8-18-2014 12:00 AM

Application of Mn(III) Oxidative Cyclizations to Natural Product Synthesis

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Chemistry

APPLICATION OF Mn(III) OXIDATIVE CYCLIZATIONS TO NATURAL PRODUCT SYNTHESIS

(Thesis format: Monograph)

by

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Graduate Program in Chemistry

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

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Abstract

This work begins with a brief review of manganese(III) acetate free radical oxidative cyclization chemistry and its application toward functionalizing nitrogen containing heterocycles. Exploration of a cyclopropane ring opening reaction using indoline, and subsequent manganese(III) cyclization chemistry will be presented as a possible route towards a family of natural products called the flinderoles.

Work on the construction of the core of several indole alkaloids from the genus *Tabernaemontana*, including tronocarpine, chippiine, and dippinine B, will be explored with utilization of manganese(III) cyclizations. Hopes of accessing an advanced common intermediate for each of these natural products will be discussed due to structural similarities that converge nicely with the use of manganese(III) as a key synthetic step.

Keywords

Manganese(III) Acetate, Natural Product Synthesis, Flinderole, Tronocarpine, Chippiine, Oxidative Radical Cyclization, Cyclopropane, Pyrroloindole

Acknowledgments

I would like to take this opportunity to thank Dr. M.A. Kerr for allowing me the opportunity and the privilege of working on this project in his laboratory throughout my 4th year project and graduate studies. His knowledge and direction proved to be invaluable and were greatly appreciated. I am indebted to each professor who taught and helped me throughout my undergraduate career and to this day; not only in relation to education but also for their general advice. Western has no shortage of excellent professors and learning from each of them has been a great experience. Thanks to Doug Hairsine and Mat Willans for their help collecting mass specs and NMR spectra as well as sharing their wisdom and knowledge. I also thank former graduate students Will Humenny and Dwayne Dias for sharing their knowledge of chemistry as well as friendship both in and outside of the lab. I would also like to thank all of the graduate students in the Kerr group for their assistance and their infinite patience. Without the help and guidance of Polydoros Kyriacou, Michael Emmett and Huck Grover *et al.*, my experience in the lab would not have been anything near as educational nor enjoyable. To my family, your patience and support with whatever decision I made throughout university will always be appreciated. I still have no idea what I will be doing in the future and that doesn't seem to bother you, so thank you. Lastly, I would like to thank my lovely girlfriend Briana. The past 6 years have been quite the journey, and despite the distance between us you were never more than a phone call or train ride away. Your love for me and my goals, regardless of whether or not they made sense to you, is just another reason why I love you so much. Thanks to all my friends throughout the years who have helped me in this experience. I will always remember that the Grad Club is never too far to grab *a* pint...

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List of Abbreviations

AcOH	acetic acid
AIBN	azobisisobutyronitrile
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-butyl
Bn	benzyl
cat.	catalytic amount
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-l,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DME	dimethoxymethane
DMSO	dimethyl sulfoxide
Et	ethyl
Equiv.	equivalents
hv	light
HMBC	heteronuclear multi-bond correlation spectroscopy
HMDS	bis(trimethylsilyl)amide
HSQC	heteronuclear single-quantum correlation spectroscopy
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz.	Hertz
IR	infrared
LDA	lithium diisopropylamine

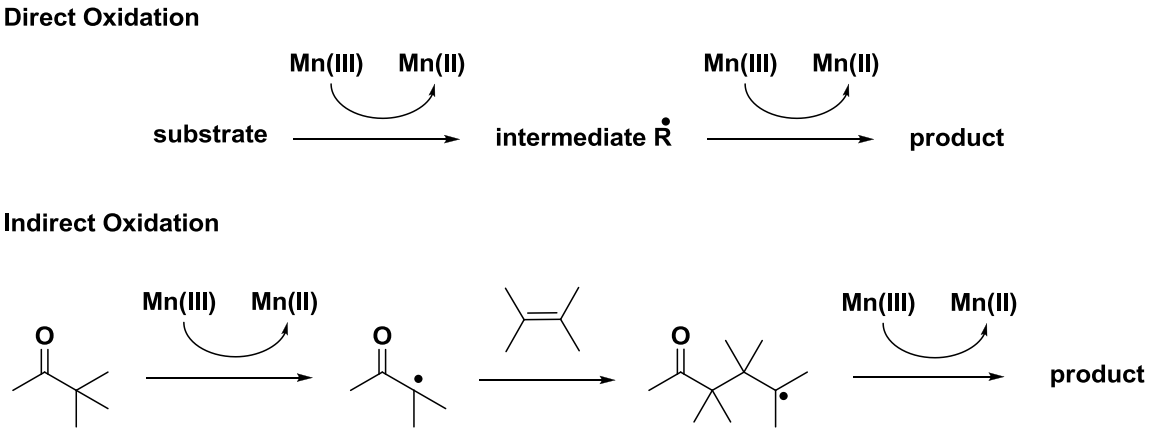
mmol	millimole
Me	methyl
Ms	methanesulfonyl
MS	molecular sieves
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
PG	unspecified protecting group
Ph	phenyl
ppm	parts per million
Phth	phthalimide
RDS	rate determining step
R_f	retention factor
rt	room temperature
S_N2	second order nucleophilic substitution
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

1 Introduction

The past two years of graduate school has seen the majority of my work focused on the use of a single reagent: manganese(III) acetate. It may then come as no surprise that this compound is the unifying component of this body of work. Chapters 1 and 2 will both discuss the use of manganese(III) acetate in performing oxidative radical cyclization reactions; however, each chapter will focus on obtaining different structural motifs. The present chapter will first provide a brief background describing the history and use of manganese(III) acetate present in the literature, with emphasis on oxidative cyclizations. The following section of this chapter will focus on the background and general reactivity of a key component to the Kerr group's research; donor-acceptor cyclopropanes. Next we will discuss the use of manganese(III) acetate in conjunction with donor-acceptor cyclopropanes to access an indole polycyclic framework which is present in a family of natural products known as the flinderoles.

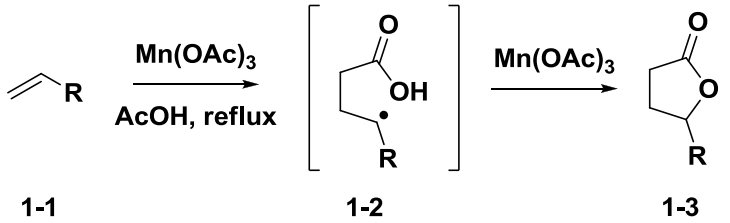
1.1.1 Manganese(III) Acetate: History, Background and Limitations

Over the past several decades much attention has been given to the reactivity of manganese(III) acetate due to its ability to undergo oxidative cyclizations with complex chemical systems.[1] The interest revolving around the oxidative radical cyclizations is due to the increased synthetic potential when compared to reductive radical cyclizations. In addition, the reaction precursors are often simpler to prepare and result in more useful products because of the oxidative termination step.[1] It is important to note that the structure of manganese(III) acetate is actually a coordination of three manganese atoms with bridging acetate units and does not reflect the simple ionic structure of $Mn(OAc)_3$.[2] There are two general classes of manganese(III) acetate oxidations as described by de Klein: [3] direct and indirect oxidations (scheme 1.1). In direct oxidations, the resulting formation of an intermediate radical can undergo many different transformations such as dimerization, disproportionation, and loss of hydrogen or oxidation depending on the reaction conditions. This pathway is less explored and much of the work in this area relies on the indirect oxidation.



Scheme 1.1. Direct vs. indirect oxidation

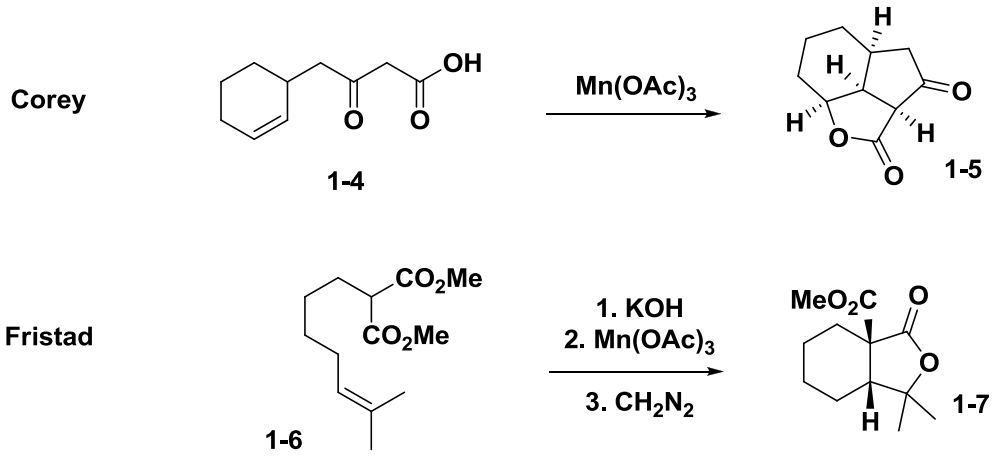
The second class of oxidation called indirect oxidation involves the formation of a stabilized radical at an enolizable position which can undergo addition and substitution reactions onto aromatic systems or olefins. The subsequent radical formed after the addition to an alkene can then undergo an additional oxidation by another equivalent of manganese(III) acetate to form a stabilized cation leading to the product.[3] The first example of this transformation using manganese(III) acetate was the conversion of an alkene, **1-1**, to a lactone, **1-3**, via addition of acetic acid to form radical intermediate **1-2,** shown in scheme 1.2.[4]



Scheme 1.2. First manganese(III) promoted radical addition into an alkene

During the next several decades the chemistry of manganese(III) acetate was extensively studied as the scope of substrates began expanding to other enolizable compounds such as β-keto-esters,[5] aldehydes,[6] and related dicarbonyl compounds.[1] It is worth noting that as the enolizable character of these compounds increased, so did the product yield, typically with lower temperature and reaction times.

It was not until the mid 1980's that Corey,[7] and then Fristad and Ernst,[8] showed the first examples of manganese(III) acetate mediated oxidative intramolecular cyclizations (scheme 1.3). In 1984, Corey[7] utilized manganese(III) acetate to conduct a double annulation reaction of **1-4** to form the cyclopentanone adduct **1-5**. The following year, Ernst and Fristad[8] were able to show the transformation of an unsaturated diester **1-6** to the bicyclic lactone **1-7**.

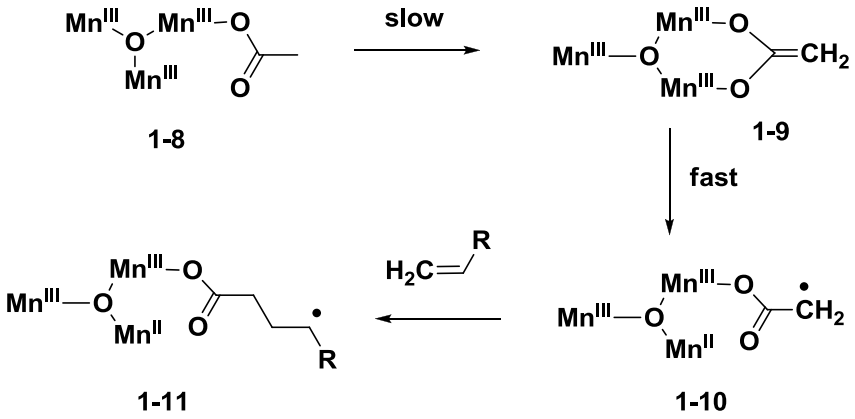


Scheme 1.3. First two manganese(III) intramolecular oxidative cyclizations

With the increase in complexity of substrates undergoing these oxidative cyclizations, the ability for their application towards natural product syntheses became much more evident. These initial discoveries spawned a large emergence of related intramolecular cyclizations during the next decade allowing for the synthesis of more complex systems and ring sizes.[1]

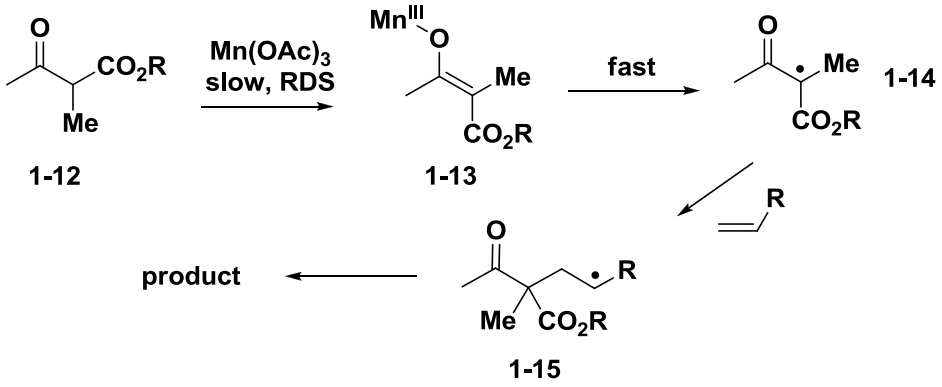
1.1.2 Mechanistic Considerations

The first work toward understanding the mechanism by which manganese(III) acetate performs radical oxidations was completed by Fristad and Peterson.[9] With acetic acid as the starting material, they determined that the rate determining step is the loss of a proton to form intermediate **1-9** shown in scheme 1.4. At this point, a rapid electron transfer gives radical **1-10**, which then undergoes addition to an alkene to yield compound **1-11**. This radical can then be further oxidized by another equivalent of manganese(III) acetate.



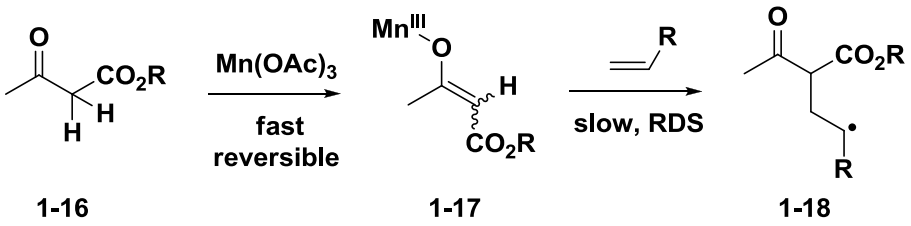
Scheme 1.4. Acetic acid mechanism**1**

A similar mechanism is believed to be occurring when manganese(III) acetate is used with α-alkyl β-keto esters as seen in scheme 1.5.[10] Enolization of **1-12** to compound **1-13** is slow and thus the rate determining step. Electron transfer to **1-14** is fast and the addition to a subsequent alkene would also be rapid. At this point, addition into an alkene will give intermediate **1-15**, which can be oxidized further leading to the product.[10]



Scheme 1.5. Mechanistic pathway of α-alkyl β-keto esters

Another accepted mechanistic pathway, which differs from the previous two examples and shown in scheme 1.6, is used when α-unsubstituted β-keto esters are used as the enolizable substrate.

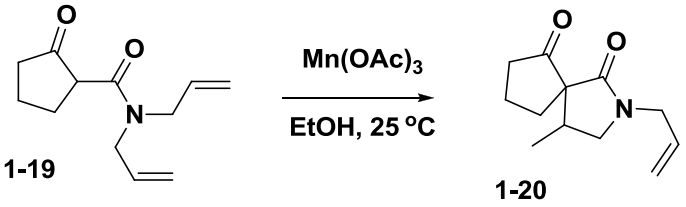


Scheme 1.6. Mechanistic pathway for α-unsubstituted β-keto esters

The enolization step of **1-16** is believed to be fast and reversible with no formation of a radical intermediate **1-17**. Addition to the alkene to give **1-18** is now the rate determining step and alkene concentration will play a role in the reaction rate. The variance in mechanistic pathways is believed to be attributed to the presence of an α-alkyl group decreasing the acidity of the proton thus reducing enolization. In addition, the formation of a tertiary radical, such as **1-14**, will be further stabilized and a radical intermediate is now much more energetically favored.[10]

1.1.3 Select Limitations and Additives

With the influx of work being conducted using manganese(III) acetate oxidative cyclizations, there have been some limitations reported. One particular limitation with these cyclizations is that its use is not general for all substrates. β-Keto amides are scarcely implemented starting material for cyclization presumably due to their lack of enol content. The relatively few published examples all possess tertiary amides (scheme 1.7)[11], which limit the scope of substrates suitable to perform the reaction.



Scheme 1.7. Example of a tertiary amide manganese cyclization

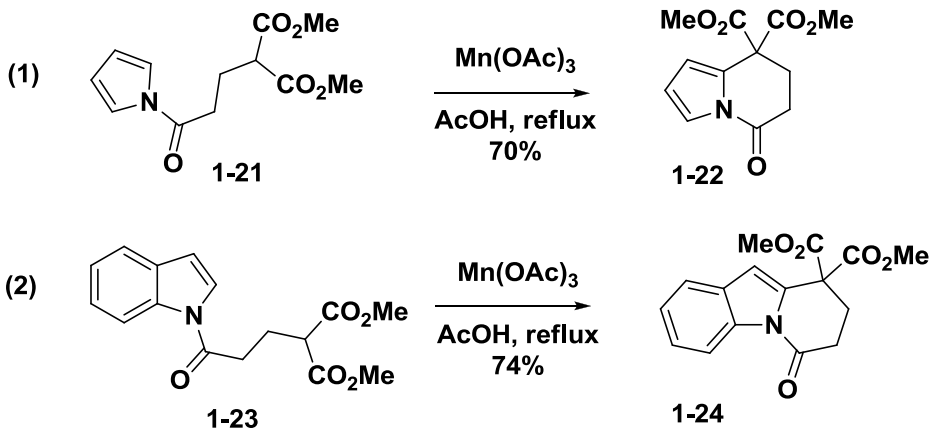
Another issue is the need for stoichiometric amounts of manganese, which increases the cost and decreases the suitability for industrial use. There have been some examples of catalytic amounts (0.2 equiv) of manganese(III) acetate being used and

regenerated electrochemically *in situ*; however, yields were frequently lower than when stoichiometric amounts were used.[12] This technique would also require the need for more complicated apparatus. Manganese(III) acetate dihydrate is available commercially for a relatively expensive price ($5.16/g, Aldrich). To circumvent this issue, the reagent can be made on a large (~60 g) scale by oxidizing the much cheaper manganese(II) acetate tetrahydrate ($0.10/g) using $KMnO_4$ and acetic acid.

To assist in the rate limiting step of manganese(III) oxidative cyclizations co-oxidants such as copper(II) acetate have been shown to help promote the rate of reaction.[13] Other sources of radical oxidation are present in the literature and use oxidants such as manganese(III) acetylacetone (amongst others), copper(II), cerium(IV), and Fe(III).1 Other additives such as trifluoroacetic acid, potassium or sodium acetate have been seen to increase the rate of the reaction although in some cases decreasing yields. Acetate anions are believed to promote enolization and act as a buffer.[1]

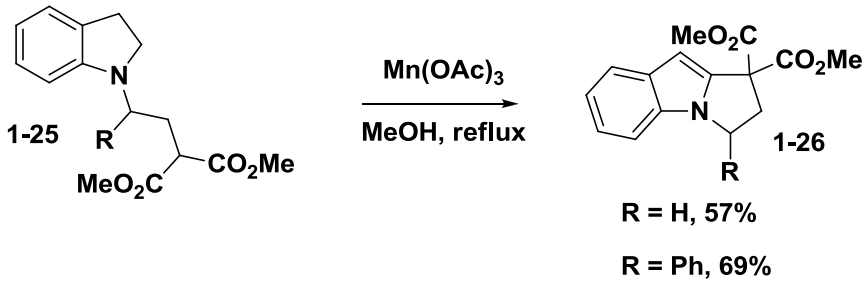
1.1.4 Manganese(III) Acetate and the Kerr Group

In 2006, Kerr and Magolan[14] published work that studied the ability of nitrogen containing heterocycles such as pyrroles and indoles as viable substrates to undergo manganese(III) acetate oxidative cyclizations. *N*-Acylation of both pyrrole (1), and indole (2) (scheme 1.7), with the appropriate acyl chloride allowed quick access to the pendant malonyl cyclization precursors **1-21** and **1-23**. These substrates then underwent a manganese(III) cyclization to give **1-22** and **1-24** in good to excellent yields.[14]



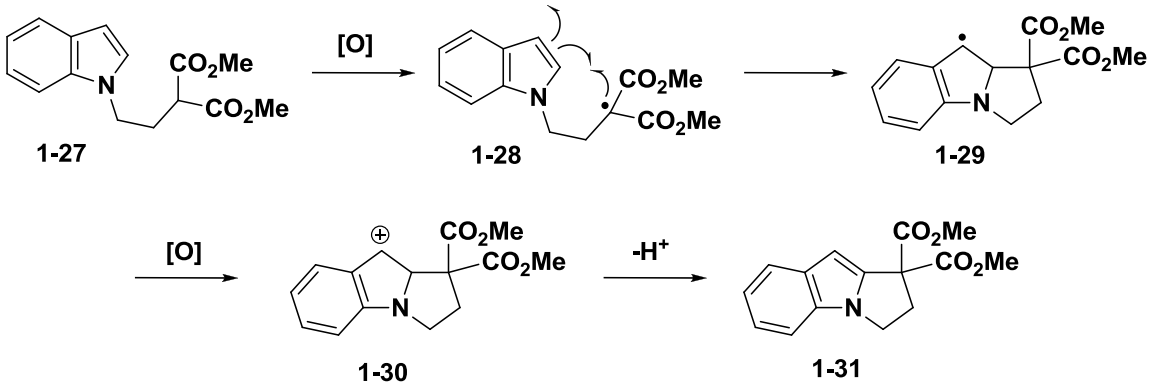
Scheme 1.8. Manganese(III) acetate cyclizations established by Kerr[14]

In the same publication, they showed a few examples of alkylated indolines **1-25** undergoing the same cyclization chemistry, to access the oxidized pyrroloindoles **1-26**. In this particular transformation, it is believed that indoline initially dehydrogenates to the indole resulting in the necessary alkene that can undergo the subsequent cyclization (scheme 1.9).[14]



Scheme 1.9. Formation of pyrroloindoles by Kerr[14]

The mechanism for these manganese(III) oxidative cyclizations has been intensively studied and depending on the reaction conditions and substrates is thought to have different pathways. The particular mechanism for the formation of these pyrroloindoles is shown in scheme 1.10.[14]



Scheme 1.10. Proposed mechanism for oxidative cyclizations

It is worth noting that in the examples where the cyclization substrate begins as an indoline, oxidation to the indole is the first step followed by the mechanistic pathway shown in scheme 1.10. The first step of the oxidative cyclization is enolization of compound **1-27**. Studies have shown that this is the rate determining step due to the decreased acidity of the malonic hydrogen.[1] Electron transfer with loss of manganese(II) forms a stabilized radical intermediate **1-28**, and occurs quite rapidly with α-substituted β diesters due to the stability of the newly formed radical. The highly electrophilic species can now be attacked forming a stabilized benzylic radical **1-29**. At this point, further oxidation using another equivalent of manganese(III) acetate forms a benzylic stabilized carbocation **1-30**, which upon proton loss re-aromatizes the indole ring to form the desired product **1-31**.

We are optimistic that the use of manganese(III) acetate to cyclize malonic radicals onto indoles will produce various ring sizes and complex structural frameworks needed to pursue an array of natural products. We will now look into the ability of cyclopropanes to be used in organic transformations.

1.2 Reactivity of Cyclopropanes, Indoles and Indolines

The application and preparation of cyclopropanes in organic synthesis has been well documented and reviewed.[15] The reactivity of these cyclopropanes can be attributed to the high ring strain of 28 kcal/mol caused by the 60° bond angles within the molecule (figure 1.1). When compared to the strength of a typical C-C bond (88 kcal/mol) it is

apparent that the high ring strain greatly weakens the C-C bonds. The poor C-C bond orbital overlap is due to the bond angles of the carbon nuclei being significantly smaller than the ideal inter-orbital angles of 109.5°.[16]

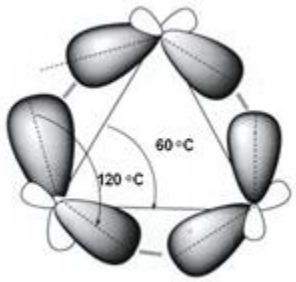


Figure 1.1. Bent bonding in cyclopropanes

Although unsubstituted cyclopropanes have been shown to undergo chemical transformations,[17] the majority of synthetic work has focused on cyclopropane activation by a combination of electron donating and/or electron accepting groups present on the molecule.[15] The presence of an electron accepting group on the cyclopropane (figure 1.2, Eq. i) allows the cyclopropane to act as a homo-Michael acceptor when combined with a nucleophile.[15] This reactivity can also allow an electrophile to subsequently be trapped by the resonance stabilized anion formed upon ring opening. Conversely, electron donating groups on the cyclopropane can react as nucleophiles towards an electrophile. The ensuing stabilized carbocation also allows for further reactivity following ring opening (figure 1.2, Eq. ii).[18] Lastly, donor-acceptor cyclopropanes (figure 1.2, Eq. iii) have an amplified reactivity due to a 'push pull' interaction further weakening the C-C bond. Nucleophilic attack occurs at the carbon vicinal to the electron donating group and the strong electron accepting groups assist in stabilizing the negative charge upon formation of the ring opened product.[15] Note, for simplicity, donor-acceptor cyclopropanes will now be referred to simply as cyclopropanes throughout this text.

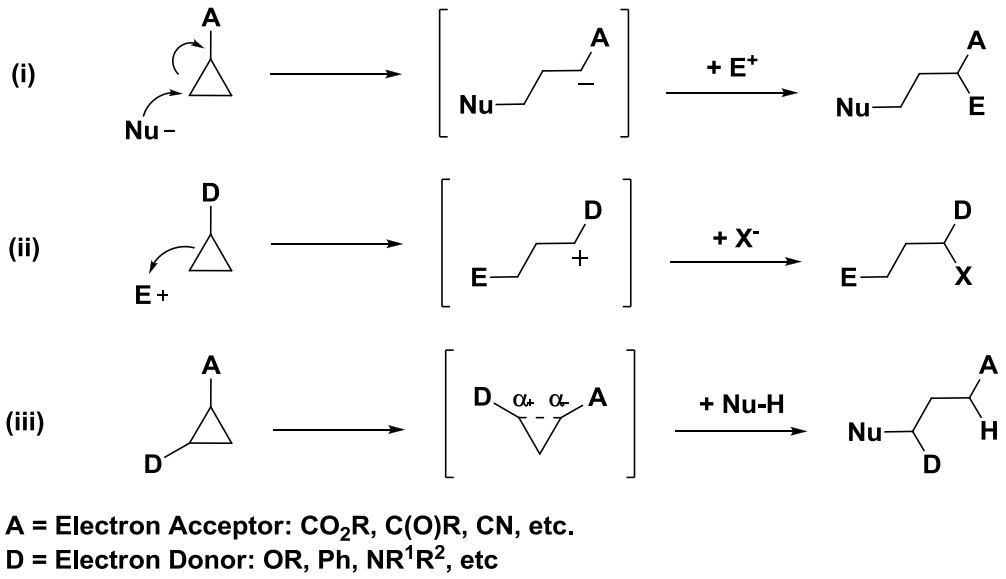
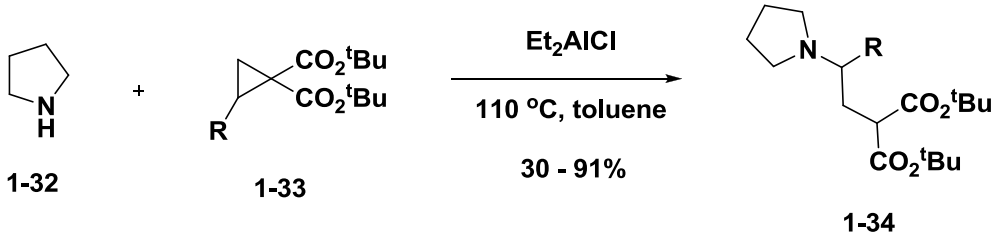


Figure 1.2. Reactivity of cyclopropanes

The use of Lewis acids in conjunction with cyclopropanes have been shown to increase reactivity by further weakening the C-C bond. This can be attributed to the increase in electron withdrawing ability of the accepting group.[15]

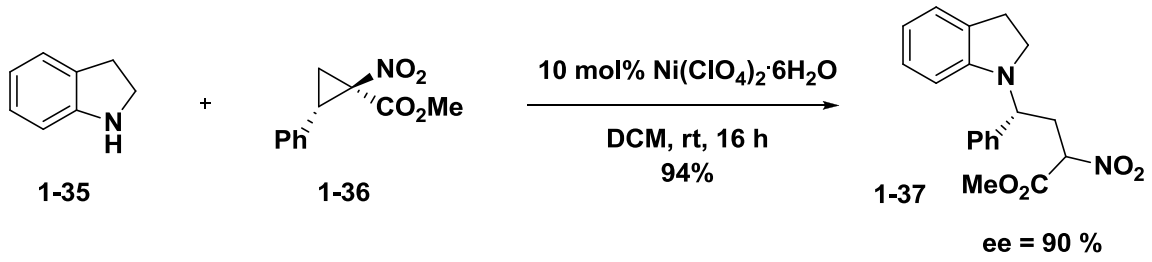
1.2.1 The Use of Heterocycles to Open Cyclopropanes

Several examples of nitrogen containing heterocycles ring-opening cyclopropanes have been reported in the literature. In 1986, Schneider[19] utilized pyrrolidine **1-32** to open 1,1 diester cyclopropanes **1-33** in the presence of an aluminum chloride catalyst to yield **1-34** (scheme 1.11). As the steric bulk increased on the 1,1 diester cyclopropane, the reaction yields began to decrease significantly.



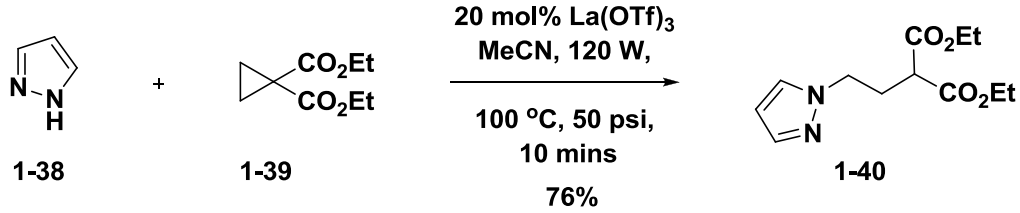
Scheme 1.11. Use of pyrrolidine to open cyclopropanes by Schneider[19]

More recently in 2008, Charette[20] and coworkers published the nucleophilic ring-opening reaction of methyl 1-nitrocyclopropanecarboxylates with various secondary amines in the presence of a Ni-catalyst (scheme 1.12). They showed that indoline **1-35** in the presence of $Ni(ClO_4)\cdot 6H_2O$ in DCM at room temperature for 16 hours successfully underwent nucleophilic ring opening of cyclopropane **1-36** to give their desired product **1-37**. They also observed the preservation of the enantiomeric purity of the cyclopropane to the acyclic product. This work is a great example of the mild conditions required to open cyclopropane substrates in excellent yields. Additionally, Charette was able to utilize this chemistry to successfully access a serotonin/norepinephrine reuptake inhibitor.



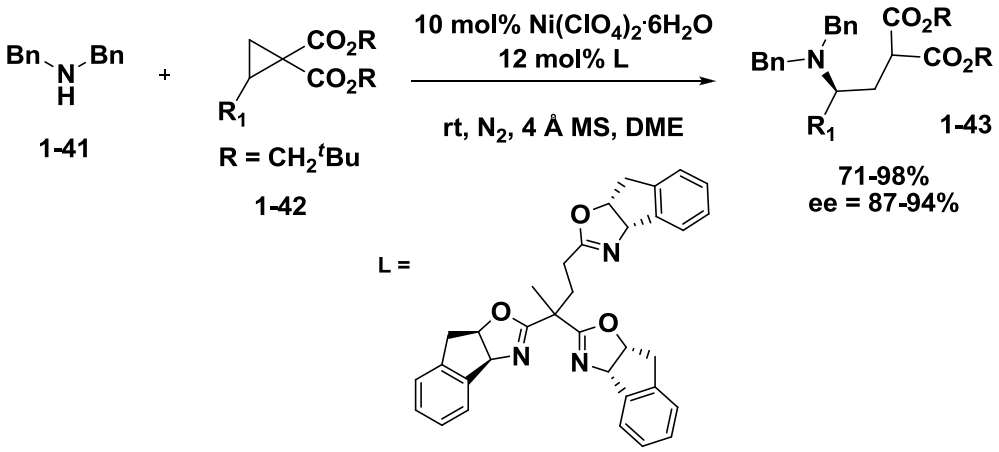
Scheme 1.12. Charette's Ni-catalyzed cyclopropane ring opening by indoline[20]

In the same year, in a similar fashion to that of Charette, Kotsuki *et al*. showed various heteroaromatics could be used to open donor acceptor cyclopropanes in the presence of $La(OTf)_3$ under microwave irradiation (scheme 1.13).[21] In this particular example, pyrazole **1-38** nucleophilically attacks cyclopropane **1-39** to yield compound **1-40** in modest yield. This chemistry is hopeful to have application towards the synthesis of γ-amino carbonyl compounds that are present in natural products and drugs.



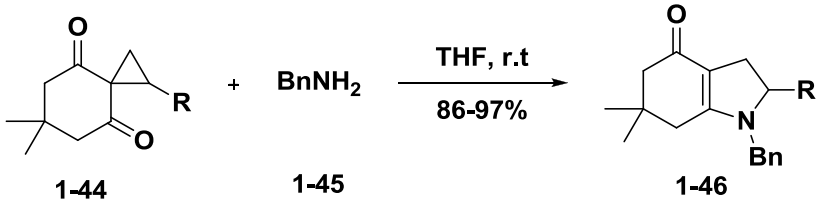
Scheme 1.13. Kotsuki's pyrazole opening cyclopropanes under microwave irradiation[21]

In 2012, Tang and coworkers[22] published work on a Ni-catalyzed promoted asymmetric 1,1 diester cyclopropane ring opening reaction using aliphatic amines such as compound **1-41** (scheme 1.14). The enantioselectivity was accomplished using the chiral indane-trisoxazoline ligand **L** with cyclopropanes **1-42**, which allows their work to also be applicable to chiral amino-acid synthesis. These reactions proceeded in both high yields (71-98%) and enantioselectivity (87-94%) of ring opened products **1-43**. This was the first example of catalytic enantioselective ring-opening of 1,1 diester cyclopropanes using secondary amines.



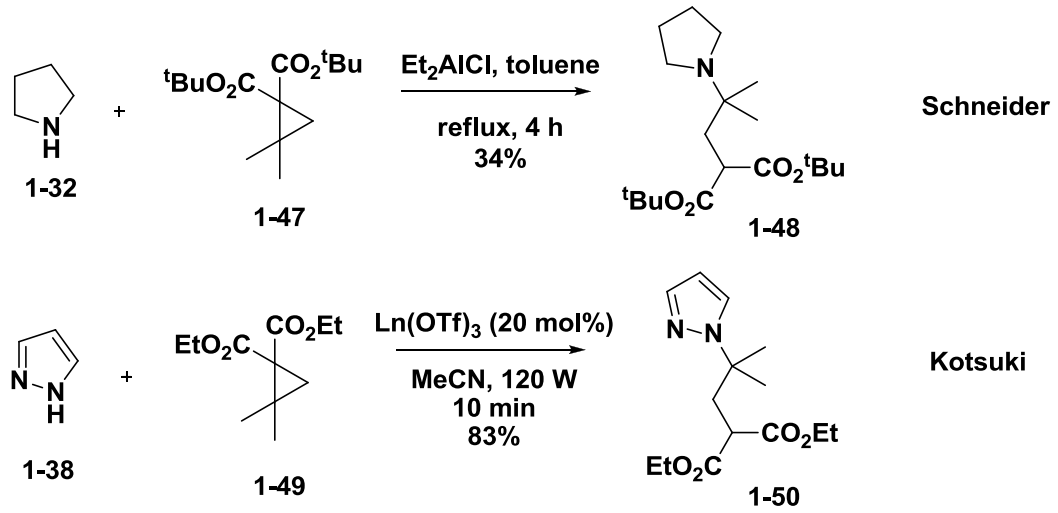
Scheme 1.14. Tang's asymmetric ring opening using secondary amines[22]

Most recently in 2014, Yakura[23] published work on an efficient ring-opening cyclization of spirocyclopropanes **1-44** using benzyl amine **1-45** (scheme 1.15). These reactions proceeded at room temperature with no additives. Yakura constructed indole frameworks such as **1-46** using this cyclopropane ring opening chemistry.



Scheme 1.15. Yakura's spirocyclopropane ring opening using benzyl amine[23]

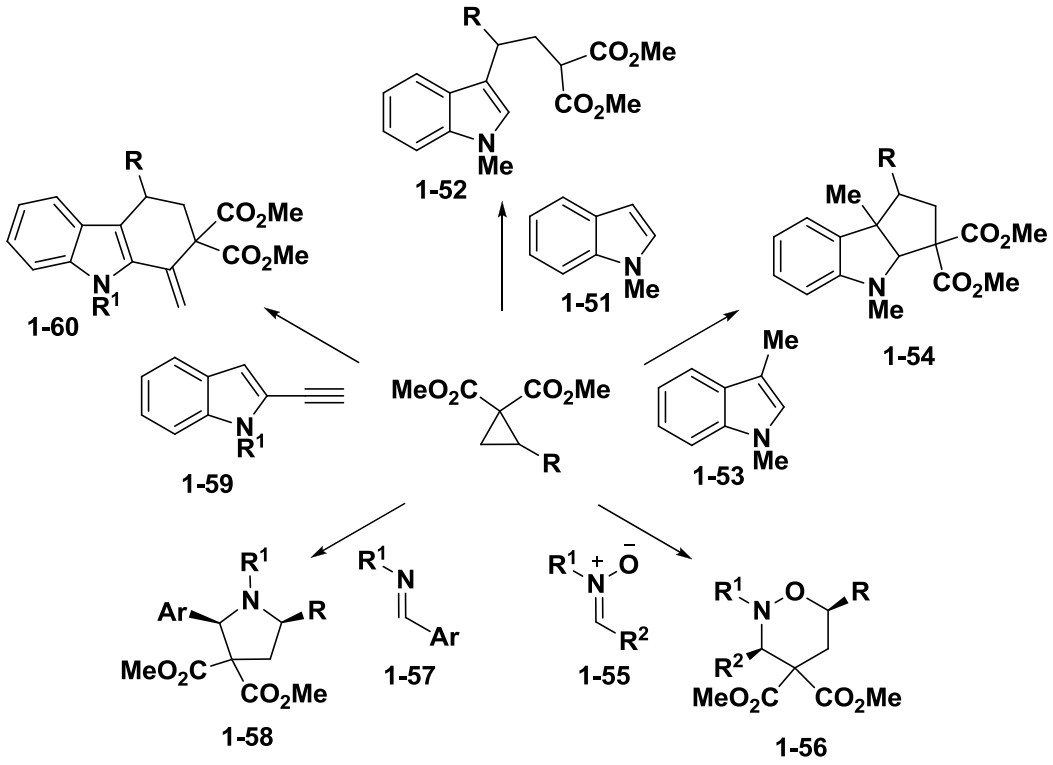
Although large efforts have been made to develop the nucleophilic ring openings of mono-substituted cyclopropanes, little work has been developed towards quaternary cyclopropanes. Two examples have been displayed in the work of Schneider and Kotsuki. Schneider and co-workers presented a pyrrolidine **1-32** opening of a vincinally dimethyl substituted quaternary cyclopropane **1-47** in modest yield to form **1-48** (Scheme 1.16).[19] Additionally, Kotsuki and co-workers showed imidazole **1-38** could also opened a dimethyl quaternary cyclopropane **1-49** under Lewis acidic conditions to yield **1-50** in excellent yield.[21]



Scheme 1.16. Examples of quaternary cyclopropane ring opening reactions

1.2.2 Use of Cyclopropanes in the Kerr Group

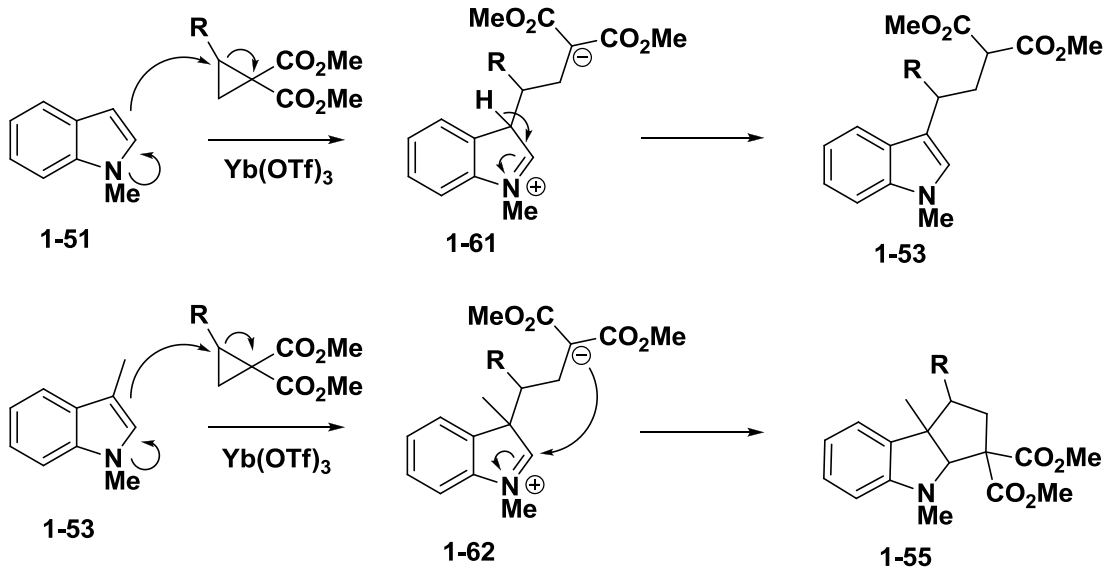
The Kerr group is renowned for its ability to use cyclopropanes effectively to access a variety of different heterocycles and incorporate them into natural product synthesis. Select uses of substituted 1,1 cyclopropane diesters within our group are summarized in scheme 1.17.



Scheme 1.17. Use of cyclopropanes in the Kerr group

The Kerr group began its research in donor acceptor cyclopropanes in 1997 when Harrington used indoles **1-51** under high pressure using Lewis acid catalysis to open cyclopropanes forming alkylated products **1-52**.[24] This work spearheaded the use of various other nucleophiles including indole **1-53**,[25] nitrones **1-55**,[26] imine **1-57**,[27] 2-alkynyl indole **1-59**,[28] amongst others.[15] Although we will not discuss it in further detail, the use of dipolarophiles has also led to formation of various five or six membered rings (such as **1-56** and **1-58**).

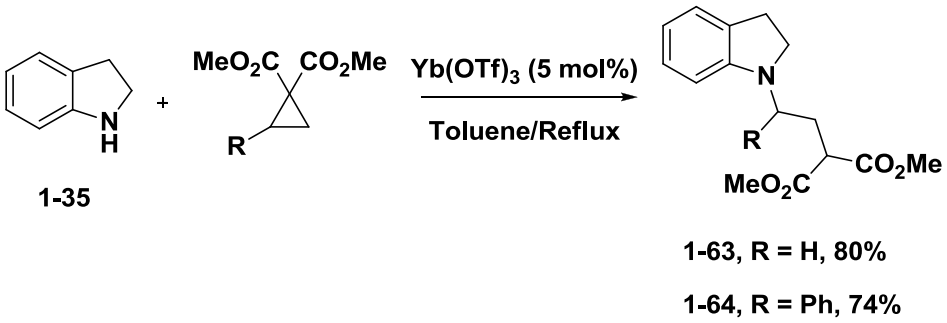
The reactivity of indoles (such as **1-51** and **1-53)** with donor acceptor cyclopropanes has been well documented within our group. Keddy and Kerr[25] in 1999 showed that by substituting the 3-position of the indole the cyclopropane forms an annulation product **1-54** instead of the typical alkylation products such as **1-52**. The mechanistic pathways of these reactions can be seen in scheme 1.18. Both pathways involve the attack of the 3-position of indole to form zwitterionic intermediates **1-61** and **1-62**, respectively.



Scheme 1.18. Substitution effects on indole reactivity with cyclopropanes

At this point both pathways vary significantly. In the case of the *N*-methyl indole zwitterion **1-61**, proton abstraction resulting in re-aromatization of the indole is the preferred mechanistic pathway forming compound **1-52**. Conversely, there is no pathway in which re-aromatization can occur with 3-methyl indole **1-62**, resulting in attack of the malonyl anion onto the iminium in a Mannich type fashion to form a ring (**1-55**). These methods are effective when trying to functionalize the 3-position of indole; however, the ability to functionalize the nitrogen of the indole with cyclopropane had not been fully explored.

In 2006, Kerr and Magolan[14] published several examples of indoline **1-35** opening cyclopropanes under Lewis acid catalysis to place a pendant malonyl group on the nitrogen atom, forming compounds such as **1-63** and **1-64** (scheme 1.19). The pendant malonyl group gave them the ability to then use manganese(III) acetate to form the 1,2 annulated products pyrroloindoles. As seen in the previous section, subjection of the malonic species to manganese(III) acetate results in the formation of a stabilized malonic radical, which readily cyclizes onto the already formed indole forming pyrroloindoles.



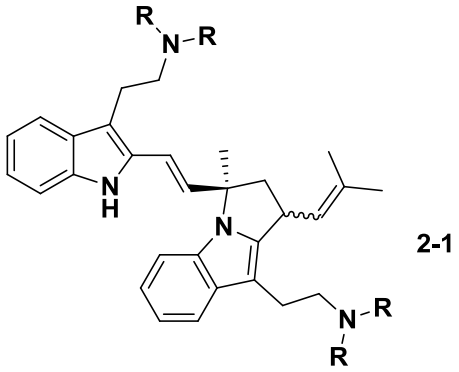
Scheme 1.19. Examples of cyclopropane ring opening by indoline[14]

With the relatively good yields obtained for this reaction sequence, it was concluded that further exploration into a complete substrate scope would be worthwhile. Knowing that quaternary cyclopropanes could be opened by nitrogen nucleophiles we envisioned using the pyrroloindole synthesis to target the flinderoles.

2 Progress towards the Flinderoles

2.1 Flinderoles: Isolation and Background

The flinderoles (Figure 2.1) were isolated from the *Flindersia acuminate* (flinderole A, **2-1a**) and *Flindersia ambionensis* (flinderole B **2-1b** and C **2-1c**) plants in 2009.[29] Isolated in Papua New Guinea, the flinderoles, **2-1a-c**, were shown to possess antimalarial activity against the *Plasmodium falciparum* parasite. Given the increase in this parasite's multi-drug resistance, greater focus has been given to exploring the flinderoles bioactivity.[30]



Flinderole A, isolated from Flindersia acuminate
Flinderole B, isolated from Flindersia ambionensis

2-1A : R = H
2-1B : R = Me

2-1C =
R = Me

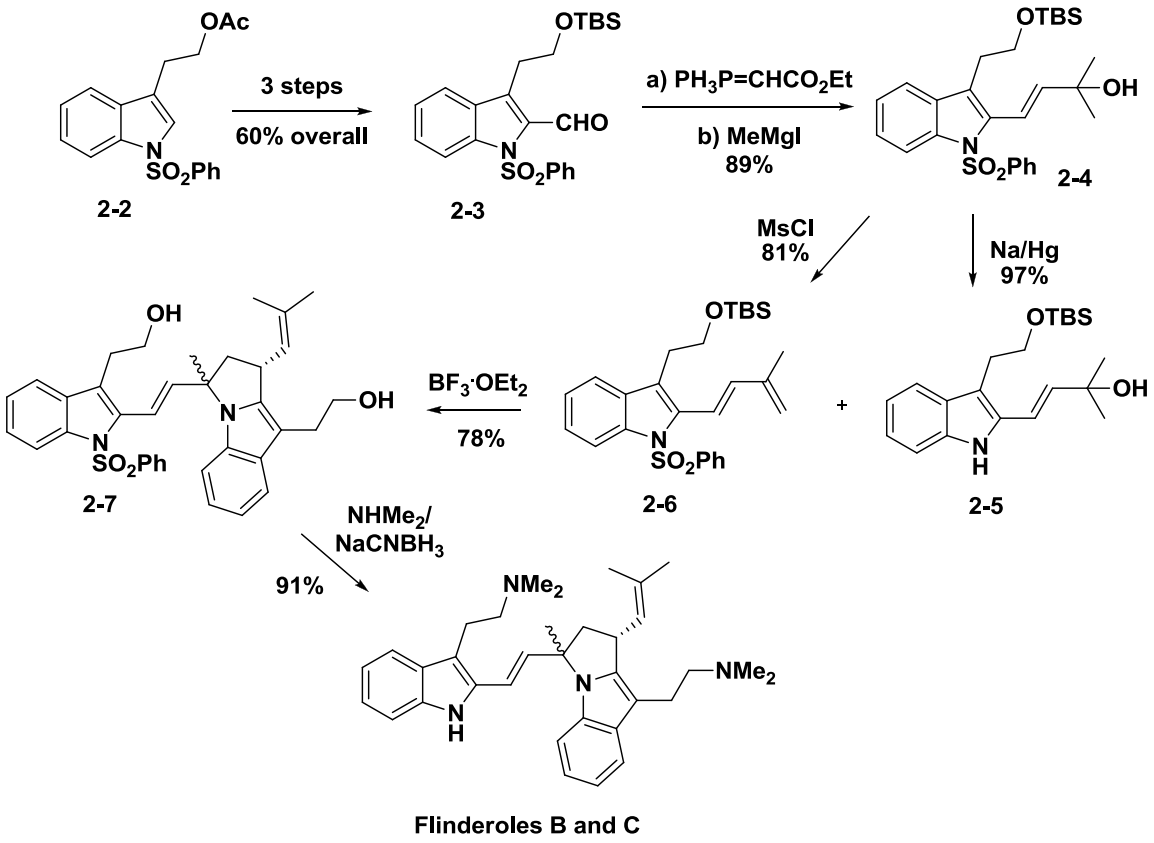
Figure 2.1. The flinderole alkaloids

Structurally, the flinderoles contains two tryptamine units bridged by a *trans*-disubstituted olefin, which is vicinal to the sole quaternary center in the compound. This chiral center is located on the pyrroloindole portion of the molecule, which also contains an isobutenyl side chain.

2.2 Previous Syntheses of the Flinderoles

There have been 3 total syntheses of the flinderoles to date. The first total synthesis was achieved in 2011 by Dethe.[31] Dethe's synthesis begins with a known protected trytophol **2-2** undergoing a protecting group switch, followed by formylation

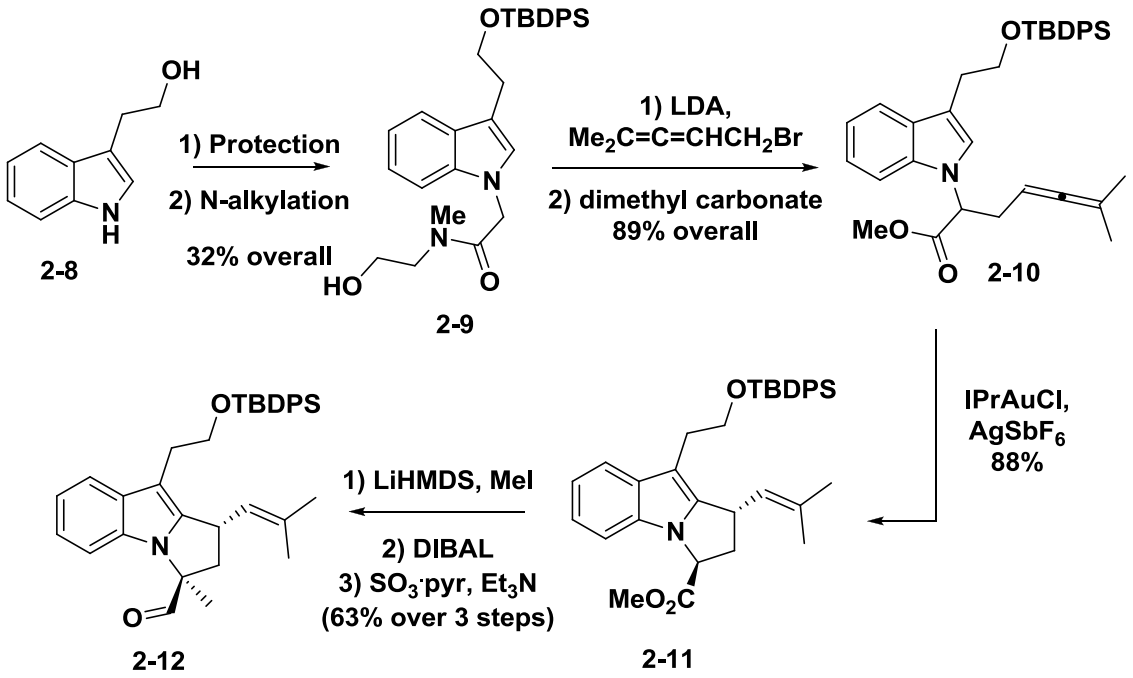
using dichloromethyl methyl ether and Horner-Wadsworth-Emmons reaction using $Ph_3P{=}CHCO_2Et$ (scheme 2.1).



Scheme 2.1. Dethe's synthesis of flinderoles B and C[31]

Treatment with methylmagnesium iodide gave tertiary alcohol **2-4**. This common intermediate was then split and carried through to different routes to access coupling partners **2-5** and **2-6** via dehydration and deprotections, respectively. Treatment of these two compounds with $BF_3{\cdot}OEt_2$ gave the desired dimerization product **2-7** (including deprotection), with moderate diastereoselectivity (4:1) in favor of the methyl and isobutylene groups being *cis*. Oxidation of the alcohols to the corresponding aldehydes, followed by reductive aminations and deprotections of the indoles, gave the flinderoles B and C, respectively. Dethe's 11 step synthesis of flinderoles B and C featured a key dimerization reaction resulting in a 17.2% overall yield.

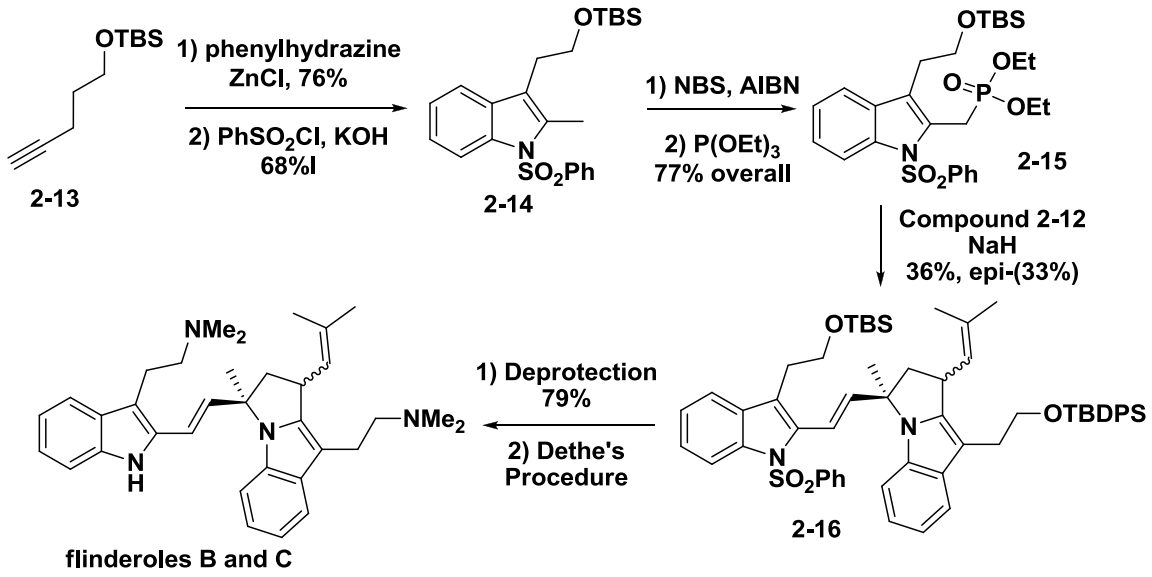
The second synthesis of the flinderoles was published only several months later by Toste and coworkers[32] using a gold-catalyzed allene hydroarylation reaction as its key step. The synthesis of the first key intermediate is summarized in scheme 2.2.



Scheme 2.2. Toste's synthesis of pyrroloindole intermediate[32]

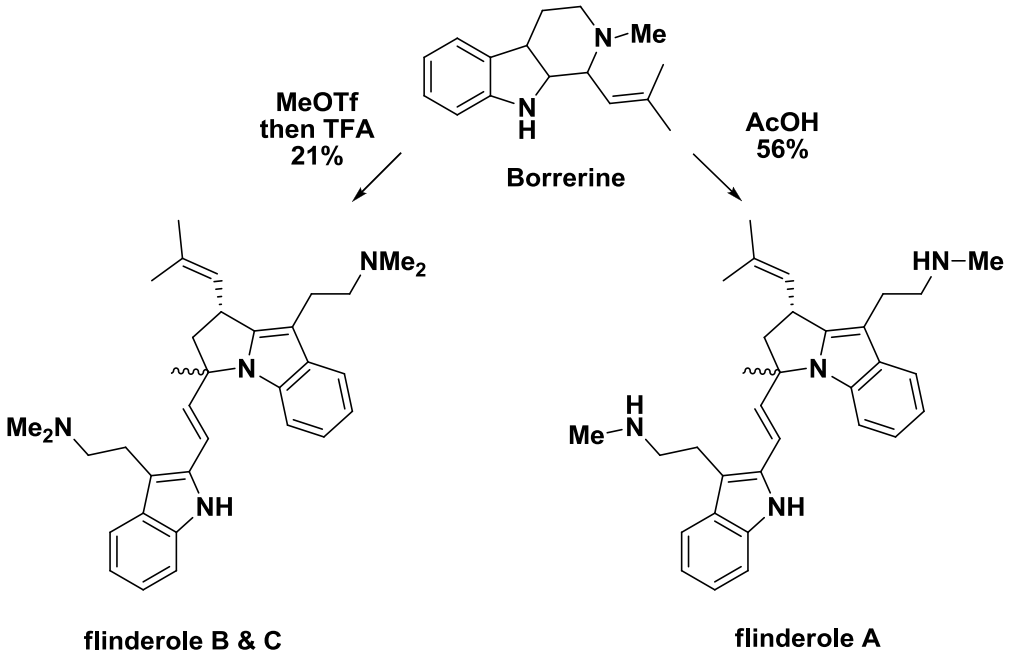
Beginning with the protection of commercially available tryptophol **2-8** followed by an alkylation of the indole nitrogen led access to amide **2-9** (scheme 2.2). Alkylation of compound **2-9** using allenyl bromide followed by conversion of the amide to the methyl ester yielded substrate **2-10** in good yield. With allene **2-10** in hand the key cyclization reaction was conducted with IPrAuCl and $AgSbF_6$ forming pyrroloindole **2-11**. Methylation and formation of the desired aldehyde **2-12** completed one of the required coupling partners. Next, Troste focused on the synthesis of the second tryptamine fragment. Protected pentyn-4-ol **2-13** was subjected to phenylhydrazine in the presence of $ZnCl_2$ followed by *N*-protection of the indole to yield compound **2-14** in good yield (scheme 2.3). A radical bromination and Arbuzov sequence resulted in phosphate **2-15**. With both fragments of the natural product in hand, a Horner-Wadsworth-Emmons olefination reaction of **2-15** and pyrroloindole **2-12** gave compound **2-16.** Deprotection of both alcohols furnished the formal synthesis, which was continued to the natural product

via the procedure described by Dethe.[31] Toste was able to synthesize flinderoles B and C in 4% overall yield.



Scheme 2.3. Toste's synthesis of flinderoles B and C[32]

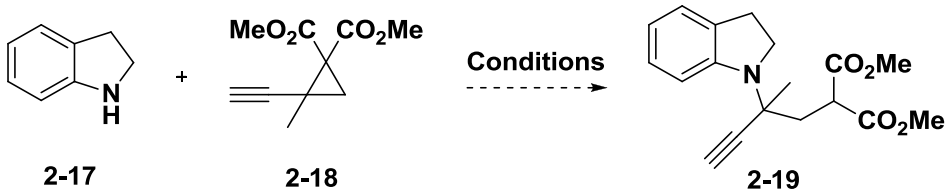
In 2013, May and coworkers[33] hypothesized that the biosynthesis of the flinderoles could stem from a dimerization of the natural product borrerine. With the key step an acid dimerization of the natural product borrerine, May was able to synthesize all of the flindersial alkaloids from only three synthetic steps from tryptamine (scheme 2.4). Each of these total syntheses is quite efficient and presents some excellent chemistry in order to construct these natural products.



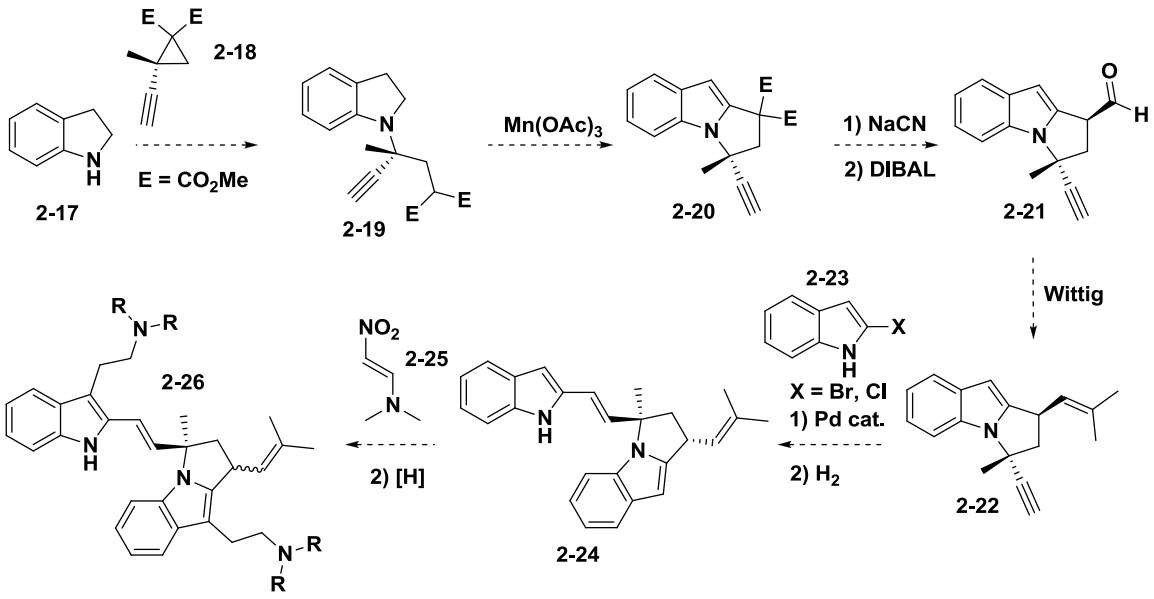
Scheme 2.4. May's biomimetic synthesis[33]

2.3 Our Proposed Synthesis

We envision accessing the flinderoles through our cyclopropane ring opening reaction using indoline as its first key step shown in scheme 2.5. With the quaternary cyclopropane ring opening of **2-18** being what we believe will give us the most difficulty, attempts towards acquiring the required compound **2-19** was my first goal within the group. In order to utilize this method we first have to develop the ideal conditions and perform a complete substrate scope.



Scheme 2.5. Our key quaternary ring opening step towards the flinderoles

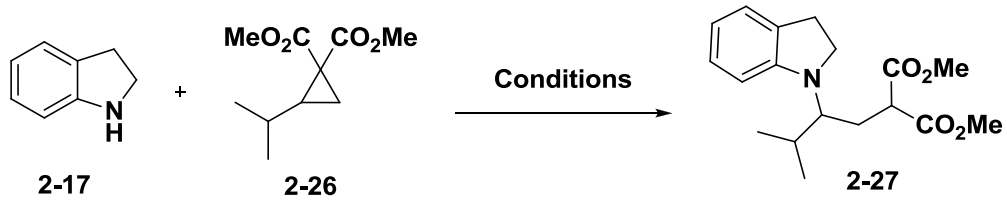


Scheme 2.6. Our proposed synthesis of the flinderoles

Should our ring opening reaction prove fruitful, our next step would be to use our manganese(III) acetate oxidative cyclization chemistry to access compound **2-20** (scheme 2.6). Krapcho decarboxylation and subsequent reduction will form aldehyde **2-21**. A Wittig olefination will yield the desired isoproylidine **2-22** and Sonogarshira coupling to a 2-haloindole **2-23** will produce compound **2-24**. Installation of both aminoethyl groups via Michael addition of **2-25** will secure the natural products.

2.4 Cyclopropane Ring Opening Reaction

The beginning of this project was focused on the expansion of the substrate scope for our cyclopropane ring opening reaction using indoline. A brief optimization of the nucleophilic attack of indoline **2-17** was investigated using an isopropyl donor acceptor cyclopropane **2-26** to form compound **2-27** as shown in table 2.1.



2-17 2-26 2-27

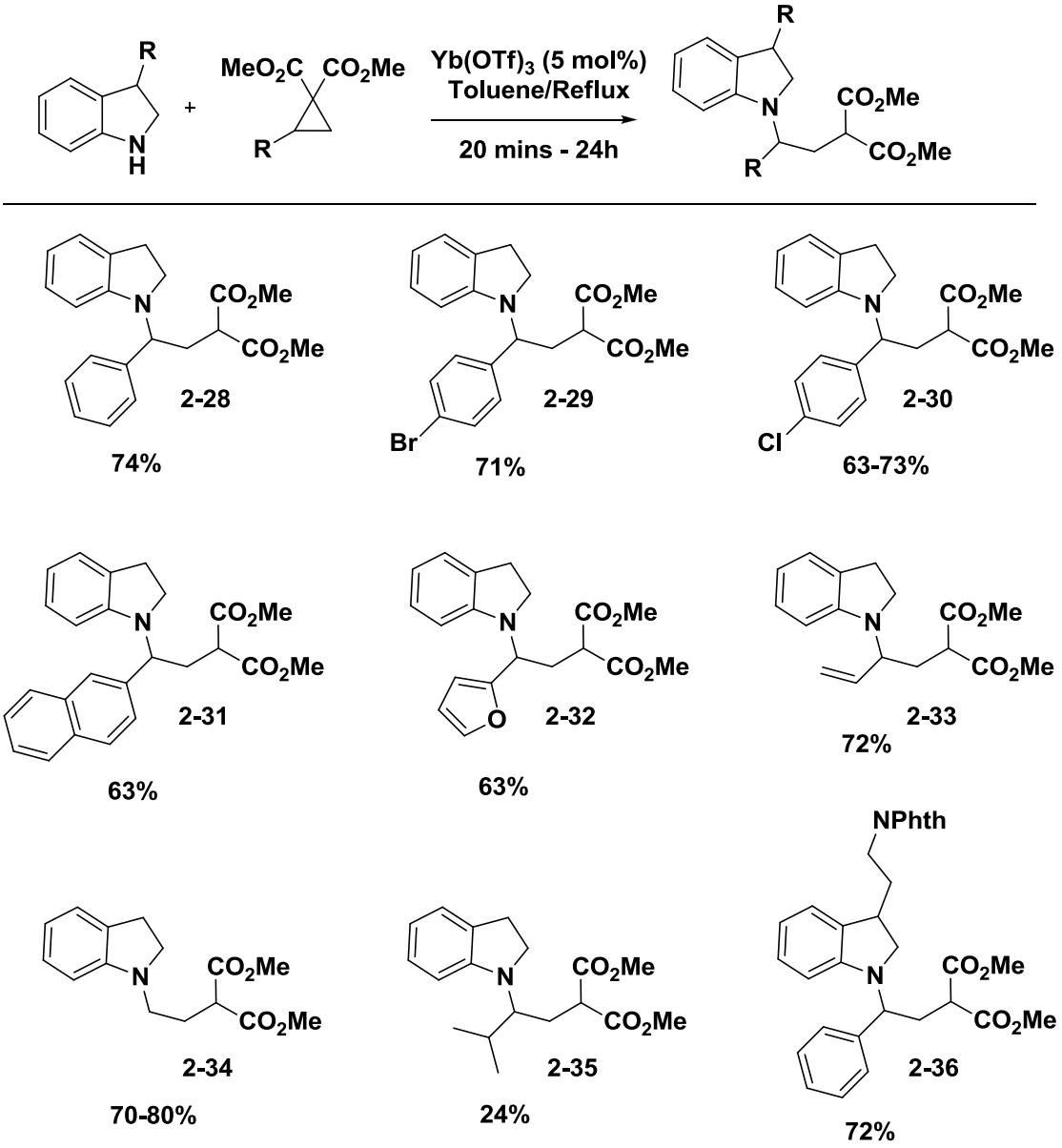
#	Equiv. 2-17:2-26	Solvent	Temp	Catalyst	Mol %	Time (h)	Yield (%)
1	1:1	Toluene	reflux	$Sc(OTf)_3$	5	24	8
2	1:1	Toluene	reflux	$Sc(OTf)_3$	5	48	8
3	1:1	Toluene	reflux	$Sc(OTf)_3$	10	48	21
4	3:1	DCE	R.T	$Sc(OTf)_3$	5	48	N/R
5	1:1	Toluene	reflux	$Yb(OTf)_3$	5	48	24
6	1:1	Toluene	reflux	$Yb(OTf)_3$	10	48	23

Table 2.1. Optimization of cyclopropane opening reaction

Based on the previous work in the group when using cyclopropanes, we began our optimization focusing on the Lewis acid catalysts: $Sc(OTf)_3$ and $Yb(OTf)_3$. In entries 1-3 of table 2.1, a catalytic amount of $Sc(OTf)_3$ was employed as the Lewis acid to promote the reaction in refluxing toluene. In the first entry using 5 mol% of the catalyst and allowing the reaction to reflux for 24 h, we were only able to isolate an 8% yield of our product **2-27**. After seeing no improvement in yield despite increasing the reaction time to 48 h, (entry 2) we decided to increase the catalyst loading from 5 mol% to 10 mol% (entry 3). This saw an improvement in yield up to 21% of our product. At this point we attempted Johnson's published conditions in which aldehydes effectively opened cyclopropanes in the presence of $Sc(OTf)_3$ at room temperature in dichloroethane in good yields (entry 4).[34] Despite our hopes that his conditions would be effective with our chemistry, they unfortunately resulted in no reaction for our substrates. At this point we decided to try switching catalysts to $Yb(OTf)_3$. Upon our first attempt, shown in entry 5, using 5 mol% of $Yb(OTf)_3$ in refluxing toluene resulted in the highest yield to date at

24%. It was postulated that increasing the catalytic loading to 10 mol% of $Yb(OTf)_3$ would increase the reaction yield, as we had seen using $Sc(OTf)_3$. We, however, did not see an increase in yield but rather a slight decrease to 23% (entry 6).

With the optimized conditions set on 5 mol% of $Yb(OTf)_3$ in refluxing toluene, the scope of our optimized reaction was to be explored. Scheme 2.7 shows the results of our cyclopropane ring openings under our optimized conditions.

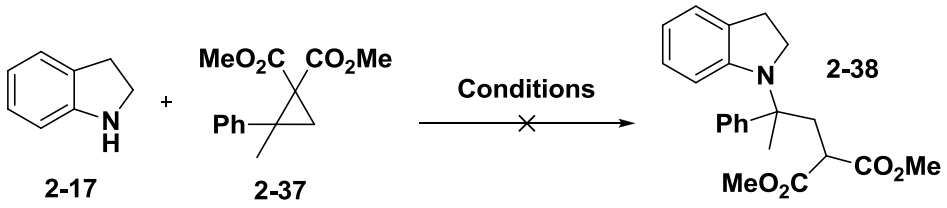


Scheme 2.7. Scope of cyclopropane ring opening reaction

A variety of different cyclopropane substrates were used, including alkyl and aryl substituents with moderate to good yields. It should be noted that an increase in steric bulk on the cyclopropanes such as **2-35** significantly decreased the overall yield of the reaction; whereas an increase in electron donating character generally resulted in improved yields. This can be explained by the donation of electrons further weakening the C-C bond. Substitution on the 3 position of the indoline **2-36** had little effect on the yield of the reaction, and allows us to construct more elaborate systems from relatively simple starting materials.

2.4.1 Attempts at Quaternary Cyclopropane Ring Openings

Despite the success of opening various mono-substituted cyclopropanes with our optimized conditions, the ability to open a quaternary cyclopropane **2-37** using indoline **2-17** has thus far proven futile (table 2.2). While most of the reaction conditions resulted in decomposition and no product **2-38**, the use of our optimized conditions (entry 1) saw the isolation of a small amount of byproduct **2-39** (figure 2.2).



Entry	Equiv.	Solvent	Conditions	Mol %	Time (h)	Yield
1	1:1	Toluene	$Yb(OTf)_3$	5	24	Decomp. + **2-39**
2	2:1	Toluene	Et_2AlCl	2 eq.	24	Decomp.
3	5:1	DCM	High Pressure/ $Yb(OTf)_3$	5	24	Decomp.

4	1.5:1	Toluene	Microwave/ $Yb(OTf)_3$	20	1	Decomp.

Table 2.2. Attempted conditions for quaternary ring opening

2-39

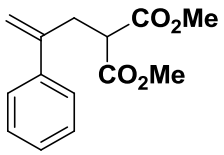
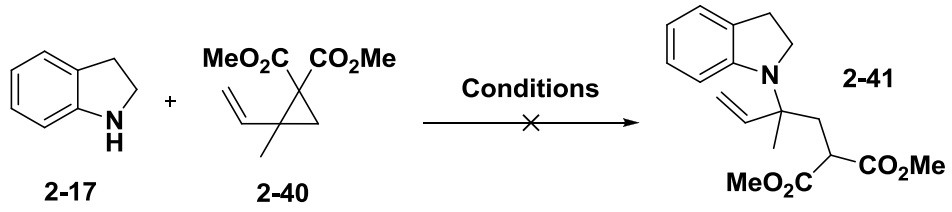


Figure 2.2. Suspected by-product

It is suspected that this byproduct results from an E1cB type mechanism in which deprotonation of the methyl group results in subsequent opening of the cyclopropane. The increase in sterics significantly decreases the ability of indoline to undergo nucleophilic attack of the cyclopropane, and elimination may become the favorable pathway for this reaction. Using our previously optimized conditions of 5 mol% of $Yb(OTf)_3$ in refluxing toluene (entry 1 of table 2.1), we were only able to isolate the suspected by-product **2-39**, as the rest of the reaction appeared to have decomposed. We then looked to use Schneider's procedure[19] of Et_2AlCl in refluxing toluene but these conditions also led to decomposition of our starting materials (entry 2). Since our group has seen success using high pressure to promote cyclopropane ring opening reactions,[24] we decided to attempt identical conditions using $Yb(OTf)_3$ and DCM at high pressure (entry 3). We were optimistic that these conditions would assist in the reaction as high pressure has been shown to promote reactions by forcing reactants into a more transition-state like orientation. Unfortunately these conditions also led to decomposition. In our final attempt to open quaternary cyclopropane **2-37** we decided to implement microwave irradiation using $Yb(OTf)_3$ and toluene. The increased temperatures obtained in the microwave did not assist in the reaction but rather led to decomposition of the materials.

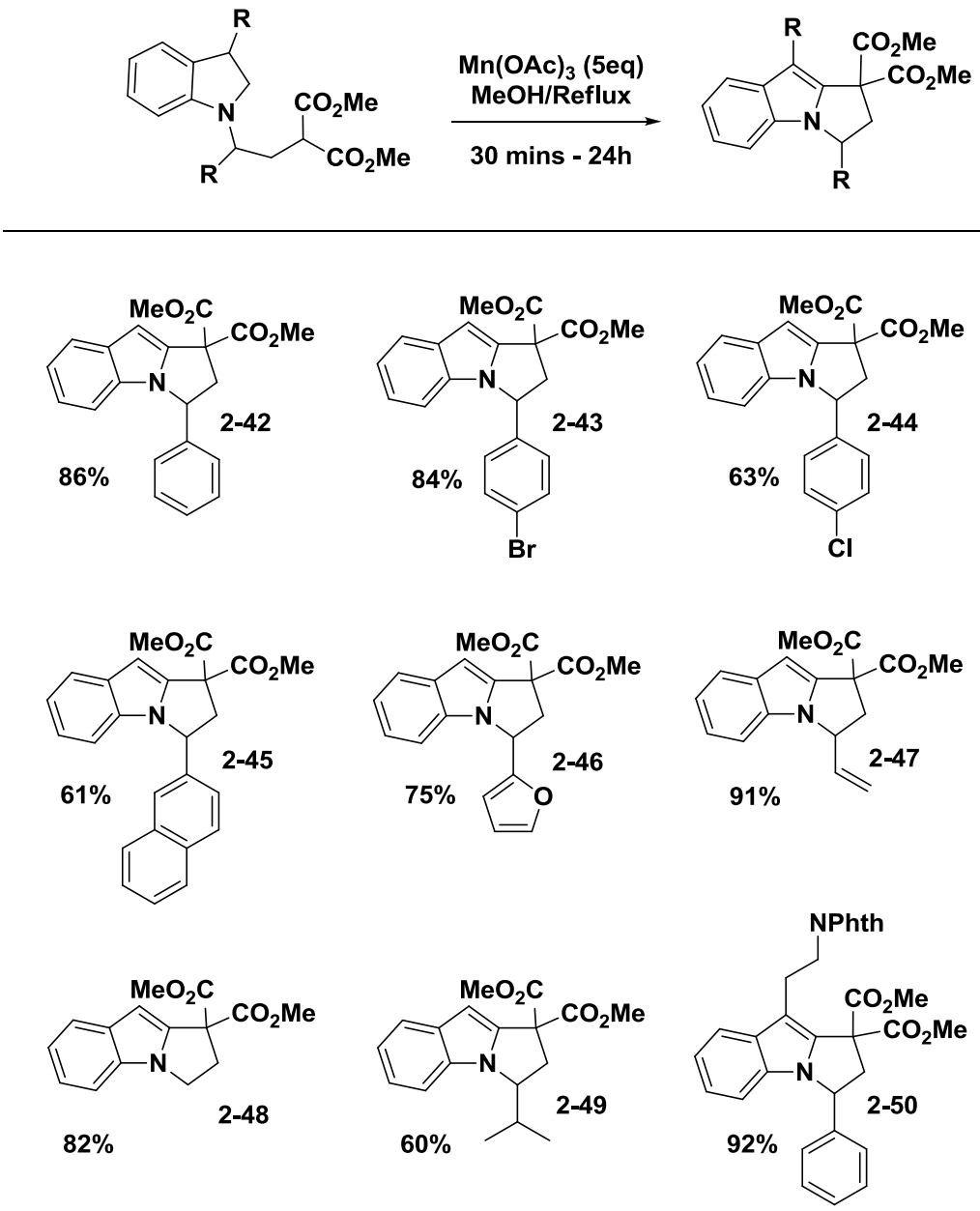
We then focused on alternative cyclopropane **2-40** in hopes that it may decrease some of the issue of sterics to yield **2-41** (scheme 2.8); however, all attempts at opening this cyclopropane also proved unsuccessful.



Scheme 2.8. Failed attempts to open an alternative quaternary cyclopropane

2.5 Formation of Pyrroloindoles

The initial formation and optimization of various pyrroloindoles was previously published by the Kerr group.[14] The indoline with pendant malonyl group was dissolved in MeOH and $Mn(OAc)_3$ was added (scheme 2.9). The reaction was heated at reflux until consumption of the starting material by TLC analysis. With several new substrates available for cyclization, $Mn(OAc)_3$ was successfully used in the formation of the pyrroloindoles in good to excellent yield. Each of these cyclization reactions proceeded with good to excellent yields ranging from 60-92%. Aryl and alkyl substituents appear to have little to no bearing on the effectiveness of these cyclizations. Substitution at the 3 position of the indoline in example **2-50** appeared to have a positive effect on the cyclization giving the highest yield of any substrates at 92%. This result could be expected due to the increased stability of the tertiary radical formed during the reaction mechanism. Overall the formation of these pyrroloindoles proceeded quickly and in good to excellent yields regardless of substrate.



Scheme 2.9. Scope of manganese(III) cyclizations to pyrroloindoles

2.6 Summary

The present chapter focused on expanding the scope of our cyclopropane ring opening reaction and attempting to apply it to the synthesis of the flinderoles. Unfortunately, attempts to open quaternary cyclopropanes using our optimized conditions

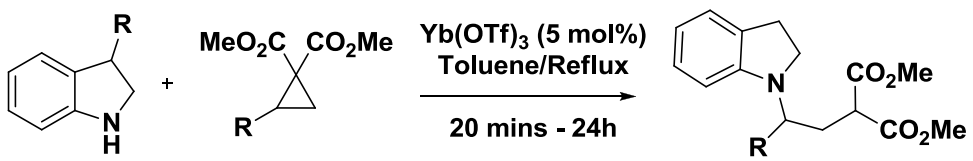
as well as other published conditions present in the literature proved unsuccessful. With other interesting projects simultaneously being studied it was decided to continue on with the methodology and begin performing the oxidative cyclizations of the substrates we had synthesized.

2.7 Experimental

General

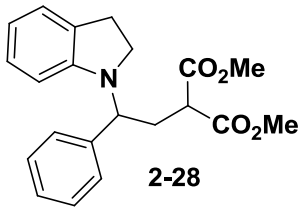
All reagents and solvents were used as purchased from Sigma Aldrich, Alfa Aesar, Caledon, Strem or VWR and used as received. Reaction progress was monitored by TLC (thin layer chromatography) (EM Science, silica gel 60 F254), visualizing with UV light, and the plates developed with vanillin. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc). NMR experiments were performed on Varian Mercury 400 and Inova 400 MHz instruments with ^{13}C operating frequencies of 100 MHz. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (J) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, spt = septet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 or 8400 mass spectrometer at an ionizing voltage of 70 eV. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}). All reactions were carried out under an atmosphere of argon unless otherwise indicated.

General Procedure for Cyclopropane Ring Opening



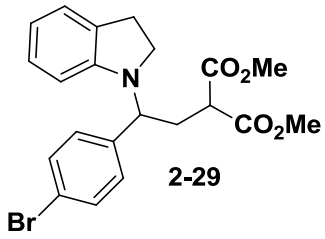
Indoline was dissolved in dry toluene in a round bottom flask equipped with a magnetic stir bar. The cyclopropane substrate and $Yb(OTf)_3$ (5 mol%) were added and the reaction

mixture was fitted with a condenser, rubber septa and purged with argon. The solution was then heated to reflux and stirred (20 mins - 24 hours) at which point TLC analysis confirmed the consumption of starting material. The solvent was removed *in vacuo* and the mixture was pre-absorbed onto silica gel and purified by flash chromatography using EtOAc/hexane solution to yield the respective alkylated indoline.



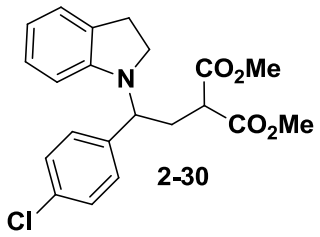
2-28

The general procedure was followed by dissolving indoline (0.047 mL, 0.419 mmol), phenyl cyclopropane (0.100 g, 0.419 mmol) and $Yb(OTf)_3$ (0.013 g, 0.021 mmol) in 5 mL of toluene. The solution was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.123 g (0.393 mmol, 72%) of compound **2-28** as a clear oil. Spectral data matched that of the literature.[14]



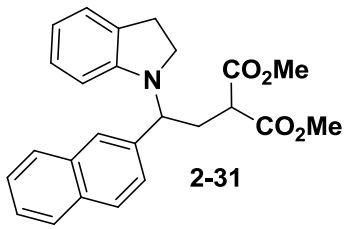
2-29

The general procedure was followed by dissolving indoline (0.030 mL, 0.272 mmol), dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (0.085 g, 0.272 mmol) and $Yb(OTf)_3$ (0.012 g, 0.019 mmol) in 5 mL of toluene . The solution was heated at refluxed overnight. Purification of the crude reaction mixture by column chromatography yielded 0.084 g (0.194 mmol, 71%) of compound **2-29** as a clear oil. Rf = 0.53 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 (broad d, J = 8.8 Hz, 1H), 7.16 (broad d, J = 8.8 Hz, 2H), 7.04 (dd, J = 8.2, 7.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H, 6.64 (dd, 7.6, 7.0 Hz, 1H), 6.54 (d, J = 7.6, 1H), 4.74 (dd, J = 9.97, 5.87 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.56 (dd, J = 7.6, 7.0 Hz, 1H), 3.4 (m, 1H), 3.07 (m, 1H), 2.90 (m, 2H), 2.67 (ddd, J = 14.1, 10.0, 7.0 Hz, 1H), 2.52 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.7, 169.6, 150.8, 137.7, 131.6, 129.40, 129.36, 127.3, 124.7, 121.5, 117.4, 106.8, 56.0, 52.6, 52.5, 49.1, 46.2, 30.4, 28.0; **FT-IR** (thin film, cm- 1) v_{max} = 2952, 2925, 2853, 1750, 1605, 1487, 1258, 1156, 746; **HRMS** calc'd for $C_{21}H_{22}BrNO_4$ [M+] 431.0732, found 431.0724.



2-30

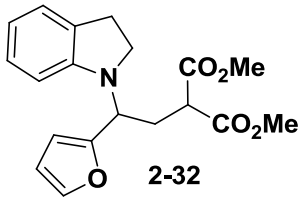
The general procedure was followed by dissolving indoline (0.041 mL, 0.373 mmol), dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate (0.100 g, 0.272 mmol) and $Yb(OTf)_3$ (0.012 g, 0.019 mmol) in 5 mL of toluene. The solution was refluxed for 3 h, at which point TLC analysis confirmed complete consumption of the starting materials. Purification of the crude reaction mixture by column chromatography yielded 0.106 g (0.274 mmol, 73%) of compound **2-30** as a clear oil. Rf = 0.48 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.27 (m, 2H), 7.21 (m, 2H), 7.03 (m, 2H), 6.61 (t, J = 7.0 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 4.77 (dd, J = 10.2, 5.5 Hz, 1H) 3.72 (s, 3H), 3.66 (s, 3H), 3.58 (dd, J = 7.4, 7.0 Hz, 1H), 3.39 (dt, J = 8.8, 5.5 Hz, 1H), 3.03 (m, 1H), 2.90 (m, 2H), 2.66 (ddd, J = 14.1, 10.2, 7.0 Hz, 1H), 2.51 (ddd, J = 14.1, 7.4, 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.7, 169.6, 137.2, 133.4, 129.5, 129.0, 128.6, 127.3, 124.7, 117.5, 106.8, 56.0, 52.6, 52.5, 49.1, 46.3, 30.4, 28.0; **FT-IR** (thin film, cm- 1) v_{max} = 2951, 2847, 1733, 1489, 1258, 1156, 746; **HRMS** calc'd for $C_{21}H_{22}ClNO_4$ [M+] 387.1237, found 387.1246.



2-31

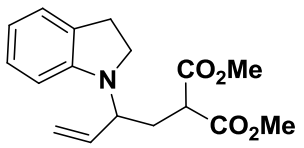
The general procedure was followed by dissolving indoline (0.039 mL, 0.352 mmol), dimethyl 2-(naphthalen-2-yl)cyclopropane-1,1-dicarboxylate (0.100 g, 0.352 mmol), and $Yb(OTf)_3$ (0.011 g, 0.017 mmol) in 5 mL of toluene . The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.089 g (0.393 mmol, 63%) of compound **2-31** as a white solid. Rf = 0.52 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.0 Hz, 1H), 7.88 (m, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 7.04 Hz, 1H), 7.51-7.47 (m, 3H), 7.14 (dd, J = 8.21, 7.6 Hz, 1H), 7.03 (d, J = 7.0 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.65 (dd, 7.6, 7.0 Hz, 1H), 5.54 (t, J = 7.6 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.56 (dd, J = 8.2, 5.9 Hz, 1H), 3.44 (m, 1H), 2.99 (m, 1H), 2.91

(m, 1H), 2.79 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.8, 169.6, 150.5, 134.3, 134.1, 132.2, 129.5, 128.7, 128.4, 127.5, 126.5, 125.8, 124.9, 124.5, 123.9, 123.6, 116.9, 106.1, 52.7, 52.5, 52.1, 48.8, 47.1, 28.3, 28.0; **FT-IR** (thin film, cm- 1) v_{max} = 3047, 2951, 2849, 1733, 1605, 1259, 1155; **HRMS** calc'd for $C_{25}H_{25}NO_4$ [M+] 403.1784, found 403.1799.



2-32

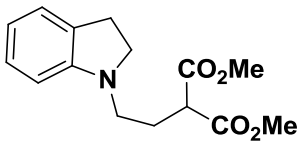
The general procedure was followed by dissolving indoline (0.050 mL, 0.446 mmol), and dimethyl 2-(furan-2-yl)cyclopropane-1,1,-dicarboxylate (0.100 g, 0.446 mmol), and $Yb(OTf)_3$ (0.014 g, 0.022 mmol) in 5 mL of toluene. The reaction was heated at reflux for 4 h. Purification of the crude reaction mixture by column chromatography yielded 0.110 g (0.320 mmol, 72%) of compound **2-32** as a light yellow oil. Rf = 0.62 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 1.8, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.64 (dd, J = 7.6, 7.0 Hz, 1H), 6.56 (d, J = 7.6 Hz, 1H), 6.26 (dd, 3.5, 1.8 Hz, 1H), 6.17 (d, J = 3.52 Hz, 1H), 4.80 (dd, J = 10.0, 6.5 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.65 (dd, J = 7.6, 7.0 Hz, 1H), 3.44 (ddd, J = 8.8, 8.2, 5.3 Hz, 1H), 3.03 (m, 1H), 2.90 (m, 2H), 2.58 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.8, 169.5, 152.7, 150.9, 142.0, 129.7, 127.1, 124.5, 117.8, 109.8, 107.8, 107.4, 52.6, 52.5, 51.2, 48.7, 47.2, 29.4, 28.1; **FT-IR** (thin film, cm- 1) v_{max} = 3024, 2952, 2847, 1734, 1606, 1486, 1259, 1156, 1013, 745; **HRMS** calc'd for $C_{19}H_{21}NO_5$ [M+] 343.1420, found 343.1421.



2-33

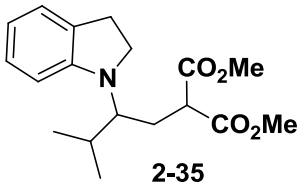
The general procedure was followed by dissolving indoline (0.060 mL, 0.543 mmol), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (0.100 g, 0.543 mmol) and $Yb(OTf)_3$ (0.017 g, 0.271 mmol) in 5 mL of toluene. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.119 g (0.393 mmol, 72%) of compound **2-33** as a clear oil. Rf = 0.55 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.06 (t, J = 7.82 Hz, 2H), 6.63 (t, J

= 7.4, 1H), 6.43 (d, J = 7.8 Hz, 1H), 5.78 (ddd, J = 17.2, 10.9, 6.3 Hz, 1H), 5.23 (m, 2H), 4.06 (dd, J = 7.0, 7.4, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.62 (m, 1H), 3.38 (m, 1H), 3.31 (m, 1H), 2.93 (m, 2H), 2.32 (t, J = 7.03, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.69. 169.93, 134.62, 130.07, 127.19, 124.51, 121.61, 119.66, 118.11, 107.76, 55.72, 52.55, 48.71, 46.74, 30.37, 28.17; **FT-IR** (thin film, cm- 1) v_{max} = 3081, 3050, 2953, 1739, 1434, 1260, 1210, 746; **HRMS** calc'd for $C_{17}H_{21}NO_4$ [M+] 303.1471, found 303.1462.



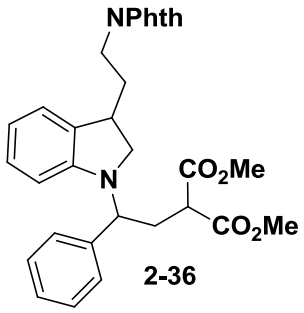
2-34

The general procedure was followed by dissolving indoline (0.071 mL, 0.633 mmol), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (0.087 mL, 0.633 mmol) and $Yb(OTf)_3$ (0.020 g, 0.031 mmol) in 5 mL of toluene. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 2.21 g (8.00 mmol, 80%) of compound **2-34** as a yellow oil. All spectral data matched that of the literature.[14]



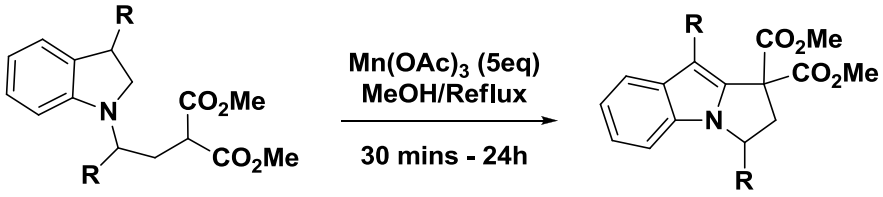
2-35

The general procedure was followed by dissolving indoline (0.060 mL, 0.543 mmol), dimethyl-2-isopropylcyclopropane-1,1-dicarboxylate (0.109 g, 0.543 mmol) and $Yb(OTf)_3$ (0.017 g, 0.027 mmol) in 5 mL of toluene. The reaction was heated at reflux for 24 h. Purification of the crude reaction mixture by column chromatography yielded 0.043 g (0.135 mmol, 24%) of compound **2-35** as a clear oil. Rf = 0.65 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.96 (m, 2H), 6.48 (t, J = 7.4 Hz, 1H), 6.22 (d, J = 7.8 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.44 (m, 2H), 3.35 (m, 2H), 2.98 (m, 2H), 2.36 (m, 1H), 2.06 (ddd, J = 9.0, 6.6, 5.1 Hz, 1H), 1.89 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 170.2, 169.8, 152.0, 128.0, 127.1, 124.4, 115.7, 105.2, 58.6 (broad, likely 2 peaks), 52.32, 52.28, 49.2, 30.9, 29.6, 28.0, 20.8, 20.4; **FT-IR** (thin film, cm- 1) v_{max} = 3024, 2952, 2847, 1734, 1606, 1486, 1259, 1156, 1013, 745; **HRMS** calc'd for $C_{18}H_{25}NO_4$ [M+] 319.1784, found 319.1780.



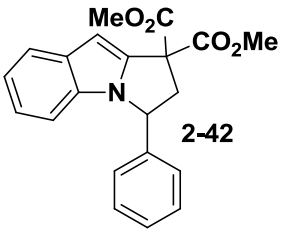
The general procedure was followed by dissolving phtalamide protected 2-(indolin-3-yl)ethanamine (0.124 g, 0.427 mmol), phenyl cyclopropane (0.100 g, 0.427 mmol) and $Yb(OTf)_3$ (0.013 g, 0.021 mmol). The reaction was heated at reflux for 20 mins. Purification of the crude reaction mixture by column chromatography yielded 0.172 g (0.327 mmol, 77%) and two diastereomers of compound **2-36** as a clear oil. Rf = 0.55 (40% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): (two diastereomers) δ = 7.84 (m, 4H), 7.71 (m, 4H), 7.28 (m, 8H), 7.25 (m, 2H), 7.06 (m, 4H), 6.62 (dd, J = 7.6, 7.6 Hz, 2H), 6.54 (m, 2H), 4.77 (m, 2H), 3.78 (m, 2H), 3.72 (diastereomer A (s, 3H)), 3.71 (diastereomer A+B (s, 6H)), 3.67 (diastereomer B (s, 3H)), 3.66-3.55 (m, 5H), 3.33 (t, J = 8.8 Hz, 1H), 3.25 (dd, J = 8.8, 5.3 Hz, 1H), 3.18 (m, 1H), 3.10 (m, 1H), 2.85 (t, J = 8.8 Hz, 1H), 2.69 (m, 2H), 2.56 (m, 2H), 2.09 (m, 2H), 1.90 (m, 1H), 1.67 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): (both diastereomers) δ = 169.7, 169.5, 168.2, 168.1, 150.7, 150.5, 138.5, 128.4, 133.8, 132.1, 132.0, 131.9, 131.8, 128.4, 127.73, 127.69, 127.6, 127.55, 127.53, 127.49, 124.0, 123.6, 123.1, 117.24, 117.23, 106.9, 106.88, 56.4, 56.3, 52.5, 52.46, 52.36, 52.1, 52.0, 49.1, 48.8, 37.8, 37.5, 35.83, 35.8, 33.5, 32.6, 30.5, 30.0; **FT-IR** (thin film, cm- 1) ν_{max} = 3029, 2951, 1750, 1732, 1712, 1604, 1487, 1397, 1262, 1158, 912, 722; **HRMS** calc'd for $C_{31}H_{30}N_2O_6$ [M+] 526.2104, found 526.2121.

General Procedure for $Mn(OAc)_3$ Cyclization



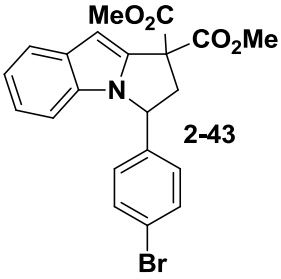
The indoline substrate was dissolved in dry MeOH in a round bottom flask equipped with a magnetic stir bar. $Mn(OAc)_3{\cdot}H_2O$ was added (5.0 eq) and the reaction mixture was

fitted with a condenser, rubber septa and purged with argon. The brown solution was then heated to reflux and allowed to stir overnight (30 mins-24 hours) at which point TLC analysis confirmed the consumption of starting material. The solvent was removed *in vacuo* and the resulting brown solid was partitioned between EtOAc and brine. The organic layer was removed and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with water three times and brine once, dried with $MgSO_4$ and solvent removed *in vacuo*. The reaction mixture was pre-absorbed onto silica gel and purified by flash chromatography using EtOAc/hexane solution to yield the respective pyrroloindole.



2-42

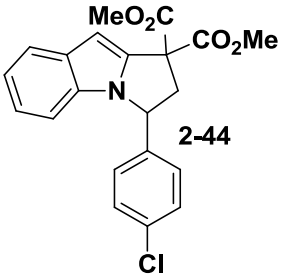
The general procedure was followed by dissolving compound **2-28** (0.050 g, 0.142 mmol), $Mn(OAc)_3 \cdot H_2O$ (0.151 g, 0.566 mmol) in 5 mL of MeOH. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.042 g (0.121 mmol, 86%) of compound **2-42** as a white solid. Rf = 0.50 (30% EtOAc in hexanes). Spectral data for this compound matched that of the literature.[14]



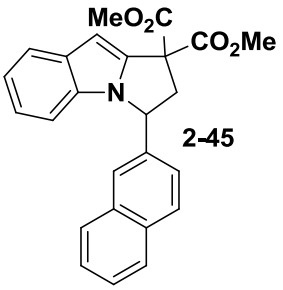
2-43

The general procedure was followed by dissolving compound **2-29** (0.075 g, 0.175 mmol), and $Mn(OAc)_3$ (0.234 g, 0.875 mmol) in 5 mL of MeOH. The reaction as heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.063 g (0.147 mmol, 84%) of compound **2-43** as a clear oil. Rf = 0.55 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.0 Hz, 1H), 7.49, (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.07 (dd, J = 7.4, 7.0 Hz, 1H), 6.99 (dd, J = 8.2, 7.0 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.61 (s, 1H), 5.49 (t, J = 7.4 Hz, 1H), 3.82 (s, 3H), 3.79 (s,

3H), 3.66 (dd, J = 13.7, 7.4 Hz, 1H), 2.96 (dd, J = 13.7, 7.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.21, 169.18, 139.2, 138.5, 132.9, 132.3, 132.1, 128.4, 122.3, 121.7, 121.4, 120.0, 110.5, 97.2, 59.5, 58.5, 53.5, 53.4, 47.2; **FT-IR** (thin film, cm- 1) v_{max} = 2953, 2923, 2850, 1738, 1257, 747; **HRMS** calc'd for $C_{21}H_{18}BrNO_4$ [M+] 427.0419, found 427.0410.

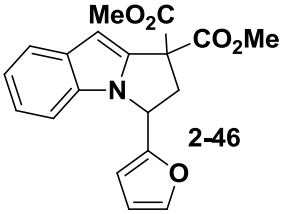


The general procedure was followed by dissolving compound **2-30** (0.048 g, 0.123 mmol), and $Mn(OAc)_3$ (0.164 g, 0.614 mmol) in 3 mL of MeOH. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.029 g (0.077 mmol, 63%) of compound **2-44** as a clear oil. Rf = 0.60 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.07 (dd, J = 8.2, 7.0 Hz, 1H), 6.98 (dd, J = 8.2, 7.0 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.61 (s, 1H) 5.50 (dd, J = 7.6, 7.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (dd, J = 13.49, 7.0 Hz, 1H), 2.97 (dd, 13.8, 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.2, 139.2, 138.0, 134.2, 132.9, 132.4, 129.2, 128.1, 121.7, 121.4, 120.0, 110.5, 105.4, 97.2, 59.5, 58.6, 53.5, 53.4, 47.3; **FT-IR** (thin film, cm- 1) v_{max} = 2953, 2924, 2852, 1739, 1274, 1258, 746; **HRMS** calc'd for $C_{21}H_{18}ClNO_4$ [M+] 383.0924, found 383.0931.



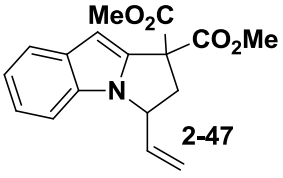
The general procedure was followed by dissolving compound **2-31** (0.068 g, 0.168 mmol), $Mn(OAc)_3 \cdot H_2O$ (0.225 g, 0.841 mmol) in 5 mL of MeOH. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.041 g (0.103 mmol, 61%) of compound **2-45** as a white solid. Rf = 0.56 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.13 (broad m, 1H), 7.94 (broad m, 1H), 7.82 (broad m, 1H), 7.67-7.52 (broad m, 4H), 7.31 (broad m, 1H), 7.08 (broad m, 1H), 7.00

(broad m, 1H), 6.91 (broad m, 1H), 6.80 (broad m, 1H), 6.69 (s, 1H), 6.37 (broad m, 1H), 4.02, broad m, 1H), 3.85, s, 3H), 3.66 (broad s, 3H), 3.06 (broad m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.4, 169.2, 135.0, 133.9, 132.9, 132.6, 130.3, 129.2, 128.3, 126.7, 125.9, 125.4, 122.8, 122.5, 121.6, 121.4, 120.0, 111.1, 97.3, 58.6, 56.0, 53.6, 53.2, 46.3, 29.7; **FT-IR** (thin film, cm- 1) v_{max} = 3052, 2953, 1739, 1454, 1251, 748; **HRMS** calc'd for $C_{25}H_{21}NO_4$ [M+] 399.1471, found 399.1461.



2-46

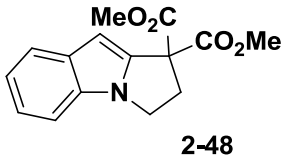
The general procedure was followed by dissolving compound **2-32** (0.150 g, 0.438 mmol), $Mn(OAc)_3{\cdot}H_2O$ (0.587 g, 2.19 mmol) in 5 mL of MeOH. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.111 g (0.327 mmol, 75%) of compound **2-46** as a white solid. Rf = 0.41 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (m, 1H), 7.41 (m, 1H), 7.06 (m, 2H), 6.97 (m, 1H), 6.57 (s, 1H), 6.39 (m, 2H), 5.64 (dd, J = 7.4, 7.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.54 (dd, J = 13.7, 7.4 Hz, 1H), 3.33 (dd, J = 13.4, 7.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.29, 169.06, 151.09, 143.02, 138.35, 132.66, 132.60, 121.72, 121.32, 119.95, 110.47, 110.04, 108.72, 97.08, 58.33, 53.53, 53.17, 43.10; **FT-IR** (thin film, cm- 1) v_{max} = 2953, 1740, 1453, 1270, 1220, 746; **HRMS** calc'd for $C_{19}H_{17}NO_5$ [M+] 339.1107, found 339.1116.



2-47

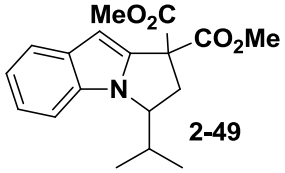
The general procedure was followed by dissolving compound **2-33** (0.077 g, 0.253 mmol), and $Mn(OAc)_3$ (0.339 g, 1.2 mmol) in 5 mL of MeOH. The reaction was heated at reflux overnight. Purification of the crude reaction mixture by column chromatography yielded 0.069 g (0.231 mmol, 91%) of compound **2-47** as a white solid. Rf = 0.60 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.21 Hz, 1H), 7.12-7.08 (m, 2H), 6.53 (s, 1H), 5.99 (ddd, J = 17.0, 10.0, 8.2 Hz, 1H), 5.50 (d, J = 17.0 Hz, 1H), 5.37 (d, J = 10.6 Hz, 1H), 5.00 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.40 (dd, J = 13.5, 7.6 Hz, 1H), 2.96 (dd, J = 13.5, 6.5 Hz, 1H); **^{13}C**

NMR (100 MHz, $CDCl_3$): δ = 169.3, 138.6, 136.8, 132.9, 132.7, 121.5, 121.3, 119.8, 118.8, 110.3, 96.8, 59.1, 58.4, 53.4, 53.3, 43.9, (41.9 artifact from NMR), 29.7; **FT-IR** (thin film, cm- 1) v_{max} = 2953, 2852, 1739, 1454, 1273, 746; **HRMS** calc'd for $C_{17}H_{17}NO_4$ [M+] 299.1158, found 299.1148.



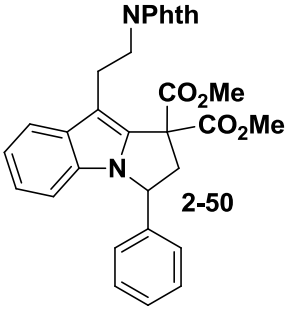
2-48

The general procedure was followed by dissolving compound **2-34** (0.120 g, 0.433 mmol), and $Mn(OAc)_3$ (0.482 g, 1.80 mmol) in 5 mL of MeOH. Purification of the crude reaction mixture by column chromatography yielded 0.097 g (0.355 mmol, 82%) of compound **2-48** as a white solid. Spectral data for this compound matched that of the literature.[14]



2-49

The general procedure was followed by dissolving compound **2-35** (0.022 g, 0.069 mmol), and $Mn(OAc)_3$ (0.093 g, 0.345 mmol) in 2 mL of MeOH. The reaction was at reflux for 6 h at which point TLC analysis confirmed consumption of the starting material. Purification of the crude reaction mixture by column chromatography yielded 0.013 g (0.042 mmol, 60%) of compound **2-49** as a clear oil. Rf = 0.67 (30% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.63 (broad dd, J = 8.2, 1.2 Hz, 1H), 7.39 (dd, J = 7.4, 0.8 Hz, 1H), 7.17 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.11 (ddd, J = 7.8, 7.03, 0.8 Hz, 1H), 6.52 (s, 1H), 4.60 (1H, ddd, J = 7.8, 6.6, 4.7 Hz, 1H), 3.87 (s, 2H), 3.77 (s, 3H), 3.21 (dd, J = 14.1, 7.8 Hz, 1H), 2.98 (dd, J = 14.1, 6.6 Hz, 1H), 2.82 (dqq, J = 7.0, 6.6, 4.7 Hz, 1H), 1.11 (d, J = 7.0 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.7, 139.4, 132.9, 132.5, 121.4, 121.3, 119.7, 110.3, 96.4, 61.4, 53.4, 53.3, 36.7, 29.6, 19.3., 14.5; **FT-IR** (thin film, cm- 1) v_{max} = 2956, 2920, 2849, 1739, 1248, 1106, 746; **HRMS** calc'd for $C_{18}H_{21}NO_4$ [M+] 315.1471, found 315.1469.



The general procedure was followed by dissolving indoline **2-36** (0.165 g, 0.313 mmol), $Mn(OAc)_3 \cdot H_2O$ (0.420 g, 1.56 mmol) and MeOH (4 mL). The reaction was at reflux for 30 mins at which point TLC analysis confirmed consumption of the starting material Purification of the crude reaction mixture by column chromatography yielded 0.151 g (0.289 mmol, 92%) of compound **2-50** as a white solid. Rf = 0.62 (40% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.2 Hz, 1H), 7.88 (m, 2H), 7.73 (m, 2H), 7.37 (m, 3H), 7.30 (m, 2H), 7.11 (apparent t, J = 7.0 Hz, 1H), 6.98 (apparent t, J = 7.0 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 5.49 (t, J = 7.4 Hz, 1H), 4.00 (m, 2H), 3.91 (s, 6H), 3.77 (dd, J = 13.3, 7.0 Hz, 1H), 3.25 (m, 2H), 2.98 (dd, J = 13.3, 7.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.5, 169.3, 168.3, 139.3, 136.0, 133.8, 132.6, 132.32, 132.27, 128.9, 128.3, 126.8, 123.1, 121.8, 119.8, 119.7, 110.6, 106.5, 59.9, 58.7, 53.6, 53.5, 48.3, 37.7, 24.0; **FT-IR** (thin film, cm- 1) ν_{max} = 3055, 3031, 2953, 1737, 1712, 1397, 1363, 1246, 911, 716; **HRMS** calc'd for $C_{31}H_{26}N_2O_6$ [M+] 522.1791, found 522.1793.

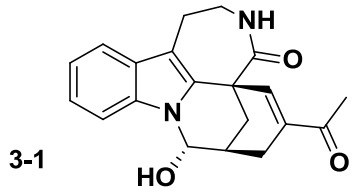
3 Progress towards Tronocarpine, Chippiine and Dippinine B

3.1 Introduction

With the scope of utilizable substrates that manganese(III) acetate can oxidatively cyclize onto indoles expanding, the search for additional natural products to pursue became enticing. The first section of this chapter contains background information on the first target we wished to pursue, tronocarpine. The following sections discuss several proposed syntheses, model studies, and our general progress towards tronocarpine. Lastly, in the final sections we came across a particular route that would allow us to construct a common intermediate that could be applied towards several related natural products including: tronocarpine, chippiine, and dippinine B.

3.2 Tronocarpine: Isolation and Background

The second natural product that appeared to be an excellent synthetic target for our oxidative cyclization chemistry is tronocarpine **3-1**, which was isolated in 2000 by Kam and co-workers.[35] It was extracted from the bark of the Malaysian flowering shrub *Tabernaemontana corymbosa*. Kam *et al.* were able to determine the structure using ^{1}H and ^{13}C NMR, COSY, HMQC, HMBC, as well as UV and IR spectra. Tronocarpine consists of a seven-membered lactam and two six-membered rings, including the presence of an unsaturated methyl ketone, and hemiaminal functionality at the indole nitrogen.



3-1

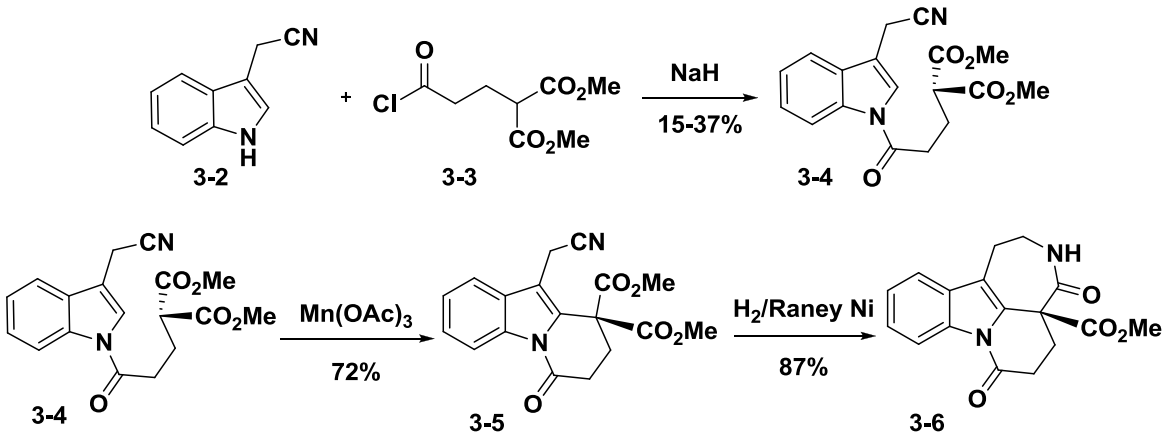
Tronocarpine, isolated from *Tabernaemontana corymbosa*

Figure 3.1. The structure of tronocarpine

While the structural framework of tronocarpine was synthesized by our group in 2006,[14] and by Martinez in 2014,[36] there have been no total syntheses to date making it a very appealing natural product to pursue.

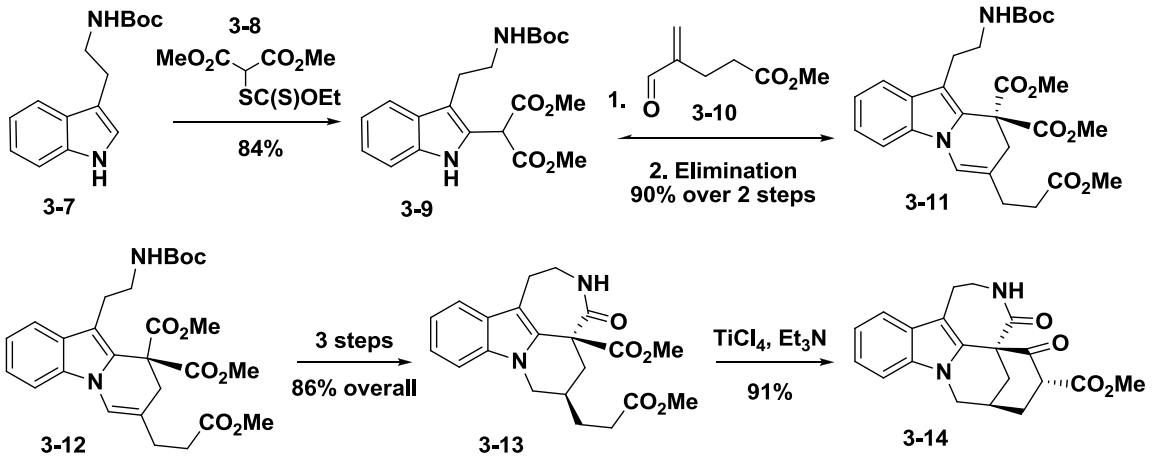
3.3 Previous Syntheses of Tronocarpine's Core

The first synthesis of tronocarpine's core was completed in 2006 by Kerr and Magolan,[14] by utilizing manganese(III) acetate as the key step to access the pyridoindole ring present in the structure (scheme 3.1). Acylation of 3-acetonitrile indole **3-2** with malonyl tether **3-3** resulted in compound **3-4**. This step proceeded in a fairly low yield as acylation of the indole nitrogen is often difficult due to its poor nucleophilicity. Cyclization onto the indole using manganese(III) acetate chemistry yielded pyridoindole **3-5** in good yield. Raney nickel reduction of the nitrile group formed the desired tryptamine subunit, which then immediately lactamized forming the required amide **3-6** in 87% yield. This work showcased the extensive ability of manganese(III) acetate to effectively cyclize complex substrates with different functionalities. Kerr and Magolan[14] were able to reach the core of tronocarpine **3-6** in 3 steps with a 16% overall yield.



Scheme 3.1. Kerr's synthesis of tronocarpines core[14]

The second synthesis of the framework of tronocarpine's was completed in 2014 by Martinez (scheme 3.2).[36] Martinez's route utilized an intermolecular radical oxidative substitution using protected tryptamine **3-7** and xanthate **3-8** to form compound **3-9**.

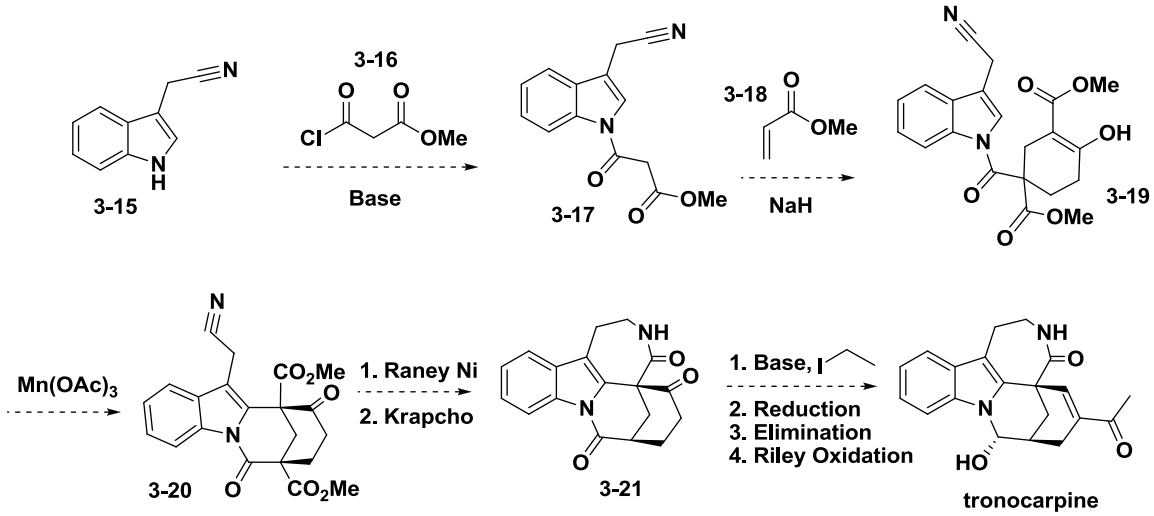


Scheme 3.2. Martinez's synthesis of tronocarpine's core[36]

Then over 2 steps, aldehyde **3-10** was added and the resultant rapid dehydration produced the advanced intermediate **3-11** in excellent yields. Removal of the Boc protecting group and reduction formed compound **3-13** as almost entirely a single diastereomer. Lastly, treatment of compound **3-13** with $TiCl_4$ and Et_3N gave the Dieckmann cyclization product **3-14** also as a single diastereomer. One of the highlights of Martinez's synthesis is the late stage Lewis acid promoted Dieckmann cyclization to access the additional ring system within the tronocarpine structure.

3.4 Our Proposed Synthesis

Our synthesis of tronocarpine will begin with acylation of 3-indoleacetonitrile **3-15** using methyl 3-chloro-3-oxopropanoate, **3-16**, to form compound **3-17** (scheme 3.3).



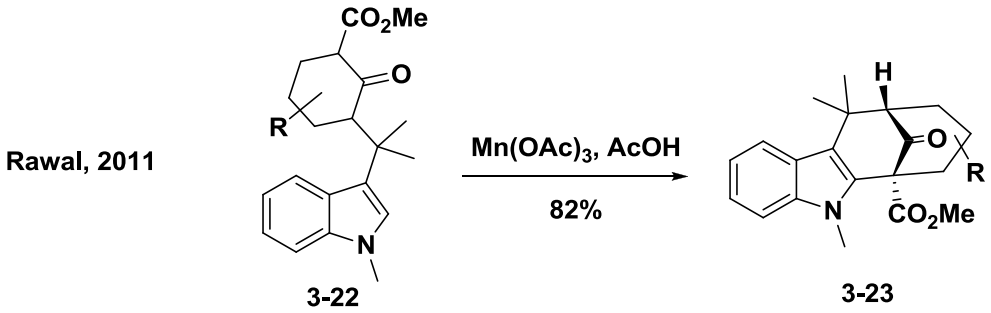
Scheme 3.3. Our proposed synthesis of tronocarpine

Treatment with excess methyl acrylate **3-18** under basic conditions would result in the double Michael addition/Dieckmann cyclized product **3-19**. This substrate would be suitable to undergo our key oxidative cyclization step using manganese(III) acetate to yield **3-20**. Raney nickel reduction of the nitrile group, followed by a Krapcho decarboxylation should yield substrate **3-21** constructing the seven-membered lactam present in the natural product. Subjection of **3-21** to basic conditions in the presence of ethyl iodide, a global reduction and subsequent elimination would yield compound would allow us to perform a Riley oxidation to provide us with tronocarpine.

3.4.1 Literature Precedence

It is worth noting that there have been numerous examples in which manganese(III) acetate has been used towards the synthesis of natural products. Some select examples include wentilactone B,[37] mersicarpine,[38] concarpan,[39] aloesaponol III,[40] 10-isothiocyanotoguaia-6-ene,[41] and podocarpic acid[42] amongst others.[1] The total synthesis of the welwitindolinones by Rawal and co-workers[43] is one particular example

that showcases the ability of manganese(III) acetate to cyclize complex systems onto indoles. The key step in their synthesis involved the oxidative cyclization of keto-ester **3-22** from the three position of indole to form compound **3-23** in good yield (scheme 3.4).

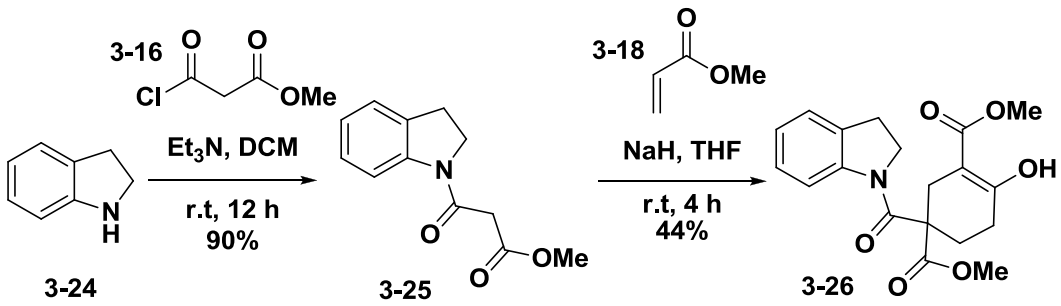


Scheme 3.4. Rawal's manganese cyclization toward welwitindolinone[43]

The ability to form this fairly complex system within the welwitindolinones provided our group with increased optimism that $Mn(OAc)_3$ would also work for our key step in the synthesis of tronocarpine.

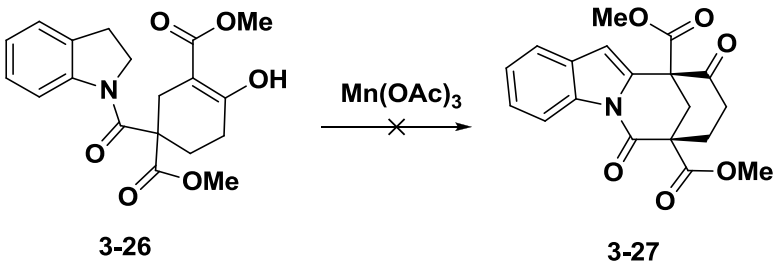
3.5 Initial Strategy to Synthesize Tronocarpine

The first step toward the synthesis of tronocarpine was a model study to investigate the suitability for manganese(III) acetate to perform our desired cyclization. Indoline **3-24**, was combined with methyl 3-chloro-3-oxopropanoate, **3-16**, in the presence of triethylamine and dichloromethane to give acylated indoline **3-25** in 90% yield (scheme 3.5). With compound **3-25** in hand, subjection to excess methyl acrylate **3-18** and NaH resulted in the double Michael addition/Dieckmann cyclization product **3-26** in 44% yield, a very satisfactory result based on the number of steps and complexity of the end product. By using this relatively simple three step procedure, we were able to access the desired compound in a moderate overall yield.



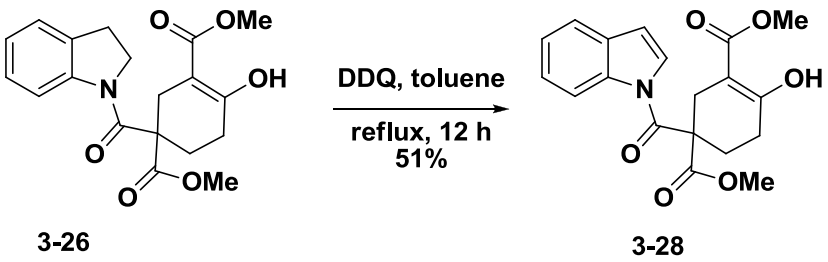
Scheme 3.5. Synthesis of Dieckmann cyclization intermediate

Based on our previous work, where we witnessed the tandem cyclization and dehydrogenation of indoline to the corresponding indole using manganese(III) acetate,[14] we were cautiously optimistic that substrate **3-26** would undergo the same transformation to compound **3-27** (scheme 3.6).



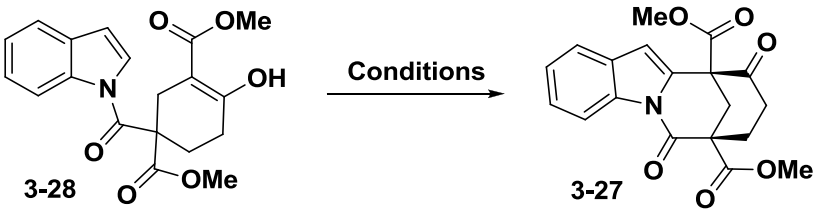
Scheme 3.6. Attempted cyclization of indoline substrate

Unfortunately we were unable to obtain our desired cyclized product and only witnessed decomposition of starting material. It was decided that oxidation to the indole **3-28** prior to subjection to our manganese conditions would assist in the cyclization step (scheme 3.7). Treatment of **3-26** with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in toluene under reflux afforded **3-28** in 51% yield.



Scheme 3.7. Dehydrogenation of Dieckmann cyclized indoline

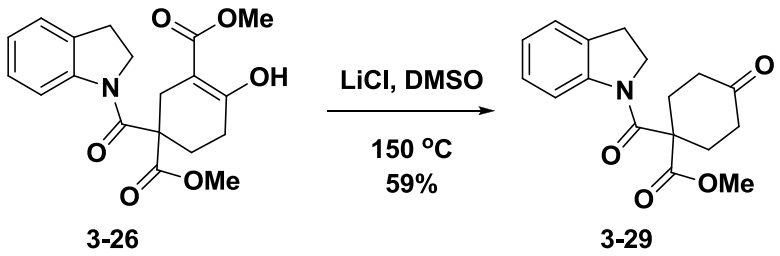
Much to our delight, the oxidative cyclization reaction that was to follow resulted in formation of our desired product. After surveying several different reaction conditions, it was discovered that subjecting **3-28** to three molar equivalents of manganese(III) acetate in acetic acid at 40 ^{o}C yielded the cyclized indole **3-27** in 55% yield (table 3.1). Several other published conditions were attempted, including procedures from Rawal[43] (entry 4), Li[44] (entry 5), and Wang[45] (entry 6).



Entry	Solvent	Conditions	Temp. ^{o}C	Time	Result
1	AcOH	$Mn(OAc)_3$	Reflux	3 h	9%
2	AcOH	$Mn(OAc)_3$	40	30 mins	55%
3	AcOH	$Mn(OAc)_3$	40	24 h	17%
4	AcOH	$Mn(OAc)_3$, NaOAc buffer	80	24 h	Decomp.
5	DCM	Cp_2FeF_6P, ^{t}BuOK	r.t.	24 h	4%
6	MeCN:H_2O	$K_2Se_2O_8$	50	12 h	Decomp.

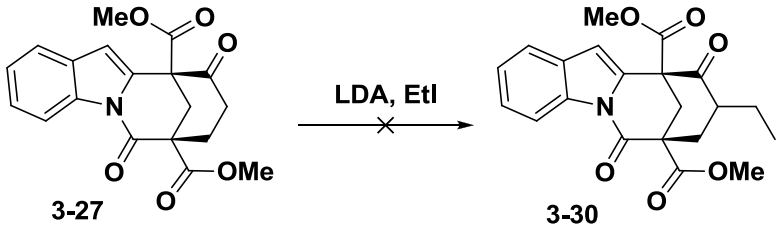
Table 3.1. Optimization of cyclization reaction

After the success of our manganese(III) acetate chemistry, it was realized that there remained several objectives and issues with this route that were worth addressing. The first was the presence of the additional ester functionality that would need to be removed to access tronocarpine. Since the selective decarboxylation of **3-27** would go through an anti-Bredt intermediate, attempts to perform the Krapcho decarboxylation was conducted on the Dieckmann precursor **3-26** (scheme 3.8).



Scheme 3.8. Undesired Krapcho decarboxylation product

Unfortunately the sole product isolated was **3-29** caused by the removal of the incorrect ester. This did not come as a big surprise because of the high enol content of the keto-ester favoring the decarboxylation mechanistic pathway. Despite this setback and potential downfall of this synthetic route, the next step in our synthesis attempted to attach the ethyl group functionality that is required in each of the natural products (scheme 3.9).



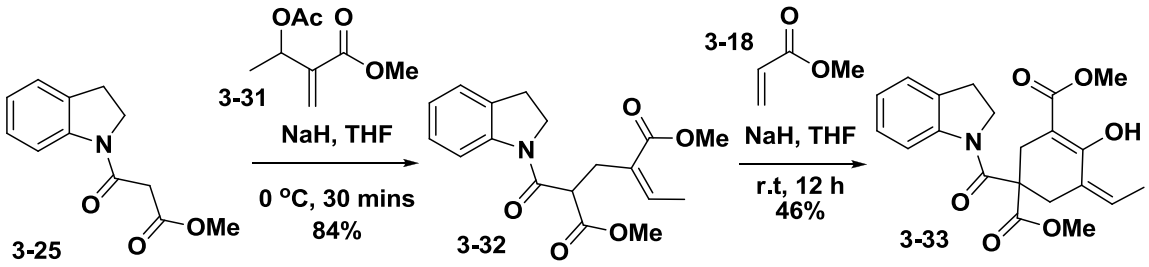
Scheme 3.9. Attempted alkylation of cyclized substrate

Since the only acidic protons present on the molecule are the α-keto hydrogens, we were optimistic that treatment with a strong base and ethyl iodide would yield our desired product **3-30**. Subjection of compound **3-27** with LDA and ethyl iodide resulted only in decomposition of starting materials. We are still hopeful that using a weaker base such as

NaH may decrease the amount of decomposition and lead to our alkylated product. At this point in the synthesis it was decided that attempting to incorporate the required alkyl chain earlier in the synthesis may prove to be beneficial.

3.6 Attempts to Incorporate an Alkyl Chain

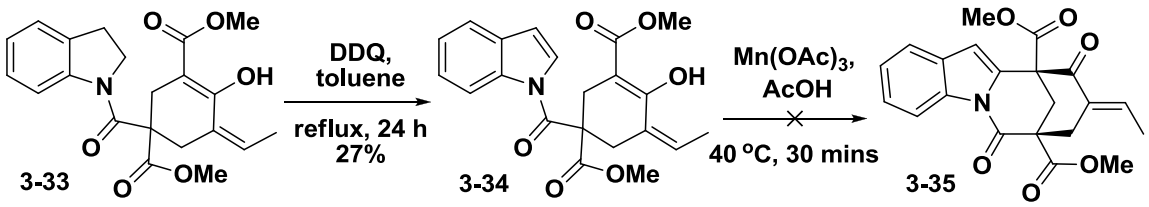
In order to include the appropriate ethyl chain at an earlier stage in the synthesis, we looked to using a Michael acceptor such as the commercially available methylene butanoate **3-31** (scheme 3.10).



Scheme 3.10. Model study with incorporation of new Michael acceptor

Addition of indoline **3-25** with Michael acceptor **3-31**, in the presence of NaH at 0 °C in THF resulted in 84% of compound **3-32**. As we anticipated, loss of the acetate group upon Michael addition formed a new α,β unsaturated ester. Although this newly formed alkene will require reduction later on in the synthesis, it gives us the appropriate carbon chain needed. Gratifyingly, addition of methyl acrylate **3-18**, NaH and compound **3-32** for 12 h in THF yielded the cyclized keto-ester **3-33** in 46% yield.

Using the same protocol as in the previous model study (scheme 3.7), DDQ oxidation was performed on indoline **3-33** resulting in only 27% of indole **3-34**. The significantly lower yield, in comparison to the previous DDQ oxidation, are hard to rationalize. The lone attempt to cyclize this indole to compound **3-35** led to inconclusive results due to the small scale of the reaction was completed on, and low yield of the only isolatable spots (scheme 3.11).

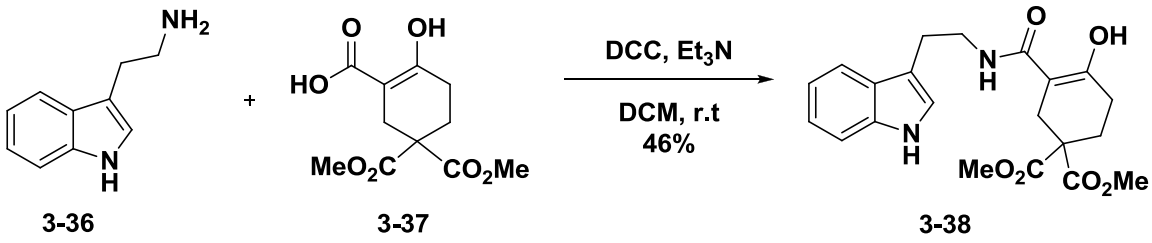


Scheme 3.11. Oxidation and attempted cyclization of new route

Although this route still holds promise, several issues are likely to arise with its continuation. There still remains the problem of removing the ester functionality that is not needed, as well as selective reduction of the alkene present. At this point alternative routes were being explored and appeared to have much greater potential than our previous methods.

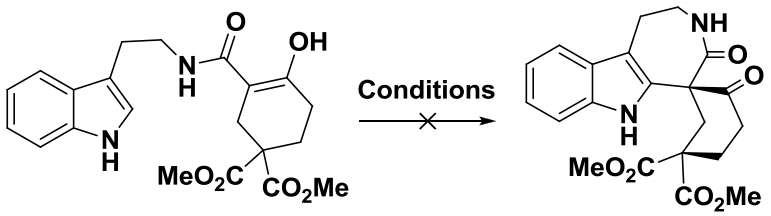
3.7 Alternate Approach to Tronocarpine

While working on the proposed synthesis of tronocarpine shown previously, it occurred to us that an alternative route towards tronocarpine could also prove to be very efficient and still showcase manganese(III) acetate oxidative cyclization chemistry. By coupling commercially available tryptamine **3-36** with readily available carboxylic acid **3-37** using DCC, β-keto-amide **3-38** was synthesized in a 46% yield (scheme 3.12).



Scheme 3.12. Formation of amide in top-down approach to tronocarpine

By subjecting amide **3-38** to manganese(III) acetate, we were optimistic that cyclization onto the two position of indole would establish the seven membered lactam present in tronocarpine. With amide **3-34** in hand, several attempts to oxidatively cyclize the substrate were tried, but have thus far proven unsuccessful (table 3.2). Entry 2 shows



3-34 3-35

Entry	Solvent	Conditions	Temp. ^{o}C	Time (h)	Result
1	AcOH	$Mn(OAc)_3$	45	4	Decomposition
2	MeOH	$Mn(OAc)_3$	60	3	Unknown
3	DCM	Cp_2FeF_6P	r.t.	24	N/R

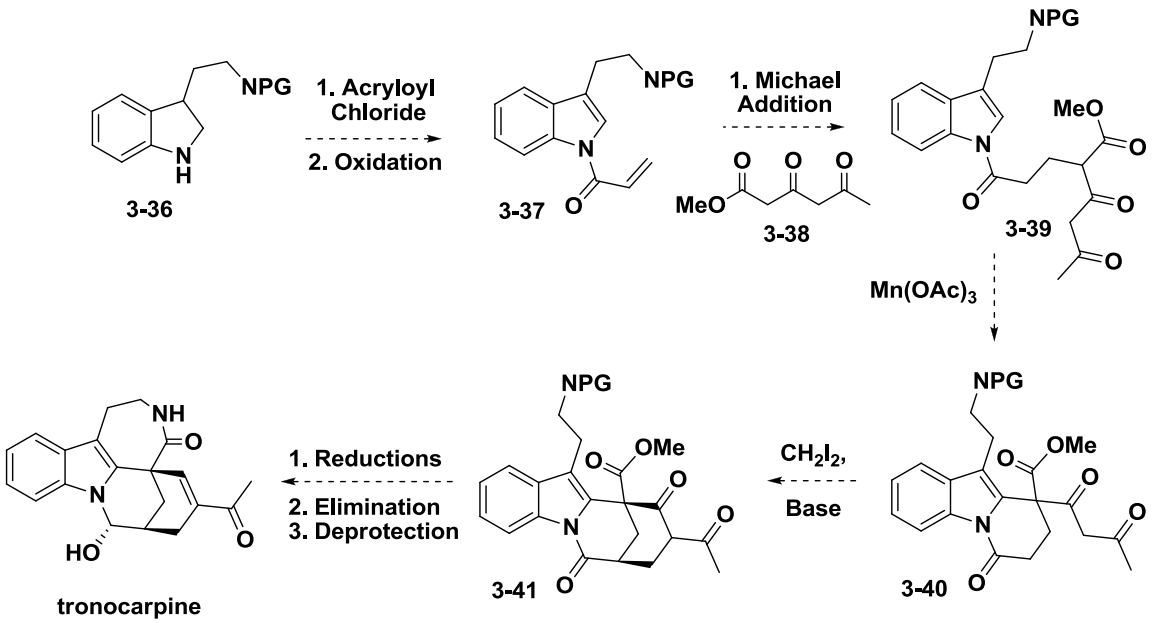
Table 3.2. Attempted cyclizations of β-keto-amide

the isolation of an unknown compound with high mass recovery. Characterization of this compound is still underway, but due to the presence of the aromatic hydrogen at the two position of indole in the ^{1}H NMR, we can conclude it is not the desired product **3-35**. Li's conditions[44] were also attempted for our substrate but resulted in no reaction. Due to the lack of literature precedence for β-keto-amide's to undergo manganese oxidative cyclization chemistry, we suspect this step may prove to cause a great deal of difficulty and so its exploration was put on hold.

3.8 New Strategy Yields a Common Intermediate

3.8.1 Proposed Synthesis

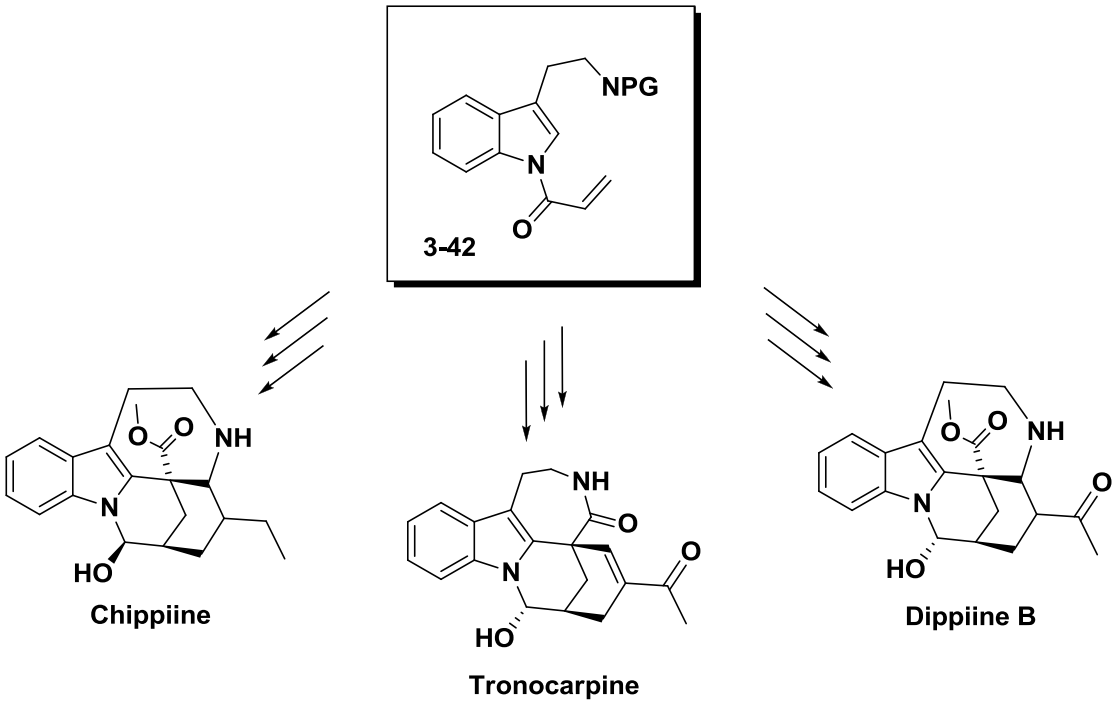
Despite some of the success of our previous routes toward synthesizing tronocarpine, there were several issues that each route possessed that made looking for an entirely new synthetic route appealing. It did not take long before a new proposed synthesis of tronocarpine arose, which appeared to reduce potential problems encountered in the previous work (scheme 3.13).



Scheme 3.13. New proposed route to tronocarpine

Beginning with protected tryptamine and performing a reduction we would hope to access indoline **3-36**. *N*-Acylation of the indoline using acryloyl chloride followed by an oxidation would furnish indole **3-37.** This compound could then be used in a Michael addition reaction with keto-ester **3-38** to yield compound **3-39**. Subjection of this substrate to our manganese cyclization conditions would allow us to access the advanced intermediate **3-40**. Building of the second cyclohexane ring required to form **3-41** could be completed by addition of diiodomethane and base. We were optimistic that, due to the only remaining acidic hydrogens on the molecule being located in the α-diketone and α-amide positions, excess base can be used with little concern for the production of unwanted side-products. At this point, selective reduction and elimination similar to our previous proposed synthesis followed by deprotection of the amine should readily form the seven-membered lactam needed to yield tronocarpine.

It was at this point while exploring this possible route to synthesize tronocarpine that we noticed a similar structural motif was present in several natural products. Tronocarpine, chippiine[46] and dippinine B[47] were all extracted from plants from the *Tabernaemontana* genus and possess a similar pentacyclic framework that we hoped could be accessed through a common intermediate **3-42** (scheme 3.14).

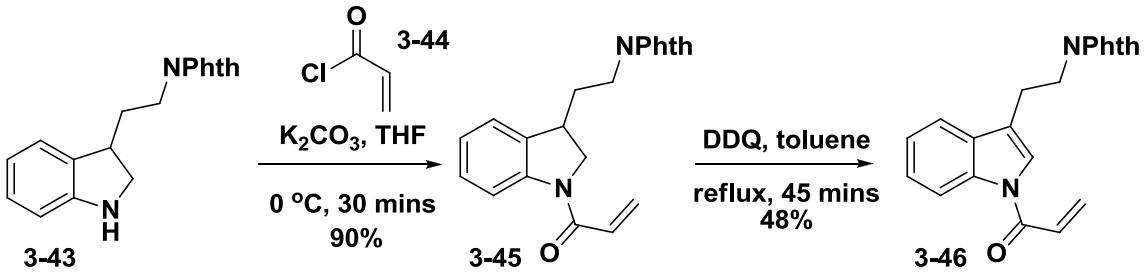


Scheme 3.14. A common intermediate to *Tabernaemontana* natural products

It was postulated that accessing each of these natural products could be obtained via a Michael addition of different keto-esters using onto this common intermediate **3-42**.

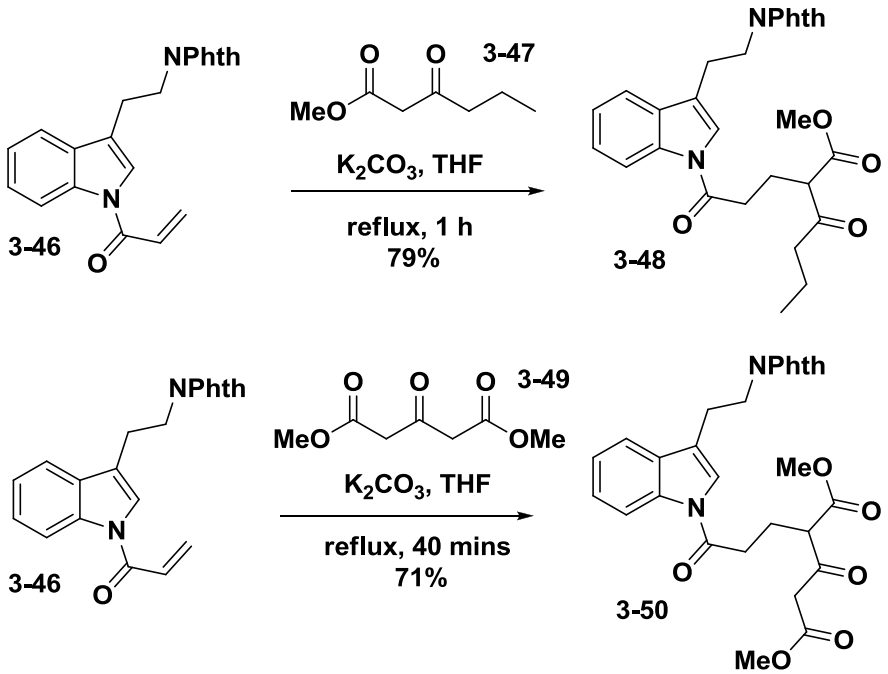
3.8.2 Synthesis of Common Intermediate

To access this intermediate, as shown in scheme 3.15, we began by dissolving known compound **3-43**[48] in THF with potassium carbonate and acryloyl chloride **3-44** to form the acylated indoline product **3-45** in 90% yield. Oxidation using DDQ in refluxing toluene for 45 mins yielded 48% of indole **3-46**. It is worth noting that the formation of indole **3-46** was also reproducible on gram-scale synthesis.



Scheme 3.15. Formation of common intermediate

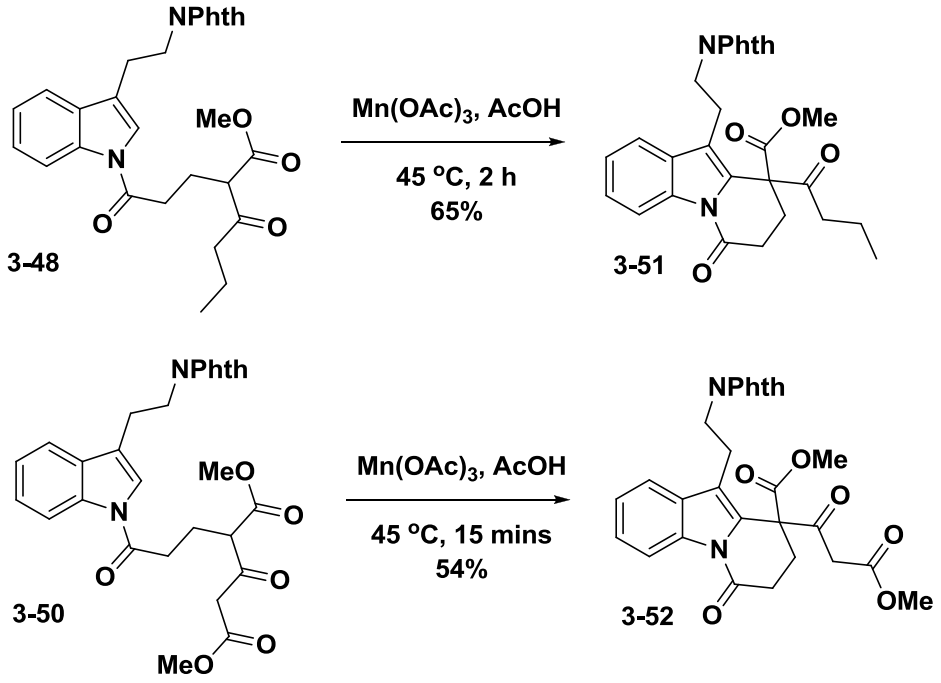
The ability to vary the nucleophile in the next step allows us to proceed toward different natural products (scheme 3.16). Addition of methyl 3-oxohexanoate **3-47** with potassium carbonate gives the appropriate functionality in compound **3-48** in 79% yield for the synthesis of chippiine. The use of keto-ester **3-49** and potassium carbonate forms compound **3-50** in 71%, which would be preferred for the synthesis of tronocarpine and dippinine B. This fine-tuning is one of the great advantages in this approach towards the natural products. It was also verified that the use of indole **3-46**, as opposed to indoline **3-45** as the Michael-acceptor would be beneficial due to the increased electrophilicity of the indole caused by delocalization of nitrogen's lone pair of electrons.



Scheme 3.16. Michael addition of different keto-esters

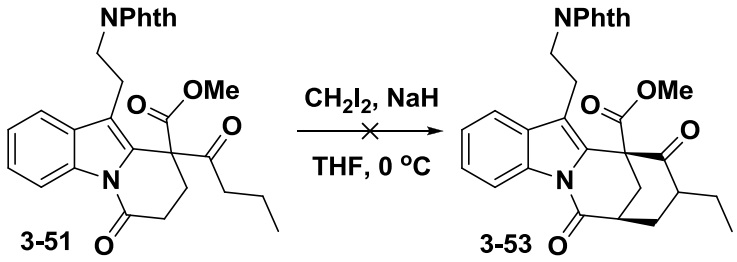
3.8.3 Success with Manganese Cyclizations

With each of these substrates possessing the keto-ester functionality necessary for our oxidative cyclization chemistry, we subjected each to our $Mn(OAc)_3$ conditions in AcOH at 45 ^oC (scheme 3.17). Substrate **3-48** required 2 hour of heating before TLC confirmed consumption of starting material and 65 % of cyclized product **3-51** was isolated. Indole **3-49** required only 15 minutes for reaction completion to yield our cyclized substrate **3-52** in a 54 % yield.



Scheme 3.17. Manganese(III) acetate cyclizations of keto-esters

These substrates possess much of the functionality present for either the chippiine or tronocarpine natural products. One key structural feature that now needs addressing is the lack of the outer cyclohexane ring. With only two positions with acidic hydrogens on the molecule, we were optimistic that under basic conditions we would be able to attach an extra carbon unit by using diiodomethane or formaldehyde. Unfortunately, the few attempts that have been made to alkylate compound **3-51** using NaH and diiodomethane have resulted in loss of material (scheme 3.18).



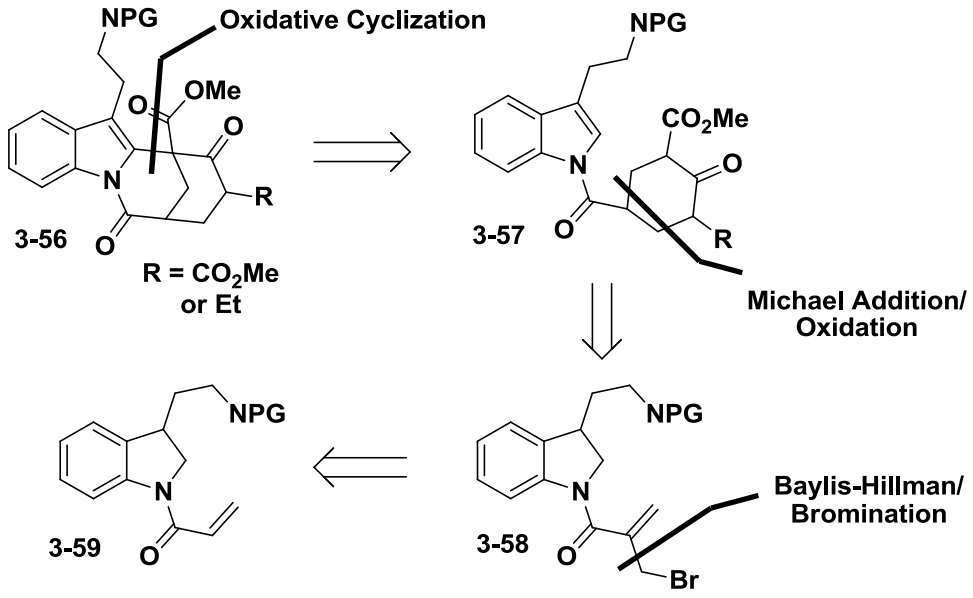
Scheme 3.18. Failed attempt to form cyclohexane ring

Despite numerous extractions of the aqueous workup with various organic solvents, we were unable to obtain any of the desired product **3-53**. The reaction did however appear promising due to consumption of starting material based on thin-layer chromatography which leaves us hopeful that upon altering conditions and solvents we may be able to isolate **3-53**. Based on previous experience in the Kerr group with these molecular structures, it is possible that solubility may become an issue when attempting to isolate and characterize these compounds.

3.9 Final Synthetic Route and Initial Results

3.9.1 Retrosynthesis

In conjunction with the previous route towards a common intermediate for tronocarpine, chippiine and dippinine B, an additional proposal was investigated. The new retrosynthesis of an advanced intermediate **3-56** is shown in scheme 3.19. This route would allow access towards the family of *Tabernaemontana* natural products.

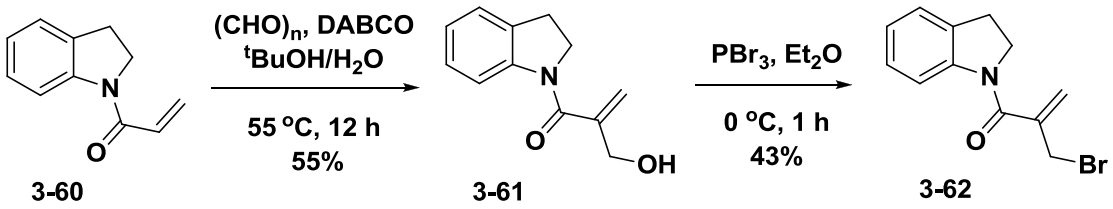


Scheme 3.19. Retrosynthesis of advanced common intermediate

Upon examination of the target molecule **3-56**, the first disconnection could result from a manganese(III) oxidative cyclization performed on indole **3-57**. We suspect this indole could be obtained by an oxidation from indoline **3-58** as well as a double-Michael addition using keto-ester **3-47** or **3-49**, depending on the natural product being targeted. Next, we propose a Baylis-Hillman reaction using formaldehyde followed by bromination of compound **3-59** to provide us with substrate **3-58** that might be suitable for the Michael addition chemistry.

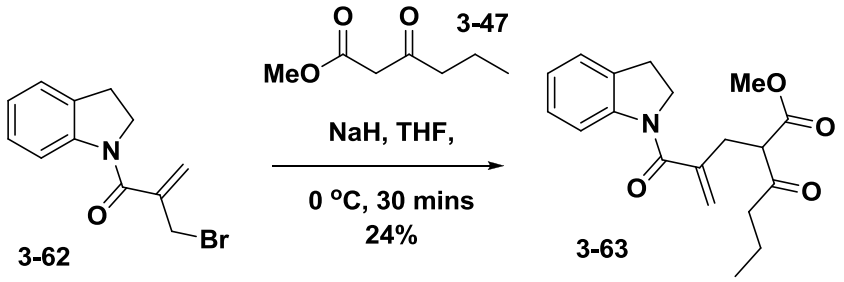
3.10 Success by Means of Baylis-Hillman

Our investigation into this proposal begins with a model study preparing indoline **3-60** as described by Kerr.[38] Subjection of **3-60** to DABCO, formaldehyde and phenol, based on conditions reported by Wang[45], yielded our desired alcohol **3-61** in a 55 % yield (scheme 3.20).



Scheme 3.20. Synthesis of new indoline Michael-acceptor

In order to form the desired ring, the alcohol must first be converted into a suitable leaving group, in our case bromine. Treatment of alcohol **3-61** with PBr_3 in Et_2O at 0 ^oC yielded brominated species **3-62** in 43% yield. In this way, addition of a nucleophile into the Michael acceptor should result in elimination of the bromide, reintroducing an additional double bond available for a subsequent Michael addition. Conversely, the bromine could simply be displaced by an S_N2 type reaction. Upon monitoring the reaction of **3-62** with K_2CO_3 and keto-ester **3-47**, it was determined that bromine was indeed being eliminated upon addition into the double bond yielding 24% of **3-63** (scheme 3.21).



Scheme 3.21. Successful Michael-addition/elimination

3.11 Summary

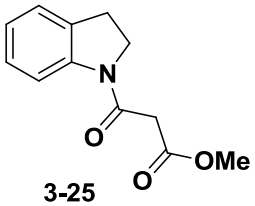
The chapter explored several different synthetic routes toward the natural product tronocarpine. Considerable progress has been made to finding the best strategy to pursue tronocarpine, and several complicated and advanced compounds were successfully synthesized. Each of the routes discussed leaves significant potential to accessing not only tronocarpine, but also similar indole-containing natural products chippiine and dippinine B. The synthesis of a common intermediate towards these compounds was

presented, as well as several steps in the proposed preparation of these particular products.

3.12 Experimental

General

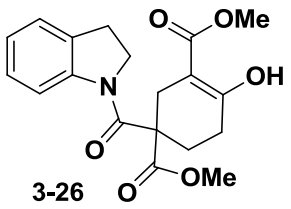
All reagents and solvents were used as purchased from Sigma Aldrich, Alfa Aesar, Caledon, Strem or VWR and used as received. Reaction progress was monitored by TLC (EM Science, silica gel 60 F254), visualizing with UV light, and the plates developed with vanillin. Column chromatography was performed using silica gel (230-400 mesh, Silicycle Chemical Division Inc). NMR experiments were performed on Varian Mercury 400 and Inova 400 MHz instruments with ^{13}C operating frequencies of 100 MHz. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$, referenced to residual $CHCl_3$ at $\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (J) are reported in Hz, and multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, spt = septet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 or 8400 mass spectrometer at an ionizing voltage of 70 eV. Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument and are reported in frequency of absorption (cm^{-1}). All reactions were carried out under an atmosphere of argon unless otherwise indicated.



3-25

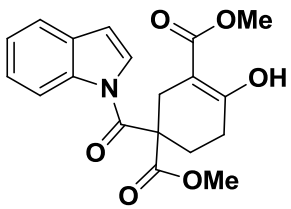
Indoline **3-24** (0.501 mL, 4.48 mmol) and 0.750 mL (5.38 mmol) of Et_3N was dissolved in 5 mL of DCM in a round bottom flask equipped with a magnetic stirrer under argon. Methyl 3-chloro-3-oxopropanoate **3-16** was slowly added to the solution and the reaction was stirred for 12 h at room temperature. The reaction was then quenched with water and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with brine and dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography yielded 0.883 g (4.03 mmol, 90%) of

compound **3-25** as a white crystalline product. Rf = 0.20 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.22 (d, J = 8.2 Hz, 1H), 7.20 (m, 2H), 7.05 (m, 1H), 4.08 (t, J = 8.2 Hz, 2H), 3.78 (s, 3H), 3.57 (s, 2H), 3.22 (t, J = 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 167.6, 163.6, 131.2, 127.6, 124.5, 124.2, 117.3, 114.9, 52.6, 48.5, 43.6, 28.0



3-26

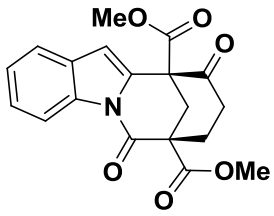
NaH (2.73 g, 68.5 mmol, 60% dispersion in oil) was dissolved in 100 mL THF at 0 ^{o}C in a round bottom flask equipped with a magnetic stir bar. 2.50 g (11.4 mmol) of compound **3-25** was slowly added and the solution was stirred for 30 mins. Methyl acrylate **3-18** (6.16 mL, 68.5 mmol) was added and the reaction was stirred for 4 h after which TLC analysis confirmed reaction completion. The reaction was quenched with cold H_2O and extracted three times with EtOAc. The combined organic layers were washed with water once, brine once, and dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography yielded 1.82 g (5.07 mmol, 44%) of compound **3-26** as a white solid; Rf = 0.40 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 12.09 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.21 (m, 2H), 7.06 (apparent t, J = 7.6 Hz, 1H), 3.96 (m, 1H), 3.88 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.14 (m, 2H), 2.85 (s, 2H), 2.44 (m, 1H), 2.33 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.9, 172.1, 170.4, 167.8, 143.7, 130.9, 127.6, 124.4, 124.3, 118.2, 94.9, 53.7, 52.9, 51.6, 47.9, 28.9, 28.5, 27.5, 26.0; **FT-IR** (thin film, cm- 1) v_{max} = 2997, 2952, 1737, 1658, 1480, 1442, 1384, 1233, 1194, 757; **HRMS** calc'd for $C_{18}H_{21}NO_5$ [M+] 359.1369, found 359.1364



3-28

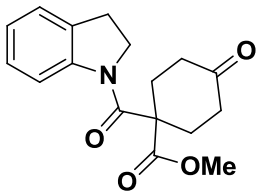
Compound **3-26** (1.12 g, 3.12 mmol) was dissolved in toluene (35 mL) in a round bottom flasked equipped with a magnetic stirrer. The solution was heated to reflux and (0.89 g, 0.140 mmol) of DDQ was then added. The reaction was stirred for 12 hours, cooled, then solution was diluted with EtOAc and poured into water. The aqueous layer was extracted three times with EtOAc, and the combined

layers were washed with water once, brine, then dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.563 g (1.58 mmol, 51%) of the indole **3-28** as a yellow crystalline solid; Rf = 0.72 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 12.12 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.39 (m, 1H), 7.37 (m, 1H), 7.30 (apparent t, J = 7.6 Hz, 1H), 6.65 (d, J = 3.5 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.00, 2.94 (ABq, J_{AB} = 16.1 Hz, 2H), 2.45 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.8, 172.0, 170.1, 168.1, 136.5, 129.8, 125.6, 124.2, 123.7, 120.8, 117.2, 110.3, 94.7, 54.2, 53.3, 51.7, 29.5, 28.2, 25.9; **FT-IR** (thin film, cm-1) v_{max} = 2953, 1739, 1702, 1664, 1450, 1323, 1230, 1213, 752; **HRMS** calc'd for $C_{19}H_{19}NO_6$ [M+] 357.1212, found 357.1212.



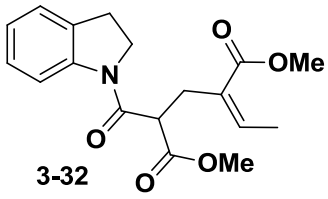
3-27

Compound **3-28** (0.110 g, 0.308 mmol) was dissolved in AcOH (3 mL) in a round bottom flask equipped with a magnetic stirrer. $Mn(OAc)_3{\cdot}H_2O$ (0.247 g, 0.924 mmol) was added and the reaction was heated to 40 ^oC and stirred for 30 mins at which TLC analysis confirmed consumption of starting material. The solution was diluted with EtOAc, and poured into water. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with water 5 times, saturated $NaHCO_3$ once, brine, then dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.060 g (0.169 mmol, 55%) of cyclized indole **3-27** as a white solid; Rf = 0.58 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.49 (d, J = 8.21 Hz, 1H), 7.56 (d, J = 7.04 Hz, 1H), 7.40 (t, J = 7.04, 1H), 7.34 (m, J = 7.63, 1H), 7.24 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.26 (dd, J = 3.52, 13.49 Hz, 1H), 2.82 (d, J = 13.66 Hz, 1H), 2.73 (m, 1H), 2.49 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 199.8, 169.8, 167.5, 167.1, 135.4, 130.6, 129.5, 126.1, 125.2, 121.1, 116.8, 111.5, 57.8, 53.3, 53.1, 52.3, 38.1, 35.1, 32.7; **FT-IR** (thin film, cm- 1) v_{max} = 2954, 1747, 1724, 1704, 1454, 1381, 1276, 1237; **HRMS** calc'd for $C_{19}H_{17}NO_6$ [M+] 355.1056, found 355.1052.



3-29

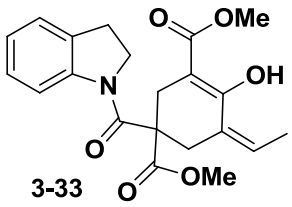
Compound **3-26** (0.100 g, 0.278 mmol) was dissolved in 3 mL of DMSO and 0.025 g (0.610 mmol) of LiCl was added. The reaction was heated to 150 ^{o}C in a round bottom flask equipped with a magnetic stir bar. The solution was stirred for 1 h after which TLC analysis confirmed reaction completion. The reaction was quenched with H_2O and extracted three times with EtOAc. The combined organic layers were washed with water once, brine once, and dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography yielded 0.049 g (0.163 mmol, 59%) of compound **3-29** as a clear oil; Rf = 0.24 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.22 (d, J = 8.2 Hz, 1H), 7.22 (m, 2H), 7.07 (m, 1H), 3.90 (t, J = 8.2 Hz, 2H), 3.80 (s, 3H), 3.13 (t, J = 8.2 Hz, 2H), 2.65-2.59 (m, 2H), 2.55-2.47 (m, 4H), 2.43-2.37 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 209.8, 173.2, 168.0, 143.5, 130.9, 127.6, 124.5, 118.1, 53.6, 53.0, 47.9, 41.8, 37.2, 30.6, 28.9.



3-32

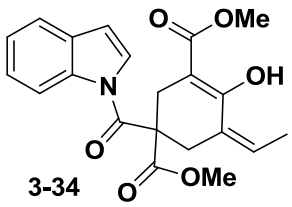
NaH (0.087 g, 2.18 mmol, 60% dispersion in oil) was dissolved in 5 mL THF at 0 ^{o}C in a round bottom flask equipped with a magnetic stir bar. 0.400 g (1.82 mmol) of compound **3-25** was slowly added and the solution was allowed to stir for 10 mins. Methyl 3-acetoxy-2-methylenebutanoate **3-31** (0.323 mL, 2 mmol), was added and the reaction was stirred for 30 mins after which TLC analysis confirmed reaction completion. The reaction was quenched with cold H_2O and extracted three times with EtOAc. The combined organic layers were washed with water once, brine once, and dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography yielded 0.507 g (1.52 mmol, 84%) of compound **3-32** as a clear oil ; Rf = 0.32 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.22 (d, J = 8.2 Hz, 1H), 7.19 (m, 2H), 7.03 (m, 2H), 4.21 (m, 1H), 4.12 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.20 (m, 2H), 3.06 (dd, J = 14.1, 7.6 Hz, 1H), 2.94 (dd, J = 13.5, 7.0 Hz, 1H), 1.92 (d, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.6, 167.9, 166.6, 142.7, 142.2, 131.6, 128.4, 127.6, 124.6, 124.2, 117.5, 52.5, 51.7, 50.2, 48.5, 28.0, 26.5,

14.7; **FT-IR** (thin film, cm- 1) v_{max} = 2951, 2851, 1748, 1707, 1659, 1482, 1407, 1275, 753; **HRMS** calc'd for $C_{18}H_{21}NO_5$ [M+] 331.1420, found 331.1417.



3-33

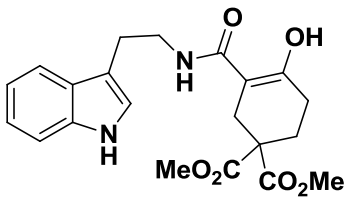
NaH (0.290 g, 7.25 mmol, 60% dispersion in oil) was dissolved in 5 mL THF at 0 ^{o}C in a round bottom flask equipped with a magnetic stir bar. 0.200 g (1.82 mmol) of compound **3-32** was slowly added and the solution was stirred for 10 mins. 0.325 mL (3.62 mmol) of methyl acrylate **3-18** was added and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with cold H_2O and extracted three times with EtOAc. The combined organic layers were washed with water once, brine once, and dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by column chromatography yielded 0.107 g (0.278 mmol, 46%) of compound **3-33** as a white solid; Rf = 0.55 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = enol 12.13 (s, 1H), 8.21 (d, J = 8.21 Hz, 1H), 7.21 (m, 2H), 7.06 (t, J = 7.6 Hz, 1H), 6.63 (q, J = 7.6 Hz), 4.05 (dt, J = 9.8, 6.2 Hz, 1H), 3.86 (m, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.19-3.11 (m, 2H), 3.07 (m, 2H), 2.91 (AB system, 2H), 1.82 (d, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.6, 172.3, 167.5, 164.5, 143.6, 130.9, 129.8, 127.5, 127.4, 124.3, 118.2, 94.1, 54.2, 52.7, 51.7, 47.8, 31.5, 28.9, 28.5, 13.6; **FT-IR** (thin film, cm- 1) v_{max} = 2998, 2952, 1737, 1659, 1598, 1441, 1385, 1264, 757; **HRMS** calc'd for $C_{21}H_{23}NO_6$ [M+] 385.1525, found 385.1520.



3-34

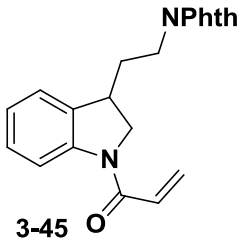
Compound **3-33** (0.045 g, 0.116 mmol) was dissolved in toluene (2 mL) in a round bottom flask equipped with a magnetic stirrer. The solution was heated to reflux and (0.031 g, 0.140 mmol, 1.2 equiv.) of DDQ was then added. The reaction was stirred for 24 hours, cooled, then diluted with EtOAc and poured into water. The aqueous layer was extracted three times with EtOAc, and the combined layers were washed with water once, brine, then dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.0123 g (0.031 mmol, 27%) of the indole **3-34** as a white

solid; Rf = 0.76 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = enol 12.16 (s, 1H), 8.46 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 3.5 Hz, 1H), 7.36 (dd, J = 8.2, 7.0 Hz, 1H), 7.29 (dd, J = 8.2, 7.0 Hz), 6.64 (m, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.12 (AB system, 2H), 1.72 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.5, 172.3, 167.7, 164.3, 136.5, 130.6, 129.7, 126.7, 125.5, 124.1, 123.7, 120.7, 117.2, 110.2, 94.0, 54.7, 53.2, 51.8, 31.7, 30.0, 13.5; **FT-IR** (thin film, cm- 1) v_{max} = 3001, 2953, 2923, 1851, 1741, 1702, 1662, 1596, 1450, 1323, 1264, 1201, 751; **HRMS** calc'd for $C_{21}H_{21}NO_6$ [M+] 383.1369, found 383.1370.



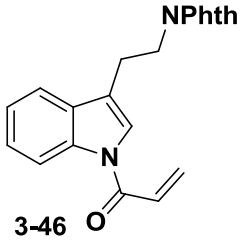
3-38

Compound **3-36** (0.175 g, 1.09 mmol) was dissolved in DCM (5 mL) in a round bottom flask equipped with a magnetic stirrer. 0.449 g (2.18 mmol) of *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 0.338 g (1.31 mmol) of carboxylic acid **3-37** was added to the flask. Et_3N (0.167 mL,1.20 mmol) was then added and the reaction was stirred overnight at room temperature. The reaction was quenched with H_2O and the aqueous later was extracted three times with DCM. The combined organic layers were washed with brine, dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.436 g (0.501 mmol, 46%) of the amide **3-38** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 12.09 (s,1H), 8.01 (broad m, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.8, 7.0 Hz, 1H), 7.14 (dd, J = 7.8, 7.0 Hz, 1H), 7.00 (s, 1H), 6.04 (broad m, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 3.61 (m, 2H), 2.97 (m, 2H), 2.82 (AB system 2H), 2.33 (m, 2H), 2.22 (m, 1H), 2.10 (m, 1H);**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 172.8, 170.8, 169.2, 136.4, 127.1, 122.3, 122.0, 119.6, 118.7, 112.6, 111.2, 95.1, 53.1, 52.9, 51.6, 40.0, 28.4, 26.9, 26.3, 25.1; **HRMS** calc'd for $C_{21}H_{21}NO_6$ [M+] 400.1634, found 400.1628.



3-45

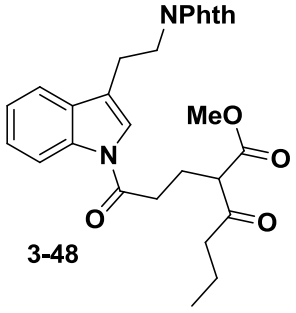
Indoline **3-43** (0.500 g, 1.71 mmol) was dissolved in THF (6 mL) in a round-bottomed flask equipped with magnetic stirrer, K_2CO_3 (0.471 g, 3.42 mmol, 2 equiv) was added and the mixture was cooled to 0 ^oC under an argon atmosphere. Acryloyl chloride **3-44** (0.206 mL, 2.56 mmol) was added dropwise via syringe with rapid stirring. A white precipitate immediately formed and the mixture was allowed to stir for an additional 30 mins. The mixture was then poured into a beaker of cooled water (10 mL) in an ice-bath. The solution was stirred for 30 mins. The solid was collected by filtration, allowed to air dry for 2 hours and placed under vacuum to complete drying and yield 0.532 g (1.53 mmol, 90%) of indoline **3-45** as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.28 (broad m, 1H), 7.86 (dd, J = 5.3, 2.9 Hz, 2H), 7.74 (dd, J = 5.9, 2.9 Hz, 2H), 7.21 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.64 (m, 1H), 6.52 (m, 1H), 5.83 (dd, J = 10.6, 1.8 Hz, 1H), 4.41 (t, J = 10.0 Hz, 1H), 3.98 (dd, J = 10.6, 6.5 Hz, 1H), 3.82 (t, J = 6.5 Hz, 2H), 3.44 (broad m, 1H), 2.25 (broad m, 1H), 1.93 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.3, 163.8, 142.5, 134.1, 131.9, 129.0, 128.1, 124.1, 123.9, 123.3, 117.6, 67.9, 53.8, 37.6, 35.5, 33.8, 25.6; **FT-IR** (thin film, cm- 1) v_{max} = 2936, 1709, 1655, 1418, 1398, 1279, 719; **HRMS** calc'd for $C_{21}H_{18}N_2O_3$ [M+] 346.1317, found 346.1329.



3-46

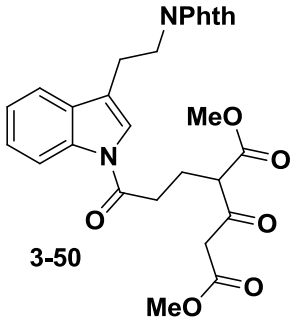
Compound **3-45** (1.08 g, 3.12 mmol) was dissolved in toluene (10 mL) in a round bottom flasked equipped with a magnetic stirrer. The solution was heated to reflux and (0.921 g, 4.05 mmol, 1.3 equiv.) of DDQ was then added. The reaction was stirred for 45 mins at which TLC analysis confirmed complete consumption of the starting material. The solution was diluted with EtOAc and poured into water. The aqueous layer was extracted three times with EtOAc, and the combined layers were washed with 1M NaOH solution three times, water once, and brine once the dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.525 g (1.52 mmol, 48%) of indole **3-46** as a yellow crystalline solid; Rf = 0.56 (40% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 8.2 Hz, 1H),

7.85 (dd, J = 5.3, 2.9 Hz, 2H), 7.72 (dd, J = 5.3, 2.9 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 7.38 (dd, J = 7.6, 7.0 Hz, 1H), 7.32 (dd, J = 7.6, 7.0 Hz, 1H), 6.96 (dd, J = 17.0, 10.6 Hz, 1H), 6.66 (dd, J = 17.0, 1.8 Hz, 1H), 6.04 (dd, J = 10.6, 1.8 Hz, 1H), 4.05 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.2, 163.6, 136.1, 134.0, 132.0, 131.8, 130.5, 128.0, 125.4, 123.9, 123.3, 122.0, 119.0, 118.9, 116.9, 37.3, 24.2; **FT-IR** (thin film, cm- 1) v_{max} = 2945, 1769, 1709, 1686, 1412, 1214, 715; **HRMS** calc'd for $C_{21}H_{16}N_2O_3$ [M+] 344.1161, found 344.1169.



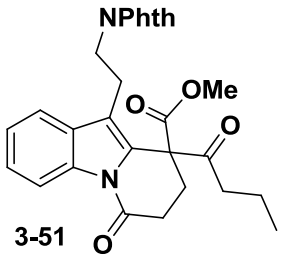
3-48

Indole **3-46** (0.1165 g, 0.338 mmol) and keto-ester **3-47** (0.094 mL, 0.677 mmol, 2.equiv.) was added to 3 mL of THF in a round bottomed flask equipped with a magnetic stir bar. After addition of K_2CO_3 (0.139 g, 1.014 mmol, 3 equiv.) the solution was heated to reflux for 1 hour at which TLC analysis verified consumption of the starting materials. The solution was allowed to cool to room temperature and diluted with EtOAc followed by water. The organic phase was separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielded 0.1302 g (2.66 mmol, 79%) of compound **3-48** as a white solid; Rf = 0.52 (40% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.41 (broad d, J = 7.8 Hz, 1H), 7.84 (dd, J = 5.5, 3.1 Hz, 2H), 7.71 (dd, J = 5.5, 3.1 Hz, 2H), 7.65 (m, 1H), 7.38 (s, 1H), 7.35 (m, 1H), 7.29 (m, 1H), 4.02 (m, 2H), 3.77 (m, 1H), 3.75 (s, 3H), 3.10 (apparent t, J = 7.8 Hz, 2H), 2.96 (apparent t, J = 7.0 Hz, 2H), 2.59 (m, 2H), 2.34 (m, 2H), 1.64 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 204.8, 170.1, 169.9, 168.2, 134.0, 132.0, 130.2, 125.5, 123.7, 123.3, 121.9, 119.1, 118.9, 116.7, 57.1, 52.5, 44.2, 41.2, 37.4, 32.9, 24.2, 22.7, 16.9, 13.5; **FT-IR** (thin film, cm- 1) v_{max} = 2955, 2874, 1741, 1710, 1454, 1395, 1365, 1210, 719; **HRMS** calc'd for $C_{28}H_{28}N_2O_6$ [M+] 488.1947 found 488.1957.



3-50

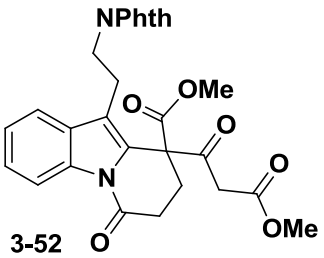
Indole **3-46** (0.100 g, 0.290 mmol) and 1,3 acetone-methyl-dicarboxylate **3-49** (0.083 mL, 0.58 mmol, 2.equiv.) was added to 3 mL of THF in a round bottomed flask equipped with a magnetic stir bar. After addition of K_2CO_3 (0.120g, 0.87 mmol, 3 equiv.) the solution was heated to reflux for 1 hour, at which point TLC analysis verified consumption of the starting materials. The solution was allowed to cool to room temperature and diluted with EtOAc followed by water. The organic phase was separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielded 0.1068 g (0.206 mmol, 71%) of compound **3-50** as a white solid; Rf = 0.32 (40% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 8.2 Hz, 1H), 7.85 (dd, J = 5.3, 2.9 Hz, 2H), 7.72 (dd, J = 5.3, 2.9 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.48 (broad s, 1H), 7.38 (dd, J = 7.6, 7.0 Hz, 1H), 7.32 (dd, J = 7.6, 7.0 Hz, 1H), 6.96 (dd, J = 10.6, 17.0 Hz, 1H), 6.65 (d, J = 17.0 Hz, 1H), 6.04 (d, J = 10.6 Hz, 1H), 4.05 (t, J= 7.6 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 204.8, 170.1, 169.9, 168.2, 134.0, 132.0, 130.2, 125.5, 123.7, 123.3, 121.9, 119.1, 118.9, 116.7, 57.1, 52.5, 44.2, 41.2, 37.4, 32.9, 24.2, 22.7, 16.9, 13.5; **FT-IR** (thin film, cm- 1) ν_{max} = 2952, 1742, 1710, 1395, 1211, 720; **HRMS** calc'd for $C_{28}H_{26}N_2O_8$ [M+] 518.1689, found 518.1690.



3-51

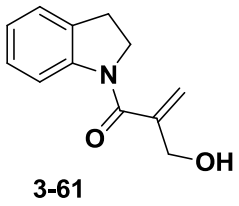
Compound **3-48** (0.108 g, 0.220 mmol) was dissolved in AcOH (2 mL) in a round bottom flask equipped with a magnetic stirrer. $Mn(OAc)_3{\cdot}H_2O$ (0.177 g, 0.662 mmol, 3 equiv.) was added and the reaction was heated to 45 ^oC and stirred for 2 hours, at which point TLC analysis confirmed consumption of starting material. The solution was diluted with EtOAc, and poured into water. The aqueous layer was

extracted three times with EtOAc, and the combined organic layers were washed with water 5 times, saturated $NaHCO_3$ once, brine, then dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.067 g (0.138 mmol, 63%) of cyclized indole **3-51** as a white solid; Rf = 0.54 (40% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.54 (m, 1H), 8.02 (m, 1H), 7.88 (dd, J = 5.3, 2.9 Hz, 2H), 7.74 (dd, J = 5.3, 2.9 Hz, 2H), 7.42 (m, 2H), 4.01 (s, 3H), 3.99-3.93 (m, 2H), 3.02 (ddd, J = 11.7, 7.0, 4.7 Hz, 1H), 2.86 (m, 3H), 2.70 (ddd, J = 11.7, 7.0, 5.3 Hz, 1H), 2.53 (m, 3H), 1.62 (m, 2H), 0.86 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 204.4, 170.2, 168.2, 167.2, 134.8, 134.1, 132.2, 129.5, 126.0, 123.3, 119.4, 117.0, 60.9, 52.8, 41.0, 36.1, 31.0, 28.8, 25.0, 17.4, 13.5; **FT-IR** (thin film, cm- 1) v_{max} = 2962, 1771, 1712, 1457, 1370, 1316, 725 ; **HRMS** calc'd for $C_{28}H_{28}N_2O_6$ [M+] 486.1791 found 486.1781.



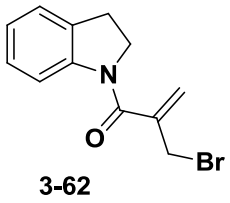
3-52

Compound **3-50** (0.089 g, 0.171 mmol) was dissolved in AcOH (2 mL) in a round bottom flask equipped with a magnetic stirrer. $Mn(OAc)_3 \cdot H_2O$ (0.138 g, 0.515 mmol) was added and the reaction was heated to 45 ^oC and stirred for 20 mins, at which point TLC analysis confirmed consumption of starting material. The solution was diluted with EtOAc, and poured into water. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with water 5 times, saturated $NaHCO_3$ once, brine, then dried using $MgSO_4$. The solvent was removed *in vacuo* and purification by flash chromatography yielding 0.048 g (0.093 mmol, 54%) of cyclized indole **3-52** as a white solid; Rf = 0.25 (40% EtOAc in hexanes);**NMR** (400 MHz, $CDCl_3$): δ = 12.60 (s, enol), 8.55 (m, 1H), 8.02 (m, 1H), 7.89 (m, 2H), 7.77 (m, 2H), 7.43 (m, 2H), 5.01 (s, enol), 4.07 (s, 3H), 4.02 (m, 1H), 3.94 (m, 1H), 3.73 (m, 1H), 3.70 (s, 1H), 3.61 (s, 1H), 3.33 (s, 3H), 3.06 (m, 1H), 2.87 (m, 2H), 2.72 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 196.3, 170.0, 168.2, 167.6, 166.1, 135.0, 134.1, 134.0, 132.1, 129.2, 128.6, 126.4, 124.6, 123.3, 123.3, 123.2, 119.4, 117.9, 116.9, 60.4, 54.2, 52.3, 48.2, 46.1, 36.0, 30.6, 28.5, 24.7; **FT-IR** (thin film, cm- 1) v_{max} = 2954, 1741, 1712, 1456, 1369, 1318, 718; **HRMS** calc'd for $C_{28}H_{24}N_2O_8$ [M+] 516.1533 found 516.1536



3-61

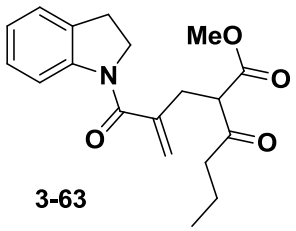
Using a modification of Wang's procedure[45], formaldehyde (1.73 g, 57.7 mmol), DABCO (1.29 g, 11.54 mmol) and phenol (0.271 g, 2.88 mmol) were dissolved in 4 mL of a 3:7 mixture of $^{t}BuOH/H_2O$ and heated to 55^{o}C. Compound **3-60** (2.00 g, 11.54 mmol) was added to the solution and stirred overnight at 55^{o}C. The solution was extracted three times using DCM. The combined organic layers were washed with water and brine and dried with $MgSO_4$. The product was filtered and concentrated *in vacuo* and purification by flash chromatography yielding 1.22 g of compound **3-61** (6.00 mmol, 52%) **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.13-7.90 (broad m, 1H), 7.20 (m, 2H), 7.05 (apparent t, J = 7.4 Hz, 1H), 5.64 (s, 1H), 5.46 (s, 1H), 4.42 (d, J = 6.3, 2H), 4.17 (t, J = 8.2 Hz, 2H), 3.13 (t, J = 8.2 Hz, 2H), 2.54 (broad t, J = 6.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 168.6, 145.2, 142.1, 132.5, 127.3, 124.8, 124.3, 117.5, 116.4, 63.4, 50.3, 28.0; **FT-IR** (thin film, cm- 1) v_{max} = 3403 broad, 2910, 1620, 1591, 1483, 1421, 1037, 756; **HRMS** calc'd for $C_{12}H_{13}NO_2$ [M+] 203.0946, found 203.0946.



3-62

Compound **3-61** (0.500 g, 2.46 mmol) was dissolved in 5 mL of Et_2O under argon and cooled to 0 ^{o}C in a round bottomed flask equipped with a magnetic stirrer. PBr_3 (0.242 mL, 2.58 mmol) was slowly added to the solution and the reaction was allowed to warm to room temperature. The formation of a white precipitate was immediately observed. The reaction was stirred for 5 hours at which point TLC analysis confirmed consumption of the starting material. Cold water was added dropwise, and the organic layer was separated. The aqueous layer was extracted 3 times using Et_2O and the combined organic layers were washed with brine and dried using $MgSO_4$. The product was filtered and the solvent removed *in* vacuo and purification by flash chromatography yielded 0.282 g (1.06 mmol, 43%) of compound **3-62** as a yellow oil. Rf = 0.72 (50% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.12 (broad m, 1H), 7.22 (m, 2H), 7.07 (dd, J = 7.0, 7.0 Hz, 1H), 5.67 (s, 1H), 5.42 (s, 1H), 4.30 (s, 2H), 4.24 (t, J = 8.2 Hz,

2H), 3.15 (t, J = 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 166.5, 142.2, 141.6, 132.5, 127.3, 124.8, 124.3, 118.9, 117.6, 50.2, 41.8, 32.4, 28.1; **FT-IR** (thin film, cm- 1) ν_{max} = 3033, 2964, 1650, 1623, 1596, 1482, 1418, 1392, 1259, 1212, 938, 756; **HRMS** calc'd for $C_{12}H_{12}BrNO$ [M+] 265.0102, found 265.0107.



3-63

NaH (0.011 g, 0.285 mmol, 60% dispersion in oil) was dissolved in 2 mL of THF under argon cooled to 0 ^{o}C in a round bottomed flask equipped with a magnetic stirrer. Keto-ester **3-47** (0.044 mL, 0.299 mmol) was added and stirred for 10 mins. Compound **3-62** (0.242 mL, 2.58 mmol) was slowly added to the solution and the reaction was kept at 0 ^{o}C. The reaction was allowed to stir for 30 mins at which point TLC analysis confirmed consumption of the starting material. Cold water was added dropwise, and the organic layer was separated. The aqueous layer was extracted 3 times using EtOAc and the combined organic layers were washed with brine and dried using $MgSO_4$. The product was filtered and the solvent removed *in* vacuo and purification by flash chromatography yielded 0.022 g (0.067 mmol, 24%) of compound **3-63** as a clear oil. Rf = 0.30 (40% EtOAc in hexanes); **^{1}H NMR** (400 MHz , $CDCl_3$): δ = 8.00 (broad m, 1H), 7.20 (m, 2H), 7.04 (dd, J = 7.6, 7.0 Hz, 1H), 5.39 (s, 1H), 5.32 (s, 1H), 4.07 (t, J = 8.2 Hz, 2H), 3.97 (t, J = 7.6 Hz, 2H), 3.71 (s, 3H), 3.11 (t, J = 8.2 Hz, 2H), 2.97 (dd, J = 14.7, 7.0 Hz, 1H), 2.86 (dd, J = 14.7, 7.6 Hz, 1H), 2.57 (m, 2H), 1.60 (qt, J = 7.6, 7.0 Hz, 2H), 0.89 (t, J = 7.6 Hz, 3H).

4 Summary

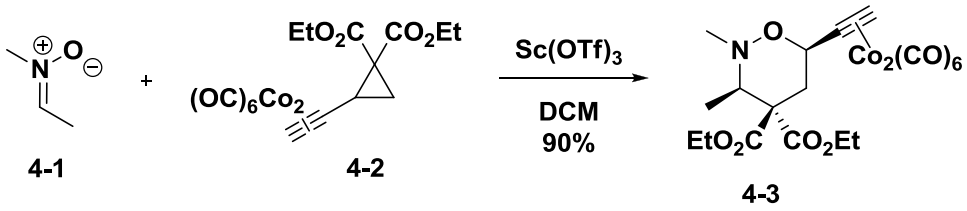
4.1 Progress Towards the Flinderoles

After a brief optimization of our cyclopropane ring opening reaction using indoline, a substrate scope was completed using tertiary cyclopropanes resulting in nine examples of substrates available for cyclization. Each of the substrates underwent ring opening in good to excellent yields. Unfortunately, attempts to open quaternary cyclopropanes using indoline under a variety of conditions led to decomposition, halting our proposed synthesis of the flinderoles.

The pendant malonyl substrates which we were able to access were then treated with manganese(III) acetate and underwent oxidative cyclizations in good yields. This work has proven that manganese(III) acetate can be very effective in the oxidative cyclization of the indoline pendent malonyl groups regardless of functionality. It is apparent that the use of manganese(III) towards other more complex systems will likely be a valuable commodity in accessing various pyrroloindole containing natural products.

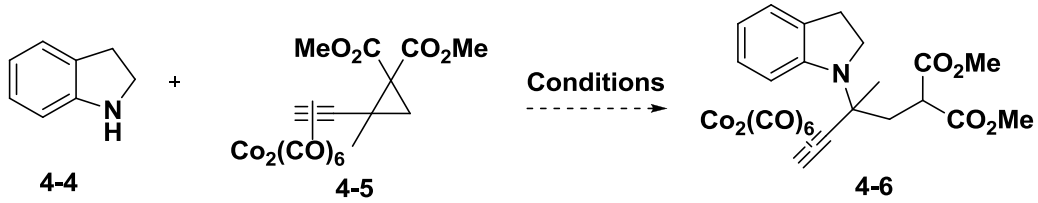
4.1.1 Future Work towards Flinderoles

Investigations into the quaternary cyclopropane ring opening reaction remain the main focus for the future work on synthesizing the flinderoles. In 2006, Kerr and Carson[49] published work showing nitrone **4-1** under Lewis acidic conditions underwent a [3+2] dipolar cycloaddition with Nicholas activated cyclopropanes **4-2** to form tetrahydro-1,2-oxazines **4-3** in increased yields and decreased reaction times compared to non-activated cyclopropanes (scheme 4.1).[49] When treated with $Co_2(CO)_8$ ethynyl cyclopropane forms the $Co_2(CO)_6$ complex, which is believed to help further stabilize the developing positive charge during the mechanism.



Scheme 4.1. Opening of Nicholas activated cyclopropanes using nitrones

Due to the difficulty we are having with the quaternary cyclopropane ring opening reaction, we anticipate employing the use of Nicholas activated ethynyl cyclopropane **4-5**, where cobalt coordination will aid in activation of the quaternary center of the cyclopropane towards nucleophilic attack from the indoline to yield **4-6** (scheme 4.2).



Scheme 4.2. Future work using Nicholas activated cyclopropane

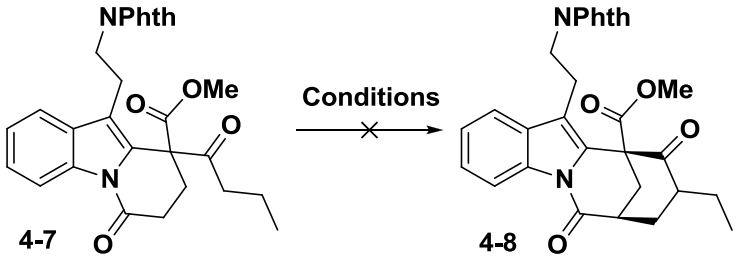
4.2 Progress towards Tronocarpine

The chapter explored several different synthetic routes toward the natural product tronocarpine. Considerable progress has been made to finding the best strategy to pursue tronocarpine, and several complicated and advanced compounds were successfully synthesized. Each of the routes discussed leaves significant potential to accessing not only tronocarpine, but also similar indole-containing natural products chippiine and dippinine B. The synthesis of a common intermediate towards these compounds was presented, as well as several steps in the proposed preparation of these particular products.

4.2.1 Future Work towards Tronocarpine

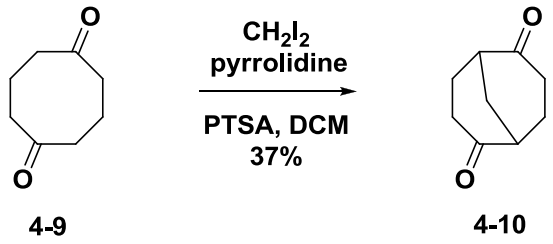
There are several appealing synthetic routes that hold great promise to access tronocarpine, chippiine and dippinine B. Future work would include investigation into the

loss of material, as well as varying reaction conditions such as base, solvent, and temperature to promote the alkylation step from compound **4-7** to compound **4-8** (scheme 4.3).



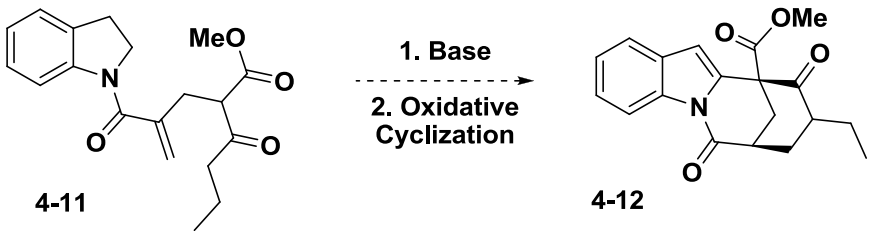
Scheme 4.3. Future work on alkylation step

One procedure published by Gerlach[50] showed that pyrrolidine and PTSA was able to activate diketone **4-9** toward nucleophilic attack of diiodomethane to yield **4-10** (scheme 4.4).



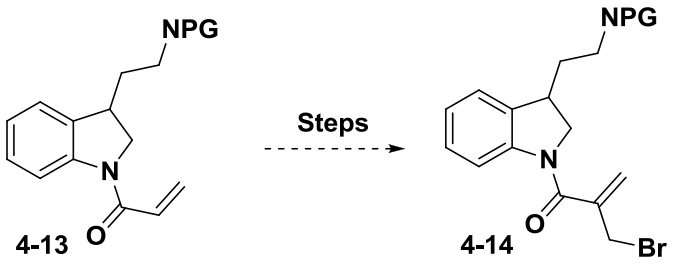
Scheme 4.4. Use of diiodomethane to form cyclohexane ring[50]

Other work that appears to hold great promise is the use of the exo-methylene functionality that is present upon addition into our Baylis-Hilman adduct (Scheme 4.5). With this Michael accepter present, it should serve as a handle for a future cyclohexane ring closing reaction. Treatment of **4-11** with excess base should promote the addition into the Michael acceptor and oxidative cyclization would yield **4-12** (scheme 4.5).



Scheme 4.5. Future work for double Michael addition

Should these steps proceed with little difficulty, application of this route to a tryptamine derivative **4-13** would likely be the next direction for this synthesis (scheme 4.6).



Scheme 4.6. Future work applied to tryptamine derivative

4.3 Conclusion

The use of manganese (III) acetate appears to have many applications toward oxidatively cyclizations with indoles and indolines. The synthesis of pyrroloindoles stemming from a cyclopropane ring opening reaction, and subsequent manganese oxidative cyclization has been well established. Application of the oxidative cyclization chemistry was proven to be effective in the synthesis of a variety of pyridoindole compounds, consistently proceeding in good yields. Regardless of complexity and ring size, the reliable success of this reagent in functionalizing the indole ring leaves many different avenues available for the total synthesis of not only the flinderoles, but tronocarpine, chippiine, and dippinine B as well.

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Appendix: ^{1}H and ^{13}C-NMR spectra

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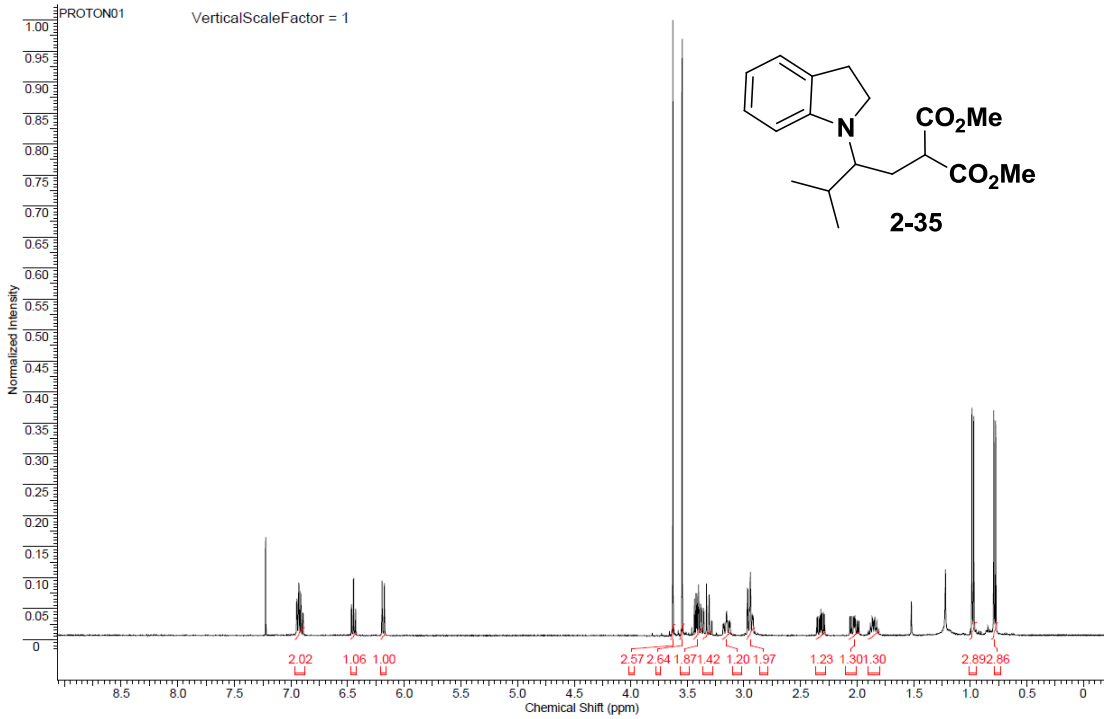

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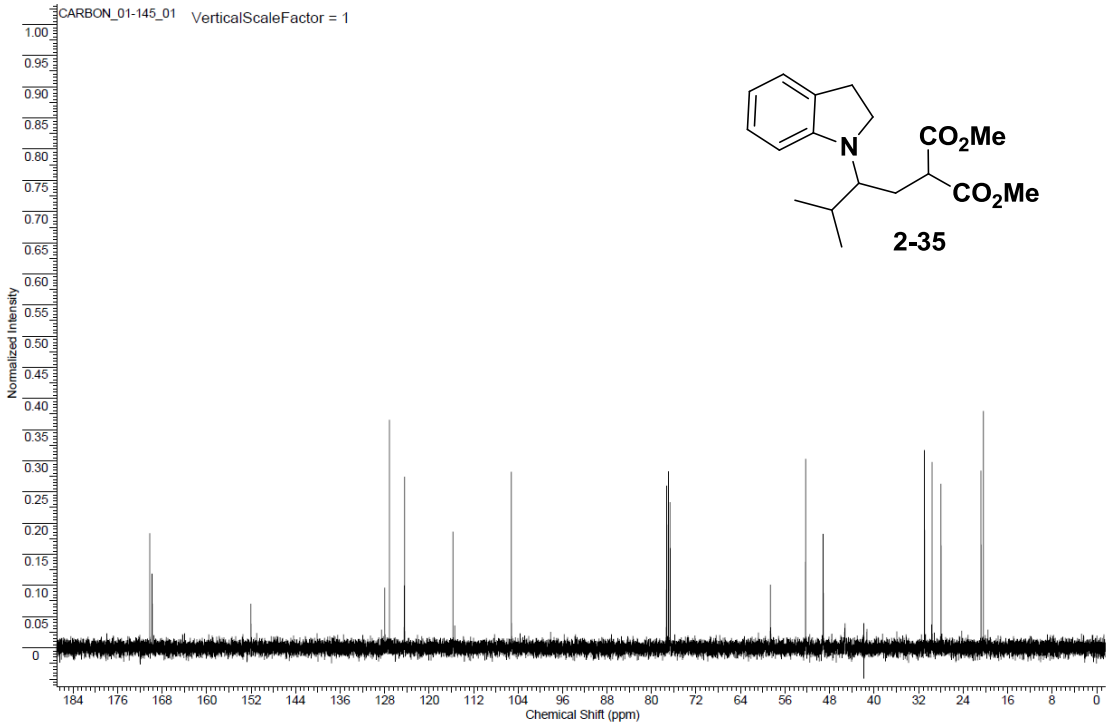

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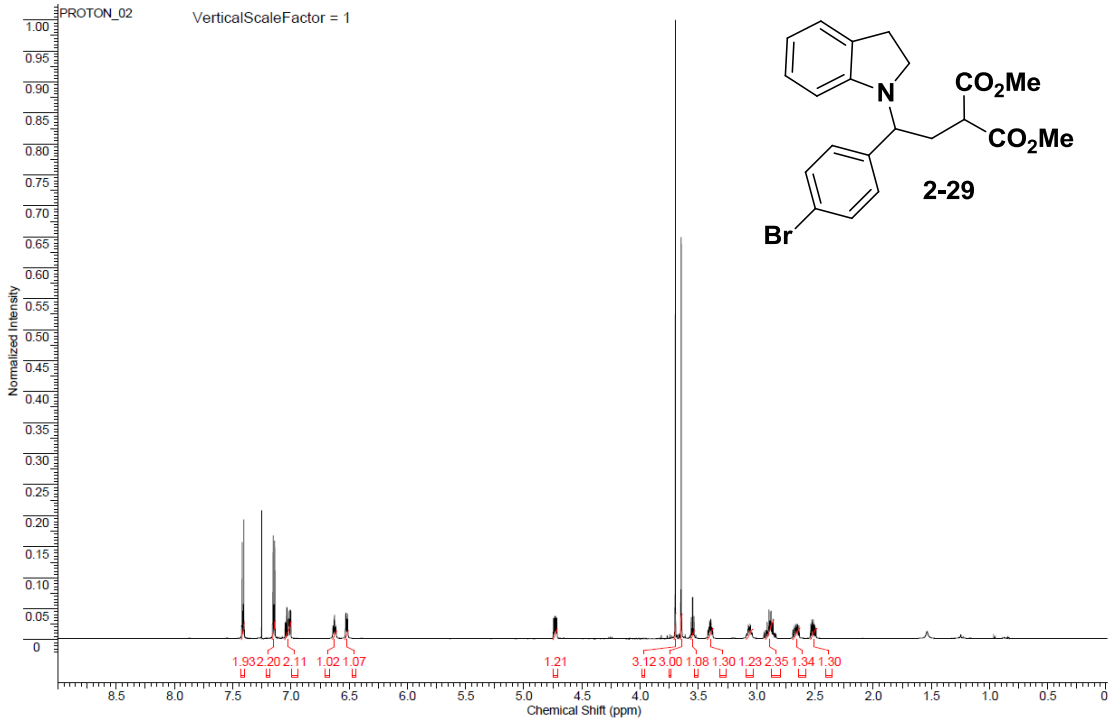

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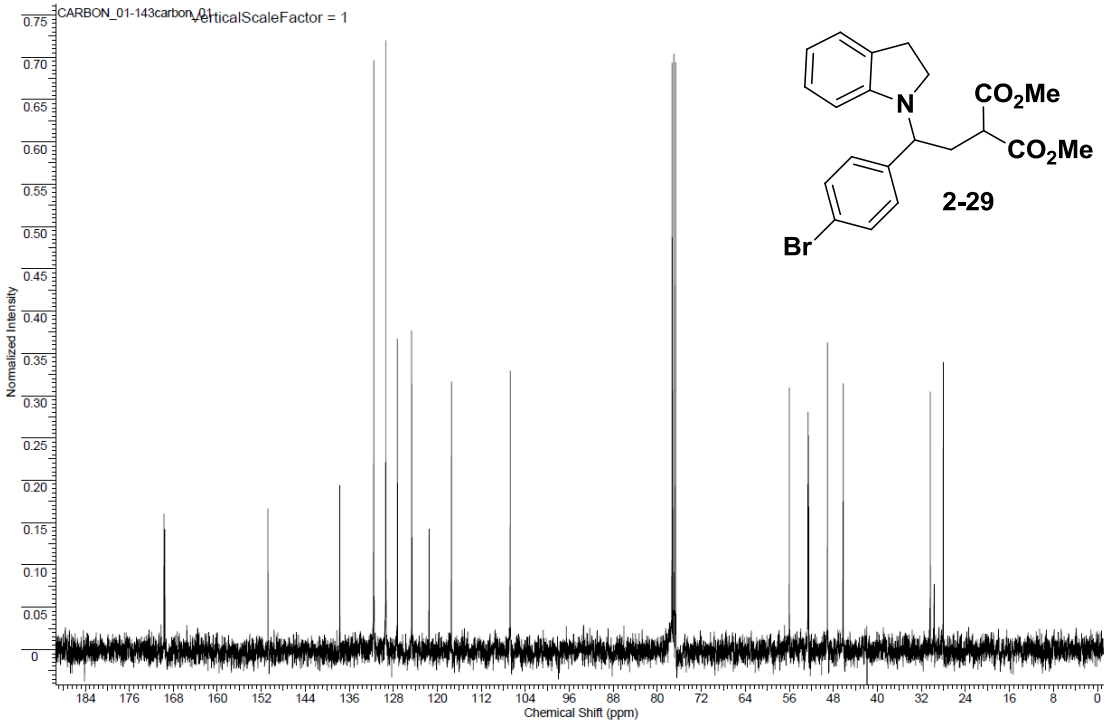

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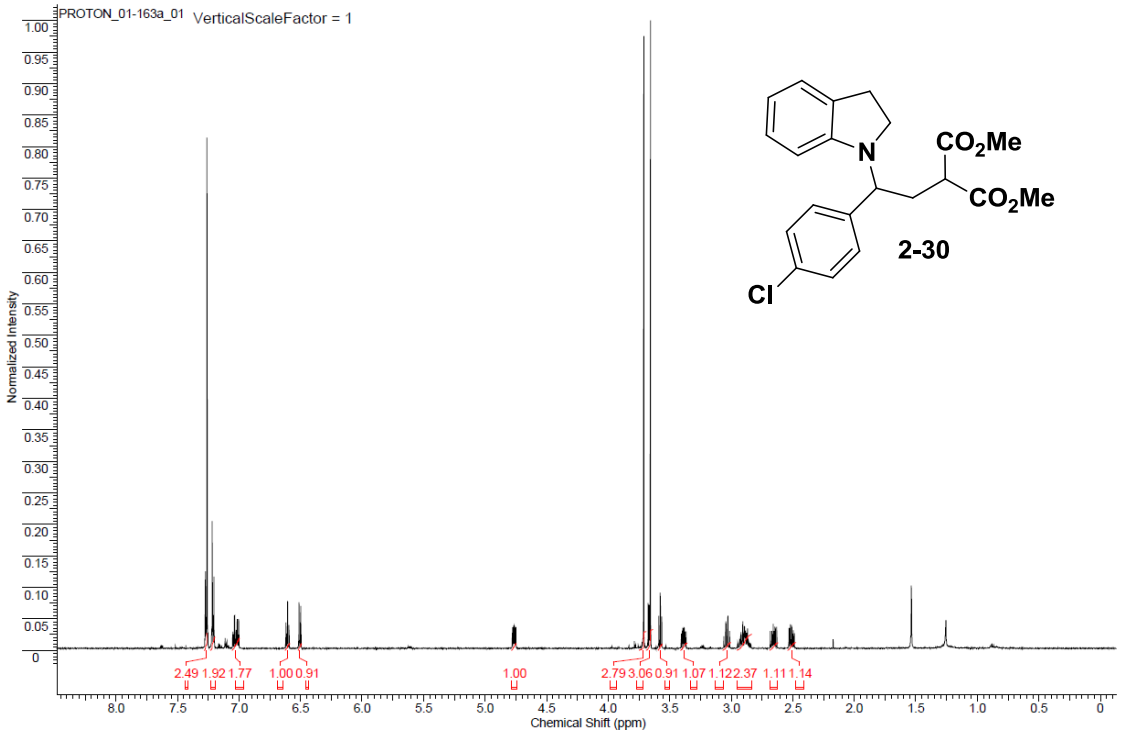

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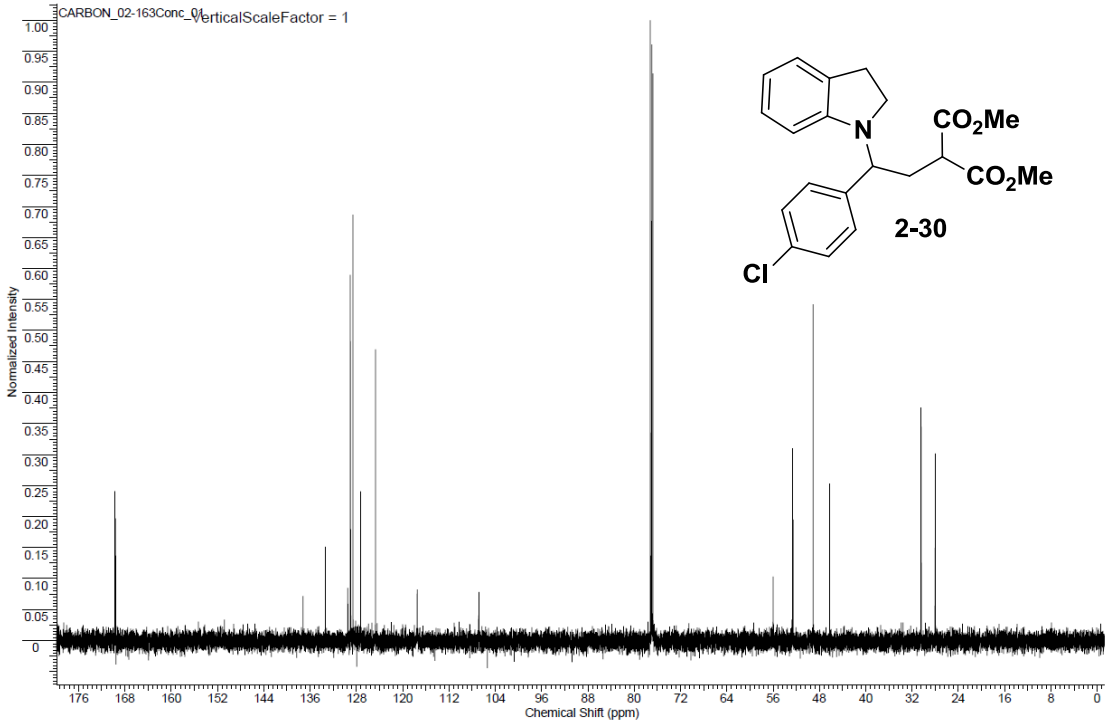

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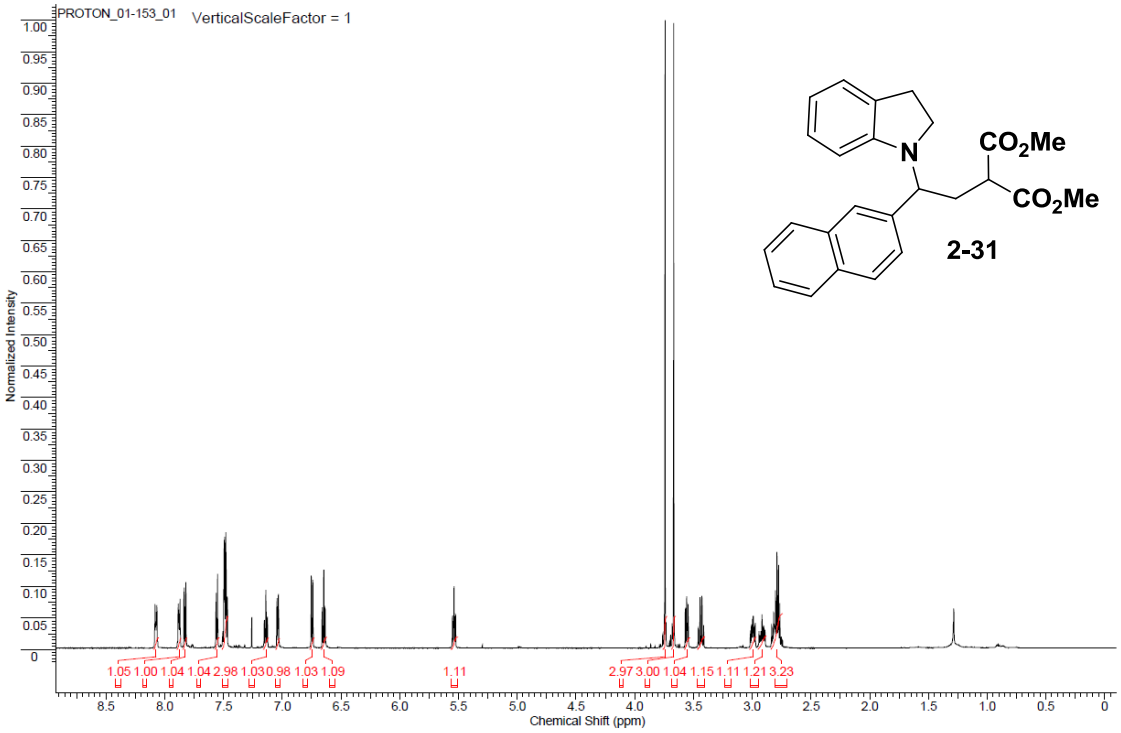

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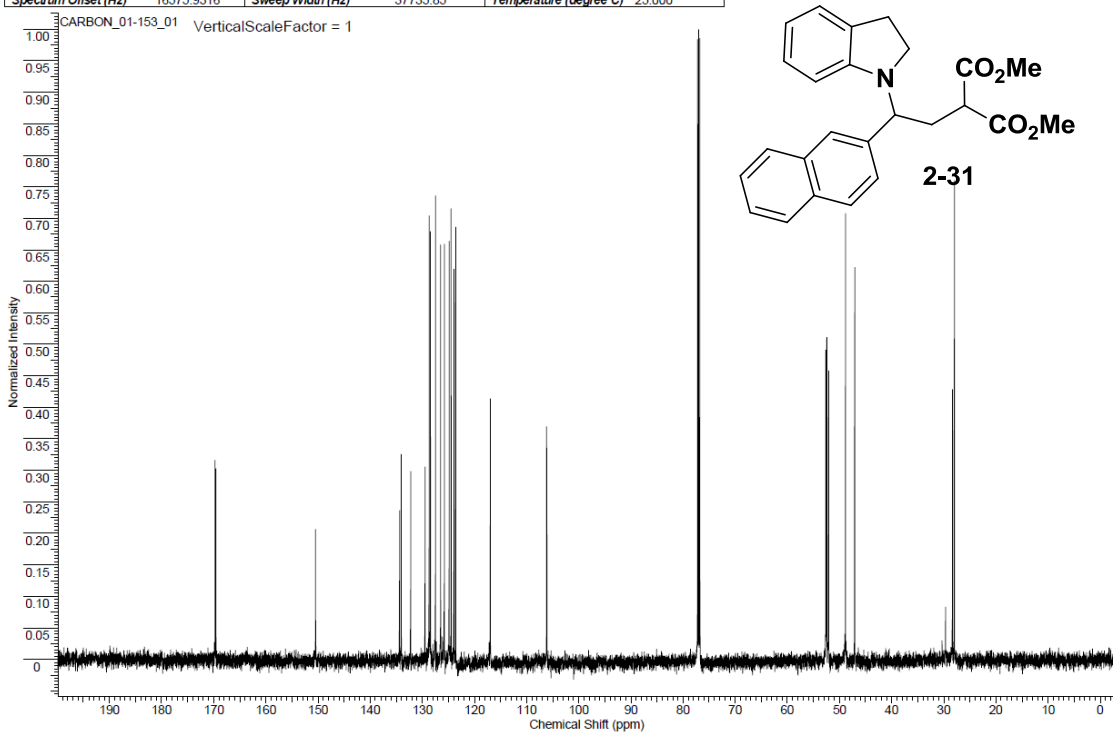

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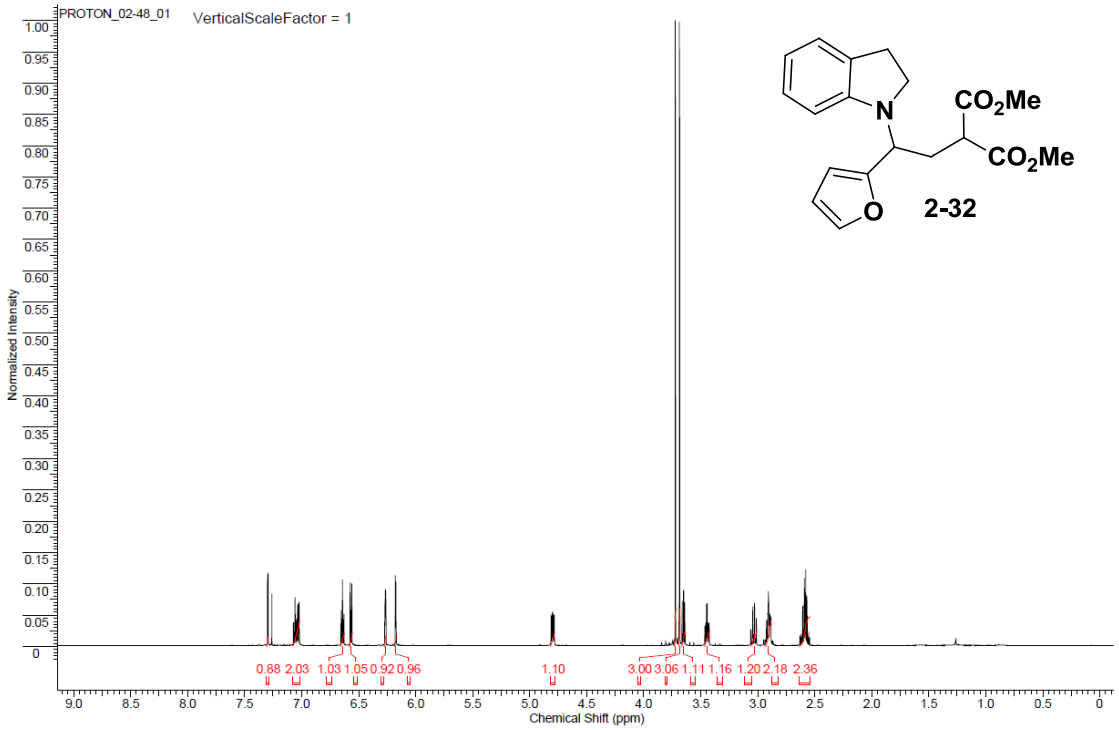

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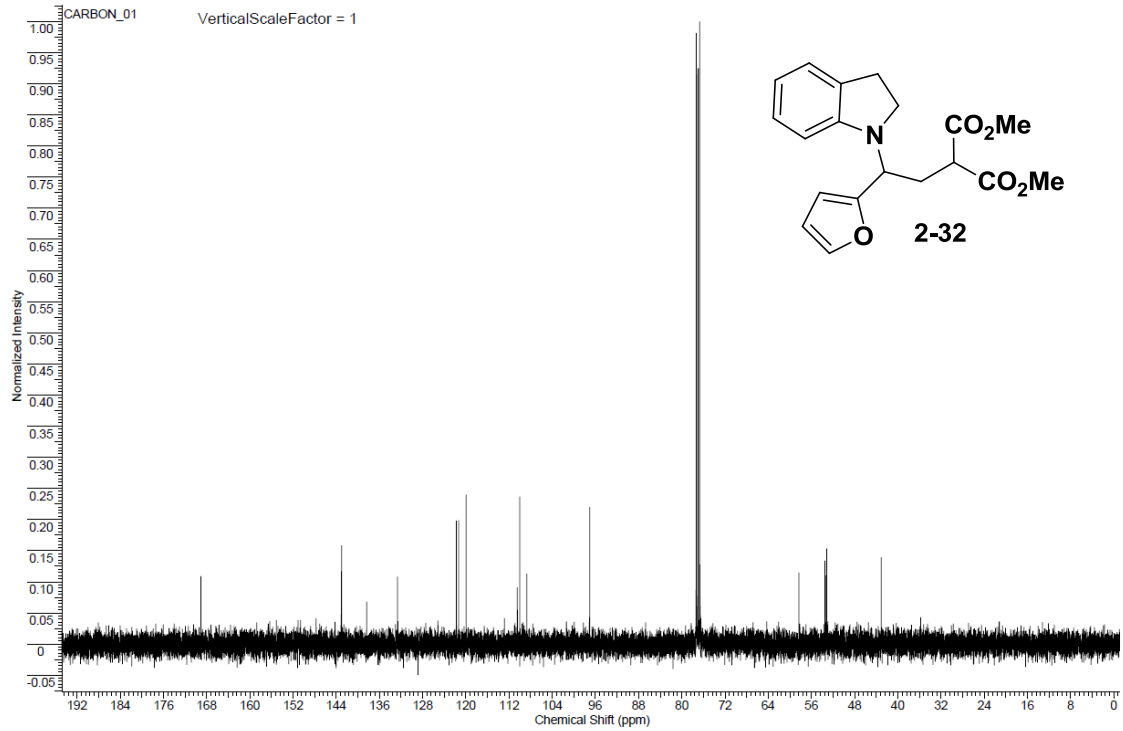

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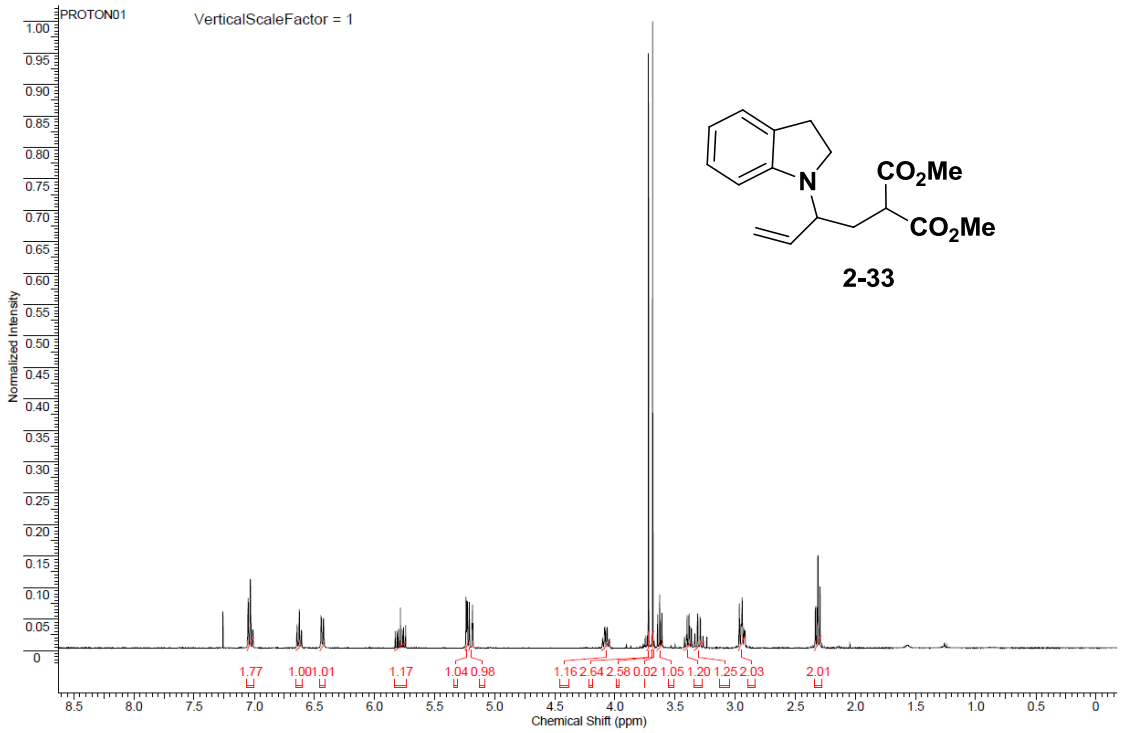

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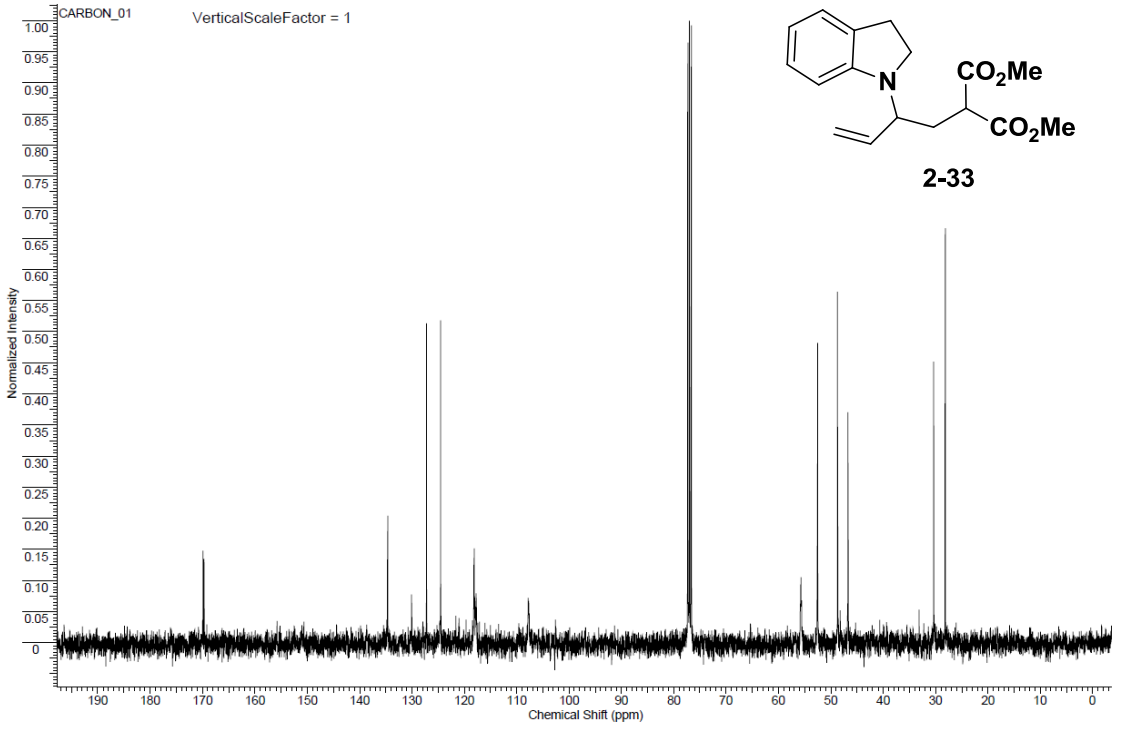

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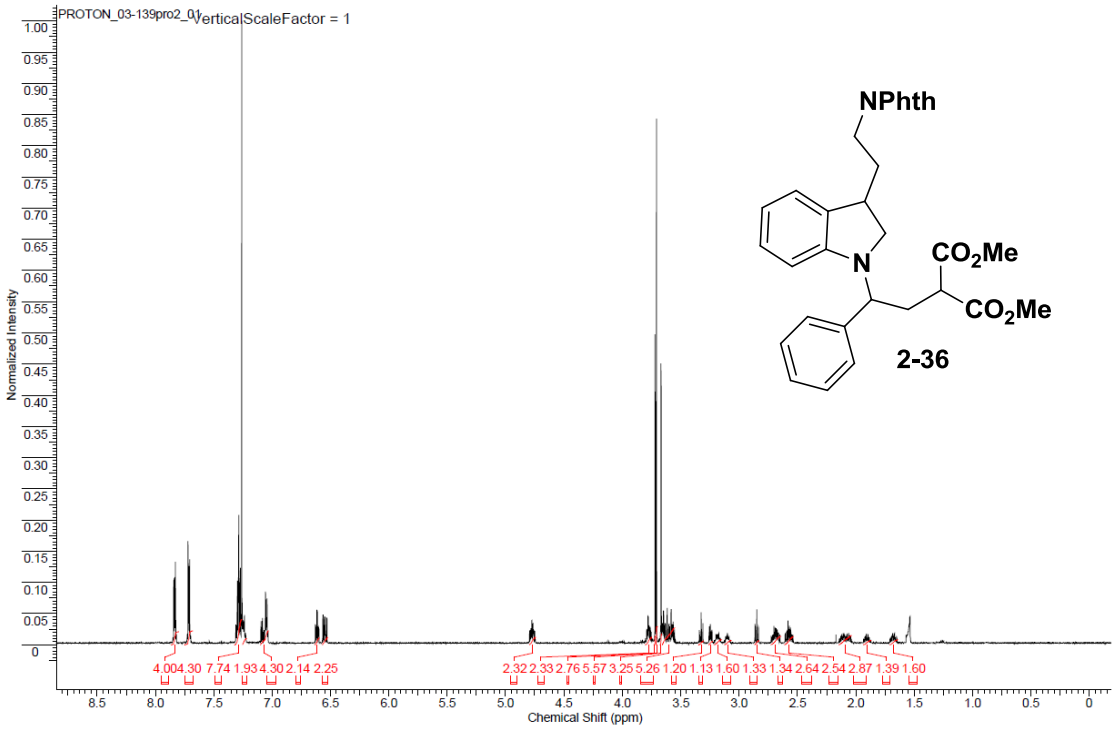

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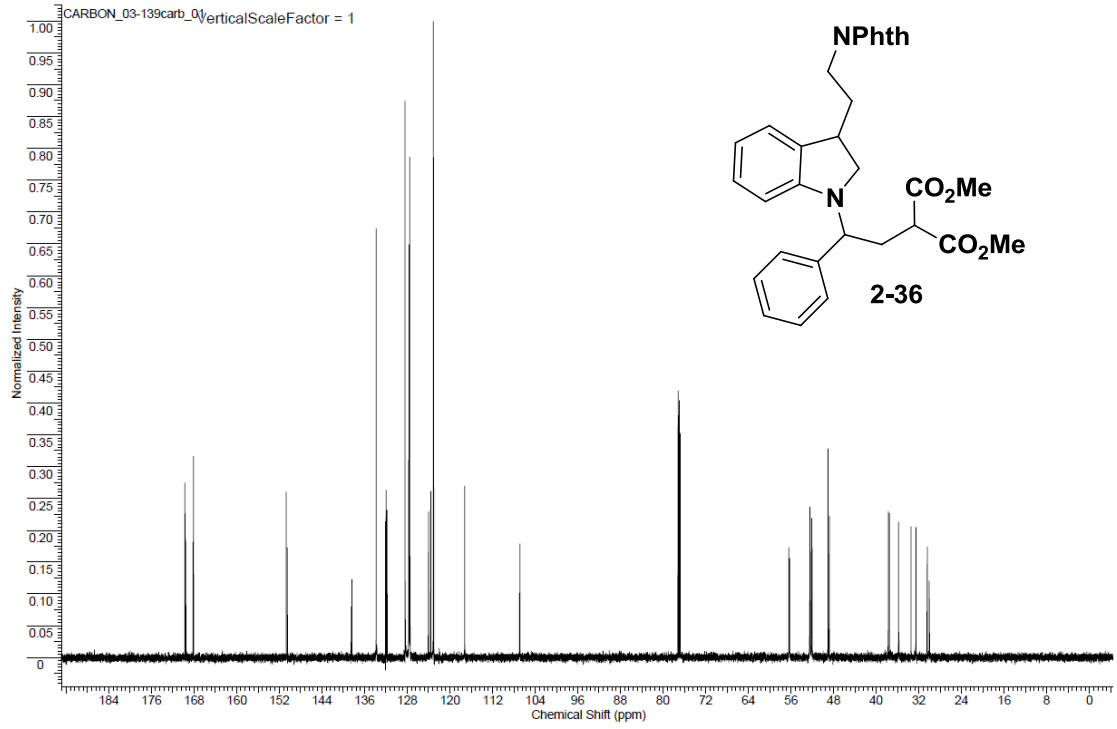

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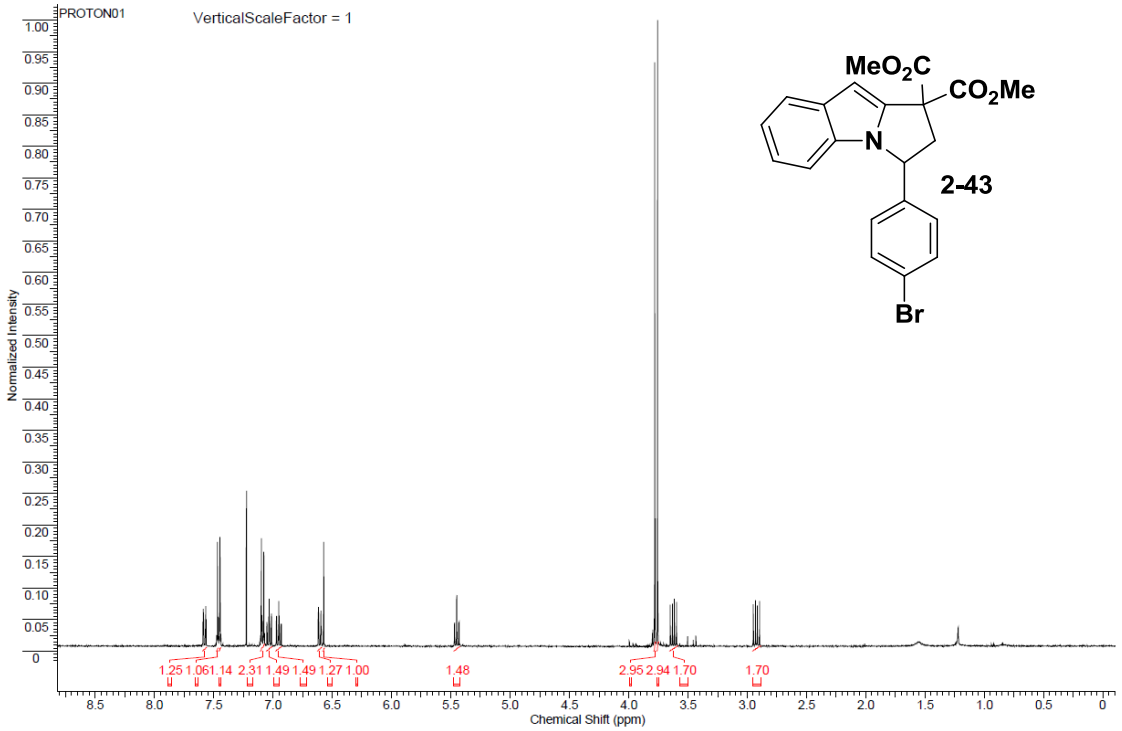

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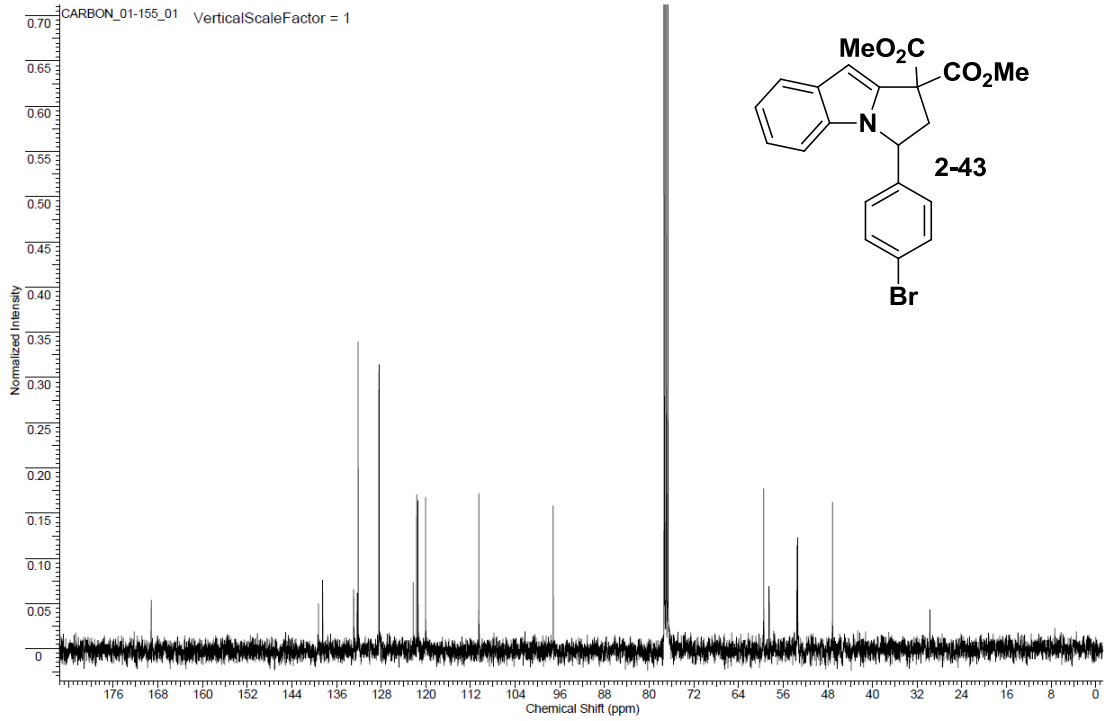
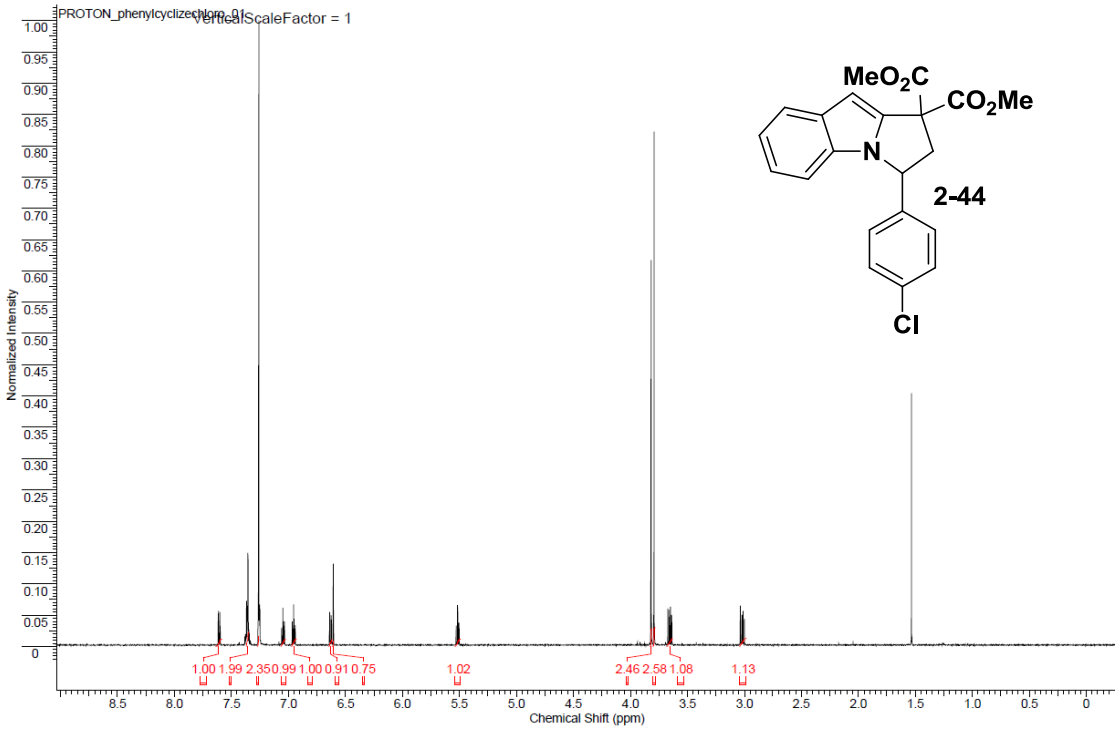
Nucleus	13C	*Number of Transients*	256	*Original Points Count*	32768	*Points Count*	131072
Pulse Sequence	s2pul	*Receiver Gain*	39.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11066.0342	*Sweep Width (Hz)*	25125.63	*Temperature (degree C)*	25.000		



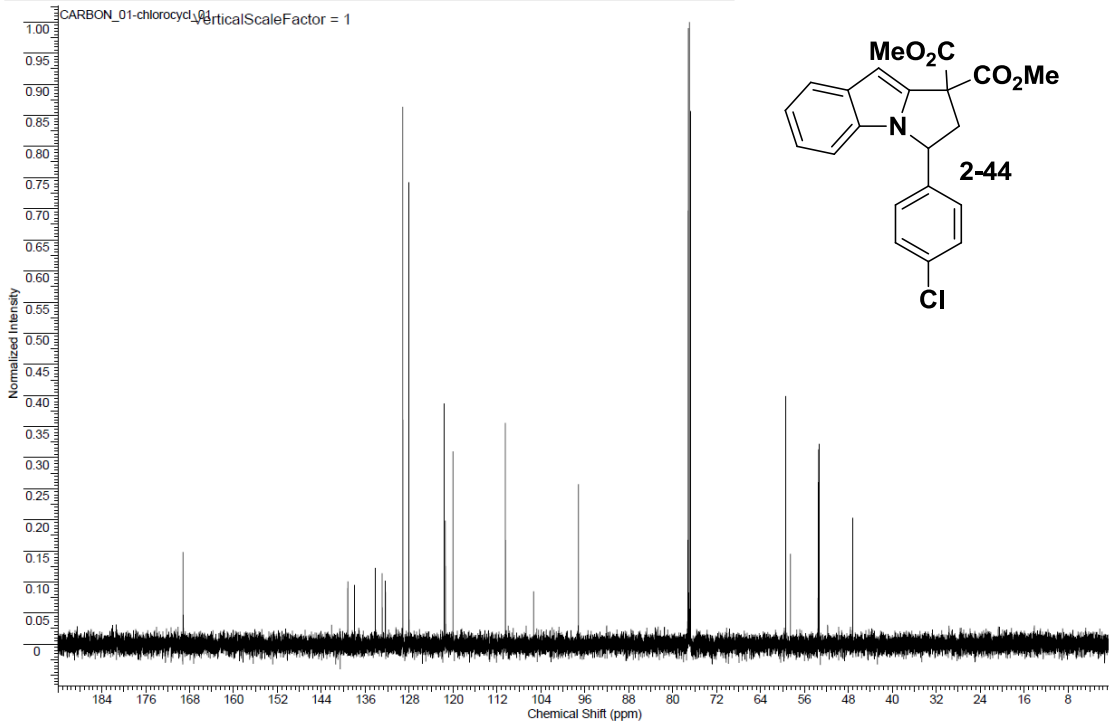
01/07/2014 11:46:08 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 23 2014	*Date Stamp*	Jun 23 2014		
File Name	C:\Users\someone\Desktop\Bryan\phenylcyclizechloro-2014.06.23_01\PROTON_phenylcyclizechloro_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	48.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3608.6177	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



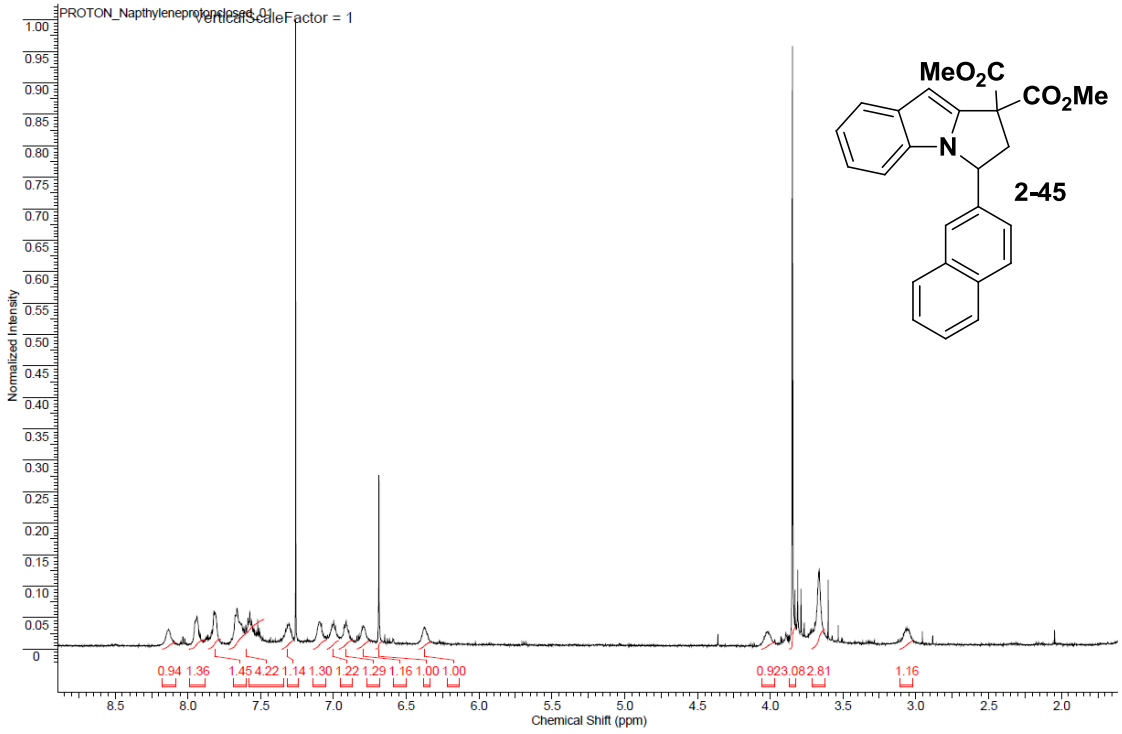
28/05/2014 3:32:47 PM

Acquisition Time (sec)	0.8684	*Date*	Dec 7 2013	*Date Stamp*	Dec 7 2013		
File Name	C:\Users\someone\Desktop\Bryan\PhCl cyclize\PhCl Cyclize\CARBON_01-chlorocycl_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	172	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16579.5879	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



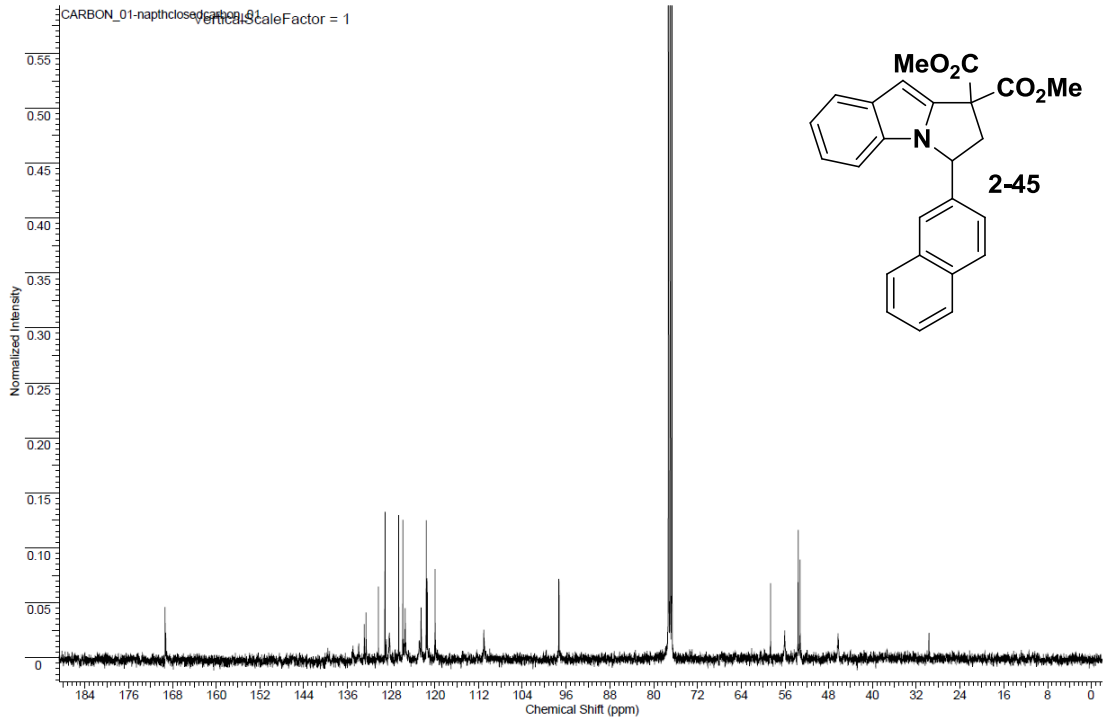
20/06/2014 1:16:01 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 19 2014	*Date Stamp*	Jun 19 2014		
File Name	C:\Users\someone\Desktop\Bryan\Napthyleneprotonclosed-2014.06.19_01\PROTON_Napthyleneprotonclosed_01						
Frequency (MHz)	599.40	*Nucleus*	1H	*Number of Transients*	8	*Original Points Count*	16384
Points Count	16384	*Pulse Sequence*	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d
Spectrum Offset (Hz)	3609.7910	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



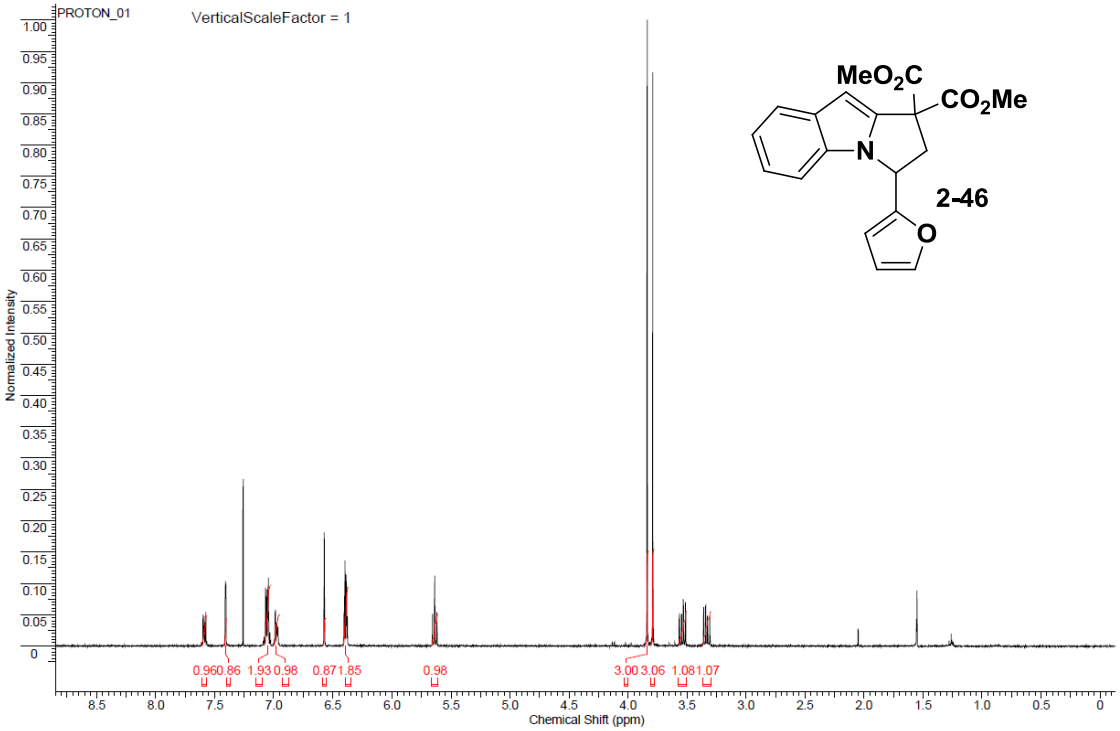
16/06/2014 11:05:41 PM

Acquisition Time (sec)	1.3042	*Comment*	Bryan	*Date*	May 30 2014	*Date Stamp*	May 30 2014
File Name	C:\Users\someone\Desktop\Bryan\01-napthclosedcarbon-2014.05.29_01\CARBON_01-napthclosedcarbon_01					*Frequency (MHz)*	100.61
Nucleus	13C	*Number of Transients*	1000	*Original Points Count*	32768	*Points Count*	131072
Pulse Sequence	s2pul	*Receiver Gain*	39.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11064.0625	*Sweep Width (Hz)*	25125.63	*Temperature (degree C)*	25.000		



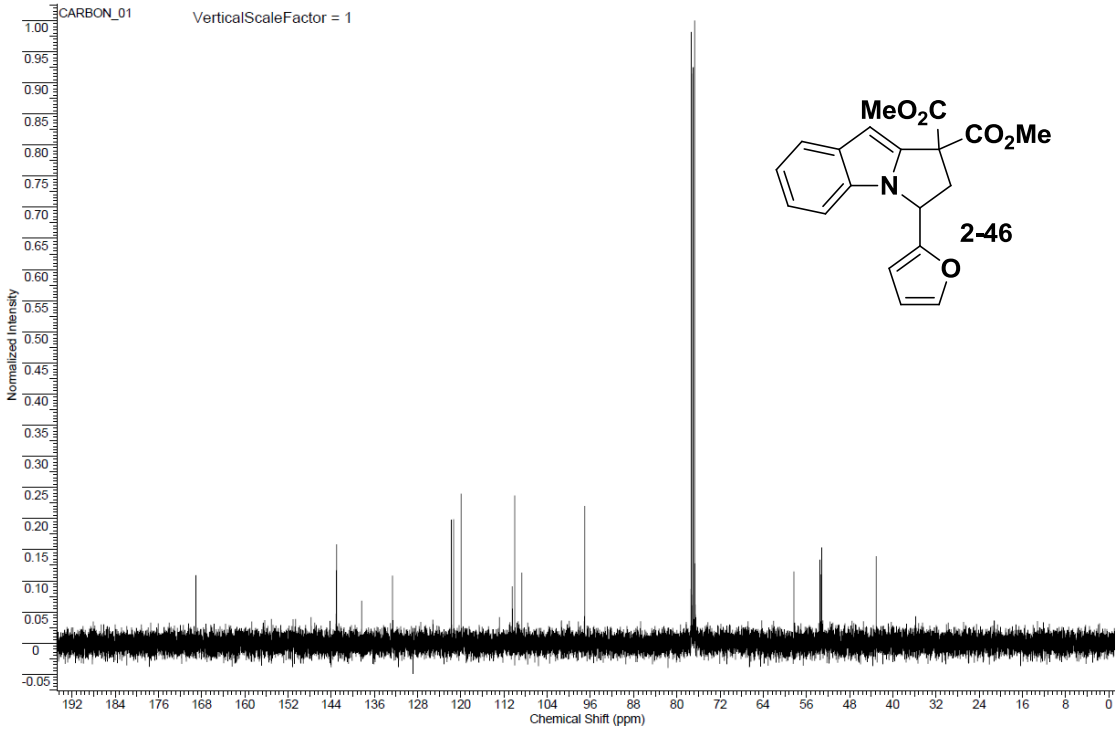
17/06/2014 1:56:26 PM

Acquisition Time (sec)	2.5592	*Comment*	Bryan	*Date*	Apr 2 2013	*Date Stamp*	Apr 2 2013
File Name	C:\Users\someone\Desktop\Bryan\02-51 Apr2 01\PROTON_01					*Frequency (MHz)*	400.08
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	39.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2402.6514	*Sweep Width (Hz)*	6402.05	*Temperature (degree C)*	25.000		



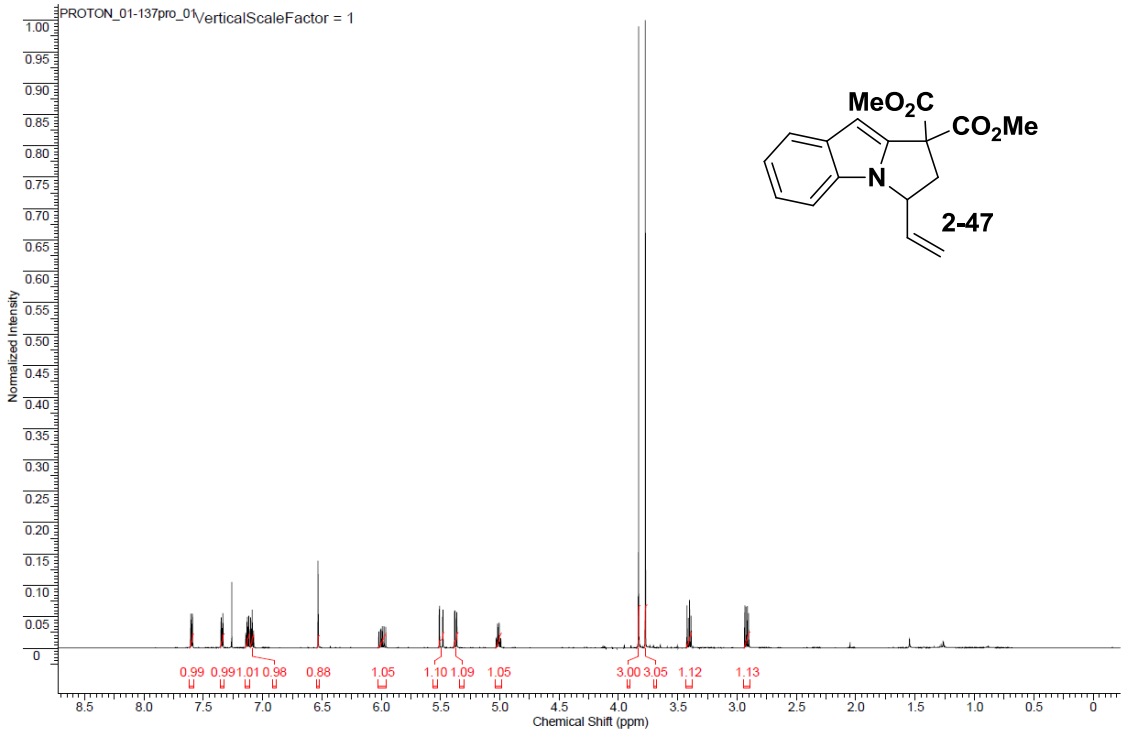
17/06/2014 2:00:16 PM

Acquisition Time (sec)	1.3042	*Comment*	Bryan	*Date*	Apr 2 2013	*Date Stamp*	Apr 2 2013
File Name	C:\Users\someone\Desktop\Bryan\02-51 Apr2 01\CARBON_01					*Frequency (MHz)*	100.61
Nucleus	13C	*Number of Transients*	1000	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	39.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11066.9189	*Sweep Width (Hz)*	25125.63	*Temperature (degree C)*	25.000		



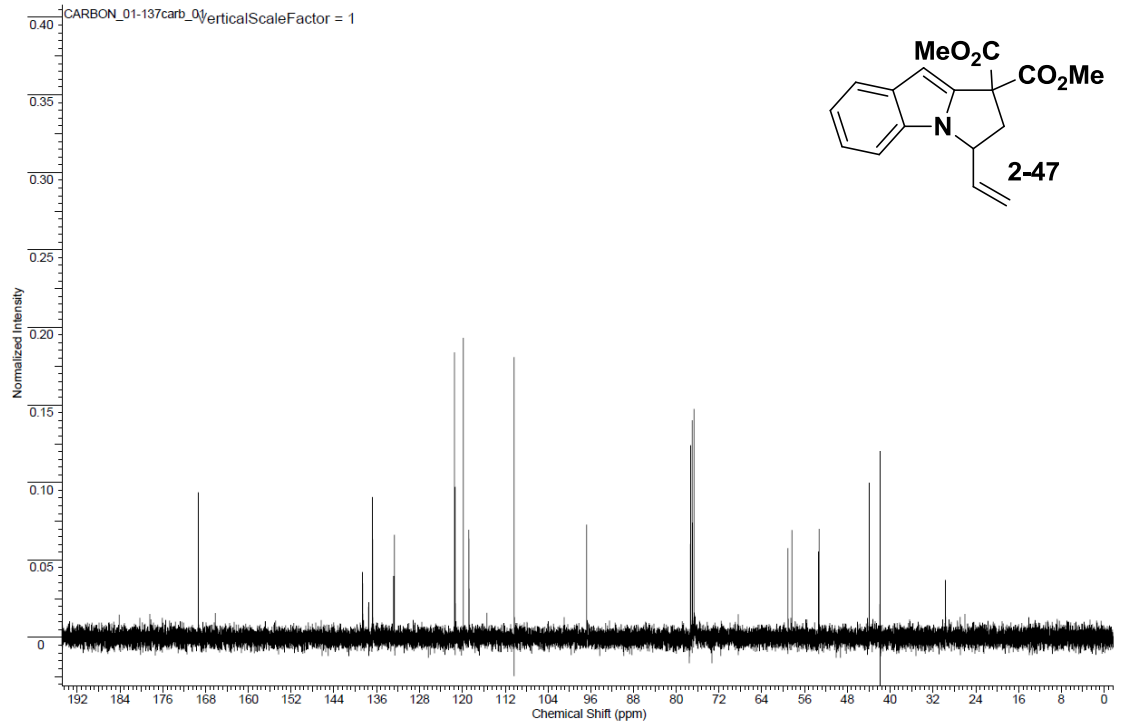
01/07/2014 11:36:34 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 25 2014	*Date Stamp*	Jun 25 2014		
File Name	C:\Users\someone\Desktop\Bryan\01-137pro-2014.06.25_01\PROTON_01-137pro_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3608.6177	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



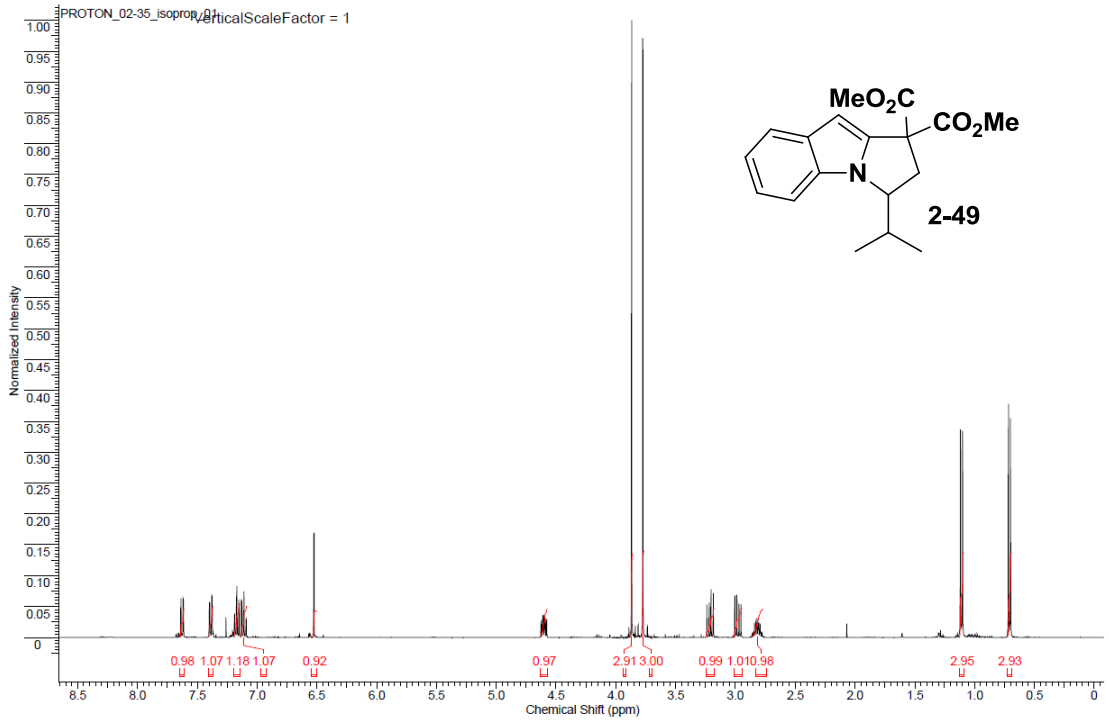
29/05/2014 6:42:41 PM

Acquisition Time (sec)	1.3038	*Date*	May 29 2014	*Date Stamp*	May 29 2014		
File Name	C:\Users\someone\Desktop\Bryan\01-137carb-2014.05.29_01\CARBON_01-137carb_01					*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	108	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11058.6875	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



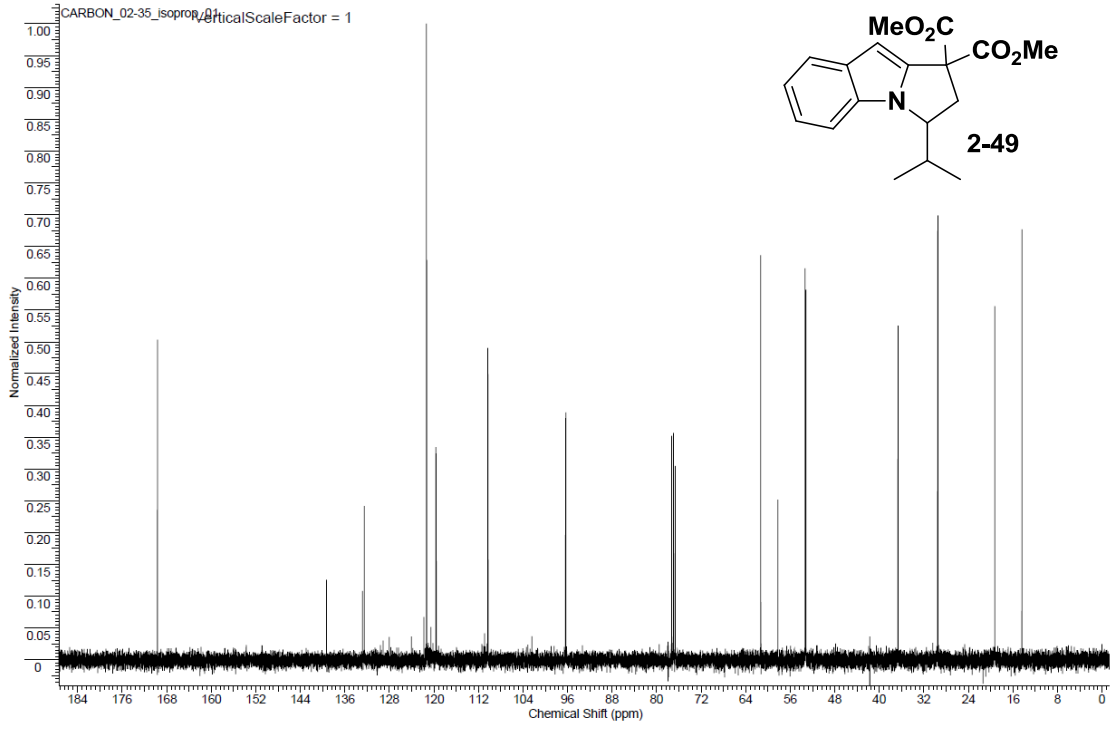
02/06/2014 5:33:03 PM

Acquisition Time (sec)	2.5616	*Comment*	INOVA 400	*Date*	Dec 10 2013	*Date Stamp*	Dec 10 2013
File Name	C:\Users\someone\Desktop\Bryan\02-35_isoprop-2013.12.10_01\PROTON_02-35_isoprop_01					*Frequency (MHz)*	399.76
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2412.9080	*Sweep Width (Hz)*	6395.91	*Temperature (degree C)*	25.000		



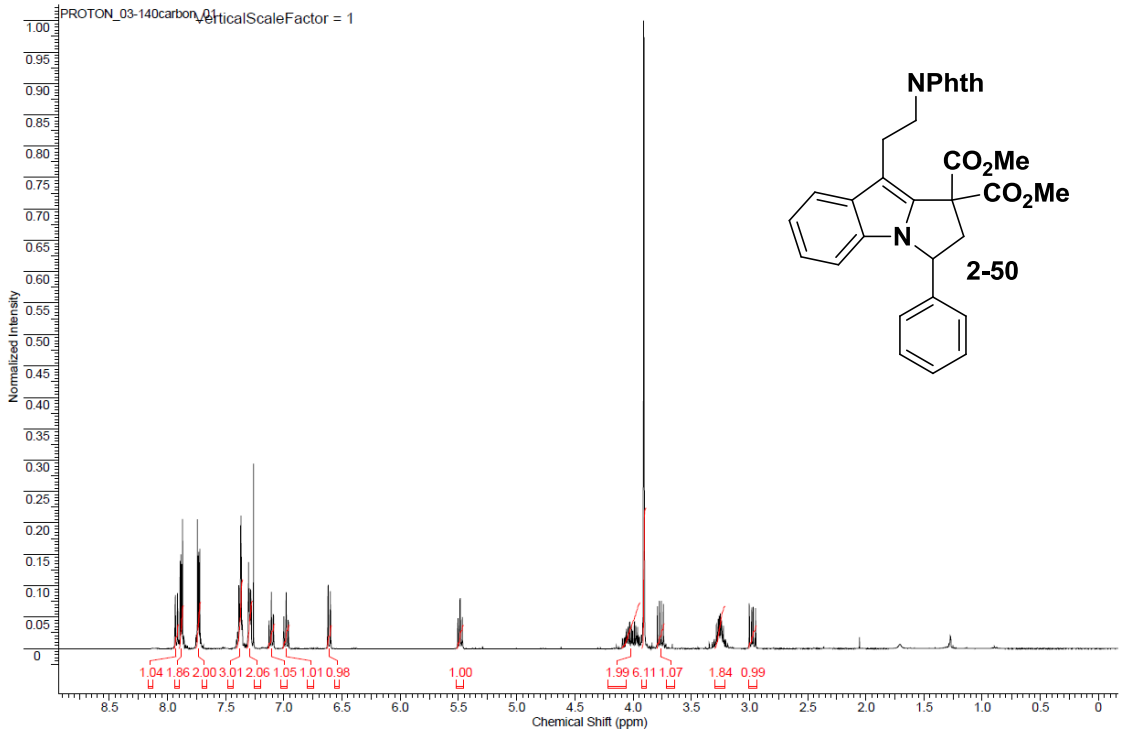
02/06/2014 5:34:46 PM

Acquisition Time (sec)	1.3038	*Comment*	INOVA 400	*Date*	Dec 10 2013	*Date Stamp*	Dec 10 2013
File Name	C:\Users\someone\Desktop\Bryan\02-35_isoprop-2013.12.10_01\CARBON_02-35_isoprop_01					*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	240	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11053.3184	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



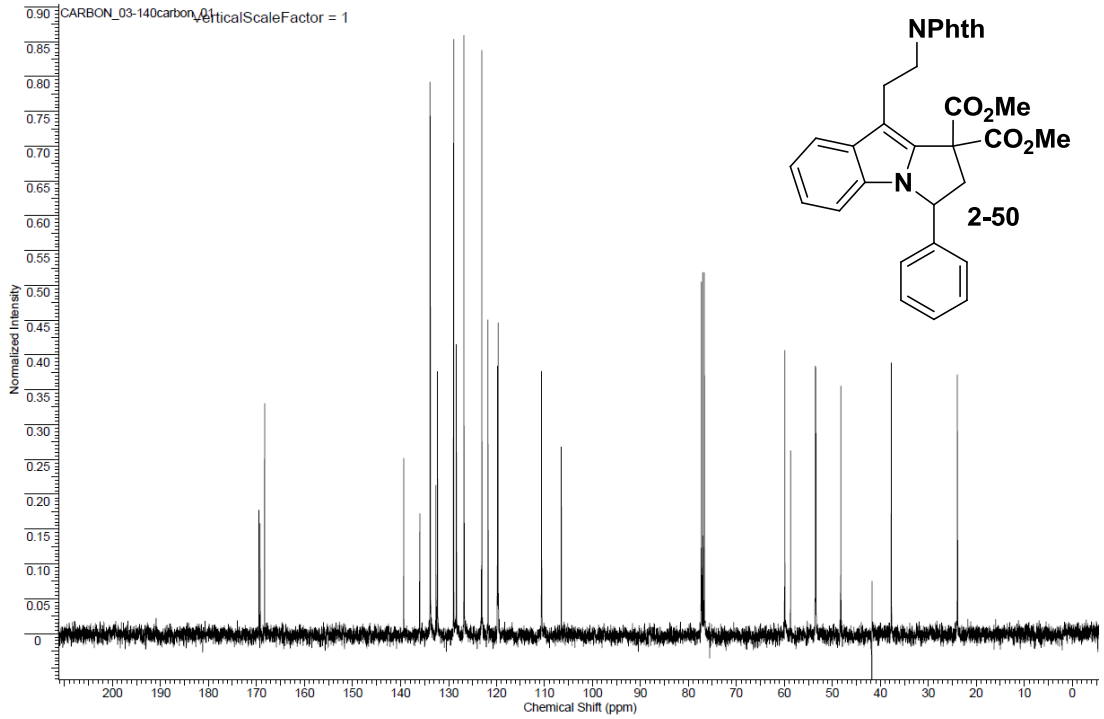
02/07/2014 12:22:14 AM

Acquisition Time (sec)	2.5616	*Comment*	MesNHC_MesNHEtCl			*Date*	Jun 30 2014
Date Stamp	Jun 30 2014	*File Name*	C:\Users\someone\Desktop\Bryan\03-140carbon-2014.06.30_01\PROTON_03-140carbon_01				
Frequency (MHz)	399.76	*Nucleus*	1H	*Number of Transients*	8	*Original Points Count*	16384
Points Count	16384	*Pulse Sequence*	s2pul	*Receiver Gain*	42.00	*Solvent*	CHLOROFORM-d
Spectrum Offset (Hz)	2412.9080	*Sweep Width (Hz)*	6395.91	*Temperature (degree C)*	25.000		



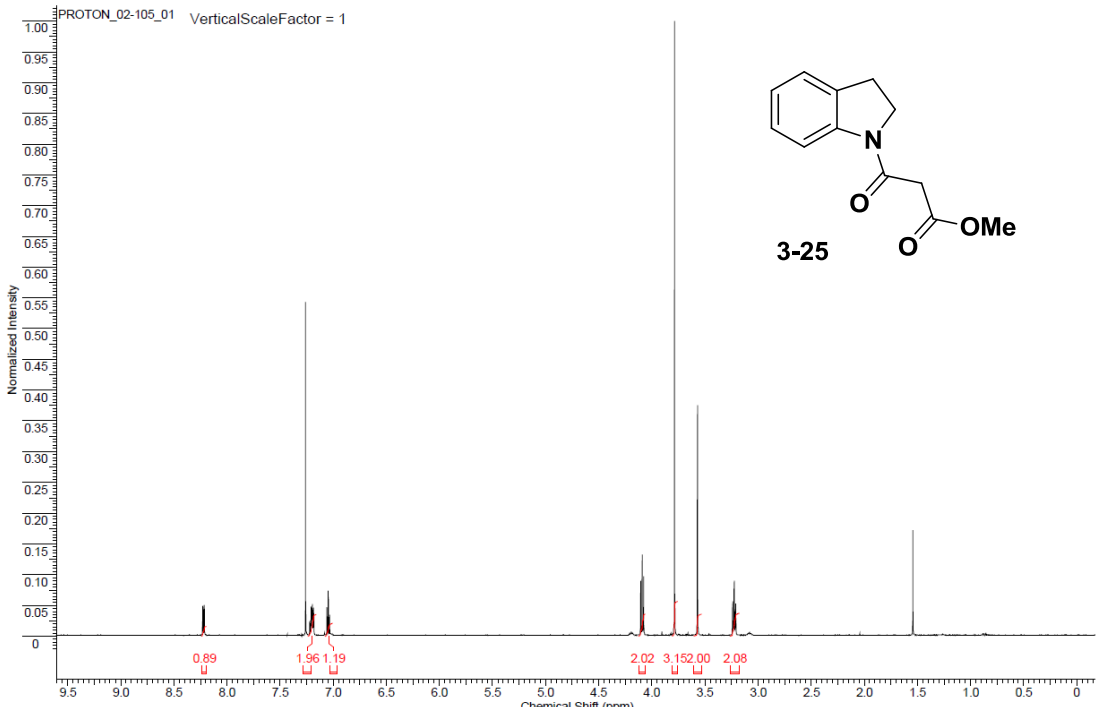
30/06/2014 8:02:21 PM

Acquisition Time (sec)	1.3038	*Comment*	MesNHC_MesNHEtCl			*Date*	Jun 30 2014
Date Stamp	Jun 30 2014	*File Name*	C:\Users\someone\Desktop\Bryan\03-140carbon-2014.06.30_01\CARBON_03-140carbon_01				
Frequency (MHz)	100.53	*Nucleus*	13C	*Number of Transients*	184	*Original Points Count*	32768
Points Count	65536	*Pulse Sequence*	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d
Spectrum Offset (Hz)	11055.3770	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



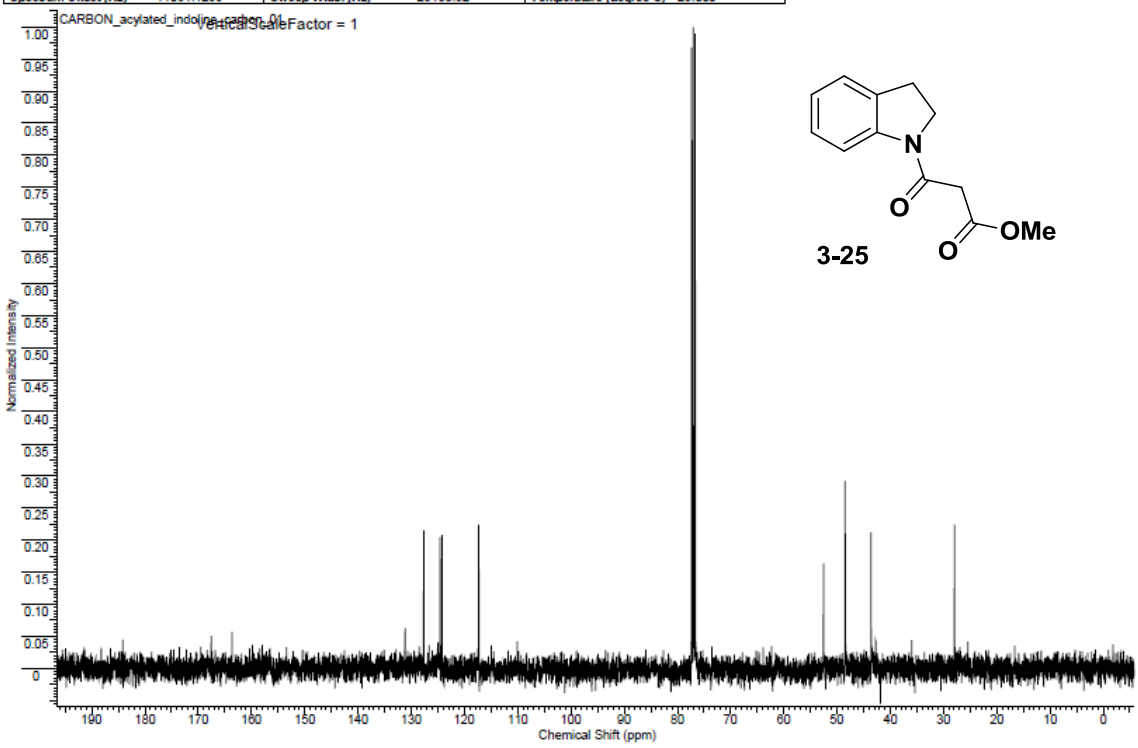
24/07/2014 2:22:43 PM

Acquisition Time (sec)	1.7046	*Date*	Jul 22 2013	*Date Stamp*	Jul 22 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-105-2013.07.22_01\PROTON_02-105_01					*Frequency (MHz)*	599.45
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	44.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3610.6997	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



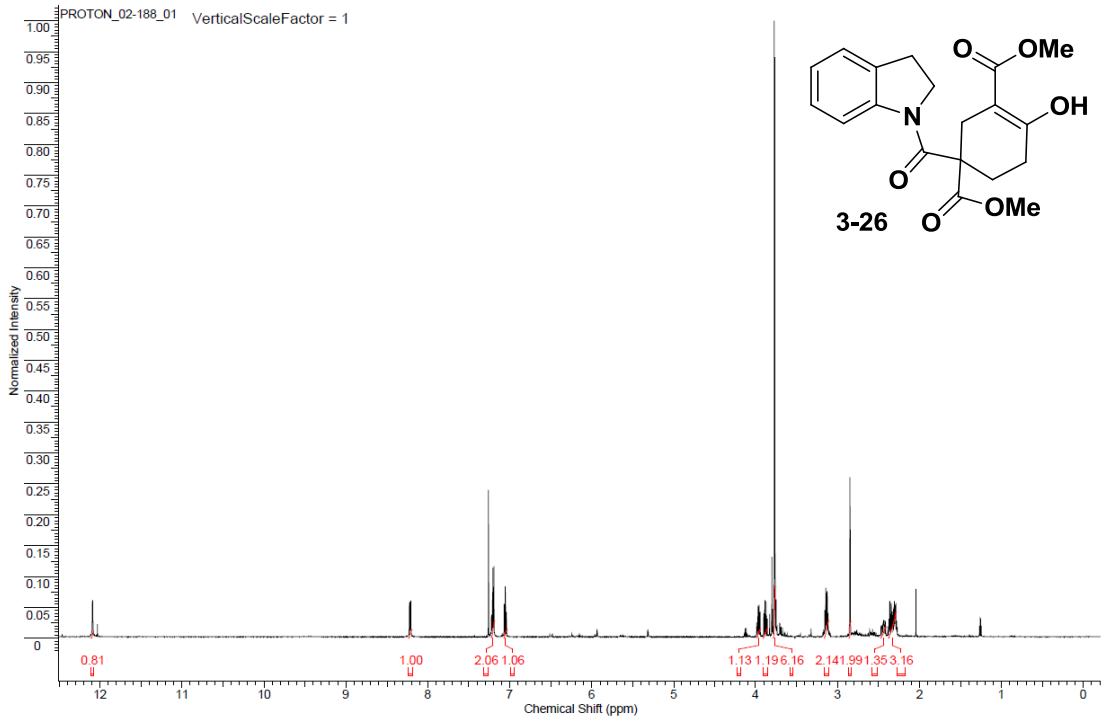
25/07/2014 4:12:07 PM

Acquisition Time (sec)	1.3038	*Date*	Jul 25 2014	*Date Stamp*	Jul 25 2014		
File Name	C:\Users\someone\Desktop\Bryan\acylated_indoline_carbon-2014.07.25_01\CARBON_acylated_indoline_carbon_01						
Frequency (MHz)	100.53	*Nucleus*	13C	*Number of Transients*	220	*Original Points Count*	32768
Points Count	65536	*Pulse Sequence*	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d
Spectrum Offset (Hz)	11061.1299	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



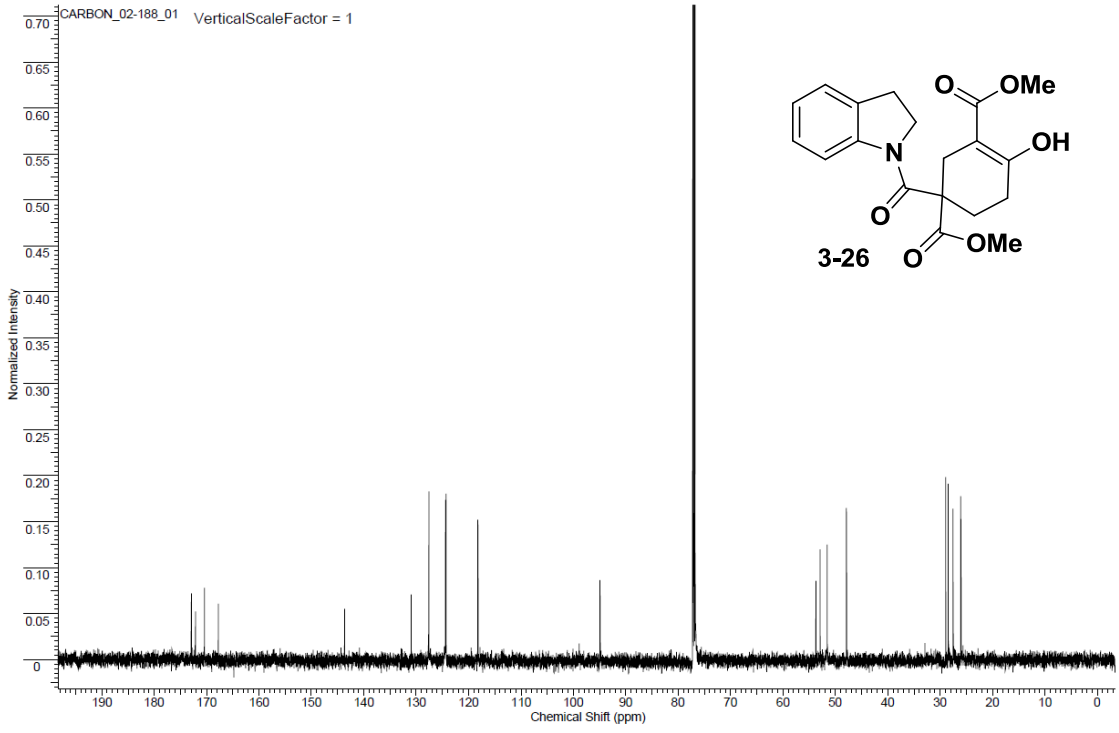
24/07/2014 2:46:17 PM

Acquisition Time (sec)	1.7046	*Date*	Nov 27 2013	*Date Stamp*	Nov 27 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-188-2013.11.27_01\PROTON_02-188_01					*Frequency (MHz)*	599.42
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3604.0332	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



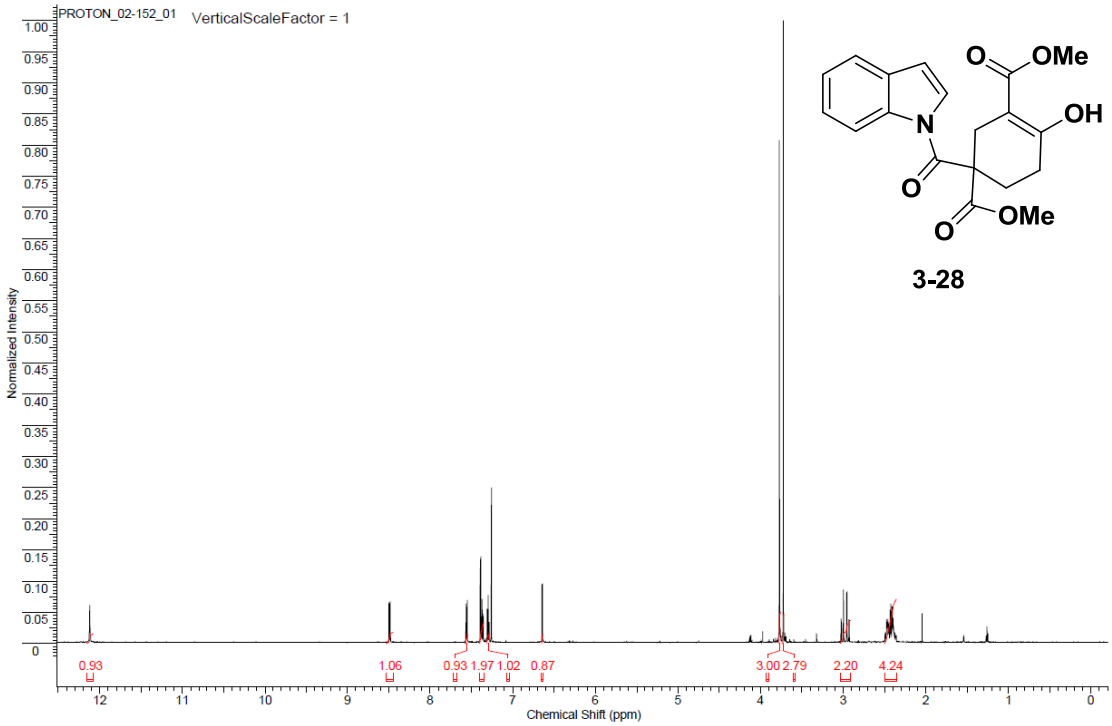
22/06/2014 8:26:01 PM

Acquisition Time (sec)	0.8684	*Date*	Nov 27 2013	*Date Stamp*	Nov 27 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-188-2013.11.27_01\CARBON_02-188_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	512	*Original Points Count*	32768	*Points Count*	131072
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16583.2344	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



22/06/2014 8:09:06 PM

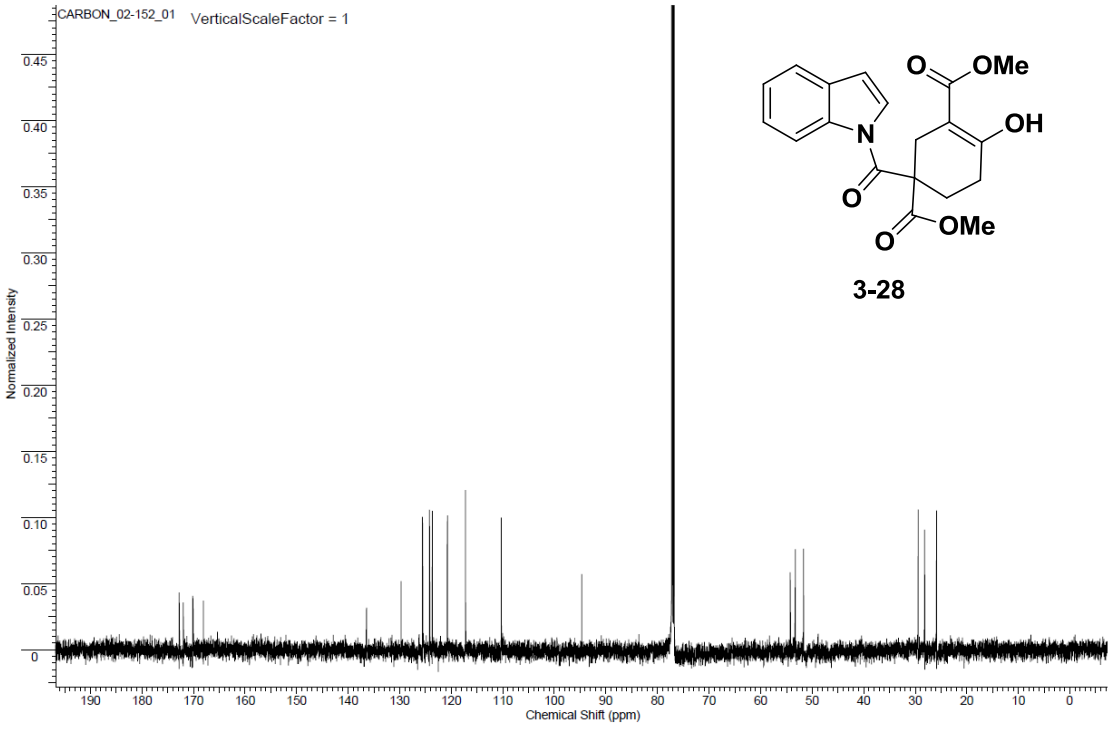
Acquisition Time (sec)	1.7046	*Date*	Nov 27 2013	*Date Stamp*	Nov 27 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-152-2013.11.27_01\PROTON_02-152_01					*Frequency (MHz)*	599.42
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3604.0332	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



3-28

22/06/2014 8:20:31 PM

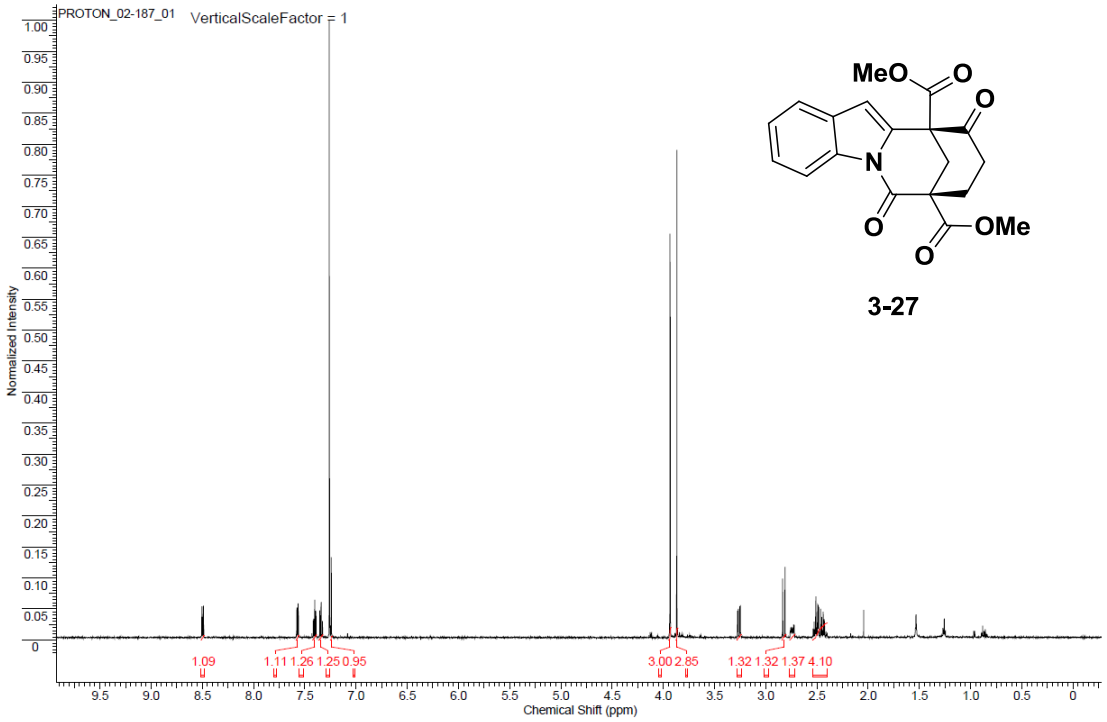
Acquisition Time (sec)	0.8684	*Date*	Nov 27 2013	*Date Stamp*	Nov 27 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-152-2013.11.27_01\CARBON_02-152_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	256	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16583.4160	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



3-28

22/06/2014 7:59:20 PM

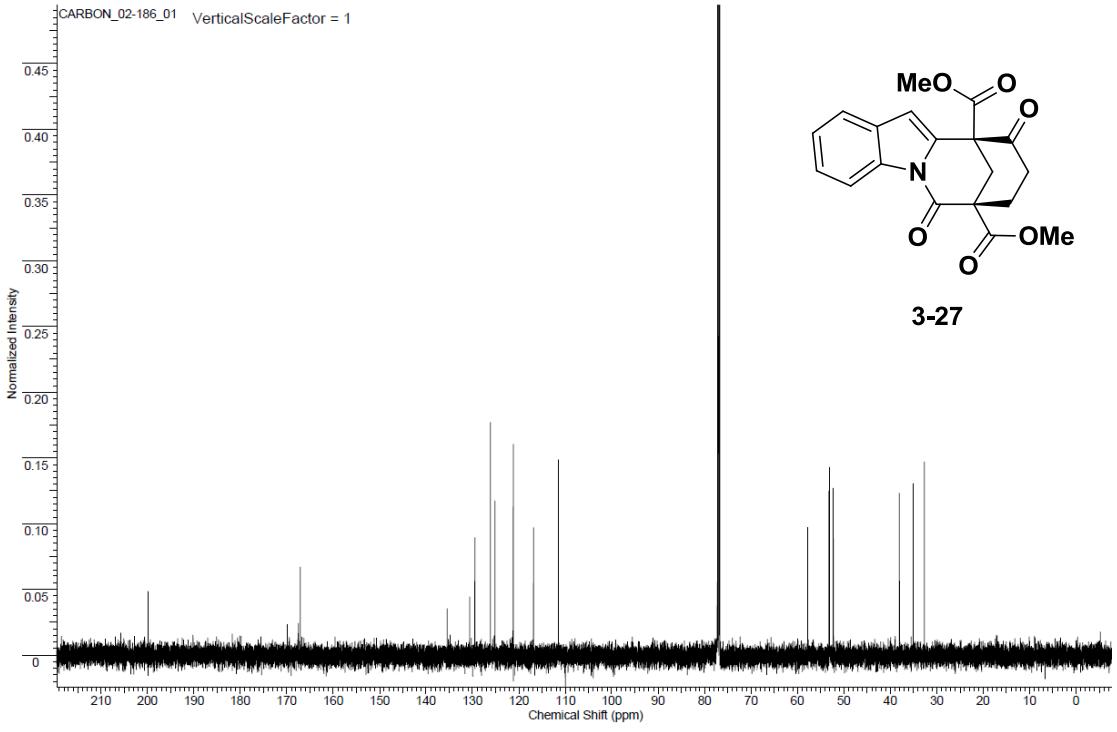
Acquisition Time (sec)	1.7046	*Date*	Nov 22 2013	*Date Stamp*	Nov 22 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-187-2013.11.22_01\PROTON_02-187_01					*Frequency (MHz)*	599.42
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	46.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3604.6194	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



3-27

22/06/2014 7:38:46 PM

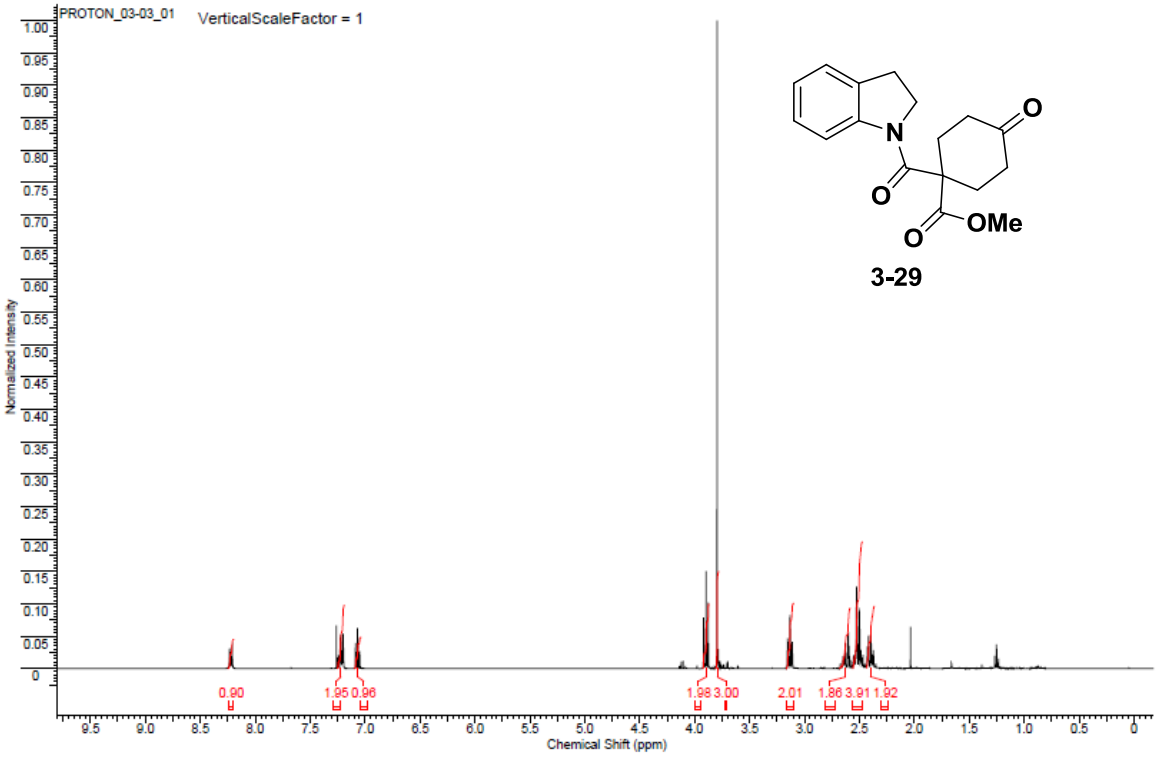
Acquisition Time (sec)	0.8684	*Date*	Nov 22 2013	*Date Stamp*	Nov 22 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-186-2013.11.22_02\CARBON_02-186_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	512	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16582.6289	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



3-27

25/07/2014 5:51:17 PM

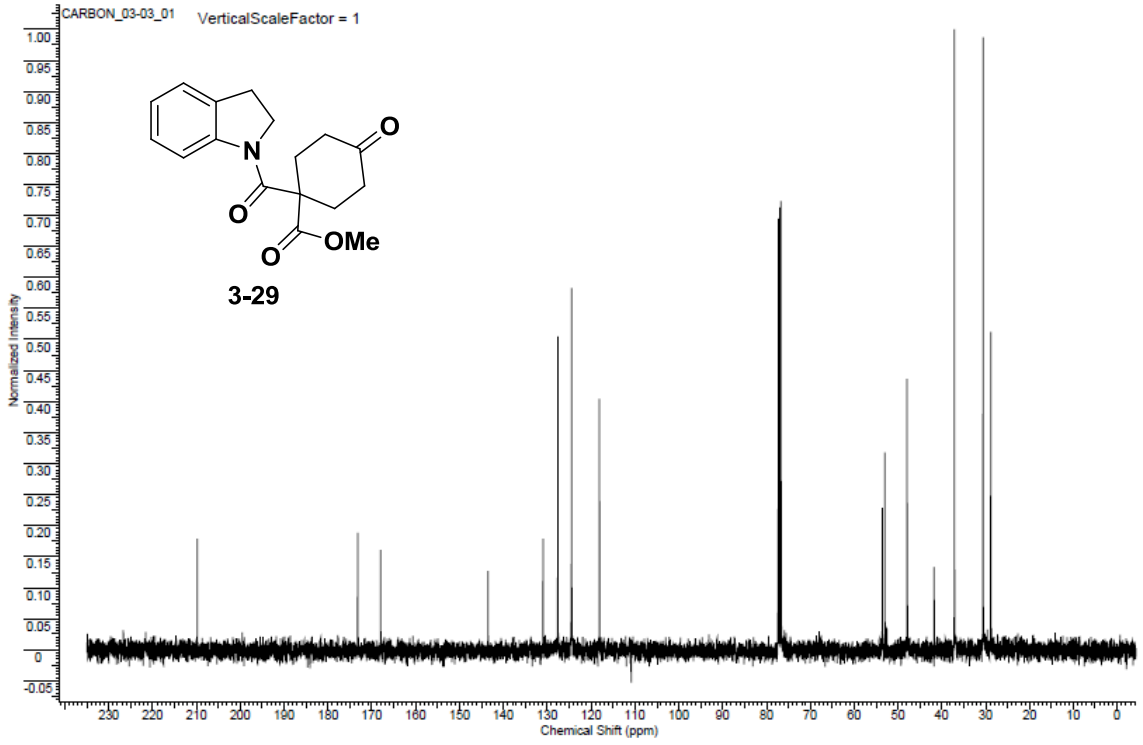
Acquisition Time (sec)	2.5616	*Date*	Dec 11 2013	*Date Stamp*	Dec 11 2013		
File Name	C:\Users\someone\Desktop\Bryan\03-03-2013.12.11_01\PROTON_03-03_01					*Frequency (MHz)*	399.76
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	50.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2412.9080	*Sweep Width (Hz)*	6395.91	*Temperature (degree C)*	25.000		



3-29

25/07/2014 5:53:50 PM

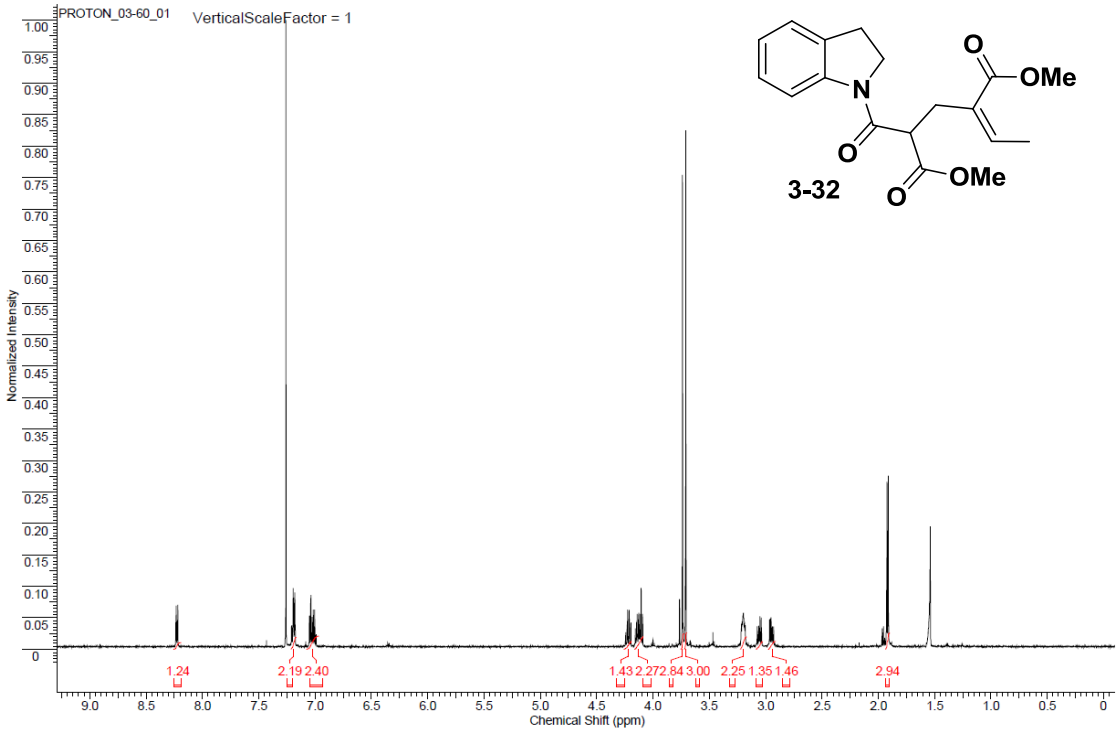
Acquisition Time (sec)	1.3038	*Date*	Dec 11 2013	*Date Stamp*	Dec 11 2013		
File Name	C:\Users\someone\Desktop\Bryan\03-03-2013.12.11_01\CARBON_03-03_01					*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	256	*Original Points Count*	32768	*Points Count*	131072
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11058.3242	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



3-29

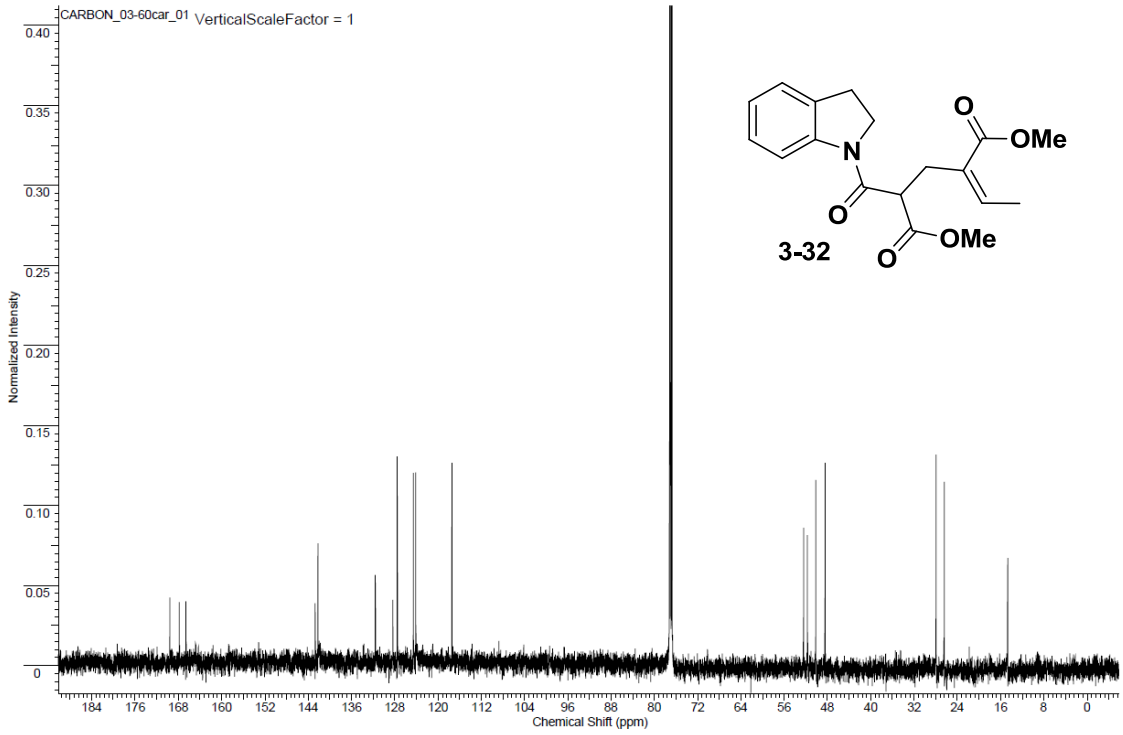
24/07/2014 2:56:26 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 23 2014	*Date Stamp*	Jun 23 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-60-2014.06.23_01\PROTON_03-60_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	44.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3608.6177	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



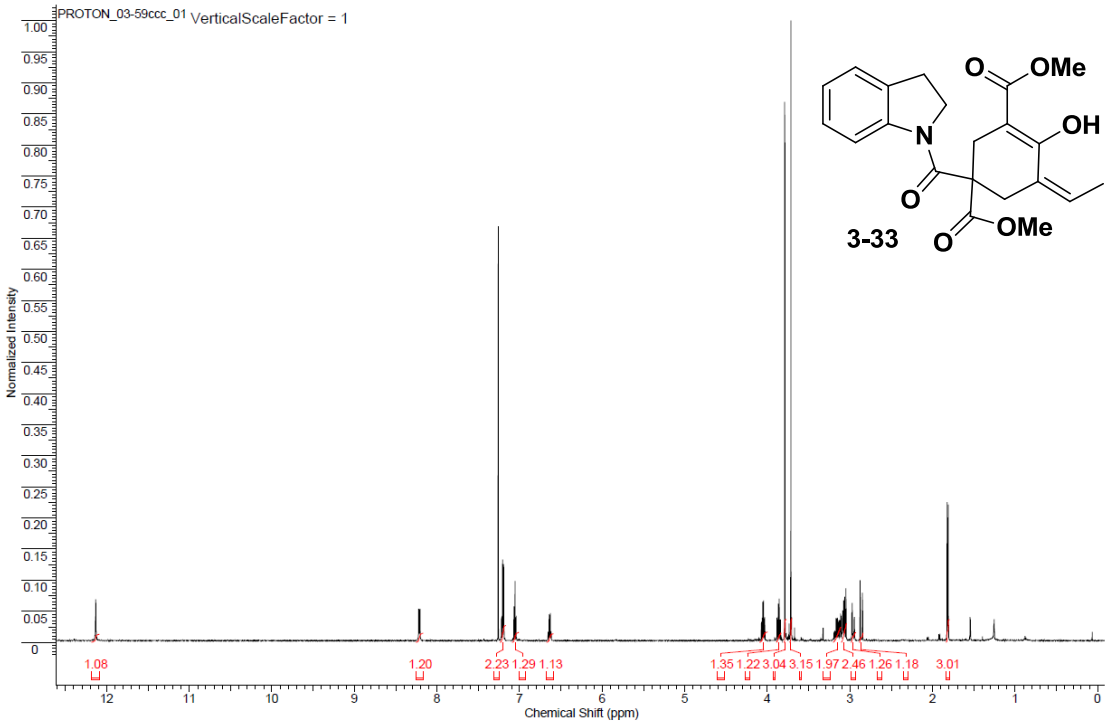
24/07/2014 2:58:10 PM

Acquisition Time (sec)	0.8684	*Date*	Mar 14 2014	*Date Stamp*	Mar 14 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-60car-2014.03.14_01\CARBON_03-60car_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	512	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16579.1699	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



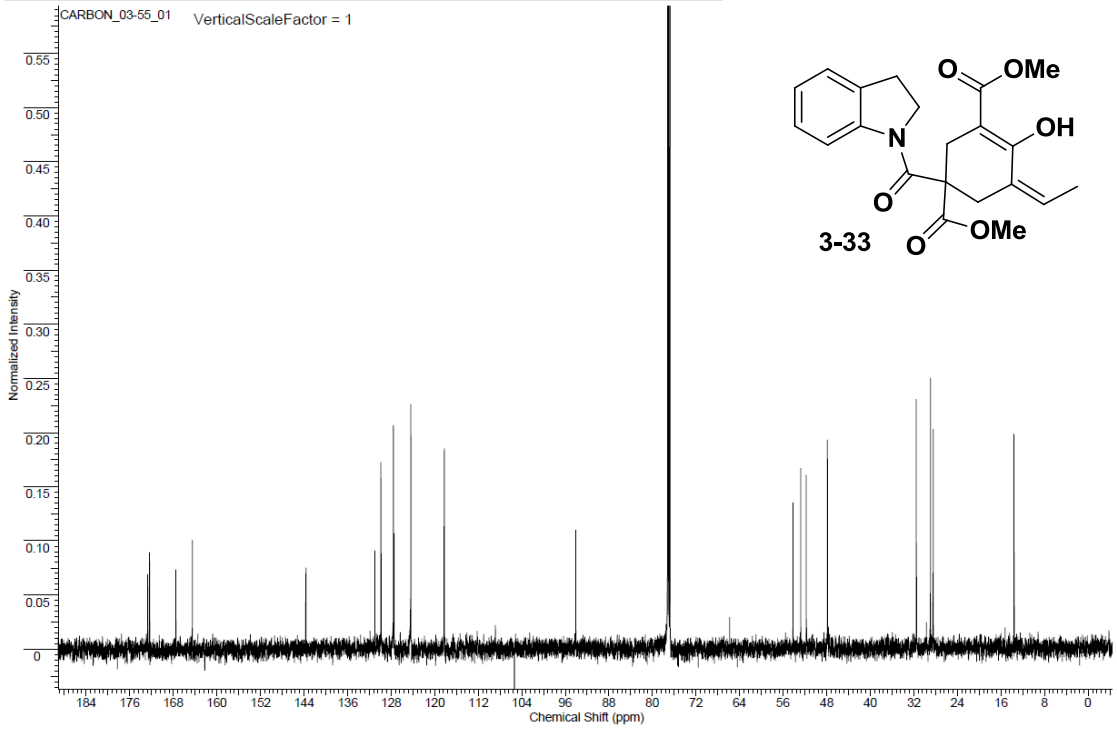
24/07/2014 3:18:59 PM

Acquisition Time (sec)	1.7046	*Date*	Mar 12 2014	*Date Stamp*	Mar 12 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-59ccc-2014.03.12_01\PROTON_03-59ccc_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	42.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3607.4446	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



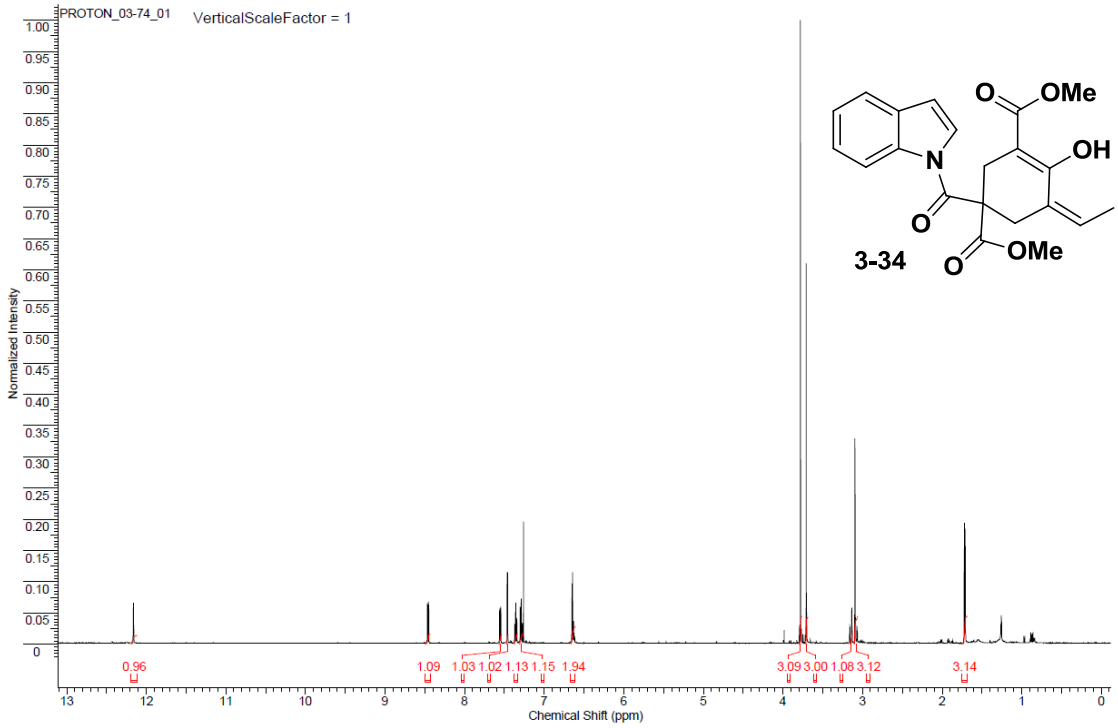
24/07/2014 3:20:57 PM

Acquisition Time (sec)	0.8684	*Date*	Feb 24 2014	*Date Stamp*	Feb 24 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-55-2014.02.24_01\CARBON_03-55_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	252	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16581.4766	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



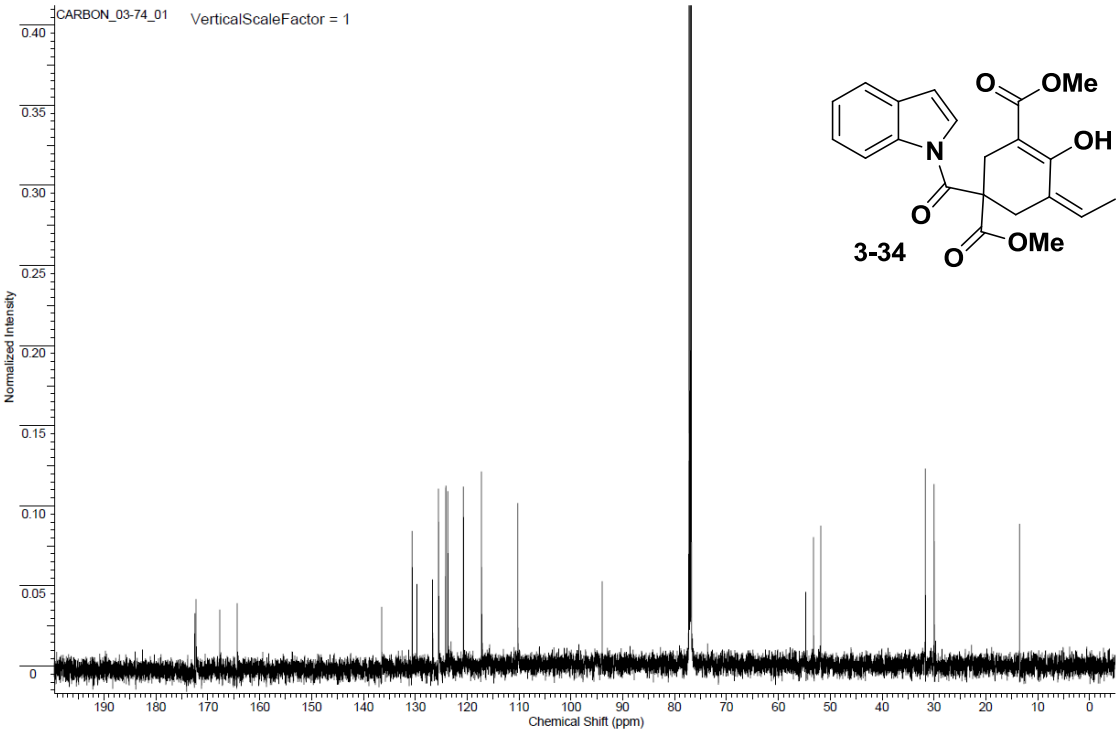
24/07/2014 3:24:48 PM

Acquisition Time (sec)	1.7046	*Date*	Mar 31 2014	*Date Stamp*	Mar 31 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-74-2014.03.31_01\PROTON_03-74_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3609.7910	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



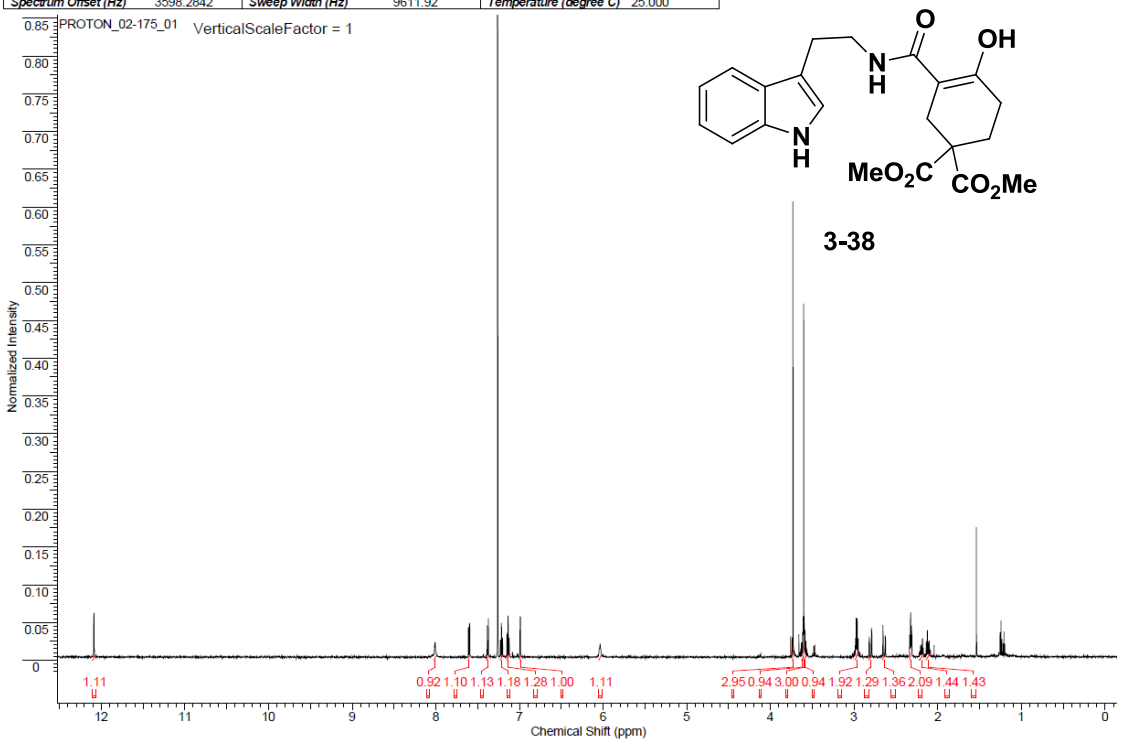
24/07/2014 3:25:43 PM

Acquisition Time (sec)	0.8684	*Date*	Mar 31 2014	*Date Stamp*	Mar 31 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-74-2014.03.31_01\CARBON_03-74_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	456	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16584.2793	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



24/07/2014 3:31:13 PM

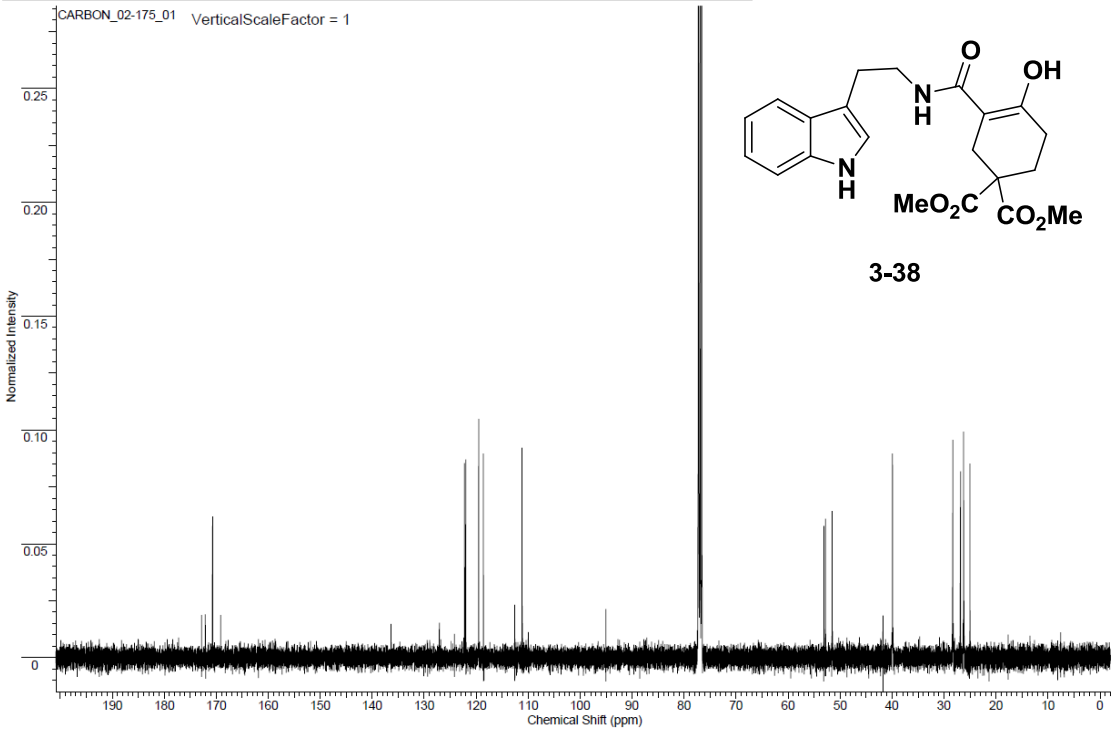
Acquisition Time (sec)	1.7046	*Date*	Nov 2 2013	*Date Stamp*	Nov 2 2013		
File Name	C:\Users\someone\Desktop\Bryan\02-175-2013.11.02 01\PROTON 02-175 01					*Frequency (MHz)*	599.44
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	46.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3598.2842	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



3-38

24/07/2014 3:32:55 PM

Acquisition Time (sec)	1.3038	*Comment*	H-1 NMR spectrum on the Inova 400			*Date*	Dec 17 2013
Date Stamp	Dec 17 2013	*File Name*	C:\Users\someone\Desktop\Bryan\02-175-2013.12.17 02\CARBON 02-175 01				
Frequency (MHz)	100.53	*Nucleus*	13C	*Number of Transients*	452	*Original Points Count*	32768
Points Count	65536	*Pulse Sequence*	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d
Spectrum Offset (Hz)	11057.1836	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



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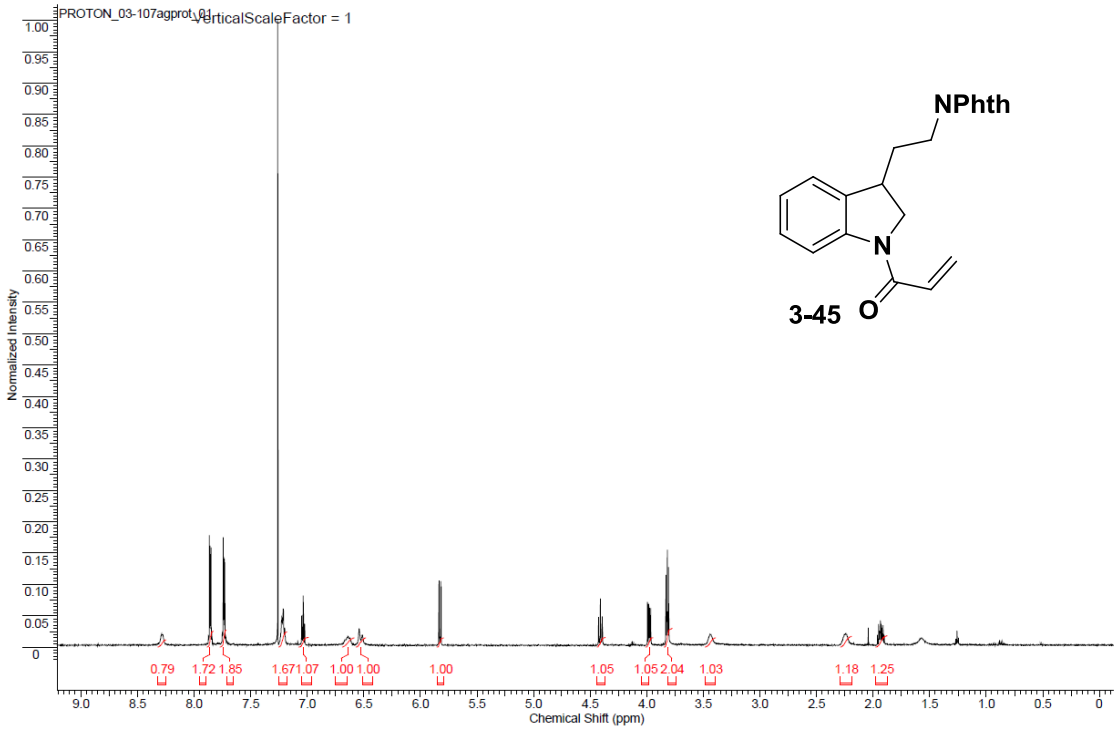
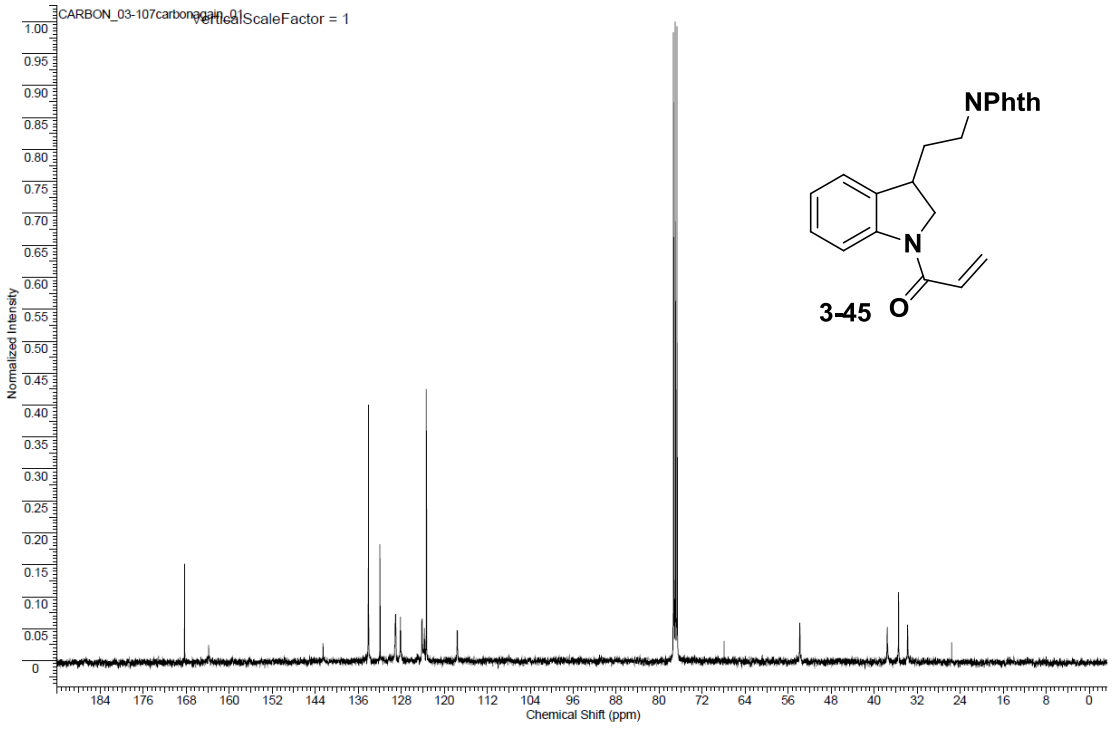
24/07/2014 4:32:50 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 26 2014	*Date Stamp*	Jun 26 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-107agprot-2014.06.26_01\PROTON_03-107agprot_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	44.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3608.6177	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



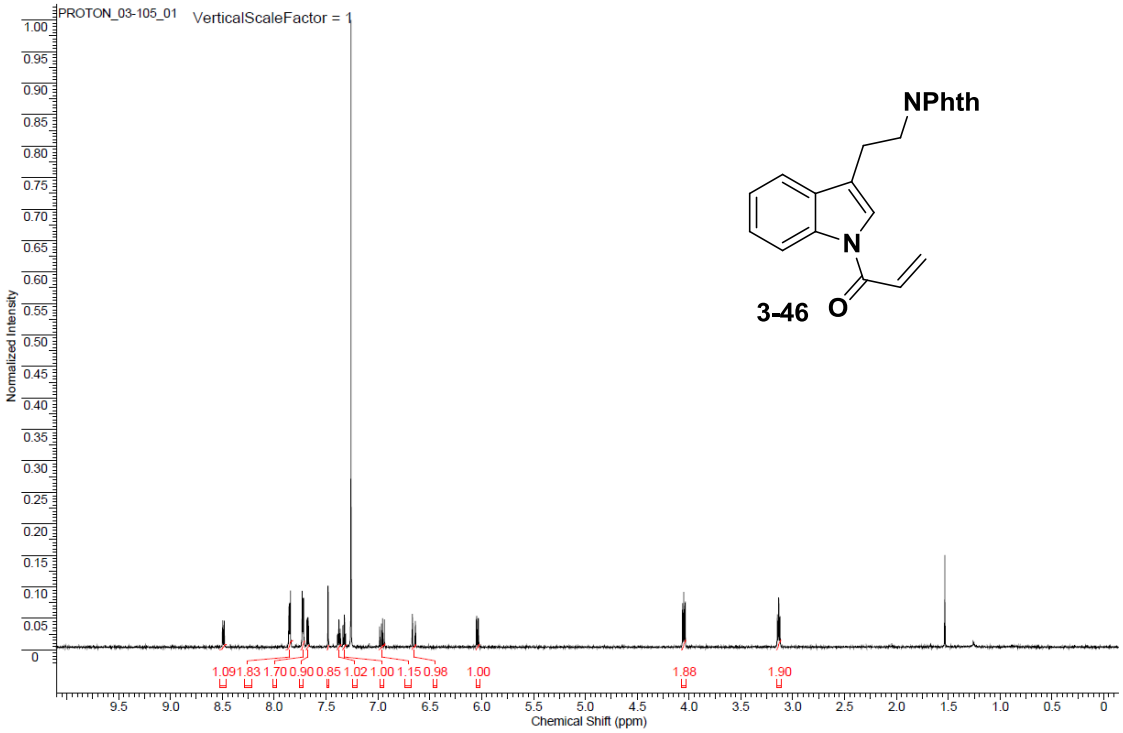
24/07/2014 4:34:39 PM

Acquisition Time (sec)	1.3042	*Comment*	Bryan	*Date*	Jun 1 2014	*Date Stamp*	Jun 1 2014
File Name	C:\Users\someone\Desktop\Bryan\03-107carbonagain-2014.06.01_01\CARBON_03-107carbonagain_01					*Frequency (MHz)*	100.61
Nucleus	13C	*Number of Transients*	2000	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	39.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11063.6094	*Sweep Width (Hz)*	25125.63	*Temperature (degree C)*	25.000		



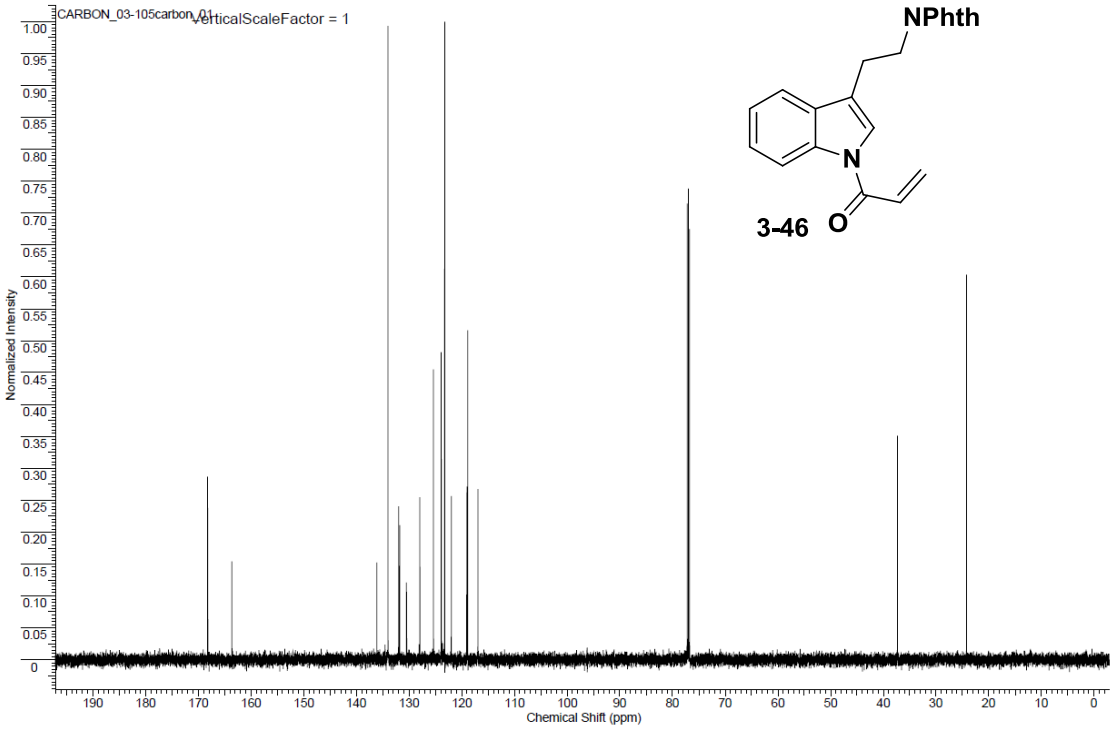
22/06/2014 9:01:40 PM

Acquisition Time (sec)	1.7046	*Date*	Apr 29 2014	*Date Stamp*	Apr 29 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-105-2014.04.29_01\PROTON_03-105_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	48.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3609.2048	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



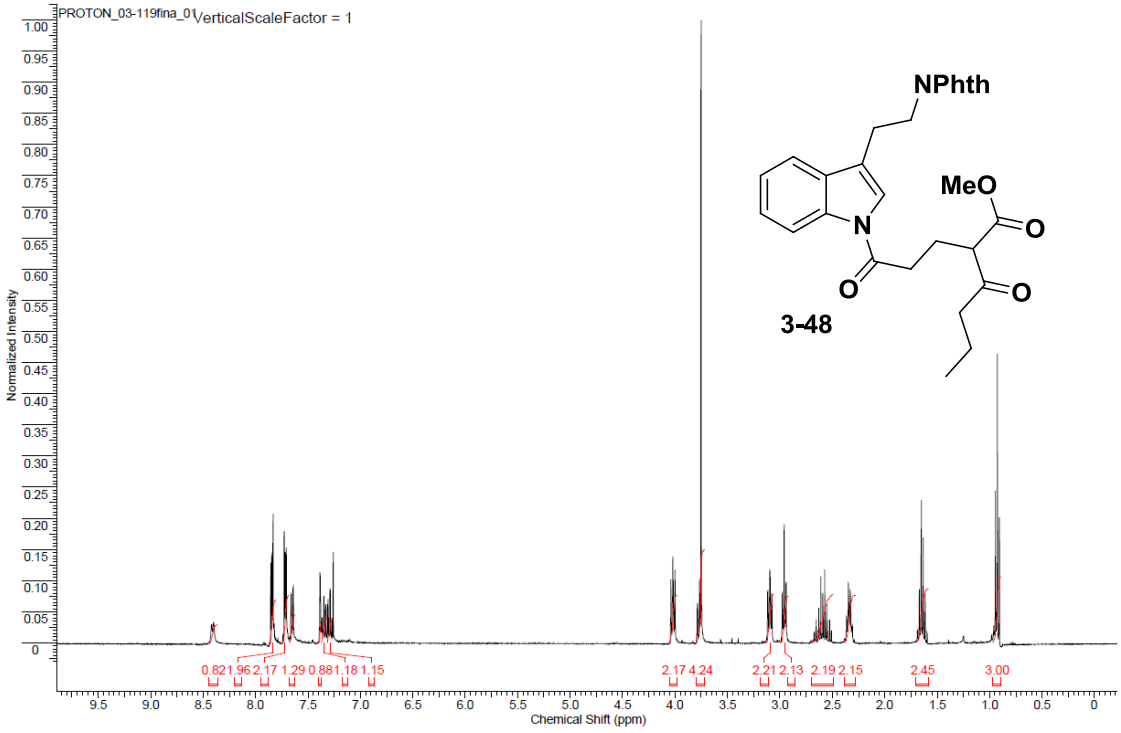
22/06/2014 9:00:03 PM

Acquisition Time (sec)	0.8684	*Date*	Apr 30 2014	*Date Stamp*	Apr 30 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-105carbon-2014.04.30_01\CARBON_03-105carbon_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	120	*Original Points Count*	32768	*Points Count*	32768
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16577.7305	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



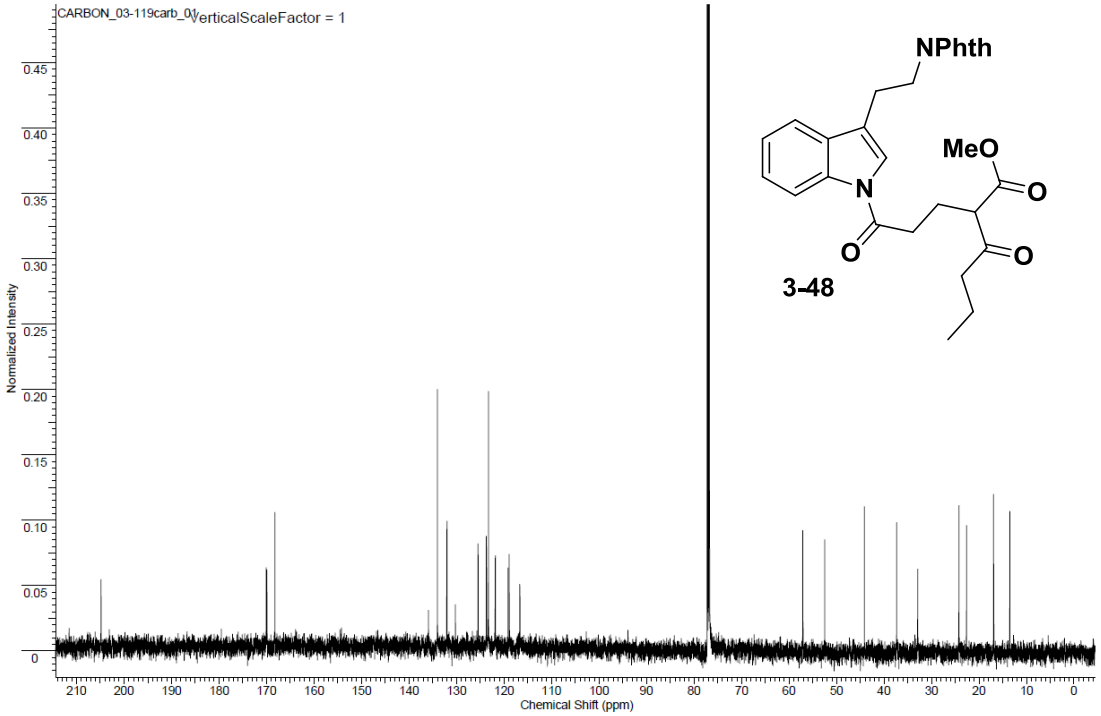
22/06/2014 9:32:42 PM

Acquisition Time (sec)	2.5592	*Comment*	Bryan	*Date*	May 23 2014	*Date Stamp*	May 23 2014
File Name	C:\Users\someone\Desktop\Bryan\03-119fina-2014.05.23_01\PROTON_03-119fina_01					*Frequency (MHz)*	400.08
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2400.6975	*Sweep Width (Hz)*	6402.05	*Temperature (degree C)*	25.000		



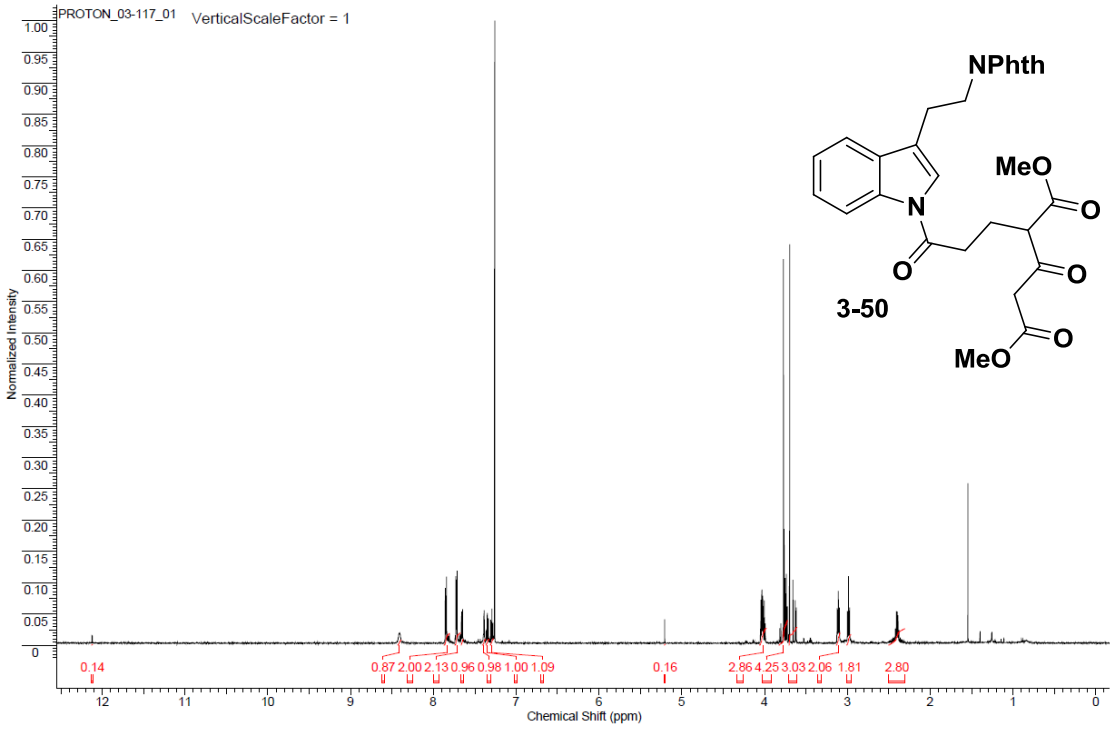
22/06/2014 9:33:48 PM

Acquisition Time (sec)	0.8684	*Date*	May 22 2014	*Date Stamp*	May 22 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-119carb-2014.05.22_01\CARBON_03-119carb_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	284	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16582.5508	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



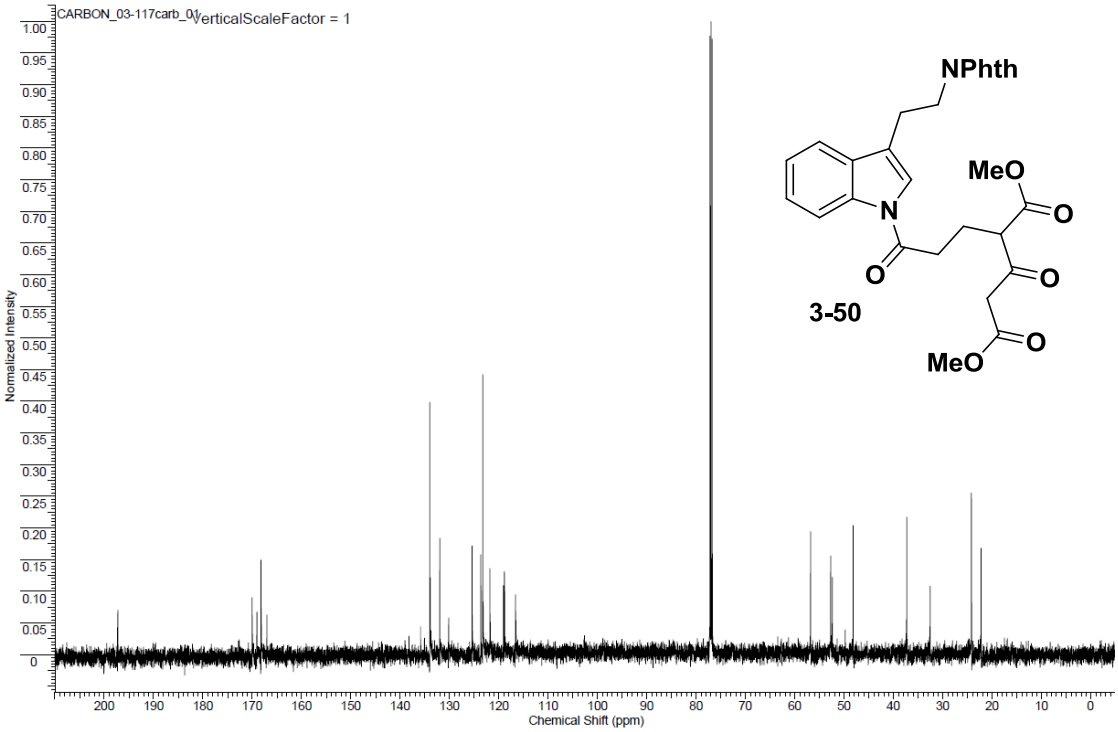
22/06/2014 9:16:06 PM

Acquisition Time (sec)	1.7046	*Date*	May 14 2014	*Date Stamp*	May 14 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-117-2014.05.14_01\PROTON_03-117_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	44.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3603.3376	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



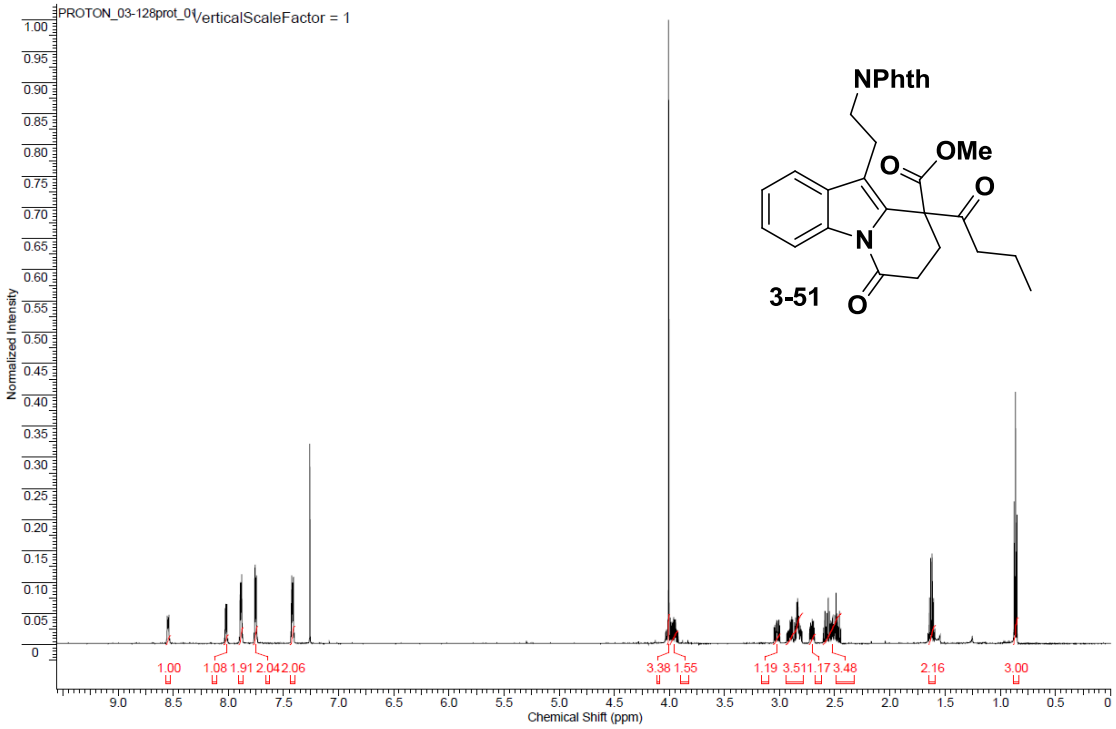
22/06/2014 9:04:53 PM

Acquisition Time (sec)	0.8684	*Date*	May 13 2014	*Date Stamp*	May 13 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-117carb-2014.05.13_01\CARBON_03-117carb_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	60	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16579.6719	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



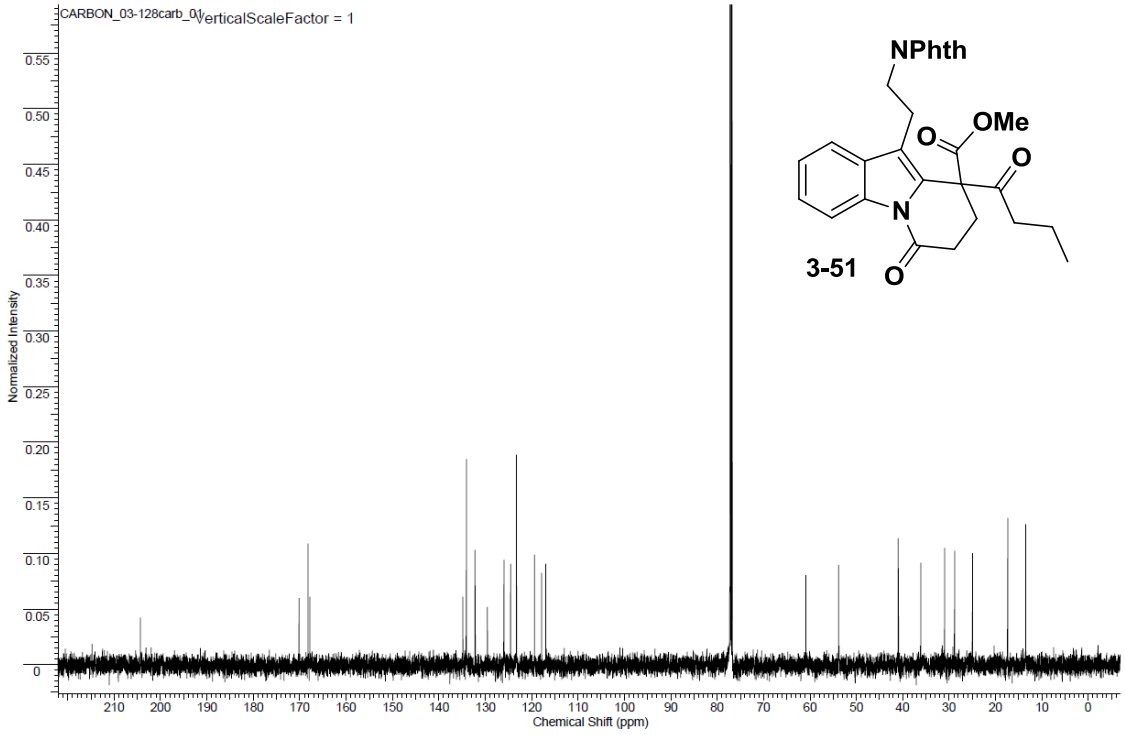
24/07/2014 4:43:25 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 26 2014	*Date Stamp*	Jun 26 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-128prot-2014.06.26_01\PROTON_03-128prot_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3608.6177	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



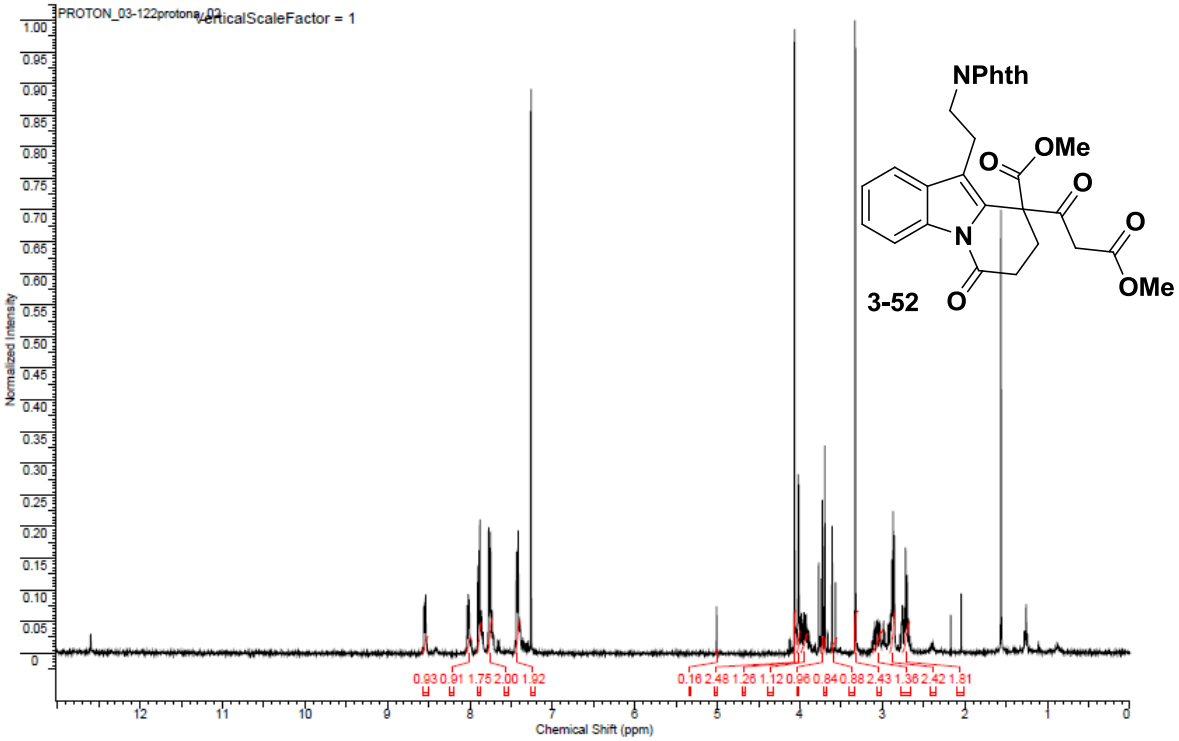
22/06/2014 9:34:59 PM

Acquisition Time (sec)	0.8684	*Date*	May 25 2014	*Date Stamp*	May 25 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-128carb-2014.05.25_01\CARBON_03-128carb_01					*Frequency (MHz)*	150.74
Nucleus	13C	*Number of Transients*	228	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	16581.9746	*Sweep Width (Hz)*	37735.85	*Temperature (degree C)*	25.000		



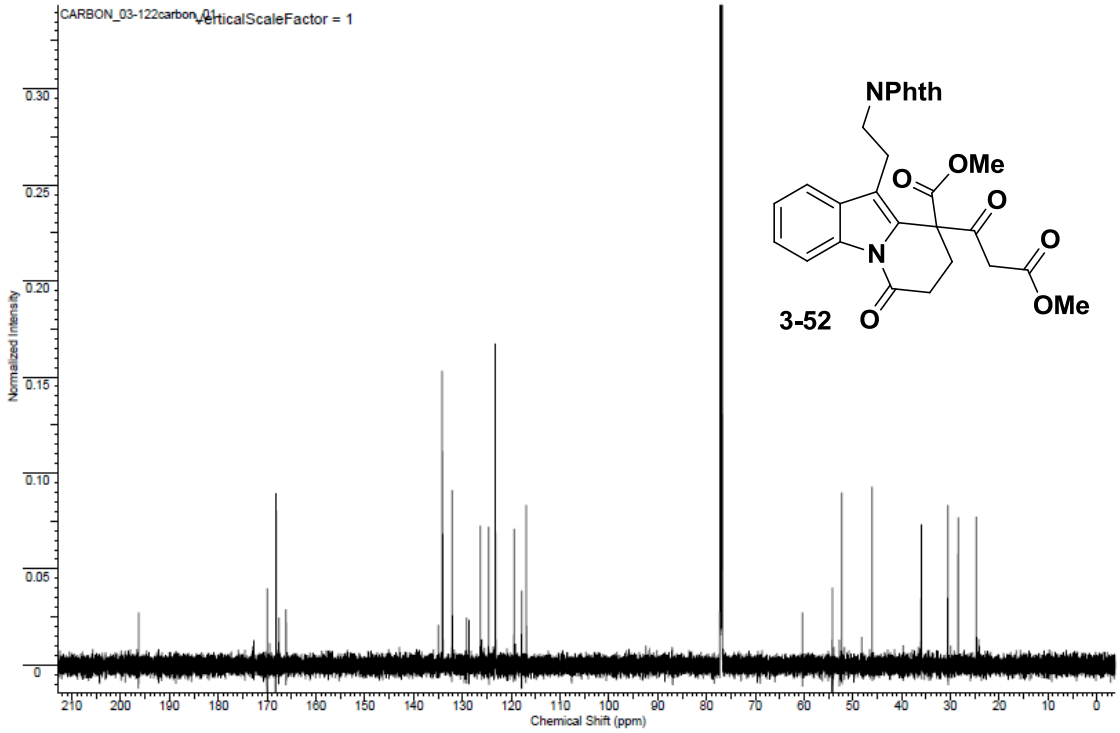
25/07/2014 6:18:56 PM

Acquisition Time (sec)	2.5616	Comment	STANDARD FLUORINE PARAMETERS			Date	Jul 25 2014
Date Stamp	Jul 25 2014	File Name	C:\Users\someone\Desktop\Bryan\03-122protona-2014.07.25_01\PROTON_03-122protona_02				
Frequency (MHz)	399.76	Nucleus	1H	Number of Transients	32	Original Points Count	16384
Points Count	16384	Pulse Sequence	s2pul	Receiver Gain	60.00	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	2414.8601	Sweep Width (Hz)	6395.91	Temperature (degree C)	25.000		



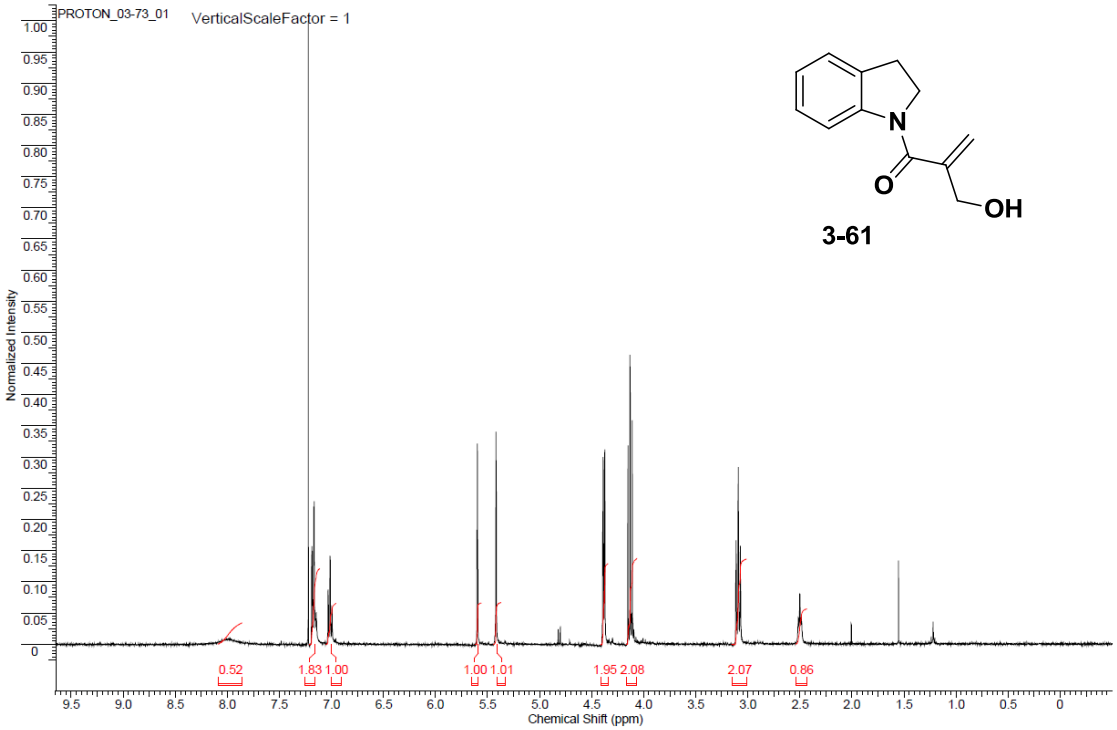
22/06/2014 9:19:14 PM

Acquisition Time (sec)	0.8684	Date	May 19 2014	Date Stamp	May 19 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-122carbon-2014.05.19_01\CARBON_03-122carbon_01					Frequency (MHz)	150.74
Nucleus	13C	Number of Transients	420	Original Points Count	32768	Points Count	65536
Pulse Sequence	s2pul	Receiver Gain	30.00	Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	16581.3984	Sweep Width (Hz)	37735.85	Temperature (degree C)	25.000		



24/07/2014 4:18:30 PM

Acquisition Time (sec)	2.5616	*Date*	Mar 26 2014	*Date Stamp*	Mar 26 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-73-2014.03.26_01\PROTON_03-73_01					*Frequency (MHz)*	399.76
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	58.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2398.5649	*Sweep Width (Hz)*	6395.91	*Temperature (degree C)*	25.000		



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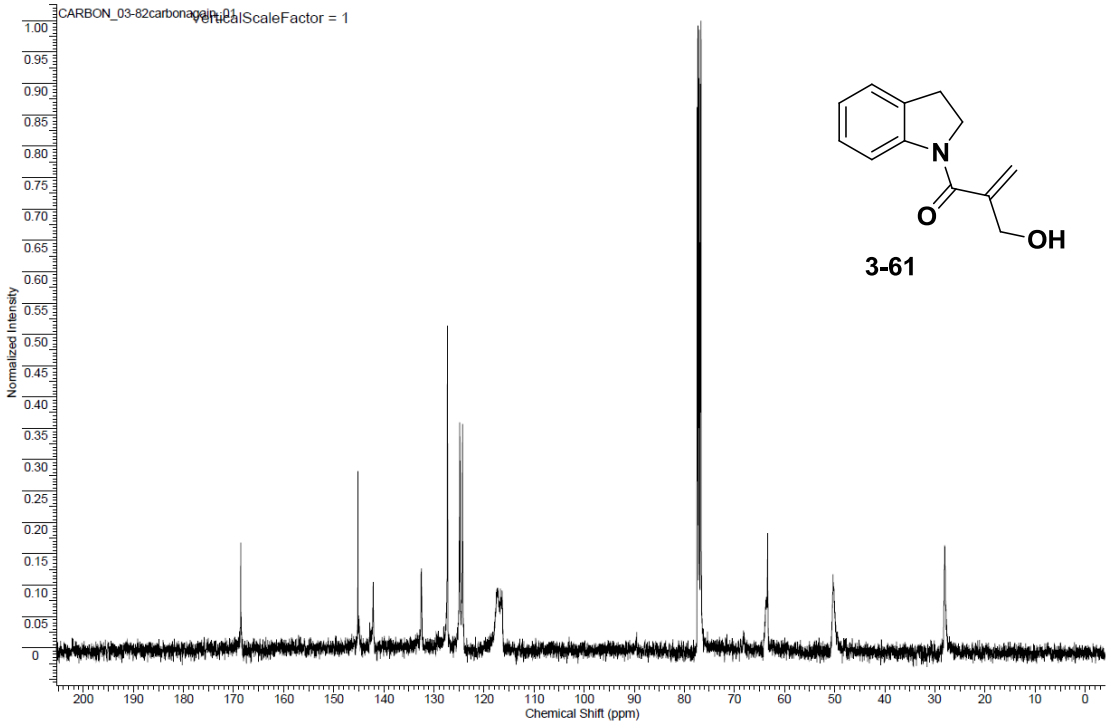
24/07/2014 4:21:30 PM

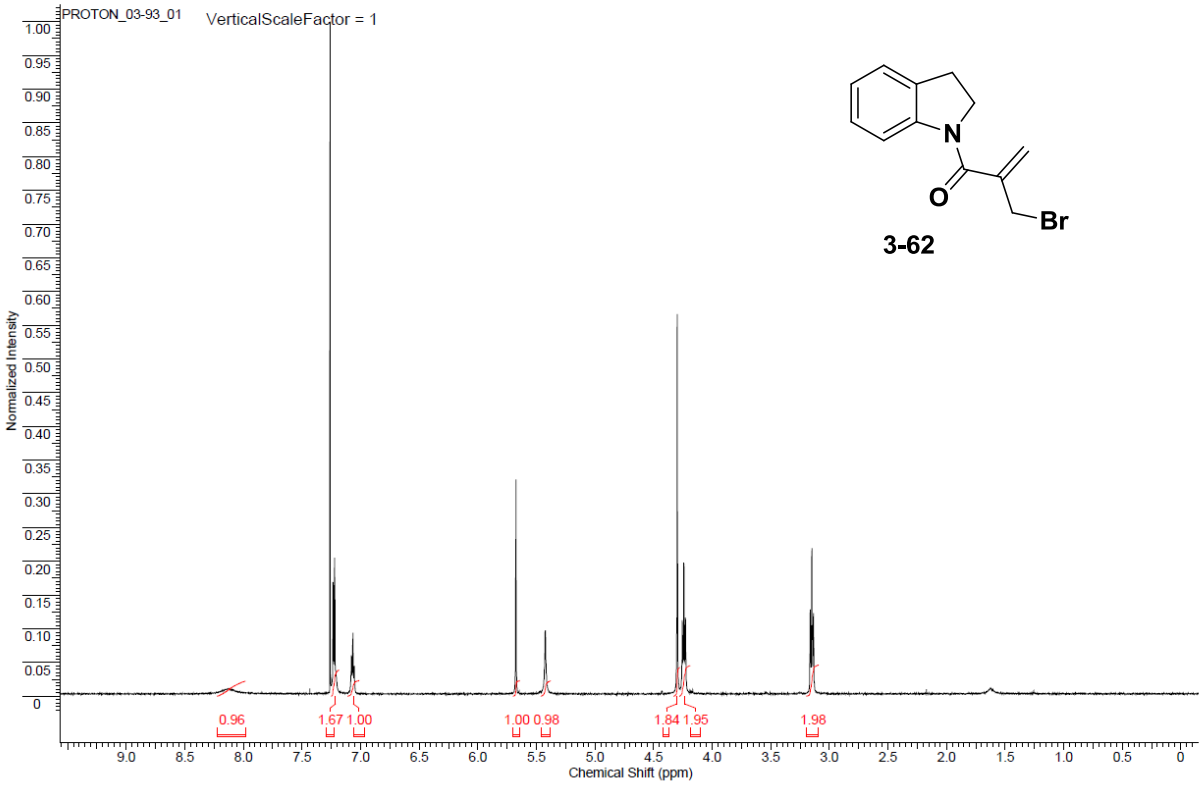
Acquisition Time (sec)	1.3042	*Comment*	Bryan	*Date*	May 31 2014	*Date Stamp*	May 31 2014
File Name	C:\Users\someone\Desktop\Bryan\03-82carbonagain-2014.05.31_01\CARBON_03-82carbonagain_01					*Frequency (MHz)*	100.61
Nucleus	13C	*Number of Transients*	2000	*Original Points Count*	32768	*Points Count*	65536
Pulse Sequence	s2pul	*Receiver Gain*	39.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11065.1426	*Sweep Width (Hz)*	25125.63	*Temperature (degree C)*	25.000		



3-61

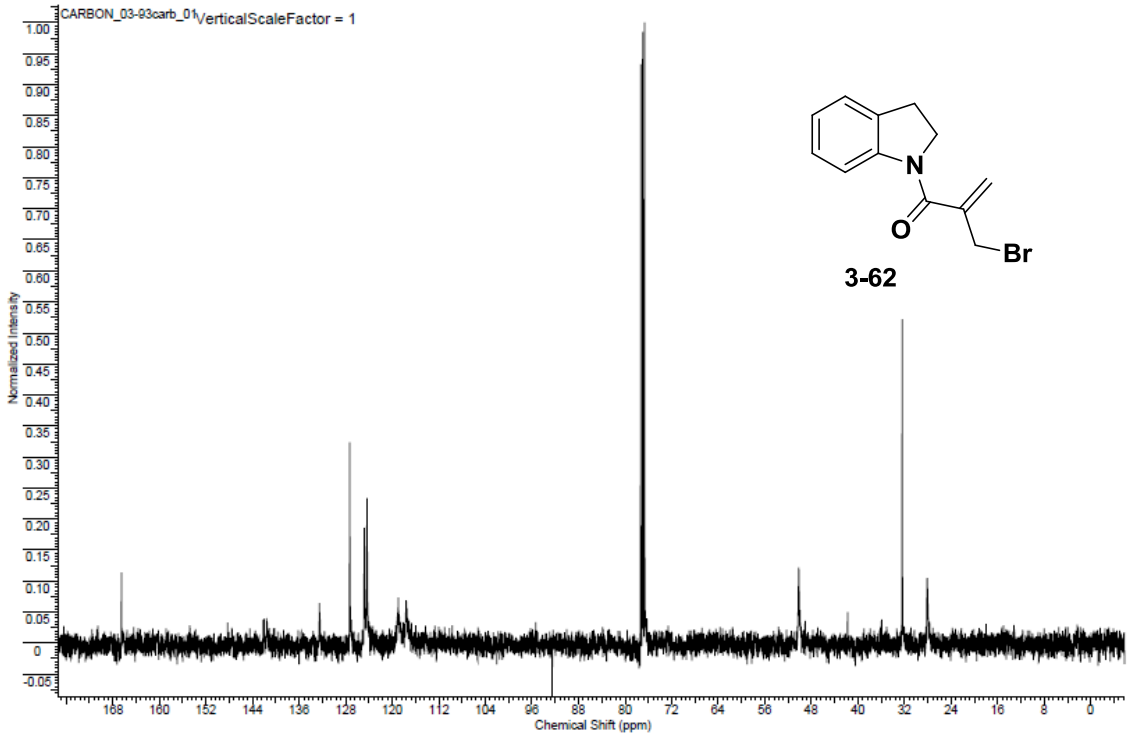
24/07/2014 4:24:56 PM

Acquisition Time (sec)	1.7046	*Date*	May 25 2014	*Date Stamp*	May 25 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-93-2014.05.25_01\PROTON_03-93_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	44.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3609.7910	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



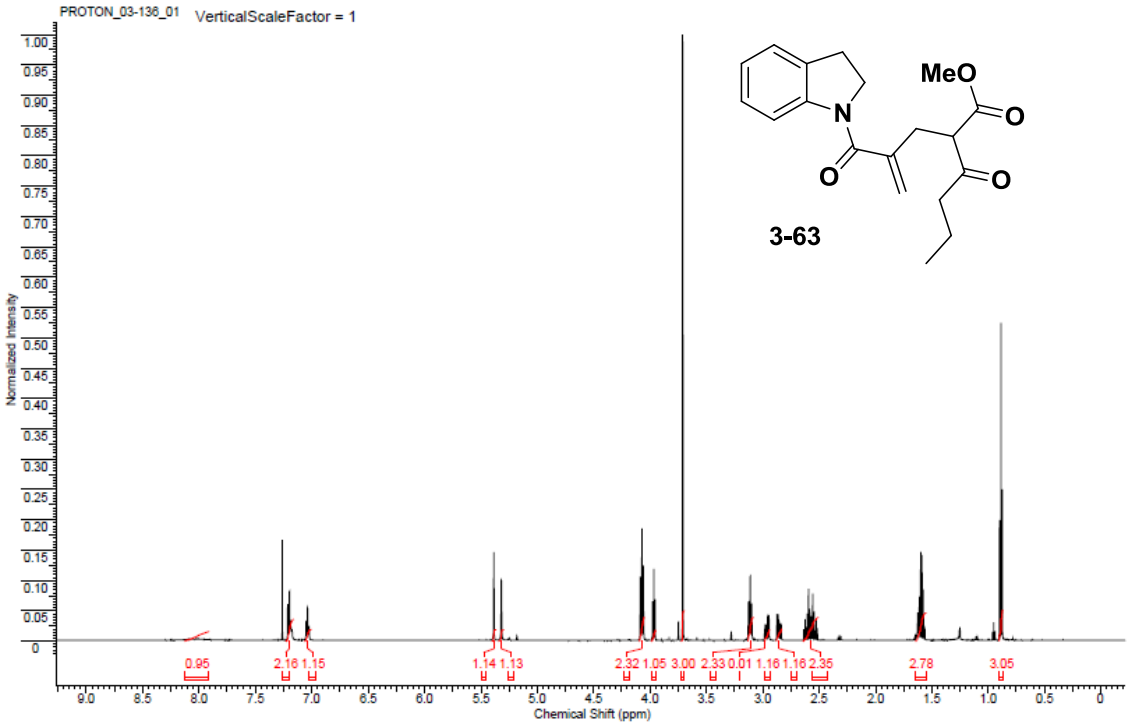
25/07/2014 4:13:33 PM

Acquisition Time (sec)	1.3038	*Date*	Jul 25 2014	*Date Stamp*	Jul 25 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-93carb-2014.07.25_01\CARBON_03-93carb_01					*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	140	*Original Points Count*	32768	*Points Count*	131072
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	11054.6094	*Sweep Width (Hz)*	25133.52	*Temperature (degree C)*	25.000		



25/07/2014 2:12:01 PM

Acquisition Time (sec)	1.7046	*Date*	Jun 12 2014	*Date Stamp*	Jun 12 2014		
File Name	C:\Users\someone\Desktop\Bryan\03-136-2014.06.12_01\PROTON_03-136_01					*Frequency (MHz)*	599.40
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	30.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	3609.7910	*Sweep Width (Hz)*	9611.92	*Temperature (degree C)*	25.000		



Curriculum Vitae

Name: Bryan Landschoot

ACADEMIC INFORMATION

Master of Science Candidate **September 2012 – Present**

Synthetic Organic Chemistry
University of Western Ontario, London, Ontario
Research Advisor: Dr. Michael A. Kerr

Master Thesis (*in progress)*:
Application of Mn(III) Oxidative Cyclizations to Natural Product Synthesis

Bachelor of Science **2008- 2012**
Honors Specialization of Chemistry
University of Western Ontario, London, Ontario
Deans Honor List (2011 & 2012)
Chemistry Alumni Award (2011)

Undergraduate Research Thesis
Diels-Alder Reaction of Azodicarboxylates at High Pressure
Research Advisor: Dr. Michael A. Kerr

RESEACH AND TEACHING EXPERIENCE

Graduate Student Researcher
University of Western Ontario, London, Ontario **September 2012 - Present**
Research Advisor: Dr. Michael A. Kerr

- Employed a nucleophilic donor-acceptor cyclopropane ring opening reaction using indolines to access the *N*-alkylated pendant malonyl chain motif.
- Successfully oxidatively cyclized *N*-alkylated products to their respective pyrroloindoles using manganese(III) acetate
- Expanded the scope of an efficient methodology utilizing high pressures (140 000 psi) to rapidly and effectively promote a Diels Alder reaction between various diazo compounds and dienes.
- Presented research results at national conferences
- Trained, supervised and mentored undergraduate student researchers
- Actively participated in weekly group meetings with the Kerr and Pagenkopf research group members to discuss recent literature advancements as well as research updates.

Graduate Teaching Assistant **September 2012 – Present**

University of Western Ontario, London, Ontario

Coordinated laboratory sessions for a second year chemistry course (UWO 2223b: Organic Chemistry of Biological Molecules)

- Conducted a pre-laboratory discussion on safety precautions, expectations, and proper techniques for each session.
- Ensured laboratory safety during the experiment
- Evaluated lab reports and techniques by students

Poster Presentations

1. Bryan K. Landschoot, William J. Humenny and Michael A. Kerr, *Diels-Alder Reactions of Azodicarboxylates at High Pressure*, Canadian Society for Chemistry (CSC), University of Calgary, Calgary, Alberta, May 26-30 **2012**.
2. Bryan K. Landschoot and Michael A. Kerr, *Application of Mn(III) to natural product synthesis*, Latest Trends in Organic Synthesis (LTOS), Brock University, St. Catherines, Ontario, Aug. 13-16, **2014**

Oral Presentations

1. Bryan K. Landschoot, *Radical Functionalization of Heterocycles*. Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (*QOMSBOC*) Conference, University of Windsor, Windsor, Ontario, Nov. 9-11, **2012**.

Awards

Chemistry Alumni Award (2011)

University of Western Ontario - $1 000

Ontario Graduate Scholarship in Science and Technology (2013 - 2014)

University of Western Ontario - $15 000

Skills and Qualifications

- Determined approach to problem solving by thinking critically and creatively
- Expertise and knowledge in the design and execution of synthetic strategies including optimization and reaction scope development
- Excellent ability in the purification, analysis and characterization of organic compounds by use of various analytic techniques such as NMR, FT-IR, UV-VIS, GC and HRMS
- Ability to work effectively independently or as a team to achieve a common goal
- Highly focused, driven and goal orientated
- Strong ability to communicate ideas and results through oral presentations and in writing
- Outstanding ability to motivate and educate students both in the classroom and laboratory