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Functionalization of Indoles and Donor-Acceptor Cyclopropanes and their Application Towards the Total Synthesis of Tronocarpine and Dippinine B

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Abstract

The work disclosed in this dissertation outlines novel reactions involving indoles and their applications towards the total synthesis of natural products, tronocarpine and dippinine B.

Showcased in Chapter 2 is a novel mode of activation for donor-acceptor cyclopropanes via an external hydrogen bond. The hydrogen bond increases the cyclopropane's electrophilicity permitting indole nucleophiles to open the ring. The result is 3-position functionalized indoles.

An external hydrogen-bond donor, HFIP (1,1,1,3,3,3-hexafluoroisopropanol), is used as a solvent to provide the medium necessary for favourable hydrogen-bond interaction with donor-acceptor cyclopropanes. Hydrogen bond activation of donor-acceptor cyclopropanes was successful in generating a multitude of functional indole products in high yields.

Chapter 3 outlines the application of single electron transfer agent, $\text{Mn}(\text{OAc})_3$, to isolate 1,2-annulated indoles in a one-pot procedure. The products generated in this novel methodology create molecular scaffolding that maps nicely onto natural products tronocarpine and dippinine B. The methodology accesses a variety of 1,2-substituted indoles that tolerated all substituents tested.

Chapter 4 explores the progress towards realizing the synthesis of the molecules tronocarpine, and dippinine B. These natural products are desired for their anti-microbial and anti-fungal properties. Paired with their challenging framework, this makes them intriguing targets for synthetic chemists. The focal point of the synthetic pathways in this chapter involves the $\text{Mn}(\text{OAc})_3$ radical methodology disclosed in Chapter 3.

Lastly, Chapter 5 reports a thermo-controlled, diastereoselective opening of oxime-ether tethered donor-acceptor cyclopropanes to generate bicyclic oxazines. The N-O heterocyclic products can be reductively cleaved to access substituted pyrrolidines with set stereochemistry from the controlled opening of the cyclopropane. This work reports high yields and diastereo-control generating cis/trans selective annulated products. Substituted pyrrolidines are highly sought for pharmaceuticals and natural product synthesis.

Keywords

Indole, tronocarpine, dippinine B, hydrogen-bond activation, donor-acceptor cyclopropanes, natural product synthesis, indole functionalization, pyrrolidines, radical cyclization, manganese, single electron transfer.

Summary for Lay Audience

Important as a component of many pharmaceuticals, indole is a biological molecule found throughout the natural world. These pharmaceuticals are important components of treatments for cancer, depression, Alzheimer's disease, viral infection, hypertension, and more. Chemists strive to develop modifications of indole molecules in search of easier, cheaper routes to both established, and novel pharmaceutical products. The research in this thesis outlines two new methods for the synthesis of further functionalized indole products. Method one involves radicals to cyclize an additional ring to an indole precursor. The products produced map onto the structure of important natural products found in Malaysian plant *Tabernaemontana corymbosa*. Method two functionalizes indoles by reacting them with strained three-membered ring molecules called cyclopropanes. This method is the first disclosed that does not require metals or high pressure as part of the reaction medium. Using the new methods developed, work towards natural products that have antifungal and antimalarial properties was under taken. The final component of this thesis develops a strategy to isolate highly substituted five-membered rings that contain nitrogen; these molecules are called pyrrolidines. The pyrrolidine structure is also highly desired in pharmaceutical targets. To access pyrrolidines, again cyclopropanes are used, but under specific reaction temperatures selective isomers of the pyrrolidine are isolated.

Co-Authorship Statement

Chapter 2- While under the supervision of me and Prof. Michael Kerr, Carling Renwick, a 4491E student, confirmed the proof of concept for hydrogen bond activation of donor-acceptor cyclopropanes resulting in co-authorship of this published manuscript. I completed all optimization of the results discussed within this thesis. All products synthesized, characterized and reported were completed by me. All components written about in Chapter 2 are my work.

Chapter 5 – Matthew Vriesen proposed the idea outlined in this chapter as a tool towards the synthesis of natural product (-)-callosine. Meredith Allen optimized the initial synthesis of oxime-ether containing cyclopropanes but I used an alternate and improved route than the one she first used. Meredith had synthesized some of the cyclized oxazine products as the thermodynamic isomer with the aid of Matthew Vriesen. However, upon taking over the project I redeveloped access to oxime-ether cyclopropanes, determined how to access the cis and trans tetrahydropyrrolo-oxazines, synthesized and characterized all the compounds discussed, plus confirmed the structural geometry of products. Everything written in Chapter 5 was performed and reported by me.

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Abbreviations

| | |
|--------------------|---|
| Å | angstrom |
| Ac | acetyl |
| AcOH | acetic acid |
| Ar | aromatic |
| ATR | attenuated total reflection |
| Bn | benzyl |
| Boc | <i>tert</i> -Butyloxycarbonyl |
| Boc ₂ O | di- <i>tert</i> -butyl dicarbonate |
| BRSM | based on recovered starting material |
| CAN | ceric ammonium nitrate |
| Cbz | carboxybenzyl |
| CSA | camphor sulfonic acid |
| DA CP | donor-acceptor cyclopropane |
| DBU | 1,8-diazabicycloundec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DFT | density functional theory |
| DIBAL-H | diisobutyl aluminum hydride |
| DIPEA | diisopropyl ethyl amine (Hünig's base) |

| | |
|----------------|--|
| DMAP | 4-(dimethylamino)pyridine |
| DMF | dimethylformamide |
| DMM | Dimethyl malonate |
| DMP | Dess-Martin periodinane |
| DMSO | dimethyl sulfoxide |
| dr | diastereomeric ratio |
| e ⁻ | electron |
| E ⁺ | electrophile |
| EDC | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| EDG | electron donating group |
| ee | enantiomeric excess |
| Equiv. | equivalents |
| Et | ethyl |
| Et | ethyl |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| EWG | electron withdrawing group |
| GI | Grubbs first generation catalyst; Benzylidene- bis(tricyclohexylphosphino)-dichlororuthenium |
| GII | Grubbs second generation catalyst; [1,3-bis-(2,4,6- trimethylphenyl)-2- imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylph osphino)ruthenium |

| | |
|------------------|---|
| Hex | hexanes |
| HFIP | 1,1,1,3,3,3-Hexafluoroisopropanol |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| <i>i</i> -PrOH | isopropanol |
| IUPAC | International Union of Pure and Applied Chemistry |
| <i>J</i> | coupling constant |
| LA | Lewis acid |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropyl amide |
| M | Molar (mol/L) |
| MA | Michael addition |
| mCPBA | <i>m</i> -chloroperoxybenzoic acid |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| mmol | millimole |
| Ms | methanesulfonyl |
| MS | molecular sieves |
| NBS | <i>N</i> -bromosuccinimide |
| NMR | nuclear magnetic resonance |
| NOESY | Nuclear Overhauser Effect spectroscopy |
| Nuc ⁻ | nucleophile |

| | |
|------------------|--|
| ORTEP | Oak Ridge Thermal Ellipsoid Plot |
| PCC | pyridinium chlorochromate |
| PDE5 | phosphodiesterase type 5 |
| Pg | protecting group |
| Ph | phenyl |
| pH | Power of hydrogen |
| PhOH | phenol |
| Phth | phthalimide |
| PPTS | Pyridinium <i>p</i> -toluenesulfonate |
| PTSA | <i>p</i> -toluenesulfonic acid |
| Pyr | pyridine |
| R _f | retardation factor |
| SET | single electron transfer |
| S _N 1 | unimolecular nucleophilic substitution |
| S _N 2 | bimolecular nucleophilic substitution |
| TBAF | tetrabutylammonium fluoride |
| TBS | tertbutyldimethylsilyl |
| ^t Bu | tert-butyl |
| TEA | triethylamine |
| TES | triethylsilane |
| Tf | triflate |
| TFA | trifluoroacetic acid |
| TFE | trifluoroethanol |
| TfOH | triflic acid |

| | |
|-----|---------------------------|
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMB | trimethoxy benzene |
| TMS | trimethylsilyl |
| Tr | triphenylmethyl |
| Ts | toluenesulfonyl |
| xs | excess |

Chapter 1

Introduction to the Reactivity and Functionalization of both Indoles and Donor-Acceptor Cyclopropanes: Including their Prevalence in Natural Products

This introduction will cover the general reactivity of indole and some of the chemistry involved in its elaboration to more complex substrates. It will delve into the novel transformations and functionalization of indoles using both, reactive donor-acceptor cyclopropanes, and, single electron oxidants. It also will cover some of the vast uses for donor-acceptor cyclopropanes due to their uniquely reactive behavior — and specifically how they can impart functionality on indoles. Additionally, this introduction will describe a selection of natural products that contain indole, and their importance as synthetic targets for organic chemists. This will put in place the foundation for the works reported in this dissertation.

1.1 Indole

1.1.1 Lord of the Rings: Indole. And Why We Should Care.

Benzo[b]pyrrole, trivially known as indole (**Figure 1**) is a heterocyclic, aromatic moiety abundant throughout the natural world. Indole (**1-1**) was first discovered in 1866 from studies pertaining to the dye indigo (**1-2**).¹ It was these studies that involved both *indigo* and *oleum* (fuming sulfuric acid) that lead to its common name, *indole*.

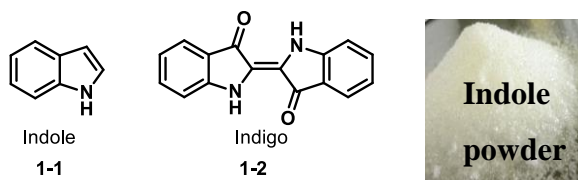
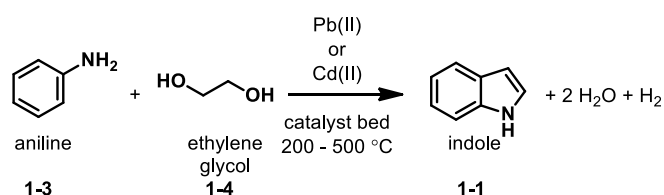


Figure 1 - Chemical structures of indole and indigo and the physical appearance of indole

Commercially, indole is extracted from coal tar but is also synthesized industrially from ethylene glycol (**1-4**) and aniline (**1-3**) (**Scheme 1**).^{2,3} Indole is a white solid (**Figure 1**), with a distinctive and pungent smell, proven by its role accounting for some of the smell in feces. However, in small concentrations indole smells pleasant, and finds commonness in perfumes and fragrant flowers, such as orange blossoms.⁴ Indole is also found in other aromatic flowers, such as jasmine, but even appears in the wood of some trees, like the American black locust.



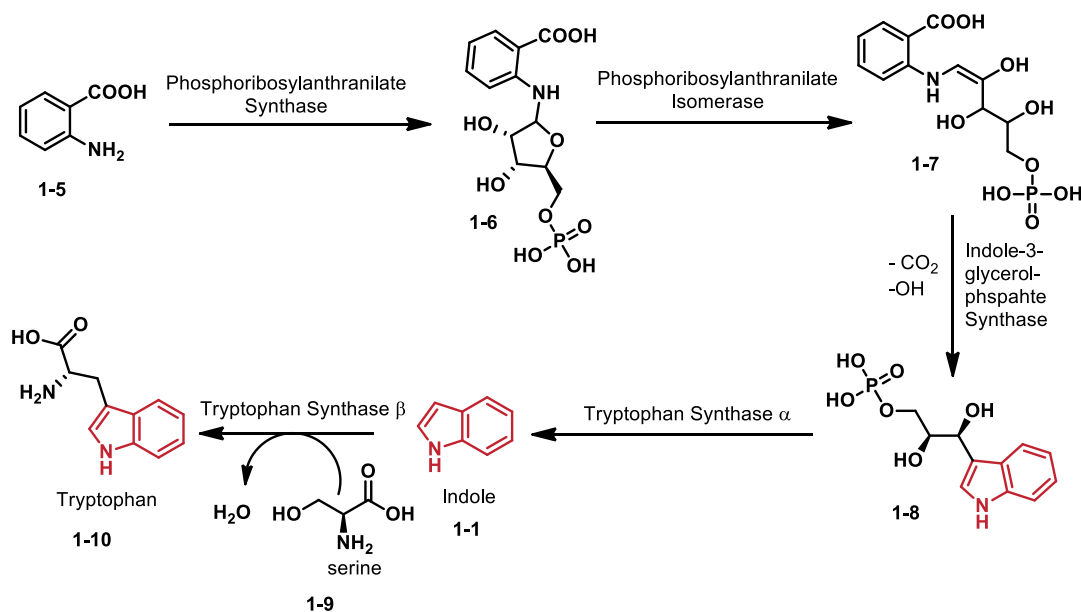
Scheme 1 - Synthesis of indole from aniline and ethylene glycol

Indole is found in both plants and animals. Indole is a decomposition product of the amino acid tryptophan (**1-10**), a molecule discussed in more detail below. This means indole is found wherever degradation of chemicals occurs in the body: the liver, the pancreas, and the intestines. Eventually becoming a waste product, indole is excreted with feces.¹

Indole is a component of tryptophan (**1-10**), one of the twenty amino acids vital to protein formation in the body. Humans do not synthesize tryptophan, rather it must come from protein in our diet. However, many plants and microorganisms synthesize their own tryptophan from shikimic acid or anthranilate (**1-5**) (**Scheme 2**).⁵ This synthesis occurs by alkylating indole with serine (**1-9**) as demonstrated in **Scheme 2**. The synthetic pathway is aided by enzymes such as tryptophan synthase to facilitate such complex reactions.

The fact that we require tryptophan to survive is an initial indication of how significant indole is to living things. Indole is a necessity to the biochemical pathways of many living organisms; it aids in vital organ production within plants⁶, is an intercellular

signaling molecule for spore formation in fungi⁷, and is a precursor to neurotransmitters such as melatonin and serotonin in the human body.⁸



Scheme 2 - Indole involvement in the biosynthesis of tryptophan in some plants and microorganisms

With their biological activity, indole-containing molecules have found desirable uses as anticancer, antibacterial and antiviral agents.⁹ This means many pharmaceuticals contain the indole heterocycle and are currently used as drugs that target disease found all over the body, covering a wide range of illnesses (**Figure 2**). From cancer to Alzheimer's disease, **Figure 2** showcases a number of indole-containing pharmaceuticals and their prescribed ailment.^{10,11} Perhaps the most famous of this class, thanks to its not-so-subtle commercials, is Tadalafil better known as *Cialis* (**Figure 3**), a drug used for the treatment of erectile dysfunction. Tadalafil is known as *Adcirca*, when it is being used to treat pulmonary hypertension.¹²

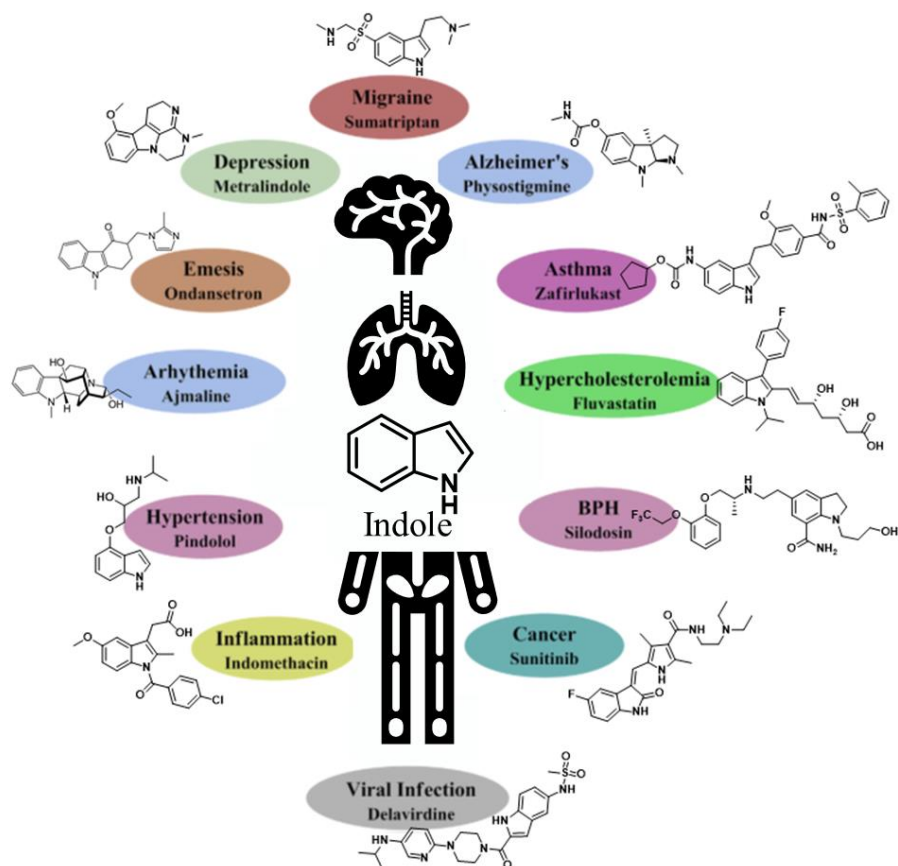


Figure 2 – Indole-containing drugs and their effects on the body

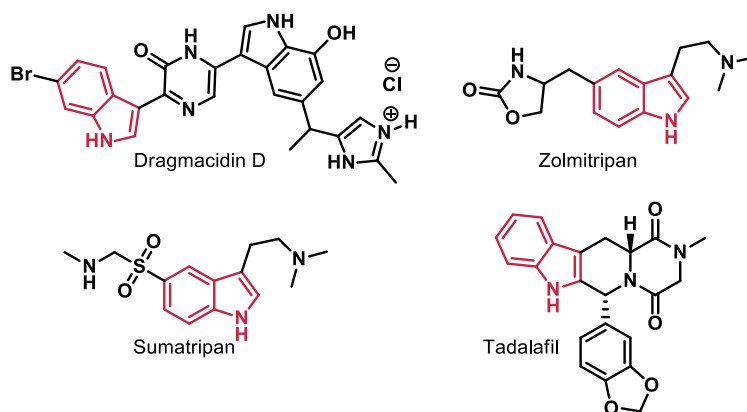


Figure 3 – Indole-containing drugs. Dragmacidin D is derived from sea sponge *Spongosorites*. Zolmitriptan and Sumatriptan are used to treat migraines.¹³ Tadalafil is a PDE5 inhibitor.

Another important indole-containing drug is the natural product (-)-reserpine (**Figure 4**). (-)-Reserpine is used as an antihypertensive and an antipsychotic. (-)-Reserpine was first isolated in 1952 from snake root, *Rauvolfia serpentina*.¹⁴ (-)-Reserpine has long been a target for synthetic chemists because of its pharmaceutical use. Its first synthesis, completed by Woodward *et al.*, dates to just a few years after its published isolation.¹⁵ With 10 complete total syntheses to date, (-)-reserpine exemplifies the importance of natural product synthesis to the chemical community.¹⁶ Scientific improvement of bond connections is important for future access to target molecules, and to define better, stream-lined routes to these targets. We must continue to research improvements connecting chemical components to ensure useful compounds are easily attainable. Whether it be for a pharmaceutical, a material, maybe even a fuel source, until we can make *anything* imaginable without struggle, the work of organic chemists is not done.

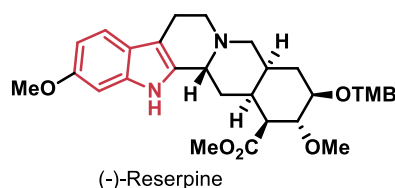


Figure 4 - (-)-reserpine, a natural product and drug that has long entertained organic chemists

A recent article published in Chemistry World compiled the wish-list of what medicinal chemists are seeking:

- “1. Fluorination – Exchanging specific hydrogen for fluorine.
2. Heteroatom alkylation – A reaction that *selectively* attaches an alkyl group onto one heteroatom in molecules that have several.
3. Carbon coupling – Stitching together aliphatic carbon atoms: ideally with chiral control.
4. Making and modifying heterocycles – Reactions to install functional groups anywhere on aromatic and aliphatic heterocycles.
5. Atom swapping – A reaction that can exchange individual atoms selectively.”¹⁷

While some of these transformations would absolutely warrant a Nobel prize, I draw your attention to wish-list item 4 – Making and modifying heterocycles. Returning to the molecule (-)-reserpine (**Figure 4**), the indole component is highlighted in red, and we can see that there is functionality stemming from the 2-position, the 3-position and the 6-position of the indole. This example falls heavily into the category of functionalizing heterocycles.

Chemists have worked hard to design efficient reactions to install bonds off all positions of the indole heterocycle. Ultimately, we must continue to find the best ways to generate valuable molecules like the natural products and drugs mentioned in this section. Being able to manipulate indole with desired components off any section of the heterocycle is something chemists are striving for. A multitude of drugs, dyes and materials have come into fruition because of indole, and it is for this reason chemists continue to be fascinated by improving the chemistry surrounding indole functionalization. To understand how we may alter indole, an understanding of its reactive nature is required.

1.1.2 General Reactivity of Indole

Indole contains 10 π electrons over 9 atoms, making it an electron-rich molecule capable of many chemical transformations (**Figure 5**).

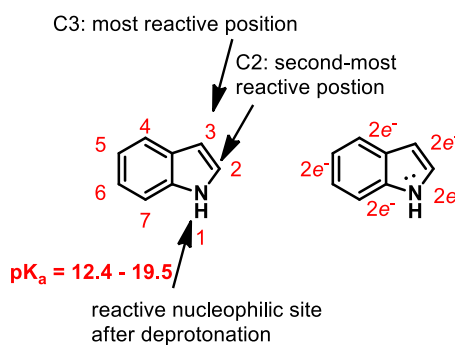
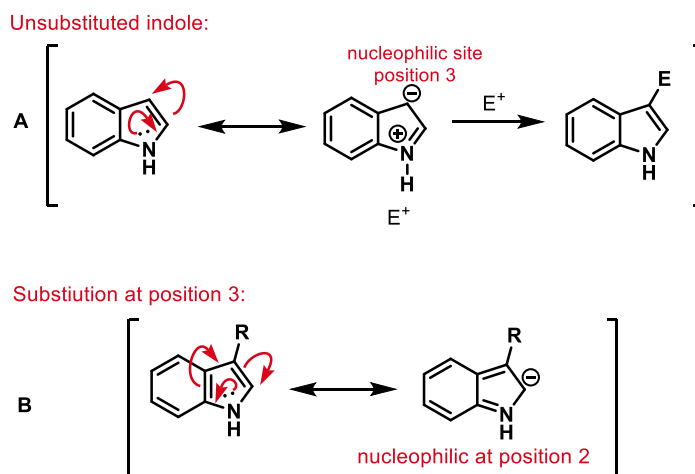


Figure 5 - (left) IUPAC counting of the atom positions around indole, and (right) the 10 π electrons of indole over 9 atoms

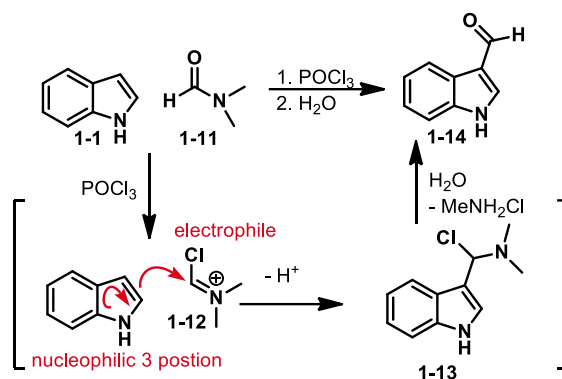
Indole is most nucleophilic at the 3-position (**Scheme 3, A**). Significant research in the 1960's studied how indole reacted by monitoring its protonation and calculating the

relative ratios of products formed. Those ratios now correlate well to electron density maps of indole that help us to explain how indole reacts.¹⁸ The initial studies on the protonation of indole found that the principle conjugate acid of indole is the 3-position protonated product (**Scheme 3, A**).¹⁹ Further deuterium exchange experiments highlighted that proton exchange occurs most prominently at the 1 and 3 positions of indole, but cases absolutely exist where protonation at the 2 position is also possible. Protonation of the 2-position is competitive with that of the 3-position; if the 3-position of indole is substituted, the 2-position will become the most nucleophilic site (**Scheme 3, B**). These studies highlight how indole act as a nucleophile most often at position 3, and this is what we observe experimentally when indoles are in the presence of an appropriate electrophile.



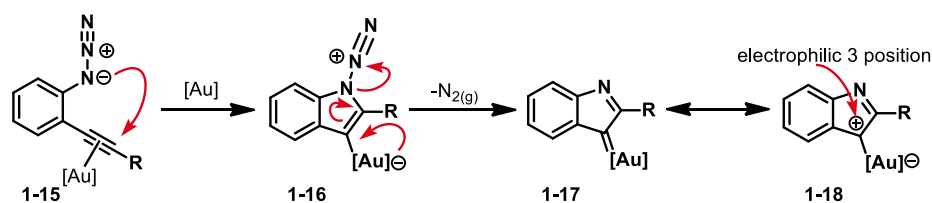
Scheme 3 - (A) Resonance structure of indole describing the observed nucleophilicity at position 3 (B) Nucleophilicity at position 2 of indole when position 3 contains substitution other than H

For example, when an indole is used as the nucleophile in the common Vilsmeier-Haack reaction (**Scheme 4**), the resulting product is an aldehyde at position 3 (**1-14**).²⁰



Scheme 4 - Vilsmeier-Haack reaction of indole, showcasing nucleophilic position 3

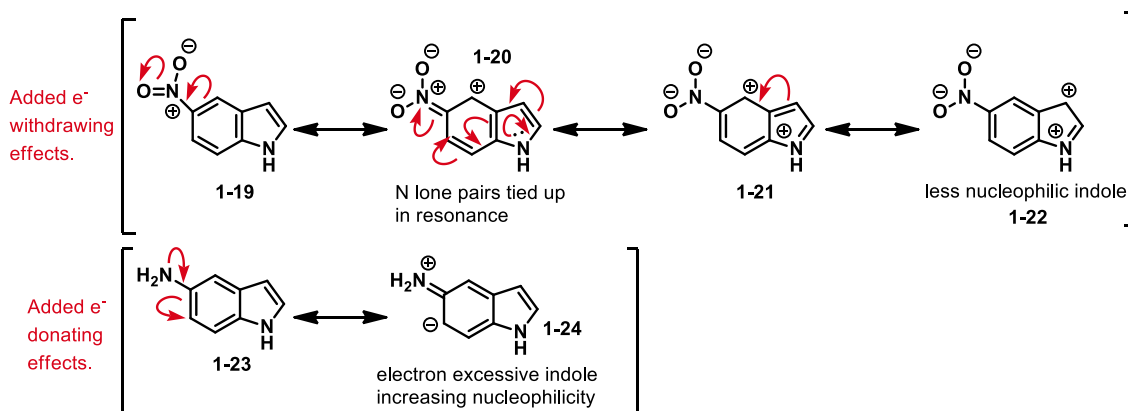
Of course, in chemistry most rules are not law. For example (Scheme 5), using gold catalysis to synthesize indoles from azides (1-15) results in a metal-bound intermediate (1-18) achieving umpolung reactivity of indole. The indole substrates in this example act as *electrophiles* at the 3-position, versus the nucleophilicity typically seen.²¹



Scheme 5 - Umpolung reactivity of indole where the 3-position acts as an electrophile

Substituents around indole also affect the molecule's reactivity. Computational chemistry has been used to generate electron density maps of a multitude of substituted indole molecules. An inclusive study of the electron density of methyl-, fluoro-, nitro-, and amino- substituted indoles confirmed how the inductive, and mesomeric effects of these groups change the nucleophilic nature of indole.¹⁸ This computational study determined electron donating groups (-CH₃ and -NH₂) on the 2 or 5 positions of indole greatly improve the nucleophilicity of position three by 29 - 88 kJmol⁻¹. However, when the two or five position of indole is substituted with -F or -NO₂, the proton affinity of position 3 drops between -6.3 and -86.1 kJmol⁻¹. The reasoning for this is further confirmed and explained by the resonance structures of indole resulting from electron donating or

withdrawing nature of these groups (**Scheme 6**). Looking at the electron density around the aromatic indole, when it bears an EWG (**1-19**) a resonant positive charge is resultant on position 3 (**1-22**). The result is a less nucleophilic carbon compared to its unsubstituted or electron donating counterparts (**1-24**).



Scheme 6 - Varied nucleophilic properties of indole due to electron withdrawing or donating substituents at position 5

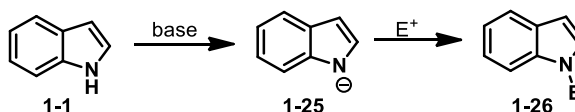
Ultimately, indole is a versatile heterocycle capable of myriad chemical transformations. Due to its reactive nature and its prevalence in the natural world, functionalization of the indole moiety to produce high-value chemicals is well studied.

1.2 Functionalization of Indoles

Adding functional groups to indoles has been immensely studied over the last ~100 years. So much so, that this section would be hundreds of pages long if it hoped to be inclusive of all the impressive chemistry in the field. For example, reviews regarding indoles exist specifically pertaining to: palladium-catalyzed functionalization²², organocatalytic strategies²³, catalytic C-C bond functionalization of indoles,²⁴ and methods for 3,4-fused tricyclic indoles²⁵, which just scrape the surface. In this section I hope to showcase the recent literature and general trends pertaining to functionalizing the 1 and 3 position of indoles, with specific emphasis on cyclization that make scaffolds like the natural products of focus in this thesis.

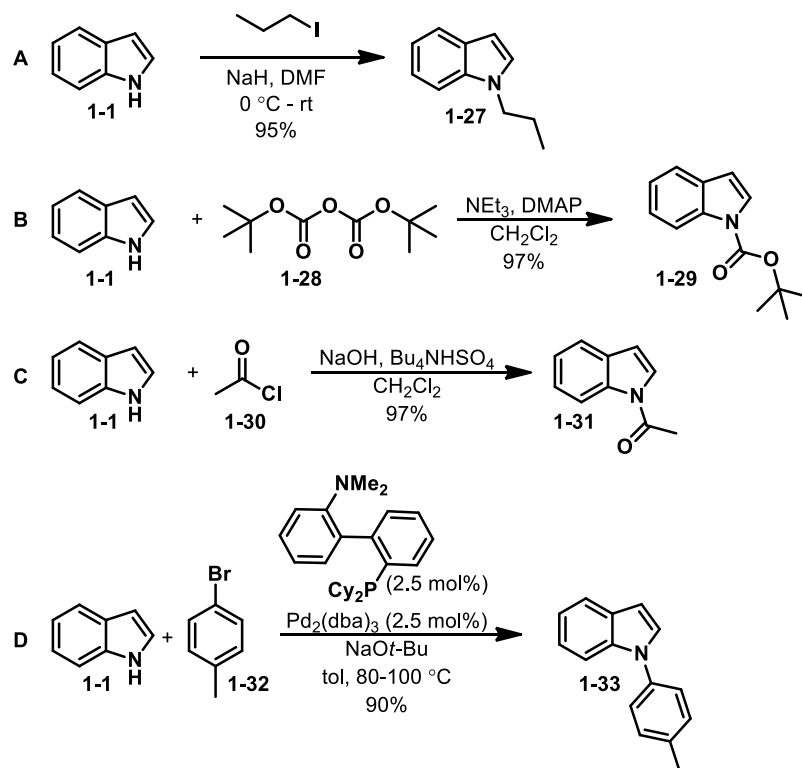
1.2.1 Functionalizing Indole Position 1

Broadly speaking, functionalization of the indole nitrogen is straightforward. It is reliable and simple. One might expect this because it is much easier to make heteroatom-carbon bonds than it is to furnish carbon-carbon bonds. To impart function on the indole nitrogen, deprotonation is required (**1-25**) and, in the presence of an electrophile, it will react to create a new N-E bond (**1-26**, **Scheme 7**).



Scheme 7- General functionalization of the indole 1 position

Cross-coupling reactions to form N-C bonds (e.g., Buchwald-Hartwig amination) and these are also used to functionalize the indole nitrogen (**Scheme 8, D**).²⁶ However, for the scope of this thesis, simple deprotonation of indole in the presence of an electrophile is the only method used to afford N-substituted indole products. The chemistry in **Scheme 8** showcases some common electrophiles and the resultant N-substituted indole products. **Scheme 8, A**, outlines a simple S_N2 -type reaction to add an alkyl chain on indole (**1-27**).²⁷ Protecting groups are often added to indole nitrogen to overcome chemoselectivity issues. **Scheme 8, B**, showcases anhydride electrophile Boc_2O (**1-28**), which protects the indole N-H with a boc group in high yield (**1-29**).²⁸ **Scheme 8, C** exemplifies acid chlorides (**1-30**) as electrophiles generating acyl indole products such as **1-31**.²⁹

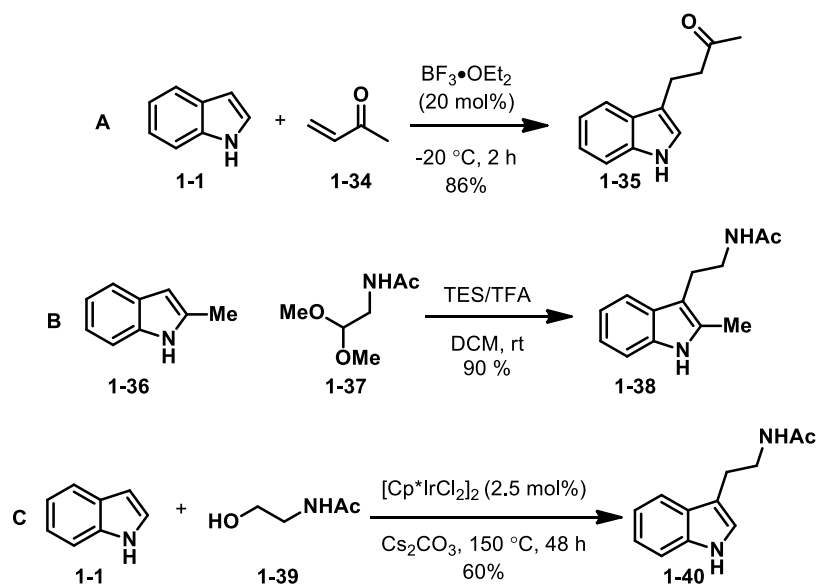


Scheme 8 - Various examples of installing substitution off indole nitrogen

1.2.2 Functionalization of Indole Position 3

In earlier discussion I concluded that the 3-position of the indole is the easiest to functionalize. Indoles are carbon nucleophiles at this position, and easily make indole-3-substituted products. Outlined in **Scheme 9** is a series of reactions that impart function on the indole 3-position. First exemplified (**Scheme 9, A**) is a straight-forward Michael addition; using $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst with methyl acrylate (**1-34**) generates elaborated indole **1-35**.³⁰ More interestingly though, and important to the indoles of interest in this document, are the recent advances synthesizing tryptamine chains off the indole-3-position. Discussed at length in earlier sections, the tryptamine chain is both important, and common in the natural world. Recently Righi *et al.* (**Scheme 9, B**) showed that from acetal species **1-37**, revealing its respective aldehyde under acidic conditions caused indole **1-36** to attack, generating a benzylic alcohol that is reduced by triethyl silane.³¹ This pathway yields indoles like **1-38** which now bear a tryptamine chain. This reaction

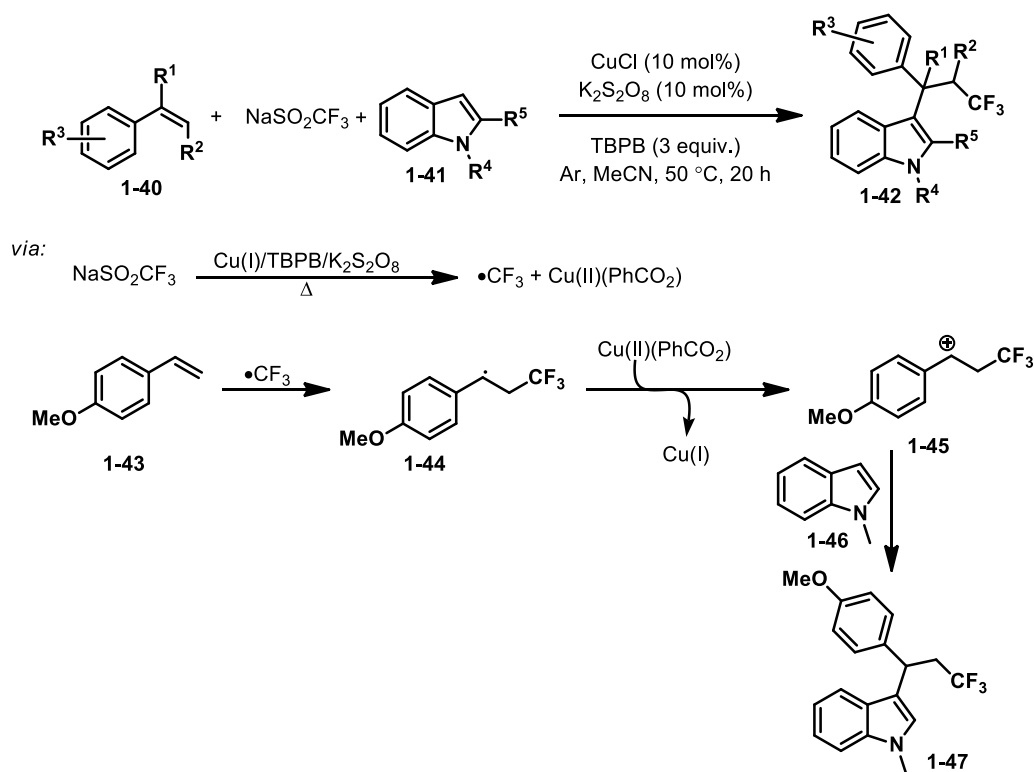
tolerated a wide variety of substitution patterns around the starting indole, but only explored examples bearing electron-donating groups. The greatest limitation was found to be the choice of protecting group on the amine component of acetal **1-37**. Unprotected amines failed to proceed, and protecting groups Cbz and Ts, caused yields to drop sharply to the 50-60% range. However, the reagents to perform this functionalization are safe, inexpensive, and offer access to the valuable tryptamine functionality discussed in **Section 1.1.1**.



Scheme 9 - Functionalizing the 3 position of indole

Further elaboration synthesizing tryptamine chains was elucidated by Batolucci *et al.* (**Scheme 9, C**). They applied a “borrowing hydrogen” strategy to provide the reducing conditions necessary to synthesize tryptamine chains from amino alcohols (**1-39**).³² Iridium catalyzed, the dehydrogenation of poorly reactive alcohol **1-39** is followed by the *in-situ* consumption of the generated hydrogen. This yields the correct oxidation state off the benzylic position of indole **1-40** furnishing the tryptamine chain (**Scheme 9, C**).

Another interesting way to functionalize position 3 of indoles is to employ single-electron transfer (SET) agents (discussed at length *vide infra*). A brief introductory example to this chemistry is outlined in **Scheme 10**, where indoles (**1-41**) were functionalized with styrenes (**1-40**).



Scheme 10 - Radical chemistry to generate functionalized indoles at the 3-position

Copper(I) is used as a single-electron oxidant to generate CF_3 radicals from NaSO_2CF_3 . The radicals react with styrenes (**1-43**) generating final elaborated indoles **1-42** (**Scheme 10**). The radical (**1-44**) is oxidized to a cationic intermediate **1-45** which is sufficiently electrophilic for indole **1-46** to attack and access highly substituted indole **1-47**. This chemistry is limited to electron-rich styrenes to obtain high yields of the substitution products. Indoles which bear substitution at their 2-position also reacted poorly under these conditions due to perceived steric interaction preventing the facile addition of indole to cationic styrene **1-45**.

1.2.3 Synthesizing Complex Indole-Containing Molecules

While functionalizing specific carbons on the indole heterocycle is valuable, molecular targets of interest often have complicated ring systems incorporating indole. These rings usually join to multiple positions of indole, completing the annulation. For example, the natural products targeted in Chapter 4 (disclosed in **Section 1.5**) contain a 6-membered ring that connects to indole at its 1 and 2 positions (**Figure 6**).

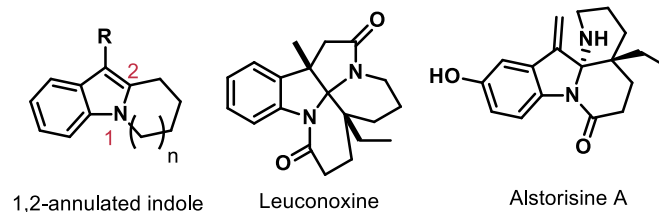
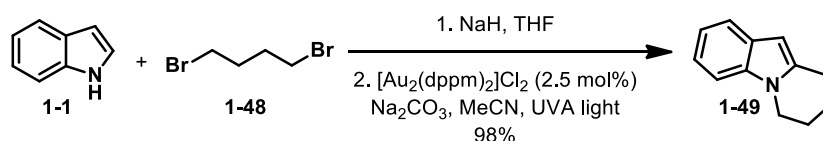


Figure 6 - Indole bearing cyclic 1,2 substitution like the molecules of interest in Chapter 4, plus a couple alternate natural product examples.

Generating annulated indole products can be done in a variety of ways: manipulating photochemistry, cycloadditions, radicals, or cross-coupling/metal insertion reactions.

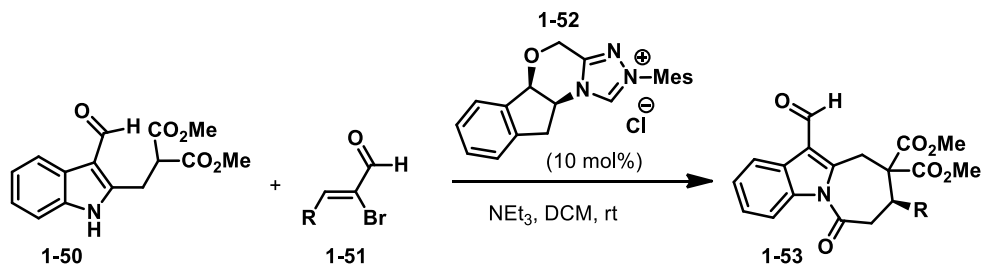
In 2015, the Barriault group constructed a straightforward method using UVA light to build 1,2-annulated indoles with simple and inexpensive alkyl halide chains (**Scheme 11**).³³ Gold containing photocatalyst ($[\text{Au}_2(\text{dppm})_2]\text{Cl}_2$) generates a radical by homolysis the C-Br bond, which rapidly adds to the 2-position of the tethered indole. Loss of a hydrogen returns the aromatic indole product **1-49**. The photochemistry tolerated substitution on the 3- and 5- positions of indoles without issue, resulting in high yields of annulated indoles.



Scheme 11 - Employing photochemistry to construct 1,2 annulated indole products.

In 2019, a unique enantioselective synthesis of 1,2-annulated indoles using NHC-catalysis was disclosed by the Hui group (**Scheme 12**).³⁴ Malonyl-substituted indoles (**1-50**) reacted with acrylaldehydes (**1-51**) facilitated by the NHC catalyst **1-52**. Due to the steric bulk of the NHC **1-52**, when connected to the acrylaldehyde component, the malonyl nucleophile can only perform a Michael addition from one face of the molecule. The single-sided attack results in the observed enantioselectivity at the quaternary carbon in molecule **1-53**. The enantiomeric excess (ee) ratios were high, ranging from 88-98% on all 20 substrates generated. The yields of the annulated indole products were also high,

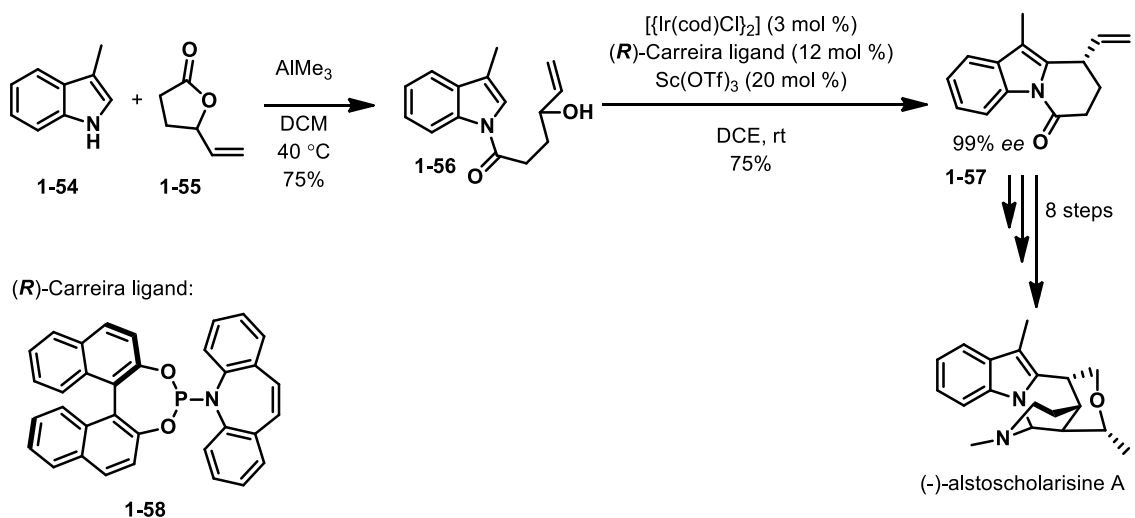
sitting above 87% for 18 of the 20 products generated. The yields drop when the R group in acrylaldehyde **1-51** is aliphatic, like a methyl or cyclohexyl group. In these cases, yields were less than 60%.



Scheme 12 - Enantioselective synthesis of 1,2- cyclized indoles taking advantage of a [3+4] annulation

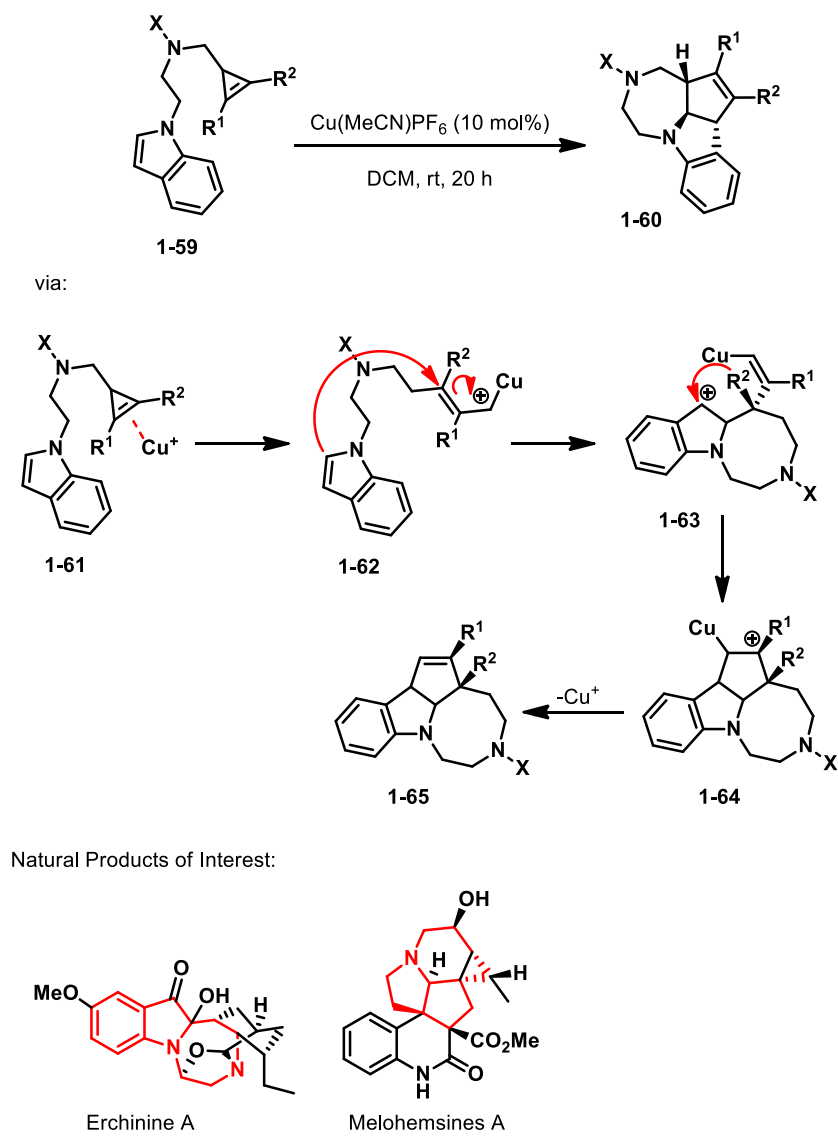
En-route to alkaloid (-)-alstoscholarisine A, a molecule that potentially prevents neuronal decline associated with Alzheimer's disease, the Yang group optimized

an enantioselective iridium catalyzed Friedel-Crafts alkylation to generate a 1,2-annulated indole **1-57** (Scheme 13).³⁵ Using Carreira's iridium catalyst³⁶ (ligand **1-58** + the iridium catalyst), acyl indole **1-56** was cyclized to enantiopure indole **1-57** — which in 8 concise steps, was successfully brought to natural product (-)-alstoscholarisine A.



Scheme 13 - Enantioselective synthesis of 1,2 annulated indole 1-57 en-route to natural product (-)-alstoscholarisine A.

Another recent and intriguing annulation of indole involved copper-catalyzed activation of intramolecular cyclopropanes (**1-59**), prompting the cyclization with indoles isolating elaborated products like **1-60** (**Scheme 14**). Coordination of the copper catalyst with the double-bond of the cyclopropane creates opened metal complex **1-62**. The tethered indole will attack the resultant electrophilic position yielding intermediate **1-63**. Annulation of the copper alkene to the resultant tertiary cation of the indole, followed by elimination of the copper catalyst yields the final product (**1-65**). This straightforward and mild procedure generated high yields of annulated indoles that the authors are hopeful will aid in the synthesis of the natural products showcased in **Scheme 14**.



Scheme 14 - Copper(I) catalyzed tandem cyclization of indoles with cyclopropenes and the target natural products the authors hope to access.

Indoles are also easily functionalized via nucleophilic opening of cyclopropanes. Although, to appreciate this chemistry an introduction to the unique reactivity of cyclopropanes is required.

1.3 Donor-Acceptor Cyclopropanes and their Reactivity with Indoles

1.3.1 Brief Introduction to Cyclopropane Reactivity

Cyclopropanes are unique 3-membered carbocycles that, because of their ring strain, are exceptionally reactive chemical participants. The internuclear distance of cyclopropane is 60° compared to a normal 109.5° for $C_{sp^3}-C_{sp^3}$ bonds, but the inter-orbital distance is widely accepted as being between $104-106^\circ$ (**Figure 7**).³⁷ Since covalent bonds are the result of orbital overlap, the greater the overlap between orbitals, the stronger the resultant covalent bond. In the case of cyclopropanes, this overlap is slight at best, and therefore the bonds are weak. Weak bonds being synonymous with greater reactivity, explain why cyclopropanes are so reactive.

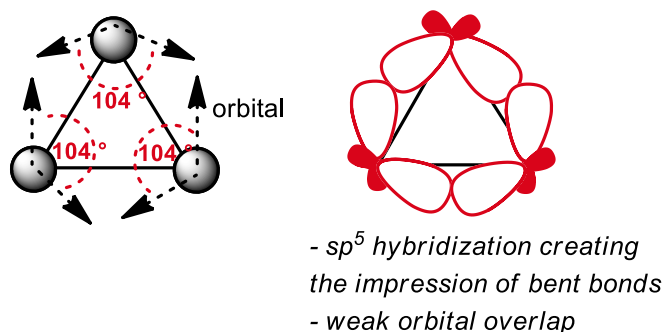


Figure 7 - Cyclopropane weak orbital overlap model

The initial description of cyclopropane bonding was the molecular orbital model proposed by Walsh, but his theory was refined by Coulson.^{37,38} Coulson explains that by distorting sp^3 hybridization of C-C bonds to technically sp^5 (1/6 s density and 5/6 p density) the C-C bonds contain greater p character to achieve the tight bond angles and the appearance of bent bonds (**Figure 7**).³⁹ This idea of hybridization containing greater p character is supported by observations of cyclopropanes undergoing addition reactions over substitution, and because of the conjugative resonance effects observed.⁴⁰ For example, vinyl cyclopropane (**Figure 8**) has 1.1-1.3 kcal/mol of empirical resonance energy as established by UV-Vis experiments. This proves the ability of cyclopropane to

conjugate with adjacent unsaturation, cementing the idea of greater p character in the bonds.⁴¹



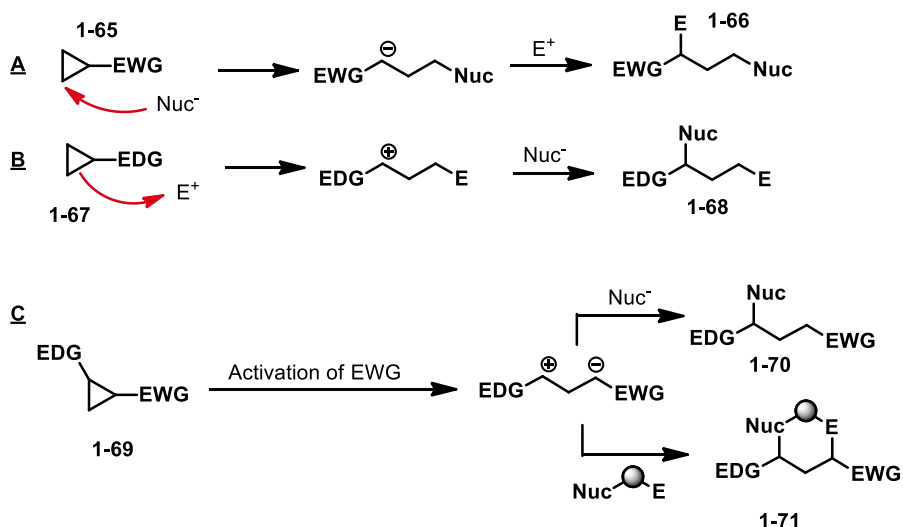
Figure 8 - Vinyl cyclopropane

Since more electron density is situated outside the internuclear axis, instead of directly between the carbon nuclei, the nucleophilicity of cyclopropane is similar to olefins, which have reactive π electrons perpendicular to the C-C bonds. For the same reasons, the reactivity of cyclopropanes is like olefins. Cyclopropanes, and olefins, with both acting as electrophiles and nucleophiles.⁴²

What makes cyclopropanes exciting is how we can tune the reactive nature of the strained molecule by adding substituents around the three-membered ring (**Scheme 15**). Adding electron withdrawing groups to a cyclopropane (**1-65**) we get an “accepting” cyclopropane, which can be opened with a nucleophile to give homo-Michael products (**1-66**, **Scheme 15, A**). Substituting the cyclopropane with an electron donating group (**1-67**) will increase its nucleophilic properties and the carbocycle can attack an electrophile (**Scheme 15, B**). When the cyclopropane is substituted with vicinal donating and accepting groups shown in example **1-69**. These are known as donor-acceptor cyclopropanes (DA CPs). Activation of the accepting moiety via heat⁴³, Lewis acid⁴⁴, hydrogen bonding⁴⁵ or high pressure⁴⁷ permits nucleophilic attack to open the cyclopropane yielding new substituted alkyl chains (**1-70**). If the nucleophile also has an appended electrophilic group, annulation reactions can occur to generate various cyclic products (**1-71**, **Scheme 15, C**).⁴⁶

The potential reactivity and applications for chemistry involving donor-acceptor (DA) type cyclopropanes (CPs) are a major focus within the Kerr group. We as a group have pioneered the involvement of indole nucleophiles with DA CPs and taken this chemistry to access valuable natural products. Within the works of this dissertation is a novel

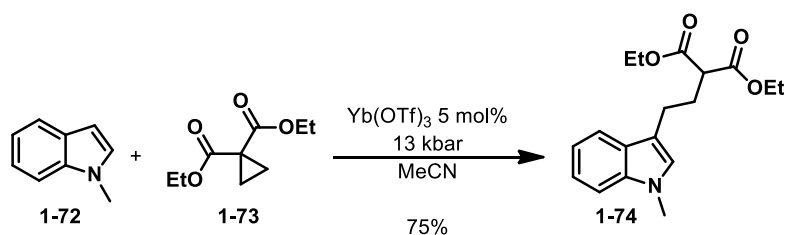
activation of DA CPs using hydrogen bonds, which means an understanding of how indoles have reacted with DA CPs in the past is of use.



Scheme 15 - Reactivity of cyclopropanes bearing electron withdrawing and/or donating groups

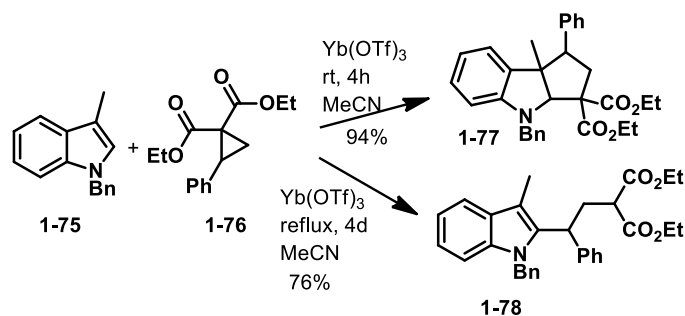
1.3.2 Seminal Work: Indoles Reacting with Donor-Acceptor Cyclopropanes

In 1997, Harrington and Kerr exploited indoles as nucleophiles for opening both acceptor, and donor-acceptor cyclopropanes.⁴⁷ Optimized results involved the use of high pressure (13 kbar) in the presence of Yb(OTf)₃ to have N-methylindole (**1-72**) open diester cyclopropane (**1-73**) giving a 70% yield of **1-74** (**Scheme 16**). The reaction was explored with diester cyclopropanes also bearing donor groups such as methyl and phenyl, and explored five different indole nucleophiles achieving high yields of the ring-opened products.



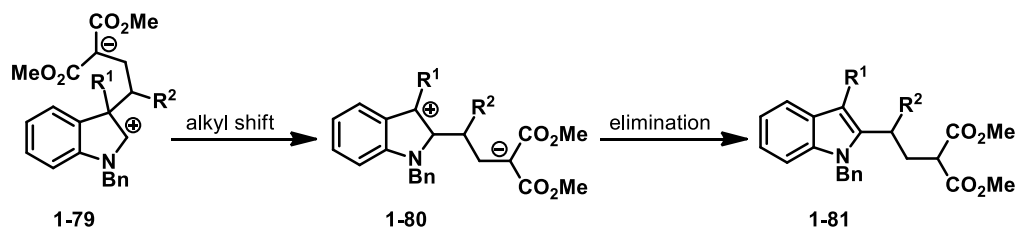
Scheme 16 - Seminal work opening cyclopropanes with indoles

Determined to find more productive and interesting products from indole nucleophiles, England *et al.* explored annulation reactions involving indoles opening DA CPs.⁴⁸ 3-substituted indoles were capable of opening DA CPs, generating 2,3-annulated indoline products (**1-77**) under Lewis acidic conditions (**Scheme 17**). Interestingly, if the reaction was left longer, an unusual rearrangement occurred resulting in 2,3-disubstituted indole products (**1-78**). This chemistry confirmed high pressure was not required, and activation of the DA CP with Lewis acid was sufficient to generate annulated products.



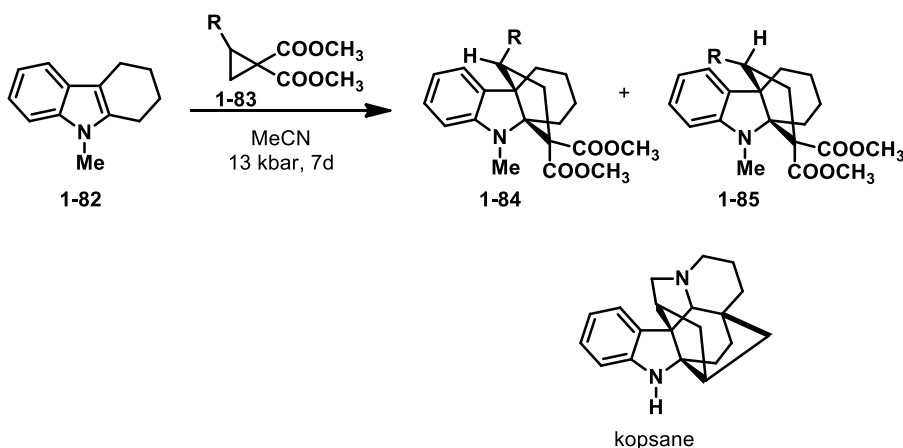
Scheme 17 - Annulation reaction of indoles and cyclopropanes (1-77) plus additional rearrangement to access alternative 2,3-disubstituted products (1-78)

After ring-opening with indole (**Scheme 18**), **1-79** undergoes favourable alkyl shift moving the cyclopropyl chain to the 2-position of the indole (**1-80**), generating a tertiary carbocation. Elimination driven by re-aromatization offered a route to 2,3-substituted indoles (**1-81**) via reaction with DA CPs.



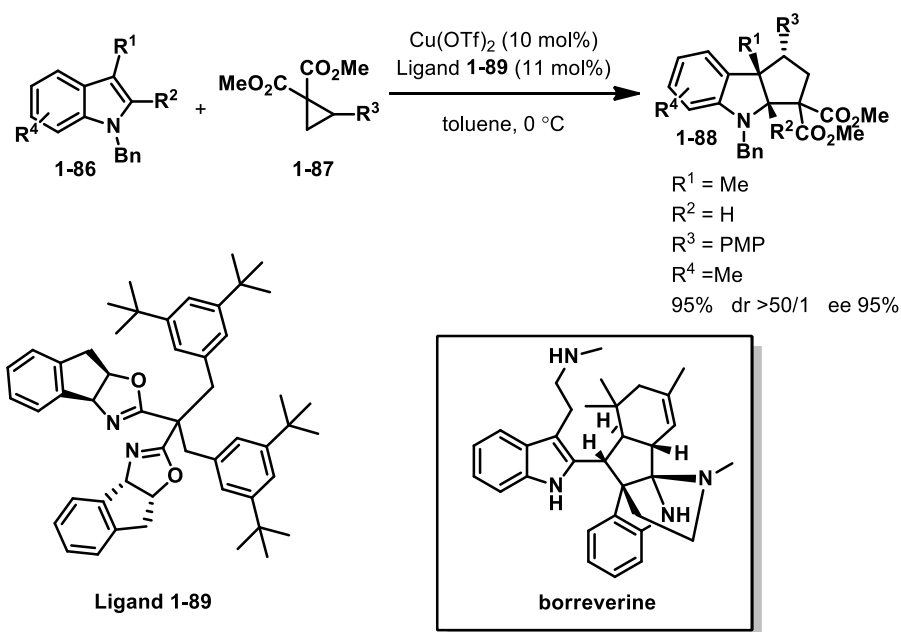
Scheme 18 - Alkyl shift generating 2,3-disubstituted indole products

This work was effectively applied by synthesizing a subunit of the kopsane alkaloids, **1-84** (Scheme 19).⁴⁹ However, accessing molecules **1-84** and **1-85** required high-pressure to furnish the caged complexity.



Scheme 19 - Methodology poised for generating the molecular scaffold of kopsane alkaloids using indoles and donor-acceptor cyclopropanes

A great improvement on this work was reported 11 years later in 2013. Tang *et al.* designed an effective methodology for the enantioselective annulation of indoles and DA CPs (Scheme 20). Catalyzed by copper, and in the presence of their optimized ligand (**1-89**), they were able to generate the cyclopentane annulated indoline products (**1-88**) like those synthesized by England, but this time with enantiomeric control.⁵⁰ Tang *et al.* generated products with greater than 86% *ee* and the chemistry was successfully applied by synthesizing the core of natural product borreverine (Scheme 20).

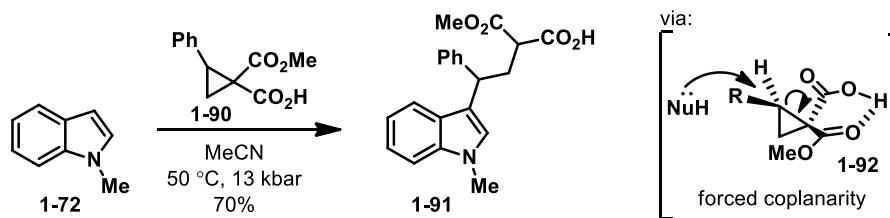


Scheme 20 - Enantioselective addition of indoles to donor-acceptor cyclopropanes

In the cases antecedent, the DA CP ring-opening reactions were activated by the presence of Lewis acid, and sometimes even required the aid of a high-pressure environment. In 2011, the Kerr group improved this model by using an internal hydrogen-bond to activate DA CPs — abolishing the requirement for Lewis acid activation. It was the start of research involving alternative reaction conditions for opening DA CPs.

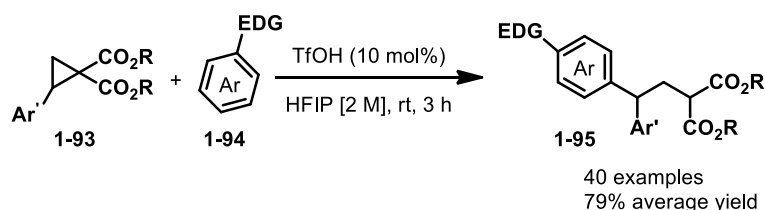
1.3.3 Activation of Donor-Acceptor Cyclopropanes without Lewis Acids

DA CPs successfully undergo ring-opening reactions with indoles in the absence of acid catalyst when they contain a both a carbohydroxy, and carboalkoxy group, geminally substituted (**1-90**, **Scheme 21**).⁵¹ Via proposed 6-membered ring intermediate (**1-92**) to induce co-planarity of the carbonyls, the cyclopropane is sufficiently reactive for nucleophilic opening with indoles without the aid of a Lewis acid. An extensive improvement to this work and a more in-depth discussion of the activation mechanism is the focus of Chapter 2.



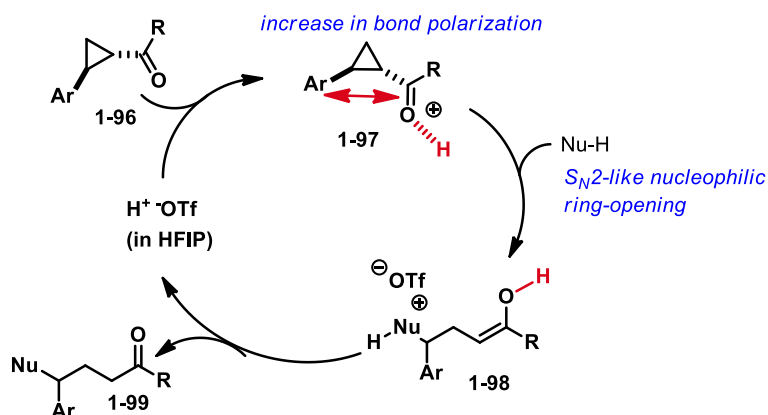
Scheme 21 - Internal Brønsted acid activation of cyclopropanes

Additional Lewis acid-free reactivity of cyclopropanes was reported by the Moran group in 2018 using Brønsted acid as the activator.⁵² This work was released just as I had submitted the manuscript on my novel findings outlined in Chapter 2. The works are similar, but complement each other well. Moran reported that using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) solvent in the presence of 10 mol% TfOH, DA CPs can be opened in high yield by electron-rich aromatic nucleophiles **1-94** (Scheme 22). This work showcased an impressive improvement on previous chemistry as it did not require an internal hydrogen bond, it avoids the use of high-pressure conditions, and it does not require a metal catalyst.



Scheme 22 - Brønsted acid catalyzed ring-opening of cyclopropanes

The chemistry worked broadly, capable of generating 40 different aromatic-substituted products in high yields. This work proposed that HFIP, a strong hydrogen-bond donor, is necessary to stabilize intermediate **1-98** and increase the C-C bond polarization of the cyclopropane (**1-96** and **1-97**) so it is sufficiently susceptible to attack via the aromatic nucleophile (Scheme 23).

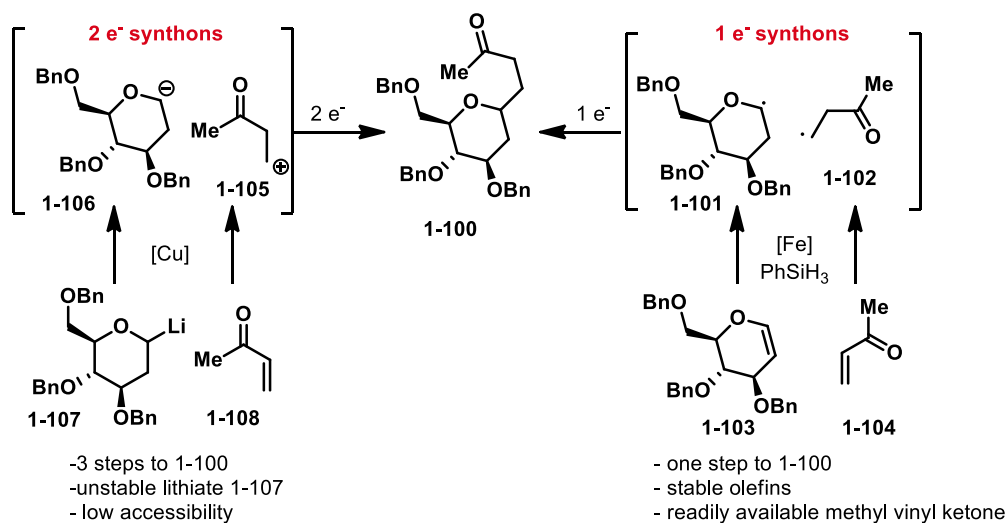


Scheme 23 - Proposed mechanism for the Brønsted activation of DA CPs

A component of work in Chapter 2 further discusses how HFIP itself is a suitable hydrogen bond donor, capable of activating cyclopropanes without the need for TfOH. In addition to functionalizing indoles via reaction with DA CPs, focus in this thesis is also given to single electron transfer (SET) agents, and their ability to passage new functionality via radical chemistry.

1.4 Single Electron Transfer Agents and Reactivity with Indoles

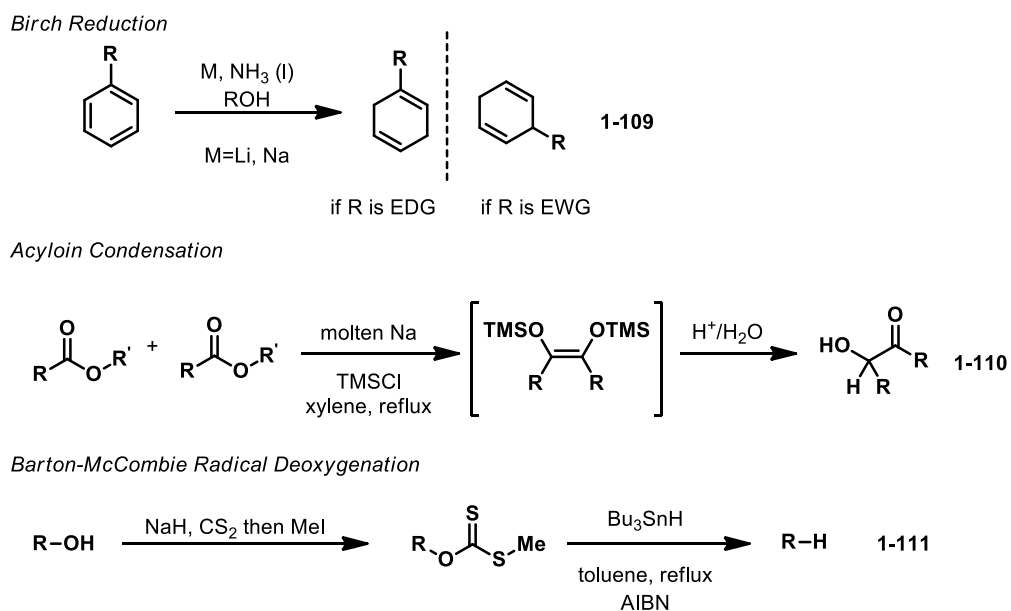
Radical reactions in synthesis, once considered too uncontrollable to be useful, are becoming increasingly popular due to their capabilities to form C-C bonds⁵³, perform tandem and cascade reactions in a single flask⁵⁴, and make complex disconnections possible for target molecules. Retrosynthetically analyzing bonds in a one e⁻ fashion, over a two e⁻ mindset, has been changing the way we build molecules.⁵⁵ Using single-electron chemistry often lessens the need to make extra adjustments compensating for chemo- and regioselectivity to generate compatible synthons. This provides one e⁻ chemistry a unique advantage. Baran *et al.* exemplify this claim in a comparison of the synthetic routes to useful glycoside derivative **1-100** (Scheme 24).^{56,57}



Scheme 24 - comparing $2 e^-$ and $1 e^-$ disconnections to better synthesize product 1-00

The single electron pathway accessed desired glycoside **1-100** in just one step, without the need to produce the unstable lithiate (**1-107**) using unsafe lithiations conditions. For these reasons, radicals are becoming valuable tools in the synthesis of organic molecules. The research outlined in Chapter 3 employs radical chemistry to functionalize indoles.

Single electron transfer (SET) agents have long been used to reduce carbon centers — generating radicals that are capable of many bond-forming reactions. Often alkali metals and tin hydrides dominate this field, especially regarding reductions (**Scheme 25**). To name a few famous examples (**Scheme 25**): Birch reduction (**1-109**)⁵⁸ (Li^0 , Na^0), acyloin condensation (**1-110**)⁵⁹ (Na^0), and the Barton-McCombie deoxygenation (**1-111**)⁶⁰ (Bu_3SnH), but a great number of milder and effective SET agents have been used successfully in chemical synthesis over the last couple years, especially those pertaining to *oxidative* radical processes.

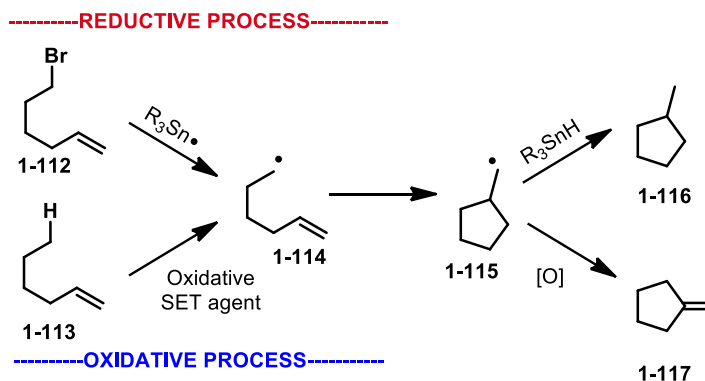


Scheme 25 - Reductive radical reactions

Cerium (IV), iron (III), manganese (III), copper (II), and vanadium (V) are high-valent metals with easily handled salts capable of exploiting their flexible oxidation states to generate carbon-centered radicals like **1-114** (**Scheme 26, oxidative process**).⁶¹

Oxidative radical processes generate products that are often the same oxidation state of the starting material. Compare the reductive and oxidative process in **Scheme 26**: the reductive process gains hydrogen replacing the starting alkene with sigma bonds.

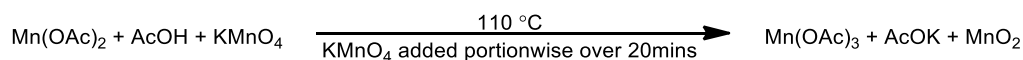
Chapter 3 expands on chemistry using Mn(III) as a SET agent, discussing its ability to oxidatively generate radicals to form C-C bonds with indole containing compounds. Mn(III) is the most established of these SET agents and the one that I will explore in great detail.



Scheme 26 - Comparison of reductive and oxidative radical processes

1.4.1 Introduction to Mn(OAc)₃: a SET Agent

Manganese(III) is an oxidative radical former; the radical is generated via formal loss of a hydrogen. Mn(III) is also known as a SET agent because of its capabilities to oxidatively produce radicals at carbon centers. Mn(III) is most commonly used as Mn(OAc)₃•2H₂O, which is safe, easy to handle, simple to prepare, and comes from the extremely inexpensive Mn(OAc)₂ (\$86/kg, MilliporeSigma). Refluxing Mn(OAc)₂ in AcOH with potassium permanganate (KMnO₄) produces Mn(OAc)₃, which is then crystallized from H₂O yielding Mn(OAc)₃•2H₂O, the active reagent (**Scheme 27**). To produce the anhydrous Mn(OAc)₃, acetic anhydride is added during the synthesis.⁶²



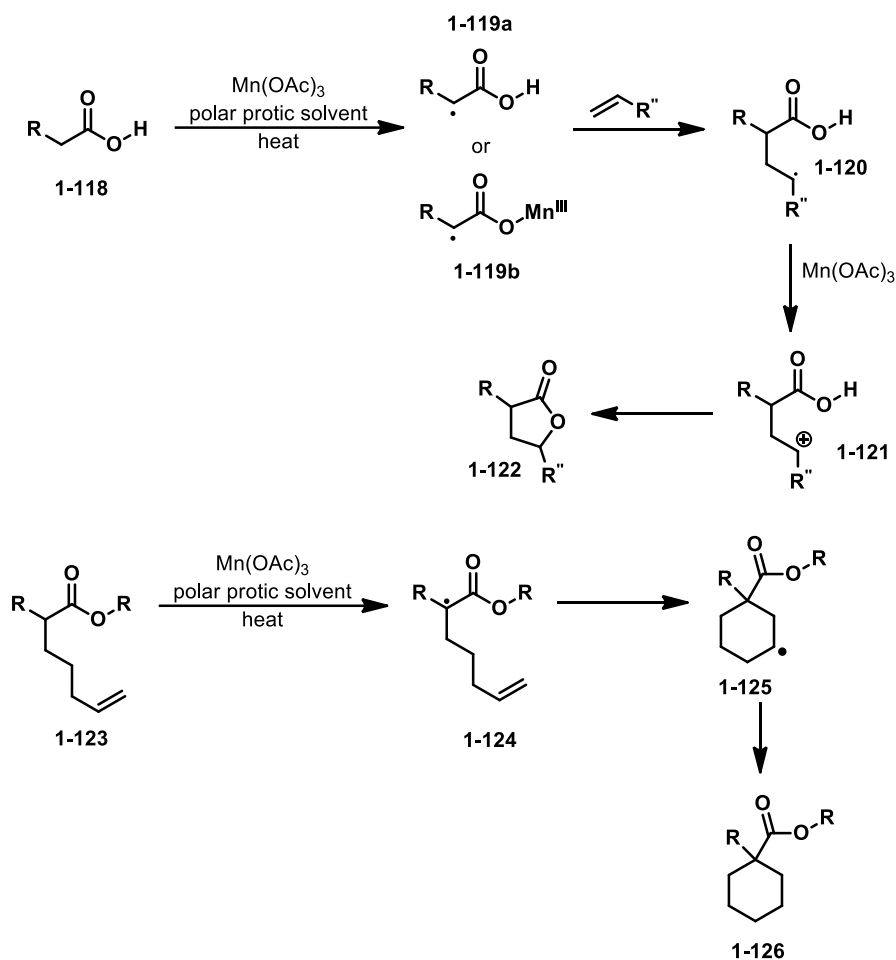
Scheme 27 - Synthesis of Mn(OAc)₃

Bush *et al.*, who first reported the synthesis of anhydrous Mn(OAc)₃, also determined that the way in which the Mn(OAc)₃ is prepared, has an effect on its capabilities as a reagent. They discovered that if water remained in the crystallographic structure of the Mn(OAc)₃, even in regards to the hydrate complexes, yields of products made from Mn(OAc)₃ radical production were lower. They hypothesized that water in the crystal structure altered the geometry of the molecule in such a way that the Mn(III) was not effective in coordinating to carbonyl groups.⁶² To produce quality Mn(OAc)₃ the operating chemist must be sure that the temperature of the acetic acid is between 105-110 °C (*no higher*)

before the portion-wise addition of permanganate. I never had any issues synthesizing $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ with this information. The procedure for the synthesis $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ used in this thesis is outlined in **Section 3.7**. From this point on, $\text{Mn}(\text{OAc})_3$, as written, implies the dihydrate material being used.

$\text{Mn}(\text{OAc})_3$ generates carbon-centered radicals on carbonyl compounds such as β -diketones, acetoacetamides and β -ketoesters. Generally speaking, $\text{Mn}(\text{OAc})_3$ works to create radicals α to carbonyls, which can then combine with another suitable partner (**Scheme 28**). $\text{Mn}(\text{OAc})_3$ works with 1,3-dicarbonyls, or other appropriate electron withdrawing groups to form lactones (**1-122**) or cyclic molecules via intramolecular annulation. Often, greater than stoichiometric amounts of $\text{Mn}(\text{OAc})_3$ are used to facilitate a second oxidation of the radical intermediates (**1-121**). In **Scheme 28**, α radical **1-124** reacts intramolecularly with the alkene generating cyclohexane **1-125**. The radical in this case undergoes hydrogen abstraction yielding **1-126**. Mn(III) chemistry also works most reliably when the radical acceptor, often an alkene or alkyne, is tethered within the molecule to access annulated products in an intramolecular fashion (**Scheme 28, 1-123**).

Publications involving $\text{Mn}(\text{OAc})_3$ largely increased in the 1980's, and the reagent has been applied in some interesting ways that will be discussed in the following subsections.



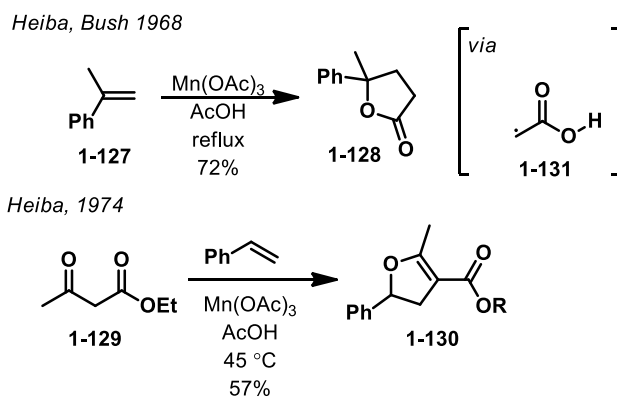
Scheme 28 - General reaction pathways for Mn(OAc)_3 radical chemistry

1.4.2 First Uses of Mn(OAc)_3 Chemistry

First reports using Mn(OAc)_3 as an oxidative radical former were outlined by Bush and Heiba in 1968. Both reports expressed the synthesis of lactones like **1-128** from olefins in the presence of Mn(OAc)_3 and acetic acid (**Scheme 29, 1968**).^{63,64} The acetic acid solvent is complexed by manganese, then deprotonation followed by electron transfer generates radical acetic acid species (**1-131**) which combined with the olefins. Both researchers found moderate yields around 70% for the synthesis of lactones from a variety of olefins.

In 1974 Heiba pushed Mn(III) radicals further by expanding the scope to β -ketoesters (**1-129**) (**Scheme 29, 1974**).⁶⁵ Dihydrofurans (**1-130**) were synthesized in modest yields

from the carbon-centered radical generated at the alpha position of ethylacetoacetate **1-129**.



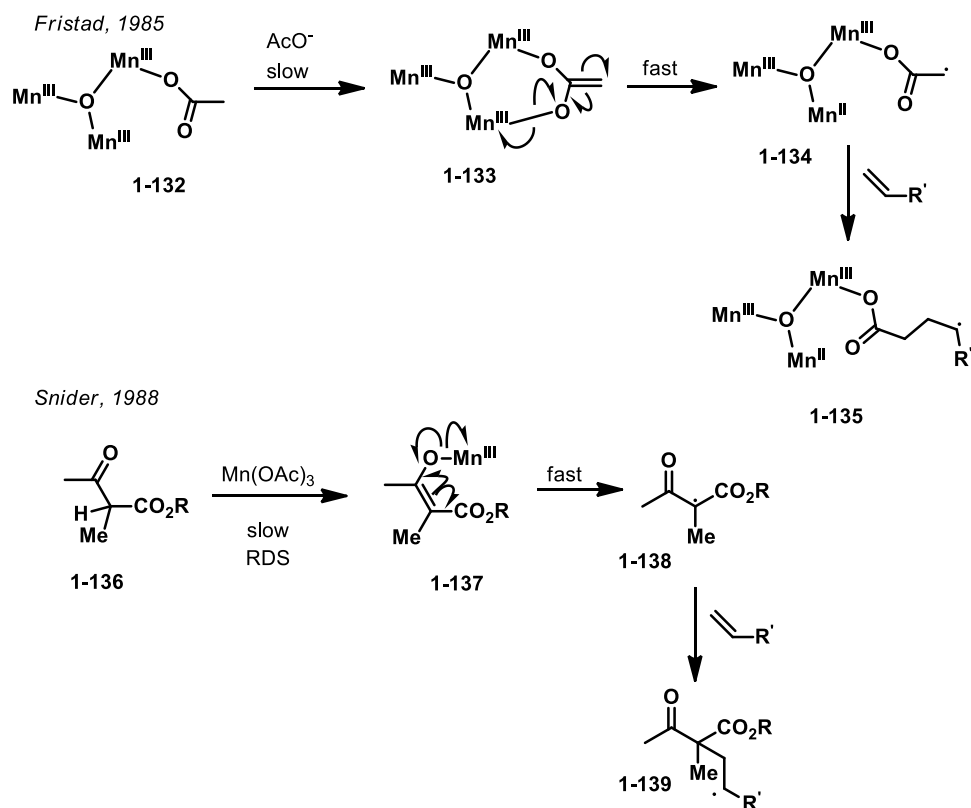
Scheme 29 - First reports of Mn(OAc)_3 as a radical initiator to synthesize lactones from olefins

From the success employing 1,3-dicarbonyl species as radical partners, the field expanded to use Mn(III) for practical syntheses of complex and desirable molecules. The chemists that took over from Heiba and Bush are now the experts in the field: Barry Snider and E. J. Corey.

First though, elucidation of the mechanism for reactions involving Mn(OAc)_3 were explored during this time and proposed by Snider and Fristad. An understanding of how this oxidative mechanism generates radicals will aid in the comprehension of my research.

1.4.3 Mn(OAc)_3 Mechanism of Action

Kinetic and mechanistic studies on how Mn(OAc)_3 generates radicals have been studied and a well-accepted model generated. The outlined mechanism below (**Scheme 30**) shows how the α -radicals of carbonyl compounds (**1-132** and **1-136**) are generated. It is agreed that the rate determining step (RDS) in the oxidation reaction is the loss of a proton from the complexed substrate either **1-132** or **1-136** (**Scheme 30**). Both Fristad and Snider proposed how the oxo-centered triangle of Mn(III) (**1-133** and **1-137**) and their bridging acetates, initiate radical formation (**Scheme 30**).^{66,67}



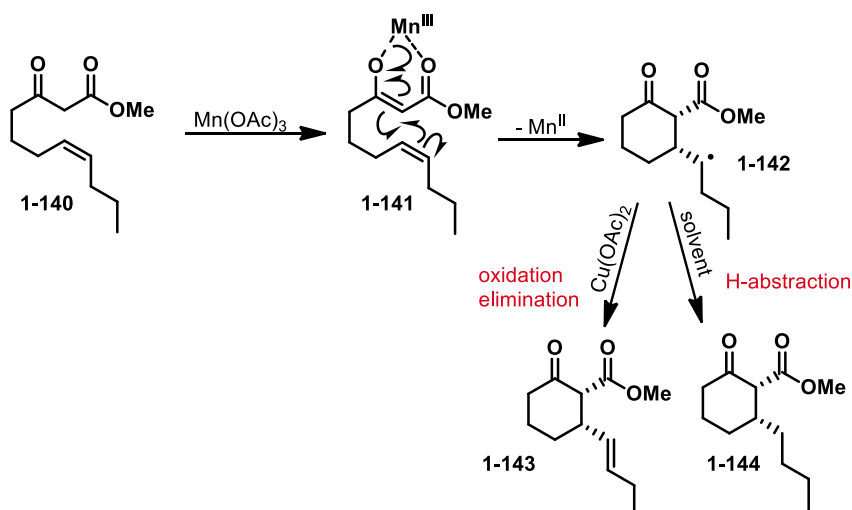
Scheme 30 - Mechanistic considerations for $\text{Mn}(\text{OAc})_3$

The deprotonation of **1-132** to form enolate coordinated product **1-133** occurs as the RDS and then undergoes rapid electron transfer to give radical **1-134**. This radical undergoes chemistry with suitable reactive partners like alkenes or alkynes. In the Snider example (**Scheme 30**), the enolization step is slow to produce **1-137**, but the electron transfer resulting in the loss of Mn(II) and generating radical **1-138** is fast. This claim is aided by the fact the concentration of alkene (or other radical acceptor) has no effect on the rate of this reaction. Sufficiently acidic/enolizable substrates are required for Mn(III) to overcome the slow and rate-determining deprotonation before generating a radical. This is why the chemistry involving Mn(III) radicals often relies on 1,3-substituted electron withdrawing substrates such as malonates, or β -ketoesters.

1.4.4 Effects of Other Oxidants in $\text{Mn}(\text{OAc})_3$ Reactions

Exemplified in **Scheme 28**, Mn(III) is often an oxidant twice in the same reaction (**1-120** to **1-121**), and will oxidize the final radical to a cation that can be quenched by different

mechanisms to create products. Alternate oxidants are sometimes added as they can control the final product acquired.⁶⁸ When manganese is the chosen oxidant its abilities are limited; only tertiary and benzylic radicals can be oxidized to their respective cation by manganese. Primary and secondary radicals will not oxidize in the presence of Mn(III), and will instead undergo H-abstraction (product **1-144** in **Scheme 31**). Using Cu(OAc)₂ in addition to Mn(OAc)₃ addresses this problem; as an external oxidant it became popular because it could generate different final products. Cu(OAc)₂ oxidizes 2° radicals 350 times *faster* than Mn(OAc)₃. It will also take primary and secondary radicals to alkenes by direct oxidative elimination instead of H-abstraction (product **1-143** in **Scheme 31**).⁶⁹



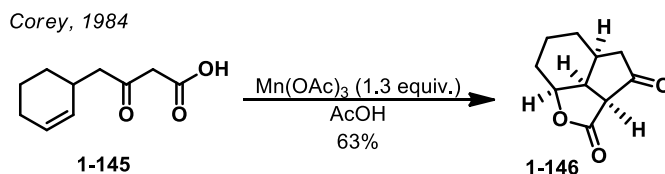
Scheme 31 - Termination processes using either external oxidant Cu(OAc)₂ or solvent in the absence of an external oxidant.

To facilitate the enolization and quenching of these reactions, polar protic solvents are the required reaction medium. DMSO and CH₃CN do work, albeit in lower yields. Typically, and as shown in most of these examples, AcOH or MeOH are the solvents of choice.

With an understanding of the mechanism and quenching routes, efficient exploitation of Mn(OAc)₃ began to offer access to complex products.

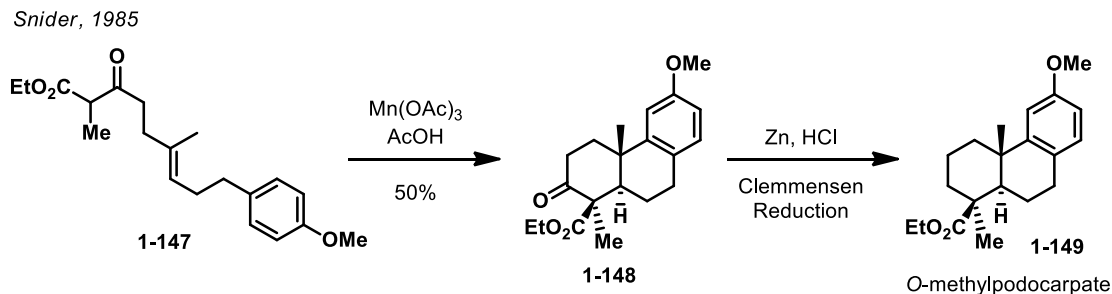
1.4.5 Applications of Mn(OAc)₃ in Natural Product Synthesis

Corey first showcased how Mn(OAc)₃ radicals could be applied reporting a cascade reaction capable of generating complex polycyclic structures (**Scheme 32**).⁷⁰ B-ketoacid **1-145** subjected to 1.3 equivalents of Mn(OAc)₃ in AcOH resulted in a 63% yield of molecule **1-146** in an impressive a single step. This work exemplifies how radicals often make for extremely economic and atom efficient reactions. The structures had impressive diastereocontrol, generating the cis-fused pentacyclic structures simply due to the nature of radical chemistry. The pentacycles map nicely onto the ginkgolide group of natural products.



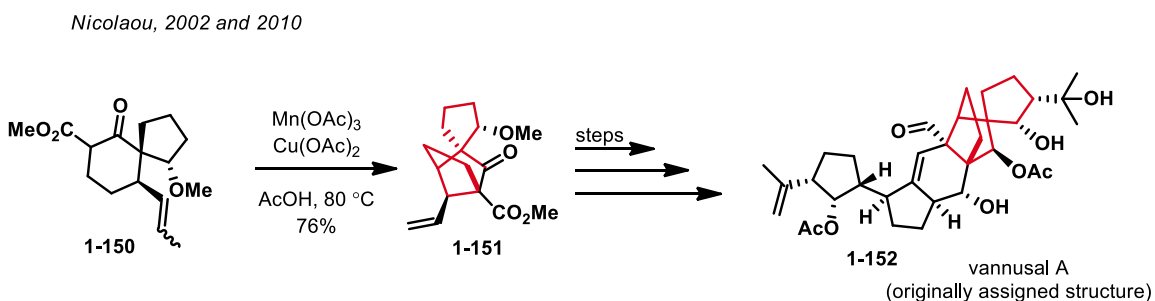
Scheme 32 - Corey's application to impressive pentacyclic structures using Mn(III)

A year later, in 1985, Snider formally synthesized natural product (±)-podocarpic acid using Mn(OAc)₃ as the focal point of the synthesis (**Scheme 33**).⁷¹ Cascade radical cyclization of elaborated olefin **1-147** via Mn(OAc)₃ furnished the core scaffolding of (±)-podocarpic acid (**1-148**). A Clemmensen reduction synthesized product **1-149**, O-methylpodocarpace, that was taken to (±)-podocarpic acid in 1956.⁷²



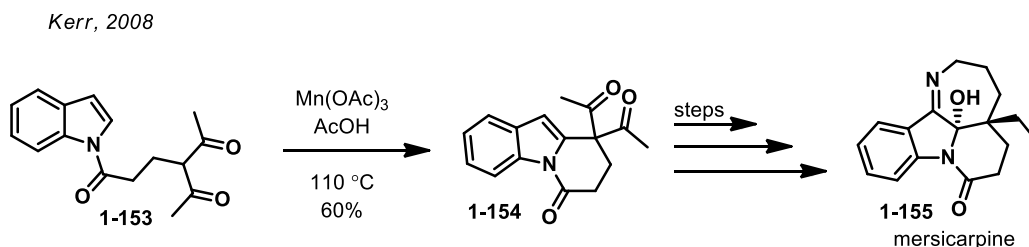
Scheme 33 - Snider's formal synthesis of (±)-podocarpic acid through intermediate **1-149** generated using Mn(OAc)₃

Later in 2002, $\text{Mn}(\text{OAc})_3$ in the presence of co-oxidant $\text{Cu}(\text{OAc})_2$ furnished the main scaffolding of natural product vannusal A (**1-152**) as reported by Nicolaou *et al* (Scheme 34).⁷³ The spirocyclic molecule **1-151**, being geometrically strained, was welcoming to a radical methodology, which is often a great choice to make tough, tight bonds. From β -ketoester **1-150**, radical cyclization worked in a 76% yield to furnish **1-151** (Scheme 34). In 2010, the Nicolaou group realized the complete total synthesis of vannusal A and corrected its originally proposed structure.⁷⁴



Scheme 34 - Nicolaou's route to vannusal A incorporating a Mn(III) mediated radical cyclization of spirocycle 1-151

Where the Kerr group expertise shines is using $\text{Mn}(\text{OAc})_3$ as a means to perform cyclization reactions with indoles. In 2008, the total synthesis of mersicarpine was achieved using an important $\text{Mn}(\text{OAc})_3$ cyclization reported by Magolan and Kerr (Scheme 35).⁷⁵ Malonyl-tethered indole **1-153**, was subjected to the oxidative radical forming conditions with $\text{Mn}(\text{OAc})_3$ generating tricyclic product **1-154**. **1-154** was taken to the target molecule, mersicarpine (**1-155**, Scheme 35).

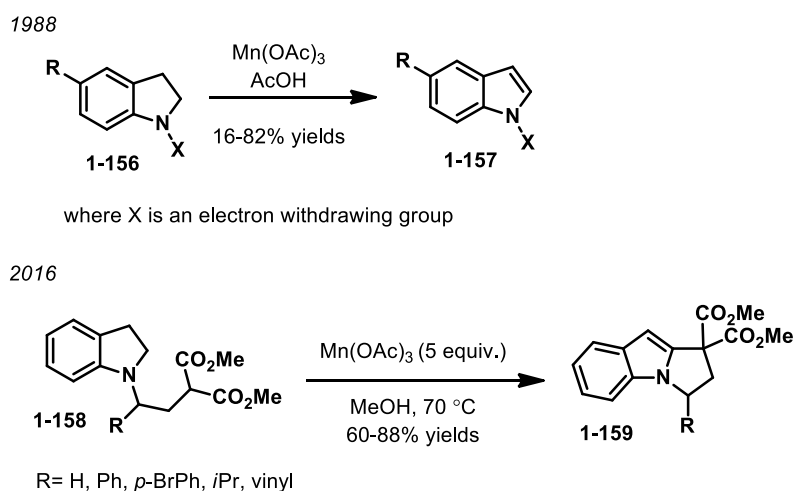


Scheme 35 - Kerr group synthesis of mersicarpine functionalizing indole 1-153 via Mn(III) radical cyclization

This segues nicely into how $\text{Mn}(\text{OAc})_3$ can be used to further functionalize indoles into desirable synthetic targets.

1.4.6 $\text{Mn}(\text{OAc})_3$ and Indole Functionalization

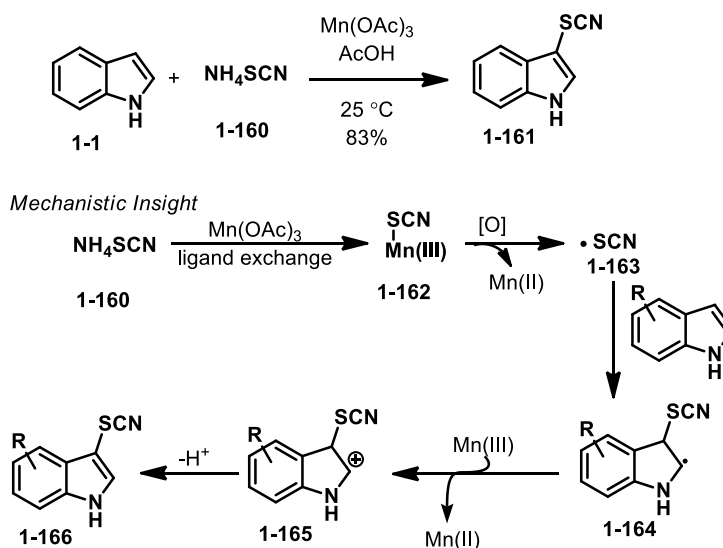
When it comes to indoles, $\text{Mn}(\text{OAc})_3$ was first used as an oxidative reagent to take indolines to their aromatic indole counterpart.⁷⁶ Original reports (**Scheme 36, 1988**) observed that only electron withdrawing components off of the indoline nitrogen (**1-156**) were tolerated. As work with Mn(III) progressed, Curiel Tejeda *et al.* demonstrated an improvement on the oxidation of indolines (**Scheme 36, 2016**). Indolines bearing electron rich substitution (**1-158**), like a methylene or phenyl group, were also capable of oxidation to indoles using $\text{Mn}(\text{OAc})_3$. The materials explored also underwent a radical cyclization with the malonyl tether in a single-step yielding annulated indole **1-159**.



Scheme 36 - $\text{Mn}(\text{OAc})_3$ as a tool to synthesize indoles

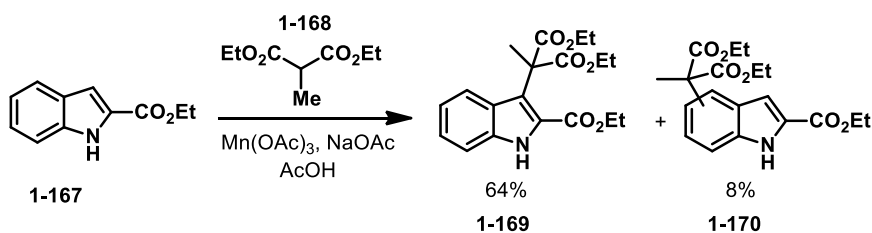
Another interesting application of $\text{Mn}(\text{OAc})_3$ is observed in its ability to regioselectively thiocyanate indoles (**Scheme 37**). At room temperature, in the presence of $\text{Mn}(\text{OAc})_3$, a variety of indoles were thiocyanated in high yields to provide a different functional handle on indoles. Indole (**1-1**) with ammonium thiocyanate (**1-160**) and $\text{Mn}(\text{OAc})_3$ produced functionalized indole **1-161** (**Scheme 37**) in an 83% yield.⁷⁷ Mechanistically, radical thiocyanate **1-163** is produced via ligand exchange with ammoniumthiocyanate and $\text{Mn}(\text{OAc})_3$. Radical **1-163** then reacts with the chosen indole, where a second

equivalent of Mn(III) oxidizes the radical to cation **1-165**. End indole **1-166** is generated by loss of a proton.



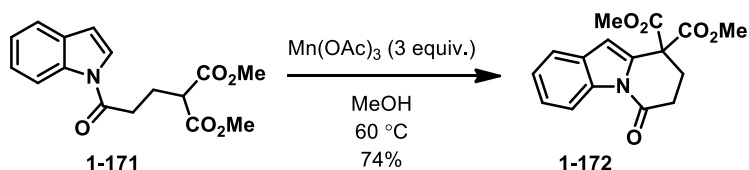
Scheme 37 - Functionalizing indoles with thiocyanate

Continuing our exploration of indoles and manganese (III), methylmalonylation of both pyrroles and indoles was reported in 1993 starting the wave of publications relating to the addition of diketone species into indoles. Baciocchi *et al.* found that methyl diethylmalonate (**1-168**) was radically added to indoles when subjected to Mn(OAc)₃. 3-substitution was the major product (**1-169**) and a minor fraction of mixed substitution around the phenyl ring of indole (**1-170**) was also isolated (**Scheme 38**).⁷⁸



Scheme 38 - Addition of malonyl groups to indoles via Mn(III) chemistry

Expansions on this work would include cyclization reactions where instead a malonyl group was in the starting indole causing intramolecular reactions (**Scheme 39**). Magolan *et al.* synthesized indoles containing malonyl tethers (**1-171**) and used a $\text{Mn}(\text{OAc})_3$ radical cyclization to generate 1,2-disubstituted indoles bearing a cyclohexane ring (**1-172**) (**Scheme 39**).⁷⁹



Scheme 39 - Tethered indoles functionalized to 1,2-cyclized product 1-172 by $\text{Mn}(\text{OAc})_3$

Cyclic substituted indoles, like that of product **1-172**, map well onto a vast selection of natural products. It matches particularly well to products isolated from plant species *Tabernaemontana corymbosa*, which will become the next topic of this introductory material.

1.5 Indole-Containing Natural Products of Interest

The *Tabernaemontana* genus of Malaysian flowering plants have produced many interesting isolated and characterized natural products. In Chapter 4 of this thesis will discuss new progress trying to synthesize two of these isolated indole-alkaloids using $\text{Mn}(\text{OAc})_3$.

The Kam group from the University of Malaya has worked over many years to extract *huge* numbers of alkaloids from *Tabernaemontana corymbosa*. Many of these alkaloids collected have been useful targets of interest to organic chemists⁸⁰, but it was first Van Beek, who had worked with plant extractions from *Tabernaemontana chippii* to isolate 45 different alkaloids.⁸¹ At the time, 34 of them were fully characterized, and 8 of them were newly discovered molecules. A screening of these new molecules revealed that they have antifungal and antimicrobial uses. A couple of the alkaloids elucidated by Van Beek, pleiocarpamine and chippiine, are showcased in **Figure 9**, with the skeleton of

interest outlined in red. Unique to this plant, we notice these molecules have a 1,2-substituted cyclic indole scaffold, which the Kerr group has become expert in generating using $\text{Mn}(\text{OAc})_3$.

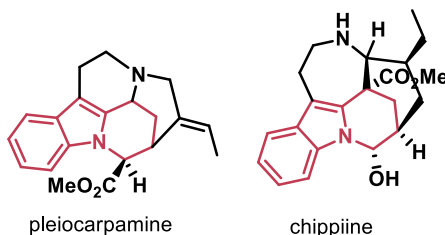


Figure 9 - Select examples of alkaloids isolated from *Tabernaemontana chippii*.

In 2000, the Kam group isolated the first novel pentacyclic indole natural product that also contained a 7-membered lactam moiety. This lactam functionality had not been seen in the alkaloids of *Tabernaemontana* before. The product isolated, and named as tronocarpine (**Figure 10**), was thought to be related to the tacaman-type alkaloids (for example chippiine (**Figure 9**) is a member of this family), but no evidence of its presence in *Tabernaemontana corymbosa* was discovered. Since this alkaloid has yet to see its total synthesis completed, and due to its interesting pentacyclic structure, tronocarpine is an enticing piece of work to the organic chemist. Again, chemistry outlined in this thesis instilled a confidence that Kerr group methodologies using $\text{Mn}(\text{OAc})_3$ would be an efficient way to fashion this natural product. In addition to its unique structure, tronocarpine has not yet been tested for its bioactivity, but because of the bioactive nature of related alkaloids, it is of interest to determine the potential pharmaceutical effects that tronocarpine may have.

Later in 2001, the Kam group isolated 4 new alkaloids named Dippinine A-D, from the plant *Tabernaemontana corymbosa*.⁸² These new indole alkaloids also contained the tricyclic scaffolding that I was confident we could generate in an efficient way. Dippinine B (**Figure 10**) was of special significance as a molecule because I could perhaps synthesize it based on the methodology generated in Chapter 3 of this thesis. I have a great way of generating acyl indoles that cyclize with $\text{Mn}(\text{OAc})_3$ and put functional handles in correct regions to access this interesting natural product. Dippinine B is also

similar to tronocarpine differing only in the attachment of their tryptamine chains. Tronocarpine and dippinine B became the target molecules of interest and work towards their syntheses is reported in Chapter 4.

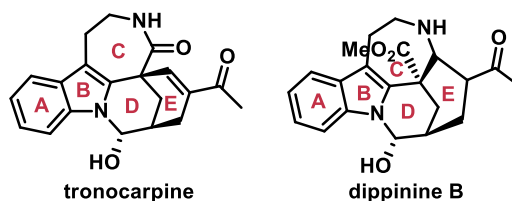


Figure 10 - Indole alkaloids tronocarpine and dippinine B isolated from *Tabernaemontana corymbosa*

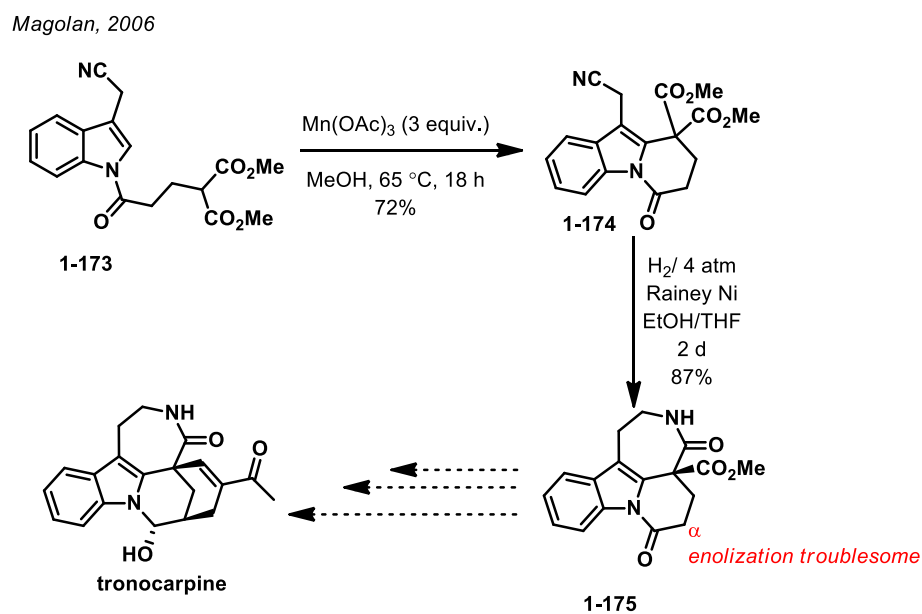
1.5.1 Previous Synthetic Attempts at Tronocarpine

To date, only three attempts at tronocarpine have been published. Original work towards the molecule was performed in the Kerr group by past students Jakob Magolan, and Katarina Sapeta.

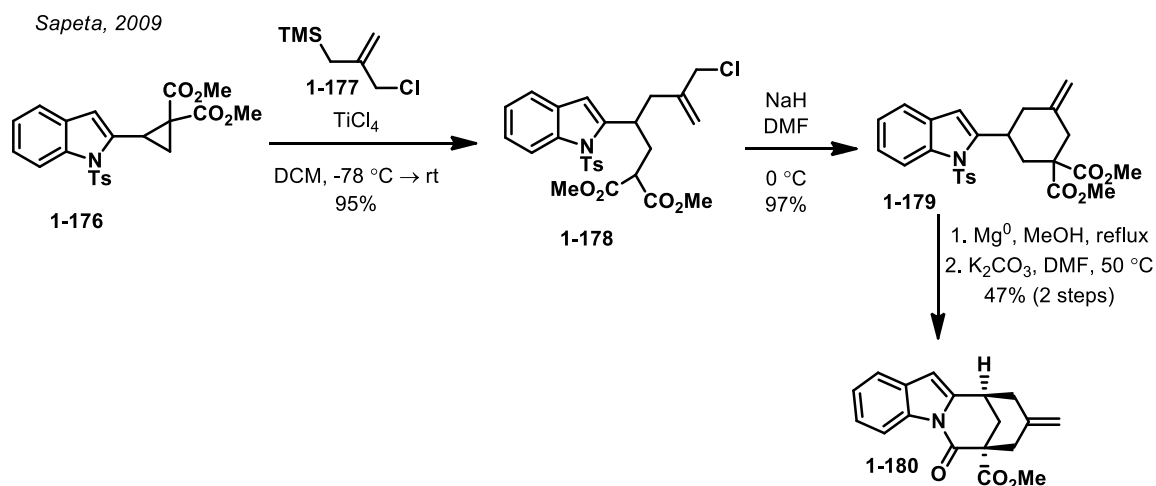
In 2006, Magolan outlined a synthesis of the tetracyclic core of tronocarpine, furnishing rings A, B, C, and D.⁷⁹ From elaborated indole-3-acetonitrile **1-173** (**Scheme 40**), the $\text{Mn}(\text{OAc})_3$ oxidative cyclization furnished the D ring of tronocarpine (**1-174**) complete with the ester handles that could generate lactam ring C. Raney Ni reduction of nitrile **1-174** resulted in the unprompted lactamization of the resultant amine onto the diastereotopically available ester to yield product **1-175** in an 87% yield. Unfortunately, attempts to enolize the α -position to the ketone in **1-175** was not possible, and appropriate functionality to complete tronocarpine could not be installed.

In 2009 Katarina Sapeta successfully furnished the A, B, D, and E rings of tronocarpine, but did not achieve the required functionality to furnish the total synthesis (**Scheme 41**).⁸³ Using donor-acceptor cyclopropane **1-176**, opening with nucleophile 2-(chloromethyl)-3-trimethylsilyl-1-propene (**1-177**) yields product **1-178**, which is then cyclized by an $\text{S}_{\text{N}}2$

reaction. Indole-substituted cyclohexyl **1-179** was synthesized in a 92% yield over 2 steps. Then deprotection of the tosyl group with Mg metal, followed by base-mediated condensation with the available ester formulated tetracyclic product **1-180** in a 47% yield over 2 steps. While Sapeta was able to close ring E, that Magolan's route could not, the ester of **1-180** is on the incorrect side of the molecule and any further functionalization was not reported.

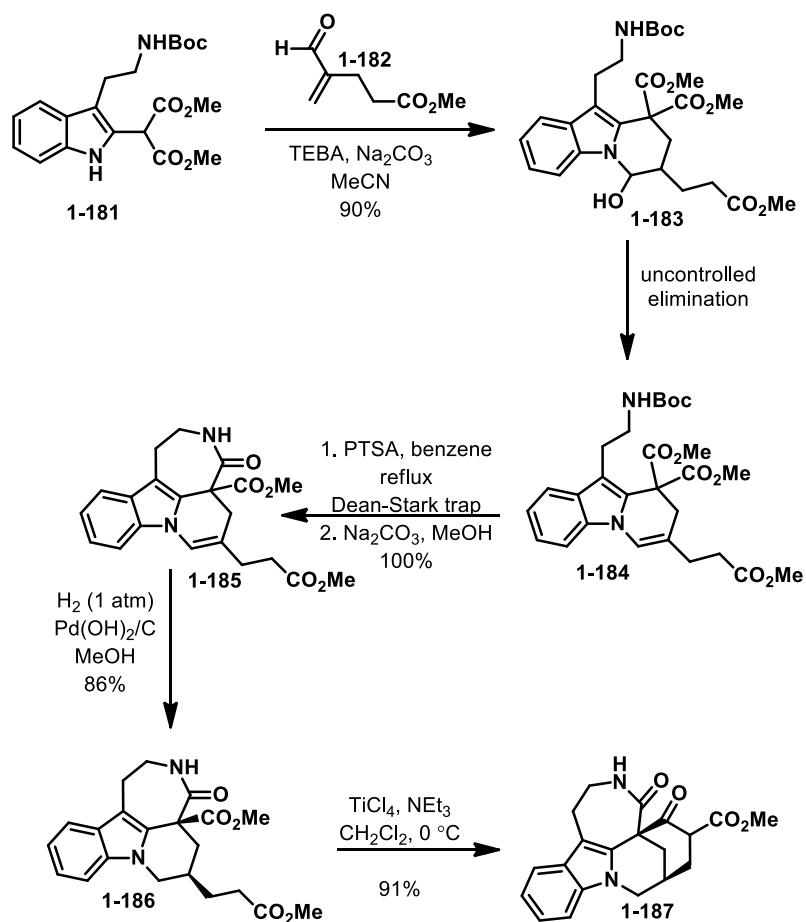


Scheme 40 - Progress towards the first total synthesis of tronocarpine in 2006



Scheme 41 - Progress towards the first total synthesis of tronocarpine in 2009

Finally, the most recent report of an attempted synthesis of tronocarpine came from the Martinez group in 2014. They successfully synthesized the pentacyclic framework of tronocarpine, but lacked correct oxidation states for both the methylene bound to the indole nitrogen and the α,β -unsaturated ketone component of ring E (**Scheme 42**).⁸⁴ The synthesis began from malonyl substituted indole **1-181**, which was subjected to a Michael addition with acrylic aldehyde **1-182**, condensation with the indole nitrogen occurred in one-pot to yield tricyclic moiety **1-183** in a 90% yield. Unfortunately, resultant alcohol **1-183** was not stable, and quickly eliminated to form the alkene product **1-184**, which the researchers were forced to work with. To impart the later required syn functionality to close ring E, lactamization first had to be performed by deprotection of the tryptamine chain to yield **1-185** in a quantitative yield. Then using palladium-catalyzed hydrogenation, they could ensure the syn addition of hydrogen to give the diastereochemistry outlined in product **1-186**. From this molecule, a titanium-catalyzed Dieckmann condensation of **1-186** gave pentacycle **1-187** in a 91% yield. The report ends here as the authors mention oxidation attempts to install the alcohol of tronocarpine were unsuccessful.



Scheme 42 - Martinez attempt at the total synthesis of tronocarpine in 2014

I was hopeful that some of the learned procedures in these attempted syntheses would aid in my design to complete the first synthesis of both tronocarpine and dippinine B. This chemistry is explored extensively in Chapter 4.

With this, I complete the material required to understand the chemistry outlined in Chapters 2 through 5. They comprise the research component of this thesis, which ultimately aimed to improve chemistry involving the heterocycle indole.

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⁸⁰ Literature of products not explicitly discussed isolated by the Kam Group from *Tabernamontana*: (a) Kam, T-S.; Sim, K-M.; Pang, H-S. *J. Nat. Prod.* **2003**, *66*, 11-16. (b) Kam, T-S.; Sim, K-M. *J. Nat. Prod.* **2002**, *65*, 669-672. (c) Lim, K-H.; Hiraku, O.; Komiyama, K.; Kam, T-S. *J. Nat. Prod.* **2008**, *71*, 1591-1594.

⁸¹ Van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *J. Nat. Prod.* **1985**, *48*, 400-423.

⁸² Kam, T-S.; Sim, K-M. *Heterocycles* **2001**, *55* 2405-2412.

⁸³ Sapeta, K.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 2081-2084,

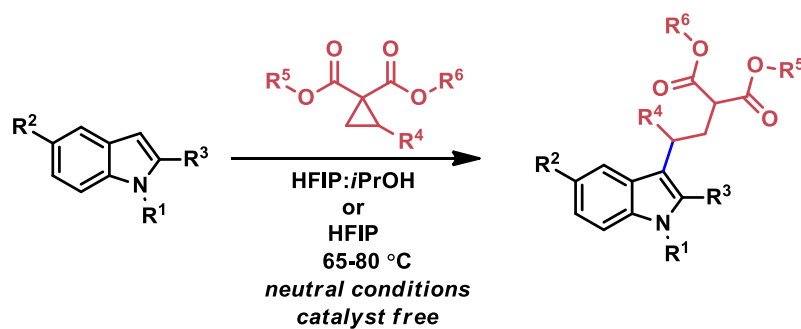
⁸⁴ Torres-Ochoa, R. O.; Reyes-Gutierrez, P. E.; Martinez, R. *Eur. J. Org. Chem.* **2014**, *2014*, 48-52.

Chapter 2: Hydrogen Bond Activation of Donor-Acceptor Cyclopropanes with 1,1,1,3,3,3-Hexafluoroisopropanol

Chapter 2 Preface

The work outlined in this chapter is adapted from: Irwin, L.C.; Renwick, C.R.; Kerr, M.A. *J. Org. Chem.* **2018**, 83(11), 6235-6242.

The Kerr group research program focuses heavily on developing novel synthetic transformations starting with donor-acceptor (DA) cyclopropanes. Chapter 2 summarizes my novel discovery activating DA cyclopropanes using hydrogen bonding (**Scheme 43**).



Scheme 43 - Reaction explored in Chapter 2. Activation of DA cyclopropanes via hydrogen bonding

2.1 Introduction

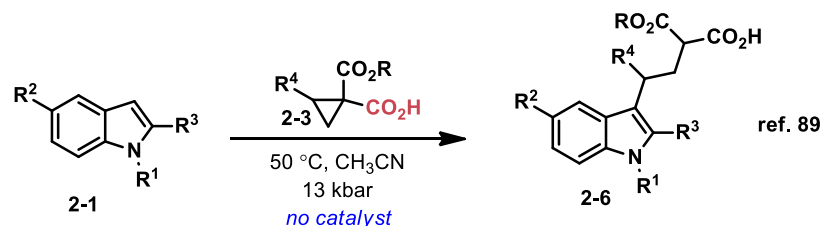
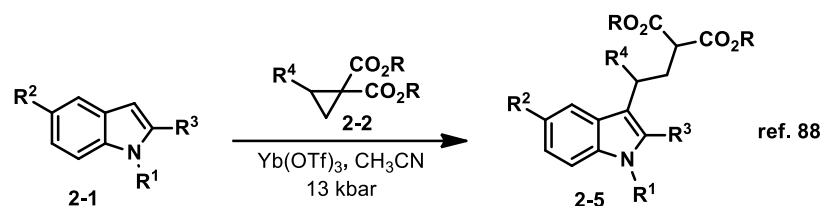
Donor-acceptor cyclopropanes (DA CPs) have long fascinated chemists and are a well-established field. Of late, there has been a resurgence of activity as new and innovative uses for these compounds have been reported.⁸⁵ Donor-acceptor cyclopropanes are often used as homo-Michael acceptors which makes them useful for functionalizing a wide variety of nucleophiles and the creation of C-C bonds.⁸⁶ As expressed in the introduction, they also behave as dipolarophiles, which has made them useful for the synthesis of heterocycles⁸⁷ and carbocycles.⁸⁸

The Kerr group first reported that indoles nucleophilically open cyclopropanes in the presence of both $\text{Yb}(\text{OTf})_3$ and high pressure back in 1997 (**Scheme 44, ref. 88**).⁸⁹ Improvements came in 2011 as we discovered that switching to hemimalonate CP **2-3** only high-pressure was required to open the cyclopropane *via* proposed hydrogen-bonding interaction (**Scheme 44, ref. 89**).⁹⁰

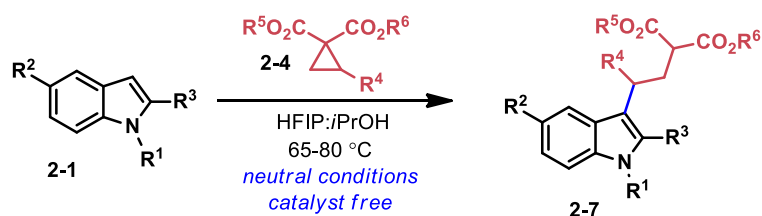
However, as the world shifts to employ more sustainable chemical processing, the notion of removing metals for catalysis is not new.⁹¹ This would help preserve the world's supply of precious metals and remove the toxic and polluting effects caused by metallic waste. Performing reactions of DA CPs without the need for environmentally and economically costly metals, or at unsafe pressure, would be a welcomed methodology. These ideals sparked this pursuit of hydrogen bonding as a mode of activation for donor-acceptor cyclopropanes.

Chapter 2 reports the results of my research in which I showcase how donor-acceptor cyclopropanes react smoothly with indoles, free from metal-catalysis and high-pressure conditions. The reaction uses 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent or co-solvent to enforce hydrogen bonding interactions with the carbonyls of the acceptor portion of DA CPs.

Previous work by our group



Chapter 2 Work



Scheme 44 - The reaction discussion in Chapter 2 and related research from our group.

Emmett *et al.* first report using high-pressure and hemimalonate DA CPs (**Scheme 44**, **ref. 90**) and proposed that an internal hydrogen bond was adequate to stereo-electronically align the two carbonyl groups to receive the impending electron density as the ring opening events (**Figure 11**). They believed this to be the case because the internal hydrogen bond meant there would be a counter-acting electron withdrawing and electron donating effecting from both the loss, and gain, of a hydrogen bond. The forced co-planarity of the cyclopropane would lower the overall energy barrier of the initial nucleophilic attack.

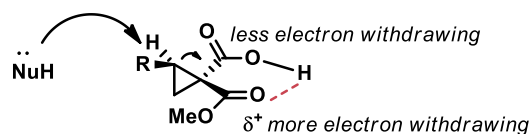


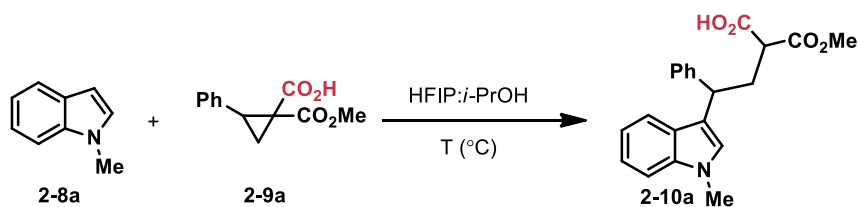
Figure 11 - Forced co-planarity of hemimalonate CPs activating them for successful nucleophilic opening.

These results in mind, I proposed that if the hydrogen bond was external, from a source like HFIP, it would provide a more electron-withdrawing situation for nucleophilic opening and perhaps work with more than just hemimalonate CPs.

2.2 Optimization of Reaction Conditions

This work commenced using hemimalonate cyclopropanes because they had already proved their hydrogen-bond receptiveness, and I hoped this would be useful for optimization (**Table 1**). I first treated cyclopropane **2-9a** with 2 equivalents of *N*-methylindole **2-8a** in pure HFIP at 60 °C and produced desired adduct **2-10a** in a 46% yield (**Table 1, entry 1**).

Table 1 - Optimization of the Reaction Conditions for the Reaction of *N*-Methylindole 2-8a with Cyclopropane Hemimalonate 2-9a



| entry | 2-8a (equiv) | 2-9a (equiv) | HFIP: <i>i</i> -PrOH | T (°C) | yield 2-10a (%) |
|-------|--------------|--------------|----------------------|--------|-----------------|
| 1 | 2.0 | 1.0 | 100:0 | 60 | 46 |
| 2 | 2.0 | 1.0 | MeCN | 80 | 0 |
| 3 | 2.0 | 1.0 | AcOH | 110 | 0 |
| 4 | 2.0 | 1.0 | PhOH | 100 | 0 |
| 5 | 2.0 | 1.0 | TFE | 70 | 0 |
| 6 | 1.1 | 1.0 | 100:0 | 60 | 28 |
| 7 | 1.1 | 1.0 | 100:0 | 25 | 19 |
| 8 | 2.0 | 1.0 | 0:100 | 40 | 17 |
| 9 | 2.0 | 1.0 | 50:50 | 65 | 56 |
| 10 | 2.0 | 1.0 | 20:80 | 65 | IC ^a |
| 11 | 2.0 | 1.0 | 50:50 | 65 | 67 ^b |
| 12 | 2.0 | 1.0 | 50:50 | 65 | 76 ^c |
| 13 | 3.0 | 1.0 | 50:50 | 65 | 70 ^c |

^a Incomplete conversion. ^b Sealed tube.

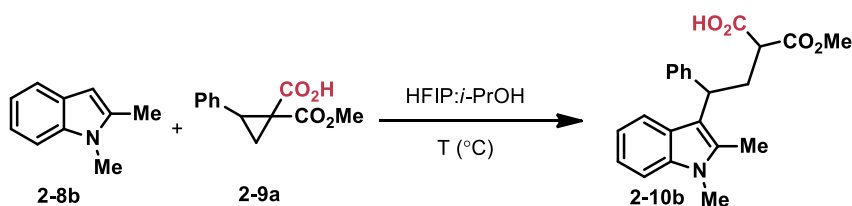
^c Changed purification to an aqueous removal of excess indole

As a control, the reaction was performed using only acetonitrile as a solvent which resulted in no product (**Table 1, entry 2**). Believing that the reaction required a hydrogen bonding solvent, we tried acetic acid, phenol, and trifluoroethanol (TFE) (**Table 1, entries 3, 4 and 5**). I chose to examine phenol because its pK_a is similar to HFIP, and we were quite surprised to learn TFE produced no product as it should have similar hydrogen bonding capabilities compared to HFIP. Intrigued by this result, we tried only isopropanol (**Table 1, entry 8**) which gave a small 17% yield of desired adduct **2-10a**. Ultimately optimized conditions were realized with a 50:50 mixture of HFIP:*i*-PrOH, at a mild 65 °C and using an aqueous purification process giving a respectable 76 % yield of **2-10a** (**Table 1, entry 12**).

I feel it is important to note that optimization was initially performed using 1,2-dimethylindole as the nucleophile. Due to its strength as a nucleophile, it proved to be an

exceptional example to optimize with. This resulted in other indole nucleophiles failing to yield products under the same mild conditions that worked for 1,2-dimethylindole. This is outlined in the reaction scope below (**Scheme 45**), where 1,2-dimethylindole produces some of the highest yields of the CP opening reaction. The results of this optimization are included below (**Table 2**). The optimized conditions of this reaction were more mild with 40:60 mixture of HFIP:*i*-PrOH at 55 °C (**Table 2, entry 5**). The milder reaction conditions ceased to perform for a broad scope of nucleophiles, and results from the 1-methylindole optimization were put in place.

Table 2 - Optimization of the Nucleophilic Opening of Cyclopropane 2-9a with 1,2-Dimethylindole 2-8b



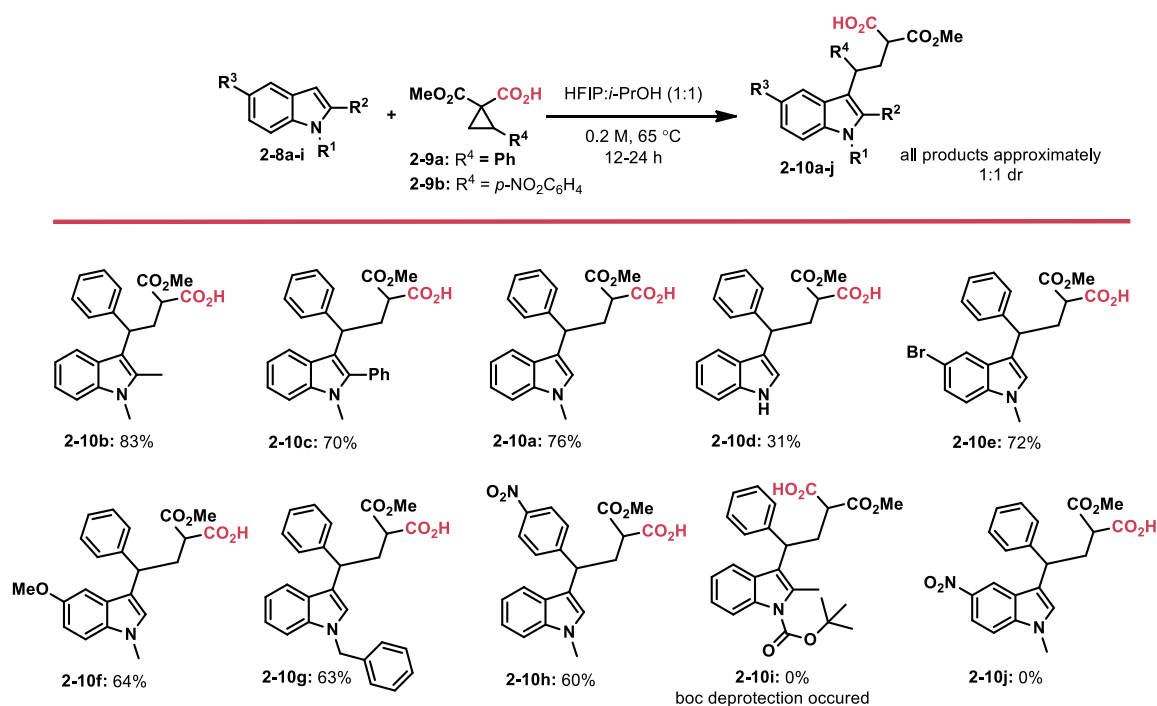
| entry | 2-8b (equiv.) | 2-9a (equiv.) | HFIP: <i>i</i> -PrOH | T (°C) | yield 2-10b (%) |
|-------|---------------|---------------|----------------------|--------|-----------------|
| 1 | 1.1 | 1.0 | 20:80 | rt | IC ^a |
| 2 | 1.5 | 1.0 | 20:80 | 40 | 30 |
| 3 | 1.1 | 1.0 | 50:50 | rt-40 | 25 |
| 4 | 1.5 | 1.0 | 40:60 | 55 | 82 |
| 5 | 2.0 | 1.0 | 40:60 | 55 | 83 |
| 6 | 1.1 | 1.0 | AcOH | 110 | 0 |
| 7 | 1.1 | 1.0 | TFE | 70 | 0 |
| 8 | 2.0 | 1.0 | PhOH | 100 | 0 |

^a Incomplete conversion after 48 h.

2.3 Substrate Scope and Expanded Use of Alternate Donor-Acceptor Cyclopropanes

Optimal reaction conditions in hand, I turned attention to studying the scope of substrate performance. I started by exploring hemimalonate cyclopropanes (**2-9a** and **2-9b**) as per the optimization discussed above. **Scheme 45** outlines the products prepared under this

protocol. A few trends were observed upon completion of this scope. Firstly, *N*-methylindole added to cyclopropane **2-9a** in a modest 76% yield (**2-10a**), while indole itself, was not a productive nucleophile for generating adduct **2-10d**. This returned only a 31% yield. Additionally, indole adduct **2-10d** was difficult to purify and only crude results were obtained. These results prompted us to also try *N*-boc indole as a substrate, but as per published findings, the indole did not react. Rather the Boc group was removed (**2-10i**).⁹²

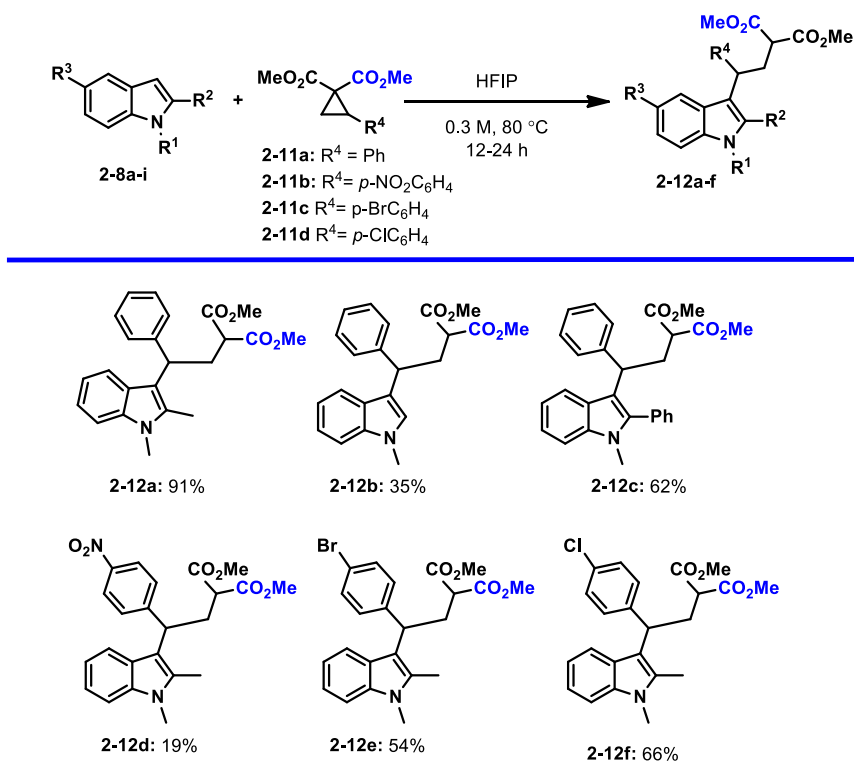


Scheme 45 - Substrate scope for the reaction of indoles with cyclopropane hemimalonates.

Substitution at the 2-position of the indole was well-tolerated as proven by examples **2-10b** and **2-10c**. In fact, 1,2-dimethylindole was the best nucleophile studied resulting in an 83% yield of adduct **2-10b**. Substitution on the benzenoid portion of the indole nucleophiles worked well for electron rich examples; **2-10f** yielded 64% of desired product, and the same was true for **2-10e**, a more electron neutral example. However, electron withdrawing substituents at the 5-position of the indole were not tolerated and

failed to yield the 5-nitroindole example **2-10j**. We tested an electron withdrawing group on the cyclopropane though, which resulted in a 60% yield of **2-10h**.

Having success with hemimalonate cyclopropanes, I looked to compare results using the parent diester cyclopropane **2-11a-d** (**Scheme 46**). Under the same conditions used for the hemimalonate products, little to no product was observed and so I had to explore some new reaction conditions.

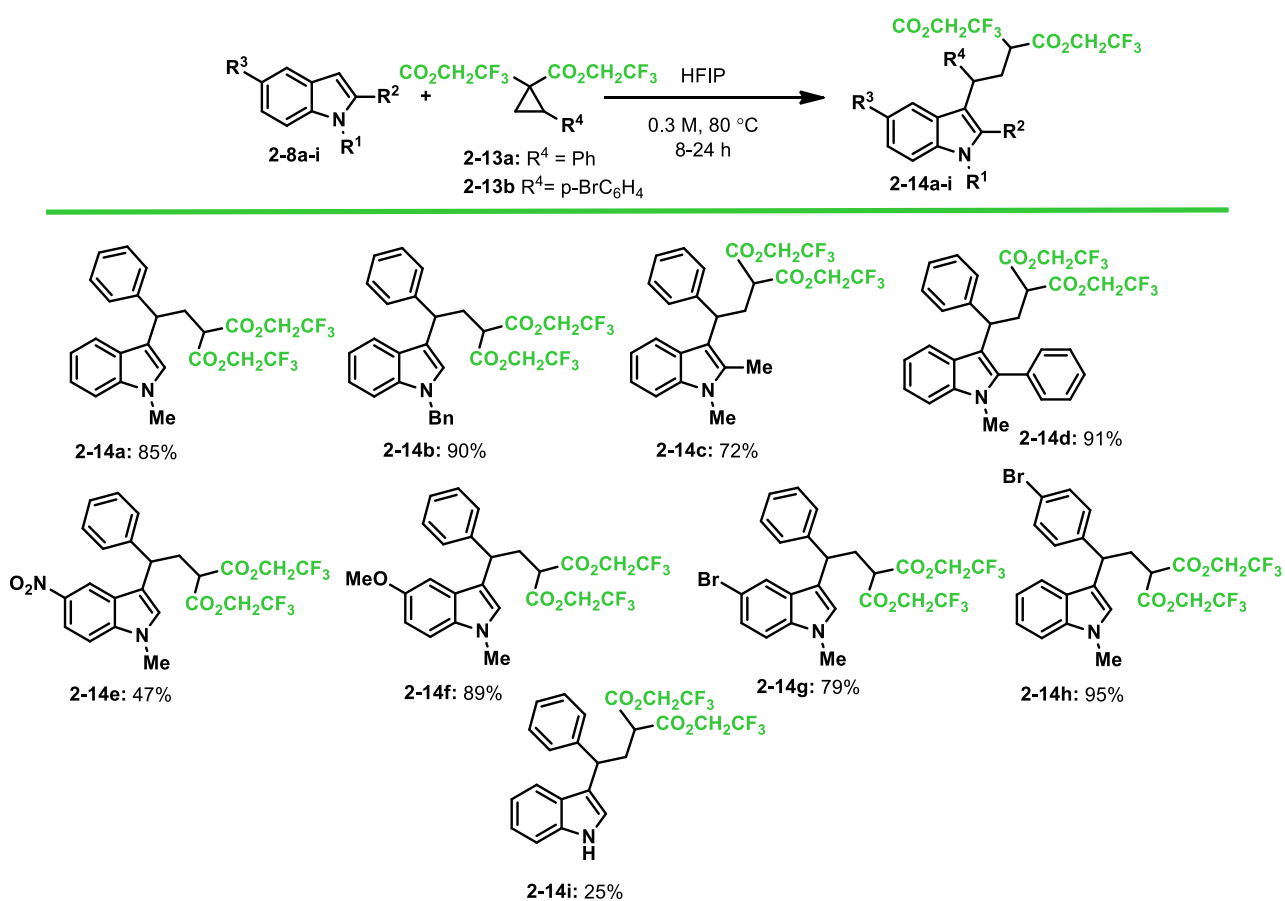


Scheme 46 - Substrate scope for the reaction of indoles with diester cyclopropanes.

Upon changing the reaction conditions to use pure HFIP and heating at 80 °C, *N*-methylindole was able to open CP **2-11a** to give a 35% yield of adduct **2-12b**. 2-position substitution on the indole greatly improved yields as we expected due to their enhanced nucleophilicity. 2-methylindole and 2-phenylindole adducts (**2-12a** and **2-12c** respectively) gave improved yields of 91% and 62%. It is suspected that the additional bulk of the phenyl substituent hindered higher yields. Substitution on the cyclopropane benzenoid was acceptable for para nitro (**2-12d**, 19%), bromo (**2-12e**, 54%) and chloro

(**2-12f**, 66%) groups. However, the electron withdrawing nature of these groups saw a drop in yields from the bare phenyl example as expected.

From the success generated by the diester cyclopropanes, I felt that bis-trifluoroethyl ester cyclopropanes (**2-14a/b**) would only improve on this methodology. Our group, as well as others, have proved that these cyclopropanes have enhanced reactivity due to the electron withdrawing nature of the added fluorines.⁹³ We were delighted to discover excellent yields of the indole opened adduct of these cyclopropanes. **Scheme 47** outlines the library of products generated.



Scheme 47 - Substrate scope for the reaction of indoles with cyclopropane fluoroesters.

N-methylindole reacted with CP **2-13a** resulting in an 85% yield of product **2-14a**. Again, indole itself resulted in a poor 25% yield of adduct **2-14i**. Electron withdrawing groups on position 5 of the indole, **2-14e**, again resulted in a lower yield compared to electron donating (**2-14f**, 89%) and electron neutral counter examples (**2-14g**, 79%). Substitution

at the 2-position was well tolerated, as 2-phenyl-1-methylindole generated a high 91% yield of **2-14d**. The excellent yields observed for the fluoroethyl ester-bearing cyclopropanes are certainly a result of their enhanced withdrawing nature; however, I also suspected that an additional hydrogen-bonding effect may have been occurring.

2.4 Possible Hydrogen Bonding Motifs

HFIP has been well reported to act as a hydrogen bond donor.⁹⁴ In the case of the fluoroethyl esters, we suspect that another interaction involving a hydrogen bond between HFIP and the fluorines of the cyclopropane could be happening as well. Such interaction has been reported by the Paquin group, and would explain the great improvement of yields for these products.⁹⁵ Outlined below are our proposed interactions of how HFIP acts as a hydrogen bond donor (**Figure 12**). While it is still unclear which is occurring, future studies should aim to elucidate how this reaction works.

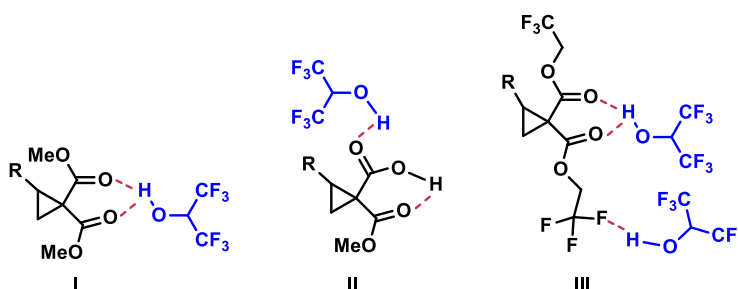


Figure 12 - Possible hydrogen bonding motifs for donor-acceptor cyclopropanes in the presence of HFIP

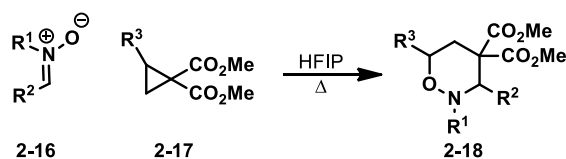
In the case of the diester CPs (**Figure 12, I**), hydrogen bonding to the carbonyl oxygen(s) should be capable of lowering of the activation energy of the nucleophilic attack by indole. With the hemimalonates CPs the situation becomes a bit more complex (**Figure 12, II**). It is possible that an internal hydrogen bond, as mentioned earlier, could occur and this would stereo-align the orbitals of the cyclopropane for the incoming electron density, but, with HFIP there could also be an additional energy lowering hydrogen bond to the carbonyl oxygen(s). Finally, examining the fluoroethyl ester CPs (**Figure 12, III**) there is the possibility of a hydrogen bond to the fluorine present. This would make the ethylfluoro groups even more withdrawing in nature facilitating the nucleophilic opening.

2.5 Other Nucleophiles and Future Directions

While this project reports a simple and catalyst-free method for activating cyclopropanes, there exists great potential for future chemistry. Firstly, exploring the mechanism of activation for this reaction is vital to understanding how hydrogen bonding allows these ring opening reactions to proceed. Simple ^{13}C NMR experiments could be used to observe the effects of HFIP on cyclopropanes. Taking up hemimalonate and fluoroethyl diester CPs (**2-9a** and **2-13a**) in CDCl_3 and running carbon NMRs at varying concentrations of HFIP, we may observe the carbonyl carbons shifting downfield as withdrawing effects are improved. We could compare these results to spectra obtained with the addition of acidic solvents, like AcOH and phenol, which did not provide ring opened adducts in the above research. We could also explore varying concentrations of TFE to determine why it also failed to yield our desired adducts. Perhaps HFIP will demonstrate a stronger interaction to the carbonyl carbons of the DA CPs.

In addition to NMR experiments, computational chemistry would prove valuable for exploring the transition states of the hydrogen-bond interactions with cyclopropanes. If we can understand how the hydrogen bond works, we could better tune substrates in the future to open greater varieties of cyclopropanes in a catalyst free fashion, or generate improved conditions using less HFIP.

On this note, this discovery makes a new tool for metal-free synthesis of valuable hetero- and carbocycles *en-route* to natural products. It would be interesting to explore if annulation reactions where DA CPs act as dipolarophiles also proceed under these catalyst-free conditions. While I took some time to explore nitron nucleophiles (**2-16**) opening DA CPs in the presence of HFIP, the results were not as expected (**Scheme 48**). A few oxazine products (**2-18**) were generated but in small yields and were not pursued further. A better understanding of the reaction activation may aid in the pursuit of useful reaction conditions for other nucleophiles.



Scheme 48 - Annulation reaction of nitrones opening cyclopropanes to yield oxazine products

Exploring imine, oxime and enamine nucleophiles would provide us interesting and catalyst free conditions for the valuable products they produce.

HFIP being such a strong hydrogen bond donor could also play a positive role in some of the single-electron oxidant chemistry discussed Chapter three. More will be discussed on this in Chapter three, but perhaps using HFIP it is possible that radical reactions will proceed at milder conditions resulting in less decomposition and/or by-products. Hopefully, HFIP would improve yields of intermediate compounds *en-route* to natural products like tronocarpine and dippinine B.

2.6 Experimental

2.6.1 General Experimental Details

Reaction flasks were oven-dried at 110 °C and cooled in a desiccator prior to use. All cyclopropane opening reactions were conducted in sealed tubes that had been flushed with argon before the addition of reagents unless otherwise indicated. The tubes were sealed with a Teflon stopper and capped with an aluminum crimping cap. All chemicals were of reagent quality and used as obtained from commercial sources. HFIP was purchased from Oakwood Chemical and dried with 3Å molecular sieves. 3Å molecular sieves were activated in a 300 °C oven for at least 24 h before use. Isopropanol was purchased as distilled in glass from Caledon Scientific and stored over 3Å molecular sieves. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Dichloromethane (DCM), acetonitrile (MeCN) and tetrahydrofuran (THF) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Alfa Aesar (VWR), or Caledon. Reaction

progress was followed by thin layer chromatography (TLC) (Merck, TLC Silica gel 60 F254) visualizing with UV light. The plates were developed using acidic *p*-anisaldehyde. Column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). All columns were performed using Still's procedure for flash chromatography.⁹⁶ IR spectra were acquired using an Attenuated Total Reflection (ATR) PerkinElmer Spectrum Two FT-IR. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. NMR data were acquired on either a Bruker AvIII 400 or Inova 600 instrument. Samples were obtained in CDCl₃ (referenced to 7.25 ppm for ¹H and 77.0 ppm for ¹³C). Coupling constants (*J*) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad.

2.6.2 General Experimental Procedure for the Synthesis of Indole Starting Materials

Commercially available indole starting materials were used as purchased. When not available the substrates were obtained by *N*-methylation or alkylation of the parent indole following published procedures and then confirmed by comparison to reported characterization data for these compounds. Methylated/alkylated indoles (**2-8a-i**) were synthesized following literature procedures^{97,98,99,100} using the following conditions:

Desired indole (1 equiv.) was dissolved in dry THF or DMF in an argon-flushed flask to give a 0.3 M solution. NaH (60% dispersed in mineral oil, 1.5 eq) was added portion wise at 0 °C and then the reaction septum was returned. The flask was evacuated and placed under argon once more. The reaction was warmed to room temperature and stirred for 1.5 h. At which point, the reaction was cooled to 0 °C and MeI (1.3 equiv.) or BnBr (1.1 eq) was added dropwise via syringe. The reactions were allowed to stir at room temperature until TLC analysis confirmed consumption of starting materials, or until 24 h had passed. Water was added to quench the reaction, and then extracted 3x with Et₂O. The organic layers were combined and washed 1x with brine, and then dried using MgSO₄. Upon filtering and concentrating, the crude mixture was purified via flash column chromatography (EtOAc:Hex) and pure product was collected.

2.6.3 Synthesis of Cyclopropane Starting Materials

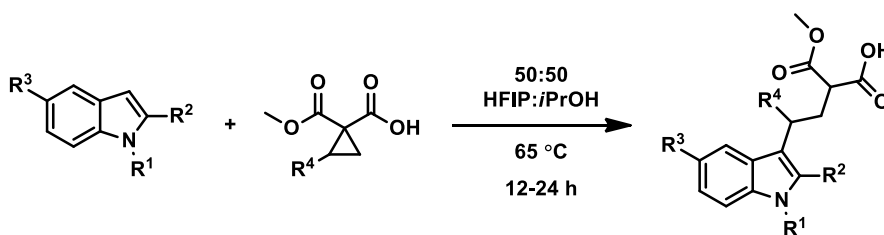
All diester and hemimalonate cyclopropanes were synthesized via literature methods and confirmed by comparison to the reported characterization data:

Hemimalonate CPs: Ph (**2-9a**) and p-NO₂ (**2-9b**) CP¹⁰¹

Diester CPs: Ph (**2-11a**), p-NO₂ (**2-11b**), p-Br (**2-11c**), p-Cl (**2-11d**)^{102 103}

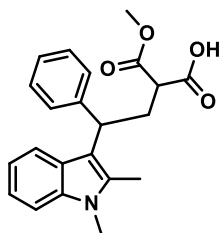
Fluorodiester CP: Ph (**2-13a**) and p-Br (**2-13b**)¹⁰⁴

2.6.4 General Experimental Procedure: Nucleophilic Opening of Hemimalonate Cyclopropanes (GP1)



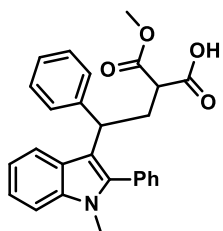
Scheme 49 - General reaction scheme for the products characterized below

Cyclopropane (1equiv.), indole substrate (2 equiv.), and 50:50 *i*-PrOH:HFIP (for a concentration of 0.2 M) were added to an argon-flushed sealed tube. The tube was sealed, submerged into an oil bath at 65–70 °C, and left to react for 12–24 h. Upon confirmation of the starting material consumption via TLC, the reactions were poured into a round-bottom flask, rinsed with DCM, and then concentrated in vacuo. The crude mixture was subjected to flash column chromatography using an appropriate eluent system of either AcOH:MeOH:DCM or AcOH:EtOAc:Hex. In some cases (indicated below), instead of a column, the crude material was taken up in 2 M NaOH and was extracted with Et₂O or DCM 3x to remove excess indole. The collected aqueous fraction was then acidified with concentrated HCl (very slowly, with cooling if needed) to a pH of 1. The resulting acidic aqueous layer was then extracted with EtOAc 3×, and the organic fractions were combined, washed with brine, dried with MgSO₄, filtered, and concentrated in vacuo to yield a purified product.



4-(1,2-dimethyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid (2-10b)

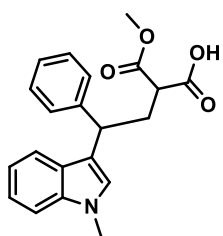
Following GP1, CP **2-9a** (0.05 g, 0.23 mmol) and 1,2-dimethylindole (0.066 g, 0.45 mmol) in 1.2 mL of HFIP:*i*-PrOH were reacted for 20 h. The reaction was concentrated *in vacuo*, then taken up in 1 M NaOH, and placed into a separatory funnel. Extractions using DCM 3× and monitoring by TLC showed that all the indole had been removed from the aqueous phase. The basic aqueous layer was then carefully acidified with concentrated HCl to pH = 1 and was extracted with DCM 3×. The organic layers were washed with brine 1× and then dried with MgSO₄. Upon being filtered and concentrated *in vacuo*, the pure product **2-10b** was isolated as a white solid (0.069 g, 83% yield). R_f = 0.26 (30% EtOAc:1% AcOH:69% Hex). Characterization data for this compound matched literature reports.¹⁰¹ **¹H NMR mixture of diastereomers (400 MHz, CDCl₃) δ:** 7.46 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.23–7.21 (m, 3H), 7.16–7.07 (m, 2H), 7.01–6.95 (m, 1H), 4.36–4.26 (m, 1H), 3.65, 3.62, and 3.56 (s, 6H total), 3.36–3.29 (m, 1H), 2.97–2.86 (m, 2H), 2.33 and 2.32 (s, 3H total).



2-(methoxycarbonyl)-4-(1-methyl-2-phenyl-1H-indol-3-yl)-4-phenylbutanoic acid (2-10c)

Following GP1, hemimalonate CP **2-9a** (0.05 g, 0.23 mmol), 2-phenyl-1-methylindole (0.10 g, 0.48 mmol) in 1.2 mL of HFIP:*i*-PrOH were reacted for 16 h. The reaction was concentrated *in vacuo* and purified directly *via* flash column chromatography. The pure product was isolated as a white solid (0.072 g, 70%). MP = 165–169 °C R_f = 0.37 (40% EtOAc: 1% AcOH: 59% Hexanes) **¹H NMR (599 MHz, CDCl₃) mixture of diastereomers δ =** 7.63 (t, *J* = 8.2 Hz, 1H), 7.45 – 7.26 (m, 8H), 7.20 – 7.05 (m, 5H), 4.13 (two t appears as ddd, *J* = 16.4, 11.0, 5.4 Hz, 1H), 3.56 and 3.55 (s, 3H), 3.46 (s, 3H), 3.29 – 3.21 (m, 1H), 2.92 – 2.71 (m, 2H) **¹³C NMR (151 MHz, CDCl₃) mixture of diastereomers δ** 169.7, 144.8, 140.0, 131.2, 129.4, 128.7, 128.0, 126.4, 122.1, 121.0, 119.9, 110.0, 52.7, 50.5, 40.6, 34.4, 31.2. **IR_{ATR} (cm⁻¹)**

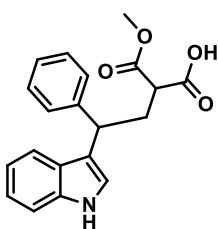
2954, 1743, 1694, 1468, 1433, 1290, 1146, 744, 699 **HRMS (EI) m/z $[M^+]$ 427.17746**
(calcd for $C_{27}H_{25}NO_4$, 427.17836)



2-(methoxycarbonyl)-4-(1-methyl-1H-indol-3-yl)-4-phenylbutanoic acid (2-10a)

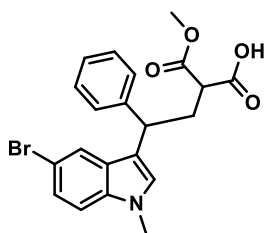
Following GP1, hemimalonate CP **2-9a** (0.10 g, 0.46 mmol) and 1-methylindole (0.126 g, 0.92 mmol) in 2.4 mL of HFIP:ⁱPrOH were reacted for 20 h. The reaction was concentrated in vacuo, taken up in 1 M NaOH. Extractions using DCM 3× and monitoring by TLC showed that all the indole had been removed from the aqueous phase. The basic aqueous layer was then carefully acidified with concentrated HCl to pH = 1 and was extracted with DCM 3×. The organic layers were washed with brine 1× and then dried with MgSO₄. The pure product was isolated as an off-white solid (0.12 g, 76% yield). R_f = 0.47 (1% AcOH:1% MeOH:8% DCM). Characterization data for this compound matched literature reports.¹⁰¹

¹H NMR mixture of diastereomers (400 MHz, CDCl₃) δ : 9.91 (br, s, 1H), 7.45 (m, 1H), 7.36–7.26 (m, 4H), 7.22–7.15 (m, 3H), 7.02 (m, 1H), 6.90 and 6.88 (s, 1H total), 4.26 (m, 1H), 3.74 and 3.68 (s, 6H total), 3.44 (m, 1H), 2.85 (m, 1H), 2.71–2.58 (m, 1H).



4-(1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid (2-10d)

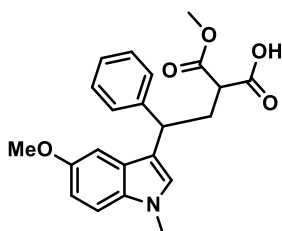
Following GP1, hemimalonate CP **2-9a** (0.05 g, 0.23 mmol) and indole (0.054 g, 0.46 mmol) in 1.2 mL of HFIP:ⁱPrOH were reacted for 20 h. The crude mixture was concentrated in vacuo and purified by flash column chromatography. R_f = 0.32 (1% AcOH:1% MeOH:98% DCM). The product was isolated as a yellow oil (0.024 g, 31%). Even after multiple purification attempts, the characterization data were unclear but had results matching the reported literature.¹⁰¹



4-(5-bromo-1-methyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid (2-10e)

Following GP1, hemimalonate CP **2-9a** (0.075 g, 0.34 mmol) and 5-bromo-1-methylindole (0.14 g, 0.68 mmol) in 1.7 mL of HFIP:ⁱPrOH were heated for 30 h. The crude mixture was subjected to the extraction method of the purification as described in GP1. The resultant solid from the extractions was further purified by recrystallization in pentane/DCM to yield a pure product as a pale-yellow solid (0.10 g, 72%). $R_f = 0.5$ (1% AcOH:1% MeOH:98% DCM). Characterization data for this compound matched literature results.¹⁰¹

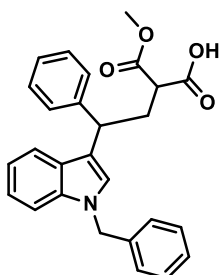
¹H NMR mixture of diastereomers (400 MHz, CDCl₃) δ : 7.54 (m, 1H), 7.31–7.27 (m, 4H), 7.25–7.18 (m, 2H), 7.13 and 7.11 (s, 1H total), 6.92 and 6.89 (s, 1H total), 4.21–4.12 (m, 1H), 3.76 and 3.73 and 3.72 and 3.69 (s, 6H total), 3.44–3.37 (m, 1H), 2.85–2.71 (m, 1H), 2.68–2.54 (m, 1H).



4-(5-methoxy-1-methyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid (2-10f)

Following GP1, hemimalonate CP **2-9a** (0.05g, 0.23 mmol) and 5-methoxy-1-methylindole (0.074 g, 0.46 mmol) in 1.2 mL of HFIP:ⁱPrOH were reacted for 16 h. The reaction was concentrated in vacuo and purified directly via flash column chromatography. The pure product was isolated as a white foam (0.056 g, 64%). $R_f = 0.27$ (40% EtOAc:1% AcOH:59% Hex).

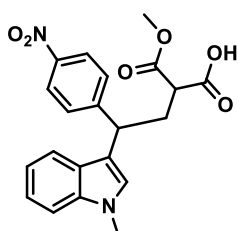
¹H NMR mixture of diastereomers (400 MHz, CDCl₃) δ : 7.34–7.26 (m, 4H), 7.19 (t, $J = 7.0$ Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 6.88 (m, 1H), 6.86–6.79 (m, 2H), 4.19 (m, 1H), 3.76 and 3.67 (s, 3H total), 3.74 and 3.73 (3H total), 3.70 (s, 3H), 3.43 (m, 1H), 2.83 (m, 1H), 2.67–2.55 (m, 1H). **¹³C NMR mixture of diastereomers (101 MHz, CDCl₃) δ :** 174.7, 169.9, 153.8, 143.4, 132.8, 128.7, 128.5, 128.1, 126.9, 126.7, 116.6, 112.0, 110.1, 101.6, 101.5, 56.0, 52.8, 50.0, 40.8, 35.1 33.0. **IR_{ATR} (cm⁻¹):** 2949, 1732, 1490, 1451, 1212, 1035, 792, 700, 587. **HRMS (EI) (m/z):** [M⁺] calcd for C₂₂H₂₃NO₅, 381.1576; found, 381.1574.



4-(1-benzyl-1H-indol-3-yl)-2-(methoxycarbonyl)-4-phenylbutanoic acid (2-10g)

Following GP1, hemimalonate CP **2-9a** (0.05 g, 0.23 mmol), 1-benzylindole (0.095 g, 0.46 mmol) in 1.2 mL of HFIP:*i*PrOH was reacted for 16 h. The reaction was concentrated *in vacuo* and purified directly via flash column chromatography. The pure product was isolated as a white solid (0.062 g, 63%) $R_f = 0.31$ 30% EtOAc: 1% AcOH: 69% Hex. Characterization data for this compound matched literature reports.¹⁰¹

¹H NMR (400 MHz, CDCl₃) mixture of diastereomers $\delta = 7.45$ (dd, $J = 11.2, 7.9$ Hz, 1H), 7.36 – 7.25 (m, 8H), 7.23 – 7.15 (m, 3H), 7.15 – 7.06 (m, 3H), 7.04 – 6.96 (m, 2H), 5.28 (d, $J = 2.2$ Hz, 1H), 4.28 (two t appearing as q, $J = 6.8$ Hz, 1H), 3.73 and 3.66 (s, 3H total), 3.44 – 3.39 (m, 1H), 2.91 – 2.78 (m, 1H), 2.70 – 2.57 (m, 1H).



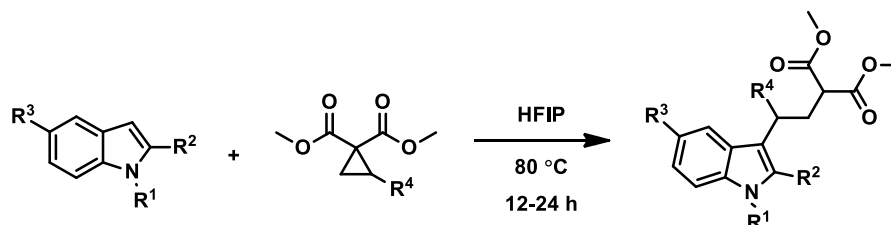
2-(methoxycarbonyl)-4-(1-methyl-1H-indol-3-yl)-4-(4-nitrophenyl)butanoic acid (2-10h)

Following GP1, hemimalonate CP **2-9b** (0.05 g, 0.19 mmol), 1-methylindole (0.05 g, 0.38 mmol) in 0.65 mL of HFIP:*i*PrOH was reacted for 24 h. The reaction was concentrated *in vacuo* and purified directly via flash column chromatography. The pure product was isolated as a yellow foam (0.044 g, 64%). Note: This compound is light sensitive and decomposed upon ¹³C NMR data acquisition as evidenced by a color change. $R_f = 0.28$ (40% EtOAc: 1% AcOH: 1% MeOH: 58% Hex).

¹H NMR (599 MHz, CDCl₃) mixture of diastereomers δ 8.07 (d, $J = 8.7$ Hz, 1H), 8.02 (d, $J = 8.7$ Hz, 2H), 7.37 (dd, $J = 8.7, 4.4$ Hz, 3H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 6.95 – 6.88 (m, 1H), 6.86 (d, $J = 11.3$ Hz, 1H), 4.27 (t, $J = 7.7$ Hz, 1H), 3.67 (apparent d, $J = 3.2$ Hz, 1.5H), 3.25 (s, 1.3H), 3.63 and 3.61 (s, 3H), 3.32 (t, $J = 8.7$ Hz, 1H), 2.81 – 2.64 (m, 1H), 2.55 (td, $J = 14.9, 8.7$ Hz, 1H) **¹³C NMR (101 MHz, CDCl₃)** mixture of diastereomers δ 177.6, 169.4, 151.6, 146.8, 141.8, 137.5, 130.1, 128.9, 128.5, 126.9, 126.4, 124.0, 123.6, 122.3, 119.5, 119.2, 115.0, 109.6, 52.9, 40.5, 34.6, 33.0, 21.5.

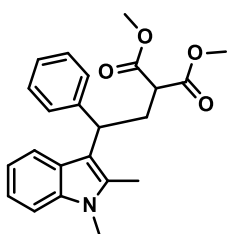
IR_{ATR} (cm⁻¹) 2953, 1733, 1706, 1598, 1514, 1343, 1289, 1152, 855, 737 **HRMS** (EI) *m/z* [M⁺] 396.1325 (calcd for C₂₁H₂₀N₂O₆ 396.1321).

2.6.5 General Experimental Procedure: Nucleophilic Opening of Bis-dimethylester Cyclopropanes (GP2)



Scheme 50 - General reaction conditions to isolate bis-dimethylester cyclopropane opened products

Cyclopropane (1 equiv.), indole substrate (3 equiv.), and HFIP (for a concentration of 0.3 M) were added to an argon-flushed sealed tube. The tube was sealed, submerged into an oil bath at 80 °C, and left to react for 12–24 h. Upon confirmation of starting material consumption *via* TLC, the reaction was poured into a round-bottom flask, rinsed with DCM, and then concentrated in vacuo. The crude material was directly subjected to flash column chromatography using an appropriate eluent system of EtOAc:Hex to isolate a purified material.



Dimethyl 2-(2-(1,2-dimethyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-12a)

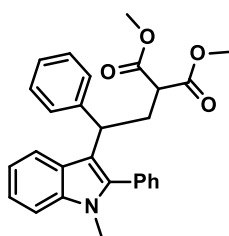
Following GP2, CP **2-11a** (0.05 g, 0.21 mmol) and 1,2-dimethylindole (0.093 g, 0.64 mmol) in HFIP (0.7 mL) were subjected to heat for 29 h. The crude material was purified via flash column chromatography 20%

EtOAc:80% Hex to collect a white solid (0.073 g, 91%).

MP = 81–83 °C *R_f* = 0.24 (20%EtOAc:80%Hex)

¹H NMR (599 MHz, Chloroform-*d*) δ = 7.46 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.33 (m, 3H), 7.25 – 7.20 (m, 4H), 7.16 – 7.10 (m, 3H), 7.00 – 6.96 (m, 1H), 4.28 (t, *J* = 8.3 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.53 (s, 3H), 3.30 (dd, *J* = 8.0, 6.8 Hz, 1H), 2.89 (dd, *J* = 8.9,

6.5 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ = 170.1, 170.0, 144.3, 137.1, 134.3, 128.4, 127.7, 126.7, 126.1, 120.6, 119.6, 119.0, 111.2, 108.8, 52.6, 52.5, 50.6, 39.7, 33.5, 29.7, 10.7. IR_{ATR} (cm^{-1}) 2950, 1748, 1724, 1472, 1431, 1249, 1229, 1147, 1033, 999. HRMS (EI) m/z [M^+] 379.1786 (calcd for $\text{C}_{23}\text{H}_{24}\text{NO}_4$, 379.1784).

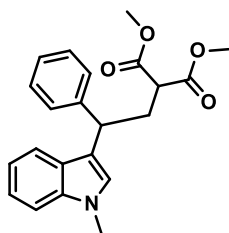


Dimethyl 2-(2-(1-Methyl-2-phenyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-12b)

Following GP2, CP **2-11a** (0.037 g, 0.16 mmol) and 2-phenyl-1-methylindole (0.036 g, 0.17 mmol, 1.1 equiv.) in HFIP (0.5 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography in 20%EtOAc:80%Hex to collect a white solid (0.044 g, 62%).

MP 119–120 °C. R_f = 0.32 (20% EtOAc:80% Hex).

^1H NMR (400 MHz, CDCl_3) δ : 7.67 (d, J = 8.0 Hz, 1H), 7.49–7.43 (m, 3H), 7.37 (t, J = 7.9 Hz, 3H), 7.33–7.29 (m, 2H), 7.26 (m, 3H), 7.21–7.15 (m, 1H), 7.12 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 4.08 (dd, J = 10.7, 5.8 Hz, 1H), 3.56 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 3.24 (dd, J = 9.2, 5.5 Hz, 1H), 2.91–2.72 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ : 169.9, 169.8, 144.7, 139.6, 137.7, 131.7, 131.0, 128.4, 127.8, 126.4, 126.1, 121.8, 120.8, 119.6, 112.8, 109.7, 52.4, 50.6, 40.5, 34.2, 31.0. IR_{ATR} (cm^{-1}): 3026, 2953, 1731, 1467, 1435, 1215, 1153, 701. HRMS (EI) (m/z): [M^+] calcd for $\text{C}_{28}\text{H}_{27}\text{NO}_4$, 441.1940; found, 441.1948.

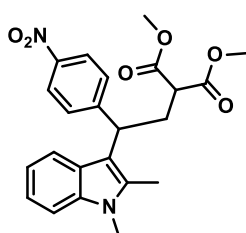


Dimethyl 2-(2-(1-Methyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-12c)

Following GP2, CP **2-11a** (0.050 g, 0.21 mmol) and 1-methylindole (0.083 g, 0.63 mmol) in HFIP (0.7 mL) were subjected to heat for 48 h. The crude material was purified via flash column chromatography in 20% EtOAc:80% Hex to collect a clear oil (0.026 g, 35%). R_f = 0.24 (20%EtOAc:80%Hex).

Characterization data matched literature reports.¹⁰⁰

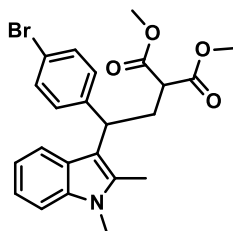
^1H NMR (599 MHz, CDCl_3) δ : 7.45 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.34–7.25 (m, 5H), 7.19 (m, 2H), 7.02 (ddd, $J = 7.9, 7.0, 1.0$ Hz, 1H), 6.88 (s, 1H), 4.22 (t, $J = 7.9$ Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 3.41 (dd, $J = 8.0, 6.6$ Hz, 1H), 2.83 (ddd, $J = 13.6, 8.0, 7.0$ Hz, 1H), 2.62 (ddd, $J = 13.6, 8.8, 6.7$ Hz, 1H). **^{13}C NMR (101 MHz, CDCl_3) δ :** 170.0, 143.6, 137.4, 128.7, 128.1, 127.3, 126.6, 126.2, 121.8, 119.6, 119.0, 117.3, 109.3, 52.7, 52.6, 50.2, 40.7, 35.1, 32.8. **IR_{ATR} (cm^{-1}):** 2952, 1754, 1488, 1282, 1159, 974.



Dimethyl 2-(2-(1,2-Dimethyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethyl)malonate (2-12d)

Following GP2, CP **2-11b** (0.022 g, 0.08 mmol) and 1,2-dimethylindole (0.034 g, 0.24 mmol) in HFIP (0.3 mL) were subjected to heat for 25 h. The crude material was purified via flash column chromatography in 30%EtOAc:70%Hex to collect a yellow oil (0.07 g, 19%). $R_f = 0.2$ (30%EtOAc:70%Hex).

^1H NMR (400 MHz, CDCl_3) δ : 8.09 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.28 (t, $J = 4.4$ Hz, 1H), 7.14 (t, $J = 8.1$ Hz, 1H), 7.02–6.97 (m, 1H), 4.37 (t, $J = 8.1$ Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.54 (s, 3H), 3.27 (dd, $J = 8.1, 6.7$ Hz, 1H), 2.88 (dd, $J = 9.0, 6.7$ Hz, 1H), 2.32 (s, 3H). **^{13}C NMR (101 MHz, CDCl_3) δ :** 169.9, 169.6, 152.1, 146.4, 137.2, 134.7, 128.5, 126.2, 123.7, 121.1, 119.5, 119.0, 109.6, 109.1, 52.7, 52.6, 50.2, 39.6, 33.0, 29.8, 10.7. **IR_{ATR} (cm^{-1}):** 2952, 1732, 1596, 1516, 1471, 1434, 1344, 1251, 1230, 853. **HRMS (EI)** (m/z): $[\text{M}^+]$ calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_6$, 424.1634; found, 424.1631.

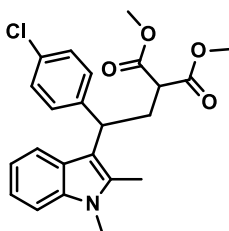


Dimethyl 2-(2-(4-Bromophenyl)-2-(1,2-dimethyl-1H-indol-3-yl)ethyl)malonate (2-12e)

Following GP2, CP **2-11c** (0.050 g, 0.16 mmol) and 1,2-dimethylindole (0.070 g, 0.48 mmol) in HFIP (0.55 mL) were

subjected to heat for 24 h. The crude material was purified via flash column chromatography in 20%EtOAc:80%Hex to collect a viscous yellow oil (0.039 g, 54%). $R_f = 0.26$ (20% EtOAc:80% Hex).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.43 (d, $J = 7.9$ Hz, 2H), 7.40–7.35 (m, 2H), 7.31–7.26 (m, 2H), 7.23 (s, 1H), 7.20–7.12 (m, 1H), 7.02 (m, 1H), 4.26 (t, $J = 8.1$ Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.57 (s, 3H), 3.30 (t, $J = 7.9$ Hz, 1H), 2.88 (m, 2H), 2.34 (s, 3H). **$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ :** 170.0, 169.8, 143.4, 137.1, 134.4, 131.4, 129.5, 126.4, 120.8, 119.9, 119.3, 119.2, 110.5, 108.9, 52.6, 52.5, 50.4, 39.1, 33.3, 29.8, 10.6. **IR_{ATR} (cm^{-1}):** 2947, 1730, 1433, 1368, 1222, 1150, 735, 691. **HRMS (EI)** (m/z): $[\text{M}^+]$ calcd for $\text{C}_{23}\text{H}_{24}\text{BrNO}_4$, 457.0889; found, 457.0889

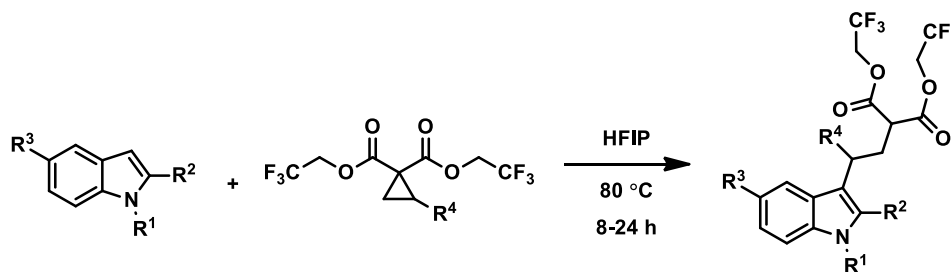


Dimethyl 2-(2-(4-Chlorophenyl)-2-(1,2-dimethyl-1H-indol-3-yl)ethyl)malonate (2-12f)

Following GP2, CP **2-11d** (0.050 g, 0.19 mmol) and 1,2-dimethylindole (0.081 g, 0.59 mmol) in HFIP (0.6 mL) were subjected to heat for 48 h. The crude material was purified via flash column chromatography in 20% EtOAc:80% Hex to collect a clear oil (0.051 g, 66%). $R_f = 0.23$ (20% EtOAc:80% Hex).

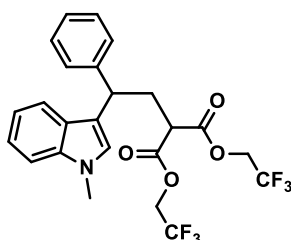
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.44 (d, $J = 7.9$ Hz, 1H), 7.34–7.27 (m, 3H), 7.26–7.22 (m, 2H), 7.20–7.14 (m, 1H), 7.04 (t, $J = 8.0$ Hz, 1H), 4.29 (t, $J = 8.1$ Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.58 (s, 3H), 3.31 (dd, $J = 7.9, 6.9$ Hz, 1H), 2.89 (m, 2H), 2.35 (s, 3H). **$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ :** 170.0, 169.8, 142.8, 137.1, 134.4, 131.8, 129.1, 128.4, 126.4, 120.8, 119.3, 119.2, 110.6, 108.9, 52.6, 52.5, 50.4, 39.1, 33.3, 29.7, 10.6. **IR_{ATR} (cm^{-1}):** 2951, 1731, 1490, 1471, 1434, 1250, 1151, 1013. **HRMS (EI)** (m/z): $[\text{M}^+]$ calcd for $\text{C}_{23}\text{H}_{24}\text{ClNO}_4$, 413.1394; found, 413.1393.

2.6.6 General Experimental Procedure: Nucleophilic Opening of Bis-trifluoroethylester Cyclopropanes (GP3)



Scheme 51 - General reaction scheme for the nucleophilic opening of bis-trifluoroethylester cyclopropanes

Cyclopropane (1 equiv), indole substrate (3 equiv), and HFIP (for a concentration of 0.3 M) were added to an argon-flushed sealed tube. The tube was sealed off, submerged into an oil bath at 80 °C, and left to react for 8–24 h. Upon confirmation of starting material consumption via TLC, the reaction was poured into a round-bottom flask, rinsed with DCM, and then concentrated down in vacuo. The crude material was directly subjected to flash column chromatography using an appropriate eluent system of EtOAc:Hex to isolate a purified material.

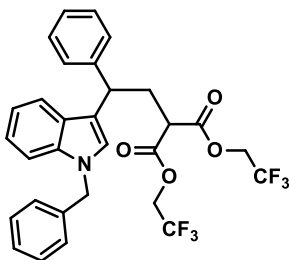


Bis(2,2,2-trifluoroethyl) 2-(2-(1-Methyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-14a)

Following GP3, CP **2-13a** (0.050 g, 0.13 mmol) and 1-methylindole (0.053 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography in 12% EtOAc:88% Hex to collect a clear oil (0.057 g, 85%). R_f = 0.38 (12% EtOAc:88% Hex).

^1H NMR (400 MHz, CDCl_3) δ : 7.47 (d, J = 8.0 Hz, 1H), 7.35–7.27 (m, 5H), 7.24–7.18 (m, 2H), 7.09–7.01 (m, 1H), 6.88 (s, 1H), 4.57–4.38 (m, 4H), 4.26 (t, J = 8.0 Hz, 1H), 3.75 (s, 3H), 3.60 (t, J = 7.2 Hz, 1H), 2.96–2.85 (m, 1H), 2.76–2.65 (m, 1H). **^{19}F NMR (376 MHz, CDCl_3)** δ : –73.74 (t, J = 7.3 Hz, 3F) –73.75 (t, J = 7.6 Hz, 3F). **^{13}C NMR**

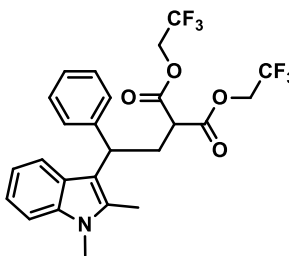
(101 MHz, CDCl₃) δ : 167.3, 143.0, 137.5, 128.8, 128.0, 127.1, 126.9, 126.4, 122.7 (q, $^1J_{C-F}$ = 277 Hz), 122.7 (q, $^1J_{C-F}$ = 277 Hz), 122.0, 119.6, 119.2, 116.5, 109.4, 61.16 (q, $^2J_{C-F}$ = 37 Hz), 49.7, 40.7, 34.8, 32.9. **IR**_{ATR} (cm⁻¹): 3028, 1754, 1410, 1281, 1216, 1164, 1136, 977, 703. **HRMS (EI) (m/z)**: [M⁺] calcd for C₂₄H₂₁F₆NO₄, 501.1375; found, 501.1372.



Bis(2,2,2-trifluoroethyl) 2-(2-(1-Benzyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-14b)

Following GP3, CP **2-13a** (0.05 g, 0.13 mmol) and 1-benzylindole (0.084 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 8 h. The crude material was purified *via* flash column chromatography in 10% EtOAc:90% Hex to collect a clear oil (0.070 g, 90%). R_f = 0.23 (10% EtOAc:90% Hex).

¹H NMR (400 MHz, CDCl₃) δ : 7.47 (d, J = 7.9 Hz, 1H), 7.35–7.25 (m, 7H), 7.22 (dt, J = 8.6, 2.8 Hz, 2H), 7.18–7.09 (m, 3H), 7.04 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (s, 1H), 5.29 (s, 2H), 4.57–4.38 (m, 4H), 4.28 (t, J = 8.0 Hz, 1H), 3.62–3.55 (m, 1H), 2.91 (dt, J = 14.1, 7.5 Hz, 1H), 2.71 (ddd, J = 13.9, 8.8, 6.8 Hz, 1H). **¹⁹F NMR (376 MHz, CDCl₃) δ** : -73.72 (t, J = 8.1 Hz, 3F), -73.75 (t, J = 8.4 Hz, 3F). **¹³C NMR (101 MHz, CDCl₃) δ** : 167.3, 167.2, 142.8, 137.5, 137.0, 128.8, 128.7, 127.9, 127.7, 127.3, 126.8, 126.7, 125.6, 122.6 (q, $^1J_{C-F}$ = 278 Hz), 122.5 (q, $^1J_{C-F}$ = 277 Hz), 122.2, 119.6, 119.4, 117.2, 109.9, 61.04 (q, $^2J_{C-F}$ = 37 Hz), 50.1, 49.5, 40.7, 34.7. **IR**_{ATR} (cm⁻¹): 3030, 1753, 1453, 1280, 1216, 1165, 977, 908. **HRMS (EI) (m/z)**: [M⁺] calcd for C₃₀H₂₅F₆NO₄, 577.1688; found, 577.1688.

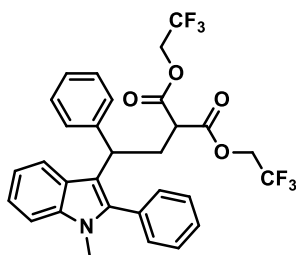


Bis(2,2,2-trifluoroethyl) 2-(2-(1,2-Dimethyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-14c)

Following GP3, CP **2-13a** (0.05 g, 0.13 mmol) and 1,2-dimethylindole (0.059 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 18 h. The crude material was purified *via*

flash column chromatography in 12.5%EtOAc:87.5%Hex to collect a clear oil (0.050 g, 72%). $R_f = 0.47$ (20% EtOAc:80% Hex).

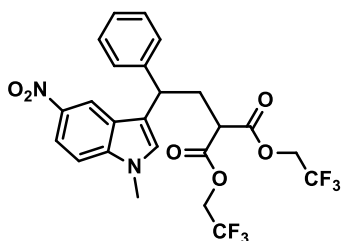
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.50 (d, $J = 8.0$ Hz, 1H), 7.36–7.32 (m, 2H), 7.30–7.22 (m, 3H), 7.20–7.11 (m, 2H), 7.02 (ddd, $J = 8.0, 7.1, 1.0$ Hz, 1H), 4.50 (m, 2H (two overlapping dq unresolved)), 4.35–4.12 (m, 1H), 3.66 (s, 3H), 3.51 (dd, $J = 9.3, 5.2$ Hz, 1H), 3.07–2.87 (m, 2H), 2.32 (s, 3H). **$^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ :** -73.71 (t, $J = 8.3$, 3F), -73.87 (t, $J = 8.3$ Hz, 3F). **$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ :** 167.3, 143.9, 137.1, 134.7, 128.5, 127.6, 126.5, 126.3, 122.7 (q, $^1J_{\text{C-F}} = 277$ Hz), 122.6 (q, $1J_{\text{C-F}} = 278$ Hz), 120.8, 119.4, 119.3, 110.3, 109.0, 61.1 (q, $^2J_{\text{C-F}} = 36$ Hz), 60.9 (q, $^2J_{\text{C-F}} = 37$ Hz), 50.0, 39.9, 33.4, 29.8, 10.5. **IR_{ATR} (cm^{-1}):** 2941, 1753, 1409, 1280, 1162, 976, 700, 561. **HRMS (EI) (m/z):** $[\text{M}^+]$ calcd for $\text{C}_{25}\text{H}_{23}\text{F}_6\text{NO}_4$, 515.1531; found, 515.1525.



Bis(2,2,2-trifluoroethyl) 2-(2-(1-Methyl-2-phenyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-14d)

Following GP3, CP **2-13a** (0.050 g, 0.13 mmol) and 2-phenyl-1-methylindole (0.084 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 4 h. The crude material was purified via flash column chromatography in 10% EtOAc:90% Hex to collect a clear oil (0.071 g, 91%). $R_f = 0.32$ (15% EtOAc:85% Hex).

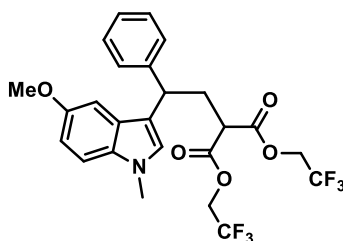
$^1\text{H NMR}$ (599 MHz, CDCl_3) δ : 7.62 (d, $J = 8.0$ Hz, 1H), 7.42 (m, 3H), 7.36 (d, $J = 8.2$ Hz, 1H), 7.32 (d, $J = 7.5$ Hz, 2H), 7.27–7.22 (m, 5H), 7.17 (t, $J = 7.3$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 4.30 (dq, $J = 12.6, 8.4$ Hz, 1H), 4.19 (dq, $J = 12.5, 8.3$ Hz, 1H), 4.15–4.08 (m, 2H), 4.00 (dq, $J = 12.6, 8.3$ Hz, 1H), 3.56 (s, 3H), 3.39 (dd, $J = 8.9, 5.4$ Hz, 1H), 2.94 (ddd, $J = 13.9, 11.5, 5.4$ Hz, 1H), 2.80 (ddd, $J = 14.1, 8.9, 5.4$ Hz, 1H). **$^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ :** -73.74 (t, $J = 8.3$ Hz, 3F), -73.88 (t, $J = 8.9$ Hz, 3F). **$^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ :** 167.0, 166.8, 144.1, 139.7, 137.6, 131.4, 130.8, 128.5, 128.4, 128.4, 127.6, 126.2, 126.1, 122.51 (q, $^1J_{\text{C-F}} = 277$ Hz), 122.4 (q, $1J_{\text{C-F}} = 277$ Hz), 121.8, 120.5, 119.7, 111.8, 109.7, 60.9 (q, $^2J_{\text{C-F}} = 36$ Hz), 60.7 (q, $^2J_{\text{C-F}} = 38$ Hz), 49.9, 40.4, 33.9, 30.9. **IR_{ATR} (cm^{-1}):** 3091, 2940, 1774, 1756, 1279, 1240, 1165, 1138, 970, 742, 699, 648. **HRMS (EI) (m/z):** $[\text{M}^+]$ calcd for $\text{C}_{30}\text{H}_{25}\text{F}_6\text{NO}_4$, 577.1688; found, 577.1693.



Bis(2,2,2-trifluoroethyl) 2-(2-(1-Methyl-5-nitro-1H-indol-3-yl)-2-phenylethyl)malonate (2-14e)

Following GP3, CP **2-13a** (0.050 g, 0.13 mmol) and 5-nitro-1-methylindole (0.071 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 20 h. The crude material was purified via flash column chromatography in 40% EtOAc:60% Hex to collect a yellow solid (0.035 g, 47%). MP 78–81 °C. R_f = 0.28 (40% EtOAc:60% Hex).

^1H NMR (400 MHz, CDCl_3) δ : 8.36 (d, J = 2.1 Hz, 1H), 8.09 (dd, J = 9.1, 2.2 Hz, 1H), 7.37–7.26 (m, 6H), 7.06 (s, 1H), 4.65–4.40 (m, 4H), 4.26 (dd, J = 9.0, 6.9 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, J = 7.9, 6.6 Hz, 1H), 2.84 (m, 1H), 2.70 (ddd, J = 14.0, 9.2, 6.6 Hz, 1H). **^{19}F NMR (376 MHz, CDCl_3) δ :** –73.69 to –73.87 (m, 6F). **^{13}C NMR (101 MHz, CDCl_3) δ :** = 167.1, 141.9, 141.5, 140.1, 129.2, 129.1, 127.9, 127.5, 126.4, 122.7 (q, $^1J_{\text{C-F}}$ = 277.5 Hz), 122.6 (q, $^1J_{\text{C-F}}$ = 277.3 Hz), 120.0, 117.9, 116.8, 109.4, 61.30 (q, $^2J_{\text{C-F}}$ = 37.2 Hz), 49.4, 40.4, 34.7, 33.4. **IR_{ATR} (cm^{-1}):** 2940, 1758, 1488, 1322, 1283, 1160, 1064, 973. **HRMS (EI) (m/z):** [M⁺] calcd for $\text{C}_{24}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_6$, 546.1226; found, 546.1226.

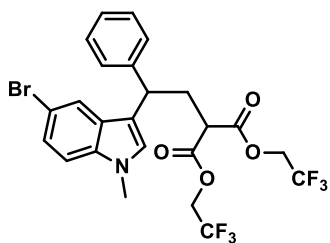


Bis(2,2,2-trifluoroethyl) 2-(2-(5-Methoxy-1-methyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-14f)

Following GP3, CP **2-13a** (0.050 g, 0.13 mmol) and 5-methoxy-1-methylindole (0.065 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 18 h. The crude material was purified via flash column chromatography in 12.5% EtOAc:87.5% Hex to collect a clear oil (0.0632 g, 89%). R_f = 0.34 (20% EtOAc:80% Hex).

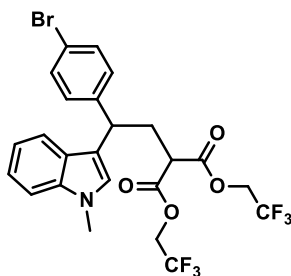
^1H NMR (400 MHz, CDCl_3) δ : 7.33–7.29 (m, 4H), 7.22 (ddd, J = 8.6, 4.8, 3.3 Hz, 1H), 7.16 (d, J = 9.1 Hz, 1H), 6.90–6.82 (m, 3H), 4.58–4.40 (m, 4H), 4.19 (t, J = 8.0 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.59 (t, J = 7.2 Hz, 1H), 2.88 (dt, J = 14.1, 7.5 Hz, 1H), 2.68

(ddd, $J = 14.0, 8.7, 6.8$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ : -73.73 (t, $J = 8.7$ Hz, 3F), -73.76 (t, $J = 8.6$ Hz, 3F). ^{13}C NMR (101 MHz, CDCl_3) δ : 167.4, 167.3, 153.9, 143.0, 132.9, 128.8, 128.0, 127.4, 126.9, 122.7 (q, $^1J_{\text{C-F}} = 277$ Hz), 116.0, 112.1, 110.2, 101.5, 61.15 (q, $^2J_{\text{C-F}} = 37$ Hz), 55.9, 49.6, 40.7, 34.7, 33.0. IR_{ATR} (cm^{-1}): 2945, 1753, 1623, 1491, 1280, 1162, 1136, 1058, 701. HRMS (EI) (m/z): $[M^+]$ calcd for $\text{C}_{25}\text{H}_{23}\text{F}_6\text{NO}_5$, 531.1481; found, 531.1483.



Bis(2,2,2-trifluoroethyl) 2-(2-(5-Bromo-1-methyl-1H-indol-3-yl)-2-phenylethyl)malonate (2-14g)

Following GP3, CP **2-13a** (0.05 g, 0.13 mmol) and 5-bromo-1-methylindole (0.085 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 16 h. The crude material was purified via flash column chromatography in 15% EtOAc:85% Hex to collect a pale-yellow oil (0.062 g, 79%). $R_f = 0.40$ (15% EtOAc:85% Hex). ^1H NMR (400 MHz, CDCl_3) δ : 7.45 (d, $J = 8.0$ Hz, 1H), 7.33–7.26 (m, 4H), 7.23–7.17 (m, 2H), 7.03 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 6.87 (s, 1H), 4.56–4.37 (m, 4H), 4.24 (t, $J = 8.0$ Hz, 1H), 3.75 (s, 3H), 3.58 (t, $J = 7.2$ Hz, 1H), 2.88 (dt, $J = 14.1, 7.5$ Hz, 1H), 2.69 (ddd, $J = 14.0, 8.6, 7.0$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ : -73.73 (t, $J = 7.6$ Hz, 3F), -73.76 (t, $J = 8.2$ Hz, 3F). ^{13}C NMR (101 MHz, CDCl_3) δ : 167.3, 143.0, 137.5, 128.8, 128.0, 127.1, 126.9, 126.4, 122.7 (q, $^1J_{\text{C-F}} = 277$ Hz), 122.6 (q, $^1J_{\text{C-F}} = 277$ Hz), 122.0, 119.6, 119.2, 116.5, 109.4, 61.17 (q, $^2J_{\text{C-F}} = 37$ Hz), 49.7, 40.7, 34.8, 32.9. IR_{ATR} (cm^{-1}): 2935, 1753, 1411, 1279, 1162, 976, 703, 664. HRMS (EI) (m/z): $[M^+]$ calcd for $\text{C}_{24}\text{H}_{20}\text{BrF}_6\text{NO}_4$, 579.0478; found, 579.0478.

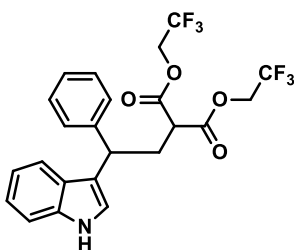


Bis(2,2,2-trifluoroethyl) 2-(2-(4-Bromophenyl)-2-(1-methyl-1H-indol-3-yl)ethyl)malonate (2-14h)

Following GP3, CP **2-13b** (0.050 g, 0.11 mmol) and 1-methylindole (0.044 g, 0.33 mmol) in HFIP (0.4 mL) were subjected to heat for 24 h. The crude material was purified via

flash column chromatography in 5% EtOAc:85% Hex to collect a clear oil (0.061 g, 95%). $R_f = 0.35$ (15% EtOAc:85% Hex).

^1H NMR (400 MHz, CDCl_3) δ : 7.45–7.37 (m, 3H), 7.29 (d, $J = 8.2$ Hz, 1H), 7.24–7.15 (m, 3H), 7.08–7.01 (m, 1H), 6.88 (s, 1H), 4.61–4.36 (m, 4H), 4.21 (t, $J = 8.0$ Hz, 1H), 3.76 (s, 3H), 3.57 (t, $J = 7.2$ Hz, 1H), 2.86 (dt, $J = 14.0, 7.6$ Hz, 1H), 2.66 (ddd, $J = 14.0, 8.1, 7.2$ Hz, 1H). **^{19}F NMR (376 MHz, CDCl_3) δ :** -73.73 (t, $J = 8.2$ Hz, 3F), -73.74 (t, $J = 7.5$ Hz, 3F). **^{13}C NMR (101 MHz, CDCl_3) δ :** = 167.3, 167.2, 142.2, 137.5, 131.9, 129.7, 126.9, 126.4, 122.7 (q, $^1J_{\text{C-F}} = 277$ Hz), 122.2, 120.7, 119.4, 115.7, 109.5, 61.20 (q, $^2J_{\text{C-F}} = 37$ Hz), 49.5, 40.1, 34.6, 32.9. **IR_{ATR} (cm^{-1}):** 3422, 2945, 1754, 1411, 1279, 1162, 976, 701, 664. **HRMS (m/z):** [M⁺] calcd for $\text{C}_{24}\text{H}_{20}\text{BrF}_6\text{NO}_4$, 579.0480; found, 579.0454.



Bis(2,2,2-trifluoroethyl) 2-(2-(1H-Indol-3-yl)-2-phenylethyl)-malonate (2-14i)

Following GP3, CP **2-13a** (0.050 g, 0.13 mmol) and indole (0.047 g, 0.41 mmol) in HFIP (0.5 mL) were subjected to heat for 24 h. The crude material was purified via flash column chromatography in 20%EtOAc:80%Hex to collect a clear oil (0.017 g, 25%). $R_f = 0.23$ (20% EtOAc:80% Hex).

^1H NMR (400 MHz, CDCl_3) δ : 8.02 (s, br, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.37–7.27 (m, 5H), 7.24–7.13 (m, 2H), 7.08–7.00 (m, 2H), 4.59–4.38 (m, 4H), 4.26 (t, $J = 8.0$ Hz, 1H), 3.58 (t, $J = 7.2$ Hz, 1H), 2.90 (dt, $J = 14.0, 7.5$ Hz, 1H), 2.70 (ddd, $J = 14.0, 8.7, 6.9$ Hz, 1H). **^{19}F NMR (376 MHz, CDCl_3) δ :** -73.75 (q, $J = 8.9$ Hz). **^{13}C NMR (101 MHz, CDCl_3) δ :** 167.4, 167.3, 142.8, 136.7, 128.8, 128.0, 127.0, 126.7, 122.7 (q, $^1J_{\text{C-F}} = 277$ Hz), 122.5, 121.5, 119.8, 119.5, 118.2, 111.3, 61.17 (q, $^2J_{\text{C-F}} = 37$ Hz), 49.7, 40.7, 34.7. **IR_{ATR} (cm^{-1}):** 3422, 1752, 1457, 1413, 1281, 1165, 977. **HRMS (EI) (m/z):** [M⁺] calcd for $\text{C}_{23}\text{H}_{19}\text{F}_6\text{NO}_4$, 487.1218; found, 487.1219

2.7 References

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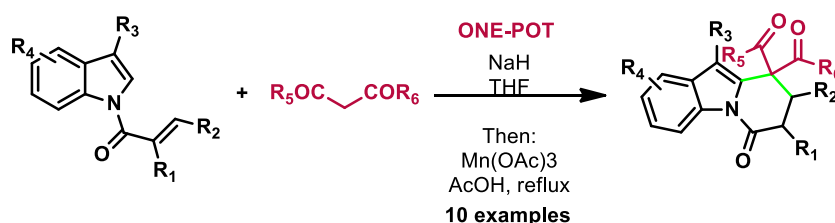
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Chapter 3 : One-Pot Michael Addition/Radical Cyclization Reaction of *N*-Acryloyl Indoles

Chapter 3 Preface

The material in this chapter is adapted from: Irwin, L.C.; Kerr, M.A. *Synlett* **2017**, 28, 2859-2864.

This chapter describes using $\text{Mn}(\text{OAc})_3$ as a single electron oxidant to generate complex multi-ring systems incorporating indoles (**Scheme 52**). The scaffolds acquired map well on to a variety of natural products. In a one-pot protocol, a Michael addition of 1,3 dicarbonyl nucleophiles results in a molonyl-tether, which is oxidized by $\text{Mn}(\text{OAc})_3$ and cyclizes onto various substituted indoles. This method is being applied to the total syntheses of tronocarpine and dippinine B (Chapter 4). A library scope to reflect on the utility of this protocol is also discussed.



Scheme 52 - Reaction explored in Chapter 2. A one-pot Michael addition then Mn(III) mediated cyclization of indoles.

3.1 Introduction

Indoles are biological powerhouses. Indoles have proven useful as a variety of anticancer, antibacterial and antiviral drugs.¹⁰⁵ Few indole alkaloids exist that bear a 6-membered ring, substituted in a 1,2 fashion, off the indole core. This type of bioactive indole has been found in the flowering Malaysian plant *Tabernaemontana corymbosa*.¹⁰⁶ These compounds, such as tronocarpine, chippiine, and ervataine, have intriguing bioactive properties and novel pentacyclic structures that present a challenge to organic chemists attempting the first total syntheses of these molecules (**Figure 13**).^{106,107}

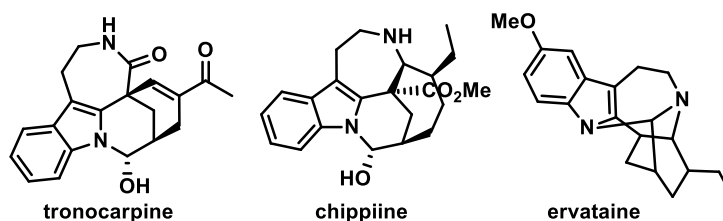
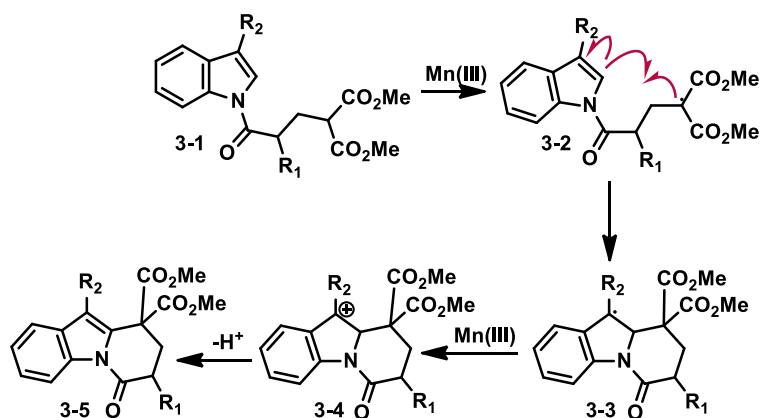


Figure 13 - Indole-containing natural products isolated from *Tabernaemontana corymbosa*.

Due to the importance of indoles in both medicinal and natural products chemistry, being able to functionalize this heterocyclic motif is important.¹⁰⁸ When it comes to further elaboration of indole scaffolds, we became interested in single electron transfer (SET) agents used to forge carbon-carbon bonds via electrophilic radicals. $Mn(OAc)_3$ is a SET agent capable of generating carbon-centered radicals from enolizable carbonyl compounds.^{109,110,111} Radicals generated by $Mn(OAc)_3$ can insert into indoles at the 2, 3, or 4 position further elaborating these heterocycles.

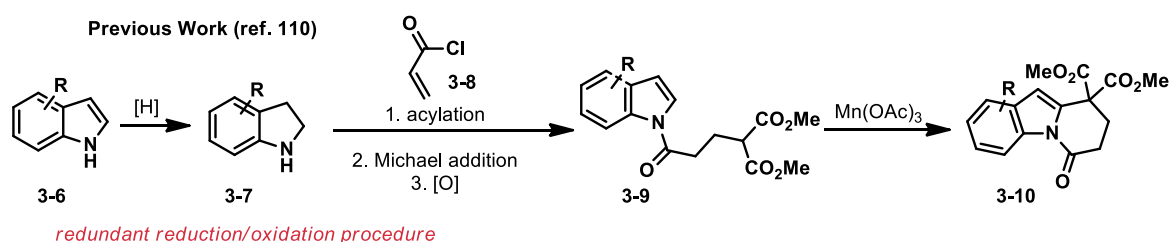
The mechanism for the oxidative radical generation and insertion into indoles, while discussed in the introductory chapter of this thesis, is outlined in detail below regarding how I sought to manipulate this chemistry to elaborate indoles (**Scheme 53**).



Scheme 53 - Mechanism for radical generation and ring closure of malonate species onto indole.

From **3-1**, $\text{Mn}(\text{OAc})_3$ oxidizes the enolizable carbon to an electrophilic radical (**3-2**). The radical attacks the two position of the indole to produce the favoured 6-membered ring (**3-3**). Another equivalent of $\text{Mn}(\text{OAc})_3$ oxidizes the remaining radical (**3-3**) to a tertiary cation (**3-4**) which, via elimination of a proton, yields the indole driven by re-aromatization. The result is the 1,2 substituted indole and cyclized product **3-5**.

Previous work from the Kerr group demonstrated that from indoline (**3-7**) starting materials we could generate indoles bearing pendant β -dicarbonyl products (**3-9**) that would undergo radical cyclization onto indoles (**Scheme 54**).¹¹² This work was restricted to acryloyl chloride **3-8** to acylate indolines, which then needed to be oxidized to acylated indoles before being subject to Michael addition (MA) with dimethyl malonate. Often to access the indolines for acylation, its indole was reduced leading to a redundant reduction/oxidation procedure (**Scheme 54**). The synthetic world is doing its best now to minimize oxidation/reduction manipulations especially when it comes to ideal total synthesis (see Baran's ideality in synthesis).¹¹³



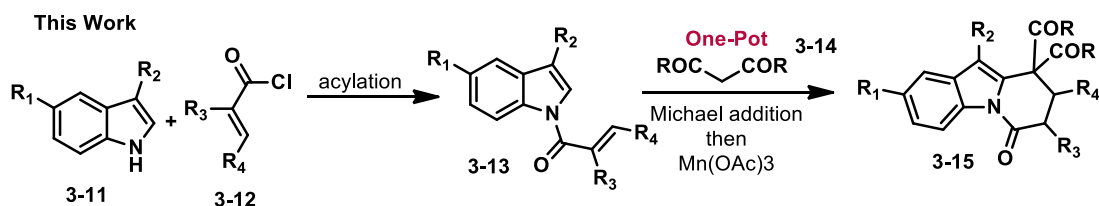
Scheme 54 - Previous Kerr group work using single-electron oxidant $\text{Mn}(\text{OAc})_3$ to perform C-H insertion at 2 position of indoles

With improvements needed, and a desire to complete the total syntheses of tronocarpine and dipiinne B, an efficient route at accessing these six-membered rings fused to the 1,2-face of an indole core was something to be sought.

3.2 Proposed Research

It was my hope that I may first obviate the isolation of intermediate substrates and generate the tricyclic scaffolds like **3-10** in a one-pot procedure. I also sought to expand the substrate scope and have greater substitution on the indoles and acryloyl components

of the starting materials. From acylated indoles **3-13**, we theorized that the Michael-addition with a malonic entity **3-14** could be performed, and then in the same pot, add SET agent $\text{Mn}(\text{OAc})_3$ to complete the radical cyclization to generate products **3-15** (Scheme 55).



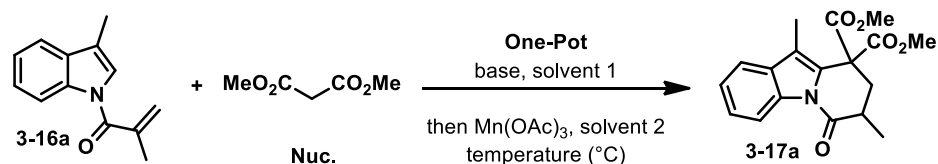
Scheme 55 - Proposed one-pot protocol to generate functionalized indoles 3-15

The proposed work would cut down three synthetic steps and yield more substituted products than our earlier work. It also removed the redundant reduction/oxidation step previously employed and it starts from cheaper materials.

3.3 Optimization of the One-Pot Michael Addition and $\text{Mn}(\text{OAc})_3$ Cyclization of Indoles

To determine if this protocol was viable, optimization attempts began by acylating 3-methylindole with methacryloyl chloride and using the resultant *N*-acryloylindole (**3-16a**) as our test subject. Dimethylmalonate was our chosen nucleophile because of its preexisting use with $\text{Mn}(\text{OAc})_3$ to generate radicals. Acylation to generate acryloyl indoles like **3-16a** was performed directly from the indoles using a modified and improved experimental procedure: the details of which are outlined in the experimental portion of this chapter (Subsection 3.7). Table 3 explores the conditions used to optimize the formation of product **3-17a**.

Table 3 - Optimization of the One-Pot Michael Addition, Radical Cyclization of *N*-acryloyl indoles



| Entry | Nuc. (equiv.) | Base | Solvent 1 | Solvent 2 | Mn(III) ^a (equiv.) | Temp (°C) | Yield of 3-17a (%) |
|-----------|---------------|--------------------------------|------------|-------------|-------------------------------|------------|-----------------------|
| 1 | 3 | - | MeOH | - | 6 | 65 | trace |
| 2 | 3 | - | AcOH | - | 6 | 110 | 5 |
| 3 | 1.5 | NEt ₃ | DCM | - | 3 | 35 | 0 |
| 4 | 2 | K ₂ CO ₃ | MeOH | - | 3 | 65 | 0 ^b |
| 5 | 2 | DBU | MeOH | - | 3 | 65 | 0 ^b |
| 6 | 2 | DBU | MeCN | MeOH | 3 | 65 | 43 ^c |
| 7 | 2 | NaH | THF | AcOH | 6 | 110 | 50 ^c |
| 8 | 2 | NaH | THF | MeOH | 6 | 65 | 36 ^c |
| 9 | 2 | NaH | THF | AcOH | 5 | 110 | 23 ^c |
| 10 | 1.2 | NaH | THF | AcOH | 4 | 110 | 42 ^d |
| 11 | 1.2 | NaH | THF | AcOH | 6 | 110 | 47 ^d |
| 12 | 1.5 | NaH | THF | AcOH | 6 | 110 | 57 ^d |
| 13 | 1.5 | NaH | THF | AcOH | 7 | 110 | 65^d |
| 14 | 1.5 | NaH | THF | AcOH | 10 | 110 | 58 ^d |

^a Mn(OAc)₃

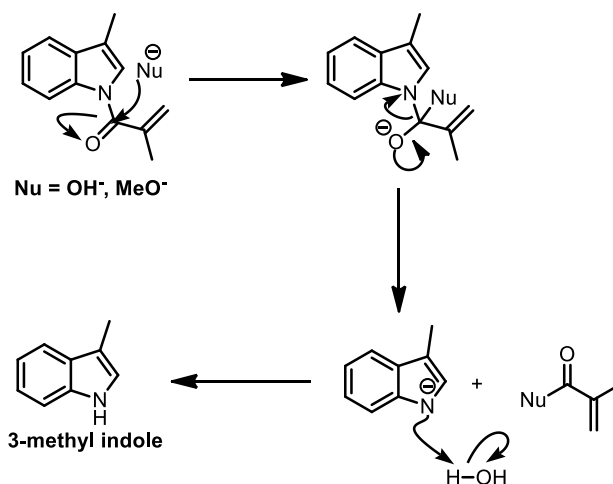
^b Deacylation occurred yielding 3-methylindole

^c Aqueous workup after the completion of both reactions

^d Nonaqueous workup after the completion of both reactions

The first attempt (**Table 3, entry 1**) involved trying the Michael addition of dimethyl malonate into the acryloyl indole using a single solvent, MeOH. MeOH, being a polar protic solvent, is an optimal choice for the radical component of the reaction and we felt as though it may be polar enough to facilitate the Michael addition of the dimethylmalonate. The Michael addition was slow and did not proceed to completion. Adding 6 equivalents of Mn(OAc)₃ yielded a messy reaction and only a trace amount of desired product **3-17a** was isolated. However, this was a promising first attempt. Upon acquiring a small amount of our desired product, we felt as though it was possible to increase the yields to a respectable value.

AcOH having a lower pH than MeOH and being a suitable polar protic solvent for the radical generation, we hoped it may have better success in mediating the Michael addition portion of the reaction (**Table 3, entry 2**). Only a small improvement was noted, isolating 5% of product **3-17a**. At this point, we turned our attention to using bases to mediate the Michael addition in an attempt for the best yield possible. NEt₃ in DCM failed to yield any desired product (**Table 3, entry 3**). This result was expected as there is no precedent for DCM being a suitable solvent for Mn(OAc)₃ radical generation. Switching back to MeOH as a solvent and using either DBU or K₂CO₃ as bases, (**Table 3, entry 4 and 5**) resulted in deacylation of the starting material. Deacylation was suspected to be the result of the production of small nucleophiles ⁻OMe and/or ⁻OH (**Scheme 56**).



Scheme 56 - Mechanism of deacylation resulting in the isolation of starting indoles.

Knowing that competitive side diacylation was possible, using water-free solvents for the Michael addition became imperative for success. This led to using acetonitrile in the presence of DBU for the Michael addition (**Table 3, entry 6**) and then adding MeOH to facilitate the radical cyclization. This change to a two-solvent system resulted in 43% of product **3-17a**. Excited, we switched to THF and NaH as the environment for the Michael addition, and using AcOH for the radical cyclization based on the positive result it gave in **entry 2**. These changes further increased the yield of **3-17a** to 50% (**Table 3, entry 7**). At this point, observations indicated that aqueous workup was troublesome and often the manganese would make emulsions that could not be broken up or dealt with. Without doubt, these emulsions were hindering my ability to isolate the maximum amount of product and so I switched to a non-aqueous workup involving only filtration and flash column chromatography to isolate pure **3-17a**. As per **Table 3, entry 12**, lowering the nucleophile equivalents and switching to the non-aqueous work-up resulted in a higher 57% yield of **3-17a**. Finally, upping the equivalents of Mn(III) from 6 to 7 provided a modest 65% yield of isolatable product **3-17a**. This would become the optimized conditions as increasing the amount of Mn(III) to 10 equivalents provided lower yields.

3.4 Library of Generated Products

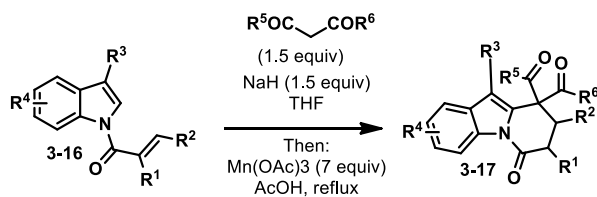
A substrate scope of the one-pot protocol was investigated on a variety of *N*-acryloyl indoles using the optimized conditions (**Table 4**). We started by testing different 1,3-

dicarbonyl reagents. Acetylacetone (**Table 4, entry 2**) and methylacetoacetate (**Table 4, entry 3**) both yielded desired products **3-17b** and **3-17c** in a 59% and 54% yield respectively. However, when first testing these reagents under the optimized procedure, competitive aldol condensation of the 1,3-dicarbonyl reagents halted the progress of any successful Michael addition.¹¹⁴ Using weaker K_2CO_3 as a base solved this competition resulting in desired annulation products **3-17b** and **3-17c**. The procedure is outlined in the experimental details of this chapter.

When comparing substituents on the acryloyl component of substrate **3-16** (R^1 and R^2) an α -methyl substituent (**3-16a**) versus a hydrogen (**3-16c**) produced slightly better yields. This is thought to be a result of a lesser tendency to polymerize, which was a problem faced when working with the acryloyl indole **3-16c**. With a bulky phenyl substituent at the β -position (R^2 , **3-16d**) yield of the *N*-acryloylindole dropped significantly. Steric hinderance of the phenyl group resulted in a tougher Michael addition lowering the overall yield of **3-17f**.

Examining the electronics of the indole, substitution was varied at the 5-position, R^4 of substrate **3-16**. Electron-neutral or -donating groups produced higher yields (**3-17i** and **3-17g**) than their electron withdrawing counterpart, the nitro group **3-17h**, where the yield was much lower at 36%. We hypothesized that because the reaction proceeds through an electrophilic radical (**Scheme 53, 3-3** and **3-4**), less electron density would destabilize its

Table 4 - Substrate Scope One-Pot MA, radical cyclization



| Entry | Substrate | 1,3 dicarbonyl | Product (Yield %) |
|-------|-----------|--|------------------------------|
| 1 | 3-16a | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17a (65) |
| 2 | 3-16a | MeOC-CH ₂ -COMe | 3-17b (59 ^a) |
| 3 | 3-16a | MeO ₂ C-CH ₂ -COMe | 3-17c (54 ^a) |
| 4 | 3-16b | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17d (45) |
| 5 | 3-16c | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17e (38) |
| 6 | 3-16d | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17f (27) |
| 7 | 3-16e | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17g (63) |
| 8 | 3-16f | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17h (36) |
| 9 | 3-16g | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17i (61) |
| 10 | 3-16h | MeO ₂ C-CH ₂ -CO ₂ Me | 3-17j (30) |

annulated products (**Table 4**). This chemistry is being used towards the total syntheses of tronocarpine and dippinnine B which is further discussed in Chapter 4.

I think that $\text{Mn}(\text{OAc})_3$ has been well exploited as a SET agent for the radical cyclization of indoles, and it does possess a downfall in its inconsistency dependent on where you source your supply (purchase vs. make). I have, however, a perfected procedure to make quality $\text{Mn}(\text{OAc})_3$ repeatably. This procedure is outlined in **Subsection 3.7.2**. $\text{Mn}(\text{OAc})_3$ can also be a tricky reagent during reaction work-up if all of it does not reduce and you are left with a thick brown emulsion that traps additional product. This will result in lowered yields. However, I observed that when the colour of a reaction changes from dark brown to bright white-orange, the manganese has reduced and becomes much easier to work up and no emulsion will exist. Yields are significantly better when this is the case. In a live video presentation facilitated by the American Chemical Society, Phil Baran presented unpublished work that originally involved the use of $\text{Mn}(\text{OAc})_3$. However, they too came across similar emulsion problems. Electrochemical generation of radicals was the solution for the transformation they were pursuing. Electrochemistry is becoming a clean, easy, and fast way to generate radicals for organic synthesis and I think that functionalizing indoles with radicals avoiding the use of metals is a better pathway to research.¹¹⁶ While the upfront cost of electrochemical cells, electrodes, and glassware is daunting, electrochemistry ultimately becomes cheaper than most traditional synthetic reactions, and often sees easier, cleaner purification.¹¹⁷

It is also likely that exploring one of the many other single electron oxidants would perhaps provide higher yields of products towards the synthesis of target molecules. Ceric ammonium nitrate (CAN, $(\text{NH}_4)_2\text{Ce}(\text{IV})(\text{NO}_3)_6$) is relatively inexpensive (although, more expensive than manganese), but is soluble in a much wider variety of organic solvents. Easily handled, it performs identical chemistry to that of $\text{Mn}(\text{OAc})_3$.¹¹⁸ Experimentation to generate the intermediates *en-route* to tronocarpine and dippinnine B using CAN might be another effective tool for increasing the yields of 1,2-annulated indole products.

3.6 Experimental

3.6.1 General Experimental Details

All reactions were conducted under an argon atmosphere unless otherwise indicated. Flasks were oven-dried and cooled in a desiccator prior to use. All chemicals were of reagent quality and used as obtained from commercial sources with the exception of the $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, which was prepared by literature procedure with heavy modification, the exact procedure used is outlined below.¹¹⁹ High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Dichloromethane (DCM), acetonitrile (MeCN), toluene, benzene, and tetrahydrofuran (THF) were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from Aldrich, Alfa Aesar (VWR), or Caledon. Reaction progress was followed by thin layer chromatography (TLC) (Merck, TLC Silica gel 60 F254) visualizing with UV light, and the plates were developed using acidic p-anisaldehyde or vanillin. Column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). All columns were performed using Still's procedure for flash chromatography.¹²⁰ IR spectra were acquired using a PerkinElmer Spectrum Two FT-IR. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. NMR experiments were performed on either a BrukerAvIII 400, Varian Inova 400 or Inova 600 instrument and samples were obtained in CDCl_3 (referenced to 7.25 ppm for ^1H and 77.0 ppm for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad.

3.6.2 Procedure for Synthesis $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$

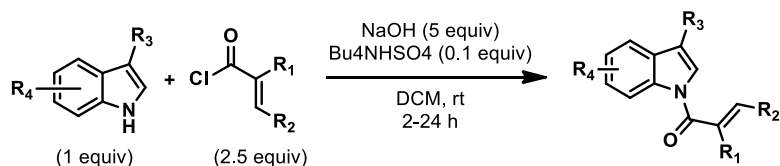
In a 2 L round bottom, add suitable stir bar and 100 g of $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$. To the flask add 700 mL of AcOH and lower into an oil bath in which the temperature reads somewhere between 105-110 °C. *Do not allow the temperature outside of this range, especially to the hotter end of the spectrum.* Equip reflux condenser and stir the reaction

vigorously. Weigh out 16.08 g of KMnO_4 in a weigh boat and monitor the reaction to see that the $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ is mostly dissolved. There will be shiny flakes when it is mixed in well. This usually takes 5-10 mins. Approximate about ten even amounts of the KMnO_4 for its addition. Add one of the 10 portions of KMnO_4 every 2 minutes to the heated mixture, with stirring, until it's all gone (10 times, 20 minutes). Let the reaction stir for 25 minutes after the complete addition of KMnO_4 , again being sure the oil bath does not exceed $110\text{ }^\circ\text{C}$. Remove the reaction from the oil bath, turning the hot plate off and allowing the mixture to cool to room temperature with stirring and without the aid of an ice bath, or other external cooling method. This will take 1-2 hours. In a large 2L or 3L Erlenmeyer, add 176 mL of water as accurately as possible. A 200 mL graduated cylinder works well enough. Add the room temperature reaction mixture of $\text{Mn}(\text{OAc})_3$ to the Erlenmeyer charged with water, and leave in a fume hood to crystallize for 2 days. You can seal the Erlenmeyer with parafilm if you'd like, ensuring plenty of air holes are added. After this time has passed, filter the mixture using a large ceramic Buchner funnel equipped with filter paper. Wash the collected solid with ether 5-7 times until the dark particulates have been washed through, and as the solid dries, it takes on an orange-brown colour versus dark brown (**Figure 14**). In a fume-hood, scrape the solid off the filter paper onto Teflon sheet, or saran wrap, and spread out the powder to a thin layer for quick drying. Allow the $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ to air dry. Do NOT subject the material to long periods of suction vacuum (even while washing with ether) or place on a high-vacuum pump. Once dry, and the material a nice bright orange, store in a glass screw top bottle. Yield: 109 g, quantitative yield.



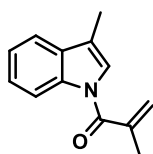
Figure 14 - Comparison of the “good” and “bad” colour of $\text{Mn}(\text{OAc})_3$ reagent.

3.6.3 Experimental Procedure A: Synthesis of Acryloyl Indoles



Scheme 58 - General procedure for the synthesis of acryloyl indoles

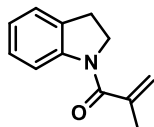
A modified procedure from the literature.¹²¹ To a round-bottom charged with DCM (0.1 M) was added indole (1 equiv.), powdered NaOH (5 equiv.) and tetrabutylammonium hydrogensulfate (Bu₄NHSO₄) (0.1 equiv.). The mixture was stirred for 30 minutes, at which point desired acid chloride (2.5 equiv.) was added to the reaction dropwise. The reaction was monitored by TLC until complete consumption of starting materials was observed. To the flask was added water and the mixture moved to a separatory funnel. The aqueous layer was extracted 3x with DCM, and the organic layers combined and washed with brine. The collected organic fraction was dried with MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Ethyl acetate: Hexanes).



2-methyl-1-(3-methyl-1H-indol-1-yl)prop-2-en-1-one (3-16a)

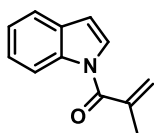
Following **Experimental Procedure A**, compound **3-16a** was obtained from commercially available 3-methylindole (skatole) (3.0 g, 22.9 mmol), Bu₄NHSO₄ (0.78 g, 2.29 mmol), NaOH (4.58 g, 114 mmol), methacryloyl chloride (5.98 g, 57.2 mmol, 5.6 mL) in 229 mL DCM. After stirring at rt for 2 h, the reaction was complete. **3-16a** was acquired as a yellow oil (2.81 g, 62 %). R_f = 0.38 (10% EtOAc in hexanes)

¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.24 (s, 1H), 5.68 – 5.59 (m, 1H), 5.47 – 5.40 (m, 1H), 2.27 (s, 3H), 2.19 – 2.11 (m, 3H). Spectral data matched literature report of this compound.¹²¹



1-(indolin-1-yl)-2-methylprop-2-en-1-one (3-20)

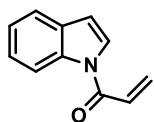
3-20 was synthesized following literature procedure.¹²² All spectral data matched. Crude product was used and pushed directly to product **3-16b**.



1-(1H-indol-1-yl)-2-methylprop-2-en-1-one (3-16b)

Indoline **3-20** (1.59 g, 8.49 mmol) was dissolved in toluene (34 mL) and DDQ (2.32 g, 10.2 mmol) was added. The reaction was heated overnight at reflux for 16 h, at which point TLC confirmed consumption of starting material. The solvent was removed from the crude mixture *in vacuo* and then re-dissolved in DCM with 6g of silica added. The DCM was removed under pressure to give the crude material adsorbed to silica. Dry loaded flash column chromatography (5% EtOAc in hexanes) yielded pure acylated indole product **3-16b** as an orange oil (0.93 g, 59% over 2-steps). *R_f* = 0.28 (5% EtOAc in hexanes)

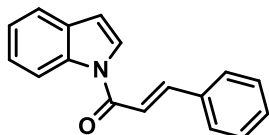
¹H NMR (400 MHz, CDCl₃) δ = 8.42 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 3.8 Hz, 1H), 7.36 (td, *J* = 8.3, 7.9, 1.3 Hz, 1H), 7.29 (td, *J* = 7.6, 1.1 Hz, 1H), 6.60 (d, *J* = 3.8 Hz, 1H), 5.68 (d, *J* = 1.0 Hz, 1H), 5.46 (s, 1H), 2.16 (s, 3H) **¹³C NMR (101 MHz, CDCl₃)** δ = 169.8, 140.0, 135.7, 131.1, 127.1, 125.0, 124.0, 122.0, 120.9, 116.6, 108.6, 20.1 **IR_{ATR} (cm⁻¹)** 2922, 1683, 1534 1449, 1378, 1343, 1200, 1154, 1075, 888 **HRMS *m/z* [M⁺]** 185.0839 (calcd for C₁₂H₁₁NO, 185.0841)



1-(1H-indol-1-yl)prop-2-en-1-one 3-16c

Acylated indole was synthesized following literature procedure.¹²² The title product was acquired as an orange solid (0.79 g, 53 % yield over 2-steps). Spectral data matched reported literature. MP = 44 - 47°C

¹H NMR (400 MHz, Chloroform-*d*) δ = 8.51 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 6.97 (dd, J = 16.7, 10.4 Hz, 1H), 6.73 – 6.60 (m, 2H), 6.04 (d, J = 10.4 Hz, 1H)

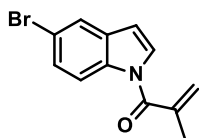


(E)-1-(1H-indol-1-yl)-3-phenylprop-2-en-1-one 3-16d

Indoline (1.50 g, 12.6 mmol) was dissolved in THF (25 mL) followed by the addition of K₂CO₃ (3.48g, 25.2 mmol) to the round bottom. The mixture was cooled to 0 °C and cinnamoyl chloride (2.31 g, 13.9 mmol dissolved in 4 mL THF) was added via syringe to the mixture dropwise. The reaction was warmed to rt and stirred for 6 h. The mixture was quenched with H₂O and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were washed with brine once, dried with MgSO₄ and concentrated under pressure. The crude mixture (3.09 g, 12.4 mmol, yellow solid) obtained was immediately pushed forward and dissolved in toluene (50 mL) followed by the addition of DDQ (3.38 g, 14.9 mmol) and refluxed for 12 h. The toluene was removed from the crude mixture *in vacuo* and then the crude re-dissolved in DCM with 6 g of silica added. The DCM was removed under pressure to give the crude material adsorbed to silica. Dry loaded flash column chromatography (10% EtOAc in hexanes) was performed to collect acylated indole **3-16d** as a yellow-solid (1.30 g, 42% over 2-steps). R_f = 0.42 (50% EtOAc in hexanes) MP = 110 – 112 °C

¹H NMR (400 MHz, Chloroform-*d*) δ = 8.54 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 15.4 Hz, 1H), 7.64 (m 3H), 7.59 (d, J = 7.7 Hz, 1H), 7.46 – 7.42 (m, 3H), 7.38 (t, J = 7.7 Hz, 1H), 7.34 – 7.19 (m, 2H), 6.70 (d, J = 4.2 Hz, 1H) **¹³C NMR (101 MHz, Chloroform-*d*)** δ = 164.4, 146.7, 136.0, 134.6, 130.9, 129.2, 128.5, 125.2, 124.7, 123.9, 121.0, 117.4, 117.0, 109.3. **IR (cm⁻¹)** 3157, 3054, 1665, 1609, 1536, 1447, 1346, 1297, 1225, 1143, 709.

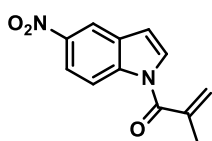
HRMS m/z [M⁺] 247.0995 (calcd for C₁₇H₁₃NO, 247.0997).



1-(5-bromo-1H-indol-1-yl)-2-methylprop-2-en-1-one (3-16e)

Following **Experimental Procedure A** compound **3-16e** was obtained from commercially available 5-bromoindole (2.0 g, 10.2 mmol), Bu₄NHSO₄ (0.35 g, 1.02 mmol), NaOH (2.04 g, 52 mmol), methacryloyl chloride (2.67 g, 25.5 mmol, 2.5 mL) in 100 mL DCM. The reaction was stirred for 20 h. **3-16e** was obtained as a white solid (1.94 g, 72%). R_f = 0.38 (10% EtOAc in hexanes). MP = 32 - 34°C *NOTE: 5-bromoindole and its acylated derivative will decompose in light over time.*

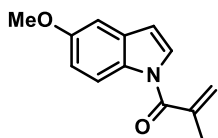
¹H NMR (400 MHz, Chloroform-*d*) δ = 8.28 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.48 (d, *J* = 3.6 Hz, 1H), 7.44 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 5.70 (s, 1H), 5.47 (s, 1H), 2.15 (s, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ = 169.6, 134.4, 132.8, 128.3, 127.8, 123.6, 122.6, 118.0, 117.3, 107.7, 20.1. **IR (cm⁻¹)** 3019, 2400, 1691, 1445, 1366, 1340, 1216, 813, 778, 669. **HRMS *m/z* [M⁺]** 262.9941 (262.9946 calcd for C₁₂H₁₀BrNO)



2-methyl-1-(5-nitro-1H-indol-1-yl)prop-2-en-1-one (3-16f)

Following **Experimental Procedure A** compound **3-16f** was synthesized from 5-nitroindole (1 g, 6.17 mmol), Bu₄NHSO₄ (0.21 g, 0.62 mmol), NaOH (1.23 g, 30.9 mmol) and methacryloyl chloride (1.61 g, 15.4 mmol, 1.5 mL) in 62 mL of DCM. The reaction was stirred for 2.5 h at which point TLC confirmed consumption of starting material. **3-16f** was obtained as a white powder (0.76 g, 53%). R_f = 0.21 (15% EtOAc in hexanes). MP = 125 - 126°C *NOTE: 5-nitroindole will decompose over time in light.*

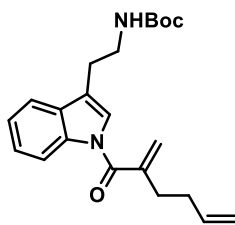
¹H NMR (400 MHz, CDCl₃) δ = 8.54 - 8.41 (m, 1H), 8.23 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.64 (d, *J* = 3.8 Hz, 1H), 6.77 - 6.69 (m, 1H), 5.80 (s, 1H), 5.55 (s, 1H), 2.18 (s, 3H) **¹³C NMR (101 MHz, CDCl₃)** δ = 169.5, 144.5, 139.3, 138.8, 130.9, 130.0, 123.8, 120.2, 117.2, 116.7, 108.8, 19.9 **IR_{ATR} (cm⁻¹)** 1695, 1517, 1536, 1442, 1333, 1193, 884, 828, 777, 745 **HRMS *m/z* [M⁺]** 230.0691 (calcd for C₁₂H₁₀N₂O₃, 230.0691)



1-(5-methoxy-1H-indol-1-yl)-2-methylprop-2-en-1-one (3-16g)

Following **Experimental Procedure A** compound **3-16g** was synthesized from 5-methoxyindole (2.0 g, 13.6 mmol), Bu₄NHSO₄ (0.46 g, 1.36 mmol), NaOH (2.72 g, 68.0 mmol) and methacryloyl chloride (3.55 g, 34.0 mmol, 3.3 mL) in 140 mL DCM. Reaction was stirred overnight for 18 h. **3-16g** was obtained as a yellow oil (2.39 g, 82%). R_f = 0.33 (15% EtOAc in hexanes).

¹H NMR (400 MHz, Chloroform-*d*) δ = 8.32 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 3.7 Hz, 1H), 7.03 (s, 1H), 6.96 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 5.65 (s, 1H), 5.44 (s, 1H), 3.85 (s, 3H), 2.15 (s, 3H) **¹³C NMR (101 MHz, CDCl₃)** δ = 169.5, 156.8, 139.9, 132.1, 130.4, 127.8, 121.8, 117.4, 113.4, 108.5, 103.7, 55.8, 20.2 **IR (cm⁻¹)** 1682, 1534, 1472, 1371, 1278, 1201, 1158, 1033, 909, 722. **HRMS *m/z* [M⁺]** 215.0954 (calcd for C₁₃H₁₃NO₂, 215.0946)



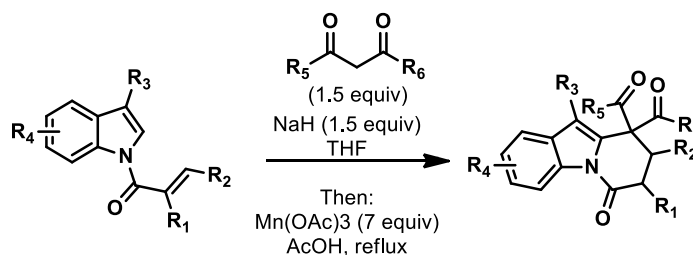
tert-butyl (2-(1-(2-methylenehex-5-enoyl)-1H-indol-3-yl)ethyl)carbamate 3-16h

Acrylic acid (2-methylenehex-5-enoic acid) (6.20 g, 49.1 mmol, 1 equiv.) was added to a 25 mL round-bottom and put under and inert atmosphere of argon. Oxalyl chloride (4.45 mL, 51.0 mmol, 1.05 equiv.) was added slowly to the flask followed by a single drop of DMF. This reaction mixture was stirred two hours. To a 500 mL round-bottom was added boc-protected tryptamine (6.39 g, 24.5 mmol, 1 equiv.) in 250 mL of DCM. Bu₄NHSO₄ (0.83 g, 2.45 mmol, 0.1 equiv.) was added to the tryptamine followed by powdered NaOH (4.91 g, 122.7 mmol, 5 equiv.). The reaction was put under and inert atmosphere of argon and allowed to stir for a minimum of 15 min. At this point the acid chloride generated in the 25 mL round bottom was cannula transferred over in its entirety (~7.10 g, 49.1 mmol, 2 equiv.). The mixture was allowed to stir under argon for 1 h, at which point TLC confirmed complete consumption of starting material. The reaction was quenched with water, and extraction with DCM 3x was performed. The combined organic extracts were washed with water once, followed by brine and then dried with MgSO₄. The solvent was removed *in vacuo* to yield the crude material. Purification of the crude compound by flash column

chromatography was performed using 30% EtOAc:Hexanes to yield the product as a slightly yellow oil (8.81 g, 83%). $R_f = 0.46$ (30% EtOAc:Hexanes)

$^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 8.43$ (d, $J = 8.2$ Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.33 – 7.27 (m, 2H), 5.81 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H), 1H), 5.65 (s, 1H), 5.45 (s, 1H), 5.08 – 4.96 (m, 2H), 4.63 (br, s, 1H), 3.44 (q, $J = 6.6$ Hz, 2H), 2.88 (t, $J = 6.9$ Hz, 2H), 2.62 (t, $J = 7.4$ Hz, 2H), 2.34 – 2.26 (m, 2H), 1.43 (s, 9H) **$^{13}\text{C NMR}$ (101 MHz, CDCl_3)** $\delta = 169.3, 156.0, 143.9, 137.2, 136.2, 131.1, 125.3, 123.9, 121.2, 119.0, 116.9, 116.0, 40.17, 32.0, 33.2, 28.5, 25.7$ **IR (cm^{-1})** 3356, 2976, 2928, 1684, 1630, 1510, 1451, 1356, 1248, 1170 **HRMS m/z [M^+]** 368.2094 (calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$, 368.2099)

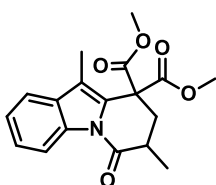
3.6.4 Experimental Procedure B: One-Pot Michael Addition, Oxidative Radical Cyclization



Scheme 59 - General reaction for the synthesis of 1,2-disubstituted indole annulation products

To an argon flushed round-bottom was added half of the total THF (0.15 M) required followed by NaH (60% dispersed in mineral oil, 1.5 equiv.). The 1,3-dicarbonyl species (1.5 equiv.) was added dropwise via syringe with stirring. The resultant mixture was stirred for 15 mins at which point the desired acryloyl indole (1 equiv.) dissolved in the other half- volume of THF and added via syringe. The Michael addition was monitored by TLC. Once TLC confirmed complete consumption of starting indole, $\text{Mn}(\text{OAc})_3$ (7 equiv.) was added to the round bottom flask followed by AcOH (0.12 M). The flask was equipped with a reflux condenser and put back under an argon atmosphere. The reaction

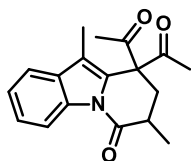
was brought to 110 °C and refluxed until the mixture changed colour from dark brown to containing obvious white solid with yellow/orange solution colour. At this point TLC analysis always indicated complete consumption of starting materials. The crude reaction mixture was cooled to rt (without ice, just resting) and then diluted with a large excess of EtOAc. The solution was filtered through a thick pad of celite and then flushed with even more EtOAc. The solvent was removed under reduced pressure with added toluene to aid in the removal of acetic acid. Obtained dried crude product was purified with flash column chromatography (EtOAc:Hexanes). The desired fractions of the column were collected to a separatory funnel and washed twice with 1 M NaOH solution to remove co-eluted dimethyl malonate (only in the cases where the malonate had the same R_f as product, when they were different the column was sufficient to purify) and then followed with a brine wash. The organic layer was collected, dried with $MgSO_4$ and concentrated *in vacuo* to yield product.



dimethyl 7,10-dimethyl-6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (3-17a)

Following **Experimental Procedure B 3-17a** was synthesized from acyl-indole **3-16a** (0.30 g, 1.51 mmol), NaH (0.091 g, 2.27 mmol), dimethyl malonate (0.30 g, 2.27 mmol, 0.26 mL) in 10 mL of THF then $Mn(OAc)_3$ (2.80 g, 10.6 mmol) in acetic acid (13 mL). **3-17a** was isolated as a yellow solid (0.33 g, 65%) $R_f = 0.40$ (20% EtOAc in hexanes) MP = 126 – 129 °C

1H NMR (400 MHz, $CDCl_3$) δ = 8.50 (d, $J = 8.2$ Hz, 1H), 7.50 (d, $J = 7.7$ Hz, 1H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.90 (ddq, $J = 12.6, 6.5, 6.3$ Hz, 1H), 2.84 (dd, $J = 13.0, 4.4$ Hz, 1H), 2.39 (t, $J = 13.0$ Hz, 1H), 2.16 (s, 3H), 1.42 (d, $J = 6.8$ Hz, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 170.9, 170.4, 169.0, 134.5, 131.1, 128.2, 125.7, 124.0, 118.6, 117.9, 116.8, 55.7, 53.6, 37.5, 35.4, 15.7, 9.2 **IR_{ATR} (cm^{-1})** 3027, 2954, 1785, 1702, 1456, 1386, 1385, 1308, 1245, 751 **HRMS m/z [M⁺]** 329.1268 (calcd for $C_{18}H_{19}NO_5$, 329.1263)



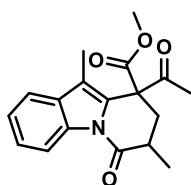
1,1'-(7,10-dimethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-9,9-diyl)diethanone (3-17b)

To an oven-dried round bottom was added acylated indole 3-16a (0.20 g, 1.00 mmol), acetylacetone (0.50 g, 5.00 mmol, 0.51 mL), K_2CO_3 (0.14 g, 1 mmol), 6 mL of THF and one drop of water. The flask was equipped with reflux condenser and the mixture heated at 55 °C for 24 h at which point starting materials had been consumed. To the reaction was then added $Mn(OAc)_3$ (1.87 g, 7.0 mmol) and acetic acid (8 mL) and refluxed at 110 °C for 3 h. The mixture was then worked up as described in

Experimental Procedure B from this point onwards. Product **3-17b** was obtained as an orange solid (0.17 g, 59%). $R_f = 0.33$ (20 % EtOAc in hexanes) MP = 158 – 161 °C

1H NMR (400 MHz, $CDCl_3$) $\delta = 8.52$ (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 7.1$ Hz, 1H), 7.40 (t, $J = 7.0$ Hz, 1H), 7.34 (t, $J = 7.4$ Hz, 1H), 2.85 – 2.69 (m, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 1.42 (d, $J = 6.6$ Hz, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 205.5$, 204.0, 171.2, 134.9, 130.9, 129.0, 126.2, 124.3, 118.7, 116.9, 67.1, 35.4, 28.8, 26.2, 16.0, 10.1 IR_{ATR} (cm^{-1}) 2936, 1708, 1607, 1455, 1364, 1305, 1190, 1153, 1128, 1080, 754.

HRMS m/z [M+] 297.1365 (calcd for $C_{18}H_{19}NO_3$, 297.1365)

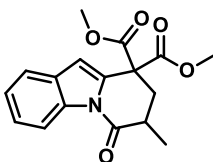


methyl 9-acetyl-7,10-dimethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-9-carboxylate (3-17c)

To an oven-dried round bottom was added acylated indole **3-16a** (0.25 g, 1.25 mmol), methyl acetoacetate (0.73 g, 6.25 mmol, 0.67 mL), K_2CO_3 (0.09 g, 0.63 mmol), 8 mL of THF and one drop of water. The flask was equipped with reflux condenser and the mixture heated at 55 °C for 24 h at which point starting materials had been consumed. To the reaction was then added $Mn(OAc)_3$ (2.35 g, 8.75 mmol) and AcOH (10 mL) and reacted at 110 °C for 6 h. The mixture was then worked up as described in **Experimental Procedure B** from this point onwards. Product **3-17c** was

obtained as a yellow solid (0.21 g, 54%). Rf = 0.34 (20% EtOAc in hexanes) MP = 107 – 111 °C

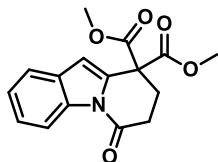
¹H NMR (400 MHz, CDCl₃) diastereomers δ = 8.50 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.41 – 7.27 (m, 2H), 3.84 (diastereomer a) and 3.78 (diastereomer b) (s, 3H), 2.97 – 2.66 (m, 2H), 2.45 – 2.31 (m, 1H), 2.27 (diastereomer a) and 2.23 (diastereomer b) (s, 3H), 2.20 (diastereomer a) and 2.17 (diastereomer b) (s, 3H), 1.44 (diastereomer b) (d, J = 6.8 Hz, 3H) and 1.38 (diastereomer a) (d, J = 6.7 Hz, 3H) **¹³C NMR (101 MHz, CDCl₃)** (both diastereomer a and b) δ = 202.8, 202.2, 171.0, 170.9, 169.4, 134.6, 130.9, 130.8, 129.1, 127.8, 124.0, 118.6, 118.4, 118.1, 116.8, 116.7, 116.5, 62.9, 59.9, 53.2, 53.2, 36.5, 35.7, 35.5, 35.0, 28.1, 25.4, 16.0, 15.5, 9.5, 9.3 **IR_{ATR} (cm⁻¹)** 2952, 1716, 1456, 1365, 1307, 1239, 1153, 1130, 1084, 754. **HRMS m/z [M⁺]** 313.1312 (calcd for C₁₈H₁₉NO₄, 313.1314)



dimethyl 7-methyl-6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (3-17d)

Following **Experimental Procedure B**, **3-17d** was synthesized from acryloyl indole 3-16b (0.25 g, 1.35 mmol), dimethyl malonate (0.27 g, 2.02 mmol, 0.23 mL), NaH (0.081 g, 2.02 mmol) in 9 mL of THF. Following completion of the Michael addition was then added Mn(OAc)₃ (2.53 g, 9.40 mmol) and acetic acid (11 mL). 3-17d was isolated as a pale orange solid (0.18 g, 45%). Rf = 0.27 (20 % EtOAc in hexanes). MP = 109 – 113 °C

¹H NMR (400 MHz, CDCl₃) δ = 8.48 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.28 (m, 1H), 6.68 (s, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 2.80 (ddd, J = 13.3, 6.7, 4.5 Hz, 1H), 2.72 (dd, J = 13.6, 4.5 Hz, 1H), 2.51 (t, J = 13.5 Hz, 1H), 1.43 (d, J = 6.8 Hz, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ = 171.0, 169.6, 168.8, 135.4, 133.0, 129.3, 125.5, 124.3, 120.8, 116.8, 109.2, 55.7, 53.7, 42.0, 36.4, 35.3, 15.9. **IR_{ATR} (cm⁻¹)** 2956, 2923, 2852, 1746, 1708, 1437, 1300, 1144, 1063, 836. **HRMS m/z [M⁺]** 315.1112 (calcd for C₁₇H₁₇NO₅, 315.1107).

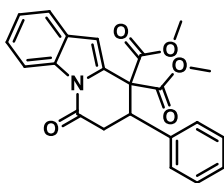


dimethyl 6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (3-17e)

Following **Experimental Procedure B**, 3-17e was synthesized from acryloyl indole 3-16c (0.30 g, 1.75 mmol), dimethyl malonate (0.27 g, 2.60 mmol, 0.30 mL), NaH (0.10 g, 2.60 mmol) in 12 mL of THF. Following the completion of the Michael addition, Mn(OAc)₃ (3.27 g, 12.2 mmol) was then added with 14 mL of acetic acid. **15e** was isolated as an orange oil (0.20 g, 38%) R_f = 0.17 (20% EtOAc in hexanes).

Or alternative procedure from indoline 3-18: Acylated indoline 3-18 was synthesized following literature procedure.¹²² To a round bottom under argon was added THF (6 mL) followed by NaH (0.10 g, 2.60 mmol) followed by dimethyl malonate (0.34 g, 2.6 mmol, 0.3 mL) dropwise via syringe and the mixture was allowed to stir for 15 min. Acylated indoline **3-18** (0.3 g, 1.70 mmol) dissolved in 5 mL THF was added to the reaction via syringe and the reaction was monitored by TLC for completion of the Michael addition. Upon completion, to the flask was added 17 mL acetic acid and Mn(OAc)₃ (4.02 g, 15.0 mmol) and the round bottom equipped with a reflux condenser. The mixture was heated to reflux for 22 h at which point TLC confirmed the reaction was complete. The mixture was cooled to room temperature and filtered through a pad of celite and rinsed thoroughly with ethyl acetate. The crude mixture was concentrated *in vacuo* and then subjected to flash column chromatography to isolate **3-17e** as an orange oil (0.083 g, 16%) the collected fraction from the column were washed once with 1M NaOH to remove traces of dimethyl malonate. R_f = 0.17 (20% EtOAc in hexanes)

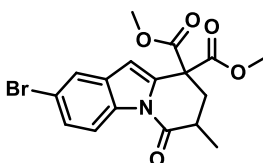
¹H NMR (400 MHz, CDCl₃) δ = 8.47 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.69 (s, 1H), 3.84 (s, 6H), 2.85 – 2.78 (m, 2H), 2.68 (t, *J* = 6.6 Hz, 2H) **¹³C NMR (101 MHz, CDCl₃)** δ = 168.0, 166.6, 134.3, 131.8, 128.0, 124.6, 123.4, 119.8, 115.8, 108.4, 54.4, 52.7, 29.9, 27.5 **IR (cm⁻¹)** **HRMS** *m/z* [M⁺] 301.0959 (calcd for C₁₆H₁₅NO₅, 301.0950)



dimethyl 6-oxo-8-phenyl-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (3-17f)

Following **Experimental Procedure B 3-17f** was synthesized from acryloylindole **3-16d** (0.30 g, 1.21 mmol), dimethyl malonate (0.24 g, 1.80 mmol, 0.21 mL), NaH (0.072 g, 1.80 mmol) in 8 mL of THF. Followed up with Mn(OAc)₃ (2.28 g, 8.50 mmol) and acetic acid (10 mL). **3-17f** was isolated as a white solid (0.12 g, 27%) R_f = 0.25 (20% EtOAc in hexanes). MP = 54 – 57 °C

¹H NMR (400 MHz, CDCl₃) δ = 8.55 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.33 (td, *J* = 7.5, 1.1 Hz, 1H), 7.22 – 7.12 (m, 3H), 7.01 (s, 1H), 6.96 (dd, *J* = 7.5, 2.0 Hz, 2H), 4.26 (dd, *J* = 6.0, 4.3 Hz, 1H), 3.76 (s, 3H), 3.72 – 3.65 (m, 1H), 3.55 (s, 3H), 3.08 (dd, *J* = 17.7, 4.3 Hz, 1H) **¹³C NMR (101 MHz, CDCl₃)** δ = 168.6, 167.5, 167.4, 138.8, 135.0, 131.3, 129.6, 128.9, 128.0, 125.7, 124.5, 121.0, 117.0, 112.9, 77.5, 58.7, 53.8, 53.0, 44.7, 42.0, 38.2 **IR_{ATR} (cm⁻¹)** 3034, 2953, 1736, 1696, 1452, 1371, 1323, 1234, 1202, 1167 **HRMS *m/z* [M⁺]** 377.126904 (calcd for C₂₂H₁₉NO₅, 377.12632)

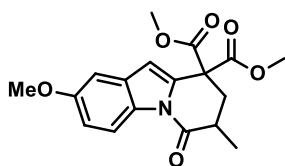


dimethyl 2-bromo-7-methyl-6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (3-17g)

Following **Experimental Procedure B 3-17g** was synthesized from acryloyl-indole **3-16e** (0.30 g, 1.14 mmol), dimethyl malonate (0.22 g, 1.70 mmol, 0.19 mL), NaH (0.068 g, 1.70 mmol) in 8 mL THF, then followed with Mn(OAc)₃ (2.14 g, 8.00 mmol) in acetic acid (10 mL). **3-17g** was isolated as a yellow solid (0.28 g, 63%) R_f = 0.29 (20% EtOAc in hexanes) MP = 118 – 122 °C

¹H NMR (400 MHz, CDCl₃) δ = 8.35 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.44 (d, *J* = 10.7 Hz, 1H), 6.62 (s, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 2.80 (ddd, *J* = 13.2, 6.7, 4.6 Hz, 1H), 2.73 (dd, *J* = 13.6, 4.5 Hz, 1H), 2.51 (t, *J* = 13.5 Hz, 1H), 1.43 (d, *J* = 6.8 Hz, 3H) **¹³C NMR (101 MHz, CDCl₃)** δ = 170.7, 169.1, 168.3, 134.1, 133.9, 130.9, 128.2, 123.3, 118.0, 117.4, 108.2, 55.5, 53.6, 36.1, 35.1, 15.6 **IR_{ATR} (cm⁻¹)** 1738, 1445, 1383, 1352,

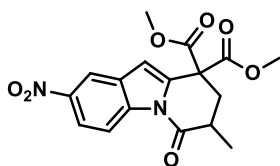
1305, 1268, 1242, 1183, 1148, 1075 **HRMS** m/z [M⁺] 393.0205 (calcd for C₁₇H₁₆BrNO₅, 393.0212)



dimethyl 2-methoxy-7-methyl-6-oxo-7,8-dihydropyrido[1,2-a]indole- 9,9(6H)-dicarboxylate (3-17i)

Following **Experimental Procedure B 3-17i** was synthesized from acryloyl-indole **3-16g** (0.30 g, 1.39 mmol), dimethyl malonate (0.28 g, 2.09 mmol, 0.24 mL), NaH (0.084 g, 2.09 mmol) in THF (9 mL) followed then by Mn(OAc)₃ (2.61 g, 9.70 mmol) and acetic acid (11 mL). **3-17i** was isolated as a pale-yellow solid (0.29 g, 61%). R_f = 0.24 (25% EtOAc in hexanes) MP = 117 – 120 °C

¹H NMR (400 MHz, CDCl₃) δ = 8.36 (d, J = 8.9 Hz, 1H), 7.02 – 6.87 (m, 2H), 6.61 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 2.83 – 2.65 (m, 2H), 2.50 (t, J = 13.4 Hz, 1H), 1.42 (d, J = 6.7 Hz, 3H) **¹³C NMR (101 MHz, CDCl₃)** δ = 170.6, 169.6, 168.7, 156.9, 133.5, 130.3, 130.1, 117.5, 113.8, 109.1, 103.6, 55.8, 53.7, 36.4, 35.1, 15.9 **IR_{ATR} (cm⁻¹)** 2955, 2837, 1732, 1615, 1435, 1383, 1105, 1073, 1030, 912.9 **HRMS** m/z [M⁺] 345.1221 (calcd for C₁₈H₁₉NO₆, 345.1212)

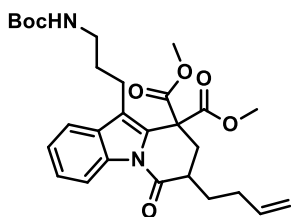


dimethyl 7-methyl-2-nitro-6-oxo-7,8-dihydropyrido[1,2-a]indole- 9,9(6H)-dicarboxylate (3-17h)

Following **Experimental Procedure B 3-17h** was synthesized from acryloyl-indole **3-16f** (0.30 g, 1.30 mmol), dimethyl malonate (0.26 g, 1.95 mmol, 0.22 mL), NaH (0.078 g, 1.95 mmol) in 9 mL of THF, followed by Mn(OAc)₃ (2.44 g, 9.10 mmol) and acetic acid (11 mL). **3-17h** was isolated as a white solid (0.17 g, 36%). R_f = 0.34 (30% EtOAc in hexanes). MP = 135 – 140 °C

¹H NMR (400 MHz, CDCl₃) δ = 8.58 (d, J = 9.5 Hz, 1H), 8.43 (d, J = 2.3 Hz, 1H), 8.22 (dd, J = 9.1, 2.3 Hz, 1H), 6.83 (s, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 2.86 (dq, J = 13.5, 6.9, 4.6 Hz, 1H), 2.76 (dd, J = 13.8, 4.5 Hz, 1H), 2.53 (t, J = 13.6 Hz, 1H), 1.45 (d, J = 6.8

Hz, 3H) ^{13}C NMR (101 MHz, CDCl_3) δ = 171.1, 168.9, 168.2, 144.7, 138.3, 136.3, 129.3, 120.7, 117.0, 109.5, 55.6, 54.0, 36.0, 35.4, 15.7 IR_{ATR} (cm^{-1}) 3128, 2959, 1739, 1717, 1562, 1516, 1443, 1333, 1232, 1174 HRMS m/z [M^+] 360.0954 (calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_7$, 360.0958)



dimethyl 7-(but-3-en-1-yl)-10-(3-((tert-butoxycarbonyl)amino)propyl)-6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (3-17j)

Following **Experimental Procedure B**, 3-17j was synthesized from acryloyl indole **3-16h** (0.26 g, 0.69 mmol), dimethyl malonate (0.18 g, 1.39 mmol, 0.16 mL), NaH (0.06 g, 1.39 mmol) in 5 mL of THF. Upon the completion of the Michael addition, to the reaction mixture was added $\text{Mn}(\text{OAc})_3$ (1.11 g, 4.14 mmol) and 10 mL of MeOH (instead of acetic acid). The mixture was heated under argon at 65 °C for a minimum of 20 h before proceeding with work-up as per **Experimental Procedure B**. 3-17j was isolated as a white solid (0.11 g, 30%) R_f = 0.27 (25% EtOAc in hexanes). MP = 106 – 110 °C

^1H NMR (400 MHz, CDCl_3) δ = 8.50 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.1 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 5.83 (ddt, J = 17.2, 10.2, 6.3 Hz, 1H), 5.13 – 5.00 (m, 2H), 4.81 (br, s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.42 (dt, J = 12.4, 6.0 Hz, 2H), 2.93 – 2.83 (m, 2H), 2.77 – 2.59 (m, 2H), 2.38 (t, J = 13.1 Hz, 1H), 2.33 – 2.17 (m, 3H), 1.67 (q, J = 8.3 Hz, 1H), 1.43 (s, 9H) ^{13}C NMR (101 MHz, CDCl_3) δ = 170.5, 170.4, 168.9, 156.0, 137.5, 134.8, 128.7, 125.9, 124.3, 119.5, 119.0, 116.9, 115.9, 55.9, 53.9, 53.7, 39.3, 35.0, 30.8, 28.9, 28.6 IR (cm^{-1}) 3272, 2956, 1736, 1697, 1456, 1377, 1242, 1167, 1075, 76 HRMS m/z [M^+] 498.2361 (calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_7$, 498.2366)

3.7 References

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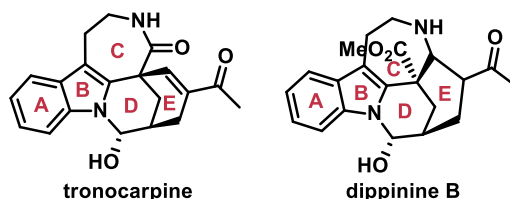
Chapter 4 : Progress Towards the Total Synthesis of Tronocarpine and Dippinine B

The work outlined in this chapter is unpublished.

4.1 Introduction and Overview

Tronocarpine and dippinine B (**Scheme 60**) are natural products isolated from the Malaysian tree, *Tabernaemontana corymbosa*. Many of the alkaloids found in this plant exhibit anti-malarial and antibiotic activity. Tronocarpine contains a novel pentacyclic framework and a 7-membered lactam not usually seen amongst previously isolated vobasiny-iboga indoles.

Outlined in this chapter is the progress, trials, and tribulations towards accessing the first total syntheses of tronocarpine and dippinine B. At the focal point of this total synthesis lies the methodology discussed in Chapter 3; Mn(III) radical cyclizations involving indoles. It is this chemistry that is used to make the main scaffold of tronocarpine.



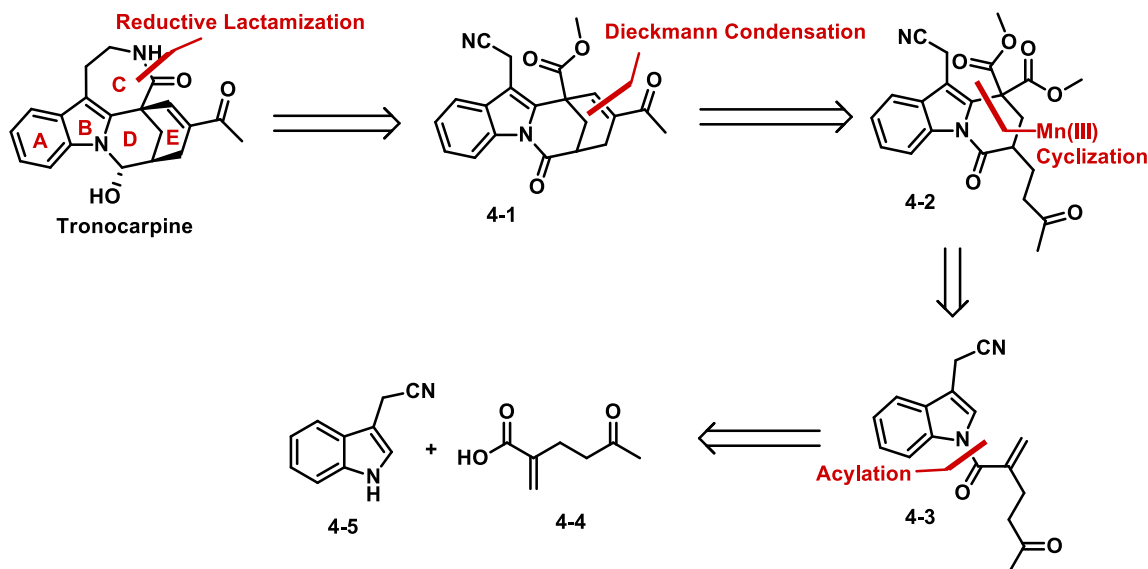
Scheme 60 – Natural product targets in Chapter 4, tronocarpine and dippinine B.

4.2 First Retrosynthetic Analysis of Tronocarpine and Dippinine B

Analyzing the bond connections of tronocarpine we strategized that its first total synthesis could be completed as outlined in **Scheme 61**. Working through **Scheme 61**: reductive lactamization of cyanoindole intermediate **4-1** will form the 7-membered C ring of tronocarpine. The reduction of the cyano group followed by lactamization on the available ester has precedent in past Kerr group work using Raney nickel and H₂.¹²³ Reduction of the ketone adjacent to the indole nitrogen (**4-1**) will fashion the desired

alcohol seen in tronocarpine. A Dieckmann condensation between the methyl ketone and diastereotopically available ester of **4-2** would fashion the E ring of tronocarpine.

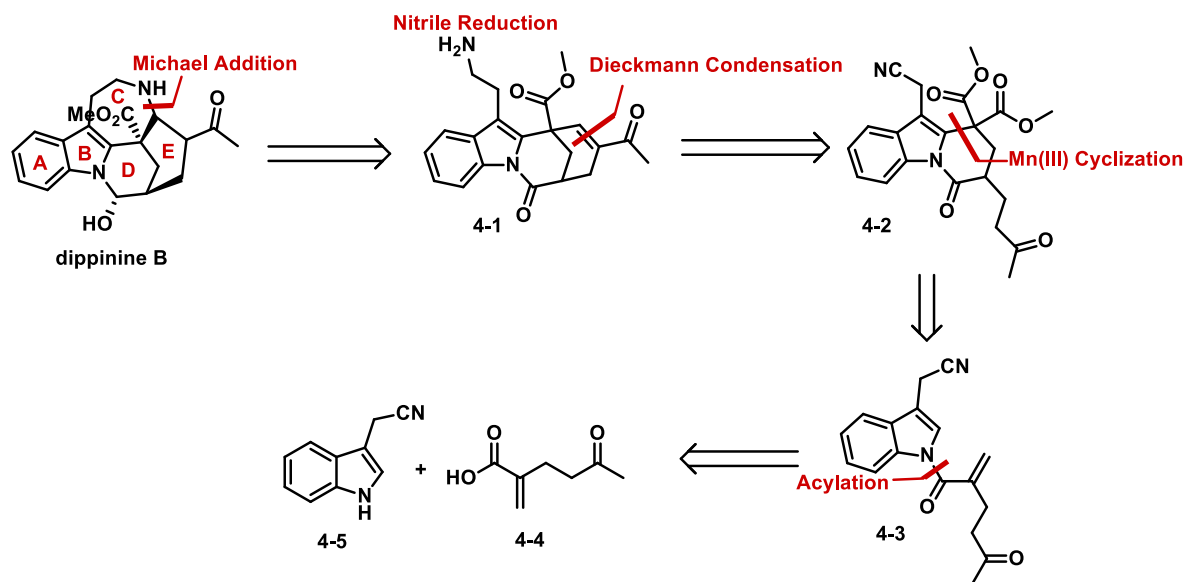
Oxidative manipulation will be required to install the α, β -unsaturation of compound **4-1**.



Scheme 61 - Retrosynthetic Analysis 1: First proposed route to tronocarpine

Manganese (III) mediated radical cyclization will construct the D ring of **4-2**. This would come from elaborated acryloyl indole **4-3** using the one-pot Michael addition, radical cyclization outlined in Chapter 3. To fashion elaborated indole **4-3**, acylation of commercially available indole-3-acetonitrile (**4-5**) with acrylic acid **4-4**, would map the carbons required for tronocarpine.

Examining dippinine B, the retrosynthetic analysis (**Scheme 62**) is identical to tronocarpine, but instead of reductive lactamization to construct the ring C, a Michael addition of nitrile reduced substrate **4-1** is required.



Scheme 62 - Retrosynthetic Analysis 2: Proposed route to dippinine B

Tronocarpine and dippinine B differ only in the connection of their tryptamine chain amine; access to both natural products would likely occur from the same intermediates. For this reason, often just one natural product is discussed, but we were always mindful that either natural product may be synthesized depending on the reactivity of the tryptamine chain. At any point, we could have generated either tronocarpine or dippinine B when trying to close the final rings; tronocarpine requiring a lactamization with one of the esters, and dippinine B requiring a Michael addition with the α,β -unsaturated methyl ketone.

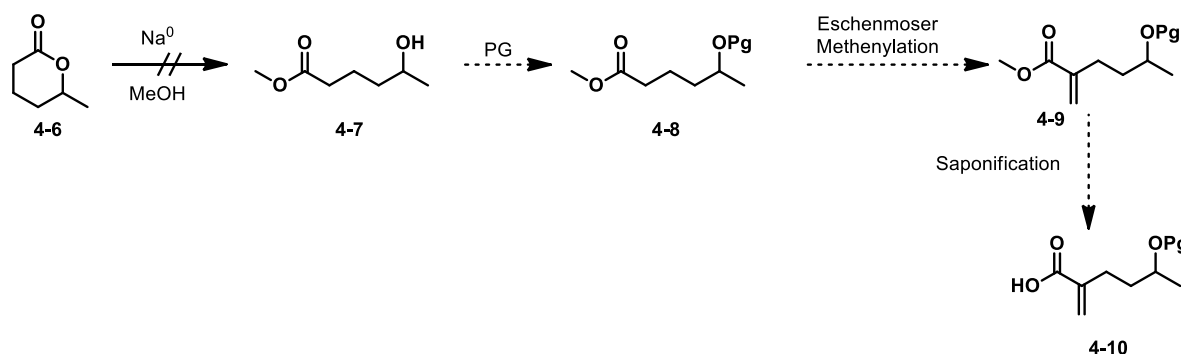
Common to both retrosynthetic analyses is acrylic acid **4-4**, and this target was the first focus of our synthetic efforts.

4.3 First Generation Synthetic Route Towards Tronocarpine

4.3.1 Accessing Acrylic Acid 4-4

Initial work had me hopeful starting from commercially available δ -hexanolactone **4-6**. We proposed that opening lactone **4-6** with sodium methoxide NaOMe, to generate ester **4-7**, would put a functional alcohol handle in the correct spot for the required ketone in acrylic acid **4-4** (Scheme 63). The protected alcohol (**4-8**) could later be oxidized to the

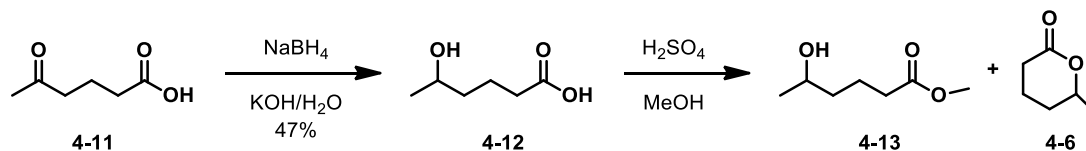
methyl ketone and Eschenmoser's methenylation would provide the acrylic olefin of **4-10**.^{124,125}



Scheme 63 - First work towards synthesizing acrylic acid **4-4**

Unfortunately, opening lactone **4-6** proved troublesome, and re-lactonization of **4-7** back to starting material was prevalent during attempts to purify the material.

We turned our attention to 4-acetylbutyric acid (**4-11**) as a better starting material for synthesizing acid **4-4** (Scheme 64). Though the ketone of **4-11** was ideal for the end goal, its existence would prove to be a chemoselective nightmare for furnishing the olefinic component of **4-4**. A redundant reduction and protection was first performed. Reduction of ketone **4-11** was trivial with NaBH_4 , but low yielding (**4-12**, 47%). Esterification to set up the precursor for Eschenmoser chemistry (**4-13**) worked, but was also low yielding, returning some δ -hexanolactone **4-6**. This route was quickly abandoned even though alternatives, such as alcohol protection, could have afforded more of the desired material.

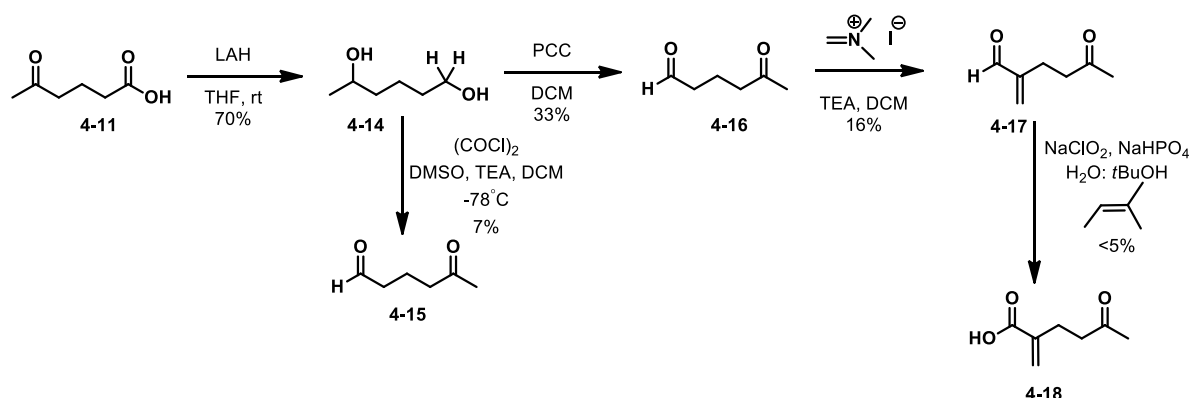


Scheme 64 - Failed route to acrylic acid **4-4** from 4-acetylbutyric acid

Rather than chemoselectively reducing the ketone of **4-11**, reduction of both the acid and ketone resulted in diol **4-14** (Scheme 65). The diol was successfully oxidized via Swern protocol or using PCC (**4-15** and **4-16**). PCC proved higher yielding, isolating 33% of

aldehyde **4-16**. Aldehyde in hand, first attempts of Eschenmoser's methenylation were performed. Success was achieved in a low yielding 16% of acrylate **4-17**. Pinnick oxidation of this material to isolate acrylic acid **4-18** worked, but crudely, and in an unviable <5% yield. Ultimately, the pathway in **Scheme 65** was plagued with low yields and a step-count that could only make a fit-bit user happy. This was not the ideal start to any synthesis.

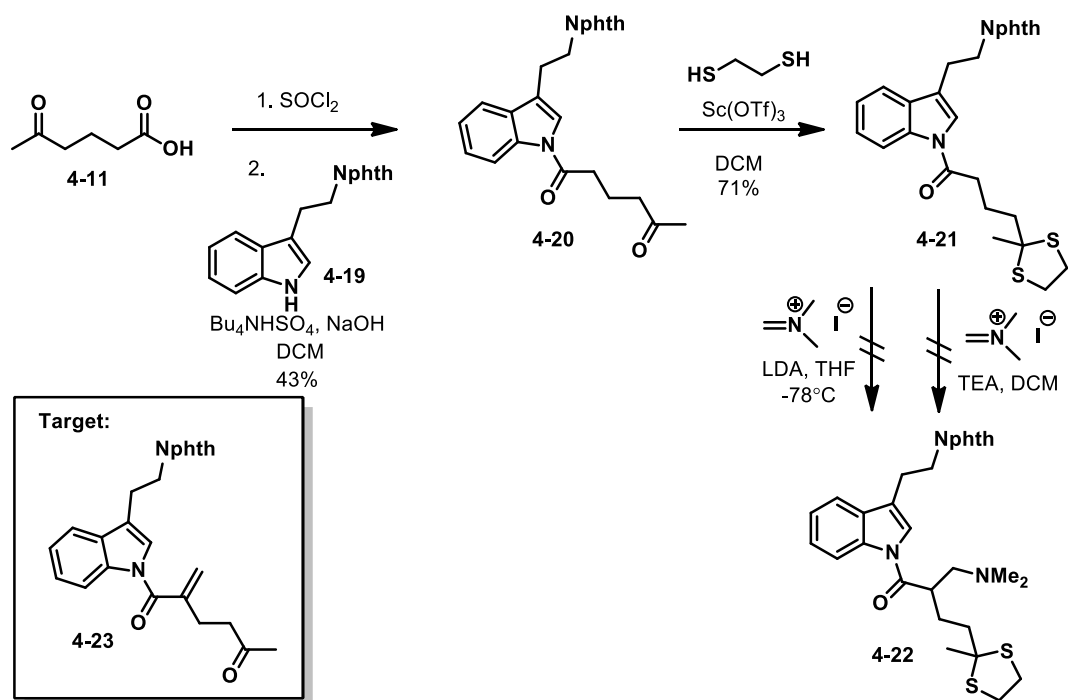
Hitting multiple dead-ends and finding it troublesome to prevent lactonization of the material being isolated, our attention had to switch to alternative routes. We hypothesized that acylation of material on to the indole first would yield a more robust substrate to work with.



Scheme 65 - Unviable route to acrylic acid 4-4.

4.3.2 Acylation of Indole First: Attempt to Access Acrylic Acid Chain

From the work in Chapter 3, the capability to acylate indoles consistently and with varying functionality, suggested an alternative route accessing intermediate **4-23** with the acryloyl component tethered to the indole nitrogen. I could take the available 4-acetylbutyric acid **4-11**, and acylate phthalimide protected tryptamine **4-19** or indole-3-acetonitrile **4-5**. I could later install the required alkene component (**Scheme 66**).

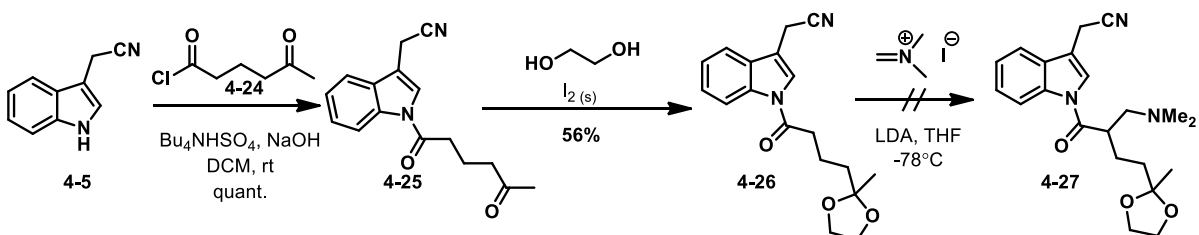


Scheme 66 - Synthetic route attempting to access acryloyl tryptamine intermediate 4-23.

Acid **4-11** smoothly converted to its acid chloride with SOCl_2 , and acylation to phthalimido-tryptamine **4-19** was successful in 43% yield over two steps. Phthalimido-tryptamine (**4-19**) was used because it was available in the lab, and indole-3-acetonitrile was expensive for pursuing optimized conditions. Protecting the ketone of intermediate **4-20** with ethanethiol resulted in thioacetal **4-21** in a 71% yield. This would inhibit any alternate Eschenmoser products in the next step. Unfortunately, attempts at the methenylation did not provide any desired product, and progression to desired acryloyl indole **4-23** was halted.

At this point, concerns regarding the use of a phthalimide protecting group were brought forward. Previous Kerr group member Bryan Landschoot had troubles getting $\text{Mn}(\text{III})$ radical chemistry to work on substrates that made use of the protecting group. To avoid future complications, the phthalimide protected tryptamine was abandoned and this route was reconsidered. Switching to indole-3-acetonitrile as per the original retrosynthesis, resulted in yet another dead-end (**Scheme 67**).

Per **Scheme 67**, acylation of **4-5** resulted in a higher yield of acryloyl indole **4-25** (>94%), and ketone protection with the more easily removed acetal of ethylene glycol was performed. **4-26** was isolated in a 56% yield. Eschenmoser olefination attempts were again fruitless under different bases and product **4-27** failed to be isolated.



Scheme 67 - Indole-3-acetonitrile as a starting indole in the attempt to isolate acryloyl indole 4-23

The Eschenmoser methenylation route to install the necessary α,β -unsaturated component of a Michael acceptor was proving to be the wrong strategy to synthesize natural products tronocarpine and dipinine B. A completely different route needed to be established.

4.3.3 Successful Generation of Acrylic Acid 4-28 and Optimization of the Synthetic Route

Attempts at synthesizing product **4-4** failed repeatedly and with methenylation proving troublesome, an alternate route was sought. Masking the ketone in earlier synthetic attempts was redundant, and we had worries it was going to become a difficult task to either: 1) unmask the ketone in whatever its protected form was or 2) prevent it from interfering with important reactions to come. In a group meeting with visiting speaker Alison Frontier, had the wisdom to suggest masking the ketone as a terminal olefin, removing all worries of chemoselective issues to come. The terminal olefin could be oxidized by a Wacker oxidation and allow control over when the ketone came into play. This proved to be an exceptional idea and the new synthetic target of **4-28** was realized (**Figure 15**).

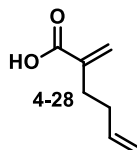
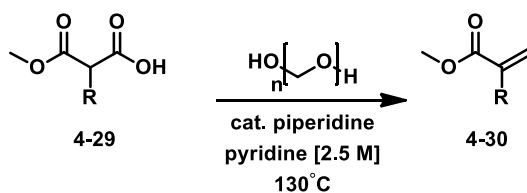


Figure 15 - New acrylic acid target 4-28

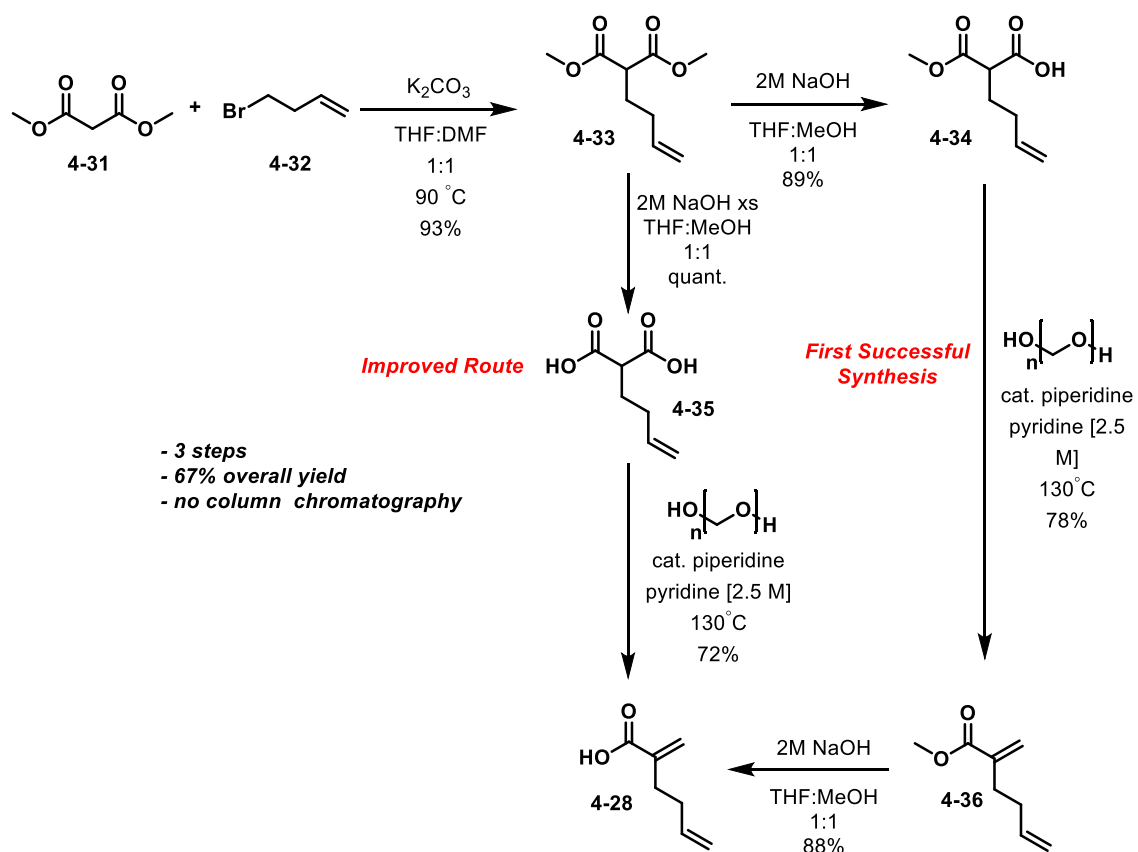
This new target would serve its purpose of being a suitable acylating reagent with indole-3-acetonitrile; it contained both the appropriate Michael accepting functionality, and the olefin capable of interconversion via Wacker oxidation to the ketone for Dieckmann cyclization.

Work published by Stetter *et al.* used hemimalonate esters (**4-29**) in the presence of formaldehyde, pyridine, and catalytic piperidine to perform decarboxylative Mannich-type reactions that generated acrylic esters (**4-30**) (**Scheme 68**).¹²⁶



Scheme 68- Stetter's work generating acrylic esters.

With knowledge of Stetter's work, I needed to develop a hemimalonate compound with the appropriate terminal alkene-bearing chain (**4-34**). **Scheme 69** outlines the chemical pathway to successfully generate acrylic acid **4-28**. Starting from dimethylmalonate (**4-31**), alkylation with 4-bromo-1-butene (**4-32**) generated alpha-substituted product **4-33** in a high 93% yield and at sufficient purity to avoid the use of column chromatography. The first route used a monosaponification of product **4-33** to access hemimalonate **4-34** in an 89% yield without requiring column purification. From the hemimalonate **4-34**, Stetter's decarboxylative Mannich-type reaction was employed and I were thrilled to isolate a 78% yield of acrylic ester **4-36**. Saponification of ester **4-36** generated an 88% yield of **4-28** for the first successful synthesis of an acrylic acid we sought. This first-generation synthesis isolated product **4-28** in 4 steps and a 57% overall yield.



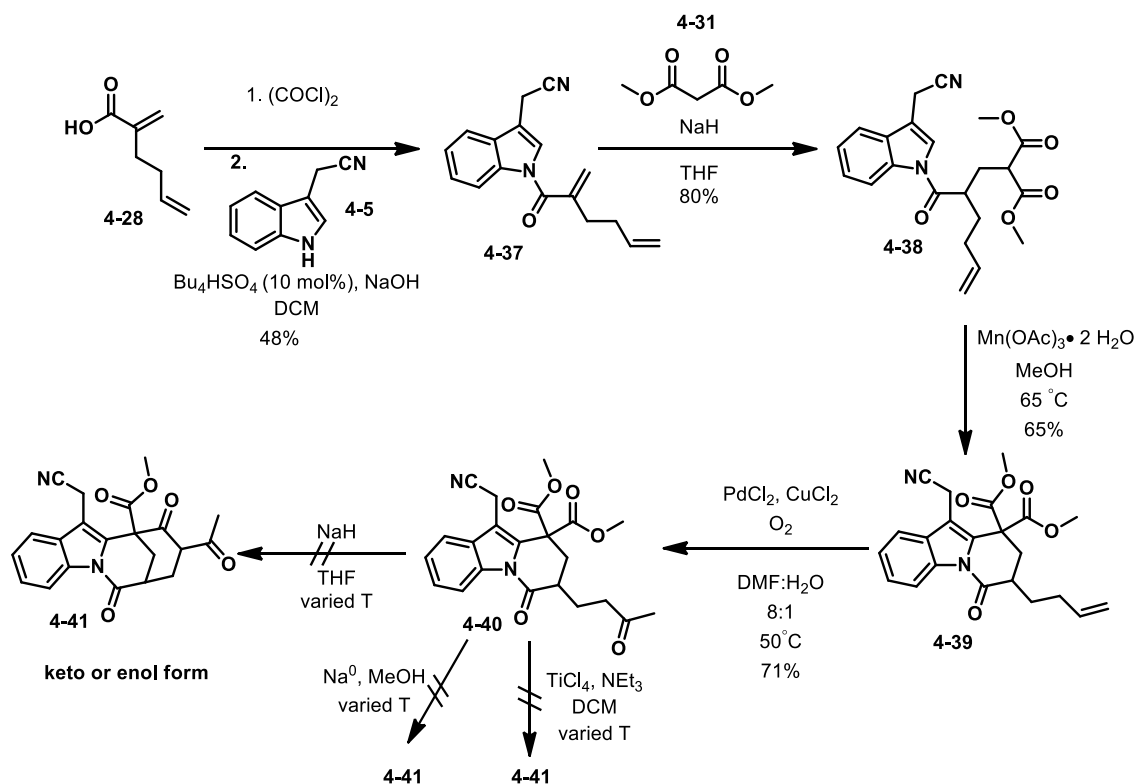
Scheme 69 - The first successful synthesis of 4-28 and its improved 3-step synthesis

However, I figured that one step could be cut from this forward synthesis to avoid working with the extremely volatile and acrid smelling **4-34**. Instead of monosaponifying product **4-33**, I performed a double saponification resulting in malonic acid **4-35**. This acid also successfully underwent the decarboxylative Mannich procedure and yielded desirable acrylate **4-28** in 3 steps and a 67% overall yield. Acid **4-28** was now easily synthesizable in large quantities (~10 g from 25 g of 4-bromo-1-butene, **4-32**) and progress towards piecing together tronocarpine could be explored further.

4.4 Second Generation Synthesis Towards Tronocarpine

4.4.1 Indole-3-acetonitrile

Acid **4-28** in hand, the second attempt at piecing together the framework of tronocarpine and dippinine B commenced and issues with this route quickly became apparent (**Scheme 70**).



Scheme 70 - Progress towards tronocarpine using indole-3-acetonitrile and acrylate 4-28.

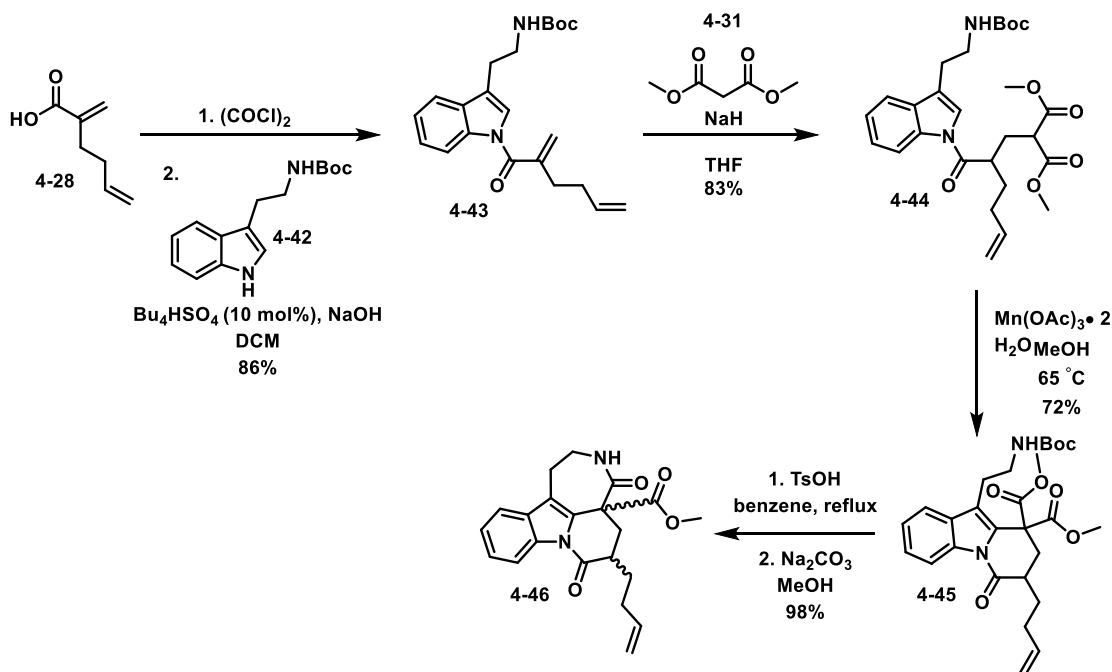
From acid **4-28** (Scheme 70), acylation of indole-3-acetonitrile (**4-5**) was troublesome, and resulted in a lot of destroyed material before realizing that after two hours, significant decomposition takes over despite indole **4-5** not being consumed. Two hours was determined to be the optimal amount of time to isolate just a 48% yield of acryloyl indole **4-37**. Many attempts were made to increase this yield because of the quantitative results achieved when acylating indole **4-5** with 4-acetylbutyric acid (**4-11**). However, this earlier reaction (Scheme 67) was complete in just 15 minutes. Although never cleanly isolated, it is suspected that a grammine-type fragmentation of indole **4-5** was occurring under these basic conditions. The maximum amount of product **4-37** isolated was 48%.

This was a significant hint that using a nitrile-substituted indole would not be ideal for the progression of this synthesis, but there was enough material to continue forward. From product **4-37**, the Michael addition with dimethyl malonate yielded tethered product **4-38** in an 80% yield (Scheme 70). The $\text{Mn}(\text{OAc})_3$ radical cyclization to the 2-

position of indole **4-39** proceeded in a respectable 65% yield and then first attempt at a Wacker oxidation resulted in a 71% yield of ketone **4-40**. Unfortunately, all attempts at a Dieckmann cyclization from this ketone product were unsuccessful. Bases such as NaH and NaOMe failed to generate any indication of product **4-41**. Decomposition was prevalent under these basic conditions. I tried a TiCl_4 catalyzed reaction to access product **4-41** and at temperatures ranging between 0 °C and -78 °C, decomposition again prevailed. With the issues of isolating product **4-41** in clean, and appreciable amounts, I hypothesized that using a boc-protected tryptamine (**4-42**) would give us more reliable results.

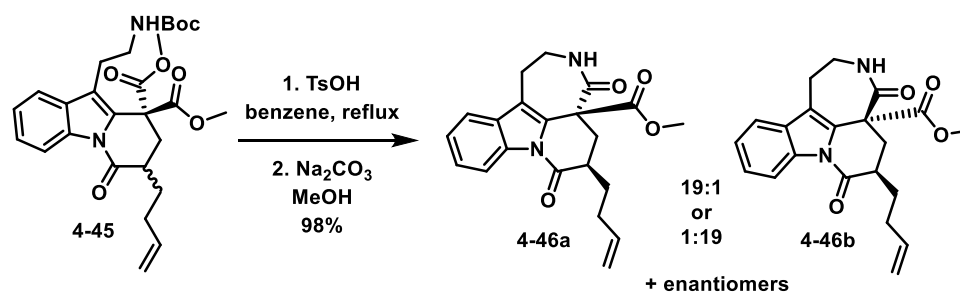
4.4.2 Boc-Tryptamine Indole Source

Chemistry was repeated using tryptamine **4-42** in place of indole-3-acetonitrile (**Scheme 71**). Initial acylation of tryptamine indole **4-42** with acrylate **4-28** proceeded in a higher 86% yield than when indole-3-acetonitrile was used, yielding **4-43** (**Scheme 71**). Michael addition with dimethylmalonate provided an 83% yield of **4-44** and the $\text{Mn}(\text{OAc})_3$ radical cyclization gave us desired 1,2-cyclized indole **4-45**.



Scheme 71 - Tryptamine as the indole source to synthesize lactam 4-46

At this point, lactamization of **4-45** was realized with the procedure outlined by Torres-Ochoa using *p*-toluenesulfonic acid followed by K_2CO_3 and methanol. The results were high yielding, generating 98% of lactam **4-46** in a single diastereomer (**Scheme 71**). Because we had performed the lactamization first, there was the possibility that the amine tether could attack either accessible ester without constraint (**Scheme 72**). It was here I hoped luck was on our side and this lactamization yielded the correct diastereomer (**4-46a**) as the molecule exists in nature (**Scheme 72**).



Scheme 72 - Possible diastereomeric results of the lactam formation 4-46.

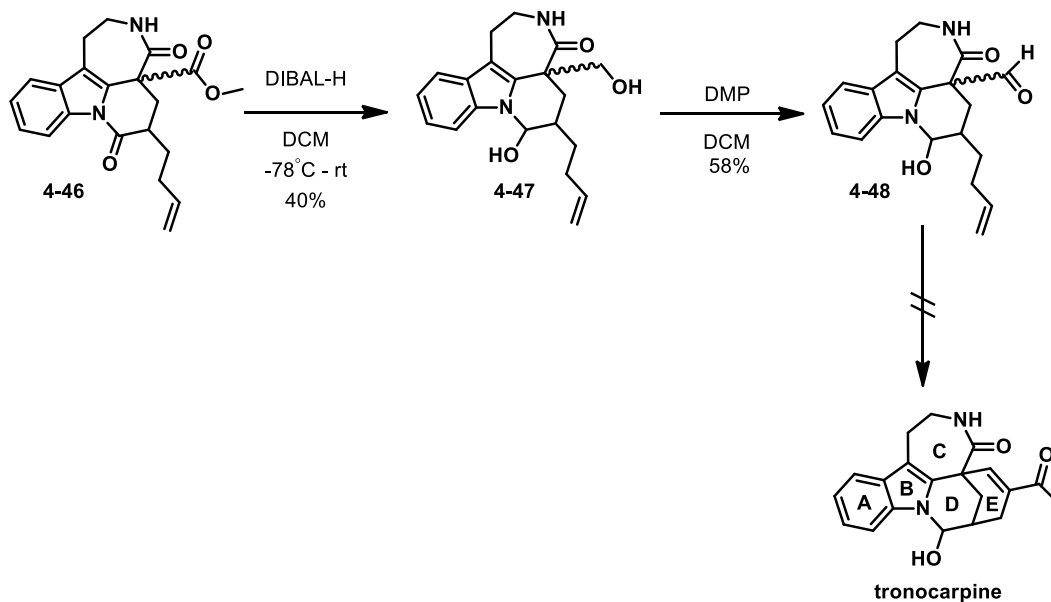
Due to geometric constraints, the wrong diastereomer (**4-46b**) of the lactamized product would not be suitable to complete the final Dieckmann cyclization to form ring E. To determine which diastereomer was isolated, we first used a 1D NOESY NMR irradiating the methyl ester protons. If the proton on the other quaternary center felt any through-space NOESY interaction to the methylester, it was likely that these protons were on the same face of the molecule (corresponding to product **4-46b**). Unfortunately, these protons were also possibly outside the detection distance of a NOESY interaction. When the NMR results were devoid of a NOESY correlation, it did not conclusively indicate that the wrong diastereomer was isolated. X-ray crystallography had to be used to determine which diastereomer of **4-46** was being generated. While crystal growing experiments were attempted, progress for generating ring D of tronocarpine was explored anyways.

4.4.3 Exploring an Aldol Reaction to Generate Ring E

3.45 g of lactam **4-46** was easily synthesized. Due to the previous shortcomings experienced when trying to complete ring E with a Dieckmann cyclization, an

intramolecular Aldol reaction was considered to form the ring. Aldehyde **4-48** (Scheme 73) would be far more reactive than ester (**4-40**), and the closed E ring would exist in the correct oxidation state seen in tronocarpine without further manipulation.

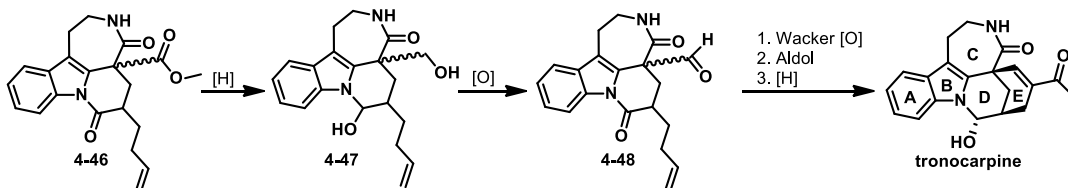
Reduction attempts of **4-46** (Scheme 73) using DIBAL-H to stop directly at the aldehyde were unsuccessful. When DIBAL-H was used at $-78\text{ }^{\circ}\text{C}$ no reaction occurred and starting material was recovered. Only upon warming the solution did we observe reduction of the indole acyl ketone and ester. The ^1H NMR evidence supported a mixture of diastereomers that was difficult to conclusively analyze as the desired product. The evidence of the indole 7-position proton shifting upfield by approximately 1 ppm indicated the reduction of indole acyl ketone **4-46** had potentially occurred. The methyl ester peak was also absent. However, it was only crude and messy mixtures of product **4-47** were isolated. The reduced product **4-47** was pushed into a DMP oxidation in attempt to get material that we could accurately elucidate, but again isolated a crude and unpurifiable mixture that had evidence of an aldehyde. This chemistry was extraordinarily finicky, unreproducible, and never gave clean results.



Scheme 73 - Attempt at accessing the full pentacyclic structure of tronocarpine

Lacking confidence in the products generated in **Scheme 73**, finding a clean and high yielding method to confidently generate diol **4-47**, preferably as one diastereomer, was sought.

Confident that an Aldol reaction would close ring E of tronocarpine, generating diol **4-47** so it could be further oxidized to product **4-48** was aggressively explored (**Scheme 74**).

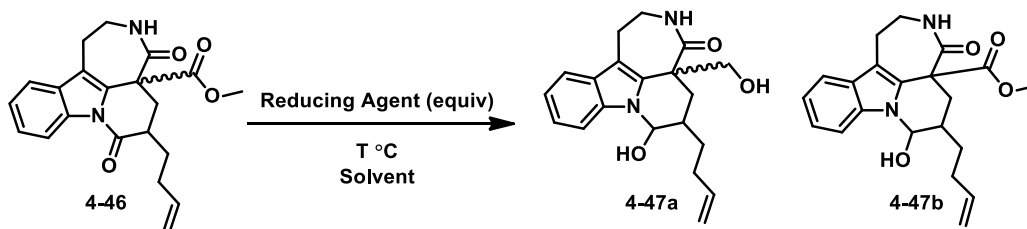


Scheme 74 - Ideal route incorporating an Aldol reaction to generate the pentacyclic framework of tronocarpine

In an attempt to isolate diol **4-47** cleanly, lactam **4-46** was subject to a variety of reducing agents under differing reaction conditions. This work is summarized in **Table 5**, and can be precisely summarized as: the methyl ester of product **4-46** is difficult to reduce, and it did not happen. It is likely that this methyl ester was sterically inaccessible.

Sterically hindered reducing agents like DIBAL-H and LiEt_3BH (**Table 5**, **entry 1** and **entry 10**) exhibited difficulty transferring hydride to the carbonyl carbon and starting material was recovered in these cases.

Table 5 - Attempts to reduce lactam 4-46 and form desired diol 4-47a



| Entry | Reducing Agent (equiv.) | Temperature (°C) | Solvent | Result or Product Yield |
|-------|-------------------------|------------------|---------|-------------------------|
| 1 | DIBAL-H (3) | -78 °C | DCM | 4-46 recovered |
| 2 | NaBH_4 (40) | reflux | MeOH | Product 4-47b |

| | | | | |
|-----|--|-------------|-----------------|---|
| 3 | DIBAL-H (5) | -78 °C | DCM | 4-46 recovered |
| 4* | DIBAL-H (10) | -78 °C | DCM | 4-46 recovered |
| 5 | LiBH ₄ | rt - 50 °C | 1:1 MeOH:THF | 4-46 recovered |
| 6 | CaCl ₂ (5), NaBH ₄ (10) | rt | 1:1 MeOH:THF | 4-47b ^{***} + Decomposition |
| 7** | DIBAL-H (5) | -78 °C - rt | DCM | 4-47a suspected as diastereomers (37%) and Product 4-47b |
| 8 | DIBAL-H (5) | rt | DCM | 4-47a suspected as diastereomers (40%) and 4-47b |
| 9 | NaBH ₄ (10), CeCl ₃ (1.5) | rt | EtOH | 4-47b (2 days) |
| 10 | LiEt ₃ BH (3) | 0 °C | DCM | 4-47b |
| 11 | LiEt ₃ BH (3) | rt | THF | 4-47a diastereomers (24%) + Product B |
| 12 | LiEt ₃ BH (10) | 0 °C | THF | Product 4-47a diastereomers (20%) + Product B |
| 13 | LiCl (5), NaBH ₄ (5) | rt | THF | SM and 4-47b |
| 14 | LAH | rt | THF | Product 4-47a (26%) Significantly one diastereomer, clean |

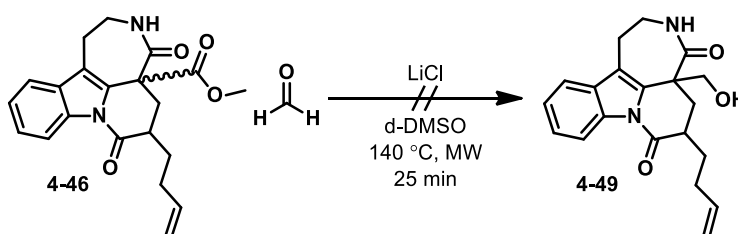
* Indicates that a different solution of DIBAL was trialed in case of decomposed/aged reagent used in previous attempts

** Indicates brand new bottle of DIBAL-H

*** Product B is undesirable and was not isolated to determine an accurate yield

A wide variety of reducing agents (LAH, LiBH₄, LiEt₃BH, DIBAL-H, NaBH₄) can reduce the indole acylated ketone, which, while good news for the final structures of tronocarpine and dippinine B, was not helpful here as the methyl ester was not reduced further. This pathway reducing the methyl ester in lactam **4-46** was not a viable pathway and no further focus was given to this route.

Additional ways to generate a more reactive ester or install a primary alcohol at that position were explored. Krapcho conditions were examined to see if the ester could be removed. It seemed plausible that the anion produced *in situ* could attack paraformaldehyde to generate a primary alcohol without the use of reductive conditions, thereby removing the possibility of also reducing the indole acyl ketone (**Scheme 75**). Unfortunately, this chemistry was also unsuccessful and under forcing microwave conditions, starting materials were recovered along with evidence of the hydrogen-containing Krapcho product (**Scheme 75**).



Scheme 75- Krapcho attempt to install alcohol chain via attack of paraformaldehyde

4.4.4 Crystal Structure and Attempts to Epimerize the Diastereotopic Center

Results of the X-ray crystal structure returned with unfortunate news. The amine had closed selectively onto the wrong ester leaving the remaining existing in the opposite plane of the alkene chain (**4-46b**) (**Figure 16**). These results meant that closure of ring E via the planned Dieckmann cyclization would be impossible unless the chain alpha to the indole acyl ketone was epimerized.

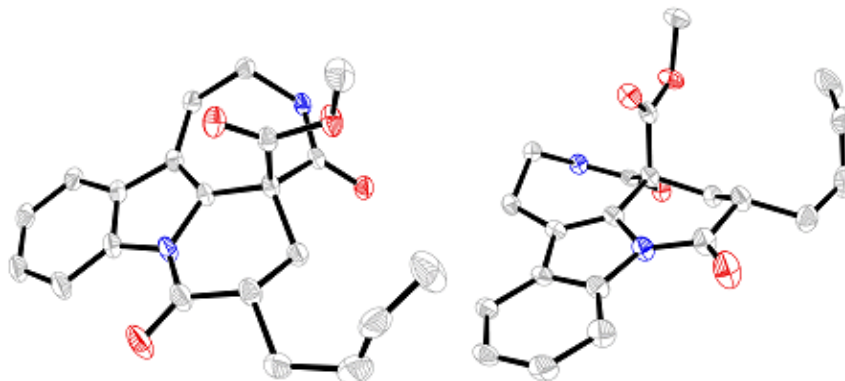


Figure 16 - Crystal structure of lactam product 4-46 indicating undesirable diastereochemistry

To test if epimerization was possible, lactam **4-46b** was deprotonated with LDA and quenched with D₂O. NMR results of this experiment concluded that exclusive deprotonation of the amide N-H had occurred (**Figure 17**). Knowing the amide proton was so easily removed allowed for re-examination of our pathway to ensure that we kept that proton protected while making any transformations under basic conditions. A route in which I explore protections of this amine are discussed *in vide*.

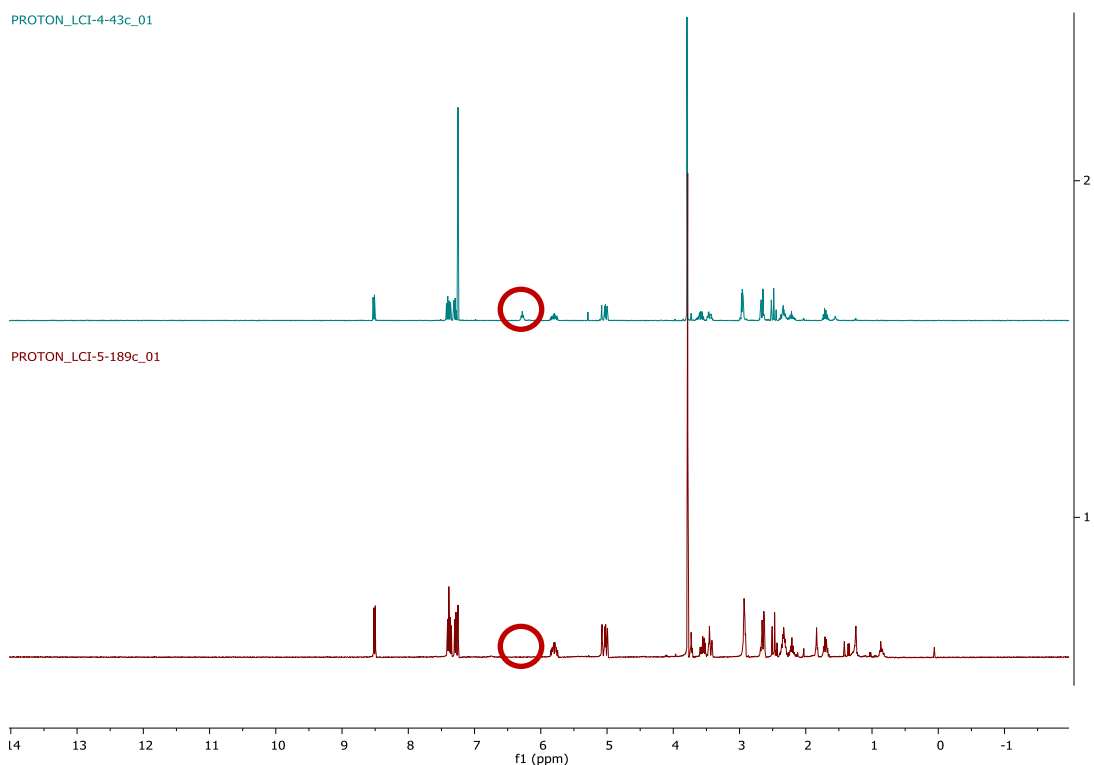
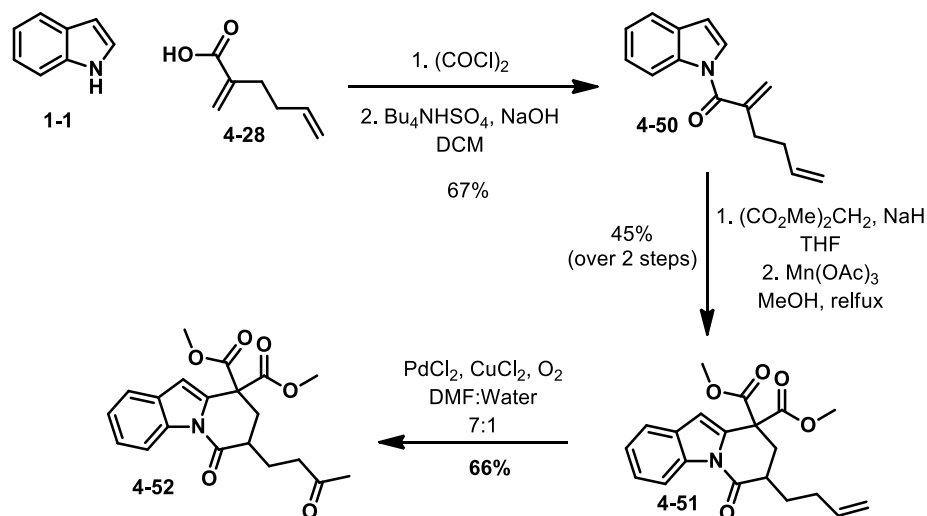


Figure 17 - ^1H NMR of deprotonated lactam showing loss of amide proton when quenched with D_2O

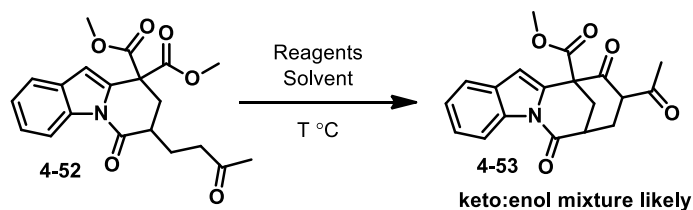
Due to the unfavourable chemical complications caused by the tryptamine chain, I opted to explore a brief model study using indole as our acylating substrate. With a lack of acidic protons, I hoped that this model would provide positive evidence that the E ring of tronocarpine could be formed by Dieckmann type condensation. The results of this model study are outlined in **Scheme 76** and **Table 6**. Acylation with indole proceeded smoothly to product **4-50** and radical cyclization afforded tricyclic product **4-51** in a 45% yield over 2 steps. The Wacker oxidation isolated ketone **4-53** in a 66% yield.



Scheme 76- Model study using indole to isolate tricyclic product 4-52 for cyclization testing

Product **4-52** in hand, attempts to cyclize the enol of the ketone to one of the esters (**4-53**) moved forward. The results of these ring-closing attempts are outlined in **Table 6**.

Table 6 - Experimental conditions explored to generate product 4-53



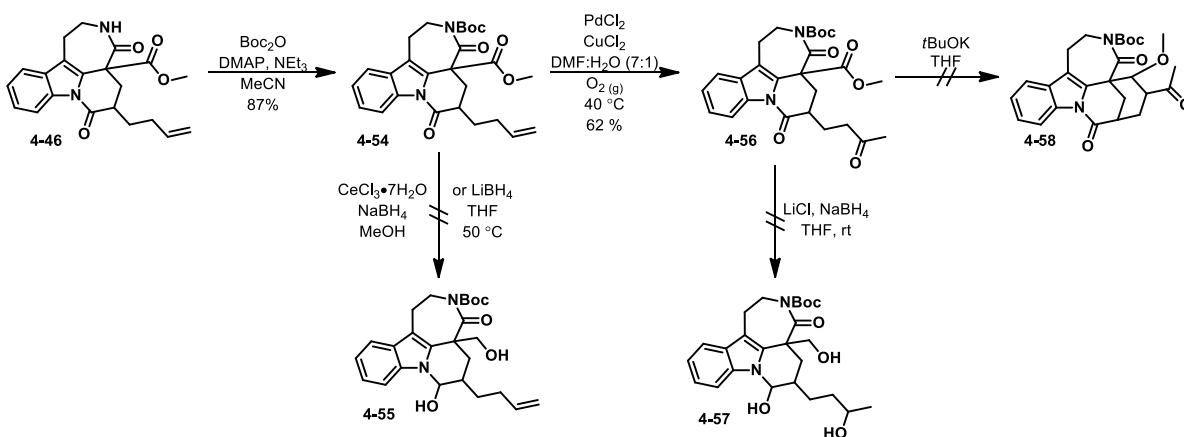
| Entry | Reagent | Solvent | Temperature (°C) | Result |
|-------|--------------------------------------|---------|------------------|---------------|
| 1 | NaH | THF | 25 | decomposition |
| 2 | NaH, MgI ₂ | THF | 25 | decomposition |
| 3 | TiCl ₄ , NEt ₃ | DCM | -10 | decomposition |

The model study provided little proof that we could successfully close ring E of tronocarpine via ketone to ester Dieckmann cyclization. At this point, and to work around

the difficulties of E-ring formation via Dieckmann, I thought varying the Michael addition nucleophile could impart alternative reactivity that would allow us to close this difficult ring. In addition to changing the nucleophile, an exploration simply protecting the amide was also constructed to determine if these changes would result in forward progress.

4.4.5 Short Exploration of Protecting the Amide

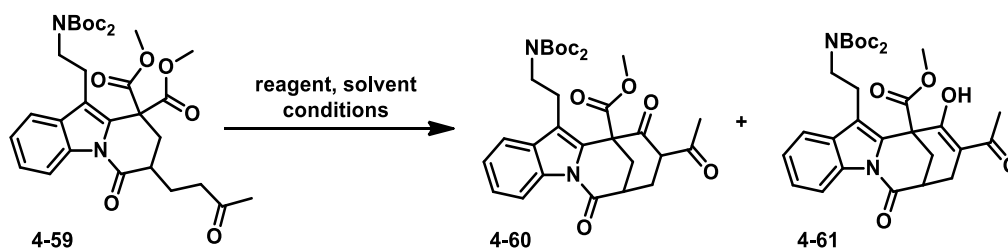
Determining that the amide N-H was preventing attempts at epimerizing the alpha diastereotopic center and preventing the formation of a reactive enolate, the obvious solution was to protect the amide (**Scheme 77**). From closed lactam product **4-46** protection of the amide proceeded smoothly with Boc_2O in an 87% yield (**4-54**). Quick attempts to reduce the methylester in product **4-54** were explored with CeBH_4 and LiBH_4 but failed to yield any of diol product **4-55**. Wacker oxidation of **4-54** generated ketone **4-56** in a 62% yield and again decomposition resulted from attempts to close ring E (**4-58**) under basic conditions.



Scheme 77 - Protection of amide N-H to try and close ring E or reduce methylester

Exhaustive attempts to close ring E from the precursor to the lactam **4-59** are outlined in **Table 7** using the fully protected tryptamine chain. Product **4-59** was subjected to a variety of basic and acidic conditions to determine if ring E would close to keto/enol product **4-60/4-61** (**Table 7**).

Table 7 - Attempts to cyclize ring E from doubly protected amine 4-59

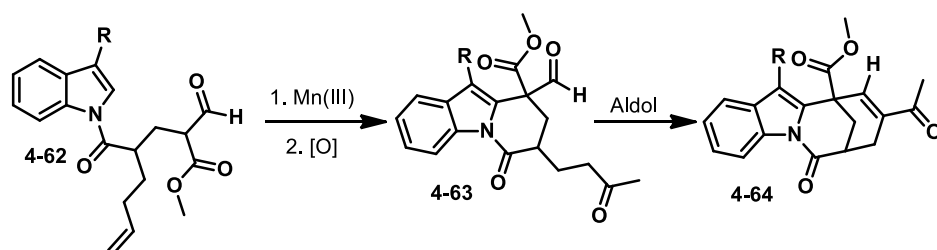


| Entry | Reagents | Solvent | Conditions | Result 4-60/4-61 |
|-------|--------------------------------------|-------------------|------------|---------------------------|
| 1 | NaH | THF | 0 °C | Unelucidated mixture |
| 2 | NaH | THF | -78 °C | 4-59 recovered |
| 3 | NaH | Benzene | 80 °C | Decomp. |
| 4 | K ₂ CO ₃ | MeOH | 70 °C | 0% |
| 5 | TiCl ₄ , NEt ₃ | DCM | 0 °C | Boc removal |
| 6 | NaOMe | Et ₂ O | rt | 0% |
| 7 | MgCl ₂ | DCM | rt | 0%, 4-59 recovered |
| 8 | MgCl ₂ , DBU | DCM | rt | 0%, 4-59 recovered |
| 9 | Na ⁰ | MeOH | 65 °C | Decomp. |
| 10 | NaH, MgCl ₂ | Benzene | 80 °C | Decomp. |
| 11 | MgCl ₂ | DCM | μw 80 °C | 4-59 recovered |

Under strongly basic conditions with NaH, decomposition of the starting material **4-59** was prevalent at temperatures above 0 °C (**Table 7, entry 1, 2, 3 & 10**). While at 0 °C with NaH, a complex inseparable and unelucidated mixture was generated, which was ultimately unhelpful for progression towards the total synthesis of tronocarpine. Attempts at using titanium catalyzed ring closure simply resulted in the deprotection of one of the Boc groups on amine **4-59** (**Table 7, entry 5**). All other attempts (using MgCl₂, MgCl₂ and base, or NaOMe) to close ring E resulted in either decomposition or the recovery of starting material (**Table 7, entry 6,7,8 & 9**). Stuck at trying to synthesize ring E of tronocarpine the synthetic route had to be modified again.

4.5 Third Generation Pathway Towards Tronocarpine: Exploration of Alternate Michael Addition Nucleophiles

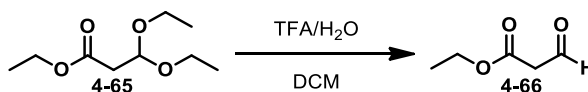
Due to the promise of similar literature reactions, forward progress was attempted following the same idea that an aldol would correctly close ring E.¹²⁷ The aldehydes electrophilicity would be greater than the methyl ester previously explored and for this reason we expected the reaction to proceed under milder conditions.¹²⁸ Exemplified in **Scheme 78**, intermediate **4-62** would provide the necessary aldehyde functionality and could come from an alternate Michael addition nucleophile, while still being susceptible to radical generation by Mn(OAc)₃.



Scheme 78 - Intermediate 4-62 that would be able to access acceptable aldol condensation candidate 4-63

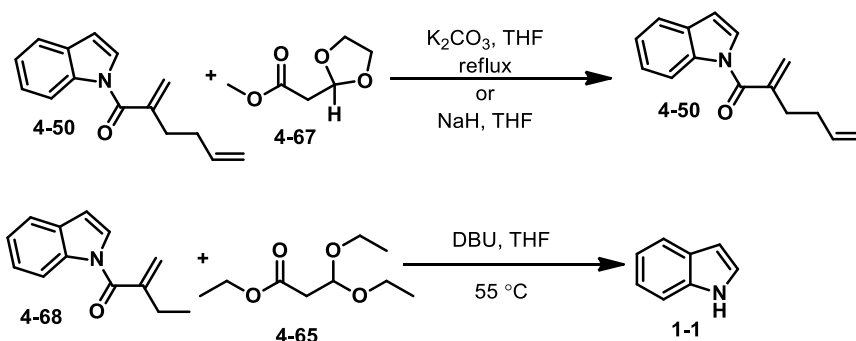
The first hypothesis tested used desired aldehyde (**4-66**) and its acetal (**4-65**) as potential nucleophiles. Product **4-65** was commercially available, and its deprotection was straightforward in TFA and water (**Scheme 79**) but the final product (**4-66**) could not be

purified without destroying the material and had to be used crude from the deprotection reaction.



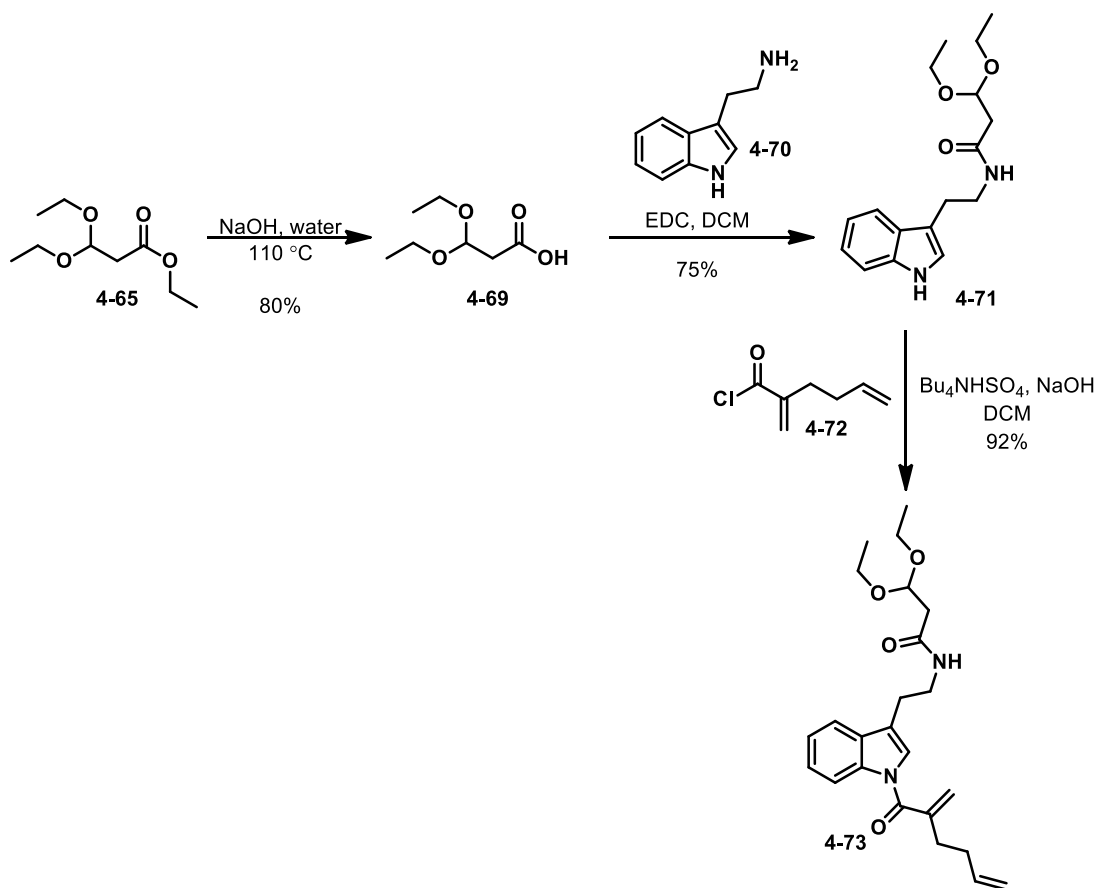
Scheme 79 - Two potential aldehyde bearing nucleophiles **4-65** and **4-66**

Any attempts to use either **4-65** or **4-67** as nucleophiles in the Michael addition with acyl indole generated either deacylated material (**1-1**) or failed (**Scheme 80**). Due to the increased difficulty of deprotonating the single carbonyl species, and the fact that E1cB elimination could expel ethoxide, which readily deacylated the starting indole, no desired product was obtained from these attempts.

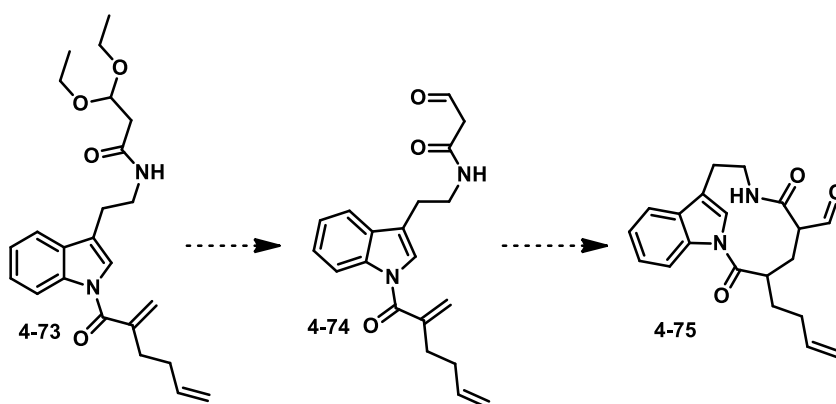


Scheme 80 - Attempts at using acetal protected aldehydes for Michael addition reactions

Since the free aldehyde species **4-66** was unstable, we turned our attention to attaching these nucleophiles to the amine of tryptamine, in hopes of accessing a stable aldehyde (**Scheme 81**). From acetal **4-65**, saponification to acid **4-69** set up an EDC coupling that worked nicely with tryptamine (**4-70**) producing a 75% yield of **4-71**. From the acetal substituted tryptamine we were able to acylate with the usual acyl chloride **4-72** and generate product **4-73**. From here we envisioned (**Scheme 82**) that revealing the aldehyde **4-74** and performing an intramolecular Michael addition would generate macrocyclic product **4-75**.



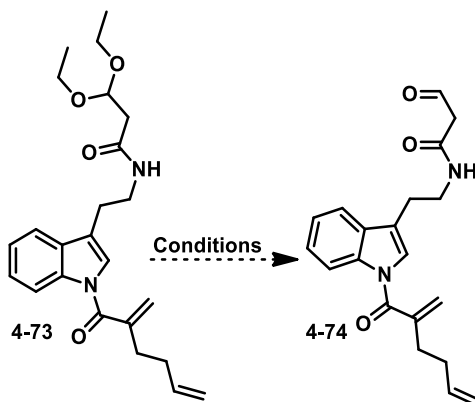
Scheme 81 - Route to product 4-73 to access a stable aldehyde.



Scheme 82 - Proposed access to macrocycle 4-75.

Unfortunately, attempts to isolate the aldehyde or the macrocycle failed to yield desired products and again we were plagued with issues of deacylating the acryloyl alkene chain (**Table 8**).

Table 8 - Experimental attempts to isolate aldehyde 4-74

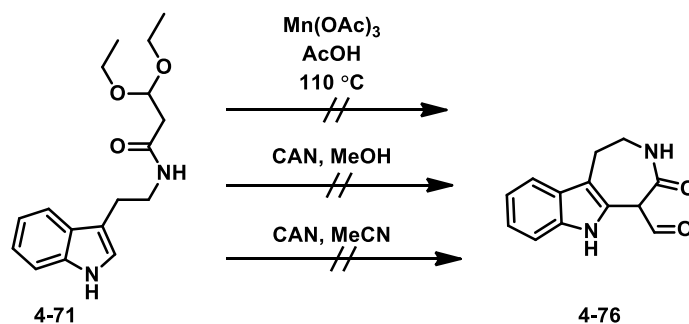


| Entry | Conditions | Result 4-74 (%) | notes |
|-------|--|-----------------|--|
| 1 | TFA, "wet" DCM | 0 | Decomp. |
| 2 | oxalic acid, H ₂ O, THF | 0 | Deacylation |
| 3 | Amberlyst-15, acetone, H ₂ O | 0 | Decomp. |
| 4 | 1. Amberlyst-15, acetone, H ₂ O, 40 °C 2. K ₂ CO ₃ , THF, 50 °C | 0 | NMR of aliquot had an aldehyde peak; in case it was sensitive, I tried the Michael addition in the same pot without aldehyde isolation. |

| | | | |
|---|-----------------------|---|--|
| 5 | 5% HCl, d-MeCN, 40 °C | 0 | Aldehyde present in crude NMR, was not successfully isolated |
| 6 | Pyrrolidine, MeOH | 0 | Deacylation |

It is likely that because water is required to free the aldehyde for the Michael addition, this was enough to cause deacylation of starting material **4-73**, and the decomposition of materials. Although it was helpful that in **Table 8 (Entries 4 and 5)** the NMR data had an aldehyde peak, I was never able to harness the aldehyde successfully. **Table 8, Entry 6** outlines the use of pyrrolidine to try to make an enamine *in-situ* that was more nucleophilic to undergo Michael addition but only deacylation occurred.

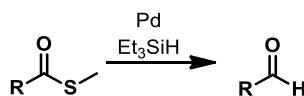
Although it is not a differing Michael addition nucleophile, and because the route had been established to product **4-71**, I thought I could try forming the product cyclized on the 2-position of the indole (**4-76**) and then work to establishing the carbon-carbon bond to the acryloyl component (**Scheme 83**). A few radical-based attempts were explored to generate cyclized product **4-76 (Scheme 83)**. Both Mn(OAc)₃ and ceric ammonium nitrate (CAN) failed to yield any cyclized product. If product **4-76** was accessible, we hoped that the 1,3-dicarbonyl containing ring could be deprotonated to under-go Michael addition after the indole was acylated. These attempts were unsuccessful at generating the reactivity required for an aldol type ring-closure, and so the research pathways were altered to explore thioesters as means to access aldehyde functionality.



Scheme 83 - Single-electron oxidants used in attempt to make product 4-76.

4.6 Fourth Generation Route: Using Thioester Reduction to Access Aldehyde Reactivity

A couple prevalent reactions exist to convert thioesters selectively to aldehydes. The Fukuyama reduction chemoselectively reduces thioesters to aldehydes in the presence of a palladium catalyst and triethylsilane (**Scheme 84**).¹²⁹



Scheme 84 - Reduction of a thioester to an aldehyde

This reaction has great chemoselectivity and works well in the presence of amides, esters, ketones, and is an alternative method of mildly reducing acids, which are easily converted to thiol esters. Using this reaction, I hoped that selective reductions of a thioester would easily install a desired aldehyde from a product **4-77** outlined in **Figure 18**.

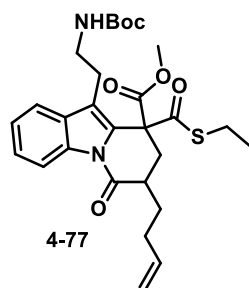
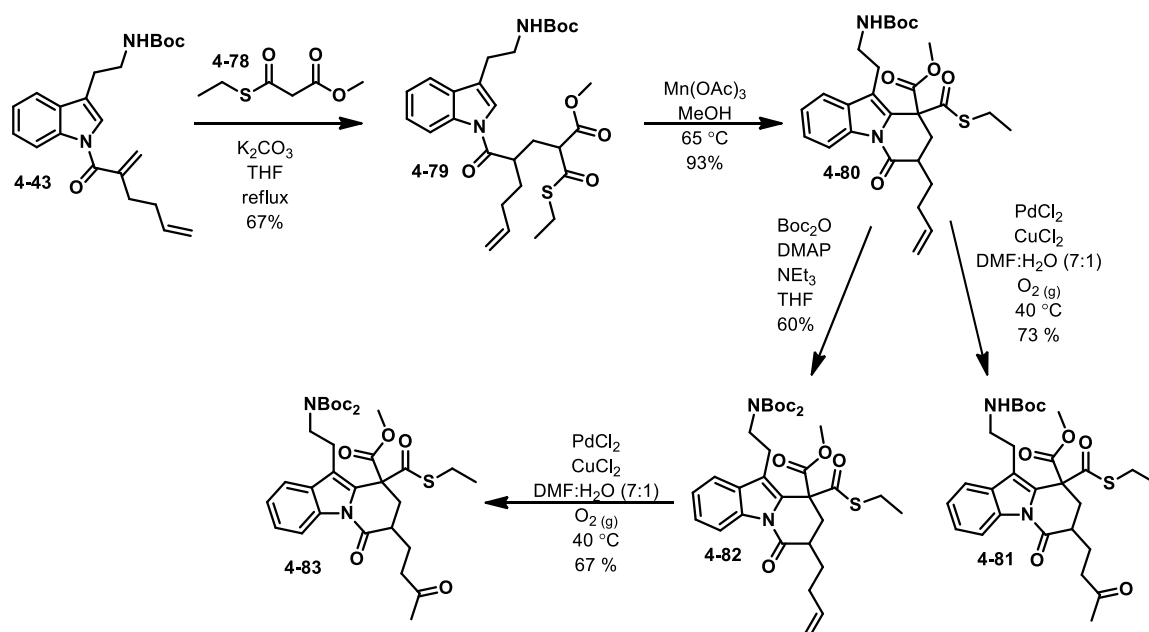


Figure 18 - Proposed intermediate to try and access a desired aldehyde via Fukuyama reduction

The chemistry to access product **4-77** proceeded with ease using the previously established route to these tricyclic indole scaffolds (**Scheme 85**). Starting from the

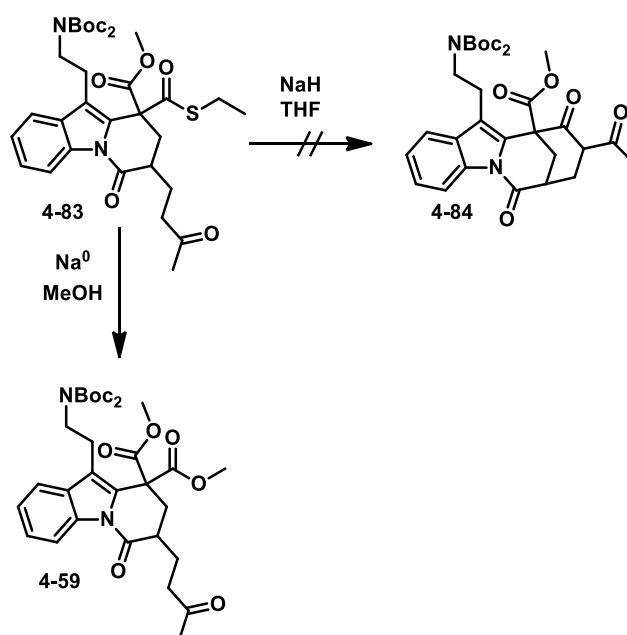


Scheme 85 - Synthetic pathway to access thioester containing scaffolds 4-81 and 4-83

acylated N-Boc protected tryptamine **4-43** (**Scheme 85**), Michael addition with a thioester malonate **4-78** worked in a 67% yield to access **4-79**. The $Mn(OAc)_3$ radical cyclization proceeded in a high 93% yield to generate 1,2-disubstituted indole **4-80**. A report indicated that terminal alkenes may interfere with the palladium catalyst, product **4-80** was therefore taken to the ketone via a Wacker oxidation (**4-81**, 73% yield) and then

to the doubly protected amine via Boc protection (**4-82**) and Wacker oxidation generated **4-83** (40% over two steps).¹³⁰

From material **4-83** I explored Dieckmann-type condensations between the methyl ketone and the thioester to test if the more reactive thioester performed favourably compared to previous attempts to closed ring E. Unfortunately, basic conditions of NaH or NaOMe failed to cyclize the generated enolate onto the thioester to access **4-84** (**Scheme 86**). Under methoxide conditions, the diester material used in previous routes was observed (**4-59**).

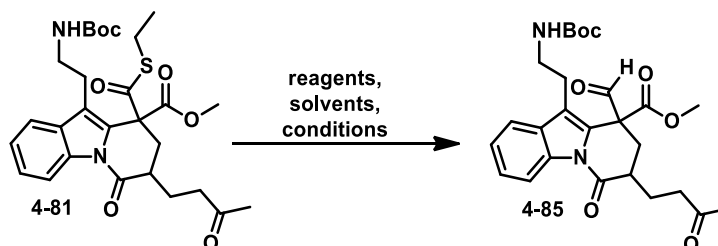


Scheme 86 - Attempts at generating ring E of tronocarpine from the thioester scaffold

From material **4-81**, the Fukuyama reduction was explored to isolate aldehyde **4-85**.¹³¹ The results of these attempts are outlined in **Table 9**. Using Pd(OAc)₂ as the palladium source, and 5 equivalents of triethyl silane (Et₃SiH) in acetone, the result was no reaction (**Table 9, Entry 1**). Despite intense bubbling, assumed to be from gaseous sulfur byproducts, only starting material was observed in the crude NMR. Changing the solvent from acetone to DCM gave no improvement (**Table 9, Entry 2**), but because DCM was easier to keep dry, it was used for remaining attempts. Adding the silane slowly over 1.5

h to release hydrogen in a more controlled manner also failed to generate aldehyde **4-85** (**Table 9, Entry 3**) and adding 2,6-lutidine, a reagent that had been known to accelerate the reaction, also failed to yield positive results (**Table 9, Entry 5&6**).

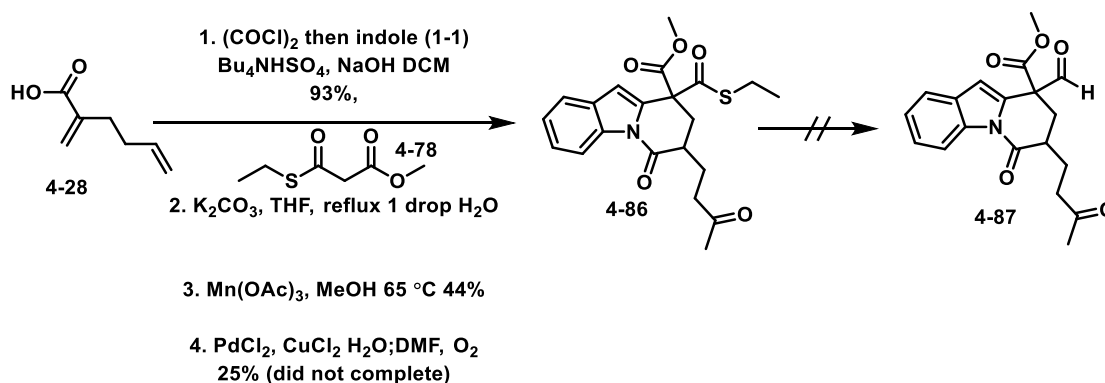
Table 9 - Fukuyama reduction attempts to isolate aldehyde 4-85



| Entry | Reagents | Solvent | Conditions | Result 4-85 (% yield) |
|-------|---|---------|------------------------------------|---------------------------------|
| 1 | Pd(OAc) ₂ (0.3 equiv). Et ₃ SiH (5 equiv.) | Acetone | rt | 0 |
| 2 | Pd(OAc) ₂ (0.3 equiv.), Et ₃ SiH (5 equiv.) | DCM | rt | 0 |
| 3 | Pd(OAc) ₂ (0.3 equiv.), Et ₃ SiH (5 equiv.) | DCM | rt, silane added slowly over 1.5 h | 0 |
| 4 | Pd(OAc) ₂ (0.3 equiv.), (Et ₃ SiH 2.3 equiv.), 2,6-lutidine | DCM | rt | 0 |

| | | | | |
|---|---|-----|---------------------------|---|
| 5 | Pd(OAc) ₂ (0.3 equiv.), Et ₃ SiH (4 equiv.), 2,6-lutidine | DCM | rt | 0 |
| 6 | Pd(OAc) ₂ (0.3 equiv.), Et ₃ SiH (5 equiv.), 2,6-lutidine | DCM | rt, silane added over 1 h | 0 |

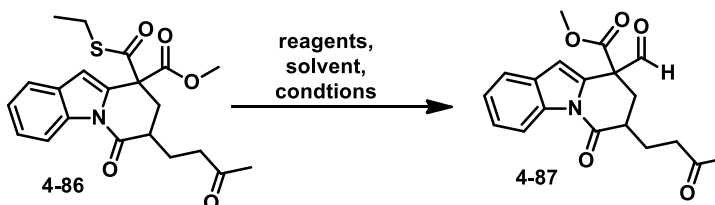
Unsure of why this reaction was failing, my best hypothesis was interference from the nitrogen-containing tryptamine -chain. Another substrate was synthesized from indole to avoid having nitrogen present, opting to add the tryptamine chain later. To access tryptamine lacking thioester intermediate **4-86**, I again applied the optimized route (**Scheme 87**); acylating indole with acrylic acid **4-28** and using methylthiomalonate **4-78** as the Michael nucleophile. Acylation of indole proceeded in a high 93% yield, and the Michael addition followed by radical cyclization occurred in a 44% yield over two-steps. Finally, Wacker oxidation elucidated methyl ketone **4-86** in a 25% yield as this reaction failed to consume all starting material.



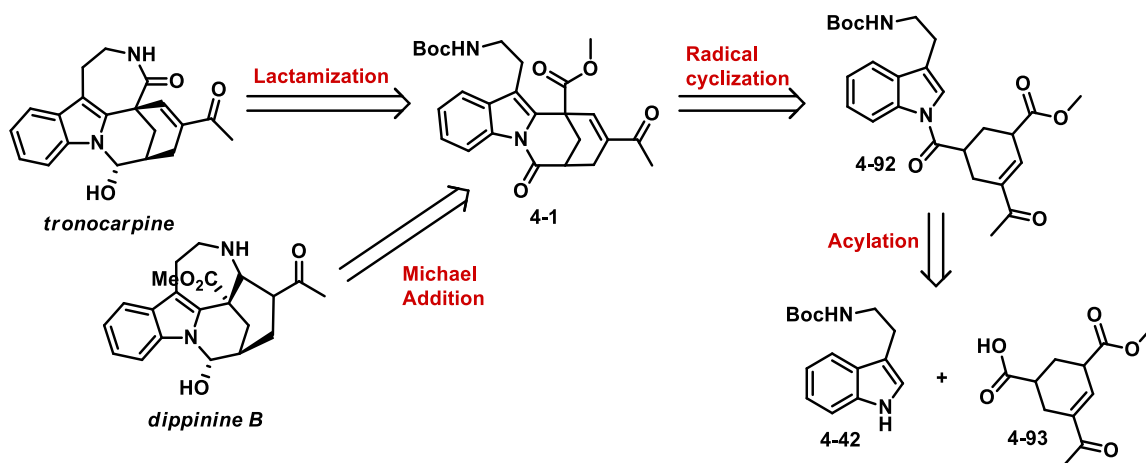
Scheme 87 - Synthetic route to product 4-86.

Fukuyama reduction attempts were applied to product **4-86** and the results are outlined in **Table 10**. Switching the palladium source to Pd/C resulted in a violently gaseous reaction which we had hoped meant we were expelling ethanethiol but only starting material was ever isolated (**Table 10, Entry 1 & 2**). Varying solvent concentration of the reactions also gave disappointing results. Addition of silane slowly also did not change the reactive outcome of this reaction (**Table 10, Entry 2&3**).

Table 10 – Fukuyama reaction conditions attempted on model product 4-86

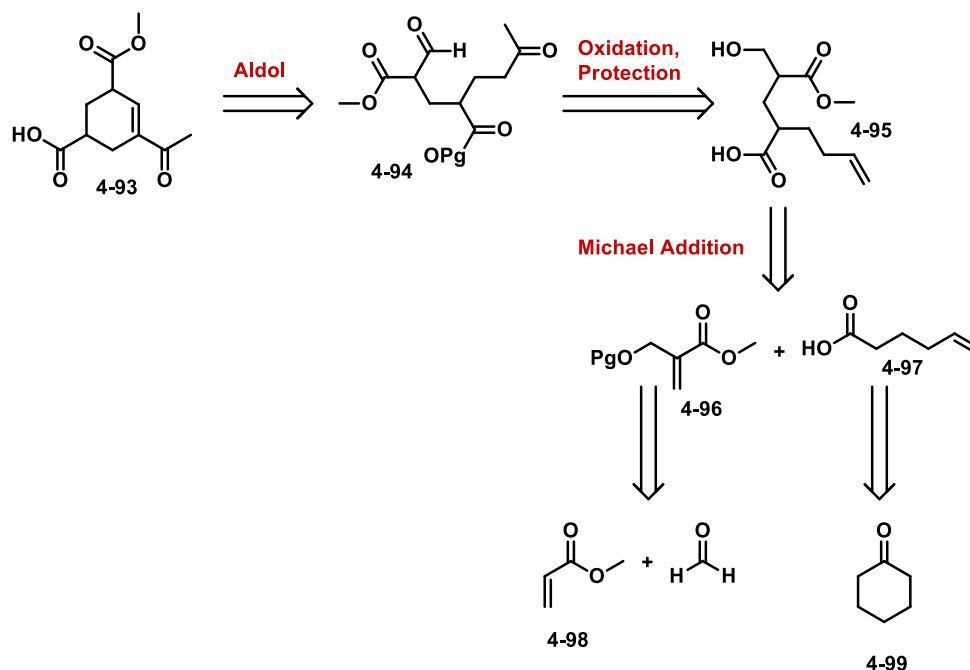


| Entry | Reagents | Solvent | Conditions | Results 4-87 (% yield) |
|-------|---|-----------------|------------------------------|---------------------------|
| 1 | Pd(Oac) ₂ (0.3 equiv.), Et ₃ SiH (5 equiv.) | DCM (0.5 M) | Silane added slowly over 1 h | 0 |
| 2 | Pd/C (0.5 equiv.), Et ₃ SiH (3 equiv.) | Acetone (0.5 M) | Silane added slowly over 1 h | 0 |
| 3 | Pd/C (0.5 equiv.), Et ₃ SiH (3 equiv.) | Acetone (0.5 M) | Silane added at one time | 0 |
| 4 | Pd/C (0.5 equiv.), Et ₃ SiH (3 equiv.) | DCM (1 M) | Silane added slowly over 1 h | 0 |



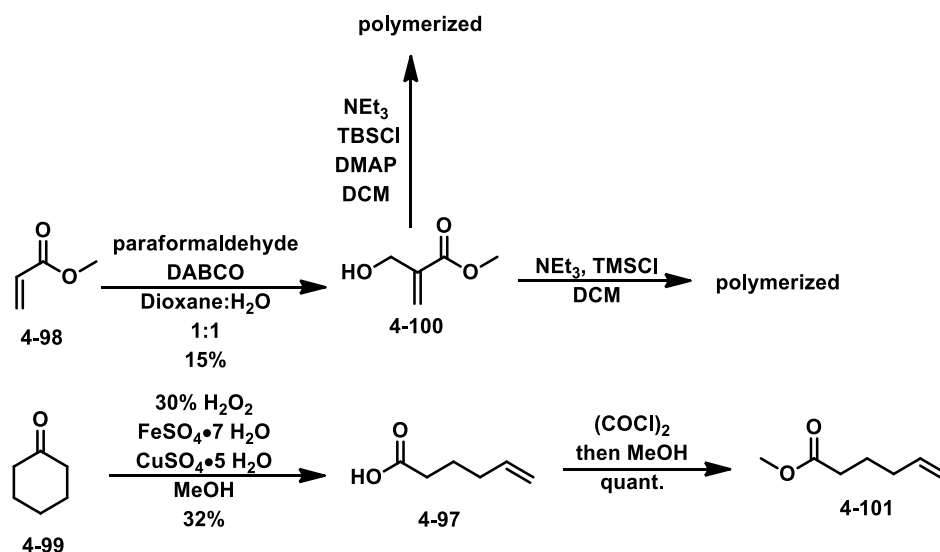
Scheme 89 – Retrosynthetic Analysis 3: pathway using a cyclic acid as an acylation agent

To generate acid **4-93** a synthesis had to be designed (**Scheme 89**). The first retrosynthesis proposed was again following the idea that an aldol between an aldehyde and methyl ketone enolate would generate the alpha/beta unsaturation observed in product **4-93**. This route would involve reactions with potential for chemoselective issues, but the retrosynthetic analysis is outlined below (**Scheme 90**). The aldol reaction of ketone/aldehyde product **4-94** would successfully furnish acid **4-93**. To generate such a complex hydrocarbon chain (**4-95**), we would use a Michael addition between acid **4-97** and acrylate **4-96** bearing protected alcohol. Both products (**4-96** and **4-97**) have literature established routes.^{132, 133}



Scheme 90 - Retrosynthetic Analysis 4: using an aldol to generate cyclic acid 4-93

Commencing synthetic progress to acid **4-93**, the alcohol acrylate **4-100** was generated first using a Baylis-Hillman reaction of methyl acrylate (**4-98**) and paraformaldehyde in the presence of DABCO (Scheme 91).



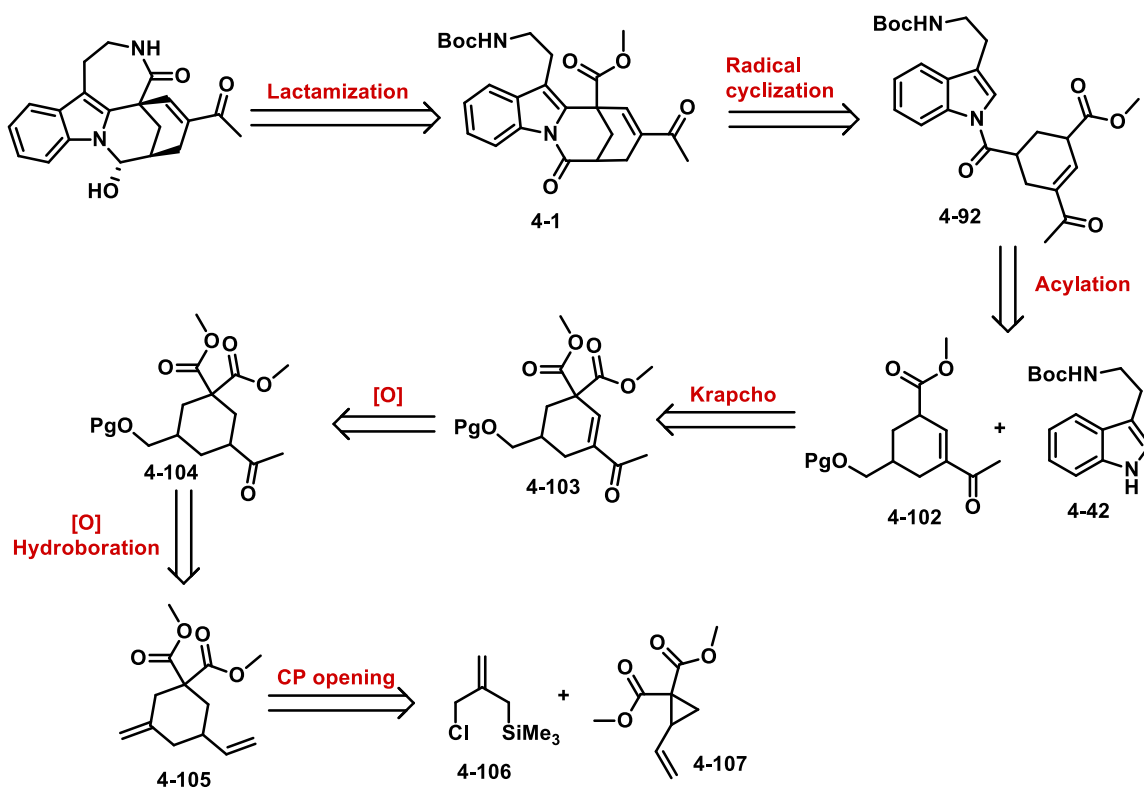
Scheme 91 - Initial attempts to synthesize acid 4-93

While it is a low yielding reaction (15%), the materials are inexpensive, and the reaction is easily scaled. There existed no previous precedence at protecting the alcohol on product **4-100** and it quickly became apparent why; in the presence of base, and either TMS-Cl or TBS-Cl, the material quickly polymerized. This polymerization problem was never overcome, and this route was quickly abandoned.

4.7.2 Second Retrosynthetic Analysis to Access Tronocarpine through Similar Cyclic Acid Moiety **4-102**

Reviewing past attempts accessing tronocarpine from previous Kerr group members, Katarina Sapeta had developed a route which successfully generating ring E, but she was unable to impart the correct functionalization for the rest of tronocarpine.¹³⁴ Her methodology elucidated that DA CPs can be opened with 2-(chloromethyl)-3-trimethylsilyl-1-propene (**4-106**) and following base-mediated ring closure would generate 1,3,5 substituted cyclohexane products (**Scheme 92**). I envisioned that this cyclohexane (**4-105**) could be modified to the cyclohexene (**4-102**) bearing the α,β unsaturated ketone required for tronocarpine (**Scheme 92**).

Starting from vinyl cyclopropane **4-107** (**Scheme 92**), opening with **4-106** would generate vinyl cyclohexane **4-105**. Manipulations using hydroboration, protection and Wacker oxidation would ideally install the primary alcohol and ketone exemplified in product **4-104**.¹³⁵ Selenoxide elimination would generate internal alkene **4-103** for the α,β unsaturated ketone **4-102**. A Krapcho decarboxylation would remove one of the esters and then product **4-102** could be acylated after the primary alcohol is oxidized via Jones oxidation to a carboxylic acid. Product **4-92** outlined earlier (**Scheme 89**) could be subjected to radical closure to the indole through the vinylogous reactivity of the 1,3-dicarbonyl moiety. If this chemistry proved troublesome, other reactions could be explored, like α -halogenation for other coupling transformations. **4-1** would furnish tronocarpine by the lactamization and reduction as discussed in the previous retroanalyses.



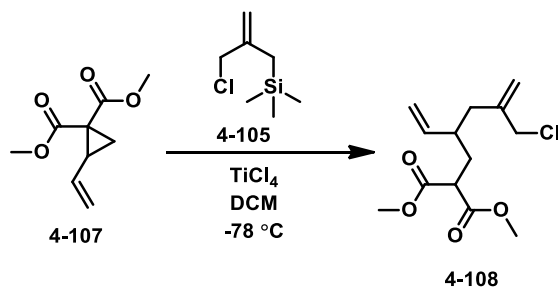
Scheme 92 - Retrosynthetic Analysis 5: Route to tronocarpine incorporating cyclohexene 4-102

4.7.3 Chemistry Employed to Realize Retrosynthetic Analysis 5

Vinyl cyclopropane **4-107** is easily synthesized and was subjected to silane **4-106**. **4-106** and TiCl_4 in DCM at $-78\text{ }^\circ\text{C}$ opened vinyl cyclopropane **4-107** in yields up to 88% of **4-108**, but the reaction became troublesome when trying to scale-up (**Table 11**). Silane piece **4-106** is also incredibly expensive at \$112/g and is strangely no cheaper to synthesize ourselves. As Sapeta *et al.* were working on a much smaller scale this was no issue, but this became the first limiting factor of this synthetic route. During scale-up, any reaction using more than 100 mg of cyclopropane saw a sharp decline in yields from around 75% down to 30-55% (**Table 11, Entry 1, 2, 3, 4, 5**). Column chromatography seemed to drastically cut yields, and because the crude NMRs were not full of impurities, I began pushing crude material forward into the cyclization, which could then be purified with ease. Interestingly, the yields increased by 10% when less than 100 mg of

cyclopropane **4-107** was used. To generate enough working material, I purchased 5 g of silane **4-106** and ran the reaction on multiple 100 mg scales.

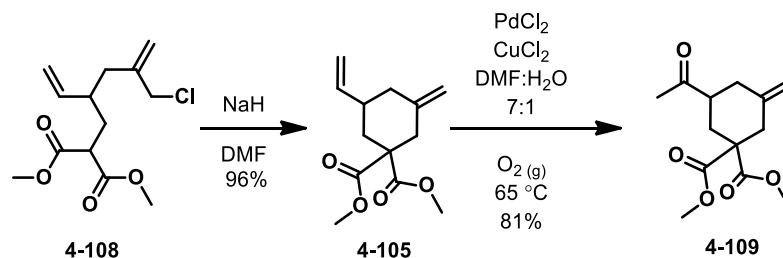
Table 11 - Effects of Scale-Up in synthesizing chain 4-108



| Entry | Scale of CP 4-107 | Yield 4-108 (%) |
|-------|--------------------------|------------------------|
| 1 | 100 mg | 76 % |
| 2 | 500 mg | 55 % ^a |
| 3 | 500 mg | 48 % ^a |
| 4 | 500 mg | 55 % ^a |
| 5 | 1 g | 36 % ^a |
| 6 | 1 g | Did not complete |
| 7 | 500 mg | 33 % ^b |
| 8 | 100 mg | 78 % |
| 9 | 50 mg | 88 % |

^a Crude yield ^b Purified yield

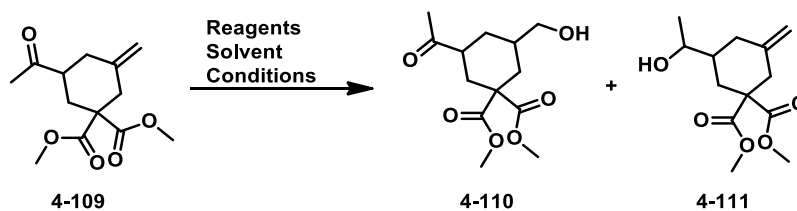
Product **4-108** in hand, cyclization with NaH in DMF worked well giving a 96% yield of 1,3,5-substituted cyclohexane product **4-105**. Wacker oxidation selectively oxidized the vinyl group to generate methyl ketone **4-109** in 81% yield.



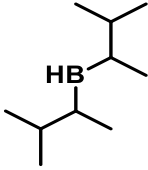
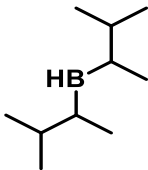
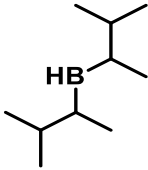
Scheme 93 - Ring closure and Wacker oxidation to access cyclohexane 4-109

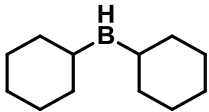
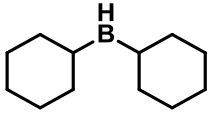
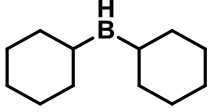
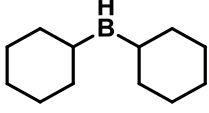
With product **4-109** accessible, it became time to optimize the synthesis of hydroboration product **4-110**. Aware that chemoselectivity with the ketone was a potential issue, I expected that I may also get reduced secondary alcohol products (**4-111**) but hoped that functionality could be restored. Literature precedent also existed for the hydroboration of alkenes in the presence of ketones that left the ketones unaffected.^{135,136,137} The results of optimizing the hydroboration product are outlined in **Table 12**.

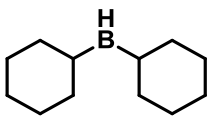
Table 12 - Optimization of hydroboration reaction



| Entry | Borane Reagent | Solvent | Condition | Result |
|-------|----------------------|---------|-----------|--------------------------|
| 1 | BH ₃ •THF | THF | 0 °C | 4-111^a |
| 2 | BH ₃ •THF | THF | 25 °C | 4-111^a |
| 3 | BH ₃ •THF | THF | -78 °C | 4-111^a |

| | | | | |
|---|---|-----|------------|---|
| 4 |  <p>(2.5 equiv.), H₂O₂, 15% NaOH</p> | THF | 0 °C-25 °C | Starting material recovered. |
| 5 |  <p>(2.5 equiv.) H₂O₂, 15% NaOH (removed stabilizer from 2-methyl-2-butene)</p> | THF | 0 °C-25 °C | Structure of isolated material inconclusive. |
| 6 |  <p>(2.5 equiv.), H₂O₂, 15% NaOH (removed stabilizer from 2-methyl-2-butene)</p> | THF | 0 °C-45 °C | - 8 spots by TLC. - 4 mg of product 4-110 (7 % yield) |
| 7 | 9-BBN (1 equiv.), NaBO ₃ | THF | 25 °C | Decomp. |

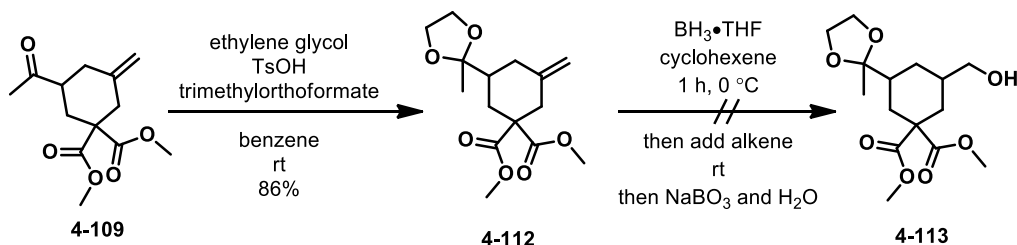
| | | | | |
|----|--|-----|--------------|--|
| 8 | 9-BBN (1.2 equiv.), H ₂ O ₂ , 3M NaOH | THF | 0 °C | 16%, 4-110 |
| 9 | 9-BBN (1.5 equiv.), H ₂ O ₂ , 3M NaOH | THF | 0 °C – 25 °C | 37%, 4-111 |
| 10 |  (1 equiv.), NaBO ₃ , H ₂ O | THF | 25 °C | 20% (brsm) 4-110 |
| 11 |  (1.2 equiv.), NaBO ₃ , H ₂ O | THF | 25 °C | 7% 4-110 |
| 12 |  (1 equiv.), NaBO ₃ , H ₂ O | THF | 0 °C | 4-109 recovered |
| 13 |  (1.2 equiv.), NaBO ₃ , H ₂ O | THF | 0 °C | 15% 4-110 Best results. Repeatable. |

| | | | | |
|----|--|-----|-------|----------|
| 14 |  (1.5 equiv.), NaBO ₃ , H ₂ O | THF | 25 °C | 8% 4-110 |
|----|--|-----|-------|----------|

^a Not purified or isolated

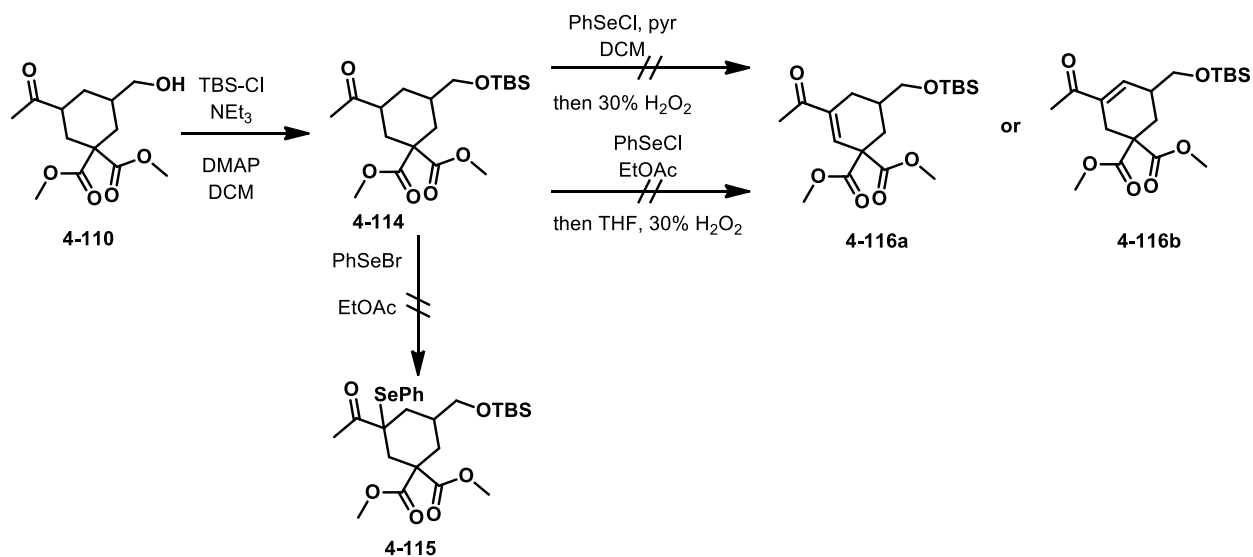
Only low yields of product **4-110** were isolated throughout the experiments detailed in **Table 12**, and the best borane reagent was determined to be cyclohexylborane (**Table 12**, **Entry 13**). When worked-up in the presence of NaBO₃ and H₂O it at least reliably produced yields of product **4-110**.

As a note, protecting the ketone with an acetal (**4-112**) and subjecting the material to the cyclohexylborane hydroboration had no positive effect on the results (**Scheme 94**). No desired product (**4-113**) was formed.



Scheme 94 - Protected acetal 4-112 also failed to produce desired hydroboration product 4-113

From the very small amount of product **4-110** generated, forward synthetic progress was pursued first protecting the newly generated alcohol (**Scheme 95**). Protection with TBS-Cl worked well (**4-114**), but attempts at selenoxide elimination were not fruitful. PhSeCl and PhSeBr were explored in attempts to generate phenylselenide product **4-115** that could be eliminated in the presence of peroxide. No desired product (**4-116a/b**) was isolated.



Scheme 95 - Synthetic progress in attempts to generate cyclohexene 4-116a

In the reality that sometimes is natural product synthesis, cost and budget became a factor in our planned route. Due to the lack of material acquired and the expense of silane **4-106**, accessing gram-scale products was not feasible. Unfortunately, again, we had to turn our attention to a new, and more supportable route, to the natural products desired.

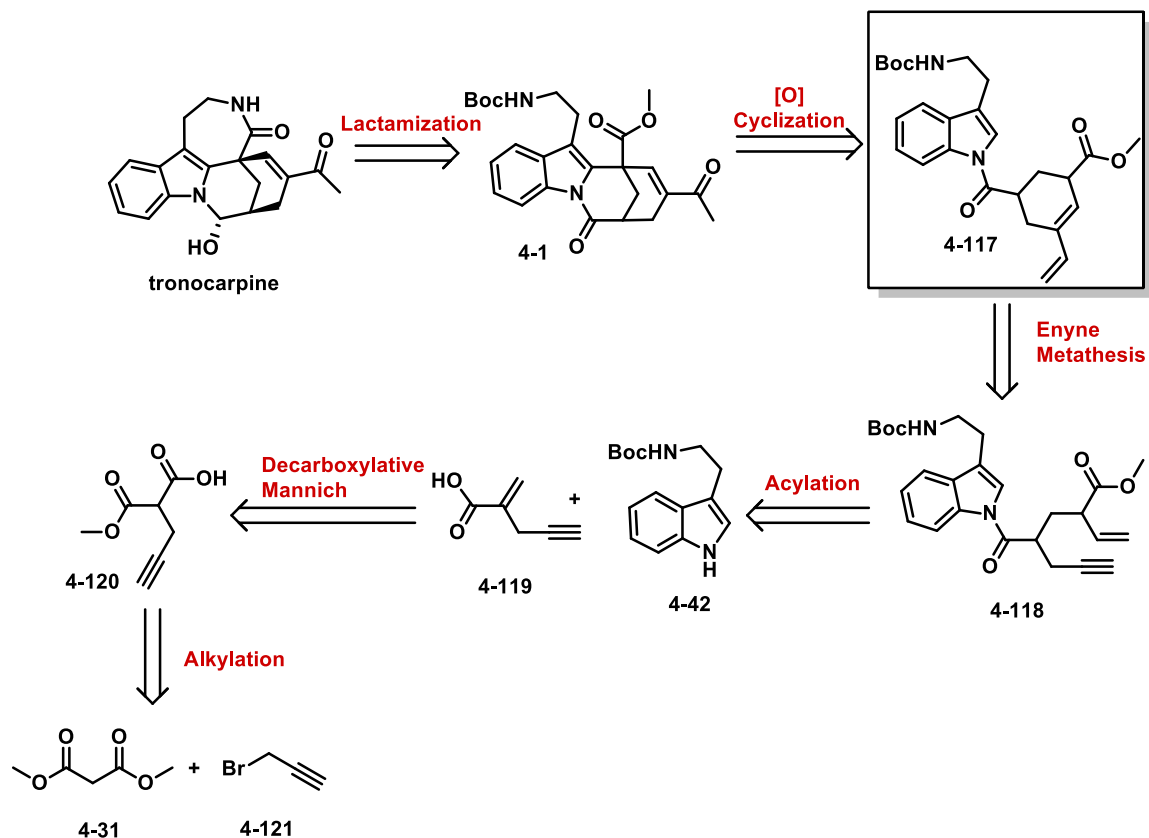
4.8 Sixth Generation Synthesis Towards Tronocarpine and Dippinine B

4.8.1 Retrosynthetic Analysis 6 Incorporating Enyne Metathesis

Enyne metathesis between an alkene and an alkyne is an extraordinarily powerful tool for generating conjugated alkene products.¹³⁸ This reaction has been used to synthesize vinyl cyclohexene rings like that showcased in product **4-117**.¹³⁹ With the reliable nature of the Wacker oxidation in all synthetic attempts up to this point, we felt confident that the alkene generated from such enyne metathesis (**4-117**), could be interconverted to desired α,β -unsaturated ketone (**4-1**) in ring E in tronocarpine (**Scheme 96**).

Retrosynthetically analyzing such a route (**Scheme 96**) meant we would require novel alkene and alkyne functional groups in our intermediates to appropriately yield desired cyclohexene **4-117**. Outlined in **Scheme 96**, lactamization between tryptamine chain and methyl ester would again close the final ring of tronocarpine from product **4-1**. **4-1** would

be generated from vinylogous 1,3-dicarbonyl cyclization via radical activation, and this cyclohexene functionality would be imparted by the enyne metathesis of substrate **4-118**. To generate substrate **4-118** acylation with a slightly different alkyne-bearing acrylic acid (**4-119**) would need to be performed. This acrylic acid would again come from the previously used decarboxylative Mannich after simple alkylation of dimethylmalone (**4-31**) with propargyl bromide (**4-121**).



Scheme 96 - Retrosynthetic Analysis 6: using enyne metathesis to generate ring E of tronocarpine

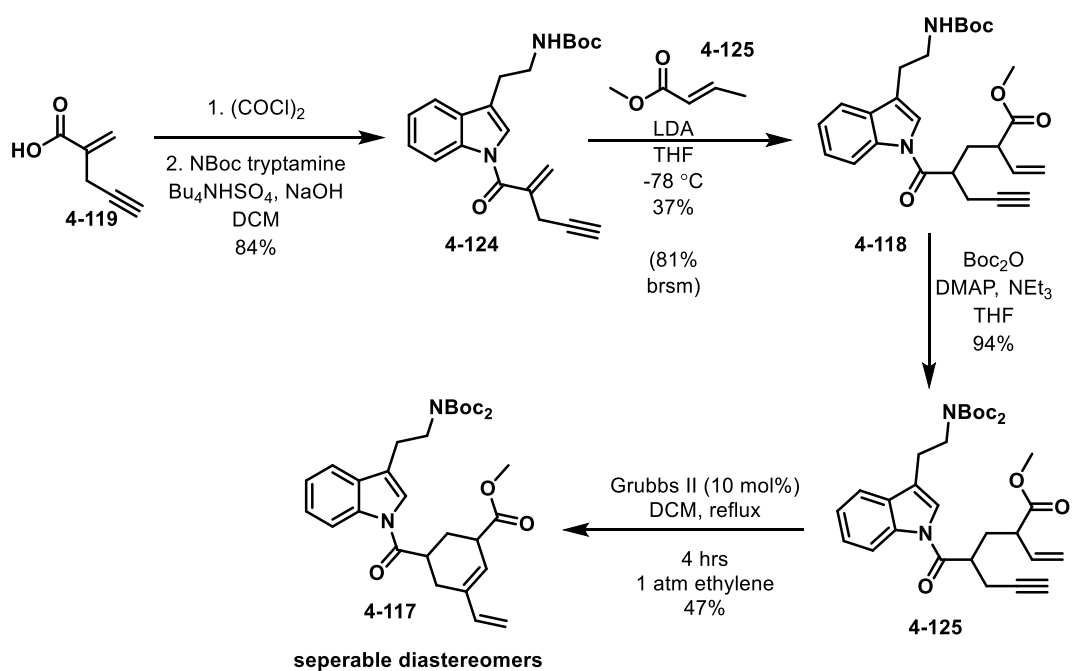
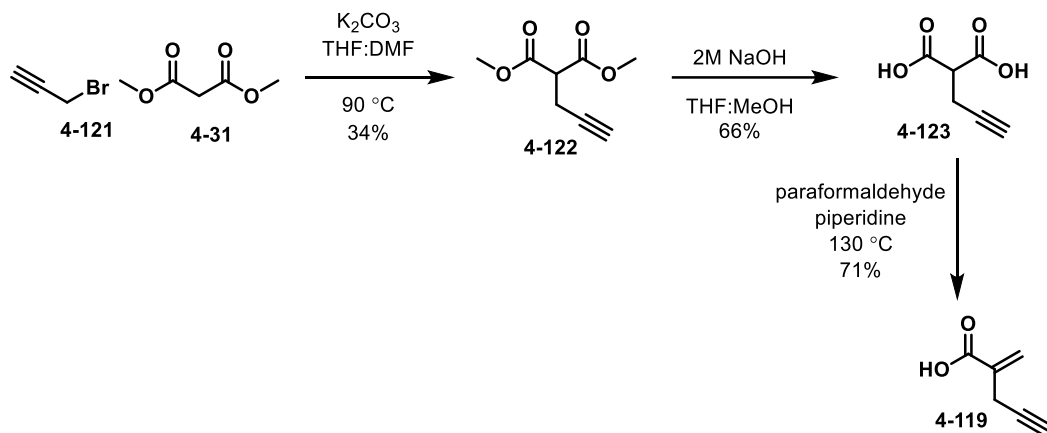
Confident that the scale up of this route would be much easier, and with cheaper starting materials, exploration of this new proposal commenced.

4.8.2 Forward Progress Exploring the Enyne Metathesis Retrosynthetic Route 6

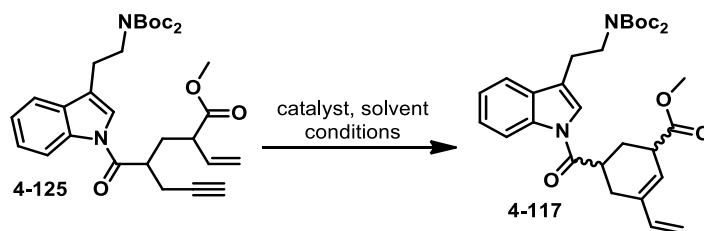
Initial progress exploring **Retroanalysis 6** proceeded exceedingly well. On a first run through we were able to finally access acylated indole containing cyclohexene ring **4-117** (**Scheme 97**). Step 1 was difficult to purify, acylating dimethylmalonate **4-31** with propargyl bromide (**4-121**), a by-product of the dialkylated species was prominent. The yield was low enough to justify purchasing commercially available **4-122**. Saponification (**4-123**) followed by decarboxylative Mannich again proved successful yielding acrylic acid **4-119** in a 47% yield over two steps.

Acrylic acid **4-119** was successfully coupled to protected tryptamine in an 84% yield, giving acryloyl indole **4-124**. A Michael addition was possible using acrylate **4-125** in the presence of LDA.^{140,141} However, this reaction was finicky, and it was necessary to quench the material at the first signs of a second new spot by TLC. This was a decomposition product that upon its formation, a 0% yield of product **4-118** would result. Because yields of **4-118** were low on this reaction because it had to be quenched while starting material remained. So, while low yielding, the terminal alkene was accessible and set up the functionality for the desired enyne metathesis. Enyne metathesis attempts were explored and using both Grubbs 1 and Grubbs 2 catalysts¹⁴² we could generate a mixture of diastereomers (**4-117**). The exploration of the enyne metathesis is outlined in

Table 13.



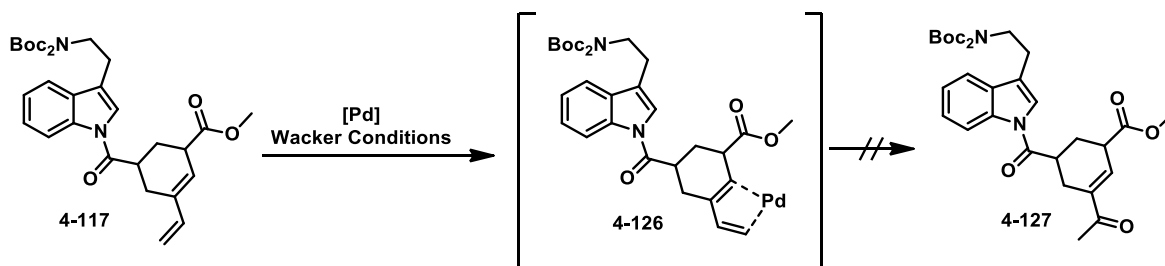
Scheme 97 - Synthetic pathway to enyne metathesis product 4-117

Table 13 - Exploration of Enyne Metathesis

| Entry | Catalyst | Solvent | Atmosphere ^a | Temperature | Result 4-117 |
|-------|---------------------|---------|-------------------------|-------------|---|
| 1 | Grubbs I (10 mol%) | DCM | Ethylene (1 atm) | rt | 41% separable diastereomers |
| 2 | Grubbs II (10 mol%) | toluene | Argon | 90 °C | 7% |
| 3 | Grubbs II (10 mol%) | DCM | Ethylene (1 atm) | 35 °C | 47% separable diastereomers |
| 4 | Grubbs II (10 mol%) | DCM | Ethylene (1 atm) | 35 °C | 38% separable diastereomers |
| 5 | Grubbs II (10 mol%) | DCM | Ethylene (1 atm) | 35 °C | 42% separable diastereomers - Tripled the scale size |
| 6 | Grubbs I (10 mol%) | DCM | Ethylene (1 atm) | 35 °C | Mixture of 4-117 and 4-125; DNC |

^a Ethylene is flushed directly into reaction solution for 5 mins before being placed under a balloon atmosphere of ethylene.

In order to generate the appropriate vinylogous reactivity for the ring closure reaction with Mn(III), a Wacker oxidation was required to generate ketone product **4-127** (**Scheme 98**). However, in all attempts of this reaction, nothing happened. Subjected to long lengths of time and heating the mixture, starting material (**4-117**) always remained. A literature investigation confirmed that these conjugated substrates can sometimes be unreactive to palladium chemistry because coordination to the conjugated alkene system (**4-126**) will trap the palladium preventing it from any further reactivity (**Scheme 98**).¹⁴³



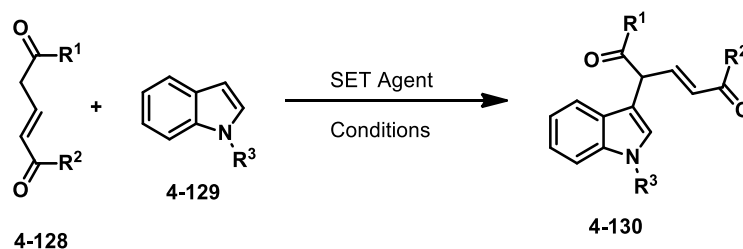
Scheme 98 - Failed reactivity of the Wacker oxidation on product 4-117

This is where the project ended. I hope a future graduate student can be convinced to give this another attempt. Perhaps my tribulations will aid in their design of a successful pathway to these molecules. I outline in the following section possible re-works that could be attempted. To the future student that may be reading this: feel free to contact me.

4.9 Conclusions and Future Outlook

Although exploration of 6 possible routes towards natural products tronocarpine and dippinine B were fruitless, a large amount of knowledge was acquired regarding ways in which the pentacyclic scaffolding of these molecules should *not* be formed. Ring E being as troublesome as it was to synthesize, should absolutely be constructed as a separate component that is later connected to the indole half of the molecule (**Figure 19**).

Using SET agents to cyclize the cyclohexene ring of these molecule, while successful, has never worked on a vinylogous substrate. I think exploration of this chemistry would in and of itself be publishable if a methodology could be developed. I suspect using a SET agent on vinylogous 1,3-dicarbonyl electrophiles (**4-129**) in the presence of indoles (**4-129**) may generate products like **4-140** (**Scheme 99**).



Scheme 99 - Chemistry worth exploring generating radical on vinylogous dicarbonyl molecules

I am also still confident that product **4-93** is a great substrate towards overcoming the hurdles outlined in this chapter.

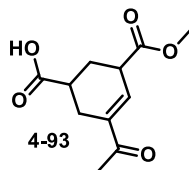
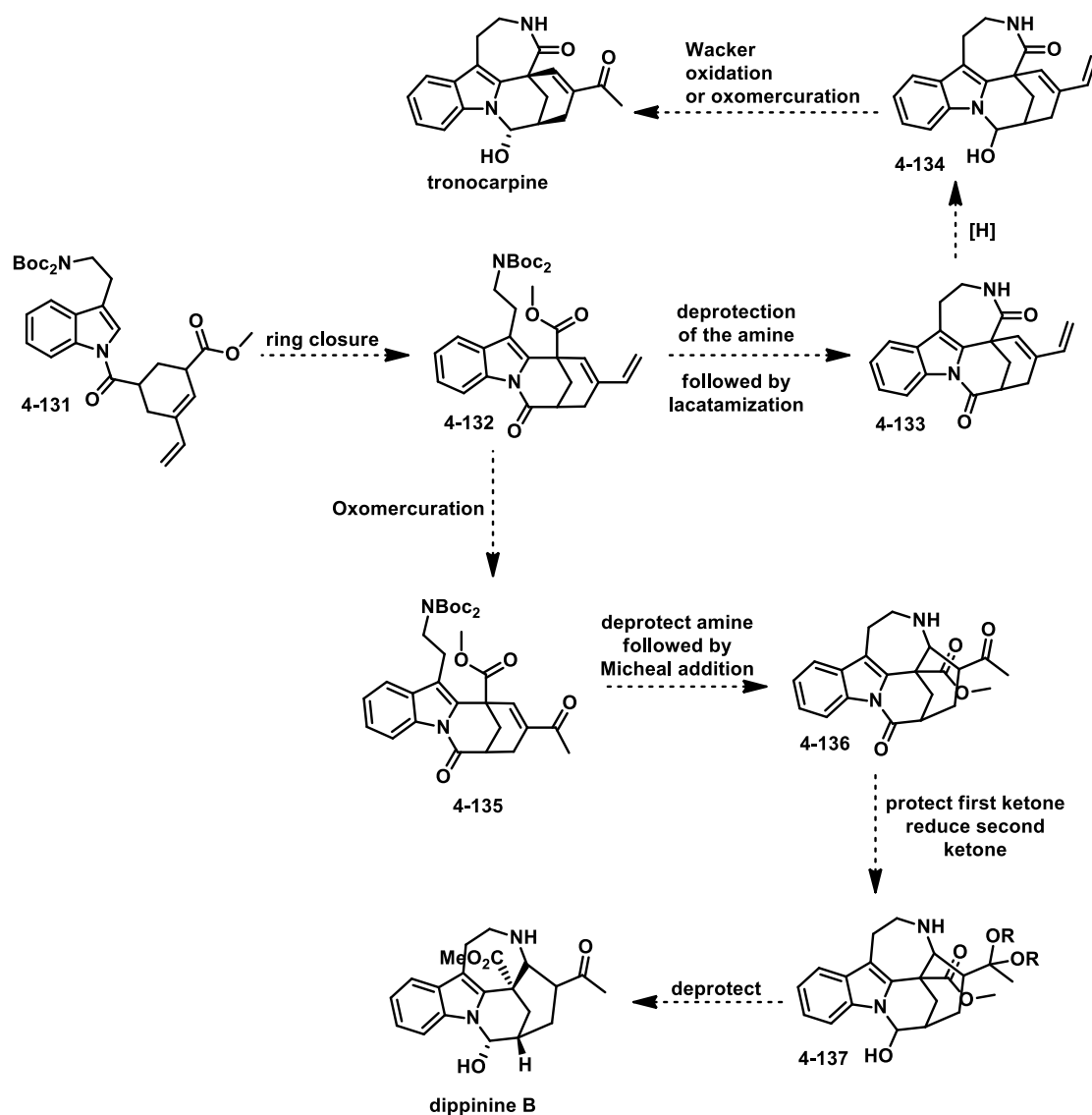


Figure 19 - Ring E component to access molecules tronocarpine and dippinine B

If substrate **4-93** can be attached to tryptamine (**4-131**), the route outlined in **Scheme 100** would theoretically be capable of overcoming the chemoselectivity and non-reactivity issues that were discovered. If chemistry can be developed to cyclize to the indole and generate a product along the lines of **4-132** or **4-134**, oxymercuration should be capable of imparting the oxidation required to the α,β unsaturated ketone in **4-135**. With a ketone installed (**4-135**), deprotection of the amine should perform the Michael addition likely in the same pot as the deprotection furnishing the ring in product **4-136** on the way to dippinine B. Protecting the methyl ketone will be crucial for successful reduction of the

indole bound ketone with NaBH_4 (**4-137**). Deprotection to elucidate methyl ketone back would complete the synthesis of dippinine B.



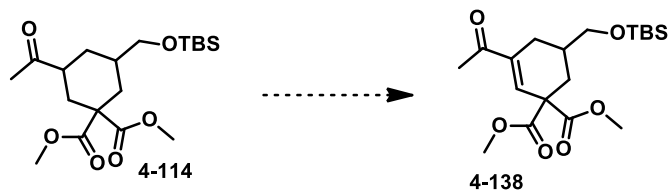
Scheme 100 - Potential route to complete natural products tronocarpine and dippinine B

At substrate **4-132**, deprotection the amine first will close the lactam ring generating **4-133**. Reduction of the ketone in product **4-133** with NaBH_4 will be easier done without the methyl ketone furnished yielding **4-134**. Finally, oxidation of **4-134** via Wacker, if the

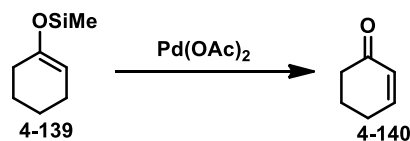
palladium is not rendered inert by this more constrained molecule or by oxymercuration, would furnish tronocarpine.

Should it become viable to further progress the route outlined in Retrosynthetic Analysis 5, **Section 4.7.3 (Scheme 92)**, I have a few suggestions of how to both improve and progress the chemistry of this synthetic pathway. Access to compound **4-114** is possible as discussed earlier, if improvements to the hydroboration step of this product can access more material, there exists the possibility that one of many oxidation reactions could install the desired α/β unsaturated functionality in desired compound **4-138 (Scheme 101)**. All of the reactions in **Scheme 101** would be worth exploring to access the valuable product **4-138**. Saegusa outlines how from silyl enol ethers (**4-139**) Pd(II) chemistry will access products like **4-140**.¹⁴⁴ Nicolaou and Stahl have outlined using IBX or palladium chemistry with oxygen as easily accessible pathways to get directly to the α/β unsaturated ketones (**4-142, 4-144**).¹⁴⁵ Brown showcases B-I-9-BBN paired with Pd to oxidize ketone substrates (**4-146**) and Legault showcases iodine reagents that add OTs groups that could be eliminated to give desired functionality (**4-150b**).¹⁴⁶ Finally, Newhouse explored zinc reagents helping to facilitate palladium oxidation chemistry again that could give the desired product **4-138**.¹⁴⁷ As a note, any work involving IBX in this way requires very dry conditions (DMSO distilled before *every* reaction) and the IBX is recommended to be made by the operating chemist.

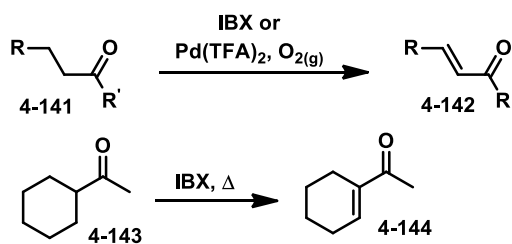
In compiling the work towards synthesizing tronocarpine and dippinine B, it became apparent that generating a macrocyclic intermediate from the thioester containing components was never attempted (**Scheme 102**). This may be a solution to getting around the road-blocks found in this project. From an intermediate like **4-151 (Scheme 102)**, the difference in reactivity between methyl ester and thioester may allow selective closure of the tryptamine amine to generate amide macrocycle **4-152**. If R of **4-151** is a carboxylic acid, an EDC coupling may fashion the same macrocycle. This macrocycle may have completely different reactivity to close ring E of tronocarpine and dippinine B. The intermediate **4-152** should have no problems with radical closure to the indole component via SET agent.



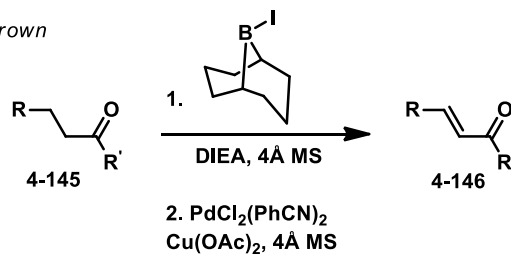
Saegusa



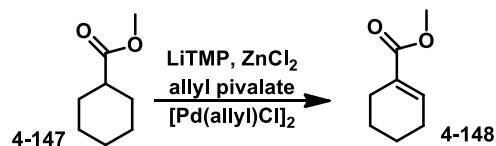
Nicolaou and Stahl



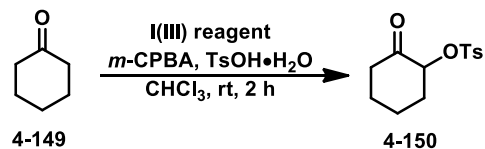
Brown



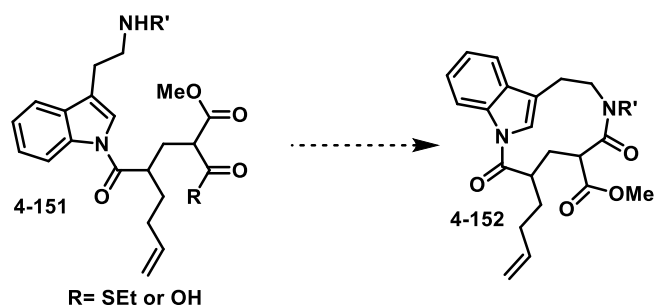
Newhouse



Legault



Scheme 101 - Oxidations worth trying to elucidate the alpha/beta functionality of compound 4-138



Scheme 102 - Generating macrocycle to access novel intermediate that may aid the synthesis of tronocarpine

I hope further progress resulting in the successful synthesis of these molecules is harnessed in the future.

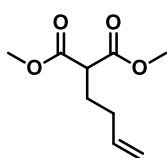
4.10 Experimental

4.10.1 General Experimental Details

All reactions were conducted under an air atmosphere unless otherwise indicated. Flasks were oven dried and cooled in a desiccator prior to use. All chemicals were of reagent quality and used as obtained from commercial sources except for the $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$, which was prepared by modified literature procedure (the exact procedure noted in Chapter 3). NMR experiments were performed on either a Bruker AvIII 400, Varian Inova 400 and Inova 600 instruments and samples were obtained in CDCl_3 (referenced to 7.25 ppm for ^1H and 77.0 ppm for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on Thermo Scientific DFS mass spectrometer using electron impact ionization. Microwave reactions were performed in a 400 W Biotage Initiator 2.0 microwave reactor. Dichloromethane (DCM), acetonitrile (MeCN), toluene, benzene and THF were dried and deoxygenated by passing the nitrogen purged solvents through activated alumina columns. THF was additionally distilled from CaH_2 and stored over 4\AA molecular sieves. All other reagents and solvents were used as purchased from Sigma-Aldrich, Alfa Aesar, Caledon or Oakwood Chemicals. Reaction progress was followed by thin layer chromatography

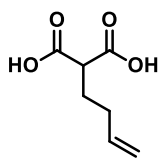
(TLC) (Merck, TLC Silica gel 60 F254) visualizing with UV light, and the plates were developed using acidic *p*-anisaldehyde or potassium permanganate. Column chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh). All columns were performed using Still's procedure for flash chromatography.⁹⁶ IR spectra were acquired using a PerkinElmer Spectrum Two FT-IR or Bruker Alpha II Di-ATR.

4.10.2 Experimental Procedures for Selected Products

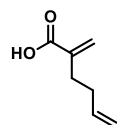


dimethyl 2-(but-3-en-1-yl)malonate (4-33)

4-bromobutene (25 g, 185 mmol, 1 equiv.) and dimethylmalonate (122 g, 926 mmol, 5 equiv.) were added to a 2L round bottom that had been flushed with argon. 356 mL of THF followed by 356 mL of DMF were added. Potassium carbonate (128 g, 926 mmol, 5 equiv.) was then added to the flask but with such a large amount the mixture was tough to stir. The flask was then equipped with a reflux condenser and argon balloon and heated at 90 °C for 20 hours. The flask was occasionally, carefully, swirled by hand to help mix the contents of the reaction. When indicated complete by TLC the reaction was diluted with hexanes and then vacuum filtered through a pad of Celite. The collected volume was concentrated *in vacuo* and then re-dissolved in Et₂O. The Et₂O layer was washed with bicarb and then the bicarb layer was extracted twice more with Et₂O. The combined organic fractions were washed 6 times with 1M NaOH or until all the malonate was gone by TLC analysis (stains purple in acidic *p*-anisaldehyde). The organic layer was then washed twice with water and once with brine. The organic layer was dried with MgSO₄, filtered and concentrated *in vacuo* yielding pure material (32 g, 93% yield, pale yellow liquid). **R_f** = 0.36 (15% EtOAc: 85% Hexanes). **¹H NMR (600 MHz, CDCl₃)** δ = 5.74 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.95 (m, 2H), 3.72 (s, 6H), 3.38 (t, *J* = 7.4 Hz, 1H), 2.08 (q, *J* = 6.6 Hz, 2H), 1.99 (q, *J* = 7.4 Hz, 2H) data matches literature report.¹⁴⁸

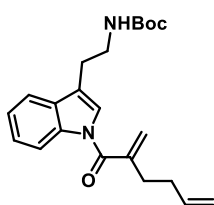
2-(but-3-en-1-yl)malonic acid (4-35)

(**4-33**) (25 g, 136 mmol, 1 equiv.) was added to a 5 L round bottom flask. THF (680 mL) and MeOH (680 mL) were added and the mixture was stirred open to air. While stirring 2M NaOH (544 mL, 1088 mmol, 8 equiv.) was added slowly over approx. 10 mins to the stirring reaction. A small amount of heat was generated. The reaction was stirred under an atmosphere of air for 20 hours. When TLC confirmed complete consumption of starting materials the reaction was concentrated *in vacuo* and extracted 1x with Et₂O to remove any left-over starting material if there was any (even if the TLC didn't show any). The water layer was then acidified to pH =1 using concentrated HCl and extracted three times with Et₂O. The combined organic fractions were washed with brine, dried with MgSO₄, filtered and then concentrated *in vacuo* to yield crude product (21 g, <94%, white, granular, "wet looking", low melting solid). The crude product was used without further purification in the next step. **R_f** = 0 (50% EtOAc: 50% Hexanes). ¹H NMR (400 MHz, CDCl₃) δ = 11.42 (s, br, 1H), 5.76 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.11 – 5.00 (m, 2H), 3.48 (t, *J* = 7.3 Hz, 1H), 2.22 – 2.12 (m, 2H), 2.09 – 2.00 (m, 2H) ¹³C NMR (101 MHz, CDCl₃) δ = 175.6, 136.7, 117.0, 51.2, 31.5, 28.1.

2-methylenehex-5-enoic acid (4-28)

Diacid (**4-35**) (16.61 g, 105 mmol, 1 equiv.) was placed into a 500 mL round-bottom containing pyridine (35 mL) followed by paraformaldehyde (3.47 g, 115 mmol, 1.1 equiv.) and piperidine (1.04 mL, 10.5 mmol, 0.1 equiv.). The round-bottom flask was equipped with reflux condenser and placed into an oil bath at 130 °C. A rubber septa containing an empty balloon was secured on top of the condenser only to observe the evolution of gasses. Note that an excessively large flask was used as the quick evolution of gasses create a foamy mixture that must be contained. The reaction was left to reflux for 2 hours at which point TLC analysis confirmed completion of the reaction. The mixture was cooled to rt, acidified with 5% HCl solution until pH 2-3 and extracted with Et₂O three times. The organic extracts were combined and washed with 5% HCl 5 times until the pyridine was gone as determined by TLC, followed by a brine

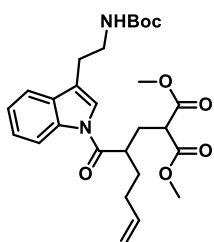
wash. The organic extract was dried with MgSO_4 and concentrated *in vacuo* to yield the product as a yellow liquid (9.49 g, 72% yield) $R_f = 0.75$ (50% EtOAc:Hexanes) $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 11.75$ (s, br, 1H), 6.32 (s, 1H), 5.80 (ddt, $J = 16.8, 10.2, 6.6$ Hz, 1H), 5.66 (s, 1H), 5.09 – 4.92 (m, 2H), 2.40 (dt, $J = 7.5, 1.2$ Hz, 1H), 2.30 – 2.21 (m, 2H) $^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta = 173, 139.4, 137.6, 127.8, 115.4, 32.6, 31.0$ IR (cm^{-1}) 2922, 2603, 1693, 1627, 1422, 1295, 1221, 1161, 997, 948 HRMS m/z [M^+] 125.06002 (calcd for $\text{C}_7\text{H}_{10}\text{O}_2$, 125.06808).



tert-butyl (2-(1-(2-methylenehex-5-enyl)-1H-indol-3-yl)ethyl)carbamate (4-43)

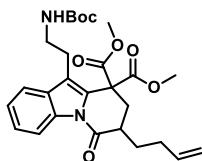
Acrylic acid (**4-28**) (6.20 g, 49.1 mmol, 1 equiv) was added to a 25 mL round-bottom and put under and inert atmosphere of argon. Oxalyl chloride (4.45 mL, 51.0 mmol, 1.05 equiv.) was added slowly to the flask followed by a single catalytic drop of DMF. This reaction mixture was stirred two hours. To a 500 mL round-bottom was added boc-protected tryptamine **4-42** (6.39 g, 24.5 mmol, 1 equiv) in 250 mL of DCM. Bu_4NHSO_4 (0.83 g, 2.45 mmol, 0.1 equiv) was added to the tryptamine followed by powdered NaOH (4.91 g, 122.7 mmol, 5 equiv.). The reaction was put under and inert atmosphere of argon and allowed to stir for a minimum of 15 min. At this point the acid chloride generated in the 25 mL round bottom was cannula transferred over in its entirety (~7.10 g, 49.1 mmol, 2 equiv). The mixture was stirred under Ar at rt for 1 hr at which point TLC confirmed complete consumption of starting material. The reaction was quenched with water and extracted with DCM 3 times. The combined organic extracts were washed with water once, followed by brine and then dried with MgSO_4 . The solvent was removed *in vacuo* to yield the crude material. Purification of the crude compound by flash column chromatography was performed using 30% EtOAc: 70% Hexanes to yield the product as a slightly yellow oil (8.81 g, 83%). $R_f = 0.46$ (30% EtOAc: 70% Hexanes) $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 8.43$ (d, $J = 8.2$ Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.33 – 7.27 (m, 2H), 5.81 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H), 5.65 (s, 1H), 5.45 (s, 1H), 5.08 – 4.96

(m, 2H), 4.63 (br, s, 1H), 3.44 (q, $J = 6.6$ Hz, 2H), 2H), 2.88 (t, $J = 6.9$ Hz, 2H), 2.62 (t, $J = 7.4$ Hz, 2H), 2.34 – 2.26 (m, 2H), 1.43 (s, 9H) ^{13}C NMR (101 MHz, CDCl_3) $\delta =$ 169.3, 156.0, 143.9, 137.2, 136.2, 131.1, 125.3, 123.9, 121.2, 119.0, 116.9, 116.0, 40.17, 32.0, 33.2, 28.5, 25.7 IR (cm^{-1}) 3356, 2976, 2928, 1684, 1630, 1510, 1451, 1356, 1248, 1170 HRMS m/z [M^+] 368.2094 (calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$, 368.2099).



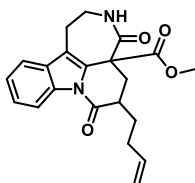
dimethyl 2-(2-(3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carbonyl)hex-5-en-1-yl)malonate (4-44)

NaH (1.56 g, 39.0 mmol, 2 equiv.) was added to an argon flushed round bottom followed by THF (98 mL, 0.2 M). The flask was placed under a balloon of argon and then cooled to 0 °C. Dimethyl malonate (4.46 mL, 39 mmol, 2 equiv.) was added dropwise at careful of violent bubbling. The mixture was stirred for 15 minutes. Indole **4-43** (7.20 g, 19.5 mmol, 1 equiv.) was added via syringe and the reaction was removed from the ice/water bath. Stirring at room temperature, when TLC indicated complete consumption of starting material, the reaction was carefully quenched with water. The mixture was transferred to a separatory funnel and extracted with EtOAc 3 times. The combined organic fractions were washed with brine and then dried with MgSO_4 . The crude solution was filtered and concentrated *in vacuo* and the isolated residue was subjected to column chromatography (25% EtOAc:75% Hexanes). The purified material **4-44** was isolated as a pale-yellow oil (8.10 g, 83% yield). $R_f = 0.23$ (25% EtOAc: 75% Hexanes). ^1H NMR (400 MHz, Chloroform- d) δ 8.50 (d, $J = 8.2$ Hz, 1H), 7.54 (d, $J = 7.7$ Hz, 1H), 7.40 – 7.27 (m, 3H), 5.83 – 5.66 (m, 1H), 5.01 (d, $J = 1.3$ Hz, 1H), 5.00 – 4.93 (m, 1H), 4.73 (s, br, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.47 (m, 3H), 2.91 (t, $J = 6.9$ Hz, 2H), 2.48 (ddd, $J = 14.5, 8.9, 6.2$ Hz, 1H), 2.27 – 2.05 (m, 3H), 1.97 (dq, $J = 14.6, 7.3$ Hz, 1H), 1.77 – 1.63 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 169.4, 169.4, 155.9, 137.2, 136.2, 130.6, 125.5, 123.8, 121.8, 120.1, 118.9, 117.2, 116.1, 60.4, 52.7, 49.2, 41.3, 31.9, 31.0, 28.4, 25.8, 21.1, 14.2. IR (cm^{-1}) 3396, 2952, 1733, 1693, 1511, 1452, 1247, 1160 HRMS m/z [M^+] 500.2529 (calcd for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_7$ 500.2523)



dimethyl 7-(but-3-en-1-yl)-10-(2-((tert-butoxycarbonyl)amino)ethyl)-6-oxo-7,8-dihydropyrido[1,2-a]indole-9,9(6H)-dicarboxylate (4-45)

Indole (**4-44**) (5.75 g, 11.5 mmol, 1 equiv.) was dissolved in 164 mL of MeOH. To the solution of indole was added $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (9.25 g, 34.5 mmol, 3 equiv.) and the mixture was fitted with a reflux condenser and purged with an atmosphere of Argon. The reaction was left to reflux for 16 h before TLC indicated complete consumption of starting materials. The crude mixture was concentrated to remove MeOH and diluted with water. The water layer was extracted 3x with EtOAc and the combined organic fractions were washed with brine 2x. The collected organic layer was dried with MgSO_4 and concentrated *in vacuo*. Pure material was isolated by flash column chromatography using an eluent of 30% EtOAc: 70% Hexanes and collected as a white solid (5.48 g, <94%). $R_f = 0.41$ (30% EtOAc: 70% Hexanes) $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 8.50$ (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 7.6$ Hz, 1H), 7.36 (t, $J = 7.1$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 5.83 (ddt, $J = 17.2, 10.2, 6.3$ Hz, 1H), 5.13 – 5.00 (m, 2H), 4.81 (br, s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.42 (dt, $J = 12.4, 6.0$ Hz, 2H), 2.93 – 2.83 (m, 2H), 2.77 – 2.59 (m, 2H), 2.38 (t, $J = 13.1$ Hz, 1H), 2.33 – 2.17 (m, 3H), 1.67 (q, $J = 8.3$ Hz, 1H), 1.43 (s, 9H) $^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta = 170.5, 170.4, 168.9, 156.0, 137.5, 134.8, 128.7, 125.9, 124.3, 119.5, 119.0, 116.9, 115.9, 55.9, 53.9, 53.7, 39.3, 35.0, 30.8, 28.9, 28.6$ IR (cm^{-1}) 3272, 2956, 1736, 1697, 1456, 1377, 1242, 1167, 1075, 76 HRMS m/z [M^+] 498.2361 (calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_7$, 498.2366).

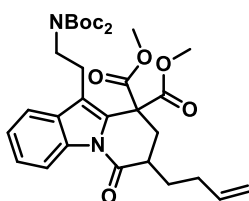


methyl 6-(but-3-en-1-yl)-4,7-dioxo-1,2,3,4,4a,5,6,7-octahydroazepino[3,4,5-hi]benzo[b]indolizine-4a-carboxylate (4-46)

Indole (**4-45**) (4.81 g, 9.65 mmol, 1 equiv.) was dissolved in benzene (96 mL) and *p*-toluenesulfonic acid (3.67 g, 19.3 mmol, 2 equiv) was added. The flask was equipped with a Dean-Stark trap and reflux condenser and put on heat at 80 °C for 1.5 h. At this point TLC indicated completion of the boc deprotection and the benzene was

removed *in vacuo*. The crude mixture was dissolved in 193 mL of MeOH and Na₂CO₃ (9.21 g, 87.0 mmol, 9 equiv) was added and put under an atmosphere of argon. The reaction was allowed to stir at rt for 3 h. MeOH was removed *in vacuo* and the crude residue was dissolved in water. DCM was used to extract from the water layer 3x followed by a brine wash of the collected organic fractions. The organic layer was washed once more using brine and dried with MgSO₄. The DCM was removed *in vacuo* to reveal the pure product as a white solid (3.45 g, 98%). **R_f** = 0.13 (50%

EtOAc:Hexanes) **¹H NMR (400 MHz, CDCl₃)** δ = 8.51 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.33 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.57 (s, 1H), 5.80 (dddd, *J* = 17.6, 10.2, 7.7, 5.6 Hz, 1H), 5.10 – 4.98 (m, 2H), 3.79 (s, 3H), 3.58 (t, *J* = 8.8 Hz, 1H), 3.58 (t, *J* = 8.8 Hz, 1H), 3.50 – 3.41 (m, 1H), 2.94 (dd, *J* = 9.1, 3.6 Hz, 2H), 2.66 (dq, *J* = 12.1, 4.2 Hz, 2H), 2.48 (t, *J* = 14.7 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.26 – 2.16 (m, 1H), 1.77 – 1.66 (m, 1H) **¹³C NMR (101 MHz, CDCl₃)** δ = 171.3, 170.8, 169.9, 137.7, 134.8, 129.7, 126.6, 126.1, 124.1, 118.2, 118.2, 116.9, 115.8, 77.5, 77.4, 77.2, 76.8, 54.1, 53.8, 38.7, 37.9, 34.0, 30.8, 28.2, 26.1 **IR (cm⁻¹)** 3213, 1732, 1695, 1672, 1614, 1457, 1366, 1291, 1228, 1193 **HRMS *m/z* [M⁺]** 366.1578 (calcd for C₂₁H₂₂N₂O₄, 366.1560).

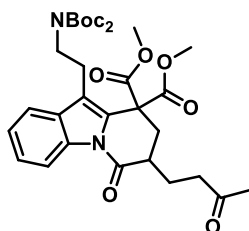


4-59 precursor

DMAP (0.039 g, 0.32 mmol, 0.17 equiv.) and Boc₂O (2.07 g, 9.5 mmol, 5 equiv.) were dissolved in 10 mL THF. The flask was purged with argon and indole (**4-45**) (0.95 g, 1.90 mmol, 1 equiv.).

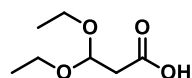
The reaction was stirred under argon for 24 hours and then concentrated *in vacuo* and purified by column chromatography (20% EtOAc: 80% Hexanes **R_f**= 0.39). Product (#) was isolated as a white solid (1.05 g, 92%). **¹H NMR (400 MHz, CDCl₃)** δ = 8.49 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 7.3 Hz, 1H), 7.37 – 7.30 (m, 2H), 5.91 – 5.76 (m, 1H), 5.10 (d, *J* = 17.8 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 3.90 (s, 3H), 3.88 – 3.81 (m, 2H), 3.80 (s, 3H), 2.98 – 2.86 (m, 2H), 2.84 – 2.72 (m, 2H), 2.34 (t, *J* = 12.8 Hz, 1H), 2.31 – 2.17 (m, 3H), 1.73 – 1.64 (m, 1H), 1.51 (s, 18H) **¹³C NMR (101 MHz, CDCl₃)** δ = 170.6, 168.8, 153.1, 137.7, 134.8, 130.5, 128.8, 125.7, 124.3, 119.9, 119.0, 116.8, 115.8, 82.5, 55.6,

54.0, 53.7, 44.6, 39.3, 35.3, 30.8, 29.0, 28.2, 24.7. **IR** (cm^{-1}) 2983, 1733, 1694, 1456, 1367, 1347, 1275, 1134, 1119, 854, 761. **HRMS** m/z [M^+] 598.2913 (calcd for $\text{C}_{32}\text{H}_{42}\text{N}_2\text{O}_9$, 598.2890).

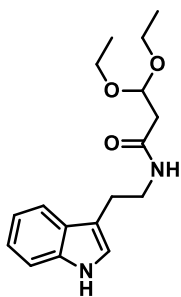
**4-59**

PdCl_2 (0.082 g, 0.46 mmol, 0.3 equiv.) and CuCl_2 (0.21 g, 1.55 mmol, 1 equiv.) were added to a round bottom flask and half the volume (15 mL) of a 7:1 mixture of DMSO:water (29 mL total) was added to the flask. The flask was evacuated and refilled with a balloon of oxygen 5 times. Starting indole (**4-59 precursor**) (1.05 g, 1.75 mmol, 1.13 equiv.) was dissolved in the other half of the DMSO:water solvent and then added dropwise to the palladium reaction. The reaction was again evacuated and refilled with oxygen. The reaction was stirred at 40 °C under 1 atm of oxygen for 12 hours at which point TLC confirmed consumption of the starting indole. The reaction was quenched with 5% HCl and extracted three times with EtOAc. The organic fraction was washed with water 5 times, then brine, dried with MgSO_4 and filtered. The filtrate was concentrated *in vacuo* to yield the crude material which was purified by column chromatography (40% EtOAc: 70% Hexanes **Rf**= 0.39) to isolate pure the material (0.87 g, 81% yield, white solid).

^1H NMR (400 MHz, CDCl_3) δ = 8.47 (dd, J = 6.2, 2.6 Hz, 1H), 7.93 – 7.84 (m, 1H), 7.38 – 7.28 (m, 2H), 3.89 (s, 3H), 3.87 – 3.82 (m, 2H), 3.80 (s, 3H), 2.93 (ddd, J = 13.6, 10.2, 6.0 Hz, 1H), 2.85 – 2.64 (m, 5H), 2.42 – 2.23 (m, 1H), 2.18 (s, 3H), 2.01 – 1.86 (m, 1H), 1.51 (s, 18H) **^{13}C NMR (101 MHz, CDCl_3)** δ 207.9, 170.4, 170.2, 168.8, 153.1, 134.7, 130.5, 128.7, 125.8, 124.4, 119.9, 119.2, 116.8, 82.5, 77.5, 77.4, 77.2, 76.8, 60.5, 55.6, 54.1, 53.8, 53.7, 44.6, 42.3, 40.9, 39.4, 35.7, 30.1, 28.2, 24.7, 24.0, 21.2, 14.3. **IR** (cm^{-1}) 2980, 1747, 1732, 1693, 1457, 1367, 1350, 1164, 1134, 1119, 856. **HRMS** m/z [M^+] 614.2836 (calcd for $\text{C}_{32}\text{H}_{42}\text{N}_2\text{O}_{10}$, 614.2840).

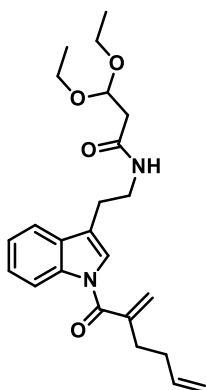
**3,3-diethoxypropanoic acid (4-69)**

Synthesized following literature procedure.¹⁴⁹



N-(2-(1H-indol-3-yl)ethyl)-3,3-diethoxypropanamide (4-71)

Tryptamine (0.20 g, 1.25 mmol) and 3,3-diethoxypropanoic acid (**4-69**) (0.20 g, 1.25 mmol) were added to a round bottom with 12.5 mL DCM (0.1 M). EDC (0.19 g, 1.25 mmol) was added portion wise, and the flask was placed under a balloon of argon. Upon TLC indication of consumption of starting material, the reaction was quenched with water and extracted 3x with DCM. The combined organic fractions were washed with brine, dried with MgSO₄, filtered and concentrated *in vacuo*. The crude oil was purified via column chromatography (90% EtOAc:10% Hexanes **R_f** = 0.5) to yield 75% of product **4-71** as an orange oil (0.28 g).

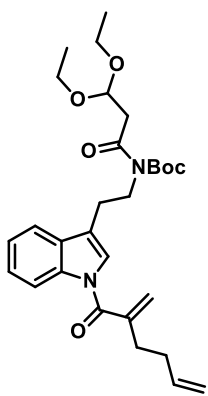


3,3-diethoxy-N-(2-(1-(2-methylenehex-5-enyl)-1H-indol-3-yl)ethyl)propenamide (4-73)

Acrylic acid (**4-28**) (0.0922 g, 0.66 mmol, 1 equiv.) was added to a round bottom flask under argon and equipped with stir bar. Oxalyl chloride (0.0937, 0.66 mmol, 1.01 equiv.) was added dropwise watching for the violent formation of gas. One drop of DMF was added to the mixture using a bleed needle for gaseous release. The mixture was stirred for 2 hours at room temperature to form desired acid chloride.

In a separate round bottom indole (**4-71**) (0.10 g, 0.33 mmol, 1 equiv. (0.5 equiv. to acid chloride)), tetrabutylammonium hydrogensulfate (0.01 g, 0.033 mmol, 0.1 equiv.) and powdered NaOH (0.066 g, 1.65 mmol, 5 equiv.) were added to 3.3 mL of DCM. The flask was purged with argon and stirred for 30 minutes before transferring (via cannula) the contents of the acid chloride reaction. After 1.5 hours TLC determined consumption of starting material and the reaction was quenched with water, extracted three times with DCM, dried with MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (60% EtOAc: 40% Hexanes) to isolate 0.057 g of

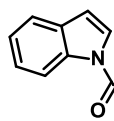
pure product (42%, yellow solid). **R_f**= 0.52 (60% EtOAc: 40% Hexanes). **¹H NMR (600 MHz, CDCl₃)** δ = 8.42 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 8.2 Hz, 1H), 7.33 – 7.28 (m, 2H), 6.36 – 6.31 (m, br, 1H amide NH), 5.82 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.65 (s, 1H), 5.45 (s, 1H), 5.07 – 4.97 (m, 2H), 4.71 (t, *J* = 5.3 Hz, 1H), 3.63 – 3.55 (m, 4H), 3.43 (dq, *J* = 9.4, 7.0 Hz, 2H), 2.90 (t, *J* = 7.1 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.51 (d, *J* = 5.3 Hz, 2H), 2.30 (q, *J* = 6.9 Hz, 2H), 1.11 (t, *J* = 7.0 Hz, 6H) **IR (cm⁻¹)** 3295, 2974, 1677, 1634, 1553, 1454, 1371, 1211, 1062, 755. **HRMS *m/z* [M⁺]** 412.2353 (calcd for C₂₄H₃₂N₂O₄, 412.2362).



tert-butyl (3,3-diethoxypropanoyl)(2-(1-(2-methylenehex-5-enoyl)-1H-indol-3-yl)ethyl)carbamate

DMAP (0.013 g, 0.10 mmol) and Boc₂O (0.66 g, 3.05 mmol) were added to THF (3 mL, 0.2 M) and the flask placed under an argon atmosphere. **4-73** (0.25 g, 0.61 mmol) was added followed by NEt₃ (0.08 mL, 0.61 mmol). The reaction was stirred at rt for 18 h at which point TLC indicated consumption of starting materials. The reaction was concentrated *in vacuo* and purified by column chromatography (10% EtOAc: 90% Hexanes **R_f**= 0.21). Pure product was isolated as a clear pale-yellow oil (0.26 g, 85% yield).

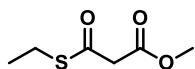
¹H NMR (599 MHz, Chloroform-*d*) δ 8.42 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.36 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.31 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27 (s, 1H), 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.65 – 5.62 (m, 1H), 5.44 (s, 1H), 5.08 – 4.97 (m, 3H), 3.97 – 3.91 (m, 2H), 3.70 (dq, *J* = 9.3, 7.0 Hz, 2H), 3.58 (dq, *J* = 9.4, 7.0 Hz, 2H), 3.22 (d, *J* = 5.7 Hz, 2H), 2.92 – 2.87 (m, 2H), 2.62 – 2.58 (m, 2H), 2.30 (tdt, *J* = 7.9, 6.5, 1.4 Hz, 2H), 1.34 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 6H). **¹³C NMR (101 MHz, CDCl₃)** δ 172.5, 169.4, 153.0, 143.9, 137.2, 136.1, 131.3, 125.3, 124.7, 124.0, 121.1, 119.1, 119.0, 116.9, 115.9, 100.3, 83.4, 62.3, 44.4, 43.7, 33.3, 32.0, 27.9, 24.3, 15.5. **IR (cm⁻¹)** 2975, 1729, 1684, 1452, 1369, 1350, 1146, 1120, 749. **HRMS *m/z* [M⁺]** 512.2901 (calcd for C₂₉H₄₀N₂O₆, 512.2886).



1-(1H-indol-1-yl)-2-methylenehex-5-en-1-one (4-50)

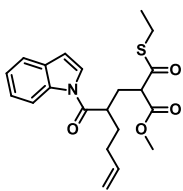
Acrylic acid (**4-28**) (2.00 g, 15.8 mmol, 1 equiv.) is added to an argon flushed round bottom. Oxalyl chloride (2.03 g, 16.0 mmol, 1.01 equiv.) was added via syringe dropwise then one drop of DMF was added. The mixture was stirred for 2 hours before being added to the other reaction below.

In a separate round bottom flask was added indole (**1-1**) (0.93 g, 7.9 mmol, 1 equiv.), tetrabutylammonium hydrogensulfate (0.27 g, 0.79 mmol, 0.1 equiv.), powdered NaOH (1.58 g, 39.5 mmol, 5 equiv.) and DCM (79 mL). The mixture was stirred under argon for 30 minutes before adding the acid chloride reaction to the flask via cannula. Then the reaction was monitored by TLC for consumption of the indole (1.5 hours). The reaction was quenched with water and extracted with DCM three times, dried with MgSO₄, and filtered. The crude oil was purified by column chromatography (5% EtOAc: 95% Hexanes) to isolate the pure product (1.65 g, 93%, pale yellow oil). **Rf**= 0.32 (5% EtOAc: 95% Hexanes). **¹H NMR (400 MHz, CDCl₃)** δ = 8.44 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 3.8 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.29 (td, *J* = 7.5, 1.1 Hz, 1H), 6.59 (d, *J* = 4.4 Hz, 1H), 5.90 – 5.76 (m, 1H), 5.67 (t, *J* = 1.2 Hz, 1H), 5.48 (s, 1H), 5.09 – 4.93 (m, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.37 – 2.26 (m, 2H) **¹³C NMR (101 MHz, CDCl₃)** δ = 169.5, 143.8, 137.1, 135.7, 131.0, 128.7, 127.2, 124.9, 123.9, 121.3, 120.8, 116.6, 115.9, 115.6, 108.4, 33.1, 31.9. **IR (cm⁻¹)** 2979, 1686, 1535, 1449, 1343, 1204, 1017, 749. **HRMS** *m/z* [M⁺] 225.1155 (calcd for C₁₅H₁₅NO, 225.1154).



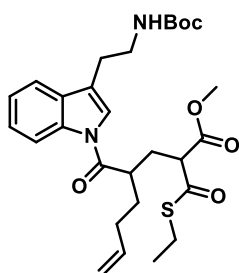
methyl 3-(ethylthio)-3-oxopropanoate (4-78)

Synthesized following literature procedure.¹⁵⁰



**methyl 2-((ethylthio)carbonyl)-4-(1H-indole-1-carbonyl)oct-7-enoate
(4-86 precursor)**

Indole (1-1) (0.79 g, 3.51 mmol), thioester **4-78** (1.19g, 7.37 mmol) and K_2CO_3 were all added to a round bottom flask with 23 mL THF (0.15 M). One drop of water was added, and the flask equipped with reflux condenser under a balloon of argon. The reaction was heated at reflux for 4 h when TLC indicated consumption of starting material. The reaction was cooled to rt and diluted with EtOAc, washed with water 3x followed by a brine was and then the organic fraction collected. The organic fraction was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (10% EtOAc: 90% Hexanes R_f = 0.3) but was inseparable from the presence of ethylthiomethyl malonate. The product was a mixture of diastereomers and used crude isolated as a colourless oil (1.45 g, >100% crude (1.35 g theoretical)).

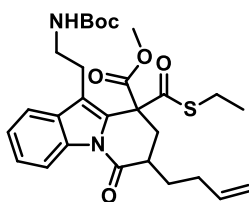


methyl 4-(3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carbonyl)-2-((ethylthio)carbonyl)oct-7-enoate (4-79)

Indole **4-43** (1.00 g, 2.70 mmol, 1 equiv.), methyl 3-(ethylthio)-3-oxopropanoate (1.10 g, 6.78 mmol, 2.5 equiv.), and K_2CO_3 (0.37 g, 2.70 mmol, 1 equiv.) were added to THF (18 mL) followed by one drop of water. The reaction was refluxed under argon for 12 hours. The mixture was diluted with EtOAc and washed with water three times and brine once. The collected organic fraction was dried with $MgSO_4$, filtered and concentrated *in vacuo* to yield crude product. Crude product was purified by column chromatography (25% EtOAc: 75% Hexanes) and (4-79) was isolated (0.97 g, 67%, yellow oil). R_f = 0.33 (25% EtOAc: 75% Hexanes).

1H NMR (600 MHz, $CDCl_3$) mixture of diastereomers δ = 8.51 (d, J = 6.5 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.33 – 7.27 (m, 2H), 5.84 – 5.65 (m, 1H), 5.06 – 4.90 (m, 2H), 4.73 (s, 1H), 3.78 – 3.58 (m, 4H), 3.55 – 3.40 (m, 2H), 3.30 –

3.12 (m, 1H), 2.89 (m, 4H), 2.55 – 2.38 (m, 1H), 2.32 – 2.20 (m, 1H), 2.12 (ddq, $J = 21.6, 14.6, 7.7$ Hz, 3H), 1.95 (dq, $J = 15.0, 8.1, 7.3$ Hz, 1H), 1.71 (dq, $J = 13.9, 6.8$ Hz, 2H), 1.43 (s, 9H), 1.30 – 1.10 (m, 3H) ^{13}C NMR (101 MHz, CDCl_3) mixture of diastereomers δ 194.9, 194.7, 173.3, 173.3, 169.0, 156.0, 137.3, 136.3, 130.8, 125.7, 124.0, 122.0, 120.3, 119.0, 117.3, 116.2, 57.3, 53.0, 41.2, 40.2, 32.1, 31.5, 31.0, 28.5, 24.1, 14.5. IR (cm^{-1}) 3356, 2936, 2830, 1743, 1686, 1452, 1164, 1025, 752. HRMS m/z [M^+] 530.2436 (calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_6\text{S}$, 530.2451)

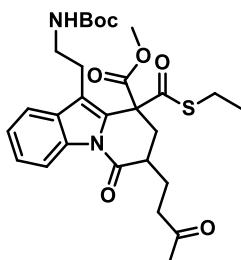


methyl 7-(but-3-en-1-yl)-10-(3-((tert-butoxycarbonyl)amino)propyl)-9-((ethylthio)carbonyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-9-carboxylate (4-80)

Indole **4-79** (0.97 g, 1.82 mmol, 1 equiv.), $\text{Mn}(\text{OAc})_3$ (1.46 g, 5.47 mmol, 3 equiv.) and MeOH (26 mL) were added to a round bottom flask equipped with stir bar and reflux condenser. The reaction was placed under a balloon atmosphere of argon and lowered into a 65 °C oil bath. When TLC indicated the complete consumption of starting material after 3 h, the reaction was cooled to room temperature and the MeOH removed *in vacuo*. The crude residue was diluted with water and EtOAc and added to a separatory funnel. The aqueous layer was extracted three times with EtOAc, and the combined organic fractions were washed with brine and then dried with MgSO_4 . The solid was filtered off and the solvent removed *in vacuo* to yield the crude residue of product **4-80** as a white solid (0.89 g, 93 % yield). The product was used as isolated in the next step without further purification. $R_f = 0.61$ (30% EtOAc: 70% Hexanes).

^1H NMR (599 MHz, Chloroform-*d*) mixture of diastereomers δ 8.53 (dd, $J = 11.2, 8.1$ Hz, 1H), 7.71 (d, $J = 7.7$ Hz, 1H), 7.38 (dt, $J = 11.2, 7.8$ Hz, 1H), 7.32 (dt, $J = 10.7, 7.5$ Hz, 1H), 5.82 (dddt, $J = 23.7, 16.8, 9.9, 6.2$ Hz, 1H), 5.14 – 5.05 (m, 1H), 5.01 (ddd, $J = 12.3, 9.9, 1.8$ Hz, 1H), 4.82 and 4.72 (each a br, s, 1H total), 3.86 and 3.82 (each a s, 3H total), 3.51 (m, 1H), 3.44 – 3.26 (m, 1H), 3.02 – 2.79 (m, 5H), 2.78 – 2.56 (m, 2H), 2.50 (t, $J = 13.2$ Hz, 0.5H) and 2.39 (t, $J = 13.1$ Hz, 0.5H) for 1H total, 2.35 – 2.12 (m, 3H), 1.67 (m, 1H), 1.45 and 1.43 (both s, 3H total), 1.32 – 1.16 (m, 3H). IR (cm^{-1}) 3411, 2931,

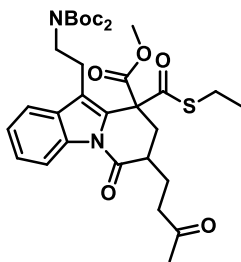
1741, 1705, 1511, 1455, 1365, 1240, 1167, 1072, 753. **HRMS** m/z [M^+] 528.2291 (calcd for $C_{28}H_{36}N_2O_6S$, 528.2294).



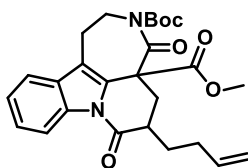
methyl 10-(2-((tert-butoxycarbonyl)amino)ethyl)-9-((ethylthio)carbonyl)-6-oxo-7-(3-oxobutyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole-9-carboxylate (4-81)

$PdCl_2$ (0.031 g, 0.18 mmol, 0.3 equiv.) and $CuCl_2$ (0.079 g, 0.59 mmol, 1 equiv.) were added to a round bottom flask and half the

volume (5.5 mL) of a 7:1 mixture of DMSO:water (11 mL total) was added to the flask. The flask was evacuated and refilled with a balloon of oxygen 5 times. Starting indole (**4-80**) (0.35 g, 0.67 mmol, 1.13 equiv.) was dissolved in the other half of the DMSO:water solvent and then added dropwise to the palladium reaction. The reaction was stirred at 40 °C for 12 hours at which point TLC confirmed consumption of the starting indole. The reaction was quenched with 5% HCl and extracted three times with EtOAc. The organic fraction was washed with water 5 times, then brine, dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to yield the crude material which was purified by column chromatography (40% EtOAc: 60% Hexanes R_f = 0.21) to give pure product (0.22 g, 60% yield, white foam solid). **1H NMR (600 MHz, $CDCl_3$) mixture of diastereomers** δ = 8.51 (t, J = 8.0 Hz, 1H), 7.76 – 7.66 (m, 1H), 7.44 – 7.29 (m, 2H), 4.79 and 4.70 (br, s, 1H total), 3.85 and 3.84 (s, 3H total), 3.51 (dq, J = 13.6, 7.2 Hz, 1H), 3.44 – 3.25 (m, 1H), 3.01 – 2.58 (m, 8H), 2.57 – 2.36 (m, 1H), 2.34 – 2.21 (m, 1H), 2.19 and 2.17 (s, 3H total), 1.93 (dq, J = 13.5, 6.0 Hz, 1H), 1.45 and 1.44 (s, br, 9H total), 1.27 (t, J = 7.5 Hz) and 1.20 (t, J = 7.6 Hz) for 3H total. **^{13}C NMR (101 MHz, $CDCl_3$) mixture of diastereomers** δ 208.0, 198.5, 197.1, 170.5, 169.2, 156.3, 135.5, 126.8, 126.5, 124.8, 120.3, 117.2, 63.4, 61.5, 54.2, 41.3, 41.1, 39.2, 37.4, 36.7, 30.5, 28.9, 25.3, 24.9, 24.4, 24.3, 14.7, 14.4. **IR (cm^{-1})** 3386, 2973, 1740, 1704, 1513, 1455, 1365, 1240, 1165, 1136, 1136, 955, 754. **HRMS** m/z [M^+] 544.2244 (calcd for $C_{28}H_{36}N_2O_7S$, 544.2243).

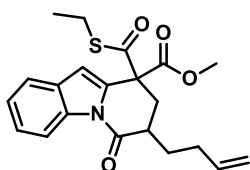
**(4-83)**

PdCl₂ (0.028 g, 0.16 mmol, 0.3 equiv.) and CuCl₂ (0.070 g, 0.52 mmol, 1 equiv.) were added to a round bottom flask and half the volume (5 mL) of a 7:1 mixture of DMSO:water (10 mL total) was added to the flask. The flask was evacuated and refilled with a balloon of oxygen 5 times. Starting indole (**4-82**) (0.37 g, 0.58 mmol, 1.13 equiv.) was dissolved in the other half of the DMSO:water solvent and then added dropwise to the palladium reaction. The reaction was again evacuated and refilled with oxygen. The reaction was stirred at 40 °C under 1 atm of oxygen for 12 hours at which point TLC confirmed consumption of the starting indole. The reaction was quenched with 5% HCl and extracted three times with EtOAc. The organic fraction was washed with water 5 times, then brine, dried with MgSO₄ and filtered. The filtrate was concentrated *in vacuo* to yield the crude material which was purified by column chromatography (30% EtOAc: 70% Hexanes **R_f**= 0.31) to isolate pure the material (0.25 g, 67% yield, yellow solid). ¹H NMR (600 MHz, CDCl₃) mixture of diastereomers δ = 8.50 (td, *J* = 7.2, 6.7, 2.0 Hz, 1H), 8.01 – 7.90 (m, 1H), 7.43 – 7.30 (m, 2H), 4.02 – 3.94 (m, 1H), 3.93 and 3.86 (each a s, 3H total), 3.84 – 3.71 (m, 1H), 3.02 – 2.76 (m, 6H), 2.76 – 2.56 (m, 2H), 2.53 – 2.22 (m, 2H), 2.19 and 2.17 (each a s, 3H total), 1.92 (td, *J* = 16.2, 15.5, 6.7 Hz, 1H), 1.51 and 1.50 (each a s, 18H), 1.24 (t, *J* = 7.4 Hz) and 1.19 (t, *J* = 7.4 Hz) (for 3H total) ¹³C NMR (101 MHz, CDCl₃) δ 207.9, 197.9, 196.7, 170.3, 170.0, 168.8, 153.1, 135.1, 130.5, 130.3, 128.9, 128.2, 126.3, 126.0, 124.5, 124.4, 120.8, 120.6, 120.3, 120.3, 116.9, 116.8, 82.6, 82.5, 62.8, 61.2, 54.2, 53.9, 44.6, 41.0, 40.8, 39.7, 38.9, 37.2, 36.6, 30.2, 28.2, 26.0, 24.9, 24.9, 24.6, 24.1, 24.0, 14.2, 14.0. IR (cm⁻¹) 2981, 1733, 1694, 1455, 1367, 1347, 1172, 1135, 1118, 855, 759 HRMS *m/z* [M⁺] 644.2765 (calcd for C₃₃H₄₄N₂O₉S, 644.2768).



3-tert-butyl 4a-methyl 6-(but-3-en-1-yl)-4,7-dioxo-1,2,4a,5,6,7-hexahydroazepino[3,4,5-hi]benzo[b]indolizine-3,4a(4H)-dicarboxylate (4-54)

Indole **4-46** (0.17 g, 0.46 mmol, 1 equiv.) was dissolved in acetonitrile (2.3 mL). DMAP (0.028 g, 0.23 mmol, 0.5 equiv.) and triethylamine (0.056 g, 0.55 mmol, 1.2 equiv.) were added and the mixture was cooled to 0 °C. Boc₂O (0.11 g, 0.51 mmol, 1.1 equiv.) was added dropwise and the reaction was warmed to room temperature and stirred for 3 hours. The mixture was concentrated *in vacuo* and columned (30% EtOAc: 70% Hexanes **R_f** = 0.45) to yield pure material (0.19 g, 87%, white solid). **¹H NMR (600 MHz, CDCl₃) mixture of diastereomers** δ = 8.55 (d, *J* = 8.2 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.36 – 7.31 (m, 1H), 5.89 – 5.75 (m, 1H), 5.13 – 5.00 (m, 2H), 4.57 (dt, *J* = 15.7, 3.5 Hz, 1H), 3.84 (s, 3H), 3.57 (ddd, *J* = 15.4, 12.2, 2.7 Hz, 1H), 3.14 – 2.93 (m, 2H), 2.79 – 2.63 (m, 2H), 2.56 (t, *J* = 14.1 Hz, 1H), 2.45 – 2.18 (m, 3H), 1.81 – 1.66 (m, 1H), 1.58 (s, 8H) **¹³C NMR (151 MHz, cdcl₃) δ mixture of diastereomers** 170.8, 170.4, 166.8, 152.5, 137.6, 137.4, 134.9, 129.2, 126.0, 124.0, 118.3, 118.2, 118.1, 116.8, 115.6, 115.4, 84.1, 56.5, 53.7, 52.6, 41.7, 37.6, 34.6, 30.6, 27.9, 24.6, 23.5. **IR(cm⁻¹)** 2987, 1710, 1458, 1371, 1284, 1198, 1132, 753. **HRMS *m/z* [M⁺]** 466.2102 (calcd for C₂₆H₃₀N₂O₆, 466.2104).



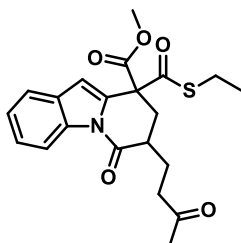
methyl 7-(but-3-en-1-yl)-9-((ethylthio)carbonyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-a]indole-9-carboxylate (4-86 precursor)

Isolated with (**4-78**) (ethylthiomethyl malonate) impurity because the molecules were the same *rf* under a variety of column eluents and could not be separated. Attempts to distill off (**4-78**) led to complete decomposition of the desired product as well. This data is crude with the malonate peaks indicated as not part of the product.

4-86 precursor (1.36 g, 3.51 mmol) and Mn(OAc)₃ (2.82 g, 10.5 mmol) were dissolved in 50 mL of MeOH (0.07 M) and refluxed under an argon atmosphere at 65 °C. After 3 h TLC indicated complete consumption of starting material and the reaction was cooled and the MeOH was concentrated off *in vacuo*. The mixture was diluted with water and EtOAc and transferred to a separatory funnel. The water layer was extracted 3x with EtOAc, the combined organic fraction washed with brine and then dried with MgSO₄,

filtered and concentrated *in vacuo*. The crude mixture was attempted to be purified by column chromatography (15% EtOAc: 85% Hexanes R_f = 0.40) but was unsuccessful in removing ethylthiomethyl malonate impurity. Isolated as a pale-yellow oil (1.29g, 96% crude)

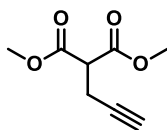
^1H NMR (400 MHz, CDCl_3) δ = 8.52-8.47 (m, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.42 – 7.26 (m, 2H), 6.83 and 6.77 (s, 1H total), 5.88-5.75 (m, 1H), 5.18 – 4.91 (m, 2H), 3.89 and 3.78 (s, 3H total), 3.74 and 3.57 MALONATE, 3.02 – 2.77 (m, 4H), 2.55 – 2.39 (m, 1H), 2.36 – 2.14 (m, 2H), 1.75-1.66 (m, 1H), 1.32 – 1.24 (m, 2H) (malonate overlapped) and 1.19 (t, J = 7.4 Hz, 1H) three total protons for the triplet SCH_2CH_3 **^{13}C NMR (101 MHz, CDCl_3)** δ 198.2, 197.1, 170.6, 169.1, 168.6, 137.5, 137.4, 135.8, 135.5, 132.2, 129.2, 129.0, 126.0, 125.7, 124.5, 124.4, 121.0, 116.9, 116.8, 116.0, 115.9, 111.2, 111.2, 61.9, 61.3, 53.7, 52.8, 49.5, 39.7, 38.6, 34.1, 33.8, 30.9, 30.7, 29.1, 28.8, 24.9, 24.6, 24.1, 14.5, 14.2, 14.1. **IR (cm^{-1})** 2952, 2931, 1750, 1705, 1669, 1451, 1235, 1180, 914, 757.



methyl 9-((ethylthio)carbonyl)-6-oxo-7-(3-oxobutyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole-9-carboxylate (4-86)

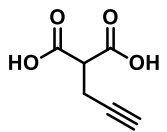
PdCl_2 (0.07 g, 0.39 mmol, 0.3 equiv.) and CuCl_2 (0.17 g, 1.3 mmol, 1 equiv.) were added to a round bottom flask and half the volume (12 mL) of a 7:1 mixture of DMSO:water (10 mL total) was added to the flask. The flask was evacuated and refilled with a balloon of oxygen 5 times. Starting indole (**4-86 precursor**) (0.59 g, 1.50 mmol, 1.13 equiv.) was dissolved in the other half of the DMSO:water solvent and then added dropwise to the palladium reaction. The reaction was again evacuated and refilled with oxygen. The reaction was stirred at 40 °C under 1 atm of oxygen for 24 hours at which point TLC confirmed consumption of the starting indole. The reaction was quenched with 5% HCl and extracted three times with EtOAc. The organic fraction was washed with water 5 times, then brine, dried with MgSO_4 and filtered. The filtrate was concentrated *in vacuo* to yield the crude material which was purified by column chromatography (30% EtOAc: 70% Hexanes) to isolate 4-86 as a yellow oil (0.15 g, 25% yield). R_f = 0.29 (30% EtOAc: 70% Hexanes).

^1H NMR (400 MHz, CDCl_3) mixture of diastereomers δ = 8.48 (m, 1H), 7.56 (t, J = 7.0 Hz, 1H), 7.43 – 7.26 (m, 2H), 6.84 and 6.78 (s, 1H total), 3.89 and 3.80 (s, 3H total), 3.01 – 2.82 (m, 3H), 2.79 – 2.64 (m, 3H), 2.56 – 2.38 (m, 1H), 2.37 – 2.23 (m, 1H), 2.19 and 2.17 (s, 3H total), 2.01 – 1.88 (m, 1H), 1.27 (t, J = 7.4 Hz, 1.5H) and 1.20 (t, J = 7.4 Hz, 1.5H) for 3H total. **^{13}C NMR (101 MHz, CDCl_3) mixture of diastereomers** δ 207.8, 198.1, 197.1, 170.2, 169.0, 168.5, 135.7, 135.5, 132.1, 129.3, 129.0, 126.1, 125.8, 124.6, 124.5, 121.1, 121.0, 116.9, 116.8, 111.5, 111.5, 61.9, 61.3, 53.8, 53.8, 41.0, 40.7, 39.8, 38.7, 34.5, 34.5, 30.2, 30.1, 25.0, 24.6, 24.3, 24.2, 14.2, 14.1. **IR**(cm^{-1}) 2952, 1735, 1715, 1671, 1589, 1565, 1451, 1349, 1241, 942, 757. **HRMS** m/z [M^+] 401.1303 (calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5\text{S}$, 401.1297).



Dimethyl propargylmalonate (4-122)

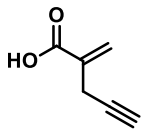
This product was purchased from Aurum Pharmatech (\$145.00/25 g) as the cheapest option but is available from MilliporeSigma (\$166.00/10g).



2-(prop-2-yn-1-yl)malonic acid (4-123)

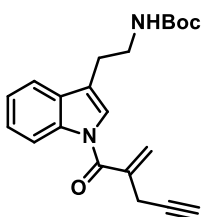
Dimethyl propargylmalonate (**4-122**) (2.81 g, 16.5 mmol) was placed into a round-bottom flask in 1:1 mixture of THF:MeOH (166 mL, 0.1 M), 2M NaOH (66 mL, 132 mmol) was added with rapid stirring and the mixture was left to stir O.N. at room temperature. When complete the reaction was concentrated *in vacuo* to remove the THF and MeOH and then was further diluted with water. The crude was extracted once with Et_2O to remove any remaining starting material and then the water later was acidified carefully with concentrated HCl to pH=1. The acidic water layer was then extracted 3x with Et_2O and the combined organic fractions were washed with brine, dried with MgSO_4 and concentrated *in vacuo* to yield pure product as a white solid (1.41 g, 66% yield).

^1H NMR data was in accordance with previously reported results.¹⁵¹

2-methylenepent-4-ynoic acid (4-119)

To an argon flushed round bottom was added **4-123** (1.41 g, 9.9 mmol), paraformaldehyde (0.36 g, 11.9 mmol), piperidine (0.1 mL, 0.99 mmol) and 5 mL of pyridine (2 M). The flask was equipped with reflux condenser and an empty balloon with a 16 gauge needle to monitor production of CO₂ gas. The reaction was placed in to a 130 °C oil bath and refluxed for 20-40 minutes depending on when gas production ceases and TLC showed consumption of starting materials. The dark burnt orange reaction was cooled to room temperature (no ice bath, just removed from the oil bath) and then acidified with 5% HCl. The aqueous mixture was added to a separatory funnel where the water layer was extracted 3x with Et₂O. Using TLC to monitor for pyridine the organic fraction was washed with 5% HCl until pyridine was no longer detectable by TLC. Then the remaining organic fraction was washed with brine, dried with MgSO₄, filtered and concentrated *in vacuo*. This product (yellow-orange solid) was pushed crude into the next step.

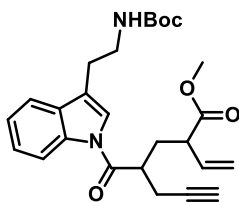
¹H NMR (400 MHz, Chloroform-*d*) δ 11.31 (br s, 1H), 6.50 (s, 1H), 6.19 (s, 1H), 3.25 (s, 2H), 2.23 (t, *J* = 2.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 171.87, 134.86, 129.42, 80.23, 72.67, 21.61. IR (cm⁻¹) 3277, 2878, 2607, 1919, 1695, 1632, 1430, 1278, 1152, 932, 666. HRMS *m/z* [M⁺] 110.0365 (calcd for C₆H₆O₂ 110.0368)

**tert-butyl (2-(1-(2-methylenepent-4-ynoyl)-1H-indol-3-yl)ethyl)carbamate (4-124)**

Acid 4-119 (0.77 g, 7.0 mmol) was added to an argon flushed round bottom. The flask was placed under a balloon of argon and oxalyl chloride (COCl)₂ (0.94 g, 7.4 mmol) was added dropwise carefully. One drop of DMF was added to catalyze the reaction, and the mixture was stirred for 2 hours. 30 minutes prior to the 2-hour mark of the acid chloride formation another round bottom was set up with the remaining required reagents: Boc-protected tryptamine (**4-42**) (0.91 g, 3.5 mmol), tetrabutylammonium hydrogensulfate (Bu₄NHSO₄) and powdered NaOH (0.70 g, 17.5 mmol) were all added

to a round bottom containing 35 mL DCM (0.1 M). The mixture was stirred vigorously for 30 minutes before transferring the contents of the acid chloride forming reaction to the tryptamine containing reaction. The mixture was stirred for room temperature for 1 h at which time TLC indicated complete consumption of starting materials. The reaction was quenched with water and the extracted 3x with DCM. The organic fractions were dried with MgSO₄, filtered, concentrated and purified by column chromatography (20% EtOAc: 80% Hexanes **R_f**= 0.4) to yield the product as a white solid (1.04 g, 84% yield).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 8.2 Hz, 1H), 7.56 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.35 – 7.29 (m, 2H), 6.11 (t, *J* = 1.8 Hz, 1H), 5.67 (t, *J* = 1.5 Hz, 1H), 4.62 (br s, 1H), 3.51 – 3.40 (m, 4H), 2.90 (t, *J* = 7.0 Hz, 2H), 2.27 (t, *J* = 2.7 Hz, 1H), 1.44 (s, 9H). **¹³C NMR (101 MHz, CDCl₃)** δ 168.19, 156.30, 138.93, 136.51, 131.51, 125.78, 124.70, 124.46, 123.18, 119.41, 117.18, 79.44, 73.32, 60.86, 40.50, 28.86, 26.09, 26.07, 23.63. **IR (cm⁻¹)** 3312, 2973, 1740, 1703, 1513, 1455, 1365, 1240, 1165, 955, 754. **HRMS *m/z* [M⁺]** 352.1787 (calcd for C₂₁H₂₄N₂O₃, 352.1787).



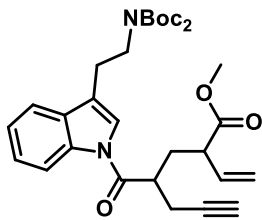
methyl 4-(3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carbonyl)-2-vinylhept-6-ynoate (4-118)

Indole **4-124** (0.16 g, 0.46 mmol) was dissolved in 1.6 mL THF (0.28 M) and left to sit under a balloon of argon. A mixture of LDA was generated by combining freshly distilled diisopropylamine in THF (1.5 mL, 0.3M) and cooling it to -78 °C. nBuLi (2.5 M in hexanes, 0.28 mL, 0.69 mmol) was added slowly dropwise and the mixture stirred for 5 minutes. (E)-methyl but-2-enoate (0.73 g, 0.73 mmol) was added slowly dropwise to the LDA solution at -78 °C and the reaction was stirred at this temperature for 20 minutes. The indole solution was then added at -78 °C and the reaction was closely monitored at this temperature every 20 minutes until the starting material was mostly consumed but a third undesired spot began forming. The reaction was quenched at -78 °C by adding wet THF followed by 5% HCl and then removed from the dry-ice bath to warm to room temperature. The mixture was extracted 3x with EtOAc,

the organic fractions washed with brine and dried with MgSO₄. The crude material was filtered, concentrated *in vacuo* and then purified by column chromatography (25% EtOAc:75% Hexanes, **R_f**= 0.43) to isolate the desired product as a yellow oil and a mixture of diastereomers. (0.072 g, 34%).

Mixture of Diastereomers:

¹H NMR (400 MHz, Chloroform-*d*) δ 8.52 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.28 (m, 3H), 5.90 – 5.69 (m, 1H), 5.24 – 4.94 (m, 2H), 4.70 (d, *J* = 13.7 Hz, 1H), 3.68 and 3.62 (s each, 3H total), 3.55 – 3.32 (m, 4H), 3.21 – 3.08 (m, 1H), 2.92 (t, *J* = 6.4 Hz, 2H), 2.75 – 2.65 (m, 1H), 2.59 – 2.40 (m, 2H), 1.43 (s, 9H). **¹³C NMR (101 MHz, CDCl₃)** δ 173.6, 172.3, 172.2, 156.0, 136.4, 135.0, 125.7, 124.1, 119.0, 118.4, 117.4, 80.8, 71.4, 60.6, 52.3, 47.7, 41.7, 34.3, 33.9, 28.6, 25.8, 22.8, 22.5, 14.4. **IR (cm⁻¹)** 2965, 1730, 1693, 1453, 1393, 1346, 1276, 1241, 1134, 750. **HRMS *m/z* [M⁺]** 452.2306 (calcd for C₂₆H₃₂N₂O₅, 452.2311).

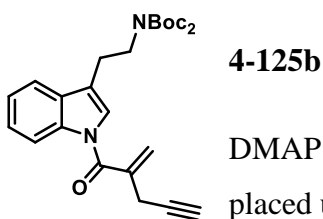


4-125

Indole **4-118** (0.92 g, 2.04 mmol) was dissolved in 7.3 mL THF (0.28 M) and left to sit under a balloon of argon. A mixture of LDA was generated by combining freshly distilled diisopropylamine (0.31 g, 3.06 mmol) in THF (6.8 mL, 0.3M) and cooling it to -78 °C. *n*BuLi (2.5 M in hexanes, 1.2 mL, 3.06 mmol) was added slowly dropwise and the mixture stirred for 5 minutes. (E)-methyl but-2-enoate (0.33 g, 3.26 mmol) was added slowly dropwise to the LDA solution at -78 °C and the reaction was stirred at this temperature for 20 minutes. The indole solution was then added at -78 °C and the reaction was closely monitored at this temperature every 20 minutes until the starting material was mostly consumed but a third undesired spot began forming. The reaction was quenched at -78 °C by adding wet THF followed by 5% HCl and then removed from the dry-ice bath to warm to room temperature. The mixture was extracted 3x with EtOAc, the organic fractions washed with brine and dried with MgSO₄. The crude material was filtered, concentrated *in vacuo* and then purified by column chromatography (15%

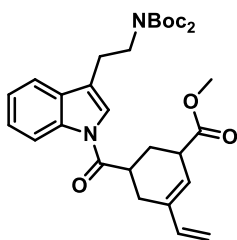
EtOAc:85% Hexanes, R_f = 0.26) to isolate the desired product as a yellow oil and a mixture of diastereomers. (0.28 g, 26%).

Mixture of diastereomers: $^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.51 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.42 – 7.27 (m, 3H), 5.90 – 5.69 (m, 1H), 5.22 – 4.97 (m, 2H), 3.93 – 3.86 (m, 2H), 3.68 and 3.63 (s each for 3H total), 3.38 (m, 1H), 3.20 – 3.10 (m, 1H), 3.05 – 2.93 (m, 2H), 2.74 – 2.62 (m, 1H), 2.58 – 2.40 (m, 2H), 2.21 (t, J = 7.2 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.47 (s, 18H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 173.6, 173.5, 172.3, 172.1, 152.7, 152.7, 136.3, 136.3, 135.1, 135.0, 131.0, 131.0, 125.6, 125.6, 124.1, 124.0, 122.3, 122.0, 120.2, 120.2, 119.2, 119.2, 119.1, 118.4, 117.3, 82.6, 82.6, 80.6, 80.5, 71.4, 71.4, 52.3, 52.2, 47.7, 47.6, 46.2, 46.2, 41.7, 41.6, 34.1, 33.8, 28.2, 24.9, 22.4, 22.3. **IR** (cm^{-1}) 2965, 1730, 1693, 1453, 1393, 1346, 1276, 1240, 1134, 856, 750, 641. **HRMS** m/z [M^+] 552.2836 (calcd for $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_7$, 552.2836).



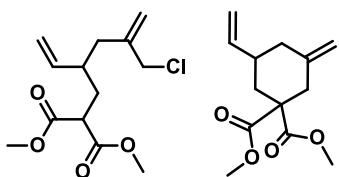
DMAP (0.04 g, 0.34 mmol) and Boc_2O in THF (10 mL, 0.2 M) were placed under a balloon of argon with stirring. **4-124** (0.7 g, 1.99 mmol) was added followed by NEt_3 (0.3 mL, 2.18 mmol) and the reaction was left to stir at room temperature overnight. When TLC indicated consumption of starting material the reaction mixture was concentrated *in vacuo* and placed directly onto column (10% EtOAc: 90 Hexanes, R_f = 0.3) to isolate the product as a white solid (0.85 g, 94%).

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.39 (d, J = 8.2 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.41 – 7.31 (m, 2H), 7.30 (s, 1H), 6.11 (t, J = 1.8 Hz, 1H), 5.68 (t, J = 1.7 Hz, 2H), 3.92 – 3.81 (m, 2H), 3.47 – 3.40 (m, 2H), 3.01 – 2.93 (m, 2H), 2.27 (t, J = 2.6 Hz, 1H), 1.45 (s, 18H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 167.9, 152.7, 138.5, 136.1, 131.4, 125.3, 124.5, 124.1, 123.0, 119.4, 119.2, 116.8, 82.5, 79.1, 73.00, 46.1, 28.2, 24.7, 23.3. **IR** (cm^{-1}) 3270, 2979, 1741, 1724, 1704, 1682, 1449, 1365, 1135, 1120, 746. **HRMS** m/z [M^+] 452.2315 (calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_5$, 452.2311).

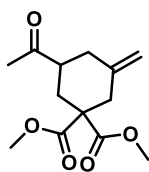
**4-117**

To indole **4-125** (0.05g, 0.09mmol) in DCM (2 mL, 0.04 M) was added Grubbs I catalyst (0.01 g, 0.009 mmol) and a balloon of ethylene gas with long needle was placed into the solution followed by a bleed needle to flush the gas through the reaction mixture for 5 minutes. The needle was then lifted out of the reaction solution and the bleed needle removed to stir the mixture under an atmosphere of ethylene equipped with reflux condenser. The mixture was heated at 35 °C for four hours and aliquots monitored by ¹H NMR was used to track the reaction progress because no R_f change was detectable by TLC. When NMR had indicated the starting material was consumed the reaction mixture was concentrated and then directly purified by column chromatography. The two diastereomers were separated to yield 2 clear oils (total mass 0.02g, 41% yield).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.34 – 7.28 (m, 3H), 6.43 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.92 (s, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.73 (s, 3H), 3.52 – 3.41 (m, 1H), 3.37 – 3.26 (m, 1H), 3.04 – 2.96 (m, 2H), 2.57 (d, *J* = 8.2 Hz, 2H), 2.45 – 2.36 (m, 1H), 2.16 – 2.07 (m, 1H), 1.46 (s, 18H). **¹³C NMR (101 MHz, CDCl₃)** δ 173.5, 173.3, 152.8, 138.4, 136.3, 130.8, 125.7, 125.4, 124.0, 121.8, 120.4, 119.2, 117.2, 113.1, 82.6, 52.3, 46.3, 42.5, 39.4, 28.6, 28.2, 27.1, 24.8. **IR (cm⁻¹)** 1694, 1453, 1349, 1135, 749. **HRMS** *m/z* [M⁺] 552.2830 (calcd for C₃₁H₄₀N₂O₇, 552.2836).



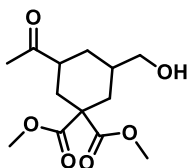
(4-108) and (4-105) synthesized following literature procedure from previous Kerr group methodology.¹³⁴

**dimethyl 3-acetyl-5-methylenecyclohexane-1,1-dicarboxylate (4-109)**

To half the desired volume of solvent DMF:H₂O (7:1) (32 mL total) in a round bottom was added PdCl₂ (0.089 g, 0.5 mmol) and CuCl₂ (0.22 g, 1.66

mmol). The flask was evacuated and refilled with a balloon of O₂ 5 times and the components left to stir for 10 minutes. Cyclohexane **4-105** (0.44 g, 1.88 mmol) was dissolved in the other half-volume of solvent system remaining and then added to the reaction flask *via* syringe. The mixture was then gently heated in a 40 °C oil bath with rapid stirring for 24 h. Upon confirmation of consumption of cyclohexane by TLC the reaction was quenched with 5% HCl and the reaction extracted 4x with EtOAc. The combined organic fractions were washed with water 5x, brine 1 x and then dried with MgSO₄, filtered and concentrated. The crude mixture was purified by column chromatography (20% EtOAc:80% Hexanes **R_f** = 0.31) to isolate the desired material as a clear, colourless oil (0.38 g, 81% yield).

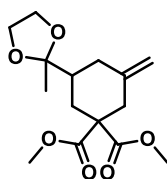
¹H NMR (400 MHz, Chloroform-*d*) δ 4.82 (dt, *J* = 5.6, 1.6 Hz, 2H), 3.73 (s, 6H), 2.91 (dt, *J* = 13.6, 1.8 Hz, 1H), 2.80 (tt, *J* = 12.6, 3.8 Hz, 1H), 2.57 (ddt, *J* = 13.6, 3.7, 2.0 Hz, 1H), 2.50 – 2.41 (m, 2H), 2.19 (s, 3H), 2.07 – 1.96 (m, 1H), 1.72 (dd, *J* = 13.5, 12.5 Hz, 1H). **IR (cm⁻¹)** 2954, 1731, 1709, 1433, 1256, 1236, 1206, 1094, 868. **HRMS *m/z* [M⁺]** 254.1149 (calcd for C₁₃H₁₈O₅, 254.1154).



dimethyl 3-acetyl-5-(hydroxymethyl)cyclohexane-1,1-dicarboxylate
(4-110)

BH₃•THF (1M in THF, 0.71 mL, 0.71 mmol) was added to a round bottom flask under argon and equipped with stir bar. The flask was cooled to 0 °C and cyclohexene (0.17 mL, 1.63 mmol) was added dropwise. This mixture was stirred at 0 °C for 1 h to generate a white slurry at which point cyclohexane **4-109** (0.15 g, 0.59 mmol) was added via syringe. The reaction was stirred again at 0 °C, monitoring by TLC after 1.5 h the starting material was gone and sodium perborate (0.32 g, 2.06 mmol) and water (0.71 mL) was added to the mixture. The reaction was warmed to rt while stirring. After 2 h the reaction mixture was transferred to a separatory funnel and extracted with EtOAc 3x. The combined organic fractions were dried with MgSO₄, filtered, concentrated and purified by column chromatography (50% EtOAc: 50% Hexanes **R_f** = 0.18) to isolate the product as a colourless oil (0.024 g, 15%).

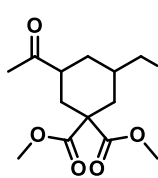
¹H NMR (400 MHz, Chloroform-*d*) δ 3.74 (s, 3H), 3.70 (s, 3H), 3.57 – 3.44 (m, 2H), 2.63 (tt, $J = 12.6, 3.4$ Hz, 1H), 2.51 (ddt, $J = 13.5, 3.4, 2.0$ Hz, 1H), 2.40 – 2.33 (m, 1H), 2.17 (s, 3H), 2.01 (ddt, $J = 9.6, 3.3, 1.6$ Hz, 1H), 1.87 (br s, 1H), 1.72 – 1.55 (m, 2H), 1.40 (t, $J = 13.1$ Hz, 1H), 0.97 (q, $J = 12.6$ Hz, 1H). **¹³C NMR (101 MHz, CDCl₃)** δ 210.39, 172.17, 171.36, 67.49, 54.72, 53.02, 52.91, 46.94, 36.42, 33.50, 32.51, 30.43, 28.36. **IR (cm⁻¹)** 3336, 2970, 2931, 1466, 1378, 1107, 1128, 950. **HRMS m/z [M⁺]** 272.1259 (calcd for C₁₃H₂₀O₆, 272.1259).



dimethyl 3-(2-methyl-1,3-dioxolan-2-yl)-5-methylenecyclohexane-1,1-dicarboxylate (4-112)

Cyclohexane **4-109** (0.075 g, 0.29 mmol), ethylene glycol (0.07 mL, 1.18 mmol), TsOH•H₂O (0.006 g, 0.029 mmol) and trimethyl orthoformate (0.15 g, 1.45 mmol) were added to benzene (1 mL, 0.3 M). The flask was placed under argon and stirred at room temperature for 48 h at which point ¹H NMR indicated complete consumption of starting material. The reaction mixture was quenched with bicarb, extracted with EtOAc 3x and the organic fractions wash with brine 1x. The organic fraction was collected was dried with MgSO₄, filtered, concentrated and purified by column chromatography (20% EtOAc:90% Hexanes **R_f** = 0.34) to collect the product as a colourless oil (0.075 g, 86% yield).

¹H NMR (599 MHz, Chloroform-*d*) δ 4.77 (d, $J = 9.5$ Hz, 2H), 4.00 – 3.85 (m, 4H), 3.71 (s, 3H), 3.70 (s, 3H), 2.90 (d, $J = 14.3$ Hz, 1H), 2.53 (d, $J = 12.9$ Hz, 1H), 2.40 (t, $J = 11.8$ Hz, 2H), 1.99 – 1.90 (m, 1H), 1.85 (t, $J = 13.0$ Hz, 1H), 1.57 (t, $J = 12.8$ Hz, 1H), 1.29 (s, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ 172.39, 170.93, 143.43, 111.60, 110.85, 64.98, 61.37, 56.51, 52.92, 52.55, 43.67, 39.56, 34.87, 32.05, 21.51. **HRMS m/z [M⁺]** 298.1419 (calcd for C₁₅H₂₂O₆, 298.1416).



dimethyl 3-acetyl-5-(((tert-butyl)dimethylsilyloxy)methyl)cyclohexane-1,1-dicarboxylate (4-114)

To an argon flushed round bottom was added cyclohexane **4-110** (0.035 g, 0.13 mmol), TBS-Cl (0.023 g, 0.15 mmol), DCM (1.3 mL, 0.1 M), NEt₃ (0.04 mL, 0.26 mmol) and DMAP (0.023 g, 0.19 mmol). The flask was placed under an atmosphere of argon and stirred for 24 h at room temperature. The reaction was quenched with H₂O, extracted with DCM 3x and the combined organic fractions washed with brine, dried with MgSO₄, filtered and concentrated. The crude residue was purified by column chromatography (20% EtOAc: 80% Hexanes **R_f** = 0.4) to isolate the desired product as a colourless oil (0.036 g, 71 % yield).

¹H NMR (400 MHz, Chloroform-*d*) δ 3.74 (s, 3H), 3.71 (s, 3H), 3.49 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.43 (dd, *J* = 10.0, 6.2 Hz, 1H), 2.65 (tt, *J* = 12.6, 3.4 Hz, 1H), 2.50 (ddt, *J* = 13.5, 3.4, 2.0 Hz, 2H), 2.39 – 2.31 (m, 2H), 2.17 (s, 3H), 2.02 – 1.93 (m, 1H), 1.64 – 1.54 (m, 2H), 1.39 (t, *J* = 13.0 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 6H). **¹³C NMR (101 MHz, CDCl₃)** δ 210.39, 172.31, 171.47, 67.72, 54.84, 52.95, 52.77, 47.08, 36.73, 33.66, 32.60, 30.71, 28.36, 26.03, 18.45, -5.24. **HRMS *m/z* [M+H]** 387.2203 (calcd for C₁₉H₃₅O₆Si, 387.2208).

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Chapter 5 : Annulation of Oxime-Ether Tethered Donor-Acceptor Cyclopropanes

5.0 Preface

This work is adapted from the following manuscript: Irwin, L. C.; Allen, M. A.; Vriesen, M. R.; Kerr, M. A. *Chem. Eur. J.* **2019**, *Accepted and in early view*.

10.1002/chem.201904521

5.1 Introduction

Donor-acceptor cyclopropanes (DA CPs) have been well-established as important building blocks for the synthesis of heterocyclic compounds.¹⁵² Heterocycles, and specifically those containing nitrogen, have widespread occurrence in highly sought natural products and bio-active molecules.¹⁵³ Our interest lies in the importance of pyrrolidine-containing molecules and the precursors to access such scaffolding, like hydropyrrolo-oxazines.¹⁵⁴ **Figure 20** showcases bio-active natural products alsaphorazine A and B (**5-1a**, **5-1b**)¹⁵⁵, preussin C (**5-4**)¹⁵⁶ and 5-methyl 2-(N-methyl-pyrrolidinane) (**5-2**)¹⁵⁷ that have yet to see their total syntheses realized. Also exhibited is Abbott's influenza neuraminidase inhibitor; A-315675 (**5-3**), yet another important pyrrolidine-containing molecule.¹⁵⁸

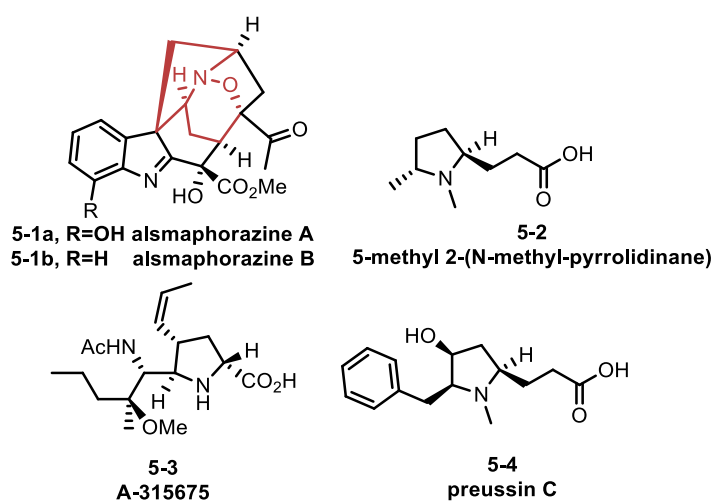
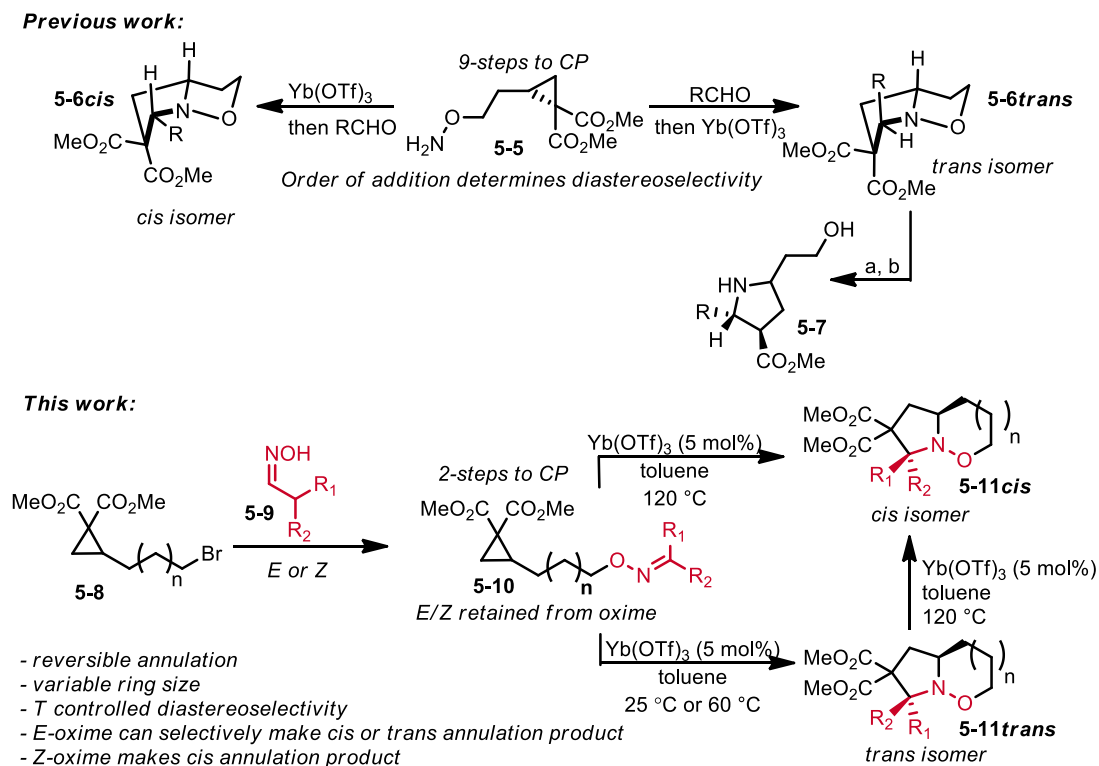


Figure 20 – Pyrrolidine-containing compounds of interest.

The task of synthesizing pyrrolidines in a diastereoselective manner is a central challenge in the synthesis of target molecules of academic and industrial importance. In efforts to address this challenge, we and others have shown that donor-acceptor cyclopropanes are convenient starting materials for synthesizing the hexahydropyrrolo-oxazines (**5-6**) and pyrrolidine molecules (**5-7**) in question.¹⁵⁹ Donor-acceptor cyclopropanes with appropriate intra- or intermolecular nucleophiles can synthesize these molecules with ease, and previous work from our group showcases these claims nicely (**Scheme 103**).¹⁶⁰

From *O*-hydroxylamine-tethered cyclopropanes (**5-5**), the addition of an aldehyde followed by Yb(OTf)₃ generates the hexahydropyrrolo-isoxazoles (**5-6**) but confined to the 5-membered bicyclic examples. The order of addition of the Lewis acid and aldehyde defined the diastereomeric outcome of the annulation products (**5-6cis/trans**, **Scheme 103**). However, these CPs (**5-5**) were not exceptionally stable and cyclize on themselves if left to sit. Accessing the *O*-hydroxylamine cyclopropanes (**5-5**) took 9 steps and did not explore any variation of the chain length off the donor acceptor cyclopropane.



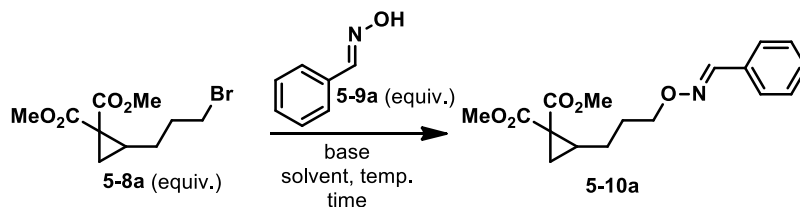
Scheme 103 - Current and related research from our group. [a] NaCN, DMSO, 140 °C [b] Pd/C (10 mol%), H₂(g) (1 atm), AcCl, MeOH

The work herein aimed to address issues with the initial research and discover a method by which more elaborate products could be synthesized. I describe a high yielding, temperature controlled, diastereoselective route to hydropyrrolo-oxazines **5-11**. The hydropyrrolo-oxazines can be taken to their respective diastereospecific pyrrolidines in a single step *via* hydrogenative N-O bond cleavage (**Scheme 103**). From a short and high yielding 2-step synthesis of oxime-ether tethered cyclopropanes (**5-10**) the intramolecular nucleophilic opening of the tethered cyclopropane proceeds with the aid of Lewis acid, Yb(OTf)₃. In one-pot, the bicyclic hydropyrrolo-oxazines (**5-11cis/trans**) are formed from the annulation of the resulting intermediate in high yield and diastereoselectively controlled by the temperature of the reaction.

5.2 Optimization of the Synthesis of Oxime-Ether Tethered DA Cyclopropanes

Requiring an accessible method for the synthesis of oxime-ether DA cyclopropanes (**5-10**), I envisioned that *via* a simple S_N2 substitution with an oxime nucleophile (**5-9**) I could access the desired material from bromocyclopropane **5-8**. Attempts to construct a reliable synthesis of **5-10a** commenced using CP and phenyl oxime **5-9a**. In the presence of base and varying the reaction conditions I was able to optimize a route to desired cyclopropanes **5-10** (Table 14).¹⁶¹ The synthesis of cyclopropane **5-12a**, and the synthesis of all oxime variants are outlined in the experimental details, Section 5.6.

Table 14 - Optimization of oxime-ether tethered donor-acceptor cyclopropanes



| Entry | Equiv. 5-12a | Equiv. 5-9a | Base | Solvent/T (°C) | Time (h) | Result 5-10a |
|-------|--------------|-------------|--|----------------|----------|------------------------|
| 1 | 1 | 1.2 | K ₂ CO ₃ (1.2 equiv.) | DMF / 60 °C | 18 | Incomplete reaction |
| 2 | 1 | 1.2 | Na ₂ CO ₃ (3.0 equiv.) | DMF/ 60-80 °C | 42 | Incomplete reaction |
| 3 | 1 | 1.5 | NaH (2.1 equiv.) | DMF/ 80 °C | 19 | 38% |
| 4 | 1 | 1.5 | Ag ₂ CO ₃ (3.0 equiv.) | Acetone/ 55 °C | 21 | Incomplete reaction |
| 5 | 1 | 1.5 | Cs ₂ CO ₃ (2.0 equiv.) | Acetone/ 55 °C | 18 | Incomplete reaction |
| 6 | 1 | 1.5 | Cs ₂ CO ₃ (3.0 equiv.) | Acetone/ 55 °C | 26 | Complete, not isolated |
| 7 | 1 | 1.0 | Cs ₂ CO ₃ (3.0 equiv.) | Acetone/ 55 °C | 18 | 76% |

First attempts at generating product **5-10a** from Table 14, entry 1, used K₂CO₃ as the base in DMF heated to 60 °C. The reaction was incomplete but crude proton NMR evidence suggested the desired product was being made. Changing the base to Na₂CO₃ resulted in an incomplete reaction after 42 h (Table 14, entry 2). Changing to a stronger base NaH (Table 14, entry 3), resulted in the isolation of a low 38% yield of product **5-10a**. I explored a few other base options because the DMF solvent became troublesome

to remove to isolate pure product. Ultimately, switching the solvent to acetone and using 3 equivalents of Cs₂CO₃ and one equivalent of each of the oxime and the bromocyclopropane afforded appreciable amounts of desired product **5-10a** (76 %) (**Table 14, entry 7**).

It is important to note that in accordance with literature reports, the *E* oximes were synthesized selectively when making aromatic substituted oximes.¹⁶² Synthesizing aliphatic oximes resulted in inseparable mixtures of *E:Z* oximes that could be separated after synthesizing the oxime-ether CP.

5.3 Oxime-Ether Donor-Acceptor Cyclopropanes Synthesized

Using the optimized conditions outlined in Table 14, a library of 15 oxime-ether products (**5-10a-o**) were generated with ease (**Table 15**).

Aromatic phenyl containing *E* oxime-ethers (**5-10a-g**) were synthesized in good to excellent yields (76%-90%). Synthesis of the thiophene-containing oxime ether **5-10h** worked, but in a lower 48% yield. When it came to synthesize the *Z* oxime-ether CPs, (**5-10d** and **5-10o**) the yields were significantly lower, 32% and 18% respectively. It was intriguing that the other isomer of the oxime would affect this displacement reaction so heavily but working amounts of product were still easily generated. 1,2-benzo substituted CP **5-10m** and **5-10o** were synthesized using an alternate bromo-cyclopropane, the synthesis of which is outlined in **Section 5.6**.

This reaction proceeds with retained configuration of the oxime.¹⁶³ If the *E* oxime (**5-9**) is the chosen nucleophile, then the resultant oxime-ether CP (**5-10**) will also be the *E* oxime-ether product. To generate the few *Z* examples of oxime-ether CPs, the *Z* oximes were synthesized by inverting the configuration of the *E* oximes using cold HCl (see **Section 5.6**). To confirm this retained configuration, we opted to use X-ray crystallography because ¹H NMR provided inconclusive results and reports in the literature were conflicting and lacked details on compounds of this type that have never

been synthesized before. I could not be certain that trends in NMR data would be the same. ORTEP drawings of *E* oxime **5-9c** and *E* oxime-ether **5-10c** are found in **Figure 21**.

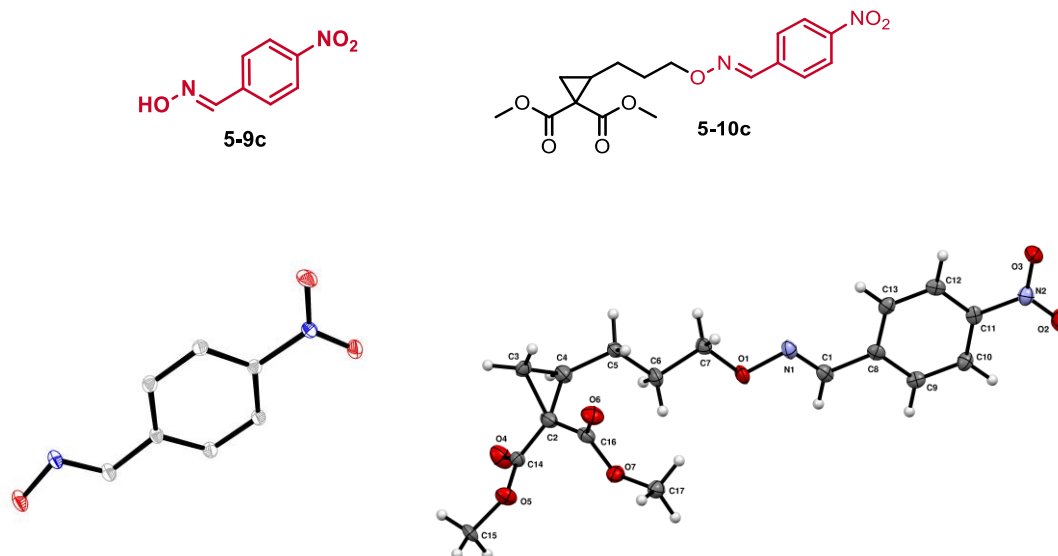
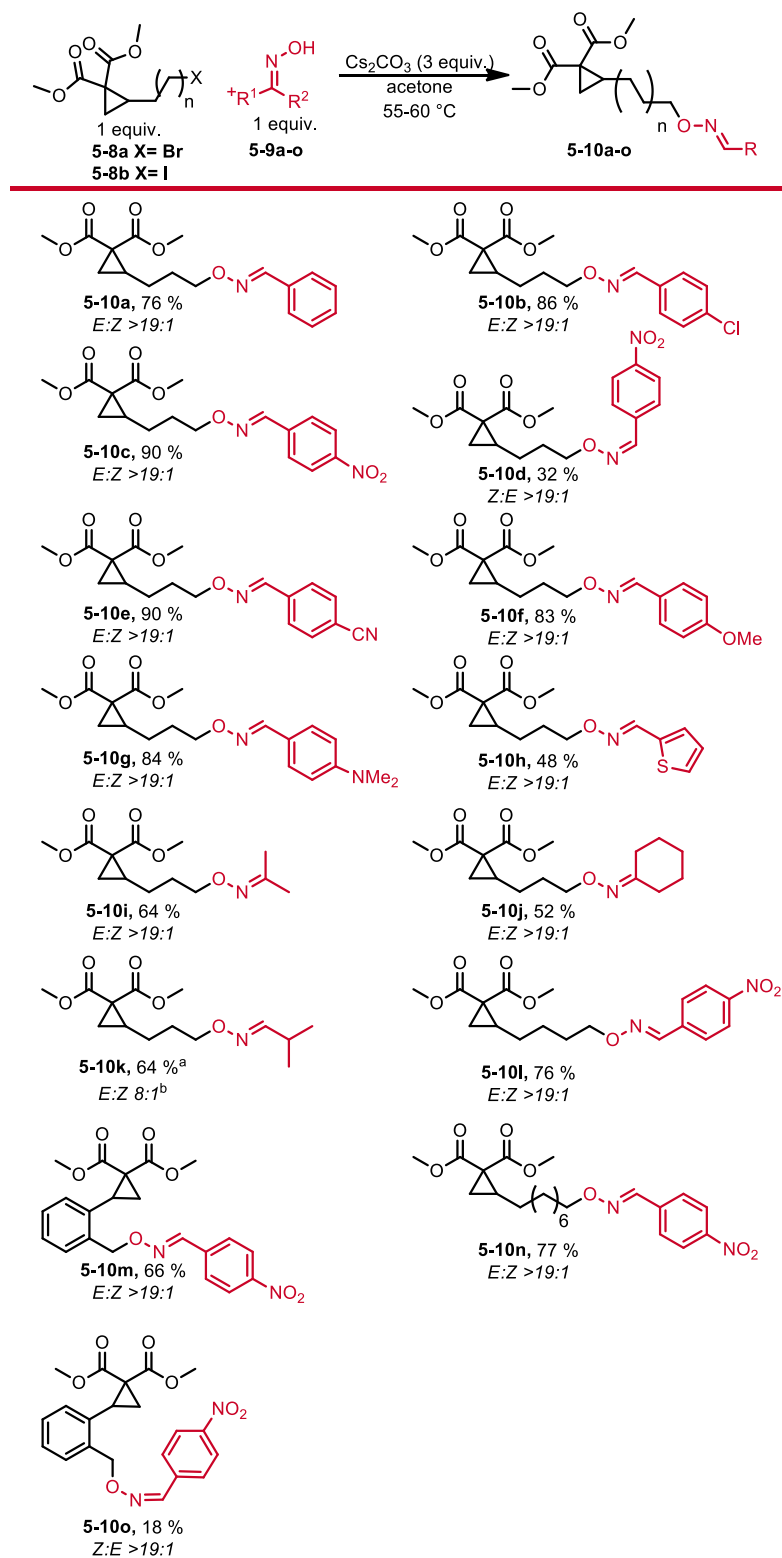


Figure 21 - ORTEP drawings of structures **5-9c** and **5-10c**. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

Table 15 - Library of generated oxime-ether tethered cyclopropanes 5-10a-o



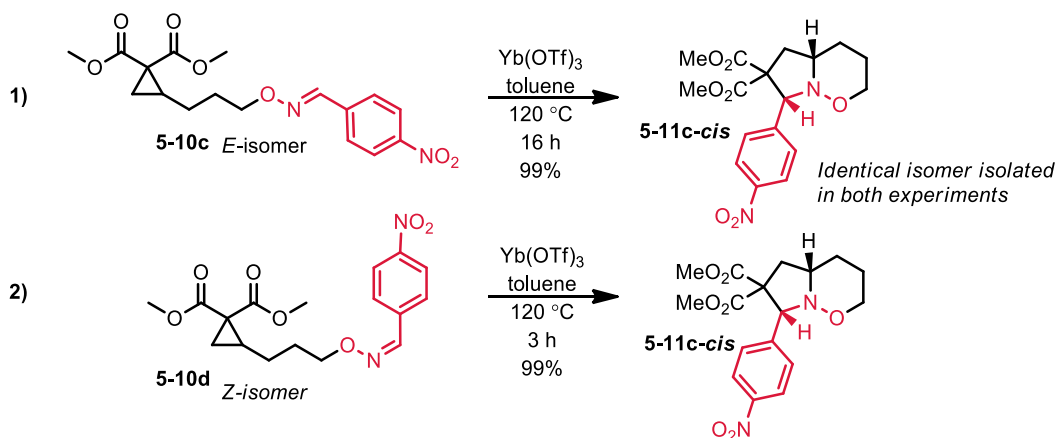
[a] Yield of combined *E* and *Z* isomers. Isolated yield of *E* isomer 46% [b] Determined from crude ¹H NMR

5.4 Annulation of Oxime-Ether Tethered Cyclopropanes

5.4.1 Initial Findings of the Annulation Reaction

With access to the desired oxime-ether starting materials cemented, experimentation with the annulation reaction was initiated and a few interesting scenarios arose. Oxime-ether **5-10c** reacted with 5 mol% of Yb(OTf)₃ in refluxing toluene to access our desired bicyclic hydropyrrolo-oxazine **5-11c** in a quantitative yield (**Scheme 104, 1**). We were thrilled to discover a single isomer of annulation product **5-11c** had been synthesized.

Repeating this reaction with the *Z*-oxime (**5-10d**) (**Scheme 104, 2**) resulted in isolating the *exact same* isomer observed in the previous reaction with the *E* oxime-ether **5-10c**. Isolating the same isomer was perturbing giving our understanding of the mechanism for this annulation. The result implied that the geometry of the oxime does not control which isomer of the annulation product is formed. I hypothesized that perhaps one of the isomers could form both *cis* and *trans* annulation products.



Scheme 104 - Initial findings during the annulation reaction of oxime-ethers **5-10c and **5-10d**.**

At this time, it could not be confirmed whether the *cis* or *trans* isomer of **5-11c** had formed using ¹H or ¹³C NMR spectroscopy. NOESY experiments failed to provide any correlation between the benzylic and the bridge head protons. We later confirmed by single X-ray crystallography that we had isolated the *cis* isomer of annulation product **5-11c** at 120 °C in both experiments shown in **Scheme 104** (see **Figure 23** for crystal

structures). The details of this, and the determination of the isomers, will be outlined further below.

5.4.2 Computational Insight on Isomer Formation

To provide some insight on which isomer we might be isolating, we turned to computational calculations of the molecular energies comparing the *cis* and *trans* isomers of **5-11a** (Table 16). DFT calculations were performed on molecule **5-11a** to keep the calculation times reasonable. Using three popular computational theories at the highest calculation level, results were similar, but conclusive to the same result; the *cis* isomer was favoured by an average 21.42 kJ/mol. Dealing with two isomers that differ by the energy of a hydrogen-bond, it definitely became apparent that both isomers were close in relative stability, but that perhaps one isomer could be isolated over the other, starting with only the *E* or *Z* oxime-ether.

Table 16 - DFT calculations of the molecular energies of *cis* and *trans* annulation products 5-11a-*cis* and 5-11a-*trans*.

DFT Results:

| Computational Theory | $\Delta E_{\text{cis-trans}}$ |
|------------------------|-----------------------------------|
| M062X/6-311+G(2d,p) | -21.46 kJ/mol <i>cis</i> favoured |
| B3LYP/6-311+G(2d,p) | -21.42 kJ/mol <i>cis</i> favoured |
| PBEh1PBE/6-311+G(2d,p) | -21.37 kJ/mol <i>cis</i> favoured |

Intrigued by this interesting result, I employed a model kit to construct the annulation reaction to help narrow our hypothesis further. The model kit informed us that likely the *E* oxime-ether cyclopropane (**5-10a**) would more easily form the *trans* isomer of the annulation product (**5-11a-*trans***) and that the *Z* oxime-ether would access the *cis* product

5-11a-cis (Figure 22). According to the computational results, the *Z* isomer **5-10d** was forming the most stable isomer and would never access the relatively less stable *trans* isomer **5-11a-trans**. This suggested that from the *E* oxime-ether **5-10c** I should be able to isolate both the *trans* and *cis* isomers. Although, I had isolated only the *cis* at this point I hypothesized that part of the mechanism was either reversible *or* the oxime-ether (**5-10c**) would isomerize to the *Z* oxime-ether (**5-10d**) before opening the cyclopropane.

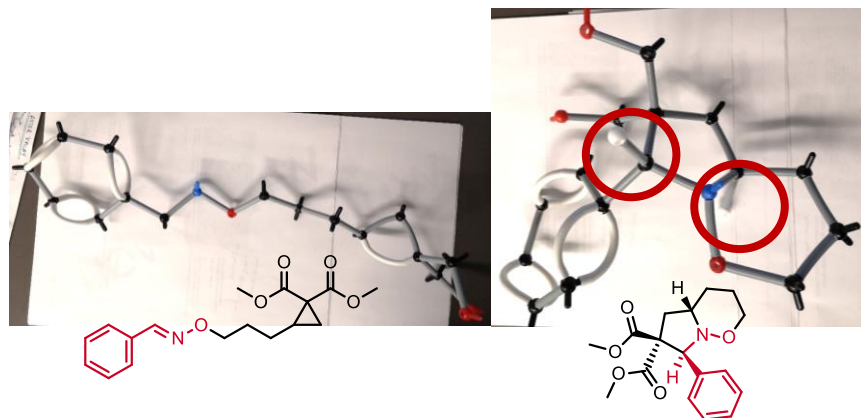
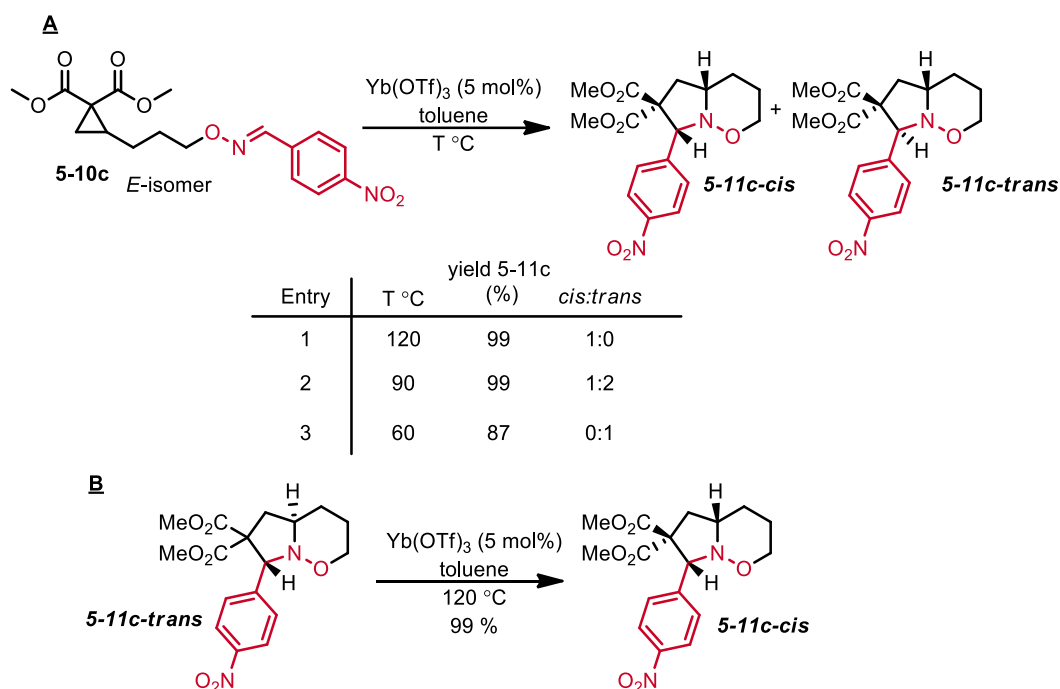


Figure 22 - Model of *E* oxime-ether 5-10a forming the *trans* annulation product 5-11a-*trans*.

5.4.3 Experimental Probing of Isomer Generation

From the computational results and the model-kit insight, we hypothesized that this reaction did not require such forcing conditions and that lowering the reaction temperature would provide different results. This was to curb either the annulation product reversibly opening and re-closing to a single isomer, or, to prevent the oxime-ether from isomerizing before opening the cyclopropane. Both scenarios would explain the interesting findings. To our delight, as we altered the temperature of the annulation reaction of oxime-ether **5-10c**, evidence of the other isomer **5-11c-*trans*** became apparent (Scheme 105).



Scheme 105 - [A] Effects of temperature on the annulation reaction of oxime-ether tethered cyclopropanes. [B] Interconversion of the trans annulation product 5-11c-*trans* to cis annulation product 5-11c-*cis*.

From the results outlined in (Scheme 104, 1), at 120 °C only the cis annulation product **5-11c-*cis*** was isolated. Lowering the reaction temperature from 120 °C to 90 °C (Scheme 105, Entry 2) resulted in a mixture of the cis:trans isomers (**5-11c**) in a 1:2 ratio by ¹H NMR. Lowering the temperature further to 60 °C resulted in isolating only the trans isomer **5-11c-*trans*** (Scheme 105, Entry 3). An exciting result, the lowering of the temperature confirmed that, from the *E*-oxime-ether CPs, we gain access to both the cis and trans isomer of the hydroxyrrolo-oxazines (**5-11c**). To solidify our findings, taking the trans isomer isolated at 60 °C and subjecting it to 5 mol% Yb(OTf)₃ at 120 °C (Scheme 105, B) resulted in quantitative conversion to the cis isomer, confirming that the cis isomer is our thermodynamic product. This finding also proved that the annulation is reversible, and access to the cis isomers is possible from the trans isomers, but that the cis isomer cannot revert to the trans because it is the thermodynamic sink.¹⁶⁴ Crystal structures of *E*-oxime cyclopropane **5-10c** and the cis isolated product (**5-11c-*cis***) were collected to confirm our identification of the isomers isolated (Figure 23).

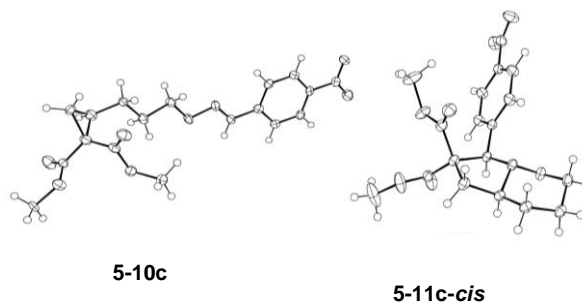
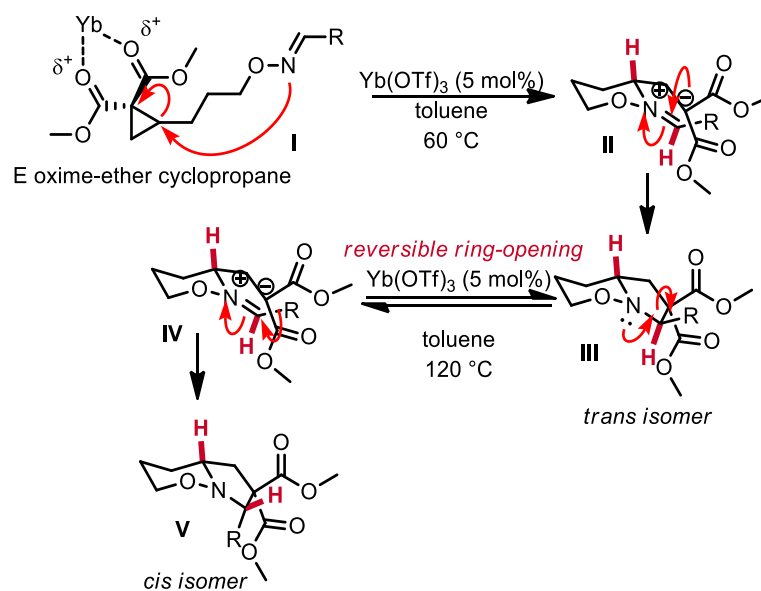


Figure 23 - ORTEP drawings of E oxime-ether 5-10c and its cis annulation product 5-11c-cis. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

The proposed mechanism for the formation of both the cis/trans annulation isomers is outlined in (Scheme 106).



Scheme 106 - Proposed mechanism for the cyclopropane ring-opening and cyclization reaction of oxime-ether tethered cyclopropanes.

Coordination of ytterbium to the methyl ester carbonyls makes cyclopropane **I** susceptible to attack *via* the oxime nitrogen. Opening the cyclopropane results in zwitterionic species **II**, and from the oxime *E* isomer, the protons of interest (Scheme 106, red hydrogens) are trans to each other (**II**). Closure via attack of the anionic carbon alpha to the esters results in desired product **III** as the trans isomer. Once closed, the

lone-pair of the nitrogen atom can break the formed ring resulting in intermediate **IV** again. At this point, closure from the opposite face occurs resulting in the thermodynamic cis isomer **V**.

The crystal structures generated, and the experimental results allowed us to confirm that we can control the diastereoselectivity of this annulation reaction by changing the reaction temperature.

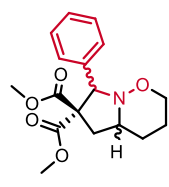
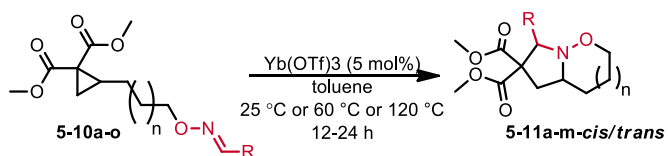
5.4.4 Substrate Scope for the Cis/Trans Isomers of the tandem Cyclopropane Opening and Annulation

Having clarified the formation of each cis and trans isomer of **5-10c**, we could expand the annulation reaction to all the synthesized oxime-ether CPs (**5-10a-o**) elaborating a library scope of the cis and trans hydropyrrolo-oxazines (**5-11a-m-cis/trans**) from reactions performed at varied temperatures (**Table 17**).

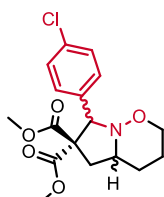
Initial trends observed that electron withdrawing substituents on the oxime aromatic ring resulted in high yields of the cis isomer at 120 °C (**5-11b-cis**, **5-11c-cis**, **5-11d-cis**). Accessing the trans isomer at 60 °C also worked well in high yields for the electron withdrawing examples (**5-11b-trans**, **5-11c-trans**, **5-11d-trans**).

However, when examining more electron-neutral examples, like phenyl **5-11a**, a mixture of the isomers was observed at 60 °C but were easily separated by column chromatography. This trend continued with electron-donating examples **5-11f** and **5-11g**, which saw the cis isomer isolated at both 120 °C and 60 °C. To combat the ease in which these examples annulated to the thermodynamic cis isomer, we lowered the reaction temperature further to 25 °C. The change resulted in electron-rich examples forming the trans isomer but in lower yields than their withdrawing counterparts. In the case of **5-11f-trans**, the reaction had unreacted starting material after 48 h. It can be rationalized by the proposed mechanism in **Scheme 106** that the electron-rich examples provide a more favourable and stabilized intermediate of **III** (**Scheme 106**) and that closure to the cis product could occur with greater ease.

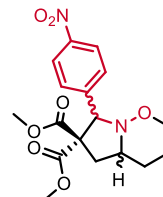
Table 17 - Substrate scope for the annulation reaction of oxime-ether cyclopropanes



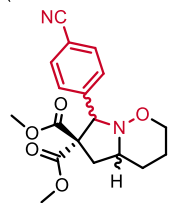
120 °C *cis*: 89%, 5-11a
60 °C *trans*: 60%, 5-11a
(95% combined isomers)



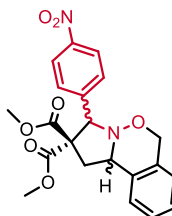
120 °C *cis*: 90%, 5-11b
60 °C *trans*: 69%, 5-11b



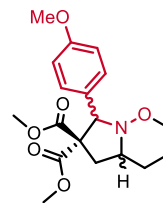
120 °C *cis*: 99%, 5-11c
60 °C *trans*: 93%, 5-11c



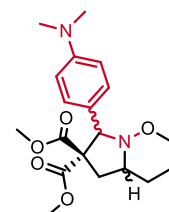
120 °C *cis*: 45%, 5-11d
(93% combined isomers)
60 °C *trans*: 85%, 5-11d



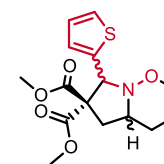
120 °C *trans*: 99%, 5-11e
60 °C *cis*: 87%^a, 5-11e



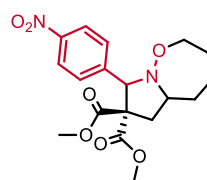
120 °C *cis*: 95%, 5-11f
60 °C: *cis* isomer formed
25 °C *trans*: 85%^b, 5-11f



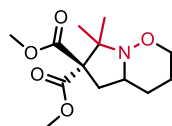
120 °C *cis*: 95%, 5-11g
60 °C: *cis* isomer formed
25 °C *trans*: 62%, 5-11g
(98% combined isomers)



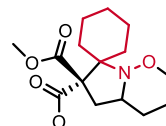
120 °C *cis*: 78%, 5-11h
60 °C: *cis* isomer formed
25 °C: *cis* isomer formed



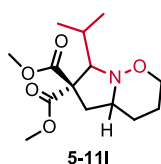
160 °C: 86%, 5-11i
60 °C: no rxn



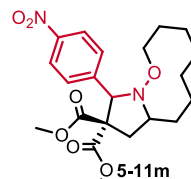
120 °C: 78%, 5-11j



120 °C: 52%, 5-11k



120 °C: 0%
60 °C: 0%



160 °C: 0%
120 °C: 0%

[a] Synthesized from Z-oxime-ether 5-10o to be able to access this *cis* product.
[b] Based on recovered starting material

Thiophene oxime-ether annulation product **5-11h** cyclized to the *cis* isomer at all temperatures explored, in a maximum yield of 78%. The aliphatic isopropyl oxime-ether product **5-10k** failed to yield annulation product **5-11i**. Dimethyl oxime annulation product **5-11j** was acquired in a 78% yield and spirocycle **5-11k** was acquired in a lower 52% yield. The lower yield of product **5-11k** is suspected to be the result of a side Beckmann rearrangement.

Exploring the alternative chain-length examples, the 7-membered product **5-11i** required higher temperatures at 160 °C to successfully annulate in an 86% yield. Unfortunately, the 10-membered ring annulation product **5-11m** was not successfully isolated.

The phenyl side chain oxime-ether CP **5-10m** annulated smoothly at 120 °C to yield product **5-11e-trans** in a 99% yield. This product had an unexpected chemical shift of the benzylic proton in the ^1H NMR spectrum at 5.74 ppm. This seemed high because the trend for all examples exhibited the *cis* isomer benzylic proton at a lower chemical shift than the *trans* isomer benzylic proton. When the reaction was performed at the lower 60 °C and the same isomer resulted, it became apparent that the phenyl side chain put alternative strain on this reaction giving us a different isomer than expected, **5-11e-trans**. To confirm these suspicions, x-ray crystallography of the oxime-ether CP **5-10m** confirmed we had made

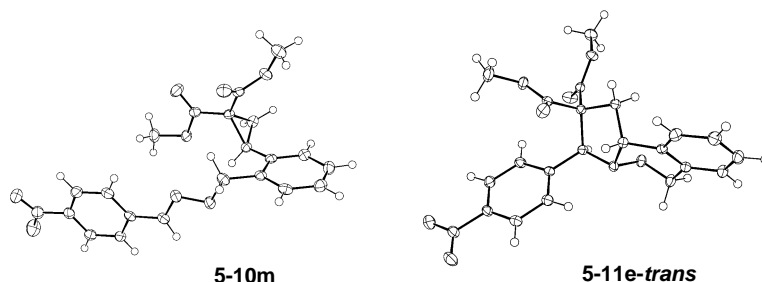


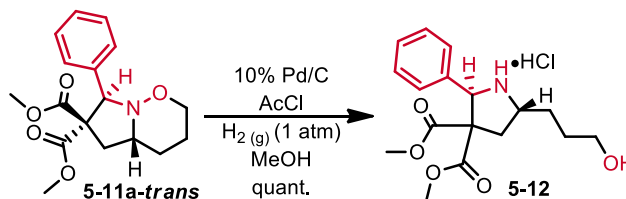
Figure 24 - ORTEP drawings of 5-10m and 5-11e-trans. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

the *E*-isomer as expected. And a crystal of **5-11e** confirmed the *trans* isomer was being isolated in this case, even at 120 °C (**Figure 24**).

Synthesis of the cis isomer **5-11e-cis** was possible using the Z-oxime-ether CP (**5-10o**) which indeed had a benzylic proton chemical shift lower than that of the trans product **5-11e-trans** at (5.04 ppm). The findings further solidify the observed chemical shift trend; that the cis products have a benzylic proton shift at a lower ppm than the trans products.

5.4.5 Elaboration to Pyrrolidine

Following the procedure outline by Jackson *et al.* we were also able to isolate the pyrrolidine (**5-12**) of hydropyrrolo-oxazine **5-11a-trans** that retained its diastereomeric relationship. The N-O bond was successfully cleaved under hydrogenative conditions to give a quantitative yield of pyrrolidine HCL salt **5-12** (**Scheme 107**). We hope to use chemistry like this in the future to access natural products.



Scheme 107 - Pyrrolidine synthesis from trans annulation product 5-11a-trans

5.5 Conclusions and Future Directions

In summary, we have developed a protocol for 2-step access to oxime-ether tethered cyclopropanes **5-10a-o** which support the synthesis of varied chain lengths. The intramolecular cyclopropane opening, and annulation reaction of the *E* oxime-ether CPs are diastereocontrolled by varying the temperature to provide access to both cis and trans hydropyrrolo-oxazines (**5-11a-m-cis/trans**). We confirmed the isomeric configurations via single crystal x-ray crystallography and the results were further supported by the findings of DFT calculations. The hydropyrrolo-oxazines (**5-11**) can be taken to their respective pyrrolidines by reductive N-O bond cleavage to access high-value heterocycles with tune-able substitution and predictable stereochemistry.

Exploring enantiopure examples of oxime-ether cyclopropanes may prove valuable to access single enantiomers of products via the temperature-controlled procedure. This is likely worth exploring in the future.

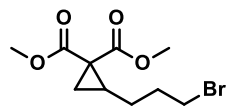
5.6 Experimental

5.6.1 General Experimental Details

All glassware was dried in a 120 °C oven for at least two hours before cooling in a desiccator or under high vacuum (0.4 torr) before use. Toluene was passed over activated alumina columns and was stored over 4Å molecular sieves and under argon for a minimum of 24 h and a maximum of 2 weeks prior to use in the oxime ether annulation reactions. Acetone was purchased as distilled in glass from Caledon and used as received. All other commercial reagents and solvents were used as obtained without further purification. Reactions were performed under a balloon of argon, but with minimal air sensitive technique. Reagents and solvents were weighed and placed into reaction flasks before the balloon of argon was added. The progress of reactions was followed by thin layer chromatography (TLC) (silica gel 60 F254) and the developed plates were stained using acidic *p*-anisaldehyde (oxime syntheses) or basic potassium permanganate (all other reactions). Some reactions required the use of ¹H NMR to monitor consumption of starting material, these experiments are indicated below. Flash chromatography was performed using silica gel (230- 400 mesh). All chromatography was performed using Still's procedure for flash chromatography.⁹⁶ Attenuated Total Reflectance (ATR) infrared spectra were obtained using Bruker Alpha II Di-ATR. NMR experiments were performed on either a Bruker AvIII 400 or Inova 600 instrument and samples were obtained in CDCl₃ (referenced to 7.25 ppm for ¹H and 77.0 ppm for ¹³C) or d₆-DMSO (referenced to 2.50 for ¹H and 39.5 for ¹³C) as indicated. Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad. CDCl₃ was kept over K₂CO₃. High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization or chemical ionization (isobutane) when electron impact proved too harsh to acquire the exact mass of a sample.

5.6.2 Cyclopropane Syntheses

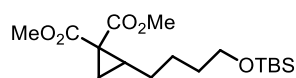
5-8a



5-bromo-1-pentene (0.98 g, 6.6 mmol, 1.3 equiv.) was added to a dry round bottom flask. CH_2Cl_2 (17 mL) was added and the flask was purged with argon. $\text{Rh}_2(\text{esp})_2$ (0.011 g, 0.015 mmol, 0.003 equiv.) was added. Diazomalonate¹⁶⁵ (0.8 g, 5.1 mmol, 1 equiv.) was dissolved in 2 mL CH_2Cl_2 and added very slowly by syringe over 35 minutes. The reaction was stirred until TLC confirmed consumption of starting material (1.5 hours). When complete, the reaction was concentrated and purified by column chromatography (20 % EtOAc/Hexanes, R_f = 0.43) to yield 1.22 g (87%) of a pale green oil (rhodium impurity).

¹H NMR (400 MHz, Chloroform-*d*) δ 3.74 (s, 3H), 3.69 (s, 3H), 3.38 (m, 2H), 1.96 (ddt, J = 14.1, 7.5, 6.8 Hz, 2H), 1.86 (p, J = 7.8 Hz, 1H), 1.55 (dq, J = 14.4, 7.2 Hz, 1H), 1.45 – 1.33 (m, 3H) **¹³C NMR (101 MHz, CDCl_3)** δ 170.7, 168.5, 52.7(4), 52.6(7), 33.9, 33.0, 31.9, 27.5, 27.2, 21.1. **HRMS m/z** 278.0149 (calc'd for $\text{C}_{10}\text{H}_{15}\text{BrO}_4$, 278.0154) **IR** 2952, 2228, 1726, 1608, 1523, 1254, 1178, 1078, 1048, 732.

Precursor A

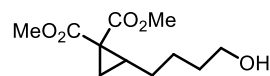


TBS-protected hexenol (1.71 g, 7.96 mmol) and $\text{Rh}_2(\text{esp})_2$ (0.006 g, 0.008 mmol) were mixed in CH_2Cl_2 (50 mL, 0.15 M) for 10 minutes at room temperature under an argon atmosphere. Diazomalonate¹⁶⁵ (1.635 g, 10.3 mmol) in CH_2Cl_2 (3 mL) was subsequently added dropwise over ten minutes. The solution was stirred at room temperature for 3 hours before the solvent was removed *in vacuo*. The crude oil was purified by flash column chromatography (10% EtOAc/hexanes) to yield 2.52 g (92%) of the desired cyclopropane as a pale-yellow oil. R_f 0.37 (10% EtOAc/hexanes).

¹H NMR (600 MHz, CDCl_3): δ = 3.75 (s, 3H), 3.72 (s, 3H), 3.59 (dd, J = 6.5 Hz, 6.5 Hz, 2H), 1.90 (dddd, J = 8.8 Hz, 8.2 Hz, 8.2 Hz, 5.9 Hz, 1H), 1.55- 1.43 (m, 5H), 1.41 (dd, J = 8.9 Hz, 4.6 Hz, 1H), 1.37 (dd, J = 7.8 Hz, 4.6 Hz, 1H), 1.21-1.13 (m, 1H), 0.89

(s, 9H), 0.03 (s, 6H).). ^{13}C NMR (101 MHz, CDCl_3) δ 171.1, 168.9, 63.1, 52.7, 52.6, 34.0, 32.6, 28.8, 28.7, 26.1, 25.3, 21.5, 18.5, -5.2. HRMS m/z [M+H] 345.2104 (calc'd for $\text{C}_{17}\text{H}_{33}\text{O}_5\text{Si}^+$, 345.2097). IR (ATR) ν_{max} = 2954, 2930, 2857, 1727, 1462, 1436, 1389, 1329, 1283, 1256, 1210, 1129, 1098, 1006, 939, 835, 776, 707, 662.

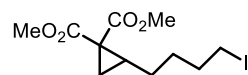
Precursor A-OH



To a solution of cyclopropane **Precursor A** (2.25 g, 6.54 mmol) in MeOH (65 mL, 0.1 M) was added PPTS (0.24 g, 0.98 mmol). After 24 hours, the solvent was removed *in vacuo*. 50 mL of a saturated solution of NaHCO_3 and 50 mL of CH_2Cl_2 were added to the crude material and the layers were separated. The aqueous phase was extracted twice with CH_2Cl_2 , and the organic layers were combined and washed once with brine. The solution was dried over MgSO_4 and the solvent was removed *in vacuo* to yield crude cyclopropyl alcohol (1.49 g, 99%). This material was used in the subsequent transformation without purification. R_f = 0.45 (60% EtOAc/hexanes)

^1H NMR (400 MHz, CDCl_3): δ = 3.74 (s, 3H), 3.70 (s, 3H), 3.61 (ddd appearing as q, J = 5.6 Hz, 2H), 1.95 – 1.83 (m, 1H), 1.63 – 1.33 (m, 8H), 1.27 – 1.15 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ = 171.0, 168.9, 62.8, 52.7, 52.6, 34.0, 32.4, 28.7, 28.6, 25.1, 21.5. HRMS m/z 231.1235 (calc'd for $\text{C}_{11}\text{H}_{19}\text{O}_5^+$, 231.1227). IR (ATR) ν_{max} = 3408, 3009, 2937, 2863, 1719, 1437, 1392, 1331, 1285, 1213, 1130, 1050, 990, 905, 753, 667.

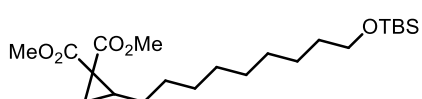
5-8b-butyl chain



Cyclopropane **Precursor A-OH** (1.51 g, 6.55 mmol) and PPh_3 (2.75 g, 10.5 mmol) were dissolved in CH_2Cl_2 (26 mL, 0.25 M) and the flask was wrapped in aluminum foil to shield it from light. Imidazole (0.893 g, 13.11 mmol) and iodine (2.66 g, 10.5 mmol) were subsequently added. The reaction was stirred at room temperature for 18 hours, after which it was quenched with NaSO_3 (aq). The layers were separated and the aqueous phase was extracted two additional times with CH_2Cl_2 . The organic layers were combined, washed once with brine, dried over MgSO_4 and the solvent was removed *in vacuo*. The crude yellow solid was purified by flash column chromatography (15% EtOAc/hexanes) to yield cyclopropane iodide **5-8b-butylchain** (1.82 g, 82%). R_f = 0.39 (15% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 3.75 (s, 3H), 3.71 (s, 3H), 3.15 (dd appearing as t, J = 7.0 Hz, 2H), 1.94-1.75 (m, 3H), 1.55-1.45 (m, 3H), 1.43-1.32 (m, 2H), 1.27-1.16 (m, 1H). **¹³C NMR (101 MHz, CDCl₃):** δ = 170.9, 168.8, 52.8, 52.7, 34.0, 33.2, 29.9, 28.4, 27.8, 21.4, 6.6; **HRMS m/z** 341.0250 (calc'd for C₁₁H₁₈O₄I⁺, 341.0244). **IR (ATR) ν_{\max}** = 3004, 2950, 2859, 1723, 1435, 1392, 1328, 1279, 1253, 1212, 1131, 990, 905, 884, 756.

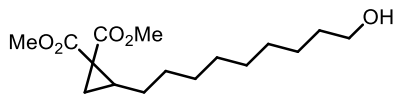
Precursor B



TBS-protected undecenol (2.52 g, 8.85 mmol) and Rh₂(esp)₂ (0.007 g, 0.009 mmol) were mixed in CH₂Cl₂ (43 mL, 0.15 M) for 10 minutes at room temperature under an argon atmosphere. Diazomalonate¹⁶⁵ (1.82 g, 11.5 mmol) in CH₂Cl₂ (3 mL) was subsequently added dropwise over ten minutes. The solution was stirred at room temperature for 15 minutes before the solvent was removed *in vacuo*. The crude oil was purified by flash column chromatography (5% EtOAc/hexanes) to yield 2.72 g (74%) of the desired cyclopropane as a pale-yellow oil. R_f 0.38 (5% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 3.75 (s, 3H), 3.71 (s, 3H), 3.59 (dd appearing as t, J = 6.7 Hz, 2H), 1.95 – 1.83 (m, 1H), 1.54 – 1.43 (m, 3H), 1.43 – 1.34 (m, 4H), 1.26 (m, 10H), 1.20 – 1.10 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). **¹³C NMR (101 MHz, CDCl₃) δ** 171.1, 168.9, 63.5, 52.7, 52.6, 34.0, 33.0, 29.7, 29.6, 29.4, 29.0, 28.8, 26.1, 25.9, 21.6, 18.5, -5.1. **HRMS m/z [M+H]** 415.2890 (calc'd for C₂₂H₄₃O₅Si⁺, 415.2874). **IR (ATR) ν_{\max}** = 2927, 2855, 1727, 1462, 1436, 1389, 1330, 1283, 1254, 1211, 1130, 1098, 1006, 836, 775, 758, 665.

Precursor B-OH

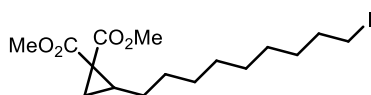


To a solution of cyclopropane **Precursor B** (2.50 g, 6.03 mmol) in MeOH (60 mL, 0.1 M) was added PPTS (0.23 g, 0.90 mmol). After 22 hours of stirring at room temperature, the solvent was removed *in vacuo*. 50 mL of a saturated solution of NaHCO₃ and 50 mL of CH₂Cl₂ were added to the crude material and the layers were separated. The aqueous phase was extracted twice

with CH_2Cl_2 , and the organic layers were combined and washed once with brine. The solution was dried over MgSO_4 and the solvent was removed *in vacuo* to yield crude cyclopropyl alcohol (1.88 g, >100% crude). This material was used in the subsequent transformation without purification. R_f 0.38 (40% EtOAc/hexanes).

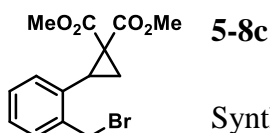
^1H NMR (400 MHz, CDCl_3): δ = 3.74 (s, 3H), 3.71 (s, 3H), 3.63 (q, J = 6.5 Hz, 2H), 1.93 – 1.84 (m, 1H), 1.60-1.52 (m, 2H), 1.50-1.35 (m, 6 H), 1.35-1.23 (m, 10H), 1.19-1.10 (m, 1H). **^{13}C NMR (101 MHz, CDCl_3)** δ 171.1, 168.9, 63.2, 52.7, 52.6, 34.0, 32.9, 29.6, 29.5, 29.5, 29.3, 29.0, 28.9, 28.8, 25.8, 21.6. **HRMS m/z [M+H]** 301.2029 (calc'd for $\text{C}_{19}\text{H}_{29}\text{O}_5^+$, 301.2010). **IR (ATR) ν_{max}** = 3390, 3020, 2927, 2865, 1721, 1437, 1332, 1285, 1214, 1132, 1052, 906, 755, 667.

8b-nonyl chain



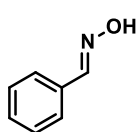
Crude cyclopropane **Precursor B-OH** (1.88 g, 6.26 mmol) and PPh_3 (2.88 g, 11.0 mmol) were dissolved in CH_2Cl_2 (27 mL, 0.25 M) and the flask was wrapped in aluminum foil to shield it from light. Imidazole (0.935 g, 13.7 mmol) and iodine (2.78 g, 11.0 mmol) were subsequently added. The reaction was stirred at room temperature for 21 hours, after which it was quenched with saturated NaSO_3 . The layers were separated and the aqueous phase was extracted two additional times with CH_2Cl_2 . The organic layers were combined, washed once with brine, dried over MgSO_4 and the solvent was removed *in vacuo*. The crude yellow solid was purified by flash column chromatography (15% EtOAc/hexanes) to yield desired cyclopropane iodide (1.82 g, 71%, 2 steps). R_f 0.56 (20% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): δ = 3.74 (s, 3H), 3.71 (s, 3H), 3.17 (dd appearing as t, J = 7.0 Hz, 2H), 1.94 – 1.84 (m, 1H), 1.80 (p, J = 7.1 Hz, 2H), 1.50 – 1.32 (m, 6H), 1.32 – 1.21 (m, 9H), 1.20 – 1.07 (m, 1H). **^{13}C NMR (101 MHz, CDCl_3)** δ 171.1, 168.9, 52.7, 52.6, 34.0, 33.7, 30.6, 29.5, 29.4, 29.3, 28.9, 28.8, 28.6, 21.6, 7.5. **HRMS m/z [M+H]** 411.1040 (calc'd for $\text{C}_{16}\text{H}_{28}\text{O}_4\text{I}^+$, 411.1027). **IR (ATR) ν_{max}** = 3024, 2925, 2864, 1725, 1436, 1330, 1283, 1211, 1131, 905, 756, 667.

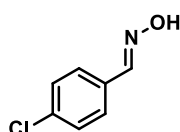


Synthesized following literature procedure.¹⁶⁶

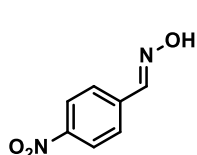
5.6.3 Oxime Syntheses



5-9a: Following a procedure by Yoon¹⁶⁷, a mixture of benzaldehyde (5.00 g, 47.2 mmol), hydroxylamine hydrochloride (3.31 g, 47.6 mmol), K_2CO_3 (7.17 g, 51.9 mmol) and MeOH (235 mL, 0.2 M) were stirred at rt until the reaction was complete by TLC. The solution was concentrated *in vacuo*, and then ether was added. The resulting suspension was filtered and the filtrate was then concentration *in vacuo* again and dried under vacuum. Yield: 48% as the *E* isomer (2.73 g) as a colourless solid. The spectroscopic data is identical to that reported and was used crude for the following alkylation.



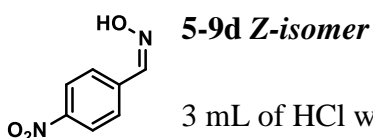
5-9b: Following a procedure by Verkman¹⁶⁸, hydroxylamine hydrochloride (2.72 g, 39.13 mmol) was dissolved in 44 mL THF, 22 mL H_2O , and 111 mL EtOH. Sodium acetate (3.21 g, 39.13 mmol), and then 4-chlorobenzaldehyde (5.00 g, 35.57 mmol) were added to this solution. After the reaction had not been completed at 40 h, another 0.5 equiv. of hydroxylamine hydrochloride were added. Once the reaction was complete by TLC, the THF and EtOH were concentrated *in vacuo*. The aqueous solution was then extracted with ether (3x), and the combined organic fractions were washed with brine (1x). The solution was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting white solid's spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 20% as the *E* oxime (1.10 g).



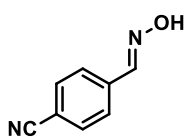
5-9c *E*-isomer

Following a procedure by Wang¹⁶⁹, 4-nitrobenzaldehyde (3.02 g, 20.0 mmol) and hydroxylamine hydrochloride (1.67 g, 24.03 mmol) were dissolved in 20 mL THF. Pyridine (1.90 g, 24.02 mL) in 2.5 mL THF was added

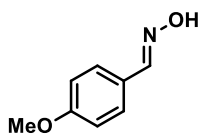
dropwise and was stirred at rt until the reaction was complete by TLC. The solution was concentrated *in vacuo*, and then water was added. It was extracted with EtOAc (2x) and the combined organic layers were washed with brine, and then concentrated *in vacuo* again. The resulting yellow solid's spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 84% as the *E* isomer (2.77 g).



3 mL of HCl was cooled in an ice/water bath for 5 minutes with stirring before *E*-isomer **5-9c** (0.55 g, 3.3 mmol) was added portion wise carefully. Once added, the suspended mixture was left to stir rapidly for 25 minutes in the ice/water bath. The mixture was then carefully vacuum filtered and washed dropwise with a minimum amount of saturated aqueous NaHCO₃. The collected solid was then added slowly, portion wise, into ~10 mL of cooled saturated aqueous NaHCO₃ solution to avoid over bubbling. Once the bubbling had ceased, the solid was vacuum filtered and washed with cold saturation bicarb solution and then dried under vacuum. *Z*-isomer **5-9d** was isolated as an off white solid (0.49 g, 89%). Spectral data matched that reported.¹⁷⁰

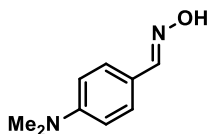


5-9e: Following a procedure by Ismail¹⁷¹, hydroxylamine hydrochloride (4.17 g, 60 mmol) was dissolved in 40 mL of H₂O and was subsequently neutralized with 2 M NaOH. A solution of 4-cyanobenzaldehyde (6.56 g, 50 mmol.) in 90 mL EtOH was added slowly to the mixture. The reaction was stirred at rt for 100 minutes until completion as monitored by TLC. The solution was concentrated *in vacuo*, and then water was added. The solution was extracted with DCM (3x), and the combined organic fractions were washed with brine (1x). The solution was dried over MgSO₄ and concentrated *in vacuo*. The resulting white solid's spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 44% as the *E* isomer (3.23 g).

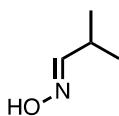


5-9f: Following a procedure by Yoon¹⁶⁷, 4-methoxybenzaldehyde (5.0 mL, 41.5 mmol), hydroxylamine hydrochloride (2.92 g, 42 mmol), and K₂CO₃ (6.29 g, 45.4 mmol) were added to 200 mL of MeOH. Once the reaction was complete as monitored by TLC, the reaction mixture was concentrated *in*

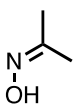
vacuo, cold ether was added, and the solution was filtered. The resulting white solid's spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 22% as the *E* isomer (1.38 g).



5-9g: Following a procedure by Zhang¹⁷², 4-(dimethylamino)benzaldehyde (3.00 g, 20.1 mmol), hydroxylamine hydrochloride (1.68 g, 24.1), and 2 M NaOH (20 mL, 40.2 mmol) were added to EtOH (20 mL). After 4 h, the ethanol was removed *in vacuo*, and the resulting reaction mixture was extracted with EtOAc (4x). The organic layers were combined and washed with brine (1x), then dried over MgSO₄, and concentrated *in vacuo*. The resulting yellow solid's spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 80% as the *E* isomer (2.65 g).

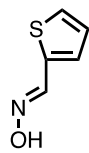


5-9h: Following a procedure by Aicher¹⁷³, K₂CO₃ (3.11 g, 22.5 mmol) was dissolved in 225 mL water, then hydroxylamine hydrochloride (3.13 g, 45 mmol) was added and stirred for 5 minutes. Isobutyraldehyde (3.24 g, 45 mmol) was added to the solution and the mixture was stirred at room temperature for 18 hours. The solution was extracted with ether (3x), and the organic layers were combined and washed with brine (1x). The solution was dried over MgSO₄ and concentrated *in vacuo*. The resulting clear liquid's spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 87% as an 8:1 mixture of *E/Z* isomers (3.41 g).

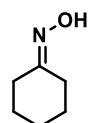


5-9i: Following a procedure by Chan¹⁷⁴, acetone (3.6 mL, 50 mmol), hydroxylamine hydrochloride (5.2 g, 75 mmol), and Na₂CO₃ (8 g, 75 mmol) were added to 10 mL of water. The reaction was stirred for 16 h, and then was extracted with ether (5x). The combined aqueous fractions were dried over MgSO₄, and concentrated *in vacuo*. The resulting white solids spectroscopic data is identical to that reported and was used crude for the following alkylation. Yield: 72% (2.63 g).

5-9j: Following a procedure by Pierce¹⁷⁵, thiophene-2-carbaldehyde (1.87 mL, 20 mmol)

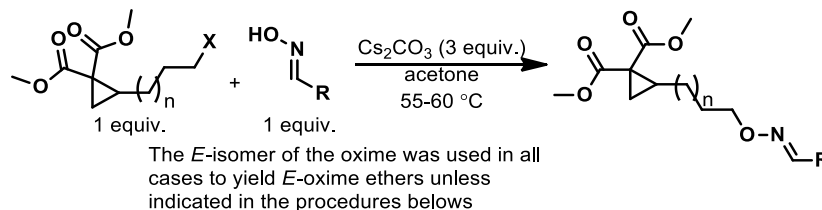


was dissolved in 40 mL EtOH. Hydroxylamine hydrochloride (1.67 g, 24 mmol) and subsequently pyridine (3.9 mL, 48 mmol) were added. The reaction mixture was stirred for 24 h at room temperature until complete by TLC. The reaction was quenched with 5% HCl. The solution was extracted with EtOAc (2x) and the combined organic fractions were washed with 5% HCl (1x) and brine (1x). The solution was then dried over MgSO₄ and concentrated *in vacuo*. To the resulting oil was added hexanes which lead to the crystallization of the oxime. The white solid was collected and washed with hexanes, then dried *in vacuo*. The *E* isomer was isolated as white crystals, which had identical spectroscopic data to that reported.¹⁷⁶ Yield: 49% (1.26 g) *E* isomer.



5-9k: Following procedure as reported by Schneider¹⁷⁷, sodium acetate (3.68 g, 44.9 mmol) was dissolved in 12 mL of methanol. Hydroxylamine hydrochloride (3.12 g, 44.9 mmol) was added to the flask and the mixture stirred at room temperature for 45 minutes. Cyclohexanone (4.00 g, 40.8 mmol) was added dropwise and the white suspension was stirred for 23 h. 12 mL of water was added to the suspension and stirred for 1 additional hour before being filtered. The collected material was washed with water and then dried under vacuum. The pure oxime was acquired as a white solid (1.93 g, 42% yield). Characterization data matched reported results.¹⁷⁸

5.6.4 Synthesis of Oxime-Ether Donor-Acceptor Cyclopropanes

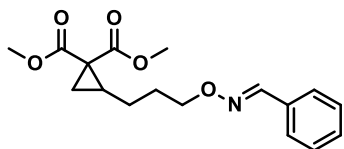


Scheme 108 - General procedure for the synthesis of oxime-ether tethered cyclopropanes 5-10a-o

A mixture of oxime (1.0 equiv), cyclopropane alkyl halide (bromo or iodo as indicated) (1.0 equiv), and cesium carbonate (3.0 equiv) in glass-distilled acetone (0.1 M) was heated in a 55 °C oil bath for the indicated time. Formation of oxime ether was primarily

monitored by thin layer chromatography but was supplemented with ^1H NMR spectroscopy when required. Once cyclopropane alkyl halide and oxime were consumed, the solution was filtered over celite and rinsed with Et_2O three times and then concentrated *in vacuo*. The crude residues were purified *via* flash column chromatography.

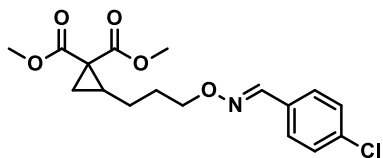
5-10a



The title compound was synthesized via General Procedure A (18.5 h). The amounts of reagents employed were: oxime **5-9a** (0.11 g, 0.87 mmol), cyclopropane **5-8a** (0.28 g, 0.87 mmol), and cesium carbonate (0.85 g, 2.6 mmol) in 9.0 mL of acetone. The resulting oil was purified via column chromatography (18% EtOAc/hexanes). Yield: 76% (0.213 g) >19:1 mixture of *E:Z* isomers as a pale yellow oil. R_f 0.33 (18% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): δ = 8.05 (s, 1H), 7.59-7.55 (m, 2H), 7.38-7.34 (m, 3H), 4.16 (dd, J = 6.4 Hz, 6.4 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 1.95 (ddt, J = 15.7 Hz, 7.9 Hz, 6.8 Hz, 1H), 1.91-1.78 (m, 2H), 1.63-1.53 (m 1H), 1.41 (m, 2H), 1.38-1.27 (m, 1H). ^{13}C NMR (101 MHz, cdcl_3) δ 171.0, 168.8, 148.6, 132.5, 129.9, 128.8, 127.1, 77.5, 77.4, 77.2, 76.8, 73.6, 52.7, 52.7, 34.1, 28.5, 28.5, 25.4, 21.5. HRMS m/z 319.1430 (calc'd for $\text{C}_{17}\text{H}_{21}\text{NO}_5^+$, 319.1420). IR (ATR) ν_{max} = 3033, 2954, 2870, 1723, 1436, 1329, 1211, 1129, 694.

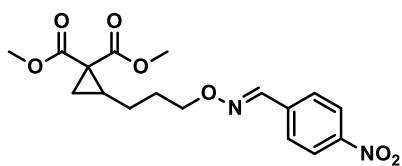
5-10b



The title compound was synthesized via General Procedure A (2 h). The amounts of reagents employed were: oxime **5-9b** (0.111 g, 0.71 mmol), bromocyclopropane **5-8a** (0.20 g, 0.71 mmol), and cesium carbonate (0.70 g, 2.15 mmol) in 7.1 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 86% (0.22 g) >19:1 mixture of *E:Z* isomers as a clear oil. R_f = 0.36 (20% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 8.00 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 4.16 (dd as apparent t, J = 6.4 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 1.99 – 1.88 (m, 1H), 1.87 – 1.76 (m, 2H), 1.62 – 1.51 (m, 1H), 1.45 – 1.37 (m, 2H), 1.37 – 1.26 (m, 1H) **¹³C NMR (101 MHz, CDCl₃)** δ 170.9, 168.8, 147.4, 135.7, 131.0, 129.1, 128.3, 73.7, 52.7, 52.6 34.1, 28.5, 28.4, 25.4, 21.4. **HRMS m/z** 353.1043 (calc'd for C₁₇H₂₀ClN₂O₅⁺, 353.1030). **IR (ATR) ν_{\max}** = 3016, 2954, 2875, 1723, 1436, 1331, 1211, 1129, 825, 754.

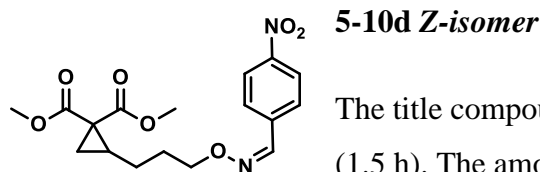
5-10c



E-isomer

The title compound was synthesized via General Procedure A (1.5 h). The amounts of reagents employed were: oxime **5-9c** (0.15 g, 0.89 mmol), cyclopropane **5-8a** (0.25 g, 0.89 mmol), and cesium carbonate (0.87 g, 2.67 mmol) in 9.0 mL of acetone. The resulting oil was purified via column chromatography (23% EtOAc/hexanes). Yield: 90% (0.29 g) >19:1 mixture of *E*:*Z* isomers as a white solid and as confirmed by x-ray crystallography. Mp = 60 – 62 °C. R_f = 0.31 (20% EtOAc/hexanes).

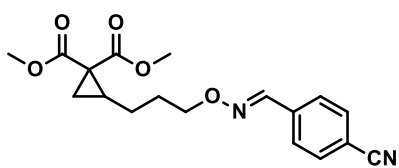
¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, J = 8.9 Hz, 2H), 8.09 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 4.22 (t, J = 6.4 Hz, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 2.00 – 1.89 (m, 1H), 1.90 – 1.79 (m, 2H), 1.64 – 1.50 (m, 1H), 1.45-1.37 (m, 2H), 1.37 – 1.27 (m, 1H) **¹³C NMR (151 MHz, CDCl₃)** δ 170.7, 168.5, 148.2, 146.1, 138.4, 127.4, 123.9, 74.1, 52.5, 52.4, 33.9, 28.2, 28.1, 25.1, 21.2. **HRMS m/z** [M+H] 365.1352 (calc'd for C₁₇H₂₁N₂O₇⁺, 365.1349). **IR (ATR) ν_{\max}** = 2963, 2892, 1723, 1518, 1335, 1296, 1209, 1132, 840, 831.



The title compound was synthesized via General Procedure A (1.5 h). The amounts of reagents employed were: oxime **5-9d** (0.12 g, 0.72 mmol), cyclopropane **5-8a** (0.20 g, 0.72 mmol), and cesium carbonate (0.70 g, 2.15 mmol) in 7.2 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 32% (0.07 g) >19:1 mixture of *Z:E* isomers as a white solid. $R_f = 0.19$ (20% EtOAc/hexanes).

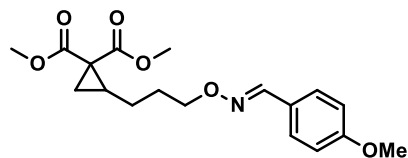
^1H NMR (400 MHz, CDCl_3) δ 8.26 (dt, $J = 9.0, 2.1$ Hz, 2H), 8.05 – 7.96 (m, 2H), 7.38 (s, 1H), 4.27 (t, $J = 6.4$ Hz, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 1.99 – 1.81 (m, 3H), 1.64 – 1.52 (m, 1H), 1.46 – 1.29 (m, 3H). **^{13}C NMR (101 MHz, CDCl_3)** δ 170.8, 168.7, 148.0, 143.5, 135.9, 131.5, 123.8, 75.1, 52.8, 34.1, 28.5, 28.2, 25.4, 21.4. **HRMS m/z [M+H]** 365.1360 (calc'd for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_7$, 365.1349) **IR (ATR)** $\nu_{\text{max}} = 2957, 1723, 1518, 1334, 1297, 1207, 1131, 1064, 1038, 990$.

5-10e



The title compound was synthesized via General Procedure A (5 h). The amounts of reagents employed were: oxime **5-9e** (0.10 g, 0.72 mmol), bromocyclopropane **5-8a** (0.20 g, 0.72 mmol), and cesium carbonate (0.70 g, 2.15 mmol) in 7.2 mL of acetone. Resulting crude was purified by flash column chromatography R_f 0.40 (20% EtOAc/hexanes); Yield: 90% (0.22 g) >19:1 mixture of *E:Z* isomers as a white solid. $\text{Mp} = 74 - 75$ °C.

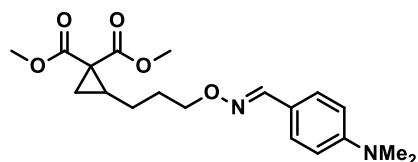
^1H NMR (400 MHz, CDCl_3): δ 8.04 (s, 1H), 7.70 – 7.59 (AA'BB' spin system m, 4H), 4.20 (t, $J = 6.4$ Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 1.99 – 1.89 (m, 1H), 1.84 (dddd, $J = 9.8, 8.1, 6.5, 3.6$ Hz, 2H), 1.62 – 1.51 (m, 1H), 1.41 (ddd, $J = 12.4, 8.4, 4.6$ Hz, 2H), 1.36 – 1.27 (m, 1H) **^{13}C NMR (101 MHz, CDCl_3)** δ 170.9, 168.7, 146.7, 136.9, 132.6, 127.5, 118.7, 113.1, 74.2, 52.7, 34.1, 28.5, 28.3, 25.3, 21.4. **HRMS m/z [M+H]** 345.1453 (calc'd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5^+$, 345.1445). **IR (ATR)** $\nu_{\text{max}} = 2958, 2884, 2227, 1720, 1444, 1326, 1295, 1213, 1133, 833$.

5-10f

The title compound was synthesized via General Procedure A (2.5 h). The amounts of reagents employed were: oxime **5-9f** (0.11 g, 0.72 mmol),

bromocyclopropane **5-8a** (0.20 g, 0.72 mmol), and cesium carbonate (0.70 g, 2.15 mmol) in 7.2 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 83% (0.21 mg) >19:1 mixture of *E:Z* isomers as a clear oil. R_f 0.26 (20% EtOAc/hexanes).

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.00 (s, 1H), 7.50 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 4.13 (t, $J = 6.4$ Hz, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 1.99-1.91 (m, 1H), 1.89 – 1.76 (m, 2H), 1.62 – 1.50 (m, 1H), 1.45 – 1.37 (m, 2H), 1.37 – 1.26 (m, 1H) **$^{13}\text{C NMR}$ (101 MHz, CDCl_3)** δ 170.7, 168.5, 160.7, 147.9, 128.2, 124.8, 114.0, 73.0, 55.1, 52.4, 52.3, 33.8, 28.2, 28.2, 25.1, 21.1. **HRMS** m/z 349.1519 (calc'd for $\text{C}_{18}\text{H}_{23}\text{NO}_6^+$, 349.1525). **IR (ATR)** ν_{max} = 3024, 2954, 2839, 2875, 1723, 1606, 1513, 1437, 1332, 1300, 1250, 1212, 1171, 1158, 1130, 1031, 832.

5-10g

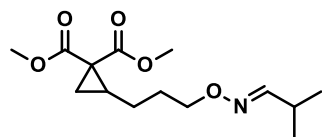
The title compound was synthesized via General Procedure A (21 h). The amounts of reagents employed were: oxime **5-9g** (0.12 g, 0.72 mmol),

bromocyclopropane **5-8a** (0.20 g, 0.72 mmol), and cesium carbonate (0.70 mg, 2.15 mmol) in 7.2 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 84% (0.22 g) >19:1 mixture of *E:Z* isomers as a yellow oil. R_f 0.28 (20% EtOAc/hexanes).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.96 (s, 1H), 7.42 (d, $J = 8.9$ Hz, 2H), 6.65 (d, $J = 8.9$ Hz, 2H), 4.11 (t, $J = 6.4$ Hz, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 2.98 (s, 6H), 1.99 – 1.90 (m, 1H), 1.82 (tdt, $J = 12.5, 8.2, 3.9$ Hz, 2H), 1.62 – 1.51 (m, 1H), 1.41 (dq, $J = 8.7, 4.6$ Hz, 2H), 1.37 – 1.28 (m, 1H) **$^{13}\text{C NMR}$ (101 MHz, CDCl_3)** δ 171.0, 168.8, 151.5, 149.1, 128.4, 120.2, 112.0, 73.1, 52.7, 40.4, 34.1, 28.5, 25.5, 21.5. **HRMS** m/z 362.1846 (calc'd for

$C_{19}H_{26}N_2O_5^+$, 362.1842). **IR (ATR)** ν_{\max} = 2950, 2861, 2809, 1723, 1609, 1525, 1436, 1337, 1278, 1212, 1130, 818.

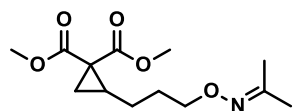
5-10k



The title compound was synthesized via General Procedure A (22 h). The amounts of reagents employed were: oxime **5-9h** (0.062 g, 0.72 mmol), cyclopropane **5-8a** (0.20 g, 0.72 mmol), and cesium carbonate (0.70 g, 2.19 mmol) in 7.2 mL of acetone. The resulting oil was purified via column chromatography (15% EtOAc/hexanes) to yield a fraction containing pure *E* isomer and a mixed fraction containing a 1.4:1 mixture of *E/Z* isomers. Total yield: 70% (0.14 g) as a clear oil. *E* fraction (46%, 0.094 g), mix fraction (24%, 0.049 g). R_f = 0.32 (15% EtOAc/hexanes)

1H NMR (400 MHz, $CDCl_3$) δ E isomer = 7.24 (d, J = 6.4 Hz, 1H), 3.98 (dd, J = 6.5 Hz, 6.5 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 2.46 (dq, J = 13.6, 6.8 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.80-1.70 (m, 2H), 1.58-1.49 (m, 1H), 1.44-1.36 (m, 2H), 1.31-1.21 (m, 1H), 1.07 (d, J = 6.8 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.0, 168.8, 155.8, 72.7, 52.7, 52.6, 34.1, 29.5, 28.5, 25.5, 21.5, 20.3. **HRMS m/z** 285.1587 (calc'd for $C_{14}H_{23}NO_5^+$, 285.1576). **IR (ATR)** ν_{\max} = 2954, 2871, 1725, 1436, 1329, 1210, 1129.

5-10i

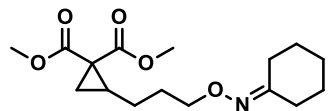


The title compound was synthesized via General Procedure A. The amounts of reagents employed were: oxime **5-9i** (0.065 g, 0.89 mmol), bromocyclopropane **5-8a** (0.25 g, 0.89 mmol), and cesium carbonate (0.87 g, 2.69 mmol) in 8.9 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes) to yield a clear colourless oil. Yield: 0.15 g (64%). R_f = 0.30 (20% EtOAc/hexanes).

1H NMR (400 MHz, $CDCl_3$) δ 4.00 (t, J = 6.4 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 1.98 – 1.88 (m, 1H), 1.84 (s, 3H), 1.82 (s, 3H), 1.79-1.66 (m, 2H), 1.53 (dq, J = 14.5, 6.5 Hz, 1H), 1.39 (ddd, J = 11.7, 8.4, 4.5 Hz, 2H), 1.25 (dq, J = 14.7, 8.2 Hz, 1H). **^{13}C NMR**

(101 MHz, CDCl₃) δ 171.0, 168.8, 154.7, 72.6, 52.7, 52.6, 34.1, 28.5, 25.5, 22.0, 21.5, 15.7. HRMS m/z 271.1421 (calc'd for C₁₃H₂₁NO₅⁺, 271.1420). IR (ATR) ν_{\max} 3020, 2952, 2874, 1724, 1436, 1369, 1329, 1210, 1129.

5-10j

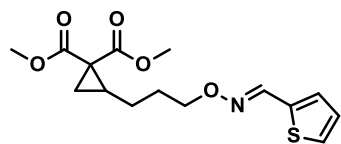


The title compound was synthesized via General Procedure A.

The amounts of reagents employed were: oxime **5-9k** (0.081 g, 0.72 mmol), bromocyclopropane **5-8a** (0.20 g, 0.72 mmol), and cesium carbonate (0.70 g, 2.15 mmol) in 7.2 mL acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes) to yield a clear colourless oil. Yield: 0.12 g (52%). R_f 0.31 (20% EtOAc/hexanes).

¹H NMR (599 MHz, CDCl₃) δ 3.99 (t, J = 6.5 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 2.42 (t, J = 5.2 Hz, 2H), 2.22 – 2.13 (m, 2H), 1.97 – 1.87 (m, 1H), 1.83 – 1.69 (m, 2H), 1.69 – 1.61 (m, 2H), 1.62 – 1.48 (m, 5H), 1.39 (dddd, J = 18.8, 7.0, 4.6, 2.2 Hz, 2H), 1.30 – 1.18 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 171.0, 168.8, 160.3, 72.4, 52.7, 52.6, 34.1, 32.4, 28.6, 28.5, 27.2, 26.0, 25.9, 25.6, 21.5. HRMS m/z 311.1739 (calc'd for C₁₆H₂₅NO₅⁺, 311.1733) IR (ATR) ν_{\max} 2931, 2860, 1724, 1435, 1327, 1280, 1208, 1127, 1056, 991, 882.

5-10h

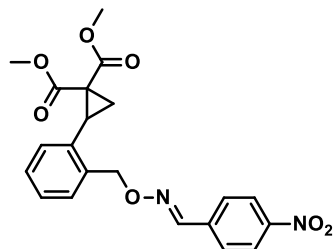


The title compound was synthesized via General Procedure A (18 h). The amounts of reagents employed were: *E*-oxime

5-9j (0.11 g, 0.89 mmol), bromocyclopropane **5-8a** (0.89 g, 0.89 mmol), and cesium carbonate (0.87 g, 2.69 mmol) in 9.0 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes) to yield the desired product (0.14 g, 48%) as the single *E*-isomer as a clear oil. R_f 0.27 (20% EtOAc/Hexanes).

¹H NMR (400 MHz, CDCl₃): δ = 7.62 (s, 1H), 7.51 (d, J = 5.1 Hz, 1H), 7.32 (dd, J = 3.7, 1.0 Hz, 1H), 7.06 (dd, J = 5.1, 3.8 Hz, 1H), 4.31 – 4.25 (m, 2H), 3.70 (s, 6H), 2.01 –

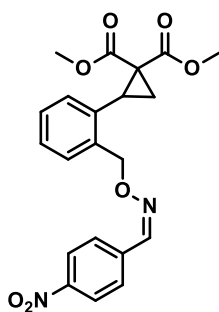
1.84 (m, 3H), 1.70 – 1.57 (m, 1H), 1.45-1.36 (m, 3H) ^{13}C NMR (101 MHz, CDCl_3) δ 171.0, 168.7, 140.3, 131.6, 131.5, 131.3, 126.3, 74.3, 52.7, 52.6, 34.1, 28.6, 28.4, 25.6, 21.4. 714 HRMS m/z 325.0994 (calc'd for $\text{C}_{15}\text{H}_{19}\text{NO}_5\text{S}^+$, 325.0984). IR (ATR) ν_{max} 2951, 1721, 1604, 1435, 1329, 1208, 1127, 1047.



5-10m *E*-isomer

The title compound was synthesized via General Procedure A with the exception of using 1.2 equiv. of cyclopropane **5-8c** in place of bromocyclopropane **5-8a** (30 min). The amounts of reagents employed were: oxime **5-9c** (0.27 g, 1.66 mmol), cyclopropane **5-8c** (0.60 g, 1.83 mmol), and cesium carbonate (1.79 g, 5.49 mmol) in 18 mL of acetone. A single *E* isomer (as confirmed by x-ray crystallography) was observed by ^1H NMR spectroscopy. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 66% (0.49 g) as a white solid. Mp = 82 – 85 °C. R_f = 0.23 (20% EtOAc/hexanes).

^1H NMR (599 MHz, CDCl_3) δ 8.21 (d, J = 8.7 Hz, 2H), 8.17 (s, 1H), 7.75-7.73 (m, 2H), 7.41 – 7.36 (m, 1H), 7.29 – 7.26 (m, 2H), 7.14 – 7.10 (m, 1H), AB system with large $\nu_{\text{ab}}/J_{\text{ab}}=11$ reported as two doublets 5.49 (d, J = 12.3 Hz, 1H) and 5.27 (d, J = 12.3 Hz, 1H), 3.77 (s, 3H), 3.43 (t, J = 8.7 Hz, 1H), 3.30 (s, 3H), 2.33 (dd, J = 8.2, 5.2 Hz, 1H), 1.77 (dd, J = 9.2, 5.1 Hz, 1H) ^{13}C NMR (101 MHz, CDCl_3) δ 170.2, 167.1, 148.5, 146.9, 138.6, 137.5, 133.4, 129.7, 128.3, 127.8, 124.1, 75.1, 53.0, 52.3, 36.8, 30.5, 18.8. HRMS m/z 412.1274 (calc'd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_7^+$, 412.1271). IR (ATR) ν_{max} = 2954, 1888, 1742, 1707, 1506, 1338, 1121, 1092, 839, 759, 693.

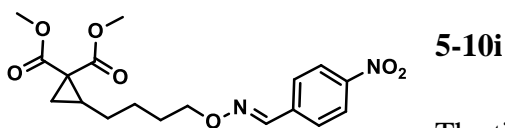


5-10o *Z*-isomer

The title compound was synthesized following General Procedure A with the exception of using 1.2 equiv. of cyclopropane **5-8c** in place of bromocyclopropane **5-8a** (30 min). The amounts of reagents employed were: *z*-oxime **5-9d** (0.10 g, 0.62 mmol), cyclopropane **5-8c** (0.24 g, 0.74

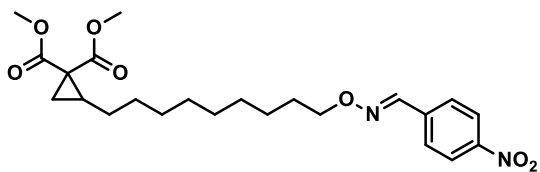
mmol), and cesium carbonate (0.60 g, 1.84 mmol) in 6.2 mL of acetone. A single *Z* isomer was observed by ^1H NMR spectroscopy. The resulting oil was pushed crude into the next step. Yield (crude): 18% (0.045 g) as a white foam. R_f 0.24 (20% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3) δ 8.27 – 8.13 (m, 2H), 8.03 (dt, $J = 9.1, 2.2$ Hz, 2H), 7.40 (s, 1H), 7.37 – 7.30 (m, 1H), 7.27 – 7.19 (m, 2H), 7.12 – 7.04 (m, 1H), 5.51 (d, $J = 12.7$ Hz, 1H), 5.27 (d, $J = 12.7$ Hz, 1H), 3.75 (s, 3H), 3.36 (dd as apparent t, $J = 8.7$ Hz, 1H), 3.28 (s, 3H), 2.27 (dd, $J = 8.2, 5.1$ Hz, 1H), 1.70 (dd, $J = 9.1, 5.2$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.1, 167.1, 148.0, 144.1, 137.5, 135.8, 133.3, 131.7, 129.4, 128.3, 127.9, 123.8, 75.5, 53.0, 52.3, 36.7, 30.1, 18.8. HRMS m/z [$\text{M}+\text{H}$] 413.1352 (calc'd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_7^+$, 413.1352) IR (ATR) $\nu_{\text{max}} = 2948, 2888, 1741, 1707, 1507, 1338, 1121, 1046, 936, 793$.



The title compound was synthesized via General Procedure A (40 h). The amounts of reagents employed were: oxime **5-9c** (0.24 g, 1.47 mmol), cyclopropane **5-8b-butylchain** (0.50 g, 1.47 mmol), and cesium carbonate (1.92 g, 5.88 mmol) in 15 mL of acetone. The resulting oil was purified via column chromatography (25% EtOAc/hexanes). Yield: 76% (0.42 g) >19:1 mixture of *E*:*Z* isomers as a pale yellow oil which slowly crystallizes in the freezer. $\text{Mp} = 59 - 61$ °C. R_f 0.50 (25% EtOAc/hexanes),

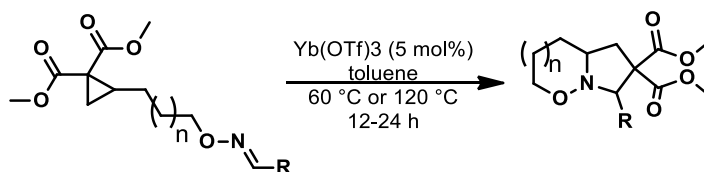
^1H NMR (400 MHz, CDCl_3): $\delta = 8.21$ (d, $J = 8.7$ Hz, 2H), 8.11 (s, 1H), 7.73 (d, $J = 8.7$ Hz, 2H), 4.20 (dd, $J = 6.4$ Hz, 6.4 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 1.92 (dddd, $J = 8.9$ Hz, 8.0 Hz, 8.0 Hz, 5.6 Hz, 1H), 1.80-1.70 (m, 2H), 1.58-1.48 (m, 3H), 1.45-1.37 (m, 2H), 1.29-1.17 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.0, 168.8, 148.4, 146.2, 138.7, 127.6, 124.1, 74.9, 52.8, 52.6, 34.0, 28.8, 28.6, 28.6, 25.3, 21.5. HRMS m/z [$\text{M}+\text{H}$] 379.1503 (calc'd for $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}_7^+$, 379.1500). IR (ATR) $\nu_{\text{max}} = 3007, 2953, 2883, 1717, 1588, 1509, 1479, 1438, 1387, 1329, 1278, 1261, 1207, 1131, 1107, 1077, 977, 945, 835$.

5-10n

The title compound was synthesized via General Procedure A (15 h). The amounts of reagents employed were: oxime **5-9c** (0.20 g, 1.22 mmol), cyclopropane **5-8b-nonylchain** (0.50 g, 1.22 mmol), and cesium carbonate (0.780 g, 2.39 mmol) in 12 mL of acetone. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 77% (423 mg) >19:1 mixture of *E:Z* isomers as a pale yellow oil which slowly crystallizes in the freezer. Mp = 50 – 52 °C. R_f 0.33 (20% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): δ = 8.24-8.21 (m, 2H), 8.10 (s, 1H), 7.76-7.72 (m, 2H), 4.20 (dd, J = 6.7 Hz, 6.7 Hz, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 1.89 (dddd, J = 8.8 Hz, 8.0 Hz, 8.0 Hz, 6.1 Hz, 1H), 1.75-1.69 (m, 2H), 1.50 – 1.32 (m, 8H), 1.33 – 1.22 (m, 8H), 1.19-1.12 (m, 1H). **^{13}C NMR (101 MHz, cdcl_3)** δ 171.0, 168.7, 148.2, 145.9, 138.7, 127.4, 124.0, 75.2, 52.6, 52.4, 33.9, 29.4, 29.4, 29.3, 29.2, 29.1, 28.8, 28.7, 25.8, 21.4. (One carbon likely overlapped near 29 ppm). **HRMS m/z [M+H]** 449.2291 (calc'd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_7^+$, 449.2282). **IR (ATR)** ν_{max} = 3020, 2952, 2930, 2857, 1727, 1436, 1369, 1330, 1279, 1251, 1210, 1129, 1101, 1006, 835, 776, 758, 665.

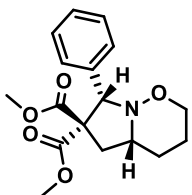
5.6.5 Annulation of Oxime-Ether Tethered Cyclopropanes



Scheme 109 - General reaction for the synthesis of hexahydropyrrolo-oxazines **5-11**

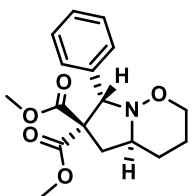
A mixture of oxime ether tethered cyclopropane (1.0 equiv) and $\text{Yb}(\text{OTf})_3$ (5 mol%) in toluene (0.1M) were heated to the indicated temperature and for the indicated time. Formation of pyrrolo-oxazine was primarily monitored by thin layer chromatography but was supplemented with ^1H NMR spectroscopy when required. When TLC or ^1H NMR

indicated complete consumption of the cyclopropane the solution was concentrated *in vacuo* prior to purification *via* flash column chromatography.



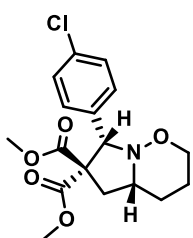
5-11a 120 °C Cis Isomer: The title compound was synthesized via General Procedure 5.2. (19 h). The amounts of reagents employed were: oxime ether **5-10a** (0.10 g, 0.32 mmol), Yb(OTf)₃ (10 mg, 5 mol%) in 3.2 mL of acetone. The resulting oil was purified via column chromatography (15% EtOAc/hexanes). A 19:1 mixture of *cis* to *trans* isomers or greater was observed by ¹H NMR spectroscopy. Yield: 89% (0.089 g) as a clear oil. R_f = 0.50 (20% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.48-7.45 (m, 2H), 7.31-7.26 (m, 2H), 4.76 (s, 1H), 3.96-3.92 (m, 2H), 3.78 (s, 3H), 3.00 (s, 3H), 2.75-2.66 (m, 1H), 2.56 (dd, *J* = 12.5 Hz, 12.5 Hz, 1H), 2.30 (dd, *J* = 13.0 Hz, 6.1 Hz, 1H), 2.01-1.95 (m, 1H), 1.75-1.61 (m, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ 171.9, 169.4, 137.7, 128.2, 128.0, 127.8, 72.3, 70.3, 62.3, 61.0, 53.1, 52.2, 35.7, 29.1, 24.9. **HRMS *m/z*** 319.1424 (calc'd for C₁₇H₂₁NO₅⁺, 319.1420). **IR (ATR)** ν_{max} 3033, 2951, 2857, 1731, 1435, 1263, 1207, 1126, 700.



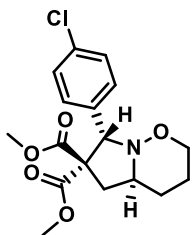
5-11a 60 °C Trans Isomer: The title compound was synthesized via General Procedure B (19 h). The amounts of reagents employed were: oxime ether **5-10a** (0.060 g, 0.32 mmol), Yb(OTf)₃ (6.0 mg, 5 mol%) in 3.2 mL of toluene. A mixture of 1.7:1 *trans* to *cis* isomers were observed in the crude reaction mixture by ¹H NMR spectroscopy. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 95% combined isomers (0.057 g) *trans* yield 60% (0.036 g) as a clear oil. R_f (*trans*) 0.34 (20% EtOAc/hexanes).

^1H NMR (599 MHz, CDCl_3) δ 7.28 – 7.21 (m, 4H), 7.20 – 7.14 (m, 1H), 5.46 (s, 1H), 3.95-3.87 (m, 2H), 3.84 (dd, $J = 10.9, 3.6$ Hz, 1H), 3.80 (s, 3H), 3.02 (s, 3H), 2.65 (dd, $J = 12.8, 6.2$ Hz, 1H), 2.54 (dd, $J = 12.8, 10.3$ Hz, 1H), 2.10-2.04 (m, 1H), 1.80-1.73 (m, 2H), 1.49-1.44 (m, 1H). **^{13}C NMR (151 MHz, CDCl_3)** δ 172.3, 170.8, 138.0, 128.2, 128.0, 127.6, 75.2, 68.2, 66.7, 63.4, 53.4, 52.3, 36.2, 23.4, 20.7. **HRMS m/z** 319.1409 (calc'd for $\text{C}_{17}\text{H}_{21}\text{NO}_5^+$, 319.1420). **IR (ATR)** ν_{max} 2950, 2854, 1728, 1496, 1251, 1204, 1135, 1115, 1082, 1028



5-11b 120 °C Cis Isomer: The title compound was synthesized via General Procedure B (20 h). The amounts of reagents employed were: oxime ether **5-10b** (0.070 g, 0.20 mmol), $\text{Yb}(\text{OTf})_3$ (6.1 mg, 5 mol%) in 2 mL of toluene. A 19:1 mixture or greater of *cis* to *trans* isomers was observed in the crude reaction mixture by ^1H NMR spectroscopy. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 90% (0.063 g) as a clear oil. R_f 0.50 (20% EtOAc/hexanes).

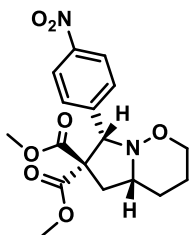
^1H NMR (400 MHz, CDCl_3): δ 7.44 – 7.37 (AA'BB', 2H), 7.28 – 7.22 (AA'BB', 2H), 4.70 (s, 1H), 3.91 (t, $J = 5.6$ Hz, 1H), 3.77 (s, 3H), 3.07 (s, 3H), 2.67 (ddt, $J = 11.9, 6.1, 2.7$ Hz, 1H), 2.57 – 2.46 (m, 1H), 2.31 (dd, $J = 13.1, 6.2$ Hz, 1H), 2.01 – 1.93 (m, 1H), 1.72 – 1.60 (m, 3H) **^{13}C NMR (101 MHz, cdcl_3)** δ 171.5, 169.0, 135.9, 133.3, 129.4, 127.8, 71.3, 70.1, 62.0, 60.5, 52.9, 52.1, 35.3, 28.7, 24.5. **HRMS m/z** 353.1037 (calc'd for $\text{C}_{17}\text{H}_{20}\text{ClNO}_5^+$, 353.1030). **IR (ATR)** ν_{max} 3011, 2853, 2951, 1732, 1435, 1263, 1207, 1172, 1126, 1046, 842.



5-11b 60 °C Trans Isomer: The title compound was synthesized via General Procedure B (20 h). The amounts of reagents employed were: oxime ether **5-10b** (0.070 g, 0.20 mmol), $\text{Yb}(\text{OTf})_3$ (6.1 mg, 5 mol%) in 2 mL of toluene. A 19:1 mixture or greater of *trans* to *cis* isomers was observed in the crude reaction mixture by ^1H NMR spectroscopy. The resulting oil was

purified via column chromatography (20% EtOAc/hexanes). Yield: 69% (0.048 g) as a clear oil. R_f 0.56 (20% EtOAc/hexanes).

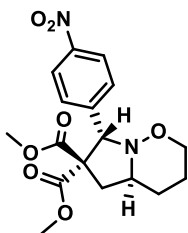
^1H NMR (400 MHz, CDCl_3): δ = 7.21 (apparent s, 4H), 5.42 (s, 1H), 3.96 – 3.88 (m, 1H), 3.84 (dt, J = 11.9, 3.8 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.74 (m, 1H), 3.09 (s, 3H), 2.64 (dd, J = 12.9, 6.1 Hz, 1H), 2.50 (dd, J = 12.9, 9.8 Hz, 1H), 2.07-1.99 (m, 1H), 1.75 (dtq, J = 17.3, 9.0, 4.4 Hz, 2H), 1.53 – 1.44 (m, 1H) **^{13}C NMR (101 MHz, CDCl_3)** δ 172.0, 170.3, 136.3, 133.2, 129.2, 128.1, 73.7, 67.5, 66.0, 62.7, 53.3, 52.2, 36.0, 23.1, 20.6. **HRMS m/z** 353.1033 (calc'd for $\text{C}_{17}\text{H}_{20}\text{ClNO}_5^+$, 353.1030). **IR (ATR)** ν_{max} 2952, 2852, 1730, 1519, 1346, 1261, 1205, 1045, 838.



5-11c 120 °C Cis Isomer: The title compound was synthesized via General Procedure B (18 h at 120 °C). The amounts of reagents employed were: oxime ether **5-10c** (0.030 g, 0.082 mmol), $\text{Yb}(\text{OTf})_3$ (2.5 mg, 5 mol%) in 1 mL of toluene. A 19:1 mixture or greater of *cis* to *trans* isomers was observed in the crude reaction mixture by ^1H NMR spectroscopy. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 99% (0.03 mg) as a white solid. R_f 0.34 (20% EtOAc/hexanes).

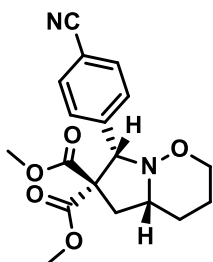
^1H NMR (400 MHz, CDCl_3): δ 8.15 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 4.80 (s, 1H), 3.96 – 3.90 (m, 2H), 3.80 (s, 3H), 3.05 (s, 3H), 2.78 – 2.67 (m, 1H), 2.54 (dd as apparent t, J = 13.2 Hz, 1H), 2.37 (dd, J = 13.2, 6.3 Hz, 1H), 2.02-1.99 (m, 1H), 1.75 – 1.62 (m, 3H) **^{13}C NMR (101 MHz, CDCl_3)** δ 171.5, 168.9, 147.6, 145.5, 129.3, 123.1, 71.6, 70.5, 62.4, 60.9, 53.4, 52.5, 35.7, 29.0, 24.7. **HRMS m/z** 364.1273 (calc'd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_7^+$, 364.1271). **IR (ATR)** ν_{max} = 3029, 2954, 2853, 1732, 1520, 1435, 1348, 1263, 1208, 1173, 1126, 1046, 697.

5-11c 60 °C Trans Isomer: The title compound was synthesized via General Procedure B (18 h at 60 °C). The amounts of reagents employed were: oxime ether **5-10c** (0.030 g, 0.082 mmol), $\text{Yb}(\text{OTf})_3$ (2.5 mg, 5 mol%). A 19:1 mixture or greater of *trans* to *cis*



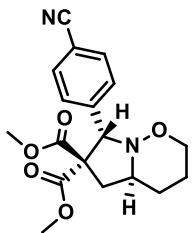
isomers was observed in the crude reaction mixture by ^1H NMR spectroscopy. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 93% (0.028 mg) as a white solid. R_f 0.22 (20% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): δ 8.09 (d, $J = 8.7$ Hz, 2H), 7.46 (d, $J = 8.9$ Hz, 2H), 5.50 (s, 1H), 3.93-3.84 (m, 2H), 3.81 (s, 3H), 3.76 (dt, $J = 12.5, 3.0$ Hz, 1H), 3.07 (s, 3H), 2.62 (dd, $J = 12.9, 6.1$ Hz, 1H), 2.52 (dd, $J = 12.9, 9.7$ Hz, 1H), 2.10 – 1.94 (m, 1H), 1.82 – 1.66 (m, 2H), 1.56 – 1.43 (m, 1H) **^{13}C NMR (101 MHz, CDCl_3)** δ 171.8, 170.1, 147.2, 145.6, 128.6, 123.1, 73.4, 67.4, 66.1, 62.7, 53.5, 52.3, 36.4, 23.1, 20.6. **HRMS m/z** 364.1263 (calc'd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_7^+$, 364.1271) **IR (ATR)** ν_{max} = 2952, 2855, 1723, 1603, 1518, 1254, 1110, 1064, 1046, 983.



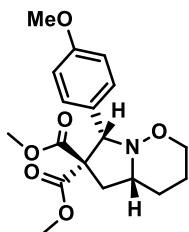
5-11d 120 °C Cis Isomer: The title compound was synthesized via General Procedure B (26 h). The amounts of reagents employed were: oxime ether **5-10e** (0.060 g, 0.17 mmol), $\text{Yb}(\text{OTf})_3$ (0.005 g, 5 mol%) in 2 mL of toluene. A 1:1 mixture of *cis* to *trans* isomers was observed in the crude reaction mixture by ^1H NMR spectroscopy. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 93% (0.056 g) of combined isomers (*cis* isomer 0.027 g) (*trans* isomer 0.029 g) as pale-yellow oils. R_f (*cis*) = 0.28 (20% EtOAc/hexanes); R_f (*trans*) = 0.17 (20% EtOAc/hexanes).

^1H NMR (599 MHz, CDCl_3) δ 7.63 – 7.51 (AA'BB', 4H), 4.75 (s, 1H), 3.94 – 3.88 (m, 2H), 3.78 (s, 3H), 3.04 (s, 3H), 2.74 – 2.65 (m, 1H), 2.52 (dd as apparent t, $J = 12.3$ Hz, 1H), 2.34 (dd, $J = 13.2, 6.3$ Hz, 1H), 2.01 – 1.95 (m, 1H), 1.71 – 1.61 (m, 3H) **^{13}C NMR (101 MHz, CDCl_3)** δ 171.5, 168.9, 143.5, 131.8, 129.2, 119.1, 111.5, 71.7, 70.4, 62.4, 60.9, 53.3, 52.4, 35.6, 29.0, 24.7. **HRMS m/z** 344.1375 (calc'd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_5^+$, 344.1372). **IR (ATR)** ν_{max} 3060, 2958, 2923, 2861, 2227, 1745, 1723, 1611, 1442, 1319, 1256, 1220, 1135, 1054.



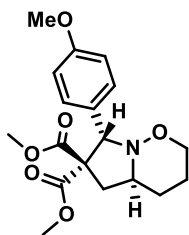
5-11d 60 °C Trans Isomer: The title compound was synthesized via General Procedure B (48 h). The amounts of reagents employed were: oxime ether **5-10e** (0.070 g, 0.2 mmol), Yb(OTf)₃ (6.0 mg, 5 mol%) in 2 mL of toluene. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 85% (0.060 g) as a white foam of a single isomer. R_f (*trans*) = 0.17 (20% EtOAc/hexanes)

¹H NMR (599 MHz, CDCl₃) δ 7.55 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 5.47 (s, 1H), 3.94 – 3.90 (m, 1H), 3.87 – 3.82 (m, 1H), 3.81 (s, 3H), 3.07 (s, 3H), 2.63 (dd, J = 12.9, 6.0 Hz, 1H), 2.52 (dd, J = 12.8, 9.7 Hz, 1H), 2.06-2.01 (m, 1H), 1.80-1.73, (m, 2H), 1.53-1.49 (m, 1H). **¹³C NMR (151 MHz, CDCl₃)** δ 171.8, 170.1, 143.5, 131.8, 128.5, 118.9, 111.2, 73.6, 67.4, 66.1, 62.8, 53.4, 52.3, 36.3, 23.1, 20.6. **HRMS m/z** 344.1369 (calc'd for C₁₈H₂₀N₂O₅⁺, 344.1372). **IR (ATR)** ν_{\max} 2952, 2228, 1728, 1609, 1505, 1434, 1255, 1175, 840, 729.



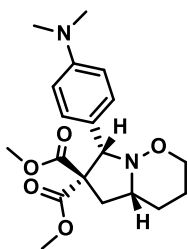
5-11f 120 °C Cis Isomer: The title compound was synthesized via General Procedure B (27 h). The amounts of reagents employed were: oxime ether **5-10f** (0.070 g, 0.20 mmol), Yb(OTf)₃ (6.0 mg, 5 mol%) in 2 mL of toluene. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 95% (0.066 g) >19:1 *cis:trans* isomer as a clear oil. R_f 0.33 (20% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.34 (m, 2H), 6.85 – 6.79 (m, 2H), 4.69 (s, 1H), 3.92 (t, J = 5.6 Hz, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.06 (s, 3H), 2.70-2.63 (m, 1H), 2.53 (dd as apparent t, J = 12.9 Hz, 1H), 2.28 (dd, J = 13.0, 6.1 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.71 – 1.59 (m, 3H) **¹³C NMR (151 MHz, CDCl₃)** δ 172.2, 169.8, 159.5, 129.9, 129.6, 113.7, 72.1, 70.6, 62.5, 61.1, 55.6, 53.3, 52.6, 35.8, 29.3, 25.1. **HRMS m/z** 349.1538 (calc'd for C₁₈H₂₃NO₆⁺, 349.1525). **IR (ATR)** ν_{\max} 2951, 2848, 2226, 1729, 1609, 1511, 1435, 1280, 1247, 1171, 1126, 1045.



5-11f 25 °C Trans Isomer: The title compound was synthesized via General Procedure B (40 h). The amounts of reagents employed were: oxime ether **5-10f** (0.045 g, 0.13 mmol), Yb(OTf)₃ (4.0 mg, 5 mol%) in 1.3 mL of toluene. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 95% (0.041 g) combined trans isomer **5-11f-trans** (0.025 g) and unreacted starting material (0.015 g). Yield of trans isomer 85% (brsm) (0.025 g) >19:1 *trans:cis* isomer as a clear oil. $R_f = 0.23$ (20% EtOAc/hexanes).

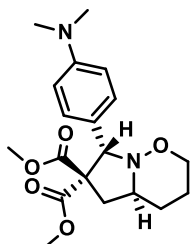
¹H NMR (599 MHz, CDCl₃) δ 7.18 (d, $J = 8.6$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 5.42 (s, 1H), 3.92 (dt, $J = 7.9, 4.3$ Hz, 1H), 3.89 – 3.80 (m, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.08 (s, 3H), 2.67 (dd, $J = 12.9, 6.3$ Hz, 1H), 2.49 (dd, $J = 12.9, 10.0$ Hz, 1H), 2.08 – 1.99 (m, 1H), 1.79 – 1.71 (m, 2H), 1.50 – 1.44 (m, 1H). **¹³C NMR (151 MHz, CDCl₃)** δ 172.2, 170.6, 158.9, 129.8, 129.0, 113.4, 74.2, 67.7, 66.1, 62.7, 55.3, 53.2, 52.2, 35.8, 23.3, 20.6. **HRMS m/z** 349.1524 (calc'd for C₁₈H₂₃NO₆⁺, 349.1525). **IR (ATR)** ν_{\max} 2951, 2852, 1728, 1613, 1512, 1434, 1246, 1174, 1029, 729.



5-11g 120 °C Cis Isomer: The title compound was synthesized via General Procedure B (25 h). The amounts of reagents employed were: oxime ether **5-10g** (0.070 g, 0.19 mmol), Yb(OTf)₃ (0.0060 g, 5 mol%) in 2 mL of toluene. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 95% (0.069 mg) >19:1 *cis:trans* isomer as a pale-yellow solid. Mp = 157 – 160 °C. $R_f = 0.22$ (20% EtOAc/hexanes).

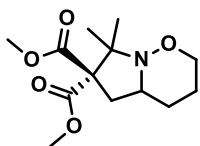
¹H NMR (400 MHz, CDCl₃): $\delta = 7.30$ (AA'BB', 2H), 6.67 (AA'BB', 2H), 4.65 (s, 1H), 3.94 – 3.89 (m, 2H), 3.76 (s, 3H), 3.08 (s, 3H), 2.88 (s, 6H), 2.70 – 2.61 (m, 1H), 2.53 (dd overlapped as an apparent t, $J = 12.4$ Hz, 1H), 2.27 (dd, $J = 12.9, 6.1$ Hz, 1H), 1.99 – 1.91 (m, 1H), 1.69-1.59 (m, 3H). **¹³C NMR (101 MHz, cdcl₃)** δ 172.1, 169.8, 150.5, 128.9,

125.4, 112.5, 72.1, 70.3, 62.3, 60.9, 53.0, 52.4, 40.9, 35.5, 29.2, 24.9. **HRMS** m/z 362.1838 (calc'd for $C_{19}H_{26}N_2O_5^+$, 362.1842). **IR (ATR)** ν_{\max} 3465, 2948, 1752, 1615, 1329, 1228, 1124, 1045, 834.



5-11g 25 °C Trans Isomer: The title compound was synthesized via General Procedure B (49 h). The amounts of reagents employed were: oxime ether **5-10g** (0.026 g, 0.07 mmol), $Yb(OTf)_3$ (0.0020 g, 5 mol%) in 1 mL of toluene. A 2:1 mixture of *trans* to *cis* isomers was observed by 1H NMR spectroscopy. The resulting oil was purified via column chromatography (25% EtOAc/hexanes). Yield: 98% combined *trans:cis* isomers (0.025 mg), *trans isomer* 62% (0.016 g, white solid) $R_f(\text{trans}) = 0.14$ (20% EtOAc/hexanes). and *cis isomer* 35% (0.009 g, white solid) $R_f(\text{cis}) = 0.22$ (20% EtOAc/hexanes).

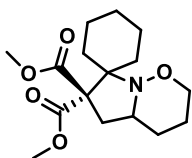
1H NMR (599 MHz, $CDCl_3$) δ 7.10 (AA'BB', 2H), 6.62 (AA'BB', 2H), 5.38 (s, 1H), 3.92 (dt, $J = 11.7, 4.1$ Hz, 1H), 3.89 – 3.80 (m, 2H), 3.79 (s, 3H), 3.11 (s, 3H), 2.87 (s, 6H), 2.70 (dd, $J = 12.9, 6.4$ Hz, 1H), 2.48 (dd, $J = 12.9, 10.0$ Hz, 1H), 2.07 – 1.99 (m, 1H), 1.78 – 1.70 (m, 2H), 1.50 – 1.42 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.3, 170.7, 150.1, 128.7, 125.4, 112.4, 74.5, 67.7, 66.1, 62.6, 53.1, 52.3, 40.8, 35.6, 23.5, 20.7. **HRMS** m/z 362.1832 (calc'd for $C_{19}H_{26}N_2O_5^+$, 362.1842). **IR (ATR)** ν_{\max} 2949, 1728, 1614, 1522, 1433, 1349, 1204, 1168, 864, 823.



5-11j The title compound was synthesized via General Procedure B (21 h). The amounts of reagents employed were: oxime ether **5-10i** (0.070 g, 0.26 mmol), $Yb(OTf)_3$ (0.008 g, 5 mol%) in 2.6 mL of toluene. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 78% (0.054 g) as a clear, colorless oil. R_f 0.47 (20% EtOAc/hexanes).

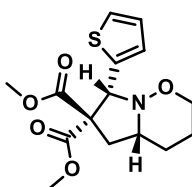
1H NMR (599 MHz, $CDCl_3$) δ 3.91 – 3.89 (m, 2H), 3.72 (s, 3H), 3.68 (s, 3H), 2.87 (tdd, $J = 9.3, 9.3, 2.6$ Hz, 1H), 2.61 (dd, $J = 13.8, 9.2$ Hz, 1H), 1.96 (dd, $J = 13.8, 8.4$ Hz, 1H), 1.93 – 1.87 (m, 1H), 1.62 – 1.51 (m, 3H), 1.39 (s, 3H), 1.04 (s, 3H) **^{13}C NMR (151 MHz,**

CDCl₃) δ 171.0, 170.6, 70.2, 62.7, 57.8, 52.5, 33.7, 29.9, 25.3, 23.1, 16.6. **HRMS** m/z 271.1410 (calc'd for C₁₃H₂₁NO₅⁺, 271.1420). **IR (ATR)** ν_{\max} 2949, 1737, 1434, 1380, 1260, 1194, 1137, 1038, 918, 887.



5-11k The title compound was synthesized via General Procedure B (18 h). The amounts of reagents employed were: oxime ether **5-10j** (0.050 g, 0.16 mmol), Yb(OTf)₃ (0.005 g, 5 mol%) in 2 mL of toluene. The resulting oil was purified via column chromatography (20% EtOAc/hexanes). Yield: 47% (0.025 g) as a clear, colorless oil. R_f 0.47 (20% EtOAc/hexanes).

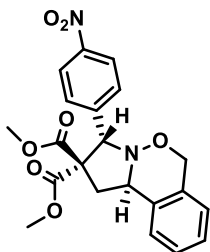
¹H NMR (599 MHz, Chloroform-*d*) δ 3.89 – 3.82 (m, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.51 (br s, 1H), 2.72 (br, 1H), 2.63 (dd, $J = 13.7, 8.5$ Hz, 2H), 1.97 (tdt, $J = 11.3, 8.7, 4.1$ Hz, 1H), 1.77 – 1.60 (m, 7H), 1.60 – 1.53 (m, 2H), 1.35 (m, 2H), 1.30 – 1.19 (m, 2H). **¹³C NMR (151 MHz, CDCl₃)** δ 171.1, 170.5, 69.0, 58.2, 52.6, 52.3, 34.8, 30.2, 26.1, 23.4, 22.4. **HRMS** m/z 311.1723 (calc'd for C₁₆H₂₅NO₅⁺, 311.1733). **IR (ATR)** ν_{\max} 2936, 2853, 1732, 1433, 1223, 1166, 1124, 1014, 965, 796.



5-11h 120 °C, 60 °C or 25 °C Cis Isomer: The title compound was synthesized via General Procedure B (2 days). The amounts of reagents employed were: oxime ether **5-10h** (0.043 g, 0.13 mmol), Yb(OTf)₃ (0.004 g, 5 mol%) in 1.5 mL of toluene. The resulting oil was purified via column chromatography (25% EtOAc/hexanes) to yield a greater than 19:1 of cis to trans isomers by ¹H NMR. (0.031 mg, 78%, colourless oil) $R_f = 0.43$ (20% EtOAc/hexanes).

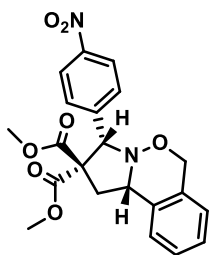
¹H NMR (400 MHz, CDCl₃): δ 7.19 (dd, $J = 5.1, 1.2$ Hz, 1H), 7.10 – 7.06 (m, 1H), 6.94 (dd, $J = 5.1, 3.5$ Hz, 1H), 4.99 (s, 1H), 3.98-3.95 (m, 2H), 3.79 (s, 3H), 3.22 (s, 3H), 2.71-2.63 (m, 1H), 2.55 (t, $J = 12.3$ Hz, 1H), 2.33 (dd, $J = 13.0, 6.1$ Hz, 1H), 1.97 – 1.94 (m, 1H), 1.72 – 1.59 (m, 3H). **¹³C NMR (101 MHz, CDCl₃)** δ 171.3, 169.0, 141.1, 126.3, 126.1, 124.8, 70.1, 68.4, 62.2, 60.8, 52.9, 52.4, 35.0, 28.7, 24.4. **HRMS** m/z 325.0977

(calc'd for $C_{15}H_{19}NO_5S^+$, 325.0984). **IR (ATR)** ν_{\max} 2948, 1726, 1507, 1431, 1283, 1264, 1207, 1004, 936, 695.



5-11e 120 °C Trans Isomer: The title compound was synthesized via General Procedure B (28 h). The amounts of reagents employed were: oxime ether **5-10m** (0.17 g, 0.27 mmol), $Yb(OTf)_3$ (0.013 g, 5 mol%) in 2.7 mL of toluene. The resulting white solid was purified via column chromatography (20% EtOAc/hexanes). Yield: 94% (0.16 g) of a white solid as the trans isomer confirmed by x-ray crystallography. Mp = 159 – 160 °C. R_f = 0.25 (20% EtOAc/hexanes).

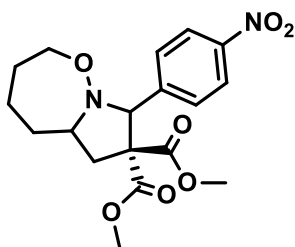
1H NMR (400 MHz, $CDCl_3$): δ = 8.16-8.12 (AA'BB', 2H), 7.55-7.51 (AA'BB', 2H), 7.29-7.23 (m, 2H), 7.10-7.06 (m, 1H), 5.74 (s, 1H), 5.14 (d, J = 14.8 Hz, 1H), 4.87 (dd, J = 11.7, 5.8 Hz, 1H), 4.75 (d, J = 14.8 Hz, 1H), 3.80 (s, 3H), 3.15 (s, 3H), 2.99 (dd, J = 12.8 Hz, 5.8 Hz, 1H), 2.68 (dd, J = 12.8 Hz, 11.7 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 171.4, 170.4, 147.4, 145.9, 133.5, 133.1, 128.7, 127.5, 127.5, 127.2, 124.7, 123.4, 76.8, 70.2, 67.8, 66.9, 53.7, 52.6, 42.3. **HRMS m/z** 412.1271 (calc'd for $C_{21}H_{20}N_2O_7^+$, 412.1271). **IR (ATR)** ν_{\max} = 2958, 2928, 1852, 1725, 1510, 1430, 1343, 1262, 1436, 1046, 698.



5-11e Cis Isomer made from Z-oxime: The title compound was synthesized via General Procedure B (1.5 h). The amounts of reagents employed were: oxime ether **5-10o** (0.044 g, 0.11 mmol), $Yb(OTf)_3$ (0.003 g, 5 mol%). The resulting white solid was purified via column chromatography (20% EtOAc/hexanes). Yield: 87% (0.035 g) of a white solid as the cis isomer. R_f = 0.25 (20% EtOAc/hexanes).

1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.9 Hz, 2H), 7.31 – 7.19 (m, 2H), 7.16 – 7.10 (m, 1H), 7.10 – 7.03 (m, 1H), 5.25 (d, J = 14.2 Hz, 1H), 5.04 (s, 1H), 4.89 (d, J = 14.3 Hz, 1H), 4.09 (t, J = 9.3 Hz, 1H), 3.87 (s, 3H), 3.09 (s, 3H), 2.87

(d, $J = 8.5$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.4, 168.5, 147.7, 144.8, 135.4, 133.6, 129.4, 127.3, 126.8, 124.7, 124.1, 123.2, 71.9, 62.1, 53.6, 52.6. HRMS m/z 412.1270 (calc'd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_7^+$, 412.1271) IR (ATR) $\nu_{\text{max}} = 2953, 1731, 1603, 1493, 1345, 1270, 1041, 1026, 747, 697$.

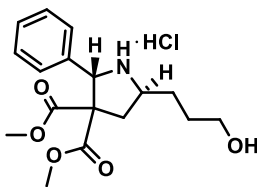


5-11i 160 °C Isomer (unconfirmed designation): $\text{Yb}(\text{OTf})_3$ (0.016 mg, 0.026 mmol) was added to a solution of oxime ether **5-10l** (0.050 g, 0.132 mmol) in toluene (1.3 mL, 0.1 M). The vial was sealed with a crimped aluminum cap bearing a teflon seal and heated to 160 °C for 8 hours. The toluene was removed *in vacuo* and the crude oil was purified by flash column chromatography (20% EtOAc/hexanes) to yield **5-11i** as a single isomer (0.043 g, 86%) as a pale-yellow solid. $\text{Mp} = 112 - 114$ °C. $R_f = 0.40$ (20% EtOAc/hexanes).

^1H NMR (400 MHz, CDCl_3): δ 8.18-8.14 (AA'BB', 2H), 7.74-7.70 (AA'BB', 2H), 4.89 (s, 1H), 3.81 – 3.77 (m, 1H), 3.76 (s, 3H), 3.47 (td, $J = 10.9, 6.4$ Hz, 1H), 3.09 (s, 3H), 2.98 (tdd, $J = 11.0, 7.6, 4.0$ Hz, 1H), 2.56 (dd, $J = 13.7, 11.3$ Hz, 1H), 2.38 (dd, $J = 13.7$ Hz, 7.8 Hz, 1H), 2.07-1.96 (m, 2H), 1.87-1.81 (m, 2H), 1.71-1.60 (m, 1H), 1.54-1.44 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.8, 169.5, 146.8, 129.7, 123.4, 73.9, 71.7, 66.6, 62.2, 53.6, 52.8, 36.9, 35.5, 30.0, 23.2. HRMS m/z 378.1434 (calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_7^+$ 378.1427). IR (ATR) $\nu_{\text{max}} 3112, 3081, 2947, 2869, 17.53, 1730, 1601, 1518, 1432, 1342, 1276, 1212, 1203, 1135, 1081, 1032, 1020, 973, 873, 839, 750, 698, 570$;

5.6.6 Pyrrolidine Synthesis

5-12



Compound **5-11a-trans** (0.030 g, 0.094 mmol) and Pd/C (10% on carbon, 0.0035 g) were dissolved in MeOH (1.2 mL). AcCl (0.016 mL, 0.20 mmol) was added. The flask was equipped with a balloon of $\text{H}_2(\text{g})$ and evacuated and refilled in 5 cycles. The flask was left to remain under a balloon

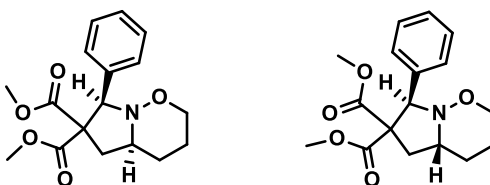
of hydrogen and was stirred at rt for 20 h. When TLC confirmed consumption of starting material the mixture was filtered through Celite and concentrated to yield salt **5-12** (0.029 g, 87% yield) as a light green foam.

¹H NMR (599 MHz, DMSO-*d*₆) δ 10.72 (s br 1H), 9.74 (s br, 1H), 7.42 (apparent s, 5H), 5.43 (s br, 1H), 4.59 (s, br, 1H), 4.16 (p br, $J = 7.5$ Hz, 1H), 3.72 (s, 3H), 3.44 (s br, 2H), 3.27 (s, 3H), 2.89 (dd, $J = 13.5, 6.5$ Hz, 1H), 2.24 (dd, $J = 13.3, 10.0$ Hz, 1H), 1.95-1.89 (m br, 1H), 1.80-1.74 (m br, 1H), 1.62 – 1.50 (m br, 2H). **¹³C NMR (101 MHz, DMSO-*d*₆)** δ 168.6, 168.2, 132.1, 129.2, 128.3, 128.2, 64.3, 63.8, 60.0, 59.4, 53.3, 52.7, 38.1, 29.0, 28.4. **HRMS m/z** 321.1554 (calcd for C₁₇H₂₃NO₅⁺ 321.1576). **IR (ATR)** ν_{\max} 3382, 2872, 1730, 1579, 1500, 1434, 1264, 1210, 1002, 699.

5.6.7 Computational Calculation Data

DFT Calculations were calculated at B3LYP, M062x¹⁷⁹ and PBEh1PBE¹⁸⁰ level of theory with 6-311G+(2d,p) basis set on Gaussian 09.¹⁸¹

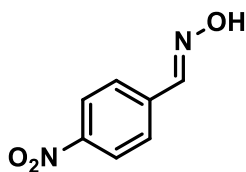
Table 18- Computational calculation data



| Computational Theory | Cis Isomer E (kJ/mol) | Trans Isomer E (kJ/mol) | E _{cis-trans} (kJ/mol) |
|------------------------|-----------------------|-------------------------|---------------------------------|
| M062X/6-311+G(2d,p) | -2864880.50868623 | 2864859.05073564 | -21.456 |
| B3LYP/6-311+G(2d,p) | -2865998.64891367 | -2865977.22496331 | -21.424 |
| PBEh1PBE/6-311+G(2d,p) | -2863027.96102236 | -2863006.58882062 | -21.371 |

5.6.8 Single Crystal X-Ray Diffraction Data

All crystals were grown by Lauren Irwin and submitted to Dr. Paul Boyle for data collection, processing and refinement.



Experimental for C₇H₆N₂O₃ (b19170) *E*-oxime

X-ray quality crystals were prepared by vapour diffusion of pentane into a saturated solution of oxime **5-9c** dissolved in CDCl₃.

Data Collection and Processing. The sample (b19170) was submitted by Lauren Irwin of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 8137 reflections with $6.72^\circ < 2\theta < 95.9^\circ$. The data collection strategy was a number of ω and ϕ scans which collected data up to 98.26° (2θ). The frame integration was performed using SAINT.¹⁸² The resulting raw data was scaled, and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.¹⁸³

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program.¹⁸⁴ All non-hydrogen atoms were obtained from the initial solution. All hydrogen atom positions were obtained from a difference Fourier map and were allowed to refine isotropically. The structural model was fit to the data using full matrix least-squares based on F^2 . The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELXTL suite of crystallographic software.¹⁸⁵ Graphic plots were produced using the XP program suite.¹⁸⁶ Additional information and other relevant literature references can be found in the reference section

of this website (<http://xray.chem.uwo.ca>).

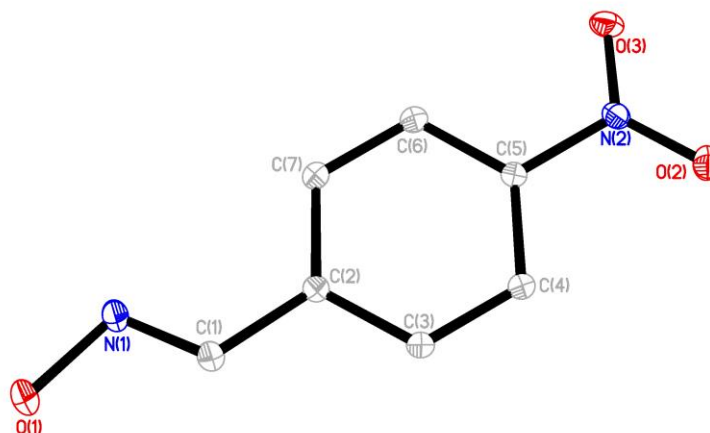


Figure 25 - ORTEP drawing of *b19170* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were omitted for clarity.

Table 19 - Summary of Crystal Data for *b19170*

| | |
|----------------------------------|-----------------------------------|
| Formula | $C_7H_6N_2O_3$ |
| Formula Weight (<i>g/mol</i>) | 166.14 |
| Crystal Dimensions (<i>mm</i>) | $0.244 \times 0.200 \times 0.194$ |
| Crystal Color and Habit | yellow square |
| Crystal System | monoclinic |
| Space Group | $P 2_1/c$ |
| Temperature, K | 110 |
| <i>a</i> , Å | 6.244(3) |
| <i>b</i> , Å | 4.822(2) |
| <i>c</i> , Å | 24.355(13) |

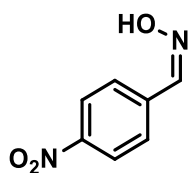
| | |
|---|---|
| $\alpha, ^\circ$ | 90 |
| $\beta, ^\circ$ | 94.782(17) |
| $\gamma, ^\circ$ | 90 |
| $V, \text{\AA}^3$ | 730.7(6) |
| Number of reflections to determine final unit cell | 8137 |
| Min and Max 2θ for cell determination, $^\circ$ | 6.72, 95.9 |
| Z | 4 |
| F(000) | 344 |
| ρ (g/cm) | 1.510 |
| $\lambda, \text{\AA}$, (MoK α) | 0.71073 |
| $\mu, (\text{cm}^{-1})$ | 0.121 |
| Diffractometer Type | Bruker Kappa Axis Apex2 |
| Scan Type(s) | phi and omega scans |
| Max 2θ for data collection, $^\circ$ | 98.26 |
| Measured fraction of data | 0.973 |
| Number of reflections measured | 34297 |
| Unique reflections measured | 7219 |
| R_{merge} | 0.0354 |
| Number of reflections included in refinement | 7219 |
| Cut off Threshold Expression | $I > 2\text{sigma}(I)$ |
| Structure refined using | full matrix least-squares using F^2 |
| Weighting Scheme | $w=1/[\text{sigma}^2(\text{Fo}^2)+(0.0653\text{P})^2+0.0586\text{P}]$ where $\text{P}=(\text{Fo}^2+2\text{Fc}^2)/3$ |
| Number of parameters in least-squares | 133 |
| R_1 | 0.0407 |
| wR_2 | 0.1139 |
| R_1 (all data) | 0.0601 |
| wR_2 (all data) | 0.1256 |
| GOF | 1.051 |
| Maximum shift/error | 0.001 |
| Min & Max peak heights on final ΔF Map ($e^-/\text{\AA}$) | -0.221, 0.768 |

Where:

$$R_1 = \Sigma(|F_o| - |F_c|) / \Sigma F_o$$

$$wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2) / \Sigma(w F_o^4)]^{1/2}$$

$$\text{GOF} = [\Sigma(w(F_o^2 - F_c^2)^2) / (\text{No. of reflns.} - \text{No. of params.})]^{1/2}$$



Experimental for C₇H₆N₂O₃ (b19175)

X-ray quality crystals were prepared by vapour diffusion of pentane into a saturated solution of oxime **5-9d** dissolved in EtOAc.

Data Collection and Processing. The sample (b19175) was submitted by Lauren Irwin of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 5015 reflections with $7.2^\circ < 2\theta < 56.28^\circ$. The data collection strategy was a number of ω and ϕ scans which collected data up to 61.106° (2θ). The frame integration was performed using SAINT. The resulting raw data was scaled, and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program. All non-hydrogen atoms were obtained from the initial solution. The hydrogen atom positions were obtained from a difference Fourier map and were allowed to refine isotropically. The structural model was fit to the data using full matrix least-squares based on F^2 . The calculated structure factors included

corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software. Graphic plots were produced using the NRCVAX program suite. Additional information and other relevant literature references can be found in the reference section of this website (<http://xray.chem.uwo.ca>).

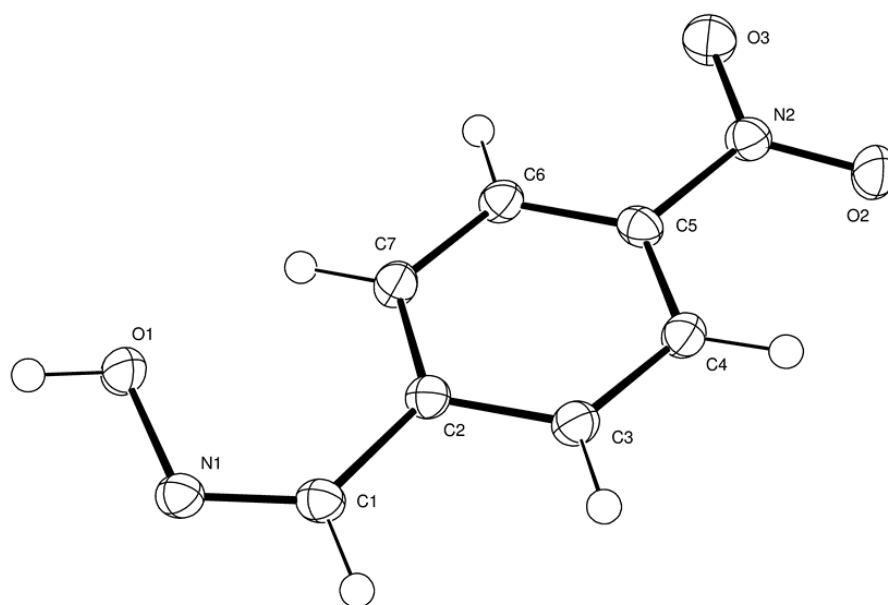


Figure 26 - ORTEP drawing of *b19175* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

Table 20 - Summary of Crystal Data for *b19175*

Formula

$C_7H_6N_2O_3$

| | |
|--|--|
| Formula Weight (<i>g/mol</i>) | 166.14 |
| Crystal Dimensions (<i>mm</i>) | 0.268 × 0.197 × 0.042 |
| Crystal Color and Habit | colourless plate |
| Crystal System | orthorhombic |
| Space Group | P 2 ₁ 2 ₁ 2 ₁ |
| Temperature, K | 110 |
| <i>a</i> , Å | 4.8632(10) |
| <i>b</i> , Å | 6.6115(17) |
| <i>c</i> , Å | 21.884(6) |
| α, ° | 90 |
| β, ° | 90 |
| γ, ° | 90 |
| <i>V</i> , Å ³ | 703.6(3) |
| Number of reflections to determine final unit cell | 5015 |
| Min and Max 2θ for cell determination, ° | 7.2, 56.28 |
| <i>Z</i> | 4 |
| F(000) | 344 |
| ρ (<i>g/cm</i>) | 1.568 |
| λ, Å, (MoKα) | 0.71073 |
| μ, (<i>cm</i> ⁻¹) | 0.126 |
| Diffractometer Type | Bruker Kappa Axis Apex2 |
| Scan Type(s) | phi and omega scans |
| Max 2θ for data collection, ° | 61.106 |
| Measured fraction of data | 0.999 |
| Number of reflections measured | 24066 |
| Unique reflections measured | 2150 |
| R _{merge} | 0.0529 |
| Number of reflections included in refinement | 2150 |
| Cut off Threshold Expression | I > 2sigma(I) |
| Structure refined using | full matrix least-squares using F ² |
| Weighting Scheme | w=1/[sigma ² (Fo ²)+(0.0469P) ² +0.0327P] where P=(Fo ² +2Fc ²)/3 |

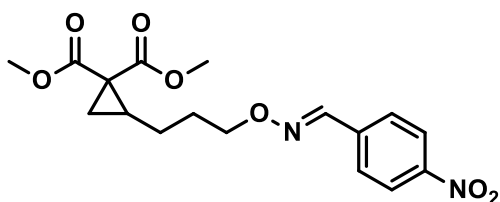
| | |
|--|---------------|
| Number of parameters in least-squares | 133 |
| R ₁ | 0.0348 |
| wR ₂ | 0.0796 |
| R ₁ (all data) | 0.0472 |
| wR ₂ (all data) | 0.0839 |
| GOF | 1.048 |
| Maximum shift/error | 0.000 |
| Min & Max peak heights on final ΔF Map (e ⁻ /Å) | -0.254, 0.201 |

Where:

$$R_1 = \sum (|F_o| - |F_c|) / \sum F_o$$

$$wR_2 = [\sum (w(F_o^2 - F_c^2))^2 / \sum (w F_o^4)]^{1/2}$$

$$GOF = [\sum (w(F_o^2 - F_c^2))^2 / (\text{No. of reflns.} - \text{No. of params.})]^{1/2}$$



Experimental for C₁₇H₂₀N₂O₇ (b19163)

X-ray quality crystal was grown by vapour diffusion of pentane into a saturated solution of compound **5-10c** in benzene.

Data Collection and Processing. The sample (b19163) was submitted by Lauren Irwin of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. It was apparent from the initial indexing that the sample crystals were non-merohedrally twinned (*vide infra*). The twin ratio was approximately 85:15 for the major

and minor twin components respectively. The unit cell dimensions were determined from a symmetry constrained fit of 8787 reflections with $4.76^\circ < 2\theta < 50.5^\circ$. The data collection strategy was a number of ω and ϕ scans which collected data up to 50.744° (2θ). The frame integration was performed using SAINT. The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program. All non-hydrogen atoms were obtained from the initial solution. The hydrogen atoms were introduced at idealized positions and were allowed to ride on the parent atom. The refinement converged with the R1 value unsatisfactorily high. Incorporating the data from the twin domain did neither alleviate the high R1 factor nor did it ameliorate the other symptoms of twinning (i.e. $F_o^2 \gg F_c^2$ for the worst fitting reflections and a high K value for the weakest data). After considerable investigation (see *Analysis of Twinning* below), it was determined that the best fitting model disregard the data from the twin altogether and refine the structure against on the data from the predominant domain. The structural model was fit to the data using full matrix least-squares based on F^2 . The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software. Graphic plots were produced using the Mercury program. Additional information and other relevant literature references can be found in the reference section of this website (<http://xray.chem.uwo.ca>).

Analysis of Twinning. Two individual domains were successfully indexed. There were other reflections which suggested additional domains but could not be sensibly indexed. The twin law for the two-domain twinning model is given below:

Twin Law, Sample 1 of 1

Transforms h1.1(1) ->h1.2(2)

```

0.62291 -1.61323 -0.00071
-0.37934 -0.62293 -0.00026
-0.05119 0.06100 -0.99998

```

As noted above, despite including the data from the second domain caused the R1 factor to worsen rather than improve. In addition, there were still indications of twinning. Therefore, a combination of two different types of twinning were considered, a so called “twin of twins”. The “twin of twins” model entailed lowering the symmetry of the structure from C 2/c to P 1 and assuming twinning by pseudo-merohedry in addition to the non-merohedral twinning. The appropriate twin law for the pseudo-merohedral was derived by the COSET program as a 180° rotation about the [210] which is expressed by the following twin law:

```

1.00 0.00 0.00
-1.00 -1.00 0.00
0.00 0.00 -1.00

```

While the R1 factor improved and the symptoms of twinning were ameliorated, this model lead to physically impossible anisotropic displacement parameters (ADPs). In addition, running the triclinic structure through the PLATON missing symmetry routines indicated that the structure was indeed C centred monoclinic. For these reasons, the triclinic structural model was discounted.

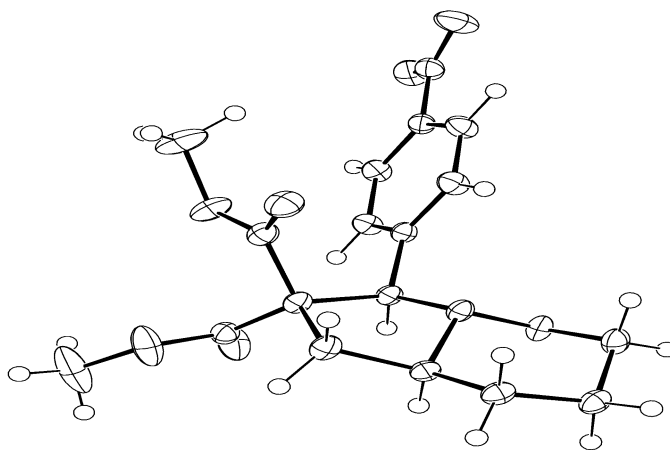


Figure 27 - ORTEP drawing of *b19163* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

Table 21 - Summary of Crystal Data for *b19163*

| | |
|----------------------------------|-----------------------------------|
| Formula | $C_{17}H_{20}N_2O_7$ |
| Formula Weight (<i>g/mol</i>) | 364.35 |
| Crystal Dimensions (<i>mm</i>) | $0.398 \times 0.384 \times 0.195$ |
| Crystal Color and Habit | colourless prism |
| Crystal System | monoclinic |
| Space Group | $C 2/c$ |
| Temperature, K | 110 |
| <i>a</i> , Å | 14.533(2) |
| <i>b</i> , Å | 7.0474(11) |
| <i>c</i> , Å | 34.203(7) |
| □, ° | 90 |
| □, ° | 90.766(7) |
| □, ° | 90 |

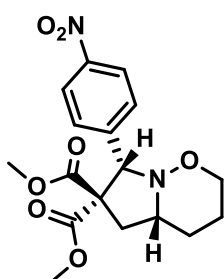
| | |
|--|---|
| V, Å ³ | 3502.8(11) |
| Number of reflections to determine final unit cell | 8787 |
| Min and Max 2θ for cell determination, ° | 4.76, 50.5 |
| Z | 8 |
| F(000) | 1536 |
| ρ (g/cm ³) | 1.382 |
| λ, Å, (MoKα) | 0.71073 |
| μ, (cm ⁻¹) | 0.108 |
| Diffractometer Type | Bruker Kappa Axis Apex2 |
| Scan Type(s) | phi and omega scans |
| Max 2θ for data collection, ° | 50.744 |
| Measured fraction of data | 0.944 |
| Number of reflections measured | 3052 |
| Unique reflections measured | 3052 |
| R _{merge} | 0.0800 |
| Number of reflections included in refinement | 3052 |
| Cut off Threshold Expression | I > 2sigma(I) |
| Structure refined using | full matrix least-squares using F ² |
| Weighting Scheme | w=1/[sigma ² (Fo ²)+(0.0430P) ² +44.7 018P] where P=(Fo ² +2Fc ²)/3 |
| Number of parameters in least-squares | 237 |
| R ₁ | 0.1020 |
| wR ₂ | 0.2263 |
| R ₁ (all data) | 0.1159 |
| wR ₂ (all data) | 0.2322 |
| GOF | 1.179 |
| Maximum shift/error | 0.000 |
| Min & Max peak heights on final ρF Map (e ⁻ /Å) | -0.367, 0.896 |

Where:

$$R_1 = \sum (|F_o| - |F_c|) / \sum F_o$$

$$wR_2 = [\sum (w(F_o^2 - F_c^2)^2) / \sum (w F_o^4)]^{1/2}$$

$$\text{GOF} = [\sum (w(F_o^2 - F_c^2)^2) / (\text{No. of reflns.} - \text{No. of params.})]^{1/2}$$



Experimental for C₁₇H₂₀N₂O₇ (b19193)

X-ray quality crystal was grown by vapour diffusion of pentane into a saturated solution of compound **5-11c-cis** in benzene.

Data Collection and Processing. The sample (b19193) was submitted by Lauren Irwin of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. It was apparent from the initial indexing that the crystal was non-merohedrally twinned. The diffraction pattern was indexed to two different unit cells and the an approximate twin law was derived. The unit cell dimensions were determined from a symmetry constrained fit of 9820 reflections with $4.66^\circ < 2\theta < 65.04^\circ$. The data collection strategy was a number of ω and ϕ scans which collected data up to 65.248° (2θ). The frame integration was performed using SAINT. The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using TWINABS.

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program. All non-hydrogen atoms were obtained from the initial solution. The asymmetric unit contains two symmetry independent molecules which were designated by the suffixes **A** and **B** in naming and numbering scheme. The hydrogen atoms were introduced at idealized positions and were allowed to refine isotropically.

Analysis of Twinning. The data were integrated as two component twin where the two

individuals were related by an approximate 180° rotation about the [100]. An analysis of the twinning is given below:

=====
 =====
 Solution number : 1

New Cell: a=10.6658 b=10.8239 c=17.2378 alpha=99.296 beta=92.069 gamma=115.950

Figure of Merit (0=ideal) : 0.03

Rotation angle (degrees) :-179.996

Rotation vector (laboratory) : 0.9047 -0.3437 0.2518

Rotation vector (reciprocal cell) : -2.00 1.00 0.00

Rotation vector (direct cell) : -1.00 0.06 -0.02

Superposition matrix : $H' = +0.939 * H -0.122 * K +0.030 * L$

$K' = -0.969 * H -0.939 * K -0.015 * L$

$L' = -0.002 * H -1.000 * L$

=====
 =====
 During the structure refinement the twin fraction of the minor component refined to a value of 0.2179(4).

The structural model was fit to the data using full matrix least-squares based on F^2 . The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software. Graphic plots were produced using the NRCVAX program suite. Additional information and other relevant literature references can be found in the reference section of this website (<http://xray.chem.uwo.ca>).

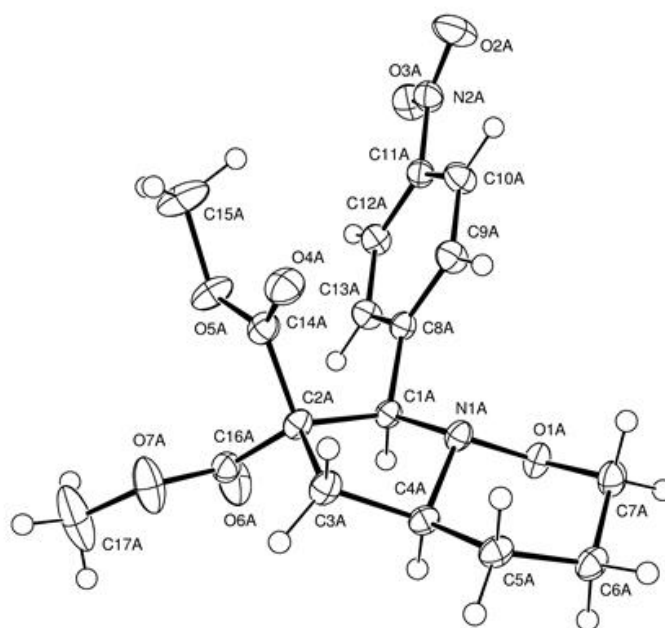


Figure 28 - ORTEP drawing of *b19193* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

Table 22 - Summary of Crystal Data for *b19193*

| | |
|--|---|
| Formula | C ₁₇ H ₂₀ N ₂ O ₇ |
| Formula Weight (<i>g/mol</i>) | 364.35 |
| Crystal Dimensions (<i>mm</i>) | 0.468 × 0.251 × 0.134 |
| Crystal Color and Habit | colourless prism |
| Crystal System | triclinic |
| Space Group | P -1 |
| Temperature, K | 110 |
| <i>a</i> , Å | 10.6658(14) |
| <i>b</i> , Å | 10.8239(18) |
| <i>c</i> , Å | 17.238(3) |
| α, ° | 99.296(4) |
| β, ° | 92.069(6) |
| γ, ° | 115.950(7) |
| <i>V</i> , Å ³ | 1753.0(5) |
| Number of reflections to determine final unit cell | 9820 |
| Min and Max 2θ for cell determination, ° | 4.66, 65.04 |
| <i>Z</i> | 4 |
| F(000) | 768 |
| ρ (<i>g/cm</i>) | 1.380 |
| λ, Å, (MoKα) | 0.71073 |
| μ, (<i>cm</i> ⁻¹) | 0.108 |
| Diffractometer Type | Bruker Kappa Axis Apex2 |
| Scan Type(s) | phi and omega scans |
| Max 2θ for data collection, ° | 65.248 |
| Measured fraction of data | 0.999 |
| Number of reflections measured | 41111 |
| Unique reflections measured | 41111 |
| R _{merge} | ? |
| Number of reflections included in refinement | 41111 |
| Cut off Threshold Expression | I > 2sigma(I) |
| Structure refined using | full matrix least-squares using F ² |

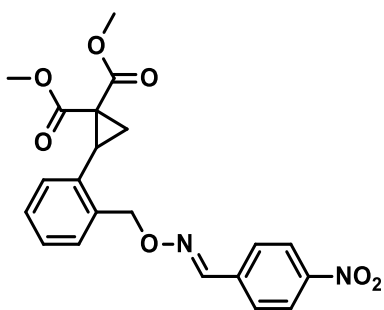
| | |
|---|--|
| Weighting Scheme | $w=1/[\sigma^2(F_o^2)+(0.0615P)^2+0.1547P]$ where $P=(F_o^2+2F_c^2)/3$ |
| Number of parameters in least-squares | 630 |
| R ₁ | 0.0439 |
| wR ₂ | 0.1115 |
| R ₁ (all data) | 0.0620 |
| wR ₂ (all data) | 0.1223 |
| GOF | 1.037 |
| Maximum shift/error | 0.001 |
| Min & Max peak heights on final ΔF Map ($e^-/\text{\AA}$) | -0.286, 0.425 |

Where:

$$R_1 = \sum (|F_o| - |F_c|) / \sum F_o$$

$$wR_2 = [\sum w (F_o^2 - F_c^2)^2 / \sum w F_o^4]^{1/2}$$

$$GOF = [\sum w (F_o^2 - F_c^2)^2 / (\text{No. of reflns.} - \text{No. of params.})]^{1/2}$$



Experimental for C₂₁H₂₀N₂O₇ (b19192)

X-ray quality crystal was grown by slow vapour diffusion of pentane into a saturated solution of compound **5-10m** in benzene.

Data Collection and Processing. The sample (b19192) was submitted by Lauren Irwin of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of

6805 reflections with $4.9^\circ < 2\theta < 50.28^\circ$. The data collection strategy was a number of ω and ϕ scans which collected data up to 50.462° (2θ). The frame integration was performed using SAINT. The resulting raw data was scaled, and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program. All non-hydrogen atoms were obtained from the initial solution. The hydrogen atoms were introduced at idealized positions and were allowed to refine isotropically. The structural model was fit to the data using full matrix least-squares based on F^2 . The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software. Graphic plots were produced using the NRCVAX program suite. Additional information and other relevant literature references can be found in the reference section of this website (<http://xray.chem.uwo.ca>).

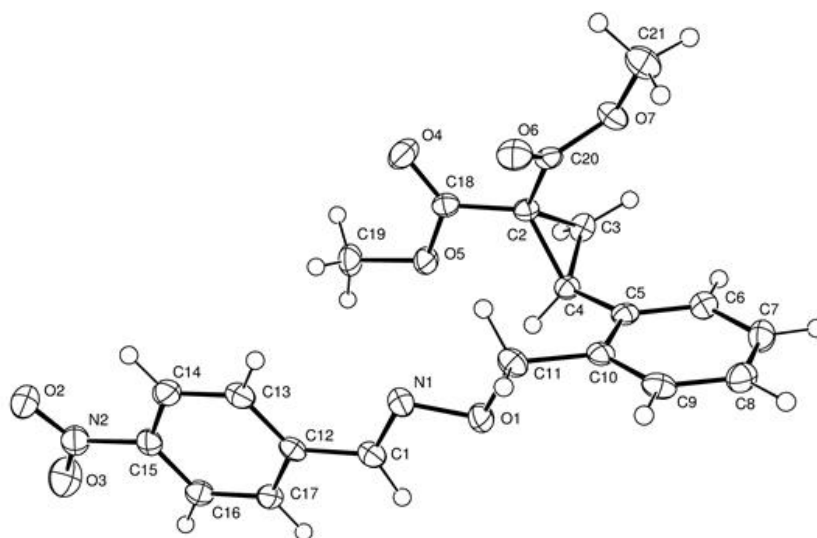


Figure 29 - ORTEP drawing of *b19192* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

Table 23 - Summary of Crystal Data for *b19192*

| | |
|--------------------------|-----------------------------------|
| Formula | $C_{21}H_{20}N_2O_7$ |
| Formula Weight (g/mol) | 412.39 |
| Crystal Dimensions (mm) | $0.127 \times 0.096 \times 0.052$ |
| Crystal Color and Habit | colourless rectangular |
| Crystal System | monoclinic |
| Space Group | $P 2_1/c$ |
| Temperature, K | 110 |
| a , Å | 17.717(12) |
| b , Å | 8.628(6) |
| c , Å | 13.831(8) |
| α , ° | 90 |

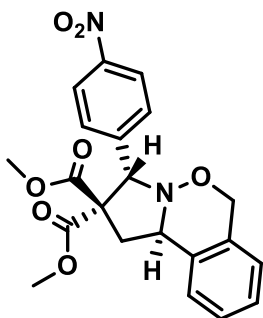
| | |
|---|---|
| $\beta, ^\circ$ | 110.043(11) |
| $\gamma, ^\circ$ | 90 |
| $V, \text{\AA}^3$ | 1986(2) |
| Number of reflections to determine final unit cell | 6805 |
| Min and Max 2θ for cell determination, $^\circ$ | 4.9, 50.28 |
| Z | 4 |
| $F(000)$ | 864 |
| ρ (g/cm) | 1.379 |
| $\lambda, \text{\AA}, (\text{MoK}\alpha)$ | 0.71073 |
| $\mu, (\text{cm}^{-1})$ | 0.105 |
| Diffractometer Type | Bruker Kappa Axis Apex2 |
| Scan Type(s) | phi and omega scans |
| Max 2θ for data collection, $^\circ$ | 50.462 |
| Measured fraction of data | 0.999 |
| Number of reflections measured | 32877 |
| Unique reflections measured | 3596 |
| R_{merge} | 0.0808 |
| Number of reflections included in refinement | 3596 |
| Cut off Threshold Expression | $I > 2\text{sigma}(I)$ |
| Structure refined using | full matrix least-squares using F^2 |
| Weighting Scheme | $w=1/[\text{sigma}^2(\text{Fo}^2)+(0.0339\text{P})^2+0.7722\text{P}]$ where $\text{P}=(\text{Fo}^2+2\text{Fc}^2)/3$ |
| Number of parameters in least-squares | 351 |
| R_1 | 0.0392 |
| wR_2 | 0.0778 |
| R_1 (all data) | 0.0752 |
| wR_2 (all data) | 0.0919 |
| GOF | 1.011 |
| Maximum shift/error | 0.000 |
| Min & Max peak heights on final ΔF Map ($e/\text{\AA}$) | -0.220, 0.210 |

Where:

$$R_1 = \sum (|F_o| - |F_c|) / \sum F_o$$

$$wR_2 = [\sum (w(F_o^2 - F_c^2)^2) / \sum (w F_o^4)]^{1/2}$$

$$\text{GOF} = [\sum (w(F_o^2 - F_c^2)^2) / (\text{No. of reflns.} - \text{No. of params.})]^{1/2}$$



Experimental for C₂₁H₂₀N₂O₇ (b19156)

X-ray quality crystal grown by slow vapour diffusion of pentane into a saturated solution of **5-11e-trans** in benzene.

Data Collection and Processing. The sample (b19156) was submitted by Lauren Irwin of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 9959 reflections with $4.48^\circ < 2\theta < 59.98^\circ$. The data collection strategy was a number of θ and ω scans which collected data up to 62.396° (2θ). The frame integration was performed using SAINT. The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.

Structure Solution and Refinement. The structure was solved by using a dual space methodology using the SHELXT program. All non-hydrogen atoms were obtained from the initial solution. The hydrogen atoms were introduced at idealized positions and were allowed to refine isotropically. The structural model was fit to the data using full matrix least-squares based on F^2 . The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software. Graphic plots were produced using the NRCVAX program suite. Additional information and other relevant literature references can be found in the reference section of this website (<http://xray.chem.uwo.ca>).

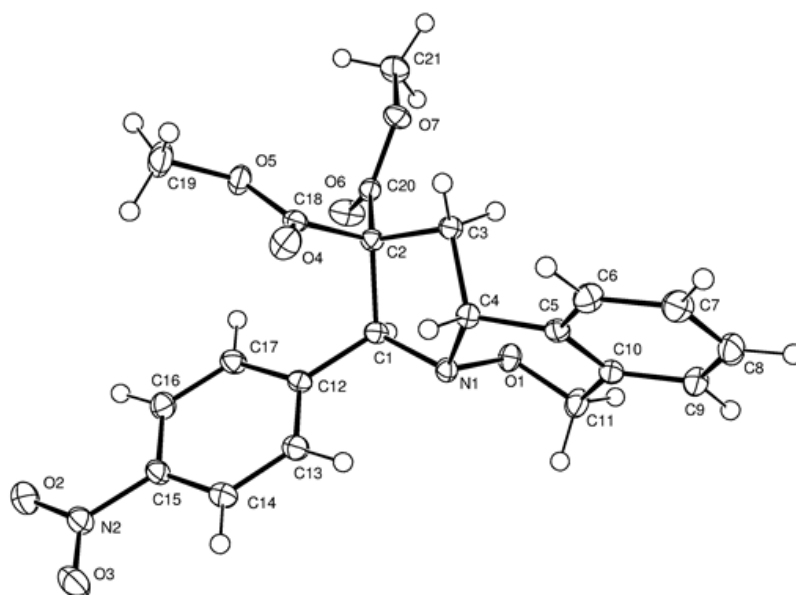


Figure 30 - ORTEP drawing of *b19156* showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were drawn with arbitrary radii for clarity.

Table 24 - Summary of Crystal Data for *b19156*

| | |
|--------------------------|-----------------------------------|
| Formula | $C_{21}H_{20}N_2O_7$ |
| Formula Weight (g/mol) | 412.39 |
| Crystal Dimensions (mm) | $0.289 \times 0.271 \times 0.079$ |
| Crystal Color and Habit | colourless prism |
| Crystal System | monoclinic |
| Space Group | $P 2_1/c$ |
| Temperature, K | 110 |
| a , Å | 11.544(4) |
| b , Å | 18.172(7) |
| c , Å | 9.560(3) |
| α , ° | 90 |

| | |
|---|---|
| $\beta, ^\circ$ | 105.803(12) |
| $\gamma, ^\circ$ | 90 |
| $V, \text{\AA}^3$ | 1929.6(11) |
| Number of reflections to determine final unit cell | 9959 |
| Min and Max 2θ for cell determination, $^\circ$ | 4.48, 59.98 |
| Z | 4 |
| $F(000)$ | 864 |
| ρ (g/cm) | 1.420 |
| $\lambda, \text{\AA}, (\text{MoK}\alpha)$ | 0.71073 |
| $\mu, (\text{cm}^{-1})$ | 0.108 |
| Diffractometer Type | Bruker Kappa Axis Apex2 |
| Scan Type(s) | phi and omega scans |
| Max 2θ for data collection, $^\circ$ | 62.396 |
| Measured fraction of data | 0.999 |
| Number of reflections measured | 71853 |
| Unique reflections measured | 6182 |
| R_{merge} | 0.0657 |
| Number of reflections included in refinement | 6182 |
| Cut off Threshold Expression | $I > 2\text{sigma}(I)$ |
| Structure refined using | full matrix least-squares using F^2 |
| Weighting Scheme | $w=1/[\text{sigma}^2(\text{Fo}^2)+(0.0445\text{P})^2+0.5572\text{P}]$ where $\text{P}=(\text{Fo}^2+2\text{Fc}^2)/3$ |
| Number of parameters in least-squares | 351 |
| R_1 | 0.0422 |
| wR_2 | 0.0909 |
| R_1 (all data) | 0.0774 |
| wR_2 (all data) | 0.1056 |
| GOF | 1.014 |
| Maximum shift/error | 0.000 |
| Min & Max peak heights on final ΔF Map ($e/\text{\AA}$) | -0.280, 0.330 |

Where:

$$R_1 = \sum (|F_o| - |F_c|) / \sum F_o$$

$$wR_2 = [\sum (w(F_o^2 - F_c^2)^2) / \sum (w F_o^4)]^{1/2}$$

$$\text{GOF} = [\sum (F_o^2 - F_c^2)^2 / (\text{No. of reflns.} - \text{No. of params.})]^{1/2}$$

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Chapter 6

6.0 Summary, Conclusions and Future Directions of Projects Discussed

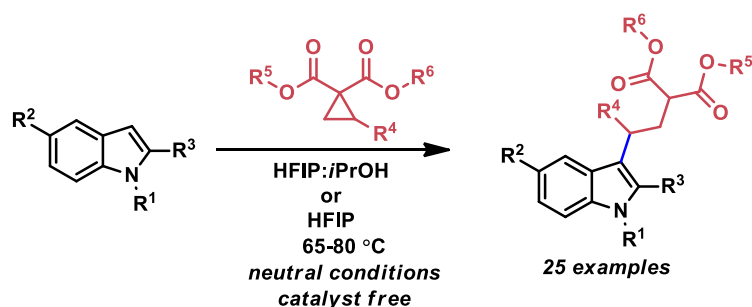
6.1 Future Directions

Future directions for the projects in this dissertation are discussed in detail at the end of their respective chapters. This was to ensure that the future directions followed the story the reader had just completed, and because many of these projects, while they share a common link of indoles and cyclopropanes, they could be taken to new projects on their own. It seemed in the best interest of comprehension to put future experimental planning before the experimental details of each chapter.

6.2 Chapter Summaries and Conclusions

The research disclosed in the antecedent sections aimed to expand chemical transformations of indole heterocycles. The research generated novel reactivity and further functionalized indoles to access value-added products while aiding the pursuit of the first total syntheses of tronocarpine and dippinine B. While the complete total syntheses were not realized, valuable chemistry was discovered, and road blocks were identified that future chemists can hopefully overcome.

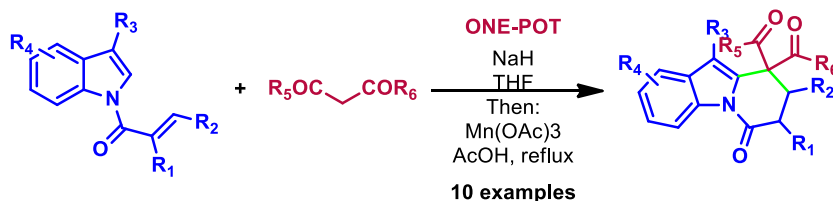
Chapter 2 disclosed the first use of hydrogen-bonding interactions as a metal-free alternative for the opening of donor-acceptor cyclopropanes. Opened using indole nucleophiles in a medium of HFIP, a variety of 3-position functionalized indole products were generated both from diester and hemi-malonate cyclopropanes (**Scheme 110**).



Scheme 110 - Graphical summary of the work in Chapter 2. Novel hydrogen-bond interaction activating DA-CPs.

This work is the first to demonstrate how donor-acceptor cyclopropanes can be opened with indole nucleophiles without the use of Lewis acids or under high-pressure reaction conditions. It expands on how indoles can be functionalized to value-added products because all substituent patterns tested worked, and both malonate and hemi-malonate cyclopropanes access the products under these neutral conditions. This work will pioneer access to other annulation and elaborated products without the need for dangerous high-pressure equipment and expensive Lewis acid catalysts.

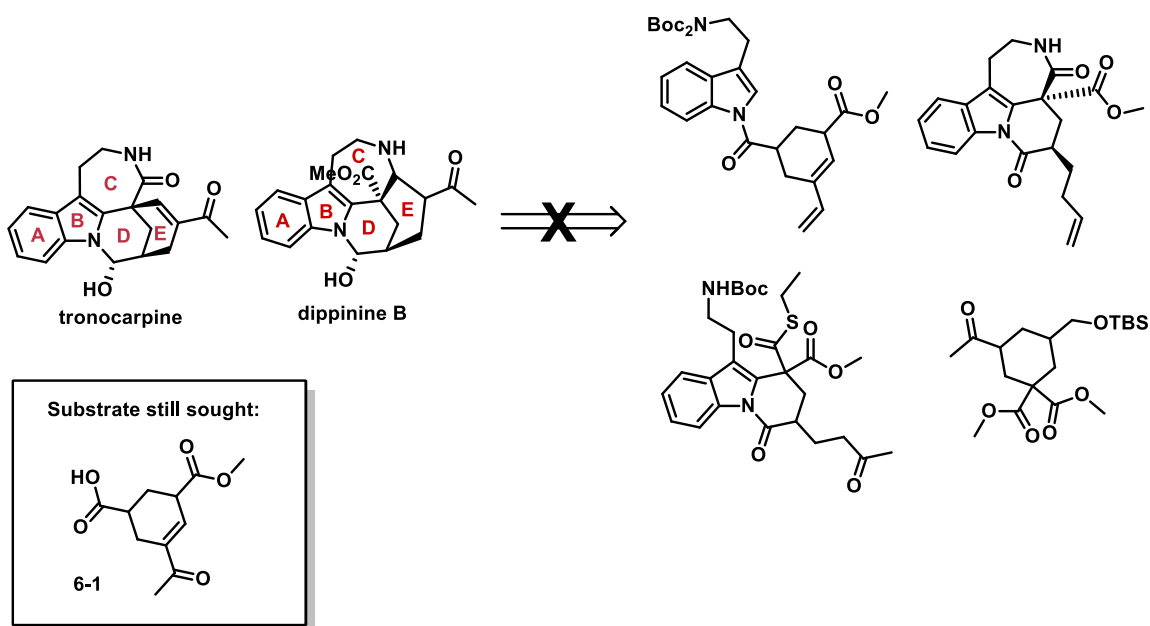
Chapter 3 reports a one-pot procedure for the generation of tricyclic indole containing molecules. The 1,2-substituted indole product map well to the scaffold and functional handles required to access natural products tronocarpine and dippinine B. Using a single electron oxidant, $\text{Mn}(\text{OAc})_3$ generates radicals of malonyl tethers resultant of a Michael addition with acryloyl indoles. 10 different products were generated in modest yields including a product which has all required carbons for the natural products sought (**Scheme 111**).



Scheme 111 - Graphical summary of the work in Chapter 3. One-pot Michael addition and cyclization of indoles.

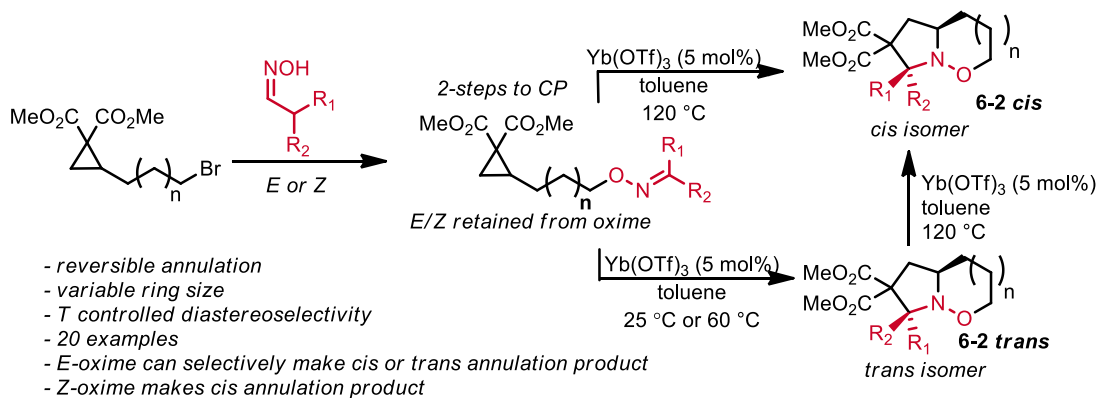
This procedure outlined is exceptional for creating highly substituted indole scaffolds which map onto many different natural products. These natural products are desirable for future pharmaceuticals and drug discovery purposes, and this methodology will easily generate unique products *en route* to developing syntheses to natural product targets. This work also gave me the opportunity to perfect a method of reproducibly acquiring $\text{Mn}(\text{OAc})_3$, a reagent that is known to have quality issues when purchased, even if from the same source. My procedure developed should be helpful to future chemists wanting to use $\text{Mn}(\text{OAc})_3$ as a SET agent in their own chemistry, and give them the highest yields possible.

Chapter 4 is tough to summarize concisely. The work reported outlines a variety of strategies towards the first syntheses of indole alkaloids tronocarpine and dippinine B. Major intermediates containing all the necessary atoms for the natural products were generated but were not successfully taken to the final products. The chemistry indicated the difficulty of employing either, a Dieckmann cyclization, or aldol ring-closing reaction to form ring E of both natural products (**Scheme 112**). Conclusions are drawn that a substrate resembling **6-1**, where the difficult ring E is synthesized as a separate component, could later join the tryptamine portion of the natural products. The work discovered many different road-blocks that provide valuable knowledge for how to overcome these unforeseen obstacles. The routes developed provide insight for how to change the chemistry in the future and avoid the ring-closing difficulties discovered. A new a successful route to synthesize dippinine B and tronocarpine can be built in future based on the difficulties discussed in Chapter 4.



Scheme 112 - Graphical representation of the work outlined in Chapter 4. Progress and major intermediates towards the synthesis of tronocarpine and dippinine B.

Chapter 5 summarizes the synthesis of novel oxime-ether containing DA CPs that rearrange in the presence of $\text{Yb}(\text{OTf})_3$ to access selectively, the *cis* or *trans* bicyclic hydropyrrollooxazine products (**6-2***cis/trans*). The diastereomer of the product obtained is controlled by the reaction temperature, with higher temperatures yielding the *cis* annulation product. The oxazines can be taken to their respective diastereo-retained pyrrolidines.

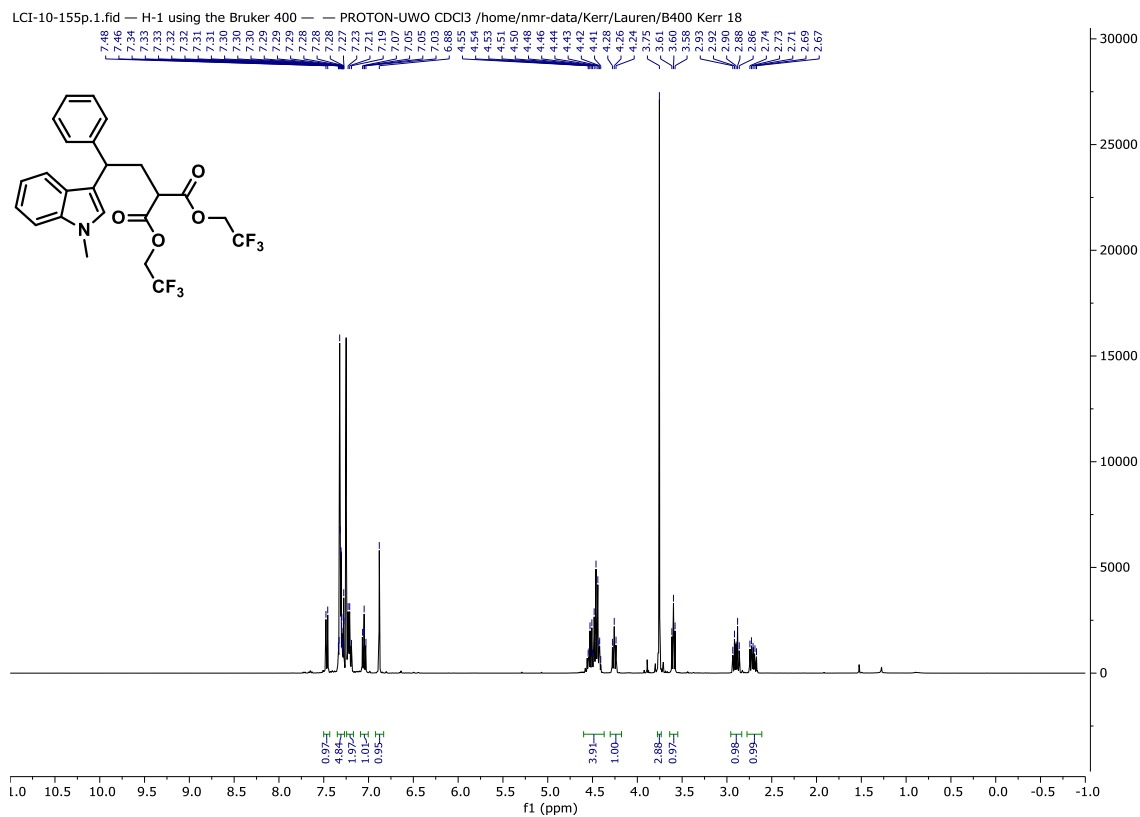


Scheme 113 - Graphical representation of the work completed in Chapter 5.

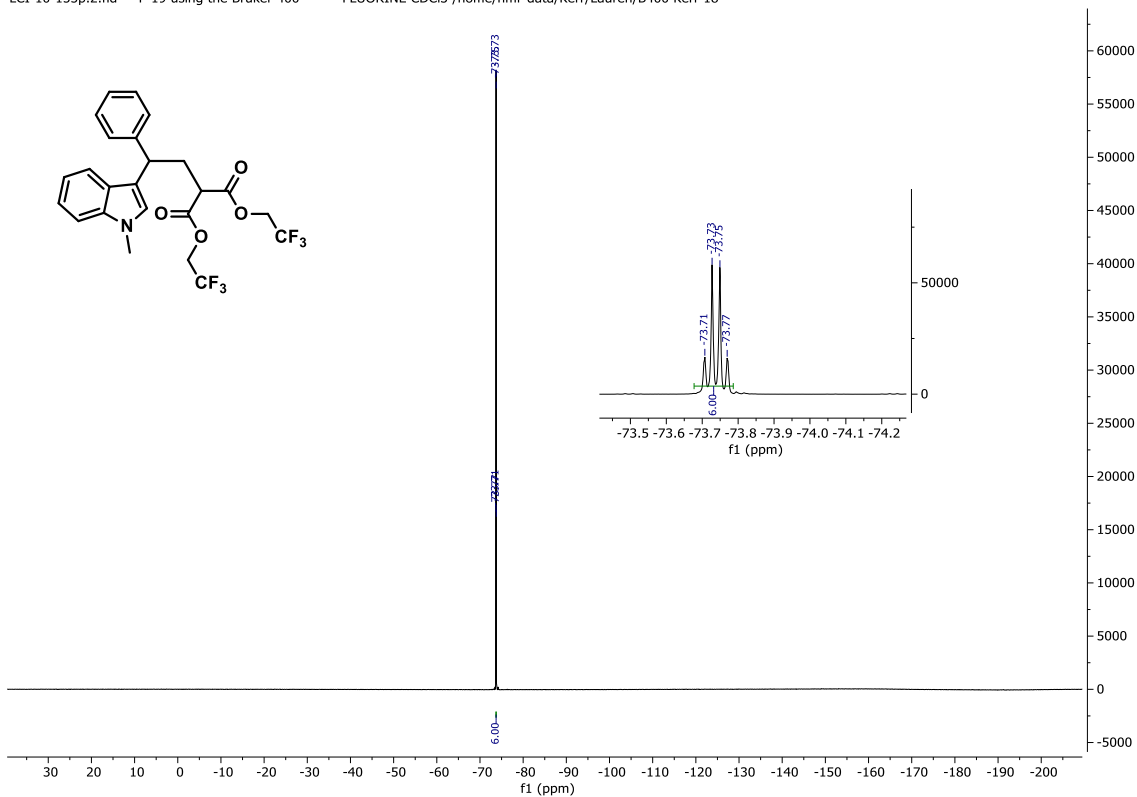
This work impressively accessed novel oxime-ether donor-acceptor cyclopropanes in only two steps. They were determined to generate tetrahydropyrrolo-oxazines in high yield and with diastereomeric control, making this an interesting and effective reaction. The operating chemist can use simple temperature changes in the reaction to access the correct diastereomers of the annulated products. These products can then be pushed forward to synthesize desirable pyrrolidine natural products or drug candidates. This work will be valuable in the future to try and synthesize natural products like preussin C. The research conducted and reported in this thesis outlines successful improvements and progress modifying indole heterocycles to access valuable products and doing so in novel ways.

Appendices – Spectral Data for Selected Compounds in Chapters 2-5

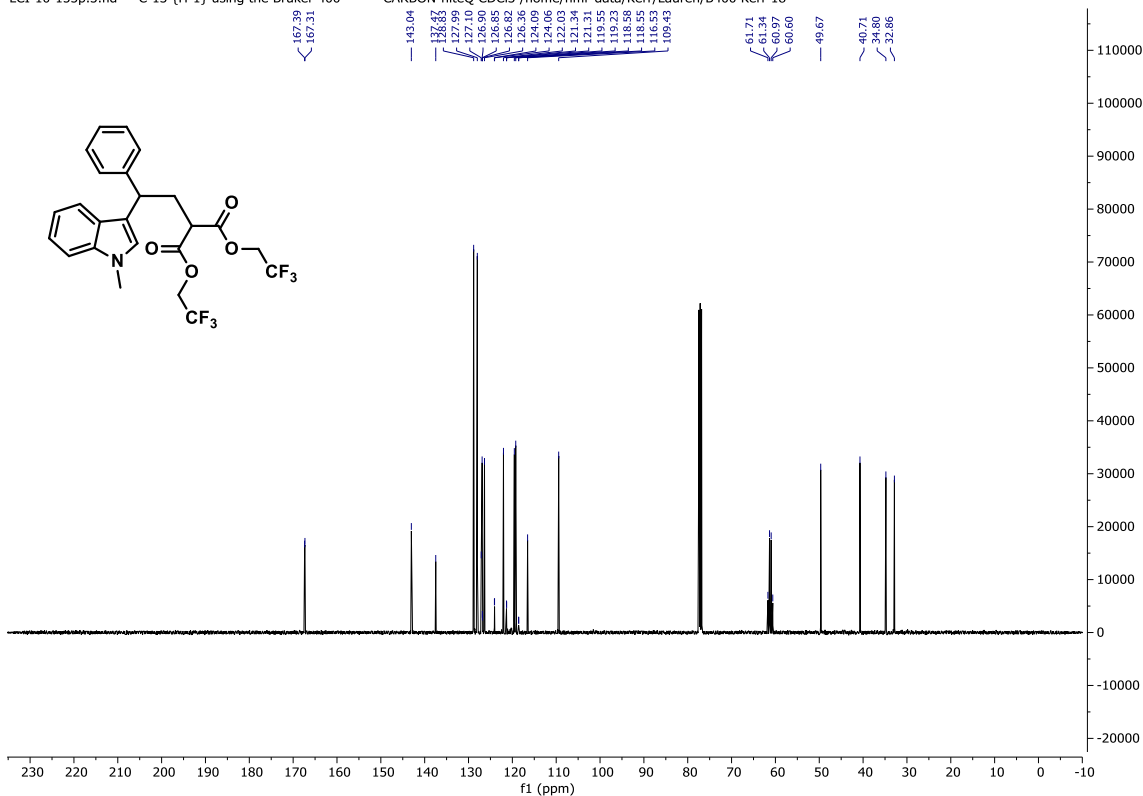
Chapter 2 ^1H , ^{19}F and ^{13}C NMR Spectra

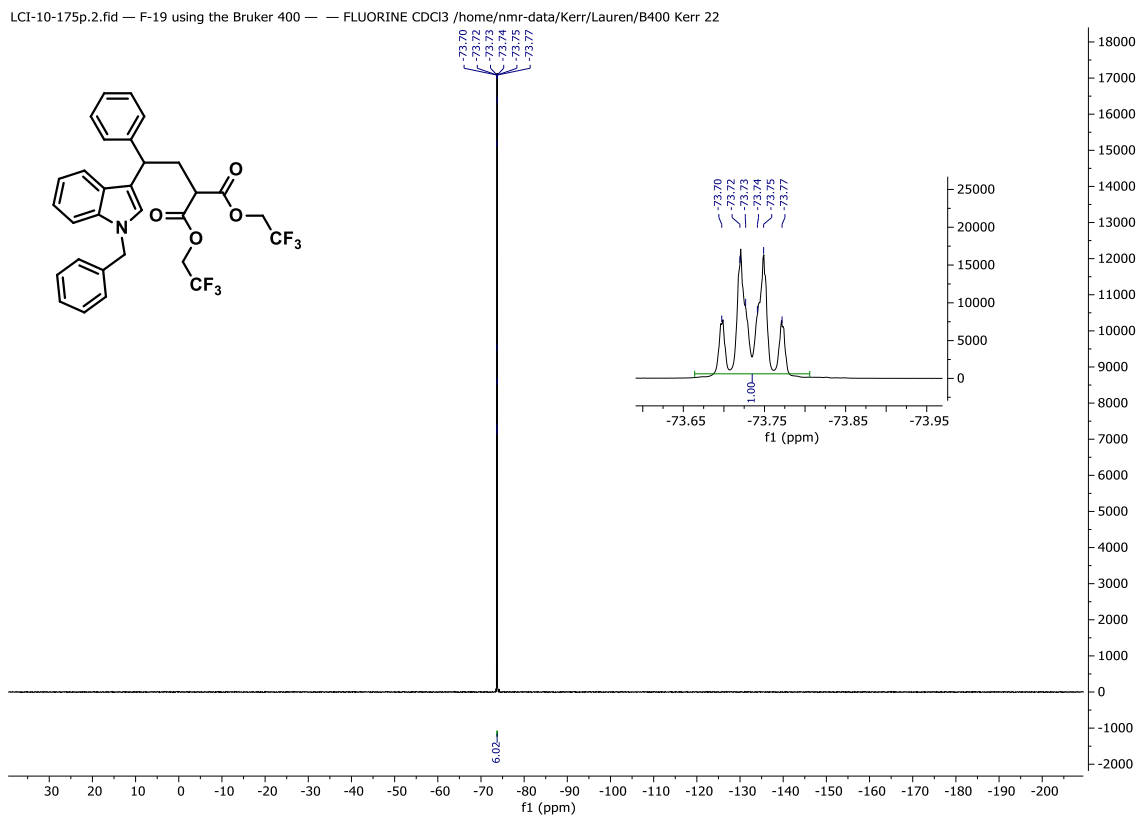
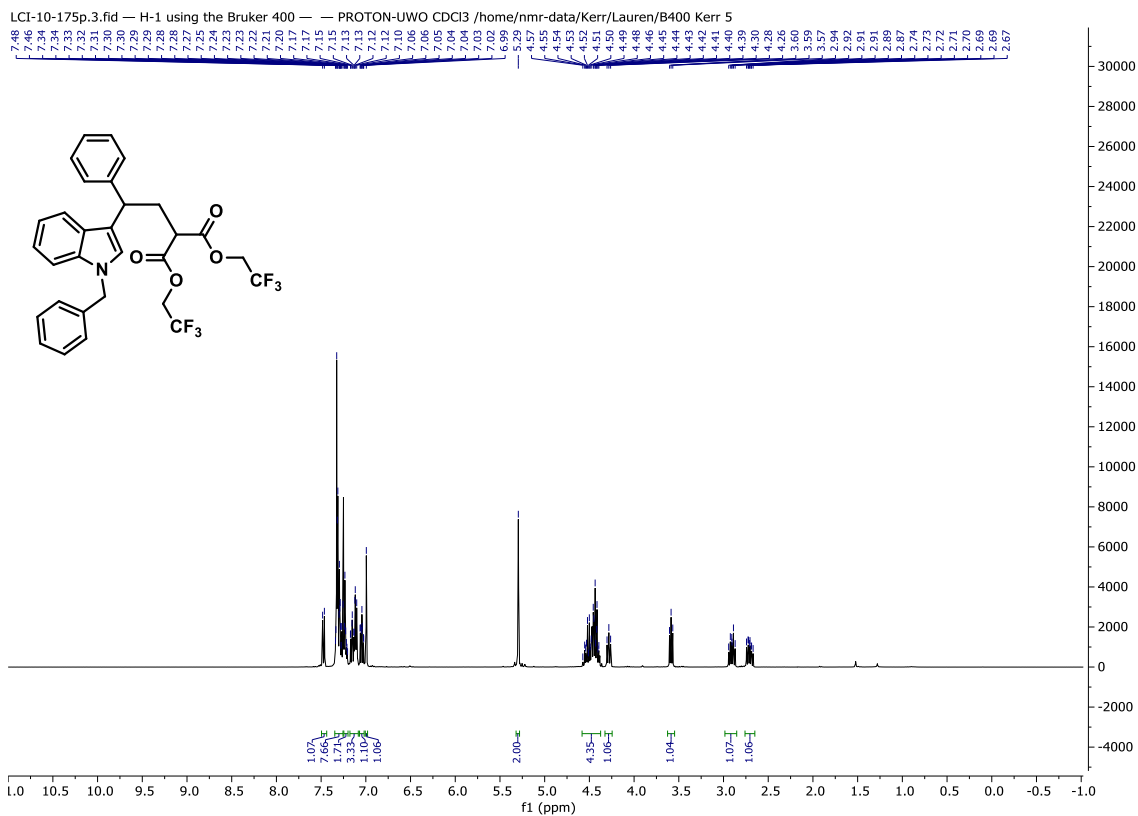


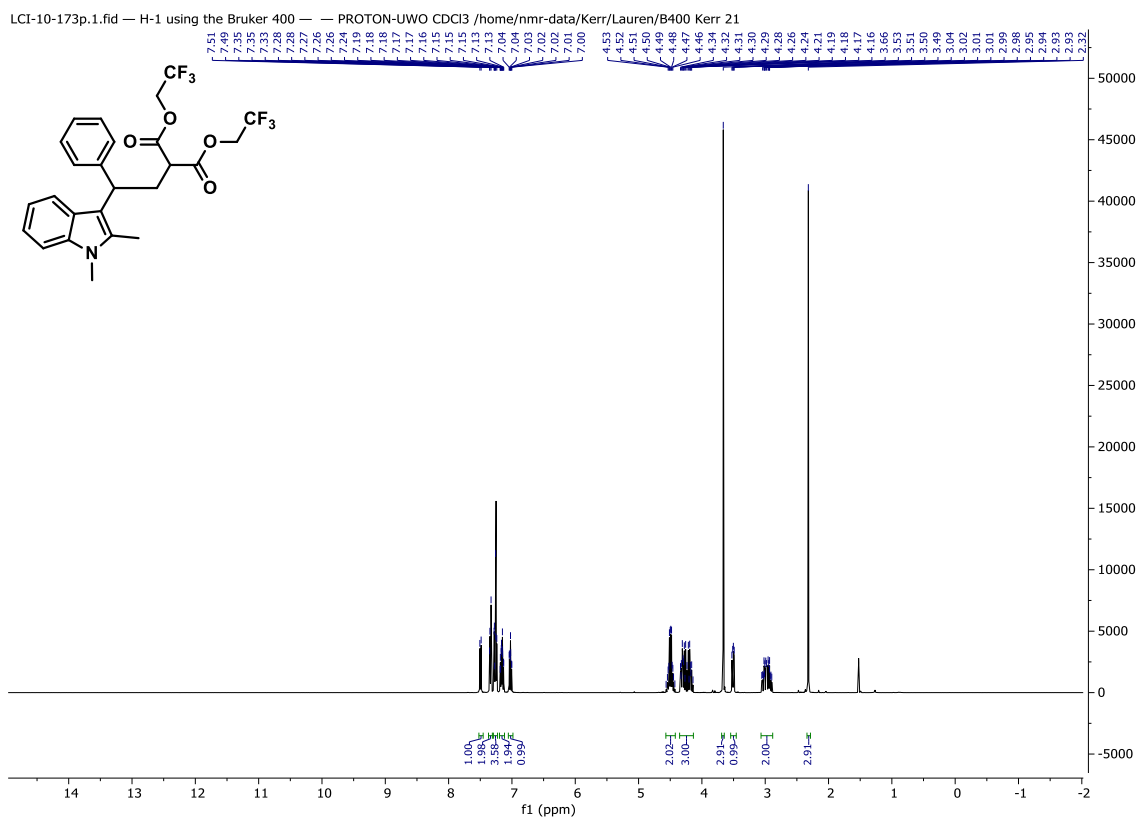
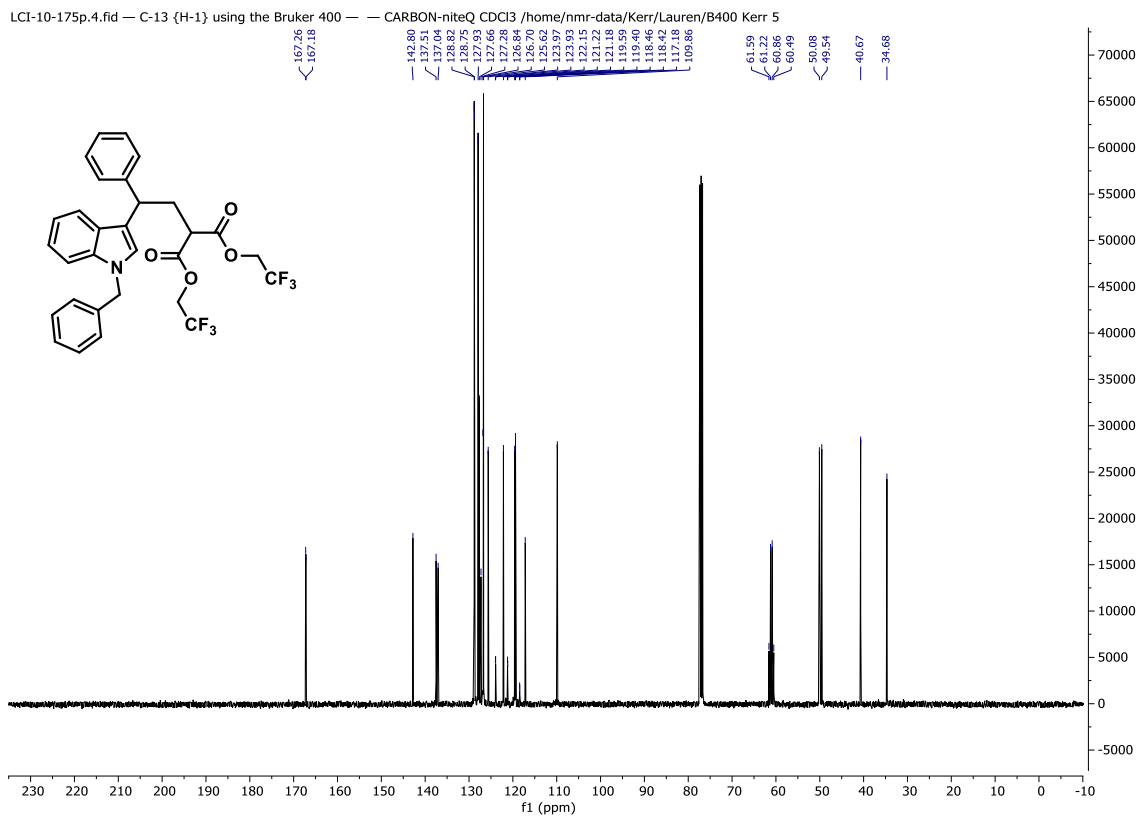
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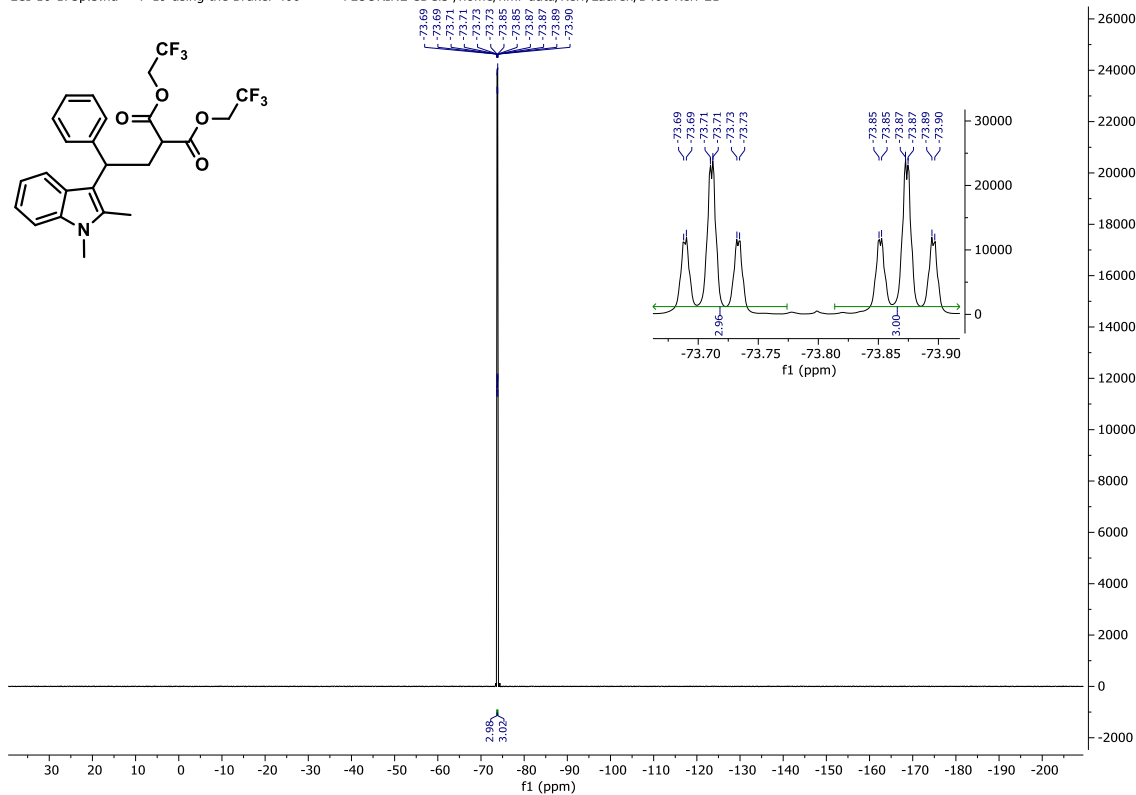
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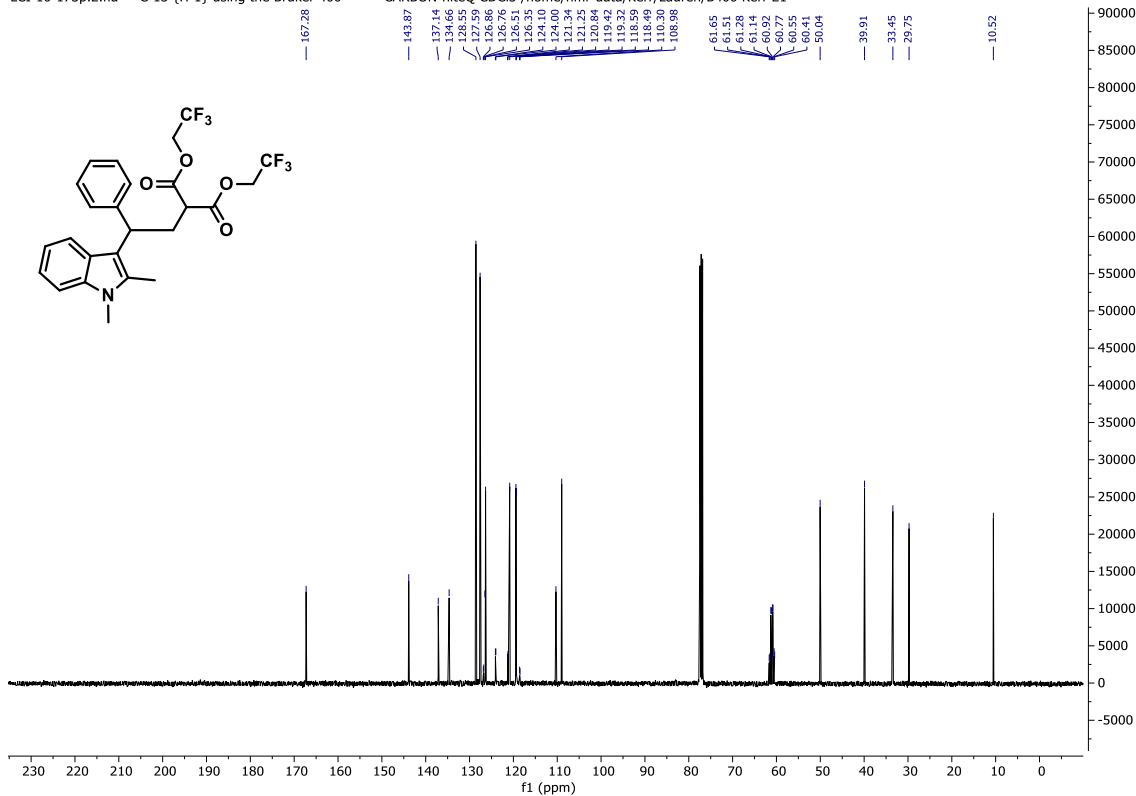




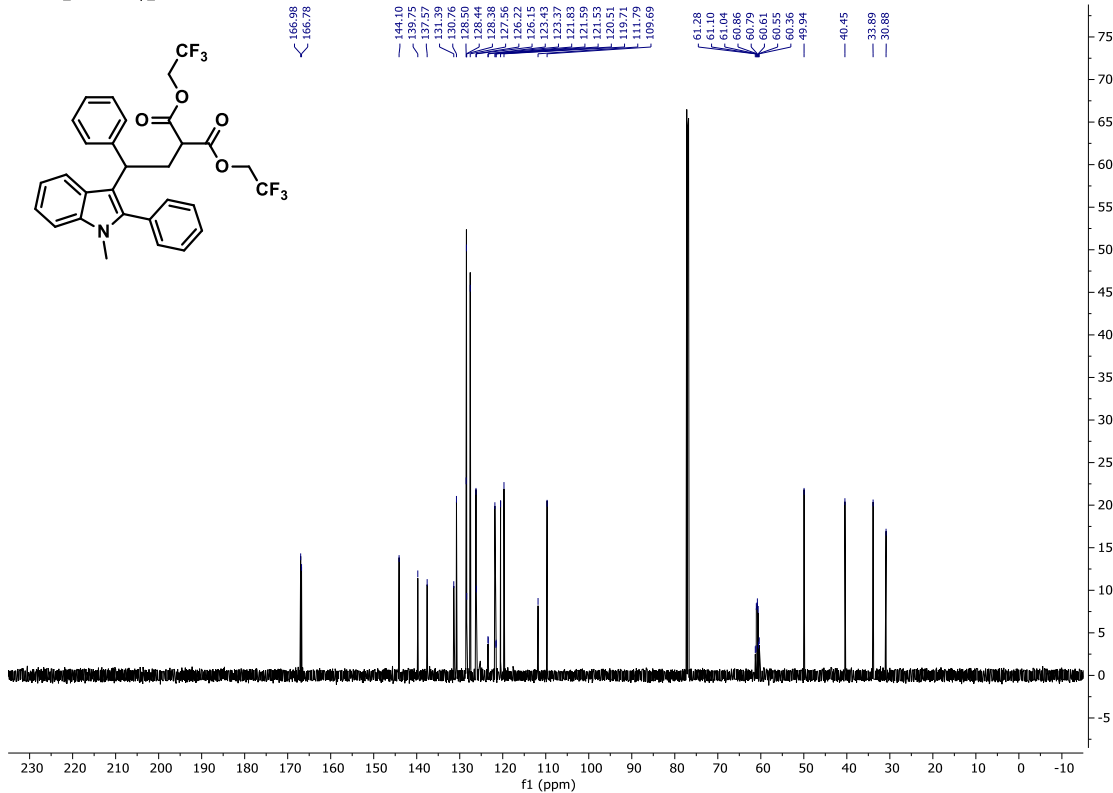
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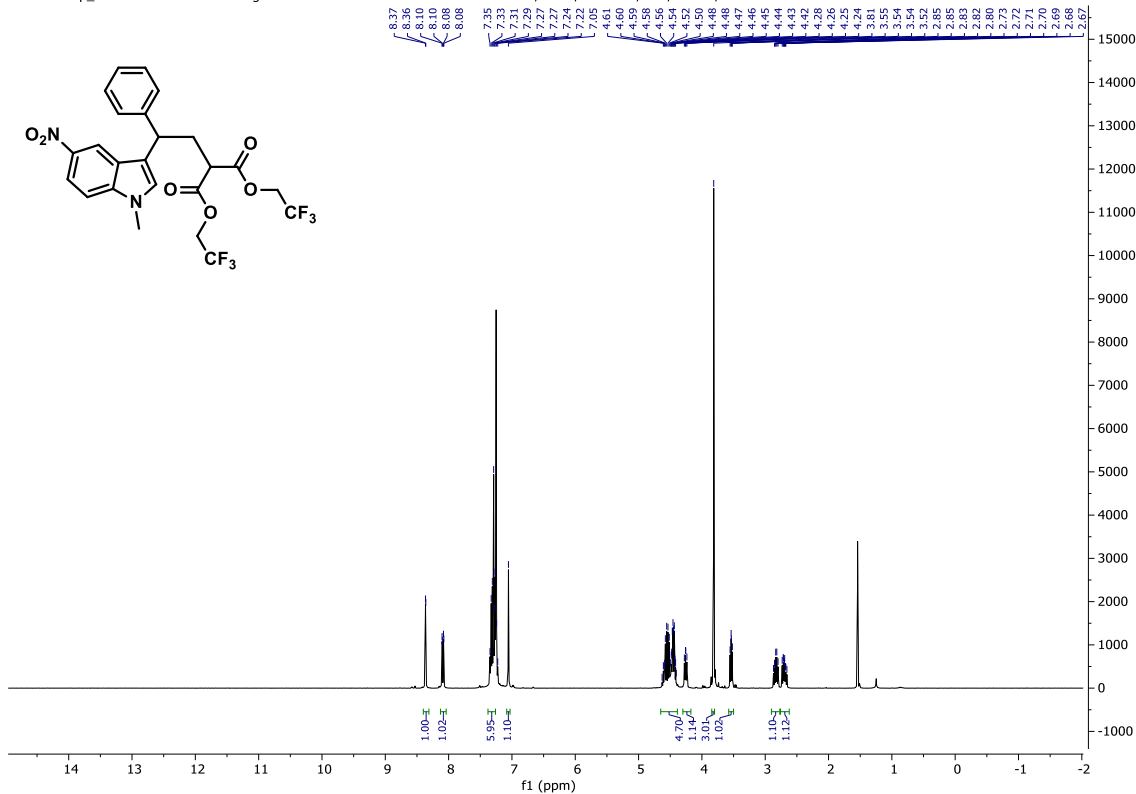
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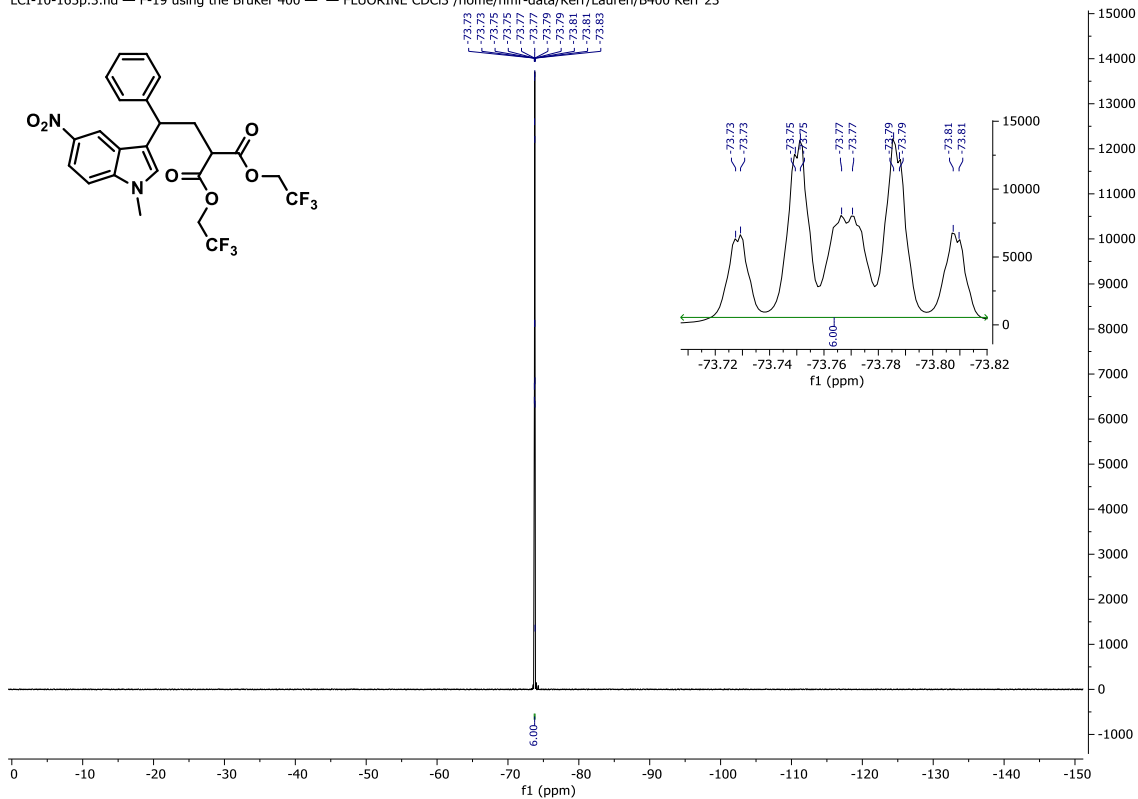
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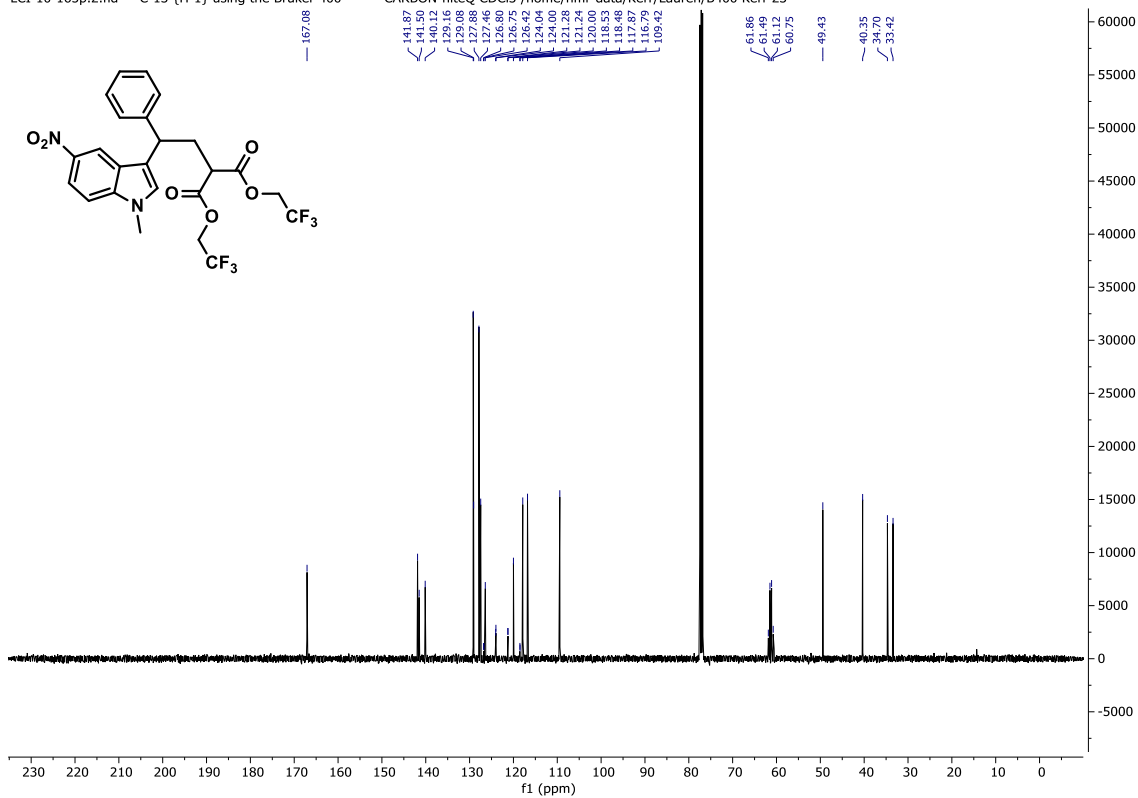
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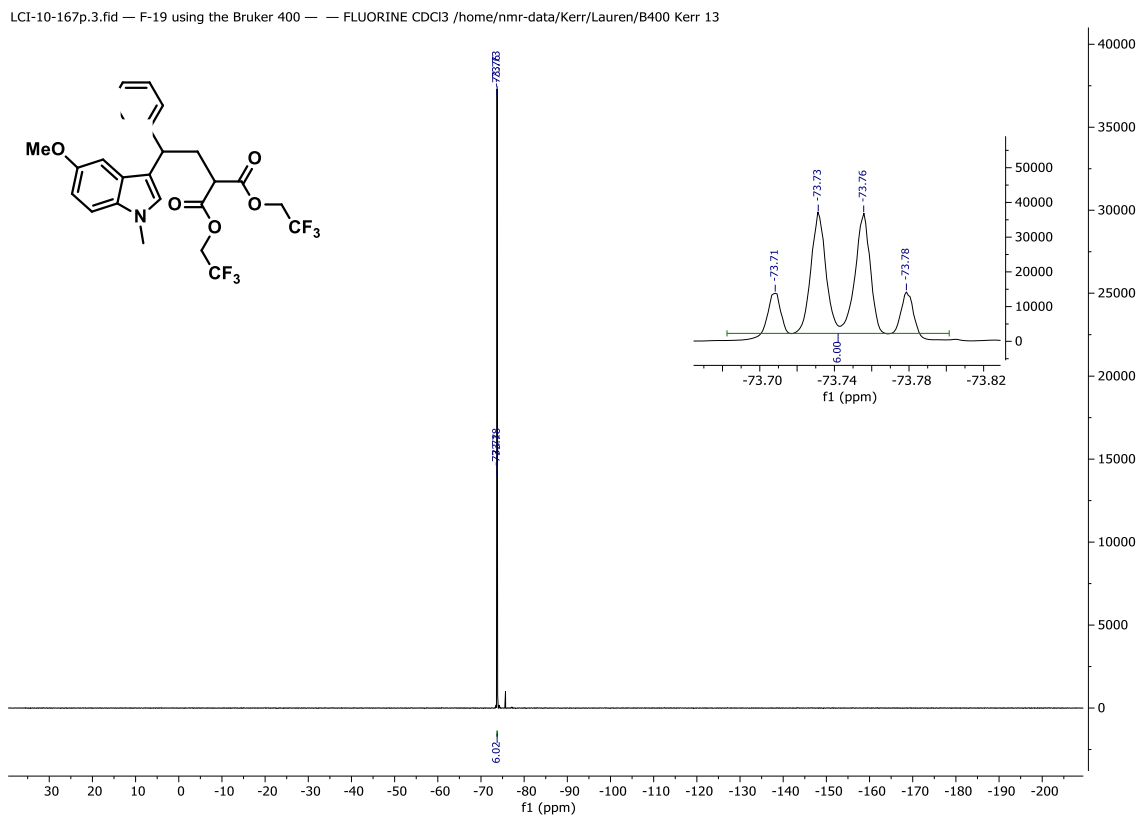
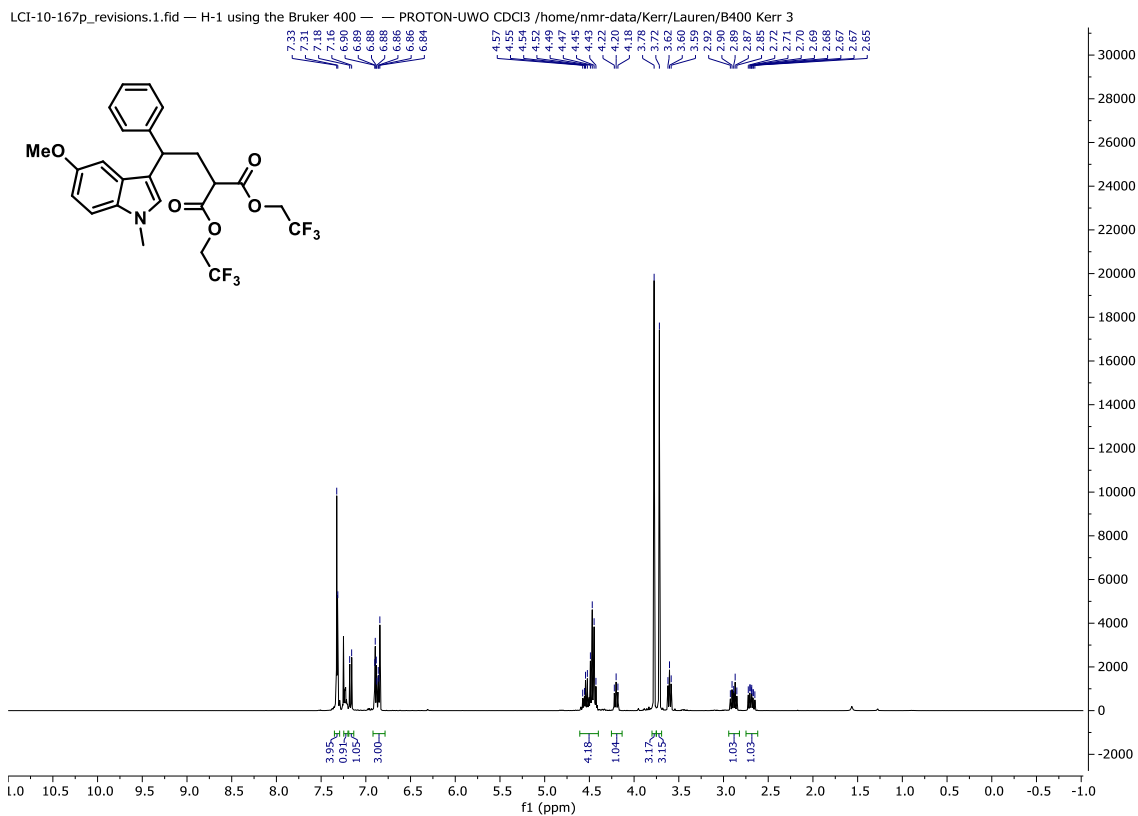


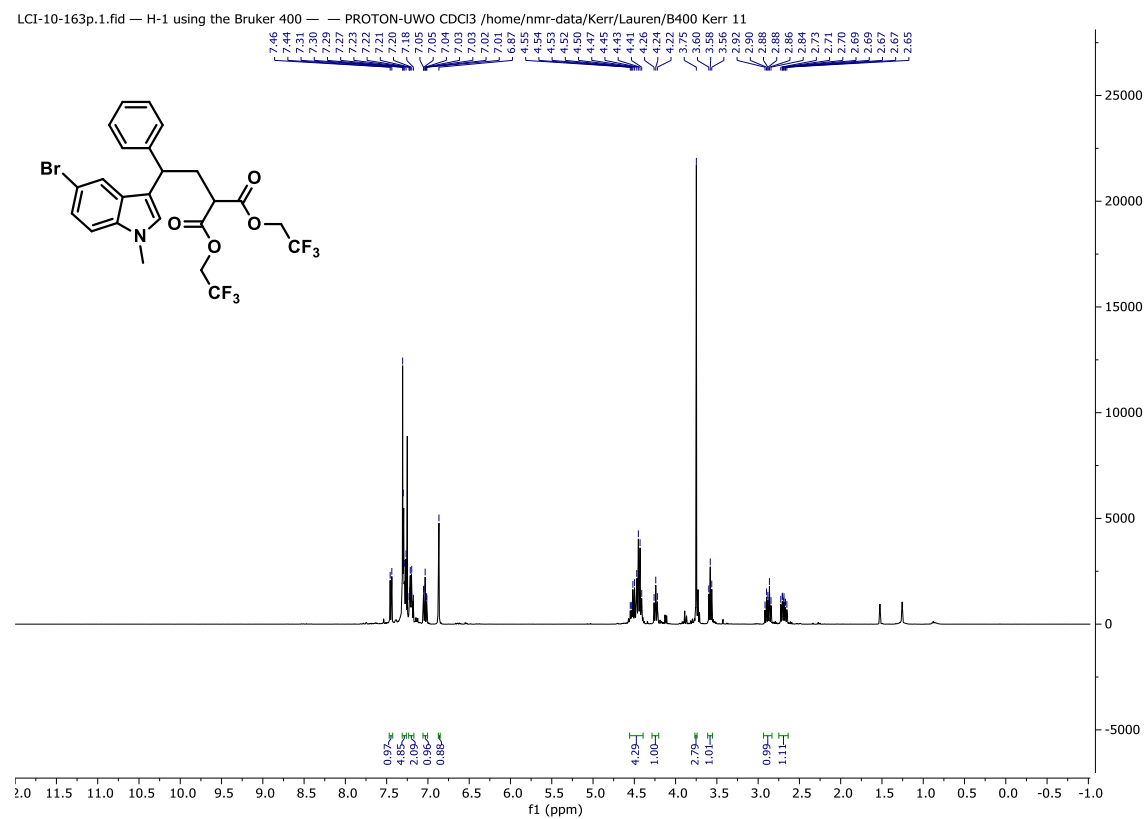
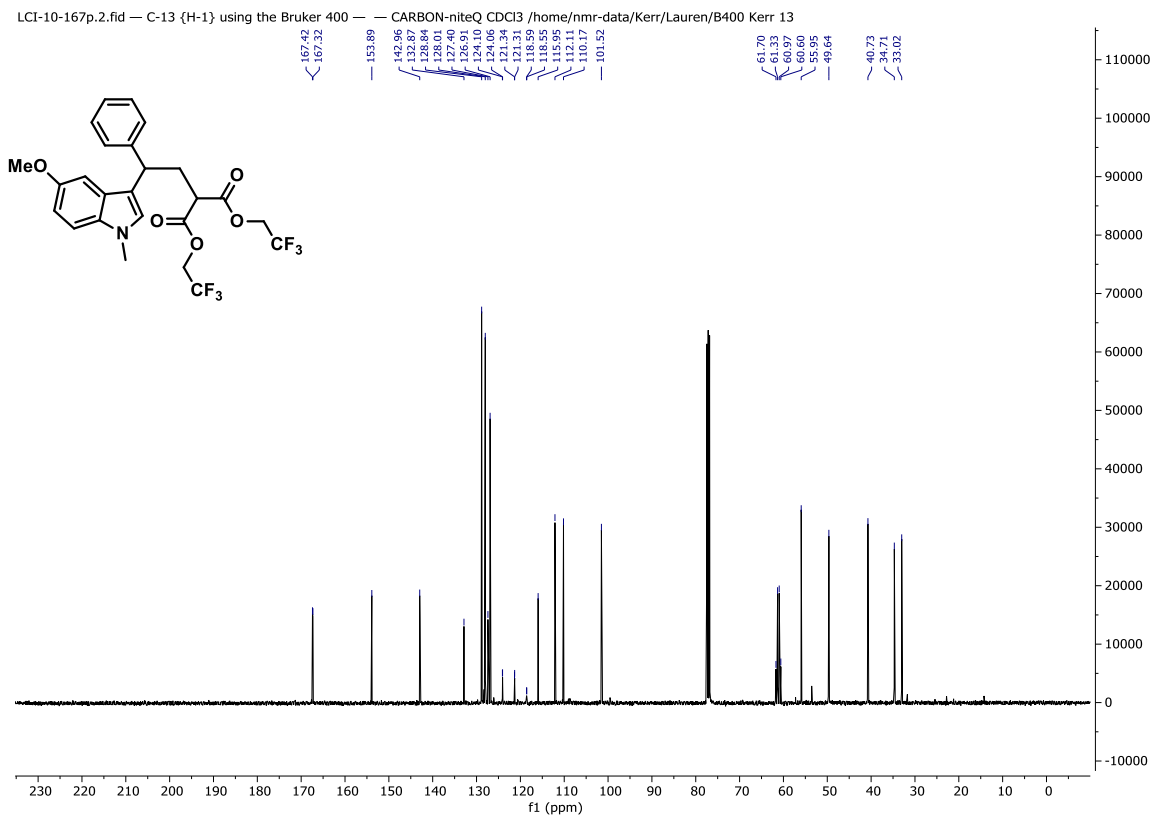
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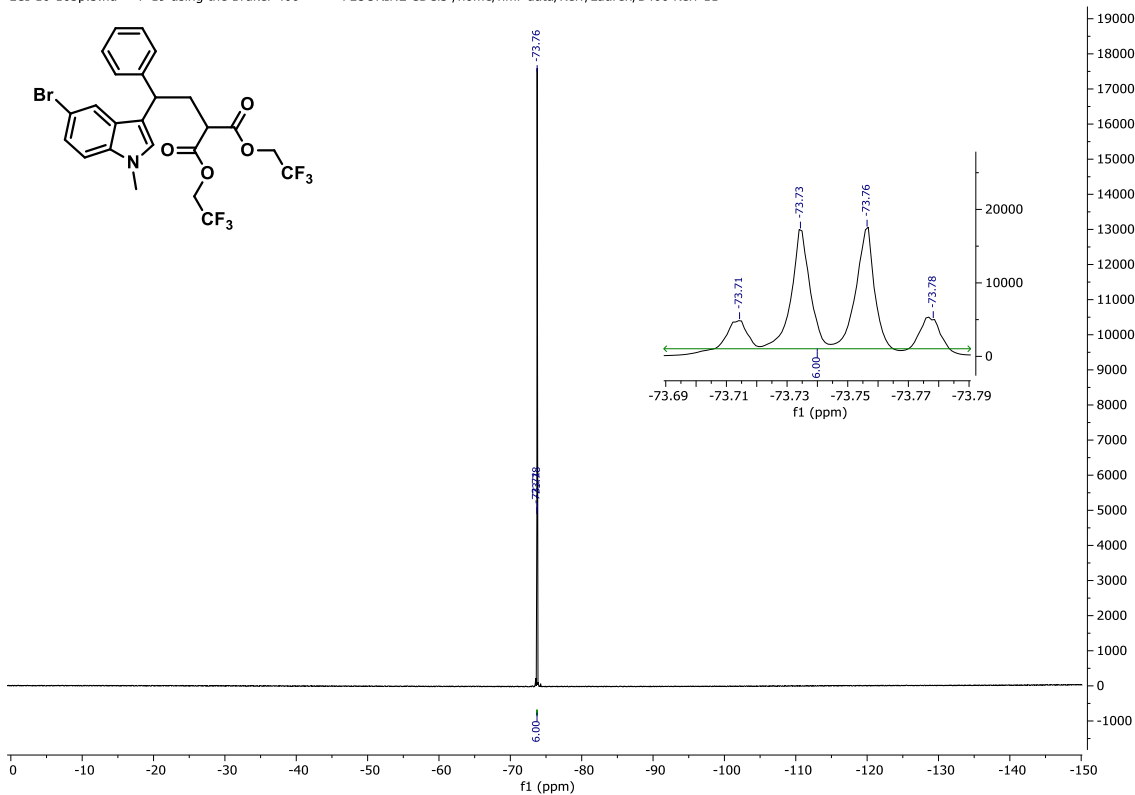
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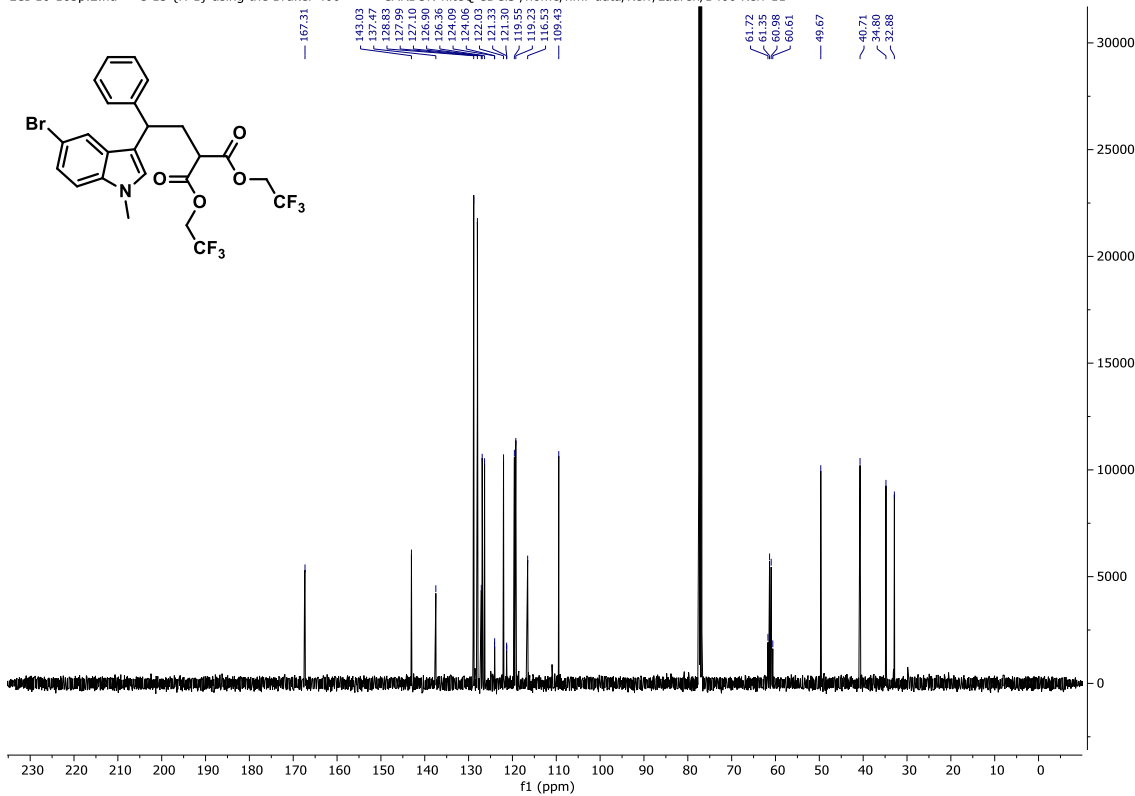


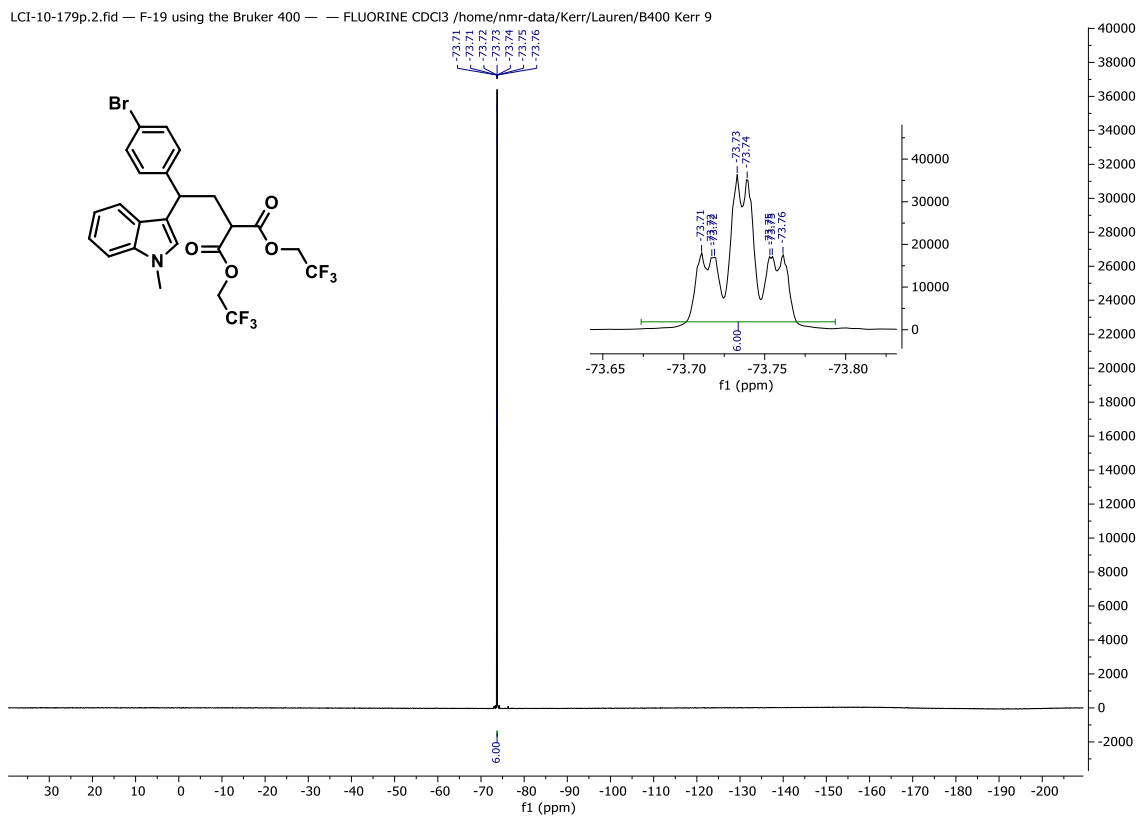
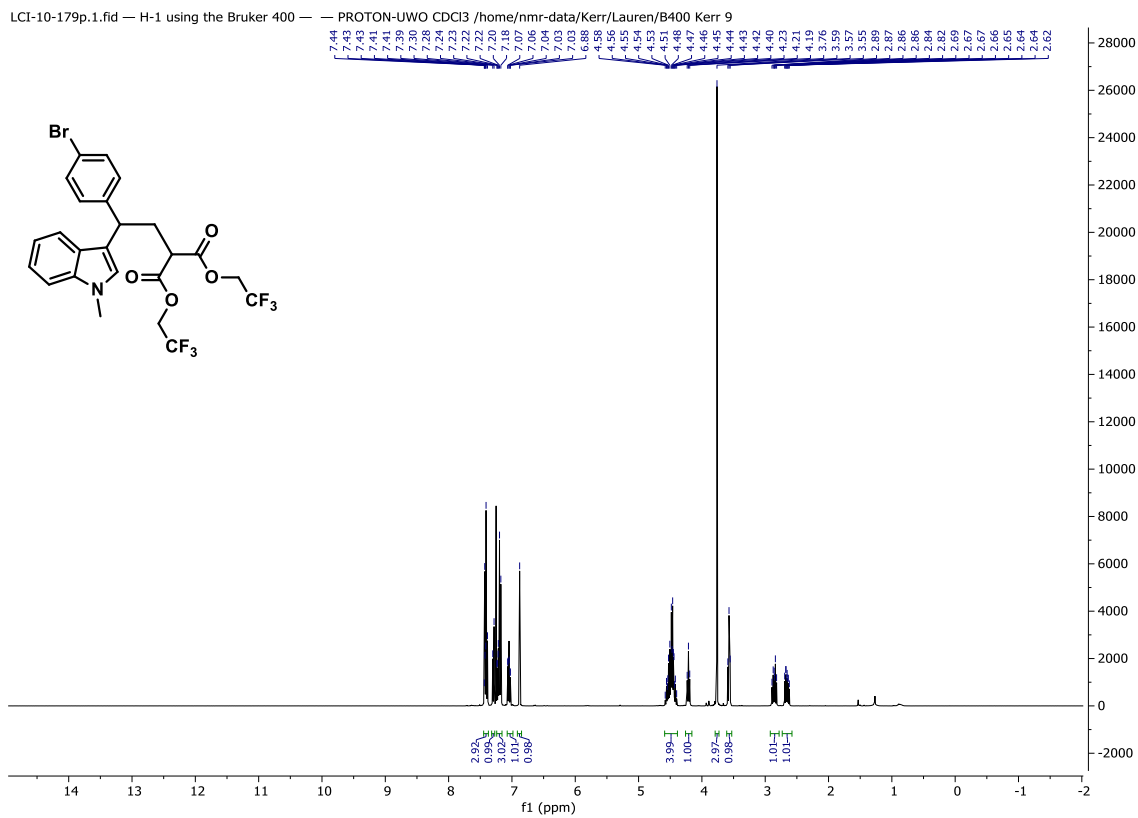


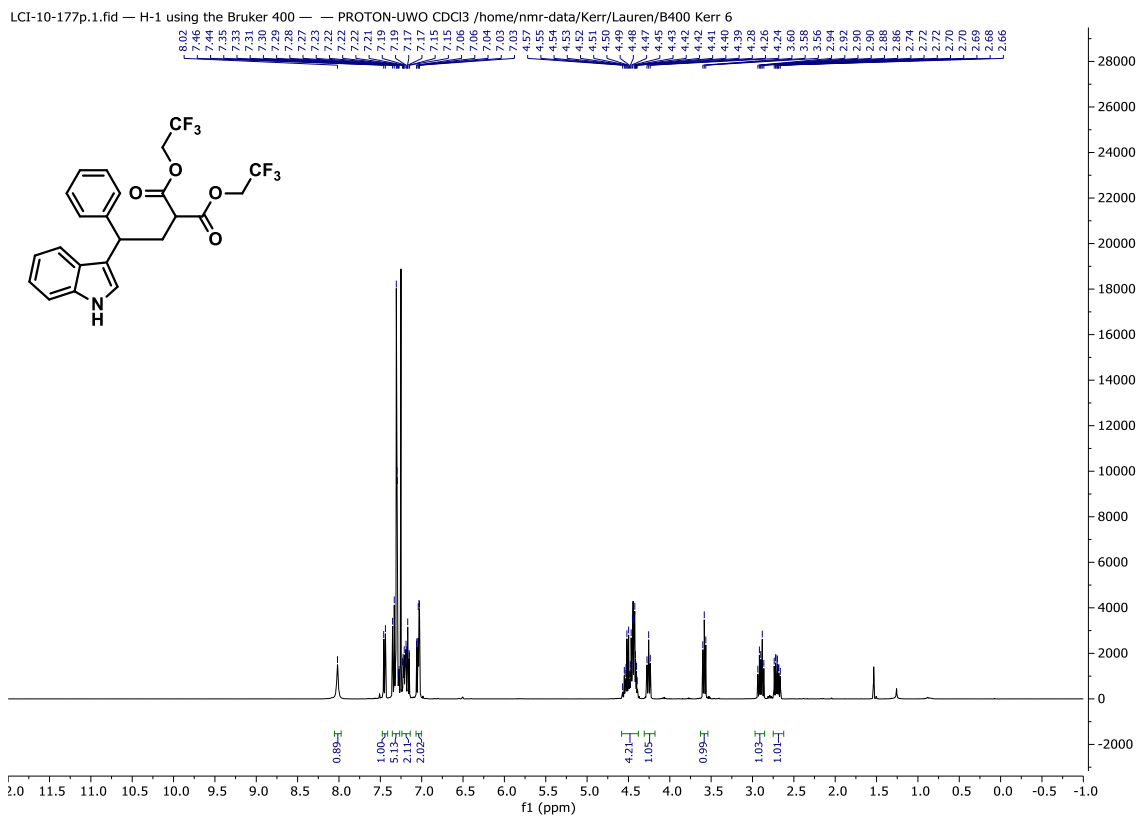
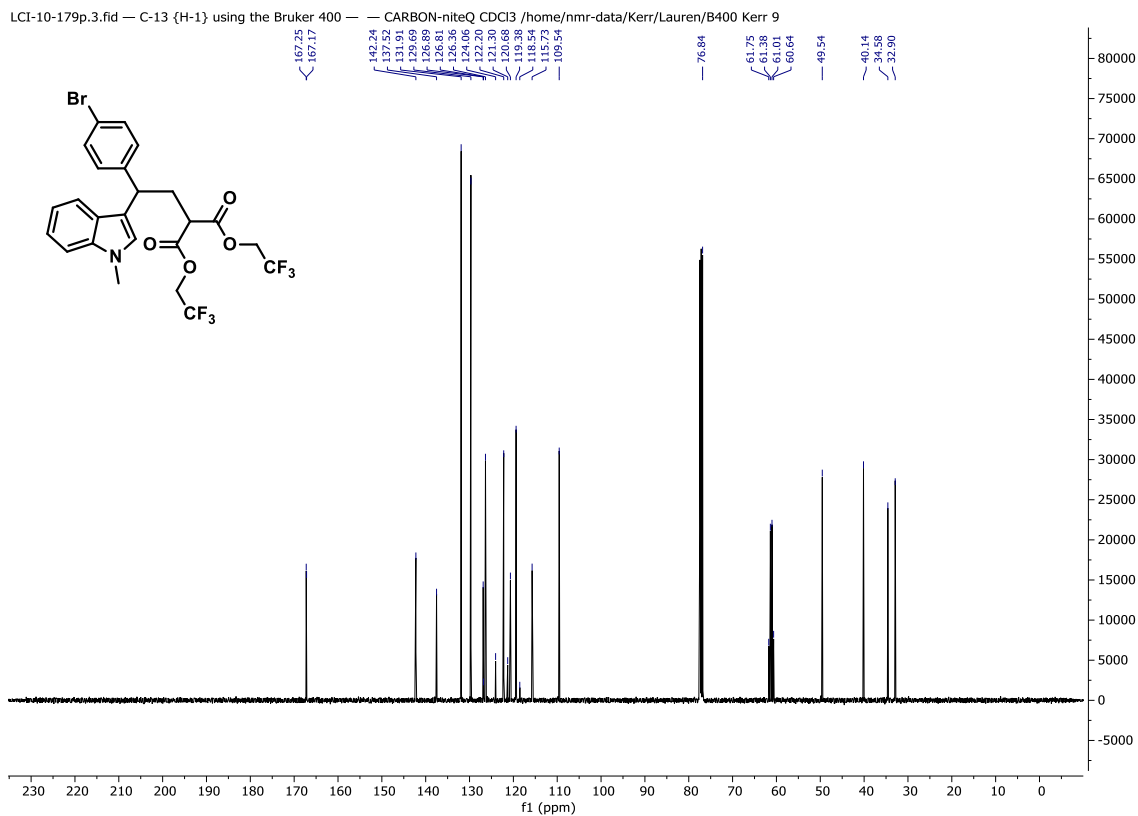
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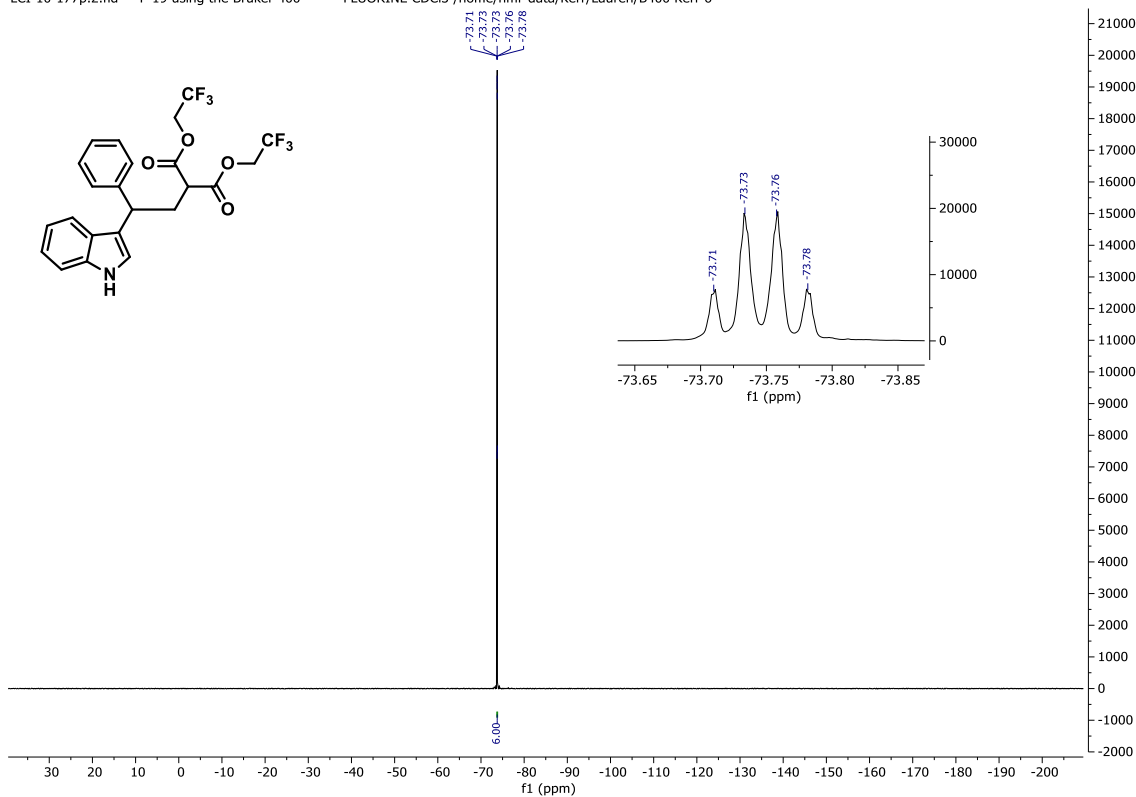
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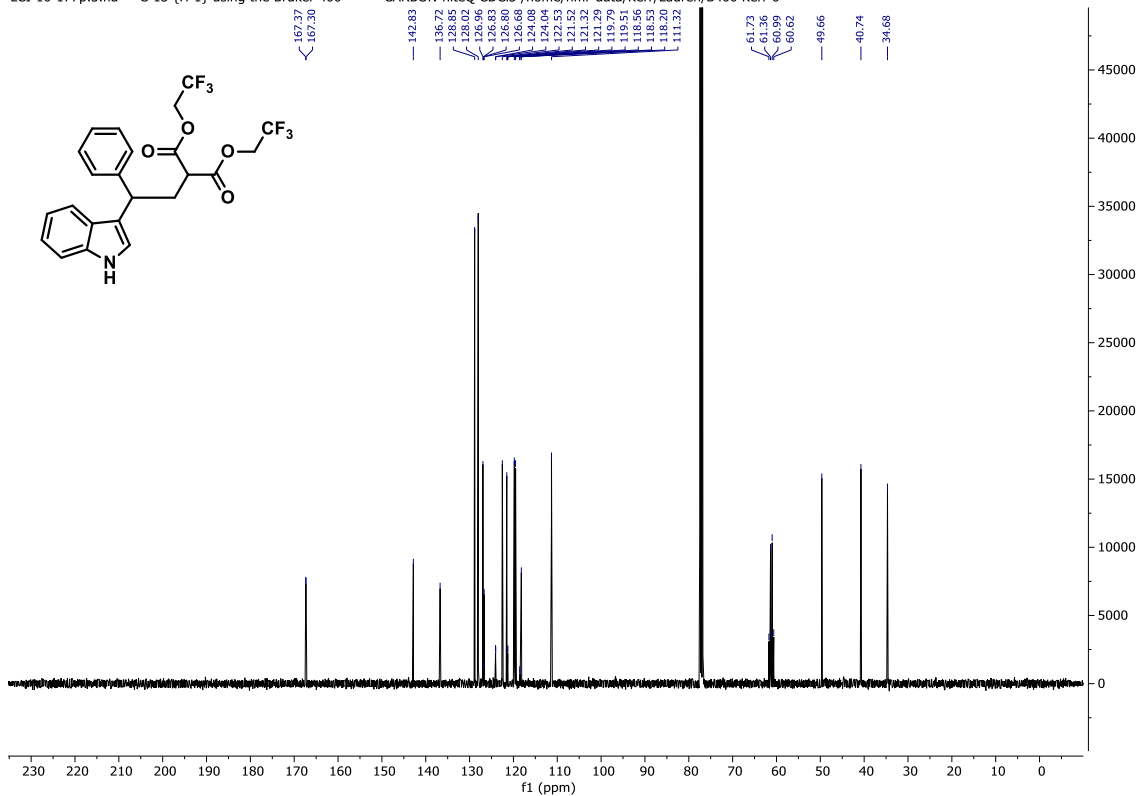




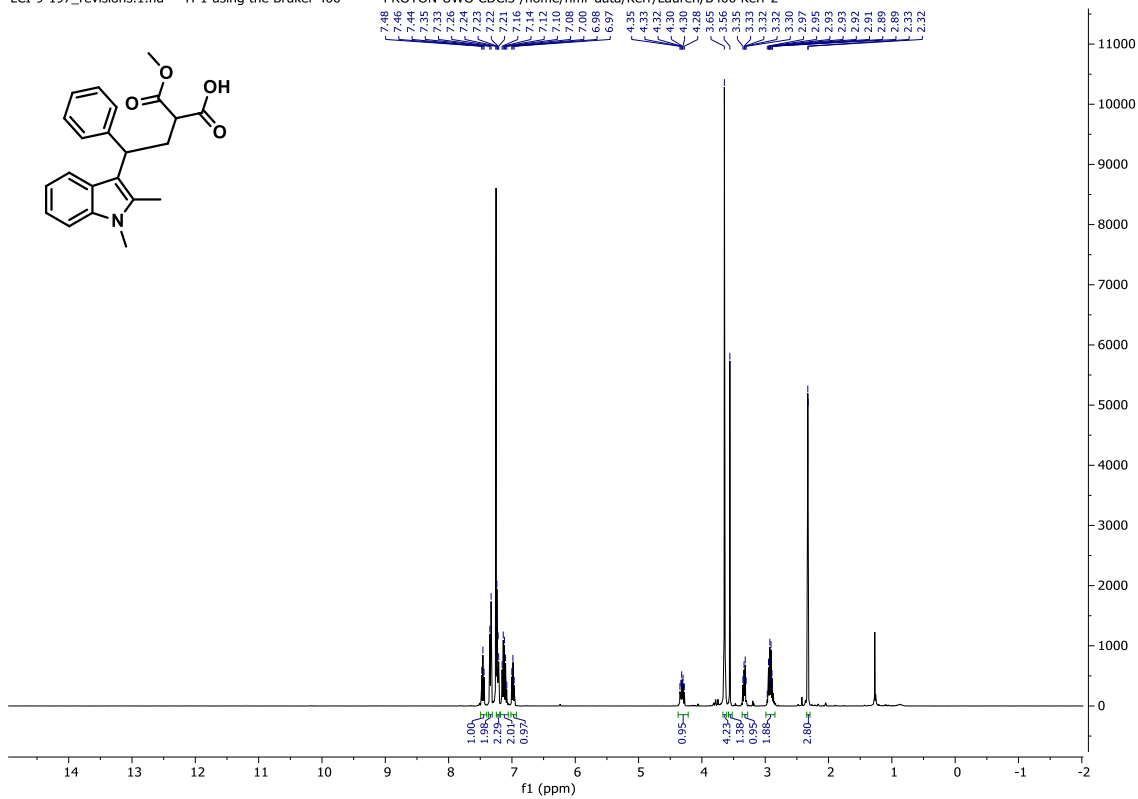
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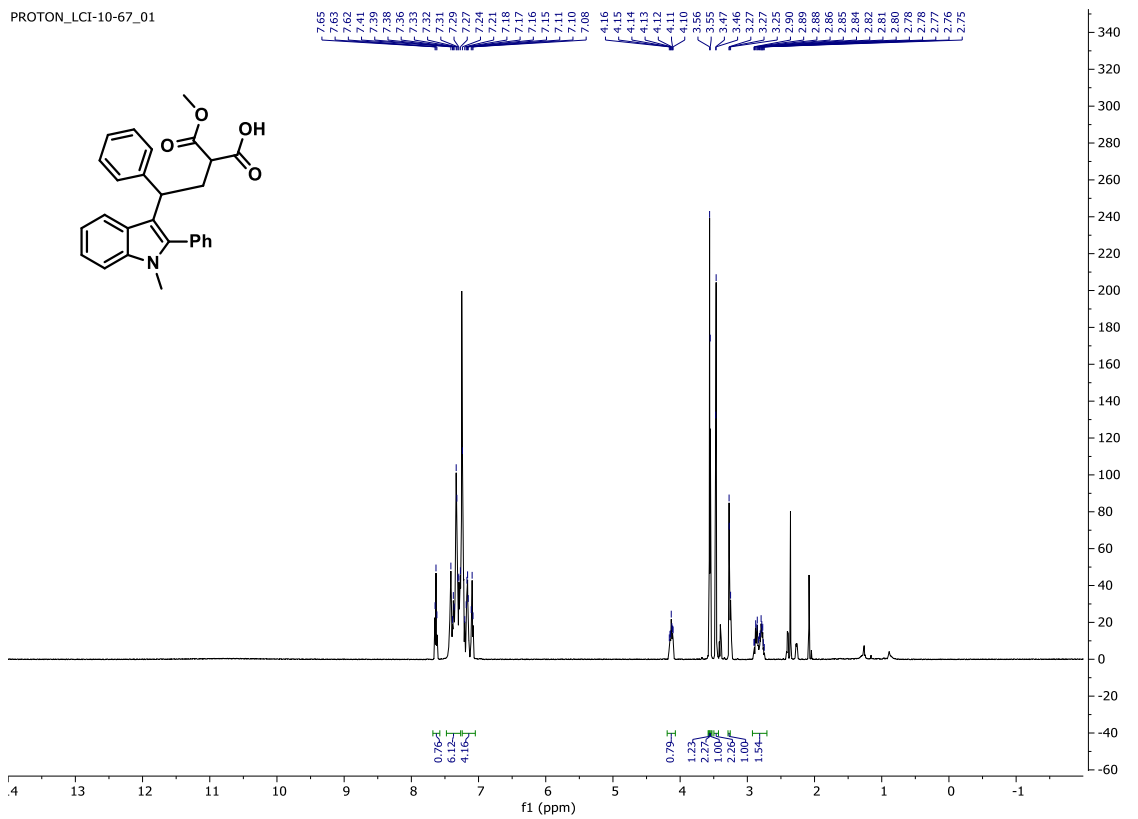
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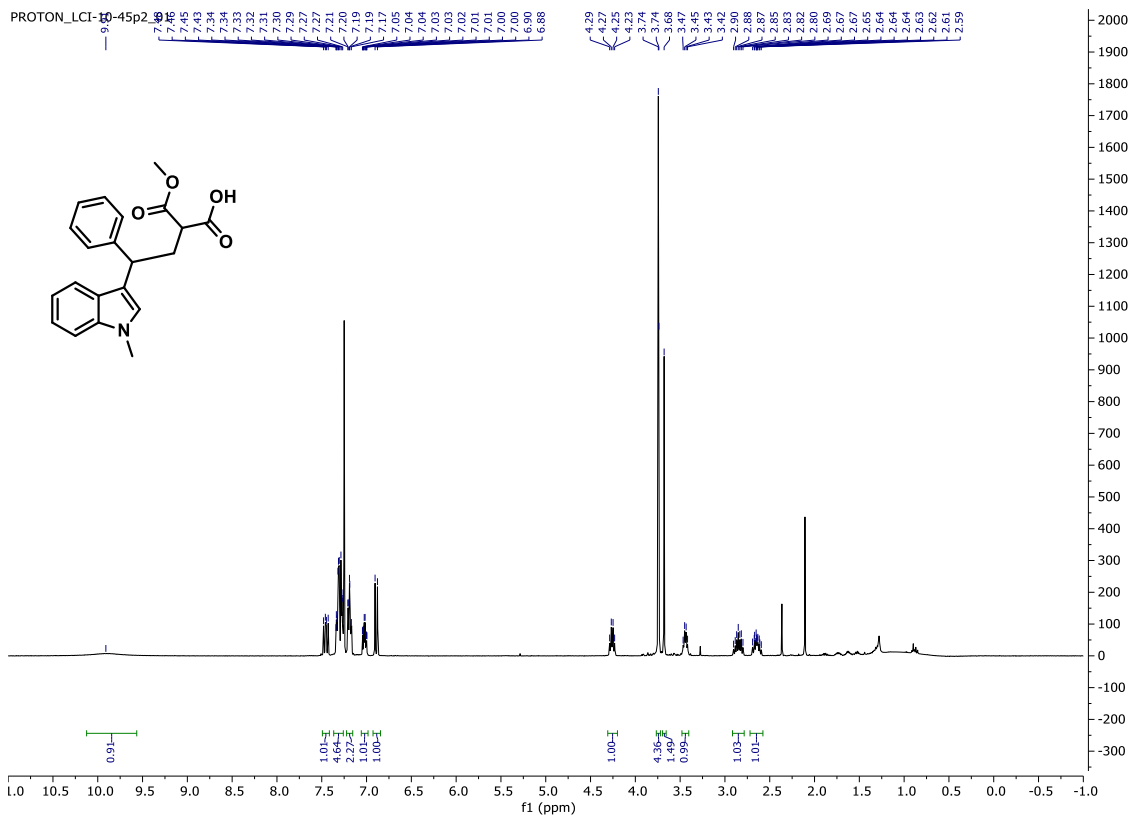
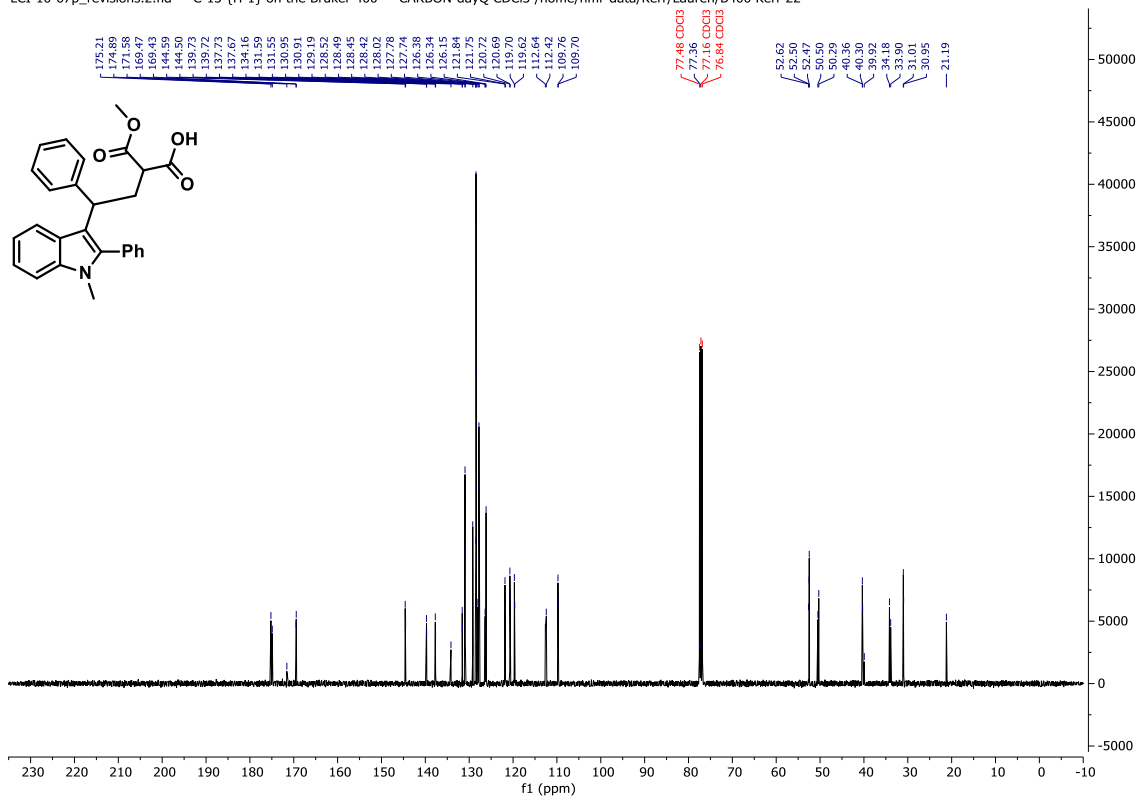
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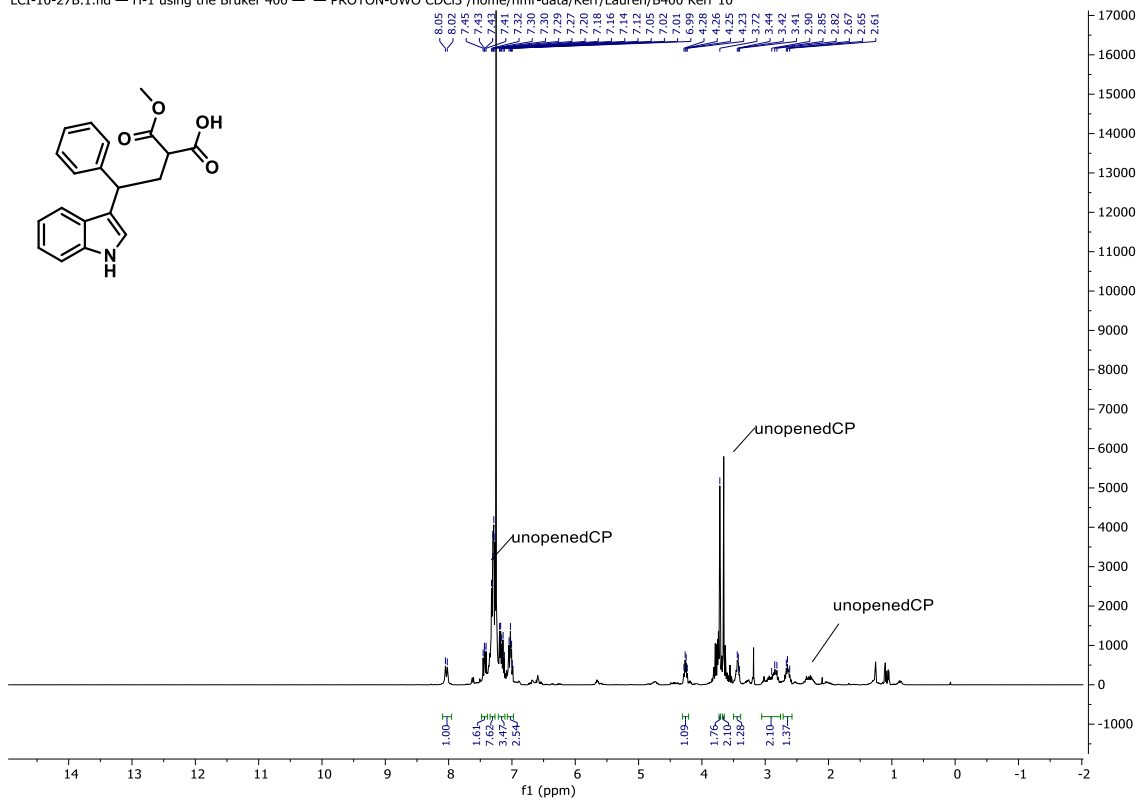
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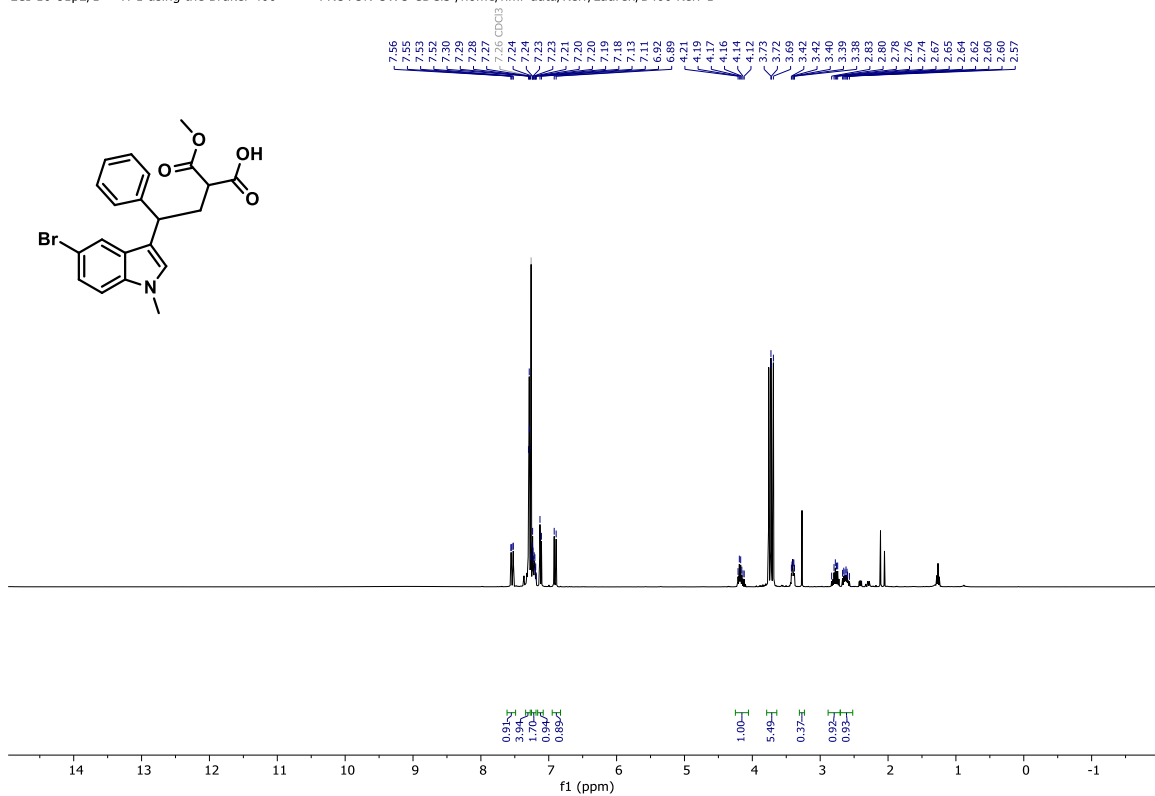
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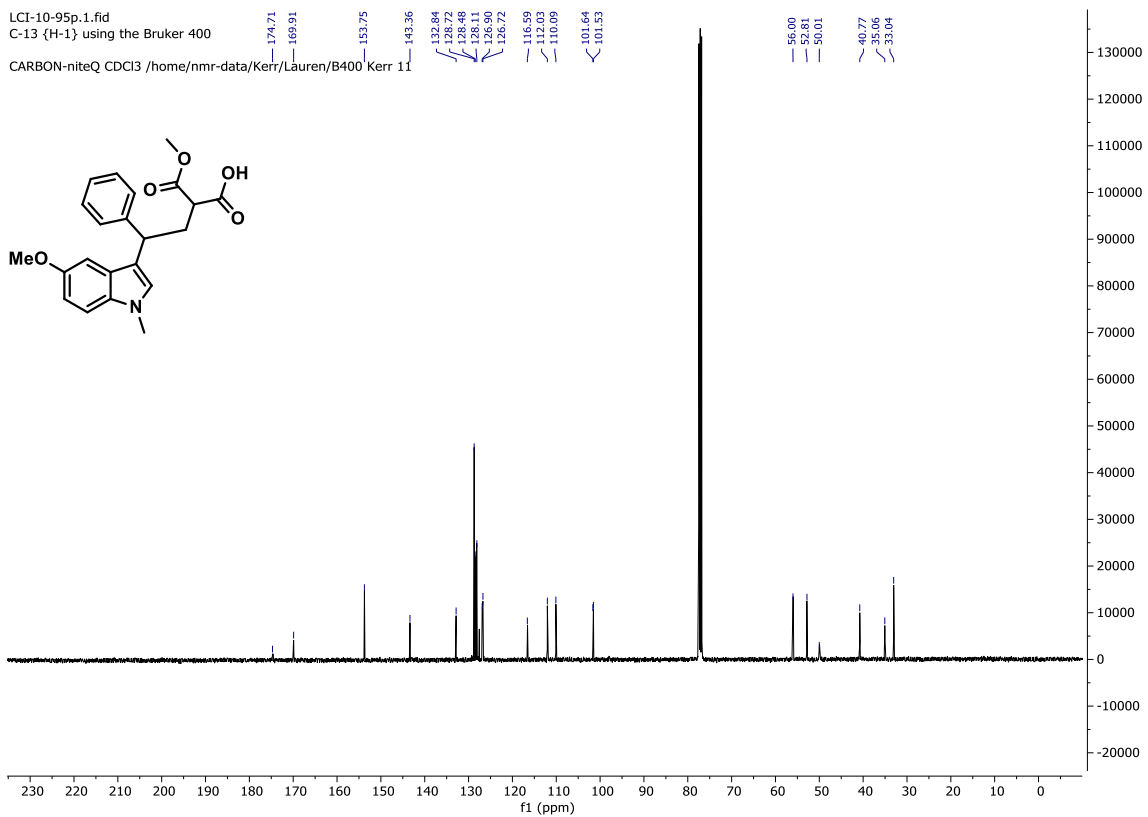
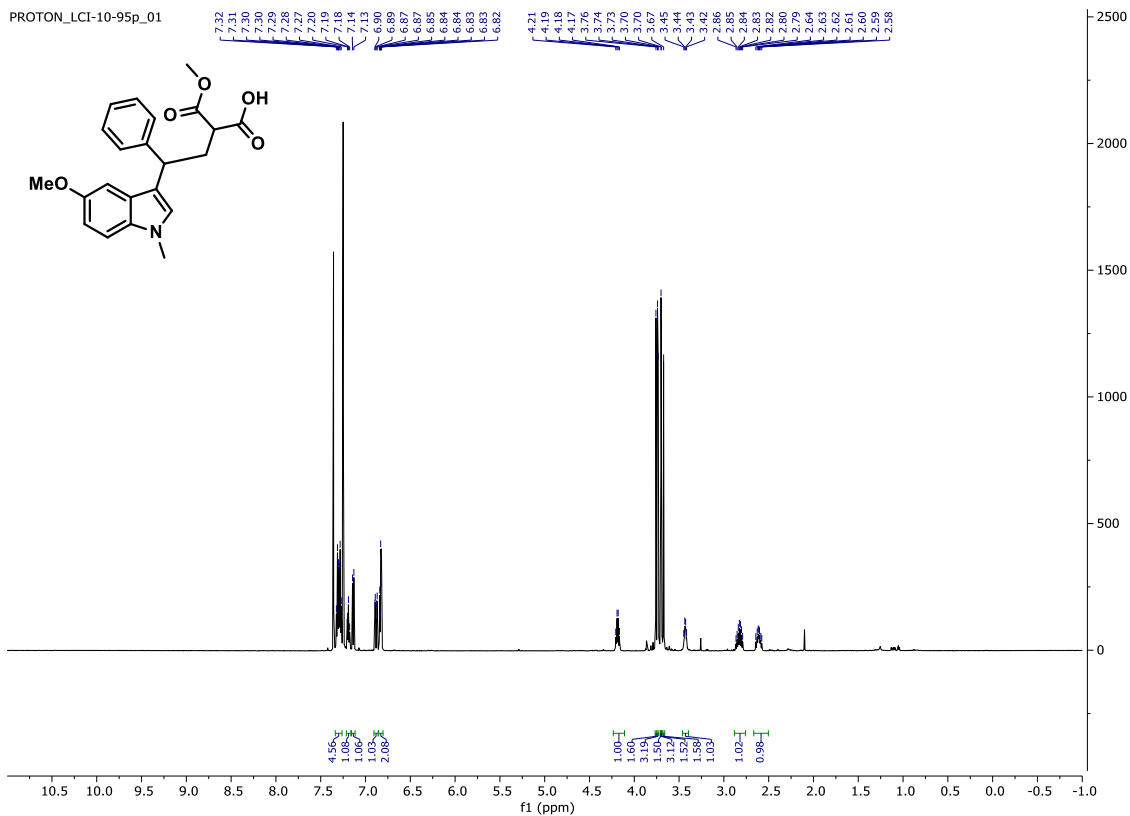


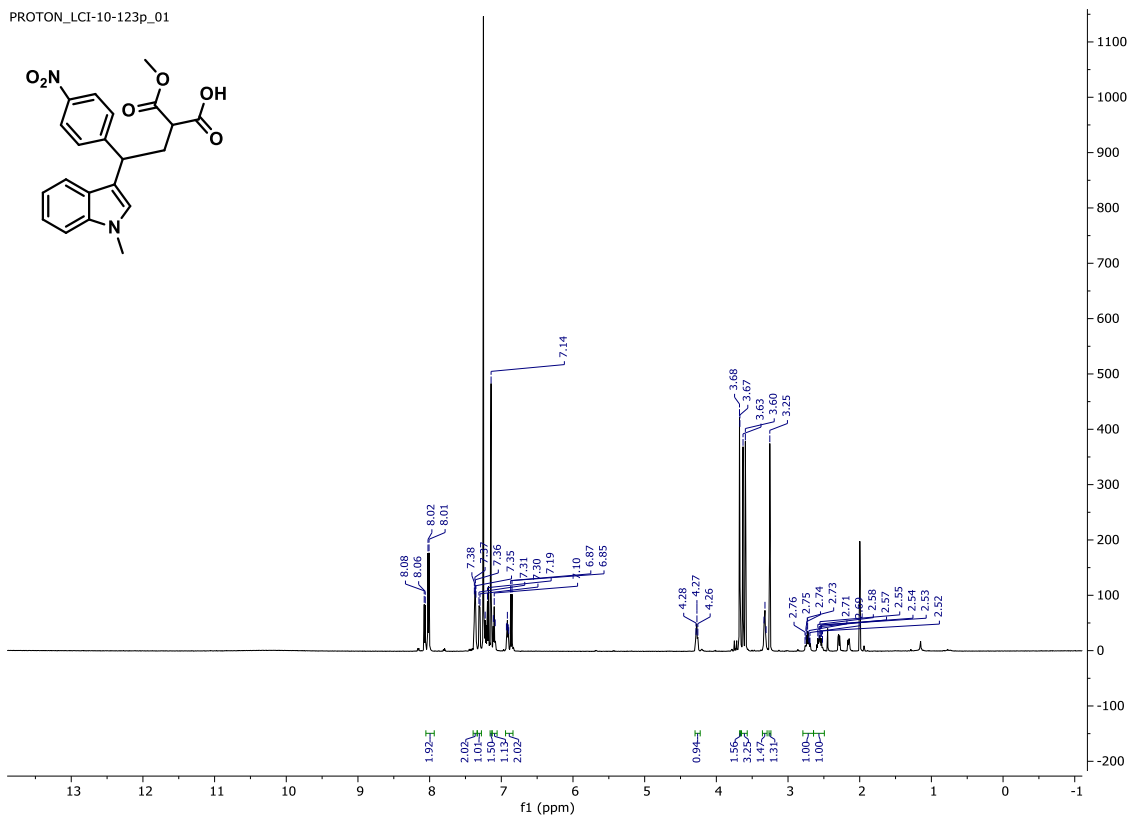
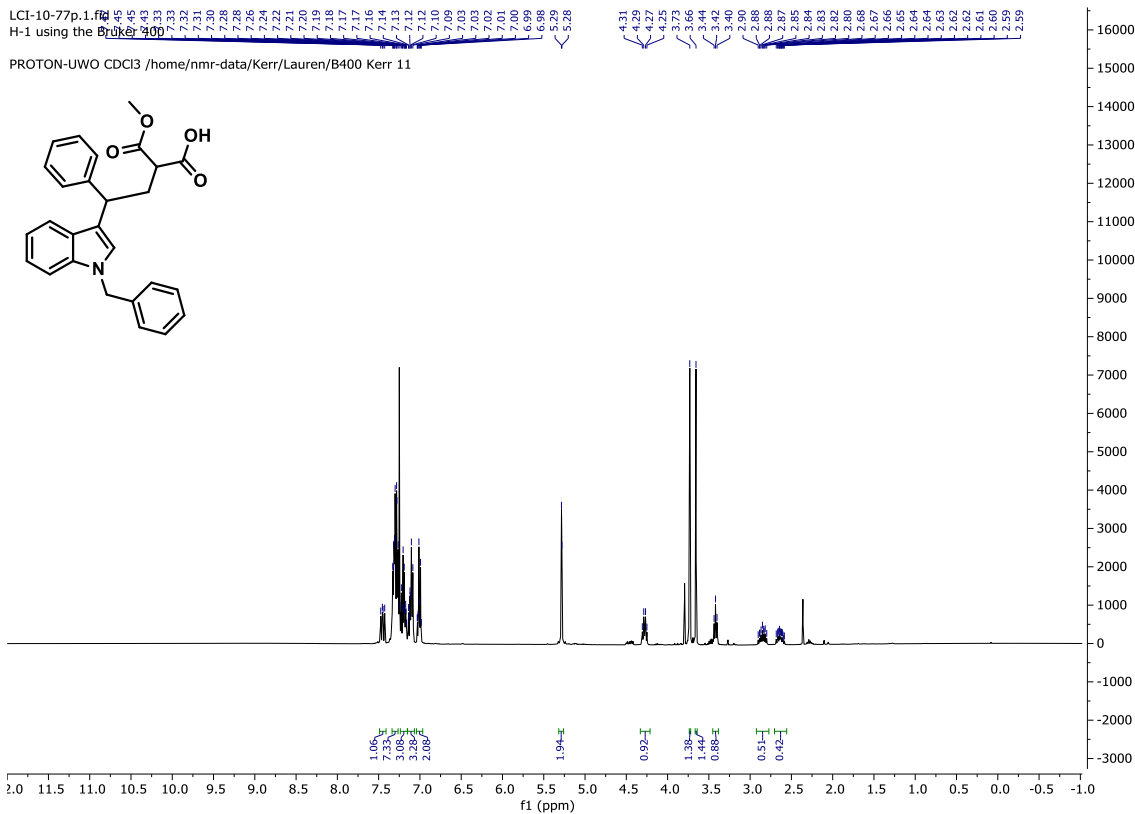
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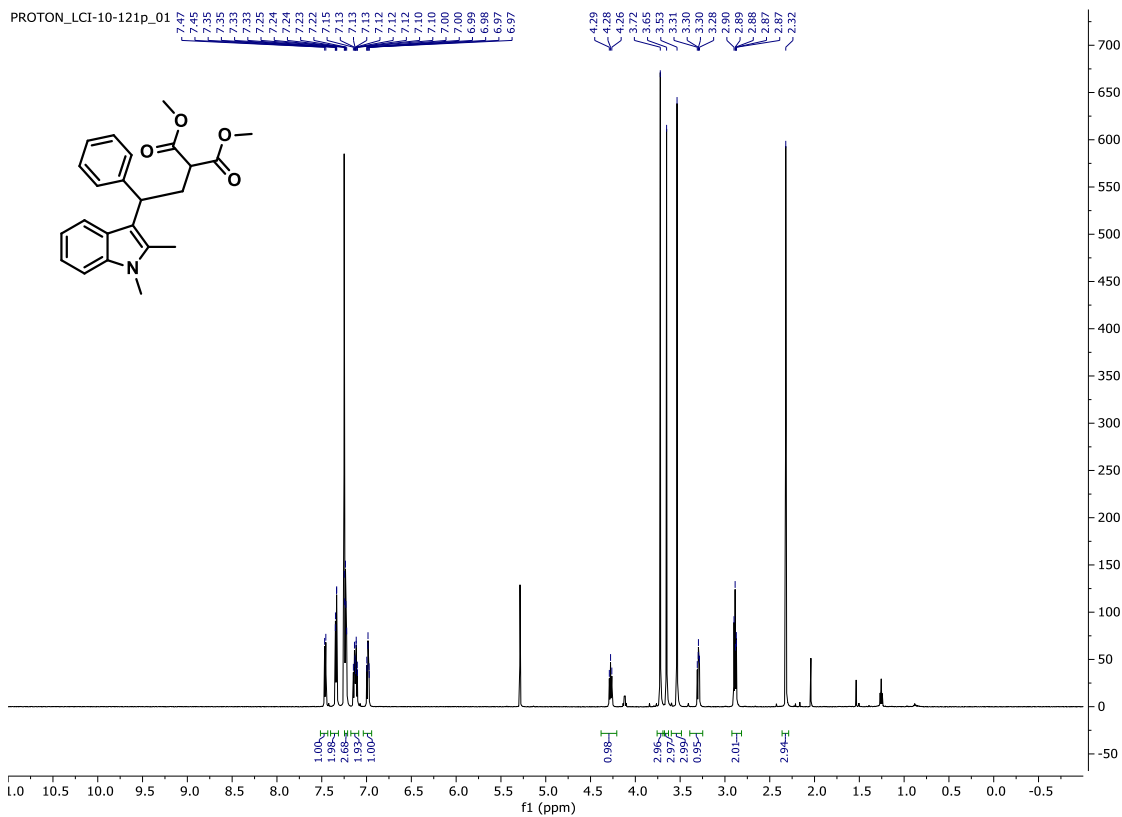
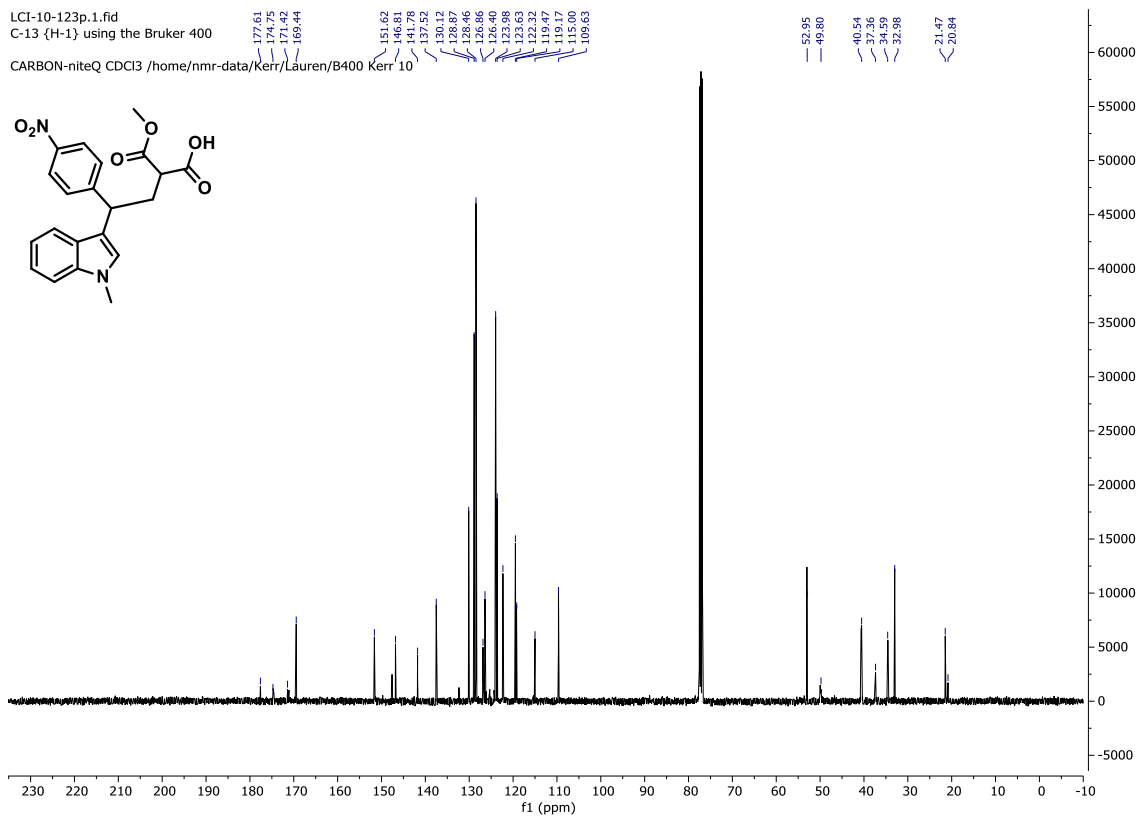


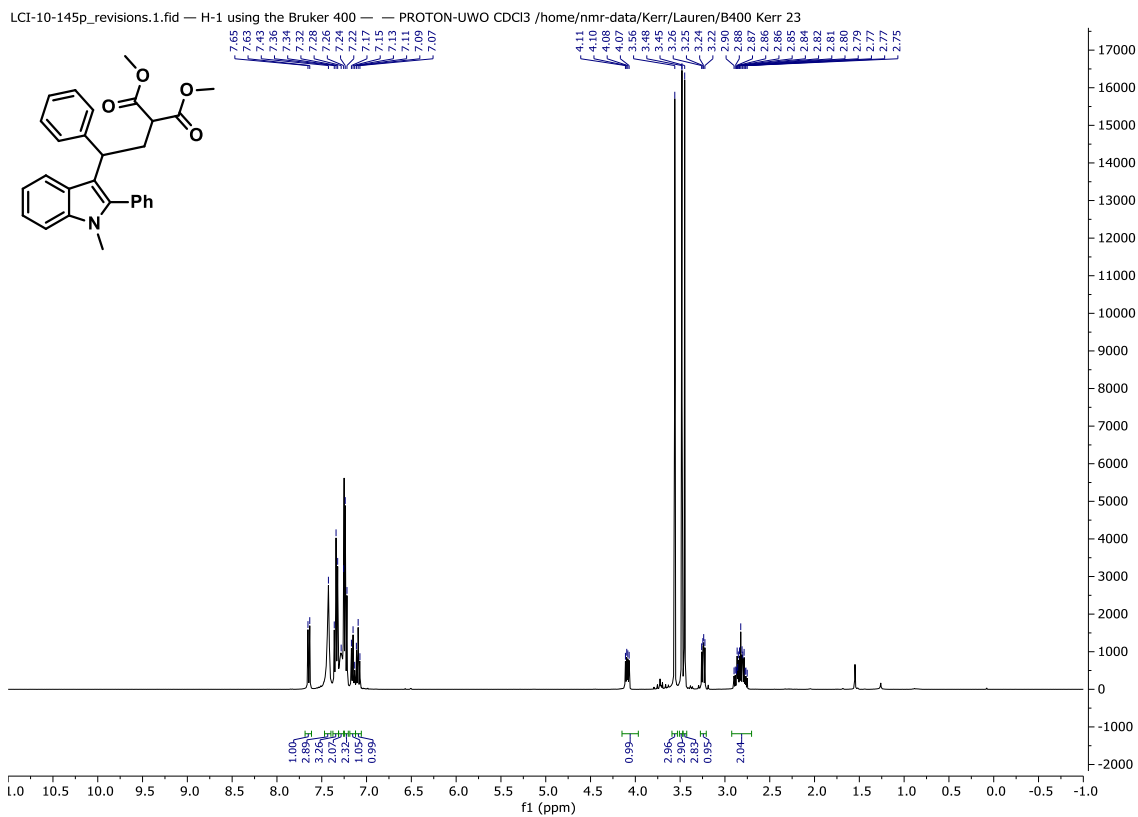
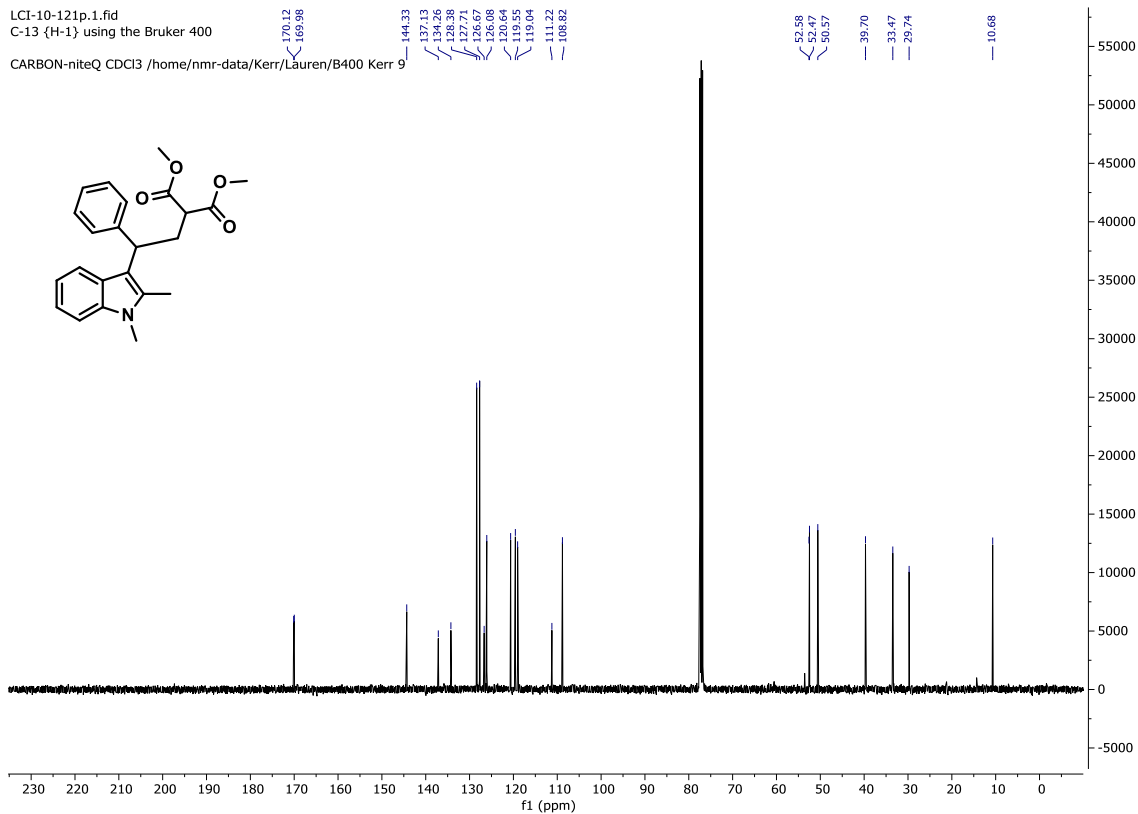
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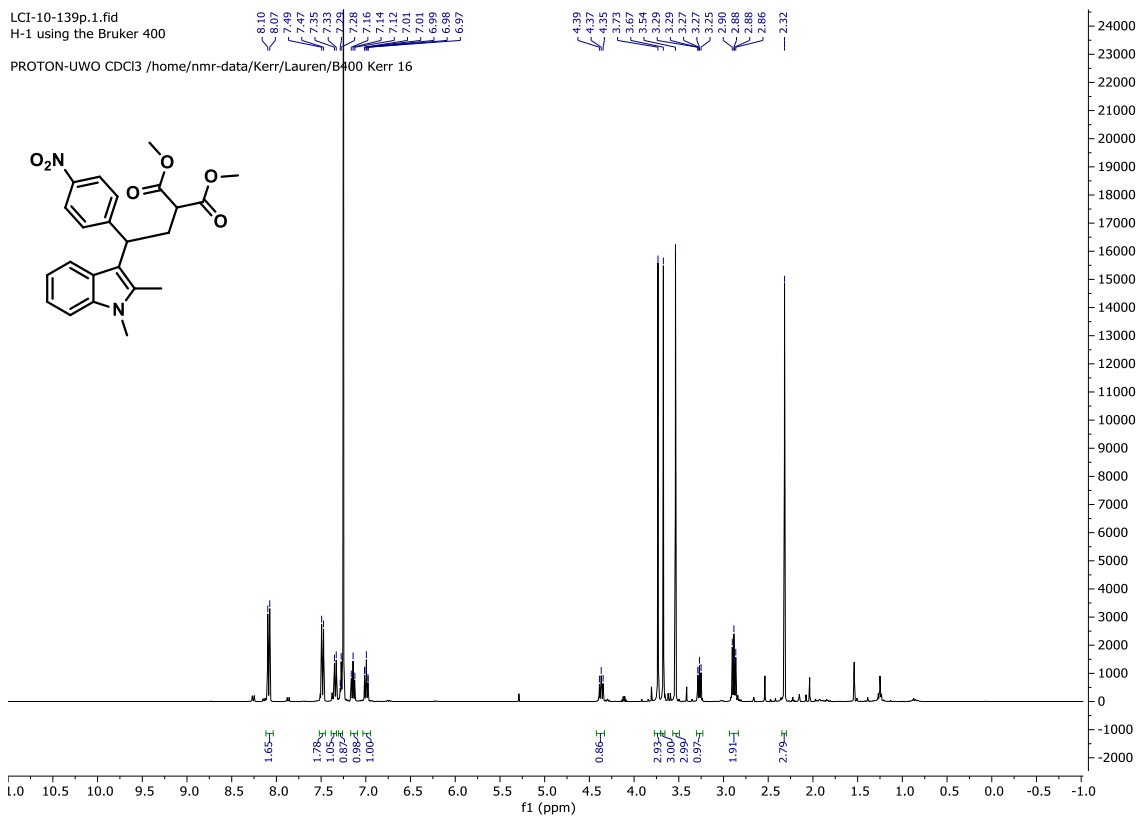
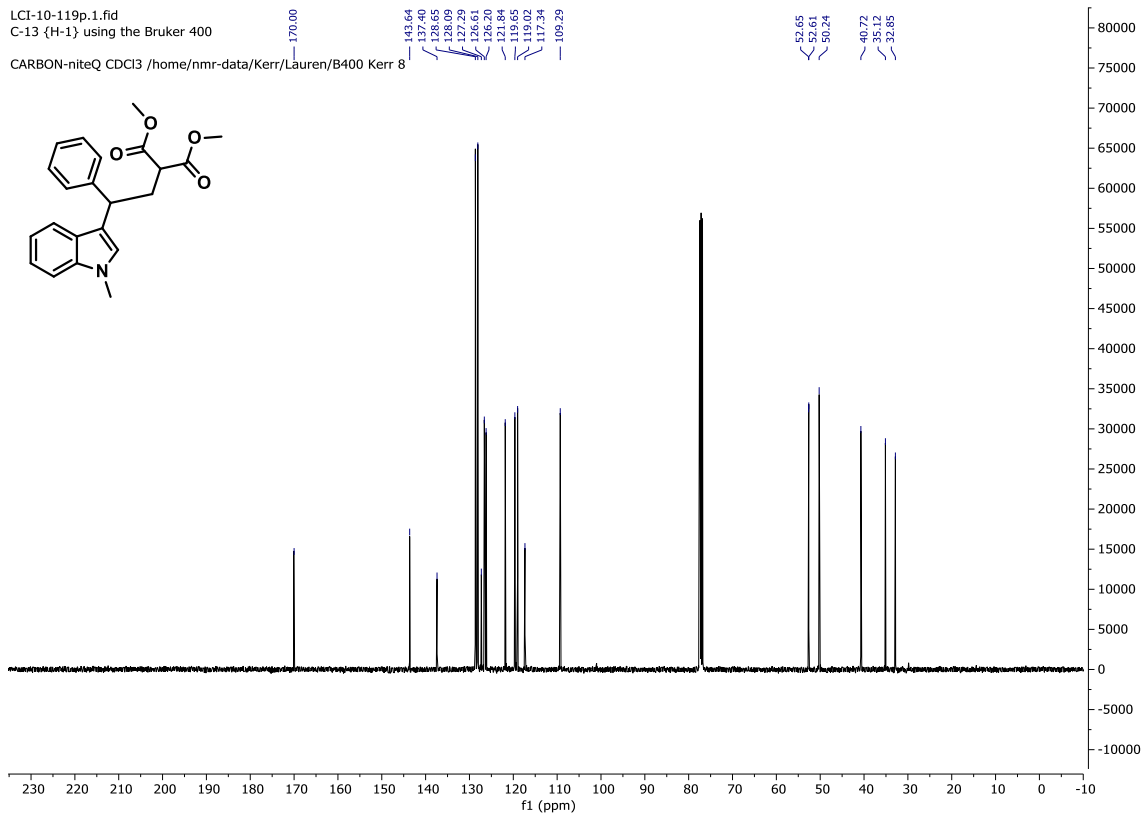


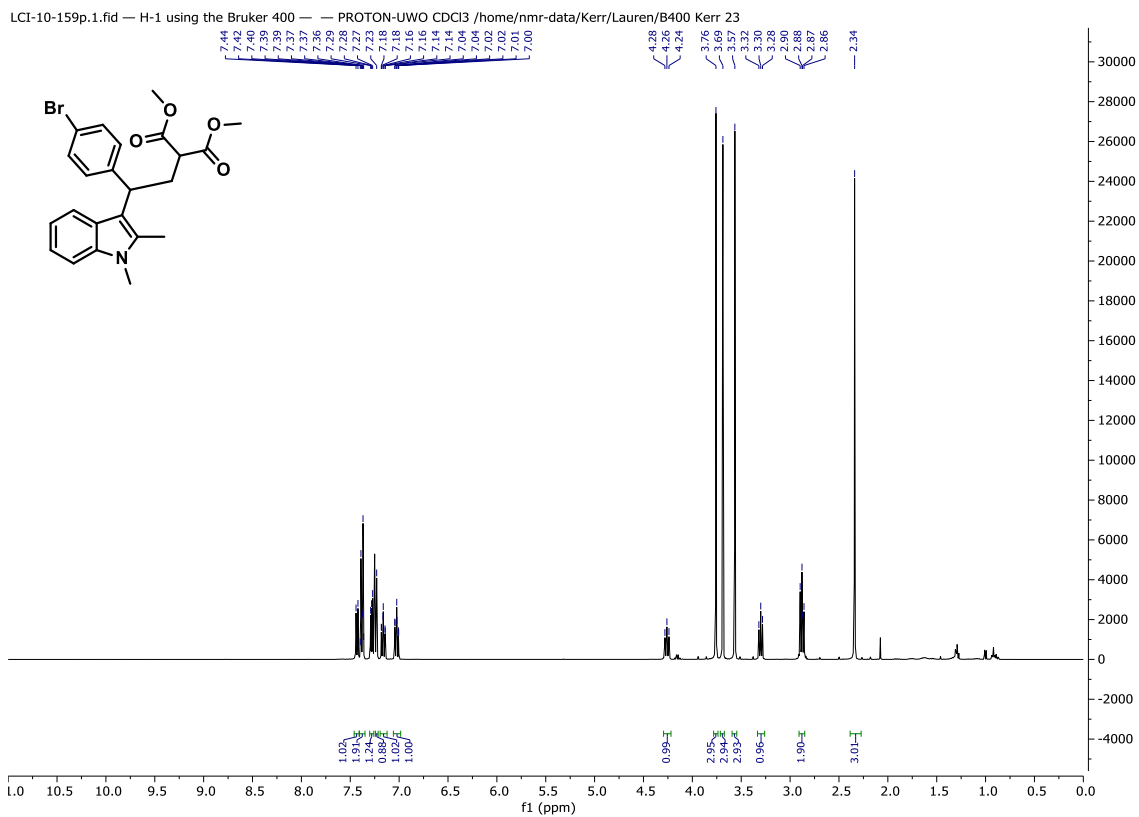
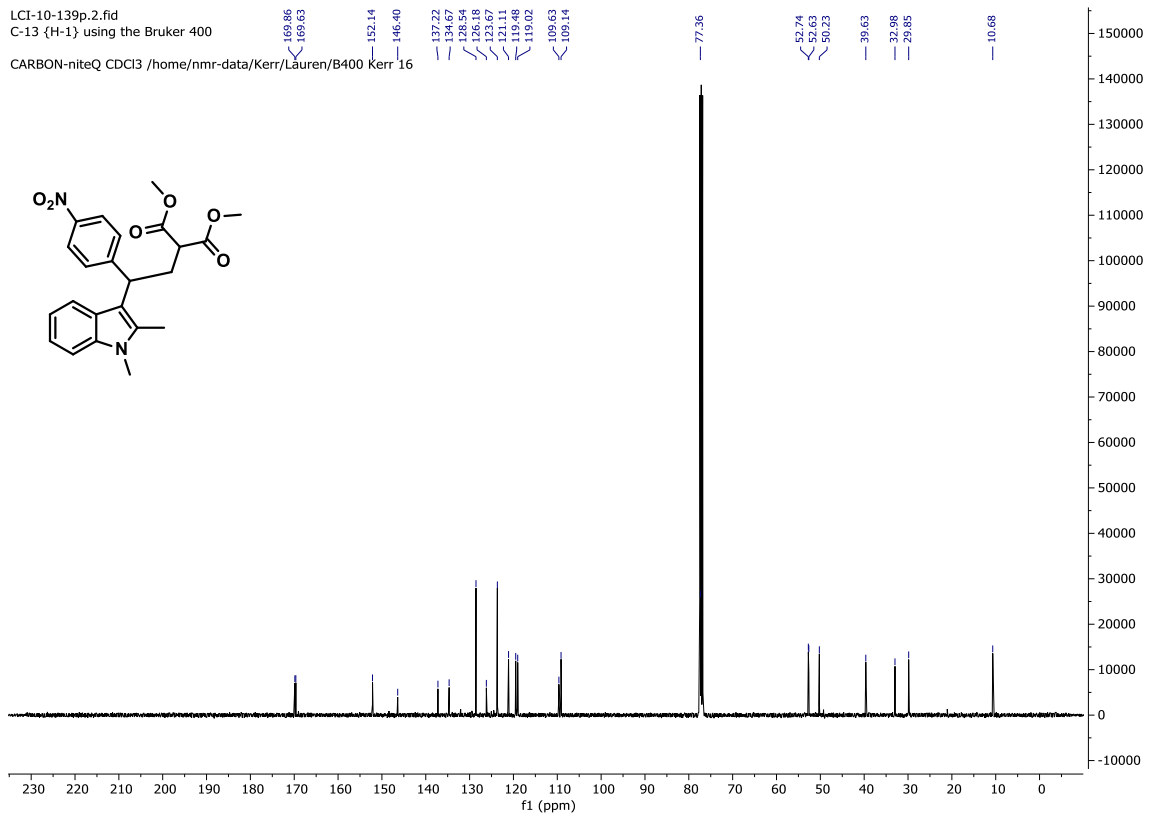




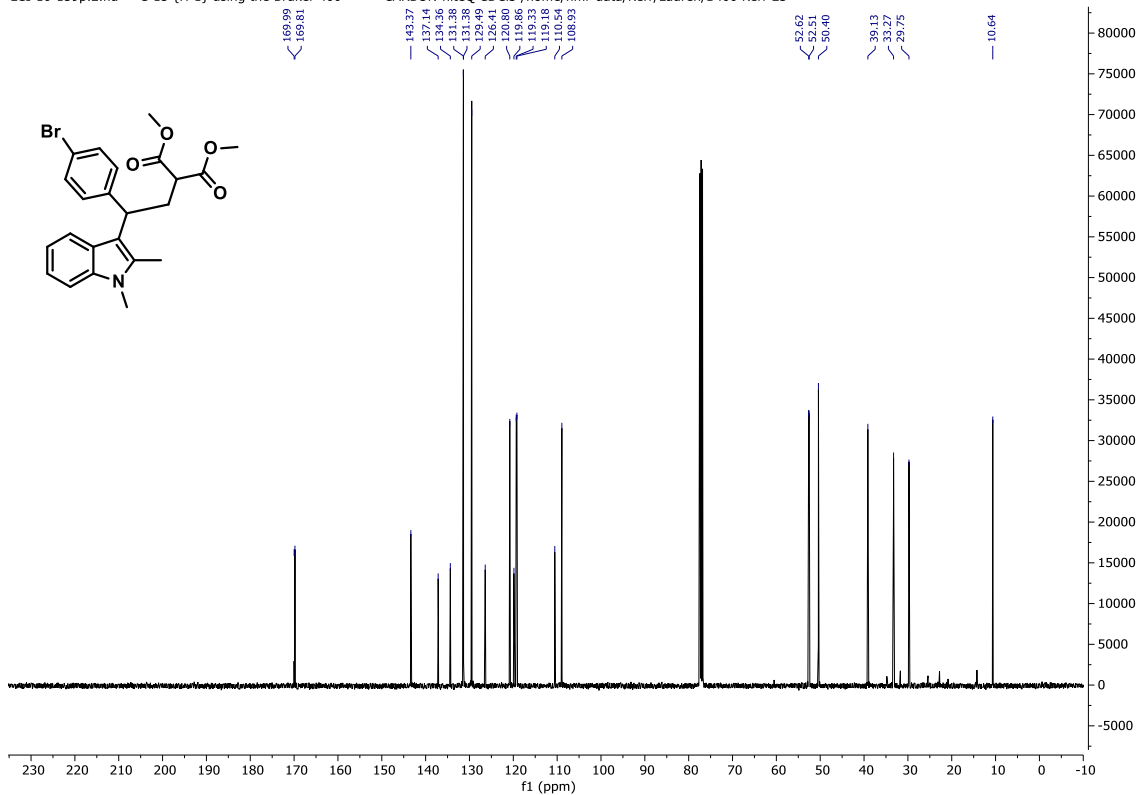




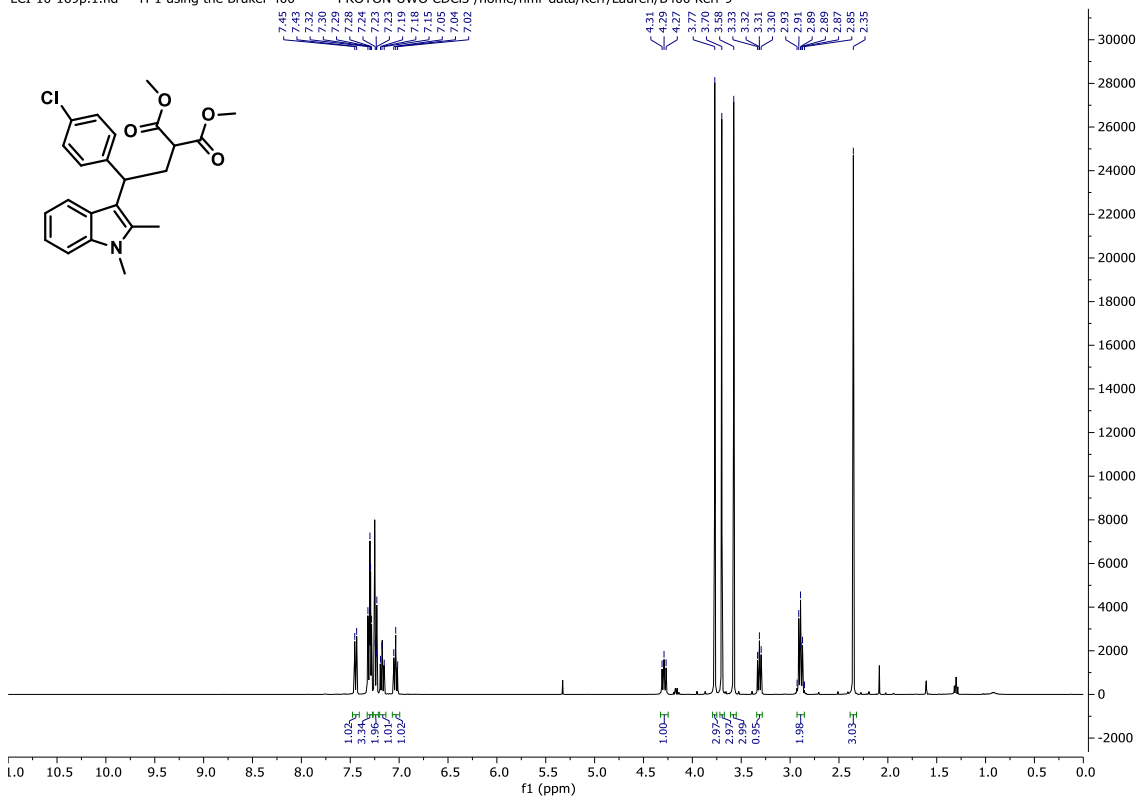


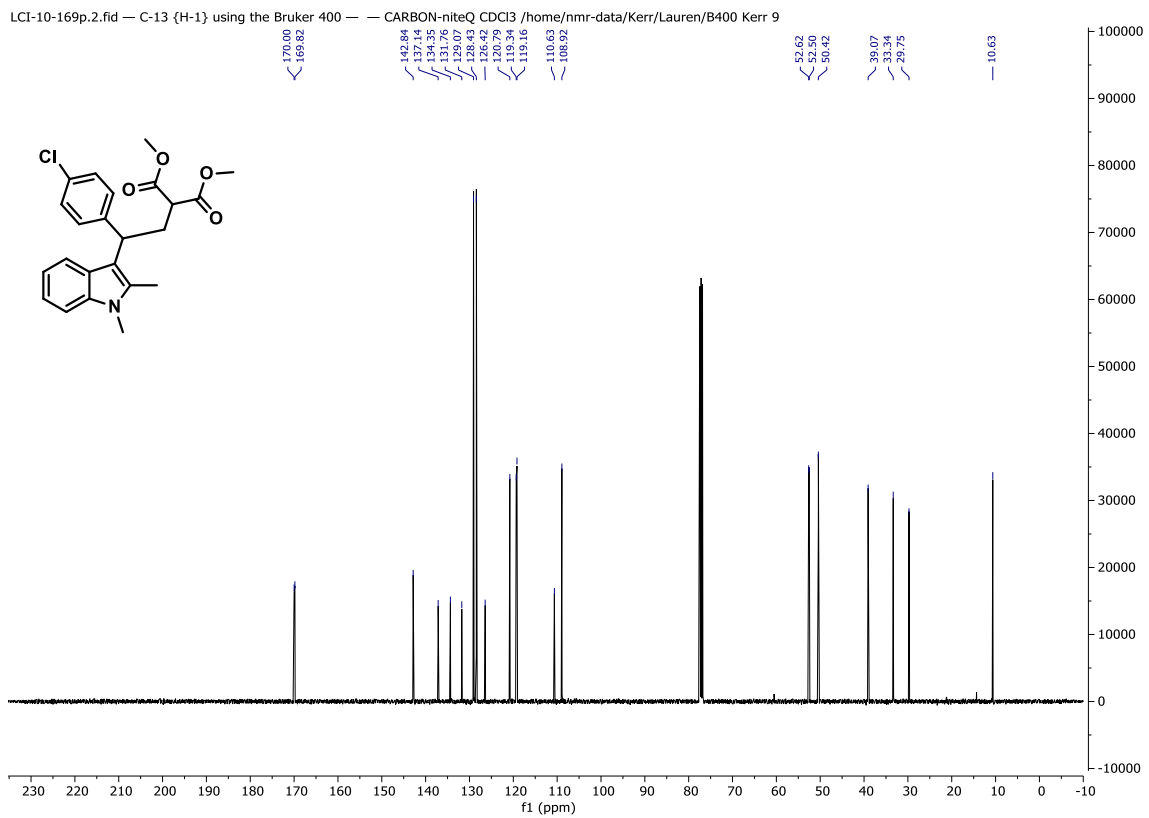


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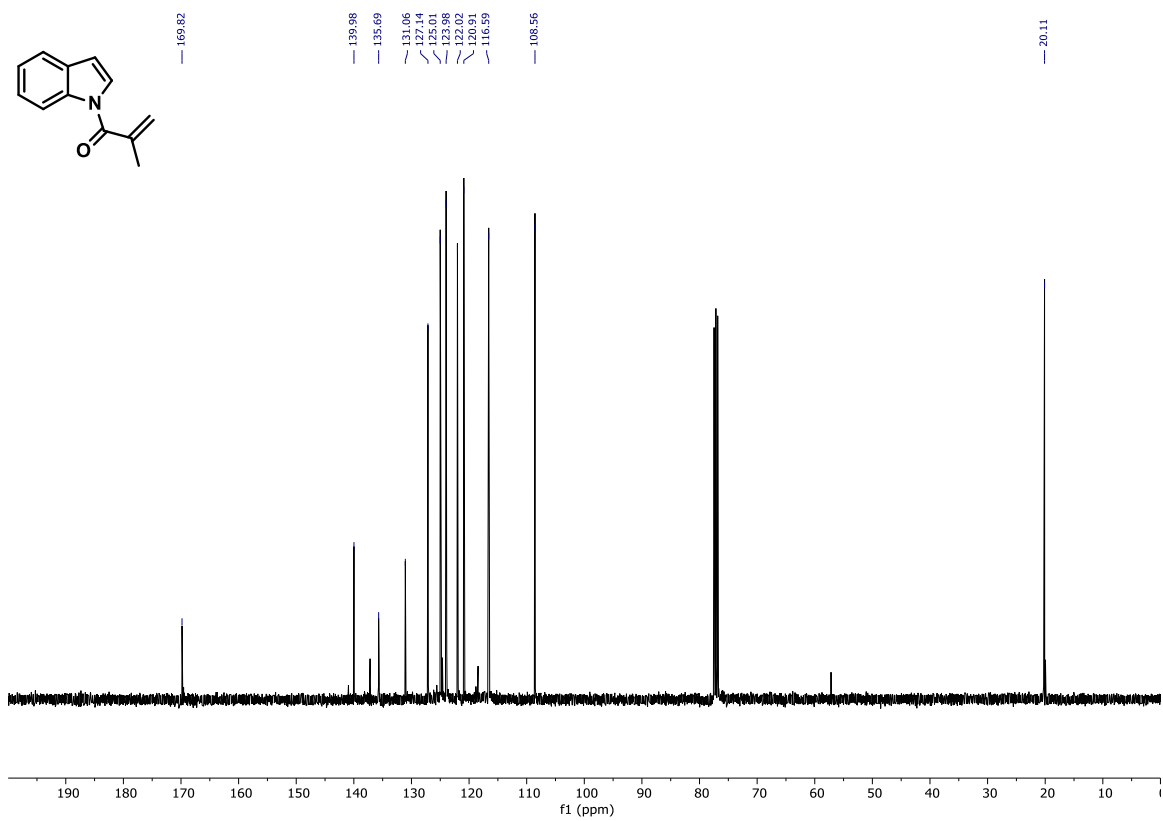
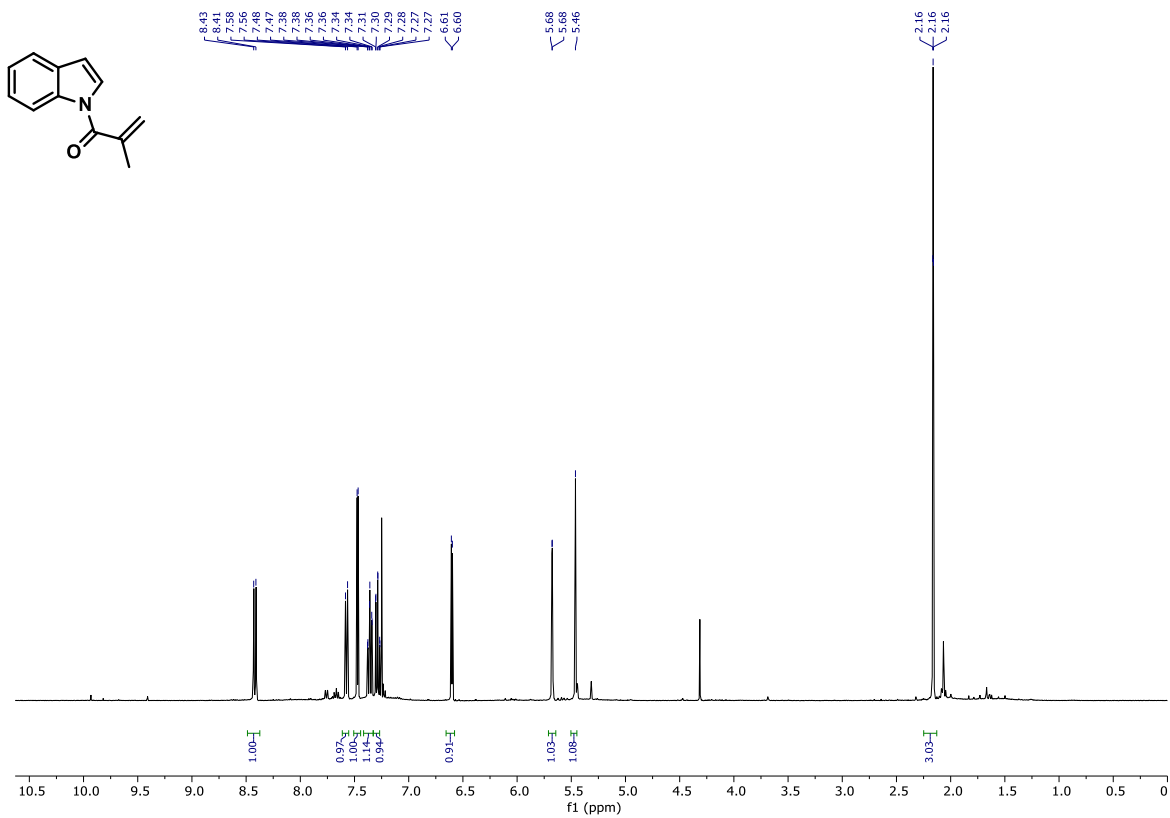


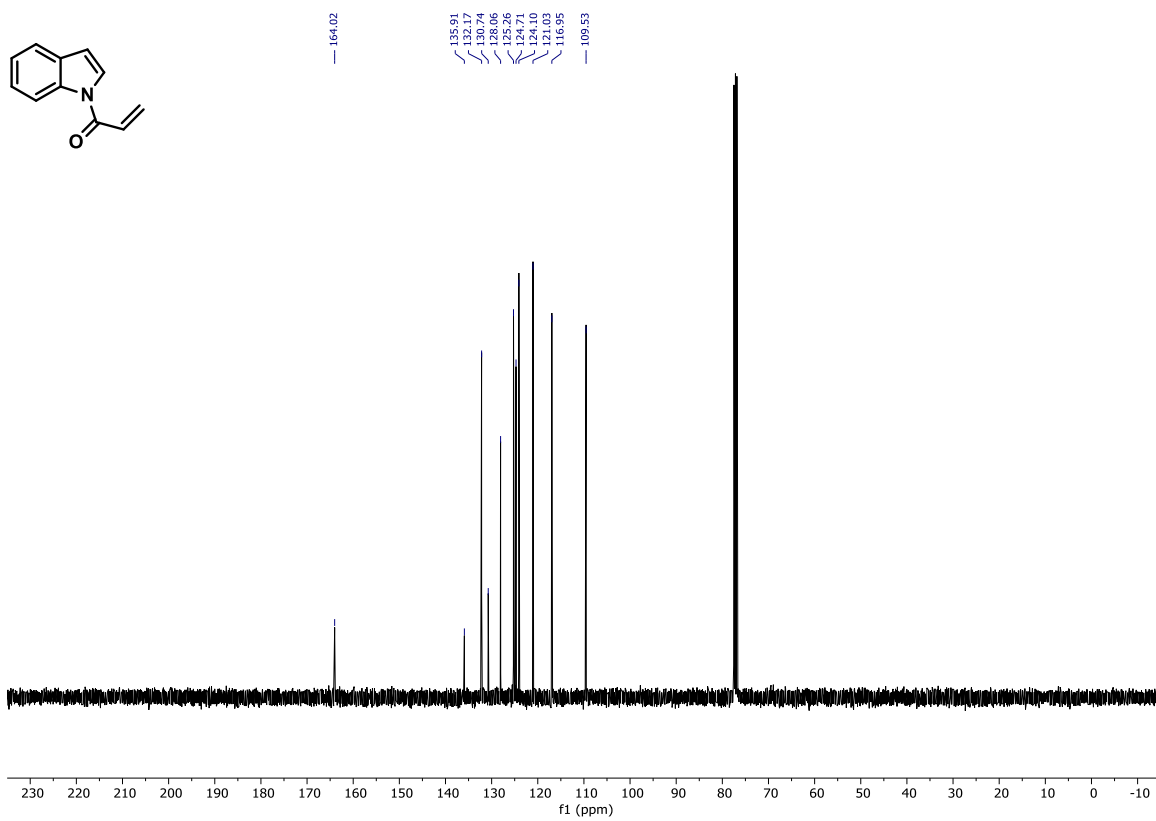
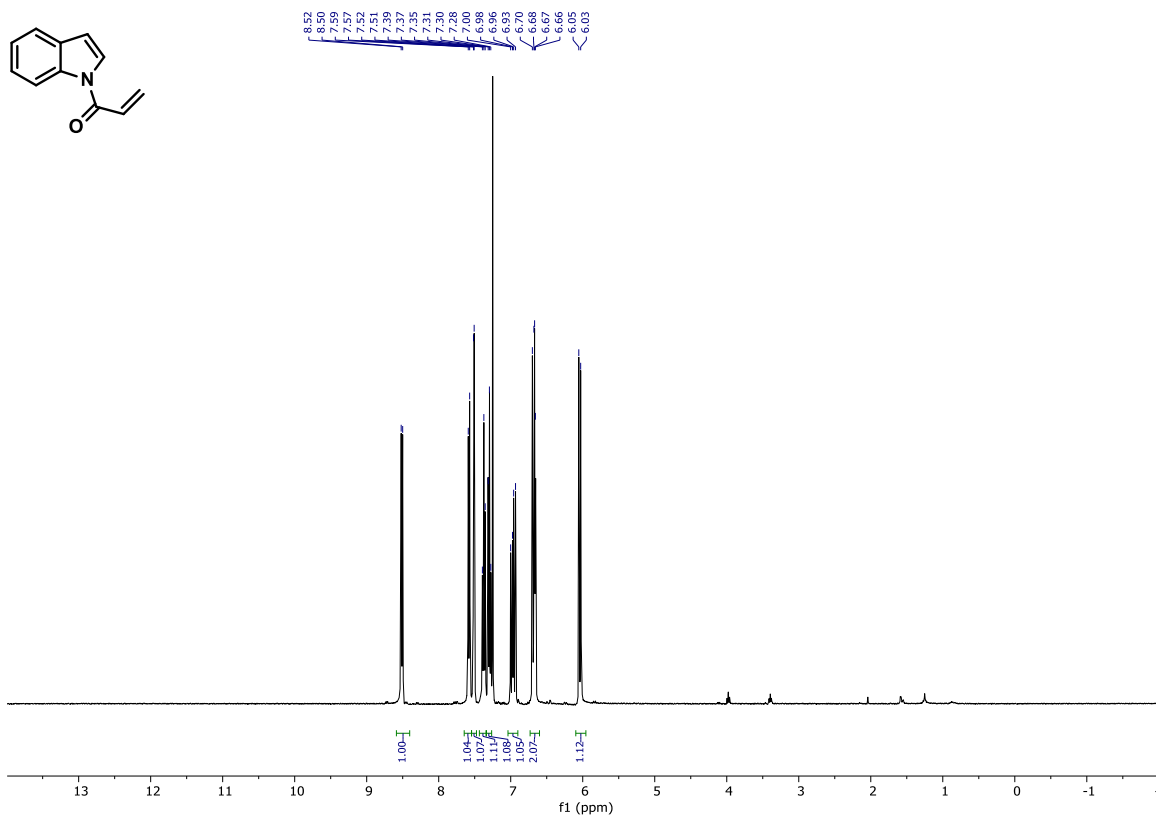
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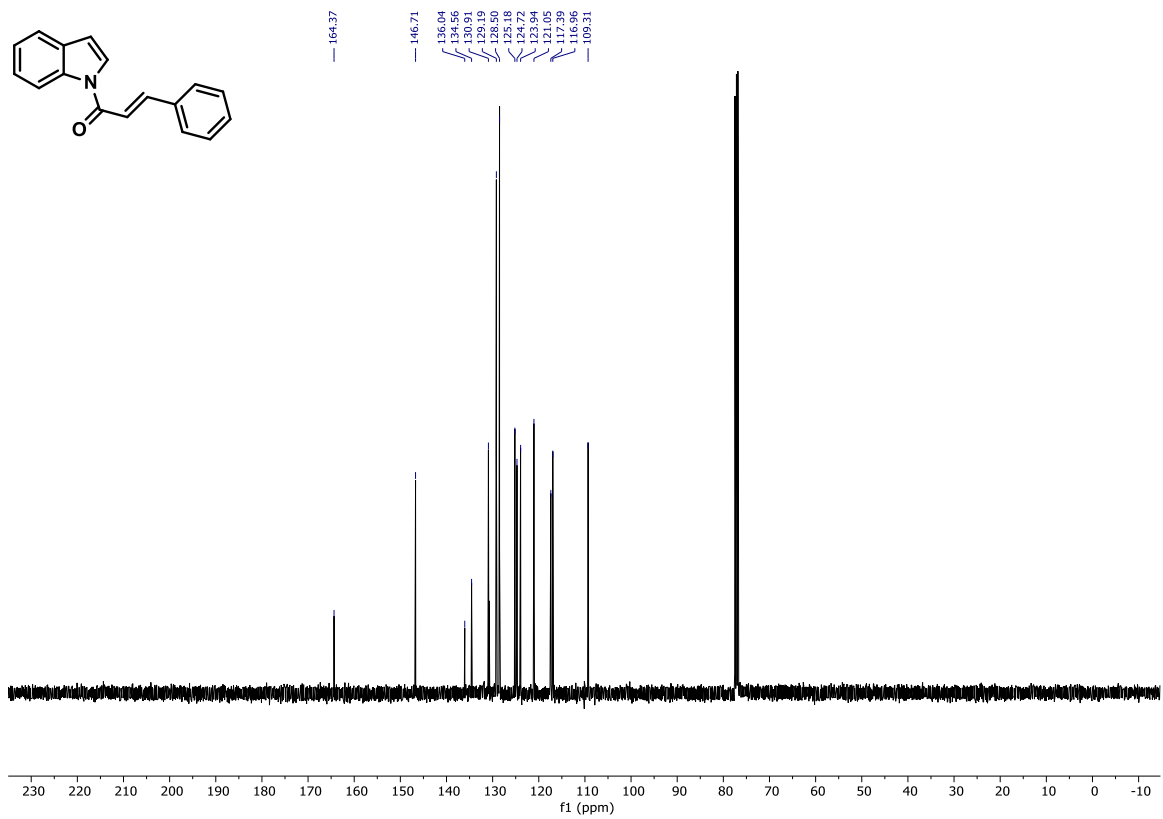
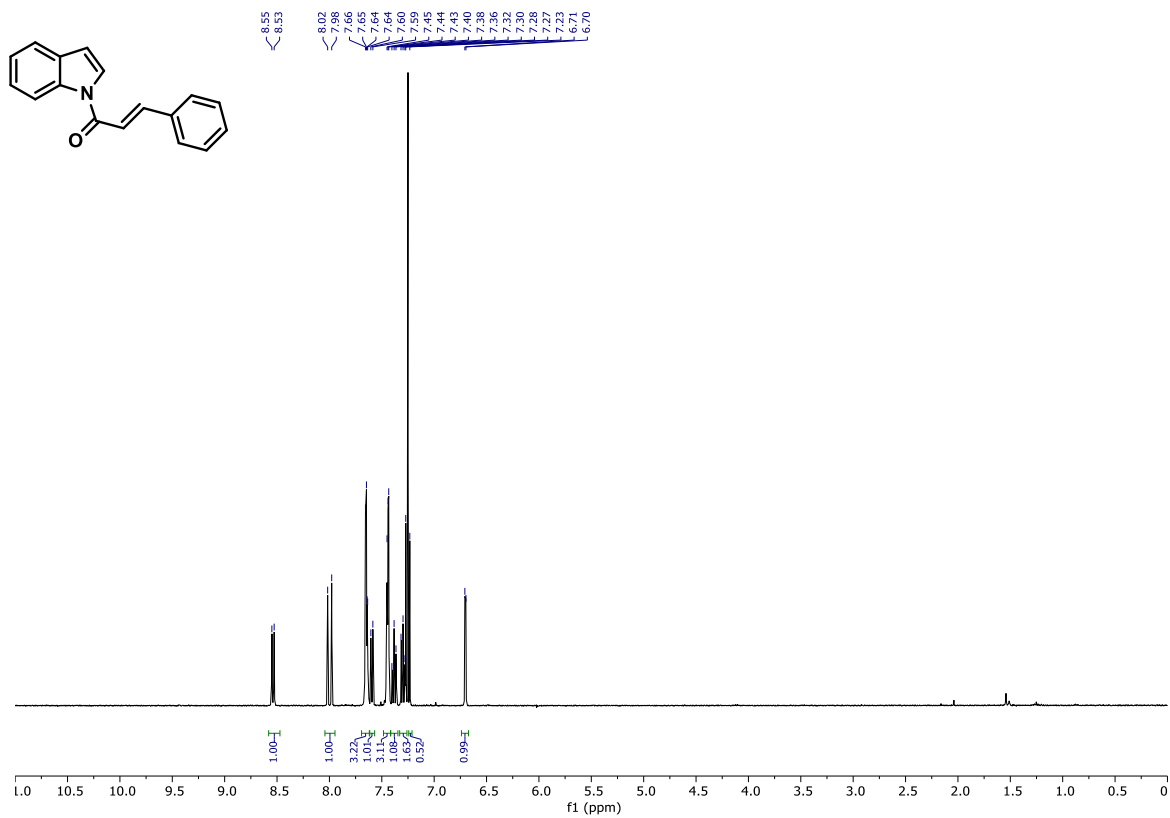


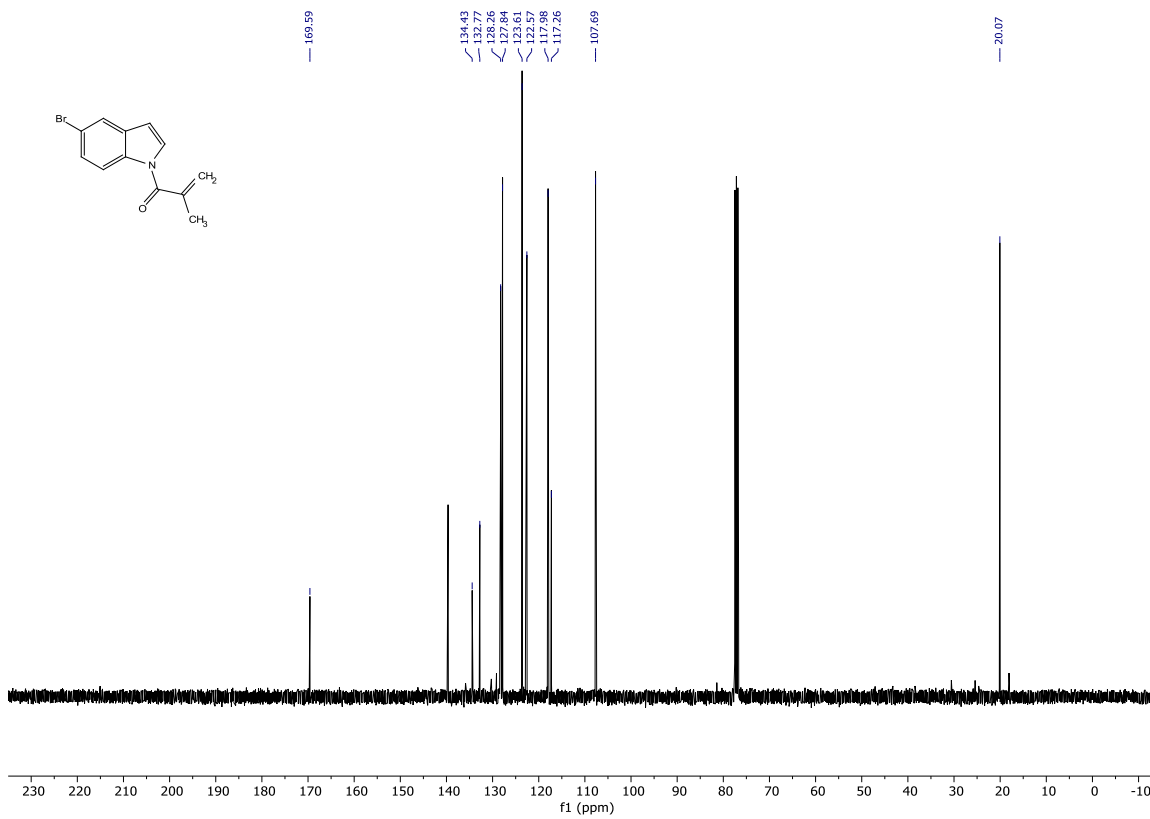
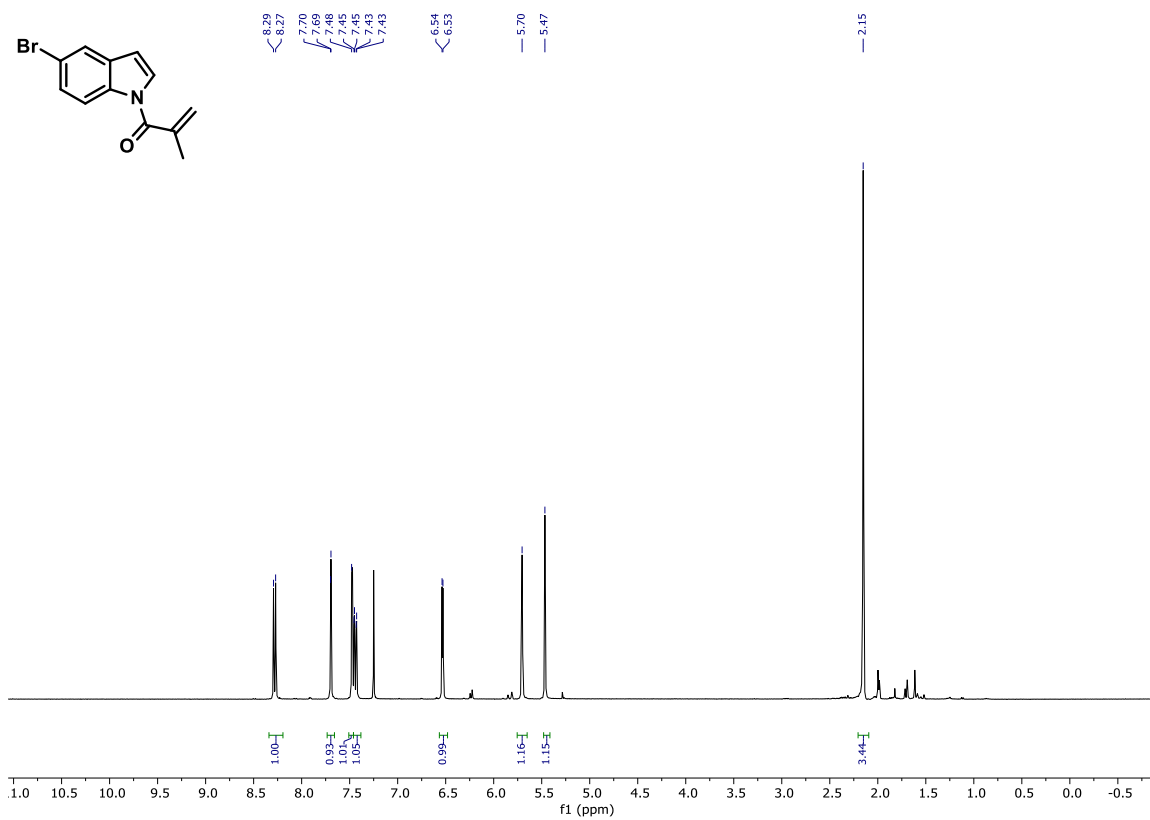


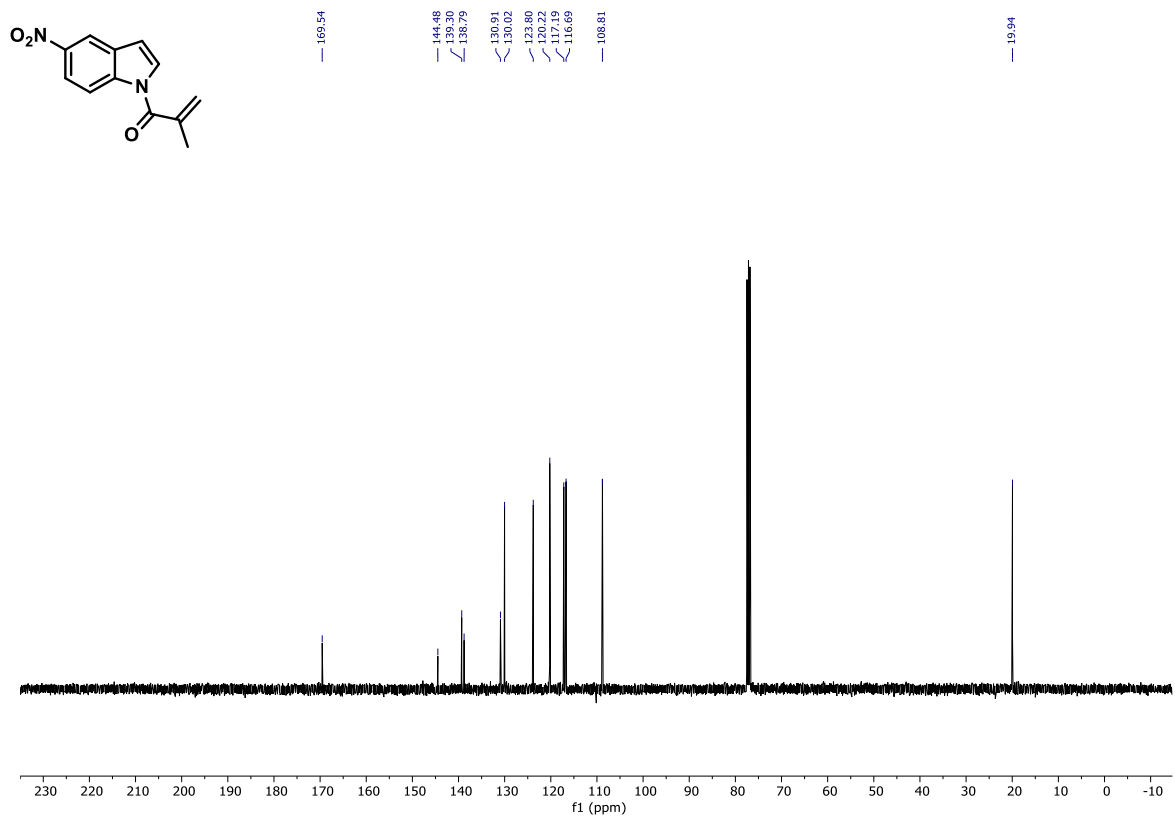
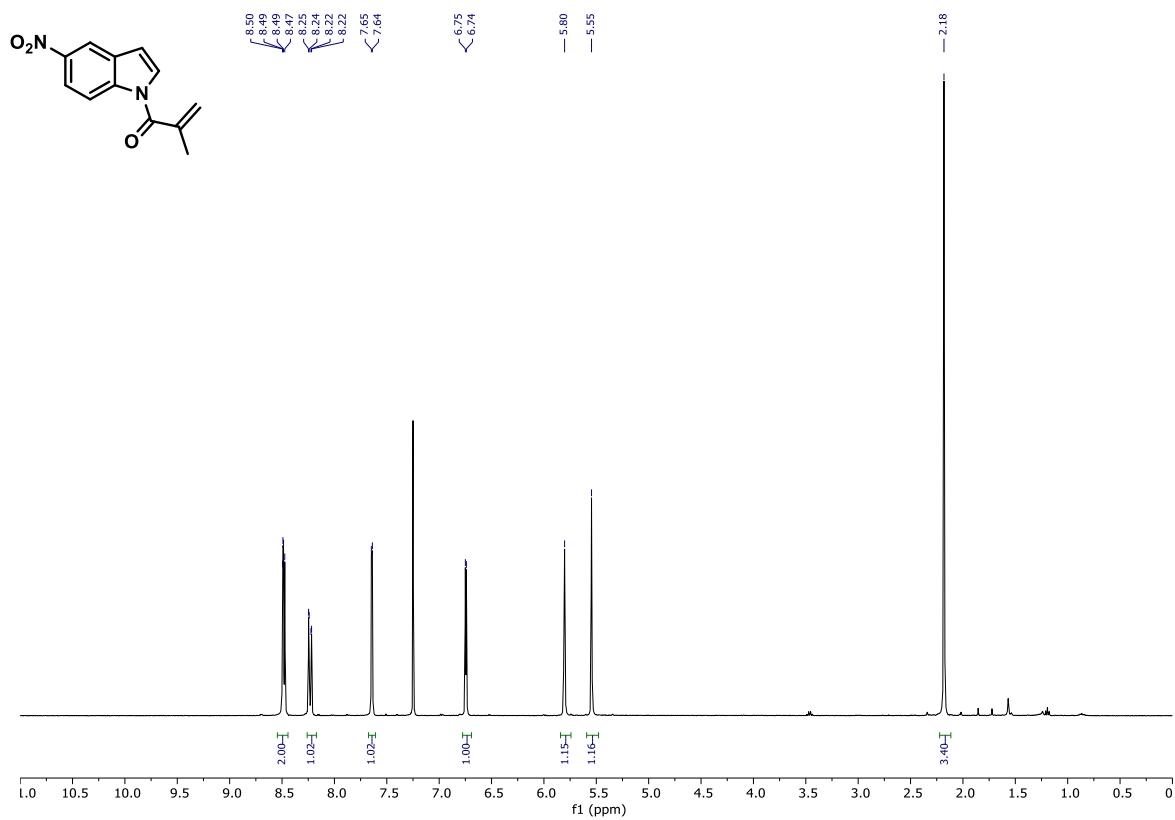
Chapter 3 ^1H and ^{13}C NMR Spectra

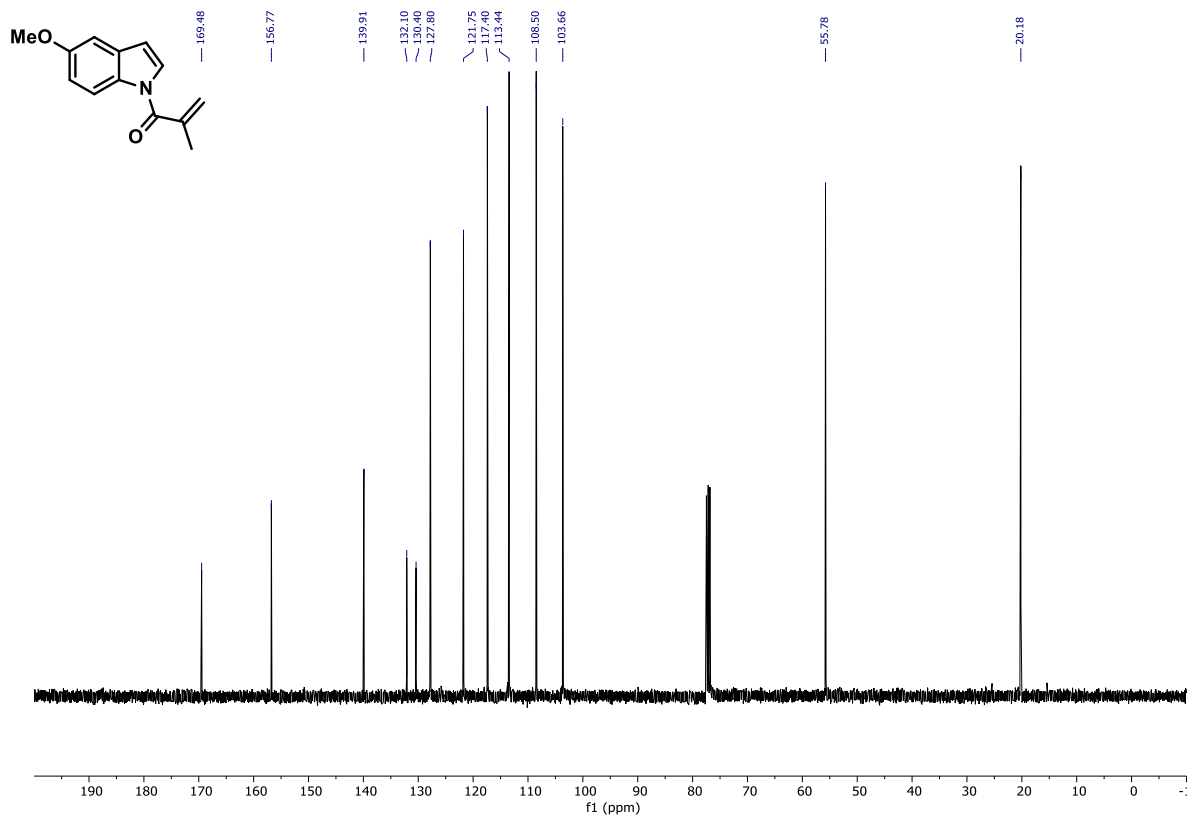
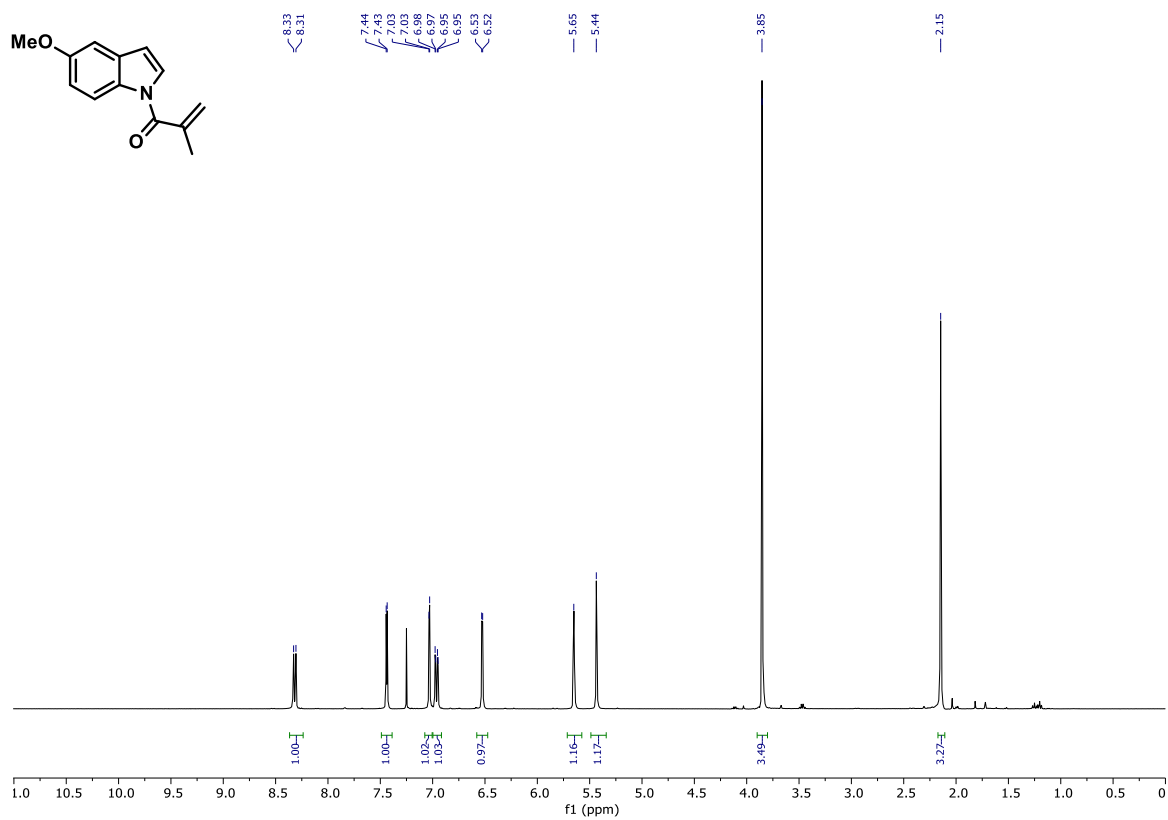


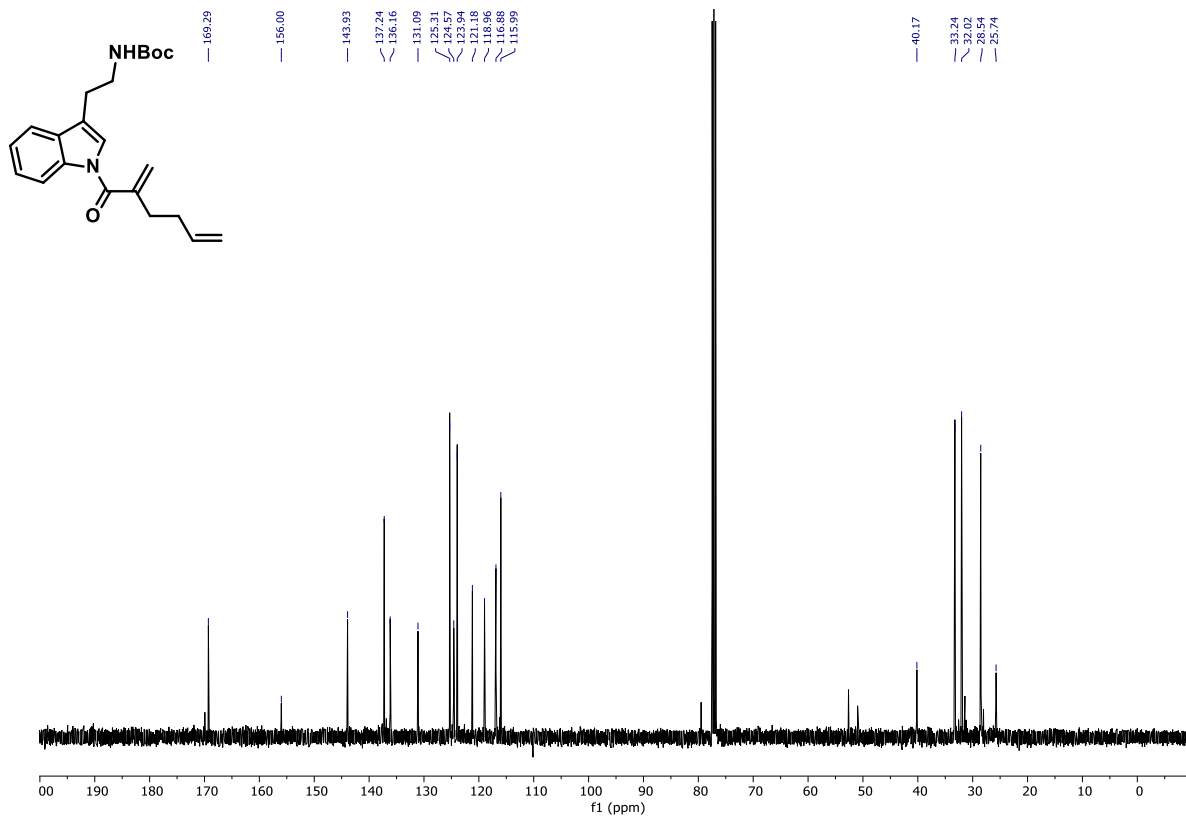
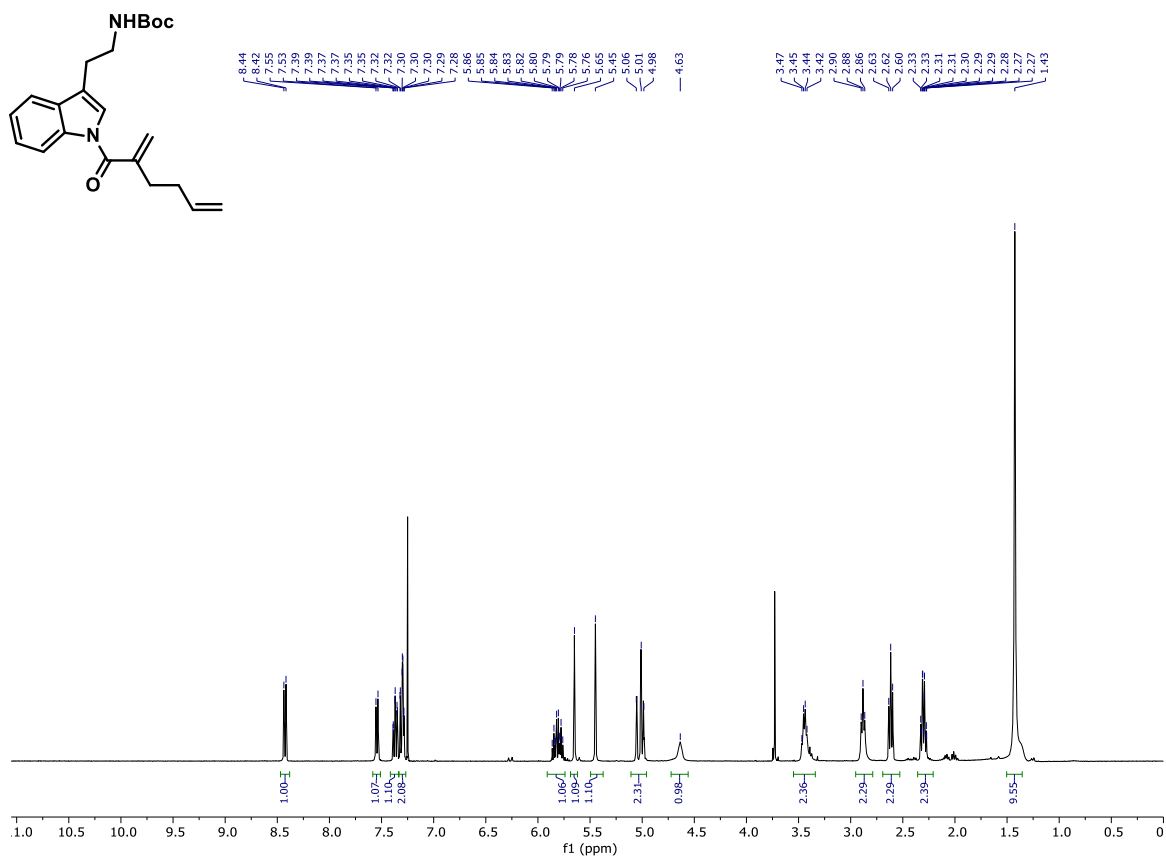


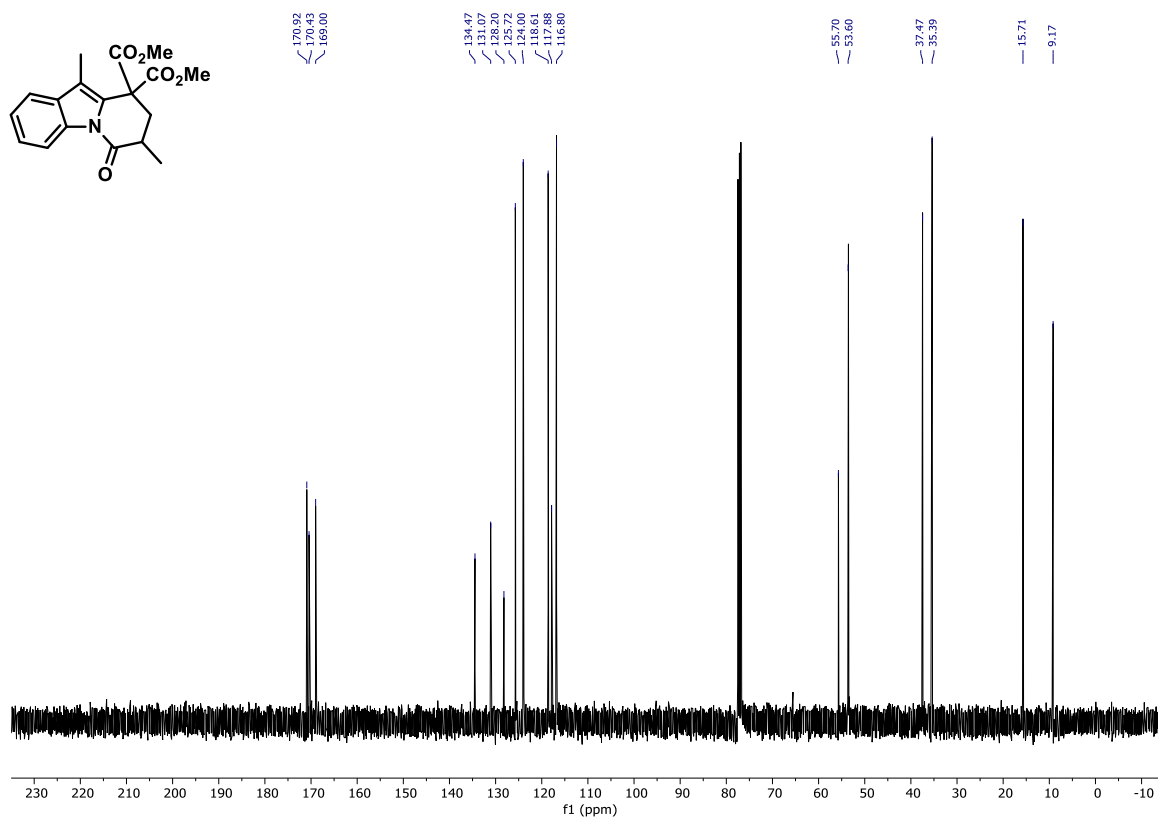
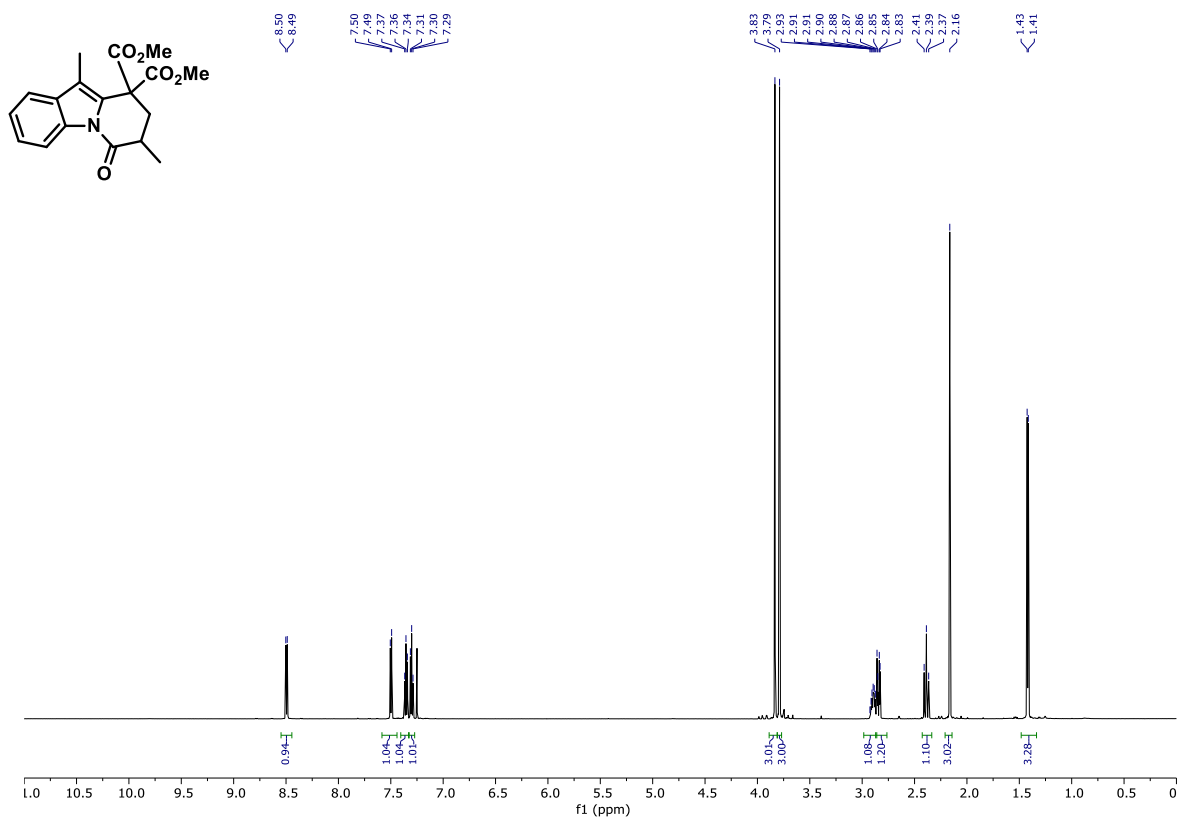


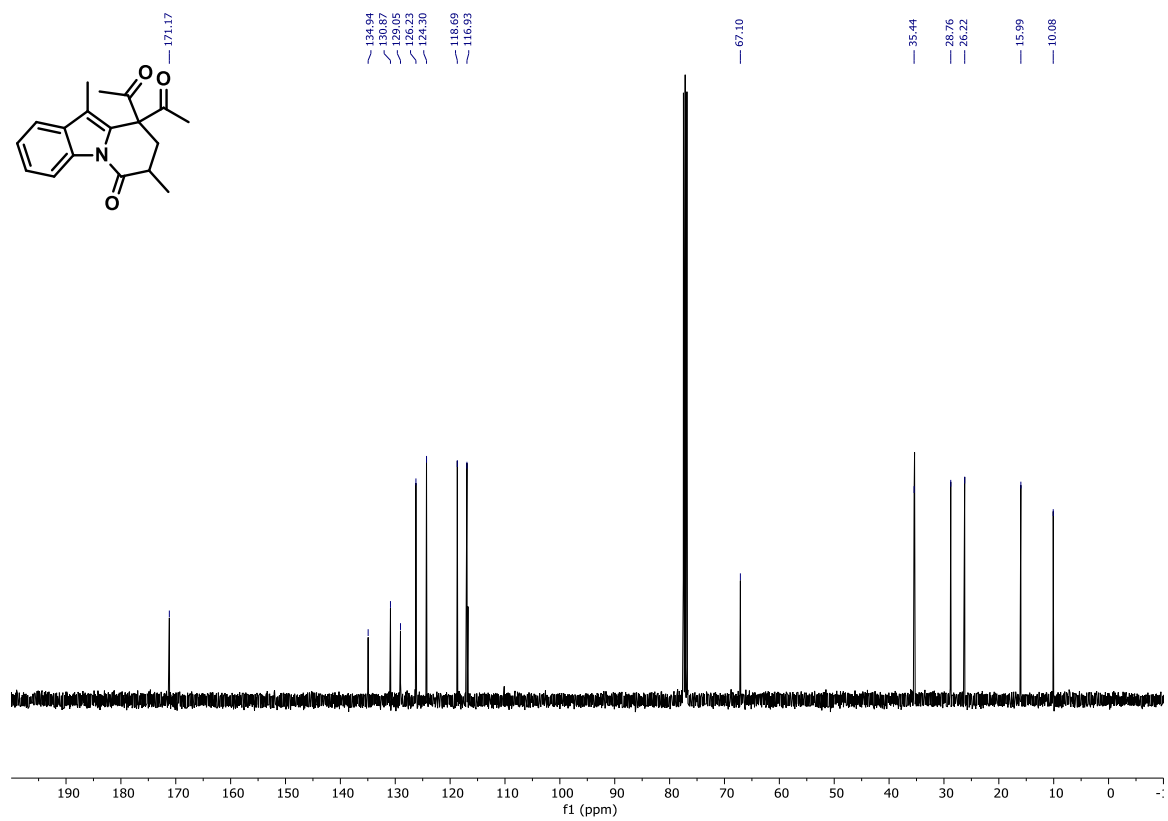
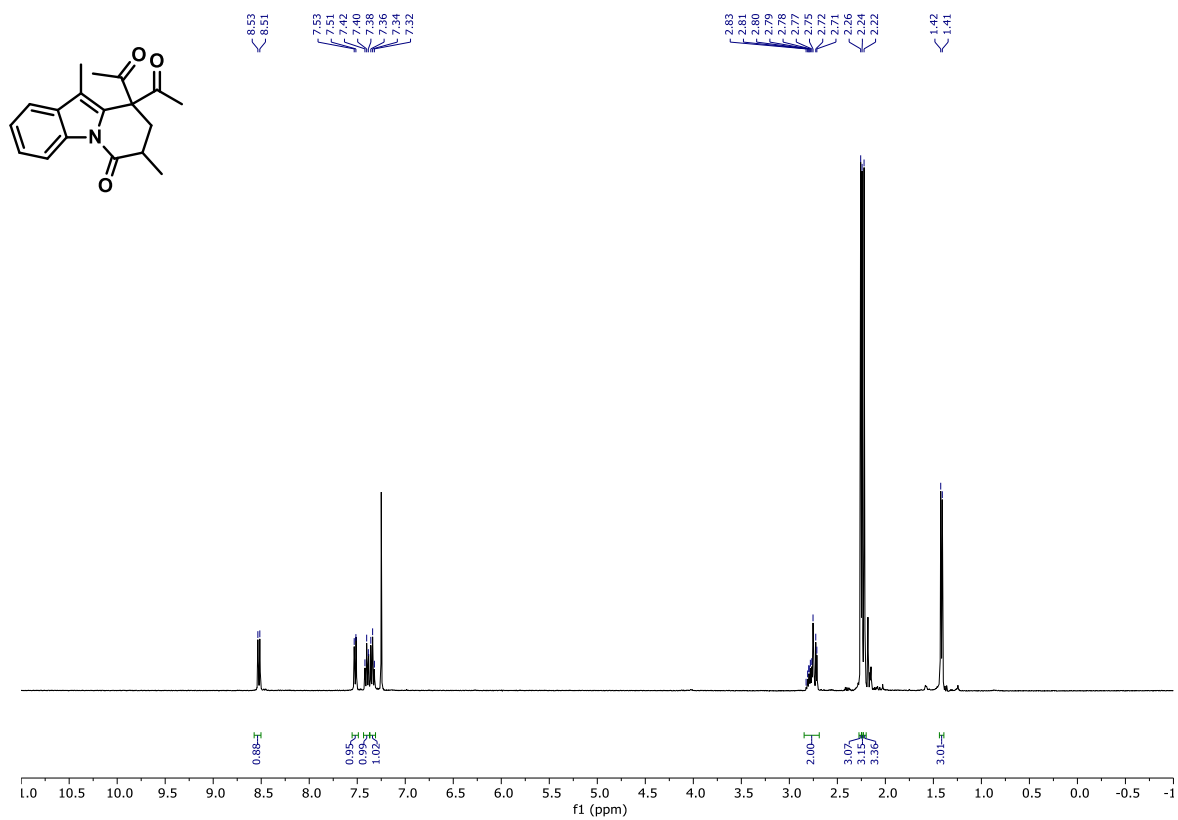


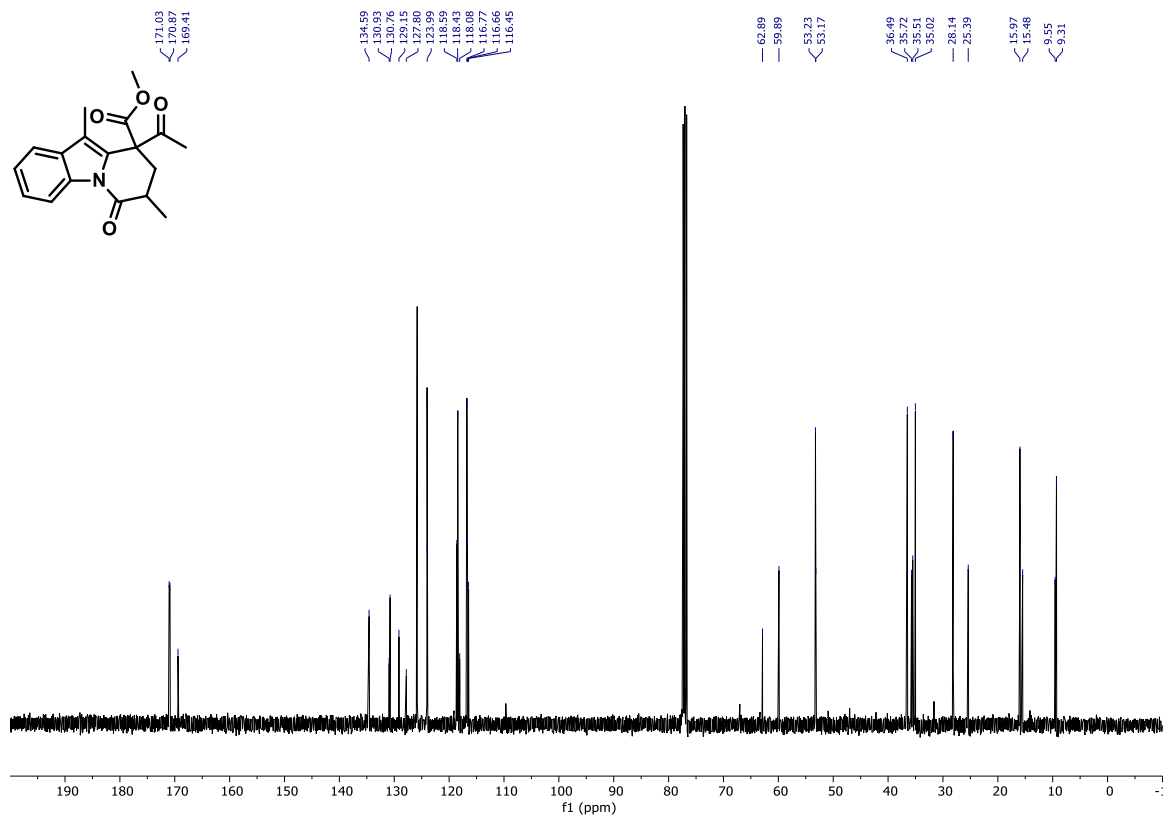
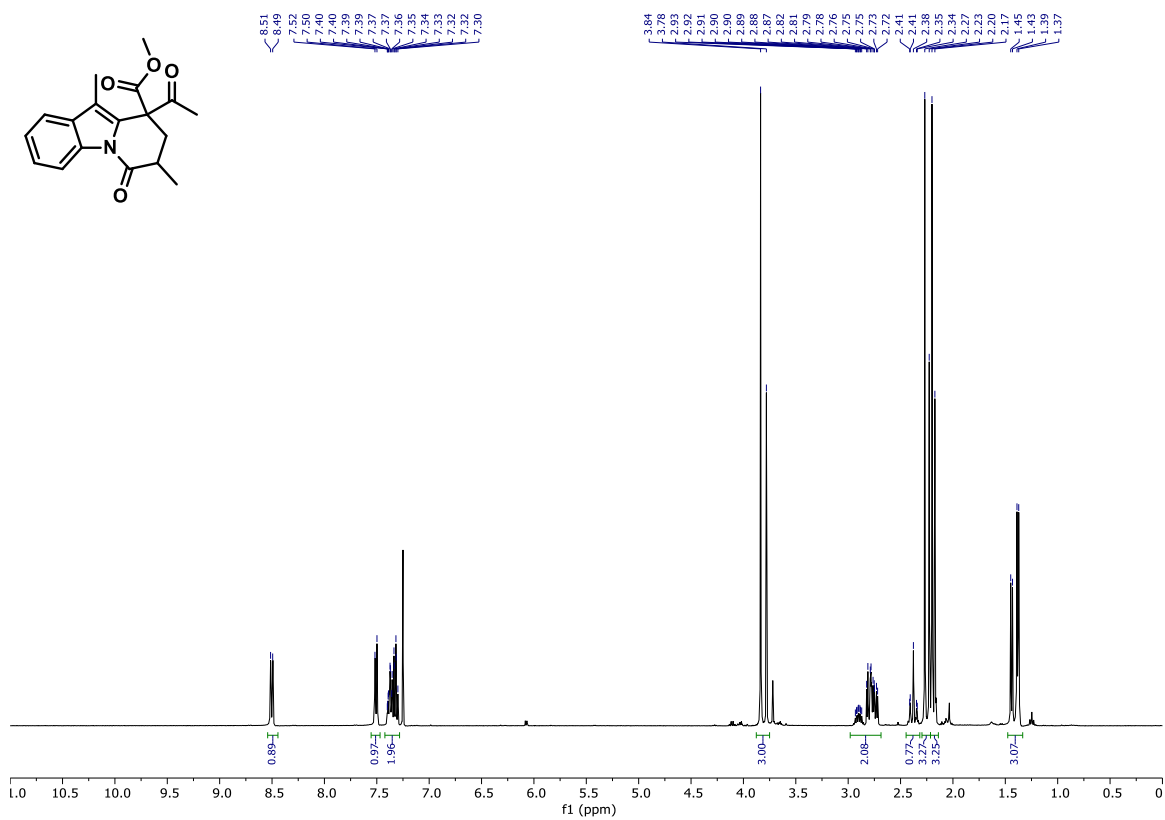


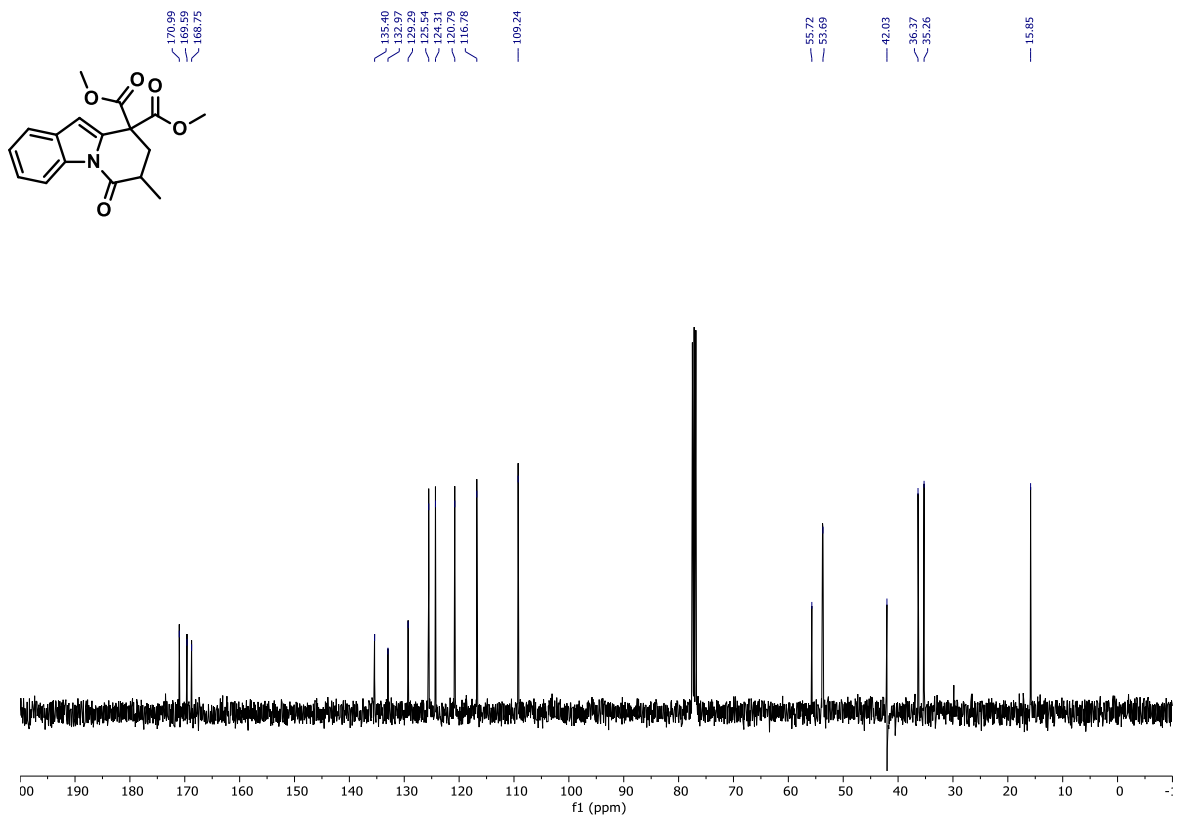
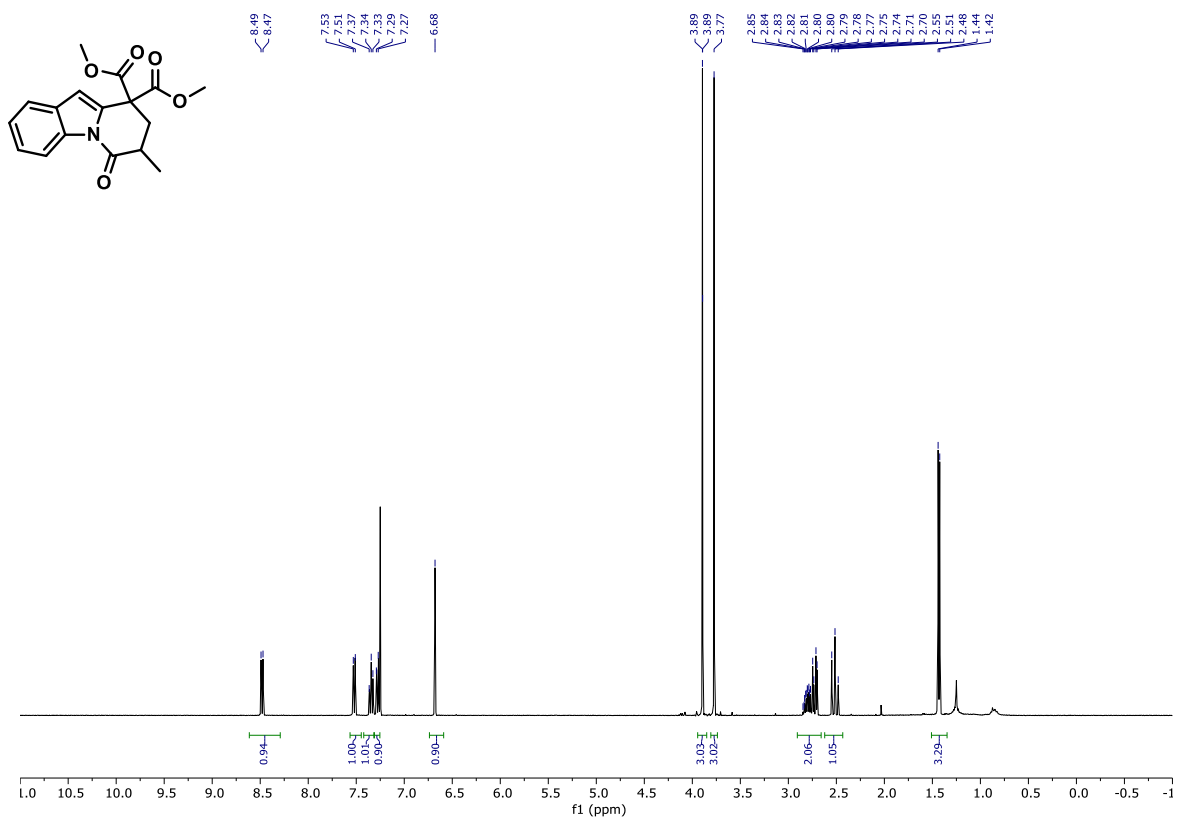


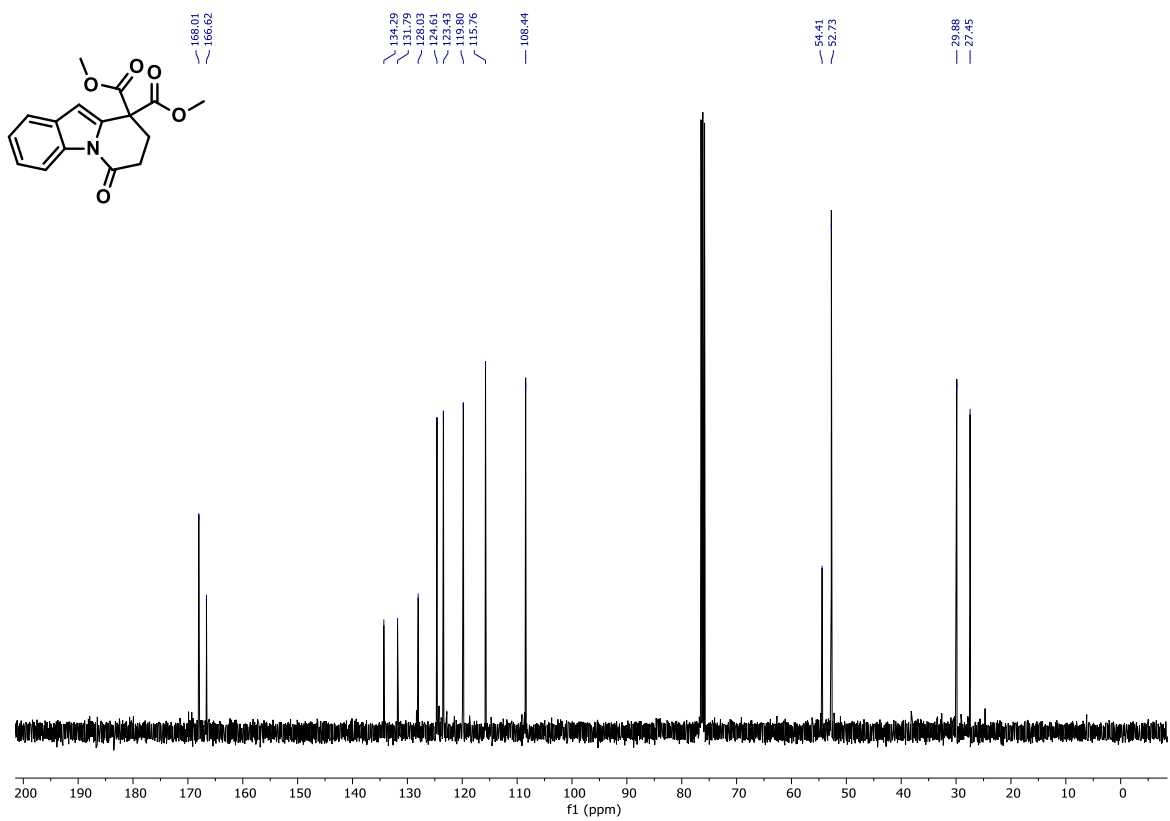
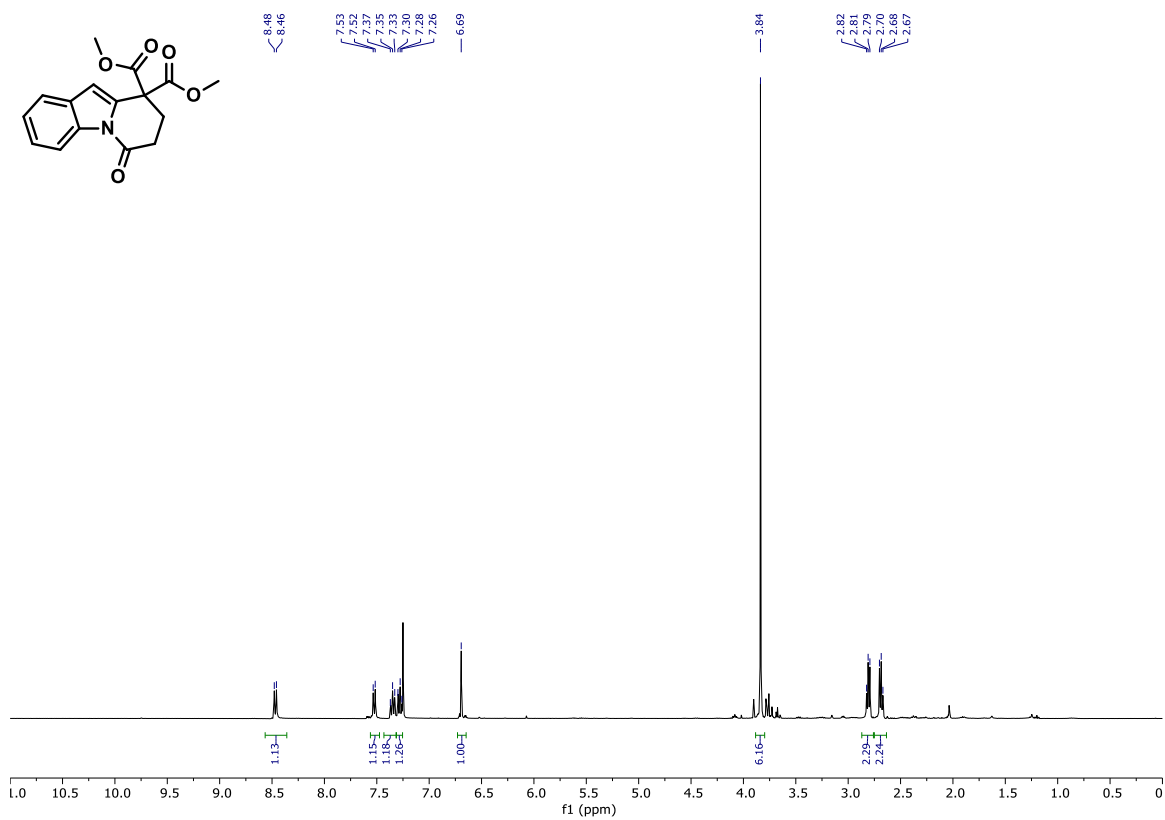


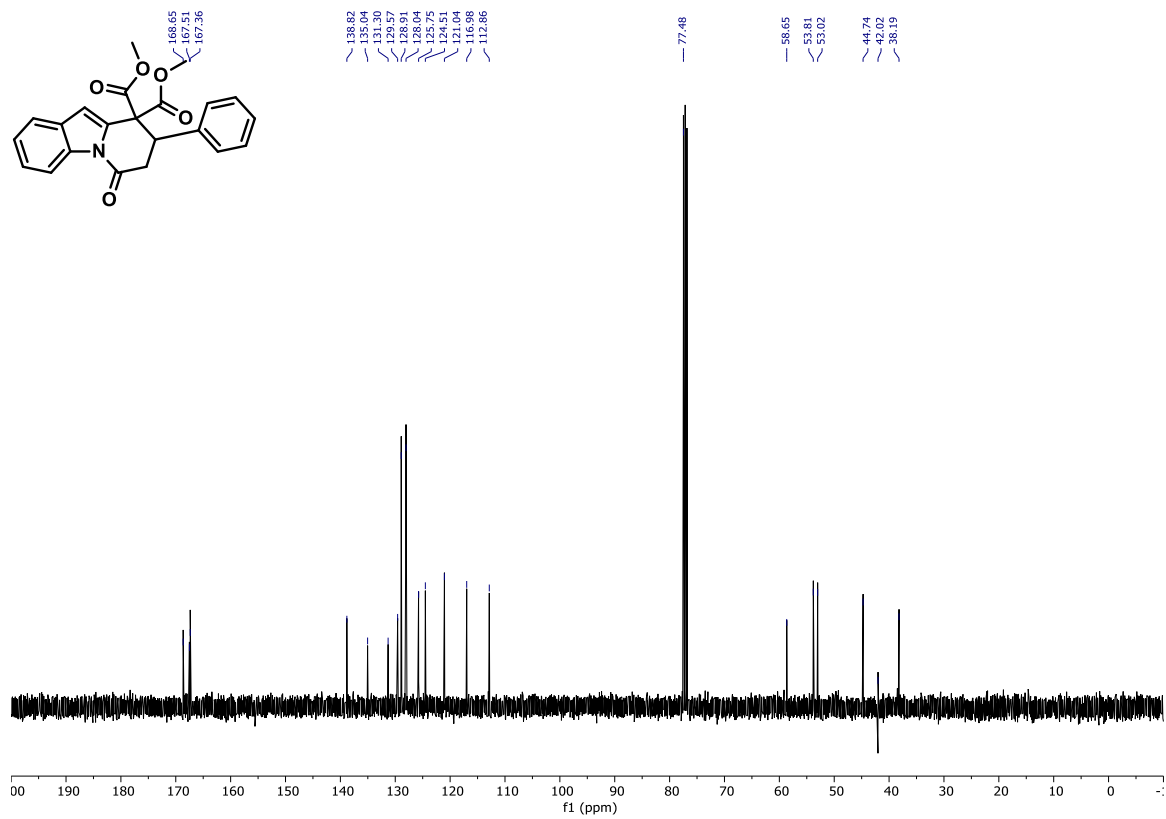
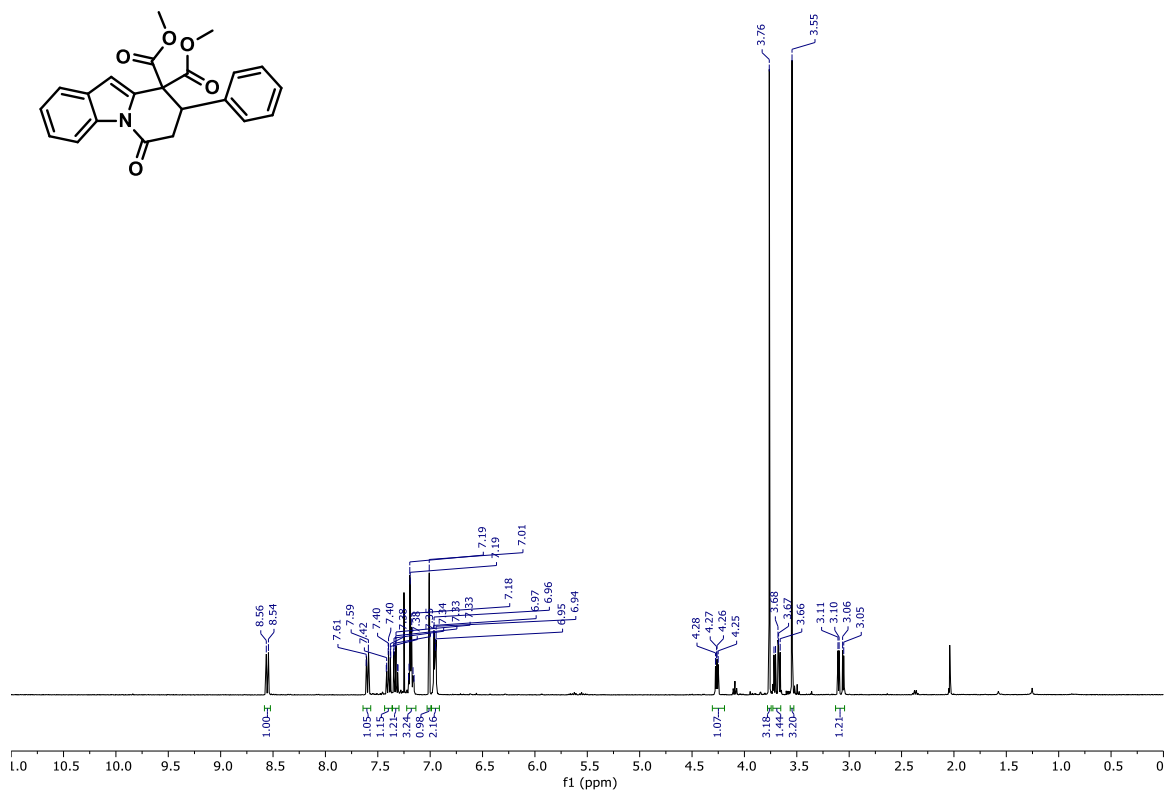


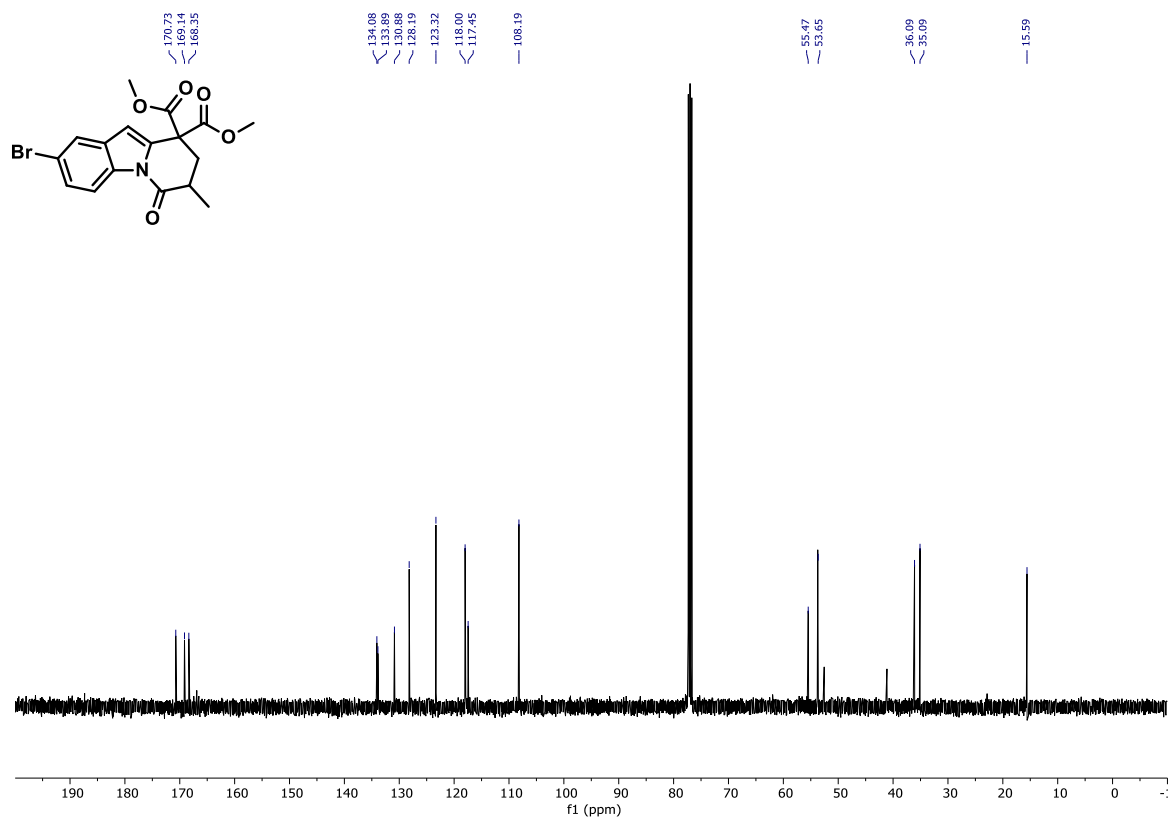
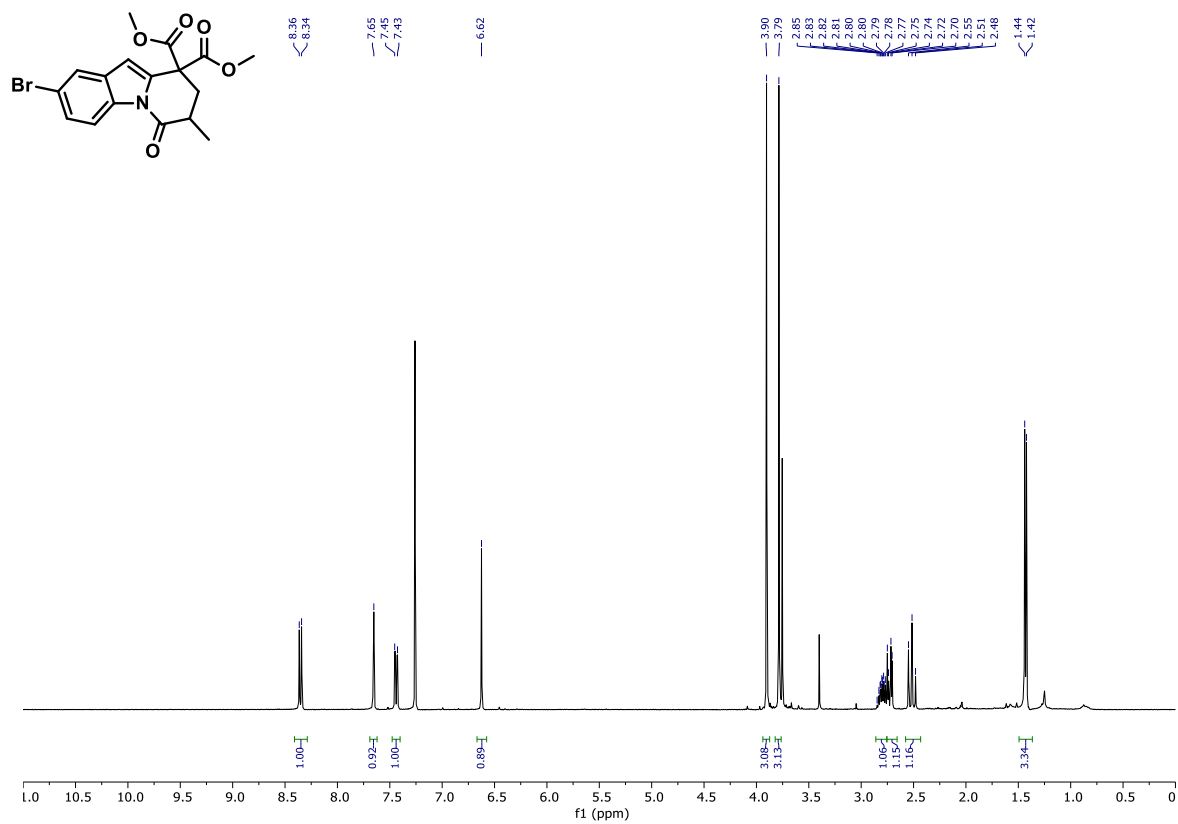


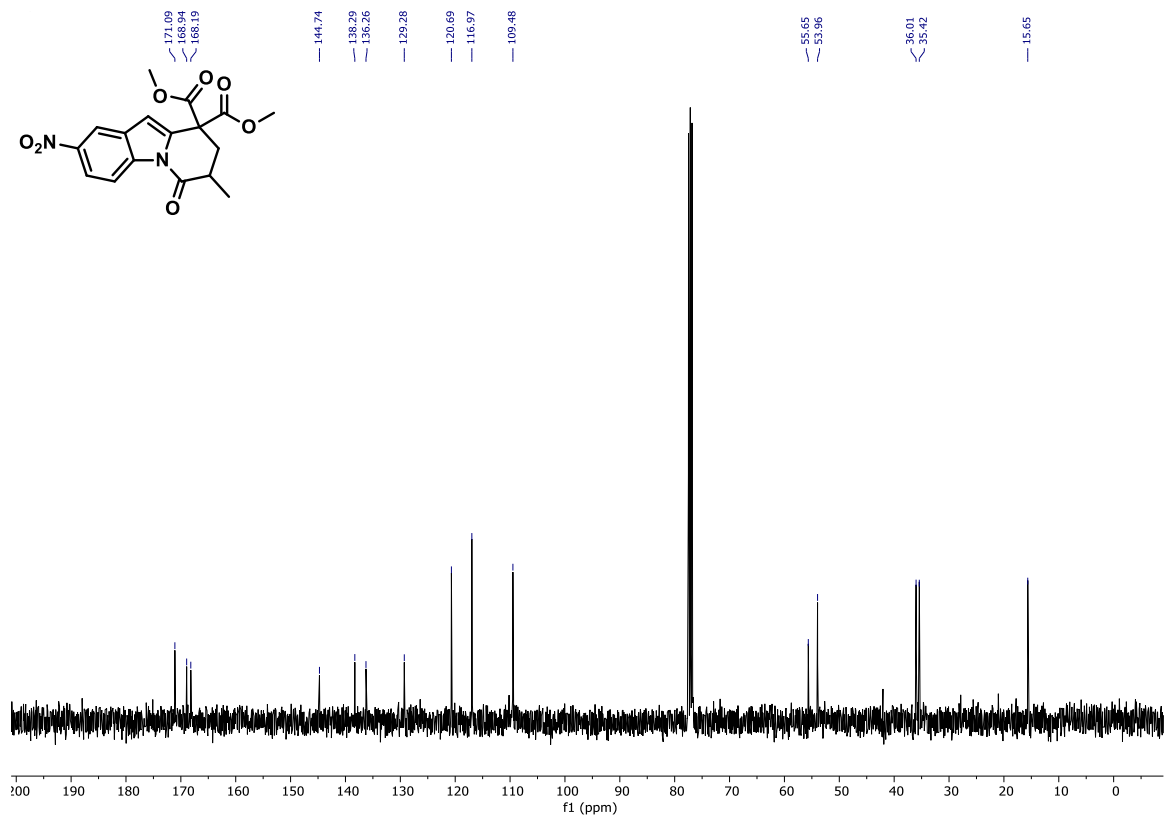
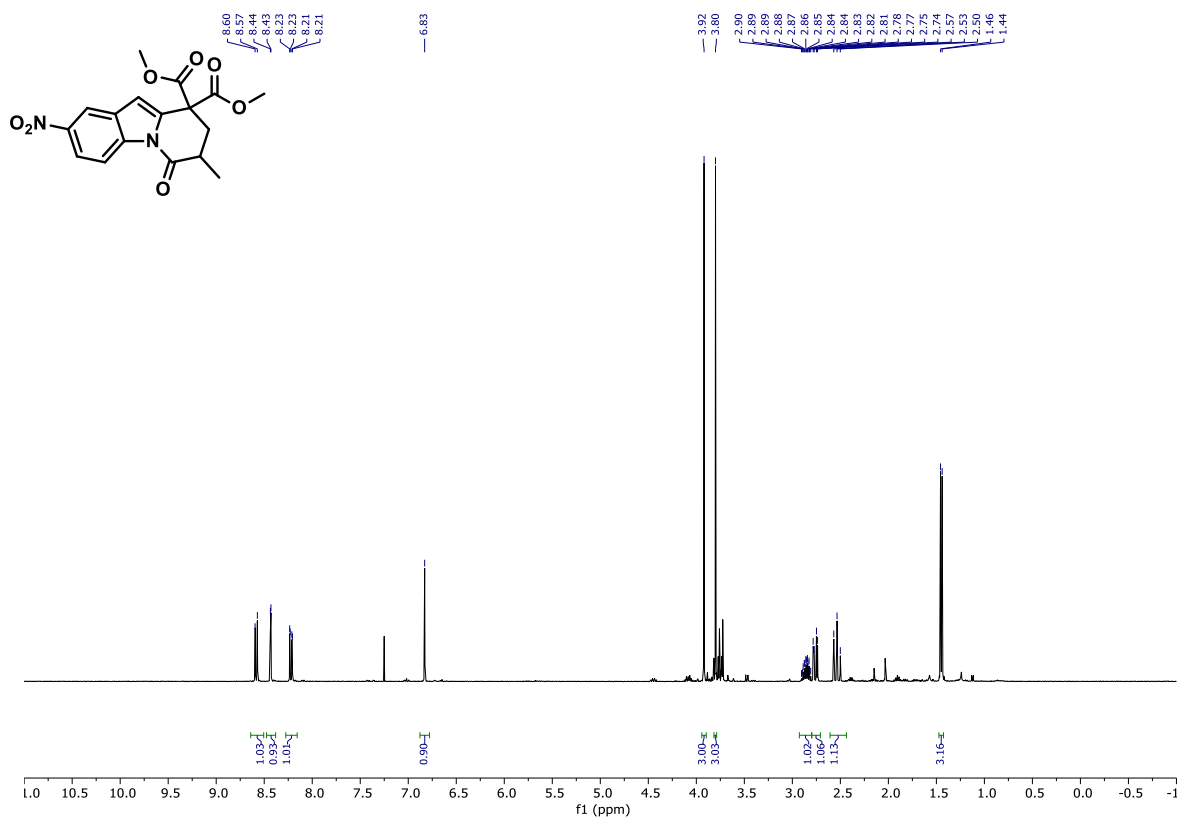


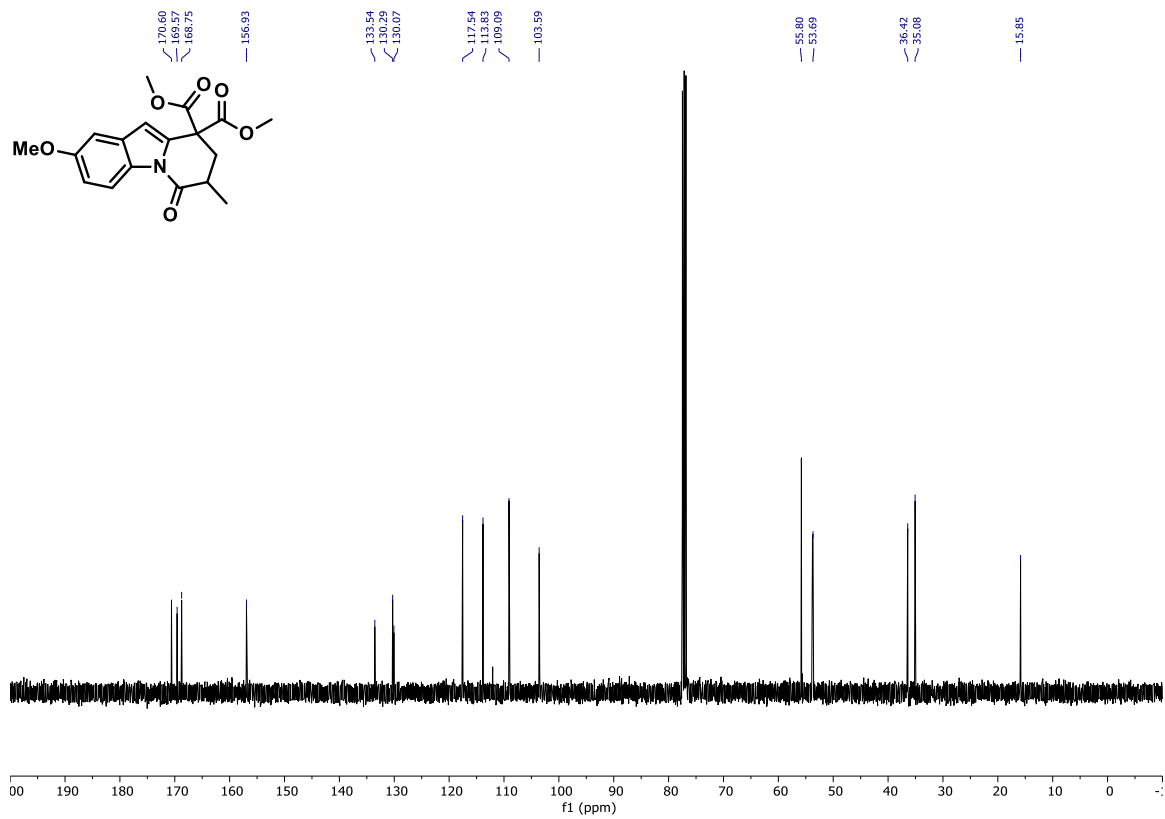
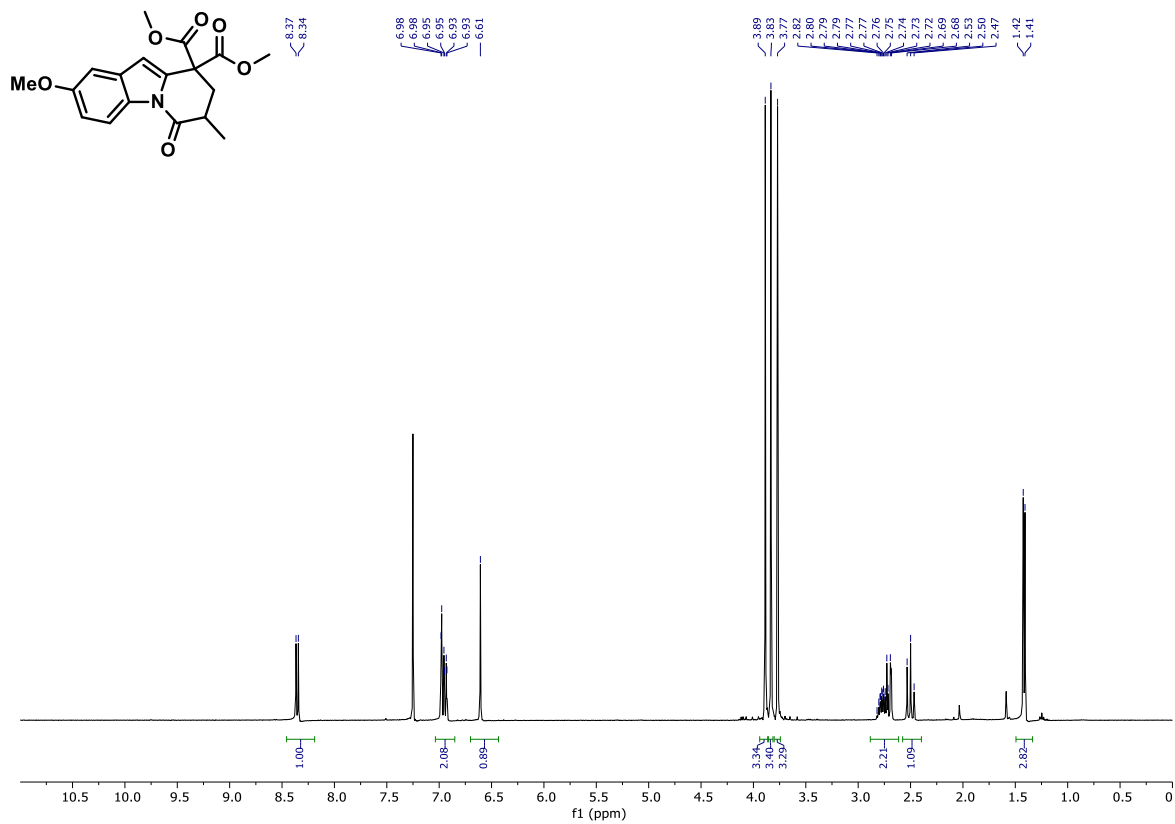


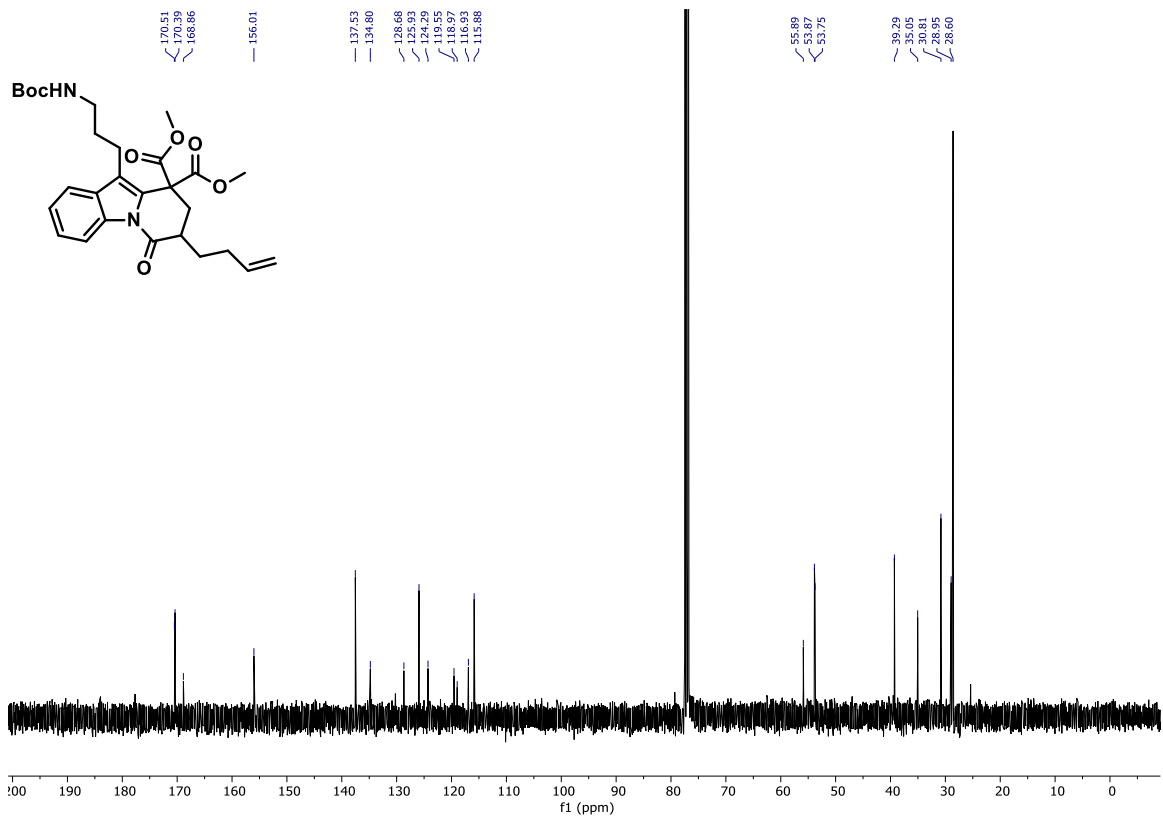
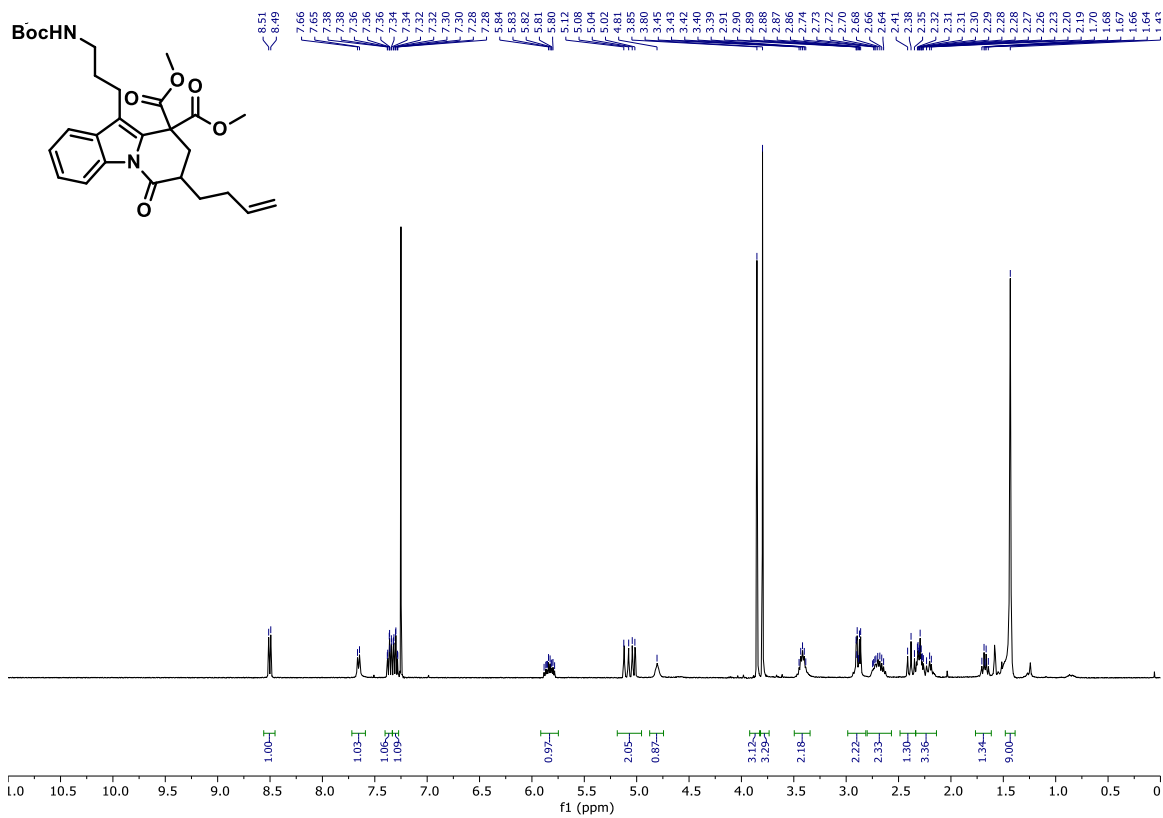


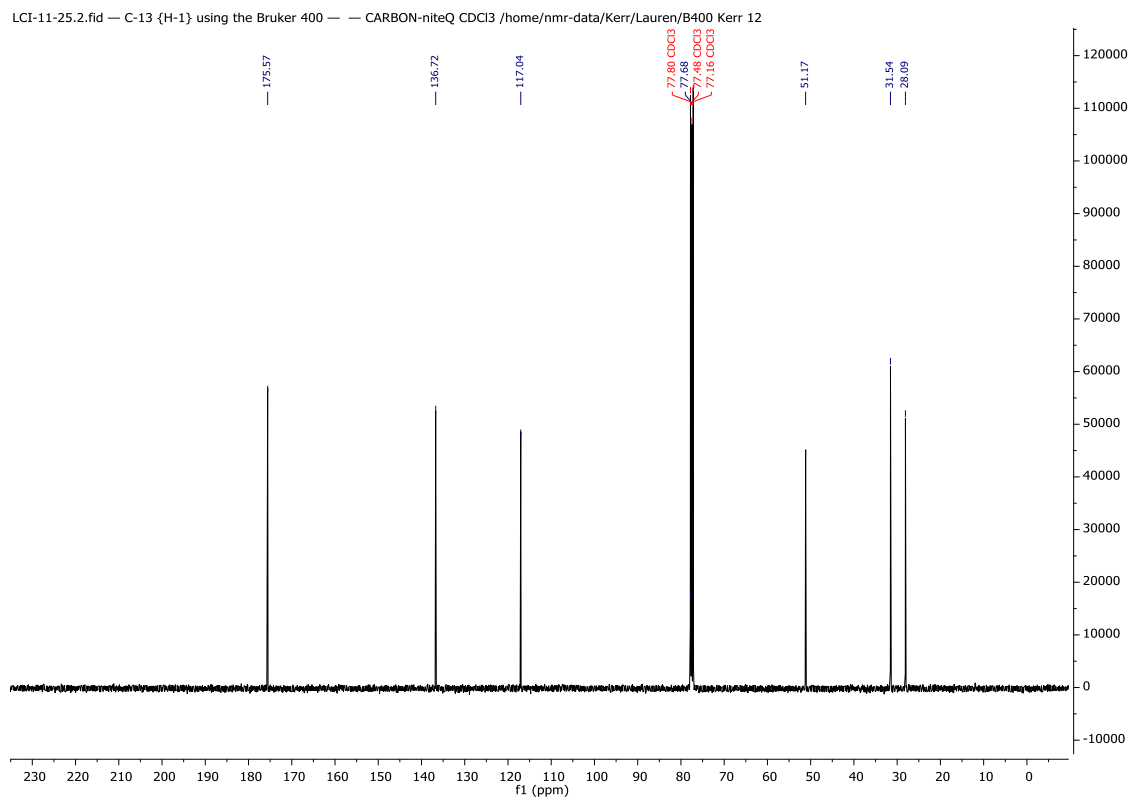
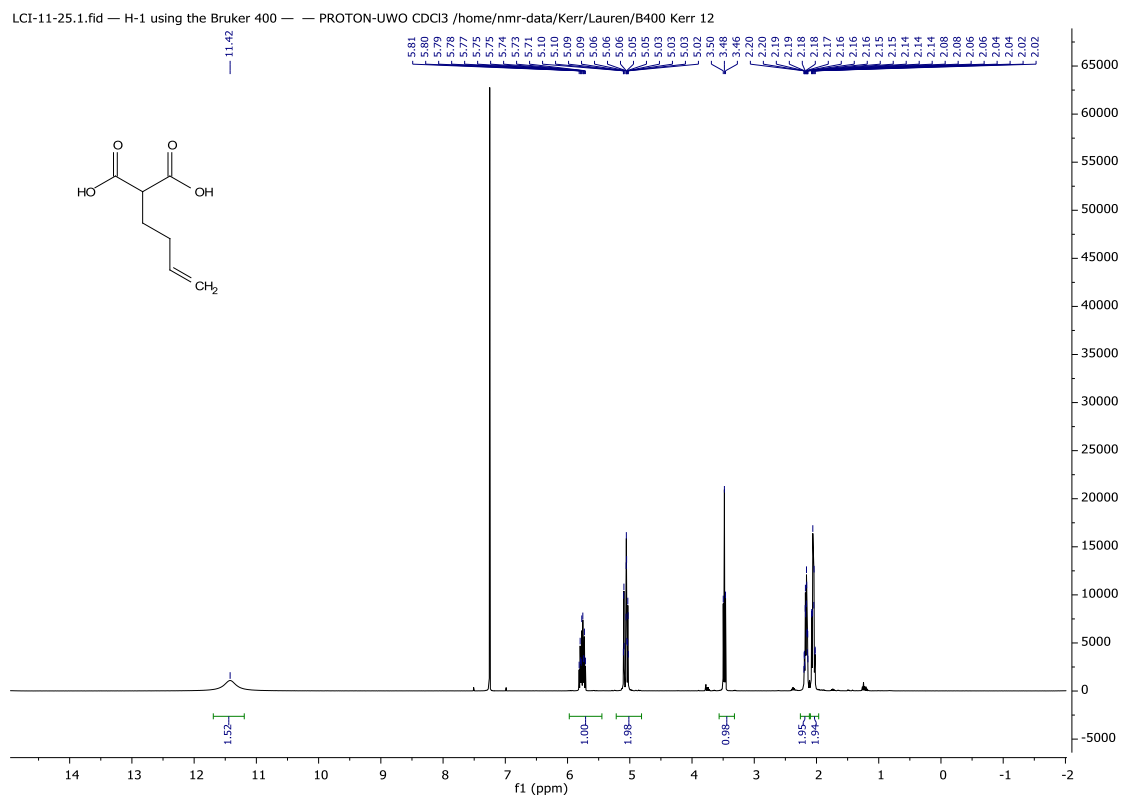




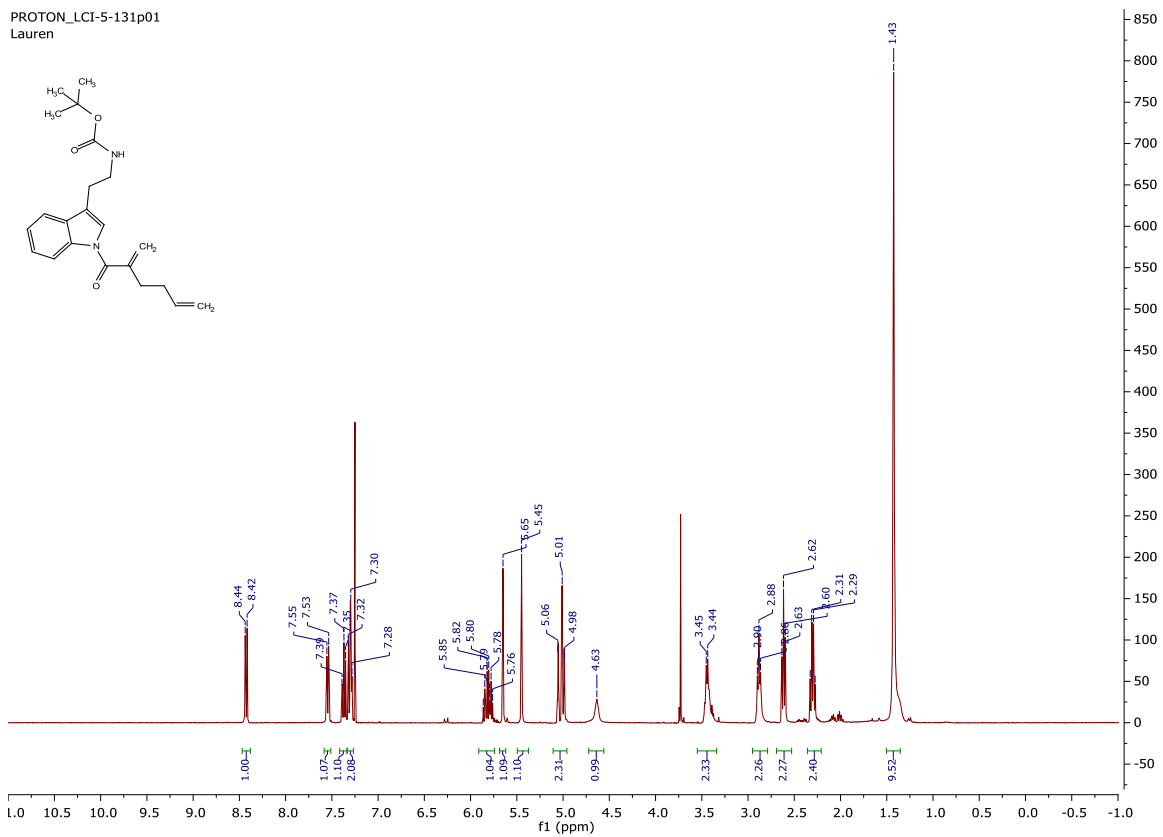




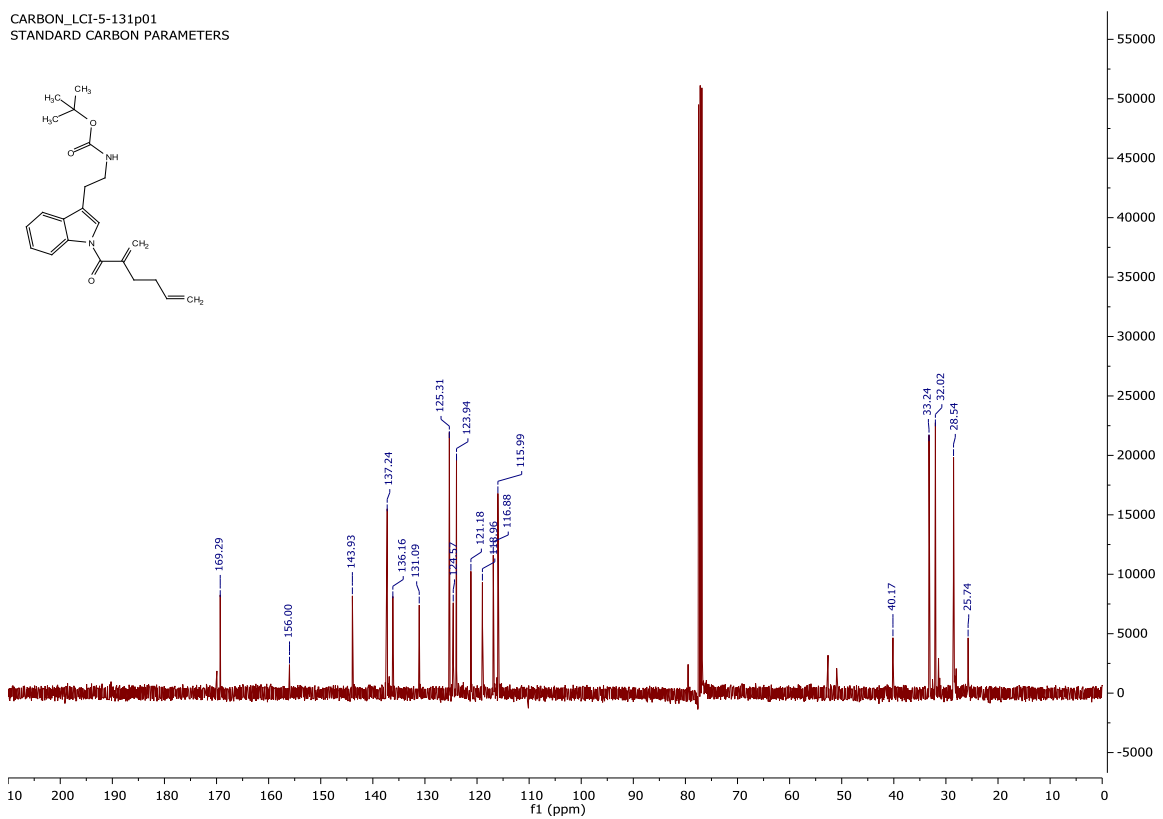


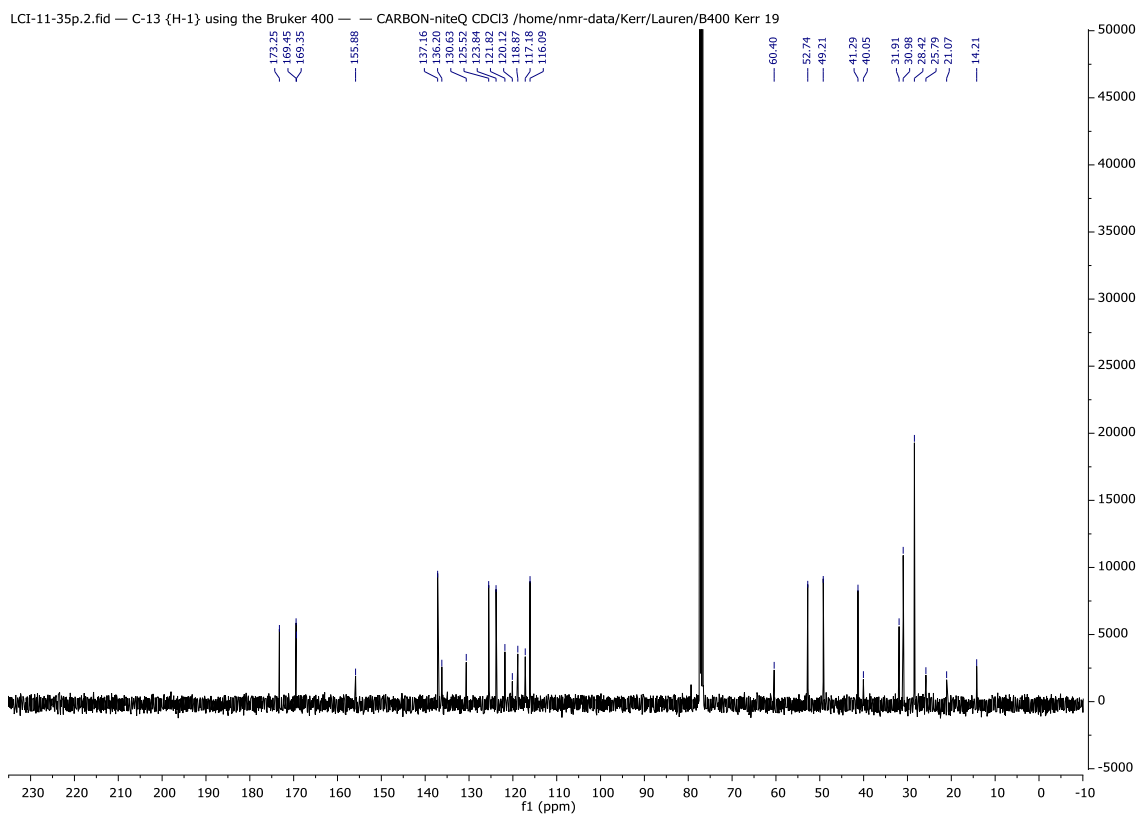
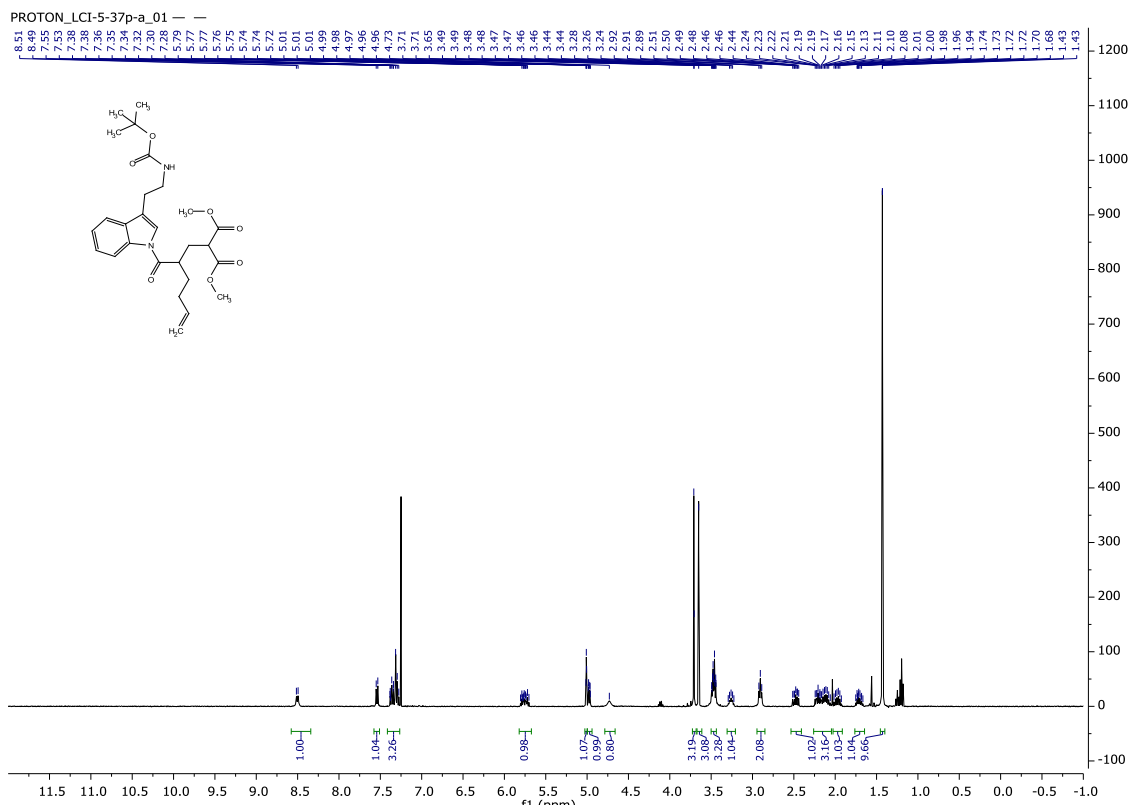
Chapter 4 ^1H and ^{13}C NMR Spectra

PROTON_LCI-5-131p01
Lauren

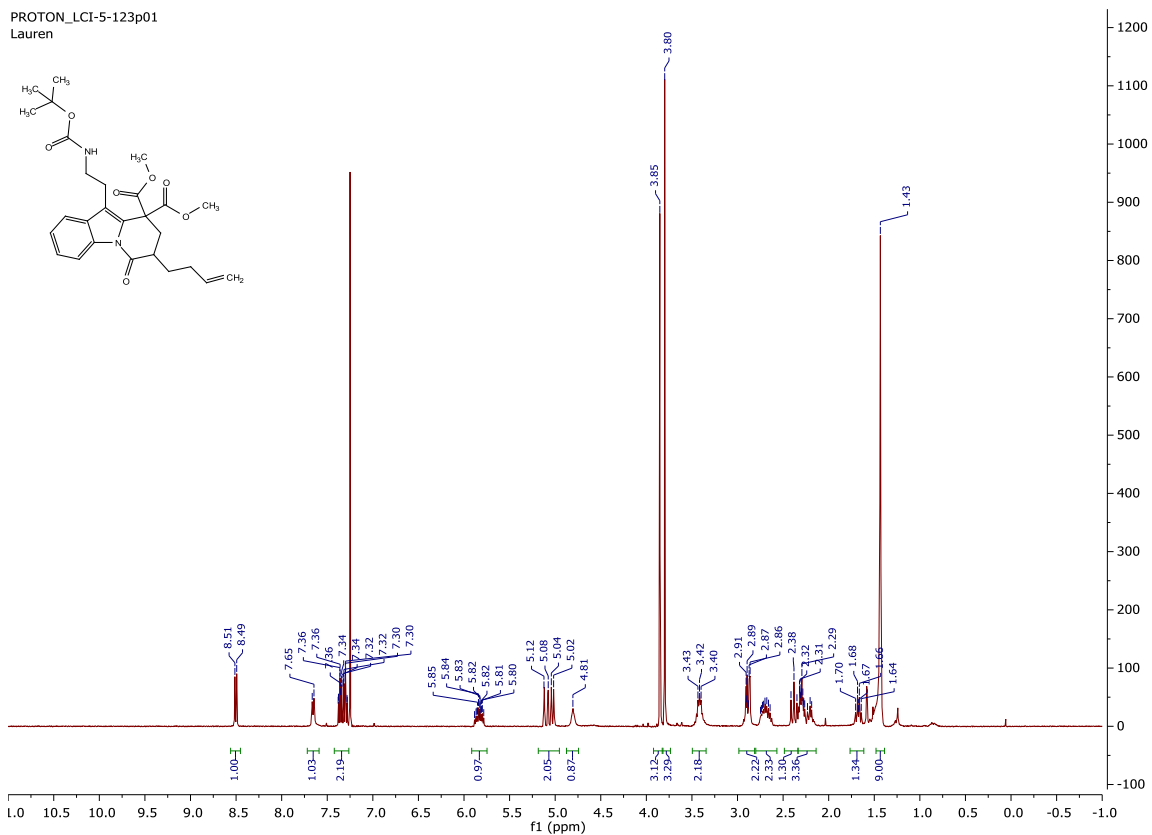


CARBON_LCI-5-131p01
STANDARD CARBON PARAMETERS

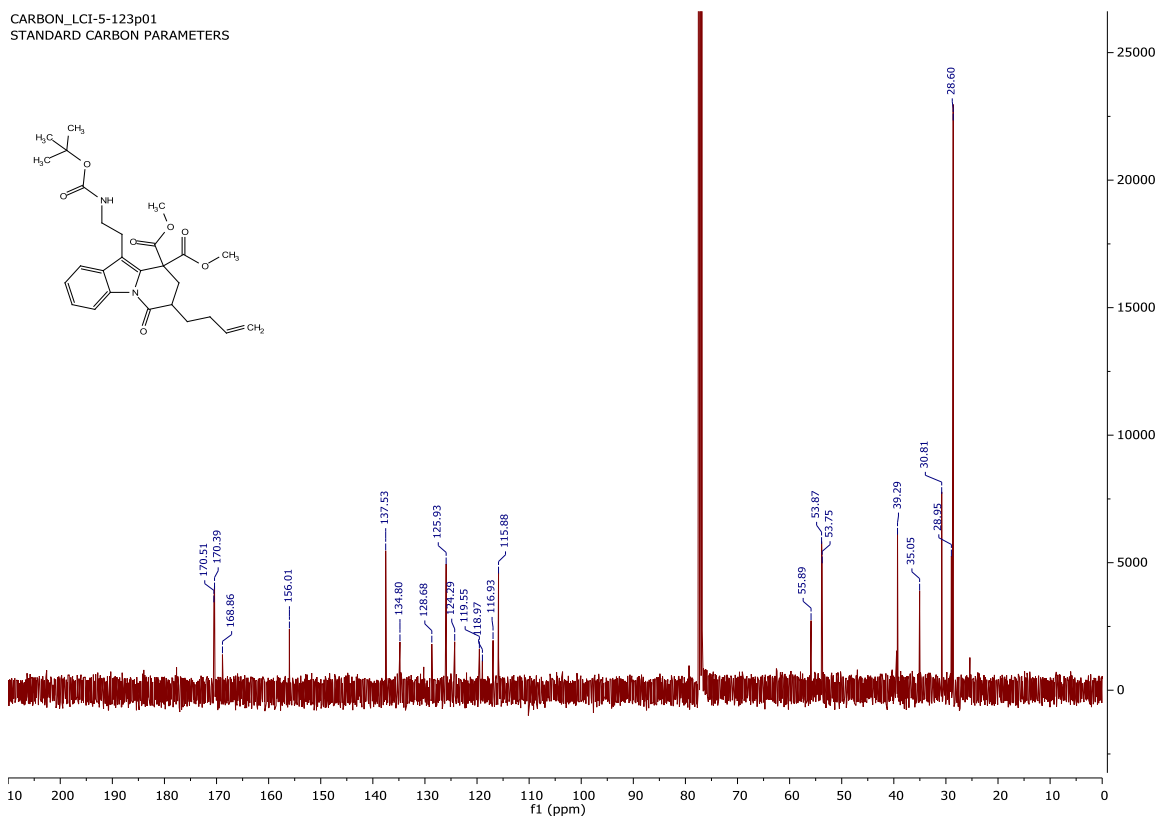




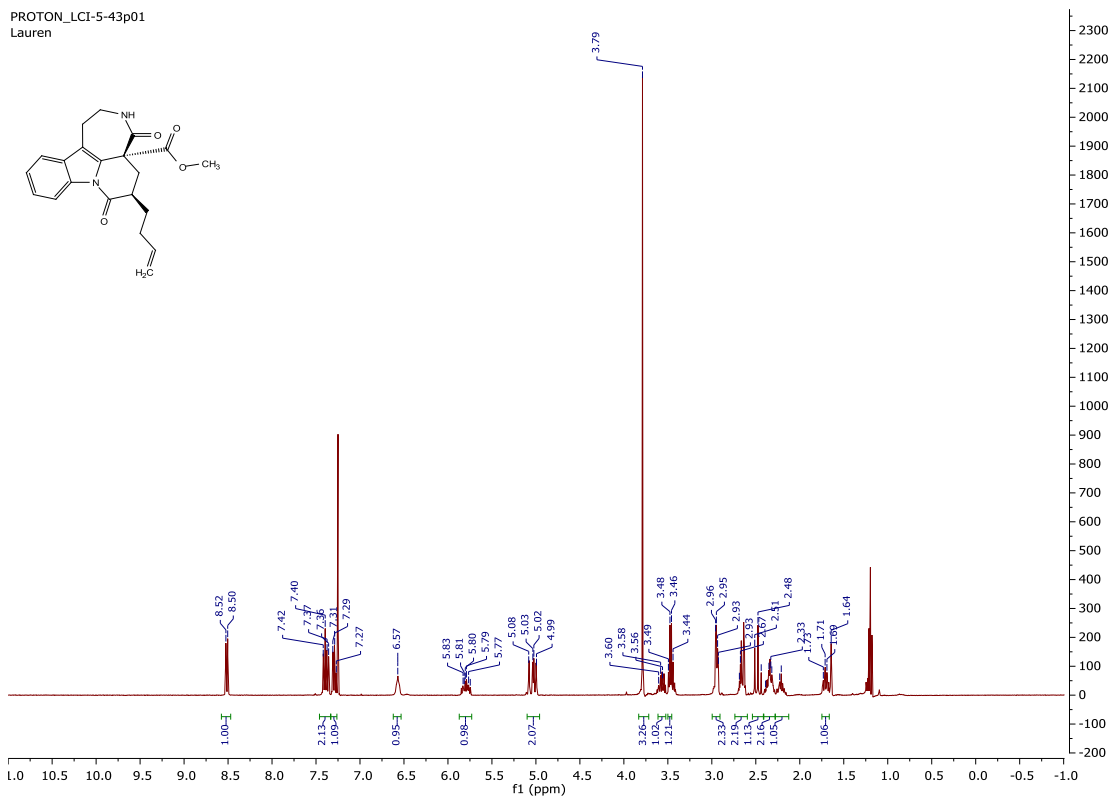
PROTON_LCI-5-123p01
Lauren



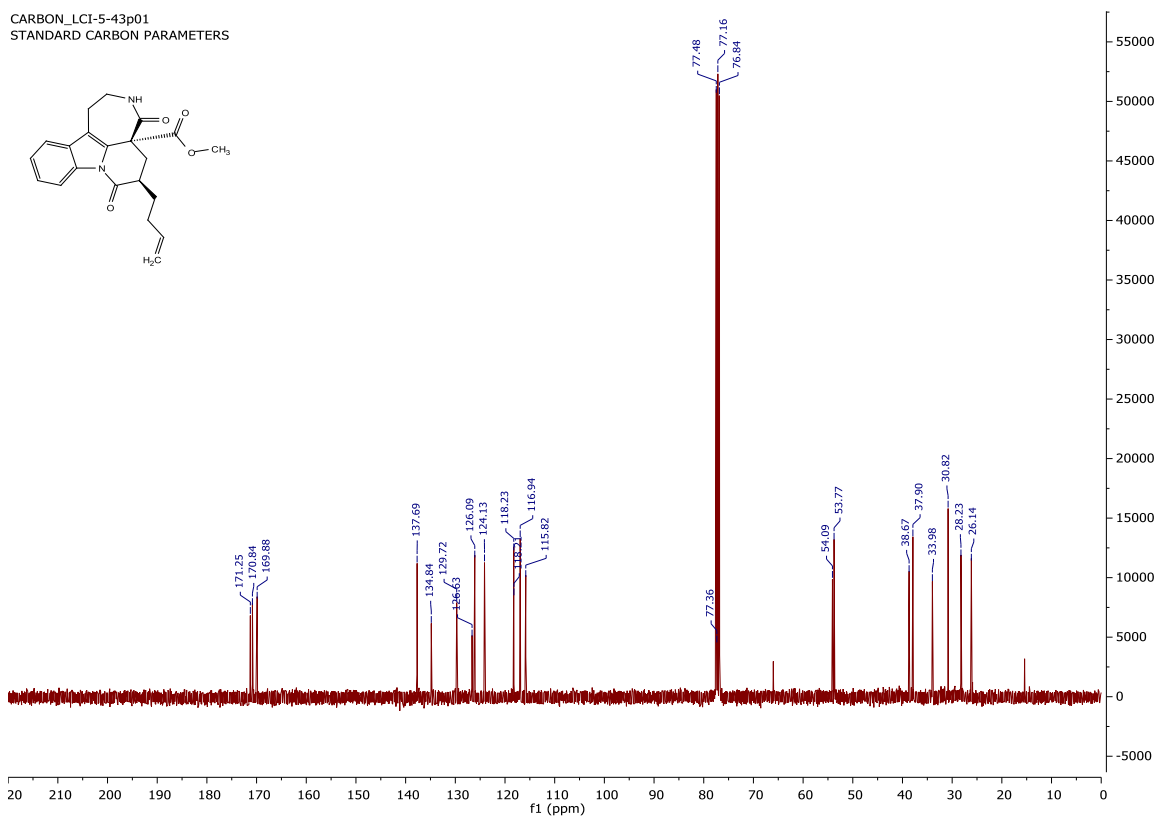
CARBON_LCI-5-123p01
STANDARD CARBON PARAMETERS



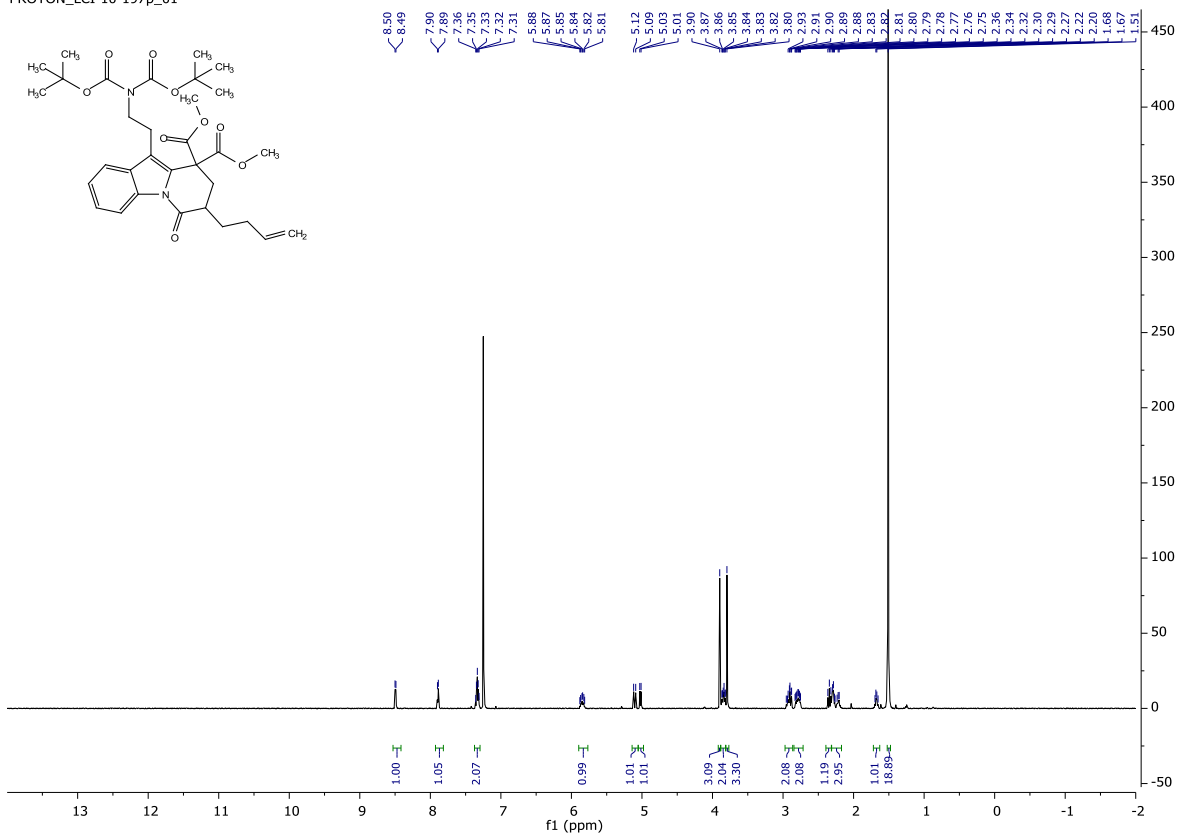
PROTON_LCI-5-43p01
Lauren



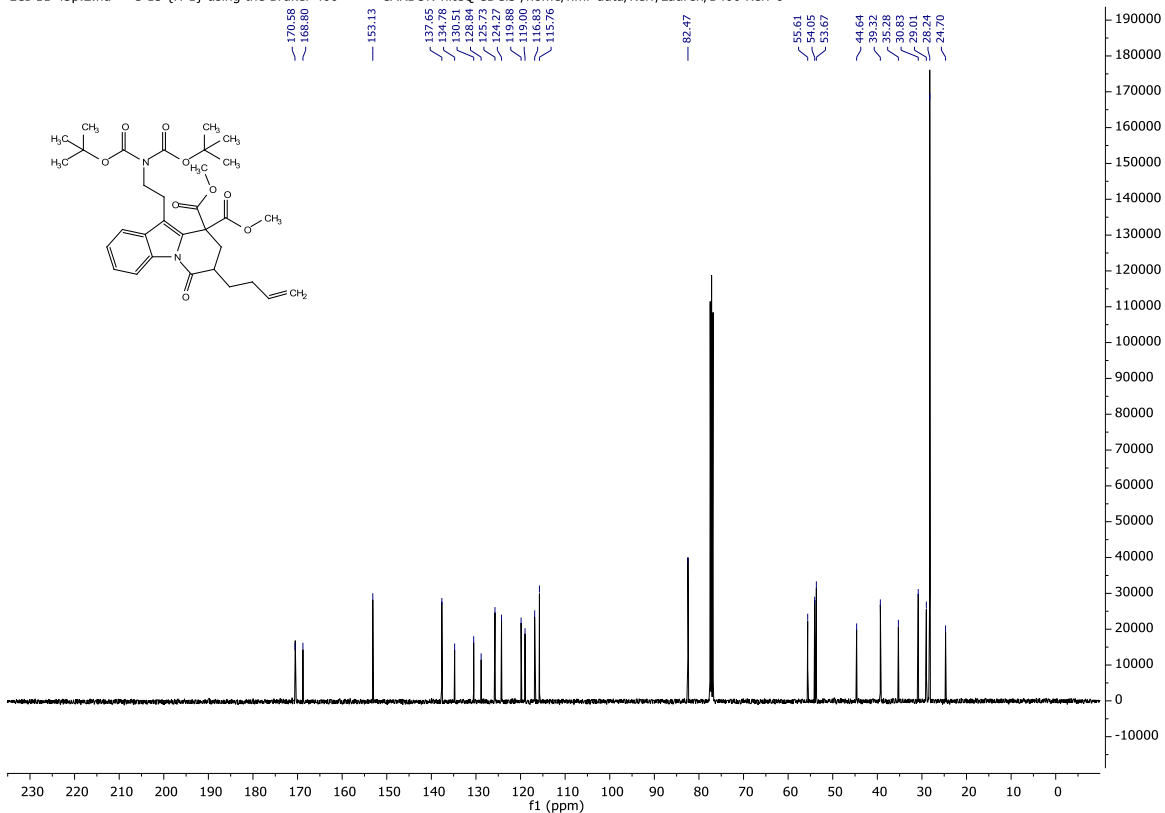
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STANDARD CARBON PARAMETERS

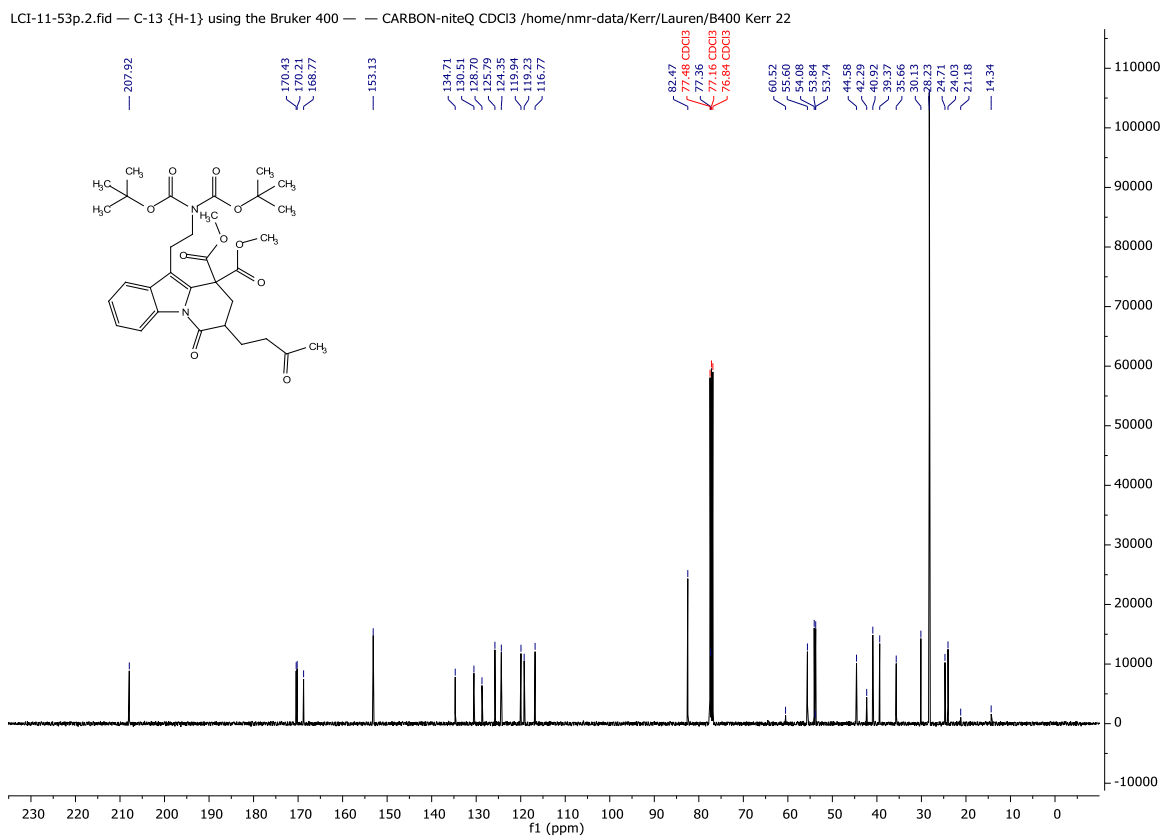
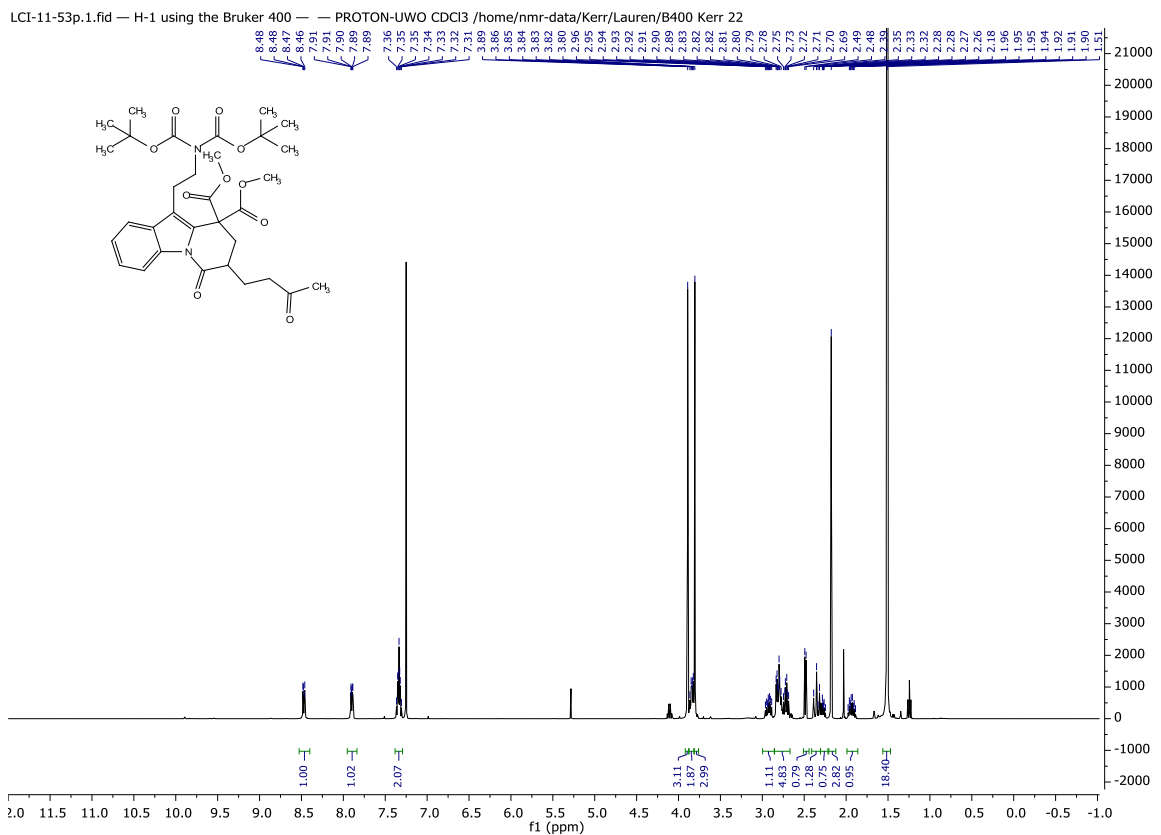


PROTON_LCI-10-197p_01 —

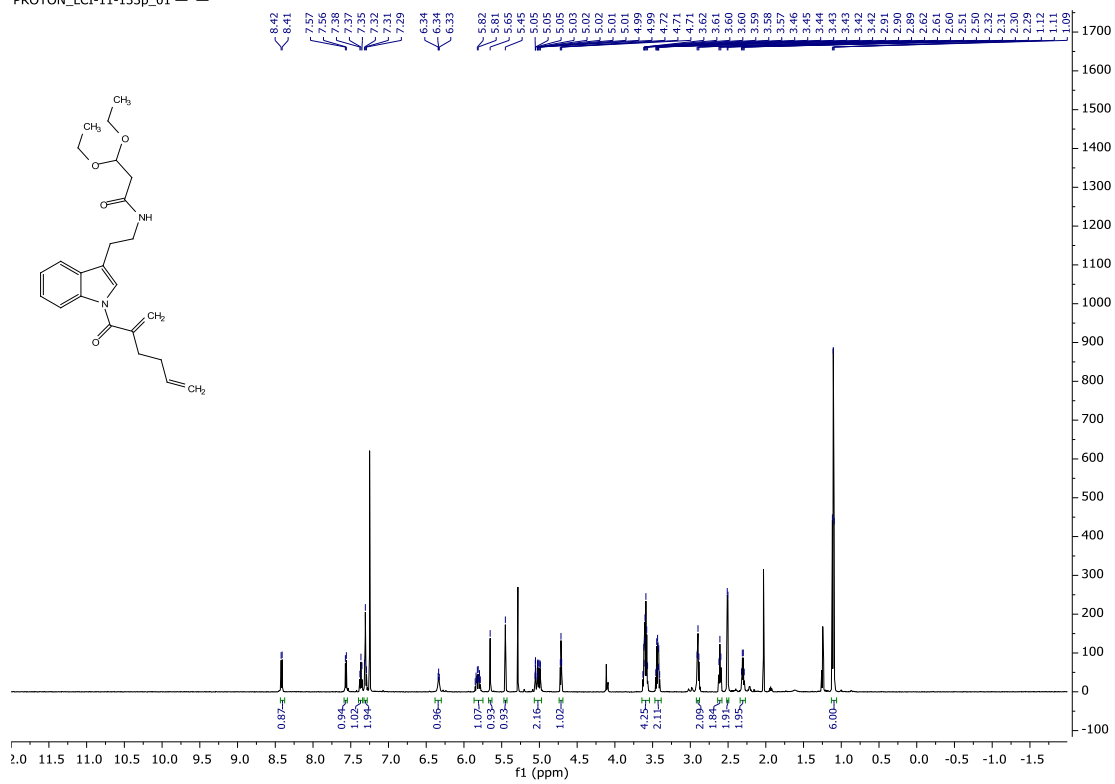


LCI-11-43p.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 6

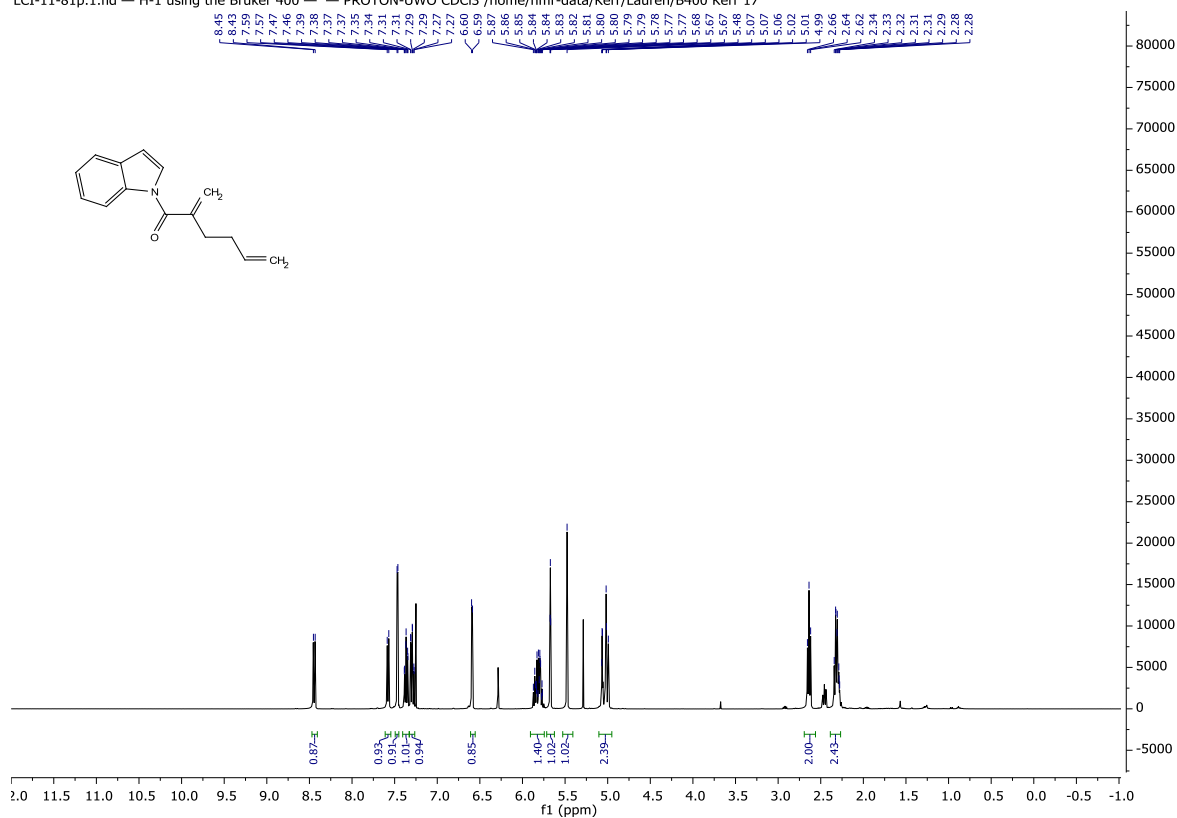




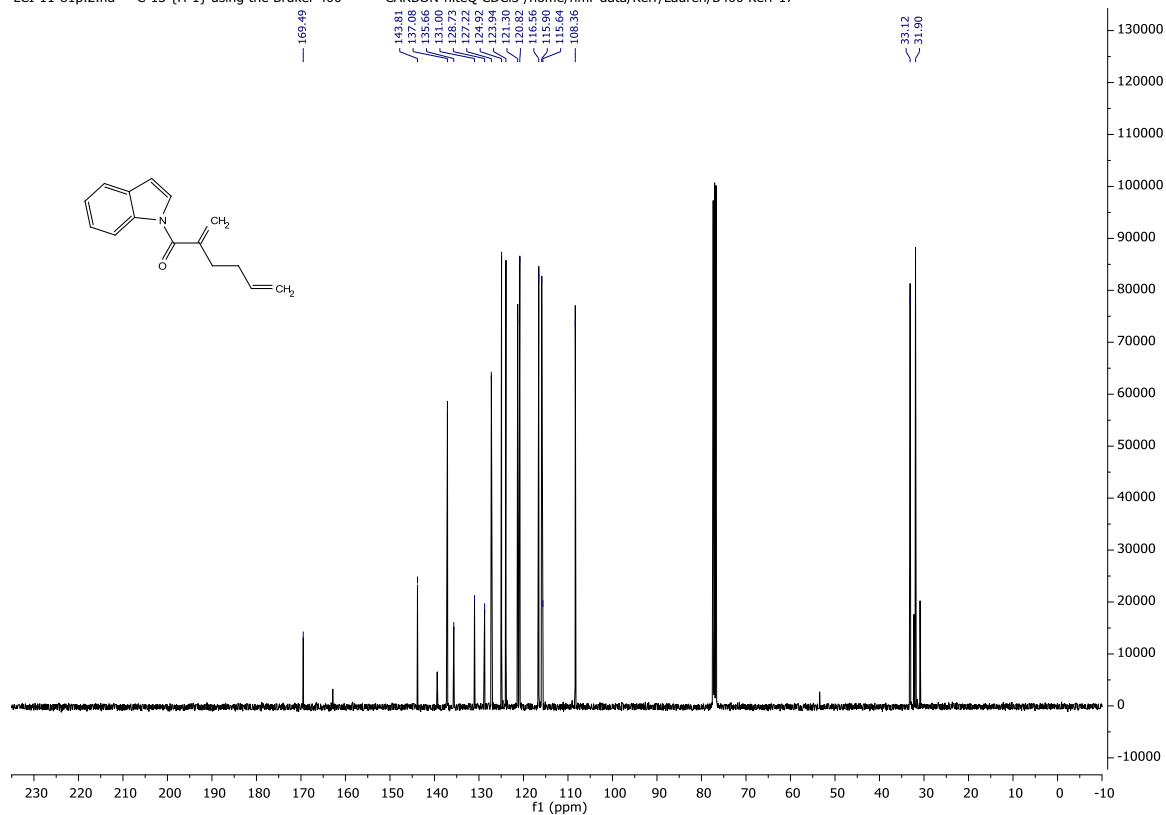
PROTON_LCI-11-133p_01

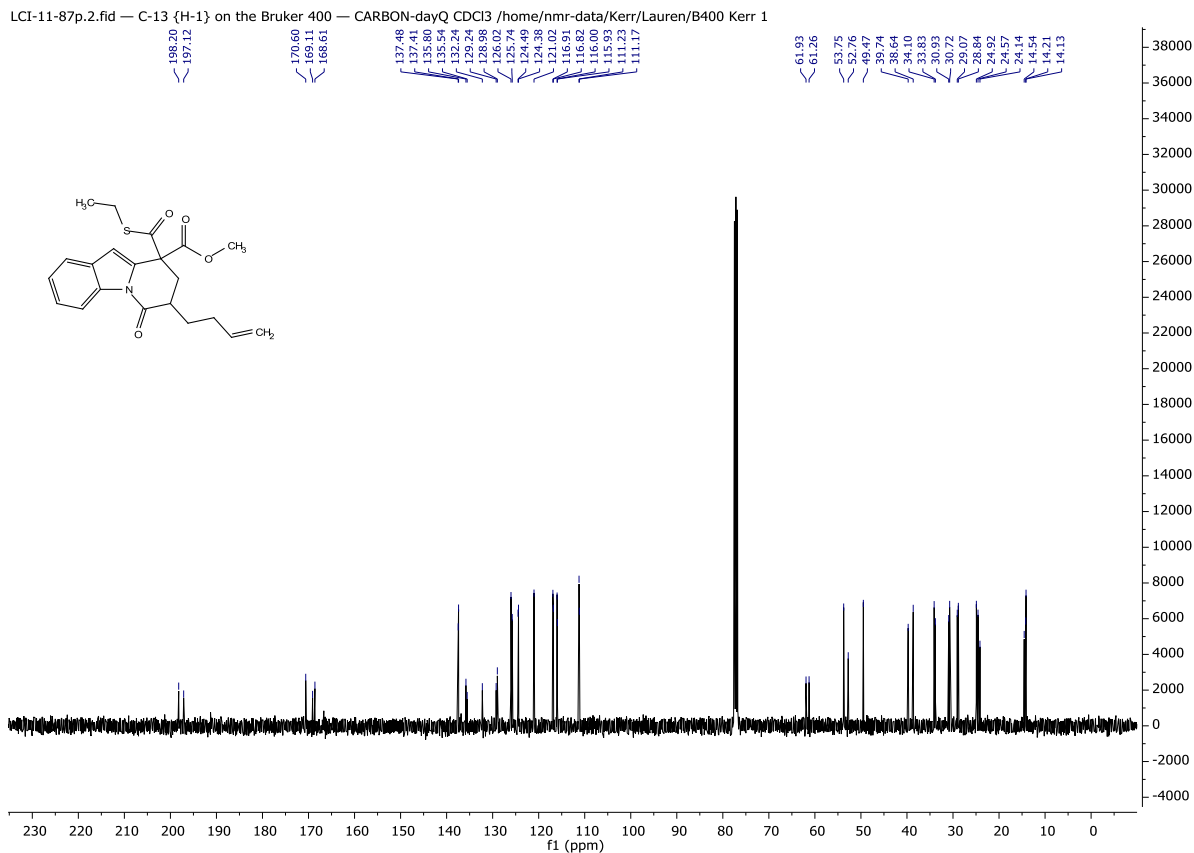
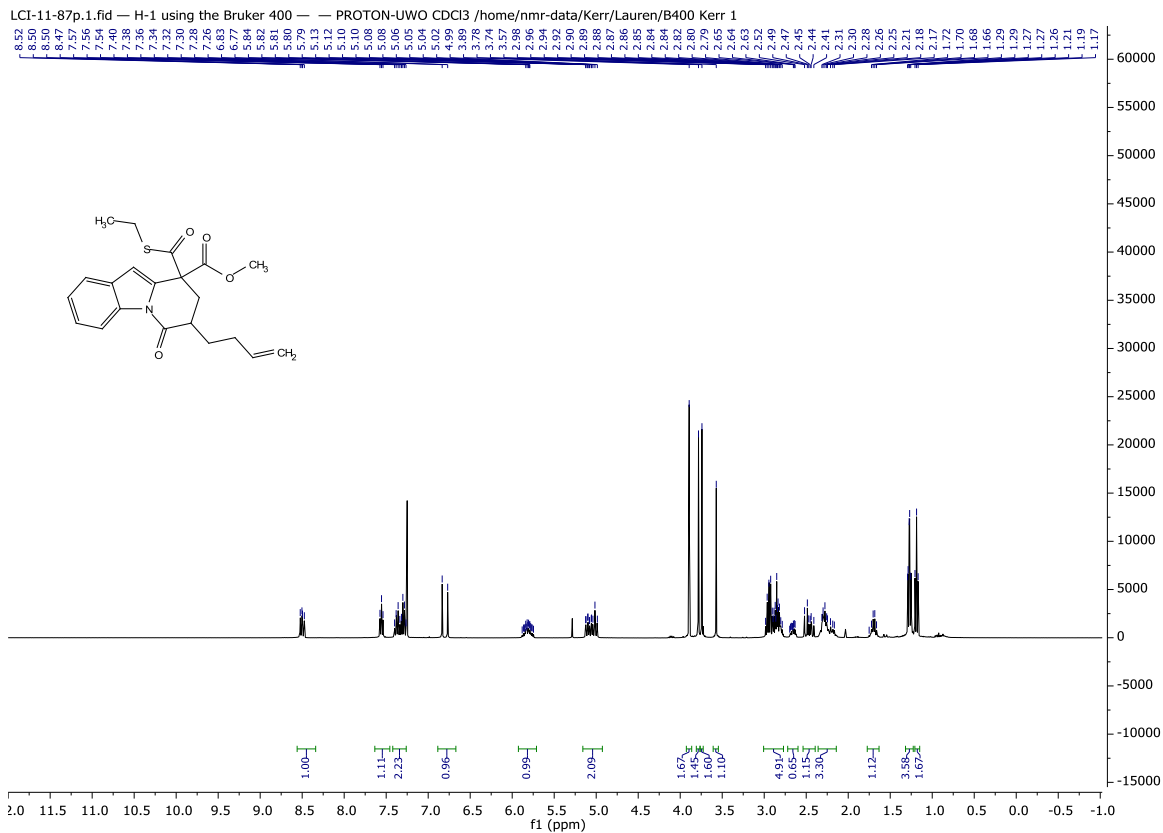


LCI-11-81p.1.fid — H-1 using the Bruker 400 — — PROTON-UWO CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 17

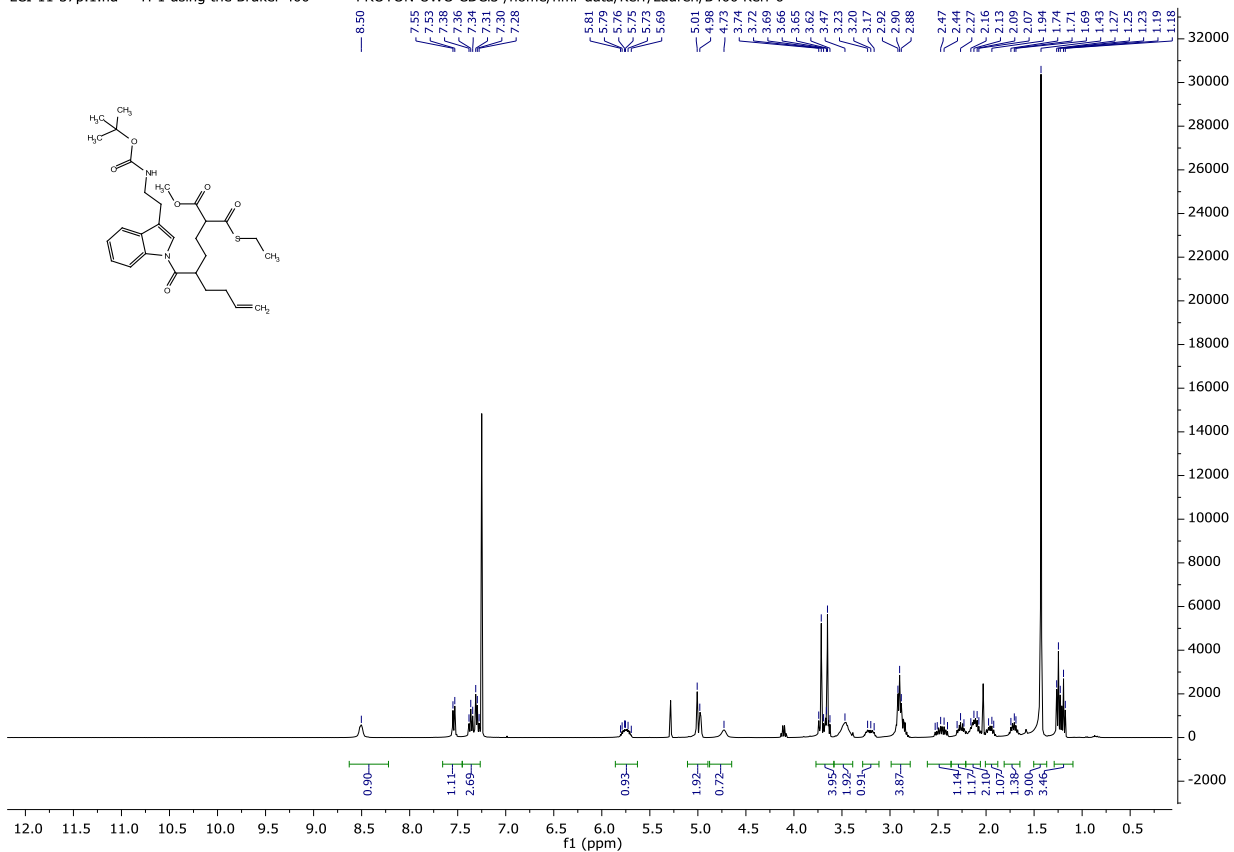


LCI-11-81p.2.fid — C-13 {H-1} using the Bruker 400 — — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 17

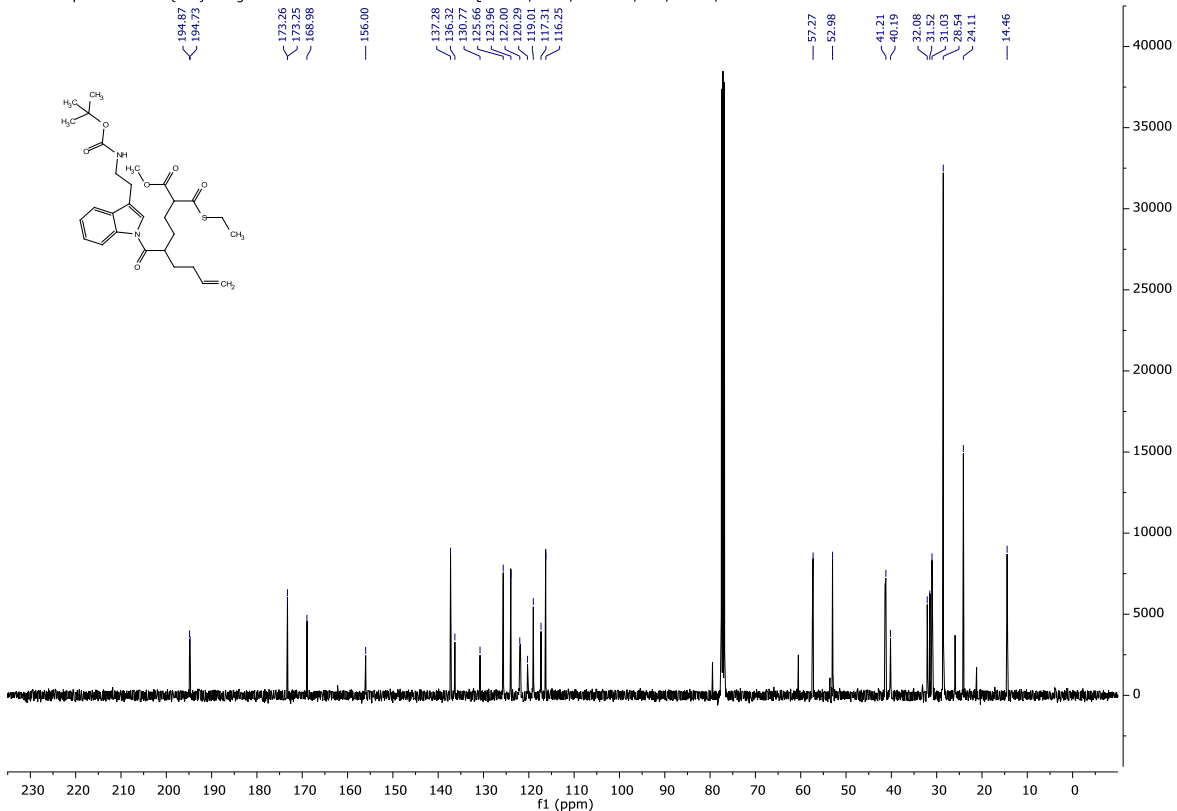


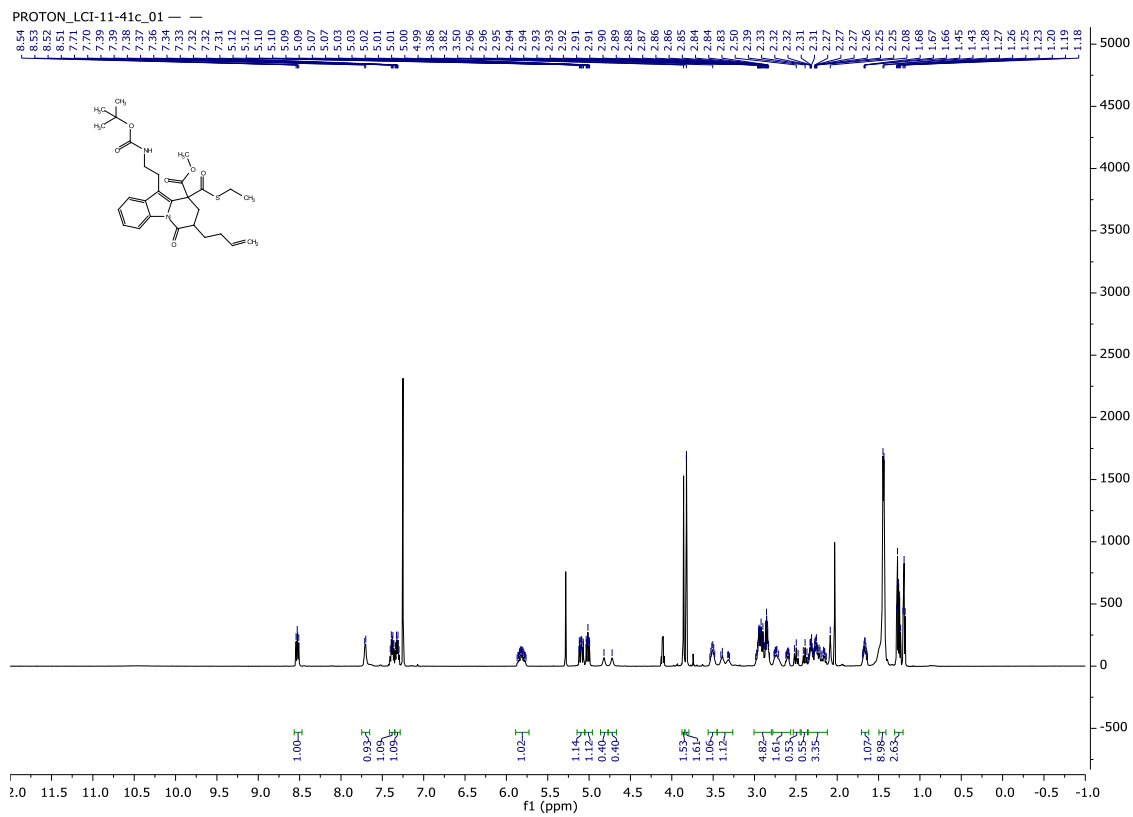


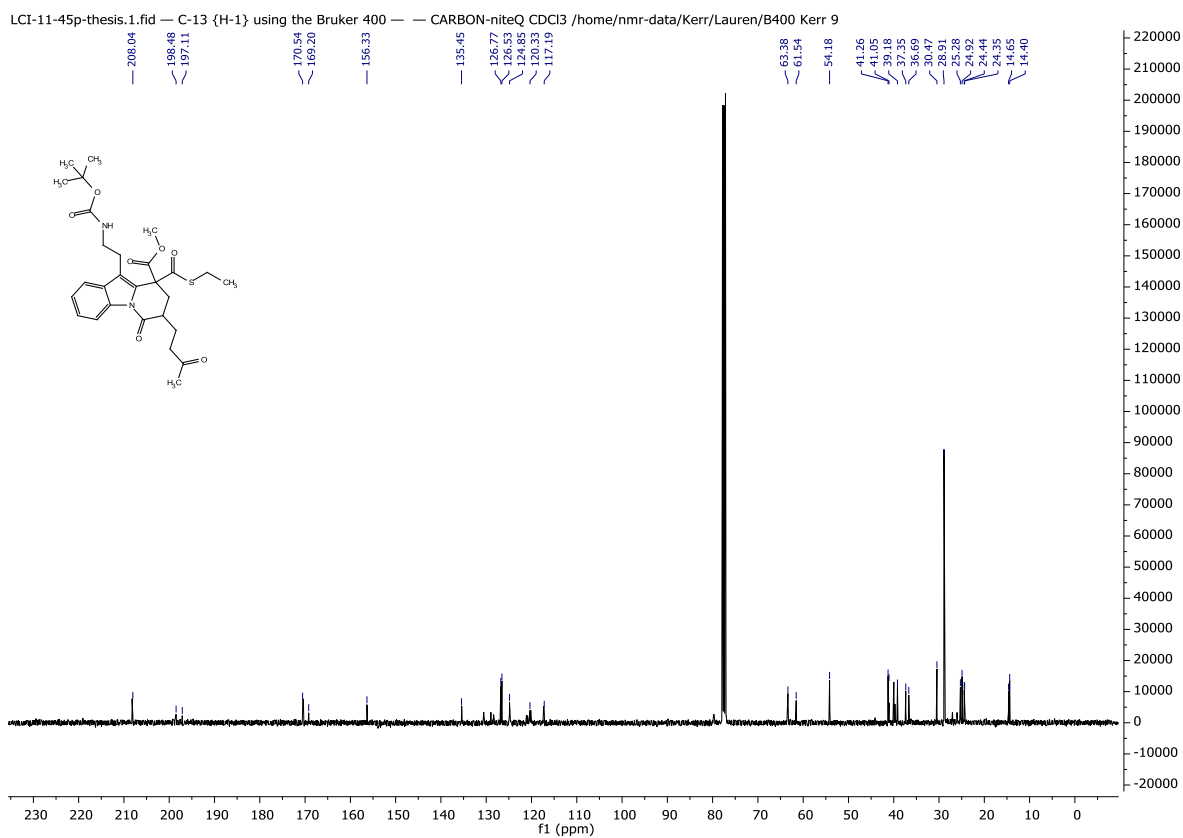
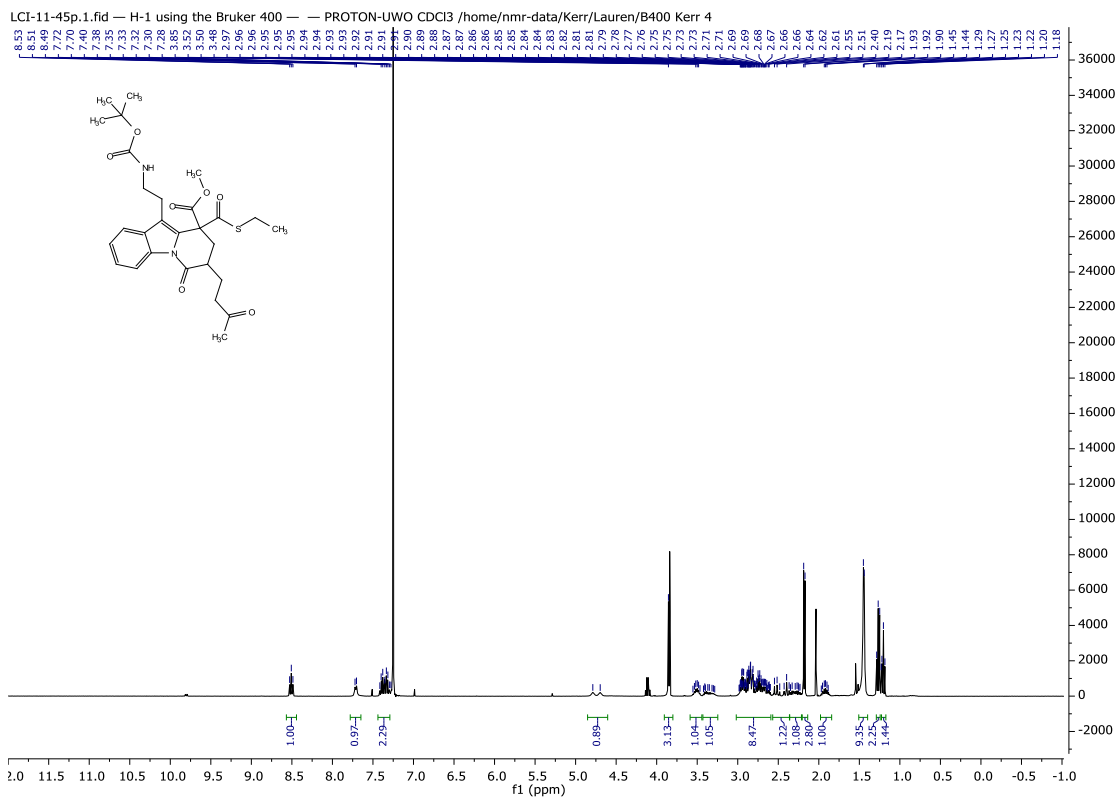
LCI-11-37p.1.fid — H-1 using the Bruker 400 — PROTON-UWO CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 6



LCI-11-37p.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 6

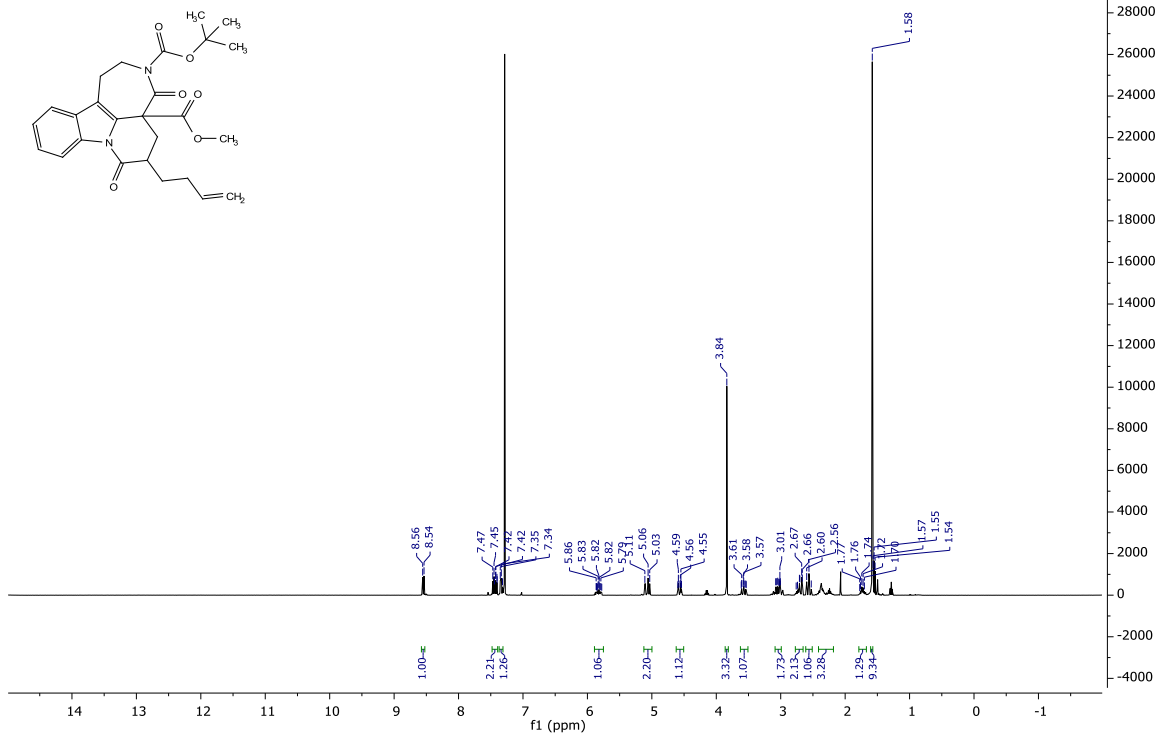




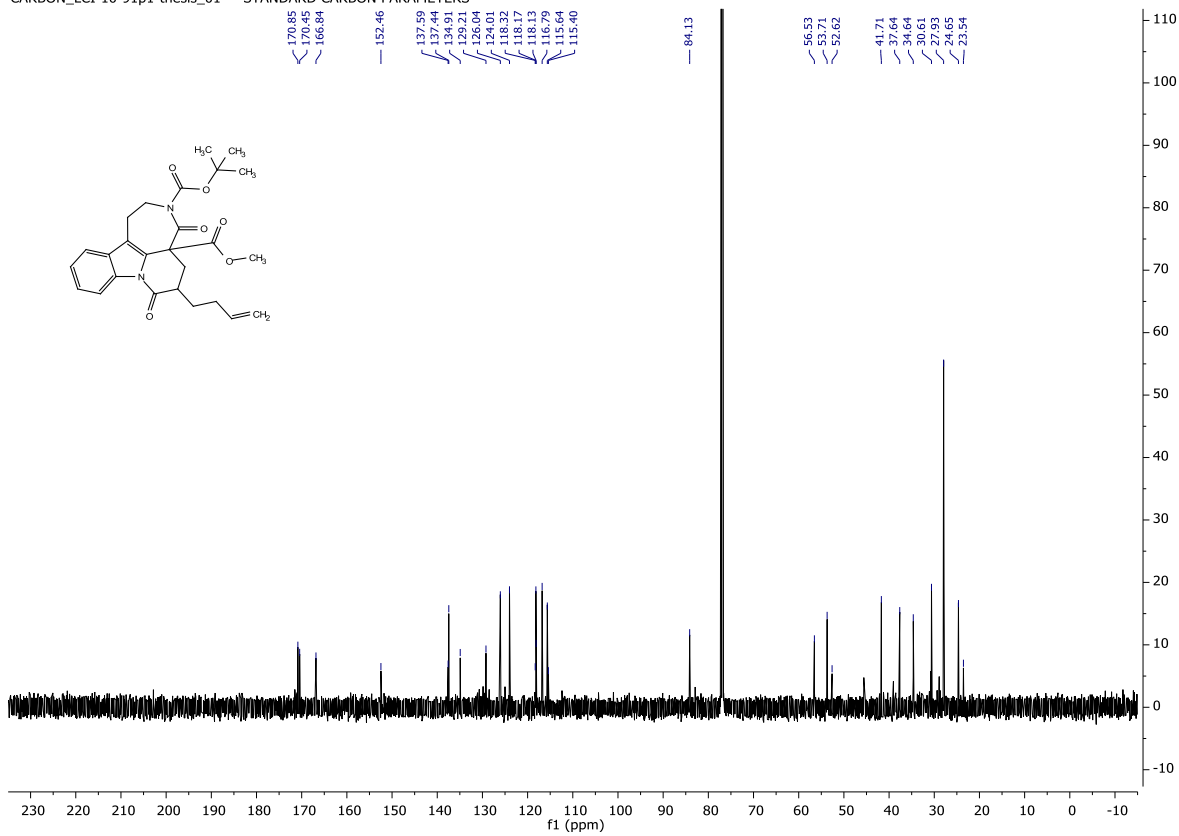


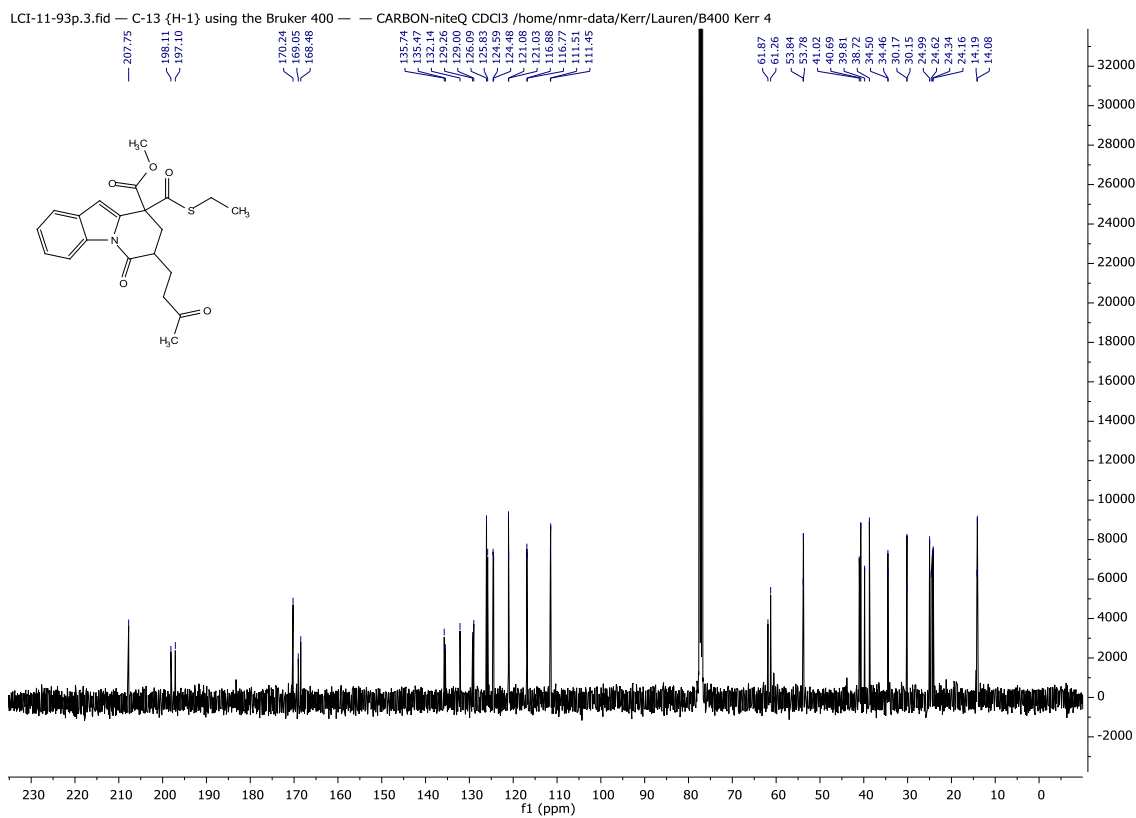
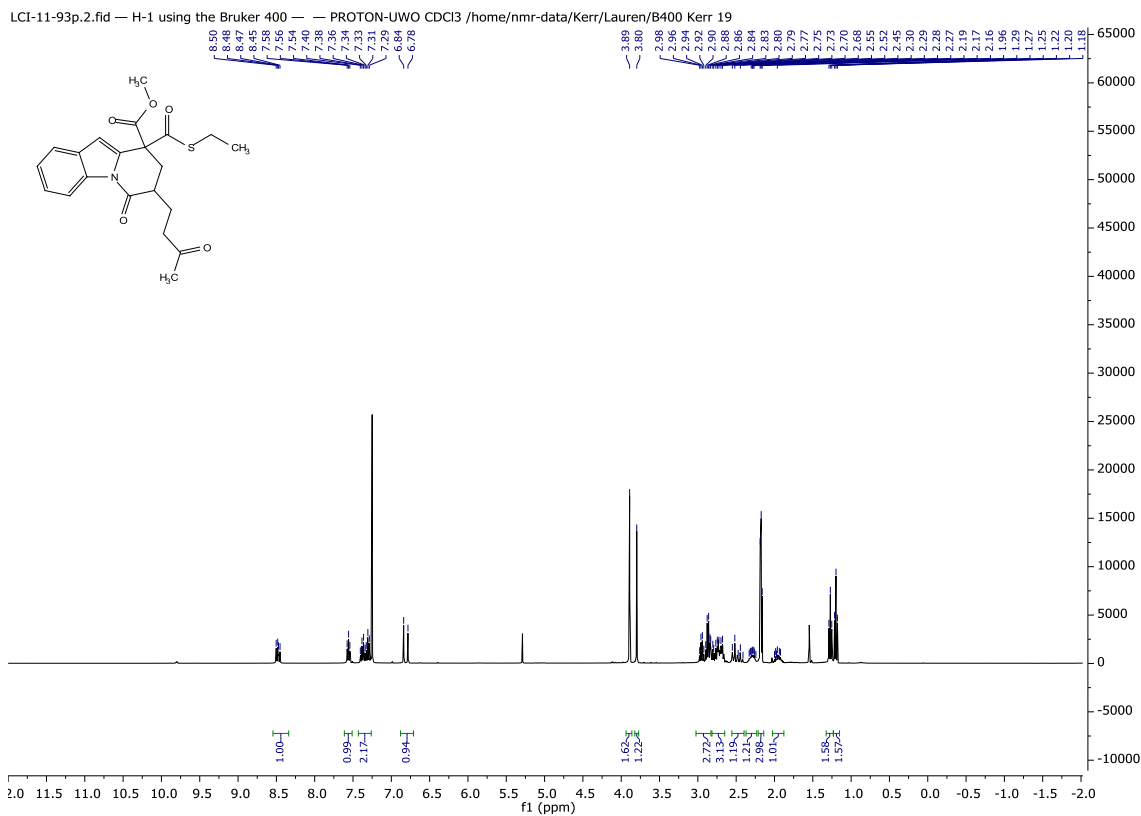
LCI-10-91p1.1.fid
H-1 using the Bruker 400

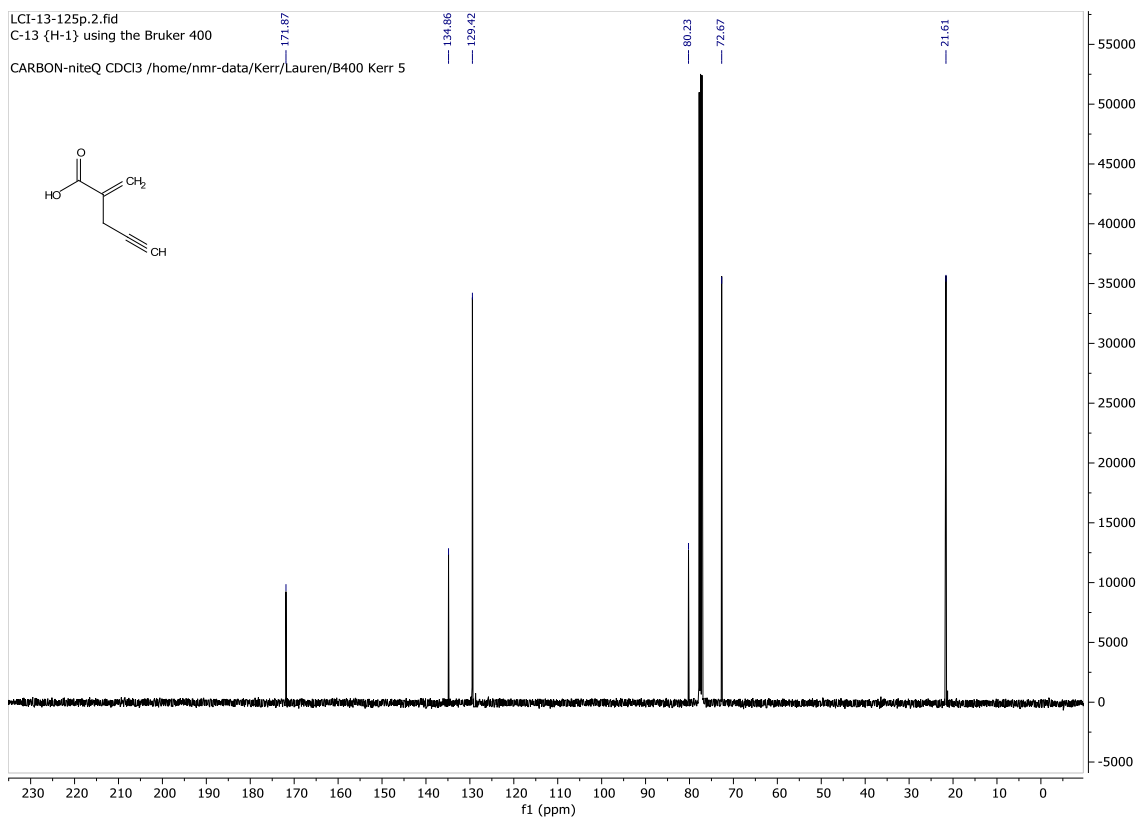
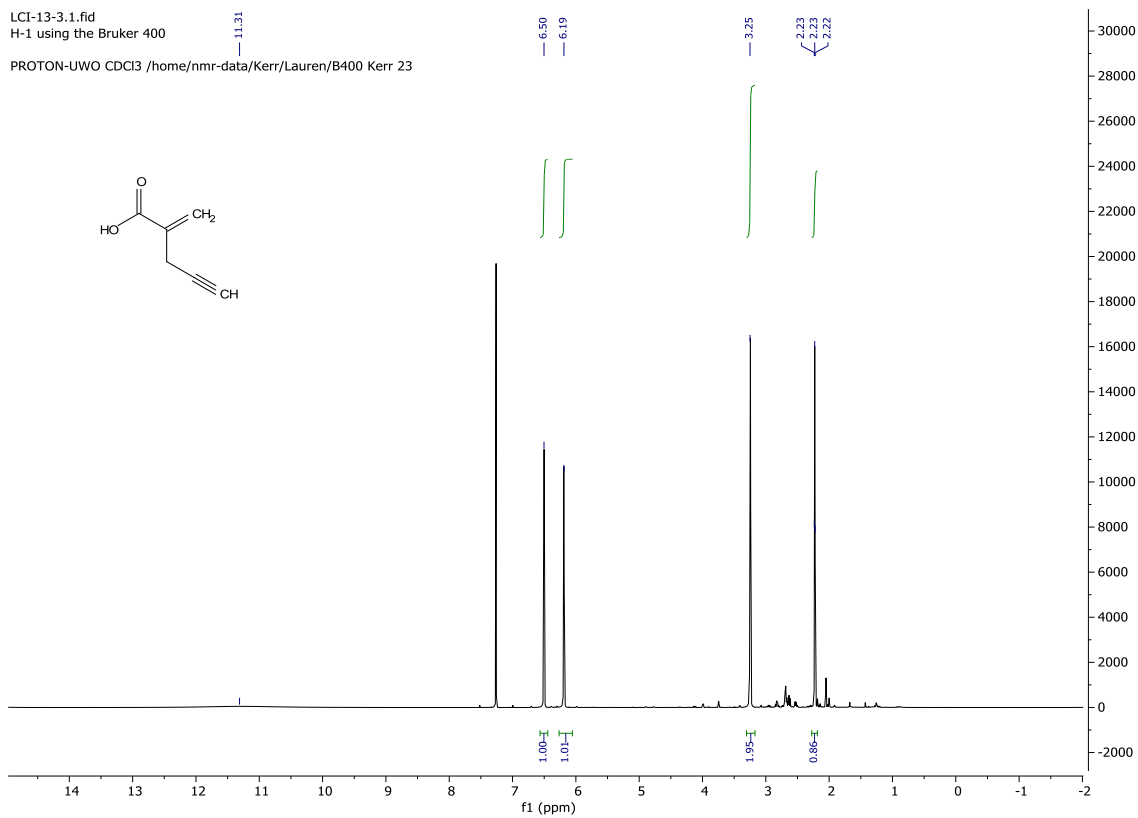
PROTON-UWO CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 9

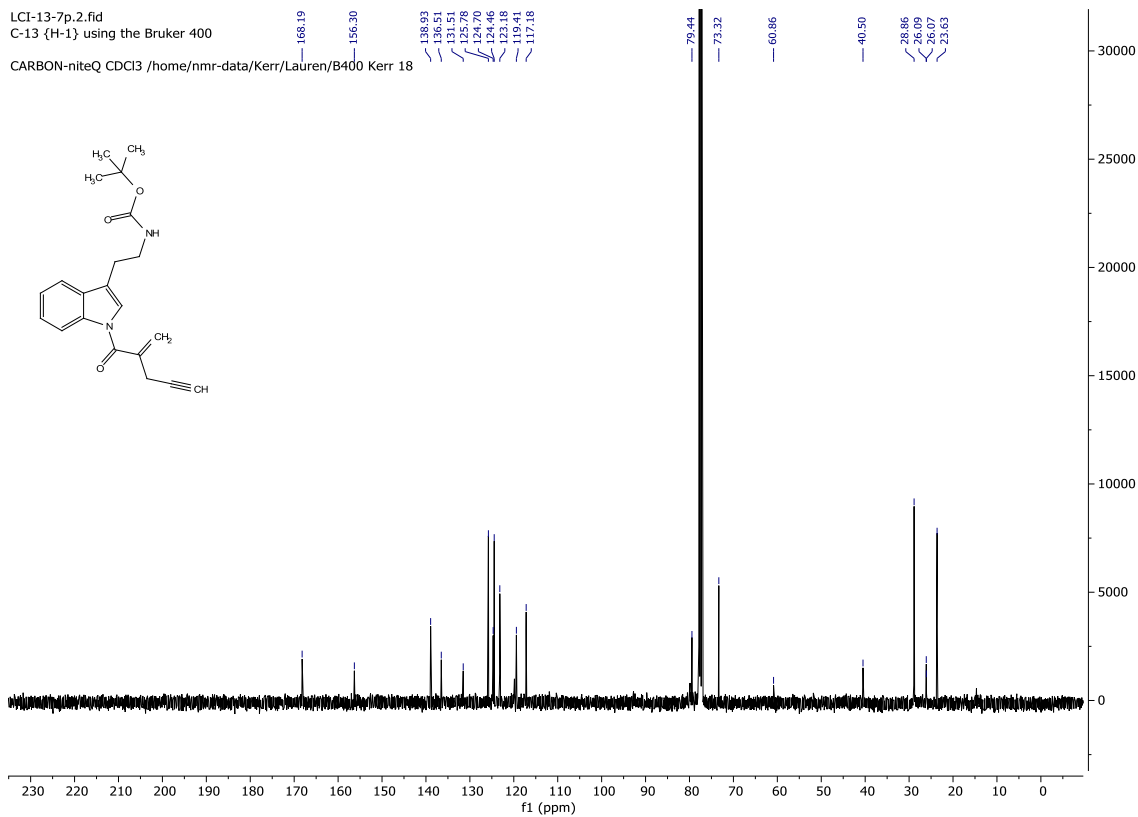
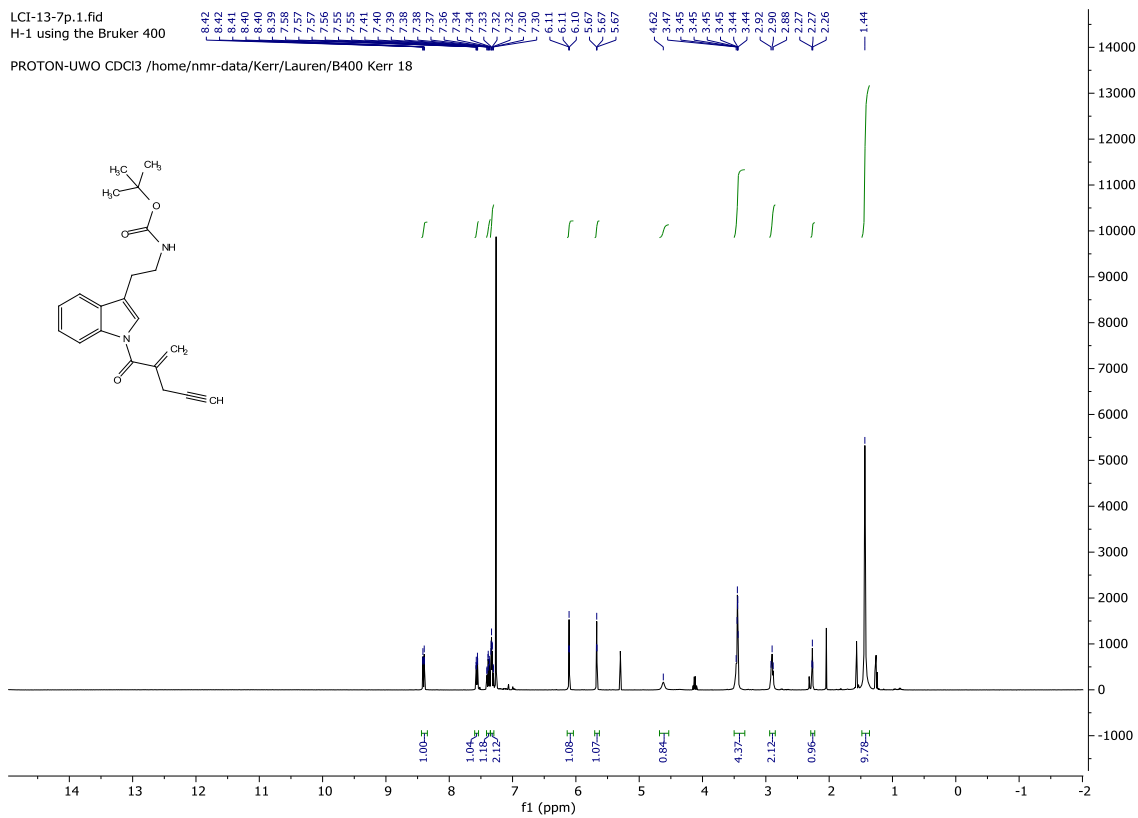


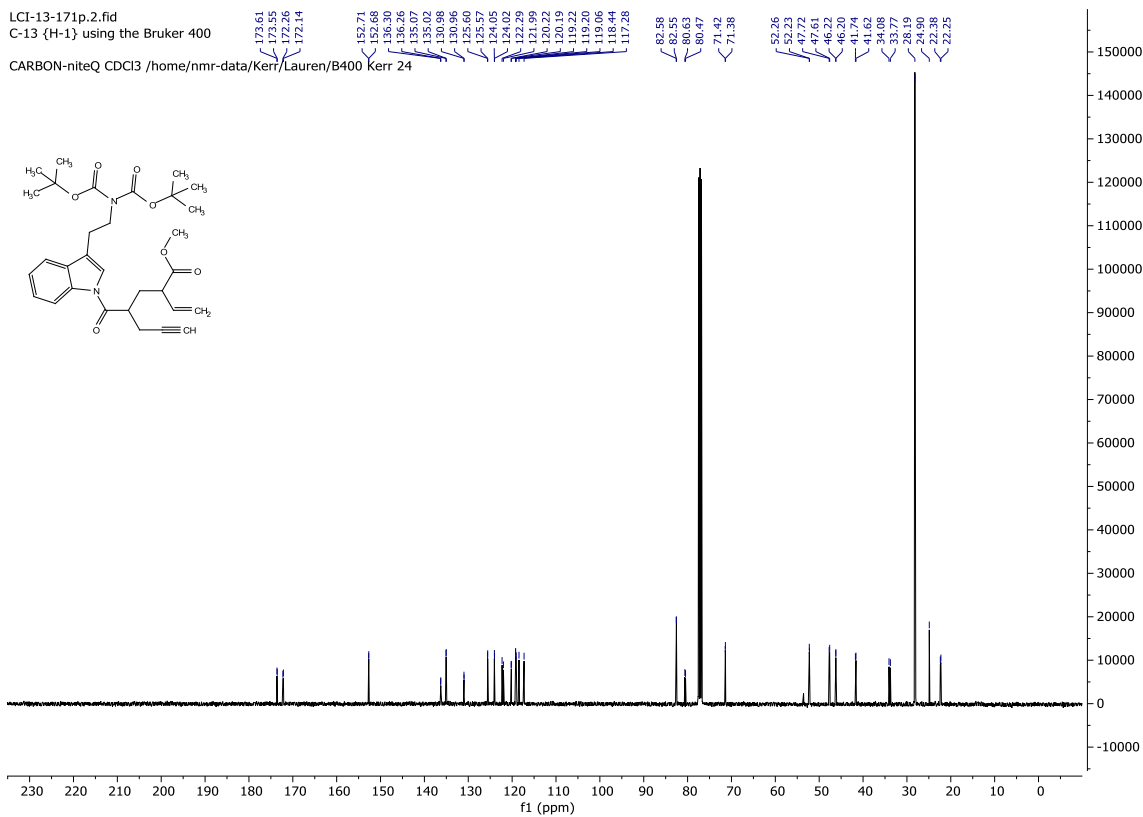
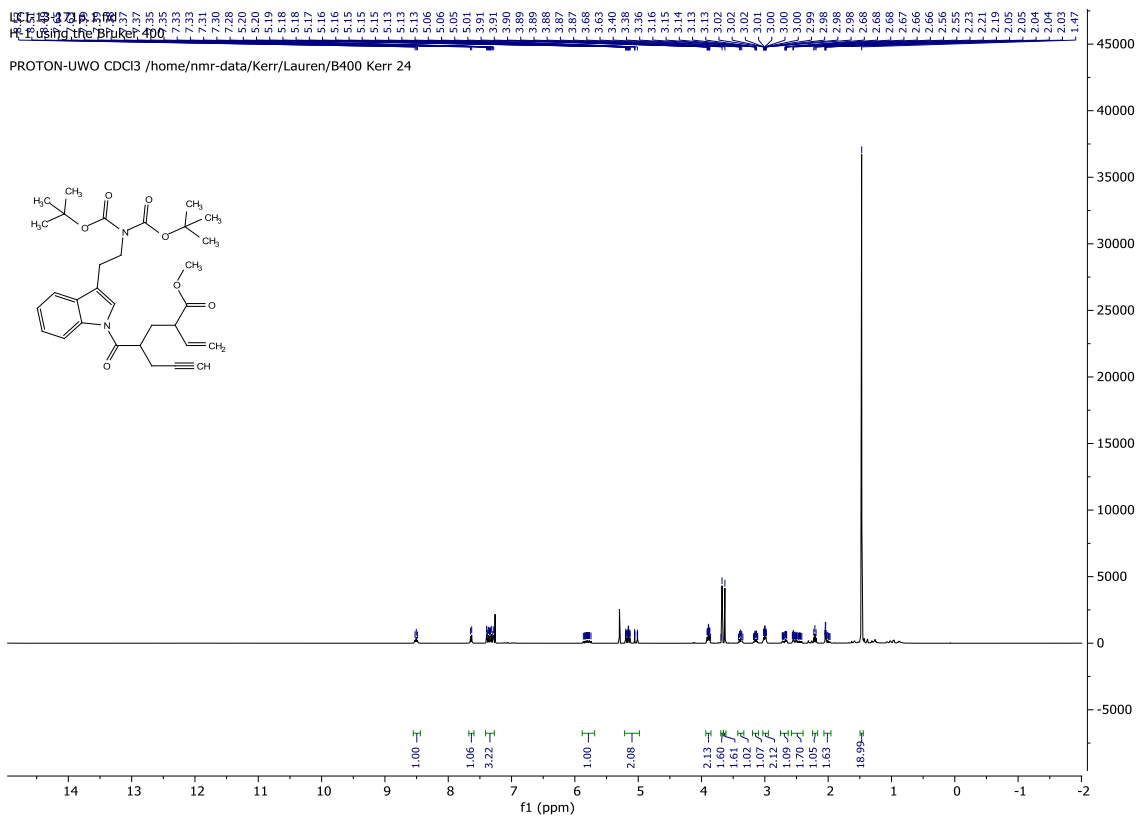
CARBON_LCI-10-91p1-thesis_01 — STANDARD CARBON PARAMETERS —

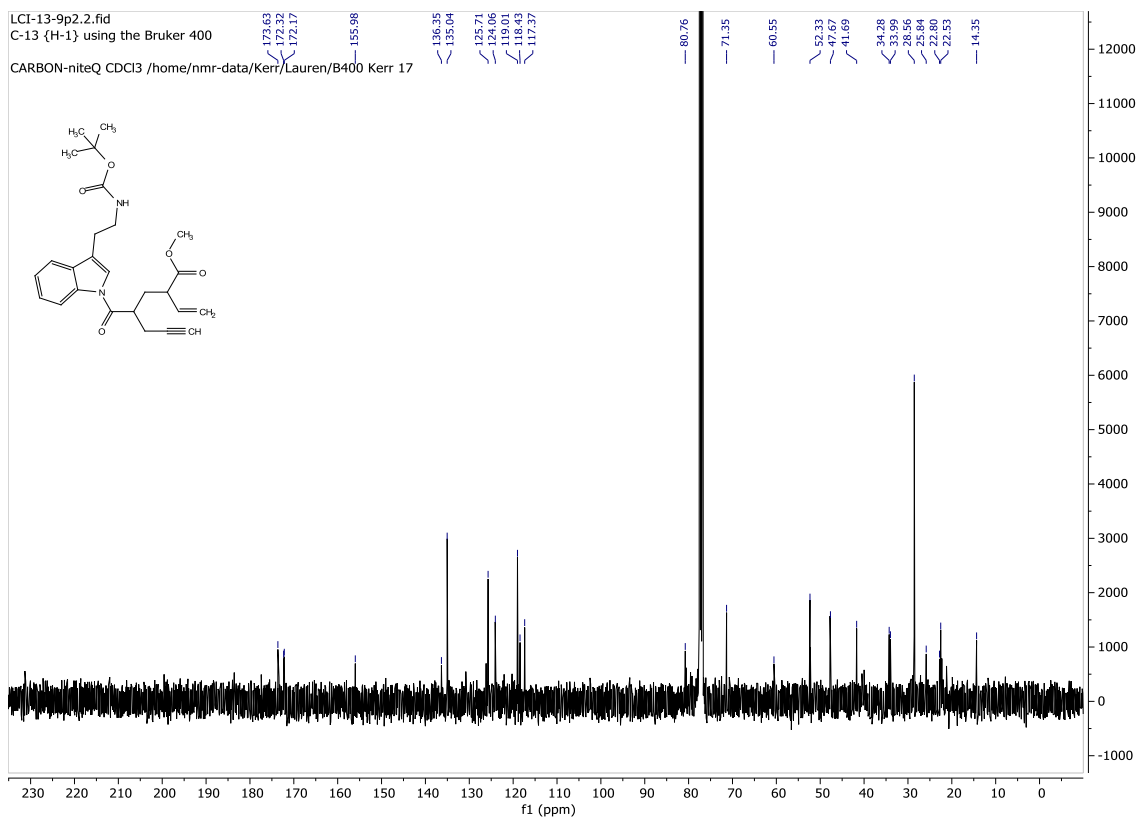
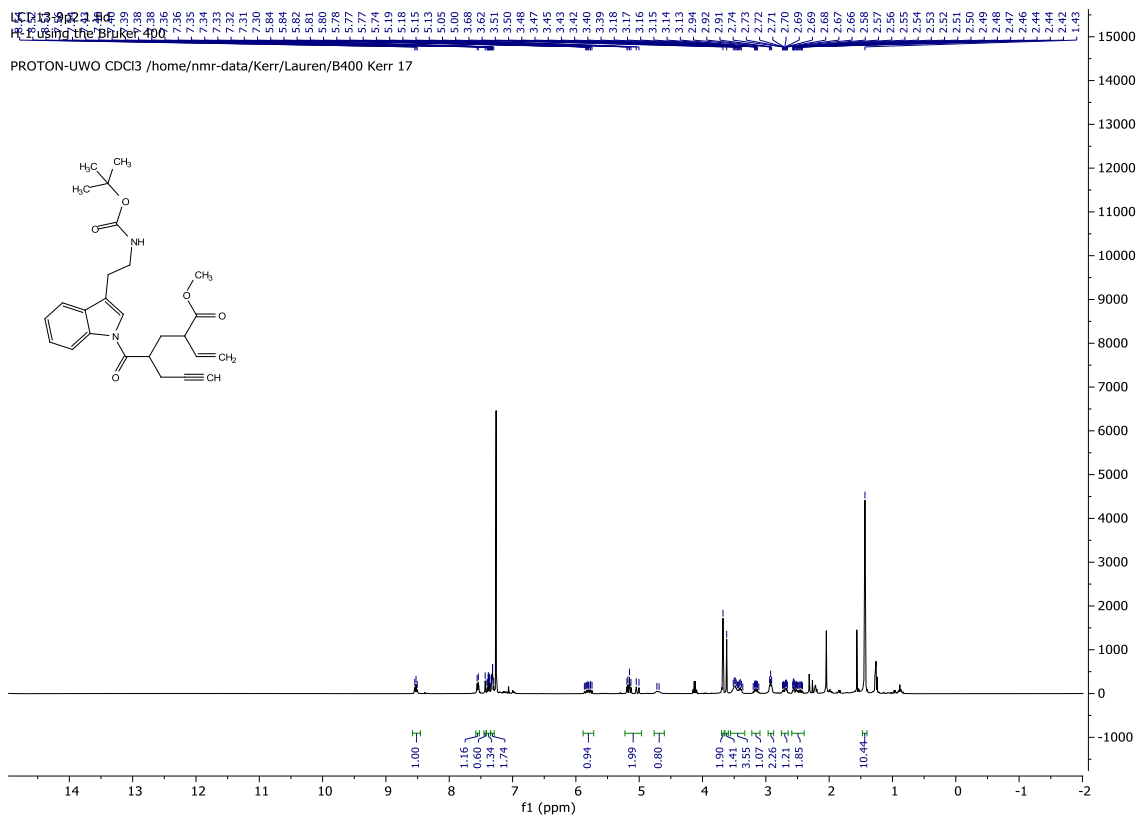


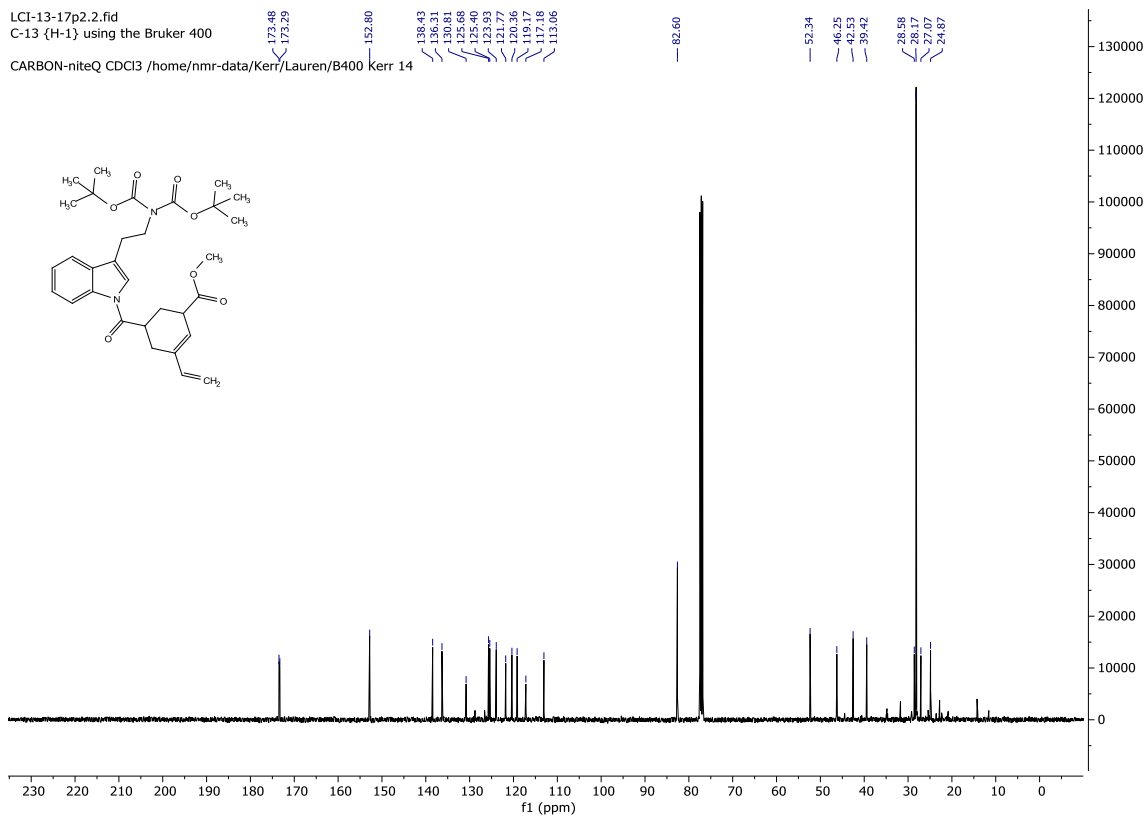
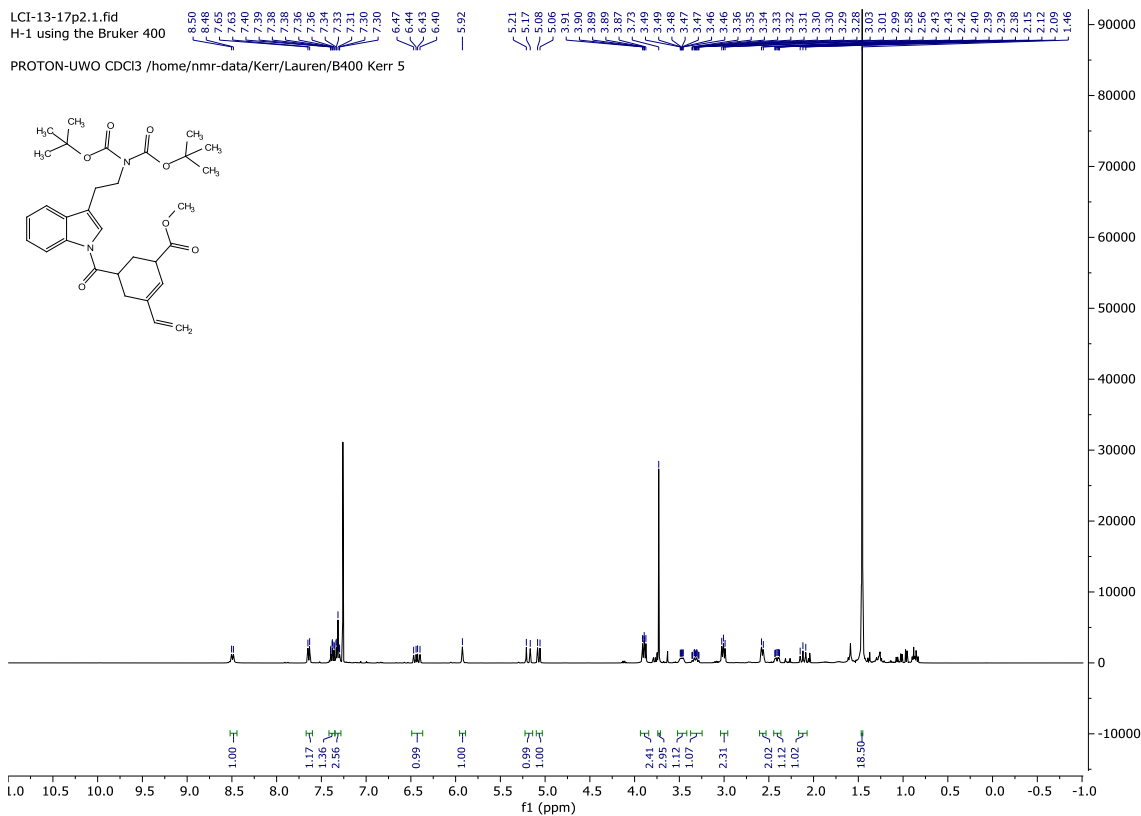




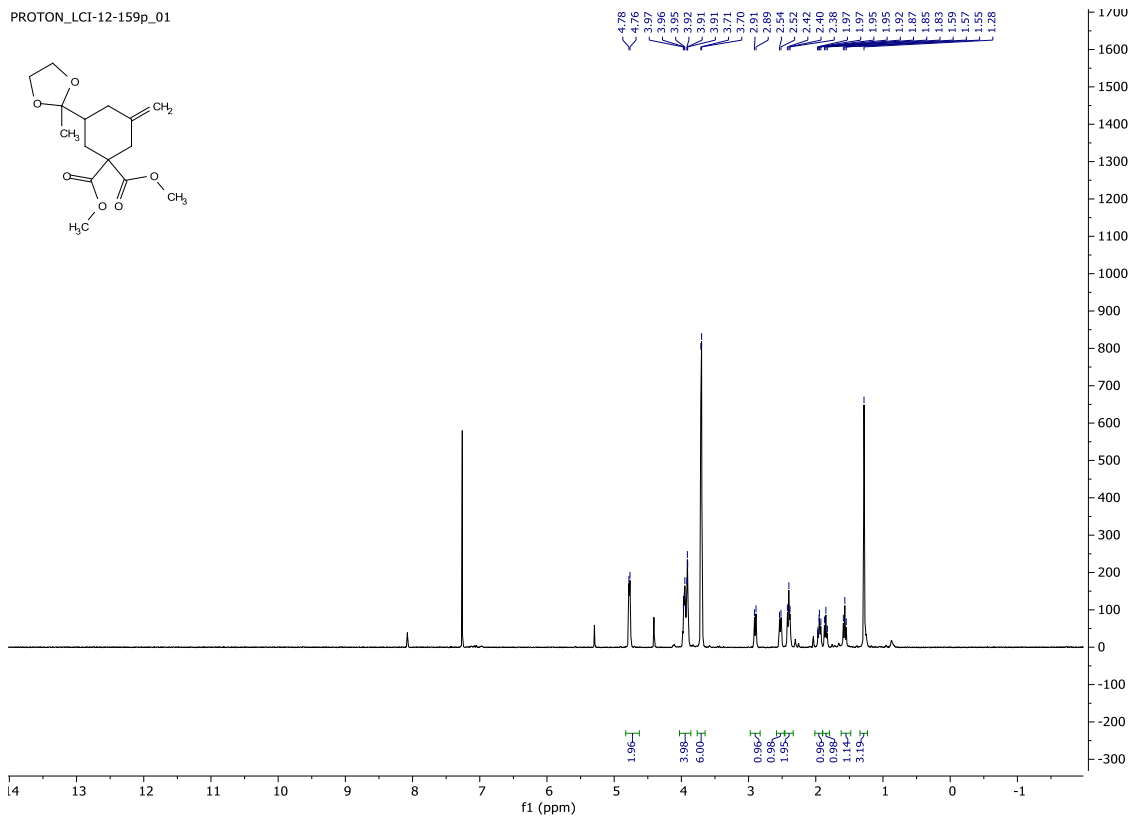








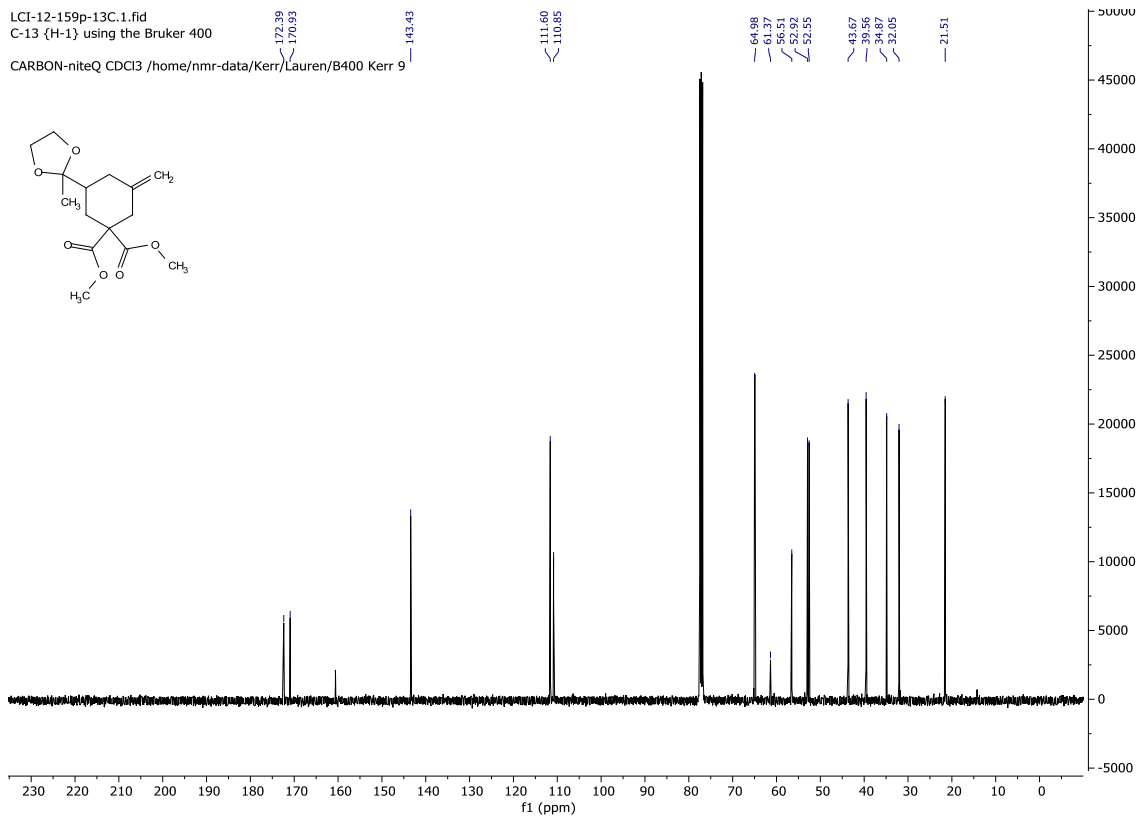
PROTON_LCI-12-159p_01



LCI-12-159p-13C.1.fid

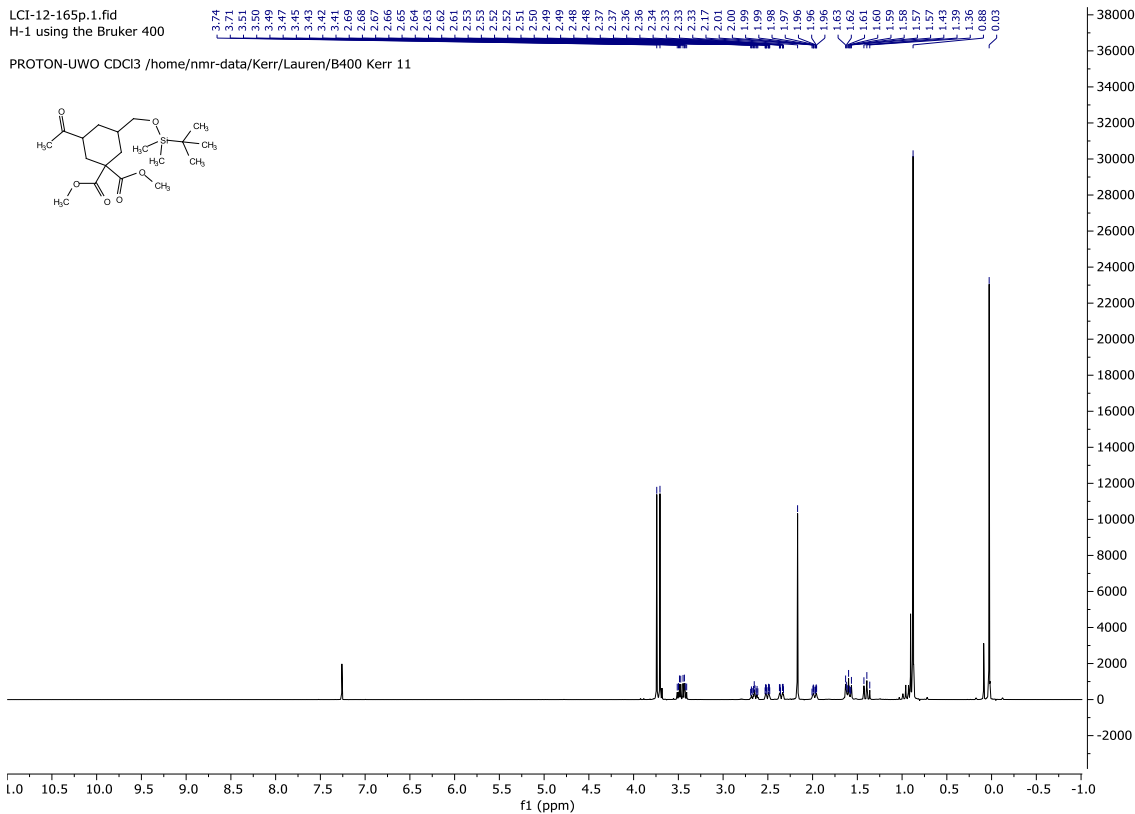
C-13 {H-1} using the Bruker 400

CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 9



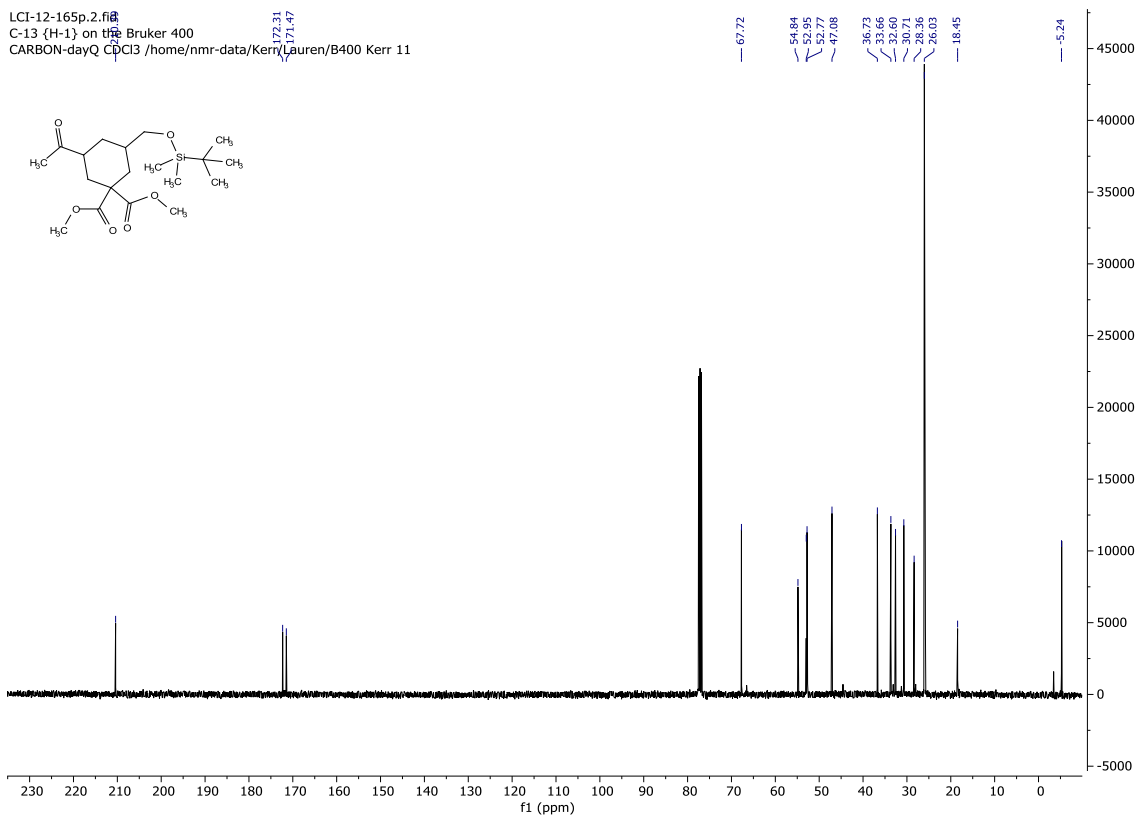
LCI-12-165p.1.fid
 H-1 using the Bruker 400

PROTON-UWO CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 11

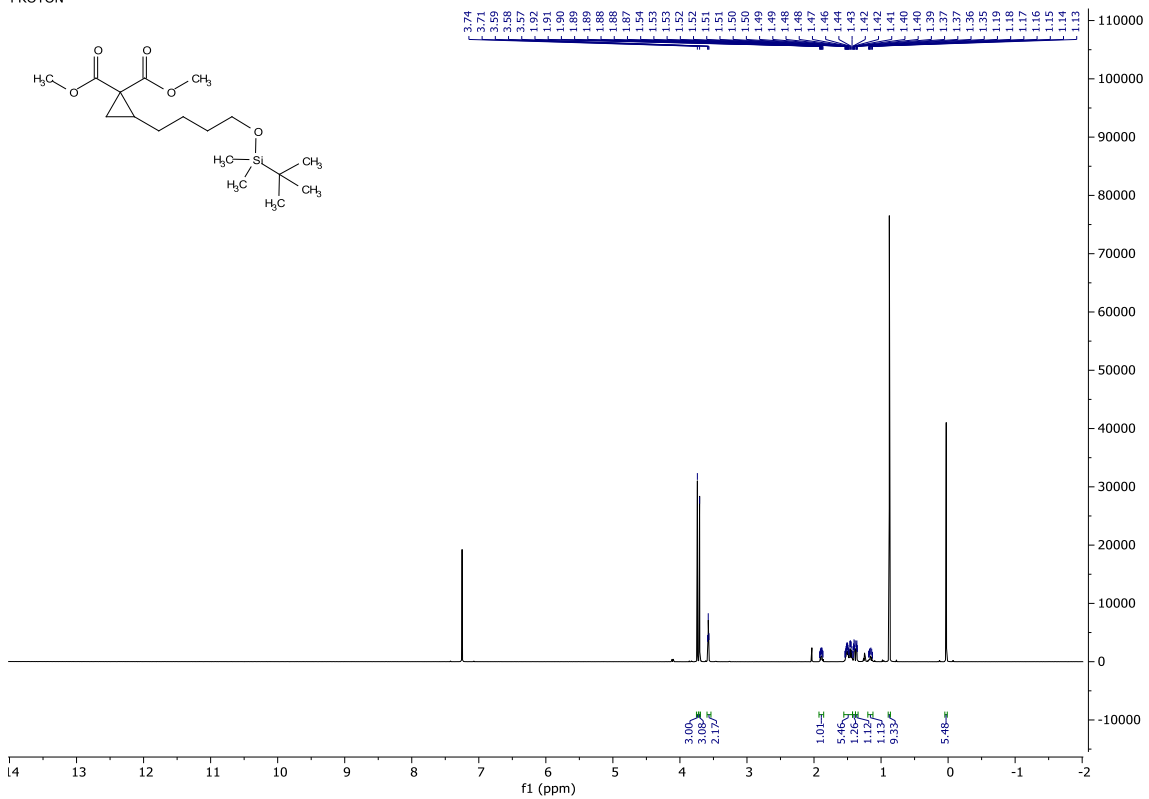


LCI-12-165p.2.fid
 C-13 (H-1) on the Bruker 400

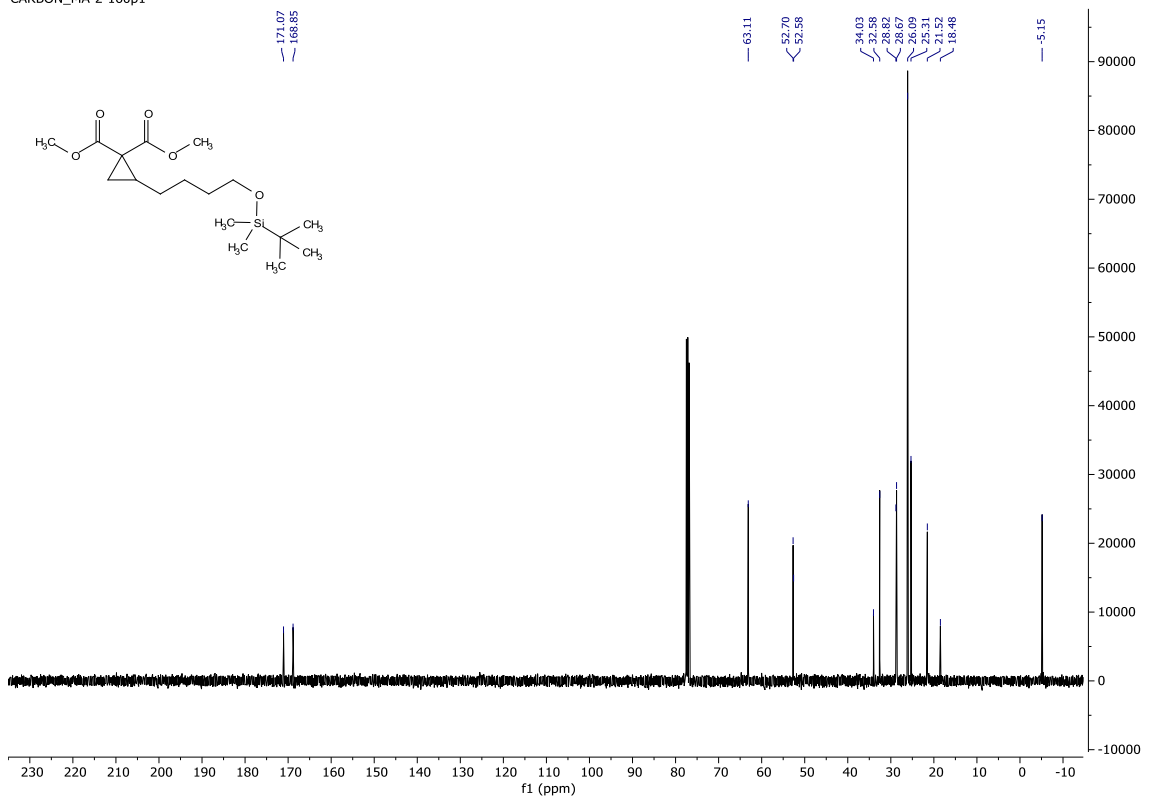
CARBON-dayQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 11



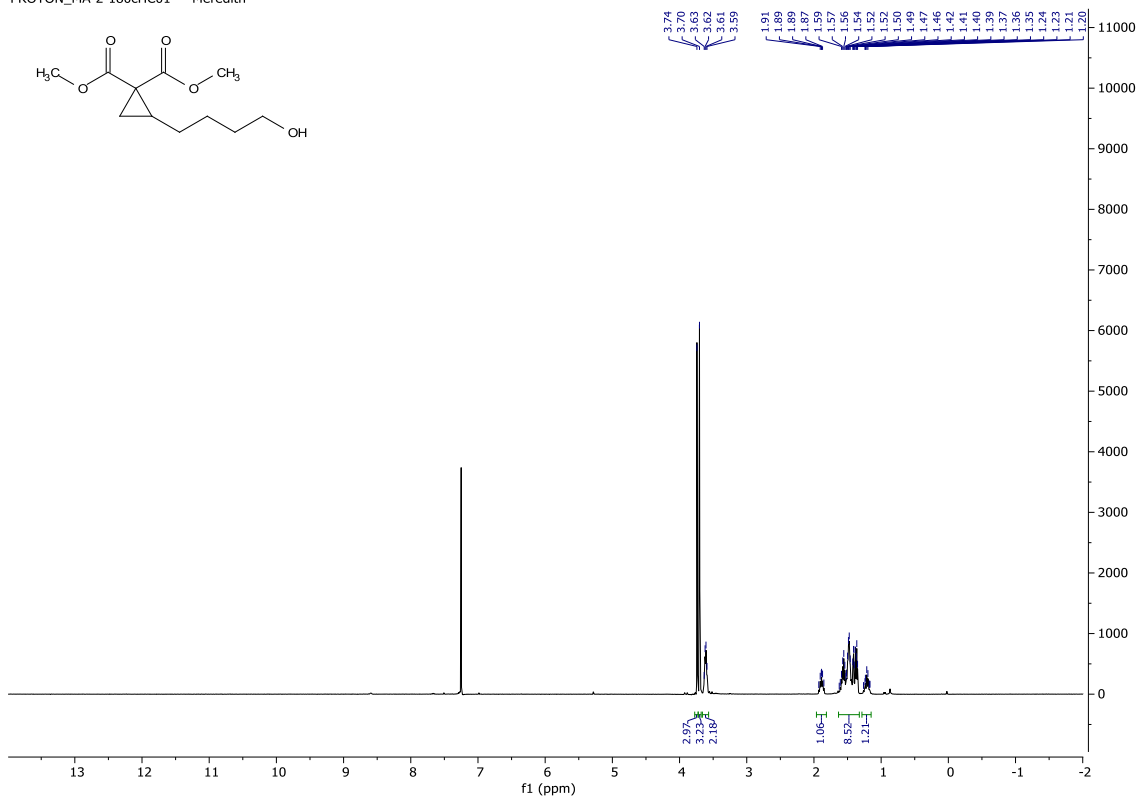
PROTON



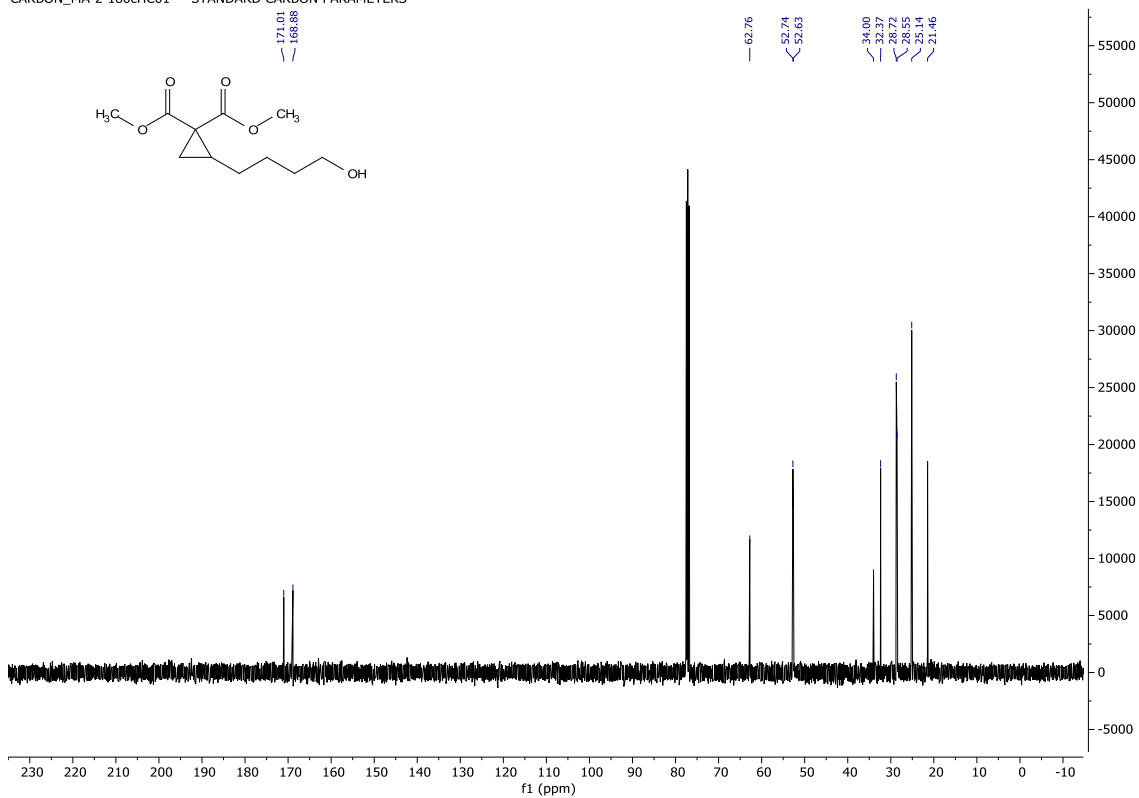
CARBON_MA-2-160p1



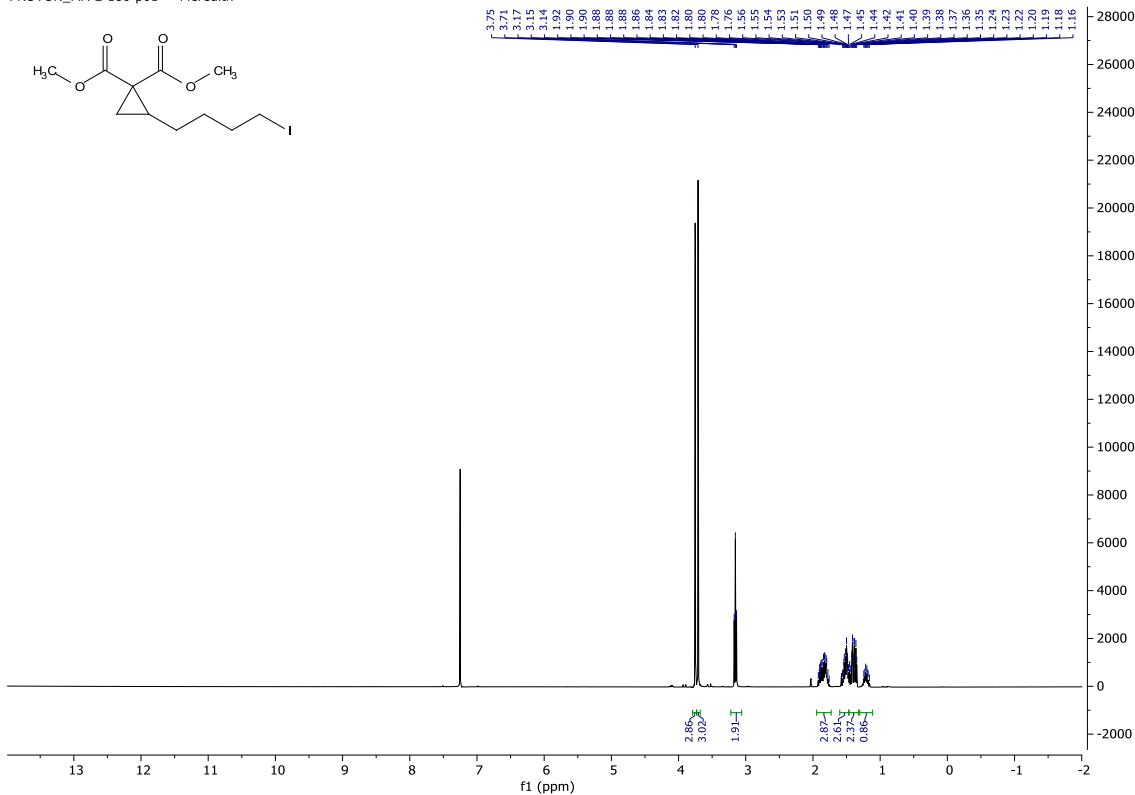
PROTON_MA-2-180cHC01 — Meredith —



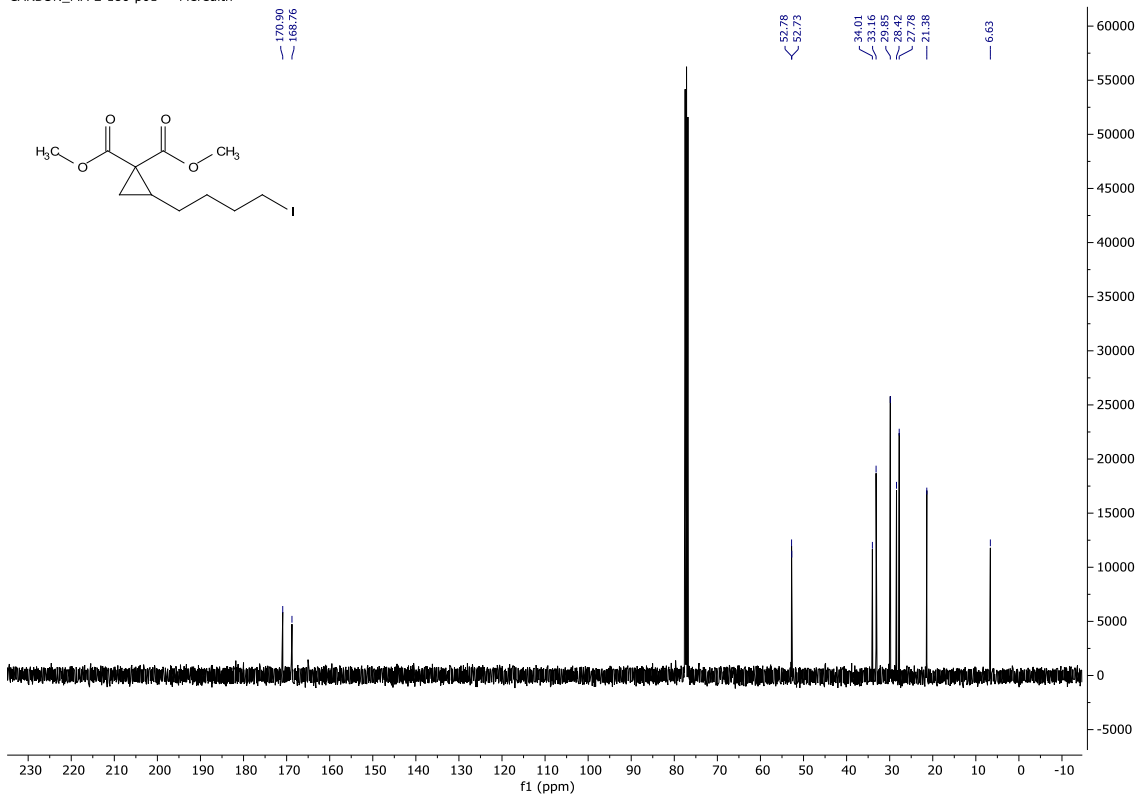
CARBON_MA-2-180cHC01 — STANDARD CARBON PARAMETERS —

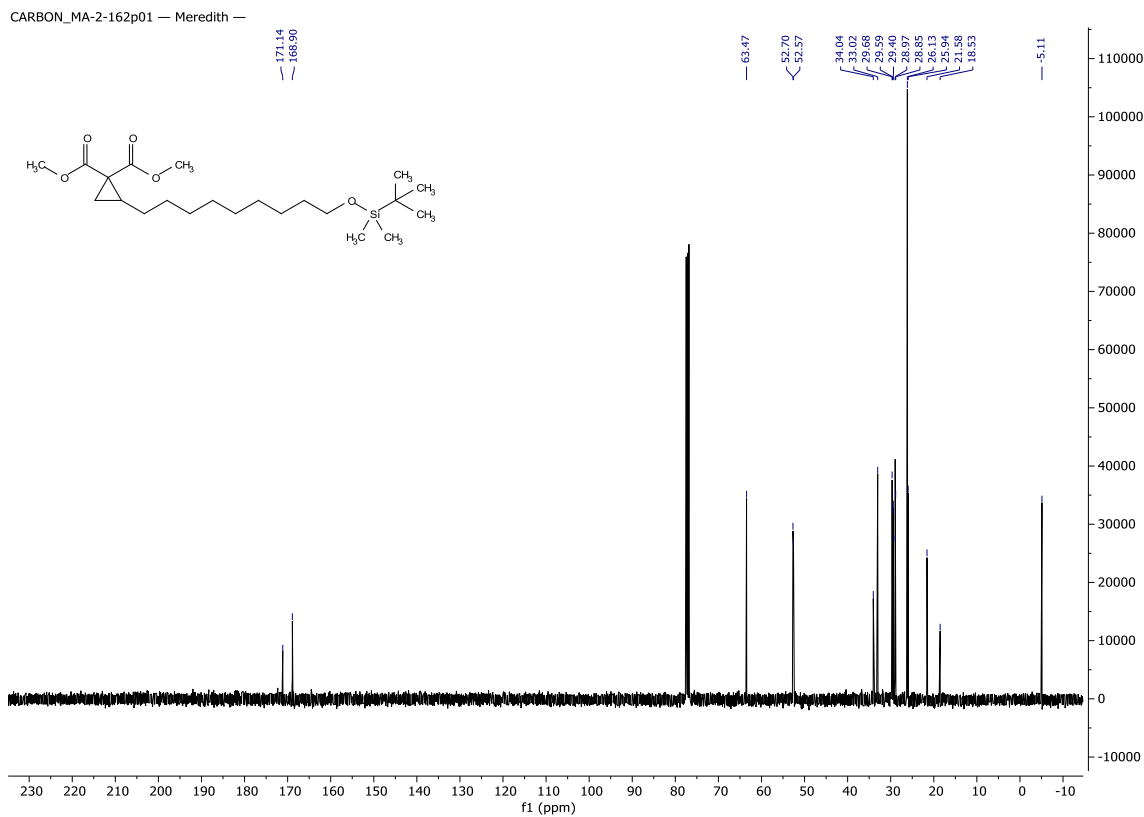
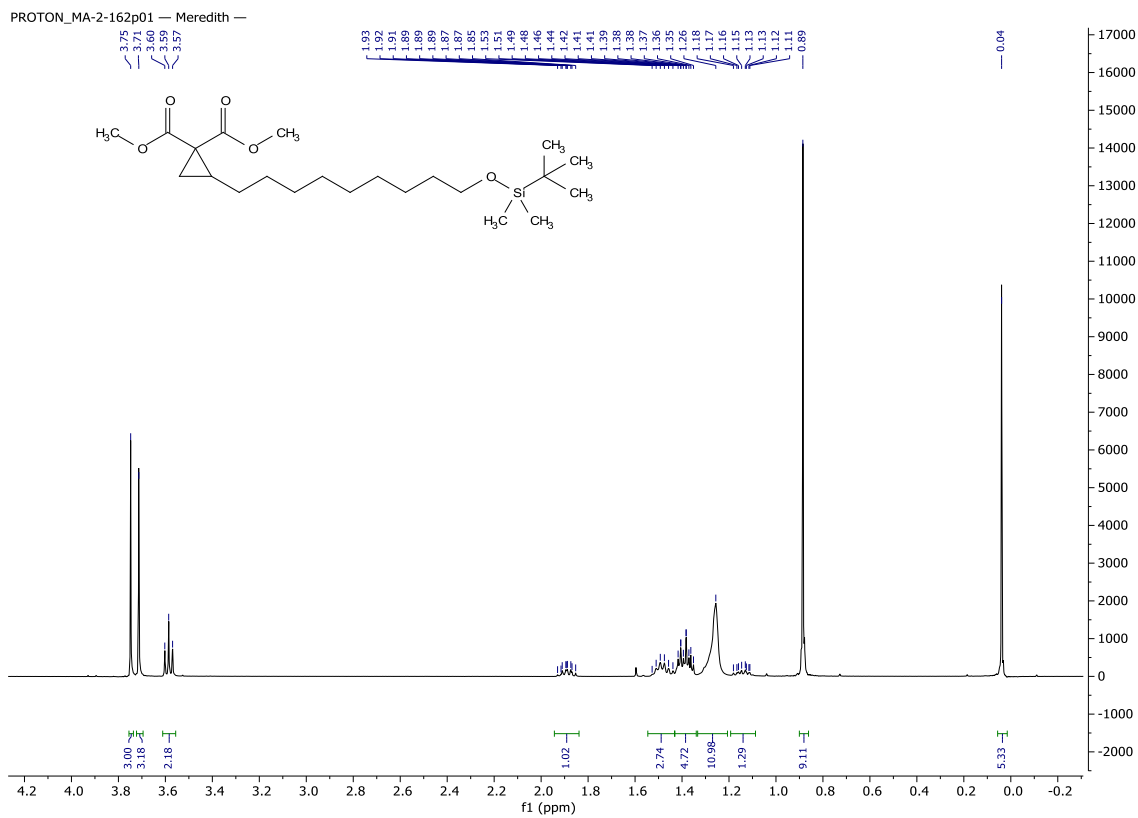


PROTON_MA-2-186-p01 — Meredith —

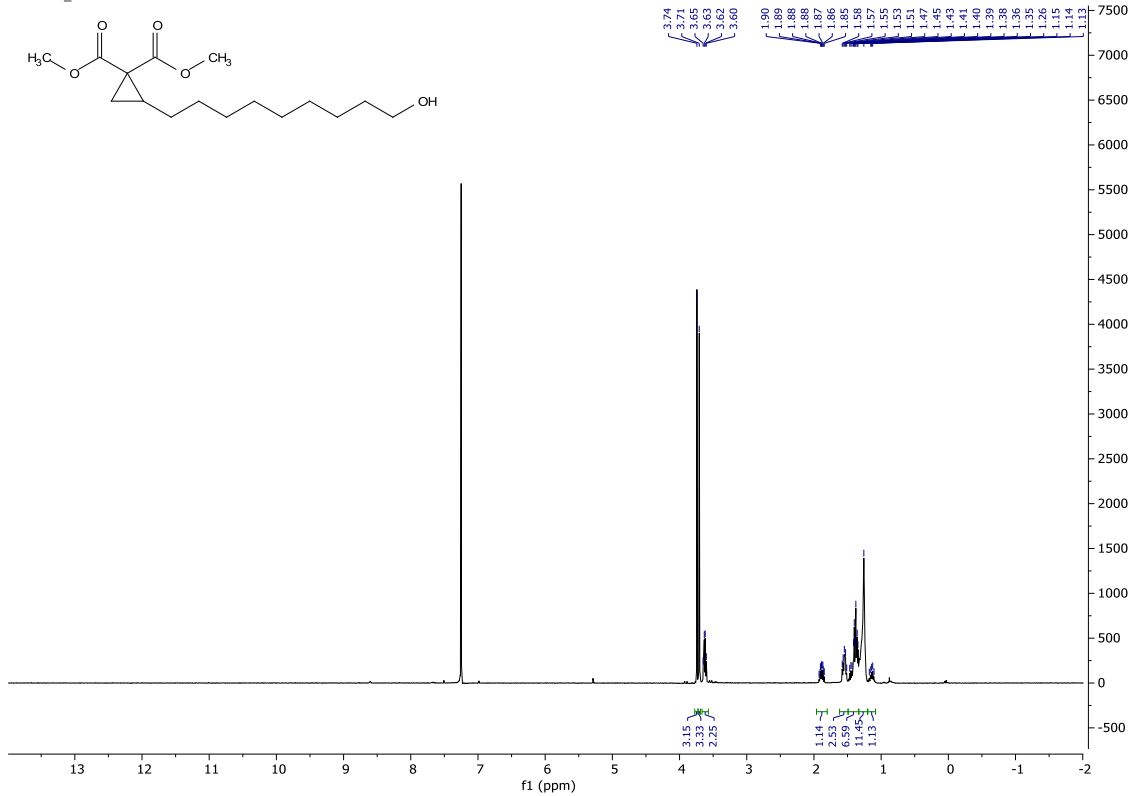


CARBON_MA-2-186-p01 — Meredith —

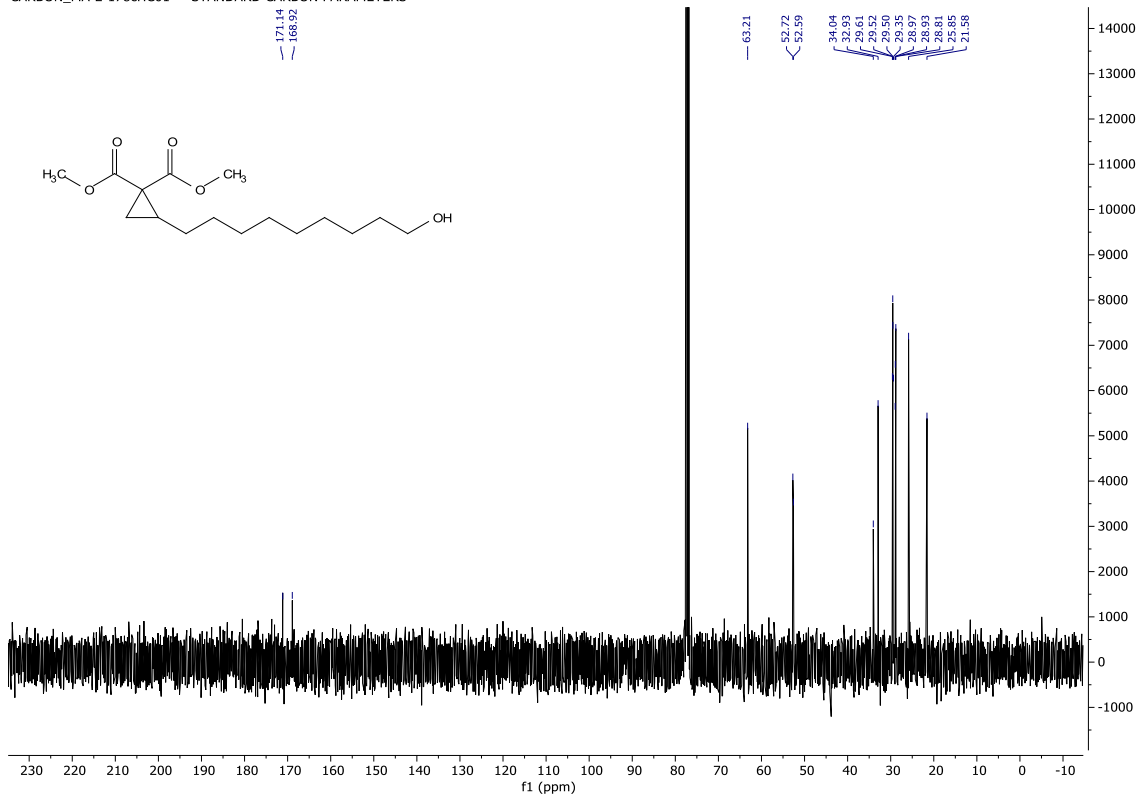




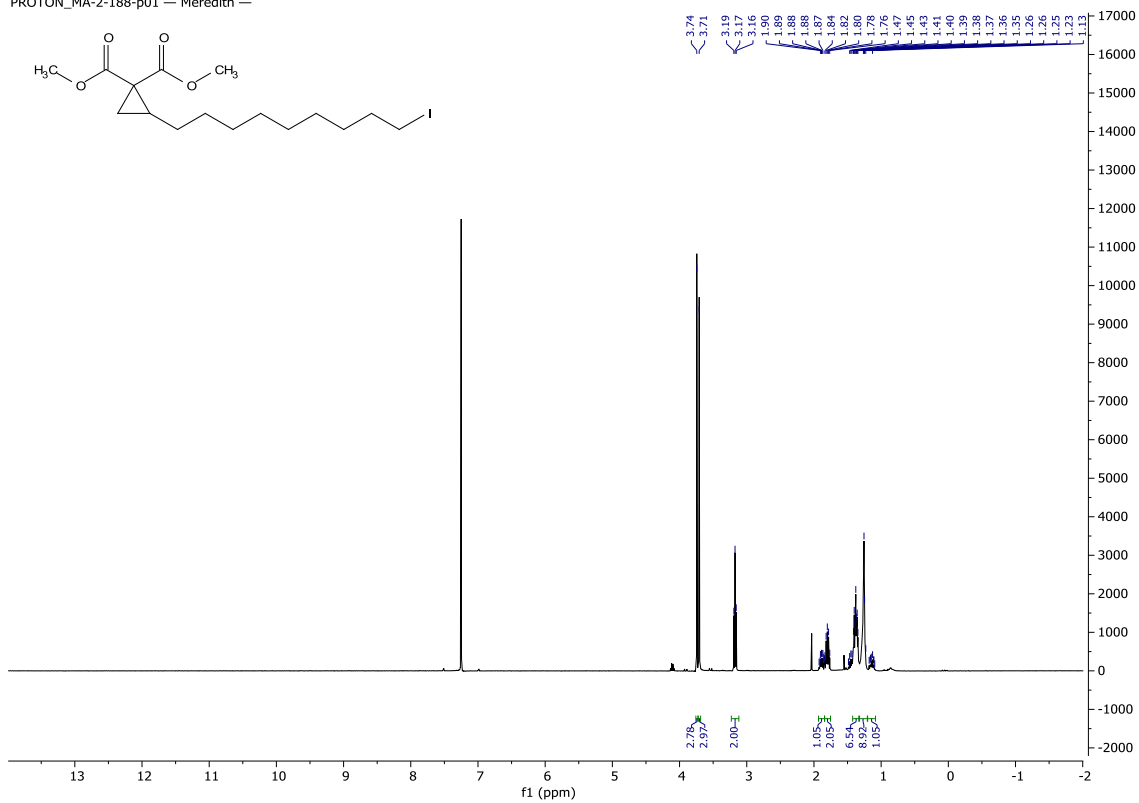
PROTON_MA-2-178cHC01 — Meredith —



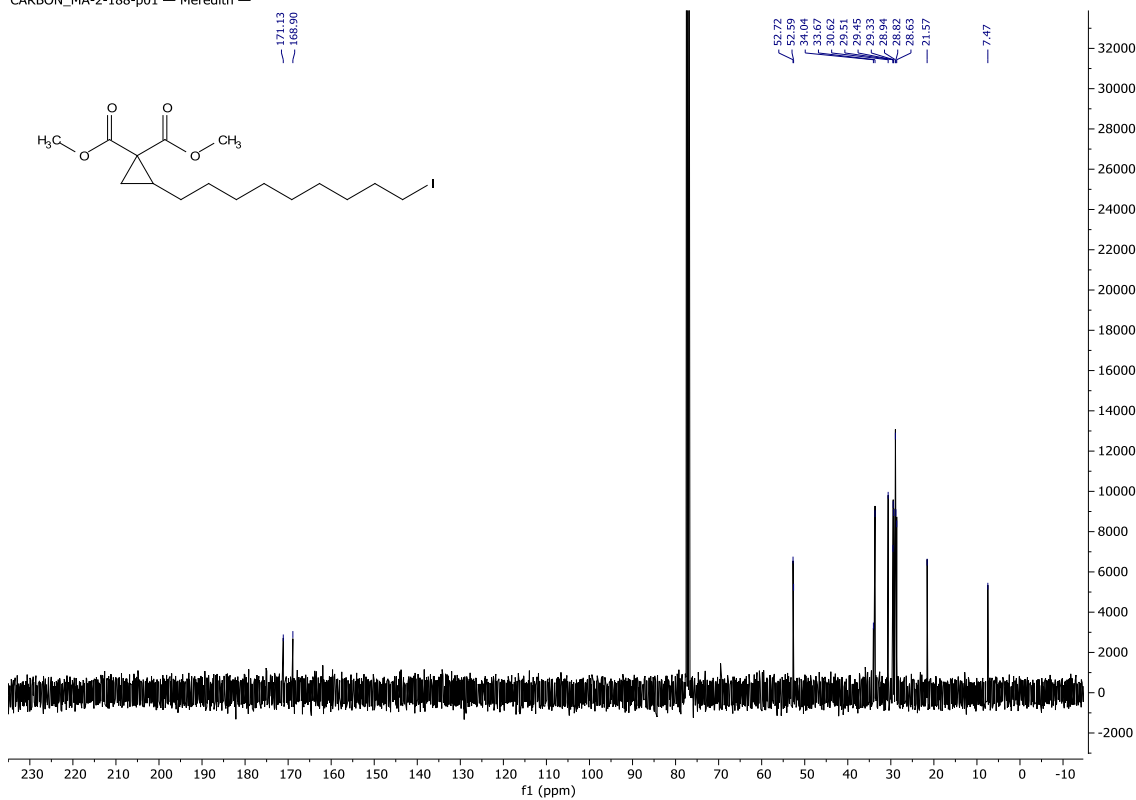
CARBON_MA-2-178cHC01 — STANDARD CARBON PARAMETERS —



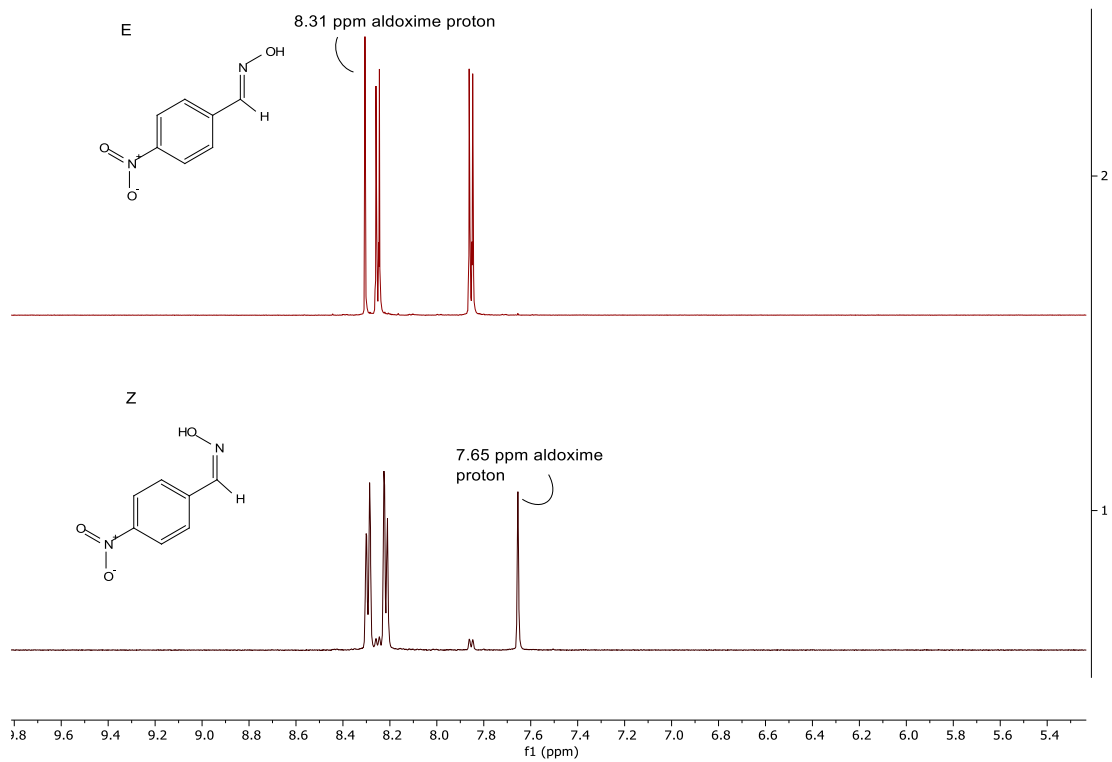
PROTON_MA-2-188-p01 — Meredith —



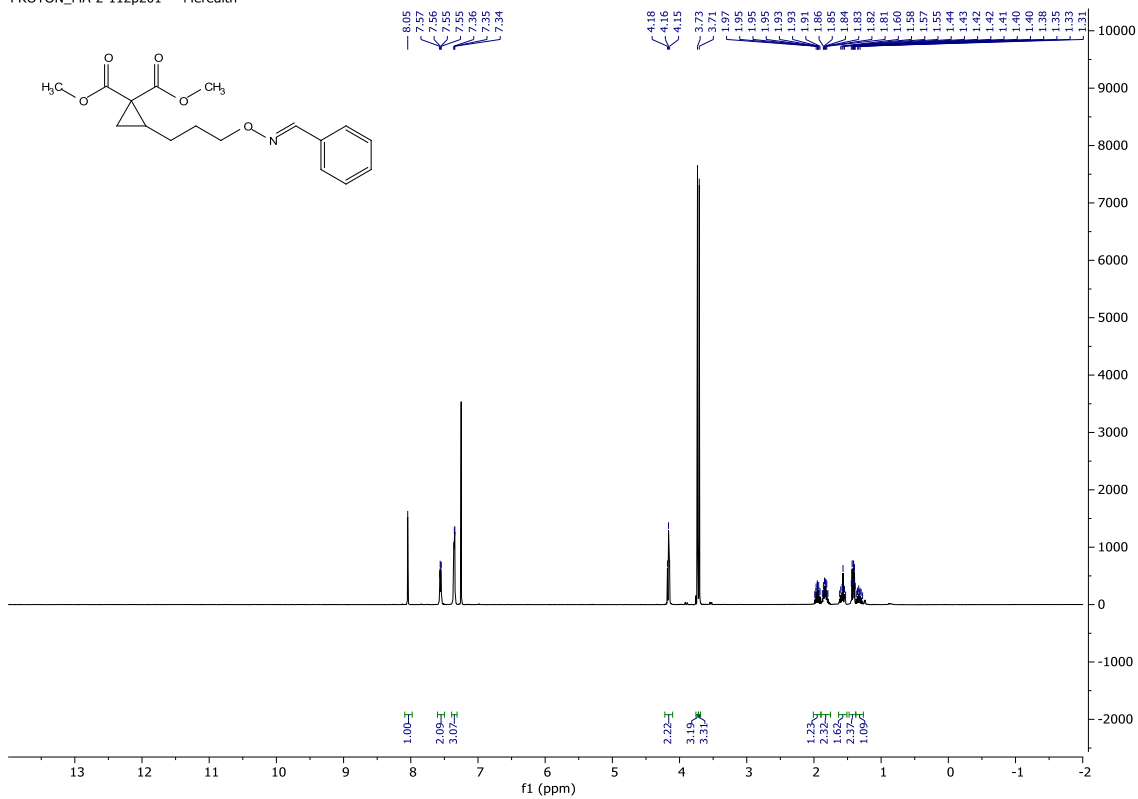
CARBON_MA-2-188-p01 — Meredith —



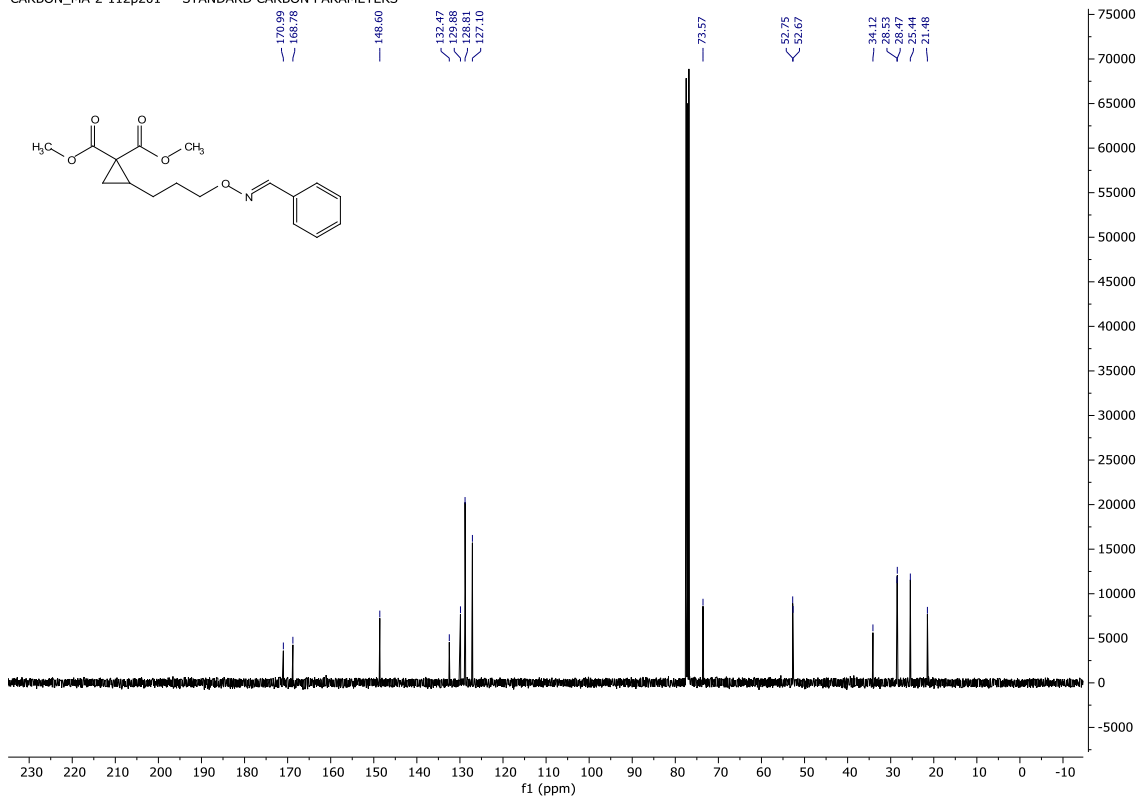
PROTON_MRvpnitroxime-dms0_01 --



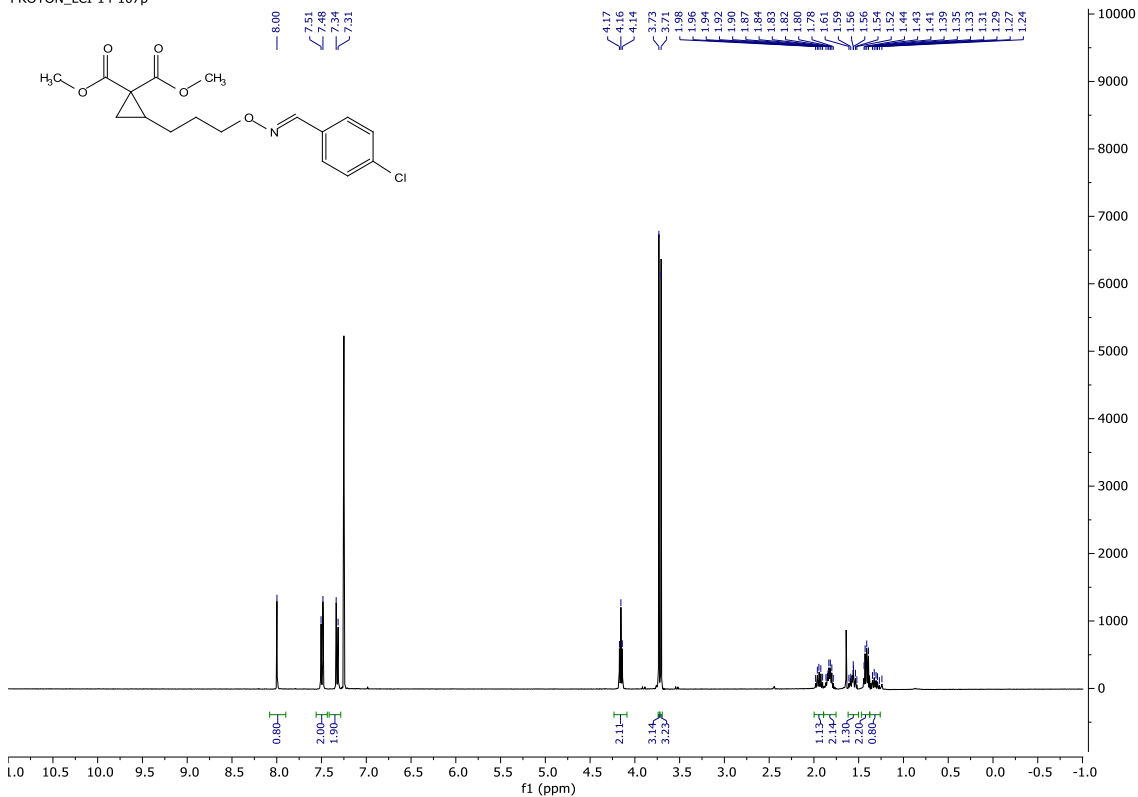
PROTON_MA-2-112p201 — Meredith —



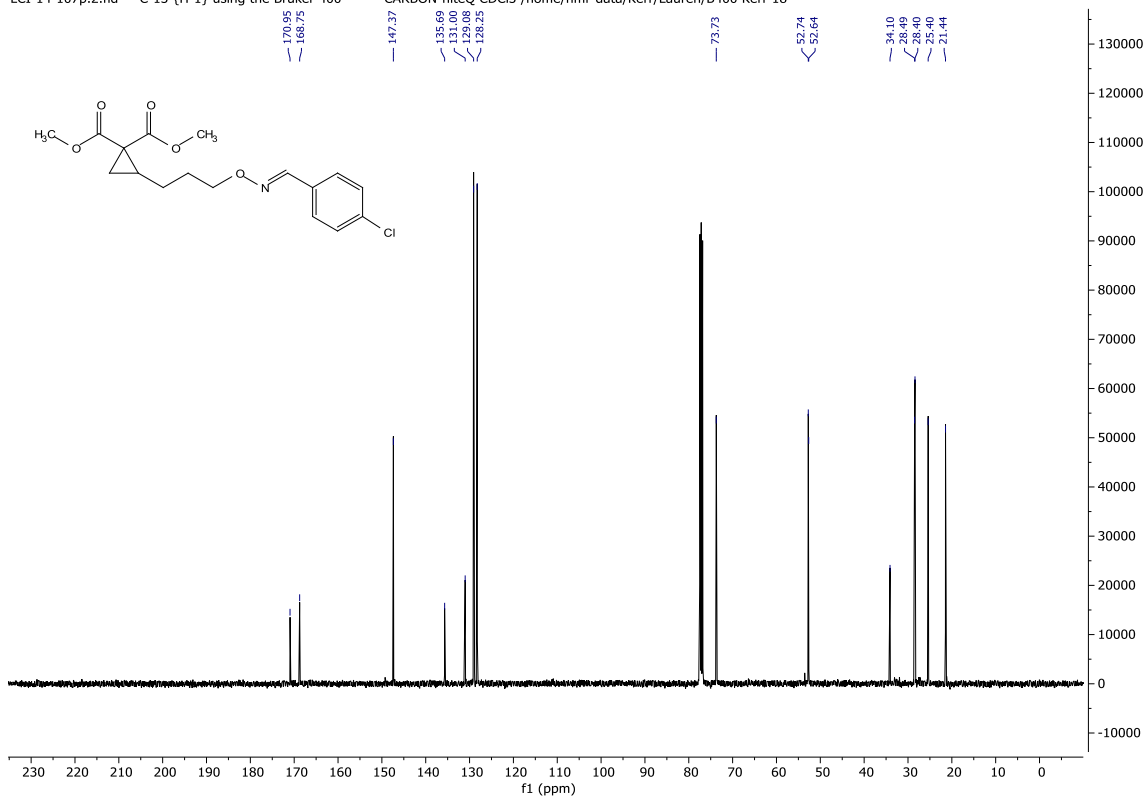
CARBON_MA-2-112p201 — STANDARD CARBON PARAMETERS —



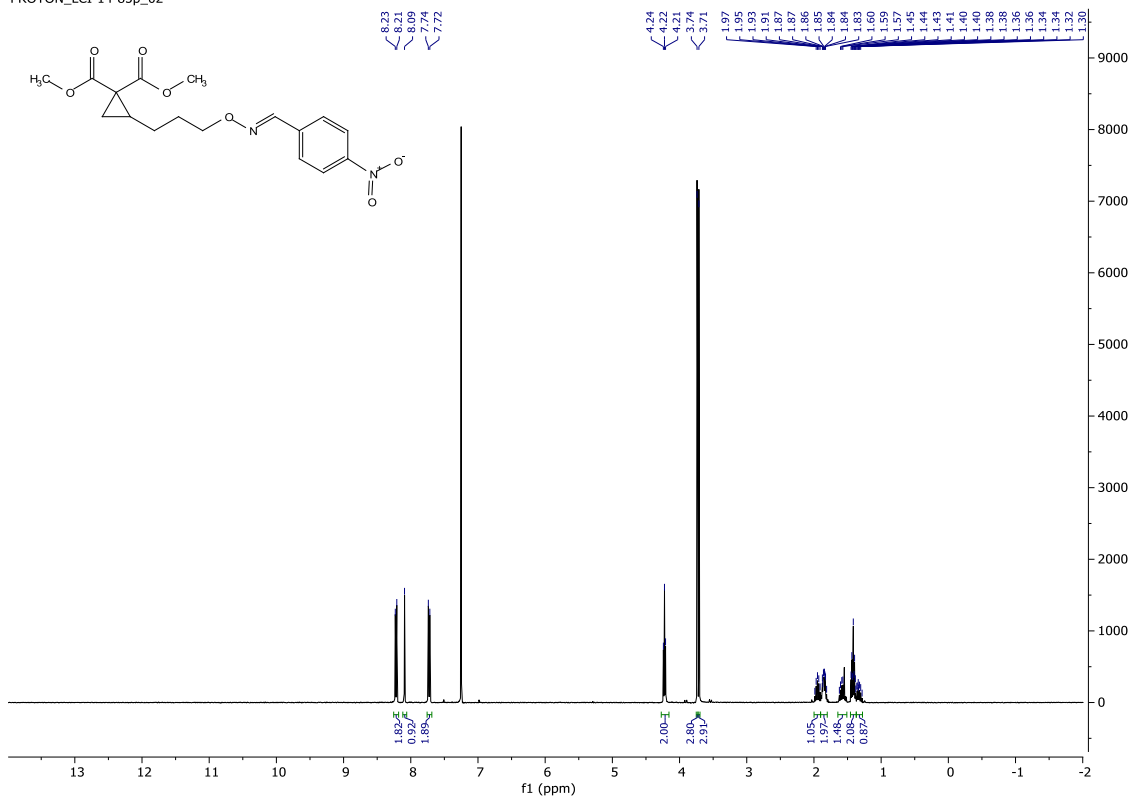
PROTON_LCI-14-107p



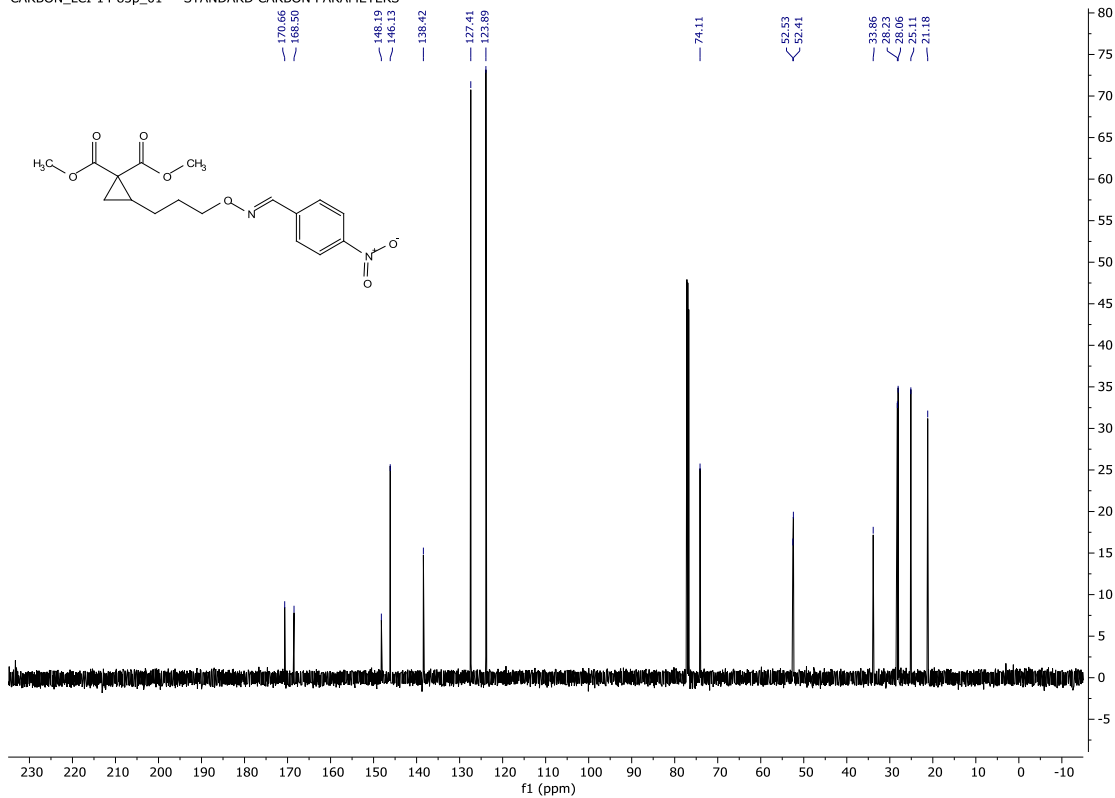
LCI-14-107p.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 18



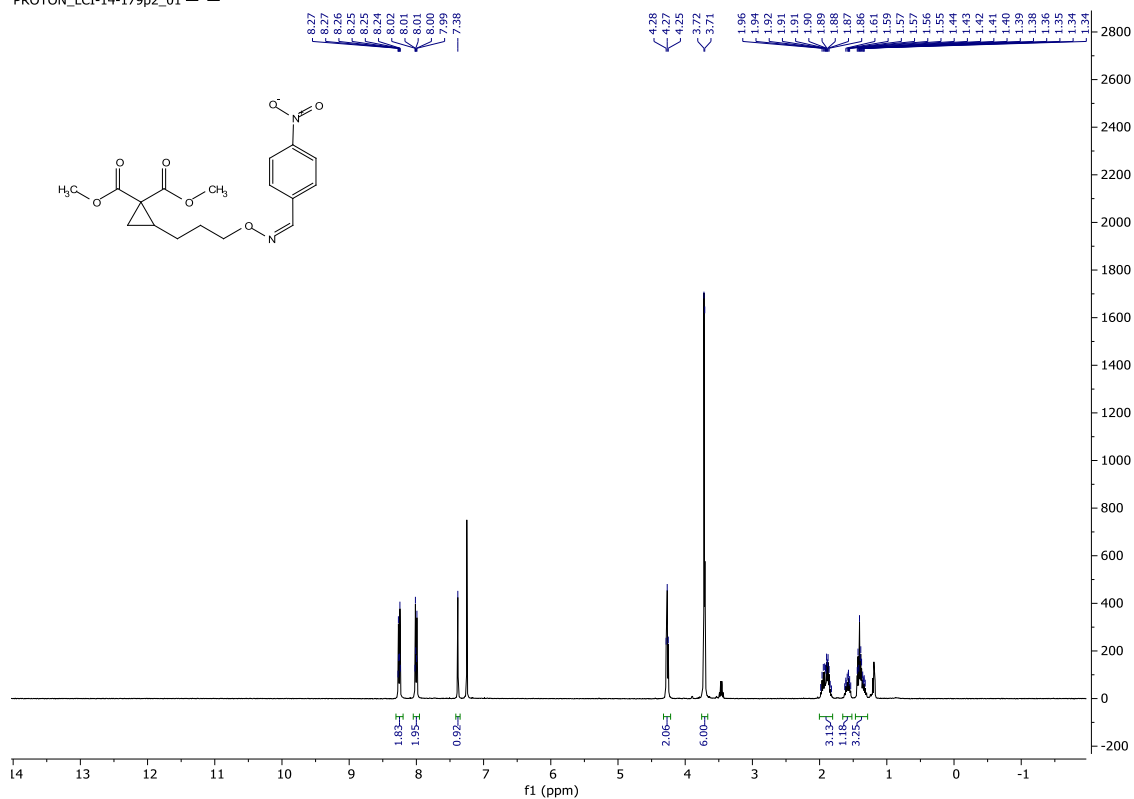
PROTON_LCI-14-85p_02



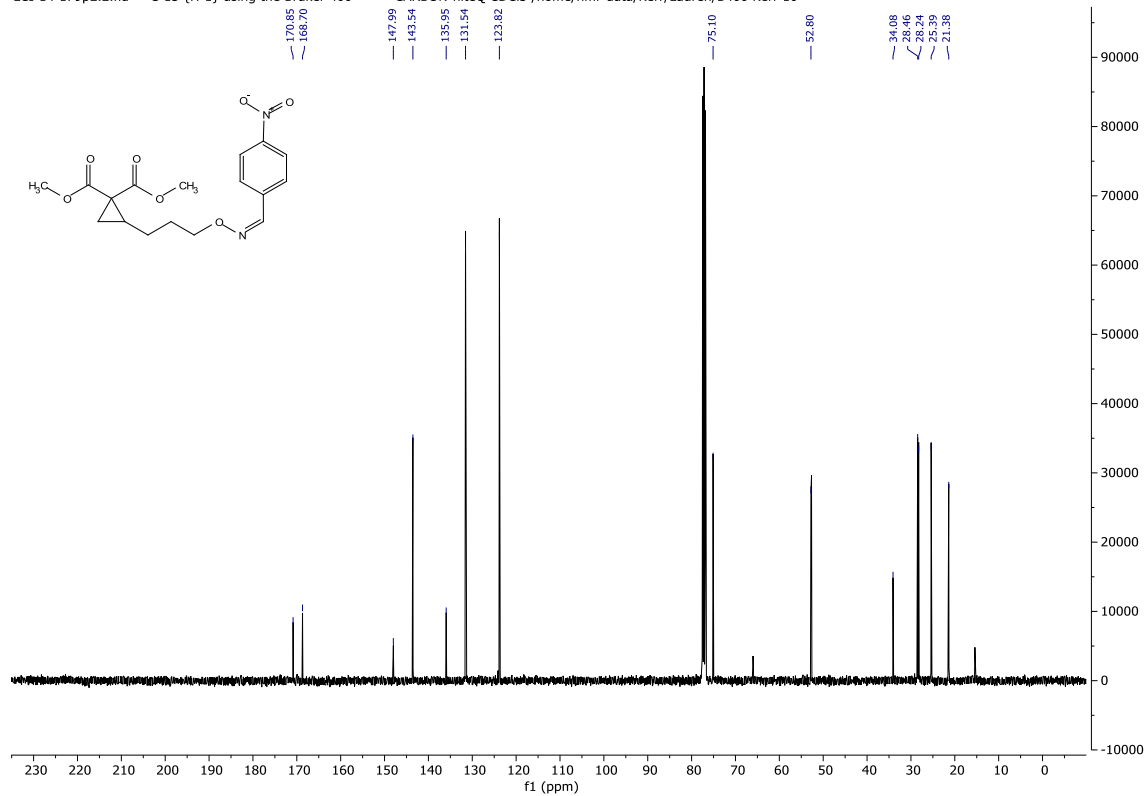
CARBON_LCI-14-85p_01 — STANDARD CARBON PARAMETERS —



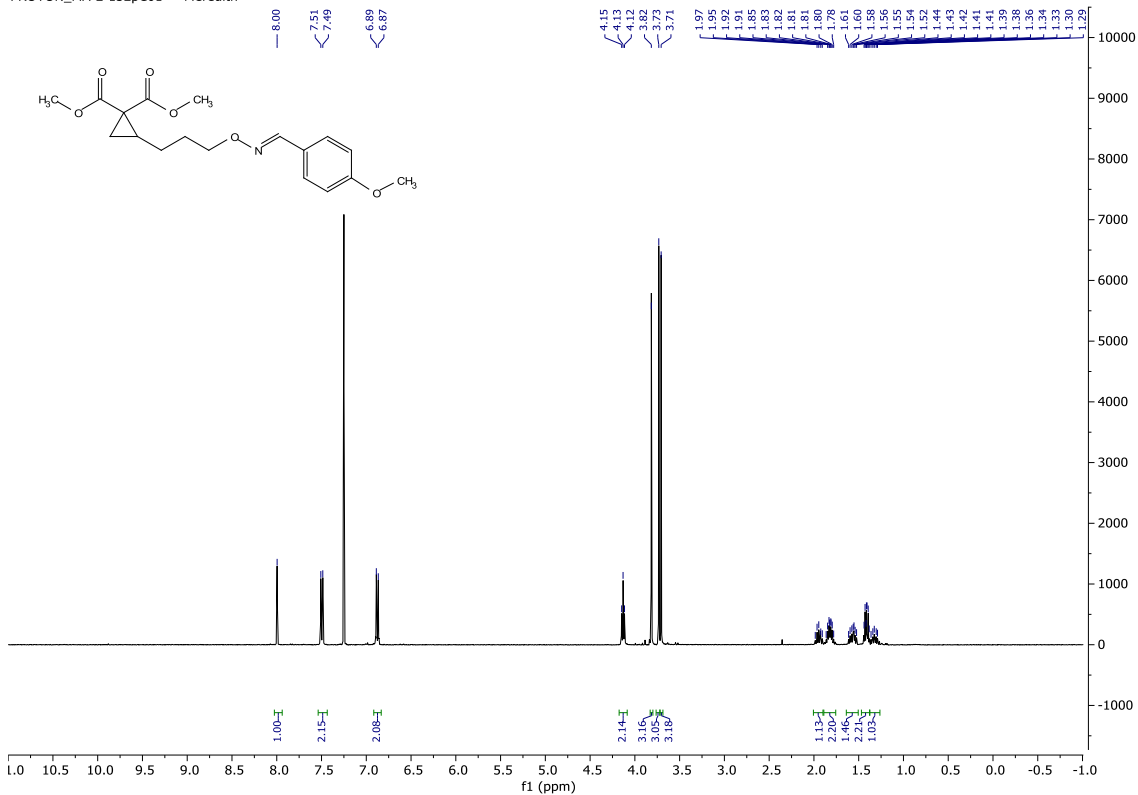
PROTON_LCI-14-179p2_01 —



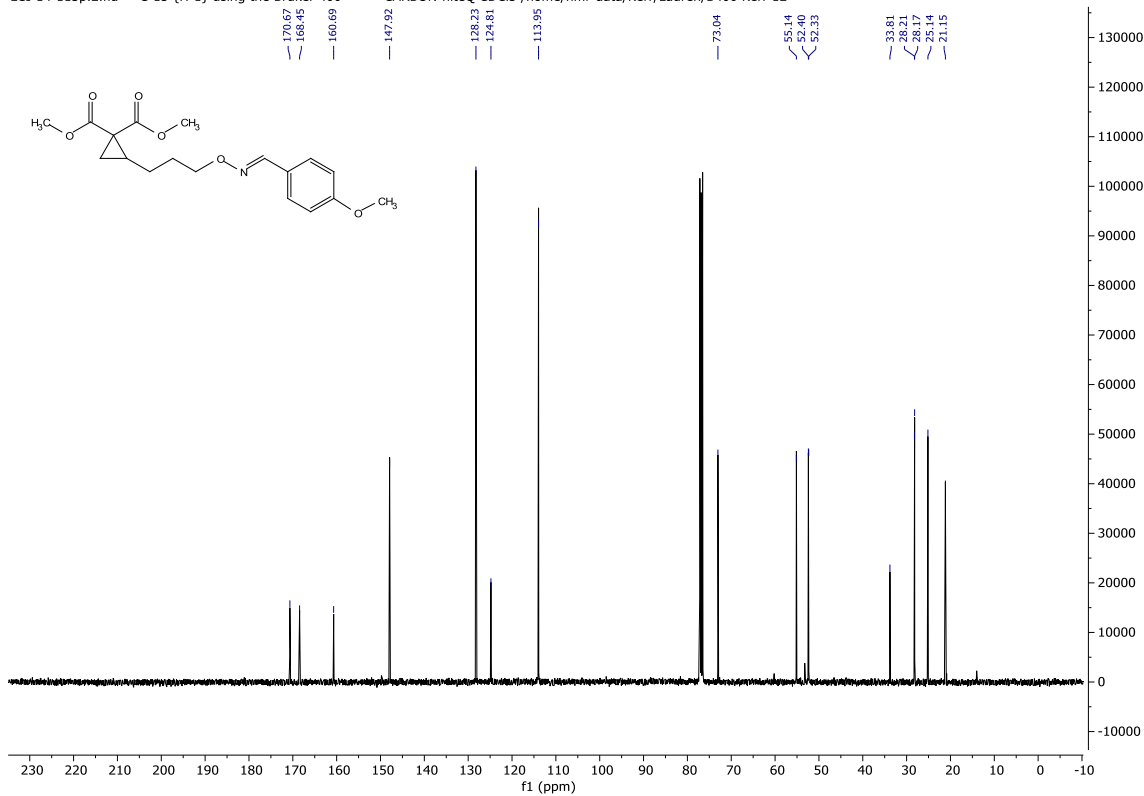
LCI-14-179p2.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 10



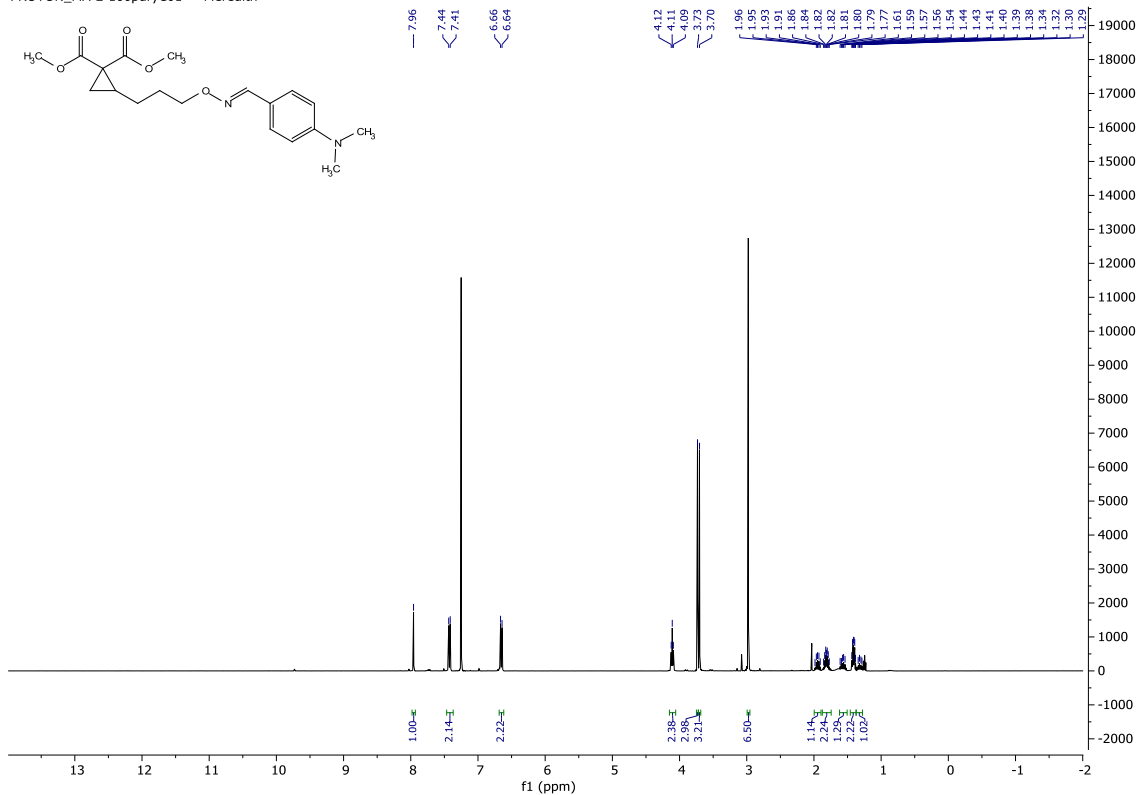
PROTON_MA-2-132pC01 — Meredith —



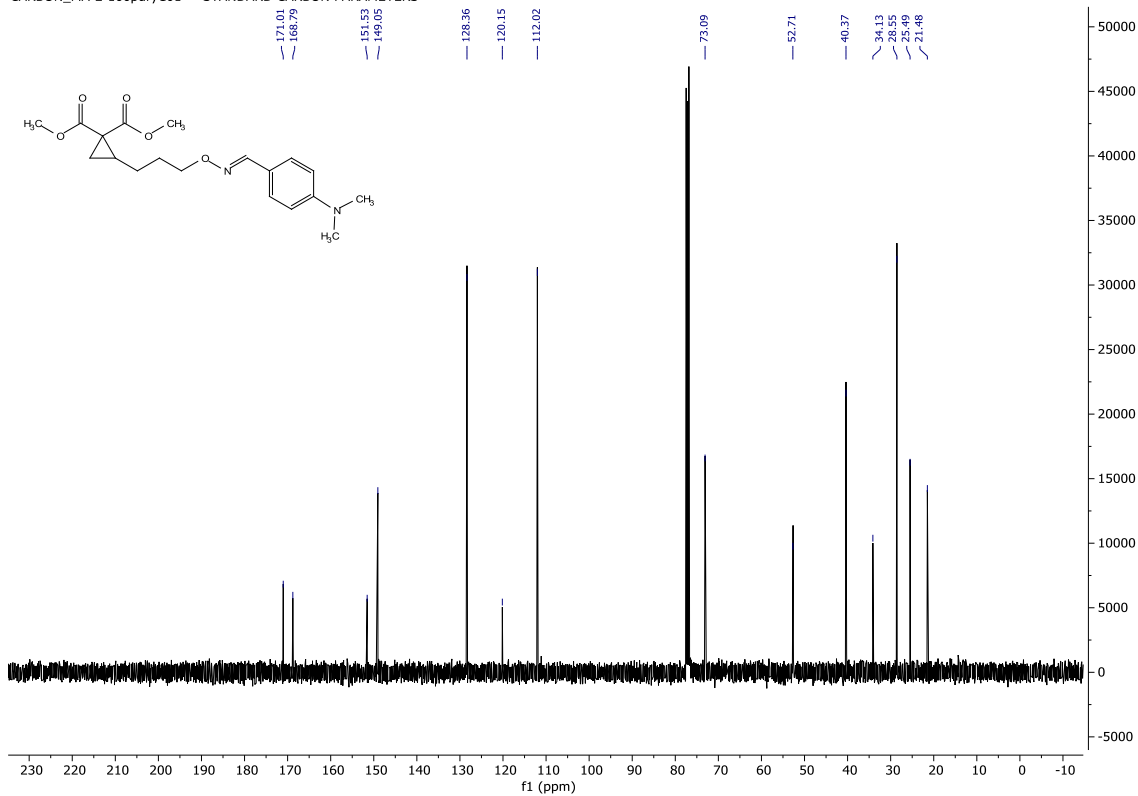
LCI-14-113p.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 12

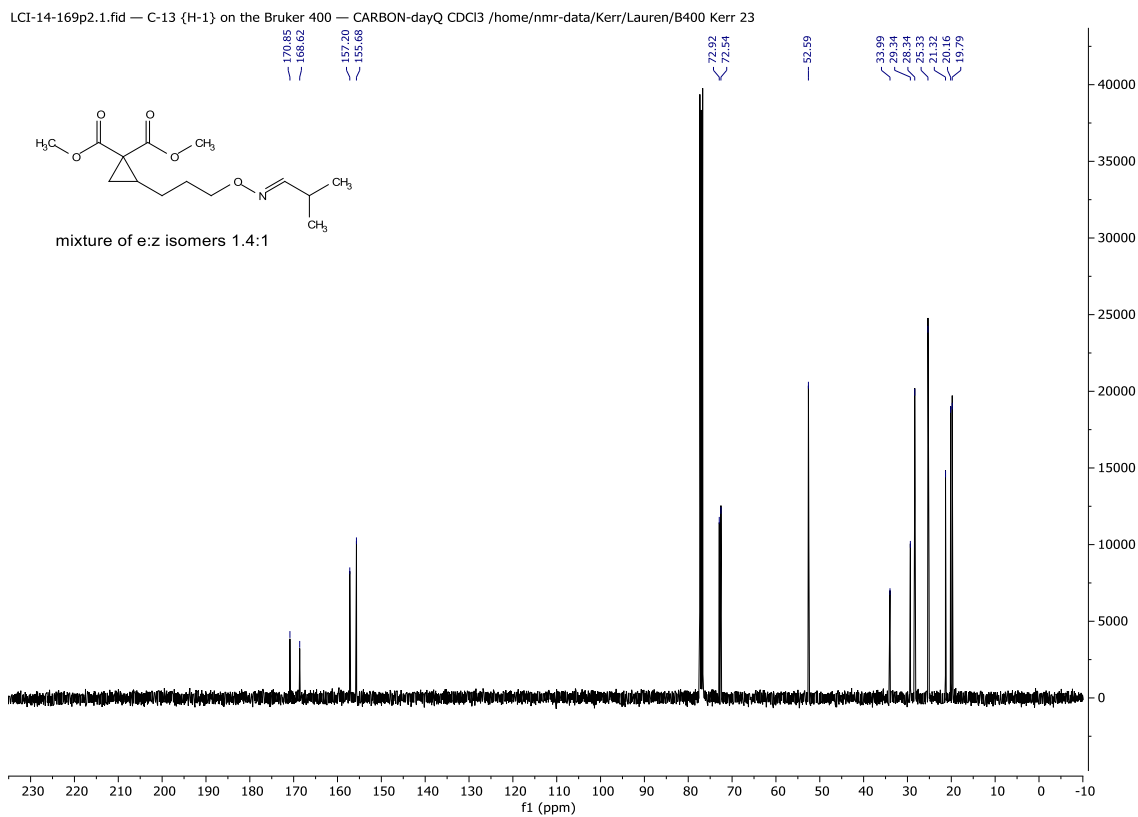
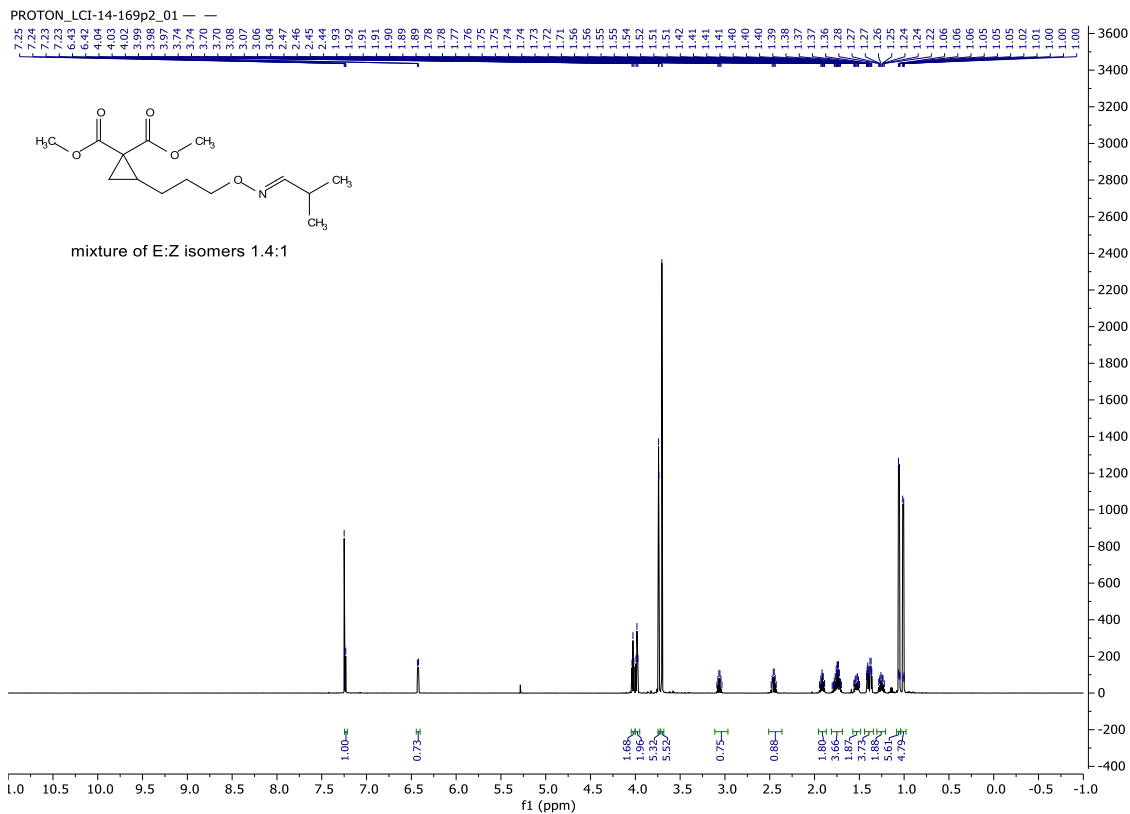


PROTON_MA-2-166pdryC01 — Meredith —

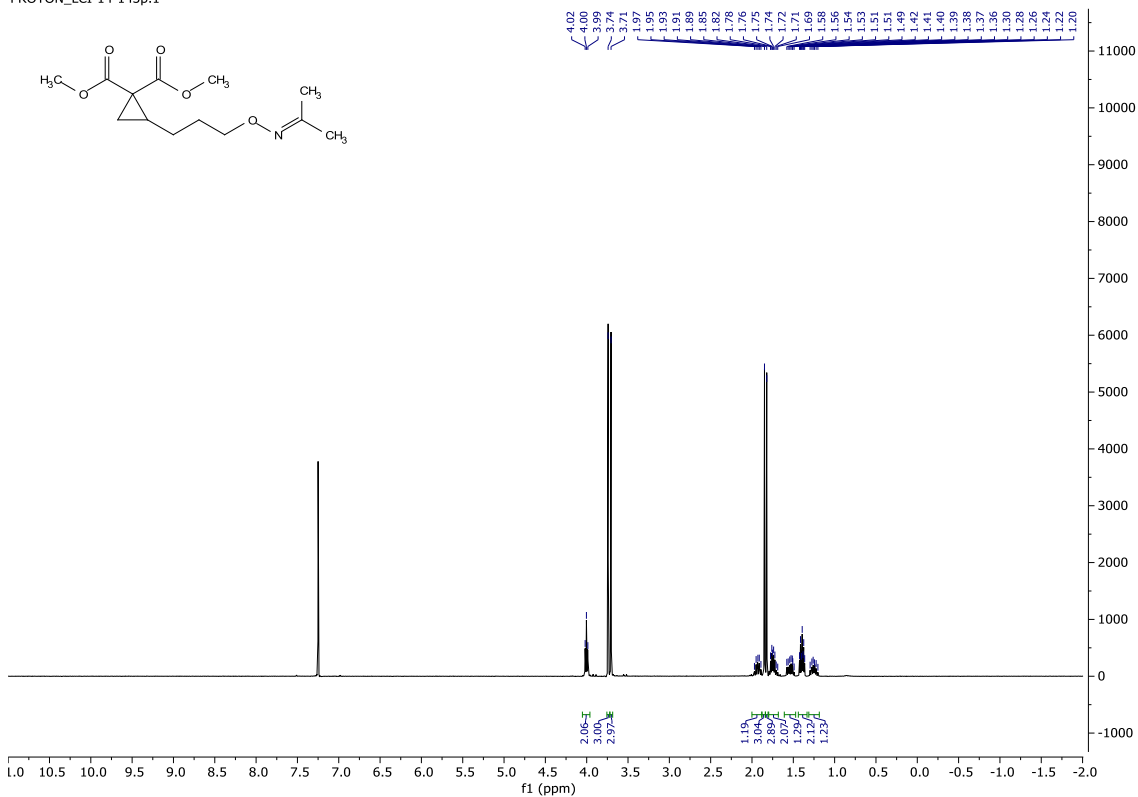


CARBON_MA-2-166pdryC01 — STANDARD CARBON PARAMETERS —

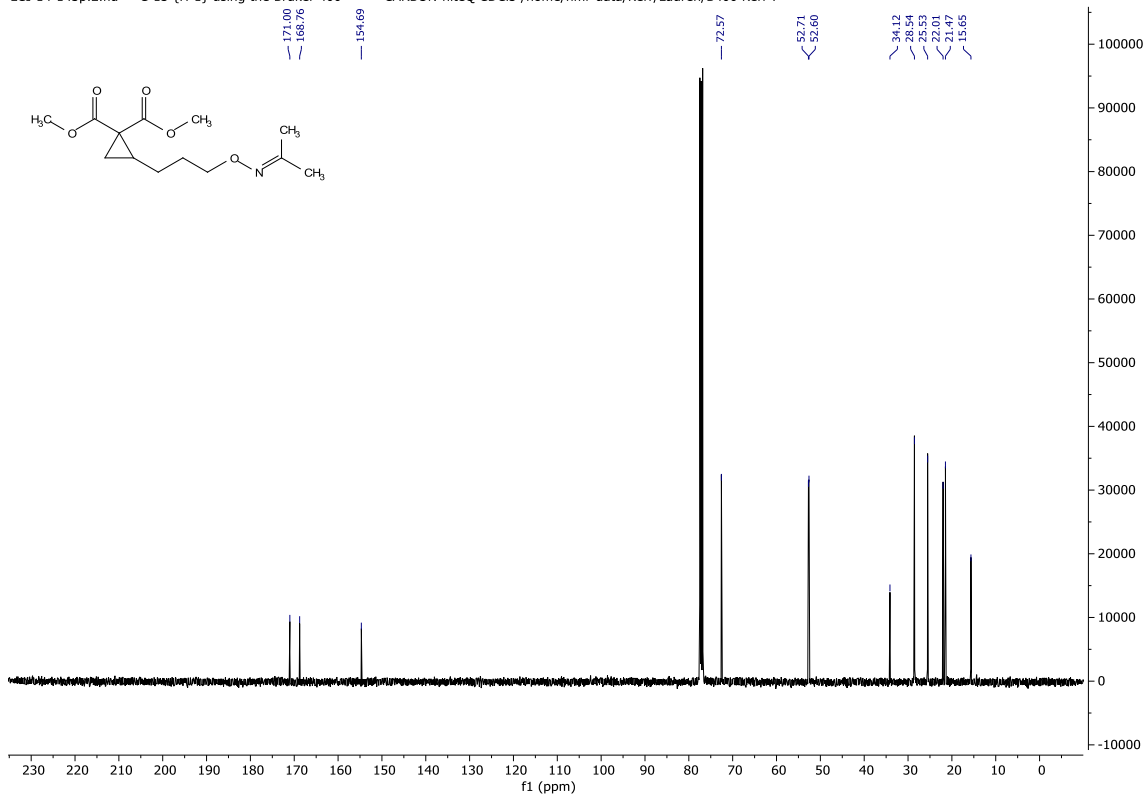


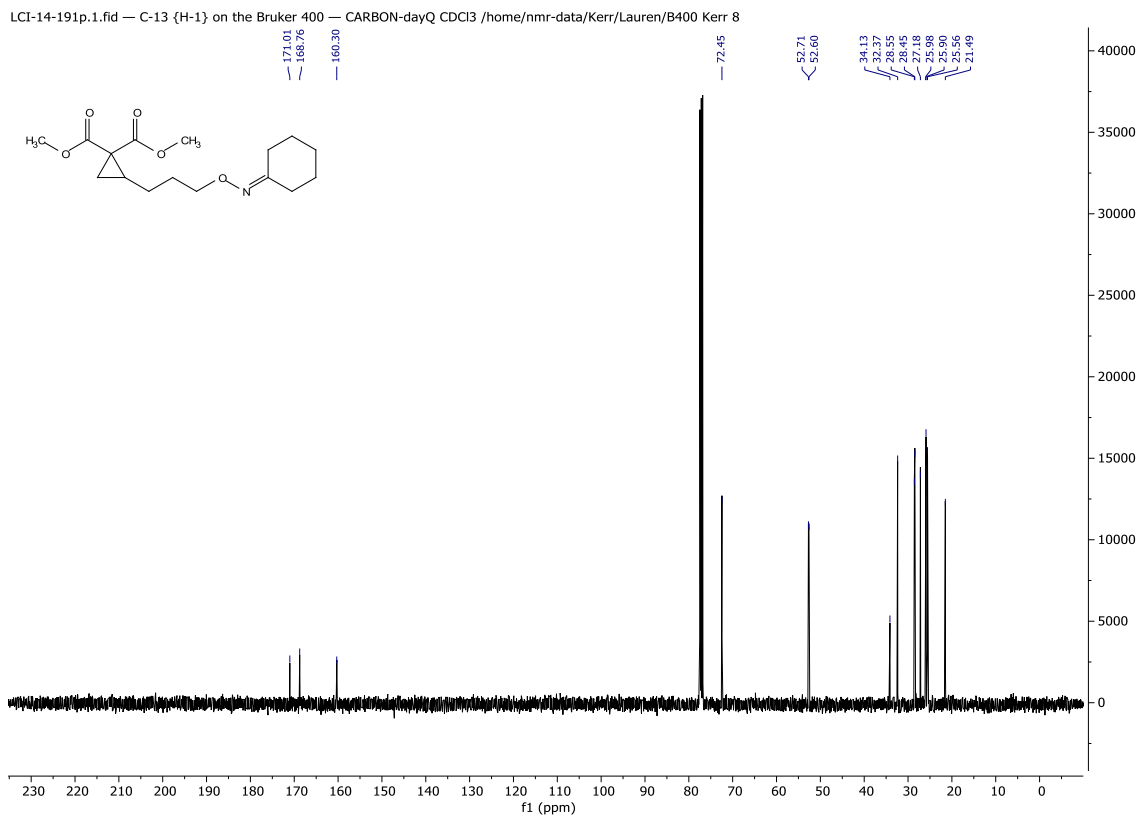
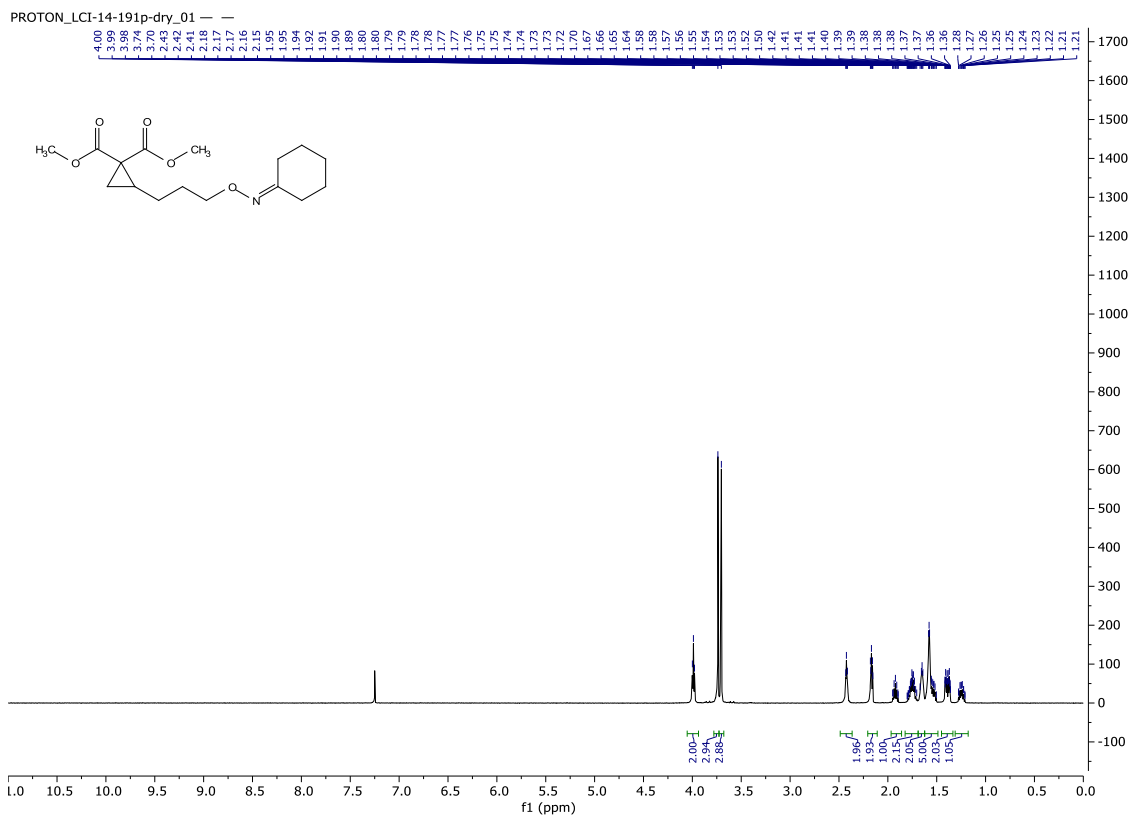


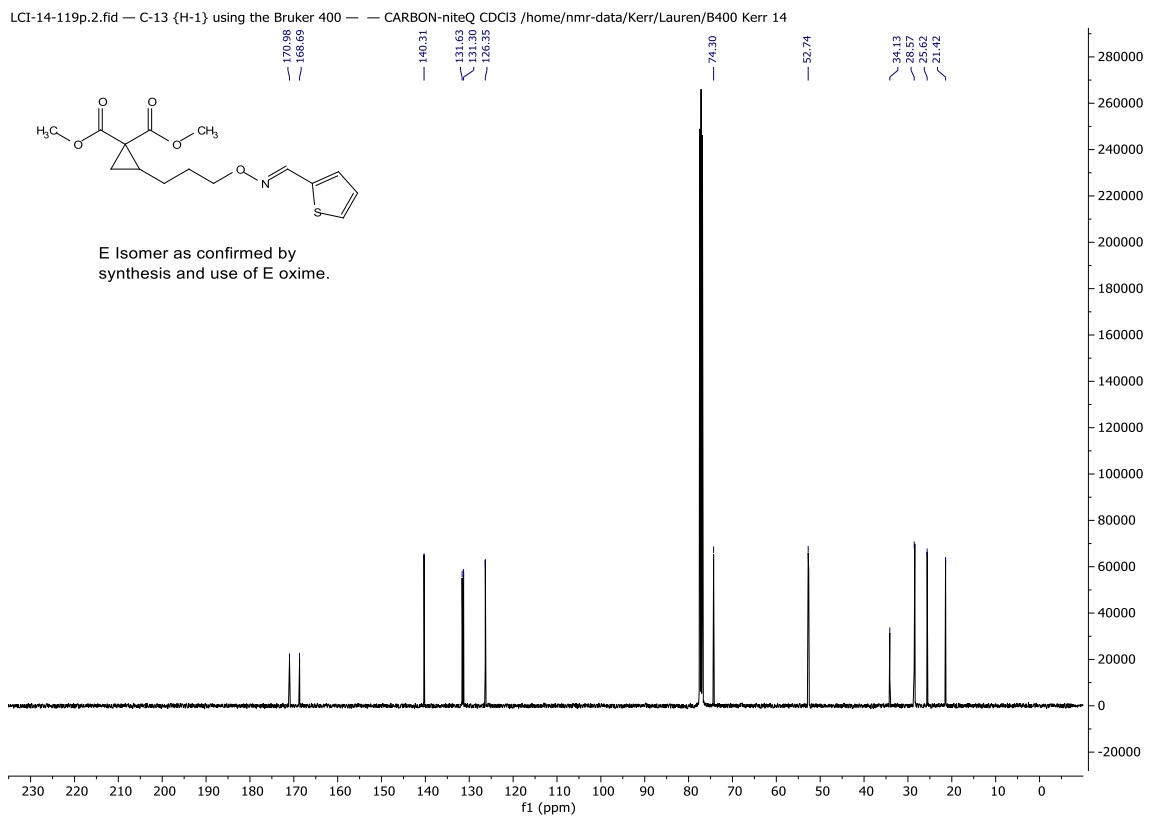
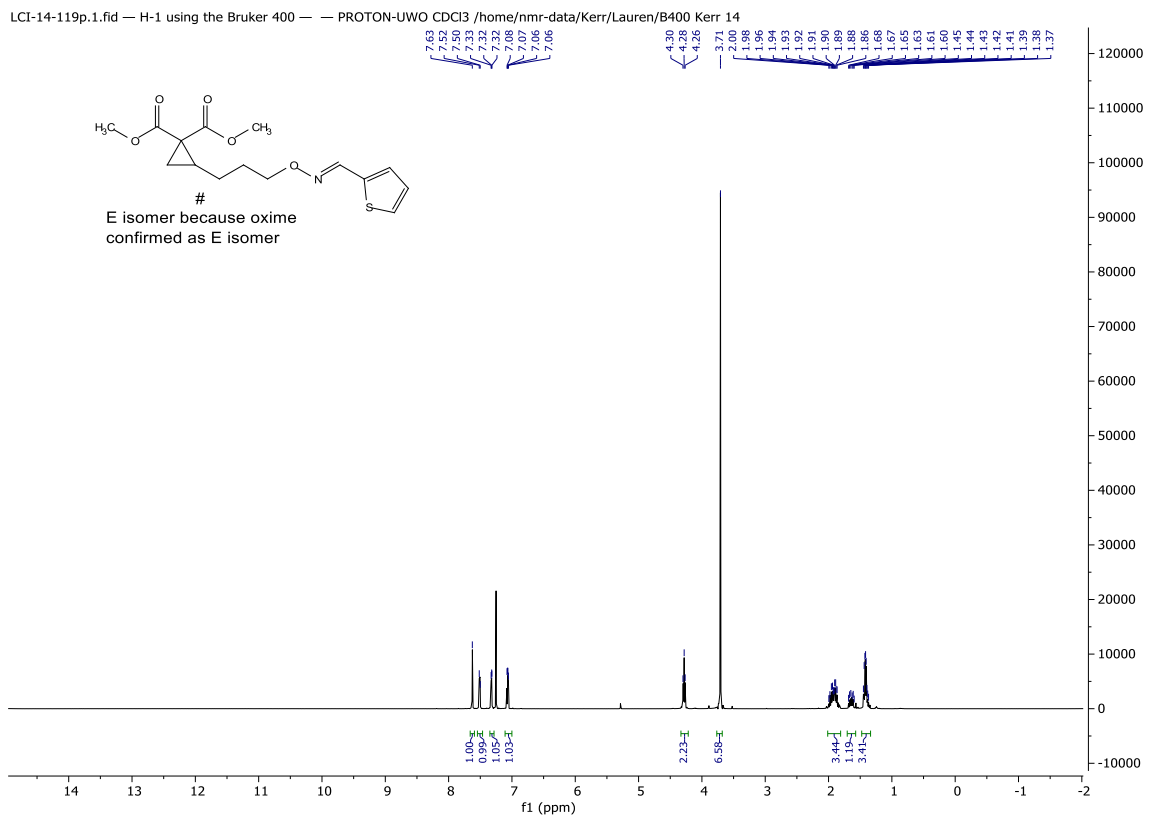
PROTON_LCI-14-143p.1



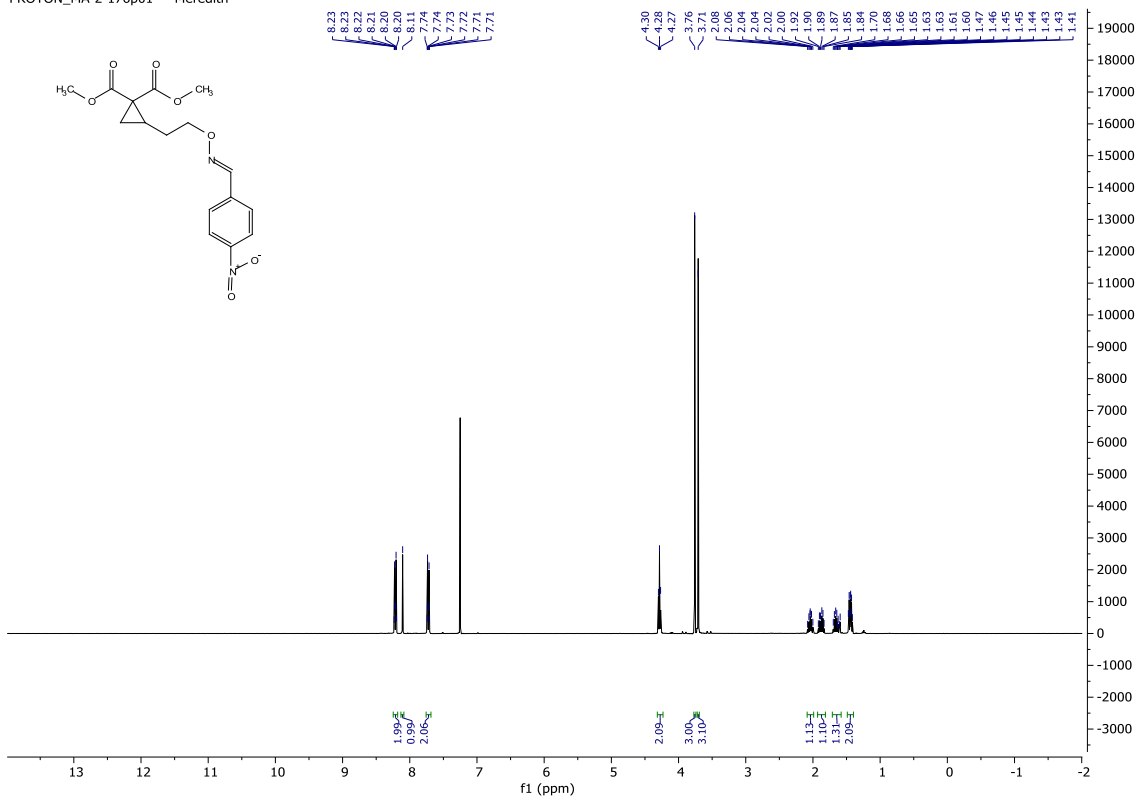
LCI-14-143p.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 7



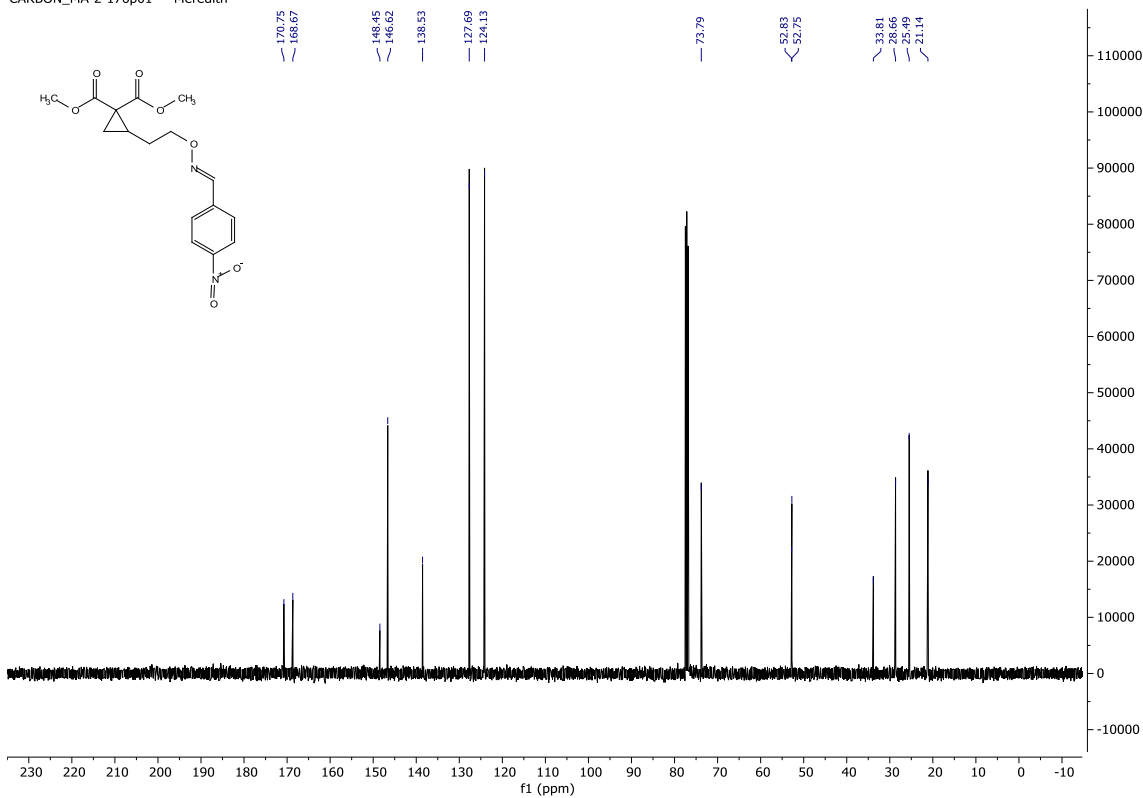




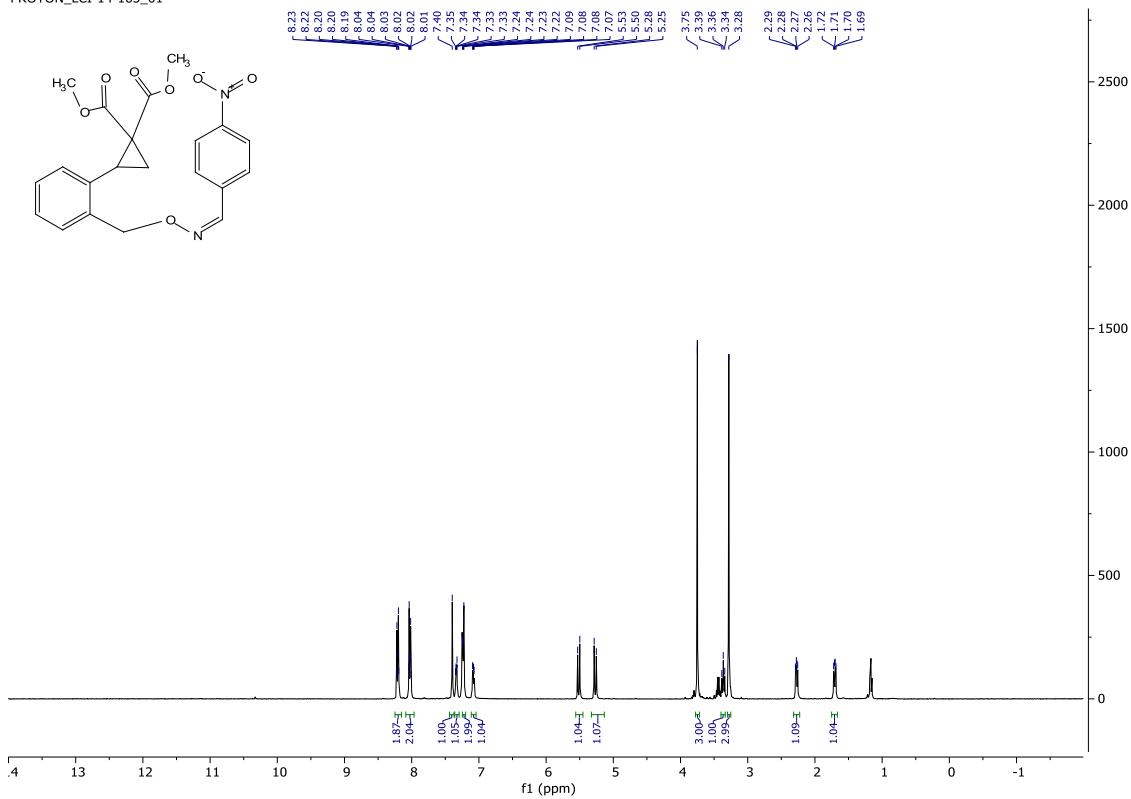
PROTON_MA-2-176p01 — Meredith —



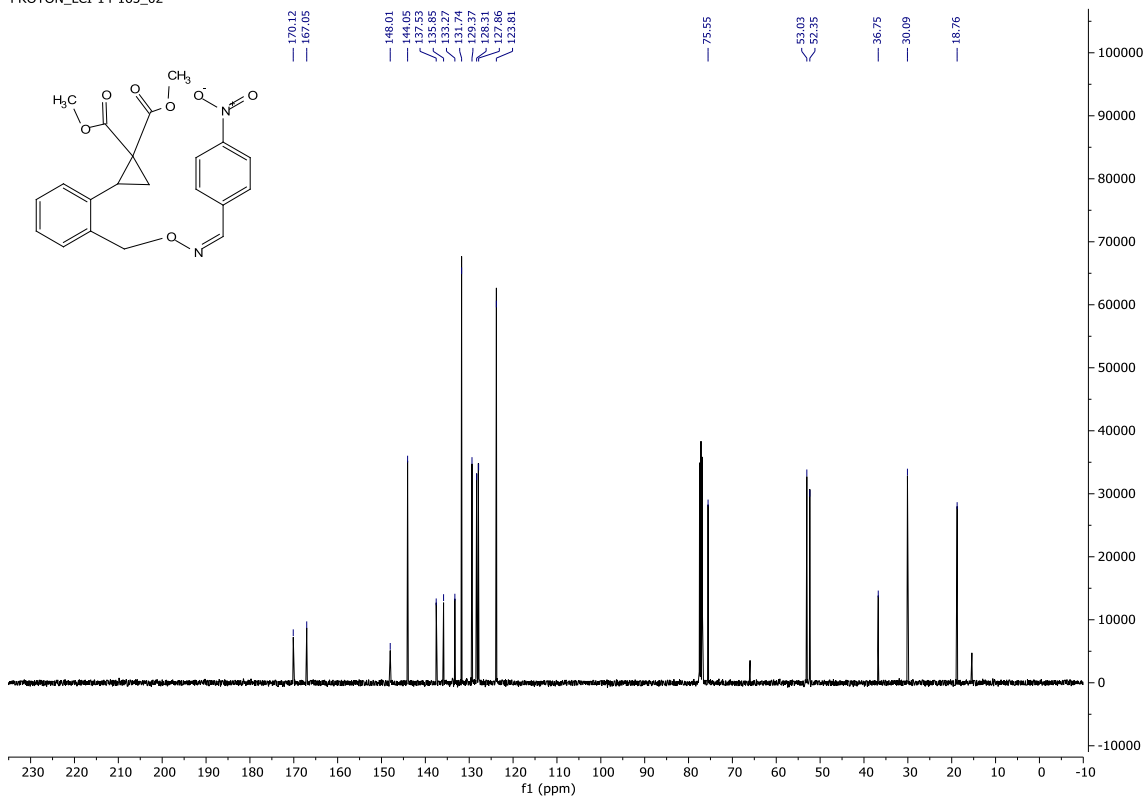
CARBON_MA-2-176p01 — Meredith —



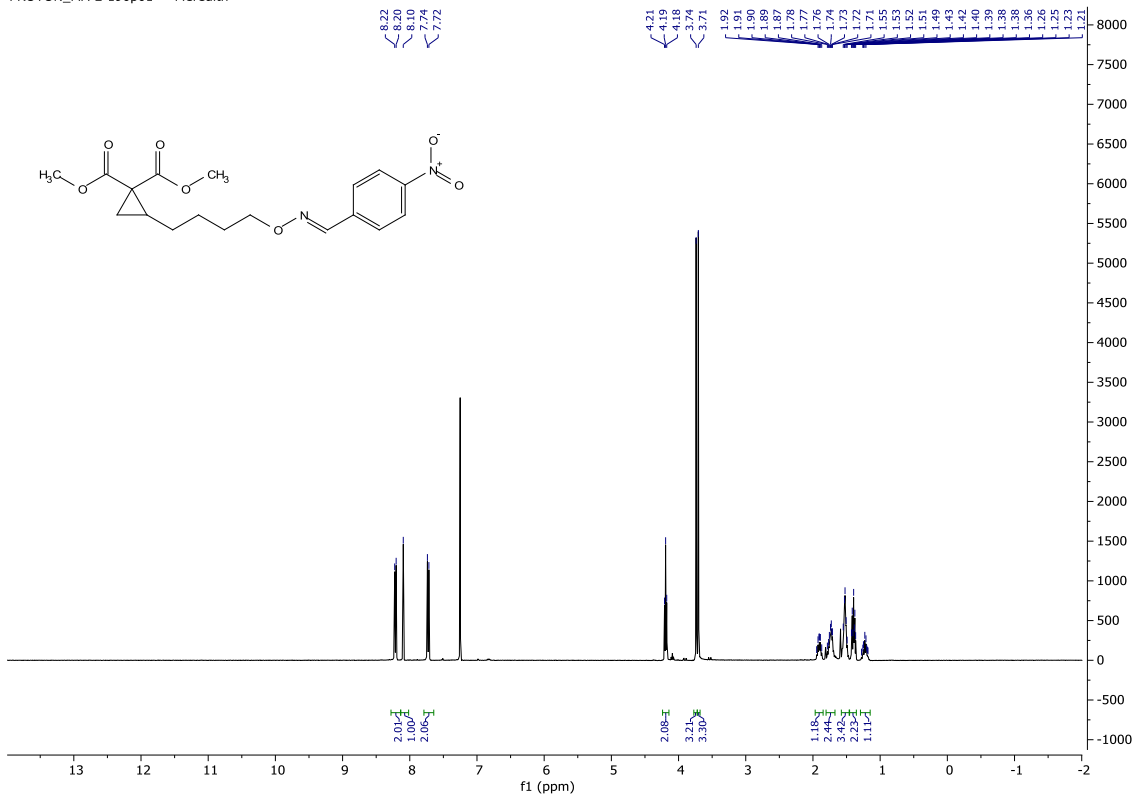
PROTON_LCI-14-165_01



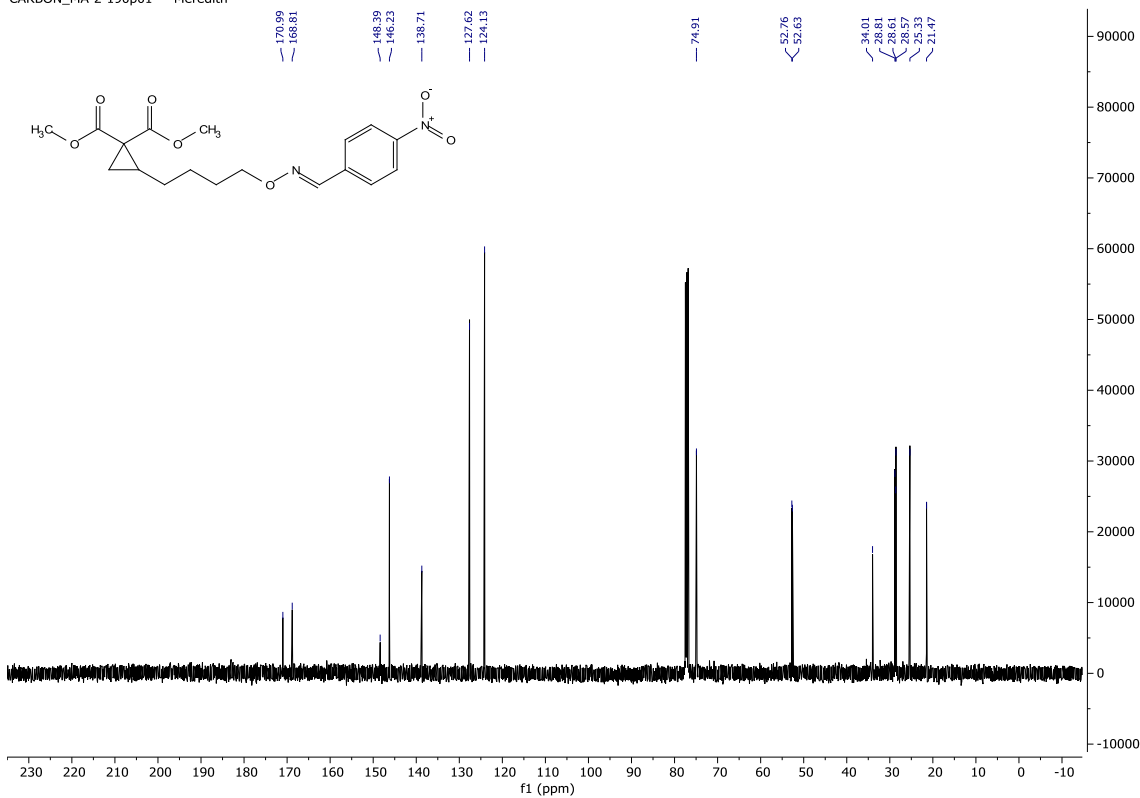
PROTON_LCI-14-165_02



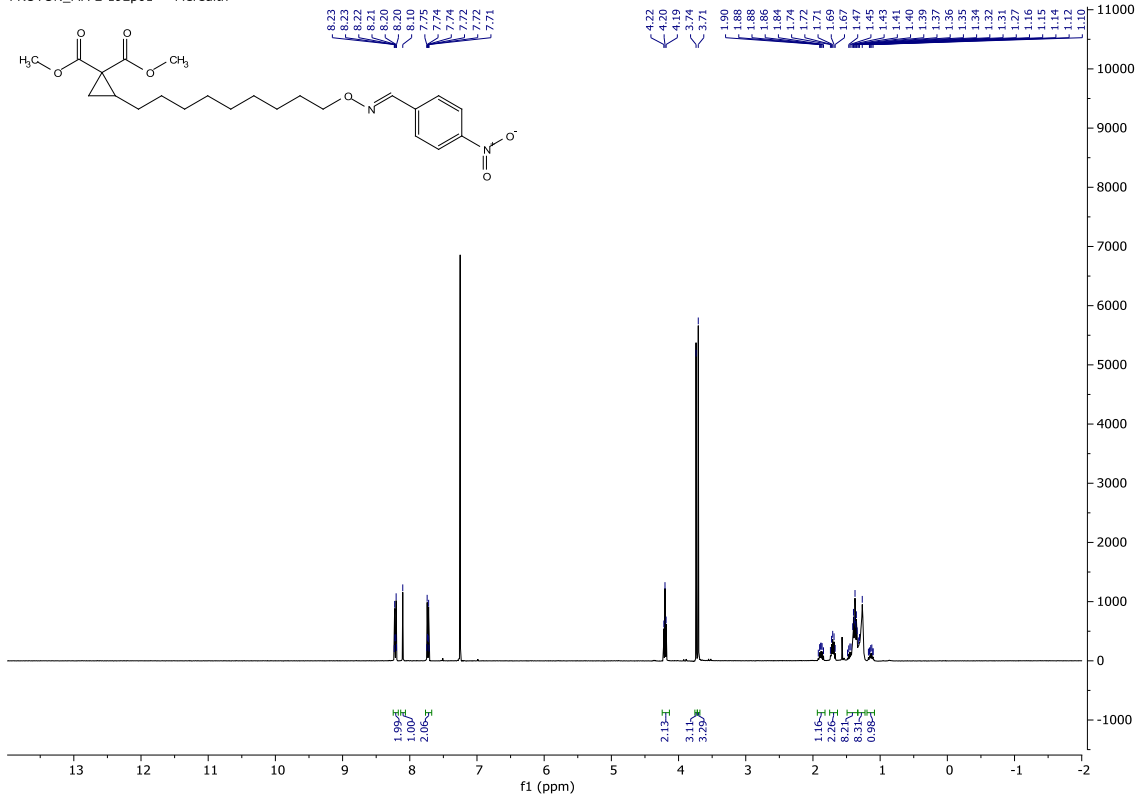
PROTON_MA-2-190p01 — Meredith —



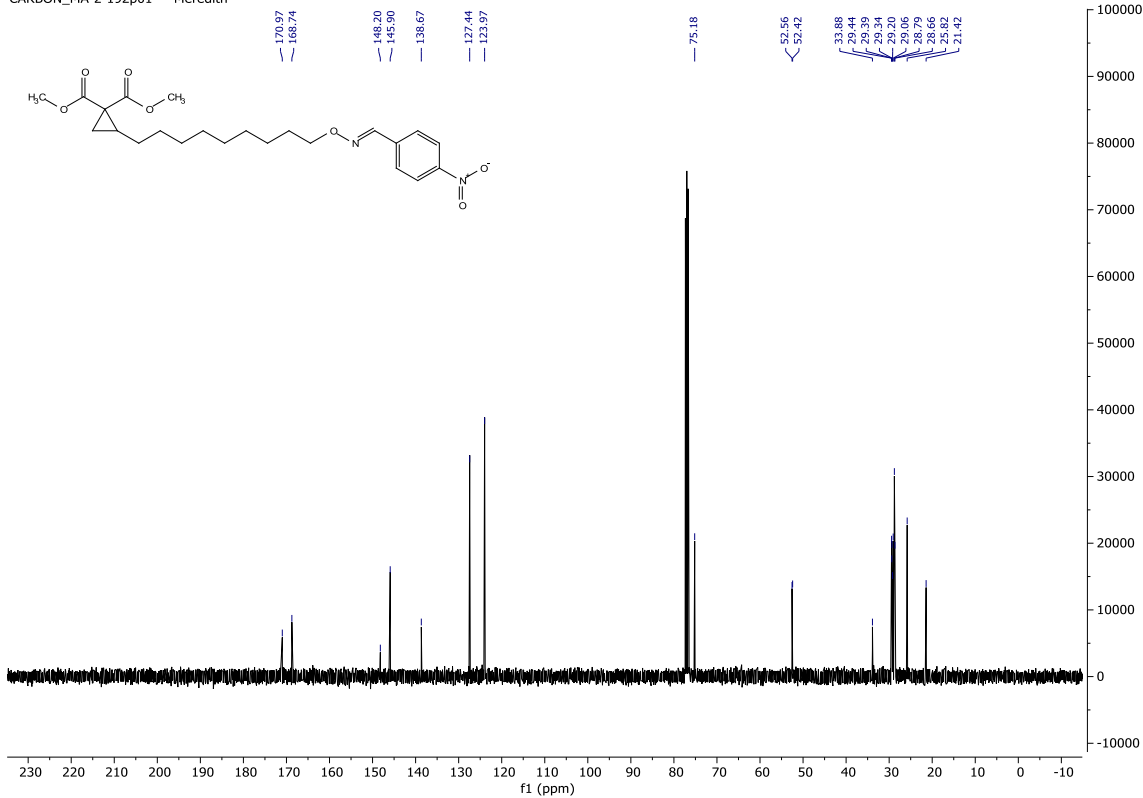
CARBON_MA-2-190p01 — Meredith —



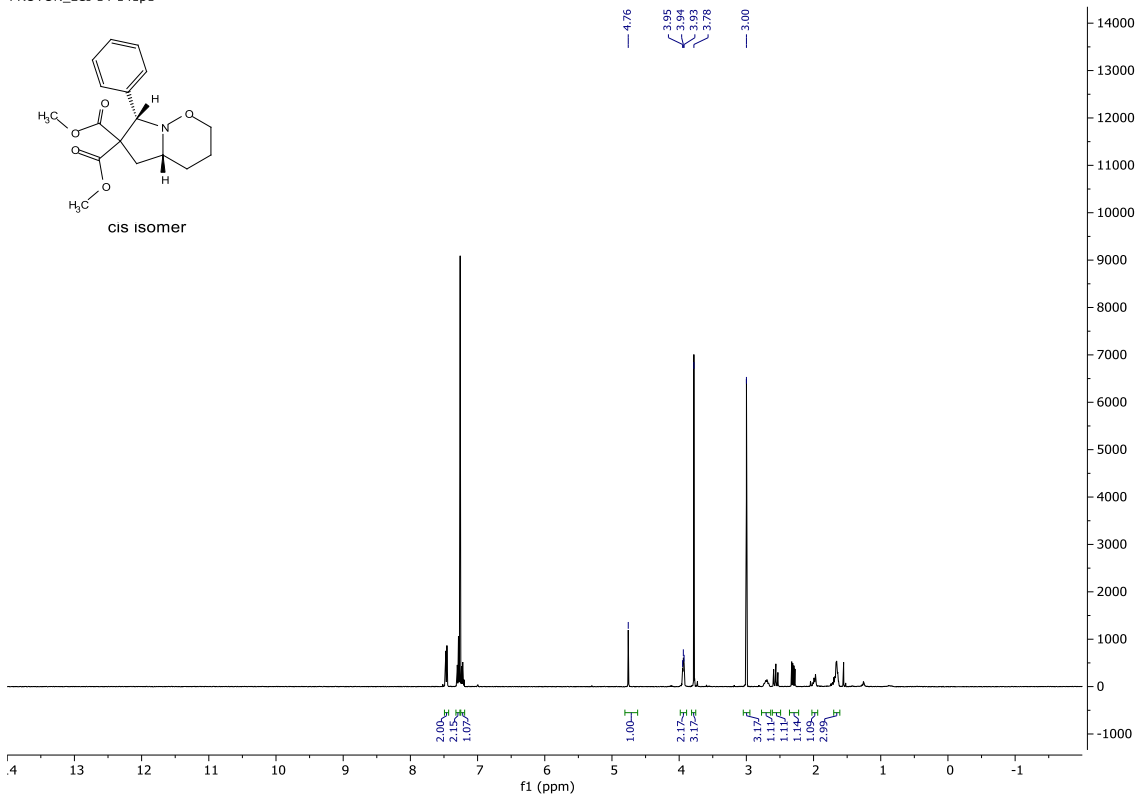
PROTON_MA-2-192p01 — Meredith —



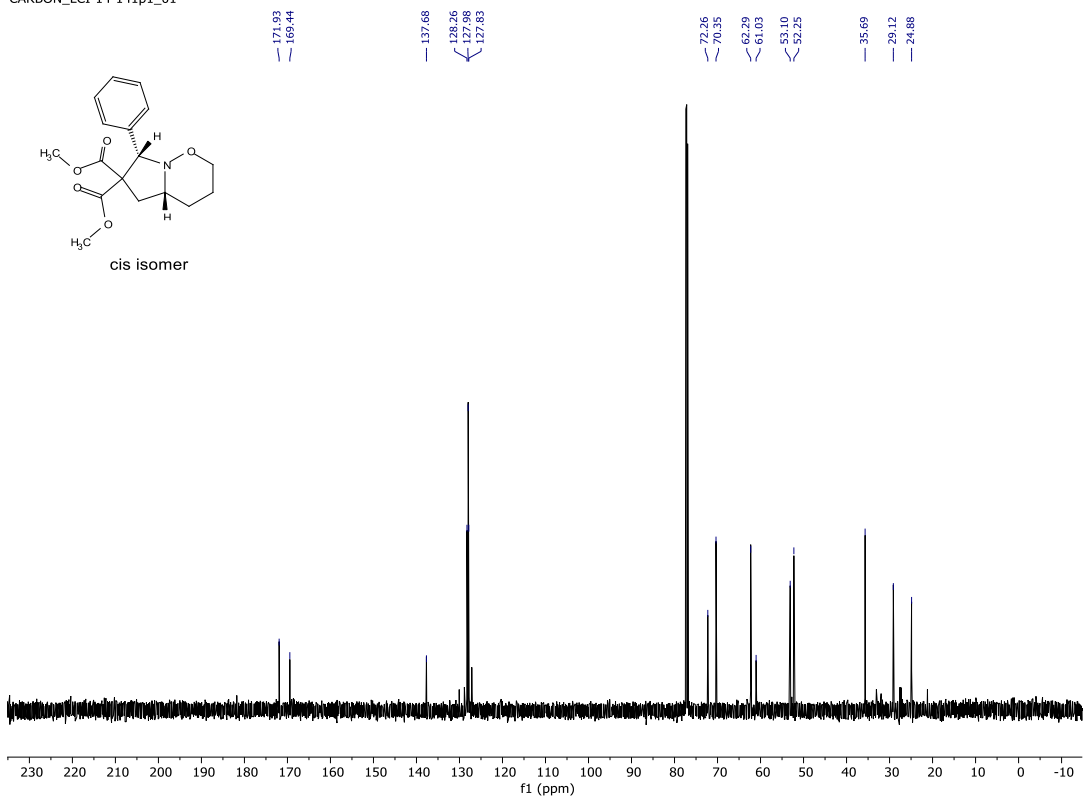
CARBON_MA-2-192p01 — Meredith —



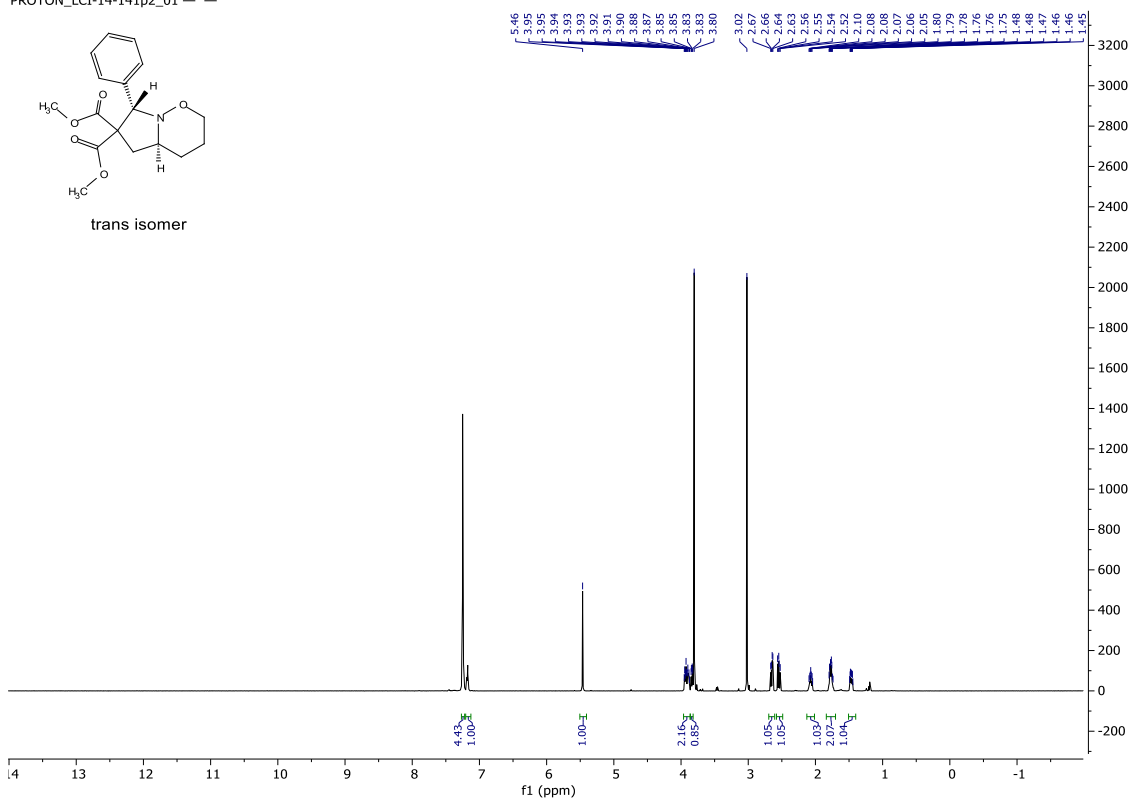
PROTON_LCI-14-141p1



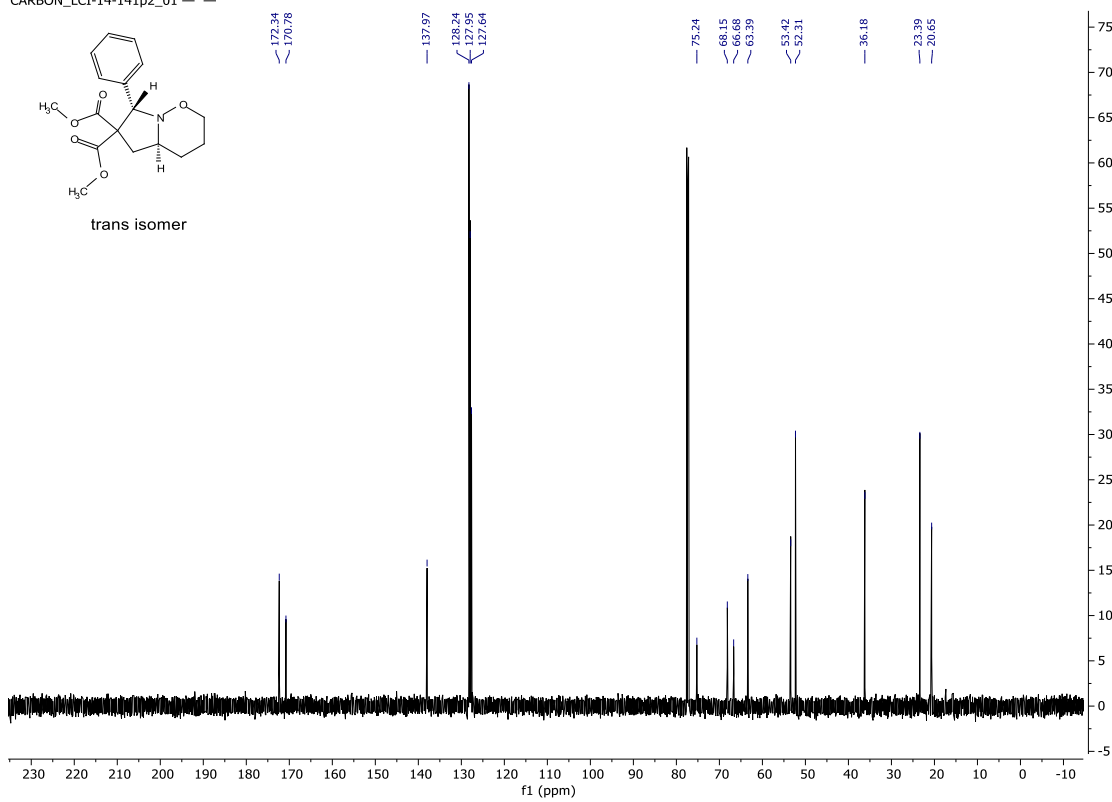
CARBON_LCI-14-141p1_01



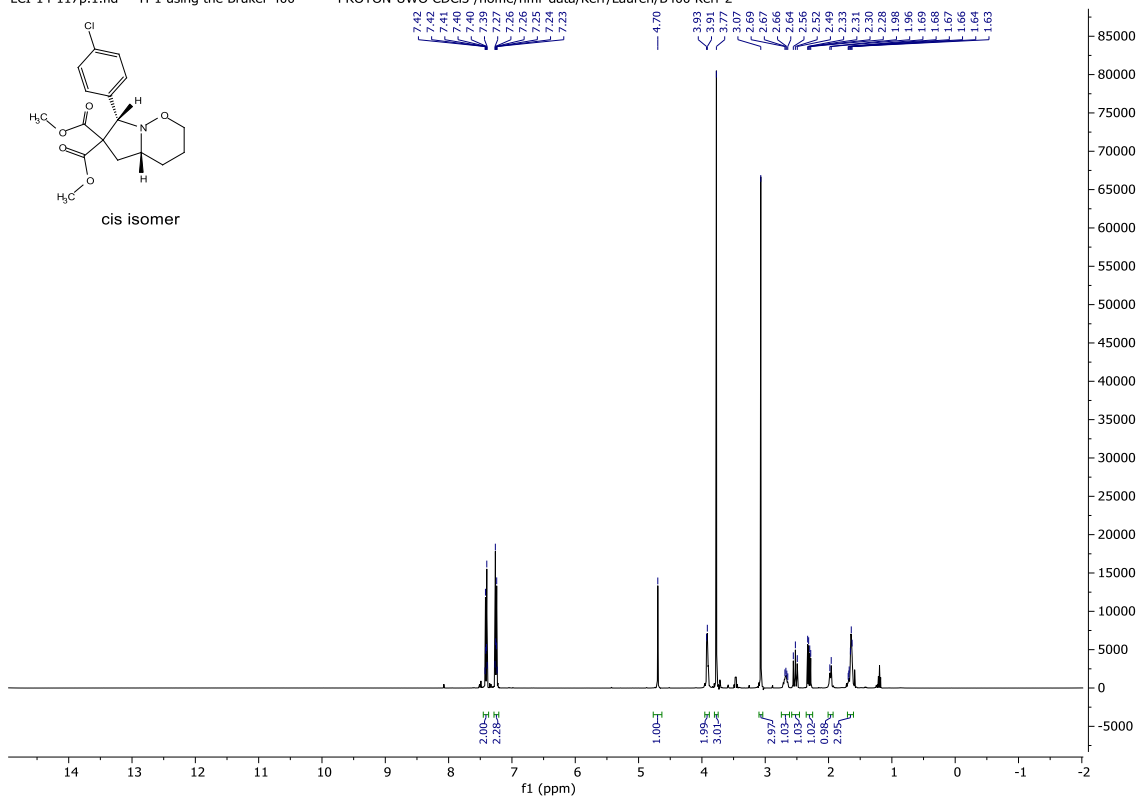
PROTON_LCI-14-141p2_01 —



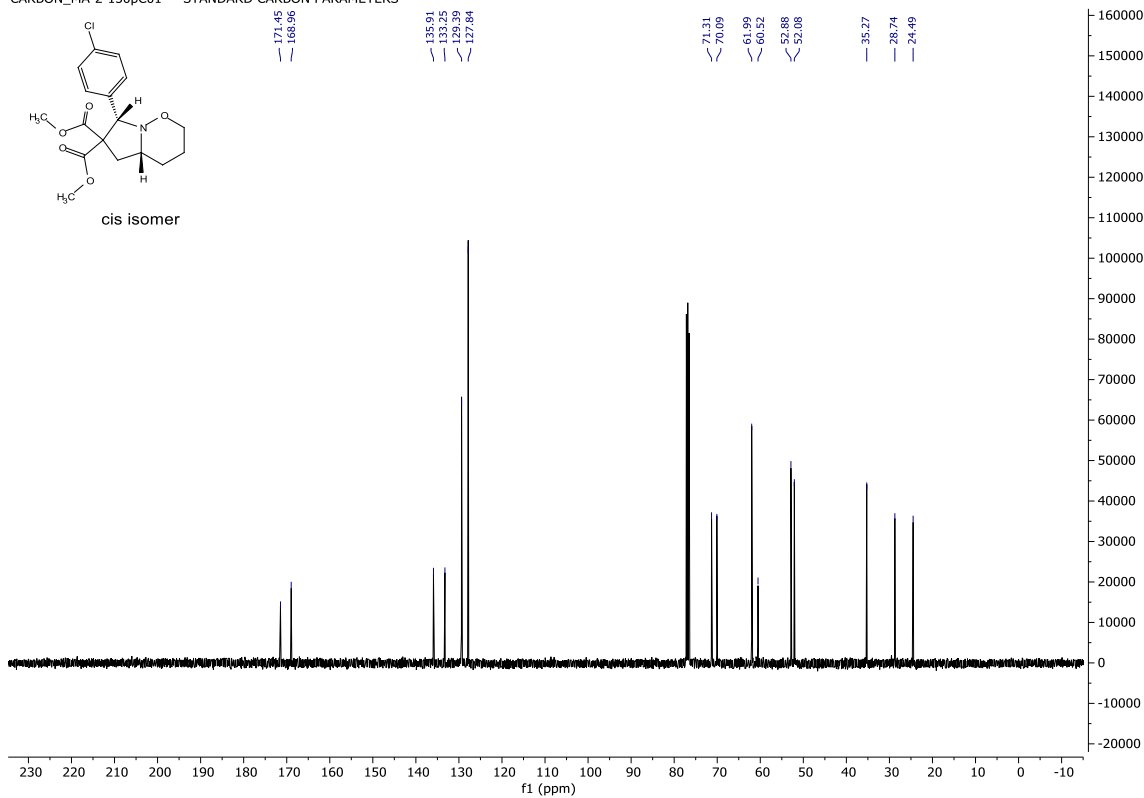
CARBON_LCI-14-141p2_01 —



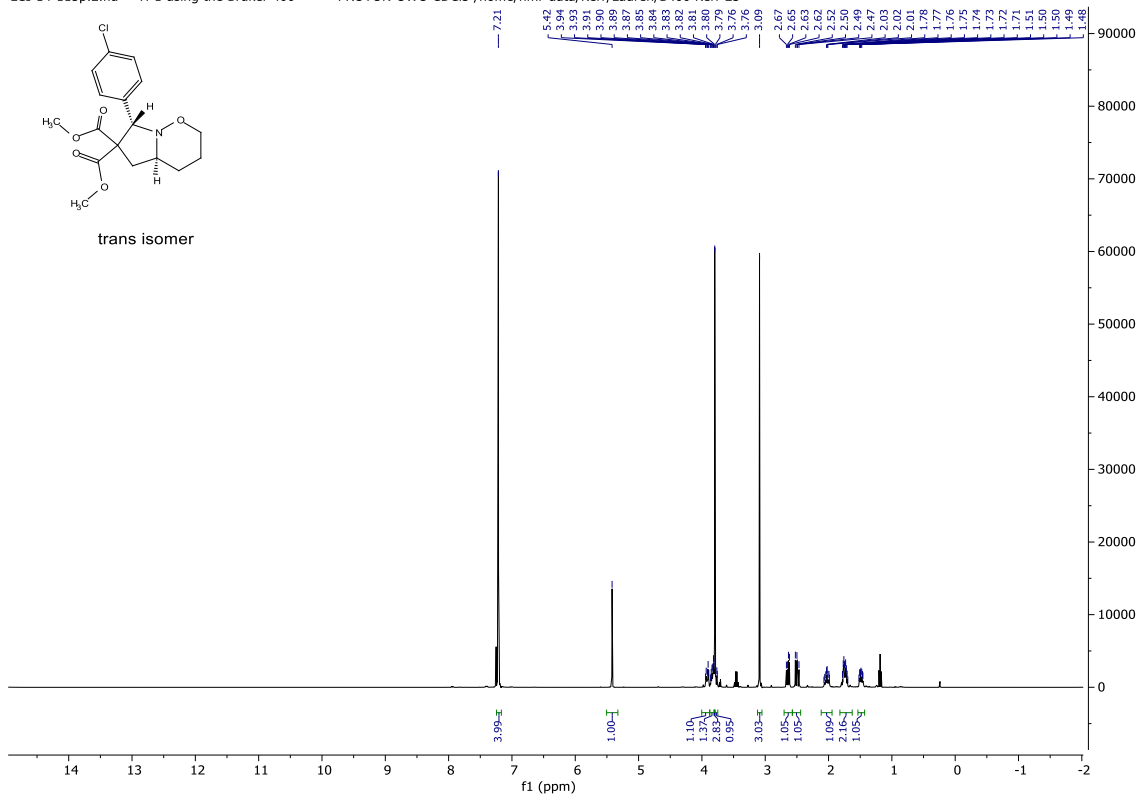
LCI-14-117p.1.fid — H-1 using the Bruker 400 — PROTON-UWO CDCl₃ /home/nmr-data/Kerr/Lauren/B400 Kerr 2



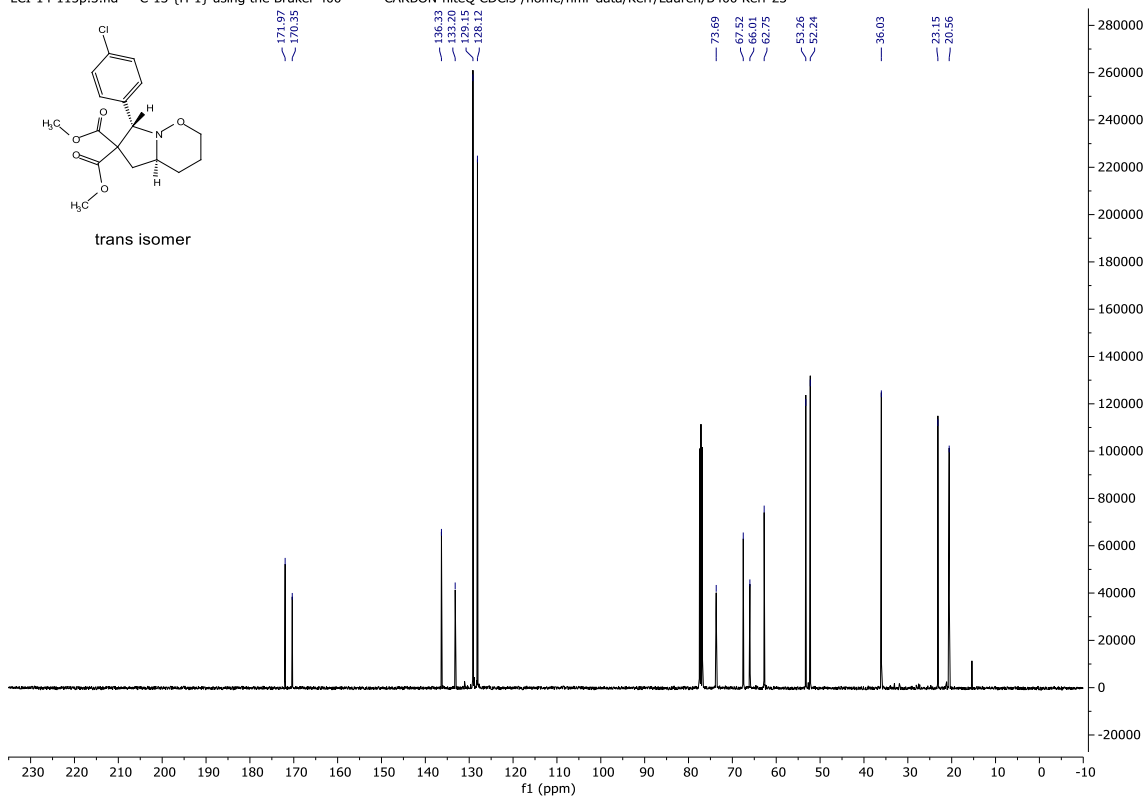
CARBON_MA-2-150p01 — STANDARD CARBON PARAMETERS —



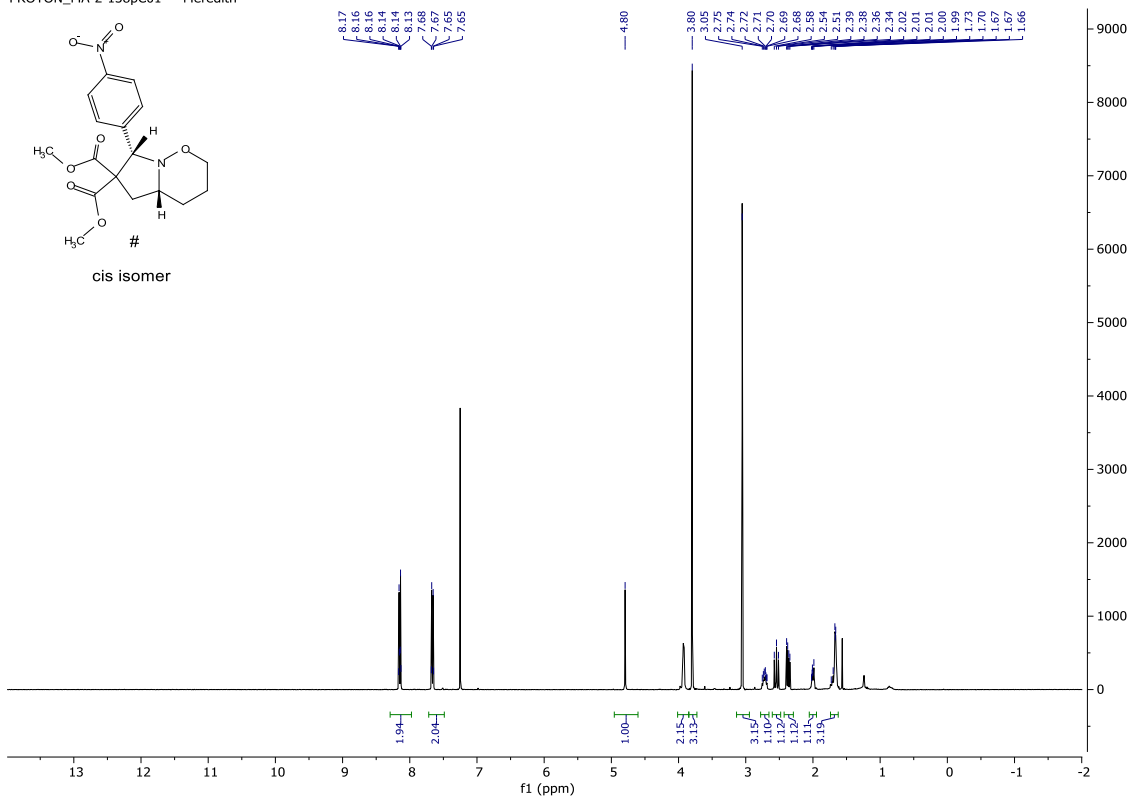
LCI-14-115p.2.fid — H-1 using the Bruker 400 — PROTON-UWO CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 23



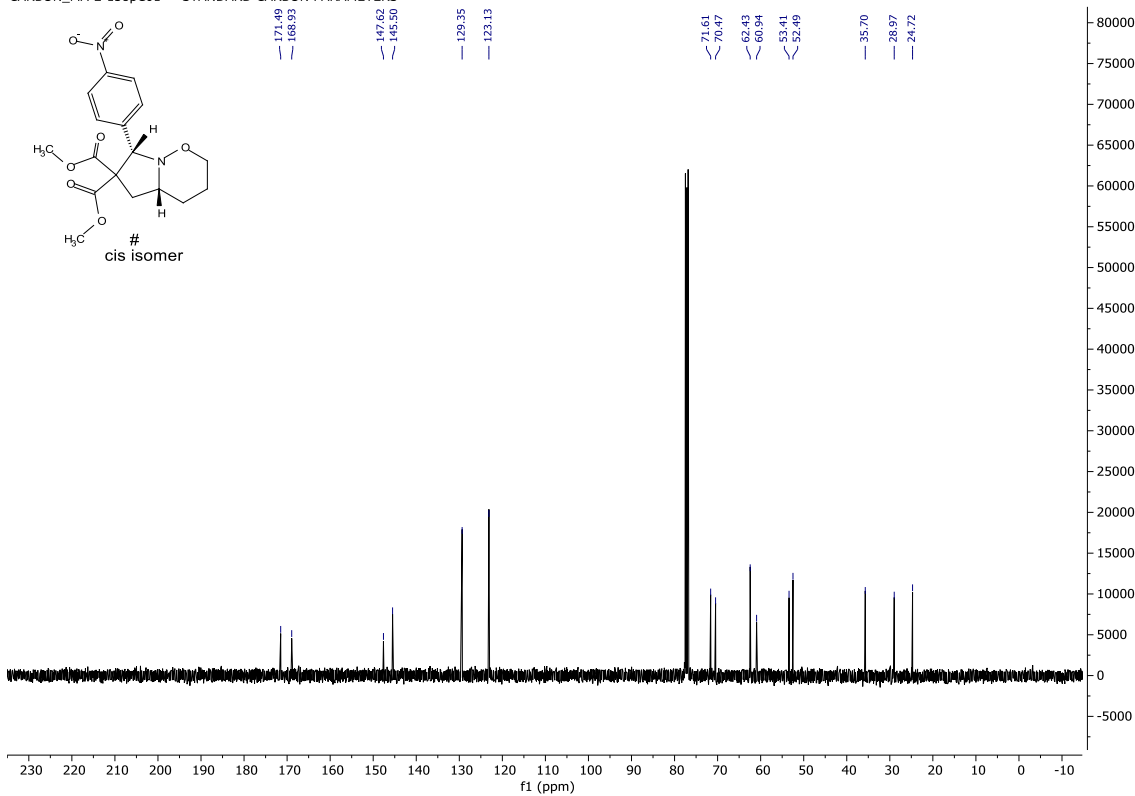
LCI-14-115p.3.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 23



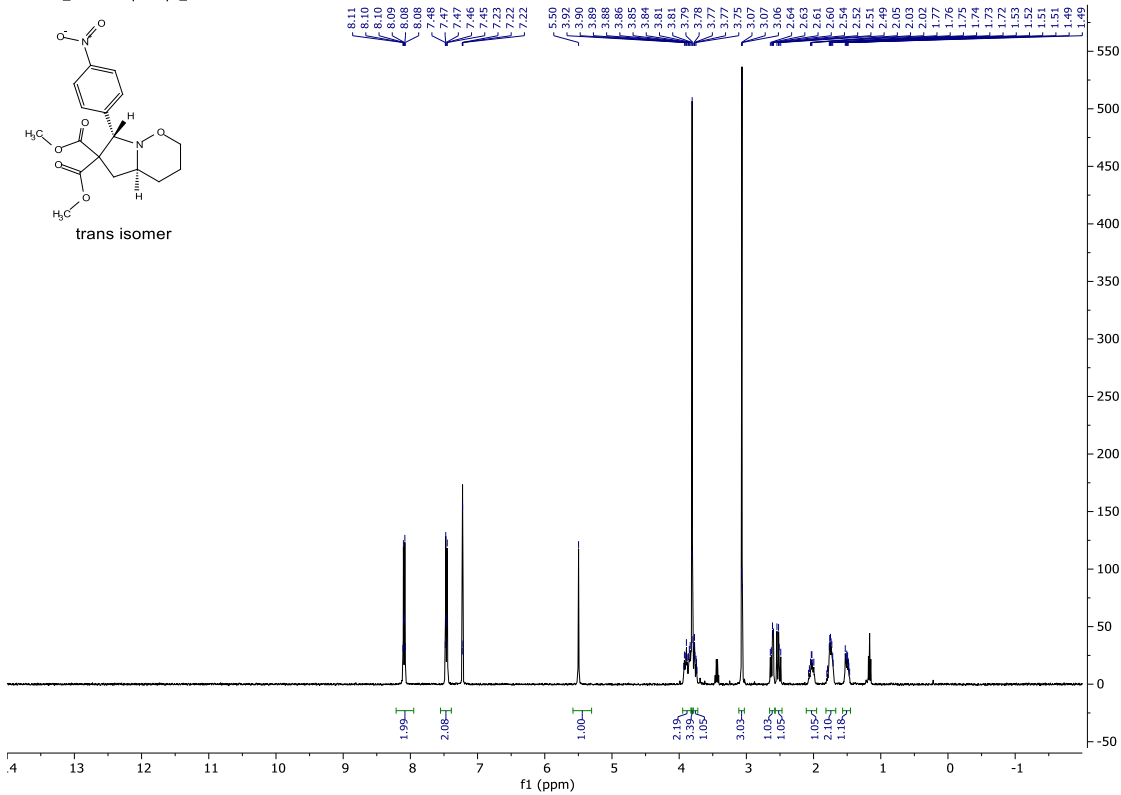
PROTON_MA-2-138pC01 — Meredith —



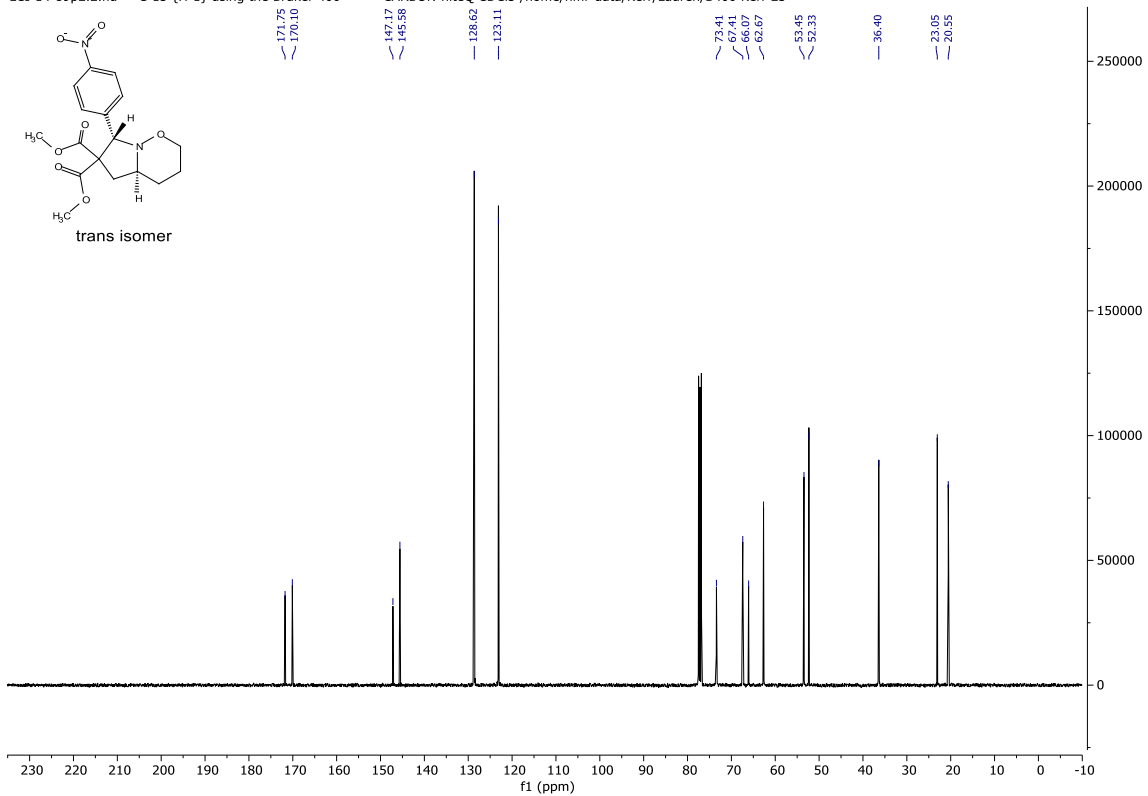
CARBON_MA-2-138pC01 — STANDARD CARBON PARAMETERS —



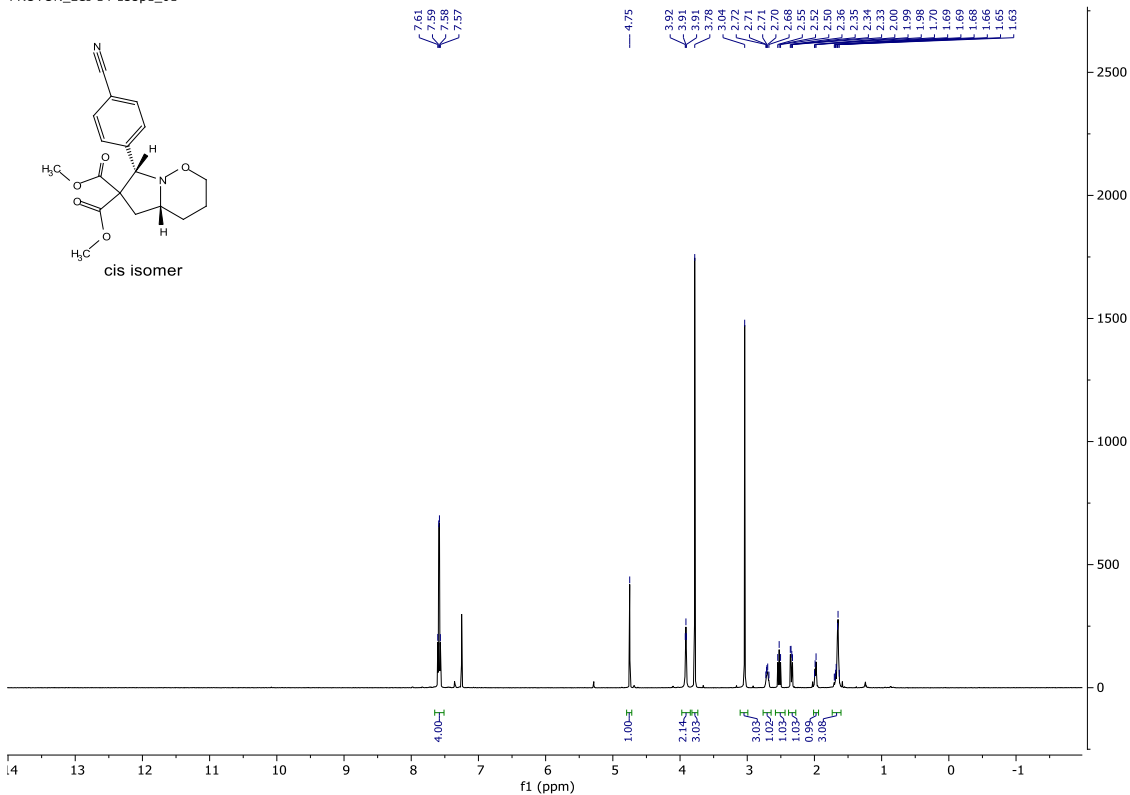
PROTON_LCI-14-89p2-dry1_01



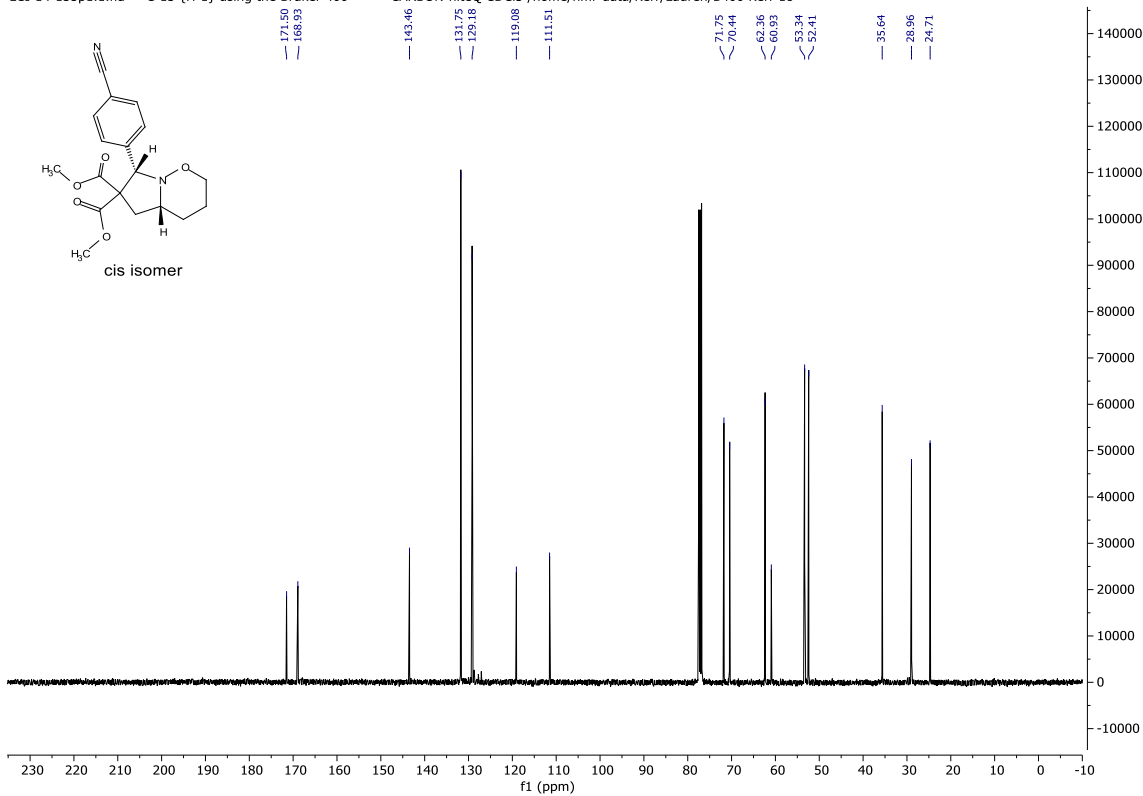
LCI-14-89p2.2.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCI3 /home/nmr-data/Kerr/Lauren/B400 Kerr 23



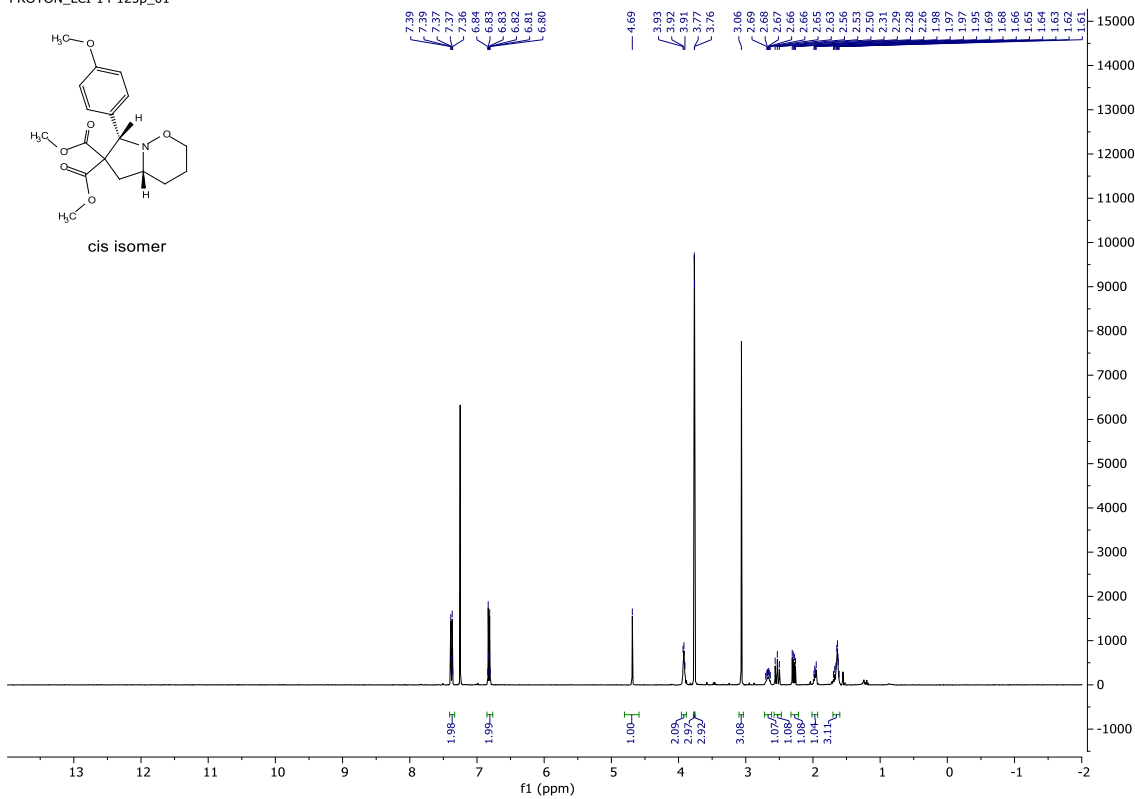
PROTON_LCI-14-135p1_01 —



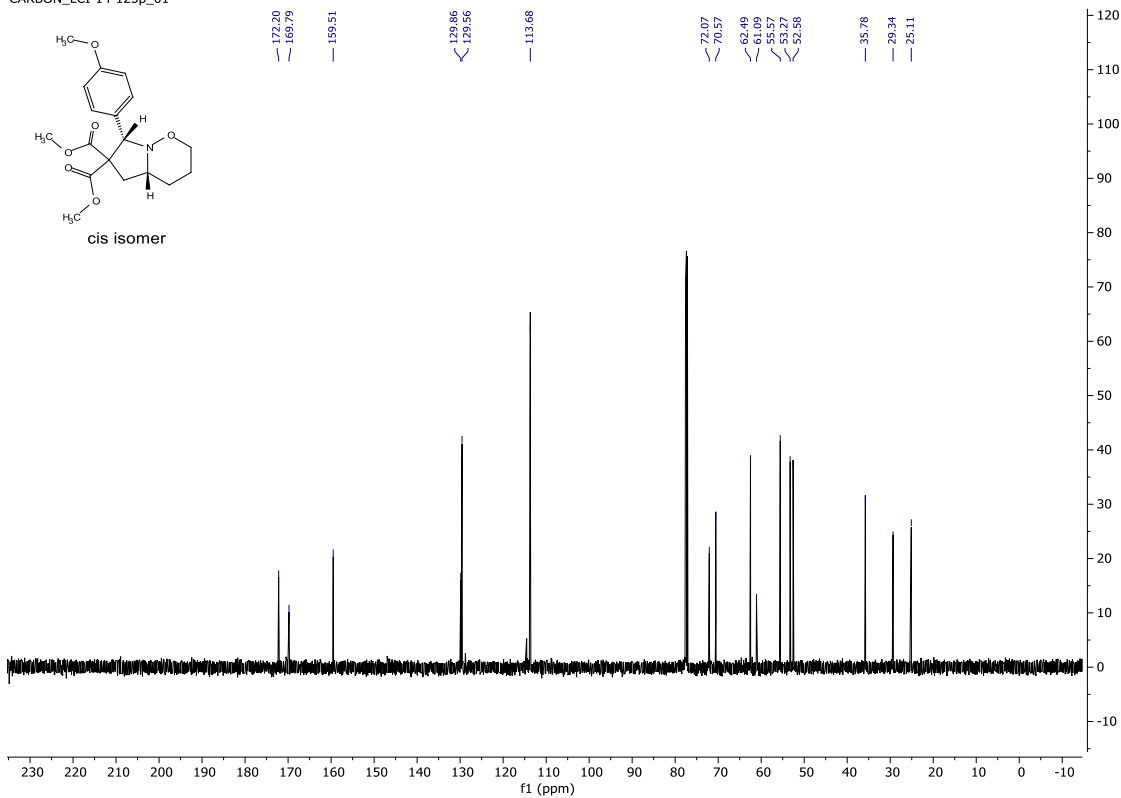
LCI-14-135p1.1.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 18



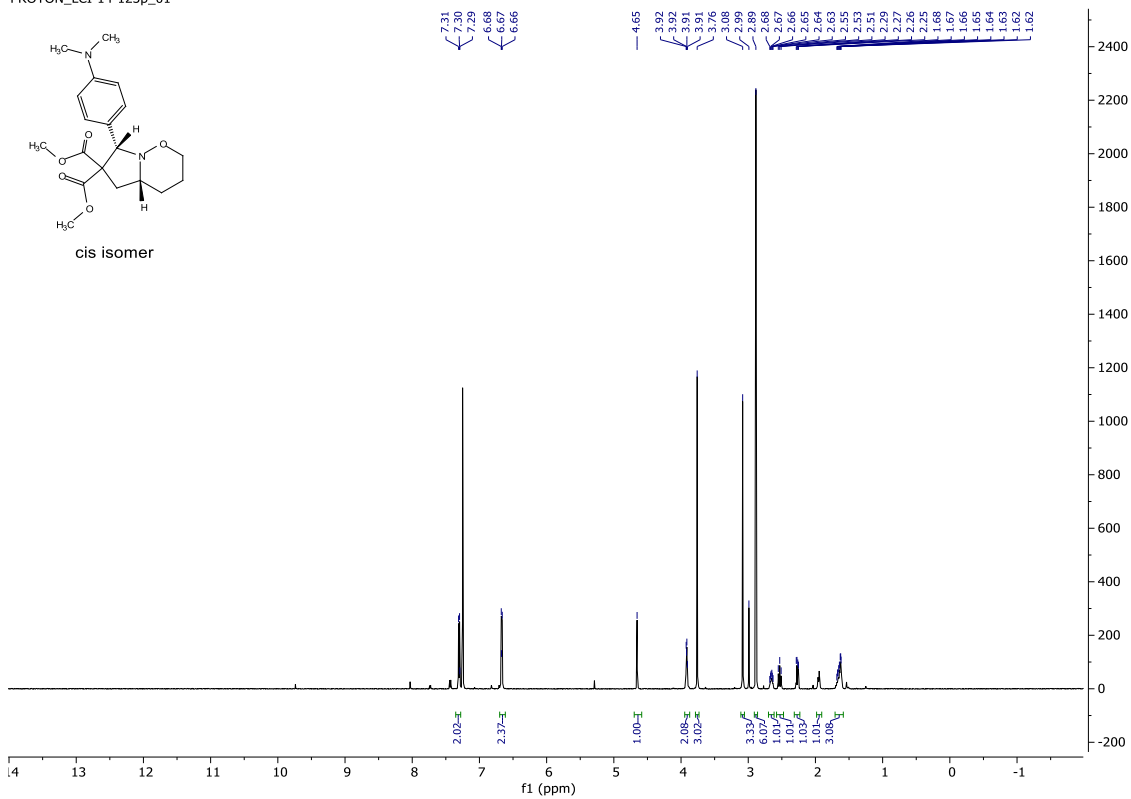
PROTON_LCI-14-125p_01



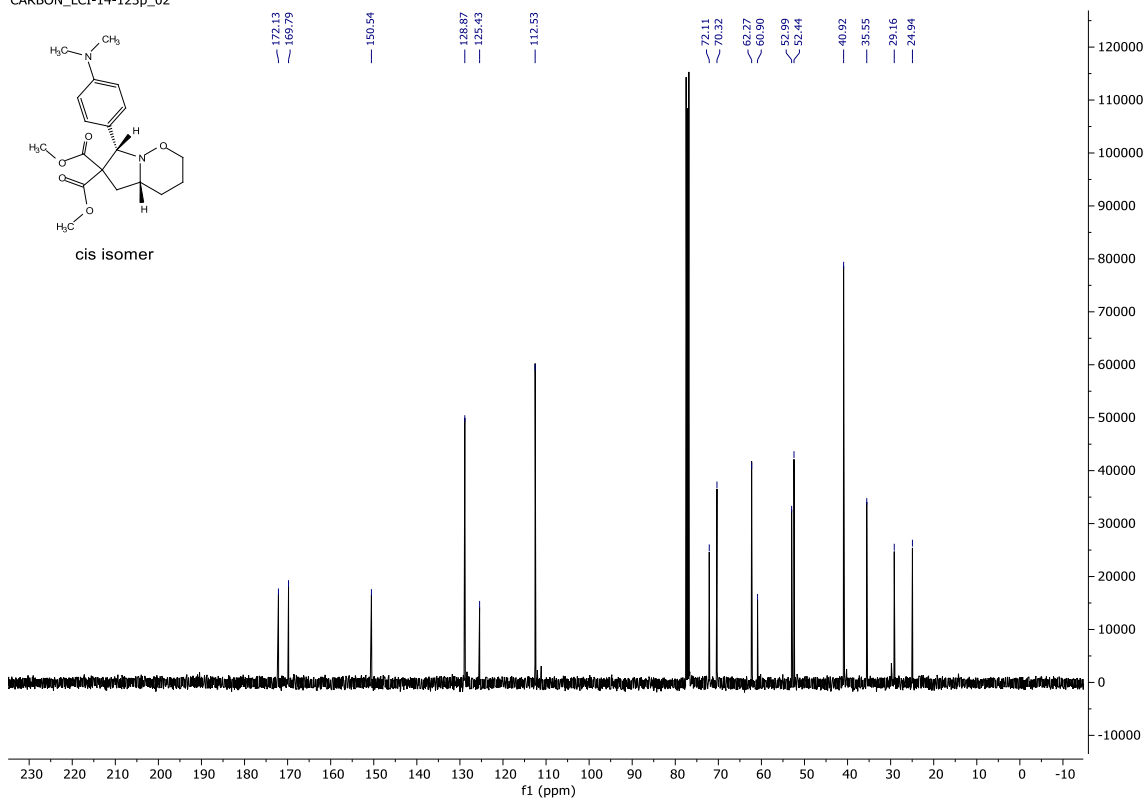
CARBON_LCI-14-125p_01

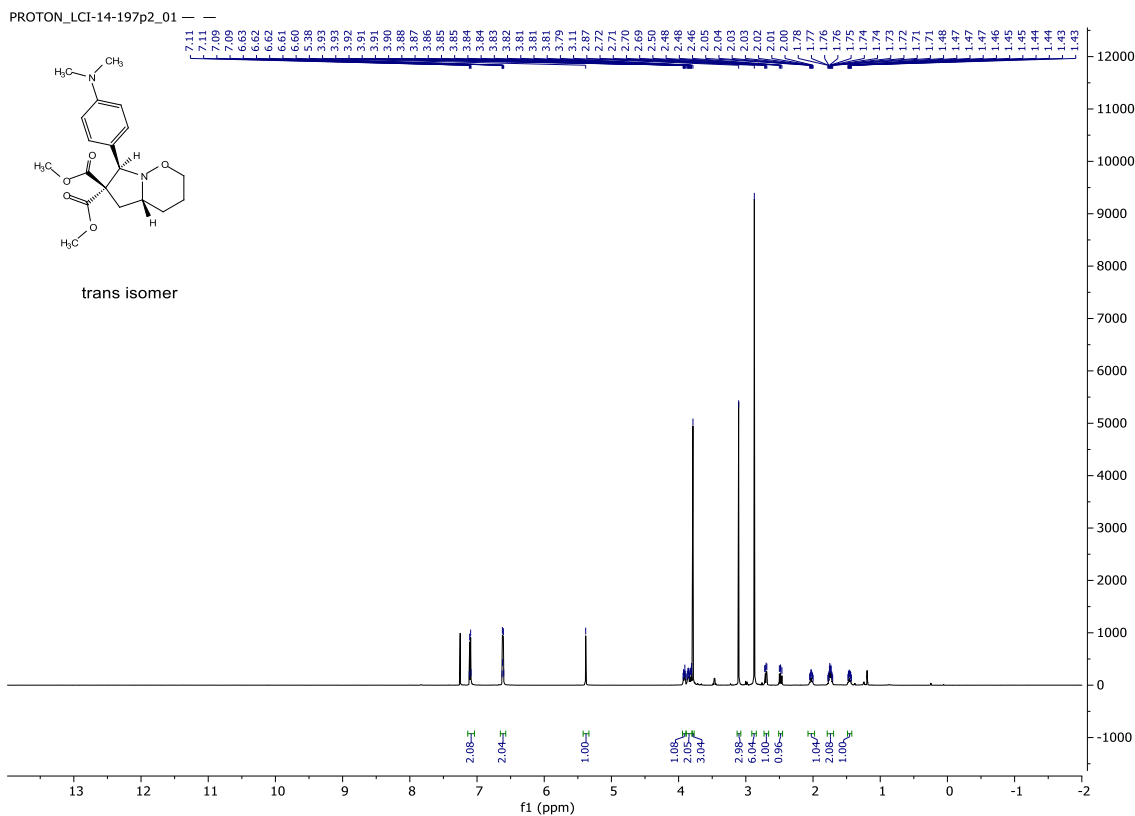


PROTON_LCI-14-123p_01

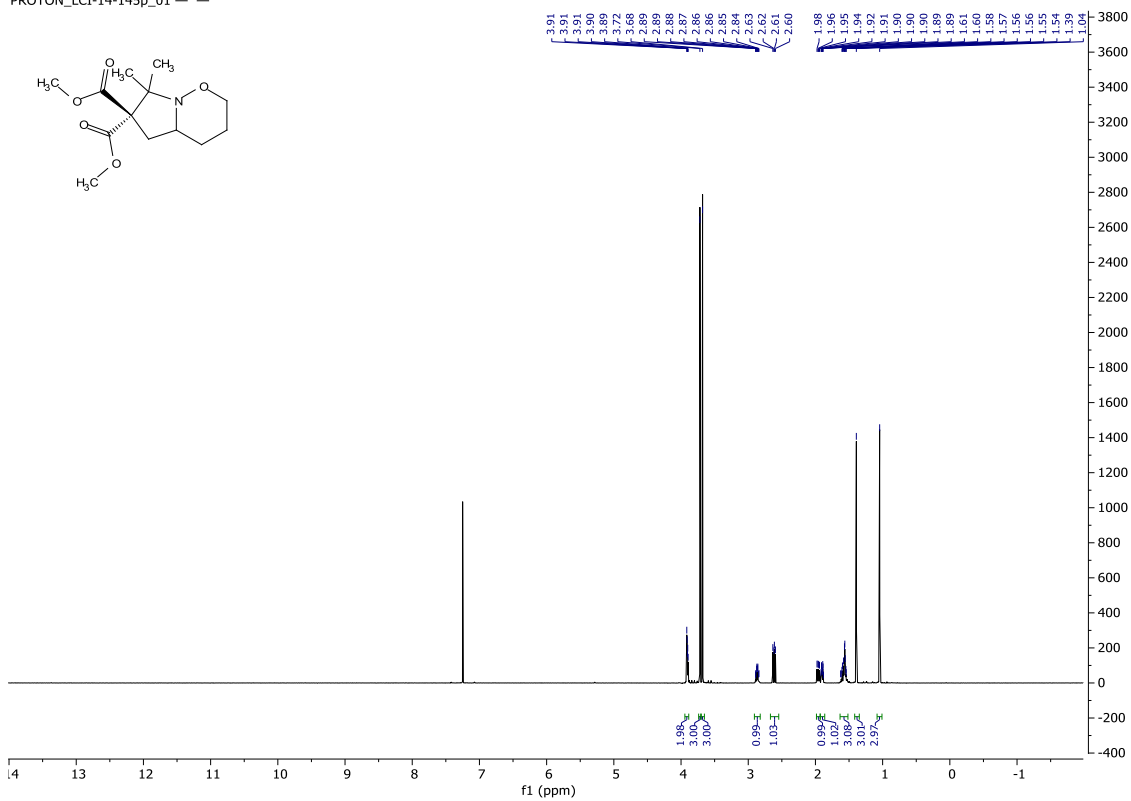


CARBON_LCI-14-123p_02

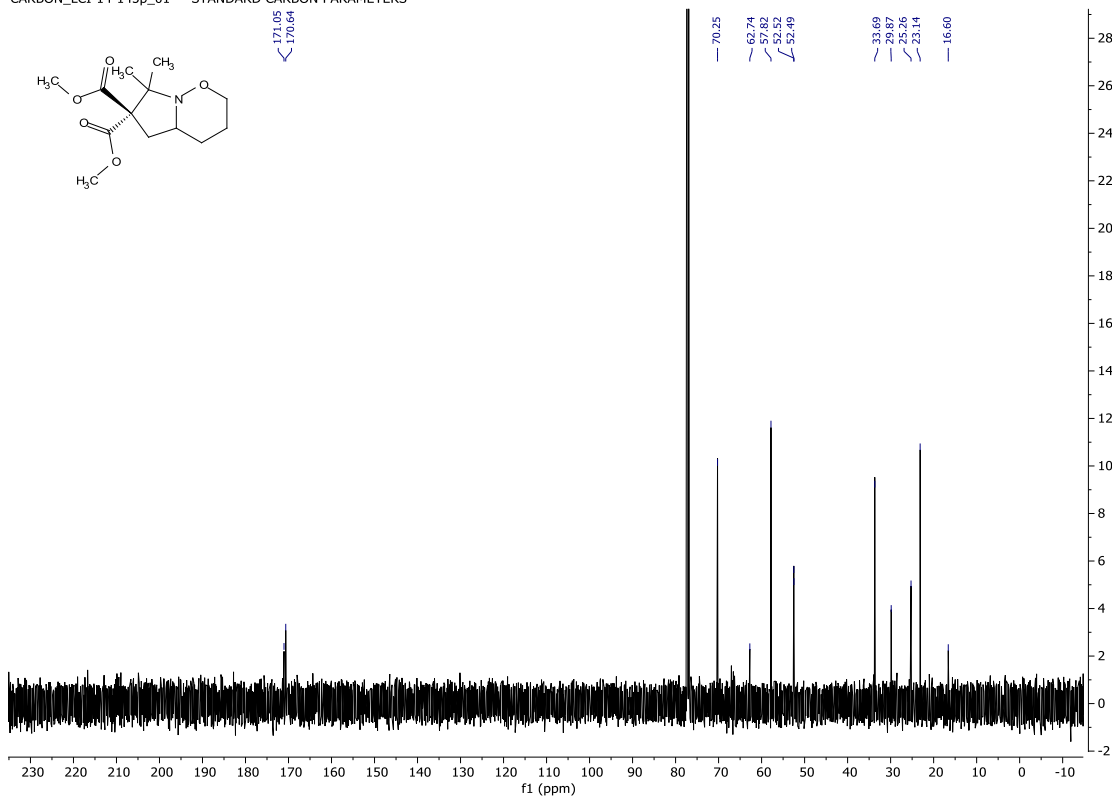


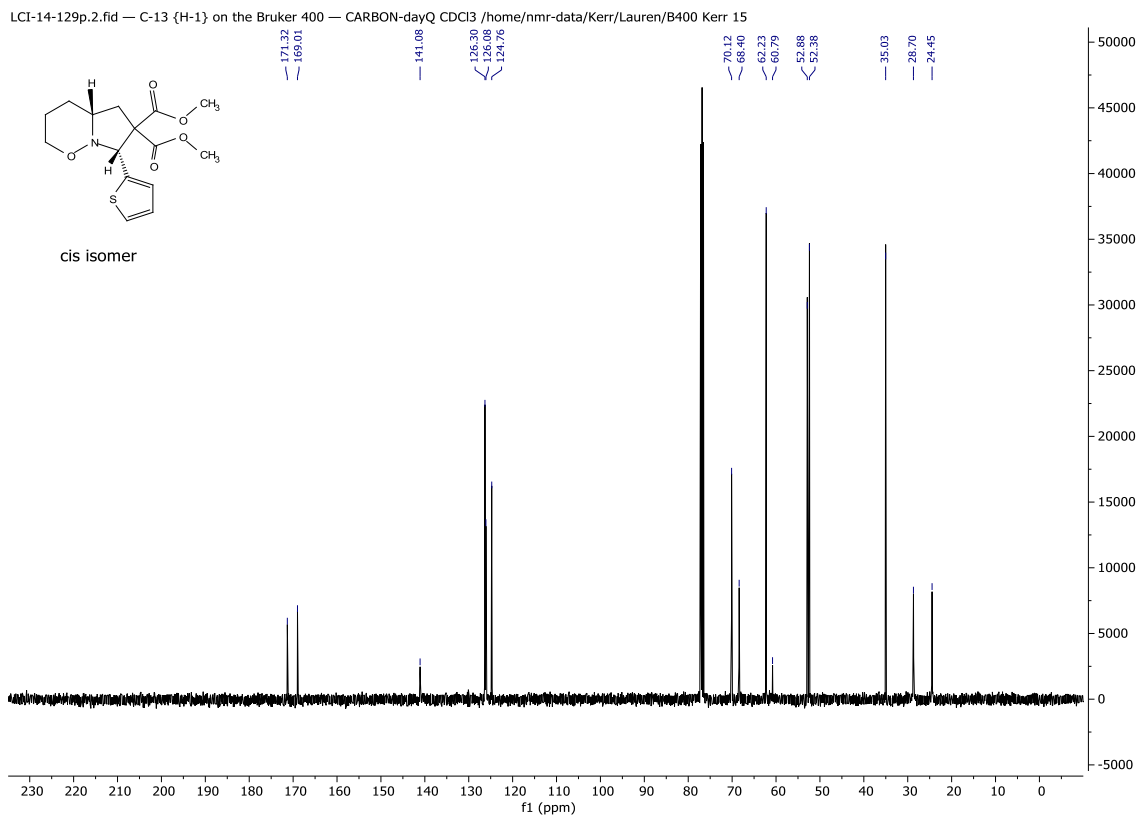
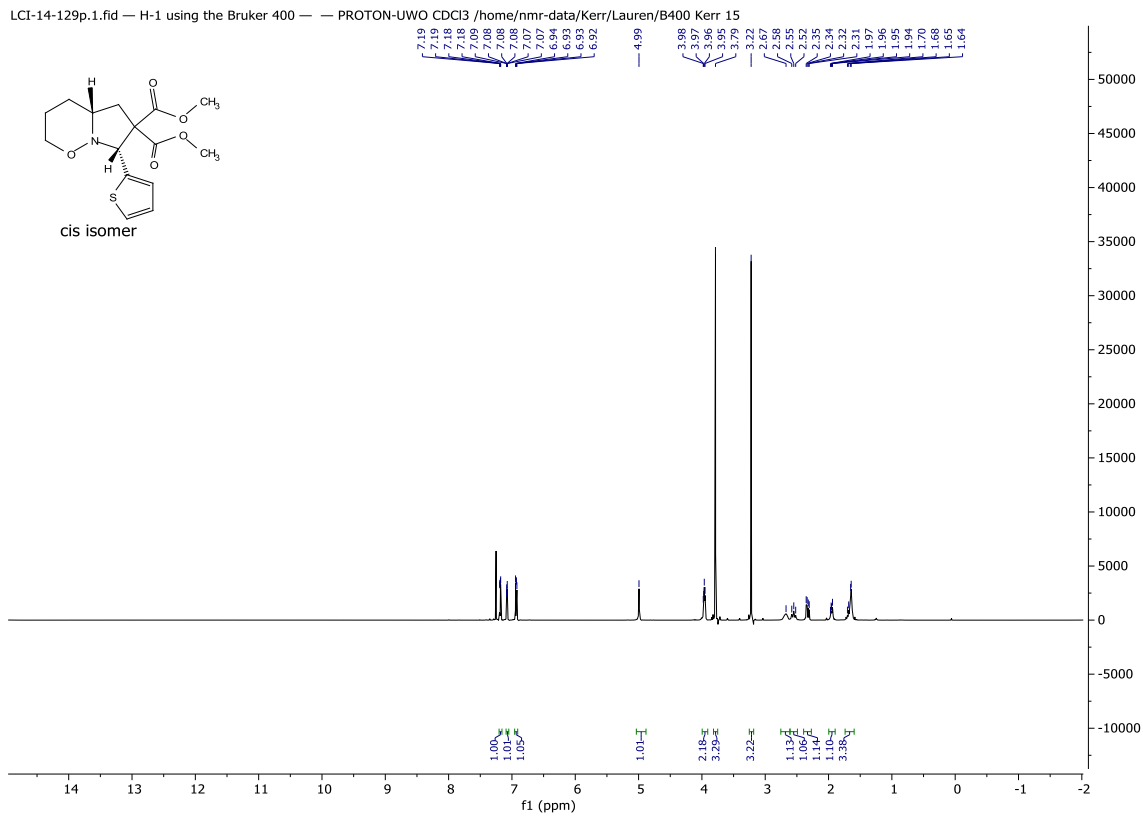


PROTON_LCI-14-145p_01 — —

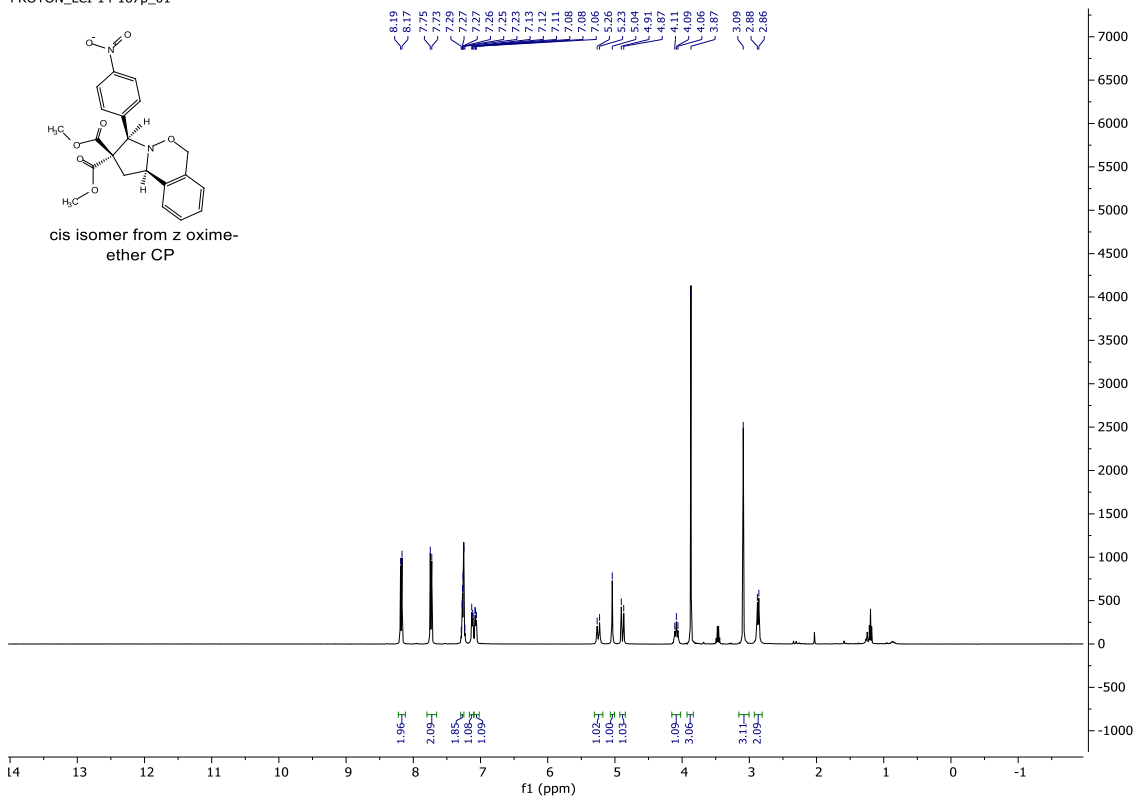


CARBON_LCI-14-145p_01 — STANDARD CARBON PARAMETERS —

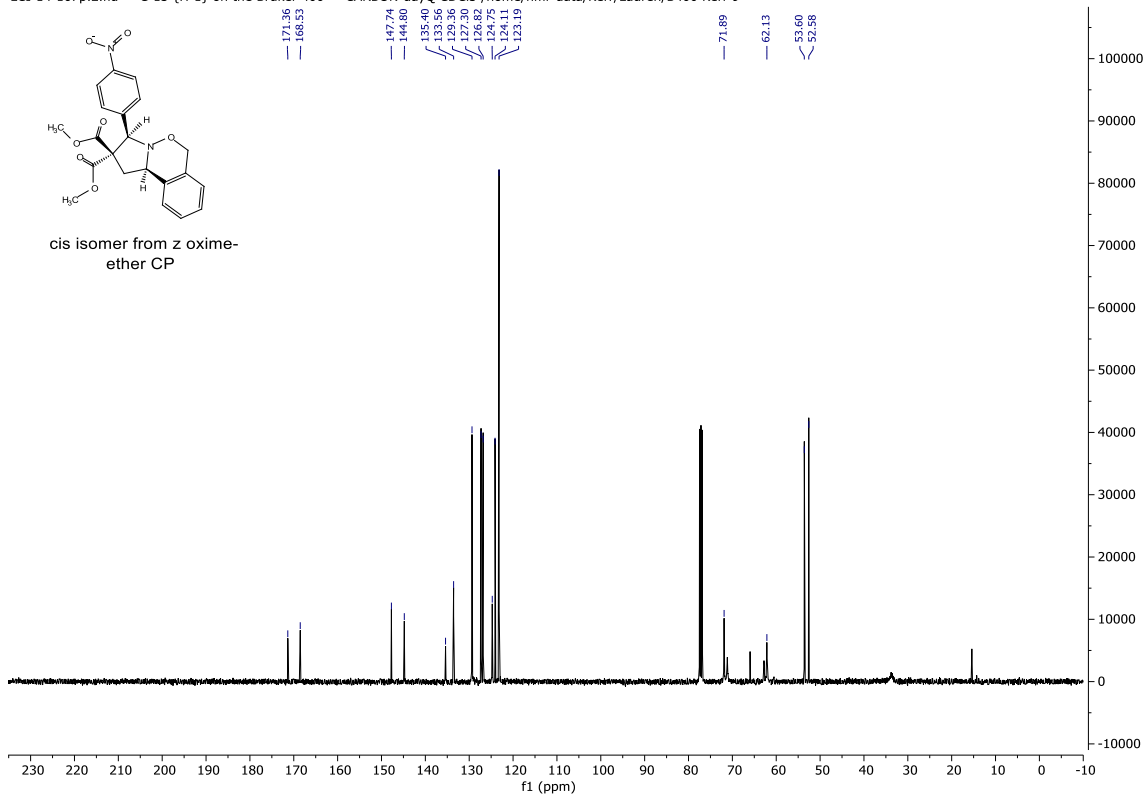




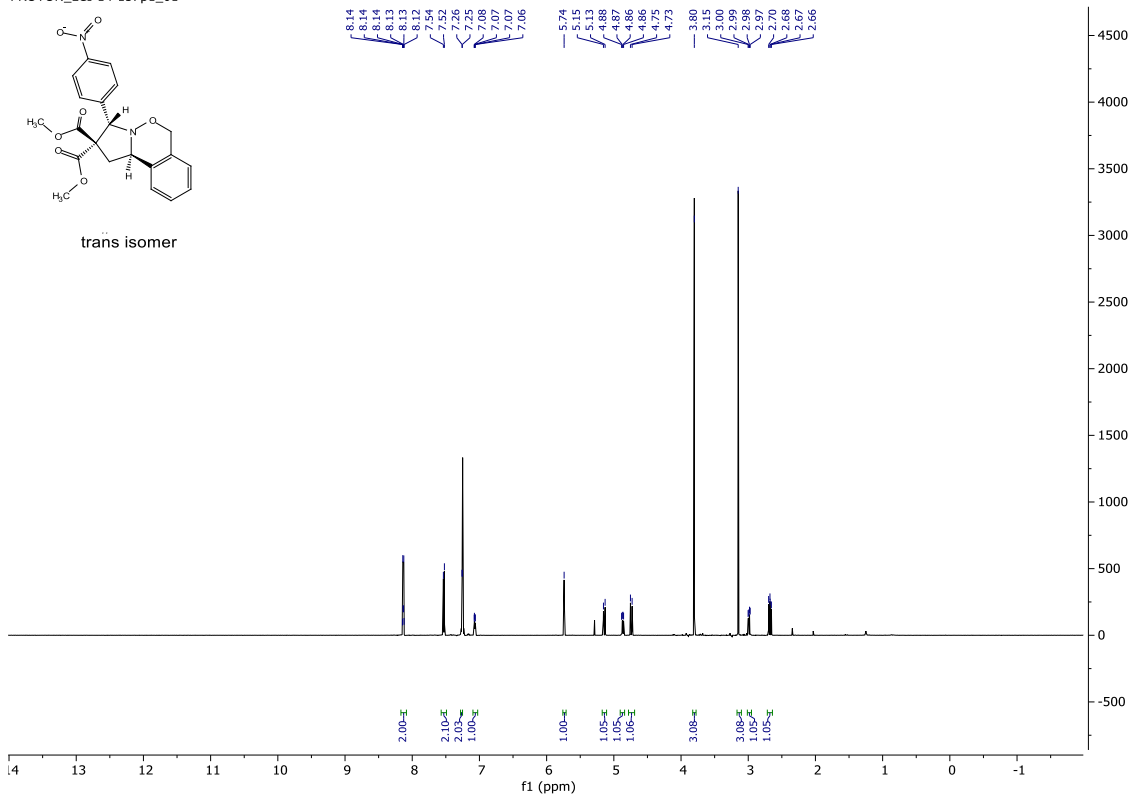
PROTON_LCI-14-167p_01 — —



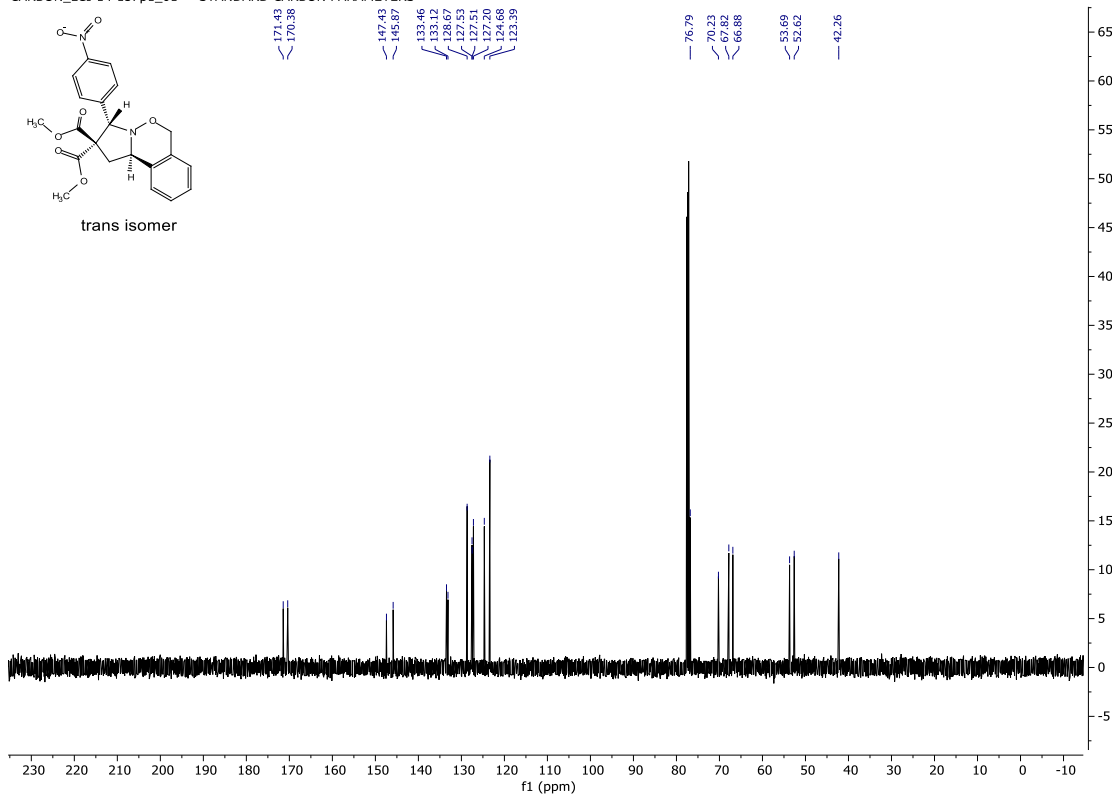
LCI-14-167p.2.fid — C-13 {H-1} on the Bruker 400 — CARBON-dayQ CDCl3 /home/nmr-data/Kerr/Lauren/B400 Kerr 9



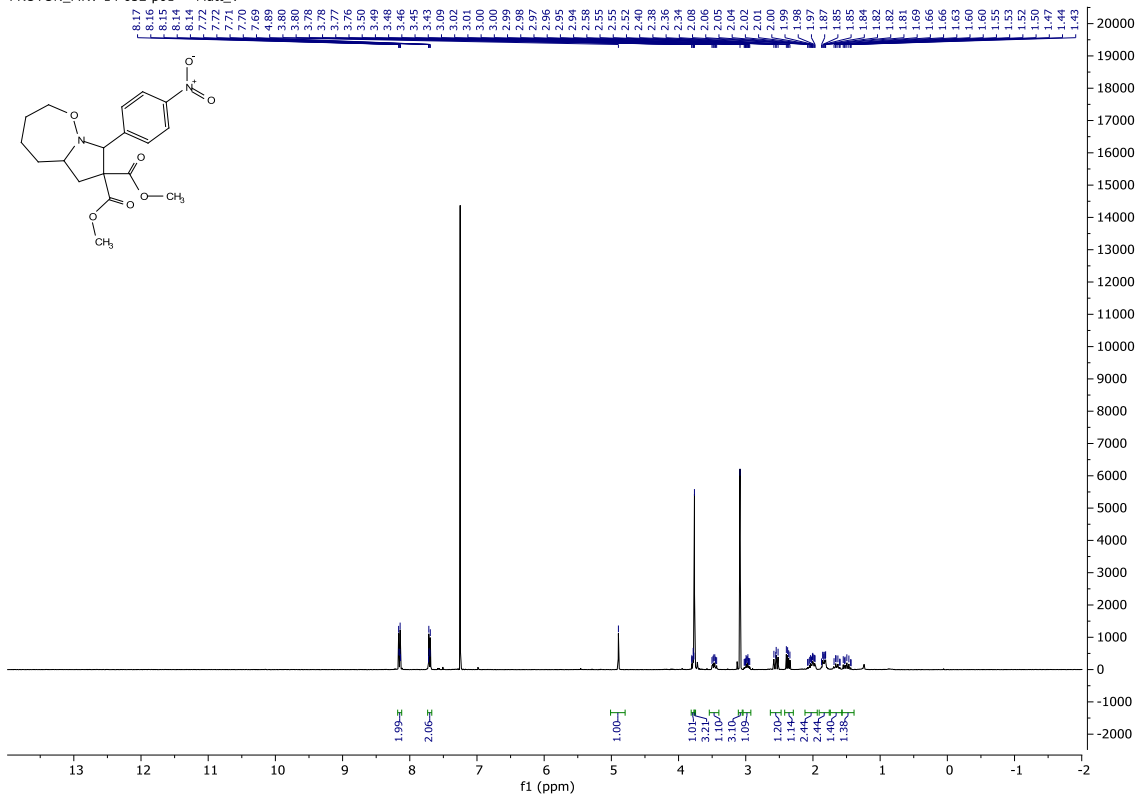
PROTON_LCI-14-157p1_01 —



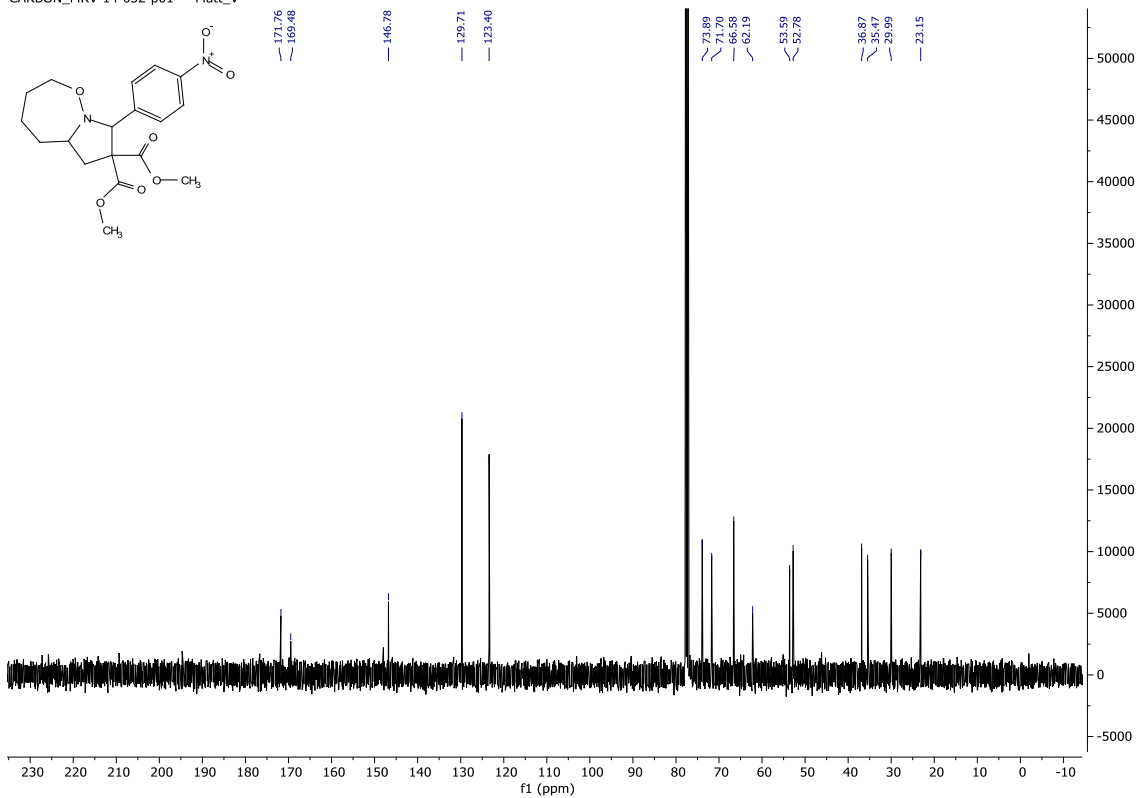
CARBON_LCI-14-157p1_01 — STANDARD CARBON PARAMETERS —



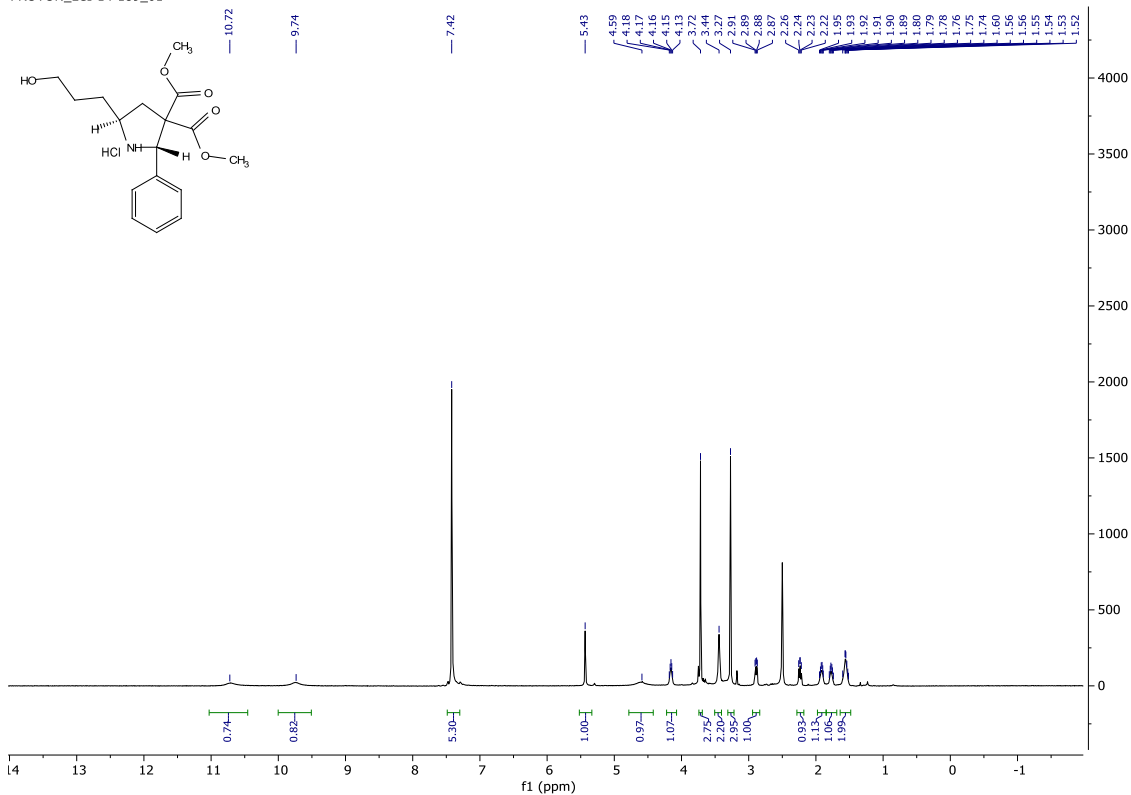
PROTON_MR-14-032-p01 — Matt_V —



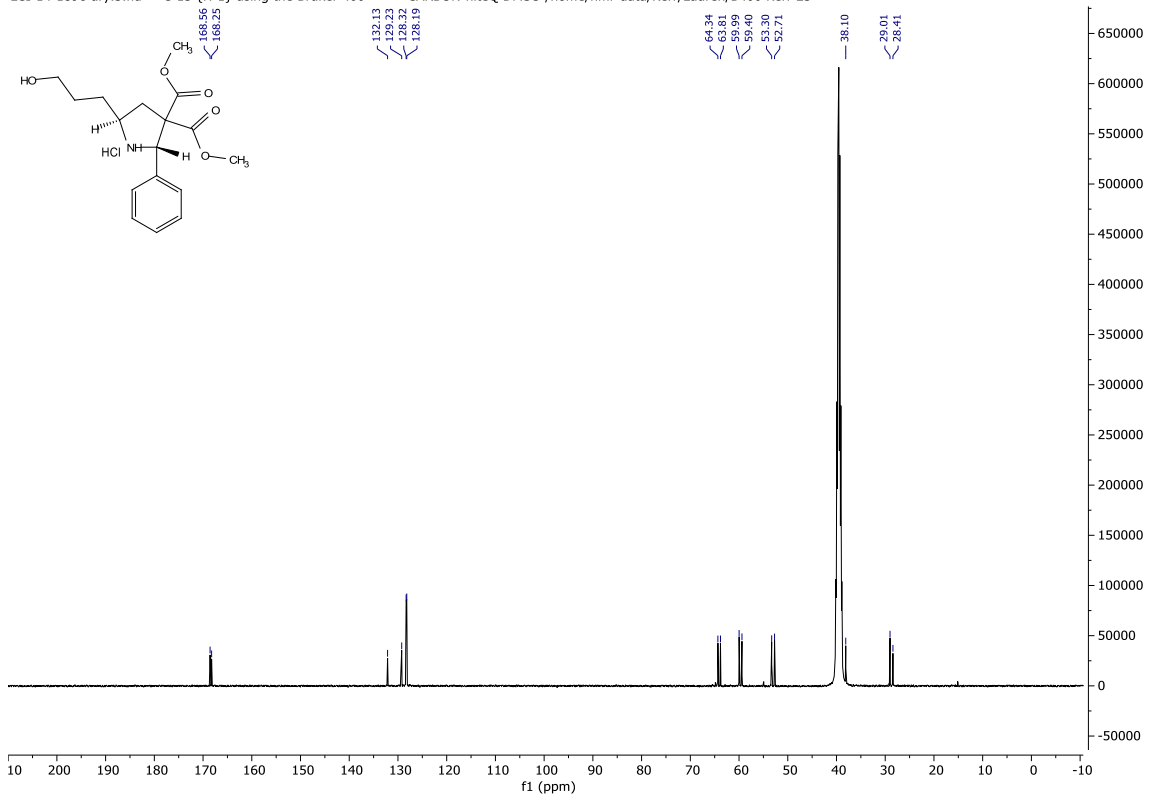
CARBON_MR-14-032-p01 — Matt_V —



PROTON_LCI-14-189_01



LCI-14-189c-dry.3.fid — C-13 {H-1} using the Bruker 400 — CARBON-niteQ DMSO /home/nmr-data/Kerr/Lauren/B400 Kerr 23



Curriculum Vitae

A. Education

2015-Present: Ph.D., University of Western Ontario

Principal Investigator: Prof. Michael A. Kerr

Thesis Dissertation: *Functionalization of Indoles and Donor-Acceptor Cyclopropanes and their Application Towards the Total Synthesis of Tronocarpine and Dippinine B*

2010-2015: B.Sc. Honours Specialization in Chemistry, University of Western Ontario

Honours Thesis: *Tandem C-H Insertions/Michael Addition Reactions of N-acryloyl Indoles*

Principle Investigator: Prof. Michael A. Kerr

B. Publications

Irwin, L. C.; Allen, M. A.; Vriesen, M. R.; Kerr, M. A. *Accepted Annulation of Oxime-Ether Tethered Donor-Acceptor Cyclopropanes 2019* 10.1002/chem.201904521

Irwin, L. C.; Renwick, C. R.; Kerr, M. A. *J. Org. Chem. Nucleophilic Opening of Donor-Acceptor Cyclopropanes with Indoles via Hydrgen Bond Activation with 1,1,1,3,3,3-Hexafluoroisopropanol 2018*, 83, 6235-6242

Irwin, L. C.; Kerr, M. A. *Synlett One-Pot Michael Addition/Radical Cyclization Reaction of N-Acryloyl Indoles 2017*, 28, 2859-2864

Curiel-Tejeda, J. E.; **Irwin, L. C.;** Kerr, M. A. *Org. Lett. Annulation Reactions of Donor-Acceptor Cyclopropanes with (1-Azidovinyl)benzene and 3-Phenyl-2H-azirine 2016*, 18 (18), 4738-4741

C. Presentations

2019 Québec City, Québec, Canada. **102nd Canadian Chemistry Conference and Exhibition**, *Annulation Reactions of Oxime-Ether Tethered Donor-Acceptor Cyclopropanes*. (Oral)

2019 Québec City, Québec, Canada. **102nd Canadian Chemistry Conference and Exhibition**, *Studies Towards the Total Synthesis of Tronocarpine and Dipinnine B* (Poster) Awarded first prize.

2017 Toronto, Ontario, Canada. **100th Canadian Society for Chemistry Conference and Exhibition**, *One-pot Michael Addition/ Radical Cyclization of Acryloyl Indoles and It's Application Towards the Total Synthesis of Alstorisine A*.

2016 University of Waterloo, **Quebec Ontario Mini-Symposium for Biorganic and Organic Chemistry**, *Progress Towards the Total Synthesis of Tronocarpine* Awarded third place. 2016.

2016 Halifax, Nova Scotia, Canada. **99th Canadian Society for Chemistry Conference and Exhibition**, *Synthetic Strategies Towards the Total Synthesis of Tronocarpine*. 2016.

2015 University of Toronto Mississauga, **Southern Ontario Undergraduate Student Chemistry Conference**, *Tandem Michael-Addition, C-H Insertions of N-Acryloyl Indoles*. Second Place in Organic Chemistry. 2015.

2014 University of Western Ontario Internship Day. *Work and Research Experiences at Lanxess Inc. International Butyl Rubber Business Unit R&D*. 2014.

2013 Irwin, L.C.; Vriesen, M. R. **2013 Analytical Poster Presentation Day, University of Western Ontario**. *The potential of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry for the identification of biogroups of Cronobacter sakazaki*. (Based on the following research paper: Karamanova *et. al*: *Rapid Commun. Mass Spectrom.* **2013**, 27 (3), 409-418). Awarded 1st place.

D. Awards/Scholarships

2019 Poster prize for organic chemistry at the 102nd CCCE; \$100

2018-2020 NSERC Post Graduate Scholarship – Doctoral; \$21,000

2018-2019 Ontario Graduate Scholarship; \$15,000 (declined)

2017-2018 Nominated for a Graduate Student Teaching Award; \$500

2017-2018 Queen Elizabeth II Graduate Scholarship in Science and Technology; \$15,000

2016-2017 Western Doctoral Scholarship; \$8,000

2016 Second Place Oral Presentation at Quebec Ontario Mini-Symposium for Bioorganic and Organic Chemistry, \$50

2015 - 2016 Queen Elizabeth II Graduate Scholarship in Science and Technology; \$15,000

2015 Second Place Oral Presentation at Southern Ontario Undergraduate Student Chemistry Conference, \$150

2011-2015 Deans Honour Roll, University of Western Ontario

E. Technical Reports

1. Gilles Arsenault, Lauren Irwin, Sharon Guo. (2013). *Butyl Rubber Aging Processes*. - Title has been modified due to Non-Disclosure Agreement Conflict. Number of Contributors: 3

F. Volunteer Work

2019 Pint of Science London: managed the coordination of speakers, advertisements and event activities for the May 22nd evening of the event.

2017-2018 Science Rendezvous: Designed, prepared and executed the Chemistry with a Bang show for the finale of Science Rendezvous events. Worked in the chemistry booth showcases chemical reactions to budding young scientists.

2015-2018 Western Chemistry Outreach Activities: Chemical preparations and equipment organization for the “Chemistry with a Bang” shows for incoming first year students, and elementary school visitors