DEVELOPMENT OF THE 2,2,6,6-TETRAMETHYLPIPERIDIN-1-YLOXYCARBONYL (TEMPOC) PROTECTING GROUP AND EFFORTS TOWARDS THE TOTAL SYNTHESIS OF α-CYCLOPIAZONIC ACID

by

Joseph R. Lizza

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DIETRICH SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Joseph R. Lizza

It was defended on

February 25, 2020

and approved by

Dr. Dennis Curran, Distinguished Service Professor of Chemistry and Bayer Professor, Department of Chemistry

Dr. Kazunori Koide, Professor, Department of Chemistry

Thesis Advisor: Dr. Peter Wipf, Distinguished University Professor, Department of Chemistry

DEVELOPMENT OF THE 2,2,6,6-TETRAMETHYLPIPERIDIN-1-YLOXYCARBONYL (TEMPOC) PROTECTING GROUP AND EFFORTS TOWARDS THE TOTAL SYNTHESIS OF A-CYCLOPIAZONIC ACID

Joseph R. Lizza, MS

University of Pittsburgh, 2020

The 2,2,6,6-Tetramethylpiperidin-1-yloxycarbonyl (Tempoc) protecting group is a new carbamate protecting group for various types of amines. Installation can be accomplished using the new reagent 4-nitrophenyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate (NPTC) under mild conditions. Tempoc is stable under strongly acidic and basic conditions, and displays orthogonal deprotection properties when used in tandem with the *tert*-butyloxycarbonyl (Boc) and benzyloxycarbony (Cbz) protective groups. Deprotection can be accomplished under thermolytic conditions at 135 °C, or under reductive conditions with *in situ* generated catalytic Cu(I). Furthermore, Tempoc has also been shown to be a useful protecting group in peptide synthesis. Protecting a broad range of biologically relevant amino esters has been accomplished in the presence of 1-hydroxybenzotriazole (HOBt) as an NPTC activator. Demonstration of Tempoc utility has been realized through the synthesis of a tripeptide fragment of Gramicidin S, a cyclic decapeptide that possesses antimicrobial activity. Unrelated, efforts toward the total synthesis of α-Cyclopiazonic acid are also discussed. The ambitious 1,3-dipolar cycloaddition of a highly substituted aziridine with relatively unactivated dipolarophiles led to interesting results that may be useful for the synthesis of other complex biologicals and natural products.

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LIST OF ABBREVIATIONS

ACP ..... Acyl carrier protein

Alloc ..... Allyloxycarbonyl

Asc ..... Ascorbic acid

Bn ..... Benzyl

Boc ..... *tert*-Butoxycarbonyl

Cbz ..... Benzyloxycarbonyl

CbzCl ..... Benzyl chloroformate

CoA ..... Coenzyme A

CPA ..... Cyclopiazonic acid

DABCO ..... 1,4-Diazabicyclo[2.2.2]octane

DBN ..... 1,5-Diazabicyclo[4.3.0]non-5-ene

DBU ..... 1,8-Diazabicyclo[5.4.0]undec-7-ene

DHA ..... 5-(1,2-dihydroxyethyl)furan-2,3,4(5H)-trione

DIBAL-H ..... Diisobutylaluminum hydride

DIPEA ..... *N*,*N*-Diisopropylethylamine

DMAP 4-Dimethylaminopyridine

DMAPP ..... Dimethylallyl pyrophosphate

DME ..... dimethoxyethane

DMF ..... Dimethyl formamide

Dpm ..... Diphenylmethyl

DPPA ..... Diphenylphosphoryl azide

DSC ..... *N,N′*-Disuccinimidyl carbonate

EDA ..... Ethyl diazoacetate

Fmoc ..... Fluorenylmethoxycarbonyl

HBTU ..... 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HFIP ..... Hexafluoroisopropanol

HMDS ..... Hexamethyldisilazane

HOBt ..... 1H-benzo[d][1,2,3]triazol-1-ol

HPLC-MS ..... High-performance liquid chromatography-mass spectrometry

HRSV ..... Human respiratory syncytial virus

IMDAF ..... Intramolecular Diels-Alder reaction furan

KHMDS ..... Potassium bis(trimethylsilyl)amide

KOTMS ..... Potassium trimethylsilanolate

LAH ..... Lithium aluminum hydride

LC-HRMS ..... Liquid chromatography-high resolution mass spectrometry

LC-MS ..... Liquid chromatography-mass spectrometry

LDA ..... Lithium diisoropylamide

MaoA ..... Monoamine oxidase A

*m*CPBA ..... *meta*-Chloroperoxybenzoic acid

NaAsc ..... Sodium ascorbate

NHS ..... *N*-Hydroxylsuccinimide

NMM ..... *N*-Methylmorpholine

NMO ..... *N*-Methylmorpholine-*N*-oxide

NMR ..... Nuclear magnetic resonance

NPTC ..... 4-Nitrophenyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate

PG(s) ..... Protecting group(s)

PMB 4-Methoxybenzyl

PMP 4-Methoxyphenyl

py ..... Pyridine

SERCA ..... Sarco(endo)plasmic reticulum calcium-ATPases

TBDPS ..... *tert*-Butyldiphenylsilyl

TBDPSCl ..... *tert*-Butyldiphenylchlorosilane

TEMPO 2,2,6,6-Tetramethyl-1-piperidinyloxy

Tempoc 2,2,6,6-Tetramethylpiperidin-1-yloxycarbonyl

TEMPO-H 2,2,6,6-Tetramethylpiperidin-1-ol

TFA ..... Trifluoroacetic acid

THF ..... Tetrahydrofuran

TMP 2,2,6,6-Tetramethylpiperidine

Z ..... Benzyloxycarbonyl

PREFACE

I would like to first and foremost thank my family for their loving support and encouragement throughout the long road it took to get to where I am today. Without them, none of this would be possible. I love you Mom and Dad!

Additionally, I would also like thank Dr. Peter Wipf for providing me with the opportunity for work in his lab. Thank you also to Dr. Dennis Curran and Dr. Kazunori Koide for serving on my committee.

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Special thanks Lori Neu in the glass shop; Tom Gasmire, Jeff Tomaszewski, and Bill Strang in the machine shop; and all members of the electronic shop for their feedback, support, and friendship during my time at the University of Pittsburgh.

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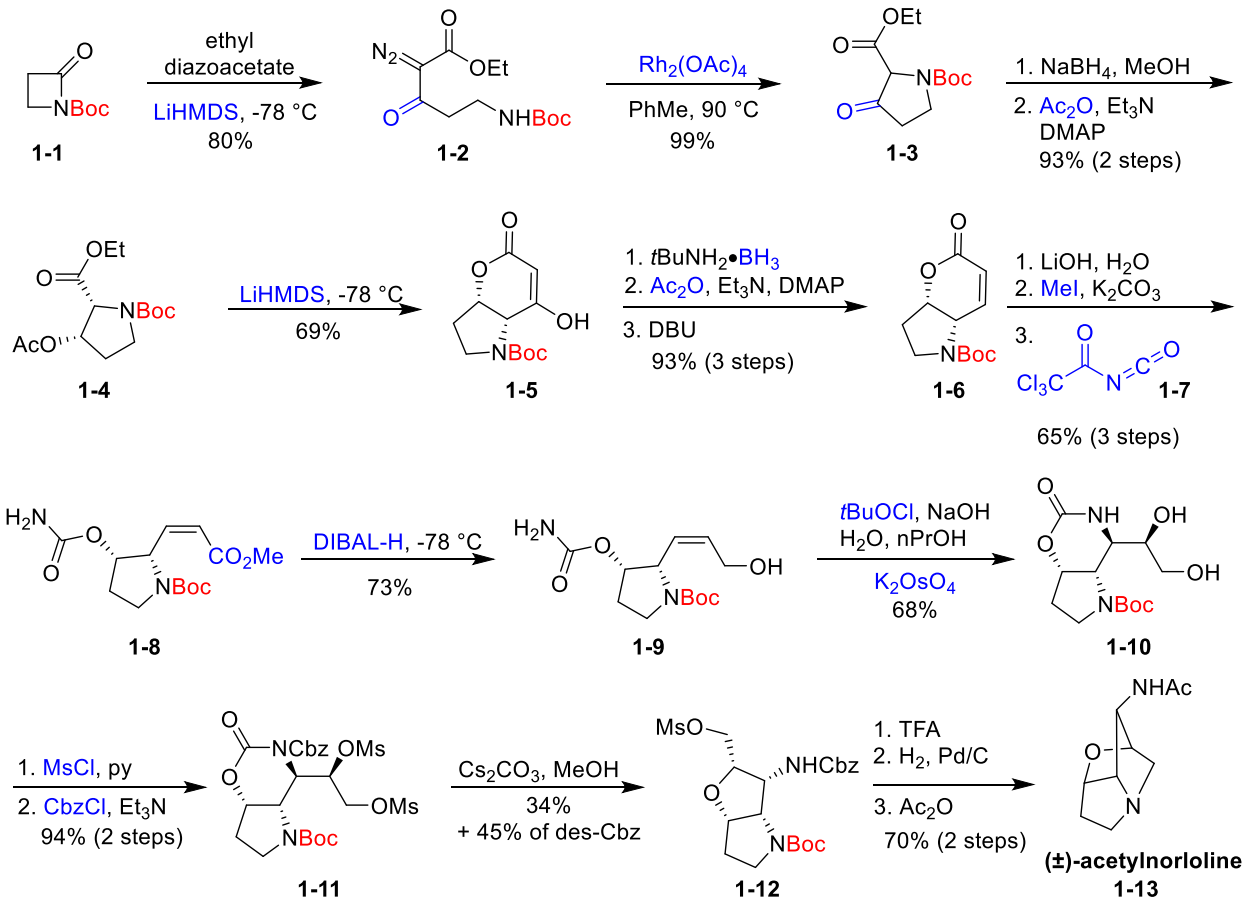
Finally, I would like to thank the members of the Wipf group, current and past, for their companionship and guidance during my time with the group.

1.0 2,2,6,6-TETRAMETHYLPIPERIDIN-1-YLOXYCARBONYL (TEMPOC): A PROTECTING GROUP FOR PRIMARY, SECONDARY AND HETEROCYCLIC AMINES[1]

1.1 INTRODUCTION

1.1.1 Protection of amines in organic synthesis

The increasing complexity of synthetic approaches to functionally dense molecular scaffolds demands the use of protecting groups (PGs).[2] The use of PGs enables targeted transformations on a desired part of a molecule in the presence of other sensitive and reactive centers. As such, PGs play a critical role in carbohydrate,[3] peptide,[4] and small molecule synthesis.[5] Synthetic chemists are continually designing functionally dense, more reactive molecules and embarking on expeditious total syntheses, requiring an adaptive and expansive library of orthogonal protecting groups.[6,7] Orthogonality is defined as the ability to remove a PG selectively in the presence of sensitive functionalities, such as other PGs.[8] Amines are among the most common functionalities found in pharmaceuticals, natural products, and their synthetic intermediates.[9–11] Amine nucleophilicity, basicity, and tendency to coordinate to transition metals, demand the use of protecting groups in order for chemical transformations to achieve proper chemoselectivity, minimal side-products, or even proceed at all. An example of amine protection is in Sheerer's synthesis of (±)-acetylnorloline in 2011 (Scheme 1).[12]



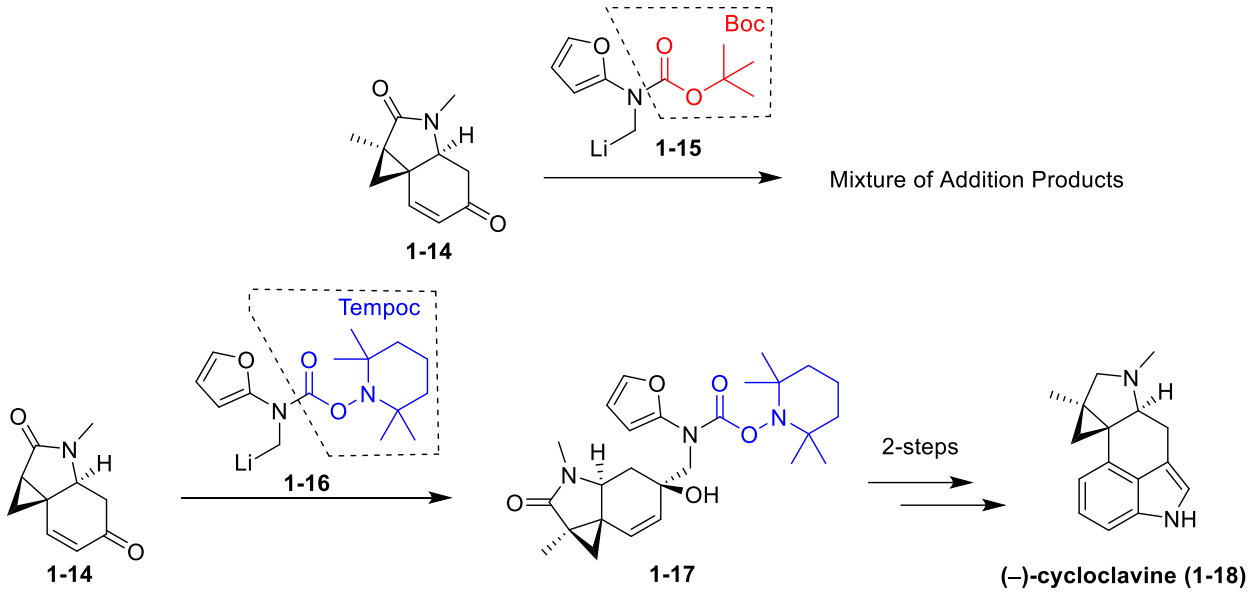
Scheme 1 An example of amine protection using the *tert*-butyloxycarbony (Boc) group from Sheerer's 2011 synthesis of racemic acetylnorloline

The authors started with N-protected lactam **1-1** and the protecting group (red) was maintained until 2-steps before the final transformation. The amine protection was crucial, as the 18-step sequence contains numerous basic-amine-incompatible reagents and functional groups (blue) such as strong bases, electrophiles, transition metals, and undesired self-condensations. While trifluoroacetyl,[13] tosyl,[14] nosyl,[15,16] phthaloyl,[17] and trityl[18] are frequently used for amine protection, carbamates with *tert*-butyloxycarbonyl (Boc),[19] benzyloxycarbonyl (Cbz),[19] 9-fluorenylmethoxycarbonyl (Fmoc),[20] and allyloxycarbonyl (Alloc)[21] substituents are among the most common and versatile amine protecting groups used across all branches of chemistry. Importantly, carbamate derived PGs find widespread use in the protection of amines due to their

robustness, ease of deployment and removal, and orthogonal nature. Consequently, new chemical variants are continually being developed.[22,23] Typical deprotection conditions involve acidic (Boc), basic (Fmoc) or hydrogenolytic (Cbz) conditions and numerous methods have been published, such as TFA,[24] HCl,[25] H_2/Pd,[26] Et_3SiH/Pd,[27] and Mg/MeOH.[28] Unfortunately, deprotection with these conditions can promote numerous side reactions (for example, over-reductions,[29] rearrangements,[30] and epimerizations[31]).

1.1.2 First use of Tempoc as a protecting group

In McCabe's recent total synthesis of (–)-cycloclavine, a base-stable amine protecting group that could be subjected to tin-lithium transmetallation followed by 1,2-addition on enone **1-14** was required, and it was strategized that the protecting group would ideally be cleaved during a subsequent intramolecular Diels-Alder furan (IMDAF) cycloaddition (Scheme 2).[32] Following a survey of carbamate protecting groups identified 2,2,6,6-tetramethylpiperidin-1-yloxycarbonyl (Tempoc) group as a superior protecting group. Specifically, Tempoc derivative **1-16** resulted in the best yield and chemoselectivity in the transmetallation/addition step to furnish prerequisite amino alcohol **1-17**, and could be cleaved during the subsequent Diels-Alder reaction using milder conditions of 135 °C in toluene versus microwave irradiation at 180 °C required for Boc derivative **1-15**. With this utility in mind, we sought to develop the Tempoc group as a synthetically useful tool for the protection of primary, secondary, and heterocyclic amines.

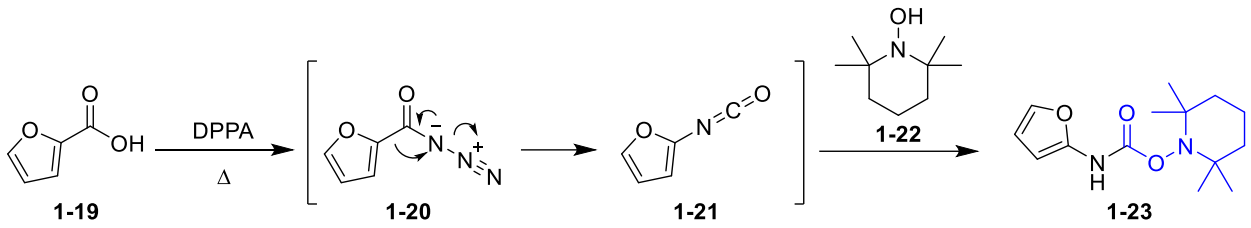


Scheme 2 The first use of the Tempoc protecting group in the 2017 synthesis of (−)-cycloclavine

1.2 RESULTS AND DISCUSSION

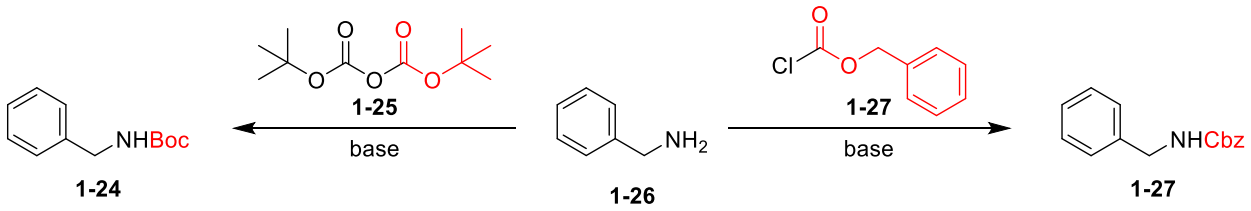
1.2.1 Development of Tempoc transfer reagent 4-nitrophenyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate (NPTC)

While in McCabe's synthesis of cycloclavine, Tempoc was installed through a diphenylphorhoryl azide (DPPA) mediated Curtius rearrangement of furan carboxylic acid **1-19** in the presence of TEMPO hydroxylamine **1-22** (TEMPO-H), this would not be practical for the general installation of Tempoc on a variety of amines (Scheme 3). Therefore, studies towards a new Tempoc transfer agent were conducted.



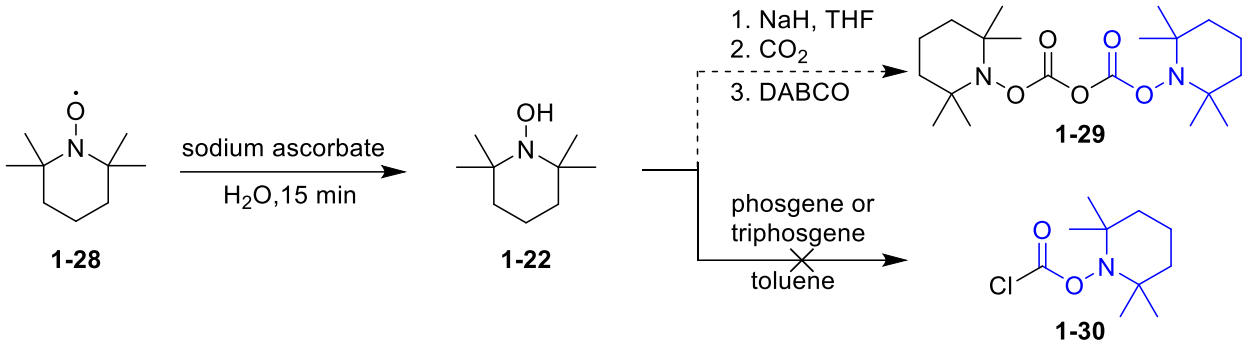
Scheme 3 The Curtius rearrangement used to form Tempoc in McCabe's 2017 synthesis of (−)-cycloclavine

Amines are typically protected through a carbamolyation reaction with an activated form of the target protecting group. For instance, the Boc protection of benzylamine **1-26** can be achieved through reaction with di-*tert*-butyl dicarbonate **1-25** (Boc anhydride or Boc_2O) (Scheme 4). Alternatively, Cbz protection is conveniently achieved upon treatment of the amine with benzyl chloroformate **1-27** (CbzCl).



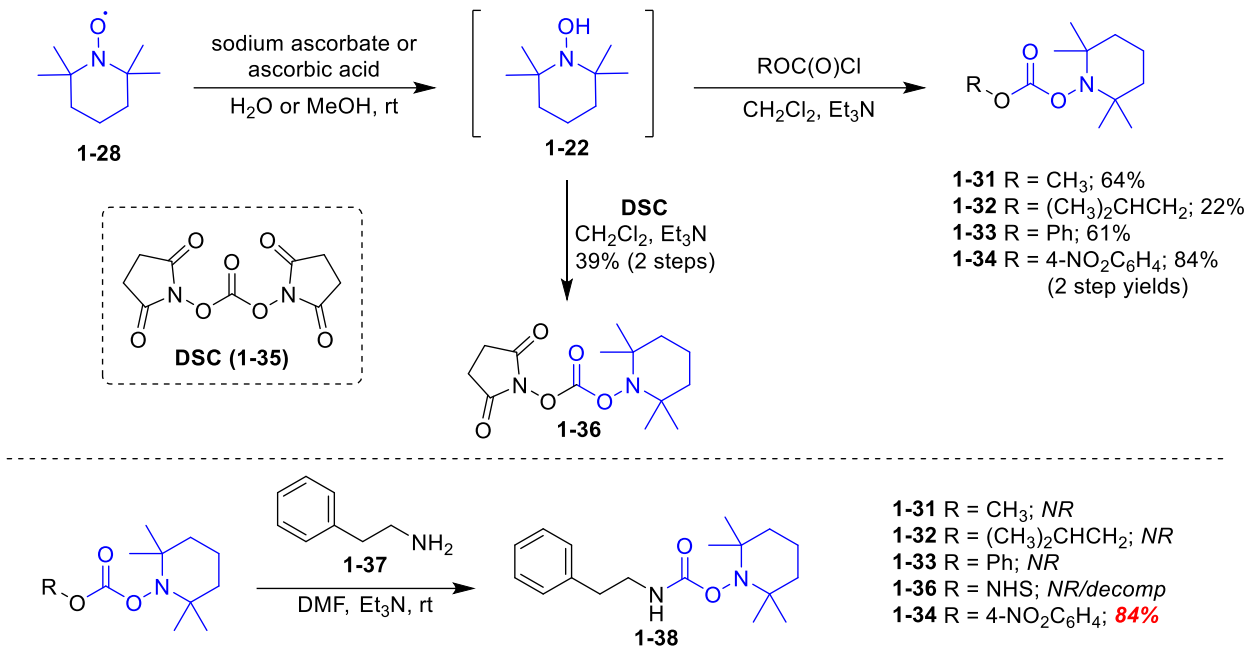
Scheme 4 The use of Boc anhydride and benzyl chloroformate for amine protection

While these reagents are generally stable and convenient for synthetic use, we hypothesized that Tempoc equivalents would be too unstable to storage, thereby limiting their convenience and practicality (Scheme 5). Tempoc anhydride **1-29** was discarded as a feasible substrate due to expected energetic decomposition. Tetramethylpiperidine chloroformate **1-30** was appealing as chloroformates react readily across a variety of basic and weakly nucleophilic amines.[33] However, after reduction of stable free radical **1-28** (TEMPO) to hydroxylamine **1-22**, and treatment with phosgene or triphosgene, the chloroformate quickly decomposed, forming a dark, complex reaction mixture with no isolable traces of the chloroformate.



Scheme 5 Planned synthesis of Tempoc anhydride and TMP chloroformate

Next, attention was turned to activated mixed carbonates, which have a long history of use for peptide couplings and amine protections.[34,35] Since mixed carbonates are easily prepared from alcohols and their respective chloroformates, we set out to synthesis a variety of mixed carbonates as potential Tempoc transfer reagents (Scheme 6). While keeping the impending workup in mind, we first sought to prepare the methyl and *iso*-butyl Tempoc carbonates **1-31** and **1-32**, expecting that the resulting alcohols could readily be removed during the reaction workup. Reduction of **1-28** in water or methanol with sodium ascorbate or ascorbic acid gave resulting hydroxylamine **1-22**, which after extraction was treated with corresponding chloroformates to give mixed carbonates **1-31** and **1-32** in good to excellent yield. These carbonates were exposed to phenethylamine **1-37** in DMF with triethylamine as base; however, no product was detected by LC-MS or NMR analysis.



Scheme 6 Synthes of Tempoc mixed carbonates and their reaction with phenethylamine **1-37**

Next, we sought to increase the leaving group ability of the carbonate, thus, phenyl carbonate **1-33**, N-hydroxylsuccinimidyl (NHS) carbonate **1-36**, and 4-nitrophenyl carbonate **1-34** were synthesized. Phenyl analog **1-33** and NHS-carbonate **1-36** were unreactive towards phenethylamine, the latter being unstable and decomposing in solution without giving any detectable product. Nitrophenyl carbonate **1-34**, however, cleanly afforded Tempoc protected phenethylamine **1-38** in 84% isolated yield. Tempoc transfer reagent 4-nitrophenyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate (NPTC, Figure 1) is a bench stable crystalline solid that has been synthesized in 100 g quantities. While NPTC bears a nitro group and weak N–O bond, differential scanning calorimetry showed only a minor exotherm of 70 cal/g at an onset temperature of 135 °C, showing that NPTC is a relatively stable compound. In fact, at this time of this writing, NPTC, via licensing from the University of Pittsburgh, has been made commercially available for purchase by the chemical supplier Millipore Sigma.

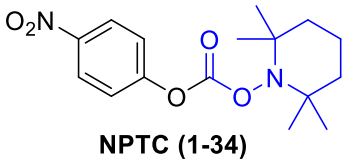
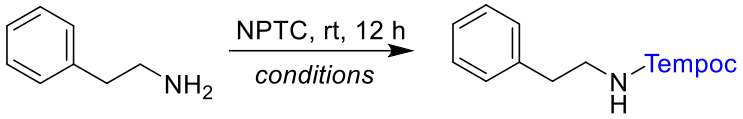


Figure 1 The structure of Tempoc transfer reagent NPTC

1.2.2 The use of NPTC to protect amines

With transfer agent NPTC in hand, we sought to optimize a set of conditions for installment of the Tempoc group onto amines. Using 2-phenethylamine **1-37** as a test substrate, we first explored typical Boc protection conditions (Table 1, Entry 1–2). Further screening showed that polar solvents were critical for good conversions (Table 1, Entries 3–5) with DMF providing the highest isolated yield. Next, screening of bases (Table 1, Entries 6–9) indicated that triethylamine was more effective than pyridine and inorganic bases. Interestingly, while potassium carbonate (Table 1, Entry 8) showed comparable yields, trace amounts of *bis*-Tempoc amine were detected by LC-MS. In attempts to increase conversion by heating, we were surprised to see the yields of Tempoc phenethylamine **1-38** decrease (Experimental Part, Table 15). We hypothesize that these conditions are met with NPTC degradation. However, excellent yields of **1-38** were obtained with increased loading of NPTC with 1.2 equivalents being ideal (Table 1, Entry 11).

Table 1 Optimization for the protection of phenethylamine with NPTC



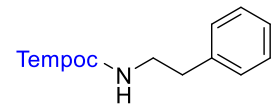
1-37 **1-38**

entry	stoichiometry[a]	solvent[b]	base	yield[c] (%)
1	1:1:3	DCM	Et_3N	28
2	1:1:3	THF	Et_3N	60
3	1:1:3	MeCN	Et_3N	57
4	1:1:3	MeOH	Et_3N	64
5	1:1:3	DMF	Et_3N	77
6	1:1:3	DMF	py	67
7	1:1:3	DMF	$NaHCO_3$	64
8	1:1:3	DMF	K_2CO_3	79[d]
9	1:1:3	DMF	Et_3N/DMAP[e]	76[e]
10	1:1.1:3	DMF	Et_3N	84
11	**1:1.2:3**	**DMF**	**Et_3N**	**91**

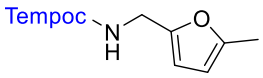
[a]amine:NPTC:base; [b]0.5 M in amine [c]isolated yields; [d]trace *bis*-Tempoc amine detected by HPLC-MS; [e]0.25 equiv DMAP

With these optimized conditions, we sought to demonstrate PG utility by exploring a range of primary, secondary, and heterocyclic amines as potential substrates (Figure 2). Unhindered primary amines were protected smoothly in high yields. Unprotected hydroxyl groups were tolerated in the protection, **1-45** and **1-46** were isolated with no traces of *O*-acylation. Tryptamine **1-47** and amino benzylamine **1-48** gave complete selectivity towards the more basic amine. Primary amine **1-49**, bearing α-substitution, showed decreased reactivity towards NPTC, giving 75% yield respectively. Sterically encumbered *tert*-butyl amine only afforded 32% of the desired product **1-50**. Tempoc hydrazide **1-51** was isolated as a highly crystalline solid in 95% yield. Using sodium hydride as base, we were able to cleanly *bis*-protect phenethylamine **1-52** in 90% isolated yield. Arylamines such as naphthylamine **1-53** showed no reactivity towards NPTC under standard, or even under forcing conditions.

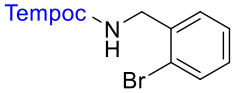
Primary Amines[a,b]



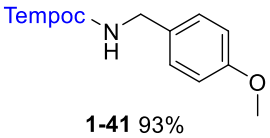
1-38 94%



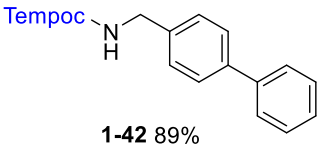
1-39 92%



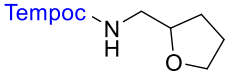
1-40 90%



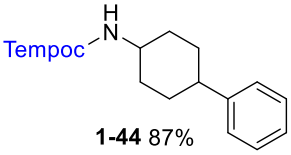
1-41 93%



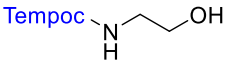
1-42 89%



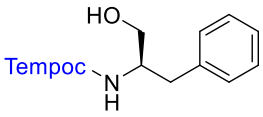
1-43 93%



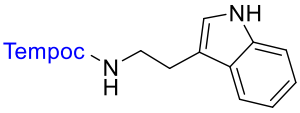
1-44 87%



1-45 94%



1-46 72%



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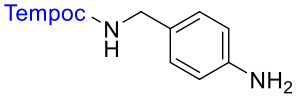
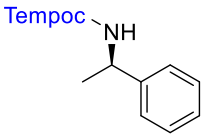
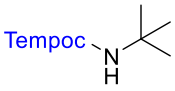


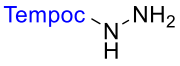
1-48 93%



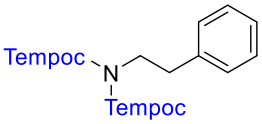
1-49 75%



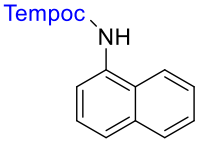
1-50 32%



1-51 95%[c]

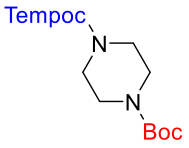


1-52 90%[d]

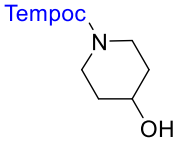


1-53 NR[e]

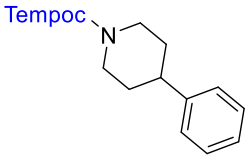
Secondary Amines[a,b]



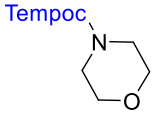
1-54 91%



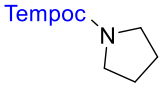
1-55 87%



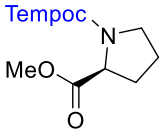
1-56 98%



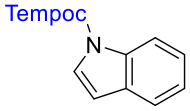
1-57 98%



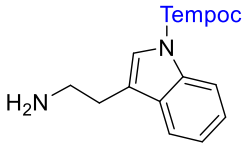
1-58 91%



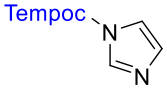
1-59 87%[f]



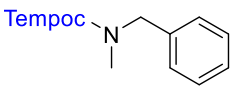
1-60 94%[g]



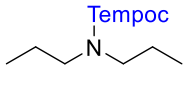
1-61 71%[h]



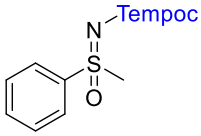
1-62 91%



1-63 97%



1-64 56%



1-65 82%[i]

[a]Reaction conditions: amine (1 equiv), NPTC (1.2 equiv), and triethylamine (3 equiv), in DMF (0.5 M), rt, 12 h. [b]Isolated yields. [c]NPTC(1 equiv), hydrazine (2 equiv). [d]Sodium hydride as base (2.6 equiv), NPTC (2.4 equiv). [e]Unreactive towards aryl amines under standard conditions. [f]4 equiv of triethylamine. [g]Sodium hydride (1.3 equiv) as base. [h]Sodium hydride, then NPTC.

Figure 2 The scope of Tempoc protected primary, secondary, and heterocyclic amines

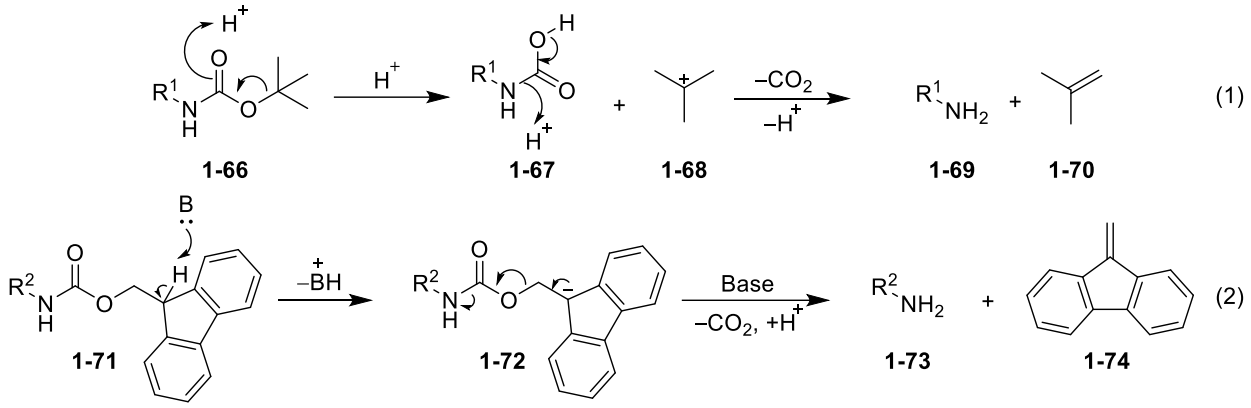
Generally, cyclic secondary amines are excellent substrates for Tempoc protection. L-Proline methyl ester gave facile protection, albeit with slightly lower yield, likely do the steric interactions. Sodium hydride was needed for indole **1-60** as the there was no observed product formation under standard conditions. Importantly, we were able to selectively protect the indole-N on tryptamine **1-61** by treatment first with sodium hydride, followed by addition of NPTC as a solution in THF. Imidazole was a highly compatible substrate for acylation, giving Tempoc protected analog **1-62** in 91% yield. Acyclic amine **1-63** gave excellent yield, however bulkier dipropyl amine **1-64** suffered from a decreased reaction rate, only giving 56% of the desired Tempoc amine. Sulfoximine **1-65** was also protected in 82% yield under sodium hydride conditions.

Driven to extend the scope to aryl amines, we hoped to accelerate the reaction of NPTC and weakly nucleophilic arylamines by other means. Increasing reaction temperature only led to decomposition of the transfer reagent, even upon switching solvents. HFIP has been known to activate Boc_2O for protection of weakly nucleophilic or hindered amines. However, in the case of NPTC only slow decomposition was observed.[36] Stronger bases such as sodium hydride or *n*-butyllithium, again, only led to slow decomposition of the transfer reagent and no isolable products. Lewis acids[37–39] such as $MgBr_2$ and various metal triflates have also been used for activation during the Boc protection, however, no desired product was observed after screening many Lewis acids (*i.e.*, $MgCl_2$, $Sc(OTf)_2$, TMSOTf). There are even reports in the literature of activation of transfer reagents using Brønsted acids.[40,41] These attempts also failed, likely due to deactivation of the aniline through protonation rather than activation of the transfer reagent. Nucleophiles such as DBU,[42] *N*-methylimidazole,[43] and DABCO[44] have been used for acyl-

transfer activation, as well as other nucleophilic reagents such as sodium azide[45] and sodium iodide.[46] However, when these reagents were tested, either no desired product was formed or decomposition of NPTC was observed.

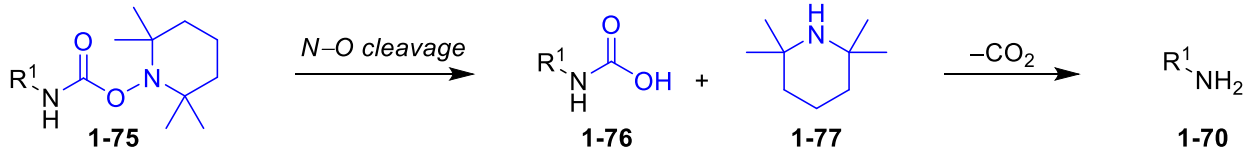
1.2.3 Deprotection of the Tempoc group

Carbamate cleavage typically takes advantage of the unstable nature of the carbamic acids, thus, after cleavage of the O-substituent on the carbamate, the resulting carbamic acid will spontaneously release carbon dioxide to generate the free amine. The deprotections of Boc and Fmoc are typically conducted in the presence of a strong acid or base respectively. The former, follows a mechanism where protonation of the carbamate oxygen generates the stable *tert*-butyl cation **1-68** and carbamic acid **1-67** (Scheme 7, Eq. 1).[47] Cation **1-68** can either undergo elimination to the give isobutylene, a gas, or the *tert*-butyl cation can be trapped with solvent or the acid counter-ion. Carbamic acid **1-67** then undergoes spontaneous decomposition to evolve CO_2 and free amine **1-69**. Fmoc, on the other hand, undergoes decomposition *via* a $E1_{cb}$ mechanism (Scheme 7, Eq. 2).[48] The nucleophilic amine base, typically used in high excess, deprotonates the 9-fluorenylmethyl ring giving intermediate anion **1-72**, which then collapses down on the carbamate to release carbon dioxide and free amine **1-73**. Dibenzofulvene **1-74** is a reactive electrophile and is typically trapped quickly by the base.



Scheme 7 The acid and basic deprotection mechanisms of Boc and Fmoc respectively

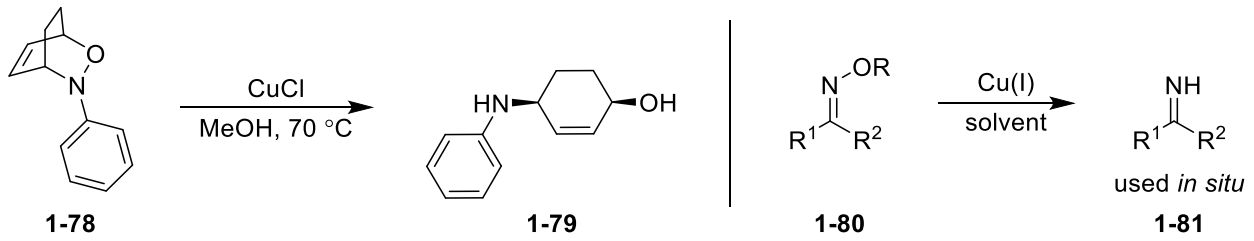
Exploitation of the entropic driving force of CO_2 extrusion in conjunction with a relatively stable by-product (*i.e.*, *tert*-butyl cation or dibenzofulvene) allows some carbamate deprotections to be mild and facile. It is with this in mind that we envisioned the scission of the labile N–O bond in Tempoc to release carbon dioxide and generate hindered 2,2,6,6-tetramethylpiperidine **1-77** and deprotected amine **1-70**.



Scheme 8 Tempoc deprotection hypothesis

1.2.3.1 Tempoc deprotection - copper

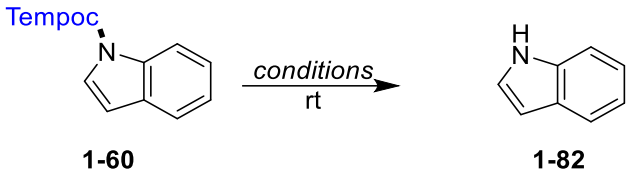
With a broad scope of primary and secondary amines efficiently protected, many in gram-scale or larger, we next sought to exact a mild set of conditions for the selective deprotection of Tempoc, and thereby significantly differentiate its deprotection conditions from that of other PGs. In order to develop an orthogonal deprotection strategy, we first thought to exploit the reductive lability of the N–O bond in the carbamate moiety. N–O bonds are known to undergo metal-catalyzed reduction in the presence of copper(I) (Scheme 9).[49–51]



Scheme 9 Literature examples of N–O bond cleavage with copper(I) salts

With Tempoc indole **1-60** as test substrate, we found that copper(I) chloride effectively cleaved the Tempoc group (Table 2, Entry 1). However, while stoichiometric Cu(I) was effective, we sought to use copper catalytically, while also removing the need for air-sensitive copper(I) salts *via* the use of copper(II) chloride and the introduction of a reductant, such as ascorbic acid. Treatment of Tempoc indole with other sources of Cu(II) were effective. However, we chose copper(II) chloride as it exhibited the best solubility and cost effectiveness (Table 2, Entries 6–10). Using optimized conditions, we found that other Tempoc substrates were sparingly soluble in the DMF/H_2O mixture. After testing various binary solvent mixtures it was found that a ternary mixture of MeCN/THF/H_2O exhibited excellent solubilizing properties for all Tempoc substrates, while concomitantly allowing for lower copper and reductant loading, and shorter reaction times that we attributed to the stabilizing effects of acetonitrile on the reduced Cu(I) species (Table 2, Entry 11). Further reduction of copper and ascorbic acid, while effective, was met with increased reaction times (Table 2, Entry 12).

Table 2 Optimization for the copper mediated deprotection of Tempoc indole

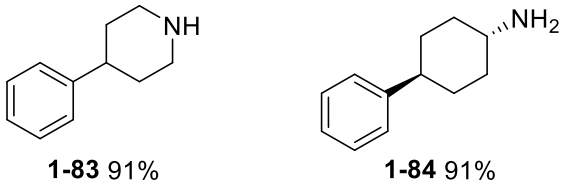


1-60 **1-82**

entry	CuX (equiv)	reductant (equiv)	solvent	yield[b] (%)
1[a]	CuCl (2.2)	-	MeCN	83
2[a]	CuI (2.2)	-	MeCN	trace
3[a]	Cu_2O (1.1)	-	MeCN	11
4[a]	$CuCl_2$ (1.1)	-	MeCN	2
5[a]	$CuCl_2$ (0.20)	NaAsc (1.1)	MeCN/H_2O (2:1)	29
6[a]	$CuCl_2$ (0.20)	Asc (5)	MeCN/H_2O (2:1)	29
7[a]	$CuCl_2$ (0.20)	Asc (5)	MeOH/H_2O (5:1)	63
8[a]	$CuCl_2$ (0.20)	Asc (5)	DMF/H_2O (5:1)	84, 84[c]
9	$CuSO_4$ (0.20)	Asc (5)	DMF/H_2O (5:1)	84
10	$CuCl_2$ (0.05)	Asc (2)	DMF/H_2O (5:1)	67[d]
11	$CuCl_2$ (0.05)	Asc (2)	MeCN/THF/H_2O (4:1:1)	84[d]
12	$CuCl_2$ (0.10)	Asc (2)	MeCN/THF/H_2O (4:1:1)	83[d]

[a]contribution (MB); [b]HPLC yield; [c]isolated yield after 12 h; [d]isolated yield after 24 h

Using these optimized reductive conditions, we explored the application for primary, secondary, and heterocyclic Tempoc amines (Figure 3). Tempoc piperidine **1-56** and cyclohexylamine *trans*-**1-44** deprotected cleanly at room temperature to afford free amines **1-83** and **1-84** in excellent yield. Primary amine *trans*-**1-44** required mild heating to achieve deprotection, presumably due to the less hindered carbamate coordinating to copper. Deprotections were scaled to >1 mmol with no decrease in yield.

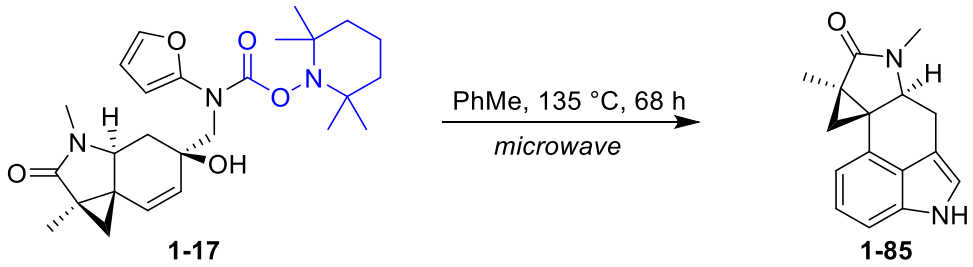


1-83 91% **1-84** 91%

Figure 3 Copper deprotection of Tempoc piperidine **1-56** and cyclohexylamine *trans*-**1-44**

1.2.3.2 Tempoc deprotection - thermolysis and mechanism

During McCabe's 2017 synthesis of (−)-cycloclavine,[32] Tempoc was cleaved during thermal IMDAF reaction conditions. Interested in applying this property of thermal Tempoc deprotection more generally, we explored the possibility of a thermolysis of Tempoc as another method of deprotection. A survey of the literature shows precedents for the thermal deprotection of carbamates, namely Boc.[52–54]

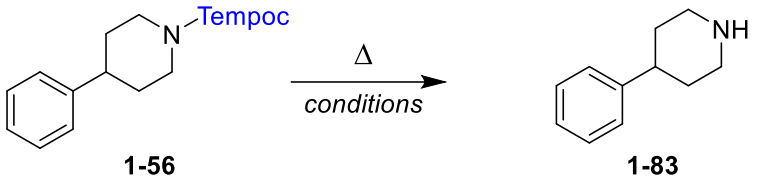


Scheme 10 Tandem IMDAF cyclization and thermolysis of Tempoc in McCabe's synthesis of **(−)**-cycloclavine

With Tempoc piperidine **1-56** as test substrate, we switched from Dr. McCabe's conditions of 135 °C in toluene under microwave irradiation to the higher boiling chlorobenzene (Table 3). Under microwave irradiation at 165 °C for 1 hour, only a trace amount of product **1-83** was observed (Table 3, Entry 1). Switching to more polar pyridine and increasing temperature to 175 °C again only produced trace amounts of detectable **1-83** by LC-MS (Table 3, Entry 2). Increasing solvent polarity further to proprionitrile showed a dramatic increase in the rate of deprotection, and after 2 h at 165 °C we isolated 48% of desired free piperidine **1-83** (Table 3, Entry 4). The highly polar solvent 1,1,3,3-hexafluroisopropanol (HFIP) has been shown to enhance the deprotection of carbamates.[24,55,56] Thus, using a 9:1 mixture of PhCl/HFIP indeed increased the rate of deprotection, and in 2 h 42% of amine **1-83** was isolated (Table 3, Entry 5). Using neat HFIP enabled the temperature to be reduced to 135 °C and in 8 h 85% of the deprotected amine

was isolated (Table 3, Entry 7). Swapping HFIP to the less acidic TFE was met with a substantial reduction in yield (Table 3, Entry 8).

Table 3 The optimization of Tempoc thermolysis of piperidine **1-56**

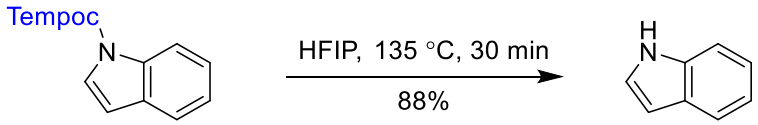


1-56 **1-83**

entry	solvent	temperature (°C)	time (h)	yield[a] (%)
1	PhCl	165	1	trace
2	pyridine	175	1	trace
3	NMP	165	1	decomp[b]
4	EtCN	165	2	48
5	PhCl-HFIP (9:1)	165	2	42
6	HFIP	135	6	73
7	HFIP	135	8	85
8	TFE	135	6	30

[a]isolated; [b]no recovered starting material or desired products

These optimized deprotection conditions, 135 °C in HFIP for 8 h under microwave irradiation, were also applied to indole **1-60**, which only required 30 min for complete conversion, affording indole **1-82** in 88% yield (Scheme 11).

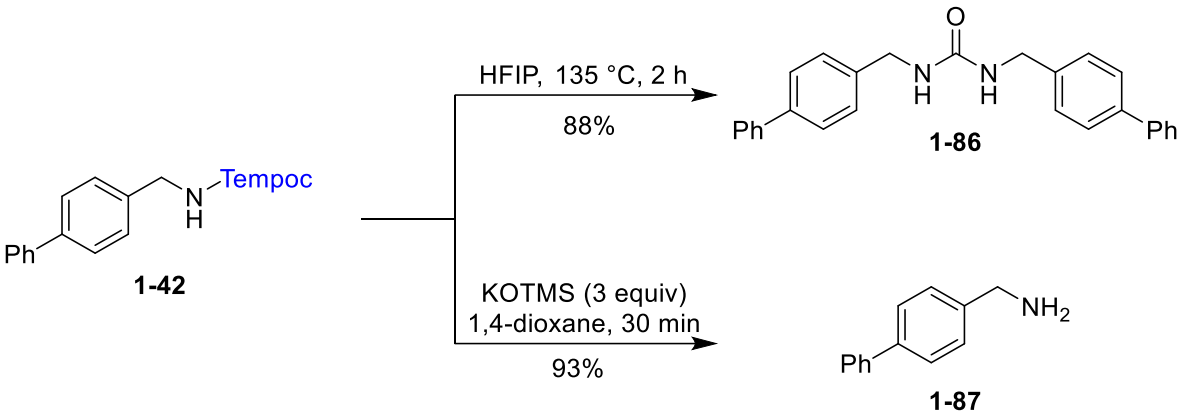


1-60 **1-82**

Scheme 11 Thermal deprotection of Tempoc indole **1-60**

Surprisingly, extension of this method to Tempoc protected primary amines only gave the symmetrical urea. When Tempoc benzylamine **1-42** was heated in HFIP, after 30 min only urea **1-86** was isolated (Scheme 12). Numerous attempts to discourage this side-reaction were met with disappointing results. However, Maximilian Bremerich (MB) discovered that potassium trimethylsilanoate (KOTMS) inhibited the urea formation. Indeed, when Tempoc amine **1-42** was

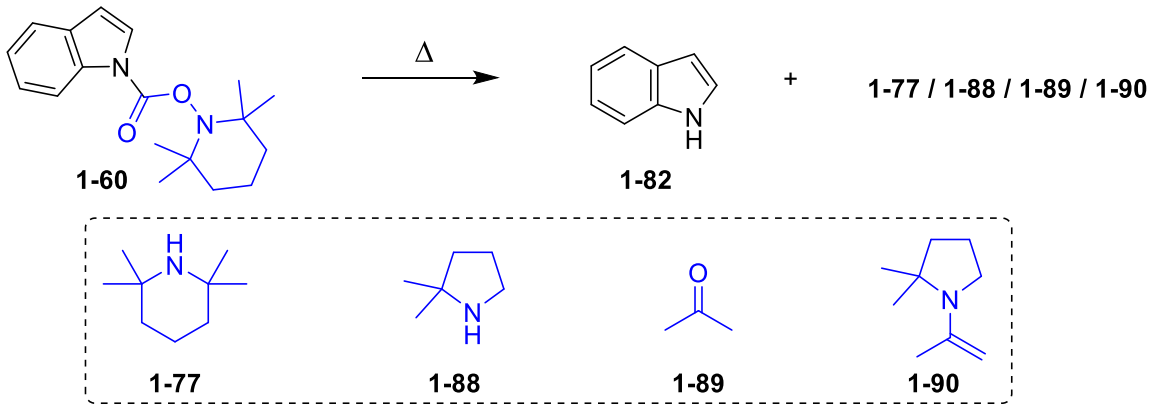
heated in 1,4-dioxane for 30 min at 135 °C in the presence KOTMS the desired primary amine **1-87** was cleanly isolated in 93% yield after filtration through a pad of silica.



Scheme 12 The thermolysis of primary amines and their products

Curious about the reaction mechanism of the thermolytic deprotection, Dr. McCabe used NMR analysis.[1] Identification of the by-products of the thermal Tempoc cleavage (Table 4) showed the presence of tetramethylpiperidine **1-77**, dimethylpyrrolidine **1-88**, and enamine **1-90**.

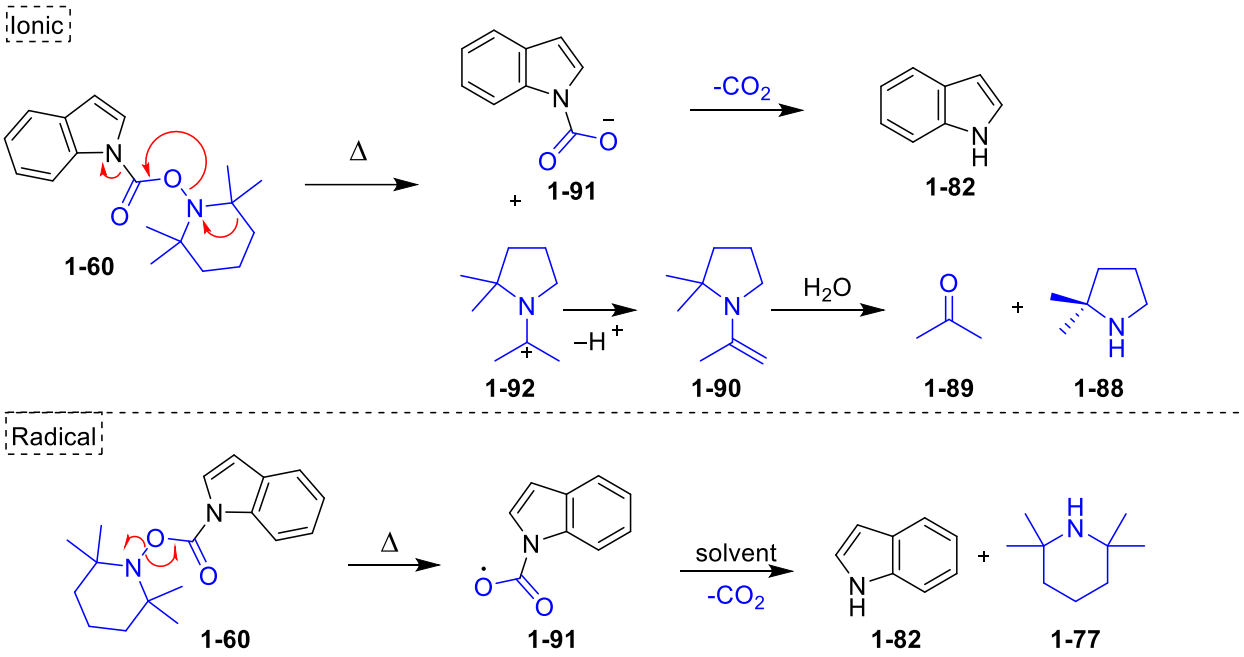
Table 4 The thermal deprotection products of Tempoc indole **1-60**



		product ratios[a]			
entry	conditions	**1-77**	**1-88**	**1-89**	**1-90**
1	150 °C, toluene-d_8, 20 h	1	1	ND	0
2	150 °C, toluene-d_8 (1 M degassed), 9 h	1	2.3	ND	0.98
3	150 °C, toluene-d_8 (1 M), H2O (4 eq), 9 h	1	3.4	ND	0
4	135-140 °C, toluene-d_8 (1 M), 32.5 h	1	1.8	ND	trace

[a]based on NMR analysis; ND = not detected

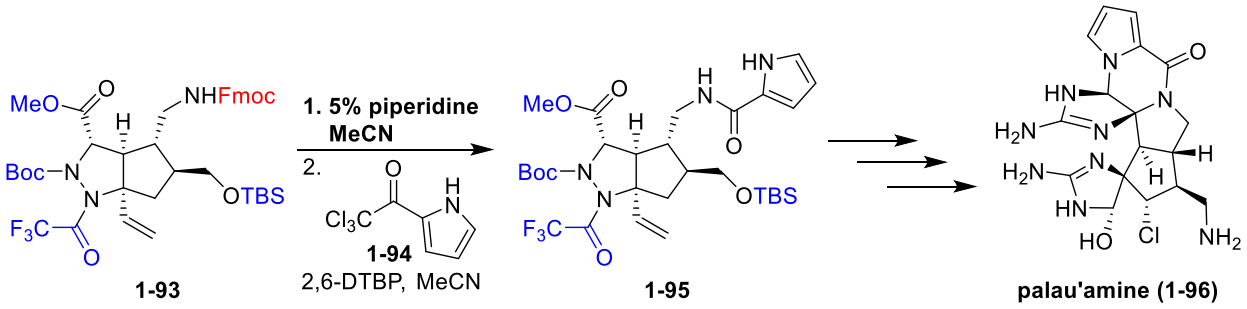
With these data a plausible mechanism was proposed, where the deprotection followed radical and ionic pathways (Scheme 13). Under thermal conditions, the ionic pathway begins with ring contraction of the piperidine ring, affording carbamic acid **1-91** and cationic pyrrolidine **1-92**. Loss of CO_2 affords indole **1-82**, and pyrrolidine **1-92** eliminates to afford enamine **1-90**, which is hydrolyzed to give acetone and dimethyl pyrrolidine **1-88**. In the ionic mechanism, we suspect homolysis of the N–O bond produces 2,2,6,6-tetramethylpiperidine radical and **1-91**. After hydrogen atom transfer from solvent and extrusion of CO_2 tetramethylpiperdine **1-77** and indole **1-82** are formed.



Scheme 13 The proposed ionic and radical pathways of thermal Tempoc deprotection

1.2.4 Orthogonality study of Tempoc deprotection

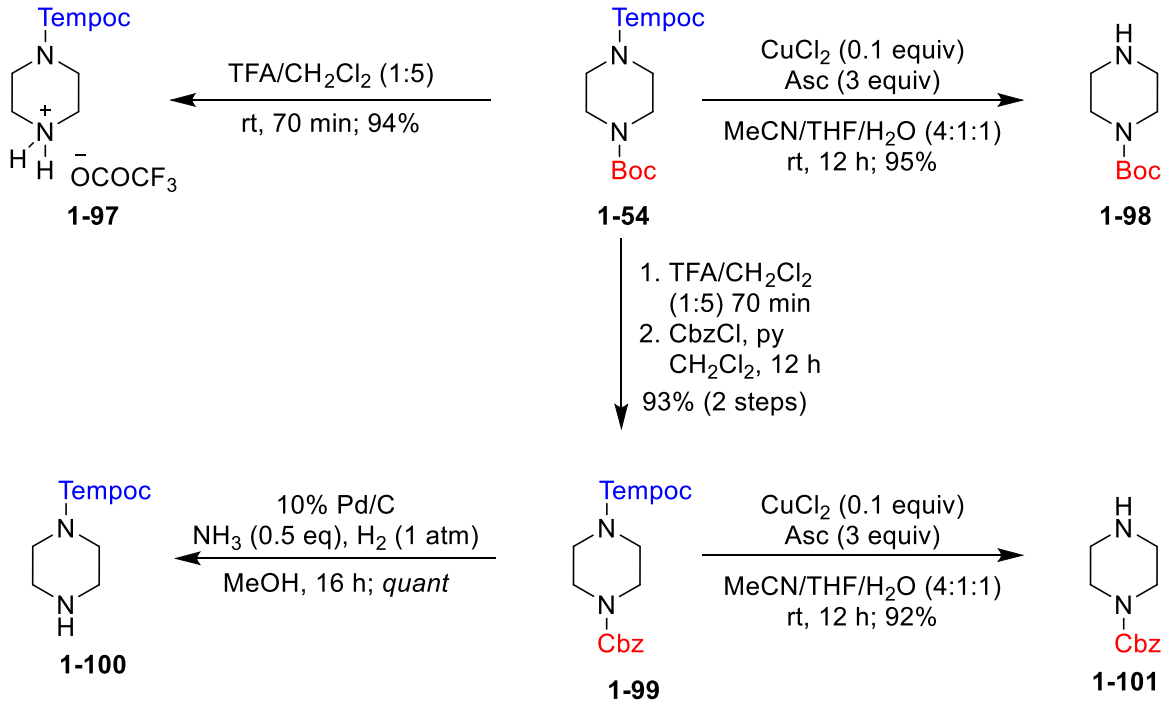
One of the key properties of a protecting group is orthogonality. Selective deprotection of one group in the presence of multiple other PGs is routinely carried out in a synthetic sequence. An example of such a selective deprotection is from Namba's 2015 synthesis of palau'amine **1-96** (Scheme 14).[57]with



Scheme 14 The selective deprotection of Fmoc in the presence of 4 other protecting groups

The Fmoc protected pendant amine needed to be removed prior to conversion to pyrrolamide **1-95**. This was accomplished with standard conditions, 5% piperidine in acetonitrile, while leaving the Boc, trifluoroacetamide, silyl ether, and methyl ester groups intact.

With respect to assessing the orthogonality of Tempoc deprotection against the popular Boc and Cbz groups, we set out the explore conditions under which selective deprotection of Boc, Cbz, and Tempoc could be employed with strategic, synthetic compatibility (Scheme 15).



Scheme 15 Orthogonality studies with Cbz/Tempoc and Boc/Tempoc protected piperazines

Bis-protected piperazines **1-54** and **1-99** were synthesized for this demonstration. Tempoc amine **1-54** and **1-99** deprotected cleanly using the optimized copper(I) conditions at room temperature to afford free amines **1-98** and **1-101** in 95% and 92% yields, respectively. Standard TFA in methylene chloride conditions removed Boc in the presence of Tempoc in 94% yield, affording the monoprotected piperazine **1-97** as the trifluoroacetate salt. Cbz was removed using a modified literature protocol, Pd/C and H_2 (balloon) in the presence of 0.5 equivalents of

ammonia, gave Tempoc piperazine **1-100** in quantitative yield. Attempts to run the reaction in the absence of ammonia led to partial cleavage of the Tempoc group.

1.3 CONCLUSIONS

In conclusion, these studies indicated that the 2,2,6,6-tetramethylpiperidin-1-yloxycarbonyl (Tempoc) is an effective amino protecting group, with excellent orthogonality to Boc and Cbz protective groups. Treatment of amines with the crystalline Tempoc transfer reagent NPTC affords corresponding Tempoc protected derivatives in high yield with excellent chemoselectivity. Removal is mild, utilizing catalytic copper(I) generated *in situ* by the reduction of copper(II) chloride with ascorbic acid. Alternatively, thermolysis of Tempoc occurs in HFIP at 135 °C. Mechanistic studies have been explored, indicating a predominant ionic mechanism, however a radical pathway cannot be ruled out. Overall, the findings from the research described herein clearly demonstrate a highly useful role for the straightforward and synthetically amenable use of Tempoc as an amino protective group.

2.0 TEMPOC: A USEFUL PROTECTING GROUP IN PEPTIDE SYNTHESIS

2.1 INTRODUCTION

2.1.1 Protection group use in peptide synthesis

Peptides and proteins play an essential role to all biological processes, while also being an integral part in the design of new therapeutics.[58] While peptides may be isolated from natural sources or specifically expressed for isolation, they are typically produced synthetically.[59–61] Furthermore, the chemical synthesis of peptides may be done without the use of protecting groups utilizing native chemical ligation. However, this method comes with many limitations.[62–64] Therefore, peptides are typically constructed using protective group based solution-phase[65] or solid-phase[66] peptide synthesis. While the *N*- and *C*-terminus on amino acids require protection during synthesis, the multitude of reactive moieties (Figure 4) contained on amino acid sidechains also require protection during synthetic sequences to avoid unwanted side-reactions.[67] The most common functional groups needing protection in peptide synthesis are amines. Of the available amine PGs, carbamates such as *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethoxycarbonyl (Fmoc) are the most common and the most synthetically useful. Carbamates offer excellent durability to standard peptide coupling conditions, while also being removed mildly and orthogonally to other protecting groups that may be present. Taken together, there is demand for the development of new orthogonal protective groups for successful construction of the complex molecules.

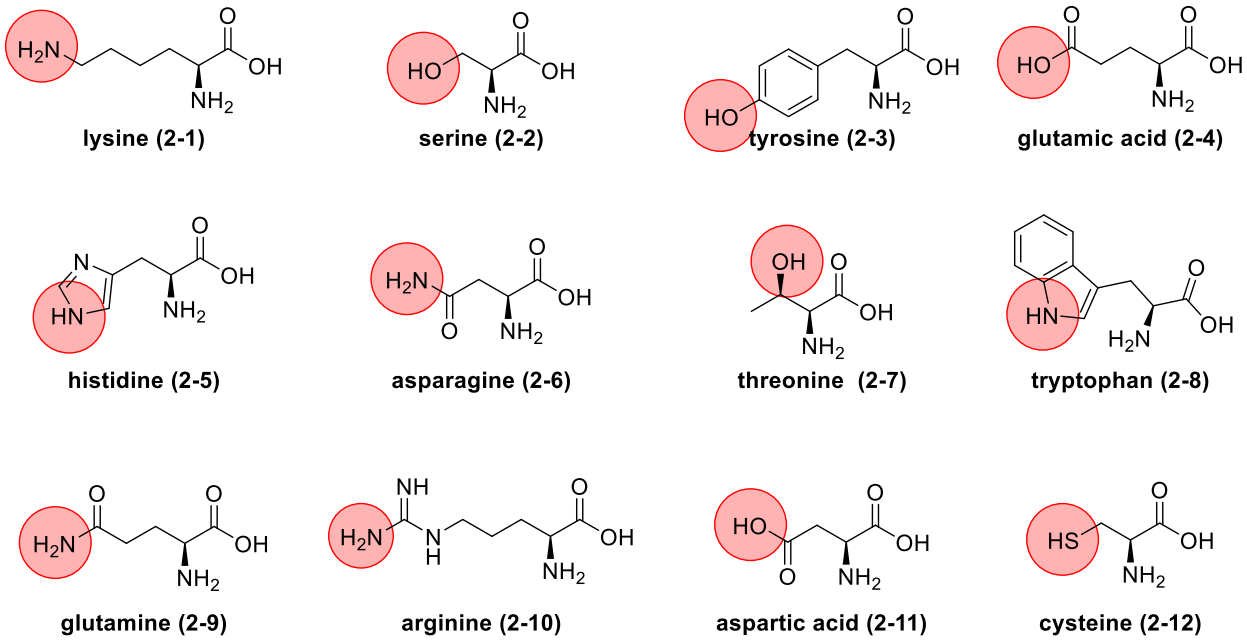
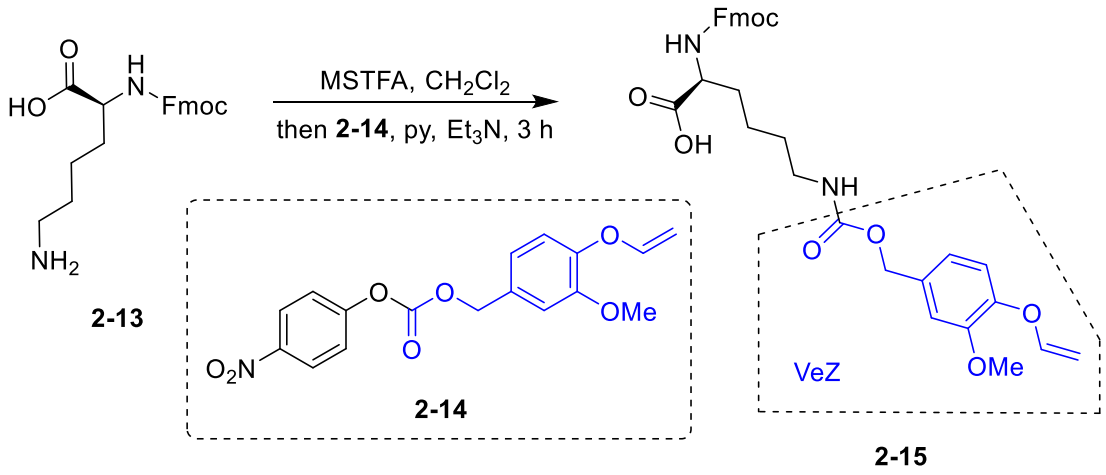


Figure 4 Representative examples of amino acid bearing reactive sidechains (green)

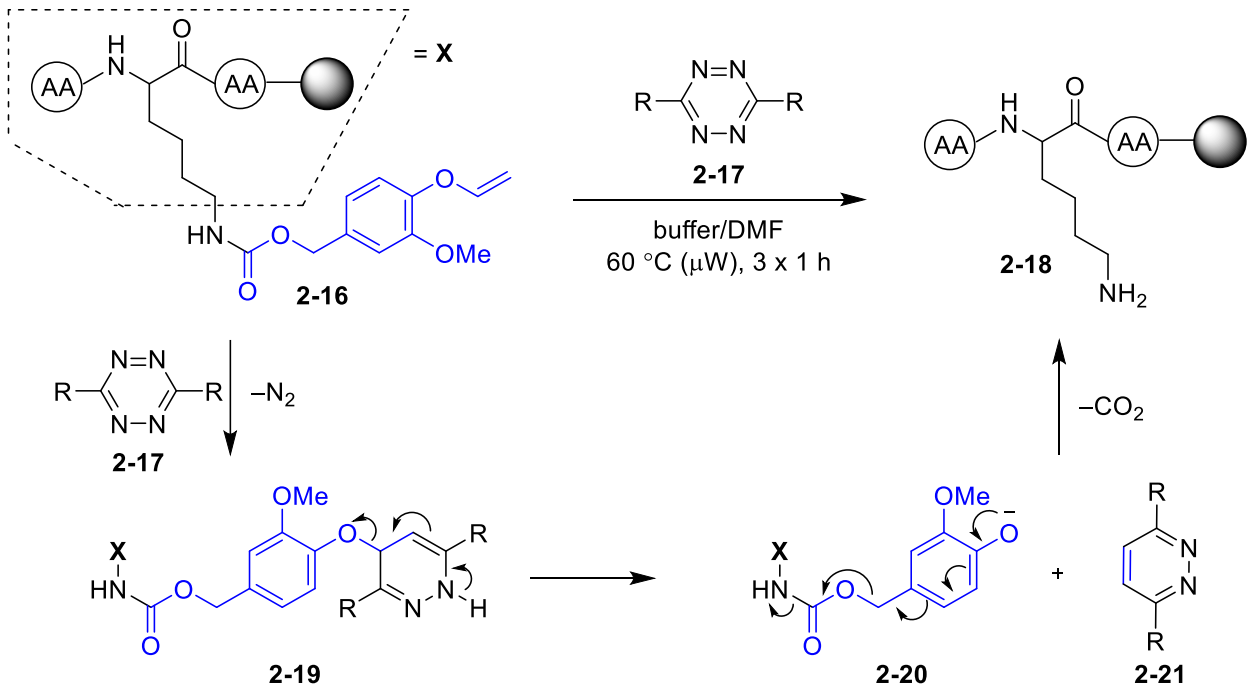
2.1.2 New carbamates in peptide synthesis

In recent years, new carbamate-based groups for N-terminus and amine side-chain protections have been developed. In 2018, Staderini introduced the tetrazine-labile aryl vinyl ether protecting group for use as lysine sidechain protecting group (Scheme 16).[68]



Scheme 16 The tetrazine labile vinyl ether benzyloxycarbonyl (VeZ) protecting group

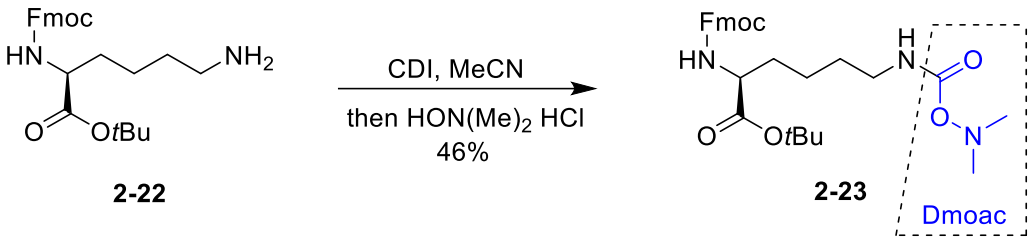
The vinyl ether benzyloxycarbonyl (Vez) protecting group is installed on Fmoc-protected lysine *via* 4-nitrophenyl mixed carbonate **2-14** after *in situ* protection of the free carboxyl with *N*-trimethylsilyl-*N*-methyl trifluoroacetamide (MSTFA). Deprotection of VeZ is performed by microwave heating in the presence of a tetrazine in an aqueous buffer-DMF mixture (Scheme 17). The mechanism proposed is that of and inverse demand Diels-Alder cyclization with subsequent extrusion of dinitrogen to form dihydropyridazine **2-19**. Aromative-elimination provides the phenoxide **2-20**, which readily undergoes 1,6-elimination to liberate carbon dioxide and free amine **2-18**. The authors further demonstrated the utility of the VeZ group in the synthesis of two cyclic peptides, melanotan II and a BAD BH3 peptide.[69,70]



Scheme 17 Mechanism for the deprotection of the VeZ protecting group

In 2019, Okamoto showcased the polar *N*,*N*-dimethylaminoxy carbonyl (Dmaoc) protecting group.[22] The Dmoac group, as was the aforementioned VeZ group, was designed for sidechain amino protection. Dmoac shares an interesting structural similarity to Tempoc in that also contains an N–O bond. Installation of the protecting group was accomplished *via*

carbamoylation by treatment of the amine with *N,N'*-carbonyldiimidazole (CDI) in the presence of *N*,*N*-dimethylhydroxylamine hydrochloride (Scheme 18).



Scheme 18 Dmoac protection of lysine using CDI and *N*,*N*-dimethylhydroxylamine

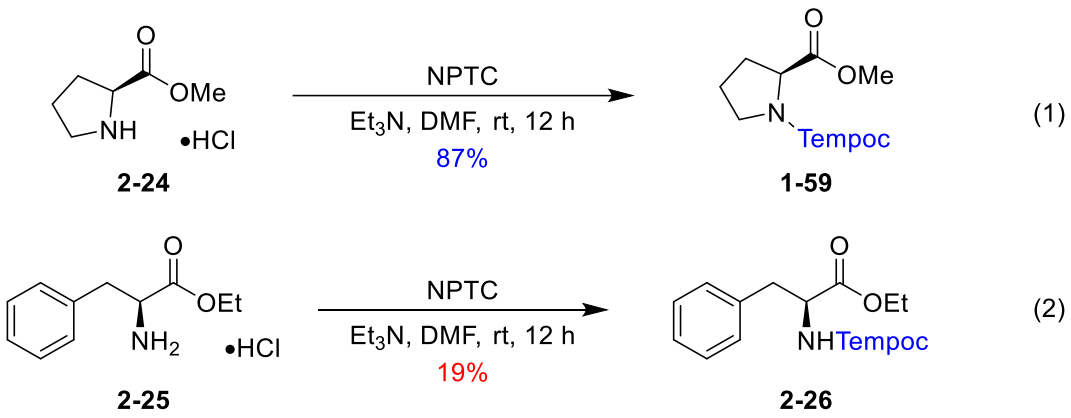
Deprotection was efficiently accomplished in a few hours by stirring in a pH 7.0 buffer containing dithiothreitol (DTT). The authors speculate that reduction of the N–O bond may be occurring as the deprotection does not proceed in the absence of reducing agents, however, DTT nucleophilicity seems to also be a major factor. Okamoto then displays Dmoac's utility through the synthesis of sunflower trypsin inhibitor SFTI.[71] SFTI is a cyclic peptide bearing 14 amino acid residues, including lysine. After cyclization of the linear peptide, Dmoac was removed utilizing the author's DTT/buffer conditions.

2.2 RESULTS AND DISCUSSION

2.2.1 Problems with initial Tempoc protection conditions

During our exploration of Tempoc as a protecting group for primary, secondary, and heterocyclic amines,[1] we showed that the amino ester proline was an excellent substrate for protection, affording 87% of Tempoc proline **1-59** using the standard protection conditions (Scheme 19, Eq. 1). Interested in expanding the versatility of Tempoc's utility for peptide

synthesis, we first attempted to protect phenylalanine ethyl ester. However, we were surprised to isolate only 19% of the desired product **2-26** (Scheme 19, Eq. 2).

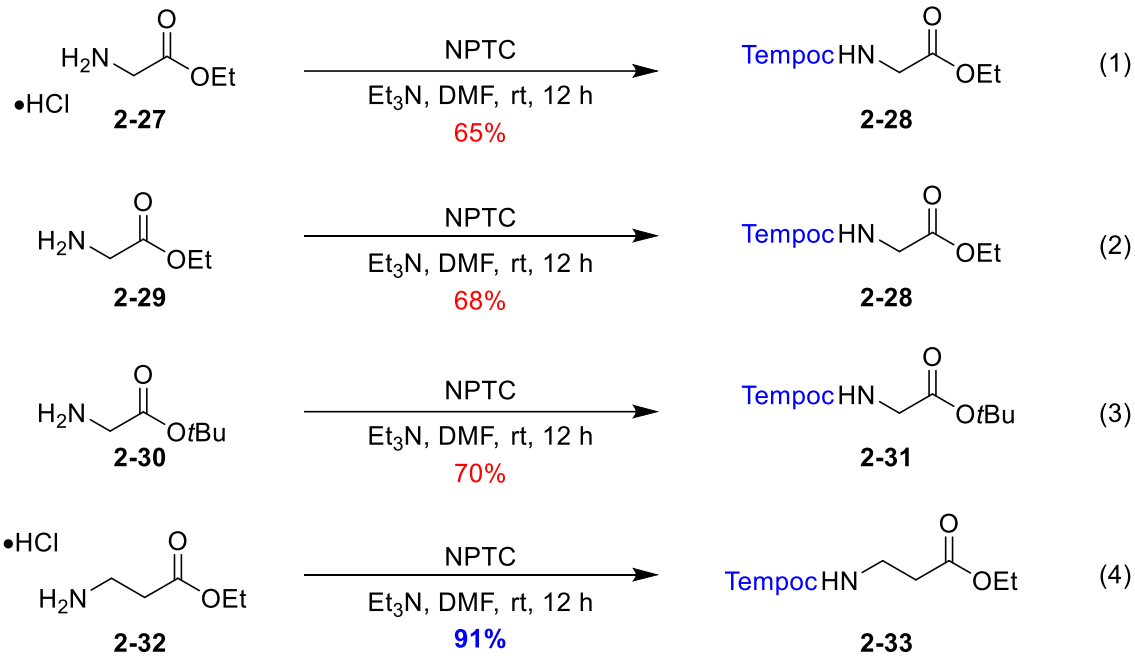


Scheme 19 The unexpected yield from the Tempo protection of phenylalanine ester **2-25** as compared to proline

2.2.2 Discovery of new protection conditions and scope

Curious about this result, we set out to elucidate the reason for the considerable drop in yield. First, we wanted to simplify our protection substrate to glycine ethyl ester, as an α-unsubstituted amino ester which should be protected in high yield. However, when glycine ethyl ester hydrochloride was subjected to the standard protection conditions, only 65% yield of **2-28** was isolated (Scheme 20, Eq. 1). Speculating that solubility of the hydrochloride in DMF could be leading to low conversion, we freebased ethyl glycinate by extraction from aqueous ammonia and subjected **2-29** to the same conditions. In spite of this, no change was observed, providing only 68% of **2-28** (Scheme 20, Eq. 2). Next, we wondered if ethyl glycinate was oligomerizing under the basic conditions of the reaction. Therefore, we switched to *tert*-butyl glycinate, which should exhibit no propensity of oligomerization, again, only 70% of glycinate **2-31** was isolated (Scheme 20, Eq. 3). Lastly, we speculated the proximity of the amine to electron withdrawing ester moiety had an inductive effect that impacted yield. As such, ethyl β-alanine **2-32** was then subjected to

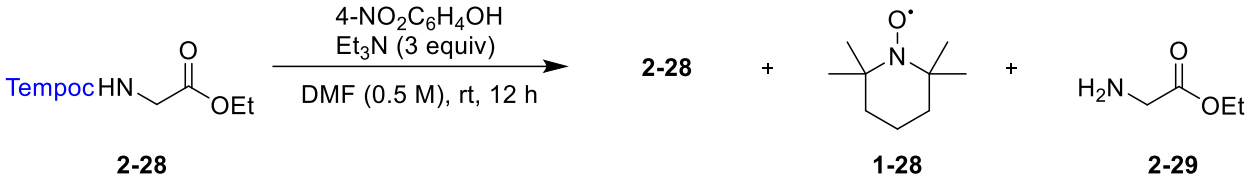
the standard conditions, providing Tempoc amino ester **2-33** in 91% yield as expected (Scheme 20, Eq. 4).



Scheme 20 Reactions to determine cause of reduced Tempoc protection yields for amino esters

Not yet convinced the electronic induction of the ester was the primary culprit for lower yields, we theorized that the Tempoc protected amino ester may be undergoing degradation in solution. Therefore, we subjected Tempoc glycinate **2-28** to the protection conditions and monitored for the expected degradations products, TEMPO **1-28** and glycine **2-29**. Stirring of the protected amine in DMF for 12 h in the presence of 4-nitrophenol and triethylamine did not produce any observable degradation products (Table 5).

Table 5 Tempoc stability studies under the standard reaction conditions

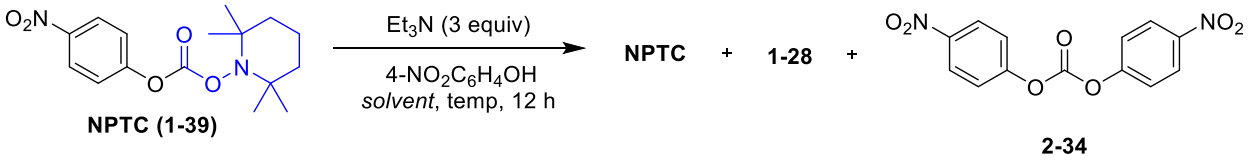


		observed products		
entry	4-$NO_2C_6H_4OH$	**2-28**	**1-28**	**2-29**
1	1 equiv	X	ND	ND
2	–	X	ND	ND

X = observed by TLC and LC-MS; ND = not detected by TLC and/or LC-MS

With Tempoc stability no longer in question, this provided stronger evidence that the inductive effect was slowing the reaction. However, with the longer reaction times, we hypothesized that NPTC degradation may also be contributing the decreased conversion rates. The stability of NPTC under the reaction conditions in the absence of an amine was then tested for expected degradation products TEMPO **1-28** and symmetrical carbonate **2-34** which could arise from attack of 4-nitrophenoxide onto NPTC. Exposure of NPTC in DMF or methylene chloride in the presence of triethylamine and 4-nitrophenol did not produce any detectable degradation products as well (Table 6).

Table 6 NPTC stability studies under the standard reaction conditions



				observed products		
entry	solvent (conc.)	temp	4-$NO_2C_6H_4OH$	**NPTC**	**1-28**	**2-34**
1	DMF (0.5 M)	ambient	1 equiv	X	ND	ND
2	DMF (0.5 M)	ambient	–	X	ND	ND
3	CH_2Cl_2 (1.0 M)	40 °C	1 equiv	X	ND	ND
4	CH_2Cl_2 (1.0 M)	40 °C	–	X	ND	ND

X = observed by TLC and/or LC-HRMS; ND = not detected by TLC or LC-HRMS

With enough evidence suggesting that inductive influences were the cause of the lower yields observed, we concluded that a more reactive Tempoc transfer reagent should be explored. Avoiding the redesign of crystalline, stable, and easily prepared NPTC, we sought to activate the reagent by means of an external activator. A survey of the literature revealed that highly polar solvents such as HFIP[36] or additives such as sodium cyanide,[72] sodium azide,[73] and HOBt[74] have been used for amine protection enhancement through reagent activation. Given the success of these activators, we set out to apply these conditions to amine protection with NPTC. We hypothesized that addition of these activators should generate a more reactive Tempoc transfer reagent *in situ* either through hydrogen bonding, or through displacement of the 4-nitrophenolate to generate a more reactive species (Figure 5).

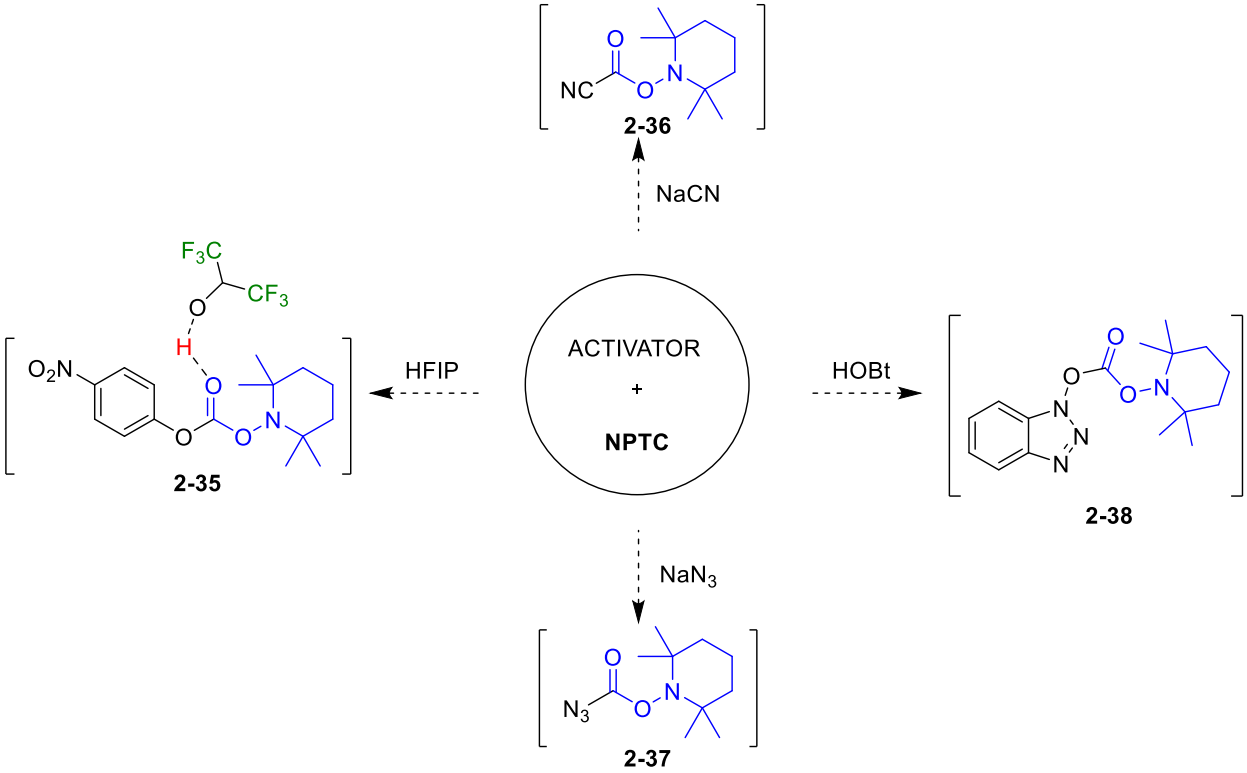
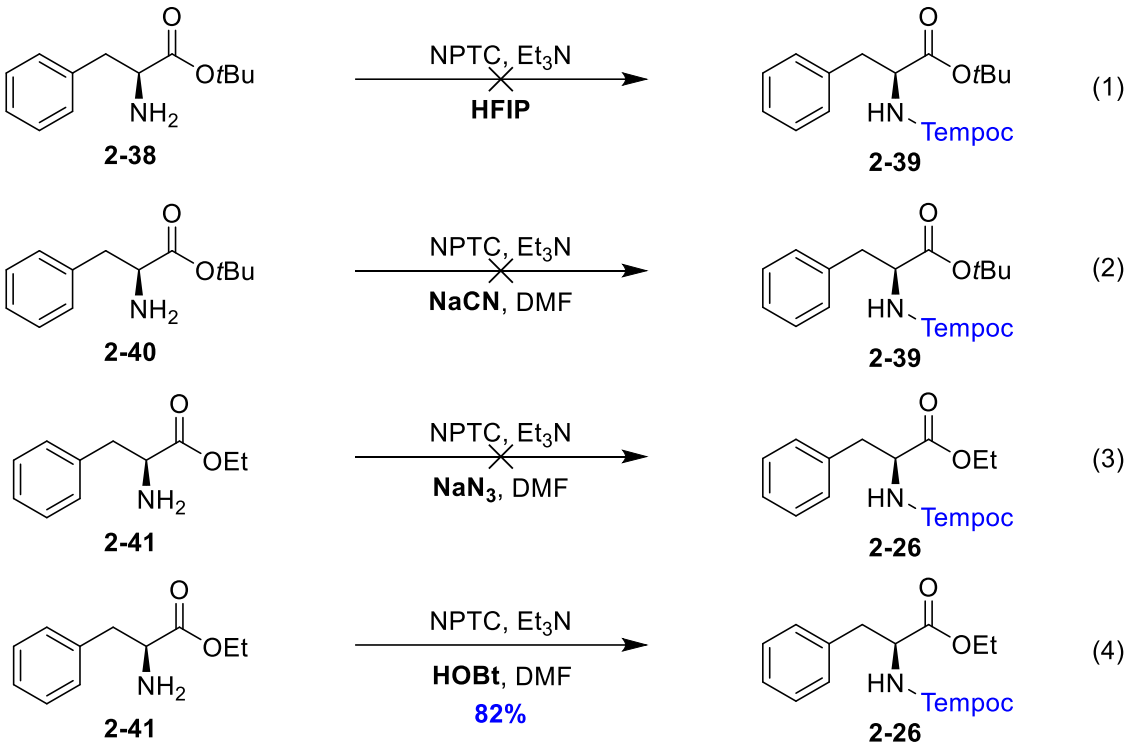


Figure 5 More reactive Tempoc transfer species generated *in situ* by addition of an activator

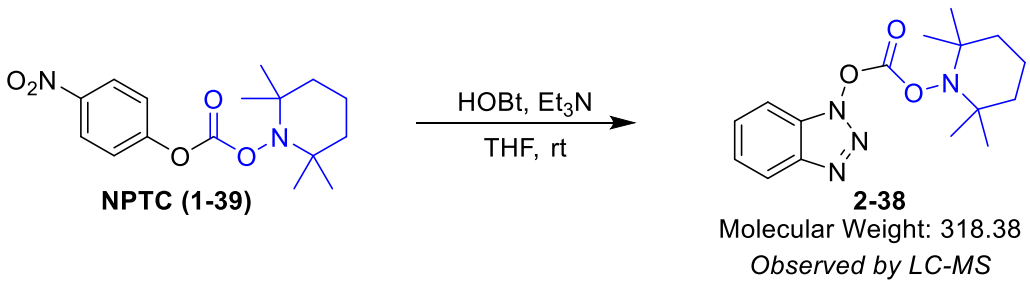
First, with the recent developments in HFIP reaction rate enhancements,[75] we proposed that switching to this highly polar solvent would activate the carbonyl of NPTC, thus making it

more susceptible to nucleophilic attack. However, when we tested this hypothesis, we only isolated decomposition products of NPTC (Scheme 21, Eq. 1). Next, sodium cyanide can act as a catalytic nucleophile to attack NPTC, thus forming Tempoc cyanoformate **2-36**, which would react readily with nucleophiles, however when phenylalanine ester **2-40** was exposed to NPTC in the presence of sodium cyanide, once again, only decomposition products of NPTC were isolated (Scheme 21, Eq. 2). Thirdly, azidoformates have a long history of being acyl transfer reagents,[76] and with this in mind, we thought the addition of catalytic amounts of sodium azide would form Tempoc azidoformate **2-37** *in situ*, and while the mass for this compound was observed by LC-MS, no reaction rate enhancement was observed, and only starting materials and decomposition products were formed (Scheme 21, Eq. 3). Finally, the use of HOBt in acylation Scheme 21 reactions is well known,[77] and when phenylalanine ester **2-41**, was treated with NPTC in DMF in the presence of 1.2 equivalents of HOBt, we were excited to isolate 82% of desired Tempoc amino ester **2-26** after 24 h (Scheme 21, Eq. 4).



Scheme 21 Test reactions of various NPTC activating additives

We hypothesized that the attack of HOBt onto NPTC forms small quantities of HOBt-adduct **2-38** which is a more reactive Tempoc transfer reagent that reacts readily with an incoming amine. While proof of this intermediate has not been proven spectroscopically, it's corresponding mass has been observed by LC-HRMS from the reaction of NPTC with HOBt in THF in the presence of triethylamine as base (Scheme 22).



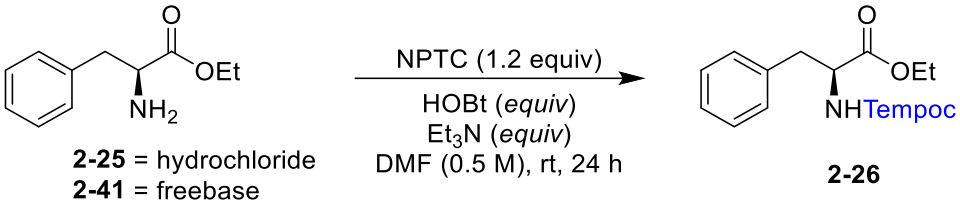
Scheme 22 Control reaction to confirm the formation of Tempoc-HOBt adduct **2-38**

With HOBt proving to be a potent NPTC activating agent, we set out to optimize the protection conditions of phenylalanine ethyl ester. As previously stated, in the absence of any

activator, protection of phenylalanine **2-25** in dry DMF with 3.0 equivalents of triethylamine, afforded only 19% of Tempoc amino ester **2-26** (Table 7, Entry 1). In the presence of 1.2 equivalents of HOBt, 3.0 equivalents of triethylamine, and molecular sieves in dry DMF, protection of **2-41** increased to 82% (Table 7, Entry 2). Interested in utilizing the commercially available and more stable hydrochloride salts, exposure of phenylalanine ester hydrochloride **2-25** to the same conditions, albeit with an extra equivalent of amine base, showed no decrease in yield, isolating Tempoc amine **2-26** in 84% (Table 7, Entry 3). Furthermore, reduction of HOBt loading to 1.0 equivalents in the presence and absence of molecular sieves led to comparable yields (Table 7, Entries 4 and 5). ACS grade solvents or also compatible with the reaction, even without molecular sieves (Table 7, Entries 6–7). Notwithstanding, we continued to use dry DMF throughout the project as we have found considerable variances in ACS grade DMF quality from different vendors. We were driven to further reduce the loading of HOBt to catalytic amounts while also reducing the equivalents of base to preclude any racemization propensity (Table 7, Entries 8–11). With 0.5 equivalents of HOBt, and 2.5 equivalents of triethylamine, Tempoc ester **2-26** was isolated in an acceptable 83% yield (Table 7, Entry 10).

HOBt hydrate water content is not precisely given on reagent bottles; therefore, to be accurate and reproducible with our reactions, we used the anhydrous reagent. However, HOBt hydrate is known to exhibit greater stability and is more readily available. Consequently, we set out to test it as an alternative to the anhydrous version. As expected, HOBt hydrate in the presence and absence of molecular sieves provided clean conversion to Tempoc phenylalanine **2-26** in 80% and 82% yields, respectively (Table 7, Entries 12 and 13). Alternative bases, solvents, HOBt substitutes, and further decreasing the loading of the activator led to diminished yields (Experimental Part, Table 16)

Table 7 Optimization of Tempoc protection of phenylalanine ethyl ester through NPTC activation



2-25 = hydrochloride
2-41 = freebase

2-26

entry	activator (equiv)	Et_3N (equiv)	4 Å MS[a]	solvent	isolated yield (%)
1	-	Et_3N (3.0)	Y	dry DMF	19
2[b]	HOBt (1.2)	Et_3N (3.0)	Y	dry DMF	82
3	HOBt (1.2)	Et_3N (4.0)	Y	dry DMF	84
4	HOBt (1.0)	Et_3N (4.0)	Y	dry DMF	88
5	HOBt (1.0)	Et_3N (4.0)	N	dry DMF	88
6	HOBt (1.0)	Et_3N (4.0)	Y	wet DMF	88
7	HOBt (1.0)	Et_3N (4.0)	N	**wet DMF**	87
8	HOBt (0.5)	Et_3N (4.0)	Y	dry DMF	83
9	HOBt (0.5)	Et_3N (3.0)	N	dry DMF	80
10	**HOBt (0.5)**	**Et_3N (2.5)**	**N**	**dry DMF**	**83**
11	HOBt (0.5)	Et_3N (2.0)	N	dry DMF	77
12	**HOBt hydrate (0.5)**[c]	Et_3N (2.5)	N	dry DMF	80
13	HOBt hydrate (0.5)[c]	Et_3N (2.5)	Y	dry DMF	82

[a]100 mg/mmol amine; [b]amine **2-41** was used; [c]HOBt (97%) contained ≥ 20% wt. water

Importantly, with our optimized conditions, Marfey's analysis was conducted on Tempoc phenylalanine **2-26**, which showed no detectable racemization under these protection conditions.[78,79] Additionally, a large scale synthesis of Tempoc transfer reagent NPTC and subsequent protection of phenylalanine ethyl ester using these optimized conditions has been detailed (Experimental Part).

With optimized conditions (*i.e.*, NPTC (1.0 equiv), HOBt (0.5 equiv), and triethylamine (2.5 equiv), in DMF (0.5 M, rt, 24 h), we set out to explore a variety of amino-esters for Tempoc protection. First, we sought to show that the reaction conditions are compatible with the range of ester protective groups used in peptide synthesis (Figure 6). Methyl, ethyl, *tert*-butyl, and benzyl glycinates were all protected in good to excellent yield. Moreover, unprotected glycine was also protected to afford Tempoc glycine amino acid **2-42** in 46% yield. Next, we tested the effect of *N*-

substitution on the amino ester; *N*-methyl ethyl glycinate was converted to its Tempoc derivative in 92% yield, whereas the *N*-benzyl analog suffered from reduced yields, only providing *N*-benzylated Tempoc amino ester **2-46** in 67% yield. Furthermore, Tempoc protection was extended to a variety of bulky substituted amino esters that all converted to their Tempoc derivatives **2-49** – **2-51** in good yields, except for α-cyclopropyl substituted amino ester **2-52**, which was isolated in only 30% yield. As in our previous work, NPTC chemoselectivity was maintained toward amines in the presence of hydroxyl groups and arylamines, even under these activated conditions. Interestingly, we were able to leverage the slow reactivity of the α-amino moiety toward NPTC in the absence of HOBt to selectively protect the side-chain of lysine ethyl ester in 90% yield.

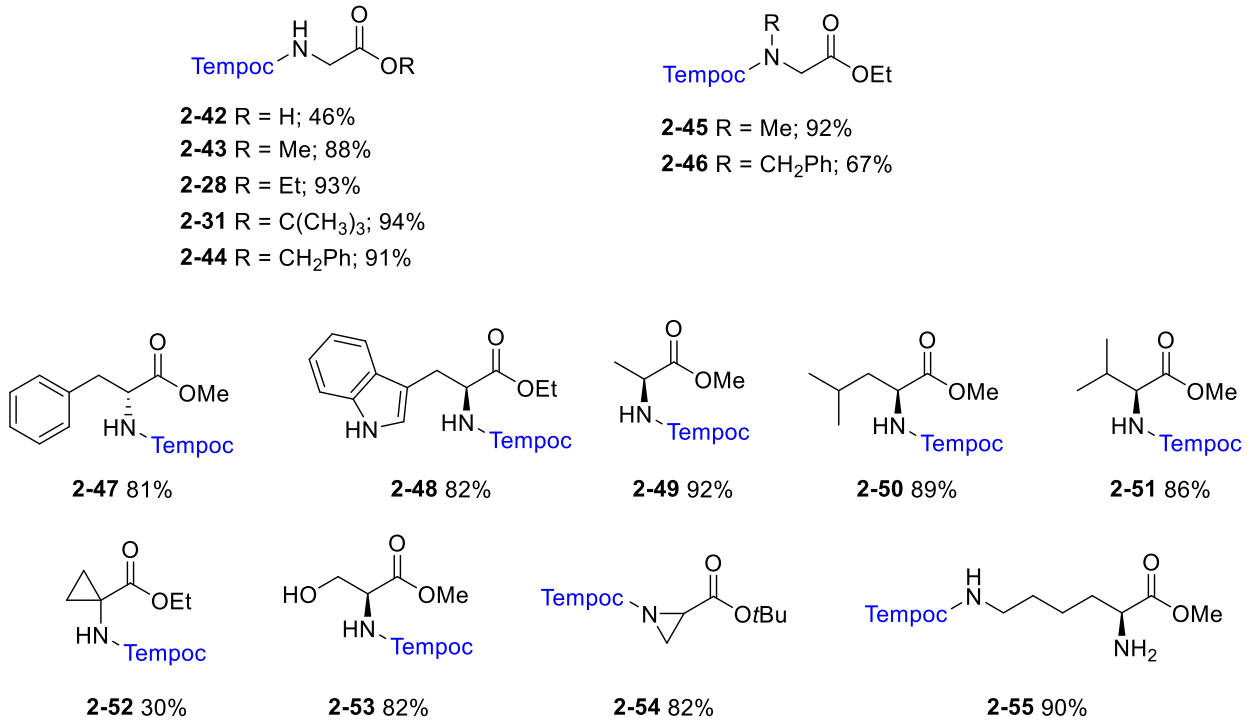
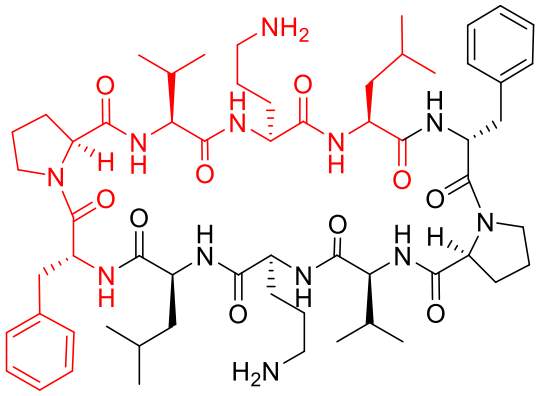


Figure 6 The scope of Tempoc protected aminno esters

2.2.3 Synthesis of Gramicidin S monomer

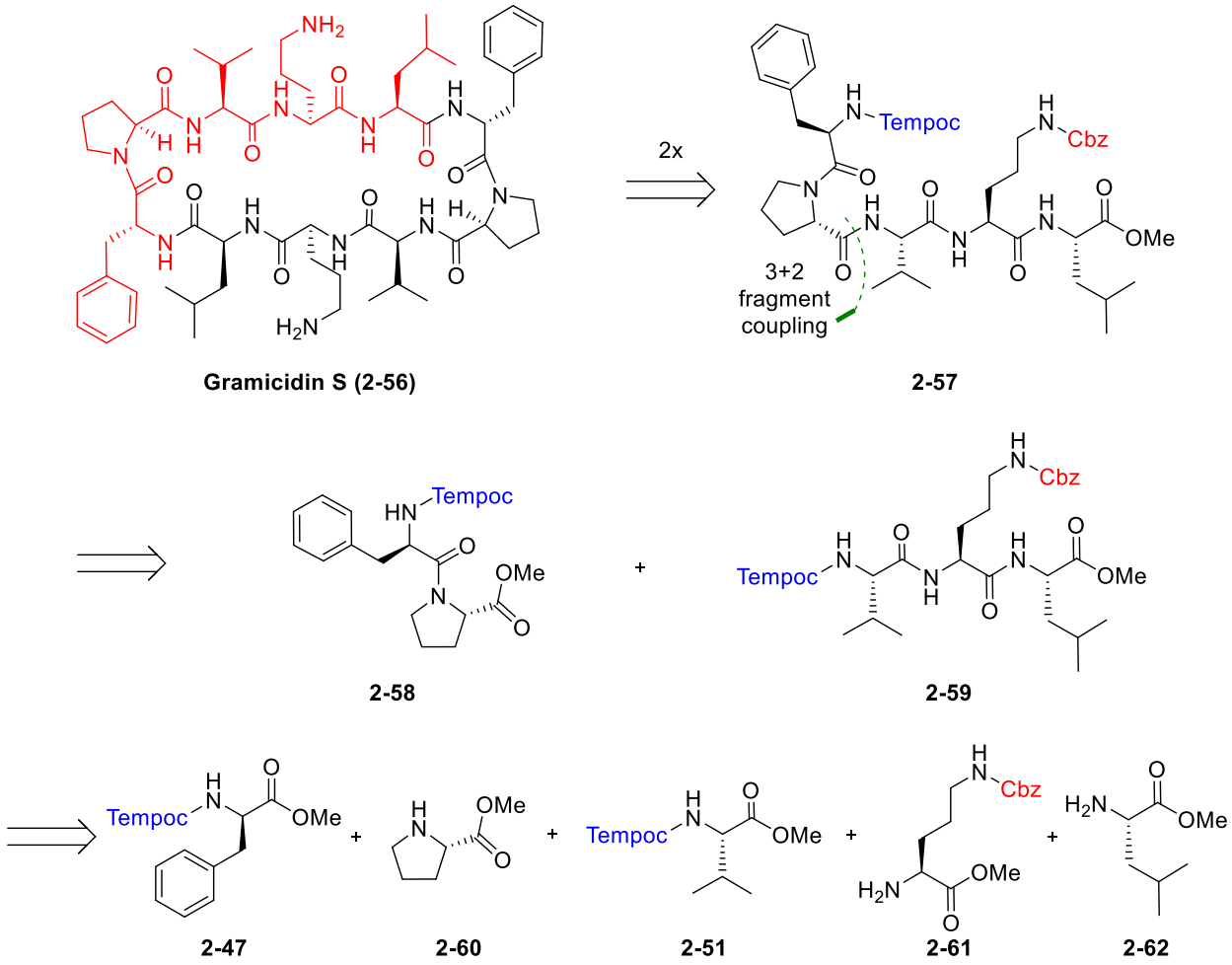
Finally, we were interested in demonstrating the utility of Tempoc as a useful protecting group for peptide synthesis be synthesizing a pentapeptide monomer of Gramicidin S (GS) (Figure 7). GS is a C_2-symmetric cyclic decapeptide that exhibits potent antibacterial effects against gram-positive and gram-negative bacteria.[80] GS, and its analogs have also been a compound of interest in our group, and we thought it appropriate to demonstrate our Tempoc methodology toward its synthesis.[81,82]



Gramicidin S (2-56)

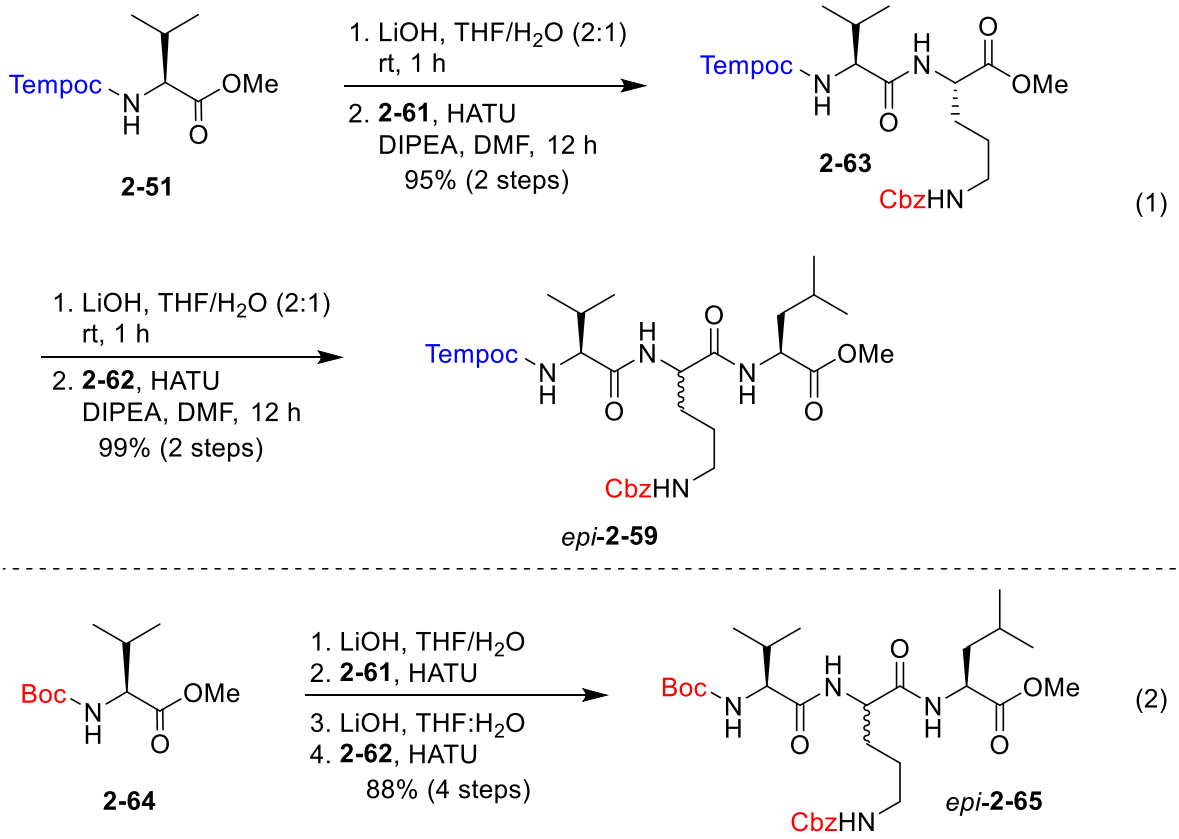
Figure 7 The structure of the cyclopeptide Gramicidin S

Our retrosynthetic analysis of Gramicidin S monomer **2-57** utilizes a 3+2 approach (Scheme 23). First, construction of Tempoc-protected tripeptide **2-59** would be carried out using typical HATU mediated coupling conditions starting with Tempoc valine **2-51**. Then, Tempoc dipeptide **2-58** would be synthesized in the same fashion staring with phenylalanine **2-47.** Final coupling of the tri- and dipeptide fragments would afford the pentapeptide monomer of Gramicidin S. Final Tempoc deprotection of **2-57** would afford the free amine, which may be further elaborated to Gramicidin S.



Scheme 23 Retorsynthetic analysis for the synthesis of Gramicidin S monomer **2-57**

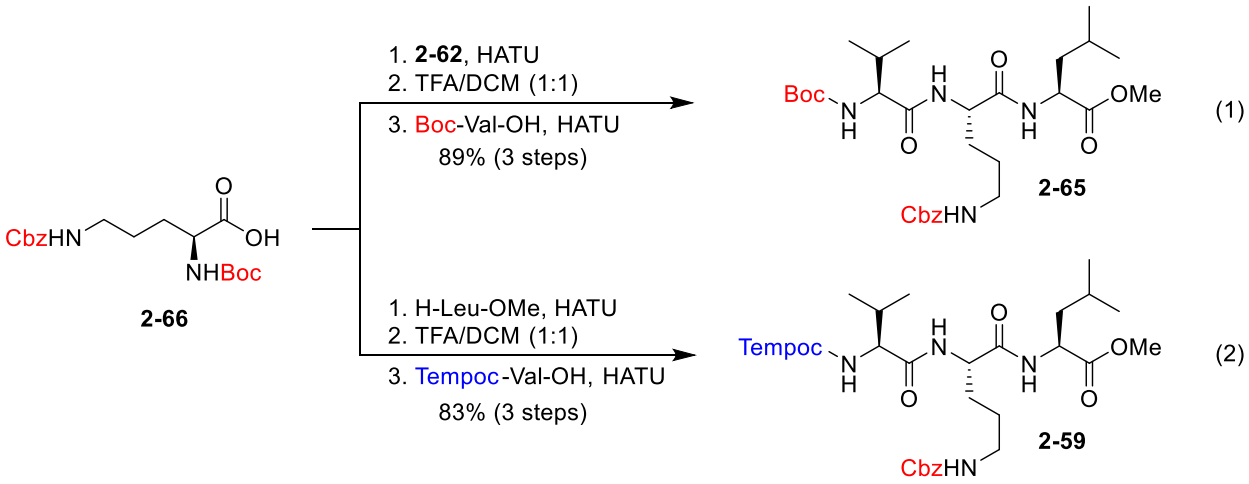
With this plan, the first objective was to synthesize tripeptide **2-59**. Our initial plan was to construct the peptide using standard solution phase methods building from the N- to the C-terminus. And indeed, the coupling steps went as expected affording tripeptide **2-59** in 94% overall yield. However, upon analysis of the NMR of tripeptide **2-59**, it was determined that epimerization had occurred, most likely at the ornithine α-carbon during the final coupling step affording tripetide *epi*-**2-59** as a 1.2:1 mixture of epimers (Scheme 24, Eq. 1).



Scheme 24 Original synthesis of Gramicidin fragment **2-59**

To confirm that this was not due to the nature of the Tempoc group, the Boc protected analog was synthesized and analyzed by NMR, which similarly produced tripepetide *epi*-**2-65** as a 1.2:1 mixture of epimers (Scheme 24, Eq. 2). In order to counteract the epimerization in the final coupling step, we switched our synthetic approach and starting from C-terminal leucine. Initially, we attempted our new synthetic approach on the Boc analog to confirm that our synthetic strategy would provide Boc-tripeptide **2-65** without any detectable racemization (Scheme 25, Eq. 1). Utilizing Boc, Cbz, *bis*-protected ornithine **2-66**, HATU mediated coupling with leucine methyl ester provided the Boc protected dipeptide intermediate which was directly deprotected with standard TFA conditions and subsequently treated once again with HATU in the presence of Boc-valine which provided tripeptide **2-65** in 89% overall yield. Tripeptide **2-65** was successfully synthesized without any detectible epimerization through NMR analysis. Our decision to use Boc-

ornithine **2-66** instead of its Tempoc equivalent was to avoid the well-known propensity of dipeptide cyclization under the mildly basic conditions required for Tempoc deprotection.[83,84] With our new synthetic route validated, we continued to construct Tempoc tripeptide **2-59** in the same manner in 83% yield over 3 steps (Scheme 25, Eq. 2).



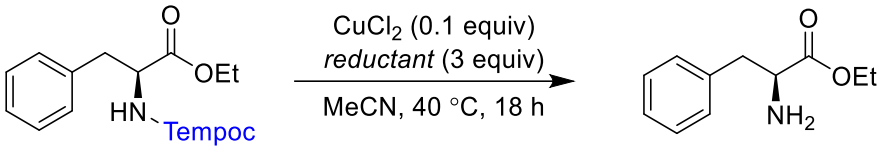
Scheme 25 Revised synthesis of Tempoc tripeptide **2-59**

2.2.4 Optimization of Tempoc deprotection

With a successful route towards tripeptide **2-59** in hand, we turned our attention to the Tempoc deprotection step. In our original publication we utilized *in situ* generated copper(I) to reductively cleave Tempoc. Our optimized conditions were copper(II) chloride (0.10 equiv) and ascorbic acid (3.0 equiv) in a ternary mixture of MeCN/THF/H_2O (0.12 M, 12 h, 40 °C). Initial reactions with Tempoc phenylalanine ethyl ester **2-26** led to a new peak in the LC-MS trace which accounted for approximately 40% of the total peak area on the UV trace at 220 nm. After careful analysis of the byproduct mass, and a thorough literature search of the known ascorbic acid byproducts, we deduced that the unidentified peak was that of the condensation product of deprotected phenylalanine **2-25** and xylosone. Xylosone is a known degradation product of

dehydroascorbic acid, which is produced stoichiometrically from the reduction of copper(II) chloride during the course of the deprotection.[85,86] We hypothesized that this imine underwent acid-mediated solvolysis during our tosic acid resin workup-isolation protocol, thus, this byproduct was never observed. Using this result as an opportunity to modify the original conditions to preclude formation of this byproduct we explored alternative reducing agents such as Zn, Mn, Fe, In, Mg, $NaHSO_3$, Na_2SO_3, and $Na_2S_2O_3$ in the presence of copper(II) chloride (0.10 equiv). However, either no product was observed or only a small amount of deprotected amino ester **2-25** was detected by HPLC-MS (Table 8). We believed that the reducing metals over-reduced copper(II) to copper(0) before the intermediate copper(I) species could enter the catalytic cycle. Moreover, the sulfur reducing agents either produced copper(0) as well, or precipitated the copper as a reddish-brown insoluble sulfite adduct believed to be Chevreul's salt (Cu(I,II) sulfite dihydrate).

Table 8 Reaction screen for alternative reducing agents for Tempoc deprotection



2-26 **2-25**

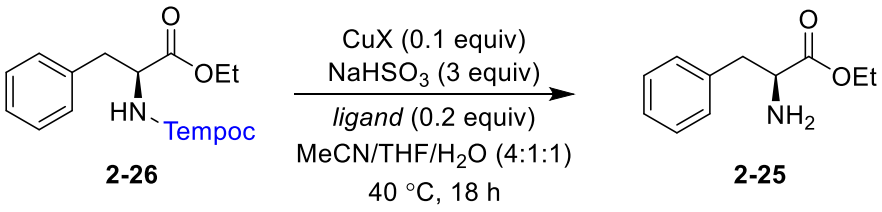
entry	reductant	conversion (HPLC-MS)	observations
1	Zn	trace	copper(0) ppt
2	Mg	trace	copper(0) ppt
3	Fe	ND	copper(0) ppt
4	In	trace	copper(0) ppt
5	Mn	ND	copper(0) ppt
6	1.5 M aq. $NaHSO_3$	< 10%	Chevreul's salt ppt
7	1.5 M aq. Na_2SO_3	< 10%	Chevreul's salt ppt
8	1.5 M aq. $Na_2S_2O_3$	trace	copper(0) ppt

ND = not detected; ppt = precipitate; HPLC-MS = conversion determined by AUC @ 220 nm; Chevreul's salt = copper(I,II) sulfite dihydrate

Still interested in utilizing an inorganic reductant to facilitate workup and preclude formation of the xylosone byproduct, we attempted to add a ligand to stabilize the copper in

solution and reduce formation of the insoluble Chevreul's salt. With sodium bisulfite as the reductant in the presence of 0.1 equivalents of copper(II) chloride, we screened 4 common ligands, tetramethylethylenediamine (TMEDA), bipyridine (bpy), ethylenediamine (en), and dimethoxyethane (DME) (Table 9). In all cases the reaction stalled with no more than 10% conversion to desired free amine **2-25**, even with increased heating (60 °C) and longer reaction time (48 h). We also utilized the commercially available copper(I) thiophenecarboxylate complex, which also stalled after no more than 10% conversion. In all cases we observed the formation of Chevreul's salt, which precipitated as a red-brown solid, indicating that the complexation of copper with sulfite is quite facile.

Table 9 Screen of copper ligands to enable utilization of inorganic reducing agents



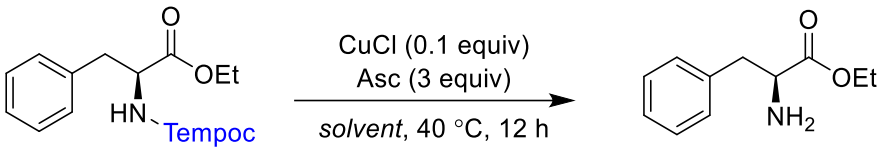
entry	CuX	ligand	conversion (HPLC-MS)
1	$CuCl_2$	TMEDA	< 10%
2	$CuCl_2$	bpy	< 10%
3	CuTC	–	< 10%
4	$CuCl_2$	en	< 10%
5	**$CuCl_2$**	DME	< 10%
6	$CuCl_2$	–	< 10%

HPLC-MS = conversion determined by AUC @ 220 nm

Since other reducing agents proved to be inferior, we resumed the use of ascorbic acid. We questioned the possibility of precipitating the DHA during the reaction by performing the reaction under anhydrous conditions. A qualitative test showed that in DME, DMF, and MeCN ascorbic acid exhibited enough solubility to reduce copper(II) to colorless copper(I). With this in mind, we ran a screen of solvent mixtures (Table 10). In all cases, the reaction developed a deep red color and HPLC-MS showed the presence of the xylosone adduct, plus several additional unidentifiable

peaks. Moreover, the reaction rate seemed to be slowed by either the absence of water, or the formation of other deleterious byproducts. Therefore, we concluded that the presence of water in the reaction was reducing the propensity of DHA to decompose into other compounds. Interestingly, we did notice that the reaction in 5:1 DME/H_2O (Table 10, Entry 3) was complete in under 12 h, while also displaying the cleanest reaction profile. This was a serendipitous discovery, which led us to swap DME for THF *and* MeCN in future optimizations. Importantly, we hypothesized that DME would fill two roles, 1) as a ligand to stabilize copper(I), and 2) as a solubilizing agent to replace THF. Additionally, DME is commonly sold inhibitor-free, thereby reducing yet another possible contaminant in the deprotection reactions.

Table 10 Solvent screen for THF replacement in Tempoc deprotection



2-26 **2-25**

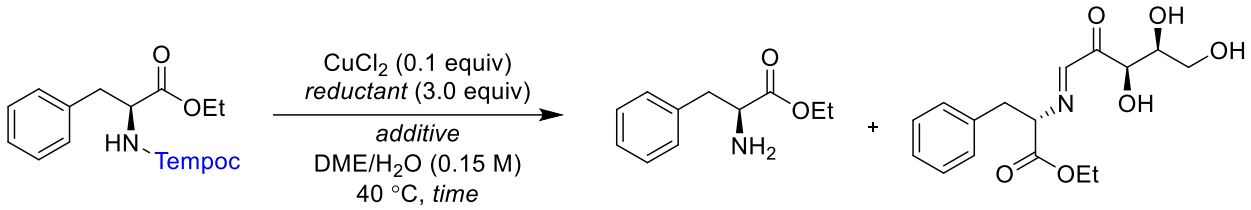
entry	solvent	conversion after 12 h (HPLC-MS)
1	MeCN	incomplete
2	MeCN:DME (10:1)	incomplete
3	**MeCN:DME (5:1)**	complete
4	MeCN:DMF (3:1)	incomplete
5	MeCN:DMF:DME (6:2:1)	complete
6	MeCN:DMF:DME (3:1:1)	complete

HPLC-MS = conversion determined by AUC @ 220 nm

With our new goal of using ascorbic acid as the reductant, and replacing acetonitrile and THF with DME, we further screened a number of deprotection modifications and monitored the formation of byproduct **2-67** by HPLC-MS analyzed at 220 nm (Table 11). To further understand the kinetics of the formation of this condensation product, we monitored the reaction over time by sampling the reaction mixture at 90-minute intervals to see if the formation of the DHA-byproduct happens immediately or slowly during the reaction. We hypothesized that increasing the

concentration of water in the reaction would help to hydrolyze imine **2-67**, thus precluding its accumulation during the reaction. Indeed, as water concentration increased, decreased amounts of imine **2-67** were observed by HPLC-MS (Table 11, Entries 1–3). Next, we hoped that lowering the pH of the reaction mixture would preclude formation of the imine by sequestering the nitrogen lone-pair *via* protonation, or by aiding the hydrolysis of **2-67** by acidic activation. Unfortunately, while lowering the pH of the mixture and increasing the water concentration did lead to a reduction of the impurity from 40% to 30% (Table 11, Entries 4–6), complete removal of the impurity was not achieved.

Table 11 Optimization towards minimization of byproduct formation in Tempoc deprotection



2-26 **2-25** **2-67**

entry	reductant	solvent ratio (DME:H2O)	additive (equiv)	conversion (h)	**2-69** (AUC %)
1	Asc	4:1	–	1.5	48
2	Asc	2:1	–	1.5	44
3	Asc	1:4	–	1.5	30
4	Asc	4:1	AcOH (3.0)	1.5	40
5	Asc	2:1	AcOH (3.0)	1.5	36
6	Asc	1:1	AcOH (3.0)	1.5	30
7	Asc	1:1	AcOH (5.0)	1.5	40
8	**NaAsc**	1:1	–	1.5	0
9	$NaHSO_3$	4:1	–	NC	0
10	Zn	1:0	–	NC	0
11	Mg	1:0	–	NC	0

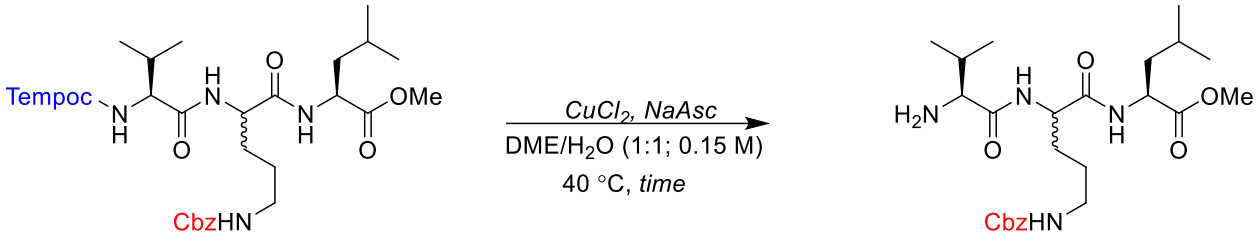
NC = reaction stalled after 1.5 h; AUC % = determined by HPLC-MS AUC @ 220 nm

Furthermore, increasing the amount of acetic acid actually increased the amount of observed imine **2-67** (Table 11, Entry 7), leading us to believe that the imine is quite stable, and acid may be catalyzing the condensation rather than the hydrolysis. However, we were excited to

discover that when the ascorbic acid was replaced by its sodium form (sodium ascorbate, NaAsc) we observed no detectable quantities of imine **2-67** (Table 11, Entry 8). Possibly, nearly neutral pH conditions reduced the rate for the formation of xylosone to lower than the rate of Tempoc deprotection. Another interesting observation made during the optimization was that all reactions were complete within 90 min. We hypothesize that with the introduction of DME as solvent and ligand, the stability of the *in situ* generated copper(I) species was greatly increased, leading to faster catalyst turnover. Finally, we retested the inorganic reductants sodium bisulfite, zinc, and magnesium once more to see if their reactivity was also enhanced by the introduction of DME as solvent. However, we observed that the reactions once again stalled after only a minimal amount of conversion (Table 11, Entries 9–11).

With these enhanced conditions (*i.e.*, sodium ascorbate in 1:1 DME/H_2O), we anticipated the ability to reduce the copper loading and equivalents of reductant needed beyond what was capable using ascorbic acid in the ternary solvent mixture. As such, we proceeded to switch to Tempoc tripeptide *epi*-**2-59** and continue our optimization utilizing this highly functionalized compound (Table 12). As expected, this functionalized tripeptide deprotected at a slower rate than Tempoc phenylalanine **2-26**, probably due to increased molecular weight and greater bulk around the target amine. The deprotection with 10 mol % copper(II) chloride, and 3.0 equivalents of sodium ascorbate was complete in under 2.5 h, as opposed to 1.5 h as was observed by HPLC-MS (Table 12, Entry 1). We were able to reduce the copper(II) loading to 3.5 mol % with only a moderate increase in reaction time to 7 h (Table 12, Entries 2–4). Further reduction in copper loading was met with poor reproducibility in conversion times (Table 12, Entries 5 and 6). Next, with 3.5 mol % copper(II) in 1:1 DME/H_2O, we were able to decrease the equivalents of sodium ascorbate down to 1.2 before reaction instability was observed (Table 12, Entries 7–11).

Table 12 Optimization of copper and reductant loading for the Tempoc deprotection of *epi*-**2-59**



epi-**2-59** **2-68**

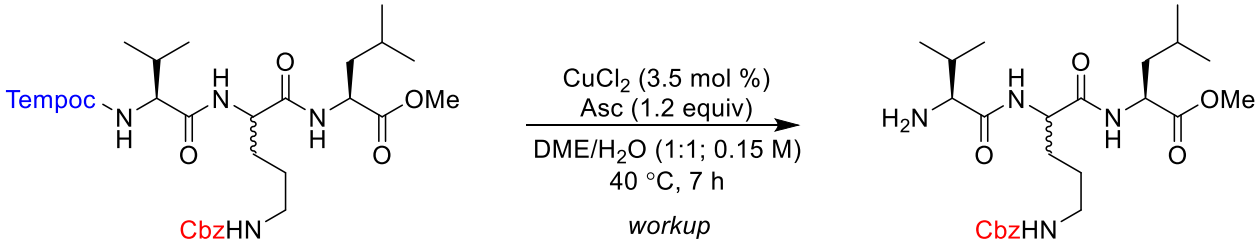
entry	$CuCl_2$ (mol %)	NaAsc (equiv)	conversion time (h)
1	10.0	3.0	< 2.5
2	7.5	3.0	< 2.5
3	5.0	3.0	5
4	3.5	3.0	7
5	2.5	3.0	6–9
6	1.0	3.0	> 12
7	3.5	2.5	7
8	3.5	2.0	7
9	3.5	1.5	7
10	**3.5**	1.2	7
11	3.5	1.0	7.5–8

Conversion time was determined by consumption of starting material as observed by LC-MS

With the deprotection conditions fully optimized (i.e. 3.5 mol % $CuCl_2$, 1.2 equiv NaAsc, in 1:1 DME/H_2O (0.15 M, 40 °C, 7 h)) we set out to reevaluate the reaction workup in order to preclude the need for chromatography. In our original publication, we utilized a catch-and-release method to purify the resultant amines.[1] While the tosic acid functionalized resin (SiliCycle Si-TsOH) was convenient and effective for our previous scope, we envisioned the use of this resin in the context of peptide synthesis to be problematic. Common protective groups used in peptide synthesis, such as trityl, Boc, and *tert*-butyl esters and ethers, could potentially be unstable to the strongly acidic resin.[87] Therefore, we wanted to devise a milder alternative method for chromatography-free amine isolation. With our target impurities being copper salts in various

oxidation states and ascorbate (and its possible degradation products), we devised a plan to isolate the peptide amine in pure form (Table 13).

Table 13 Optimization of the chomatography-free Tempoc deprotection of tripeptide *epi*-**2-59**



epi-**2-59** **2-68**

entry	workup/isolation	phase	result
1	catch and release	IRC-86	amine not retained
2	catch and release	MAC-3	amine not retained
3	catch and release	CG-50	amine not retained
4	extraction	1 M NH_4OH	emulsion
5	extraction	1 M $(NH_4)_2SO_4$	emulsion
6	extraction	0.5 M Na_3-citrate	emulsion
7	extraction then chromatography	sat. NaCl then SiO_2	phase split
8	extraction	sat. NH_4Cl-NH_4OH (pH=10)	phase split and copper removal

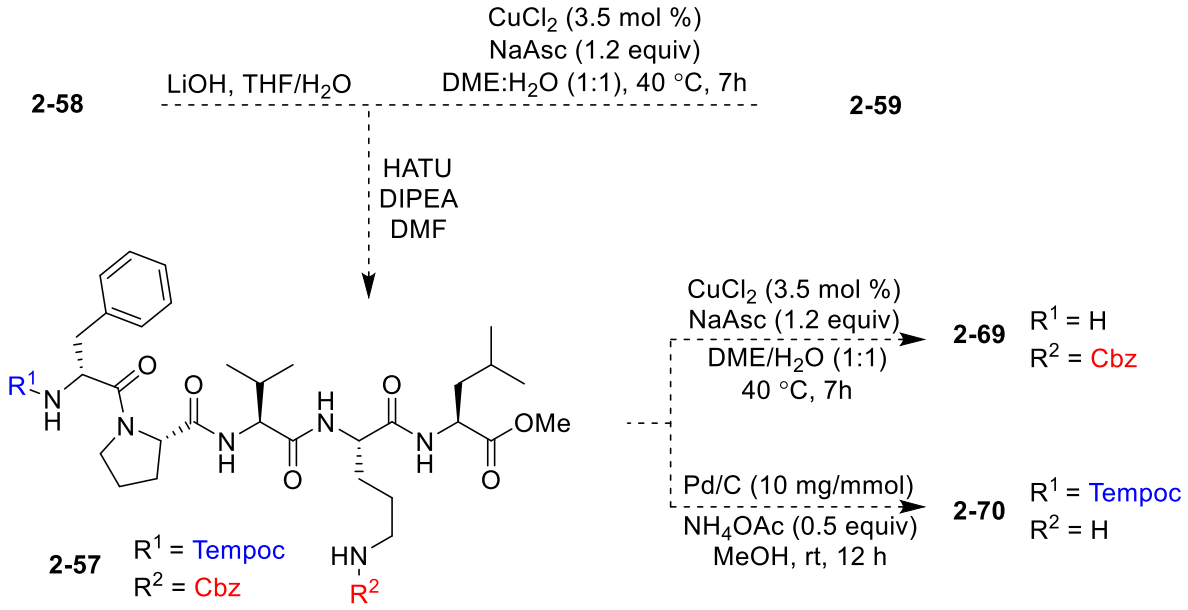
First, to amend our original catch-and-release method of purification, we attempted to switch the resin from the strong sulfonic acid to a weaker carboxylic acid functionalized resin. We envisioned the weaker acid being compatible with the sensitive protective groups used in peptide synthesis while maintaining the ability to 'catch' the liberated free amine. However, when the reaction mixture was passed through a 1.5" plug of carboxylic acid functionalized resins IRC-78, MAC-3, and CG-50, we observed no retention of the basic amine (Table 13, Entries 1–3). We then tried stirring of the crude reaction mixture for 60 min in the presence of the resin, followed by filtration, and once again, we observed no retention of the amine. It is worth noting that copper was effectively removed by stirring in all three of the resins. Next, we thought that a creative extractive workup could provide deprotected peptide **2-68** in pure form. Initial aqueous workups

on **2-68** typically resulted in the formation of persistent emulsions that resulted in low mass recovery. In an attempt to simultaneously remove the residual copper salts, and also remove the ascorbate byproducts, we targeted three high-ionic strength aqueous phases, and directly washed our crude reaction mixtures with them after dilution with ethyl acetate (Table 13, Entries 4–6). High-ionic strength solutions should preclude emulsion formation while also ensuring excellent recovery of the possibly water-soluble peptide **2-68**.[88] While the 1 M ammonium hydroxide, 1 M ammonium sulfate, and 0.5 M trisodium citrate aqueous phases did remove the copper salts and ascorbate byproducts, unfortunately, persistent emulsions or complex rag-layers also formed, resulting in low recovery of peptide **2-68**. Granted that when we then tested a saturated sodium chloride extraction a clean phase-split of the aqueous/organic layers was observed, copper salts also partitioned into the organic layer with varying amounts of ascorbate byproducts, and the resulting extract required subsequent chromatography (Table 13, Entry 7). Finally, utilizing the promising results from ammonia solutions, we sought to create a buffered ammonia solution of considerable ionic strength while also maintaining ease of work-up by using standard laboratory resources. Thus, we adjusted the pH of a saturated ammonium chloride solution to pH = 10 by the addition of concentrated ammonium hydroxide. After dilution of the reaction mixture with ethyl acetate, and treatment of the organic layer with this solution, we observed a clean phase-split, which after separation resulted in complete removal of the copper and ascorbate impurities, resulting in clean recovery of deprotected tripetide **2-68** (Table 13, Entry 8).

2.2.5 Future directions

With optimized deprotection conditions in hand, and synthesis of Tempoc protected Gramicidin fragment **2-59** completed, we propose the completion of the synthetic sequence to **2-**

57 (Scheme 26). Dipeptide **2-58** should be easily accessible using standard HATU mediated coupling, which after saponification with lithium hydroxide would afford the carboxylic acid. Subsequently, this intermediate would be coupled with the free amine of **2-59** after Tempoc deprotection. Finally, an orthogonal deprotection of pentapeptide **2-57** would selectively afford Tempoc deprotected **2-69**, or alternatively, Cbz deprotected **2-70**.



Scheme 26 Proposed completion of Gramicidin monomer **2-57**

3.0 EFFORTS TOWARDS THE TOTAL SYNTHESIS OF α-CYCLOPIAZONIC ACID

3.1 INTRODUCTION

3.1.1 α-Cyclopiazonic acid structure and activity

α-Cyclopiazonic acid (CPA) is a mycotoxin produced by the fungi *Aspergillus* and *Penicillium*.[89] The first isolation and structure elucidation was by Holzapfel in 1968, who isolated the compound from cereal grains that were infected by *Penicillium cyclopium Westling*.[90] This small indole-tetramic acid molecules possesses activity against sarcoplasmic reticulum Ca^{2+} ATPases (SERCA), which has been linked to heart failure, carcinogenesis, diabetes, and cardiac hypertension.[91,92] SERCA is a calcium pump that is essential for calcium transportation to the muscles, and cyclopiazonic acid has been shown to be one of a very limited number of specific inhibitors of this biological target.[93] More recently, CPA has been shown to have antiviral activity against the human respiratory syncytial virus (HRSV).[94]

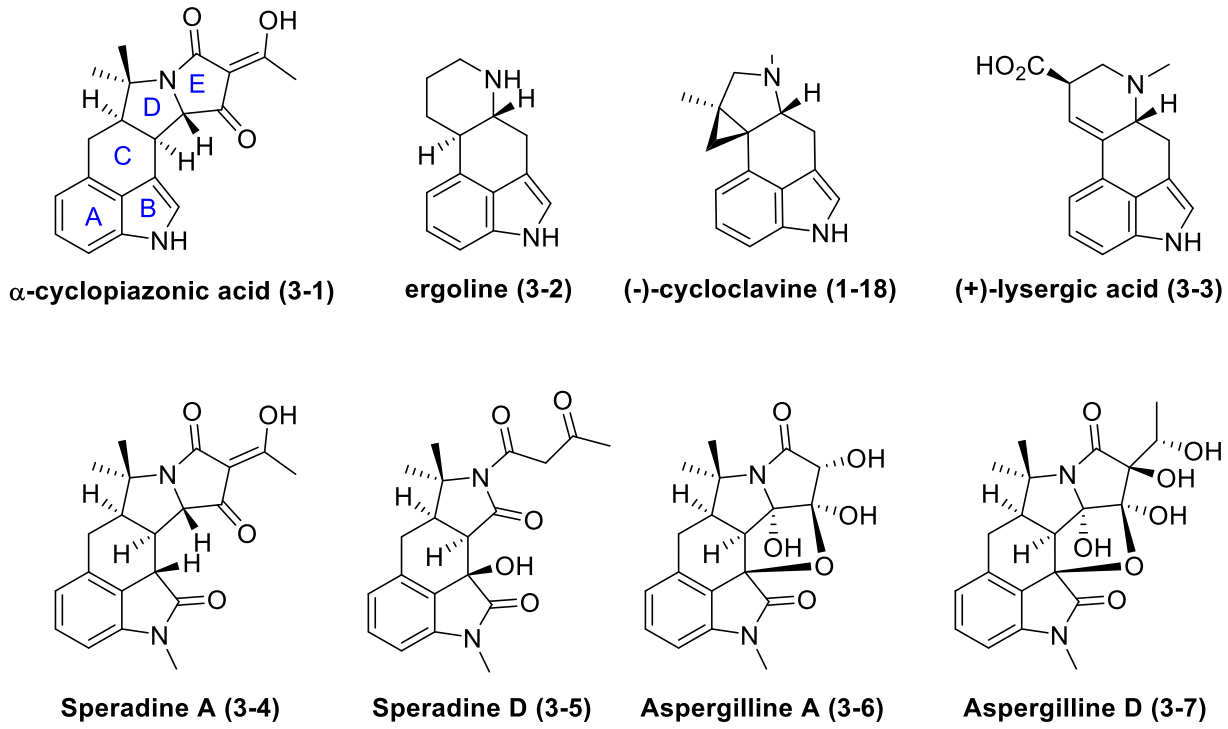
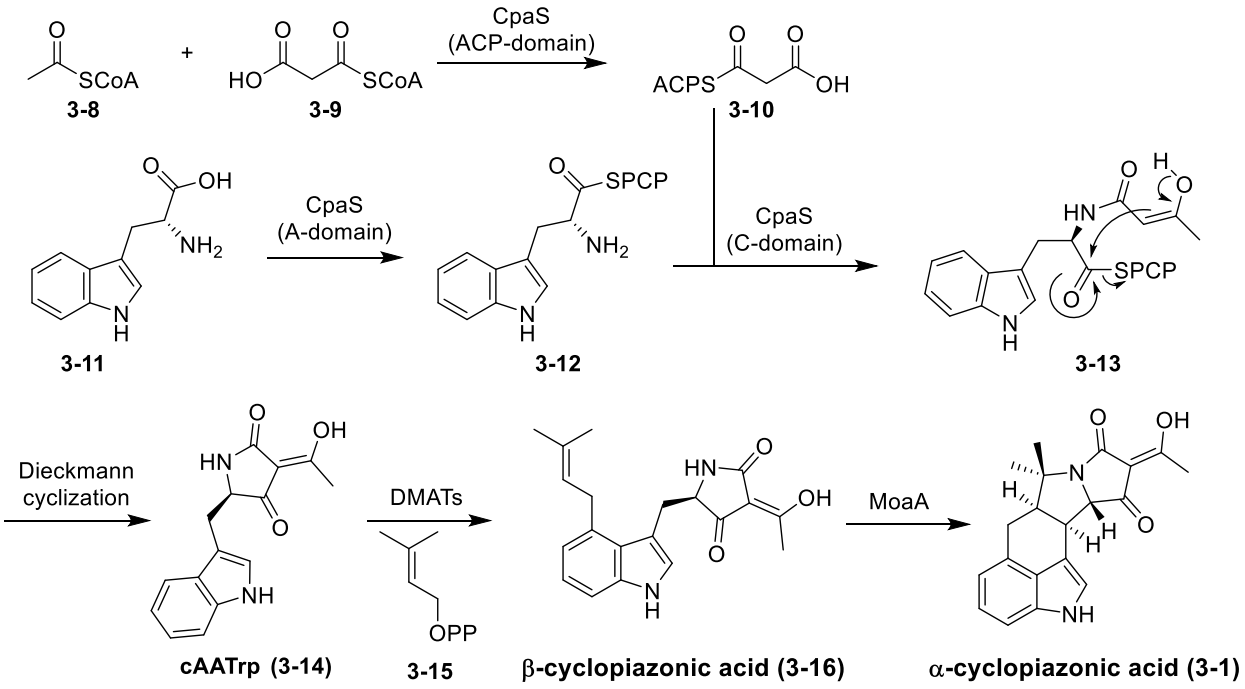


Figure 8 The structures of CPA and selected Speradines and Aspergillines

The pentacyclic structure of CPA closely resembles the ergoline family of alkaloids, including cycloclavine and lysergic acid (Figure 8). Furthermore, highly oxygenated congeners of cyclopiazonic acid, such as Speradines B-F[95–97] and Apergillines A-E,[98] have been isolated and have been receiving much attention in the synthetic community.[99–101]

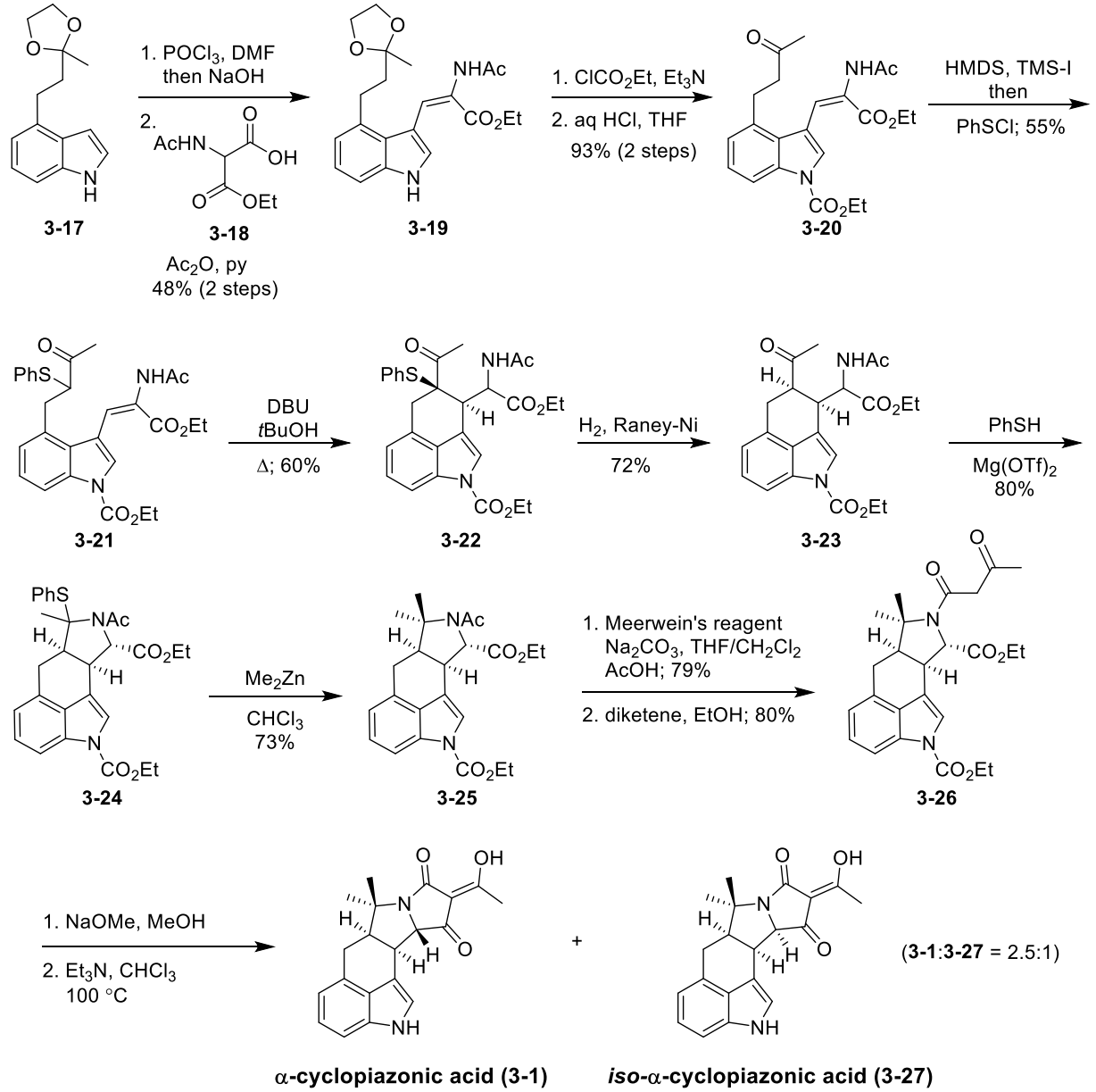


Scheme 27 Biosynthesis of CPA

Cyclopiazonic acid is synthesized biologically from *L*-tryptophan.[102,103] Pyrrolidinedione **3-14,** *cyclo*-acetoacetyl-L-tryptophan (*c*AATrp), is the first stable intermediate in the biosynthetic pathway. This is derived from the Dieckmann cyclization of acetoacetamide **3-13**, which is formed through an acylation of tryptophan with an acetoacetyl-tethered ACP (acyl carrier protein). Next, C(4) alkylation of the indole ring with DMAPP, **3-15** (dimethylallyl pyrophosphate) gives β-cyclopiazonic acid **3-16**, and subsequent reductive ring closure of the pyrrolidinedione onto the prenyl moiety affords α-cyclopiazonic acid **3-1**. This final annulation is catalyzed by the FAD-dependent enzyme monoamine oxidase A (MaoA).

3.1.2 Previous syntheses of cyclopiazonic acid

The unique biological properties of CPA have aroused the interest of synthetic chemists for decades. However, since its discovery in 1968 there have only been three syntheses of racemic CPA, and two enantioselective syntheses of (–)-CPA. The first total synthesis of racemic cyclopiazonic acid were reported in 1984 by Kozikowski and Greco (Scheme 28).[104]

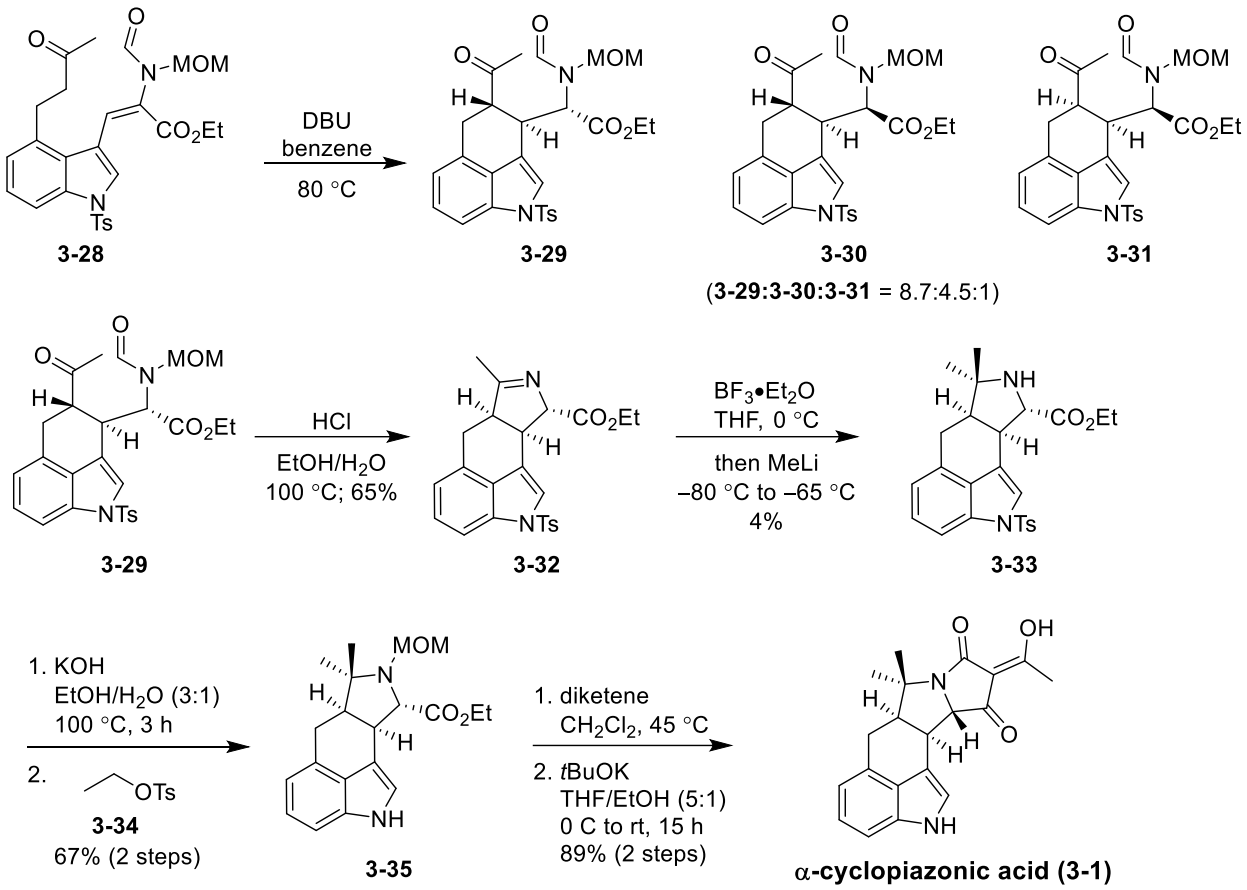


Scheme 28 Kozikowski and Greco's total synthesis of racemic CPA

Indole **3-17** was prepared in 4 steps from 1-tosyl-indole-4-carboxyaldehyde with an overall yield of 82%. Vilsmeier-Haack formylation and subsequent condensation with acetamidomalonic acid ester **3-18** gave intermediate acetal **3-19**. Protection of the indole nitrogen and deacetalization liberated ketone **3-20**. Pyrrolidine **3-24** was elaborated through trimethylsilyl iodide mediated thermodynamic enolization, and treatment of the enolate with phenylsulfenylchloride provided sulfide **3-21** in 55% yield. Under basic conditions, intramolecular Michael addition afforded tricycle **3-22** in good yield. Desulfurization with Raney nickel provided pyrrolidine **3-23** with *cis* configuration. Magnesium triflate-catalyzed condensation of the acetamide onto the ketone in the presence of thiophenol produces the pyrrolidine sulfide adduct **3-24**. Treatment of the sulfide with dimethyl zinc in chloroform finalized construction of the *gem*-dimethyl substitution. Exposure of acetamide **3-25** to Meerwein's reagent deprotected the amine, which reacted smoothly with diketene to afford the penultimate cyclopiazonic acid precursor **3-26**. Sodium methoxide promoted the intramolecular Dieckmann condensation onto the ethyl ester, providing *iso*-α-cyclopiazonic acid **3-27**, which was epimerized to desired isomer **3-1** with heating in the presence of triethylamine. Ultimately, the epimerization provided a 2.5:1 mixture of desired isomer **3-1** to *iso*-compound **3-27**.

A year later, in 1985, Natsume published a variant of the total synthesis of racemic cyclopiazonic acid (Scheme 29).[105] In a similar fashion to Kozikowski, he utilized an intramolecular Micheal addition to construct the C-ring, which led to a mixture of stereoisomers **3-29**, **3-30**, and **3-31** in a ratio of 8.7:4.5:1 with an overall yield of 84%. Isomer **3-29** was exposed to hydrogen chloride in a mixture of ethanol and water, which produced cyclic imine **3-32** in good yield. Installation of the *gem*-dimethyl proved difficult using organometallic reagents, and after treatment of the imine with boron trifluoride diethyl etherate, methyl lithium was added to produce

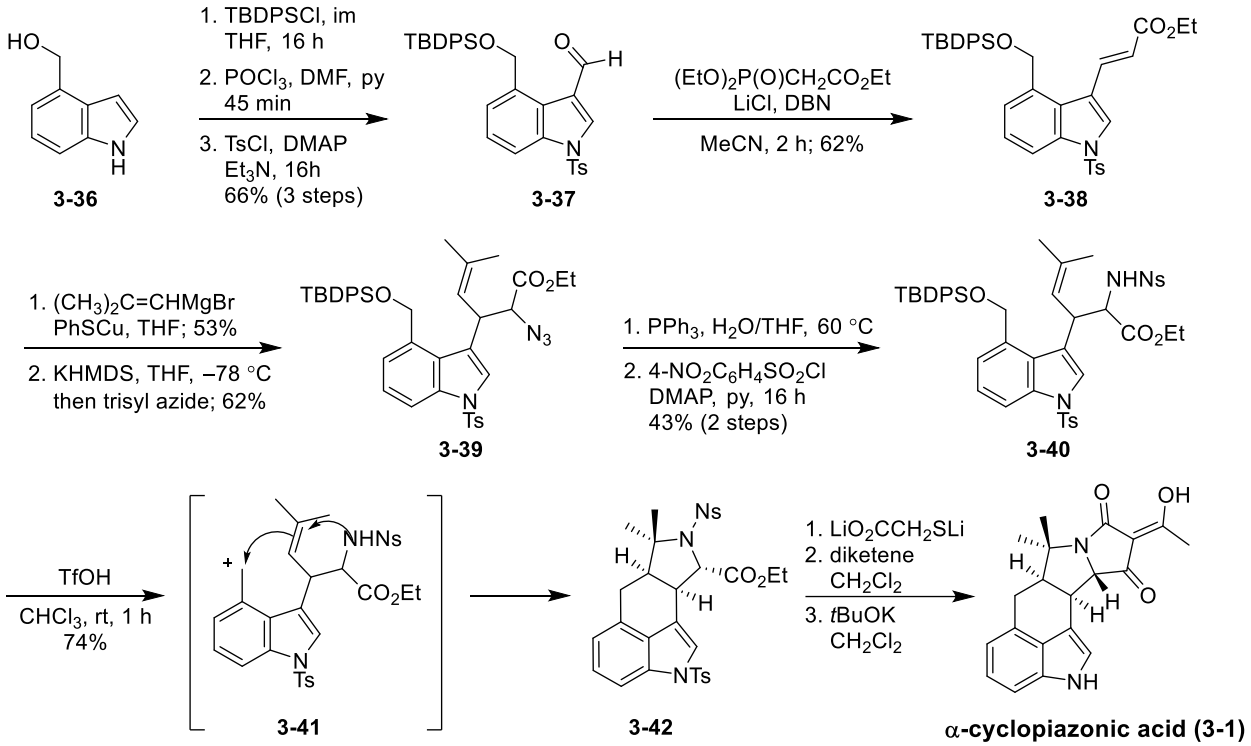
dimethyl product **3-33** in 4% yield. Deprotection of indole **3-33** was accomplished using basic hydrolysis with KOH, and the resulting acid was re-esterified with ethyl tosylate **3-34** to afford amino ester **3-35**. Dieckmann cyclization with diketene furnished α-cyclopiazonic acid **3-1** in 89% over two steps.



Scheme 29 Natsume's 1985 total synthesis of **3-1**

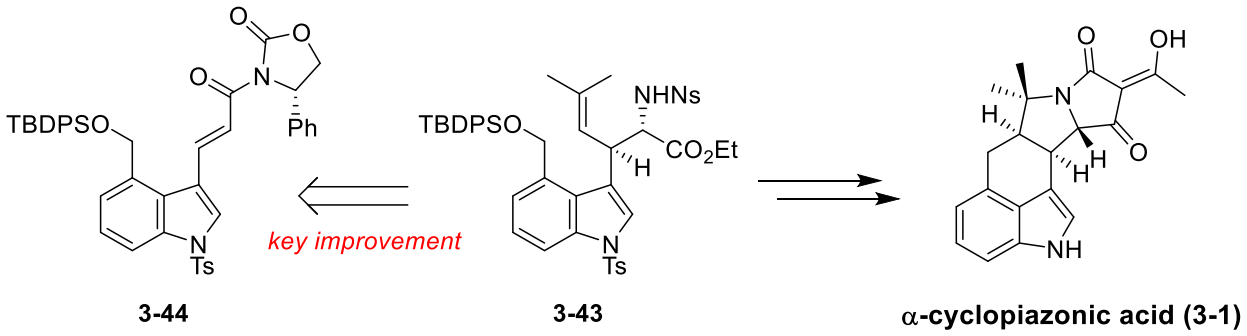
Another synthesis of racemic cyclopiazonic acid was published in 2005 by Haskins and Knight.[106] In their synthesis, they utilized a creative cationic cascade reaction to construct the C- and D-rings (Scheme 30). Beginning with 4-hydroxylmethyl indole **3-36**, protection of the free hydroxyl as the silyl ether followed by Vilsmeier-Haack formylation and tosylation of the indole nitrogen gave intermediate **3-37** in 66% yield over 3 steps. Horner-Wadswroth-Emmons homologation of the aldehyde afforded unsaturated ester **3-38** in good yield. Phenylthiocuprate

mediated conjugate addition of proprenylmagnesium bromide onto ester **3-38**, followed by enolization and nucleophilic azidolysis provided azidoester **3-39**. Staudinger reduction and protection of the free amine gave nosylate **3-40** in reasonable yield over 2 steps. Triflic acid promoted cationic cascade cyclization provided the C- and D-rings of intermediate **3-42** in 74% yield. Finally, deprotection of the nosylate, and tetramic acid formation utilizing treatment of the free amine with diketene and subsequent base-mediated condensation cleanly afforded racemic cyclopiazonic acid.



Scheme 30 Knight's 2005 synthesis of racemic 3-1

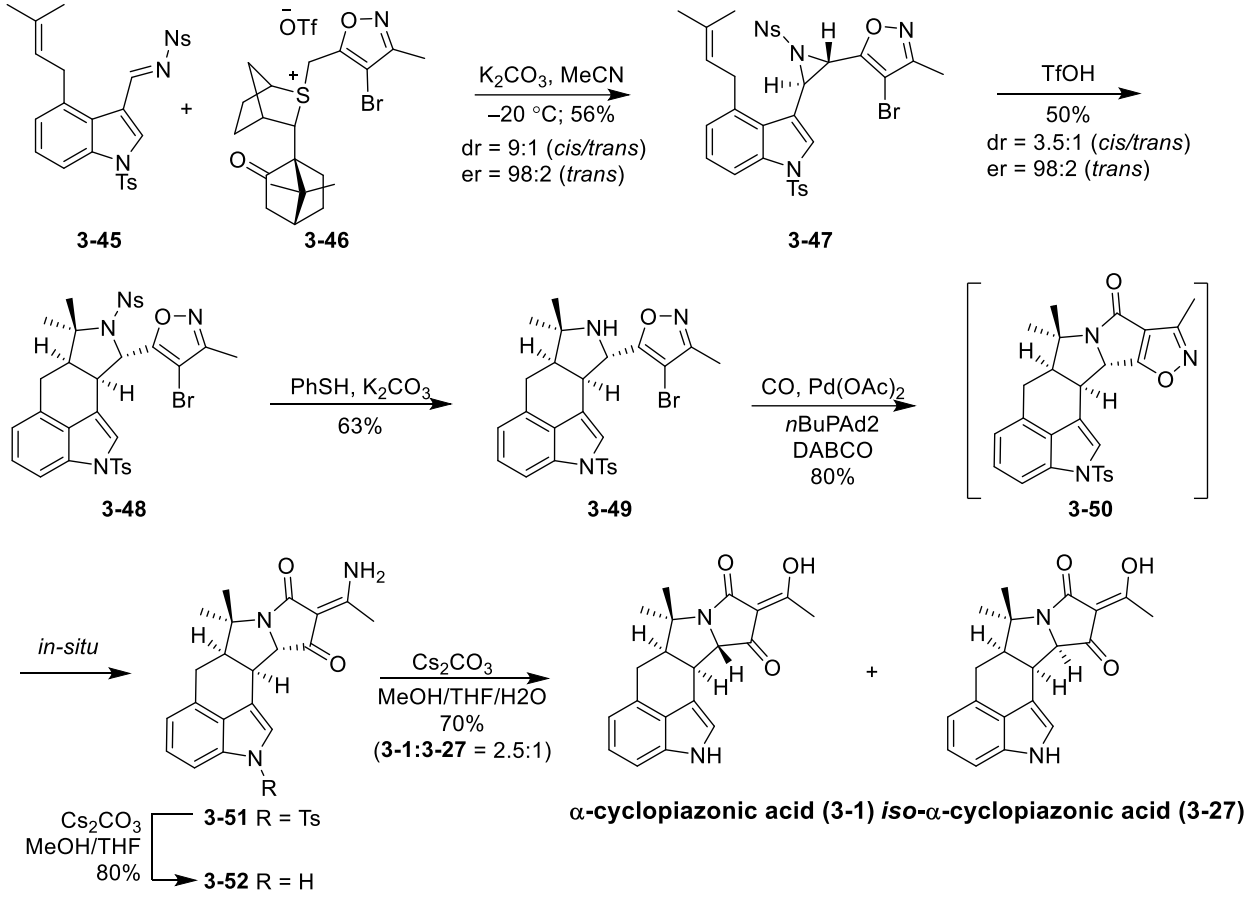
An improvement of Knight's synthesis was published by the Sherkenbeck group a few years later in 2012.[107] The use of a chiral auxiliary on indolyl acrylate **3-43** gave complete stereofacial control during the isoproprenylcuprate conjugate addition (Scheme 31). This marks the first asymmetric total synthesis of α-cyclopiazonic acid.



Scheme 31 Beyer's asymmetric total synthesis of **3-1**

More recently, in 2018 Zhurakovskyi published an asymmetric synthesis of the cyclopiazonic acid family of natural products utilizing their sulfur ylide aziridination chemistry (Scheme 32).[108] Prenylated indole imine **3-45** was prepared in 67% yield over 4 steps from 4-bromo-indole-3-carbaldehyde. Camphor derived sulfonium **3-46** was synthesized in 4 steps from propargyl alcohol in 43% overall yield. Sulfur ylide formation and subsequent symmetric aziridination to furnish intermediate was carried out at –20 °C and afforded the desired aziridine in a 9:1 *trans:cis* ratio in favor of desired *trans*-diastereomer **3-47** with high enantiospecificity (er = 98:2). The authors report that *trans*-aziridine **3-47** was prone to epimerization and was telescoped into the cycloaddition step without further purification. Upon exposure of the crude aziridine to triflic acid, the 3+2 cycloaddition proceeded smoothly to give pyrrolidine **3-48** in 50% yield with complete enantiomeric retention and a diastereomeric ratio of 3.5:1. Potassium thiolate promoted nosylate deprotection gave the free amine, at which point the diastereomers were separated to give pyrrolidine **3-49**. A cascade palladium-catalyzed carbonylation of the bromo-isoxazole and subsequent acylation, followed by reductive cleavage of the N–O bond afforded penultimate *N*-tosyl cyclopiazonic acid imine **3-51** in good yield. Tosyl deprotection and hydrolysis of the imine gave cyclopiazonic acid **3-1** and *iso*-cyclopiazonic acid **3-27** as a 2.5:1 mixture of stereoisomers, which were separated by HPLC to provide enantiopure CPA. The authors also note that when the

detosylation was carried out under anhydrous conditions, cyclopiazonic acid imine **3-52** can be isolated in 80% yield.



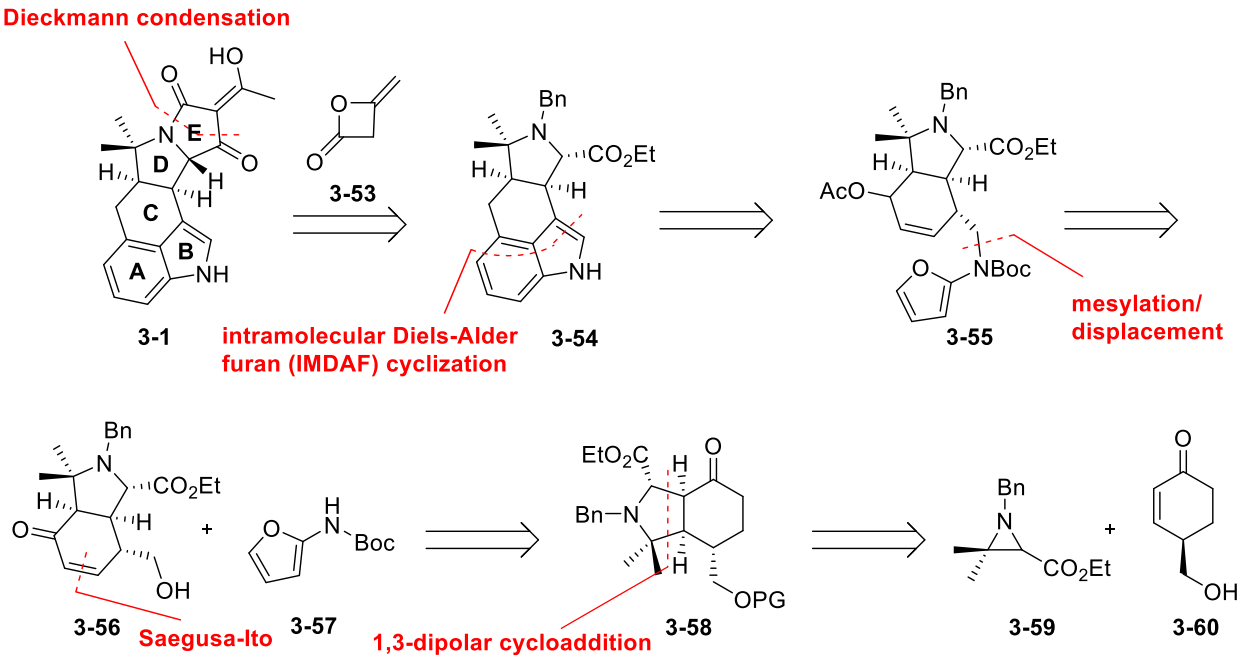
Scheme 32 Zhurakovski's asymmetric total synthesis of **3-1**

3.2 RESULTS AND DISCUSSION

3.2.1 Retrosynthetic analysis of cyclopiazonic acid

Since five total syntheses, two of which as asymmetric variants, have already been reported, we were compelled to improve on the synthetic sequence while taking on more ambitious

transformations. All five syntheses start with the A- and B-rings in place as functionalized indoles. We set out to showcase our advancements in the intramolecular Diels-Alder furan (IMDAF) cyclizations by constructing the indole moiety at a later stage in the synthetic sequence (Scheme 33).[32,109–111]



Scheme 33 Retrosynthetic analysis of cyclopiazonic acid **3-1**

We envisioned installation of C- and D-rings early in the synthetic route with a diastereoselective 1,3-dipolar cycloaddition of 3,3-dimethyl aziridine carboxylate **3-59** and chiral cyclohexanone **3-60**. With this approach, all stereogenic carbon centers would be set early, along with the *gem*-dimethyl, which was proven to be difficult in Kozikowski and Natsume's total syntheses, which suffered from either low yields or requiring multiple synthetic steps. Cycloadditions of 3,3-dialkyl aziridines are unprecedented in the literature, and we thought to explore this as a viable option for facile construction of highly substituted pyrrolidines. After formation of the C- and D-rings we envisioned a Seagusa-Ito type oxidation to form enone **3-56**. Luche reduction of the carbonyl and acylation affords the allylic acetate, which undergoes further

transformation *via* mesylation and displacement with protected furylamine **3-57** to furnish the IMDAF precursor **3-55**. Palladium catalyzed intramolecular Diels-Alder furan cyclization would form the indolinic A- and B-rings. Finally, deprotection of the pyrrolidine nitrogen tetramic acid formation through treatment with diketene, base, and heat would finish the synthesis of cyclopiazonic acid.

3.2.2 Progress towards the total synthesis of α-cyclopiazonic acid

The retrosynthetic design allows a key step to be very early, if not the first step, in the synthesis. This allows for an expeditious assessment of feasibility and troubleshooting. With this in mind, we set out to develop a model system before exploring this aziridine cycloaddition. In the mid to late 1960s, Hüisgen showed that aziridine dicarboxylates undergo thermal ring openings to form azomethine ylides.[112–114] These ylides have since been extensively shown to undergo facile cycloaddition reactions with various dipolarophiles to generate substituted pyrrolidines and pyrroles; however, cycloadditions from 3,3-dialkyl aziridines have not been reported.[115–122] As such, we set out to design a model system for the testing of this cycloaddition strategy.

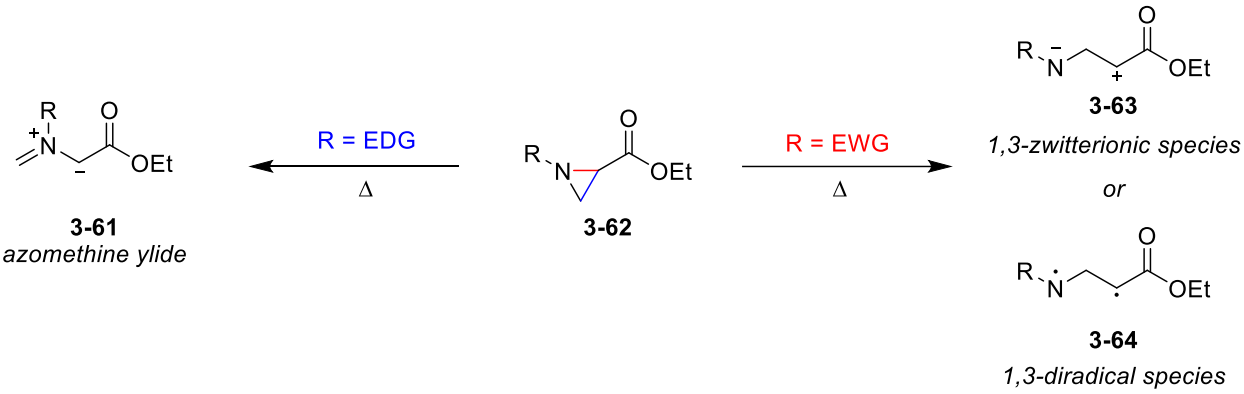
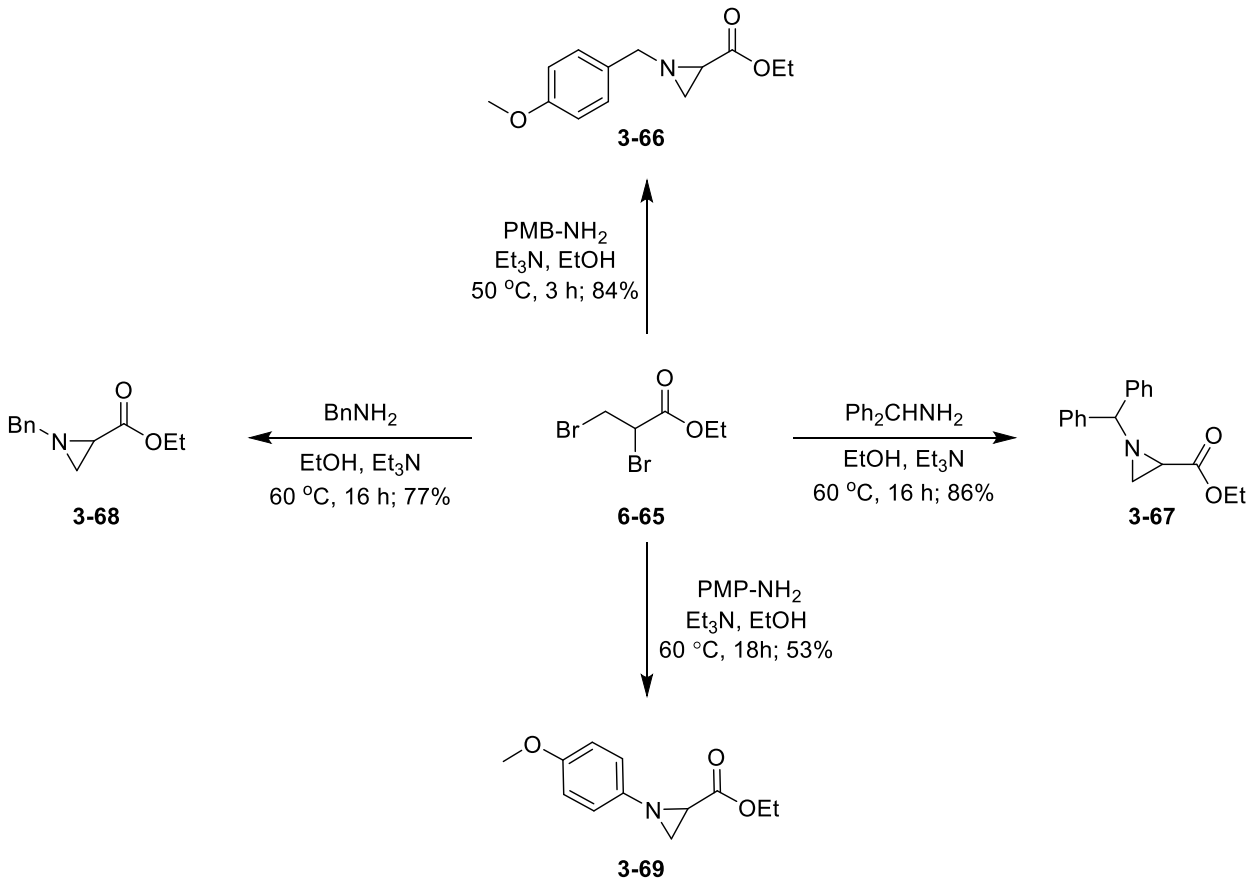


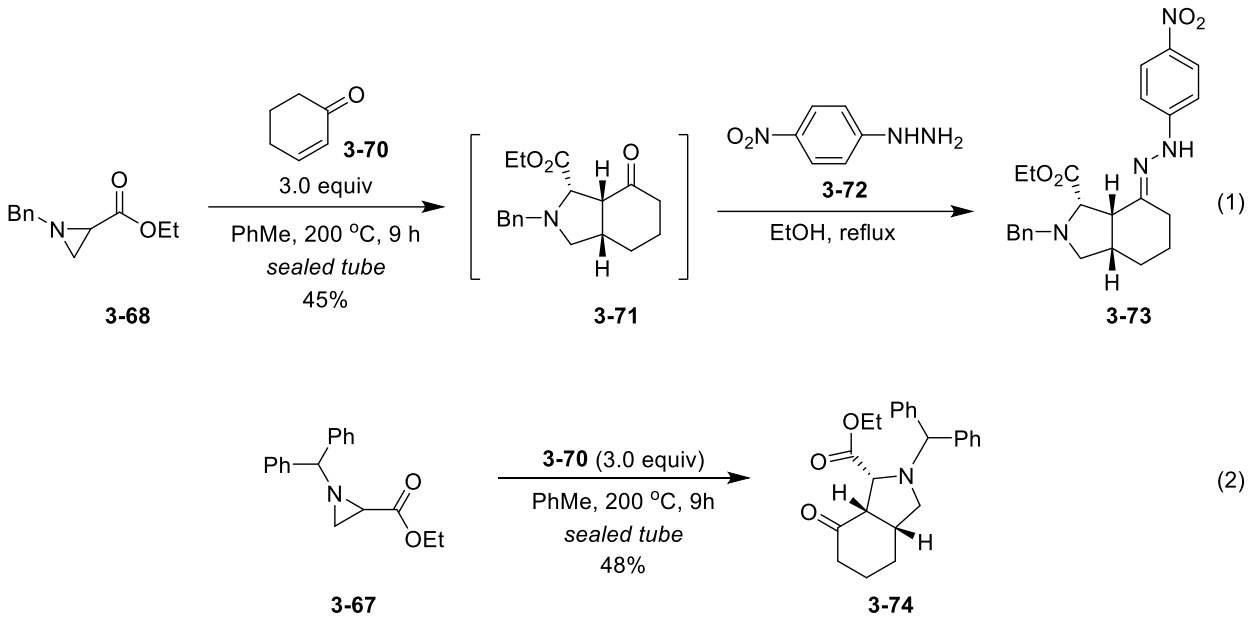
Figure 9 Competitive pathways of aziridine heterolysis based on N-protecting group

With the expectation that electron donating groups on the *N*-protecting group would facilitate the heterolysis of the C–C bond in the aziridine as opposed to competitive C–N cleavage (Figure 9), a series of *N*-protected 3,3-unsubstituted aziridine carboxylates were synthesized readily on large scale from various amines and dibromopropionate **3-65** (Scheme 34). Aziridine carboxylate **3-66** was prepared from 4-methoxybenzylamine in 84% yield in gram-quantities. Benzyl (Bn) and benzhydryl (Dpm) protected aziridines **3-68** and **3-67** were prepared from benzylamine and benzhydrylamine, respectively, in 77% and 86% yields. Finally, *para*-methoxyphenyl (PMP) protected aziridine **3-69** was prepared in the same fashion from *p*-anisidine in 53% yield.



Scheme 34 Synthesis of *N*-protected 3,3-unsubstituted aziridine carboxylates

With these aziridines in hand, we next sought to explore thermal cycloaddition with cyclohexenone **3-70** as a model dipolarophile. After minimal optimization we discovered that benzyl protected aziridine **3-68** reacted smoothly with enone **3-70** with heating to 200 °C in a sealed tube to afford cycloadduct **3-71** in 45% yield, which after purification, was condensed with 4-nitrophenylhydrazine **3-72** gave hydrazone **3-73** as a single diastereomer whose structure was confirmed by x-ray crystallography (Figure 11). Furthermore, when benzhydryl aziridine **3-67** was heated in the presence of **3-70**, cycloadduct **3-74** were isolated as a crystalline solid in 48% yield (Scheme 35, Eq. 2). The structure of this analog was also confirmed by x-ray crystallography (Figure 11).



Scheme 35 Results of the cycloaddition of aziridines **3-68** and **3-67** with cyclohexenone **3-70**

To our surprise, however, the adducts **3-71** and **3-74** were found to display a different regioselectivity than expected. The adducts were formed by head-to-head coupling of the dipole and the dipolarophile rather than the expected head-to-tail adduct as based on the frontier molecular orbitals of the azomethine ylide.[123] The PMP and PMB protected aziridines **3-66** and **3-**

69 also produced cycloaddition products by crude NMR and LC-MS analysis, but the reaction mixtures were more complex than their benzyl and benzhydryl counterparts.

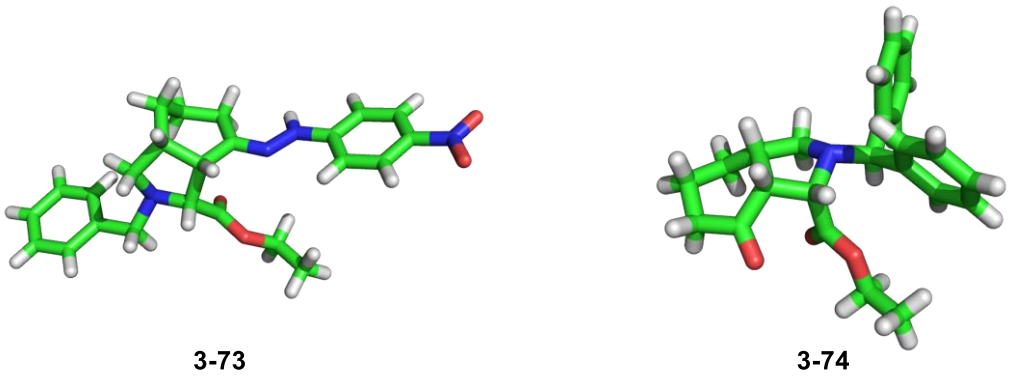
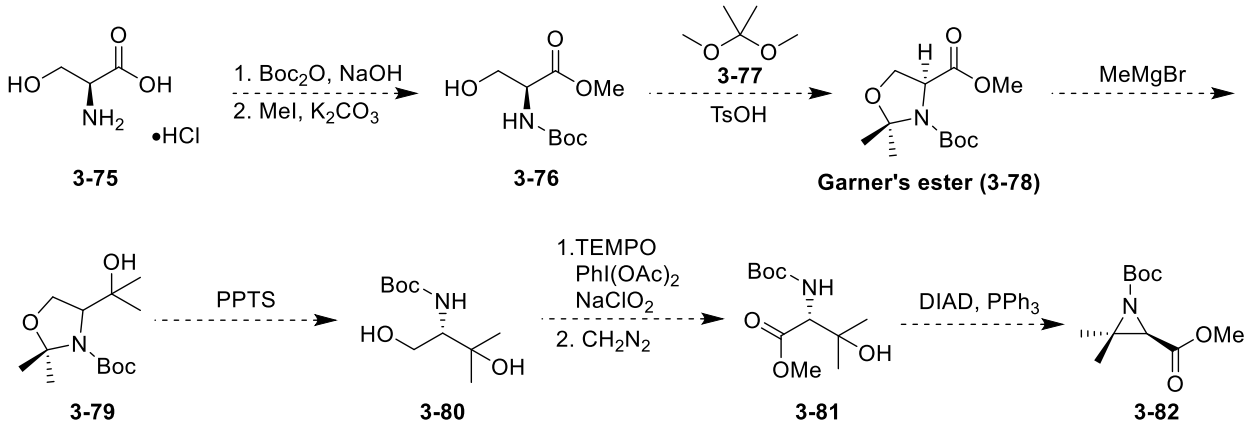


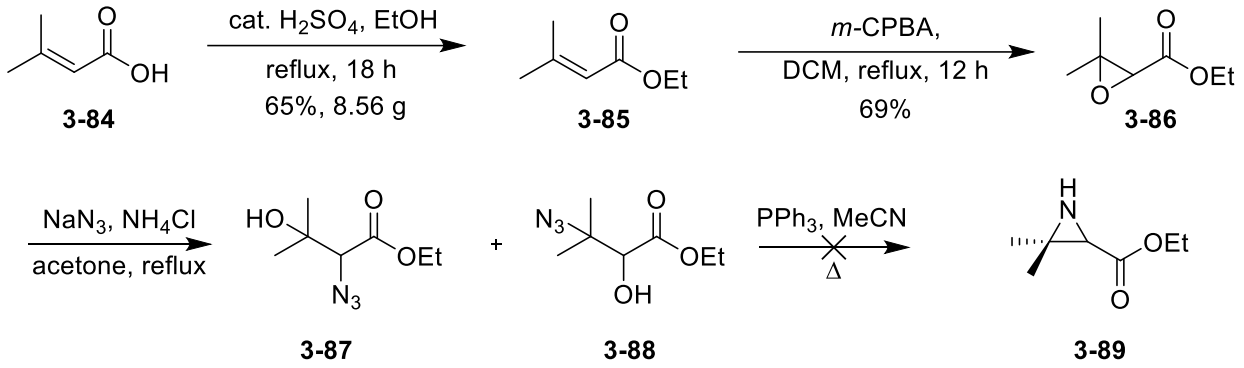
Figure 10 The X-ray structures of **3-73** and **3-74**

Since it was not clear if this regioselectivity also applied to the cycloaddition with the *gem*-dimethyl aziridine carboxylate **3-59**, we began the exploration of a viable route to synthesize the target 3,3-dimethyl aziridine carboxylate **3-59**. A survey of the literature showed two predominant methods for this target molecule. A first route begins from the amino acid serine, and after 8-chemical steps would afford *N*-Boc aziridine **3-82** (Scheme 36).[124,125] This aziridine would have to undergo Boc deprotection and subsequent benzylation or benzhydrylation to afford aziridine. This route, while primarily amendable to large scale, was discarded due to its overall length.



Scheme 36 The literature synthesis of aziridine **3-82** from serine

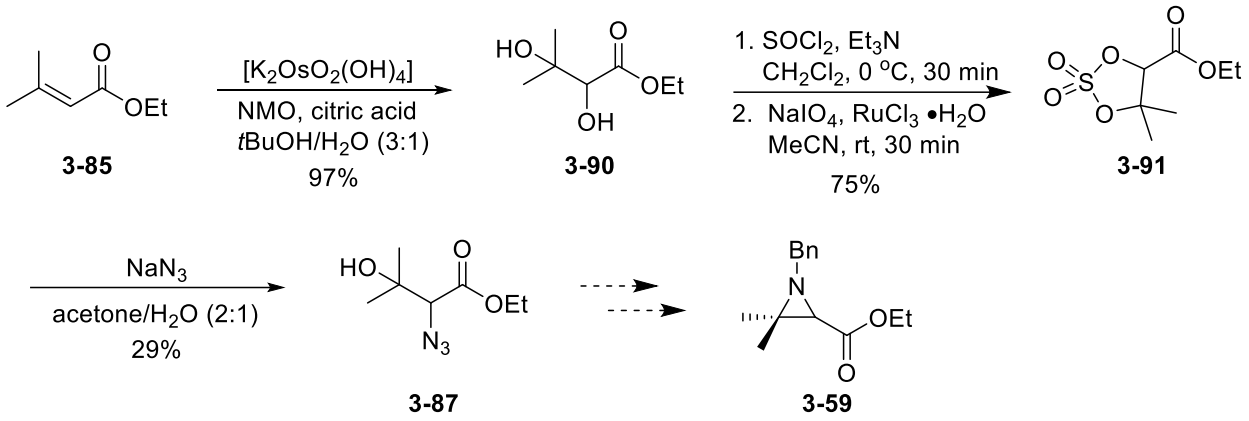
The next prevalent example used azido alcohol **3-87** and subsequent reduction and cyclization after treatment with triphenylphosphine (PPh_3) (Scheme 37).[126] Starting with acrylic acid **3-84**, Fisher esterification in ethanol with catalytic sulfuric acid afforded acrylic ester **3-85** in 63% yield, which was lower than expected, most likely due to its volatility. The acrylate was then treated with *meta*-chloroperoxybenzoic acid in methylene chloride at reflux which gave 69% of desired epoxide **3-86**. Azidolysis with sodium azide in refluxing acetone with ammonium chloride gave a 2:3 mixture of regioisomeric azido alcohols **3-87** and **3-88**. After chromatography, the mixture of low molecular weight azido alcohols was used immediately in the reduction/cyclization step. However, no desired aziridine was observed by NMR.



Scheme 37 Attempted synthesis of aziridine **3-89** from acrylic acid **3-84**

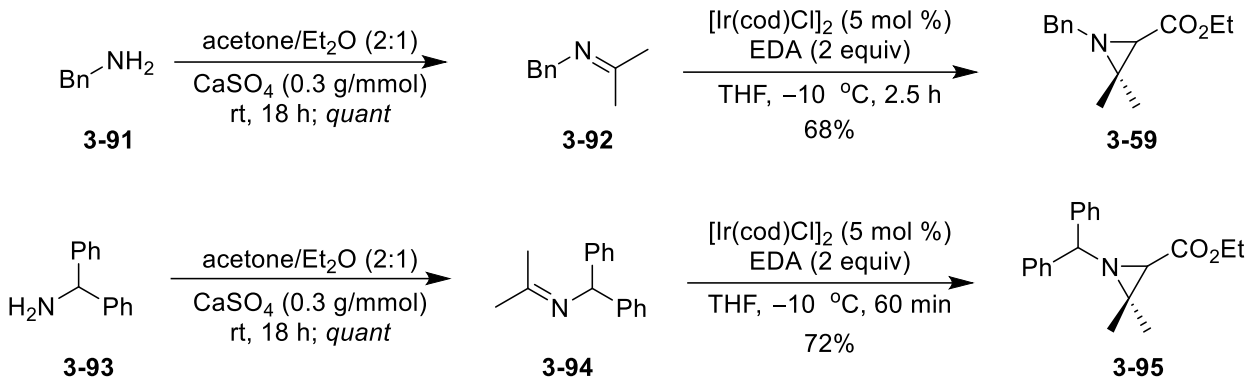
In parallel to the epoxide route, a regioselective route to azido alcohol **3-87** was being explored. This was accomplished using the Sharpless cyclic sulfate method for regioselective azidolysis (Scheme 38).[127] Upjohn dihydroxylation with potassium osmate and *N*-methylmorpholine oxide as the stochiometric oxidant gave vicinal diol **3-90** in excellent yield. Exposure of the diol to thionyl chloride gave the cyclic sulfite, which was oxidized to sulfate **3-91** with sodium periodate and catalytic ruthenium chloride. Azidolysis of the cyclic sulfate occurs regioselectively with sodium azide in a 2:1 mixture of acetone/water. Hydrolysis of the sulfate to the alcohol typically uses acidic conditions, which gave the azido alcohol in 29% yield, however,

this route was abandoned due to the potentially explosive hydrazoic acid generation from the excess sodium azide used in the sulfate opening step. Sharpless' method for aziridination was followed by lithium aluminum hydride reduction and hydrolysis of the sulfate with potassium hydroxide, but since both steps would not be amendable to the sensitive ethyl ester this route was abandoned.



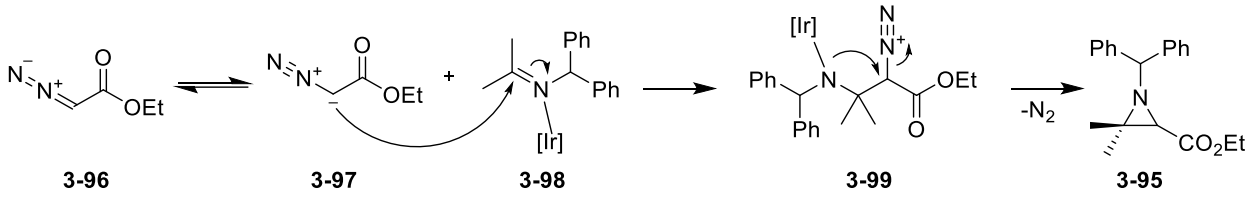
Scheme 38 Regioselective synthesis of azido alcohol **3-87** from acrylic ester **3-85**

At this point, a method for the iridium catalyzed aziridination of imines and ethyl diazoacetate was used.[128] While the majority of Kubo's work was on the aziridination of imines derived from aldehydes, an example existed for the aziridination of nonan-5-one. First, we needed to synthesize the imine from acetone, which has limited precedence in the literature, however, after some modification of literature protocols, we were able to isolate imine **3-92** and **3-94** quantitatively in excellent purity after filtration and concentration (Scheme 39). The former, being a crystalline solid, could be stored in the freezer for months without degradation. The later, an oil, was more sensitive and was used immediately after being prepared. Upon treatment with ethyl diazoacetate (EDA), imines **3-93** and **3-94** were converted to their aziridine products in 68% and 72% yield respectively. Aziridine **3-95** was a crystalline and was isolated without chromatography by recrystallization from ethanol.



Scheme 39 Synthesis of **3-59** and **3-95** *via* iridium catalyzed aziridination of imines **3-92** and **3-94**

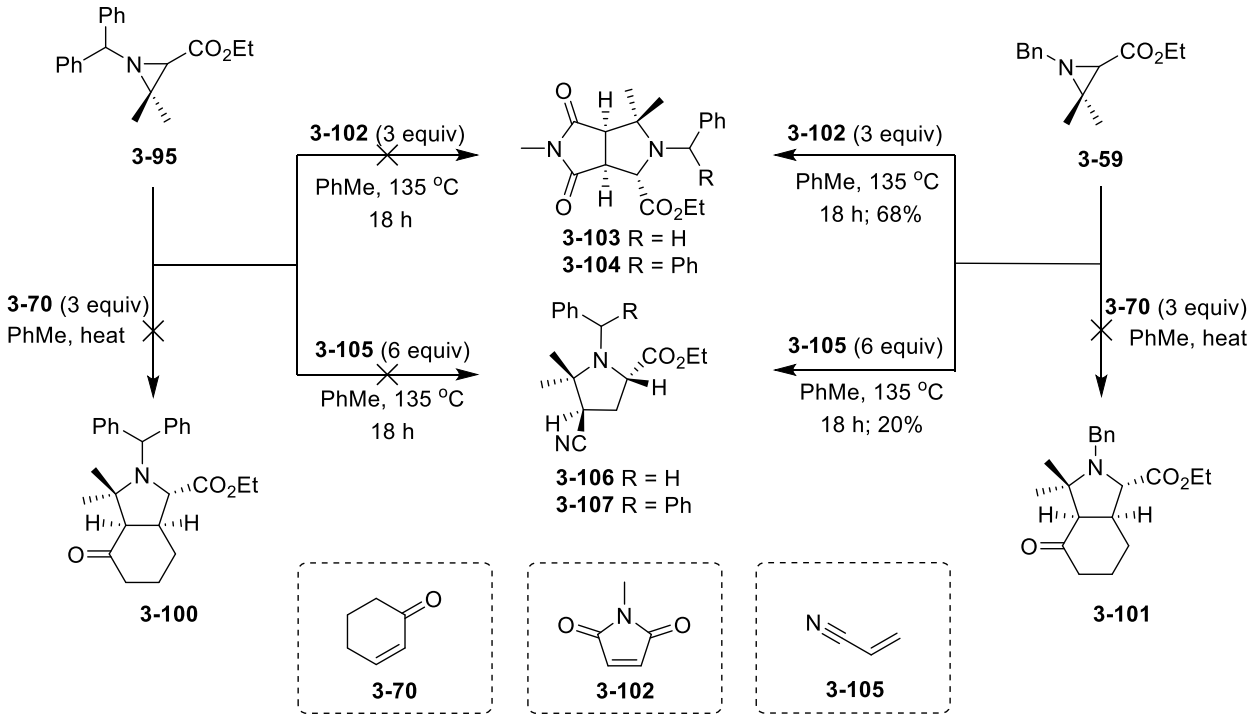
The authors proposed a stepwise mechanism for the aziridination (Scheme 40). First, coordination of the imine to the iridium forms complex **3-98** which is followed by nucleophilic addition of the diazoacetate to the imine forms intermediate **3-99**. Subsequent cyclization of this intermediate with the loss of dinitrogen gives aziridine **3-95**. This method for construction of 3,3-dialkyl aziridines should be further explored.



Scheme 40 Mechanism for iridum catalyzed aziridination

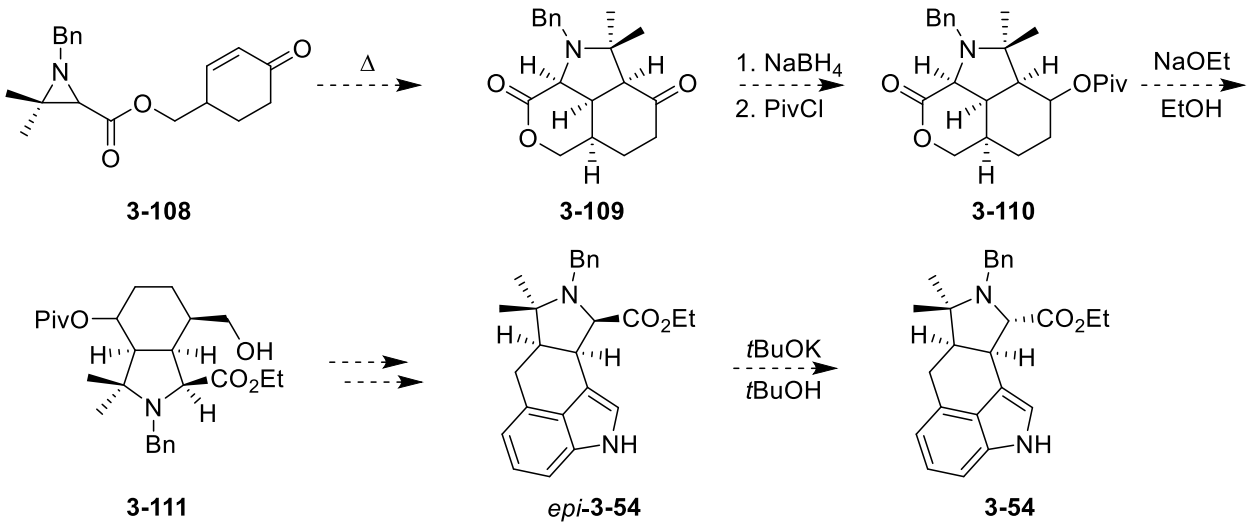
With the aziridine in hand, and the ability to produce multiple grams at a time, we set out to test the optimized cycloadditions with cyclohexenone (Scheme 41). Heating of aziridines **3-95** and **3-59** in the presence of cyclohexenone **3-70** did not afford any isolable products, only decomposition of the starting materials was observed. Curious if the cycloaddition would work in the presence of a more reactive dipolarophile would result in product formation, we heated aziridines **3-95** and **3-59** in toluene with *N*-methylmaleimide **3-102** and acrylonitrile **3-105**. While the benzhydryl analog did not produce product, we were excited to see that the benzyl derivative reacted with the dipolarophiles to produce bicycle **3-104** and pyrrolidine **3-107** in 68% and 20%

yield respectively as single diastereomers. The relative configurations of the of the stereocenters were assigned by comparison with literature examples and through 2-D NMR analysis.



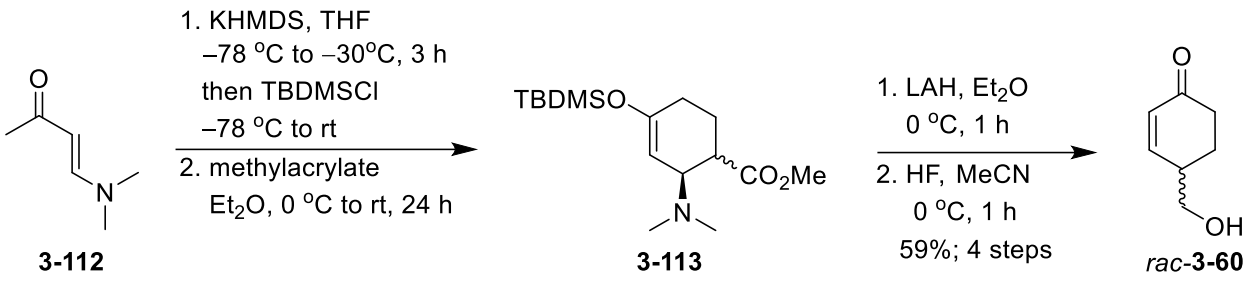
Scheme 41 Cycloadditions of aziridines **3-95** and **3-59**

While the model system using cyclohexenone **3-70** did react with the *gem*-dimethyl aziridines, we thought that the ester on the aziridine and hydroxylmethyl cyclohexenone **3-60** detailed in our retrosynthetic hypothesis would allow for the possibility of in intramolecular cycloaddition utilizing tethered enone-ester **3-108** (Scheme 42). Solvolysis of lactone **3-109** would provide the free hydroxyl group for the mesylation and displacement by Boc-furanamine **3-57**. While this would give us all-*cis* configuration on the pyrrolidine, we hypothesized that a late-stage epimerization could be performed on *epi*-**3-54**, providing the more favorable *trans*-isomer **3-54**.



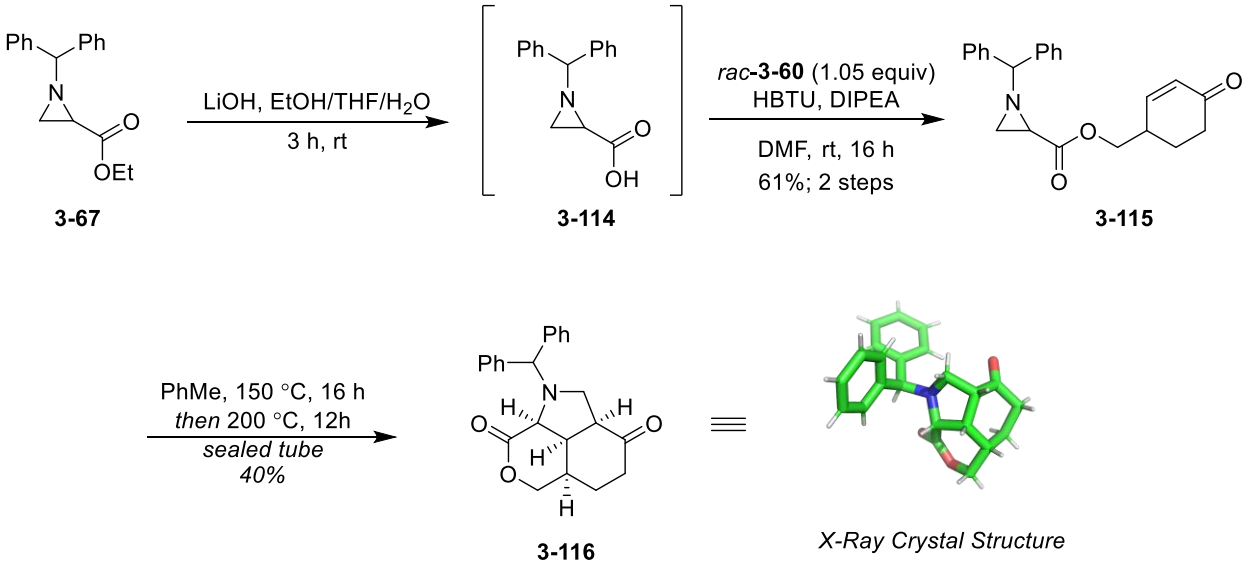
Scheme 42 Proposed synthetic route to cyclopiazonic acid utilizing an intramolecular aziridine cycloaddition

Intramolecular cycloadditions are known to be more facile than their intermolecular counterparts.[118] Before this could be explored, however, hydroxymethyl cyclohexenone **3-60** would need to be synthesized. This was accomplished utilizing chemistry published by Rawal in 1997 (Scheme 43).[129,130] Starting with Danishefsky's diene, we first converted the vinylogous ester to amide **3-112** by condensation with dimethylamine in THF. Upon treatment of amide **3-112** with potassium hexamethylsilazide (KHMDS), subsequent trapping of the enolate with *tert*-butyldimethylsilyl chloride (TBDMSCl) gave the corresponding siloxy diene. Exposure of this diene to methyl acrylate gave clean conversion to the Diels-Alder adduct **3-113**, which after reduction with lithium aluminum hydride, provided intermediate hydroxymethyl silylenol**.** The TBDMS group was deprotected with HF in acetonitrile and *in situ* elimination of dimethylamine gave racemic cyclohexenone *rac*-**3-60,** which was isolated in good yield, only requiring one chromatographic step. An asymmetric variant towards **3-60** has also been published.[131]



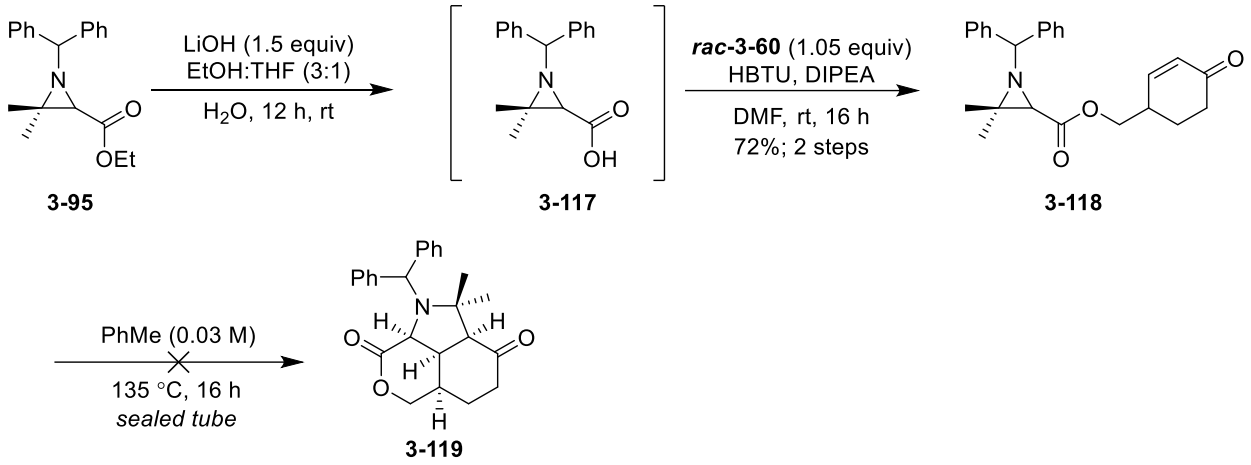
Scheme 43 Synthesis of hydroxylmethyl cyclohexenone *rac*-**3-60**

Our intramolecular hypothesis was first tested with 3,3-unsubstituted aziridine **3-67** (Scheme 44). Saponification of aziridine **3-67** in a mixture of ethanol/THF and a few drops of water to solubilize the lithium hydroxide, and after acidification and extraction, gave aziridine acid **3-114**, which was used directly in the esterification step due to stability concerns. HBTU mediated coupling of alcohol *rac*-**3-60** and acid **3-114** proceeded smoothly to provide tethered aziridine **3-115** in 61% isolated yield. Heating of this compound in toluene in a sealed tube 150 °C for 16 h and then to 200 °C for 12 h provided the expected tricyclic cycloadduct **3-116** as a single diastereomer in 40% yield. The structure of **3-116** was confirmed by x-ray crystallography.



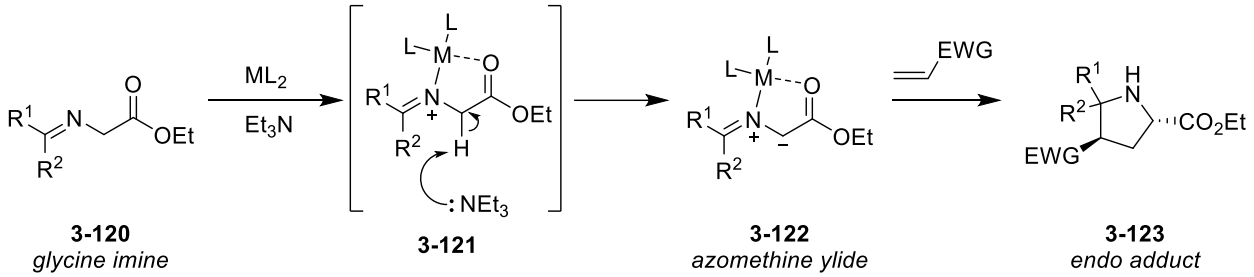
Scheme 44 Synthesis and intramolecular cyclization of tethered aziridine **3-115**

Encouraged by this result, we synthesized the *gem*-dimethyl aziridine variant (Scheme 45). Following the same saponification-esterification procedure, we were able to synthesize tethered aziridine **3-116** in 72% yield. However, when this aziridine was heated in toluene to 135 °C, only decomposition of the starting material was observed. Attempts to synthesize the benzyl protected analog failed at the saponification step, as this aziridine may be more prone to decomposition under the basic conditions required.



Scheme 45 Synthesis and attemted cycloaddition of cyclohexenone tethered *gem*-dimethyl aziridine **3-118**

While the direct cycloaddition onto a cyclohexenone of an azomethine ylide formed from thermolysis of an aziridine was unsuccessful, an alternative approach is the generation of an azomethine ylide from the condensation of a glycinate onto an aldehyde or ketone in the presence of base and a Lewis acid, such as a silver or lithium salt, or even under metal-free thermal conditions.[132–134] While to the best of our knowledge, no examples of ylides generated from dialkyl ketones have been reported utilizing this method, we thought to explore this as a possible route to fused-bicyclic intermediate **3-58** (Scheme 46).

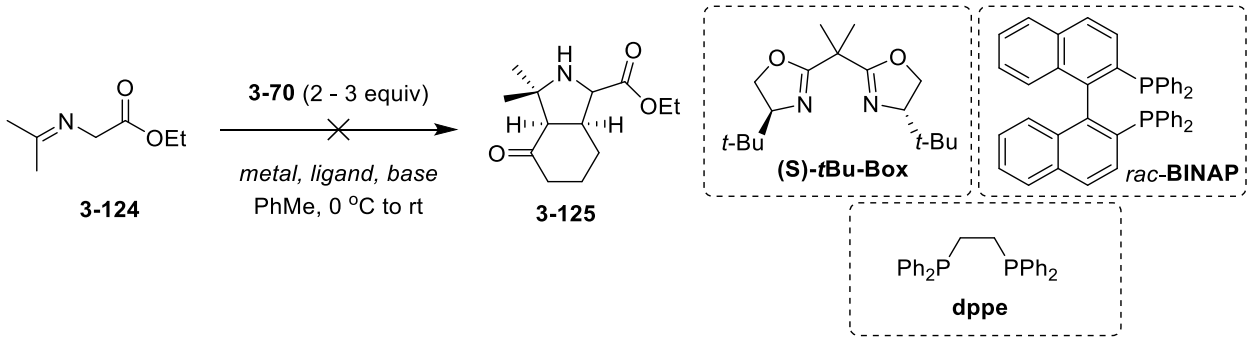


Scheme 46 Proposed mechanism of metal mediated dipolar cycloaddition of glycine imine

Generation of the glycine-acetone imine **3-120** from ethyl glycinate hydrochloride was accomplished by extraction of the freebase from aqueous ammonia and concentration of the rich organic extract. The amine freebase was then subjected to the optimized conditions (*vida supra*) affording glycine imine **3-120** in good yield and excellent purity after extraction. Imine **3-120** was relatively unstable upon exposure to moisture at ambient temperatures and was used immediately in subsequent reactions. However, storage of the imine as a solution in toluene at −20 °C was accomplished for up to 5 days without significant decomposition or hydrolysis as detectable by NMR.

With a route to glycine imine **3-124** accessible, we screened an array of Lewis acid promoted cycloadditions that are typically found in the literature.[135–137] Lithium bromide, and various silver and copper salts have been used previously, typically on imines derived from benzaldehydes. However, when we exposed imine **3-124** to these conditions, in the presence of various ligands and bases, we observed no detectable traces of cycloadduct **3-125** (Table 14).

Table 14 Condition screen for the Lewis acid promoted cycloaddition of glycine imine **3-124**

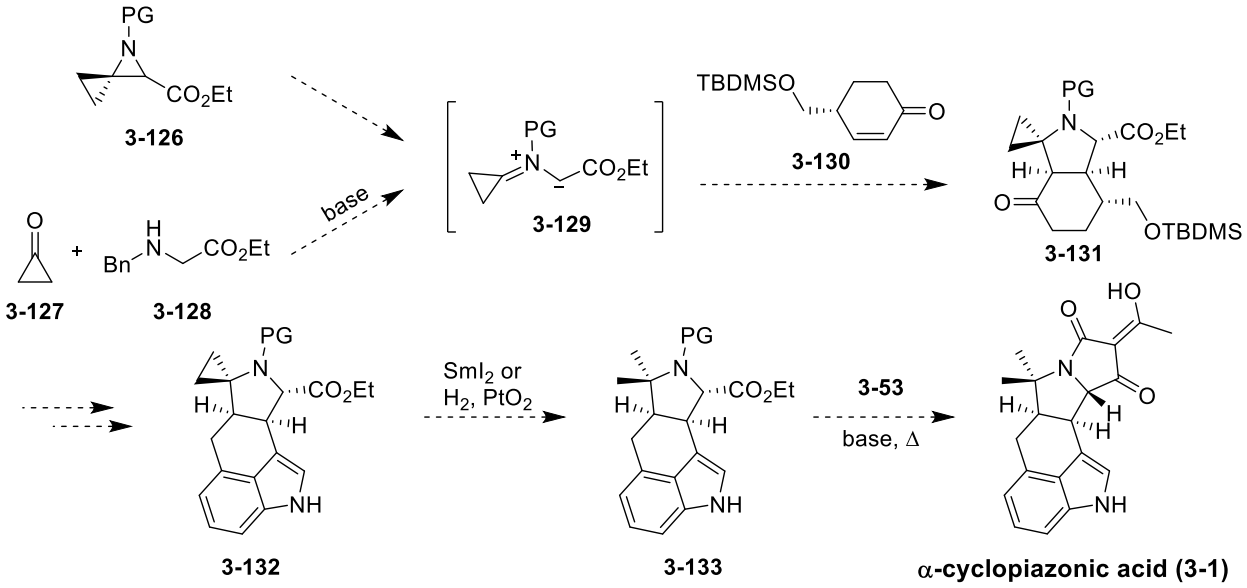


entry	metal (equiv)	ligand (equiv)	base (equiv)
1	LiBr (1.5)	–	Et_3N (1.5)
2	LiBr (1.5)	–	Et_3N (1.5)
3	AgOAc (1.5)	–	Et_3N (1.5)
4	AgOAc (1.5)	–	Et_3N (1.5)
5	AgOAc (0.05)	–	DIPEA (0.15)
6	AgOAc (0.05)	dppe	DIPEA (0.15)
7	AgOAc (0.05)	*rac*-BINAP	DIPEA (0.15)
8	AgOAc (0.05)	(*S*)-*t*Bu-Box	DIPEA (0.15)
9	$AgSbF_6$ (0.05)	–	DIPEA (0.15)
10	$Cu(CN)_4PF_6$ (0.05)	–	DIPEA (0.15)
11	$Cu(CN)_4PF_6$ (0.05)	dppe	DIPEA (0.15)
12	$Cu(CN)_4PF_6$ (0.05)	*rac*-BINAP	DIPEA (0.15)
13	$Cu(CN)_4PF_6$ (0.05)	(*S*)-*t*Bu-Box	DIPEA (0.15)

3.2.3 Future directions

To complete the synthesis of cyclopiazonic acid using the aziridine cycloaddition/IMDAF approach, we propose utilizing a cyclopropane to install the *gem*-dimethyl group in a late-stage reductive cleavage (Scheme 47). The prerequisite cyclopropyl 1,3-dipole **3-129** could be generated *in situ* through ring opening of spirocyclic aziridine **3-126**, or through the *in situ* condensation of *N*-benzyl ethyl glycinate **3-128** and cyclopropanone in the presence of base. This dipole should be

less sterically encumbered and substantially more reactive due to the reactive nature of methylene cyclopropyl compounds. Aziridine **3-126** can be prepared from methyl 2-chloro-2-cyclopropylidineacetate.[138–141] The synthesis and utility of cyclopropanone **3-127** is also well known.[142–144] Cycloadduct **3-131** could be further elaborated to spirocyclic intermediate **3-132**, which could then be reductively cleaved and converted to its *gem*-dimethyl analog with samarium diiodide or with catalytic hydrogenolysis with platinum dioxide.[145,146]



Scheme 47 Proposed route for synthesis of cyclopiazonic acid

4.0 EXPERIMENTAL PART

4.1 EXPERIMENTAL – TEMPOC AMINES

4.1.1 General experimental protocols

Reactions were performed without inert atmosphere with ACS grade solvents unless otherwise stated. Inert reactions were performed under a N_2 or argon atmosphere and glassware was flame dried prior to use. Deionized water, CH_2Cl_2, diethyl ether, and Et_3N for NPTC synthesis were sonicated for 1 h under a steady stream of nitrogen prior to use. DMF, THF, and Et_3N used for alkyl amine protections were not dried prior to use, although DMF was stirred vigorously under vacuum (2 Torr) at ambient temperature for 5 min to remove any volatile contaminants. THF used for aryl amine protections was distilled over sodium/benzophenone ketyl, or dried using an alumina column filtration system. Commercial grade reagents were used as-is unless otherwise noted. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254}) and spots were visualized by UV (254 nm), iodine, ninhydrin (1.5 g of ninhydrin in 100 mL of absolute ethanol, then 3.0 mL of glacial acetic acid), *p*-anisaldehyde (5 mL of conc. H_2SO_4 and 1.5 mL of glacial AcOH in 135 mL of absolute ethanol, then 3.7 mL of *p*-anisaldehyde), 2,4-DNP (12 g of 2,4-dinitrophenylhydrazine, 60 mL of conc. H_2SO_4, 80 mL of water, in 200 mL of 95% ethanol) or a $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of K_2CO_3, and 1.25 mL of 10% NaOH in 200 mL of water). It is worth noting that iodine was an excellent general visualization method for all Tempoc protected amines, but $KMnO_4$ may also be used with heating. DMF was removed on a rotary evaporator connected to a doubly-trapped high-vac pump (4.5 Torr) in a 35 °C water-bath.

Purifications by chromatography were performed using SiO_2 (40-60 μm). $^{1}H/^{13}C$ NMR spectra were recorded on Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz, Bruker Avance 500/125 MHz instrument, or Bruker Avance 600/150 MHz instrument. Chemical shifts were reported in parts per million (ppm) with the residual solvent peak or tetramethylsilane (TMS) used as the internal standard. Chemical shifts were tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, b = broad, app = apparent), coupling constants, and integration. IR spectra were obtained on a Perkin-Elmer 100 IR-ATR spectrometer. Microwave reactions were performed using a Biotage Initiator or an Anton Paar Monowave 300 reactor in glass microwave vials (cap sealed) with continuous magnetic stirring and internal ruby thermometer and/or external infrared surface temperature sensor. LC-HRMS and ELS data were obtained on a Thermo Scientific Exactive Orbitrap LC-HRMS (ESI positive ion mode) coupled to an Agilent Technologies 385-ELSD and a Thermo Scientific Accela HPLC system using a 3.5 μm Waters XTerra C18 column (2.1 x 50 mm; 10 min gradient elution with MeCN/H_2O/MeOH containing 0.1% formic acid at a flow rate of 500 μL/min from 3:92:5 at 0-0.5 min to 93:2:5 at 4.0 min, back to 3:92:5 from 6.0 to 7.5 min). Melting points (uncorrected) were obtained using a Mel-Temp instrument. DSC exotherms were obtained on a Perkin-Elmer Pyris 6 differential scanning calorimeter with a scan rate of 10 °C/min and a scan range of 80–200 °C (2 sweeps).

4.1.2 General methods and workup protocols

General Method 1-A: Tempoc Protection of Alkyl Amines. A round bottom flask containing a stirbar was charged with amine (1.00 mmol, 1 equiv) and triethylamine (3.00 mmol, 3.00 equiv) in DMF (2.0 mL) and the 0.5 M solution was cooled to 0 °C on an ice-bath before

treatment with NPTC (1.20 mmol, 1.20 equiv) as a solid in two portions. The reaction mixture turned yellow upon addition of the reagent. The heterogeneous solution was stirred for 5 min before being removed from the ice-bath (NPTC undergoes dissolution upon warming) and allowed to stir at ambient temperature for 12 h with monitoring by TLC and LC-MS. If necessary, for solubility, THF or CH_2Cl_2 may be added. For example, addition of a co-solvent in small quantities was necessary for the N-Boc and 4-phenylpiperidine substrates; however, if used in larger quantities, reaction rate decreased vs DMF. For some optimization studies varying solvents and bases, see Table 1. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2 (5 mL) and poured into a separatory funnel containing ice-cold 1 M aqueous NaOH (20 mL) [sat. Na_2CO_3 may also be used] and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were successively washed with water (15 mL), brine (15 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a residue which was subjected to further purification on SiO_2.

General Method 1-B: Procedure for Tempoc Protection of Heterocyclic Amines. A flame dried round bottom flask containing a stirbar was charged with 90% sodium hydride (1.30 mmol, 1.30 equiv) and dry THF (6 mL), and the solution was cooled to 0 °C on an ice-bath before dropwise addition of heterocyclic amine (1.00 mmol, 1 equiv) by syringe as a solution in dry THF (2 mL). This mixture was stirred for 30 min (or until effervescence was no longer observed) at ambient temperature before being cooled to 0 °C. NPTC (1.20 mmol, 1.20 equiv) was added dropwise by syringe as a solution in dry THF (2.0 mL). The reaction mixture was stirred at ambient temperature for 3 h with monitoring by TLC and LC-MS, and a bright orange sodium 4-nitrophenoxide precipitated. Crushed ice (3 g ice per gram of amine) was added and the mixture was concentrated to half the volume under reduced pressure before addition of CH_2Cl_2 (10 mL).

The biphasic mixture was poured into a separatory funnel containing ice-cold 1 M aqueous NaOH (20 mL) [sat. Na_2CO_3 may also be used] and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were successively washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was further purified by chromatography on SiO_2.

Work-up Procedure 1-1 for Tempoc Protection. Upon completion of the reaction, the mixture was poured onto a sintered vacuum funnel containing a 1" pad (for reaction scale of <1 g) or a 1.5" pad (for reaction scale of ≥1 g) of pre-wetted (CH_2Cl_2) basic alumina (Brockmann Grade I) to remove *p*-nitrophenol. The product was then eluted with 3-4 column volumes of CH_2Cl_2 (or for more polar substrates, until yellow color approaches frit), and the filtrate was concentrated to afford a residue which was further purified by chromatography on SiO_2.

General Method 1-C: Procedure for Copper-Catalyzed Deprotection of Tempoc Amines. A sealable vessel containing a stirbar was charged with Tempoc amine (1.00 mmol, 1 equiv), ascorbic acid (3.00 mmol, 3.00 equiv), and anhydrous copper(II) chloride (0.100 mmol, 0.100 equiv). A 4:1:1 mixture of MeCN/THF/H_2O (556 μL:139 μL:139 μL) was added, and the 0.12 M reaction mixture was sparged with nitrogen under sonication for 1 min before being sealed and allowed to stir at ambient temperature (40 °C for Tempoc protected primary amines) with monitoring by TLC and LC-MS.

Work-up Procedure 1-2 for Tempoc Deprotection. Upon completion of the reaction (≈ 12 h), the volatiles were removed under reduced pressure to afford a green solution that was partitioned between CH_2Cl_2 (10 mL) and 2 M aqueous NH_4OH (10 mL). During the extraction, a blue color was observed to migrate to the organic layer; this is believed to be a result of a disproportionation of Cu(I), and the colored impurity was removed upon filtration. The organic

layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with 2 M aqueous NH_4OH (5 mL), deionized water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated to afford a mixture of amine product and 2,2,6,6-tetramethylpiperidine (TMP). TMP was removed at 1.5 Torr at 35 °C to afford the pure amine product. Purification by chromatography, if necessary, may performed using triethylamine deactivated SiO_2 (CH_2Cl_2/MeOH/Et_3N). Traces of copper salts were removed, if necessary, by stirring the concentrated residue with a 0.5 M solution of ethylenediaminetetraacetic acid tetrasodium salt (Na_4-EDTA) [5 equiv with respect to the initial loading of copper] in MeOH for 30 min at ambient temperature. The mixture was concentrated and the aqueous residue was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (3 mL) and brine (3 mL), dried ($MgSO_4$), filtered and concentrated to afford pure amine.

Work-up Procedure 1-3 for Tempoc Deprotection. Upon completion of the reaction (≈ 12 h), the mixture was kept sealed to prevent further oxidation of the copper and consumption of the reducing agent and purified by chromatography on Si-Tosic Acid (SiliCycle, R60530B) [5 g / mmol starting material] with MeOH. Elution with 3 column volumes of MeOH followed by 3 column volumes of MeCN ensured that all non-basic byproducts, and some of the copper was washed off the column. A ca. 2 M ammonia-methanol solution (prepared by bubbling ammonia gas through a gas dispersion tube submerged into chilled (ice-bath) MeOH for 30 min; the gas was generated by dropwise addition of conc. NH_4OH directly onto KOH flakes and directing the gas thus produced through an empty bubbler (backflow preventer) to the gas dispersion tube. This solution was used to elute the amine with 4 column volumes. During elution, a blue color appeared on the column, but did not completely elute (this was presumed to be, again, disproportionation of

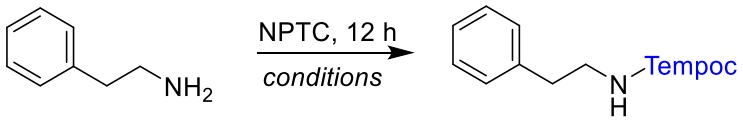
Cu(I) on the column to Cu(II) and colloidal Cu(0) which was trapped by the stationary phase). The eluent was concentrated to afford the amine product. Residual trace metal was removed by adding a 0.5 M solution of Na_4-EDTA (5 equiv with respect to initial copper loading) to a solution of the residue in MeOH. This solution was stirred at ambient temperature for 30 min, concentrated, and extracted with an organic solvent (Et_2O, CH_2Cl_2, or $CHCl_3$). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford the desired amine in high purity.

General Method 1-D: Thermal Deprotection of Tempoc Secondary and Aryl Amines. A microwave tube was charged with Tempoc amine (1.00 mmol, 1 equiv) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, 10 mL) and the 0.1 M mixture was sonicated under a steady stream of nitrogen for 1 min before the tube was sealed and heated in a microwave reactor (conventional heating afforded comparable results) at 135 °C for 8 h for secondary alkylamines, or for 30 min for heterocyclic amines. Upon consumption of the starting material, the reaction mixture was concentrated under reduced pressure and the residue purified by chromatography on SiO_2 (hexanes/EtOAc or CH_2Cl_2/MeOH). For more polar substrates, the SiO_2 catch-and-release method mentioned below may also be utilized.

General Method 1-E: Procedure for Thermal Deprotection of Tempoc Primary Amine. A pressure tube or microwave vial was charged with a solution of Tempoc amine (1.00 mmol, 1 equiv) in 1,4-dioxane (6.7 mL, 0.15 M) and treated with technical grade potassium trimethylsilanolate (3.00 mmol, 3.00 equiv). The tube was sealed and heated to 135 °C for 30 min, during which time the reaction mixture formed a heavy white precipitate and turned pink. Upon consumption of the starting material as observed by TLC, the mixture was cooled in a room temperature water bath, treated with SiO_2 (1 g/mmol Tempoc amine) and stirred for 10 min to hydrolyze the silanoate ester. The reaction mixture was poured directly onto a 1”-pad of SiO_2 and

eluted with EtOAc. Once TLC indicated that TEMPO and TEMPO-H were eluted, the amine was eluted with 3% Et_3N in EtOAc. The filtrate was concentrated to afford the desired amine.

Table 15 Complete optimization table for the Tempoc protection of 2-phenethylamine

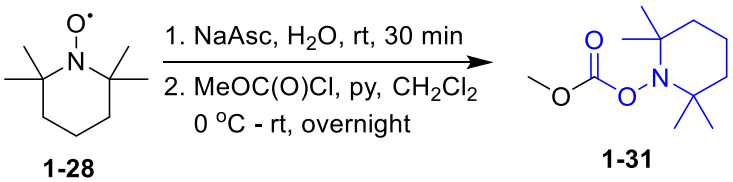


1-37 **1-38**

entry	stoichiometry[a]	solvent[b]	temp (°C)	base	yield[c] (%)
1	1:1:3	DCM	23	Et_3N	28
2	1:1:3	THF	23	Et_3N	60
3	1:1:3	MeCN	23	Et_3N	57
4	1:1:3	MeOH	23	Et_3N	64
5	1:1:3	DMF	23	Et_3N	77
6	1:1:3	DMF	23	py	67
7	1:1:3	DMF	23	$NaHCO_3$	64
8	1:1:3	DMF	23	K_2CO_3	79[d]
9	1:1:3	DMF	23	Et_3N/DMAP[e]	76[e]
10	1:1:3	DMF	40	Et_3N	41[f]
11	1:1:3	DMF	60	Et_3N	38[f]
12	1:1:3	DMF	80	Et_3N	14[f]
13	1:1.1:3	DMF	23	Et_3N	84
14	1:1.2:3	DMF	23	Et_3N	91
15	1:1.3:3	DMF	23	Et_3N	92

[a]amine:NPTC:base; [b]0.5 M in amine [c]isolated yields; [d]trace *bis*-Tempoc amine detected by HPLC-MS; [e]0.25 equiv DMAP; [f]slow NPTC decomposition is suspected to occur at higher temperatures

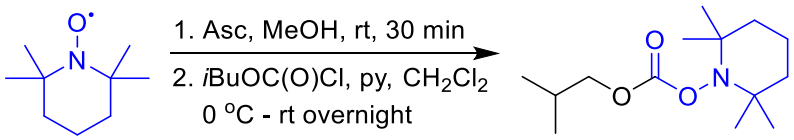
4.1.3 Synthetic procedures and spectral characterization for Tempoc transfer reagents



1-28 **1-31**

Methyl (2,2,6,6-tetramethylpiperidin-1-yl)carbonate (1-31). A vigorously stirred solution of sodium ascorbate (5.02 g, 25.1 mmol, 2 equiv) in deionized water (50 mL) was treated

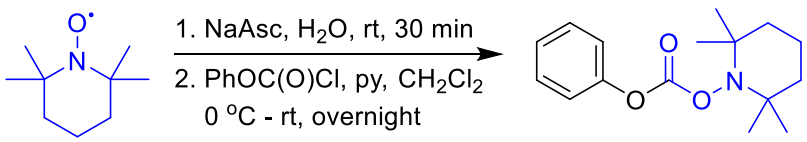
with TEMPO (2.00 g, 12.5 mmol, 1 equiv). After ca. 30 min, decolorization was observed and a white precipitate formed. The heterogeneous mixture was extracted with diethyl ether (3 x 25 mL), and the combined organic layers were washed with deionized water and brine, dried ($MgSO_4$), and concentrated to afford TEMPO-H (1.59 g, 80%) as a pale-red oil which was dissolved in dry CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C and treated with pyridine (1.19 g, 1.24 mL, 15.1 mmol) and dropwise over 1 min with ethyl chloroformate (1.47 g, 1.20 mL, 15.1 mL). The reaction was warmed to ambient temperature, stirred for 14 h, and quenched by addition of water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to afford crude product that was purified by chromatography on SiO_2 (1:19, EtOAc/hexanes) to afford **1-31** (1.73 g, 80%) as a colorless oil: R_f = 0.46 (1:4, EtOAc/hexanes); ATR-IR (neat) 2978, 2936, 1776, 1221, 940, 784 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 1.74–1.48 (m, 5 H), 1.42–1.35 (m, 1 H), 1.16 (s, 6 H), 1.11 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 157.3, 60.5, 54.9, 39.2, 31.5, 20.3, 16.9; HRMS (ESI) *m/z* calcd for $C_{11}H_{22}NO_3$ (M+H) 216.1594, found 216.1592.



1-28 **1-32**

***iso*-Butyl (2,2,6,6-tetramethylpiperidin-1-yl)carbonate (1-32).** A solution of TEMPO (0.500 g, 3.14 mmol, 1 equiv) in deoxygenated MeOH (26 mL) was treated with ascorbic acid (663 mg, 3.76 mmol, 1.2 equiv) as a solid in one portion. The clear-pink, to orange, to clear yellow reaction mixture was stirred for 30 min, concentrated, and the residue was partitioned between deoxygenated diethyl ether (15 mL) and deionized water (15 mL). The organic layer was separated and the aqueous layer was extracted with deoxygenated diethyl ether (4 x 10 mL). The combined

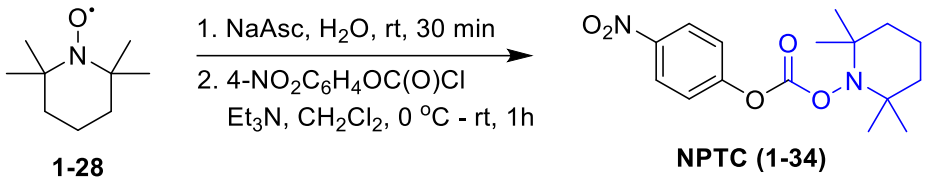
organic layers were dried ($MgSO_4$) and concentrated to afford TEMPO-H (204 mg, 41%) as a colorless oil that was dissolved in dry deoxygenated CH_2Cl_2 (7.78 mL), cooled to 0 °C and treated with pyridine (113 mg, 117 µL, 1.43 mmol), and dropwise over 1 min with *iso*-butyl chloroformate (325 mg, 311 µL, 1.43 mmol). The reaction mixture was warmed to ambient temperature, stirred for 2 h, quenched with 1 M HCl (5 mL), and transferred to separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to afford a residue which was purified by chromatography on SiO_2 (1:19, EtOAc/hexanes) to afford **1-32** (692 mg, 53%) as a colorless oil: R_f = 0.59 (1:4, EtOAc/hexanes); ATR-IR (neat) 2966, 2937, 1776, 1217, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (d, *J* = 6.8 Hz, 2 H), 2.00 (nonet, *J* = 6.8 Hz, 1 H), 1.73–1.51 (m, 5 H), 1.44–1.36 (m, 1 H), 1.17 (s, 6 H), 1.12 (s, 6 H), 0.95 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 74.0, 60.4, 39.2, 31.5, 27.9, 20.4, 18.9, 16.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}NO_3$ (M+H) 258.2064, found 258.2062.



1-28 **1-33**

Phenyl (2,2,6,6-tetramethylpiperidin-1-yl)carbonate (1-33). A solution of sodium ascorbate (2.08 g, 10.4 mmol, 1.66 equiv) and TEMPO (1.00 g, 6.27 mmol, 1 equiv) in water (18.0 mL) was vigorously stirred for 30 min while decolorization was observed and a white precipitate formed. The heterogeneous mixture was extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to afford TEMPO-H (955 mg, 97%). A solution of TEMPO-H (100 mg, 0.636 mmol) in dry CH_2Cl_2 (0.636 mL) was cooled to 0 °C and treated dropwise with pyridine (63.5 mg, 65.0 µL, 0.801 mmol) and

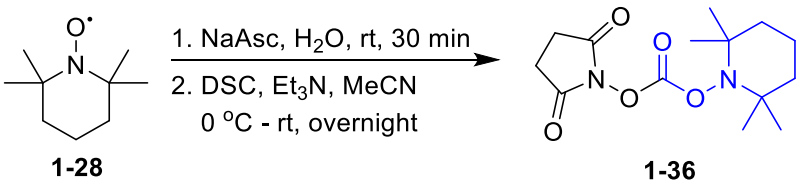
phenyl chloroformate (132 mg, 106 µL, 0.827 mmol). The reaction was warmed to room temperature and stirred for 3 h, diluted with CH_2Cl_2 (5 mL), and organic layer was washed with 1 M NaOH (5 mL), 1 M HCl (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated to afford a residue which was purified by chromatography on SiO_2 (1:19, EtOAc/hexanes) to afford **1-33** (112 mg, 63%) as a colorless oil: R_f = 0.57 (1:4, EtOAc/hexanes); ATR-IR (neat) 2979, 2935, 1791, 1198, 1177, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (m, 2 H), 7.25–7.14 (m, 3 H), 1.73–1.50 (m, 5 H), 1.46–1.34 (m, 1 H), 1.21 (s, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 151.4, 129.4, 125.7, 120.9, 60.8, 39.3, 31.6, 20.5, 16.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}NO_3$ (M+H) 278.1751, found 278.1749.



1-28 **NPTC (1-34)**

4-Nitrophenyl (2,2,6,6-tetramethylpiperidin-1-yl)carbonate (1-34, "NPTC"). A three-neck 3-L round bottom flask was fitted with an internal temperature probe and charged with a 0.35 M solution of sodium ascorbate (145 g, 724 mmol, 2.00 equiv) in deoxygenated deionized water (1.03 L). The pale translucent-yellow solution was treated with TEMPO (57.2 g, 362 mmol, 1 equiv) as a solid under vigorous mechanical stirring at ambient temperature. After ca. 30 min, decolorization was observed and a white precipitate formed, accompanied by a slight, yet rapid increase in internal temperature of ca. 5 °C. Deoxygenated diethyl ether (800 mL) was added and the reaction mixture was stirred for 5 min, and poured into a separatory funnel. The organic layer was separated and the aqueous layer was extracted with deoxygenated diethyl ether (1 x 500 mL). The combined organic layers were poured directly through a funnel containing anhydrous Na_2SO_4 and the filtrate was concentrated to afford TEMPO-H as a pale-red oil which was dissolved in

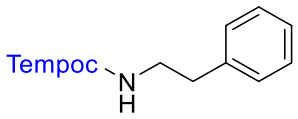
deoxygenated CH_2Cl_2 (950 mL), transferred to a three-neck 3-L round bottom flask, and cooled to -15 °C. The flask was then fitted with an addition funnel and an internal temperature probe before addition of deoxygenated triethylamine (73.2 g, 102 mL, 724 mmol, 2.00 equiv) in one portion, and *p*-nitrophenyl chloroformate (82.7 g, 434 mmol, 1.10 equiv) as a solution in deoxygenated CH_2Cl_2 (256 mL) by addition funnel at a rate that maintained an internal temperature of <10 °C (≈60 min). The solution was allowed to slowly warm to ambient temperature for 1 h, quenched with 1 L of ice-cold 2 M NaOH, and vigorously stirred. The organic layer was separated, dried ($MgSO_4$), and concentrated to afford a solid orange residue which was dissolved in hot acetone (1.0 L) and allowed to slowly cool to ambient temperature, and kept at -20 °C for 12 h. The precipitated crystals were removed by vacuum filtration, and the filter cake was washed with ice-cold acetone (500 mL). The mother liquor was concentrated to 400 mL and allowed to stand in a freezer (-20 °C) overnight to yield another crop of crystals which were filtered and washed with ice-cold acetone (200 mL). This procedure was again repeated to yield a third crop. The combined solids were washed with water (250 mL) and ice-cold acetone (100 mL) to remove any residual triethylamine hydrochloride, and dried under vacuum in a desiccator over $CaSO_4$ to afford **1-34** (97.4 g, 302 mmol, 84%) as off-white crystals: R_f = 0.53 (4:1, hexanes/EtOAc); Mp 137-140 °C; ATR-IR (neat) 2985, 1781, 1519, 1345, 1175, 914, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 1.75–1.54 (m, 5 H), 1.45–1.39 (m, 1 H), 1.22 (s, 6 H), 1.20 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 153.9, 145.2, 125.2, 121.6, 61.0, 39.2, 31.5, 20.4, 16.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}N_2O_5$ (M+H) 323.1601, found 323.1602.



1-28 **1-36**

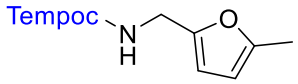
2,5-Dioxopyrrolidin-1-yl (2,2,6,6-tetramethylpiperidin-1-yl)carbonate (1-36). A solution of sodium ascorbate (2.51 g, 12.5 mmol, 2 equiv) and TEMPO (1.00 g, 6.27 mmol, 1 equiv) in water (25 mL) was vigorously stirred for 30 min while decolorization was observed and a white precipitate formed. The reaction mixture was extracted with ether (100 mL) and the aqueous layer was discarded. The organic layer was filtered ($MgSO_4$) and concentrated to afford TEMPO-H (886 mg, 90%). A solution of bis(2,5-dioxopyrrolidin-1-yl)carbonate (2.17 g, 8.45 mmol) in deoxygenated MeCN (20.0 mL) was cooled to 0 °C and treated with triethylamine (1.15 g, 1.60 mL, 11.3 mmol) and dropwise with a solution of crude TEMPO-H (886 mg, 5.63 mmol) in deoxygenated MeCN (8 mL). The reaction mixture was warmed to room temperature, stirred for 12 h, and concentrated to afford a residue that was purified by chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) to afford **1-36** (724 mg, 43%) as a viscous pale-yellow oil: R_f = 0.53 (1:1, EtOAc/hexanes); ATR-IR (neat) 2978, 2938, 1827, 1794, 1741, 1194, 1171, 900, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.82 (s, 4 H), 1.70–1.54 (m, 5 H), 1.43–1.37 (m, 1 H), 1.21 (s, 6 H), 1.19 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 153.0, 61.6, 39.4, 31.3, 25.5, 20.3, 16.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{23}N_2O_5$ (M+H) 299.1601, found 299.1601.

4.1.4 Synthetic procedures and spectral characterization for Tempoc protected amines



1-38

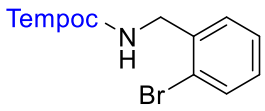
2,2,6,6-Tetramethylpiperidin-1-yl phenethylcarbamate (1-38). According to General Method 1-A, 2-phenethylamine (27.0 mg, 0.223 mmol), triethylamine (68.3 mg, 94.9 µL, 0.668 mmol), NPTC (86.2 mg, 0.267 mmol), DMF (0.5 mL), and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-38** (63.6 mg, 94%) as a colorless solid: R_f = 0.60 (1:1, EtOAc/hexanes); Mp 95-98 °C; ATR-IR (neat) 3292, 3025, 2977, 2932, 1698, 1475, 949, 747, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.28 (m, 2 H), 7.29–7.17 (m, 3 H), 6.77 (bs, 1 H), 3.50 (td, *J* = 6.9, 5.6 Hz, 2 H), 2.85 (t, *J* = 7.0 Hz, 2 H), 1.65–1.48 (m, 3 H), 1.42–1.29 (m, 3 H), 1.16 (s, 6 H), 0.93 (s, 6H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.5, 138.7, 128.7, 128.6, 126.5, 60.6, 41.7, 39.6, 35.5, 31.5, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_2$ (M+H) 305.2224, found 305.2223.



1-39

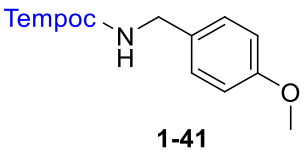
2,2,6,6-Tetramethylpiperidin-1-yl ((5-methylfuran-2-yl)methyl)carbamate (1-39). According to General Method 1-A, 5-methylfurfurylamine (55.0 mg, 0.485 mmol), triethylamine (149 mg, 207 µL, 1.46 mmol), NPTC (188 mg, 0.582 mmol), DMF (1.0 mL) and chromatography on SiO_2 (1:19 to 1:9, EtOAc/hexanes) afforded **1-39** (131 mg, 92%) as a colorless solid: R_f = 0.70 (1:1, EtOAc/hexanes); Mp 88-89 °C; ATR-IR (neat) 3370, 2977, 2929, 1709, 1497, 1184, 781 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (bs, 1 H), 6.08 (d, *J* = 3.0 Hz, 1 H), 5.86 (bd, *J* = 3.0, 1 H),

4.33 (d, *J* = 5.9 Hz, 2 H), 2.23 (s, 3 H), 1.73–1.34 (m, 6 H), 1.20 (s, 6 H), 1.05 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.4, 151.7, 149.5, 107.9, 106.1, 60.7, 39.7, 37.9, 31.5, 20.5, 16.7, 13.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{27}N_2O_3$ (M+H) 295.2016, found 295.2015.



1-40

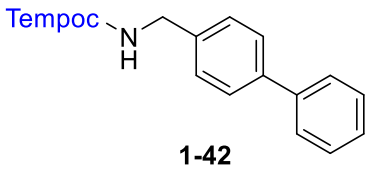
2,2,6,6-Tetramethylpiperidin-1-yl (2-bromobenzyl)carbamate (1-40). According to General Method 1-A, 2-bromobenzylamine (63.0 mg, 0.332 mmol), triethylamine (102 mg, 141 µL, 0.996 mmol), NPTC (128 mg, 0.398 mmol), DMF (0.7 mL) and chromatography on SiO_2 (1:19 to 1:9, EtOAc/hexanes) afforded **1-40** (111 mg, 90%) as a fluffy colorless solid: R_f = 0.74 (1:1, EtOAc/hexanes); Mp 165-167 °C; ATR-IR (neat) 3310, 2939, 1698, 1473, 1187, 929, 741 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.54 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.41 (dd, *J* = 7.6, 1.8 Hz, 1 H), 7.35 (bs, 1 H), 7.27 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.13 (td, *J* = 7.7, 1.8 Hz, 1 H), 4.48 (d, *J* = 6.4 Hz, 2 H), 1.72–1.44 (m, 5 H), 1.44–1.35 (m, 1 H), 1.20 (s, 6 H), 1.04 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.5, 137.4, 132.7, 130.3, 129.1, 127.7, 123.5, 60.7, 45.1, 39.7, 31.6, 20.6, 16.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}BrN_2O_2$ (M+H) 369.1172, found 369.1173.



1-41

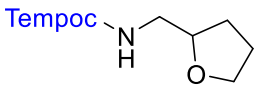
2,2,6,6-Tetramethylpiperidin-1-yl (4-methoxybenzyl)carbamate (1-41). According to General Method 1-A, 4-methoxybenzylamine (50.0 mg, 0.354 mmol), triethylamine (108 mg, 151 µL, 1.06 mmol), NPTC (137 mg, 0.424 mmol), DMF (0.7 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-41** (106 mg, 93%) as a colorless solid: R_f = 0.62 (1:1, EtOAc/hexanes); Mp 95-98 °C; ATR-IR (neat) 3321, 2930, 1697, 1510, 1249, 929, 706 cm^{-1}; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 2 H), 6.95 (bs, 1 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 4.32 (d, *J* = 5.9 Hz, 2 H), 3.75 (s, 3 H), 1.65–1.30 (m, 6 H), 1.17 (s, 6 H), 1.03 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.5, 130.3, 128.9, 113.9, 60.6, 55.2, 44.3, 39.5, 31.7, 20.5, 16.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_3$ (M+H) 321.2173, found 321.2173.



1-42

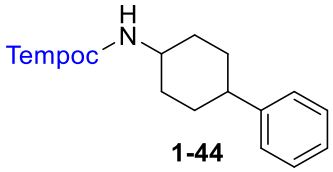
2,2,6,6-Tetramethylpiperidin-1-yl ([1,1'-biphenyl]-4-ylmethyl)carbamate (1-42). According to General Method 1-A, 4-phenylbenzylamine (1.50 g, 7.94 mmol), triethylamine (2.44 g, 3.38 mL, 23.8 mmol), NPTC (3.07 g, 9.53 mmol), DMF (16 mL) and chromatography on SiO_2 (1:19 to 3:7, EtOAc/hexanes) afforded **1-42** (2.60 g, 89%) as a fluffy colorless solid: R_f = 0.61 (1:1, EtOAc/hexanes); Mp 134-137 °C; ATR-IR (neat) 3252, 2971, 2930, 1694, 1484, 1254, 933, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.55 (m, 4 H), 7.44 (t, *J* = 7.9 Hz, 2 H), 7.39–7.33 (m, 3 H), 7.09 (bs, 1 H), 4.48 (d, *J* = 6.1 Hz, 2 H), 1.71–1.44 (m, 5 H), 1.42–1.35 (m, 1 H), 1.24 (s, 6 H), 1.11 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 140.5, 140.2, 137.3, 128.6, 127.9, 127.2, 127.2, 126.9, 60.7, 44.5, 39.5, 31.7, 20.5, 16.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_2$ (M+H) 367.2380, found 367.2377.



1-43

2,2,6,6-Tetramethylpiperidin-1-yl ((tetrahydrofuran-2-yl)methyl)carbamate (1-43). According to General Method 1-A, tetrahydrofurfurylamine (50.0 mg, 0.480 mmol), triethylamine (147 mg, 204 µL, 1.44 mmol), NPTC (186 mg, 0.575 mmol), DMF (1 mL) and chromatography on SiO_2 (1:19 to 3:7, EtOAc/hexanes) afforded **1-43** (126 mg, 93%) as a colorless solid: R_f = 0.41

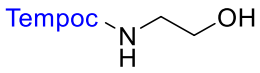
(1:1, EtOAc/hexanes); Mp 74-76 °C; ATR-IR (neat) 3328, 2933, 1712, 1501, 1250, 1084, 953 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (bs, 1 H), 3.97–3.88 (m, 1 H), 3.83 (A of ABX_2, *J* = 8.4, 6.6 Hz, 1 H), 3.75 (B of ABX_2, *J* = 8.1, 6.7 Hz, 1 H), 3.47 (A of ABMX, *J* = 13.9, 6.9, 3.6 Hz, 1 H), 3.17 (B of ABMX, *J* = 13.9, 6.6, 5.3 Hz, 1 H), 2.01–1.82 (m, 3 H), 1.70–1.45 (m, 6 H), 1.44–1.35 (m, 1 H), 1.20 (s, 6 H), 1.10 (2s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.9, 78.0, 68.0, 60.7, 60.6, 44.3, 39.7, 39.6, 31.7, 31.5, 28.3, 25.8, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}N_2O_3$ (M+H) 285.2173, found 285.2169.



1-44

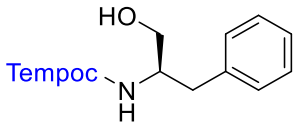
2,2,6,6-Tetramethylpiperidin-1-yl (4-phenylcyclohexyl)carbamate (1-44). According to General Method 1-A and Workup Procedure 1-1, 4-phenylcyclohexylamine (455 mg, 2.60 mmol), triethylamine (796 mg, 1.11 mL, 7.79 mmol), NPTC (1.00 g, 3.12 mmol), DMF (5 mL) and chromatography on SiO_2 (1:19 to 3:17, EtOAc/hexanes) afforded **1-44** (811 mg, 87%) as a fluffy colorless solid in a 1:5 *cis*/*trans*-diastereomeric mixture: R_f = 0.56 (1:1, EtOAc/hexanes); Mp 114-126 °C; ATR-IR (neat) 3357, 2976, 2930, 1708, 1492, 1131, 989, 755, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2 H), 7.22–7.17 (m, 3 H), 6.72 (bd, *J* = 8.5 Hz, 1 H), 3.67 (tdt, *J* = 12.3, 8.8, 4.1 Hz, 1 H), 2.50 (tt, *J* = 12.2, 3.5 Hz, 1 H), 2.21–2.09 (m, 2 H), 2.02–1.91 (m, 2 H), 1.70–1.20 (m, 10 H), 1.23 (s, 6 H), 1.12 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 146.5, 128.4, 126.7, 126.1, 60.7, 49.6, 43.5, 39.8, 33.6, 32.9, 31.8, 20.6, 16.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{35}N_2O_2$ (M+H) 359.2693, found 359.2692. A sample of *trans*-2,2,6,6-tetramethylpiperidin-1-yl (4-phenylcyclohexyl)carbamate (*trans*-**1-44**) was isolated for characterization: R_f = 0.60 (:1, EtOAc/hexanes); Mp 150-152 °C; ATR-IR (neat) 3327, 2976, 2930, 1703, 1492, 1132, 989, 733, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2 H), 7.22–7.16 (m, 3 H), 6.72 (bd, *J* = 8.8

Hz, 1 H), 3.67 (tdt, *J* = 12.3, 8.8, 4.1 Hz, 1 H), 2.50 (tt, *J* = 12.2, 3.4 Hz, 1 H), 2.18–2.08 (m, 2 H), 1.98–1.90 (m, 2 H), 1.70– 1.50 (m, 7 H), 1.50-1.20 (m, 3 H), 1.23 (s, 6 H), 1.12 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 146.5, 128.4, 126.7, 126.1, 60.7, 49.6, 43.5, 39.8, 33.6, 32.9, 31.8, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{35}N_2O_2$ (M+H) 359.2693, found 359.2693.



1-45

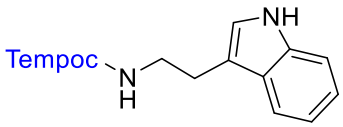
2,2,6,6-Tetramethylpiperidin-1-yl (2-hydroxyethyl)carbamate (1-45). According to General Method 1-A, ethanolamine (61.1 mg, 0.648 mmol), triethylamine (199 mg, 276 µL, 1.95 mmol), NPTC (251 mg, 0.778 mmol), DMF (1.3 mL) and chromatography on SiO_2 (1:19 to 1:1, EtOAc/hexanes) afforded **1-45** (148 mg, 94%) as a colorless, crystalline solid: R_f = 0.29 (4:1, EtOAc/hexanes); Mp 102-105 °C; ATR-IR (neat) 3316, 2936, 1697, 1501, 1525, 955, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (bs, 1 H), 3.69 (q, *J* = 5.0 Hz, 2 H), 3.36 (q, *J* = 5.2 Hz, 2 H), 2.75 (t, *J* = 4.9 Hz, 1 H), 1.71–1.45 (m, 5 H), 1.43–1.34 (m, 1 H), 1.19 (s, 6 H), 1.09 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 159.5, 62.1, 60.7, 43.1, 39.6, 31.5, 20.5, 16.7; HMRS (ESI) *m/z* calcd for $C_{12}H_{25}N_2O_3$ (M+H) 245.1860, found 245.1849.



1-46

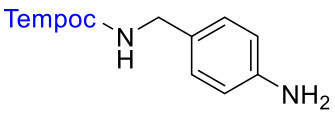
2,2,6,6-Tetramethylpiperidin-1-yl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (1-46). According to General Method 1-A, L-phenylalaninol (0.150 g, 0.972 mmol), triethylamine (298 mg, 414 µL, 2.92 mmol), NPTC (376 mg, 1.17 mmol), DMF (1.9 mL), and chromatography on SiO_2 (1:19 to 1:1, EtOAc/hexanes) afforded **1-46** (234 mg, 72%) as a fluffy colorless solid: R_f = 0.47 (1:1, EtOAc/hexanes); Mp 108-111 °C; ATR-IR (neat) 3370, 2976, 2933, 1698, 1494, 1030,

701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.16 (m, 5 H), 7.01 (bs, 1 H), 4.06–3.90 (m, 1 H), 3.75–3.58 (m, 2 H), 3.09 (bs, 1 H), 2.95 (A of ABX, *J* = 13.9, 6.6 Hz, 1 H), 2.82 (B of ABX, *J* = 13.9, 8.2 Hz, 1 H), 1.69–1.26 (m, 6 H), 1.16 (s, 3 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 159.0, 137.4, 129.2, 128.7, 126.7, 64.6, 60.7, 60.6, 54.2, 54.1, 39.6, 39.4, 37.0, 31.6, 31.0, 20.5, 20.4, 16.6; HRMS (ESI) *m/z* calcd for $C_{19}H_{31}N_2O_3$ (M+H) 335.2329, found 335.2328.



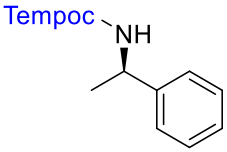
1-47

2,2,6,6-Tetramethylpiperidin-1-yl (2-(1*H*-indol-3-yl)ethyl)carbamate (1-47). According to General Method 1-A, tryptamine (1.00 g, 6.12 mmol), triethylamine (1.88 g, 2.61 mL, 18.4 mmol), NPTC (2.37 g, 7.34 mmol), DMF (12.2 mL), and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-47** (1.92 g, 92%) as an off-white solid: R_f = 0.47 (1:1, EtOAc/hexanes); Mp 150-152 °C; ATR-IR (neat) 3310, 2976, 2935, 1706, 1501, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (bs, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 7.05 (bs, 1 H), 6.83 (bs, 1 H), 3.59 (q, *J* = 6.5 Hz, 2 H), 3.02 (t, *J* = 6.9 Hz, 2 H), 1.67–1.43 (m, 3 H), 1.37–1.22 (m, 3 H), 1.15 (s, 6 H), 0.91 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.7, 136.4, 127.3, 122.1, 119.5, 118.7, 112.9, 111.2, 60.6, 41.1, 39.5, 31.4, 25.2, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}N_3O_2$ (M+H) 344.2333, found 344.2329.



1-48

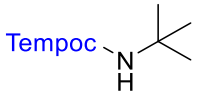
2,2,6,6-Tetramethylpiperidin-1-yl (4-aminobenzyl)carbamate (1-48). According to General Method 1-A, 4-aminobenzylamine (1.18 g, 9.47 mmol), triethylamine (2.90 g, 4.03 mL, 28.4 mmol), NPTC (3.66 g, 11.4 mmol), DMF (19 mL) and chromatography on SiO_2 (1:19 to 1:1, EtOAc/hexanes) afforded **1-48** (2.81 g, 93%) as a yellow solid: R_f = 0.32 (1:1, EtOAc/hexanes); Mp 118-120 °C; ATR-IR (neat) 3450, 3362, 2977, 2933, 1688, 1493, 1255, 928, 830, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.3 Hz, 2 H), 6.88 (bs, 1 H), 6.62 (d, *J* = 8.3 Hz, 2 H), 4.29 (d, *J* = 5.8 Hz, 2 H), 3.67 (s, 2 H), 1.65–1.39 (m, 5 H), 1.41–1.29 (m, 1 H), 1.20 (s, 6 H), 1.05 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 145.8, 128.9, 128.1, 115.1, 60.7, 44.5, 39.6, 31.7, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{28}N_3O_2$ (M+H) 306.2176, found 306.2176.



1-49

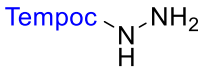
2,2,6,6-Tetramethylpiperidin-1-yl (*S*)-(1-phenylethyl)carbamate (1-49). According to General Method 1-A, (*S*)-(-)-1-phenethylamine (50.0 mg, 0.404 mmol), triethylamine (124 mg, 172 µL, 1.21 mmol), NPTC (156 mg, 0.485 mmol), DMF (0.8 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-49** (92 mg, 75%) as a fluffy colorless solid: R_f = 0.71 (1:1, EtOAc/hexanes); Mp 127 °C; ATR-IR (neat) 3289, 2973, 2929, 1696, 1493, 1187, 986, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5 H), 7.03 (bd, *J* = 8.6 Hz, 1 H), 4.97 (p, *J* = 7.2 Hz, 1 H), 1.72–1.34 (m, 6 H), 1.51 (d, *J* = 6.9 Hz, 1 H), 1.23 (s, 3 H), 1.19 (s, 3 H), 1.15 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 157.6, 143.0, 128.5, 127.3, 126.1, 60.9, 60.6, 50.2,

39.8, 39.7, 31.9, 31.8, 21.8, 20.6, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_2$ (M+H) 305.2224, found 305.2221.



1-50

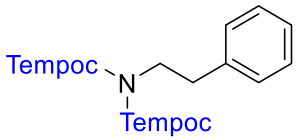
2,2,6,6-Tetramethylpiperidin-1-yl *tert*-butylcarbamate (1-50). According to General Method 1-A, *tert*-butylamine (35.0 mg, 0.469 mmol), triethylamine (144 mg, 0.200 mL, 1.41 mmol), NPTC (181 mg, 0.563 mmol), DMF (1 mL) and chromatography on SiO_2 (0:1 to 1:19, EtOAc/hexanes) afforded **1-50** (38 mg, 32%) as a colorless solid: R_f = 0.51 (1:4, EtOAc/hexanes); Mp 108-109 °C; ATR-IR (neat) 3290, 2976, 2923, 1704, 1494, 1263, 1021, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (bs, 1 H), 1.67–1.46 (m, 5 H), 1.45–1.34 (m, 1 H), 1.31 (s, 9 H), 1.18 (s, 6 H), 1.08 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 156.6, 60.6, 50.1, 39.8, 31.8, 28.7, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{29}N_2O_2$ (M+H) 257.2224, found 257.2223.



1-51

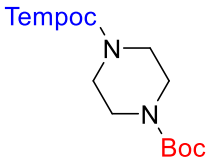
2,2,6,6-Tetramethylpiperidin-1-yl hydrazinecarboxylate (1-51). A solution of anhydrous hydrazine (60.3 mg, 18.6 mmol) and triethylamine (2.85 g, 3.96 mL, 28.0 mmol) in DMF (37 mL) was treated at 0 °C with NPTC (3.00 g, 9.31 mmol) in 2 portions over 2 min. The cooling bath was removed and the reaction mixture was stirred for 2 h at room temperature, diluted with CH_2Cl_2 (20 mL), and partitioned between ice-cold 1 M NaOH (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to afford a residue which was purified by chromatography on SiO_2 (1:19 to 1:0, EtOAc/hexanes) to afford **1-51** (1.90 g, 95%) as transparent crystals: R_f = 0.39 (EtOAc); Mp 146-149 °C (dec.);

ATR-IR (neat) 3285, 2980, 2932, 1716, 1618, 1451, 1040, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (bs, 1 H), 3.75 (s, 2 H), 1.64–1.40 (m, 5 H), 1.39–1.31 (m, 1 H), 1.14 (s, 6 H), 1.05 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 60.8, 39.5, 31.4, 20.3, 16.6; HRMS (ESI) *m/z* calcd for $C_{10}H_{22}N_3O_2$ (M+H) 216.1707, found 216.1705.



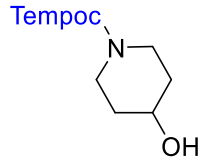
1-52

2,2,6,6-Tetramethylpiperidin-1-yl *N*-(2-phenylethyl)-*N*-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]carbonyl}carbamate (1-52). A suspension of 90% sodium hydride (57.2 mg, 2.15 mmol) in dry THF (6 mL) was cooled to 0 °C and treated dropwise with a solution of 2-phenethylamine (0.100 g, 0.825 mmol) in dry THF (1 mL). The reaction mixture was stirred at 0 °C for 30 min, treated dropwise with a solution of NPTC (638 mg, 1.98 mmol) in dry THF (1.3 mL), and stirred at room temperature for 1 h while the color turned from yellow to bright orange. After addition of diethyl ether (50 mL) and crushed ice (20 g), the organic layer was washed with sat. Na_2CO_3 (2 x 25 mL), water, and brine, dried ($MgSO_4$), and concentrated to give a residue which was purified by chromatography on SiO_2 (1:19 to 1:9, EtOAc/hexanes) to afford **1-52** (363 mg, 90%) as an off-white solid: R_f = 0.55 (1:1, EtOAc/hexanes); Mp 125-126 °C; ATR-IR (neat) 2935, 1779, 1751, 1262, 1148, 1043, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H), 7.28–7.19 (m, 2 H), 3.92 (AA' of AA'XX', $J_{AA'}$ = -10 Hz, J_{AX} = 10 Hz, $J_{AX'}$ = 5.2 Hz, 2 H), 2.99 (XX' of AA'XX', $J_{XX'}$ = -11 Hz, J_{AX} = 10 Hz, $J_{AX'}$ = 5.2 Hz, 2 H), 1.77–1.60 (m, 7 H), 1.58–1.53 (m, 4 H), 1.44–1.39 (m, 2 H), 1.23 (s, 12 H), 1.14 (s, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 138.2, 128.9, 128.6, 126.5, 60.6, 48.3, 39.1, 35.7, 31.7, 21.1, 16.9; HRMS (ESI) *m/z* calcd for $C_{28}H_{46}N_3O_4$ (M+H) 488.3483, found 488.3481.



1-54

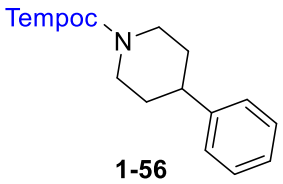
1-(*tert*-Butyl) 4-(2,2,6,6-tetramethylpiperidin-1-yl) piperazine-1,4-dicarboxylate (1-54). According to General Method 1-A and Workup Procedure 1-1, *tert*-butyl 1-piperazinecarboxylate (1.00 g, 5.37 mmol), triethylamine (1.65 g, 2.29 mL, 16.1 mmol), NPTC (2.08 g, 6.44 mmol), DMF (11 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-54** (1.82 g, 91%) as a colorless solid: R_f = 0.55 (1:1, EtOAc/hexanes); Mp 146-147 °C; ATR-IR (neat) 2974, 2931, 1733, 1698, 1410, 1218, 1170, 1001, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52–3.46 (m, 4 H), 3.45–3.40 (m, 4 H), 1.75–1.48 (m, 5 H), 1.46 (s, 9 H), 1.44–1.36 (m, 1 H), 1.14 (s, 6 H), 1.09 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 156.3, 154.6, 80.1, 60.2, 44.0, 39.0, 31.8, 28.4, 21.0, 17.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{36}N_3O_4$ (M+H) 370.2700, found 370.2699.



1-55

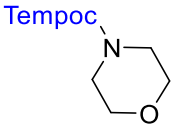
2,2,6,6-Tetramethylpiperidin-1-yl 4-hydroxypiperidine-1-carboxylate (1-55). According to General Method 1-A, 4-hydroxypiperidine (51.0 mg, 0.494 mmol), triethylamine (152 mg, 0.210 mL, 1.48 mmol), NPTC (191 mg, 0.593 mmol), DMF (1 mL) and chromatography on SiO_2 (1:19 to 1:1, EtOAc/hexanes) afforded **1-55** (122 mg, 87%) as a colorless solid: R_f = 0.29 (1:4, EtOAc/hexanes); Mp 156-157 °C; ATR-IR (neat) 3422, 2937, 1708, 1420, 1214, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.01–3.79 (m, 3 H), 3.11 (ddd, *J* = 13.3, 9.7, 3.3 Hz, 2 H), 2.25 (s, 1 H), 1.93–1.82 (m, 2 H), 1.76–1.42 (m, 7 H), 1.41–1.32 (m, 1 H), 1.12 (s, 6 H), 1.06 (s, 6 H); ^{13}C

NMR (76 MHz, $CDCl_3$) δ 156.4, 67.3, 60.0, 41.7, 39.0, 34.3, 31.7, 20.9, 16.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}N_2O_3$ (M+H) 285.2173, found 285.2171.



1-56

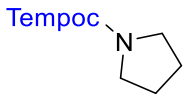
2,2,6,6-Tetramethylpiperidin-1-yl 4-phenylpiperidine-1-carboxylate (1-56). According to General Method 1-A and Workup Procedure 1-1, 4-phenylpiperidine (1.00 g, 6.08 mmol), triethylamine (1.86 g, 2.59 mL, 18.2 mmol), NPTC (2.35 g, 7.29 mmol), DMF (12 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-56** (2.05 g, 98%) as a colorless solid: R_f = 0.56 (1:1, EtOAc/hexanes); Mp 143-145 °C; ATR-IR (neat) 3002, 2972, 2933, 1727, 1209, 1010, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 2 H), 7.26–7.17 (m, 3 H), 4.38–4.26 (m, 2 H), 2.95-2.85 (m, 2 H), 2.69 (tt, *J* = 12.2, 3.7 Hz, 1 H), 1.90–1.86 (m, 2 H), 1.85-1.62 (m, 5 H), 1.57-1.52 (m, 2 H), 1.46–1.35 (m, 1 H), 1.17 (s, 6 H), 1.14 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 145.5, 128.5, 126.7, 126.3, 60.1, 44.9, 42.6, 38.9, 33.3, 31.8, 21.0, 17.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}N_2O_2$ (M+H) 345.2537, found 345.2535.



1-57

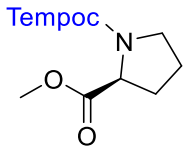
2,2,6,6-Tetramethylpiperidin-1-yl morpholine-4-carboxylate (1-57). According to General Method 1-A, morpholine (50.0 mg, 0.568 mmol), triethylamine (174 mg, 242 µL, 1.71 mmol), NPTC (0.220 g, 0.682 mmol), DMF (1.1 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-57** (151 mg, 98%) as a clear viscous oil: R_f = 0.42 (1:1, EtOAc/hexanes); ATR-IR (neat) 2970, 2929, 1726, 1227, 1116, 858, 757 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 3.67 (2AA' of AA'XX', $J_{AA'}$ = -12 Hz, J_{AX} = 7 Hz, $J_{AX'}$ = 4 Hz, 4 H), 3.50 (2XX' of AA'XX', $J_{XX'}$ = -12 Hz, J_{AX} = 7 Hz, $J_{AX'}$ = 4 Hz, 4 H), 1.78–1.46 (m, 5 H), 1.44–1.35 (m, 1 H), 1.13 (s, 6 H), 1.09 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 156.4, 66.7, 60.1, 44.4, 39.0, 31.8, 21.0, 16.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{27}N_2O_3$ (M+H) 271.2016, found 271.2019.



1-58

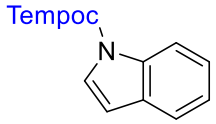
2,2,6,6-Tetramethylpiperidin-1-yl pyrrolidine-1-carboxylate (1-58). According to General Method 1-A, pyrrolidine (50.0 mg, 0.696 mmol), triethylamine (213 mg, 296 µL, 2.09 mmol), NPTC (269 mg, 0.835 mmol), DMF (1.4 mL) and chromatography on SiO_2 (0:1 to 1:1, EtOAc/hexanes) afforded **1-58** (161 mg, 91%) as a white solid: R_f = 0.44 (1:1, EtOAc/hexanes); Mp 74-76 °C; ATR-IR (neat) 2972, 2932, 1726, 1388, 1060, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (t, *J* = 6.7 Hz, 4 H), 1.95–1.77 (m, 4 H), 1.77–1.44 (m, 5 H), 1.42–1.33 (m, 1 H), 1.13 (s, 6 H), 1.09 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 156.0, 59.9, 46.5 (b), 45.4 (b), 38.9, 31.9, 25.9 (b), 24.7 (b), 20.8, 17.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{27}N_2O_2$ (M+H) 255.2067, found 255.2065.



1-59

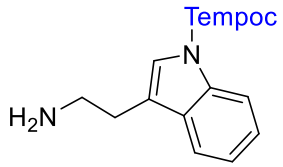
2-Methyl 1-(2,2,6,6-tetramethylpiperidin-1-yl) (*R*)-pyrrolidine-1,2-dicarboxylate (1-59). According to General Method 1-A and Workup Procedure 1-1, L-proline methyl ester hydrochloride (1.00 g, 5.98 mmol), triethylamine (2.44 g, 3.39 mL, 23.9 mmol), NPTC (2.31 g, 7.17 mmol), DMF (12 mL) and chromatography on SiO_2 (1:19 to 1:1, EtOAc/hexanes) afforded **1-59** (1.62 g, 87%) as an off-white solid: R_f = 0.56 (1:1, EtOAc/hexanes); Mp 91-93 °C; ATR-IR

(neat) 2977, 2935, 1740, 1721, 1386, 1363, 1201, 1185, 1065, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 4.30 (dd, *J* = 8.8, 3.1 Hz, 1 H), 3.66 (s, 3 H), 3.47 (t, *J* = 6.7 Hz, 2 H), 2.35–2.20 (m, 1 H), 1.99–1.85 (m, 3 H), 1.52 (s, 6 H), 1.09 (s, 6 H), 1.06 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, 2:3 mixture of rotamers) δ 173.3, 173.0, 155.8, 155.0, 60.0, 59.9, 59.8, 59.4, 58.4, 52.0, 51.9, 47.3, 45.9, 39.1, 39.0, 38.9, 31.9, 31.7, 31.5, 31.4, 31.3, 29.5, 24.4, 23.2, 20.9, 20.8, 20.7, 20.3, 16.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{29}N_2O_4$ (M+H) 313.2122, found 313.2125.



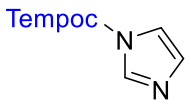
1-60

2,2,6,6-Tetramethylpiperidin-1-yl 1H-indole-1-carboxylate (1-60). According to General Method 1-B, indole (50.0 mg, 0.423 mmol), sodium hydride 90% (14.7 mg, 0.549 mmol), NPTC (164 mg, 0.507 mmol), THF (0.25 mL) and chromatography on SiO_2 (1:49 to 1:19, EtOAc/hexanes) afforded **1-60** (119 mg, 94%) as a crystalline white solid: R_f = 0.63 (1:4, EtOAc/hexanes); Mp 103-105 °C; ATR-IR (neat) 2973, 2935, 1761, 1452, 1321, 1227, 1114, 988, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1 H), 7.57 (d, *J* = 3.8 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.26 (dt, *J* = 8.1, 1.5 Hz, 1 H), 7.16 (dt, *J* = 7.8, 1.5 Hz, 1 H), 6.54 (d, *J* = 3.7 Hz, 1 H), 1.78–1.45 (m, 5 H), 1.42–1.33 (m, 1 H), 1.22 (s, 6 H), 1.10 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 151.8, 135.4, 130.3, 125.2, 124.5, 122.9, 120.9, 115.3, 108.1, 60.8, 39.3, 31.7, 21.3, 16.9; HRMS (ESI) *m/z* calcd for $C_{18}H_{25}N_2O_2$ (M+H) 301.1911, found 301.1907.



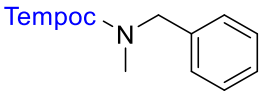
1-61

2,2,6,6-Tetramethylpiperidin-1-yl 3-(2-aminoethyl)-1*H*-indole-1-carboxylate (1-61). A suspension of sodium hydride (90% in mineral oil, 74.2 mg, 2.78 mmol) in freshly distilled THF (10 mL) was stirred vigorously under nitrogen at 0 °C on an ice-bath for 10 min, and treated dropwise with a solution of tryptamine (0.350 g, 2.14 mmol) in distilled THF (5.0 mL) over 1 min. The cooling bath was removed and the reaction mixture was stirred at ambient temperature. After 4 h, the mixture was cooled to 0 °C and a solution of NPTC (828 mg, 2.60 mmol) in distilled THF (6.0 mL) was added over 1 h by syringe pump. During the addition, the reaction mixture turned yellow, then deep orange. The solution was stirred at 0 °C for an additional 1 h, quenched with sat. ammonium chloride (2 mL), concentrated, and diluted with CH_2Cl_2 (50 mL) and sat. sodium carbonate (25 mL). The organic layer was washed with sat. sodium carbonate until the aqueous layer remained colorless (complete removal of 4-nitrophenol, typically 2-3 washes), dried ($MgSO_4$) and concentrated to give a residue that was purified by chromatography on SiO_2 (0 to 1:4, MeOH:CH_2Cl_2) to afford **1-60** (523 mg, 71%) as a pale yellow oil: R_f = 0.35 (1:4, MeOH:CH_2Cl_2); ATR-IR (neat) 2974, 2934, 2871, 1754, 1364, 1453, 1364, 1221, 988, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.2 Hz, 1 H), 7.57 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.50 (s, 1 H), 7.36 (dt, *J* = 7.9, 1.2 Hz, 1 H), 7.27 (dt, *J* = 7.9, 1.2 Hz, 1 H), 3.09 (bs, 2 H), 2.89 (t, *J* = 6.6 Hz, 2 H), 1.88–1.57 (m, 7 H), 1.50–1.43 (m, 1 H), 1.32 (s, 6 H), 1.19 (s, 6 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 151.7, 135.7, 130.4, 124.7, 122.6, 122.4, 119.1, 119.0, 115.4, 60.7, 41.4, 39.2, 31.7, 29.0, 21.4, 16.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{30}N_3O_2$ (M+H) 344.2333, found 344.2330.



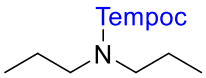
1-62

2,2,6,6-Tetramethylpiperidin-1-yl 1*H*-imidazole-1-carboxylate (1-62). According to General Method 1-A, imidazole (0.250 g, 3.66 mmol), triethylamine (1.12 g, 1.56 mL, 11.0 mmol), NPTC (1.42 g, 4.39 mmol), DMF (7.3 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-62** (838 mg, 91%) as a fluffy colorless solid: R_f = 0.48 (1:1, EtOAc/hexanes); Mp 133-135 °C; ATR-IR (neat) 3133, 3109, 2937, 2937, 1771, 1376, 1245, 986, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.46 (t, *J* = 1.5 Hz, 1 H), 7.11 (dd, *J* = 1.5, 0.9 Hz, 1 H), 1.81–1.56 (m, 5 H), 1.50–1.42 (m, 1 H), 1.25 (s, 6 H), 1.16 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 136.9, 130.7, 117.0, 61.2, 39.2, 31.7, 20.8, 16.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{22}N_3O_2$ (M+H) 252.1707, found 252.1712.



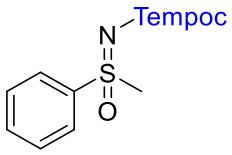
1-63

2,2,6,6-Tetramethylpiperidin-1-yl benzyl(methyl)carbamate (1-63). According to General Method 1-A, *N*-methylbenzylamine (1.00 g, 8.01 mmol), triethylamine (2.46 g, 3.41 mL, 24.0 mmol), NPTC (3.10 g, 9.61 mmol), DMF (1 mL) and chromatography on SiO_2 (0:1 to 1:19, EtOAc/hexanes) afforded **1-63** (2.36 g, 97%) as an off-white solid: R_f = 0.58 (1:1, EtOAc/hexanes); Mp 56-58 °C; ATR-IR (neat) 2973, 2932, 1723, 1378, 1117, 925, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5 H), 4.52 (bs, 2 H), 2.90 (b, 3 H), 1.80–1.45 (m, 5 H), 1.45– 1.30 (m, 1 H), 1.13 (b, 12 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 137.8, 128.5, 127.3, 60.1, 52.8 (b), 39.0, 35.5 (b), 31.8, 20.9, 17.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_2$ (M+H) 305.2224, found 305.2222.



1-64

2,2,6,6-Tetramethylpiperidin-1-yl dipropylcarbamate (1-64). According to General Method 1-A, di-*n*-propylamine (0.200 g, 1.96 mmol), triethylamine (0.600 g, 0.833 mL, 5.87 mmol), NPTC (757 mg, 2.35 mmol), DMF (3.9 mL) and chromatography on SiO_2 (1:19 to 1:4, EtOAc/hexanes) afforded **1-64** (310 mg, 56%) as a clear oil: R_f = 0.67 (1:1, EtOAc/hexanes); ATR-IR (neat) 2966, 2933, 1729, 1232, 1147, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.20 (2AA' of AA'XX', $J_{AA'}$ = -8 Hz, J_{AX} = 9 Hz, $J_{AX'}$ = 5 Hz, 4 H), 1.76–1.45 (m, 9 H), 1.42–1.33 (m, 1 H), 1.13 (s, 6 H), 1.08 (s, 6 H), 0.88 (t, *J* = 6.6 Hz, 3 H), 0.84 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 157.2, 59.9, 49.4, 48.6, 39.1, 31.7, 22.2, 21.2, 21.0, 17.0, 11.4, 11.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{33}N_2O_2$ (M+H) 285.2537, found 285.2534.

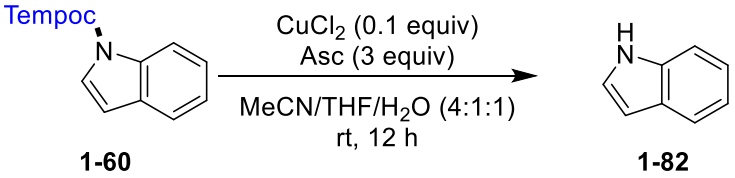


1-65

2,2,6,6-Tetramethylpiperidin-1-yl (methyl(oxo)(phenyl)-λ^6-sulfanylidene)carbamate (1-65). A suspension of sodium hydride (60% dispersion in mineral oil, 28.4 mg, 0.709 mmol) in dry DMF (6.5 mL) was treated dropwise at 0 °C under nitrogen with a solution of methyl sulfoximine (0.100 g, 0.664 mmol) in dry DMF (0.5 mL). The reaction mixture was stirred at 0 °C for 1 h before a solution of NPTC (265 mg, 0.821 mmol) in dry DMF (0.5 mL) was added. The cooling bath was removed, and the solution was stirred at room temperature for 12 h, quenched with crushed ice (5 g), and partitioned between 1 M NaOH (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous slayer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with deionized water and brine, dried ($MgSO_4$), filtered,

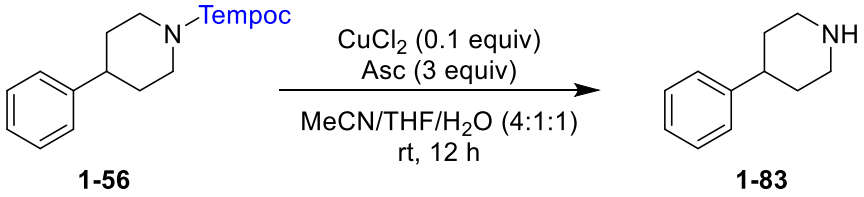
and concentrated to give a residue which was purified by chromatography on SiO_2 (1:49 to 1:19, CH_2Cl_2:MeOH) to afford **1-65** (178 mg, 82%) as a fluffy white solid: R_f = 0.36 (4:1, EtOAc/hexanes); Mp 196-198 °C (dec.); ATR-IR (neat) 3015, 2930, 1726, 1682, 1220, 978, 743, 518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02–7.95 (m, 2 H), 7.67–7.54 (m, 3 H), 3.23 (s, 3 H), 1.65–1.23 (m, 6 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 0.91 (s, 3 H), 0.64 (s, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.1, 139.4, 133.7, 129.6, 127.3, 60.1, 59.7, 45.2, 39.0, 31.5, 31.4, 20.6, 20.2, 16.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}N_2O_3S$ (M+H) 339.1737, found 339.1732.

4.1.5 Synthetic procedures and spectral characterization for Tempoc deprotections and orthogonality studies



1-60 **1-82**

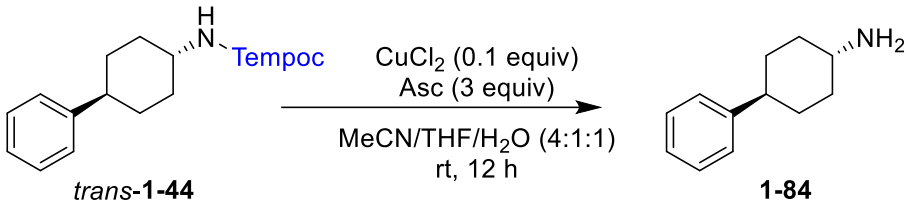
1*H*-Indole (1-82). According to General Method 1-C and Workup Procedure 1-3, **1-60** (475 mg, 1.58 mmol), ascorbic acid (844 mg, 4.74 mmol), and copper(II) chloride (21.5 mg, 0.158 mmol) in MeCN/THF/H_2O (8.8 mL/2.2 mL/2.2 mL) afforded **1-82** as an off-white crystalline solid (179 mg, 91%) that spectrally matched a commercial sample.



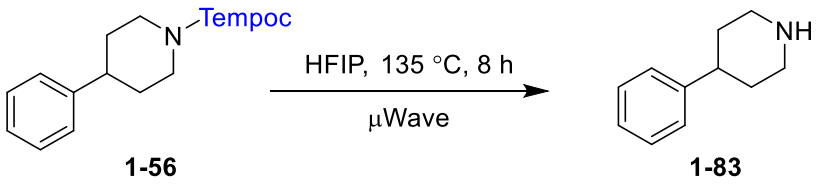
1-56 **1-83**

4-Phenylpiperidine (1-83). According to General Method 1-C and Workup Procedure 1-3, **1-56** (1.02 g, 2.95 mmol), ascorbic acid (1.57 g, 8.84 mmol), copper(II) chloride (40.0 mg, 0.295

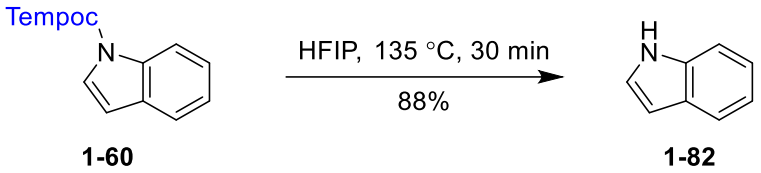
mmol), and MeCN/THF/H_2O (16.4 mL/4.1 mL/4.1 mL) afforded **1-83** as an off-white solid (435 mg, 91%) which spectrally matched a commercial sample.



***trans*-Phenylcyclohexan-1-amine (1-84).**[147] According to General Method 1-C and Workup Procedure 1-3, *trans*-**1-44** (132 mg, 0.368 mmol), ascorbic acid (196 mg, 1.11 mmol), and copper(II) chloride (5.00 mg, 0.0368 mmol) in MeCN/THF/H_2O (2.0 mL/0.5 mL/0.5 mL) afforded **1-84** as an off-white solid (59.0 mg, 91%) which matched literature spectra: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2 H), 7.23–7.15 (m, 3 H), 2.74 (tt, *J* = 11.1, 3.9 Hz, 1 H), 2.48 (tt, *J* = 12.2, 3.6 Hz, 1 H), 2.03–1.86 (m, 4 H), 1.60–1.46 (m, 4 H), 1.27 (dq, *J* = 12.4, 3.2 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 128.3, 126.8, 125.9, 50.4, 43.7, 37.0, 33.1; HRMS (ESI) *m/z* calcd for $C_{12}H_{18}N$ ($[M+H]^+$) 176.1434, found 176.1434.

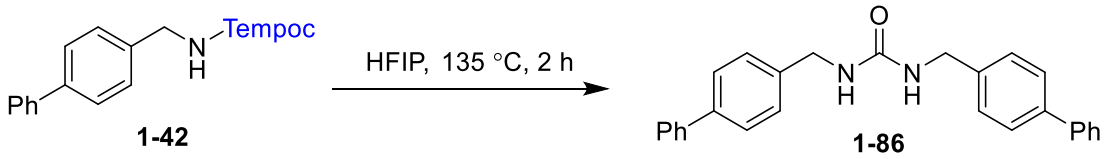


4-Phenylpiperidine (1-83). According to General Method 1-D, **1-56** (0.200 g, 0.581 mmol), HFIP (5.8 mL) and chromatography on SiO_2 (0:1 to 3:7, MeOH:CH_2Cl_2) afforded **1-83** (86 mg, 85%) as a colorless solid which spectrally matched a commercial sample: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 2 H), 7.27–7.17 (m, 3 H), 3.30–3.13 (m, 2 H), 2.76 (td, *J* = 12.2, 2.6 Hz, 2 H), 2.62 (tt, *J* = 12.0, 3.8 Hz, 1 H), 2.02 (bs, 1H), 1.92–1.78 (m, 2 H), 1.63 (dq, *J* = 12.0, 3.6 Hz, 2 H); HRMS (ESI) *m/z* calcd for $C_{11}H_{17}N$ (M+H) 162.1277, found 162.1277.



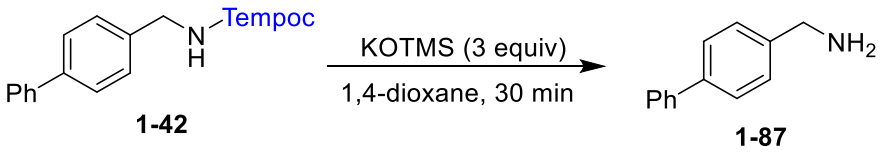
1-60 **1-82**

1*H*-Indole (1-82). According to General Method 1-D, **1-60** (0.200 g, 0.666 mmol), HFIP (6.7 mL) and chromatography on SiO_2 (1:19 to 1:9, EtOAc/hexanes) afforded **1-82** (68.3 mg, 88%) as an off-white solid that spectrally matched a commercial sample: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (bs, 1 H), 7.70 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.41 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.31–7.11 (m, 3 H), 6.63–6.57 (m, 1 H).



1-42 **1-86**

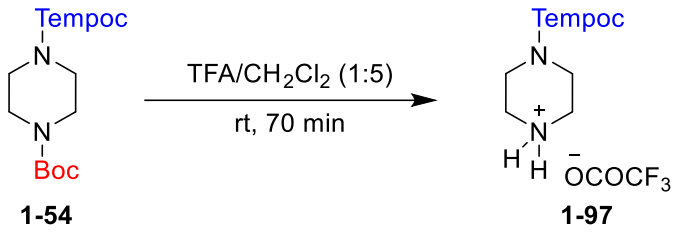
1,3-Bis([1,1'-biphenyl]-4-ylmethyl)urea (1-86). According to General Method 1-D, **1-42** (0.100 g, 0.273 mmol), HFIP (2.7 mL), a 2 h reaction time, and trituration with hexanes/diethyl ether (1:1) afforded **1-86** (39.4 mg, 74%) as an off-white solid: R_f = 0.82 (1:4, MeOH/CH_2Cl_2); Mp >250 °C; ATR-IR (neat) 3355, 3326, 3034, 1628, 1576, 1486, 1254, 753 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 90 °C) δ 7.69–7.55 (m, 8 H), 7.49–7.42 (m, 4 H), 7.41–7.27 (m, 6 H), 6.30 (t, *J* = 6.0 Hz, 2 H), 4.32 (d, *J* = 6.0 Hz, 4 H); ^{13}C NMR (101 MHz, DMSO, 90 °C) δ 157.7, 139.7, 139.6, 138.2, 128.2, 127.1, 126.6, 126.0, 42.5; HRMS (ESI) *m/z* calcd for $C_{27}H_{25}N_2O$ (M+H) 393.1961, found 393.1959.



1-42 **1-87**

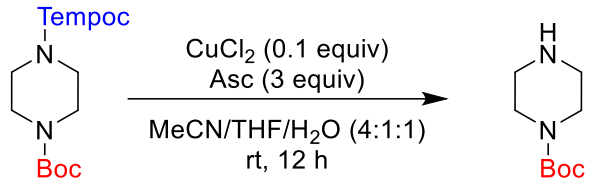
[1,1'-Biphenyl]-4-ylmethanamine (1-87).[1] According to General Method 1-E, **1-42** (0.550 g, 1.50 mmol), potassium trimethylsilanolate (642 mg, 4.50 mmol), 1,4-dioxane (10 mL)

and chromatography on SiO_2 (0:1 to 3:97, Et_3N:EtOAc) afforded **1-87** (255 mg, 93%) as a colorless solid which matched literature spectra: R_f = 0.47 (15:4:1, CH_2Cl_2/MeOH/Et_3N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.54 (m, 4 H), 7.52–7.30 (m, 5 H), 3.93 (s, 2 H), 1.52 (s, 2 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 142.4, 140.9, 139.8, 128.7, 127.5, 127.3, 127.1, 127.0, 46.2.



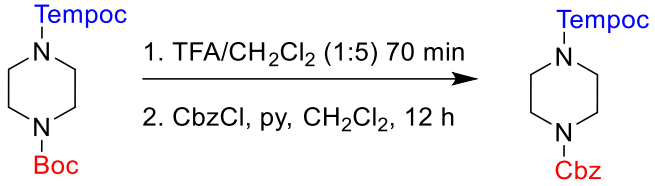
1-54 **1-97**

2,2,6,6-Tetramethylpiperidin-1-yl piperazine-1-carboxylate trifluoroacetic acid salt (1-97). A solution of piperazine **1-54** (0.250 g, 0.677 mmol) in CH_2Cl_2 (5.6 mL) was treated at 0 °C dropwise with trifluoroacetic acid (1.13 mL), and stirred at room temperature for 70 min until starting material disappeared by TLC and LC-MS analysis. The reaction mixture was concentrated under reduced pressure and the oily residue was dissolved in diethyl ether (10 mL). A colorless precipitate formed and was filtered, washed with ice-cold diethyl ether (10 mL), and dried under vacuum to afford **1-97** (243 mg, 94%) as crystalline solid: R_f = 0.36 (1:9, MeOH/CH_2Cl_2); Mp 164-167 °C (dec.); ATR-IR (neat) 2972, 2946, 1733, 1686, 1172, 1125, 719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (bs, 2 H), 3.85-3.82 (m, 4 H), 3.21-3.18 (m, 4 H), 1.75–1.52 (m, 5 H), 1.45–1.39 (m, 1 H), 1.15 (s, 6 H), 1.09 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8 (q, *J* = 37.4 Hz, $\underline{C}OCF_3$), 155.9, 115.9 (q, *J* = 289.7 Hz, $CO\underline{C}F_3$), 60.7, 43.4, 41.0, 39.0, 31.6, 21.0, 16.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}N_3O_2$ (M+H) 270.2176, found 270.2175.



1-54 **1-98**

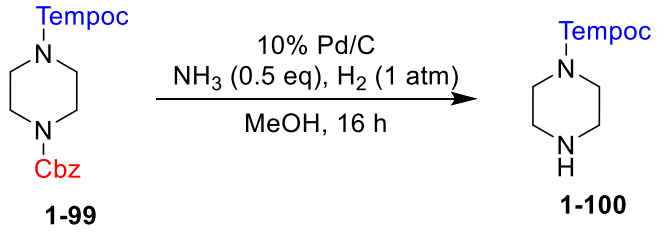
***tert*-Butyl piperazine-1-carboxylate (1-98).** According to General Method 1-C and Workup Procedure 1-2, **1-54** (408 mg, 1.11 mmol), ascorbic acid (0.590 g, 3.31 mmol), and copper(II) chloride (15.0 mg, 0.111 mmol) in MeCN/THF/H_2O (6.2 mL/1.5 mL/1.5 mL) afforded **1-98** as a white semi-solid (196 mg, 95%) which spectrally matched a commercial sample: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28 (2AA' of AA'XX', $J_{AA'}$ = -12 Hz, J_{AX} = 6.2 Hz, $J_{AX'}$ = 4.2 Hz, 4 H), 2.70 (2XX' of AA'XX', $J_{XX'}$ = -12 Hz, J_{AX} = 6.2 Hz, $J_{AX'}$ = 4.2 Hz, 4 H), 1.98 (bs, 1 H), 1.36 (s, 9 H).



1-54 **1-99**

1-Benzyl 4-(2,2,6,6-tetramethylpiperidin-1-yl) piperazine-1,4-dicarboxylate (1-99). A solution of **1-54** (1.50 g, 4.06 mmol) in CH_2Cl_2 (33.8 mL) was treated at 0 °C dropwise with trifluoroacetic acid (6.77 mL). The reaction stirred at room temperature for 70 min until consumption of the starting material was observed by TLC and LC-MS analysis, concentrated in vacuo, and the oily residue was dissolved in diethyl ether (20 mL). A colorless precipitate formed and was filtered, washed with ice-cold diethyl ether (10 mL), and dried in vacuo. The residue was suspended in dry CH_2Cl_2 (41 mL), and treated dropwise at 0 °C under nitrogen with pyridine (1.61 g, 1.66 mL, 20.3 mmol) and benzyl chloroformate (762 mg, 0.635 mL, 4.47 mmol). The reaction mixture was stirred at room temperature for 12 h, quenched with water (30 mL) extracted with a

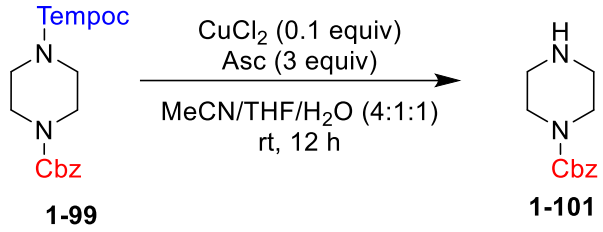
mixture of saturated $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated, and chromatographed on SiO_2 (1:19 to 1:1, EtOAc/hexanes) to afford **1-99** (1.52 g, 93%) as a viscous oil which solidified to a colorless solid on standing: R_f = 0.50 (1:1, EtOAc/hexanes); Mp 103-105 °C; ATR-IR (neat) 2973, 2932, 1731, 1703, 1215, 1075, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5 H), 5.13 (s, 2 H), 3.50 (app s, 8 H), 1.76–1.47 (m, 5 H), 1.45–1.38 (m, 1 H), 1.13 (s, 6 H), 1.08 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 155.1, 136.3, 128.4, 128.0, 127.9, 67.3, 60.1, 43.8, 38.9, 31.7, 20.9, 16.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{34}N_3O_4$ (M+H) 404.2544, found 404.2538.



1-99 **1-100**

2,2,6,6-Tetramethylpiperidin-1-yl piperazine-1-carboxylate (1-100).[4] A Schlenk flask containing **1-99** (0.200 g, 0.496 mmol) was purged and back-filled 3 times with hydrogen gas, and 10% Pd/C (5.0 mg, [10 mg/mmol]) was added, followed by dry MeOH (1 mL) and 2 M methanolic ammonia (0.124 mL, 0.5 equiv). The flask was fitted with a H_2 balloon and stirred at room temperature for 16 h. The reaction mixture was diluted with methanol (10 mL) and filtered through a pad of Celite pre-wetted with methanol. The filtrate was concentrated to afford **1-100** (135 mg, quant) as an off-white solid: R_f = 0.31 (1:9, MeOH/CH_2Cl_2); Mp 126-128 °C; ATR-IR (neat) 3304, 2933, 1715, 1416, 1227, 1046, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (2AA' of AA'XX', $J_{AA'}$ = -12 Hz, J_{AX} = 6 Hz, $J_{AX'}$ = 4 Hz, 4 H), 2.85 (2XX' of AA'XX', $J_{XX'}$ = -9 Hz, J_{AX} = 6 Hz, $J_{AX'}$ = 4 Hz, 4 H), 2.00 (bs, 1 H), 1.77–1.46 (m, 5 H), 1.44–1.35 (m, 1 H), 1.14 (s, 6 H), 1.10 (s, 6 H);

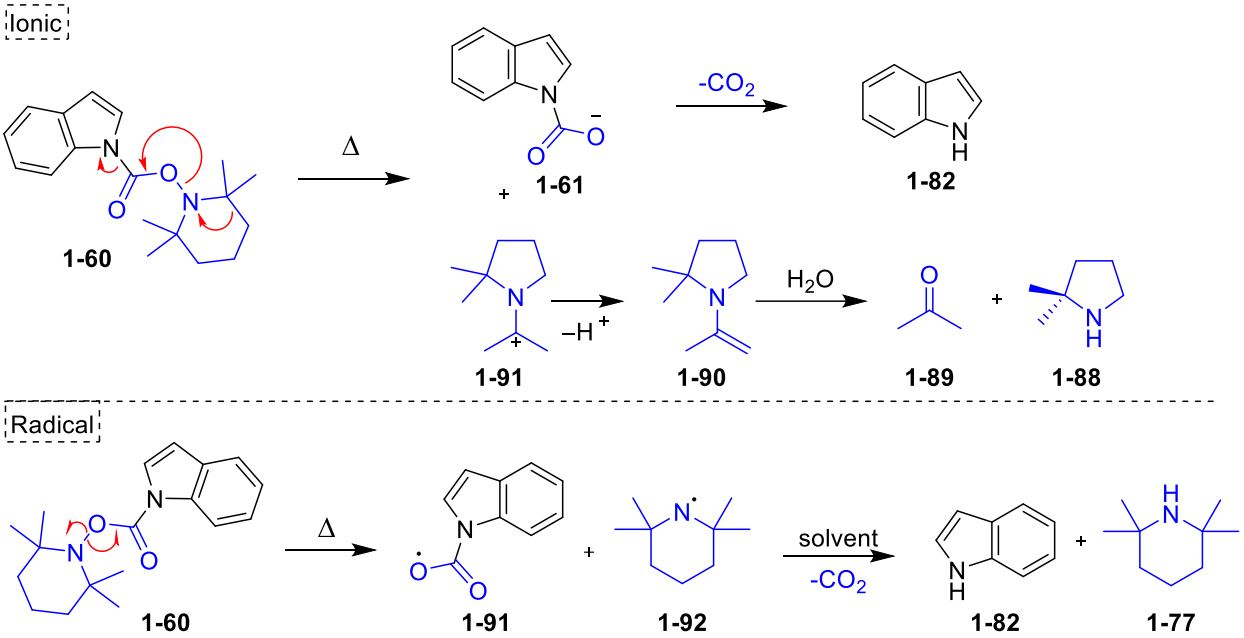
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 60.1, 46.0, 45.2, 39.0, 31.8, 21.0, 17.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}N_3O_2$ (M+H) 270.2176, found 270.2177.



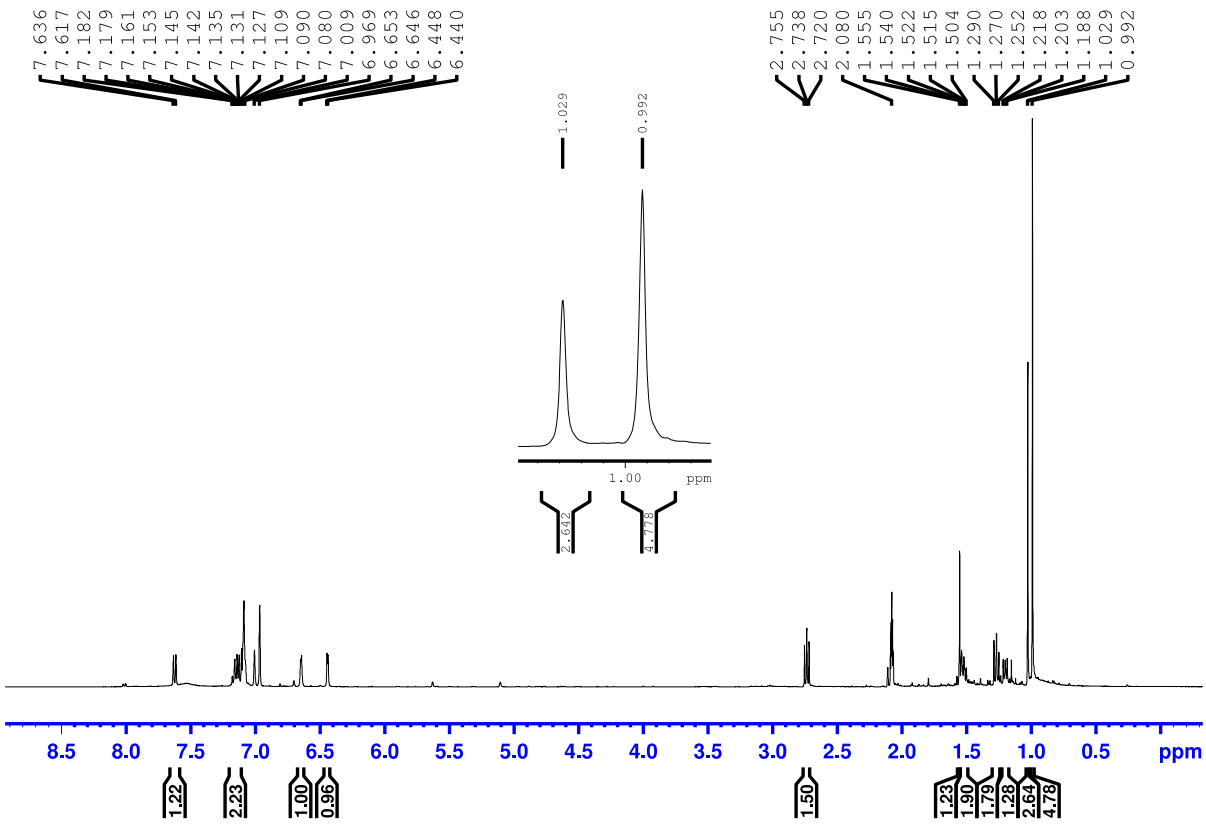
1-99 **1-101**

Benzyl piperazine-1-carboxylate (1-101).[148] According to General Method 1-C and Workup Procedure 1-3, **1-99** (297 mg, 0.736 mmol), ascorbic acid (393 mg, 2.21 mmol), and copper(II)chloride (10.0 mg, 0.0736 mmol) in MeCN/THF/H_2O (4.1 mL/1.0 mL/1.0 mL) afforded **1-101** as a colorless oil (165 mg, 92%) which matched literature reported spectra: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H), 5.12 (s, 2 H), 3.46 (2AA' of AA'XX', $J_{AA'}$ = -12 Hz, J_{AX} = 6.2 Hz, $J_{AX'}$ = 4.2 Hz, 4 H), 2.88–2.76 (m, 4 H), 1.82 (bs, 1 H); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}N_2O_2$ (M+H) 221.1285, found 221.1284.

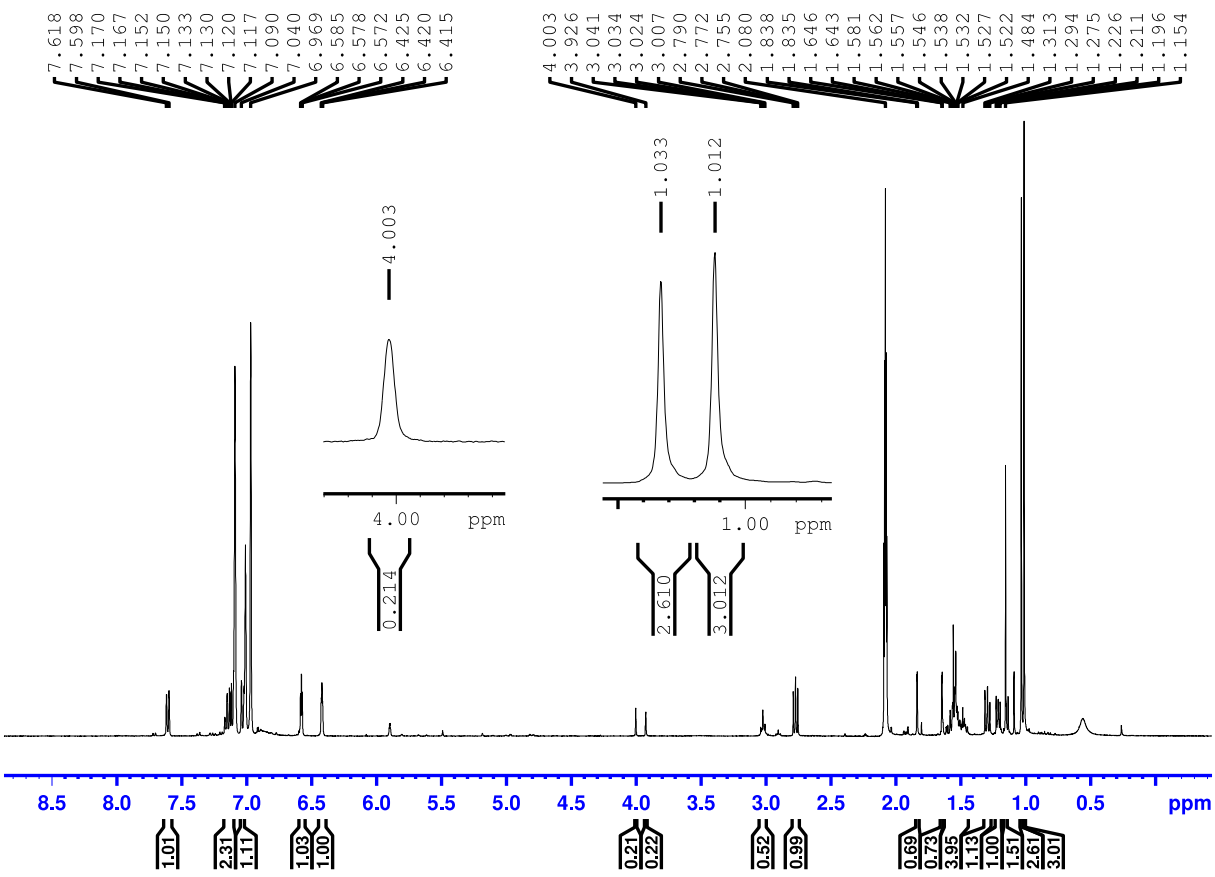
4.1.6 Thermolysis of Tempoc protected indole 1-60



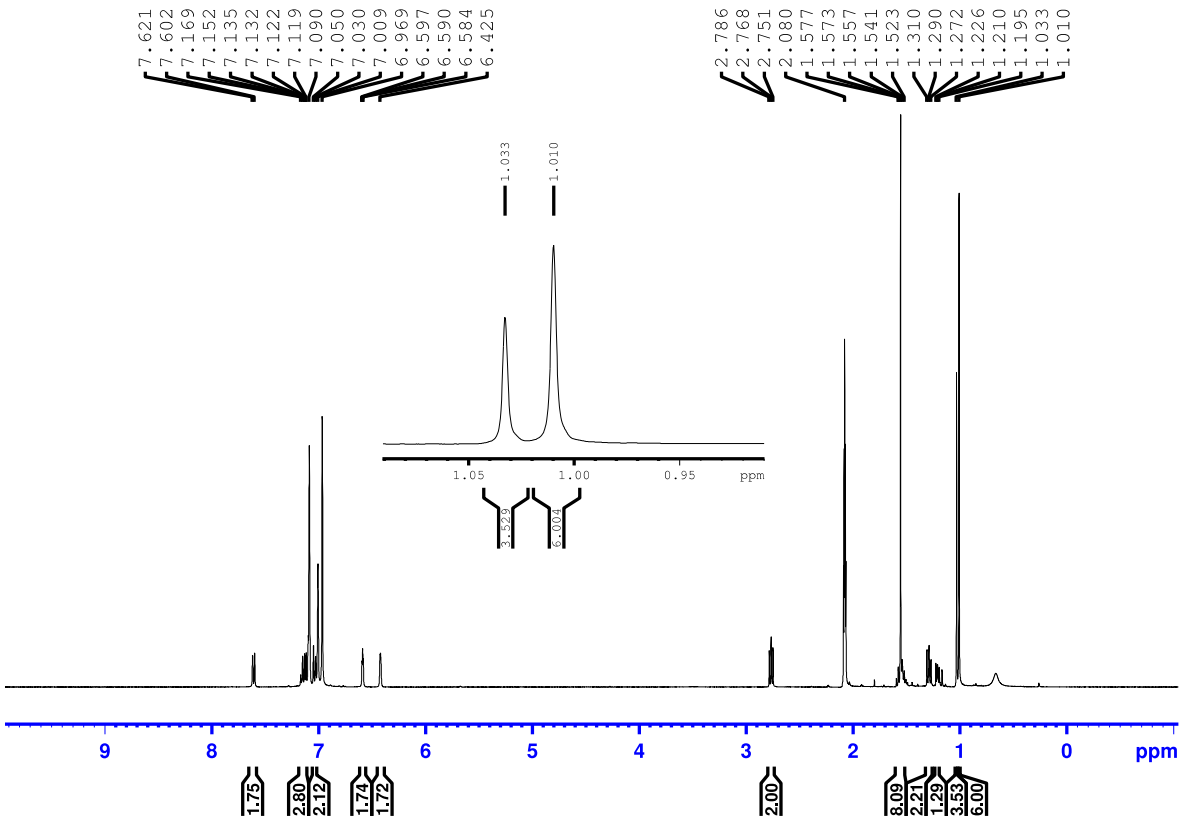
Experiment 1. A microwave vial containing a solution of Tempoc protected indole **1-60** (0.150 g, 0.499 mmol) in toluene-d_8 was heated at 150 °C in an oil bath. After 20 h, the brown reaction mixture was cooled to room temperature. ^{1}H NMR analysis of the solution showed a 3.6:1 ratio of pyrrolidine **1-88** (δ 0.99 ppm) to tetramethylpiperidine **1-77** (δ 1.03 ppm).



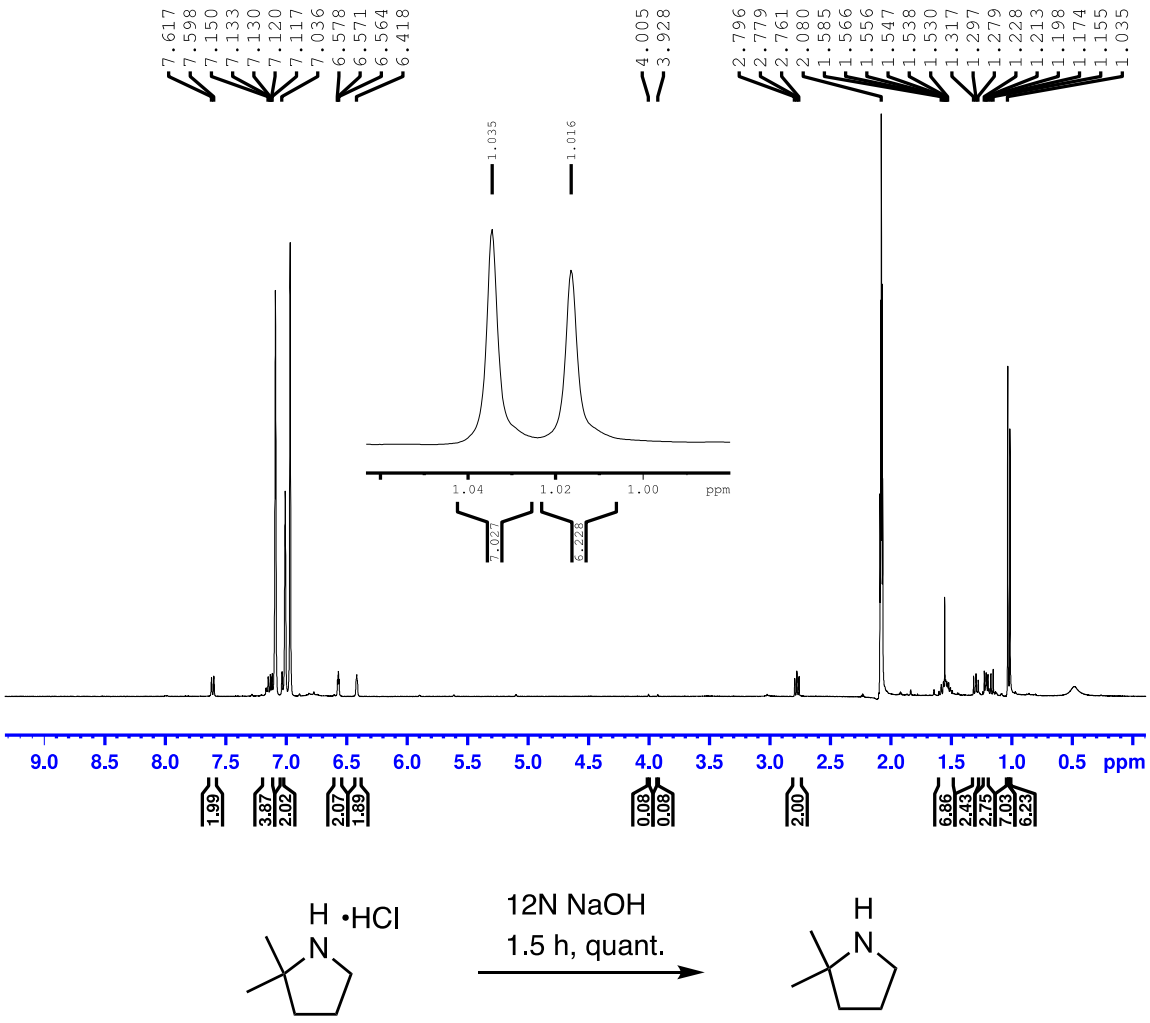
Experiment 2. A microwave vial containing a solution of Tempoc protected indole **1-60** (0.150 g, 0.499 mmol) in toluene-d_8 (0.5 mL) was degassed (4 cycles of freeze-pump-thaw) and on the last cycle purged with nitrogen, sealed, and heated in an oil bath maintaining an external temperature of 150 °C for 9 h. The reaction mixture turned from clear and colorless to dark brown. ^{1}H NMR analysis of the solution showed a 2.3:1.0:1.0 ratio of pyrrolidine **1-88** (□ 1.01 ppm) to tetramethylpiperidine **1-77** (δ 1.03 ppm) to enamine **1-90** (δ 4.00 ppm).



Experiment 3. A microwave vial containing a solution of Tempoc protected indole **1-60** (0.100 g, 0.332 mmol) and HPLC-grade water (0.024 mL, 1.33 mmol) in toluene-d_8 (0.33 mL) was heated in an oil bath at an external temperature of 150 °C for 21.5 h. The brown solution was cooled to room temperature and ^{1}H NMR analysis showed conversion to indole **1-82** and a 3.4:1 ratio of pyrrolidine **1-88** (δ 1.01 ppm) to tetramethylpiperidine **1-77** (δ 1.03 ppm). The reaction was concentrated and the resulting brown residue was purified by chromatography on SiO_2 (0:1 to 1:9, EtOAc/hexanes) to afford indole **1-82** (0.034 g, 87%) as a tan solid.



Experiment 4. A microwave vial containing a solution of Tempoc protected indole **1-60** (0.100 g, 0.332 mmol) in toluene-d_8 (0.33 mL) was heated in an oil bath at an external temperature of 135-140 °C for 32.5 h. The reaction mixture turned from clear and colorless to dark brown. The solution was cooled to room temperature and ^{1}H NMR analysis showed a 1.8:1 ratio of pyrrolidine **1-88** (δ 1.02 ppm) to tetramethylpiperidine **1-77** (δ 1.04 ppm).



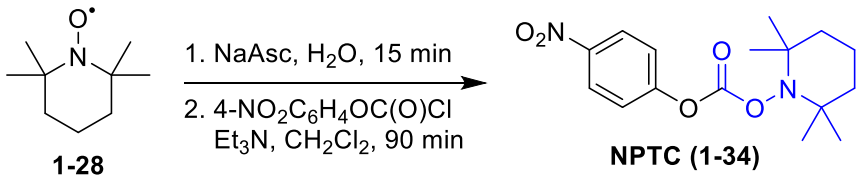
2,2-Dimethylpyrrolidine (1-88). A solution of 2,2-dimethylpyrrolidine•HCl (0.050 g, 0.35 mmol) in 12 N NaOH (1.25 mL) was stirred vigorously at room temperature for 1.5 h, treated with toluene-d_8 (1 mL), and stirred vigorously. The organic layer was dried (Na_2SO_4) to give a sample of **1-88**: ^{1}H NMR (400 MHz, $C_6D_5CD_3$) δ 2.77 (t, *J* = 7.0 Hz, 2 H), 1.57 (p, *J* = 7.3 Hz, 2 H), 1.30 (t, *J* = 7.6 Hz, 2 H), 1.01 (s, 6 H); ^{13}C NMR (100 MHz, $C_6D_5CD_3$) δ 58.8, 46.3, 39.9, 28.9, 26.4.

4.2 EXPERIMENTAL – TEMPOC PEPTIDES

4.2.1 General experimental protocols

Reactions were performed without inert atmosphere unless otherwise stated. DMF was dried over 4 Å molecular sieves which were activate in a muffle furnace at 350 °C for 16 h prior to use. Basic alumina (Brockmann Grade I) was purchased from Acros Organics and was stored in an oven (140 °C) before use. Anhydrous HOBt was purchased from Amatek Chemical. Anhydrous HOBt was used for reactions for uniformity (different lots of HOBt hydrate contain varying amounts of water). Amberlite IRC-748 resin was purchased from Sigma-Aldrich and was washed sequentially with water, methanol, then methylene chloride, and dried before use. All other reagents and solvents are commercially available and were used as received. HPLC analyses were conducted on a Shimadzu Prominence HPLC system utilizing a Phenomenex 4.6 mm x 250 mm C18 column with a 5-micron particle size. Elution with water/acetonitrile (both containing 0.1% (v/v) trifluoroacetic acid) was conducted at a constant a flow rate of 1.0 mL/min. A linear gradient of 10-60% acetonitrile over 60 min and a 100-minute acquisition time.

4.2.2 Second generation synthesis of NPTC (1-34)



1-28 **NPTC (1-34)**

A 500-mL Erlenmeyer containing a magnetic stirbar and a temperature probe was charged with sodium ascorbate (25.4 g, 127 mmol, 2.0 equiv) and deionized water (180 mL), affording a

pale-yellow solution. The stirring is increased slowly until a stable vortex is established. An initial temperature reading is taken and the probe is removed before freshly ground TEMPO (10.0 g, 63.4 mmol, 1.0 equiv) is added in one portion. The probe is reinserted and the red suspension is stirred vigorously at ambient temperature. Once the red solids are fully converted to a white precipitate, and internal temperature no longer increases (*ca.* 15 min), CH_2Cl_2 (100 mL) is added and stirring is continued for an additional 10 min. The stirbar is removed, and the biphasic mixture is transferred to a 500-mL separatory funnel. The organic layer is separated and the aqueous layer extracted with methylene chloride (100 mL). The aqueous phase is re-extracted with an additional aliquot of CH_2Cl_2 (50 mL). The combined organics are dried (Na_2SO_4) and decanted into a 500-mL 3-neck flask containing a stirbar. An additional aliquot of methylene chloride (25 mL) is used to wash the drying agent and the flask. The 3-neck flask is clamped inside a large crystallization dish. One of the flask necks was fitted with a 125-mL pressure-equalizing addition funnel. A dry-ice/brine bath is prepared around the flask and the solution is stirred until a stable internal temperature (−11 ± 2 °C) is achieved. The addition funnel is charged with 4-nitrophenyl chloroformate (14.6 g, 69.7 mmol, 1.1 equiv) as a solution in methylene chloride (55 mL). Triethylamine (18.0 mL, 127 mmol, 2.0 equiv) is added *via* syringe and the addition of the chloroformate solution commenced. The addition rate is continually adjusted to maintain an internal temperature of −11 ± 2 °C (*ca*. 30 min). Once addition of the reagent is complete, the addition funnel is washed with CH_2Cl_2 and the cooling bath is removed. The reaction is stirred for an additional 90 min. The reaction is transferred to a 1-L separatory funnel with methylene chloride (50 mL). Saturated sodium carbonate (250 mL) is then added, and the contents shaken vigorously. The organic layer is separated and the orange aqueous layer extracted with methylene chloride (1 x 100 mL). The combined organic layers are washed sequentially with saturated sodium carbonate

(2 x 250 mL), water (150 mL), and brine (200 mL). Drying (Na_2SO_4) and filtration through a course fritted vacuum funnel affords a red-orange solution, which is concentrated on a rotary evaporator produce a solid orange residue. The solid is dried under high-vacuum for 30 min. The yellow-orange residue is dissolved in acetone (250 mL) with swirling to give a reddish solution before being sealed and placed in a freezer (−20 °C) for 16 h. The crystals thus formed are collected by suction filtration on a 5 cm Büchner funnel. The filter-cake is compressed and then washed with cold acetone (−20 °C, 2 x 25 mL). The crystallization is repeated two more times with the mother liquor and the crops combined to give **1-36 "NPTC"** (14.4 g, 71%) as an off-white crystalline solid. Characterization data *vida supra*.

4.2.3 General methods and workup procedures

Caution! 1-hydroxybenzotriazole (HOBt) is potentially explosive, especially in its anhydrous form, however, anhydrous HOBt was used without incident.

General Method 2-A: Tempoc Protection of Amino Esters. A round bottom flask containing a stirbar was charged with target amino ester freebase or hydrochloride (1.00 mmol, 1.0 equiv), NPTC (1.20 mmol, 1.2 equiv), and anhydrous HOBt (0.500 mmol, 0.5 equiv). Dry DMF (2.0 mL, 0.5 M) was added ensuring that all solids are washed down the walls of the vessel. The mixture was stirred for 3 min before addition of triethylamine (1.50 mmol, 1.5 equiv for amine freebases ***or*** 2.50 mmol, 2.5 equiv for amine hydrochlorides) in one portion. Upon addition of the base the reaction forms a heavy precipitate which undergoes partial dissolution within a couple minutes and is accompanied by formation of a yellow color (4-nitrophenoxide). The reaction is stirred at ambient temperature for 24 h during which time the reaction turned yellow or yellow-orange in color.

Workup Procedure 2-1. At this point the reaction was diluted with methylene chloride or ethyl acetate (4 mL) and the reaction mixture was filtered through a 2.5 cm pad of pre-wetted (CH_2Cl_2 or EtOAc) basic alumina (Brockmann Grade I) in a 4.5 cm diameter coarse-fritted funnel. The crude product was washed through with methylene chloride or ethyl acetate (75 mL). HOBt and 4-nitrophenol are effectively retained by the alumina. If desired, DMF may be removed at this stage by washing the organic filtrate with water. The filtrate is concentrated on a rotary evaporator and the residue dissolved in a minimal amount of toluene and purified by chromatography on SiO_2 using the specified solvent systems.

Workup Procedure 2-2. At this point the reaction is poured into a separatory funnel containing ethyl acetate (100 mL) and water is added (30 mL). The aqueous layer is separated and organic is washed with saturated sodium carbonate (2 x 30 mL) and then brine (20 mL). Concentration of the organic layer afforded a residue which was purified by chromatography on SiO_2 using the specified solvent systems.

General Method 2-B: Tempoc Deprotection of Peptides. A vial containing a stirbar was charged with Tempoc protected peptide (1.00 mmol, 1.0 equiv) and sodium ascorbate (1.20 mmol, 1.2 equiv) before a 1:1 mixture of DME/H_2O (6.7 mL, 0.15 M) was then added resulting in a colorless turbid mixture. To this suspension was added a 0.50 M aqueous $CuCl_2$ solution (70.0 μL, 35.0 μmol, 0.035 equiv) [Various concentrations of the aqueous metal were used depending on the scale of the reaction (e.g. 0.50, 0.25, 0.10 M) with identical results. Additionally, $CuCl_2$ can be added as a solid for larger scale reactions]. The reaction vessel headspace was flushed with nitrogen for 15 seconds and placed in a pre-heated aluminum block (38–41 °C). [The reaction can be run in a sealed vessel or under an inert atmosphere (balloon) to preclude oxygen.] After stirring for a few minutes, the reaction became a yellow-green color. After 3 h of heating the reaction

became orange-tan and a precipitate began to collect on the glass at the solvent-headspace interface, this precipitate is believed to be a dehydroascorbate by-product and need not be mechanically removed from the vessel walls. The reaction is typically complete in 7 h as determined by HPLC-MS and/or TLC, at this point the reaction was cooled before being diluted with ethyl acetate (20 mL).

Workup Procedure 2-3. After dilution, the biphasic mixture saturated with solid NaCl to increase the ionic strength of the aqueous layer and induce good partitioning of the layers. The mixture is then transferred to a separatory funnel and the aqueous layer is removed and discarded. The organic layer is dried ($MgSO_4$), concentrated, and the residue purified by catch and release on a 1" pad of SiO_2 (the pad was first washed with 2 column volumes of ethyl acetate, then with 15% methanol in ethyl acetate or 5% triethylamine in ethyl acetate for more polar substrates). During the elution with the more polar eluent, the copper can be seen oxidizing on the silica as made apparent by the appearance of a slight blue color. Concentration of the second filtrate gave the pure peptide freebase as a yellow oil which formed a collapsible foam under high vacuum.

NOTE: Depending on the nature of the peptide, copper may also elute through the plug and contaminate the product. The presence of copper was made apparent by line broadening in the NMR. Residual copper is expeditiously removed with Amberlite IRC-748 resin (iminodiacetic acid resin, Na-form) using the following protocol: The peptide freebase is made 0.3 M in chloroform of methylene chloride and to it is added Amberlite IRC-748 resin 50 mass %. Stirring for 1 hour at ambient temperature in an open vessel and subsequent filtration removed all traces of copper.

Workup Procedure 2-4. After dilution, the mixture is transferred to a separatory funnel. Additional ethyl acetate is added (30 mL) and the mixture is washed with a pH 10 ammonium

chloride buffer of high ionic strength (to preclude the formation of an emulsion.) This buffer was easily prepared from 100 mL of saturated ammonium chloride and enough concentrated ammonium hydroxide to achieve a pH = 10 (typically 15–20 mL). The organics were washed with this buffer (2 x 15 mL) with swirling, which removes dehydroascorbate (and byproducts) and copper salts from the organic phase. The organic layer is then dried ($MgSO_4$), filtered, and concentrated to give the crude tripeptide freebase in sufficient purity for subsequent couplings.

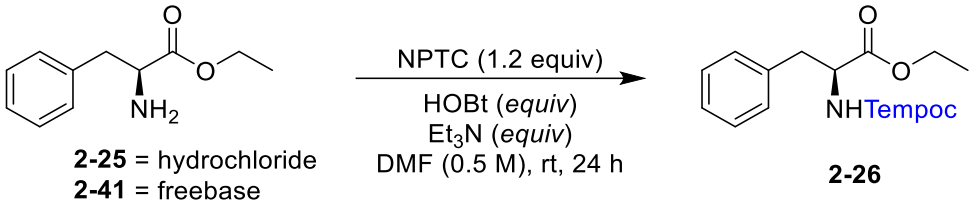
General Method 2-C: Saponification and Peptide Coupling Procedure for N- to C-Terminus. A round bottom flask containing a stirbar was charged with protected amino ester (1.00 mmol, 1.0 equiv) in a 2:1 THF/H_2O mixture (2.9 mL, 0.35 M). This turbid mixture is cooled to 0°C on an ice-bath before additions of lithium hydroxide monohydrate (1.50 mmol, 1.5 equiv) as a solid in one portion. The cooling bath is removed and the reaction is stirred at ambient temperature until disappearance of the starting material is observed by TLC or LC-MS (typically 2.5–3 h). The reaction mixture is transferred to a separatory funnel containing ethyl acetate (25 mL). The mixture is then acidified to pH = 2 with 2 M aqueous $KHSO_4$. The aqueous layer is discarded and the organic layer is washed with brine (10 mL), then dried ($NaSO_4$), filtered, and concentrated to afford the protected amino acid which was directly dissolved in dry DMF (4.0 mL, 0.25 M) and cooled to 0°C on an ice-bath before sequential addition of HATU (1.05 mmol, 1.05 equiv), and DIPEA base. The clear mixture becomes yellow after addition of the base. This mixture is stirred for 5 min before addition of the target amino ester (1.05 mmol, 1.05 equiv) as a solid in two portions. The cooling bath is removed and the reaction stirred at ambient temperature for 2 h. At this point, the reaction is poured into a separatory funnel containing ice-cold water (15 mL). Ethyl acetate is then added (50 mL) and the contents shaken vigorously. The aqueous layer is discarded and the organic is washed with an additional 15 mL aliquot of water which is also

discarded. The organic layer is then washed sequentially with 2 M aqueous $KHSO_4$ (10 mL), sat. sodium carbonate (10 mL), then brine (10 mL). The organic layer is then dried ($MgSO_4$), filtered, and concentrated to give a crude oil which was dissolved in toluene and loaded onto a 1.5" pad of silica gel (pre-wetted with 5% EtOAc/hexanes.) The compound is then washed with two volumes of 5% EtOAc-hexanes, then the peptide is washed through with the appropriate solvent given below. Concentration of the filtrate affords the desired peptide in excellent purity. Alternatively, the peptide may be purified by chromatography on SiO_2 using the detailed solvent systems.

General Method for Marfey's Analysis. Tempoc amino ester (0.05 mmol) was heated (105–110 °C) in 6 M aqueous HCl (10 mL) on an aluminum block in a sealed vessel for 24 h. After cooling of the solution to ambient temperature, the bulk of the HCl gas was removed by sparging with nitrogen for 10 min. 0.600 mL of the mixture was transferred to a 1-dram vial and concentrated with heating (40 °C) under high-vacuum (5 mbar) for 60 min. The white solid residue was taken up in 0.060 mL of deionized water and transferred to an auto-sampler vial before being treated with 118 μL of a 36 mM solution of Marfey's reagent in freshly distilled acetone. The solution was made alkaline by addition of 48 μL of 1.0 mM aqueous $NaHCO_3$. The vial was sealed and placed in an aluminum block at 40 °C for 1 hour with exclusion of ambient light. During this time the bright-yellow solution becomes fluorescent orange. Once cooled, 24 μL of 2.0 M aqueous HCl was added and the sample was shaken before being passed through a micron-filter into an amber auto-sampler vial and kept refrigerated in the dark until analysis (not more than 24 h) by HPLC. HPLC analysis was conducted on a Shimadzu Prominence HPLC system utilizing a Phenomenex 4.6 mm x 250 mm C18 column with a 5-micron particle size. Elution with water/acetonitrile (both containing 0.1% (v/v) trifluoroacetic acid) was conducted at a constant a flow rate of 1.0 mL/min. A linear gradient of 10–60% acetonitrile over 60 min and a 100-minute

acquisition time. Injection volume should be no larger than 2 μL as larger volumes resulted in saturation of the detector. Under these conditions the excess FDAA reagent eluted first (tR ca. 45 min) followed by the L-isomer (tR ca. 63 min), an unidentified peak (tR ca. 67 min), and finally the D-isomer (tR ca. 69 min). Standards were prepared using the aforementioned conditions of: Tempoc protected DL-PheOEt (synthesized correspondingly (*vida supra*) from the commercial DL-phenylalanine ethyl ester hydrochloride) and from commercial DL-PheOH and L-PheOEt ·HCl.

Table 16 Complete optimization table for the Tempoc protection of phenylalaline **2-26**



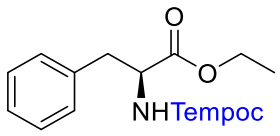
2-25 = hydrochloride
2-41 = freebase

2-26

entry	additive (equiv)	base (equiv)	4 Å MS[b]	solvent	isolated yield (%)
1	-	Et_3N (3.0)	Y	dry DMF	19
2[a]	HOBt (1.2)	Et_3N (3.0)	Y	dry DMF	82
3	HOBt (1.2)	Et_3N (4.0)	Y	dry DMF	84
4	Oxyma (1.2)	Et_3N (4.0)	Y	dry DMF	59
5	K-Oxyma (1.2)	Et_3N (4.0)	Y	dry DMF	55
6	HOBt (1.0)	Et_3N (4.0)	Y	dry DMF	88
7	HOBt (1.0)	Et_3N (4.0)	N	dry DMF	88
8	HOBt (1.0)	Et_3N (4.0)	Y	wet DMF	88
9	HOBt (1.0)	Et_3N (4.0)	N	**wet DMF**	87
10	HOBt (0.1)	Et_3N (3.0)	Y	dry DMF	60
11	HOBt (0.15)	Et_3N (3.0)	Y	dry DMF	62
12	HOBt (0.25)	Et_3N (3.0)	Y	dry DMF	68
13	HOBt (0.5)	Et_3N (4.0)	Y	dry DMF	83
14	HOBt (0.5)	Et_3N (3.0)	N	dry DMF	80
15	**HOBt (0.5)**	**Et_3N (2.5)**	**N**	**dry DMF**	**83**
16	HOBt (0.5)	Et_3N (2.0)	N	dry DMF	77
17	HOBt (0.5)	Na_2CO_3 (2.5)	N	dry DMF	71
18	HOBt (0.5)	pyridine (2.5)	N	dry DMF	–[c]
19	**HOBt hydrate (0.5)**[d]	Et_3N (2.5)	N	dry DMF	80
20	HOBt hydrate (0.5)[d]	Et_3N (2.5)	Y	dry DMF	82
21	HOBt (0.5)	Et_3N (2.5)	N	dry CH_2Cl_2	19
22	HOBt (0.5)	Et_3N (2.5)	N	dry THF	40
23	HOBt (0.5)	Et_3N (2.5)	N	dry MeCN	32

[a]amine **2-41** was used; [b]100 mg/mmol amine; [c]only recovered starting materials were isolated; [d]HOBt (97%) contained ≥ 20% wt. water

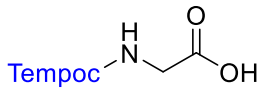
4.2.4 Synthetic procedures and spectral characterization for Tempoc protected amino esters



2-26

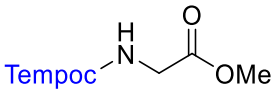
Ethyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-phenylalaninate(2-26). Following General Method 2-A and Workup Procedure 2-1, A two-neck 250-mL round-bottom flask containing a stirbar was charged with **NPTC** (12.6 g, 38.8 mmol), L-phenylalanine ethyl ester hydrochloride (7.50 g, 32.3 mmol), and HOBt (2.25g, 16.2 mmol). DMF (65 mL) was then added and the heterogeneous solution is stirred for 5 min. At this point, triethylamine (11.5 mL, 80.8 mmol) is added in two portions over 2 min *via* syringe. This mixture is stirred at ambient temperature for 24 h, during which time the mixture turns an orange-yellow color. The reaction is diluted with 100 mL of toluene and transferred to a vacuum-funnel containing basic alumina which has been pre-wetted with toluene. Filtration through basic alumina gives a transparent light-tan filtrate that is concentrated on a rotary evaporator to afford a heavy liquid that begins to crystallize. At this point the residue is statically dried on the high-vac for an additional 10 h to afford a colorless solid. The solid is purified by chromatography on silica gel to afford **2-26**, (9.96 g, 80%) as a colorless solid. Unreacted **NPTC** (3.35 g) is also recovered from the purification and recycled in subsequent protections. $[\alpha]_D^{23}$ −8.8 (*c* 0.12, CH_2Cl_2); R_f = 0.27 (4:1 hexanes/EtOAc, UV active); Mp 80–82 °C; ATR-IR (neat) 3353, 2979, 2936, 1726, 1492, 1183, 1030, 743, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3 H), 7.18–7.14 (m, 2 H), 4.64 (dt, *J* = 7.7, 6.3 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.21–3.11 (m, 2 H), 1.67–1.49 (m, 3 H), 1.48–1.34 (m, 3 H), 1.23 (t, *J* = 7.1

Hz, 3 H), 1.16 (s, 3 H), 1.15 (s, 3H), 1.03 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 157.8, 135.9, 129.3, 128.6, 127.1, 61.4, 60.8, 60.6, 54.6, 39.6, 39.6, 38.0, 31.6, 31.5, 20.6, 20.5, 16.7, 14.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}N_2O_4$ (M+H) 377.2435, found 377.2430.



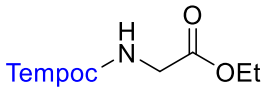
2-42

(((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)carbonyl)glycine (2-42). According to General Method 2-A, glycine (80.0 mg, 1.07 mmol), **NPTC** (412 mg, 1.28 mmol), HOBt (74.2 mg, 0.533 mmol), triethylamine (272 mg, 378 μL, 2.66 mmol), DMF (2.1 mL), after 24 h was diluted with diethyl ether (30 mL) and transferred to a separatory funnel. The mixture was acidified with 1 N $KHSO_4$ (10 mL). The aqueous layer was separated and the organic layer washed with 1 N $KHSO_4$ (10 mL). The combined aqueous layers were back-extracted once with diethyl ether (30 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and concentrated to afford an oily solid which was reslurried in toluene (30 mL). The white precipitate was filtered off under vacuum and the filtrate was concentrated *in vacuo* to afford a residue which was purified by chromatography on silica gel (isocratic, 99:1 EtOAc/AcOH) to afford **2-42** (132 mg, 46%) as an oil that foamed to a beige solid under high vacuum which contained 3.5% HOBt by mass (factored into yield): R_f = 0.52 (EtOAc, bromocresol green active); Mp 122.5 °C (dec.); ATR-IR (neat) 3359, 2978, 2936, 1709, 1505, 1185, 1048, 945 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 12.57 (bs, 1 H), 7.62 (bs, 1 H), 3.71 (d, *J* = 6.0 Hz, 2 H), 1.63–1.44 (m, 5 H), 1.40–1.32 (m, 1 H), 1.11 (s, 6 H), 1.06 (s, 6 H); ^{13}C NMR (101 MHz, DMSO) δ 171.2, 158.0, 59.8, 42.2, 38.8, 31.1, 20.3, 16.4; ; HRMS (ESI) *m/z* calcd for $C_{12}H_{23}N_2O_4$ (M+H) 259.1652, found 259.1648.



2-43

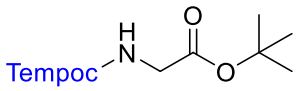
Methyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)glycinate (2-43). Following General Method 2-A and Workup Procedure 2-1, glycine methyl ester hydrochloride (0.150 g, 1.17 mmol), **NPTC** (453 mg, 1.41 mmol), HOBt (81.6 mg, 0.585 mmol), triethylamine (299 mg, 416 μL, 2.93 mmol), DMF (2.4 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-43** (279 mg, 88%) as a colorless solid: R_f = 0.23 (1:1 Hexanes/Et_2O, I_2 active); Mp 110.5–112 °C; ATR-IR (neat) 3298, 2979, 3943, 1763, 1702, 1505, 1171, 940, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (bs, 1 H), 4.04 (d, *J* = 5.6 Hz, 2 H), 3.74 (s, 3 H), 1.68–1.53 (m, 5 H), 1.45–1.35 (m, 1 H), 1.21 (s, 6 H), 1.14 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 158.4, 60.9, 52.2, 42.4, 39.7, 31.6, 20.6, 16.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{25}N_2O_4$ (M+H) 273.1809, found 237.1807.



2-28

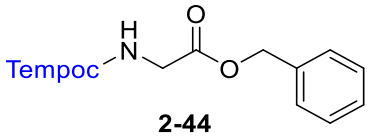
Ethyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)glycinate (2-28). Following General Method 2-A and Workup Procedure 2-1, glycine ethyl ester hydrochloride (0.150 g, 1.06 mmol), **NPTC** (412 mg, 1.28 mmol), HOBt (74.1 mg, 0.532 mmol), triethylamine (272 mg, 378 μL, 2.66 mmol), DMF (2.1 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded 2-**28** (283 mg, 93%) as a colorless solid: R_f = 0.38 (1:1 hexanes/Et_2O, I_2 active); Mp 109–110.5 °C; ATR-IR (neat) 3275, 2976, 2942, 1757, 1698, 1497, 1178, 1040, 945, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (bs, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.01 (d, *J* = 5.6 Hz, 2 H), 1.68–1.48 (m, 5 H), 1.43–1.35 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.20 (s, 6 H), 1.13 (s, 6 H); ^{13}C NMR (101

MHz, CDCl3) δ 169.8, 158.3, 61.3, 60.8, 42.5, 39.6, 31.6, 20.5, 16.7, 14.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{27}N_2O_4$ (M+H) 287.1965, found 287.1962.



2-31

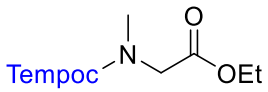
***tert*-Butyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)glycinate (2-31).** Following General Method 2-A and Workup Procedure 2-1, glycine *tert*-butyl ester hydrochloride (175 mg, 1.02 mmol), **NPTC** (396 mg, 1.23 mmol), HOBt (71.3 mg, 0.512 mmol), triethylamine (261 mg, 363 μL, 2.56 mmol), DMF (2.0 mL), and chromatography on SiO_2 (19:1 to 3:1 hexanes/Et_2O) afforded **2-31** (303 mg, 94%) as a colorless solid: R_f = 0.50 (1:1 hexanes/Et_2O, I_2 active); Mp 152-154 °C; ATR-IR (neat) 3340, 2978, 2938, 2871, 1702, 1491, 1455, 1367, 1158, 1133, 1041, 933, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (s, 1 H), 3.92 (d, J = 5.4 Hz, 2 H), 1.68–1.56 (m, 5 H), 1.46 (s, 9 H), 1.44–1.38 (m, 1 H), 1.21 (s, 6 H), 1.14 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 158.3, 82.1, 60.8, 43.3, 39.7, 31.7, 28.1, 20.6, 16.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{31}N_2O_4$ (M+H) 315.2278, found 315.2274.



2-44

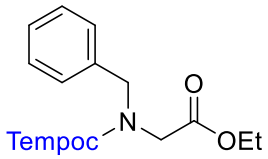
Benzyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)glycinate (2-44). Following General Method 2-A and Workup Procedure 2-1, glycine benzyl ester hydrochloride (225 mg, 1.11 mmol), **NPTC** (0.430 g, 1.33 mmol), HOBt (77.3 mg, 0.555 mmol), triethylamine (284 mg, 394 μL, 2.78 mmol), DMF (2.2 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-44** (351 mg, 91%) as a heavy oil which turned to a colorless solid on standing: R_f = 0.35 (1:1 hexanes/Et_2O, I_2 active); Mp 93–94.5 °C; ATR-IR (neat) 3336, 2977, 2936, 2874, 1707, 1498,

1171, 940, 739, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5 H), 7.26 (bs, 1 H), 5.17 (s, 2 H), 4.09 (d, *J* = 5.6 Hz, 2 H), 1.68–1.48 (m, 5 H), 1.45–1.37 (m, 1 H), 1.21 (s, 6 H), 1.12 (s, 6 H); ^{13}C NMR (101 MHz, CDCl3) δ 169.6, 158.3, 128.6, 128.5, 128.4, 67.1, 60.8, 42.6, 39.6, 31.6, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}N_2O_4$ (M+H) 349.2122, found 349.2123.



2-45

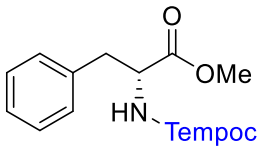
Ethyl N-methyl-*N*-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)glycinate (2-45). Following General Method 2-A and Workup Procedure 2-1, sarcosine ethyl ester hydrochloride (175 mg, 1.11 mmol), **NPTC** (432 mg, 1.33 mmol), HOBt (77.0 mg, 0.553 mmol), triethylamine (282 mg, 392 μL, 2.76 mmol), DMF (2.2 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-45** (306 mg, 92%) as a heavy clear oil: R_f = 0.25 (1:1 hexanes/Et_2O, I_2 active); ATR-IR (neat) 2975, 2935, 1729, 1378, 1199, 1125, 1037, 928, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (dq, *J* = 14.7, 7.1 Hz, 2 H), 4.01 (d, *J* = 11.5 Hz, 2 H), 3.03 (s, 3 H), 1.74–1.34 (m, 6 H), 1.32–1.21 (m, 3 H), 1.17 (s, 3 H), 1.12 (s, 3 H), 1.09 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 169.6, 157.7, 156.8, 61.2, 61.0, 60.1, 51.2, 50.6, 39.0, 36.7, 35.2, 31.7, 31.6, 20.9, 20.8, 17.0, 16.9, 14.2, 14.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}N_2O_4$ (M+H) 301.2122, found 301.2119.



2-46

Ethyl *N*-benzyl-*N*- (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl) glycinate (2-46). Following General Method 2-A and Workup Procedure 2-1, *N*-benzyl glycine ethyl ester

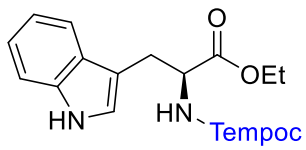
hydrochloride (0.250 g, 1.07 mmol), **NPTC** (417 mg, 1.28 mmol), HOBt (74.3 mg, 0.533 mmol), triethylamine (273 mg, 379 μL, 2.67 mmol), DMF (2.1 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-46** (303 mg, 94%) as a heavy clear oil: R_f = 0.39 (1:1 hexanes/Et_2O, I_2 active); ATR-IR (neat) 2974, 2936, 1732, 1453, 1364, 1183, 1091, 1028, 928, 760, 700 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5 H), 4.62 (d, *J* = 2.6 Hz, 2 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 3.99 (s, 1 H), 3.87 (s, 1 H), 1.77–1.35 (m, 6 H), 1.25 (td, *J* = 7.2, 3.4 Hz, 3 H), 1.14 (s, 6 H), 1.09 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 169.7, 157.5, 157.1, 137.3, 137.3, 128.7, 128.6, 128.2, 127.6, 127.5, 127.1, 61.2, 61.1, 60.2, 60.2, 52.0, 51.5, 49.0, 47.5, 39.1, 31.7, 31.6, 20.9, 17.0, 14.2, 14.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{33}N_2O_4$ (M+H) 377.2435, found 377.2429.



2-47

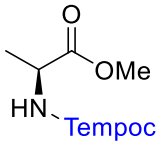
Methyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-D-phenylalaninate (2-47). Following General Method 2-A and Workup Procedure 2-1, D-phenylalanine methyl ester hydrochloride (785 mg, 3.64 mmol), **NPTC** (1.41 mg, 4.37 mmol), HOBt (254 mg, 1.82 mmol), triethylamine (0.930 g, 1.29 mL, 9.10 mmol), DMF (19 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-47** (1.07 g, 81%) as a colorless solid: $[\alpha]_D^{23}$ +17.4 (*c* 0.16, CH_2Cl_2); R_f = 0.33 (1:1 hexanes/Et_2O, I_2 active); Mp 84–85.5 °C; ATR-IR (neat) 3346, 2935, 1721, 1491, 1181, 988, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.21 (m, 3 H), 7.21–7.10 (m, 3 H), 4.66 (dt, *J* = 7.6, 6.2 Hz, 1H), 3.73 (s, 3H), 3.21–3.10 (m, 2H), 1.66–1.50 (m, 3 H), 1.47–1.34 (m, 3 H), 1.16 (s, 3 H), 1.15 (s, 3 H), 1.02 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0,

157.9, 135.8, 129.2, 128.6, 127.1, 60.8, 60.6, 54.5, 52.2, 39.6, 39.6, 37.9, 31.5, 20.6, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{20}H_{31}N_2O_4$ (M+H) 363.2278, found 363.2279.



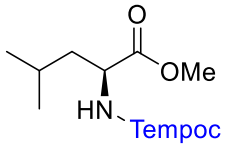
2-48

Ethyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-tryptophanate (##). Following General Method 2-A and Workup Procedure 2-1, L-tryptophan ethyl ester hydrochloride (0.300 g, 1.08 mmol), **NPTC** (423 mg, 1.30 mmol), HOBt (75.4 mg, 0.541 mmol), triethylamine (277 mg, 384 μL, 2.71 mmol), DMF (2.2 mL), and chromatography on SiO_2 (19:1 to 2:1 hexanes/Et_2O) afforded **2-48** (371 mg, 83%) as a colorless foam which collapsed to a clear oil on standing: $[\alpha]_D^{23}$ +4.9 (*c* 0.292, CH_2Cl_2); R_f = 0.48 (1:1 hexanes/Et_2O, UV active); ATR-IR (neat) 3340, 2978, 2936, 2244, 1708, 1491, 1250, 986, 912, 735 cm^{-1}; ^1H NMR (601 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.2 (overlapped, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.05 (d, *J* = 2.3 Hz, 1 H), 4.66 (q, *J* = 6.7 Hz, 1 H), 4.20–4.09 (m, 2 H), 3.33 (qd, *J* = 15.0, 6.4 Hz, 2 H), 1.59–1.39 (m, 3 H), 1.32–1.21 (m, 3 H), 1.19 (t, *J* = 7.2 Hz, 3 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 0.99 (s, 3 H), 0.73 (s, 3 H); ^{13}C (151 MHz, $CDCl_3$) δ 172.0, 158.1, 136.0, 127.6, 122.6, 122.2, 119.7, 118.5, 111.2, 110.2, 61.3, 60.6, 60.5, 54.5, 39.5, 39.3, 31.6, 31.1, 27.5, 20.5, 20.5, 16.6, 14.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}N_3O_4$ (M+H) 416.2544, found 416.2553.



2-49

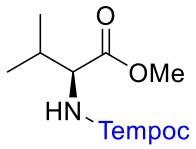
Methyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-alaninate (2-49). Following General Method 2-A and Workup Procedure 2-1, L-alanine methyl ester hydrochloride (0.200 g, 1.18 mmol), **NPTC** (462 mg, 1.42 mmol), HOBt (82.3 mg, 0.591 mmol), triethylamine (302 mg, 419 μL, 2.95 mmol), DMF (2.4 mL), and chromatography on SiO_2 (19:1 to 2:1 hexanes/Et_2O) afforded **2-49** (310 mg, 92%) as a colorless solid: $[\alpha]_D^{24}$ +10.2 (*c* 0.248, CH_2Cl_2); R_f = 0.30 (1:1 hexanes/Et_2O, I_2 active); Mp 66–67.5 °C; ATR-IR (neat) 3367, 2979, 2937, 1716, 1495, 1454, 1167, 1023, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (bd, *J* = 8.0 Hz, 1 H), 4.55–4.39 (m, 1 H), 3.74 (s, 3 H), 1.67–1.52 (m, 5 H), 1.41 (d, *J* = 7.2 Hz, 3 H), 1.41 (overlapped, 1 H), 1.21 (s, 6 H), 1.14 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 157.6, 60.8, 60.8, 52.3, 49.3, 39.7, 39.6, 31.6, 31.5, 20.5, 20.5, 18.8, 16.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{27}N_2O_4$ (M+H) 287.1965, found 287.1990.



2-50

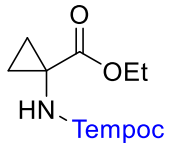
Methyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-leucinate (2-50). Following General Method 2-A and Workup Procedure 2-1, L-leucine methyl ester hydrochloride (225 mg, 1.21 mmol), **NPTC** (474 mg, 1.46 mmol), HOBt (84.5 mg, 0.607 mmol), triethylamine (0.310 mg, 431 μL, 3.04 mmol), DMF (2.4 mL), and chromatography on SiO_2 (19:1 to 17:3 hexanes/Et_2O) afforded **2-50** (355 mg, 89%) as a colorless solid: $[\alpha]_D^{25}$ −7.0 (*c* 0.141, CH_2Cl_2); R_f = 0.53 (1:1 hexanes/Et_2O, I_2 active); Mp 90–91.5 °C; ATR-IR (neat) 3281, 2951, 1757, 1697,

1504, 1187, 991, 922, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (bs, 1 H), 4.48 (td, *J* = 9.0, 4.5 Hz, 1 H), 3.72 (s, 3 H), 1.71–1.52 (m, 8 H), 1.46–1.39 (m, 1 H), 1.22 (s, 6 H), 1.16 (s, 3 H), 1.11 (s, 3 H), 0.95 (d, *J* = 5.9 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 173.4, 157.9, 60.9, 60.8, 52.2, 52.1, 42.1, 39.8, 39.7, 31.8, 31.6, 24.8, 22.9, 21.8, 20.6, 20.6, 16.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{33}N_2O_4$ (M+H) 329.2435, found 329.2434.



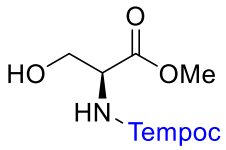
2-51

Methyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-valinate (2-51). Following General Method 2-A and Workup Procedure 2-1, L-valine methyl ester hydrochloride (3.24 g, 19.1 mmol), **NPTC** (7.48 g, 23.0 mmol), HOBt (1.33 g, 9.57 mmol), triethylamine (6.79 mL, 4.89 g, 47.9 mmol), DMF (38 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-51** (5.18 g, 86%) as a heavy clear oil which solidified on standing to a colorless solid: $[\alpha]_D^{24}$ −6.5 (*c* 0.318, CH_2Cl_2); R_f = 0.40 (1:1 hexanes/Et_2O, I_2 active); Mp 78–79.5 °C; ATR-IR (neat) 3371, 2967, 2935, 1729, 1492, 1211, 1148, 991, 764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1 H), 4.38 (dd, *J* = 9.2, 4.6 Hz, 1 H), 3.73 (s, 3 H), 2.20 (heptd, *J* = 6.9, 4.8 Hz, 1 H), 1.71–1.54 (m, 5 H), 1.46–1.38 (m, 1 H), 1.23 (s, 3 H), 1.22 (s, 3 H), 1.17 (s, 3 H), 1.15 (s, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 158.2, 77.3, 76.7, 60.9, 60.7, 58.8, 52.0, 39.8, 39.7, 32.3, 31.5, 20.6, 20.6, 19.1, 17.7, 16.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{31}N_2O_4$ (M+H) 315.2278, found 315.2296.



2-52

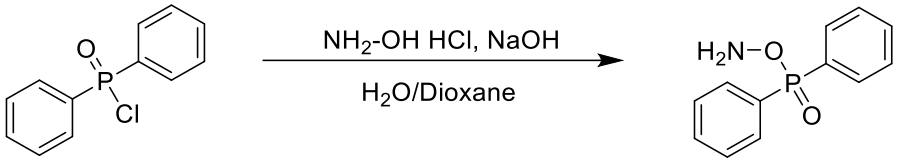
Ethyl 1-((((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)amino)cyclopropane-1-carboxylate (2-52). Following General Method 2-A and Workup Procedure 2-1, ethyl-1-aminocyclopropanecarboxylate hydrochloride (135 mg, 1.02 mmol), **NPTC** (0.400 g, 1.23 mmol), HOBt (71.3 mg, 0.512 mmol), triethylamine (262 mg, 364 µL, 2.56 mmol), DMF (2.0 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-52** (97 mg, 30%) as a fluffy colorless solid: R_f = 0.35 (1:1 hexanes/Et_2O, I_2 active); Mp 125–128 °C; ATR-IR (neat) 3272, 2981, 2941, 1725, 1709, 1472, 1175, 1030, 954, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (bs, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 1.70–1.48 (m, 7 H), 1.45–1.38 (m, 1 H), 1.25–1.16 (m, 11 H), 1.13 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 158.1, 61.4, 60.9, 39.7, 33.9, 31.7, 20.6, 18.1, 16.7, 14.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{29}N_2O_4$ (M+H) 313.2122, found 313.2118.



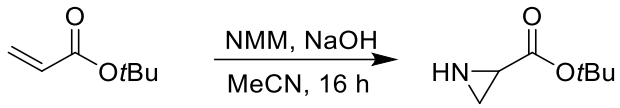
2-53

Methyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-serinate (2-53). Following General Method 2-A and Workup Procedure 2-2, L-serine methyl ester hydrochloride (0.200 g, 1.26 mmol), **NPTC** (492 mg, 1.51 mmol), HOBt (87.8 mg, 0.630 mmol), triethylamine (322 mg, 447 µL, 3.15 mmol), DMF (2.5 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-53** (311 mg, 82%) as a heavy oil which solidified to colorless solid on standing: $[\alpha]_D^{25}$ +16.8 (*c* 0.268, CH_2Cl_2); R_f = 0.54 (EtOAc, $KMnO_4$ active); Mp 93.5–95.5 °C;

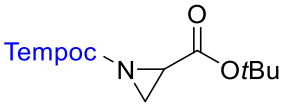
ATR-IR (neat) 3377, 2978, 2934, 1705, 1500, 1211, 1035, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 4.50 (dt, *J* = 7.6, 3.6 Hz, 1 H), 4.01 (ddd, *J* = 11.1, 5.7, 3.7 Hz, 1 H), 3.90 (ddd, *J* = 11.1, 5.9, 3.5 Hz, 1 H), 3.78 (s, 3 H), 2.42 (td, *J* = 5.9, 1.7 Hz, 1 H), 1.67–1.55 (m, 5 H), 1.45–1.38 (m, 1 H), 1.21 (s, 6 H), 1.16 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 158.4, 63.4, 60.9, 55.8, 52.6, 39.6, 39.6, 31.6, 31.5, 20.5, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{27}N_2O_5$ (M+H) 303.1914, found 303.1937.



(Aminooxy)diphenylphosphine oxide (S-1).[149] Hydroxylamine hydrochloride (1.98 g, 28.2 mmol) was charged into a round bottom flask and dissolved in water (4.25 mL). This solution was vigorously stirred and treated with NaOH (0.970 g NaOH, 24.3 mmol) in water (3.5 mL). This mixture was then immediately transferred into a NaCl/ice bath (1:3) and to it was added 1,4-dioxane (15 mL). The solution was allowed to cool for 5 min before diphenylphosphinyl chloride (2.50 g, 2.02 mL, 10.5 mmol) which was diluted to 12.5 mL in 1,4-dioxane, was ran in by syringe. A white precipitate was immediately formed. This precipitate thickened over the next 5 min to the point where the reaction seized. After 5 min, ice-cold water (15 mL) was added and the solids were removed by vacuum filtration and the filter cake washed with ice-cold water (15 mL). The filter cake was then transferred to a vacuum desiccator and dried over calcium sulfate under reduced pressure overnight. The tacky solids were then slurried in ice-cold 0.25 M aq. NaOH (25 mL) for 30 min in an ice-bath before being filtered one more time and washed with ice cold water (15 mL). This filter cake was dried in a vacuum desiccator for 24 h to afford **S-1** (1.20 g, 49%) as a colorless solid which matched literature reported spectra: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.81 (m, 4H), 7.59–7.53 (m, 2H), 7.52–7.44 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.6.



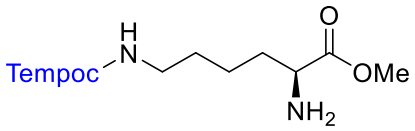
***tert*-Butyl aziridine-2-carboxylate (S-2).**[149] A flame dried flask was charged with (aminooxy)diphenylphosphine oxide (1.14 g, 4.87 mmol) in dry MeCN (77 mL, 0.06 M). This solution was then treated with NMM (55 µL, 502 mg, 4.87 mmol) dropwise over 3 min. The white mixture stirred for 30 min before sequential addition of NaOH (371 mg, 9.27 mmol) and *tert*-butyl acrylate (68 µL, 0.600 g, 4.64 mmol). After stirring for an additional 16 h at ambient temperature, the reaction was quenched with sat. NH_4Cl. Extraction with diethyl ether, and concentration gave a residue which was purified by chromatography on silica gel (gradient,1:19 to 1:0 Et_2O/hexanes) to afford **S-2** as a slightly volatile yellow liquid which matched literature reported spectra: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (dd, J = 5.5, 3.0 Hz, 1 H), 1.92 (dd, J = 3.0, 1.6 Hz, 1 H), 1.79 (d, J = 5.4 Hz, 1 H), 1.48 (s, 9 H), 1.45 (d, J = 6.2 Hz, 1 H).



2-54

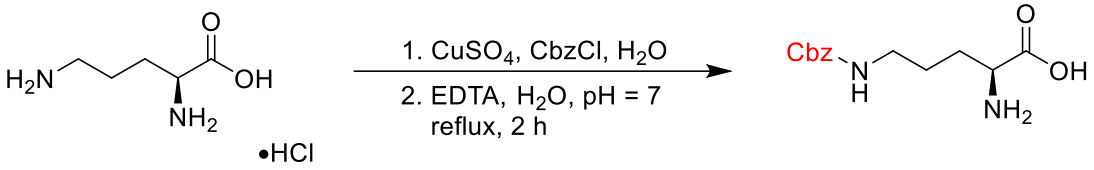
(±) 2-(tert-Butyl) 1-(2,2,6,6-tetramethylpiperidin-1-yl) aziridine-1,2-dicarboxylate (2-24). Following General Method 2-A and Workup Procedure 2-1, *tert*-butyl aziridine-2-carboxylate (269 mg, 1.79 mmol), **NPTC** (697 mg, 2.14 mmol), HOBt (124 mg, 0.892 mmol), triethylamine (274 mg, 363 µL, 2.56 mmol), DMF (3.6 mL), and chromatography on SiO_2 (19:1 to 17:3 hexanes/Et_2O) afforded **2-54** (475 mg, 82%) as a heavy clear oil: R_f = 0.26 (3:1 hexanes/Et_2O); ATR-IR (neat) 2977, 2935, 1761, 1733, 1367, 1319, 1146, 992, 846, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01 (dd, *J* = 5.5, 3.2 Hz, 1 H), 2.55 (dd, *J* = 3.3, 1.4 Hz, 1 H), 2.43 (dd, *J* = 5.5, 1.4 Hz, 1 H), 1.74–1.59 (m, 5 H), 1.49 (s, 9 H), 1.42–1.36 (m, 1 H), 1.18 (s, 3 H), 1.15 (s, 3 H),

1.13 (s, 3 H), 1.11 (s, 3 H);^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 167.2, 161.9, 82.6, 60.5, 39.2, 35.3, 31.6, 31.6, 31.0, 28.0, 20.4, 16.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{31}N_2O_4$ (M+H) 327.2278, found 327.2276.



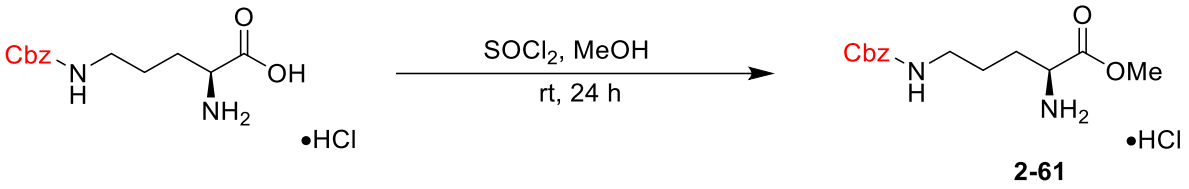
2-55

Methyl Nε-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)-L-lysinate (2-55). Following General Method 2-A and Workup Procedure 2-1, L-valine methyl ester hydrochloride (3.24 g, 19.1 mmol), **NPTC** (7.48 g, 23.0 mmol), HOBt (1.33 g, 9.57 mmol), triethylamine (6.79 mL, 4.89 g, 47.9 mmol), DMF (38 mL), and chromatography on SiO_2 (19:1 to 1:1 hexanes/Et_2O) afforded **2-55** (5.18 g, 86%) as a heavy clear oil which solidified on standing to a colorless solid (conversion to the hydrochloride salt by means of HCl-ether gave a white precipitate which deliquesced rapidly on the filter paper): $[\alpha]_D^{24}$ +3.7 (*c* 0.297, CH_2Cl_2); R_f = 0.52 (4:1 EtOAc:MeOH, ninhydrin active); ATR-IR (neat) 3367, 2935, 3871, 1706, 1603, 1499, 1251, 1186, 956, 734 cm^{-1}; ^{1}H NMR (601 MHz, $CDCl_3$) δ 6.81 (bs, 1 H), 3.72 (s, 3 H), 3.44 (dd, *J* = 7.5, 5.4 Hz, 1 H), 3.23 (q, *J* = 6.8 Hz, 2 H), 1.78–1.72 (m, 1 H), 1.67–1.49 (m, 10 H), 1.41 (ddq, *J* = 12.6, 6.3, 2.9 Hz, 3 H), 1.21 (s, 6 H), 1.09 (s, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 158.6, 60.7, 54.3, 52.0, 40.5, 39.7, 34.4, 31.7, 29.7, 22.9, 20.5, 16.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{33}N_3O_4$ (M+H) 343.2471, found 343.2543.



(*S*)-2-amino-5-(((benzyloxy)carbonyl)amino)pentanoic acid hydrochloride (H-Orn(Z)-OH) (S-3). An Erlenmeyer flask was charged with L-ornithine hydrochloride (10.0 g, 58.7 mmol, 1.0 equiv) in water (47 mL) and to it was added solid sodium hydroxide (4.70 g, 117 mmol, 2.0 equiv). Upon complete dissolution a mixture of copper(II) sulfate pentahydrate (7.33 g, 29.4 mmol, 0.5 equiv) was added as a solution in water (24 mL) resulting in a deep blue solution. The blue mixture was stirred for 15 min before being cooled to 0°C on an ice-bath and receiving benzyl chloroformate (11.2 mL, 13.4 g, 76.3 mmol, 1.3 equiv) dropwise over 10 min. After addition was complete the reaction was slowly allowed to warm to ambient temperature and stir for 12 h. The blue copper complex that precipitated was collected by suction filtration and the filter cake was washed with water (2 x 100 mL) and acetone (2 x 100 mL) then air dried to give the copper complex as a light blue powder which was used directly without purification. In a large Erlenmeyer flask, a suspension of EDTA dihydrate (21.6 g, 64.6 mmol, 1.1 equiv) in water (235 mL) was brought to reflux and the pH was adjusted to 7 by addition of solid sodium hydroxide. To this refluxing solution was added the powdered complex (the complex should be free of large chunks) portion-wise with vigorous stirring (polygon stirbar necessary). The complex tends to float on top of the vortex so periodically a scoopula was inverted and inserted down the wall of the flask into the vortex to act as a baffle. Once the blue powder has been converted into a white precipitate (typically 2 h), the pH is checked and adjusted to 7 if necessary. The slurry is cooled to ambient temperature and the white precipitate is collected by filtration. The filter-cake washed with liberally with water and then with methanol (200 mL). The cake was then dried under vacuum to afford the neutral amino acid **S-3** (13.4 g, 86%) as a white solid. The neutral Cbz amino acid is

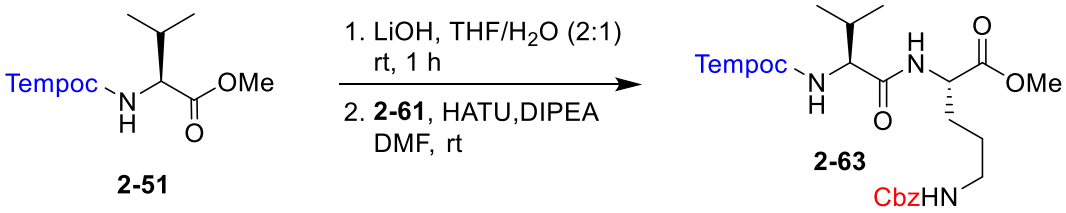
insoluble in DMSO, $CHCl_3$, and methanol and therefore a sample was converted to the hydrochloride salt for NMR analysis: a small amount of the above product is dissolved in a minimal amount of 4 M aqueous HCl and dried to a colorless solid under vacuum before being dissolved in DMSO-d_6 which spectrally matched commercial material: ^{1}H NMR (400 MHz, DMSO) δ 13.80 (bs, 1 H), 8.29 (bs, 3 H), 7.41–7.29 (m, 5 H), 5.01 (s, 2 H), 3.90 (s, 1 H), 3.01 (q, *J* = 6.5 Hz, 2 H), 1.85–1.68 (m, 2 H), 1.63–1.39 (m, 2 H).



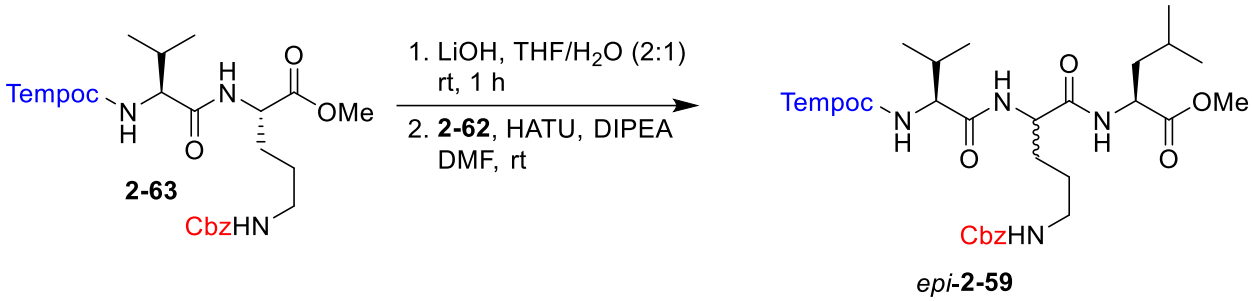
2-61

methyl (*S*)-2-amino-5-(((benzyloxy)carbonyl)amino)pentanoate hydrochloride (H-Orn(Z)-OMe) (2-61).[150] A suspension of **S-3** (10.0 g, 37.2 mmol, 1.0 equiv) in dry methanol (148 mL, 0.25 M) was cooled to 0 °C on an ice-bath before dropwise addition of thionyl chloride (16.6 mL, 22.1 g, 186 mmol, 5.0 equiv) by addition funnel over 10 min (the suspension underwent dissolution on addition). The reaction mixture was stirred at this temperature for 1 hour and before the cooling bath was removed and stirring continued for an addition 24 h. The reaction was concentrated and the residue chased with methanol twice then once with toluene. The waxy solid was reslurried in diethyl ether (500 mL) under vigorous stirring for 1 hour (any large chunks were granulated manually with a teflon stirbar retriever). Collection of the liberated solids on a vacuum funnel gave a cake which was washed with ether (150 mL) and dried under vacuum to give **2-61** (10.5 g, quant) as a fluffy colorless solid that matched literature reported spectra: $[\alpha]_D^{20}$ +17.0 (*c* 4.018, CH_2Cl_2) ^{1}H NMR (500 MHz, DMSO) δ 8.58 (bs, 3 H), 7.40–7.31 (m, 5 H), 4.02 (t, *J* = 6.4 Hz, 1 H), 3.73 (s, 3 H), 3.00 (q, *J* = 6.5 Hz, 2 H), 1.78 (dtd, *J* = 9.3, 6.3, 2.8 Hz, 2 H), 1.59–1.38

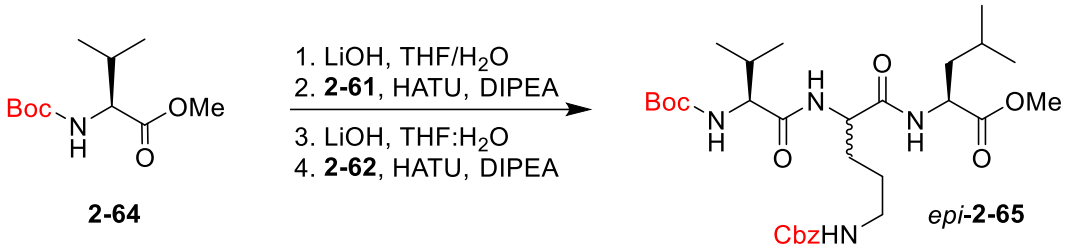
(m, 2 H); ^{13}C NMR (126 MHz, DMSO) δ 169.9, 156.1, 137.2, 128.3, 127.7, 127.7, 65.2, 52.7, 51.6, 27.4, 24.9.



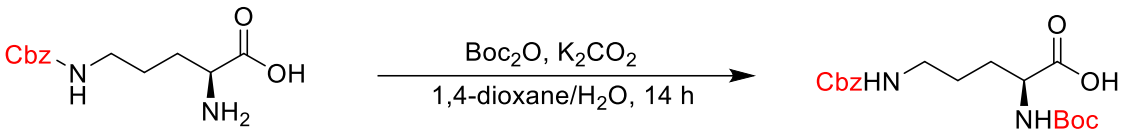
Methyl (S)-5-(((benzyloxy)carbonyl)amino)-2-((*S*)-3-methyl-2-((((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)amino)butanamido)pentanoate (Tempoc-Val-Orn(Cbz)-OMe) (2-63). Following General Method 2-C. **2-51** (1.53 g, 4.87 mmol, 1.0 equiv), lithium hydroxide monohydrate (313 mg, 7.30 mmol, 1.5 equiv), in a 2:1 mixture of THF/H_2O (15 mL, 0.35 M), gave the acid after which was used immediately in the next step. **2-61** (1.70 g, 5.35 mmol, 1.1), HATU (2.08 g, 5.35 mmol, 1.1 equiv) in dry DMF (8.2 mL, 0.25 M) afforded an oil which was purified by chromatography on SiO_2 (gradient, 19:1 to 1:1, hexanes/EtOAc) to give **2-63** (2.63 g, 95%) as a colorless foam: $[\alpha]_D^{24}$ +5.0 (*c* 0.274, CH_2Cl_2); R_f = 0.63 (1:4 hexanes/EtOAc, I_2 active); ATR-IR (neat) 3320, 2965, 2935, 2874, 1711, 1666, 1497, 1250, 1132, 1021, 733 cm^{-1}; ^{1}H NMR (601 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5 H), 6.46 (d, J = 7.9 Hz, 1 H), 5.09 (s, 2 H), 4.91 (t, J = 6.2 Hz, 1 H), 4.57 (td, J = 7.9, 5.0 Hz, 1 H), 4.01 (dd, J = 9.0, 6.8 Hz, 1 H), 3.74 (s, 3 H), 3.21 (qd, J = 6.8, 3.1 Hz, 2 H), 2.11 (h, J = 6.8 Hz, 1 H), 1.87 (tt, J = 10.1, 4.9 Hz, 1 H), 1.70–1.45 (m, 9 H), 1.44–1.38 (m, 1 H), 1.22 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H), 1.08 (s, 3 H), 1.00–0.95 (m, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 170.9, 158.5, 156.5, 136.5, 128.5, 128.1, 128.0, 66.6, 60.9, 60.7, 60.4, 52.4, 51.8, 40.2, 39.7, 39.4, 32.1, 31.4, 31.3, 29.1, 25.9, 20.6, 19.2, 18.2, 16.7; HRMS (ESI) *m/z* calcd for $C_{29}H_{47}N_4O_7$ (M+H) 563.3439, found 563.3432.



Methyl (5-(((benzyloxy)carbonyl)amino)-2-((*S*)-3-methyl-2-((((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)amino)butanamido)pentanoyl)-L-leucinate (*epi*-2-59). Following General Method 2-C, **2-63** (6.90 g, 12.3 mmol), lithium hydroxide monohydrate (788 mg, 18.4 mmol), in a 2:1 mixture of THF/H_2O (35 mL) gave the acid after extraction which was used immediately in the coupling step. **2-62**•HCl (2.50 g, 13.5 mmol), HATU (5.18 g, 13.5 mmol), and DIPEA (7.16 mL, 5.60 g, 42.9 mmol) in dry DMF (49 mL) afforded an oil which was purified by chromatography on SiO_2 (gradient, 19:1 to 1:1, hexanes/EtOAc) to give *epi*-**2-59** (8.29 g, 99%) as a colorless foam in a 1.2:1 mixture of epimers: $[\alpha]_D^{23}$ +5.9 (*c* 0.576, CH_2Cl_2); R_f = 0.55 (1:4 hexanes/EtOAc, I_2 active); ATR-IR (neat) 3304, 2960, 1706, 1645, 1497, 1248, 1156, 1132, 1022, 848, 696 cm^{-1}; ^1H (601 MHz, DMSO, mixture of epimers) δ 8.43–8.13 (m, 2 H), 7.46–7.20 (m, 7 H), 5.08–4.95 (m, 2 H), 4.38–4.22 (m, 2 H), 4.15–3.99 (m, 1 H), 3.60 (s, 3 H), 3.07–2.87 (m, 2 H), 2.02–1.90 (m, 1 H), 1.65–1.34 (m, 12 H), 1.31–1.21 (m, 1 H), 1.14–1.07 (m, 9 H), 0.98–0.96 (m, 3 H), 0.91–0.73 (m, 12 H),^{13}C NMR (126 MHz, DMSO, mixture of epimers) δ 173.2, 172.0, 171.8, 170.9, 170.7, 157.8, 157.6, 156.6, 156.5, 137.7, 128.8, 128.2, 128.2, 128.1, 65.6, 65.6, 60.5, 60.3, 60.3, 59.3, 59.0, 52.4, 52.3, 52.3, 52.3, 50.6, 50.6, 40.0, 32.2, 32.2, 32.2, 32.0, 31.5, 31.4, 30.3, 29.7, 26.4, 24.7, 24.6, 23.3, 21.6, 20.8, 20.7, 19.8, 19.6, 18.0, 17.9, 16.8; HRMS (ESI) *m/z* calcd for $C_{35}H_{58}N_5O_8$ (M+H) 676.4280, found 676.4283.

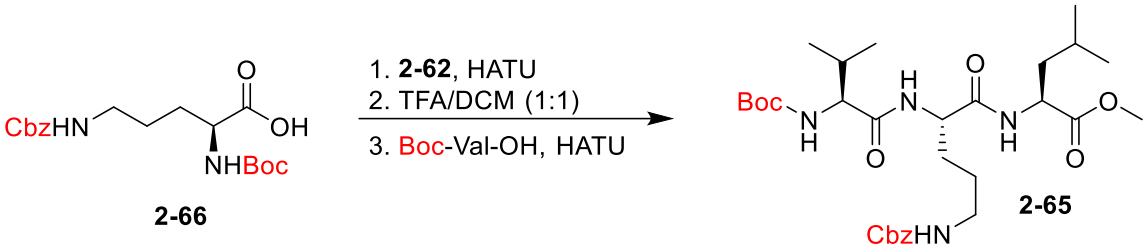


Methyl (5-(((benzyloxy)carbonyl)amino)-2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)pentanoyl)-L-leucinate (*epi*-2-65). Following General Method 2-C, **2-64** (0.600 g, 2.76 mmol), lithium hydroxide monohydrate (174 mg, 4.14 mmol), in a 2:1 mixture of THF/H_2O (7.9 mL) gave the acid after extraction which was used immediately in the coupling step. **2-61** (928 mg, 2.90 mmol), HATU (1.10 g, 2.90 mmol), and DIPEA (1.60 mL, 9.67 mmol) in dry DMF (11 mL) and filtration through a 1.5" plug of SiO_2 afforded the dipeptide as a hygroscopic colorless foam which was used in the next step without further purification. Following General Method 2-C, (0.600 g, 2.76 mmol), lithium hydroxide monohydrate (174 mg, 4.14 mmol), in a 2:1 mixture of THF/H_2O (7.9 mL) gave the acid after extraction which was used immediately in the coupling step. **2-62**•HCl (538 mg, 2.90 mmol), HATU (1.10 g, 2.90 mmol), and DIPEA (1.60 mL, 9.67 mmol) in dry DMF (11 mL) and purification by chromatography on SiO_2 (gradient, 19:1 to 1:1, hexanes/EtOAc) to give *epi*-**2-65** (1.44 g, 88%) as a colorless foam in a 1.2:1 mixture of epimers: ATR-IR (neat) 3298, 2960, 2871, 1692, 1641, 1524, 1247, 1160, 1019, 698 cm^{-1}; ^1H NMR (601 MHz, DMSO, mixture of epimers) δ 8.33–8.17 (m, 1 H), 8.01–7.77 (m, 1 H), 7.43–7.21 (m, 6 H), 6.79–6.66 (m, 1 H), 5.07–4.92 (m, 2 H), 4.36–4.22 (m, 2 H), 3.85–3.74 (m, 1 H), 3.67–3.53 (m, 3 H), 3.04–2.91 (m, 2 H), 1.98–1.86 (m, 1 H), 1.66–1.32 (m, 16 H), 0.90–0.76 (m, 12 H); ^{13}C NMR (151 MHz, DMSO, mixture of epimers) δ 173.2, 172.0, 171.9, 171.7, 171.5, 156.6, 156.5, 156.0, 155.9, 137.7, 128.8, 128.2, 128.2, 78.5, 78.5, 65.6, 65.6, 60.3, 60.2, 52.3, 52.3, 52.2, 50.6, 50.6, 40.0, 34.7, 31.5, 30.8, 30.8, 30.2, 28.7, 28.6, 26.3, 25.3, 24.7, 24.6, 23.3, 23.2, 22.6, 21.8, 21.6, 19.7, 18.6, 18.6.



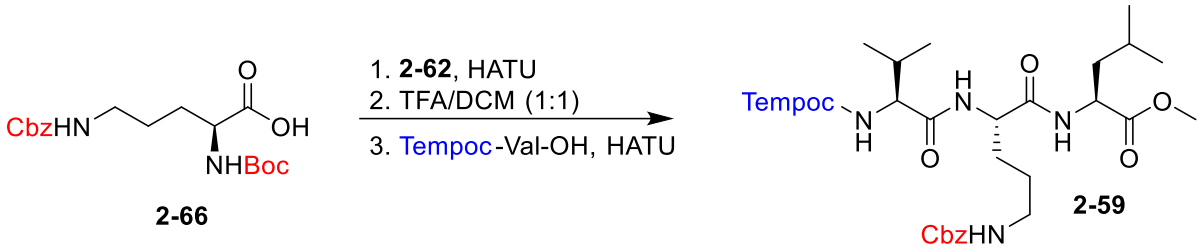
2-66

(*S*)-5-(((Benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)pentanoic acid (2-66). To a suspension of **S-3** (4.20 g, 15.8 mmol) in water (48 mL) and 1,4-dioxane (18 mL) was cooled on an ice-bath before addition potassium carbonate (2.41 g, 17.4 mmol) followed by dropwise addition of Boc anhydride (3.65 g, 16.6 mmol) as a solution in 1,4-dioxane (40 mL) over 30 min *via* addition funnel. After the addition was complete the cooling bath was removed and the reaction (still heterogeneous) was stirred at ambient temperature for 14 h. During this time the solid underwent dissolution. The bulk of the dioxane was removed by rotary evaporation and the aqueous mixture poured into a separatory funnel containing ice. 2 M $KHSO_4$ was then added to pH = 2, resulting in a milky precipitate which was dissolved in ethyl acetate (200 mL). The aqueous layer was separated and the organic was washed with saturated ammonium chloride (100 mL). The rich extract was then dried ($MgSO_4$), filtered, and concentrated to afford **2-66** (4.88 g, 84%) as a hygroscopic amorphous solid. This crude material was used in subsequent couplings without further purification: ^{1}H NMR (400 MHz, DMSO) δ 12.45 (bs, 1 H), 7.39–7.28 (m, 5 H), 7.25 (t, *J* = 5.6 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 5.00 (s, 2 H), 3.94–3.73 (m, 1 H), 3.12–2.86 (m, 2 H), 1.72–1.59 (m, 1 H), 1.58–1.41 (m, 3 H), 1.38 (s, 9 H).



Methyl ((*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)pentanoyl)-L-leucinate (2-65). A flask was charged with **2-66** (484 mg, 1.32 mmol), in dry DMF (5.3 mL). This clear solution was cooled to 0 °C on an ice-bath before sequential addition of HATU (533 mg, 1.39 mmol) and DIPEA base (604 mg, 772 µL, 1.39 mmol). This pale-yellow solution was stirred for a few minutes before addition of **2-62**•HCl (245 mg, 1.32 mmol) as a solid in 1 portion. The reaction turned yellow and the cooling bath was removed. The reaction was stirred for 2 h before being diluted with ethyl acetate (30 mL) and transferred to a separatory funnel. The organic was washed with water (2 x 15 mL), 2 M $KHSO_4$ (10 mL), sat. Na_2CO_3 (10 mL), then brine (10 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated to give a foam which was taken up in ether and passed through a 1.5" pad of silica. 3 plug-volumes was used to washed the product through. Concentration of the filtrate gave the dipeptide methyl ((*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino) pentanoyl)-L-leucinate **(S-4)** as a colorless foam which was used in the next step without further purification. A sample gave the following data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5 H), 7.08 (bd, *J* = 8.0 Hz, 1 H), 5.44–5.30 (m, 2 H), 5.04 (AB, *J* = 12.3 Hz, 2 H), 4.61–4.42 (m, 1 H), 4.38–4.19 (m, 1 H), 3.64 (s, 3 H), 3.41–3.24 (m, 1 H), 3.18–3.02 (m, 1 H), 1.89–1.45 (m, 7 H), 1.39 (s, 9 H), 0.87 (t, *J* = 6.2 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 172.2, 156.9, 155.6, 136.4, 128.3, 127.9, 79.6, 66.4, 52.8, 52.0, 50.6, 40.8, 39.6, 29.8, 28.1, 25.9, 24.5, 22.7, 21.5. **S-4** was taken up in methylene chloride (2.7 mL) and the solution was cooled to 0 °C on an ice-bath before addition of TFA (2.7 mL) dropwise by syringe. The cooling bath was removed and the

reaction stirred at ambient temperature until consumption of the starting material was observed (HPLC-MS, about 1.5 h). At this point the reaction was concentrated and the oily residue taken up in fresh methylene chloride and washed with sat. Na_2CO_3. The free amine was dried ($MgSO_4$) and concentrated to give the amine methyl ((*S*)-2-amino-5-(((benzyloxy)carbonyl)amino)pentanoyl)-L-leucinate **(S-5)** as a pale-yellow oil which was used immediately in the next step. A vial was charged with Boc-Val-OH (287 mg, 1.32 mmol) in dry DMF (3.0 mL). This clear solution was cooled to 0 °C on an ice-bath before sequential addition of HATU (533 mg, 1.39 mmol) and DIPEA base (604 mg, 772 µL, 1.39 mmol). This pale-yellow solution was stirred for a few minutes before addition of **S-4** as a solution in dry DMF (2.3 mL). The reaction turned bright-yellow and the cooling bath was removed. The reaction was stirred for 2 h before being diluted with ethyl acetate (30 mL) and transferred to a separatory funnel. The organic was washed with water (2 x 15 mL), 2 M $KHSO_4$ (10 mL), sat. Na_2CO_3 (10 mL), then brine (10 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated to give a foam which was purified by reslurrying in Et_2O to give **2-65** (699 g, 89%) as a colorless solid after filtration: $[\alpha]_D^{24}$ -16.4 (*c* 0.061, CH_2Cl_2); R_f = 0.65 (1:4 hexanes/EtOAc; UV active); Mp 154–156 °C; ATR-IR (neat) 3291, 3079, 2958, 1690, 1636, 1525, 1245, 1167, 1026, 695 cm^{-1}; ^1H NMR (601 MHz, DMSO) δ 8.29 (d, J = 7.7 Hz, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 7.44–7.21 (m, 6 H, Ar*H* overlapping TempocN*H*), 6.75 (d, *J* = 9.0 Hz, 1 H), 5.00 (s, 2 H), 4.40–4.19 (m, 2 H), 3.78 (dd, *J* = 9.0, 6.7 Hz, 1 H), 3.59 (s, 3 H), 2.98 (q, *J* = 6.5 Hz, 2 H), 1.91 (h, *J* = 6.8 Hz, 1 H), 1.65–1.39 (m, 7 H), 1.37 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.83–0.77 (m, 9 H); ^{13}C NMR (151 MHz, DMSO) δ 173.2, 172.0, 171.5, 156.6, 155.9, 137.7, 128.8, 128.2, 78.5, 65.6, 60.2, 52.3, 52.2, 50.6, 30.8, 30.2, 28.6, 26.3, 24.6, 23.3, 21.6, 19.7, 18.6; HRMS (ESI) *m/z* calcd for $C_{30}H_{49}N_4O_8$ (M+H) 593.3545, found 593.3555.



Methyl ((*S*)-5-(((benzyloxy)carbonyl)amino)-2-((*S*)-3-methyl-2-((((2,2,6,6-tetramethylpiperidin-1-yl)oxy)carbonyl)amino)butanamido)pentanoyl)-L-leucinate (2-59). A flask was charged with **2-66** (484 mg, 1.32 mmol), in dry DMF (5.3 mL). This clear solution was cooled to 0 °C on an ice-bath before sequential addition of HATU (533 mg, 1.39 mmol) and DIPEA base (604 mg, 772 µL, 1.39 mmol). This pale-yellow solution was stirred for a few minutes before addition of **2-62**•HCl (245 mg, 1.32 mmol) as a solid in 1 portion. The reaction turned yellow and the cooling bath was removed. The reaction was stirred for 2 h before being diluted with ethyl acetate (30 mL) and transferred to a separatory funnel. The organic was washed with water (2 x 15 mL), 2 M $KHSO_4$ (10 mL), sat. Na_2CO_3 (10 mL), then brine (10 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated to give a foam which was taken up in ether and passed through a 1.5" pad of silica. 3 plug-volumes was used to washed the product through. Concentration of the filtrate gave the dipeptide methyl **S-4** as a colorless foam which was used in the next step without further purification. **S-4** was taken up in methylene chloride (2.7 mL) and the solution was cooled to 0 °C on an ice-bath before addition of TFA (2.7 mL) dropwise by syringe. The cooling bath was removed and the reaction stirred at ambient temperature until consumption of the starting material was observed (HPLC-MS, about 1.5 h). At this point the reaction was concentrated and the oily residue taken up in fresh methylene chloride and washed with sat. Na_2CO_3. The free amine was dried ($MgSO_4$) and concentrated to give the amine **S-5** as a pale-yellow oil which was used immediately in the coupling step. Following General Method 2-C, **2-51** (416 mg, 1.32 mmol), lithium hydroxide monohydrate (84.9 mg, 1.98 mmol), in a 2:1

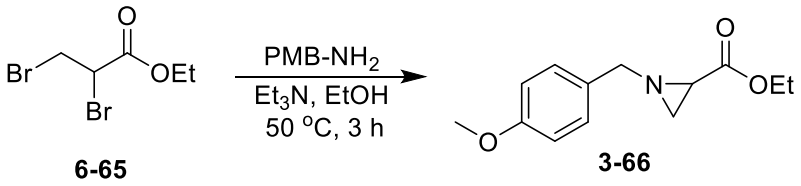
mixture of THF/H_2O (3.6 mL) gave the acid Tempoc-Val-OH after extraction which was used immediately in the coupling step. Tempoc-Val-OH was combined with **S-5,** HATU (1.10 g, 2.90 mmol), and DIPEA (1.60 mL, 9.67 mmol) in dry DMF (5.3 mL) gave the crude tripeptide after extraction which was purified by reslurrying in Et_2O to give **2-59** (743 mg, 83%) as a colorless amorphous solid after filtration: $[\alpha]_D^{24}$ -6.5 (*c* 0.185, CH_2Cl_2); R_f = 0.63 (100% EtOAc; UV active); ATR-IR (neat) 3293, 2958, 2873, 1707, 1640, 1497, 1250, 1017, 910, 729 cm^{-1}; ^{1}H NMR ^{1}H NMR (601 MHz, $CDCl_3$) δ 7.38–7.27 (m, 6 H; Ar*H* overlapping TempocN*H*), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 8.3 Hz, 1 H), 5.14–5.03 (m, 3 H), 4.70 (td, *J* = 8.5, 4.3 Hz, 1 H), 4.52 (ddd, *J* = 9.4, 8.0, 5.1 Hz, 1 H), 4.04 (dd, *J* = 8.9, 6.8 Hz, 1 H), 3.68 (s, 3 H), 3.47 (dq, *J* = 14.0, 7.3 Hz, 1 H), 3.11–3.04 (m, 1 H), 2.07 (h, *J* = 6.8 Hz, 1 H), 1.93–1.84 (m, 1 H), 1.72–1.45 (m, 11 H), 1.43–1.38 (m, 1 H), 1.20 (s, 3 H), 1.18 (s, 3 H), 1.15 (s, 3 H), 1.06 (s, 3 H), 0.96–0.88 (m, 12 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.2, 171.5, 171.0, 158.4, 157.3, 136.4, 128.5, 128.1, 128.0, 66.7, 60.9, 60.6, 60.4, 52.2, 51.2, 50.8, 40.9, 39.7, 39.5, 39.2, 32.1, 31.4, 31.4, 29.8, 26.1, 24.7, 22.8, 21.7, 20.5, 19.3, 18.2, 16.7; HRMS (ESI) *m/z* calcd for $C_{35}H_{58}N_5O_8$ (M+H) 676.4280, found 676.4283.

4.3 EXPERIMENTAL – CYCLOPIAZONIC ACID

4.3.1 General experimental protocols

Reactions were performed without inert atmosphere with ACS grade solvents unless otherwise stated. Inert reactions were performed under a N_2 or argon atmosphere and glassware was flame dried prior to use. Absolute ethanol was stored over 4 Å molecular sieves. Diethyl ether and THF were distilled over sodium/benzophenone ketyl. Dry toluene was distilled from CaH_2 or dried by passage through an alumina filtration system. Acetone for imine formations was pre-dried with $MgSO_4$, decanted, then distilled under an inert atmosphere. DMF was dried over 4 Å molecular sieves which were activate in a muffle furnace at 350 °C for 16 h prior to use. Commercial reagents were used as-is unless otherwise noted.

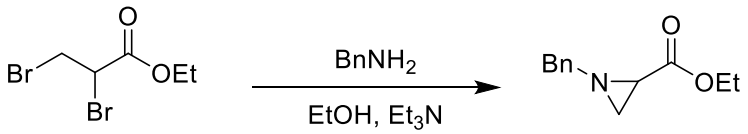
4.3.2 Synthetic procedures and spectral characterization



6-65 **3-66**

Ethyl 1-(4-methoxybenzyl)aziridine-2-carboxylatecarbonate (3-66).[151] A flame dried sealable flask was charged with ethyl 2,3-dibromopropanoate (3.79 g, 2.12 mL, 14.1 mmol) in absolute ethanol (70.7 mL) and the mixture cooled to 0 °C on an ice-bath under nitrogen. The cooled solution then received sequentially 4-MeO-benzylamine (1.00 g, .952 mL, 7.07 mmol) and triethylamine (2.17 g, 3.01 mL, 21.2 mmol) drop-wise by syringe. The flask was removed from the bath and the reaction was allowed to warm to ambient temperature, and then was sealed and

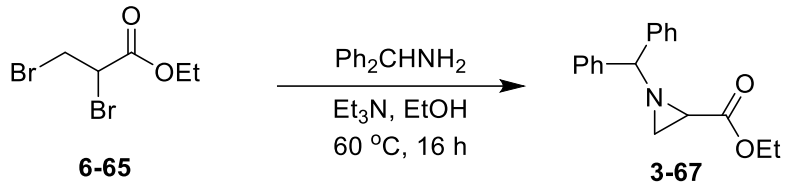
heated to 50 °C for 3 h. Upon completion of the reaction, the solvent was removed under reduced pressure and the residue thus obtained was purified by chromatography on SiO_2 (gradient, 19:1 to 4:1 hexanes/EtOAc) to afford **3-66** (1.48 g, 84%) as a yellow liquid that matched literature reported spectra: R_f = 0.49 (1:1 hexanes/EtOAc, UV active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.17 (m, 2 H), 6.94–6.75 (m, 2 H), 4.30–4.06 (m, 2 H), 3.80 (s, 3 H), 3.49 (s, 2 H), 2.23 (dd, *J* = 3.2, 1.2 Hz, 1 H), 2.17 (dd, *J* = 6.5, 3.2 Hz, 1 H), 1.72 (dd, *J* = 6.5, 1.2 Hz, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.8, 158.9, 129.9, 129.3, 113.8, 63.3, 61.1, 55.3, 37.4, 34.3, 14.2.



6-65 **3-68**

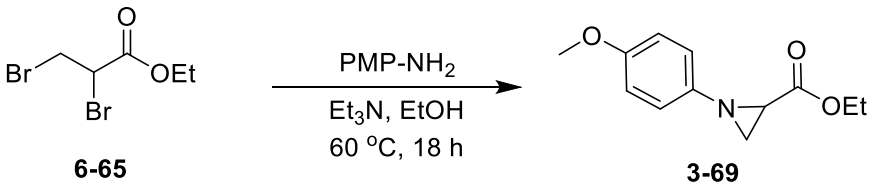
Ethyl 1-benzylaziridine-2-carboxylate (3-68).[151] A flame dried flask was charged with ethyl 2,3-dibromopropanoate (3.68 g, 2.06 mL, 13.7 mmol) in absolute ethanol (125 mL, 0.11 M) and the mixture was cooled to 0 °C under nitrogen and stirring before sequential addition of benzylamine (1.50 g, 1.53 mL, 13.7 mmol) and triethylamine (2.81 g, 3.90 mL, 27.4 mmol) by syringe. The reaction mixture was then heated to 60 °C in a sealed flask (septum secured with wire) and stirred for 16 h. The resulting yellow solution was concentrated in vacuo to give an oily solid. The solid was suspended in ether and stirred for 30 min. The solids were then removed by filtration and washed with ether. The filtrate was concentrated to afford a residue which was purified by chromatography on SiO_2 (gradient, 19:1 to 17:3 hexanes/EtOAc) to afford **3-68** (2.15 g, 77%) as a yellow liquid which matched literature reported spectra: R_f = 0.49 (1:1 hexanes/EtOAc, UV-active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–6.56 (m, 5 H), 4.82–3.79 (m, 2 H), 3.70–3.45 (m, 2 H), 2.26 (dd, *J* = 3.2, 1.2 Hz, 1 H), 2.19 (dd, *J* = 6.4, 3.1 Hz, 1 H), 1.74 (dd, *J*

= 6.5, 1.1 Hz, 1 H), 1.27 (t, *J* = 7.1 Hz, 3 H); ^{13}C (76 MHz, $CDCl_3$) δ 170.7, 137.8, 128.4, 128.0, 127.3, 63.9, 61.1, 37.5, 34.4, 14.2.



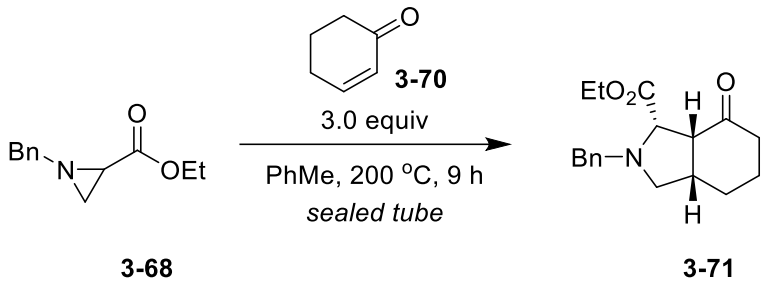
6-65 **3-67**

Ethyl 1-benzhydrylaziridine-2-carboxylate (3-67). A flame dried flask was charged with ethyl 2,3-dibromopropanoate (2.84 g, 1.59 mL, 10.6 mmol) in absolute ethanol (96 mL, 0.11 M) and the mixture was cooled to 0 °C under nitrogen and stirring before sequential addition of benzhydrylamine (2.00 g, 1.88 mL, 10.6 mmol) and triethylamine (2.16 g, 3.01 mL, 21.2 mmol) by syringe. The reaction mixture was then slowly heated to 60 °C in a sealed flask (septum secured with wire) and stirred for 16 h. The resulting yellow solution was concentrated in vacuo to give an oily solid. The solid was suspended in ether and stirred for 30 min. The solids were then removed by filtration and washed with ether. The filtrate was concentrated to afford a residue which was purified by chromatography on SiO_2 (gradient, 19:1 to 17:3 hexanes/EtOAc) to afford the **3-67** (2.57 g, 86%) as off-white crystals: R_f = 0.54 (1:1 hexanes/Et_2O, UV-active); ATR-IR (neat) 3062, 2983, 1740, 1493, 1453, 1189, 1075, 1031, 862 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.40 (m, 4 H), 7.37–7.20 (m, 6 H), 4.19 (qd, *J* = 7.1, 1.6 Hz, 2 H), 3.63 (s, 1 H), 2.32 (dd, *J* = 3.2, 1.0 Hz, 1 H), 2.25 (dd, *J* = 6.4, 3.2 Hz, 1 H), 1.84 (dd, *J* = 6.4, 1.0 Hz, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 170.5, 142.5, 142.5, 128.4, 127.6, 127.4, 127.2, 127.1, 77.8, 61.0, 38.3, 34.7, 14.1; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}NO_2$ (M+H) 282.1489, found 282.1495.



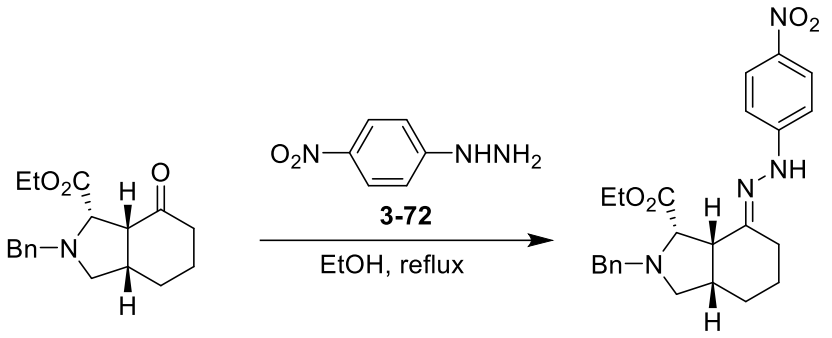
6-65 **3-69**

Ethyl 1-(4-methoxyphenyl)aziridine-2-carboxylate (3-69).[151] A flame dried flask was charged with ethyl 2,3-dibromopropanoate (3.00 g, 1.68 mL, 11.2 mmol) in absolute ethanol (102 mL, 0.11 M) and the mixture was cooled to 0 °C under nitrogen and stirring before sequential addition of *p*-anisidine (1.39 g, 11.2 mmol) and triethylamine (2.29 g, 3.18 mL, 22.4 mmol) by syringe. The reaction mixture was then slowly heated to 60 °C in a sealed flask (septum secured with wire) and stirred for 16 h. The resulting yellow solution was concentrated in vacuo to give an oily solid. The solid was suspended in ether and stirred for 30 min. The solid was partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous layer was removed and the organic layer was washed with water (100 mL), then brine. The organic was dried ($MgSO_4$), filtered, and the filtrate was concentrated to afford a residue which was purified by chromatography on SiO_2 (gradient, 19:1 to 3:1 hexanes/EtOAc) to afford **3-69** (1.32 g, 53%) as a yellow oil which freezes at −20 °C and matched literature reported spectra: R_f = 0.32 (1:1 hexanes/Et_2O, UV active); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (d, *J* = 8.9 Hz, 2 H), 6.79 (d, *J* = 8.9 Hz, 2 H), 4.33–4.20 (m, 2 H), 3.76 (s, 3 H), 2.71 (dd, *J* = 6.4, 3.1 Hz, 1 H), 2.62 (dd, *J* = 3.2, 1.7 Hz, 1 H), 2.25 (dd, *J* = 6.4, 1.8 Hz, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 155.7, 145.8, 121.4, 114.3, 61.4, 55.5, 37.9, 34.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}NO_3$ (M+H) 221.1125, found 222.1123.



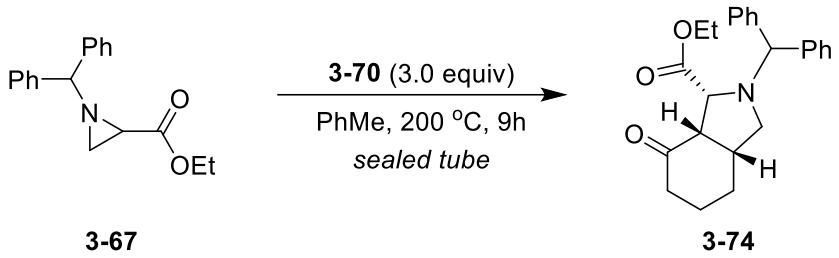
3-68 **3-71**

(±)-Ethyl (1S,3aS,7aR)-2-benzyl-7-oxooctahydro-1H-isoindole-1-carboxylate (3-71). A flame dried microwave tube was charged with **3-70** (1.08 g, 1.08 mL, 11.0 mmol) and **4** as a 2.6 M solution in dry toluene (0.750 g, 1.41 mL, 3.65 mmol), in dry toluene (10.8 mL). The mixture was sparged with argon under sonication for 2 min before being sealed under argon and heated to 195 °C on an aluminum block for 6 h then the heat was turned off and the reaction was allowed to cool to ambient temperature in the block slowly. The reaction mixture was concentrated and placed on the high vacuum for an hour before being purified by chromatography on SiO_2 (gradient, 19:1 to 3:1 PhMe/Et_2O) gave **3-71** (0.500 g, 45%) as a pale yellow oil: R_f = 0.33 (1:1 hexanes/Et_2O, UV active); ATR-IR (neat) 3028, 2936, 2805, 1722, 1701, 1183, 1029, 744, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.28 (m, 4 H), 7.26–7.22 (m, 1 H), 4.13 (qd, *J* = 7.1, 2.9 Hz, 2 H), 3.79 (d, *J* = 9.0 Hz, 1 H), 3.76 (d, *J* = 13.1 Hz, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 3.17 (t, *J* = 9.3 Hz, 1 H), 2.81–2.74 (m, 2 H), 2.66–2.57 (m, 1 H), 2.39–2.26 (m, 2 H), 2.00–1.93 (m, 1 H), 1.85–1.79 (m, 1 H), 1.74–1.66 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.6, 171.7, 138.4, 128.7, 128.1, 127.0, 67.6, 60.5, 57.5, 56.9, 53.5, 39.9, 38.5, 27.1, 22.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_3$ (M+H) 302.1751, found 302.1747.



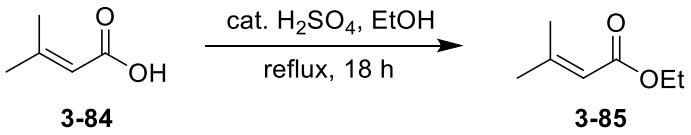
3-71 **3-73**

(±)-Ethyl (1S,3aS,7aR,E)-2-benzyl-7-(2-(4-nitrophenyl)hydrazono)octahydro-1H-isoindole-1-carboxylate (3-73). A flame dried 2 mL microwave tube was charged with **3-71** (50.0 mg, 0.158 mmol) in abs. EtOH (790 µL, 0.2 M) and to it was added 4-nitrophenylhydrazine (25.9 mg, 0.166 mmol) in one portion and the tube was sealed under nitrogen and heated to 80 °C until consumption of the starting material was visualized (TLC, ≈ 18 h). The reaction mixture was concentrated and purified by chromatography on SiO_2 (isocratic, CH_2Cl_2) to afford **3-73** (22 mg, 32%) as a yellow solid. Single crystals were grown by liquid-liquid diffusion (hexanes/CH_2Cl_2) which were isolated as prisms and submitted for x-ray analysis: R_f = 0.61 (1:1 hexanes/EtOAc, I_2 active); Mp 154-158 °C; ATR-IR (neat) 3328, 2933, 1724, 1592, 1315, 1261, 1107, 844, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.3 Hz, 1 H), 7.63 (s, 1 H), 7.37–7.27 (m, 4 H), 7.25 (d, *J* = 4.9 Hz, 1 H), 7.01 (d, *J* = 9.2 Hz, 2 H), 3.98–3.82 (m, 2 H), 3.76 (dd, *J* = 13.3, 11.3 Hz, 2 H), 3.57 (d, *J* = 13.0 Hz, 1 H), 3.51 (td, *J* = 9.6, 1.6 Hz, 1 H), 2.81 (dd, *J* = 9.1, 3.5 Hz, 1 H), 2.74 (dd, *J* = 9.1, 6.8 Hz, 1 H), 2.51–2.40 (m, 2 H), 2.17 (dddd, *J* = 16.4, 9.4, 6.6, 1.7 Hz, 1 H), 2.10–1.99 (m, 1 H), 1.77–1.61 (m, 3 H), 1.48 (dtdd, *J* = 13.2, 9.7, 5.9, 3.2 Hz, 1 H), 1.07 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 151.8, 150.2, 140.0, 138.4, 128.9, 128.2, 128.1, 127.1, 126.0, 111.7, 70.4, 60.2, 58.8, 57.6, 46.7, 37.4, 27.7, 24.7, 20.7, 14.2.; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}N_4O_4$ (M+H) 437.2183, found 437.2182.



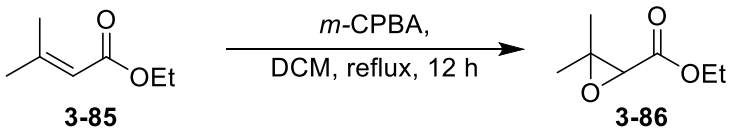
3-67 **3-74**

(±)-Ethyl (1R,3aR,7aS)-2-benzhydryl-7-oxooctahydro-1H-isoindole-1-carboxylate (3-75). A flame dried microwave tube was charged with **3-70** (209 mg, 211 µL, 2.13 mmol) and **3-67** (0.200 g, 0.711 mmol) in dry PhMe (2.4 mL). The mixture was sparged with argon under sonication for 2 min before being sealed under argon and placed in a preheated (200 °C) aluminum block for 9 h then heat was turned off and the reaction was allowed to cool to ambient temperature in block slowly. The reaction was concentrated and by chromatography on SiO_2 (gradient, 5-30% Et_2O/hexanes) gave a small forerun of unreacted aziridine (40 mg) and **3-74** (130 mg, 48%) as off-white crystals. A single crystal was grown from absolute ethanol and submitted for X-ray analysis: R_f = 0.36 (1:1 hexanes/Et_2O, UV active); ATR-IR (neat) 3062, 2938, 1724, 1702, 1453, 1453, 1186, 1029, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (ddd, *J* = 8.1, 2.7, 1.3 Hz, 4 H), 7.25 (ddd, *J* = 14.9, 8.1, 6.8 Hz, 4 H), 7.21–7.14 (m, 2 H), 4.60 (s, 1 H), 3.99 (d, *J* = 9.4 Hz, 1 H), 3.98–3.88 (m, 2 H), 3.21 (t, *J* = 9.8 Hz, 1 H), 2.90 (dd, *J* = 9.6, 7.3 Hz, 1 H), 2.83 (dd, *J* = 9.5, 6.1 Hz, 1 H), 2.61 (td, *J* = 10.4, 6.5 Hz, 1 H), 2.36 (ddd, *J* = 17.6, 5.1, 3.7 Hz, 1 H), 2.22 (ddd, *J* = 17.7, 11.2, 6.3 Hz, 1 H), 2.01–1.93 (m, 1 H), 1.87–1.61 (m, 3 H), 1.11 (t, *J* = 7.2 Hz, 3 H).; ^{13}C NMR R (76 MHz, CDCl3) δ 212.1, 172.3, 142.8, 142.2, 128.4, 128.3, 127.9, 127.6, 127.1, 71.4, 65.8, 60.2, 57.2, 53.5, 39.8, 38.3, 27.2, 22.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}NO_3$ (M+H) 378.2064, found 378.2062.



3-84 **3-85**

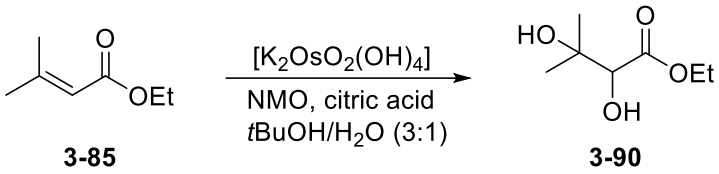
Ethyl 3-methylbut-2-enoate (3-85). A flask was charged with 3,3-dimethyacrylic acid (10.0 g, 96.9 mmol) in absolute EtOH (48.5 mL, 2.0 M) and the mixture was stirred until complete dissolution took place. The flask then received H_2SO_4 (0.950 g, 516 µL, 9.69 mmol) dropwise by syringe. The mixture was then heated to reflux for 18 h, after which point the solution was allowed to cool to ambient temperature and was poured into a separatory funnel containing CH_2Cl_2 (100 mL) and ice-water (100 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 x 100 mL). The pooled organics were successively washed with sat $NaHCO_3$, water, brine, then dried ($MgSO_4$), filtered, and concentrated to afford a pale green liquid which was purified by chromatography on SiO_2 (gradient, 1:0 to 19:1 hexanes/EtOAc) to afford **3-85** (8.56 g, 65%) as a light green liquid which spectrally matched commercial material: R_f = 0.48 (4:1 hexanes/EtOAc, $KMnO_4$ & UV active); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.42 (m, 1 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 2.10 (d, *J* = 1.4 Hz, 3 H), 1.82 (d, *J* = 1.5 Hz, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 166.5, 156.0, 116.0, 59.2, 27.1, 19.9, 14.1.



3-85 **3-86**

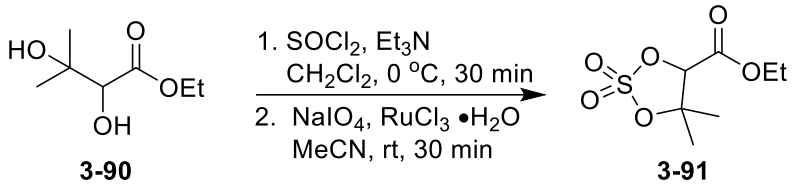
Ethyl 3,3-dimethyloxirane-2-carboxylate (3-86).[152] A flame dried flask was charged with **3-85** (1.00 g, 1.09 mL, 7.41 mmol) in dry CH_2Cl_2 (29.6 mL, 0.2 M) and the solution was cooled to 0 °C on an ice-bath. The cooled solution was then treated with *m*-CPBA (2.05 g, 8.90 mmol) as a solid, portion-wise over 5 min. The cooling bath was removed and the reaction stirred at ambient temperature overnight. Conversion was slow so after 12 h the reaction was fitted with an oil bath and heated at reflux for an additional 12 h. After 12 h of heating the acrylate was almost

consumed (TLC). Reaction was cooled, diluted with CH_2Cl_2 (20 mL) and quenched with sat. sodium bisulfite and washed with sat. sodium bicarbonate (2 x 20 mL). The organics were dried ($MgSO_4$) and concentrated to afford a clear liquid that was purified by chromatography on SiO_2 (gradient, 19:1 to 9:1 hexanes/EtOAc) to afford **3-86** (737 mg, 69%) as a clear liquid which matched literature reported spectra: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (qd, *J* = 7.1, 4.5 Hz, 2 H), 3.33 (s, 1 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H).



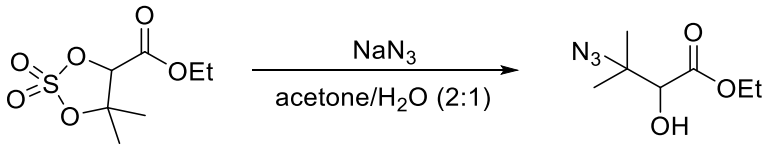
3-85 **3-90**

Ethyl 2,3-dihydroxy-3-methylbutanoate (3-90). A flask was charged with **3-85** (3.00 g, 3.26 mL, 22.2 mmol) in *tert*-butanol (67 mL) and to it was added water (22 mL) and 4-methylmorpholine N-oxide (3.49 g, 28.9 mmol), citric acid (4.67 g, 22.2 mmol), and potassium osmate (82.8 mg, 0.222 mmol). The reaction was stirred at ambient temperature for 12 h during which time the reaction color changed from translucent green to tan. The reaction was then diluted with water (20 mL) and *tert*-butanol was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford a residue which was purified by chromatography on SiO_2 (gradient, 19:1 to 1:1 hexanes/EtOAc) to afford **3-90** (3.50 g, 97%) as a colorless oil: R_f = 0.45 (1:4 hexanes/EtOAc, $KMnO_4$ active); ATR-IR (neat) 3450, 2980, 2939, 1729, 1201, 1090, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39–4.21 (m, 2 H), 3.96 (d, *J* = 6.6 Hz, 1 H), 3.15 (d, *J* = 6.7 Hz, 1 H), 2.59 (s, 1 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.30 (s, 3 H), 1.22 (s, 3 H).; ^{13}C NMR (76 MHz, $CDCl_3$) δ 173.2, 77.1, 72.0, 62.0, 25.6, 24.9, 14.2; HRMS (ESI) *m/z* calcd for $C_7H_{15}O_4$ (M+H) 163.0965, found 163.0963.



3-90 3-91

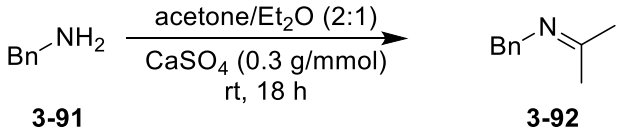
Ethyl 5,5-dimethyl-1,3,2-dioxathiolane-4-carboxylate 2,2-dioxide (3-91). To a stirred solution of **3-90** (0.650 g, 4.01 mmol) in CH_2Cl_2 (13.4 mL) at 0 °C was added $SOCl_2$ (722 mg, 443 µL, 6.01 mmol) and Et_3N (1.02 g, 1.42 mL, 10.0 mmol). After 30 min, a saturated solution of $NaHCO_3$ (15 mL) was added. After separation of the layers, the organic layer was dried (Na_2SO_4) and concentrated to dryness. The residue was dissolved in the mixture of MeCN (13.4 mL) and H_2O (6.68 mL). To the stirred mixture at room temperature, $NaIO_4$ (874 mg 4.09 mmol) and $RuCl_3 \cdot H_2O$ (8.31 mg, 0.0401 mmol) was added. H_2O was added to the reaction after 30 min and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was purified by chromatography on SiO_2 (gradient, 19:1 to 4:1 hexanes/EtOAc) to afford **3-91** (676 mg, 75%) as a clear oil: R_f = 0.55 (1:1 hexanes/EtOAc, $KMnO_4$ active); ATR-IR (neat) 2989, 1764, 1742, 1375, 1209, 1054, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (q, *J* = 7.2 Hz, 2 H), 1.79 (s, 3 H), 1.58 (s, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 163.5, 91.8, 83.8, 63.1, 26.1, 22.1, 14.1; HRMS (ESI) *m/z* calcd for $C_7H_{13}O_6$ (M+H) 225.0427, found 225.0431.



3-91 3-88

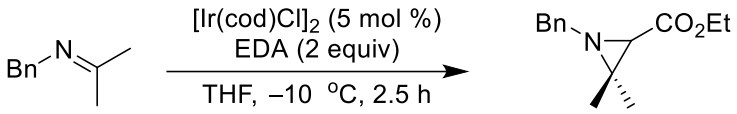
Ethyl 2-azido-3-hydroxy-3-methylbutanoate (3-88). A flask was charged with **3-91** (0.670 g, 2.99 mmol) in 9:1 acetone/water (18 mL/ 2.0 mL) and to it was added sodium azide (294 mg, 4.48 mmol) in one portion and the mixture was stirred at 50 °C for 5 h or until consumption

of the SM as visualized by TLC. Acetone was removed under reduced pressure and diethyl ether (58 mL) and water (1.7 mL) was added and then the solution was chilled on an ice bath before dropwise addition of 20% H_2SO_4 (1.6 mL/mmol, 4.8 mL) and the mixture stirred vigorously overnight. Separation of the organics and washing with saturated sodium carbonate, followed by drying with $MgSO_4$, and concentration afforded **3-88** (164 mg, 29%) as a clear oil which was used immediately in the next step as it is a low molecular weight azide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (qd, *J* = 7.1, 0.7 Hz, 2 H), 3.79 (s, 1 H), 2.81 (bs, 1 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.30 (s, 3 H), 1.30 (s, 3 H).



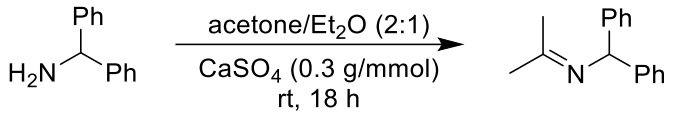
3-91 **3-92**

***N*-benzylpropan-2-imine (3-92).** A flame-dried flask was charged with a 1:2 mixture of dry ether and distilled acetone (12.2 mL:6.1 mL) and anhydrous calcium sulfate (2.75 g, about 0.3 g/mmol). This mixture was then treated with benzylamine (1.00 g, 1.02 mL, 9.15 mmol). The reaction was stirred vigorously at ambient temperature for 18 h after which point it was filtered through a pad of dried HyFlo Celite. The Celite was washed with dry ether and the filtrate concentrated to afford **3-92** (1.40 g, quant) as a clear oil which was used immediately in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 4 H), 7.25–7.21 (m, 1 H), 4.46 (s, 2 H), 2.09 (t, *J* = 1.3 Hz, 3 H), 1.94 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 140.4, 128.4, 127.8, 126.5, 77.3, 77.0, 76.7, 55.4, 29.4, 29.2, 18.7.



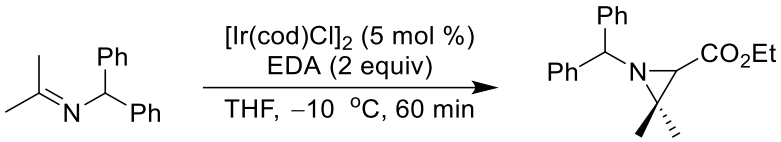
3-92 **3-59**

Ethyl 1-benzyl-3,3-dimethylaziridine-2-carboxylate (3-59). A flame dried flask was charged with $[Ir(cod)Cl]_2$ catalyst in the glovebox (322 g, 0.476 mmol) and the flask was placed in a -10 °C bath (15 wt % aq. NaCl/dry-ice, bath temp remains −11 °C as long as a slush is maintained by slow addition of dry-ice) and to it was added freshly distilled THF (6.0 mL) under and argon atmosphere. The mixture was stirred for 5 min before the red solution received **3-92** (1.40 g, 9.51 mmol) as a solution in distilled THF (3.5 mL) in one portion which turned the solution bright yellow. This mixture was stirred for an additional 10 min before ethyl diazoacetate (2.49 g, 2.27 mL, 19.0 mmol) was added dropwise by syringe over 1 minute. The reaction was stirred at this temperature for 60 min, then the reaction was allowed to warm slowly to ambient temperature and stir for an additional 12 h during which time the mixture turned from yellow to brown. Wet diethyl ether was then added and the reaction was poured through a 1" pad of SiO_2 and the silica was washed with diethyl ether (3 x column volumes). Concentration under reduced pressure and 1 hour on the high vacuum gave a residue which was purified by chromatography on SiO_2 (gradient, 19:1 to 3:1 hexanes/Et_2O) to afford **3-59** (1.51 g, 68%) as a yellow liquid: R_f = 0.44 (1:1 hexanes/Et_2O, $KMnO_4$ & I_2 active); ATR-IR (neat) 3063, 2982, 2930, 1741, 1302, 1175, 1037, 732, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2 H), 7.31 (dd, *J* = 8.4, 6.8 Hz, 2 H), 7.25–7.21 (m, 1 H), 4.20 (qd, *J* = 7.1, 5.1 Hz, 2 H), 3.83–3.74 (m, 2 H), 2.12 (s, 1 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 139.2, 128.3, 127.3, 126.7, 60.7, 56.0, 49.3, 44.6, 21.8, 17.9, 14.3; HMRS (ESI) *m/z* calcd for $C_{14}H_{20}NO_2$ (M+H) 234.1489, found 234.1487.



3-93 **3-94**

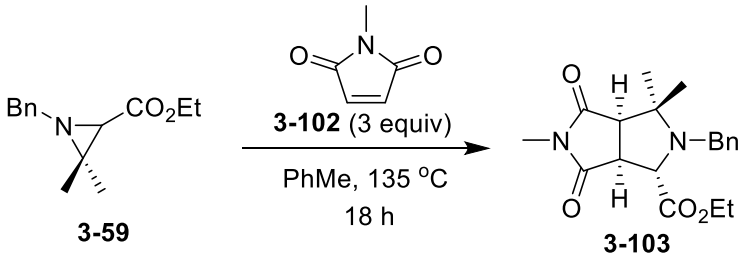
***N*-benzhydrylpropan-2-imine (3-94).** A flame dried flask was charged with a 1:2 mixture of dry ether and distilled acetone (13 mL:40 mL) and anhydrous calcium sulfate (8.00 g, about 0.3 g/ mmol). This mixture was then treated with benzhydrylamine (5.00 g, 4.72 mL, 26.5 mmol). The reaction was stirred vigorously at ambient temperature for 18 h after which point it was filtered through a pad of dried HyFlo Celite. The Celite was washed with dry ether and the filtrate concentrated to afford **3-94** (4.55 g, 77%) as an off-white solid that can be recrystallized from dry hexanes but was >95% pure by ^{1}H NMR and was used directly in the next step: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.36 (m, 4 H), 7.34–7.30 (m, 4 H), 7.26–7.19 (m, 2 H), 5.66 (s, 1 H), 2.16 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 144.5, 128.3, 127.6, 126.6, 68.0, 29.7, 19.1.



3-94 **3-95**

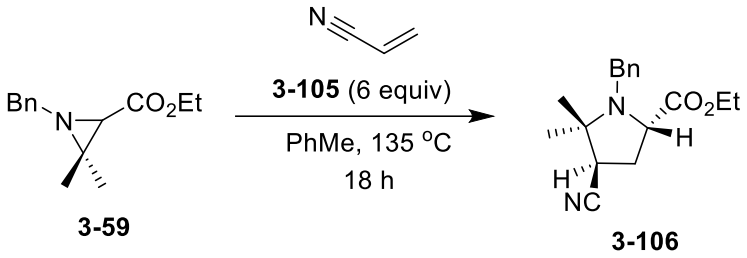
Ethyl 1-benzhydryl-3,3-dimethylaziridine-2-carboxylate (3-95). A flame dried flask was charged with $[Ir(cod)Cl]_2$ catalyst in the glovebox (.250 g, 0.369 mmol) and the flask was placed in a −10 °C bath (15 wt % aq. NaCl/dry-ice) and to it was added freshly distilled THF (2.94 mL, 1.0 M) under and argon atmosphere. The mixture was stirred for 5 min before the red solution received **3-94** (1.65 g, 7.37 mmol) as a solid in one portion which turned the solution yellow. This mixture was stirred for an additional 10 min before ethyl diazoacetate (1.93 g, 1.76 mL, 14.7 mmol) by syringe over 1 minute. The reaction was stirred at this temperature for 30 min then the reaction was allowed to warm slowly for 30 min to about 0 °C during which time the mixture

turned from yellow to brown. Wet diethyl ether was then added and the reaction was poured through a 1" pad of silica gel and eluted with diethyl ether. Concentration under reduced pressure and 1 hour on the high vacuum gave dark brown solid which was dissolved in 95% ethanol (25 mL) at 60 °C and allow to slowly cool to ambient temperature, then was placed in the freezer (−20 °C) for 12 h. The crystals thus formed were collected by filtration and the filter cake was washed with water and ice-cold 95% ethanol. Drying of the solids afforded **3-95** (1.65 g, 72%) as tan crystals in >95% purity: R_f = 0.23 (9:1 hexanes/Et_2O, UV active); Mp = 120-122 °C; ATR-IR (neat) 3061, 3027, 2983, 1742, 1454, 1180, 1032, 746, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.50 (m, 4 H), 7.31–7.25 (m, 4 H), 7.22–7.17 (m, 2 H), 4.34 (s, 1 H), 4.15 (qq, *J* = 10.8, 7.1 Hz, 2 H), 2.17 (s, 1 H), 1.34 (s, 3 H), 1.29 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 144.0, 143.4, 128.3, 128.3, 127.3, 126.9, 126.9, 126.8, 70.1, 60.5, 48.3, 45.8, 21.9, 18.0, 14.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}NO_2$ (M+H) 310.1802, found 310.1809.



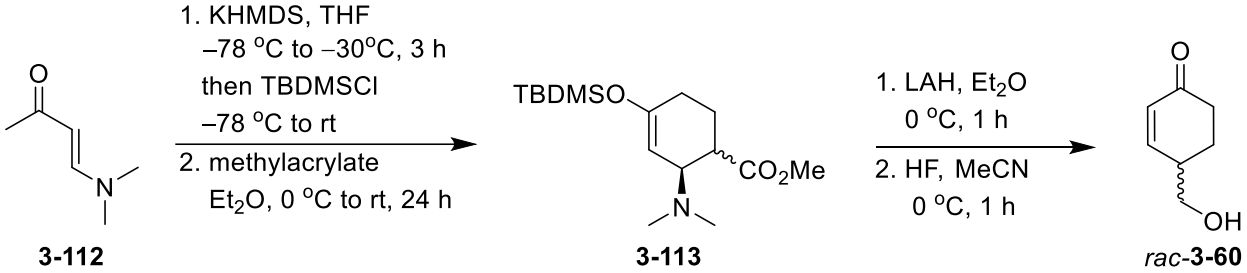
(±)-Ethyl (1S,3a*R*,6a*S*)-2-benzyl-3,3,5-trimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (3-103). A flame dried microwave tube was charged with *N*-methylmaleimide (146 mg, 1.29 mmol) and **3-59** (0.100 g, 0.429 mmol) in dry PhMe (1.4 mL). The mixture was sparged with argon under sonication for 2 min before being sealed under argon and placed in a preheated (135 °C) aluminum block for 18 h. The heat was then turned off and the reaction was allowed to warm to ambient temperature in block slowly. The reaction was then concentrated and the residue purified by chromatography on SiO_2 (gradient, 19:1 to 1:1

hexanes/EtOAc) to afford **3-103** (101 mg, 68%) as a colorless solid: R_f = 0.41 (1:1 hexanes/EtOAc, UV active); Mp 122-124 °C; ATR-IR (neat) 2969, 1694, 1433, 1379, 1284, 1129, 1021, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2 H), 7.25–7.15 (m, 3 H), 3.79 (d, *J* = 13.6 Hz, 1 H), 3.90–3.69 (m, 3 H), 3.46 (d, *J* = 14.6 Hz, 1 H), 3.44 (d, *J* = 17.3 Hz, 1 H), 2.96 (s, 3 H), 2.88 (d, *J* = 8.2 Hz, 1 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 175.9, 170.3, 139.1, 128.6, 127.8, 126.9, 66.9, 63.9, 60.9, 54.3, 51.1, 45.6, 24.9, 24.6, 21.2, 13.7; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}N_2O_4$ (M+H) 245.1809, found 345.1806.



(±)-Ethyl (2*R*,4*S*)-1-benzyl-4-cyano-5,5-dimethylpyrrolidine-2-carboxylate (3-106). A flame dried microwave tube was charged with **3-59** (0.100 g, 0.429 mmol) in dry PhMe (1.4 mL). The mixture was sparged with nitrogen under sonication for 2 min before addition of acrylonitrile [MEHQ removed by Brockmann 1 basic alumina and degassed with N_2 sparging (69.6 mg, 87 µL, 1.29 mmol)] The mixture was sealed under argon and placed in a preheated (135 °C) aluminum block for 18 h. The heat was then turned off and the reaction was allowed to warm to ambient temperature in block slowly. The reaction was then concentrated and the residue purified by chromatography on SiO_2 (gradient, 19:1 to 1:1 hexanes/EtOAc) to afford **3-106** (25.1 mg, 20%) as a clear oil: R_f = 0.61 (1:1 hexanes/EtOAc, UV active); ATR-IR (neat) 2975, 2238, 1728, 1452, 1368, 1187, 1150, 1027, 749, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 4 H), 7.22–7.17 (m, 1 H), 3.92 (d, *J* = 14.2 Hz, 1 H), 3.84 (q, *J* = 7.2 Hz, 2 H), 3.69 (d, *J* = 14.3 Hz, 1 H), 3.55 (dd, *J* = 9.2, 6.1 Hz, 1 H), 2.80 (dd, *J* = 8.4, 6.7 Hz, 1 H), 2.51 (dt, *J* = 13.5, 8.8 Hz, 1 H), 2.23 (dt,

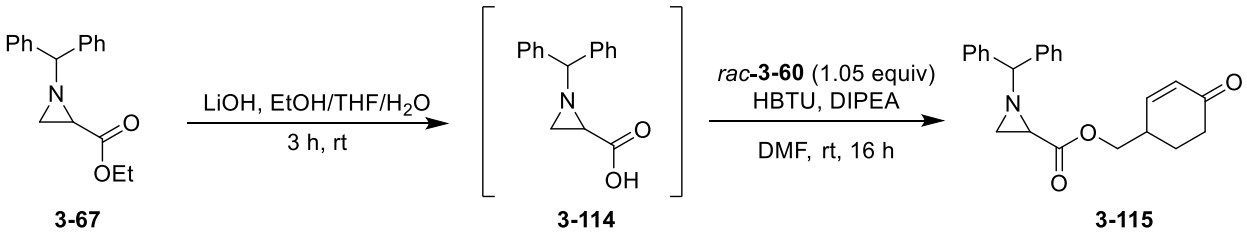
J = 13.2, 6.4 Hz, 1 H), 1.38 (s, 3 H), 1.22 (s, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.00, 138.98, 128.32, 128.06, 126.97, 119.86, 63.69, 62.54, 60.70, 49.98, 40.23, 31.02, 23.37, 23.18, 13.85; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}N_2O_2$ (M+H) 287.1754, found 287.1751.



3-112 **3-113** ***rac*-3-60**

4-(Hydroxymethyl)cyclohex-2-en-1-one (*rac*-3-60).[153] A flame dried flask was charged with solid KHMDS (1.95 g, 9.28 mmol) in the glove box. The solid was then dissolved in distilled THF (35 mL, 0.25 M) and the solution cooled to −78°C on a dry-ice/acetone bath. This cooled mixture was treated with *trans*-4-(dimethylamino)-3-buten-2-one (1.00 g, 8.84 mmol) as a solution in distilled THF (8.9 mL, 1.0 M) over a period of 30 min (syringe pump). The mixture was then allowed to warm to −30 °C over 30 min before being cooled back down to −78 °C and treated with TBDMSCl (1.48 g, 7.72) as a solution in THF (7.7mL, 1.0 M). The reaction was warmed to ambient temperature before being diluted with diethyl ether and passed through a pad of celite and concentrated to afford the aminosiloxydiene in good purify for the next step. A flame dried flask was charged with this siloxydiene (2.00 g, 8.79 mmol) in distilled Et_2O (11 mL, 0.8 M) and the yellow solution was cooled to 0 °C on an ice-bath before being treated with deinhibited (Brockann 1 basic alumina) methyl acrylate (1.53 g, 1.60 mL, 17.6 mmol) dropwise by syringe under nitrogen. The reaction was warmed slowly to ambient temperature and stirred for 24 h. The reaction was then concentrated and re-dissolved in ether and polish filtered through a 1" pad of silica. Concentration of the eluent afforded the crude cycloadduct (2.32 g) as a 1.3:1 mixture of exo:endo products containing 10 mass % TBDMSCl. This crude material was dissolved in distilled THF (17

mL). The mixture was cooled to 0 °C on an ice-bath before dropwise addition of LAH 1M in Et_2O (10.9 mL, 10.9 mmol) over 30 min. The reaction stirred for an additional 30 min at this temperature before being diluted with ether (30 mL) and quenched by addition of water (3.3 mL; 0.3 mL/mmol LAH) dropwise by syringe with good ventilation. This turbid mixture was then warmed to ambient temperature before addition of anhydrous Na_2SO_4. The inorganics were removed by filtration and the ethereal portion was concentrated to afford the desired alcohol as a colorless oil which was used in the next step without further purification. This material (1.67 g, 5.38 mmol) was taken up in MeCN (5.4 mL, 1 M) and cooled to 0 °C on an ice-bath. To this cooled mixture was added 10% HF in MeCN (2.5 mL, 2.2 mL/mmol) dropwise by syringe over 3 min. Upon addition of HF, the reaction mixture turned colorless to yellow. The reaction was warmed to ambient temperature and stirred for 1.5 h with monitoring by TLC. Upon completion of the reaction, the reaction mixture was loaded directly on to a column layered with sodium sulfate for purification by chromatography on SiO2 (isocratic, diethyl ether) to *rac*-**3-60** (645 mg, 59% over 4 steps) as a viscous clear oil which matched literature spectra: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10–6.04 (m, 1 H), 3.78–3.64 (m, 2 H), 2.69–2.59 (m, 1 H), 2.55 (dt, *J* = 16.8, 4.7 Hz, 1 H), 2.40 (ddd, *J* = 16.9, 12.6, 5.1 Hz, 1 H), 2.14 (dqd, *J* = 13.4, 4.9, 1.4 Hz, 1 H), 1.82 (tdd, *J* = 12.9, 9.7, 4.5 Hz, 1 H), 1.69 (d, *J* = 5.0 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 151.1, 130.4, 77.3, 76.7, 65.3, 39.0, 36.6, 25.4.

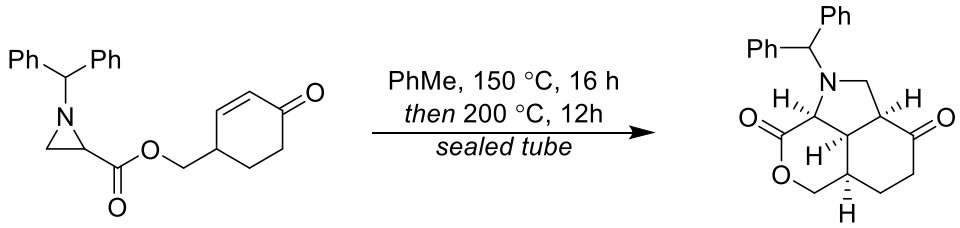


3-67 **3-114** **3-115**

(4-Oxocyclohex-2-en-1-yl)methyl 1-benzhydrylaziridine-2-carboxylate (3-115). Ethyl 1-benzhydrylaziridine-2-carboxylate (0.350 g, 1.24 mmol) was suspended in EtOH (1.24 mL) and cooled to 0 °C on an ice-bath. Bench grade THF was added until dissolution of the starting material

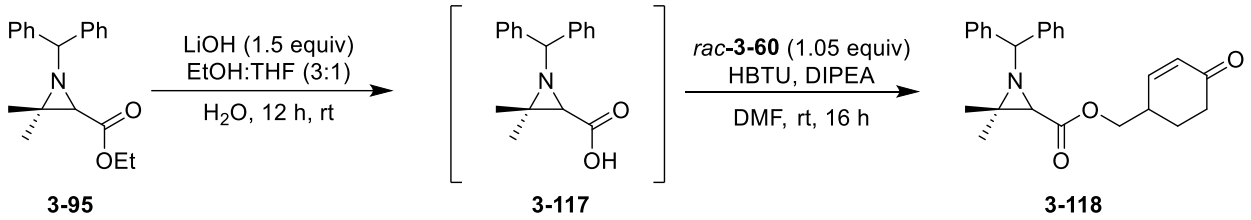
was visualized (about 300 µL). Lithium hydroxide monohydrate (79.9 mg, 1.87 mmol) was added in one portion followed by a drop of water. The reaction was stirred while warming to ambient temperature. After about 3 h the reaction mixture had seized and the white solid was slurried in ether and collected by filtration. The solids were washed with ether, dried on the filter, then dissolved in 6 mL of water and to it was added and equal volume of half-saturated aqueous citric acid resulting in a formation of a white precipitate. Methylene chloride was added, and the two layers were transferred to a separatory funnel. The organic layer was separated, and the aqueous layer extracted with methylene chloride (2 x 25 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated to afford an oil which foamed to a light colorless solid under high vacuum. This material was charged into a flame-dried vial with HBTU (383 mg, 0.999 mmol), and DIPEA (258 mg, 330 µL, 2.00 mmol) in dry DMF (2.5 mL, 0.4 M). The mixture was stirred for 30 min at ambient temperature before *rac*-**3-60** (139 mg, 1.10 mmol) was added as a solution in dry DMF (1 mL). Stirring was continued for 16 h at which point the reaction was diluted with diethyl ether 100 mL and washed with water (2 x 25 mL), brine (25 mL), dried (MgSO4), filtered, and concentrated to afford a yellow oil which was purified by chromatography on SiO_2 (gradient, 1:1 to 0:1 hexanes/Et_2O) to afford **1** (275 mg, 61%) as a colorless solid**:** R_f = 0.41 (1:1 hexanes/EtOAc, UV active); Mp 91.5–93 °C; ATR-IR (neat) 3062, 3028, 2953, 1742, 1677, 1177, 749, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 4 H), 7.34–7.21 (m, 6 H), 6.79–6.74 (m, 1 H), 6.05 (dt, *J* = 10.2, 3.0 Hz, 1 H), 4.29–4.05 (m, 2 H), 3.62 (s, 1 H), 2.80–2.73 (m, 1 H), 2.53 (ddt, *J* = 17.2, 8.8, 4.7 Hz, 1 H), 2.42–2.32 (m, 2 H), 2.28 (ddd, *J* = 6.4, 3.2, 1.1 Hz, 1 H), 2.11–2.02 (m, 1 H), 1.88 (d, *J* = 6.4 Hz, 1 H), 1.75 (qdd, *J* = 12.9, 9.7, 4.5 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$, 1:1 diastereomers) δ 198.8, 198.8, 170.4, 170.4, 149.5, 149.4, 142.5, 142.2,

130.7, 128.5, 128.5, 127.5, 127.4, 127.2, 127.1, 77.9, 77.9, 66.3, 66.3, 37.9, 37.9, 36.5, 35.9, 35.9, 35.1, 35.1, 25.6, 25.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{24}NO_3$ (M+H) 362.1751, found 362.1760.



3-115 **3-116**

(±)–(2a*S*,2a1*R*,5a*R*,8a*S*)-1-Benzhydryloctahydro-3*H*-pyrano[3,4,5-cd] isoindole-3,8 (1*H*)-dione (3-116). A flame dried 30 mL microwave vial was charged with **3-115** (0.100 g, 0.277 mmol) in distilled PhMe (9.2 mL, 0.03 M), and the mixture was sparged with nitrogen under sonication for 2 min before the vial was sealed and placed in a preheated aluminum block (150 °C) for 34 h. At this point the reaction was directly purified by chromatography on SiO_2 (gradient, 0:1 to 1:9 acetone/CH_2Cl_2) to afford **3-116 (**40 mg, 40%) as an off-white solid: R_f = 0.75 (9:1 CH_2Cl_2/acetone, UV active); Mp 195–196 °C; ATR-IR (neat) 3058, 3025, 2900, 1737, 1709, 1493, 1453, 1125, 1072, 750, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 9 H), 7.24–7.18 (m, 1 H), 5.52 (s, 1 H), 4.39 (dd, *J* = 11.0, 6.7 Hz, 1 H), 4.20 (dd, *J* = 11.0, 2.7 Hz, 1 H), 3.46 (dd, *J* = 9.8, 3.7 Hz, 1 H), 3.43 (d, *J* = 10.0 Hz, 1 H), 3.19 (td, *J* = 10.1, 7.9 Hz, 1 H), 2.76 (ddd, *J* = 10.5, 6.9, 3.6 Hz, 1 H), 2.50–2.33 (m, 4 H), 2.09 (dtd, *J* = 14.4, 7.0, 4.0 Hz, 1 H), 1.95 (dtd, *J* = 14.3, 8.3, 5.8 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 171.4, 141.7, 137.7, 130.2, 128.1, 128.1, 127.6, 127.5, 126.8, 69.3, 66.1, 60.7, 48.3, 47.3, 40.5, 36.6, 32.6, 22.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{24}NO_3$ (M+H) 362.1751, found 362.1751.

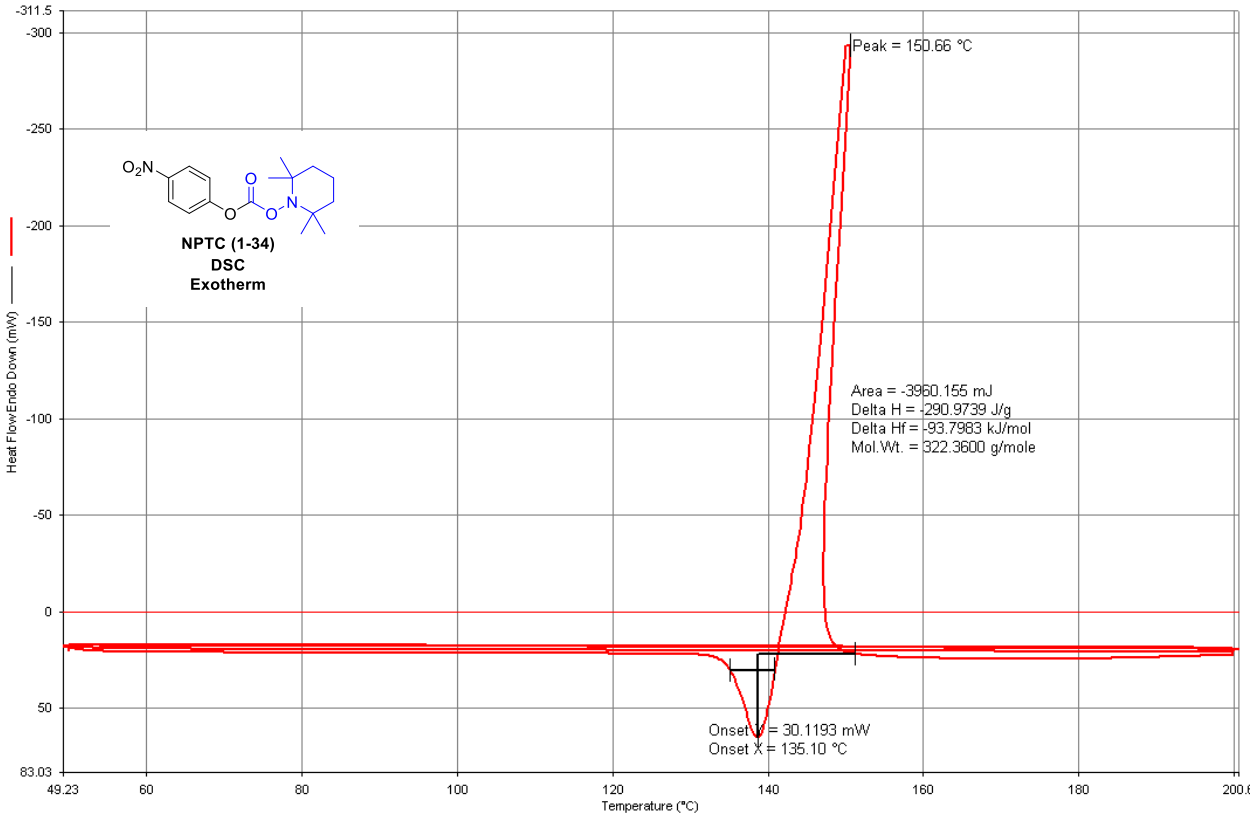


3-95 **3-117** **3-118**

(4-Oxocyclohex-2-en-1-yl)methyl 1-benzhydryl-3,3-dimethylaziridine-2-carboxylate (3-118). 3-95 (0.400 g, 1.29 mmol) was dissolved in 3:1 EtOH/THF (2.0 mL:0.60 mL) and cooled to 0 °C on an ice-bath. Lithium hydroxide monohydrate (83.0 mg, 1.94 mmol) was added in one portion followed by a 12 drops of water from a glass pipette (about 3 drops/20 mg LiOH). The reaction was stirred while warming to ambient temperature and stirred for 12 h during which time the reaction seized. The solid was transferred to a separatory funnel and half-saturated aqueous citric acid (20 mL) was then added which resulted in a white precipitate. 30 mL of methylene chloride was added to the funnel and the contents was shaken vigorously. The organics were separated, and aqueous layer extracted with methylene chloride (2 x 30 mL) ensuring the aqueous layer remained acidic (pH < 2). The cloudy combined organics were washed with brine (20 mL) resulting in a transparent pale-yellow solution which was dried (Na_2SO_4), filtered, and concentrated to produce an oil which foamed to a solid on the high vacuum. Diethyl ether (10 mL) was added to this foam and swirled under the high vacuum. One more chasing of ether gave the aziridine carboxylic acid as a white solid which was used immediately due to instability. This crude acid (363 mg, 1.29 mmol) was charged into a flame dried vial with HBTU (494 mg, 1.29 mmol) in dry DMF (5.0 mL). The mixture was cooled to 0 °C on an ice-bath before addition of and DIPEA (258 mg, 330 μL, 2.00 mmol). The bath was removed and the mixture was stirred for 30 min at ambient temperature before *rac*-**3-60** (171 mg, 1.36 mmol) was added as a solution in dry DMF (2 mL). Stirring was continued for 16 h at which point the reaction was diluted with ethyl acetate (120 mL) and washed with water (2 x 30 mL), brine (25 mL), dried ($MgSO_4$), filtered,

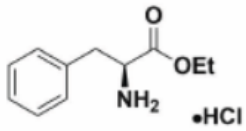
and concentrated to afford a yellow oil which was purified by chromatography on SiO_2 (gradient, 1:0 to 1:1 hexanes/Et_2O) to afford **3-118** (361 mg, 72%) as an off-white solid: R_f = 0.68 (Et_2O, UV active); Mp 95–96 °C; ATR-IR (neat) 3062, 3027, 2956, 2870, 1743, 1678, 1453, 1169, 1134, 748, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.46 (m, 4 H), 7.32–7.16 (m, 6 H), 6.78–6.71 (m, 1 H), 6.03 (ddd, *J* = 10.3, 7.8, 2.5 Hz, 1 H), 4.32 (s, 1 H), 4.18 (dt, *J* = 11.1, 6.1 Hz, 1 H), 4.07 (ddd, *J* = 11.0, 6.5, 2.2 Hz, 1 H), 2.78–2.67 (m, 1 H), 2.52 (ddt, *J* = 12.3, 8.3, 4.4 Hz, 1 H), 2.41–2.31 (m, 1 H), 2.18 (d, *J* = 1.4 Hz, 1 H), 2.10–1.98 (m, 1 H), 1.81–1.62 (m, 1 H), 1.35 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR 126 MHz, $CDCl_3$, 1:1 diastereomers) δ 198.9, 198.9, 170.1, 170.1, 149.7, 149.7, 143.7, 143.3, 130.6, 128.4, 127.4, 127.4, 127.1, 127.0, 126.8, 70.3, 66.0, 66.0, 48.0, 48.0, 46.5, 46.5, 36.5, 36.5, 36.0, 35.9, 25.6, 25.6, 22.1, 18.0, 18.0; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}NO_3$ (M+H) 390.2064, found 390.2056.

APPENDIX A : DSC ANALYSIS OF NPTC (1-34)

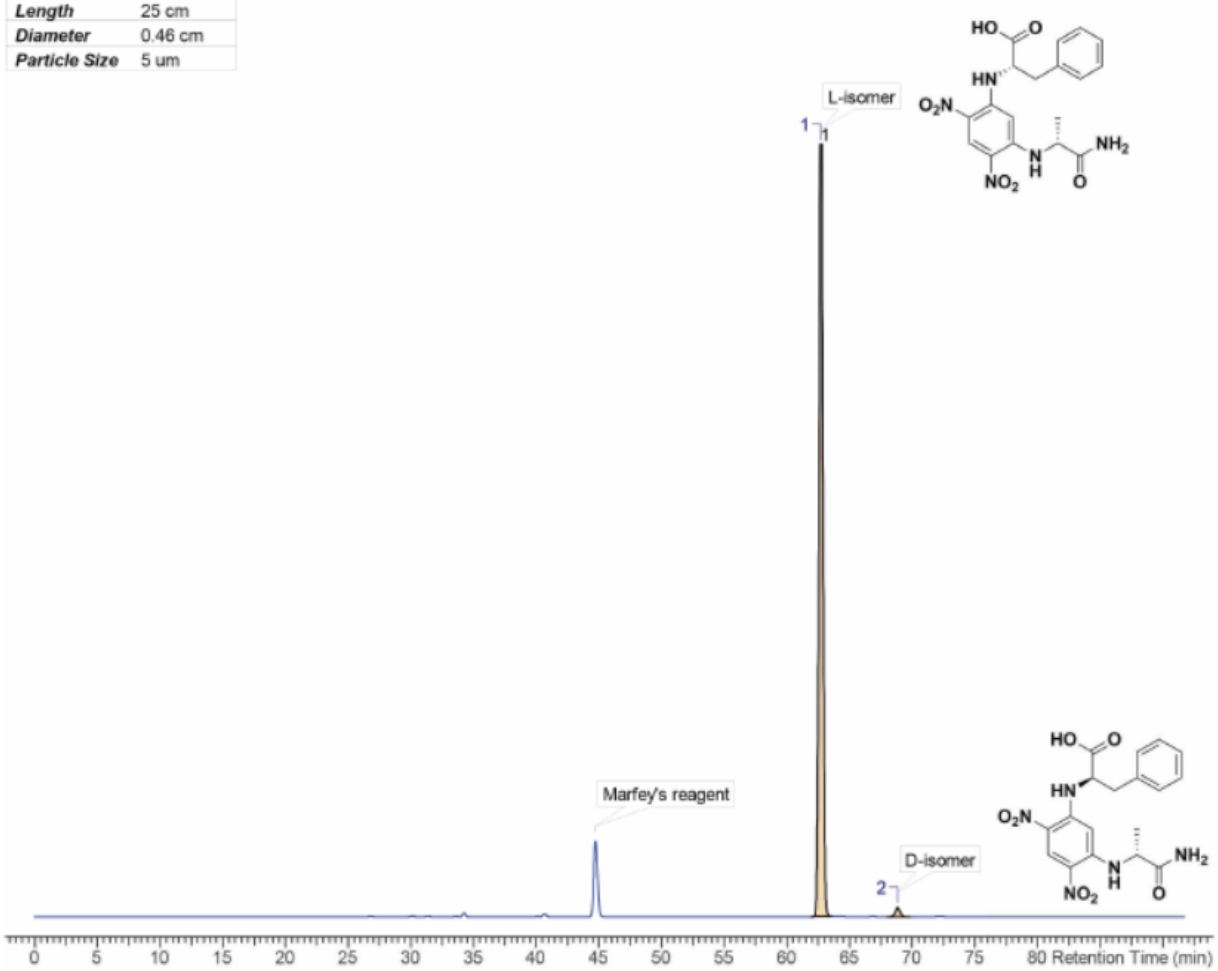

Peak = 150.66 °C
NPTC (1-34)
DSC
Exotherm
Area = -3960.155 mJ
Delta H = -290.9739 J/g
Delta Hf = -93.7983 kJ/mol
Mol.Wt. = 322.3600 g/mole
Onset Y = 30.1193 mW
Onset X = 135.10 °C
Heat Flow Endo Down (mW)
Temperature (°C)
-311.5
-300
-250
-200
-150
-100
-50
0
50
83.03
49.23
60
80
100
120
140
160
180

APPENDIX B : MARFEY'S ANALYSIS OF 2-26

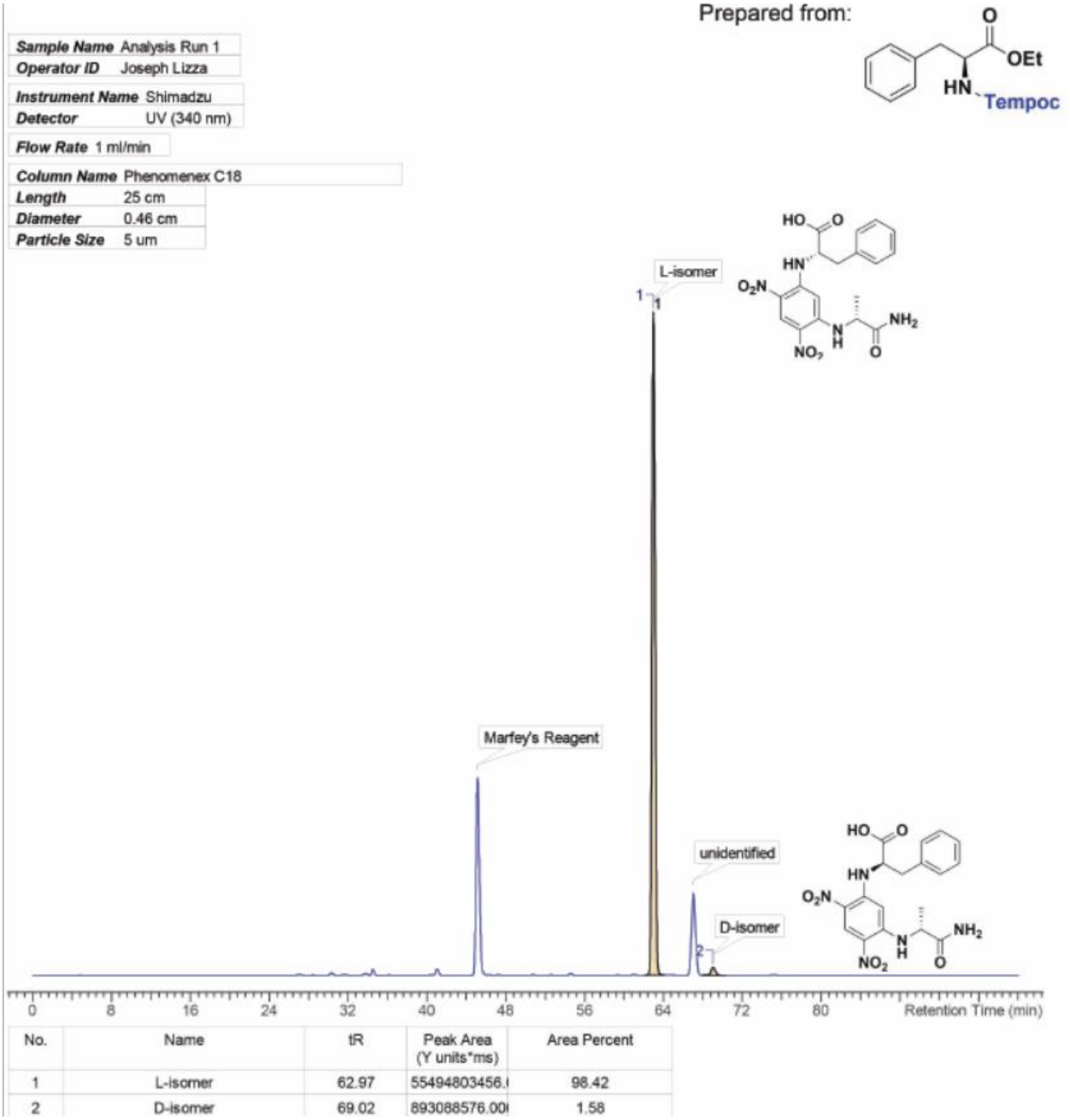
Prepared from:



Sample Name	Analysis Run 1 Control
Operator ID	Joseph Lizza
Instrument Name	Shimadzu
Detector	UV (340 nm)
Flow Rate	1 ml/min
Column Name	Phenomenex C18
Length	25 cm
Diameter	0.46 cm
Particle Size	5 um

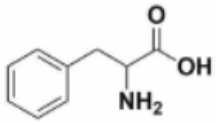


No.	Name	tR	Peak Area (Y units*ms)	Area Percent
1	L-isomer	62.72	85201469440.(	98.46
2	D-isomer	68.82	1335493376.0(	1.54



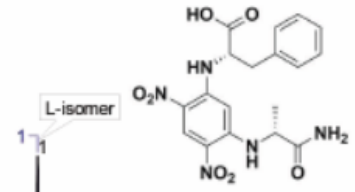
No.	Name	tR	Peak Area (Y units*ms)	Area Percent
1	L-isomer	62.97	55494803456.(	98.42
2	D-isomer	69.02	893088576.00(	1.58

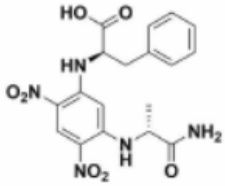
Prepared from:

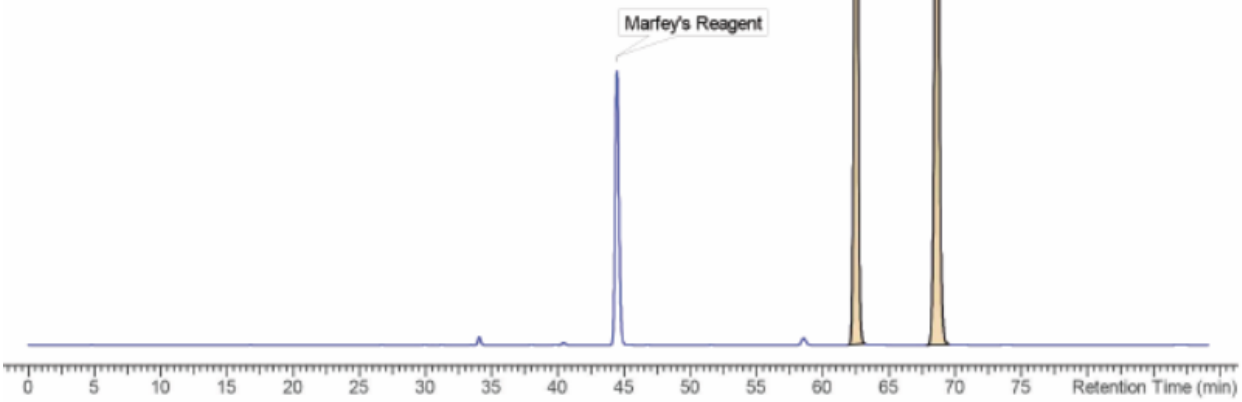


racemic

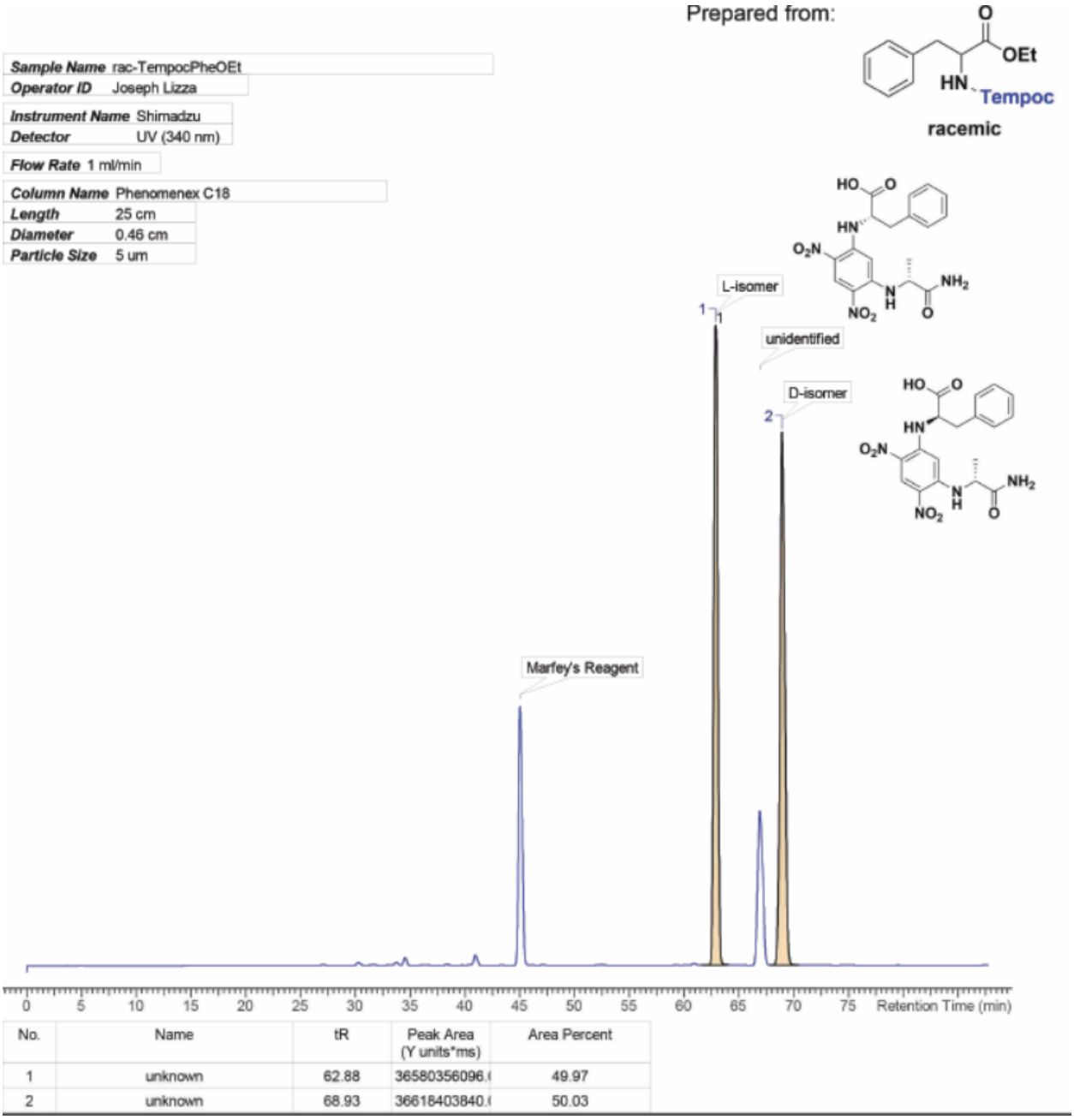
Sample Name	racemic-PheOH-Control
Operator ID	Joseph Lizza
Instrument Name	Shimadzu
Detector	UV (340 nm)
Flow Rate	1 ml/min
Column Name	Phenomenex C18
Length	25 cm
Diameter	0.46 cm
Particle Size	5 um







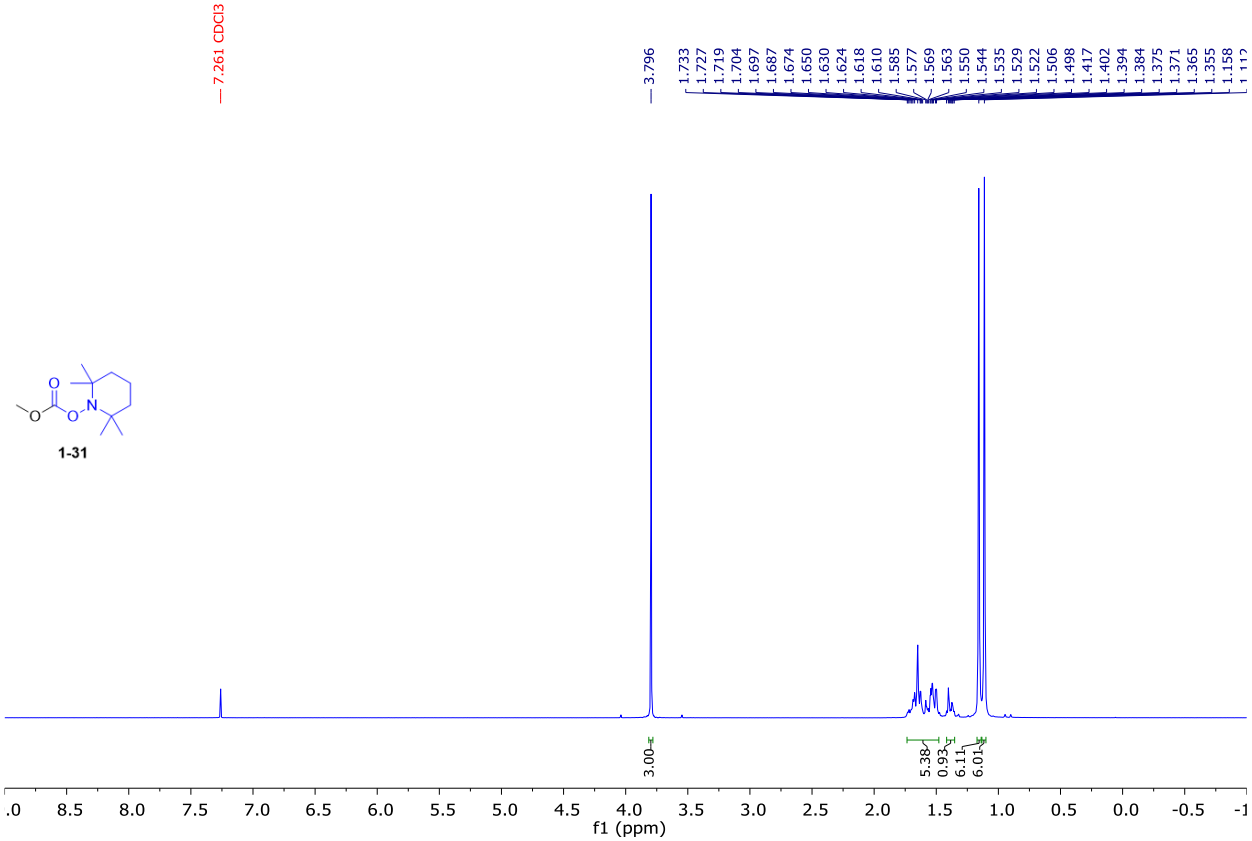
No.	Name	tR	Peak Area (Y units*ms)	Area Percent
1	L-isomer	62.57	43076165632.(	49.61
2	D-isomer	68.62	43761025024.(	50.39



No.	Name	tR	Peak Area (Y units*ms)	Area Percent
1	unknown	62.88	36580356096.(	49.97
2	unknown	68.93	36618403840.(	50.03

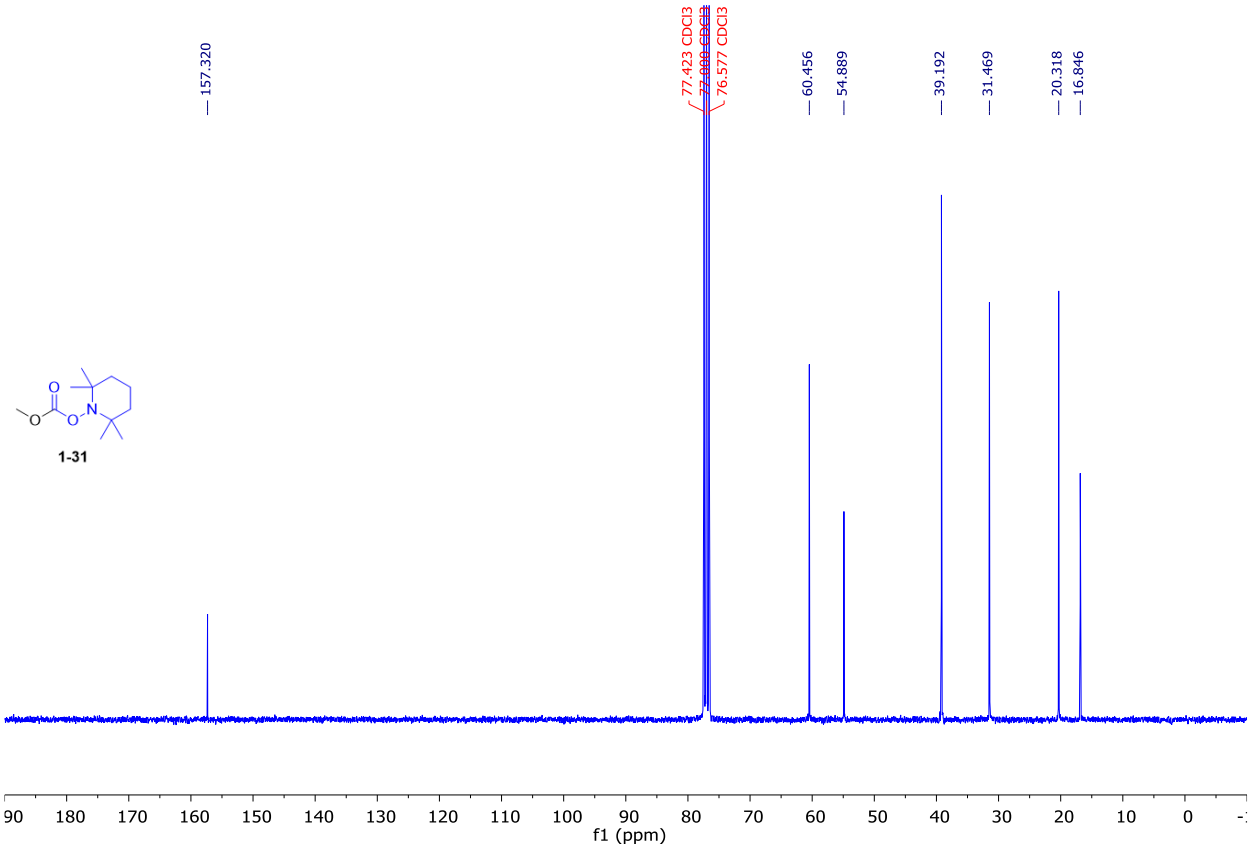
APPENDIX C : SELECTED NMR SPECTRA (CHAPTER 1)

CDCl3 -- 300.23 MHz -- 1H



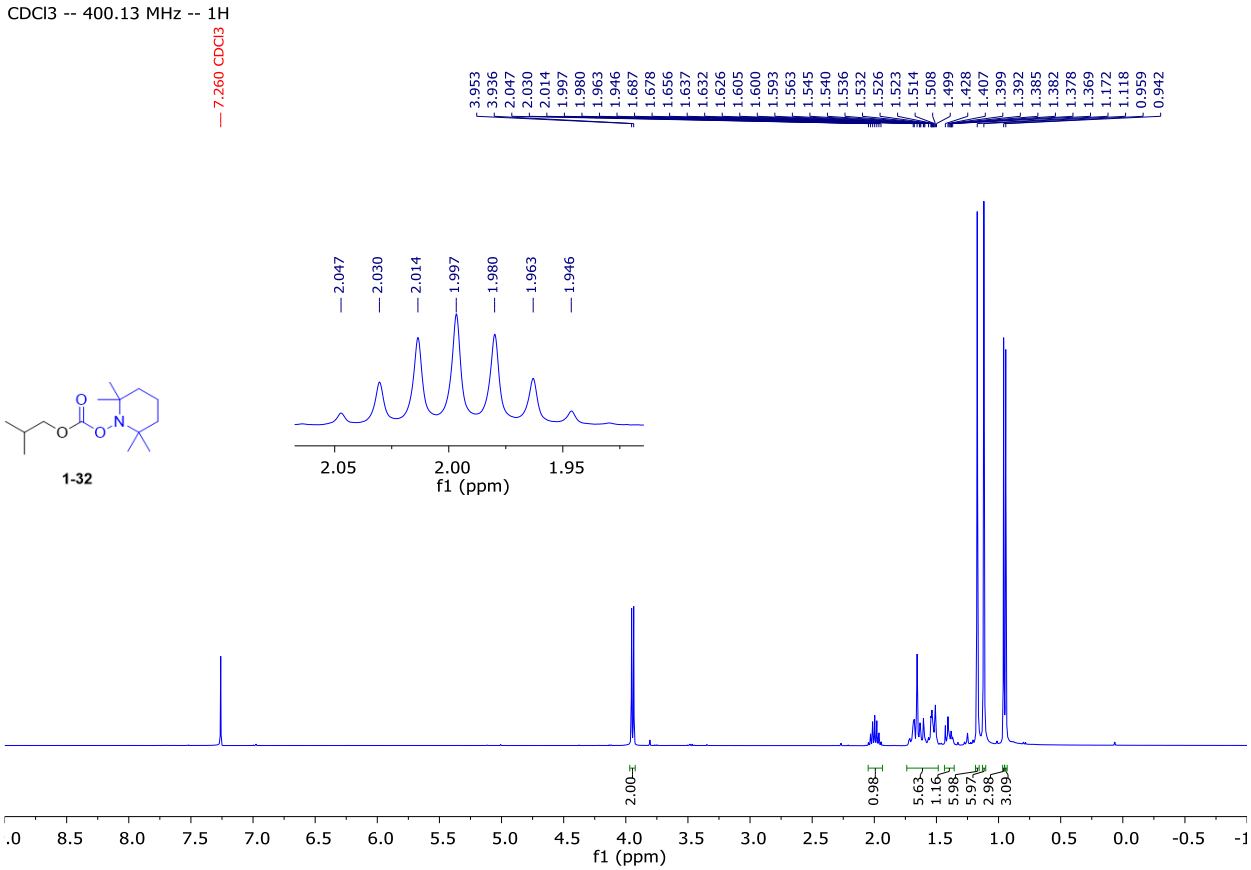
1-31

CDCl3 -- 75.50 MHz -- 13C

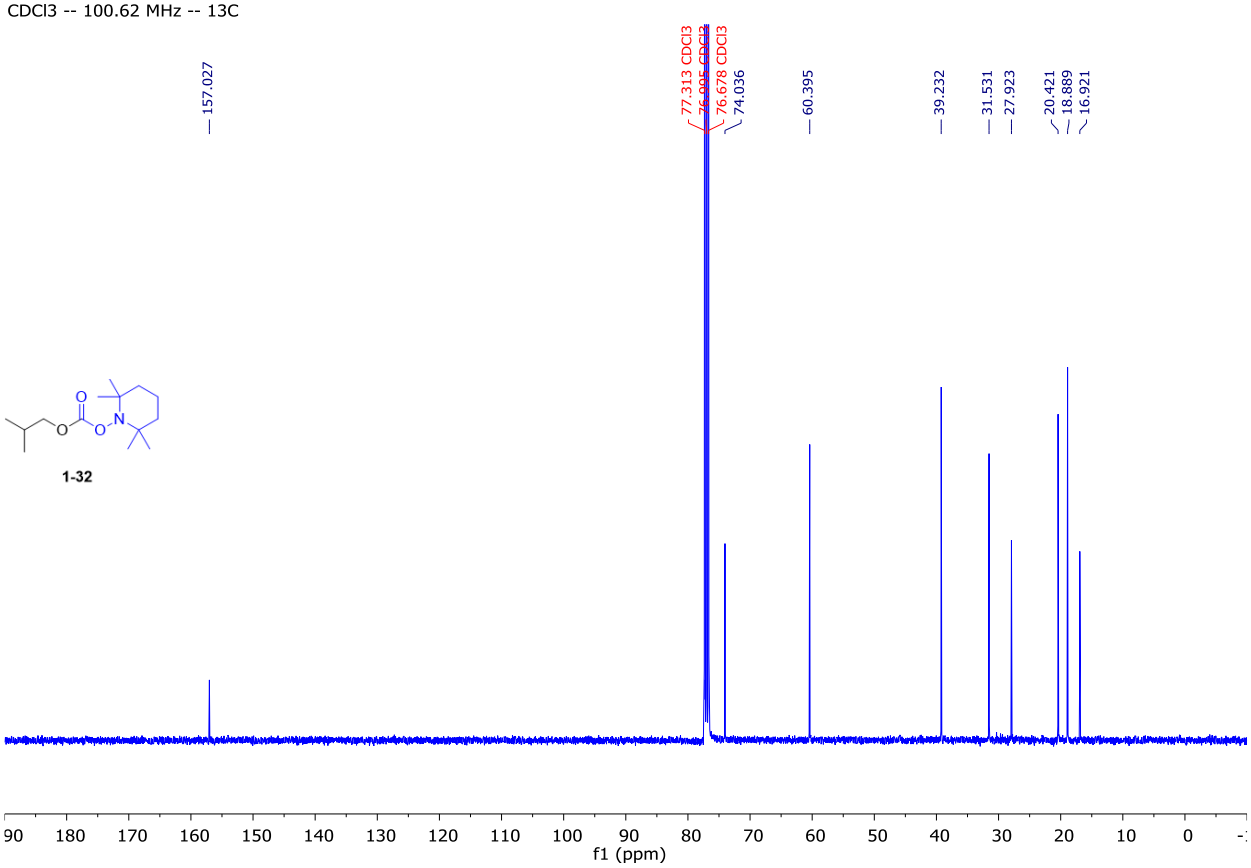


1-31

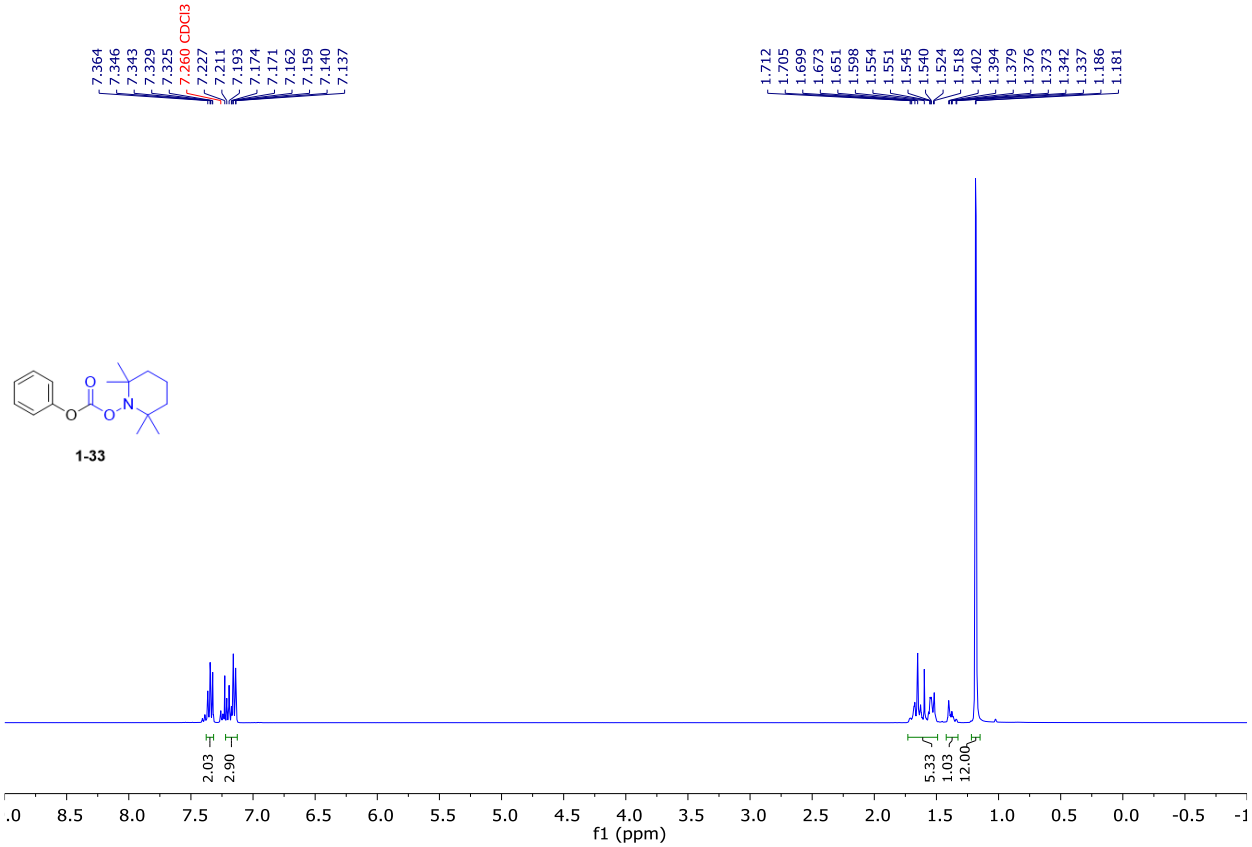
CDCl3 -- 400.13 MHz -- 1H



CDCl3 -- 100.62 MHz -- 13C

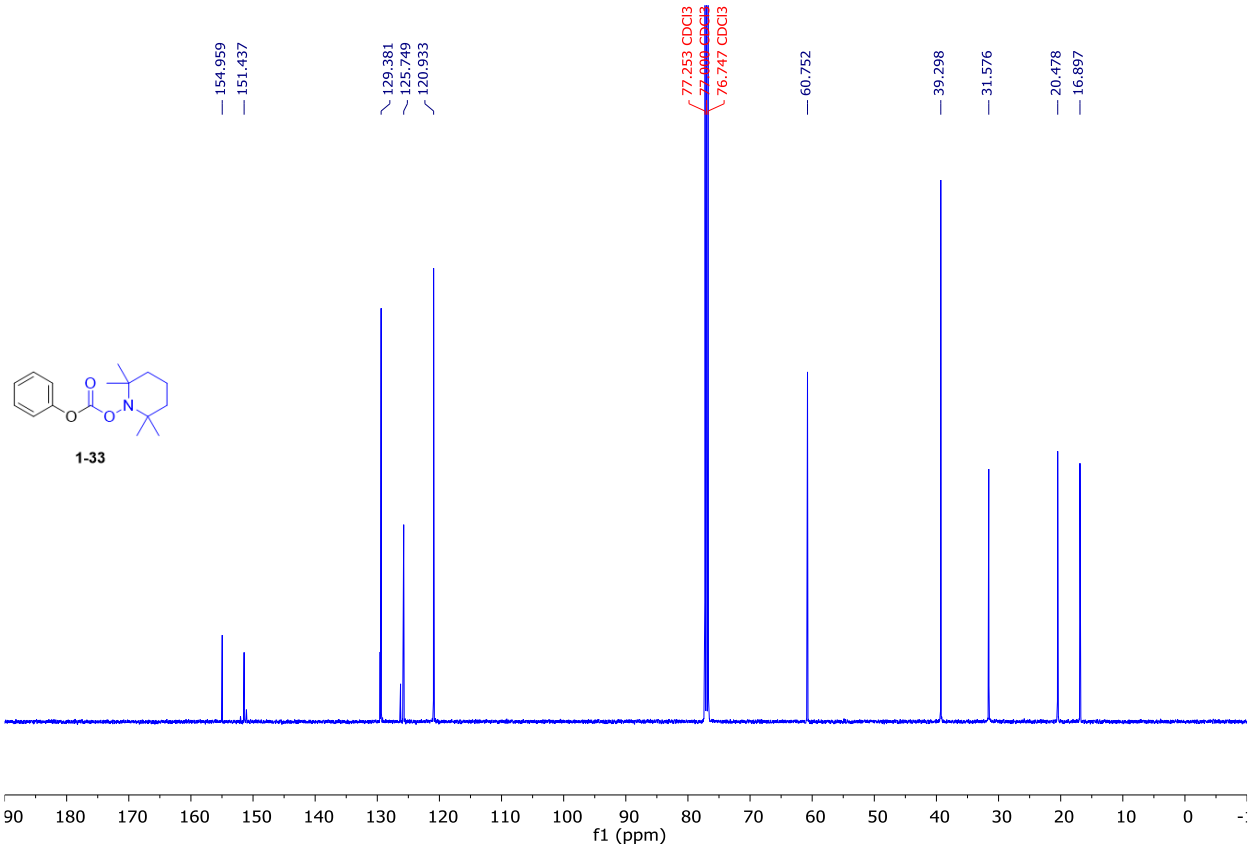


CDCl3 -- 400.13 MHz -- 1H



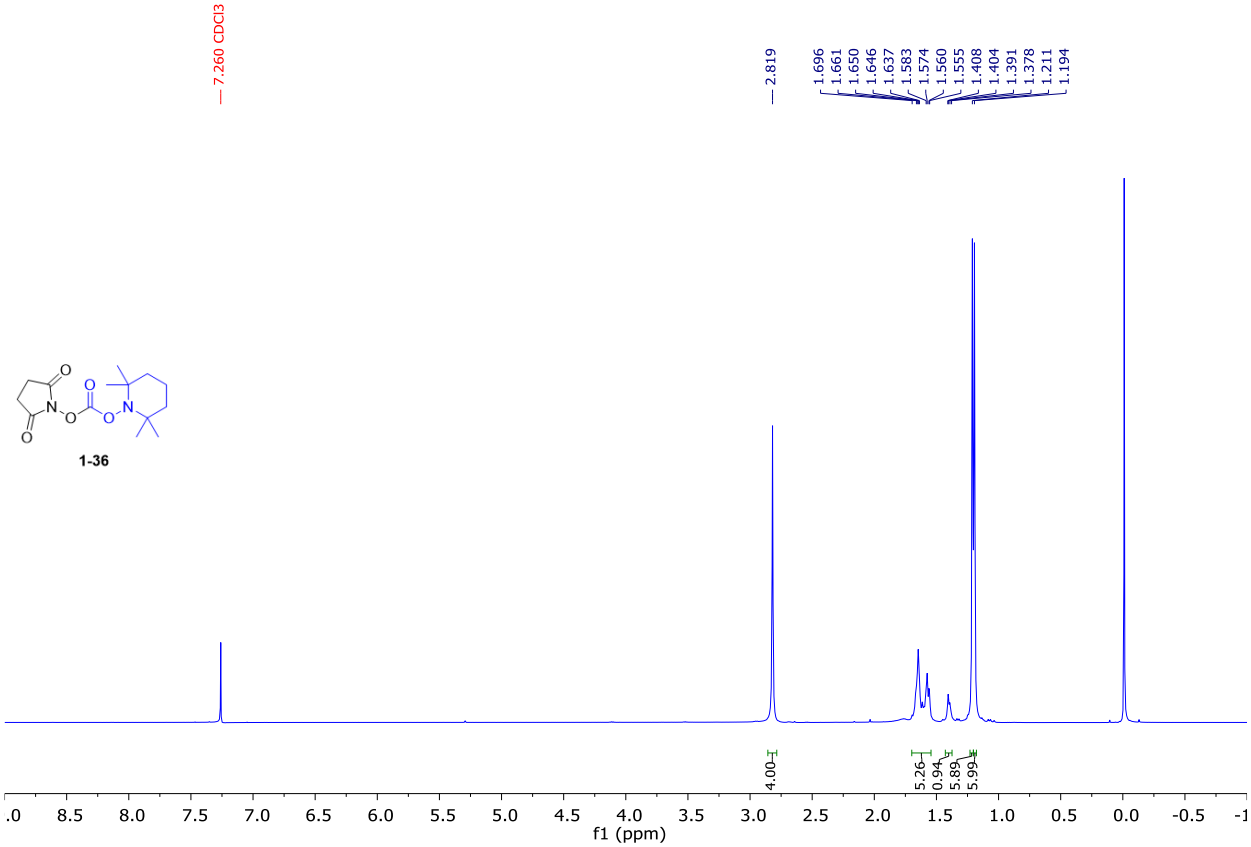
1-33

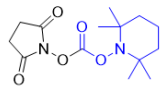
CDCl3 -- 125.78 MHz -- 13C



1-33

CDCl3 -- 500.16 MHz -- 1H



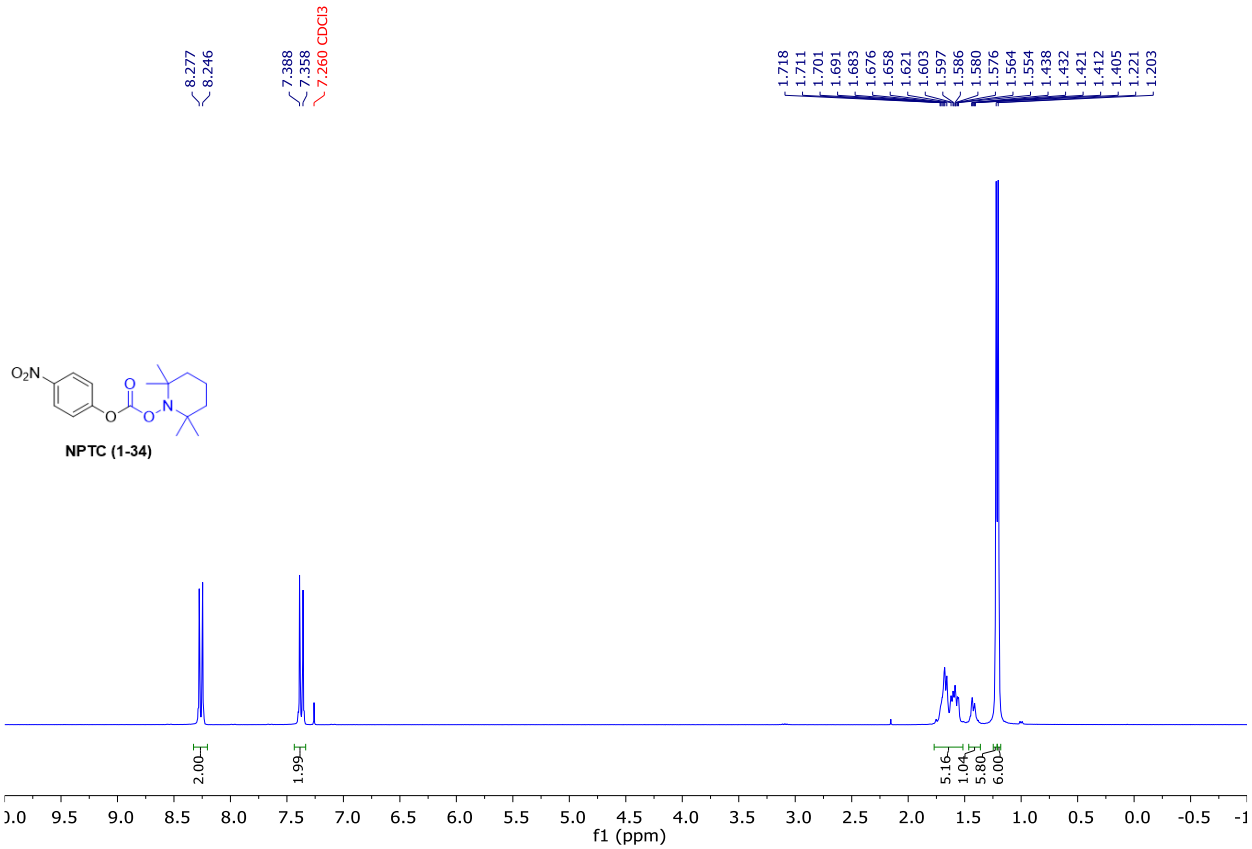


1-36

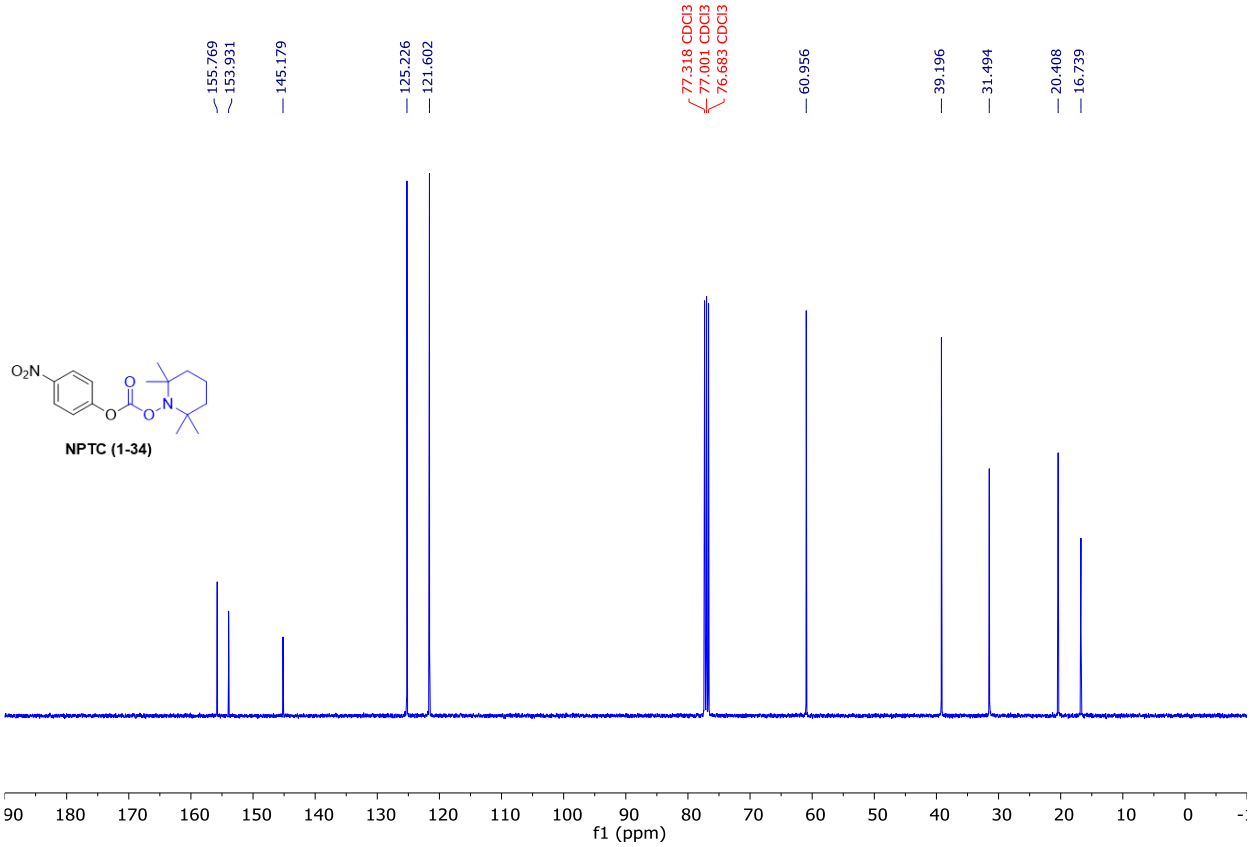
CDCl3 -- 125.78 MHz -- 13C

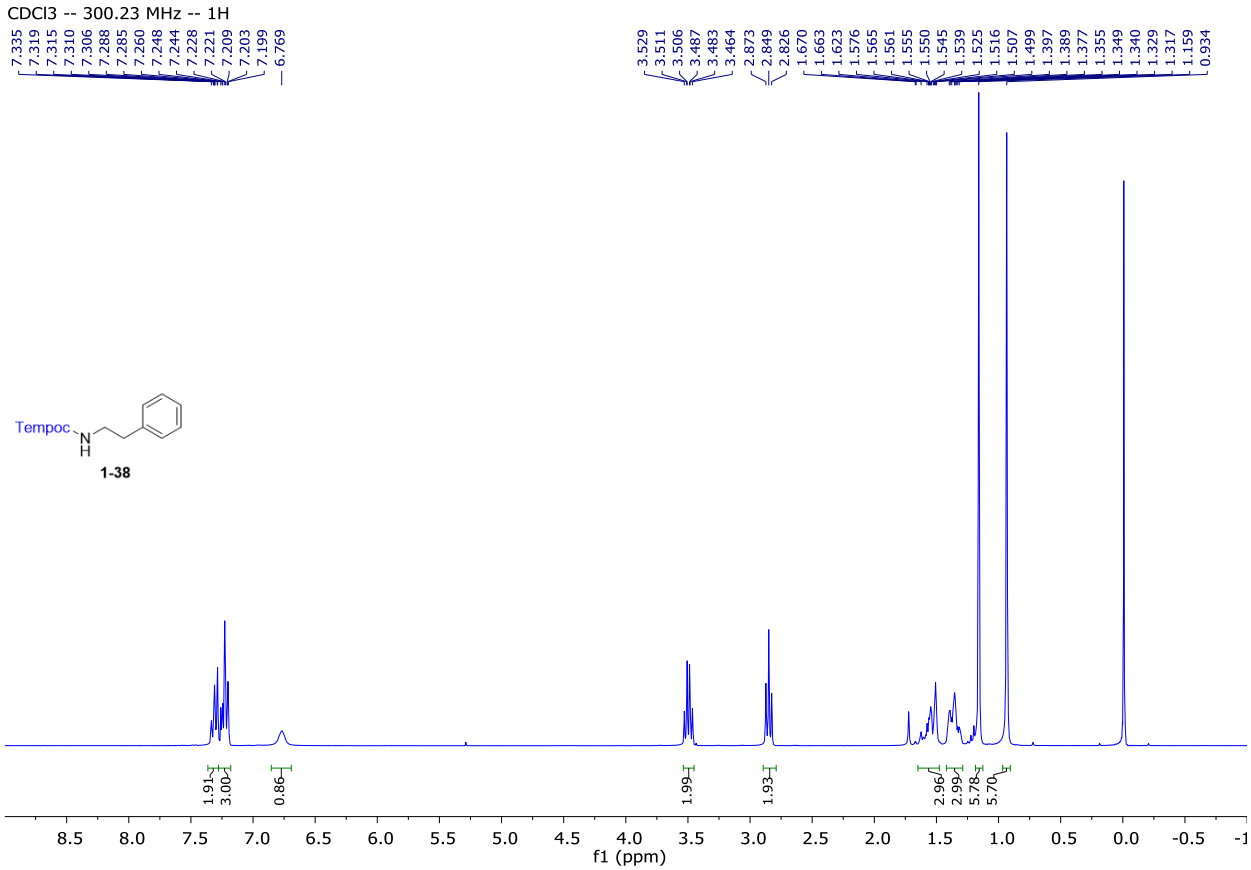
1-36

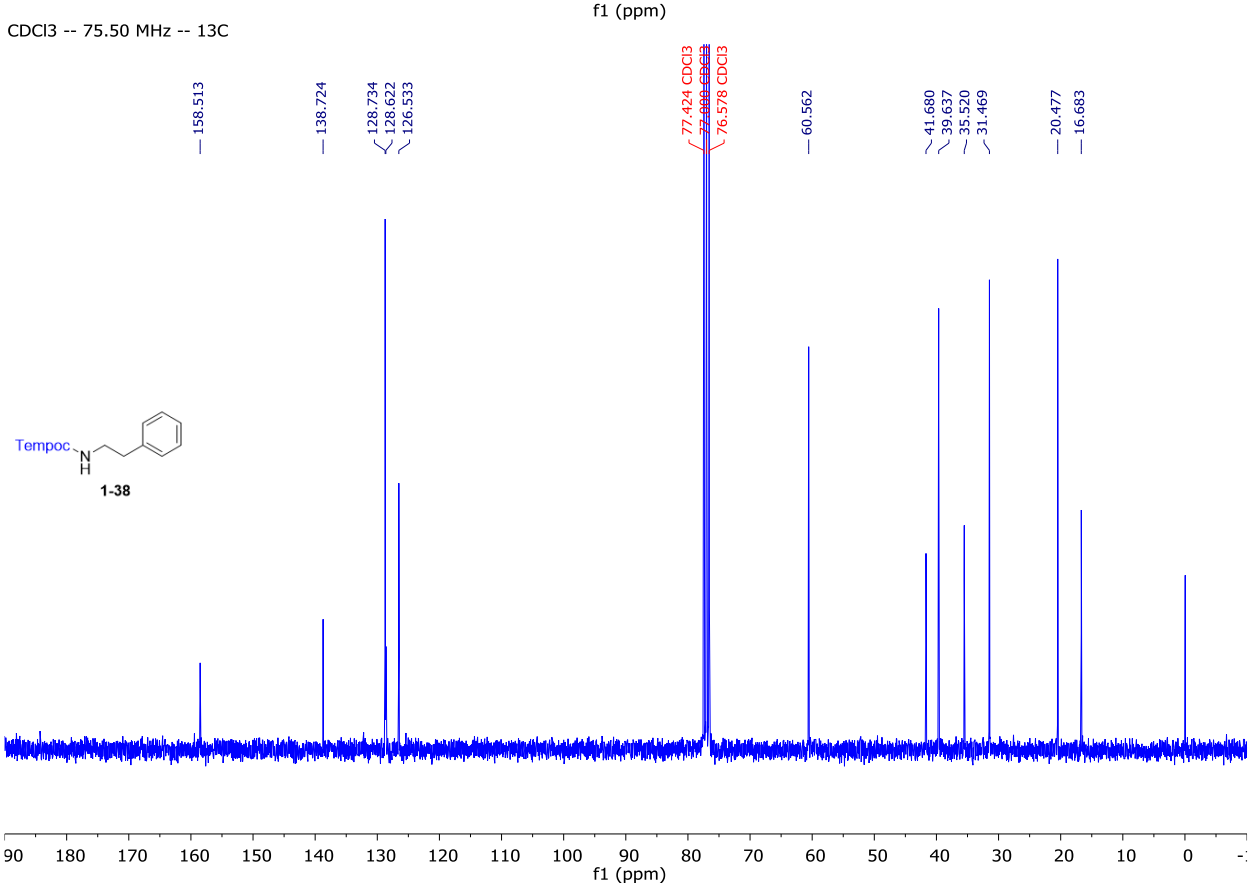
CDCl3 -- 300.23 MHz -- 1H



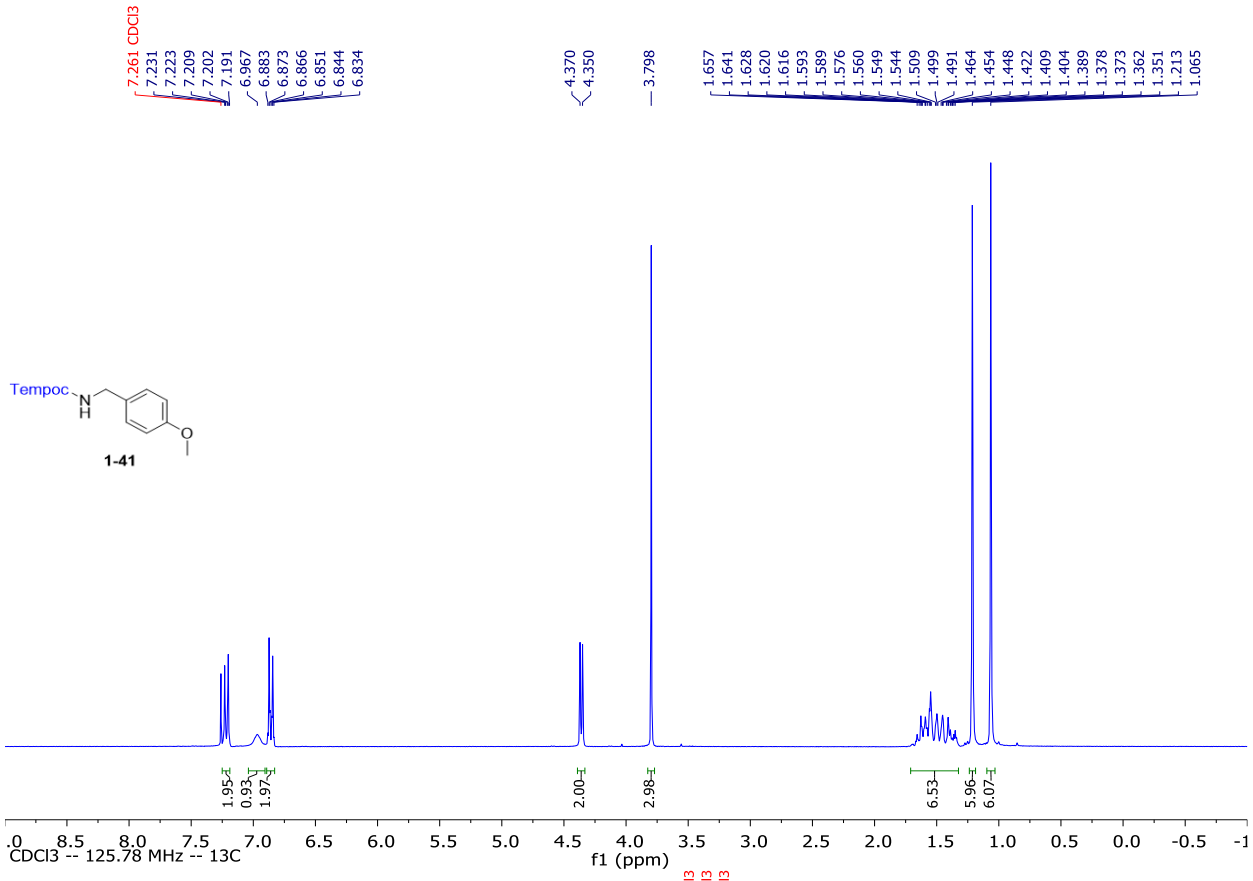
CDCl3 -- 100.62 MHz -- 13C



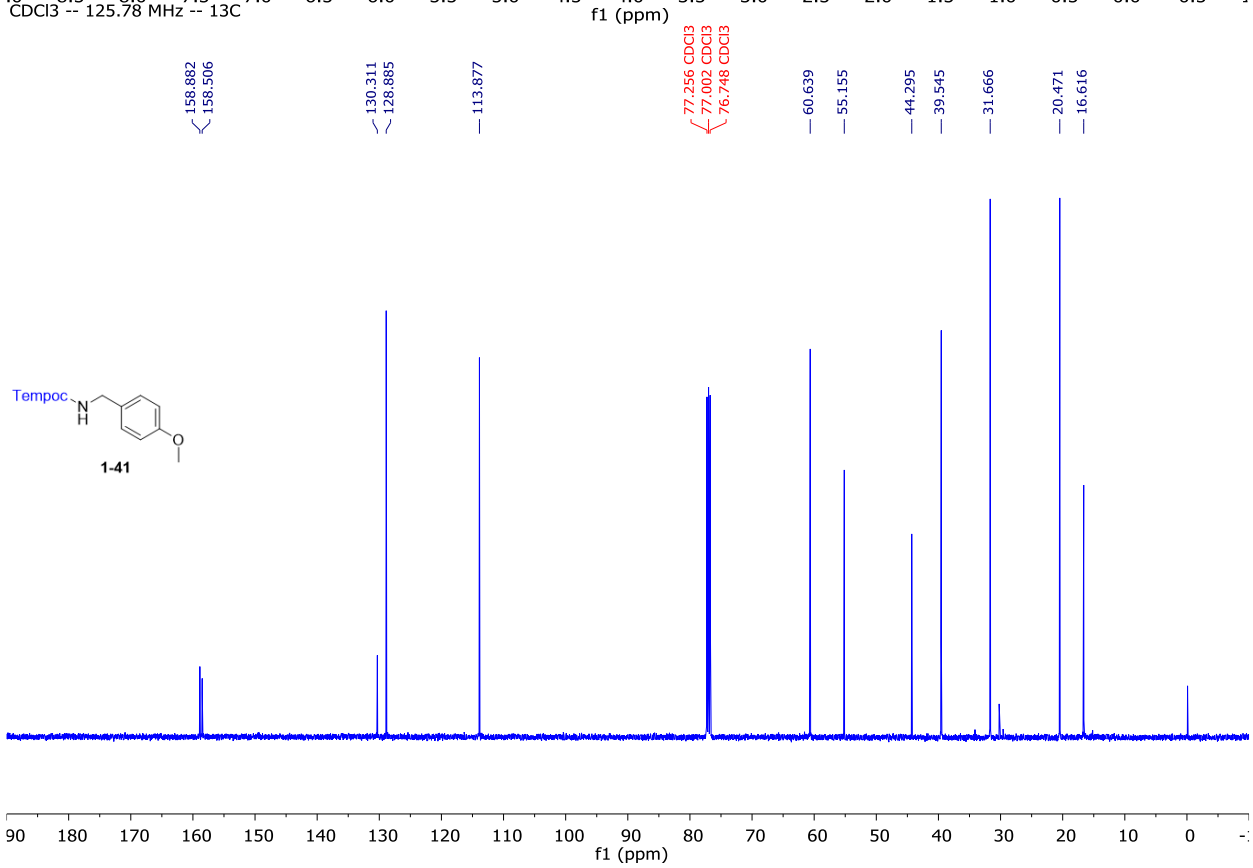

CDCl3 -- 300.23 MHz -- 1H
7.335
7.319
7.315
7.310
7.306
7.288
7.285
7.260
7.248
7.244
7.228
7.221
7.209
7.203
7.199
6.769
3.529
3.511
3.506
3.487
3.483
3.464
2.873
2.849
2.826
1.670
1.663
1.623
1.576
1.565
1.561
1.555
1.550
1.545
1.539
1.525
1.516
1.507
1.499
1.397
1.389
1.377
1.355
1.349
1.340
1.329
1.317
1.159
0.934
Tempoc
N
H
1-38
1.91
3.00
0.86
1.99
1.93
2.96
2.99
5.78
5.70
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

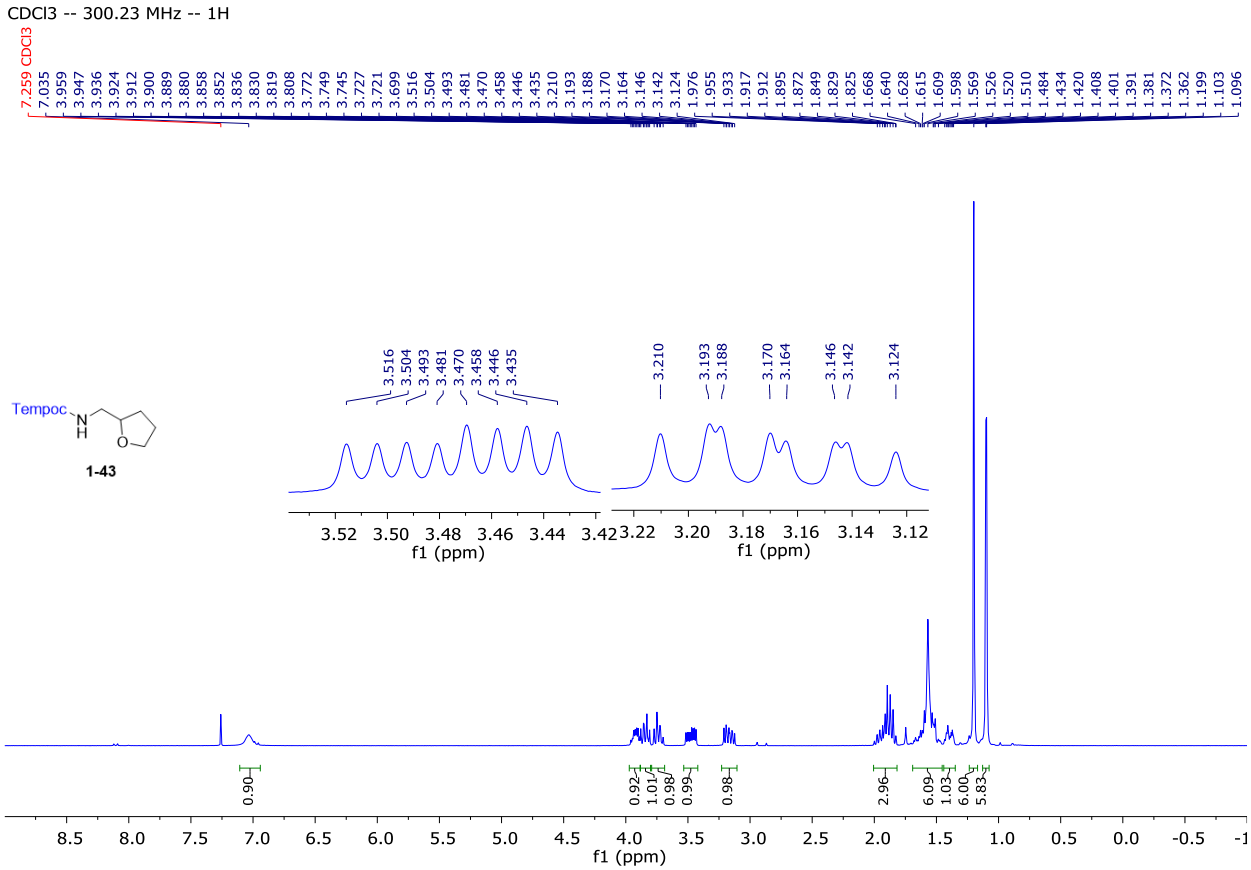

CDCl3 -- 75.50 MHz -- 13C
158.513
138.724
128.734
128.622
126.533
77.424 CDCl3
76.578 CDCl3
60.562
41.680
39.637
35.520
31.469
20.477
16.683
Tempoc
N
H
1-38
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

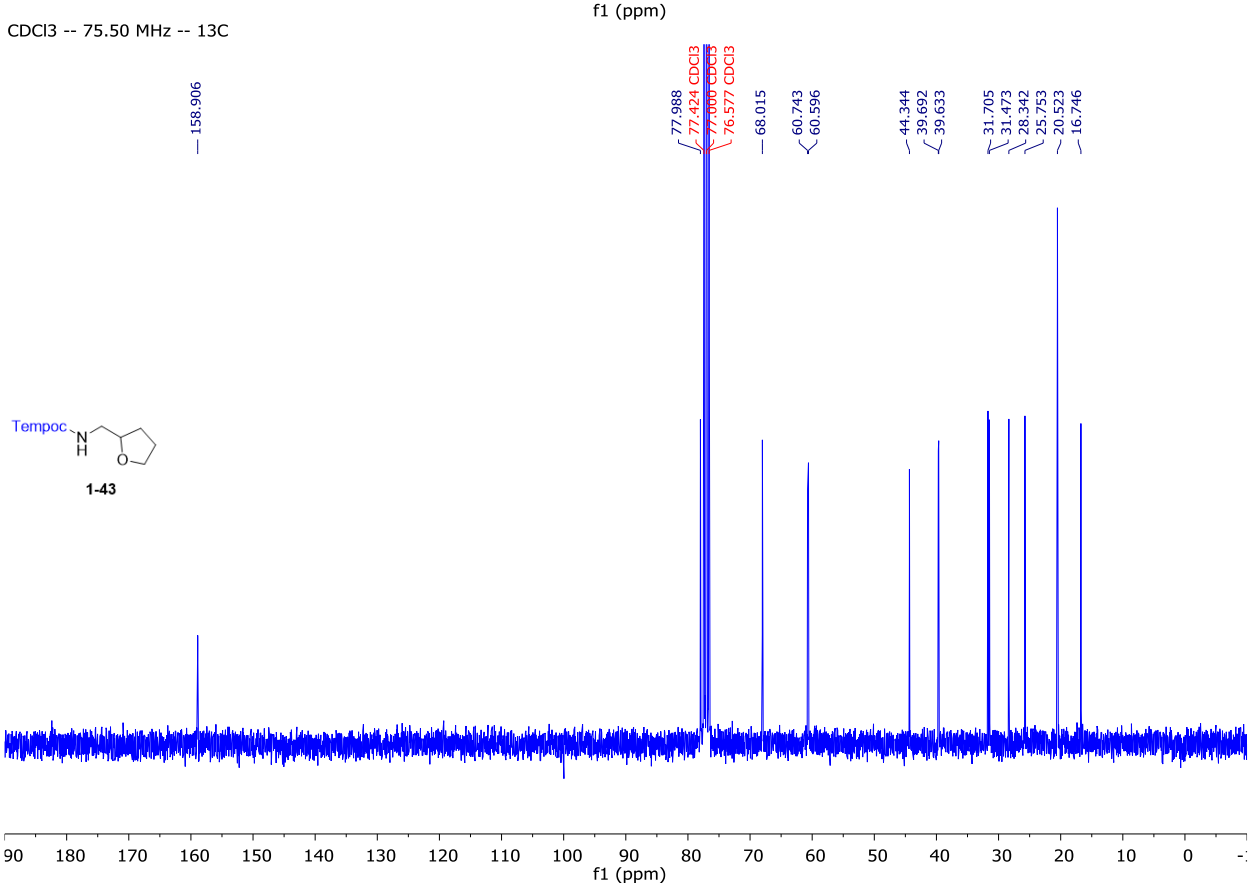
CDCl3 -- 300.23 MHz -- 1H

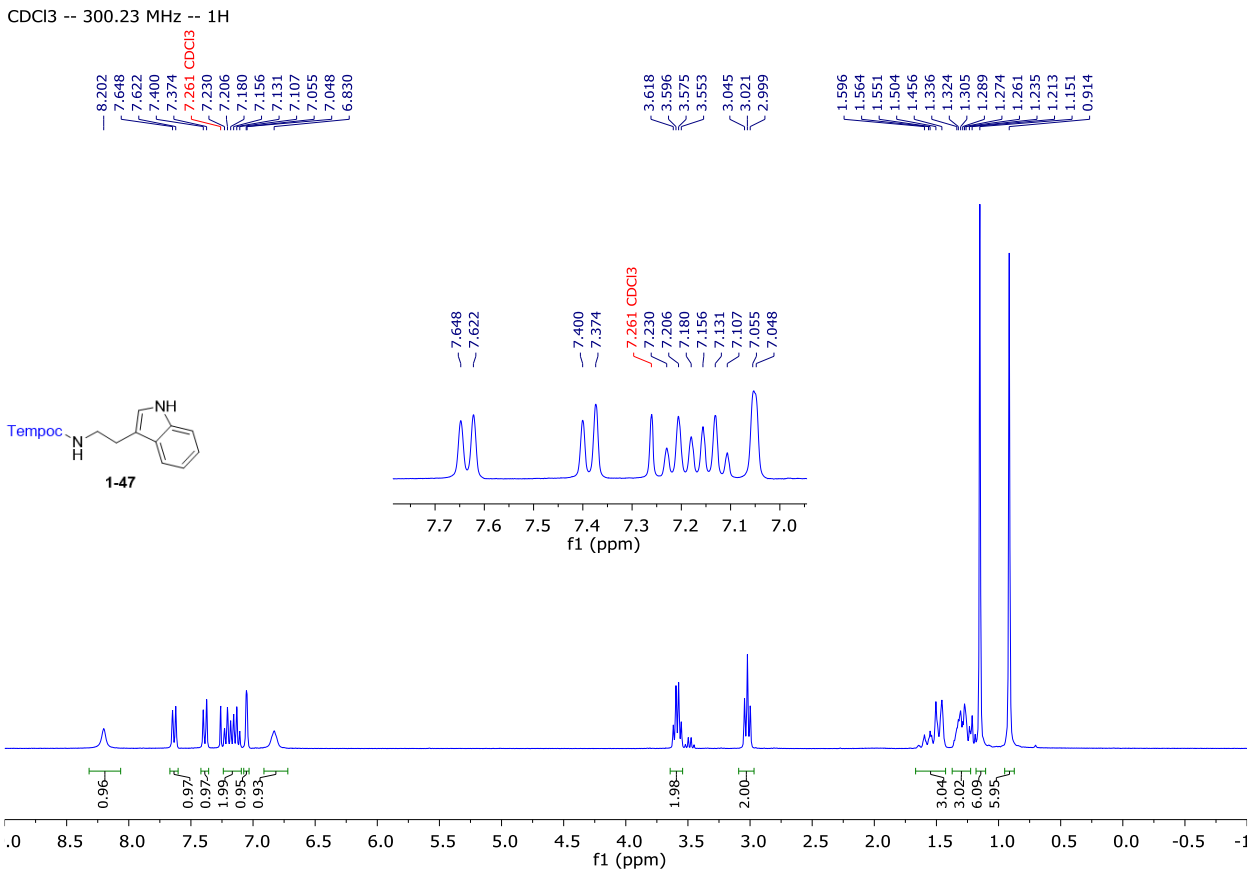


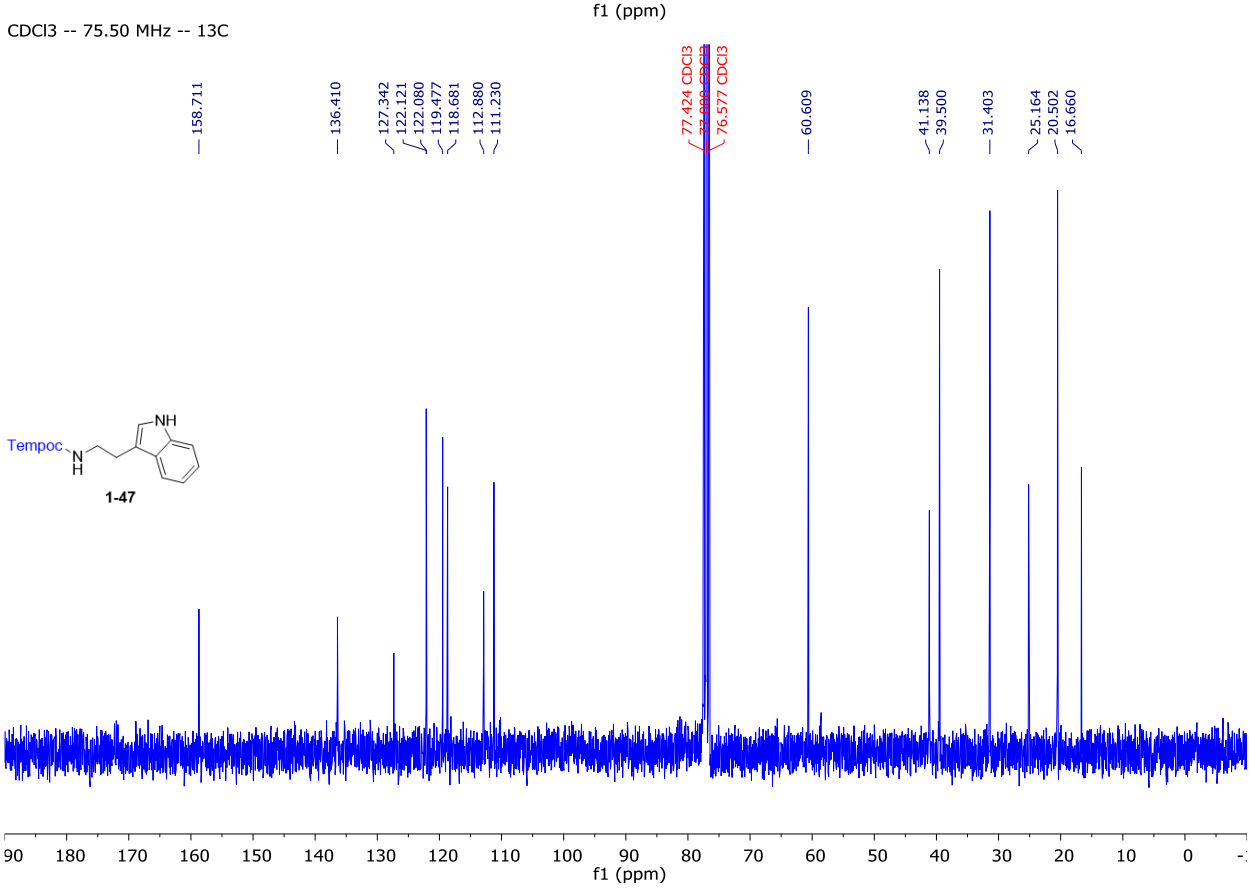
CDCl3 -- 125.78 MHz -- 13C



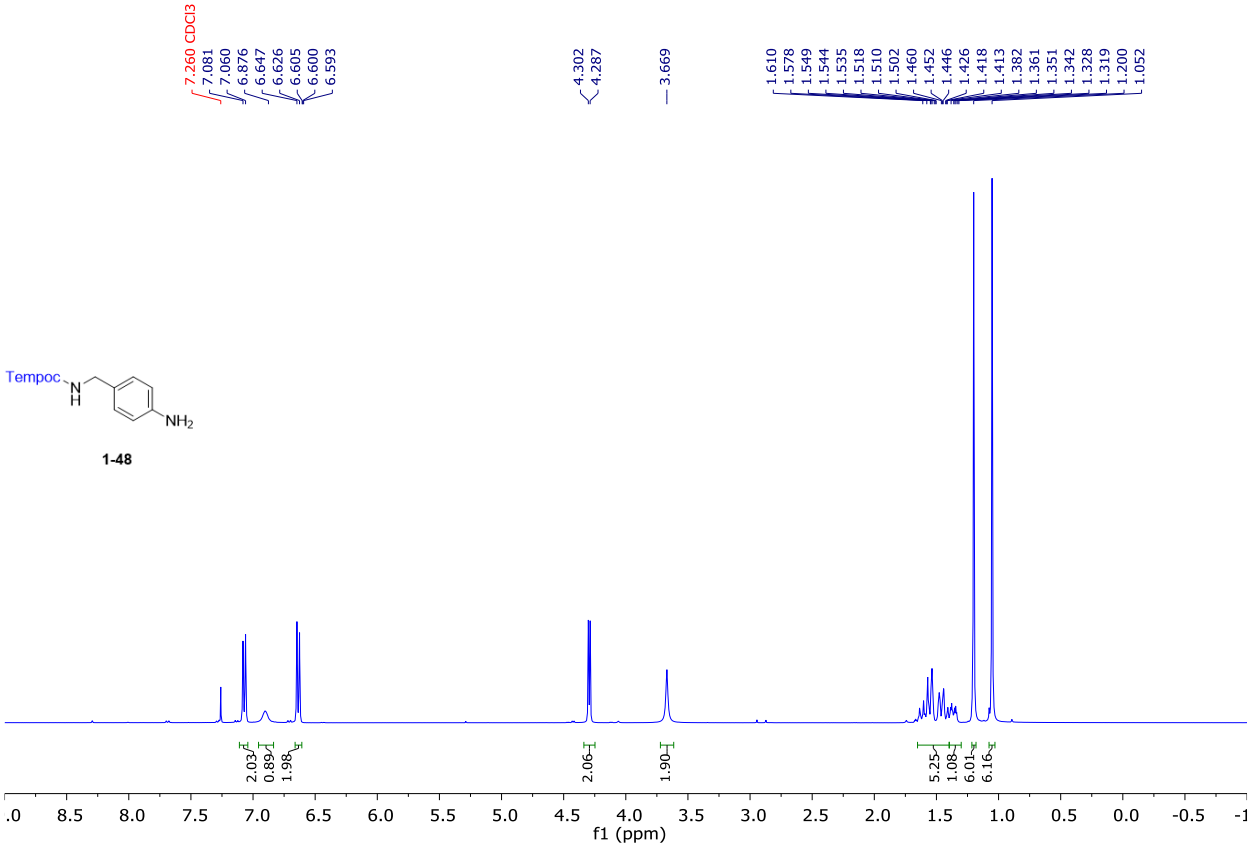

CDCl3 -- 300.23 MHz -- 1H
7.259 CDCl3
7.035
3.959
3.947
3.936
3.924
3.912
3.900
3.889
3.880
3.858
3.852
3.836
3.830
3.819
3.808
3.772
3.749
3.745
3.727
3.721
3.699
3.516
3.504
3.493
3.481
3.470
3.458
3.446
3.435
3.210
3.193
3.188
3.170
3.164
3.146
3.142
3.124
1.976
1.955
1.933
1.917
1.912
1.895
1.872
1.849
1.829
1.825
1.668
1.640
1.628
1.615
1.609
1.598
1.569
1.526
1.520
1.510
1.484
1.434
1.420
1.408
1.401
1.391
1.381
1.372
1.362
1.199
1.103
1.096
Tempoc
N
H
O
1-43
3.52 3.50 3.48 3.46 3.44 3.42
f1 (ppm)
3.22 3.20 3.18 3.16 3.14 3.12
f1 (ppm)
0.90
0.92
1.01
0.98
0.99
0.98
2.96
6.09
1.03
6.00
5.83
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


CDCl3 -- 75.50 MHz -- 13C
158.906
77.988
77.424 CDCl3
77.000 CDCl3
76.577 CDCl3
68.015
60.743
60.596
44.344
39.692
39.633
31.705
31.473
28.342
25.753
20.523
16.746
Tempoc
N
H
O
1-43
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CDCl3 -- 300.23 MHz -- 1H
8.202
7.648
7.622
7.400
7.374
7.261 CDCl3
7.230
7.206
7.180
7.156
7.131
7.107
7.055
7.048
6.830
3.618
3.596
3.575
3.553
3.045
3.021
2.999
1.596
1.564
1.551
1.504
1.456
1.336
1.324
1.305
1.289
1.274
1.261
1.235
1.213
1.151
0.914
Tempoc
NH
N
H
1-47
f1 (ppm)
0.96
0.97
0.97
1.99
0.95
0.93
1.98
2.00
3.04
3.02
6.09
5.95
f1 (ppm)

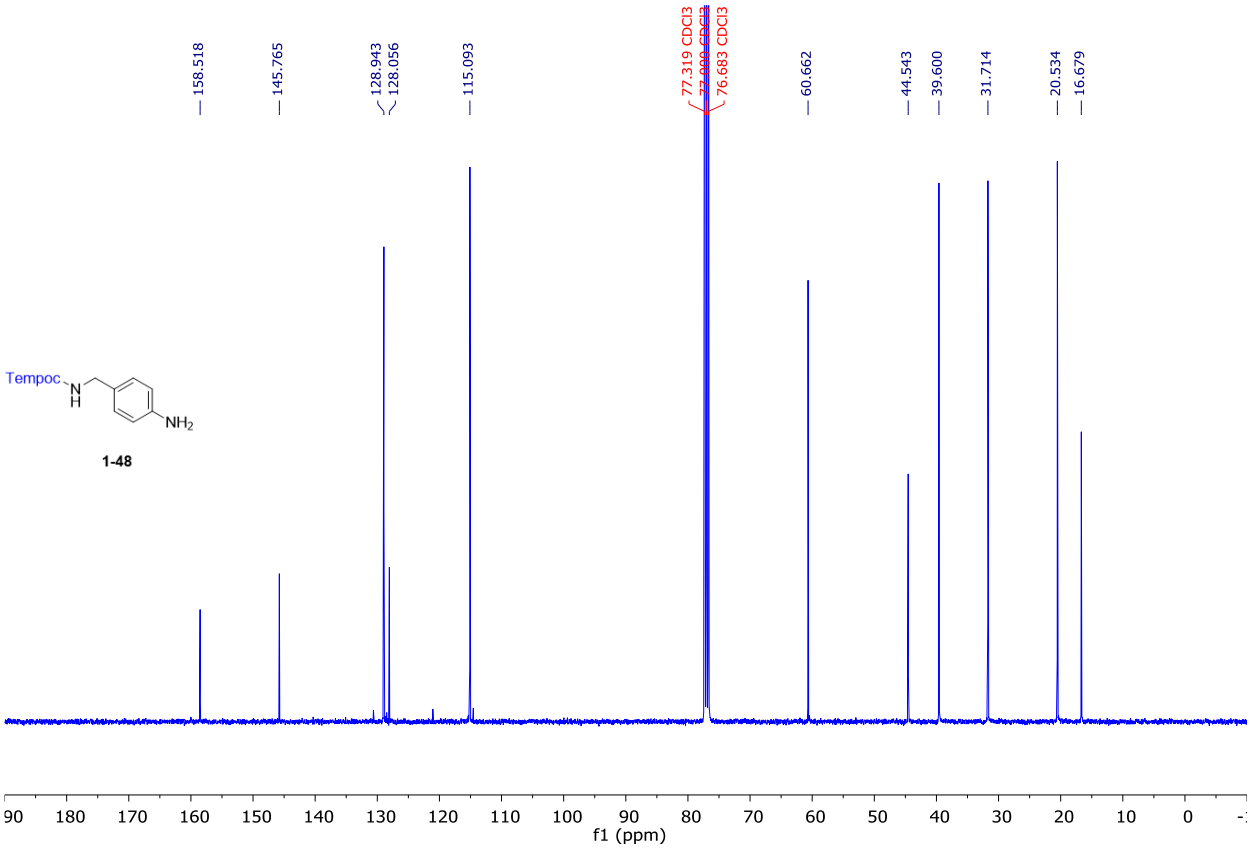

CDCl3 -- 75.50 MHz -- 13C
158.711
136.410
127.342
122.121
122.080
119.477
118.681
112.880
111.230
77.424 CDCl3
76.577 CDCl3
60.609
41.138
39.500
31.403
25.164
20.502
16.660
Tempoc
NH
N
H
1-47
f1 (ppm)

CDCl3 -- 400.13 MHz -- 1H

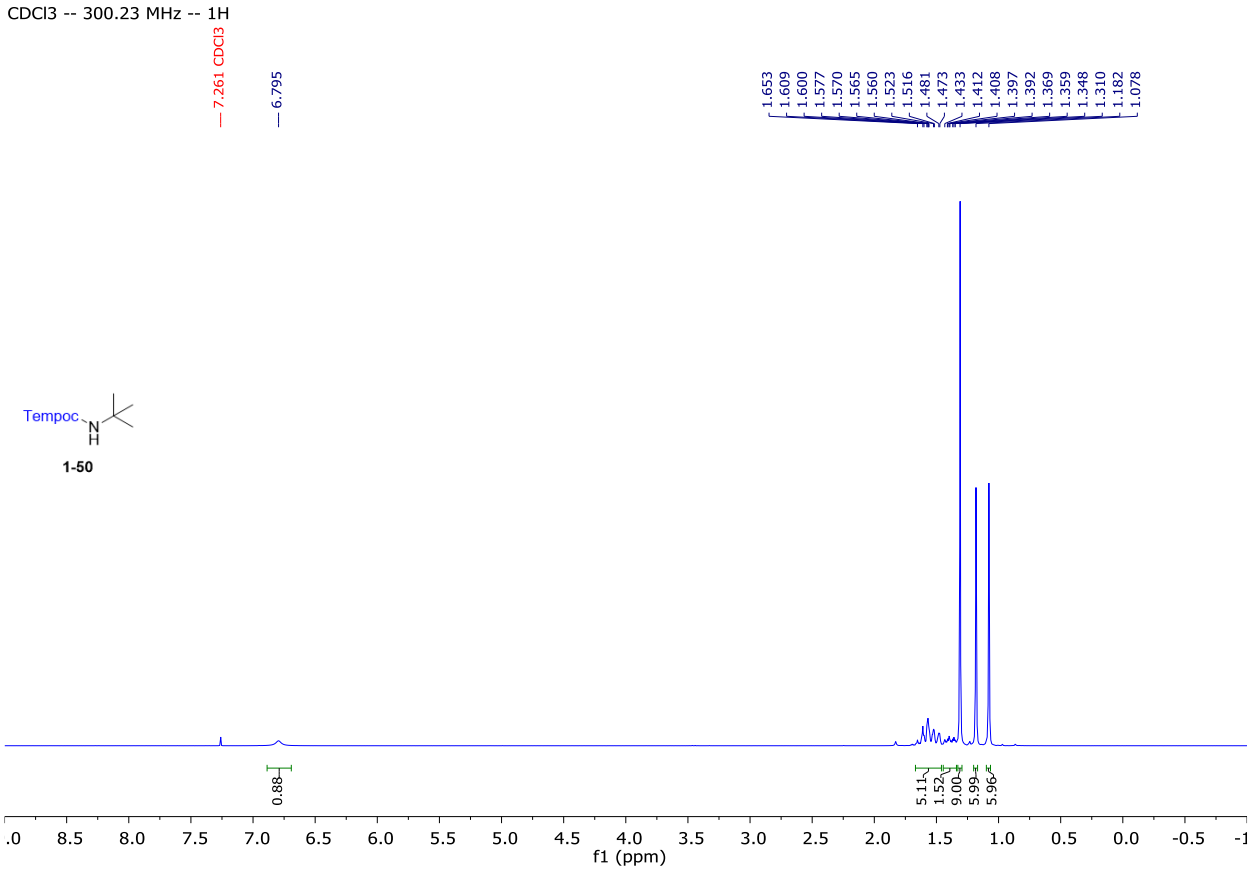


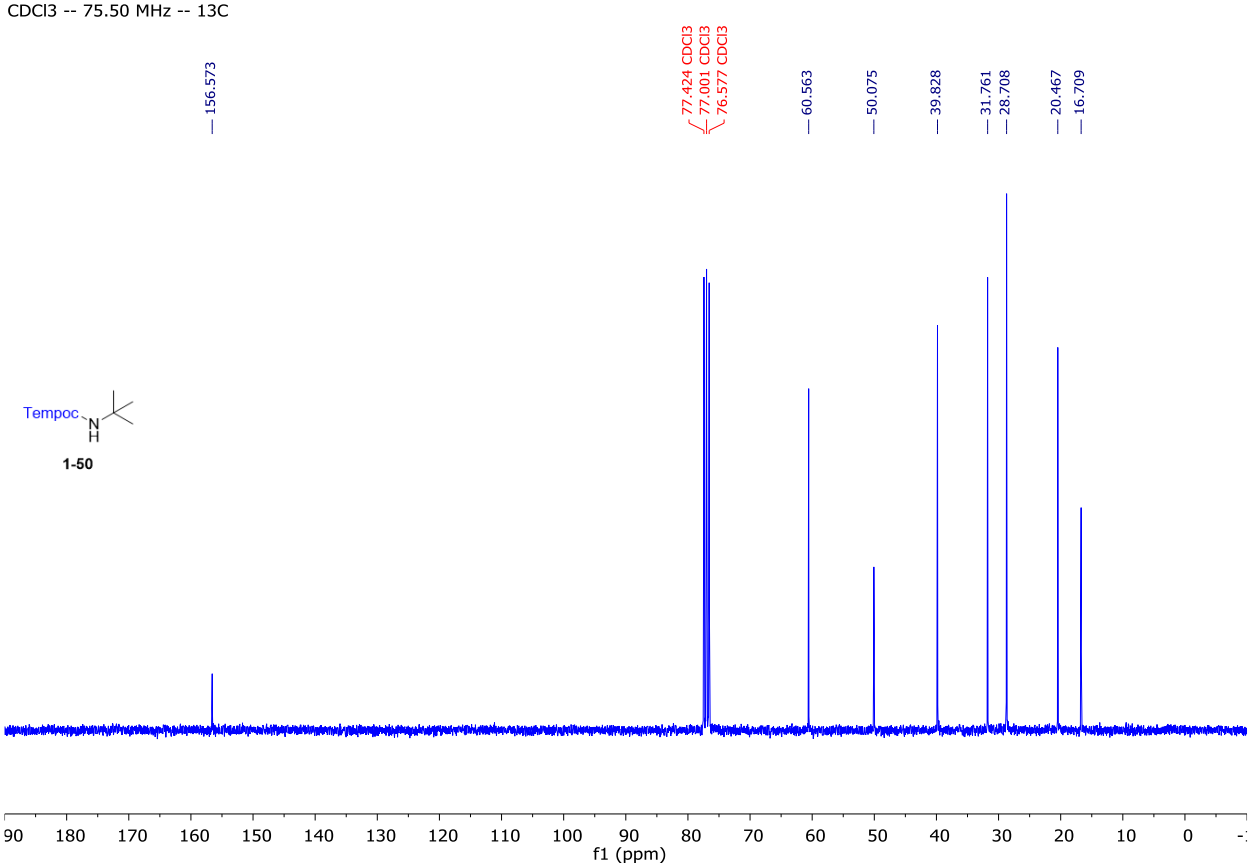
1-48

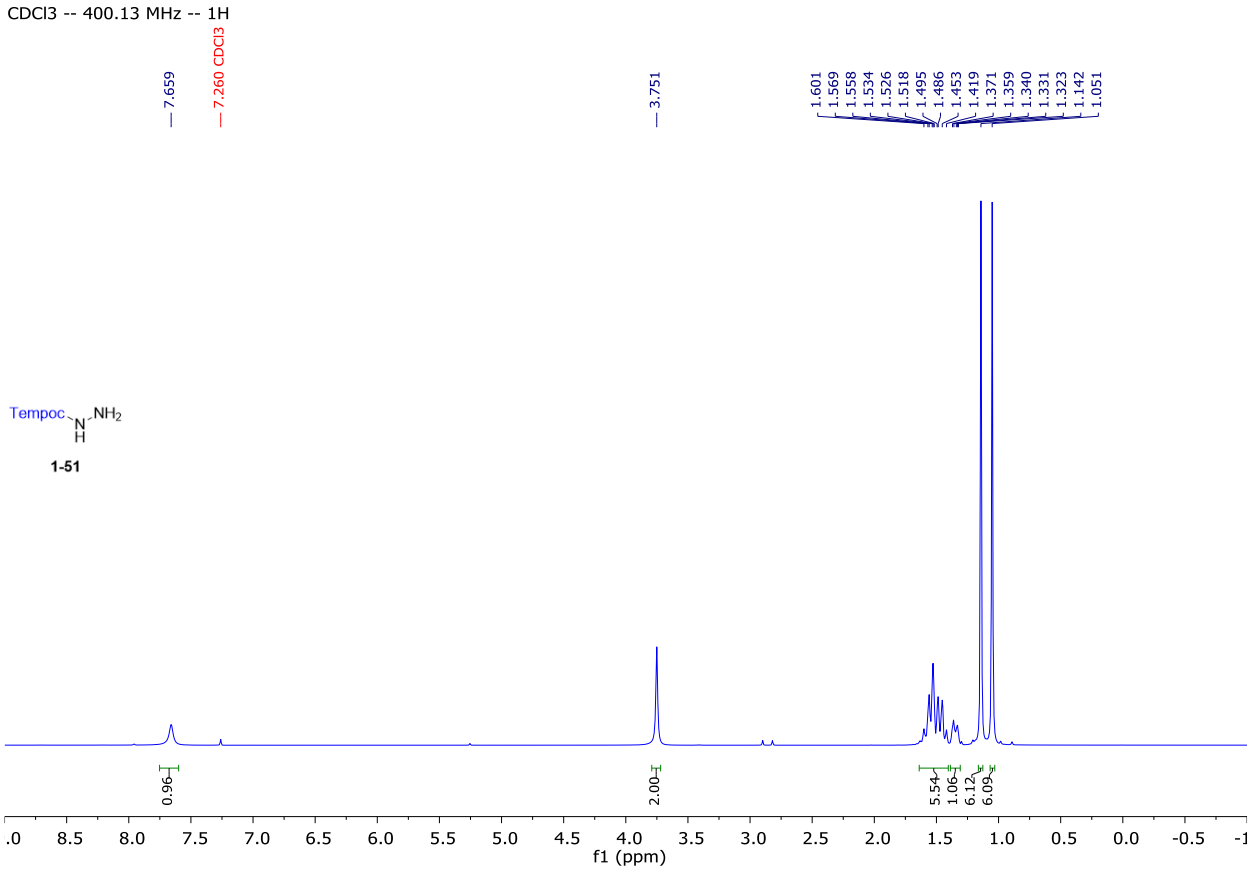
CDCl3 -- 100.62 MHz -- 13C

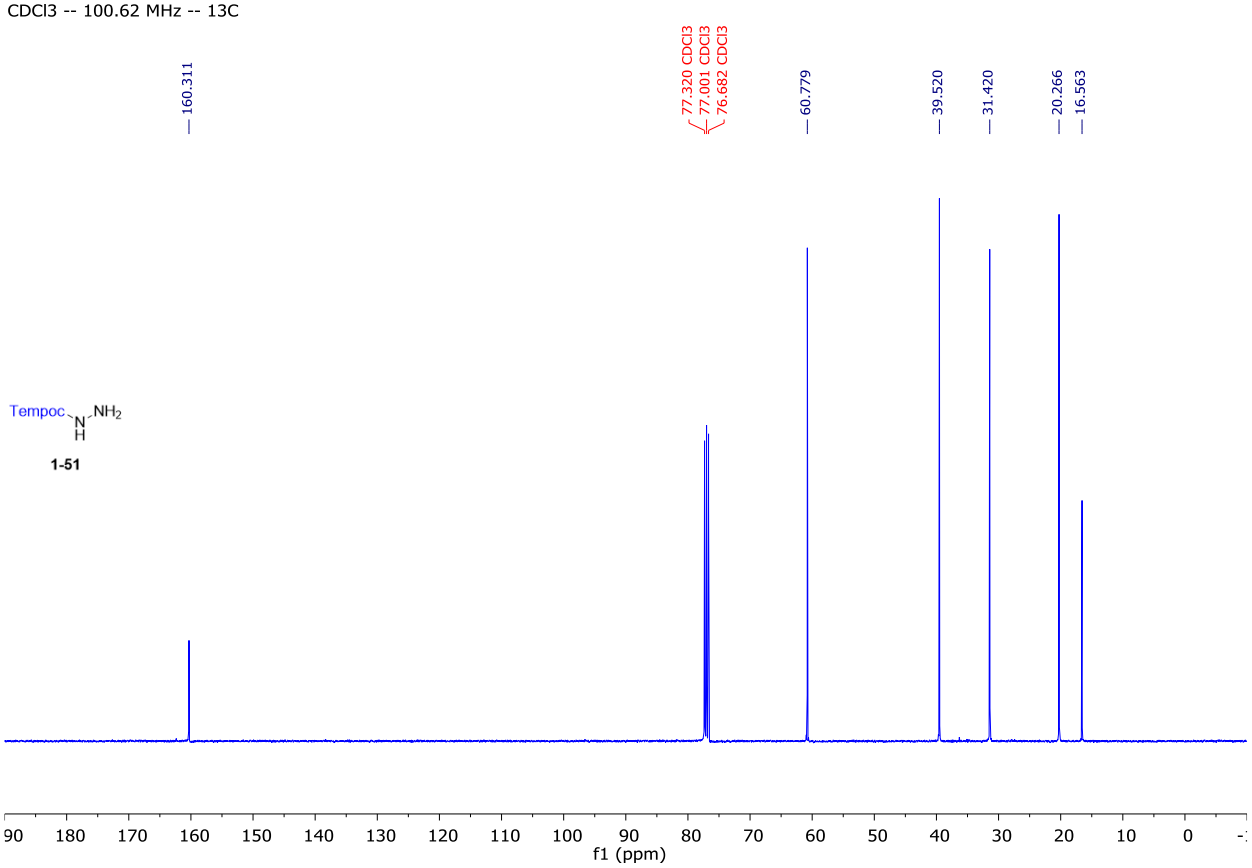


1-48

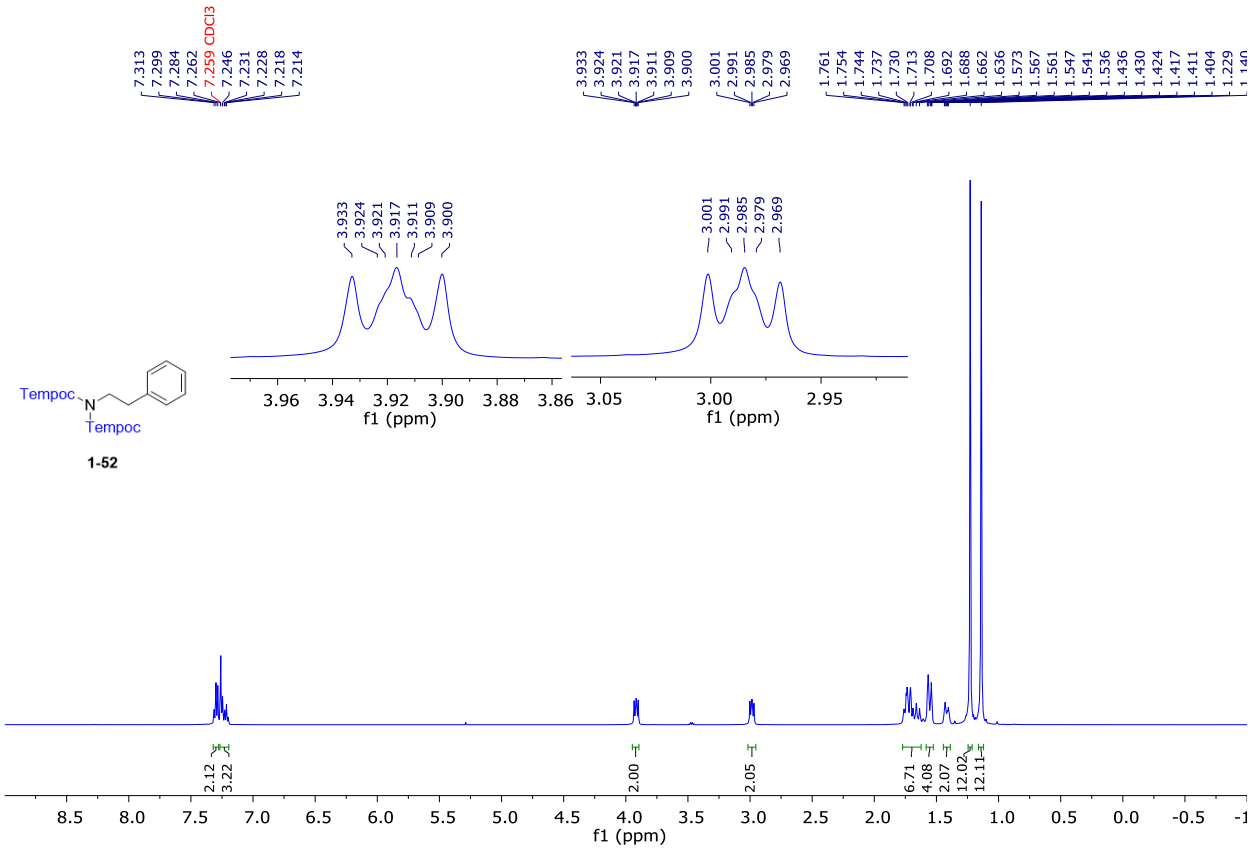

CDCl3 -- 300.23 MHz -- 1H
7.261 CDCl3
6.795
1.653
1.609
1.600
1.577
1.570
1.565
1.560
1.523
1.516
1.481
1.473
1.433
1.412
1.408
1.397
1.392
1.369
1.359
1.348
1.310
1.182
1.078
Tempoc
N
H
1-50
0.88
5.11
1.52
9.00
5.99
5.96
f1 (ppm)


CDCl3 -- 75.50 MHz -- 13C
156.573
77.424 CDCl3
77.001 CDCl3
76.577 CDCl3
60.563
50.075
39.828
31.761
28.708
20.467
16.709
Tempoc
N
H
1-50
f1 (ppm)

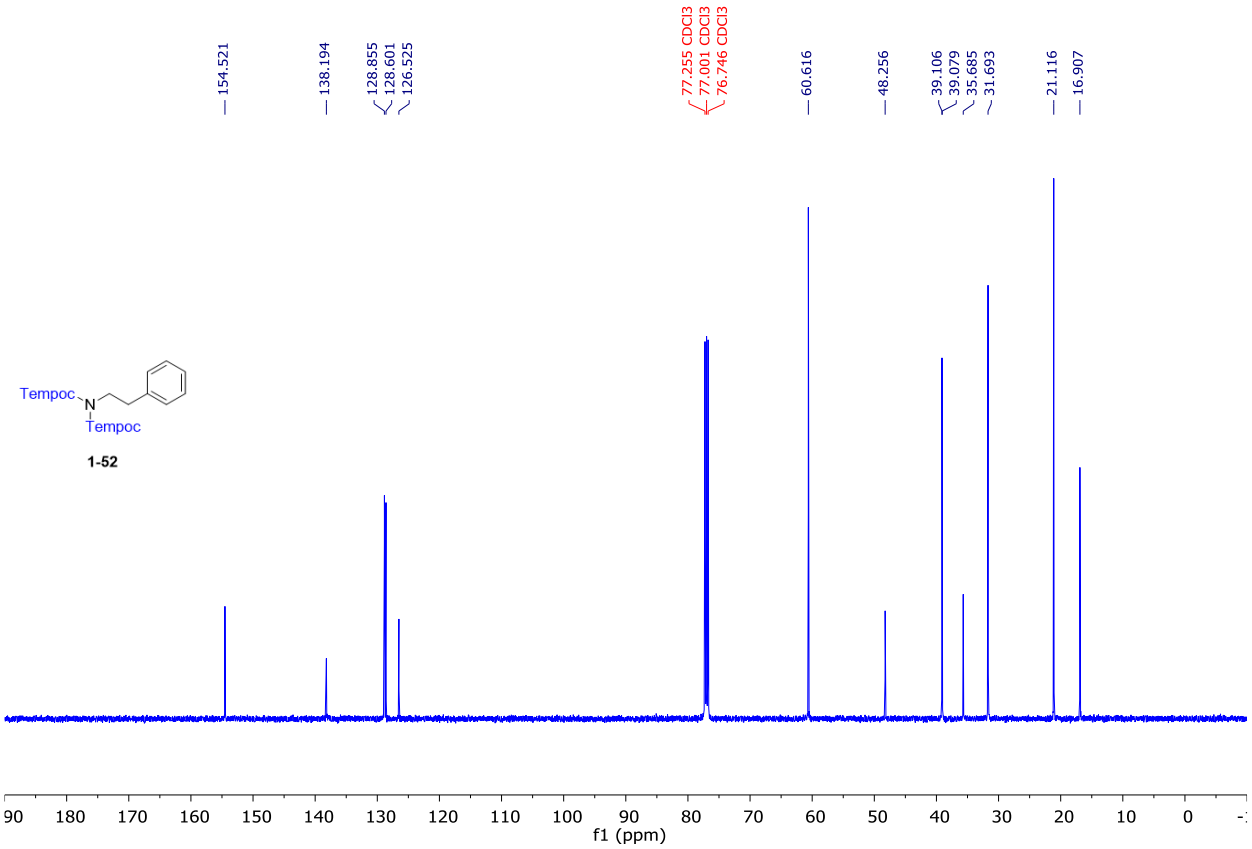

CDCl3 -- 400.13 MHz -- 1H
7.659
7.260 CDCl3
3.751
1.601
1.569
1.558
1.534
1.526
1.518
1.495
1.486
1.453
1.419
1.371
1.359
1.340
1.331
1.323
1.142
1.051
Tempoc
NH2
N
H
1-51
0.96
2.00
5.54
1.06
6.12
6.09
f1 (ppm)

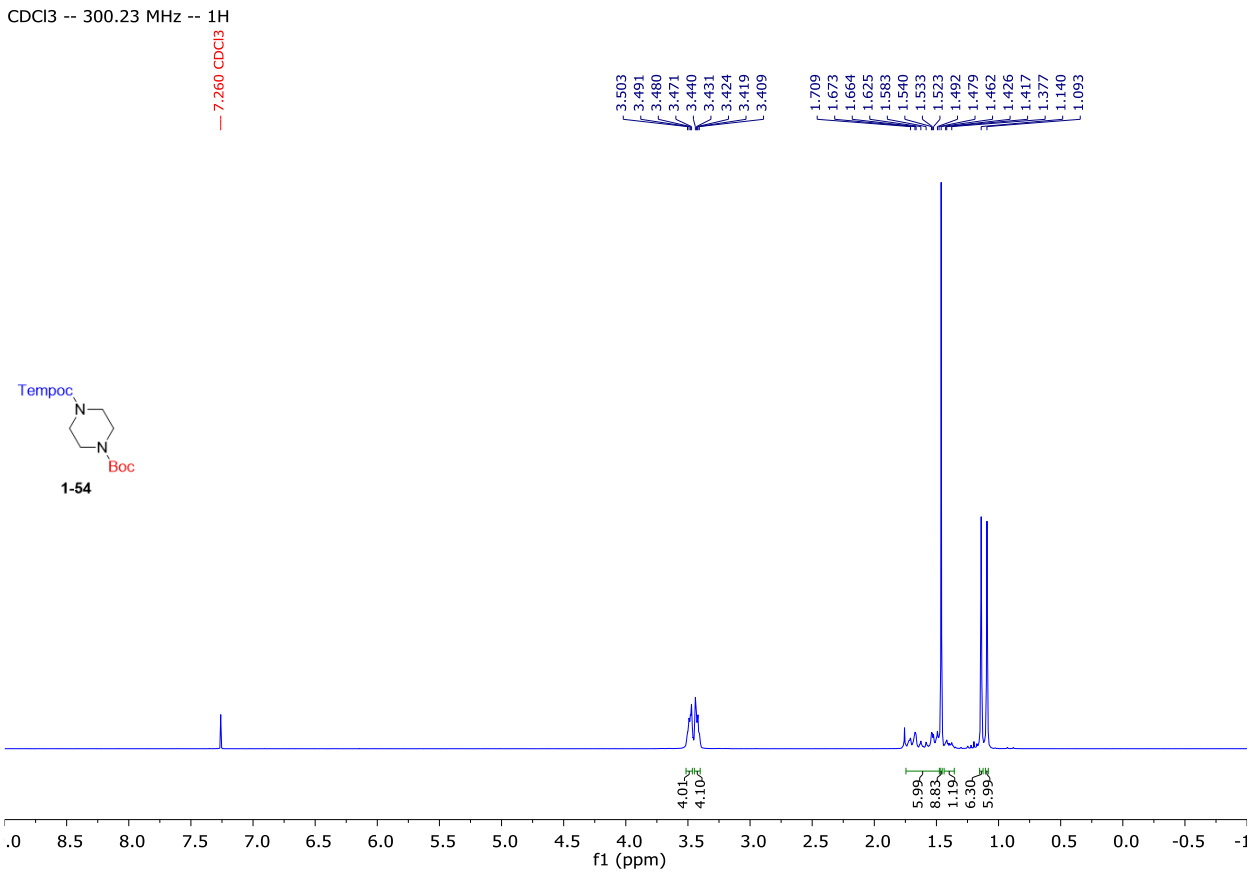

CDCl3 -- 100.62 MHz -- 13C
160.311
77.320 CDCl3
77.001 CDCl3
76.682 CDCl3
60.779
39.520
31.420
20.266
16.563
Tempoc
NH2
N
H
1-51
f1 (ppm)

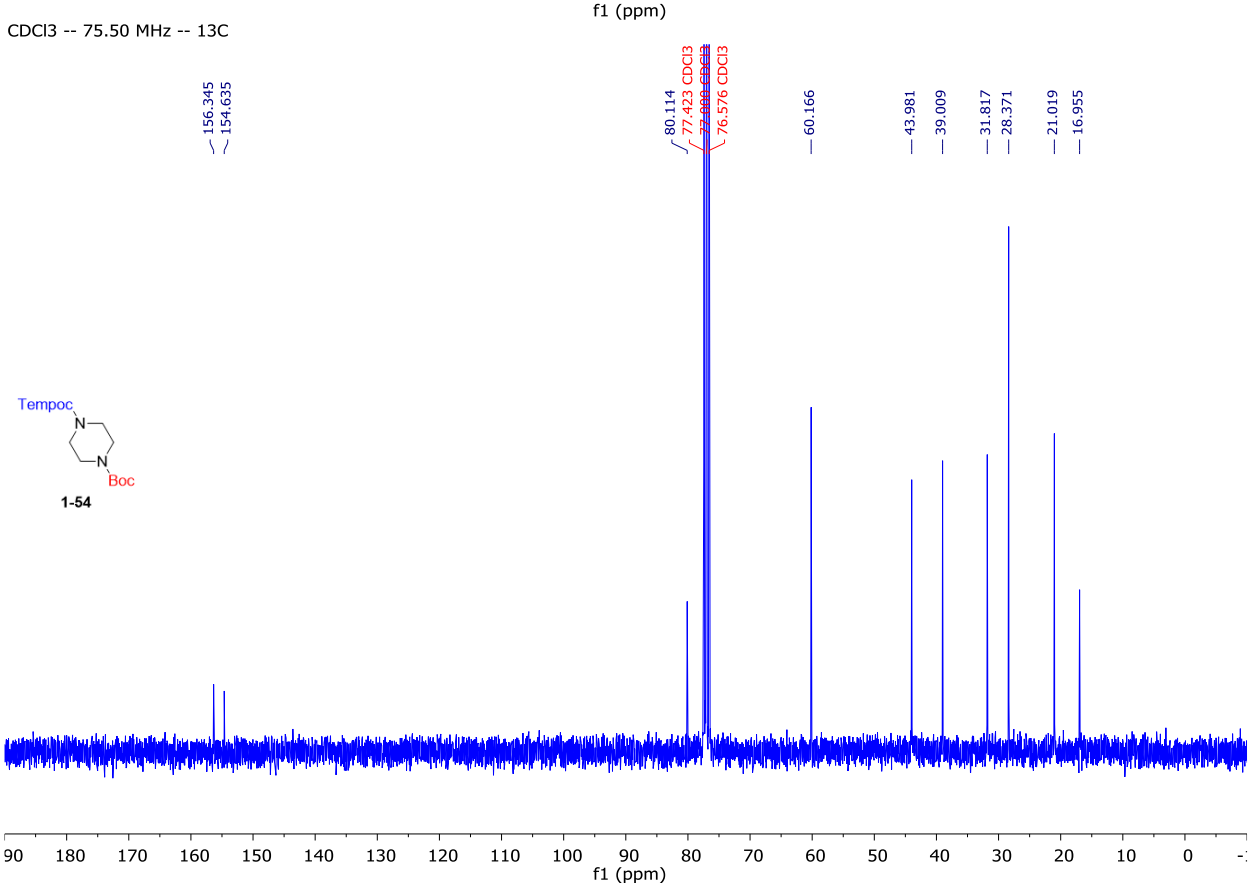
CDCl3 -- 500.16 MHz -- 1H



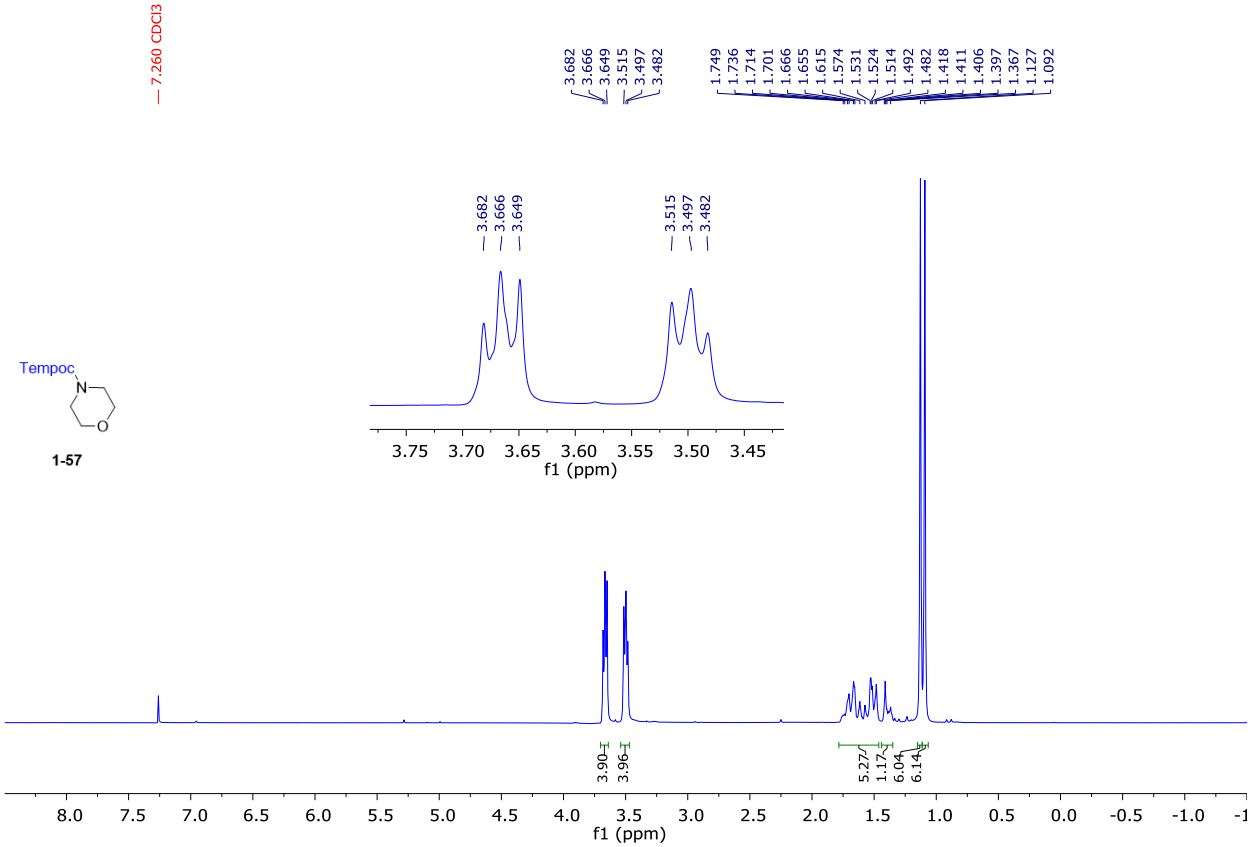
CDCl3 -- 125.78 MHz -- 13C



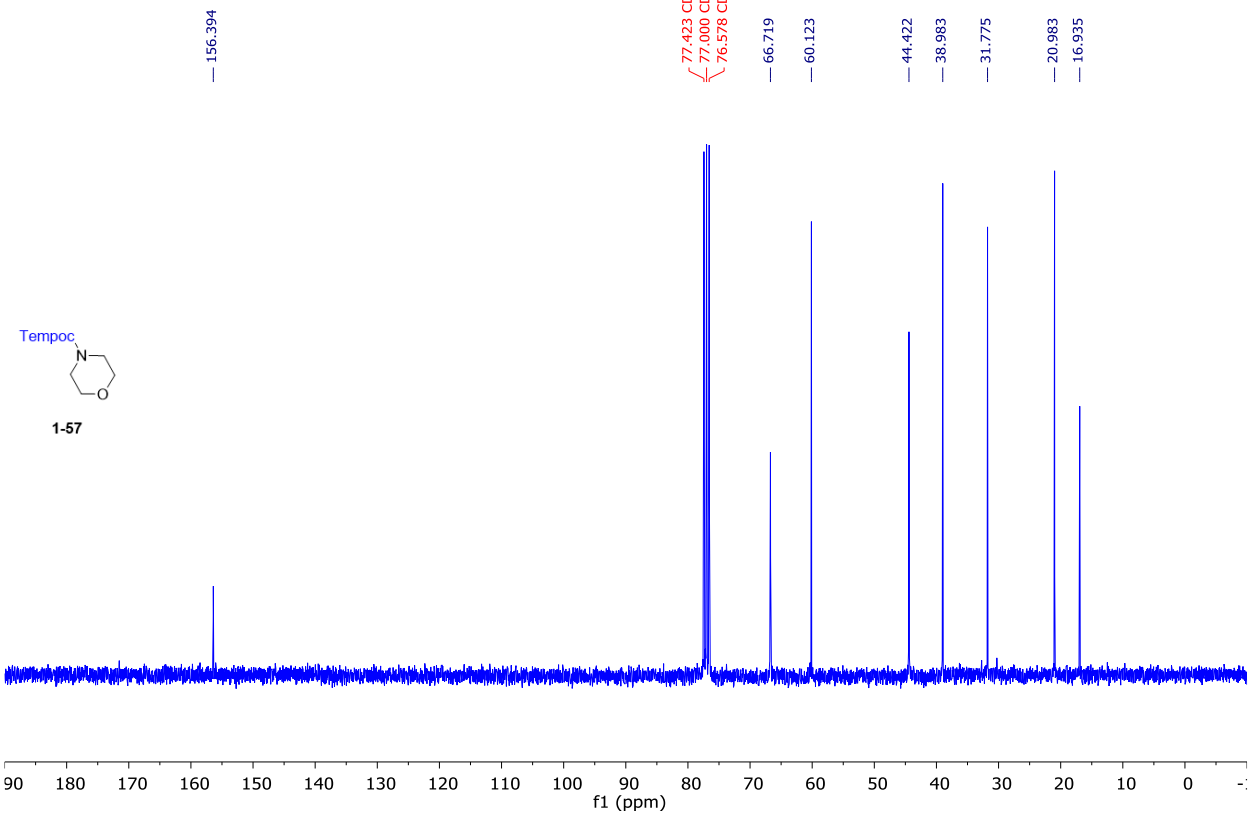

CDCl3 -- 300.23 MHz -- 1H
7.260 CDCl3
3.503
3.491
3.480
3.471
3.440
3.431
3.424
3.419
3.409
1.709
1.673
1.664
1.625
1.583
1.540
1.533
1.523
1.492
1.479
1.462
1.426
1.417
1.377
1.140
1.093
Tempoc
N
N
Boc
1-54
4.01
4.10
5.99
8.83
1.19
6.30
5.99
f1 (ppm)


CDCl3 -- 75.50 MHz -- 13C
156.345
154.635
80.114
77.423 CDCl3
76.576 CDCl3
60.166
43.981
39.009
31.817
28.371
21.019
16.955
Tempoc
N
N
Boc
1-54
f1 (ppm)

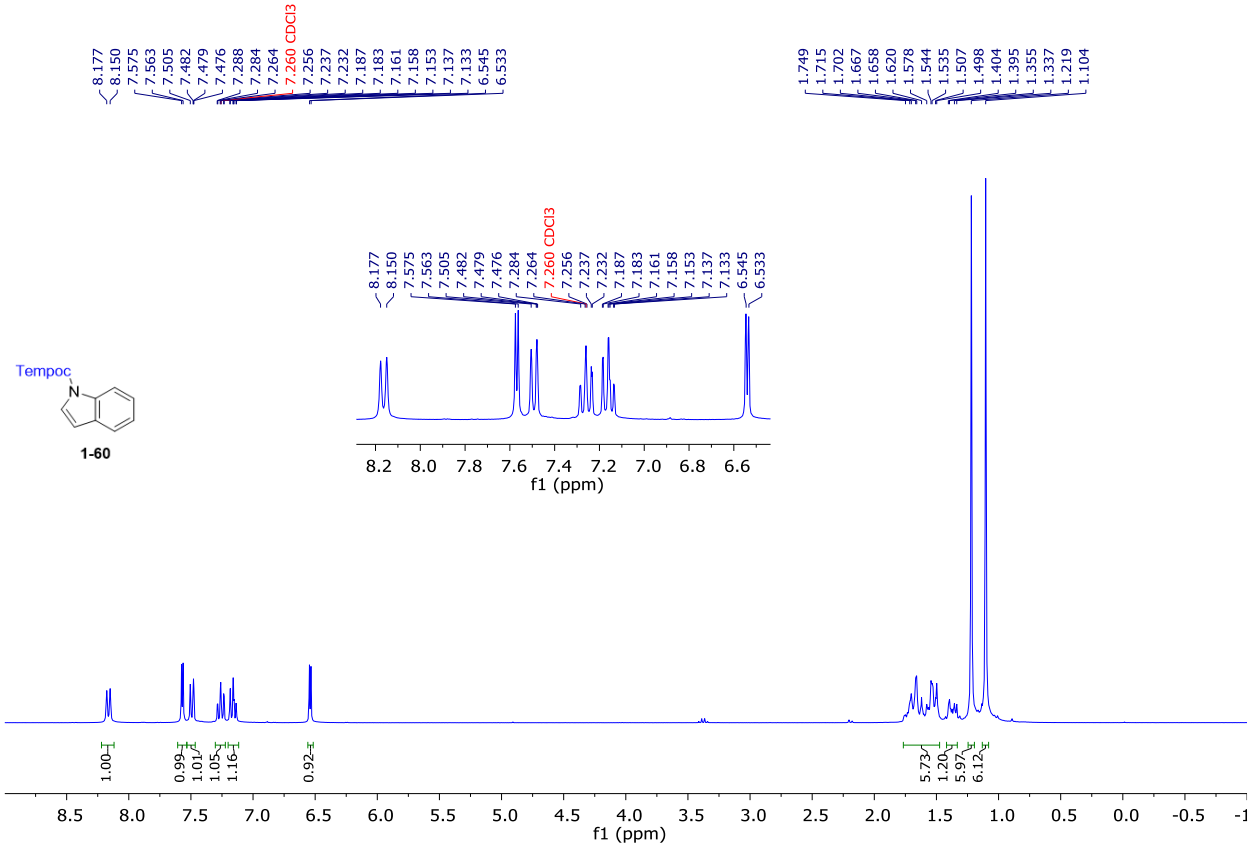
CDCl3 -- 300.23 MHz -- 1H



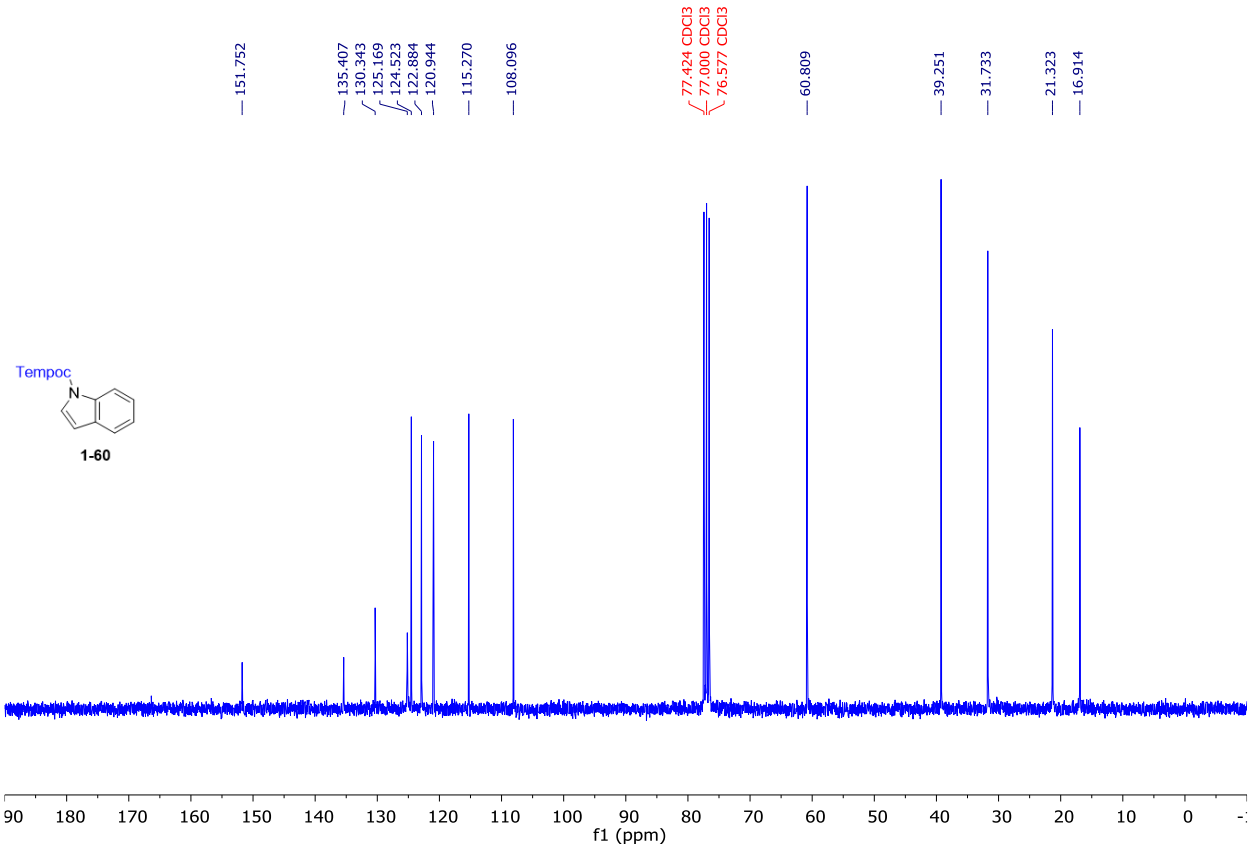
CDCl3 -- 75.50 MHz -- 13C



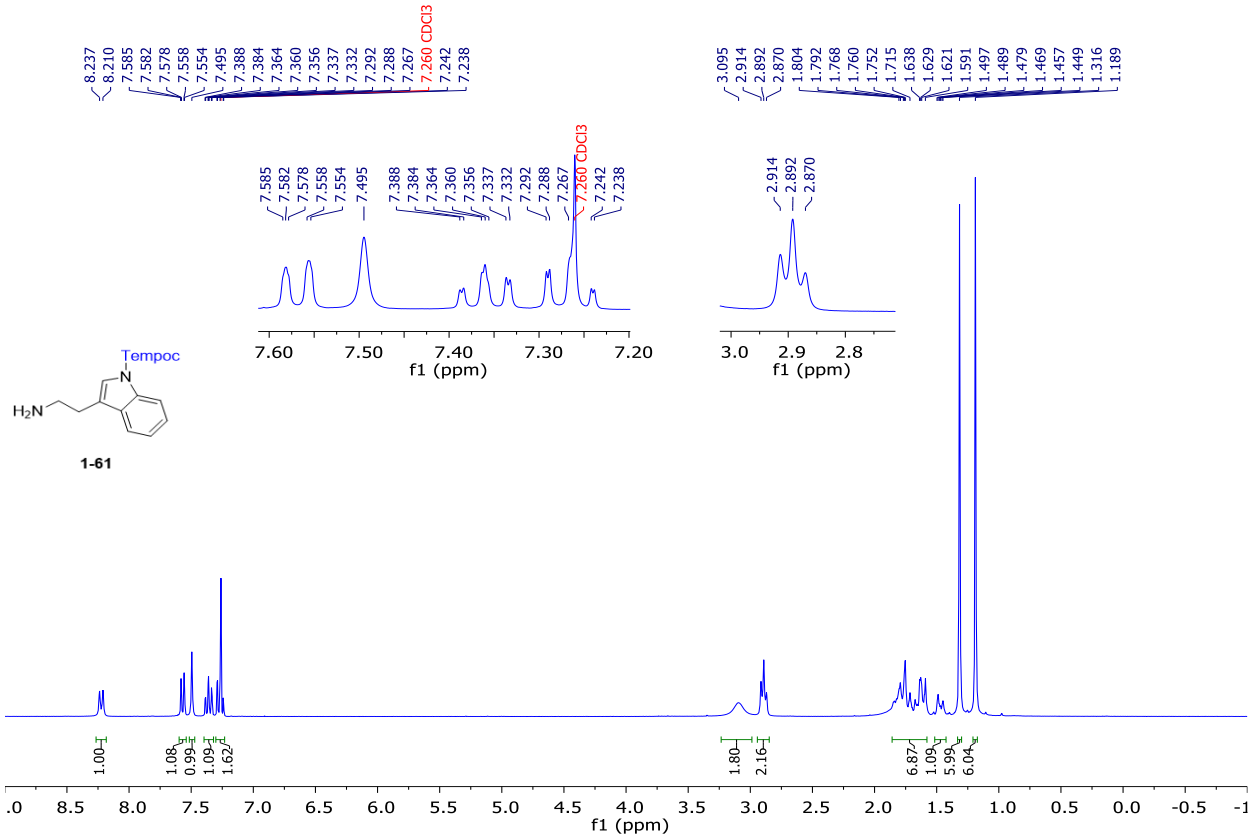
CDCl3 -- 300.23 MHz -- 1H



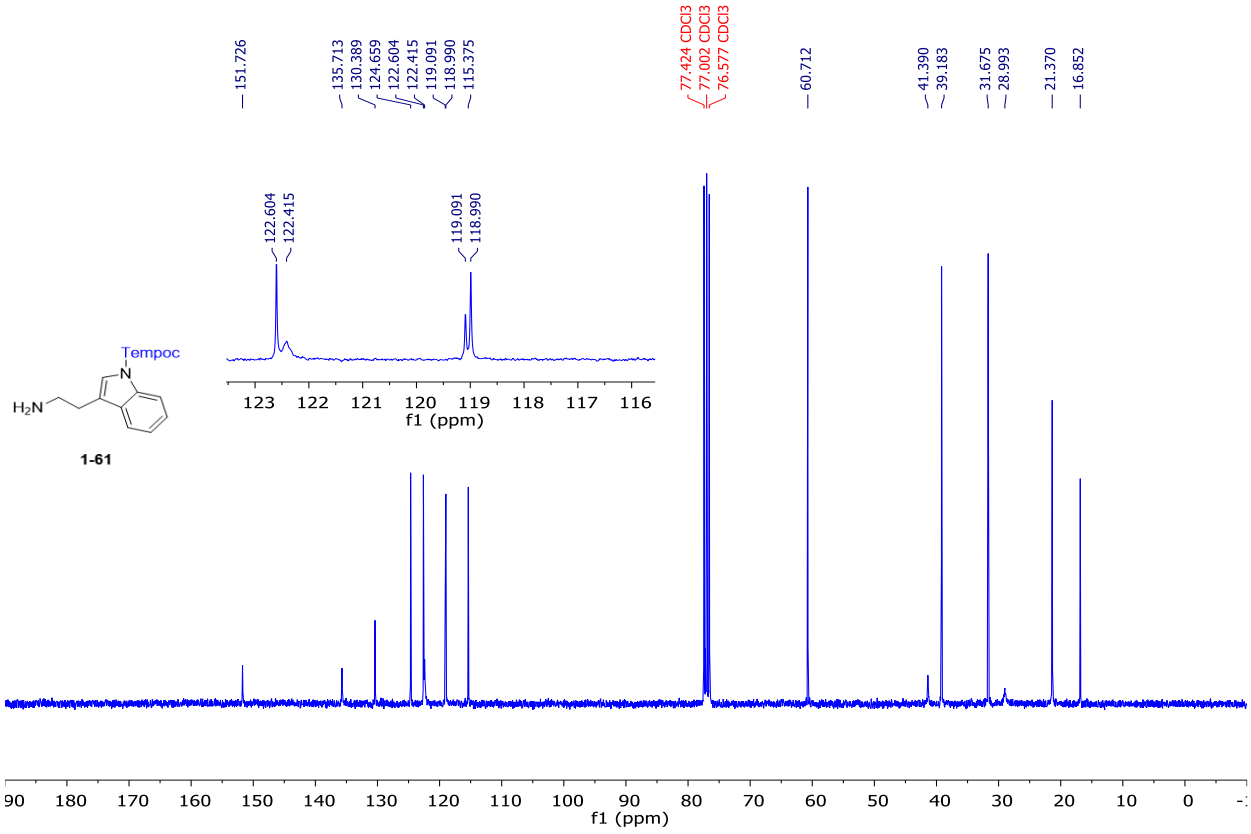
CDCl3 -- 75.50 MHz -- 13C

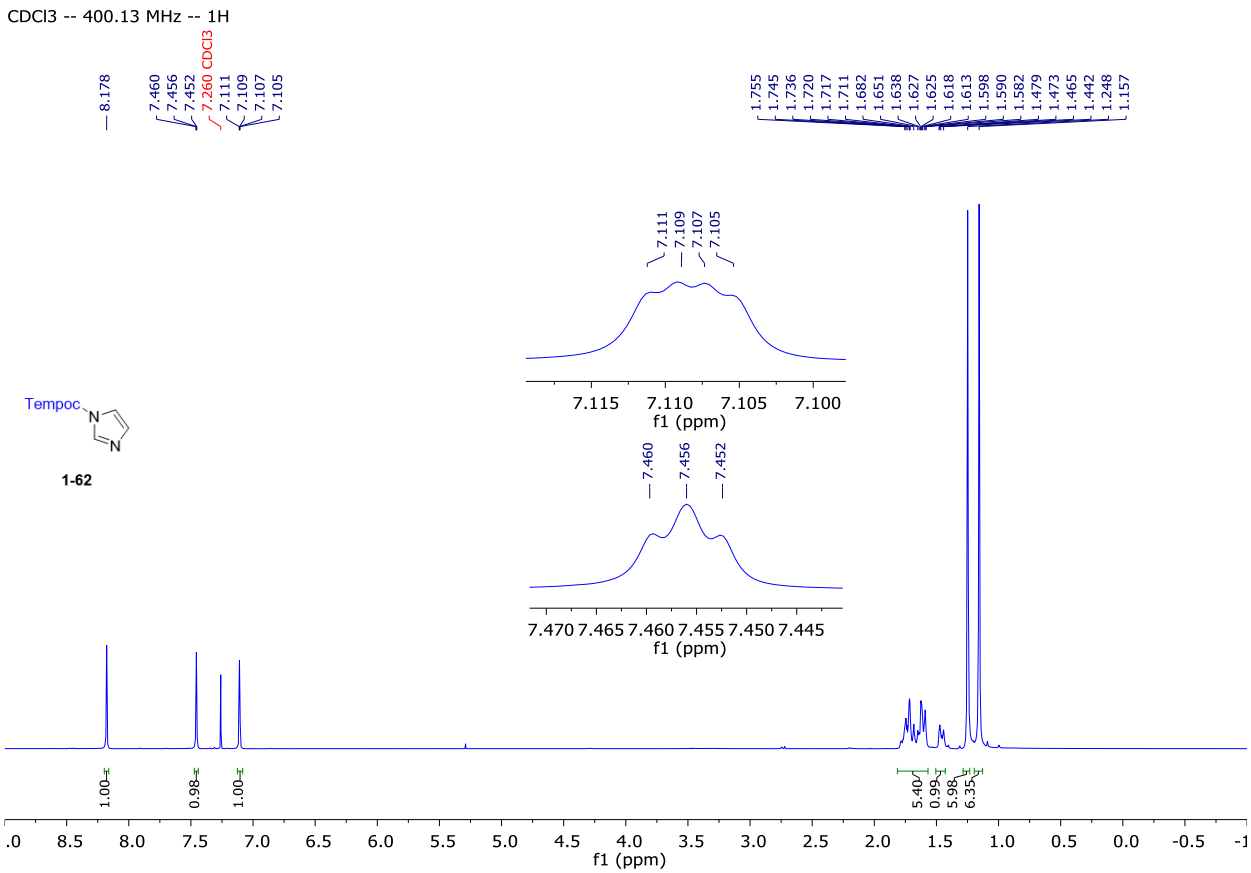


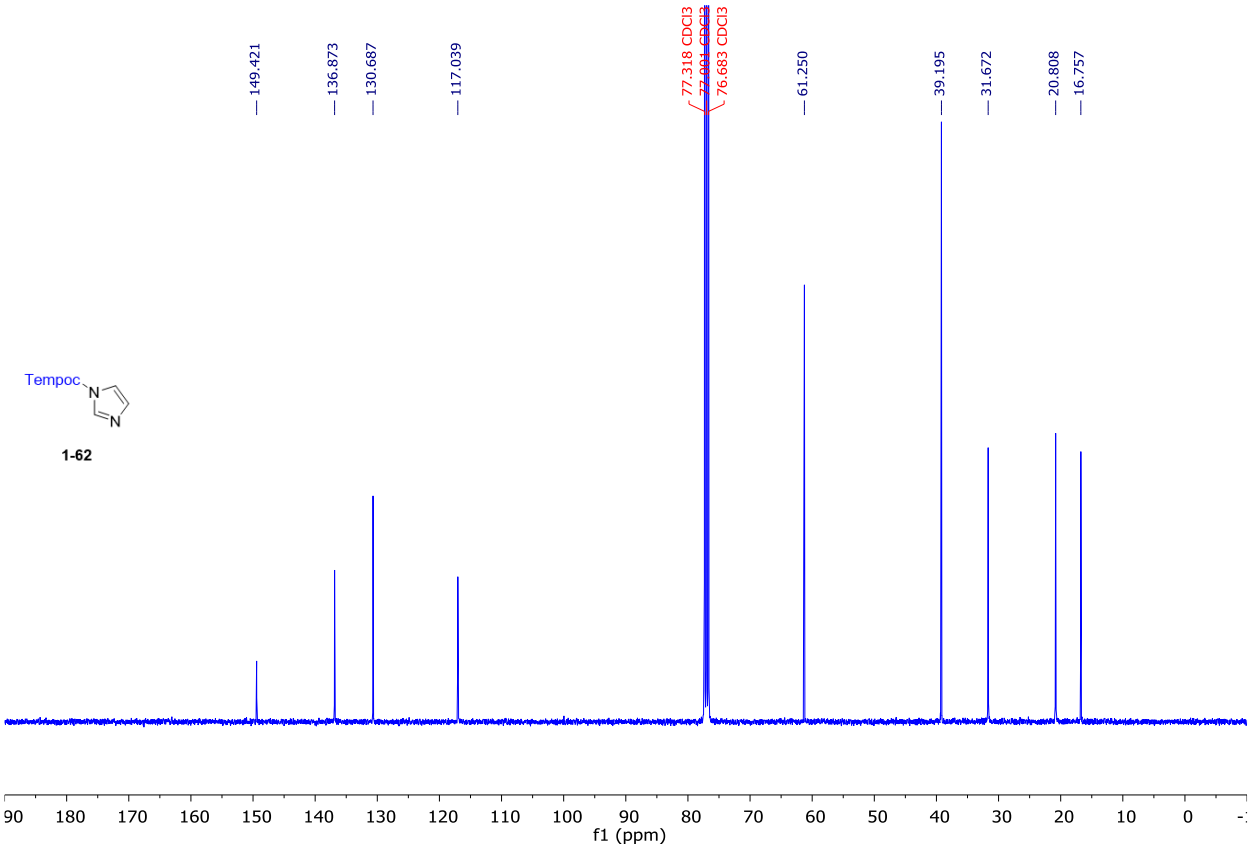
CDCl3 -- 300.23 MHz -- 1H



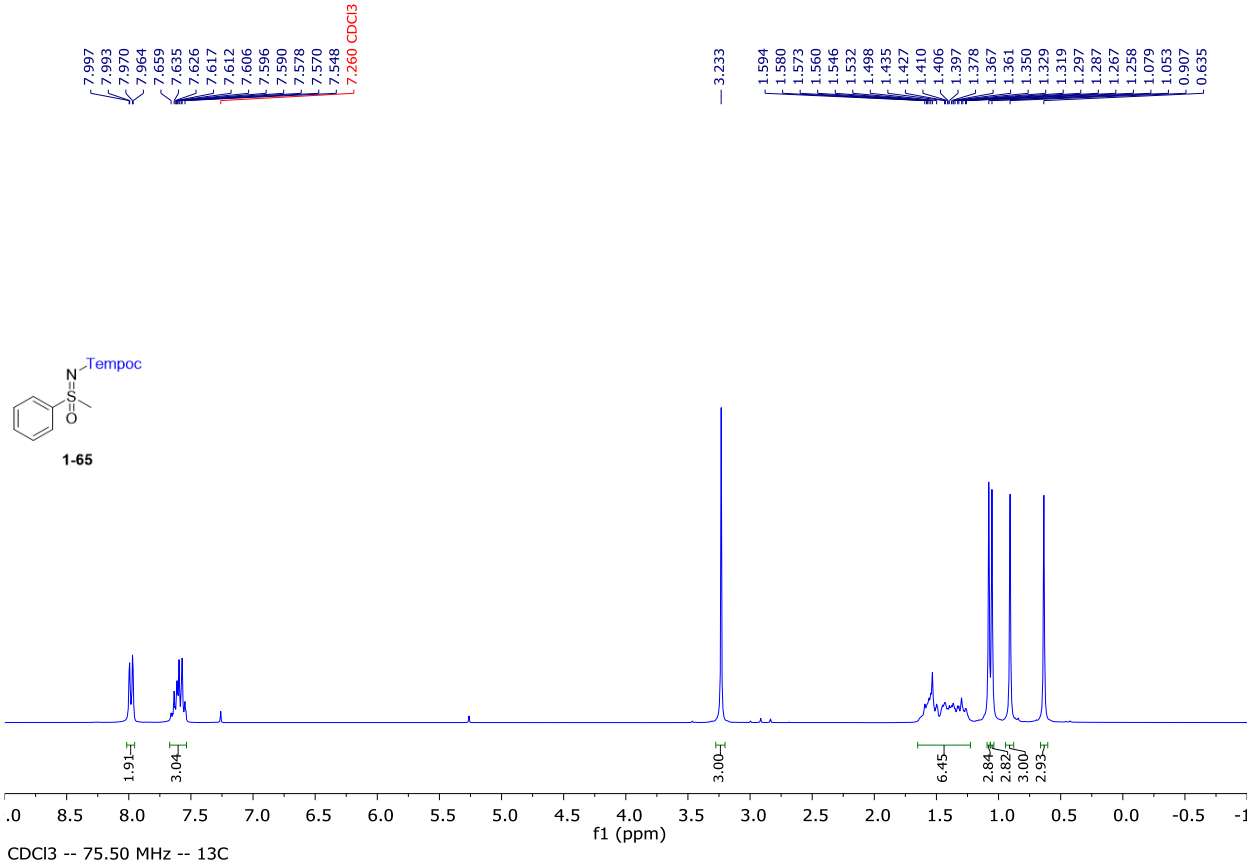
CDCl3 -- 75.50 MHz -- 13C



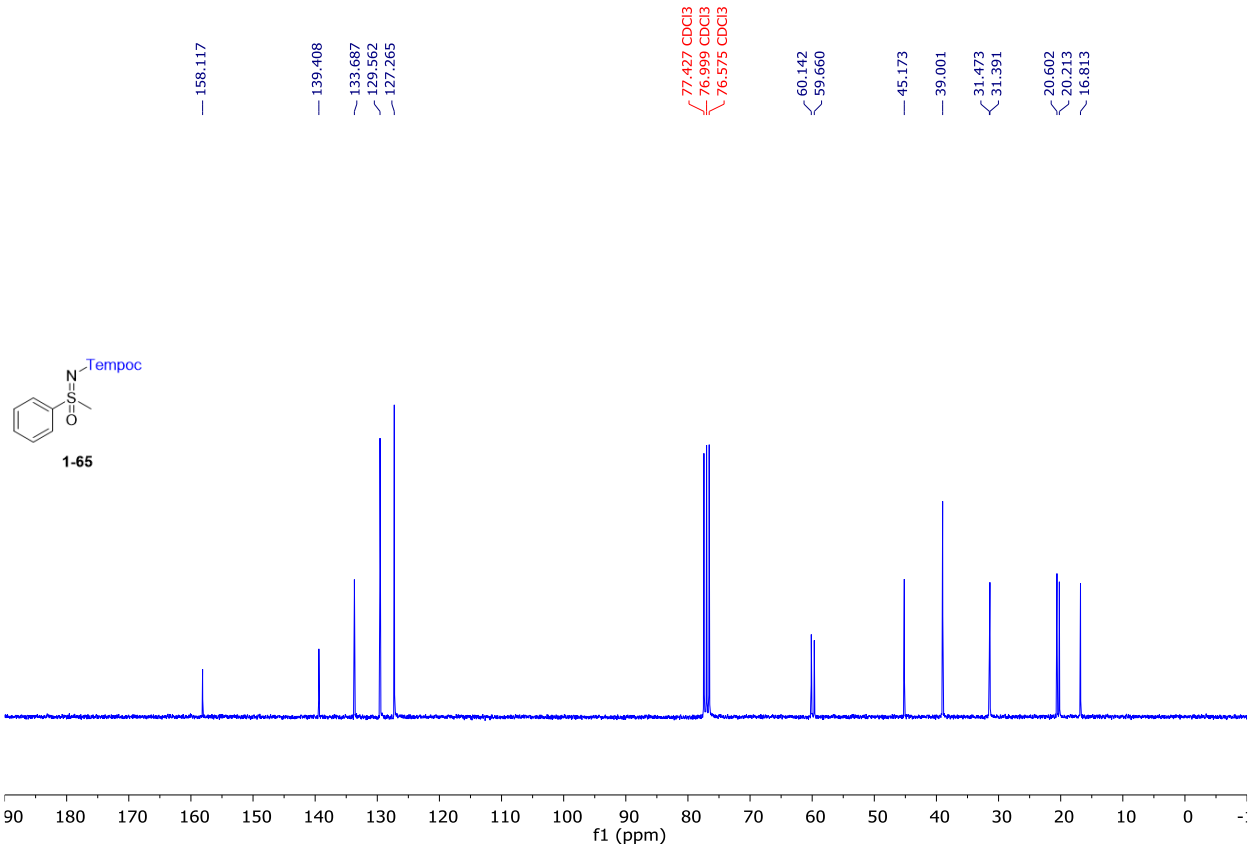

CDCl3 -- 400.13 MHz -- 1H
8.178
7.460
7.456
7.452
7.260 CDCl3
7.111
7.109
7.107
7.105
1.755
1.745
1.736
1.720
1.717
1.711
1.682
1.651
1.638
1.627
1.625
1.618
1.613
1.598
1.590
1.582
1.479
1.473
1.465
1.442
1.248
1.157
Tempoc
1-62
7.115 7.110 7.105 7.100
f1 (ppm)
7.470 7.465 7.460 7.455 7.450 7.445
f1 (ppm)
1.00
0.98
1.00
5.40
0.99
5.98
6.35
f1 (ppm)


CDCl3 -- 100.62 MHz -- 13C
149.421
136.873
130.687
117.039
77.318 CDCl3
77.001 CDCl3
76.683 CDCl3
61.250
39.195
31.672
20.808
16.757
Tempoc
1-62
f1 (ppm)

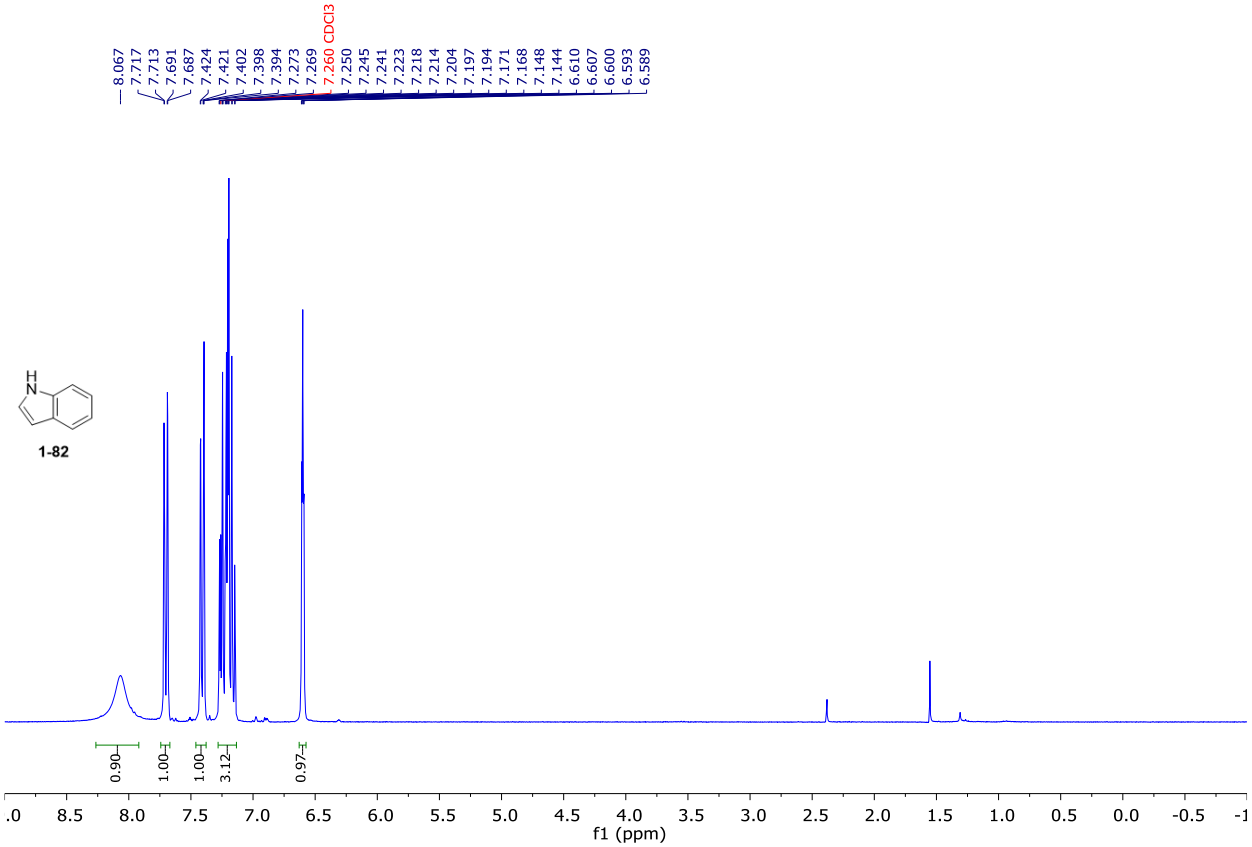
CDCl3 -- 300.23 MHz -- 1H



CDCl3 -- 75.50 MHz -- 13C

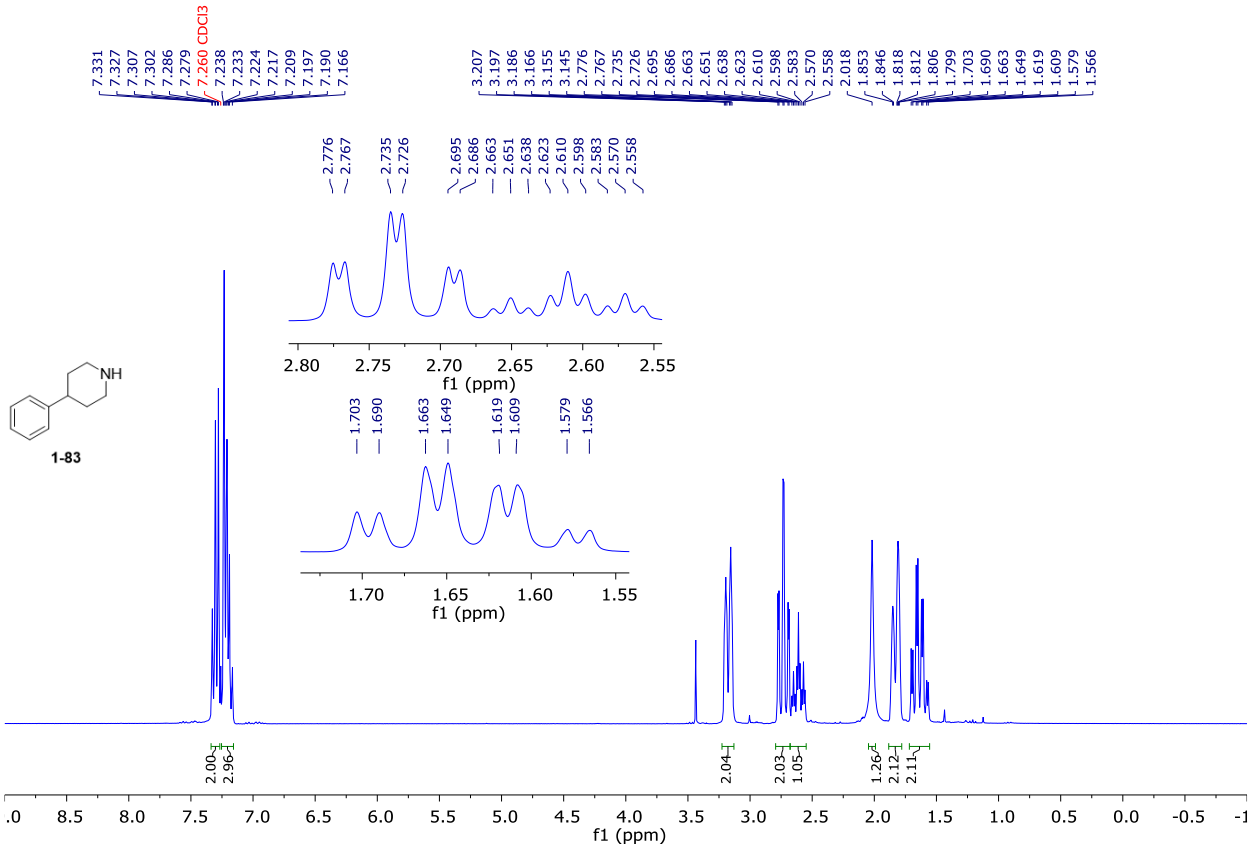


CDCl3 -- 300.23 MHz -- 1H

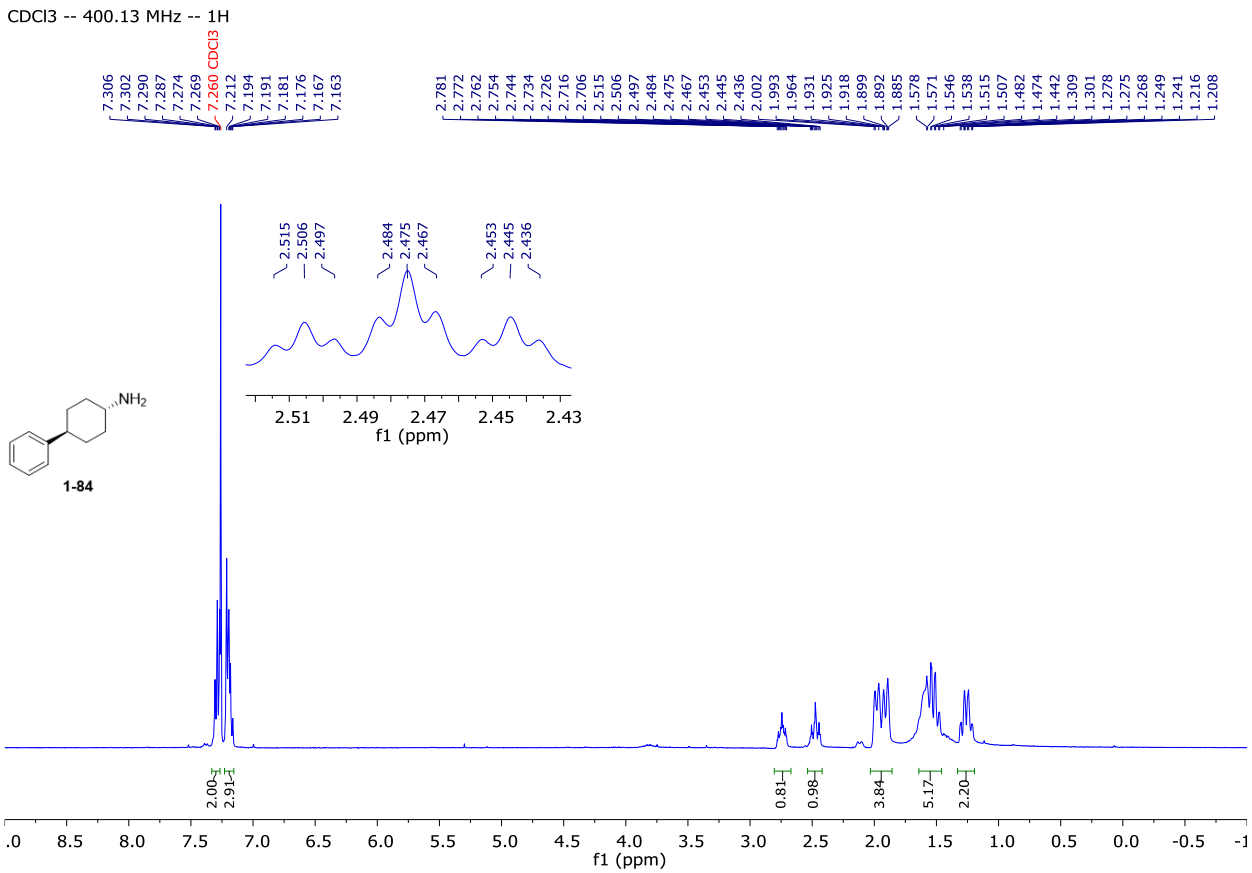


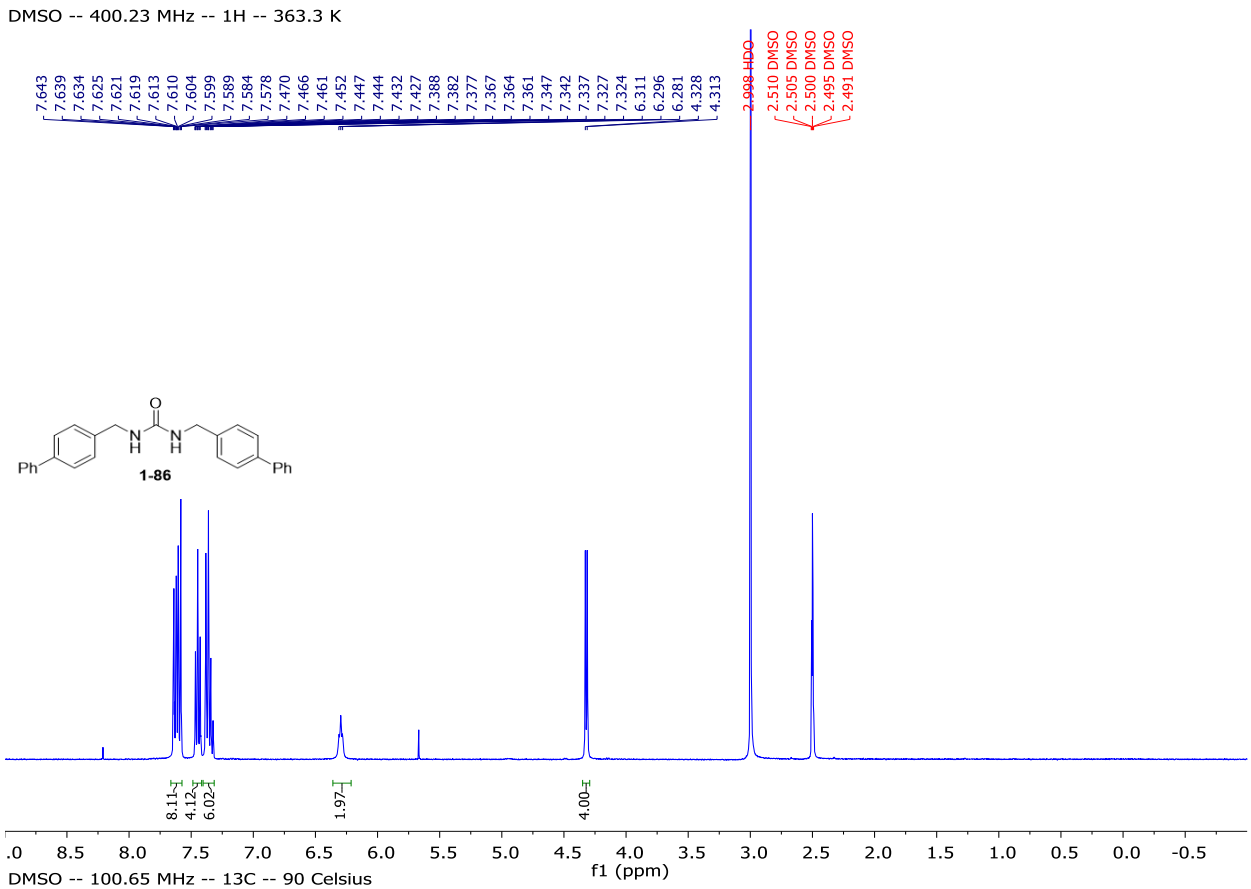
1-82

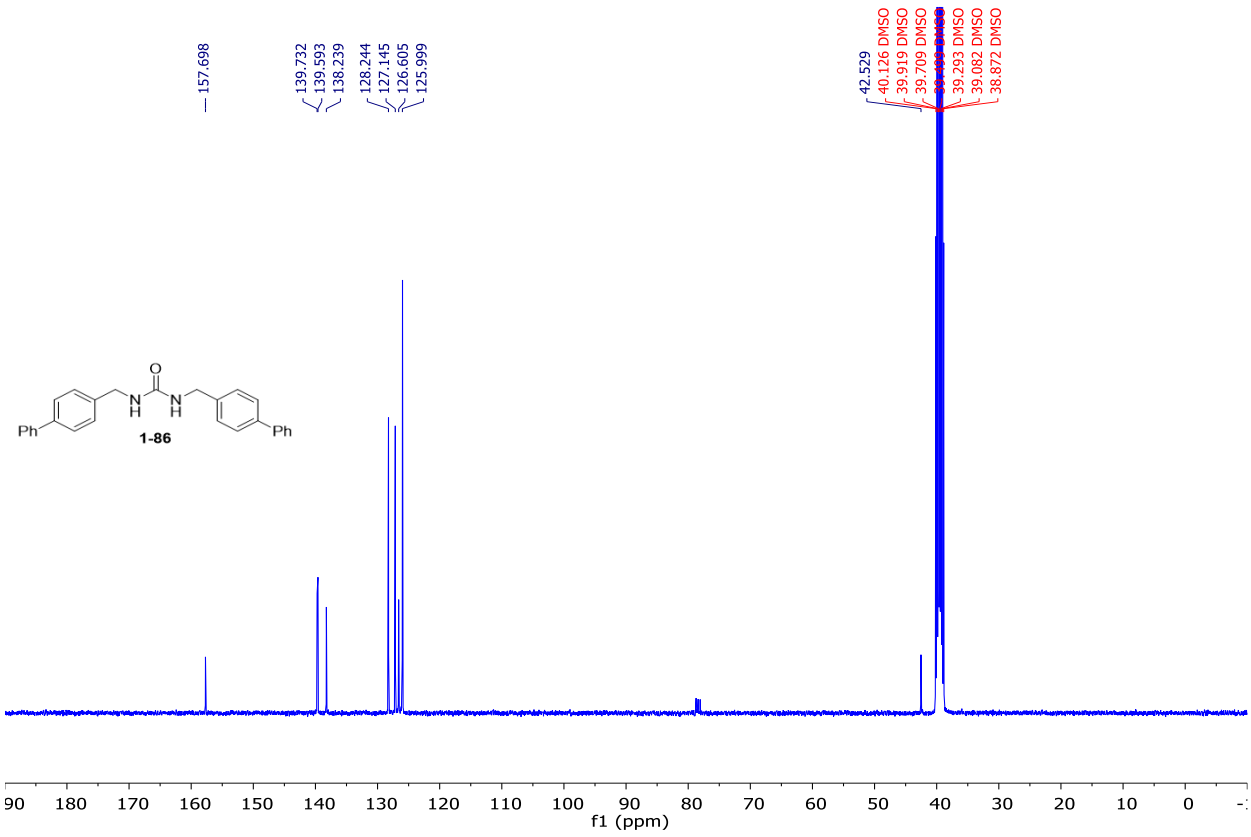
CDCl3 -- 300.23 MHz -- 1H



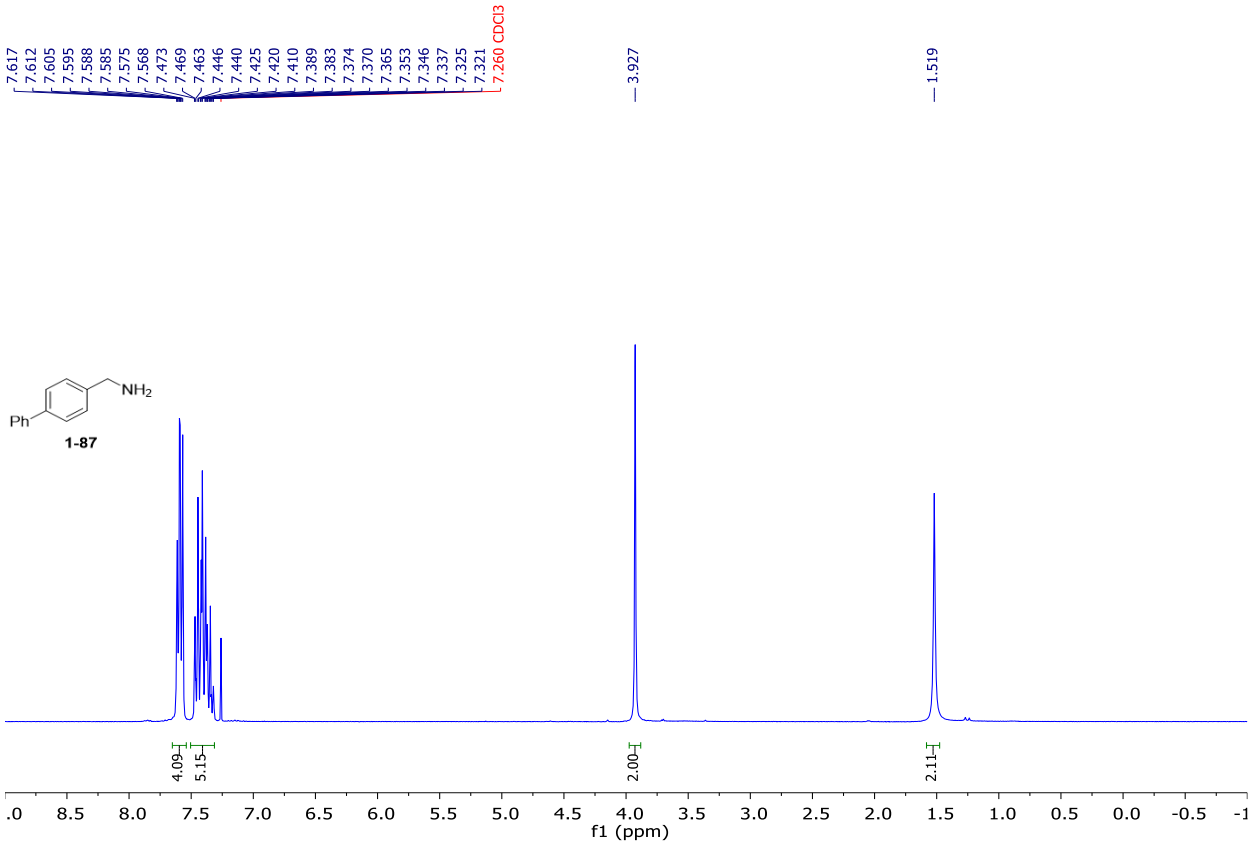
1-83


CDCl3 -- 400.13 MHz -- 1H
7.306
7.302
7.290
7.287
7.274
7.269
7.260 CDCl3
7.212
7.194
7.191
7.181
7.176
7.167
7.163
2.781
2.772
2.762
2.754
2.744
2.734
2.726
2.716
2.706
2.515
2.506
2.497
2.484
2.475
2.467
2.453
2.445
2.436
2.002
1.993
1.964
1.931
1.925
1.918
1.899
1.892
1.885
1.578
1.571
1.546
1.538
1.515
1.507
1.482
1.474
1.442
1.309
1.301
1.278
1.275
1.268
1.249
1.241
1.216
1.208
NH2
1-84
2.51
2.49
2.47
2.45
2.43
f1 (ppm)
2.00
2.91
0.81
0.98
3.84
5.17
2.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

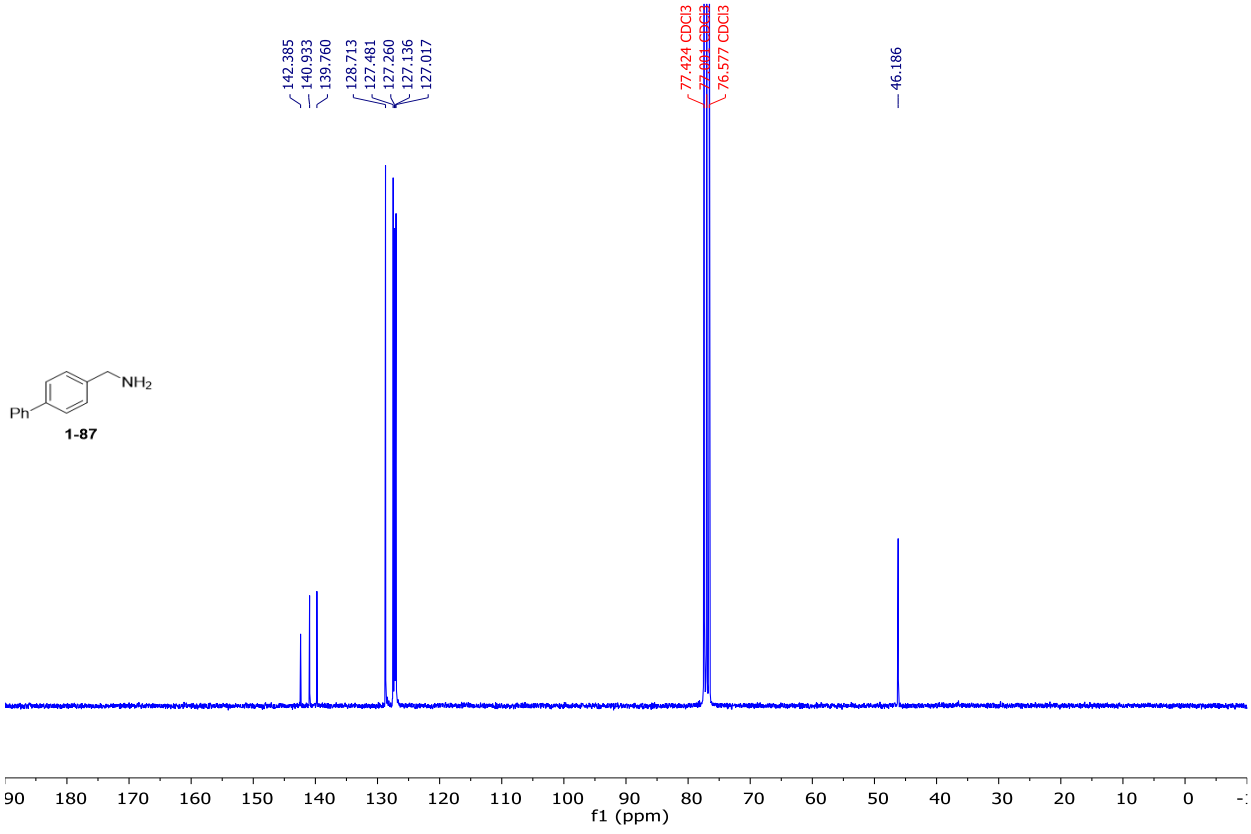

DMSO -- 400.23 MHz -- 1H -- 363.3 K
7.643
7.639
7.634
7.625
7.621
7.619
7.613
7.610
7.604
7.599
7.589
7.584
7.578
7.470
7.466
7.461
7.452
7.447
7.444
7.432
7.427
7.388
7.382
7.377
7.367
7.364
7.361
7.347
7.342
7.337
7.327
7.324
6.311
6.296
6.281
4.328
4.313
2.998 HDO
2.510 DMSO
2.505 DMSO
2.500 DMSO
2.495 DMSO
2.491 DMSO
Ph
N
H
O
N
H
Ph
1-86
8.11
4.12
6.02
1.97
4.00
f1 (ppm)

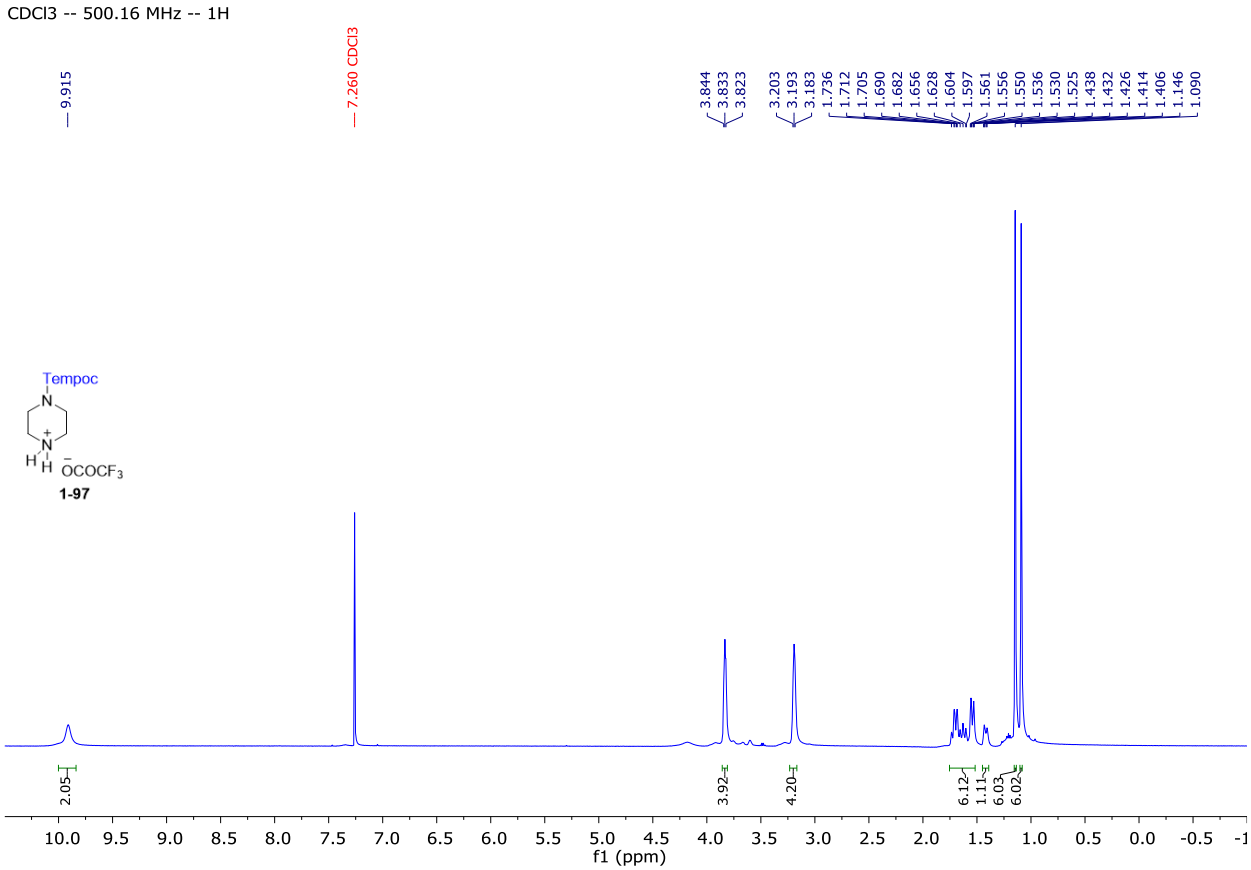

DMSO -- 100.65 MHz -- 13C -- 90 Celsius
157.698
139.732
139.593
138.239
128.244
127.145
126.605
125.999
42.529
40.126 DMSO
39.919 DMSO
39.709 DMSO
39.293 DMSO
39.082 DMSO
38.872 DMSO
Ph
N
H
O
N
H
Ph
1-86
f1 (ppm)

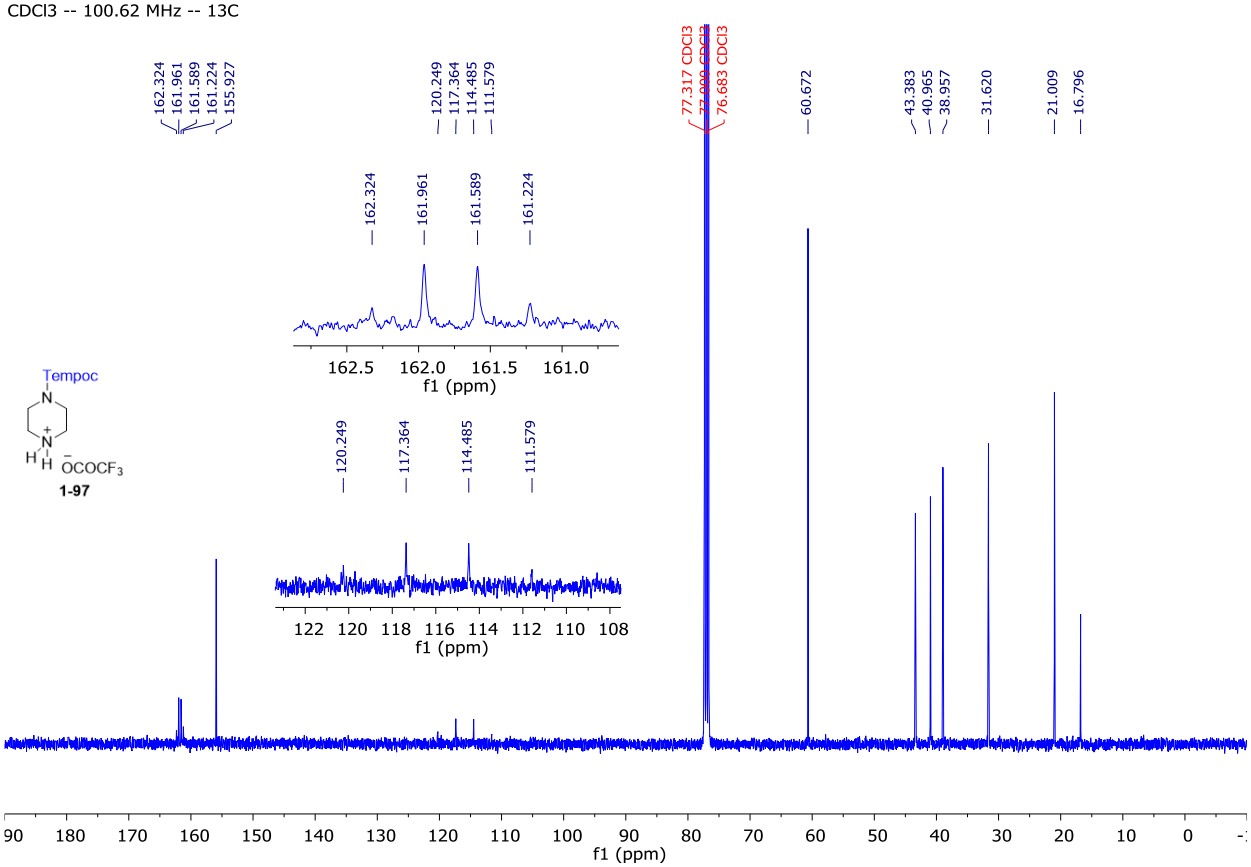
CDCl3 -- 300.23 MHz -- 1H

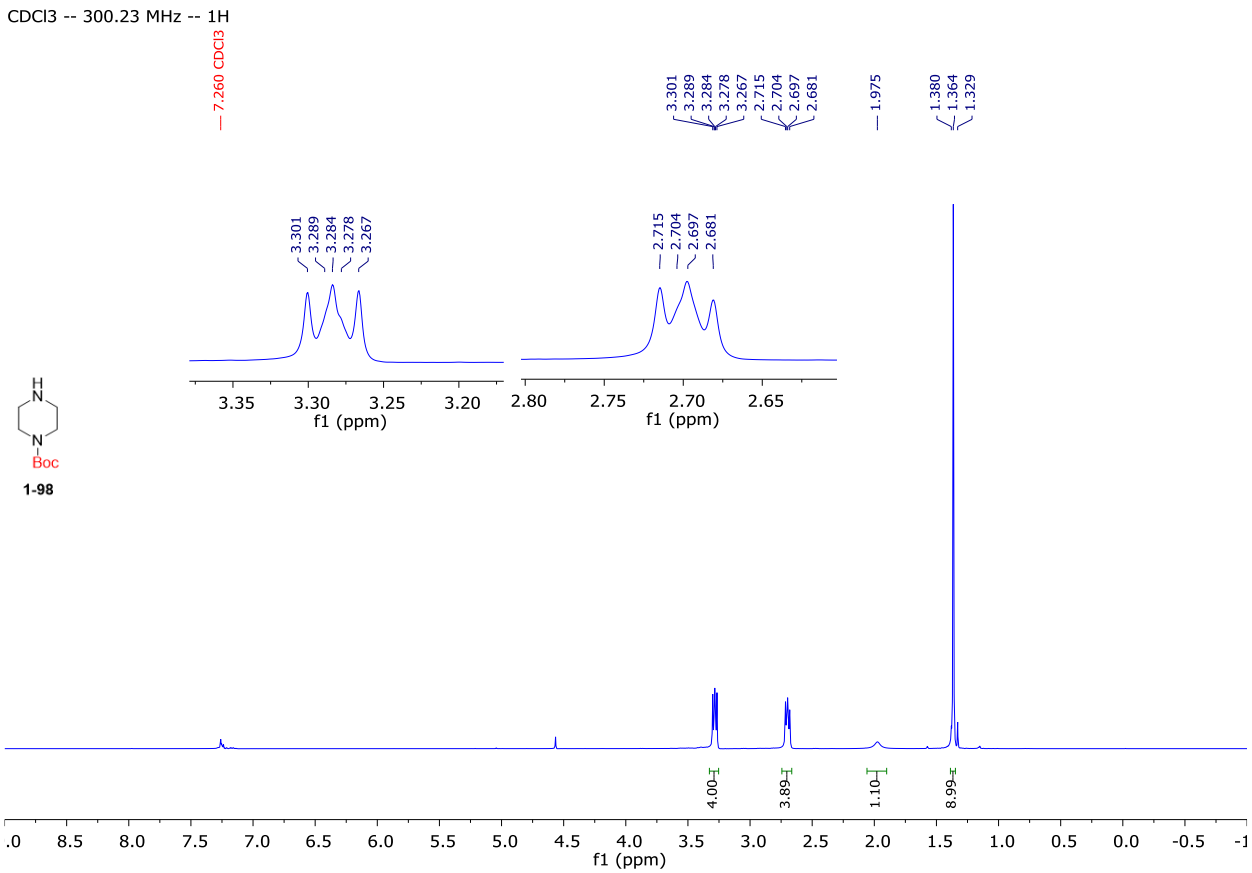


CDCl3 -- 75.50 MHz -- 13C

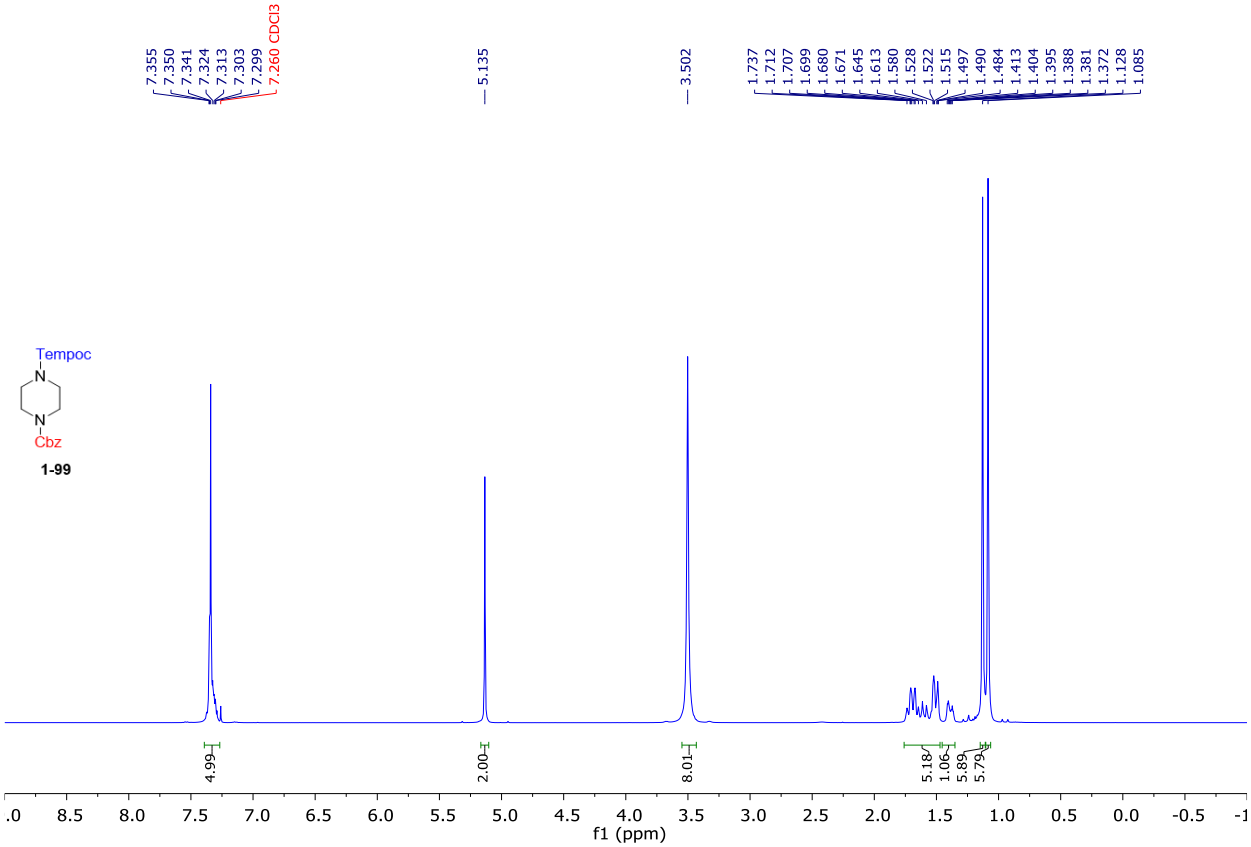



CDCl3 -- 500.16 MHz -- 1H
9.915
7.260 CDCl3
3.844
3.833
3.823
3.203
3.193
3.183
1.736
1.712
1.705
1.690
1.682
1.656
1.628
1.604
1.597
1.561
1.556
1.550
1.536
1.530
1.525
1.438
1.432
1.426
1.414
1.406
1.146
1.090
Tempoc
OCOCF3
1-97
2.05
3.92
4.20
6.12
1.11
6.03
6.02
f1 (ppm)

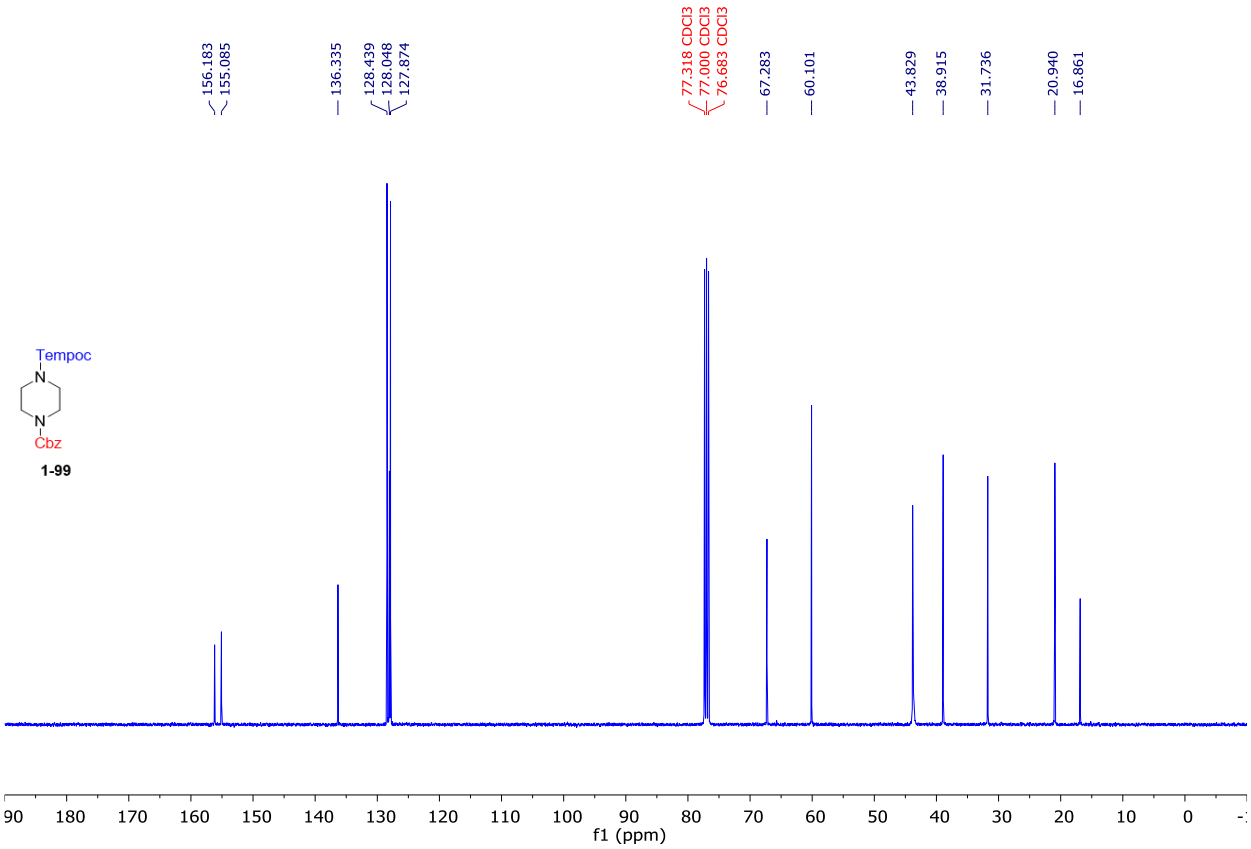

CDCl3 -- 100.62 MHz -- 13C
162.324
161.961
161.589
161.224
155.927
120.249
117.364
114.485
111.579
77.317 CDCl3
77.000 CDCl3
76.683 CDCl3
60.672
43.383
40.965
38.957
31.620
21.009
16.796
Tempoc
OCOCF3
1-97
f1 (ppm)
f1 (ppm)
f1 (ppm)

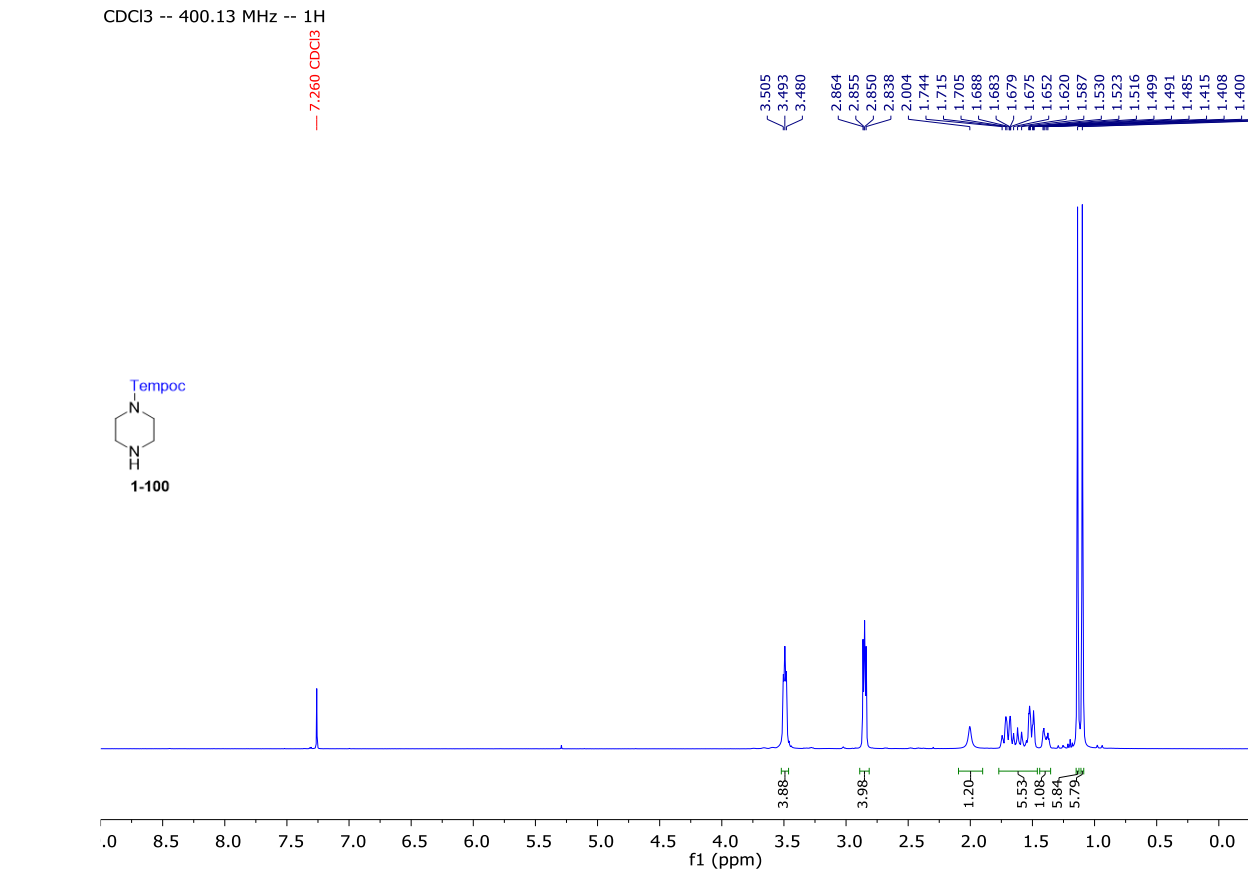

CDCl3 -- 300.23 MHz -- 1H
7.260 CDCl3
3.301
3.289
3.284
3.278
3.267
2.715
2.704
2.697
2.681
1.975
1.380
1.364
1.329
H
N
N
Boc
1-98
3.35
3.30
3.25
3.20
f1 (ppm)
2.80
2.75
2.70
2.65
f1 (ppm)
4.00
3.89
1.10
8.99
f1 (ppm)

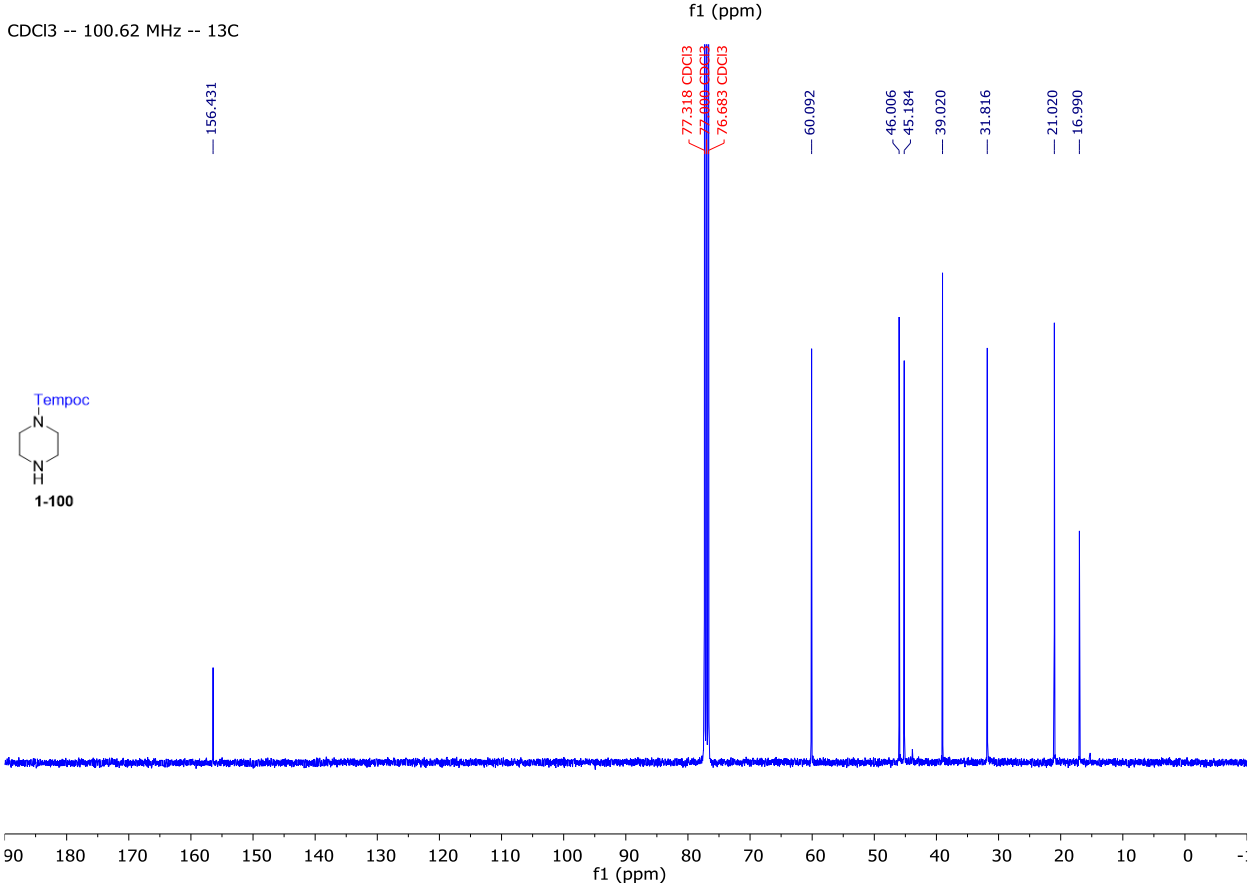
CDCl3 -- 400.13 MHz -- 1H

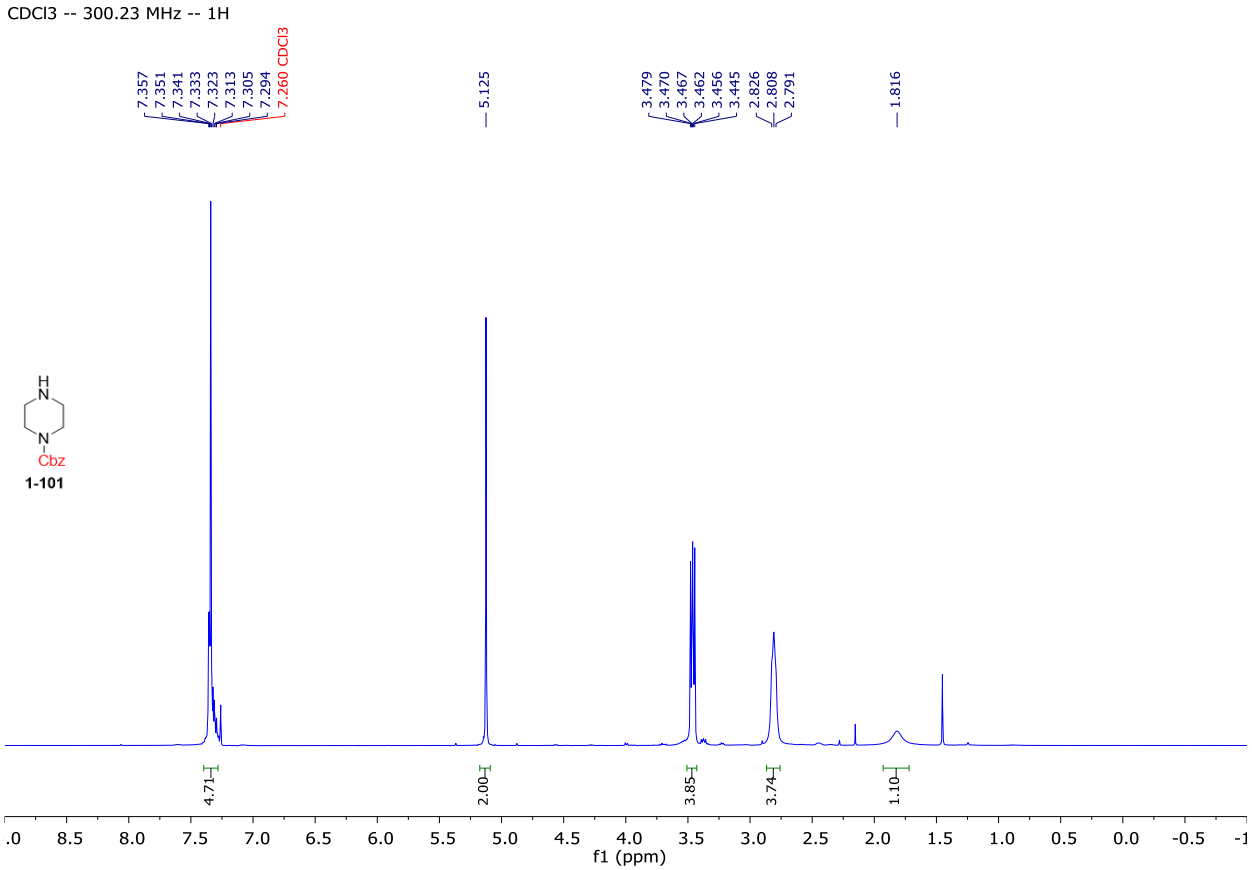


CDCl3 -- 100.62 MHz -- 13C



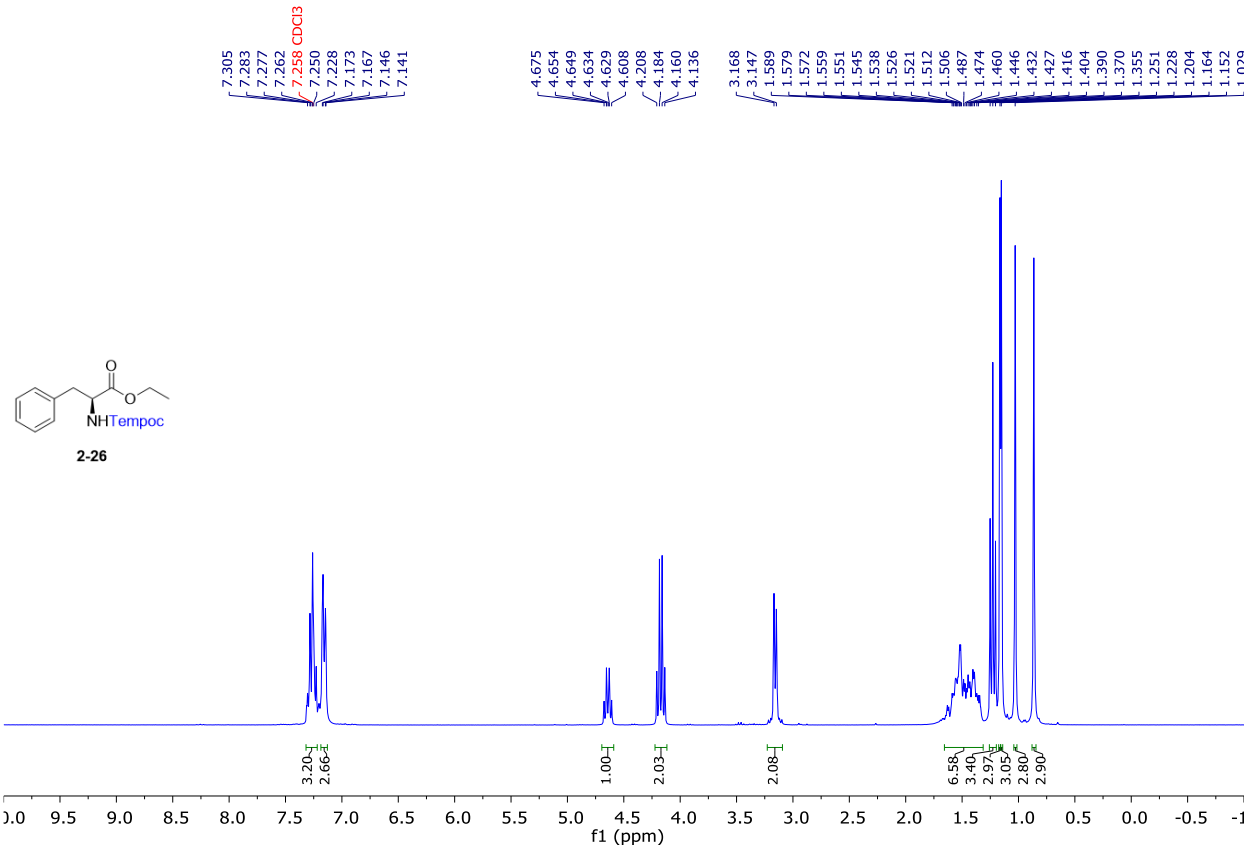

CDCl3 -- 400.13 MHz -- 1H
7.260 CDCl3
3.505
3.493
3.480
2.864
2.855
2.850
2.838
2.004
1.744
1.715
1.705
1.688
1.683
1.679
1.675
1.652
1.620
1.587
1.530
1.523
1.516
1.499
1.491
1.485
1.415
1.408
1.400
Tempoc
1-100
3.88
3.98
1.20
5.53
1.08
5.84
5.79
f1 (ppm)


CDCl3 -- 100.62 MHz -- 13C
156.431
77.318 CDCl3
76.683 CDCl3
60.092
46.006
45.184
39.020
31.816
21.020
16.990
Tempoc
1-100
f1 (ppm)


CDCl3 -- 300.23 MHz -- 1H
7.357
7.351
7.341
7.333
7.323
7.313
7.305
7.294
7.260 CDCl3
5.125
3.479
3.470
3.467
3.462
3.456
3.445
2.826
2.808
2.791
1.816
H
N
N
Cbz
1-101
4.71
2.00
3.85
3.74
1.10
f1 (ppm)

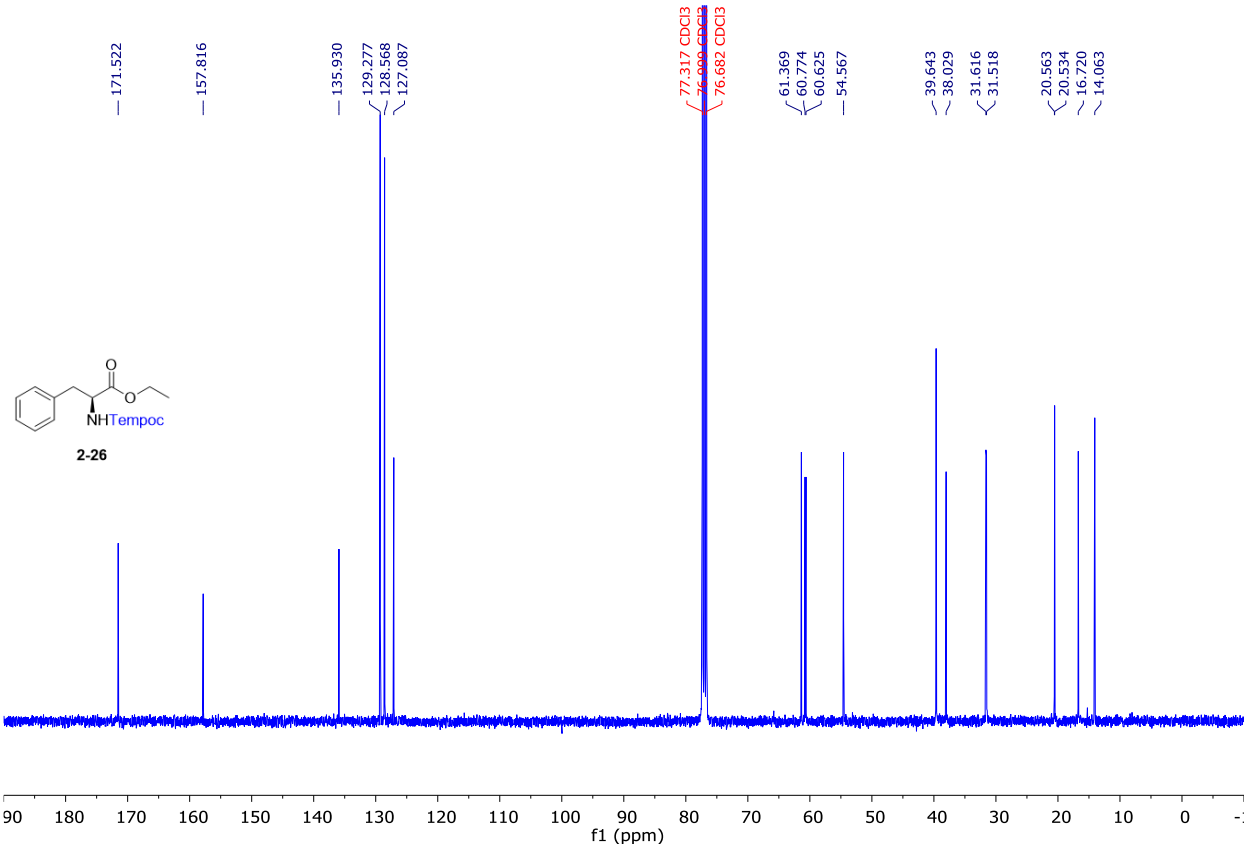
APPENDIX D : SELECTED NMR SPECTRA (CHAPTER 2)

300.23 MHz — CDCl3 — 1D — 1H



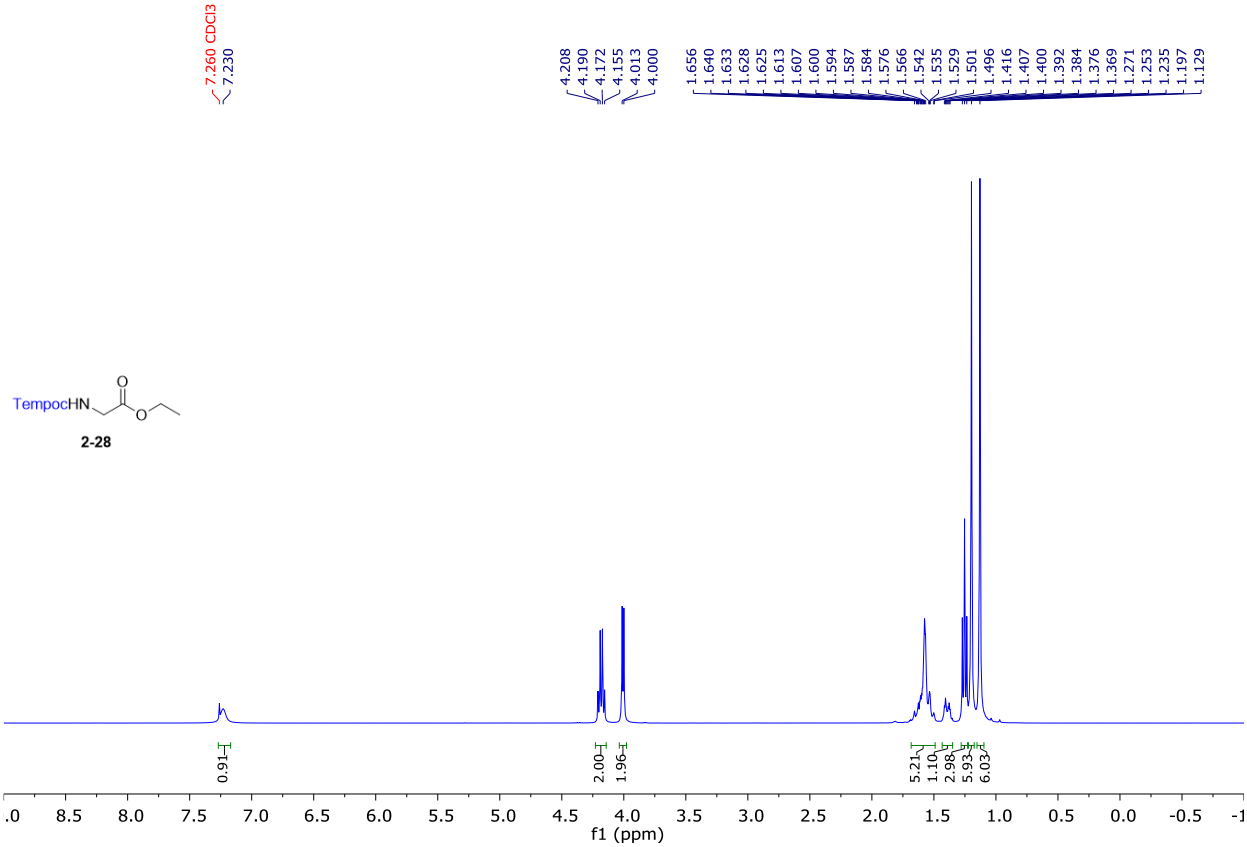
2-26

100.62 MHz — CDCl3 — 1D — 13C

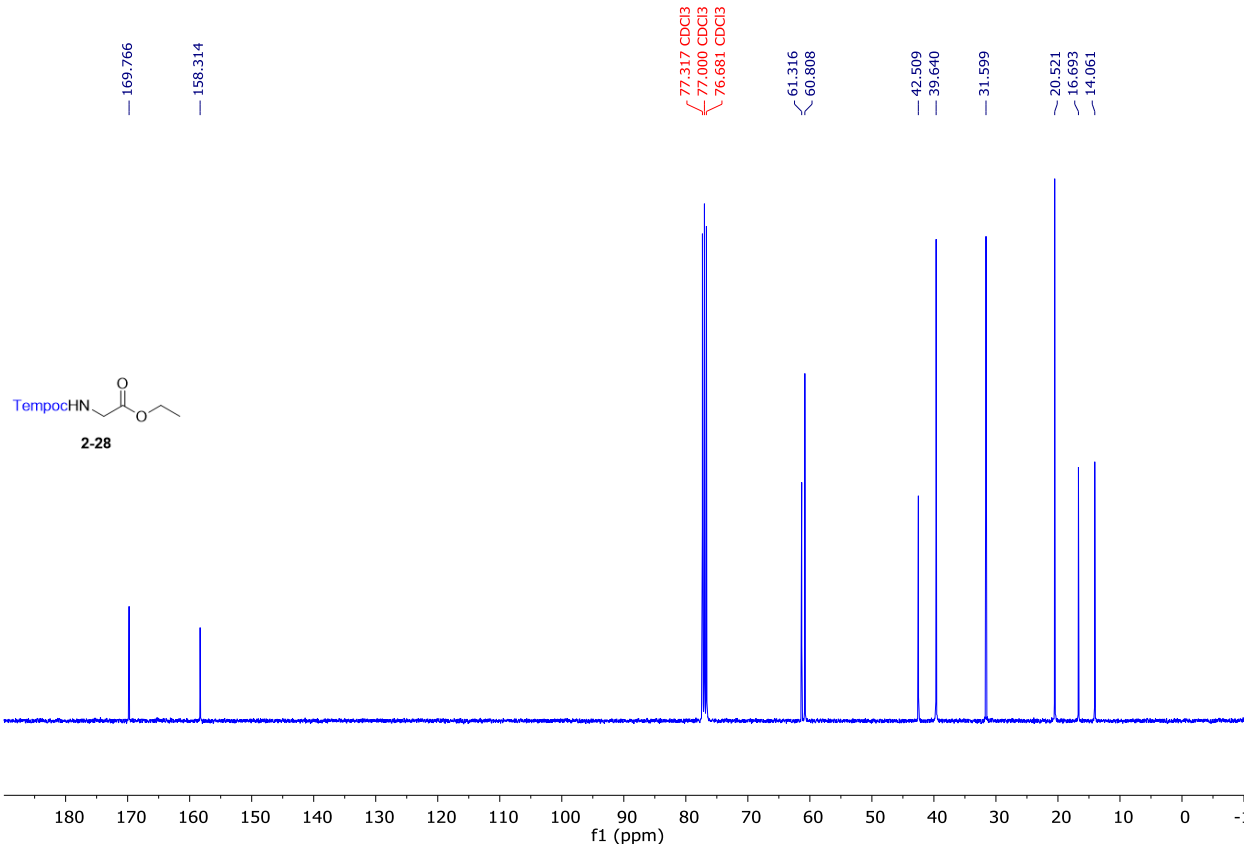


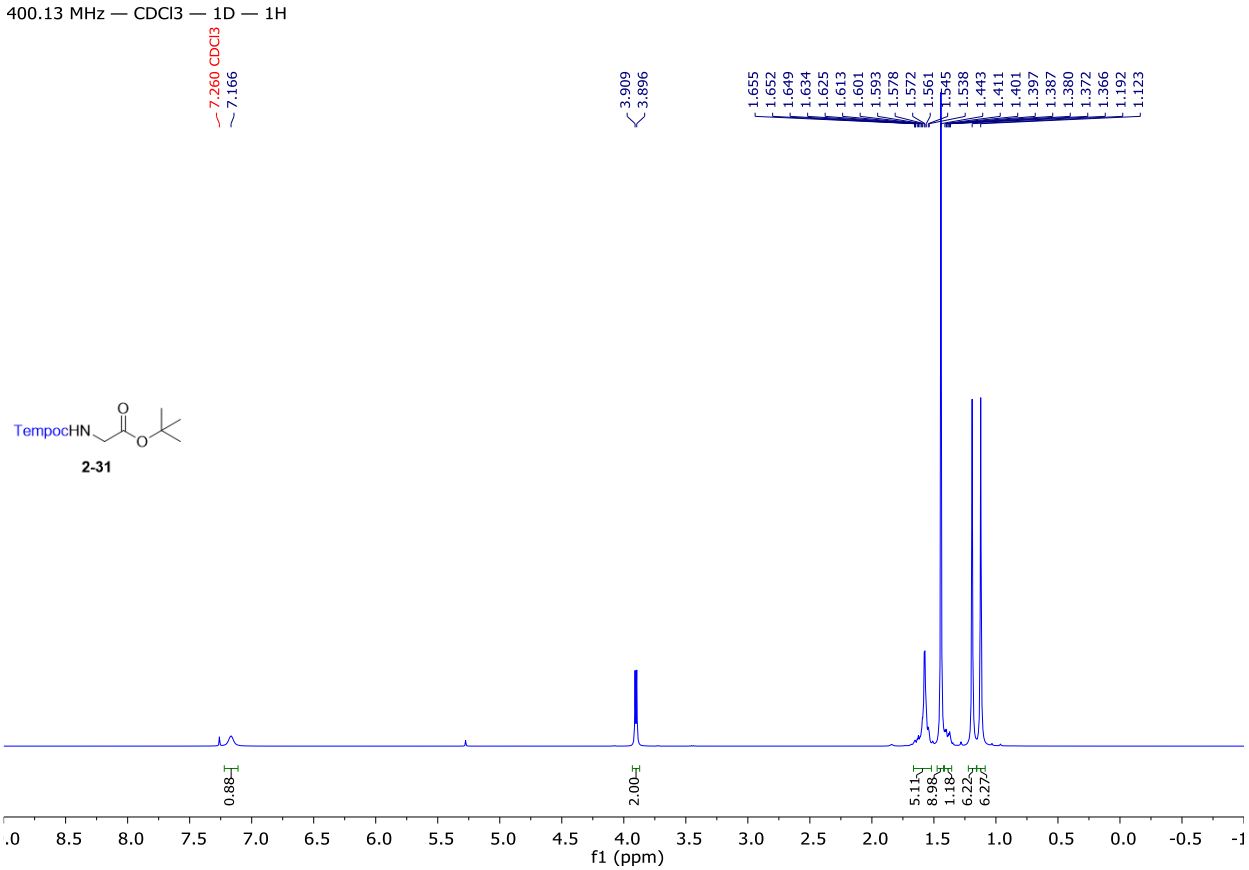
2-26

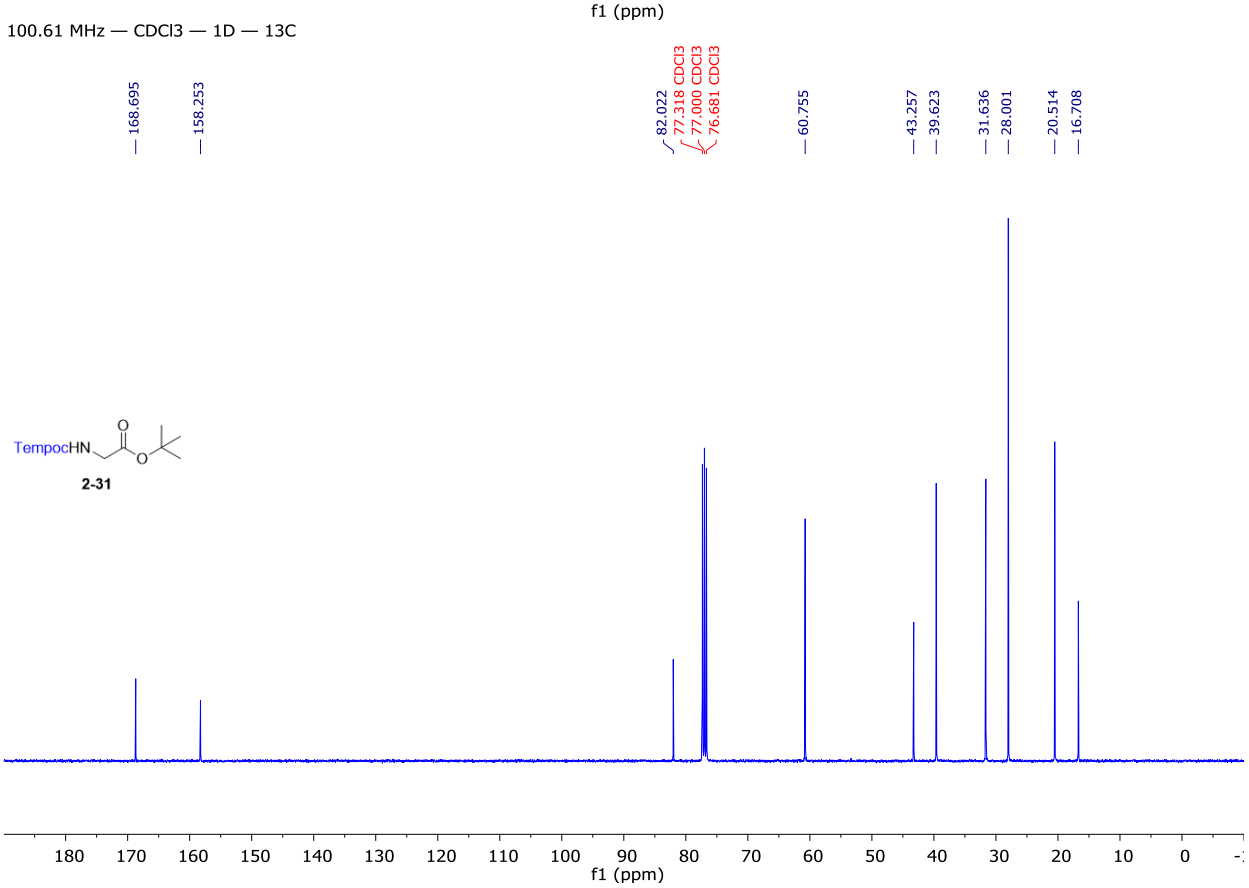
400.13 MHz — CDCl3 — 1D — 1H



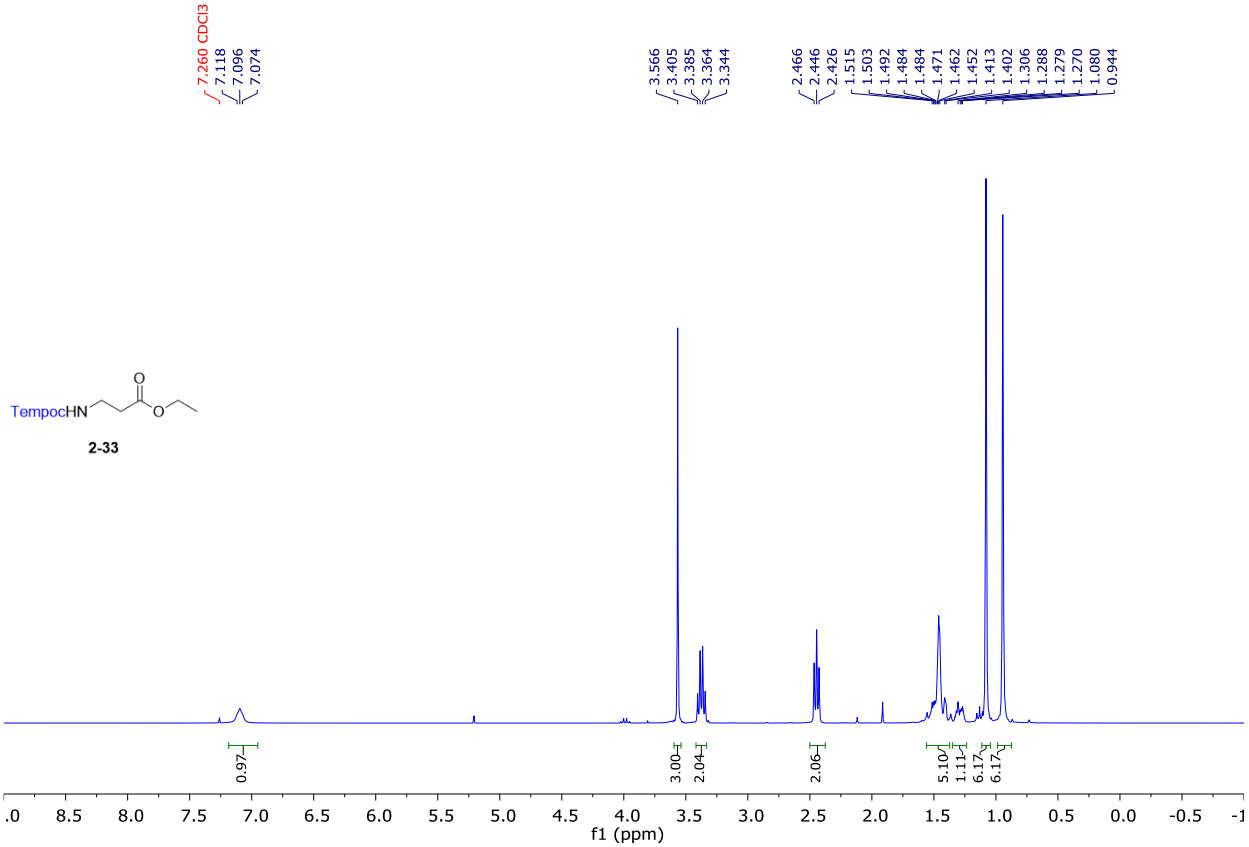
100.61 MHz — CDCl3 — 1D — 13C



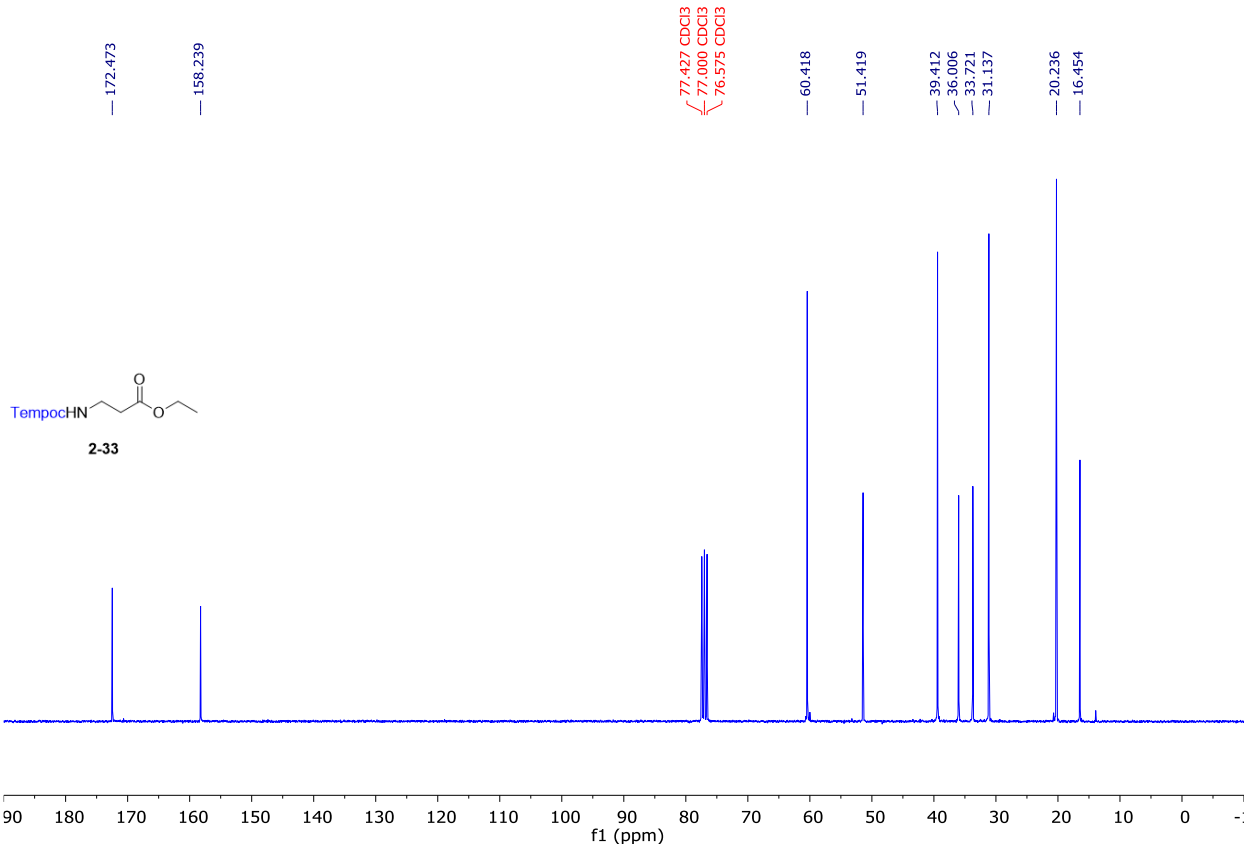

400.13 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
7.166
3.909
3.896
1.655
1.652
1.649
1.634
1.625
1.613
1.601
1.593
1.578
1.572
1.561
1.545
1.538
1.443
1.411
1.401
1.397
1.387
1.380
1.372
1.366
1.192
1.123
TempocHN
O
O
2-31
0.88
2.00
5.11
8.98
1.18
6.22
6.27
f1 (ppm)


100.61 MHz — CDCl3 — 1D — 13C
168.695
158.253
82.022
77.318 CDCl3
77.000 CDCl3
76.681 CDCl3
60.755
43.257
39.623
31.636
28.001
20.514
16.708
TempocHN
O
O
2-31
f1 (ppm)

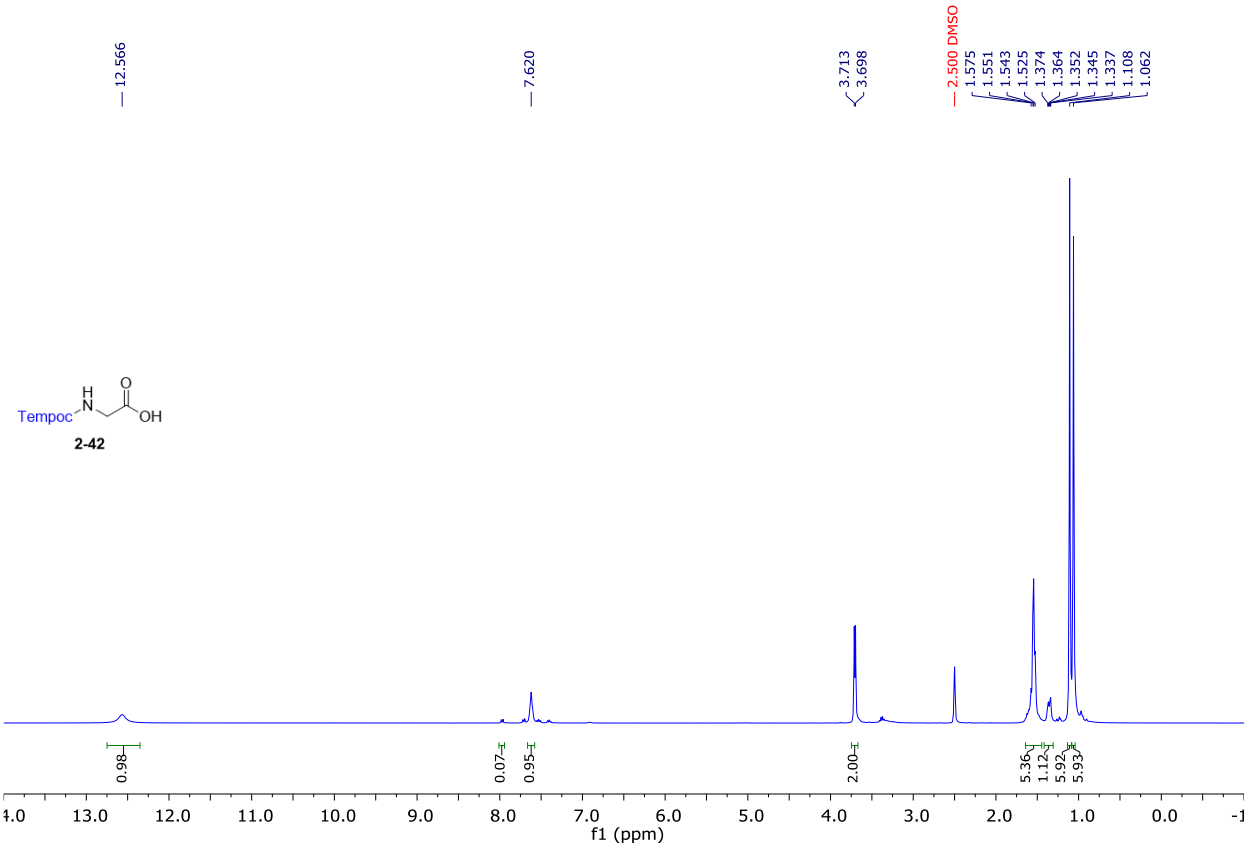
300.23 MHz — CDCl3 — 1D — 1H



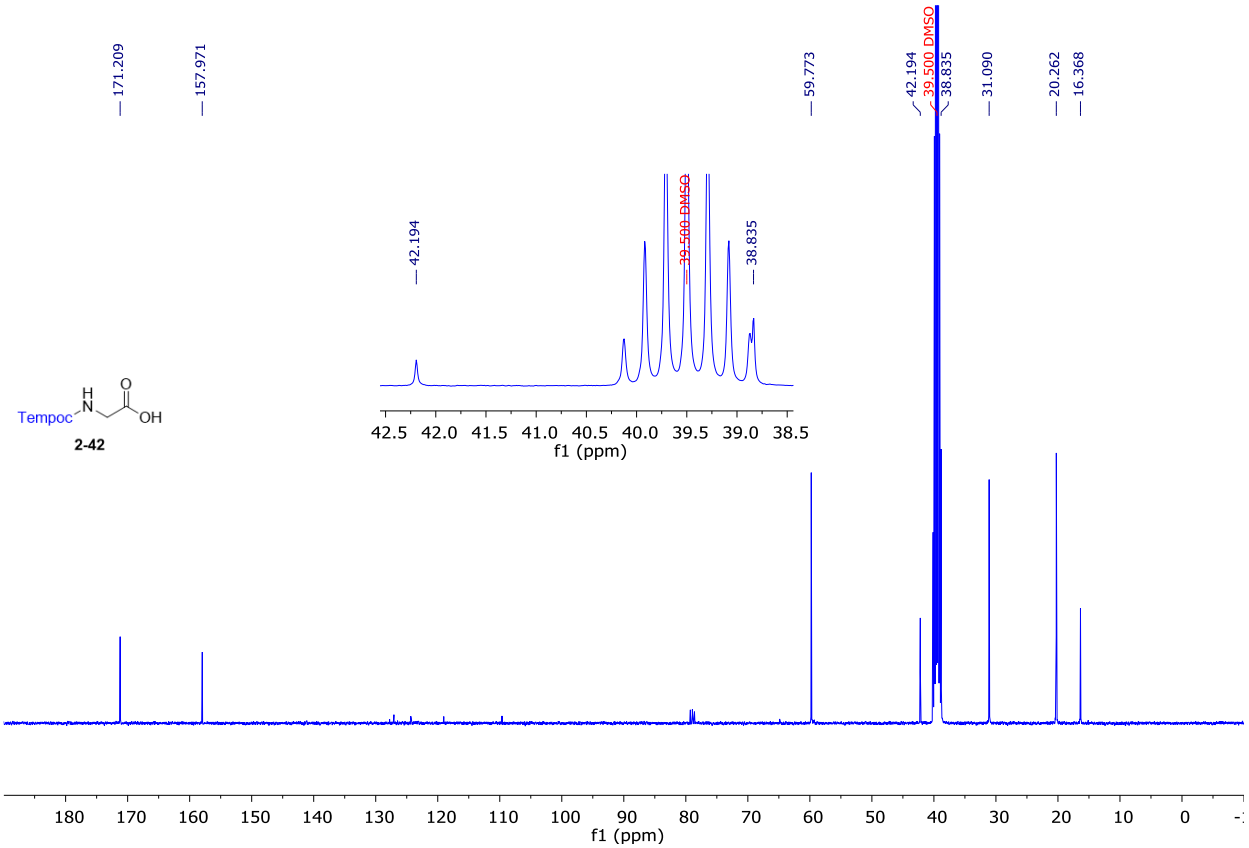
75.50 MHz — CDCl3 — 1D — 13C



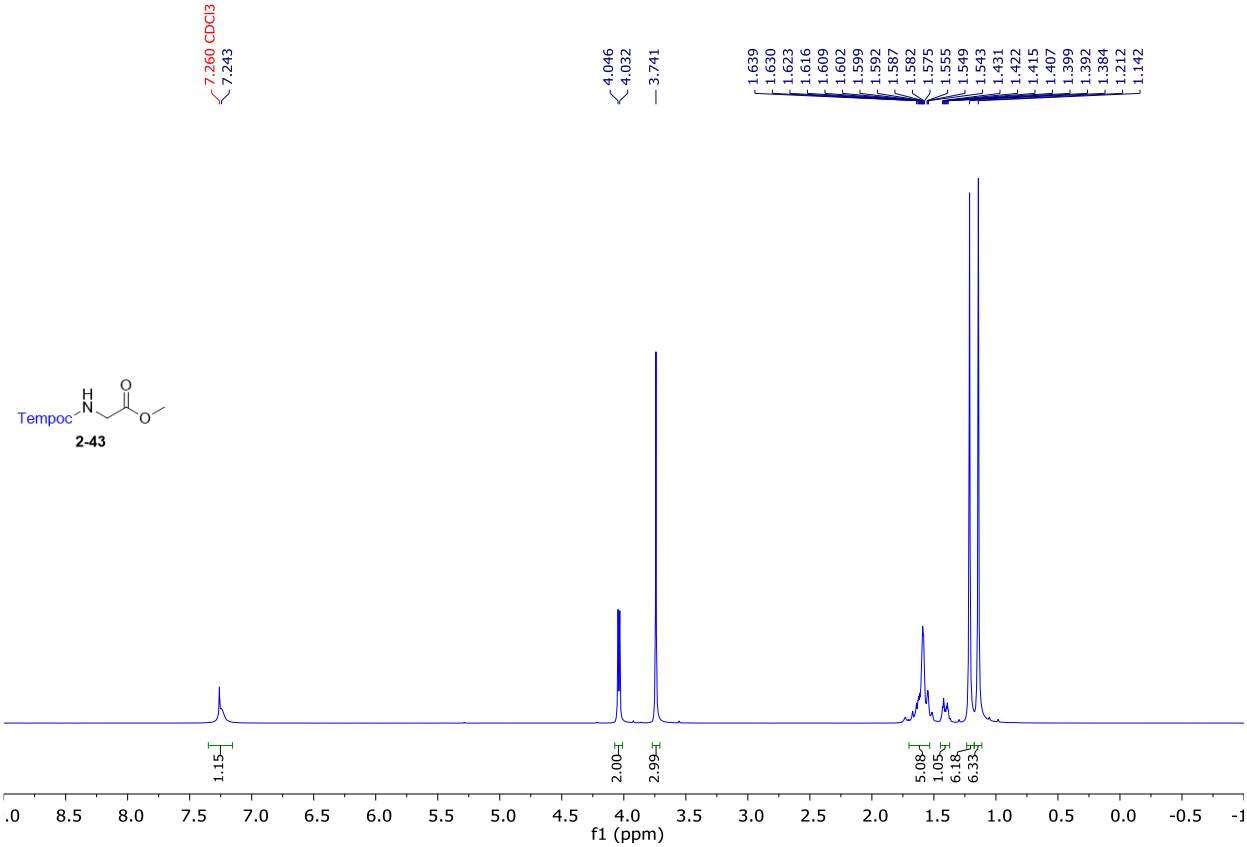
400.13 MHz — DMSO — 1D — 1H



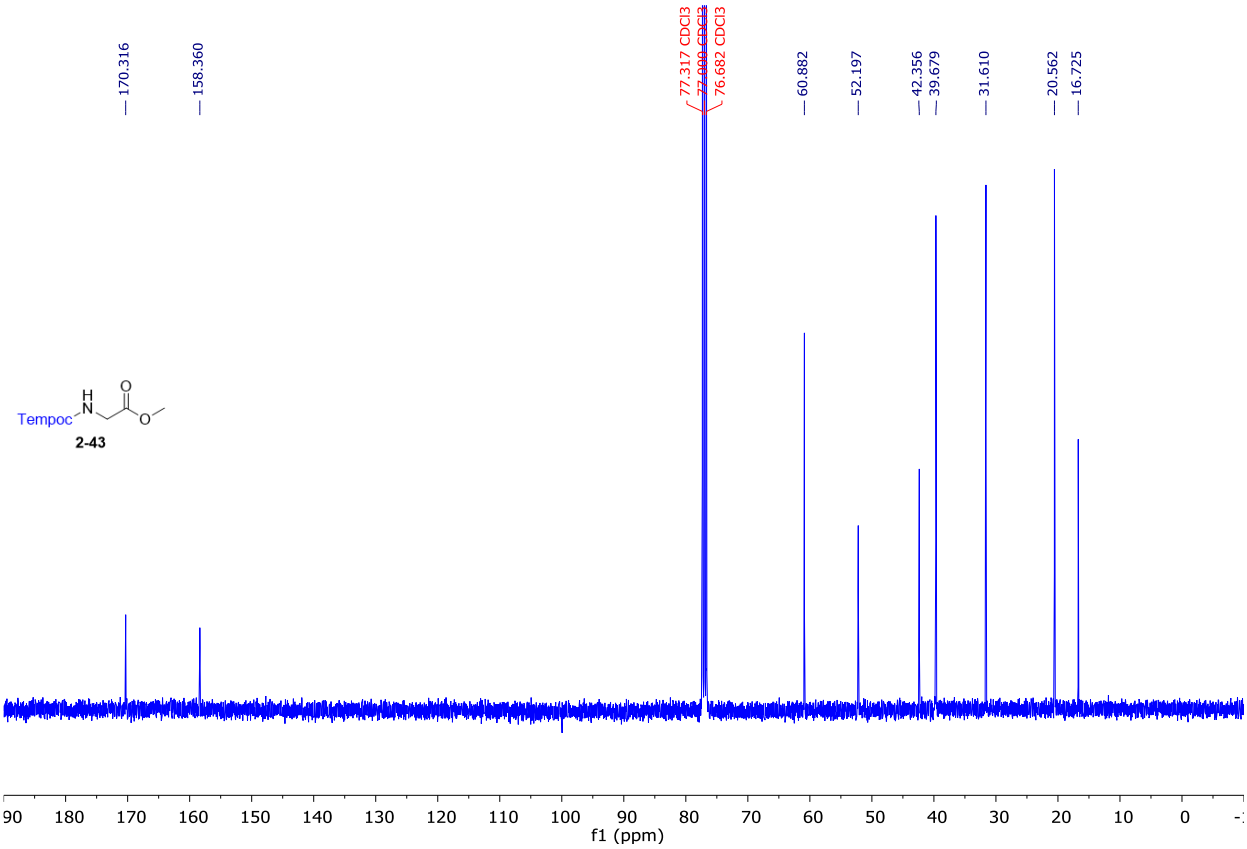
100.61 MHz — DMSO — 1D — 13C



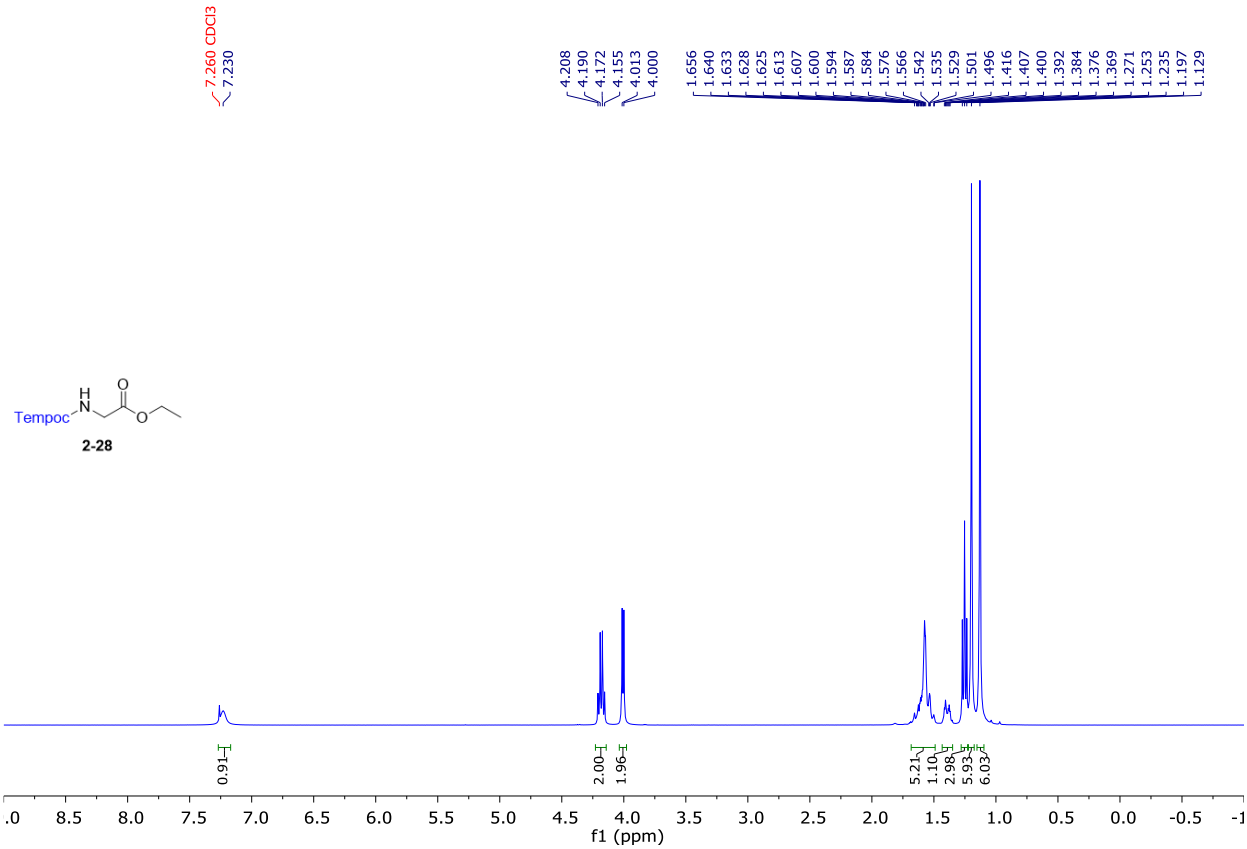
400.13 MHz — CDCl3 — 1D — 1H



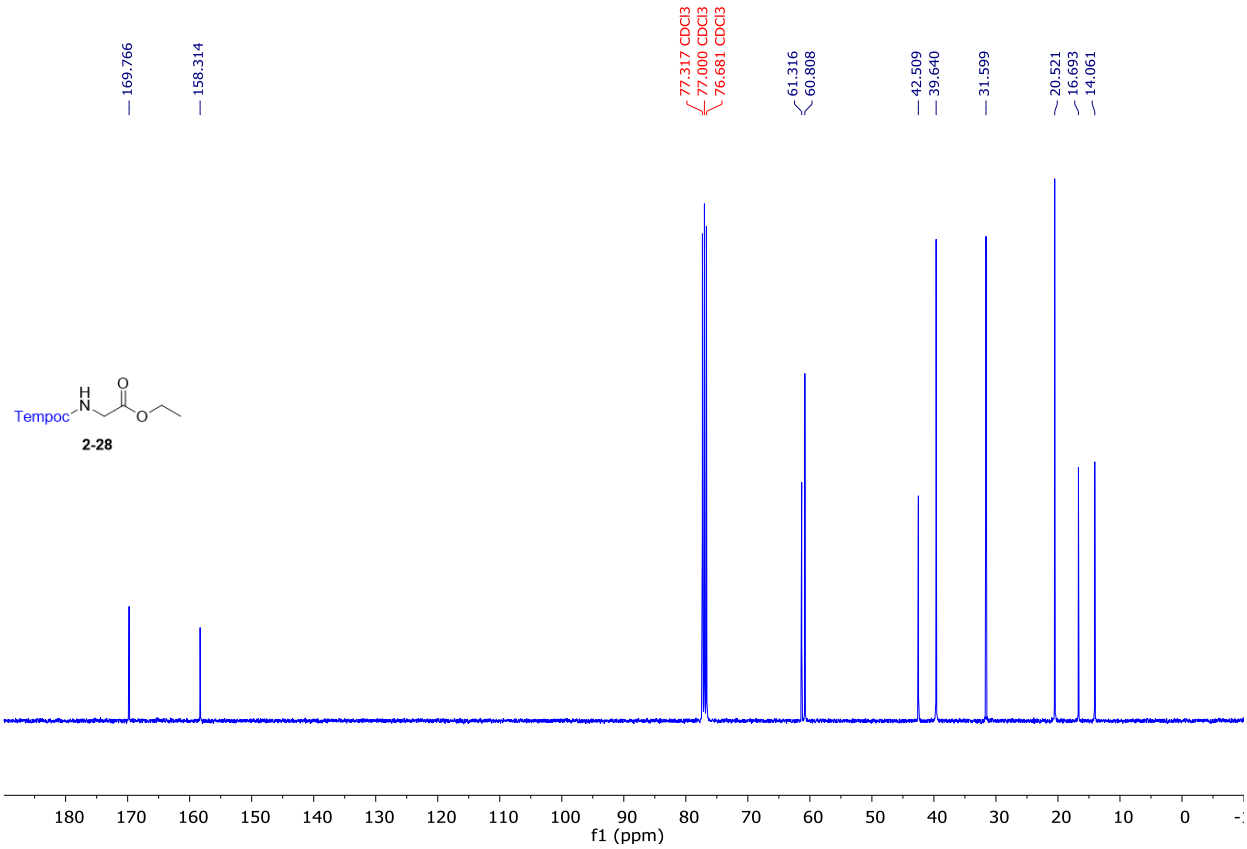
100.62 MHz — CDCl3 — 1D — 13C



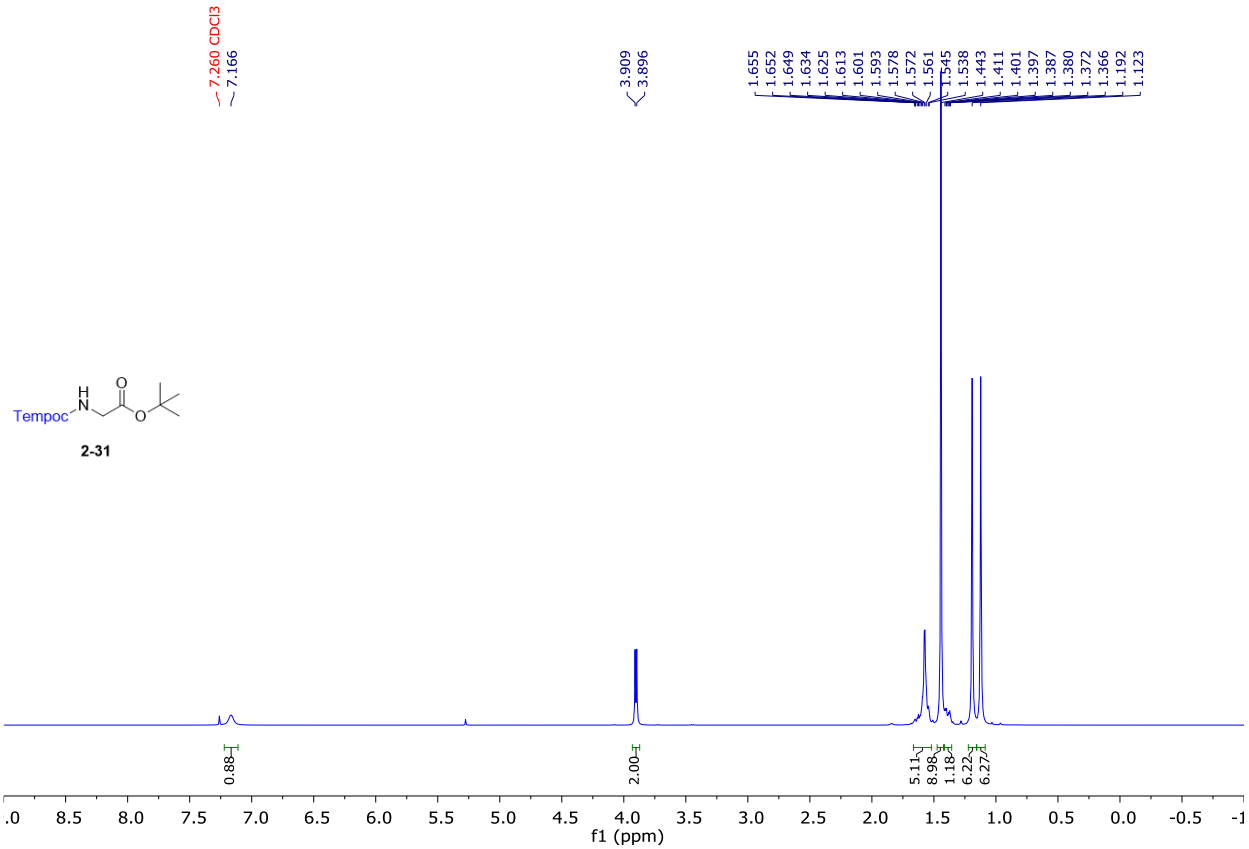
400.13 MHz — CDCl3 — 1D — 1H



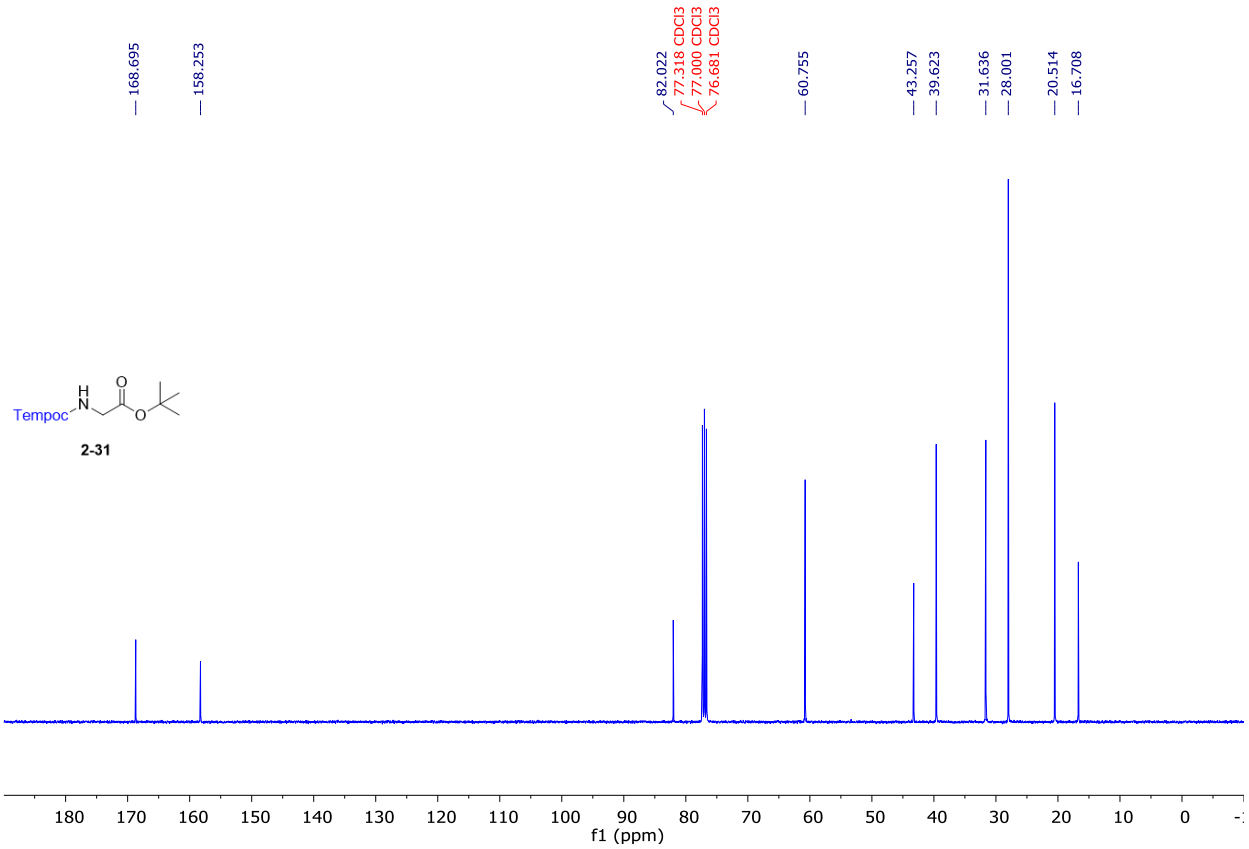
100.61 MHz — CDCl3 — 1D — 13C

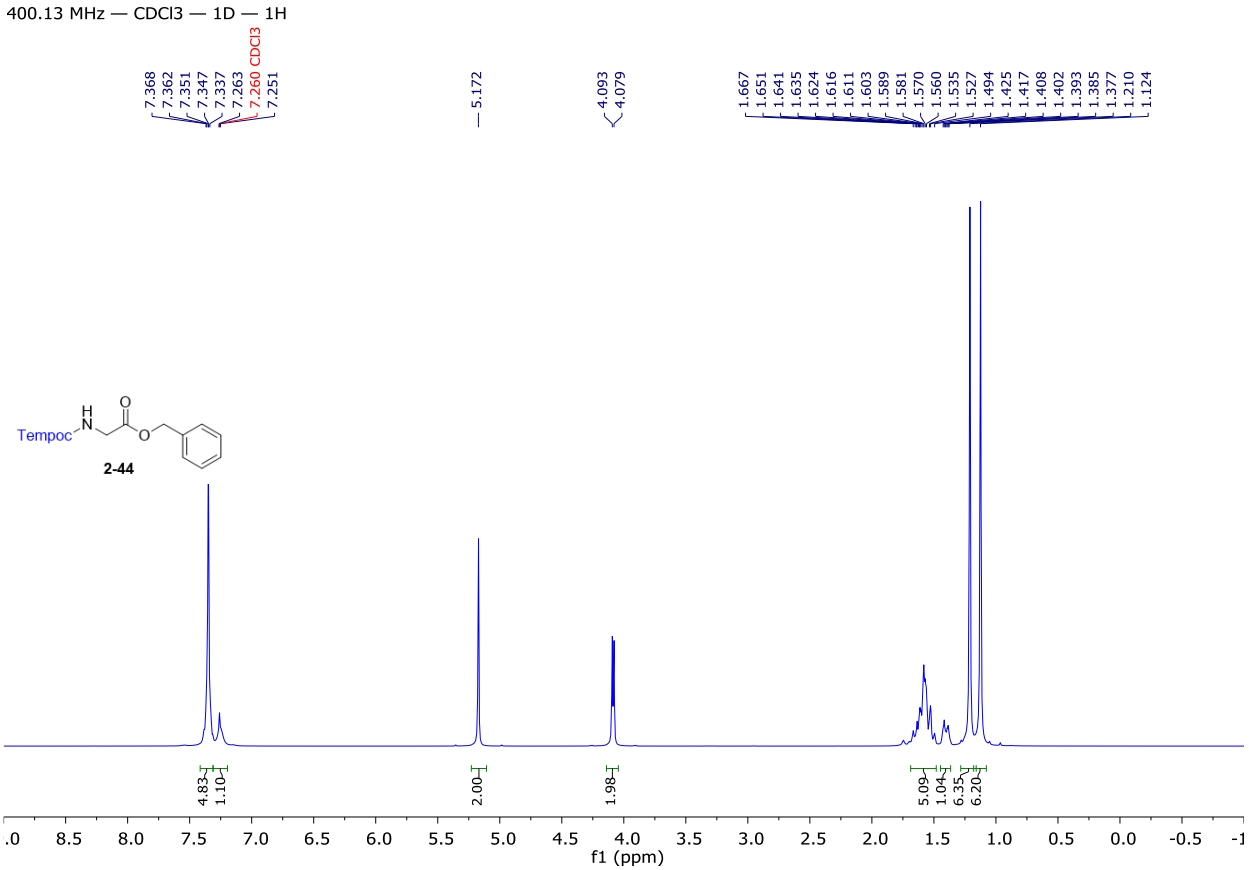


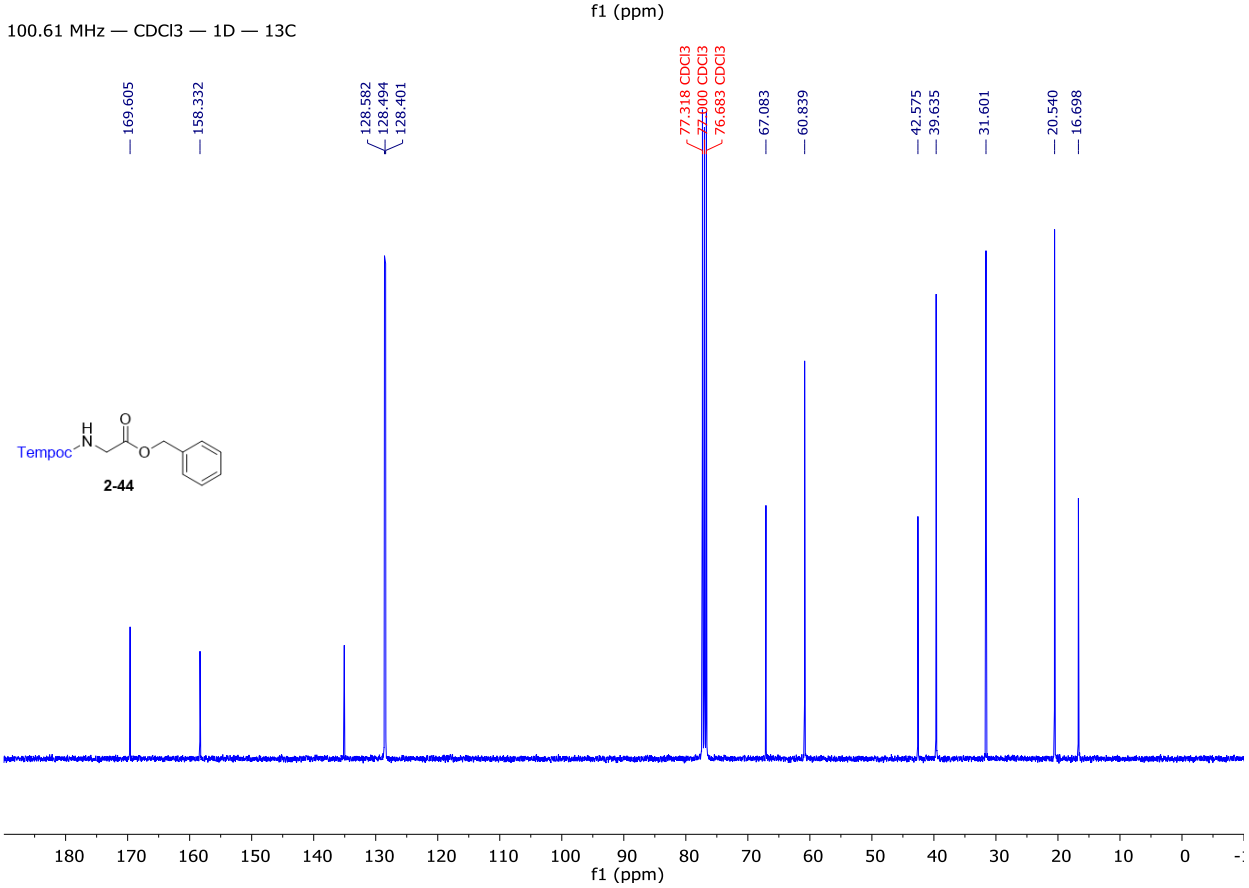
400.13 MHz — CDCl3 — 1D — 1H



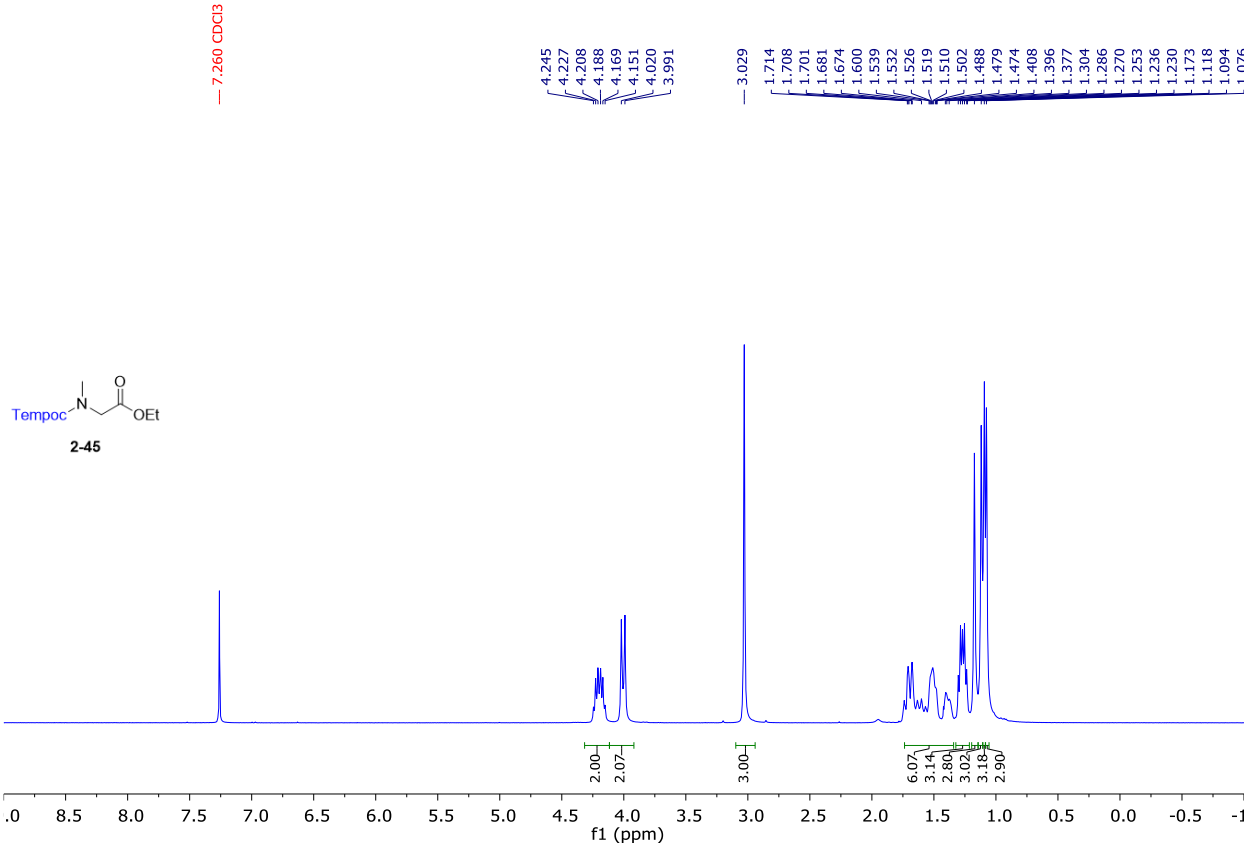
100.61 MHz — CDCl3 — 1D — 13C



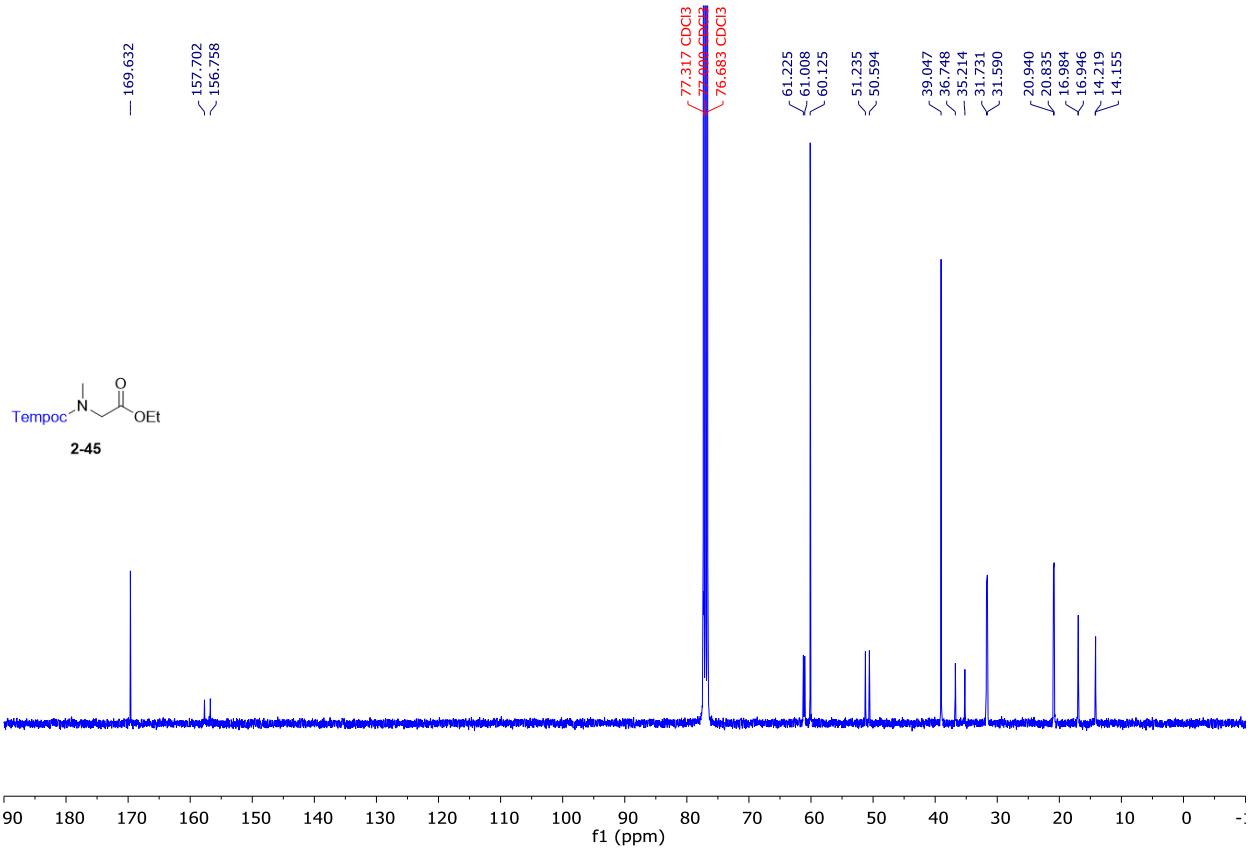

400.13 MHz — CDCl3 — 1D — 1H
7.368
7.362
7.351
7.347
7.337
7.263
7.260 CDCl3
7.251
5.172
4.093
4.079
1.667
1.651
1.641
1.635
1.624
1.616
1.611
1.603
1.589
1.581
1.570
1.560
1.535
1.527
1.494
1.425
1.417
1.408
1.402
1.393
1.385
1.377
1.210
1.124
Tempoc
2-44
4.83
1.10
2.00
1.98
5.09
1.04
6.35
6.20
f1 (ppm)

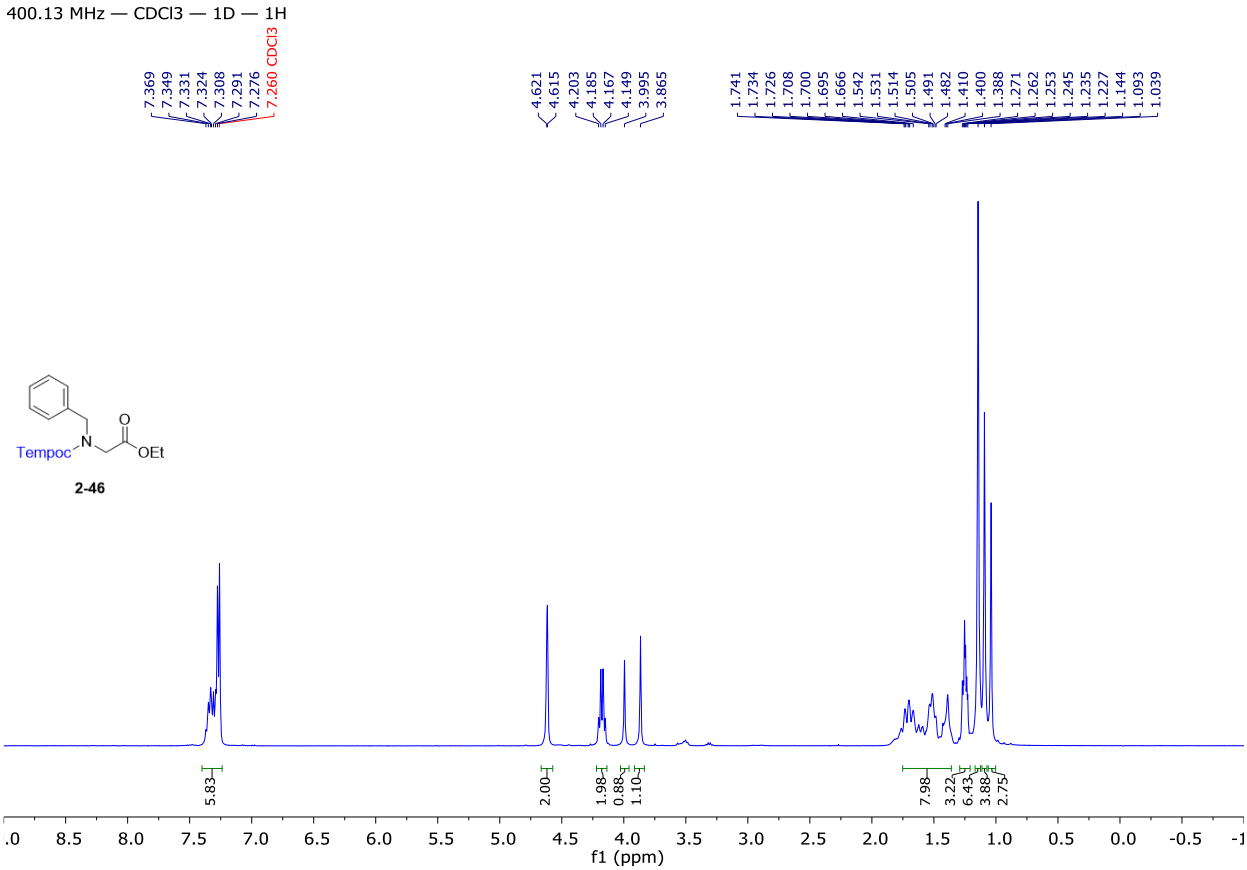

100.61 MHz — CDCl3 — 1D — 13C
169.605
158.332
128.582
128.494
128.401
77.318 CDCl3
77.000 CDCl3
76.683 CDCl3
67.083
60.839
42.575
39.635
31.601
20.540
16.698
Tempoc
2-44
f1 (ppm)

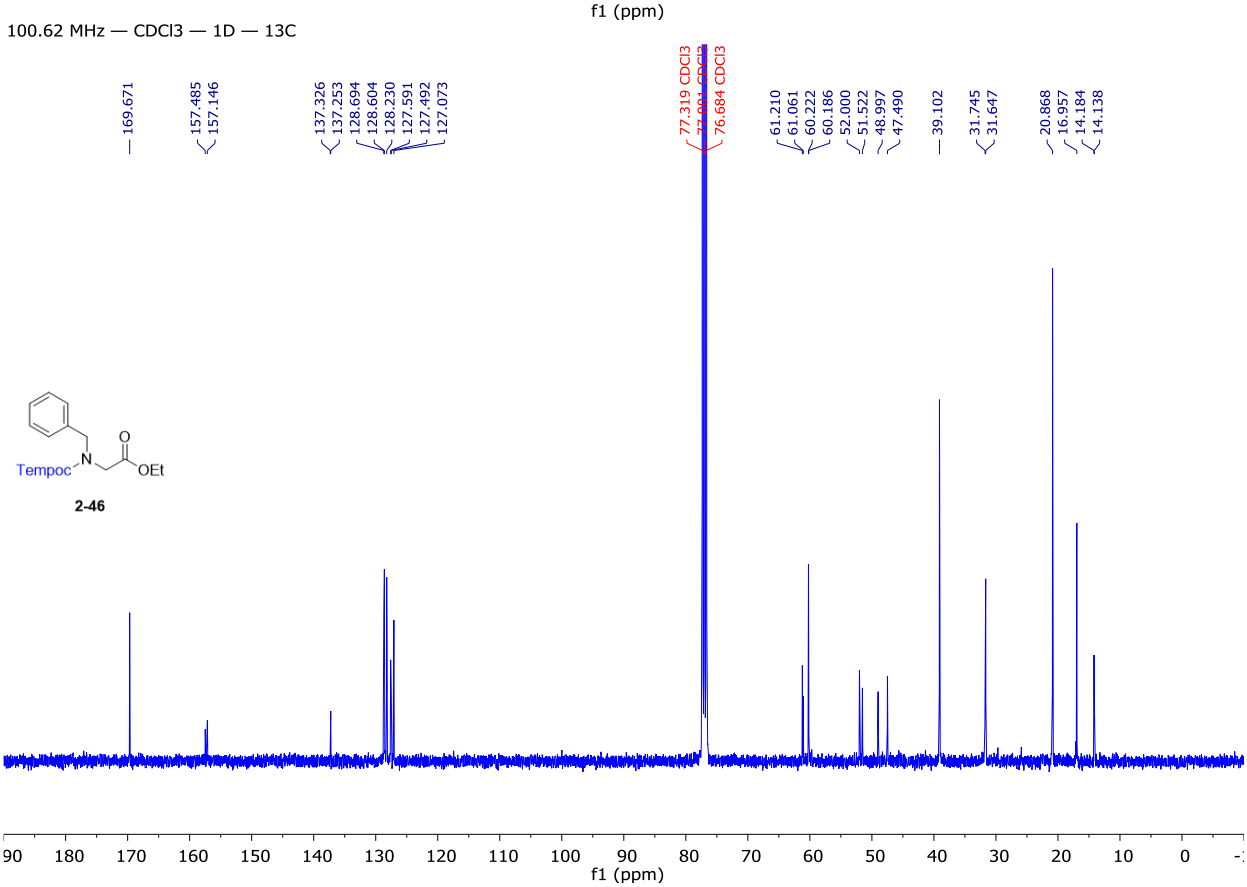
400.13 MHz — CDCl3 — 1D — 1H

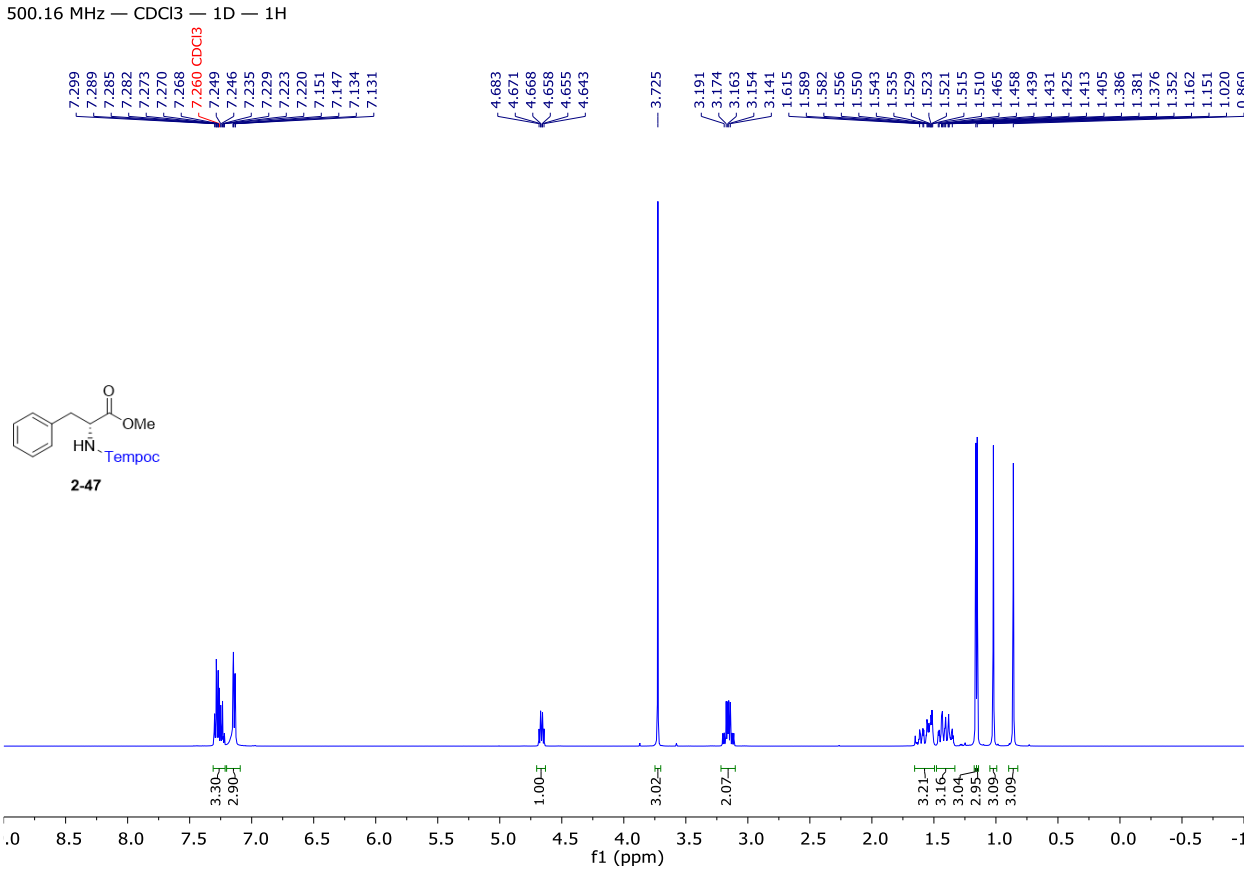


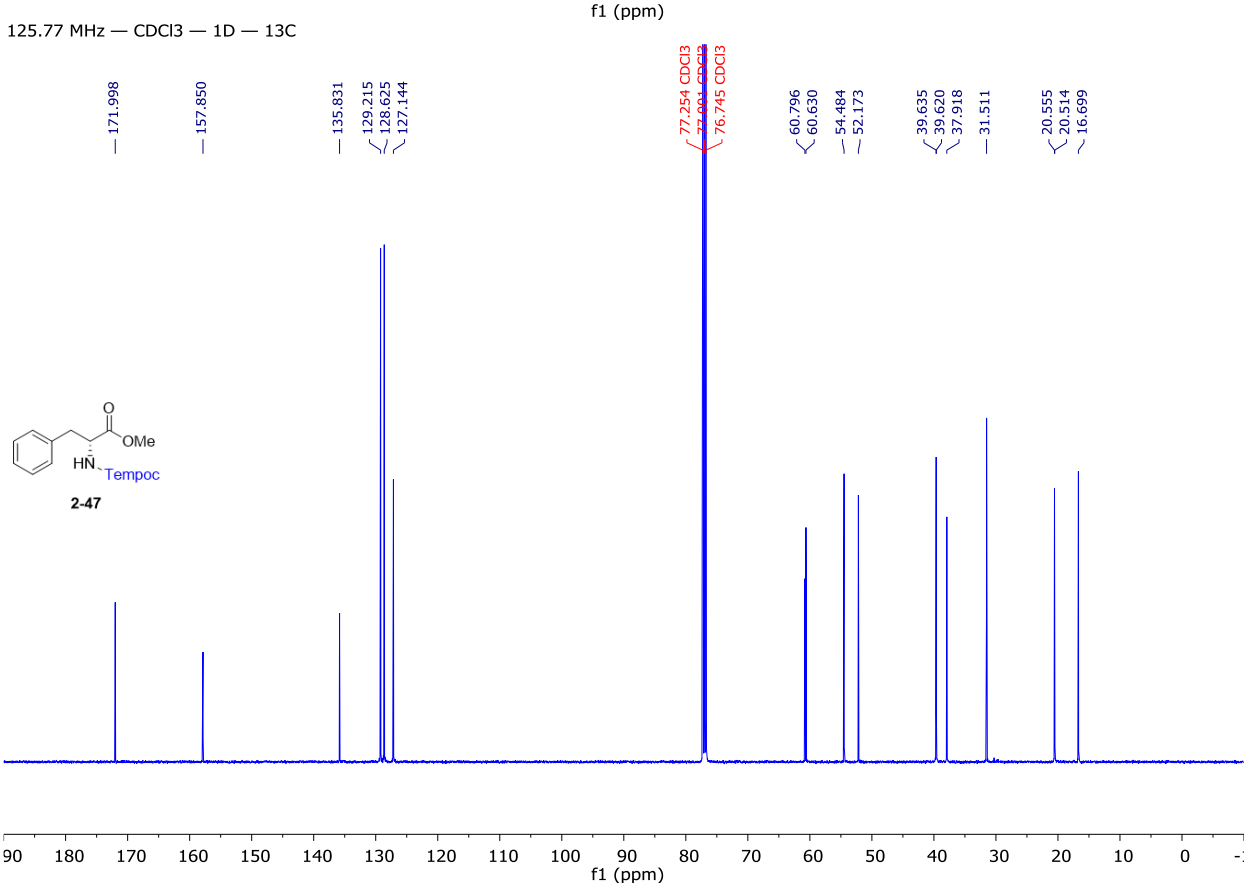
100.62 MHz — CDCl3 — 1D — 13C

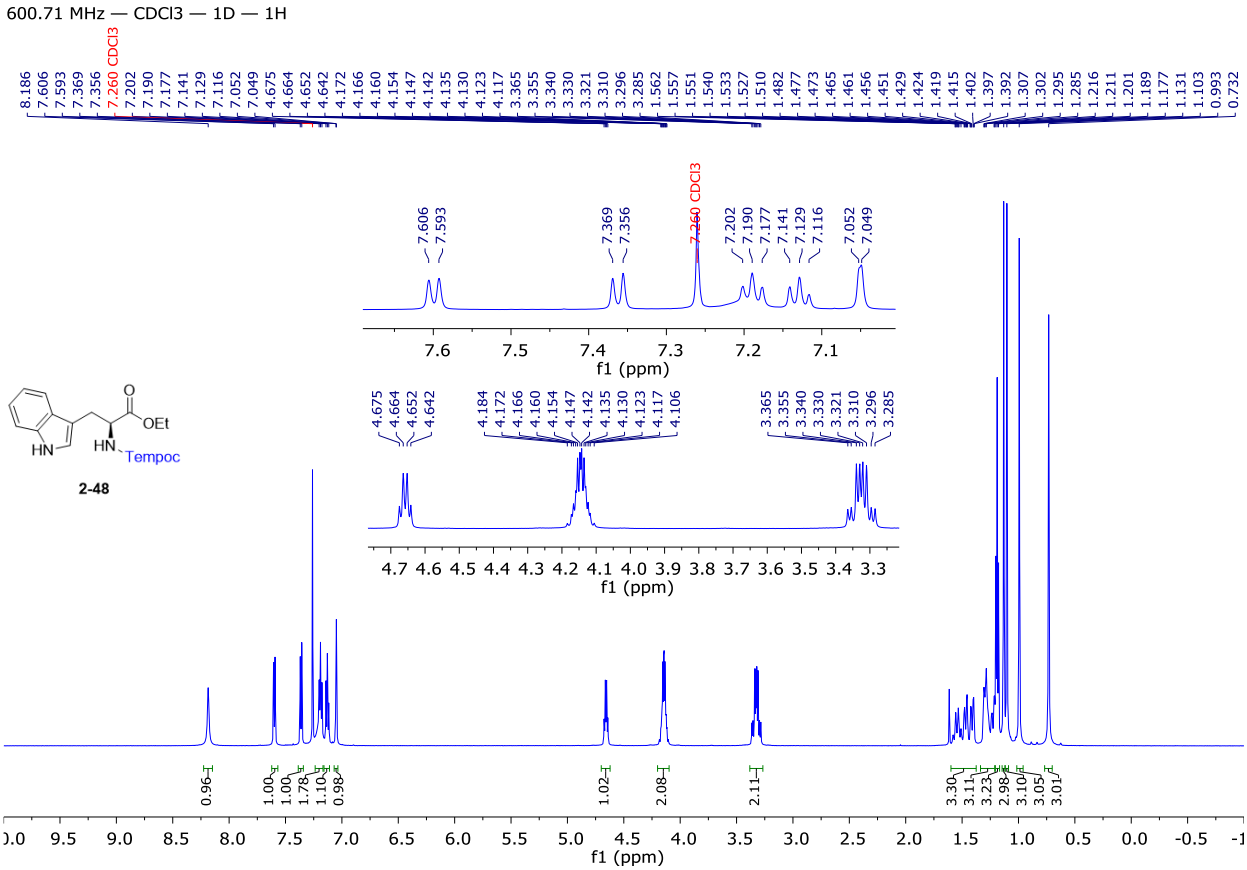


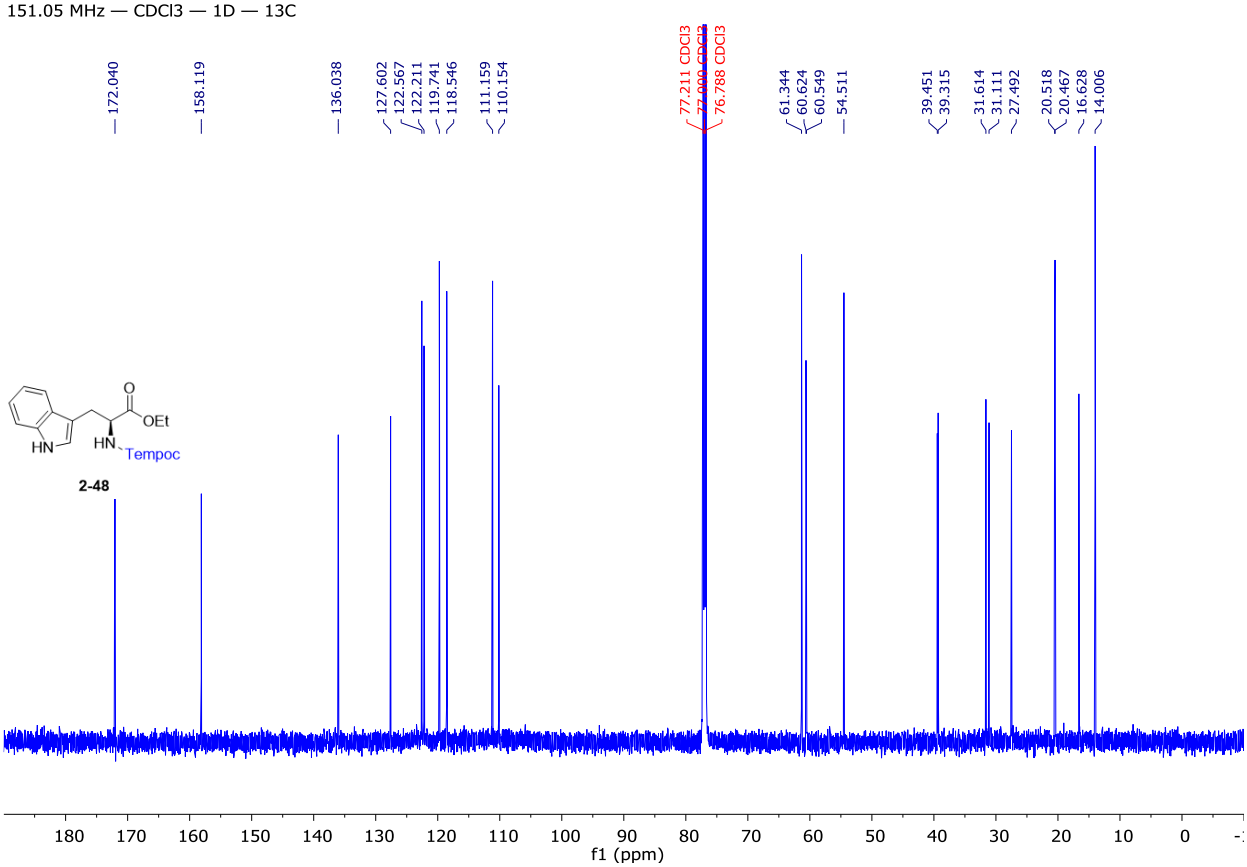

400.13 MHz — CDCl3 — 1D — 1H
7.369
7.349
7.331
7.324
7.308
7.291
7.276
7.260 CDCl3
4.621
4.615
4.203
4.185
4.167
4.149
3.995
3.865
1.741
1.734
1.726
1.708
1.700
1.695
1.666
1.542
1.531
1.514
1.505
1.491
1.482
1.410
1.400
1.388
1.271
1.262
1.253
1.245
1.235
1.227
1.144
1.093
1.039
Tempoc
N
O
OEt
2-46
5.83
2.00
1.98
0.88
1.10
7.98
3.22
6.43
3.88
2.75
f1 (ppm)


100.62 MHz — CDCl3 — 1D — 13C
169.671
157.485
157.146
137.326
137.253
128.694
128.604
128.230
127.591
127.492
127.073
77.319 CDCl3
77.001 CDCl3
76.684 CDCl3
61.210
61.061
60.222
60.186
52.000
51.522
48.997
47.490
39.102
31.745
31.647
20.868
16.957
14.184
14.138
Tempoc
N
O
OEt
2-46
f1 (ppm)

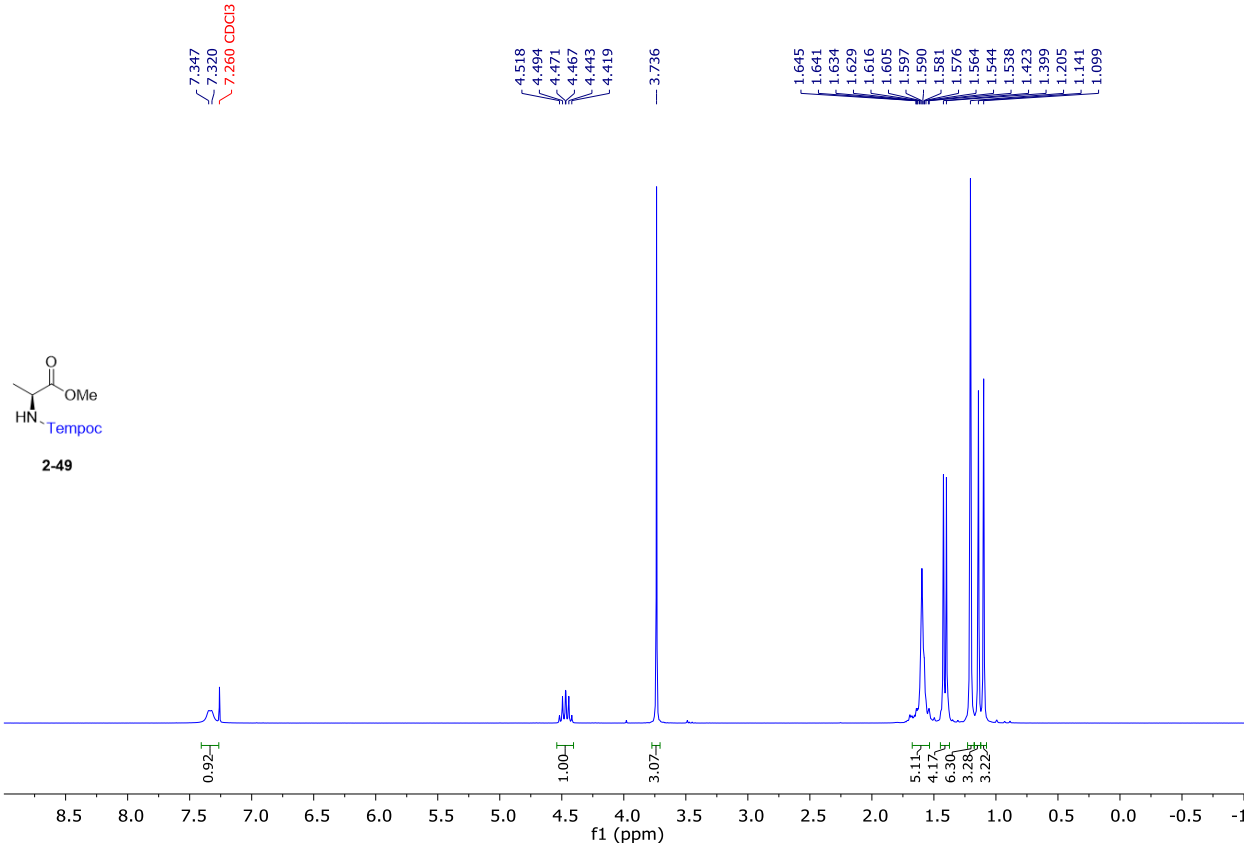

500.16 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
OMe
HN
Tempoc
2-47
f1 (ppm)


125.77 MHz — CDCl3 — 1D — 13C
77.254 CDCl3
76.745 CDCl3
OMe
HN
Tempoc
2-47
f1 (ppm)


600.71 MHz — CDCl3 — 1D — 1H
f1 (ppm)
2-48

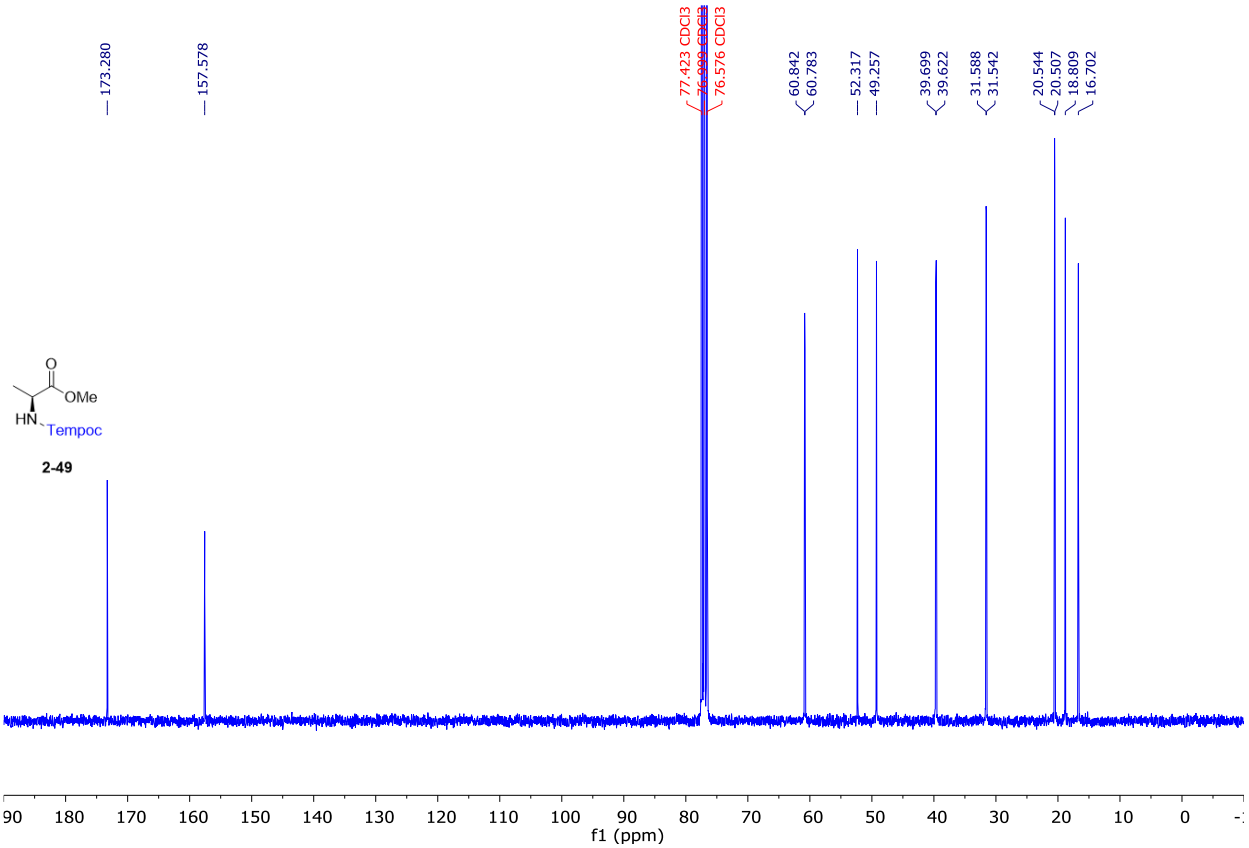

151.05 MHz — CDCl3 — 1D — 13C
f1 (ppm)
2-48

300.23 MHz — CDCl3 — 1D — 1H



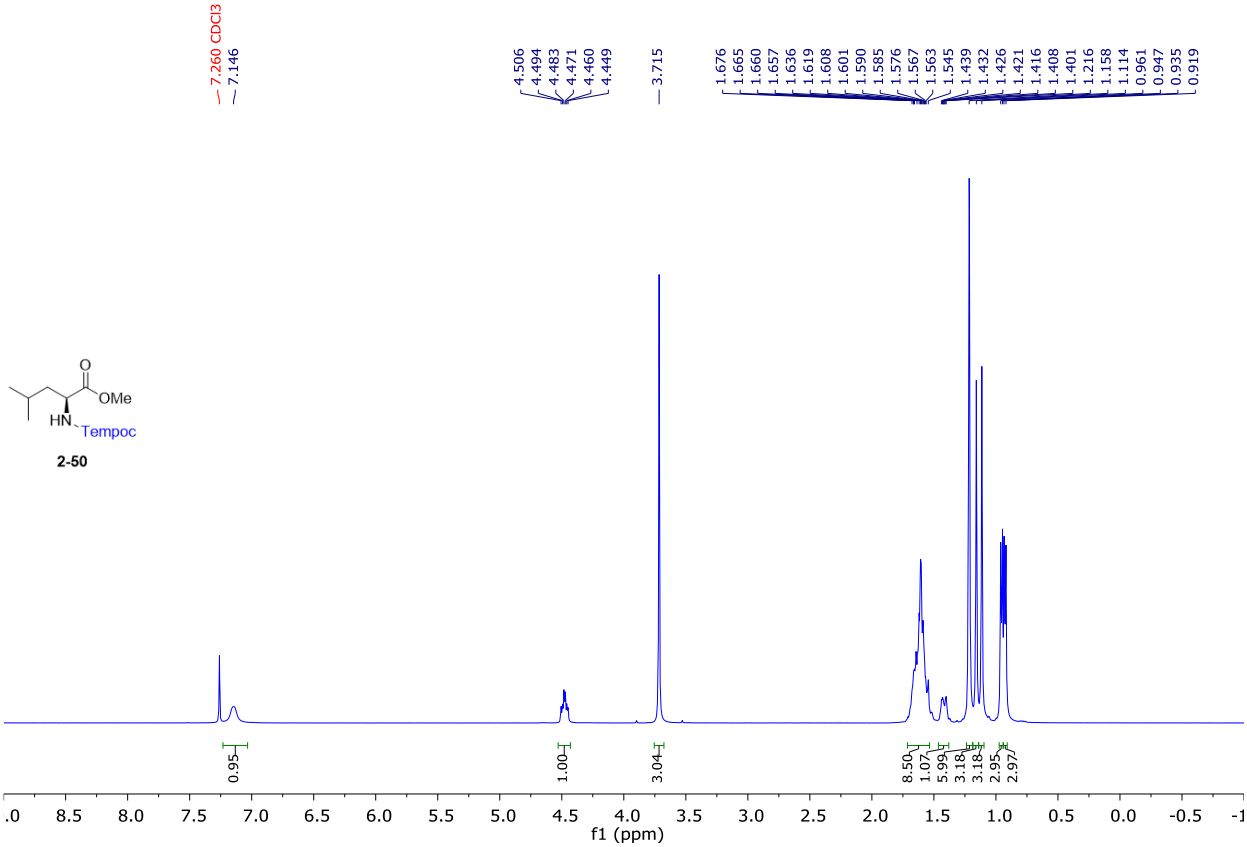
2-49

75.49 MHz — CDCl3 — 1D — 13C

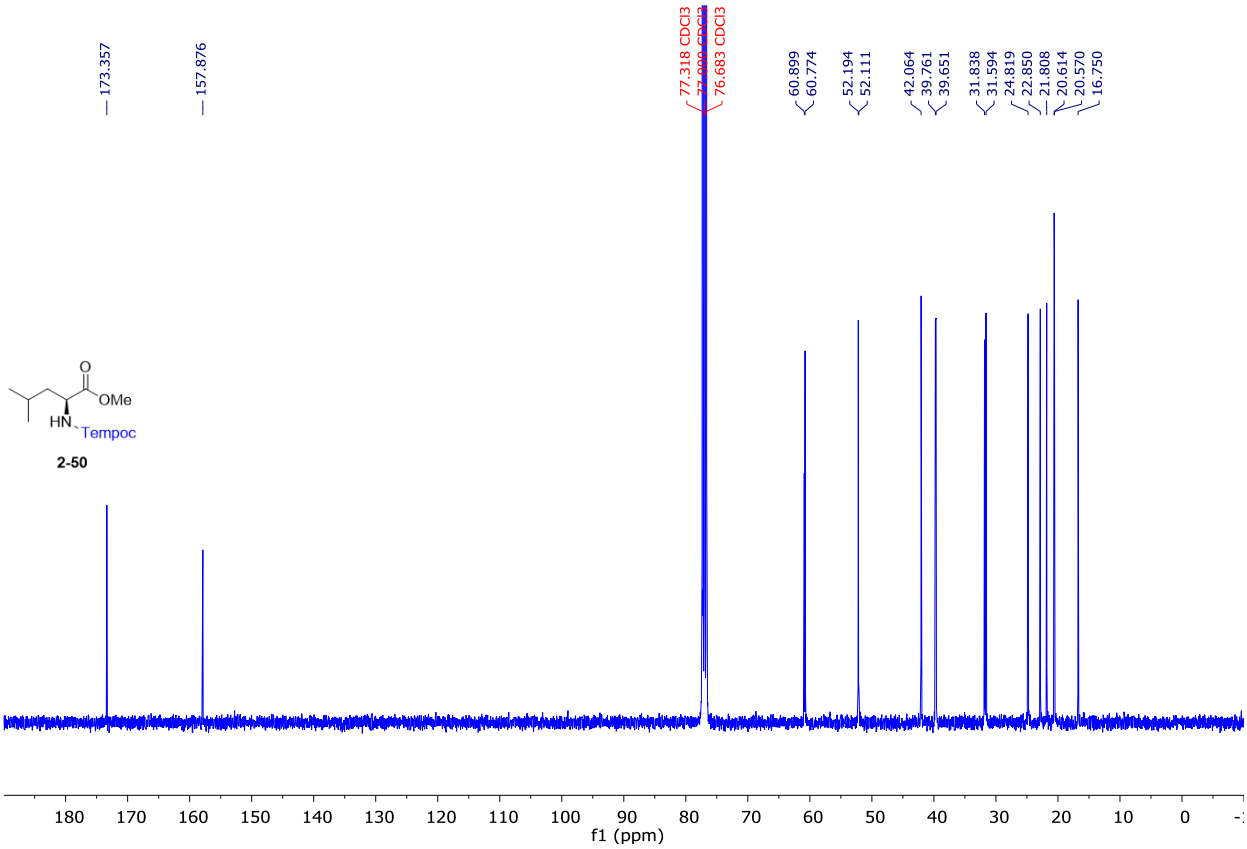


2-49

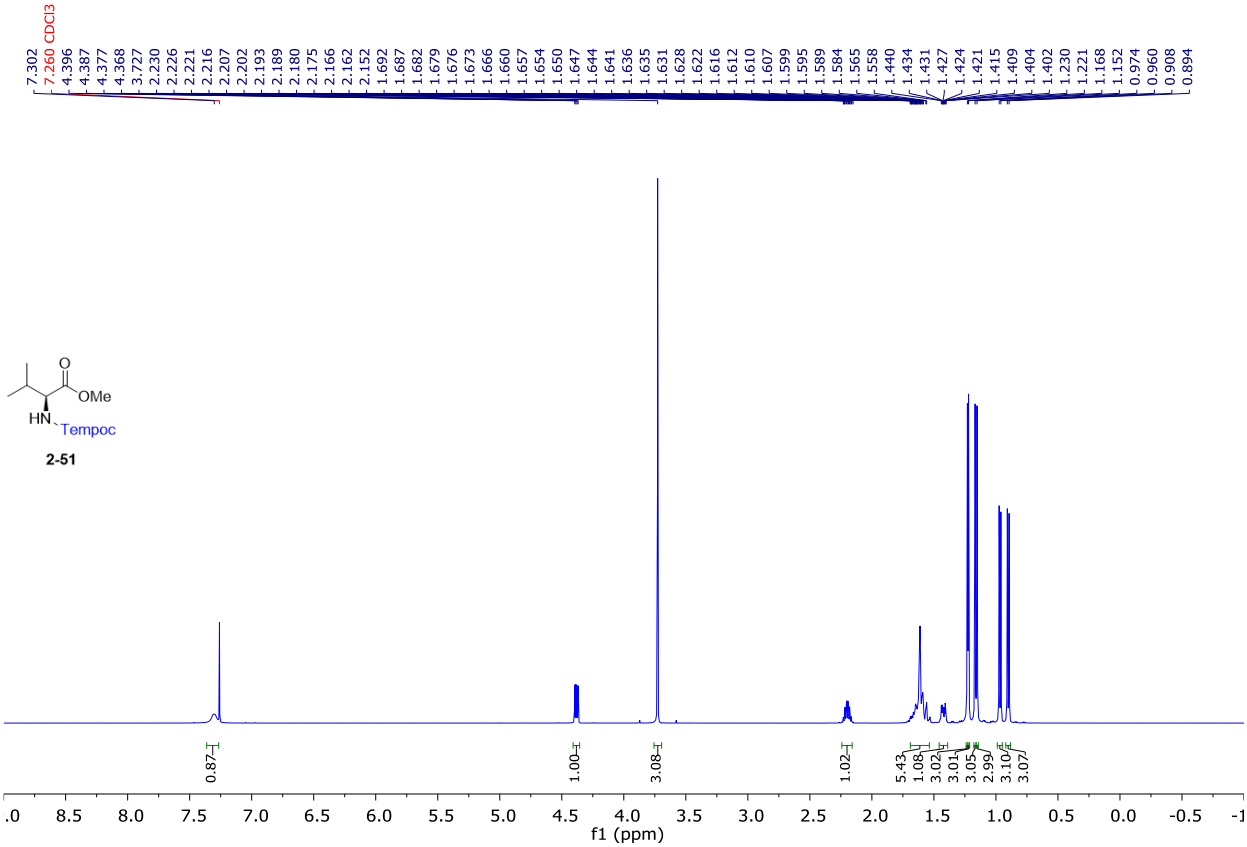
400.13 MHz — CDCl3 — 1D — 1H



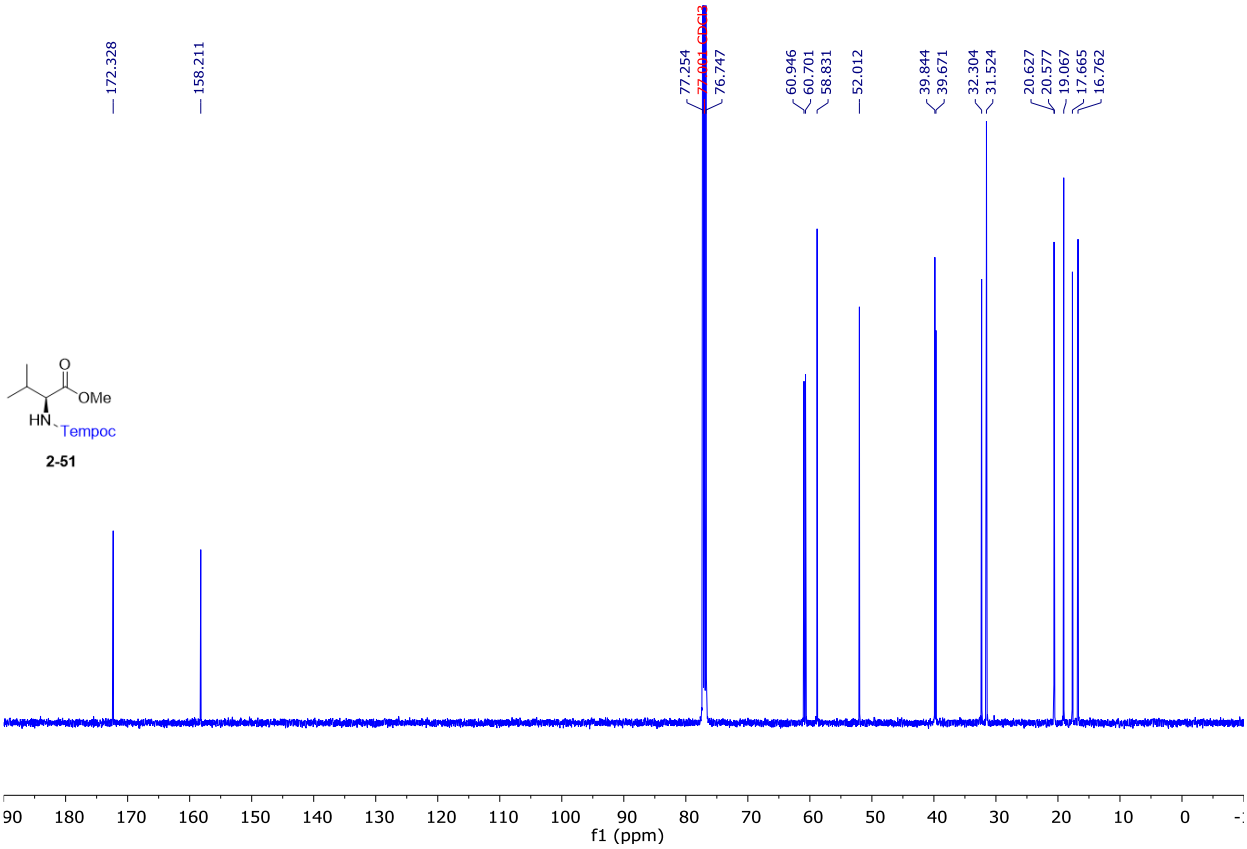
100.61 MHz — CDCl3 — 1D — 13C



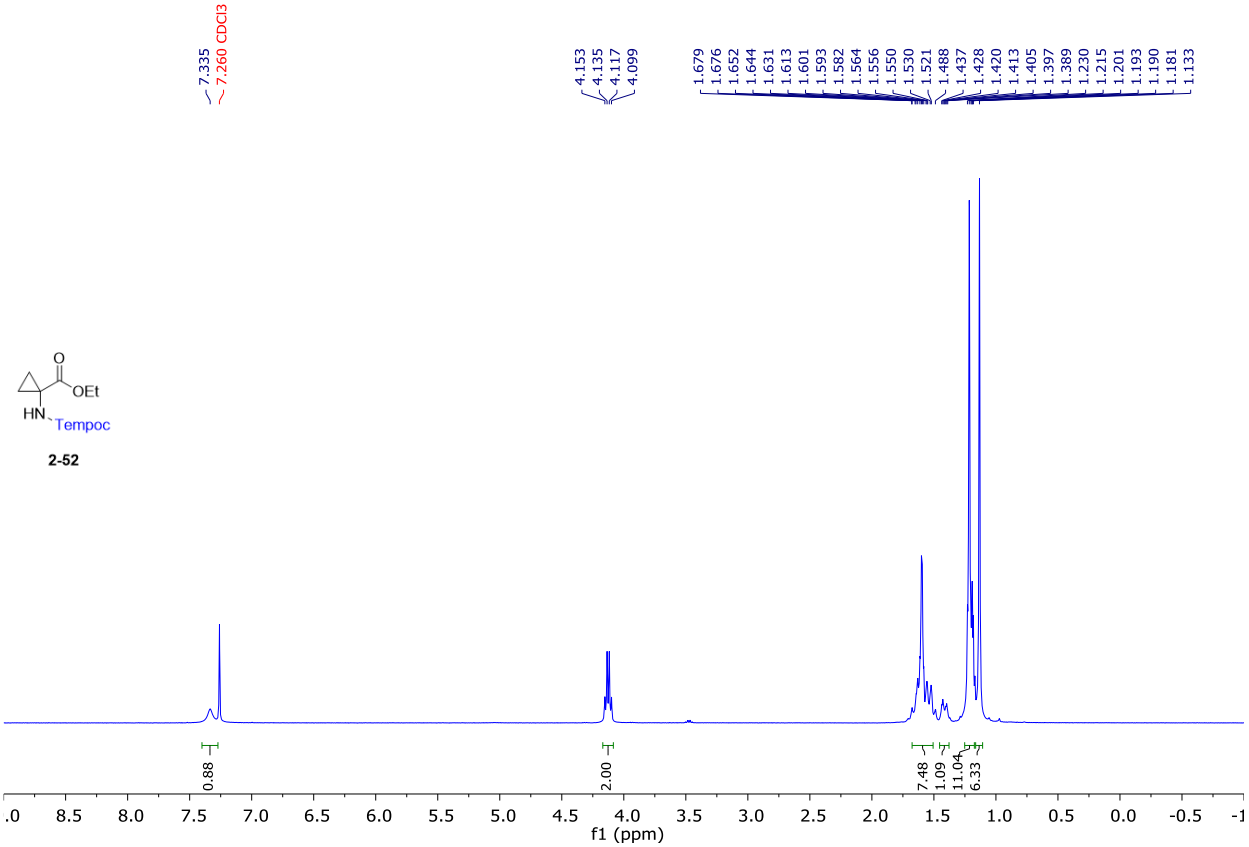
500.16 MHz — CDCl3 — 1D — 1H



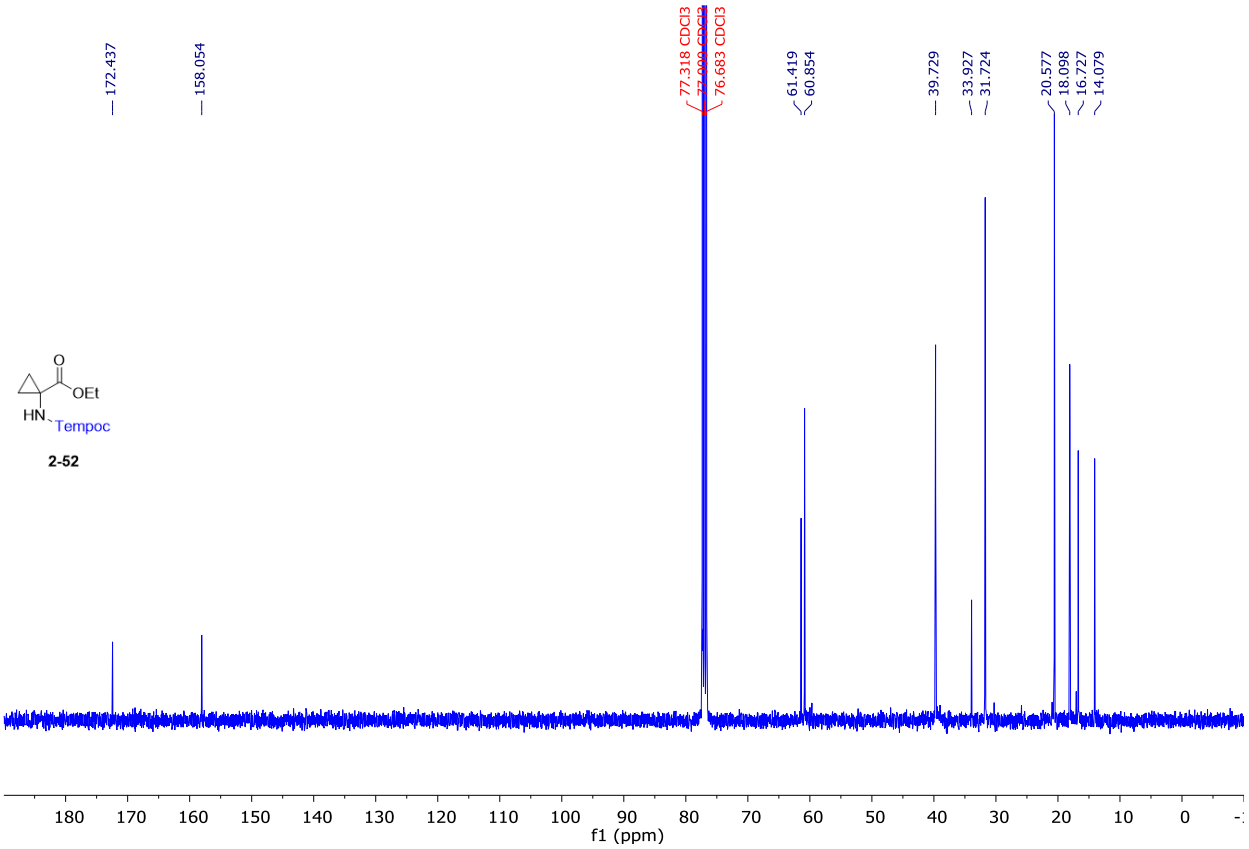
125.77 MHz — CDCl3 — 1D — 13C

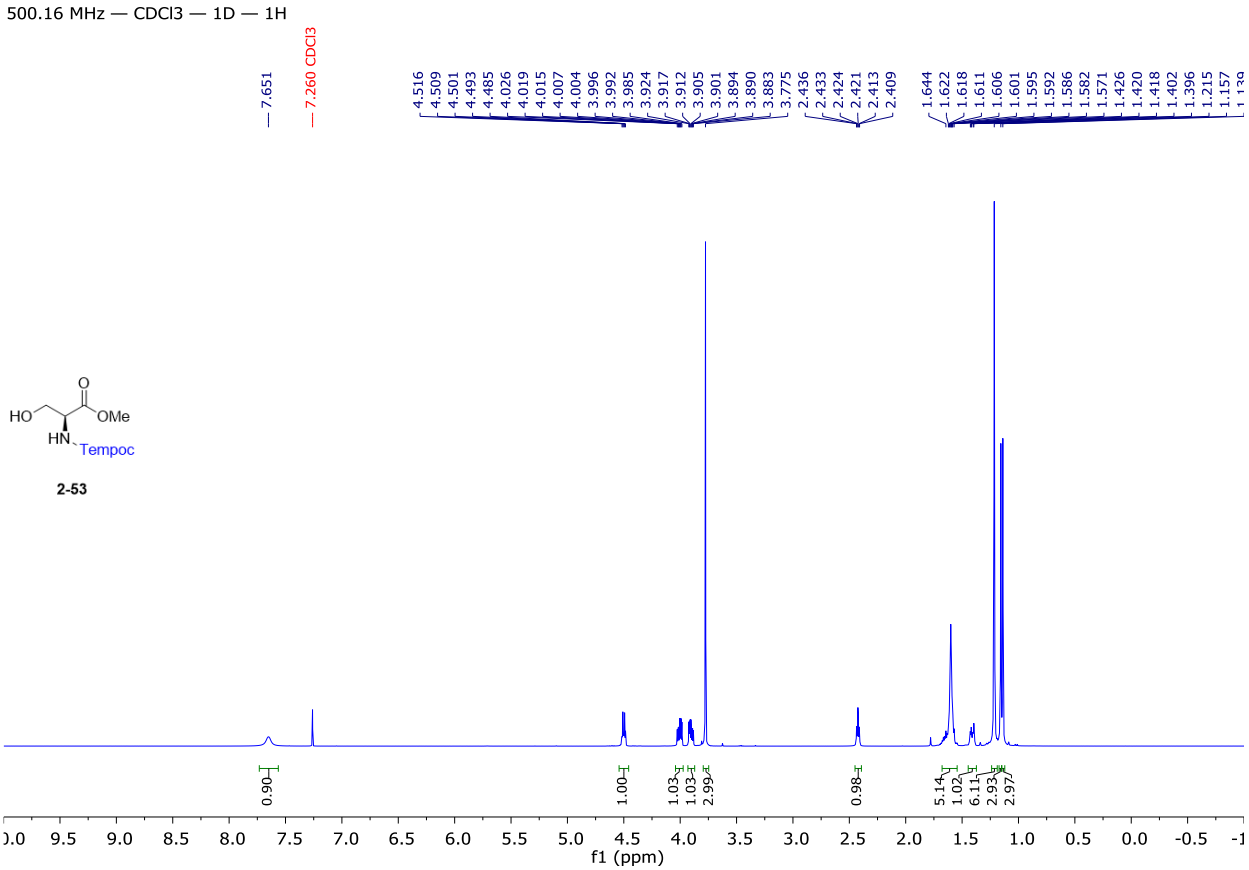


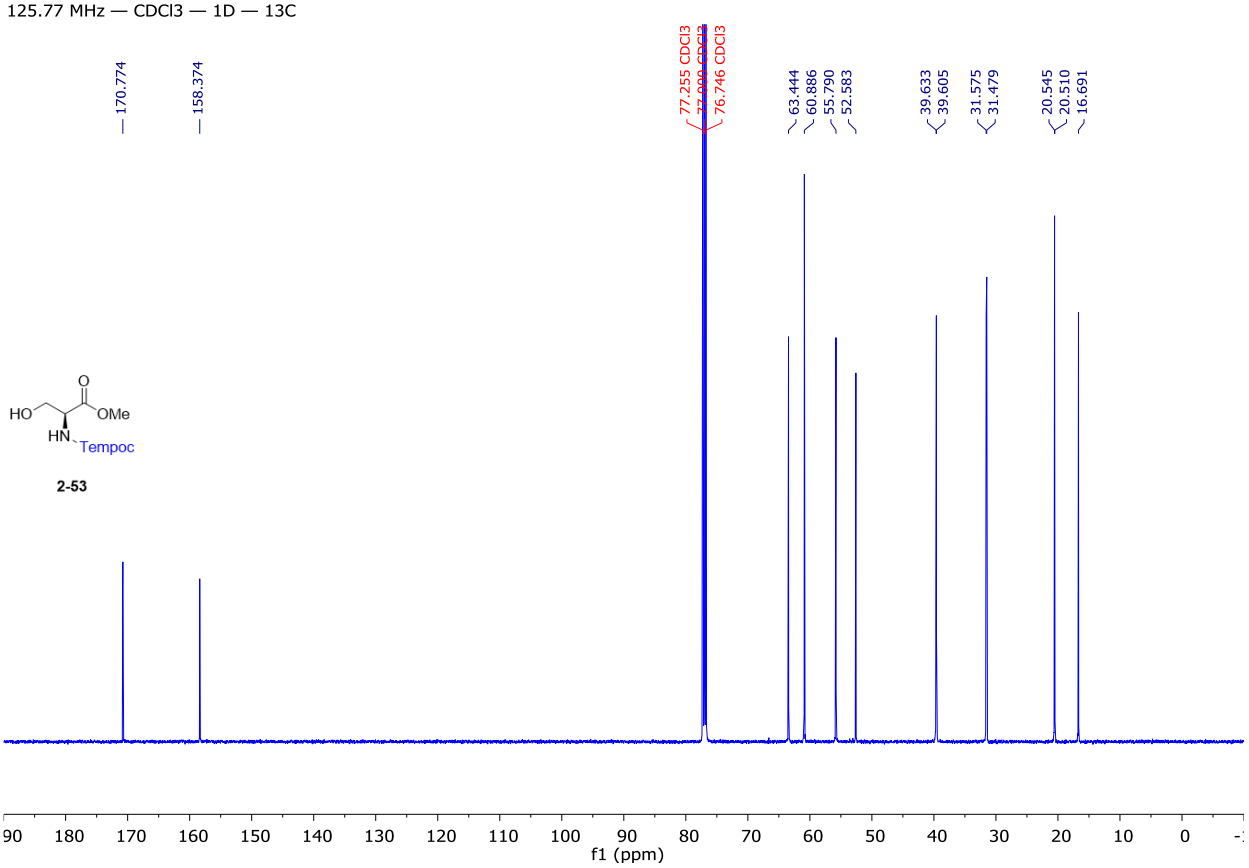
400.13 MHz — CDCl3 — 1D — 1H

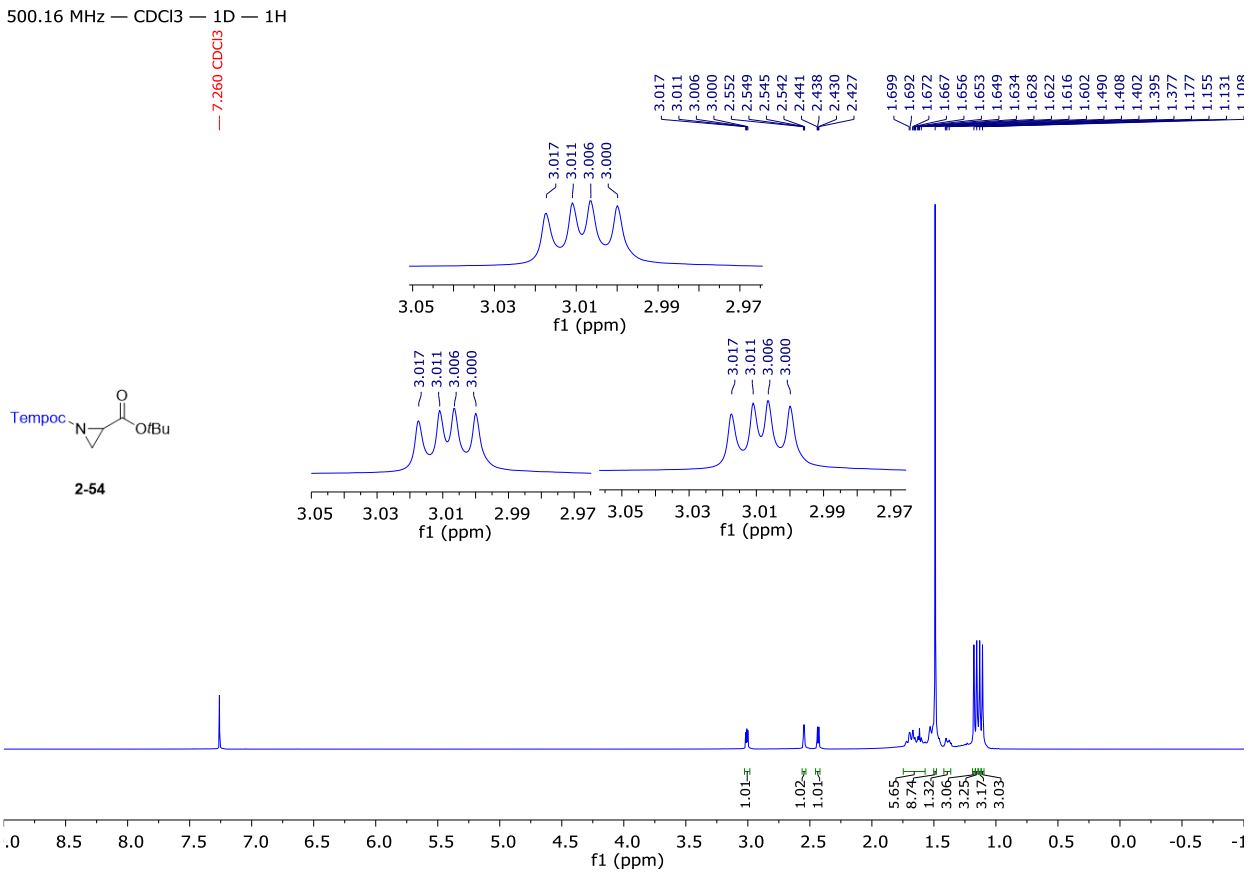


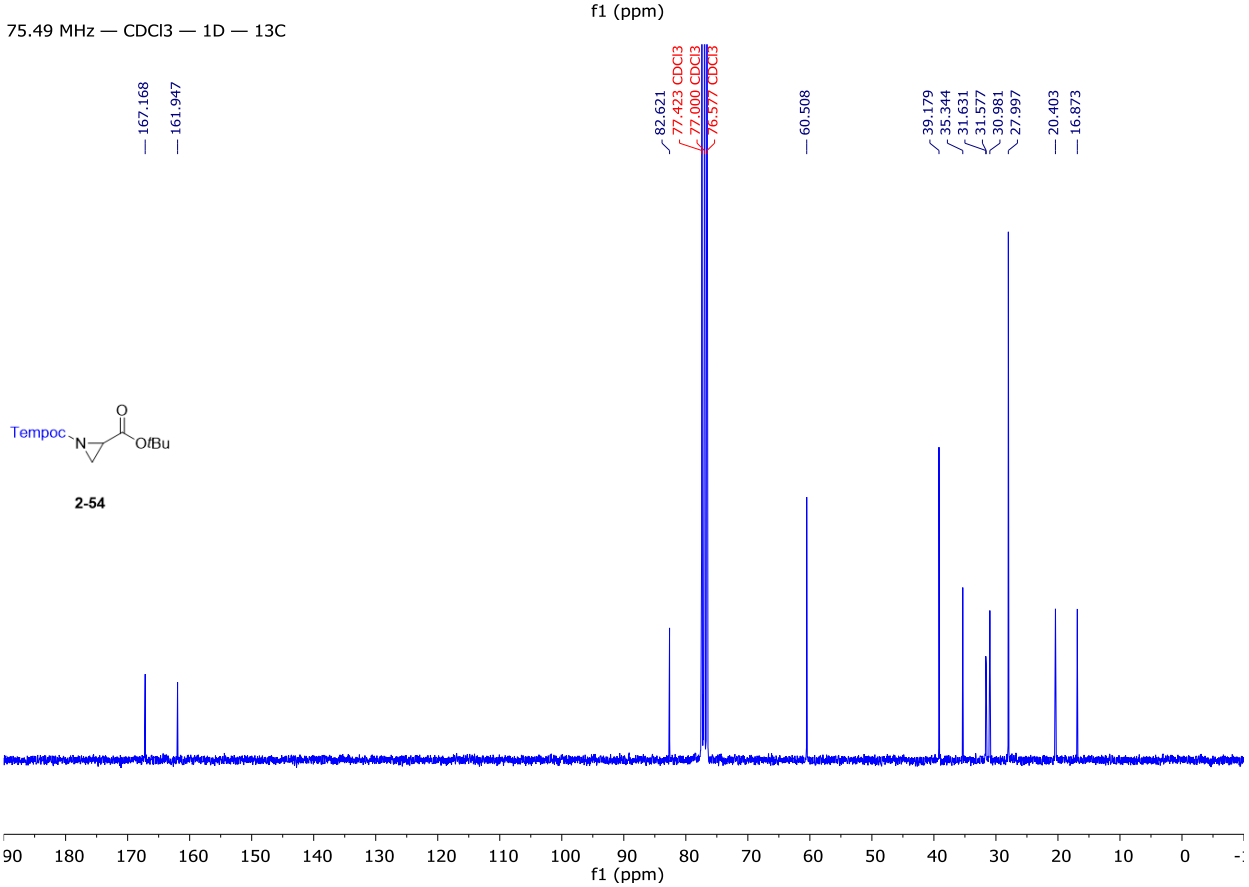
100.61 MHz — CDCl3 — 1D — 13C

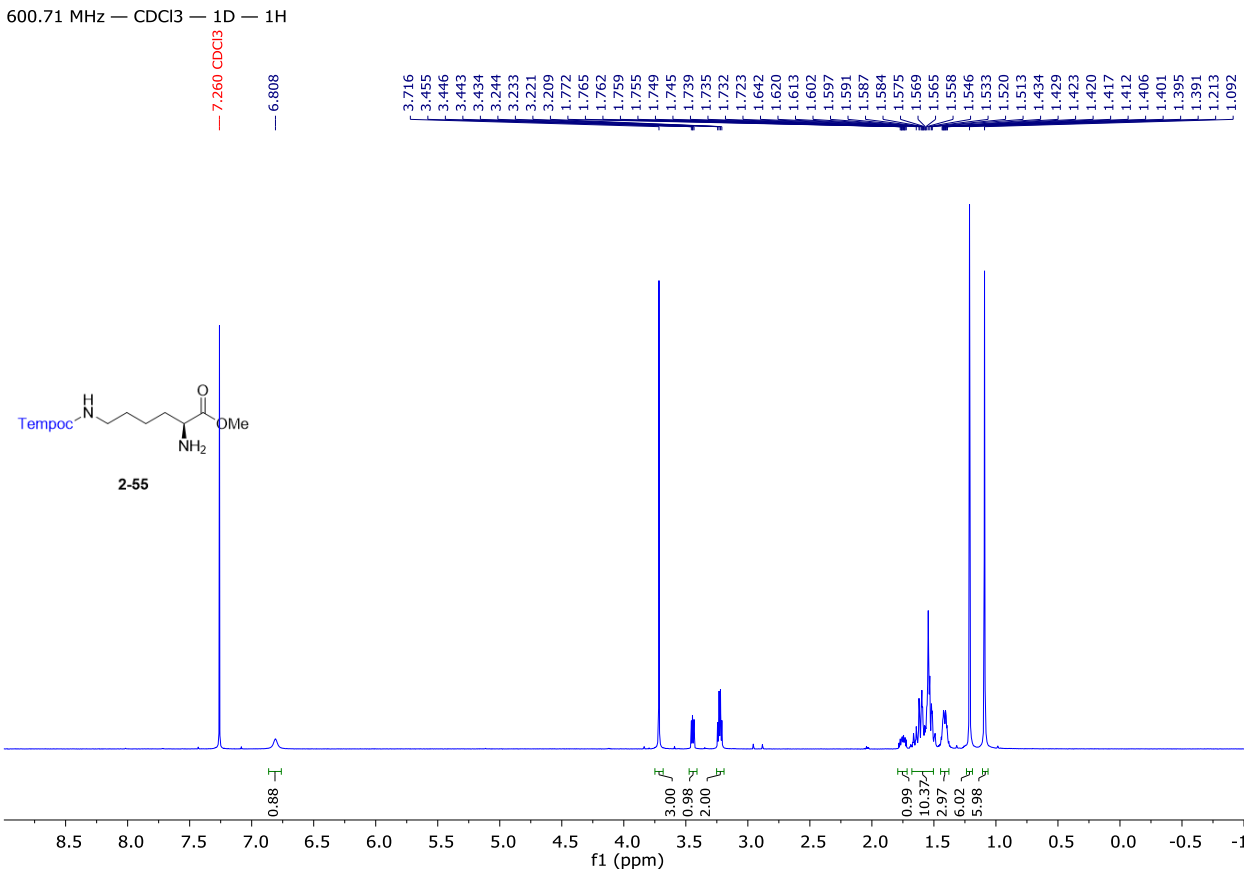


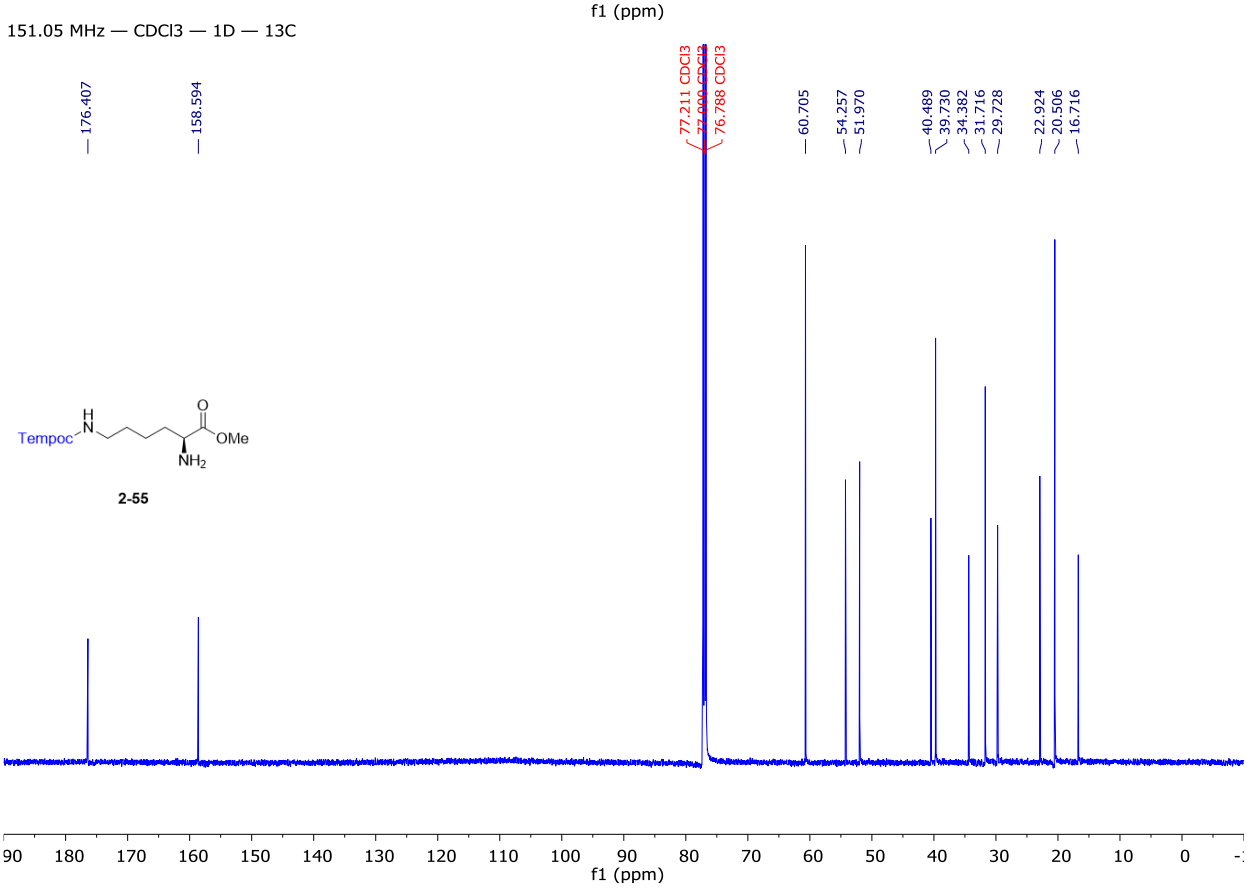

500.16 MHz — CDCl3 — 1D — 1H
7.651
7.260 CDCl3
4.516
4.509
4.501
4.493
4.485
4.026
4.019
4.015
4.007
4.004
3.996
3.992
3.985
3.924
3.917
3.912
3.905
3.901
3.894
3.890
3.883
3.775
2.436
2.433
2.424
2.421
2.413
2.409
1.644
1.622
1.618
1.611
1.606
1.601
1.595
1.592
1.586
1.582
1.571
1.426
1.420
1.418
1.402
1.396
1.215
1.157
HO
OMe
HN
Tempoc
2-53
0.90
1.00
1.03
1.03
2.99
0.98
5.14
1.02
6.11
2.93
2.97
f1 (ppm)


125.77 MHz — CDCl3 — 1D — 13C
170.774
158.374
77.255 CDCl3
76.746 CDCl3
63.444
60.886
55.790
52.583
39.633
39.605
31.575
31.479
20.545
20.510
16.691
HO
OMe
HN
Tempoc
2-53
f1 (ppm)

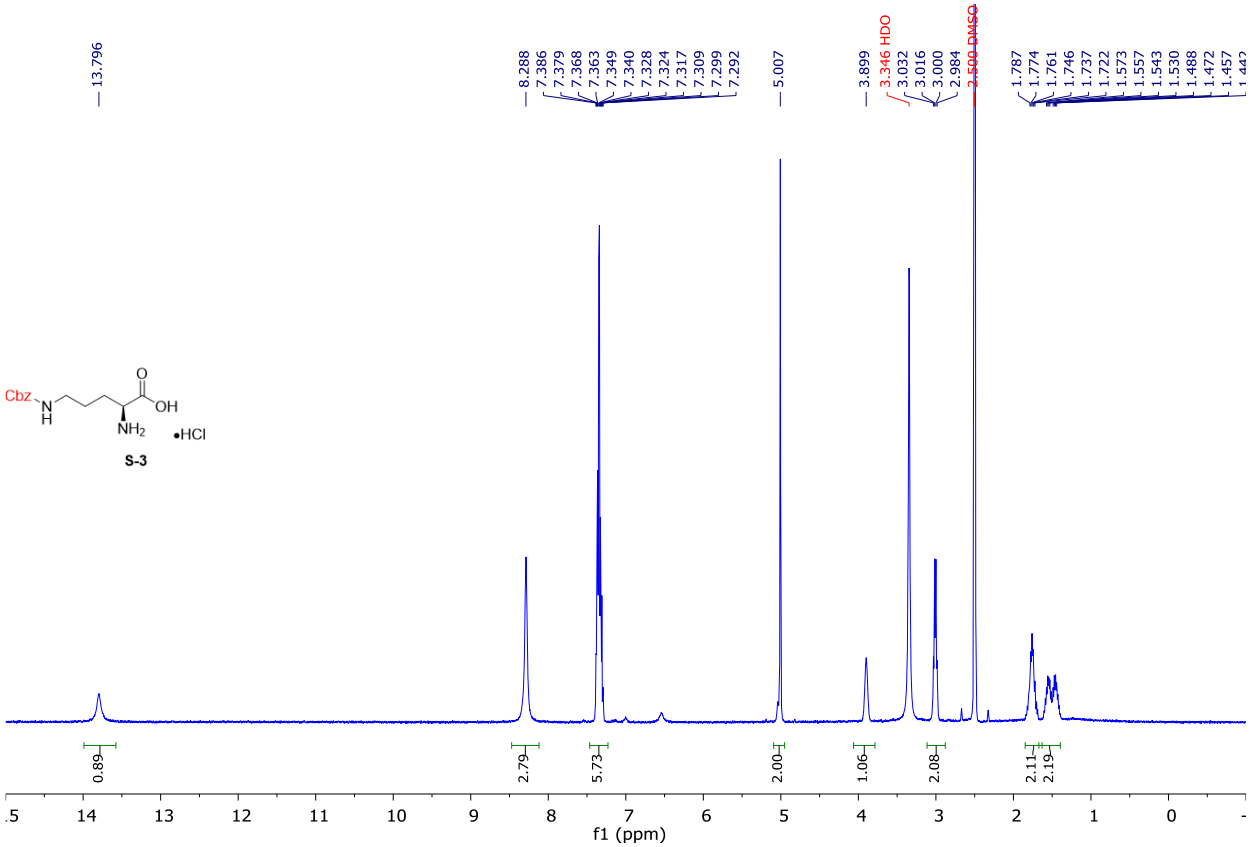

500.16 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
3.017
3.011
3.006
3.000
2.552
2.549
2.545
2.542
2.441
2.438
2.430
2.427
1.699
1.692
1.672
1.667
1.656
1.653
1.649
1.634
1.628
1.622
1.616
1.602
1.490
1.408
1.402
1.395
1.377
1.177
1.155
1.131
Tempoc
OtBu
2-54
f1 (ppm)
1.01
1.02
1.01
5.65
8.74
1.32
3.06
3.25
3.17
3.03


75.49 MHz — CDCl3 — 1D — 13C
167.168
161.947
82.621
77.423 CDCl3
77.000 CDCl3
76.577 CDCl3
60.508
39.179
35.344
31.631
31.577
30.981
27.997
20.403
16.873
Tempoc
OtBu
2-54
f1 (ppm)

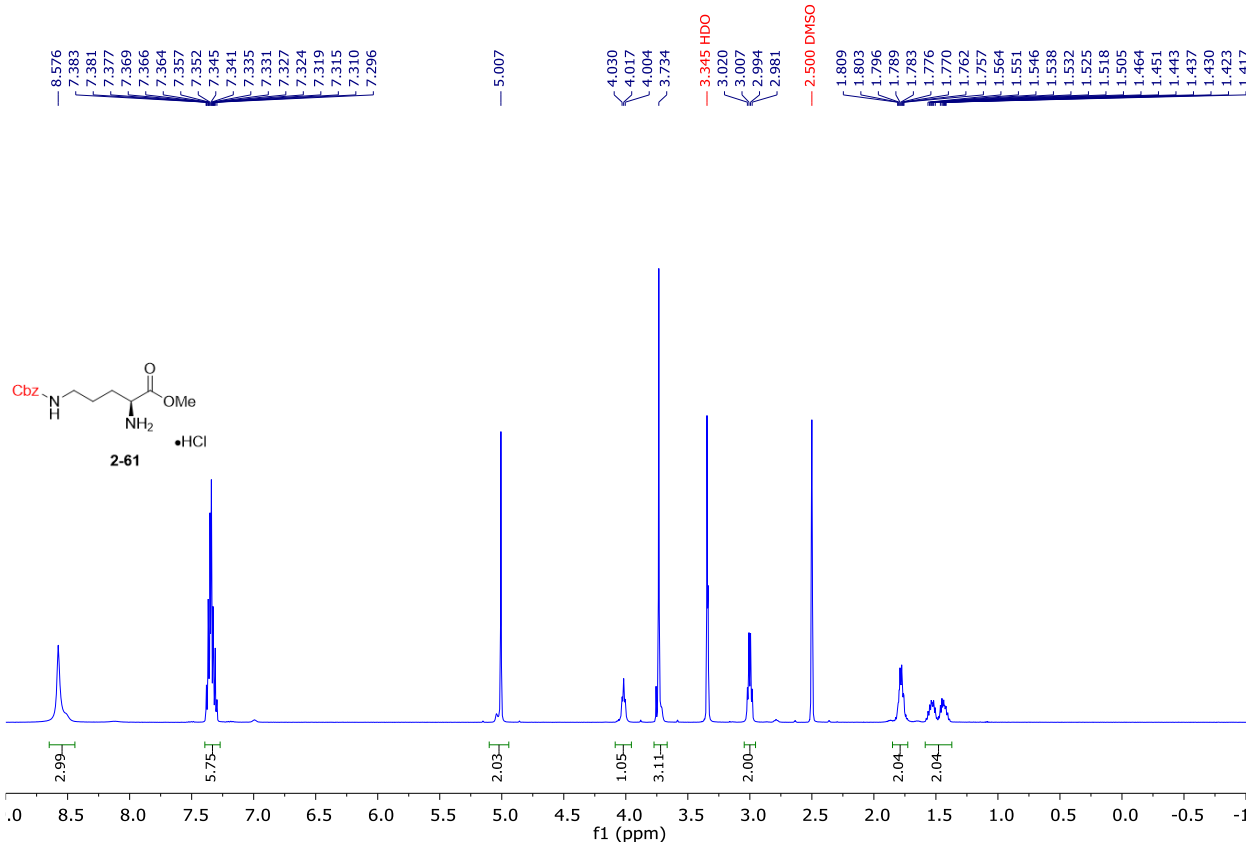

600.71 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
6.808
3.716
3.455
3.446
3.443
3.434
3.244
3.233
3.221
3.209
1.772
1.765
1.762
1.759
1.755
1.749
1.745
1.739
1.735
1.732
1.723
1.642
1.620
1.613
1.602
1.597
1.591
1.587
1.584
1.575
1.569
1.565
1.558
1.546
1.533
1.520
1.513
1.434
1.429
1.423
1.420
1.417
1.412
1.406
1.401
1.395
1.391
1.213
1.092
Tempoc
OMe
NH2
2-55
0.88
3.00
0.98
2.00
0.99
10.37
2.97
6.02
5.98
f1 (ppm)

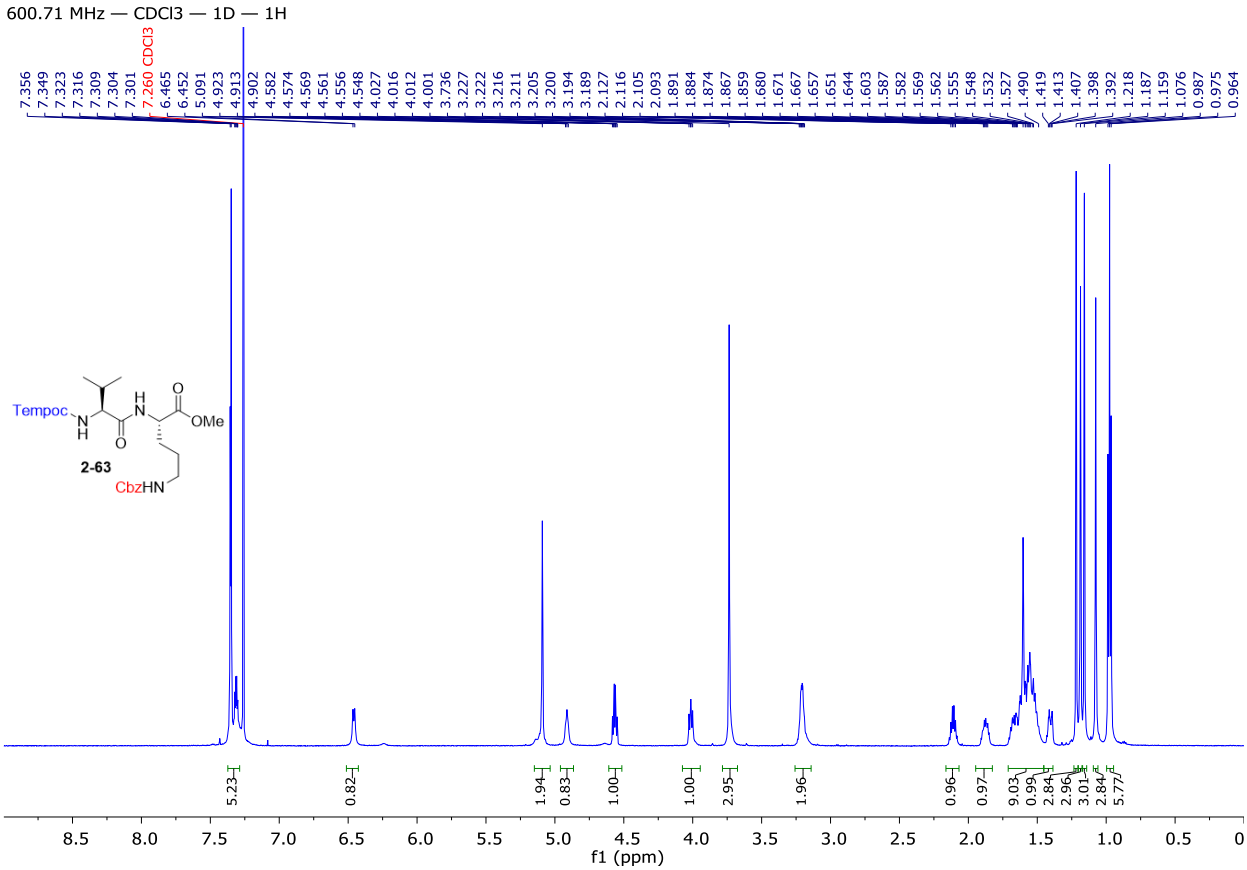

151.05 MHz — CDCl3 — 1D — 13C
176.407
158.594
77.211 CDCl3
77.000 CDCl3
76.788 CDCl3
60.705
54.257
51.970
40.489
39.730
34.382
31.716
29.728
22.924
20.506
16.716
Tempoc
OMe
NH2
2-55
f1 (ppm)

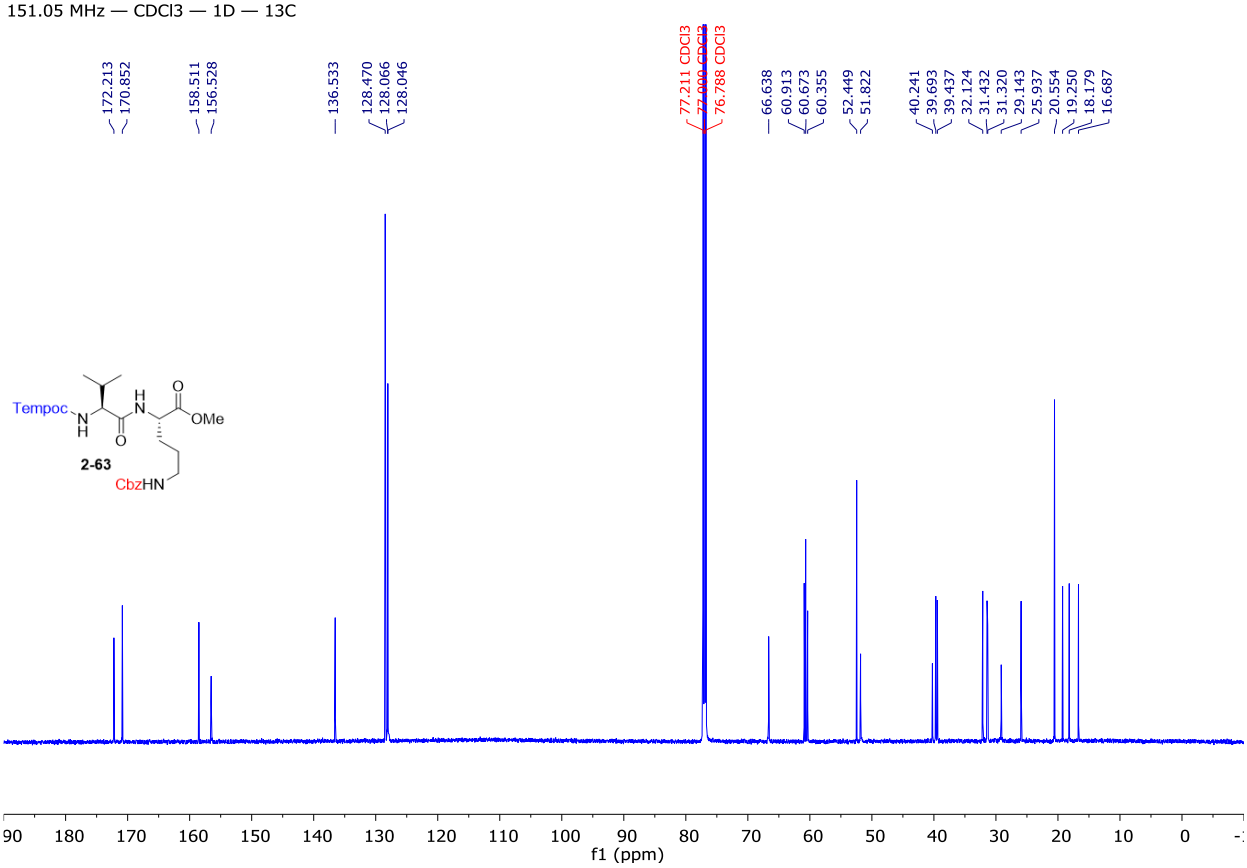
400.13 MHz — DMSO — 1D — 1H

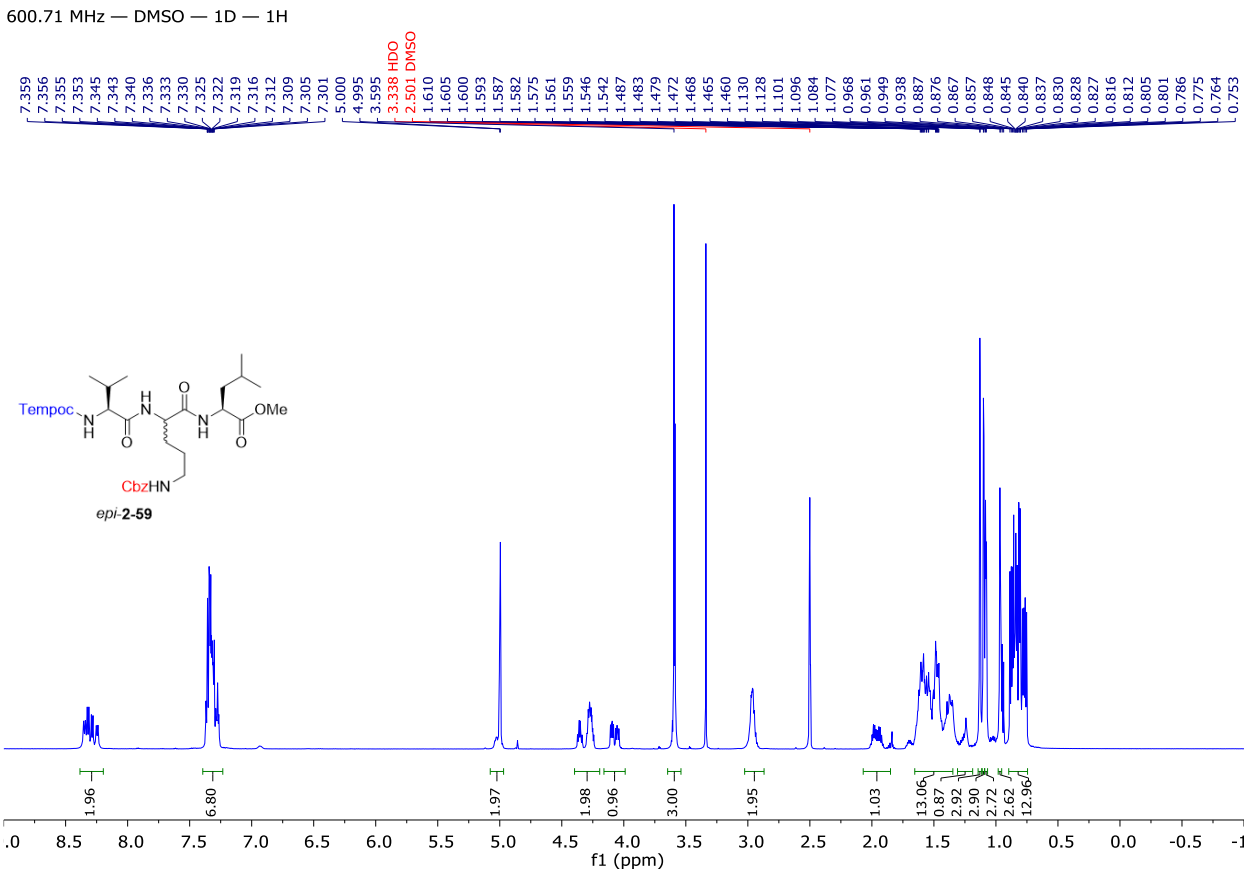


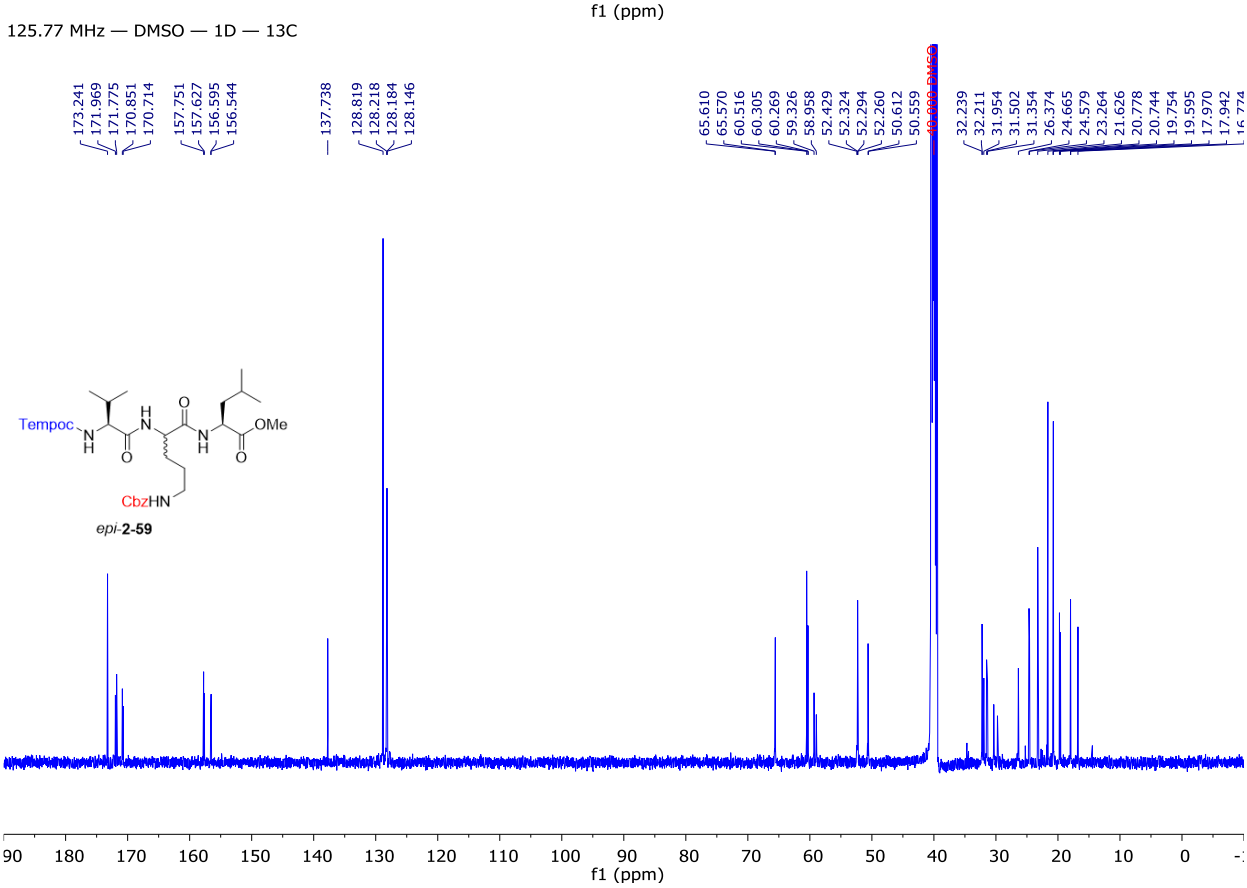
500.16 MHz — DMSO — 1D — 1H



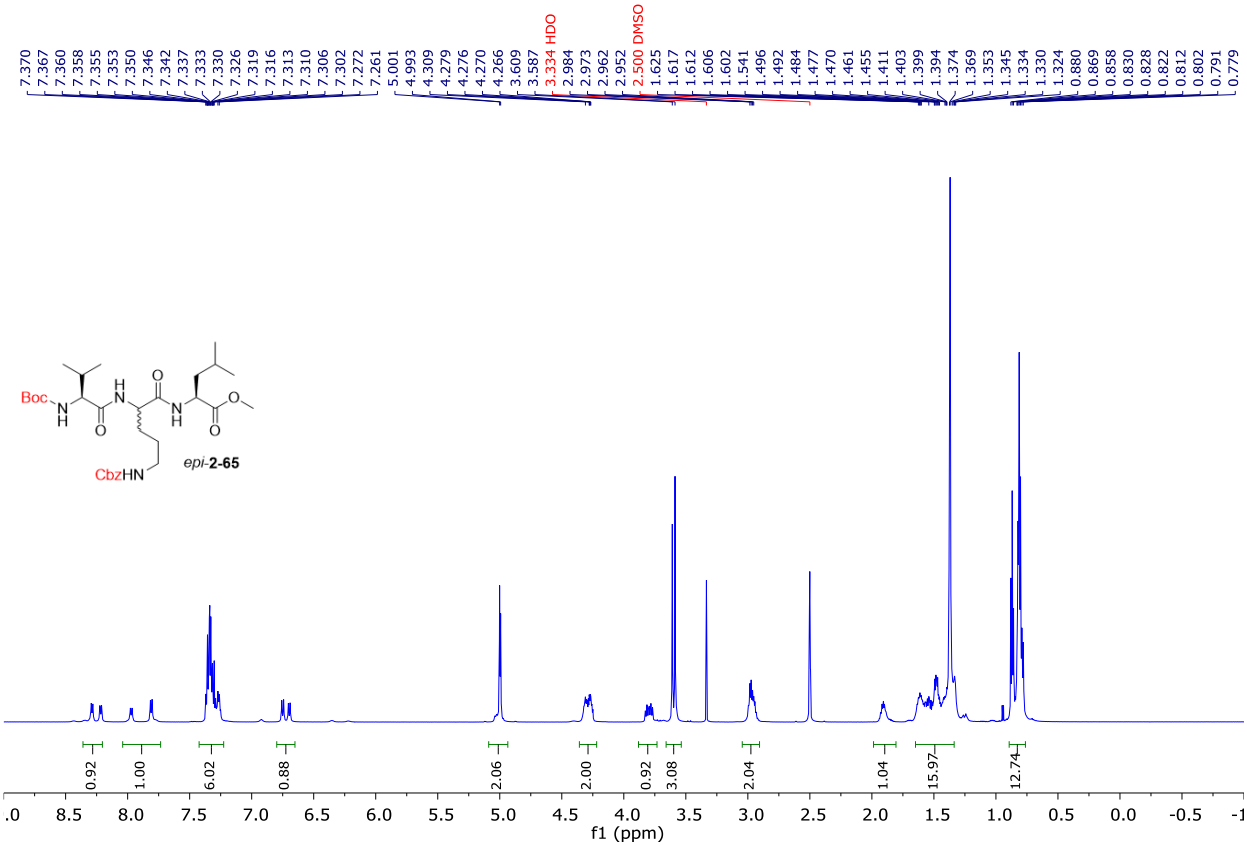

600.71 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
Tempoc
OMe
2-63
CbzHN
f1 (ppm)


151.05 MHz — CDCl3 — 1D — 13C
77.211 CDCl3
76.788 CDCl3
Tempoc
OMe
2-63
CbzHN
f1 (ppm)

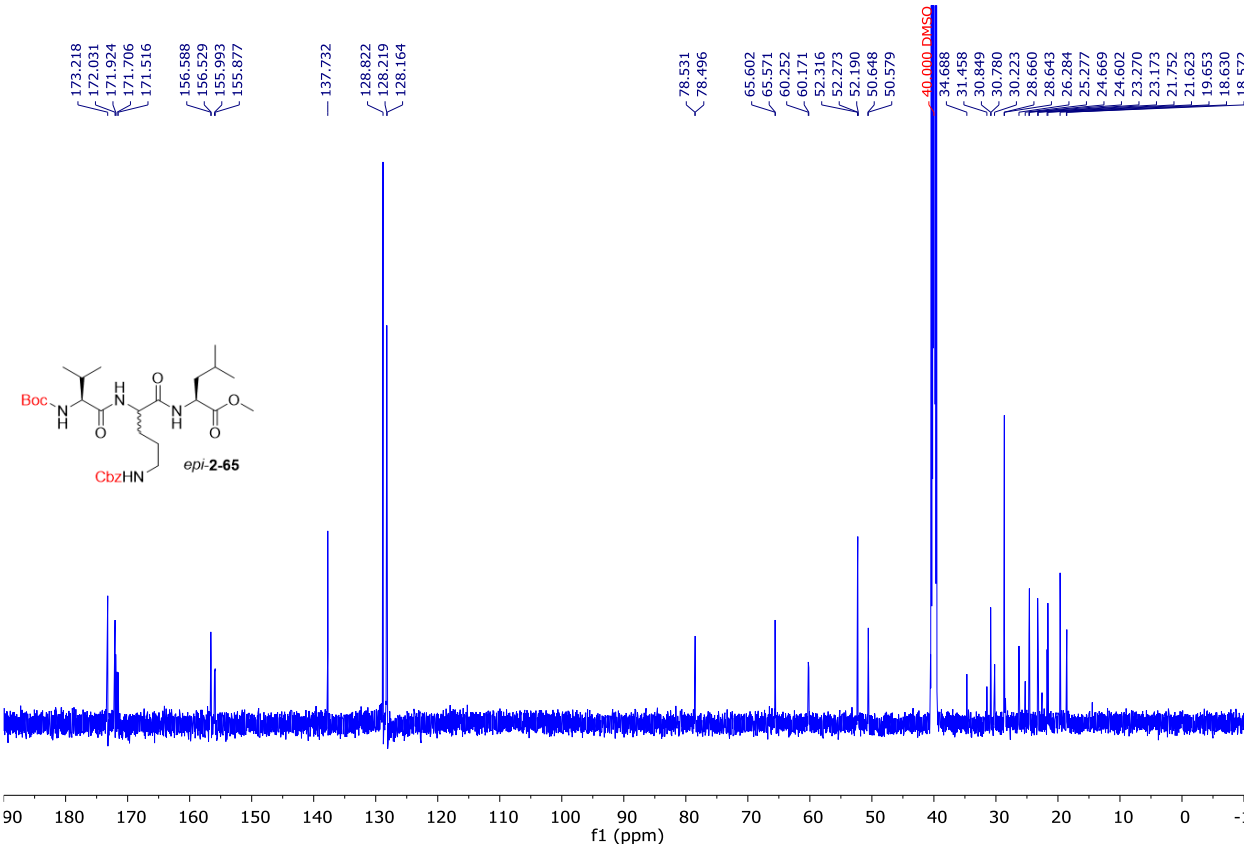

600.71 MHz — DMSO — 1D — 1H
3.338 HDO
2.501 DMSO
Tempoc
OMe
CbzHN
epi-2-59
1.96
6.80
1.97
1.98
0.96
3.00
1.95
1.03
13.06
0.87
2.92
2.90
2.72
2.62
12.96
f1 (ppm)


125.77 MHz — DMSO — 1D — 13C
Tempoc
OMe
CbzHN
epi-2-59
f1 (ppm)

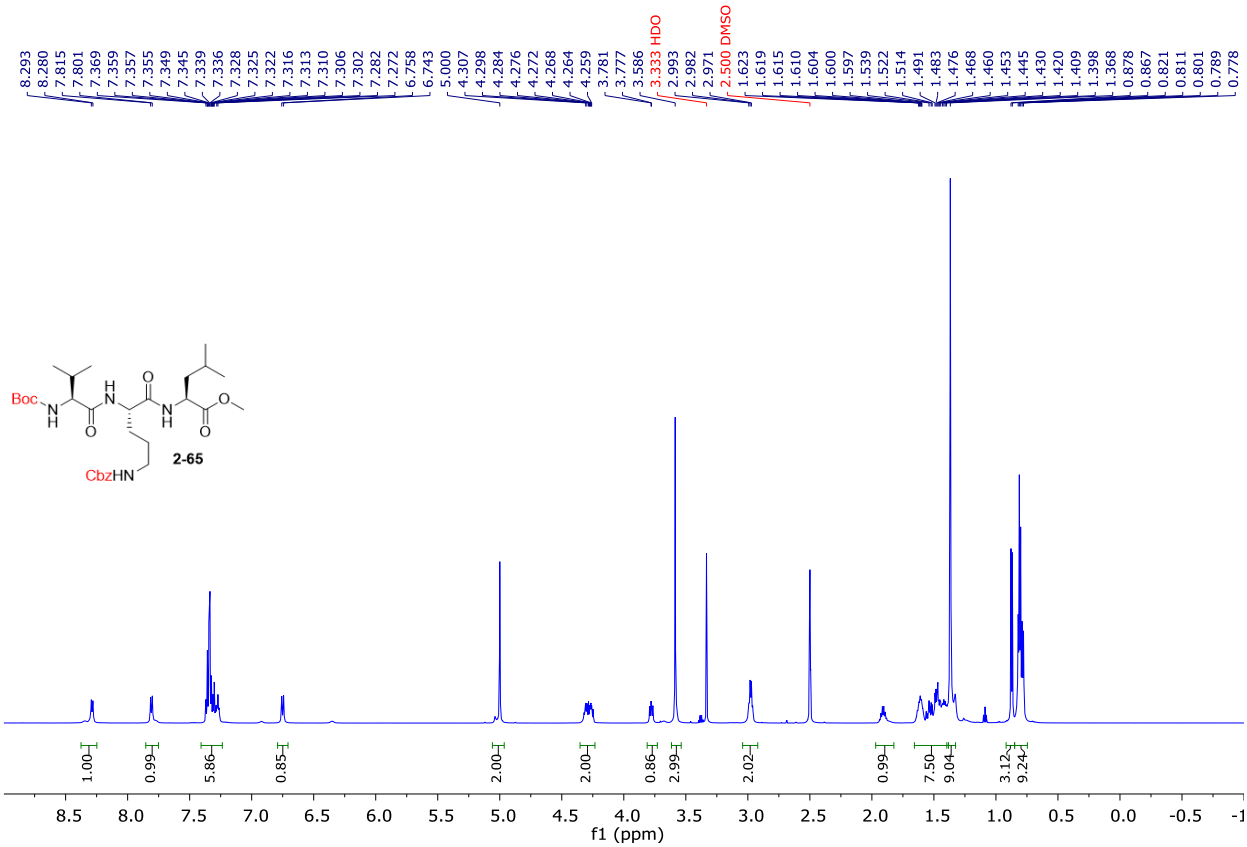
600.71 MHz — DMSO — 1D — 1H



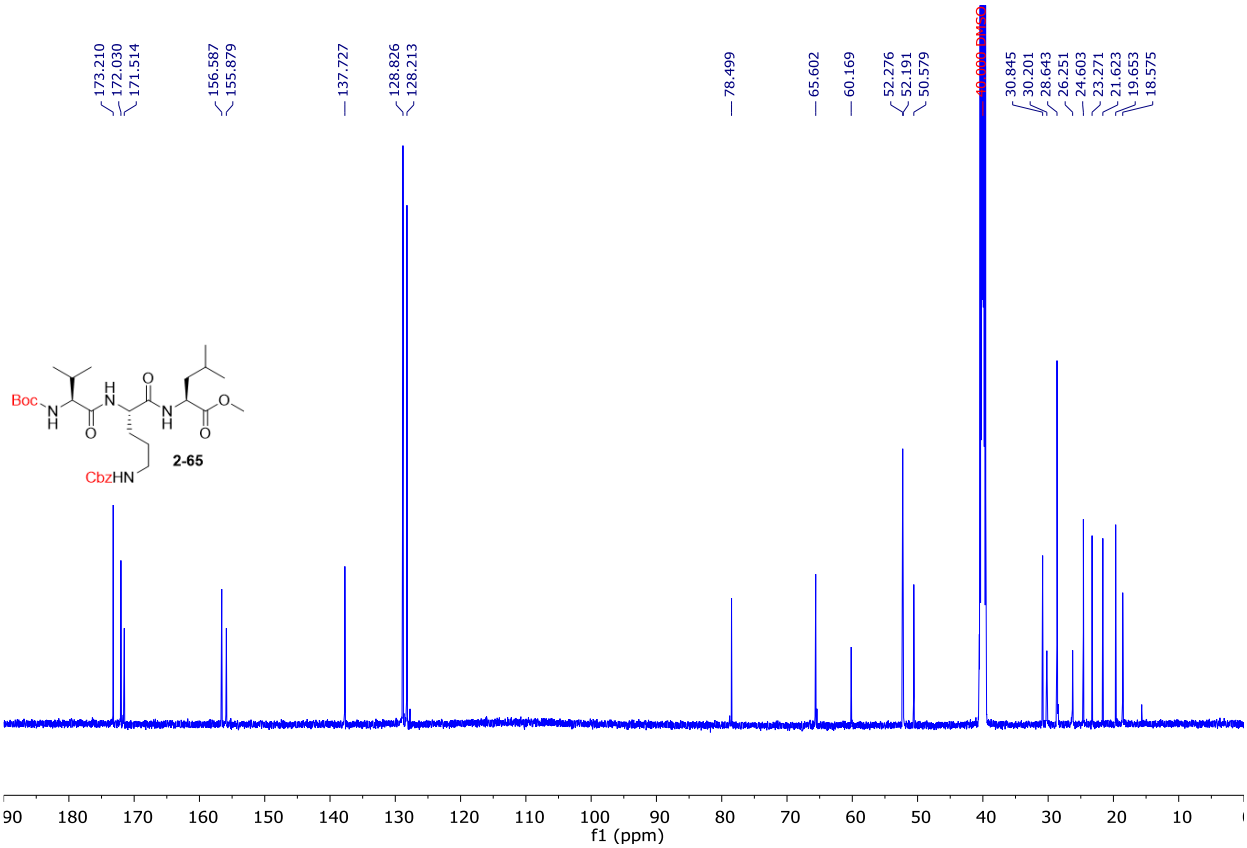
151.06 MHz — DMSO — 1D — 13C

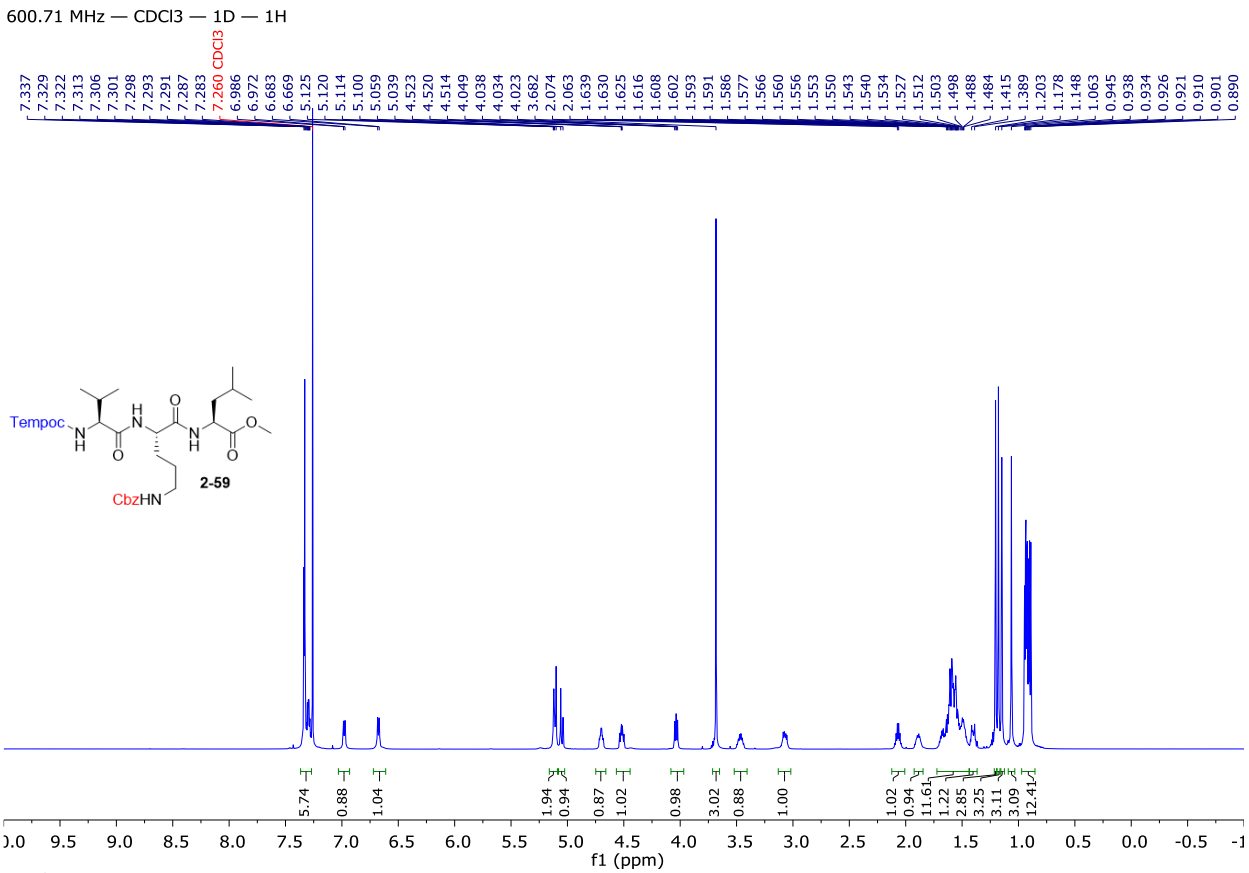


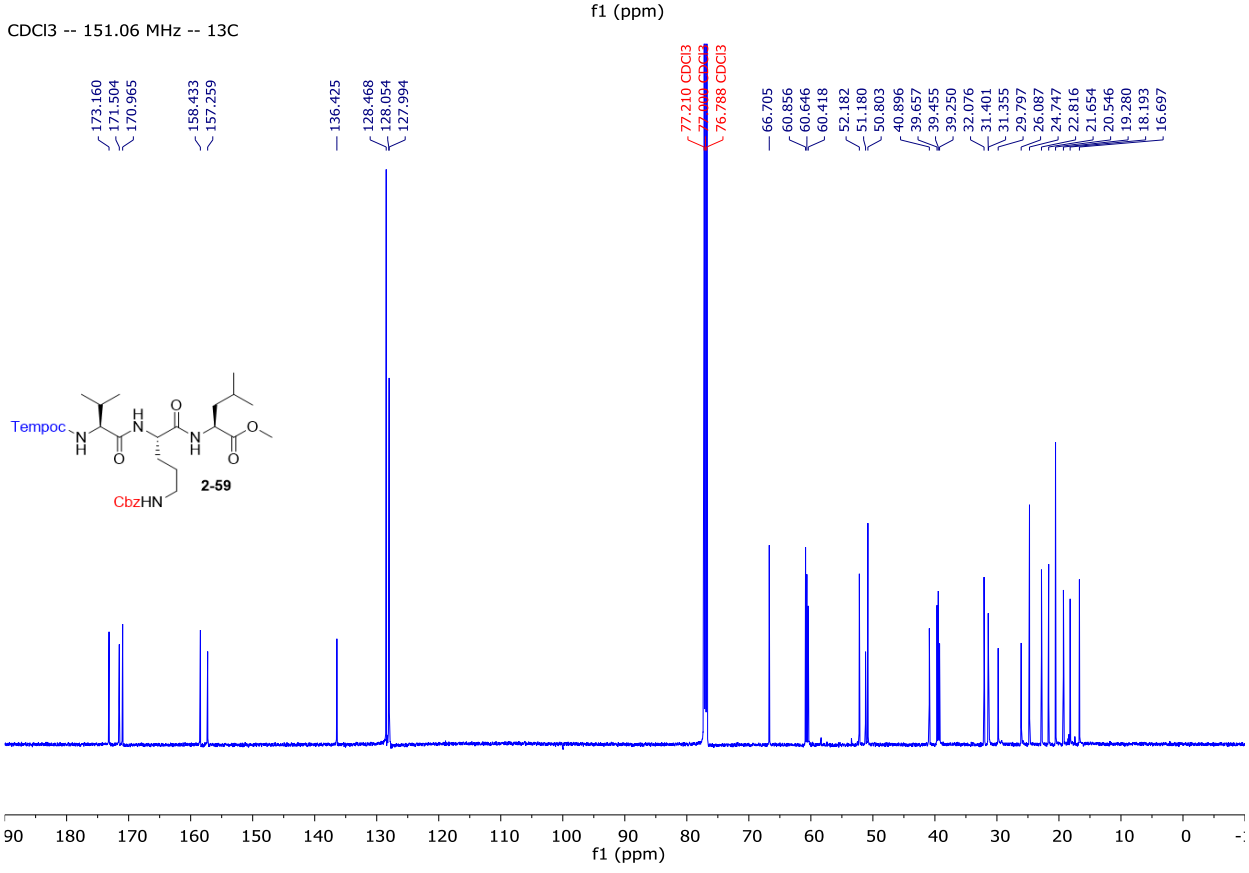
600.71 MHz — DMSO — 1D — 1H



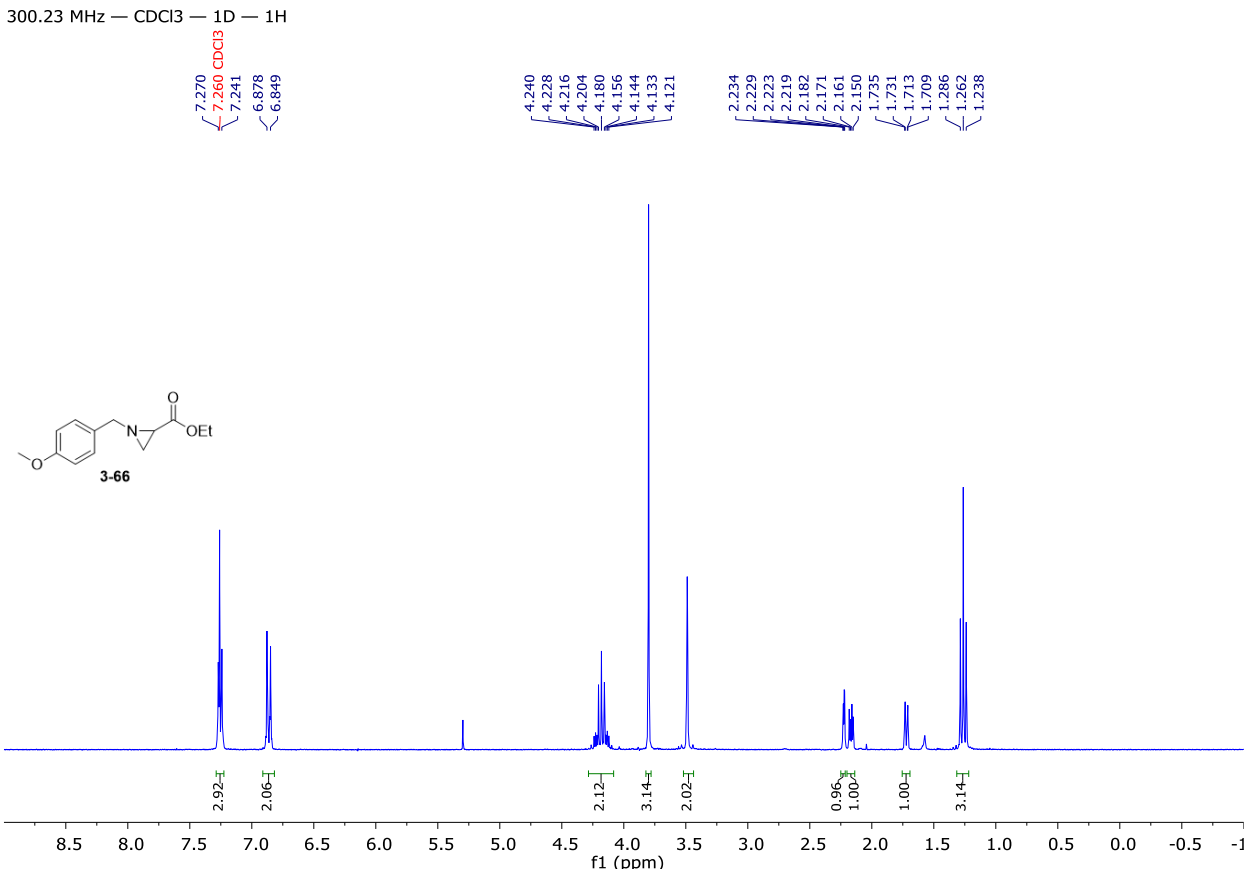
151.06 MHz — DMSO — 1D — 13C

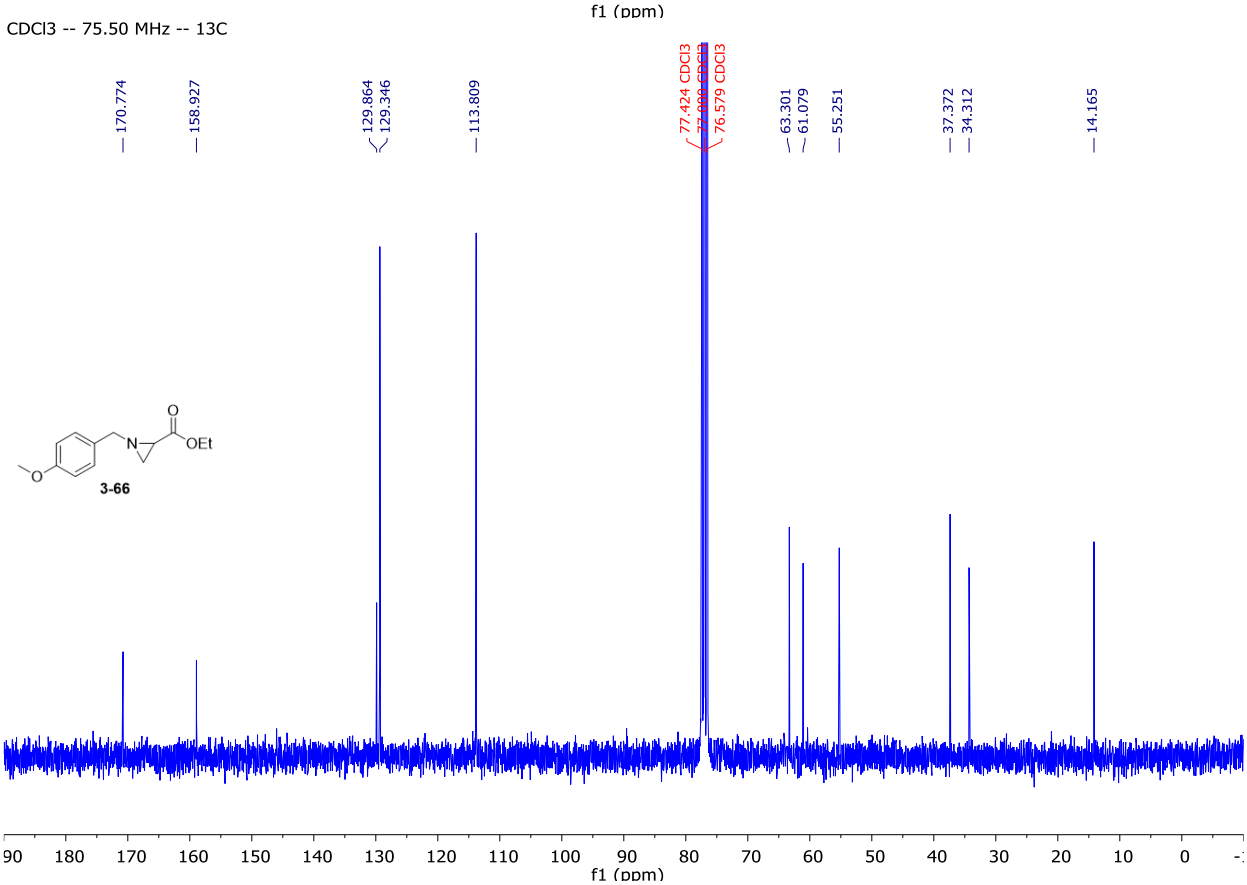


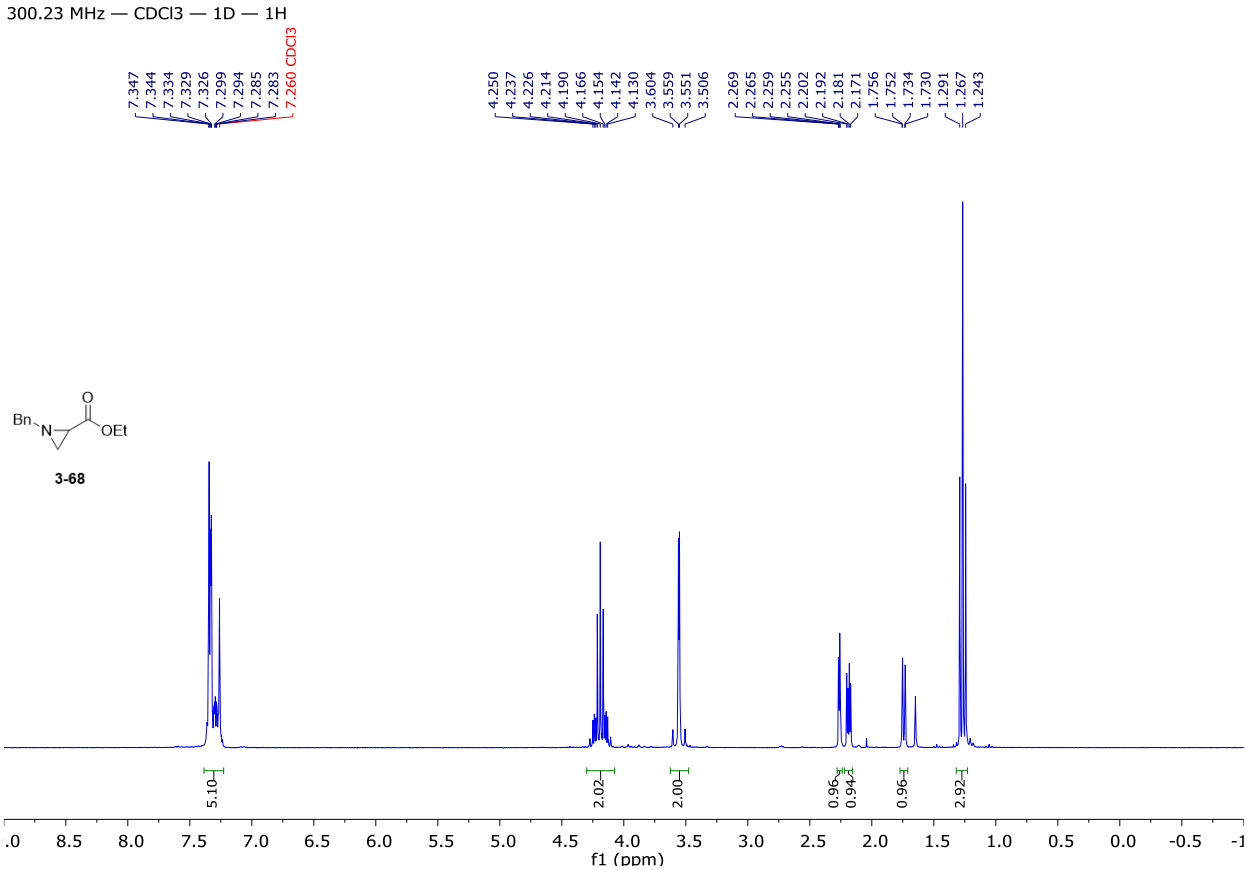

600.71 MHz — CDCl3 — 1D — 1H
Tempoc
CbzHN
2-59
f1 (ppm)

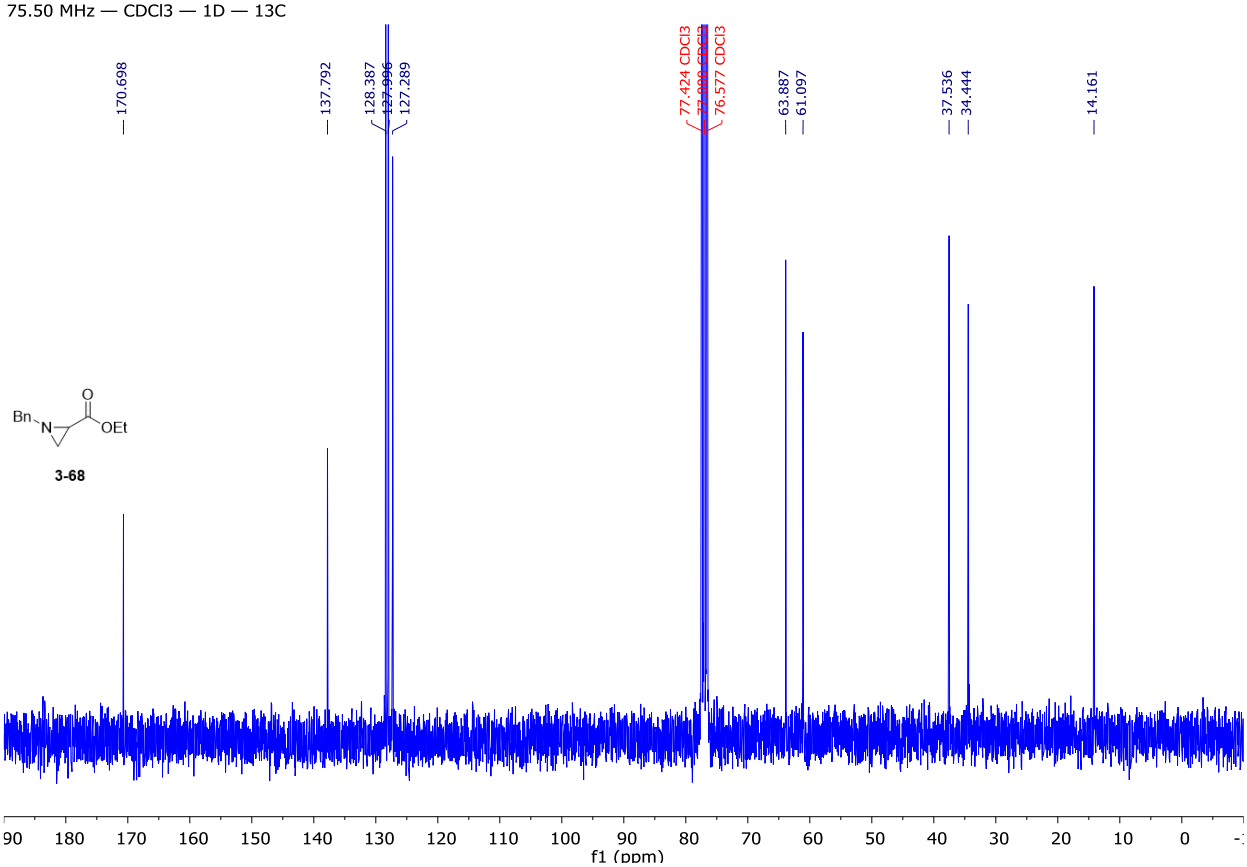

CDCl3 -- 151.06 MHz -- 13C
Tempoc
CbzHN
2-59
f1 (ppm)

APPENDIX E : SELECTED NMR SPECTRA (CHAPTER 3)

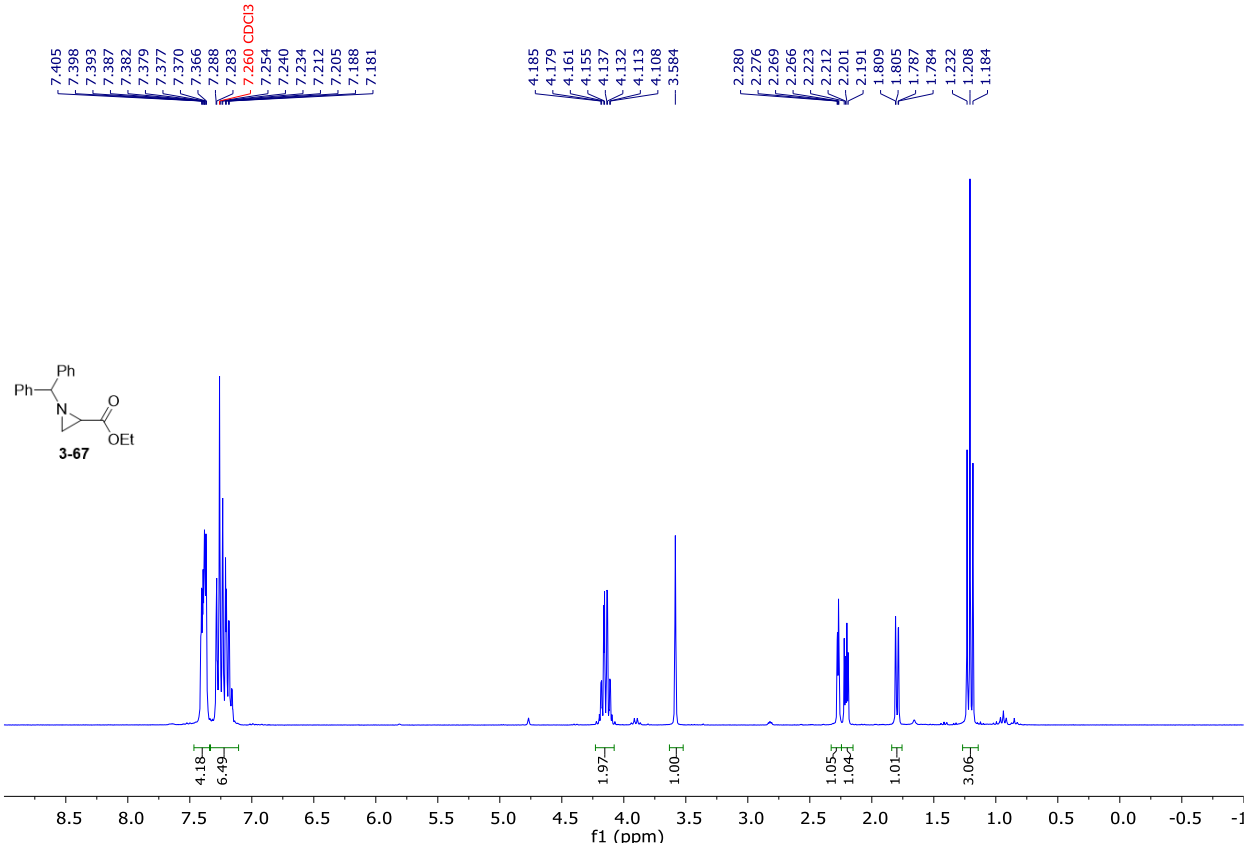

300.23 MHz — CDCl3 — 1D — 1H
7.270
7.260 CDCl3
7.241
6.878
6.849
4.240
4.228
4.216
4.204
4.180
4.156
4.144
4.133
4.121
2.234
2.229
2.223
2.219
2.182
2.171
2.161
2.150
1.735
1.731
1.713
1.709
1.286
1.262
1.238
O
N
OEt
O
3-66
2.92
2.06
2.12
3.14
2.02
0.96
1.00
1.00
3.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


CDCl3 -- 75.50 MHz -- 13C
170.774
158.927
129.864
129.346
113.809
77.424 CDCl3
77.000 CDCl3
76.579 CDCl3
63.301
61.079
55.251
37.372
34.312
14.165
O
N
OEt
O
3-66
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

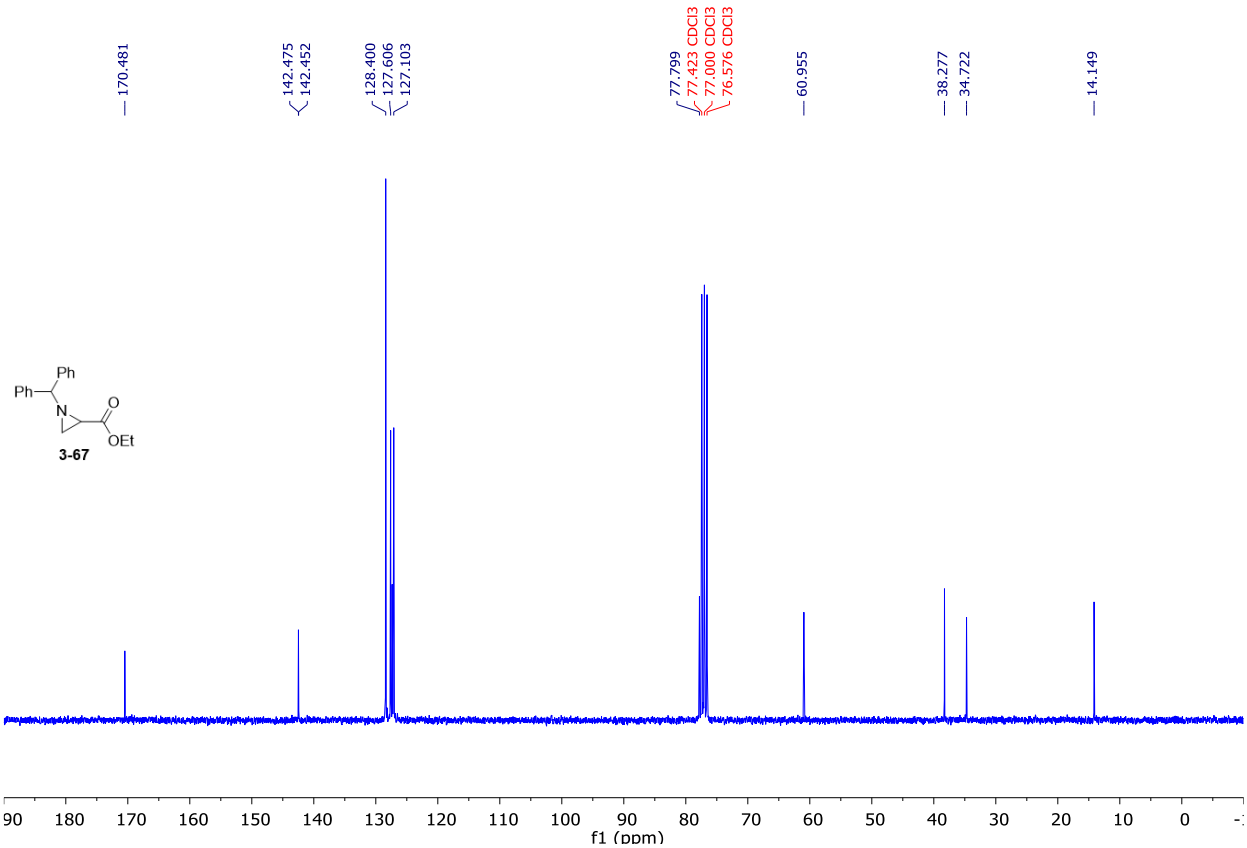

300.23 MHz — CDCl3 — 1D — 1H
7.347
7.344
7.334
7.329
7.326
7.299
7.294
7.285
7.283
7.260 CDCl3
4.250
4.237
4.226
4.214
4.190
4.166
4.154
4.142
4.130
3.604
3.559
3.551
3.506
2.269
2.265
2.259
2.255
2.202
2.192
2.181
2.171
1.756
1.752
1.734
1.730
1.291
1.267
1.243
Bn
N
O
OEt
3-68
5.10
2.02
2.00
0.96
0.94
0.96
2.92
f1 (ppm)


75.50 MHz — CDCl3 — 1D — 13C
170.698
137.792
128.387
127.996
127.289
77.424 CDCl3
77.000 CDCl3
76.577 CDCl3
63.887
61.097
37.536
34.444
14.161
Bn
N
O
OEt
3-68
f1 (ppm)

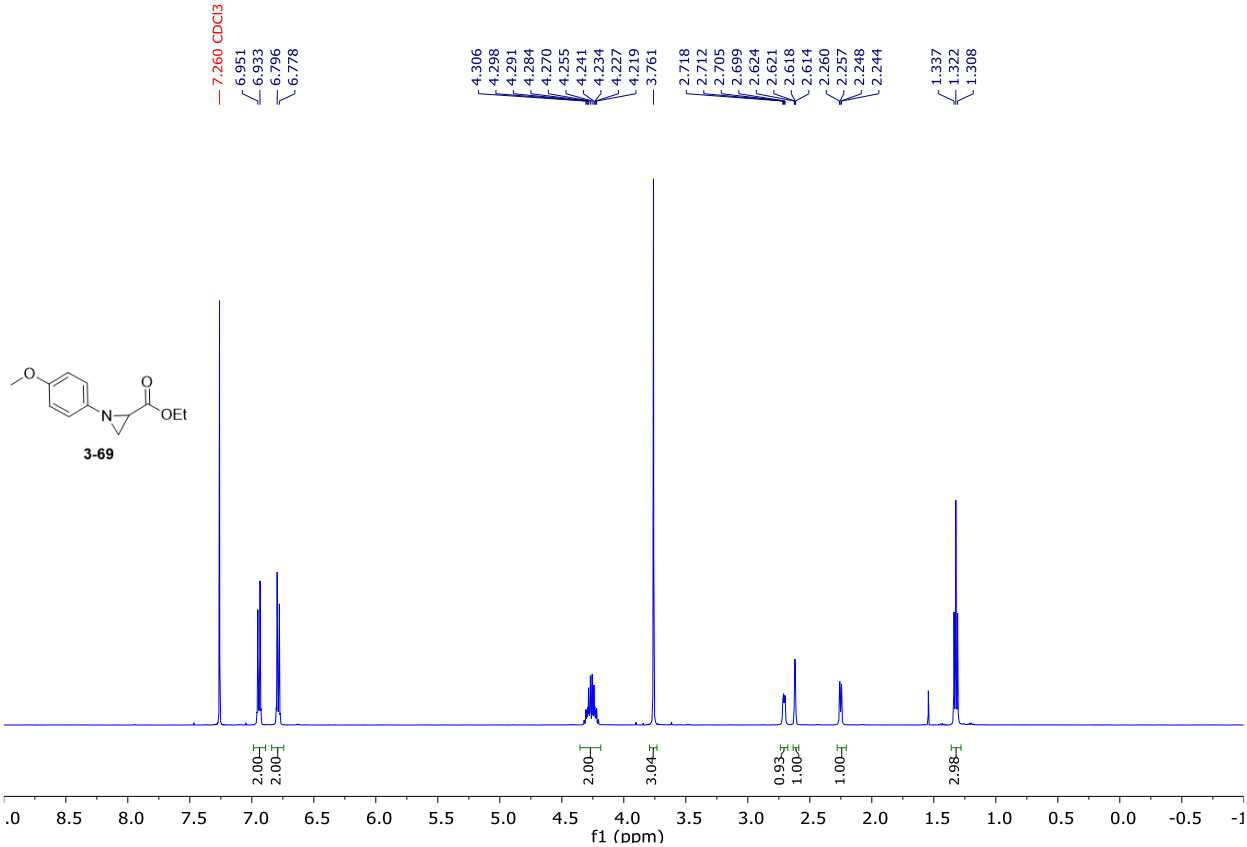
300.23 MHz — CDCl3 — 1D — 1H



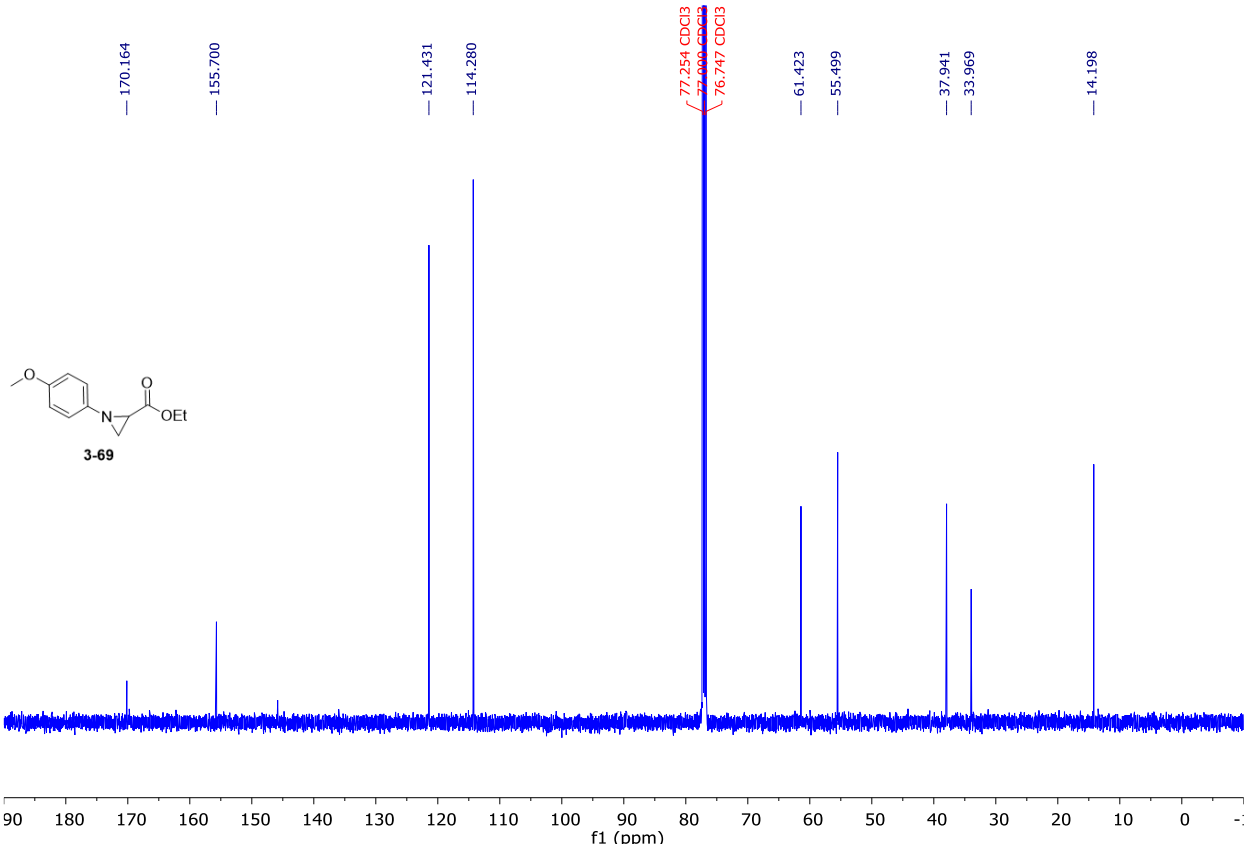
75.50 MHz — CDCl3 — 1D — 13C



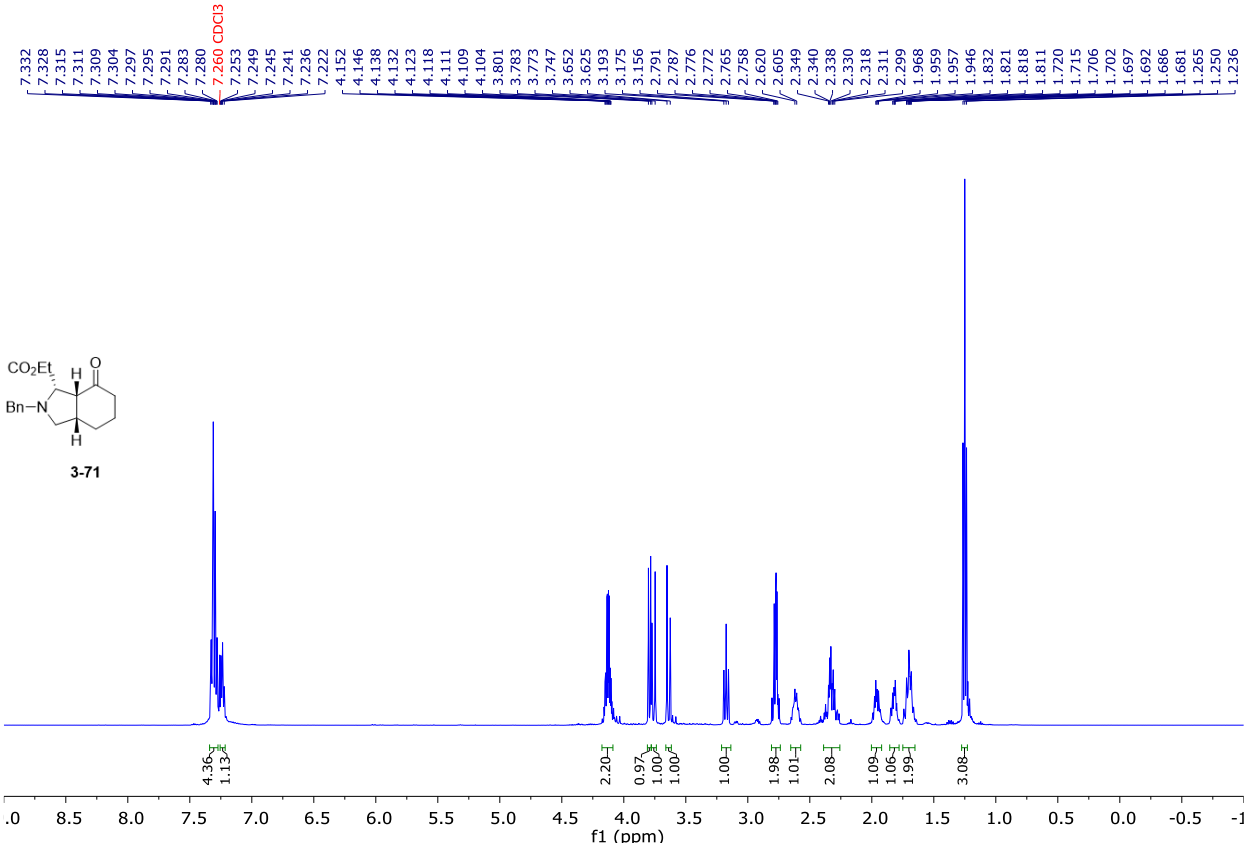
500.16 MHz — CDCl3 — 1D — 1H



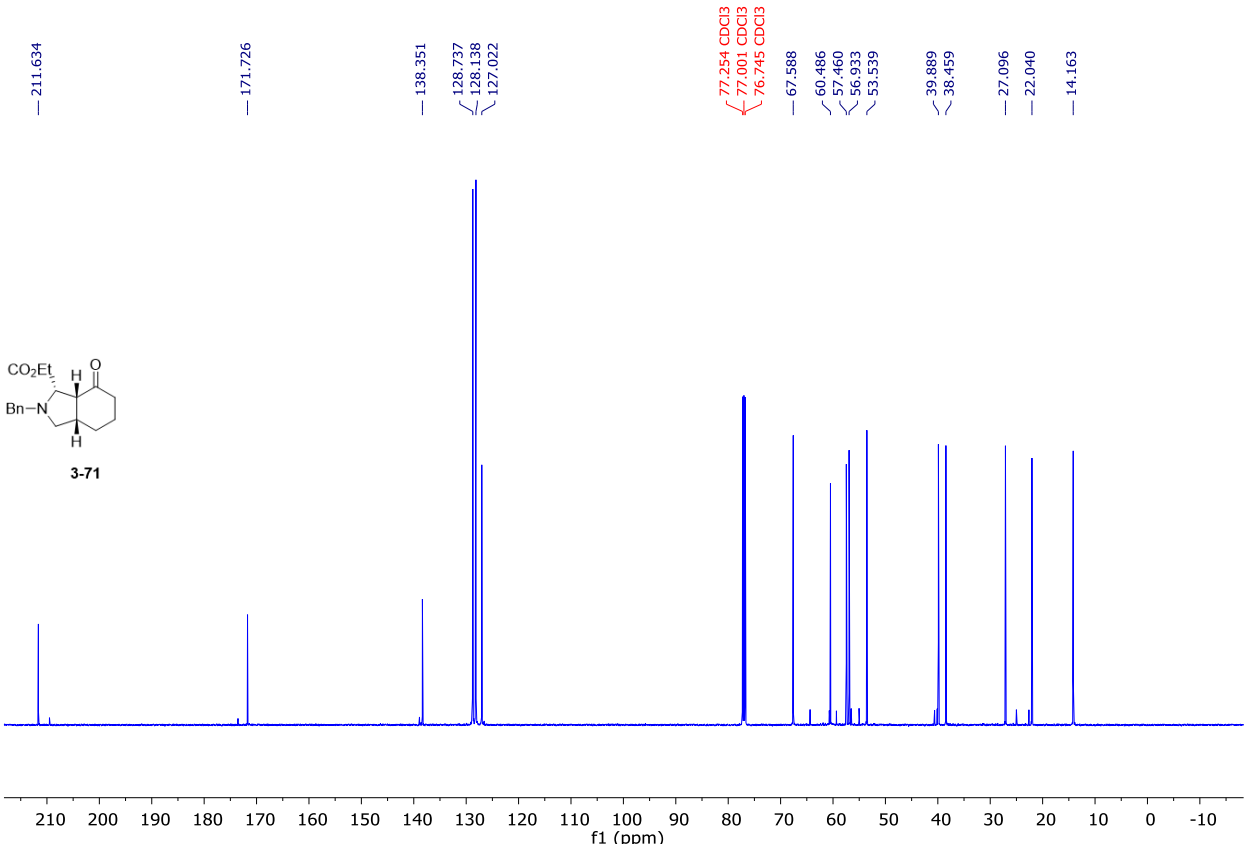
125.78 MHz — CDCl3 — 1D — 13C

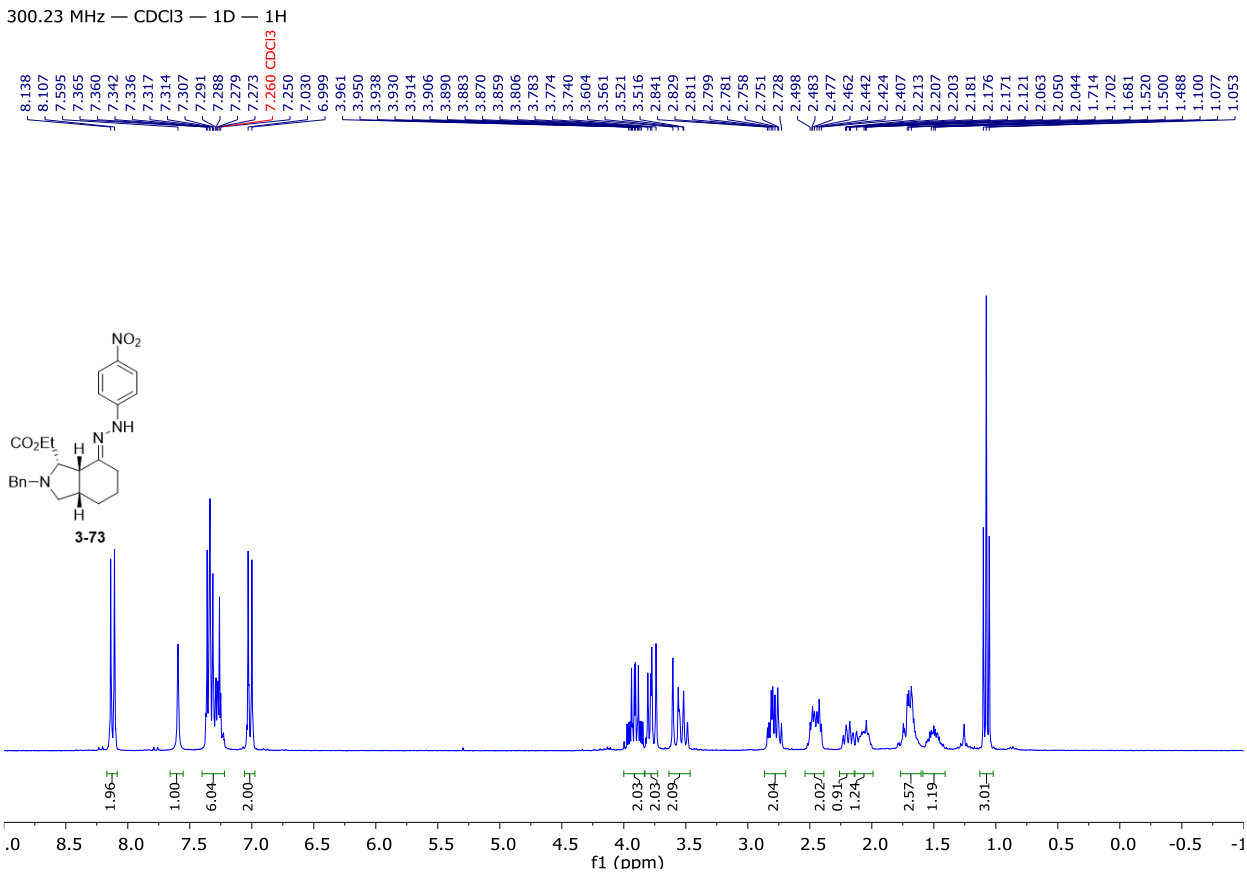


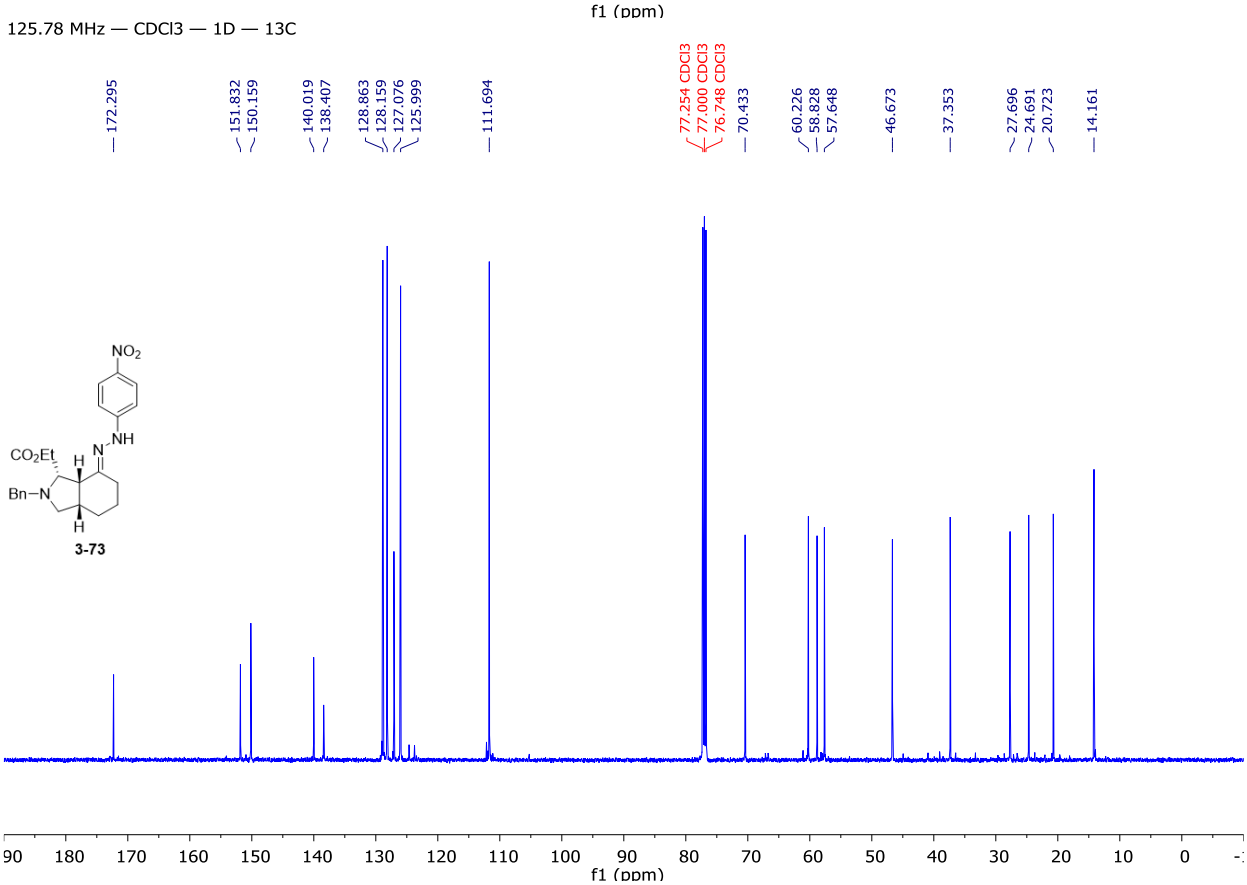
500.16 MHz — CDCl3 — 1D — 1H

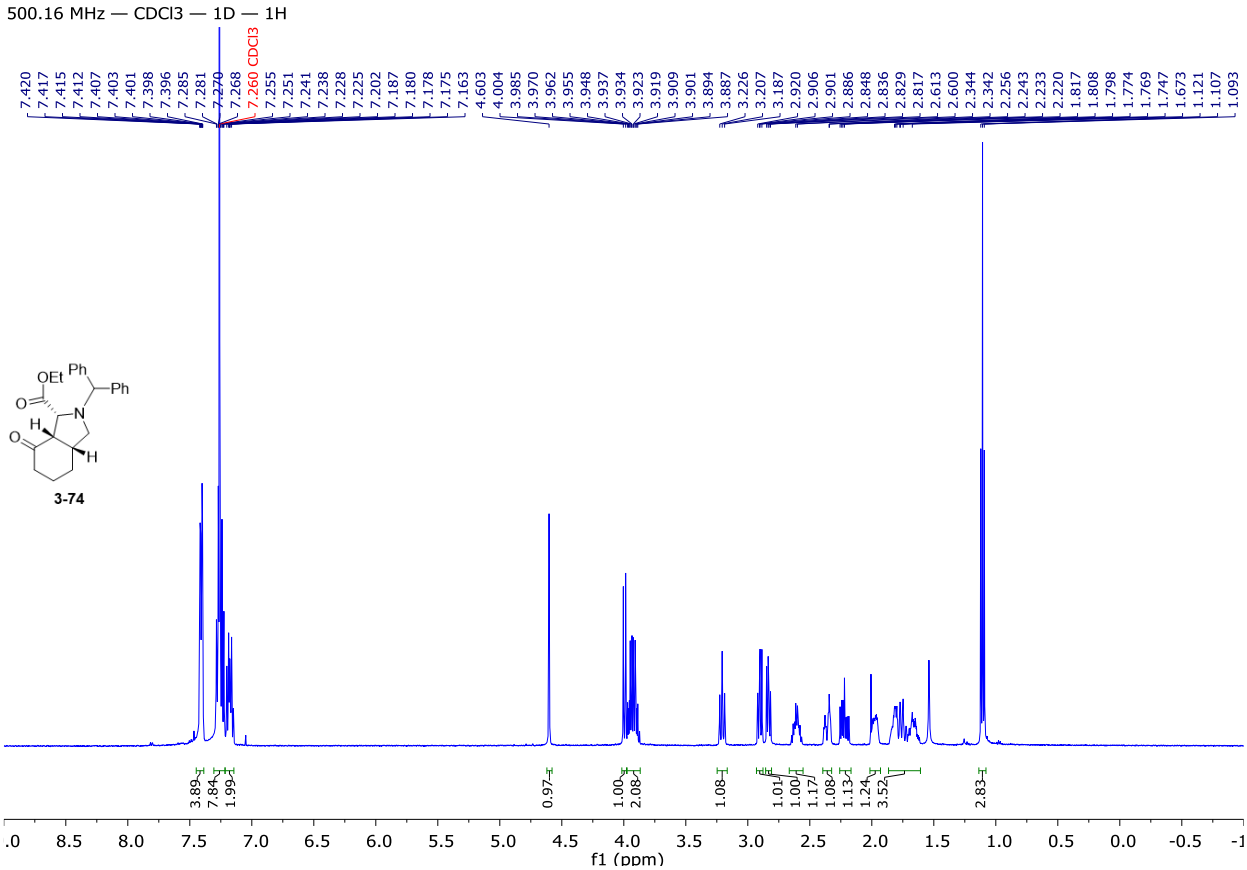


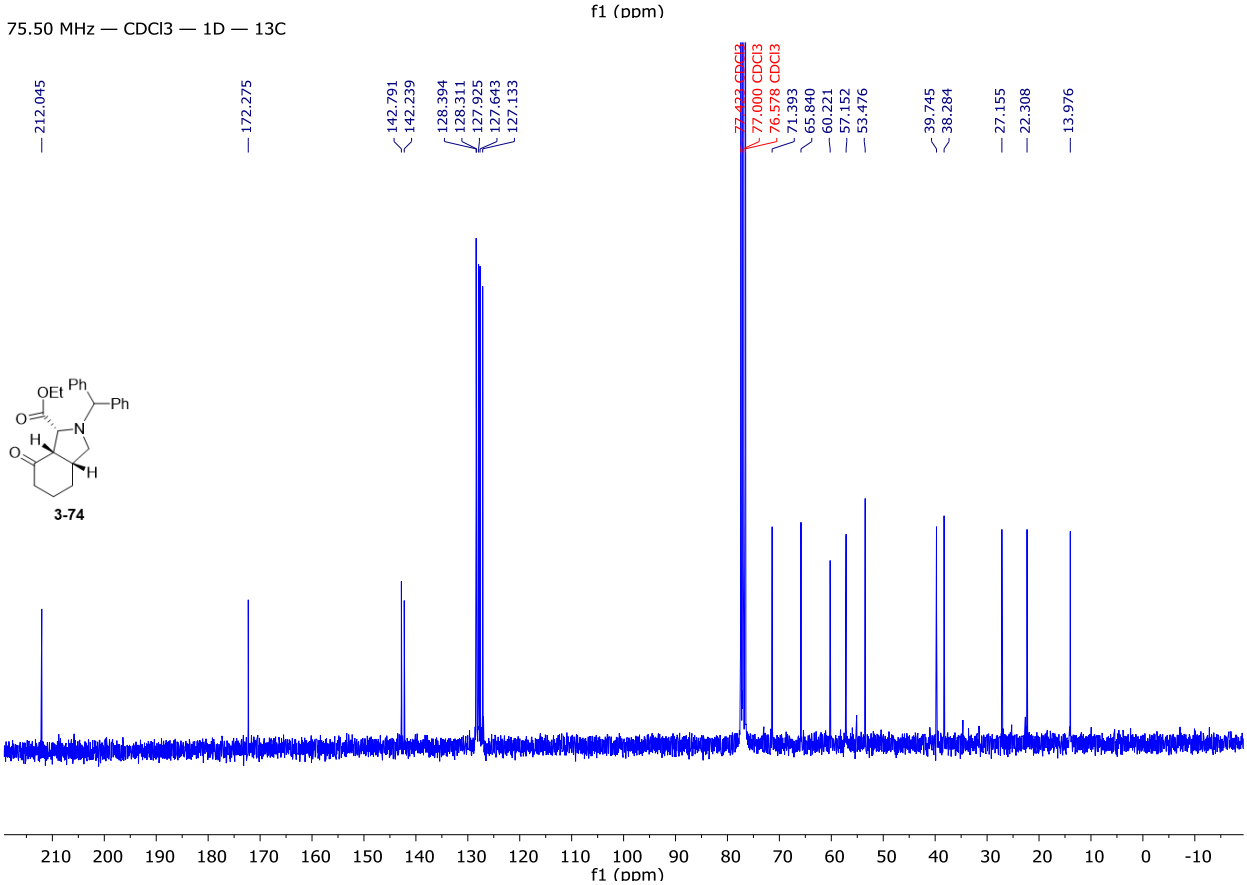
125.78 MHz — CDCl3 — 1D — 13C

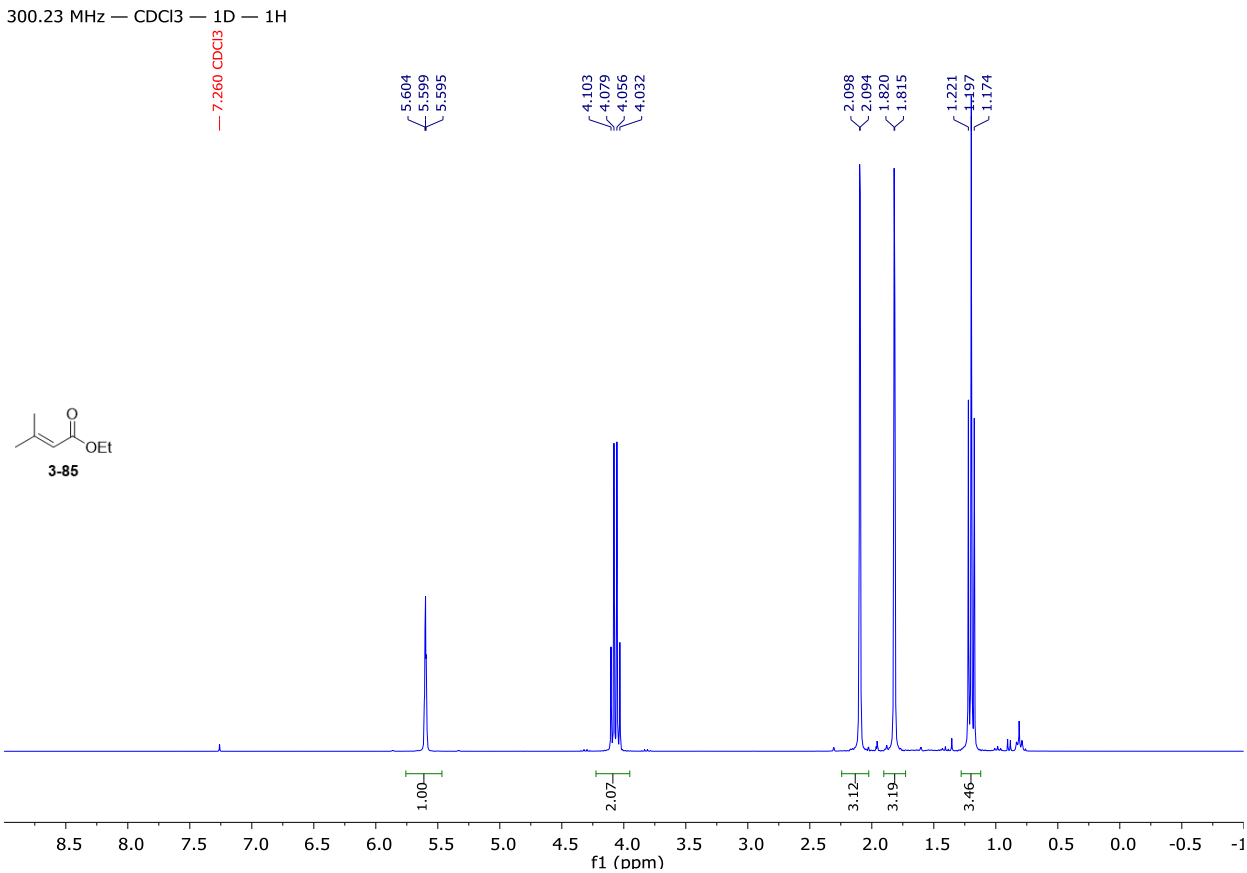


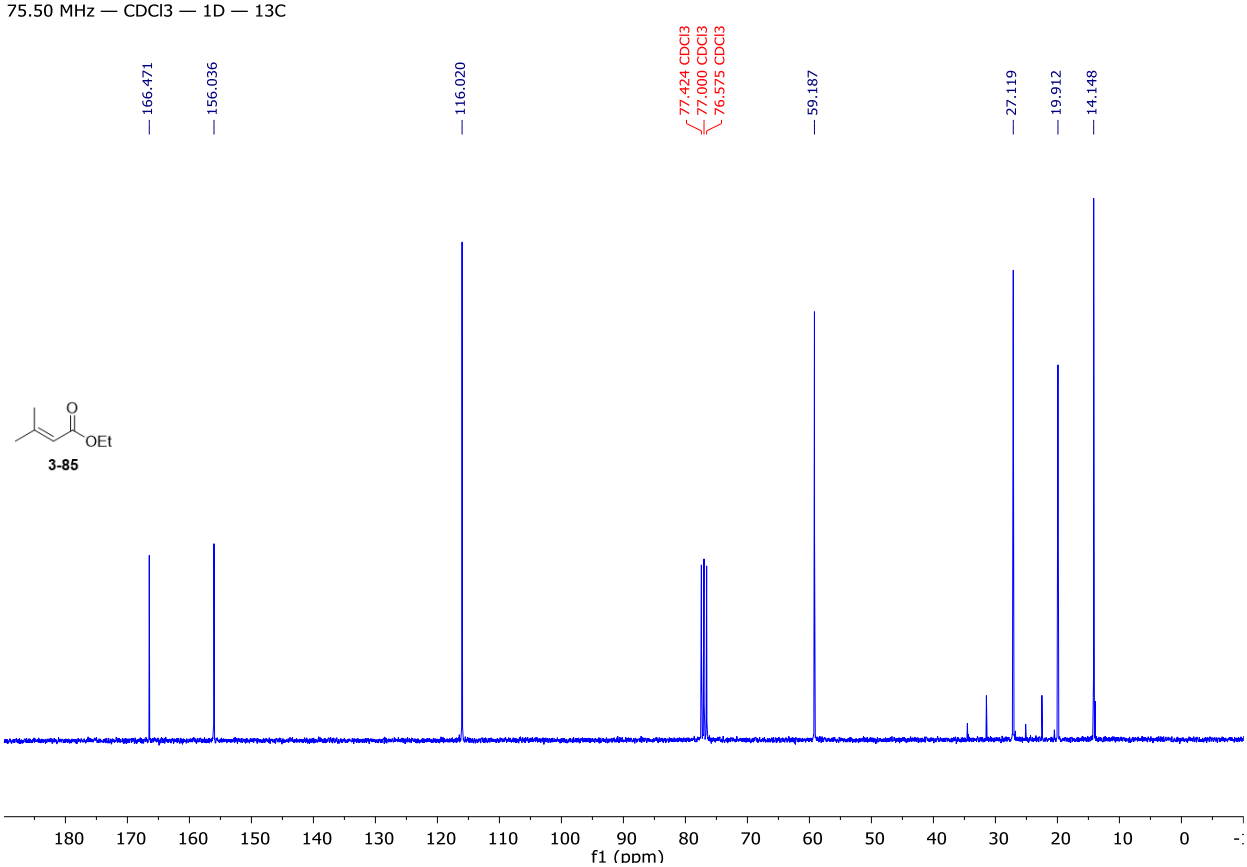

300.23 MHz — CDCl3 — 1D — 1H
8.138
8.107
7.595
7.365
7.360
7.342
7.336
7.317
7.314
7.307
7.291
7.288
7.279
7.273
7.260 CDCl3
7.250
7.030
6.999
3.961
3.950
3.938
3.930
3.914
3.906
3.890
3.883
3.870
3.859
3.806
3.783
3.774
3.740
3.604
3.561
3.521
3.516
2.841
2.829
2.811
2.799
2.781
2.758
2.751
2.728
2.498
2.483
2.477
2.462
2.442
2.424
2.407
2.213
2.207
2.203
2.181
2.176
2.171
2.121
2.063
2.050
2.044
1.714
1.702
1.681
1.520
1.500
1.488
1.100
1.077
1.053
NO2
NH
N
CO2Et
H
Bn–N
H
3-73
1.96
1.00
6.04
2.00
2.03
2.03
2.09
2.04
2.02
0.91
1.24
2.57
1.19
3.01
f1 (ppm)


125.78 MHz — CDCl3 — 1D — 13C
172.295
151.832
150.159
140.019
138.407
128.863
128.159
127.076
125.999
111.694
77.254 CDCl3
77.000 CDCl3
76.748 CDCl3
70.433
60.226
58.828
57.648
46.673
37.353
27.696
24.691
20.723
14.161
NO2
NH
N
CO2Et
H
Bn–N
H
3-73
f1 (ppm)

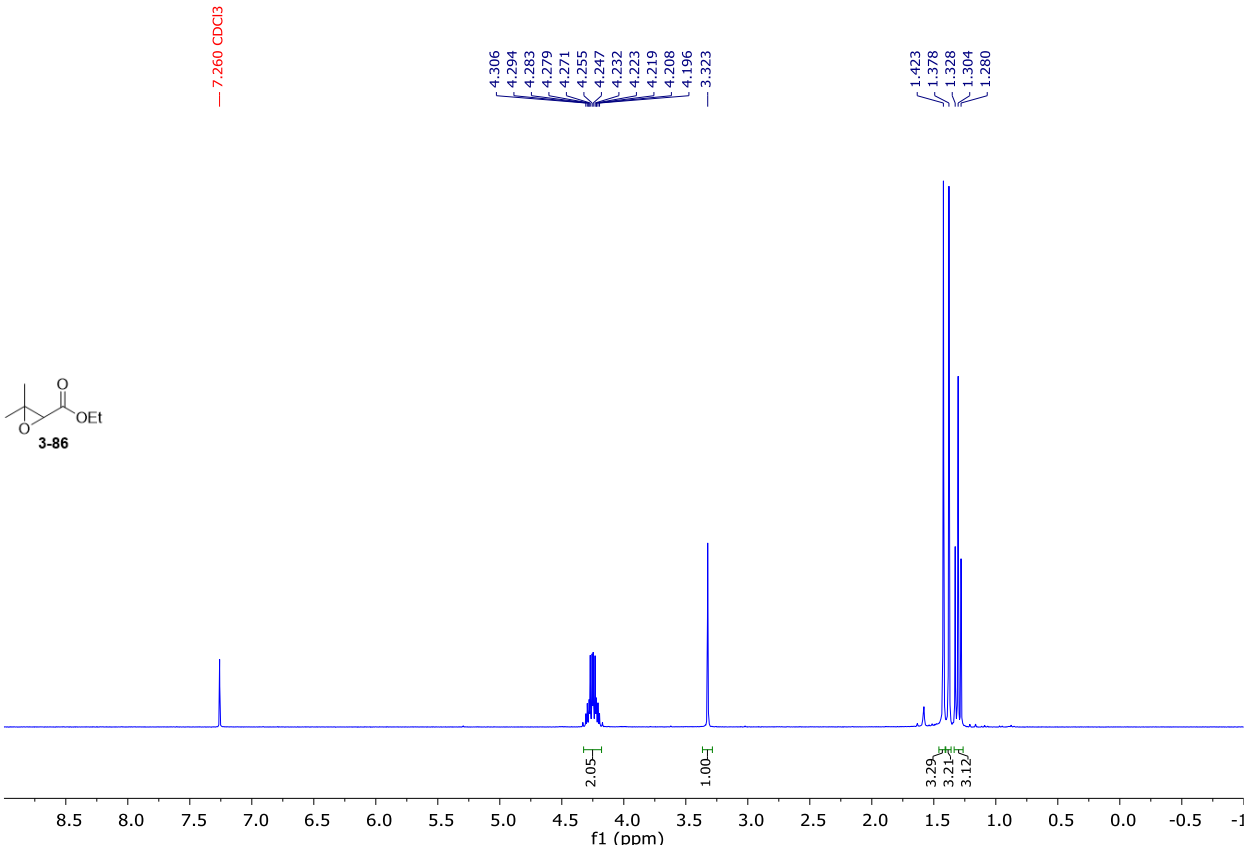

500.16 MHz — CDCl3 — 1D — 1H
7.420
7.417
7.415
7.412
7.407
7.403
7.401
7.398
7.396
7.285
7.281
7.270
7.268
7.260 CDCl3
7.255
7.251
7.241
7.238
7.228
7.225
7.202
7.187
7.180
7.178
7.175
7.163
4.603
4.004
3.985
3.970
3.962
3.955
3.948
3.937
3.934
3.923
3.919
3.909
3.901
3.894
3.887
3.226
3.207
3.187
2.920
2.906
2.901
2.886
2.848
2.836
2.829
2.817
2.613
2.600
2.344
2.342
2.256
2.243
2.233
2.220
1.817
1.808
1.798
1.774
1.769
1.747
1.673
1.121
1.107
1.093
OEt
Ph
Ph
O
N
H
O
H
3-74
3.89
7.84
1.99
0.97
1.00
2.08
1.08
1.01
1.00
1.17
1.08
1.13
1.24
3.52
2.83
f1 (ppm)

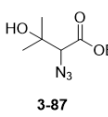

75.50 MHz — CDCl3 — 1D — 13C
212.045
172.275
142.791
142.239
128.394
128.311
127.925
127.643
127.133
77.422 CDCl3
77.000 CDCl3
76.578 CDCl3
71.393
65.840
60.221
57.152
53.476
39.745
38.284
27.155
22.308
13.976
OEt
Ph
Ph
O
N
H
O
H
3-74
f1 (ppm)


300.23 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
5.604
5.599
5.595
4.103
4.079
4.056
4.032
2.098
2.094
1.820
1.815
1.221
1.197
1.174
OEt
3-85
1.00
2.07
3.12
3.19
3.46
f1 (ppm)


75.50 MHz — CDCl3 — 1D — 13C
166.471
156.036
116.020
77.424 CDCl3
77.000 CDCl3
76.575 CDCl3
59.187
27.119
19.912
14.148
OEt
3-85
f1 (ppm)

CDCl3 -- 300.23 MHz -- 1H

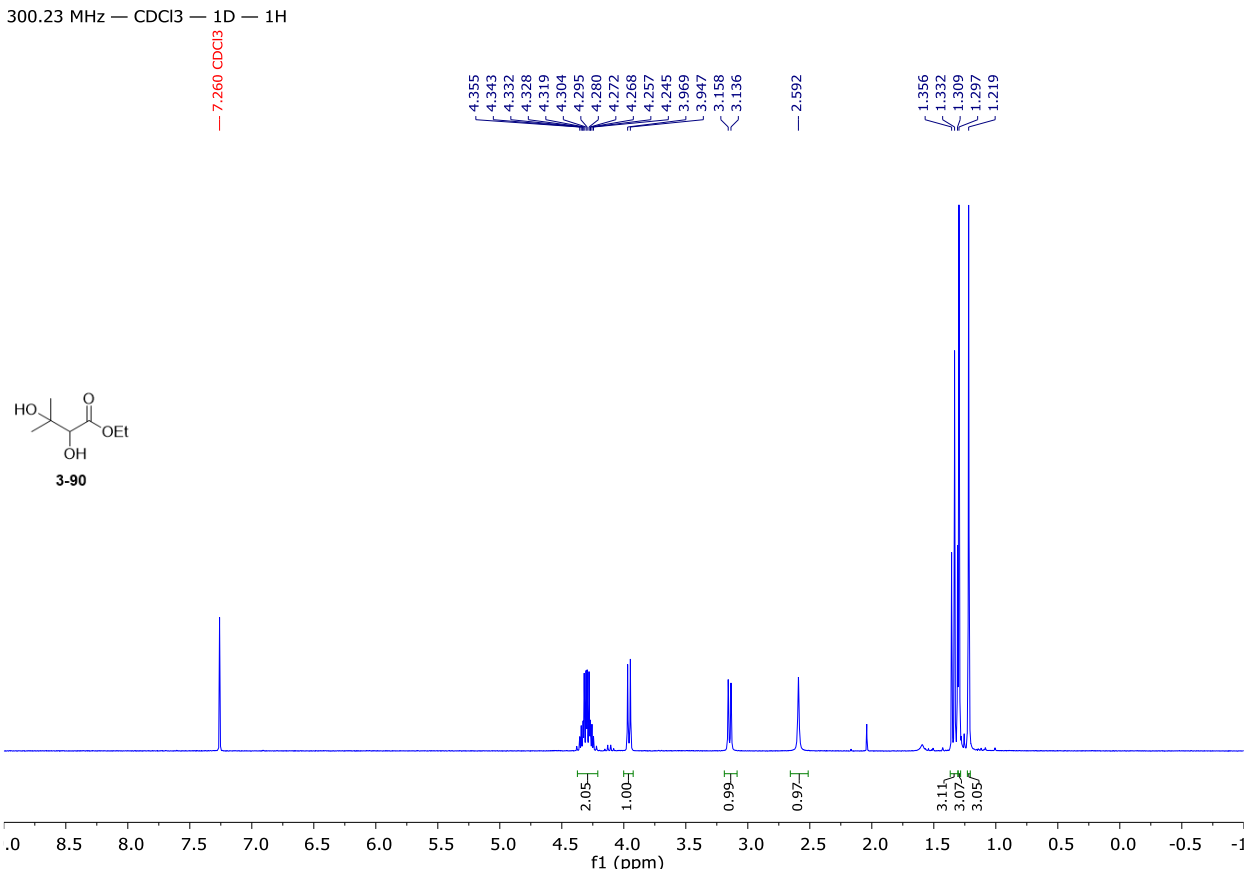


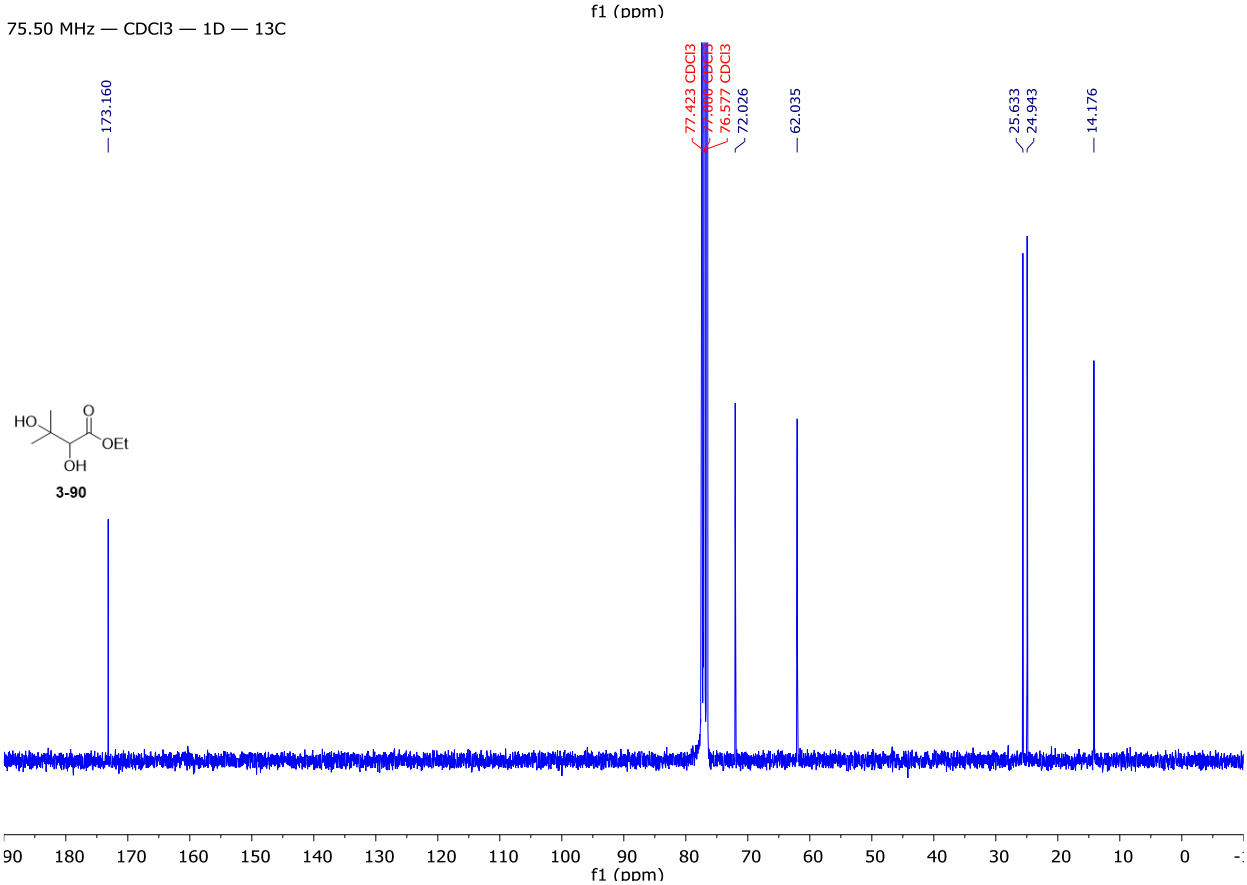


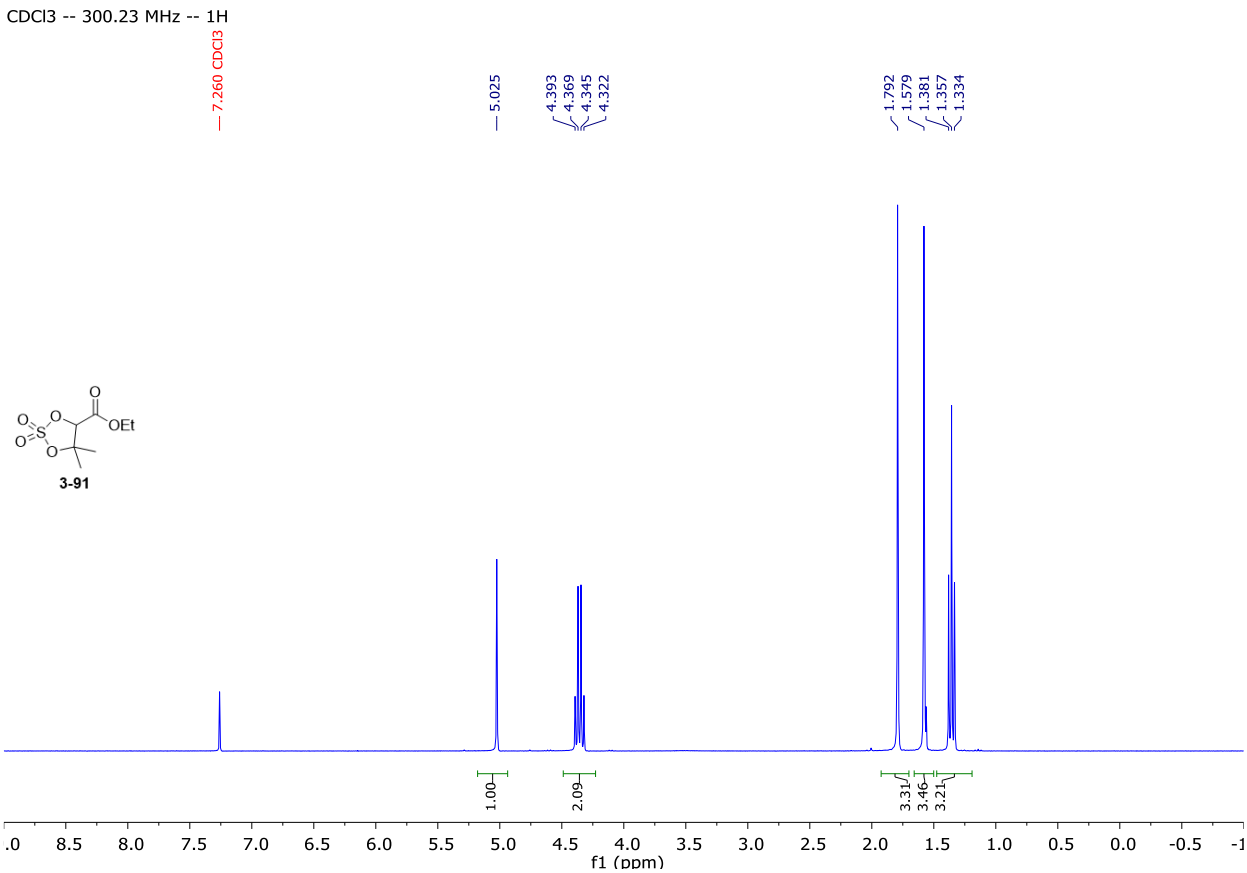
3-86

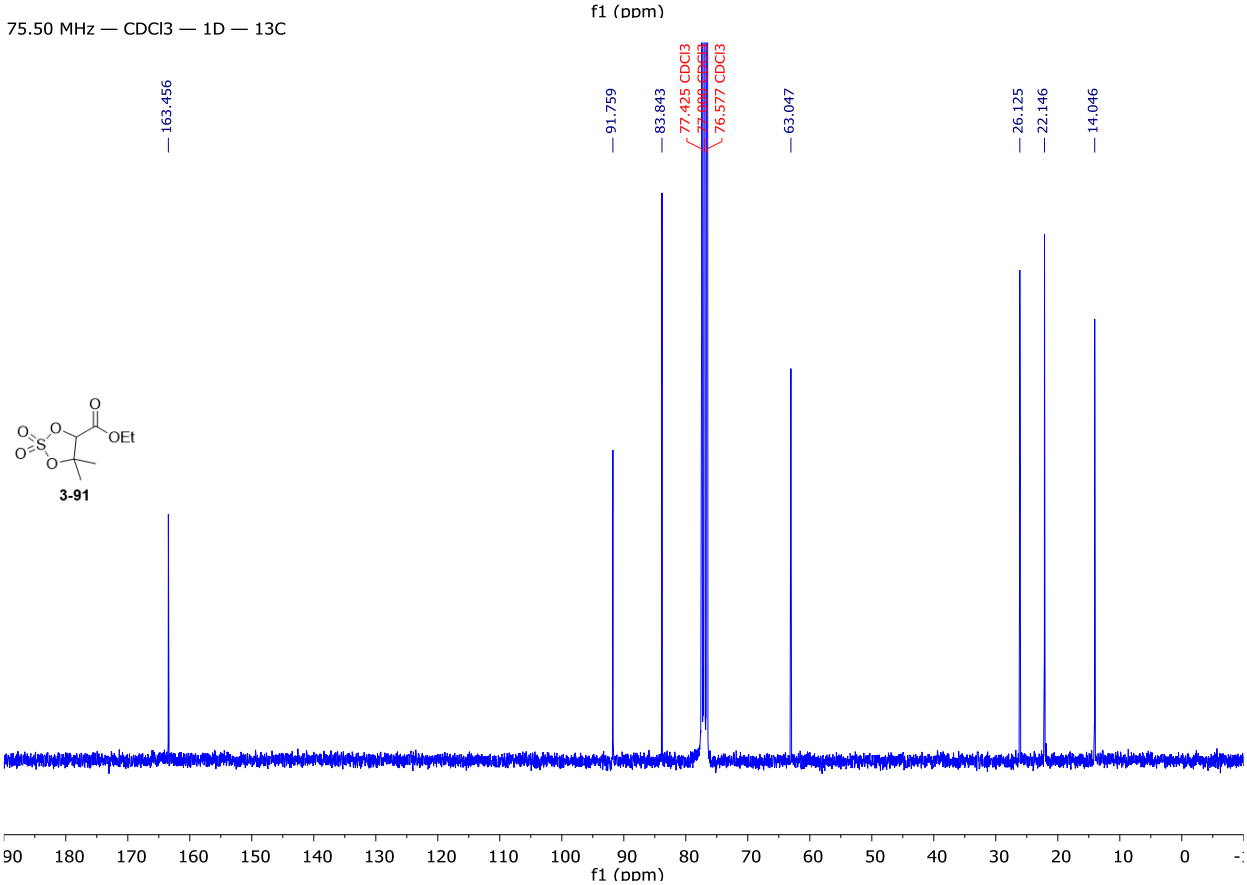
CDCl3 -- 300.23 MHz -- 1H

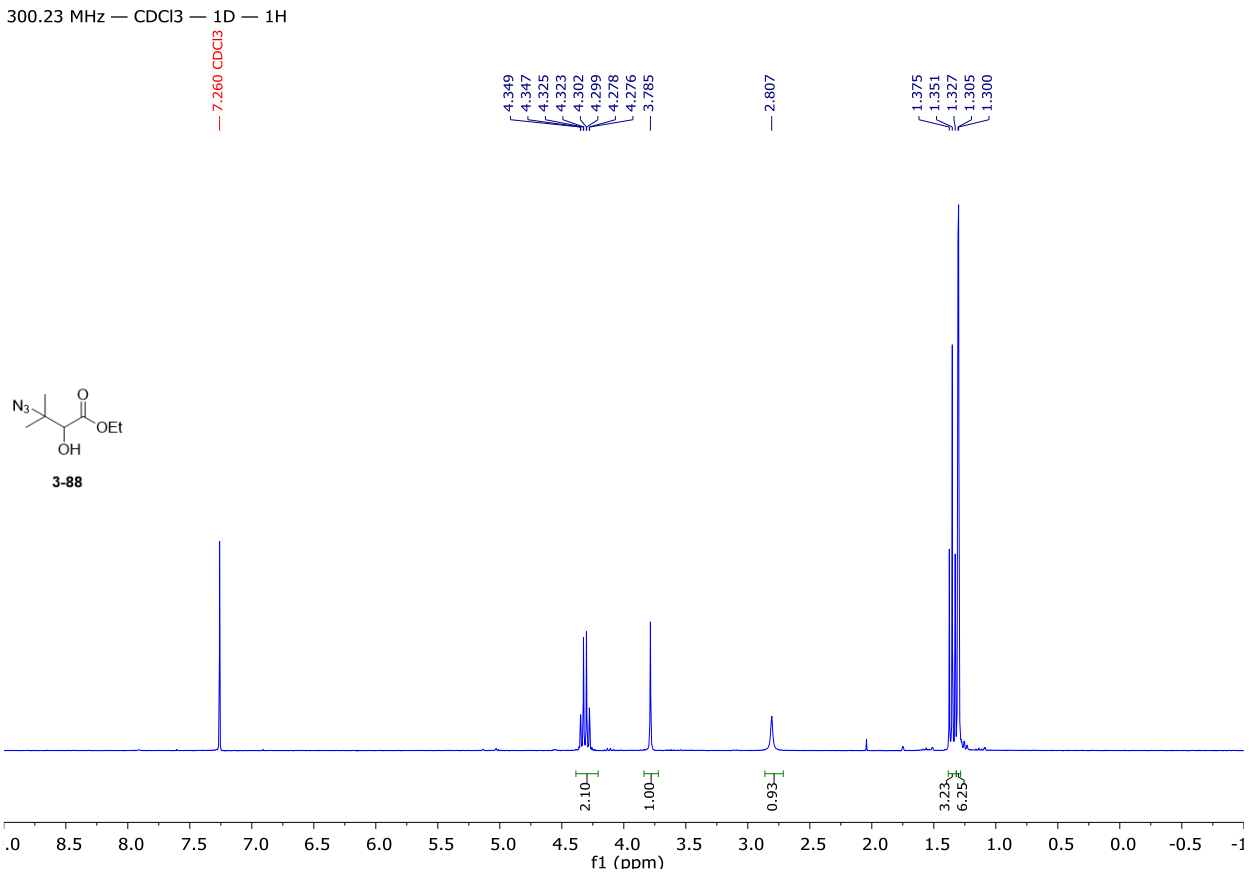
3-87


300.23 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
4.355
4.343
4.332
4.328
4.319
4.304
4.295
4.280
4.272
4.268
4.257
4.245
3.969
3.947
3.158
3.136
2.592
1.356
1.332
1.309
1.297
1.219
HO
O
OEt
OH
3-90
2.05
1.00
0.99
0.97
3.11
3.07
3.05
f1 (ppm)

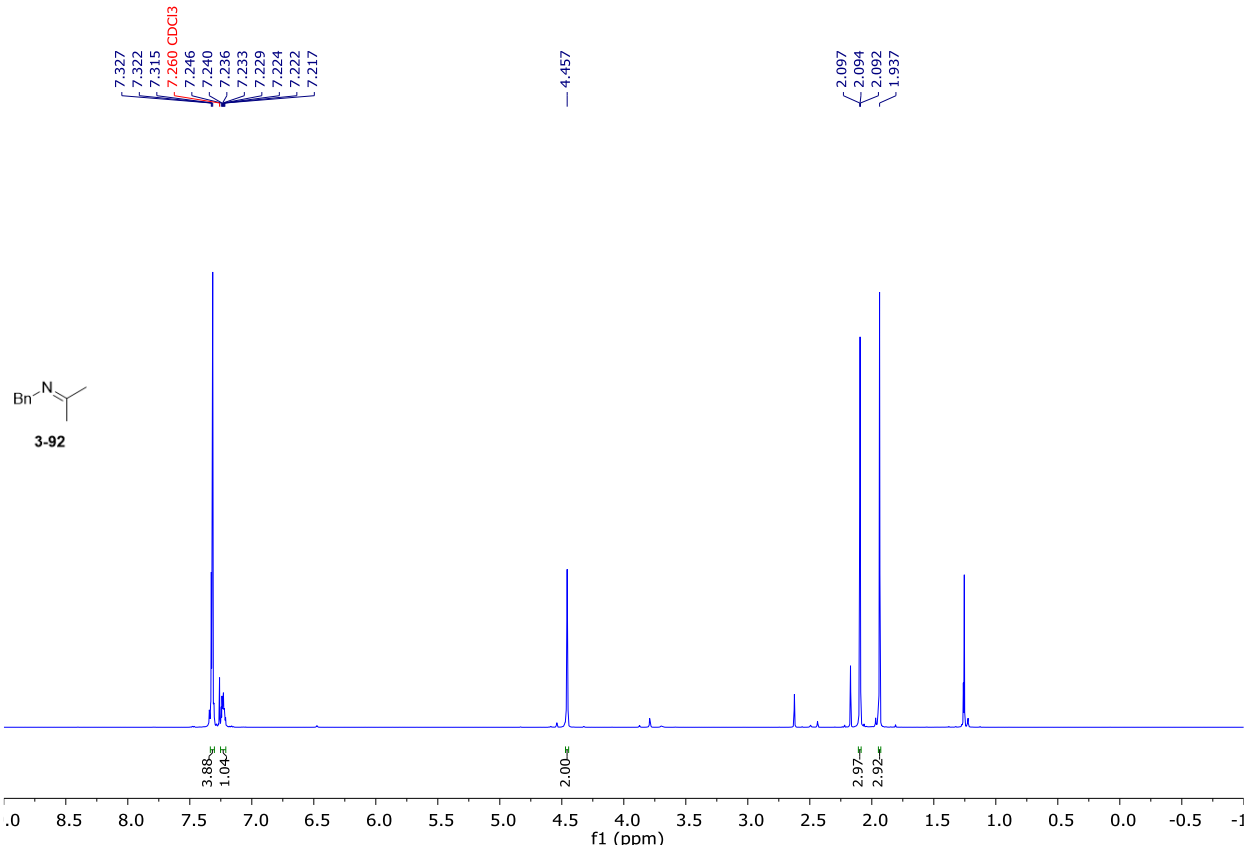

75.50 MHz — CDCl3 — 1D — 13C
173.160
77.423 CDCl3
77.000 CDCl3
76.577 CDCl3
72.026
62.035
25.633
24.943
14.176
HO
O
OEt
OH
3-90
f1 (ppm)


CDCl3 -- 300.23 MHz -- 1H
7.260 CDCl3
5.025
4.393
4.369
4.345
4.322
1.792
1.579
1.381
1.357
1.334
OEt
3-91
1.00
2.09
3.31
3.46
3.21
f1 (ppm)

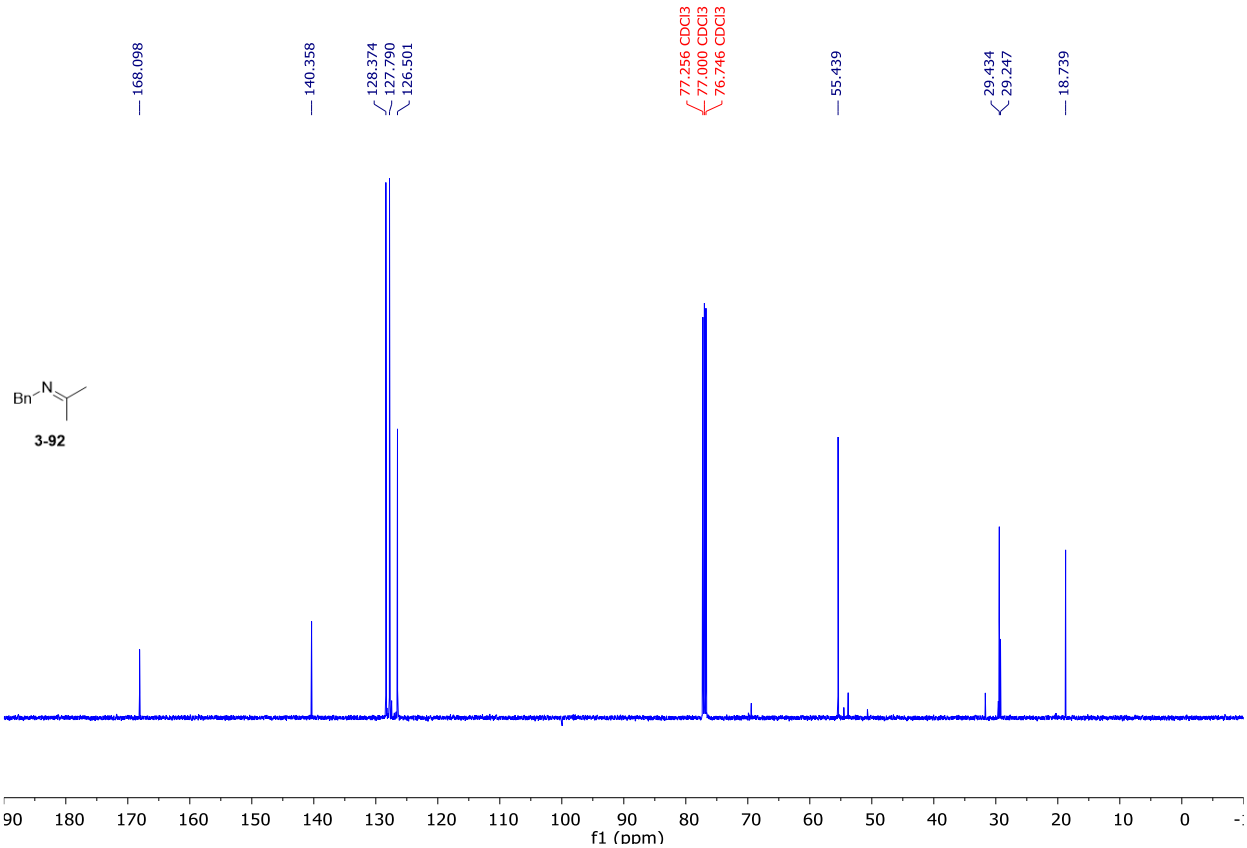

75.50 MHz — CDCl3 — 1D — 13C
163.456
91.759
83.843
77.425 CDCl3
76.577 CDCl3
63.047
26.125
22.146
14.046
OEt
3-91
f1 (ppm)

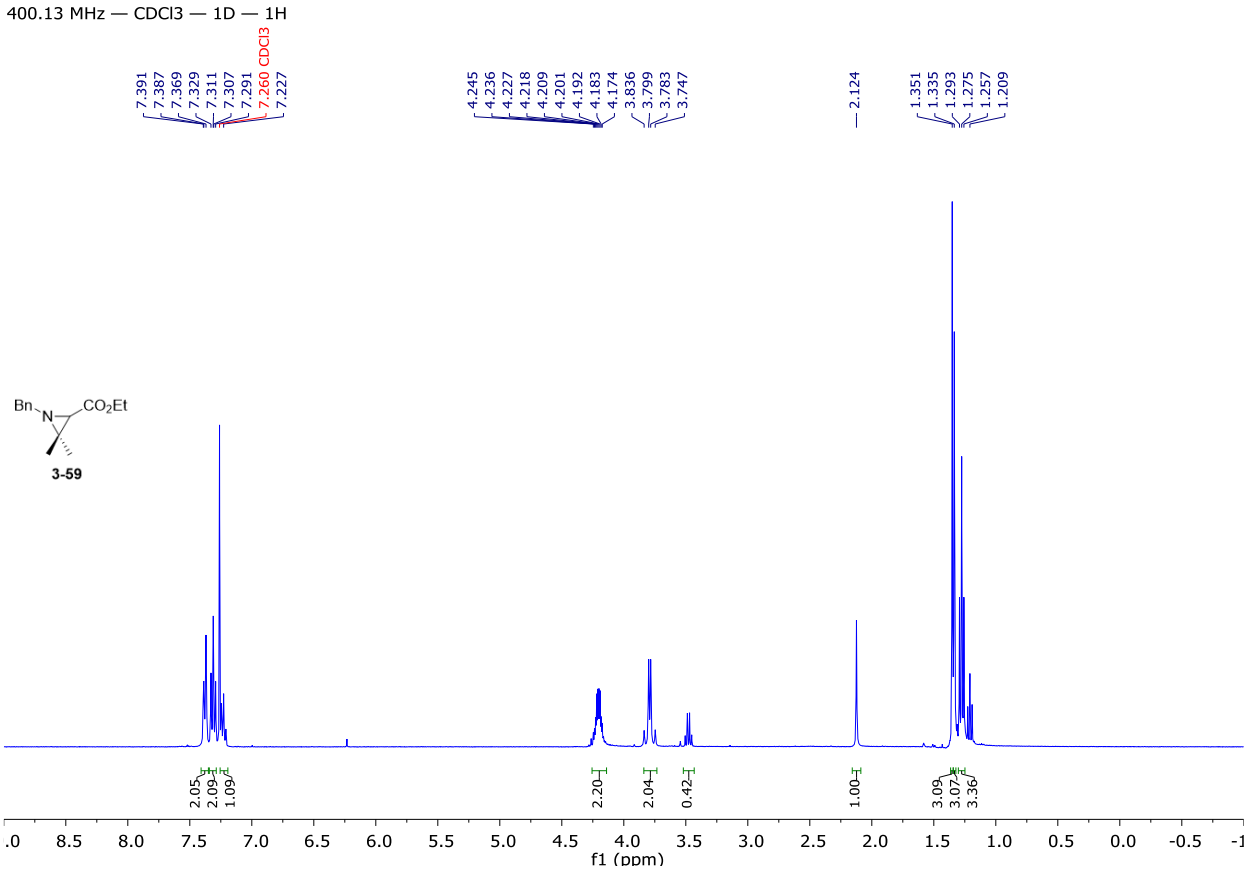

300.23 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
4.349
4.347
4.325
4.323
4.302
4.299
4.278
4.276
3.785
2.807
1.375
1.351
1.327
1.305
1.300
N3
O
OEt
OH
3-88
2.10
1.00
0.93
3.23
6.25
f1 (ppm)

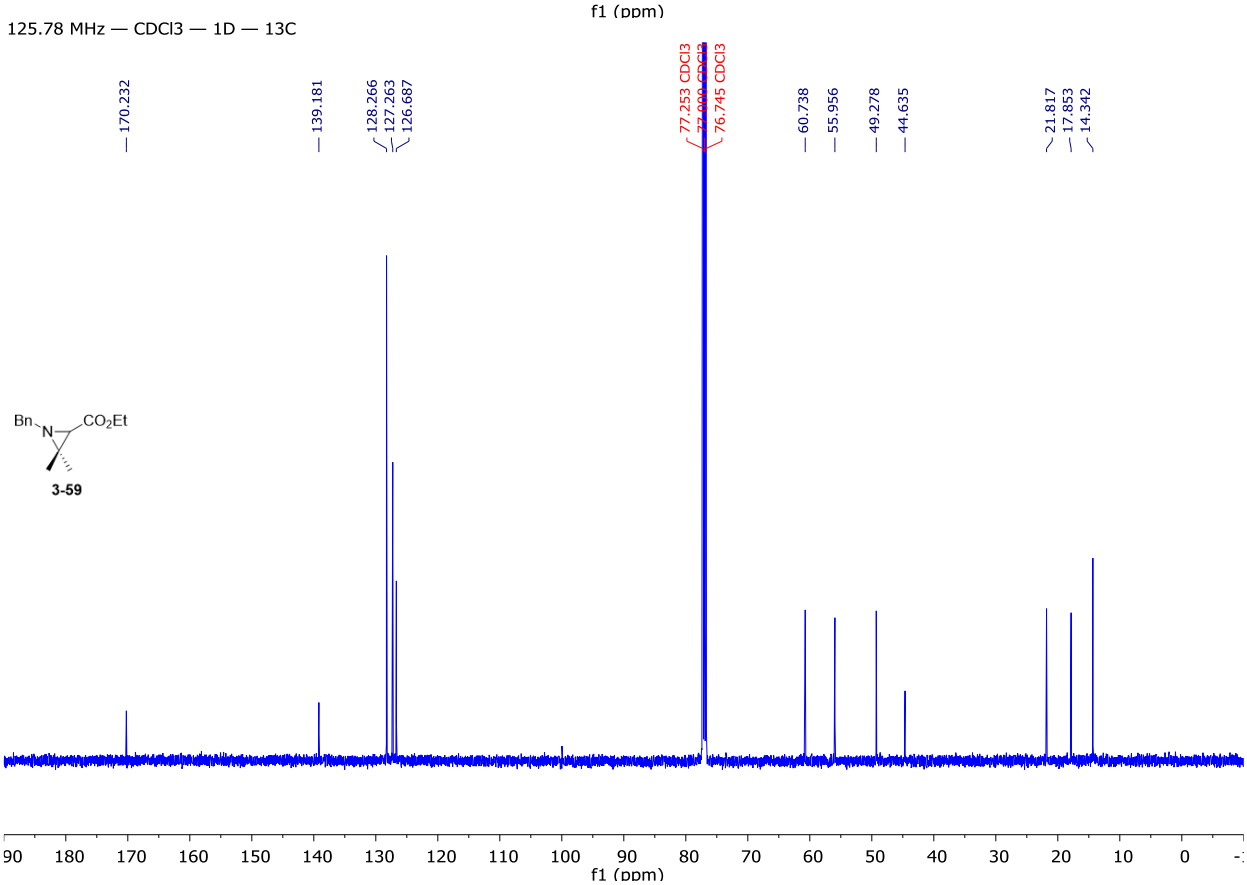
500.16 MHz — CDCl3 — 1D — 1H

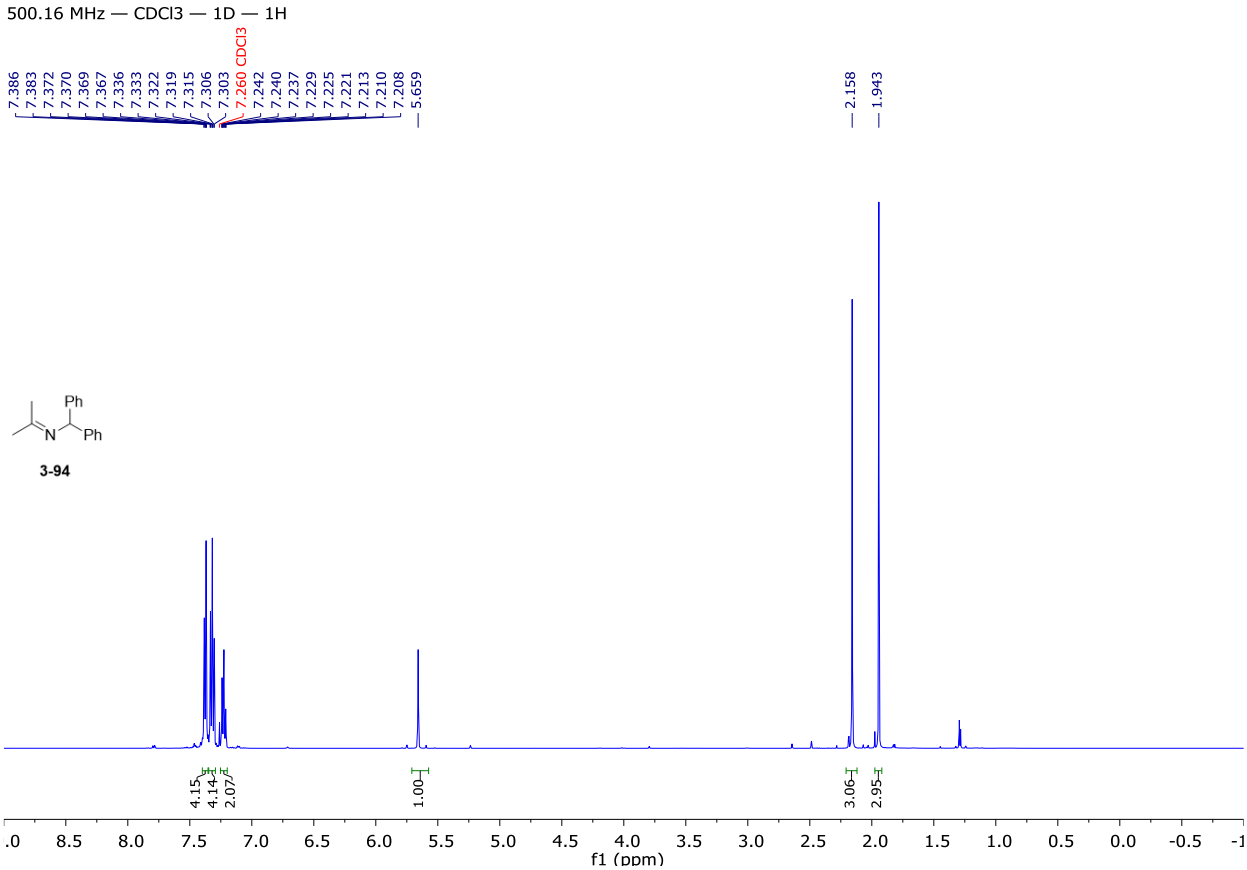


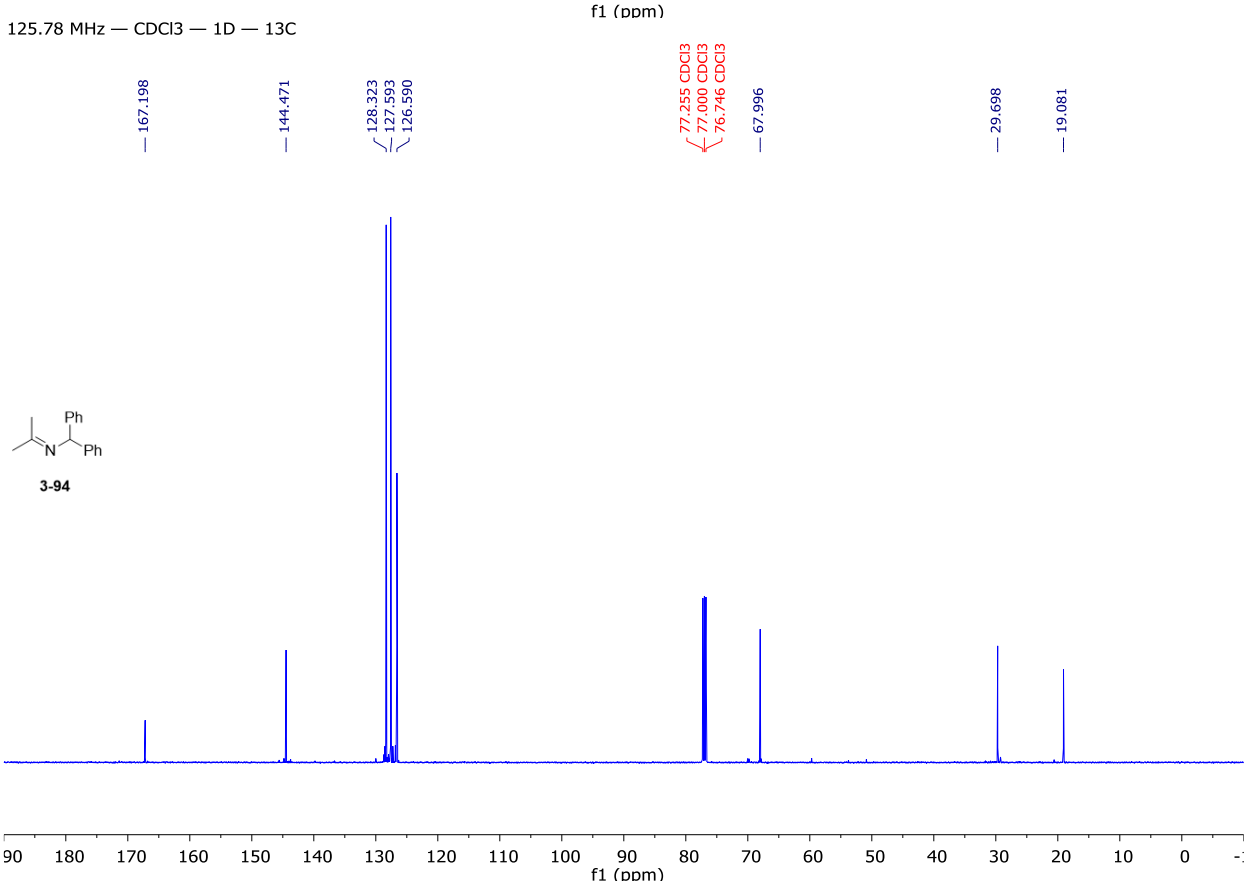
125.78 MHz — CDCl3 — 1D — 13C



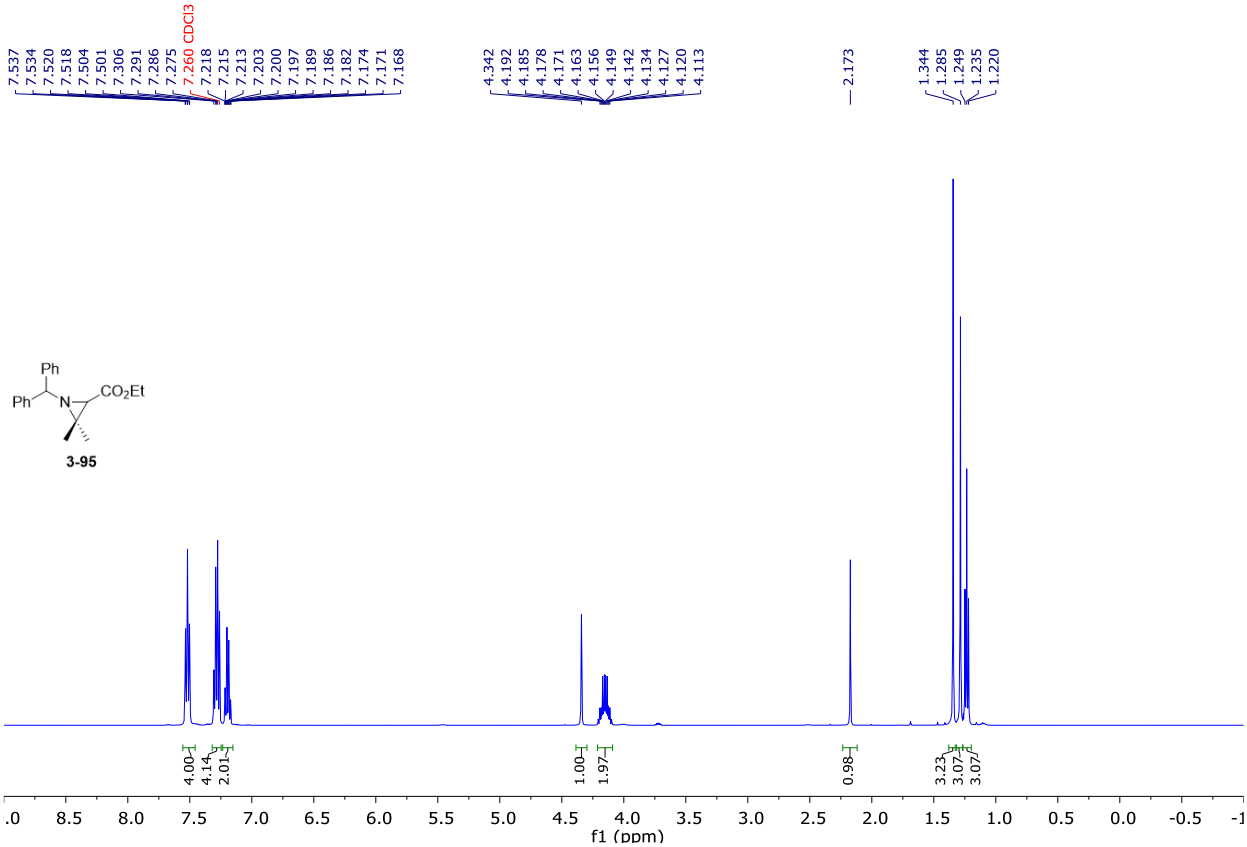

400.13 MHz — CDCl3 — 1D — 1H
7.391
7.387
7.369
7.329
7.311
7.307
7.291
7.260 CDCl3
7.227
4.245
4.236
4.227
4.218
4.209
4.201
4.192
4.183
4.174
3.836
3.799
3.783
3.747
2.124
1.351
1.335
1.293
1.275
1.257
1.209
Bn
N
CO2Et
3-59
2.05
2.09
1.09
2.20
2.04
0.42
1.00
3.09
3.07
3.36
f1 (ppm)


125.78 MHz — CDCl3 — 1D — 13C
170.232
139.181
128.266
127.263
126.687
77.253 CDCl3
77.000 CDCl3
76.745 CDCl3
60.738
55.956
49.278
44.635
21.817
17.853
14.342
Bn
N
CO2Et
3-59
f1 (ppm)

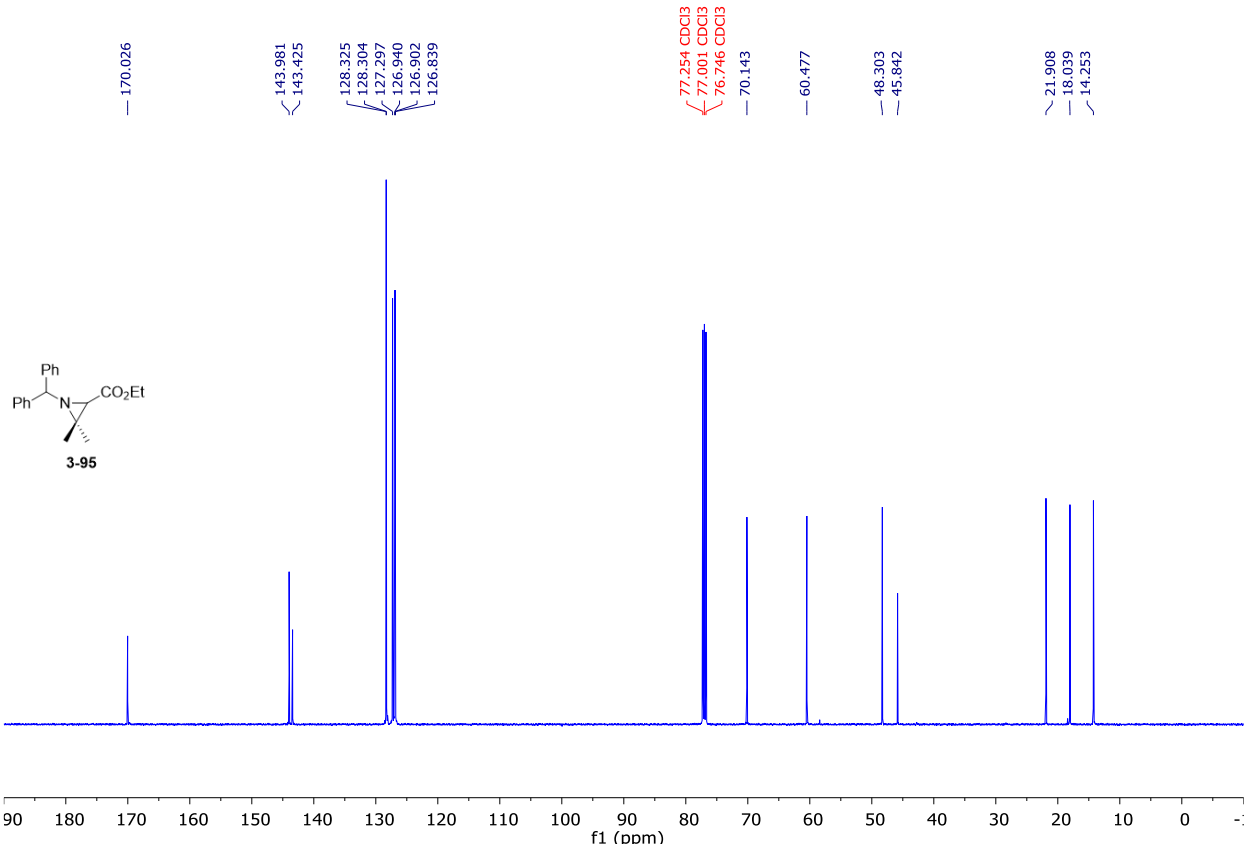

500.16 MHz — CDCl3 — 1D — 1H
7.386
7.383
7.372
7.370
7.369
7.367
7.336
7.333
7.322
7.319
7.315
7.306
7.303
7.260 CDCl3
7.242
7.240
7.237
7.229
7.225
7.221
7.213
7.210
7.208
5.659
2.158
1.943
Ph
N
Ph
3-94
4.15
4.14
2.07
1.00
3.06
2.95
f1 (ppm)


125.78 MHz — CDCl3 — 1D — 13C
167.198
144.471
128.323
127.593
126.590
77.255 CDCl3
77.000 CDCl3
76.746 CDCl3
67.996
29.698
19.081
Ph
N
Ph
3-94
f1 (ppm)

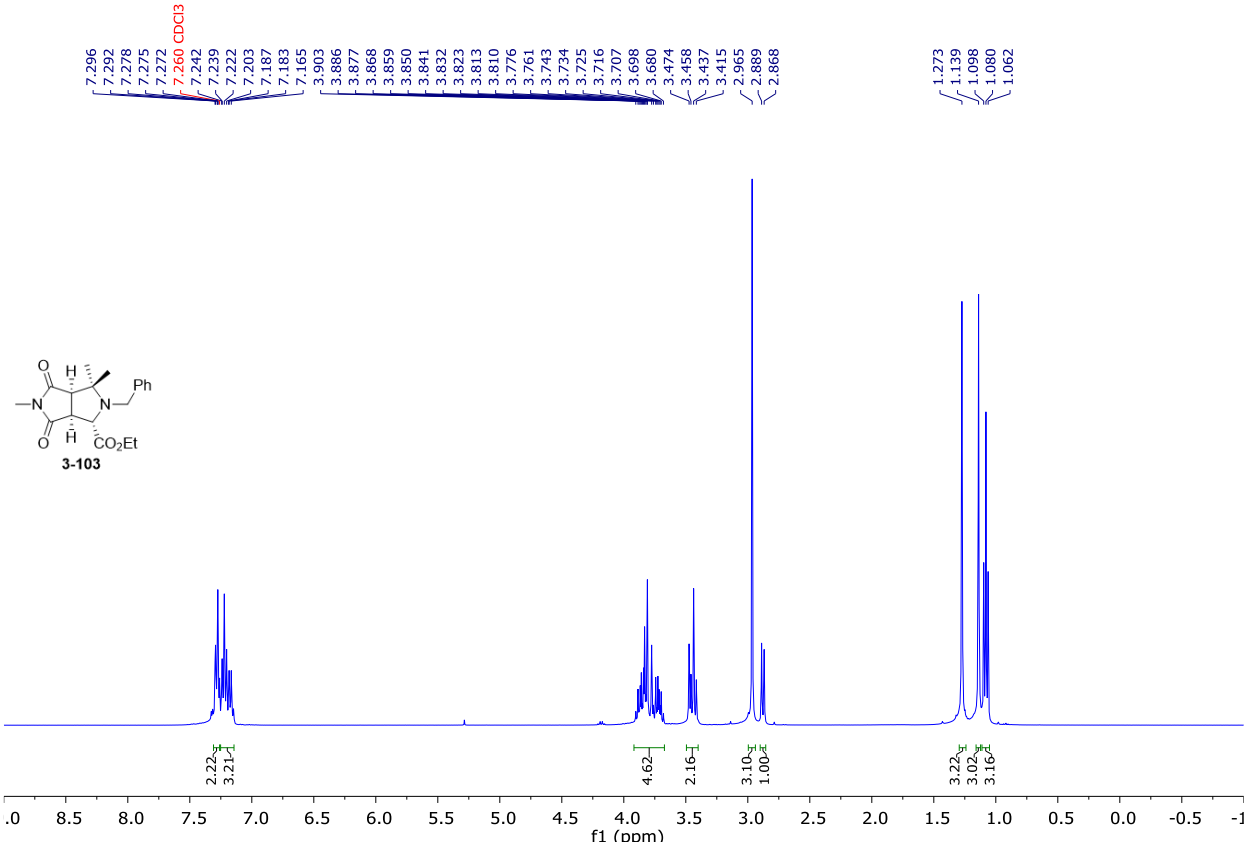
500.16 MHz — CDCl3 — 1D — 1H



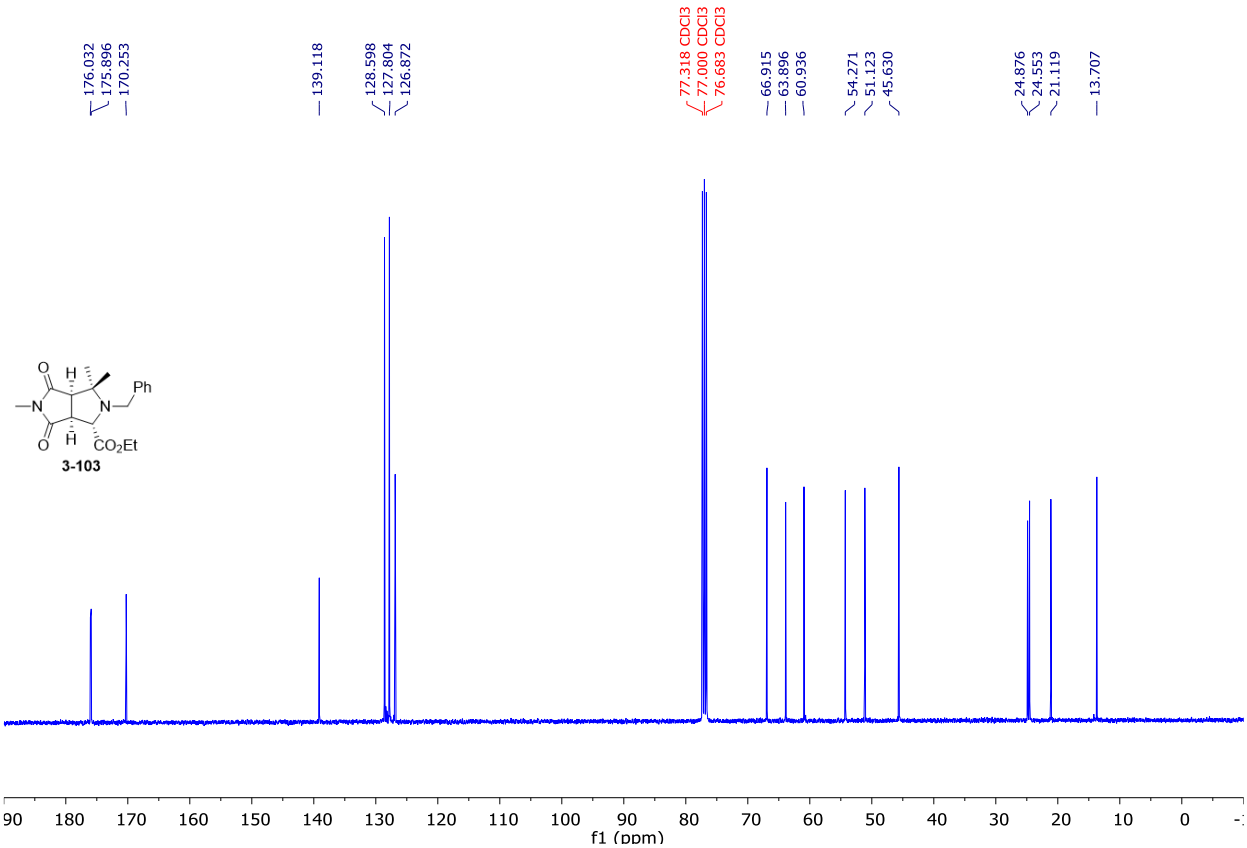
125.78 MHz — CDCl3 — 1D — 13C



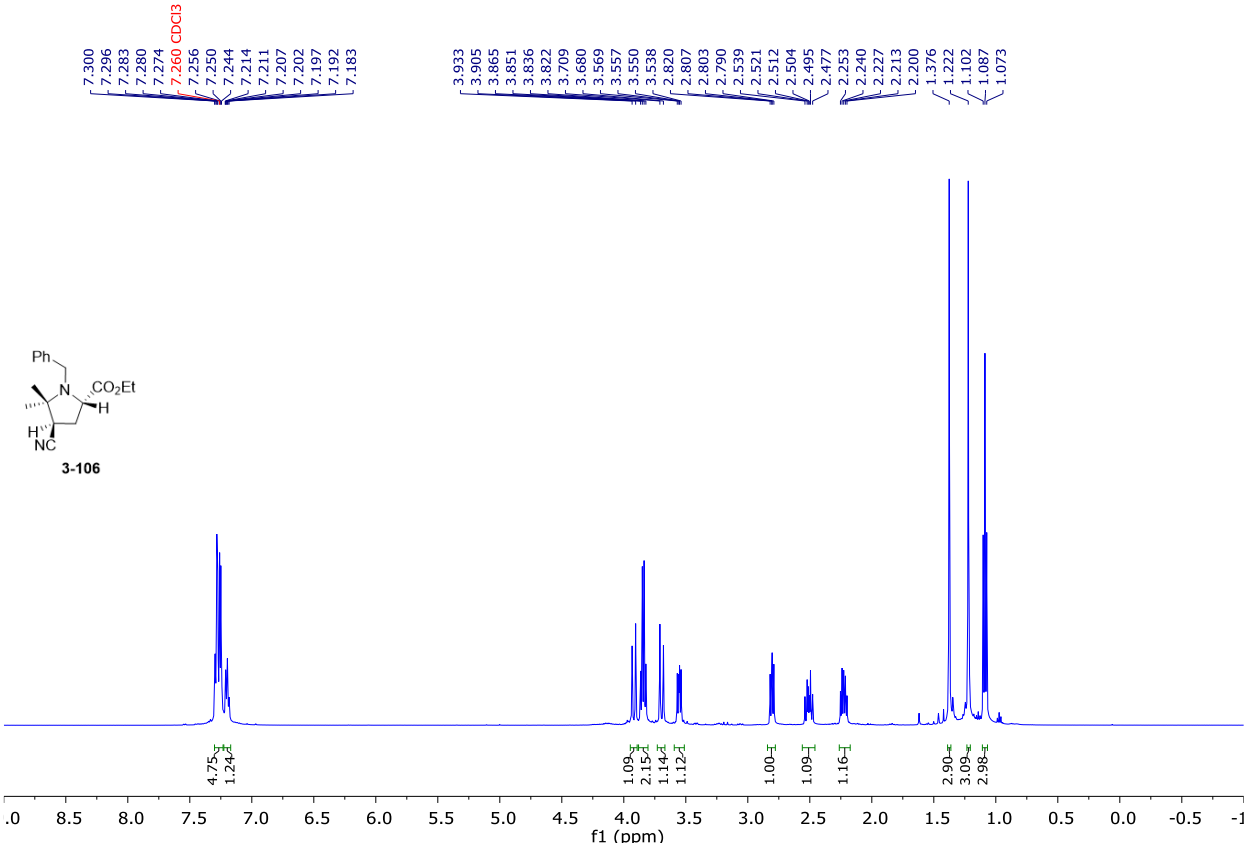
400.13 MHz — CDCl3 — 1D — 1H



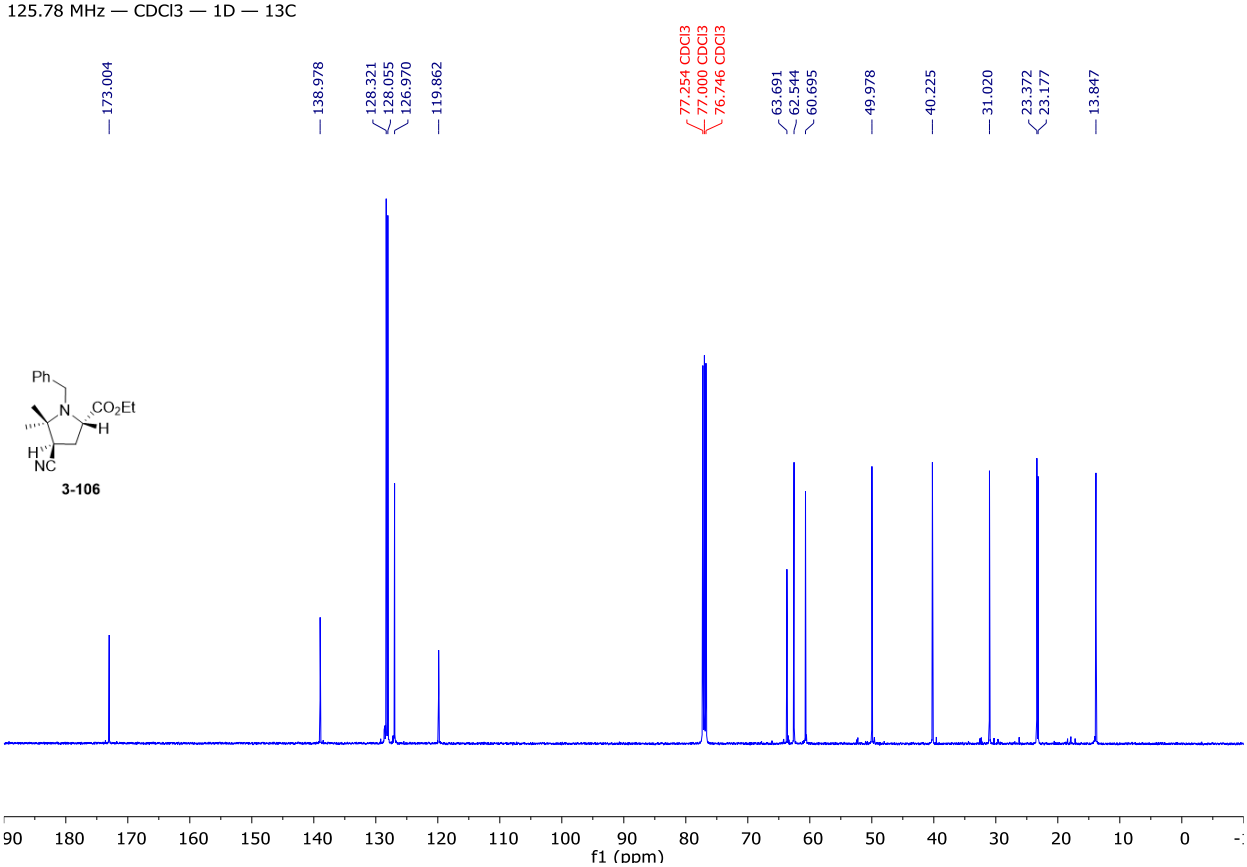
100.62 MHz — CDCl3 — 1D — 13C

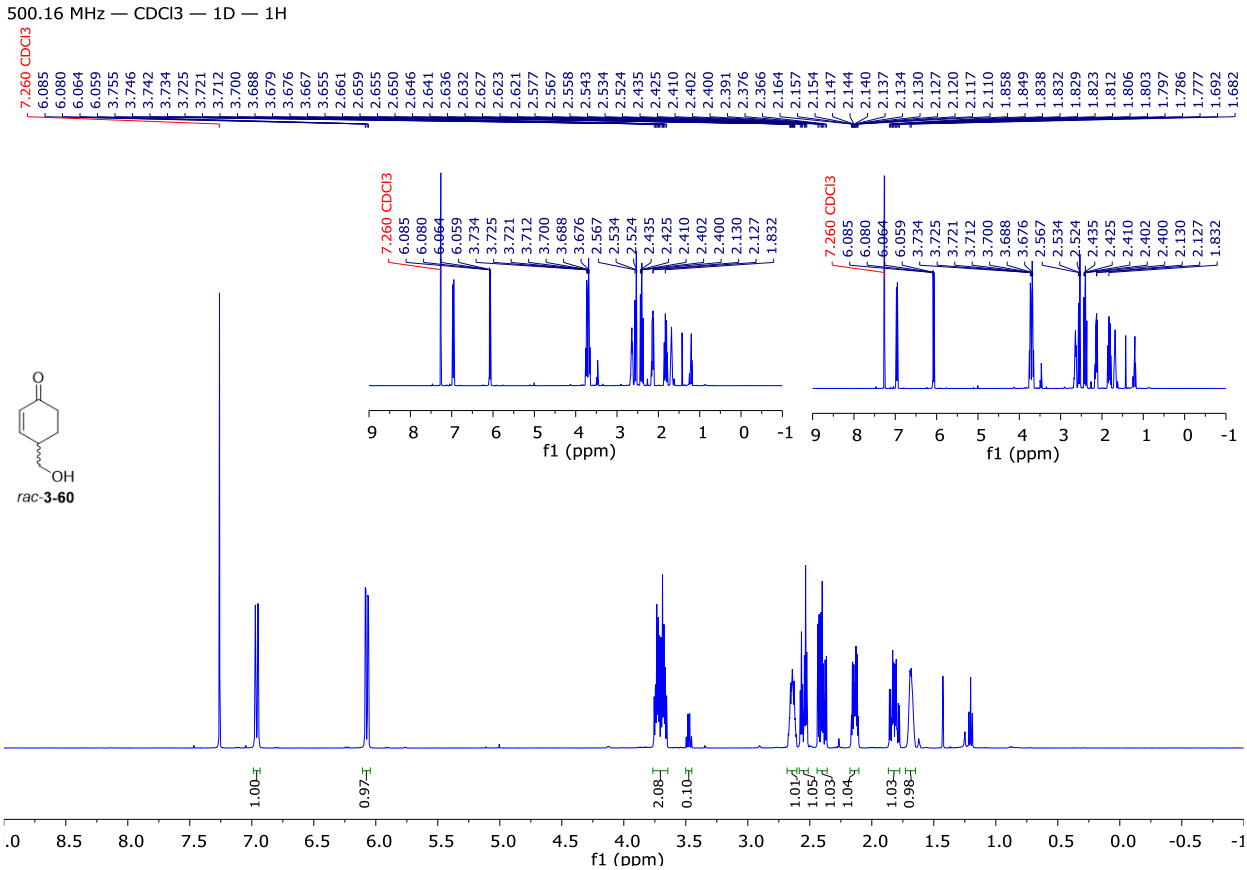


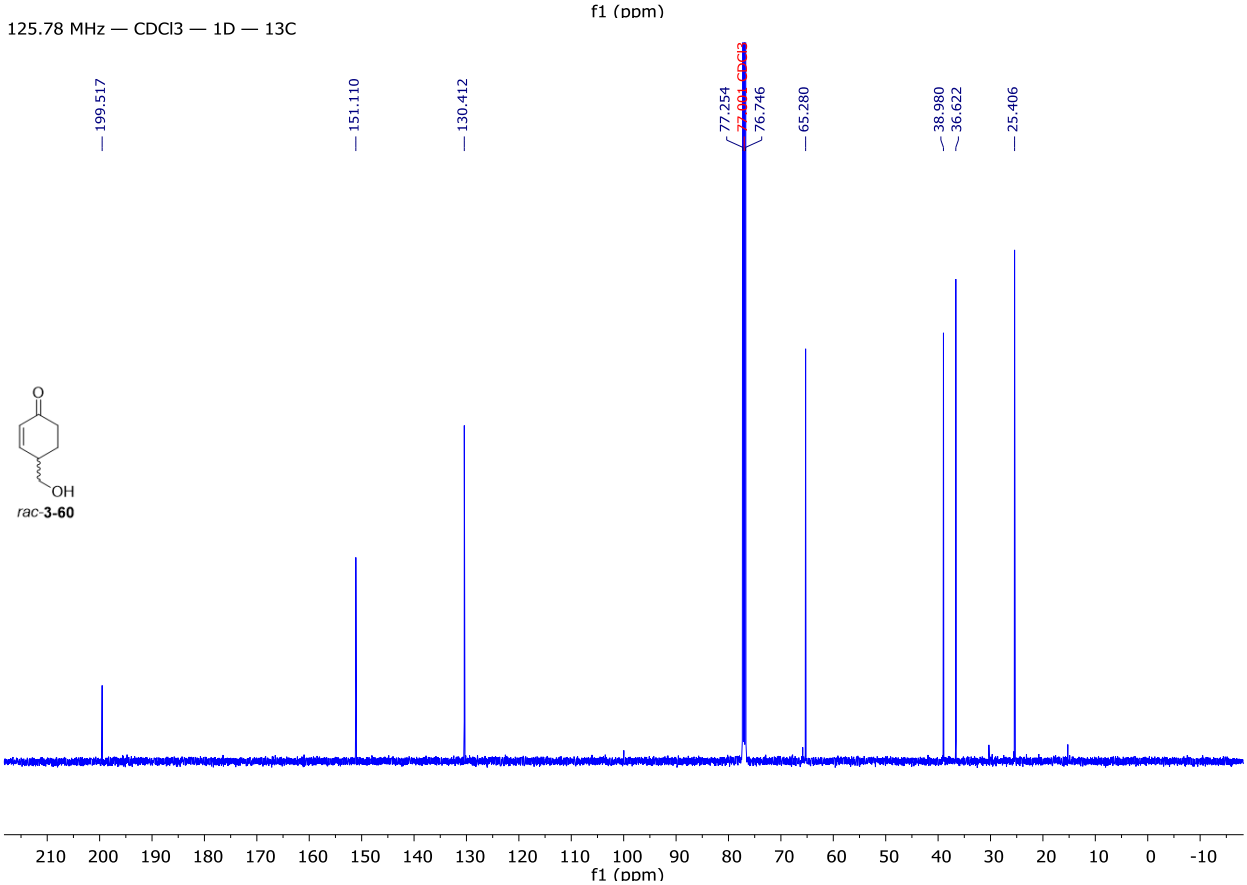
500.16 MHz — CDCl3 — 1D — 1H



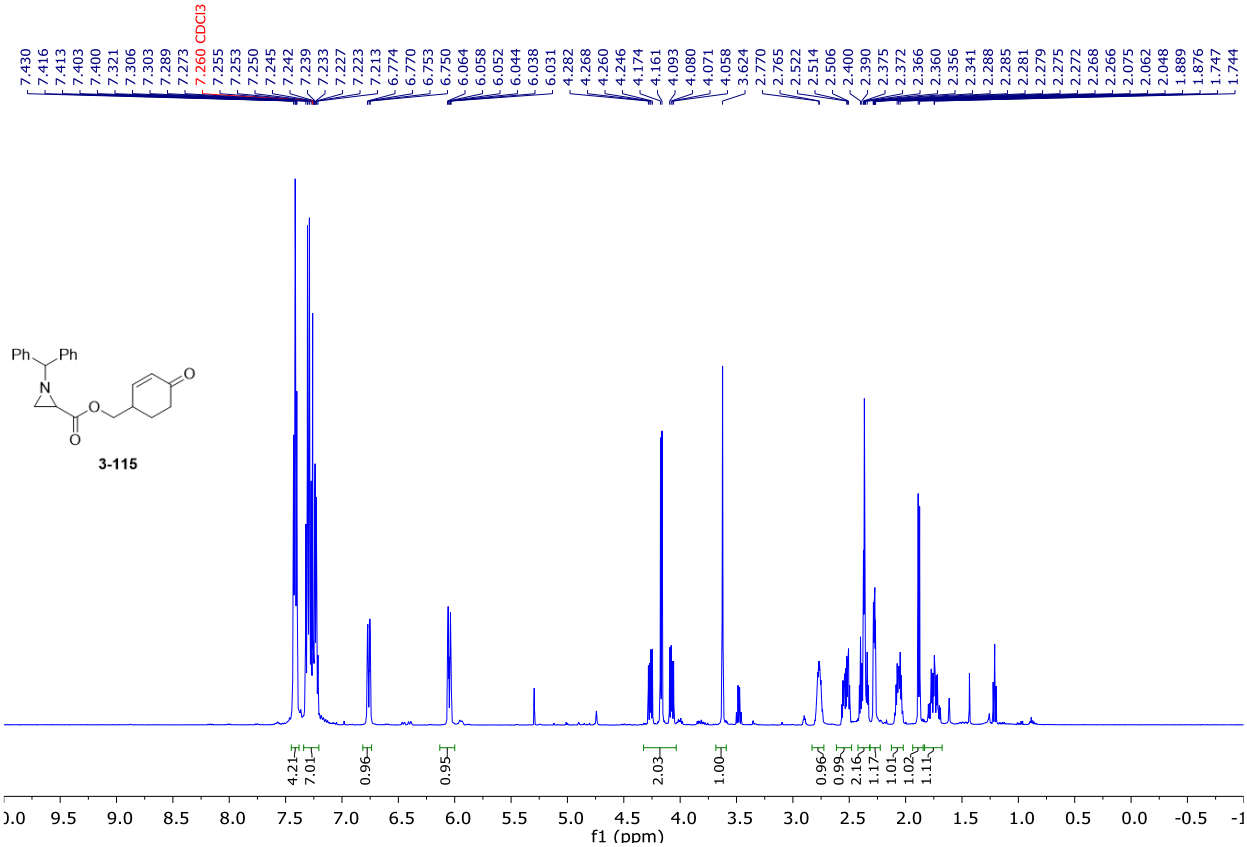
125.78 MHz — CDCl3 — 1D — 13C



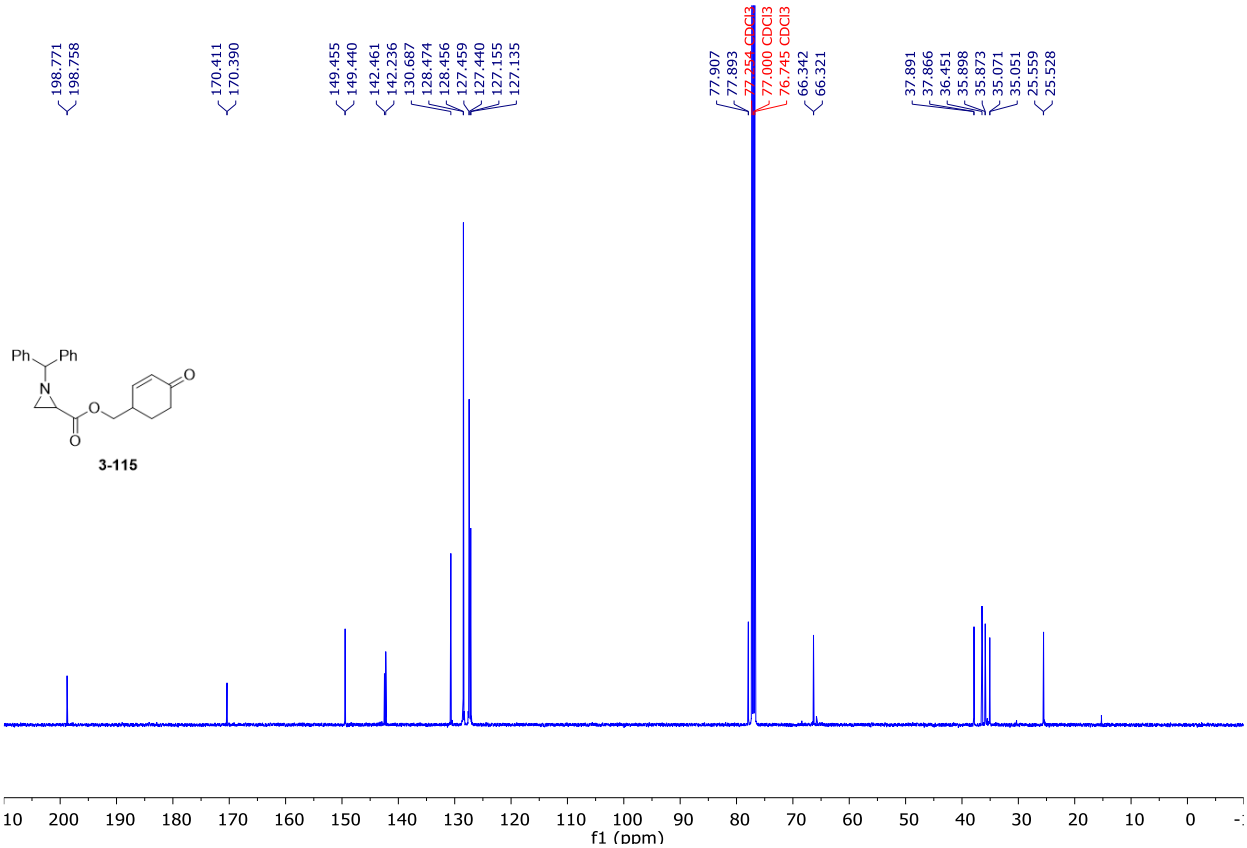

500.16 MHz — CDCl3 — 1D — 1H
7.260 CDCl3
6.085
6.080
6.064
6.059
3.755
3.746
3.742
3.734
3.725
3.721
3.712
3.700
3.688
3.679
3.676
3.667
3.655
3.661
2.659
2.655
2.650
2.646
2.641
2.636
2.632
2.627
2.623
2.621
2.577
2.567
2.558
2.543
2.534
2.524
2.435
2.425
2.410
2.402
2.400
2.391
2.376
2.366
2.164
2.157
2.154
2.147
2.144
2.140
2.137
2.134
2.130
2.127
2.120
2.117
2.110
1.858
1.849
1.838
1.832
1.829
1.823
1.812
1.806
1.803
1.797
1.786
1.777
1.692
1.682
f1 (ppm)
OH
rac-3-60
1.00
0.97
2.08
0.10
1.01
1.05
1.03
1.04
1.03
0.98

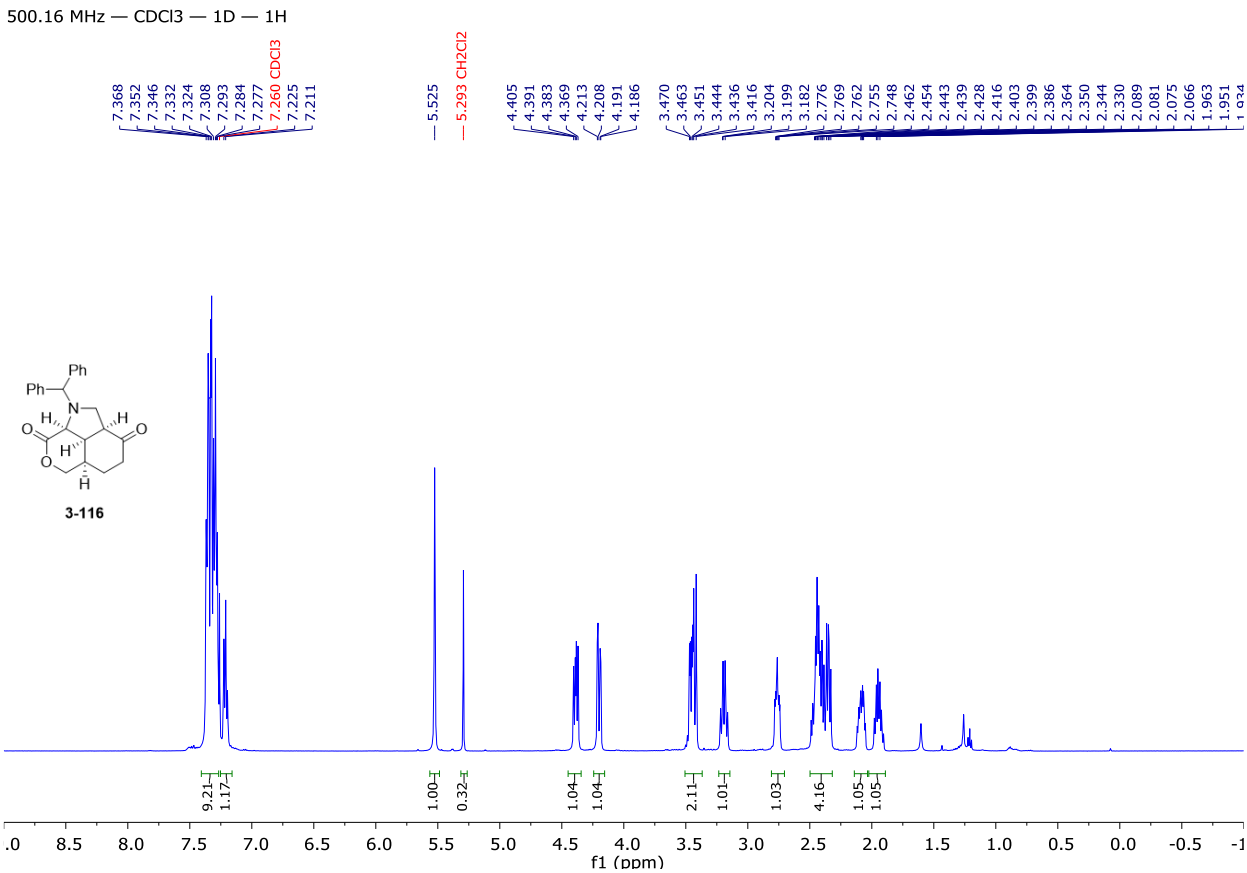

125.78 MHz — CDCl3 — 1D — 13C
199.517
151.110
130.412
77.254
77.001 CDCl3
76.746
65.280
38.980
36.622
25.406
f1 (ppm)
OH
rac-3-60

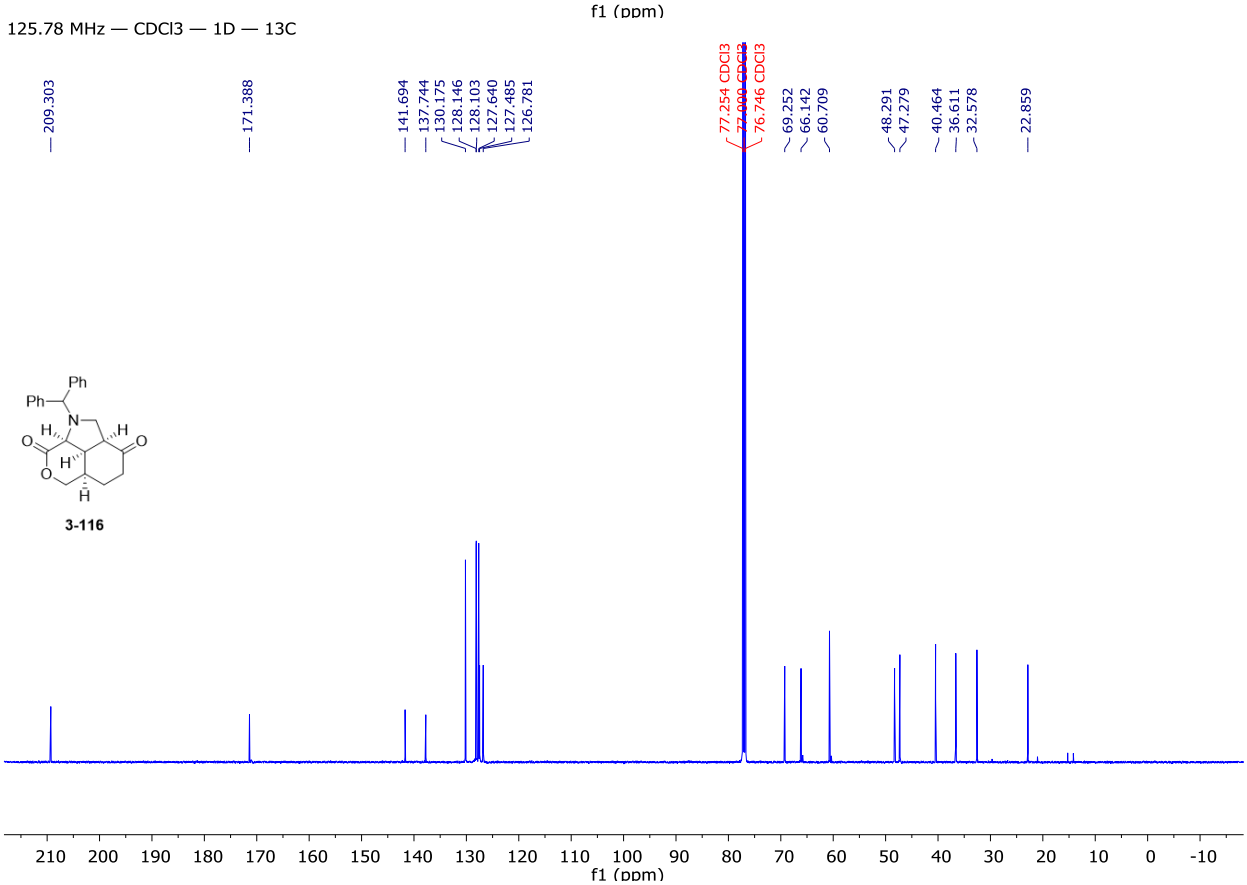
500.16 MHz — CDCl3 — 1D — 1H



125.78 MHz — CDCl3 — 1D — 13C




500.16 MHz — CDCl3 — 1D — 1H
7.368
7.352
7.346
7.332
7.324
7.308
7.293
7.284
7.277
7.260 CDCl3
7.225
7.211
5.525
5.293 CH2Cl2
4.405
4.391
4.383
4.369
4.213
4.208
4.191
4.186
3.470
3.463
3.451
3.444
3.436
3.416
3.204
3.199
3.182
2.776
2.769
2.762
2.755
2.748
2.462
2.454
2.443
2.439
2.428
2.416
2.403
2.399
2.386
2.364
2.350
2.344
2.330
2.089
2.081
2.075
2.066
1.963
1.951
Ph
Ph
N
H
H
H
O
O
O
H
3-116
9.21
1.17
1.00
0.32
1.04
1.04
2.11
1.01
1.03
4.16
1.05
1.05
f1 (ppm)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130.175
128.146
128.103
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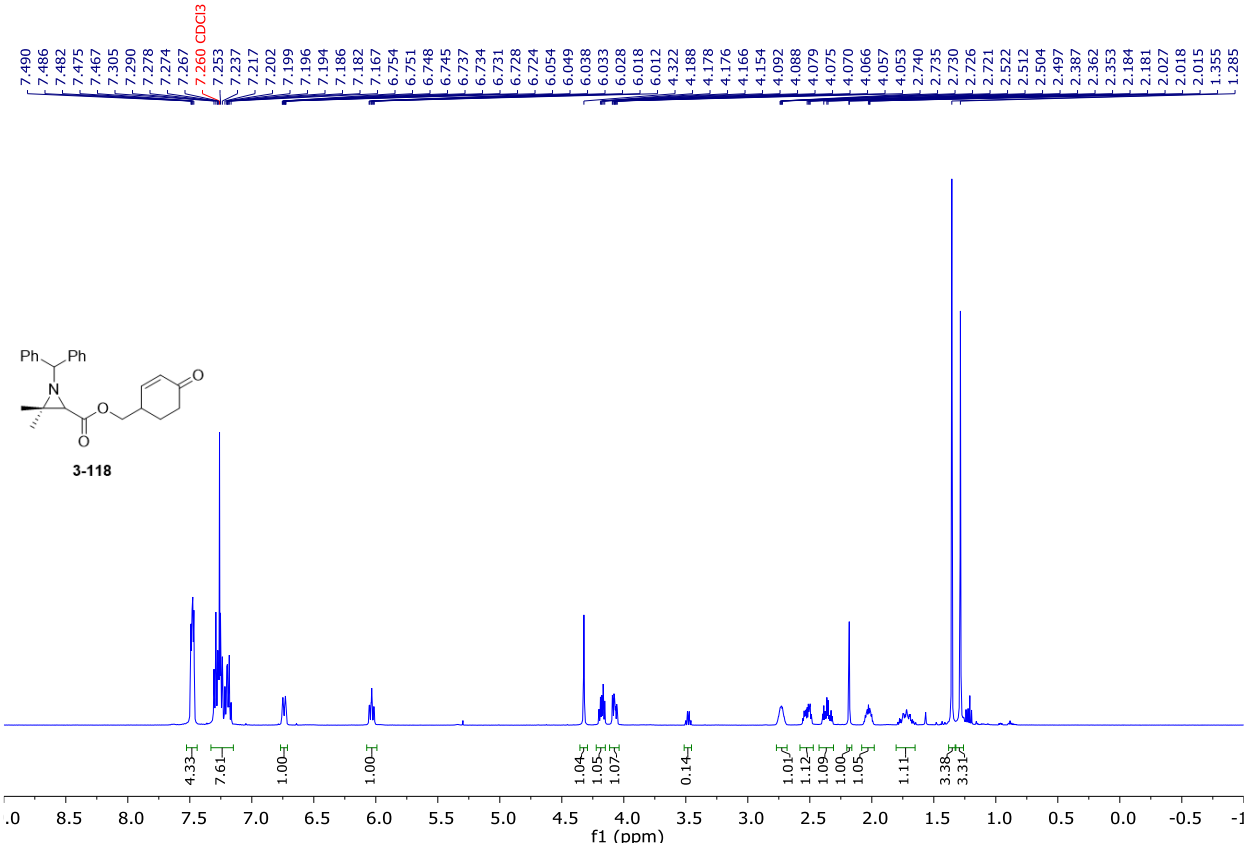
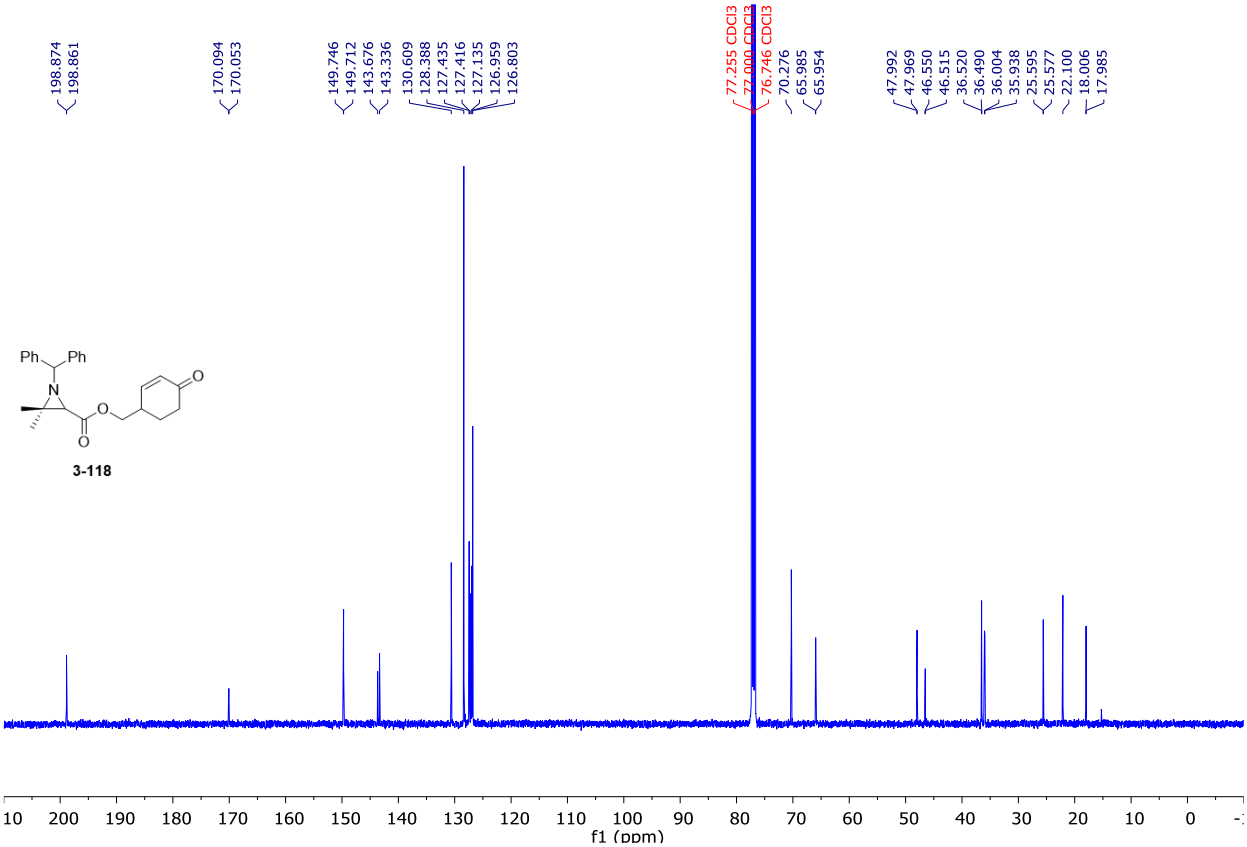
127.485
126.781
77.254 CDCl3
77.000 CDCl3
76.746 CDCl3
69.252
66.142
60.709
48.291
47.279
40.464
36.611
32.578
22.859
Ph
Ph
N
H
H
H
O
O
O
H
3-116
f1 (ppm)

500.16 MHz — CDCl3 — 1D — 1H



125.78 MHz — CDCl3 — 1D — 13C



APPENDIX F : X-RAY CRYSTALLOGRAPHY DATA

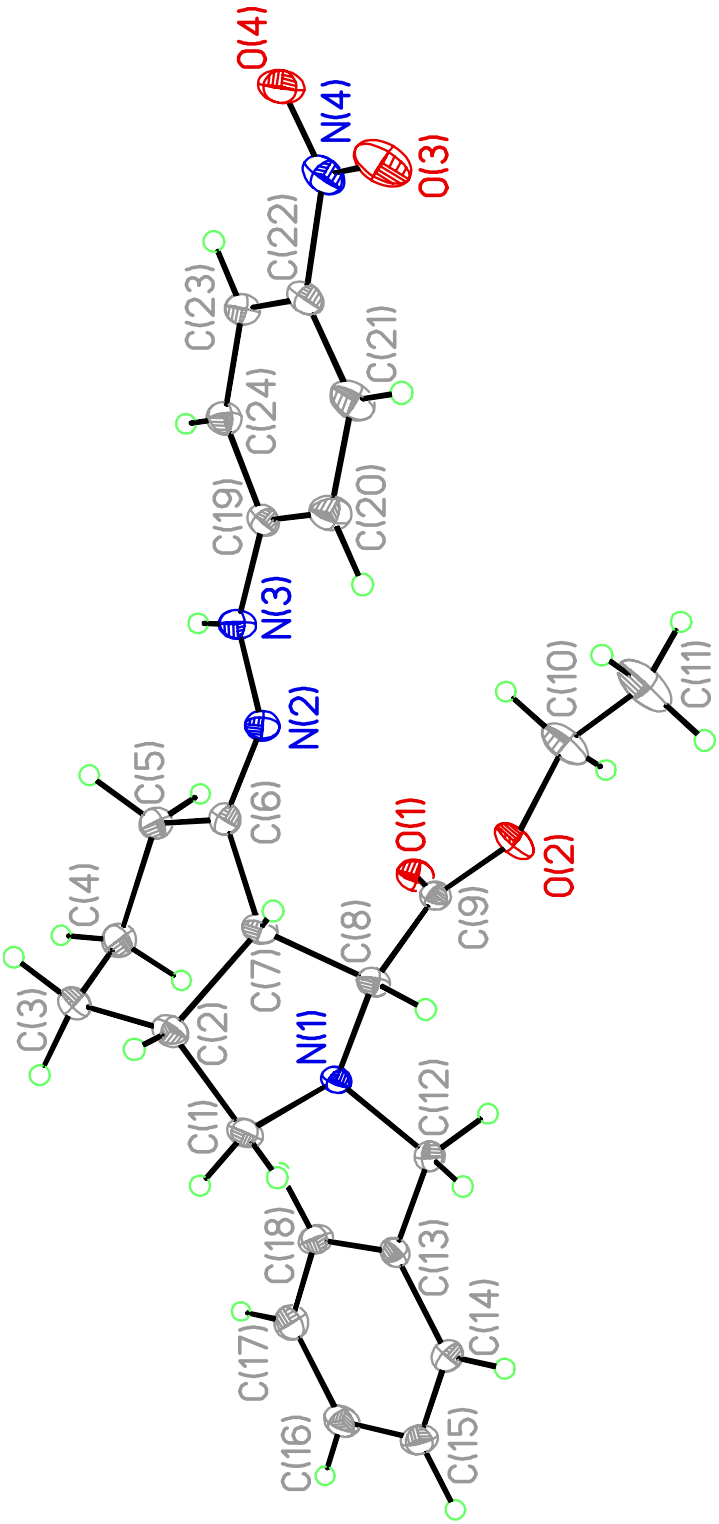


Figure 11 ORTEP strucuture of **3-73**

Table 17 Sample and crystal data for **3-73**

Chemical formula	$C_{24}H_{28}N_4O_4$	
Formula weight	436.50 g/mol	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal size	0.030 x 0.050 x 0.130 mm	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.5702(3) Å	α = 105.875(2)°
	b = 11.2776(3) Å	β = 109.9772(16)°
	c = 11.4692(4) Å	γ = 108.8025(18)°
Volume	1097.46(6) $Å^3$	
Z	2	
Density (calculated)	1.321 g/cm^3	
Absorption coefficient	0.744 mm^{-1}	
F(000)	464	

Table 18 Data collection and structure refinement for **3-73**

Theta range for data collection	4.55 to 70.20°	
Index ranges	-12<=h<=12, -13<=k<=13, -13<=l<=13	
Reflections collected	17806	
Independent reflections	4046 [R(int) = 0.0377]	
Coverage of independent reflections	96.7%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9800 and 0.9100	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	4046 / 0 / 294	
Goodness-of-fit on F^2	1.486	
Final R indices	3499 data; I>2σ(I)	R1 = 0.0448, wR2 = 0.1350
	all data	R1 = 0.0515, wR2 = 0.1398
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0680P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.716 and -0.344 $eÅ^{-3}$	
R.M.S. deviation from mean	0.051 $eÅ^{-3}$	

Table 19 Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for **3-73**

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	**y/b**	**z/c**	**U(eq)**
C1	0.78797(17)	0.97374(16)	0.17860(16)	0.0242(3)
C2	0.81594(17)	0.11089(16)	0.28163(16)	0.0237(3)
C3	0.91762(17)	0.14674(18)	0.43175(17)	0.0285(4)
C4	0.83191(17)	0.06555(17)	0.48986(16)	0.0267(4)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
C5	0.71509(17)	0.11316(16)	0.50222(15)	0.0224(3)
C6	0.62968(16)	0.12938(15)	0.37760(15)	0.0198(3)
C7	0.65267(16)	0.08993(15)	0.25225(15)	0.0199(3)
C8	0.54854(16)	0.93279(15)	0.14755(14)	0.0187(3)
C9	0.41926(16)	0.86776(15)	0.17510(15)	0.0194(3)
C10	0.17339(19)	0.8409(2)	0.1322(2)	0.0377(5)
C11	0.0584(2)	0.8703(3)	0.0467(3)	0.0549(6)
C12	0.58104(17)	0.73626(16)	0.04117(15)	0.0217(3)
C13	0.68046(16)	0.66468(15)	0.05237(15)	0.0200(3)
C14	0.67829(17)	0.58448(16)	0.93426(15)	0.0233(3)
C15	0.76474(18)	0.51427(17)	0.94152(17)	0.0278(4)
C16	0.85419(18)	0.52203(17)	0.06644(18)	0.0281(4)
C17	0.85807(18)	0.60198(18)	0.18503(17)	0.0285(4)
C18	0.77227(18)	0.67300(17)	0.17758(16)	0.0253(4)
C19	0.41386(16)	0.28079(15)	0.46918(15)	0.0202(3)
C20	0.34159(19)	0.29732(18)	0.35164(16)	0.0274(4)
C21	0.26156(19)	0.37261(18)	0.35309(17)	0.0291(4)
C22	0.25286(16)	0.43149(16)	0.47117(17)	0.0230(3)
C23	0.31943(17)	0.41280(16)	0.58699(16)	0.0241(3)
C24	0.39784(17)	0.33618(16)	0.58555(15)	0.0229(3)
N1	0.64880(13)	0.86821(13)	0.16146(12)	0.0187(3)
N2	0.53280(14)	0.17675(13)	0.36587(13)	0.0205(3)
N3	0.50115(15)	0.21226(14)	0.47349(13)	0.0227(3)
N4	0.17446(15)	0.51620(14)	0.47441(16)	0.0292(3)
O1	0.42443(12)	0.82028(11)	0.25803(11)	0.0245(3)
O2	0.29844(12)	0.87724(12)	0.09908(12)	0.0272(3)
O3	0.11929(15)	0.53415(15)	0.37100(14)	0.0427(4)
O4	0.16770(13)	0.56784(12)	0.57998(13)	0.0354(3)

Table 20 Bond lengths (Å) for **3-73**

C1-N1	1.4714(19)	C1-C2	1.531(2)
C1-H1A	0.99	C1-H1B	0.99
C2-C3	1.535(2)	C2-C7	1.563(2)
C2-H2A	1.0	C3-C4	1.522(2)
C3-H3A	0.99	C3-H3B	0.99
C4-C5	1.529(2)	C4-H4A	0.99
C4-H4B	0.99	C5-C6	1.503(2)
C5-H5A	0.99	C5-H5B	0.99
C6-N2	1.2846(19)	C6-C7	1.511(2)
C7-C8	1.571(2)	C7-H7A	1.0
C8-N1	1.4576(17)	C8-C9	1.510(2)
C8-H8A	1.0	C9-O1	1.2067(18)
C9-O2	1.3345(17)	C10-O2	1.4623(19)
C10-C11	1.473(3)	C10-H10A	0.99

C10-H10B	0.99	C11-H11A	0.98
C11-H11B	0.98	C11-H11C	0.98
C12-N1	1.4647(19)	C12-C13	1.511(2)
C12-H12A	0.99	C12-H12B	0.99
C13-C18	1.389(2)	C13-C14	1.396(2)
C14-C15	1.385(2)	C14-H14A	0.95
C15-C16	1.381(2)	C15-H15A	0.95
C16-C17	1.390(2)	C16-H16A	0.95
C17-C18	1.387(2)	C17-H17A	0.95
C18-H18A	0.95	C19-N3	1.3785(19)
C19-C20	1.400(2)	C19-C24	1.402(2)
C20-C21	1.379(2)	C20-H20A	0.95
C21-C22	1.384(2)	C21-H21A	0.95
C22-C23	1.384(2)	C22-N4	1.4536(19)
C23-C24	1.377(2)	C23-H23A	0.95
C24-H24A	0.95	N2-N3	1.3762(17)
N3-H3N	0.88(2)	N4-O4	1.2290(19)
N4-O3	1.2340(19)		

Table 21 Bond angles (°) for **3-73**

N1-C1-C2	104.91(12)	N1-C1-H1A	110.8
C2-C1-H1A	110.8	N1-C1-H1B	110.8
C2-C1-H1B	110.8	H1A-C1-H1B	108.8
C1-C2-C3	113.48(13)	C1-C2-C7	103.50(12)
C3-C2-C7	112.96(13)	C1-C2-H2A	108.9
C3-C2-H2A	108.9	C7-C2-H2A	108.9
C4-C3-C2	112.25(13)	C4-C3-H3A	109.2
C2-C3-H3A	109.2	C4-C3-H3B	109.2
C2-C3-H3B	109.2	H3A-C3-H3B	107.9
C3-C4-C5	109.49(13)	C3-C4-H4A	109.8
C5-C4-H4A	109.8	C3-C4-H4B	109.8
C5-C4-H4B	109.8	H4A-C4-H4B	108.2
C6-C5-C4	112.59(12)	C6-C5-H5A	109.1
C4-C5-H5A	109.1	C6-C5-H5B	109.1
C4-C5-H5B	109.1	H5A-C5-H5B	107.8
N2-C6-C5	124.89(13)	N2-C6-C7	113.70(12)
C5-C6-C7	121.41(12)	C6-C7-C2	115.39(12)
C6-C7-C8	113.44(12)	C2-C7-C8	103.60(11)
C6-C7-H7A	108.0	C2-C7-H7A	108.0
C8-C7-H7A	108.0	N1-C8-C9	113.53(12)
N1-C8-C7	105.51(11)	C9-C8-C7	111.09(11)
N1-C8-H8A	108.9	C9-C8-H8A	108.9
C7-C8-H8A	108.9	O1-C9-O2	124.10(14)
O1-C9-C8	125.99(13)	O2-C9-C8	109.81(12)
O2-C10-C11	107.56(15)	O2-C10-H10A	110.2
C11-C10-H10A	110.2	O2-C10-H10B	110.2

C11-C10-H10B	110.2	H10A-C10-H10B	108.5
C10-C11-H11A	109.5	C10-C11-H11B	109.5
H11A-C11-H11B	109.5	C10-C11-H11C	109.5
H11A-C11-H11C	109.5	H11B-C11-H11C	109.5
N1-C12-C13	112.96(11)	N1-C12-H12A	109.0
C13-C12-H12A	109.0	N1-C12-H12B	109.0
C13-C12-H12B	109.0	H12A-C12-H12B	107.8
C18-C13-C14	118.29(14)	C18-C13-C12	121.77(13)
C14-C13-C12	119.93(13)	C15-C14-C13	120.92(14)
C15-C14-H14A	119.5	C13-C14-H14A	119.5
C16-C15-C14	120.25(14)	C16-C15-H15A	119.9
C14-C15-H15A	119.9	C15-C16-C17	119.50(14)
C15-C16-H16A	120.2	C17-C16-H16A	120.2
C18-C17-C16	120.12(15)	C18-C17-H17A	119.9
C16-C17-H17A	119.9	C17-C18-C13	120.92(14)
C17-C18-H18A	119.5	C13-C18-H18A	119.5
N3-C19-C20	121.58(14)	N3-C19-C24	119.27(13)
C20-C19-C24	119.15(14)	C21-C20-C19	120.11(14)
C21-C20-H20A	119.9	C19-C20-H20A	119.9
C20-C21-C22	119.66(15)	C20-C21-H21A	120.2
C22-C21-H21A	120.2	C23-C22-C21	121.15(14)
C23-C22-N4	119.35(14)	C21-C22-N4	119.49(14)
C24-C23-C22	119.43(14)	C24-C23-H23A	120.3
C22-C23-H23A	120.3	C23-C24-C19	120.38(14)
C23-C24-H24A	119.8	C19-C24-H24A	119.8
C8-N1-C12	111.24(11)	C8-N1-C1	103.44(11)
C12-N1-C1	113.08(12)	C6-N2-N3	118.04(12)
N2-N3-C19	117.89(13)	N2-N3-H3N	122.7(13)
C19-N3-H3N	118.9(13)	O4-N4-O3	123.10(14)
O4-N4-C22	118.76(14)	O3-N4-C22	118.13(14)
C9-O2-C10	115.93(13)		

Table 22 Anisotropic atomic displacement parameters (Å^2) for **3-73**

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	0.0208(7)	0.0274(8)	0.0294(8)	0.0118(7)	0.0157(6)	0.0130(6)
C2	0.0213(7)	0.0234(8)	0.0314(8)	0.0133(7)	0.0161(7)	0.0107(6)
C3	0.0187(7)	0.0309(9)	0.0294(8)	0.0063(7)	0.0093(6)	0.0117(7)
C4	0.0263(8)	0.0304(9)	0.0229(8)	0.0104(7)	0.0075(6)	0.0180(7)
C5	0.0247(7)	0.0237(8)	0.0209(7)	0.0102(7)	0.0105(6)	0.0132(6)
C6	0.0203(7)	0.0175(7)	0.0226(7)	0.0096(6)	0.0105(6)	0.0085(6)
C7	0.0218(7)	0.0229(8)	0.0230(7)	0.0136(7)	0.0130(6)	0.0134(6)
C8	0.0203(7)	0.0243(8)	0.0187(7)	0.0126(6)	0.0106(6)	0.0140(6)
C9	0.0198(7)	0.0213(7)	0.0190(7)	0.0085(6)	0.0090(6)	0.0119(6)
C10	0.0263(9)	0.0504(11)	0.0557(11)	0.0349(10)	0.0265(8)	0.0213(8)
C11	0.0323(10)	0.0821(17)	0.0733(15)	0.0493(14)	0.0306(10)	0.0324(11)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C12	0.0201(7)	0.0254(8)	0.0180(7)	0.0073(6)	0.0076(6)	0.0119(6)
C13	0.0172(7)	0.0204(7)	0.0223(7)	0.0089(6)	0.0102(6)	0.0077(6)
C14	0.0234(7)	0.0249(8)	0.0196(7)	0.0081(7)	0.0097(6)	0.0107(6)
C15	0.0313(8)	0.0256(8)	0.0290(8)	0.0082(7)	0.0182(7)	0.0146(7)
C16	0.0251(8)	0.0275(8)	0.0367(9)	0.0134(8)	0.0165(7)	0.0159(7)
C17	0.0277(8)	0.0332(9)	0.0258(8)	0.0133(7)	0.0095(7)	0.0183(7)
C18	0.0287(8)	0.0301(8)	0.0204(7)	0.0094(7)	0.0125(7)	0.0173(7)
C19	0.0173(7)	0.0202(7)	0.0242(7)	0.0103(6)	0.0096(6)	0.0093(6)
C20	0.0315(8)	0.0373(9)	0.0244(8)	0.0169(7)	0.0166(7)	0.0215(7)
C21	0.0290(8)	0.0415(10)	0.0315(9)	0.0247(8)	0.0166(7)	0.0225(7)
C22	0.0185(7)	0.0221(7)	0.0338(8)	0.0149(7)	0.0138(6)	0.0114(6)
C23	0.0225(7)	0.0246(8)	0.0264(8)	0.0092(7)	0.0130(6)	0.0123(6)
C24	0.0243(7)	0.0269(8)	0.0211(7)	0.0120(7)	0.0103(6)	0.0149(6)
N1	0.0171(6)	0.0220(6)	0.0200(6)	0.0086(5)	0.0094(5)	0.0118(5)
N2	0.0224(6)	0.0224(6)	0.0215(6)	0.0109(6)	0.0129(5)	0.0118(5)
N3	0.0271(7)	0.0308(7)	0.0199(6)	0.0136(6)	0.0133(6)	0.0195(6)
N4	0.0225(7)	0.0261(7)	0.0451(9)	0.0197(7)	0.0168(6)	0.0134(6)
O1	0.0277(6)	0.0293(6)	0.0262(6)	0.0164(5)	0.0163(5)	0.0161(5)
O2	0.0195(5)	0.0384(6)	0.0363(6)	0.0243(6)	0.0152(5)	0.0180(5)
O3	0.0429(7)	0.0530(8)	0.0566(8)	0.0375(7)	0.0248(7)	0.0360(7)
O4	0.0324(6)	0.0311(7)	0.0496(8)	0.0146(6)	0.0238(6)	0.0198(5)

Table 23 Hydrogen atomic coordinates and isotropic atomic displacemnt parameters ($Å^2$) for **3-73**

	x/a	**y/b**	**z/c**	**U(eq)**
H1A	0.7740	-0.0229	0.0899	0.029
H1B	0.8741	-0.0465	0.2147	0.029
H2A	0.8640	0.1875	0.2591	0.028
H3A	1.0033	0.1263	0.4374	0.034
H3B	0.9601	0.2474	0.4884	0.034
H4A	0.9038	0.0811	0.5815	0.032
H4B	0.7801	-0.0350	0.4285	0.032
H5A	0.6422	0.0446	0.5158	0.027
H5B	0.7675	0.2031	0.5842	0.027
H7A	0.6284	0.1474	0.2039	0.024
H8A	0.5059	-0.0739	0.0522	0.022
H10A	0.2102	-0.1034	0.2309	0.045
H10B	0.1293	-0.2586	0.1125	0.045
H11A	-0.0284	-0.1556	0.0647	0.082
H11B	0.0248	-0.1835	-0.0506	0.082
H11C	0.1024	-0.0304	0.0692	0.082
H12A	0.5612	-0.2464	-0.0418	0.026
H12B	0.4825	-0.3262	0.0296	0.026
H14A	0.6167	-0.4220	-0.1523	0.028
H15A	0.7625	-0.5394	-0.1397	0.033
H16A	0.9126	-0.5269	0.0713	0.034

	x/a	y/b	z/c	U(eq)
H17A	0.9196	-0.3920	0.2713	0.034
H18A	0.7764	-0.2719	0.2593	0.03
H20A	0.3477	0.2566	0.2708	0.033
H21A	0.2126	0.3840	0.2735	0.035
H23A	0.3111	0.4525	0.6668	0.029
H24A	0.4413	0.3208	0.6638	0.027
H3N	0.544(2)	0.204(2)	0.549(2)	0.036(5)

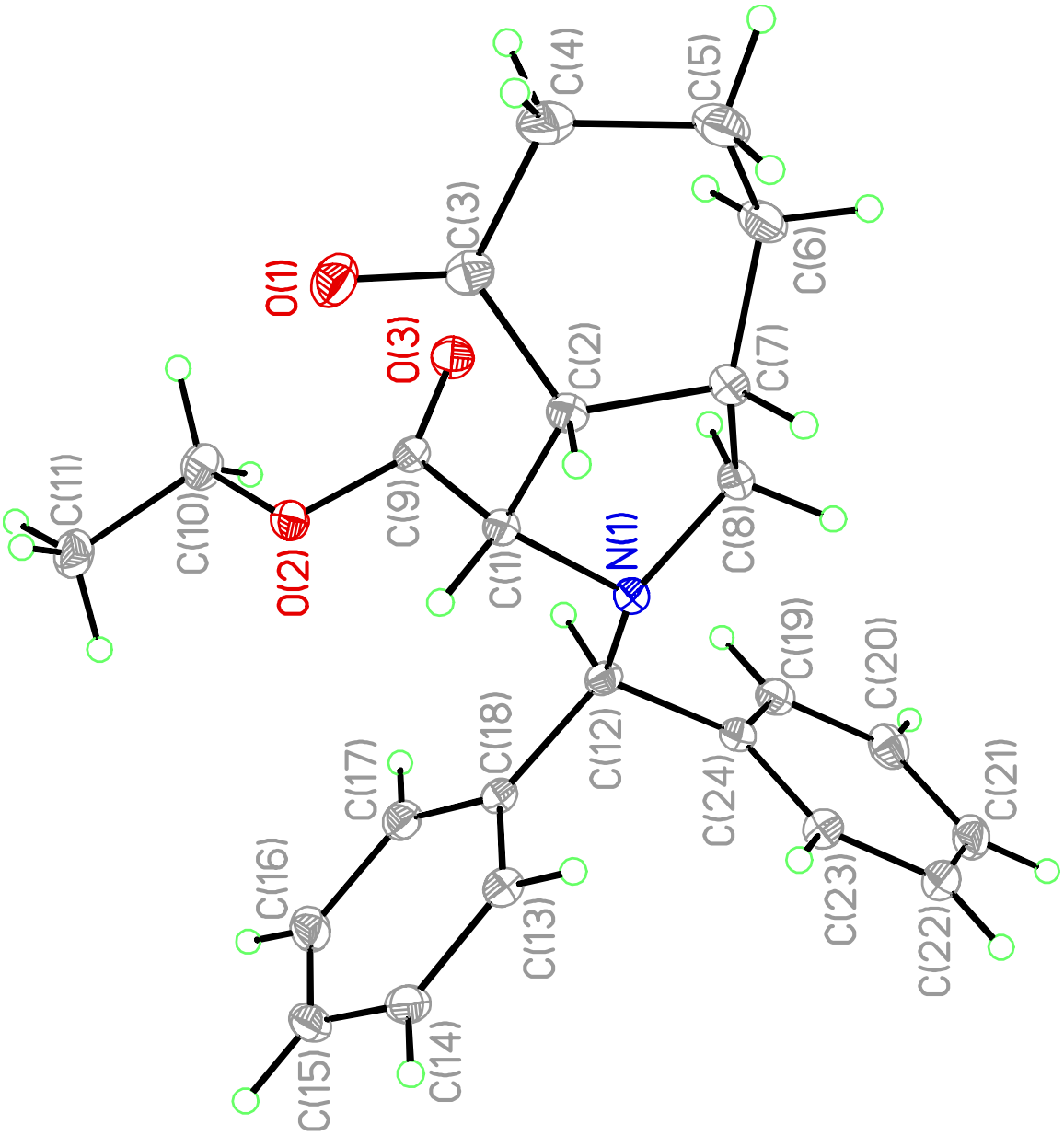


Figure 12 ORTEP structure of **3-74**

Table 24 Sample and crystal data for **3-74**

Chemical formula	$C_{24}H_{27}NO_3$	
Formula weight	377.46 g/mol	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal size	0.030 x 0.130 x 0.220 mm	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 15.8756(4) Å	α = 90°
	b = 5.98440(10) Å	β = 106.6901(12)°
	c = 21.9116(5) Å	γ = 90°
Volume	1994.03(8) $Å^3$	
Z	4	
Density (calculated)	1.257 g/cm^3	
Absorption coefficient	0.654 mm^{-1}	
F(000)	808	

Table 25 Data collection and structure refinement for **3-74**

Theta range for data collection	4.21 to 68.31°	
Index ranges	-18<=h<=19, -7<=k<=7, -23<=l<=26	
Reflections collected	22788	
Independent reflections	3617 [R(int) = 0.0670]	
Max. and min. transmission	0.9800 and 0.8700	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3617 / 0 / 253	
Goodness-of-fit on F^2	1.338	
Final R indices	3236 data; I>2σ(I)	R1 = 0.0405, wR2 = 0.1145
	all data	R1 = 0.0445, wR2 = 0.1181
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0680P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.312 and -0.239 $eÅ^{-3}$	
R.M.S. deviation from mean	0.050 $eÅ^{-3}$	

Table 26 Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for **3-74**

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	**y/b**	**z/c**	**U(eq)**
N1	0.26000(6)	0.55685(16)	0.19506(4)	0.0184(2)
O1	0.26618(6)	0.77519(17)	0.01334(4)	0.0322(2)
C1	0.23340(7)	0.63400(19)	0.12813(5)	0.0178(2)
O2	0.14264(5)	0.41125(15)	0.04707(4)	0.0237(2)
C2	0.30819(7)	0.79540(19)	0.12639(5)	0.0192(3)

	x/a	y/b	z/c	U(eq)
O3	0.28658(5)	0.32382(15)	0.07769(4)	0.0244(2)
C3	0.32459(8)	0.8133(2)	0.06162(6)	0.0231(3)
C4	0.41455(9)	0.8896(3)	0.05915(7)	0.0341(3)
C5	0.48501(8)	0.8911(2)	0.12363(7)	0.0323(3)
C6	0.47175(8)	0.6913(2)	0.16315(6)	0.0280(3)
C7	0.38854(7)	0.7272(2)	0.18326(5)	0.0216(3)
C8	0.35591(7)	0.5248(2)	0.21239(5)	0.0217(3)
C9	0.22560(7)	0.44100(19)	0.08096(5)	0.0182(2)
C10	0.12420(8)	0.2307(2)	0.00074(6)	0.0286(3)
C11	0.02705(8)	0.2411(2)	0.96772(6)	0.0287(3)
C12	0.21124(7)	0.36181(19)	0.20820(5)	0.0180(2)
C13	0.07974(8)	0.6111(2)	0.20511(5)	0.0215(3)
C14	0.98957(8)	0.6445(2)	0.19164(6)	0.0254(3)
C15	0.93141(8)	0.4774(2)	0.16212(6)	0.0281(3)
C16	0.96362(8)	0.2769(2)	0.14647(6)	0.0275(3)
C17	0.05379(8)	0.2425(2)	0.16075(5)	0.0227(3)
C18	0.11279(7)	0.4087(2)	0.19032(5)	0.0191(3)
C19	0.28169(7)	0.0821(2)	0.29476(6)	0.0222(3)
C20	0.31269(8)	0.0183(2)	0.35848(6)	0.0272(3)
C21	0.30767(8)	0.1655(2)	0.40644(6)	0.0284(3)
C22	0.27259(8)	0.3768(2)	0.39035(6)	0.0266(3)
C23	0.24230(8)	0.4407(2)	0.32682(6)	0.0228(3)
C24	0.24614(7)	0.2936(2)	0.27822(5)	0.0193(3)

Table 27 Bond lengths (Å) for **3-74**

N1-C8	1.4722(14)	N1-C12	1.4739(15)
N1-C1	1.4786(14)	O1-C3	1.2114(16)
C1-C9	1.5310(15)	C1-C2	1.5396(16)
C1-H1A	1.0	O2-C9	1.3252(14)
O2-C10	1.4538(14)	C2-C3	1.5185(16)
C2-C7	1.5598(15)	C2-H2A	1.0
O3-C9	1.2140(15)	C3-C4	1.5152(18)
C4-C5	1.530(2)	C4-H4A	0.99
C4-H4B	0.99	C5-C6	1.5257(19)
C5-H5A	0.99	C5-H5B	0.99
C6-C7	1.5232(16)	C6-H6A	0.99
C6-H6B	0.99	C7-C8	1.5278(16)
C7-H7A	1.0	C8-H8A	0.99
C8-H8B	0.99	C10-C11	1.5050(17)
C10-H10A	0.99	C10-H10B	0.99
C11-H11A	0.98	C11-H11B	0.98
C11-H11C	0.98	C12-C18	1.5243(15)
C12-C24	1.5295(15)	C12-H12A	1.0
C13-C14	1.3906(17)	C13-C18	1.3943(17)
C13-H13A	0.95	C14-C15	1.388(2)

C14-H14A	0.95	C15-C16	1.385(2)
C15-H15A	0.95	C16-C17	1.3901(18)
C16-H16A	0.95	C17-C18	1.3924(17)
C17-H17A	0.95	C19-C24	1.3911(17)
C19-C20	1.3937(18)	C19-H19A	0.95
C20-C21	1.391(2)	C20-H20A	0.95
C21-C22	1.386(2)	C21-H21A	0.95
C22-C23	1.3896(18)	C22-H22A	0.95
C23-C24	1.3963(16)	C23-H23A	0.95

Table 28 Bond angles (°) for **3-74**

C8-N1-C12	114.11(9)	C8-N1-C1	106.03(8)
C12-N1-C1	115.13(8)	N1-C1-C9	112.25(9)
N1-C1-C2	102.58(8)	C9-C1-C2	111.72(9)
N1-C1-H1A	110.0	C9-C1-H1A	110.0
C2-C1-H1A	110.0	C9-O2-C10	117.36(9)
C3-C2-C1	114.06(9)	C3-C2-C7	116.40(9)
C1-C2-C7	106.01(9)	C3-C2-H2A	106.6
C1-C2-H2A	106.6	C7-C2-H2A	106.6
O1-C3-C4	121.23(11)	O1-C3-C2	120.61(11)
C4-C3-C2	118.10(10)	C3-C4-C5	114.54(11)
C3-C4-H4A	108.6	C5-C4-H4A	108.6
C3-C4-H4B	108.6	C5-C4-H4B	108.6
H4A-C4-H4B	107.6	C6-C5-C4	109.66(11)
C6-C5-H5A	109.7	C4-C5-H5A	109.7
C6-C5-H5B	109.7	C4-C5-H5B	109.7
H5A-C5-H5B	108.2	C7-C6-C5	109.03(11)
C7-C6-H6A	109.9	C5-C6-H6A	109.9
C7-C6-H6B	109.9	C5-C6-H6B	109.9
H6A-C6-H6B	108.3	C6-C7-C8	115.80(10)
C6-C7-C2	112.58(10)	C8-C7-C2	104.10(9)
C6-C7-H7A	108.0	C8-C7-H7A	108.0
C2-C7-H7A	108.0	N1-C8-C7	103.79(9)
N1-C8-H8A	111.0	C7-C8-H8A	111.0
N1-C8-H8B	111.0	C7-C8-H8B	111.0
H8A-C8-H8B	109.0	O3-C9-O2	124.78(11)
O3-C9-C1	124.35(10)	O2-C9-C1	110.75(9)
O2-C10-C11	106.13(10)	O2-C10-H10A	110.5
C11-C10-H10A	110.5	O2-C10-H10B	110.5
C11-C10-H10B	110.5	H10A-C10-H10B	108.7
C10-C11-H11A	109.5	C10-C11-H11B	109.5
H11A-C11-H11B	109.5	C10-C11-H11C	109.5
H11A-C11-H11C	109.5	H11B-C11-H11C	109.5
N1-C12-C18	111.17(9)	N1-C12-C24	110.36(9)
C18-C12-C24	110.87(9)	N1-C12-H12A	108.1
C18-C12-H12A	108.1	C24-C12-H12A	108.1

C14-C13-C18	120.58(11)	C14-C13-H13A	119.7
C18-C13-H13A	119.7	C15-C14-C13	120.10(12)
C15-C14-H14A	119.9	C13-C14-H14A	119.9
C16-C15-C14	119.72(11)	C16-C15-H15A	120.1
C14-C15-H15A	120.1	C15-C16-C17	120.15(11)
C15-C16-H16A	119.9	C17-C16-H16A	119.9
C16-C17-C18	120.69(12)	C16-C17-H17A	119.7
C18-C17-H17A	119.7	C17-C18-C13	118.75(11)
C17-C18-C12	119.41(10)	C13-C18-C12	121.79(10)
C24-C19-C20	120.69(11)	C24-C19-H19A	119.7
C20-C19-H19A	119.7	C21-C20-C19	120.20(12)
C21-C20-H20A	119.9	C19-C20-H20A	119.9
C22-C21-C20	119.45(11)	C22-C21-H21A	120.3
C20-C21-H21A	120.3	C21-C22-C23	120.28(12)
C21-C22-H22A	119.9	C23-C22-H22A	119.9
C22-C23-C24	120.81(12)	C22-C23-H23A	119.6
C24-C23-H23A	119.6	C19-C24-C23	118.56(11)
C19-C24-C12	120.48(10)	C23-C24-C12	120.95(10)

Table 29 Anisotropic atomic displacement parameters (Å^2) for **3-74**

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
N1	0.0159(5)	0.0226(5)	0.0165(5)	0.0001(4)	0.0045(3)	-0.0008(4)
O1	0.0371(5)	0.0372(5)	0.0210(5)	0.0038(3)	0.0064(4)	-0.0071(4)
C1	0.0163(5)	0.0207(6)	0.0165(5)	0.0005(4)	0.0050(4)	0.0015(4)
O2	0.0192(4)	0.0303(5)	0.0209(4)	-0.0072(3)	0.0047(3)	-0.0021(3)
C2	0.0181(5)	0.0192(6)	0.0210(6)	-0.0003(4)	0.0065(4)	0.0008(4)
O3	0.0239(4)	0.0244(5)	0.0251(4)	-0.0022(3)	0.0072(3)	0.0043(3)
C3	0.0265(6)	0.0201(6)	0.0241(6)	0.0031(4)	0.0095(5)	0.0009(5)
C4	0.0312(7)	0.0437(8)	0.0321(7)	0.0067(5)	0.0167(5)	-0.0022(6)
C5	0.0213(6)	0.0384(8)	0.0399(8)	0.0052(6)	0.0130(5)	-0.0031(5)
C6	0.0182(6)	0.0340(7)	0.0326(7)	0.0041(5)	0.0083(5)	0.0003(5)
C7	0.0174(5)	0.0252(6)	0.0216(6)	-0.0010(4)	0.0046(4)	-0.0013(4)
C8	0.0165(5)	0.0287(6)	0.0186(6)	0.0017(4)	0.0032(4)	0.0004(4)
C9	0.0189(5)	0.0204(6)	0.0157(5)	0.0021(4)	0.0058(4)	-0.0001(4)
C10	0.0288(7)	0.0313(7)	0.0243(6)	-0.0111(5)	0.0055(5)	-0.0030(5)
C11	0.0295(7)	0.0319(7)	0.0219(6)	-0.0057(5)	0.0029(5)	-0.0054(5)
C12	0.0197(6)	0.0189(6)	0.0169(6)	-0.0022(4)	0.0074(4)	-0.0003(4)
C13	0.0228(6)	0.0241(6)	0.0184(6)	-0.0003(4)	0.0072(4)	0.0004(4)
C14	0.0248(6)	0.0309(7)	0.0229(6)	0.0037(5)	0.0106(5)	0.0065(5)
C15	0.0171(5)	0.0428(8)	0.0253(6)	0.0071(5)	0.0077(4)	0.0022(5)
C16	0.0217(6)	0.0338(7)	0.0255(6)	0.0017(5)	0.0043(5)	-0.0076(5)
C17	0.0240(6)	0.0250(6)	0.0195(6)	-0.0003(4)	0.0070(4)	-0.0026(5)
C18	0.0193(6)	0.0239(6)	0.0150(5)	0.0016(4)	0.0064(4)	-0.0004(4)
C19	0.0194(6)	0.0230(6)	0.0247(6)	-0.0009(4)	0.0070(4)	0.0000(4)
C20	0.0227(6)	0.0261(6)	0.0301(7)	0.0056(5)	0.0033(5)	0.0000(5)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C21	0.0240(6)	0.0389(7)	0.0202(6)	0.0059(5)	0.0032(4)	-0.0060(5)
C22	0.0242(6)	0.0358(7)	0.0203(6)	-0.0037(5)	0.0071(4)	-0.0039(5)
C23	0.0226(6)	0.0244(6)	0.0217(6)	-0.0017(4)	0.0069(4)	0.0000(4)
C24	0.0154(5)	0.0242(6)	0.0190(6)	0.0004(4)	0.0062(4)	-0.0015(4)

Table 30 Hydrogen atomic coordinates and isotropic atomic displacemnt parameters ($Å^2$) for **3-73**

	x/a	**y/b**	**z/c**	**U(eq)**
H1A	0.1764	0.7169	0.1188	0.021
H2A	0.2896	0.9472	0.1366	0.023
H4A	0.4092	1.0424	0.0411	0.041
H4B	0.4343	0.7904	0.0298	0.041
H5A	0.5441	0.8836	0.1171	0.039
H5B	0.4811	1.0314	0.1466	0.039
H6A	0.4664	0.5527	0.1377	0.034
H6B	0.5230	0.6756	0.2013	0.034
H7A	0.4000	0.8509	0.2153	0.026
H8A	0.3709	0.3838	0.1943	0.026
H8B	0.3817	0.5219	0.2592	0.026
H10A	0.1400	0.0847	0.0223	0.034
H10B	0.1582	0.2506	-0.0303	0.034
H11A	0.0110	0.1221	-0.0642	0.043
H11B	-0.0056	0.2216	-0.0009	0.043
H11C	0.0125	0.3866	-0.0532	0.043
H12A	0.2211	0.2344	0.1815	0.022
H13A	0.1192	0.7271	0.2246	0.026
H14A	-0.0323	0.7819	0.2027	0.03
H15A	-0.1302	0.5004	0.1527	0.034
H16A	-0.0760	0.1628	0.1259	0.033
H17A	0.0754	0.1040	0.1502	0.027
H19A	0.2849	-0.0200	0.2623	0.027
H20A	0.3373	-0.1262	0.3692	0.033
H21A	0.3281	0.1215	0.4499	0.034
H22A	0.2692	0.4783	0.4229	0.032
H23A	0.2187	0.5862	0.3163	0.027

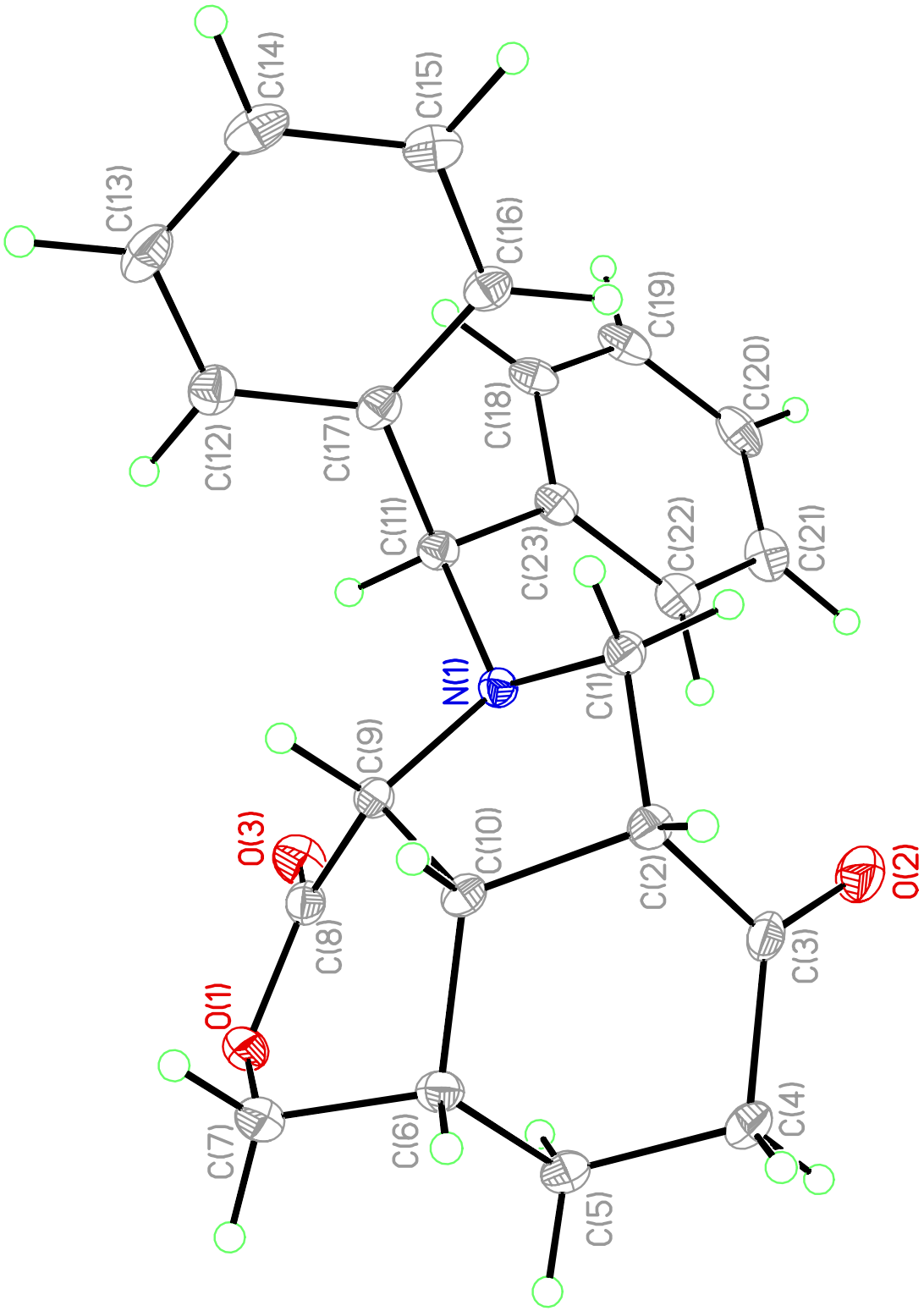


Figure 13 ORTEP structure of **3-116**

Table 31 Sample and crystal data for **3-116**

Chemical formula	$C_{23}H_{23}NO_3$	
Formula weight	361.42 g/mol	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal size	0.080 x 0.150 x 0.210 mm	
Crystal system	monoclinic	
Space group	C 1 c 1	
Unit cell dimensions	a = 16.9789(3) Å	α = 90°
	b = 7.49480(10) Å	β = 102.6470(10)°
	c = 14.4748(2) Å	γ = 90°
Volume	1797.28(5) $Å^3$	
Z	4	
Density (calculated)	1.336 g/cm^3	
Absorption coefficient	0.705 mm^{-1}	
F(000)	768	

Table 32 Data collection and structure refinement for **3-116**

Theta range for data collection	5.34 to 70.09°	
Index ranges	-20<=h<=20, -8<=k<=8, -17<=l<=17	
Reflections collected	15918	
Independent reflections	3286 [R(int) = 0.0233]	
Max. and min. transmission	0.9800 and 0.9200	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/4 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3286 / 2 / 336	
Goodness-of-fit on F^2	1.052	
Final R indices	3270 data; I>2σ(I)	R1 = 0.0264, wR2 = 0.0736
	all data	R1 = 0.0265, wR2 = 0.0737
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0680P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.04(4)	
Largest diff. peak and hole	0.155 and -0.197 $eÅ^{-3}$	
R.M.S. deviation from mean	0.041 $eÅ^{-3}$	

Table 33 Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$) for **3-116**

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
C1	0.49574(9)	0.6434(2)	0.60916(12)	0.0180(3)
N1	0.53575(7)	0.52915(17)	0.55088(9)	0.0160(3)
O1	0.71761(7)	0.26829(15)	0.64600(9)	0.0232(3)

	x/a	y/b	z/c	U(eq)
C2	0.56008(9)	0.6625(2)	0.69918(11)	0.0179(3)
O2	0.60627(8)	0.92868(17)	0.63604(10)	0.0321(3)
C3	0.62186(10)	0.8077(2)	0.69232(12)	0.0205(3)
O3	0.66139(7)	0.33364(18)	0.49869(9)	0.0277(3)
C4	0.70152(10)	0.7895(2)	0.76199(14)	0.0266(4)
C5	0.73799(9)	0.6060(2)	0.75028(13)	0.0228(3)
C6	0.68296(9)	0.4559(2)	0.76940(12)	0.0189(3)
C7	0.71317(10)	0.2758(2)	0.74528(13)	0.0234(4)
C8	0.65567(9)	0.3316(2)	0.58003(12)	0.0196(3)
C9	0.58024(9)	0.3907(2)	0.61310(11)	0.0159(3)
C10	0.59540(9)	0.47245(19)	0.71434(11)	0.0163(3)
C11	0.48540(8)	0.4682(2)	0.46004(11)	0.0173(3)
C12	0.39897(11)	0.1998(2)	0.47684(12)	0.0231(3)
C13	0.32754(12)	0.1213(2)	0.49027(12)	0.0267(4)
C14	0.26233(11)	0.2273(3)	0.49723(12)	0.0263(4)
C15	0.26747(10)	0.4118(2)	0.49035(13)	0.0249(4)
C16	0.33850(10)	0.4891(2)	0.47569(11)	0.0206(3)
C17	0.40560(9)	0.3841(2)	0.46975(11)	0.0186(3)
C18	0.42014(9)	0.5989(2)	0.30078(12)	0.0213(3)
C19	0.41244(10)	0.7284(2)	0.23051(13)	0.0257(4)
C20	0.45889(12)	0.8833(2)	0.24695(14)	0.0267(4)
C21	0.51328(12)	0.9050(2)	0.33289(14)	0.0270(4)
C22	0.52163(10)	0.7736(2)	0.40297(12)	0.0221(3)
C23	0.47435(9)	0.6193(2)	0.38726(12)	0.0191(3)

Table 34 Bond lengths (Å) for **3-116**

C1-N1	1.4686(19)	C1-C2	1.513(2)
C1-H1A	0.93(2)	C1-H1B	1.04(2)
N1-C9	1.4699(19)	N1-C11	1.4753(18)
O1-C8	1.343(2)	O1-C7	1.457(2)
C2-C3	1.530(2)	C2-C10	1.542(2)
C2-H2	0.96(2)	O2-C3	1.209(2)
C3-C4	1.506(2)	O3-C8	1.202(2)
C4-C5	1.533(2)	C4-H4A	0.95(2)
C4-H4B	0.99(3)	C5-C6	1.526(2)
C5-H5A	0.95(2)	C5-H5B	0.99(3)
C6-C7	1.512(2)	C6-C10	1.5304(19)
C6-H6	0.96(3)	C7-H7A	0.98(2)
C7-H7B	0.95(3)	C8-C9	1.5276(19)
C9-C10	1.557(2)	C9-H9A	0.97(2)
C10-H10	0.95(2)	C11-C17	1.528(2)
C11-C23	1.530(2)	C11-H11	0.99(2)
C12-C17	1.392(2)	C12-C13	1.399(2)
C12-H12	0.97(3)	C13-C14	1.384(3)
C13-H13	0.99(3)	C14-C15	1.390(3)

C14-H14	0.97(2)	C15-C16	1.395(2)
C15-H15	0.97(3)	C16-C17	1.402(2)
C16-H16	1.00(2)	C18-C23	1.390(2)
C18-C19	1.391(2)	C18-H18	0.99(2)
C19-C20	1.394(3)	C19-H19	0.95(3)
C20-C21	1.387(3)	C20-H2-0	0.98(3)
C21-C22	1.398(2)	C21-H21	1.01(3)
C22-C23	1.398(2)	C22-H22	0.98(3)

Table 35 Bond angles (°) for **3-116**

N1-C1-C2	102.26(12)	N1-C1-H1A	112.0(12)
C2-C1-H1A	111.2(13)	N1-C1-H1B	110.3(13)
C2-C1-H1B	115.2(13)	H1A-C1-H1B	106.1(17)
C1-N1-C9	107.45(13)	C1-N1-C11	116.22(12)
C9-N1-C11	116.55(12)	C8-O1-C7	119.10(12)
C1-C2-C3	112.80(13)	C1-C2-C10	102.71(12)
C3-C2-C10	114.55(12)	C1-C2-H2	113.3(14)
C3-C2-H2	105.5(14)	C10-C2-H2	108.1(13)
O2-C3-C4	123.48(15)	O2-C3-C2	121.68(15)
C4-C3-C2	114.83(14)	C3-C4-C5	109.44(13)
C3-C4-H4A	110.8(15)	C5-C4-H4A	110.6(14)
C3-C4-H4B	110.4(15)	C5-C4-H4B	107.6(15)
H4A-C4-H4B	108.(2)	C6-C5-C4	111.29(14)
C6-C5-H5A	107.5(13)	C4-C5-H5A	112.5(14)
C6-C5-H5B	110.2(13)	C4-C5-H5B	109.1(13)
H5A-C5-H5B	106.1(19)	C7-C6-C5	111.36(14)
C7-C6-C10	106.98(13)	C5-C6-C10	114.18(13)
C7-C6-H6	105.6(17)	C5-C6-H6	110.1(17)
C10-C6-H6	108.2(16)	O1-C7-C6	110.83(13)
O1-C7-H7A	109.4(14)	C6-C7-H7A	109.9(14)
O1-C7-H7B	105.7(16)	C6-C7-H7B	113.2(16)
H7A-C7-H7B	108.(2)	O3-C8-O1	118.82(14)
O3-C8-C9	123.79(14)	O1-C8-C9	117.34(14)
N1-C9-C8	111.48(13)	N1-C9-C10	104.81(12)
C8-C9-C10	115.58(12)	N1-C9-H9A	112.4(14)
C8-C9-H9A	106.8(13)	C10-C9-H9A	105.7(13)
C6-C10-C2	116.87(12)	C6-C10-C9	113.57(12)
C2-C10-C9	104.51(12)	C6-C10-H10	106.8(11)
C2-C10-H10	107.5(11)	C9-C10-H10	107.1(11)
N1-C11-C17	113.47(12)	N1-C11-C23	110.12(12)
C17-C11-C23	113.00(12)	N1-C11-H11	104.8(14)
C17-C11-H11	108.3(13)	C23-C11-H11	106.6(14)
C17-C12-C13	120.92(16)	C17-C12-H12	116.1(14)
C13-C12-H12	122.9(14)	C14-C13-C12	120.03(17)
C14-C13-H13	121.1(14)	C12-C13-H13	118.8(14)
C13-C14-C15	120.12(16)	C13-C14-H14	120.6(14)

C15-C14-H14	119.3(14)	C14-C15-C16	119.57(17)
C14-C15-H15	118.9(18)	C16-C15-H15	121.6(18)
C15-C16-C17	121.14(15)	C15-C16-H16	118.9(14)
C17-C16-H16	119.9(14)	C12-C17-C16	118.19(15)
C12-C17-C11	120.23(14)	C16-C17-C11	121.53(14)
C23-C18-C19	121.30(16)	C23-C18-H18	120.6(13)
C19-C18-H18	117.9(13)	C18-C19-C20	119.79(17)
C18-C19-H19	120.3(16)	C20-C19-H19	119.8(16)
C21-C20-C19	119.43(16)	C21-C20-H2-0	120.7(14)
C19-C20-H2-0	119.9(14)	C20-C21-C22	120.66(17)
C20-C21-H21	121.0(15)	C22-C21-H21	118.3(15)
C23-C22-C21	120.08(17)	C23-C22-H22	121.1(13)
C21-C22-H22	118.8(13)	C18-C23-C22	118.74(16)
C18-C23-C11	119.72(15)	C22-C23-C11	121.40(15)

Table 36 Anisotropic atomic displacement parameters (Å^2) for **3-116**

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	0.0170(7)	0.0182(7)	0.0194(8)	-0.0023(5)	0.0052(6)	-0.0003(5)
N1	0.0163(6)	0.0157(6)	0.0158(6)	-0.0009(4)	0.0031(5)	0.0010(4)
O1	0.0190(5)	0.0223(6)	0.0271(7)	-0.0020(4)	0.0027(4)	0.0045(4)
C2	0.0169(7)	0.0195(8)	0.0181(8)	-0.0033(6)	0.0058(6)	-0.0010(5)
O2	0.0361(7)	0.0201(6)	0.0372(8)	0.0023(5)	0.0020(5)	-0.0050(5)
C3	0.0224(7)	0.0148(7)	0.0248(8)	-0.0053(6)	0.0062(6)	-0.0022(6)
O3	0.0263(6)	0.0334(7)	0.0259(7)	-0.0016(5)	0.0112(5)	0.0052(5)
C4	0.0216(8)	0.0207(9)	0.0351(11)	-0.0056(6)	0.0011(7)	-0.0059(6)
C5	0.0164(7)	0.0225(8)	0.0280(9)	-0.0008(6)	0.0019(6)	-0.0035(6)
C6	0.0169(7)	0.0208(8)	0.0177(7)	0.0016(5)	0.0009(6)	-0.0010(5)
C7	0.0219(8)	0.0230(9)	0.0231(9)	0.0027(6)	0.0000(7)	0.0013(6)
C8	0.0184(7)	0.0162(8)	0.0247(9)	-0.0018(5)	0.0061(6)	-0.0003(5)
C9	0.0155(7)	0.0154(7)	0.0172(8)	0.0010(5)	0.0041(5)	-0.0012(5)
C10	0.0159(7)	0.0180(8)	0.0156(7)	-0.0007(5)	0.0049(6)	-0.0036(5)
C11	0.0173(7)	0.0195(8)	0.0148(7)	-0.0012(6)	0.0028(6)	0.0006(5)
C12	0.0269(8)	0.0229(8)	0.0183(8)	-0.0015(6)	0.0027(6)	-0.0014(6)
C13	0.0352(9)	0.0236(9)	0.0191(8)	-0.0012(6)	0.0009(7)	-0.0114(6)
C14	0.0248(8)	0.0355(10)	0.0177(8)	-0.0010(6)	0.0028(6)	-0.0116(6)
C15	0.0203(8)	0.0321(9)	0.0215(8)	-0.0009(6)	0.0031(6)	-0.0023(6)
C16	0.0207(7)	0.0228(9)	0.0172(7)	-0.0006(6)	0.0020(5)	-0.0028(6)
C17	0.0215(8)	0.0205(8)	0.0129(7)	-0.0015(5)	0.0018(6)	-0.0027(5)
C18	0.0154(7)	0.0301(9)	0.0192(9)	0.0020(6)	0.0059(6)	0.0039(6)
C19	0.0201(8)	0.0383(9)	0.0197(9)	0.0050(7)	0.0065(6)	0.0107(7)
C20	0.0301(8)	0.0283(9)	0.0249(9)	0.0103(7)	0.0132(7)	0.0120(6)
C21	0.0322(9)	0.0242(9)	0.0282(9)	0.0035(7)	0.0143(7)	0.0025(6)
C22	0.0234(8)	0.0238(8)	0.0202(8)	0.0018(6)	0.0075(6)	0.0012(6)
C23	0.0186(7)	0.0226(7)	0.0178(8)	0.0010(5)	0.0078(6)	0.0037(5)

Table 37 Hydrogen atomic coordinates and isotropic atomic displacemnt parameters ($Å^2$) for **3-116**

	x/a	**y/b**	**z/c**	**U(eq)**
H2	0.5389(14)	0.693(3)	0.7531(17)	0.019(5)
H4A	0.7375(14)	0.882(3)	0.7533(18)	0.025(5)
H4B	0.6937(15)	0.797(3)	0.828(2)	0.029(6)
H5A	0.7894(14)	0.589(3)	0.7919(16)	0.019(5)
H5B	0.7472(14)	0.596(3)	0.6855(18)	0.022(5)
H6	0.6830(16)	0.451(4)	0.836(2)	0.036(7)
H9A	0.5480(14)	0.285(3)	0.6153(16)	0.019(5)
H10	0.5634(11)	0.407(2)	0.7486(14)	0.006(4)
H11	0.5182(14)	0.375(3)	0.4373(17)	0.021(5)
H12	0.4460(15)	0.131(3)	0.4711(18)	0.027(6)
H13	0.3245(14)	-0.011(4)	0.4939(18)	0.032(6)
H15	0.2213(19)	0.484(4)	0.496(2)	0.039(6)
H16	0.3416(15)	0.621(3)	0.4711(17)	0.022(5)
H18	0.3889(14)	0.488(3)	0.2857(17)	0.023(5)
H19	0.3785(16)	0.708(3)	0.170(2)	0.031(6)
H2-0	0.4543(15)	0.973(4)	0.1971(19)	0.031(6)
H21	0.5492(15)	1.014(4)	0.3456(18)	0.032(6)
H22	0.5609(15)	0.793(3)	0.4630(17)	0.018(5)
H1A	0.4495(12)	0.590(3)	0.6210(14)	0.012(4)
H1B	0.4771(13)	0.762(3)	0.5738(17)	0.019(5)
H7A	0.6771(14)	0.181(3)	0.7584(17)	0.026(6)
H7B	0.7660(17)	0.249(4)	0.780(2)	0.029(6)
H14	0.2121(15)	0.174(3)	0.5056(17)	0.028(6)

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