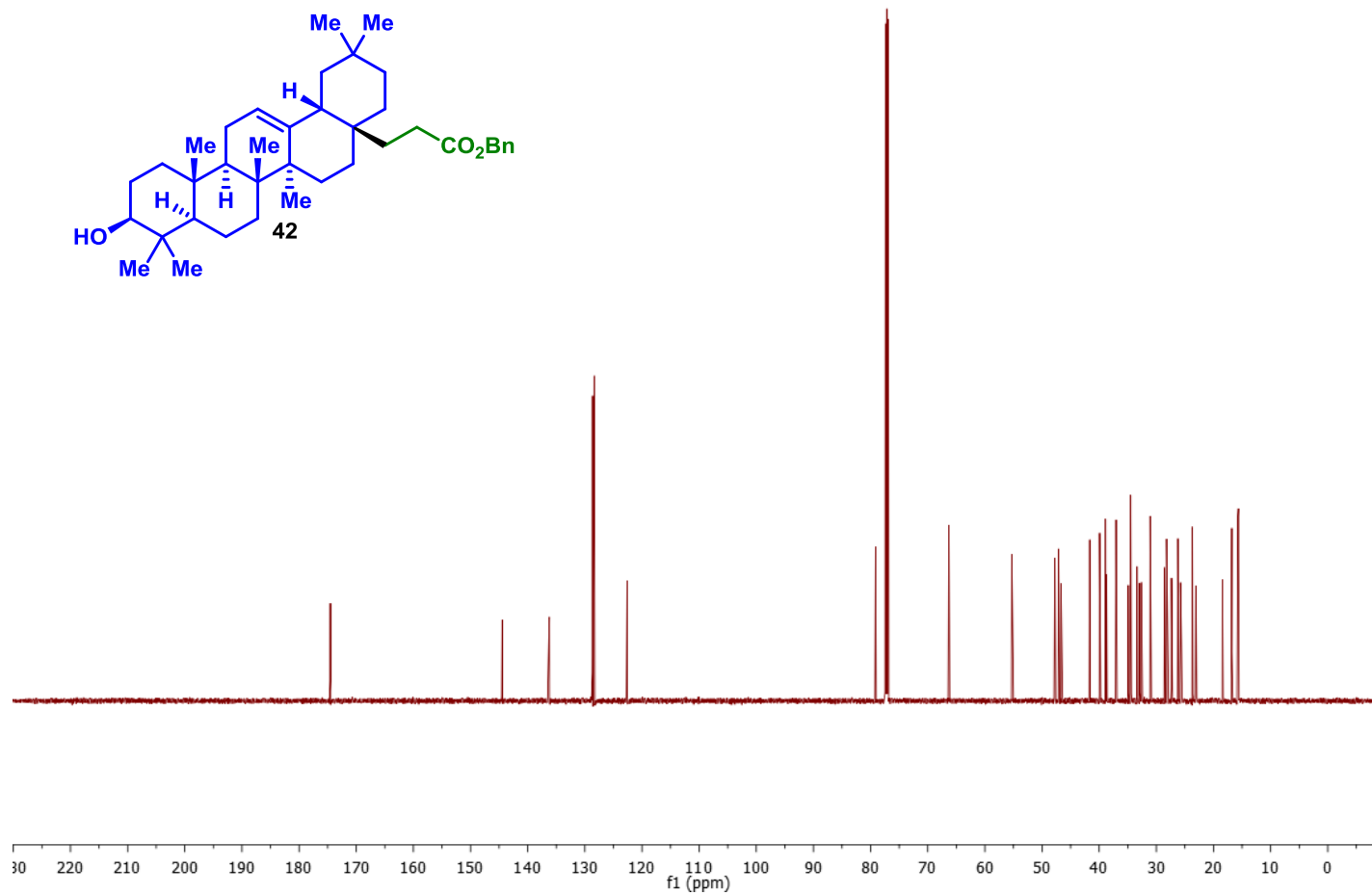
Compound 41 ^{13}C NMR



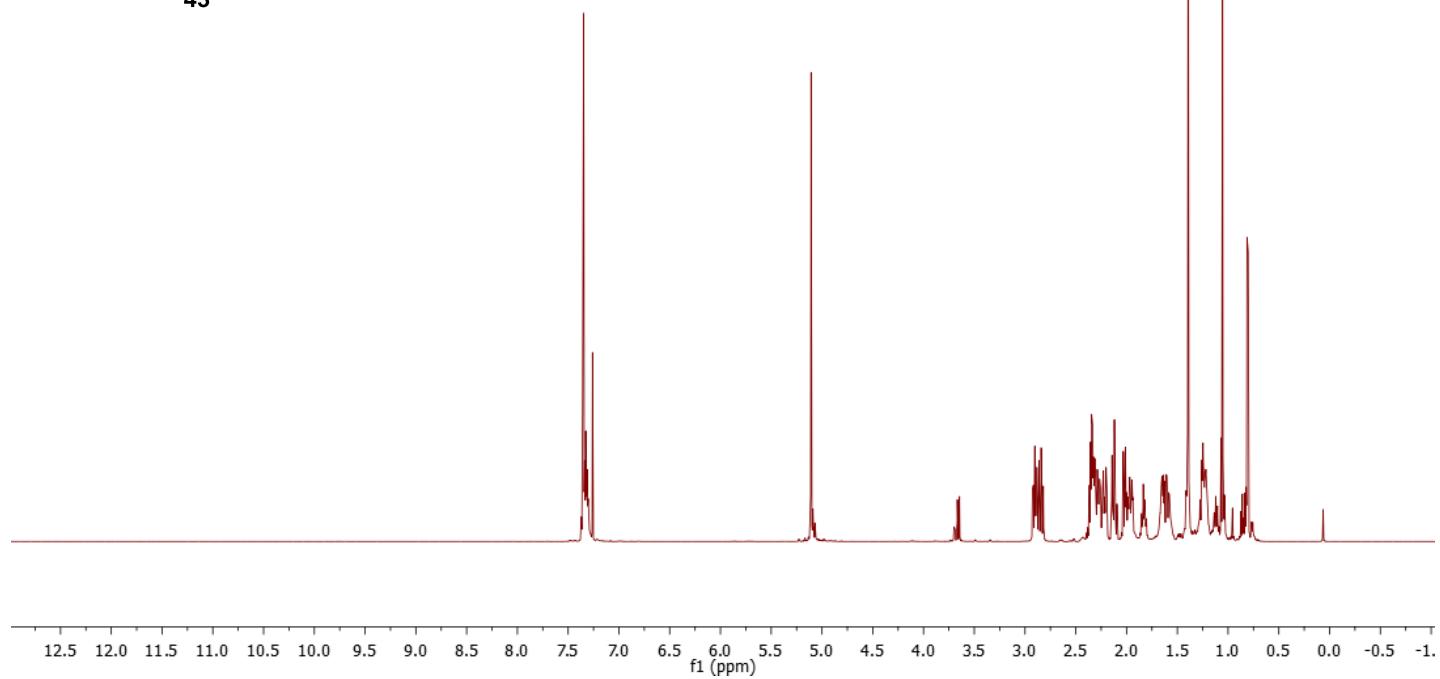
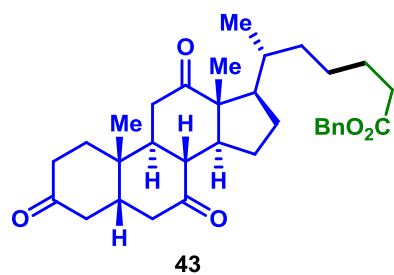
Compound 42 ^1H NMR



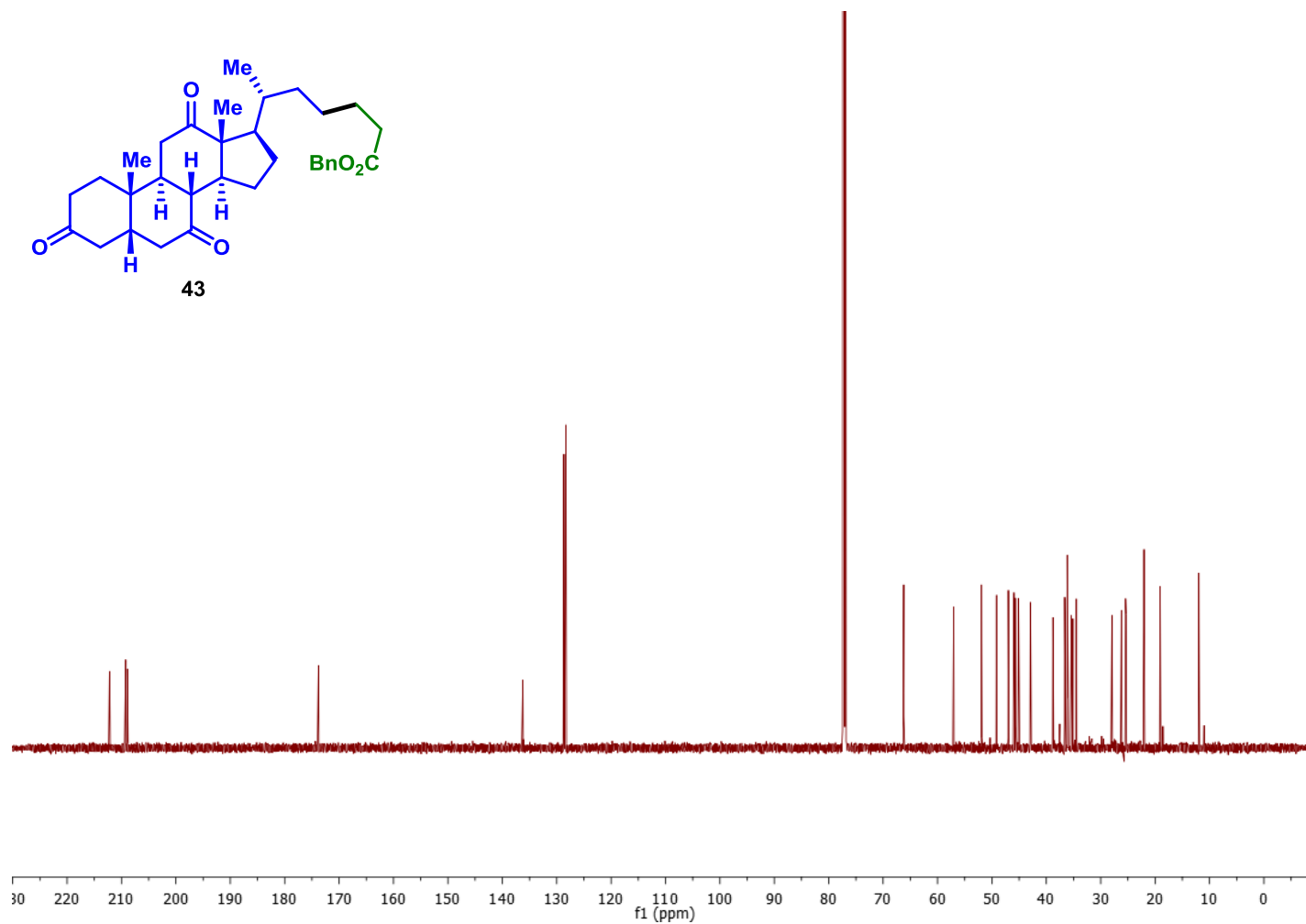
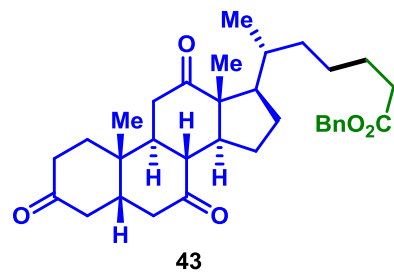
Compound 42 ^{13}C NMR



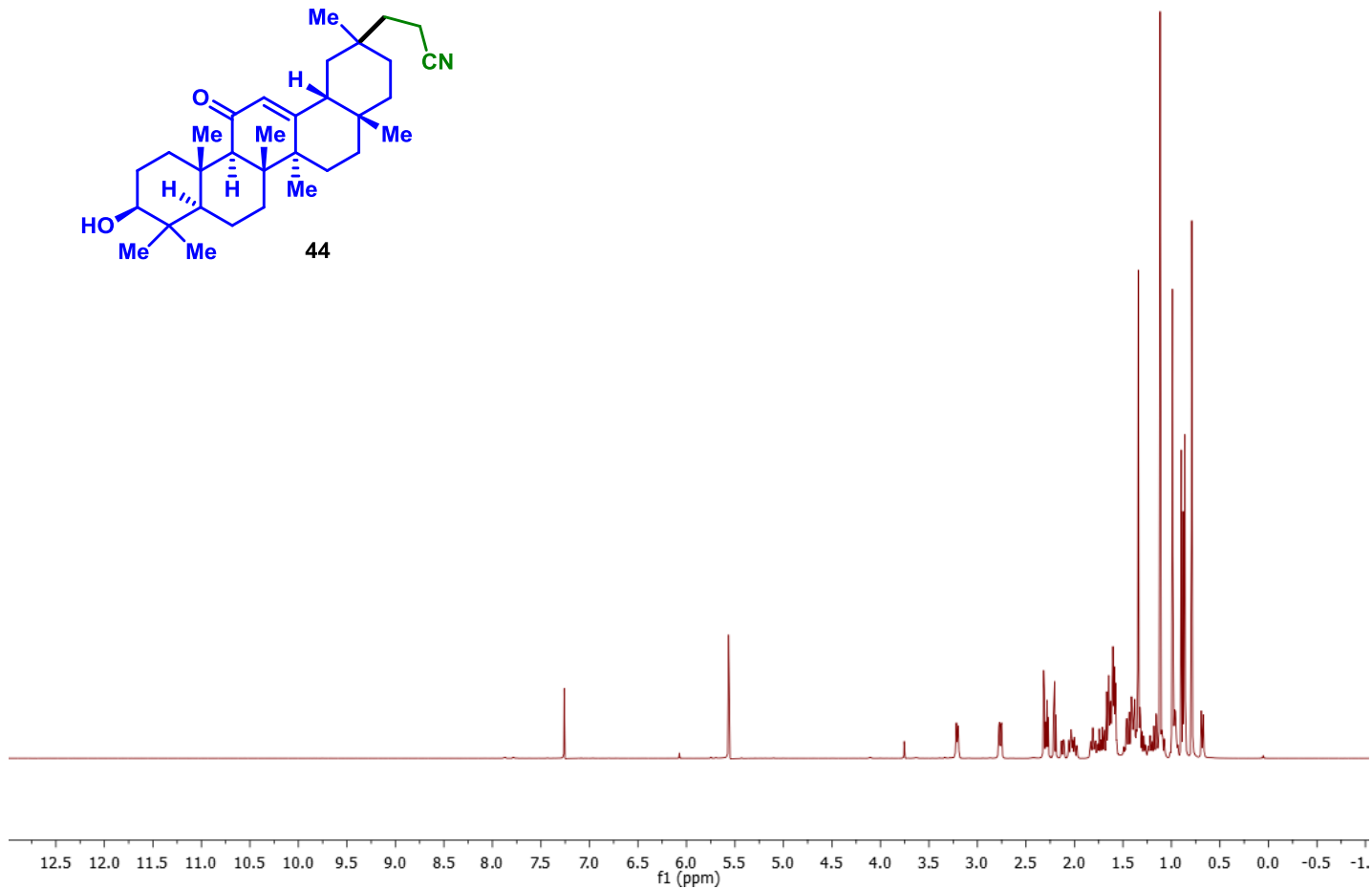
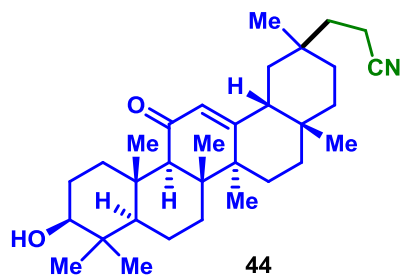
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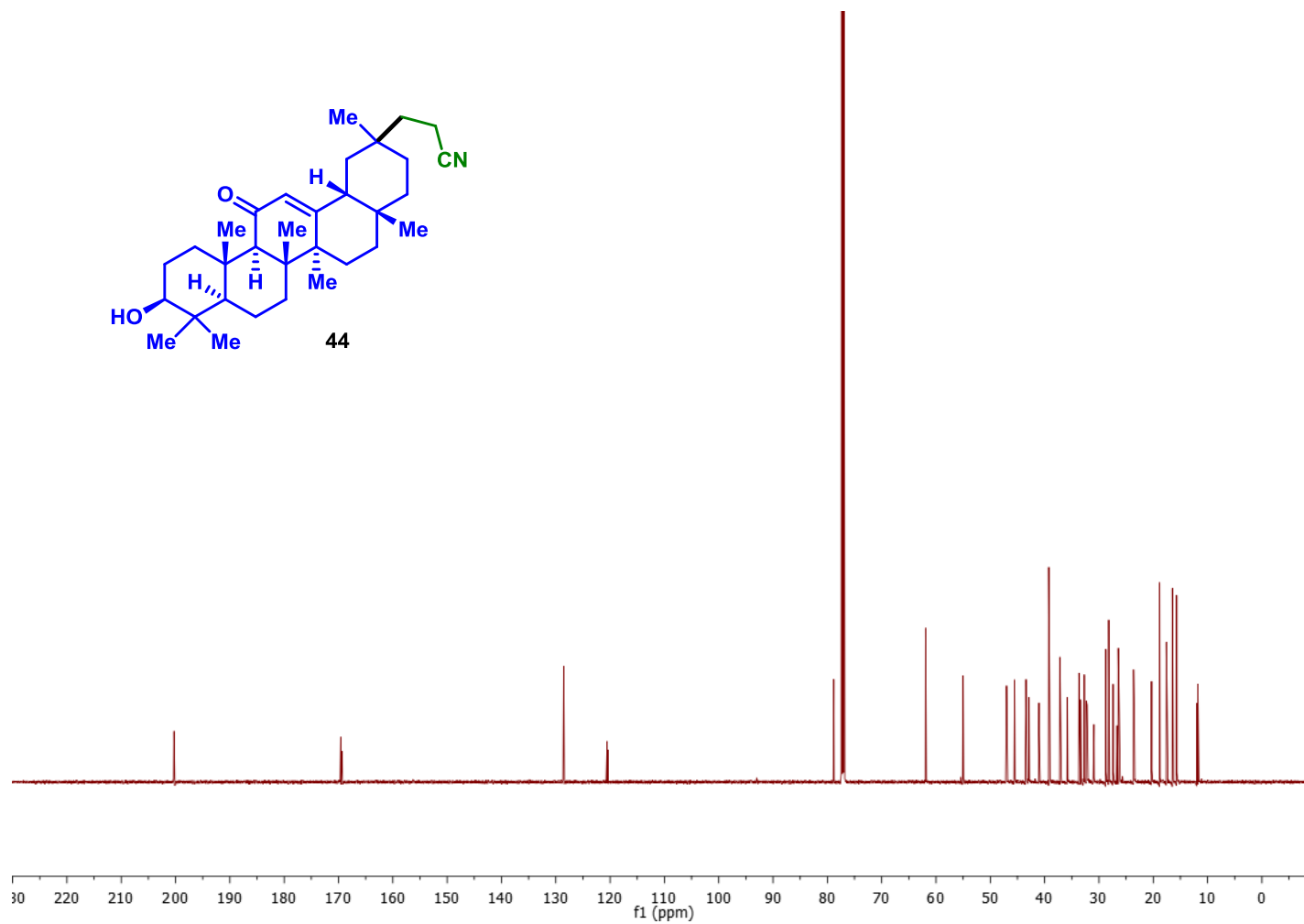
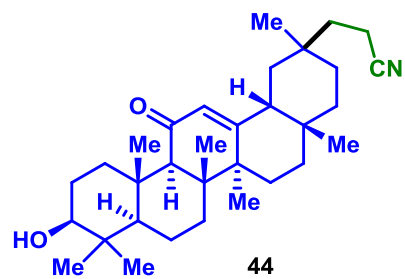
Compound 43 ^{13}C NMR



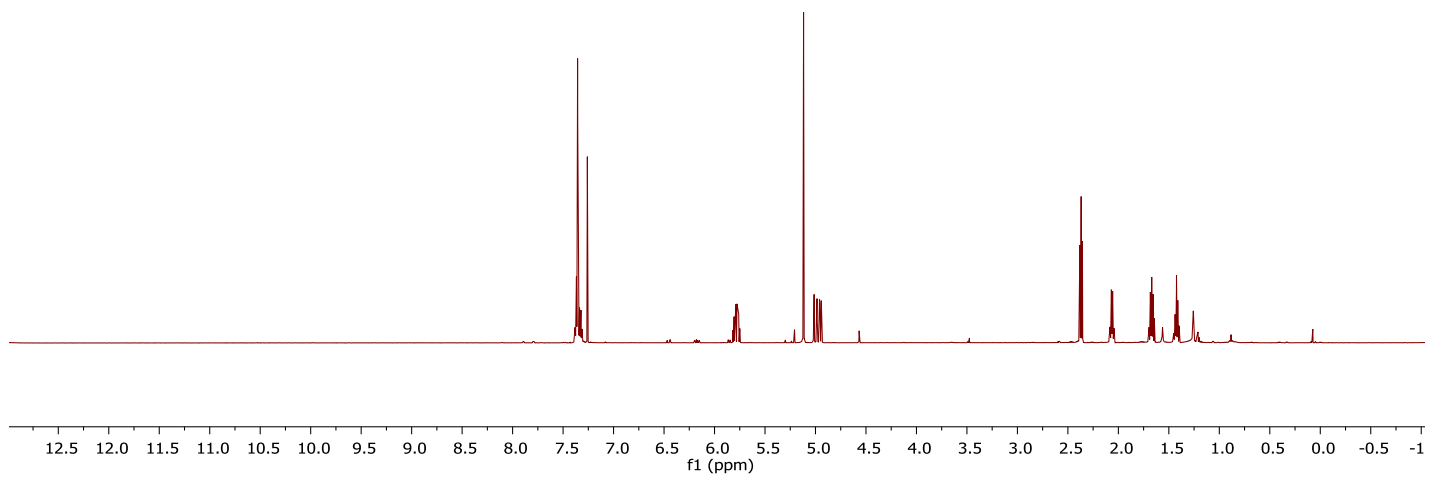
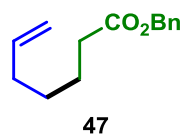
Compound 44 ^1H NMR



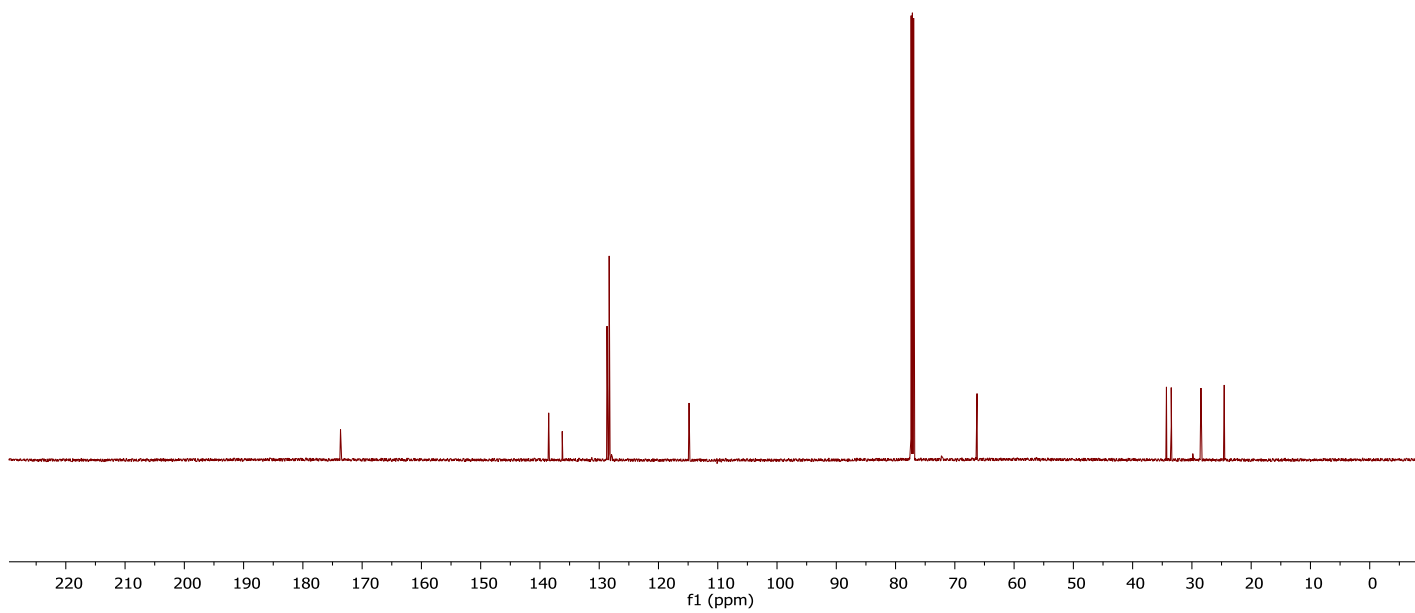
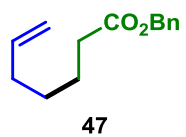
Compound 44 ^{13}C NMR



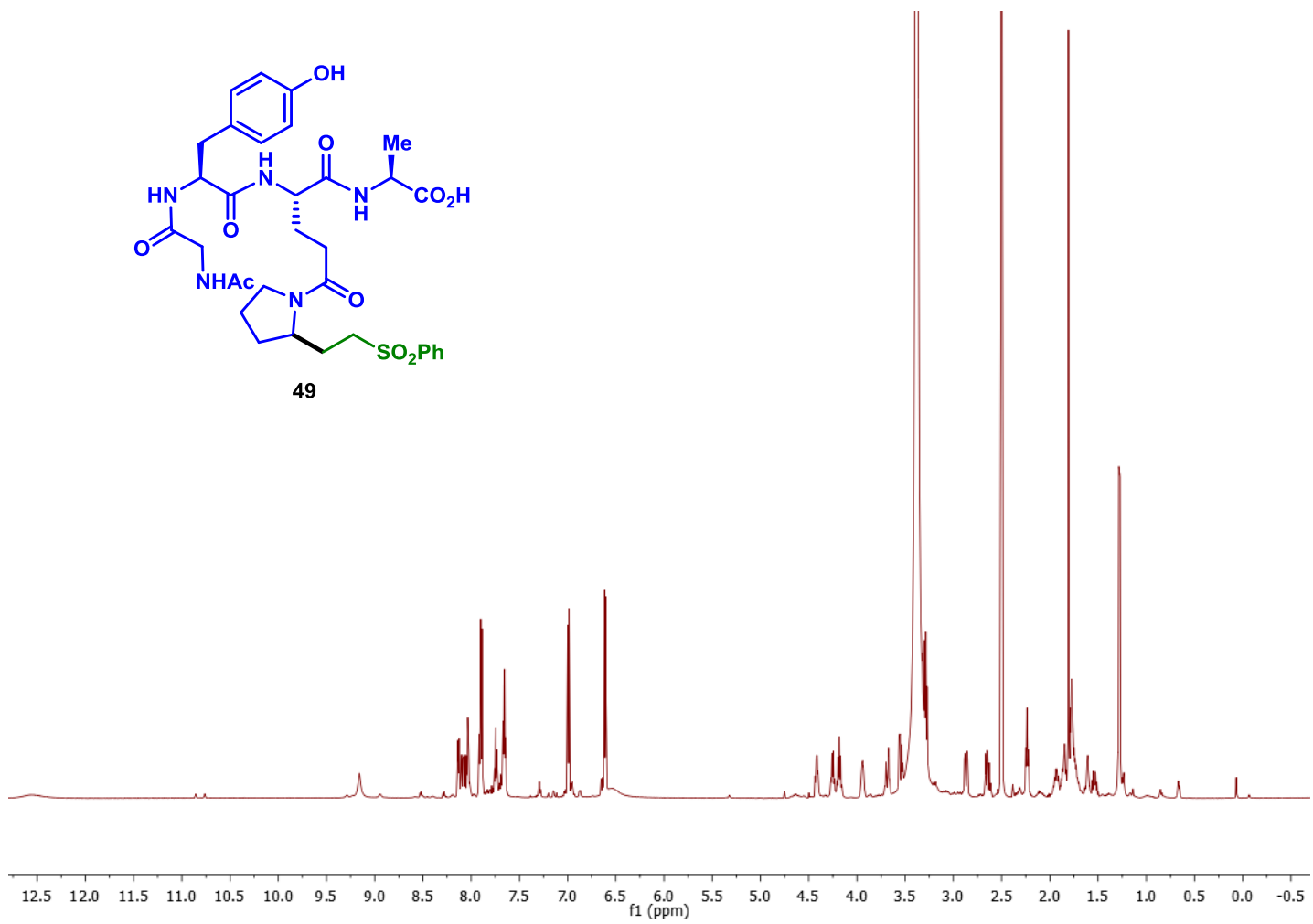
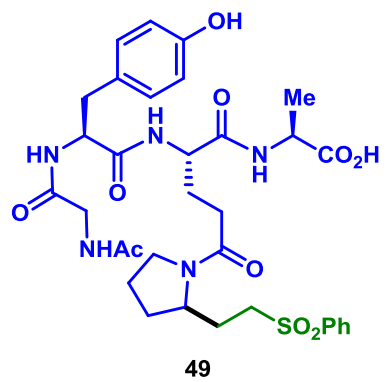
Compound 47 ¹H NMR



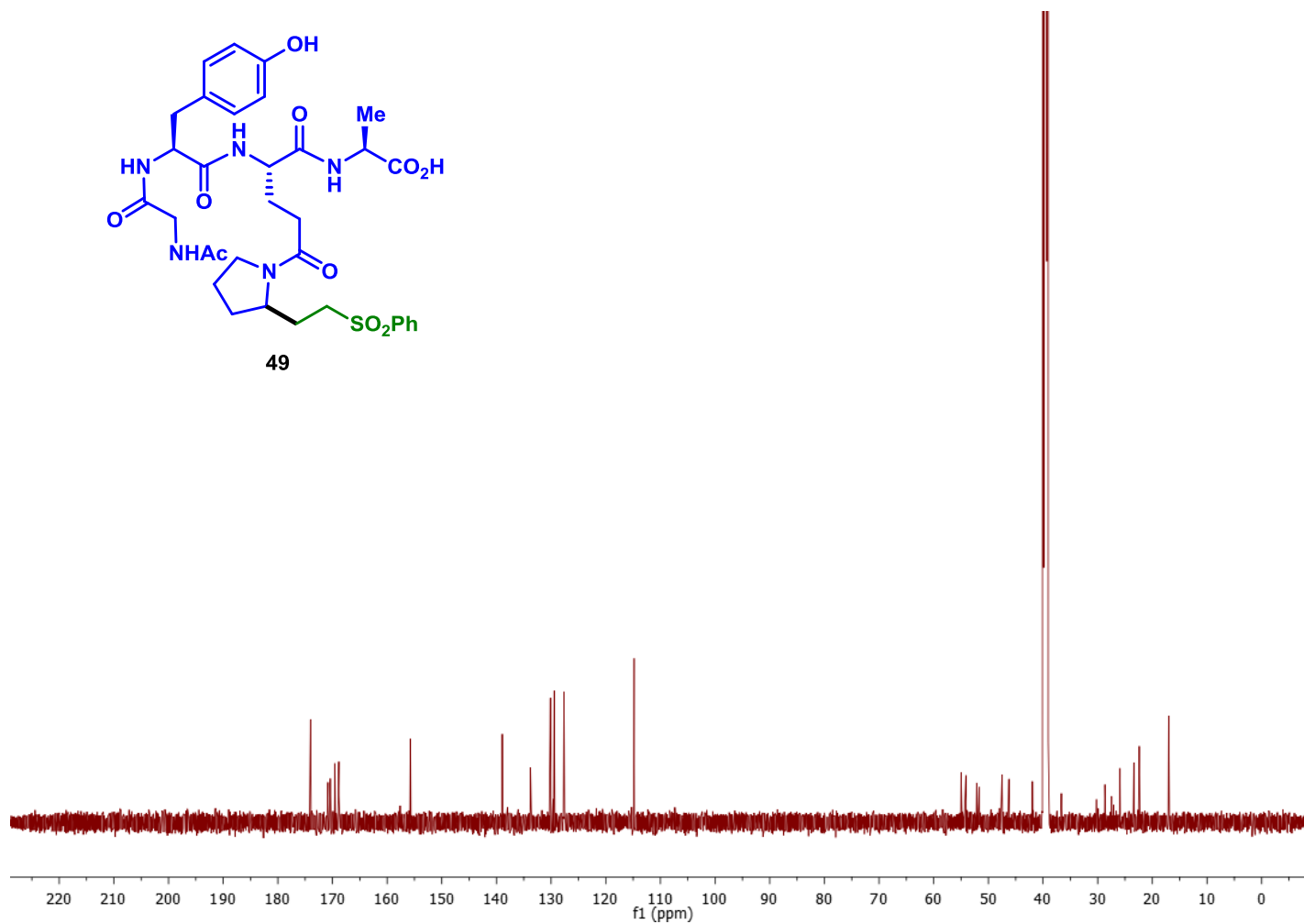
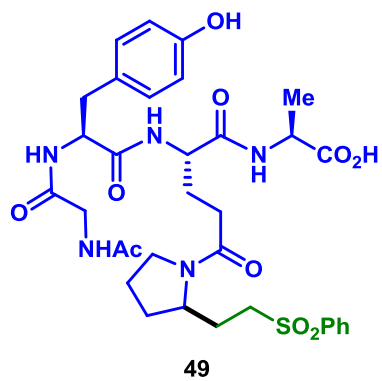
Compound 47 ^{13}C NMR



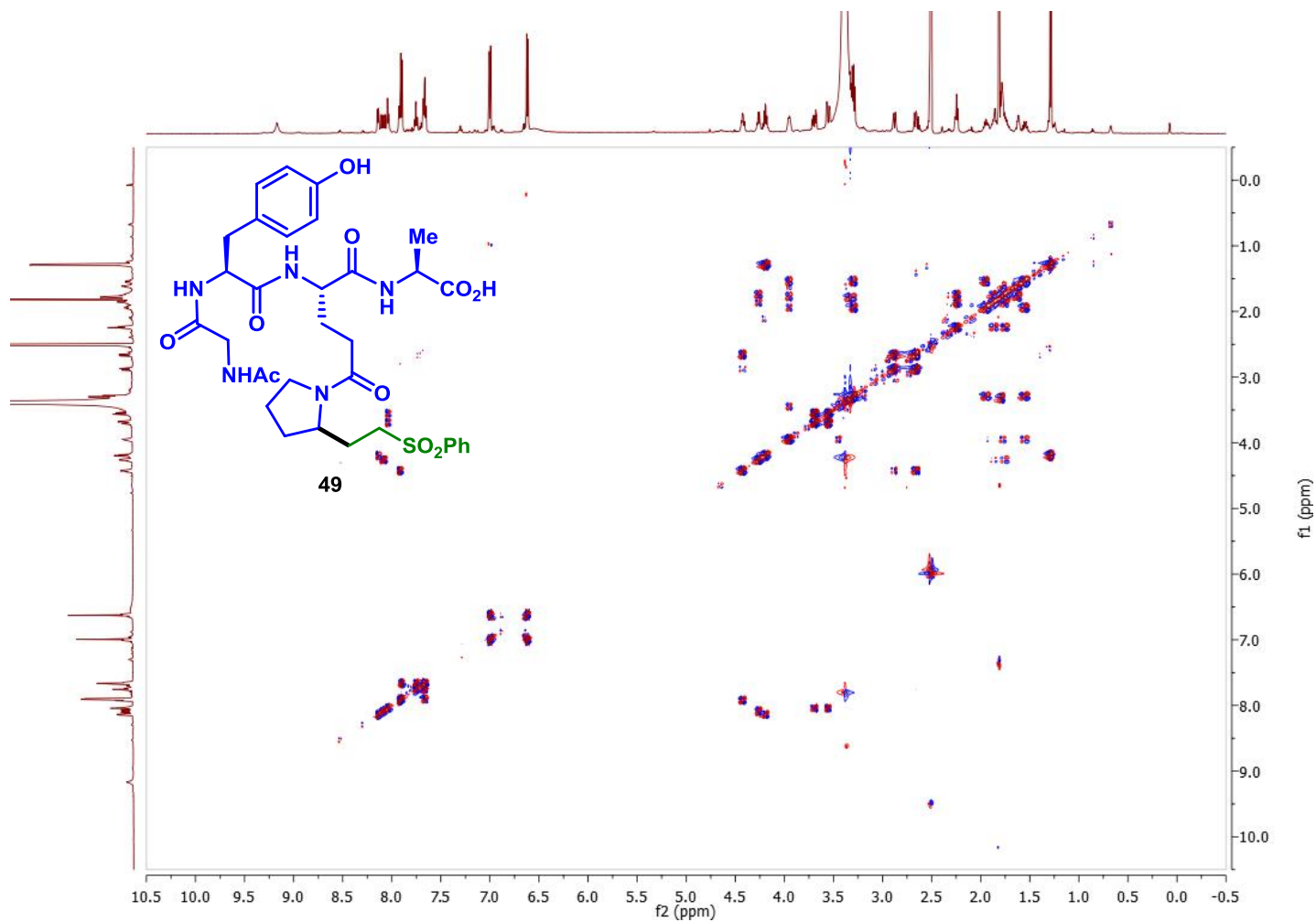
Compound 49 ^1H NMR



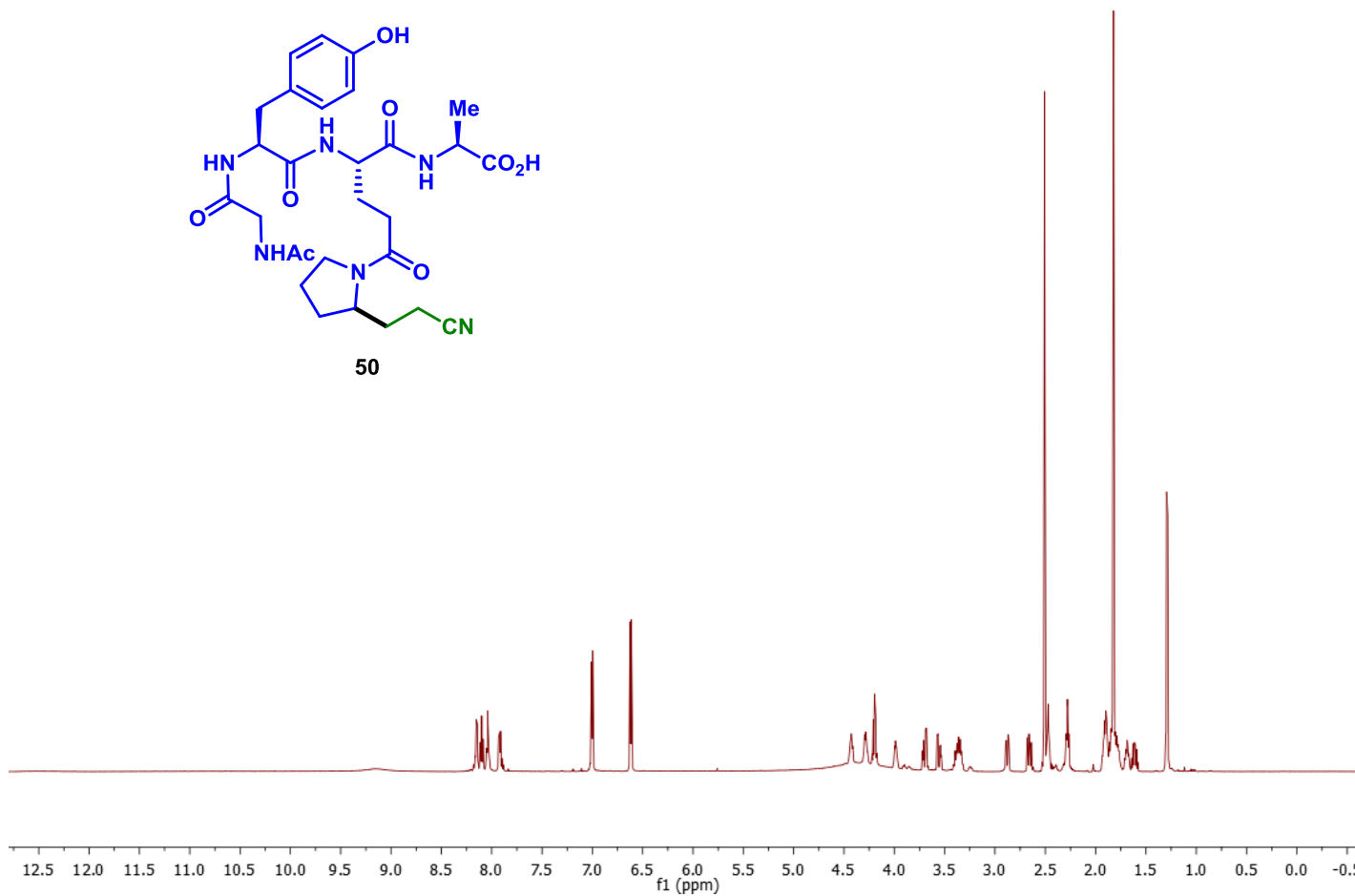
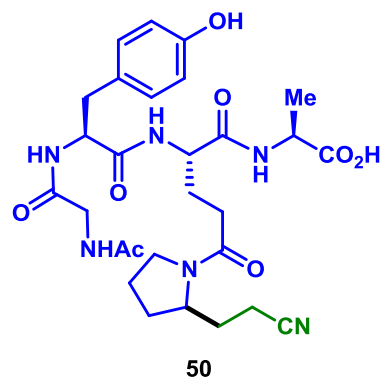
Compound 49 ^{13}C NMR



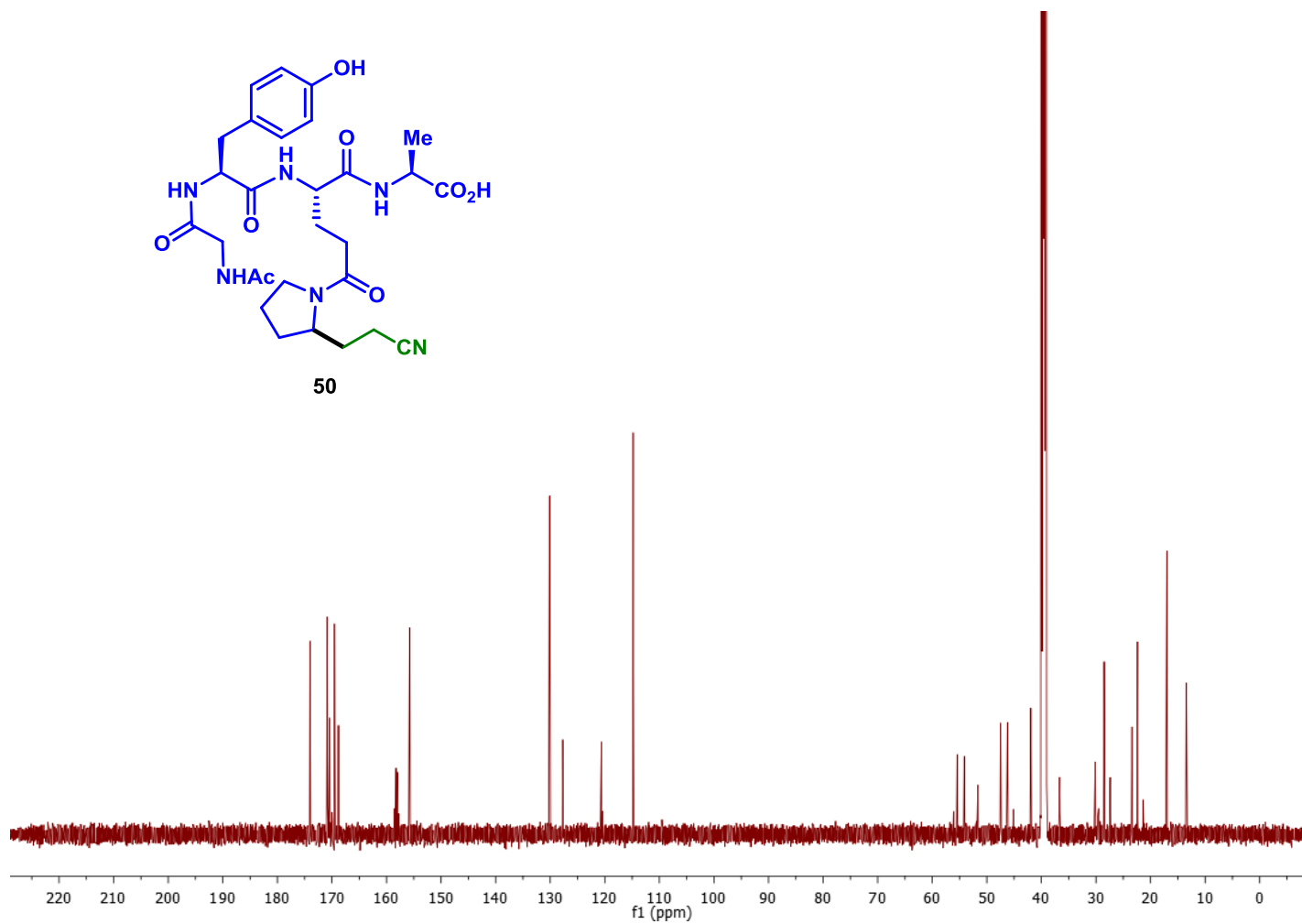
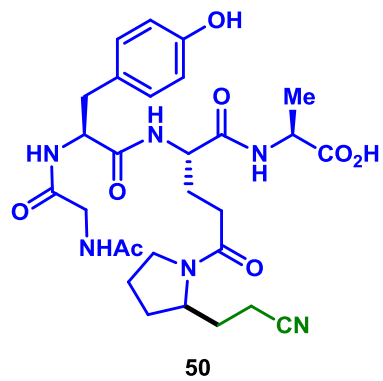
Compound 49 COSY



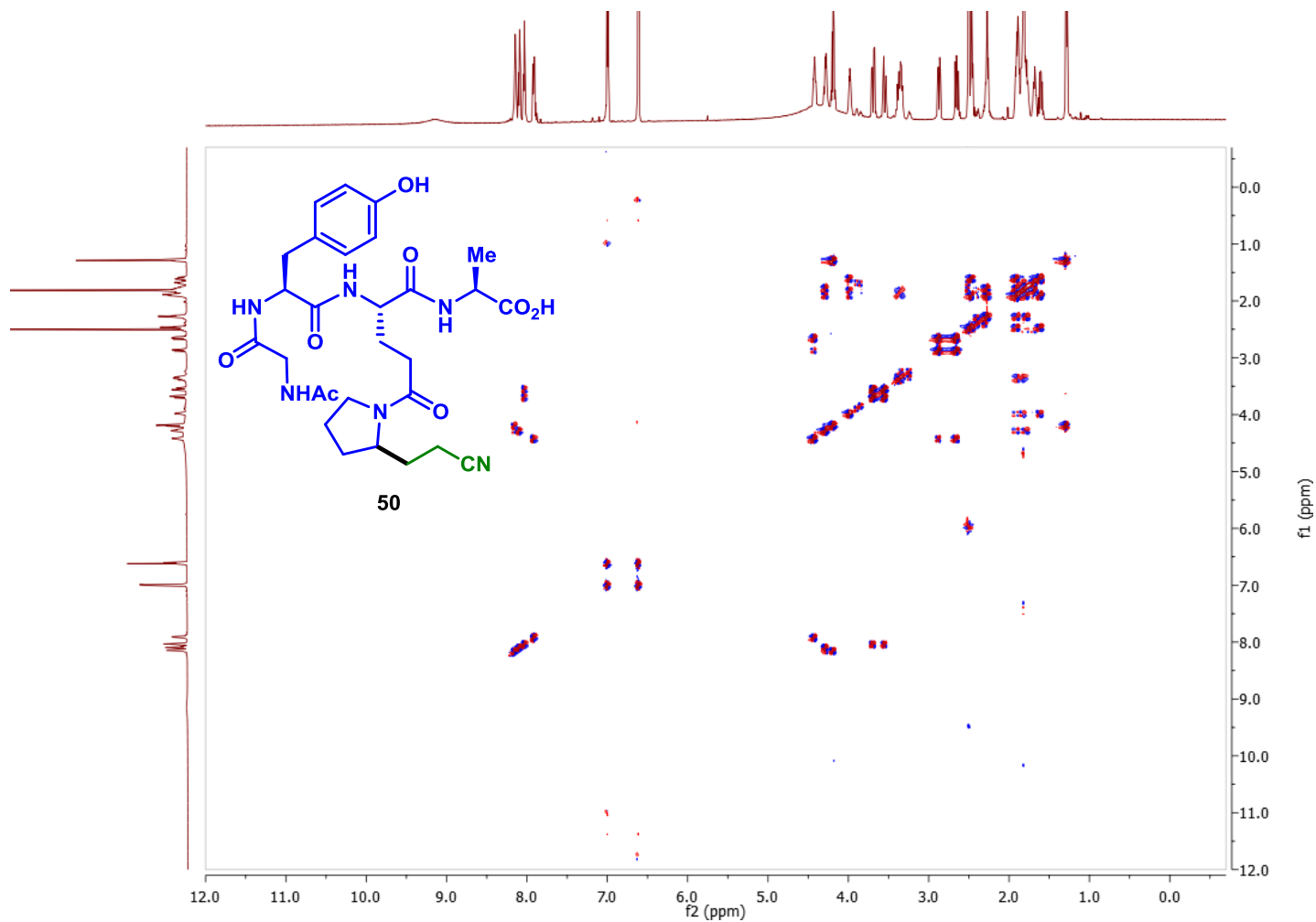
Compound 50 ^1H NMR



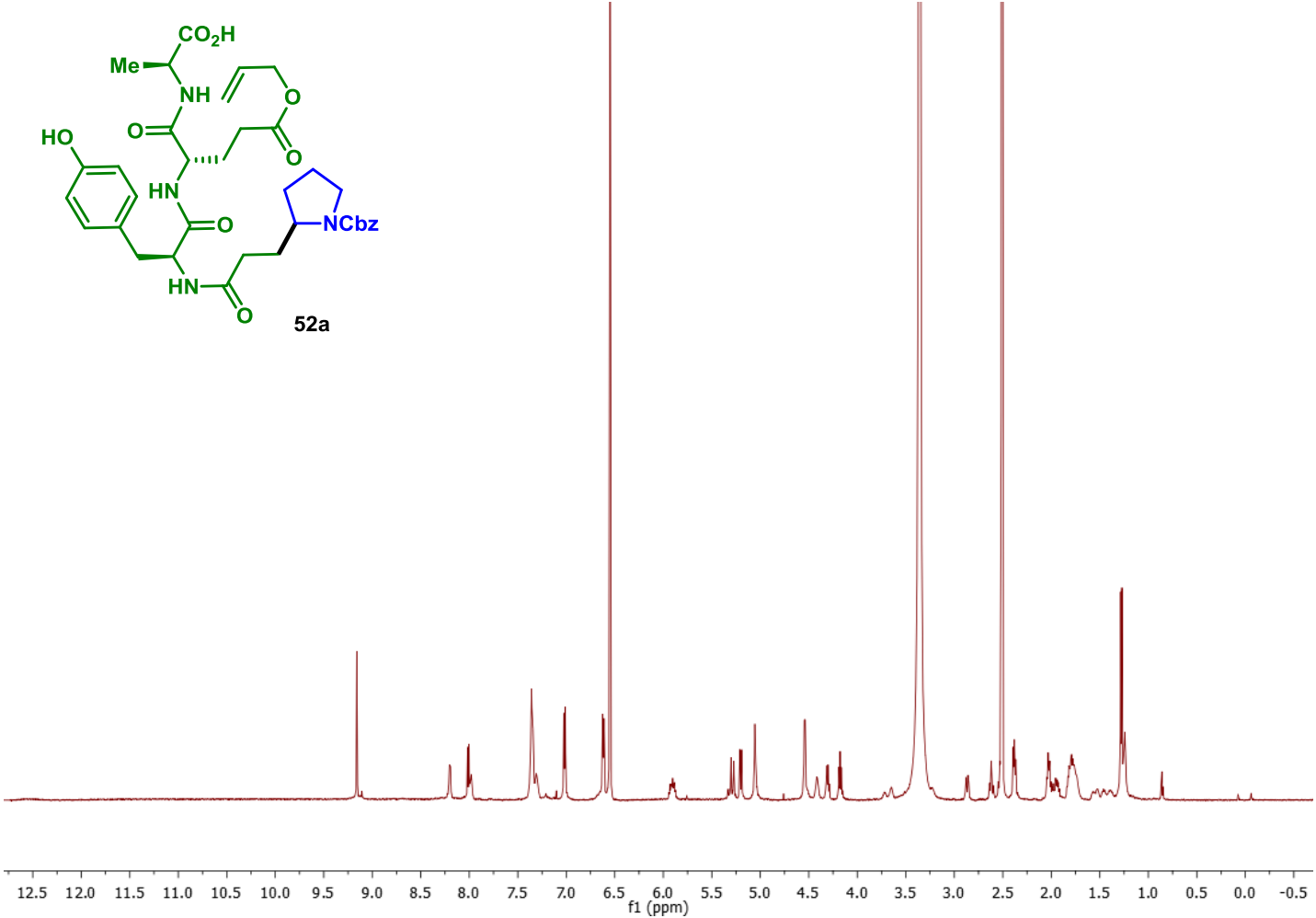
Compound 50 ^{13}C NMR



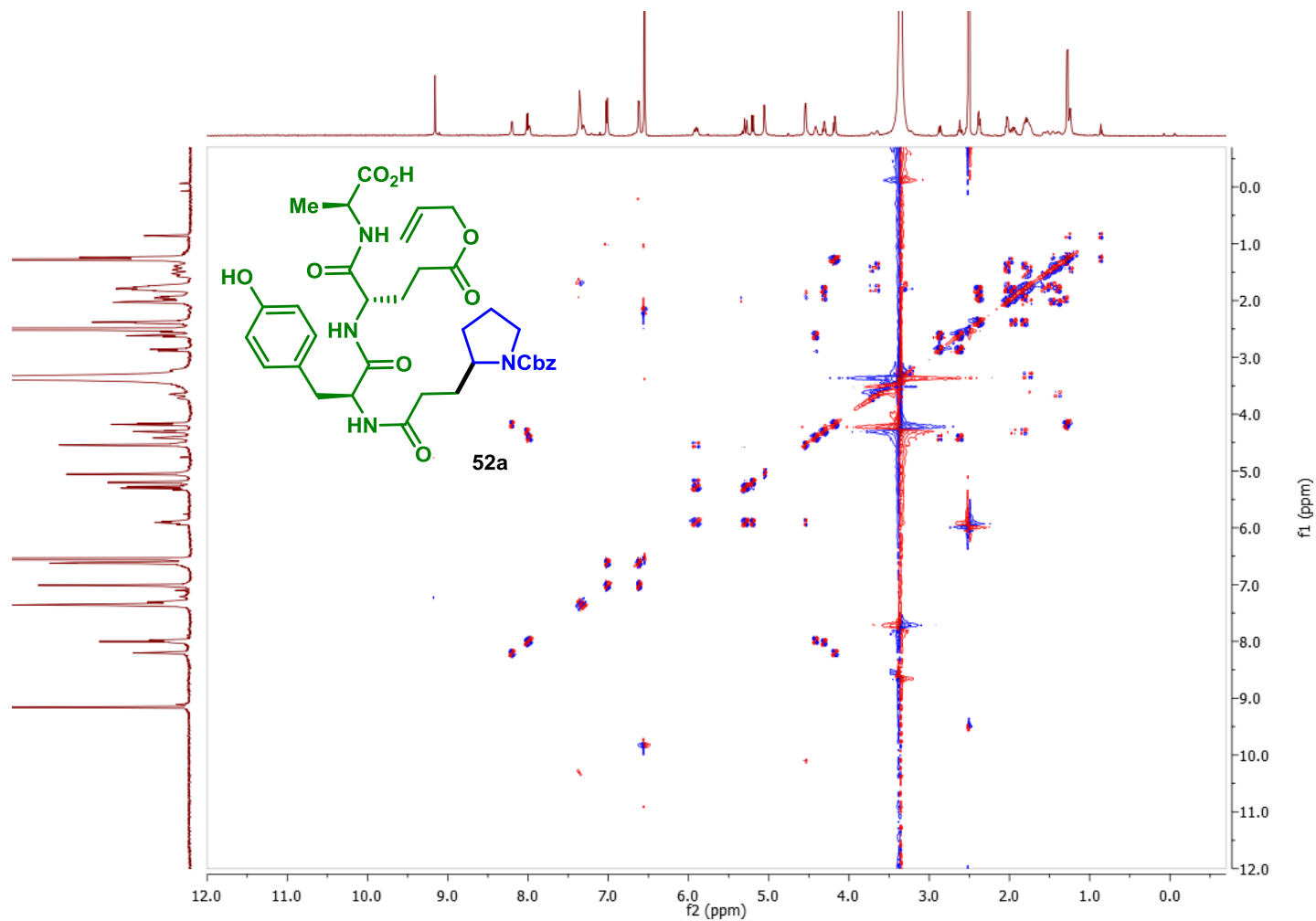
Compound 50 COSY



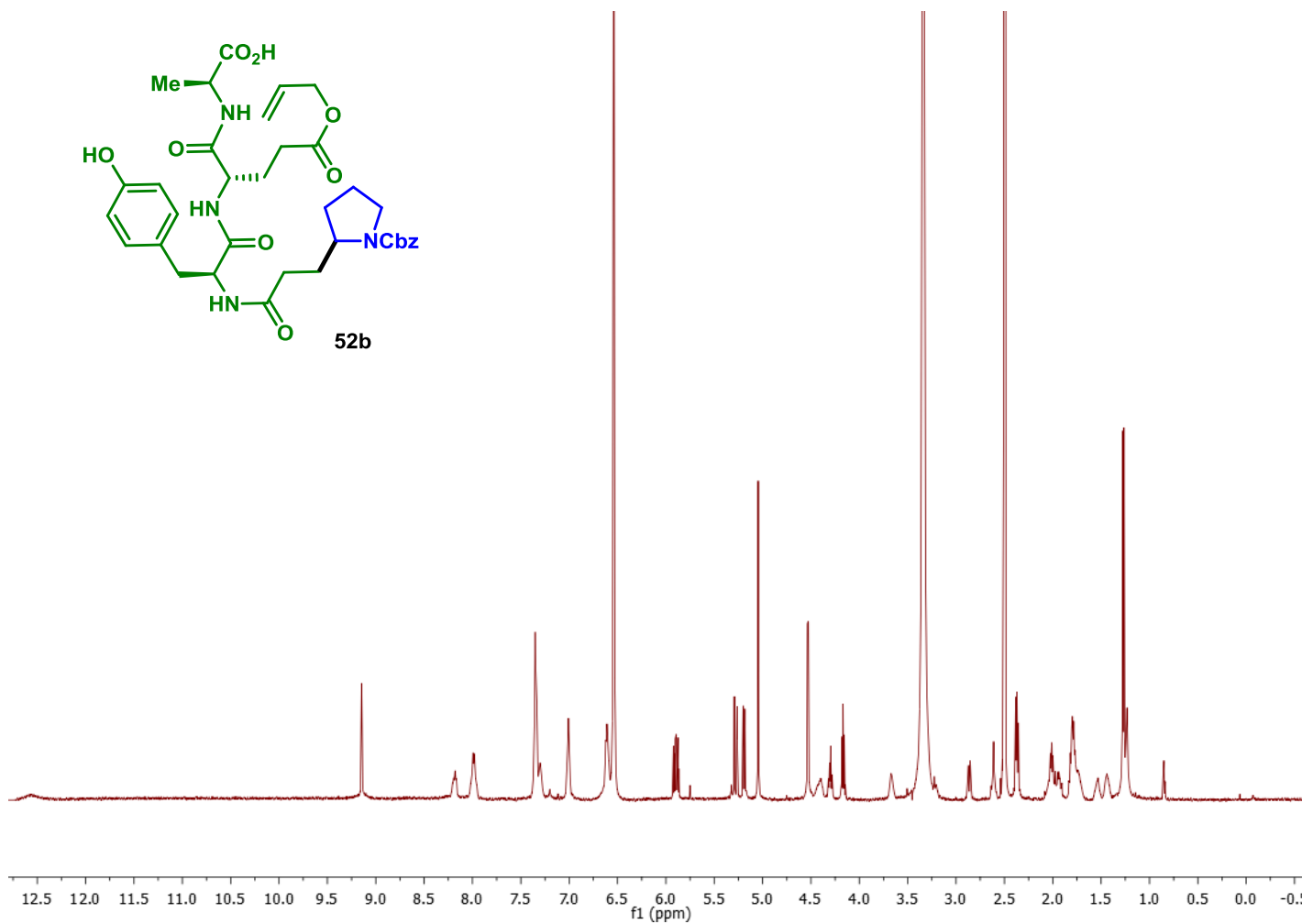
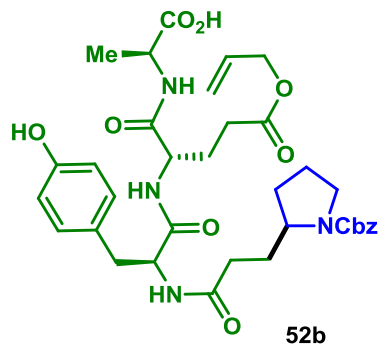
Compound 52a ¹H NMR



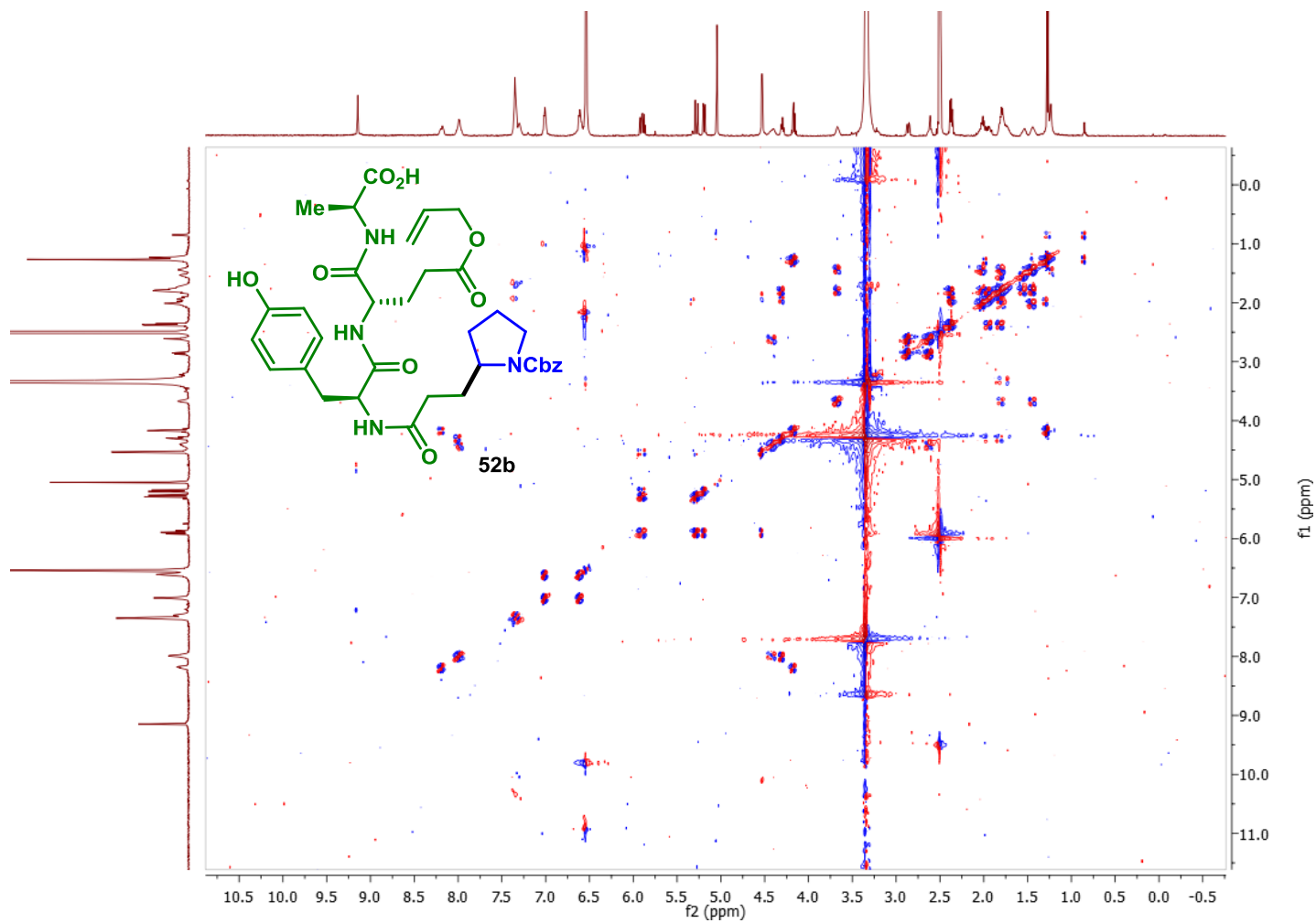
Compound 52a COSY



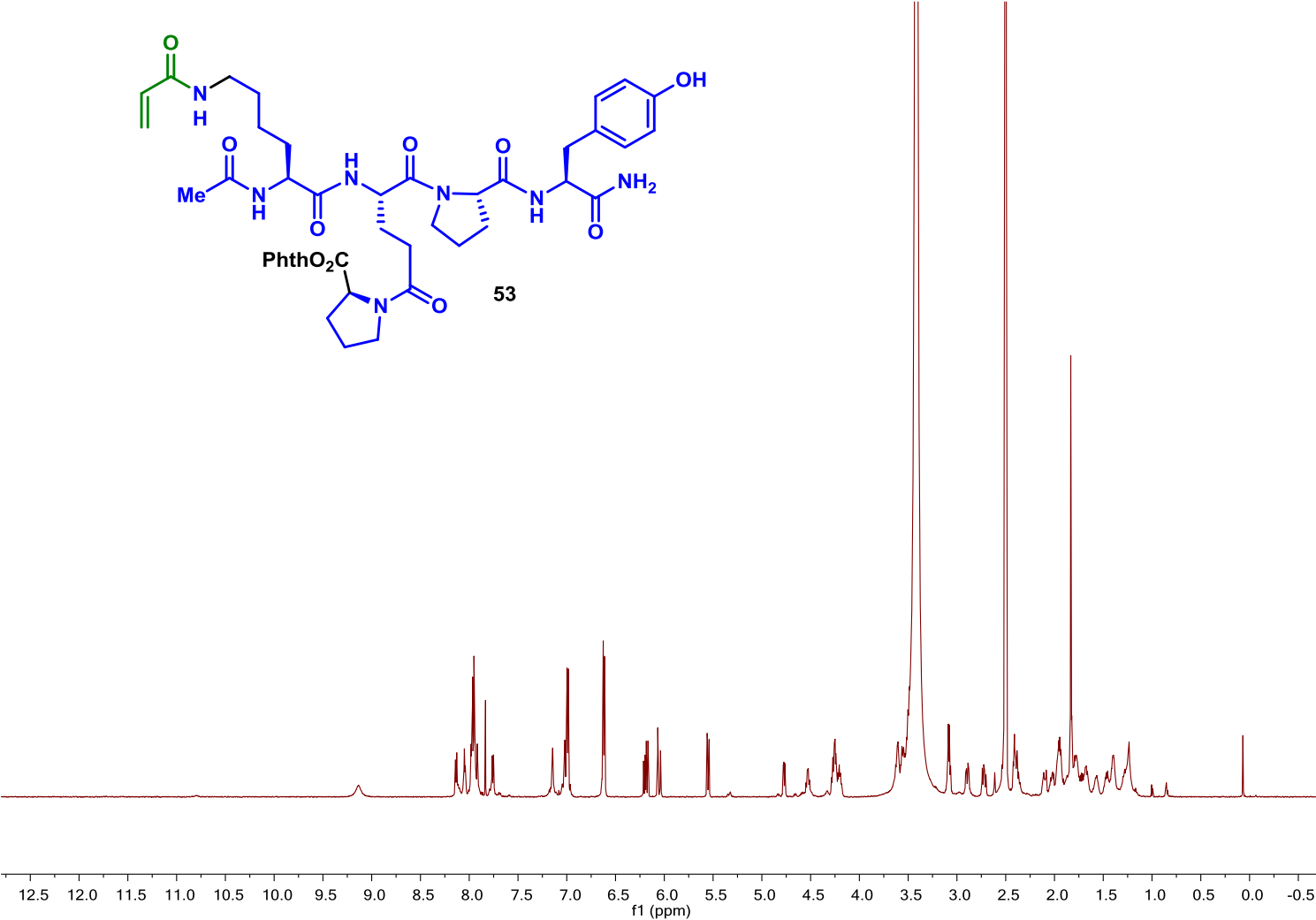
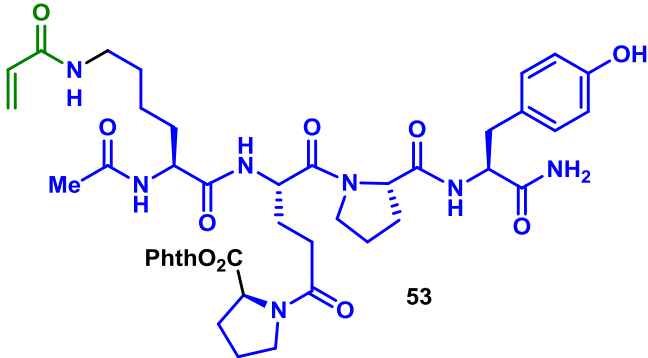
Compound 52b ^1H NMR



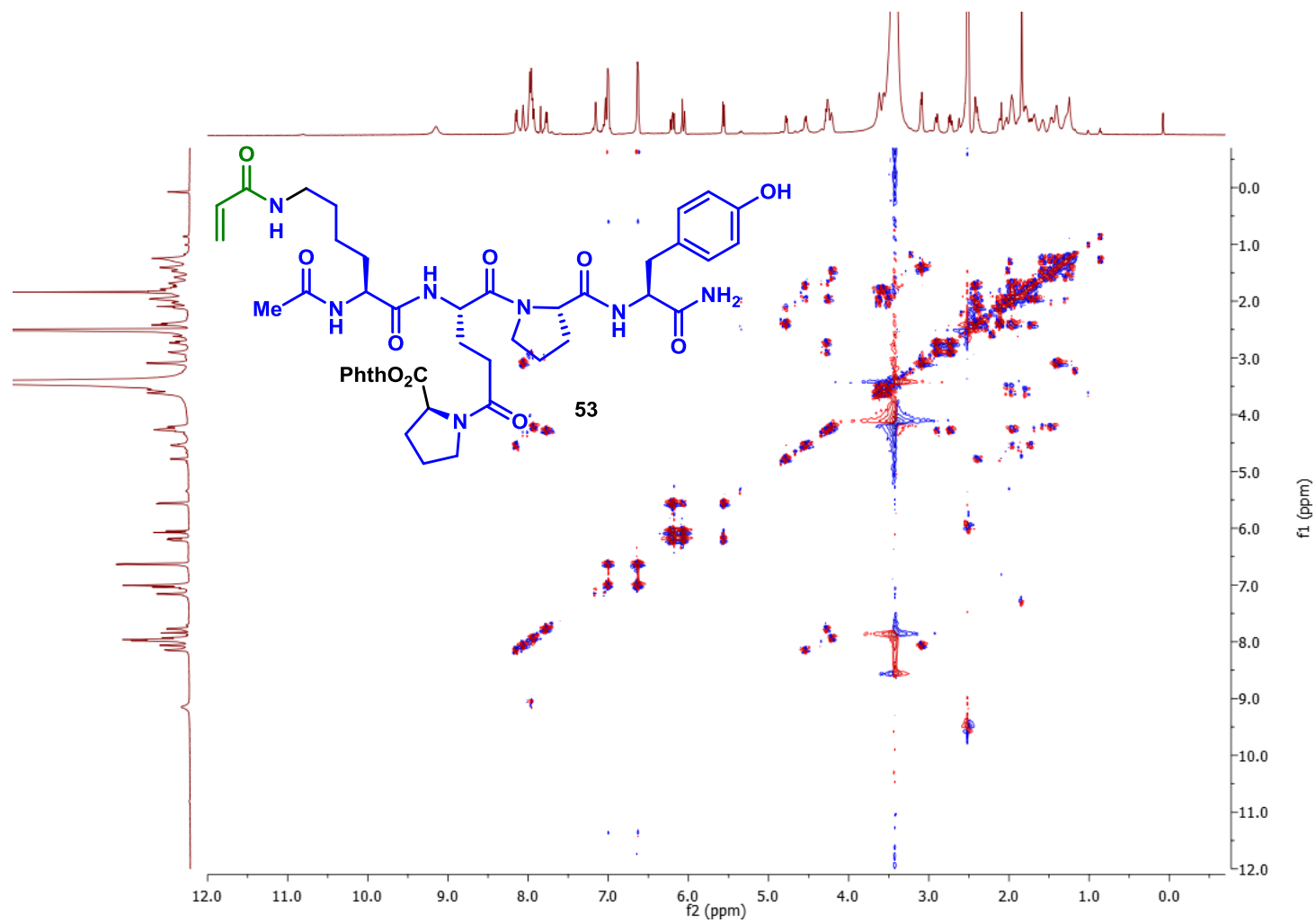
Compound 52b COSY



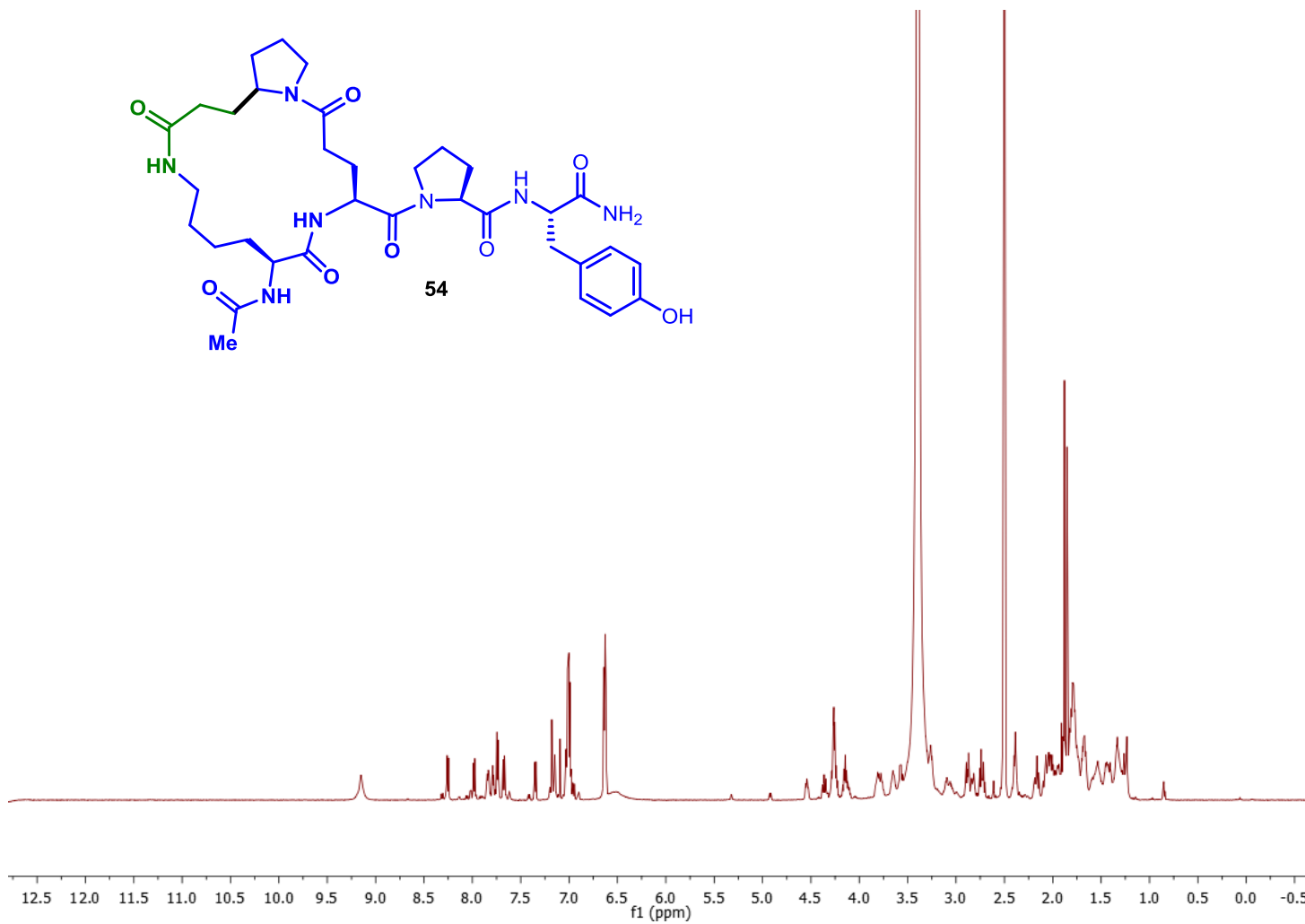
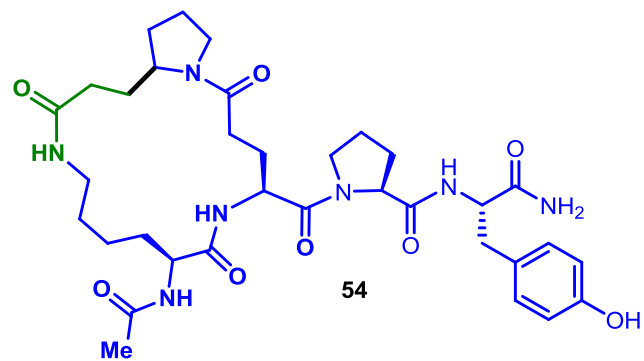
Compound 53 ¹H NMR



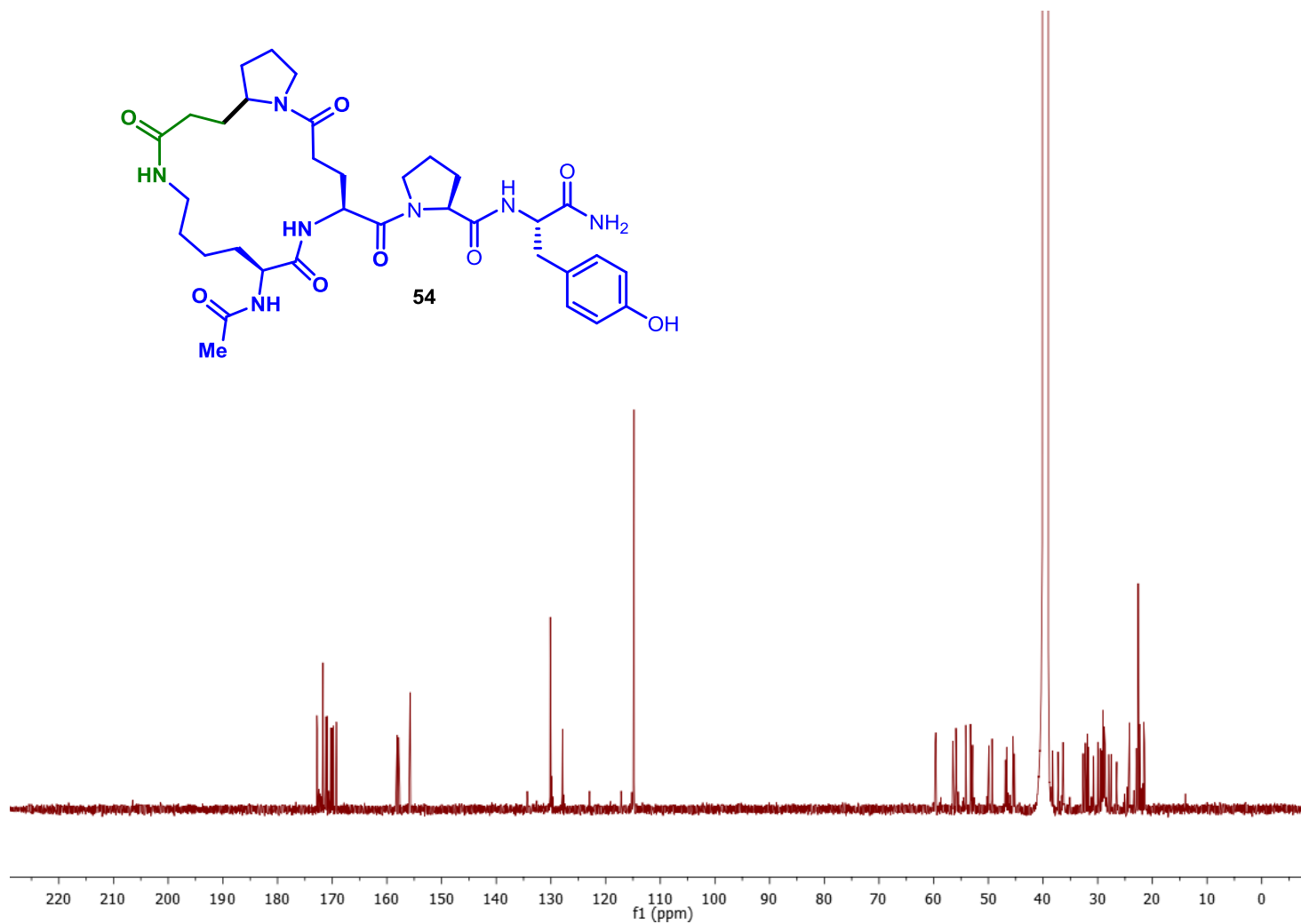
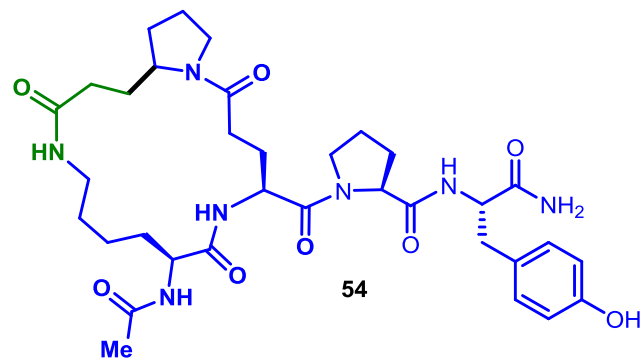
Compound 53 COSY



Compound 54 ^1H NMR



Compound 54 ^{13}C NMR



Compound 54 COSY

