2021

# Synthesis of Tetrahydroxanthones via Formal [4+2] Cycloadditions

JULIA RUTH NOEL

# Synthesis of Tetrahydroxanthones via Formal [4+2] Cycloaddition

A Major Qualifying Project Proposal
submitted to the Faculty of
Worcester Polytechnic Institute
in partial fulfilment of the requirements
for the degree of Bachelor of Science

By
Julia Noel

Date:
4/5/2021

Report Submitted to:

Professor Anita E. Mattson
Worcester Polytechnic Institute

# Abstract

The synthesis of natural product-inspired oxygen heterocycles has long been hindered by the development of enantioselective methods for forming important cores, such as chromane and xanthone cores. Through the investigation of enantioselective methods for the synthesis of tetrahydroxanthones, a method was developed using copper bisoxazoline catalysis. This method utilized [4+2] cycloaddition to set two stereocenters at once, one of which is a quaternary carbon. This product can be further derivatized to an intermediate of morphine and provides opportunity for the synthesis of natural product-inspired chromane and xanthone cores. The tolerance of this method shows its amenability to a structure activity relationship study. This reaction mechanism was investigated using a Linear Free Energy Relationship Study. Hammett plots revealed that a positive charge was built up during the reaction which agreed with our proposed mechanism. However, it appeared that when a more substituted ligand was used, the more sterically demanding environment decreased the effect of the electronic properties of the substrate on the reaction.

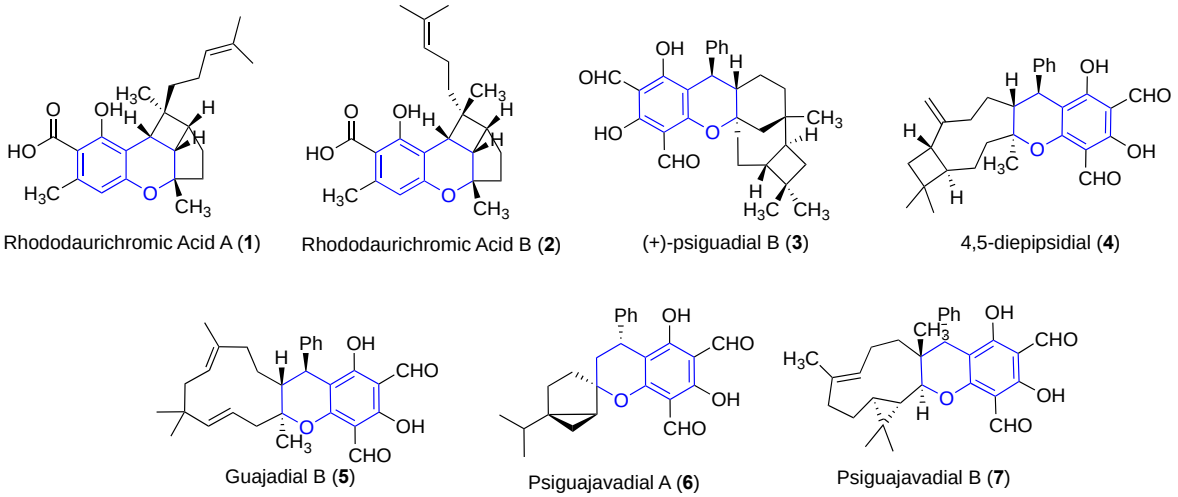
# Table of Contents

# Introduction

## Bioactive Targets

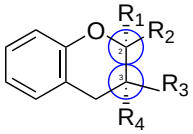
Oxygen heterocycles are a common structural feature in many natural products. A common core within these heterocycles is chromane structure. These chromane core molecules often possess desirable bioactive properties. Rhododaurichromic acids A (**1**) and B (**2**) are examples of natural products with chromane cores that were originally isolated from the leaves and twigs of *Rhododendron dauricum*.[1] These two compounds have potent anti-HIV activity in acutely affected H9 cells. Rhododaurichromic Acid A was found to have an $EC_{50}$ value of 0.37 mg/mL and a therapeutic index of 91.9 making it a promising anti-HIV agent.[1] Beyond anti-HIV potential, (+)-psiguadial B (**3**), a natural product isolated from the leaves of *Psidium guajva* by the Shao group, has antiproliferative activity against hepatoma cells.[2] Other secondary metabolites which have been isolated from *Psidium guajva* have very desirable bioactivies.[3] 4,5-diepipsidial A (**4**) and guajadial B (**5**) both showed strong cytotoxicity against A549 cells, a human cancer line, with $IC_{50}$ values of 160 nM and 150 nM respectively.[3] Also from the same meroterpenoid family, psiguajavadials A (**6**) and B (**7**) both showed potent antiproliferative effects in human cancer cell line HCT-116.[3]

Figure 1: Chromane Core Natural Products



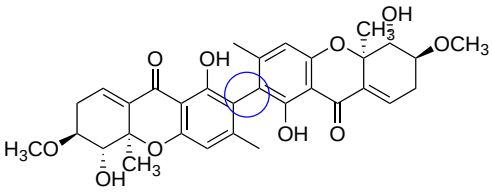

While these structures possess valuable bioactivities, they are structurally challenging from a synthetic perspective. All structures possess a chromane core (highlighted in blue in Fig. 1). **1**, **2**, and **3** have been successfully synthesized, allowing for further study.[1,2] However, **4**, **5**, **6**, and **7** still remain to be synthesized. The extra challenge which is presented in these molecules arising from the presence of an enantioenriched quaternary center at either the 2 or 3 position of the chromane (circled in blue in Fig. 2). The quaternary center at the 3 position is particularly difficult to establish due to the lack of publications on this chemistry.

Figure 2: Chromane Core

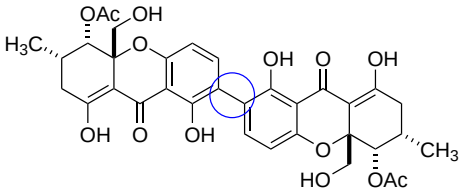


Another promising oxygen-heterocycle core is the xanthone core. There are many natural products which have been isolated with a xanthone core, including several which possess desirable bioactivities (Figure 3). Dimeric xanthones have been isolated from endophytes and fungi.[4] For example, ascherxanthone A (**8**), isolated from the mycelia of *Aschersonia* sp. BCC 8401, has anticancer activity against three cancer cell lines, KB, BC, and NCI-H187 with $IC_{50}$ values between 1.7 and 0.16 μg/mL.[4,5] The dicerandrols are another family of dimeric xanthones which can be isolated from *Phomopsis longicolla*.[4] Dicerandrol A (**9**), B (**10**), and C (**11**) all have been found to have activity against both the HCT-116 and A549 cancer cell lines. More specifically, **11** possesses increased cytotoxicity against human breast cancer, colon cancer, lung cancer, liver cancer, and breast epithelial cell lines when compared with **9** and **10**.[4] The phomoxanthones are another family of dimeric xanthones that offer wealth of biological activity. Isolated from *Phomopsis* sp. BCC 1323, phomoxanthone A (**12**) and B (**13**) both showed antimalarial, antitubercular, and cytotoxicity against KB cell, BC-1 cell, and Vero cell lines. **12** has been further studied to reveal that it can inhibit the proliferation of lymphoma cell line L5178Y and some cisplatin resistant cell lines, with cytotoxicity of **12** towards lymphoma cells increased 100-fold in comparison to healthy cells. This indicates great potential for the medicinal application of **12**.[4]

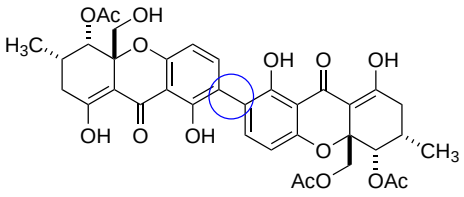
Figure 3: Xanthone Dimers



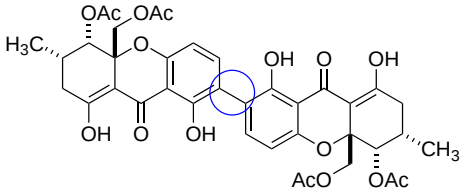
Ascherxanthone A (**8**)



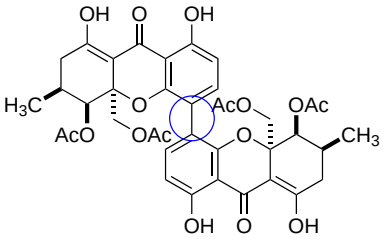
Dicerandol A (**9**)



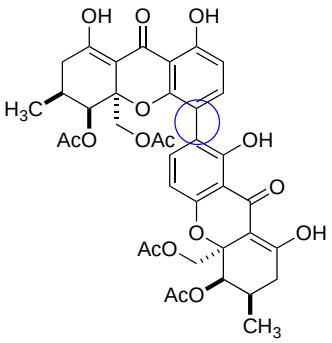
Dicerandol B (**10**)



Dicerandol C (**11**)



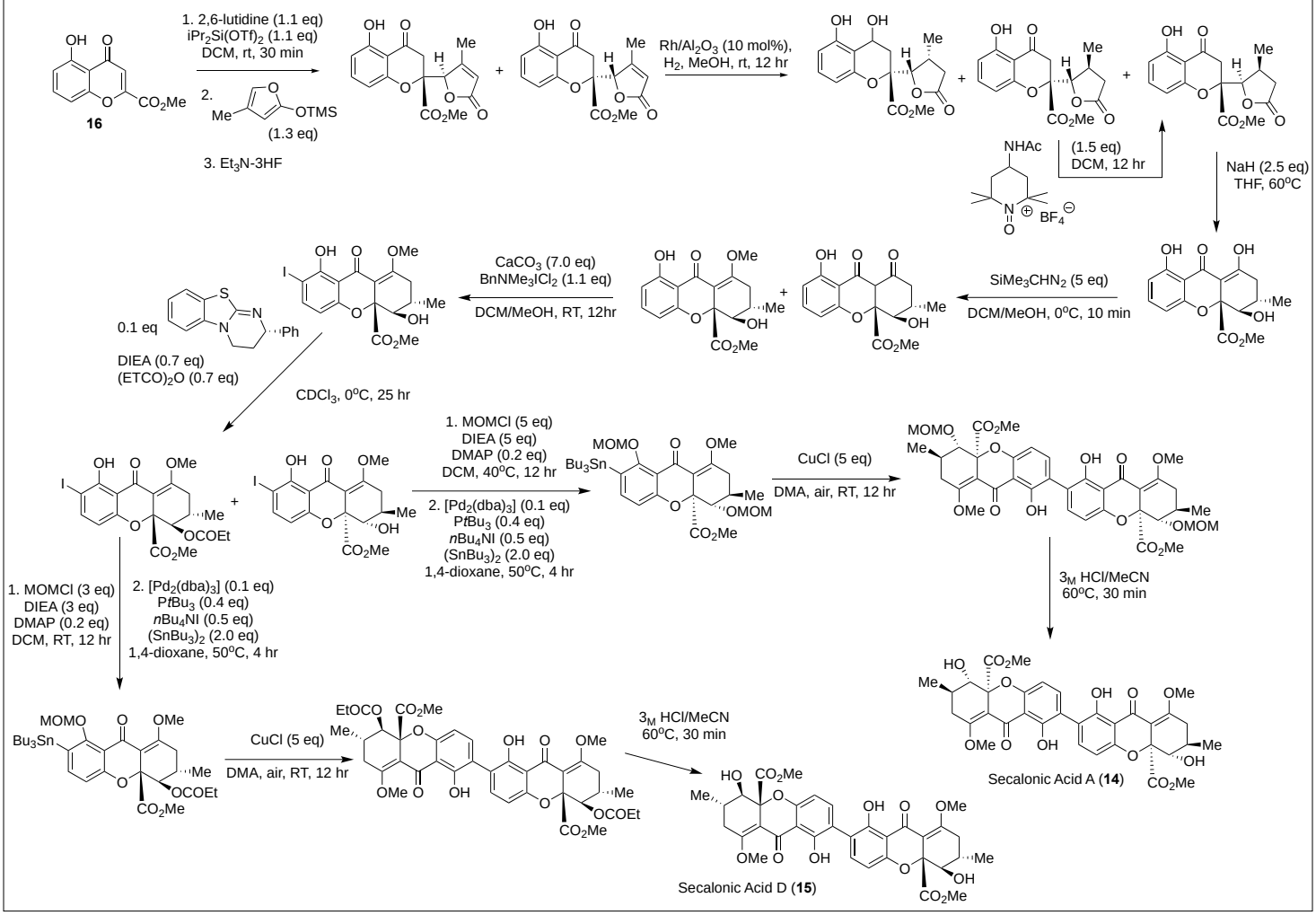
Phomoxanthone A (**12**)



Phomoxanthone B (**13**)

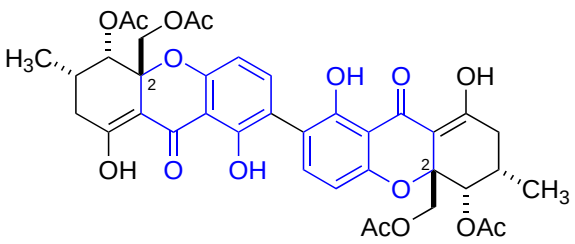
The promising biological activities along with the synthetic challenge offered by these dimeric xanthones has not gone unnoticed by the chemistry community and a limited number of investigators have studied the total synthesis of these types of natural products. The first synthesis of a dimeric tetrahydroxanthone was reported in 2013 by Porco and coworkers.[4] Utilizing a copper didestannylative coupling, Porco was able to synthesize secalonic acids A (**14**) and D (**15**) from chromone ester starting material (**16**) (Scheme 1).[6,7] This synthesis took nine

Scheme 1: Total Synthesis of Secalonic Acids A and B

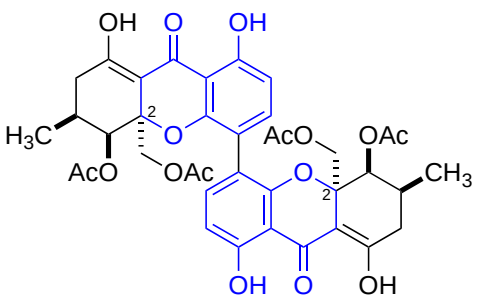



steps to reach both **14** and **15**. The method used by Porco and co-workers emphasized the importance of chromone starting materials and their usage in the synthesis of natural product-inspired xanthone dimers. This synthesis of **14** and **15** shows the synthetic challenge presented by dimeric xanthones. Similar to the natural products with a chromane core, it is challenging to set multiple stereogenic centers including the tertiary ether stereocenter at the 2 position of the 2-alkylchroman-4-one (highlighted in blue in Figure 4). Beyond this, the biaryl bond has also

Figure 4: Steric and Synthetic Challenge of Xanthone Dimers




Dicerandol C (**11**)

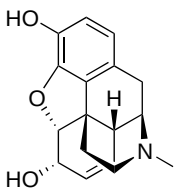



Phomoxanthone A (**12**)

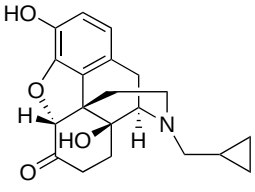
proved complicated for form due to the steric hinderance surrounding it from the bulky tetrahydroxanthone monomers (circled in blue in Figure 4).

In addition to both the chromane and xanthone oxygen heterocycles, there is another promising group of molecules, the morphine alkaloids. The morphine alkaloids have a long history of use as medicinal agents. After morphine's (**17**) original isolation from the latex of the opium poppy in 1806, it took 21 years for Merck to put **17** on the market in 1825.[8,9] **17** is still today is one of the most potent analgesic agents available and is often used for cancer patients.[9] Derivatives of **17** also have important medicinal applications. naltrexone (**18**) and naloxone (**19**) both have been used to treat opiate overdoses and drug or alcohol addiction.[10] Codeine (**20**), another derivative of **17** has similar properties and is often used as an analgesic agent for moderately severe pain. Thebaine (**21**) and oripavine (**22**) are both important intermediates for the synthesis of **17** and **20**.

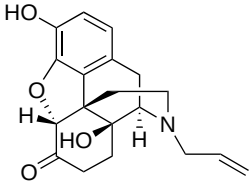
Figure 5: Morphine Alkaloids




Morphine (**14**)

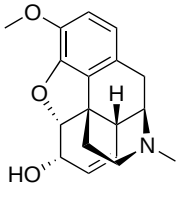



Naltrexone (**15**)

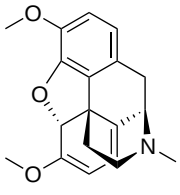



Naloxone (**16**)

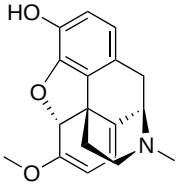
‘




Codeine (**17**)



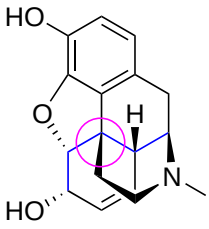

Thebaine (**18**)




Oripavine (**19**)

While the structure of **17** has been known since 1925 and the first total synthesis was completed in 1952, the majority of the worlds' morphine is still extracted due to the production cost.[8,9] The need for a commercially applicable synthetic route is obvious despite over thirty routes already existing.[8] The synthetic challenge posed by **17** and its derivatives arises from the complex pentacyclic framework with five continuous stereocenters (highlighted in blue in Figure 6).[9] Additionally, there is a quaternary carbon center, which is synthetically challenging to build (circled in Figure 6). The lack of a commercially applicable synthetic route is extremely disconcerting as **17**'s importance as a medical agent is extreme.

Figure 6: Synthetic Challenge of **17**




## Structure Activity Relationship Studies

Structure activity relationship (SAR) studies attempt to understand how biological activity is related to chemical structure. Often times during these studies derivatives of one key compound are tested to see if they have similar bioactivities. After an in-depth study the pharmacophore, the chemical structure whose electronic and steric properties are responsible for their bioactivity, can be found. When looking at the case of **17**, a study was completed by Breanden, Eddy, and Halbach in 1955 where the hydroxyl groups, saturation of the alicyclic ring, modification of the nitrogen, substituents on the aromatic or acyclic ring, and opening of the oxygen bridge were all explored synthetically in order to determine the moieties which contributed to the analgesic properties of **17**.[11] Within this study they found the important moieties to be the tertiary nitrogen, with a small R group, the quaternary carbon, the phenyl group connected to the quaternary carbon, and that maximum bioactivity is found when the nitrogen is connected to the quaternary carbon by a two carbon chain.[11] This pharmacophore (**23**) is found in **20** and **21** (highlighted in blue in Figure 7). One of the benefits from completing an SAR study is the ability to develop more structurally simple molecules which still possess similar bioactivities. In the case of **20** and **17**, Tramadol (**24**) and M1 (**25**) respectively, are examples of this (Figure 8).[12] Beyond this substitution to **25** with N-phenyl-carbon chains saw in an increase in binding affinity with a two-carbon chain in comparison to **17**.[12]

Figure 7: Pharmacophore of Morphine

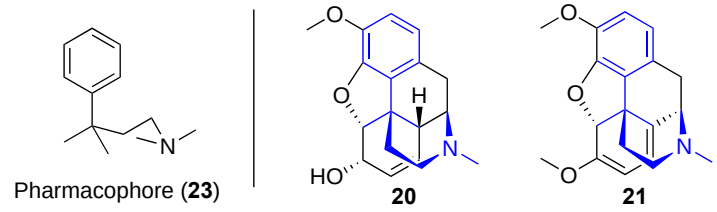
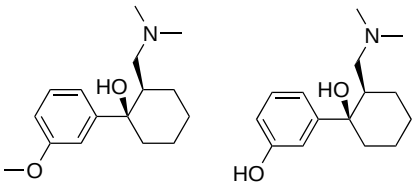



Figure 8: Simplified Structures of **20** and **17**



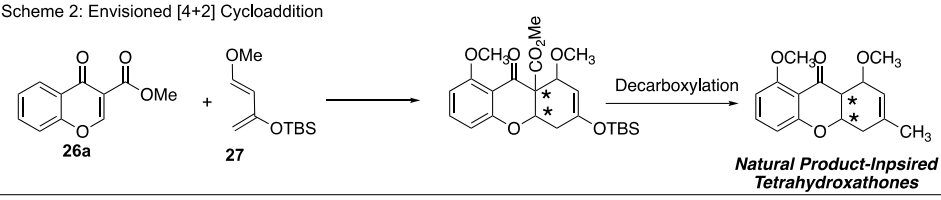

When considering completing a SAR study, it is important to have a method which allows for functionalization of the target molecule. Whether this means that the synthetic method tolerates multiple functional groups or that the target molecule can withstand functionalization is important and necessary. Additionally, there

are times when synthetic analogs of highly bioactive target compounds have increased bioactivities, less side effects, and more specific binding within the body, making them better candidates for medicinal applications.

## Enantioselective Tetrahydroxanthone Synthesis

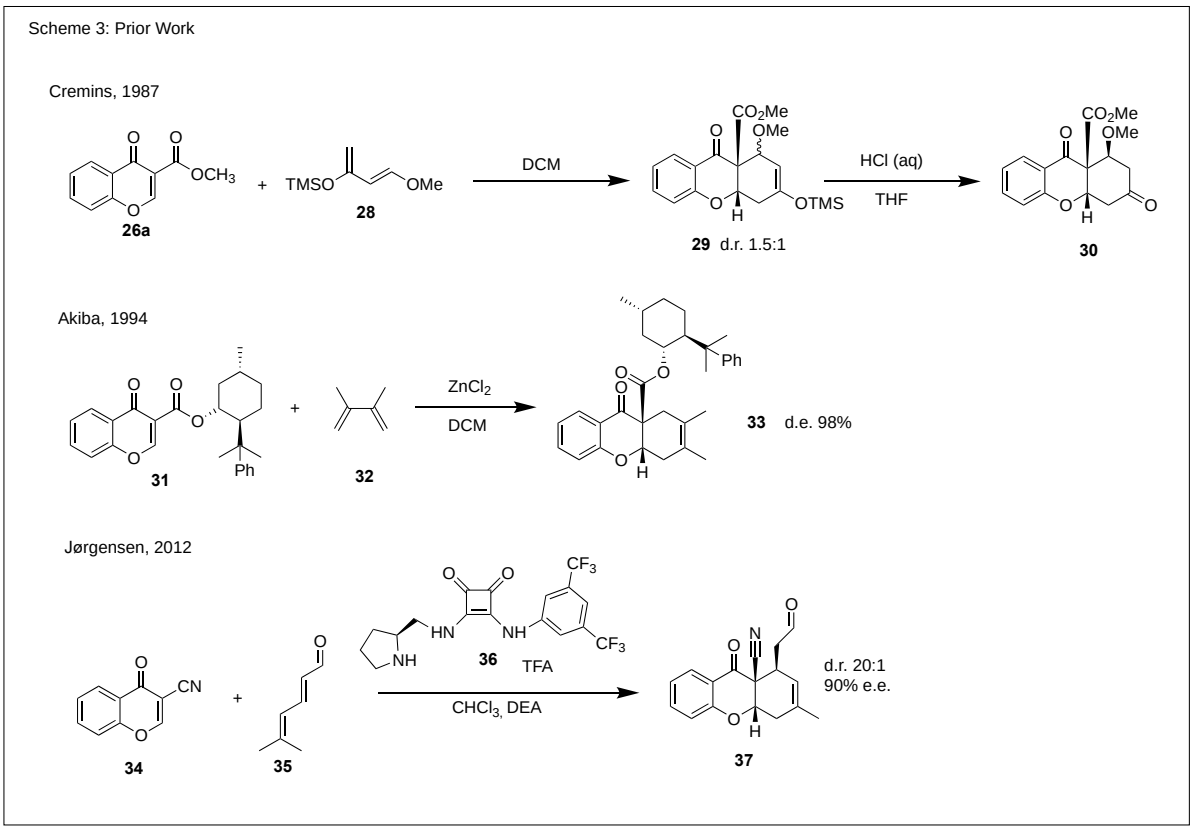
There is a lack of effective methods to establish both the 2 and 3 stereocenters observed in the chromane and xanthone cores. A chromenone (**26a**) provides an attractive starting material for the enantioselective synthesis of tetrahydroxanthones, a common core in bioactive molecules as see above. This has sparked interest within the synthetic field, although there has not been the development of a method which can establish both stereocenters. In pursuit of the development of a method which could set both stereocenters at once and allow for the functionalization of the molecule making it amenable to SAR studies, we envisioned the addition of **26a** and diene (**27**) via a [4+2] cycloaddition which could provide access natural product-inspired tetrahydroxanthones (Scheme 2).

Scheme 2: Envisioned [4+2] Cycloaddition




Literature precedent inspired our investigation of the enantioselective [4+2]-type cycloaddition reactions of **26a** and **27**. In 1987, Cremins and co-workers investigated the cycloaddition of **26a** and Danishefsky's diene (**28**).[13] This method afforded them with the

Scheme 3: Prior Work



cycloadducts (**29**) which they found to be unstable at room temperature. Under treatment with hydrochloric acid in tetrahydrofuran **29** yielded product (**30**) racemically (Scheme 3). A similar investigation was completed by Akiba and co-workers in 1994.[14] Beginning with **26a** and diene (**31**), they were unable to complete the cycloaddition with diastereoselectivity. For example, the cycloaddition reaction of chromanone (**32**) with diene **31** afforded desired product (**33**) with greater than 98% d.e (Scheme 3).[14] While this is impressive selectivity, the reaction relies on a stoichiometric amount of a chiral auxiliary.

One of the first publications describing a catalytic, enantioselective [4+2]-type cycloaddition reaction of chromenones was reported in 2012 from Jørgensen and co-workers.[15] Using substituted 2,4-dienals (**34**) and 3-cyanochromones (**35**) they were able to achieve high enantioselectivity and diastereoselectivity, up to 94% e.e. and 20:1 d.r., using a squareamide hydrogen donor catalyst (**36**) in the synthesis of **37 (**Scheme 3).[15] Over the course of their studies it was found that the use of a cyano substituent in the 3-position of the chromenone starting material was necessary to achieve this high enantiomeric excess, likely due electronic its properties, ultimately limiting the scope of the reaction. While this demonstrated that activated chromones are able to undergo enantioselective [4+2] cycloadditions, it still left unanswered the synthetic challenge of a general [4+2] approach for enantioselective tetrahydroxanthone synthesis.

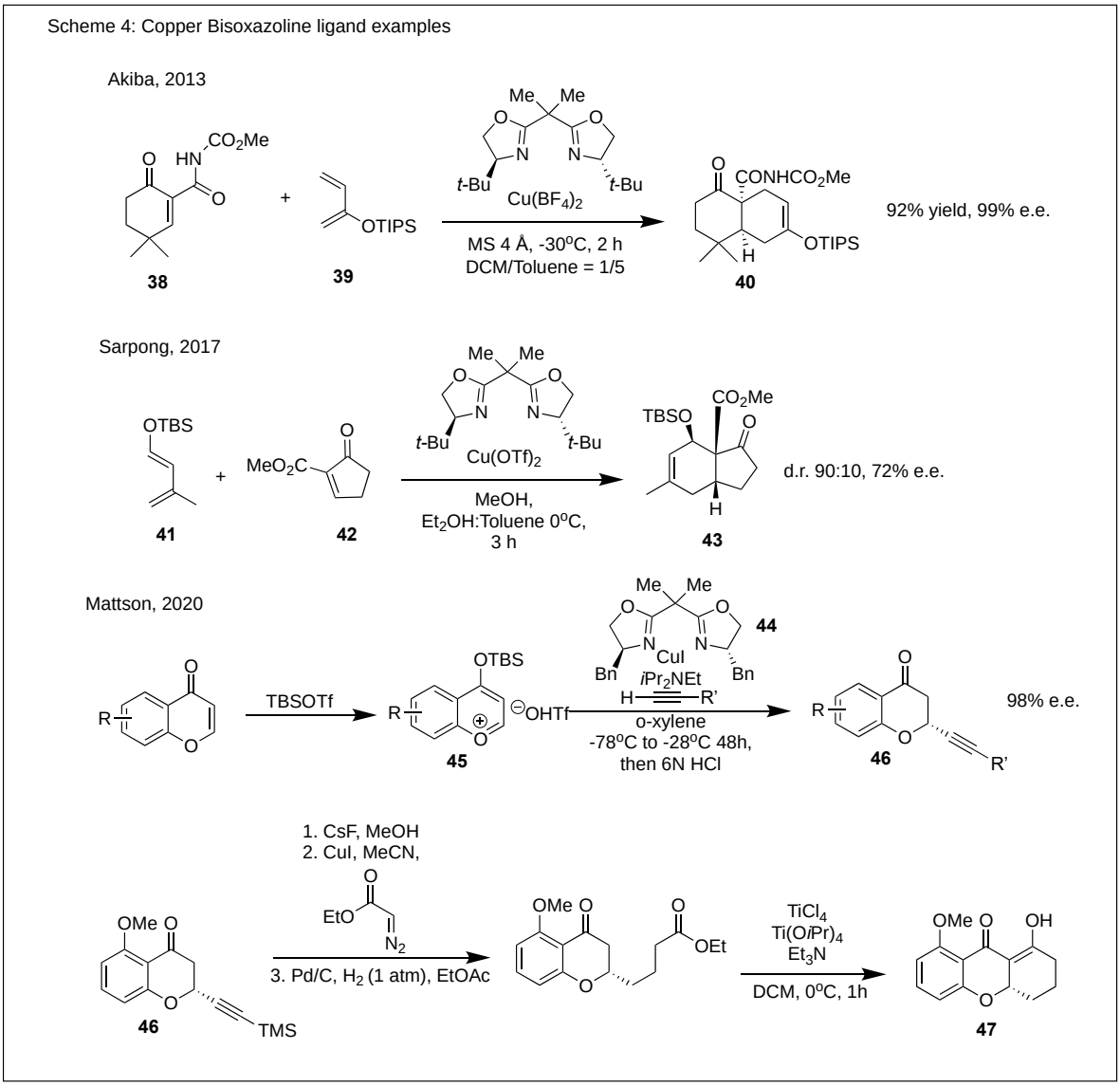
## Copper Bisoxazoline Catalysis

Copper (II) BOX catalysis has been utilized in many enantioselective reactions, including cycloadditions, Aldol, Michael, and carbonyl ene reactions.[15] The usage of copper has been found to be key over other metals. Copper (II) forms a more stable ligand-metal complexes than other metals such as manganese, iron, cobalt, nickel, and zinc.[16] Beyond this, there is not a problem with the disassociation of the copper from the BOX ligands. The anion is another extremely important factor. It is important to choose an anion which is a weak bonding anion, allowing for dissociation and ligand binding to occur. In addition to this, the bisoxazoline framework allows for catalyst tuning. The ability to substitute different groups on the pyrrole ring and on the bridged backbone allows for the testing of a variety of ligands with different steric and electronic properties. Beyond this, BOX ligands are synthetically accessible with an established route that provides high enantioselectivity.[16] Copper BOX catalysis offers an attractive asymmetric catalytic system due to the substrate tolerance, catalytic tunability, and the chiral environment which it creates.

There are many literature examples of the application of copper bisoxazoline catalysis to affect enantioselectivity. In 2013, Nakada and co-workers found that applying copper (II) BOX catalysis to [4+2] cycloadditions of α-alkylidene β-keto imides (**38**) with diene (**39**) afforded them product (**40**) with 99% e.e. and 92% yield (Scheme 2).[17] However, in order to achieve this high enantioselectivity, the usage for hydrogen bonding of the long side chain was necessary for orientation of the substrate when coordinated to copper. This limits the options for future derivatization. Similarly, Sarpong and co-workers were able to achieve cycloaddition of diene (**41**) and β-keto ester (**42**) affording them the product (**43**) with 72% e.e. through the addition of a hydrogen bond donor additive, methanol (Scheme 2).[18] While this method was able to address the long side chain which Nakada needed to increase selectivity with the copper BOX catalyst system, it still was unable to achieve high enantioselectivity.[19] Additionally, Sarpong and co-workers did not test the tolerance of their reaction on other dienes or dienophiles. Inspired by the extensive literature surrounding copper bis(oxazoline) catalysis[15,17,18], the Mattson group has

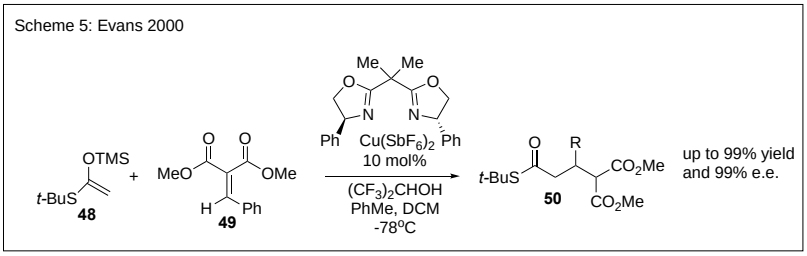
found success constructing chromanones with high enantiomeric excesses under the influence of copper bisoxazoline catalysis (**44**). Specifically, in 2020, the Mattson group reported the alkynylation of benzopyrilium ions (**45**) affording product (**46**, Scheme 4) in up to 98% enantiomeric excess (e.e.).[19] Further functionalization of 4**6** (R = OMe) yielded **47** which has direct applications to bioactive compound synthesis.

Scheme 4: Copper Bisoxazoline ligand examples



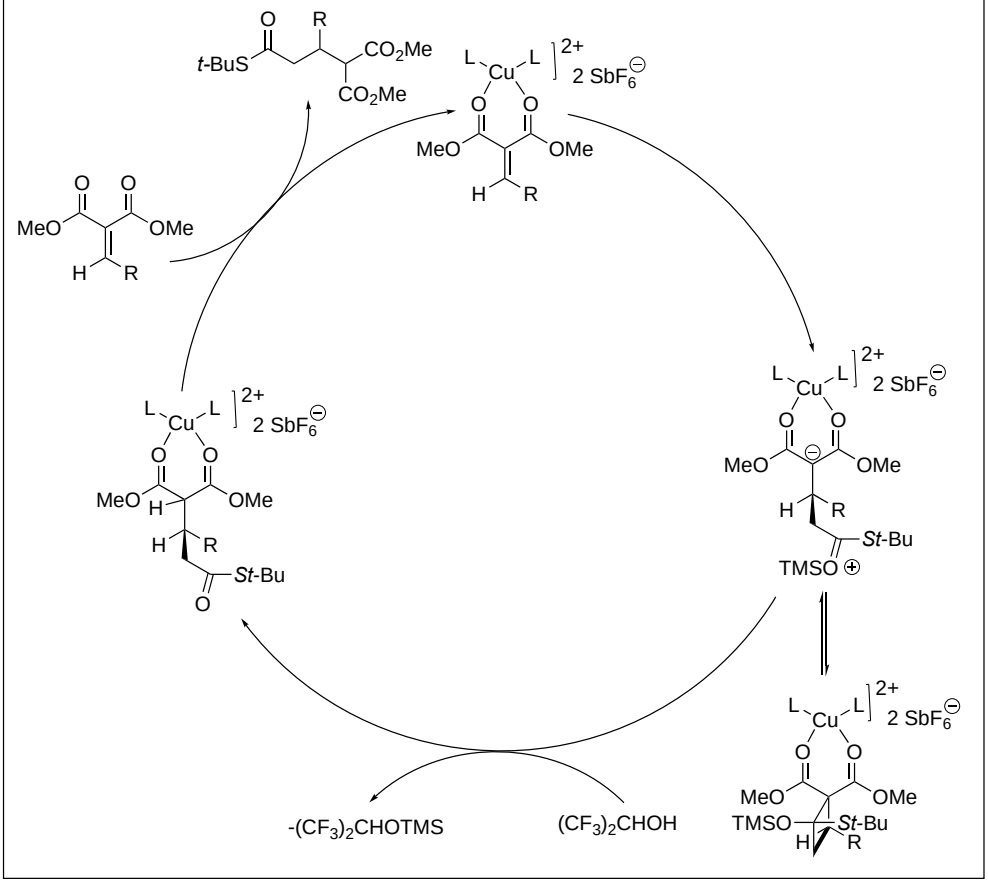

These literature examples show that copper bisoxazoline catalysis can be used to afford products with high selectivity. Due to the prevalence of copper bisoxazoline catalysis in the literature there have been investigations into the mechanism. In 2000, Evans and co-workers investigated the mechanism of the addition of enolsilanes (**48**) to alkylidene malonates (**49**)

Scheme 5: Evans 2000



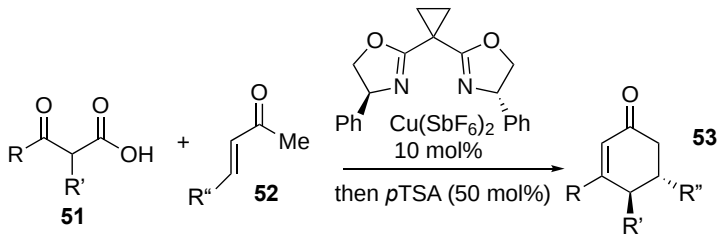
catalyzed by copper bisoxazoline catalysis to afford them **50** with up 99% e.e. (Scheme 5).[20] Through crystal structures of the alkylidene malonate and copper bisoxazoline catalyst complex, Evans and co-workers identified that there is two-point binding of the alkylidene malonate through the carbonyl moieties. Additionally, this crystal structure shows that coordination complex geometry is a distorted octahedral geometry where the counterions are weakly bound to the copper. This distorted octahedral geometry is seen phenyl and tert-butyl bisoxazoline ligands are used.[20] They proposed a catalytic cycle where the addition of the enolsilane to the alkylidene malonate proceeds through an open transition state and can form a zwitterion or close to form a cylobutane (Figure 9). This intermediate is then resolved with hexafluoro-2-propanol as a proton acceptor, generating a neutral complex which disassociates from the copper.[20]

Figure 9: Catalytic Cycle Proposed by Evans et. al.



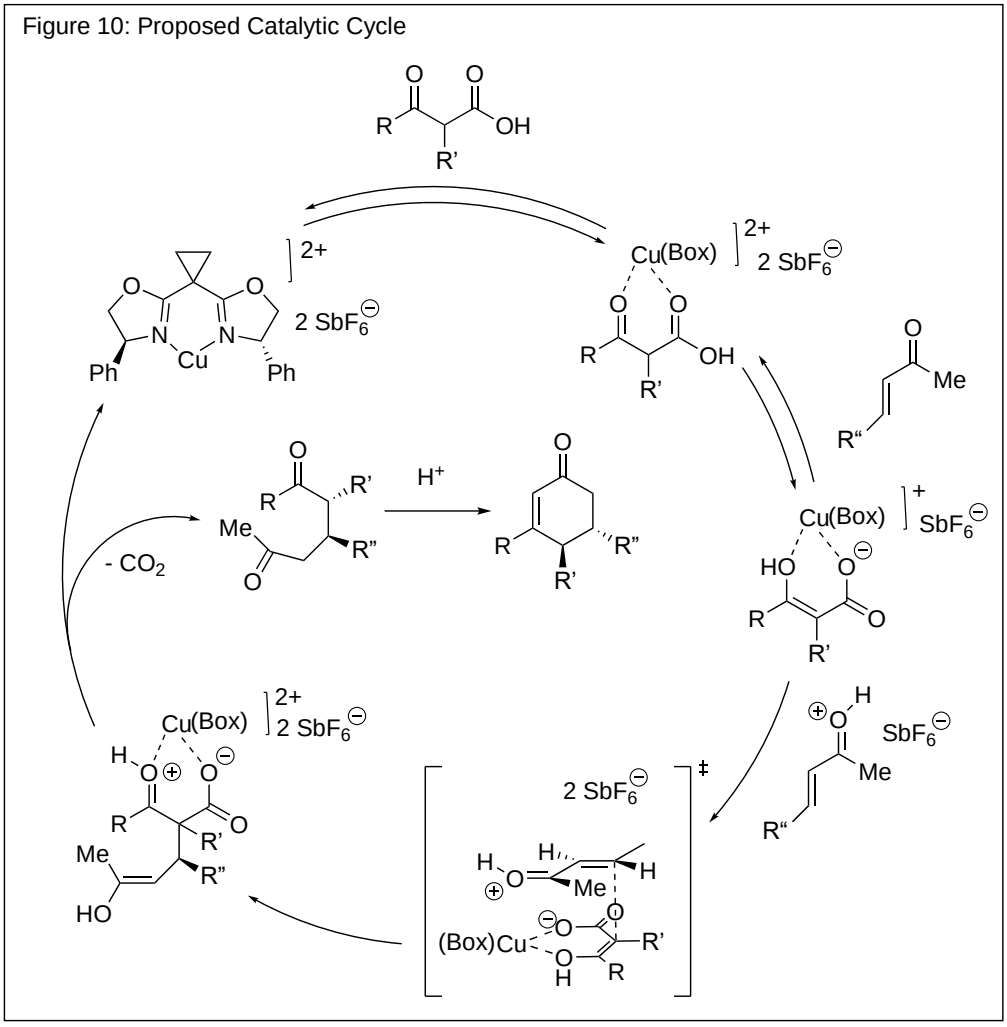

In 2018, Nagorny and co-workers investigated the Michael reaction between β-keto acids (**51**) and enones (**52**), which can undergo aldolization when in the presence of copper bisoxazoline catalysis to afford highly functionalized chiral cyclohexenones (**53**) in up to 94% e.e. (Scheme 6).[21] Additionally, they proposed a catalytic cycle where once coordinated to the copper bisoxazoline catalyst the β-keto acid forms an activated complex with which increases reactivity (Figure 10). Once this species is formed, the enone is activated

Scheme 6: Nagorny, 2018



either through protonation or hydrogen bonding. This newly activated enone can undergo a Michael reaction with the coordinated activated β-keto acid. This step is followed by decarboxylation and aldol condensation affording them with highly functionalized chiral cyclohexenones.[21] These mechanistic investigations provide insight into how copper bisoxazoline catalysis affords extreme selectivity over a broad range of reactions.

Figure 10: Proposed Catalytic Cycle



## Linear Free Energy Relationship Studies

Linear free energy relationship (LFER) studies can provide insight into the mechanism of a reaction. These studies are extremely useful when the mechanism is being investigated or there is interest in why the reaction provides certain selectivity. LFER studies take advantage of the steric and electronic affects which different functional groups have on a reaction. LFER studies originated through the correlation of the change in rate constant of reaction a to the change in rate constant of reaction b in order to determine the energy change in reaction b when compared to reaction a. This relationship can be expressed through **equation 1** where $G_i^{AB}$ describes the sensitivity of reaction a and b to change from $x_o$ to $x_i$ and $X_i$ describes the impact of the change on reaction a.[22]

$$\log(k_i/k_o)_B = G_i^{AB} X_i \quad (\mathbf{1})$$

This relationship is applied to all LFER studies which look to investigate what the impact of change on a reaction in comparison to a reference reaction can reveal about the mechanism of a reaction. These relationships are developed through the study of specific reactions which lead to the development of parameters related to different substituents.

The Hammett Equation, represented by **equation 2**, is based on the study of the impact of meta and para substituents on the disassociation constant of benzoic acid.

$$\log(k_i/k_o) = \rho\,\sigma \quad (\mathbf{2})$$

Hammett originally used equilibrium constants when investigating this relationship, but the σ values can be applied to rate constant as well as enantiomeric ratio (e.r.). These σ values are derived from the electronic influence which the substituent has on the acid disassociation of benzoic acid. Electron donating substituents have a negative σ value, electron withdrawing substituents have a positive σ value, and hydrogen has a σ value of zero. The information regarding the charge in the transition state is provided by the ρ value (**Table 1**).[22]

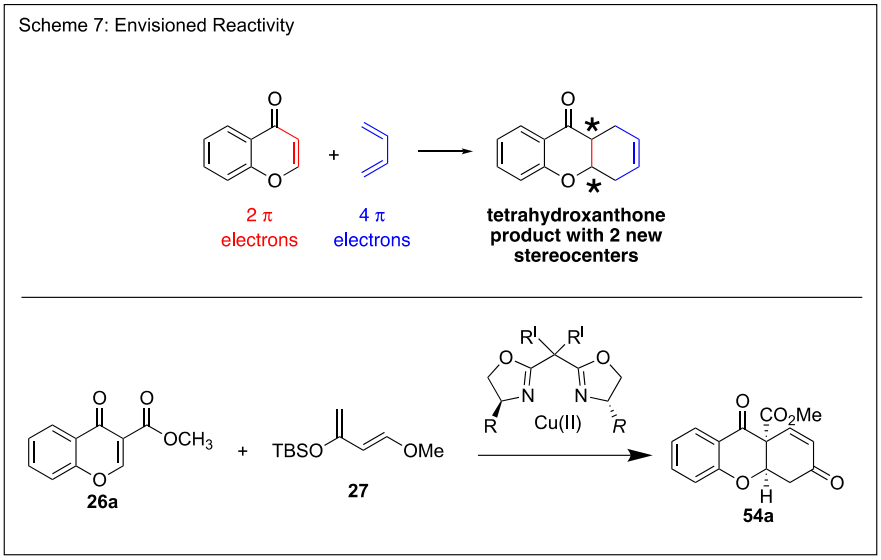
| Table 1: ρ value meanings | |
|---|---|
| $\rho > 1$ | Negative charge is built up |
| $0 < \rho < 1$ | Weak negative charge is built or loss of positive charge |
| $\rho = 0$ | No charge is built or lost |
| $-1 < \rho < 0$ | Weak positive charge is built or loss of negative charge |
| $\rho < -1$ | Positive charge is built up |

This information regarding the charge which is built up in the reaction provides key information regarding the mechanism of the reaction which can help lead to better catalyst tuning, therefore improving the selectivity of a reaction.

## Project Goal

The goal of this project was to address the synthetic knowledge gap in the enantioselective synthesis of tetrahydroxanthones with two key stereocenters utilizing a method which allowed further derivatization and was amenable to SAR and LFER studies. Previous work completed by Cremins and co-workers showed that the cycloaddition of **26a** and **28** was chemically possible. Recent work within the Mattson group showed the enantiocontrol which the Copper (II) BOX catalytic system was able to effect on the alkynylation or benzopyrilium ions. With both of these in mind, the formal [4+2] cycloaddition of **26a** and **27** using a copper BOX catalytic system to yield deprotected product with high enantioselectivity (**54a**) was envisioned (Scheme 7). The investigations in this work focused on the optimization of the synthesis of chromenone substrates, synthesis of key tetrahydroxanthones, optimization of the deprotection reaction, and a mechanistic investigation via Hammett Plot Analysis.

Scheme 7: Envisioned Reactivity

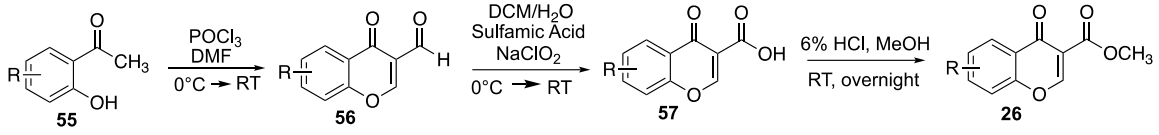


# Results and Discussion

## Chromenone Synthesis

The chromenones (**26**) were synthesized through a three-step synthetic route (Scheme 8).

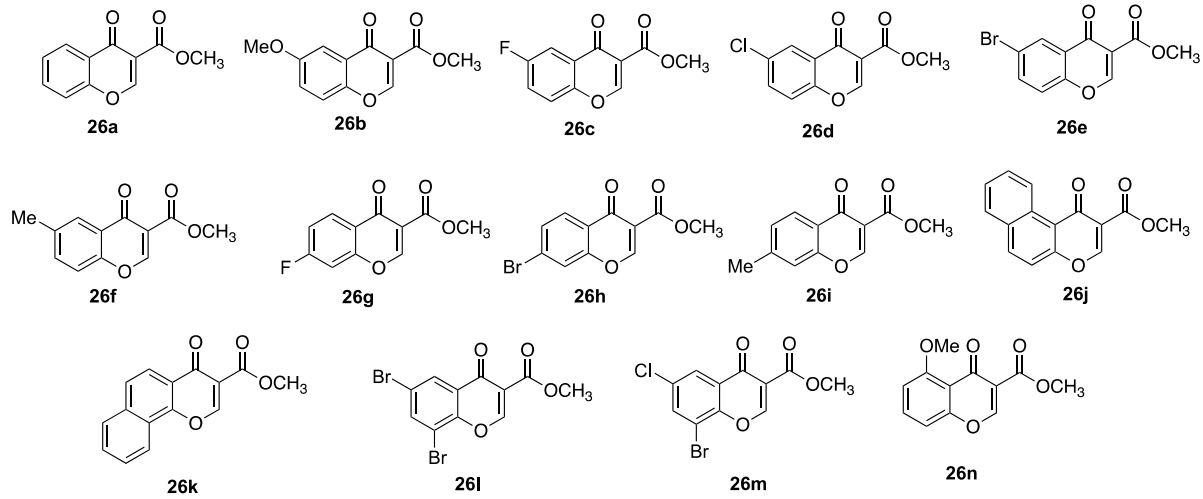
Scheme 8: Chromenone Synthesis




The treatment of with acetophenone derivative **55** with $POCl_3$ and DMF gave rise to chromenone **56** containing and aldehyde in the 3-position. The oxidation of the aldehyde to the carboxylic acid **57** was affected with sulfamic acid and NaClO2. The esterification of the carboxylic acid afforded the methyl ester under acidic conditions with HCl in methanol.

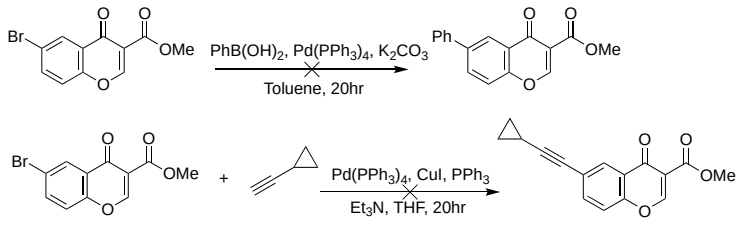
The scope of this synthetic route to generate the chromenone substrates was broad, tolerating electron donating, electron withdrawing, and sterically demanding groups at nearly every position (Figure 11). Electron withdrawing and weakly electron donating groups were

Figure 11: Substrate Scope




tolerated at the 7 position, but stronger electron donating groups, such as methoxy were not tolerated at the 7 position for the first step of the synthesis. Additionally, disubstituted substrates (**26k**, **26l**, **26m**, and **26n**) were not as stable or reactive as the monosubstituted substrates. Coupling reactions were attempted on the chromenone substrates in order to expand the substrate scope (Scheme 8). However, both of these couplings led to material that was

Scheme 8: Attempted Couplings



unstable and decomposed as seen by TLC. In order to successfully complete couplings, the initial starting material, acetophenone, must be protected and then it can be coupled. Despite this set back, this route still provides access to a variety of substrates with different handles for further functionalization.

## Tetrahydroxanthone Synthesis

The chromenone substrates were used as starting material for the enantioselective synthesis of tetrahydroxanthones via a formal [4+2] cycloaddition. This cycloaddition was completed using a copper BOX catalytic system. The reaction conditions were previous optimized by Jon Attard, a 5th year graduate student in the Mattson group (Scheme 9). Six key substrates were chosen which represented electron donating groups and electron withdrawing groups in order to complete a linear free energy relationship study. Initially, these substrates were tested using bisoxazoline ligand **58**, which was good but ultimately not the best ligand structure identified for this reaction. Substrates **26c**, **26d**, and **26e** all gave lower yields and enantiomeric excess in comparison to substrates **26a**, **26b**, and **26f** (Table 2). **26c** gave such extremely low yields that there was not enough material to take an HPLC spectra in order to determine enantiomeric excess. Additionally, copper-**58** complex was not stable which resulted in the decomposition of the ligand which could lead to the deprotection of the product. This decomposition would leave free copper in the solution which could decrease both the yield of the reaction and the enantioselectivity of the reaction. This issue led to the usage of bisoxazoline ligand **59**, the most optimal ligand for the reaction system, affording greater enantioselectivity. **59** proved to be more stable, even allowing for the recovery of the ligand after purification of the adducts. The yields were easily reproducible with **53** and enough material was made to determine enantiomeric excess for all substituents (Table 2). However, the enantiomeric excess of **54b** was lower with **59** then with **58**. This could be due to the increased steric constraints of **59** or changed electronic properties in the transition state due to the increased pi system of the ligand.

Scheme 9: Optimized Reaction Conditions and two BOX Ligands

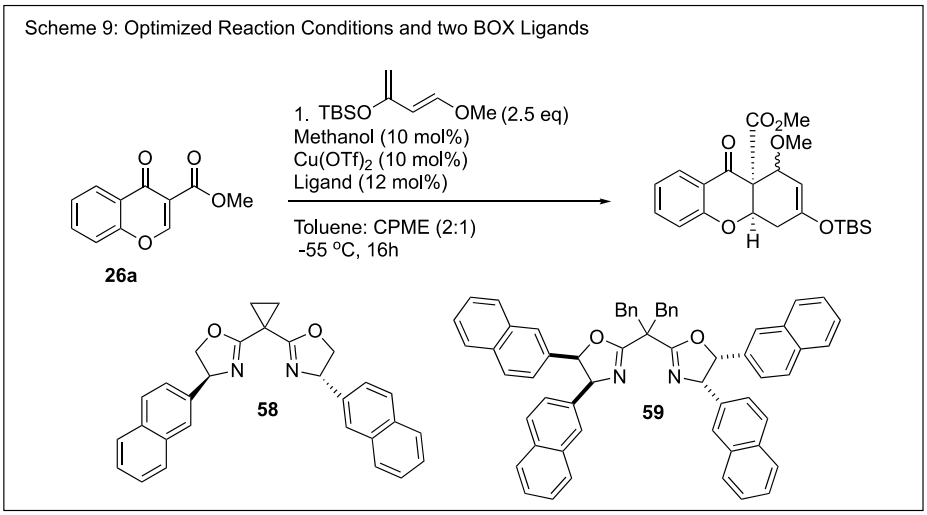
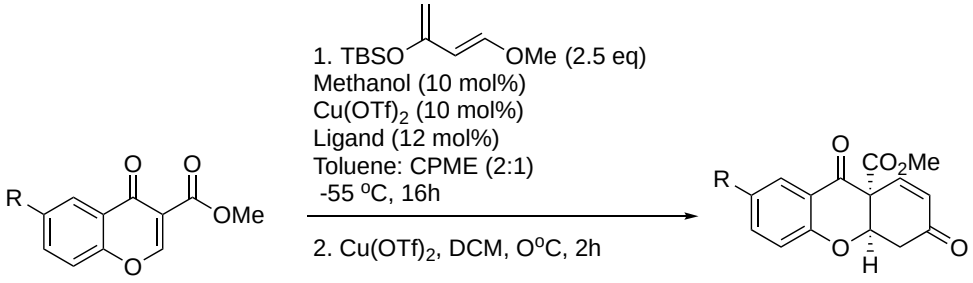


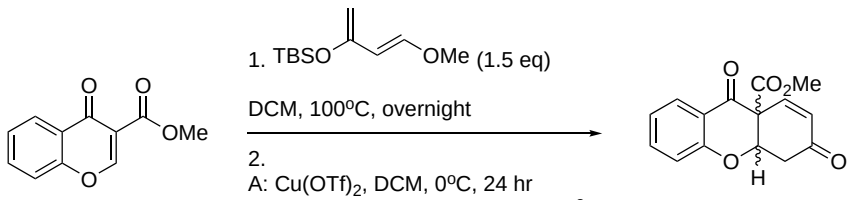

Table 2: Average Yield and Enantiomeric Ratio for **58** and **59**



| Ligand **58** | | | | |
|---|---|---|---|---|
| R | Starting Material | Product | Average Yield | Average Enantiomeric Ratio |
| H | **26a** | **54a** | 61% | 91:1 |
| MeO | **26b** | **54b** | 67% | 92:8 |
| F | **26c** | **54c** | 14% | N/A |
| Br | **26d** | **54d** | 12% | 89:11 |
| Cl | **26e** | **54e** | 12% | 81:19 |
| Me | **26f** | **54f** | 45% | 93:7 |
| Ligand **59** | | | | |
| H | **26a** | **54a** | 89% | 92:8 |
| MeO | **26b** | **54b** | 43% | 87:13 |
| F | **26c** | **54c** | 35% | 93:7 |
| Br | **26d** | **54d** | 33% | 94:6 |
| Cl | **26e** | **54e** | 42% | 94:6 |
| Me | **26f** | **54f** | 40% | 93:7 |

The deprotection conditions still needed to be optimized in order to achieve the desired product. A racemic adduct was subjected to four different conditions summarized in Table 4. Conditions A, B, and D all ran for twenty-four hours, while condition C only required four hours for conversion as judged by TLC and produced the desired compound with a 35% yield with little impurity, as observed by $^1$H-NMR. Upon further analysis condition D did not provide the deprotected product as observed by TLC and only starting material remained. Condition A provided product in a 44% yield with a significant amount of ring opened phenolic impurities due to side reactions. Condition B only yielded 2% of the desired product and a significant amount of starting material remained, as observed by $^1$H-NMR spectroscopy. The main comparison in order to determine the optimized deprotection methods was in comparing purity of the crude product as the phenolic impurities are hard separate from the desired product. Condition C provided the cleanest reaction as indicated by $^1$H-NMR spectroscopy of the crude product. Thus, the deprotection step we used for the remainder of the study was condition c.

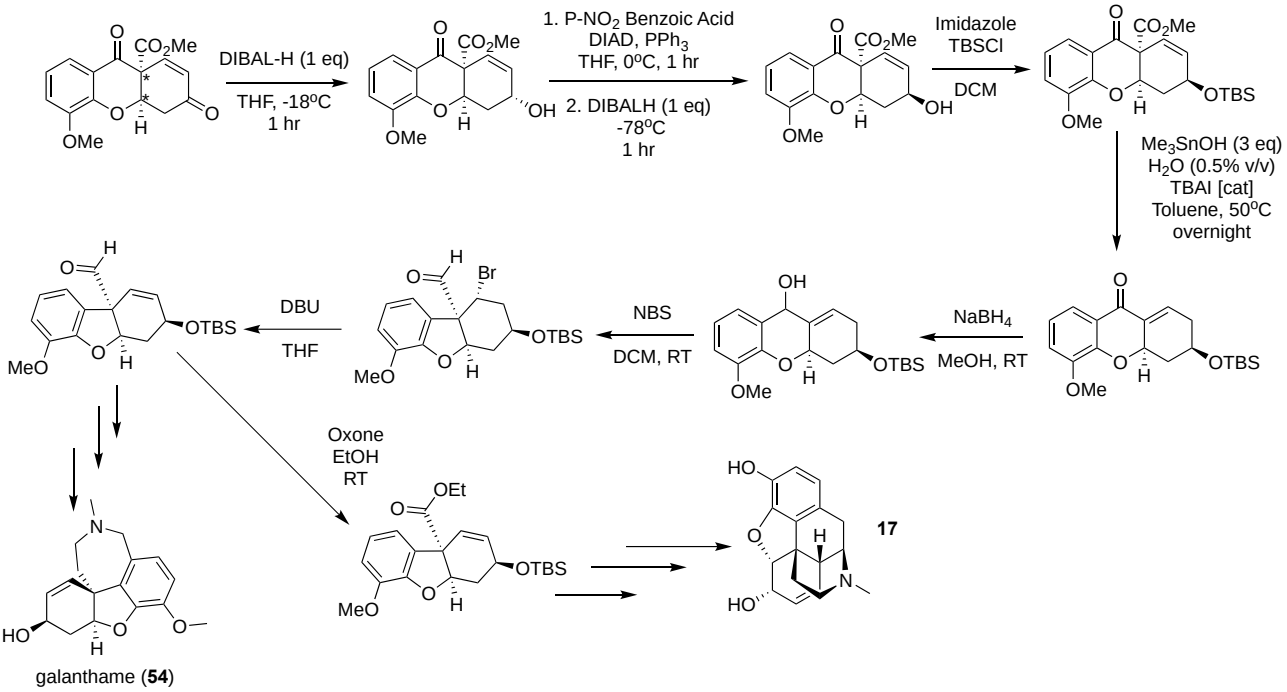
Table 3: Optimization of Deprotection Conditions




| Condition | Yield |
|---|---|
| A | 44% |
| B | 2% |
| C | 35% |
| D | NR |

The product generated by this new enantioselective [4+2] method sets two stereocenters in a tetrahydroxanthone core (starred in Scheme 10), one of which is a quaternary carbon. Additionally, this product allows for further derivatization, such as the synthesis of dihyrdobenzofurans with biological relevance (Scheme 10). There are also future possibilities for the further derivatization of the decarboxylated product. This product can used in the synthesis of natural product-inspired chromane and tetrahydroxanthone molecules. The tolerance of the process is seen as it has been applied to chromenones with electron donating, electron withdrawing, and sterically challenging groups around the ring system.

Scheme 10: Further Derivatization

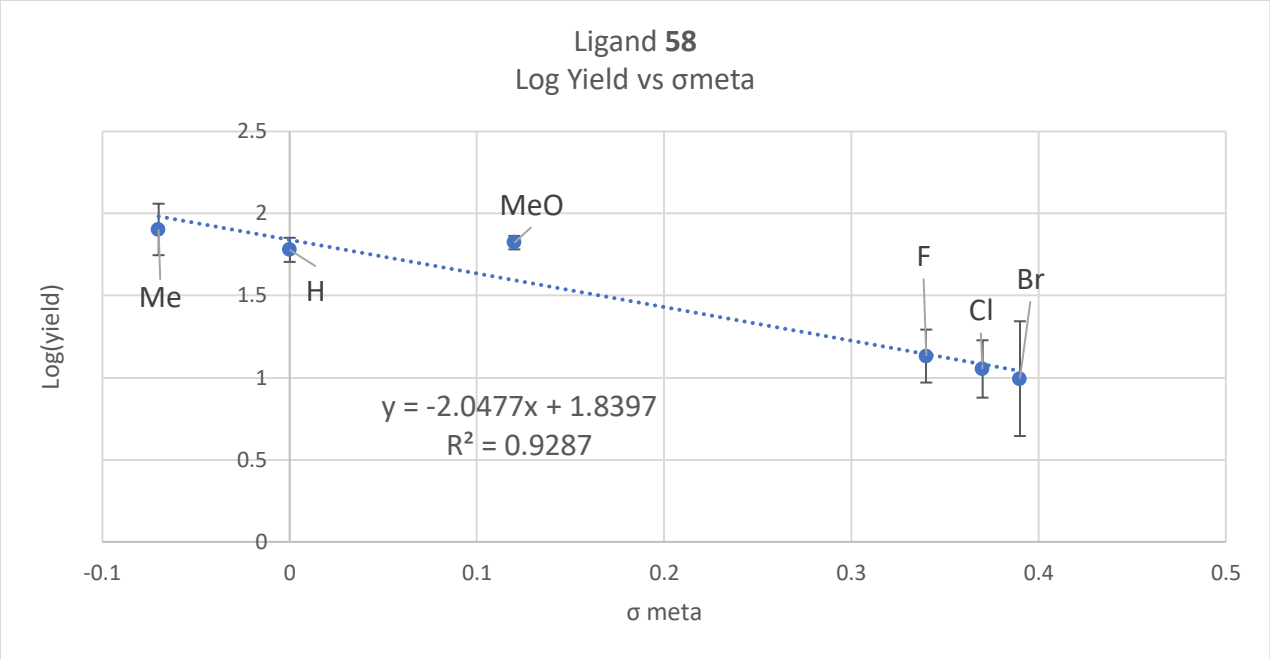



## Hammett Plot Analysis

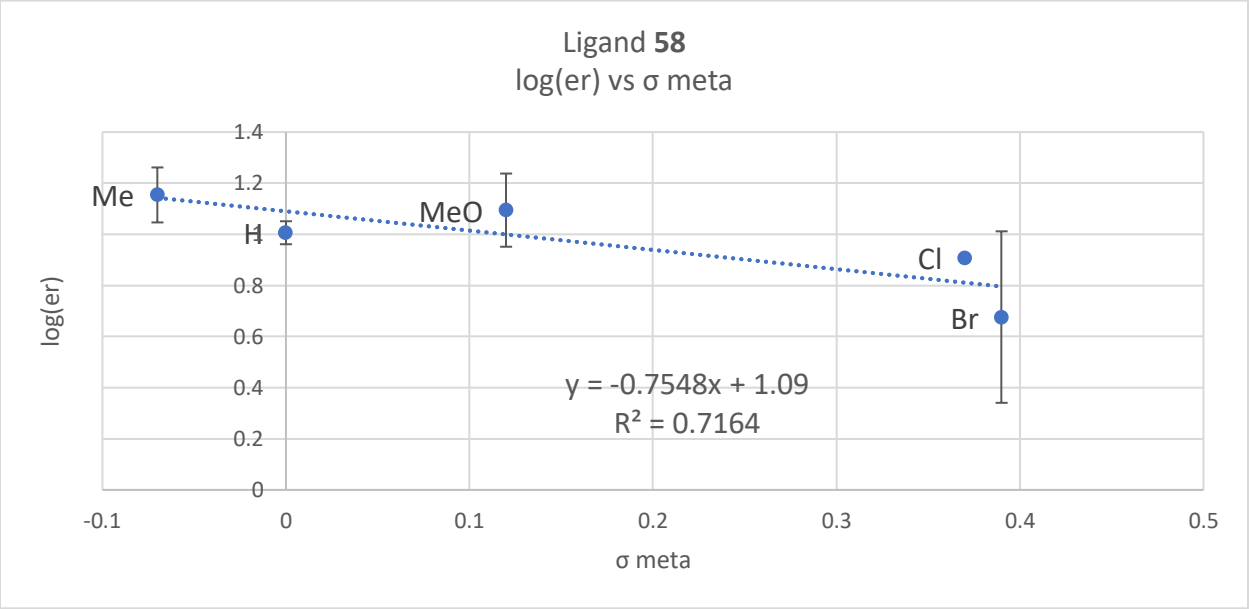
The six key tetrahydroxanthones, **26a-f**, were used to complete Hammett plot analysis. Their corresponding Hammett parameters were the $\sigma_{meta}$ values (Table 4)[20]. For analysis, plots were made from the reactions with both ligands **58** and **59**. Four plots were made in total, comparing the log of yield of each reaction to the $\sigma_{meta}$ value and comparing the log of the enantiomeric ratio to the $\sigma_{meta}$ value. For the plot comparing the log of yield of each reaction to the $\sigma_{meta}$ value, adduct yield was used. For ligand **58**, a minimum of three trials were completed for all substrates, but HPLC traces were only able to be gathered for **54a**, **54b**, **54d**, and **54f**. For **54e**, only one trial yielded enough material for a HPLC trace and no HPLC traces were able to be collected for **54c**. For ligand **59**, two trials were completed for all substrates. These trials were compared with previously collected data. All trials yielded enough material for HPLC traces. These values were then plotted as previously described.

Table 4

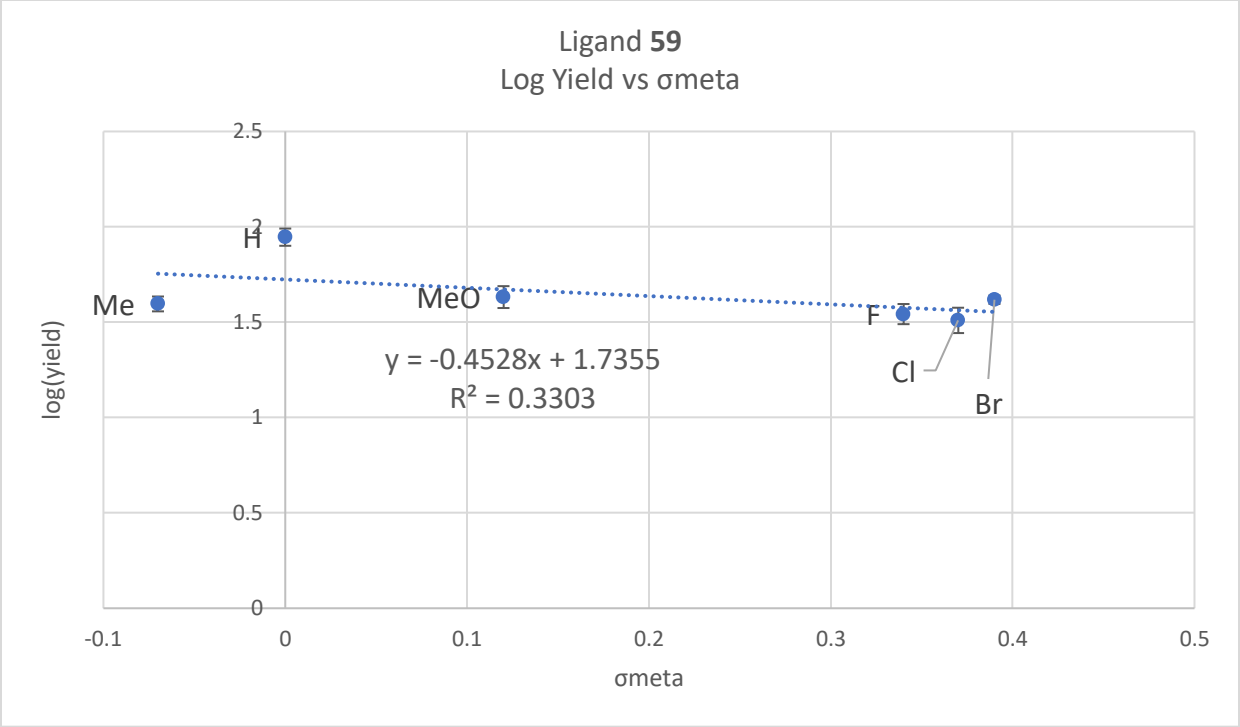
| R | $\sigma_{meta}$ value |
|---|---|
| H | 0.00 |
| Me | -0.07 |
| MeO | 0.12 |
| F | 0.34 |
| Cl | 0.37 |
| Br | 0.39 |



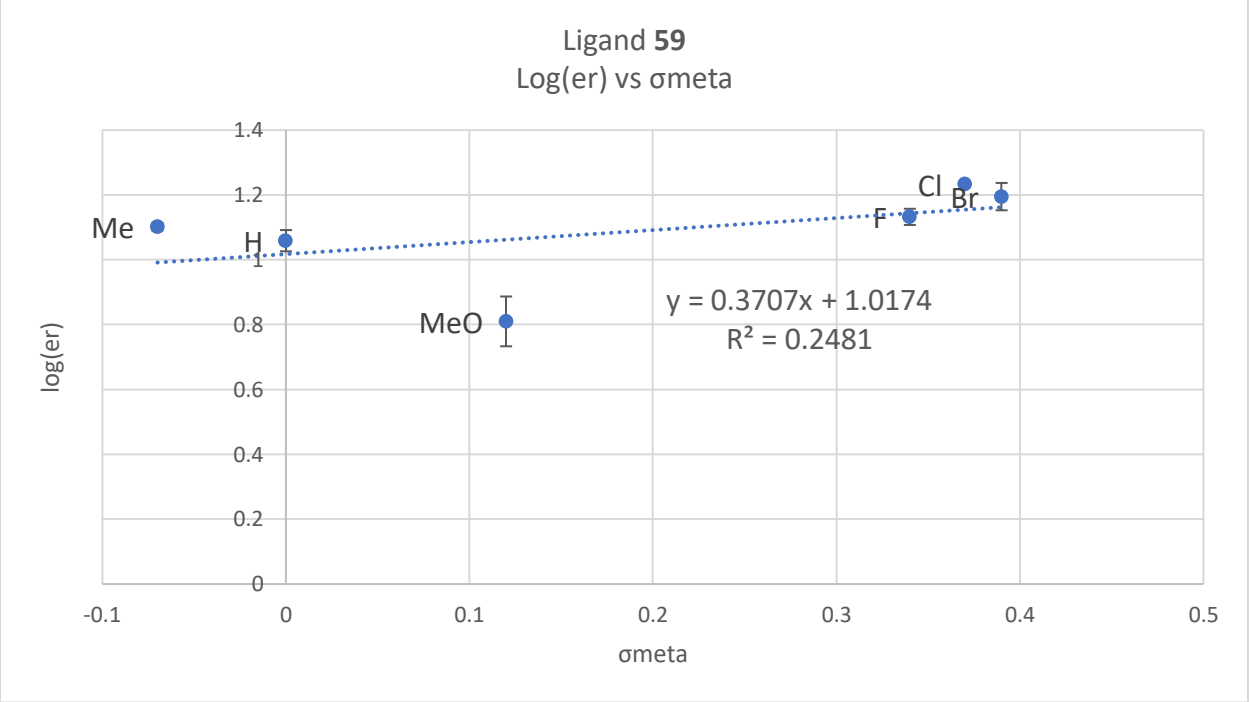

Graph 1: Ligand **58** Yield Hammett Plot




Graph 2: Ligand **59** Enantiomeric Ratio Hammett Plot




Graph 3: Ligand **59** Yield Hammett Plot




Graph 4: Ligand **59** Enantiomeric Ratio Hammett Plot

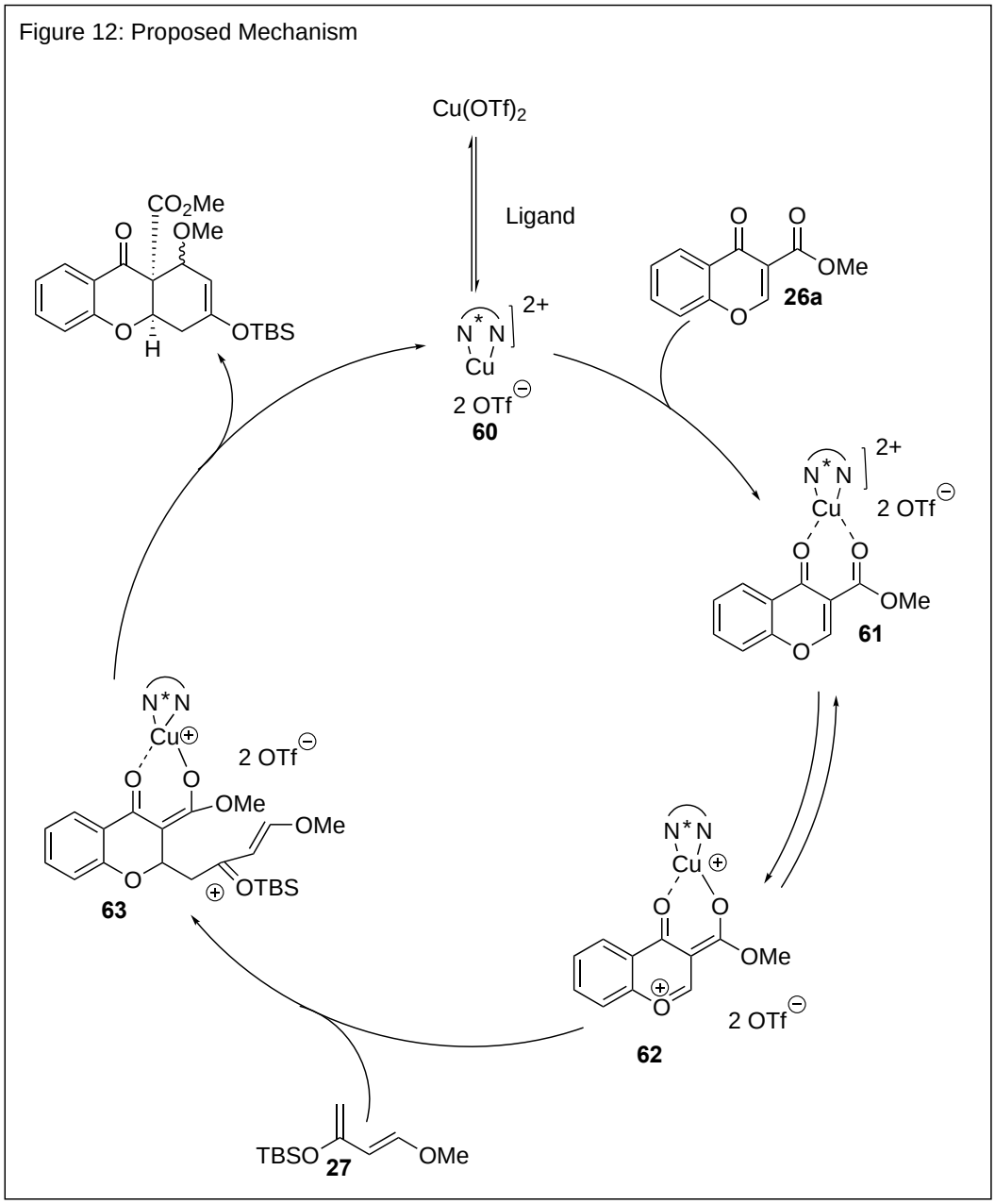
There are clear trends when considering the data collected from ligand **58** reactions. The ρ values were both negative. The log(yield) plot had a negative ρ value less than negative one and the log (er) plot had a negative ρ value greater than negative one but less than zero. This indicates that a positive charge is throughout the reaction. Additionally, the $R^2$ values of the log(yield) plot and log(er) plot for ligand **58** was 0.9287 and 0.7164 respectively. This shows a strong correlation between the $\sigma_{meta}$ Hammett parameters and the yield and the enantiomeric ratio. This indicates that the yield and the selectivity of the reaction are impacted by electronic effects from the substituent.

When considering the plots made with the ligand **59** there is not a clear trend. However, the $R^2$ values of the log(yield) plot and log(er) plot for ligand **59** were 0.3303 and 0.2481 respectively. This shows there is not a strong linear correlation between the $\sigma_{meta}$ Hammett parameters and the yield or enantiomeric ratio. This means that the electron donating or electron withdrawing nature of substituent does not strongly impact the yield or selectivity of the reaction which can be confirmed by comparing the differences in yield and selectivity between substrates. As seen in reactions using **58** the yield is much more dependent on the substituent. The selectivity is also seen to depend on the substituent, but not as significantly. The opposite is seen when look at the yield and selectivity of the reaction using **59**. While yield still shows minimally more dependency on substituent than selectivity, there is little to no dependency on the electronic properties of the substituents. The greatest impact can be seen when looking at the enantiomeric ratio of **54b**. This could be due to the difference in steric environment which is made. One reason for this difference could be the steric environment which is generated by **59** versus the environment which is generated by **58**. The increase in ligand size limits the ability of the substrate to rotate when coordinated to the copper. This would lead to an increase in yield and selectivity, which is seen. Additionally, if the substrate is bound and held in a specific position due to steric control, this could potentially decrease the dependence of the reaction on the electronic properties of substrate. Beyond this, the distance which the substituent is from the site where the reaction occurs could impact its ability to affect the yield and selectivity of the reaction, therefore decreasing the dependency of the reaction on electronic properties. However, further studies are needed to determine if this theory is applicable.

A plausible mechanism for this cycloaddition is proposed in Figure 12. This mechanism begins with the association of the bisoxazoline ligand to the copper forming complex **60**. This visually can be seen as the reaction mixture will change from a clear color to a green color. Upon addition of **26a**, complex **61** will form with the coordination between **26a** and copper occurring through the two-point binding of the carbonyl moieties.[20] **61** has a resonance structure **62**, where an enolate is formed through the bonding of one of the carbonyl oxygen atoms to the copper.[21] **62** is a very reactive species that upon the addition of **27** undergoes nucleophilic attack. This [4 + 2] addition proceeds through a stepwise addition yielding **63**. The ring then closes through nucleophilic attack on the enolate, and the carbonyl is reformed, the neutral species is able to disassociate from the copper.[20] We propose that the enantio-determining step is the addition of **27** to **62**. This addition is sterically controlled by the bisoxazoline ligand, which blocks the top face of **26a**, forcing addition to occur on the bottom face. According to Wallace and co-workers, the ring closure occurs on the same face as the addition, leading a sin product, therefore the side which **27** adds to determines the stereochemistry.[13] The buildup of positive charge in the transition as indicated by Hammett analysis, agree with this proposal. The buildup of positive charge is seen in **62** where there is a positive charge on the benzopyrilium during the transition from **62** and **63**. It is this positive charge that affords the enantioselective addition of **27**.

Additionally, only the electronic effects of the chromenone were studied so the results of Hammett analysis must relate to a positive charge buildup on the chromenone. The results of the Hammett analysis agree with our proposed mechanism and proposed enantio-determining step.

Figure 12: Proposed Mechanism



# Conclusions

Access to chromane and tetrahydroxanthone cores with enantioselectivity is an area within organic synthesis that possess a significant gap. Previous work has shown that tetrahydroxanthones can be synthesized using a chromenone starting material and dienes via a [4+2] cycloaddition. However, there lacks a method to effectively synthesize these tetrahydroxanthones with selectivity and the possibility for further functionalization or derivatization. Within the Mattson group, progress has been seen regarding the application of copper bisoxazoline catalysis for enantioselective synthesis. Beyond this, copper bisoxazoline catalysis has been used for various [4+2] cycloadditions with high enantioselectivities. Herein, copper bisoxazoline catalysis was applied to the [4+2] cycloaddition of chromenones and dienes selectively affording tetrahydroxanthones with two stereocenters.

Our studies found that the chromenones could be synthesized from acetophenones through a three-step synthetic route. These chromenones were then subjected to previously optimized conditions to selectively yield a set of adducts. The deprotection step was optimized to yield a tetrahydroxanthone product with the least amount of impurity. Six key substrates were chosen in order to complete Hammett plot analysis. These substrates were evaluated in the reaction using two bisoxazoline ligands. The less sterically demanding environment created by the less substituted ligand showed greater susceptibility to changes in electronic properties of the substrate. These Hammett plots showed that there was positive charge build up during the transition state of the reaction, which appears to support the proposed reaction mechanisms. However, there seemed to be less of a relation between the electronic properties and the yield and selectivity of the reaction when a more sterically demanding environment was created by the tetranaphthyl substituted ligand. The method which was developed provides a product which can be further derivatized to an intermediate of morphine. Additionally, the decarboxylated product provides the possibility of further derivatization to natural product-inspired chromane and tetrahydroxanthone cores with the setting of two key stereocenters. The tolerance of this method shows the amenability of this method to a SAR study.

# References


1. Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. Total Synthesis of the Highly Potent Anti-HIV Natural Product Daurichromenic Acid along with Its Two Chromane Derivatives, Rhododaurichromanic Acids A and B. *Org. Lett.* **2003**, *5* (23), 4481–4484.
2. Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. Enantioselective Total Synthesis of (+)-Psiguadial B. *J. Am. Chem. Soc.* **2016**, *138* (31), 9803–9806.
3. Qin, X.-J.; Yu, Q.; Yan, H.; Khan, A.; Feng, M.-Y.; Li, P.-P.; Hao, X.-J.; An, L.-K.; Liu, H.-Y. Meroterpenoids with Antitumor Activities from Guava (Psidium Guajava). *J. Agric. Food Chem.* **2017**, *65* (24), 4993–4999.
4. Wezeman, T.; Bräse, S.; Masters, K.-S. Xanthone Dimers: A Compound Family Which Is Both Common and Privileged. *Nat. Prod. Rep.* **2015**, *32* (1), 6–28.
5. Isaka, M.; Palasarn, S.; Kocharin, K.; Saenboonrueng, J. A Cytotoxic Xanthone Dimer from the Entomopathogenic Fungus Aschersonia Sp. BCC 8401. *J. Nat. Prod.* **2005**, *68* (6), 945–946.
6. Qin, T.; Johnson, R. P.; Porco, J. A., Jr. Vinylogous Addition of Siloxyfurans to Benzopyryliums: A Concise Approach to the Tetrahydroxanthone Natural Products. *J. Am. Chem. Soc.* **2011**, *133* (6), 1714–1717.
7. Qin, T.; Porco, J. A., Jr. Total Syntheses of Secalonic Acids A and D. *Angew. Chem. Weinheim Bergstr. Ger.* **2014**, *126* (12), 3171–3174.
8. Reed, J. W.; Hudlicky, T. The Quest for a Practical Synthesis of Morphine Alkaloids and Their Derivatives by Chemoenzymatic Methods. *Acc. Chem. Res.* **2015**, *48* (3), 674–687.
9. Brousseau, J.; Xolin, A.; Barriault, L. A Nine-Step Formal Synthesis of (±)-Morphine. *Org. Lett.* **2019**, *21* (5), 1347–1349.
10. Bennett, H. N.; Tomas, H.; Josephine, W. R.; Johann, M.; Dirk, T. Morphine Synthesis and Biosynthesis-An Update. *Current Organic Chemistry* **2000**, *4*(3), 343–362.
11. Braenden, O. J.; Eddy, N. B.; Halbach, H. Synthetic Substances with Morphine-like Effect; Relationship between Chemical Structure and Analgesic Action. *Bull. World Health Organ.* **1955**, *13* (6), 937–998
12. Shen, Q.; Qian, Y.-Y.; Xu, X.-J.; Li, W.; Liu, J.-G.; Fu, W. Design, Synthesis and Biological Evaluation of N-Phenylalkyl-Substituted Tramadol Derivatives as Novel μ Opioid Receptor Ligands. *Acta Pharmacol. Sin.* **2015**, *36* (7), 887–894.
13. Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. Cycloadditions of Substituted Benzopyran-4-Ones to Electron-Rich Dienes: A New Route to Xanthone Derivatives. *Tetrahedron* **1987**, *43* (13), 3075–3082.
14. Katsuo Ohkata, Tomotaka Kubo, Keiko Miyamoto, Makiko Ono, Junko Yamamoto, Kin-ya Akiba. Highly Asymmetric Induction in the Diels-Alder Reaction of 3-Alkoxycarbonyl-Substituted. *Heterocycles* **1994**, *38* (7), 1483–1486.
15. Johnson, J. S.; Evans, D. A. Chiral Bis(Oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael, and Carbonyl Ene Reactions. *Acc. Chem. Res.* **2000**, *33* (6), 325–335.
16. Albrecht, Ł.; Acosta, F. C.; Fraile, A.; Albrecht, A.; Christensen, J.; Jørgensen, K. A. Enantioselective H-Bond-Directing Approach for Trienamine-Mediated Reactions in Asymmetric Synthesis. *Angew. Chem. Int. Ed Engl.* **2012**, *51*(36), 9088–9092.

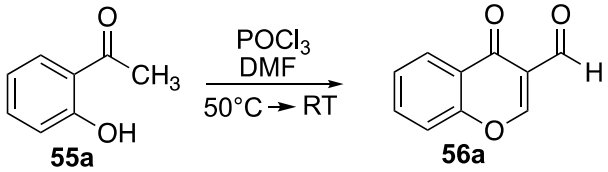
17. Orimoto, K.; Oyama, H.; Namera, Y.; Niwa, T.; Nakada, M. Catalytic Asymmetric [4 + 2] Cycloadditions and Hosomi-Sakurai Reactions of α-Alkylidene β-Keto Imides. *Org. Lett.* **2013**, *15* (4), 768–771.
18. Lindsay, V. N. G.; Murphy, R. A.; Sarpong, R. Effect of Protic Additives in Cu-Catalysed Asymmetric Diels-Alder Cycloadditions of Doubly Activated Dienophiles: Towards the Synthesis of Magellanine-Type Lycopodium Alkaloids. *Chem. Commun. (Camb.)* **2017**, *53* (74), 10291–10294.
19. Guan, Y.; Attard, J. W.; Mattson, A. E. Copper Bis(Oxazoline)-Catalyzed Enantioselective Alkynylation of Benzopyrylium Ions. *Chemistry* **2020**, *26* (8), 1742–1747.
20. Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. Enantioselective Lewis Acid Catalyzed Michael Reactions of Alkylidene Malonates. Catalysis By C2-Symmetric Bis(Oxazoline) Copper(II) Complexes in the Synthesis of Chiral, Differentiated Glutarate Esters. *J. Am. Chem. Soc.* **2000**, *122* (38), 9134–9142.
21. Lee, J.; Wang, S.; Callahan, M.; Nagorny, P. Copper(II)-Catalyzed Tandem Decarboxylative Michael/Aldol Reactions Leading to the Formation of Functionalized Cyclohexenones. *Org. Lett.* **2018**, *20* (7), 2067–2070.
22. Wells, P. R. Linear Free Energy Relationships. *Chem. Rev.* **1963**, *63* (2), 171–219.
23. Lewis Acid Catalyzed Procedure for Selective Conversion of the Carbocyclic Diels-Alder Adducts of Danishefsky's Diene to 2-Cyclohexenones and Its Extension to Their One-Pot Syntheses. *Synlett* **2000**, *2000* (11), 1549–1552.

# Appendix 1: Procedures

## General Methods

Anhydrous toluene and dichloromethane were dried using a pure process technologies solvent system. All other reagents were used directly as received from the manufacturer unless otherwise noted. Preparative silica gel chromatography was performed using SiliaFlash F60 silica gel (40 - 63 µm). Analytical thin layer chromatography was performed using Analtech 250 µm silica gel HLF plates and visualized under UV 254nm. All $^{1}H$ NMR spectra were acquired using a Bruker BioSpin 500 MHz Avance III Digital NMR spectrometer and calibrated using the solvent signal (CDCl3 7.26 ppm). J Coupling constants are reported in Hz. Multiplicities are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; b, broad; dd, doublet of doublets; ddd, doublet of doublet of doublets; td, triplet of doublets; ddt, doublet of doublet of triplets; dtd, doublet of triplet of doublets. Chiral HPLC analysis was performed using an Agilent 1260 equip with a diode array detector using Chiralcel OD-H or AD-H columns.

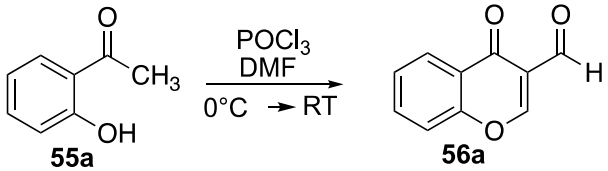
### *A – VILSMEIR-HAACK*



**55a** **56a**

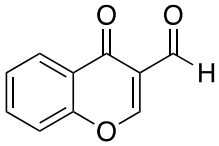
**3-formylchromone (55a)** was prepared according to an established procedure.[13] To a 100 mL round bottom flask was added dimethyl formamide (10 mL) and $POCl_3$ (2.75 mL, 29 mmol, 4.0 eq). Reaction mixture was heated at 50°C for 1 h. A solution of Acetophenone **55a** (1.0 g, 0.88 mmol, 1.0 eq) in dimethyl formamide (14 mL) was added dropwise to the reaction mixture. Reaction mixture was heated at 50°C for 2 h, heat was removed, and allowed to react for 16 h. The reaction solution was recrystallized from ice water, and then filtered and washed with water to afford an off white solid **56a** (69% yield).

### *B – OPTIMIZED VILSMEIER-HAACK*

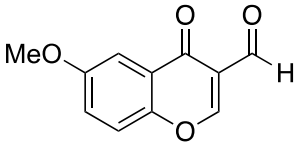


**55a** **56a**

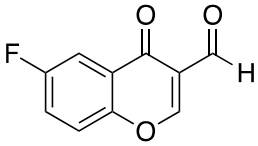
To a 100 mL round bottom flask was added acetophenone **55a** (7 g, 51 mmol, 1.0 eq) and dimethyl formamide (31 mL). The reaction was cooled to 0°C and $POCl_3$ (14.4 mL, 154 mmol, 3.0 eq) was added dropwise and allowed to react for 16 h. The reaction solution was recrystallized from ice water, and then filtered and washed with water to afford an off white solid **56a** (75% yield).



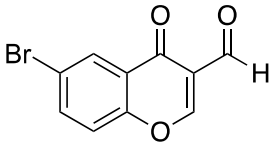
**3-formylchromone (56a):** Prepared according to procedure *B*, using acetophenone **55a** (7 g, 51 mmol), DMF (31 mL), and $POCl_3$ (14.4 mL, 154 mmol). **56a** was isolated as an off white solid (0.883 g, 5.07 mmol, 69% yield). $R_f$ = 0.48 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d), δ 10.39 (s, 1H), 8.55 (s, 1H), 8.31 (d, J= 7.8, 1H), 7.76 (t, J = 10.8 Hz, 1H) 7.55 – 7.49 (m, 2H).



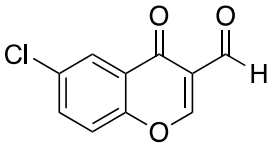
**3-formyl-6-methoxychromone (56b):** Prepared according to procedure *B*, using acetophenone **55b** (5.12 g, 31 mmol), DMF (19 mL), and $POCl_3$ (8.7 mL, 93 mmol). **56b** was isolated as an off white solid (5.1 g, 25 mmol, 80% yield). $R_f$ = 0.56 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.41 (s, 1H), 8.53 (s, 1H), 7.66 (dd, J = 3.1 Hz, 1H), 7.48 (d, J = 9.2 Hz, 1H), 7.34 – 7.31 (m, 1H), 3.93 (s, 3H).



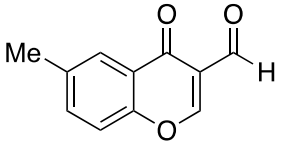
**6-fluoro-3-formylchromone (56c):** Prepared according to procedure *B*, using acetophenone **55c** (5.4 g, 35 mmol), DMF (22 mL), and $POCl_3$ (9.8 mL, 105 mmol). **56c** was isolated as an off white solid (6.4 g, 33 mmol, 95% yield). $R_f$ = 0.60 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.38 (s, 1H), 8.55 (s, 1H), 7.95 (dd, J = 7.9, 3.1 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.50 – 7.47 (m, 1H).



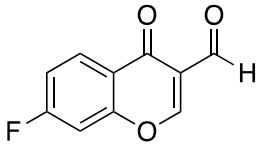
**6-bromo-3-formylchromone (56d):** Prepared according to procedure *B*, using acetophenone **55d** (5.2 g, 24 mmol), DMF (15 mL), and $POCl_3$ (6.7 mL, 72 mmol). **56d** was isolated as an off white solid (5.6 g, 24 mmol, 100% yield). $R_f$ = 0.78 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.54 (s, 1H), 8.43 (d, J = 2.5 Hz, 1H), 7.84 (dd, J = 8.9, 2.5 Hz, 1H), 7.44 (d, J = 8.9 Hz, 1H).



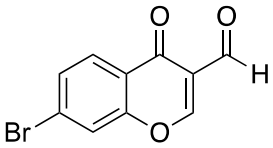
**6-chloro-3-formylchromone (56e):** Prepared according to procedure *B*, using acetophenone **55e** (3 g, 17.5 mmol), DMF (11 mL), and $POCl_3$ (4.9 mL, 53 mmol). **56e** was isolated as an off white solid (3.3 g, 16.1 mmol, 92% yield). $R_f$ = 0.54 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.54 (s, 1H), 8.27 (d, J = 2.5 Hz, 1H), 7.70 (dd, J = 9.0, 2.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H).



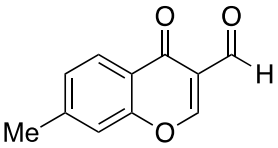
**3-formyl-6-methylchromone (56f):** Prepared according to procedure *B*, using acetophenone **55f** (1.5 g, 10 mmol), DMF (6.2 mL), and $POCl_3$ (2.8 mL, 30 mmol). **56f** was isolated as an off white solid (1.5 g, 8 mmol, 80% yield). $R_f$ = 0.6 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.39 (s, 1H), 8.53 (s, 1H), 8.08 (d, J = 1 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.43 (d, J = 8.6 Hz, 1H), 2.49 (s, 3H).



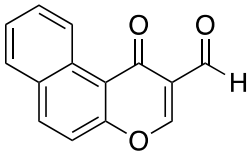
**7-fluoro-3-formylchromone (56g):** Prepared according to procedure *A*, using acetophenone **55g** (0.5 g, 3.24 mmol), DMF (13 mL), and $POCl_3$ (1.2 mL, 13 mmol). **56g** was isolated as a yellow solid (0.282 g, 1.47 mmol, 45% yield). $R_f$ = 0.70 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.39 (s, 1H), 8.53 (s, 1H), 8.36 – 8.33 (m, 1H), 7.25 (d, J = 8.6 Hz, 2H).



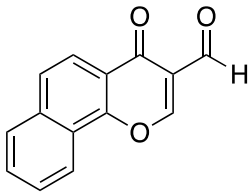
**7-bromo-3-formylchromone (56h):** Prepared according to procedure *A*, using acetophenone **55h** (1.0 g, 4.65 mmol), DMF (18 mL), and $POCl_3$ (1.7 mL, 18.6 mmol). **56h** was isolated as a tan solid (1.04 g, 4.10 mmol, 88% yield). $R_f$ = 0.81 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.59 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.63 (dd, J = 8.6, 1.8 Hz, 1H).



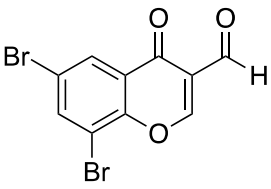
**3-formyl-7-methylchromone (56i):** Prepared according to procedure *B*, using acetophenone **55i** (3.8 g, 25 mmol), DMF (16 mL), and $POCl_3$ (7 mL, 75 mmol). **56i** was isolated as an orange solid (4.7 g, 24.8 mmol, 99% yield). $R_f$ = 0.46 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.39 (s, 1H), 8.51 (s, 1H), 8.19 (d, J = 8 Hz, 1H), 7.33 (d, J = 9.6 Hz, 2H), 2.52 (s, 3H).



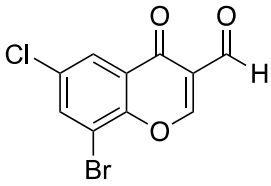
**5,6-benzo-3-formylchromone (56j):** Prepared according to procedure *B*, using acetophenone **55j** (3.5 g, 18.7 mmol), DMF (12 mL), and $POCl_3$ (5.3 mL, 57 mmol). **56j** was isolated as a white solid (4.2 g, 18.5 mmol, 99% yield). $R_f$ = 0.66 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.52 (s, 1H), 10.00 (d, J = 10.8 Hz, 1H), 8.57 (s, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.96 (d, J = 10 Hz, 1H), 7.82 (t, J = 10.6 Hz, 1H), 7.69 (t, J = 10.1 Hz, 1H), 7.53 (d, J = 11.3 Hz, 1H).



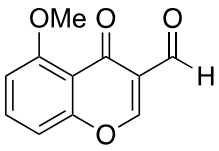
**7,8-benzo-3-formylchromone (56k):** Prepared according to procedure *A*, using acetophenone **55k** (1.5 g, 8.06 mmol), DMF (28 mL), $POCl_3$ (3 mL, 32 mmol). **56k** was isolated as an orange solid (1.66 g, 7.41 mmol, 92% yield). $R_f$ = 0.71 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.48 (s, 1H), 8.73 (s, 1H), 8.53 – 8.50 (m, 1H), 8.24 – 8.22 (m, 1H), 7.99 – 7.97 (m, 1H), 7.89 – 7.87 (m, 1H), 7.78 – 7.72 (m, 2H).



**6,8-bromo-3-formylchromone (56l):** Prepared according to procedure *A*, using acetophenone **55l** (1.0 g, 3.40 mmol), DMF (15 mL), and $POCl_3$ (1.3 mL, 13.6 mmol). **56l** was isolated as an off white solid (1.10 g, 3.30 mmol, 97% yield). $R_f$ = 0.76 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.35 (s, 1H), 8.59 (s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H).

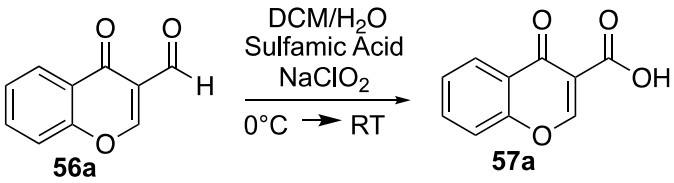


**8-bromo-6-chloro-3-formylchromone (56m):** Prepared according to procedure *A*, using acetophenone **55m** (1.0 g, 4.00 mmol), DMF (16 mL), and $POCl_3$ (1.5 mL, 16 mmol). **56m** was isolated as an off white solid (0.821 g, 2.86 mmol, 71% yield). $R_f$ = 0.64 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.35 (s, 1H), 8.59 (s, 1H), 8.22 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 2.5 Hz, 1H).



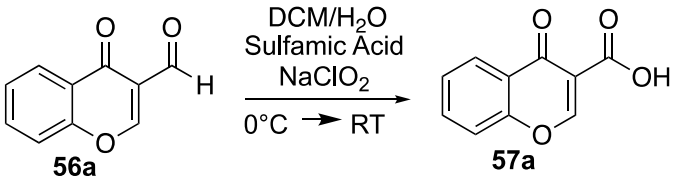
**3-formyl-5-methoxychromone (56n):** Prepared according to procedure *B*, using acetophenone **55n** (3 g, 18 mmol), DMF (11 mL), and $POCl_3$ (5.1 mL, 54 mmol). **56n** was isolated as an off white solid (2.67 g, 13.1mmol, 73% yield). $R_f$ = 0.24 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 10.36 (s, 1H), 8.39 (s, 1H), 7.62 (t, J = 8.4, 1H), 7.07 (dd, J = 8.5, 0.9 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.02 (s, 3H).

## *C – PINNICK OXIDATION*

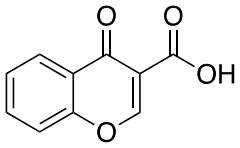



To a 250 mL round bottom flask was added chromone **56a** (0.75 g, 4.3 mmol, 1.0 eq) and dichloromethane (86 mL). A solution of sulfamic acid (0.84 g, 8.6 mmol, 2.0 eq) in water (15 mL) was added and the reaction was cooled to 0°C. A solution of technical grade $NaClO_2$ (1.5 g, 17.2 mmol, 4.0 eq) in water (69 mL) was added dropwise and allowed to react for 16 h. The reaction mixture was extracted with dichloromethane (3 x 50 mL), dried over anhydrous $NaSO_4$, and the solvent was removed under vacuum to obtain the crude product. The crude product was washed with diethyl ether to afford an off white solid **57a** (54% yield).

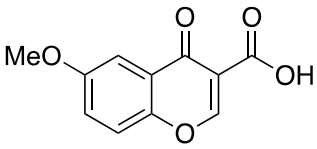
## *D – OPTIMIZED PINNICK OXIDATION*



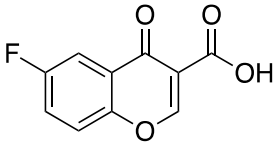

To a 500 mL Erlenmeyer flask was added chromone **56a** (75 mg, 4.3 mmol, 1.0 eq) and dichloromethane (172 mL). A solution of sulfamic acid (6.7 g, 69 mmol, 2.0 eq) in water (86 mL) was added and the reaction was cooled to 0°C. A solution of technical grade $NaClO_2$ (7.8 g, 69 mmol, 2.0 eq) in water (86 mL) was added dropwise and allowed to react for 16 h. The reaction mixture was extracted with dichloromethane (3 x 100 mL), dried over anhydrous $NaSO_4$, and the solvent was removed under vacuum to obtain the crude product. The crude product was washed with diethyl ether to afford an off white solid **57a** (54% yield).



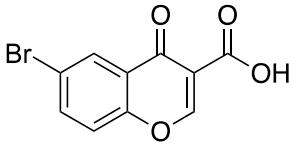
**3-carboxychromone (57a):** Prepared according to procedure *D*, using 3-formylchromone **56a** (6 g, 34.5 mmol), sulfamic acid (6,7 g, 69 mmol), $NaClO_2$ (7.8 g, 69 mmol), DCM (172 mL), and water (172 mL). The crude product was washed with diethyl ether to afford an off white solid **57a** (3.5 g, 18.6 mmol, 5% yield). $R_f$ = 0.21 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.39 (s, 1H), 0.2 (s, 1H), 8.35 (dd, J = 8, 1.5 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.66 (dd, J = 8.5, 0.55 Hz, 1H), 7.62 – 7.59 (m, 1H).



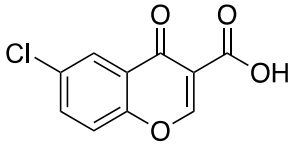
**3-carboxy-6-methoxychromone (57b):** Prepared according to procedure *D*, using 3-formylchromone **56b** (4.8 g, 24 mmol), sulfamic acid (4.7 g, 48 mmol), $NaClO_2$ (5.4 g, 48 mmol), DCM (117 mL), and water (117 mL). The crude product was washed with diethyl ether to afford an off white solid **57b** (3.1 g, 13.9 mmol, 58% yield). $R_f$ = 0.15 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.51 (s, 1H), 8.99 (s, 1H), 7.64 – 7.51 (m, 2H), 7.44 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H).



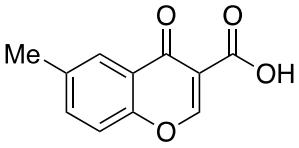
**3-carboxy-6-fluorochromone (57c):** Prepared according to procedure *D*, using 3-formylchromone **56c** (6.0 g, 31 mmol), sulfamic acid (6.0 g, 62 mmol), $NaClO_2$ (6.9 g, 62 mmol), DCM (155 mL), and water (155 mL). The crude product was washed with diethyl ether to afford an off white solid **57c** (1.8 g, 8.6 mmol, 28% yield). $R_f$ = 0.14 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.15 (s, 1H), 9.02 (s, 1H), 7.97 (dd, J = 7.7, 3.1 Hz, 1H), 7,67 (dd, J = 9.2, 4.1 Hz, 1H), 7.62 – 7.59 (m, 1H).



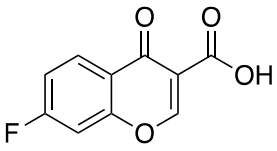
**3-carboxy-6-bromochromone (57d):** Prepared according to procedure *D*, using 3-formylchromone **56d** (5.6 g, 22 mmol), sulfamic acid (4.7 g, 48 mmol), $NaClO_2$ (5.4 g, 48 mmol), DCM (120 mL), and water (120 mL). The crude product was washed with diethyl ether to afford an off white solid **57d** (2.7 g, 9.9 mmol, 45% yield). $R_f$ = 0.17 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.09 (s, 1H), 9.01 (s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.9, 2.4 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H).



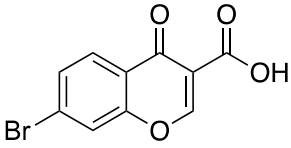
**3-carboxy-6-chlorochromone (57e)** Prepared according to procedure *D*, using 3-formylchromone **56e** (3.0 g, 14.4 mmol), sulfamic acid (2.8 g, 29 mmol), $NaClO_2$ (3.3 g, 29 mmol), DCM (72 mL), and water (72 mL). The crude product was washed with diethyl ether to afford an orange solid **57e** (1.6 g, 7.2 mmol, 50% yield). $R_f$ = 0.1 (3:2, Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.09 (s, 1H), 9.01 (s, 1H), 8.30 (d, J = 2.5 Hz, 1H), 7.81 (dd, J = 9.0, 2.6 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H).



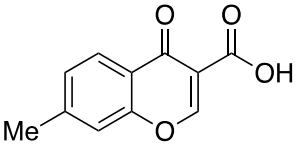

**3-carboxy-6-methylchromone (57f):** Prepared according to procedure *D*, using 3-formylchromone **56f** (0.14 g, 0.75 mmol), sulfamic acid (0.15 g, 1.5 mmol), $NaClO_2$ (0.17 g, 1.5 mmol), DCM (3.7 mL), and water (3.7 mL). The crude product was washed with diethyl ether to afford an off white solid **57f** (0.088 g, 0.43 mmol, 57% yield). $R_f$ = 0.08 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.48 (s, 1H), 8.99 (s, 1H), 8.11 (s, 1H), 7.68 – 7.65 (m, 1H), 7.54 (d, J = 8.6 Hz, 1H), 2.53 (s, 3H).



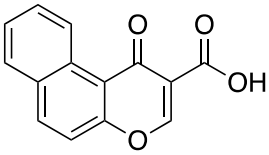

**3-carboxy-7-fluorochromone (57g):** Prepared according to procedure *C*, using 3-formylchromone **56g** (0.50 g, 2.6 mmol), sulfamic acid (0.51 g, 5.2 mmol), $NaClO_2$ (0.94 g, 10.4 mmol), DCM (52 mL), and water (51 mL). The crude product was washed with diethyl ether to afford an off white solid **57g** (0.172 g, 0.826 mmol, 32% yield). $R_f$ = 0.23 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.24 (s, 1H), 8.99 (s, 1H), 8.30-8.36 (m, 1H), 7.35 – 7.31 (m, 2H).



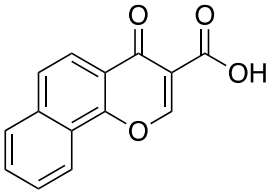

**7-bromo-3-carboxychromone (57h):** Prepared according to procedure *C*, using 3-formylchromone **56h** (0.90 g, 3.56 mmol), sulfamic acid (0.69 g, 7.1 mmol), $NaClO_2$ (1.3 g, 14.2 mmol), DCM (71 mmol), and water (69 mL). The crude product was washed with diethyl ether to afford a yellow-orange solid **57h** (0.683 g, 2.54 mmol, 71% yield). $R_f$ = 0.13 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.15 (s, 1H), 8.97 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 1.7 Hz, 1H), 7.72 (dd, J = 8.6, 1.7 Hz, 1H).



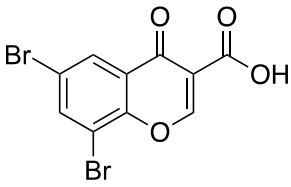

**3-carboxy-7-methylchromone (57i):** Prepared according to procedure *D*, using 3-formylchromone **56i** (4.4 g, 24 mmol), sulfamic acid (4.66 g, 48 mmol), $NaClO_2$ (5.4 g, 48 mmol), DCM (117 mL), and water (117 mL). The crude product was washed with diethyl ether to afford an off white solid **57g** (0.172 g, 0.826 mmol, 32% yield). $R_f$ = 0.16 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.52 (s, 1H), 8.97 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.43 – 7.39 (m, 2H), 2.57 (s, 3H).



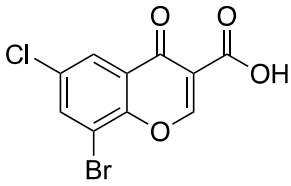

**5,6-benzo-3-carboxychromone (57j):** Prepared according to procedure *D*, using 3-formylchromone **56j** (0.65 g, 2.9 mmol), sulfamic acid (0.56 g, 5.8 mmol), $NaClO_2$ (0.65 g, 5.8 mmol), DCM (15 mL), and water (15 mL). The crude product was washed with diethyl ether to afford a white solid **57j** (0.38 g, 1.6 mmol, 54% yield). $R_f$ = 0.34 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.71 (s, 1H), 9.92 (d, J = 8.7Hz, 1H), 9.08 (s, 1H), 8.28 (d, J = 9.1 Hz, 1H), 8.01(d, J = 7.6 Hz, 1H), 7.88 (t, J = 8.5 Hz, 1H), 7.66 (d, J = 9.1 Hz, 1H).



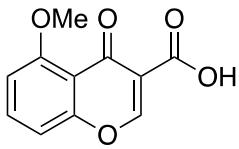
**7,8-benzo-3-carboxychromone (57k):** Prepared according to procedure *C*, using 3-formylchromone **56k** (1.5 g, 6.69 mmol), sulfamic acid (1.3 g, 13.4 mmol), $NaClO_2$ (2.4 g, 27 mmol), DCM (134 mL), and water (129 mL). The crude product was washed with diethyl ether to afford a yellow solid **57k** (1.05 g, 4.38 mmol, 66% yield). $R_f$ = 0.06 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.69 (s, 1H), 9.19 (s, 1H), 8.58 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.85 – 7.78 (m, 2H).



**6,8-bromo-3-carboxychromone (57l):** Prepared according to procedure *D*, using 3-formylchromone **56l** (0.25 g, 0.74 mmol), sulfamic acid (0.14 g, 1.5 mmol), $NaClO_2$ (0.17 g, 0.15 mmol), DCM (3.7 mL), and water (3.7 mL). The crude product was washed with diethyl ether to afford an off white solid **57l** (0.099 g, 0.28 mmol, 38% yield). $R_f$ = 0.06 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 12.87 (s, 1H), 9.06 (s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.20 (d, J = 2.4 Hz, 1H).

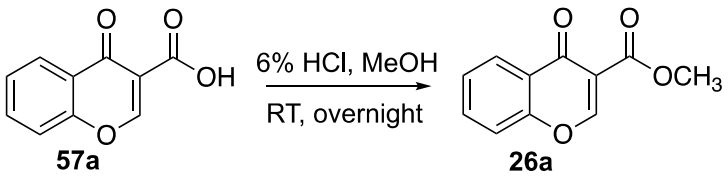


**8-bromo-6-chloro-3-carboxychromone (57m):** Prepared according to procedure *D*, using 3-formylchromone **56m** (0.39 g, 1.4 mmol), sulfamic acid (0.27 g, 2.8 mmol), $NaClO_2$ (0.31 g, 2.8 mmol), DCM (6.8 mL), and water (6.8 mL). The crude product was washed with diethyl ether to afford an off white solid **57m** (0.25 g, 0.85 mmol, 61% yield). $R_f$ = 0.30 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 12.84 (s, 1H), 9.06 (s, 1H), 8.25 (d, J = 2.5 Hz, 1H), 8.06 (d, J = 2.5 Hz, 1H).



**3-carboxy-5-methoxychromone (57n):** Prepared according to procedure *C*, using 3-formylchromone **56n** (1.3 g, 6.4 mmol), sulfamic acid (1.2 g, 13 mmol), $NaClO_2$ (2.3 g, 25 mmol), DCM (128 mL), and water (123 mL). The crude product was washed with diethyl ether to afford an off white solid **57n** (1.11 g, 5.04 mmol, 79% yield). $R_f$ = 0.06 (3:2, Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 13.75 (s, 1H), 8.88 (s, 1H), 7.75 (t, J = 8.5 Hz, 1H), 7.18 (dd, J = 8.5, 0.85 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 4.05 (s, 3H).

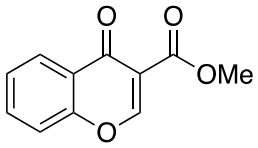
## *E – FISCHER ESTERIFICATION*



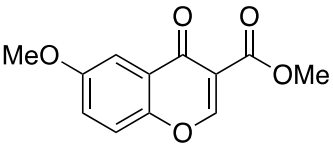

**57a** **26a**

To a 100 mL round bottom flask was added 3-carboxychromone **57a** (0.56 g, 2.95 mmol, 1.0 eq) and methanol (29 mL). Reaction was cooled to 0°C and acetyl chloride (3.29 mL, 48 mmol) added dropwise, allowed to react for 16 h. Solvent was removed under vacuum and reaction mixture was extracted with EtOAc (3 x 20 mL), washed with saturated $NaHCO_3$, washed with saturated NaCl, and dried over anhydrous $NaSO_4$. Solvent was removed under

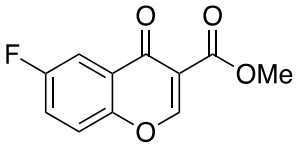
vacuum to afford the crude product. The crude product was purified by column chromatography on silica gel with Hexanes:EtOAc (3:2) to afford an off white solid **26a** (85%).



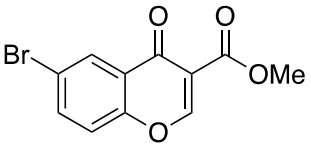
**Methyl-4H-chromen-4-one-3-carboxylate (26a):** Prepared according to procedure *E*, using 3-carboxychromone **57a** (0.56 g, 2.95 mmol), acetyl chloride (3.3 mL), and methanol (29 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM), to afford an off-white solid **26a** (0.512 g, 2.51 mmol, 85% yield). $R_f$ = 0.71 (8:2 EtOAc:DCM), $^1$H NMR (500 MHz, Chloroform-d) δ 8.69 (s, 1H), 8.30 (d, J = 8.0, 1.4 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.51 – 7.45 (m, 2H), 3.95 (s, 3H).



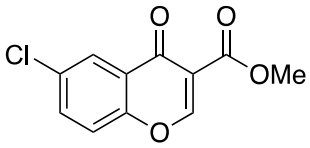
**6-methoxy-methyl-4H-chromen-4-one-3-carboxylate (26b):** Prepared according to procedure *E*, using 3-carboxychromone **57b** (2.8 g, 13 mmol), acetyl chloride (52 mL), and methanol (435 mL). The crude product was purified by column chromatography on $SiO_2$ (3:2 Hexanes:EtOAc) to afford an off white solid **26b** (2.6 g, 11.3 mmol, 87% yield). $R_f$ = 0.28 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 8.67 (s, 1H), 7.65 (d, J = 3.1 Hz, 1H), 7.43 (d, J = 9.2 Hz, 1H), 7.28 (dd, J = 9.1, 3.2 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H).



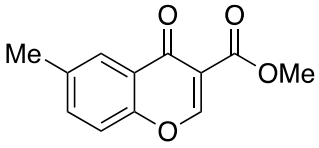
**6-fluoro-methyl-4H-chromen-4-one-3-carboxylate (26c):** Prepared according to procedure *E*, using 3-carboxychromone **57c** (1.6 g, 7.8 mmol), acetyl chloride (31 mL), and methanol (263 mL). The crude product was purified by column chromatography on $SiO_2$ (3:2 Hexanes:EtOAc) to afford a pink solid **26c** (1.4 g, 6.4 mmol, 82% yield). $R_f$ = 0.34 (3:2 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 8.68 (s, 1H), 7.92 (dd, J = 8.1, 3.1 Hz, 1H), 7.53 (dd, J = 9.2, 4.1 Hz, 1H), 7.44 (t, J = 9.2 Hz, 1H), 3.92 (s, 3H).



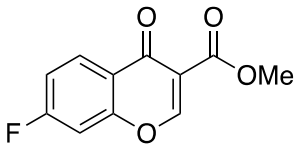
**6-bromo-methyl-4H-chromen-4-one-3-carboxylate (26d):** Prepared according to procedure *E*, using 3-carboxychromone **57d** (1.9 g, 7.1 mmol), acetyl chloride (30 mL), and methanol (250 mL). The crude product was purified by column chromatography on $SiO_2$ (3:2 Hexanes:EtOAc) to afford a tan solid **26d** (1.3 g, 4.8 mmol, 67% yield). $R_f$ = 0.43 (3:2 Hexanes:EtOAc),$^1$H NMR (500 MHz, Chloroform-d) δ 8.68 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 8.9, 2.5 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 3.93 (s, 3H).



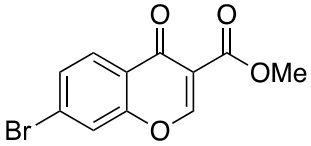
**6-chloro-methyl-4H-chromen-4-one-3-carboxylate (26e):** Prepared according to procedure *E*, using 3-carboxychromone **57e** (1.0 g, 4.45 mmol), acetyl chloride (5.4 mL), and methanol (45 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM) to afford an off white solid **26e** (0.607 g, 2.54 mmol, 57% yield). $R_f$ = 0.80 (8:2 EtOAc:DCM),$^1$H NMR (500 MHz, Chloroform-d) δ 8.68 (s, 1H), 8.24 (d, J = 2.5 Hz, 1H), 7.65 (dd, J = 8.9, 2.6 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 3.94 (s, 3H).



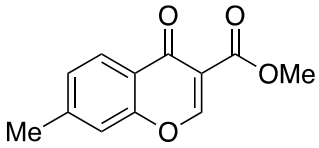

**6-methyl-methyl-4H-chromen-4-one-3-carboxylate (26f):** Prepared according to procedure *E*, using 3-carboxychromone **57f** (0.9 g, 4.4 mmol), acetyl chloride (11 mL), and methanol (88 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM) to afford an off white solid **26f** (0.72 g, 3.3 mmol, 74% yield). $R_f$ = 0.75 8:2 EtOAc:DCM) $^1$H NMR (500 MHz, Chloroform-d) δ 8.66 (s, 1H), 8.05 (s, 1H), 7.51 (dd, J = 8.5, 1.8 Hz, 1H), 7.39 (d, 8.6 J = Hz 1H), 3.93 (s, 3H) 2.47 (s, 3H).



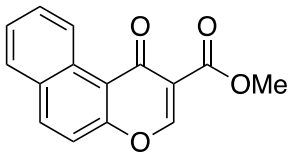

**7-fluoro-methyl-4H-chromen-4-one-3-carboxylate (26g):** Prepared according to procedure *E*, using 3-carboxychromone **57g** (0.08 g, 0.38 mmol), acetyl chloride (1 mL), and methanol (8 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM) to afford an off white solid **26g** (0.083 g, 0.29 mmol, 99% yield). $R_f$ = 0.65 (8:2 EtOAc:DCM), $^1$H NMR (500 MHz, Chloroform-d) δ 8.66 (s, 1H), 8.31 – 8.29 (m, 1H), 7.20 – 7.18 (m, 2H), 3.93 (s, 3H).



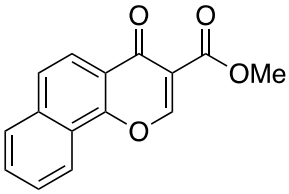

**7-bromo-methyl-4H-chromen-4-one-3-carboxylate (26h):** Prepared according to procedure *E*, using 3-carboxychromone **57h** (0.4 g, 1.5 mmol), acetyl chloride (3.6 mL), and methanol (30 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM) to afford a tan solid **26h** (0.35 g, 1.3 mmol, 84% yield). $R_f$ = 0.75 (8:2 EtOAc:DCM), $^1$H NMR (500 MHz, Chloroform-d) δ 8.64 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.59 – 7.57 (m, 1H), 3.93 (s, 3H).



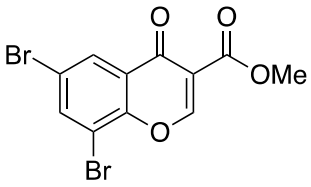

**7-methyl-methyl-4H-chromen-4-one-3-carboxylate (26i):** Prepared according to procedure *E*, using 3-carboxychromone **57i** (1.6 g, 8.3 mmol), acetyl chloride (33 mL), and methanol (280 mL). The crude product was purified by column chromatography on $SiO_2$ (3:2 Hexanes:EtOAc) to afford an off white solid **26i** (1.2 g, 5.3 mmol, 64% yield). $R_f$ = 0.38 (3:2 Hexanes:EtOAc) $^1$H NMR (500 MHz, Chloroform-d) δ 8.64 (s, 1H), 8.18 (d, J = 7.9, 1H), 7.28 – 7.26 (m, 2H), 3.93 (s, 3H), 2.49 (s, 3H).



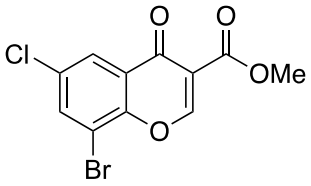

**5,6-benzo-methyl-4H-chromen-4-one-3-carboxylate (26j):** Prepared according to procedure *E*, using 3-carboxychromone **57j** (0.24 g, 1 mmol), acetyl chloride (4.2 mL), and methanol (36 mL). The crude product was purified by column chromatography on $SiO_2$ (3:2 Hexanes:EtOAc) to afford an off white solid **26j** (0.09 g, 0.35 mmol, 35% yield). $R_f$ = 0.45 (3:2 Hexanes:EtOAc) $^1$H NMR (500 MHz, Chloroform-d) δ 8.67 (s, 1H), 8.13 (d, J = 9.1 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.66 (t, J = 6.9 Hz, 1H), 7.53 (d, J = 9.1 Hz, 1H), 3.97 (s, 3H).



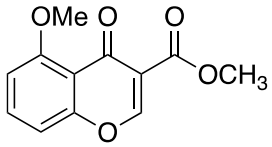
**7,8-benzo-methyl-4H-chromen-4-one-3-carboxylate (26k):** Prepared according to procedure *E*, using 3-carboxychromone **57k** (0.90 g, 3.75 mmol), acetyl chloride (8.9 mL), and methanol (75 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM) to afford an orange solid **26k** (0.506 g, 1.99 mmol, 53% yield). $R_f$ = 0.68 (8:2 EtOAc:DCM), $^1$H NMR (500 MHz, Chloroform-d) δ 8.86 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.74 – 7.70 (m, 2H), 3.97 (s, 3H).



**6,8-dibromo-methyl-4H-chromen-4-one-3-carboxylate (26l):** Prepared according to procedure *E*, using 3-carboxychromone **57l** (0.09 g, 0.25 mmol), acetyl chloride (1.6 mL), and methanol (14 mL). The reaction solution was worked up to afford a tan solid **26l** (3.2 mg, 0.009 mmol, 36% yield). $R_f$ = 0.28 (4:1 Hexanes:EtOAc),$^1$H NMR (500 MHz, Chloroform-d) δ 8.74 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 3.94 (s, 3H).

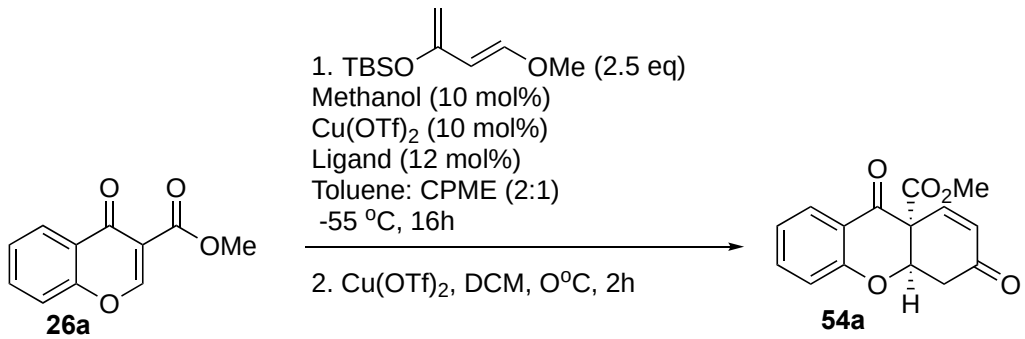


**8-bromo-6-chloro -methyl-4H-chromen-4-one-3-carboxylate (26m):** Prepared according to procedure *E*, using 3-carboxychromone **57m** (0.23 g, 0.75 mmol), acetyl chloride (3 mL), and methanol (25 mL). The crude product was purified by column chromatography on $SiO_2$ (3:2 Hexanes:EtOAc) to afford a tan solid **26m** (0.083 mg, 0.26 mmol, 35% yield). $R_f$ = 0.39 (3:2 Hexanes:EtOAc),$^1$H NMR (500 MHz, Chloroform-d) δ 8.74 (s, 1H), 8.19 (d, J = 2.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 3.94 (s, 3H).



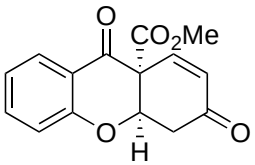
**5-methoxy-methyl-4H-chromen-4-one-3-carboxylate (26n):** Prepared according to procedure *E*, using 3-carboxychromone **57n** (1.0 g, 4.5 mmol), acetyl chloride (11 mL), and methanol (91 mL). The crude product was purified by column chromatography on $SiO_2$ (8:2 EtOAc:DCM) to afford an off white solid **26n** (0.76 g, 3.3 mmol, 72% yield). $R_f$ = 0.80 (8:2 EtOAc:DCM), $^1$H NMR (500 MHz, Chloroform-d) δ 8.47 (s, 1H), 7.56 (t, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.4, 0.9 Hz, 1H), 6.85 (d, J = 7.8, 1H), 3.96 (s, 3H), 3.90 (s, 3H).

## *F – ENANTIOSELECTIVE CYCLOADDITION*

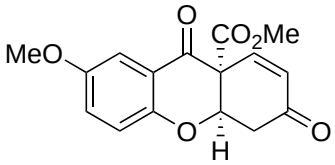



**26a** **54a**

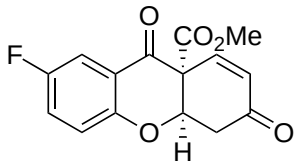
To a flame dried 2 dram vial was added methyl-4H-chromen-4-one-3-carboxylate **26a** (20.4 mg, 0.1 mmol, 1.0 eq), $Cu(OTf)_2$ (3.6 mg, 0.01 mmol, 0.1 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), toluene (1.33 mL), methanol (0.4 μL), and cyclopentyl methyl ester (0.66 mL). Reaction mixture was stirred until green color appeared indicating the formation of the copper-ligand complex. Reaction mixture was cooled to -55°C, (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** was added (60 μL, 0.25 mmol, 2.5 eq), and was allowed to react for 16 h. Reaction mixture was quenched with water (1 mL), extracted with diethyl ether (2.5 mL), washed with water (3 x 2 mL), and dried over anhydrous $NaSO_4$. The solvent was removed under vacuum to afford the crude product. The crude product was purified by preparative thin layer chromatography with Hexane:EtOAc (9:1) to yield a yellow oil of adducts. The yield of the desired product was determined by $^1$H-NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference (82%). The purified adducts were added to a 1 dram vial with $Cu(OTf)_2$ (3.6 mg, 0.01 mmol, 0.1 eq) and dichloromethane (1 mL). The reaction mixture was allowed to react at -18°C for 2 h. Reaction mixture was quenched with water (0.5 mL), washed with 1.0 M NaOH (3 x 5 mL), dried over $NaSO_4$, and flushed through a silica plug with EtOAc. The solvent was removed under vacuum to afford the crude product. The crude product was purified by preparative thin layer chromatography with Hexane:EtOAc (6:4) to afford an off white solid **54a** (42%).



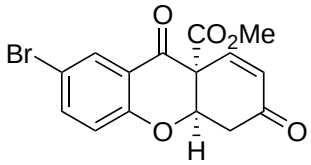

**Methyl (4a*R*,9a*R*)-3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (54a)**: Prepared according to procedure *F*, using methyl-4H-chromen-4-one-3-carboxylate **26a** (20.4 mg, 0.1 mmol, 1.0 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (60 μL, 0.25 mmol, 2.5 eq). Purified by preparative thin layer chromatography with Hexanes:EtOAc (9:1) to yield a yellow oil (82%). **54a** was isolated after deprotection as a white solid (42%). $R_f$ = 0.33 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.95 (dd, J = 7.9, 1.7 Hz, 1H), 7.57 (t, J = 8.5 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 10.1, 2.0 Hz, 1H), 6.29 (d, J = 10.1 Hz, 1H), 5.42 – 5.39 (m, 1H), 3.87 (s, 3H), 3.03 (dd, J = 16.2, 3.6 Hz, 1H), 2.71 (dd, J = 17.3, 2.7 Hz, 1H).



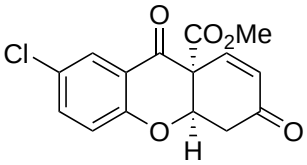

**Methyl (4a*R*,9a*R*)-7-methoxy-3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (54b)**: Prepared according to procedure *F*, using 6-methoxy-methyl-4H-chromen-4-one-3-carboxylate **26b** (23.4 mg, 0.1 mmol, 1.0 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (60 μL, 0.25 mmol, 2.5 eq). Purified by preparative thin layer chromatography with Hexanes:EtOAc (9:1) to yield a yellow oil (39%). **54b** was isolated after deprotection as a white solid (41%). $R_f$ = 0.23 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.32 (d, J = 3.2 Hz, 1H), 7.18 (dd, J = 9.1, 3.2 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 6.64 (dd, J = 10.1, 4.3 Hz, 1H), 6.29 (d, J = 10.1 Hz, 1H), 5.35 – 5.33 (m, 1H), 3.87 (s, 1H), 3.81 (s, 1H), 3.01 (dd, J = 17.2, 4.6 Hz, 1H), 2.67 (dd, J = 17.2, 2.7 Hz, 1H).



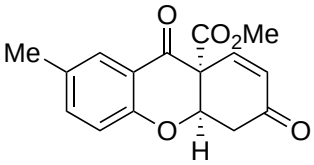

**Methyl (4a*R*,9a*R*)-7-fluoro-3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (54c)**: Prepared according to procedure *F*, using 6-fluoro-methyl-4H-chromen-4-one-3-carboxylate **26c (**22.2 mg, 0.1 mmol, 1.0 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (60 μL, 0.25 mmol, 2.5 eq). Purified by preparative thin layer chromatography with Hexanes:EtOAc (9:1) to yield a yellow oil (32%). **54c** was isolated after deprotection as a white solid (43%). $R_f$ = 0.24 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.59 (dd, J = 7.9, 3.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.01 (dd, J = 9.1, 4.1 Hz, 1H), 6.64 (dd, J = 9.1, 2.1 Hz, 1H), 6.30 (d, J = 10.1 Hz, 1H), 5.39 – 5.38 (m, 1H), 3.87 (s, 1H), 3.02 (dd, J = 17.3, 4.7 Hz, 1H), 2.71 (dd, J = 17.3, 2.7 Hz, 1H).




**Methyl (4a*R*,9a*R*)-7-bromo-3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (54d)**: Prepared according to procedure *F*, using 6-bromo-methyl-4H-chromen-4-one-3-carboxylate **26d (**28.3 mg, 0.1 mmol, 1.0 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (60 μL, 0.25 mmol, 2.5 eq). Purified by preparative thin layer chromatography with Hexanes:EtOAc (9:1) to yield a yellow oil (40%). **54d** was isolated after deprotection as a white solid (42%). $R_f$ = 0.38 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 8.04 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 8.9, 2.5 Hz, 1H), 6.92 (d, J = 8.9 Hz, 1H), 6.64 (dd, J = 10.1, 2.0 Hz, 1H), 6.29 (d, J = 10.1 Hz, 1H), 5.40 – 5.38 (m, 1H), 3.87 (s, 3H), 3.02 (dd, J = 17.3, 4.8 Hz, 1H), 2.71 (dd, J = 17.3, 2.8 Hz, 1H).



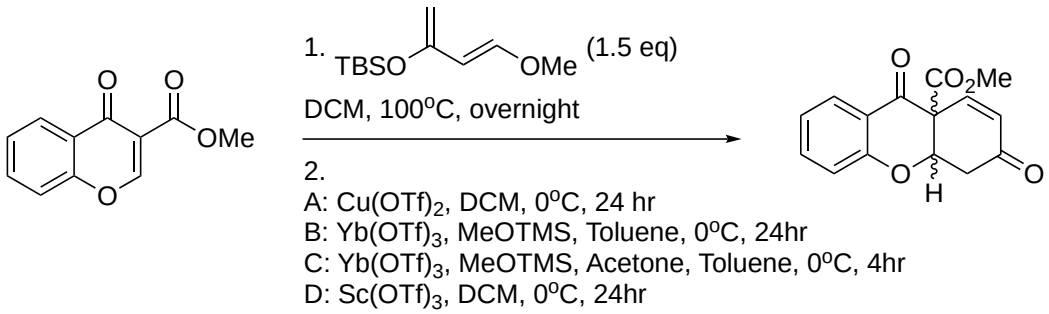

**Methyl (4a*R*,9a*R*)-7-chloro-3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (54e)**: Prepared according to procedure *F*, using 6-chloro-methyl-4H-chromen-4-one-3-carboxylate **26e (**28.3 mg, 0.1 mmol, 1.0 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (60 μL, 0.25 mmol, 2.5 eq). Purified by preparative thin layer chromatography with Hexanes:EtOAc (9:1) to yield a yellow oil (29%). **54e** was isolated after deprotection as a white solid (42%). $R_f$ = 0.24 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.89 (d, J = 2.7 Hz, 1H), 7.51 (dd, J = 12.0, 2.7 Hz, 1H), 6.98 (d, J = 8.9 Hz, 1H), 6.64 (dd, J = 10.1, 2.0 Hz, 1H), 6.29 (d, J =10.1 Hz, 1H), 5.40 – 5.38 (m, 1H), 3.87 (s, 3H), 3.02 (dd, J = 17.3, 4.7 Hz, 1H), 2.72 (dd, J = 17.3, 2.7 Hz, 1H).




**Methyl (4a*R*,9a*R*)-7-methyl-3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (54f)**: Prepared according to procedure *F*, using 6-methyl-methyl-4H-chromen-4-one-3-carboxylate **26f (**28.3 mg, 0.1 mmol, 1.0 eq), ligand **59** (10.07 mg, 0.012 mmol, 0.12 eq), and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (60 μL, 0.25 mmol, 2.5 eq). Purified by preparative thin layer chromatography with Hexanes:EtOAc (9:1) to yield a yellow oil (42%). **54f** was isolated after deprotection as a white solid (56%). $R_f$ = 0.36 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.71 (s, 1H), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.65 (dd, J

= 10.1, 2.0 Hz, 1H), 6.28 (d, J = 10.1 Hz, 1H), 5.37 – 5.35 (m, 1H), 3.87 (s, 3H), 3.01 (dd, J = 17.3, 4.7 Hz, 1H), 2.69 (dd, J = 17.3, 2.7 Hz, 1H), 2.32 (s, 3H).

## *H – DEPROTECTION OPTIMIZATION*



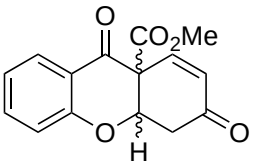

**Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate** was prepared according to an established procedure.[13, 23] To a 2 dram vial was added methyl-4H-chromen-4-one-3-carboxylate **26a** (50 mg, 0.25 mmol, 1.0 eq), (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (90 µL, 0.38 mmol, 1.5 eq), and 5 mL toluene. Reaction solution was heated to 100°C and allowed to react for 16 hours. The solvent was removed under reduced pressure and the crude material was purified by column chromatography on $SiO_2$ with Hexanes:EtOAc (9:1) to afford a yellow oil (89%). Adducts were divided and subjected to four methods:

A) To a 1 dram vial was added adducts (27.8 mg, 0.066 mmol, 1.0 eq), and DCM (0.66 mL). Reaction solution was cooled to 0°C and $Cu(OTf)_2$ (2.4 mg, 0.0066 mmol, 0.1 eq) was added and allowed to react for 48 h. Reaction solution was quenched with water. (0.5 mL), washed with 1.0 M NaOH (3 x 5 mL), dried over $NaSO_4$, and flushed through a silica plug with EtOAc. The solvent was removed under vacuum to afford the crude product. The yield of the desired product was determined by $^1$H-NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference (44%).

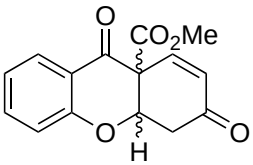
B) To a 1 dram vial was added adducts (21.8 mg, 0.052 mmol, 1.0 eq), and toluene (0.15 mL). Reaction solution was cooled to 0° and premixed solution of $Yb(OTf)_3$ (0.64 mg, 0.00104 mmol, 0.02 eq), MeOTMS (0.7 µL, 0.0052 mmol, 0.1 eq) in toluene (0.15 mL) was added and allowed to react for 48 h. Reaction solution was quenched with water. (0.5 mL), washed with 1.0 M NaOH (3 x 5 mL), dried over $NaSO_4$, and flushed through a silica plug with EtOAc. The solvent was removed under vacuum to afford the crude product. The yield of the desired product was determined by $^1$H-NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference (2%).

C) To a 1 dram vial was added adducts (30.9 mg, 0.074mmol, 1.0 eq), and toluene (0.25 mL). Reaction solution was cooled to 0° and premixed solution of $Yb(OTf)_3$ (0.92 mg, 0.00147 mmol, 0.02 eq), MeOTMS (1 µL, 0.0074 mmol, 0.1 eq) in acetone (0.25 mL) was added and allowed to react for 4 h. Reaction solution was quenched with water. (0.5 mL), washed with 1.0 M $K_2CO_3$ (3 x 5 mL), dried over $NaSO_4$, and flushed through a silica plug with EtOAc. The solvent was removed under vacuum to afford the crude product. The yield of the desired product was determined by $^1$H-NMR spectroscopy using 1,3,5-trimethoxy benzene as the reference (35%).

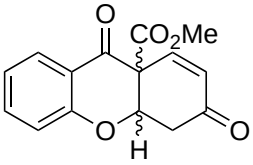
D) To a 1 dram vial was added adducts (12.5 mg, 0.029 mmol, 1.0 eq), and DCM (0.3 mL). Reaction solution was cooled to 0°C and $Sc(OTf)_3$ (1.4 mg, 0.0029 mmol, 0.1 eq) was added and allowed to react for 48 h. No conversion was seen via TLC




**Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate** was prepared according to procedure *Ha*, using methyl-4H-chromen-4-one-3-carboxylate **26a** (50 mg, 0.25 mmol, 1.0 eq) and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (90 μL, 0.38 mmol, 1.5 eq). Purified by column chromatography on $SiO_2$ with Hexanes:EtOAc (9:1) to afford a yellow oil (89%). Deprotection method A yielded Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (44%). $R_f$ = 0.33 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.95 (dd, J = 7.9, 1.7 Hz, 1H), 7.57 (t, J = 8.5 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 10.1, 2.0 Hz, 1H), 6.29 (d, J = 10.1 Hz, 1H), 5.42 – 5.39 (m, 1H), 3.87 (s, 3H), 3.03 (dd, J = 16.2, 3.6 Hz, 1H), 2.71 (dd, J = 17.3, 2.7 Hz, 1H).




**Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate** was prepared according to procedure *Hb* using methyl-4H-chromen-4-one-3-carboxylate **26a** (50 mg, 0.25 mmol, 1.0 eq) and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (90 μL, 0.38 mmol, 1.5 eq). Purified by column chromatography on $SiO_2$ with Hexanes:EtOAc (9:1) to afford a yellow oil (89%). Deprotection method B yielded Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (2%). $R_f$ = 0.33 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.95 (dd, J = 7.9, 1.7 Hz, 1H), 7.57 (t, J = 8.5 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 10.1, 2.0 Hz, 1H), 6.29 (d, J = 10.1 Hz, 1H), 5.42 – 5.39 (m, 1H), 3.87 (s, 3H), 3.03 (dd, J = 16.2, 3.6 Hz, 1H), 2.71 (dd, J = 17.3, 2.7 Hz, 1H).




**Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate** was prepared according to procedure *Hc*, using methyl-4H-chromen-4-one-3-carboxylate **26a** (50 mg, 0.25 mmol, 1.0 eq) and (1,1-Dimethylethyl)[(3-methoxy-1-methylene-2-propen-1-yl)oxy]dimethylsilane **27** (90 μL, 0.38 mmol, 1.5 eq). Purified by column chromatography on $SiO_2$ with Hexanes:EtOAc (9:1) to afford a yellow oil (89%). Deprotection method C yielded Methyl 3,9-dioxo-4,4a-dihydro-3*H*-xanthene-9a(9*H*)-carboxylate (35%). $R_f$ = 0.33 (4:1 Hexanes:EtOAc), $^1$H NMR (500 MHz, Chloroform-d) δ 7.95 (dd, J = 7.9, 1.7 Hz, 1H), 7.57 (t, J = 8.5 Hz, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 10.1, 2.0 Hz, 1H), 6.29 (d, J = 10.1 Hz, 1H), 5.42 – 5.39 (m, 1H), 3.87 (s, 3H), 3.03 (dd, J = 16.2, 3.6 Hz, 1H), 2.71 (dd, J = 17.3, 2.7 Hz, 1H).

# Appendix 2: Analytical Methods

*Characterization of Compounds*

$^1$H-NMR spectroscopy was primarily used to confirm the composition of the starting materials and products. $^1$H-NMR (Proton Nuclear Magnetic Spectroscopy) uses magnetic fields to verify the organization of hydrogens within a molecule. The molecules of interest in this investigation could be reliably identified using characteristics of the spectra such as number of peaks, chemical shift, and splitting patterns (See Appendix 1 for the identification of the protons in each compound). All $^1$H-NMR spectra were obtained in $CDCl_3$ solutions.

$^1$H-NMR spectroscopy was also used to determine the yield of the addition reaction. A known quantity (between 0.005-0.010 g) of the internal standard, 1, 3, 5-trimethoxy benzene, was added to the crude of the product prior to purification via preparative TLC. This standard produces a peak representing 3 protons in the $^1$H NMR spectra at 6ppm. The integration of that signal was calibrated to 3. A peak known to be only corresponding to the desired product was subsequently integrated and the yield of the desired product was calculated.

*Determination of Enantioselectivity*

The enantioselectivity of the cycloaddition to the 2 and the 3 position of the chromenone was determined using High Performance Liquid Chromatography (HPLC). In this method, products **54c-54f** were purified and flushed through the HPLC using a 90% Hexanes and 10% IPA solution in an AD-H column. After approximately, 20 minutes, both enantiomers become separated. This is evident in the spectra that shows 2 separate and distinct peaks as shown in figure 13a. Peak 1 corresponds to the S,S enantiomer and peak 2 corresponds to the R,R enantiomer. In this method, product **54a** was purified and flushed through the HPLC using an 80% Hexanes and 20% IPA solution in an OD-H column. After approximately, 20 minutes, both enantiomers become separated. This is evident in the spectra that shows 2 separate and distinct peaks as shown in figure 13b. Peak 1 corresponds to the R,R enantiomer and peak 2 corresponds to the S,S enantiomer. In this method, product **54b** was purified and flushed through the HPLC using a 70% Hexanes and 30% IPA solution in an OD-H column. After approximately 30 minutes, both enantiomers become separated. This is evident in the spectra that shows 2 separate and distinct peaks as shown in figure 13c. Peak 1 corresponds to the R,R enantiomer and peak 2 corresponds to the S,S enantiomer.

Figure 13a:

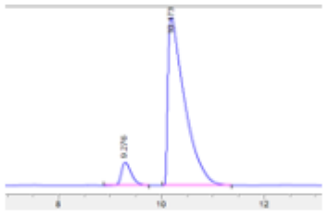


Figure 13b:

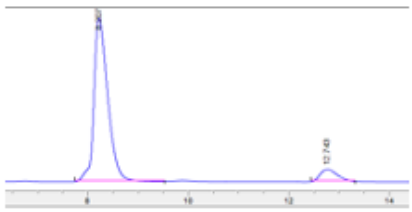
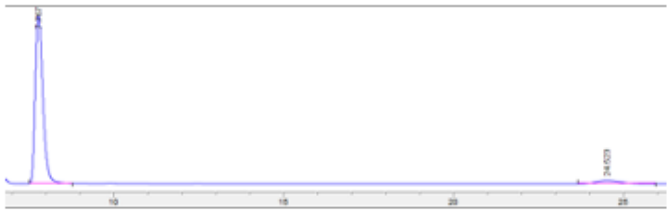


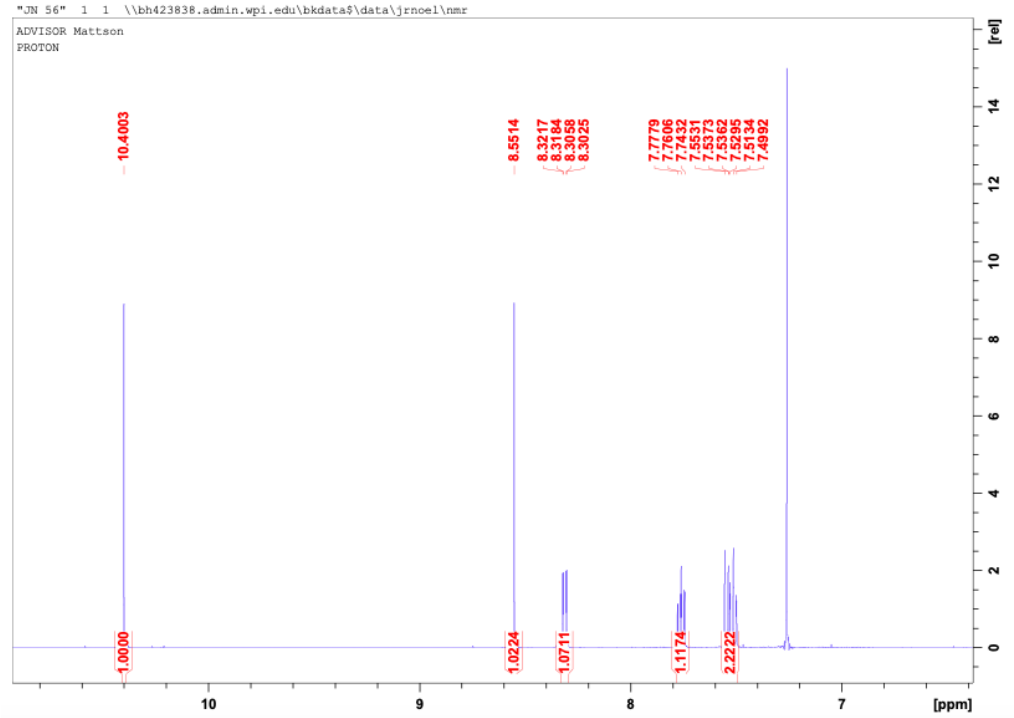
Figure 13 C



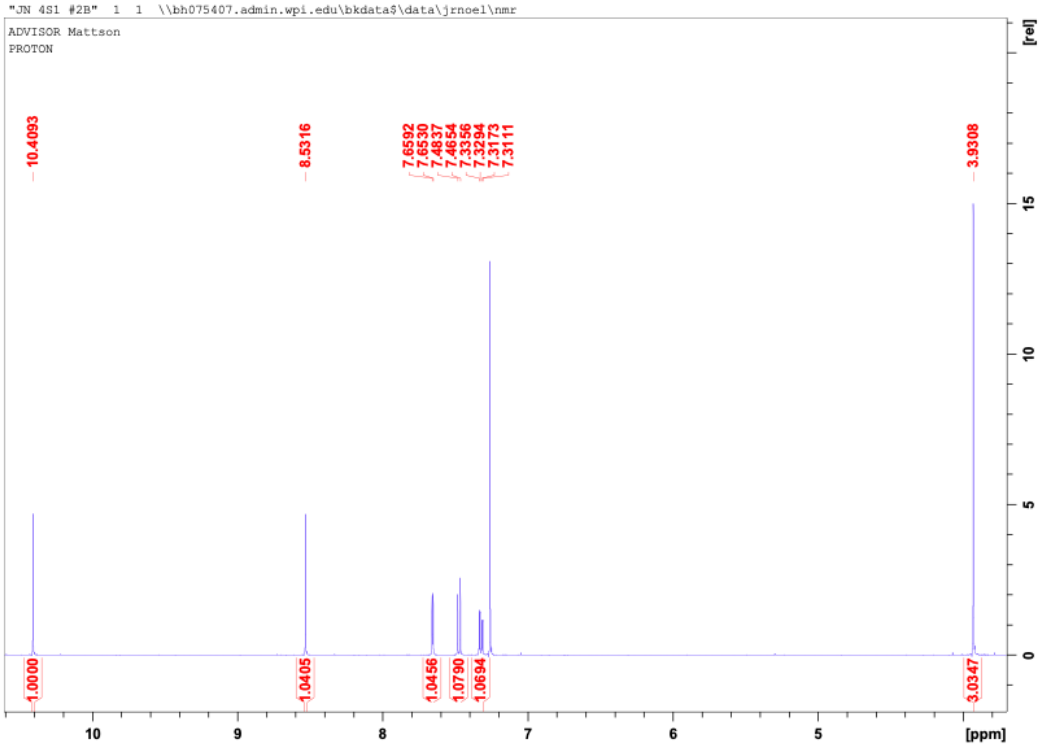
# Appendix 3: Characterization Data

## *[1]H-NMR SPECTRA*

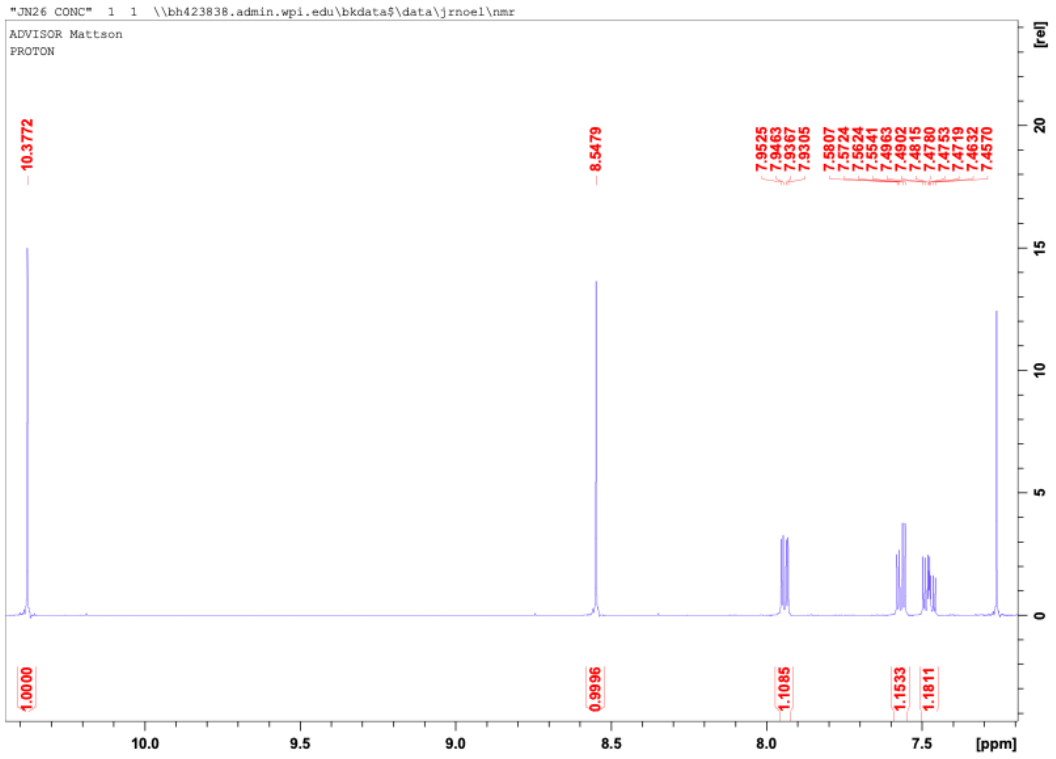
**56a**



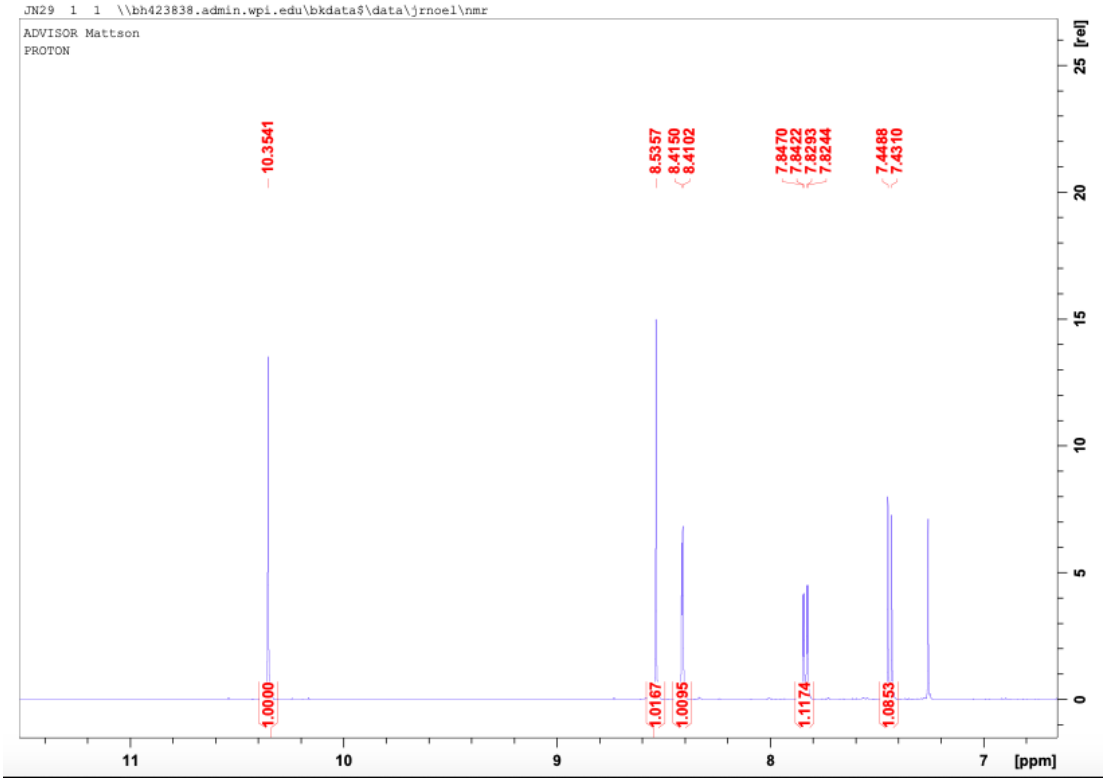

**56b**



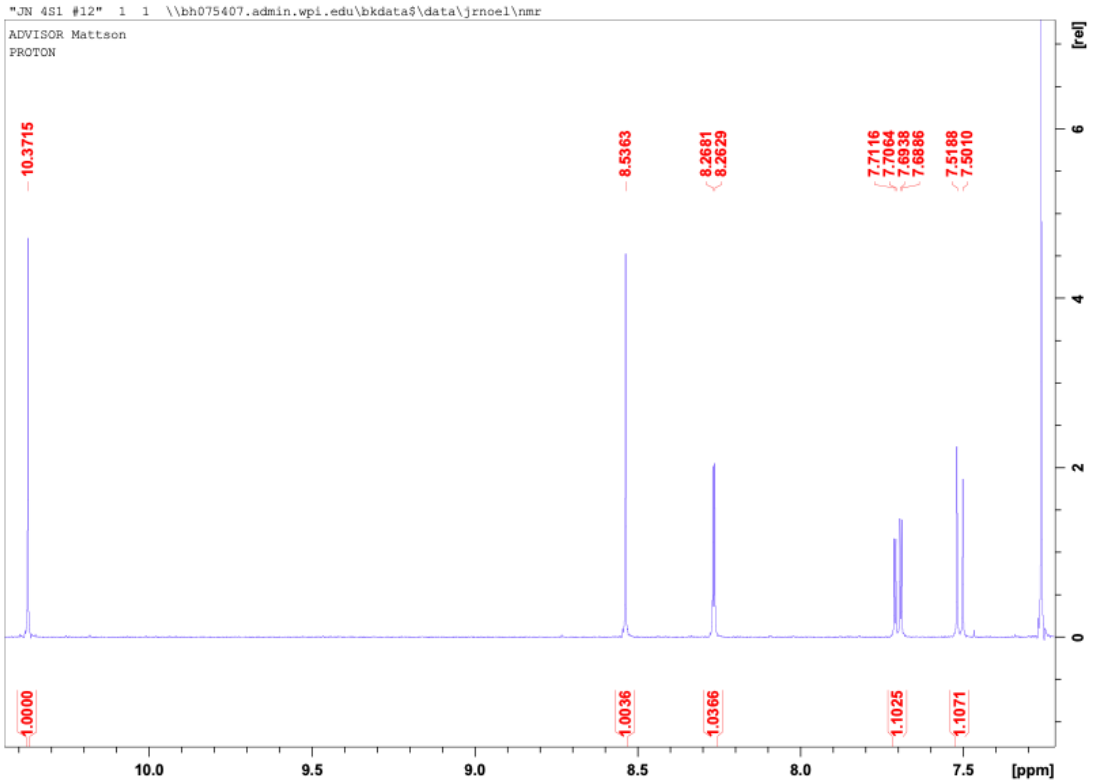
**56c**


"JN26 CONC" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3772
8.5479
7.9525
7.9463
7.9367
7.9305
7.5807
7.5724
7.5624
7.5541
7.4963
7.4902
7.4815
7.4780
7.4753
7.4719
7.4632
7.4570
1.0000
0.9996
1.1085
1.1533
1.1811
[rel]
[ppm]

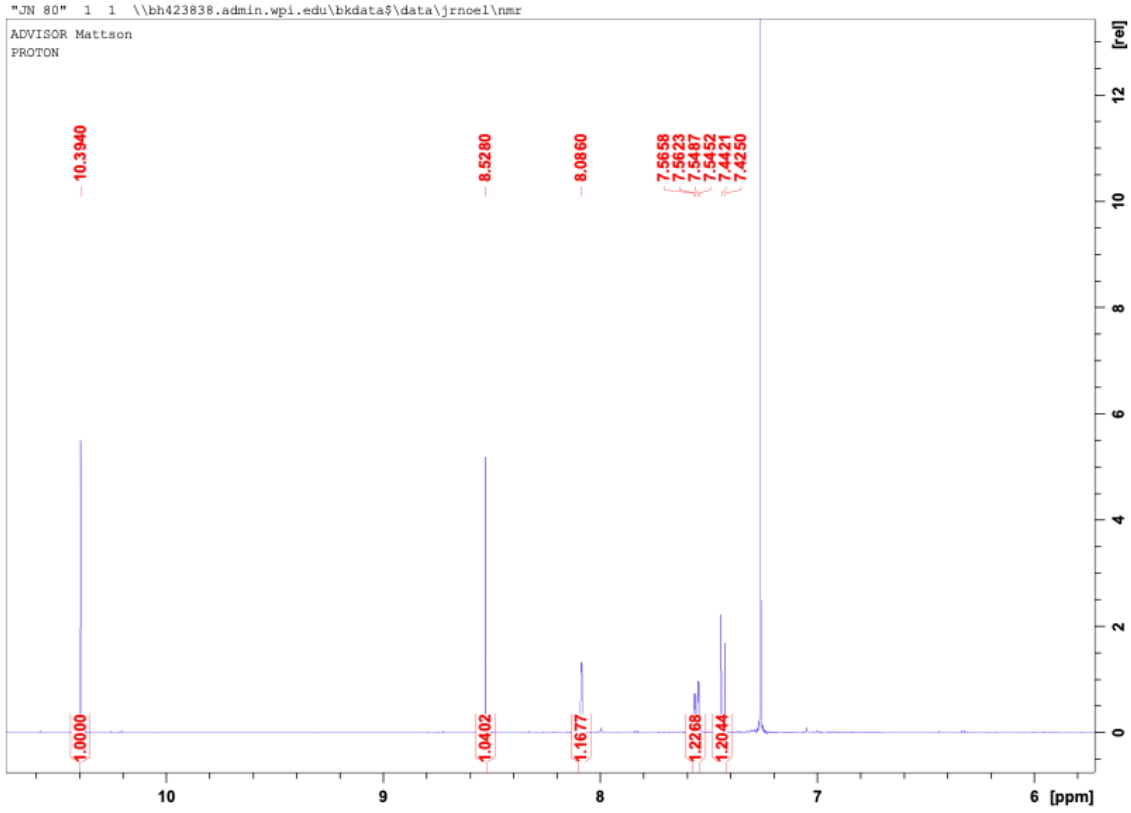
**56d**


JN29 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3541
8.5357
8.4150
8.4102
7.8470
7.8422
7.8293
7.8244
7.4488
7.4310
1.0000
1.0167
1.0095
1.1174
1.0853
[rel]
[ppm]

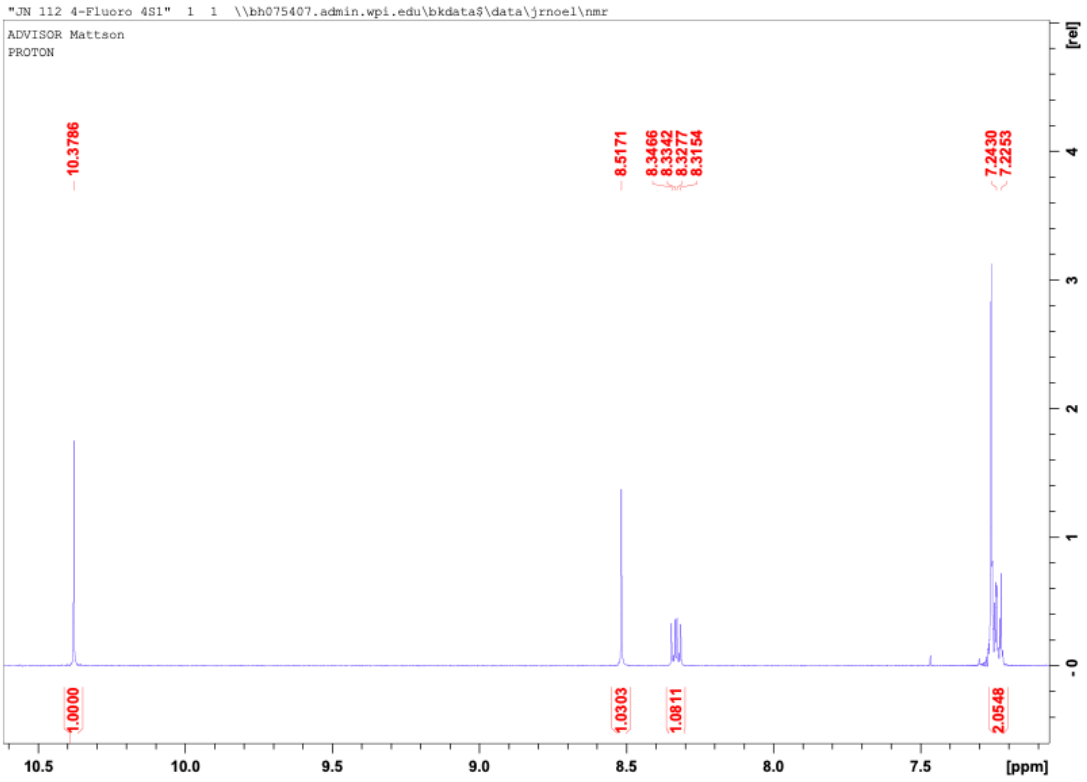
**56e**


"JN 4S1 #12" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3715
8.5363
8.2681
8.2629
7.7116
7.7064
7.6938
7.6886
7.5188
7.5010
1.0000
1.0036
1.0366
1.1025
1.1071
[rel]
[ppm]

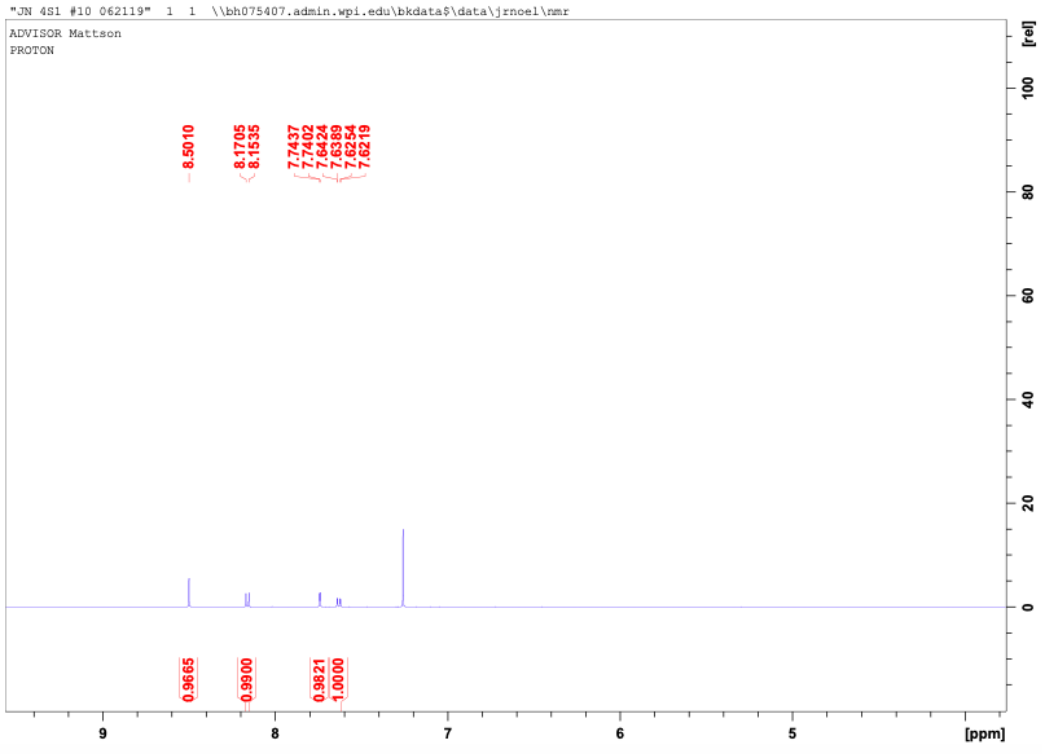
**56f**


"JN 80" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3940
8.5280
8.0860
7.5658
7.5623
7.5487
7.5452
7.4421
7.4250
1.0000
1.0402
1.1677
1.2268
1.2044
[rel]
[ppm]

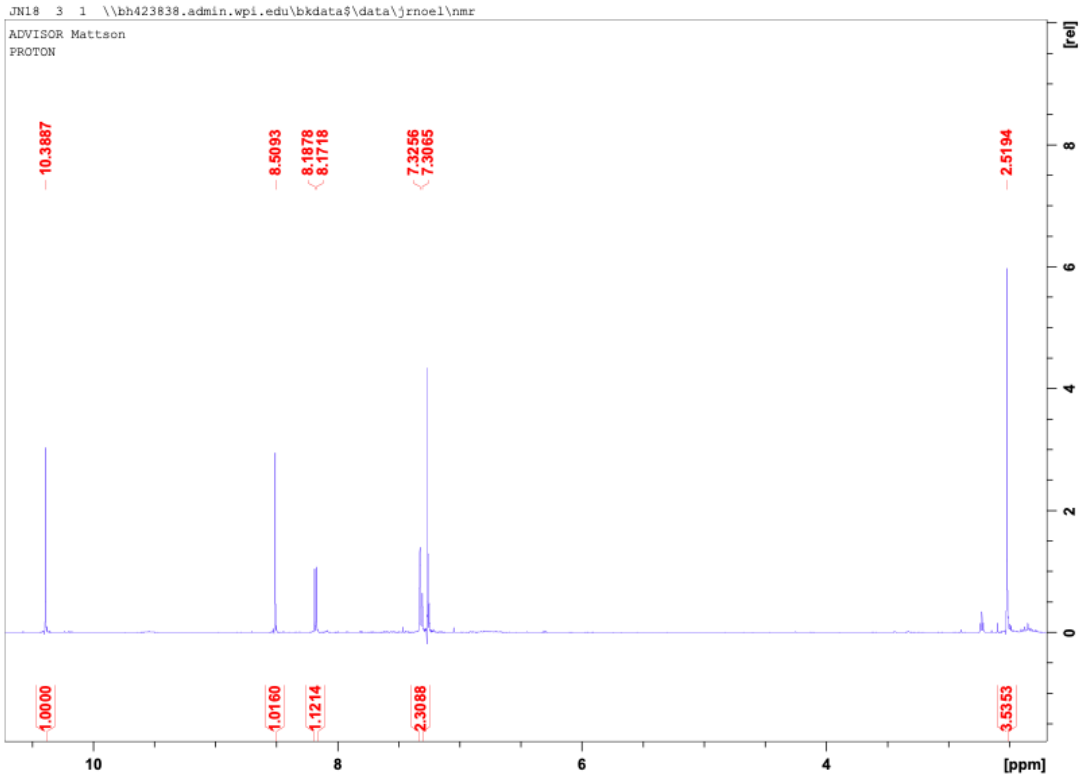
**56g**


"JN 112 4-Fluoro 4S1" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3786
8.5171
8.3466
8.3342
8.3277
8.3154
7.2430
7.2253
1.0000
1.0303
1.0811
2.0548
[ppm]
[rel]

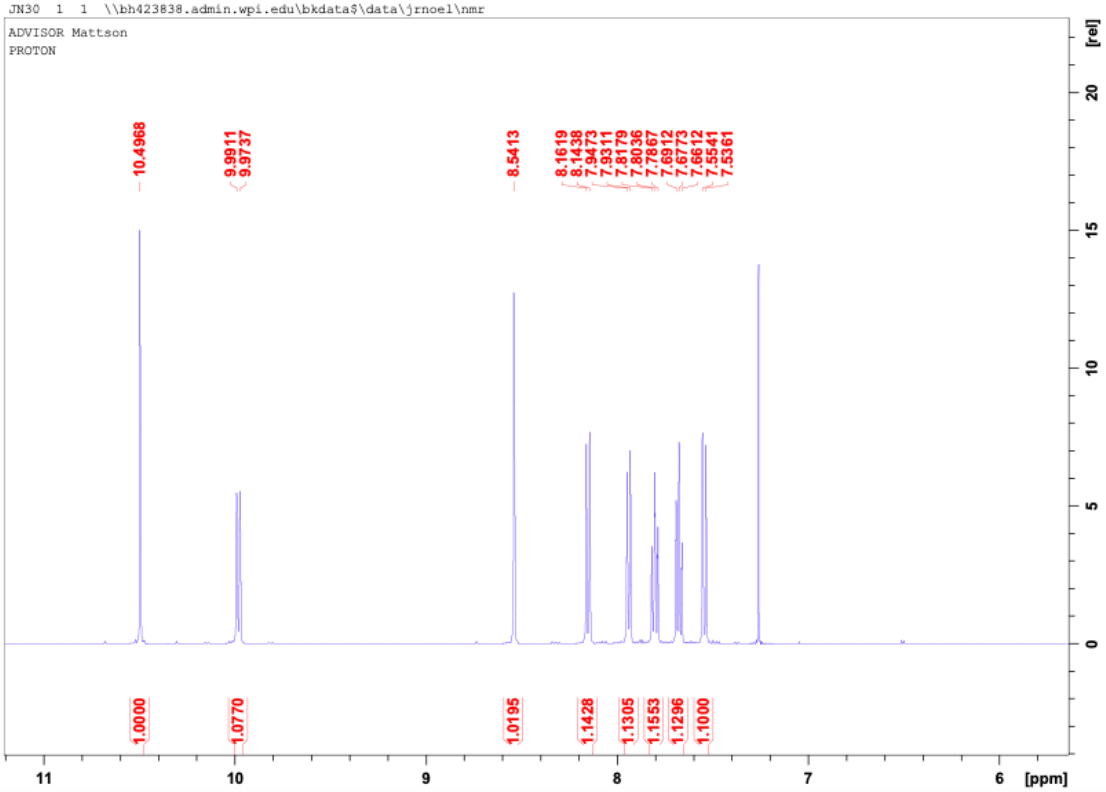
**56h**


"JN 4S1 #10 062119" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.5010
8.1705
8.1535
7.7437
7.7402
7.6424
7.6389
7.6254
7.6219
0.9665
0.9900
0.9821
1.0000
[ppm]
[rel]

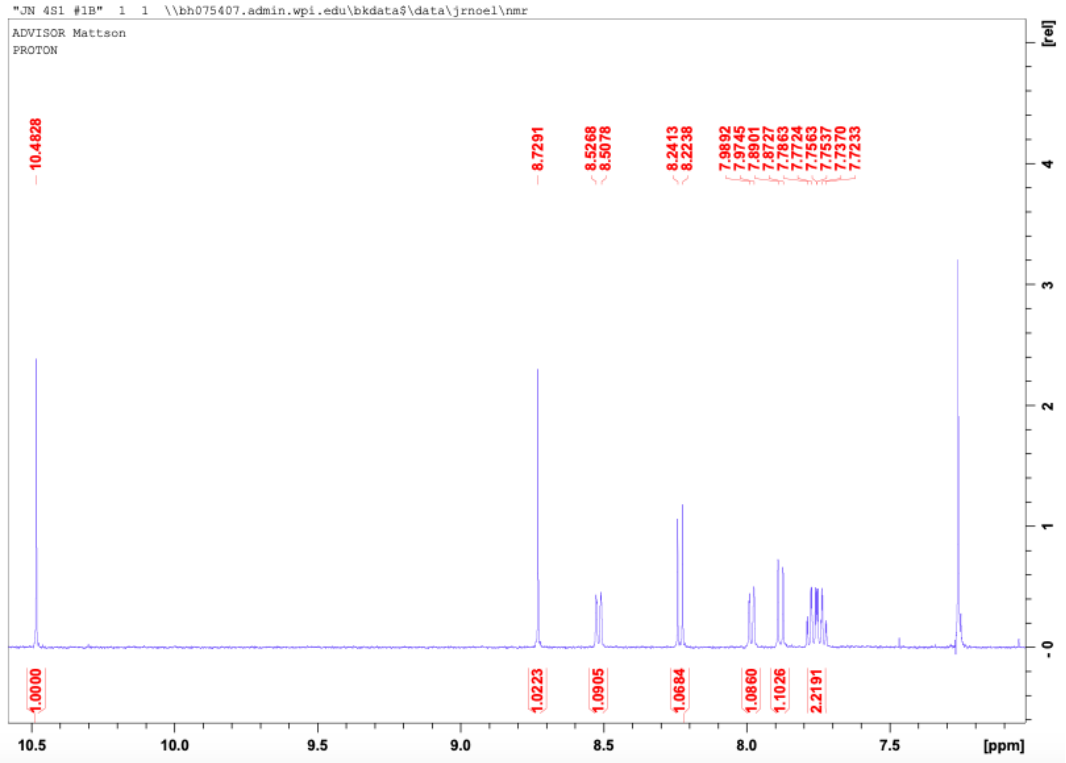
**56i**


JN18 3 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3887
8.5093
8.1878
8.1718
7.3256
7.3065
2.5194
1.0000
1.0160
1.1214
2.3088
3.5353
[rel]
[ppm]

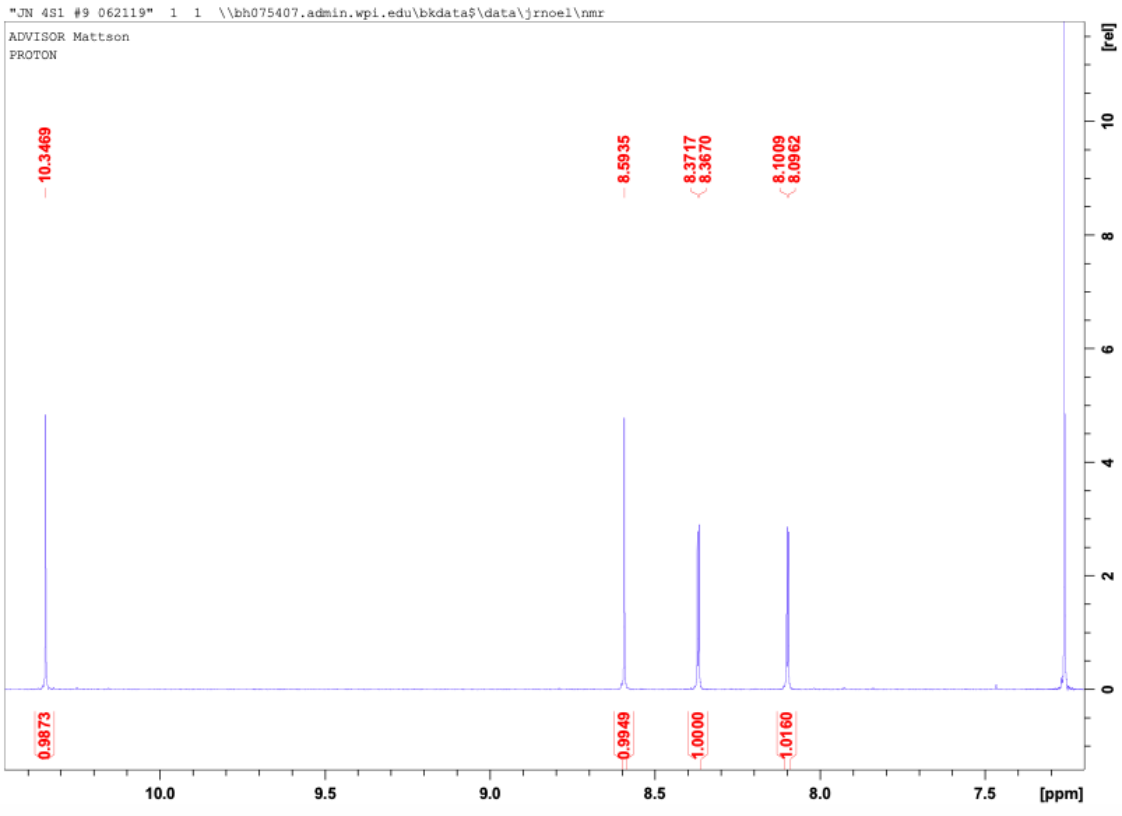
**56j**


JN30 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.4968
9.9911
9.9737
8.5413
8.1619
8.1438
7.9473
7.9311
7.8179
7.8036
7.7867
7.6912
7.6773
7.6612
7.5541
7.5361
1.0000
1.0770
1.0195
1.1428
1.1305
1.1553
1.1296
1.1000
[rel]
[ppm]

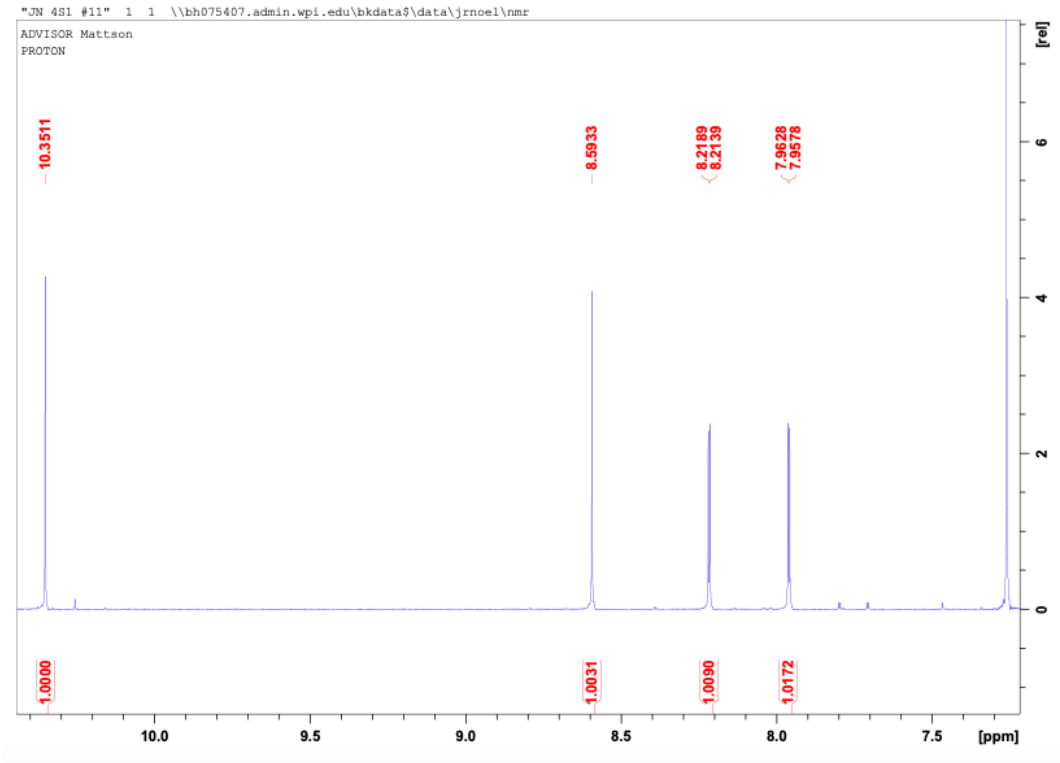
## 56k


"JN 4S1 #1B" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.4828
8.7291
8.5268
8.5078
8.2413
8.2238
7.9892
7.9745
7.8901
7.8727
7.7863
7.7724
7.7563
7.7537
7.7370
7.7233
1.0000
1.0223
1.0905
1.0684
1.0860
1.1026
2.2191
10.5
10.0
9.5
9.0
8.5
8.0
7.5
[ppm]
[rel]

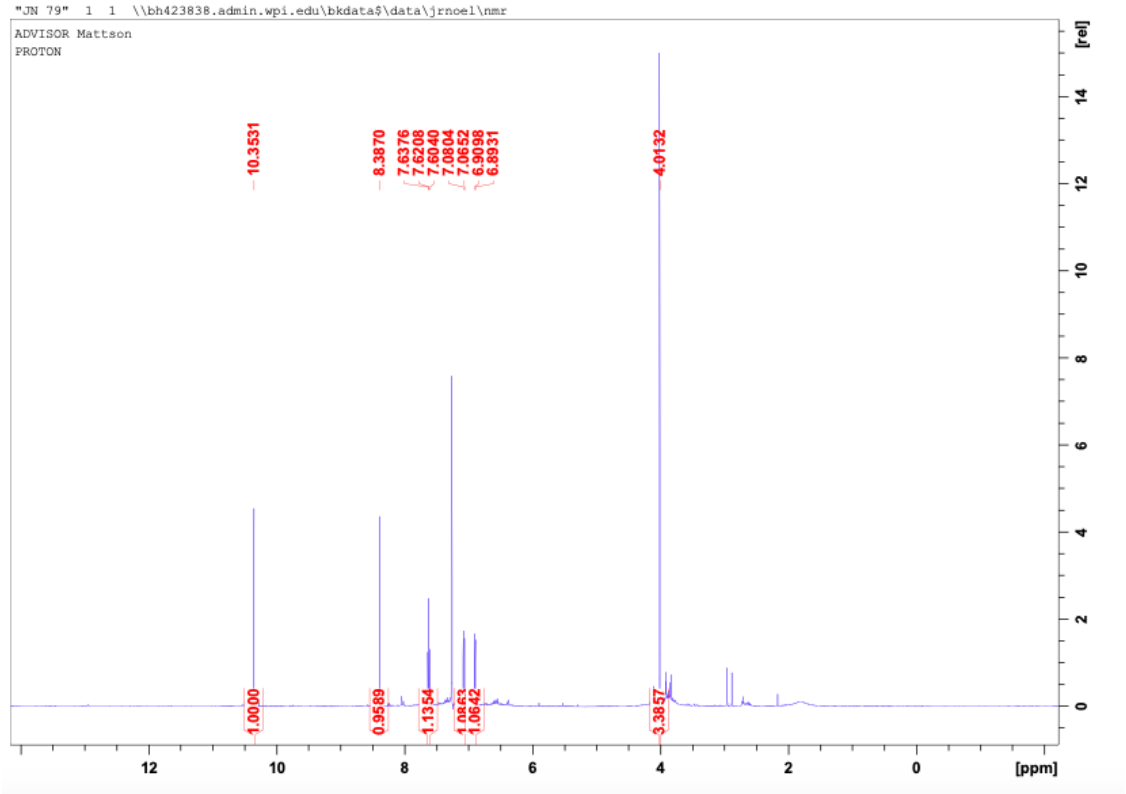
## 56l


"JN 4S1 #9 062119" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3469
8.5935
8.3717
8.3670
8.1009
8.0962
0.9873
0.9949
1.0000
1.0160
10.0
9.5
9.0
8.5
8.0
7.5
[ppm]
[rel]

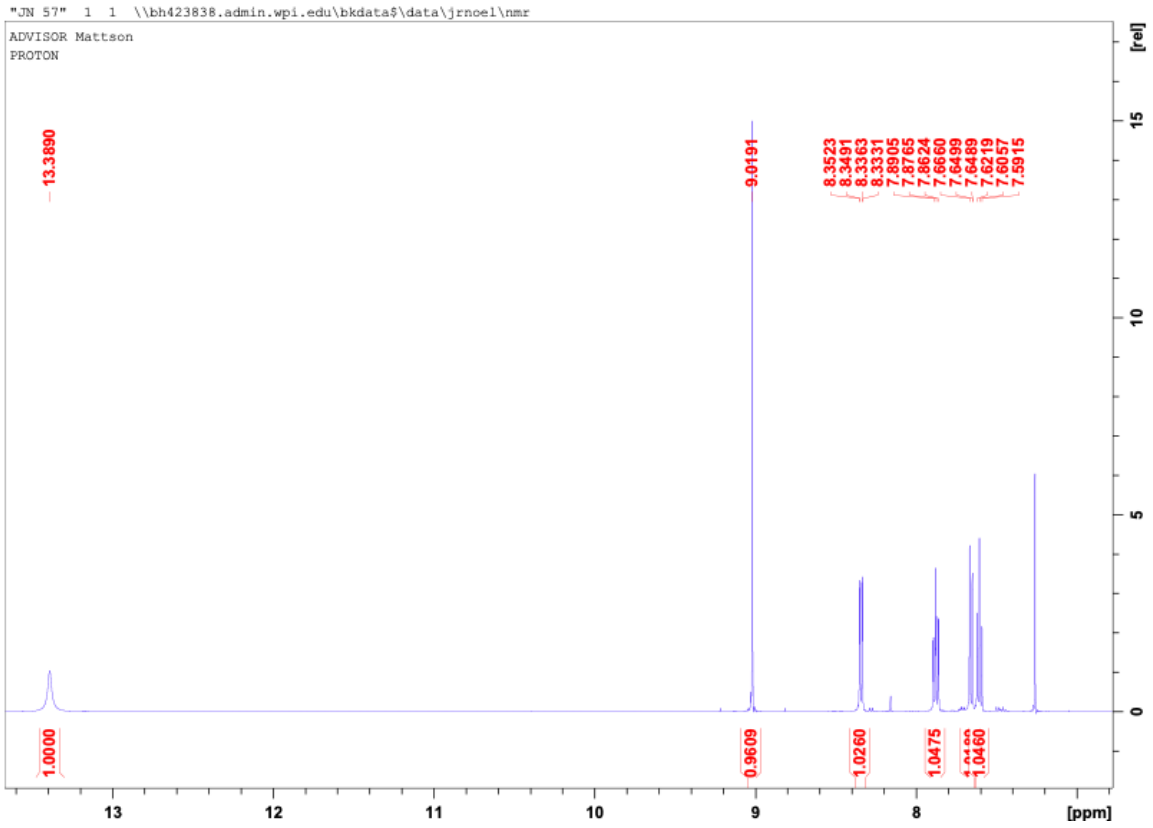
## 56m


"JN 4S1 #11" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3511
8.5933
8.2189
8.2139
7.9628
7.9578
1.0000
1.0031
1.0090
1.0172
[rel]
[ppm]

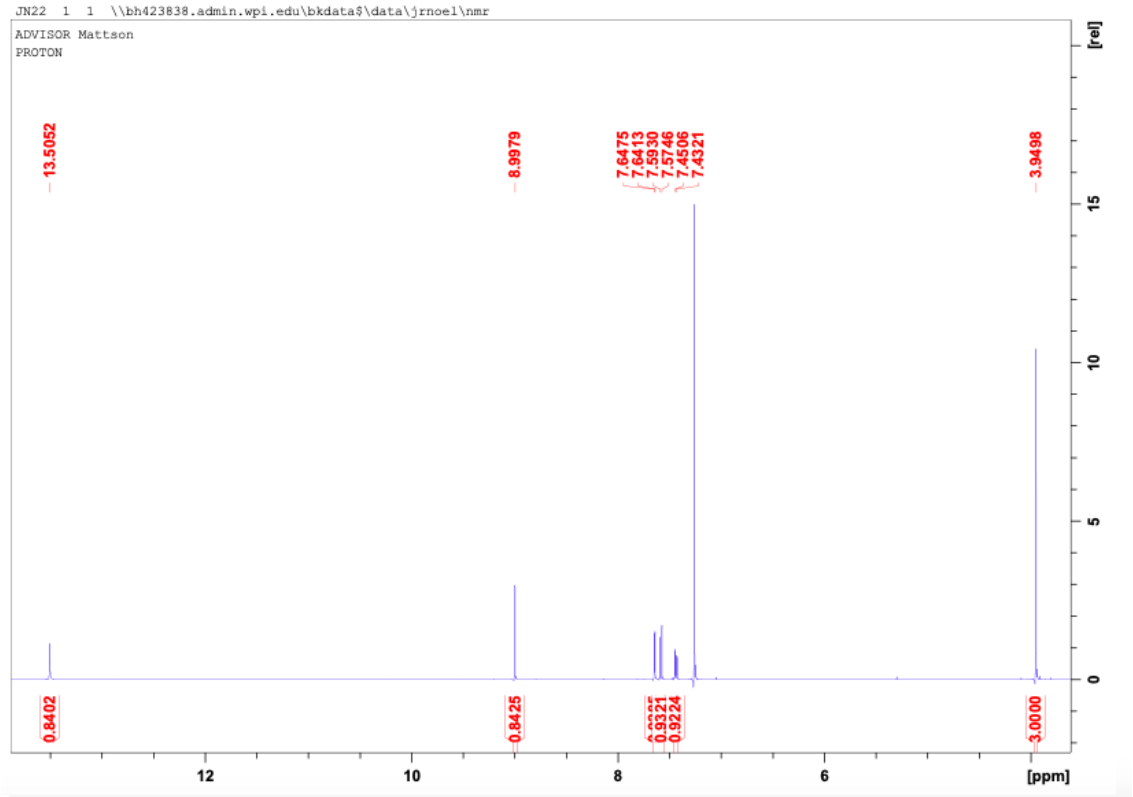
## 56n


"JN 79" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.3531
8.3870
7.6376
7.6208
7.6040
7.0804
7.0652
6.9098
6.8931
4.0132
1.0000
0.9589
1.1354
3.3857
[rel]
[ppm]

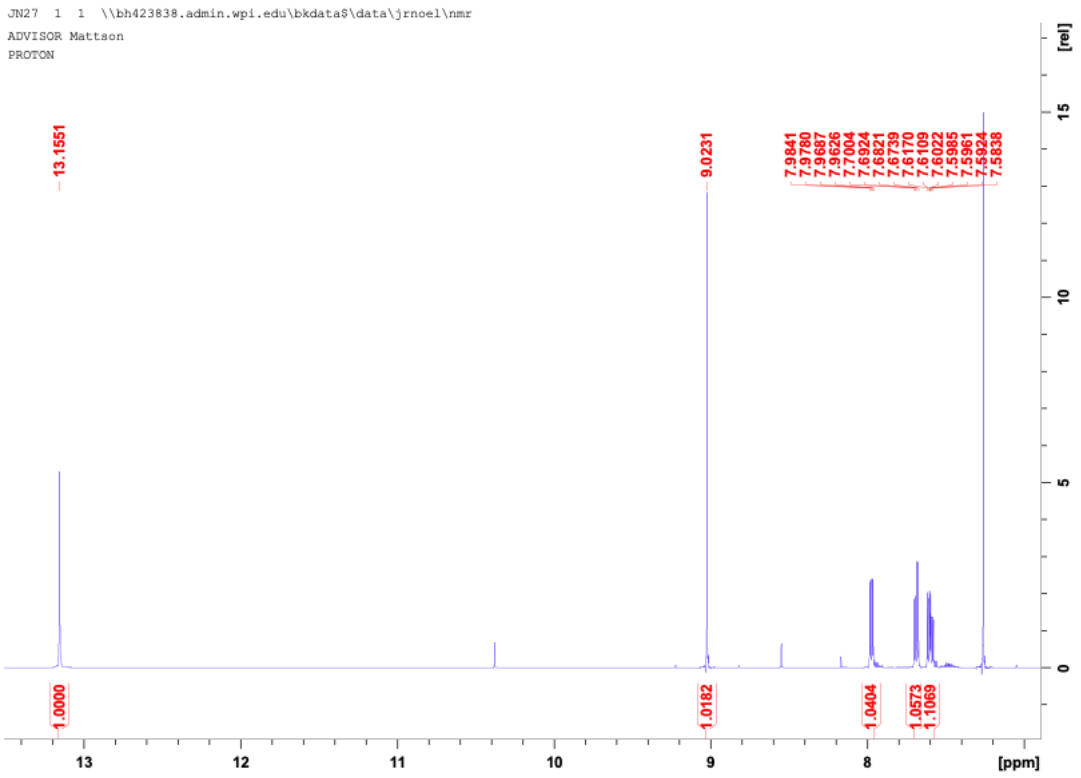
**57a**


"JN 57" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.3890
9.0191
8.3523
8.3491
8.3363
8.3331
7.8905
7.8765
7.8624
7.6660
7.6499
7.6489
7.6219
7.6057
7.5915
1.0000
0.9609
1.0260
1.0475
1.0460
[rel]
[ppm]

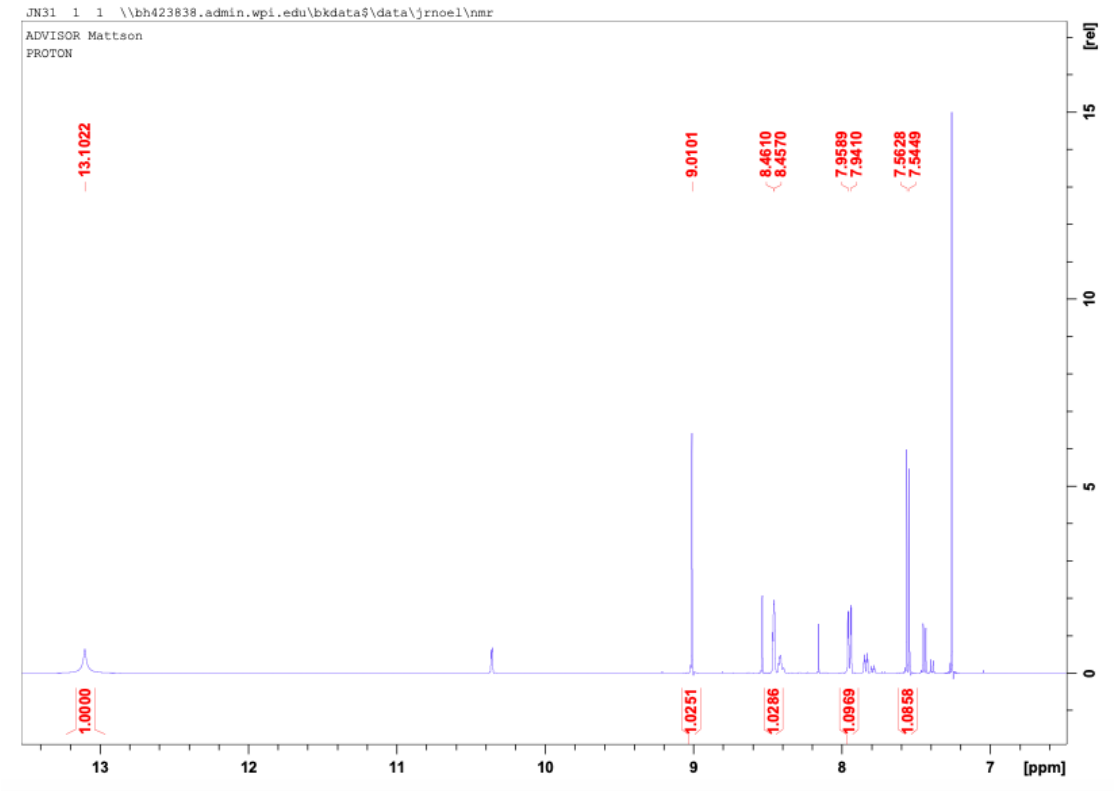
**56b**


JN22 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.5052
8.9979
7.6475
7.6413
7.5930
7.5746
7.4506
7.4321
3.9498
0.8402
0.8425
0.9321
0.9224
3.0000
[rel]
[ppm]

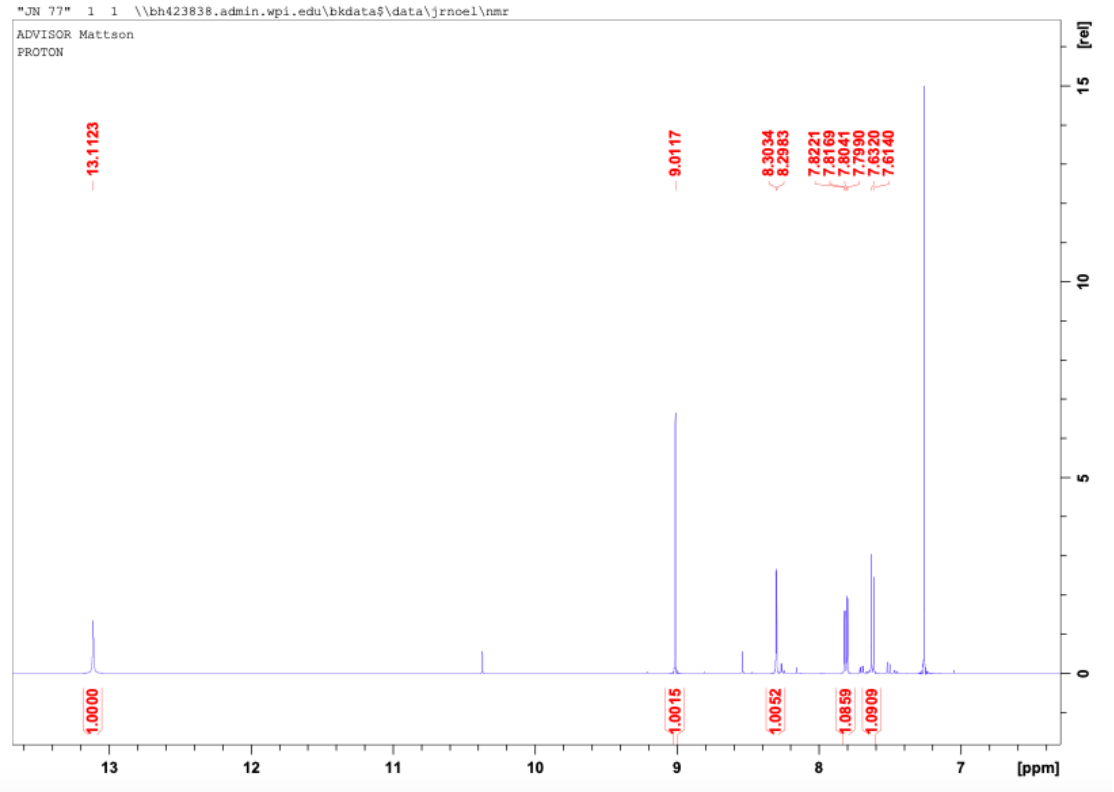
**56c**


JN27 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.1551
9.0231
7.9841
7.9780
7.9687
7.9626
7.7004
7.6924
7.6821
7.6739
7.6170
7.6109
7.6022
7.5985
7.5961
7.5924
7.5838
1.0000
1.0182
1.0404
1.0573
1.1069
[rel]
[ppm]

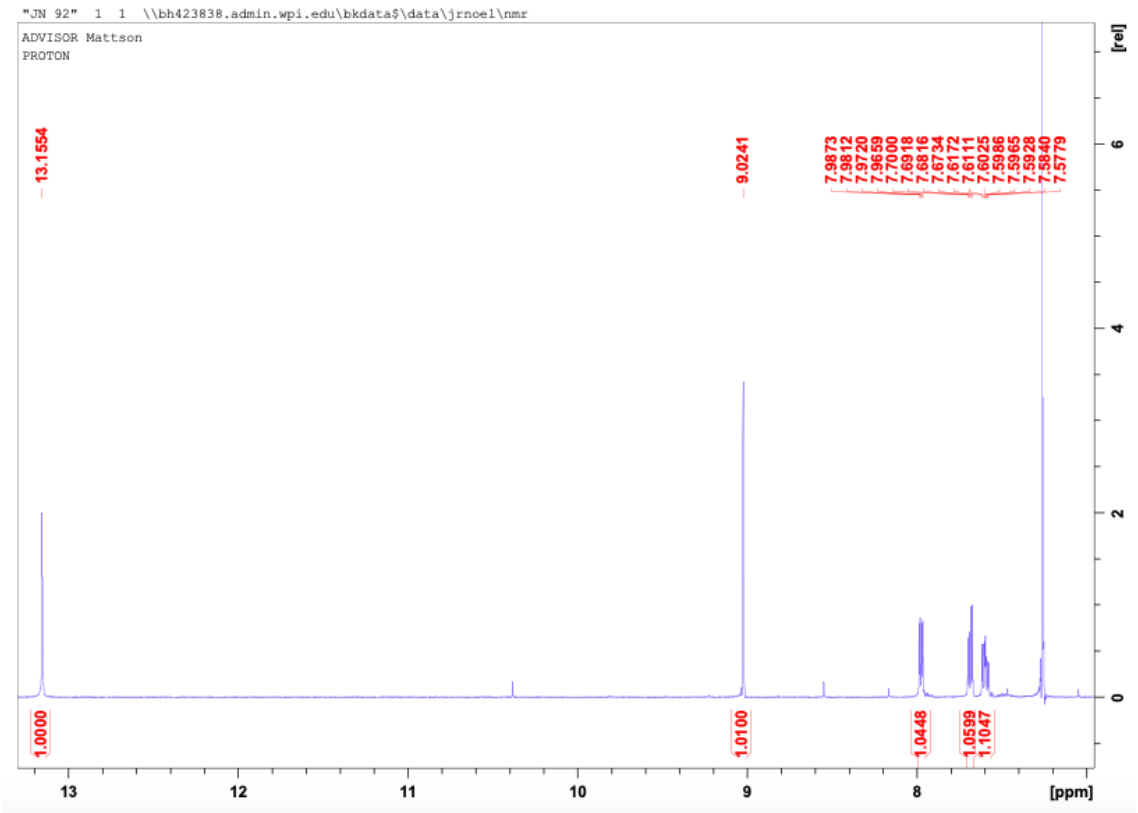
**56d**


JN31 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.1022
9.0101
8.4610
8.4570
7.9589
7.9410
7.5628
7.5449
1.0000
1.0251
1.0286
1.0969
1.0858
[rel]
[ppm]

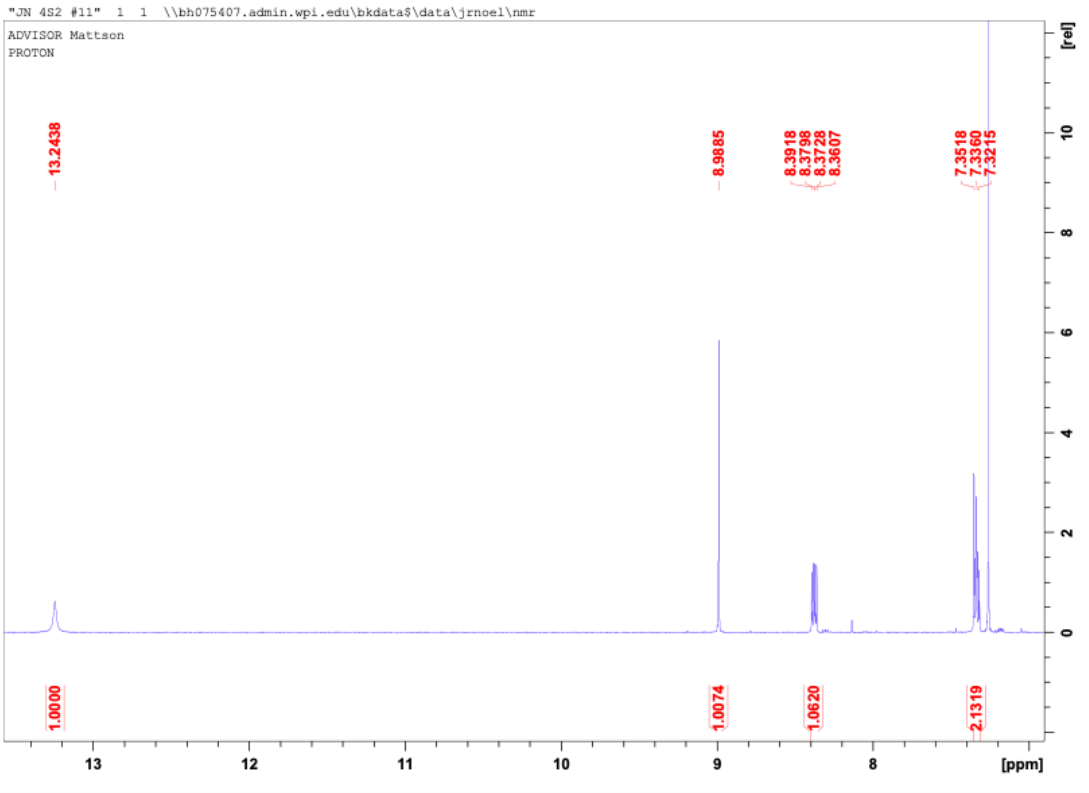
**56e**


"JN 77" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.1123
9.0117
8.3034
8.2983
7.8221
7.8169
7.8041
7.7990
7.6320
7.6140
1.0000
1.0015
1.0052
1.0859
1.0909
[rel]
[ppm]

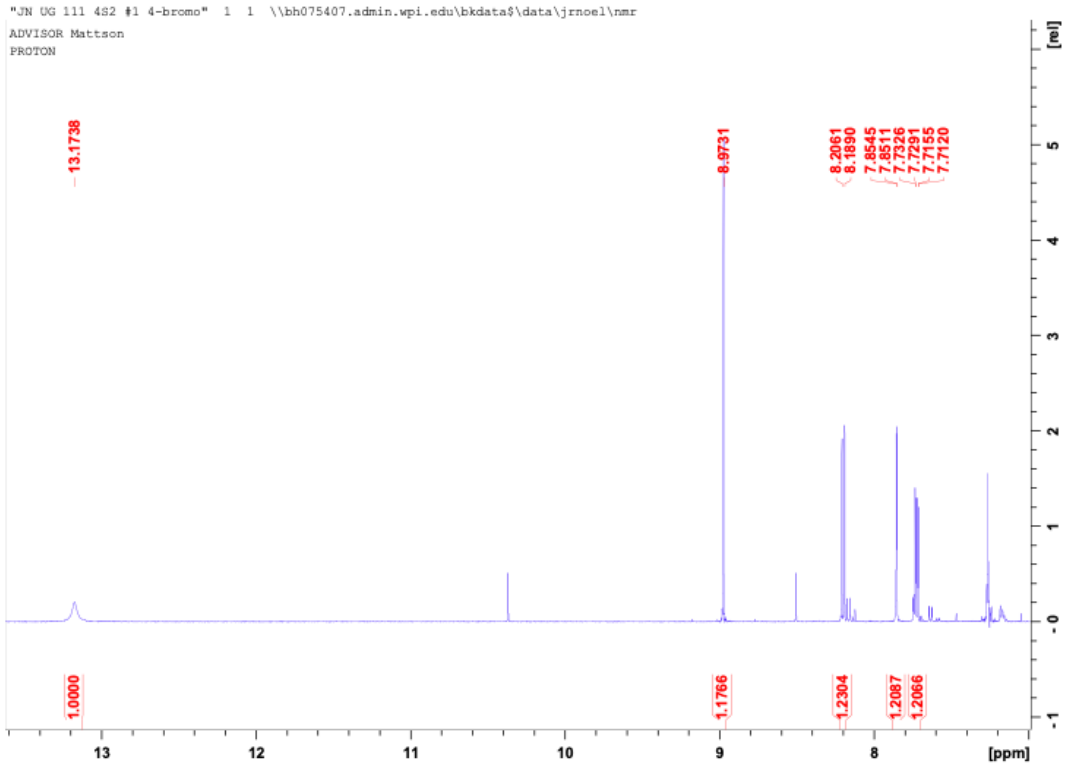
**56f**


"JN 92" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.1554
9.0241
7.9873
7.9812
7.9720
7.9659
7.7000
7.6918
7.6816
7.6734
7.6172
7.6111
7.6025
7.5986
7.5965
7.5928
7.5840
7.5779
1.0000
1.0100
1.0448
1.0599
1.1047
[rel]
[ppm]

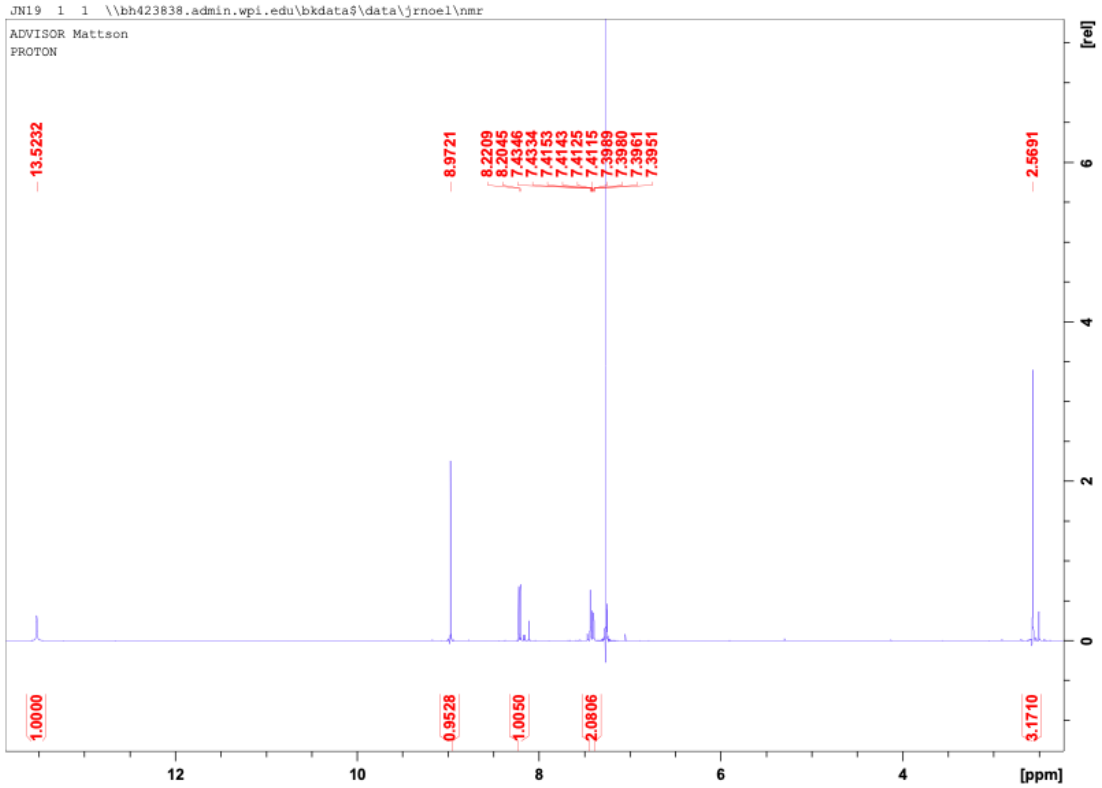
## 56g


"JN 4S2 #11" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.2438
8.9885
8.3918
8.3798
8.3728
8.3607
7.3518
7.3360
7.3215
[rel]
1.0000
1.0074
1.0620
2.1319
[ppm]

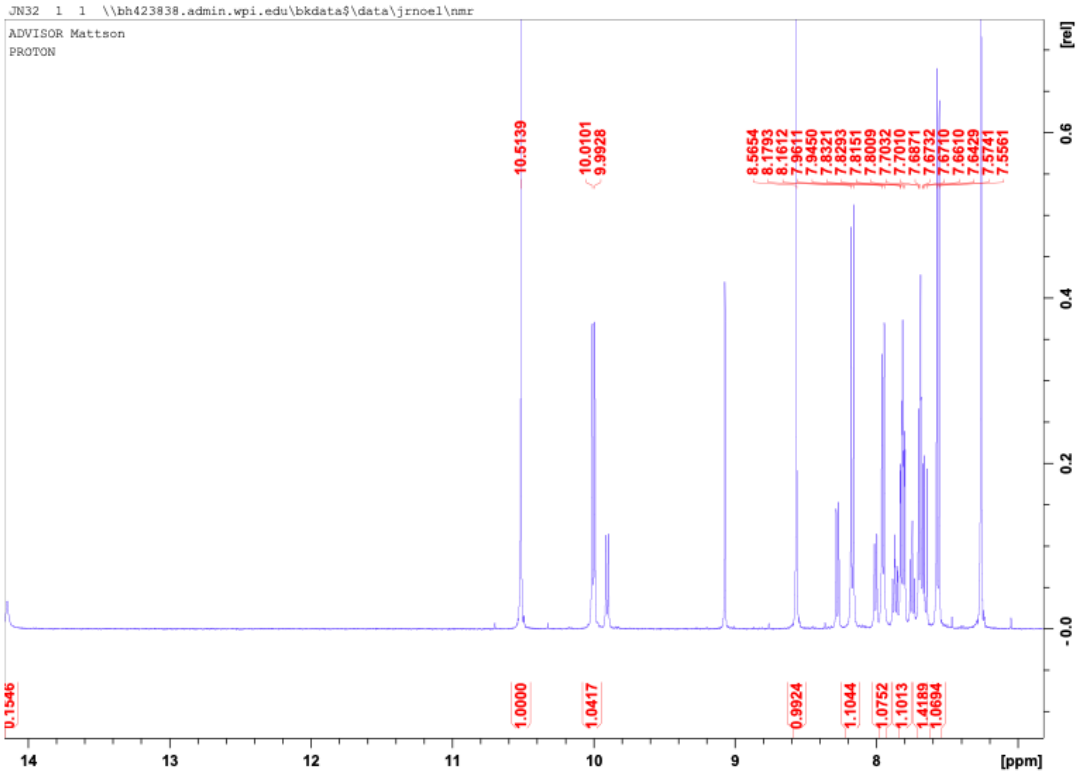
## 56h


"JN UG 111 4S2 #1 4-bromo" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.1738
8.9731
8.2061
8.1890
7.8545
7.8511
7.7326
7.7291
7.7155
7.7120
[rel]
1.0000
1.1766
1.2304
1.2087
1.2066
[ppm]

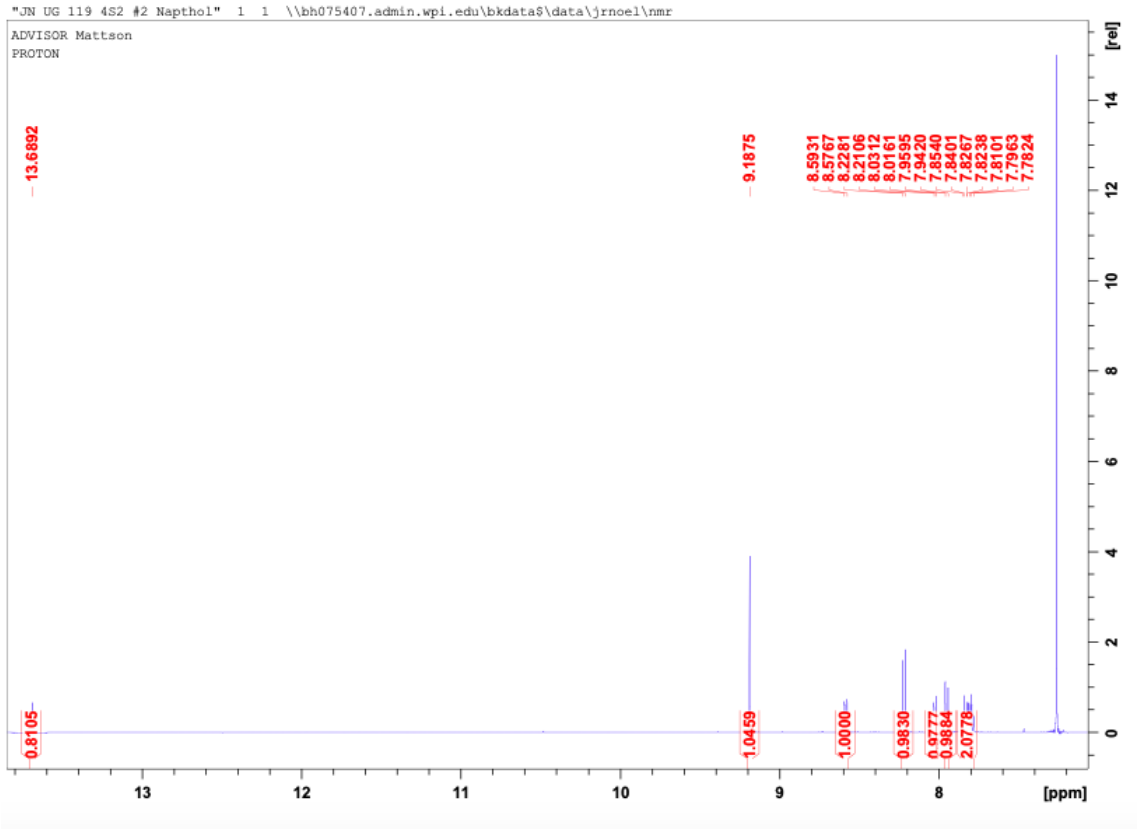
**56i**


JN19 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.5232
8.9721
8.2209
8.2045
7.4346
7.4334
7.4153
7.4143
7.4125
7.4115
7.3989
7.3980
7.3961
7.3951
2.5691
1.0000
0.9528
1.0050
2.0806
3.1710
12
10
8
6
4
[ppm]
[rel]

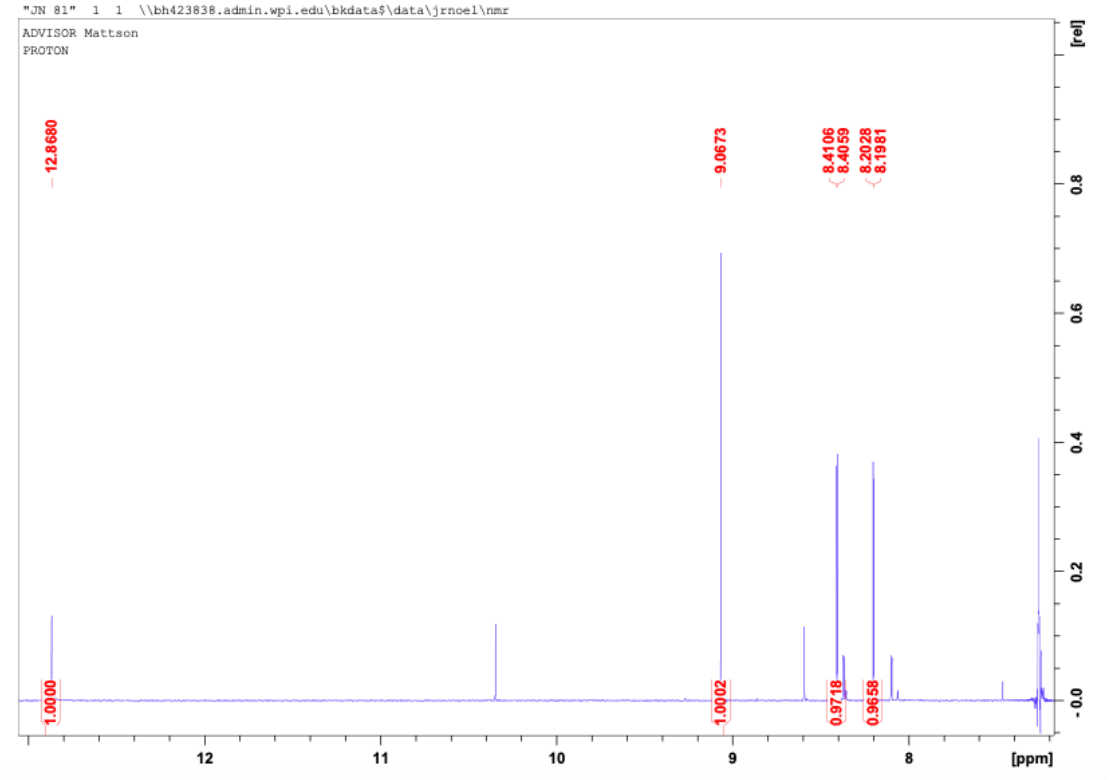
**57j**


JN32 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
10.5139
10.0101
9.9928
8.5654
8.1793
8.1612
7.9611
7.9450
7.8321
7.8293
7.8151
7.8009
7.7032
7.7010
7.6871
7.6732
7.6710
7.6610
7.6429
7.5741
7.5561
0.1546
1.0000
1.0417
0.9924
1.1044
1.0752
1.1013
1.4189
1.0694
14
13
12
11
10
9
8
[ppm]
[rel]

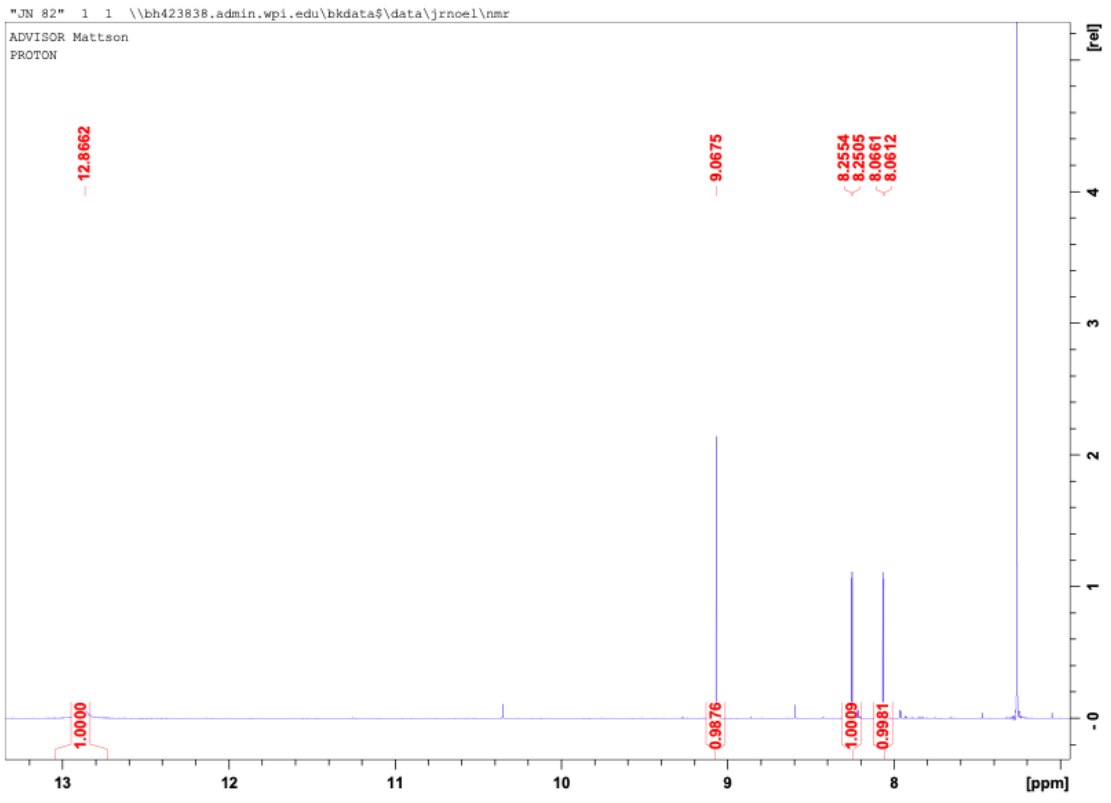
**57k**


"JN UG 119 4S2 #2 Napthol" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.6892
9.1875
8.5931
8.5767
8.2281
8.2106
8.0312
8.0161
7.9595
7.9420
7.8540
7.8401
7.8267
7.8238
7.8101
7.7963
7.7824
0.8105
1.0459
1.0000
0.9830
0.9777
0.9684
2.0778
[rel]
[ppm]

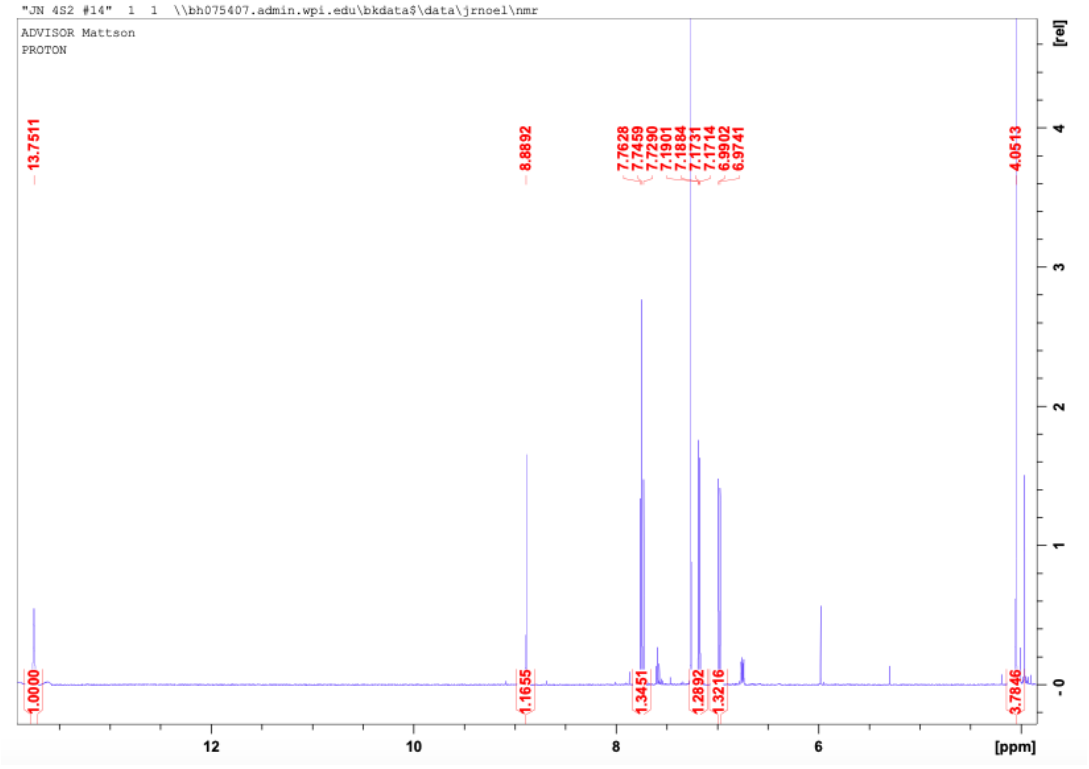
**56l**


"JN 81" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
12.8680
9.0673
8.4106
8.4059
8.2028
8.1981
1.0000
1.0002
0.9718
0.9658
[rel]
[ppm]

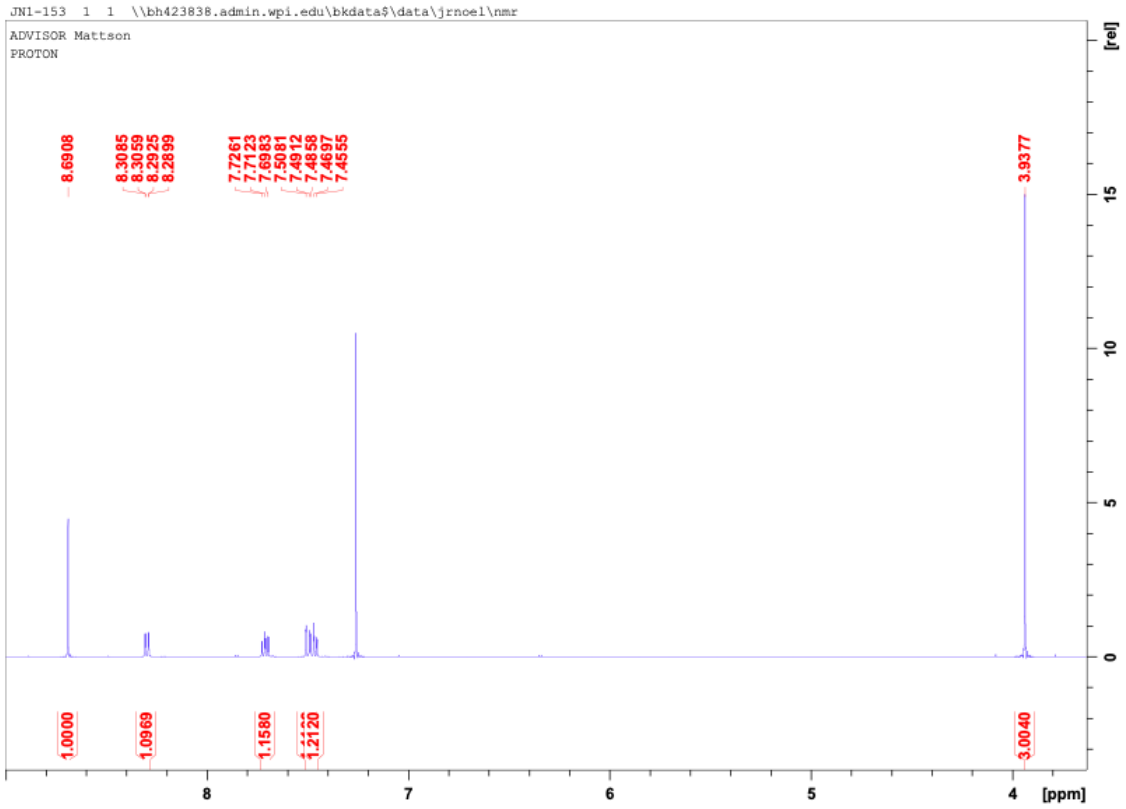
## 57m


"JN 82" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
12.8662
9.0675
8.2554
8.2505
8.0661
8.0612
1.0000
0.9876
1.0009
0.9981
[rel]
[ppm]

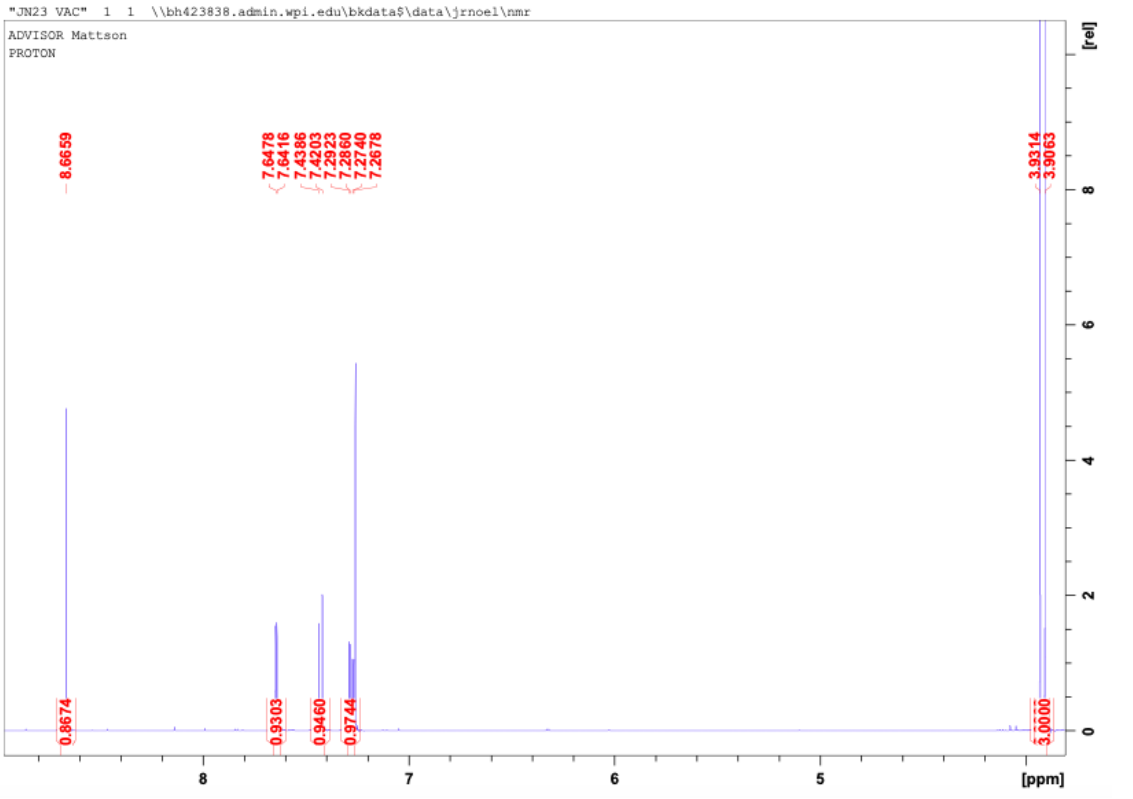
## 57n


"JN 4S2 #14" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
13.7511
8.8892
7.7628
7.7459
7.7290
7.1901
7.1884
7.1731
7.1714
6.9902
6.9741
4.0513
1.0000
1.1655
1.3451
1.2892
1.3216
3.7846
[rel]
[ppm]

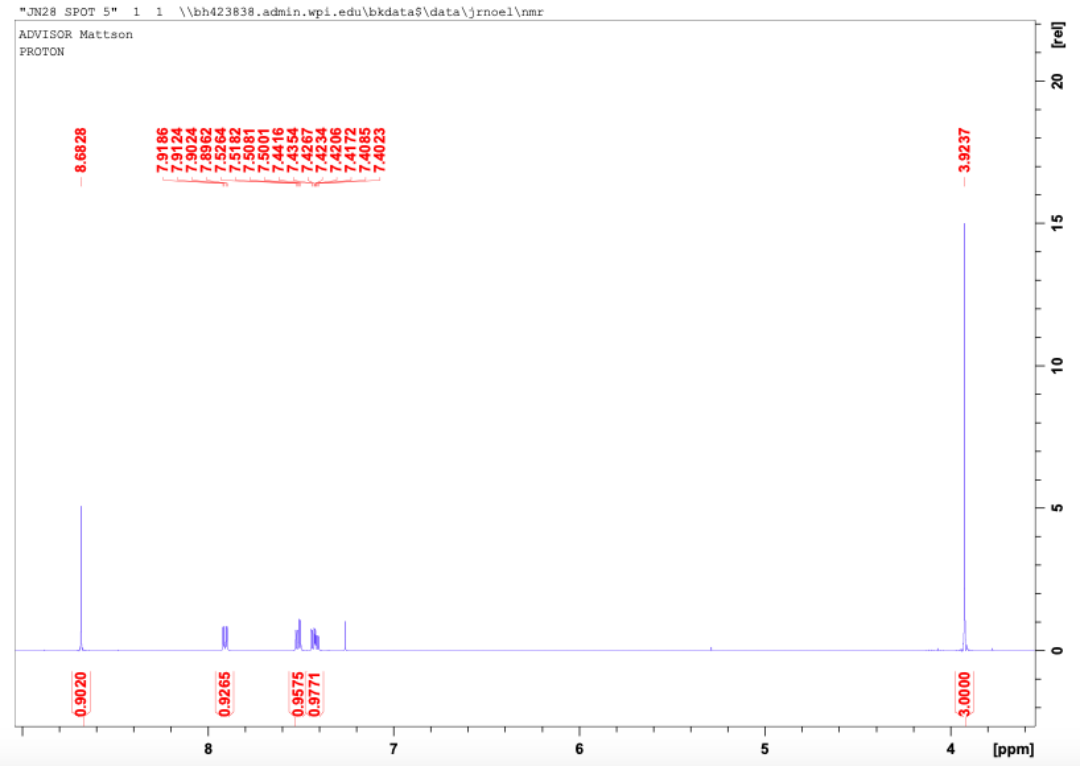
**26a**


JN1-153 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6908
8.3085
8.3059
8.2925
8.2899
7.7261
7.7123
7.6983
7.5081
7.4912
7.4858
7.4697
7.4555
3.9377
1.0000
1.0969
1.1580
1.2120
3.0040
[rel]
[ppm]

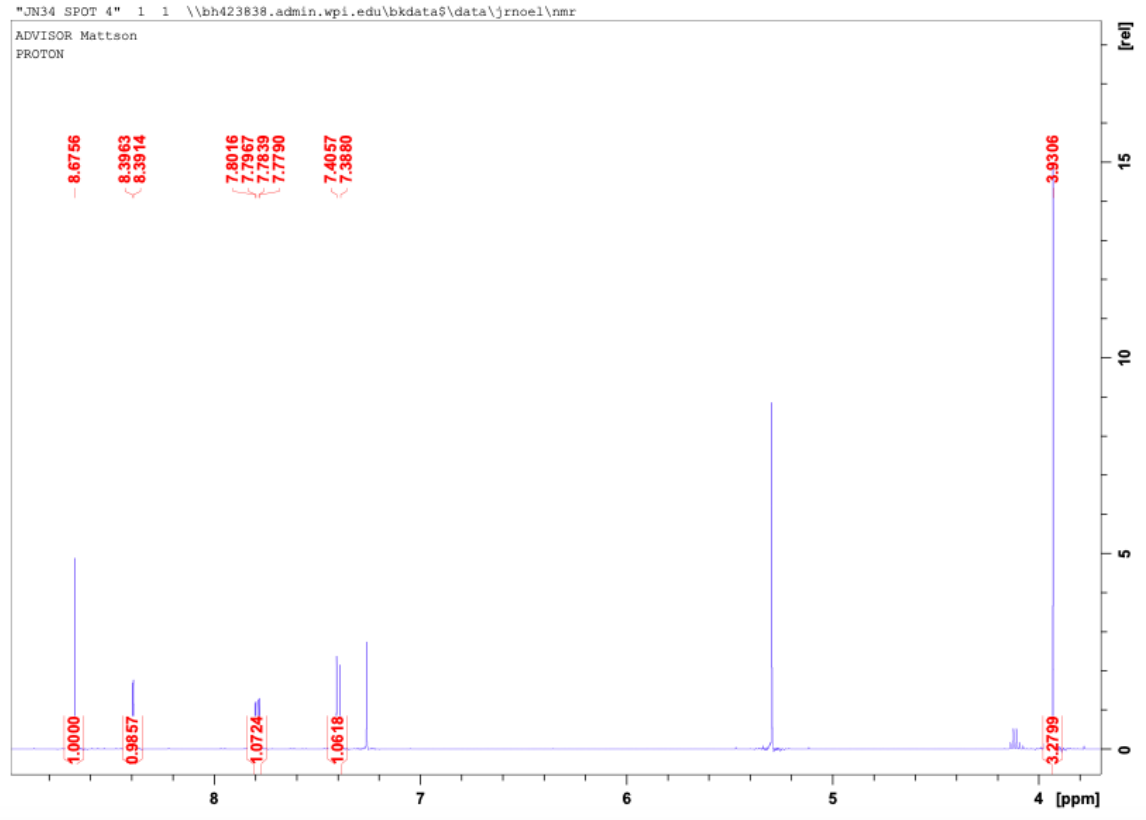
**26b**


"JN23 VAC" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6659
7.6478
7.6416
7.4386
7.4203
7.2923
7.2860
7.2740
7.2678
3.9314
3.9063
0.8674
0.9303
0.9460
0.9744
3.0000
[rel]
[ppm]

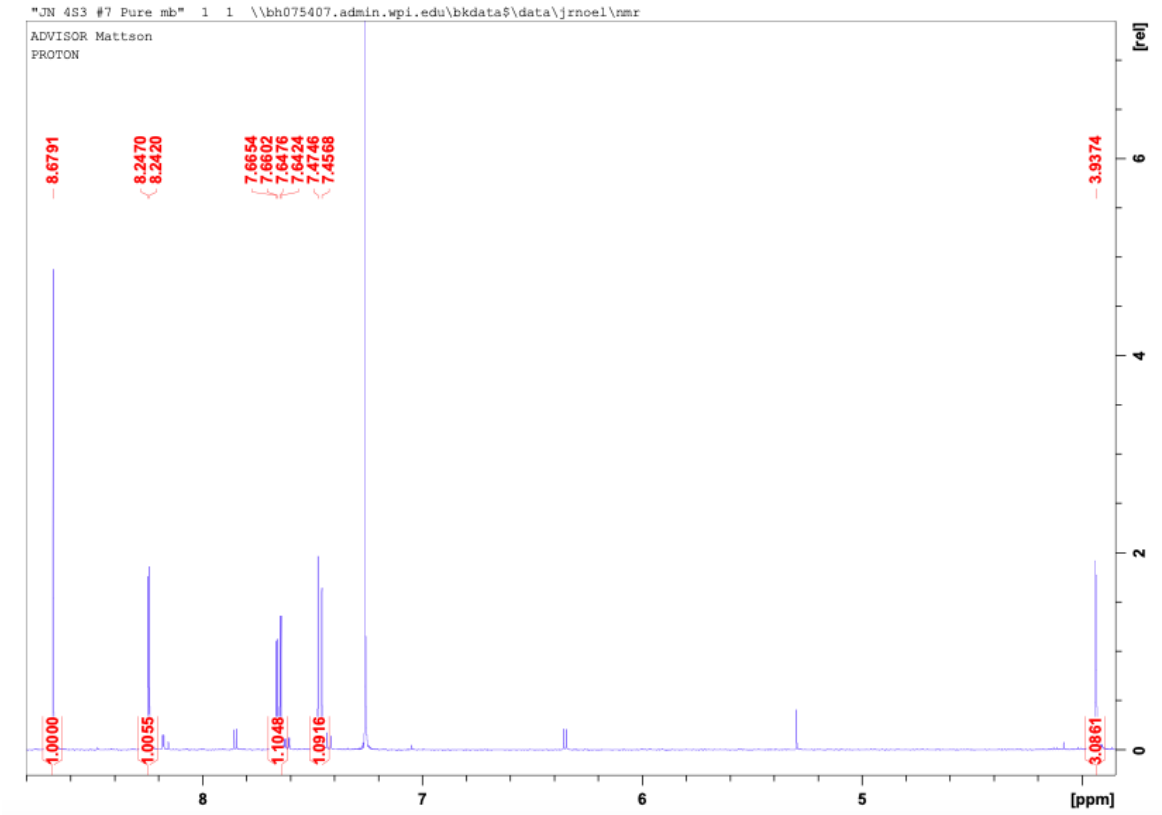
**26c**


"JN28 SPOT 5" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6828
7.9186
7.9124
7.9024
7.8962
7.5264
7.5182
7.5081
7.5001
7.4416
7.4354
7.4267
7.4234
7.4206
7.4172
7.4085
7.4023
3.9237
0.9020
0.9265
0.9575
0.9771
3.0000
[rel]
[ppm]

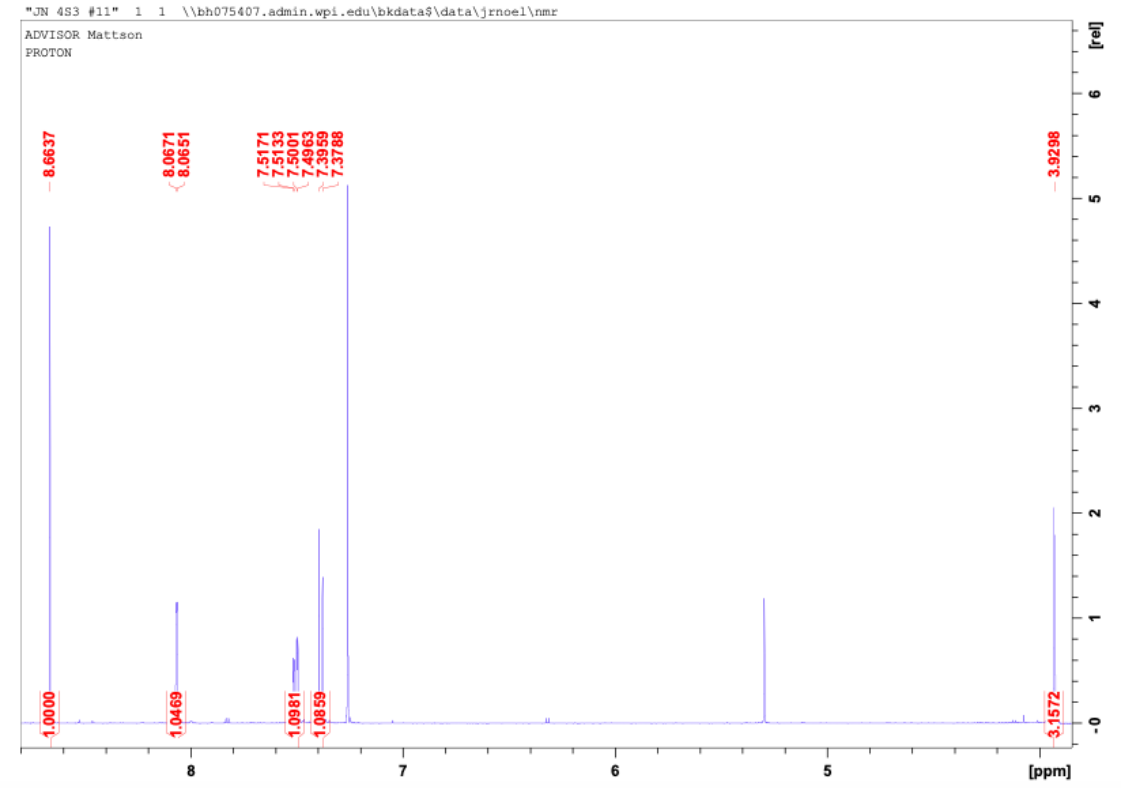
**26d**


"JN34 SPOT 4" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6756
8.3963
8.3914
7.8016
7.7967
7.7839
7.7790
7.4057
7.3880
3.9306
1.0000
0.9857
1.0724
1.0618
3.2799
[rel]
[ppm]

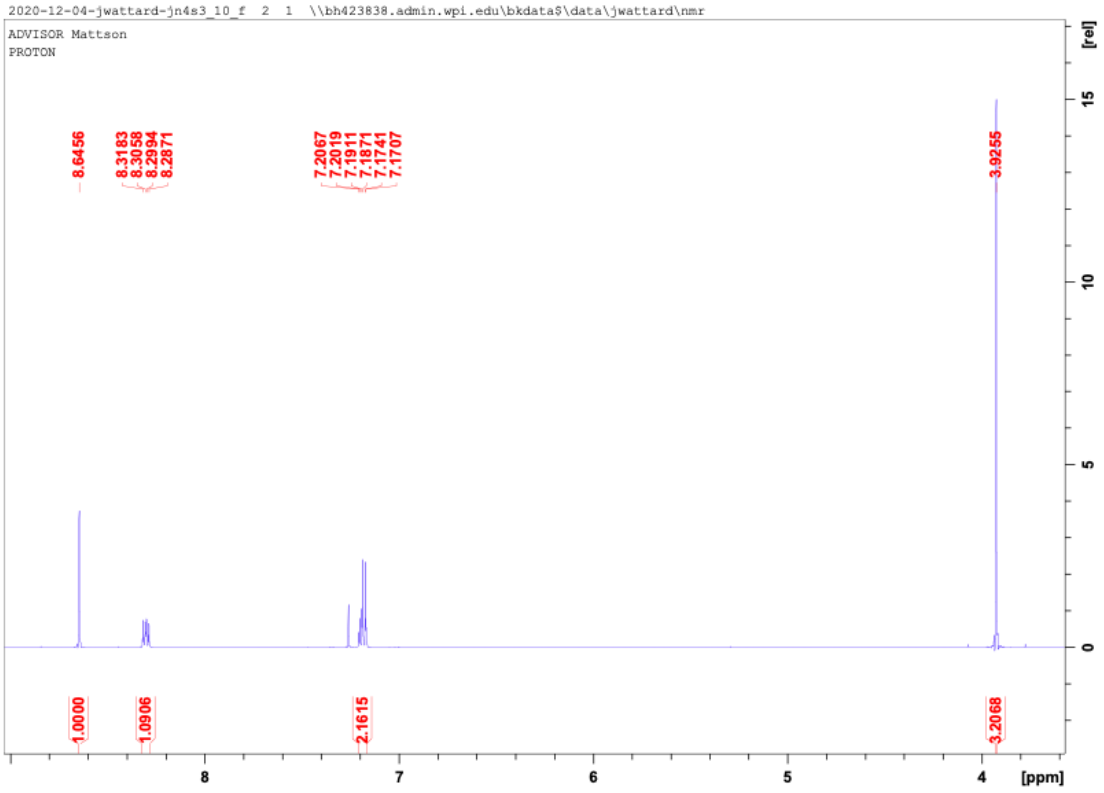
**26e**


"JN 4S3 #7 Pure mb" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6791
8.2470
8.2420
7.6654
7.6602
7.6476
7.6424
7.4746
7.4568
3.9374
1.0000
1.0055
1.1048
1.0916
3.0861
[rel]
[ppm]

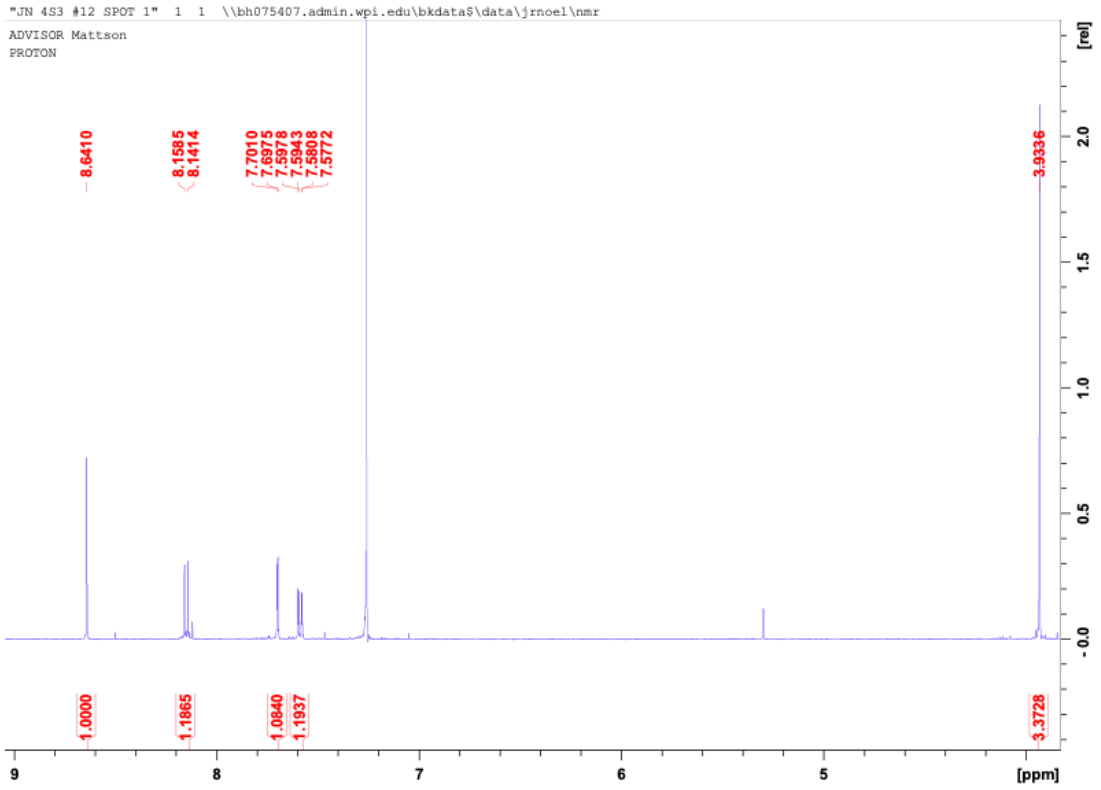
**26f**


"JN 4S3 #11" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6637
8.0671
8.0651
7.5171
7.5133
7.5001
7.4963
7.3959
7.3788
3.9298
1.0000
1.0469
1.0981
1.0859
3.1572
[rel]
[ppm]

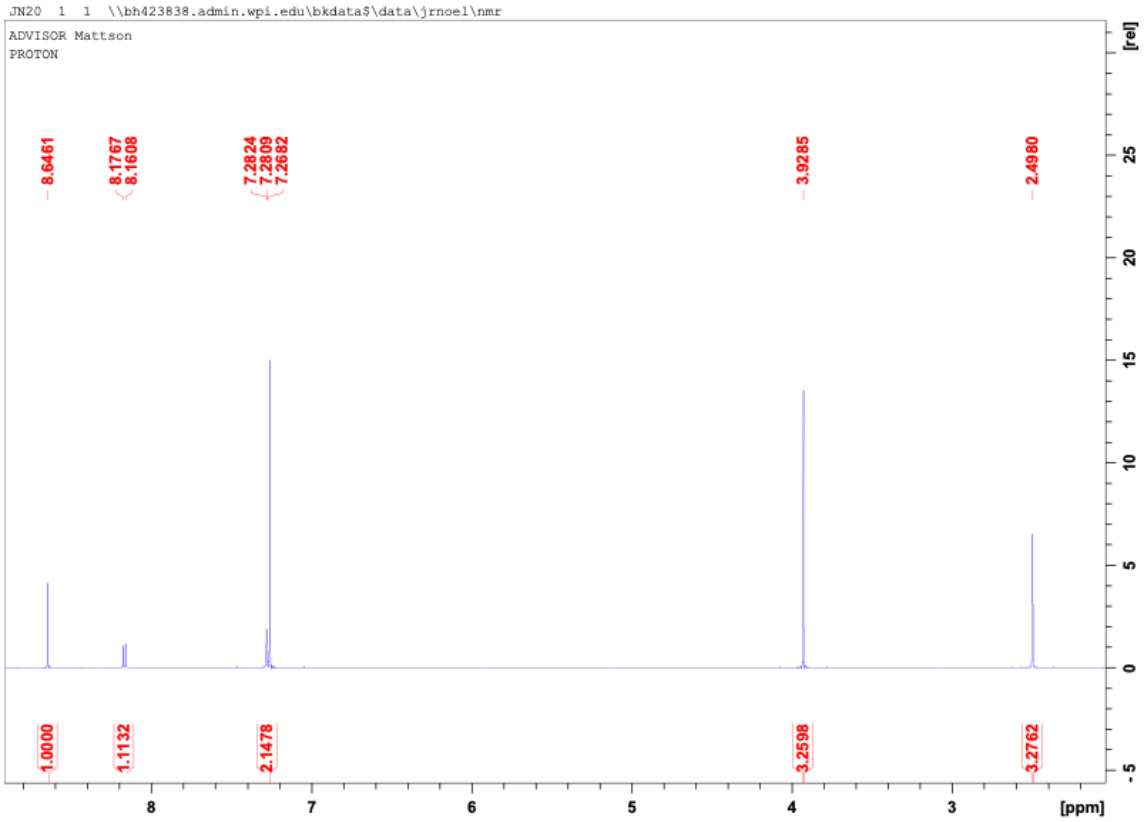
**26g**


2020-12-04-jwattard-jn4s3_10_f 2 1 \\bh423838.admin.wpi.edu\bkdata$\data\jwattard\nmr
ADVISOR Mattson
PROTON
8.6456
8.3183
8.3058
8.2994
8.2871
7.2067
7.2019
7.1911
7.1871
7.1741
7.1707
3.9255
1.0000
1.0906
2.1615
3.2068
[rel]
[ppm]

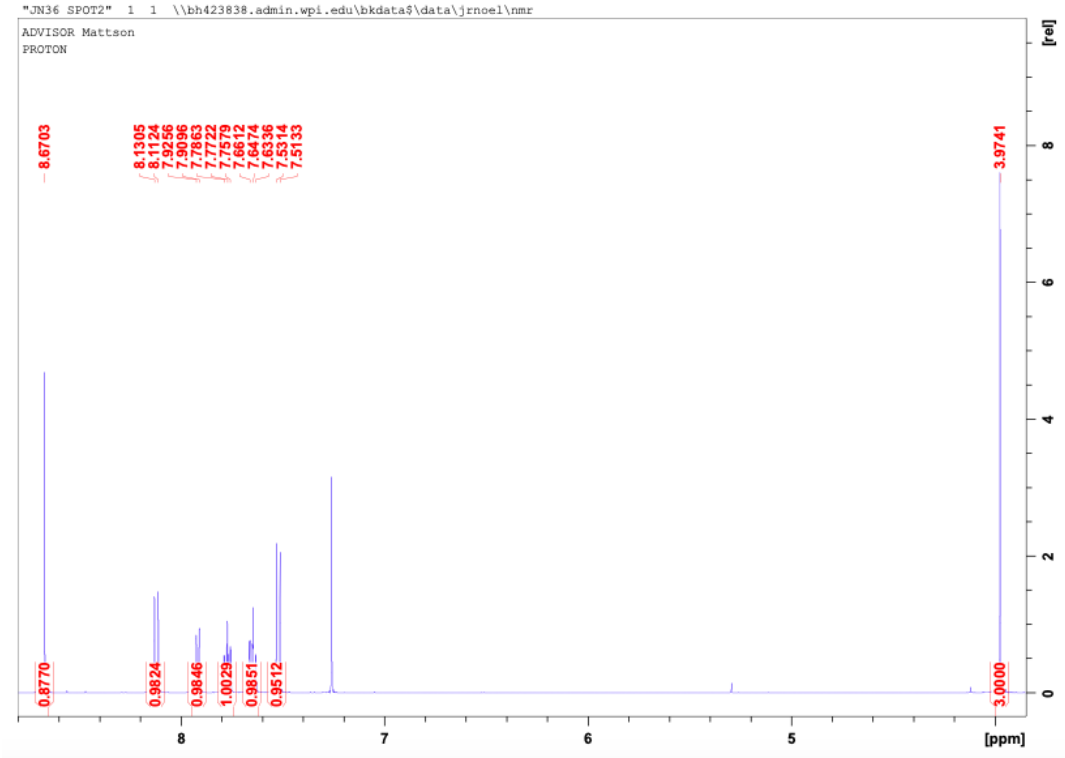
**26h**


"JN 4S3 #12 SPOT 1" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6410
8.1585
8.1414
7.7010
7.6975
7.5978
7.5943
7.5808
7.5772
3.9336
1.0000
1.1865
1.0840
1.1937
3.3728
[rel]
[ppm]

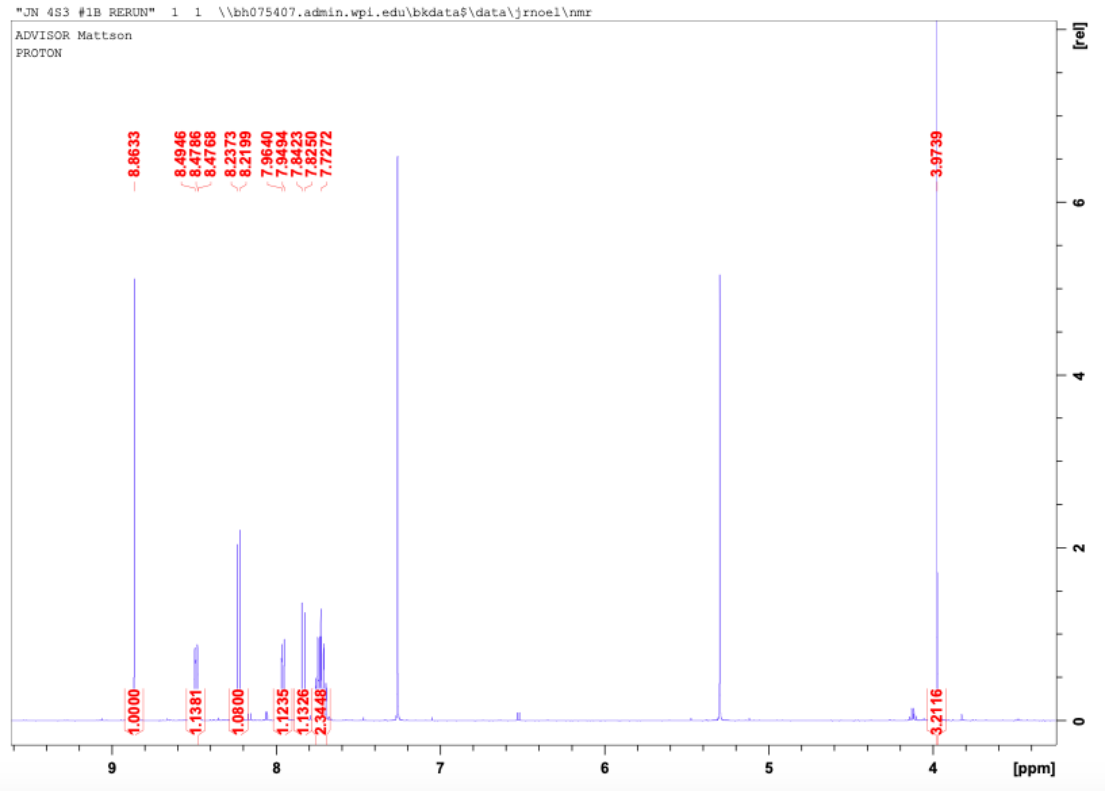
**26i**


JN20 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6461
8.1767
8.1608
7.2824
7.2809
7.2682
3.9285
2.4980
1.0000
1.1132
2.1478
3.2598
3.2762
[rel]
[ppm]

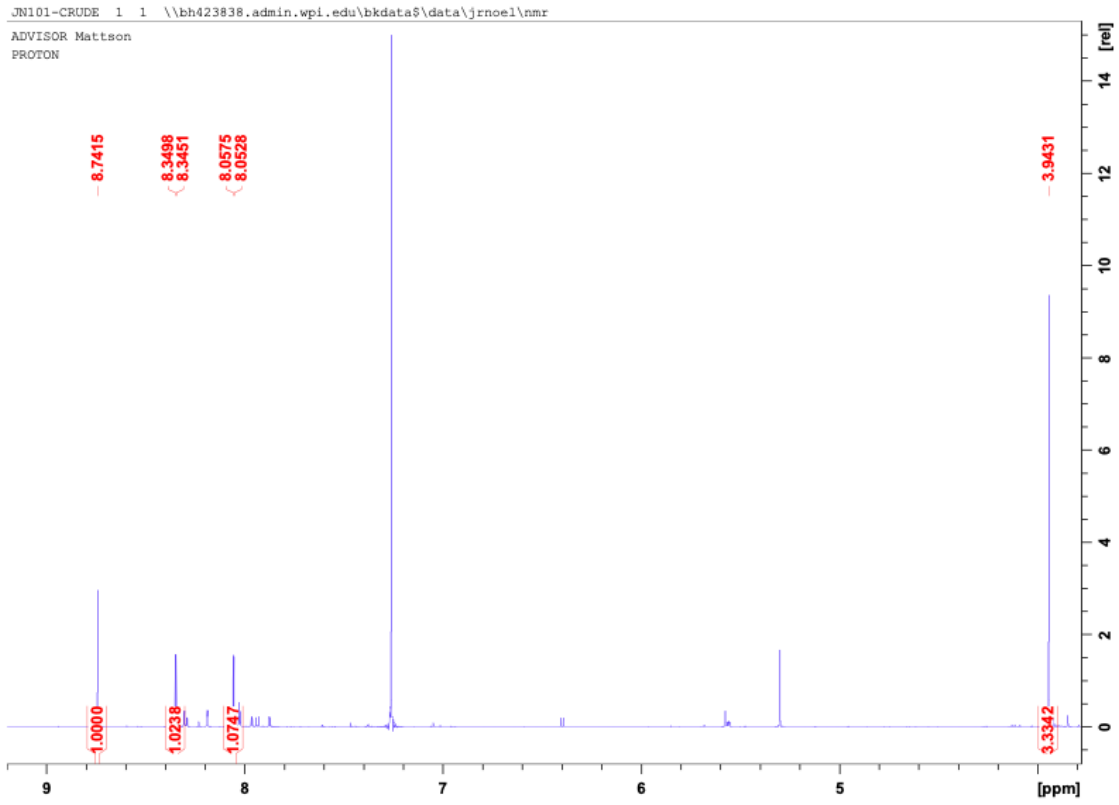
**26j**


"JN36 SPOT2" 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.6703
8.1305
8.1124
7.9256
7.9096
7.7863
7.7722
7.7579
7.6612
7.6474
7.6336
7.5314
7.5133
3.9741
0.8770
0.9824
0.9846
1.0029
0.9851
0.9512
3.0000
[rel]
[ppm]

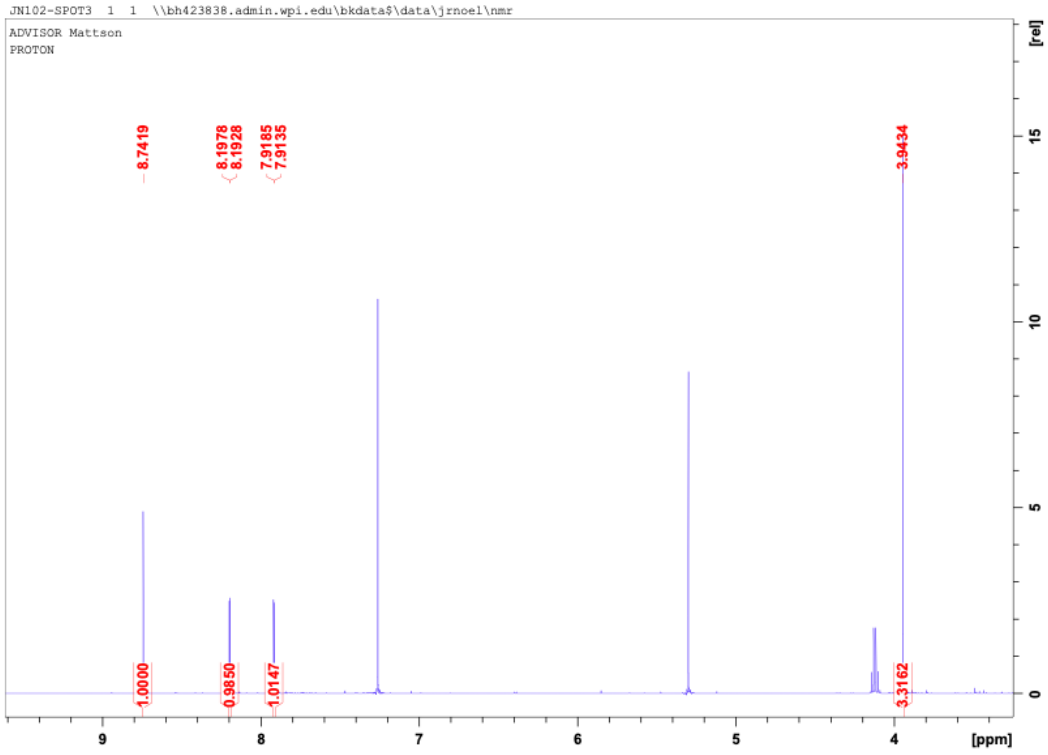
**26k**


"JN 4S3 #1B RERUN" 1 1 \\bh075407.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.8633
8.4946
8.4786
8.4768
8.2373
8.2199
7.9640
7.9494
7.8423
7.8250
7.7272
3.9739
1.0000
1.1381
1.0800
1.1235
1.1326
2.3448
3.2116
[rel]
[ppm]

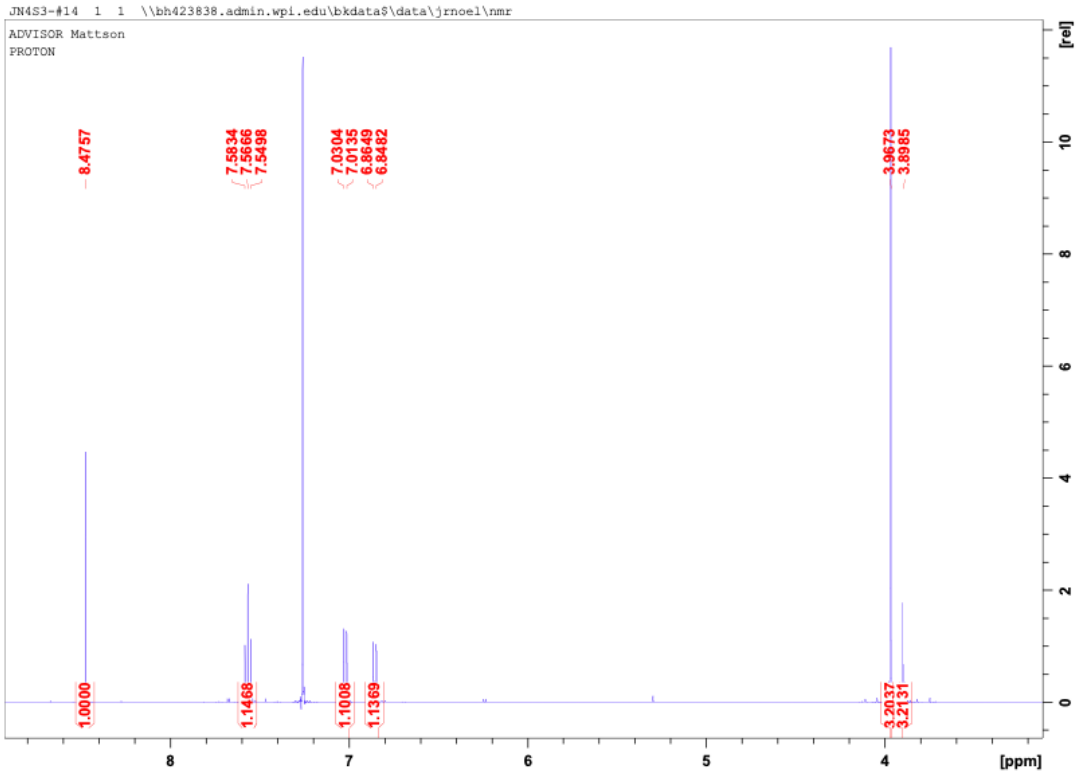
**26l**


JN101-CRUDE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.7415
8.3498
8.3451
8.0575
8.0528
3.9431
1.0000
1.0238
1.0747
3.3342
[rel]
[ppm]

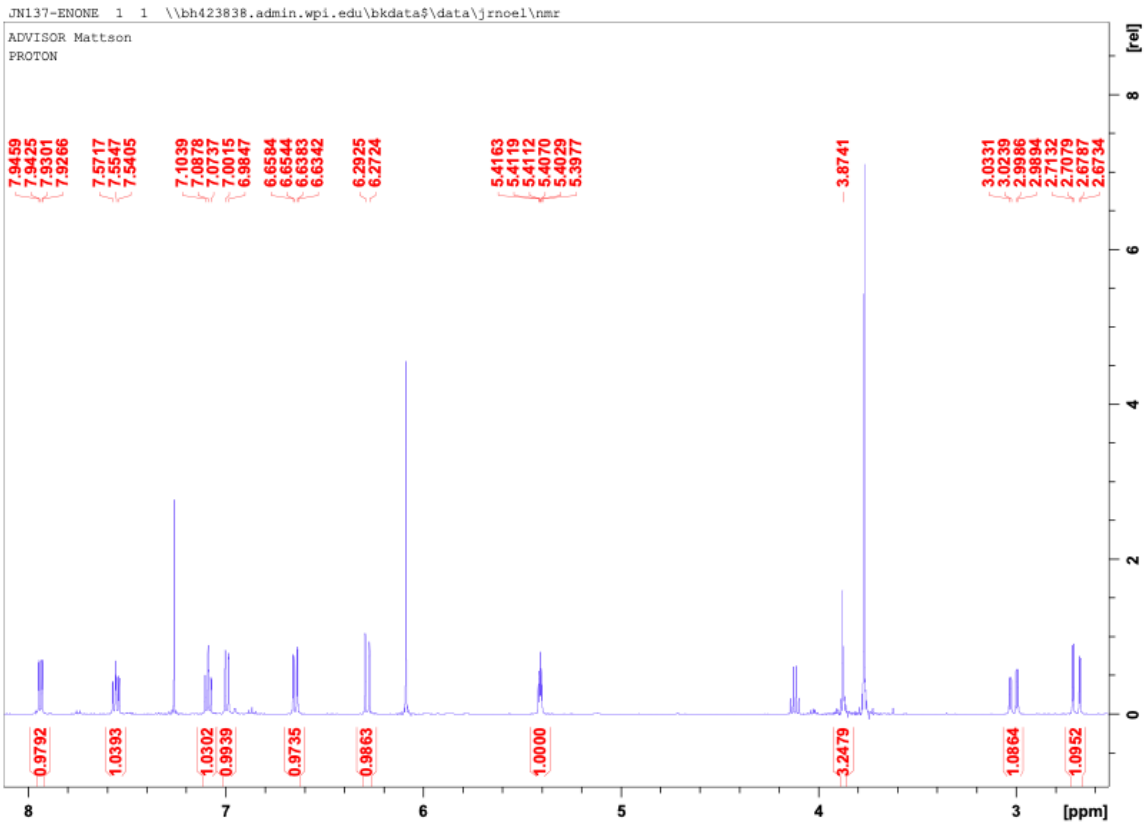
**26m**


JN102-SPOT3 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.7419
8.1978
8.1928
7.9185
7.9135
3.9434
1.0000
0.9850
1.0147
3.3162
[rel]
[ppm]

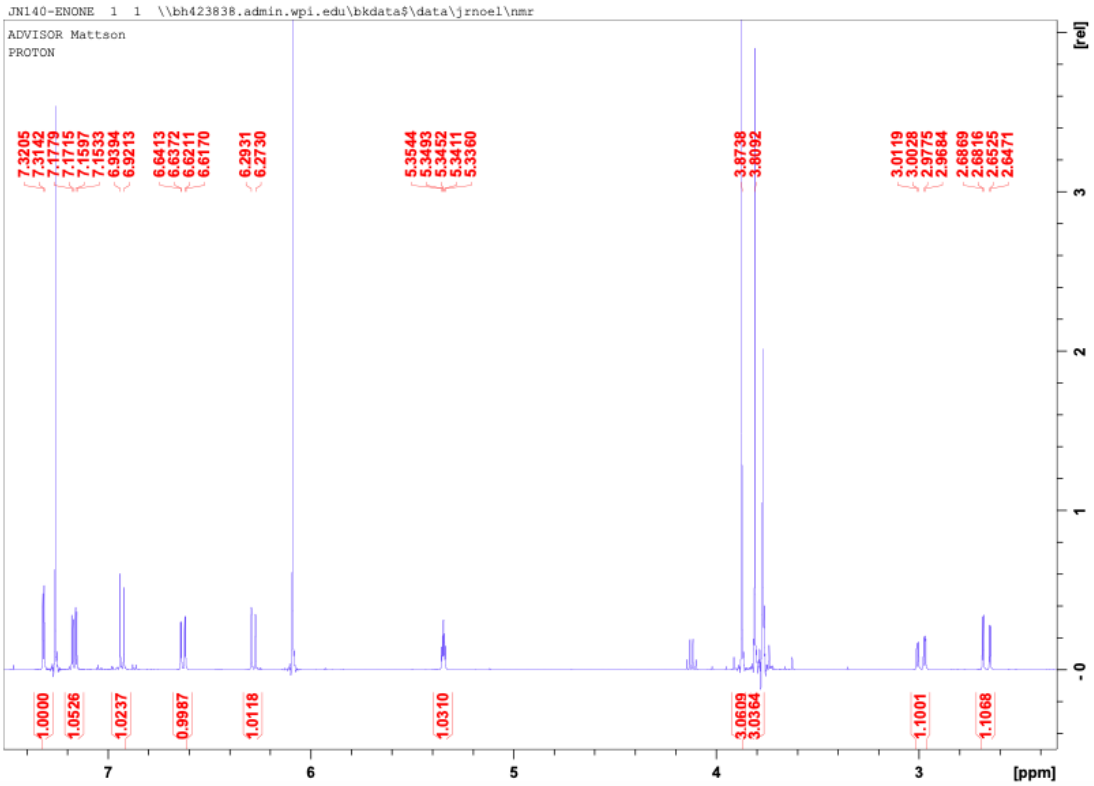
**26n**


JN4S3-#14 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.4757
7.5834
7.5666
7.5498
7.0304
7.0135
6.8649
6.8482
3.9673
3.8985
1.0000
1.1468
1.1008
1.1369
3.2037
3.2131
[rel]
[ppm]

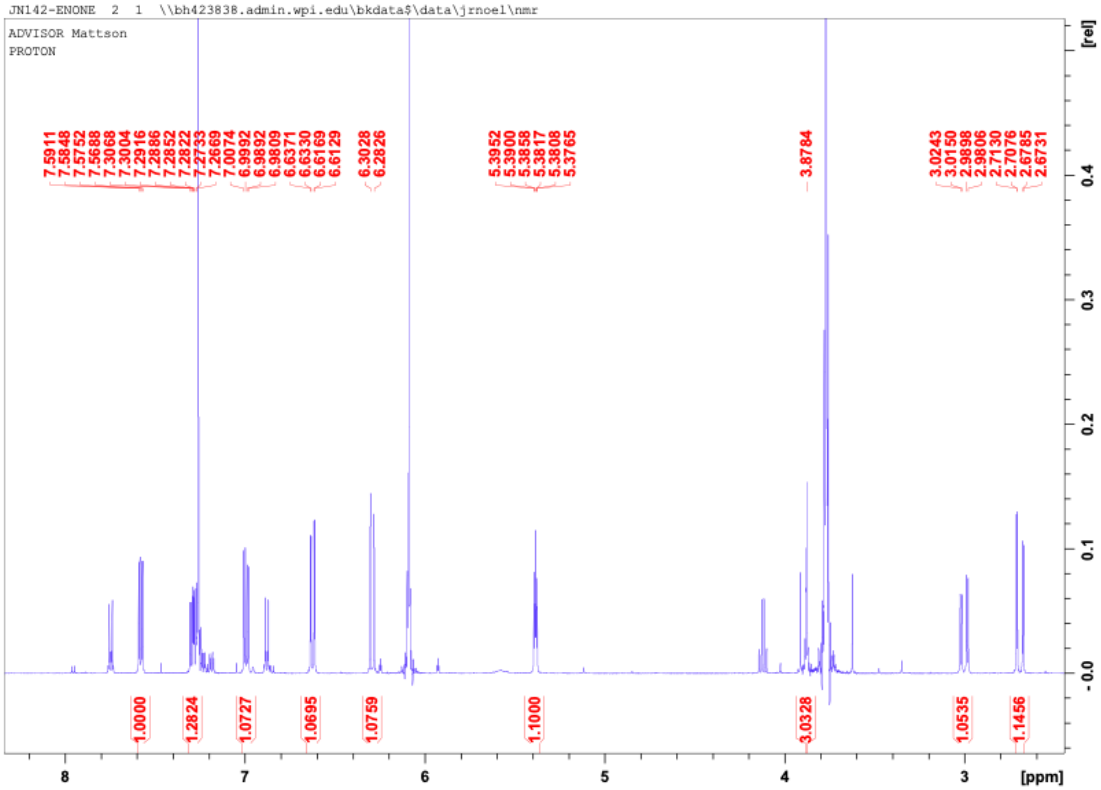
**54a**


JN137-ENONE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.9459
7.9425
7.9301
7.9266
7.5717
7.5547
7.5405
7.1039
7.0878
7.0737
7.0015
6.9847
6.6584
6.6544
6.6383
6.6342
6.2925
6.2724
5.4163
5.4119
5.4112
5.4070
5.4029
5.3977
3.8741
3.0331
3.0239
2.9986
2.9894
2.7132
2.7079
2.6787
2.6734
0.9792
1.0393
1.0302
0.9939
0.9735
0.9863
1.0000
3.2479
1.0864
1.0952
[rel]
[ppm]

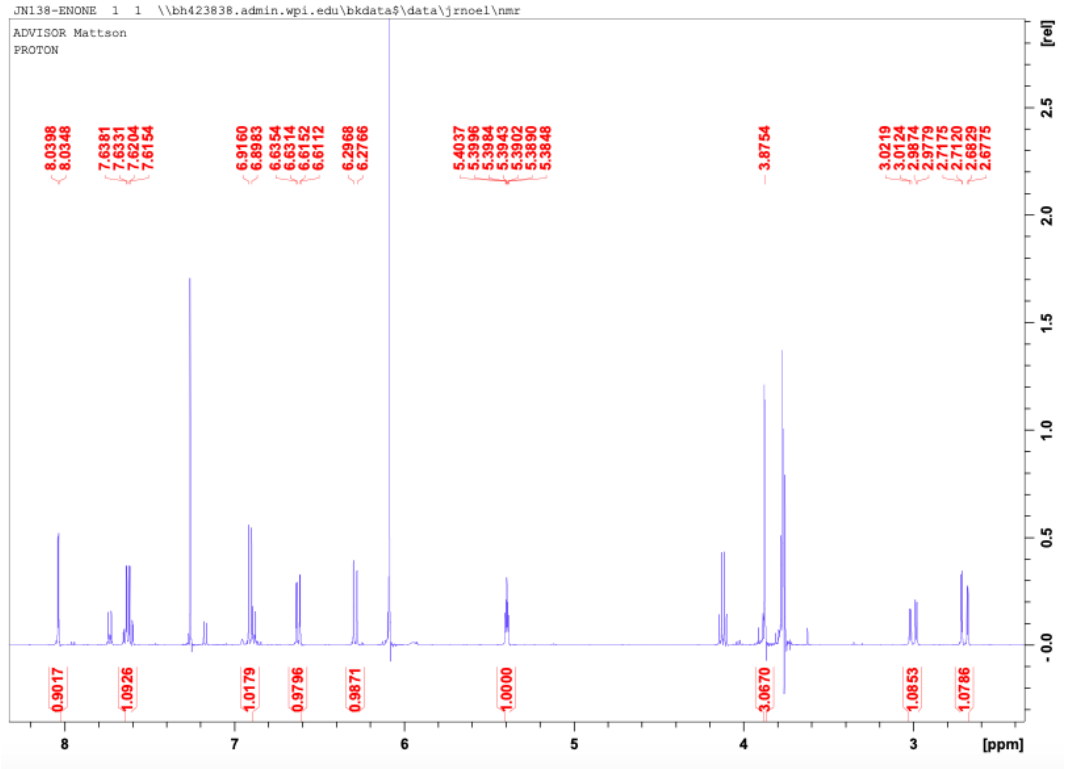
**54b**


JN140-ENONE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.3205
7.3142
7.1779
7.1715
7.1597
7.1533
6.9394
6.9213
6.6413
6.6372
6.6211
6.6170
6.2931
6.2730
5.3544
5.3493
5.3452
5.3411
5.3360
3.8738
3.8092
3.0119
3.0028
2.9775
2.9684
2.6869
2.6816
2.6525
2.6471
1.0000
1.0526
1.0237
0.9987
1.0118
1.0310
3.0609
3.0364
1.1001
1.1068
[rel]
[ppm]

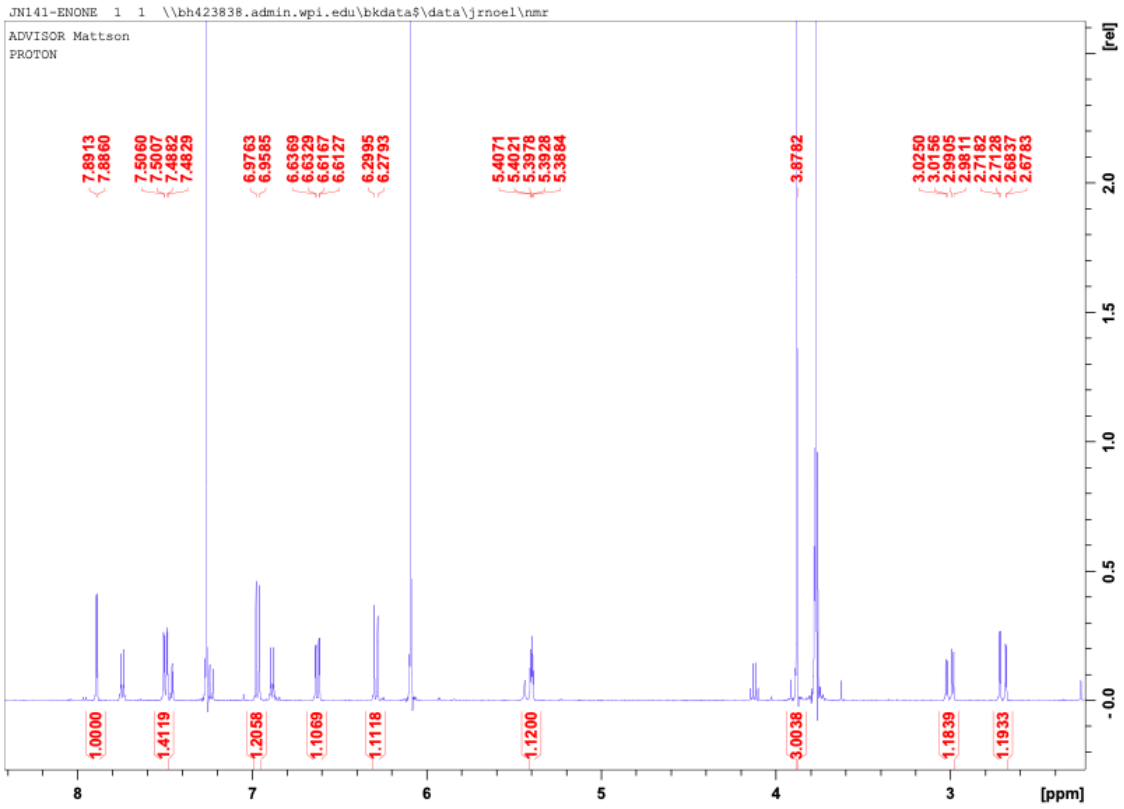
**54c**


JN142-ENONE 2 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.5911
7.5848
7.5752
7.5688
7.3068
7.3004
7.2916
7.2886
7.2852
7.2822
7.2733
7.2689
7.0074
6.9992
6.9892
6.9809
6.6371
6.6330
6.6169
6.6129
6.3028
6.2826
5.3952
5.3900
5.3858
5.3817
5.3808
5.3765
3.8784
3.0243
3.0150
2.9898
2.9806
2.7130
2.7076
2.6785
2.6731
1.0000
1.2824
1.0727
1.0695
1.0759
1.1000
3.0328
1.0535
1.1456
[rel]
[ppm]

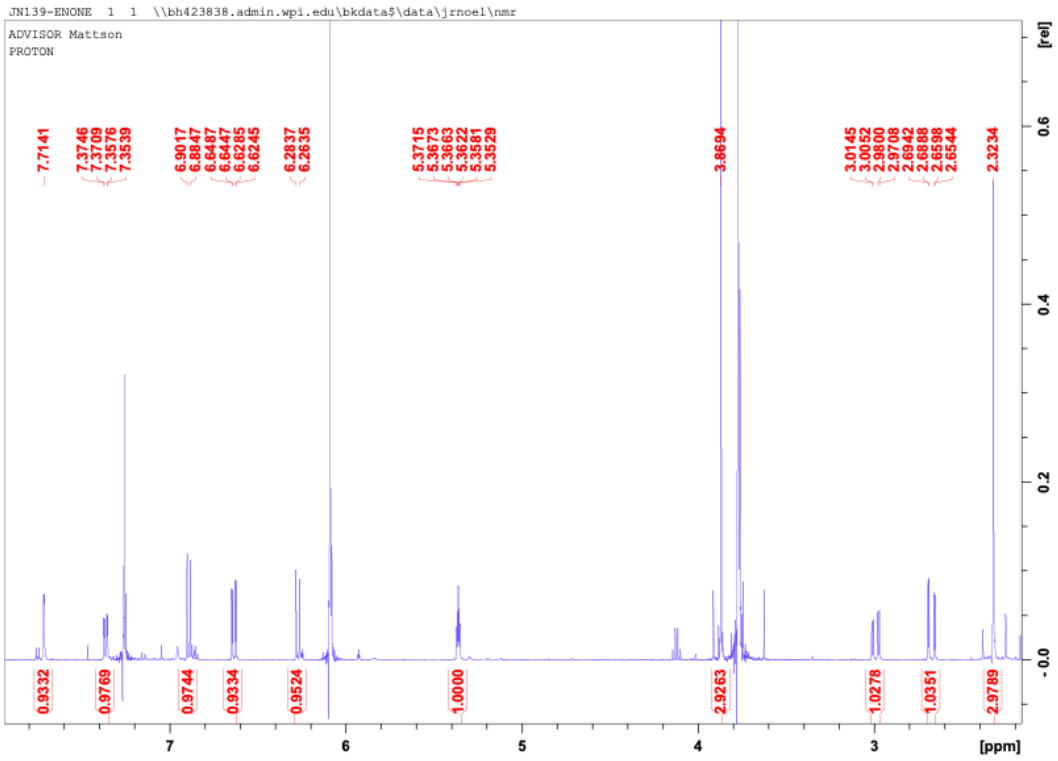
**54d**


JN138-ENONE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
8.0398
8.0348
7.6381
7.6331
7.6204
7.6154
6.9160
6.8983
6.6354
6.6314
6.6152
6.6112
6.2968
6.2766
5.4037
5.3996
5.3984
5.3943
5.3902
5.3890
5.3848
3.8754
3.0219
3.0124
2.9874
2.9779
2.7175
2.7120
2.6829
2.6775
0.9017
1.0926
1.0179
0.9796
0.9871
1.0000
3.0670
1.0853
1.0786
[rel]
[ppm]

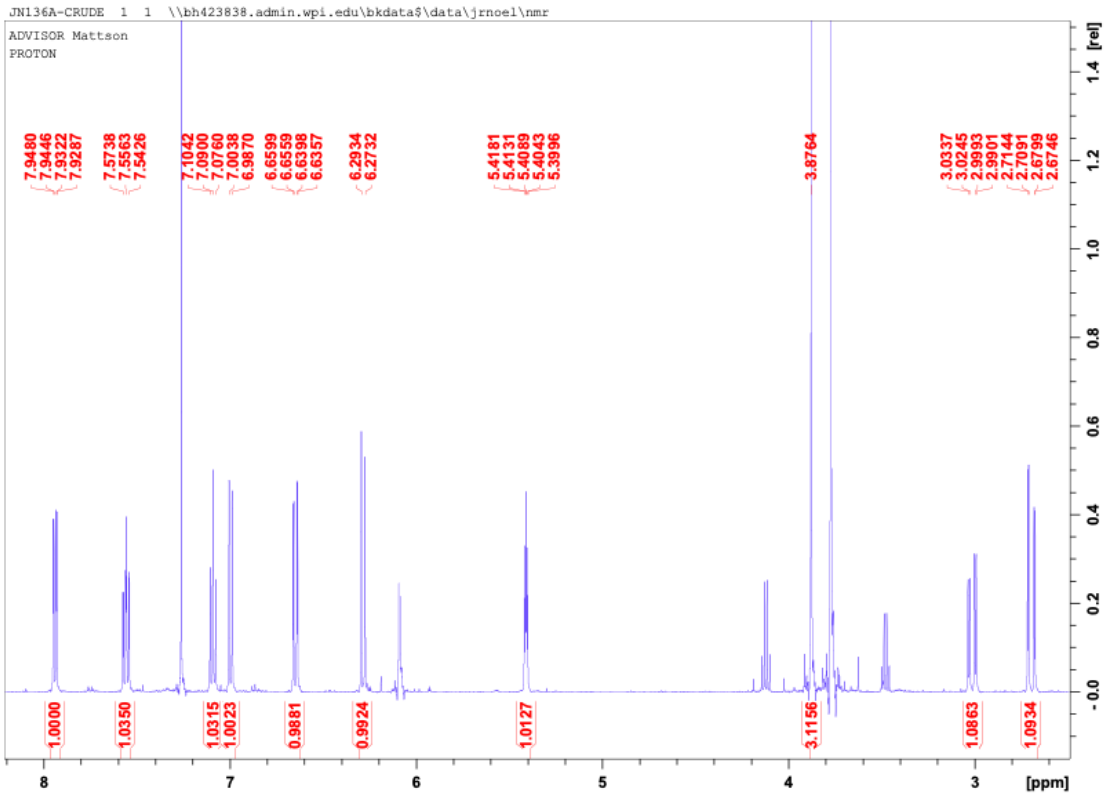
**54e**


JN141-ENONE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.8913
7.8860
7.5060
7.5007
7.4882
7.4829
6.9763
6.9585
6.6369
6.6329
6.6167
6.6127
6.2995
6.2793
5.4071
5.4021
5.3978
5.3928
5.3884
3.8782
3.0250
3.0156
2.9905
2.9811
2.7182
2.7128
2.6837
2.6783
1.0000
1.4119
1.2058
1.1069
1.1118
1.1200
3.0038
1.1839
1.1933
[rel]
[ppm]

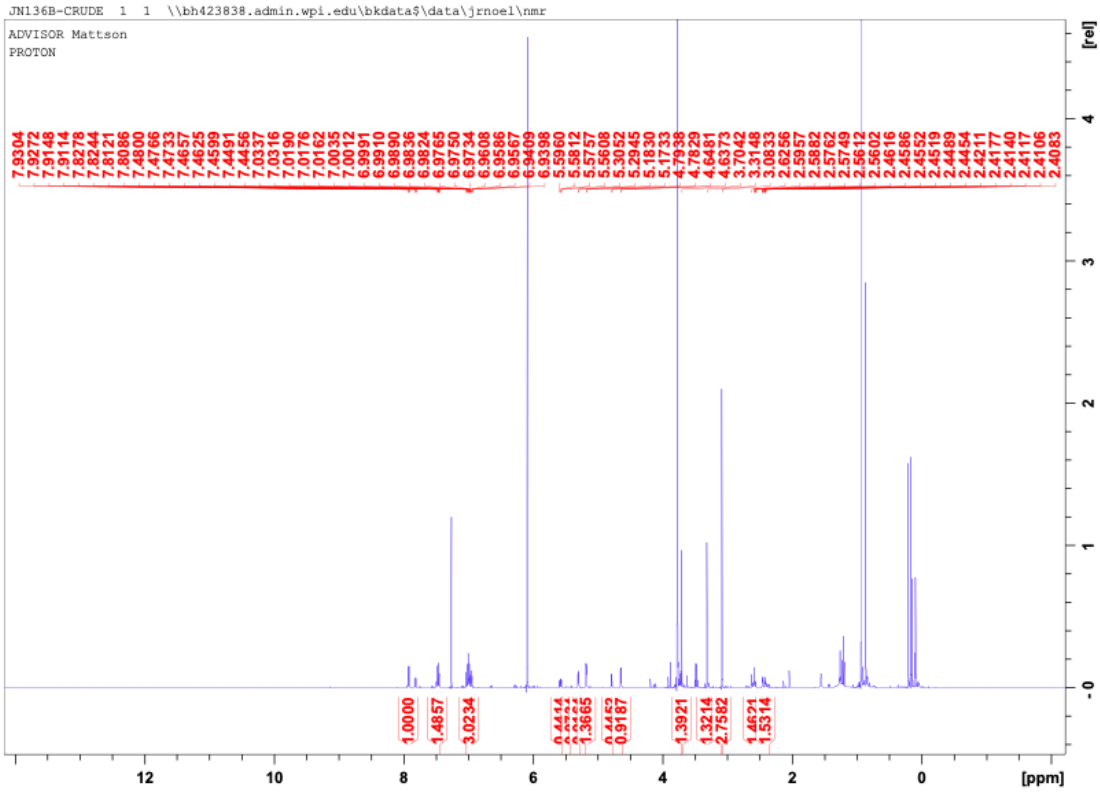
**54f**


JN139-ENONE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.7141
7.3746
7.3709
7.3576
7.3539
6.9017
6.8847
6.6487
6.6447
6.6285
6.6245
6.2837
6.2635
5.3715
5.3673
5.3663
5.3622
5.3581
5.3529
3.8694
3.0145
3.0052
2.9800
2.9708
2.6942
2.6888
2.6598
2.6544
2.3234
0.9332
0.9769
0.9744
0.9334
0.9524
1.0000
2.9263
1.0278
1.0351
2.9789
[rel]
[ppm]

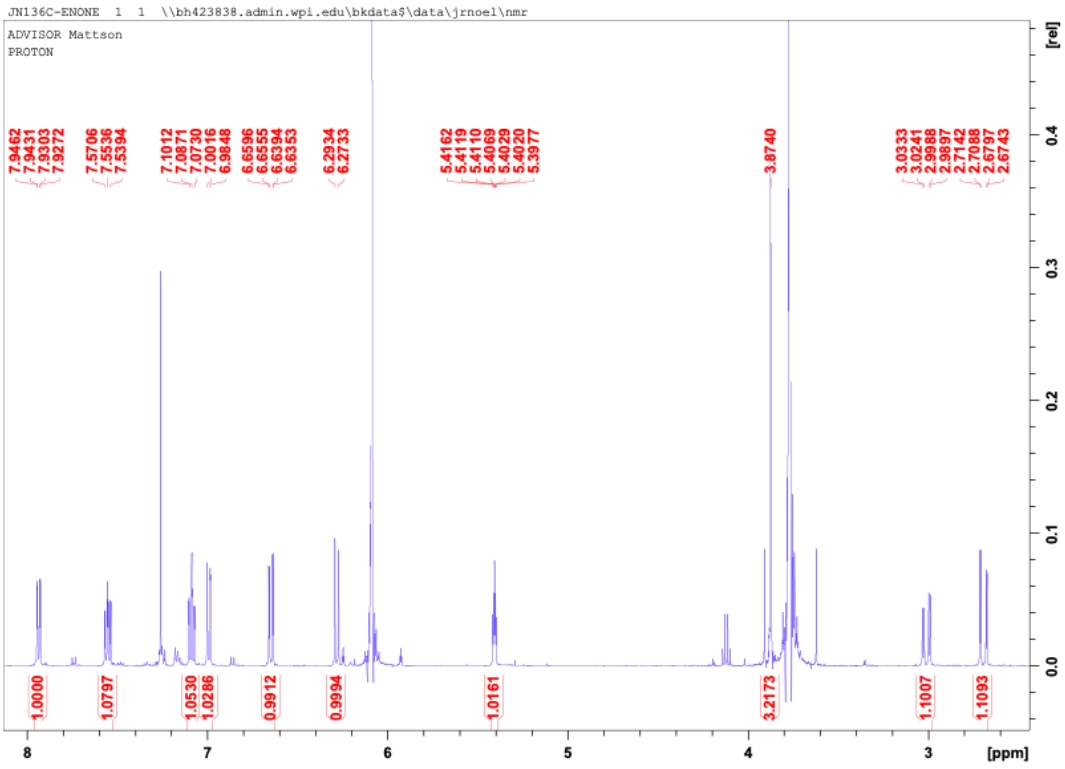
**Ha**


JN136A-CRUDE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.9480
7.9446
7.9322
7.9287
7.5738
7.5563
7.5426
7.1042
7.0900
7.0760
7.0038
6.9870
6.6599
6.6559
6.6398
6.6357
6.2934
6.2732
5.4181
5.4131
5.4089
5.4043
5.3996
3.8764
3.0337
3.0245
2.9993
2.9901
2.7144
2.7091
2.6799
2.6746
1.0000
1.0350
1.0315
1.0023
0.9881
0.9924
1.0127
3.1156
1.0863
1.0934
[rel]
[ppm]

**Hb**


JN136B-CRUDE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
1.0000
1.4857
3.0234
1.3921
1.3214
2.7582
1.4621
1.5314
[rel]
[ppm]

**Hc**


JN136C-ENONE 1 1 \\bh423838.admin.wpi.edu\bkdata$\data\jrnoel\nmr
ADVISOR Mattson
PROTON
7.9462
7.9431
7.9303
7.9272
7.5706
7.5536
7.5394
7.1012
7.0871
7.0730
7.0016
6.9848
6.6596
6.6555
6.6394
6.6353
6.2934
6.2733
5.4162
5.4119
5.4110
5.4069
5.4029
5.4020
5.3977
3.8740
3.0333
3.0241
2.9988
2.9897
2.7142
2.7088
2.6797
2.6743
1.0000
1.0797
1.0530
1.0286
0.9912
0.9994
1.0161
3.2173
1.1007
1.1093
8
7
6
5
4
3
[ppm]
[rel]
0.0
0.1
0.2
0.3
0.4

*HPLC DATA*

| Entry | Compound | Ligand | Area % | |
|---|---|---|---|---|
| | | | R,R | S,S |
| JN103 | 54a | 58 | 90 | 10 |
| JN117 | 54a | 58 | 91.5 | 8.5 |
| JN123 | 54a | 58 | 91.5 | 8.5 |
| JN108 | 54b | 58 | 89.5 | 10.5 |
| JN119 | 54b | 58 | 94 | 6 |
| JN125 | 54b | 58 | 93.5 | 6.5 |
| JN76 | 54d | 58 | 92 | 8 |
| JN109 | 54d | 58 | 73.5 | 26.5 |
| JN121 | 54d | 58 | 77 | 23 |
| JN106 | 54e | 58 | 89 | 11 |
| JN86 | 54f | 58 | 94 | 6 |
| JN107 | 54f | 58 | 94.5 | 5.5 |
| JN120 | 54f | 58 | 91.5 | 8.5 |
| JN132 | 54a | 59 | 92.4 | 7.6 |
| JN137 | 54a | 59 | 91.5 | 8.5 |
| JN134 | 54b | 59 | 85.1 | 14.9 |
| JN140 | 54b | 59 | 88 | 12 |
| JN131 | 54c | 59 | 93.4 | 6.6 |
| JN142 | 54c | 59 | 92.9 | 7.1 |
| JN135 | 54d | 59 | 94.4 | 5.6 |
| JN138 | 54d | 59 | 93.6 | 6.7 |
| JN129 | 54e | 59 | 94.5 | 5.5 |
| JN141 | 54e | 59 | 94.5 | 5.5 |
| JN133 | 54f | 59 | 93.5 | 6.5 |
| JN139 | 54f | 59 | 92.8 | 7.2 |