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ENDEAVORS TOWARD NOVEL SYNTHETIC ROADMAPS IN THE SYNTHESIS OF PERTINENT PHARMACOLOGICAL MOLECULAR SCAFFOLD MOIETIES

by

Justin D. Horgan

A Thesis

Submitted to the
Department of Chemistry and Biochemistry
College of Science and Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
August 25, 2020

Thesis Chair: Gustavo Moura-Letts Ph.D.

Committee Members:
Gustavo Moura-Letts Ph.D.
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Kandalam Ramanujachary Ph.D.

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Dedications

I would like to dedicate this manuscript to my loving mother and father, Casey M. Horgan and James J. Horgan. Thank you for always supporting me in every single endeavor I have ever encountered and raising me to be aware of the greatness within myself as well as the people I surround myself with from all walks of life. I am eternally grateful.

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I am truly grateful towards the faculty and staff at Rowan University's Department of Chemistry and Biochemistry who have helped me through my undergraduate and graduate research. I would like to thank Pulakesh Das for always being there to answer any questions I need as well as giving me moral support throughout all of the trials and tribulations that come with organic synthesis research. I would also like to thank Nicholas Cinti and Rebekah Strong for troubleshooting with me and also acting as additional moral supports. Finally, I would like to thank Dr. Gustavo Moura-Letts who allowed me to join the GML lab group and has supported me through every step of my research at Rowan University. Thank you for taking a chance on me and I will forever bring your teachings wherever I end up in the future.

Abstract

Justin D. Horgan
ENDEAVORS TOWARD NOVEL SYNTHETIC ROADMAPS IN THE SYNTHESIS OF PERTINENT PHARMACOLOGICAL MOLECULAR SCAFFOLD MOIETIES
2019-2020
Gustavo Moura-Letts Ph.D.
Master of Science in Pharmaceutical Sciences

One of the main goals in the GML lab group is the development of novel, economical, and environmentally friendly organic methods for the synthesis of pharmacologically relevant molecular moieties. The most salient pieces of data to the GML lab group members, reading dependable organic journals, are finding organic moieties that are largely unexplored, finding organic moieties which various research groups are having difficulty synthesizing, and finding complex organic procedures to key organic structures that can be easily reduced, or reconstructed, into novel methods that are more economical and environmentally friendly. By looking at these unexplored molecules, as well as hard to reach organic moieties, the GML lab group employs various organic methods to break down the target moiety at hand in order to recreate these compounds using superior novel methodologies. In my time working within the GML lab group , I successfully introduced a novel synthesis route for the Lewis acid catalyzed synthesis of hexahydrobenzofuranones, a selective synthesis of pyrrolidines, pyrrolines, and azepines from haloaziridines, and a photoisomerization reaction of vinyl oxaziridines from vinyl nitrones. It is the hope of the GML lab to use these synthetic strategies, and the respective synthesis routes developed from them, to improve on existing synthetic organic chemistry through reactions which rely on mild conditions to afford crucial organic moieties.

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Chapter 1

Novel Synthesis of Hexahydrofuran-4(2H)-Ones

Hexahydrofuran-4(2H)-ones, one of the current GML lab group target moieties, are a part of a large family of organic compounds known as fused heterocycles; compounds containing two, mainly carbon based, organic ring structures which are bridged together at two carbons. Heterocyclic compounds are commonly used as privileged pharmacophores in the creation of new pharmaceutical agents. Fused heterocycles play this fundamental roll in drugs design as they are often good sources of scaffolding molecules in both blockbuster drugs and natural products in part due to do the structural rigidity, as well as other key features, that fused heterocycles can bring to an experimental pharmacophore. As mentioned before, the heterocyclic compound of current interest to the GML lab group is hexahydrofuran-4(2H)-ones specifically through the novel synthesis of fused, cyclic ethers via cycloaddition reactions between aldehydes and substituted cyclopropanes. Through this novel method, the GML lab group has been able to successfully access hexahydrofuran-4(2H)-ones, with a wide variety of functionalization, thus helping to meet the continuous demand for the development of more efficient and systematic methods to reach these key structures. Before going through previous synthetic routes to afford hexhydrofuran-4(2H)-ones, it is vastly important to cover key chemical features that these hexahydrofuran-4(2H)-one products embody for chemical context.

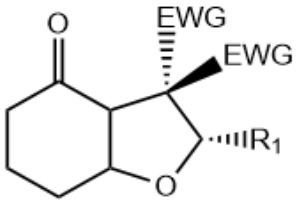
The chemical structure of hexahydrofuran-4(2H)-ones, as shown in Figure 1, is characterized by a bicyclic moiety containing a six membered cyclic carbon ring structure

with one carbonyl functional group attached to the cyclohexane ring. If the six membered cyclic hydrocarbon ring, as previously mentioned, was the complete molecular structure, it would have the IUPAC name cyclohexanone. The cyclohexanone ring shares two adjacent carbons with a five membered cyclic organic ring made up of one oxygen atom and four carbon atoms, known by the systematic name tetrahydrofuran. The tetrahydrofuran ring, in the hexahydrobenzofuran-4(2H)-one final product, is further substituted by two electron withdrawing groups, both sharing a single carbon on the tetrahydrofuran ring. Various mono- and di-ester hydrocarbon chains have been implemented into each of the hexahydrobenzofuran-4(2H)-one moieties synthesized, through the second step of the novel synthesis of hexahydrobenzofuran-4(2H)-ones, in order to test which mono- or di-ester complex would afford the best yielding hexahydrobenzofuran-4(2H)-one products using the GML synthesis route. Each of the ester hydrocarbon complexes tested are attached to the carbon atom on the tetrahydrofuran ring by the mono- or di-ester carbon that is in between each of the carbonyl groups on the di-ester complex or adjacent to the single carbonyl functional group of the of the mono-ester hydrocarbon chain. This specific substituent addition creates an inverse stereochemical configuration of each half of the mono- or di-ester hydrocarbon complex. Adjacent to the electron withdrawing ester hydrocarbon substituents, labeled as "EWG" in Figure 1, is a "R_1" labeled substituent which represents a variety of heterocyclic functional groups, derived from heterocyclic aldehydes substituted in "R_1" position, in the novel synthesis of hexahydrobenzofuran-4(2H)-one. Using heterocyclic aldehyde substituents as the "R_1" substituent gives the hexahydrobenzofuran-4(2H)-one moiety further rigidity and stability as well as granting

the final product complex the ability to be further synthesized into more complex fused heterocyclic compounds.

Figure 1

Hexahydrobenzofuran-4(2H)-One Target Moiety



Now that some basic chemical characterization of hexhydrobenzofuran-4(2H)-ones have been covered, it is important to have an overview of organic synthesis routes from the past towards hexahydrofuran-4(2H)-one-like products but also to envelop the scientific findings that laid the foundation for the optimized, novel synthesis route designed for the synthesis of hexahydrofuran-4(2H)-ones.

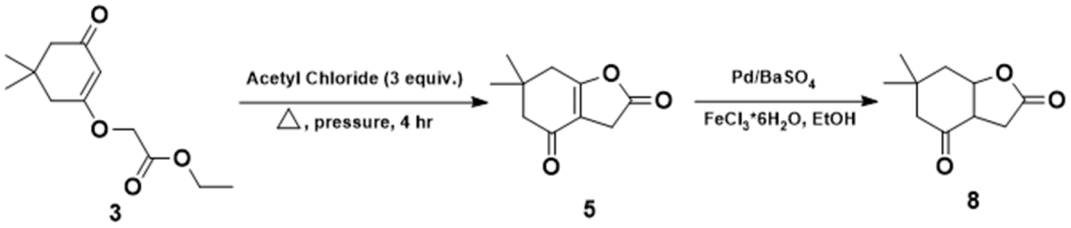
1.1 Review of Hexahydrobenzofuranones

In order to successfully add to the paradigm of knowledge on the synthesis of hexahydrobenzofuranone moieties, organic chemists must first study the synthesis routes towards hexahydrobenzofuranones which have already been exploited. These studies give key insights into the target moiety as well as potential challenges that one might run into

when attempting to synthesize hexahydrobenzofuranones. One of the first instances of the synthesis of hexahydrobenzofuranones comes from the Pharmaceutical Institute of the University of Kiel in 1954 by German chemists Karl W. Rosenmund, Horst Herzberg, and Hartwig Schutt. Rosenmund and his colleagues used hexahydrobenzofuranones as synthetic building blocks for the creation of a class of antiparasitic drugs known as anthelmintics. The synthesis for these hexahydrobenzofuranones is depicted below in Figure two, showing the eventual stepwise formation of the hexahydrobenzofuranone product 8.

Figure 2

Hexahydrobenzofuranone Building Blocks for Anthelmintic Synthesis



The synthesis route, depicted above in Figure 2, begins with combining molecule 3 with three equivalences of acetyl chloride for four hours under high pressure and heat. The work-up of this step then begins with cooling the reaction in an ice and salt bath while slowly adding 100 milliliters of ether to the crude reaction solution through rubber tubing to keep the reaction pressure stable. The crude reaction was then dried, to remove

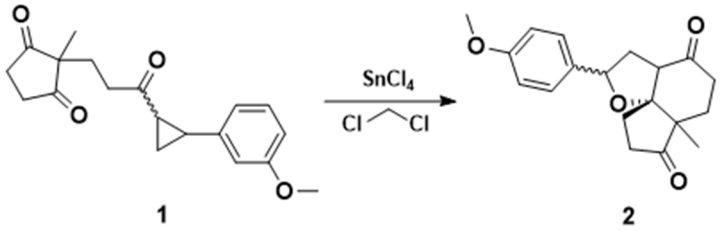
organic solvent present, and then resuspended in twenty-five milliliters of acetic acid followed by dilution of the reaction with seventy-five milliliters of petroleum ether. Crystals were then formed and isolated in the reaction vessel to isolate compound 5. One gram of five molar percent palladium/barium sulfate catalyst, also known as the Rosenmund catalyst, 13.5 milligrams of hydrated iron three chloride in 100 milliliters of ethanol, and two grams of compound 5 were resuspended in 30 milliliters of ethanol until one mole of hydrogen had dissipated from the reaction. The Rosenmund catalyst was removed via centrifugation and the solution was rotatory evaporated to yield the semi-pure, white crystal of hexahydrobenzofuranone 8. (5) The purification process was completed via an ether-carbonate precipitation to successfully yield the pure crystalized compound 8. Rosenmund and his colleagues successfully employed hexahydrobenzofuranones to synthesize enol-lactone complexes of hydrogenated cyclic 1,3-diketones containing useful anthelmintic properties. This first publication, illustrated above, shows that from the very genesis of the synthesis of hexahydrobenzofuranones, chemists intended to exploit this powerful moiety to create complex structures with pharmacological properties to be used in the synthesis of new pharmaceutical agents.

Daniewski and Kowalcyk-Przewloka have shown that hexahydrobenzofuranones can be used precursors in the total synthesis of cyclic steroids. Figure 3 shows a step in the synthesis route towards cyclic steroids with molecule 1 being converted into molecule 2 containing the hexahydrobenzofuranone moiety under relatively benign conditions. This process was completed by adding the inorganic catalyst tin (IV) chloride in methylene chloride to the starting material at room temperature. Tin (IV) chloride is commonly employed by organic chemists as a Lewis acid catalyst in Friedel-craft

reactions for alkylation and cyclization transformations as well as used with fuming nitric acid for selective nitration of aromatic organic structures. (7) The reaction was left overnight to stir which was then followed by the addition of 20 mL of water, the extraction of methylene chloride, drying of the reaction using sodium sulfate, and purification completed via flash chromatography. This reaction led to over eighty percent conversion of the pure diastereo-isomer of molecule 2 in figure 3 according to analyzed NMR spectrum data. (6)

Figure 3

Hexahydrobenzofuranone Precursor in Total Synthesis of Aromatic Steroids

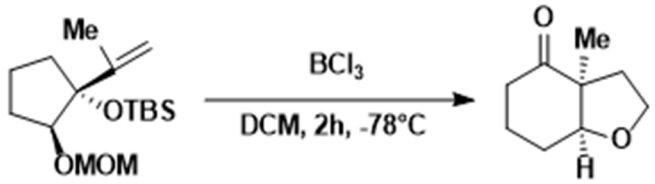


It is important to note that the functionalized tetrahydrofuran molecule, which is contained within the hexahydrobenzofuranone moiety, is a sought-after structure to synthesis in an economic fashion as it is found in plenty of natural products as well as active medicinal agents. Therefore, when exploring the different synthetic methods to establish hexahydrobenzofuranones, it is not unlikely to come across methodologies that are initially intended for the synthesis functionalized, stereo-controlled tetrahydrofurans. Functionalized tetrahydrofurans are commonly established by intramolecular

etherification reactions from acyclic fragments as well as from C-C bond formation. (10) A versatile C-C bond formation methodology used to create 3-acyltetrahydrofurans by stitching the carbonyl carbon of aldehydes and ketones in between the alkene and alcohol termini of an allylic diol. (11) While this process has high stereoselectivity as well as being a cornerstone reaction for the synthesis of numerous oxacyclic natural products, the reaction holds the limitation of an inability to synthesize tetrahydrofurans with two hydrogen substituents on the C5 carbon of the tetrahydrofuran produced. In the following procedure depicted in figure 4, Gasparski and her colleagues modify the synthesis of 3-acyltetrahydrofurans previously mentioned, to solve the reaction's shortcoming, through the development of formaldehyde oxonium ion intermediates which allow for 5-unsubstituted tetrahydrofurans to be prepared. In order to form the oxonium ions, the homoallylic alcohol of the allylic diol precursors were protected with methoxymethyl, OMOM, and to prevent the formation of 1,3-dioxolane the allylic alcohol was protected via a tert-butyldimethylsilyl, TBS, functional group. As seen in Figure 4, the allylic diol precursor on the left is exposed to a solution of boron trichloride in the organic solvent dichloromethane, DCM, at -78 degrees Celsius for one to two hours. The mechanistic studies, reported by Gasparski's group, showed a Prins cyclization-pinacol rearrangement pathway for the synthesis of 5-unsubstituted tetrahydrofurans. The Lewis acid catalyzed organic synthesis shown in this example successfully proves the synthesis of hexahydrobenzofuranones to be carried out under mild, stereo-selective conditions. (9)

Figure 4

Synthesis of Cis-Hexahydrobenzofuranones From Derived Trans-1-Alkenylcyclopentane-1,2-Diols



Another interesting method employed Yu et al was to utilize hydrogenation reactions to create multi-substituted cyclohexanes with discrete stereogenic centers. In Yu's lab group esterified 1,3-cyclohexanediones were employed to build polysubstituted cyclohexane skeletons. These esterified 1,3-cyclohexanediones underwent desymmetrization/transesterification cascade reactions when exposed to a chiral ruthenium catalyst and a formic acid/triethylamine solution in ethyl acetate at 25 degrees Celsius for 24 hours in order to afford hexahydrobenzofuranones. (16) Yu et al's method allows for the continuous access to chiral multi-substituted cyclohexane skeletons to be then transformed, in future organic projects, for natural product synthesis.

As seen in some of strategies mentioned before, the creation of hexahydrobenzofuranones is commonly accomplished under the addition of specific Lewis acids, but the mechanistic strategies to achieve these key moieties differs in each research group. Stereo-selective synthesis of hexahydrobenzofuranones was pursued by Herrinton et al through ring enlarging furan annulations. (12) In this synthesis, a variety of substituted cis-fused hexahydrobenzofuranones, octahydrobenzofuranones, and

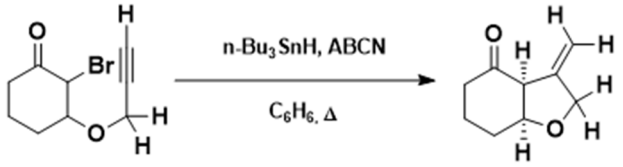
cycloheptanetetrahydrofuranones were established through acid-promoted rearrangement of acetals derived from 1-alkenyl-2-hydroxycyclopentanols as well as 1-alkenyl-2-hydrocyclopentanols. Several Lewis acids were successfully utilized by Herrinton and his colleagues towards this synthesis route including boron trifluoro etherate, tin tetrachloride, ethylaluminum dichloride, and magnesium bromide. It was later discovered that the Lewis acid dimethylaluminum chloride was ineffective for these procedures. While this strategy for creating fused bicyclic moieties was tested with organic rings of only three sizes, Herrinton and his group believe that this can be applied to even larger rings as well as applying this route to the synthesis of pharmaceutically relevant complex cyclic ethers. (12)

Radical reagents are also used to catalyze the synthesis of hexahydrobenzofuranones, such as tri-n-butyltin hydride, which can be employed to induce reductive cleavage, radical dehalogenation, and radical cyclization reaction. (15) This is exemplified by Macdonald and Burnell as they developed a synthetic pathway towards the natural product Pestaloficiol A, using the hexahydrobenzofuranone moiety as a molecular foundation, which was found to have anti-HIV activity. (13) In this section, the synthesis towards the hexahydrobenzofuranone moiety will only be described as the rest of the synthesis pathway towards Pestaloficiol A will be explored in the hexahydrobenzofuranone pharmaceutical application section. As shown in Figure 5, Macdonald and Burnell prepared the hexahydrobenzofuranone precursor for Pestaloficiol A by first reaction propargyl alcohol with cyclohexanone in the presence of NBS and sulfuric acid to give the bromo ether starting material in Figure 5. This was then followed

by inducing radical cyclization of the bromo ether starting material with tri-n-butyltin hydride to give the hexahydrobenzofuranone complex in 88% -92% yield. (14)

Figure 5

Hexahydrobenzofuranone Moiety Within Pestaloficiol A Synthesis



Recent organic studies completed by Xiao's group found that phosphine catalysts can be applied towards dearomative [4+2] cycloadditions in order to create hexahydrobenzofuranone containing moieties. It was found from Xiao's group, after exploring various phosphine catalysts used by other organic research groups, that phosphine catalysts which were substituted by fused bicyclic as well as 3,5-dimethylphenyl substituents showed greater success in producing hexahydrobenzofuranone moieties. In this synthesis strategy, 1-(benzofuran-3-yl) prop-2-en-1-one was reacted with a highly electrophilic 3-olefinic 7-azaoxindole catalyzed by the cyclic phosphine catalyst at 5 degrees Celsius for twelve hours synthesized hexahydrobenzofuranones containing moieties in 88% stereoselective yields. (17) This methodology could prove to be quite economically useful in industry as it creates

principle hexahydrobenzofuranone moieties in a one pot reaction under relatively mild conditions.

Photo-organocatalytic reactions have been a staple strategy employed by organic chemists as they provide simple organic procedures under lenient conditions to create otherwise hard to reach organic scaffolds. The next two synthetic examples will cover two groups that have employed photocatalytic reactions to afford hexahydrobenzofuranone moieties. The first synthetic schematic, applied by Perego's group, explored single-electron transfer (SET) activation of allenes through a light-driven enantioselective organocatalytic process. (18) To begin this process, chiral iminium ions were photocatalytically transformed into their excited state to activate allenes through the SET oxidation. The activated allene cation radicals then participated in stereo-controlled cascade reactions to deliver chiral bicyclic hexahydrobenzofuranone scaffold with good enantioselectivity and diasteroeselectivity. Lewis acids were later employed for Perego's synthetic strategy in order to assist in the formation of the activated chiral iminium ion providing higher yields and full diastereoselective control of the reaction. (19)

While photochemical reactions have proven to be useful tools in the synthesis of complex organic scaffolds such as hexahydrobenzofuranones, the efficiency of these photo-induced reactions are restrained, especially when using batch reactors, by the amount of light that is able to penetrate through the reaction media. (20) To combat this drawback to photochemical, El Achi's group employs the use of a continuous flow system reactor as microfluidic systems have small optical path lengths to ensure more efficient sample irradiation as well as being a simple and cost-effective reaction system. (21) El Achi's group uses the continuous flow system to provide kinetic and optimization

studies on their intramolecular [2+2] photocycloaddition of 3-alkenyloxy-2-cycloalkenones derivates under UV-A irradiation. El Achi's group successfully demonstrated a photo-catalytically sensitized intramolecular [2+2] cycloaddition using the photosensitizer DMBP in a commercial photomicroreactor irradiated by High Power UV-A LEDs forming hexahydrobenzofuranone containing structures in a 2-hour reaction time. (22)

Photo-organocatalyzed cycloadditions reactions are known to undergo free-radical mechanisms but inducing radical cyclization reactions through other catalytic systems can also be a versatile method applied to synthesize polycyclic fused heterocycles which contain similar organic moieties to the hexahydrobenzofuranone scaffolds. The use of radicals allows organic chemists to include high functionality tolerance, within mild reaction conditions, which leads to high levels of regio- and stereoselectivity within the achieved organic products. (23) Namely, reductive radical cyclization has been a prominent organic strategy to afford 6-5 fused bicyclic structures which closely resemble hexahydrobenzofuranones.

In these reductive methodologies, the initial radical is generated via a one-electron transfer agent towards the precursor of the reaction. (24) This method is quite suitable for cyclization reactions as the nucleophilic radicals enabled by this method are not easily reduced. A good example of this reductive radical reaction outlined previously is Molander and Harring's work in which samarium (II) iodide in the organic solvent tetrahydrofuran is mixed with hexamethylphosphoramide at 25 degrees Celsius to transform 1-(allyloxy)-2-iodobenzene into a dihydrobenzofuran complex. In this reductive method, aryl iodides and/or bromides are used as precursors which generate an

aryl radical through single-electron transfer followed by the loss of iodide. The cyclic radical is then reduced to an organometallic intermediate, often involving the metal complex mentioned previously, samarium (II) iodide, for its solubility in organic solvents, high reducing power, and excellent chemo-selectivity. (25) This organometallic intermediate is then able to react with electrophilic molecules completing this radical cyclization reaction and affording hexahydrobenzofuranone structures.

Another radical organic strategy involving the use of samarium (II) iodide is in sequential radical cyclization, specifically where fragmentation of the precursor precedes the cyclization. Sequential reactions are useful in radical reactions as most radical reactions such as fragmentation, cyclization, or addition product a new radical that can serve as a precursor for the second radical reaction to occur. (26) As seen by the reaction schematic below in figure 6, the initial radical is formed by fragmentation of the cyclopropyl ketone in order to then produce chiral radicals through a secondary radical reaction. This reaction is possible as cyclopropanation methods can produce precursors for radical reactions which are optically pure. (27) This same method can also be employed for an oxygen centered radical if epoxide is used in place of the cyclopropane ring, as shown in Figure 6, to design hexahydrobenzofuranone molecular skeletons.

Figure 6

Hexahydrobenzofuranone Synthesis Through Sequential Radical Cyclization

While metal hydride-based reagents are commonplace in initiating radical cyclization reactions, chain transfer agents can also be utilized to conduct fragmentation reactions of cyclic radicals which contain hexahydrobenzofuranone-like moieties.(23) One example of this, completed by Smith et al, generated a sulfone radical through reversible addition to a double bond to initiate radical isomerization reaction. During this reaction, an allylic sulfone was cyclized with benzoyl peroxide and carbon tetrachloride in reflux. The main advantage for this synthetic pathway lies in the fact that there is no competition with side reactions occurring in the direct reduction of the radical acceptor due to the lack of the metal hydride in the reaction. With this lack of reaction competition, slow cyclization reactions can be conducted with less reactive precursors as well as the ability to maintain double bonds within the transformed structure. (28) As seen in the last few synthetic examples, radical cyclization reactions allow for diverse strategies to afford hexahydrobenzofuranones, or structures that are easily transformed into them. As seen through this selection of works to produce hexahydrobenzofuranones, there are many organic strategies that have employed a variety of catalytic systems to

create hexahydrobenzofuranones, but there are still many unexplored organic strategies which can be exploited for innovative and economical reactions that create and use these crucial organic structures.

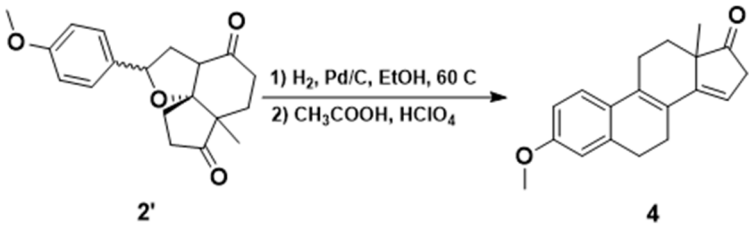
1.2 Pharmaceutical Relevance

One of the major focuses of the Moura-letts lab group is the development of novel organic methods to synthesis small organic molecules that are likely to have biological activity. The creation of new biologically active organic compounds act as the foundation for the entire process of creating new pharmaceuticals. When a scope of organic compounds is first synthesized, which have a high likelihood of being biologically active, it can then be run through a series of biochemical experiments such as biological-activity matrices, high-throughput phenotypic screens, various protein-binding assays to confirm their activity. (3) Once the organic molecules within the new organic scope are vetted through screening for biologically active, they have the chance of being manipulated as scaffolding molecules, building blocks for complex pharmacophores, or even used as a complete pharmacophores, in the pharmaceutical industry and academia, for the development of pharmaceutical agents of the future. Pharmacophores can be characterized as an ensemble of organic moieties and/or functional groups which contain crucial steric and electronic features. These key features are required to ensure optimal organic supramolecular interactions with a specific biological target as well as trigger/block the target's effects. (2) A large family of organic compounds known as fused heterocycles, two adjacent ring structures that share two carbons, are commonly used as privileged pharmacophores. (1) The following section will discuss a range of synthetic methods for the application of hexahydrobenzofuranones, used by organic

chemists in academia and in industry, to develop new pharmaceutical agents as well as the medicinal properties that these pharmaceutical agents hold.

Figure 7

Steroid Synthesis From Hexahydrobenzofuranone Intermediate



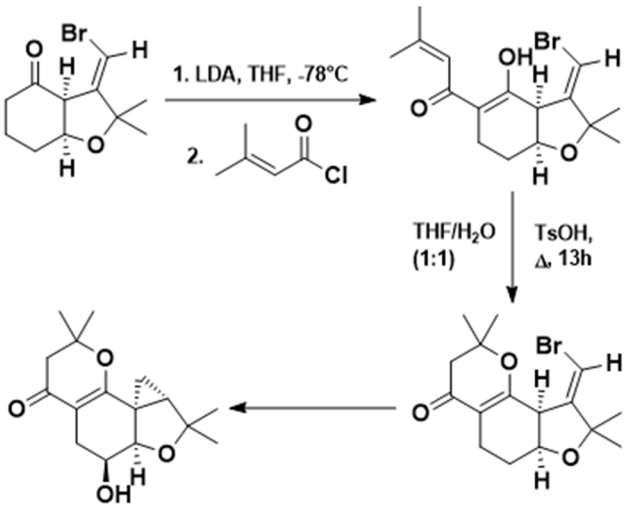
As mentioned previously, hexahydrobenzofuranones are crucial target moieties as they can lead to the novel development of featured organic structures as well as serve as the backbone for new biologically active molecular scaffolds. Daniewski's work on the synthesis route towards hexahydrobenzofuranones, within the total synthesis of aromatic steroids, is a great example of just one of the synthetic applications that hexahydrobenzofuranones can bring. In Figure 7, shown above, it can be seen how once synthesized, the hexahydrobenzofuranone containing structure on the left can undergoes a simple hydrogenation reaction followed by acetic acid and perchloric acid catalyzed cyclization to afford the 6,6,6,5 steroidal backbone. (6) At this point the steroidal backbone can be easily converted in any steroid for use as pharmacological agents or for

further manipulation to create even more complex, biologically active polycyclic structures.

Coming up with novel synthetic strategies for the total synthesis of natural products is a crucial endeavor which is undertaken by many organic chemists. The following examples include natural product synthesis where hexahydrobenzofuranones are used as synthetic precursors to afford natural products. One of the most profound features of hexahydrobenzofuranones are their ability to be transformed into featured natural products. As mentioned in Figure 5, Macdonald and Burnell aimed to use the hexahydrobenzofuranone skeleton in order to complete the natural product synthesis of Pestaloficiol A. Pestaloficiol A is a colorless oil isolated from the plant endophyte *Pestalotiopsis fici* which has shown to be a rich source of bioactive secondary metabolites with diverse structural features. (29) One of the most prominent bioactive metabolites that have been isolated from this plant source thus far is chloropupukeananin, the first chlorinated pupukeanane derivate which possesses anti-HIV-1 properties from its highly functionalized tricyclo-decane skeleton. (30) As seen in Figure 8 above, the hexahydrobenzofuranone skeleton, formed by through a radical cyclization reaction, was acylated by a R, β-unsaturated acid chloride to afford the molecule on the top right of Figure 8. This molecule was then headed in 1:1 THF/water solution with 0.1 equivalences of TsOH to induce cyclization to afford polycyclic structure, in 80 percent yields, which can be then converted through further organic transformations into Pestaloficiol A.

Figure 8

Pestaloficiol A Natural Product Synthesis

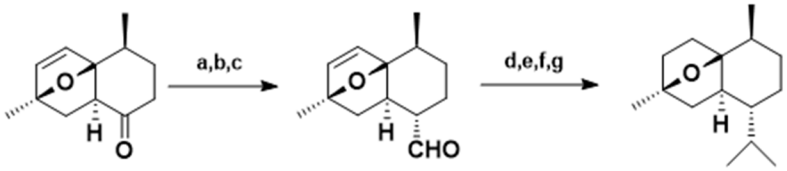


Rogers and Keay have also utilized and studied the effects of hexahydrobenzofuranones as a key intermediate for the synthesis of the natural product 1,4-epoxycadinane. 1,4-epoxycadinane is an important organic target as it is isolated from the brown algae *Dilophus fasciola* and known to have a large variety of biological activity, such as antimicrobial and adhesive properties, which are applicable in pharmacology. (31) The hexahydrobenzofuranone moiety was synthesized via an intramolecular Diels-Alder reaction of the Furan diene (IMDAF) connecting the furan diene to the dienophile which was separated by a four-carbon chain. The furan diene was dissolved in dichloromethane containing florisil and stirred under argon for an allotted amount of time. (32) Once the hexahydrobenzofuranone containing structure was isolated, depicted in Figure 9, it was applied to the synthesis of 1,4-epoxycadinane.

Another application of the hexahydrobenzofuranone skeleton was deployed by Endoma-Arias and Dela Paz in developing derivatives of 10-keto opiates as well as 10-hydroxy-morphinans for use as selective, opioid receptor κ analgesics. (33) Of the three types of opioid receptors, μ, δ, and κ, in the body the κ-opioid receptor has piqued the interest of researchers recently as, when activated, the κ receptor produces analgesia with minimal physical dependence. (34) This means that drugs that come about as highly selective κ-opioid receptor agonists would prove to be useful analgesics as well as free from abusive potential. (35) In order to synthesize key structures such as 10-keto opiates, 10-hydroxy-morphinans, and related morphine alkaloids, a hexahydrobenzofuranone containing lactam intermediate was planned to reach these molecular skeletons more easily.

Figure 9

Natural Product Synthesis of 1,4-Epoxycadinane



a) H_2, Pd/C, EtOAc b) Ph_3P=CHOMe, THF c) 10% HCl:THF (1:1)
d) MeLi, THF, -78°C e) Swem [O] f)Ph_3P=CH_2, THF g) H_2, PtO_2, EtOH

In another application of hexahydrobenzofuranones for useful synthetic transformations, Yu's group have synthesized a hexahydrobenzofuranone-containing,

fused 6,3,5-tricyclic intermediate in order to afford the antibiotic mycorrhizin A. Mycorrhizin A was first isolated and characterized by Wickberg and Trofast in 1977 from a sterile mycelium of an endomycorrhizinal fungus. (36) This target compound possesses a variety of biological activities which could be employed in antifungal and antibiotic pharmaceutical agents. (37) Previous efforts towards the synthesis of the basic angularly fused 6,3,5-tricyclic skeleton has been limited to date as only two elegant strategies have been reported for such tricyclic ring systems. The first synthetic approach was revealed by Smith's group, in which an intramolecular SN2 reaction was utilized for construction of the cyclopropane ring of the tricyclic system, and the second was introduced Brown and co-workers reporting the synthesis of these structures through cycloaddition of diazomethane and an olefin followed by extrusion, through ultraviolet irradiation, of the nitrogen from the reaction, leading to the formation of the cyclopropane ring of the tricyclic system. (38) (39) Yu and colleagues provided a new method to afford this 6,3,5-tricyclic structure through intramolecular cyclization of a π-nucleophile with an epoxide-containing adduct. Yu and his co-worker's reaction proceed via an initial attack of the double bond on the epoxide ring leading to a cyclopropylcarbinyl cation intermediate. The intermediate formed, however, is to be considered as a nonclassical or delocalized cation that is unstable without the correct substituents at the appropriate positions. If these substituents were not in place, ring-opening and rearrangement procedures would be induced on the intermediate. Among the Lewis acids employed by Yu to catalyze this reaction, BF_3OET_2 and CF_3SO_3H, in acetonitrile at room temperature for 3-5 minutes, were found to promote the 3-exo cyclization of the allylic epoxide to give the desired fused 6,3,5-tricyclic product in the

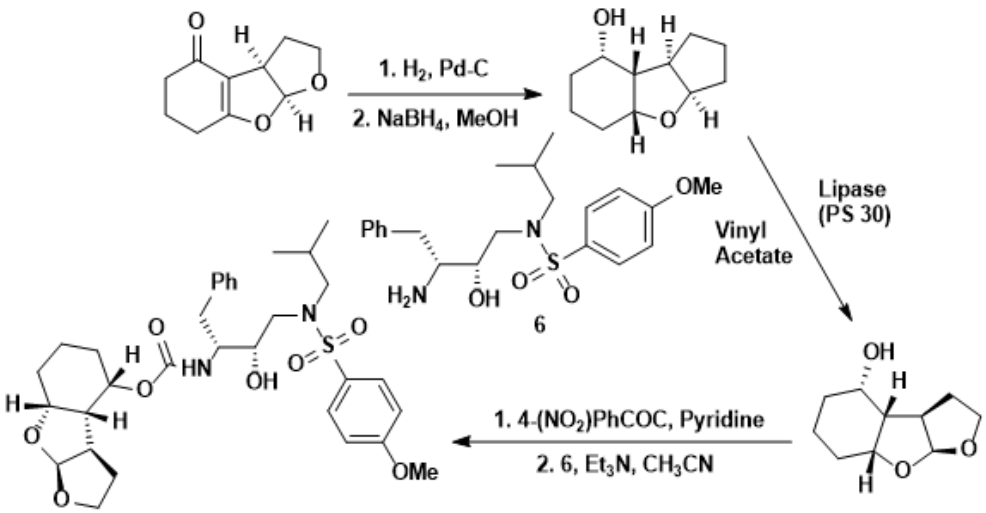
best yields. (40) With the formation of this tricyclic, hexahydrobenzofuranone-containing intermediate, the subsequent transformations are easily performed to afford the biologically active Mycorrhizin A molecule.

One final example of the application of the hexahydrobenzofuranone moiety can be seen by the work of Ghosh and co-workers in their synthesis of a series of HIV-1 protease inhibitors which incorporate, hexahydrobenzofuranone-containing, fused tricyclic P2 ligands. While HIV-1 protease inhibitors have always been a staple among antiretroviral drug therapies, the rapid advancement of drug-resistance had interrupted the clinical benefits that HIV-1 protease inhibitors can bring. (41) To combat this issue, Ghosh and co-workers focused their inhibitory design on maximizing the active sit interactions with protease by promoting substantial hydrogen-bonding interactions with the backbone atoms throughout the active site. (42) Through the development of Ghosh's HIV-1 protease inhibitors from structure-based design targeting the protein backbone, it was found that the syn-anti-syn-fused tricyclic P2 ligand moiety within the HIV-1 protease inhibitor was responsible for enhanced broad-range potency as well as effectiveness against a range of multidrug-resistant HIV-1 variants. (43) (44) The synthesis of these tricyclic P2 ligand derivatives and subsequent HIV-1 protease inhibitor, depicted in Figure 10, shows the hexahydrobenzofuranone-containing enone exposed to hydrogenation over 10% Pd-C in MeOH at 65 psi hydrogen pressure to afford the resulting ketone. The reduction of the ketone with $NaBH_4$ in MeOH followed resulting in the endo alcohol formation shown in the bottom right of Figure 10. The ligand alcohol was then reacted with *para*-nitrophenyl chloroformate and pyridine in dichloromethane to provide mixed carbonates. The mixed carbonates were then

transformed into the subsequent HIV-1 protease inhibitors by exposing them to the optically active amine, labeled as molecule 6 in Figure 10, in the presence of triethyl amine in acetonitrile. (45) The synthesized protease inhibitor derivatives were then evaluated in antiviral assays to access their antiviral and enzymatic potencies. The protease inhibitor at the bottom left of Figure 10 showed impressive antiviral and enzymatic properties having an IC_{50} of 1.9nM. The IC_{50} values for each protease inhibitor were determined via an MTT assay which assesses cell metabolic activity through exposing tetrazolium dye MTT, usually yellow in color, to be reduced to its insoluble formazan, qualitatively indicated by a yellow to purple color change. The protease inhibitors developed by Ghosh and co-workers proved to maintain activity against a panel of multidrug resistant HIV-1 variants along with giving insights into the ligand-binding site interactions through X-ray crystal structures. As shown through the examples in this section, hexahydrobenzofuranones are crucial organic structures as they are available for a wide variety of organic applications and transformations, affording truly powerful pharmaceutical agents. For this reason, it is imperative to continue to develop mild, easy-to-reproduce, and economical organic conditions to afford these key structures for the construction of pharmacophores, natural products, and thus pharmaceutical agents of the future.

Figure 10

Tricyclic P2 Ligand HIV-1 Protease Inhibitor Synthesis



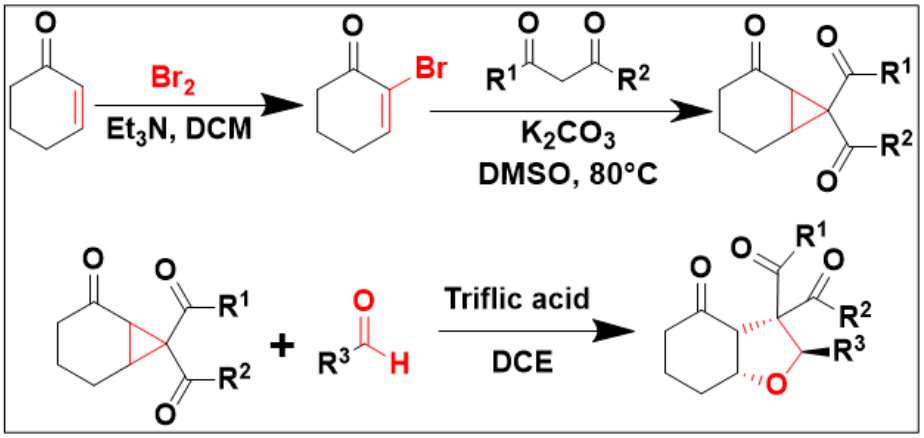
1.3 Method Discovery

As there are many instances of the hexahydrobenzofuranone moiety featured within key natural products and biologically active molecules, utilized in the development of new pharmacophores, there is a continuous need for new synthetic strategies to be developed to gain access these organic structures. To afford these crucial structures within mild reaction procedures, the GML lab group proposed a hexahydrobenzofuranone reaction hypothesis depicted in Table 1. The GML hexahydrobenzofuranone reaction hypothesis begins with the bromination of commercially bought cyclohex-2-ene-1-one in the presence of triethylamine in the organic solvent dichloromethane. A subsequent Michael-initiated cyclopropanation

reaction was conducted on the constructed 2-bromocyclohex-2-ene-1-one to afford the oxobicyclo [4.1.0] heptane-7,7-dicarboxylate moiety. (54) Finally, a Lewis acid catalyzed [3+2] cycloaddition reaction between benzaldehyde derivatives and the previously established oxobicyclo [4.1.0] heptane-7,7-dicarboxylates to generate the hexahydrobenzofuranone moiety. (55)

Table 1

Synthesis of Hexahydrobenzofuranone Reaction Hypothesis



1.4 Results and Discussion

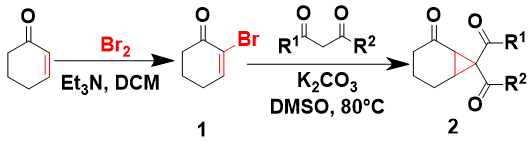
As this combination of reaction procedures and organic complexes have never been explored previously, optimization studies on this synthetic route are necessary in order to ensure that the oxobicyclo [4.1.0] heptane-7,7-dicarboxylate products, and subsequent synthesis of hexahydrobenzofuranones products, are constructed in the highest yielding,

stereo- and regioselective manners. As seen in Table 2, optimization studies for the synthesis of oxobicyclo [4.1.0] heptane-7,7-dicarboxylates began with changing the organic solvent the reaction was run in to see which would afford the highest yields. As dimethyl sulfoxide, DMSO, was proven to be the best choice for this reaction the reaction concentration was then tested to optimize the appropriate amount of reaction collisions within the organic solvent media. DMSO at a reaction molarity of 0.1M provided the best conversion rate in this case which was confirmed by chromatographic methods such as TLC as well as by proton and carbon NMR spectra analysis. Finally, it was important to find the highest yielding malonic acid derivative, which acted as the Michael donor in the cyclopropanation reaction, in order to accurately access the subsequent benzaldehyde scope within the [3+2] cycloaddition to afford the hexahydrobenzofuranone moiety. The optimized reaction conditions for the cyclopropanation step of the synthesis of hexahydrobenzofuranones used ethyl 3-oxoheptanoate as the malonic acid Michael donor, 0.1M DMSO organic solvent to promote higher yields, potassium carbonate to promote trans-stereochemistry in the cyclopropanation product, inert reaction conditions under elemental nitrogen gas, heating the reaction to eighty degrees Celsius on a hotplate, and stirred for twenty-four hours which produced oxobicyclo [4.1.0] heptane-7,7-dicarboxylates in 85% isolated yields. The reaction work-up, as well as the purification. of these oxobicyclo [4.1.0] heptane-7,7-dicarboxylates was especially troublesome as DMSO is an extremely polar solvent which made it very difficult to dry the reaction in preparation for flash chromatography. A secondary issue encountered in this step of the reaction was the crude TLC of each oxobicyclo [4.1.0] heptane-7,7-dicarboxylate had four to five spots on each TLC plate of very similar Rf values, making the following flash

chromatographic procedures exceedingly difficult. The reaction scope for the synthesis of oxobicyclo [4.1.0] heptane-7,7-dicarboxylates can be seen in Table 5.

Table 2

Synthesis of Oxobicyclo [4.1.0] Heptane-7,7-Dicarboxylates Optimization Studies



Entry[a]	R^1	R^2	solvent	concentration (M)	yield (%)[b]
1	OEt	*OEt*	toluene	0.1	44
2	OEt	$(CH_2)_3CH_3$	toluene	0.1	64
3	OEt	$(CH_2)_3CH_3$	CH_3CN	0.1	70
4	OEt	$(CH_2)_3CH_3$	DMSO	0.1	85
5	OEt	$(CH_2)_3CH_3$	DMSO	0.025	60
6	OEt	$(CH_2)_3CH_3$	DMSO	0.05	71
7	OEt	$(CH_2)_3CH_3$	DMSO	0.075	63
8	OEt	$(CH_2)_3CH_3$	DMSO	0.01	55
9	OEt	CH_3Cl	DMSO	0.025	45
10	OEt	CF_3	DMSO	0.05	55

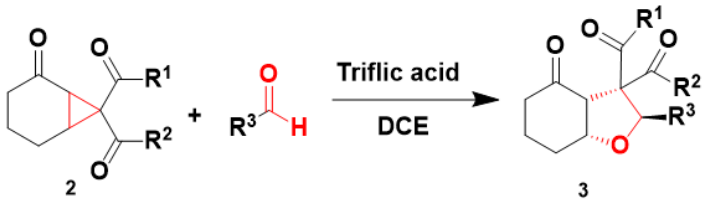
a. Spun on hotplate at 80C for 24 h. *b*. Isolated yields.

Following the optimization of the synthesis of oxobicyclo [4.1.0] heptane-7,7-dicarboxylates and the production of the oxobicyclo [4.1.0] heptane-7,7-dicarboxylate reaction scope, the optimization of the final step of the synthesis of hexahydrobenzofuranones was began by using the ethyl 2-oxo-7-pentanoyl bicyclo [4.1.0] heptane-7-carboxylate as the oxobicyclo [4.1.0] heptane-7,7-dicarboxylates precursor for the Lewis acid catalyzed [3+2] cycloaddition reaction. For this reaction step, dichloromethane and dichloroethane were used as organic solvents with a variety of

reaction concentrations to access the best yielding reaction. It was found that dichloroethane with a solvent concentration of 0.1M, using the 4-pyridine carboxaldehyde afforded the best yield to produce the hexahydrobenzofuranone moiety. The mechanism for the final step of the synthesis of hexahydrobenzofuranones is thought to occur via a Lewis acid induced dipole along the carbonyl of the benzaldehyde derivative, causing the benzaldehyde to act as nucleophile, inducing an inversion of stereochemistry at the C2 carbon of the cyclopropane ring of the ethyl 2-oxo-7-pentanoyl bicyclo [4.1.0] heptane-7-carboxylate structure. This inversion of stereochemistry of the C2 carbon opens the cyclopropane ring in the ethyl 2-oxo-7-pentanoyl bicyclo [4.1.0] heptane-7-carboxylate structure allowing for the [3+2] cycloaddition to then occur. Challenges were met with the purification of the hexahydrobenzofuranones as diastereomeric forms of hexahydrobenzofuranones were produced from the reaction having Rf values, by crude TLC, that were almost identical. Table 6 shows the afforded reaction scope of the hexahydrobenzofuranones produced.

Table 3

Synthesis of Hexahydrobenzofuranone Optimization Studies



2 3

Entry[a]	R^1	R^2	R^3	solvent	concentration (M)	yield (%)[b]
1	OEt	$(CH_2)_3CH_3$	4-Pyridine	DCM	0.1	55
2	OEt	$(CH_2)_3CH_3$	4-Pyridine	DCM	0.05	40
3	OEt	$(CH_2)_3CH_3$	4-Pyridine	DCM	0.075	41
4	OEt	$(CH_2)_3CH_3$	4-Pyridine	DCM	0.025	36
5	OEt	$(CH_2)_3CH_3$	Ph	DCM	0.1	60
6	OEt	$(CH_2)_3CH_3$	4-Pyridine	DCE	0.1	65
7	OEt	$(CH_2)_3CH_3$	Furan	DCE	0.1	25
8	OEt	$(CH_2)_3CH_3$	para- PhBr	DCE	0.1	55

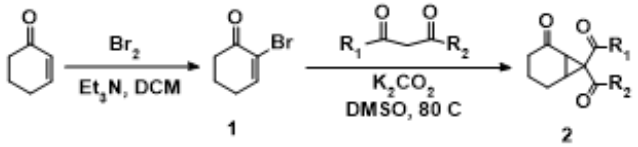
a. Spun on hotplate at rt for 24 h. *b*. Isolated yields.

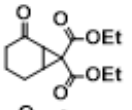
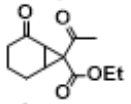
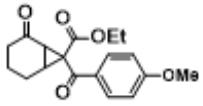
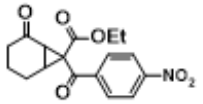
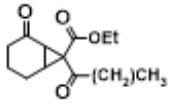
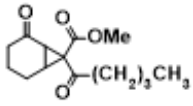
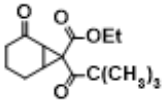
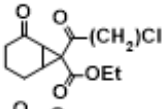
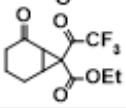
While the novel synthesis of hexahydrobenzofuranones has been afforded by the GML lab group, there are still other complimentary synthetic routes to be explored, through future organic synthetic endeavors, to afford fused bicyclic organic constructs from the oxobicyclo [4.1.0] heptane-7,7-dicarboxylate derivatives generated in the GML novel synthetic strategy. As seen in Table 6, nitrones, diaziridines, cyclic alkynes, imines, oxaziridines, isocyanates, and nitriles can be used in place of the benzaldehyde derivatives to form these bridged heterocycles through novel synthetic strategies. With this collection of fused bicyclic structures, a multitude of transformations can be tested in

order to form crucial pharmacophores, which are likely to have biologically active, through mild, novel reaction conditions.

Table 4

Synthesis of Oxobicyclo [4.1.0] Heptane-7,7-Dicarboxylates Reaction Scope

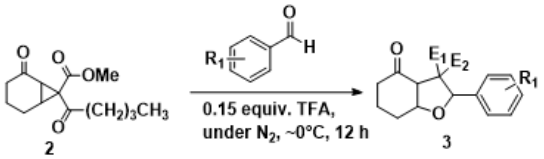


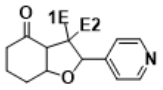
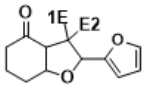
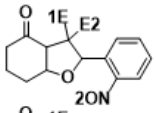
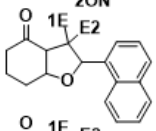
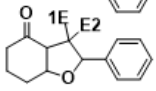
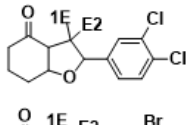
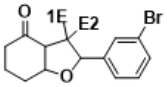
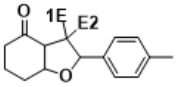
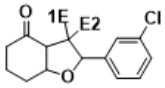
Entry		Substituted Cyclopropane Products	Yield (%)[a,b,c]
JDH-83	2a		88
JDH-81	2b		84
JDH-11	2c		86
JDH-91	2d		60
JDH-45	2e		80
JDH-103	2f		90
JDH-92	2g		80
JDH-46	2h		71
JDH-90	2i		74

a. Conditions:2-bromocyclohex-2-en-1-one (0.57 mmol), Methyl-3-oxoheptanoate (0.685 mmol), Potassiumcarbonate (1.713 mmol) in DMSO(0.1M) under N_2 for 24 hrs.
b. Isolated yields. c. Reaction crude was purified by standard silica gel chromatography.

Table 5

Synthesis of Hexahydrobenzofuranones Reaction Scope

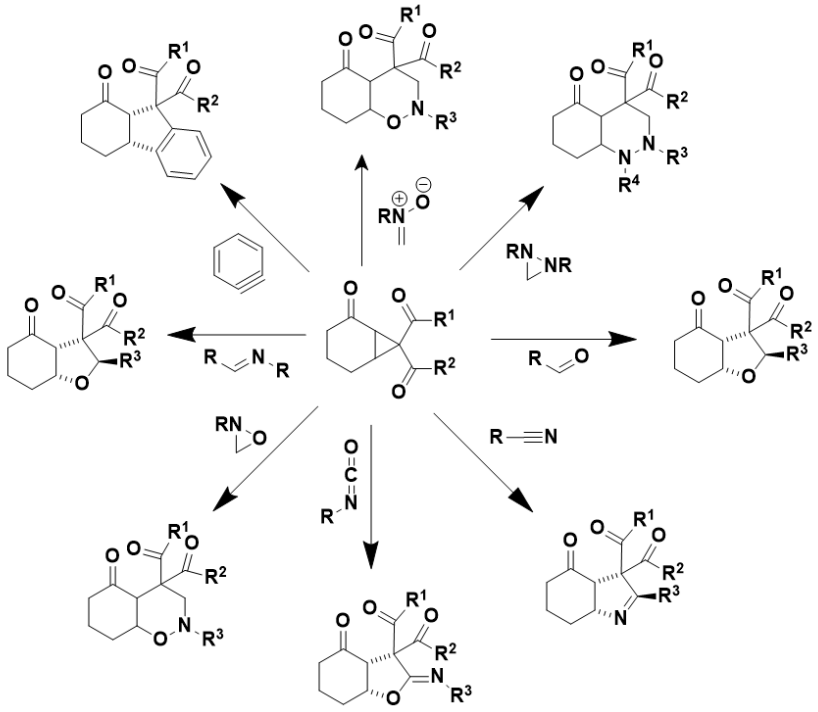


Entry	Benzaldehydes	Hexahydrobenzofuranone Derivatives	Yield (%)[a,b,c]
JDH-78	3a		80
JDH-59	3b		84
JDH-99	3c		65
JDH-65	3d		75
JDH-56	3e		75
JDH-95	3f		75
JDH-64	3g		65
JDH-63	3h		71
JDH-61	3i		74

a. Conditions:Methyl 2-oxo-7-pentanoylbicyclo[4.1.0]heptane-7-carboxylate(0.22 mmol), 4-pyridine carboxyaldehyde (0.15 mmol), and Triflic Acid (0.015 mmol) in 0.1M DCM ~0°C, under N2, reacted for 48 hours. b. Semi-isolated crude yields. c. Reaction crude was purified by silica gel flash chromatography.

Table 6

Future Endeavors for Synthesis of Fused Heterocyclic Complexes



1.5 Conclusion

Using the optimized novel synthetic conditions developed by the GML lab group, a diastereoselective, efficient, and convergent approach towards the selective synthesis of fused-cyclic hexahydrobenzofuranones from oxobicyclo [4.1.0] heptane-7,7-dicarboxylates and aldehydes have been developed under mild Lewis acid reaction conditions. The novel synthesis of hexahydrobenzofuranones has shown to occur under a wide variety of substitution patterns along with producing complex organic products in

high yields. This reaction provides competent access to highly functionalized heterocyclic structures from simple-to-synthesize scaffolds allowing for future synthetic approaches towards more complex heterocyclic pharmacophores. A large variety of derivative synthetic routes have also begun development, using this novel synthesis for foundational knowledge, to apply these synthetic strategies towards the creation of a wide variety of fused-cyclic complexes.

1.6 Experimental

Organic reagents were obtained from Aldrich Chemical, Acros Organics, and Alfa Aesar. Organic reactions were performed with 20 milliliter glass vials that allowed for magnetic stirring. TLC analysis was performed via a 0.25mm E. Merck silica gel 60 F254 plates and visualized under 254 nm UV light as well as staining with potassium permanganate solution ($KMnO_4$). Products were purified via manual silica-gel flash chromatography and collected based on NMR analysis and Rf values of UV spots by TLC. NMR spectrum were recorded via Varian Mercury II 400 MHz Spectrometer at 24 degrees Celsius in CDCl. Chemical shifts are expressed in ppm relative to solvent signals: CDCl, (1 H, 7.23 ppm; 13C, 77.0ppm; coupling constants expressed in Hz)

1.6.1 General Method for Synthesis of Oxobicyclo [4.1.0] Heptane-7,7-Dicarboxylates

The procedures for the first step in the synthesis of the functionalized hexahydrobenzofuran-4(2H)-one products is bromination of commercially bought cyclohexa-2-en-1-one into 2-bromocyclohex-2-en-1-one. To set up this first step bromination reaction, the solvent dichloromethane (DCM) was added into a round bottom to stir in an ice bath; enough DCM was added to achieve a reaction concentration of 0.1M. Once the solvent was cooled to zero degrees Celsius, 1.1 equivalence of elemental

bromine (Br_2) was added dropwise followed by dropwise addition of 1.1 equivalence triethylamine. The reaction was left to stir overnight for workup the following day. The reaction was worked up via liquid/liquid extraction with a polar solvent, such as ethyl acetate, and the organic layer was then collected. The organic layer was washed with saturated sodium bicarbonate solution, water, and finally brine. The organic layer was then dried with sodium sulfate followed by gravity filtration, drying of solvent via rotatory evaporation, and finally analysis/confirmation of product of first step product via proton/carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS). Once 2-bromocyclohex-2-en-1-one was confirmed via analysis, the set up for the second step of the synthesis of functionalized hexahydrobenzofuran-4(2H)-one was begun.

The procedures for the second step of the synthesis of functionalized hexahydrobenzofuran-4(2H)-ones aimed to transform pure, crystalized 2-bromocyclohex-2-en-1-one into 1,1'-(2-oxobicyclo[4.1.0]heptane-7,7-diyl)bis(ethan-1-one), which is depicted on the top right of the substrate synthesis schematic in figure 2. Pure, crystalized 2-bromocyclohex-2en-1-one was weighed to the reaction scale and added into the organic solvent dimethyl sulfoxide, (DMSO), to create a reaction concentration of 0.1M. Two equivalences of potassium carbonate were then added into the reaction vial and a rubber stopper was secured to the top of the 20 mL reaction vial via parafilm. The reaction vial was then made inert with elemental nitrogen gas (N_2) and the nitrogen gas was continuous run through the reaction vial while the pentane-2,4-dione was syringed into the stirring reaction. The reaction stirred overnight at 80º Celsius for workup the following day.

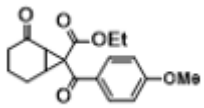
The reaction was taken off the heat and allowed to cool to room temperature followed by gravity filtration. Liquid-liquid extraction was performed on the resulting product solution with 3:1 ratio of ethyl acetate (EtoAc) to di methyl sulfoxide (DMSO) reaction solution and the ethyl acetate layer was collected. The ethyl acetate organic layer was washed with water twice and dried with sodium sulfate followed by gravity filtration. The crude product organic solution was rotatory evaporated down and the resulting crude oil was characterized/confirmed by proton and carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS). Once the crude product was confirmed, manual, silica-based, flash column chromatography was performed to isolate the pure second step product shown in the top right of figure 2. The pure second step product was characterized/confirmed via proton/carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS). Once the creation of one of the 1,1'-(2-oxobicyclo [4.1.0] heptane-7,7-diyl) bis(ethan-1-one) products were confirmed, the third and final step of the synthesis of functionalized hexahydrobenzofuran-4(2H)-ones were set up.

1.6.2 General Method for the Synthesis of Hexahydrofuranones

Each pure 1,1'-(2-oxobicyclo [4.1.0] heptane-7,7-diyl) bis(ethan-1-one) product, of the second step of the functionalized hexahydrobenzofuran-4(2H)-ones synthesis, was added to a stock solution of the solvent dichloroethane (DCE) under elemental nitrogen gas. Inert dichloroethane was poured into a clean 250 mL round bottom under argon gas, via an inert solvent dispenser, and a rubber stopper was placed to cap the round bottom. Elemental nitrogen gas was set to flow throw the round bottom and out of a syringe vent in the rubber stopper. The scaled number of milliliters of pure 1,1'-(2-oxobicyclo [4.1.0] heptane-7,7-diyl) bis(ethan-1-one) product dichloroethane stock solution was added into

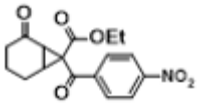
the 250-milliliter round bottom while the elemental nitrogen gas was running through the round bottom. The aldehyde was then syringed into the 250-milliliter round bottom while the nitrogen gas was still running and finally the triflic acid was diluted to 10 mol % stock solution of dry dichloroethane under argon and was then carefully syringed into the 250 mL reaction round bottom. Positive pressure was added to the round bottom by removing the vent syringe and then the nitrogen gas syringe a few seconds later. The reaction was run overnight. Once the crude product was confirmed, manual, silica-based, flash column chromatography was performed to isolate the pure final step product shown in Figure 2. The pure final step of the synthesis of hexahydrobenzofuran-4(2H)-ones was characterized/confirmed via proton/carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS).

1.6.3 Synthesis of Hexahydrobenzofuranones From Table 4 & 5



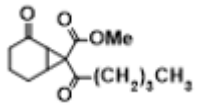
JDH-11-2c

Ethyl 7-(4-methylbenzoyl)-2-oxobicyclo[4.1.0]heptane-7-carboxylate (2c): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 1:1 heptanes/EtOAc) afforded the oxobicyclo [4.1.0] heptane-7,7-dicarboxylates product **2c (**86% yield) as an amber oil. **^{1}H NMR:** (400 MHz, Chloroform-*d*) δ 1.28 (3H, t, *J* = 7.1 Hz), 1.66-1.95 (5H, 1.74 (dtdd, *J* = 13.4, 10.2, 2.9, 2.3 Hz), 1.76 (dddd, *J* = 13.1, 7.9, 2.9, 2.6 Hz), 1.77 (dddd, *J* = 13.1, 10.2, 3.2, 2.8 Hz), 1.82 (ddd, *J* = 8.1, 7.9, 2.8 Hz), 1.87 (ddddd, *J* = 13.4, 3.3, 3.2, 2.6, 2.2 Hz)), 2.18 (1H, d, *J* = 8.1 Hz), 2.32-2.58 (2H, 2.39 (ddd, *J* = 14.6, 3.3, 2.3 Hz), 2.50 (ddd, *J* = 14.6, 10.2, 2.2 Hz)), 3.79 (3H, s), 4.09-4.20 (2H, 4.14 (q, *J* = 7.1 Hz), 4.14 (q, *J* = 7.1 Hz)), 7.08 (2H, ddd, *J* = 8.3, 1.2, 0.4 Hz), 8.02 (2H, ddd, *J* = 8.3, 1.8, 0.4 Hz).



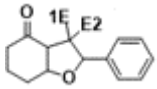
JDH-91-2d

Ethyl 7-(4-nitrobenzoyl)-2-oxobicyclo[4.1.0]heptane-7-carboxylate (2d): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 1:1 heptanes /EtOAc) afforded the oxobicyclo [4.1.0] heptane-7,7-dicarboxylates product **2d (**60% yield) as an amber oil. **^{1}H NMR:** (400 MHz, Chloroform-*d*) ^{1}H NMR: δ 1.28 (3H, t, *J* = 7.1 Hz), 1.66-1.95 (5H, 1.74 (dtdd, *J* = 13.4, 10.2, 2.9, 2.3 Hz), 1.76 (dddd, *J* = 13.1, 7.9, 2.9, 2.6 Hz), 1.77 (dddd, *J* = 13.1, 10.2, 3.2, 2.8 Hz), 1.82 (ddd, *J* = 8.1, 7.9, 2.8 Hz), 1.87 (ddddd, *J* = 13.4, 3.3, 3.2, 2.6, 2.2 Hz)), 2.20 (1H, d, *J* = 8.1 Hz), 2.32-2.58 (2H, 2.39 (ddd, *J* = 14.6, 3.3, 2.3 Hz), 2.50 (ddd, *J* = 14.6, 10.2, 2.2 Hz)), 4.09-4.20 (2H, 4.14 (q, *J* = 7.1 Hz), 4.14 (q, *J* = 7.1 Hz)), 7.80 (2H, ddd, *J* = 8.6, 1.5, 0.5 Hz), 8.17 (2H, ddd, *J* = 8.6, 1.8, 0.5 Hz).



JDH-103-2f

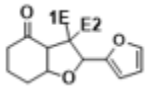
Ethyl 2-oxo-7-pentanoylbicyclo[4.1.0]heptane-7-carboxylate (2f): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 1:1 heptanes/EtOAc) afforded the oxobicyclo [4.1.0] heptane-7,7-dicarboxylates product **2f** (90% yield) as an amber oil. **^{1}H NMR:** (400 MHz, Chloroform-*d*) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.21-1.37 (5H, 1.28 (tq, *J* = 7.0, 6.5 Hz), 1.28 (tq, *J* = 7.0, 6.5 Hz), 1.31 (t, *J* = 7.1 Hz)), 1.47-1.61 (2H, 1.54 (tt, *J* = 7.4, 7.0 Hz), 1.54 (tt, *J* = 7.4, 7.0 Hz)), 1.65-1.95 (5H, 1.74 (dddd, *J* = 13.0, 7.9, 2.9, 2.6 Hz), 1.74 (dtdd, *J* = 13.4, 10.2, 2.9, 2.3 Hz), 1.78 (dddd, *J* = 13.0, 10.2, 3.2, 2.8 Hz), 1.81 (ddd, *J* = 8.1, 7.9, 2.8 Hz), 1.87 (ddddd, *J* = 13.4, 3.3, 3.2, 2.6, 2.2 Hz)), 2.19 (1H, d, *J* = 8.1 Hz), 2.32-2.58 (4H, 2.40 (ddd, *J* = 14.6, 3.3, 2.3 Hz), 2.49 (ddd, *J* = 14.6, 10.2, 2.2 Hz), 2.52 (t, *J* = 7.4 Hz), 2.52 (t, *J* = 7.4 Hz)), 4.08-4.20 (2H, 4.14 (q, *J* = 7.1 Hz), 4.14 (q, *J* = 7.1 Hz)).



JDH-78-3a

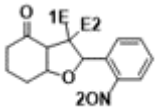
2-pyridine-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3a): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product **3a (**80% yield) as an amber oil. **^{1}H NMR:** (400 MHz, Chloroform-*d*) δ 0.88 (3H, t, *J* = 6.5 Hz), 1.23-1.34 (2H, 1.28 (h, *J* = 6.5 Hz), 1.28 (h, *J* = 6.5 Hz)), 1.46-1.75 (4H, 1.52 (tt, *J* = 7.4, 6.5 Hz), 1.52 (tt, *J* = 7.4, 6.5 Hz), 1.62 (dtdd, *J* = 13.1, 10.2, 3.1, 2.4 Hz), 1.68 (dddt, *J* = 13.1, 3.2, 3.1, 2.5 Hz)), 1.79-2.03 (2H, 1.88 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz),

1.96 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.38-2.57 (4H, 2.46 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.48 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.51 (t, *J* = 7.4 Hz), 2.51 (t, *J* = 7.4 Hz)), 3.49 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.22 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.75 (1H, s), 7.17 (2H, ddd, *J* = 4.8, 1.5, 0.5 Hz), 8.56 (2H, ddd, *J* = 4.8, 1.9, 0.5 Hz).



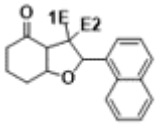
JDH-59-3b

2-furan-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3b): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product **3b (**84% yield) as an amber oil. **^{1}H NMR:** δ 0.88 (3H, t, *J* = 6.5 Hz), 1.22-1.35 (2H, 1.28 (tq, *J* = 6.6, 6.5 Hz), 1.28 (tq, *J* = 6.6, 6.5 Hz)), 1.46-1.75 (4H, 1.52 (tt, *J* = 7.4, 6.6 Hz), 1.52 (tt, *J* = 7.4, 6.6 Hz), 1.62 (dtdd, *J* = 13.1, 10.2, 3.1, 2.4 Hz), 1.67 (dddt, *J* = 13.1, 3.2, 3.1, 2.5 Hz)), 1.79-2.03 (2H, 1.88 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz), 1.95 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.38-2.57 (4H, 2.45 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.48 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.51 (t, *J* = 7.4 Hz), 2.51 (t, *J* = 7.4 Hz)), 3.62 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.19 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.23 (1H, s), 6.18-6.33 (2H, 6.23 (dd, *J* = 3.4, 1.1 Hz), 6.27 (dd, *J* = 3.4, 1.8 Hz)), 7.40 (1H, dd, *J* = 1.8, 1.1 Hz).



JDH-99-3c

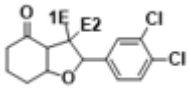
2-(1-nitrobenzene)-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3c): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product **3c (**65% yield) as an amber oil. **^{1}H NMR:** δ 0.88 (3H, t, *J* = 6.5 Hz), 1.23-1.34 (2H, 1.28 (h, *J* = 6.5 Hz), 1.28 (h, *J* = 6.5 Hz)), 1.46-1.75 (4H, 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.62 (dtdd, *J* = 13.1, 10.2, 3.1, 2.4 Hz), 1.68 (dddt, *J* = 13.1, 3.2, 3.1, 2.5 Hz)), 1.79-2.04 (2H, 1.88 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz), 1.96 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.38-2.57 (4H, 2.46 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.48 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.51 (t, *J* = 7.4 Hz), 2.51 (t, *J* = 7.4 Hz)), 3.51 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.11 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.74 (1H, s), 7.55 (1H, ddd, *J* = 8.3, 7.7, 1.7 Hz), 7.67-7.87 (2H, 7.73 (td, *J* = 7.7, 1.7 Hz), 7.81 (ddd, *J* = 7.6, 1.7, 0.5 Hz)), 8.09 (1H, ddd, *J* = 8.3, 1.7, 0.5 Hz).



JDH-65-3d

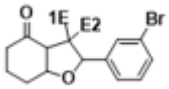
3-napthalene-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3d): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product

3d (75% yield) as an amber oil. **^{1}H NMR:** δ 0.88 (3H, t, *J* = 6.5 Hz), 1.23-1.34 (2H, 1.29 (h, *J* = 6.5 Hz), 1.29 (h, *J* = 6.5 Hz)), 1.46-1.75 (4H, 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.61 (dtdd, *J* = 13.0, 10.2, 3.1, 2.4 Hz), 1.68 (dddt, *J* = 13.0, 3.2, 3.1, 2.5 Hz)), 1.76-2.08 (2H, 1.85 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz), 2.00 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.39-2.61 (4H, 2.47 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.52 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.51 (t, *J* = 7.4 Hz), 2.51 (t, *J* = 7.4 Hz)), 3.54 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.15 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.38 (1H, s), 7.37 (1H, dddd, *J* = 8.0, 6.9, 1.8, 0.5 Hz), 7.44-7.69 (3H, 7.51 (ddd, *J* = 9.7, 8.0, 0.5 Hz), 7.59 (ddd, *J* = 8.5, 6.9, 1.7 Hz), 7.62 (ddd, *J* = 9.7, 1.8, 0.5 Hz)), 7.85-8.05 (3H, 7.91 (dddt, *J* = 8.0, 2.6, 1.8, 0.5 Hz), 7.93 (dddt, *J* = 8.0, 2.6, 1.7, 0.5 Hz), 7.98 (ddq, *J* = 8.5, 1.8, 0.5 Hz)).



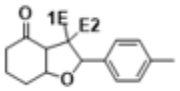
JDH-95-3f

3-(3,4 dichlorobenzene)-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3f): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product **3f (**75% yield) as an amber oil. **^{1}H NMR:** δ 0.88 (3H, t, *J* = 6.5 Hz), 1.23-1.34 (2H, 1.28 (h, *J* = 6.5 Hz), 1.28 (h, *J* = 6.5 Hz)), 1.46-1.75 (4H, 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.62 (dtdd, *J* = 13.1, 10.2, 3.1, 2.4 Hz), 1.68 (dddt, *J* = 13.1, 3.2, 3.1, 2.5 Hz)), 1.79-2.04 (2H, 1.88 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz), 1.96 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.38-2.57 (4H, 2.46 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.48 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.50 (t, *J* = 7.4 Hz), 2.50 (t, *J* = 7.4 Hz)), 3.50 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.11 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.33 (1H, s), 7.32 (1H, dd, *J* = 8.3, 1.9 Hz), 7.49-7.71 (2H, 7.55 (dd, *J* = 8.3, 0.5 Hz), 7.66 (dd, *J* = 1.9, 0.5 Hz)).



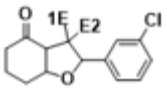
JDH-64-3g

3-(2-bromobenzene)-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3g): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product **3g (**65% yield) as an amber oil. **^{1}H NMR:** δ 0.88 (3H, t, *J* = 6.5 Hz), 1.23-1.34 (2H, 1.28 (h, *J* = 6.5 Hz), 1.28 (h, *J* = 6.5 Hz)), 1.46-1.75 (4H, 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.62 (dtdd, *J* = 13.1, 10.2, 3.1, 2.4 Hz), 1.68 (dddt, *J* = 13.1, 3.2, 3.1, 2.5 Hz)), 1.79-2.04 (2H, 1.88 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz), 1.96 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.38-2.57 (4H, 2.46 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.48 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.51 (t, *J* = 7.4 Hz), 2.51 (t, *J* = 7.4 Hz)), 3.50 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.11 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.31 (1H, s), 6.95 (1H, ddd, *J* = 8.0, 1.7, 1.2 Hz), 7.24-7.42 (2H, 7.30 (ddd, *J* = 8.0, 1.7, 1.5 Hz), 7.36 (td, *J* = 8.0, 0.5 Hz)), 7.58 (1H, ddd, *J* = 1.5, 1.2, 0.5 Hz).



JDH-63-3h

3-toluene-3-(methoxymethyl)-3-pentanoylhexahydro-1-benzofuran-4(2*H*)-one—formaldehyde (3h): Purification via manual silica gel flash chromatography (20:1 heptanes/EtOAc to 4:1 heptanes/EtOAc) afforded the hexahydrobenzofuranone product **3h (**71% yield) as an amber oil. **^{1}H NMR:** δ 0.88 (3H, t, *J* = 6.5 Hz), 1.23-1.34 (2H, 1.28 (h, *J* = 6.5 Hz), 1.28 (h, *J* = 6.5 Hz)), 1.46-1.75 (4H, 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.53 (tt, *J* = 7.4, 6.5 Hz), 1.62 (dtdd, *J* = 13.1, 10.2, 3.1, 2.4 Hz), 1.68 (dddt, *J* = 13.1, 3.2, 3.1, 2.5 Hz)), 1.79-2.04 (2H, 1.88 (dddd, *J* = 14.5, 10.2, 2.8, 2.5 Hz), 1.96 (dddd, *J* = 14.5, 3.2, 2.9, 2.4 Hz)), 2.27 (3H, s), 2.38-2.57 (4H, 2.46 (ddd, *J* = 14.9, 3.1, 2.5 Hz), 2.48 (ddd, *J* = 14.9, 10.3, 3.1 Hz), 2.51 (t, *J* = 7.4 Hz), 2.51 (t, *J* = 7.4 Hz)), 3.50 (1H, d, *J* = 4.8 Hz), 3.76 (3H, s), 4.10 (1H, ddd, *J* = 4.8, 2.9, 2.8 Hz), 5.38 (1H, s), 7.16-7.35 (4H, 7.22 (ddd, *J* = 8.0, 1.2, 0.5 Hz), 7.29 (ddd, *J* = 8.0, 0.9, 0.5 Hz)).



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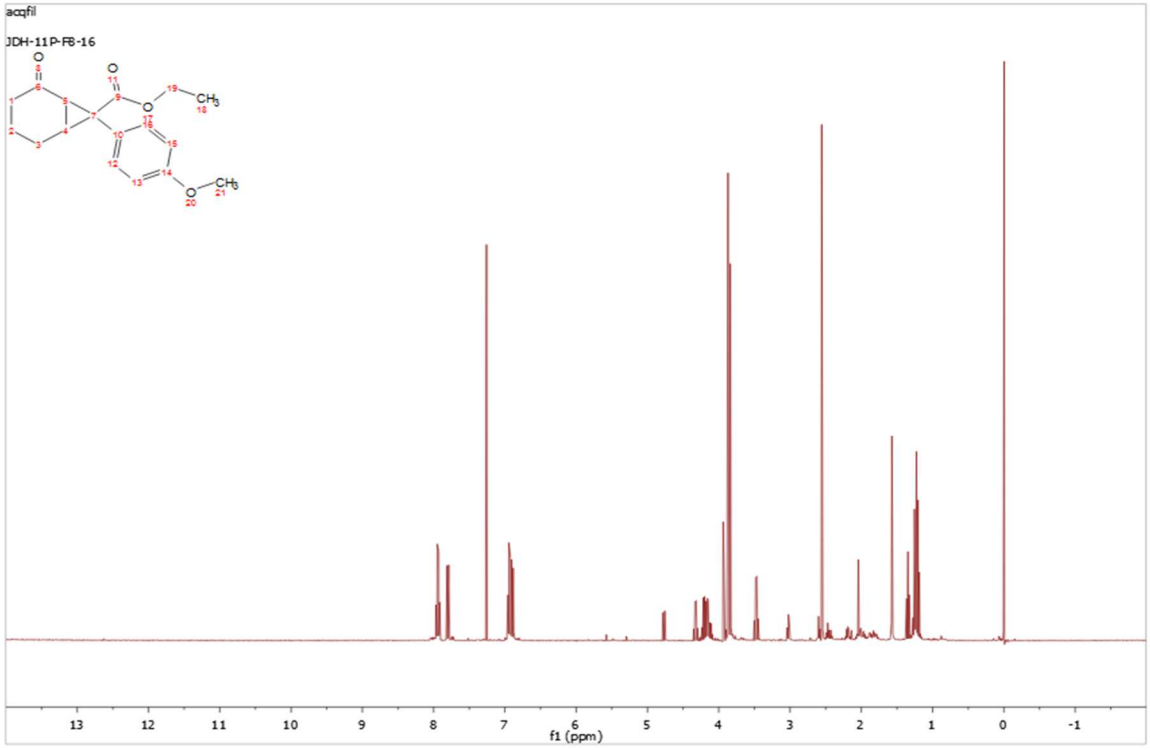
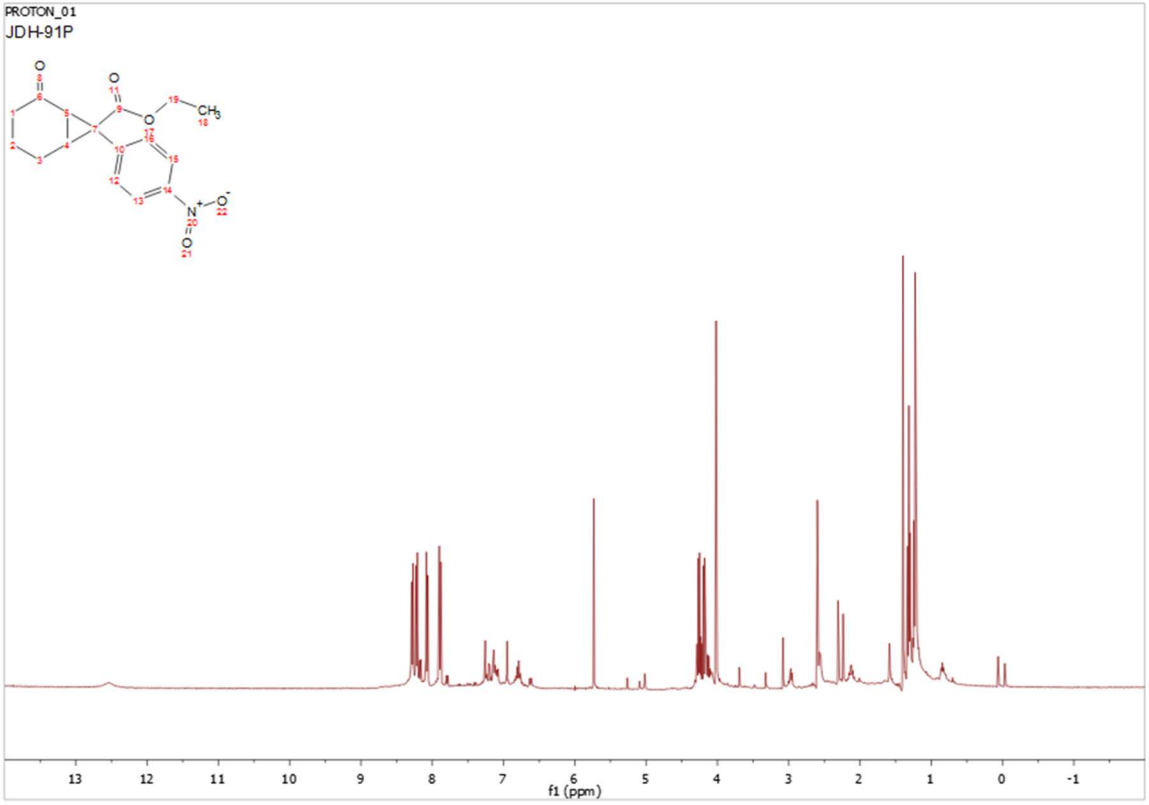
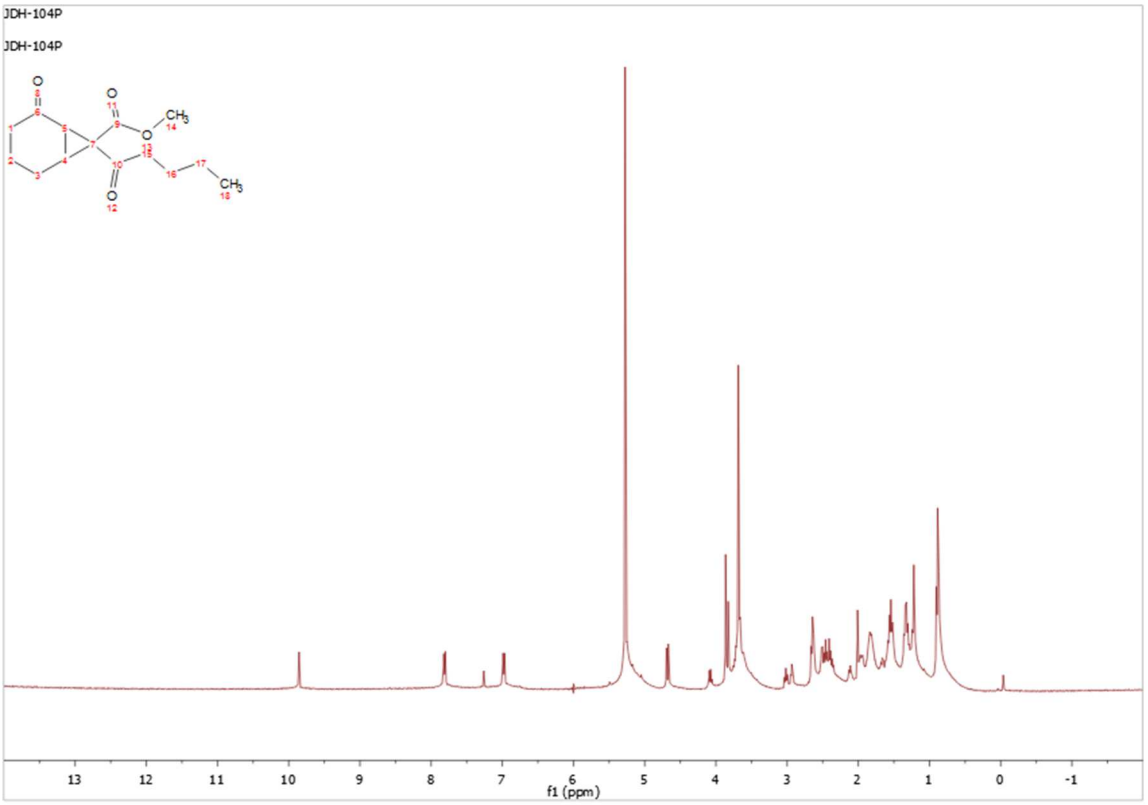
1.6.4 Synthesis of Hexahydrobenzofuranones – ^{1}H NMR Spectra



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JDH-104P
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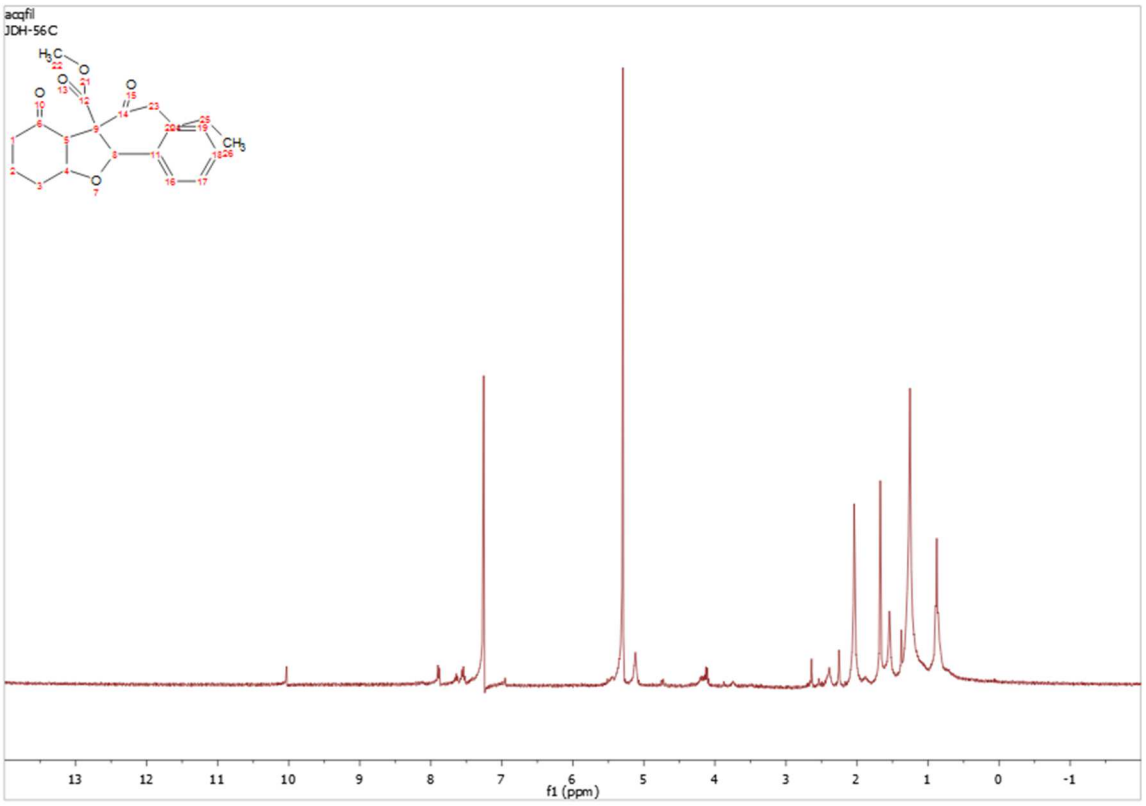
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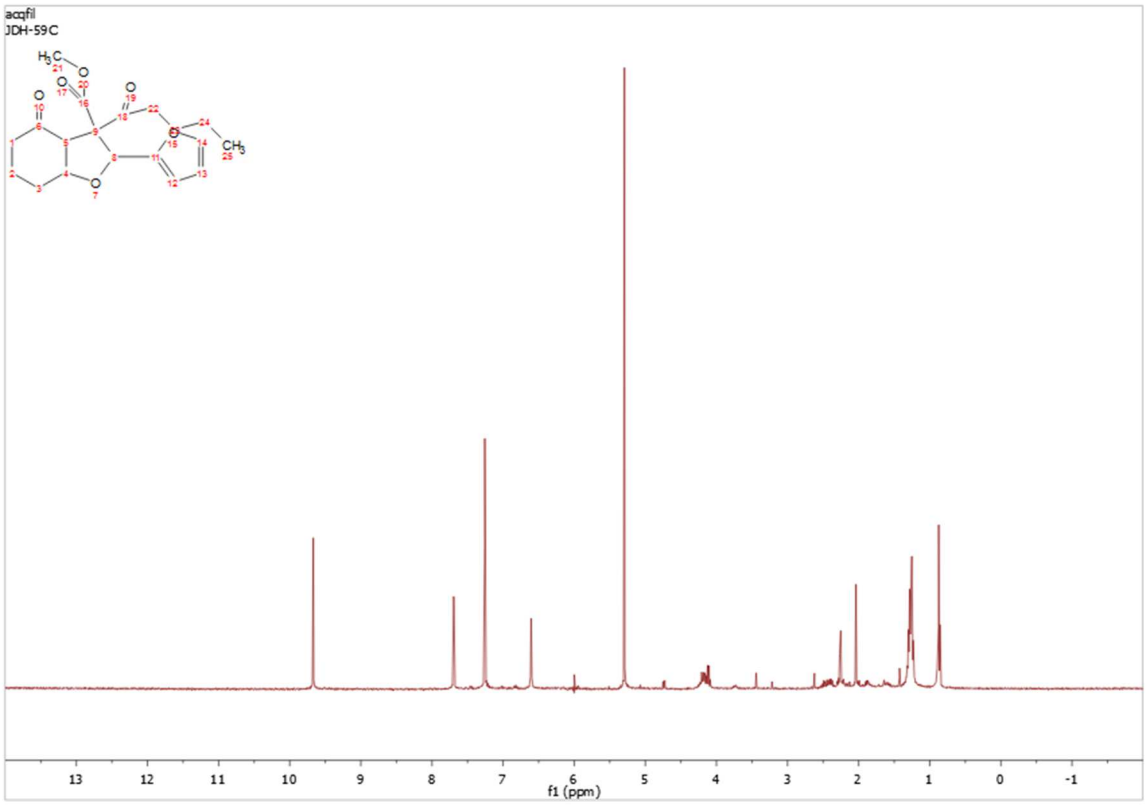
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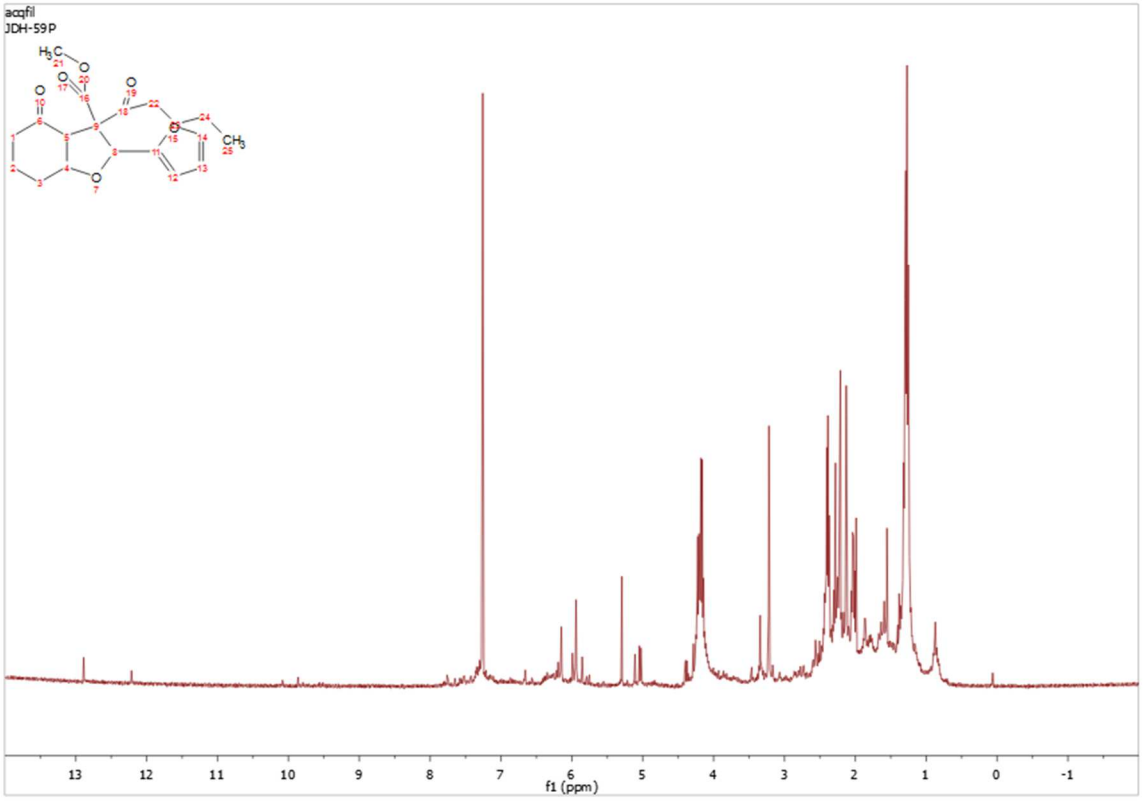
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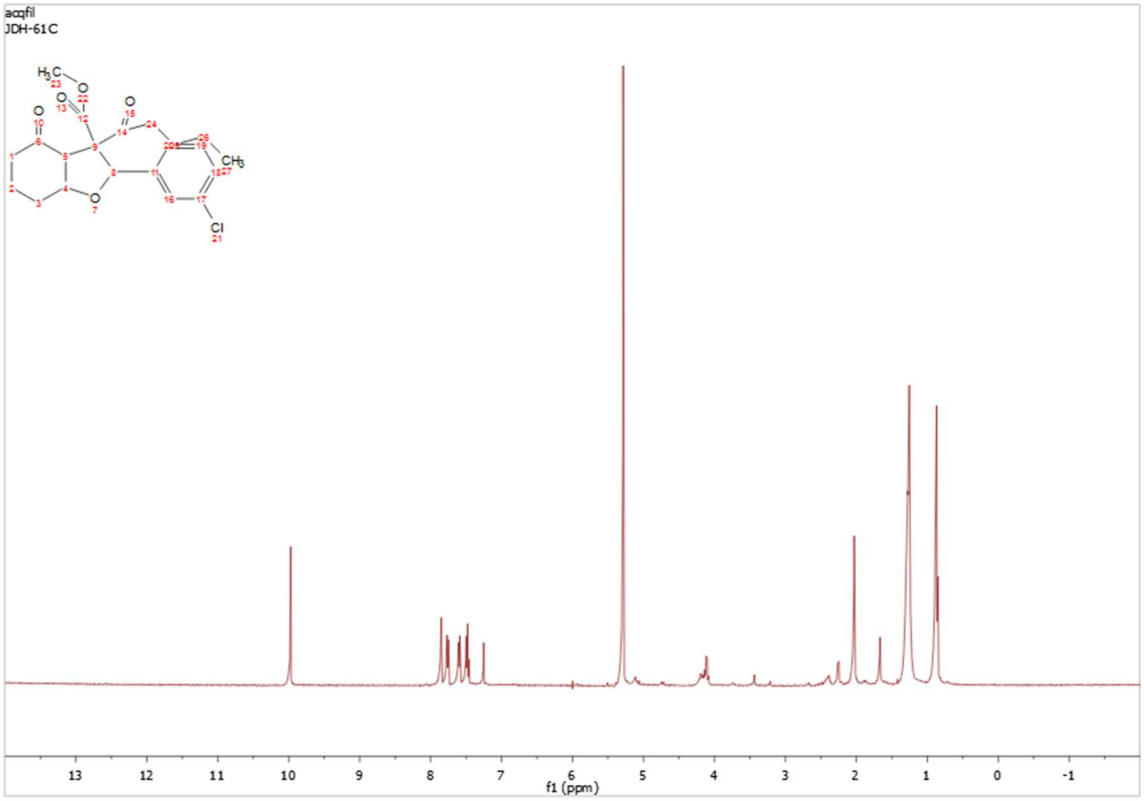
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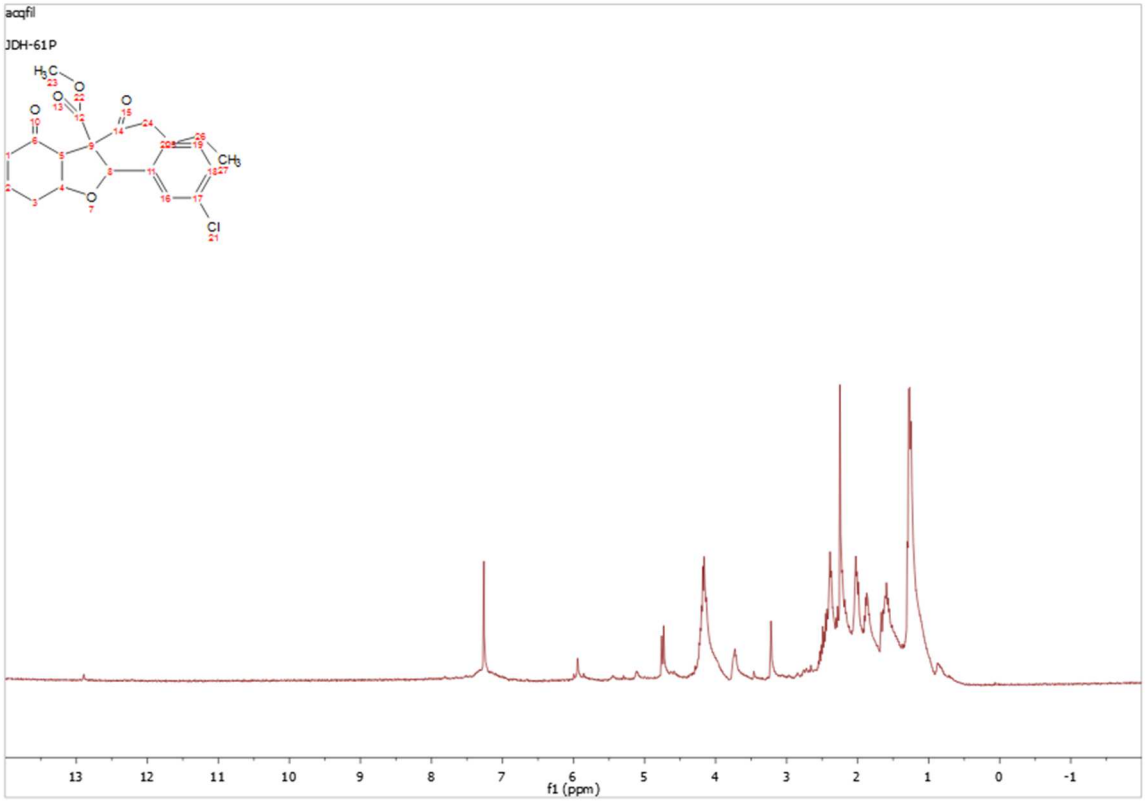
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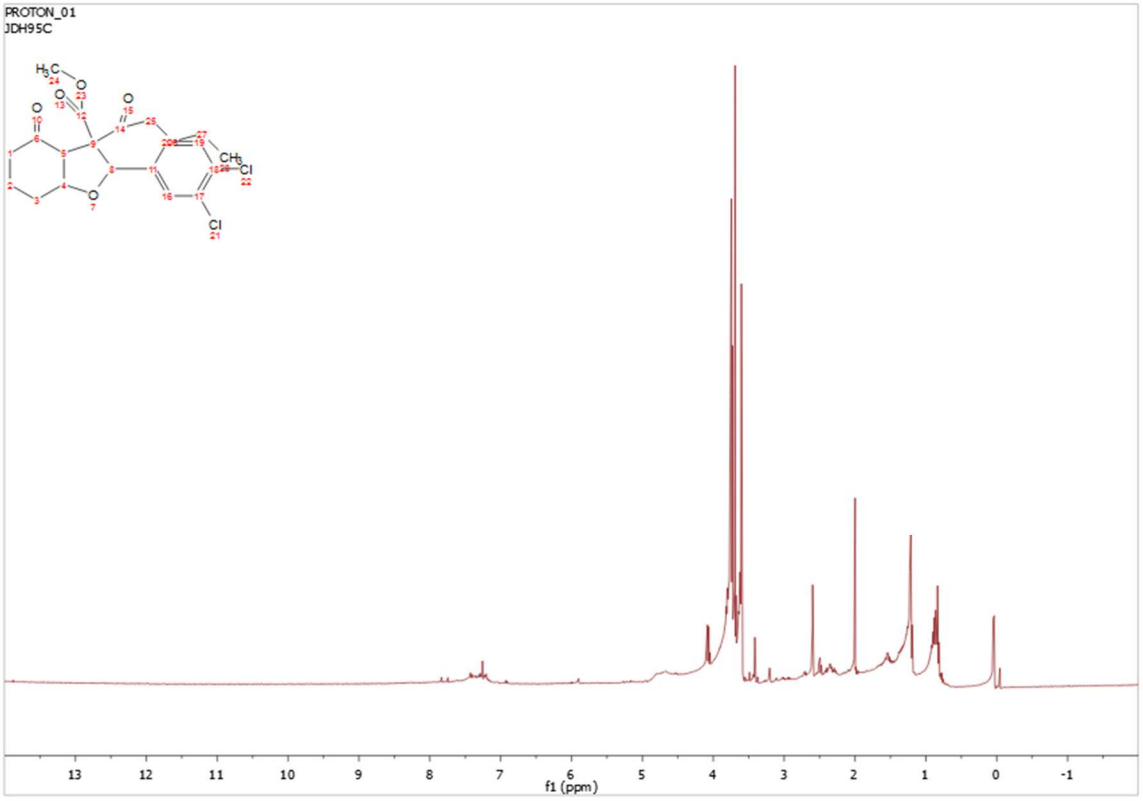
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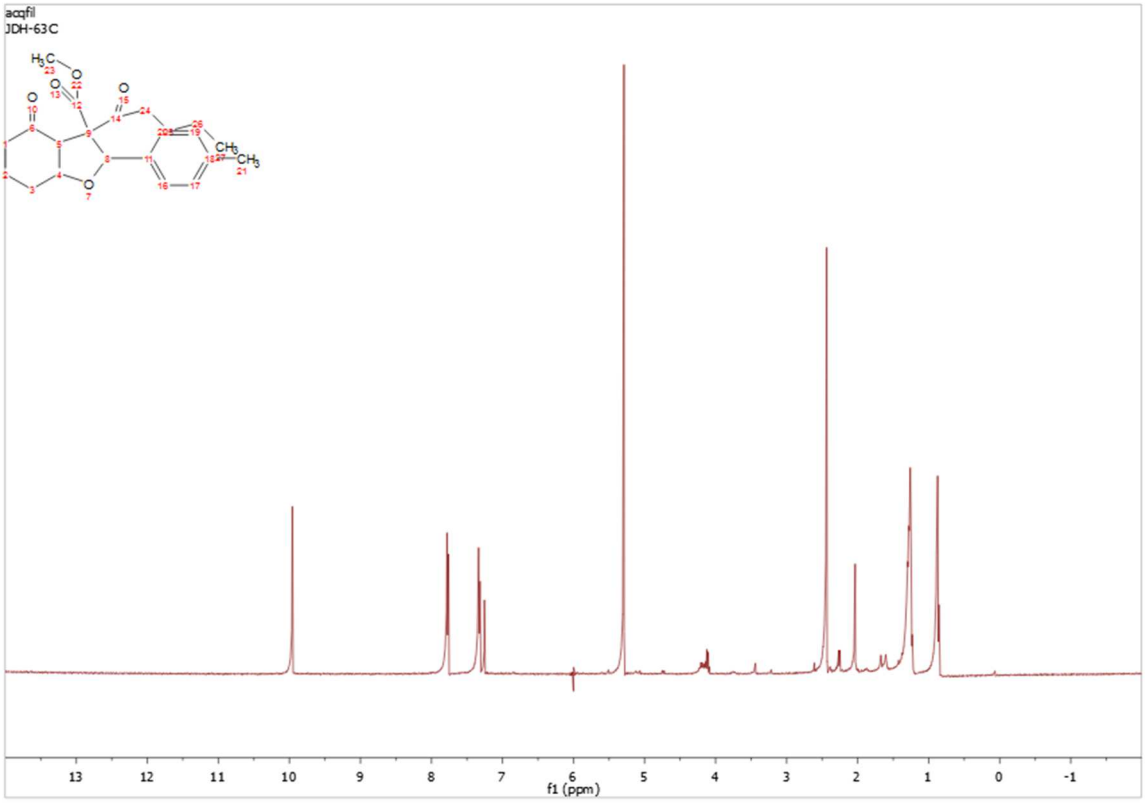
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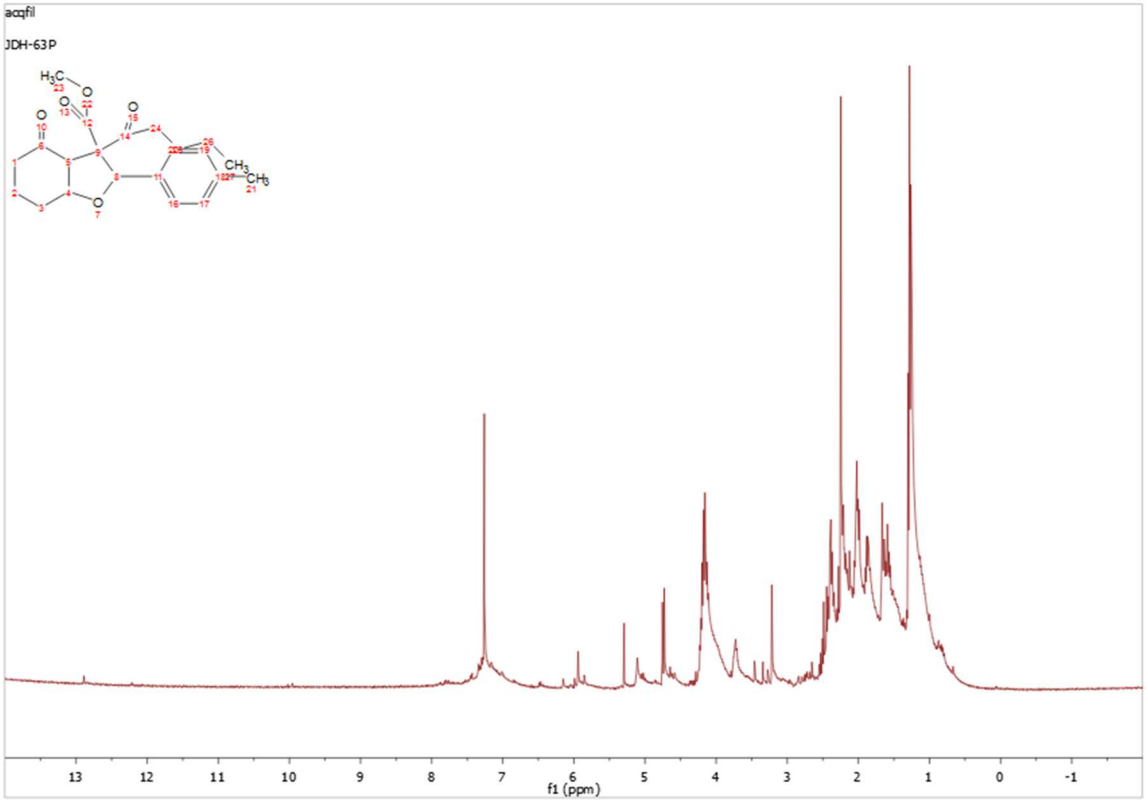
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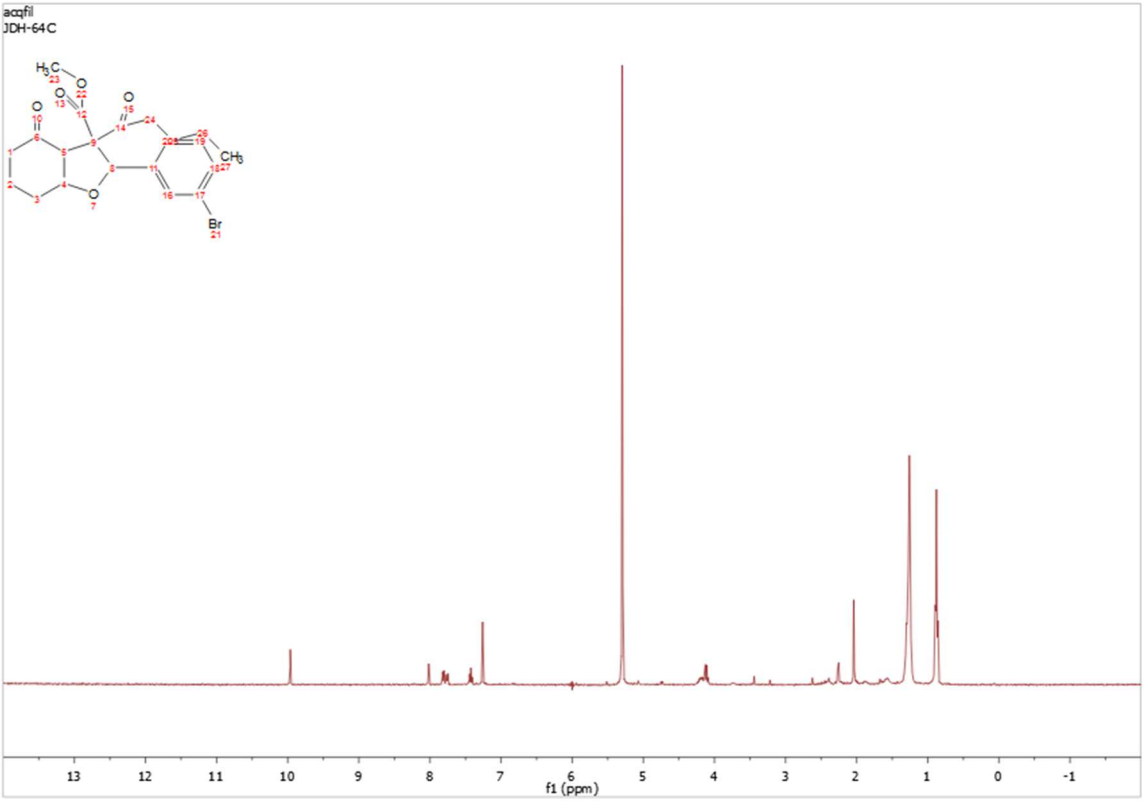
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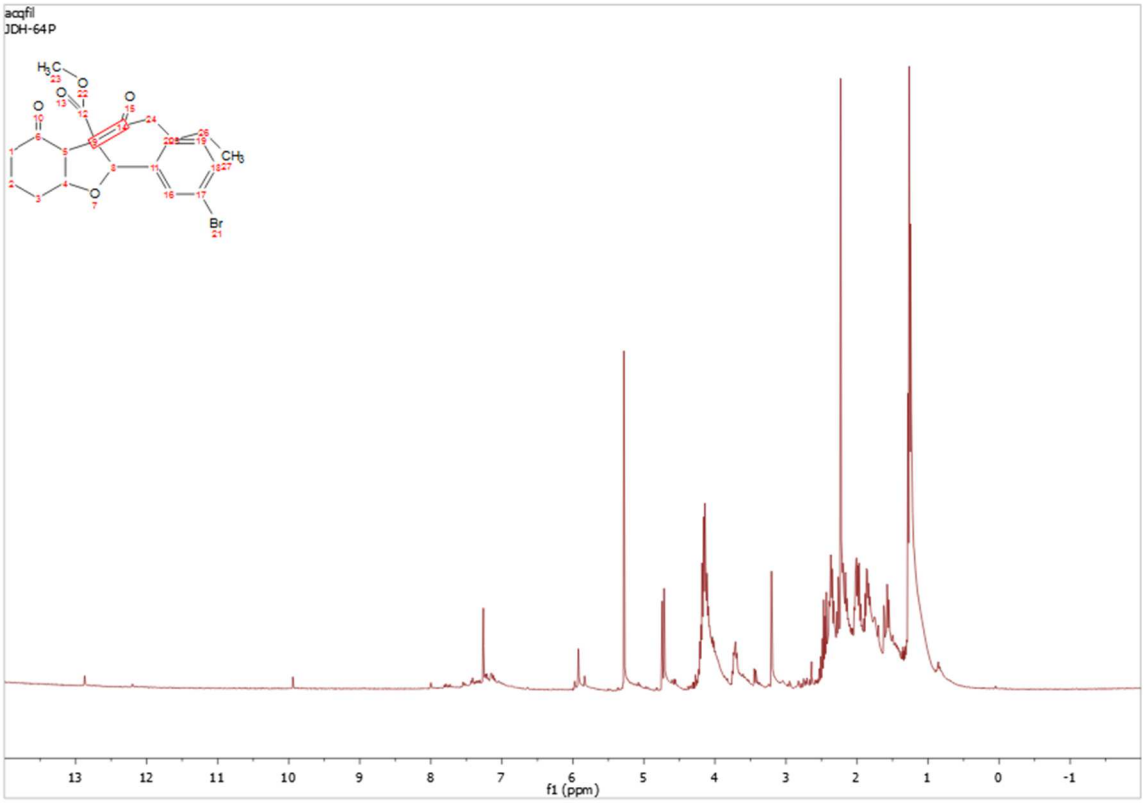
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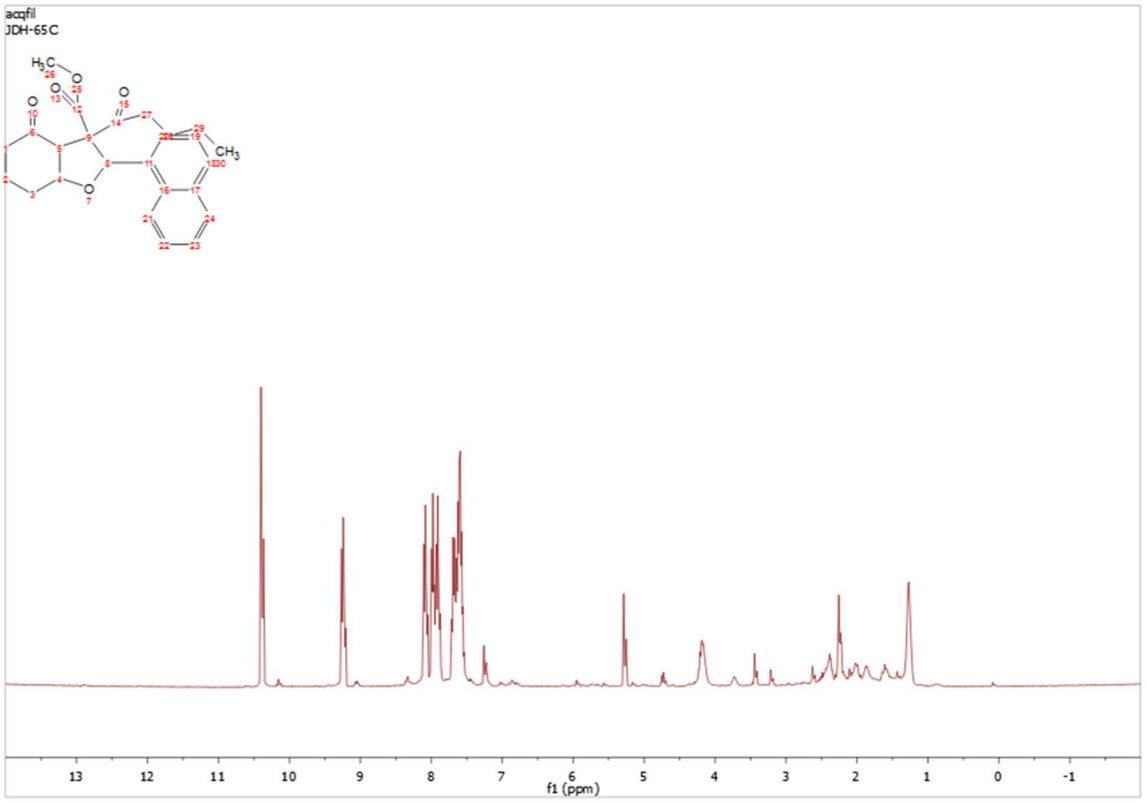
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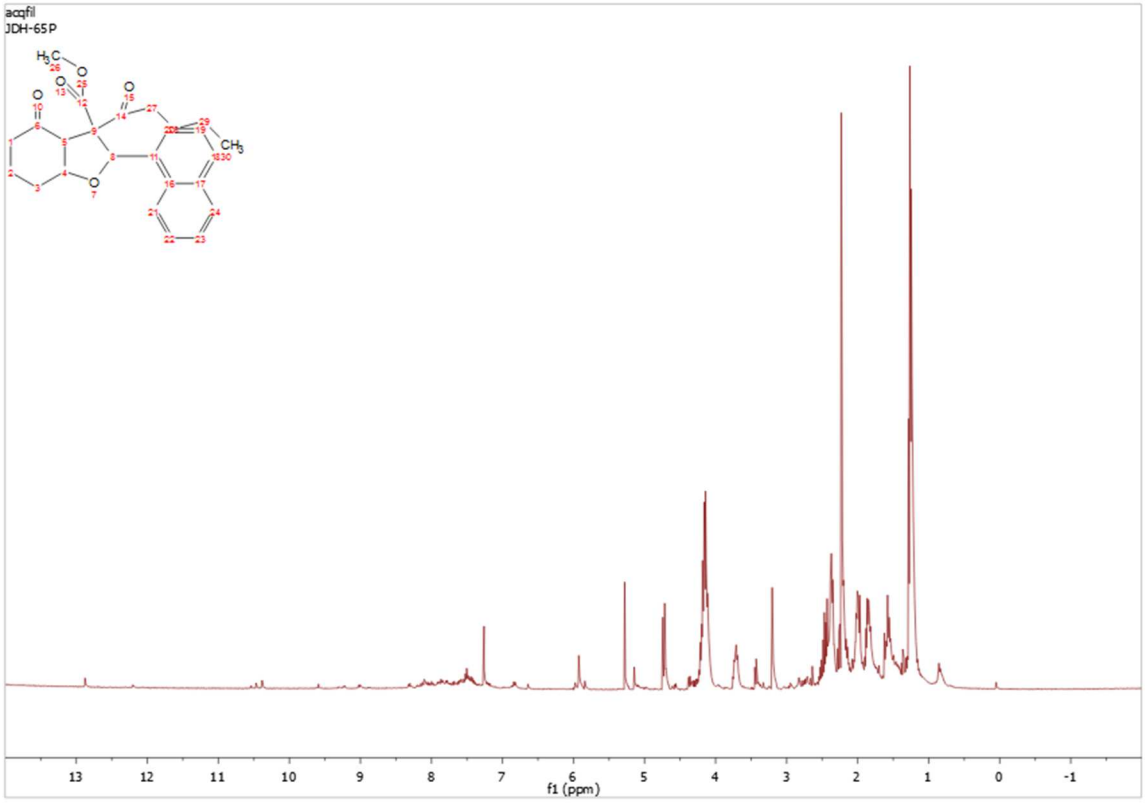
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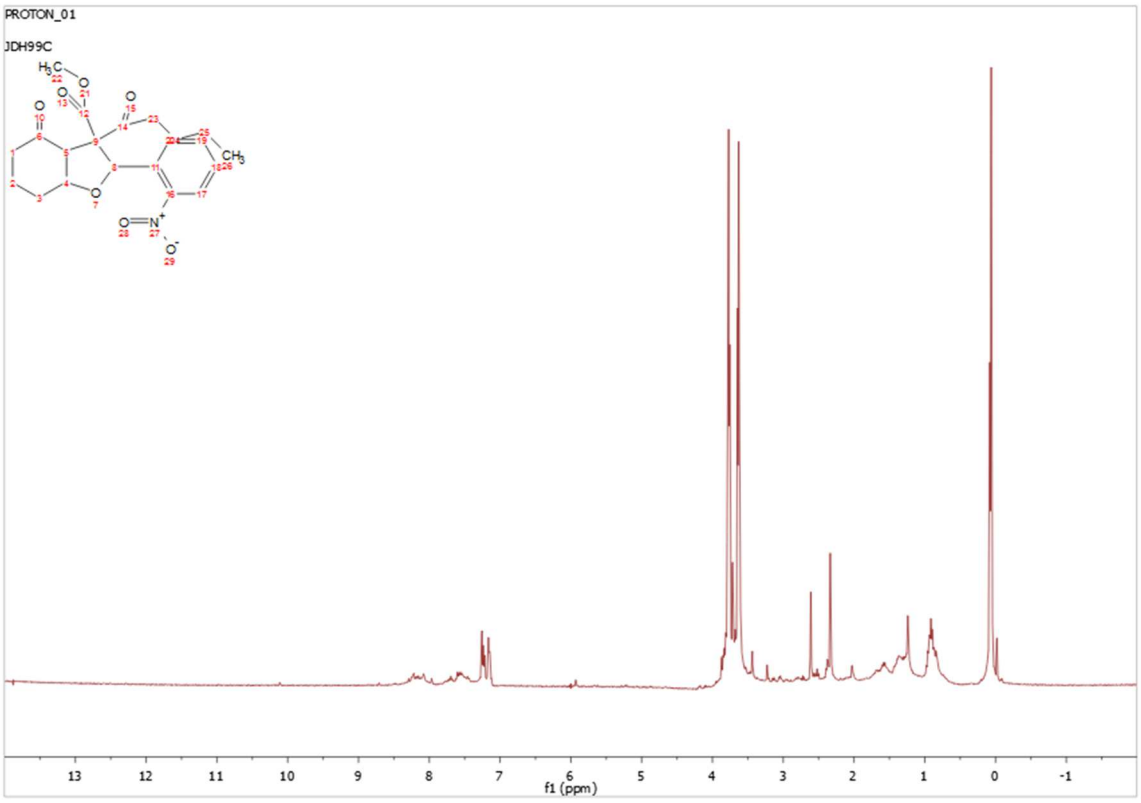
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f1 (ppm)

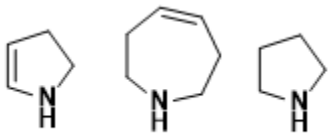
Chapter 2

Selective Synthesis of Pyrrolidines, Pyrrolines, and Azepines From Haloaziridines

Pyrrolidines, pyrrolines, and azepines and their derivatives are critically important classes of heterocyclic compounds that contain one nitrogen atom. The GML lab group is interested in the development of novel methodologies for the synthesis of these key organic skeletons and, more specifically, the selective synthesis of halogenated nitrogen containing heterocyclic compounds from haloaziridine precursors. Pyrrolidines, also known by the chemical name tetrahydropyrrole, are a class of organic compounds which are characterized by a pentane ring containing four carbons and one nitrogen. Pyrrolidines have the chemical formula C_4H_9N and the molecular formula $(CH_2)_4NH$. Pyrrolines and its isomeric forms, 1-pyrroline, 2-pyrroline, and 3-pyrroline are a class of organic compounds distinguished by a pentane ring containing four carbon atoms and one nitrogen atom with the chemical formula C_4H_7N. Azepines are denoted by a heptane ring containing six carbon atoms and one nitrogen atm and have the chemical formula $C_6H_{11}N$. Figure 11 illustrates, pyrroline, azepine, and pyrrolidine respectively from left to right, the nitrogen containing heterocyclic target moieties previously mentioned that will be discussed in this chapter. The general synthesis routes and applications of each organic moiety, pyrroline, pyrrolidine, and azepine, will be touched upon in the following section but synthesizing halogenated versions of these nitrogen-containing heterocycles will be the major focus of this chapter as these are the GML lab groups focus for this endeavor.

Figure 11

Pyrroline, Pyrrolidine, and Azepine Moiety



2.1 Synthesis of Pyrrolidines, Azepines, and Pyrrolines

When studying various organic methods designed to synthesize a target moiety in mind, it is crucial to locate one of the first examples of the synthesis of the target moiety to receive insight into where the development of these compounds began. One of the first methods to synthesize pyrrolines and pyrrolidines was completed by Bucherer and Seyde in 1908 by reacting 3-hydroxy-2-naphthoic acid with phenyl hydrazine in the presence of sodium bisulfate under reflux for 18 hours. This procedure afforded pyrroline-containing, sodium salt of benzo-carbazole sulfonic acid as a yellow crystalline mass in 75% yield. (46) An initial synthetic route to bear azepine-containing moieties was for the multi-step synthesis of substituted tetrahydrobenzazepines by Bobowski and co-workers in 1979. The substituted tetrahydrobenzazepines are important organic moieties as they were found to exhibit arrhythmic activity in an ouabain-induced arrythmia. (47) To begin this synthesis route, arylaldehydes and 2-nitropropanes were run through a condensation reaction to generate nitro-alcohols which were then reduced to alcohol amines catalyzed by zinc and acetic acid. Another condensation reaction was run between the provided nitro-alcohols and arylacetaldehydes to give an imino complex derivative which was

reduced with borohydride to achieve a secondary amine complex. Finally, the secondary amine complex was reacted with various mineral acids to complete the final cyclization reaction to give the tetrahydrobenzazepines derivative. (48)

Now that initial synthetic examples of pyrroline, pyrrolidine, and azepines have been given, general synthetic routes to afford these moieties will be considered along with, in the following section, synthetic methods that grant the ability to produce halogenated pyrroline, pyrrolidine, and azepine moieties. The synthesis of pyrrolines and pyrrolidines will be briefly discussed by reviewing current organic methods including catalytic and non-catalytic cyclization reactions, ring expansion reactions, ring close metathesis and a few other instances. (49) In the first general synthetic method of catalytic/non-catalytic cyclization reactions, an efficient aza-Cope-Mannich cyclization was presented by Ruben and coworkers in which 2-hydroyl homoallyl tosylamine and aldehydes were reacted in the presence of iron(III) salts to afford 3-alkyl-1-tosyl pyrrolines in good yields. This cyclization process involved the generation of a γ-unsaturated iminium ion followed by a sigmatropic rearrangement and finally an intramolecular Mannich reaction. (50) Iron (III) salts are shown in Ruben's work to be excellent catalysts for new aza-Cope-Mannich cyclization using 2-hydroxy homopropargyl tosylamine.

Liang Y and collaborators have also developed an efficient one-pot synthesis of substituted pyrrolines in aqueous media. This method involves the treatment of a range of various chalcone derivatives with aqueous sodium hydroxide in *N,N*-dimethylformamide to undergo a room temperature Michael addition reaction with nitroalkanes. The resulting adducts were then directly reduced *in situ* with Zn/HCl which

induced intramolecular cyclization generating the corresponding substituted pyrrolines in high yields. (51) A non-catalytic cyclization reaction to afford the pyrroline moiety was completed by Ohno and colleagues in which alpha amino allenes bearing an amino protecting group were reacted with potassium carbonate in DMF under reflex without the presence of a transition-metal catalyst giving the corresponding 3-pyrrolines in excellent yields. This non-catalytic cyclization reaction occurred via an *endo-trig* cycloisomerization as internal allenes with axial chirality were able to form the 3-pyrrolines in a stereoselective manner. (52)

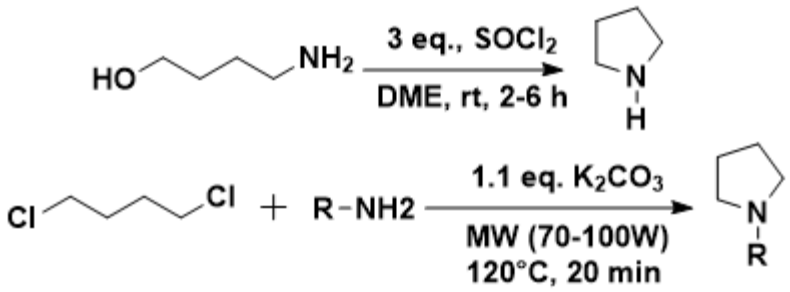
Kumar and colleagues have reported the synthesis of pyrrolines through a ring expansion reaction using aziridines as molecular precursors. In this organic procedure, silver nitrate and chloramine-T were used for the transformation of alkene derivatives into the respective aziridines. The rendered aziridines were reacted in the ring expansion reaction with acrylo-nitrile and ethyl acrylate using solid sodium hydroxide as the base in the organic solvent tetrahydrofuran to bear 1-pyrrolines in 40-58% yields. (THF) (56)

Pyrrolidines have also been afforded through catalytic cyclization reactions such as in the Hofmann-Loffler-Freytag reaction. In this organic procedure, cyclic amines are generated through thermal or photo-chemical decomposition of N-halogenated amine in the presence of a strong acid such as triflic acid or sulfuric acid. This reaction occurs via intramolecular hydrogen atom transfer of the N-halogenated amine to a nitrogen-centered radical which enables intramolecular free radical C-H functionalization and cyclization, under basic conditions, to yield pyrrolidines. (49)

Another two catalytic cyclization reactions to afford pyrrolidines can be found in a one-pot synthesis routes depicted in Figure 12. The first one-pot pyrrolidine synthesis route, shown at the top of Figure 12, uses an amino alcohol to go through a halogenation-cyclization reaction which is induced by 3 equivalences of thionyl chloride in the organic solvent dimethyl ethane at room temperature for two to six hours. (53) The second one-pot pyrrolidine synthesis, shown at the bottom of Figure 12, reacts dihaloalkanes with alkyl and aryl amines separately in the presence of 1.1 equivalences of potassium chloride under 70-100W of microwave irradiation at 120 degrees Celsius for 20 minutes to produce pyrrolidines. (57)

Figure 12

One-Pot Synthesis of Pyrrolidines



Yang, Alper, and Xiao have displayed an efficient manner for the synthesis of chiral pyrrolidines via a ring-closing enyne metathesis. To complete this reaction, 1 mmol of enyne precursor was dissolved into 17 milliliters of freshly distilled and degassed dichloromethane under elemental nitrogen gas. Positive pressure was induced with nitrogen gas syringed into the reaction vial and the reaction stirred for 10 minutes in reflux. A ruthenium catalyst was then syringed into the reaction vial and the reaction was left to run for 14-20 hours in reflux to generate the respective chiral pyrrolidines. (58)

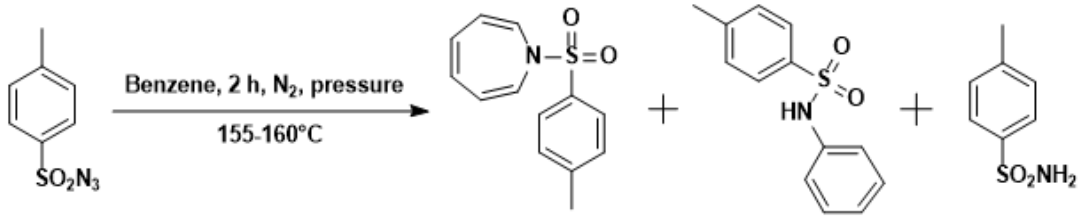
Metal catalyzed cyclization and cycloaddition reactions have also been presented to impart the production of complex pyrrolidines. Shi and co-workers have prepared synthesized pyrrolidines through a gold catalyzed reaction between methylene cyclopropanes and sulfonamide in toluene at 85 degrees Celsius. (59) In another metal catalyzed cyclization reaction to afford pyrrolidines occurred from Komeyama and colleagues through hydroamination via inactivated olefins. These olefins are activated by by iron (III) chloride in dichloroethane at 80 degrees Celsius for 2-38 hours producing pyrrolidines in an efficient manner. (60)

Now that a brief overview at the current methods to synthesize both pyrrolines and pyrrolidines have been discussed, the focus will now turn to the synthesis of azepines that are currently available. Azepines have been synthesized by a multitude of groups using organic methods such as insertion reactions, cyclo-expansion reaction, ring-closing metathesis, and many more. (61) In the first synthetic example of azepines, depicted in Figure 13, shows intermolecular insertion of nitrenes across a benzene double bond at high temperature and pressure to produce the ring-expanded product H-soulfonyl-1H-azepine.This thermolysis reaction of toluene-9-sulfonyl azide was

performed with excess benzene under high nitrogen pressure at 155 to 160 degrees Celsius and afforded side products in miniscule yields. (62)

Figure 13

Azepine Synthesis via Nitrene and Benzene Insertion Reaction



Another insertion rection between nitrene and benzene was generated *in situ* through reaction of phenyl nitrene and benzene. This reaction undergoes an addition reaction to form an intermediate which then catalyzes the insertion reaction to afford the N-phenyl-1H-azepines in high yields. (63) Conjugative addition of secondary formamide to nitroalkenes gives INOC precursors within 2-4 hours in yet another synthetic strategy to afford azepines. The intramolecular nitrile oxide cycloaddition, INOC, precursors are exposed to phenyl isocyanate under basic conditions and afford nitrile oxides which immediate react with internal alkenes to give bicyclic isoxazole-fused azepines in fair yields. (64)

One final example of a synthetic strategy to afford azepine moieties is through ring closing metathesis reactions. Fürstner and colleagues have shown that α,ω-

diene or ene-yne systems can undergo ring closing metathesis, catalyzed by the Grubbs catalyst, to provide pyrrolidine-derived α,ω-dienes such as pyrrolidinoazepinone. (65) Now that a brief review of the current methods employed to synthesize pyrrolidine, pyrrolines, and azepines has been discussed, the pharmaceutical application of these featured organic structures will be reviewed.

2.2 Pharmaceutical Relevance

Pyrrolidines, pyrrolines, and azepines are a crucially important families of nitrogen containing heterocyclic, organic compounds which are shown to have varied biological activities. When pyrrolidines, pyrrolines, or azepines are further functionalized, or substituted, the resulting complex heterocyclic derivatives have shown a wide variety of different antibacterial effects and significant biological activities. Complex pyrrolidine moieties, for example, are used as scaffolding molecules to synthesize unnatural oligomers. These synthetically made polymers, also known as unnatural oligomers, show many diverse applications in the pharmaceutical industry as antidiabetic, anticancer, antimalarial, antiviral, antimicrobial, anti-inflammatory, and antibacterial agents. The following section will illustrate a few pharmaceutical applications which employ pyrrolidines, pyrrolines, and azepines.

One of the first pharmaceutical applications that can be considered for nitrogen-containing heterocyclic compound can be seen through the presence of these structures within natural products that are used in daily life as well as in synthetic organic chemistry. Natural alkaloids including nicotine, hygrine, atropinone, and proline are just a few examples of widely used natural products that have the pyrrolidine ring substructure within each of the natural product's molecular skeleton. (61) For

applications within synthetic organic research, the pyrrolidine substructure acts as a great nucleophile which can easily perform electrophilic substitution reaction with different electrophiles including alkyl halides and acyl halides to provide substituted pyrrolidine derivatives. Once these pyrrolines are formed, they can undergo even further transformations such as N-alkylpyrrolidines which can produce quaternary salts on further reaction with alkyl halides. Pyrrolidines have also been shown to react with ketene thioacetals to synthesize mono- and di-pyrrolidino derivatives. One final example of the synthetic application of pyrrolidines can be seen between the reaction of pyrrolidines with alkyl/aryl isocyanates or isothiocyanates deliver the respective 1,3-disubstituted urea/thiourea products. (61)

Gataullin and co-workers have synthesized N-tosyl-2-(1-halogeneethyl)-3-methylindolines through halocyclization of homologues of N-tosyl2-(1-methylbut-2-en-1-yl)aniline and 2-chloro-, 2-bromo-, and 4-bromo-derivatives. N-tosyl-2-(1-halogeneethyl)-3-methylindolines synthesized by Gataullin and co-workers have shown selective toxicity against SH-SY5Y cell lines which are often used as *in vitro* models of neuronal function and differentiation. The synthesis of these N-tosyl-2-(1-halogeneethyl)-3-methylindolines begins with the N-alkenylation of halogenated anilines which chloropentene in triethylamine at 80 degrees Celsius. A thermal Claisen rearrangement was then conducted on the hydrochloride penteneyl aniline in the presence of xylene. The aniline derivatives produced then undergo reaction with tosyl chloride in pyridine to afford cis and trans toluene sulfonyl amide derivatives which then undergo hetero-cyclization reaction in the presence of molecular iodine and sodium bicarbonate in

dichloromethane at 20 degrees Celsius. The corresponding cis and trans isomers of N-tosyl-2-(1-halogeneethyl)-3-methylindolines are then produced. (82)

Pyrrolines have also been shown to have useful biological applications within the pharmaceuticals industry. Pyrroline-5-carboxylate synthase (P5CS), for example, is a bifunctional enzyme that exhibits glutamate kinase (GK) and gamma-glutamyl phosphate reductase (GPR) activities. This P5CS enzyme is highly relevant in humans as it belongs to a combined biochemical route for the conversion of glutamate, ornithine and proline. Humans that have a P5CS deficiency exhibit a rare, metabolic disease that can be life threatening if not addressed. It is well established that some bacteria and plants also accumulate prolines in response to osmotic stress. The analyzed structures of GK and GPR exemplify the importance of prolines in P5CS's as they are present in a variety of different species. (68)

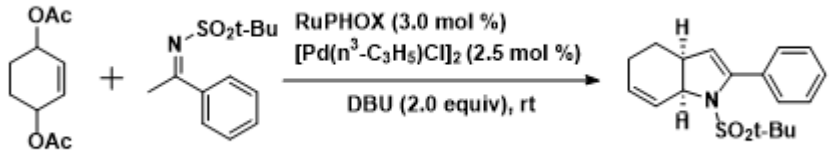
Another biologically crucial proline derivative can be seen in D-Pyrroline-5-carboxylic acid, an intermediate in both the biosynthesis and degradation of L-proline. D-pyrroline-5-carboxylic acid was recently synthesized and isolated as a pure compound through enzymatic assay with pyrroline-5-carboxylate reductase from *Escherichia coli* by the periodate oxidation of hydroxylysine. (69)

As chiral, pyrroline moiety-containing, tetrahydroindoles are represented in natural products such as strychnine and mesembrine, a synthesis of chiral tetrahydroindoles has been developed via a Pd-catalyzed asymmetric allylic substitution annulation using unstable enolizable ketimines as nucleophiles and t-BuRuPHOX as a chiral ligand. This reaction is depicted in Figure 14 below. The tetrahydroindole synthesis

proceeds via an asymmetric desymmetrization of the mesodiacetate cycloalkenes, generating the desired chiral tetrahydroindoles in excellent, 96% ee, yields. The annulation reaction could be performed on a gram-scale in high yields and the resulting products can be transformed to several types of N-hetereo bicyclic derivatives. (83)

Figure 14

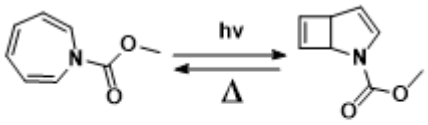
Palladium Catalyzed Synthesis of Tetrahydroindoles



Azepines have also shown to be malleable organic constructs that can undergo useful transformations to generate complex scaffolds that are likely characterized with biological activities. As shown in Figure 15, if the nitrogen atom of 1H-azepines contains an electron withdrawing group, of 2-azabicyclo [3.2.0] hepta-3,6-dienes can be produced under photochemical conditions. Interestingly, the reverse reaction can occur by producing 1H-azepines from of 2-azabicyclo [3.2.0] hepta-3,6-dienes through thermal ring opening. (66)

Figure 15

Functionalization of EWG Substituted 1H-Azepines



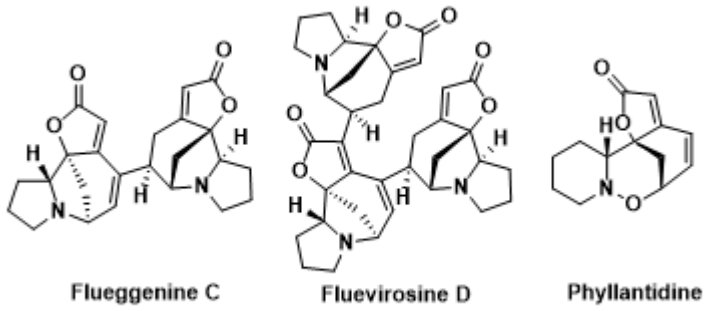
Azepines can also undergo alkylation reactions as tricarbonyl [4-1-(ethoxycarbonyl)-1H-azepine] iron complex alkylation occurs through a Friedel-Craft approach by using a 2-oxallyl cation. This cation is first generated by the reaction of 2,4-dibromo-2,4-dimethylpentan-3-one and $Fe(CO)_9$. (67)

Finally, azepines can be seen in innate natural products such as flueggenine C, fluevirosine D, and phyllantidine which are depicted in Figure 16. Lee and colleagues studied various synthetic routes that are currently available to afford these structures. In the first mode of diversification to produce flueggenine C, as well as fluevirosine D, a Rauhut-Currier reaction is undertaken each respective natural product precursor which involves the formation of a carbon-carbon bond. (84) The other notable mode of diversification that was used in the organic precursors by Lee and colleagues to afford these azepine natural product derivatives was through oxidation procedures. The oxidation of the tertiary amine moiety of securinega precursors yielded nitrogen-oxide derivatives which could serve as a branching point for various high-oxidation state securinega alkaloids. An example of the production of a high-oxidation state securinega alkaloid natural products from nitrogen-oxide derivatives could use the Meisenheimer

rearrangement on these produced nitrogen-oxide derivatives to yield the natural product phyllantidine, also depicted in Figure 16. (85)

Figure 16

Azepine-Containing Natural Products



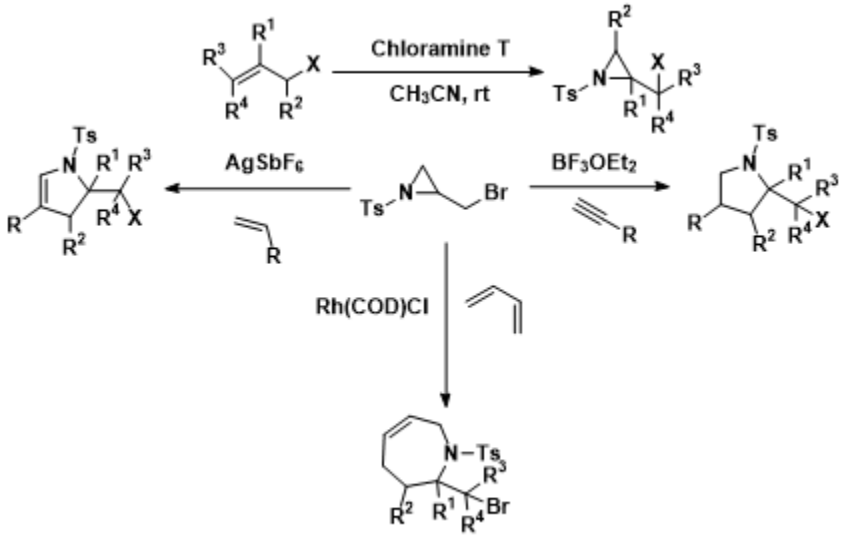
2.3 Results and Discussion

As depicted in the previous sections of this chapter, pyrrolidines, pyrrolines, and azepines are crucial nitrogen-containing, heterocyclic organic structures that show up extensively within valuable natural products, in the molecular skeleton of pharmacophores, and as intermediates for the synthesis of complex pharmacophores. Because of the scarcely of novel synthetic methods to afford pyrrolidines and azepines the GML lab group developed a reaction hypothesis, depicted in Table 7, to provide these nitrogen containing heterocycles from haloaziridines. Halogen bonding was an important aspect to the products formed by the GML lab group as it added a layer of diversification to the nitrogen containing heterocycles synthesized. Halogen bonding is exemplified as

covalent bonding formed between a halogen atom, such as bromine or iodine, and a nucleophile such as a Lewis base. Halogen bonding that exists within organic products are highly directional and specific organic interactions that emulate the reactivity of hydrogen bonding. (78) Due to the anisotropy of the charge distribution of halogen atoms, a positively charged electrostatic region on the extension of the halogen bond, termed the σ-hole, interacts attractively with a nucleophile to make the attached halogen atom a good leaving group. (79) Over the past few years halogen bonding has more attention for its role in drug discovery which has led the GML lab group to include them in their novel synthetic methods. The haloaziridines produced in the reaction hypothesis, in Table 7, are formed by transformation of halogenated allylic alkene derivatives through reaction with chloramine T in the organic solvent acetonitrile at room temperature. From this point, the haloaziridine derivatives produced are to undergo cycloaddition with various catalytic methods to afford the pyrrolidine, pyrroline, and azepine structures.

Table 7

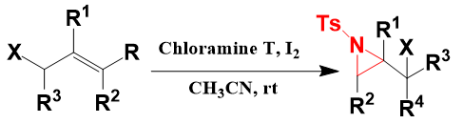
Selective Synthesis of Pyrrolidines, Pyrrolines, and Azepines From Haloaziridines Reaction Hypothesis



Once the reaction hypothesis was formed, optimization studies for the synthesis of haloaziridines was started by trying to maximize the haloaziridine yields. At the beginning of the optimization studies, haloaziridine conversion was lacking so the GML lab group employed the addition of iodine sublimed as a co-additive in order to convert major side product of the halo-aziridination reaction, N-allyl-4-methylbenzenesulfonamide into the aforementioned haloaziridine product. A solvent study was also conducted on the reaction including the use of dichloromethane, acetonitrile, chloroform, and benzene. As acetonitrile proved to show the best conversion by NMR analysis, an organic solvent concentration study was performed which resulted in the 0.05 M concentration of the acetonitrile. The scope of the haloaziridines produced by the GML lab group can be seen in Table 9.

Table 8

Synthesis of Haloaziridines Optimization Studies



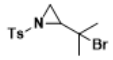
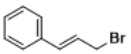
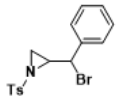
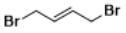
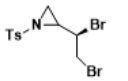
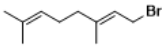
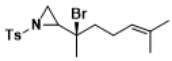
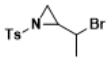
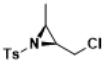
1

Entry	R^3	additive	solvent	concentration (M)	yield (%)[b]
1	I	Chloramine T	CH_3CN	0.05	
2	I	Chloramine T	CH_3CN	0.075	
3	I	Chloramine T	CH_3CN	0.01	
4	I	Chloramine T	CH_3CN	0.025	
5	I	Chloramine T, I_2	CH_3CN	0.1	
6	I	Chloramine T, I_2	CH2Cl2	0.05	
7	I	Chloramine T, I_2	DCM	0.05	
8	I	Chloramine T, I_2	Chloroform	0.05	
9	Br	Chloramine T, I_2	benzene	0.05	

a. Let run overnight at rt. b. Isolated yields.

Table 9

Synthesis of Haloaziridines Reaction Scope

Entry	Allylic Halogens Derivatives	Haloaziridines
JDH-189 2a		
JDH-182 2b		
JDH-154 2c		
JDH-186 2d		
JDH-165 2e		
JDH-184 2f		
JDH-181 2g		
JDH-185 2h		

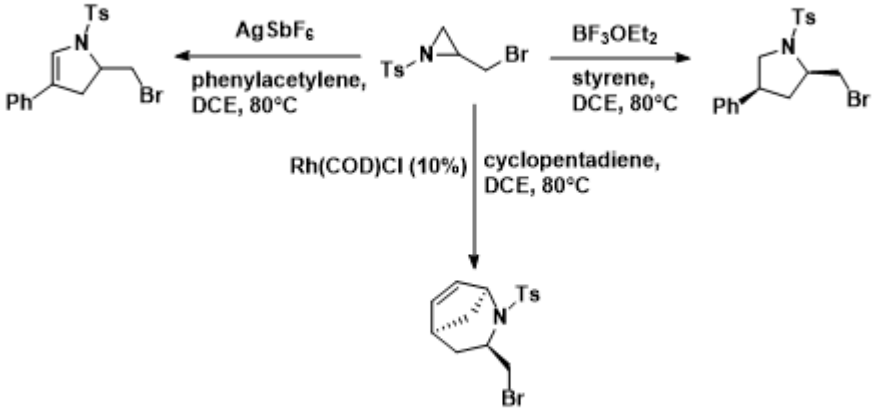
a. Conditions:Allylic bromide (0.2066 mmol), Chloramine T (0.4132 mmol), 0°C to rt, acetonitrile, stirred for 12 h.

2.3.1 Haloaziridine Cycloaddition Initial Studies

Initial studies were conducted on the transformation of the allylic bromide haloaziridine derivative into the pyrrolidine, pyrroline, and azepine moieties. Boron trifluoride ethyl etherate, silver hexafluoroantimonate(V), and chloro (1,5-cyclooctadiene) rhodium(I)dimer were reacted with the haloaziridine derivative in dichloroethane at 80 degrees Celsius to afford the pyrrolidine, pyrroline, and azepine moieties, respectively. The presence of these heterocyclic constructs were confirmed by NMR analysis in the crude products but further optimization is still required to maximize the nitrogen containing heterocyclic products.

Table 10

Initial Cycloaddition Studies of Haloaziridines Into Pyrrolidines, Pyrrolines, and Azepines



2.4 Conclusion

A diastereoselective and efficient methodology was developed for the selective synthesis of complex haloaziridines from allylic alkene derivatives. This overall reaction will allow for the direct conversion of commercially available alkenyl halides in the corresponding haloaziridines in the presence of chloramine T as the nitrogen source and iodine sublimed to convert the main predicted organic side product into haloaziridines. Initial studies on the conversion of these afforded haloaziridines into pyrrolidines, pyrrolines, and azepines has been conducted and further optimization is needed. Initial studies have proven that haloaziridines can be used as suitable templated for the synthesis of nitrogen-containing heterocycles with high product conversion and stereoselectivity.

2.5 Experimental

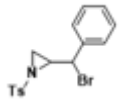
Organic reagents were obtained from Aldrich Chemical, Acros Organics, and Alfa Aesar. Organic reactions were performed with 20 milliliter glass vials that allowed for magnetic stirring. TLC analysis was performed via a 0.25mm E. Merck silica gel 60 F254 plates and visualized under 254 nm UV light as well as staining with potassium permanganate solution ($KMnO_4$). Products were purified via manual silica-gel flash chromatography and collected based on NMR analysis and Rf values of UV spots by TLC. NMR spectrum were recorded via Varian Mercury II 400 MHz Spectrometer at 24 degrees Celsius in CDCl. Chemical shifts are expressed in ppm relative to solvent signals: CDCl, (1 H, 7.23 ppm; 13C, 77.0ppm; coupling constants expressed in Hz)

2.5.1 General Method for the Synthesis of Haloaziridines

A twenty-milliliter vial was obtained for this reaction and was filled with 0.1 M of the organic solvent acetonitrile. Alkenes that had functional groups in the allylic position were of interest for this project's transformation. 0.4132 mmol of dry chloramine T was put into a separate vial and put under high vacuum pressure for thirty minutes in order to ensure it was completely dry. 0.2066 mmol of allyl bromide was syringed into the reaction vial containing the 0.1M acetonitrile as well as a magnetic stir bar. The dry chloramine T was then poured into the vial. The reaction was left to spin on a hotplate for fifteen minutes at which point 0.2066 mmol of iodine sublimed was added to the reaction vial. The reaction was then left to run overnight.

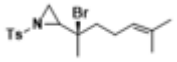
The following day the workup, characterization, and analysis of the halo-aziridine formation took place. The aziridine reaction was taken off the hotplate, the stir bar was removed with a magnetic stir rod, and the stir bar was cleaned. A clean 250 milliliter Erlenmeyer flask was obtained along with a plastic funnel and a circular piece of filter paper. The filter paper was folded and placed into the funnel and the funnel was then placed into the 250 milliliter Erlenmeyer flask. A glass pipette was obtained with an attached rubber bulb and used to squirt acetonitrile on the filter paper before the gravity filtration of the reaction began. Gravity filtration was complete to remove the chloramine T. Once the crude product was confirmed by TLC and NMR, manual, silica-based, flash column chromatography was performed to isolate the pure haloaziridine product. The pure haloaziridine was characterized/confirmed via proton/carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS).

2.5.2 Synthesis of Pyrrolidines, Pyrrolines, and Azepines From Table 9



JDH-154-2c

2-[bromo(phenyl)methyl]-1-(4-methylbenzene-1-sulfonyl)aziridine (2c): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2c** as a clear oil. **^{1}H NMR:** δ 2.32 (3H, s), 3.13 (1H, dd, *J* = 8.1, 4.1 Hz), 3.29-3.47 (2H, 3.36 (dd, *J* = 7.6, 4.1 Hz), 3.39 (ddd, *J* = 8.1, 7.6, 6.5 Hz)), 4.85 (1H, d, *J* = 6.5 Hz), 7.23-7.53 (7H, 7.30 (tt, *J* = 7.7, 1.5 Hz), 7.33 (dddd, *J* = 7.9, 1.5, 1.3, 0.5 Hz), 7.34 (ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.46 (dddd, *J* = 7.9, 7.7, 1.7, 0.5 Hz)), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).



JDH-165-2e

2-(2-bromo-6-methylhept-5-en-2-yl)-1-(4-methylbenzene-1-sulfonyl)aziridine (2e): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2e** as a clear oil. **^{1}H NMR:** δ 1.19 (3H, s), 1.46-1.59 (8H, 1.52 (t, *J* = 7.4 Hz), 1.52 (t, *J* = 7.4 Hz), 1.54 (s), 1.54 (s)), 1.97-2.10 (2H, 2.04 (td, *J* = 7.4, 7.1 Hz), 2.04 (td, *J* = 7.4, 7.1 Hz)), 2.32 (3H, s), 3.07-3.23 (2H, 3.13 (dd, *J* = 8.1, 4.1 Hz), 3.16 (dd, *J* = 8.1, 7.6 Hz)), 3.39 (1H, dd, *J* = 7.6, 4.1 Hz), 5.27 (1H, t, *J* = 7.1 Hz), 7.34 (2H, ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).

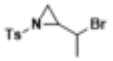
JDH-181-2g

2-(Iodomethyl)-1-(4-methylbenzene-1-sulfonyl)aziridine (2g): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2g** as a clear oil. **^{1}H NMR:** δ 2.32 (3H, s), 3.13 (1H, dd, *J* = 8.1, 4.1 Hz), 3.30-3.59 (4H, 3.37 (dd, *J* = 7.6, 4.1 Hz), 3.48 (d, *J* = 3.2 Hz), 3.48

(d, *J* = 3.2 Hz), 3.52 (ddt, *J* = 8.1, 7.6, 3.2 Hz)), 7.32 (2H, ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).

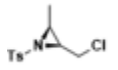
JDH-189-2a

2-(bromomethyl)-1-(4-methylbenzene-1-sulfonyl)aziridine (2a): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2a** as a clear oil. **^{1}H NMR:** δ 2.32 (3H, s), 3.13 (1H, dd, *J* = 8.1, 4.1 Hz), 3.33 (1H, dd, *J* = 7.6, 4.1 Hz), 3.49 (1H, ddt, *J* = 8.1, 7.6, 3.2 Hz), 3.98-4.09 (2H, 4.04 (d, *J* = 3.2 Hz), 4.04 (d, *J* = 3.2 Hz)), 7.34 (2H, ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).



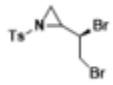
JDH-184-2f

2-(1-bromoethyl)-1-(4-methylbenzene-1-sulfonyl)aziridine (2f): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2f** as a clear oil. **^{1}H NMR:** δ 1.45 (3H, d, *J* = 6.7 Hz), 2.32 (3H, s), 3.07-3.40 (3H, 3.13 (dd, *J* = 8.1, 4.1 Hz), 3.23 (ddd, *J* = 8.1, 7.6, 4.3 Hz), 3.34 (dd, *J* = 7.6, 4.1 Hz)), 4.21 (1H, qd, *J* = 6.7, 4.3 Hz), 7.32 (2H, ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).



JDH-185-2h

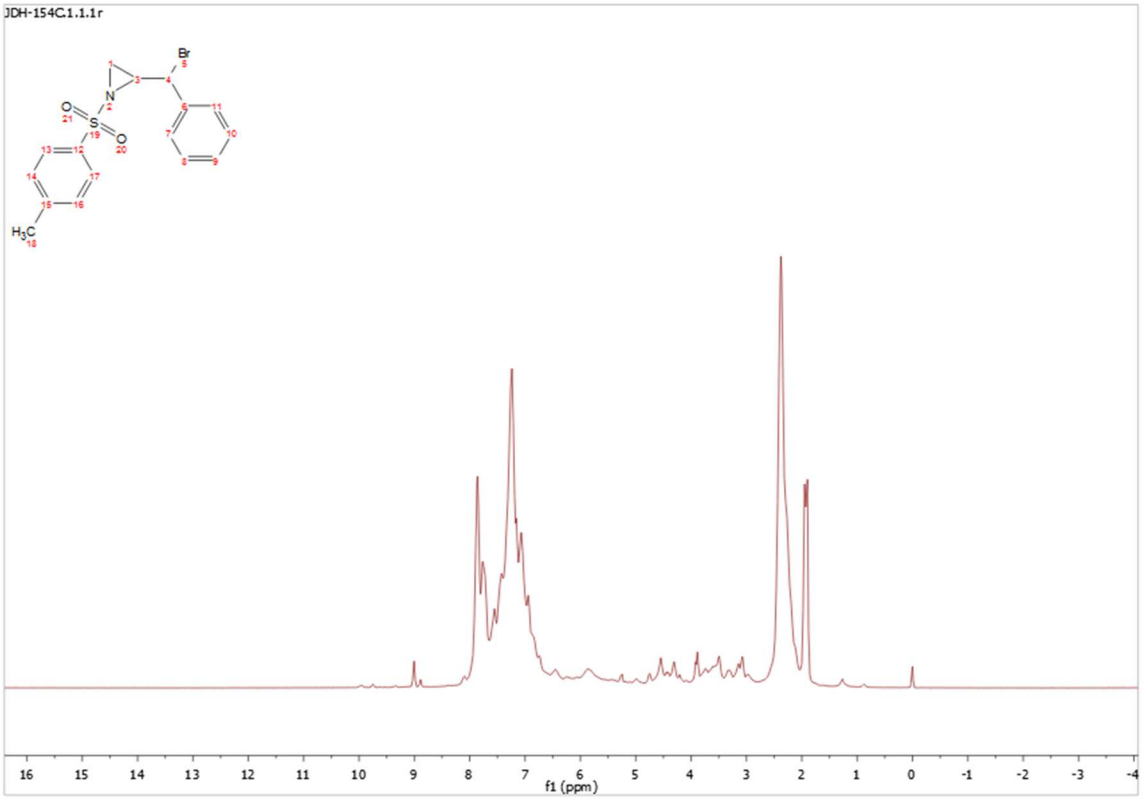
2-(chloromethyl)-1-(4-methylbenzene-1-sulfonyl)aziridine (2h): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2h** as a clear oil. **^{1}H NMR:** δ 1.36 (3H, d, *J* = 5.4 Hz), 2.32 (3H, s), 3.37-3.53 (2H, 3.44 (dq, *J* = 8.1, 5.4 Hz), 3.47 (dt, *J* = 8.1, 3.3 Hz)), 4.11-4.22 (2H, 4.16 (d, *J* = 3.3 Hz), 4.16 (d, *J* = 3.3 Hz)), 7.32 (2H, ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).

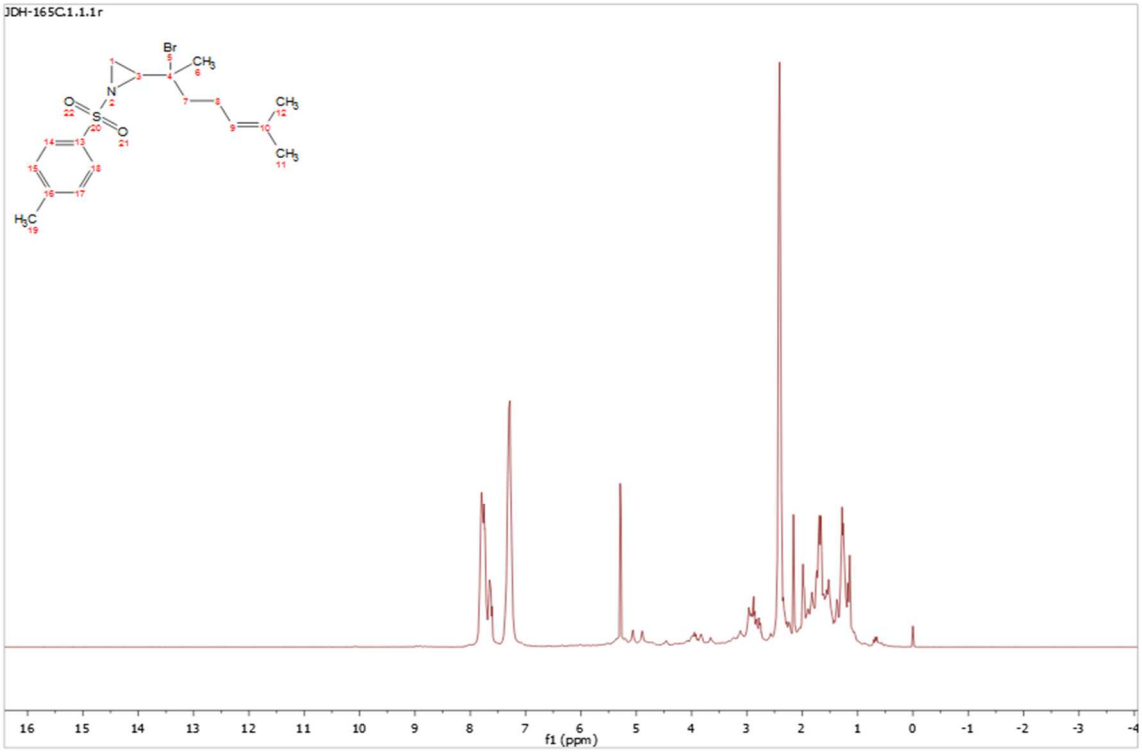


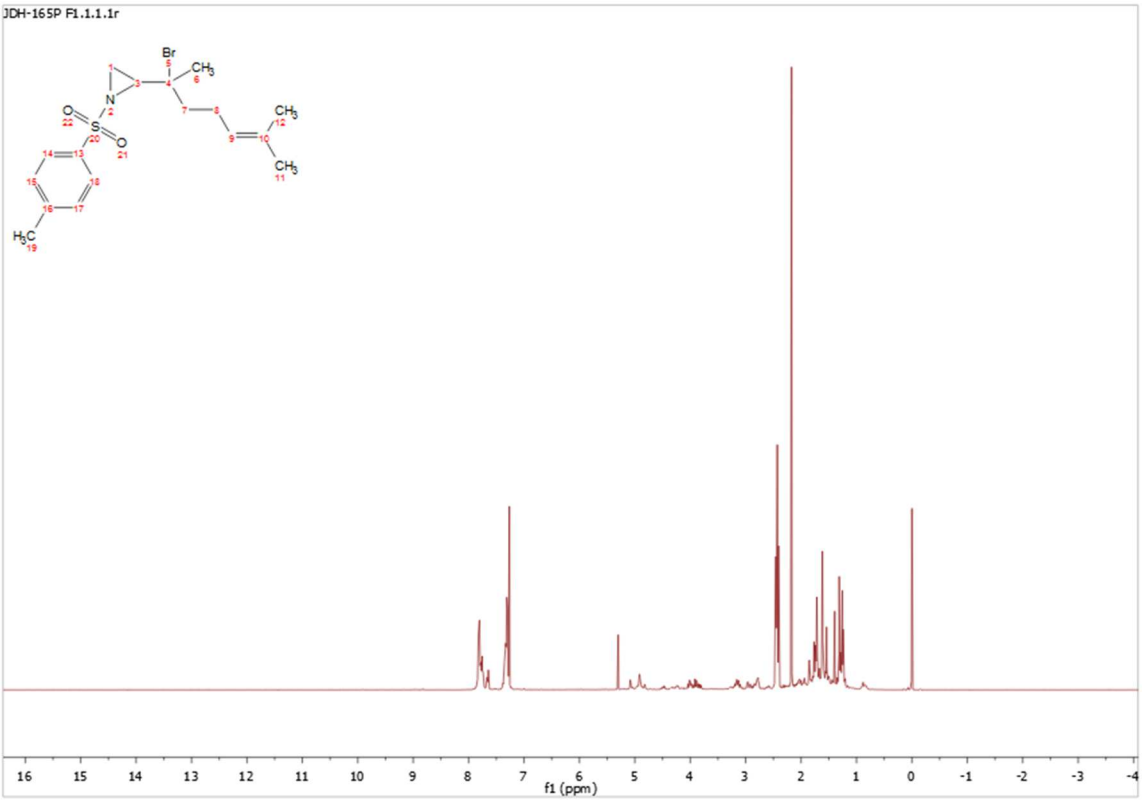
JDH-186-2d

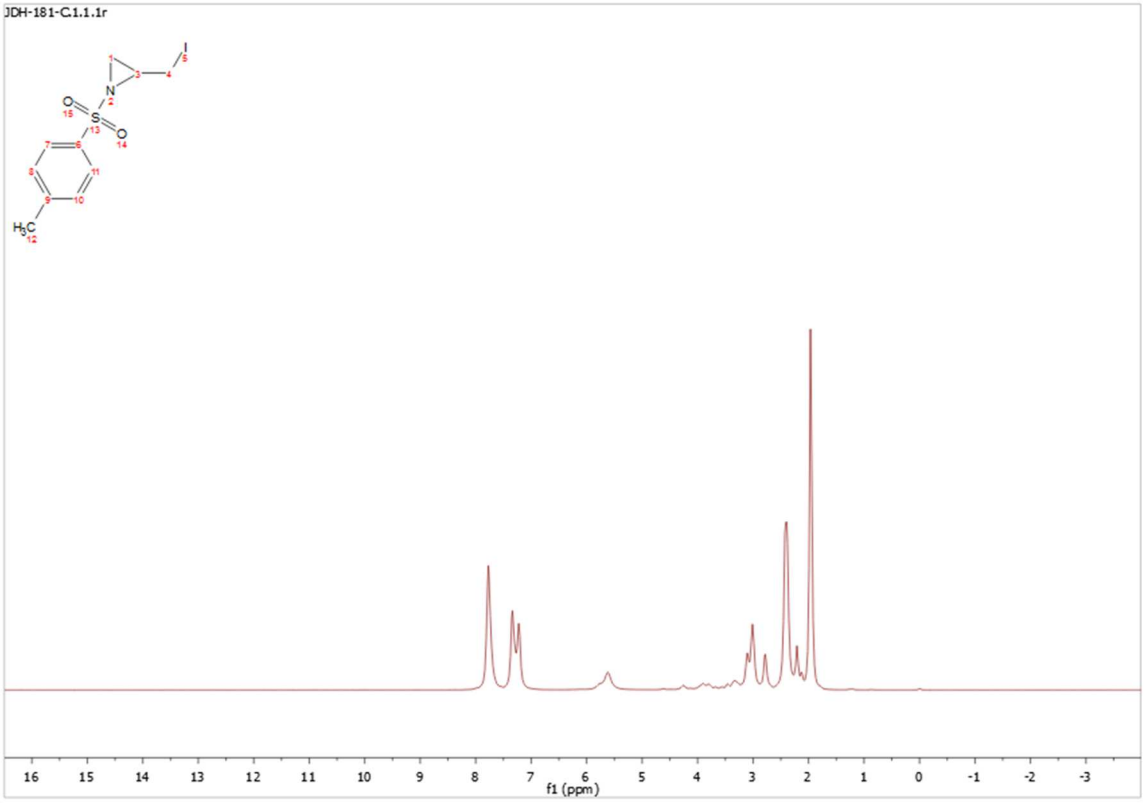
2-(1,2-dibromoethyl)-1-(4-methylbenzene-1-sulfonyl)aziridine (2d): Purification via manual silica gel flash chromatography (100:1 heptanes/EtOAc to 20:1 heptanes/EtOAc) afforded the haloaziridine product **2d** as a clear oil. **^{1}H NMR:** δ 2.32 (3H, s), 3.09-3.46 (3H, 3.16 (dd, *J* = 8.1, 4.1 Hz), 3.28 (ddd, *J* = 8.1, 7.6, 3.2 Hz), 3.39 (dd, *J* = 7.6, 4.1 Hz)), 3.50-3.61 (2H, 3.56 (d, *J* = 5.4 Hz), 3.56 (d, *J* = 5.4 Hz)), 4.32 (1H, td, *J* = 5.4, 3.2 Hz), 7.32 (2H, ddd, *J* = 7.9, 1.8, 0.4 Hz), 7.70 (2H, ddd, *J* = 7.9, 1.5, 0.4 Hz).

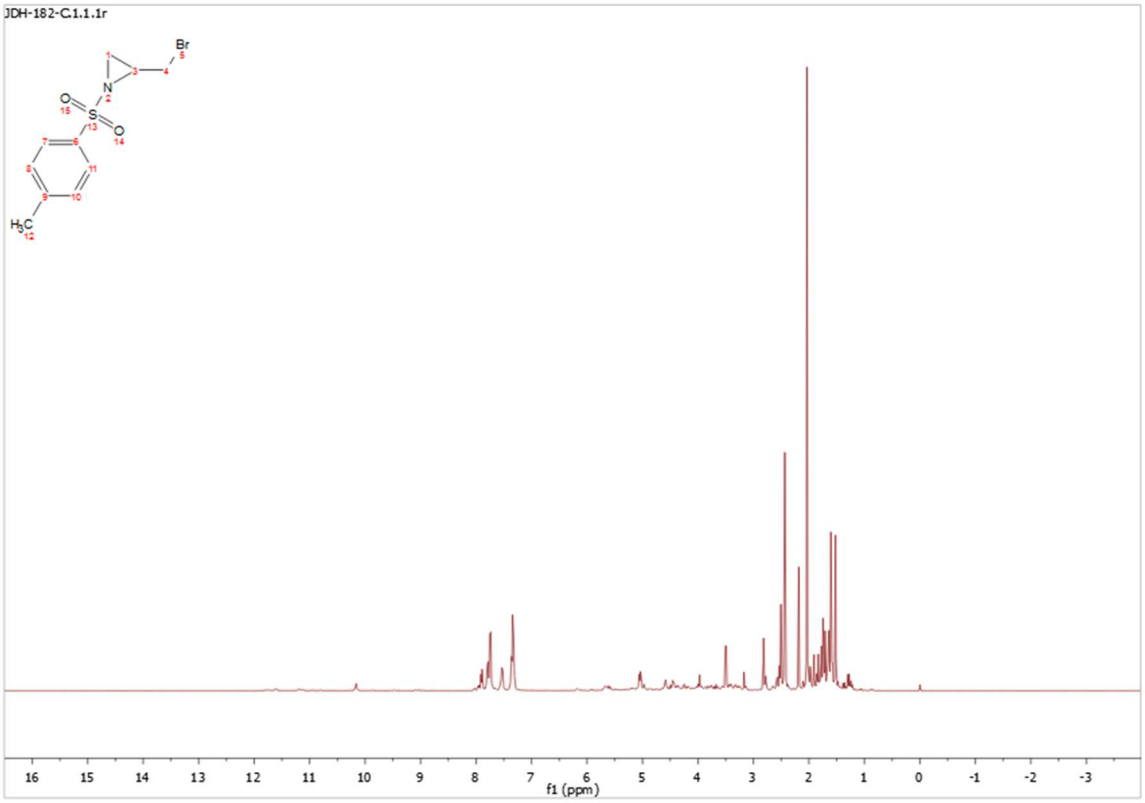
2.5.3 Synthesis of Pyrrolidines, Pyrrolines, and Azepines – ^{1}H NMR Spectra

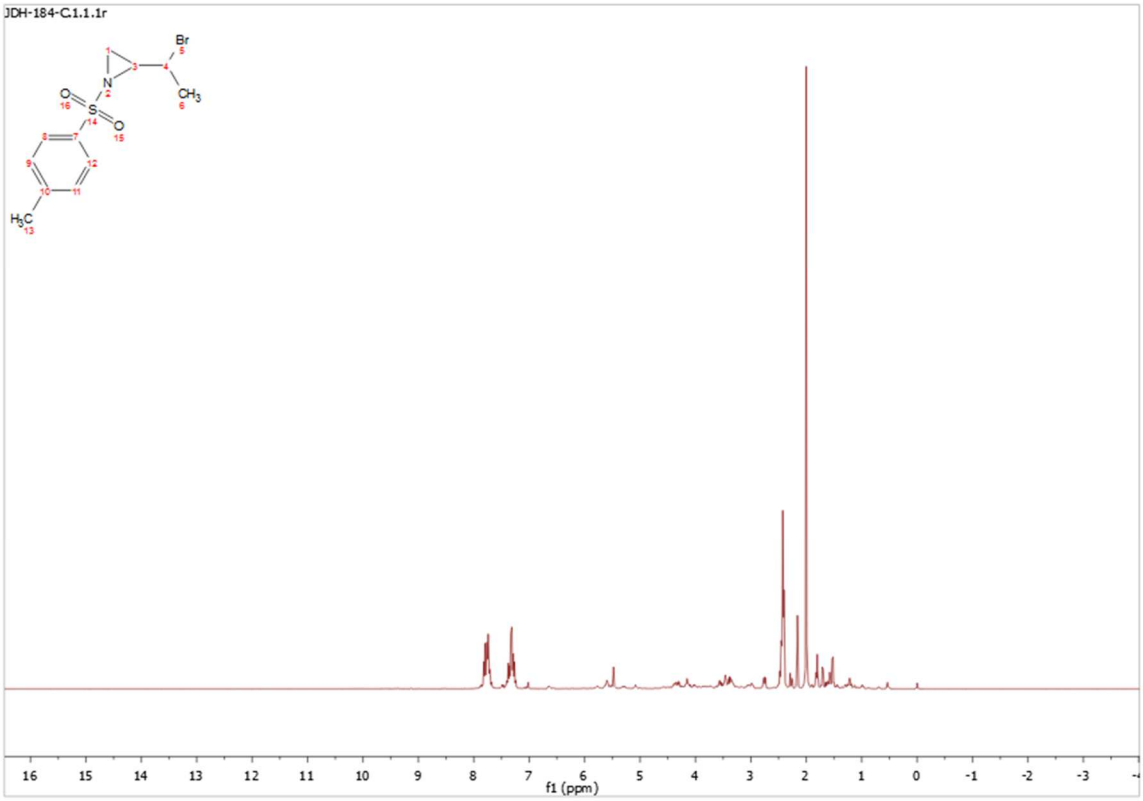


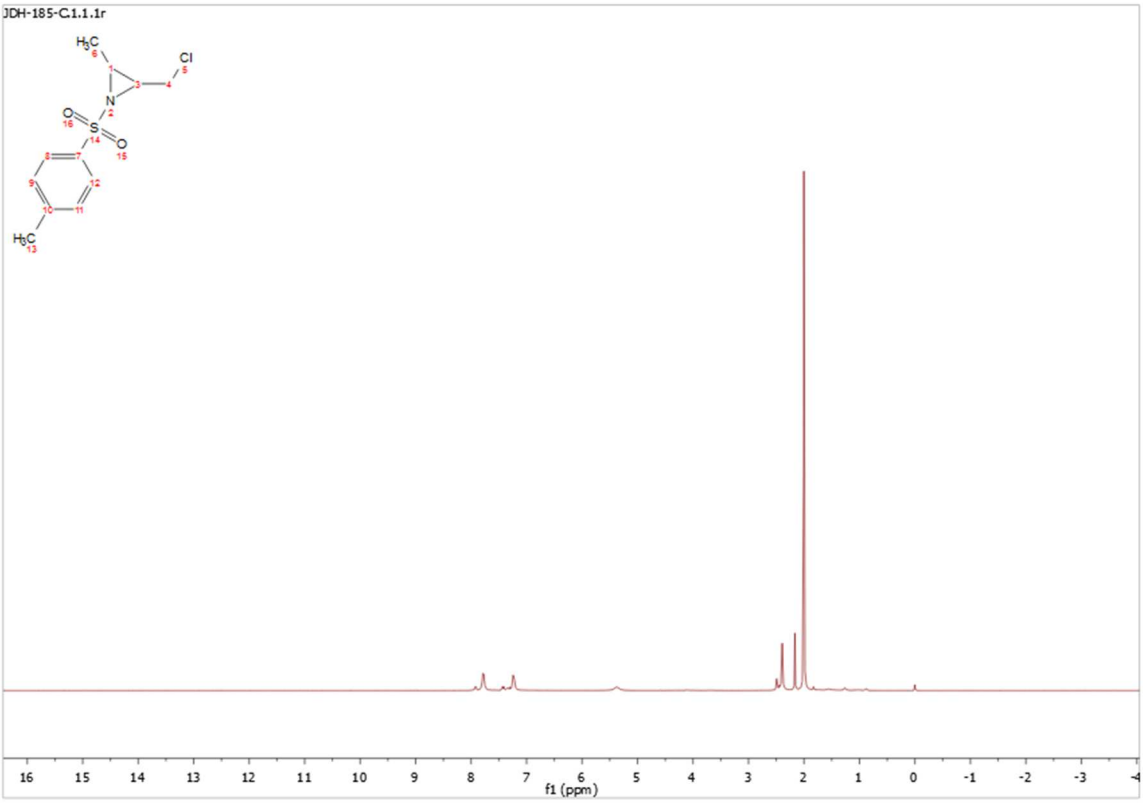

JDH-165C1.1.1r
f1 (ppm)

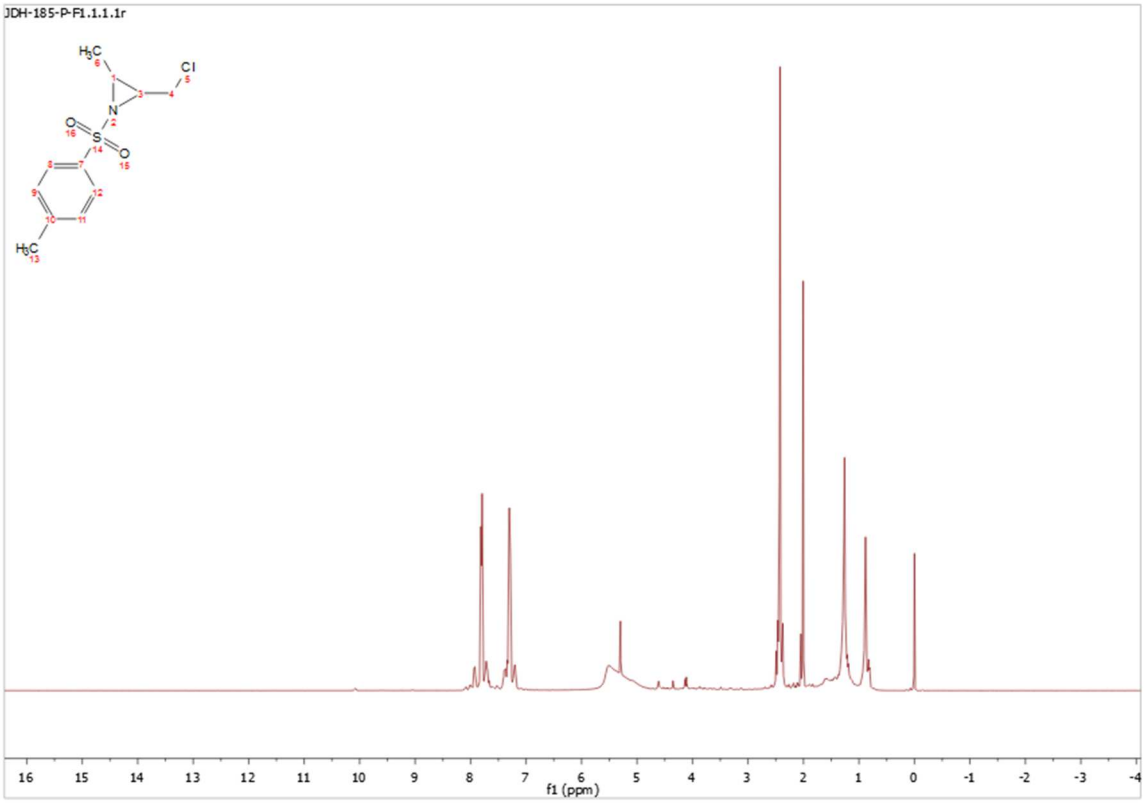

JDH-165P F1.1.1.1r
f1 (ppm)

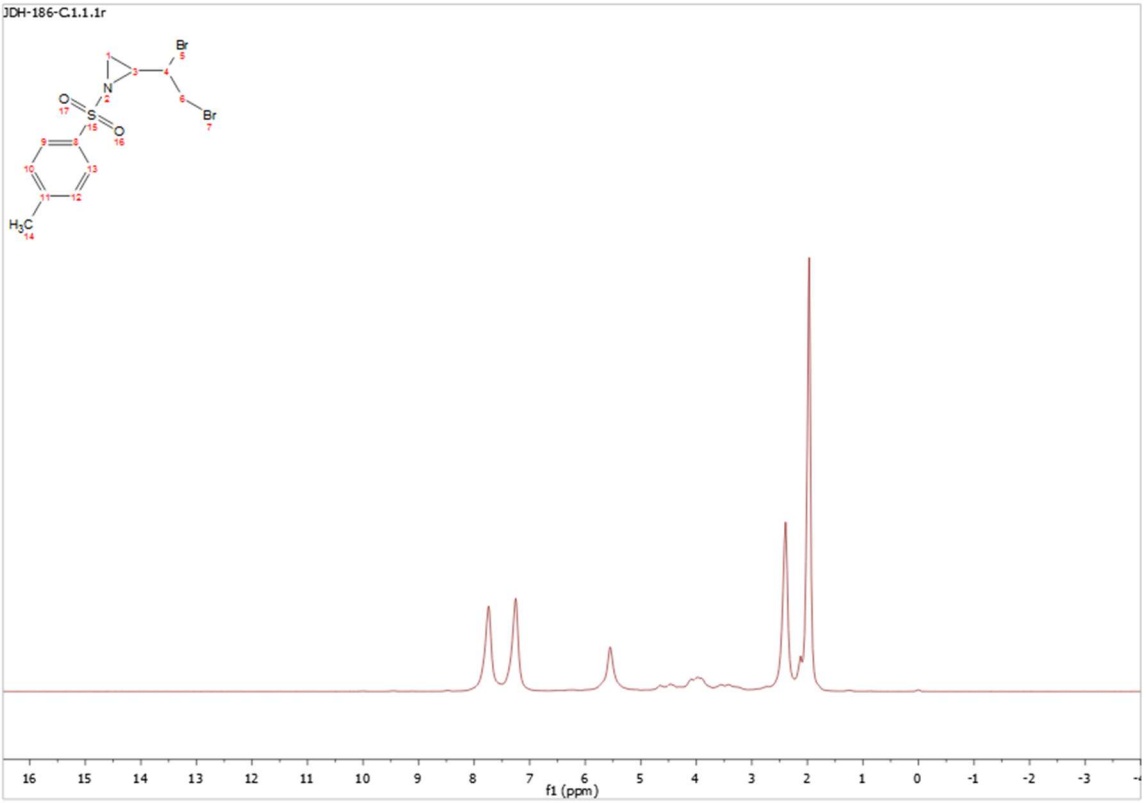

JDH-181-C.1.1.1r
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


JDH-182-C.1.1.1r
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


JDH-184-C.1.1.1r
Br
CH3
O
S
O
H3C
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


JDH-185-C.1.1.1r
H3C
Cl
N
O
S
O
H3C
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


JDH-185-P-F1.1.1.1r
f1 (ppm)


JDH-186-C.1.1.1r
f1 (ppm)

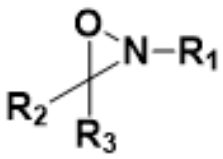
Chapter 3

Photo-Induced Isomerization of Vinyl Nitrones to Vinyl Oxaziridines

Oxaziridines are classically valuable moieties that become the targets for many organic chemists looking to improve on the organic methodologies involved with making complex pharmacophores as well as natural products. Research involving oxaziridines over the past five decades has been motivated by the unusual physical properties possessed by these compounds as well as their distinctive reactivity. Oxaziridines can be characterized in Figure 17 by a three membered organic ring containing one carbon atom, one nitrogen, and one oxygen atom. The presence of these two electronegative atoms allow for further functionalization of oxaziridines into more complex heterocycles as, under varying reaction conditions, the carbon-nitrogen bond, carbon-oxygen bond, and oxygen-nitrogen bond can all be cleaved in order to afford a slew of heterocycles with an added level of functionalization. The following section will introduce oxaziridines by reviewing a few synthetic organic methods developed in order to synthesize oxaziridines.

Figure 17

Oxaziridine Moiety



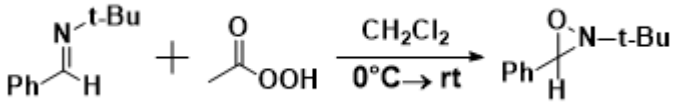
3.1 Synthesis of Oxaziridines

Oxaziridines have shown to be crucial organic scaffolds as well as acting as reagents for the synthesis of even more complex heterocyclic containing complexes. One of the most well characterized reactivities that oxaziridines can provide to organic chemists is their ability to serve as electrophilic oxygen transfer reagents. Numerous, thorough reviews have been published with a focus on oxaziridines used as electrophilic oxygen transfer reagents. (70) There has been recent significant growth of synthetic routes that have become available in oxaziridine chemistry allowing for the synthesis of highly functionalized, stereospecific oxaziridine moieties. The following brief review, in this section, of the current methods to provide oxaziridines will be organized via the substituent of the nitrogen atom in the oxaziridine moiety.

The first class of N-substituted oxaziridines explored by organic chemists were N-alkyl-substituted oxaziridines, initially synthesized by Emmons and coworkers in 1957. The standard method for Emmon's preparation of the N-alkyl-substituted oxaziridines involves the oxidation of an imine to then afford the corresponding oxaziridine. The use of peroxy-acids, described in Emmons initial report and depicted in Figure 18, such as m-chloroperbenzoic acid (mCPBA) to oxidize imines continues to be the most common method utilized by organic chemists today for oxaziridine synthesis. Experimental and theoretical studies of Emmon's oxaziridines synthesis support a two-step mechanism for imine oxidation. (71)

Figure 18

Emmons Synthesis of N-Alkyl Substituted Oxaziridines



The next class of oxaziridines which will be discussed are N-unsubstituted oxaziridines. N-Unsubstituted oxaziridines are useful organic moieties as they are highly reactive toward nucleophiles and are usually formed *in situ* in inert solvents and reacted further without the need for additional purification procedures. (70) Oxaziridines bearing unsubstituted nitrogen atoms are generally not synthesized by standard peracid oxidation methods due to the instability of N-H imines. Schmitz et al. have reported the preparation of N- unsubstituted oxaziridines through the reaction of cyclohexanone with ammonia and sodium hypochlorite. (72)

Another notable type of N-substituted oxaziridines, to which previously developed methods exist, are N-sulfonyloxaziridines. N-sulfonyloxaziridines are highly selective, neutral, aprotic oxidizing reagents that have found, and are continuing to find, increased utility in organic synthesis. Enantiomerically pure examples of N-sulfonyloxaziridines are useful asymmetric oxidizing reagents to afford high stereoselectivities for the asymmetric oxidation of sulfides (selenides) to sulfoxides (selenoxides) (66 to >95% ee), for the epoxidation of alkenes (up to 65% ee), and for the asymmetric oxidation of enolates to optically active hydroxycarbonyl compounds (55-

95% ee). (73) The earliest attempts to prepare optically active N-sulfonyloxaziridines relied on catalysis from chiral camphor-based peracids. (74) This was not viable for continued use as the approach suffers from low selectivity and repeated fractional recrystallizations are required to achieve high optical purity using this protocol. The first synthetically useful approach to chiral N-sulfonyloxaziridines was based on the synthesis of camphor sulfonic acid derived imines which can be selectively oxidized with oxone to give the corresponding chiral N-sulfonyloxaziridines. This oxidation can only take place from the endo face of the carbon and nitrogen double bond due to the steric blocking of the exo-face, resulting in a single oxaziridine isomer (75) Because of the multitude of uses discovered with N-sulfonyloxaziridines chemistry, N-sulfonyloxaziridines have quickly become the most extensively utilized class of oxaziridines in organic synthesis research due of their stability, ease of synthesis, and superior oxidizing ability compared to N-alkyloxaziridines. Now commonly referred to as "Davis' oxaziridines", N-sulfonyloxaziridines are prepared through oxidation of the corresponding N-sulfonyl imines, which in turn can be prepared by condensation of sulfonamides ($R\text{-}SO_2NH_2$) with aromatic aldehydes using either Bronsted or Lewis acids. (70)

The final N-substituted oxaziridines that will be discussed in this chapter are N-phosphinoyl substituted oxaziridines. Oxaziridines bearing the N-phosphinoyl substitution groups were first synthesized by Boyd et al. (76) This featured class of substituted oxaziridines are typically accessed via a reaction of an aryl oximes with chlorodiphenylphosphine, followed by oxidation of the corresponding, rearranged N-phosphinoyl imines with mCPBA. The oxaziridines produced from this method are characterized as stable compounds that have a low barrier to nitrogen inversion (~13

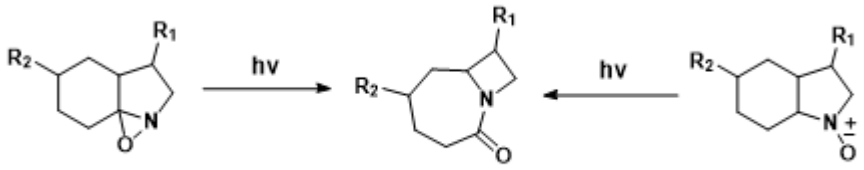
kcal/mol) and exist in the trans-configuration. This barrier of inversion is lower than for the related N-sulfonyloxaziridines due to the effect of a stronger conjugative interaction between nitrogen and phosphorus atoms in N-phosphinoyl oxaziridines than the interaction between nitrogen and sulfur atoms in N-sulfonyloxaziridines in the transition state for epimerization. (77) Now that current methods for the synthesis of oxaziridines have been discussed, pharmaceutical and synthetic applications of oxaziridines will be reviewed.

3.2 Pharmaceutical Relevance

Oxaziridines have been proven time and time again to be useful reagents in both organic synthesis as well as in the production of molecularly complex pharmacophores. In each case, the stereochemistry and conformation of the afforded oxaziridines used, and its substituents, are critical to exploring what types of further transformations they can then undergo. N-Alkyl oxaziridines are useful intermediates, for example, for the synthesis of amides and lactams and have been used more recently to prepare chiral pyrrolidines and aziridines via nitrogen-centered radicals. The potential of oxaziridines as enzyme inhibitors has also been recognized from the findings of the previously mentioned application of N-alkyl oxaziridines. (80)

Figure 19

Synthesis of Fused Bicyclic Lactams From Oxaziridine Derivatives



Another example of the application of oxaziridines, depicted in Figure 19, is through the synthesis of fused bicyclic lactams as non-peptide scaffolds mimicking peptidyl alpha-turn topology. The final product of this synthesis, the 1-azabicyclo [5.2.0] nonan-2-one bicyclic skeleton, has very few existing synthesis methods but the available routes are not straightforward and usually result in low product yields. The synthesis of 1-azabicyclo [5.2.0] nonan-2-one lactam, containing a bridgehead nitrogen atom, is offered in Figure 19 by the photolysis of a cyclic oxaziridine derivative or the corresponding nitrone shown on the right of Figure 19. The photolysis of the cyclic nitrone leads to an oxaziridine intermediate before completing the transformation in the corresponding lactam. (86)

Figure 20

Lewis Acid Promoted [3+2] Cycloaddition of Oxaziridines & Allylic Alcohols

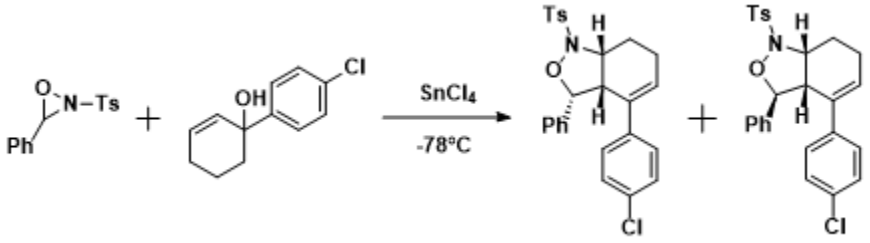


Figure 20 illustrates another application of oxaziridines through the synthesis of novel bicyclic isoxazolidine-containing compounds through 1,3-dipolar cycloaddition reactions between cyclic allylic alcohols and oxaziridines as substrates. The power of this synthetic route is that the current methods for the synthesis of isoxazolidines, through the carbonyl imine intermediates, are currently limited to monosubstituted olefin substrates. This reaction shows high product conversion and the reaction substrates tolerate various functional groups including the cyclopropyl and amine substituents. Mechanistic studies suggest the stereochemistry and diasteroeselectivity of the produced isoxazolidines are due to the allylic cation and a carbonyl imine intermediate. (87)

The final example of the application of oxaziridines, discussed in this section, is a collection of cycloaddition reactions involving the cleavage of the N−O bond of an oxaziridine as this type of reaction mechanism has received increased attention in the past few years. The value of this synthetic route comes from the fact that direct, uncatalyzed oxyamination reactions between oxaziridines and olefinic substrates are quite hard to

achieve. Desmarteau and colleagues however have reported that electron-deficient 1,1-difluoroalkenes reacted with perfluoro-oxaziridine affords 1,3-oxazolidine in excellent yields. One caveat to Desmarteau's reaction is that only electron deficient alkenes undergo this atypical amino-hydroxylation transformation. (88) While only a few of the many examples of the applications of oxaziridines have been discussed in this section, it is clear to see why the GML lab group have chosen these valuable moieties as target structures for selective synthesis within mild conditions.

3.3 Results and Discussion

As mentioned before, oxaziridines continue to become an ever-present molecular target for synthetic chemists as they are common intermediates for the synthesis of biologically active, complex scaffolds used in the creation of new pharmacophores. The work I completed in the GML lab group finished the reaction scope of the novel synthetic pathway for the photocatalytic synthesis of vinyl oxaziridines from vinyl nitrones. Vinyl oxaziridines are seen as more valuable targets than oxaziridines alone as they add two points of diversification to the oxaziridines structure allowing for even greater opportunities for further functionalization of the molecule. This pathway was initially achieved by first looking at the methods previously developed to synthesize the oxaziridine moiety. As seen in a few synthetic examples discussed in previous sections, imine oxidation is a preferred pathway to afford oxaziridines as imines provide superior heteroatom transfer agents in oxaziridine synthesis. The GML lab group had previously synthesized a library of vinyl nitrones which were now available for photoisomerization to form their respective vinyl oxaziridines. Photoisomerization of vinyl nitrones to vinyl oxaziridines was an attractive organic method to explore as it provides mild reaction

conditions to afford the valuable oxaziridine moiety. This photocatalytic reaction pathway was first realized by leaving the vinyl nitrones in solution on a windowsill for 18 hours, in the visible light from the sun, showing the lowest conversion. This method was then further developed to use LED light bulbs as the visible light source instead of sunlight as sunlight is not nearly as direct as white LED light bulbs and the vinyl nitrones in solution were not being excited to a state where isomerization occurs. T-cinnamaldehydes derived nitrones were used along with white LED light in a lightbox, with and without catalyst, during the optimization studies which produced oxaziridines in excellent yields. (81) The optimization studies for this reaction can be seen in Table 12. The reaction hypothesis for this photoisomerization transformation can be seen in Table 11. These results were surprising as previous reports of nitrone isomerization required UV irradiation in order to promote a similar transformation. (89) The reaction scopes for the photoisomerization transformation can be seen in Table 14 and Table 15.

Table 11

Photo-Induced Isomerization of Vinyl Nitrones to Vinyl Oxaziridines Reaction Hypothesis

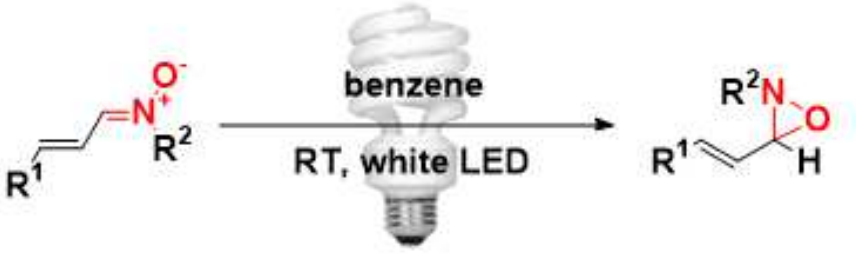
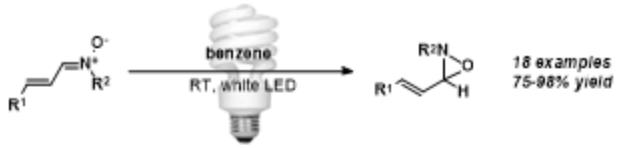


Table 12

Synthesis of Vinyl Oxaziridines Optimization Studies



Entry	R^1	additive	solvent	concentration (M)	yield (%)[d]
1	Ph[c]	visible light[b]	benzene	0.05	12
2	Ph	visible light[b]	benzene	0.05	48
3	Ph	$Ru(bpy)_3Cl_2$ 5 mol %[c]	CH_3CN	0.05	38
4	Ph	visible light[b]	CH_3CN	0.05	40
5	Ph	visible light[b]	toluene	0.05	44
6	Ph	visible light[b]	CH_2Cl_2	0.05	20
7	Ph	$Ru(bpy)_3Cl_2$ 5 mol %[c]	CH_3CN	0.05	40
8	Ph	visible light[b]	benzene	0.01	28
9	Ph	visible light[b]	benzene	0.025	20
10	cinnamyl	visible light[b]	benzene	0.05	96
11	cinnamyl[c]	visible light[b]	benzene	0.05	28
12	cinnamyl	visible light[b]	CH_3CN	0.05	75
13	cinnamyl	visible light[b]	CH_2Cl_2	0.05	35
14	cinnamyl	$Ru(bpy)_3Cl_2$ 5 mol %	CH_3CN	0.05	82
15	cinnamyl	visible light[b]	benzene	0.01	80
16	cinnamyl	visible light[b]	benzene	0.025	64

a. By the windowsill over 18 h. *b*. White LED. *c*. Nitrone intermediate was isolated prior to photocyclization. *d*. Isolated yields.

Table 13

Synthesis of Vinyl Oxaziridines Hypothesized Visible-Light Photosensitized Mechanism

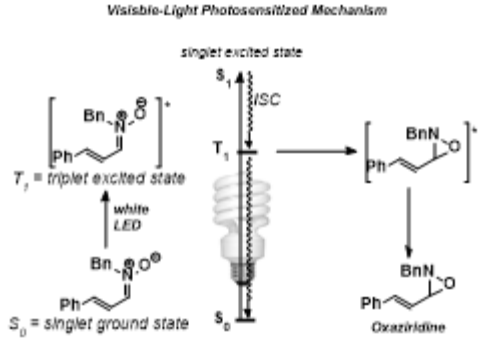
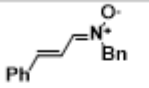
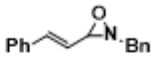
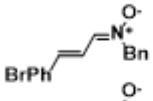
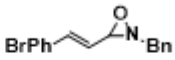
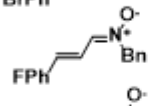
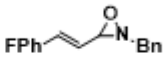
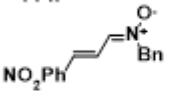
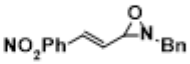
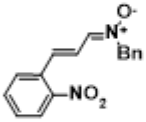
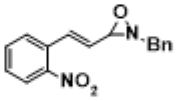
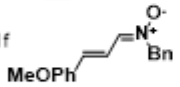
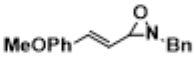
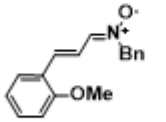
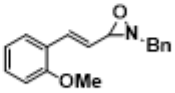
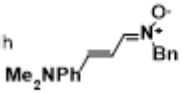
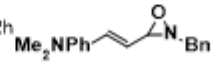
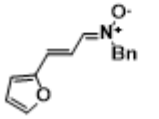
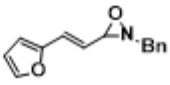


Table 14

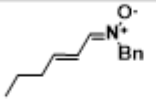
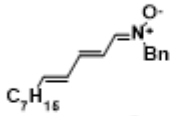
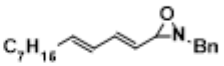
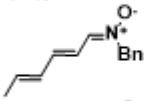
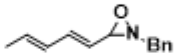
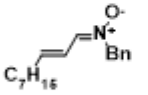
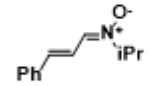
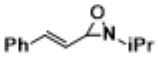
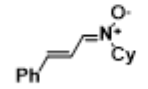
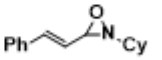
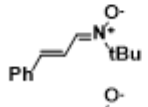
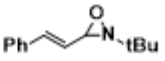
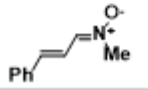
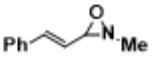
Synthesis of Vinyl Oxaziridines Reaction Scope 1

Entry	nitrone		product[c]		Yield (%)[a,b]
1	1a		2a		98
2	1b		2b		93
3	1c		2c		84
4	1d		2d		92
5	1e		2e		91
6	1f		2f		97
7	1g		2g		96
8	1h		2h		95
9	1i		2i		93

a. Conditions: Nitrone (1 mmol) in benzene (0.05M) for 22h. b. Isolated yields.
c. Reaction crude was purified by silica gel flash chromatography.

Table 15

Synthesis of Vinyl Oxaziridines Reaction Scope 2

Entry	nitrone		product[c]		Yield (%)[a,b]
1	1j		2j		79
2	1k		2k		82
3	1l		2l		84
4	1m		2m		75
8	1n		2n		91
7	1o		2o		92
8	1p		2p		91
9	1q		2q		95

a. Conditions: Nitrone (1 mmol) in benzene (0.05M) for 22h. b. Isolated yields.
c. Reaction crude was purified by silica gel based flash chromatography.

3.4 Experimental

Organic reagents were obtained from Aldrich Chemical, Acros Organics, and Alfa Aesar. Organic reactions were performed with 20 milliliter glass vials that allowed for magnetic stirring. TLC analysis was performed via a 0.25mm E. Merck silica gel 60 F254 plates and visualized under 254 nm UV light as well as staining with potassium permanganate solution ($KMnO_4$). Products were purified via manual silica-gel flash chromatography and collected based on NMR analysis and Rf values of UV spots by TLC. NMR spectrum were recorded via Varian Mercury II 400 MHz Spectrometer at 24 degrees Celsius in CDCl. Chemical shifts are expressed in ppm relative to solvent signals: CDCl, (1 H, 7.23 ppm; 13C, 77.0ppm; coupling constants expressed in Hz)

3.4.1 General Method for Synthesis of Vinyl Nitrones

A reaction vial was obtained and 0.1M of the organic solvent acetonitrile (ACN) was pipetted into the vial. Next, 1.296 mmol of magnesium sulfate was weighed out and placed into the 20-milliliter reaction vial. 1.944 mmol of N-benzyl hydroxylamine was measured and added to the reaction vial followed by the final reagent which was 1.296 mmol of a vinyl ketone or vinyl aldehyde. The reaction was run overnight at room temperature.

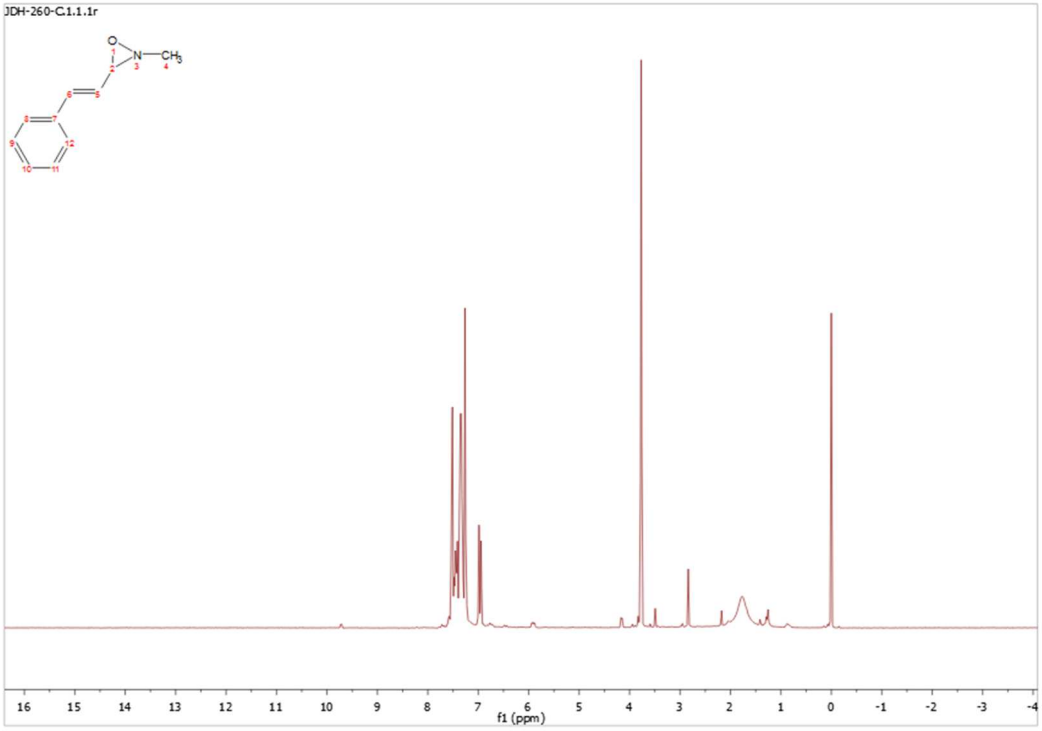
The workup of the crude product was started the following day. The workup of the vinyl nitrone created from the first step involved gravity filtration to remove the excess magnesium sulfate in the reaction which was then run in the rotatory evaporator to remove the acetonitrile in the reaction. 10 milliliters of DI water were added to the reaction vial and liquid/liquid extraction was performed with the water and three washes

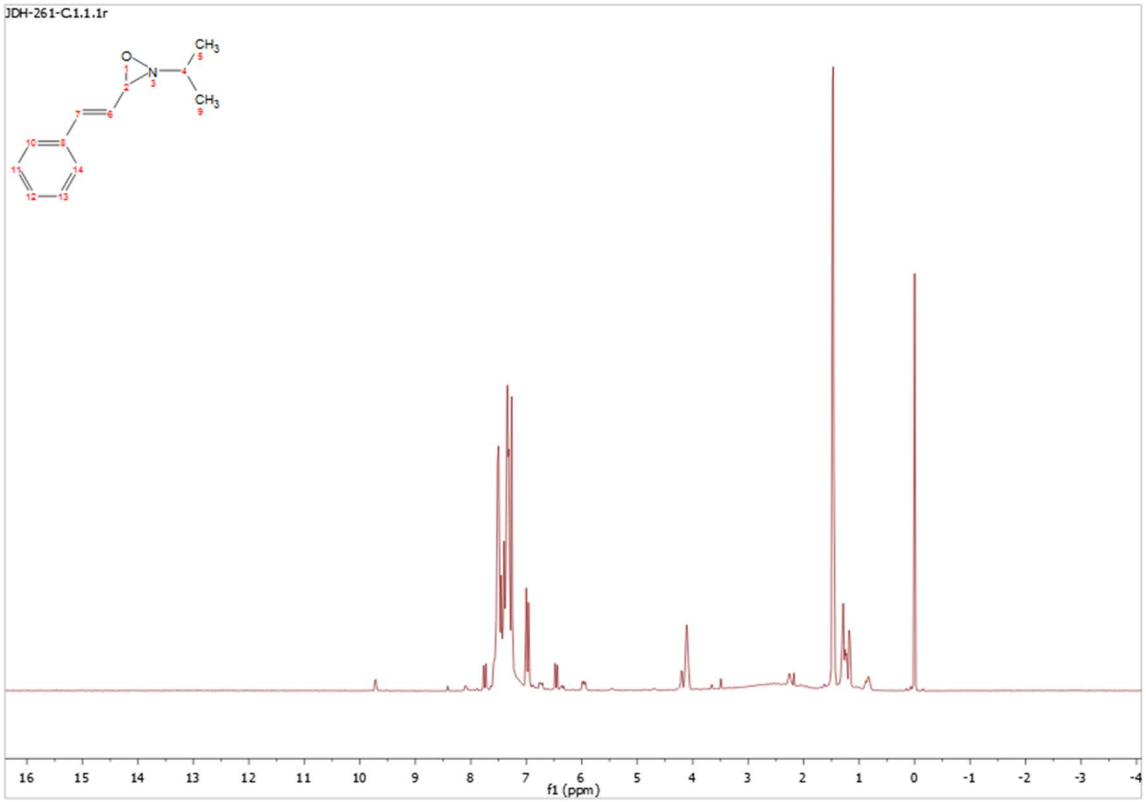
of ethyl acetate. The ethyl acetate layer was collected, and sodium sulfate was added to remove any of the remaining water with the reaction. The reaction was then gravity filtered to remove the magnesium sulfate previously added. The reaction was rotatory evaporated and the crude product was confirmed by TLC and NMR. It was at this point that if the crude was an oil, manual, silica-based, flash column chromatography was performed to isolate the pure vinyl nitrone product. If the crude product at the end of the work up was a solid, then a pentane decanting was performed in order to isolate the vinyl nitrone shown on the left of Figure 6. The pure vinyl nitrone was characterized/confirmed via proton/carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS).

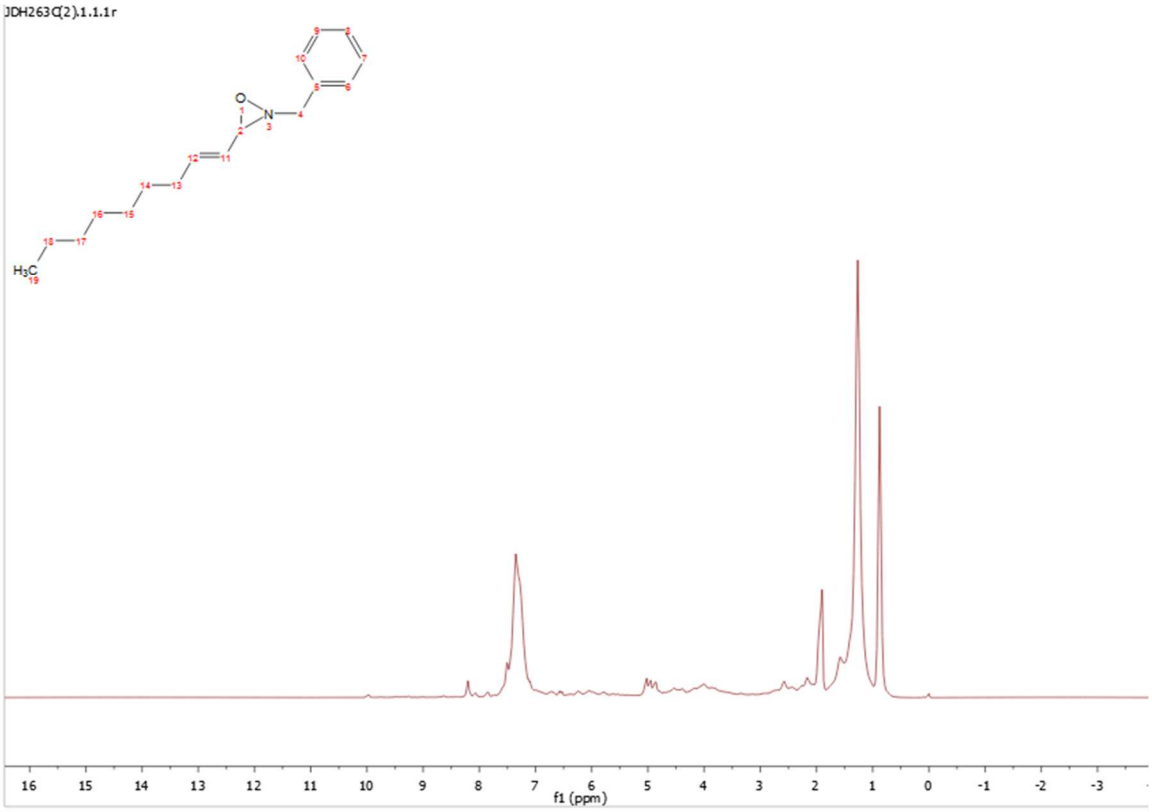
3.4.2 General Method for Synthesis of Vinyl Oxaziridines

The final step of the synthesis of vinyl oxaziridines involved taking a new 20-milliliter reaction vial and filling it with 0.1M of the organic solvent acetonitrile. The pure vinyl nitrone product was weight or measured out in a syringe and added to the 20-milliliter reaction vial. 0.005M of the $[Ru(bpy)_3]^{2+}$ photocatalyst was added to the reaction vial. One equivalence of molecular sieves was also added to the reaction vial to keep the creation dry. The reaction vial was then placed into a lightbox with the lightbox fan turned on for a total of 24 hours. The following day, the reaction was worked up through gravity filtration to remove the molecular sieves followed by rotatory evaporation of the crude reaction solution to remove organic solvent. The crude vinyl oxaziridine reaction was purified via flash chromatography. The pure vinyl oxaziridine was characterized/confirmed via proton/carbon NMR, infrared spectroscopy (IR), and mass spectrometry (MS). The reaction schematic of the final step of the synthesis of vinyl oxaziridine is shown below in Figure 6.

3.4.3 Synthesis of Vinyl Oxaziridines – ^{1}H NMR Spectra






JDH263C(2),1.1.1r
f1 (ppm)

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