4-2016

Domino Reactions Involving Merged Cycloaddition and Cycloreversion Processes Affording Pyridine Products

Jill Williamson
College of William and Mary

Domino Reactions Involving Merged Cycloaddition and Cycloreversion Processes Affording Pyridine Products

A thesis submitted in partial fulfillment of the requirement
for the degree of Bachelor of Science in Chemistry from
The College of William and Mary

by

Jill Williamson

Accepted for HONORS

Associate Professor Jonathan Scheerer, Director

Professor Christopher Abelt

Professor Elizabeth Harbron

Associate Professor Oliver Kerscher

Williamsburg, VA
April 27, 2016

Abstract

This thesis explores oxazinone and pyrazinone intermediates in the merged Diels-Alder and retro-Diels-Alder strategies for the synthesis of substituted pyridines. Dihydrooxazinone substrates are prepared and investigated in a domino reaction sequence that comprises an aldol condensation, alkene isomerization, Diels-Alder, and retro-Diels-Alder reaction. Preliminary efforts intended to expand the reaction scope to include aliphatic aldehydes are included and potentially applicable to the synthesis of guaipyridine alkaloids including the rupestines.

Dedication

This work is dedicated to my parents, Wendy and Neil Williamson, for their constant encouragement and support throughout my years at William & Mary.

Acknowledgements

First and foremost, I must thank Dr. Scheerer for his support and guidance throughout my undergraduate research experience. Without Dr. Scheerer, I would never have been a chemistry major, experienced undergraduate research, or be continuing onto chemistry graduate school. He is a wonderful mentor that puts tremendous effort into shaping his students into great chemists, writers, and people. Additionally, I would like to thank Dr. Chris Abelt, Dr. Elizabeth Harbron, and Dr. Oli Kerscher for serving on my Honor's committee. This thesis would not have been possible without their involvement.

I would also like to thank my friends within the chemistry department. For those who took the time to edit my thesis or help me practice my defense, I sincerely appreciate the diligent effort made to make me a better chemist. They will go wonderful places in the world and I am lucky to call them my friends. Research would not have been nearly as enjoyable without my lab mates. Please continue to DJ pop hits from the 90s, contemplate for too long about which is the aqueous layer, and make the best ice cream in the entire department.

Finally, I would like to thank my family, especially my brother Mark. Although they are not chemists, I appreciate the effort they make to learn about my passion. Their unfailing support permeates through these pages. I rarely express my sincere gratitude for their undying devotion to my success.

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CHAPTER ONE

Introduction

2-Pyridones and pyridines are of interest to organic chemists due to their various biological activities ranging from antihistamine function to chemotherapeutic agents.[1] Pyridones, piperidine, and picoline are all structurally related but somewhat distinct from pyridines (**Figure 1.1**).

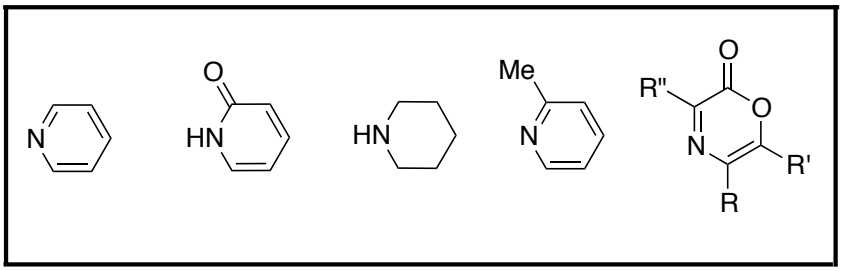
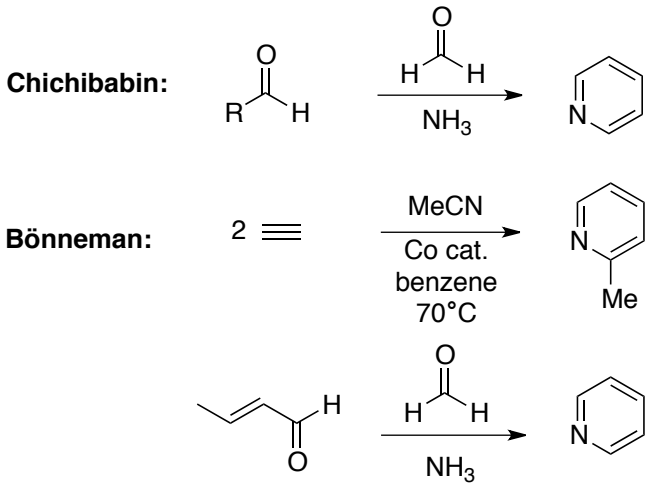
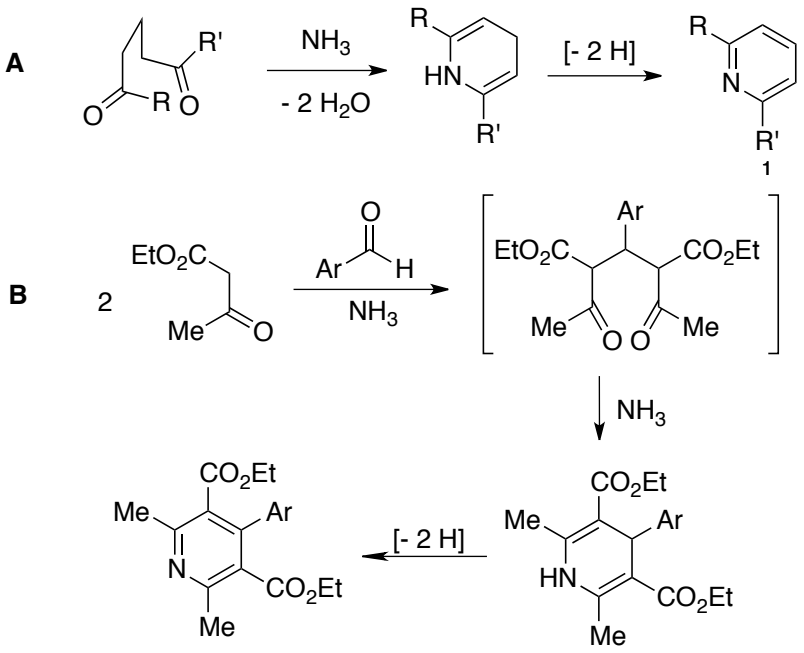


Figure 1.1 General structures of pyridine, 2-pyridone, piperidine, picoline, and trisubstituted 2*H*-1,4-oxazin-2-one

Syntheses of pyridines were mass-produced via the Chichibabin pyridine synthesis, the Bönneman reaction, or the aerobic gas-phase condensation of croton aldehyde, formaldehyde, and ammonia (**Scheme 1.1**). The most commonly implemented method for achieving substitution of pyridines is classic condensation of ammonia or hydroxylamine with a corresponding 1,5-diketone (**Scheme 1.2 A**). Another route towards substitution reacts ammonia with an aldehyde and 2 equivalents of a 1,3-dicarbonyl compound to perform a Hantzsch dihydropyridine synthesis (**B**). While this is not an exhaustive summary, the five reactions below demonstrate the variety of methods that have been previously implemented to afford pyridine compounds.[2,3]



Scheme 1.1 Syntheses of pyridine for mass-production



Scheme 1.2 Syntheses of di- and penta-substituted pyridines

The diverse synthetic methods for the preparation and derivation of pyridine and pyridone structures enable the practicing chemist to efficiently access many substitution patterns. Continued efforts directed toward the development of new methods for pyridine synthesis are warranted (in part due to the interesting biological and physical properties of the compounds).

Medicinal Relevance of Pyridine Structures

Six-membered nitrogen-containing ring structures, such as pyridines and pyridones, are highly prevalent structures in pharmaceutically active molecules.[1] Not only do six-membered nitrogen-containing ring structures comprise half of the 12.5 million compounds currently known and characterized, but the majority are bioactive, highlighting their utility as drug candidates.[2] In particular, 2-pyridone cores have drawn the attention of chemists in multiple fields of study, including natural products, pharmaceuticals, agrochemicals, polymer and materials chemistry, and even fluorescence imaging.[3]

Thomas Anderson first discovered pyridine in 1851 in bone oil, a common animal repellent generated from the destructive distillation of bones. Later it was also identified in coal tar and as a substituent of many alkaloids. By observing the excretions of dogs exposed to pyridine, Dr. His determined that pyridine was metabolized and excreted as methylpyridylammoniumhydroxide, unlike piperidine and picoline. Investigating the effect of pyridine on the central nervous system, Dewar and McKendrick found that pyridine initiates convulsions and eventually kills the organism via respiratory paralysis. Heart muscle paralysis occurs if pyridine is administered in large quantities. As the experiments above show, large exposure to pyridine can be concluded to be dangerous, but the toxicity was minimal in normal doses of pyridine.[4]

However unlike pyridine itself, derivatives of pyridine do have medicinal properties. A data bank of compounds, including pyridine derivatives, from the Research Institute for the Biological Testing of Chemical Compounds and the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR were tested for their biological

activity via a search engine that can discern moieties and bioactivities. The program revealed 46 types of activity among the pyridine derivatives (**Table 1.1**). It is important to note that the program does not address some of the more commonly known uses of pyridine derivatives. **Table 1.1** was gathered to elucidate the frequency that pyridine derivatives are used for five general pharmacological actions. Pyridine derivatives are commonly utilized as anti-allergic drugs. Of 342 antihistamines in the bank, 43 (12.6%) of the compounds contained a pyridine structure, a greater percentage than any other category analyzed. However, pyridine derivatives are most commonly used as chemotherapeutics, accounting for 32% of the pyridine compounds studied.[5]

		Number of Compounds		
Rank	Pharmacological Action	Active	Pyridine	Percentage
1	Histamine agonists and antagonists, anti-allergic	342	43	12.6%
2	Anti-inflammatory	916	74	8.1%
3	Cardiovascular	1050	65	6.2%
4	Chemotherapeutic	2962	115	3.9%
5	Central Nervous System Activity	1933	58	3.0%

Table 1.1 Distributions of Pyridine Compounds According to General Pharmacological Action

Select pyridine and pyridone structures with interesting bioactivity are illustrated in **Figure 1.2**. Syntheses of these complex organic structures have been previously published.[6-11] Pyridone-L-697661 was initially analyzed in a combination study with zidovudine in 1996. Zidovudine, not pictured, is an antiretroviral drug used for the treatment of HIV and AIDS. L-697661 reacted very well in combination therapy with zidovudine for the treatment of human immunodeficiency virus (HIV-1) when administered to a small study, but the clinical trials had to be halted due to lack of support. (+)-Camptothecin inhibits the nuclear enzyme DNA topoisomerases (Type I), an

essential enzyme for DNA replication; therefore, (+)-Camptothecin has shown to be cytotoxic to some forms of carcinoma. Papaverine is used as a drug for the control of angina, lung embolism, baby colic, and erectile dysfunction by relaxing blood vessels and muscles. Cananodine is a guaipyridine alkaloid isolated from *Cananga odorata* (ylang-ylang), a tree whose bark, leaves, and oil have been used in the traditional medicines of southeast Asia. Cananodine was recently discovered to be cytotoxic against human liver carcinoma. Lycopladine A has shown slight selective cytotoxicity toward murine lymphoma L1210 cells. (–) -Huperzine A is a useful drug for the treatment of memory loss, dementia, and the muscular disorder myasthenia gravis.

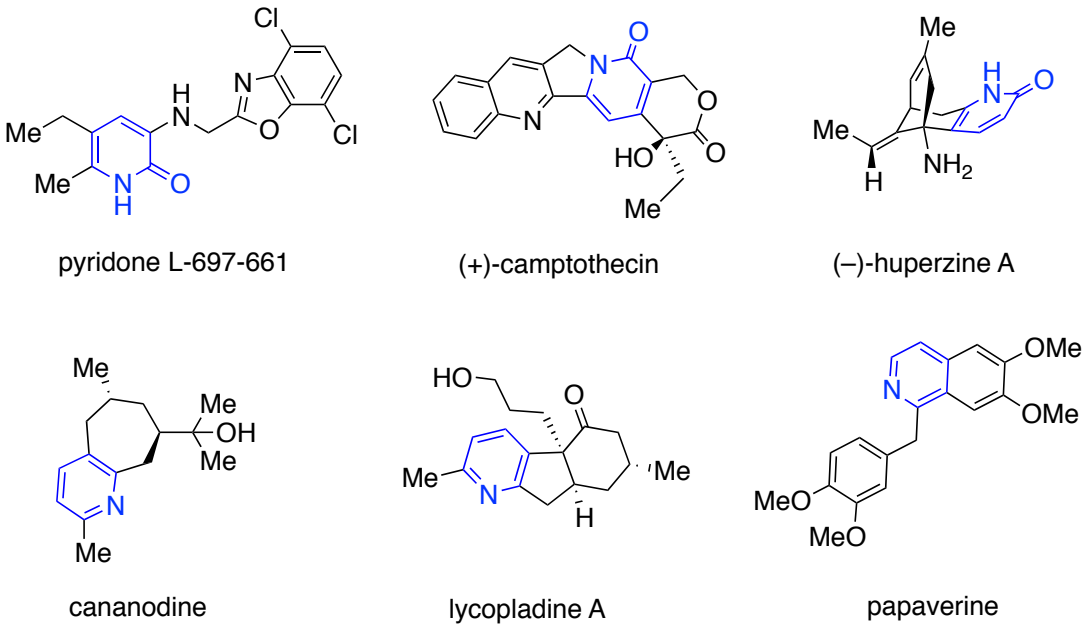


Figure 1.2 Bioactive pyridine/pyridone-containing structures

Diels-Alder/retro-Diels-Alder Reactions

Diels-Alder reactions are [4+2] cycloaddition of diene and dienophile (**Figure 1.3**). Retro-Diels-Alder reactions are observed by cycloreversion of a cyclic system to afford a diene and a dienophile as products. The cycloreversion is favorable when

expelling one of the bridges generates a more stable product.[12] In **Figure 1.3**, ethylene is expelled in the retro-Diels-Alder reaction of cyclohexene.

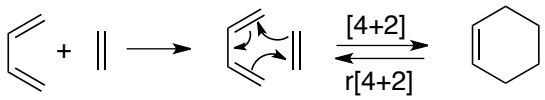


Figure 1.3 General Diels-Alder and retro-Diels-Alder reactions

Diels-Alder reactivity has been determined to be dependent on HOMO/LUMO energy levels of educts, the distance between the reactive centers of the diene and dienophile, and the ΔH° for the overall reaction. By the principle of microscopic reversibility, retro-Diels-Alder reactivity depends on identical factors. A general reactivity trend (**Table 1.2**) has been established for common dienes and dienophiles involved in retro-Diels-Alder (rDA) reactions, depending on how easily extruded and/or unreactive the compound is once formed.[12]

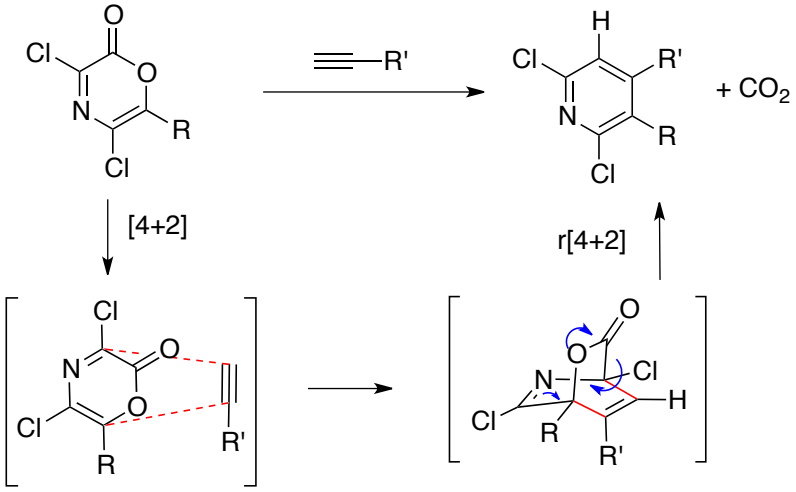
	Most Readily Extruded				Less Optimal
Diene ($4\pi\ e^-$)	O	NH			
Dienophile ($2\pi\ e^-$)	N_2	CO_2			RCN

Table 1.2 Retro-Diels-Alder reactivity trend

The retro-Diels-Alder mechanism can occur as a concerted or asynchronous process depending on the timing of the bond cleavage. A concerted reaction occurs with fast bond cleavage and subsequent bond formation; whereas, an asynchronous reaction would require further reactants to proceed to the final product. As with Diels-Alder reactions, stereochemical considerations must be made in regards to *endo/*exo geometry with the retro-Diels-Alder.[12]

Oxazinone Synthesis

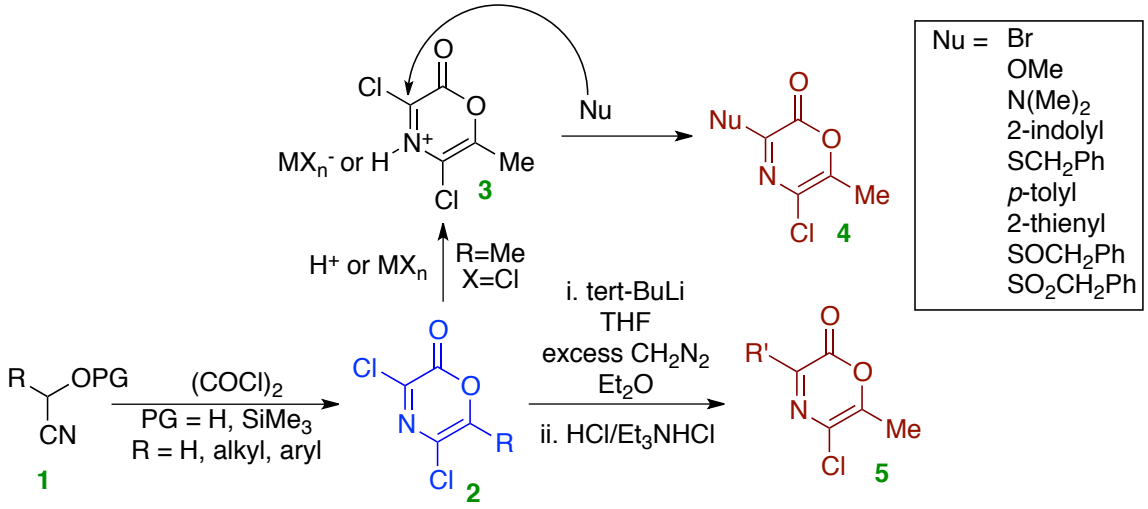
The oxazinone structure was intended to be viable for Diels-Alder cycloaddition reactions through the azadiene system. After cycloaddition with alkynes, adducts undergo a retro-Diels-Alder reaction, extruding carbon dioxide and affording polysubstituted pyridines (**Scheme 1.2**). As seen in the reactivity trend, carbon dioxide is readily extruded, propelling this reaction to the cycloreversion product. With a dihalogenated oxazinone starting material, the Diels-Alder/retro-Diels-Alder reaction yields a pyridine core containing up to 3 substituents excluding the halogen atoms.



Scheme 1.2 General oxazinone merged cycloaddition-cycloreversion reaction

Previous oxazinone syntheses were scarce, lengthy, poor yielding, and did not give an opportunity to vary the substituent pattern.[14] Two syntheses were developed to target an oxazinone containing two alkyl groups and one halogen. One option is treatment of tertbutyllithium to the 3,5-dichloro-*2H*-1,4-oxazin-2-one **2**, in which diazoimino-triazolo equilibrium shifts the product towards the desired trisubstituted oxazinone **5**. Another pathway involves nucleophilic attack to the imidoyl chloride **3** at the most electrophilic position under acidic conditions (**Scheme 1.3**). Only tri-substituted

oxazinones, such as 3,5-dichloro-*2H*-1,4-oxazin-2-one, could successfully complete the Diels-Alder/retro-Diels-Alder experiment designed. Substituent addition at position 3 stabilizes the adduct and allows the [4+2] cycloaddition to move forward in the presence of alkenes or alkynes.[15]

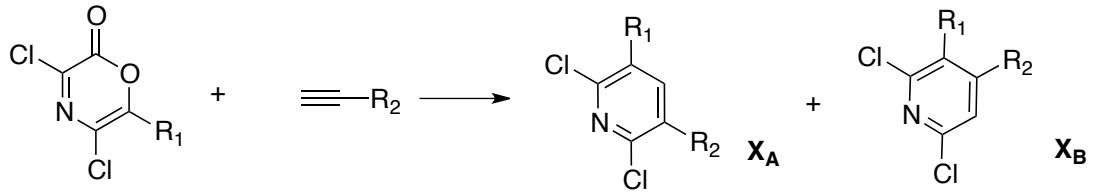


Scheme 1.3 Syntheses of trisubstituted oxazinones

Prior Art of Oxazinone Diels-Alder/retro-Diels-Alder Reactions

The oxazinones, synthesized using either route shown above, have been shown to undergo [4+2] cycloaddition and cycloreversion with alkynes in multiple publications.[15-21] The generalized reaction is shown between 6-alkyl-3,5-dichloro-2*H*-1,4-oxazin-2-one and an acetylenic derivative (**Table 1.3**).[12-21] Each reaction efficiently produces a polysubstituted pyridine, which could potentially be bioactive, even after variation of the substrate at position 6. Electron donating and electron withdrawing groups were attached to determine whether the cycloaddition/cycloreversion would occur only under certain electronic demands. The electronics of the cycloaddition/cycloreversion cascade have been probed by varying the substitution at position 6 of the oxazinone scaffold.[15-21] Both electron donating and withdrawing groups were observed and displayed little to no

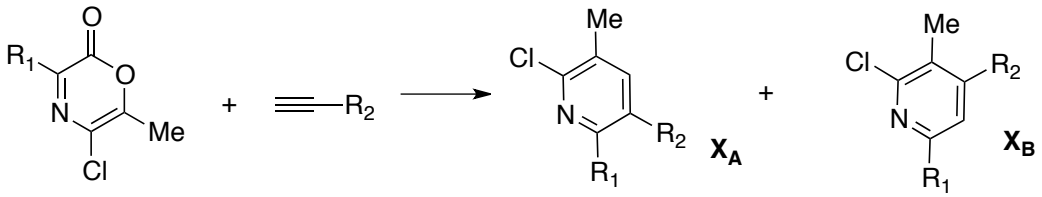
change in yield or regioselectivity. From these results, it is clear that factors other than the relative electronics at position 6 play major roles in the reaction sequence.



Entry	R_1	R_2	Conditions	Regio-isomer	Yield
1	Me	CH_2Br	tol, 80°C, 12 h	X_A	92%
2	Ph	CH_2Br	tol, 80°C, 12 h	X_A	92%
3	Et	CH_2Br	tol, 80°C, 12 h	X_A	84%
4	H	CH_2Br	tol, 80°C, 12 h	X_A	85%

Table 1.3 Variation at position 6 of oxazinone effects on DA/rDA reaction

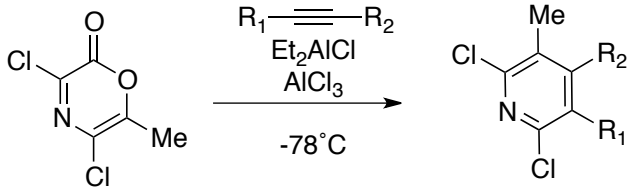
Position 3 also was tested in this manner. From these results, it is clear that changing position 3 does not influence reactions with varied acetylenic compounds, regardless of the electronics of the oxazinone (**Table 1.4**).[13-21]



Entry	R_1	R_2	Conditions	Regio	Yield
1	4-MePh	CH_2Cl	neat, reflux, 19h	X_A	95%
2	2-thienyl	CH_2Cl	neat, reflux, 14h	X_A	95%
3	3,4-MeOPh	CO_2Me	tol, 80°C, 4h	X_A	91%
4	OMe	CO_2Me	neat, 80°C, 2h	$X_A/X_B > 10$	92%
5	*p*-tolyl	CO_2Me	neat, 80°C, 1h	$X_A/X_B > 10$	90%
6	OMe	Ph	neat, 80°C, 1d	$X_A/X_B > 10$	83%
7	*p*-tolyl	Ph	neat, 80°C, 1h	$X_A/X_B > 10$	81%

Table 1.4 Variation at position 3 of oxazinone effects on DA/rDA reaction

In both tables, the reaction had to be run at 80°C for extended periods of time. *2H*-1,4-oxazin-2-ones also require excess dienophiles and high pressure to undergo the DA/rDA reaction with alkenes or alkynes. To avoid such harsh conditions, catalyst trials were conducted using 6-methyl-3,5-dichloro-*2H*-oxazin-2-one as the model compound with various alkenes and alkynes. The effect of the Lewis acid catalysts Et_2AlCl and $AlCl_3$ was explored by a comparing an uncatalyzed, elevated-temperature run with a catalyzed, cool (at -78˚C or room temperature) run. The catalyst lowered the energy of the lowest unoccupied molecular orbital (LUMO) of the oxazinone. In the inverse electron demand system, adduct formation becomes favored at lower temperatures when the LUMO of the azadiene system directly interacts with the HOMO of the dienophile. Catalysis also greatly improves the regio- and stereoselectivity, forming the *endo*-cyclization product exclusively. However, *exo*- products can be formed if the dienophile contains heteroatoms.[17]

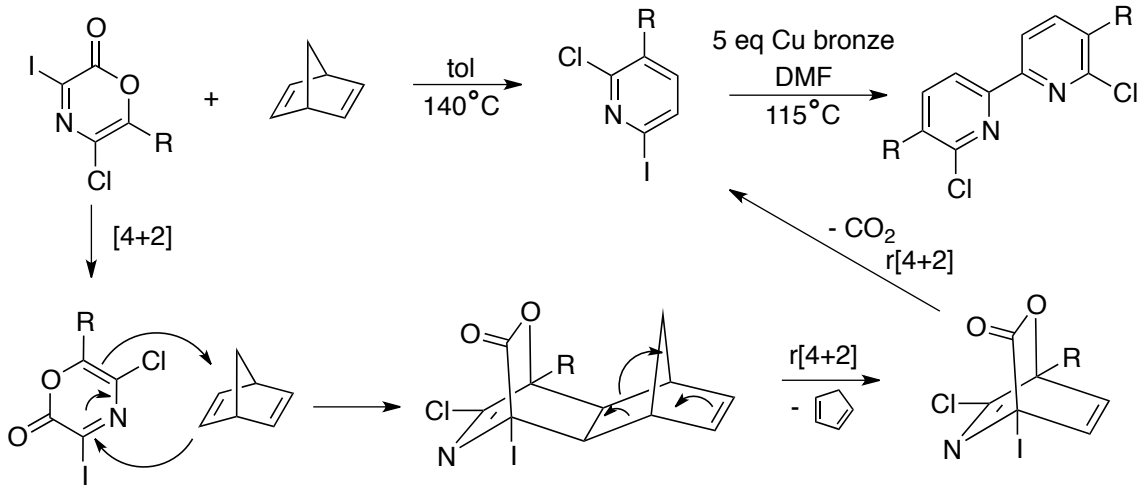


Scheme 1.4 Model reaction for the Lewis Acid catalyzed, low temperature trial

Oxazinone Chemistry in Natural Product Synthesis

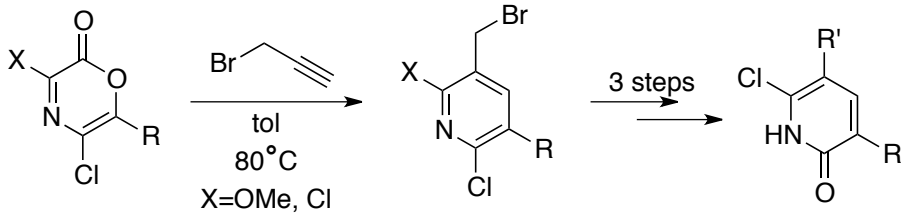
5,5'-dialkyl-6,6'-bipyridines are of interest to the scientific community because of their appearance as a substructure on cancer therapy drugs, such as camptothecin and its derivatives. In the synthesis of 5,5'-dialkyl-6,6'-dichloro-2,2'-bipyridines, the oxazinone architecture was implemented as the penultimate step towards the bicyclic species. 2,5-norbornadiene undergoes 2 retro-Diels-Alder reactions after [4+2] cyclization with the

oxazinone (**Scheme 1.5**). The trisubstituted oxazinone offers a source of chlorine and alkyl substituents as well as an azadiene system that easily converts to pyridine products via merged cycloaddition and cycloreversion.[18]



Scheme 1.5 Oxazinone reaction with norbornadiene

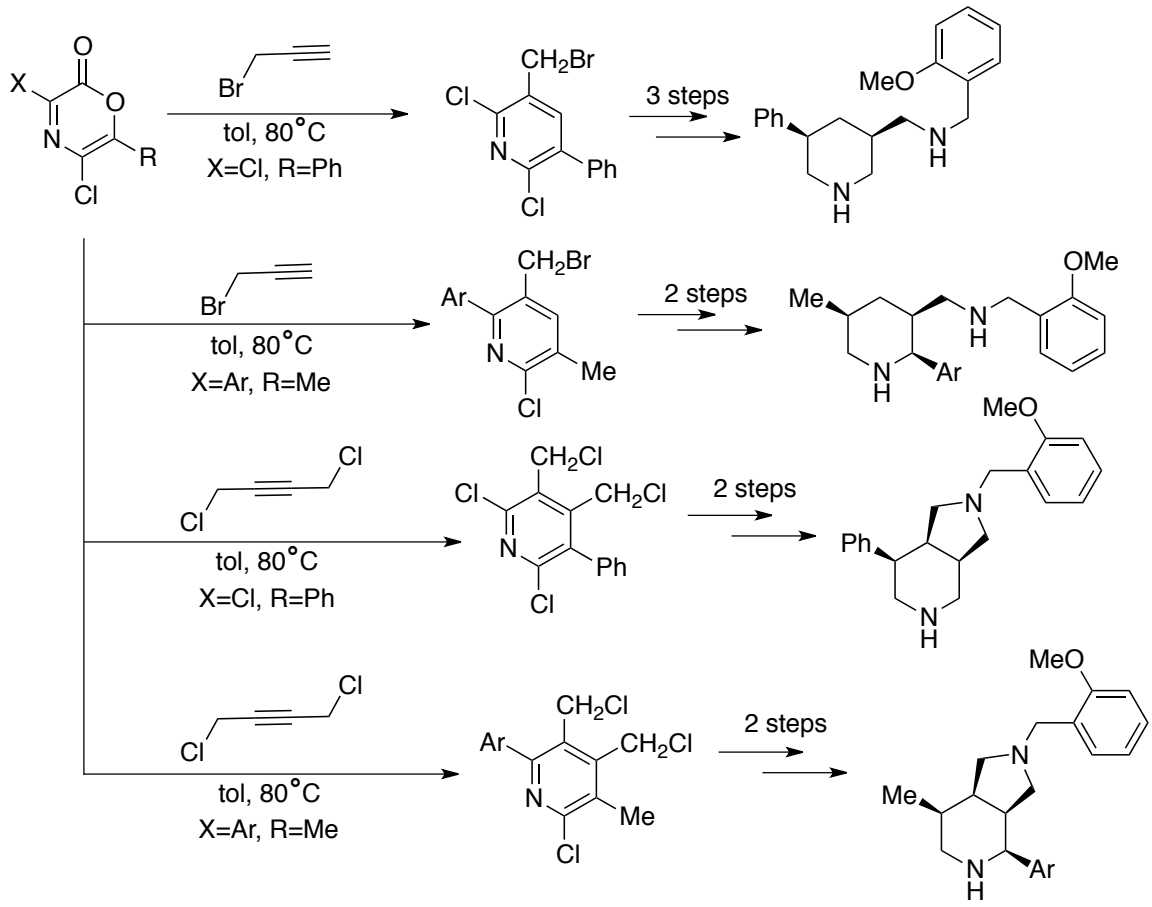
An oxazinone DA/rDA was implemented as the initial step in a synthetic sequence towards 6-chloro-2(1*H*)-pyridinone. Shown in **Figure 1.5**, 3-methoxy and 3-chloro-*2H*-1,4-oxazin-2-ones reacts with propargyl bromide, yielding 3-bromomethylpyridines regioselectively, eventually yielding the desired product in four total steps.[19]



Scheme 1.6 Regioselective cycloaddition of oxazinone to afford 3-bromomethylpyridines

Oxazinones were also used in the synthesis of 2,3,5-*cis*-substituted piperidines and the *cis*-substituted [3,4-c]pyrrolopiperidines, which are potential Substance P

antagonists. Such antagonists are valuable to the maintenance of pain, inflammatory diseases, migraines, rheumatoid arthritis, asthma, and nausea. In **Scheme 1.7**, all oxazinone DA/rDA reaction sequences are highlighted. All of these reactions exhibit regioselectivity towards the desired product.[20]



Scheme 1.7 Four natural product syntheses beginning with a regioselective DA/rDA reaction

Conclusion

Oxazinone reactions with alkynes are well known and have been implemented in multiple natural product syntheses as key steps. The [4+2] cycloaddition is immediately followed by cycloreversion with the loss of the carbon dioxide bridge to yield a substituted pyridine product, which could possibly be active in a pharmacological general

bioactivity. Though oxazinone syntheses were previously scarce, two syntheses have been conducted to produce trisubstituted oxazinone structures capable of undergoing a [4+2] Diels-Alder cycloaddition. In summary, pyridines have been synthesized in many different ways ranging from classic condensation to organometallic chemistry. Now, pyridines can be synthesized using a Diels-Alder/retro-Diels-Alder reaction sequence, which will broaden the scope of products that can be synthesized in order to procure other pyridine-containing compounds that display bioactivity.

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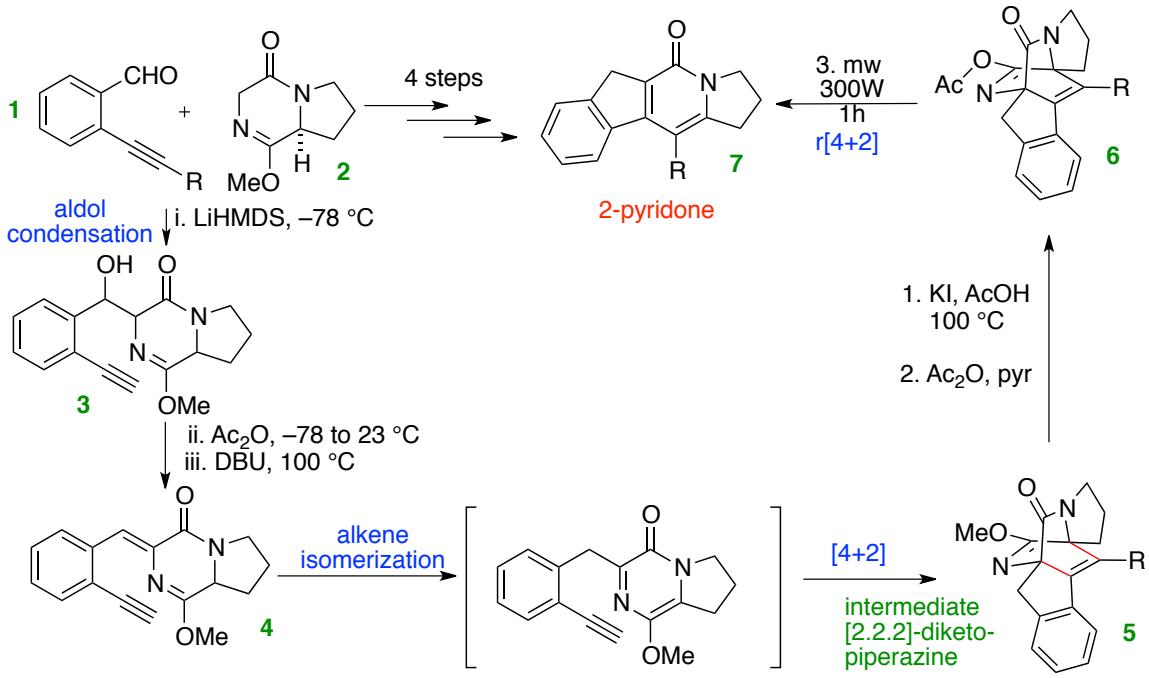
CHAPTER TWO

Introduction

Our goal is to accomplish an intramolecular Diels-Alder and retro-Diels-Alder sequence featuring oxazinone chemistry. This novel reaction would only be successful if the substrate was able to align the alkyne and the 4π electron system to undergo [4+2] cycloaddition. Oxazinone architecture has proven to be highly reactive when exposed to alkyne substrates, affording 2-pyridine compounds. However, these reactions have only been explored using 6-alkyl-3,5-dichloro-2*H*-oxazin-2-ones. Diketopiperazine **2** contains pyrollidine and piperazine substructures, and is very similar to 6-alkyl-3,5-dichloro-2*H*-oxazin-2-one with an electrophilic site between the carbonyl and nitrogen within the ring. It can isomerize to form a diene system that would cyclize [4+2] with an alkyne and extrude isocyanate derivatives to accomplish the retro-Diels-Alder reaction. Diketopiperazine can therefore be considered a substitute for the previous oxazinone studied.

In **Scheme 2.1**, Benzaldehyde **1** was chosen as the alkyne substrate because it reacts first as an aldol condensation, leaving the alkyne essentially unchanged and forming the 4π electron system. The aldol product **3** isomerizes the alkene via acetylation to align the 4π electron system with the terminal alkyne. Intermediate [2.2.2]-diketo-piperazine is thermally stable up to 180°C. The second reaction oxidizes methyl formimide to pyridone, where the third reaction acetylates the carbonyl, so the lactam bridge **6** can be extruded as an isocyanate derivative upon microwave heating to afford 2-pyridone **7**.[1]



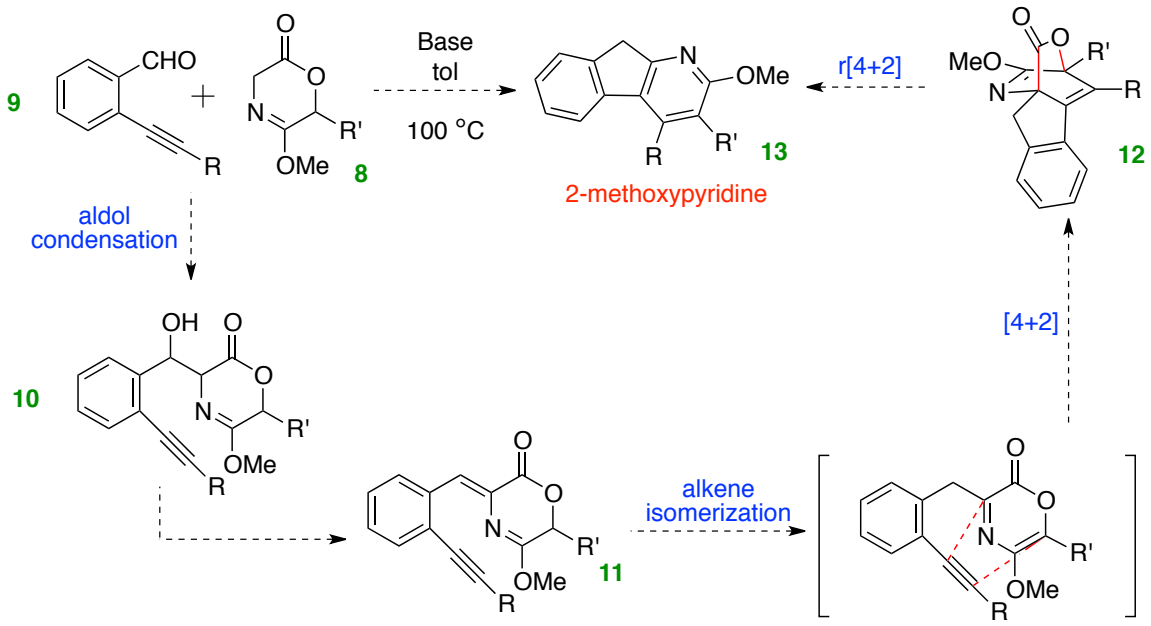
Scheme 2.1 Diketopiperazine and ethynylbenzaldehyde Diels-Alder/retro-Diels-Alder reaction

Proposed Mechanism of Oxazinone One-Pot Reaction

The reaction sequence consisting of aldol condensation, alkene isomerization, and Diels-Alder was reasonably efficient. For example, **1** reacts with **2** to form compound **5** in one reaction vessel by sequential addition of reagents. In most cases, the cycloreversion step required a three-step sequence in order to activate one lactam bridge for extrusion. We desired a more efficient overall sequence that would undergo the same reactions, but with an easier retro-Diels-Alder reaction that can occur *in situ* without addition of other reagents.

An analogous domino reaction with a dihydro-2*H*-1,4-oxazin-2-one would accomplish the same sequence as the diketopiperazine model system all in one pot (**Scheme 2.2**). Also, the intermediates (products **10-12**) would not be isolable since the reaction would progress towards the final product. The sequence would be initiated by

deprotonation at C_3, alpha to the lactone, to form an enolate. Addition of the enolate to aldehyde **9** would generate the aldol addition product **10**, which can be deprotonated by base at C_3 to lose water to give a 4π electron system **11**. The alkene would isomerize to align [4+2] cyclization to reveal the cycloadduct **12**. Following the extrusion of carbon dioxide, the retro-Diels-Alder product **13** would be isolated as a tricyclic, pyridine-containing structure.



Scheme 2.2 Proposed mechanism of one pot oxazinone Diels-Alder/retro-Diels-Alder reaction

The features of the dihydrooxazinone make this mechanism theoretically possibly, whereas diketopiperazine would not be able to accomplish the one-pot mechanism due to the difficulty of the isocyanate derivative expulsion. The extrusion of carbon dioxide is known to be more facile than isocyanate derivatives. There are two major obstacles in the sequence. First, dihydrooxazinone **8** is an unknown compound. A synthesis would need to be derived to obtain the starting material. Secondly, the analogous aldol condensation

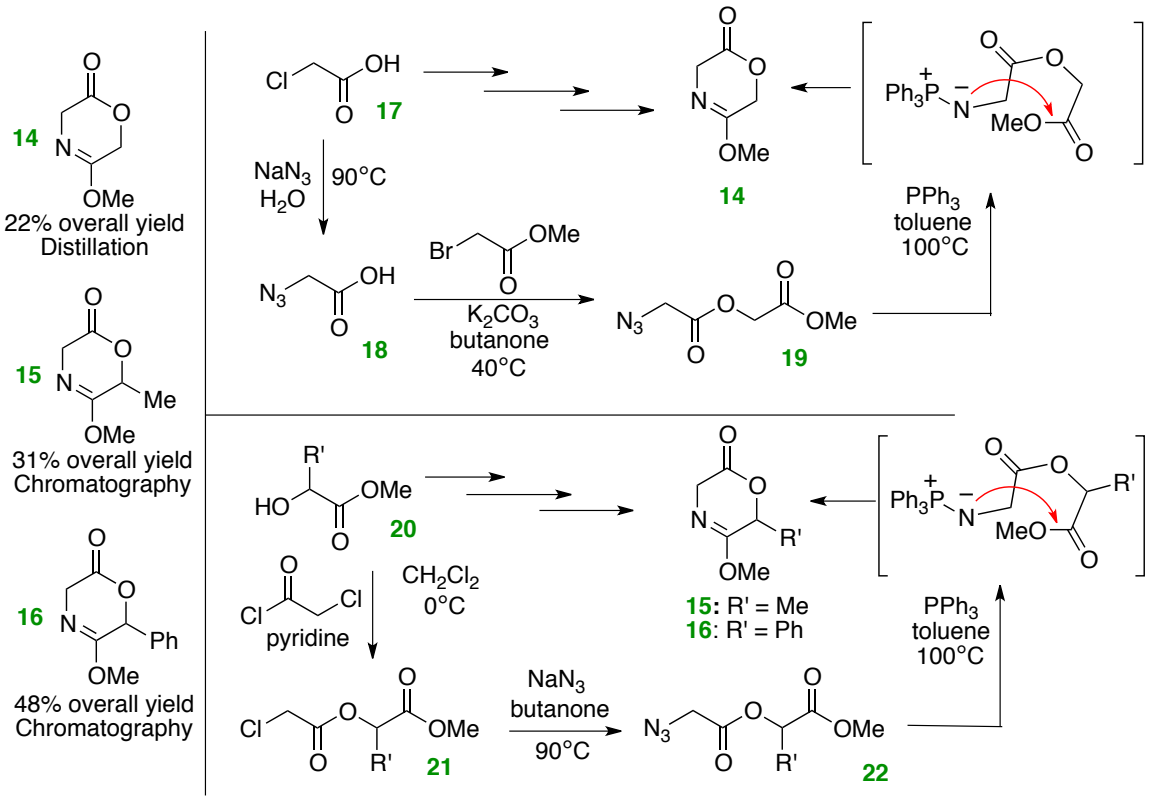
and alkene isomerization sequence may not even be possible. There is no literature for this sequence using an oxazinone substrate.

Synthesis of Starting Material

In order to explore this chemistry and determine the viability, we first needed to prepare the dihydrooxazinone precursors. The synthesis route of dihydrooxazinones varies slightly with the substituent at position 6: hydrogen in **14**, methyl in **15**, and phenyl in **16** (**Scheme 2.3**). All dihydrooxazinones utilize the steps of azide displacement, substitution of an ester group, and a Staudinger reduction. For **14**, the azide displacement occurs first followed by the ester substitution and *vice versa* for **15** and **16**. Staudinger reduction and cyclization occurs with triphenylphosphine in moderate yields to afford the desired dihydrooxazinone. The Staudinger reduction reacts triphenylphosphine with an azide to form an aza-Wittig intermediate, which releases nitrogen gas to generate an iminophosphorane. The double bond occurs in resonance with a positive charge on phosphine and a negative charge on nitrogen. In this resonance structure, as shown in **Scheme 2.3** as the transition state, the lone pair on nitrogen can attack the carbonyl of the methyl ester, cyclizing the compound. The triphenylphosphine substituent is expelled as triphenylphosphine oxide.

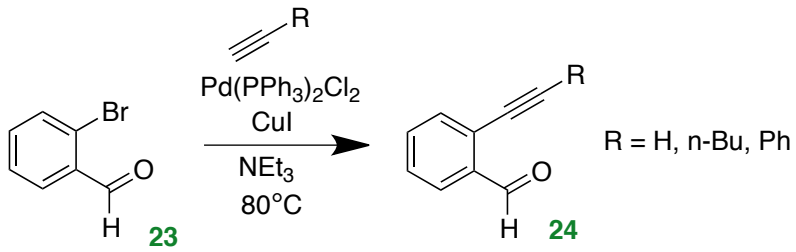
Triphenylphosphine oxide makes purification difficult. Stoichiometric equivalents of the oxide are generated and cause the desired product to be trapped within the black tar of the oxide. Kügelrohr distillation separates compounds based on boiling point. Considering triphenylphosphine oxide boils around 330°C, dihydrooxazinones are expected to boil around 120°C and can be purified via Kügelrohr. The consequence of this mode of purification is that not all desired product can be collected, so the yield

decreases significantly due to purification issues and not due to reaction completion. Compounds **15** and **16** can be purified on flash column chromatography. We investigated the possibility of purifying via chromatography when compound **16** could not be purified via distillation. Using an additive of toluene, compound **16** could be separated in sufficient yield from triphenylphosphine oxide and the impurity of the hydrolysis product **20**. Once chromatography was successful for compound **16**, the same conditions were tested for compound **15** and also proved higher yielding than distillation. Compound **14** did not significantly capture any pure product with chromatography, so it remains to be purified via Kügelrohr.



Scheme 2.3 Syntheses of 5-methoxy-3,6-dihydro-2*H*-1,4-oxazin-2-one, 5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one, and 5-methoxy-6-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one

The benzaldehydes also required synthesis to attach an alkyne to the aromatic aldehyde. 2-bromobenzaldehyde **23** reacts in a Sonogashira coupling (**Scheme 2.5**) with palladium and copper catalysts and the necessary alkyne to afford compound **24** as 2-ethynylbenzaldehyde, 2-(hex-1-yn-1-yl)benzaldehyde, and 2-(phenylethynyl)benzaldehyde. Herein, the benzaldehydes will be designated **a**, **b**, and **c** respectively. 2-ethynylbenzaldehyde is commercially available, so it is typically purchased instead of synthesized in this manner.

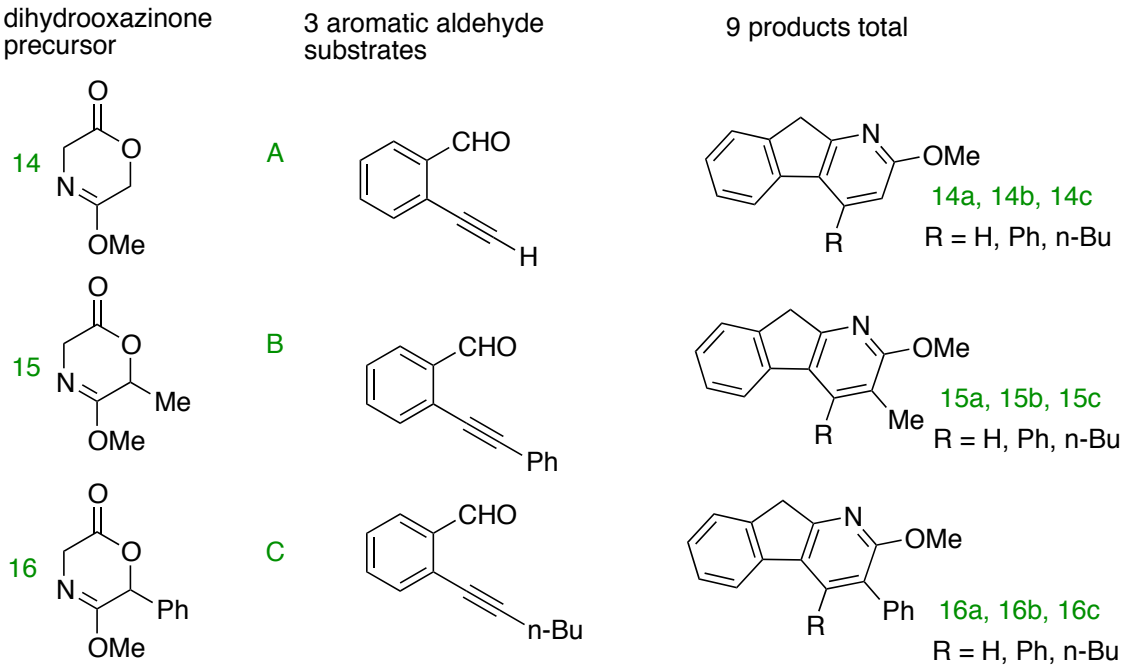


Scheme 2.4 Synthesis of 2-ethynylbenzaldehyde, 2-(hex-1-yn-1-yl)benzaldehyde, 2-(phenylethynyl)benzaldehyde

Reaction Scope

The three dihydrooxazinones **14-16** each were tested in reactions with **24a-c**. The alkyl substituents of the dihydrooxazinone were chosen to elucidate the efficiency of the reaction with distinct steric and electronic properties. Compounds **14** and **a** contain the least steric strain. However, hydrogen is not an effective directing group due to its insignificant electron donating or electron withdrawing capacity. Compounds **15** and **b** offer mild steric hindrance and tension on the cycloadduct as it mediates the methyl or n-butyl attachment. Compound **16** and **c** are aromatic and large hydrocarbons with substantial electronic and steric effects. In theory, the reaction yields should differ slightly depending on the steric or electronic preference for the reaction progress. Discrepancies in yield between reactions **14a-c**, **15a-c**, and **16a-c** should not be very

large considering all species are undergoing the same sequence outlined in **Scheme 2.2**. The nine expected products are shown with each starting material in **Scheme 2.5.**



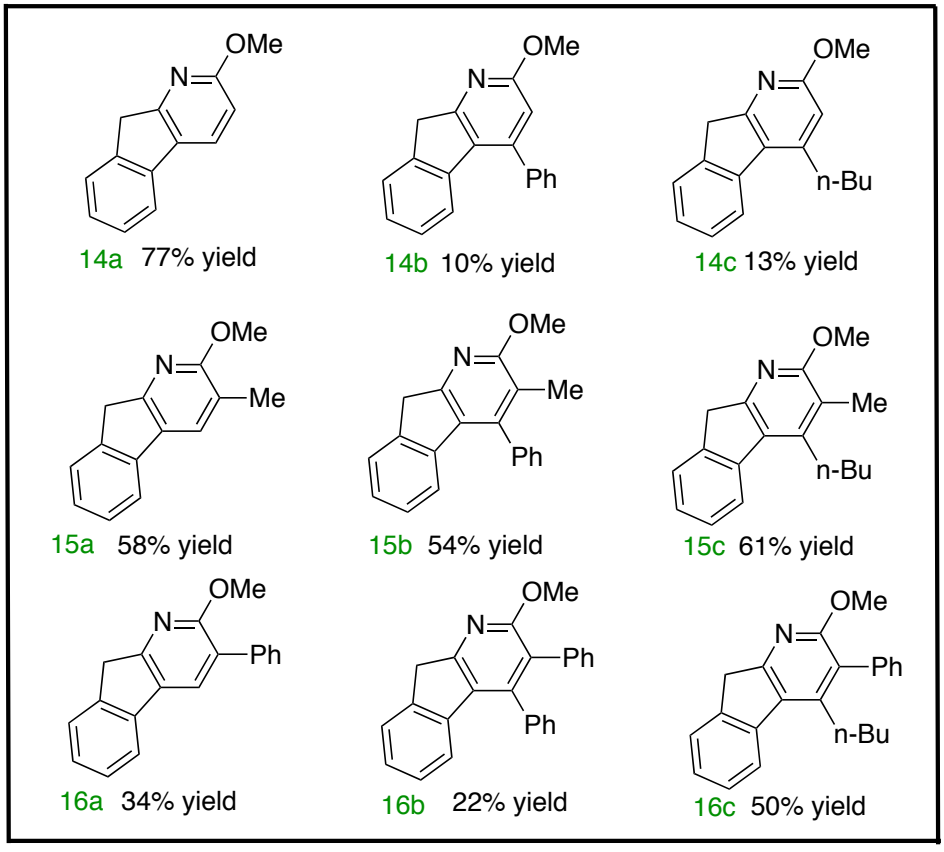
Scheme 2.5 Overview of reaction scope with 3 dihydrooxazinones and 3 benzaldehydes to afford 2-pyridine products

Results

The one-pot mechanism proved to be successful in cascading through the aldol condensation, alkene isomerization, Diels-Alder, and retro-Diels-Alder with only the desired product isolable. Experimentally, each reaction differed greatly in yield depending on the starting material (**Scheme 2.6**).

When designing the experiment, we conceived that slow addition of the benzaldehyde via syringe pump would optimize yield. Decreasing the rate of addition only influenced the yield of products **14a-c**. After examination of initial low recovery of **15a-c**, a Dean-Stark apparatus was utilized to remove water from the system to prevent hydrolysis byproducts from forming. As seen in the **Scheme 2.2**, there is a loss of water

upon alkene isomerization; so one equivalent of water is introduced to the system for every equivalent of product generated. The Dean-Stark apparatus allows the reflux to occur along a larger column that has a two-path condenser. The reflux of toluene occurs in one arm, and in the other arm, 10 mL of toluene sits in a graduated separatory funnel. If water evaporates out of the system with toluene, the water and solvent will reflux through the long arm and condense onto the 10 mL of toluene in the 2nd arm. The density of water sinks the equivalent to the bottom of the graduated separatory funnel, displacing toluene into the reaction flask and removing water from interacting with the desired product. The addition of the Dean-Stark apparatus dramatically increased the affordance and was applied in the procedure to all other remaining reactions.



Scheme 2.6 Results of dihydrooxazinone and benzaldehyde reactions

Discussion

Dihydrooxazinone **14** demonstrates the largest fluctuation between its reactions with benzaldehydes **a-c**. The simplest reaction of the scope, hydrogens on both dihydrooxazinone and benzaldehyde, experienced high rates of conversion towards the desired product **14a**. The methyl and phenyl groups on dihydrooxazinone however added more strain to the cycloadduct, so **14b** and **14c** were afforded equally poor yield.

Notably, all of the reactions involving dihydrooxazinone **15** formed products efficiently. We hypothesize that the methyl substituent stabilizes the cycloadduct to carry the reaction to completion. Amongst the three benzaldehydes that reacted with dihydrooxazinone **15**, little difference is observed.

Reactions **16a-c** show that dihydrooxazinone **16** generates varying yields for the one-pot mechanism depending on which benzaldehyde **a-c** is reacted. The reaction proceeds mildly towards the desired product **16a**. Benzaldehyde **a** contains the smallest substituent, so the cycloadduct might not be stabilized sufficiently to carry through the remainder of the mechanism. The lowest yield of the reactions of dihydrooxazinone **16** was **16b**. While it is not the lowest yield in the entire scope of the reaction, it proves that the strain of generating a product with two neighboring phenyl groups prohibits the mechanism from proceeding to completion. The product **16c** displayed fairly high yield (50%); therefore, the reaction is favorable.

Conclusion

This body of work cements the argument that a dihydrooxazinone species will undergo a domino one-pot mechanism if introduced to a mild base and an ethynylbenzaldehyde. The dihydrooxazinone forms an enolate that reacts via aldol

condensation with the benzaldehyde. The subsequent intermediate undergoes alkene isomerization for the substrate to be a good candidate for a [4+2] cyclization. Upon cyclization, the carbon dioxide bridge is extruded and the desired product is afforded as 2-pyridine derivatives. In conclusion, we were able to successfully synthesize the nine desired products, proving the mechanism in **Scheme 2.2** to be correct. Also, we established that the reaction contains non-isolable intermediates.

The yields of products **14b**, **14c**, **16a**, and **16b** were reproducible as the lowest within the reaction scope. An area that could improve would be the synthesis of the dihydrooxazinones. Depending on the substituent attached, the overall yield of the three step synthesis varies between 22-48% yield. The greatest loss of material occurs during the Staudinger reaction cyclization, likely during purification. If the triphenylphosphine oxide was easier to remove from the desired product, the synthesis would be more efficient.

The merged cycloaddition and cycloreversion sequence using dihydrooxazinones and alkyne-containing benzaldehydes has the opportunity to be implemented in natural product synthesis. Oxazinone chemistry has been utilized in previous natural product syntheses by use of merged cycloaddition and cycloreversion. A new aim of study would be to synthesize molecules similar to the 2-pyridine structures produced in **Scheme 2.6** that could ultimately be manipulated into a bioactive natural product.

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CHAPTER THREE

Guaipyridines and Rupestines

Characterized by a pyridine ring fused to a seven-membered carbocycle, the guaipyridines were first isolated from patchouli oil in 1966 as two sesquiterpene alkaloids, named epiguaipyridine and pacthoulipyridine (**Figure 3.1**).[1] Cananodine was isolated in 1999 from *Cananga odorata*, a fruitful evergreen tree medicinally known to treat fevers and infections. Recently, 12 related compounds were discovered and isolated from *Artemisia rupestris L*, a plant that has been used in traditional Chinese medicine for liver health, antitumor, antibacterial, and antiviral applications.[1,2] Cananodine shows the most promising activity, but the family in general is relatively unexplored for bioactivity despite historic involvement in traditional medicines.

Syntheses of Guaipyridine

Multiple groups have undertaken syntheses of the guaipyridines (**Figure 3.2**).[1-5] Patchoulipyridine was obtained in two steps from β-patchoulene in an overall yield of 30%.[1] Craig and Henry published the first total synthesis of (+)-cananodine, a known bioactive molecule cytotoxic to liver carcinoma, in 17 steps with 4% overall yield from citronelle.[5] The synthesis towards dihydroguaipyridine used guaiol as its starting material and obtained its desired product in 3 steps and 0.1% overall yield.[1] Dihydroepiguaipyridine also was synthesized via guaiol in 5 steps and 0.8% overall yield.[1] With dihydroguaipyridine, dihydroepiguaipyridine, and cananodine synthesized, only the rupestines have yet to be accessed by laboratory synthesis.[5]

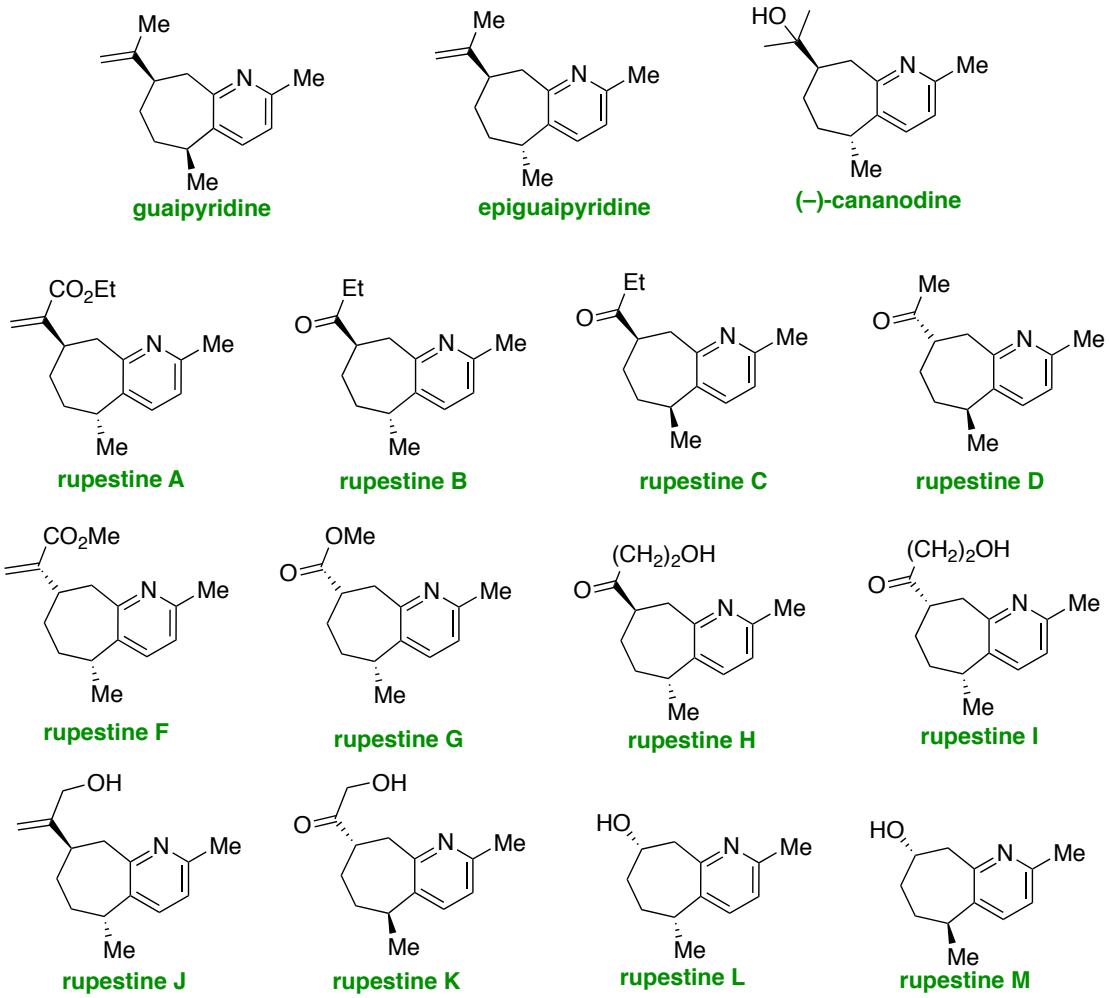


Figure 3.1 Guaipyridines are natural products that resemble the products of an aliphatic aldehyde domino reaction.

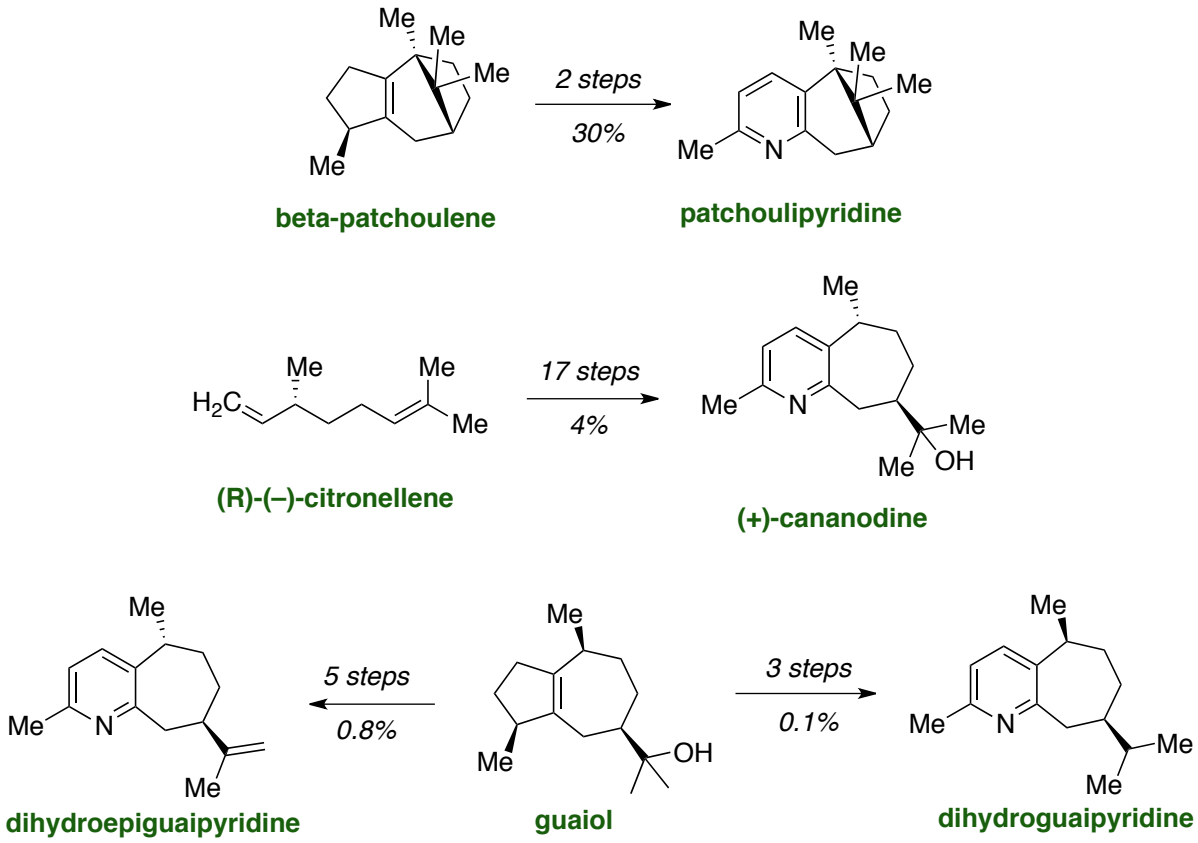


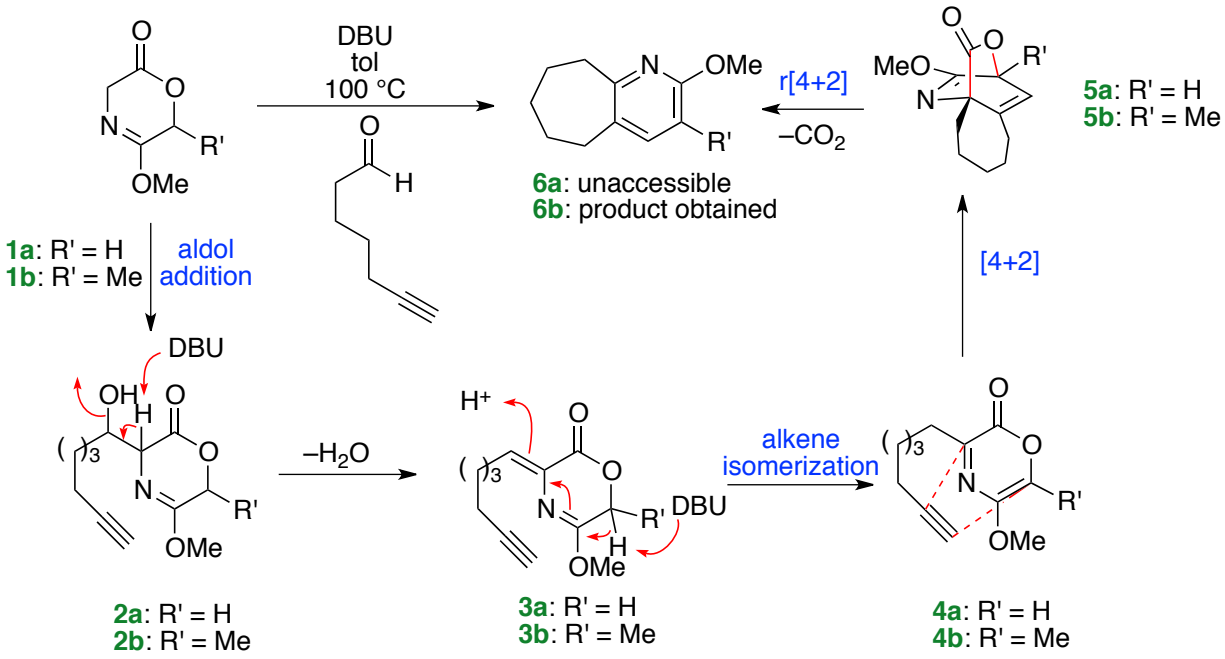
Figure 3.2 Previous syntheses towards guaipyridine and related compounds

Aliphatic Aldehydes in Domino Reaction

As demonstrated in Chapter 2, 2-methoxypyridines can be synthesized from dihydrooxazinones via a merged cycloaddition and cycloreversion process. The substrate scope of the "one pot" domino reaction sequence was focused on three dihydrooxazinone and three alkynylbenzaldehyde precursors. One attempt to expand the scope by using aliphatic aldehydes was explored (**Scheme 3.1**).

When 6-heptynal was explored in the reaction sequence, the anticipated product was a seven-membered ring fused to the pyridine core **6**. Using substrate **1a**, the desired product was not afforded. Instead, the reaction formed the aldol condensation product **3a**

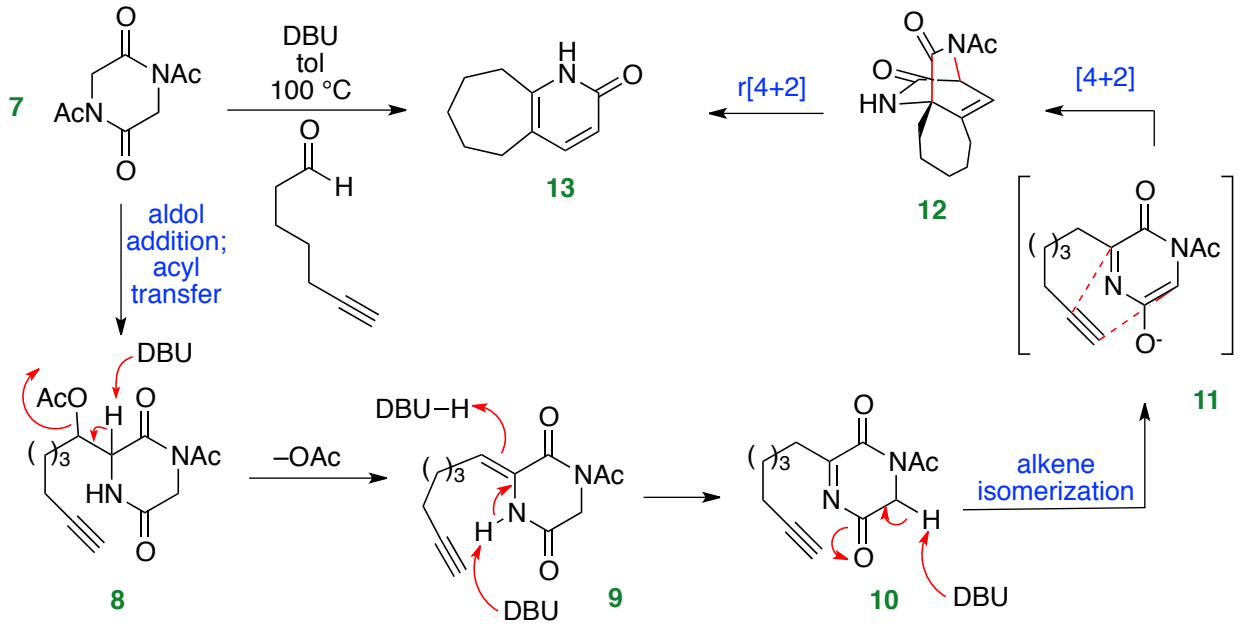
in low yield**.** However, this intermediate appeared unable to undergo alkene isomerization to **4a**. When the reaction was attempted with **1b**, the full sequence including the Diels-Alder and retro-Diels-Alder reactions was executed and pyridine **6b** was obtained in up to 8% yield. A portion (22%) of the desired product remained at the aldol condensation product **4**, demonstrating congruence with the findings of **6a**.



Scheme 3.1 Aliphatic aldehydes react in the same manner as the benzaldehydes, but generate a seven-membered ring fused to a pyridine rather than a tricyclic 2-pyridine.

A complementary process for aldol condensation, alkene isomerization, Diels-Alder, and retro-Diels-Alder is possible with bis(acetoxy)glycine anhydride (**7**) rather than dihydrooxazinone **1a**. Although we obtained some preliminary results with oxazinone **1b** and aliphatic aldehydes, we ultimately decided to explore the reaction sequence in more detail with diketopiperazine **7**. Also, dihydrooxazinones required three steps to synthesize with minimal yields and experienced extreme difficulty in purification. Diketopiperazine **7** is easily accessed through acetylation of glycine

anhydride. Furthermore, diketopiperazine **7** will produce a similar product, a pyridone fused to a seven-membered ring, as compared to dihydrooxazinone, producing 2-methoxypyridine fused to a seven-membered ring. We decided that the mechanism in **Scheme 3.2** would be more fruitful with diketopiperazine rather than dihydrooxazinone.

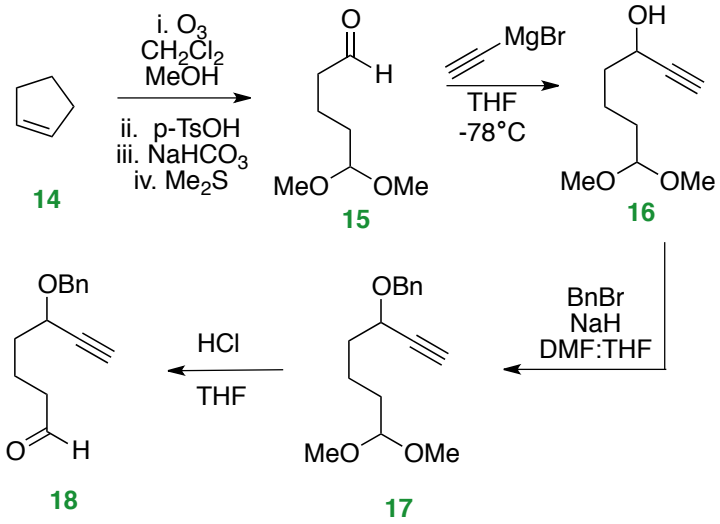


Scheme 3.2 Mechanism of diketopiperazine with aliphatic aldehyde to afford 2-pyridone fused to a 7-membered ring

Strategy Towards Rupestine Compounds

We viewed the rupestines as instructive target molecules to approach using a synthetic strategy based on incorporating the merged cycloaddition and cycloreversion sequence with diketopiperazine **7** and an aliphatic aldehyde. Synthesis of the aliphatic aldehyde needed to be developed. All rupestine molecules have two functional groups (alcohol and methyl) attached to the seven-membered ring. Aldehyde **18** was selected as an easily accessible substrate that bore necessary functional handles that would enable exploration of the proposed [4+2] cycloaddition and cycloreversion sequence but also be viable in a synthesis of rupestines. Benzyl ether protection also allows for vacuum

concentration; whereas 6-heptynal in **Scheme 3.2** is extremely volatile. Aldehyde **18** was easily delivered in a six-step route (**Scheme 3.3**). Desymmetrization of cyclopentene **14** was achieved via an oxidative cleavage intermediate to reveal **15** as a mono-protected 1,5-dialdehyde. Exposure of the aldehyde in **15** to the magnesium acetylide afforded propargyl alcohol **16**. This was then protected by benzyl bromide, followed by acidic acetal removal to generate desired aldehyde **18**.

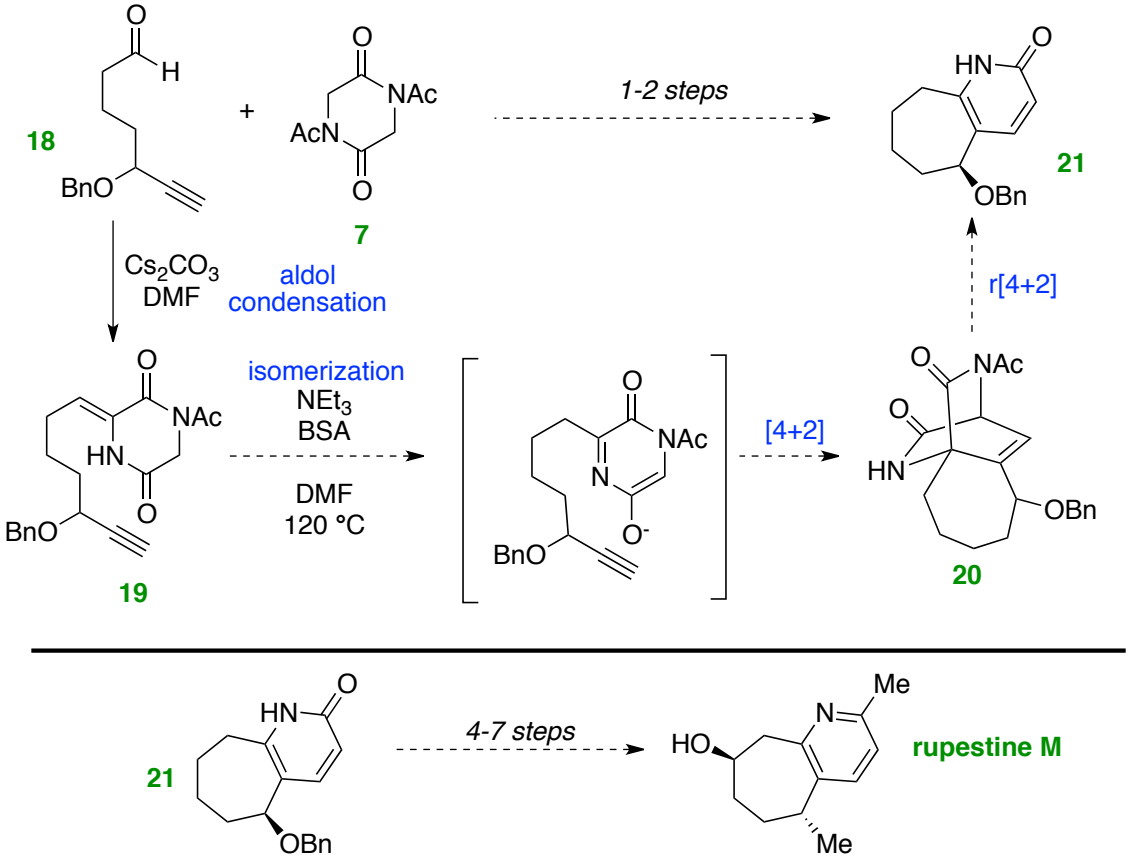


Scheme 3.3 Synthesis of desired aldehyde starting from cyclopentene involved 4 steps from cyclopentadiene.

The aldehyde reacts in the cascade reaction, through aldol condensation, alkene isomerization, Diels-Alder, and retro-Diels-Alder reactions (**Scheme 3.4**). Diketopiperazine **7** was deprotonated, forming an enolate, and aldol condensation occurred with the aliphatic aldehyde **18**. The product **19** isomerizes to align the substrate for an intramolecular [4+2] cycloaddition **20**. The lactim bridge is extruded in a cycloreversion process, yielding the desired product **21**.

The final four to seven steps of the synthesis are still being investigated, but having the ability to isolate a seven-membered ring fused to a pyridone core with

functionality at the methyl position of rupestine M gives great hope for the total synthesis to be fruitful.



Scheme 3.4 Using the cascade reaction of aldol condensation, alkene isomerization, Diels-Alder, retro-Diels-Alder, a target compound leading towards rupestine M is synthesized.

Conclusion

Oxazinone architecture has been extensively proven to easily facilitate Diels-Alder and retro-Diels-Alder reactions. Previous chemists accomplished the intermolecular Diels-Alder and retro-Diels-Alder sequence, fully exploring the nature of stereochemistry and regiochemistry in the reaction. The intramolecular case of merged cycloaddition and cycloreversion was also observed to be successful through analysis of a one-pot mechanism with preceding steps of aldol condensation and alkene isomerization.

Finally, the same sequence including aldol condensation and alkene isomerization is being tested in a synthesis towards rupestine M. Diketopiperazine **7** shares similar architecture to oxazinone and can perform aldol condensation, alkene isomerization, Diels-Alder, and retro-Diels-Alder reactions to reveal a seven-membered ring with a fused pyridone core, only four to seven steps away from the natural product. In conclusion, rapid access to 2-methoxypyridine or pyridone products from simple acyclic aldehyde precursors is warranted given the many applications of such structures.

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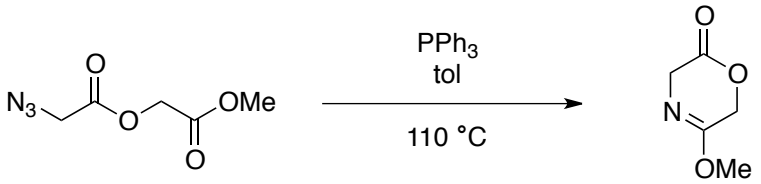
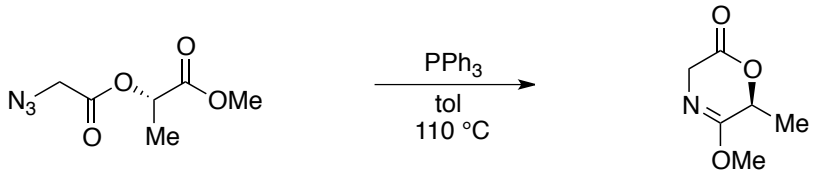
Chapter 2 Experimentals

The experimentals for compounds **1-7** can be found in a previously published paper.[1] Compounds **17** and **20** are available for purchase. Compounds **24a**, **24b**, and **24c** are all known molecules.[2-4]



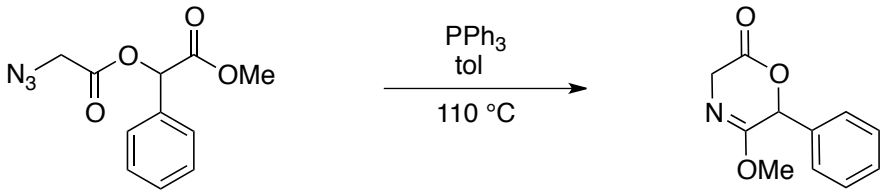
2-methoxy-2-oxoethyl 2-azidoacetate *5-methoxy-3,6-dihydro-2H-1,4-oxazin-2-one*

14 *5-methoxy-3,6-dihydro-2H-1,4-oxazin-2-one.* A dry flask was charged with 2-methoxy-2-oxoethyl 2-azidoacetate (3.2g, 18.5 mmol), fitted with a Dean-Stark apparatus and condenser, and flushed with nitrogen. The starting material was dissolved in dry toluene (100 mL), triphenylphosphine (4.85g, 18.5 mmol) was added, and the reaction was heated to reflux in an oil bath (bath temp. 130 °C). Reaction progress was monitored by NMR on an aliquot. After 16 h, the reaction was cooled to RT and concentrated *in vacuo*. The resulting residue was purified by Kügelrohr distillation (1 mmHg, 160 °C) to afford the title compound (650 mg, 27% yield) as a clear oil: **IR** (film) 1678, 1437, 1188, 1165, 1119, 1072, 997, 754, 719, 694 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 4.82 (s, 2H), 4.23 (s, 2H), 3.79 (s, 3H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 167.1, 159.8, 64.9, 53.6, 47.4; **HRMS** submitted.



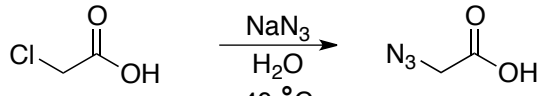
(S)-methyl 2-(2-azidoacetoxy)propanoate *(S)-5-methoxy-6-methyl-3,6-dihydro-2H-1,4-oxazin-2-one*

15 *(S)-5-methoxy-6-methyl-2H-1,4-oxazin-2-one.* A dry flask was charged with (S)-methyl 2-(2-azidoacetoxy)propanoate (3.349 g, 17.9 mmol) and flushed with nitrogen. The starting material was dissolved in dry toluene (60 mL), introduced to triphenylphosphine (4.69 g, 17.9 mmol), and heated to reflux in an oil bath (bath temp. 130 °C). Reaction progress was monitored by NMR on an aliquot. After 20 h, the reaction was cooled to RT and concentrated *in vacuo*. A portion (3.79 g) of the resulting residue (7.51 g) was purified by Kügelrohr distillation (1 mmHg, 190 °C) to afford the title compound (796 mg, 62% yield) as a yellow oil: **IR (film, cm^{-1})** 2992, 2951, 1748, 1695, 1456, 1391, 1375, 1354, 1339, 1321, 1294, 1265, 1231, 1206, 1128, 1101, 1080, 1043, 988, 959, 853, 773, 692, 667, 602 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 4.92 (q, J = 1.6 Hz, 1H), 4.26 (s, 2H), 3.76 (s, 3H), 1.57 (d, J = 3.9 Hz, 3H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 167.7, 162.5, 72.70, 53.6, 47.7, 18.4; **HRMS** submitted.



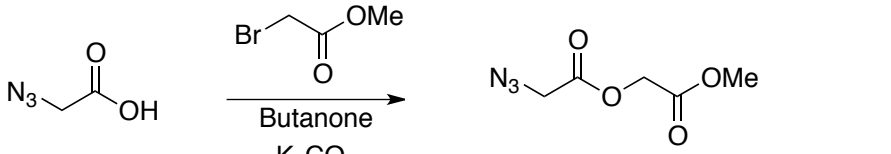
methyl 2-(2-azidoacetoxy)-2-phenylacetate *5-methoxy-6-phenyl-3,6-dihydro-2H-1,4-oxazin-2-one*

16 *5-methoxy-6-phenyl-3,6-dihydro-2H-1,4-oxazin-2-one.* A flame-dried flask was charged with methyl 3-(2-azidoacetoxy)-2-phenylpropanoate (161 mg, 0.645 mmol), fitted with a Dean-Stark apparatus and condenser, and flushed with nitrogen. The starting material was dissolved in toluene (5 mL), triphenylphosphine (169 mg, 0.645 mmol) was added, and the reaction was heated to reflux in an oil bath (bath temp. 130°C). Reaction progress was monitored by NMR on an aliquot. After 24 h, the reaction was cooled to RT and concentrated *in vacuo*. The resulting residue (310 mg) was purified by flash column chromatography on silica gel (gradient elution: 5→50% EtOAc in Hexanes, 50% toluene additive) to afford the title compound (64 mg, 48% yield) as slightly yellow oil: **TLC** (15% EtOAc, 35% hexanes, 50% toluene), R_f = 0.33 (CAM); **IR (film)** 3065, 2948, 2989, 2921, 2850, 2359, 2343, 1754, 1705, 1495, 1458, 1442, 1378, 1330, 1308, 1283, 1254, 1201, 1111, 1079, 1050, 1002, 976, 934, 914, 846, 806, 776, 759, 700, 682, 668 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.43 (m, J = 6.2 Hz, 3H), 7.33 (m, J = 7.4 Hz, 2H), 5.85 (s, 1H), 4.41 (dd, J = 20.7 Hz, 2H), 3.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.6, 161.1, 134.3, 129.4, 129.1, 126.4, 76.7, 53.9, 47.7; **HRMS** Exact mass calc'd for $C_{11}H_{11}NO_3$ [M+Na^+] = 228.0631, found 228.0632.



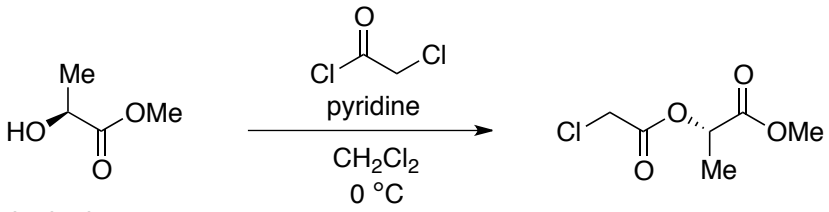
2-chloroacetic acid *2-azidoacetic acid*

18 *2-azidoacetic acid.* A dry flask was charged with chloroacetic acid (2.06 g, 21.8 mmol) and dissolved in deionized water (20 mL). Sodium azide (2.70g, 41.6 mmol) was added and the reaction vessel was heated slightly to 40 °C for 24 h. The reaction was diluted and made acidic with 1M HCl (25 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting oil (1.034g, 49% yield) was used without further purification: **IR** (film) 2106, 1717, 1418, 1279, 1192, 1001, 943, 874, 721, 669 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.91 (s, 1H), 3.98 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) 174.6, 49.9; **HRMS** submitted. Spectral data agrees with published values.[5]



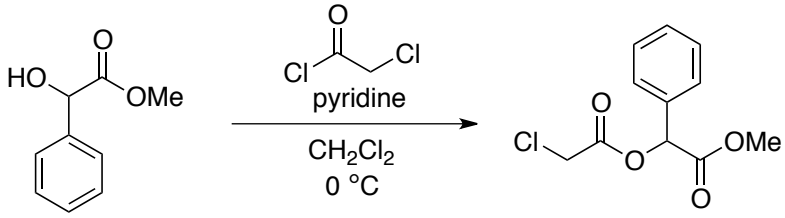
2-azidoacetic acid *2-methoxy-2-oxoethyl 2-azidoacetate*

19 *2-methoxy-2-oxoethyl 2-azidoacetate.* A dry flask was charged with 2-azidoacetic acid (889 mg, 8.80 mmol) and dissolved in butanone (15 mL). Methyl bromoacetate (1.26 mL, 13.2 mmol) and potassium carbonate (1.82 g, 13.2 mmol) were added to the reaction mixture. The reaction vessel was warmed to 40 °C and stirred until 2-azidoacetic acid was entirely consumed as observed by TLC (22 h). The reaction was cooled to RT, diluted with Et_2O, and filtered to remove most inorganic salts. The filtrate was washed with H_2O (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic layer was removed and the aqueous portion was extracted with additional Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting colorless oil (1.113 g, 73% yield) was used without purification: **TLC** (40% EtOAc in hexanes) R_f= 0.47 ($KMnO_4$); **IR** (film): 2959, 2106, 1748, 1423, 1383, 1287, 1225, 1165, 1059 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): 4.78 (s, 2H), 4.01 (s, 2H), 3.79 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.8, 167.4, 61.2, 52.5, 50.0; **HRMS** submitted.



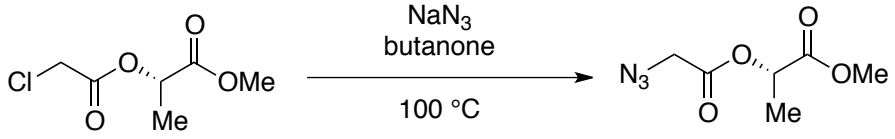
(S)-methyl 2-hydroxypropanoate *(S)-methyl 2-(2-chloroacetoxy)propanoate*

21a *(S)-methyl 2-(2-chloroacetoxy)propanoate.* Methyl-*S*(–)-lactate (4.59 mL, 48.1 mmol) was dissolved in CH_2Cl_2 (100 mL). Pyridine (7.75 mL, 96.2 mmol) was introduced to the solution and the reaction vessel was cooled to 0 °C in an ice bath. Chloroacetyl chloride (4.17 mL, 52.9 mmol) was added dropwise to the solution over 1 h. After stirring for 2.5 h, the reaction was warmed to RT, diluted with 1.0 M HCl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (8.26 g) was purified by flash column chromatography on silica gel (gradient elution: 0→40% EtOAc in hexane) to afford the title compound (7.32 g, 83% yield) as clear oil: **TLC** (40% EtOAc in hexane) R_f = 0.6 ($KMnO_4$); **IR** (film): 2997, 2959, 1744, 1452, 1437, 1412, 1381, 1356, 1319, 1283, 1217, 1167, 1132, 1094, 1045, 980, 951, 930, 893, 853, 839, 789, 704, 635, 613, 604 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$): δ 3.98 (s, 2H), 10.91 (s, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 170.4, 166.7, 77.5, 77.1, 76.8, 69.9, 52.4, 40.5, 16.7; **HRMS** exact mass calc'd for $C_6H_9ClO_4Na$ $[M + Na]^+$ =203.0082, found 203.0083.



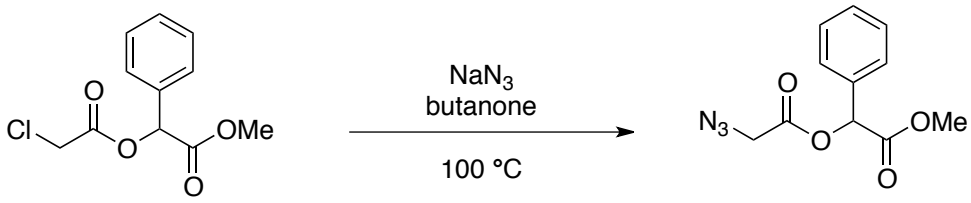
methyl 2-hydroxy-2-phenylacetate *methyl 2-(2-chloroacetoxy)-2-phenylacetate*

21b *Methyl 2-(2-chloroacetoxy)-2-phenylacetate.* Methyl-DL-mandelate (5.00 g, 30 mmol) was dissolved in CH_2Cl_2 (100 m). Pyridine (4.84 mL, 0.060 mol) was introduced to the solution and the reaction vessel was cooled to 0 °C in an ice bath. Chloroacetyl chloride (2.60 mL, 30 mmol) was added dropwise to the solution over 1 h. After 2 h, the reaction was warmed to RT, diluted with 1M HCl (30 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was then washed with $NaHCO_3$ (30 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue (8.25 g) was purified by flash column chromatography on silica gel (gradient elution: 0→30% EtOAc in hexane) to afford the title compound (6.47 g, 89% yield) as a clear oil: **TLC** (40% EtOAc in hexane) R_f = 0.6 (CAM); **IR** (film) 3036, 2957, 1748, 1497, 1437, 1410, 1352, 1314, 1271, 1258, 1217, 1155, 1080, 1038, 1005, 978, 953, 926, 854, 785, 735, 696, 617 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.46 (m, J = 3.2 Hz, 2H), 7.41 (m, J = 3.2 Hz, 3H), 6.01 (s, 1H), 4.21(q, J = 15.2 Hz, 2H), 3.74 (s, 3H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 168.5, 166.8, 133.0, 129.6, 128.9, 127.7, 75.6, 52.8, 40.6; **HRMS** exact mass calc'd for $C_{11}H_{11}ClO_4Na$ $[M + Na]^+$= 265.0204, found 265.0239.



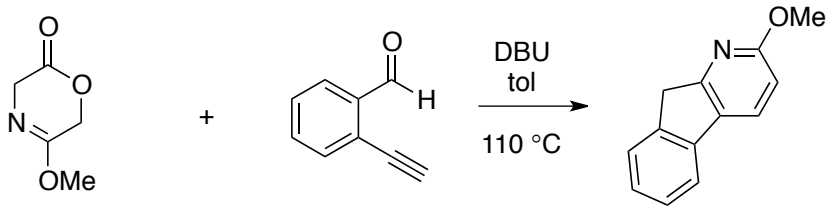
(S)-methyl 2-(2-chloroacetoxy)propanoate *(S)-methyl 2-(2-azidoacetoxy)propanoate*

22a *(S)-methyl 2-(2-azidoacetoxoxy)propanoate.* Methyl 2-(2-chloroacetoxy)propanoate (10.2 g, 41.9 mmol) was dissolved in 2-butanone (160 mL), sodium azide (5.45 g, 83.8 mmol) was added, and the reaction was heated to 100 °C in an oil bath. Reaction progress was monitored by NMR on an aliquot. After 16 h, the reaction was cooled to RT and concentrated *in vacuo*. The resulting product (7.75 g, 99% yield) obtained as a clear oil and used without further purification: **IR** (film) 2998, 2959, 2106, 1744, 1452, 1368, 1281, 1180, 1094, 1045, 980 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.22 (q, J=7.1 Hz, 1H), 3.97 (d, J=7.1 Hz, 2H), 3.78 (s, 3H), 1.55 (d, J=7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.4, 167.7, 69.6, 52.4, 49.9, 16.7; **HRMS** submitted.



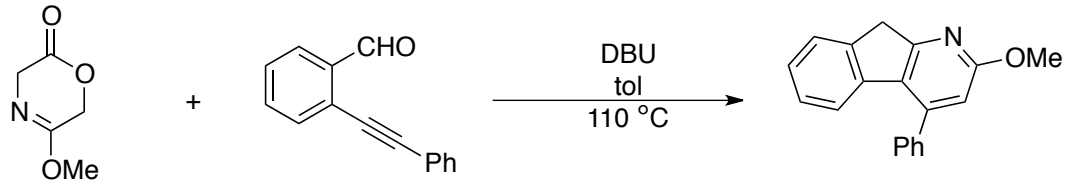
methyl 2-(2-chloroacetoxy)-2-phenylacetate *methyl 2-(2-azidoacetoxy)-2-phenylacetate*

22b *Methyl 2-((azidocarbonyl)oxy)-2-phenylacetate.* Methyl 2-((chlorocarbonyl)oxy)-2-phenylacetate (5.27 g, 21.8 mmol) was dissolved in 2-butanone (140 mL), sodium azide (3.79 g, 58 mmol) was added, and the reaction was heated to 100 °C in an oil bath. Reaction progress was monitored by NMR on an aliquot. After 24 h, the reaction vessel was cooled to RT and then concentrated *in vacuo*. The resulting clear oil (5.10 g) was purified by flash column chromatography on silica gel (gradient elution: 0→30% EtOAc in hexane) yielding the desired product (5.09 g, 94% yield) as a clear oil: **IR** (film): 2957, 2106, 1746, 1437, 1275, 1217, 1167, 1038, 976, 733, 696 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, J=2.7 Hz, 2H), 7.42 (m, J=1.5 Hz, 3H), 6.04 (s, 1H), 4.04 (d, J=17.2 Hz, 1H), 4.04 (d, J = 16.9 Hz, 1H), 3.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.6, 167.8, 133.0, 129.6, 128.9, 127.7, 75.3, 52.8, 50.0; **HRMS** exact mass calc'd $C_{11}H_{11}N_3O_4Na$ $[M + Na]^+$ = 272.0642, found 272.0644.



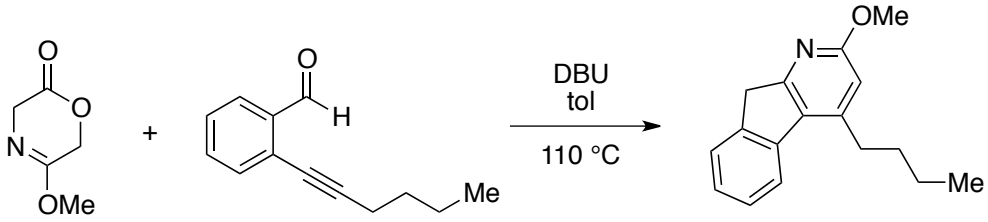
5-methoxy-3,6-dihydro-2H-1,4-oxazin-2-one *2-ethynyl benzaldehyde* *2-methoxy-9H-indeno[2,1-b]pyridine*

14a *2-methoxy-9H-indeno[2,1-b]pyridine.* 5-methoxy-3,6-dihydro-2*H*-1,4-oxazin-2-one (50 mg, 0.38 mmol) was dissolved in toluene (3.0 mL) and introduced to 1,8-Diazabicyclo[5.4.0]undec-7-ene (85 μL, 0.57 mmol). 2-ethynylbenzaldehyde (74 mg, 0.57 mmol) was added slowly and the reaction vessel was heated in an oil bath (bath temp. 120 °C). After 18 h, the reaction was cooled to RT, transferred to a separatory funnel, and partitioned between sat. aq. NH_4Cl (10 mL) and EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered through Celite, and concentrated *in vacuo*. The resulting residue (82 mg) was purified by flash column chromatography on silica gel (gradient elution: 20%→80% of $CHCl_3$ in hexane) to afford the title compound (57 mg, 77% yield) as a yellow-tinted oil: **TLC** (50% $CHCl_3$/Hex) R_f=0.20 ($KMnO_4$); **IR** (film) 3044, 2983, 2948, 2901, 1594, 1586, 1463, 1382, 1307, 1297, 1186, 1167, 1029, 1000, 828, 772, 744, 714, 668 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.88 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 4.00 (s, 3H), 3.87 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.9, 162.5, 140.4, 139.8, 130.0, 128.4, 126.9, 126.0, 125.0, 119.2, 108.7, 53.7, 38.6; **HRMS** Exact mass calc'd for $C_{13}H_9NONa$ $[M + Na]^+$ = 198.0913, found 198.0913.



5-methoxy-3,6-dihydro-2H-1,4-oxazin-2-one *2-(phenylethynyl)benzaldehyde* *2-methoxy-4-phenyl-9H-indeno[2,1-b]pyridine*

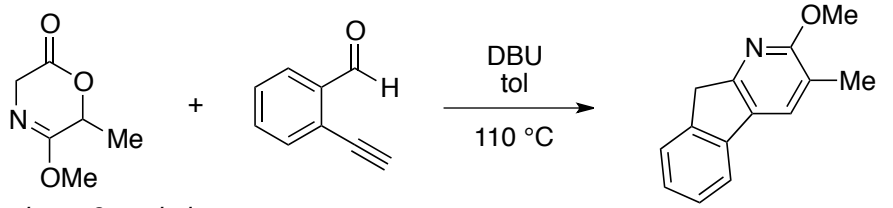
14b *2-methoxy-4-phenyl-9H-indeno[2,1-b]pyridine.* 5-methoxy-3,6-dihydro-2*H*-1,4-oxazin-2-o ne (24.1 mg, 0.19 mmol) was dissolved in toluene (4 mL). The reaction flask was fitted with a Dean-Stark apparatus and condenser, 1,8-Diazabicyclo[5.4.0]undec-7-ene (42 μL, 0.281 mmol) was added, and the reaction was heated in an oil bath (bath temp. 130 °C). In a separate flask, a solution of 2-(phenylethynyl)benzaldehyde (46 mg, 0.22 mmol) in toluene (2 mL) was prepared and added to the reaction vessel via a syringe pump over 1h. After 24h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue (118 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→20% EtOAc in hexane) to afford the title compound (5.5 mg, 10% yield) as a yellow-tinted powder: **TLC** (10% EtOAc/Hexanes) R_f= 0.55 ($KMnO_4$); **IR** (film): 3057, 3020, 2945, 1685, 1591, 1560, 1498, 1477, 1460, 1444, 1396, 1351, 1242, 1214, 1194, 1113, 1048, 1027, 862, 767, 745 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.51 (m, J = 7.4 Hz, 4H), 7.19 (t, J = 7.4 Hz, 2H), 7.08 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.60 (s, 1H), 4.03 (s, 3H), 3.94 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 163.3, 147.7, 140.7, 139.7, 138.6, 128.4, 128.3, 126.4, 125.8, 124.7, 121.8, 109.4, 53.8, 38.7; **HRMS** exact mass calc'd for $C_{19}H_{15}NONa$ $[M + Na]^+$ = 296.1045, found 296.1044.



5-methoxy-3,6-dihydro-2H-1,4-oxazin-2-one *2-(hex-1-yn-1-yl)benzaldehyde* *4-butyl-2-methoxy-9H-indeno[2,1-b]pyridine*

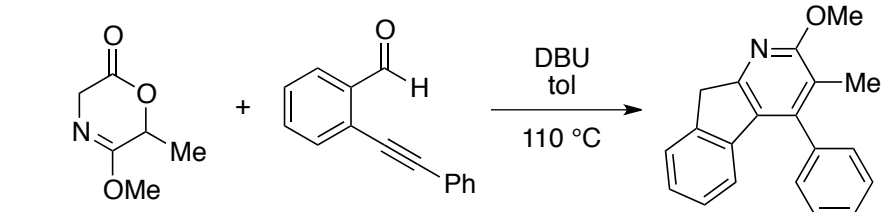
14c *4-butyl-2-methoxy-9H-indeno[2,1-b]pyridine.* 5-methoxy-3,6-dihydro-2*H*-1,4-oxazin-2-one (30 mg, 0.23 mmol) was dissolved in toluene (1.5 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (42 μL, 0.27 mmol) was added, and the reaction vessel heated in an oil bath (bath temp. 130 °C). In a separate flask, a solution of 2-(phenylethynyl) benzaldehyde (55 mg, 0.29 mmol) in toluene (1 mL) was added to the reaction vessel via syringe pump over 2.5 h. After 24 h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10

mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue (54 mg) was purified by flash column chromatography on silica gel (gradient elution: 3%→6% EtOAc in hexanes with additives of 2% acetic acid and 3% $CHCl_3$) to afford the title compound (7.7 mg, 13%) as a yellow-tinted oil: **TLC** (10% $CHCl_3$, 5% EtOAc, 85% n-Hexanes) R_f= 0.24 ($KMnO_4$); **IR** (film): 2956, 1597, 1570, 1381, 1345, 1320, 1192, 1161, 1050, 855, 743, 671, 665 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.70 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 6.53 (s, 1H), 4.00 (s, 3H), 3.89 (s, 2H), 2.97 (t, J = 7.9 Hz, 2H), 1.74 (m, J = 2.3 Hz, 2H), 1.70 (t, J = 2.0 Hz, 2H), 1.51 (m, J = 7.4 Hz, 2H), 0.97 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.9, 162.9, 149.2, 140.8, 140.5, 127.0, 126.9, 125.4, 124.9, 121.9, 108.7, 76.7, 53.6, 38.9, 33.2, 30.9, 22.6, 13.9; **HRMS** submitted.



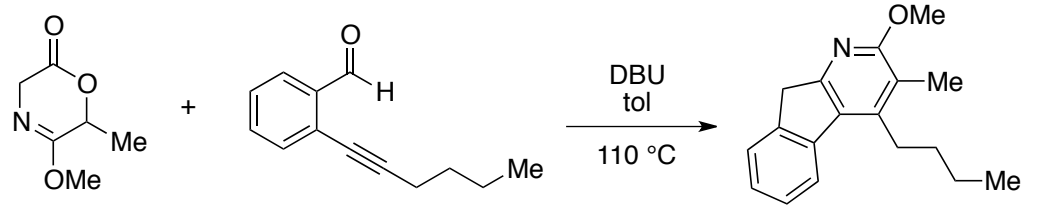
5-methoxy-6-methyl-3,6-dihydro-2H-1,4-oxazin-2-one *2-ethynylbenzaldehyde* *2-methoxy-3-methyl-9H-indeno[2,1-b]pyridine*

15a *2-methoxy-3-methyl-9H-indeno[2,1-b]pyridine.* 5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (32 mg, 0.22 mmol) was dissolved in toluene (0.5 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (31 μL, 0.25 mmol) was added, and the reaction vessel was heated in an oil bath (bath temp. 100 °C). In a separate flask, a solution of 2-ethynylbenzaldehyde (33 mg, 0.25 mmol) in toluene (0.5 mL) was prepared and added to the reaction vessel in portions over 1 h, approximately 0.2 mL every 10 min. After 24 h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (45 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→20% EtOAc in hexanes) to afford the title compound (11 mg, 47% yield) as a yellow-tinted oil: **TLC** (40% EtOAc/hexanes) R_f=0.71 ($KMnO_4$); **IR** (film) 3854, 3745, 3675, 3588, 2373, 2370, 2321, 1734, 1696, 1646, 1636, 1617, 1576, 1521, 1472, 1463, 1457, 1437, 1393, 1339, 1315, 1294, 1239, 1203, 1179, 1036, 942, 768, 715 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.61 (d, J=7.4 Hz, 1H), 7.51 (d, J=7.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.25 (t, J=7.4 Hz, 1H), 4.04 (s, 3H), 3.84 (s, 2H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.2, 159.4, 140.7, 140.2, 130.2, 128.3, 126.8, 125.7, 124.9, 119.1, 118.7, 53.67, 38.3, 16.4; **HRMS** Exact mass calc'd for $C_{14}H_{14}NO$ $[M+H]^+$ = 212.1070, found 212.1071.



5-methoxy-6-methyl-3,6-dihydro-2H-1,4-oxazin-2-one | *2-(phenylethynyl) benzaldehyde* | *2-methoxy-3-methyl-4-phenyl-9H-indeno[2,1-b]pyridine*

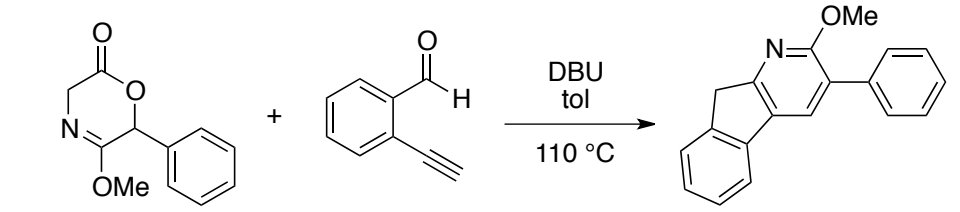
15b *2-methoxy-3-methyl-4-phenyl-9H-indeno[2,1-b]pyridine.* 6-methyldihydrooxazinone (43 mg, 0.30 mmol) was dissolved in toluene (1 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (45 μL, 0.30 mmol) was added, and the reaction vessel was heated to reflux in an oil bath (bath temp. 130 °C). In a separate flask, a solution of 2-(phenylethynyl)benzaldehyde (74.0 mg, 0.36 mmol) in toluene (2 mL) was prepared and added to the reaction vessel in portions over 20 min. After 24 h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (69 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→50% EtOAc in hexane with additive of 50% toluene) to afford the title compound (46 mg, 54% yield) as a yellow-tinted oil: **TLC** (20% EtOAc/hexanes) R_f = 0.29 ($KMnO_4$); **IR** (film) 3855, 3059, 2946, 2857, 1608, 1583, 1567, 1443, 1374, 1345, 1329, 1301, 1270, 1251, 1207, 1189, 1168, 1137, 1095, 1072, 1056, 1028, 1008, 970, 948, 918, 787, 766, 753, 720, 668, 640, 612 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.55 (m, J=7.4 Hz, 4H), 7.28 (m, J = 7.4Hz, 2H), 7.15 (t, J=7.4 Hz, 1H), 7.00 (t, J=7.4 Hz, 1H), 6.33 (d, J=7.4 Hz, 1H), 4.08 (s, 3H), 3.90 (s, 2H), 1.99 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.0, 159.0, 146.0, 140.9, 140.4, 138.0, 128.9, 128.3, 127.9, 126.6, 126.4, 125.3, 124.6, 121.3, 116.7, 53.9, 38.4, 12.6; **HRMS** Exact mass calc'd for $C_{20}H_{17}NONa$ $[M + Na]^+$ = 288.1383, found 288.1384.



5-methoxy-6-methyl-3,6-dihydro-2H-1,4-oxazin-2-one | *2-(hex-1-yn-1-yl) benzaldehyde* | *4-butyl-2-methoxy-3-methyl-9H-indeno[2,1-b]pyridine*

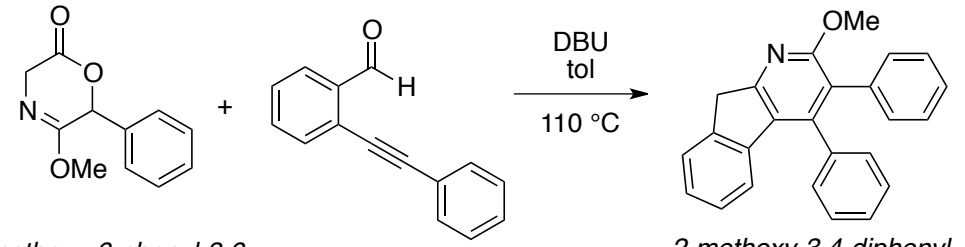
15c *4-butyl-2-methoxy-3-methyl-9H-indeno[2,1-b]pyridine.* 5-methoxy-6-methyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (64 mg, 0.24 mmol) was dissolved in toluene (3 mL). The reaction flask was fitted with a Dean-Stark apparatus and condenser, 1,8-Diazabicyclo[5.4.0]undec-7-ene (122 μL, 0.82 mmol) was added, and the reaction vessel was heated to reflux in an oil bath (bath temp. 130 °C). In a separate flask, a solution of 2-(hexynyl)benzaldehyde (100 mg, 0.54 mmol) in toluene (2 mL) was prepared and added to the reaction vessel in portions over 20 min. After 24 h, the reaction was cooled

to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (100 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→10% EtOAc in hexane) to afford the title compound (18 mg, 30% yield) as a yellow-tinted oil: **TLC** (5% EtOAc in hexane) R_f = 0.34 ($KMnO_4$); **IR** (film) 3745, 2956, 2928, 2872, 2858, 1735, 1700, 1696, 1685, 1653, 1576, 1520, 1507, 1472, 1453, 1377, 1339, 1287, 1271, 1234, 1207, 1189, 1170, 1159, 1143, 1124, 1102, 1059, 1030, 1018, 999, 944, 923, 784, 751, 719, 668 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.74 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 4.02 (s, 3H), 3.85 (s, 2H), 3.05 (t, J = 7.4 Hz, 2H), 2.24 (s, 3H), 1.58 (m, J = 7.4 Hz, 4H), 1.02 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.8, 159.3, 146.8, 141.1, 140.9, 126.8, 126.7, 125.1, 124.9, 121.6, 116.1, 53.7, 38.6, 30.7, 29.3, 23.2, 14.0, 11.0; **HRMS** Exact mass calc'd for $C_{18}H_{21}NOH$ $[M+H]^+$ = 268.1696, found 268.1697.



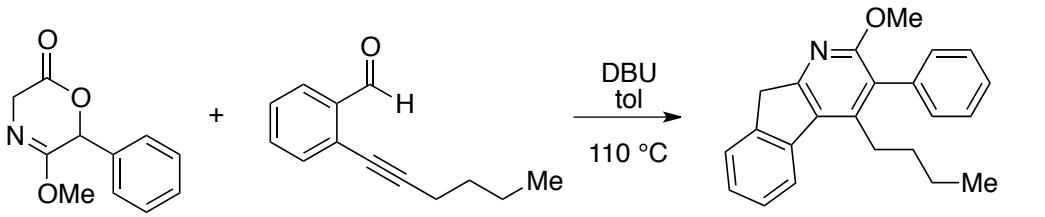
5-methoxy-6-phenyl-3,6-dihydro-2H-1,4-oxazin-2-one *2-ethynylbenzaldehyde* *2-methoxy-3-phenyl-9H-indeno[2,1-b]pyridine*

16a *2-methoxy-3-phenyl-9H-indeno[2,1-b]pyridine.* 5-methoxy-6-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one (40 mg, 0.20 mmol) was dissolved in toluene (20 mL). The reaction flask was fitted with a Dean-Stark apparatus and condenser, 1,8-Diazabicyclo[5.4.0]undec-7-ene (44 μL, 0.29 mmol) was added, and the reaction vessel was heated to reflux in an oil bath (bath temp. 130 °C). In a separate flask, a solution of 2-ethynylbenzaldehyde (51 mg, 0.39 mmol) in toluene (5 mL) was prepared and added to the reaction vessel after 5 min. After 24 h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (141 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→40% EtOAc in hexane) to afford the title compound (18 mg, 34% yield) as a yellow-tinted oil: **TLC** (10% EtOAc/hexanes) R_f=0.40 ($KMnO_4$); **IR** (film) 2946, 2346, 1603, 1581, 1560, 1457, 1443, 1427, 1391, 1343, 1314, 1286, 1261, 1226, 1197, 1174, 1075, 1030, 1008, 998, 947, 905, 779, 765, 751, 697, 668 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.94 (s, 1H), 7.66 (m, J = 7.8 Hz, 1H), 7.60 (m, J = 7.8 Hz, 2H), 7.54 (m, J = 7.8 Hz, 1H), 7.47 (m, J = 7.8 Hz, 2H), 7.44 (m, J = 7.8 Hz, 1H), 7.33 (m, J = 7.8 Hz, 1H), 4.05 (s, 3H), 3.94 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.3, 160.7, 140.6, 139.9, 137.5, 130.3, 129.4, 128.9, 127.4, 127.0, 126.1, 125.0, 122.8, 119.4, 53.9, 38.5; **HRMS** Exact mass calc'd for $C_{19}H_{16}NO$ $[M+H]^+$= 274.1226, found 274.1228.



5-methoxy-6-phenyl-3,6-dihydro-2H-1,4-oxazin-2-one *2-(phenylethynyl) benzaldehyde* *2-methoxy-3,4-diphenyl-9H-indeno[2,1-b]pyridine*

16b *2-methoxy-3,4-phenyl-9H-indeno[2,1-b]pyridine.* 5-methoxy-6-phenyl-3,6-dihydro-*2H*-1,4-oxazin-2-one (31 mg, 0.15 mmol) was dissolved in toluene (4 mL). The reaction flask was fitted with a Dean-Stark apparatus and condenser, 1,8-Diazabicyclo[5.4.0]undec-7-ene (33 μL, 0.220 mmol) was added, and the reaction vessel was heated to reflux in an oil bath (bath temp. 130 °C). In a separate flask, a solution of 2-(phenylethynyl)benzaldehyde (45 mg, 0.22 mmol) in toluene (2 mL) was prepared and added to the reaction vessel in portions over 20 min. After 24 h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (60 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→20% EtOAc in hexane, additive of 50% toluene) to afford the title compound (11 mg, 22% yield) as a yellow-tinted oil: **TLC** (10% EtOAc/hexanes) R_f= 0.3 ($KMnO_4$); **IR** (film) 3076, 3022, 2947, 1564, 1495, 1456, 1439, 1373, 1344, 1260, 1217, 1057, 1026, 799, 756, 718, 698, 644, 603 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,): δ 7.54 (d, J = 1.6 Hz, 1H), 7.29 (m, J = 1.6 Hz, 3H), 7.18 (m, J = 1.6 Hz, 3H), 7.13 (m, J = 1.6 Hz, 5H), 7.09 (t, J = 1.6 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 4.01 (s, 3H), 4.00 (s, 2H). **^{13}C NMR** (400 MHz, $CDCl_3$): δ 161.4, 161, 140.8, 140.2, 137.2, 135.4, 130.9, 129.1, 128.2, 127.5, 127.4, 126.8, 126.6, 126.5, 125.6, 124.7, 122.1, 121.7, 77.2, 54.1, 38.7; **HRMS** Exact mass calc'd for $C_{25}H_{19}NONa$ $[M + Na]^+$ = 372.1359, exact mass calc'd for $[M_2 + Na]^+$ = 721.2826, found = 721.282568.



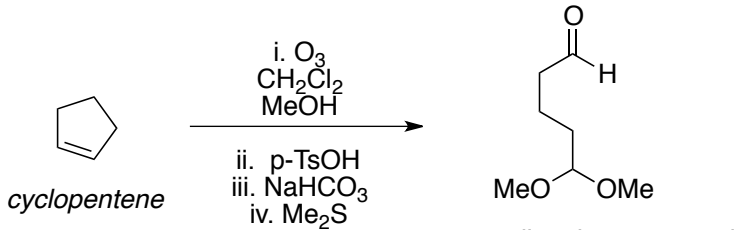
5-methoxy-6-phenyl-3,6-dihydro-2H-1,4-oxazin-2-one *2-(hex-1-yn-1-yl) benzaldehyde* *4-butyl-2-methoxy-3-phenyl-9H-indeno[2,1-b]pyridine*

16c *4-butyl-2-methoxy-3-phenyl-9H-indeno[2,1-b]pyridine.* 5-methoxy-6-phenyl-3,6-dihydro-*2H*-1,4-oxazin-2-one (31 mg, 0.15 mmol) was dissolved in toluene (4 mL). The reaction flask was fitted to a Dean-Stark apparatus and condenser, 1,8-Diazabicyclo[5.4.0]undec-7-ene (45 μL, 0.30 mmol) was added, and the reaction vessel was heated to reflux in an oil bath (bath temp. 100 °C). In a separate flask, a solution of 2-(hex-1-yn-1-yl)benzaldehyde (56 mg, 0.30 mmol) in toluene (2 mL) was prepared and

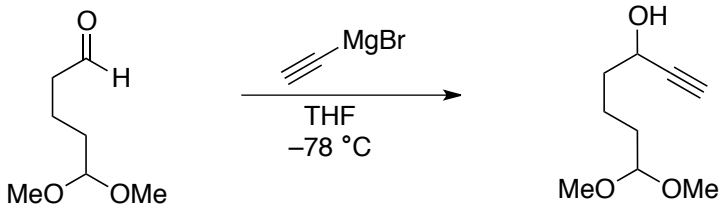
added to the reaction vessel in portions over 20 min. After 20 h, the reaction was cooled to RT, diluted with sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (10 mL). The organic layer was removed and the aqueous portion was extracted with additional EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue (80 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→8% EtOAc in hexane, additive of 50% toluene) to afford the title compound (25 mg, 50% yield) as a yellow-tinted oil: **TLC** (10% EtOAc/hexanes) R_f = 0.3 ($KMnO_4$); **IR** (film) 2956, 2926, 2859, 1726, 1564, 1454, 1375, 1341, 1221, 1206, 1190, 1107, 1057, 1028, 1007, 945, 797, 758, 721, 700 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.70 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.0 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.30 (m, J = 7.0 Hz, 3H), 3.95 (s, 2H), 3.93 (s, 3H), 2.76 (q, J = 8.2 Hz, 2H), 1.54 (m, J = 6.6 Hz, 2H), 1.30 (m, J = 7.4 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.5, 147.1, 141.0, 136.2, 130.3, 128.1, 127.1, 127.0, 126.8, 125.4, 124.9, 121.8, 7.210, 54.0, 38.9, 31.3, 29.8, 22.9, 13.7; **HRMS** Exact mass calc'd for $C_{23}H_{24}NO$ $[M+H]^+$ = 352.1672, found 352.1673.

Chapter 3 Experimentals

Compound **7** has been previously characterized.[6]

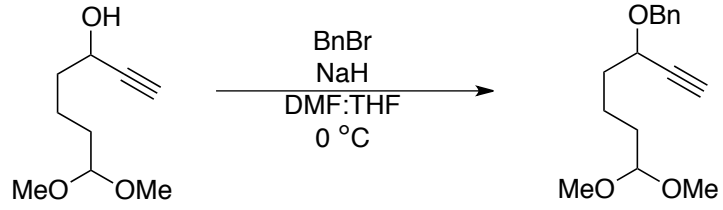


15 *5,5-dimethoxypentanal*. Following the procedure of Schreiber[7], cyclopentene (5.0 g, 74 mmol) was dissolved in dry dichloromethane (250 mL) and methanol (50 mL). The reaction vessel was cooled to –78 °C and connected to an ozonolysis flow reactor. The reaction was stirred until an iridescent blue remains in solution (3 h). Excess ozone is displaced with O_2, followed by N_2. p-Toluenesulfonic acid (1.12 g, 80 mmol) was added under inert gas. The reaction vessel was warmed to RT and stirred. After 1.5 h, $NaHCO_3$ (1.85 g, 30 mmol) was added to the system and stirred for 15 min. Dimethyl sulfide (10.77 mL, 2.0 mol) was introduced, stirred at RT for 12 h, and the heterogeneous mixture was concentrated. The resulting product was partitioned between CH_2Cl_2 (100 mL) and H_2O (75 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product (14 g) was contained desired product and was used without further purification: **IR** (film) 1722, 1192, 1152, 1121, 1059, 1009, 943, 920, 895 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$,) δ 9.77 (s, 1H), 4.37 (t, J = 8.4 Hz, 1H), 3.49 (t, J = 8.6 Hz, 2H), 3.32 (s, 6H), 1.69 (m, J = 8.6 Hz, 2H), 1.64 (m, J = 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.1, 100.9, 52.8, 40.9, 31.8, 17.2; **HRMS** submitted.



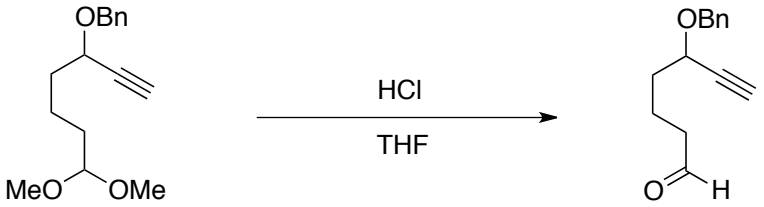
5,5-dimethoxypentanal *7,7-dimethoxyhept-1-yn-3-ol*

16 *7,7-dimethoxyhept-1-yn-3-ol.* 5,5-dimethoxypentanal (3.00 g, 21 mmol) was dissolved in THF (100 mL) and cooled to –78 °C. Ethynylmagnesium bromide (0.5 M in THF, 116 mL, 58 mmol) was added to the reaction vessel via syringe over 2 h. After 2.5 h, the reaction was quenched with sat. aq. NH_4Cl (100 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue (2.50 g) was purified via flash column chromatography on silica gel (gradient elution: 25→70% EtOAc in hexane), yielding desired product (1.41 g, 40%) as a colorless oil: **TLC** (30% EtOAc in hexane) R_f = 0.26 ($KMnO_4$); **IR** (film) 2089, 2095, 2116, 2832, 2949 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$,): δ 4.40 (t, J = 5.8, 1H), 4.38 (t, J = 5.8, 1H), 3.33 (s, 6H), 2.48 (s, 1H), 1.84 (br s, 1H), 1.74 (m, J = 5.5 Hz, 2H), 1.64 (m, J = 5.5 Hz, 2H), 1.56 (m, J = 5.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 104.4, 73.0, 62.0, 52.8, 52.7, 37.3, 32.0, 20.2; **HRMS** submitted.



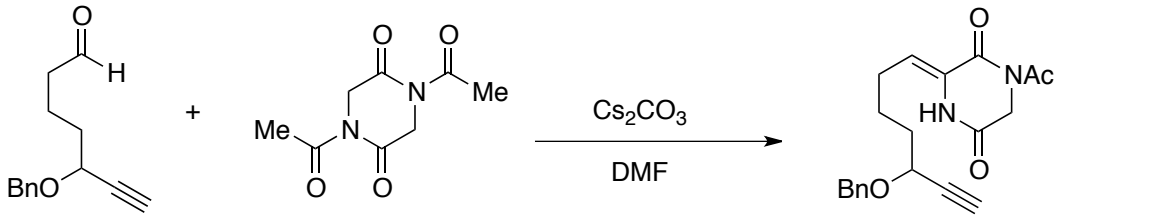
7,7-dimethoxyhept-1-yn-3-ol *(((7,7-dimethoxyhept-1-yn-3-yl)oxy)methyl)benzene*

17 *(((7,7-dimethoxyhept-1-yn-3-yl)oxy)methyl)benzene.* 7,7-dimethoxyhept-1-yn-3-ol (158 mg, 0.92 mmol) was dissolved in THF (5 mL). In a separate reaction vessel, sodium hydride (50% dispersion on oil, 46 mg, 1.10 mmol) was taken up in DMF (5 mL) and the flask was cooled to 0 °C. The starting material in THF is transferred to the reaction funnel, followed by benzyl bromide (0.13 mL, 1.10 mmol). After 3 h, the reaction mixture was diluted in sat. aq. NH_4Cl (10 mL) and H_2O (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue (363 mg) was purified by flash column chromatography on silica gel (gradient elution: 0→30% EtOAc in hexane) to afford the title compound (67 mg, 28%) as a colorless oil: **TLC** (30% EtOAc in hexane) R_f = 0.64 ($KMnO_4$); **IR** (film) 2112, 2833, 2868, 2947, 3032, 3063, 3088 cm^{-1}; **^{1}H NMR** (400MHz, $CDCl_3$) δ 7.35 (m, J = 6.3 Hz, 4H), 7.32 (m, J = 5.5 Hz, 1H), 4.81 (d, J = 8.9 Hz, 1H), 4.49 (d, J = 5.5 Hz, 1H), 4.36 (t, J = 5.5 Hz, 1H), 4.08 (t, J = 5.5 Hz, 1H), 3.31 (s, 6H), 2.48 (s, 1H), 1.78 (m, J = 7.1 Hz, 2H), 1.61 (m, J = 7.0 Hz, 2H), 1.52 (m, J = 5.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 128.5, 128.4, 128.0, 127.7, 104.4, 82.7, 74.1, 70.5, 68.2, 52.7, 35.4, 32.1, 20.4; **HRMS** submitted.



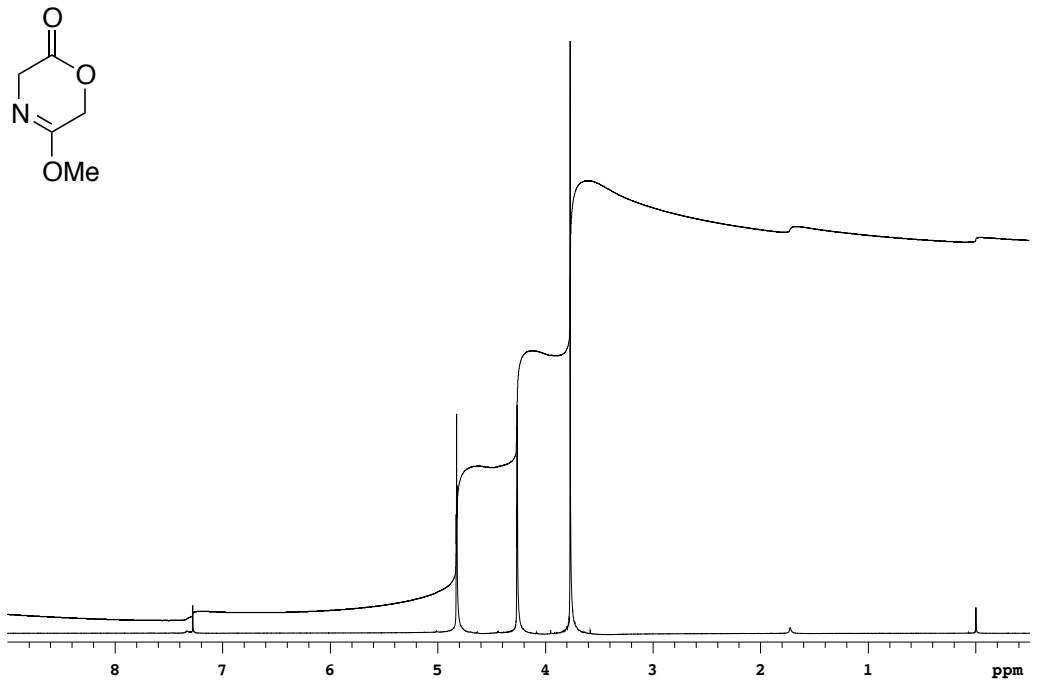
(((7,7-dimethoxyhept-1-yn-3-yl)oxy)methyl)benzene *5-(benzyloxy)hept-6-ynal*

18 *5-(benzyloxy)hept-6-ynal*. (((7,7,-dimethoxyhept-1-yn-3-yl)oxy)methyl)benzene (61 mg, 0.23 mmol) was dissolved in THF (13 mL). 3M HCl (13 mL) was added via syringe. After 25 h, the reaction was diluted with sat. aq. $NaHCO_3$ (15 mL) and the resulting aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product (109 mg) was purified via flash column chromatography on silica gel (gradient elution: 0→20% EtOAc in hexane) to afford the desired product (18 mg, 36%) as a colorless oil: **TLC** (10% EtOAc in hexane) R_f = 0.44 (CAM); **^{1}H NMR** (400MHz, $CDCl_3$,) δ 9.76 (s, 1H), 7.35 (d, J = 4.3 Hz, 2H), 7.33 (m, J = 5.0 Hz, 2H), 7.30 (m, J = 5.5 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.11 (t, J = 5.5 Hz, 1H), 2.49 (s, 1H), 2.45 (t, J = 7.4 Hz, 2H), 1.83 (m, J = 7.0 Hz, 2H), 1.80 (m, 2H, J = 7.8 Hz); **HRMS** submitted.



5-(benzyloxy)hept-6-ynal *1,4-diacetylpiperazine-2,5-dione* *(Z)-1-acetyl-3-(5-(benzyloxy) hept-6-yn-1-ylidene)piperazine-2,5-dione*

19 *(Z)-1-acetyl-3-(5-(benzyloxy)hept-6-yn-1-ylidene)piperazine-2,5-dione*. 5-(benzyloxy)hept-6-ynal (14 mg, 0.063 mmol) was diluted with DMF (0.5 mL) and introduced to 1,4-diacetylpiperazine-2,5-dione (14 mg, 0.069 mmol). Oxygen was evacuated from the reaction vessel and nitrogen was backfilled three times. Cesium carbonate (23 mg, 0.069 mmol) was added and the oxygen evacuation and nitrogen backfill was repeated three times. After stirring for 24 h, the reaction was quenched with H_2O (10 mL). The resulting aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried ($NaSO_4$), and concentrated *in vacuo*. The crude product (26 mg) was purified via flash column chromatography on silica gel (gradient elution: 25→70% EtOAc in hexane) to afford the title compound (3.5 mg, 16%) as a colorless oil: **TLC** (40% EtOAc in hexane) R_f = 0.22 (CAM); **^{1}H NMR** (400MHz, $CDCl_3$,) δ 7.36 (m, J = 4.3 Hz, 2H), 7.34 (m, J = 4.7 Hz, 2H), 7.31 (m, J = 5.1 Hz, 1H), 6.29 (t, J = 7.5 Hz, 1H), 4.60 (s, 2H), 4.42 (s, 2H), 4.14 (t, J = 2.0 Hz, 1H), 2.53 (s, 3H), 2.23 (q, J = 7.5 Hz, 2H), 1.81 (q, J = 7.5 Hz, 2H), 1.77 (m, J = 6.3 Hz, 2H); **HRMS** submitted.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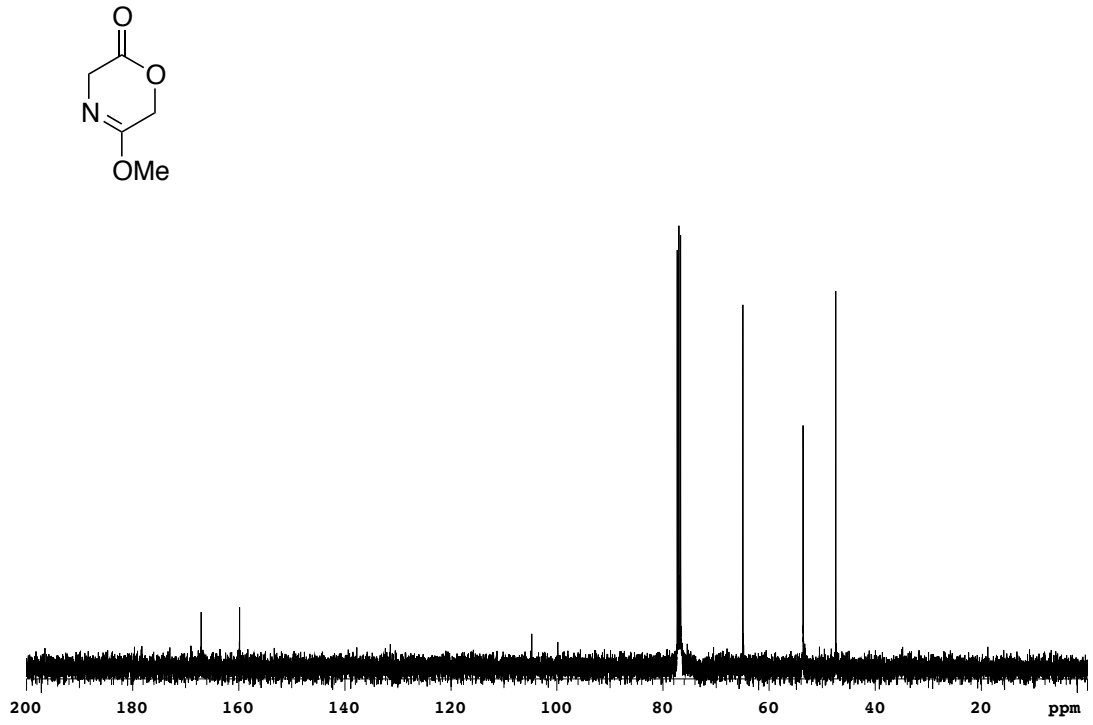
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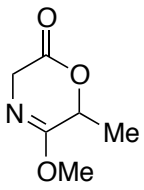
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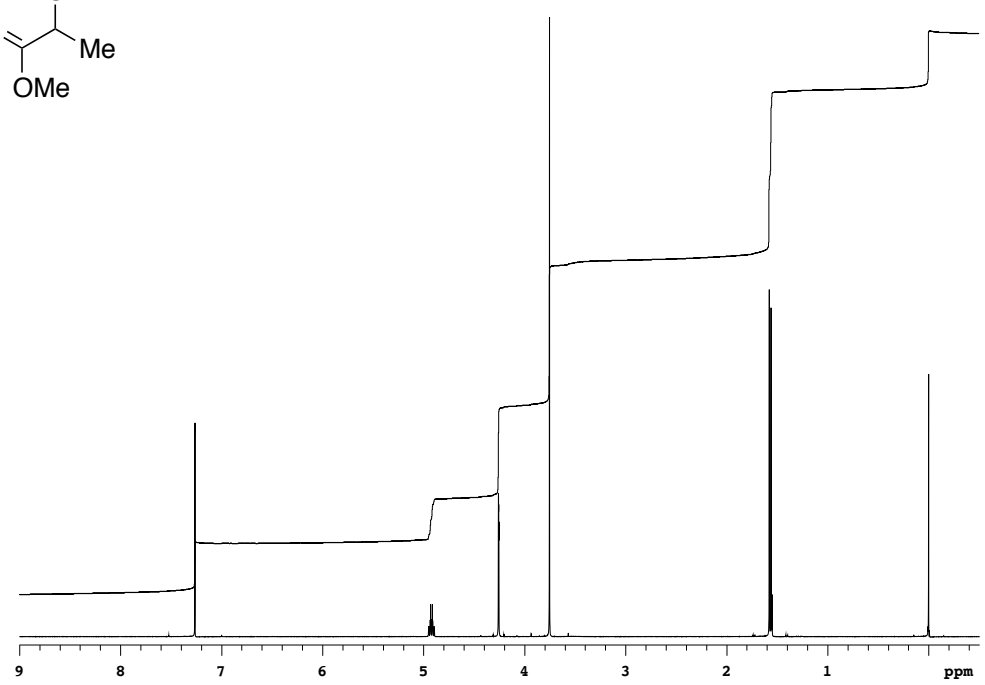
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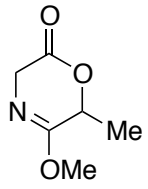
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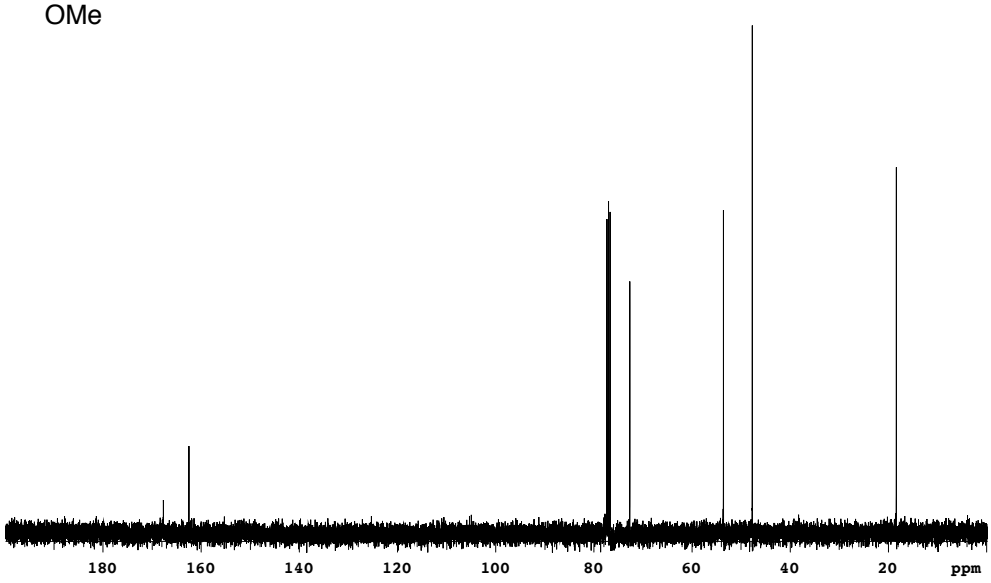
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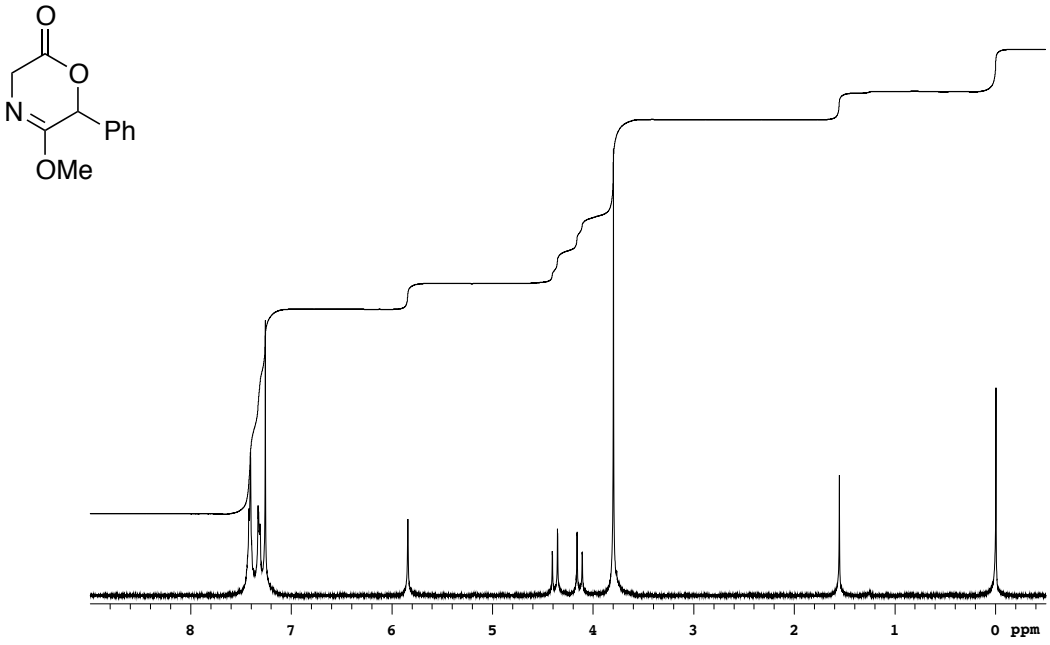
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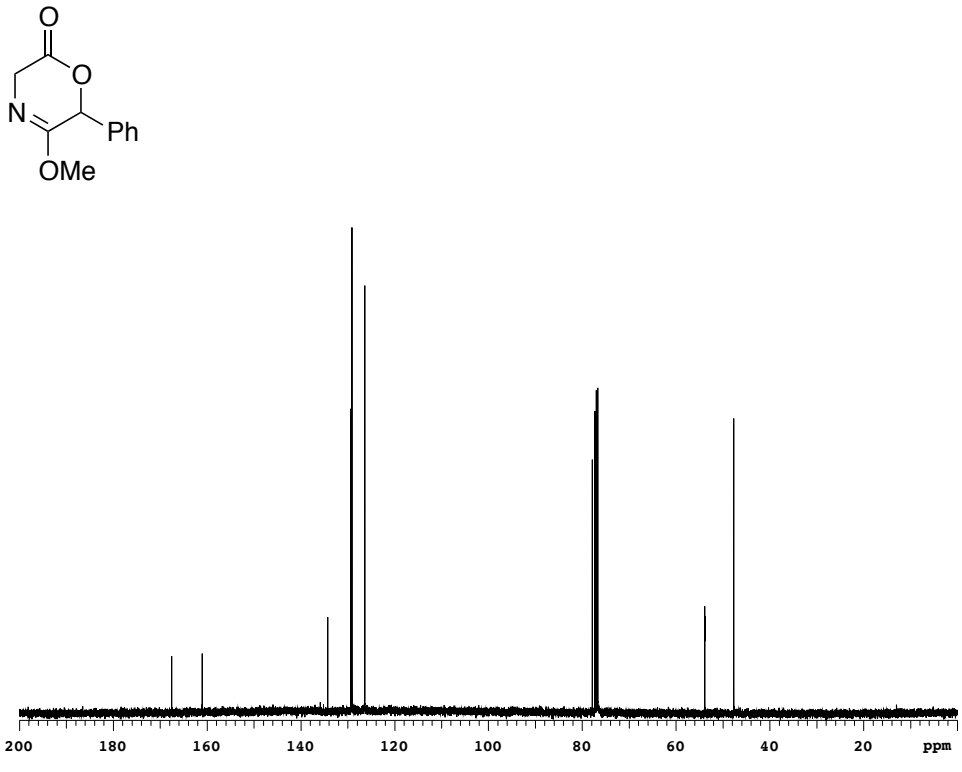
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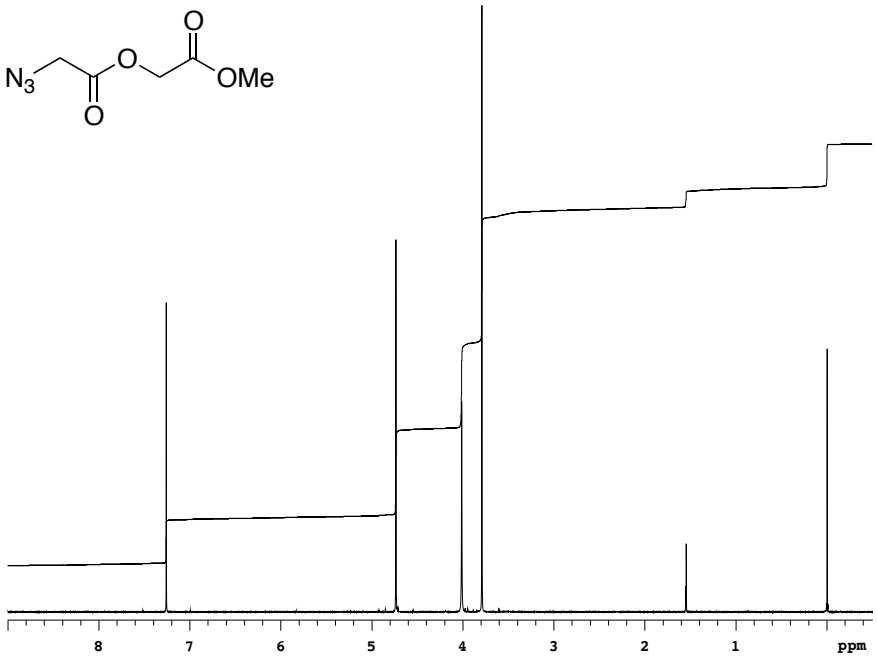
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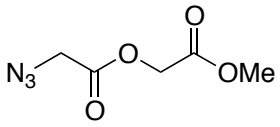
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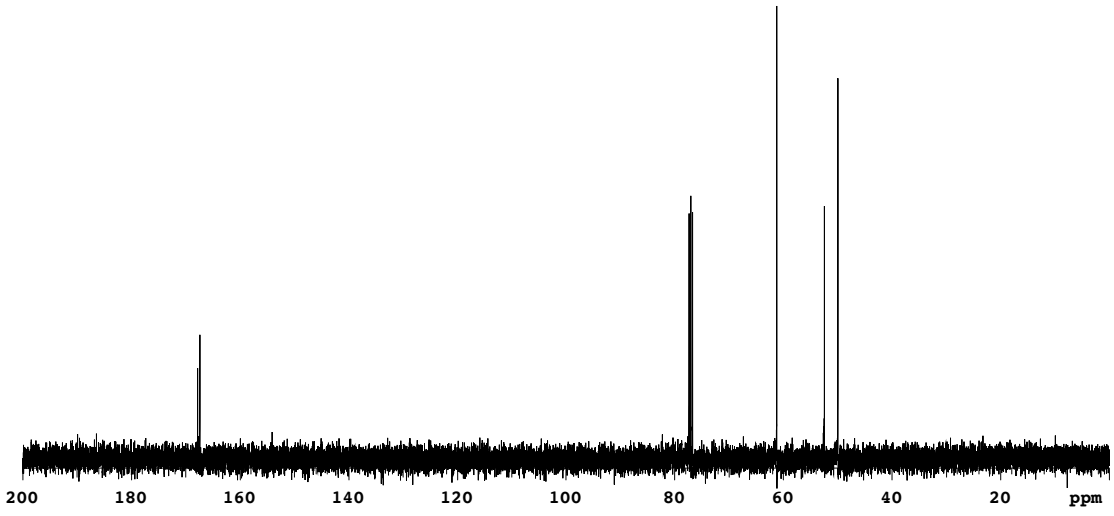
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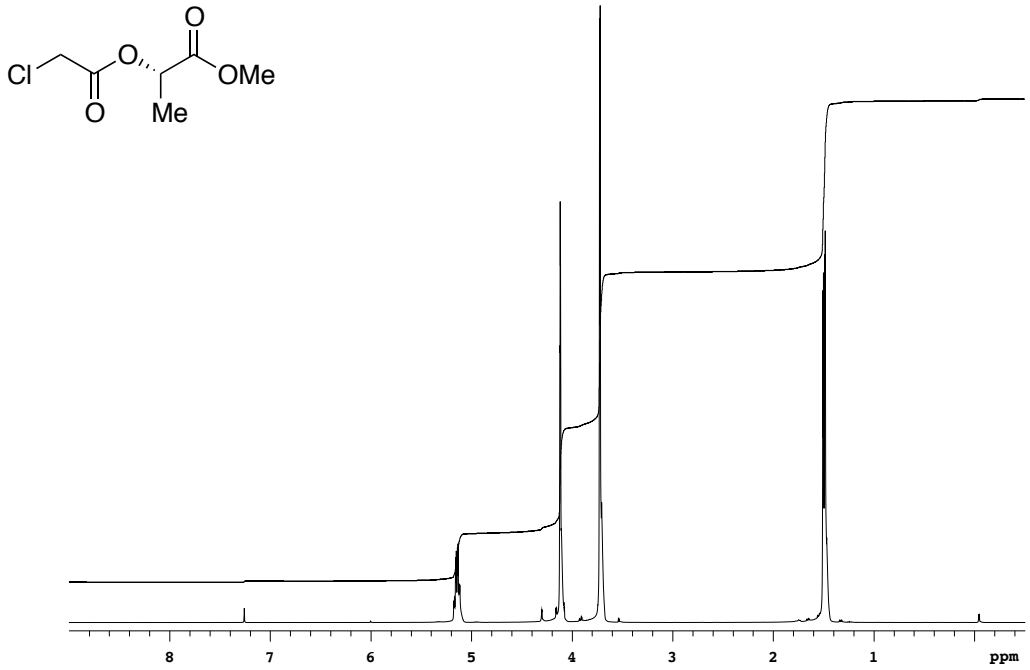
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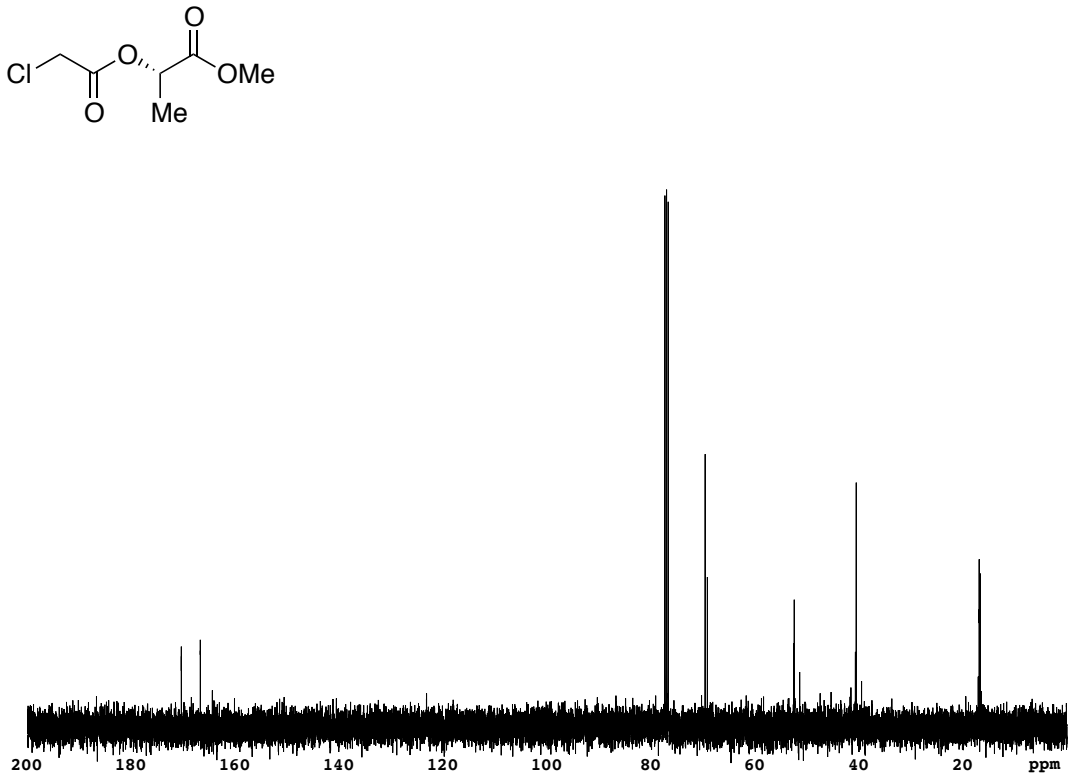
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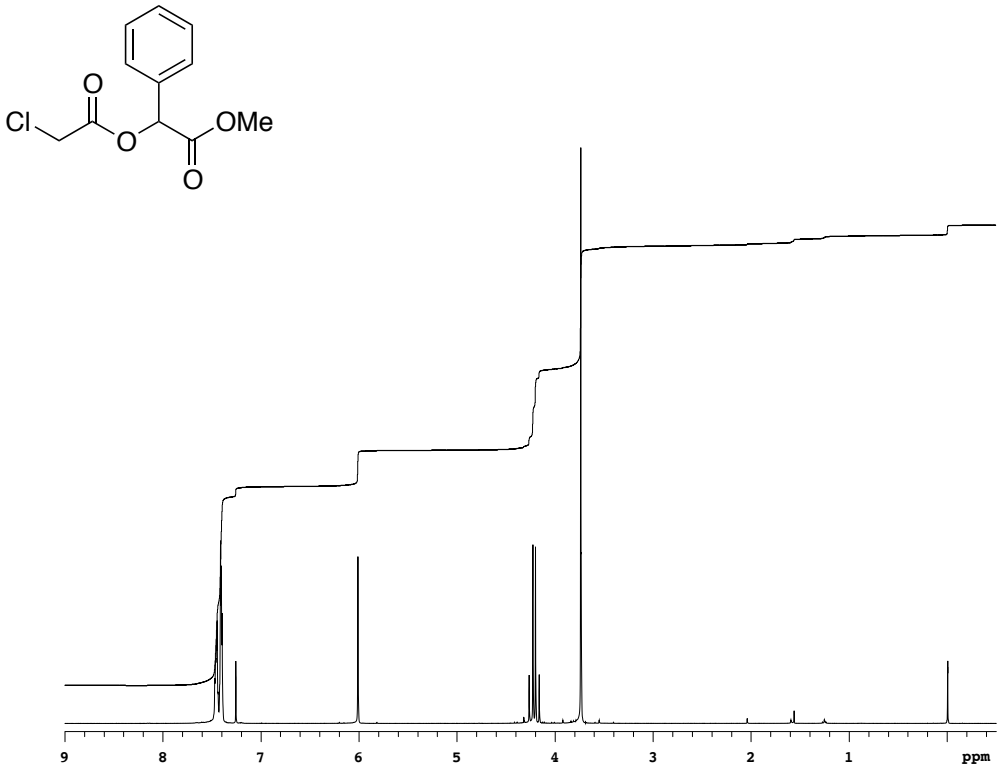
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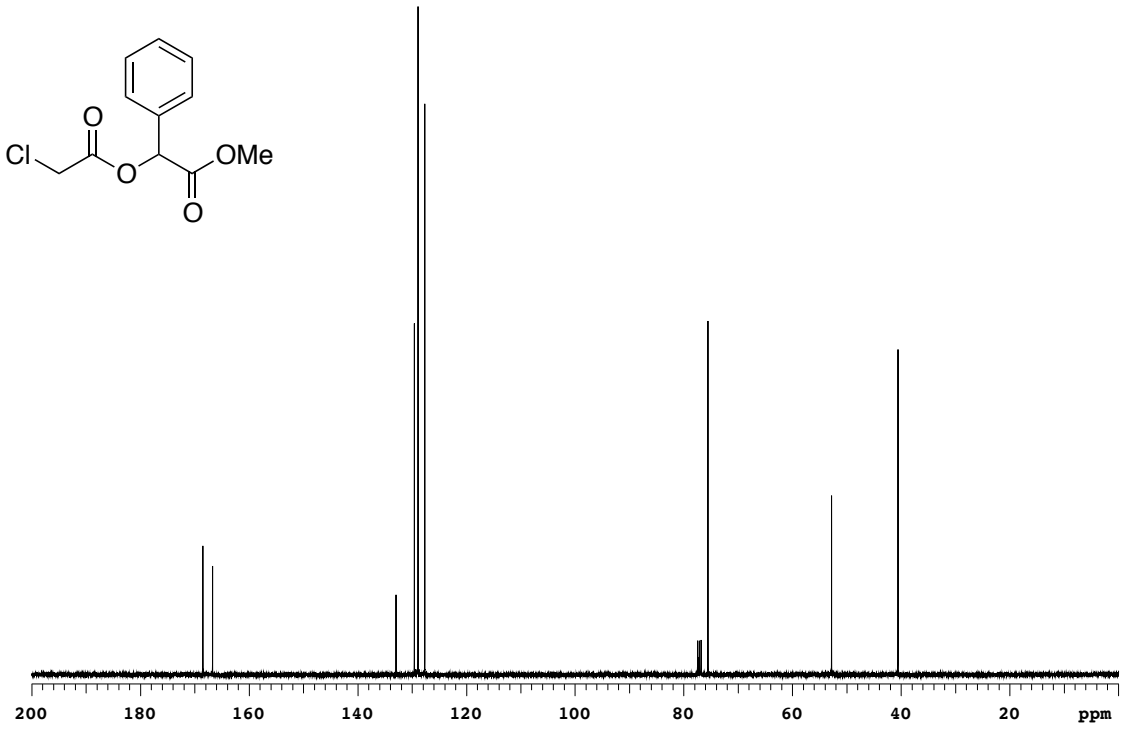
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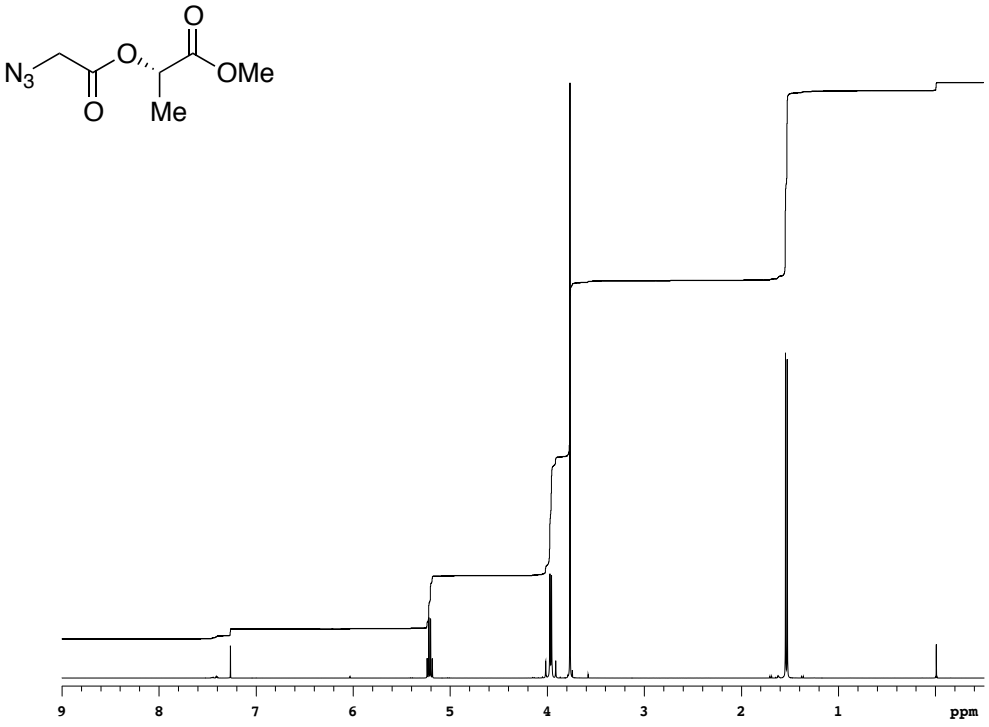
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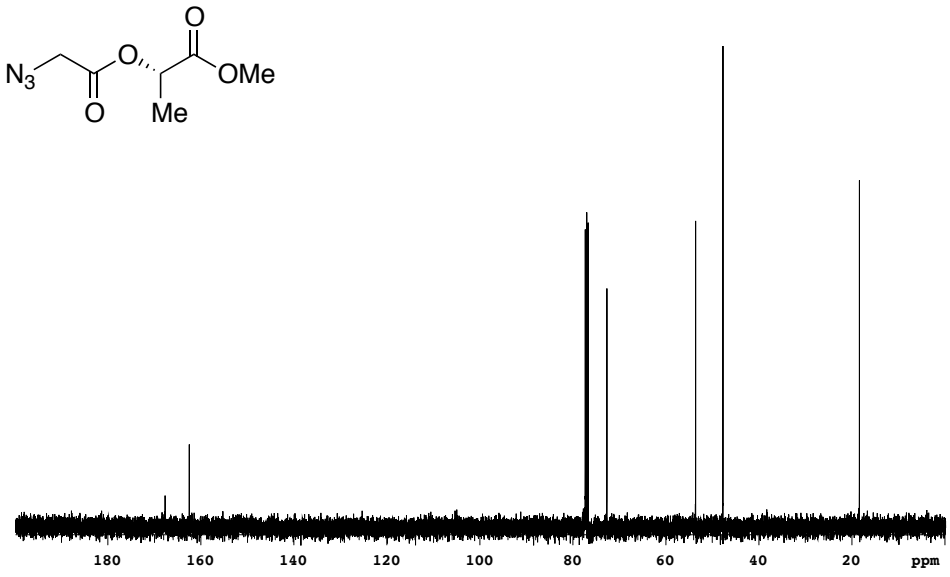
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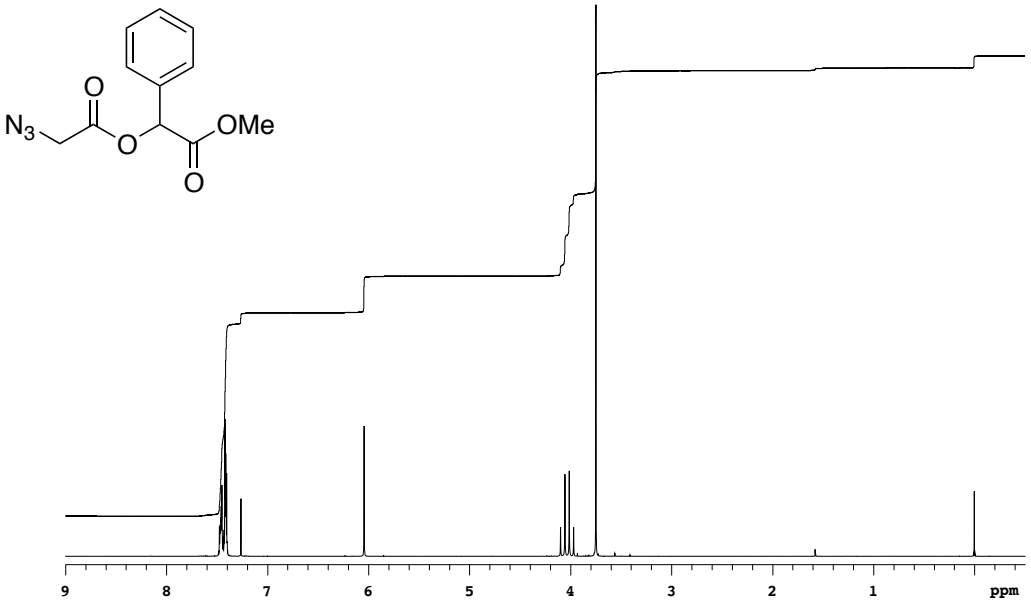
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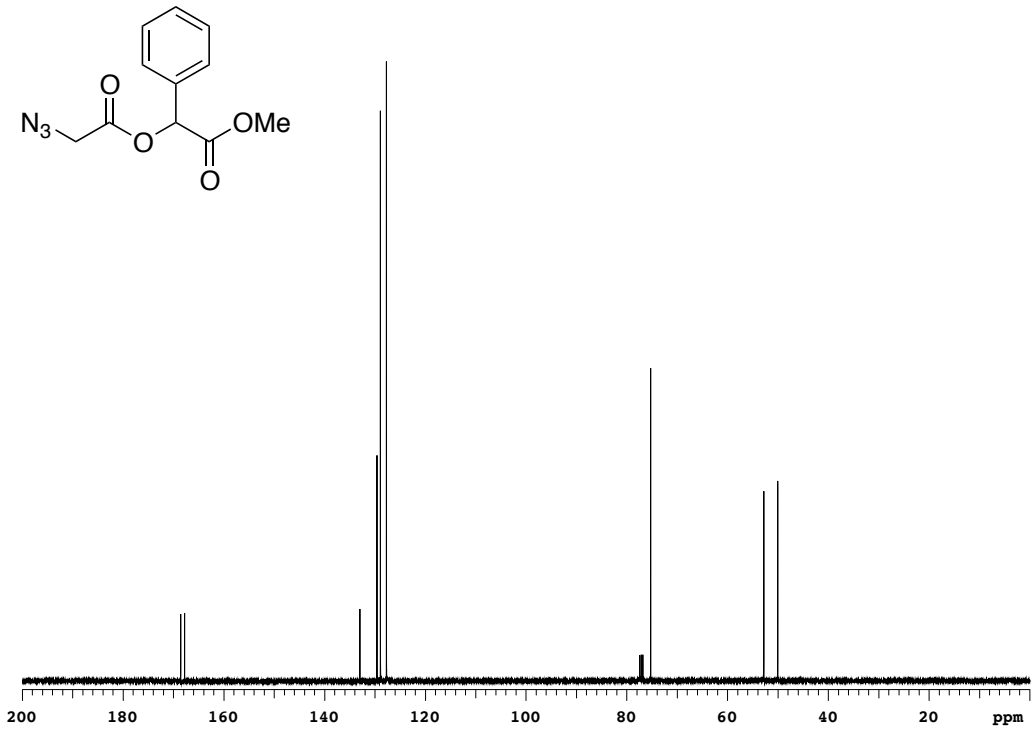
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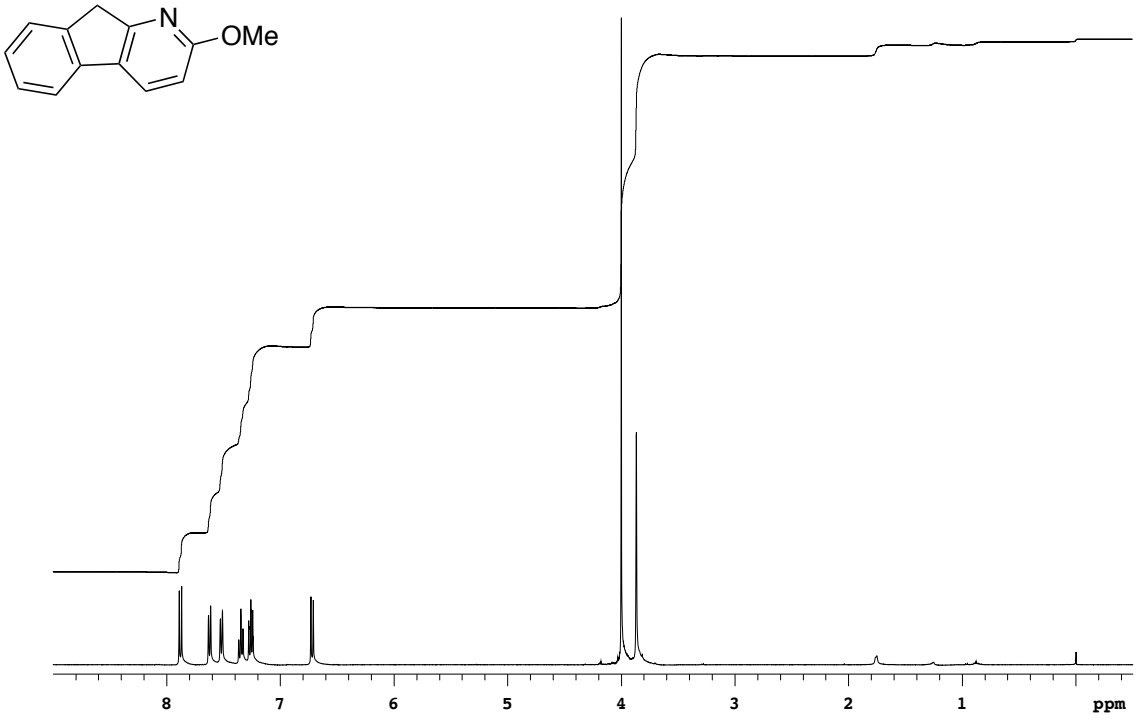
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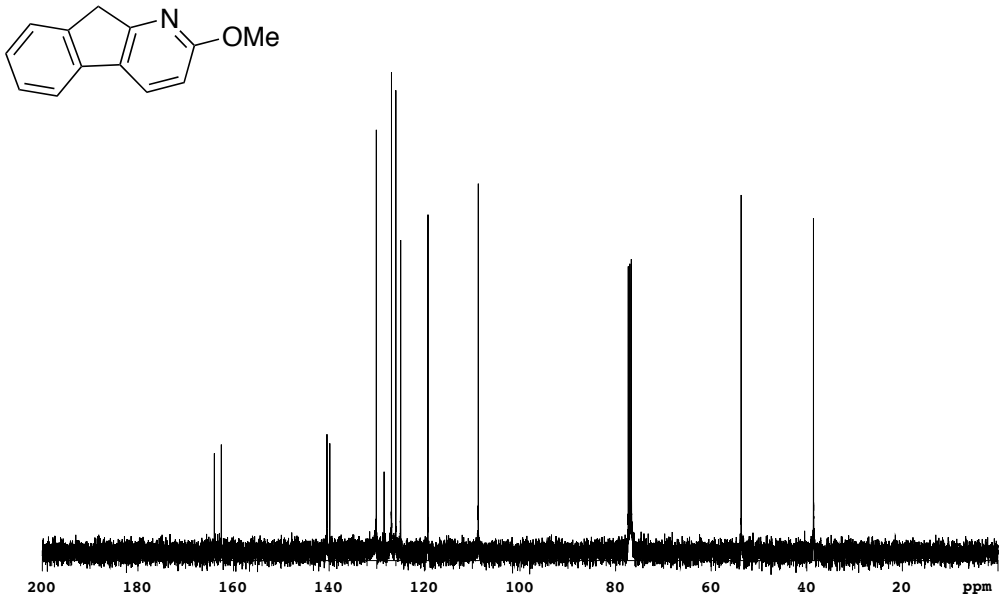
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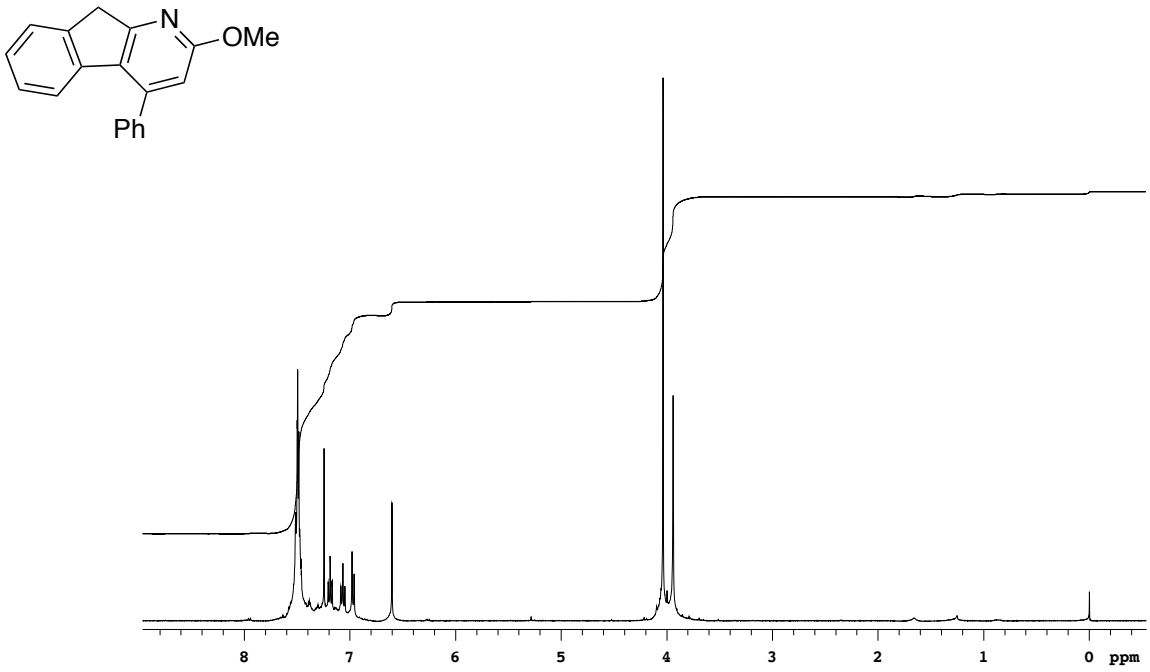
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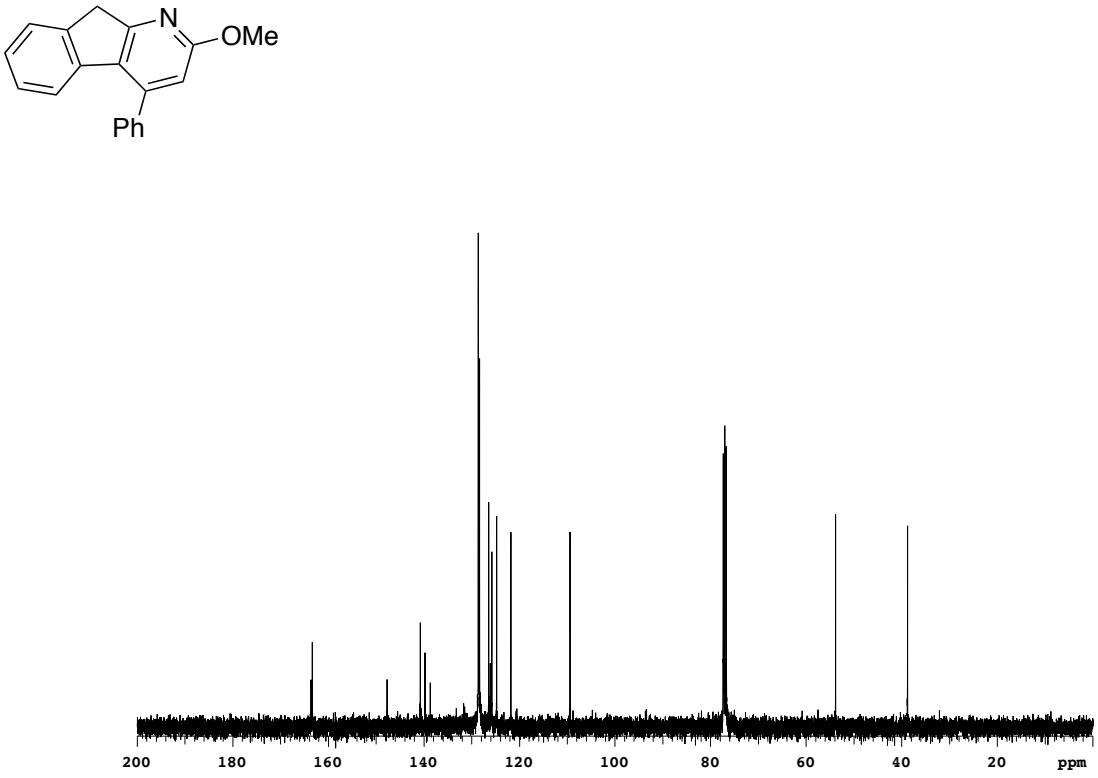
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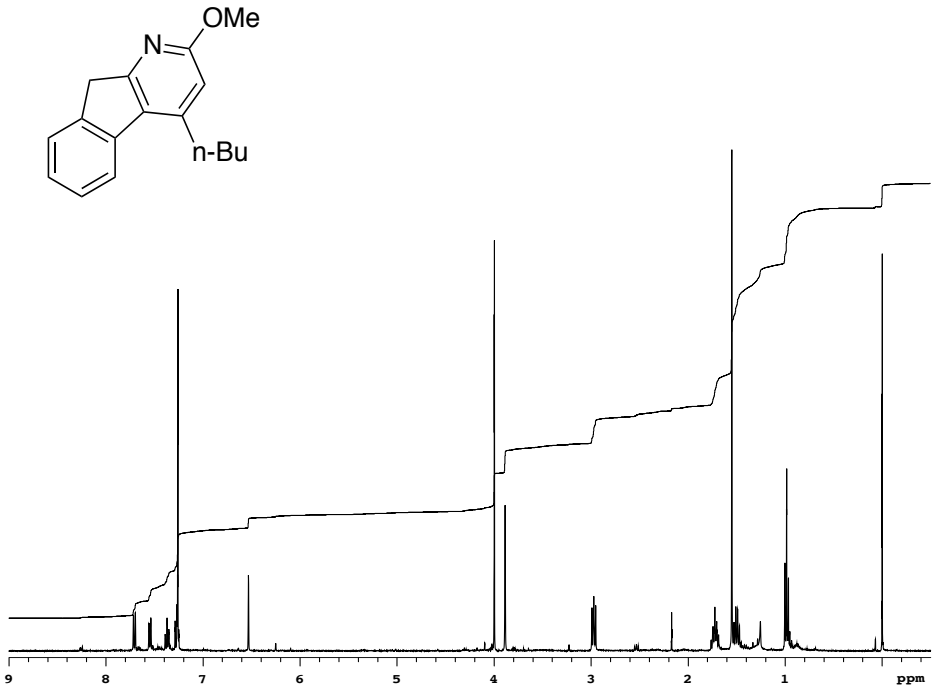
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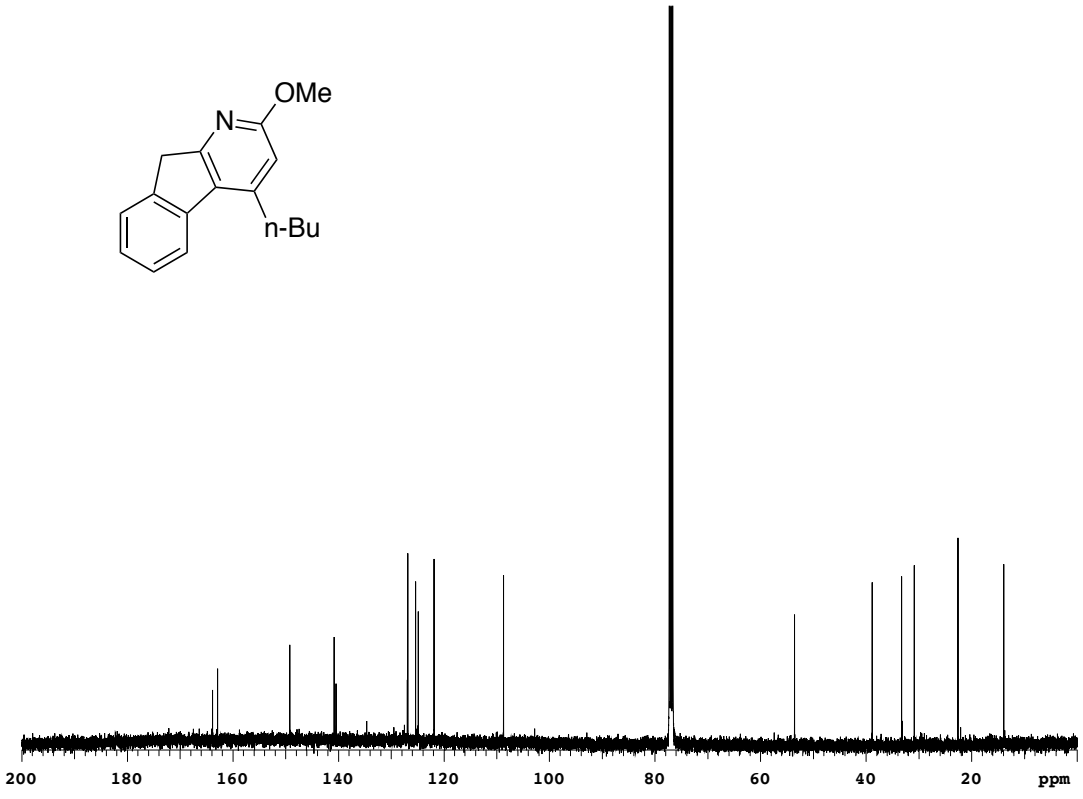
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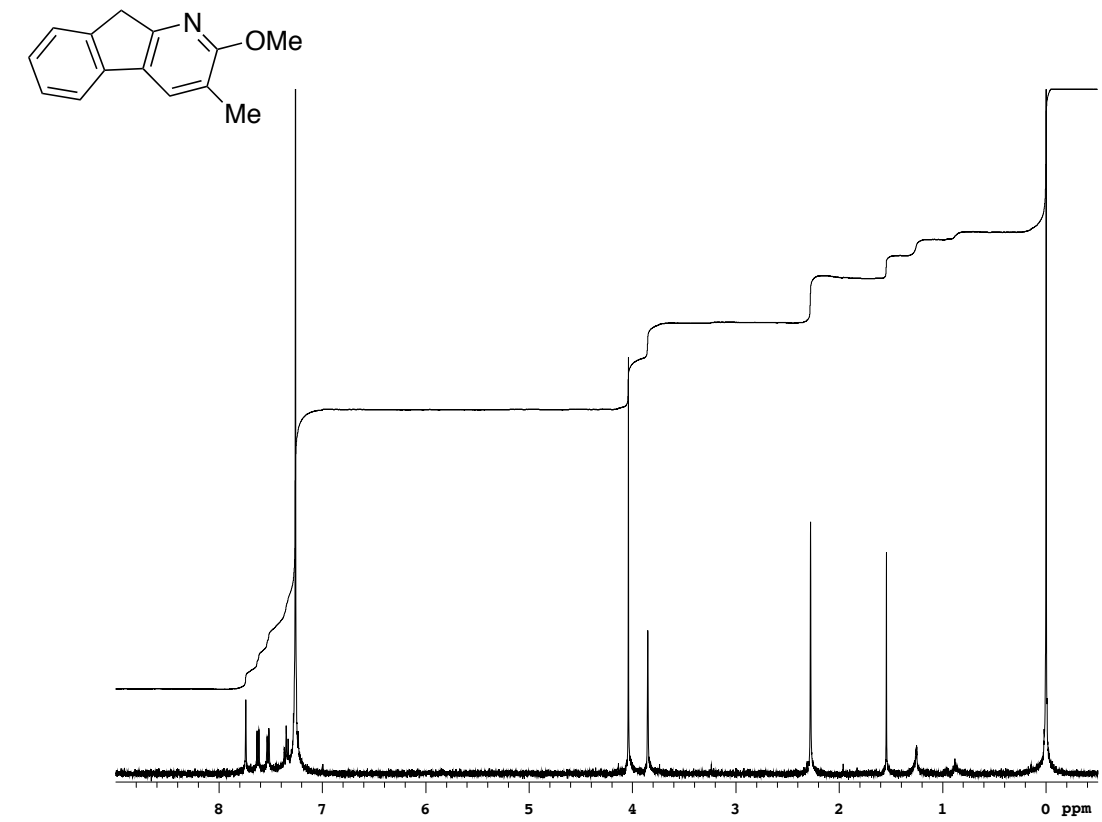
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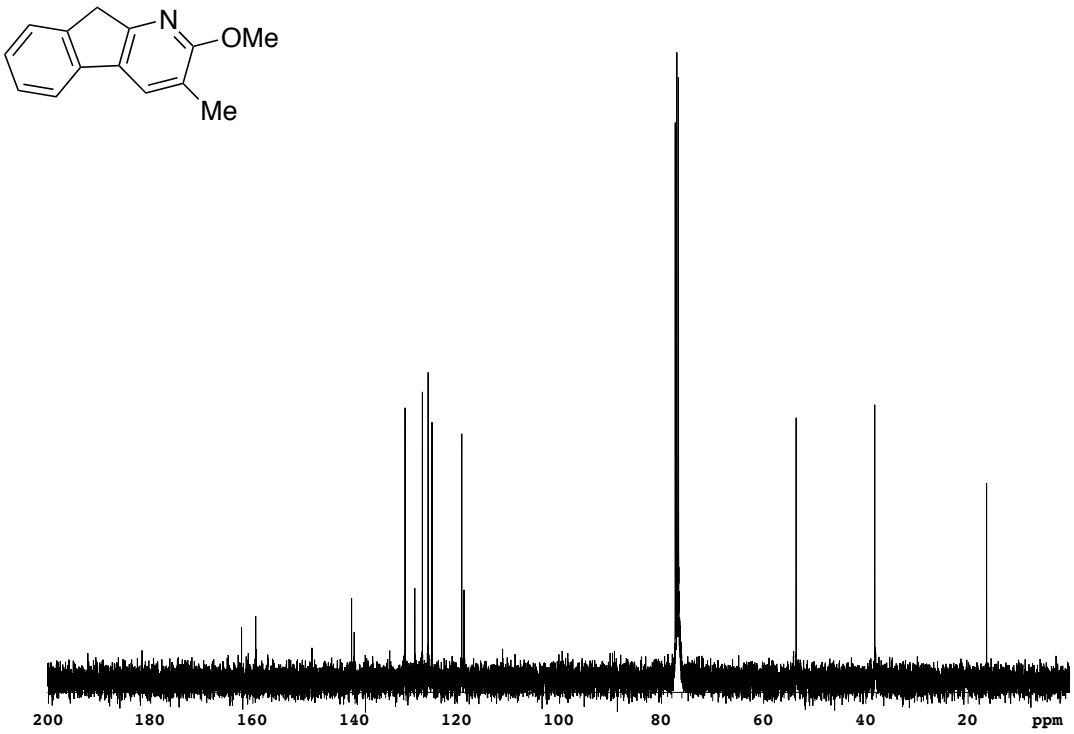
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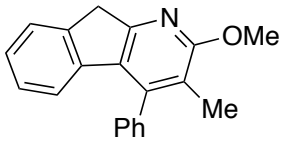
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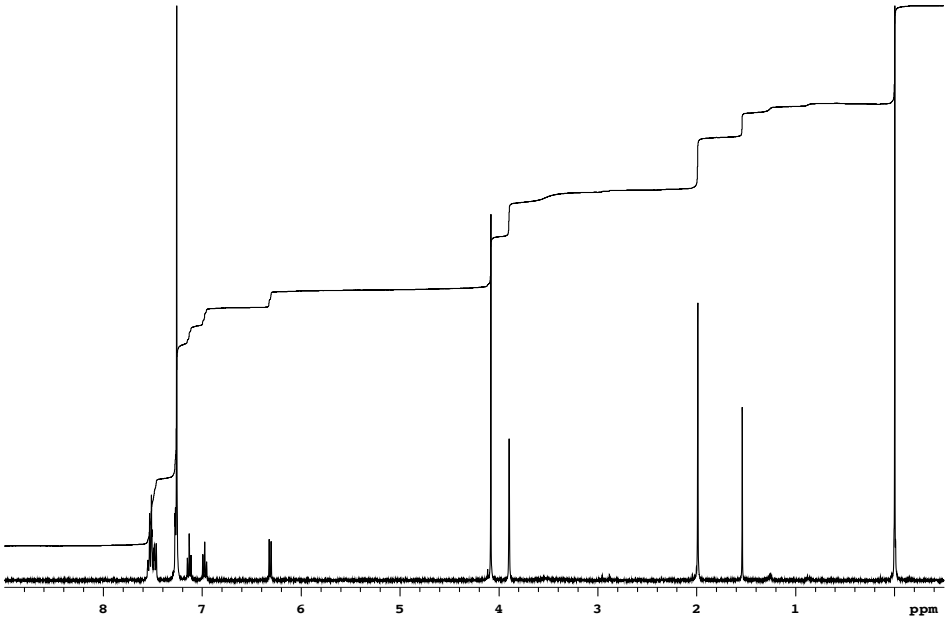
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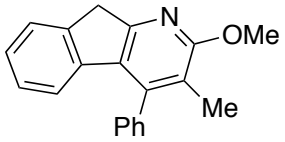
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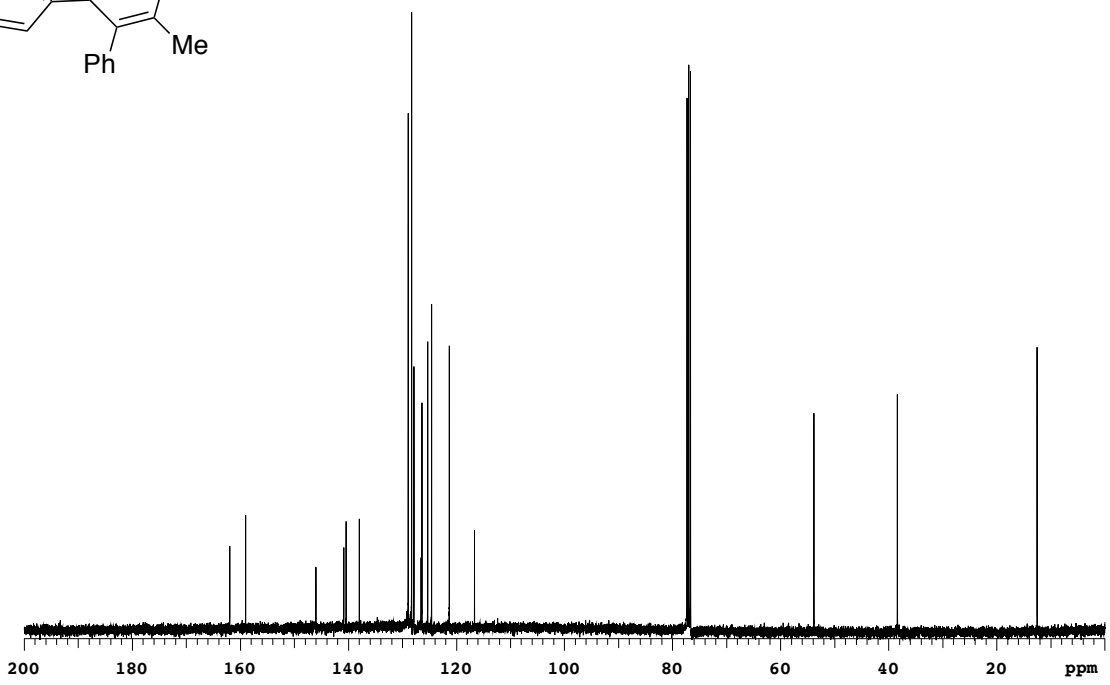
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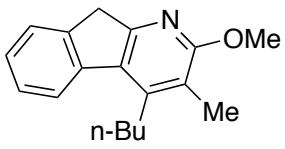
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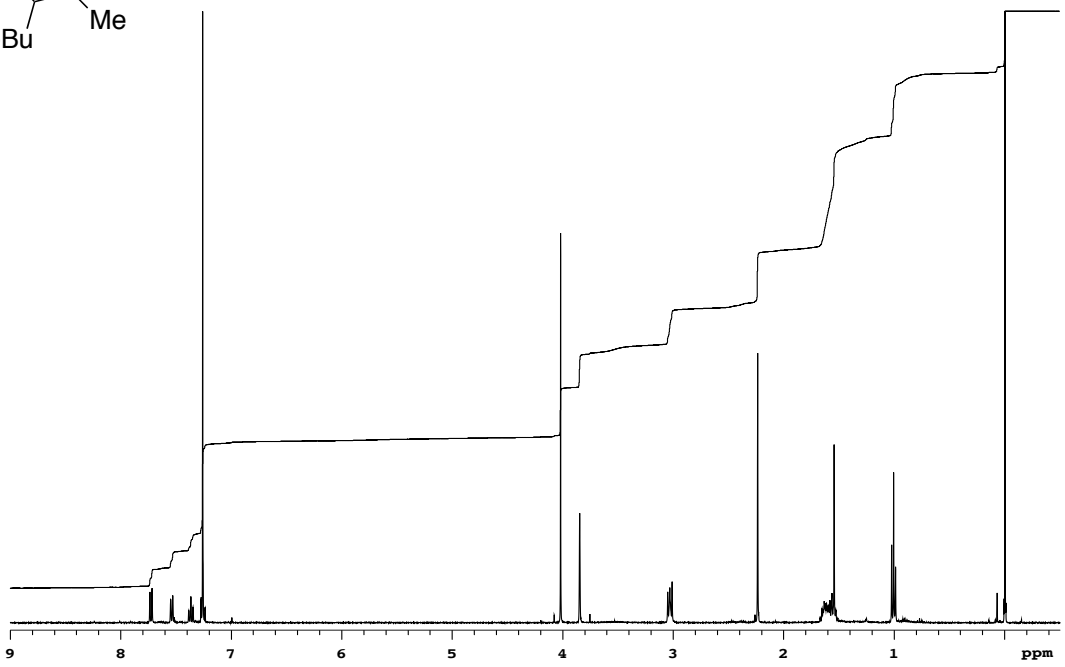
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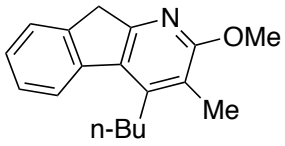
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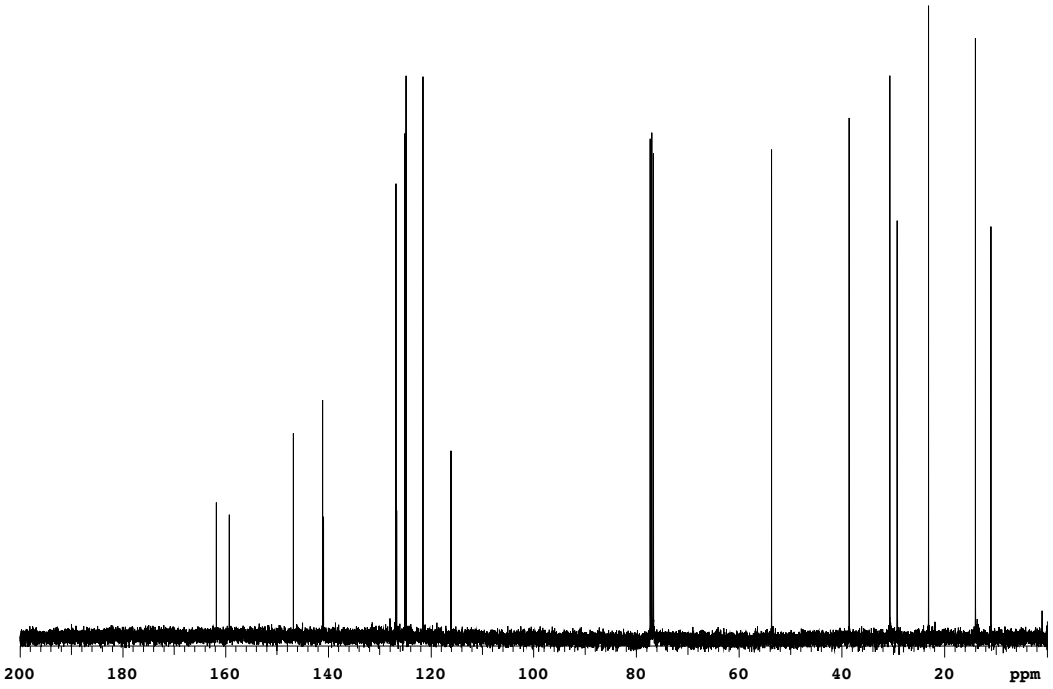
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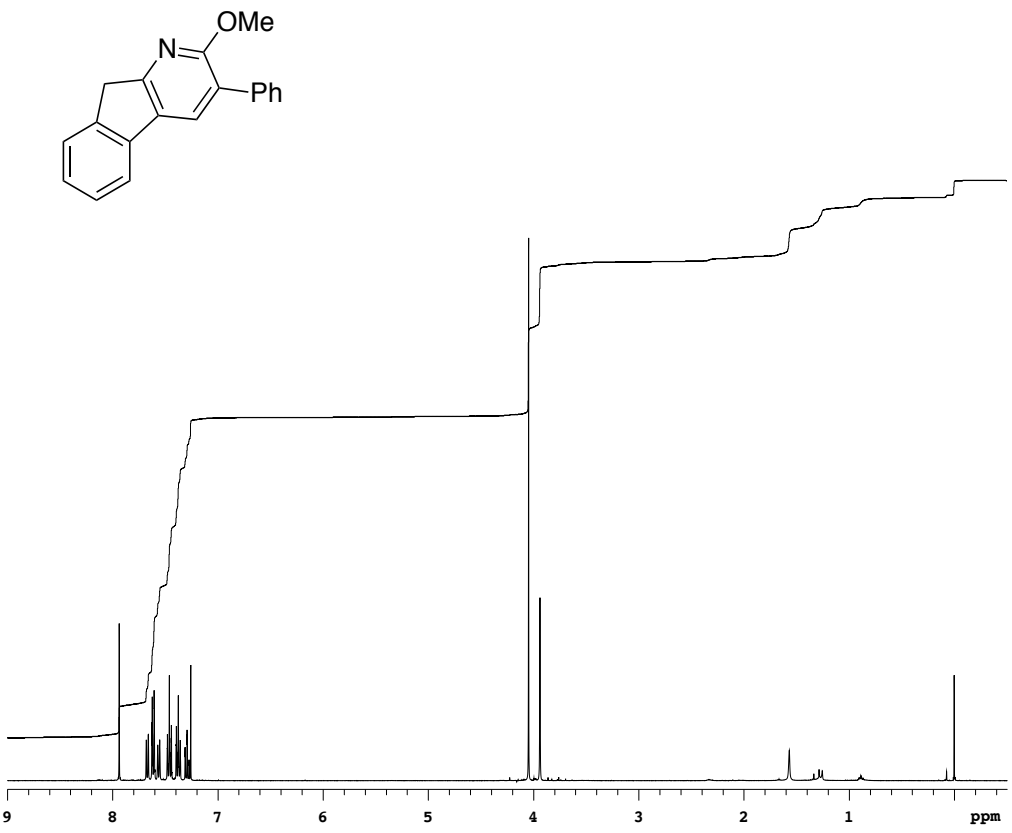
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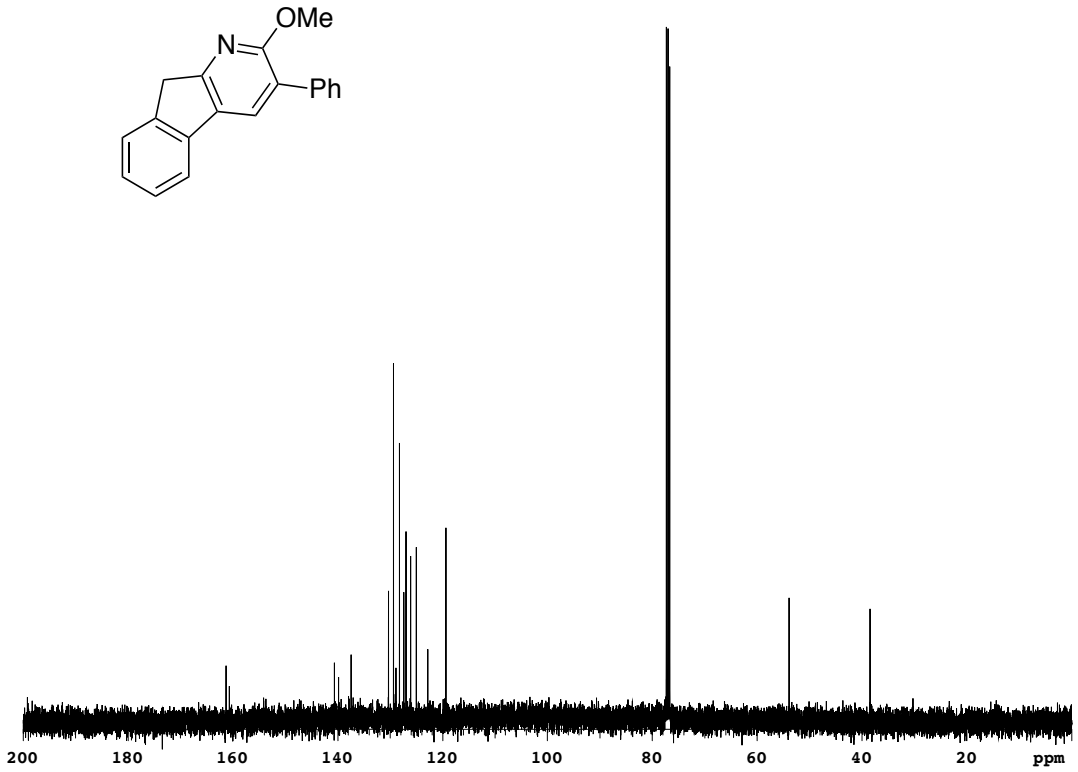
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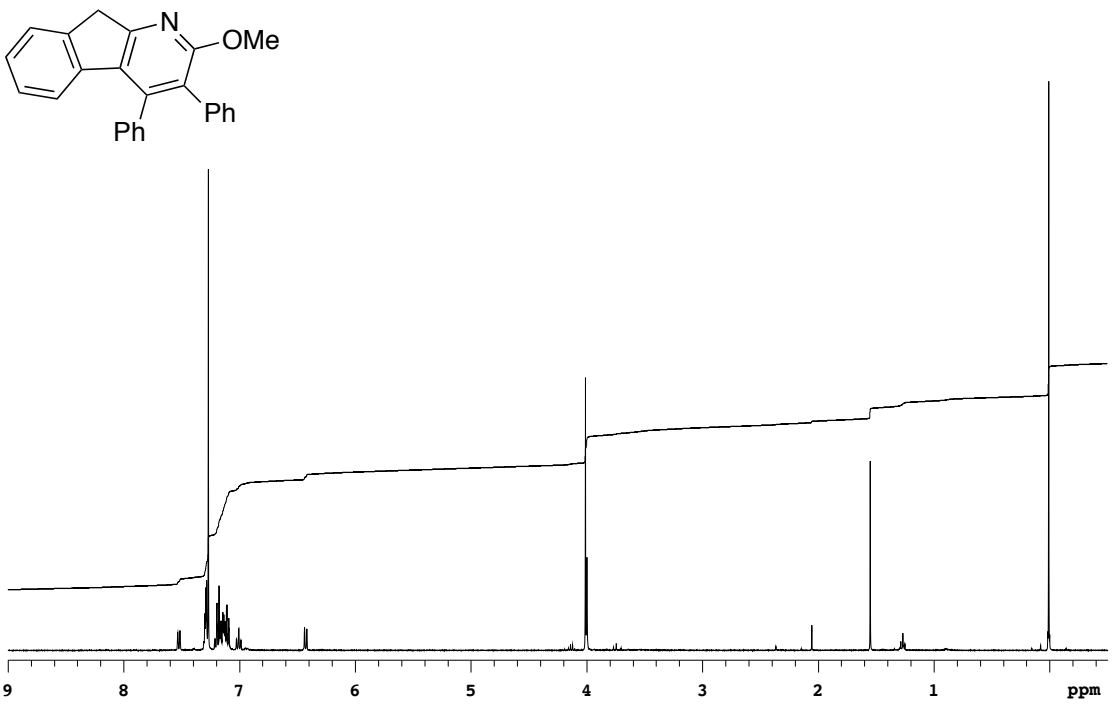
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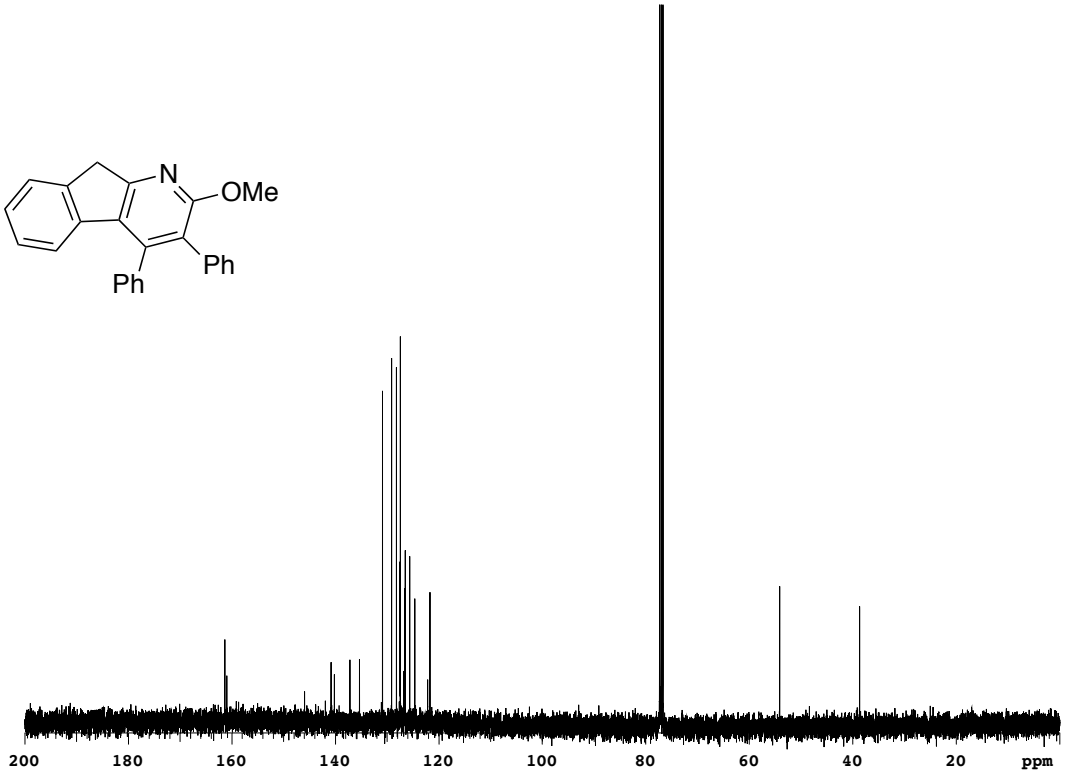
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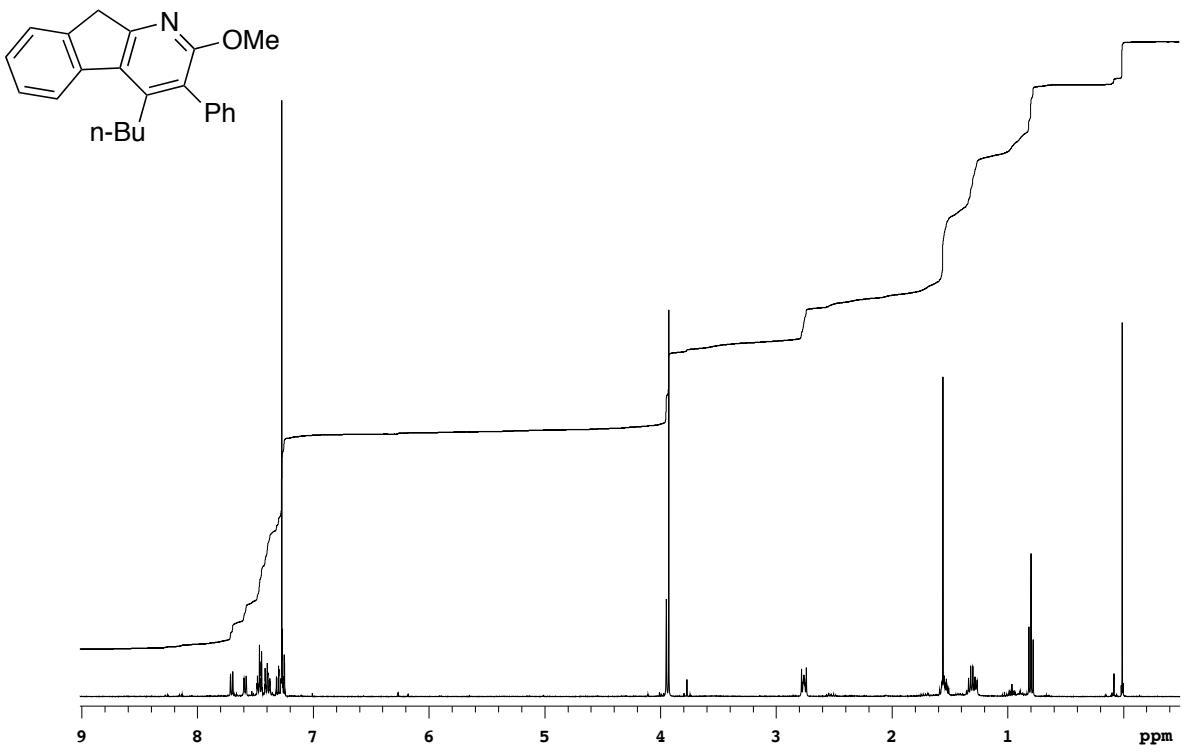
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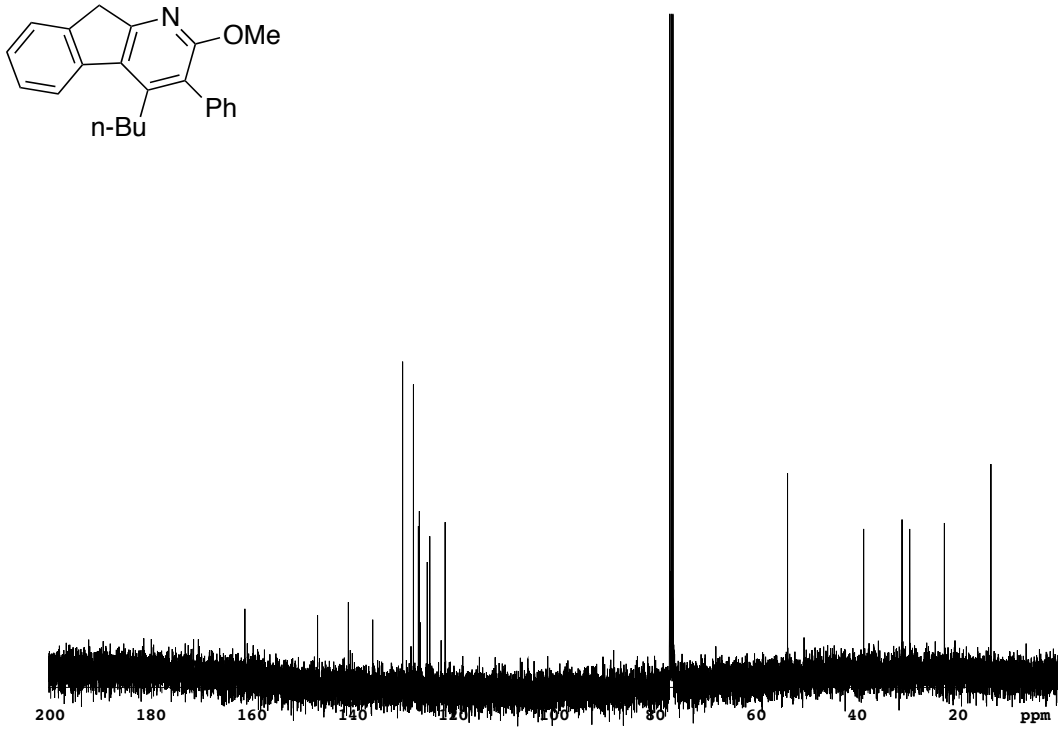
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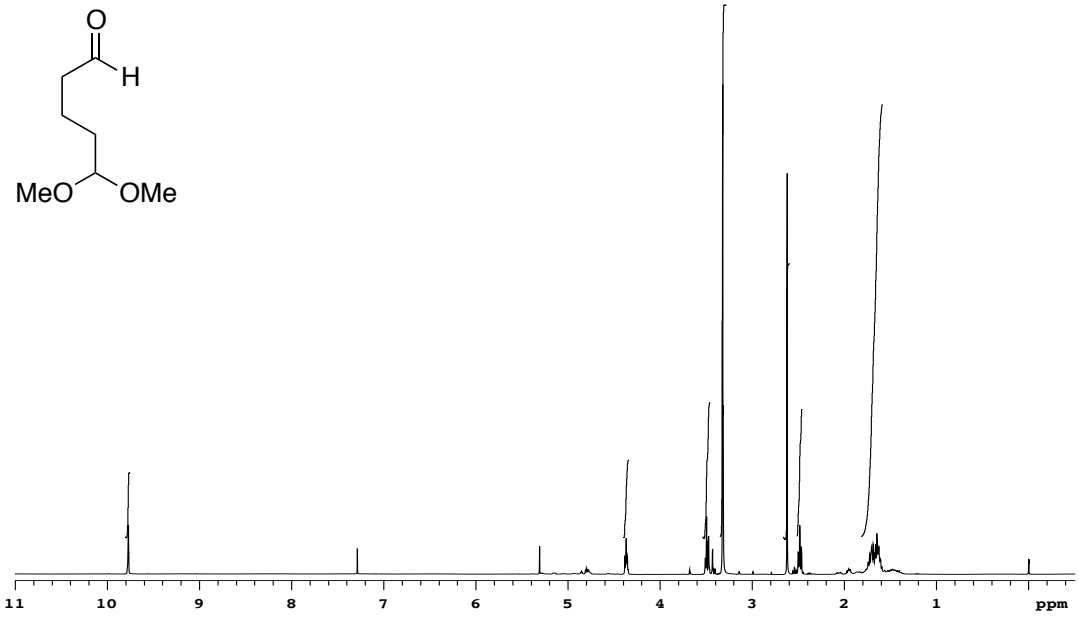
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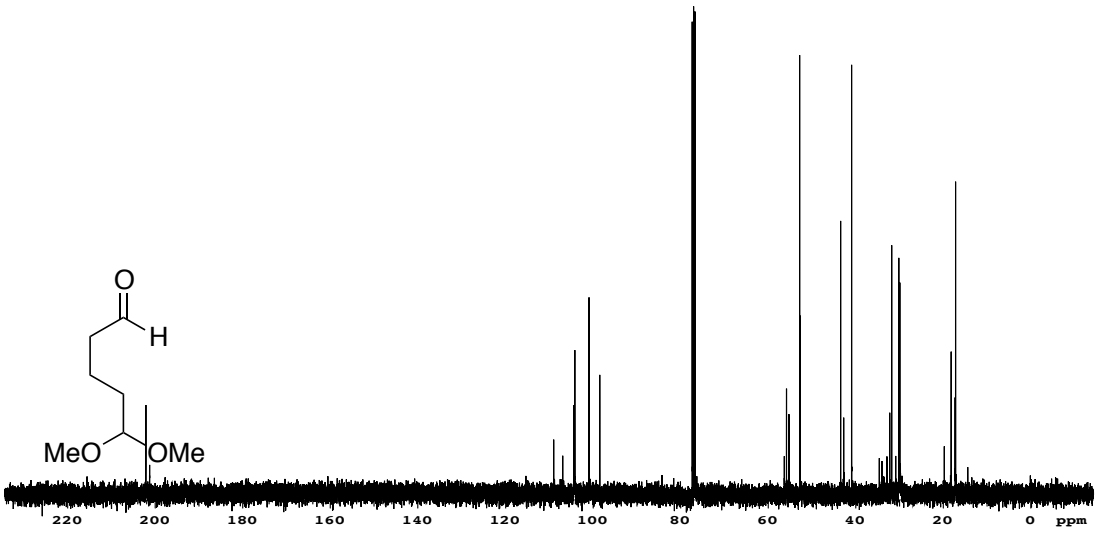
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OMe
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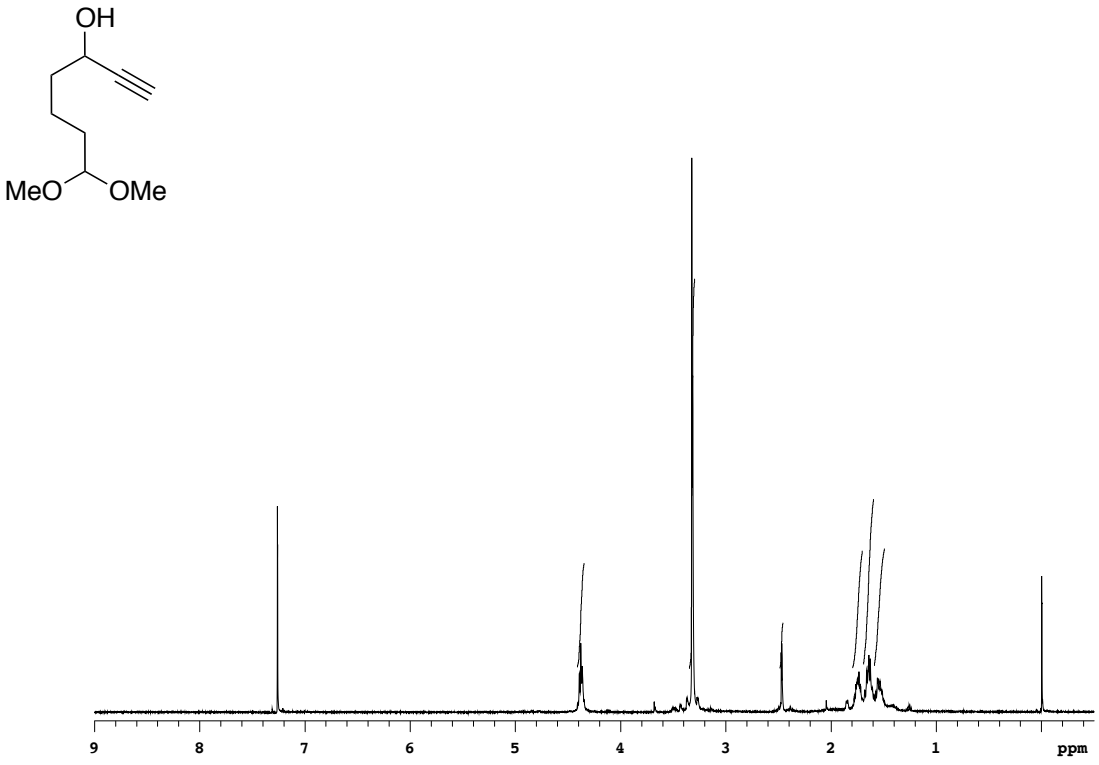
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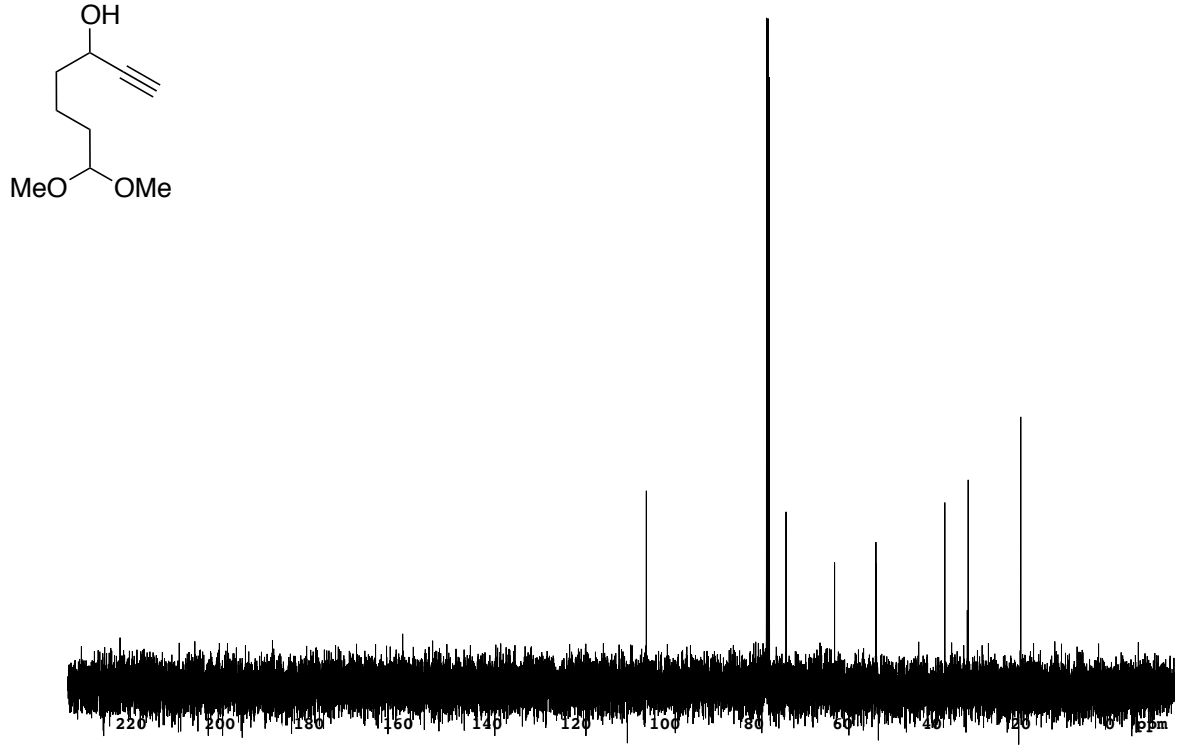
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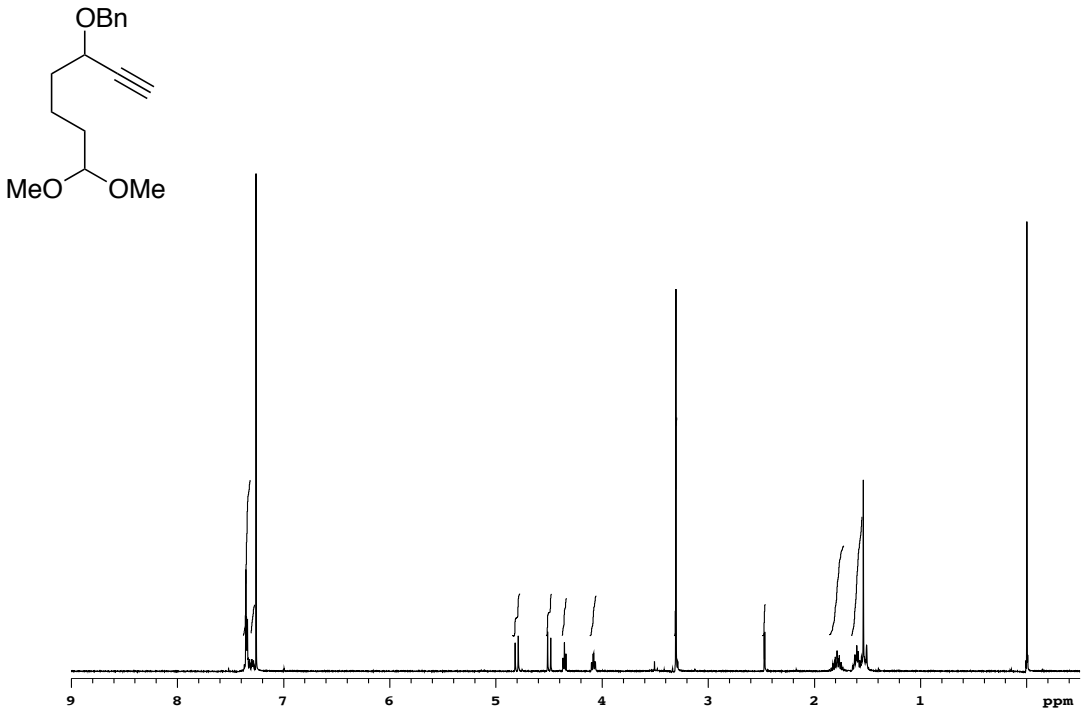
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MeO
OMe
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8
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2
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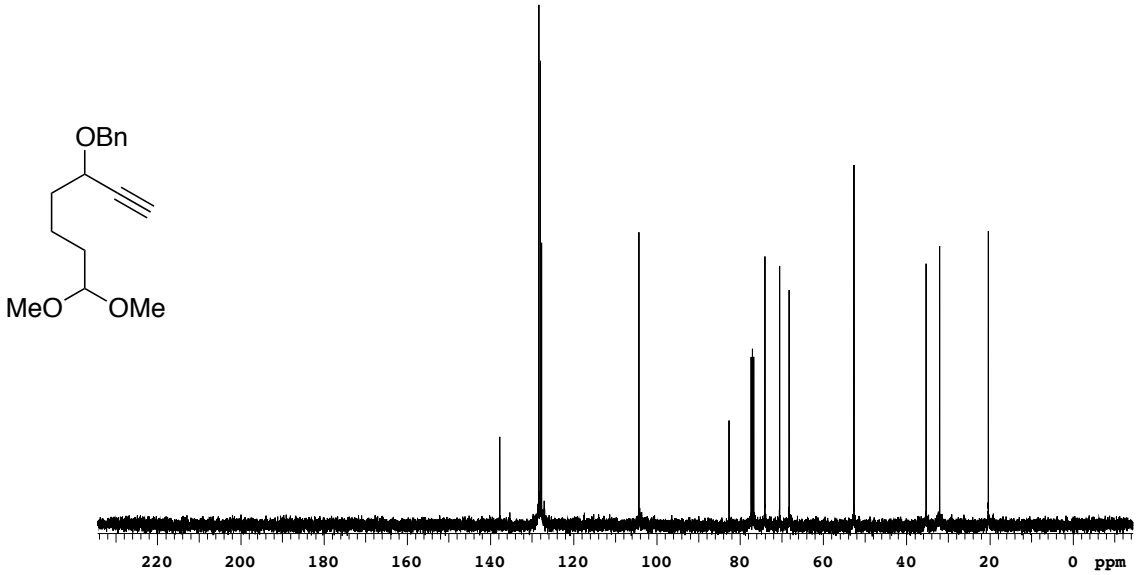
ppm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OMe
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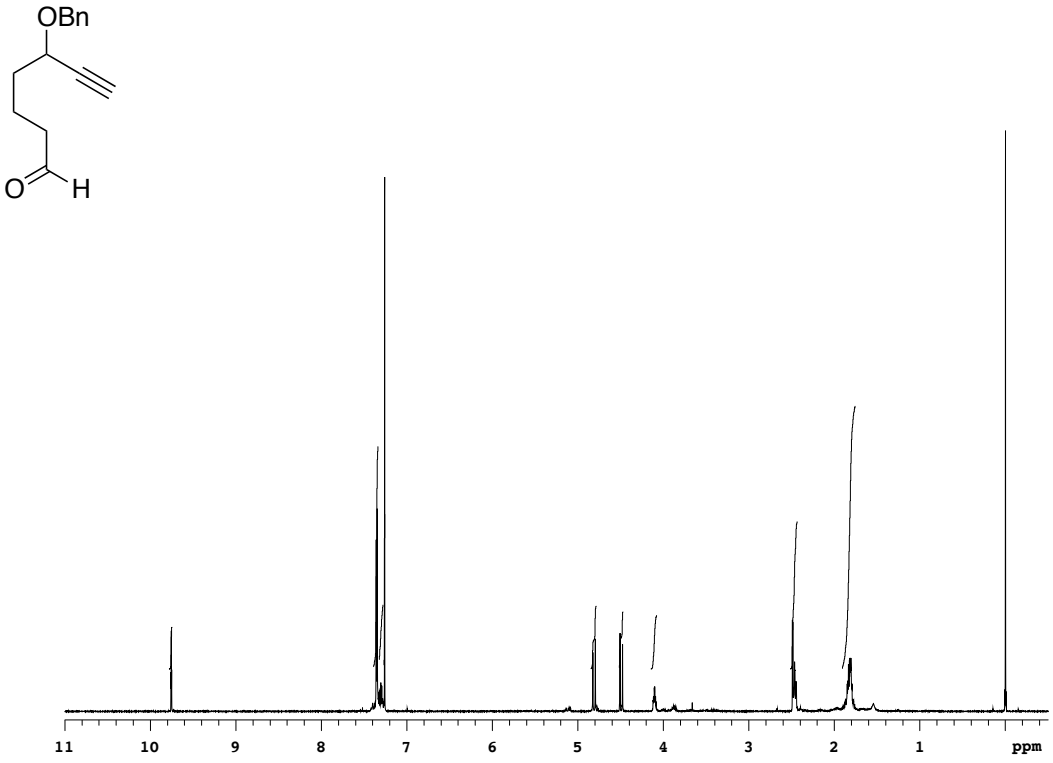
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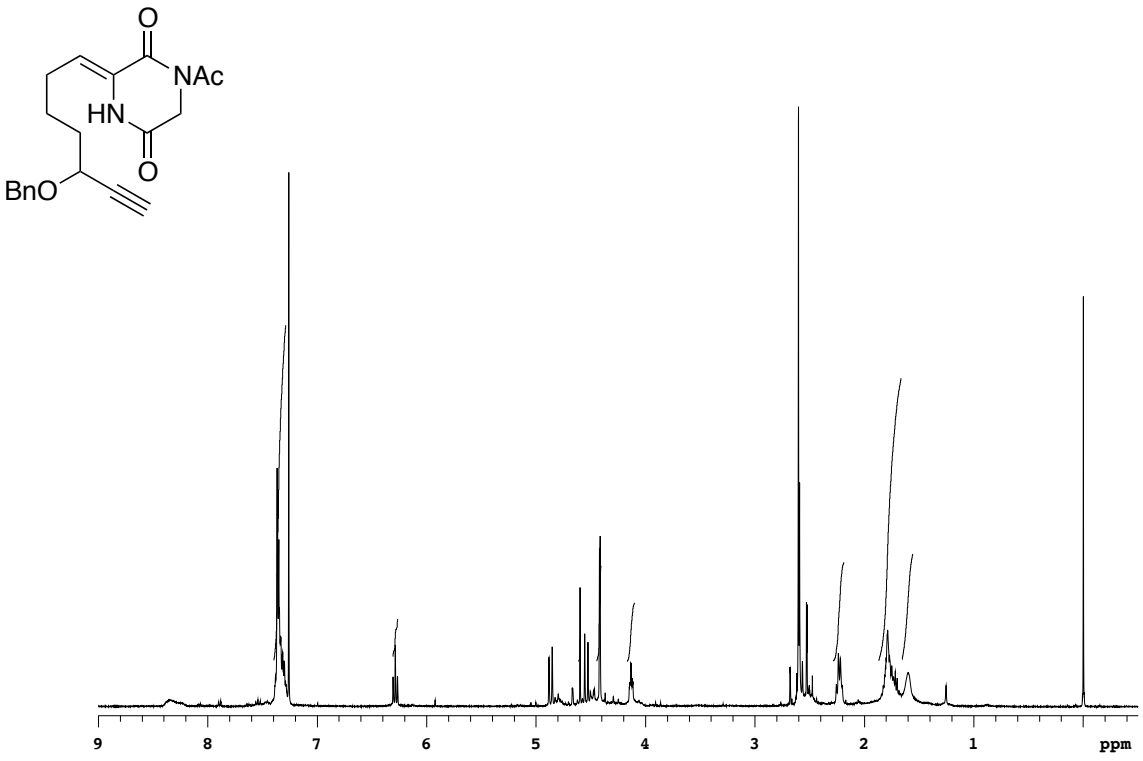
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NAc
HN
O
BnO
9
8
7
6
5
4
3
2
1
ppm