Operation Hot Sandwich: Incorporating pyrones in [4 + 2] cycloaddition reactions to prepare thermorubin

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Abstract

The current increase in antibiotic resistance is of growing concern to the global community. Once easily-treated infections now require last-resort antibiotics with further application only encouraging the eventual buildup of resistance. New drugs are required to fight these infections, specifically with novel mechanisms of action that bacteria have no resistance for. Generally, these drugs will have different scaffolds, contributing to their different mechanisms of action. The literature contains a vast number of antimicrobial metabolites that are understudied but could serve as potential leads for future drugs. One such metabolite is thermorubin, a molecule with a unique scaffold and bacteriostatic mechanism of action. It shows promising sub micromolar activity against both Gram-positive and negative bacteria but suffers from poor oral bioavailability.

Difficulties in obtaining this material have led to our development of a total synthetic strategy including a new method for incorporating pyrone moieties into aromatic systems. Based off the Hauser annulation, these conditions were successfully used to insert 15 different pyrones esters and amides into an aromatic system as a dieneophile or a 2-electron component. Modification of the electron-donor, the 4 -electron sulfoxide diene, was also attempted and proved to be somewhat effective. After attempts to use single sulfoxide cycloaddition products failed to propagate, a new donor substrate needed to be created: a symmetrical intermediate already containing both phenyl sulfoxide functionalities. This material was tested and proved successful with further optimization needed to complete the total synthesis of thermorubin.

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General Audience Abstract

Over the past few decades, the decline in effective ways to treat bacterial infections has become a serious threat to our survival as a species. Easily-treated infections are now becoming impossible to treat, requiring new solutions in the forms of new drugs or drug derivatives. Looking back into the literature, however, potential molecules may have already been discovered but may have been underdeveloped due to having undesirable properties. One such molecule is thermorubin, which shows high selectivity towards bacteria and high activity against a broad range of bacteria. Thermorubin is not water soluble, so part of this work would involve making thermorubin while also making small changes to it to make it more soluble in water.

The synthetic construction of thermorubin has never been performed before. The route we would like to use would involve an annulation reaction, a chemical reaction that produces an aromatic ring, with a material that has not been reported in the literature. The structure of this material would also allow for the formation of unwanted side materials. After careful testing, the ideal conditions were developed for product formation, and twenty-one various pyrone esters and amides were applied in the reaction. This optimized reaction was also attempted in the pathway for thermorubin and proved successful, although the product could not be further modified. Due to this inability to be modified, the starting material was altered to already include these modifications before the annulation reaction. Further annulation proved successful, though continued work is required to finish the construction of thermorubin.

Overview

Chapter 1 discusses the growing concern of antibiotic resistance and the need for new drugs with novel mechanisms of action. Thhermorubin is introduced as a candidate that can serve as a potential lead molecule for derivatization.

Chapter 2 is the introduction to the initial synthetic work on thermorubin. The initial trials to try and obtain this metabolite focused on a Staunton-Weinreb approach. When this proved unsuccessful, modification of the electron-donor was attempted to overcome this feature. Incorporation of pyrones into Hauser-type annulations has not been reported in the literature.

Chapter 3 focuses on the optimization of the pyrone annulation conditions with a modified electron-donor, one that was easier to create. Optimized conditions were deduced and were applied to a 21 different pyrone esters and amides. These reaction conditions also proved successful when the electron donor itself was altered, further verifying the scope of this annulation.

Chapter 4 details the implementation of the optimized reaction conditions into the total synthetic route. While successful, further alterations had to be made to the electron-donor, specifically the creation of a symmetrical bissulfoxide molecule that also was successfully used in the annulation.

Chapter 5 explores the future direction of the total synthesis and offers ideas on how to complete construction of thermorubin. Further outlined is a technique for late-stage salicylate derivatization of thermorubin, as well as suggestions for other electron substrates for future Hauser-type annulations.

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Attributions

Chapters 1, 2, and 4 are part of a manuscript in preparation. The manuscript is being written and was conceived by Zachary Kohanov and Andrew Lowell. Zachary Kohanov performed all of the synthetic chemistry.

Chapter 3 is a reprint of a manuscript published in the *Journal of Organic Chemistry*. The manuscript has been modified for use in this dissertation. The original manuscript was written by Zachary Kohanov, Suzzudul Shuvo, and Andrew Lowell and edited by Zachary Kohanov and Andrew Lowell. Zachary Kohanov and Andrew Lowell conceived of the project, Zachary Kohanov performed all of the synthetic chemistry (except for preparation of pyrone esters and amides, prepared by Suzzudul Shuvo).

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Chapter 1: Introduction

1.1 Fighting Nature with Nature

One of the largest problems that society faces in the 21st century is the growing threat of antimicrobial resistance. The inherent ability of bacteria to overcome antibiotics by horizontal gene transfer and mutations inexorably leads to resistance against these drugs. Even last resort drugs to treat infections now have a resistance gene embedded in their bacterial genome, decreasing their effective use.[1,2] Overuse of antibiotics to treat illnesses other than bacterial infections also led to acquisition of resistance genes selecting for bacteria that are immune to them.

1.2 Importance of Scaffolds

The first wave of natural product antibiotics and their approval for use in medical settings occurred between the 1940s and 1960s. This time was marked by the discovery of many antibacterial metabolites and the recognition of shared scaffolds that have general antimicrobial activity, such as first-generation antibiotics tetracycline and streptomycin, which represent drugs from the tetracycline and aminoglycoside classes, respectively. **Figure 1.1** illustrates the discovery of a class of antibiotics and the subsequent amount of years between the first drug of that class being FDA approved. While generational synthesis continues to be important in the fight against antibiotic resistant pathogens, it is crucial to find new active drug scaffolds that will behave in novel ways that bacteria will have difficulty combatting. These can be sourced from the overlooked metabolites, such as the case of pleuromutilin and Retapamulin, which took over fifty years to see the first FDA approved drug of this class.

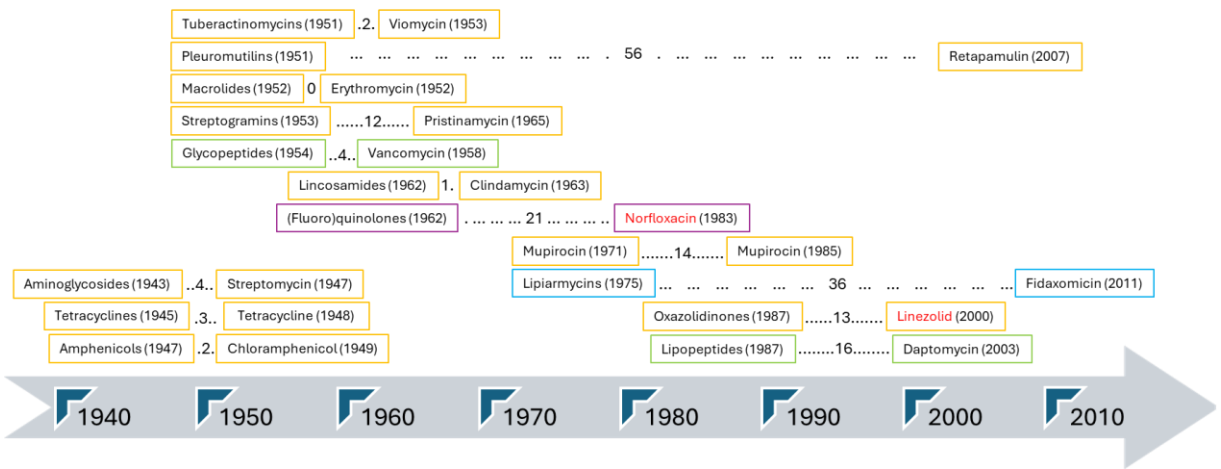


Figure 1.1: Discovery of natural product scaffolds (left) and their implementation as FDA approved drugs. The values in-between boxes represent the number of years between discovery and implementation, with the box colors denoting types of bacterial targets (orange = ribosome; green = cell wall synthesis; purple = DNA synthesis; blue = RNA polymerase).

The astounding complexity of naturally produced metabolites is a critical source of new scaffolds. The majority of clinically relevant antibiotics are derivatives of naturally occurring metabolites isolated from biological sources, with others derived using synthetic means.[3] Isolating and characterizing additional new compounds, which are ideally new classes of antibiotics with novel mechanisms of action, is therefore of high importance. Besides identifying previously unknown scaffolds, new drugs can also be derived from forgotten antibiotics, molecules that have been previously reported to exhibit antibacterial properties but were not developed. Exploration into these drugs was limited at the time due to lack of methodology, lack of availability, challenging properties, or general cytotoxicity. However, current technologies lend themselves to successful SAR campaigns to develop these compounds into lead molecules for new classes of antibiotics. This approach could be more efficient than de novo discovery by overcoming the time needed to collect, extract, isolate, and characterize new metabolites from biological sources as well as avoiding the chance of rediscovery of previously known molecules.

1.3 Thermorubin

One such forgotten antibiotic is thermorubin, a tetracyclic molecule that displays promising activity against pathological infections from Gram positive bacteria. It is distinguished from other biologically active molecules, such as tetracyclines and quinone-type molecules, in that most of its functionality is located along one side of the ring. Thermorubin was first isolated by Craveri[4] and colleagues in 1964, with an initial structural configuration being proposed in 1971 by Moppett[5] and coworkers. Their investigations involving NMR analyses and comparison to similarly structured xanthone molecules led to the assignment of structure **1.1**. However, this structure was not universally agreed upon and further investigation by Johnson and coworkers using X-ray diffraction corrected the structure assignment to **1.2**.

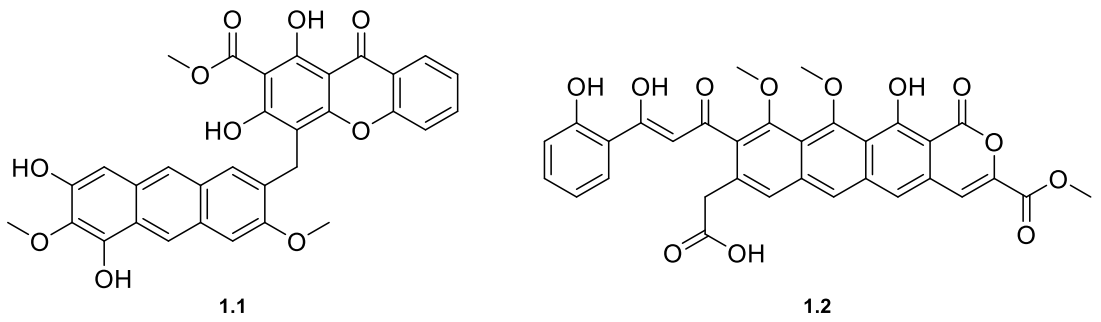


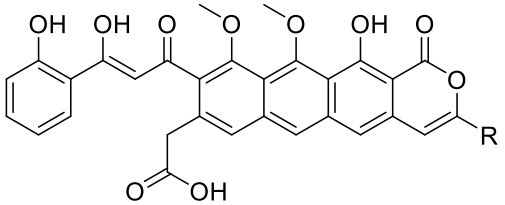
Figure 1.2: Original thermorubin structure **1.1** and corrected structure **1.2**.

1.3.1 Thermorubin Derivatives

Early exploration into derivatization of thermorubin focused on semisynthetic modification of the metabolite directly isolated from its producing strain.[6] Modification of the metabolite was therefore limited to functional group conversion of the most reactive centers. The most active derivatives were those that converted the external methyl ester to the methyl amide **1.3** and reduction to the primary alcohol **1.4**, with activity being comparable to or less potent

compared to the parent molecule (**Table 1.1**). These modifications did not lead to a more orally bioavailable drug. More complex derivatization techniques would be required to make a more orally available and potent derivative, a task that may not be possible when attempting functionalization changes on thermorubin itself.

Table 1.1: Activity of thermorubin compared to its most active derivatives



1.2 R = $COOCH_3$
1.3 R = $CONHCH_3$
1.4 R = CH_2OH

	Antibacterial activity (ug/mL)		
Organism	**1.2**	**1.3**	**1.4**
S. aureus ATCC 6538	0.006	0.05	0.025
S. pyogenes C203 SKF 13400	0.025	0.1	0.05
S. pneumoniae UC 41	0.05	0.05	0.05
P. vulgaris X19H ATCC 881	3.12	1.6	12.5
E. coli SKF 12140	6.25	6.2	12.5

Along with its unique structure, thermorubin has a unique mechanism of action, binding near the intersubunit ribosomal bridge within the bacterial ribosome.[7] Initially thought to inhibit translation initiation,[7] this molecule inhibits elongation and termination steps by preventing delivery of aminoacyl-tRNA and release factor binding within the A-site.[8] The high binding affinity that it has for the bound ribosomal complex as opposed to either individual unit also prevents the complex from disassociating, further reducing ribosomal productivity by stalling ribosome recycling.[9] The pivotal interactions can be seen in **Figure 1.2** with crucial interactions occurring with the oxygen motifs along the top portion of thermorubin and A1913 and the carboxylic acid with A1916, as well as aromatic pi-stacking observed between the salicylate ring and U1915. Given these interactions and that the bottom portion of thermorubin remains within a

hydrophobic pocket, derivatization of the oxygen-rich side of the metabolite is not favorable.

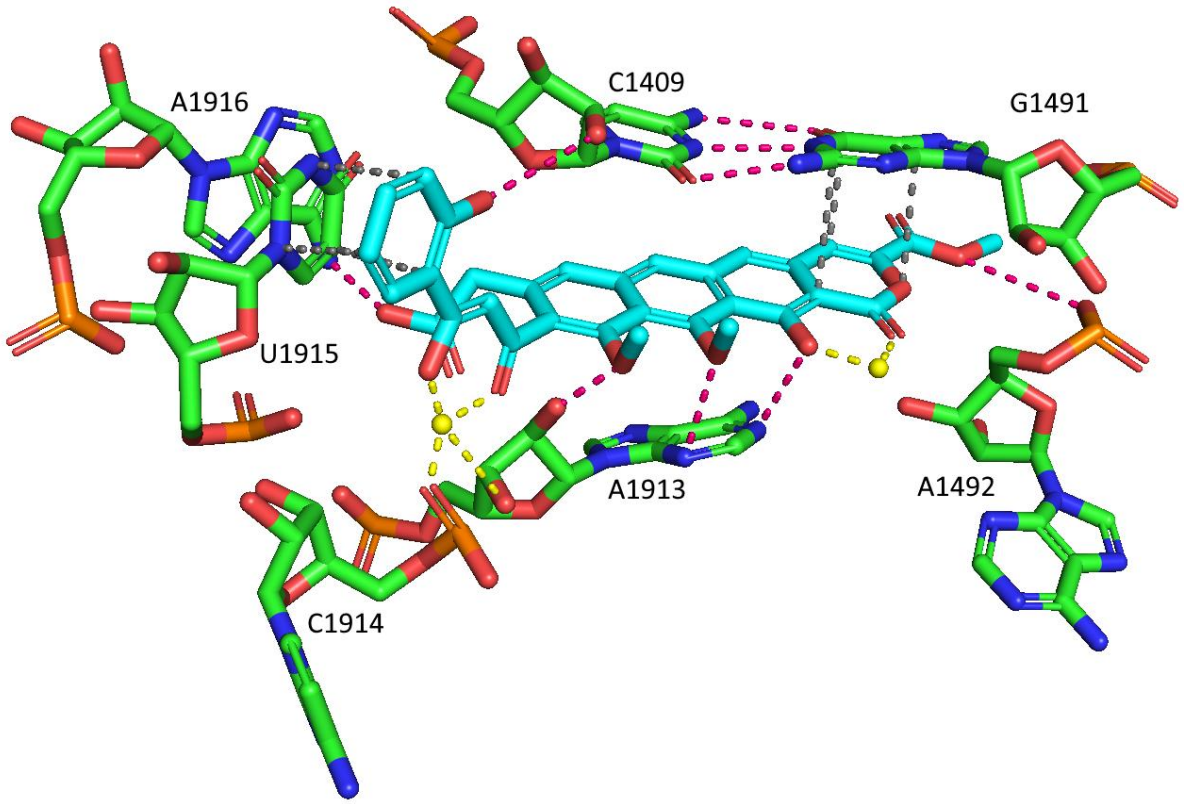


Figure 1.2: Crystal structure of thermorubin bound to the *T thermophilus* ribosome, with relevant contacts shown (red dashes = hydrogen bonds; gray dashes = pi stacking; yellow dashes = Mg coordination). PDB 4V8A.

1.3.2 Previous Synthetic Work

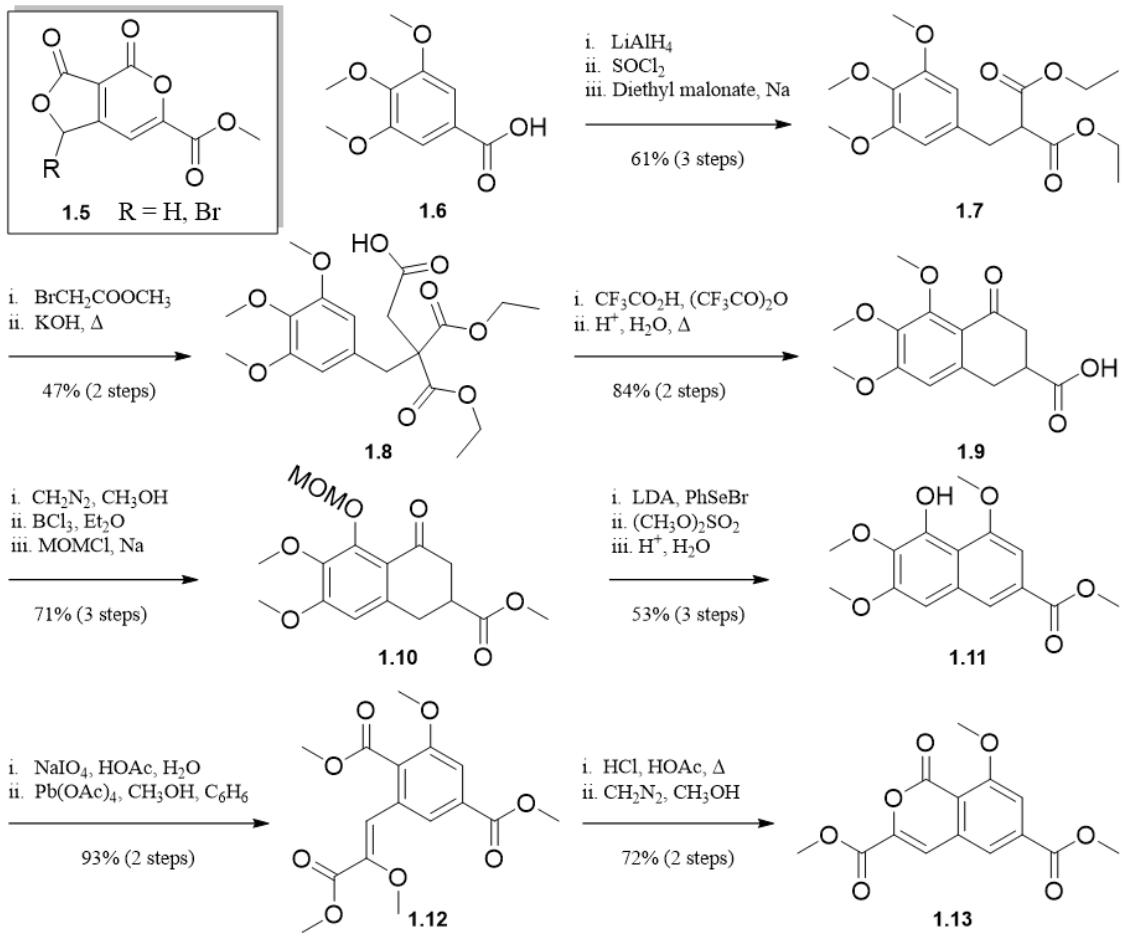
There has only been one previous attempt to synthesize thermorubin, that by Johnson and colleagues in 1986. They sought to partially construct the tetracyclic core of the metabolite,[10] focusing on the CD portion. The group initially had an idealized structure in their mind for the construction of the core, synthon **1.5** (**Scheme 1.1**, inset) as well as its conformational isomer with the furanone ring inverted in its connectivity, but further work using this synthon proved incompatible with reported annulation conditions and its initial construction proved challenging. It should be noted that utilizing this synthon would have also generated a product containing a

diol, which is not observed in thermorubin, and subsequent dehydration would have been required.

Thus, their work focused on a synthetic route to construct the pyrone (**1.13**) portion without its direct incorporation utilizing an annulation (**Scheme 1.1**). Adapting precedent from Drake and Tuemmler,[11] the trimethoxy benzoic acid (**1.6**) was reduced and converted to the benzyl chloride, which allowed for alkylation using ethyl malonate in a 61% yield over three steps furnishing **1.7**. Subsequent alkylation using methyl bromoacetate and its hydrolysis using one equivalent of KOH resulted in intermediate **1.8** in a 47% yield over two steps, possibly suffering from a reduced yield due to over-hydrolysis of the other methyl esters. Anhydride formation and Fridel-Crafts acylation created the C-ring and treatment under acidic conditions hydrolyzed the remaining esters and induced decarboxylation leading to intermediate **1.9** in an 84% yield. Further modification of the acid to the ester using diazomethane and selective demethylation and MOM protection enabled isolation of intermediate **1.10**. Formation of the α-phenylselenyated intermediate followed by elimination formed the aromaticity of the C ring, followed by methylation of the generated phenol and MOM deprotection furnished **1.11**. Oxidation with sodium periodate under acidic conditions created the diketone with exposure to lead acetate in methanol cleaved the diketone and resulted in the formation of dimethyl ester **1.12** in a 93% yield.

The final steps to the CD component involved the acid-catalyzed cyclization of the ester and ether moieties to form the pyrone through an intramolecular cyclization, followed by methylation using diazomethane. This led to the desired precursor **1.13** in a 72% yield. When factoring in the initial steps required to make the diethyl ester intermediate **1.6**, the overall

precursor is obtained in a 6% yield over 17 steps. While this cleaving synthetic approach furnished synthon **1.13**, to achieve authentic thermorubin, the AB system would still need to be



Scheme 1.1: Johnson's approach to the synthesis of the thermorubin C and D rings (**1.13**). *Inset*: An initial approach that would have utilized pyrone **1.5** as the 4-electron unit and its isomer.

appended. Thus, while this seminal work revealed ideas and methods to construct a portion of the thermorubin core, an easier method for forming the pyrone is desirable.

1.4 Unmasking Symmetrical Intermediate

Our lab's interest in thermorubin is based on its promise as an antibiotic and its potential for derivatization, but direct derivatization is currently hindered by its difficult isolation and specific growth techniques. Previous work by our lab to investigate the biosynthetic pathway of thermorubin's formation proved successful,[12] but large-scale isolation of the metabolite was difficult and could not be replicated. This problem led us to pursue synthetic strategies to obtain thermorubin. The formation of this material would not only provide material for further study, but would also enable the construction of structurally different molecules that could not be produced via biosynthesis. Of particular interest is the phenol ring, which could potentially be further functionalized. The key to our approach, as described in the subsequent chapters, focuses on symmetric intermediate (**1.14, Figure 1.2**), as this material could serve as one of the central B ring in the construction of thermorubin.

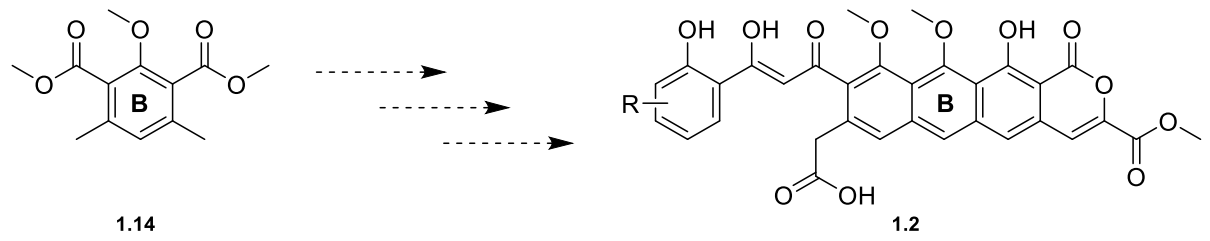


Figure 1.2: Identification of preceding symmetrical intermediate en route to thermorubin

1.5 References

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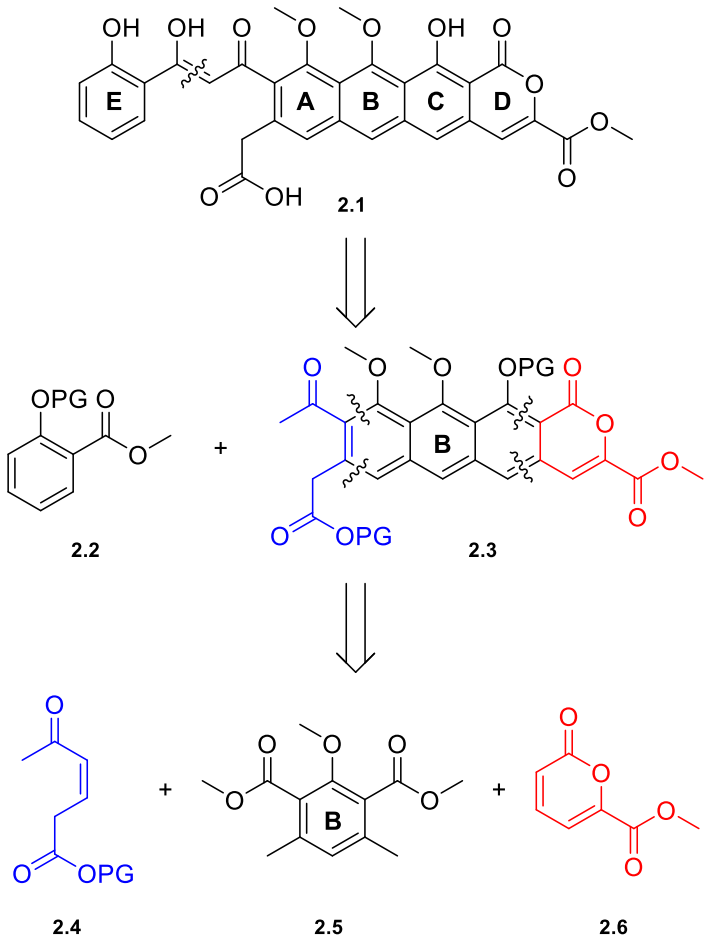
Chapter 2: Exploration of Phthalide and Monosulfoxide in Annulation Reactions

2.1 Retrosynthesis

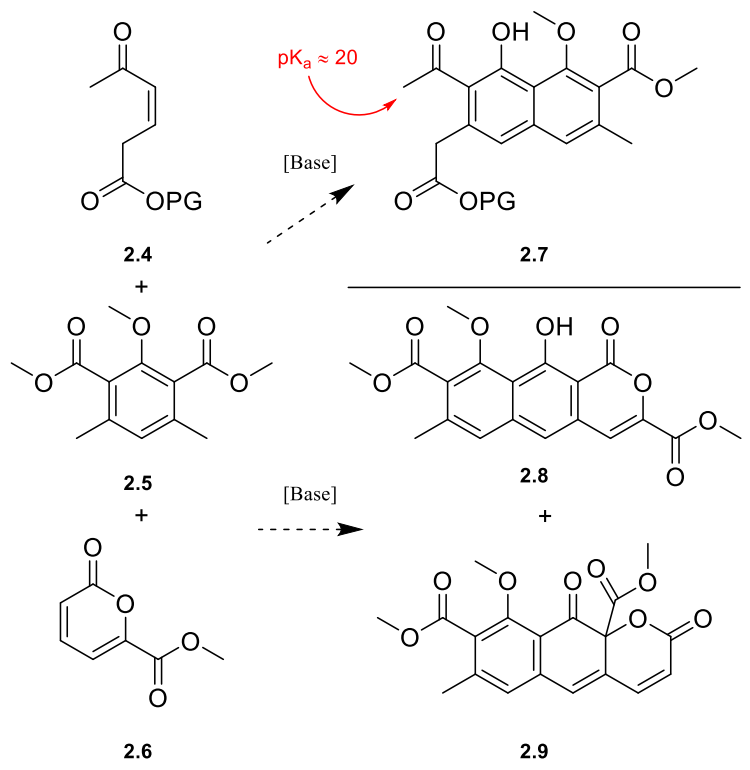
Based upon the need for new antibiotics, especially those with novel mechanisms of action, it was essential to obtain thermorubin and ideally its derivatives for study. Past attempts to isolate this material from its producing strain, *L. sacchari*, have proved difficult. Our work reproducing the original isolation work, conducted by Dr. Jen McCord and Timilehin Adegboyega, was not successful. Attempts to modify these growth conditions produced only trace amounts of metabolite. It was therefore advantageous to create a synthetic route to make this material to enable further study of thermorubin and its derivatives.



Scheme 2.1: Proposed retrosynthesis of thermorubin **2.1**.

This early synthetic work on the CD ring system of thermorubin (**Chapter 1**, **Scheme 1.1**) helped inspire our proposed synthetic route. Annulations could not only make the aromatic core but could also be used to regioselectively install functionality. We believed that an approach based on a central hidden symmetric element

was preferable. Within the B ring is a masked symmetrical phthalide (**2.5**) that can be used as two 4-electron donors to form the ABCD core, **2.3**. The initial thermorubin disconnection is removal of the salicylate moiety E ring (**2.2**), which also enables easy late-stage derivatization. The core ring system can then disconnect in one of two stages: either implementing annulation of the unsaturated ketone **2.4** with phthalide **2.5**, creating the AB system followed by connection of the D ring; or annulation of the phthalide with the methyl ester pyrone **2.6**, creating the BCD system followed by a second annulation to form the A ring.



Scheme 2.2: Annulation of **2.5** with each electron acceptor system **2.4** and **2.6** and its products, **2.7** as well as **2.10** and **11**, respectively.

Both annulation pathways (**Scheme 2.2**) initially seemed viable, but examination of the literature showed reaction of **2.5** with the unsaturated ketone (**2.4**) to give **2.7** to be more strongly precedented. Various reaction conditions utilizing unsaturated ketones as Michael acceptors have been reported, while the use of a two-electron system with two α,β-unsaturated esters viable to attack, such as with pyrone **2.6**, was unknown without directing groups. For α-pyrones, including these 6-carboxy substituted α-pyrones, it was not clear that annulation would be possible and if it did occur, could potentially result in the formation of two different regioisomers (**2.8** and **2.9**). Alternatively, while more

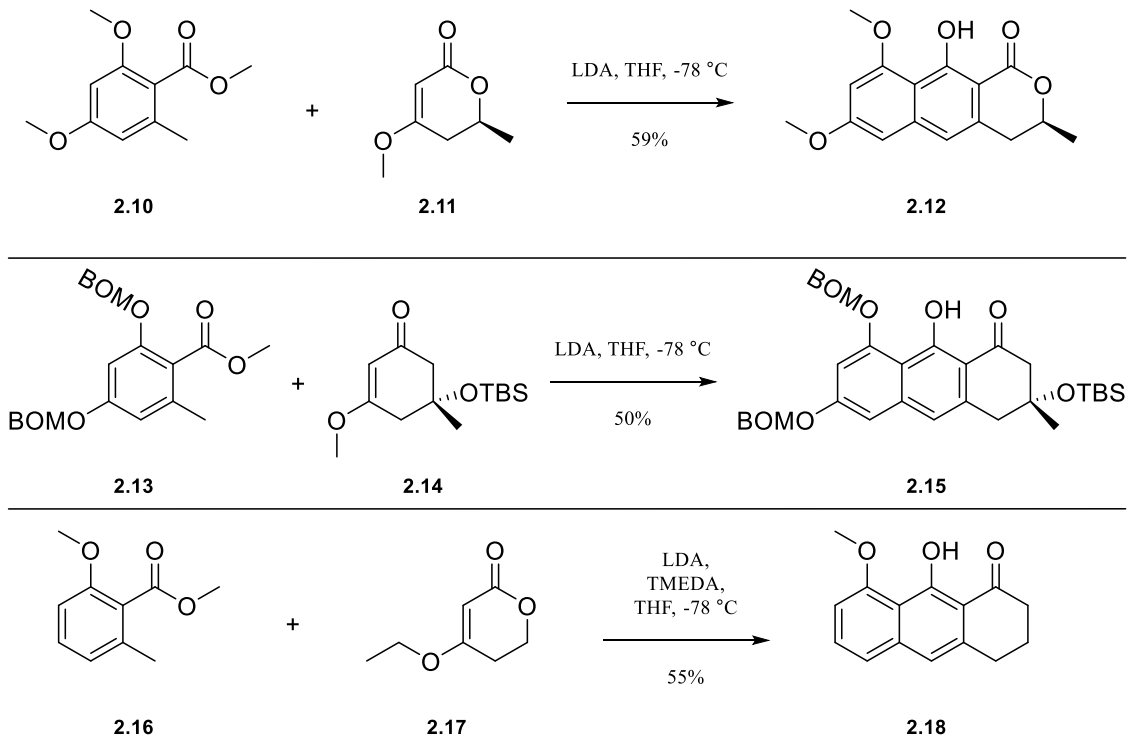
regioselective, the generated bicycle (**2.7**) that forms upon annulation of **2.5** with ketone **2.4** will generate an external ketone with a low pKa, which will have to undergo protection steps before subsequent annulation of the pyrone moiety. While unprecedented, annulation of **2.5** to the pyrone **2.6** first would not present this pKa problem.

Outlining the retrosynthesis allowed for the identification of the symmetrical moiety (**2.5**). Practically, the symmetrical intermediate **2.5** could be used in a Staunton-Weinreb approach[1] where deprotonation of a benzylic position initiates its activity as a 4-electron donor for reaction with **2.4** or **2.6** or their derivatives. Alternatively, the benzylic positions of **2.5** could be activated with functional groups to enhance their acidity enabling other annulations, such as a Hauser-type[2,3] to be pursued.

2.2 Background

The Staunton-Weinreb annulation was discovered by both James Staunton[4] and was further adapted by Steve Weinreb.[5] Its early use in the construction of polycyclic cores has been reported and could potentially be adapted for the synthesis of thermorubin. Mechanistically, an initial deprotonation of the benzylic methyl is followed by a Michael addition, with a Dieckmann condensation preceding the final aromatization. Previous annulations, shown in **Scheme 2.3**, illustrate its effectiveness[6] with annulation conditions have been reported to be orthogonal to TBS and BOM[7] protecting groups, which will prove useful when selecting protecting groups in the total synthesis. Additives such as TMEDA[8] have also been shown to improve the yield of annulated material by further stabilizing the enolate intermediate. It should be noted that all precedented 2-electron systems used are cyclic, therefore Staunton-Weinreb annulation conditions were not attempted on the unsaturated ketone.[9] For all Staunton-Weinreb annulations, a leaving group on the 2-electron system β to the activating carbonyl was critical for activity

meaning **2.24** (**Scheme 2.4**) would need to be used instead of **2.6** in our systems to reattain aromaticity.

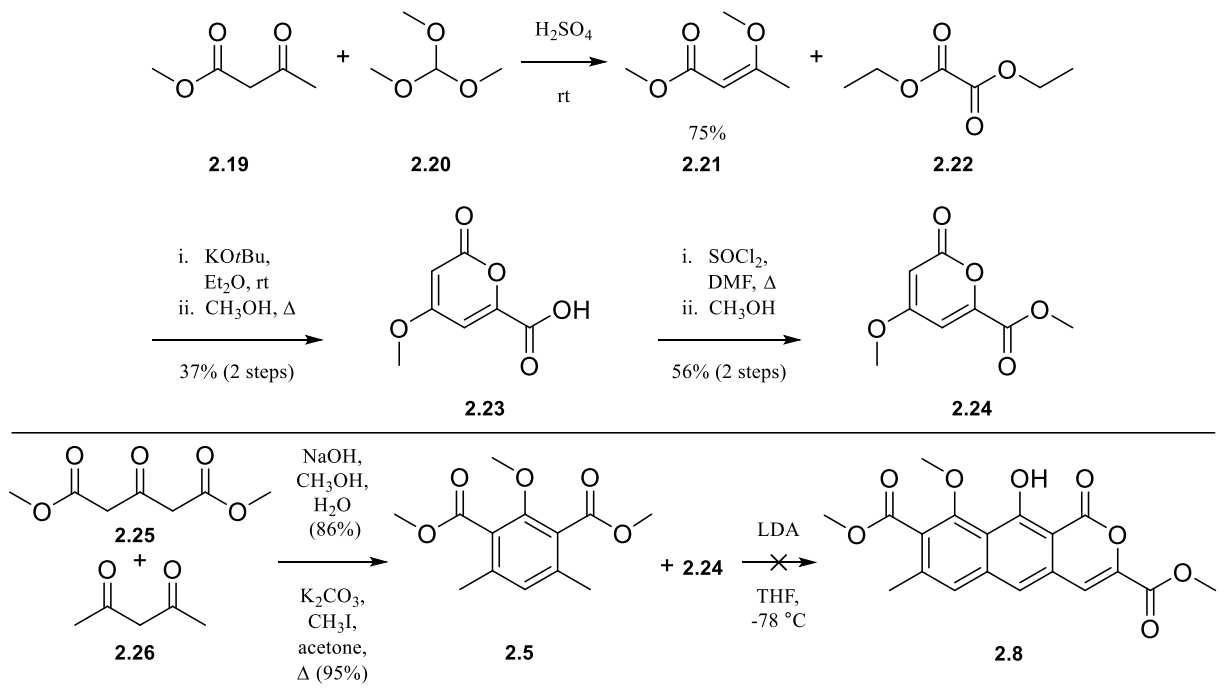


Scheme 2.3: Past literature precedent inspiring total synthesis of thermorubin.

2.3 Attempted Staunton-Weinreb Annulation

Thus, testing annulation conditions utilizing 3-methoxy pyrone **2.24** as the 2-electron component was the initial focus. Drawing inspiration from the work of Staunton and colleagues, the construction of **2.23** (**Scheme 2.4**) proceeded in modest yield, because of known difficulties in purifying these types of intermediates.[10] Methyl ester **2.24** was formed by treating **2.23** with thionyl chloride and methanol. Condensation of **2.26** with dimethyl oxoglutarate (**2.25**) and subsequent aromatization to form the phenol[11] proceeded as reported, as did methylation to form **2.5**.[12] Despite similar precedent,[6] the use of **2.24** as a 2-electron donor with isopthtalate **2.5** was unsuccessful. Recovered starting materials proved that the benzylic positions are either not

susceptible to LDA or the initial intermediate was unable to aromatize, instead reverting to starting material. Previous studies, such as in the synthesis of thysanone,[6] utilized a methoxy substituted pyrone lacking the external ester, eliminating potential formation of other annulated materials and were not aromatic, thereby having higher electrophilicity compared to our system.

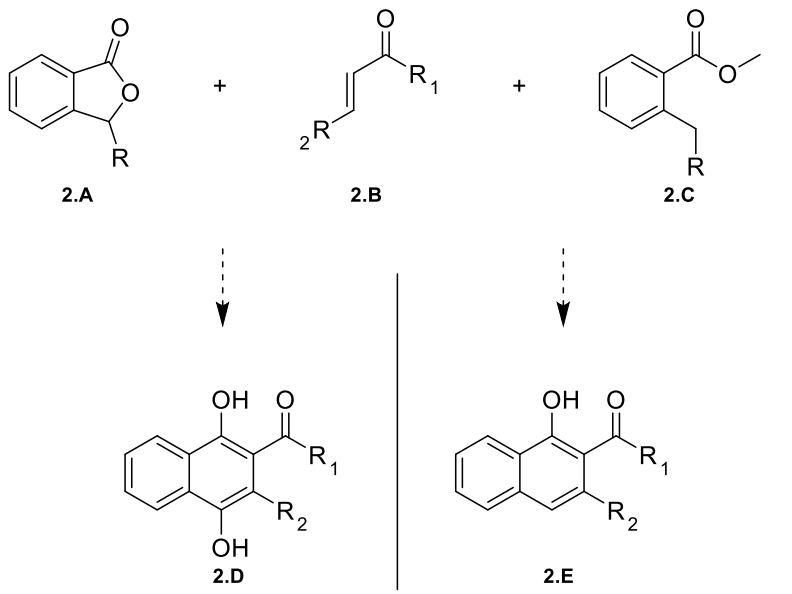


Scheme 2.4: Formation of **2.24** and attempted annulation with **2.5**.

2.4 Hauser-Kraus Substrate Preparation

Lack of annulated material from altering the pyrone resulted in reconsidering the activation level of the symmetrical intermediate. Our sights turned to a similar type of annulation which can create similar annulation products from slightly different starting materials. The Hauser annulation focuses on altering the acidic position of the electron-donor, while allowing the use of a less activated 4-electron acceptor. Most literature precedent focuses on the implementation of isobenzofuranones (**2.A**, **Scheme 2.5**) with electron withdrawing groups (R = SOPh, SO_2Ph, CN, halogens) at the C3 position to facilitate deprotonation and achieve a quinone

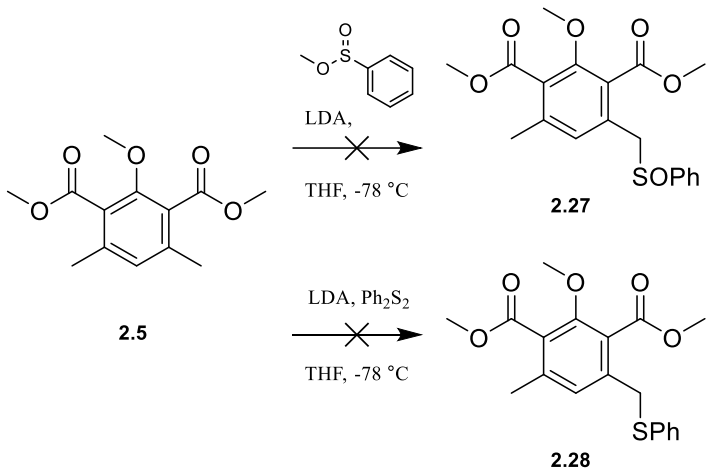
or hydroxyquinone (**2.D**) because of the prevalence of this functionality in natural products. By using an alternative Hauser substrate that is not a furanone, such as the mono sulfoxide ester **2.C**, only a single phenol will form (**2.E**).



Scheme 2.5: Undesired product from annulation of **2.D** from **2.A** and **2.B**, and desired formation of **2.E** from **2.B** and **2.C**.

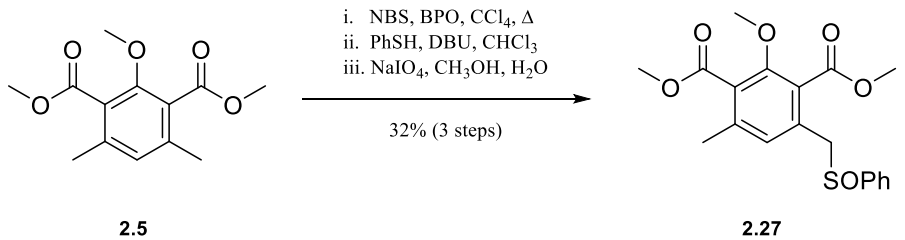
2.4.1 Sulfoxide Formation

With the phthalide already constructed (**2.5**, **Scheme 2.4**), direct installation of the sulfoxide functionality was attempted (**Scheme 2.6**). Previous reports were able to convert fairly unreactive benzylic positions directly into thiophenyl sulfoxides,[13] but in our hands, these conditions resulted in no sulfoxide material (**2.27**) being generated. A less direct method of incorporating the sulfoxide involved installing the thiophenyl ether moiety[14,15] (**2.28**) using diphenyldisulfide, but these conditions showed a similar lack of reactivity with our system.



Scheme 2.6: Attempted mono sulfoxide creation from **2.5**.

A more practical yet longer formation of the sulfoxide proceeded in a manner similar to that reported by Patra.[16] Radical bromination of the symmetrical isophthalate (**2.5**, **Scheme 2.7**) provided a difficult to purify mixture, likely the desired monobrominated material mixed with the dibrominated side product. Thus, the initial bromide was carried forward unpurified. Likewise, the S_N2 displacement of the bromide mixture with thiophenol to the thioether resulted in a mixture and was not purified either. Purification was instead completed after the final step, oxidation of the thioether to the sulfoxide with sodium periodate. This process was reasonably efficient, providing sulfoxide **2.27** in a 32% yield over three steps.



Scheme 2.7: Formation of monosulfoxide **2.27** from phthalide **2.5.**

2.4.2 Unsaturated Ketone Formation

With a suitably activated, mono-functionalized 4-electron donor (**2.27**) in hand, our attention turned to the unsaturated ketone and how to prepare this synthon. If a dicarbonyl containing system were to be used, isomerization of the internal bond occurs[17] (**2.4$_a$** and **2.4$_b$**) because of the chain length (**Figure 2.1**). This enol driven tautomerization could contribute to lower yields, either because of reduced activity or annulation occurring at the unsaturated ester tautomer as opposed to the α,β-unsaturated ketone. To overcome this potential problem, we targeted a protected alcohol (**2.29**) in lieu of the ester with the intention of deprotecting and oxidizing later in the route.

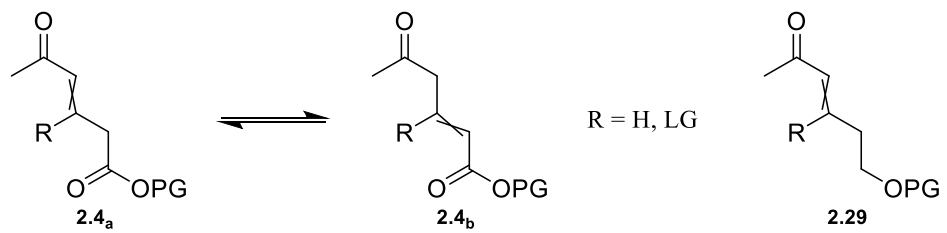
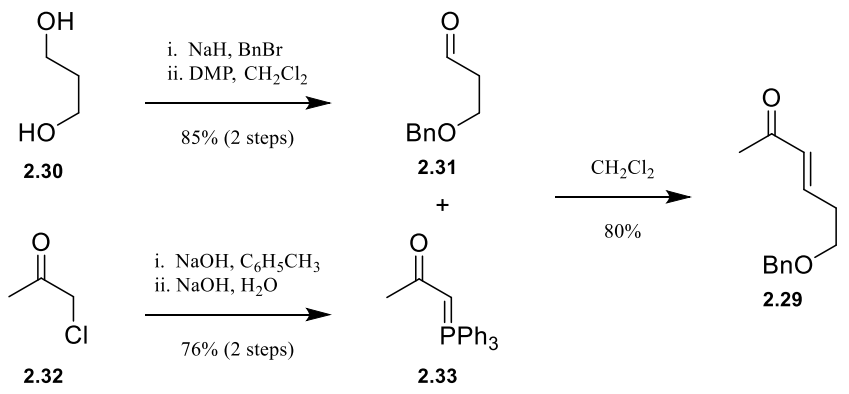


Figure 2.1: Tautomerization of unsaturated ketone **2.4** and its less oxidized partner **2.29**, a potential solution to the resonance problem.

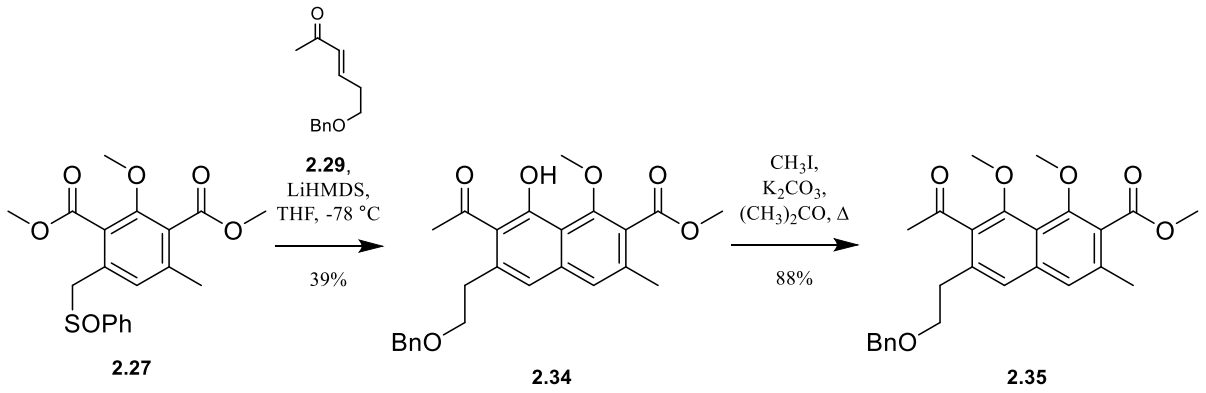
As per the work of Nwabufo and Heuser, protection of a hydroxy group in propane diol[18] (**2.30**, **Scheme 2.8**) as the benzyl ether and the ensuing oxidation[19] led to the aldehyde (**2.31**) in an 85% yield over two steps. Conversion of chloroacetyl chloride (**2.32**) to the ylidene (**2.33**) proceeded in slightly lower yields than previously reported,[20,21] but its Wittig coupling with (**2.31**) proceeded as reported,[22] yielding **2.29**.



Scheme 2.8: formation of unsaturated ketone **2.24**.

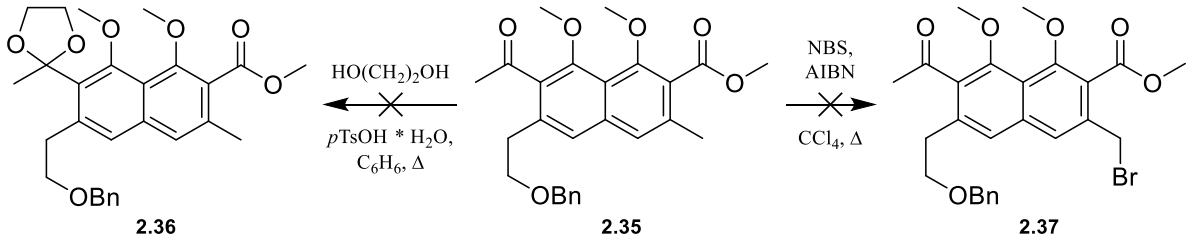
2.5 Hauser-Kraus Annulation AB Ring Formation

With coupling partners in hand, we tested the annulation conditions based on the seminal work of Hauser and colleagues.[23] General reaction procedures call for a slight excess of the unsaturated ketone **2.29** (**Scheme 2.9**), adding this material slowly to a cold solution of the 4-electron unit **2.27** premixed with base. When applied to this system, the annulated product **2.34** was obtained in a 39% yield. Methylation (**2.35**) of the resulting phenol proceeded in an 88% yield (**Scheme 2.9**).



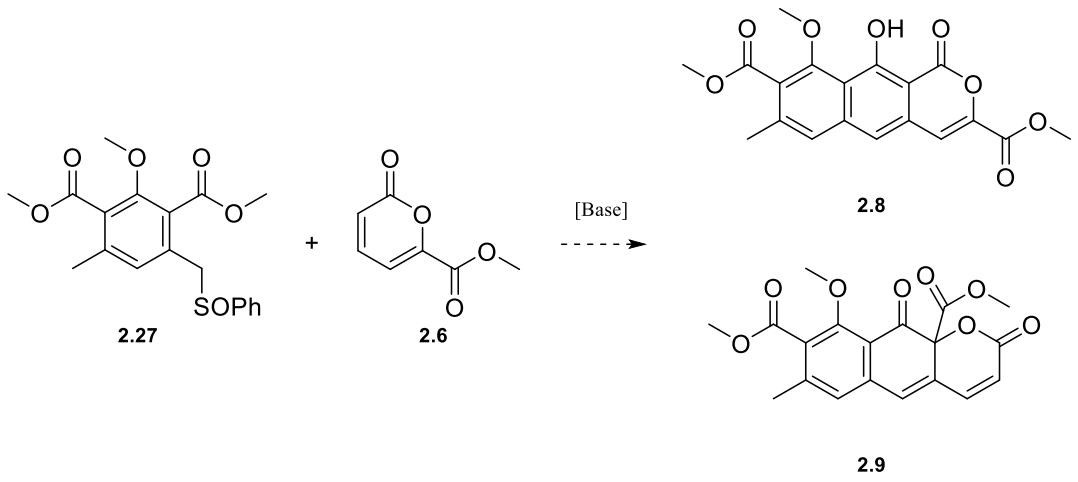
Scheme 2.9: Annulation of unsaturated ketone and methylation of product.

Despite this early success, the bicycle (**2.35**, **Scheme 2.10**) was incapable of being further functionalized. When attempting to protect the external ketone as the dioxolane (**2.36**), the protected intermediate was only generated in 1:8 ratio relative to the starting material, potentially due to steric interference from the neighboring methyl ether and alkyl chain. An alternative strategy sought to brominate the benzylic methyl group (**2.37**), but due to a lack of directing groups and the presence of an additional benzylic carbon, bromination was not chemoselective. Instead, an inseparable mixture of differentially brominated materials was generated.



Scheme 2.10: failed functionalization of the methylated intermediate **2.35.**

Because of this lack of success advancing the completed AB ring into the complete core structure, annulation of a phthalide, such as **2.27** with the methyl ester pyrone moiety (**2.6**) was the next natural approach (**Scheme 2.11**). If successful, this would allow for direct annulation of the intact D ring to the symmetric B ring forming the BCD ring system. Annulation reactions using methyl ester pyrones as Michael acceptors have not been reported, with the most similar substrates being used including cyclohexanone and a partially unsaturated pyrone.[6] Thus, we would need to create chemistry to enable this annulation to proceed and determine if desired product **2.8** was formed or if competing 2-electron units (**2.9**) from the pyrone were also reactive. This process is further discussed in Chapter 3.



Scheme 2.11: Illustration of the next viable annulation pathway utilizing **2.27** instead of **2.5**.

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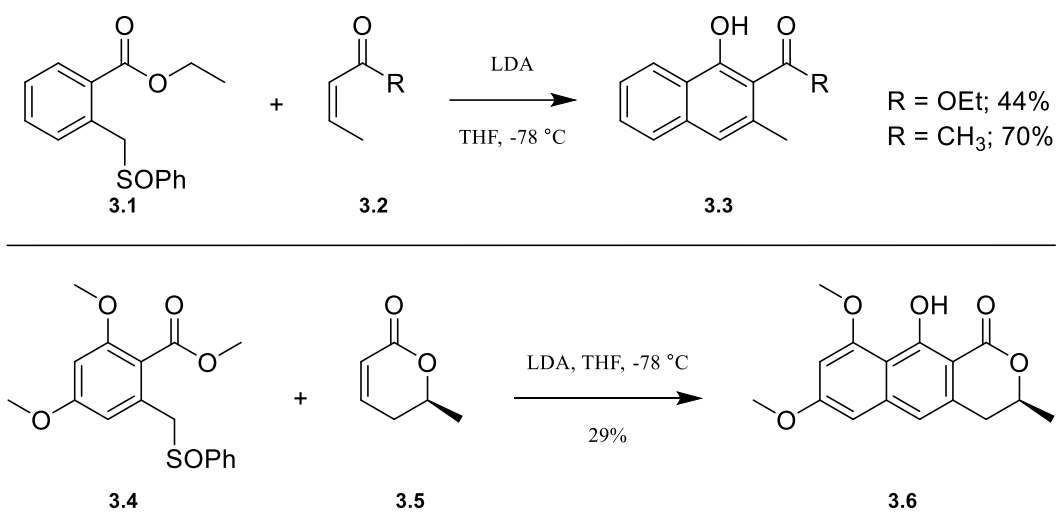
Chapter 3: Regioselective Annulation of 6-Carboxy-Substituted Pyrones as a Two-Carbon Unit in Formal [4 + 2] Cycloaddition Reactions

3.1 Hauser Annulation Precedent

With the initial annulation to the pyrone the most viable route, conditions now needed to be developed. This reaction would enable direct installation of a pyrone moiety into an aromatic system, but its use in Hauser-type annulations has not been reported. The early work of Hauser and Rhee[1] explored utilizing the sulfoxide **3.1** (**Scheme 3.1**) and various unsaturated carbonyl substrates (**3.2)** where an excess of **3.2** was added to the pre-generated anion of **3.1** at -80 °C. Successful yields of **3.3** were reported when both an unsaturated ketone and ester as the 2-electron substrate. Further incorporation of sulfoxides as Hauser donors has been reported using ketones[2-6] as the electron acceptor, with the work of Sperry[7] being closely related to this synthesis. The 2-electron donor **3.5** is fairly similar to that of pyrone, although incorporation of a substrate containing two α,β-unsaturated sites of annulation has not been reported.



Scheme 3.1: Past precedent performed by Hauser and Sperry, respectively, serving as annulation inspiration.

We envisioned directly annulating an intact pyrone to form a polycycle, such as thermorubin, rather than the traditional approach of decorating an aromatic ring and subsequently cyclizing to generate the pyrone. Detractions of the traditional approach are the typical necessity of protecting groups for other substituents on the aromatic ring[8] and harsh conditions[9] or costly metal catalysts[10] to facilitate closure to the pyrone. Regioselective use of an unactivated pyrone as a two-carbon unit in what is formally a [4+2] cycloaddition is scarce, with only the 5-substituted pyrone enabling regio, though not chemo, -selectivity.[11] Other substitution formats resulted in a mixture of diene and dienophile roles for the pyrone and a lack of regioselectivity, especially for 6-substuted pyrones.[12] These findings made it unclear what conditions would enable the successful use of 6-substituted pyrones (**3.7a**) as dienophiles (their use as dienes is known)[13,14] and what substitution pattern would result in the absence of a directing Staunton-Weinreb–type leaving group. Thus, we investigate the parameters that would enable regioselective use of pyrones as dienophiles toward the synthesis of thermorubin.

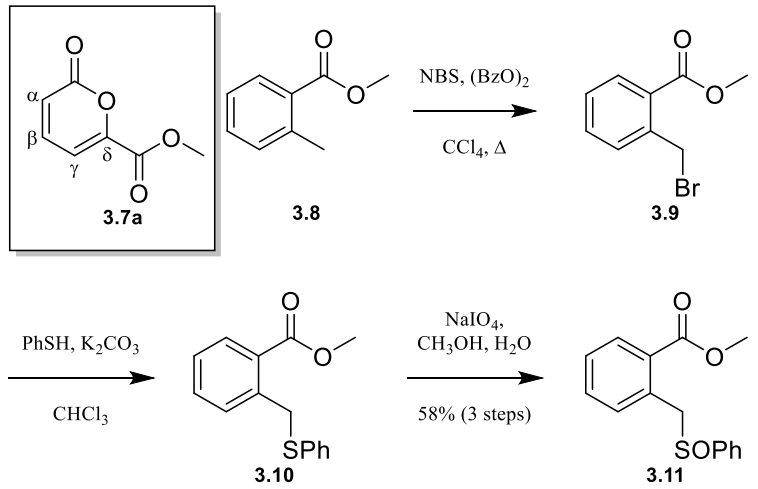
Beyond thermorubin, the pyrone scaffold (**3.7a**, **Scheme 3.2**, *inset*) is an important heterocycle found in various pharmaceuticals and natural products.[15,16] Many ring-forming reactions to establish annulated pyrones exist,[17-19] but all effectively proceeding through esterification to form the lactone. The enforced geometry and aromatic character of the pyrone make it fairly robust, thus its formation could occur early in a synthetic sequence, as we are proposing for thermorubin, rather than as a late step.

3.2 Formation of Annulation Substrates

For the diene portion, several synthons[20] are available that would enable rearomatization after reaction with pyrones, forming either a single phenol *peri* to the pyrone carbonyl or a *p*-hydroquinone. We selected methylbenzoate sulfoxide **3.11** (**Scheme 3.2**)[1] as a representative test

partner that we could prepare from **3.8** via a bromination (**3.9**), thioetherification (**3.10**), and oxidation (**3.11**) sequence[21] in good yield. Annulation of **3.11** with the pyrone diene such as such as **3.7a**, which could be prepared according to literature precedent,[22,23] would provide the functionality pattern present in the thermorubin C-ring.

With a suitable diene-equivalent in hand, the questions to resolve were ones of activity and regiochemistry. We hypothesized that the pyrone would be sufficiently active to react with a diene in either a stepwise or concerted fashion and that the diene would add to the α-β position relative to the pyrone carbonyl, although the structures of pyrones such as **3.7a** (**Scheme 3.2**), which mimics the D-ring of thermorubin, contain an additional site of unsaturatation, the δ position, which is also conjugated to the lactone. The γ position is further activated because of conjugation to the *exo*-ester. However, the enforced *syn* orientation of the pyrone ester makes them strong electron-withdrawing groups, more so than the *exo*-ester, and coupled with cross conjugation from the lactone oxygen, we expected the lactone to dominate, suppressing the electrophilicity of the γ position. Furthermore, if initial attachment of the diene nucleophile has



Scheme 3.2: Hauser annulation substrate **3.7a** (inset) and formation of sulfoxide **3.11**.

any reversibility, addition to the more sterically hindered δ position—which cannot reachieve aromaticity because the intermediate is a quaternary center—would be reversible.

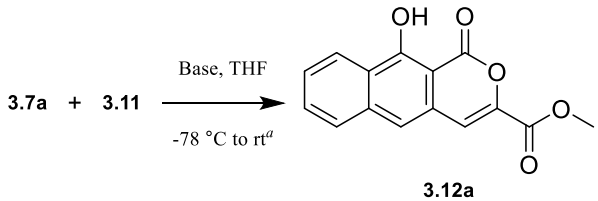
3.3 Optimization of Pyrone Annulation Trials

Our initial trials used sulfoxide **3.11** with methyl ester pyrone **3.7a** (**Scheme 2.2**, prepared in Chapter 2), as their annulation product would be analogous to the BCD ring of thermorubin. To optimize production of annulated product **3.12a** (**Table 3.1**), we began screening conditions based on prior work using sulfoxide **3.11** with α-β unsaturated esters[1,7,24] and ketones.[4,21,25] Initial trials varying the equivalencies of LDA base (entries 1 – 5) showed a decrease in the production of **3.12a** when fewer equivalencies of base were used (entries 1 and 2) and a modest increase with 3.0 equivalents (entry 3). Further increases in the amount of base abolished production of **3.12a** (entries 4 and 5). Reducing the equivalents of pyrone also decreased the yields (entries 6 and 7) while excess (entry 8) or proportionate (entry 9) increases of pyrone relative to base increased the yield. A large increase (entry 10) decreased the yield, likely due to interference by excess base as per entries 4 and 5. Altering the addition order (entries 11– 14) decreased the yield or resulted in no product when the pyrone was mixed with LDA first. Changing the addition temperature and quenching protocol slightly decreased the yield (entry 15). Screening of different bases showed that alkoxides and hydrides were unsuitable (entries 16 – 18) while LiHMDS (entry 19) was essentially as effective of a base as LDA.

While this process enabled initial optimization of this reaction, batch-to-batch variation made comparisons difficult, necessitating a concurrent control reaction. Furthermore, the pyrone **3.7a**, along with separation of the product from other materials proved challenging, significantly slowing progress. Besides the desired product **3.12**, we were able to isolate recovered sulfoxide

3.11 and pyrone **3.7a**, along with a byproduct that showed features similar to the pyrone. Characterization of this material revealed it to be solvolyzed **3.7a**, where methoxide generated during the course of the reaction acted on the pyrone carbonyl to form **3.13** (**Scheme 3.3**, *inset*).

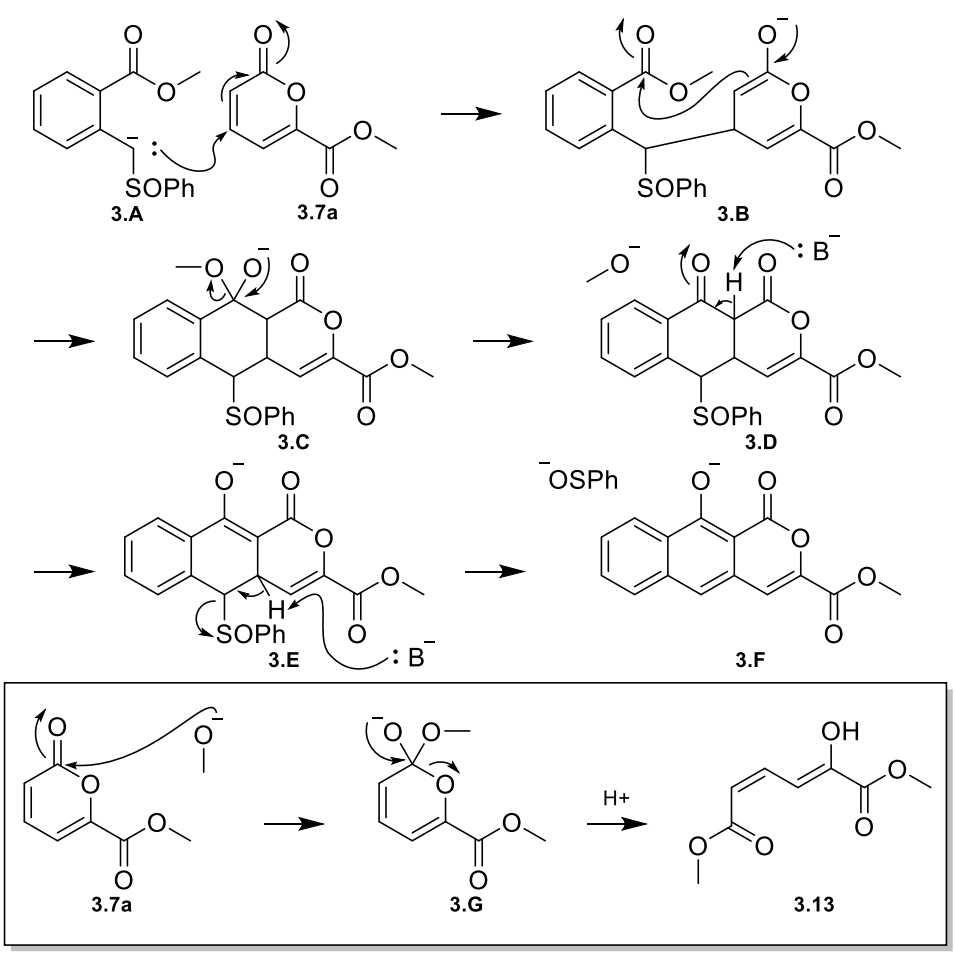
Table 3.1: Optimization conditions for the formartion of tricycle **3.12a**.



Entry	base	base equiv.	pyrone equiv.	% yield
1	LDA	1.1	2.4	28
2	LDA	1.65	2.4	28
3	LDA	3.0	2.4	43
4	LDA	4.4	2.4	<1
5	LDA	8.8	2.4	<1
6	LDA	2.2	1.2	<9
7	LDA	2.2	1.9	<9
8	LDA	2.2	4.8	48
9	LDA	4.4	4.8	47
10	LDA	6.6	7.2	22
11[b]	LDA	2.2	2.4	19
12[c]	LDA	2.2	2.4	17
13[d]	LDA	2.2	2.4	13
14[e]	LDA	2.2	2.4	0
15[f]	LDA	2.2	2.4	26
16	*t*-BuOLi	2.2	2.4	3
17	*t*-BuOK	2.2	2.4	3
18	NaH	2.2	2.4	0
19	LiHMDS	2.2	2.4	27

[a]Sulfoxide **3.11** added to base followed by **3.7a** unless otherwise noted. [b]Addition of base to **3.11** [c]Addition of base to **3.7a** and **3.11**. [d]A premixture of **3.11** and base were added to **3.7a**. [e]Addition of **3.7a** to base followed by **3.11**. [f]Reaction warmed to -40 °C before addition of **3.7a**, quenched at this temperature.

This finding spurred careful analysis of the proposed mechanism (**Scheme 3.3**) to build on the isolated yield data and identify potential pitfalls. Three equivalents of base are needed, one to generate the initial sulfoxide anion (**3.A**), a second to deprotonate C10a of **3.D**, and a third to establish aromaticity by deprotonating C4a and eliminating sulfenate from **3.E**. While the methoxide generated when **3.C** converts into **3.D** would be sufficient to deprotonate C10a, the resulting methanol would be deprotonated by remaining stronger base, and it was unclear if methoxide would be sufficient to cause elimination (**3.E** to **3.F**). The methoxide also reacts with pyrone **3.7a** (*inset*), requiring extra equivalents of this starting material, and the conjugate base



Scheme 3.3: Hauser reaction mechanism with pyrone as **3.7a** as the 2-electron unit. *Inset* degradation of **3.7a** and methanol to form **3.13.**

of **3.13** is certainly not sufficient for elimination. While we were worried that competitive deprotonation of the C5 position in the presence of strong base would interfere with the desired annulation reaction, we were never able to isolate unaromatized byproducts and had good mass balance of the desired product **3.12a** and recovered sulfoxide **3.11**. Three equivalents of base are ideal and necessary, but we found that LDA would also consume pyrone **3.7a**, which prevented high yields through the unwanted reaction of LDA with pyrone.

3.3.1 NMR-Guided Reaction Assessment

To continue optimizing the reaction while avoiding purification difficulties, we employed an NMR-based assessment method in order to quantify yields more rapidly than we could with isolation. By running the reaction through workup, collecting the mass of the dry, impure material, and then adding a known quantity of *o*-xylene as an internal standard to a portion of the product mixture, we could reliably quantify the absolute ratio of each component and easily ascertain how varying conditions affected the yield.

Using this approach, we continued experimentation (**Table 3.2**) with different bases, additives, and equivalents. The use of precedented[1] 2.2 equivalents of LDA as a base gave a modest yield (entry 20) and did not show significant change when DMSO was added as a cosolvent (entry 21). In contrast to the isolated results showing LiHMDS being unsuitable, use of it in this case showed a slight improvement in yield (entry 22). Increasing the equivalents of base increased the yield (entry 23), but additional lithium (entry 24) or its sequestration with 12-crown-4 (entry 25) did not increase yields. Experimentation with other bases showed that LiTMP reduced the yield (entry 26) while use of LiHMDS at three equivalents again improved outcomes, surpassing a 50% yield for the first time (entry 27). Use of other alkali metals as the counterion with the HMDS anion gave product (entries 28 and 29), but in lower yields.

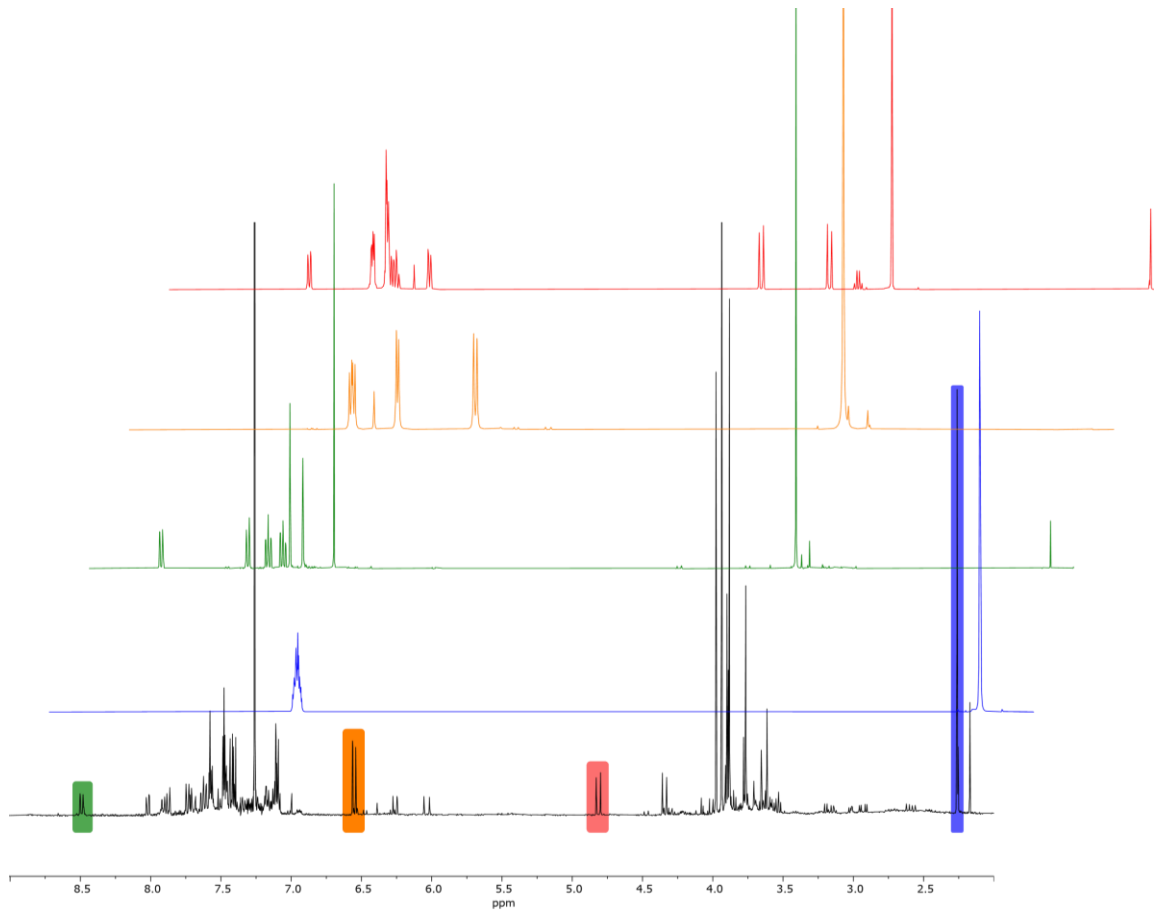
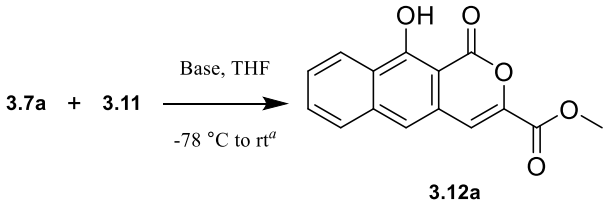


Figure 3.1: Crude NMR comparison. Overlay of sulfoxide **3.11** (red), pyrone **3.7a** (orange), product **3.12a** (green), and *o*-xylene standard (blue) with unpurified reaction (black).

Mirroring the isolation experiments, use of excess LDA and **3.7a** decreased yields (entries 30 and 31), although this decrease could be rescued somewhat by the addition of TMEDA (entry 32). Incubation of LiHMDS with pyrone **3.7a** in the absence of sulfoxide **3.11** revealed that while LDA degraded **3.7a**, LiHMDS did not. Thus, we shifted our focus to LiHMDS. Addition of TMEDA with LiHMDS did not increase yields (entry 33), nor did increased equivalents of LiHMDS (entry 34), though product was observed in this case, unlike with LDA. Premixing LiHMDS with pyrone **3.7a** followed by sulfoxide (**3.11**) addition gave reasonable product formation (entry 35) and increasing the concentration by reducing the amount

Table 3.2: Yield of **3.12a** calculated on addition of internal standard to crude NMR.



entry	base	base equiv.	cosolvent/ additive	% yield
20	LDA	2.2	–	27
21	LDA	2.2	DMSO[b]	30
22	LiHMDS	2.2	–	37
23	LDA	3.0	–	48
24	LDA	3.0	LiCl[c]	34
25	LDA	3.0	12-crown-4[d]	34
26	LiTMP	3.0	–	25
27	LiHMDS	3.0	–	57
28	NaHMDS	3.0	–	21
29	KHMDS	3.0	–	19
30[e]	LDA	4.4	–	34
31[f]	LDA	6.6	–	1
32[e]	LDA	4.4	TMEDA[g]	45
33	LiHMDS	3.0	TMEDA[g]	44
34	LiHMDS	8.0	–	33
35[h]	LiHMDS	3.0	–	48
36[h,i]	LiHMDS	3.0	–	64

[a]Sulfoxide **3.11** added to base followed by 2.4 equiv of pyrone **3.7a** with a final concentration of 0.042 M unless otherwise noted. [b]100 equiv. [c]5.6 equiv. [d]3.0 equiv. [e]4.8 equiv. of **3.7a** used [f]7.2 equiv. of **3.7a** used. [g]3.3 equiv. [h]Sulfoxide added to base and **3.7a** [i]Concentration increased 1.8-fold

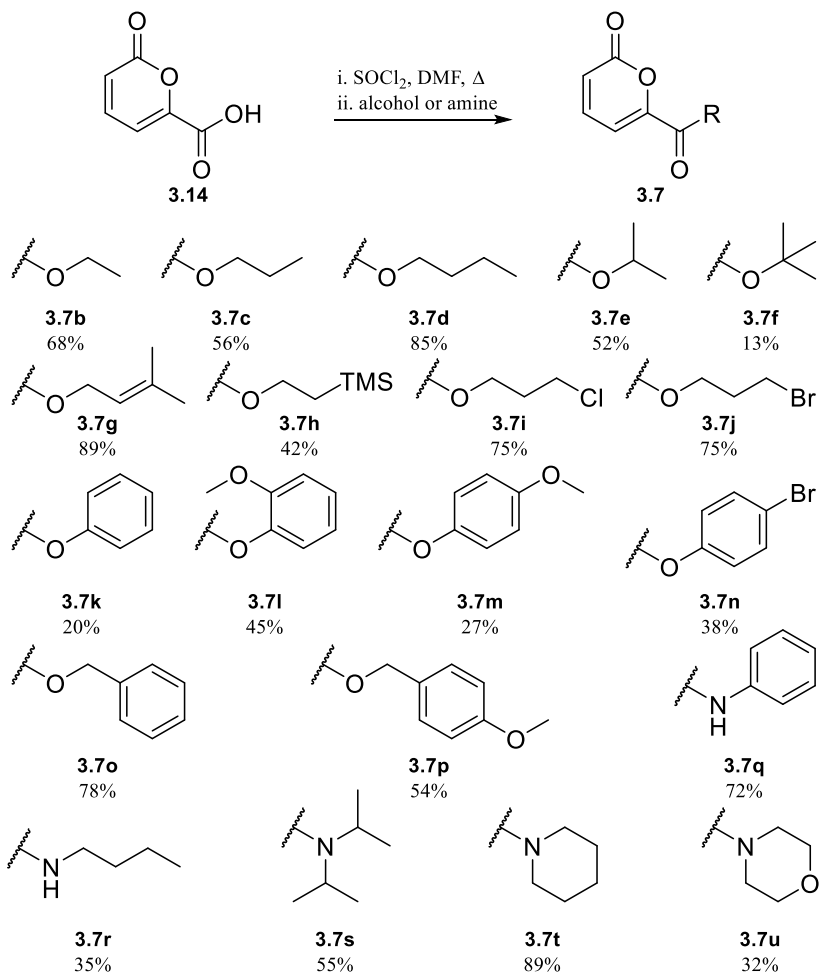
of solvent used to dissolve sulfoxide **3.11** and prepare the base (entry 36) gave a good yield. We believe this highest yield results from a combination of less water contamination during the dissolution of sulfoxide **3.11** and more available base to quickly push the intermediates, especially **3.E** (**Scheme 3.3**) through the elimination. With optimized conditions in hand, we

proceeded to isolate the products of the reaction and were pleased to find we could synthesize **3.12a** in a 53% isolated yield.

3.4 Formation of Various Pyrone Esters and Amides

Besides using these conditions for the total synthesis of thermorubin, we sought to explore the generality of this reaction using **3.11** and other pyrone derivatives. Other pyrone esters could be made from **3.14** (**Scheme 3.4**) in an analogous manner to **3.7a**. Generation of alkyl esters **3.7b** – **3.7f** by reaction of the acid chloride with the corresponding alcohol generally

Scheme 3.4: Generation of various pyrone esters and amides **3.7b – 3.7u**.



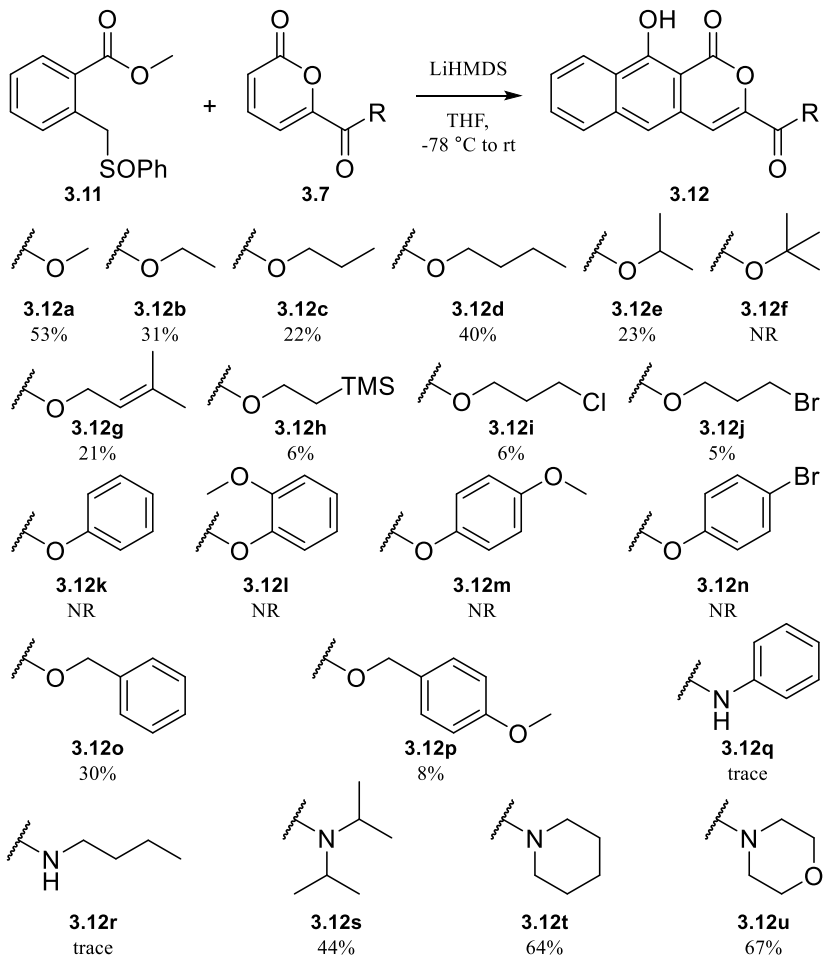
proceeded well, except with sterically bulky *tert*-butanol, as did alkene (**3.7g**), silyl (**3.7h**), and halogen (**3.7i** and **3.7k**) containing materials. Aryl (**3.7k** – **3.7n**) and aryl-containing (**3.7o** and **3.7p**) esters were also synthesized in reasonable yields. Addition of primary and secondary amines to the acid chloride of **3.14** in place of alcohols furnished the corresponding secondary aromatic (**3.7q**) and aliphatic (**3.7r**) amides as well as tertiary amides **3.7s** – **3.7u**.

3.5 Incorporating Pyrone Derivatives into Cycloaddition Reaction

Application of the optimized annulation conditions to alkyl pyrone esters was generally effective, furnishing **3.12a-u** (**Scheme 3.5**) in 22-53% isolated yields. The more sterically hindered *tert*-butyl pyrone **3.7f** did not react. Lower yields resulted from difficulties with chromatographic separation of the naphthyl-pyrones from closely eluting byproducts, an issue compounded by their low solubility in most organic solvents. Transesterification also complicated purification. The equivalent of methoxy produced upon reaction of the pyrone enolate with the sulfoxide (**Scheme 3.3**, **3.B** to **3.D**) in some cases reacted with the desired annulated products (**3.12k-p**), converting them into **3.12a**. These could be separated by HPLC, but yields suffered accordingly. Despite formation of this unwanted product, a variety of functional groups including an exogenous alkene (**3.12g**), a silyl group (**3.12h**), and halogens (**3.12i** and **3.12j**) proceeded through annulation, though required HPLC purification. For aryl esters, no appreciable amount of **3.12k** – **3.12n** could be isolated, presumably due to transesterification. Aromatic ester functionality in the form of benzyl esters worked, but products **3.12o** and **3.12p** required HPLC purification to separate them from **3.12a**. Production of secondary amide products **3.12q** and **3.12r** was detected, but due to deprotonation of the nitrogen and corresponding consumption of needed base, low yields precluded isolation and characterization, a problem that could conceivably be overcome by protection. Tertiary amides

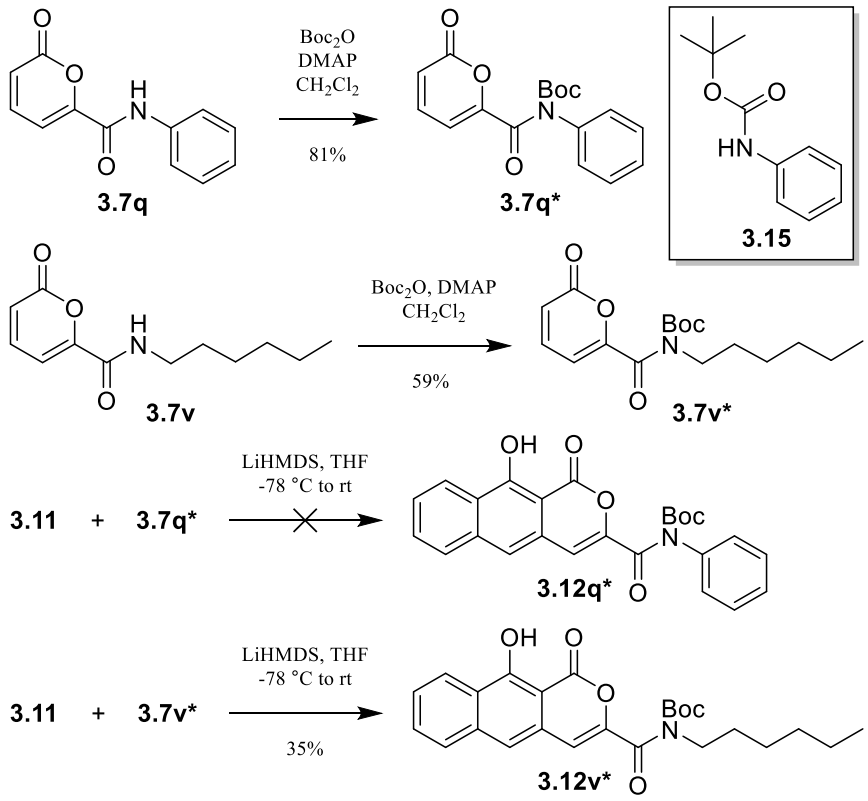
performed well (**3.12s** – **3.12u**) with yields equivalent to that of the optimized methyl ester. These results show that pyrones with a variety C6 carbonyl substitution are tolerated as dienophiles using this annulation approach.

Scheme 3.5: Isolated annulation yields with various pyrones.



To investigate issues around low yielding annulations and gain additional insight into reaction scope, protected pyrones and additional sulfoxide variants were prepared. A BOC-protected analog (**3.7q***, **Scheme 3.6**) of aniline amide **3.7q** was prepared, as was the BOC-protected variant (**3.7v***) of the secondary hexyl amide **3.7v**, an alkyl amide analogous to **3.7r** selected because of its larger size. Unexpectedly, **3.7q*** did not annulate. In this reaction, pyrone **3.7q*** was completely consumed and BOC-protected aniline[26] (**3.15**, *inset*) was isolated.

This result stems from the stability of **3.15** as a leaving group; with an effective pKa of ~10, LiHMDS reacts with **3.7q***, similar to the decomposition of **3.7a** observed with LDA. In the case of protected alkyl amide **3.7v*** however, the expected product **3.12v** was obtained.

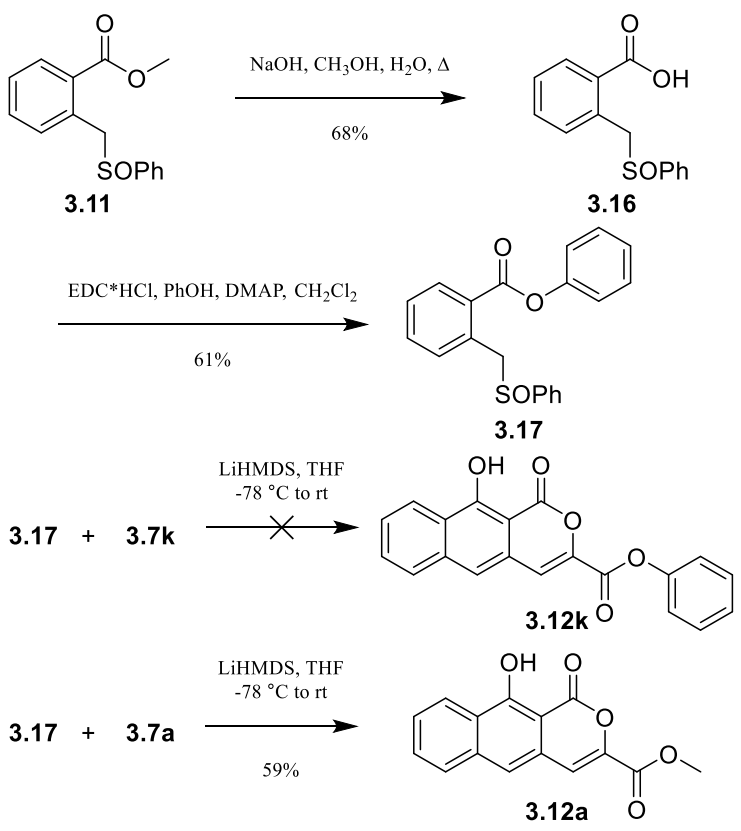


Scheme 3.6: Scope of protected pyrone amide annulation using aniline **3.7q*** and hexylamide **3.7v***.

3.6 Scope of the 4-Electron Unit

To test if transesterification could be suppressed by matching the leaving group of the sulfoxide ester with the esters of pyrones **3.11k** – **3.11n**, we prepared an alternative sulfoxide, swapping a phenyl ester (**3.17**, **Scheme 3.7**) for the methyl ester of **3.11**. This was accomplished by hydrolyzing **3.11** to its acid (**3.16**) and subsequently using peptide coupling conditions with phenol to create **3.17**. Reaction of **3.17** with **3.11k** under annulation conditions did not produce

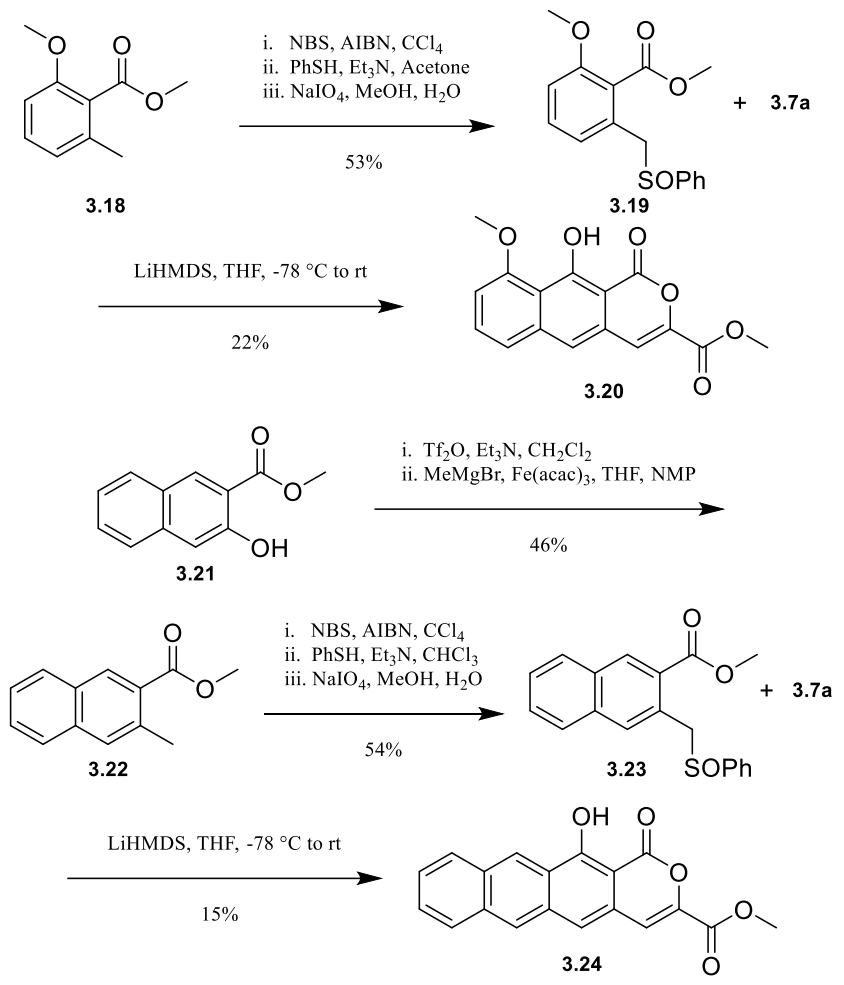
3.12k. Starting sulfoxide **3.17** was recovered while **3.7k** was not. Combined with the findings from BOC-protected pyrone variant **3.11q***, the inability of **3.7k** to annulate suggests a sufficiently labile leaving group off the C6' carbaldehyde precludes successful annulation; the base instead degrades the pyrone. However, a control reaction, where **3.17** was reacted with **3.7a**, produced **3.12a** in the highest isolated yield along with recovered **3.7a**. This result shows that generating and using the more costly phenyl ester (**3.17**) instead of **3.11**—which produces the less basic phenolate ion in lieu of the methoxide during **C** to **D** (**Figure 3.2**)—increases yields by suppressing unwanted reactions resulting from free methoxide, such as transesterification and ring-opening of **3.7a** to **3.13**.



Scheme 3.7: Attempted sulfoxide phenyl ester **3.17** with phenyl ester pyrone **3.7k** and methyl ester **3.7a.**

The α-pyrone was also tested in the annulation reaction, but poor solubility and similar polarity profiles of the resulting compounds prevented complete separation and characterization. Two major masses consistent with product were identified from the purified reaction mixture, suggesting that in the absence of C6-substitution to enforce regiochemistry, annulation can occur at either the α-β or γ-δ positions. A quaternary carbon also appears to be necessary off of the C6 position. When tested, 2,3-dimethyl-4*H*-pyran-4-one did not undergo annulation, likely because competitive deprotonation of the methyl group which is made acidic due to conjugation with the ester.

To assess the applicability of this method toward thermorubin production, we sought to use ring systems more applicable to the natural product in the annulation with **3.7a** (**Scheme 3.8**). Application of a radical bromination, thioetherification, oxidation sequence[21] to methoxy benzoate **3.18**, as was used to produce **3.11**, gave sulfoxide **3.19** in good yield. Annulation with **3.19** furnished **3.7a** in a 22% yield. To test a complete ring system, hydroxynaphthoate **3.21** was activated as the triflate and nucleophilic aromatic substitution with methylmagnesium bromide produced **3.22**, a naphthalene analogous to methyl toluate **3.8** and methoxy-containing material **3.18**. Application of an identical radical bromination, thioetherification, oxidation sequence[21] gave naphthoate sulfoxide **3.23** in good yield. Use of **3.23** with **3.71** under reaction conditions optimized for **3.11** yielded anthracenepyrone **3.24**. These results successfully demonstrate that functionalized and larger ring systems are achievable using pyrone dienophiles. However, the yield in these cases was low, indicating that optimization will be required for this step during the natural product campaign.



Scheme 3.8: Sulfoxide derivative annulation scope.

Despite their extensive presence in drugs and natural products, the synthesis of fused heterocycles is a challenging process that would benefit from additional methods for their formation. Here, we show that instead of creating an annulated pyrone from suitably functionalized aromatics[18,27,28] it is possible to anneal this intact heterocycle onto existing rings in the absence of guiding[29] functionality. This annulation is selective for the α,β double bond of the pyrone when a carbonyl is present at the C6 position. The presence of the electron-withdrawing carbonyl at the δ position did not affect regiochemistry, likely because of cross

conjugation from the pyrone ring oxygen diminishing the electron-withdrawing effect of the *exo*-ester and the enforced *syn* geometry of the pyrone enhancing its electron withdrawing ability. While acidity issues prevented us from conclusively demonstrating annulation with alkyl substituents at C6, it is likely this same regioselectivity would be observed with this substitution in other reactions when milder base can be used or the C6 substituent is quaternary. When only a hydrogen was present at C6, however, rearomatization after attachment to the γ-δ position was enabled and a mixture of both regioisomers was observed. Conversion of methyl ester sulfoxide diene surrogates to their corresponding phenyl esters reduced the impact of deleterious side reactions involving liberated methoxide. A substituted and polycyclic sulfoxide were also suitable reactants.

These successful annulations with pyrones containing C6-carbonyl groups proves that this moiety is efficient as a selective dienophile in sulfoxide-type annulation to generate polycycles and may be suitable in other cycloaddition reactions. This method shows that intact pyrone rings can be incorporated into more complex systems. Application of a symmetrical B intermediate and its subsequent ring building applications towards the synthesis of thermorubin is discussed further in Chapter 4.

3.7 References

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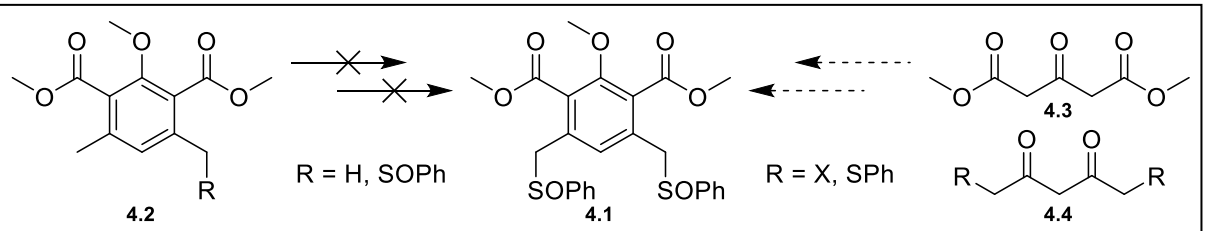
Chapter 4: Optimized Annulation Conditions and Bis Sulfoxide Annulations

4.1 Implementing Optimized Annulation Conditions

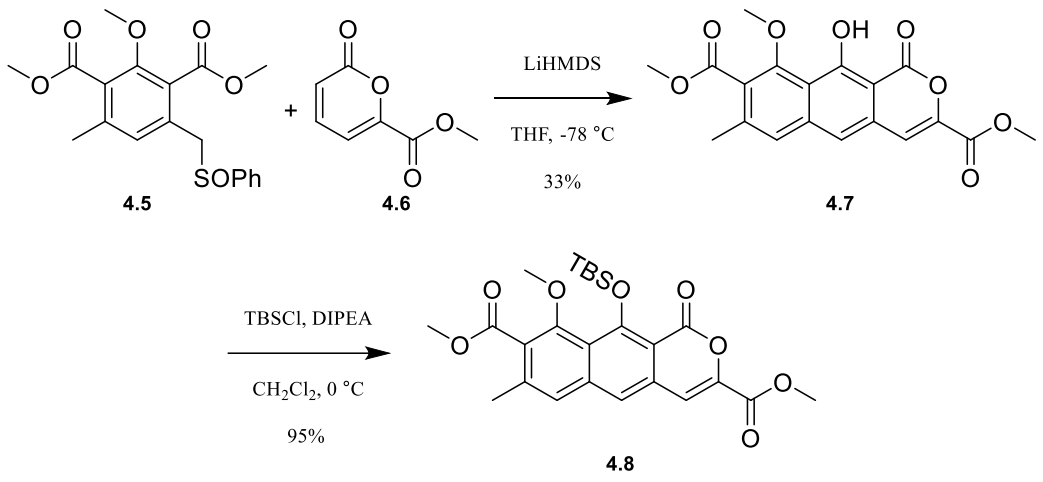
With the successful demonstration of pyrones as 2-electron units in annulation reactions, especially to **3.20** and **3.24 (Scheme 3.8**) as simplified analogs of the thermorubin BCD and ABCD rings, respectively, our attention turned back to completing the authentic ABCD scaffold. Because selective installation of functionality along the annulated AB ring system (**2.34**, **Scheme 2.9**) was unsuccessful, our focus turned to annulating derivatives of the symmetric B ring with pyrone to first complete the BCD system. Initial work had shown that use of unactivated **4.2** (R = H) was unsuitable, but derivatives similar to this intermediate could potentially be used. The most likely candidates were monosulfoxide **4.2** (R = SOPh) or disulfoxide **4.1**. Regioselective installation of the sulfoxide groups for **4.1** could be installed by 1) modification of the mono sulfoxide or isophthalate material (**4.2**) directly or 2) simultaneous installation of both electron withdrawing groups (**4.4**) before cyclization with **4.3** — or convertible surrogates — during construction of the symmetric B ring. It was unclear which approach would be more efficient. Disulfoxide **4.1** may suffer from overannualtion problems while **4.2** would not, but **4.1** has the advantage of avoiding late-stage installation of a critical electron-withdrawing group.

Initial efforts focused on using the monosulfoxide as this material had been used successfully for annulations in the past to form the AB ring (**Scheme 2.9**). Annnulation of **4.5** with pyrone **4.6**



Scheme 4.1: Previously attempted functionalization (left) and new cyclization approach (right).

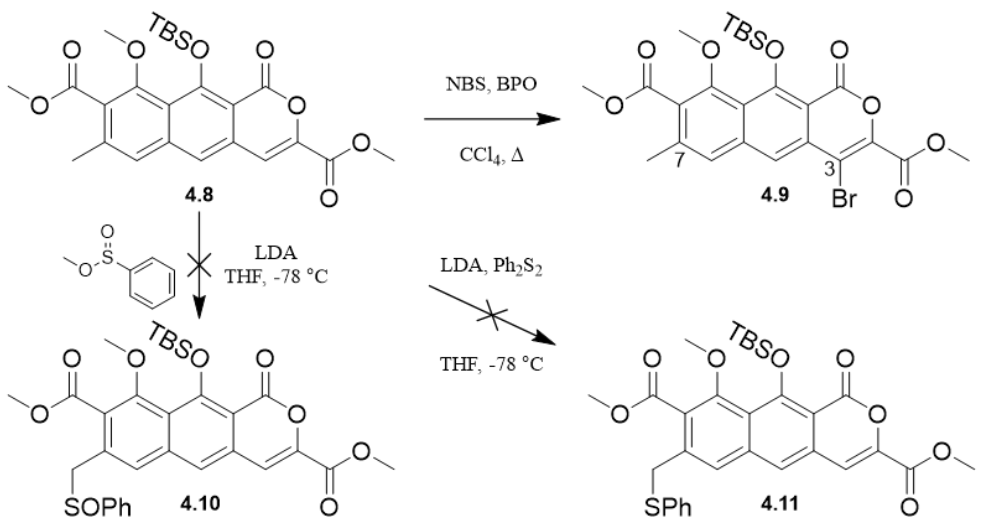
under the optimized conditions discussed in chapter 3 included adding the 4-electron donor **4.5** to a solution of LiHMDS and **4.6,** which furnished **4.7** in a 33% yield. The annulated material was protected as the silyl ether (**4.8**).



Scheme 4.2: Optimized annulation conditions from Chapter 3 applied to mono sulfoxide **4.5** and subsequent protection of produced phenol.

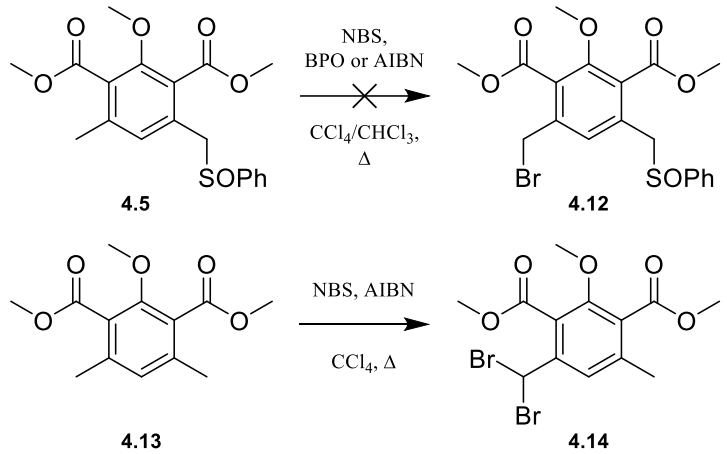
4.2 Unsuccessful Modification of the Annulated Material

Several attempts were made to activate the C7 benzylic position of **4.8** (**Scheme 4.3**) to carry this material forward through the A-ring annulation. Conditions identical to those conducted on the symmetrical phthalide were performed first. While halogenation was successful, it was not regioselective, with the EAS material **4.9** being generated and conclusively identified by ^{1}H NMR as occurring at the C3 position.[1] Direct sulfonylation (**4.10**) and sulfinylation (**4.11**) were also attempted. Generation of the carbanion was possible as indicated by the bright color change of the reaction mixture after addition of LDA, but both diphenyldisulfide and methyl benzenesulfinate proved to be poor electrophiles and none of the desired products were detected.



Scheme 4.3: Attempted functionalization of annulated intermediate **4.8.**

With direct conversion of previously constructed BCD rings to activated sulfoxides not possible, our focus shifted to the synthesis and use of di-activated B-rings. Modification of the previously generated monosulfoxide material **4.5** (**Scheme 4.4**) was initially attempted. Due to the presence of the sulfoxide electron withdrawing group on a benzylic position, there was concern that conditions to generate the benzylic anion on the benzylic methyl carbon would be outcompeted by reaction at the methylene. Various bromination conditions were attempted but did not result in regioselective brominated product **4.12**. Dibromination of the initial phthalide



Scheme 4.4: Attempted functionalization of mono sulfoxide **4.12** and its phthalide precursor.

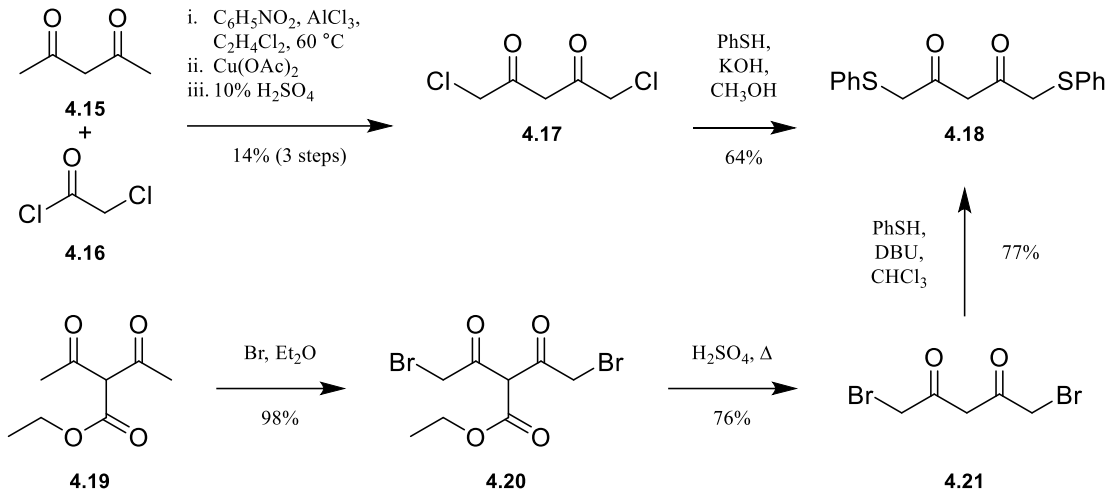
4.13 was also attempted, but use of two or more equivalents of brominating agent only resulted in dibromination at one of the benzylic positions (**4.14**), likely because the same electron-withdrawing effect was in play.

4.3 Preemptive Installation of Halogens

To circumvent this problem, we sought to install groups on the diketone before cyclization that were suitable for eventual conversion to the bis-sulfoxide. This approach would solve the problem of selective halogenation as installation would already have been achieved prior to cyclization. To achieve this goal directly would require simultaneous halogenation of acetylacetone (**4.15**, **Scheme 4.5**), which has not been reported; however, various precedents have been used to create the 1,5-dichloro[2] (**4.17**) and dibromo[3] (**4.21**) acetylacetone through other means. These would serve as the new foundation for formation of the symmetrical bis-sulfoxide material with halogens already installed at the benzylic positions.

Formation of 1,5-dicholoro acetylacetone (**4.17**) was first attempted[4] from acetylacetone (**4.15**) and chloroacetyl chloride (**4.16**). The precedented separation of the product involved complexing it as a copper salt, with further adaptations using distillation. While the copper salt was successfully formed, its separation was never completely successful. It always required further purification via flash chromatography; attempts at distillation resulted in a charred black material despite reports of an unreproducable high yield.[4] The small amounts of **4.17** provided material for initial testing, but a more reliable route was sought using the dibromo analogue. Dibromination (**4.20**) of ethyl diacetoacetate (**4.19**) proceeded as reported,[5] as did subsequent decarboxylation to **4.21**. Displacement of the bromides with thiophenol resulted in the dithiophenylether acetylacetone (**4.18**). This pathway required more steps to acquire the product but produced **4.18** in a higher yield overall compared to the dichloro pathway. The dithiophenyl

ether **4.18** was also obtained from the dichloro species **4.17**, albeit in lower yields, in part due to difficult isolation of this precursor.

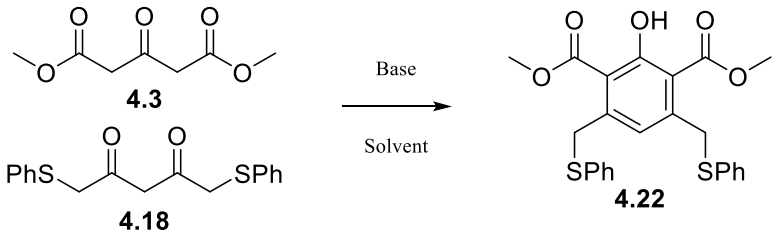


Scheme 4.5: Formation of the di halogenated diones **4.17** and **4.21** and their following conversion into the dithiophenyl ether **4.18**.

4.4 Optimization of Bisthiophenyl Ether Cyclization

With an efficient route to disubstituted acetoacetone in hand, our attention turned to cyclization of this material into the B-ring. The original precedent for cyclization specifically utilized unsubstituted acetylacetone molecules for cyclization with oxoglutarate. In this work, it was observed that more sterically hindered acetylacetone moieties will participate in the cyclization reaction, albeit in poor yields.[6] This decrease in yield was observed in the reaction of **4.3** with **4.18** (**Table 4.1**, Entry 1), compared to a yield of 86% when the unsubstituted acetylacetone was used (See **Scheme 2.4**). Increasing equivalencies of base resulted in a lower yield (Entry 2) and an additional hour of reflux in these conditions seemed to have no impact (Entry 3). Increasing reaction time to 13 days seemed to promote the highest amount of product formation with the smallest amount of base (Entry 4). Deprotonation of the diketone intermediate led to the formation of an enolate salt that was not soluble in methanol, and it is thought that

Table 4.1: Optimization of cyclization conditions to form **4.23**.



Entry	Base	Solvent	Equiv.	Time	% yield
1	$NaOH_{(aq)}$	CH_3OH	0.5	48	40
2	$NaOH_{(aq)}$	CH_3OH	1.0[a]	48	32
3	$NaOH_{(aq)}$	CH_3OH	1.0	25[b]	33
4	$NaOH_{(aq)}$	CH_3OH	0.1	312	36
5	$NaOH_{(aq)}$	CH_3OH	1.0	312	13
6	$NaOH_{(s)}$	CH_3OH	0.1	48	45
7	$NaOH_{(s)}$	CH_3OH	1.0[a]	48	26
8	$NaOH_{(s)}$	CH_3OH	1.0[a]	48[c]	0
9	Na	CH_3OH	1.0	120	35
10	Na	CH_3OH	1.1	80	40
11	NaH	THF	1.1	60	10
12	TEA	CH_3CN	3.0	72	40
13	DBU	CH_3CN	1.5	12	26
14	TMP	CH_3CN	1.5	12	25

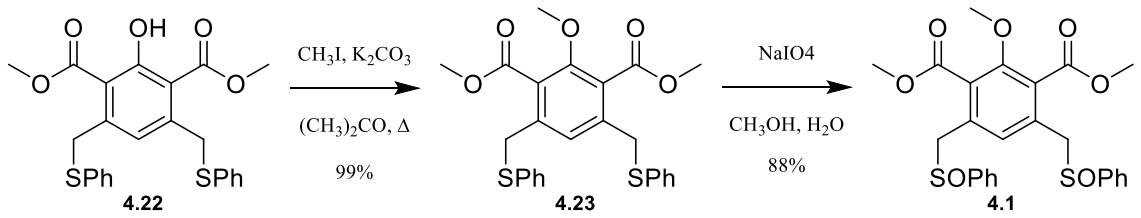
[a]Additional 1/2 equiv. of base added halfway through reaction; [b]Refluxed for 1 hr; [c]Refluxed for 24 hr.

precipitation of this salt is responsible for the lower than 50% isolated yields, as illustrated by the time trials Entries 4 and 5. Removing water by adding solid NaOH promoted formation of the product, which is surprising for the enolate salt would be less soluble in an anhydrous methanolic system. Trials using solid NaOH (Entries 6-8) as opposed to an aqueous 1 M solution also produced more product when less equivalencies were used. In anhydrous conditions, product formation was highest with 1.1 equivalencies of sodium (Entry 10) being optimal compared to an

equimolar amount (entry 9). Other reactions conditions were attempted using different solvents and bases (Entries 11-14) but were not as high-yielding as the sodium-mediated reactions.

4.5 Bisphenylsulfoxide Construction and Implementation in Annulation

Thus, synthesis of bisphenylsulfoxide **4.24** was scaled up using reaction conditions established with earlier systems (**Scheme 4.6**). Phenol **4.22** was methylated under basic conditions[7] in a 99% yield. Oxidation of the thioether moieties **4.23** proceeded with 2.5 equivalencies of sodium periodate to obtain key bis sulfoxide **4.1**. It should be noted that when only two equivalents of oxidant were used, the mono sulfoxide was isolated. Selective formation of the mono sulfoxide was not desired, however, its fortuitous isolation and use are further discussed in Chapter 5.

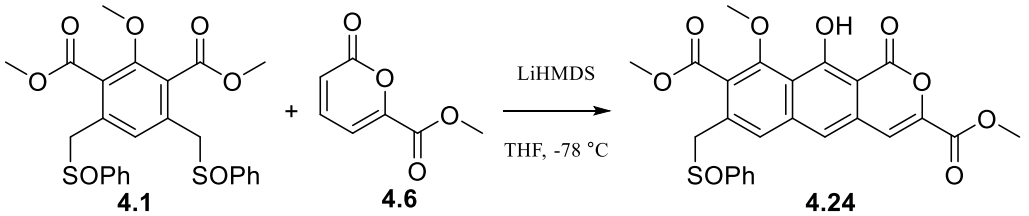


Scheme 4.6: Formation of the bis sulfoxide intermediate.

As per our findings in Chapter 3,[8] it was clear that reactions of pyrone with **4.24** would require optimization. We started with the optimized pyrone reaction conditions previously established but when applied to this system, the product was only obtained in 19% yield (**Table 4.2**, Entry 1). Using less equivalencies of base and pyrone resulted in lower yields (Entries 2-4), as the mechanism would not proceed without additional base present (see **Chapter 3, Scheme 3.3**). A time trial letting the reaction run for an additional 11 hours (Entry 5) did not improve yields. Increasing the amount of pyrone and base appeared to help product formation (Entries 6 and 7), as some of its degradation could be overcome by having an excess present, although this

increase was only slight. Excess equivalencies of base with less pyrone appeared to produce the same amount of product (Entry 7). The best results were obtained when 4 equivalencies of base and 2.4 of pyrone were used giving a 32% yield. Four equivalents of base are likely required because the other methylene is a fourth basic center that must be deprotonated during the reaction. While an additional equivalent of base may be required to deprotonate the additional methylene, its di-anionic characteristics does not react with additional pyrone as no di-addition product was detected.

Table 4.2: Optimization of bis sulfoxide annulation with methyl ester pyrone.

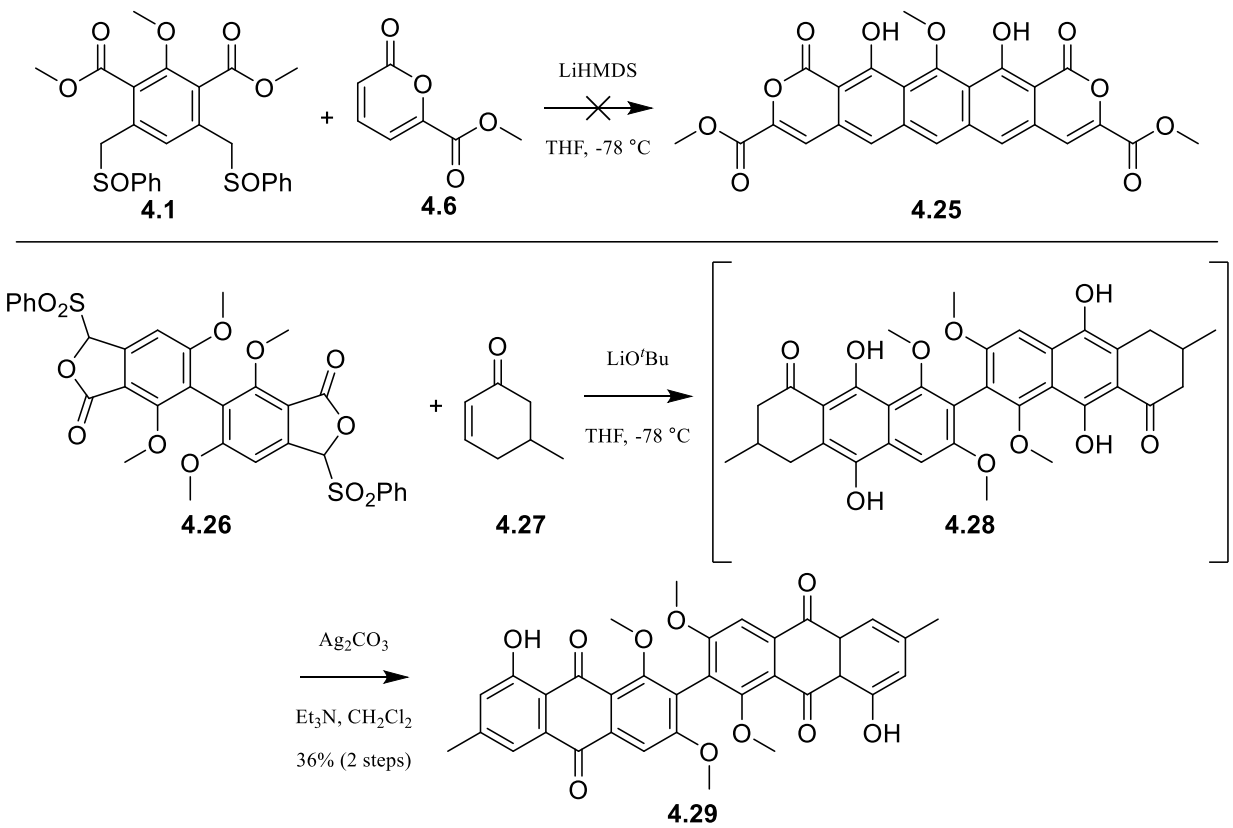


Entry	Base Equiv.	Pyrone Equiv.	Time	% yield
1[a]	3.0	2.4	1	19
2	1.5	1.1	1	0
3	2.5	1.1	1	18
4	3.0	1.1	12	12
5	3.0	2.0	1	23
6	3.1	1.8	1	17
7	4.0	2.4	12	32

[a]Order of additions as reported in Chapter 3: pyrone **4.6** is added to a solution of THF cooled to -78 °C using a dry ice/acetone bath, follwed by addition of LiHMDS and **4.25** dissolved in THF.

Curiously, the formation of the diannulated material was never observed. Mechanistically, at least 3 equivalancies of base are required to fully form the desired annulated product, and with the presence of an additional site for deprotonation, the additional base could potentially form some di-annulated material (**4.29**, **Scheme 4.7**). Diannulations of this type have been reported, albeit with their own distinctions that may limit the formation of byproduct in our

circumstances. The work done by Hauser on the synthesis of biphyscion illustrates diannulation,[9] utilizing sulfone functionality (**4.26**) to activate the benzylic positions. These annulated systems are also non-conjugated, separate, aromatic systems, connect by a covalent bond. That both react to form **4.28**, while our annulation would have annulations occur on the same aromatic system. The inability to simultaneously deprotonate at both sites may prevent both from reacting within the same aromatic system.



Scheme 4.7: Possible pentacycle **4.25** byproduct from over addition of base during the first annulation; previously reported diannulation to create intermediate **4.28** on the pathway to biphyscion.

The resulting annulation optimization campaign starting with sulfoxide **3.11** has led to the formation of the key intermediate **4.24**, with production of **2.20** and **2.24** providing further evidence into the applicability of this annulation. These results offer a promising route towards

not only thermorubin, but potential derivatives that could be formed utilizing addition of differently substituted moieties. Further research will explore the incorporation of the unsaturated ketone in the annulation with protected phenol **4.26** and further reactions towards the total synthetic target.

4.6 References

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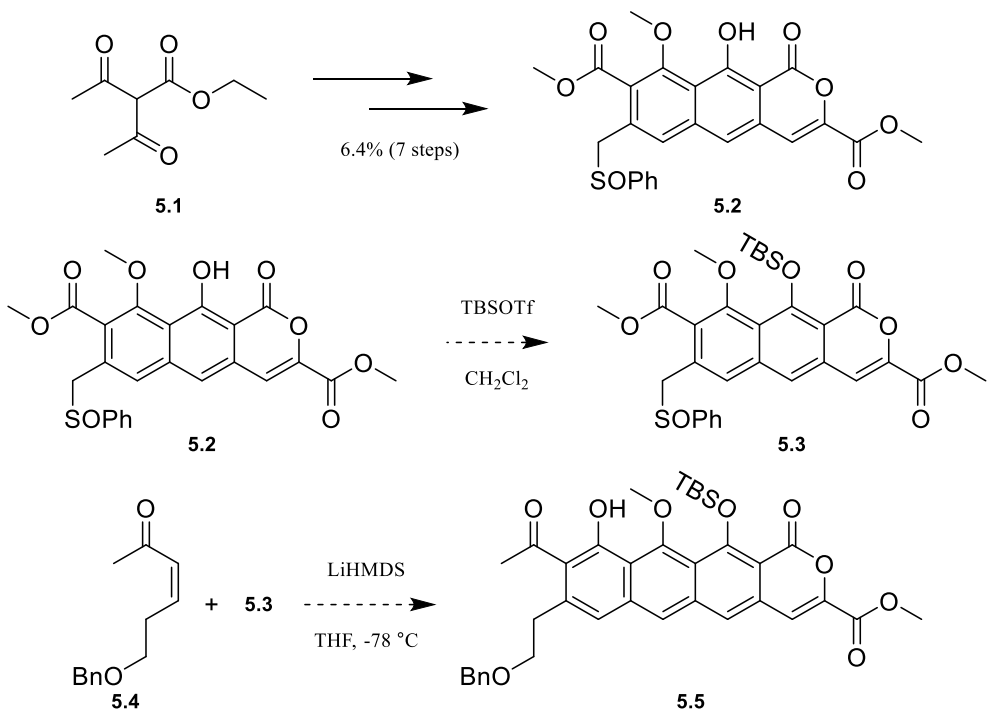
Chapter 5: Conclusion and Future Directions

5.1 Successful Annulation and Finishing the Total Synthesis

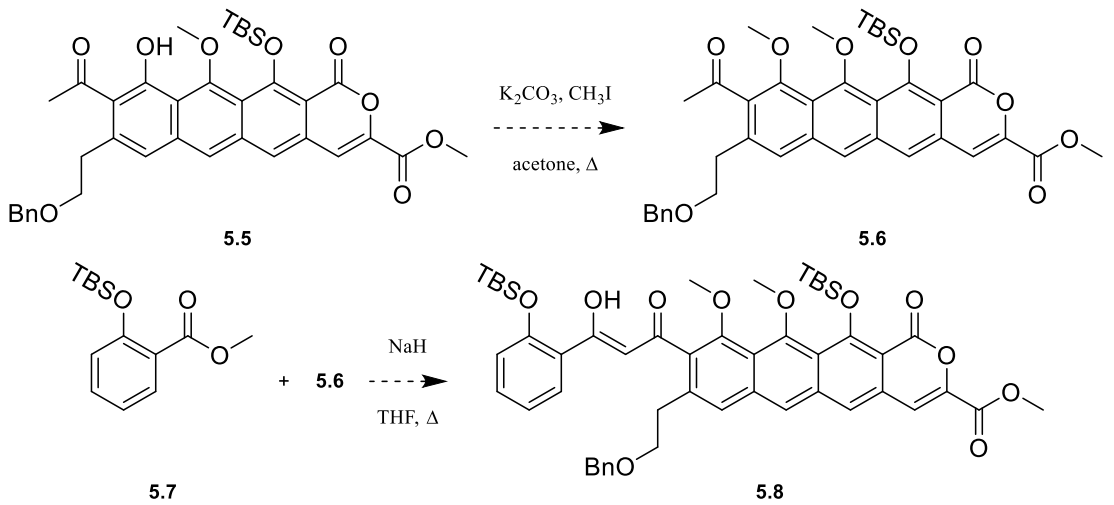
The use of an unprecedented two electron substrate, 6-methoxy-2 -pyrone carboxylate, in a Hauser-type annulation enabled incorporation of the pyrone moiety in one step (Chapter 3, **Table 3.2**). Starting from ethyl diacetoacetate (**5.1**), this process was applied for the construction of the BCD ring of thermorubin **5.2**, which proceeded in a 6.4% yield over seven steps (**Scheme 5.1**, as per previous synthetic work; Chapter 4, **Scheme 4.5-6**, **Table 4.2**). Further steps will need to be taken to optimize this annulation, but formation of intermediate **5.2** is crucial in the next annulation step. Other steps in the pathway, such as the decarboxylation and cyclization steps forming **4.22** and **4.23**, respectively (**Scheme 4.5**, **Table 4.1**), could also see improvement in their yields. The generated phenol **5.2**, once protected as the TBS ether (**5.3**), or conceivably another ether, can undergo annulation with unsaturated ketone **5.4** under similar conditions to



Scheme 5.1: Current progress and expected route towards the tetracycle **5.5**.

yield the tetracycle **5.5** over two steps.

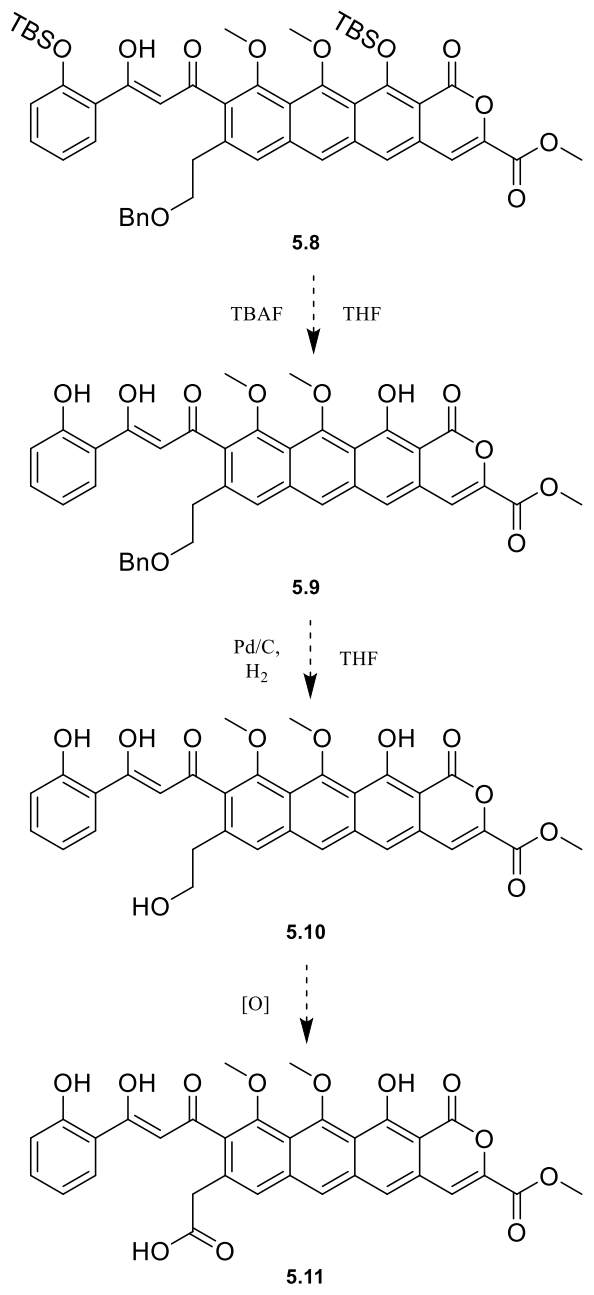
The tetracycle **5.5** will allow for some slight changes in the forward pathway, depending on any unforeseen difficulties (**Scheme 5.2**). The first proposed pathway involves methylation of the generated tetracycle (**5.6**) under previously used conditions followed by addition of the salicylate moiety as the protected phenol **5.7**. A Claisen addition would provide the means for salicylate addition, resulting in the complete ABCDE carbon skeleton of thermorubin (**5.8**). Multiple reaction conditions will be attempted to complete the Claisen addition, starting with commonly reported NaH mediated acylation.



Scheme 5.2: Addition of protected salicylate moiety **5.7** to tetracycle **5.6**.

Formation of the final portion of thermorubin's skeleton (**5.8**) will allow for global deprotection of the silyl ethers[1,2] located along the newly added ring and the B-ring phenol (**5.9**, **Scheme 5.3**). Subsequent removal of the benzyl ether[3,4] will unmask the primary alcohol (**5.10**) for oxidation to generate thermorubin **5.11**. Initially, the Jones reagent will be used because pyrones show no susceptibility to degradation in these conditions.[5] Pyrones have also been reported to be resilient to TEMPO oxidation and subsequent Pinnick reaction conditions[6] to

generate the acid from the aldehyde as the next alternative, although the literature may need to be consulted for other oxidation methods.[7,8] Through this proposed pathway, thermorubin **5.11** could be formed in as little as seven more steps, depending on the oxidation conditions. Alternatively, the order of operations could be reversed with the debenzylation and oxidation occurring prior to phenol protecting group removal.

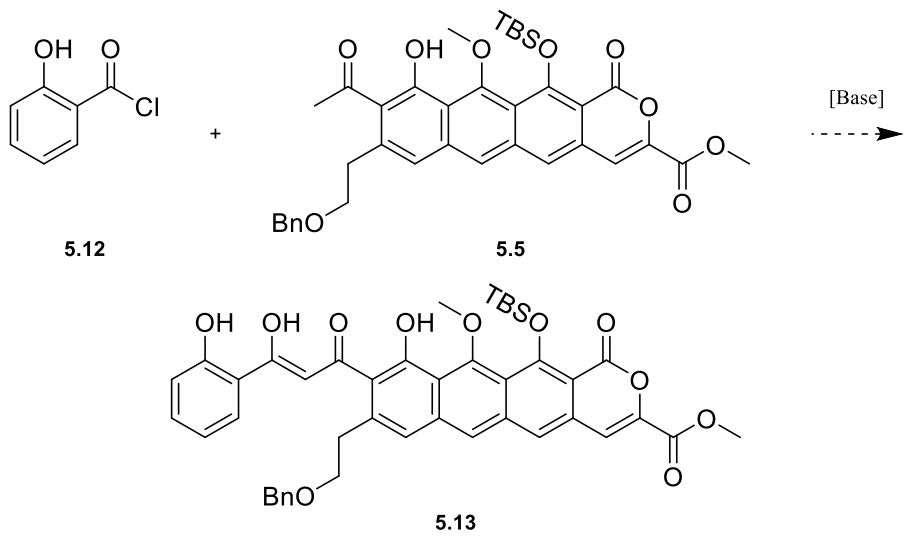


Scheme 5.3: Final proposed pathway to form thermorubin (**5.11**).

5.1.1 Baker-Venkataraman Rearrangement

Installation of the salicylate moiety may be more successful through a Baker-Venkataraman type rearrangement, a method utilizing acyl chlorides and *o* - keto phenols to form 1,3 diketones. This would begin with intercepting intermediate **5.5** before methylation and treating this with the acyl chloride[9] of salicylic acid (**5.13**). While this route initially seems to be possible the formation of intermediate **5.13** presents some serious troubles, specifically methylation of the internal phenol in **5.5** which would have been methylated a step earlier along the previous route. The presence of an additional

phenol along the E ring and the tautomerization of the generated diketone bridge could allow for competing unselective methylation products, preventing selective methylation. Xanthone formation may also occur due to the presence of the *o*-phenol and the orientation of the 1,3-diketone moiety under acidic conditions.[9] Thus, this pathway is an alternative to the Claisen addition pathway.



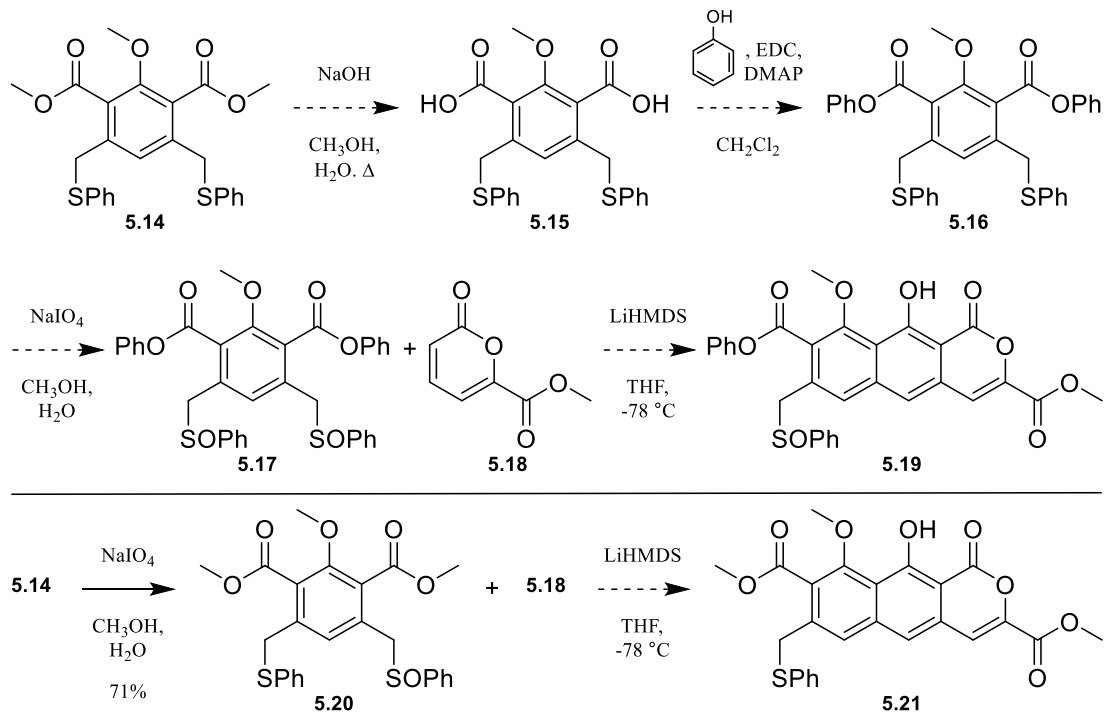
Scheme 5.4: Synthesis of intermediate **5.13** which would originate from intermediate **5.5** and would be isolated upon Baker-Venkataraman conditions if other pathways prove fallible.

5.1.2 Proposed Modification of the 4-Electron Substrate

Due to the low yielding reaction conditions reported earlier (Chapter 4, **Table 4.2**), further optimization would improve the total synthesis. Aside from the various base and pyrone equivalency testing, modification of the symmetrical intermediate may warrant testing to achieve improved yields in the annulations. To this end, transesterification of the methyl esters to phenyl esters may serve as more reactive annulating substrates. Extensive annulation work has been done[10] on the implementation of phenyl esters in a Staunton-Weinreb annulation to prepare a

new tetracycline scaffold, as well as their advantage as 4-electron substrates in Hauser-type annualtions.[11] This material could be prepared from saponification[12] of the bis-thiophenyl ether (**5.14** to **5.15**, **Scheme 5.5**, formation reported in Chapter 4, **Scheme 4.6**) followed by peptide coupling conditions with phenol. Diphenyl ester **5.16** could then be oxidized to the bisulfoxide **5.17**, which could be coupled with pyrone **5.18** to give BCD ring **5.19**. This approach would take advantage of the higher yields observed when the mono-phenyl ester was used in annulations with pyrone (**Scheme 3.7**) and it is expected that subsequent coupling of **5.17** with unsaturated ketones (such as **5.4** in **Scheme 5.1**) would also be more efficient.

During oxidation of the bisthiophenyl ether, it was noted that the single oxidized material (**5.20**) could be isolated (**Scheme 5.5**), and when attempts were made to selectively produce this material it was isolated at a 71% yield. This material could also be used in the annulation with



Scheme 5.5: Modification of the Hauser ester moieties (top box) to form the diphenylester bis sulfoxide intermediate **5.19**; modification of the sulfoxide moieties to form mono thiophenylether intermediate **5.21**.

the pyrone, and may avoid the low yield or diacidic systems, such as in **Table 4.2** and **Scheme 4.7**. Its product **5.21** may also be more readily isolated, as the sulfoxide intermediates along this synthetic pathway are relatively incredibly polar and require multiple rounds of column chromatography to isolate.

5.2 Late-stage Salicylate Derivatization

Our proposed route to form thermorubin allows for the addition of different salicylate rings to the system. Initial derivatives developed by Cavalleri and colleagues[13] focused on altering the isolated metabolite, only allowing for specific functional group changes (Chapter 1, **Table 1.1**) and slight modification of the E ring. The only notable structural changes were the formation of two new rings utilizing the oxygen functionality: the F ring (**Scheme 5.6**, **5.22**,

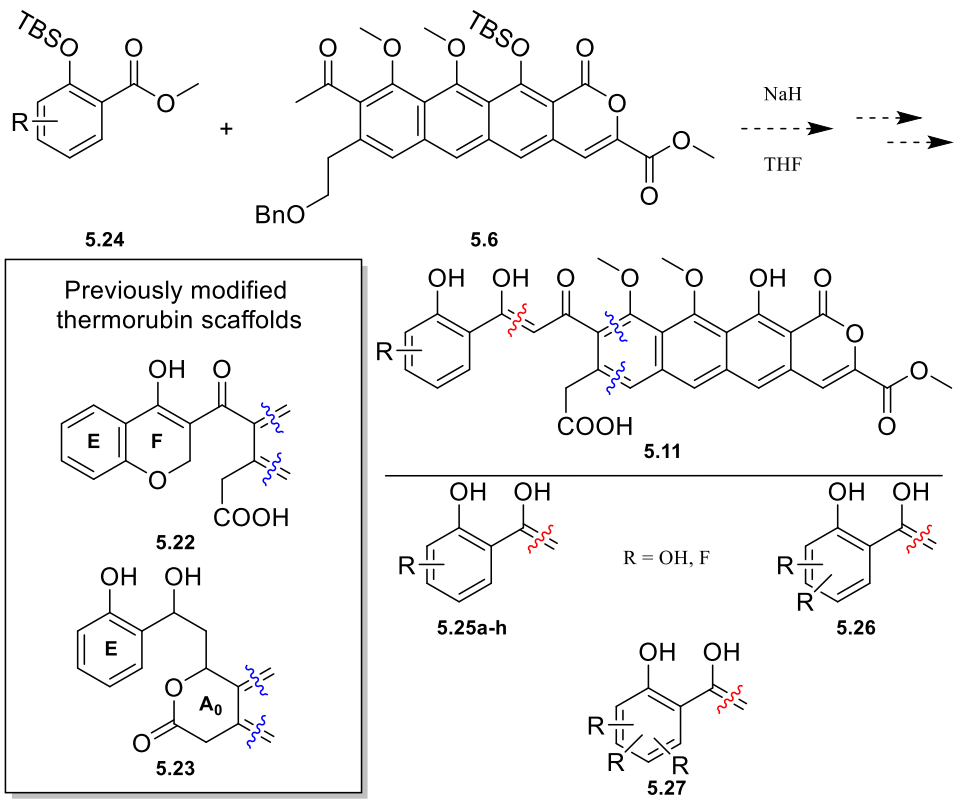


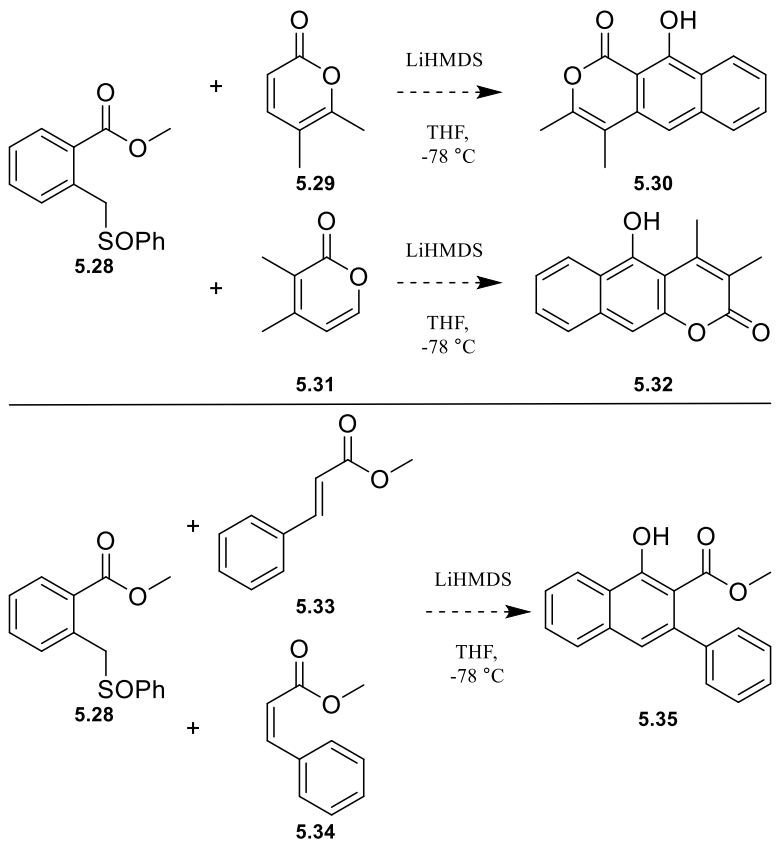
Figure 5.6: Previously made semisynthetic thermrorubin derivatives **5.22** and **5.23** as well as proposed formation of salicylate derivatives.

inset) upon exposure to $NaBH_4$ and acidic cyclization; and the A_0 ring (**5.24**), under Mannich conditions forming the a-pyran ring. Activity testing[13] concluded these structural derivatives were ineffective against bacteria at micromolar concentrations, except for the F ring-containing molecule (**5.22**), which was slightly less active compared to the parent molecule. These structural changes allowed for a closer look at the entire salicylate moiety and how potential changes to this portion could impact activity. Incorporating substituted salicylates will allow for the selective addition of functional groups, as there are a large number of commercially available salicylates. The first round of salicylates should focus on incorporating more polar functionality in order to aid its poor oral bioavailability as well as its activity, focusing specifically on different locations of fluorine and hydroxyl groups.

5.3 Further Modified 4-electron Donors

The inner workings of the Hauser mechanism can still be studied, specifically the conjugation susceptibility of the 2-electron donor systems as well as the *cis/trans* orientation of these systems and their impact on the annulation products. This type of γ-δ addition was initially noted in the forward synthesis (Chapter 2, **Scheme 2.2**) and was initially thought to have been a competing side product. The γ-δ annulated byproduct was never isolated using the pyrone model system, and so it was thought that a potential derivative may be able to drive this type of addition. For example, material **5.29** is a substituted pyrone containing two methyl groups in the γ,δ - positions (**Scheme 5.7**) and would be suitable on a substrate for annulation. Compared to substrate **5.30**, only γ,δ - addition would be allowed for **5.31**, and may be possible due to its conjugation with the internal ester. However, for both **5.30** and **5.31**, a methyl group is in conjugation with the pyrone ester, and deprotonation of the pyrone may suppress annulation. Other molecules with multiple sites of unsaturation could be utilized to test the scope and

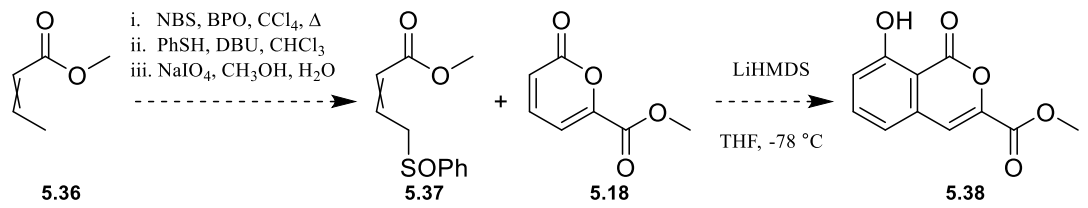
viability of conjugated annulation substrates. Different 2-electron substrates such as phenyl alkenes **5.33** and **5.34** could also be prepared by stereoselective reduction of the preceding alkyne, with these alkenes being used to generate the same product (**5.35**) where the yields can be compared.



Scheme 5.7: Further proposed investigations into the viability of different 2-electron substrates for annulation.

During past investigations involving Hauser substrates, it was proposed that a potentially simpler substrate may be possible for cyclization. Sulfinyl alkenyl **5.37** may be produced using conditions identical to those used to create the previous phenyl sulfinyl materials (**Scheme 5.8**). Its utilization in an annulation pathway would allow for the synthesis of benzopyrone **5.38** creation of variously substituted bicycles. One of the largest distinctions between this molecule

and other 4-electron systems is that it lacks an aromatic ring capable of stabilizing the generated anion. This in turn may make the reaction less favorable yields but would also offer an alternative for isocoumarin formation.



Scheme 5.8: Proposed formation and annulation of simple Hauser substrate **5.37**.

The future of thermorubins formation lies with the success of the next steps as well as optimizing the current annulation reactions established. Given that the final formation of the metabolite is only seven more additional steps away, further work should be accomplished to improve the low yielding steps along the route. Further improvents will also lead to the eventual creation of salicylate derivatives in order to improve water solubility and its efficacy as an orally available drug.

5.4 References

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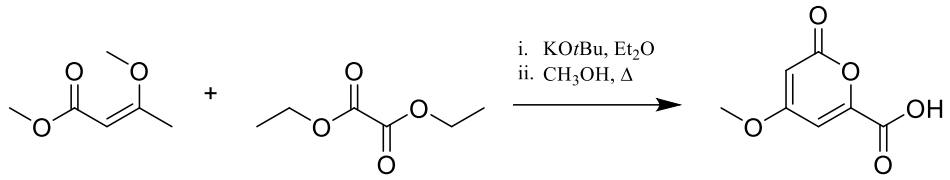
Chapter 6: Experimental Section

6.1 General Experimental

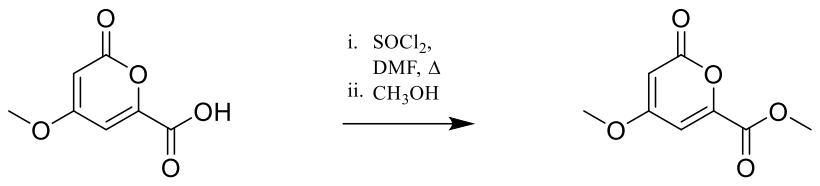
Chemical reagents and solvents were purchased from EMD Millipore, Oakwood Chemical, Sigma-Aldrich, Beantown Chemical, Acros, and Thermo Fisher Scientific. Unless otherwise specified, all non-aqueous reactions were carried out under an atmosphere of dry nitrogen in dried glassware. Commercially available starting materials and reagents were used as received or purified prior to use if necessary. Anhydrous[1] THF was obtained commercially or from a solvent purification system.[2] Diisopropylethylamine was distilled from calcium hydride. *n*BuLi was titrated using 3,5-di-*tert*-butyl-4-hydroxytoluene in THF using fluorene as an indicator. Analytical thin layer chromatography was performed using Supelco 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished by irradiation with a 254 nm UV lamp or by staining with a basified aqueous solution of potassium permanganate. Chromatography was performed using a forced flow of the indicated solvent system on SiliCycle SiliaFlash P60 silica gel or prepacked commercial columns. Deionized water was obtained from the house deionized water system.

^{1}H NMR spectra were recorded on a Bruker Avance II 500 MHz spectrometer or Agilent U4-DD2 400 MHz spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane (0 ppm) using the solvent resonance as an internal standard ($CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet, br=broad), coupling constant, and number of protons. Proton decoupled ^{13}C NMR were recorded on a Bruker Avance II 500 MHz (126 MHz) spectrometer, Agilent U4-DD2 400 MHz (101 MHz) spectrometer, or Bruker Avance III 600 MHz (151 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane

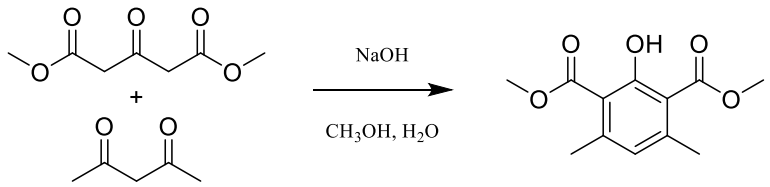
(0 ppm) using the solvent resonance as an internal standard ($CDCl_3$ 77.2 ppm, CD_3OD 49.0 ppm). High resolution mass spectra were obtained on an Agilent Technologies 6220 TOF LC/MS or a Waters Synapt Q-TOF G2 in the Department of Chemistry and the VT-Mass Spectrometry Incubator at the Virginia Polytechnic Institute and State University.



<u>4-Methoxy-2-oxo-2H-pyran-6-carboxylic acid (2.23):</u> To a flask charged with KO*t*Bu (8.04 g, 71.7 mmol) and diethyl ether (120 mL) under an atmosphere of dry nitrogen was added diethyl oxalate (5.24 g, 35.9 mmol). After the bright-yellow solution had stirred for 15 minutes, methyl (*Z*)-3-methoxybut-2-enoate (4.60 g, 35.3 mmol) was added dropwise to the reaction, and it was left to stir overnight. The precipitate was collected (filter paper) and added back to a flask containing methanol (125 mL). After refluxing overnight, the reaction was concentrated (N_2 stream) and the resulting material dissolved in a minimal amount of water. The solution was then acidified using drops of conc. H_2SO_4 until a solid formed. The solid was collected by filtration and concentrated under reduced pressure to yield **2.23** as a light brown amorphous solid (2.20 g, 37%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.74 (d, *J* = 2.3 Hz, 1H), 5.71 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.3, 166.7, 165.3, 157.6, 105.1, 91.7, 57.1. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_7H_7O_5$ 171.0293; found 171.0289.

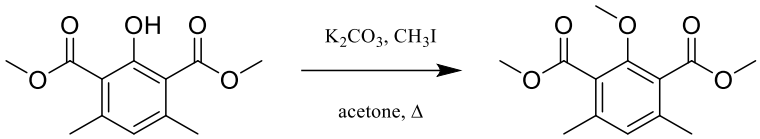


<u>Methyl 4-methoxy-2-oxo-2H-pyran-6-carboxylate (2.24):</u> To a flask containing acid **2.23** (0.278 g, 1.63 mmol) was added $SOCl_2$ (3 mL) slowly. Once the reaction had stopped smoking, DMF (0.01 mL, 0.137 mmol) was added, and the reaction was sealed and refluxed for 2 h. Once the residual solvent was removed via distillation, anhydrous methanol (5 mL) was added and the reaction was left to stir for 24 h. The solid was collected via filtration (filter paper) and dried under reduced pressure. The solid material was purified using flash chromatography (SiO_2, 0% → 1% EtOAc:$CHCl_3$) to yield **2.24** as a white-brown solid (0.169 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 2.3 Hz, 1H), 5.69 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 162.2, 159.9, 149.1, 107.8, 93.6, 56.6, 53.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_8H_9O_5$ 185.0450; found 185.0444.

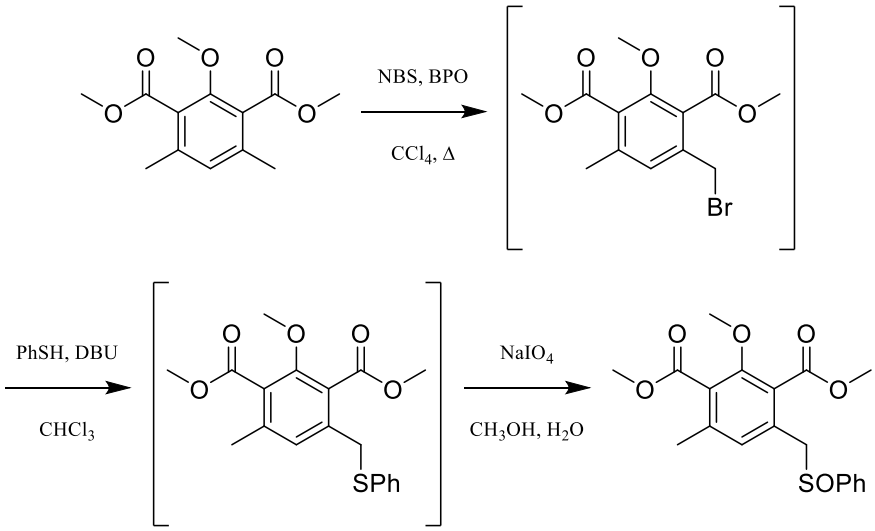


<u>Dimethyl 2-hydroxy-4,6-dimethylisophthalate:</u> To a flask containing acetylacetone (10.0 g, 0.100 mmol) was added a solution of NaOH (100 mL, 0.1 M) and methanol (50 mL). Dimethyl-1,3-acetonedicarboxylate (17.4 g, 0.100 mmol) dissolved in methanol (50 mL) was added. The reaction was stirred for 24 h at rt, at which point a white solid had formed. The reaction was diluted with additional water (50 mL), filtered (filter paper, water), and the precipitate washed with additional water (50 mL). The solid was dried under vacuum to yield isopthalate as a white

amorphous solid (20.5 g, 86%). Spectra data were in accordance with those previously published.[3]



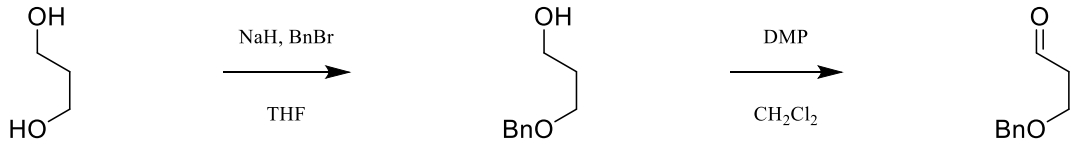
<u>Dimethyl 2-methoxy-4,6-dimethylisophthalate (2.5, 4.14):</u> To a round-bottomed flask charged with anhydrous K_2CO_3 (14.1 g, 102 mmol) and dry acetone (230 mL) under an atmosphere of dry nitrogen was added dimethyl 2-hydroxy-4,6-dimethylisophthalate (20.2 g, 84.9 mmol). To the stirring mixture was added CH_3I (10 mL, 160 mmol), and the reaction mixture was heated at reflux overnight. After the reaction had cooled, it was filtered using filter paper, acetone (20 mL). The filtrate was diluted with diethyl ether (250 mL). The filtrate waswashed with a saturated aqueous Na_2CO_3 solution (2 x 80 mL) and brine (80 mL), dried (Na_2SO_4), and concentrated to yield **2.5** (20.5 g, 96%) as a white amorphous solid. Spectra data were in accordance with that previously published.[4]



<u>Dimethyl 2-methoxy-4-methyl-6-((phenylsulfinyl)methyl)isophthalate (2.27, 4.5):</u> To a dried round-bottomed flask was added dimethyl 2-methoxy-4,6-dimethlisophthalate (10.3 g, 40.7 mmol), followed by NBS (7.3 g, 40.7 mmol) and benzoyl peroxide (197 mg, 0.813 mmol). The vessel was purged with nitrogen and CCl_4 (90 mL) was added. The stirring mixture was refluxed for 2 h. After cooling, the reaction was filtered (filter paper, CCl_4), and the filtrate concentrated to yield an orange oil. This residue was carried onto the next step without further purification.

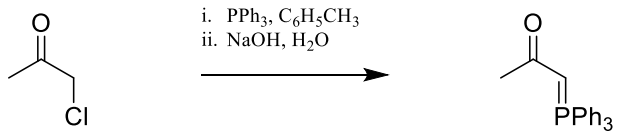
The oil was dissolved in $CHCl_3$ (100 mL) and DBU (6.1 mL, 41 mmol) and thiophenol (4.2 mL, 41 mmol) were added. After stirring for 24 h at rt, additional DBU (1.5 mL, 10 mmol) was added and the mixture was stirred for an additional 24 h. A solution of aqueous NaOH (0.67 M, 75 mL) was added to the reaction and the layers were separated. The aqueous layer was washed with diethyl ether (2 x 100 mL), and the combined organic layers were washed with aqueous NaOH (0.33 M, 75 mL), HCl (3 M, 75 mL), water (75 mL), and brine (75 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield a dark orange oil that was carried onto the next step without further purification.

The oil was dissolved in methanol (107 mL) and water (16 mL). To this stirring solution was added $NaIO_4$ (8.7 g, 41 mmol), and the reaction was stirred overnight. The reaction was filtered and the precipitate washed with additional methanol. The filtrate was concentrated and suspended in CH_2Cl_2 (100 mL). The mixture was filtered (Celite, CH_2Cl_2) and the filtrate concentrated. The residue was purified using flash chromatography (SiO_2, 38% → 45% EtOAc:hexanes) to yield sulfoxide **2.27** (4.8 g, 32%) as an off-white to yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 5H), 6.69 (s, 1H), 4.17 (d, J = 12.7 Hz, 1H), 4.08 (d, J = 12.9 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 167.1, 156.1, 143.3, 139.3, 131.6, 131.4, 129.21, 129.20, 129.17, 125.3, 124.3, 63.7, 62.0, 52.7, 52.6, 19.4.; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_6S$ 377.1059; found 377.1043.

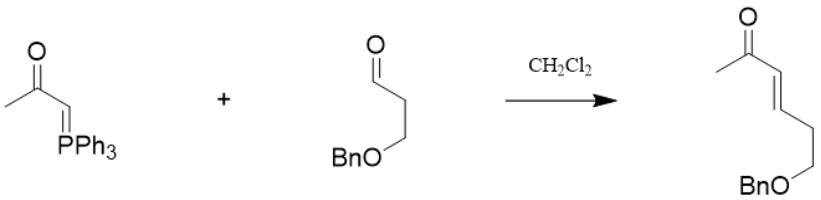


<u>3-(Benzyloxy)propanal (2.31):</u> To a round-bottomed flask containing 1,3-propanediol (6.00 mL, 83.6 mmol) cooled in an ice/water bath was added NaH (0.483 g, 12.1 mmol) in portions. After stirring cold for 15 minutes, BnBr (3.02 g, 17.7 mmol) was added dropwise. The mixture was slowly warmed to room temperature and then heated to reflux for 16 h. After cooling, water (10 mL) was added and the mixture was stirred for 15 min. The mixture was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic layers were rinsed with water (3 x 25 mL). Once dried (Na_2SO_4) and concentrated, the residue was carried onto the next step without further purification.

3-(Benzyloxy)propan-1-ol was dissolved in CH_2Cl_2 (36 mL). Dess-Martin periodinane (5.85 g, 20.4 mmol) was added, and the mixture was stirred for 2 h. The mixture was filtered (filter paper, CH_2Cl_2) and the filtrate was washed with water (12 mL), dried (Na_2SO_4), and concentrated. The residue was purified using flash chromatography (SiO_2, EtOAc:Hex 25 % → 60 %) to yield **2.31** (1.47 g, 74%) as a slightly yellow, clear oil. Spectral data were in accordance with previously recorded.[5]

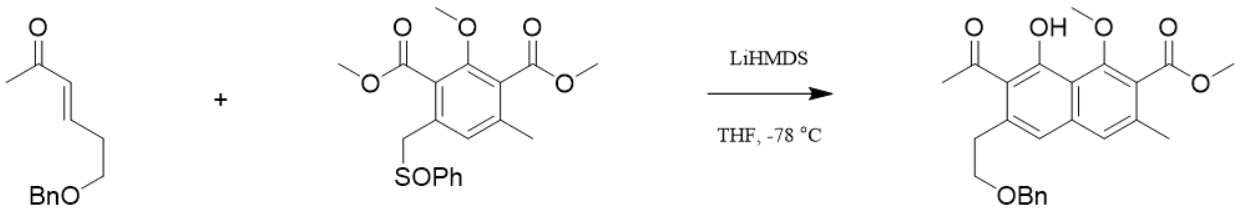


<u>1-(Triphenylphosphoranylidene)-2-propanone (2.33):</u> Triphenyl phosphine (8.3 g, 31.5 mmol) was dissolved in benzene (10 mL). The reaction vessel was purged with nitrogen, and chloroacetone (2.5 mL, 31.0 mmol) was added. The reaction was stirred overnight, at which point the solid material was filtered off and rinsed with additional benzene (10 mL). The solid material was dissolved in water (50 mL) and basified (pH 10) by the dropwise addition of NaOH (5 M). The resulting precipitate was collected by filtration, dissolved in CH_2Cl_2, dried (Na_2SO_4), and concentrated to yield **2.33** (7.6 g, 76%) as a white solid. Spectral data was in accordance with that previously recorded.[6]



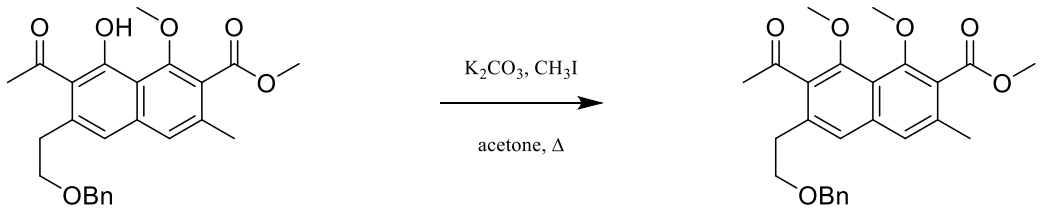
<u>6-(Benzyloxy)hex-3-en-2-one (2.29):</u> To a stirring solution of **2.33** (0.504 g, 1.58 mmol) dissolved in CH_2Cl_2 (12 mL) was added **2.31** (0.204 g, 1.242 mmol) dissolved in CH_2Cl_2 (12

mL). After stirring overnight, the mixture was concentrated and the residue dissolved in Et_2O (30 mL). The mixture was filtered (filter paper, Et_2O) to remove the triphenylphosphine oxide and the filtrate was concentrated. Purification of this residue using flash chromatography (SiO_2, 15% → 25% EtOAc:Hex) resulted in **2.29** (0.203 g, 80%) as a clear and colorless oil. Spectral data were in accordance with those previously reported.[7]

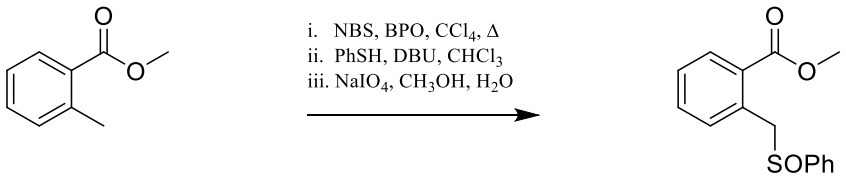


<u>Methyl 7-acetyl-6-(2-(benzyloxy)ethyl)-8-hydroxy-1-methoxy-3-methyl-2-naphthoate (2.34):</u> To a flask containing THF (1 mL) was added *i*Pr_2NH (0.180 mL, 1.28 mmol). The solution was cooled in a water/ice bath and *n*BuLi (0.58 mL, 2.02 M, 1.17 mmol) was added dropwise. The stirring mixture was warmed to rt over 15 min and then cooled to -78 °C using a dry ice/acetone bath. After stirring cold for 15 min, **2.27** (0.200 g, 0.531 mmol) dissolved in THF (1.75 mL) was added dropwise and stirred for 15 min, after which **2.29** (0.261 g, 1.28 mmol) dissolved in THF (1.75 mL) was added dropwise. The mixture was stirred cold for 60 min, and stirring with warming to room temperature over 120 min. The mixture was then quenched using aqueous HCl (1 M, ~3 mL) and concentrated under reduced pressure. The concentrate was extracted with $CHCl_3$ (3 x 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 2 → 10% acetone:$CHCl_3$) to yield **2.34** (0.088 g, 39%) as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.40 – 7.28 (m, 6H), 7.12 (s, 1H), 4.51 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.70 (t, *J* = 6.7 Hz, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.58 (s, 3H), 2.42 (s, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 205.3, 168.1, 154.5, 152.3, 138.4, 137.1, 136.7, 134.8, 130.2, 128.4, 127.8, 127.7, 124.9, 123.7, 119.8, 113.6, 73.0, 70.8, 64.5, 52.7, 33.9, 32.6, 20.0; ESI calculated for $C_{25}H_{27}O_6$ 423.1808; found 423.1788.



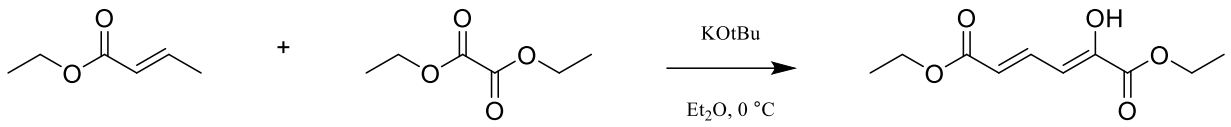
<u>Methyl 7-acetyl-6-(2-(benzyloxy)ethyl)-1,8-dimethoxy-3-methyl-2-naphthoate (2.35):</u> To flame-dried, nitrogen-purged K_2CO_3 (0.039 g, 0.28 mmol) was added **2.34** (0.098g, 0.23 mmol) dissolved in acetone (6 mL). CH_3I (0.029 mL, 0.46 mmol) was added and the mixture was refluxed (oil bath) for 20 h. After cooling, the mixture was filtered (filter paper, CH_2Cl_2) and concentrated. The mixture was redissolved in CH_2Cl_2 (6 mL) and washed with water (2 x 3 mL), dried (Na_2SO_4), and concentrated. The residue was purified using flash chromatography (SiO_2, 0 → 1% CH_3OH:$CHCl_3$) to yield **2.35** (0.088 g, 88%) as a red-orange amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.36 (s, 1H), 7.34 – 7.24 (m, 5H), 4.51 (s, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 3.71 (t, *J* = 7.0 Hz, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.56 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9, 168.9, 153.1, 152.7, 138.3, 137.5, 135.0, 134.7, 134.0, 128.5, 127.9, 127.8, 127.5, 125.2, 124.7, 118.6, 73.1, 70.5, 64.23, 64.19, 52.5, 33.3, 33.0, 19.6; ESI calculated for C26H26NaO6 459.1784: found, 459.1784.



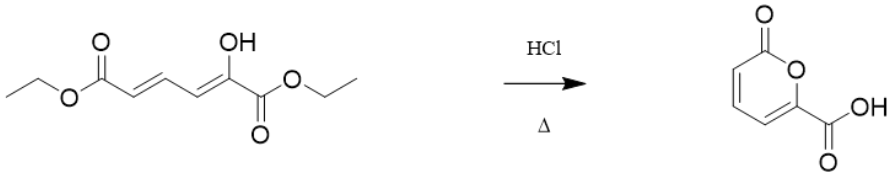
<u>Methyl 2-((phenylsulfinyl)methyl)benzoate (3.11, 5.28):</u> The following reactions were carried out in an analogous manner to the published procedure.[8] **Caution!** Carbon tetrachloride is highly toxic and should be handled exclusively in a fume cabinet to avoid vapor exposure. *N*-Bromosuccinimide (14.3 g, 80.1 mmol) and benzoyl peroxide (0.97 g, 4.0 mmol) were combined in a flame-dried flask under nitrogen, and CCl_4 (100 mL) was added. Methyl *O*-toluate (12.0 g, 80.0 mmol) was added, the mixture was heated to reflux and stirred for 2 h. After cooling to rt, the mixture was filtered and the solid washed with CCl_4 (25 mL). The filtrate was concentrated to yield methyl 2-(bromomethyl)benzoate as a yellow oil that was used directly without further purification.

Crude oil from previous step was dissolved in $CHCl_3$ (25 mL) and added to a stirring solution of PhSH (8.5 mL, 83.3 mmol) and K_2CO_3 (14.2 g, 103 mmol) in $CHCl_3$ (75 mL). After stirring overnight, the mixture was diluted with Et_2O (100 mL) and washed sequentially with solutions of NaOH (1 M, 50 mL), water (50 mL), and brine (50 mL). Concentration resulted in methyl 2-((phenylthiol)methyl)benzoate was used directly without further purification.

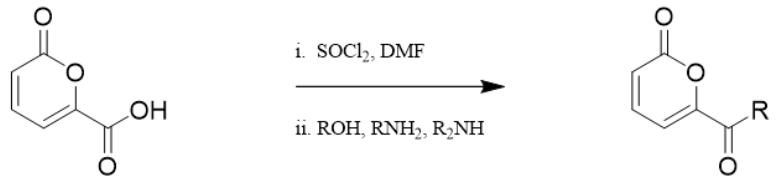
The crude oil was dissolved in methanol (170 mL) and water (26 mL) and $NaIO_4$ (17.8 g, 83.3 mmol) was added portion-wise. After stirring for 18 h, the mixture was diluted with water (100 mL) and EtOAc (200 mL) and the layers were separated. The organic layer was washed with water (2 x 50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. The residue was purified using flash chromatography (40% EtOAc/hexanes, SiO_2) to yield **3.11** (12.8 g, 58%) as an amorphous white solid. Spectral data were in accord with those previously reported.[8]



<u>6-Ethyl 1-methyl (2*Z*,4*E*)-2-hydroxyhexa-2,4-dienedioate:</u> To a flame-dried flask was added *t*-BuOK (24.7 g, 0.220 mol) and Et_2O (86 mL). The flask was purged with nitrogen, and after the mixture had cooled to 0 °C (cryocool), diethyl oxalate (27.1 mL, 0.200 mol) dissolved in Et_2O (16 mL) was added dropwise over 15 min, followed by ethyl crotonate (24.9 mL, 0.200 mol) in a dropwise fashion. The mixture was stirred at 4 °C (cryocool) overnight, after which the reaction was filtered, and the precipitate washed with Et_2O (100 mL). The yellow-orange precipitate was dissolved in cold water (750 mL) and 50% aqueous acetic acid (35 mL) was added. Filtration (water) and drying of the precipitate resulted in dienedioate (30 g, 75%) as an amorphous yellow solid. Spectra data were in accord with those previously reported.[9]



<u>2-oxo-2*H*-pyran-6-carboxylic acid (3.14):</u> Dienedioate (11.65 g, 54.39 mmol) was dissolved in concentrated HCl (325 mL), heated to reflux, and stirred for 8 h. The mixture was cooled to rt and then cooled at -20 °C for 4 h. The precipitate was collected by filtration and the filtrate stored at -20 °C for 12 h, after which additional filtrate was collected. Drying yielded **3.14** (6.71 g, 88%) as an amorphous gold-yellow solid. Spectra data were in accord with those previously reported.[9]



General procedure for the preparation of pyrone ester derivatives (3.7): The following reactions were carried out in an analogous manner to the published procedure (unless otherwise stated).[9,10] Pyrone carboxylic acid **3.14** (1 equiv.) was dissolved in $SOCl_2$ (10-20 equiv.) and a catalytic amount of DMF (0.05 equiv.) was added. The reaction was heated to reflux and stirred for 15 h, after which the excess solvent was removed via distillation. The resulting acid chloride was dissolved in the appropriate alcohol (1-5 equiv.) and the mixture was stirred at rt for 1 h. The resulting solid material was either filtered and the filtrate concentrated to give **3.7** or dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and the residue purified using flash chromatography (SiO_2) to yield **3.7**.

<u>Methyl 2-oxo-2*H*-pyran-6-carboxylate (2.6, 3.7a, 4.6, 5.18):</u> Purified by filtration to give **2.6** (0.516 g, 91%) as an amorphous white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 9.4, 6.6 Hz, 1H), 7.10 (dd, J = 6.5, 1.0 Hz, 1H), 6.55 (dd, J = 9.4, 1.0 Hz, 1H), 3.94 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8, 159.6, 149.4, 141.7, 121.1, 109.9, 53.1. HRMS (ESI) calcd for $C_7H_7O_4$ $[M+H]^+$ 155.0344, found 155.0343.

<u>Ethyl 2-oxo-2*H*-pyran-6-carboxylate (3.7b):</u> Purified using $CHCl_3$ to give **3.7b** (0.490 g, 68%) as an amorphous pink solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 9.4, 6.5 Hz, 1H), 7.08 (dd, J = 6.6, 1.0 Hz, 1H), 6.52 (dd, J = 9.4, 1.0 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.9, 159.5, 149.8, 141.9, 121.0, 109.9, 62.7, 14.2; HRMS (ESI) calcd for $C_8H_9O_4$ $[M+H]^+$ 169.0501, found 169.0499.

Propyl 2-oxo-2*H*-pyran-6-carboxylate (3.7c): Purified using CH_2Cl_2 to give **3.7c** (0.367 g, 56%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 9.4, 6.6 Hz, 1H), 7.04 (dd, J = 6.6, 1.2 Hz, 1H), 6.47 (dd J = 9.4, 1.2 Hz, 1H), 4.21 (dd, J = 7.1, 6.4 Hz, 2H), 1.70 (qt, J = 7.4, 6.7 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.0, 159.6, 149.8, 141.9, 121.0, 109.9, 68.2, 22.0, 10.4; HRMS (ESI) calcd for $C_9H_{11}O_4$ $[M+H]^+$ 183.0657, found 183.0658.

Butyl 2-oxo-2*H*-pyran-6-carboxylate (3.7d): Purified using a 2%-4% EtOAc/CH_2Cl_2 to give **3.7d** (0.596 g, 85%) as a yellow-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 9.4, 6.6 Hz, 1H), 7.09 (dd, J = 6.5, 1.0 Hz, 1H), 6.54 (dd, J = 9.4, 1.0 Hz, 1H), 4.33 (t, J = 6.7 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.51 – 1.35 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.0, 159.6, 149.9, 141.9, 121.0, 109.9, 66.5, 30.6, 19.2, 13.8; HRMS (ESI) calcd for $C_{10}H_{13}O_4$ $[M+H]^+$ 197.0814, found 197.0814.

Isopropyl 2-oxo-2*H*-pyran-6-carboxylate (3.7e): Purified using 3% acetone/PhH to give **3.7e** (0.35 g, 52%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 9.4, 6.6 Hz, 1H), 7.07 (d, J= 7.0 Hz, 1H), 6.53 (d, J = 9.4 Hz, 1H), 5.27 – 5.18 (heptet, J=6.3 Hz, 1H), 1.36 (d, J = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.3, 159.2, 150.4, 142.2, 121.1, 110.0, 71.1, 22.1; HRMS (ESI) calcd for $C_9H_{11}O_4$ $[M+H]^+$ 183.0657, found 183.0657

***tert*-Butyl 2-oxo-2*H*-pyran-6-carboxylate (3.7f):** Purified using $CHCl_3$ to give **3.7f** (0.051 g, 13%) as an orange amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 9.4, 6.6 Hz, 1H), 7.01 (dd, *J* = 6.6, 1.0 Hz, 1H), 6.50 (dd, *J* = 9.4, 1.1 Hz, 1H) 1.56 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.3, 158.4, 150.9, 142.0, 120.6, 109.2, 84.2, 28.1; HRMS (ESI) calcd for $C_{10}H_{12}NaO_4$ $[M+Na]^+$ 219.0633, found 219.0628.

3-Methylbut-2-en-1-yl 2-oxo-*2H*-pyran-6-carboxylate (3.7g): Purified using CH_2Cl_2 to give **3.7g** (0.251 g, 89%) as an orange amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 9.4, 6.6 Hz, 1H), 7.07 (d, J = 6.5 Hz, 1H), 6.51 (d, J = 9.4 Hz, 1H), 5.45-5.38 (m, 1H), 4.79 (d, J = 7.4 Hz, 2H), 1.78 (s, 3H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.9, 159.5, 149.9, 141.9, 140.9, 120.9, 117.6, 109.9, 63.3, 25.9, 18.2; HRMS (ESI) calcd for $C_{11}H_{12}O_4Na$ $[M+Na]^+$ 231.0633, found 231.0626.

2-(Trimethylsilyl)ethyl 2-oxo-2*H*-pyran-6-carboxylate (3.7h): Purified using $CHCl_3$ to give **3.7h** (0.192 g, 42%) as a pale-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 9.4, 6.6 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.55 – 6.51 (m, 1H), 4.46 – 4.38 (m, 2H), 1.16 – 1.09 (m, 2H), 0.08 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.9, 159.6, 150.1, 141.9, 121.0, 109.7, 65.2, 17.5, -1.4; HRMS (ESI) calcd for $C_{11}H_{16}O_4NaSi$ $[M+Na]^+$ 263.0716, found 263.0724.

3-Chloropropyl 2-oxo-*2H*-pyran-6-carboxylate (3.7i): Purified using a 0%-15% acetone/$CHCl_3$ to give **3.7i** (0.324 g, 75%) as a red-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 9.4, 6.6 Hz, 1H), 7.12 (dd, J = 6.6, 1.0 Hz, 1H), 6.56 (dd, J = 9.4, 1.0 Hz, 1H), 4.50 (t, J = 6.1 Hz, 2H), 3.68 (t, J = 6.3 Hz, 2H), 2.31 – 2.15 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8, 159.4, 149.5, 141.8, 121.3, 110.2, 63.3, 41.0, 31.4; HRMS (ESI) calcd for $C_9H_{10}ClO_4$ $[M+H]^+$ 217.0268, found 217.0267.

3-Bromopropyl 2-oxo-*2H*-pyran-6-carboxylate (3.7j): Purified using 90% CH_2Cl_2/hexanes, then CH_2Cl_2 to give **3.7j** (0.53 g, 52% as an amorphous white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 1H), 7.11 (ddt, J = 6.6, 2.5, 1.0 Hz, 1H), 6.55 (ddt, J = 9.4, 2.6, 1.0 Hz, 1H), 4.52 – 4.39 (m, 2H), 3.58 – 3.44 (m, 2H), 2.36 – 2.25 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz,

$CDCl_3$) δ 159.5, 159.1, 149.2, 141.6, 121.0, 110.0, 64.0, 31.2, 28.9; HRMS (ESI) calcd for $C_9H_{10}BrO_4$ $[M+H]^+$ 260.9762, found 260.9760.

Phenyl 2-oxo-2*H*-pyran-6-carboxylate (3.7k): Purified using 0%-10% acetone/$CHCl_3$ to give **3.7k** (0.090 g, 20%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 9.4, 6.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.32 – 7.29 (m, 1H), 7.27 (dd, *J* = 6.6, 1.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 6.62 (dd, *J* = 9.4, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.5, 157.9, 150.0, 149.0, 141.6, 129.7, 126.6, 121.6, 121.2, 111.0; HRMS (ESI) calcd for $C_{12}H_9O_4$, $[M+H]^+$ 217.0495, found 217.0494.

2-Methoxyphenyl 2-oxo-2*H*-pyran-6-carboxylate (3.7l): Purified using 0%-15% acetone/$CHCl_3$ to give **3.7l** (0.239 g, 45%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 9.4, 6.6 Hz 1H), 7.29-7.24 (m, 2H), 7.12 (dd, J = 8.0, 1.5 Hz 1H), 7.04-6.96 (m, 2H), 6.61 (dd, J = 9.4, 1.0 Hz, 1H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 157.4, 151.0, 149.1, 141.7, 139.1, 127.8, 122.6, 121.7, 121.0, 112.8, 111.1, 56.0; HRMS (ESI) calcd for $C_{13}H_{11}O_5$ $[M+H]^+$ 247.0606, found 247.0608.

4-Methoxyphenyl 2-oxo-2*H*-pyran-6-carboxylate (3.7m): Purified using 75%-100% $CHCl_3$/hexanes to give **3.7m** (0.151 g, 27%) as an off-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 9.5, 6.5 Hz, 1H), 7.26 (dd, J = 6.5, 1.1 Hz, 1 H) 7.15 – 7.07 (m, 2H), 6.97 – 6.89 (m, 2H), 6.62 (dd, J = 9.4, 1.0 Hz, 1H), 3.82 (s, 3 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 158.3, 157.9, 149.3, 143.6, 141.8, 122.1, 121.7, 114.8, 111.0, 55.8; HRMS (ESI) calcd for $C_{13}H_{11}O_5$ $[M+H]^+$ 247.0606, found 247.0604.

4-Bromophenyl 2-oxo-2*H*-pyran-6-carboxylate (3.7n): Purified using 0%-25% EtOAc/$CHCl_3$ to give **3.7n** (0.154 g, 38%) as a white, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.47 (dd, *J* = 9.4, 6.6 Hz, 1H), 7.26 (dd, *J* = 6.6, 1.0 Hz, 1H), 7.12 – 7.06 (m, 2H),

6.61 (dd, J = 9.4, 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 157.6, 149.0, 148.7, 141.5, 132.8, 123.0, 121.8, 119.8, 111.2; HRMS (ESI) calcd for $C_{12}H_8BrO_4$, $[M+H]^+$ 294.9600, found 294.9592.

Benzyl 2-oxo-*2H*-pyran-6-carboxylate (3.7o): Purified using 80% CH_2Cl_2/hexanes to give **3.7o** (0.640 g, 78%) as a white amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.31 (m, 6H), 7.11 (d, J = 6.6 Hz, 1H), 6.54 (d, J = 9.4 Hz, 1H), 5.35 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.8, 159.3, 149.5, 141.8, 134.7, 128.9, 128.84, 128.76, 121.2, 110.2, 68.2; HRMS (ESI) calcd for $C_{13}H_{11}O_4$ $[M+H]^+$ 231.0657, found 231.0665.

4-Methoxybenzyl 2-oxo-*2H*-pyran-6-carboxylate (3.7p): Isolated by filtration and concentration to give **3.7p** (0.43 g, 52%) as an orange amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 1H), 7.38-7.35 (m, 2H) 7.09 (dd, J = 6.5, 1.0 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.53 (dd, J = 9.4, 1.0 Hz, 1H), 5.28 (s, 2H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.1, 159.9, 159.4, 149.6, 141.9, 130.8, 126.8, 121.1, 114.2, 110.15, 68.1, 55.4; HRMS (ESI) calcd for $C_{14}H_{12}NaO_5$ $[M+Na]^+$ 283.0577, found 283.0576.

2-Oxo-*N*-phenyl-2*H*-pyran-6-carboxamide (3.7q): Isolated by filtration and concentration to give **3.7q** (0.56 g, 72%) as a white amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.69 – 7.65 (m, 2H), 7.52 (dd, J = 9.4, 6.6 Hz, 1H), 7.43-7.37 (m, 2H), 7.25 (dd, J = 6.6, 1.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 6.54 (dd, J = 9.4, 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.8, 156.3, 152.6, 143.4, 136.8, 129.6, 125.8, 120.7, 119.8, 107.7; HRMS (ESI) calcd for $C_{12}H_{10}NO_3$ $[M+H]^+$ 216.0661, found 216.0679.

***N*-Butyl-2-oxo-2*H*-pyran-6-carboxamide (3.7r):** Purified using 20% EtOAc/CH_2Cl_2 to give **3.7r** (0.25 g, 35%) isolated as a brown amorphous solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (ddd, J = 9.4, 6.6, 0.5 Hz, 1H), 7.12 (dd, J = 6.6, 1.0 Hz, 1H), 6.84 (s, 1H), 6.48 (dd, J = 9.4, 1.1

Hz, 1H), 3.41 (td, J = 7.1, 5.9 Hz, 2H), 1.67 – 1.51 (m, 2H), 1.46 – 1.31 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 159.9, 158.3, 152.6, 143.2, 119.1, 106.7, 39.6, 31.5, 20.1, 13.8; HRMS (ESI) calcd for $C_{10}H_{14}NO_3$ $[M+H]^+$ 196.0974, found 196.0970.

***N,N*-Diisopropyl-2-oxo-2*H*-pyran-6-carboxamide (3.7s):** Purified using CH_2Cl_2, then 0.25% MeOH/CH_2Cl_2, then 0.5% MeOH/CH_2Cl_2 to give **3.7s** (0.44 g, 55%) as an amorphous off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 9.6, 6.7 Hz, 1H), 6.44 (d, J = 6.6 Hz, 1H), 6.33 (d, J = 9.7 Hz, 1H), 3.84 (br s, 1H), 3.51 (br s, 1H), 1.45 (br s, 6H), 1.26 (br s, 6H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 161.1, 160.1, 157.7, 143.2, 116.8, 104.8, 51.1, 46.5, 20.8, 20.1. HRMS (ESI) calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287, found 224.1287.

6-(Piperidine-1-carbonyl)-2*H*-pyran-2-one (3.7t): Purified using 60% EtOAc/CH_2Cl_2 to give **3.7t** (0.67 g, 89%) as an amorphous orange solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 9.4, 6.6 Hz, 1H), 6.58 (d, *J* = 6.6 Hz, 1H), 6.36 (d, *J* = 9.4 Hz, 1H), 3.61 (br s, 2H), 3.46 (br s, 2H) 1.72-1.59 (m, 6H); $^{13}C\{^{1}H\}$ NMR (126 MHz, CDCl3) δ 160.3, 160.1, 156.3, 143.1, 117.5, 106.7, 48.2, 44.0, 26.6, 25.6, 24.5; HRMS (ESI) calcd for $C_{11}H_{14}NO_3$ $[M+H]^+$ 208.0974, found 208.0967.

6-(Morpholine-4-carbonyl)-2*H*-pyran-2-one (3.7u): Purified using EtOAc to give **3.7u** (0.074 g, 32%) as an amorphous white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (dd, *J* = 9.5, 6.6, 1H), 6.70 (dd, *J* = 6.6, 0.9 Hz, 1H), 6.44 (dt, *J* = 9.5, 0.9 Hz, 1H), 3.71 (br s, 4 H), 3.67 (br s, 4H); $^{13}C\{^{1}H\}$ NMR (151 MHz, CD_3OD) δ 162.3, 161.9, 155.5, 144.9, 118.7, 108.5, 67.9, 67.5, 44.2; HRMS (ESI) calcd for $C_{10}H_{12}NO_4$ $[M+H]^+$ 210.0766, found 210.0765.

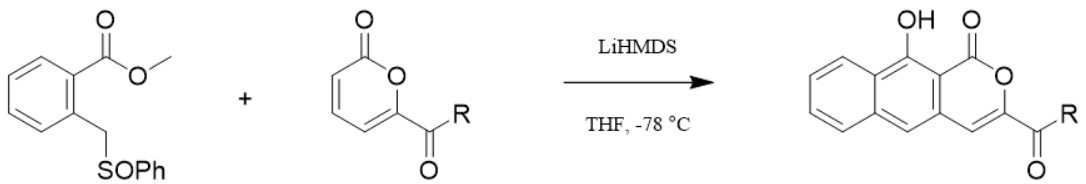
***N*-Hexyl-2-oxo-2H-pyran-6-carboxamide (3.7v):** Purified using 20% EtOAc in CH_2Cl_2 to give **3.7v** (0.25 g, 63%) as a brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 9.4, 6.6 Hz, 1H), 7.12 (dd, *J* = 6.6, 1.0 Hz, 1H), 6.87 (s, 1H), 6.48 (dd, *J* = 9.4, 1.0 Hz, 1H), 3.40 (td, *J* = 7.2,

6.0 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.33 – 1.28 (m, 6H), 0.92 – 0.86 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 158.2, 152.5, 143.1, 119.1, 106.6, 39.8, 31.4, 29.3, 26.6, 22.5, 14.0; HRMS (ESI) calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1287, found 224.1290.

tert*-Butyl (2-oxo-2H-pyran-6-carbonyl)(phenyl)carbamate (3.7q*):** To a stirring solution of **3.7q** (0.278 g, 1.29 mmol) in CH_2Cl_2 (15 mL) was added DMAP (17.0 mg, 0.139 mmol) and Boc_2O (0.60 mL, 2.6 mmol). The mixture was stirred at rt for 24 h, quenched by the addition of NH_4Cl solution (10 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The residue purified was using flash chromatography (SiO_2, CH_2Cl_2) to give **3.7q as a light-brown amorphous solid (0.333 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 4H), 7.25 – 7.21 (m, 2H), 6.81 (dd, *J* = 6.6, 1.0 Hz, 1H), 6.49 (dd, *J* = 9.5, 1.0 Hz, 1H), 1.40 (s, 9H); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ 163.8, 159.4, 155.1, 152.1, 142.7, 137.6, 129. 5, 128.7, 128.1, 119.3, 107.4, 85.0, 27.8; HRMS (ESI) calcd for $C_{17}H_{17}NO_5Na$ $[M+Na]^+$ 338.1004, found 338.1005.

tert*-Butyl hexyl(2-oxo-2H-pyran-6-carbonyl)carbamate (3.7v*):** To a stirring solution of **3.7v** (0.294 g, 1.32 mmol) in CH_2Cl_2 (12 mL) was added DMAP (17.0 mg, 0.139 mmol), Et_3N (0.25 mL, 1.794 mmol) and Boc_2O (0.45 mL, 2.0 mmol). The mixture was stirred at room temperature for 24 h, quenched by addition of NH_4Cl (6 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 6 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The residue was purified using flash chromatography (SiO_2, 10% - 20% EtOAc/hexanes) to **3.7v give as a brown oil (0.253 g, 59%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 9.4, 6.6 Hz, 1H), 6.66 (dd, J = 6.6, 1.0 Hz, 1H), 6.43 (dd, J = 9.4, 1.0 Hz, 1H),

3.73 – 3.66 (m, 2H), 1.66 – 1.54 (m, 2H), 1.42 (s, 9H), 1.36 – 1.26 (m, 6H), 0.92 – 0.86 (m, 3H); 13C{1H} NMR (101 MHz, CDCl3) δ 164.0, 159.6, 155.9, 152.2, 142.9, 118.6, 106.3, 84.5, 46.0, 31.5, 28.6, 27.8, 26.5, 22.7, 14.1; HRMS (ESI) calcd for $C_{17}H_{25}NO_5Na$ $[M+Na]^+$ 346.1630, found 346.1614.



General procedure for pyrone annulation (3.12). Hexamethyldisilane (1.2 mmol) was added to a round bottom flask containing THF (0.2 mL). The mixture was placed in an ice bath, and *n*BuLi (1.1 mmol) was added dropwise. After addition was complete, the mixture was stirred for 10 min, warmed to rt and stirred for 15 min, and then cooled to -78 °C (dry ice/acetone bath) for 15 min. Commercial 1 M LiHMDS solution in THF could be successfully used as well. Pyrone **3.7** (0.80 mmol) dissolved in THF (3 mL) was added and the mixture was stirred at -78 °C (dry ice/acetone bath) for 15 min. Sulfoxide **3.11** (0.37 mmol) dissolved in THF (0.8 mL) was added dropwise, and the mixture was stirred at -78 °C (dry ice/acetone bath) for 1 h. The mixture was slowly warmed to rt, and after stirring for 2 hours, HCl (4 mL, 10% in water) was added. The THF was removed under reduced pressure, and the residual aqueous solution was extracted with $CHCl_3$ (3 x 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified using automated flash chromatography (SiO_2) to yield **3.12**. Because of the highly similar nature of the impurities (mainly **3.7a**), additional purification using HPLC was

needed for some derivatives. These were performed using a Cogent Bidentate C18 column (100 Å, 4 mm, 250 x 10 mm) on a Shimadzu system equipped with a manual injector, CBM-20A communication bus module, DGU-20A degassing unit, LC-20AR liquid chromatography binary pump, SPD-20A UV/Vis detector, and FRC-10A fraction collector with water containing 0.1% formic acid as solvent A and CH_3CN containing 0.1% formic acid as solvent B.

Methyl 10-hydroxy-1-oxo-1H-benzo[g]isochromene-3-carboxylate (3.12a): Purified using 75%-100% $CHCl_3$ in hexanes to give 3.**12a** (0.093 g, 48%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.49 (ddt, J = 8.4, 1.5, 0.8 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.73 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.62 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.57 (s, 1H), 7.48 (d, J = 0.8 Hz, 1H), 3.98 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.3, 162.2, 160.9, 141.4, 137.7, 131.2, 128.7, 128.2, 127.1, 124.6, 124.5, 117.6, 114.8, 100.7, 53.1. HRMS (ESI) calcd for $C_{15}H_{11}O_5$ $[M+H]^+$ 271.0601, found 271.0604.

Ethyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12b): Purified using 80% $CHCl_3$/hexanes to give **3.12b** (0.030 g 31%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.47 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.75-7.69 (m, 1H), 7.64-7.58 (m, 1H), 7.54 (s, 1H), 7.45 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 162.1, 160.4, 141.6, 137. 7, 131.1, 128.8, 128.2, 127.0, 124.6, 124.5, 117.5, 114.5, 100.7, 62.4, 14.4; HRMS (ESI) calcd for $C_{16}H_{13}O_5$ $[M+H]^+$ 285.0757, found 285.0749.

Propyl 10-hydroxy-1-oxo-1H-benzo[g]isochromene-3-carboxylate (3.12c): Purified using a 90%-100% $CHCl_3$/petroleum ether to give impure **12c** (0.029 g) as an orange, amorphous solid. A portion of this material (6.0 mg) was purified by HPLC (75% B for 15 min, 75-100% B over 2

min, 100% B for 4 min, 100-75% B over 1 min, 75% B for 3 min) to give **3.12c** (5.0 mg, 22%) as an orange, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.65 – 7.58 (m, 1H), 7.55 (s, 1H), 7.47 (s, 1H), 4.33 (t, *J* = 6.5 Hz, 2H), 1.83 (sextet, *J* = 7.1 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 162.0, 160.3, 141.5, 137.6, 131.0, 128.7, 128.0, 126.9, 124.4, 124.4, 117.3, 114.3, 100.6, 67.8, 22.0, 10.4. HRMS (ESI) calcd for $C_{17}H_{15}O_5$ $[M+H]^+$ 299.0914, found 299.0907.

Butyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12d): Purified using 0%-10% acetone in 50% $CHCl_3$/petroleum ether to give **3.12d** (0.046 g, 40%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.62 – 7.57 (m, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 4.37 (t, *J* = 6.7 Hz, 2H), 1.78 (p, *J* = 6.8 Hz, 2H), 1.49 (sextet, *J* = 7.3 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.4, 162.2, 160.5, 141.7, 137.7, 131.1, 128.8, 128.2, 127.0, 124.6, 124.5, 117.5, 114.5, 100.8, 66.3, 30.7, 19.3, 13.9.; HRMS (ESI) calcd for $C_{18}H_{17}O_5$ $[M+H]^+$ 313.1071, found 313.1074.

Isopropyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12e): Purified using 0%-10% acetone in 50% $CHCl_3$/petroleum ether to give impure **3.12e** (0.036 g) as a yellow, amorphous solid. A portion of this material (10.0 mg) was purified by HPLC (80% B for 10 min, 80-100% B over 3 min, 100% B for 4 min, 100-80% B over 1 min, 80% B for 3 min) to give **3.12e** (7.0 mg, 23%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.63 – 7.57 (m, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 5.33 – 5.23 (septet. *J* = 6.2 Hz, 1H), 1.41 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5, 162.1, 159.9, 141.9, 137.7, 131.1, 128.9, 128.2, 127.0, 124.6,

124.5, 117.4, 114.3, 100.8, 70.2, 22.z0; HRMS (ESI) calcd for $C_{17}H_{15}O_5$ $[M+H]^+$ 299.0914, found 299.0919

3-Methylbut-2-en-1-yl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12g): Purified using 75%-100% $CHCl_3$/hexanes to give impure **3.12g** (0.034 g) as an orange, amorphous solid. A portion of this material (7.0 mg) was purified by HPLC (75-100% B over 13 min, 100% B for 4 min, 100-75% B over 1 min, 75% B for 3 min) to give **3.12g** (5.0 mg, 21%) as an orange, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (s, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.74 - 7.70 (m, 1H), 7.64 - 7.59 (m, 1H), 7.56 (s, 1H), 7.47 (s, 1H), 5.51 – 5.44 (m, 1H), 4.87 (d, *J* = 7.4 Hz, 2H), 1.81 (s, 3H), 1.79 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 166.3, 162.0, 160.3, 141.6, 140.5, 137.68, 131.0, 128.7, 128.1, 126.9, 124.5, 124.4, 117.8, 117.4, 116.9, 114.4, 63.1, 25.9, 18.2; HRMS (ESI) calcd for $C_{19}H_{16}O_5Na$ $[M+Na]^+$ 347.0890, found 347.0884

2-(Trimethylsilyl)ethyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12h): Purified using 75%-100% $CHCl_3$/hexanes to give impure **3.12h** (0.014 g) as a yellow, amorphous solid. A portion of this material (9.0 mg) was purified by HPLC (75-100% B over 10 min, 100% B for 4 min, 100-90% B over 2 min, 90% B for 4 min) to give **3.12h** (5.0 mg, 6%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.48 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.75-7.69 (m, 1H), 7.64 – 7.59 (m, 1H), 7.55 (s, 1H), 7.48 (s, 1H), 4.58 – 4.39 (m, 2H), 1.23 – 1.14 (m, 2H), 0.11 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 166.2, 162.0, 160.4, 141.6, 137.5, 130.9, 128.7, 128.0, 126.8, 124.4, 124.3, 117.3, 114.2, 100.1, 64.7, 17.41, -1.5; HRMS (ESI) calcd for $C_{19}H_{20}O_5SiNa$ $[M+Na]^+$ 379.0972, found 379.0962.

3-Chloropropyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12i): Purified using 70%- 100% $CHCl_3$/hexanes to give impure **3.12i** (0.036 g) as a yellow, amorphous solid.

A portion of this material (7.7 mg) was purified by HPLC (70% B for 15 min, 70-100% B over 2 min, 100% B for 4 min, 100-70% B over 1 min, 70% B for 3 min) to give **3.12i** (1.6 mg, 6%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.65-7.60 (m, 1H), 7.57 (s, 1H), 7.49 (s, 1H), 4.54 (t, *J* = 6.1 Hz, 2H), 3.73 (t, *J* = 6.3 Hz, 2H), 2.27 (p, *J* = 6.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 162.1, 160.2, 141.2, 137.5, 131.1, 128.5, 128.1, 127.0, 124.5, 124.4, 117.5, 114.8, 100.58, 62.9, 41.0, 31.4; HRMS (ESI) calcd for $C_{17}H_{14}ClO_5$ $[M+H]^+$ 333.0524, found 333.0515.

<u>3-Bromopropyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12j):</u> Purified using 60%-100% $CHCl_3$/hexane to give impure **3.12j** (0.020 g) as a yellow, amorphous solid. A portion of this material (9.0 mg) was purified by HPLC (70% B for 15 min, 70-100% B over 2 min, 100% B for 4 min, 100-70% B over 1 min, 70% B for 3 min) to give **3.12j** (3.0 mg, 5%) as a yellow, amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.66 – 7.60 (m, 1H), 7.58 (s, 1H), 7.50 (s, 1H), 4.52 (t, *J* = 6.1 Hz, 2H), 3.57 (t, *J* = 6.4 Hz, 2H), 2.36 (p, *J* = 6.2 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.3, 162.2, 160.3, 141.3, 137.7, 131.2, 128.7, 128.2, 127.2, 124.7, 124.6, 117.7, 115.0, 100.7, 64.0, 31.7, 29.3; HRMS (ESI) calcd for $C_{17}H_{14}BrO_5$ $[M+H]^+$ 377.0019, found 377.0010.

<u>Benzyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12o):</u> Purified using 75%-100% $CHCl_3$/hexanes to give impure **3.12o** (0.046 g) as a yellow, amorphous solid. A portion of this material (6.0 mg) was purified by HPLC (90-100% B over 13 min, 100% B for 4 min, 100-90% B over 1 min, 90% B for 3 min) to give **3.12o** (5.0 mg, 30%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.85 (d,

J = 8.2 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.64 – 7.55 (m, 2H), 7.50 -7.34 (m , 6H), 5.40 (s, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 162.0, 160.1, 141.2, 137.5, 135.0, 131.0, 128.67, 128.65, 128.58, 128.5, 128.1, 127.0, 124.5, 124.4, 117.5, 114.8, 100.6, 67.8; HRMS (ESI) calcd for $C_{21}H_{15}O_5$ $[M+H]^+$ 347.0914, found 347.0904.

4-Methoxybenzyl 10-hydroxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.12p): Purified using 75%-100% $CHCl_3$/hexane to give impure **3.12p** (0.026 g) as a yellow, amorphous solid. A portion of this material (5.0 mg) was purified by HPLC (75-100% B over 13 min, 100% B for 4 min, 100-75% B over 1 min, 75% B for 3 min) to give **3.12p** (2.0 mg, 8%) as a yellow, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (s, 1H), 8.50 – 8.46 (m, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.72 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.55 (d, *J* = 0.5 Hz, 1H), 7.46 (s, 1H), 7.44 – 7.37 (m, 2H), 6.90-6.96 (m, 2H), 5.34 (s, 2H), 3.83 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 166.3, 162.2, 160.3, 160.1, 141.5, 137.7, 131.1, 130.8, 128.8, 128.2, 127.3, 127.1, 124.6, 124.5, 117.6, 114.8, 114.3, 100.8, 67.8, 55.5; HRMS (ESI) calcd for $C_{22}H_{16}O_6Na$ $[M+Na]^+$ 399.0839, found 399.0831.

10-Hydroxy-*N*,*N*-diisopropyl-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxamide (3.12s): Purified using 0%-20% EtOAc/$CHCl_3$ to give **3.12s** (0.054 g, 44%) as an orange, amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.54 (dt, *J* = 8.2, 6.8 Hz, 1H), 7.30 (s, 1H), 6.88 (s, 1H), 3.96 (br s, 1H), 3.63 (br s, 1H), 1.41 (br s, 12H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 162.0, 161.9, 148.3, 138.0, 130.9, 129.8, 127.8, 126.2, 124.3, 123.7, 115.5, 108.6, 100.6, 51.2 (br), 46.8 (br), 20.7 (br); HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 330.1543, found 330.1536.

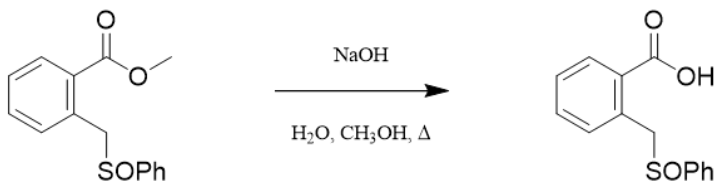
10-Hydroxy-3-(piperidine-1-carbonyl)-1*H*-benzo[*g*]isochromen-1-one (3.12t): Purified using 5%-30% acetone in 66% $CHCl_3$/petroleum ether to give **3.12t** (0.076 g, 64%) as an amorphous,

orange solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.37 (s, 1H), 7.04 (s, 1H), 3.63 (br s, 4H), 1.71 (br s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 162.1, 161.3, 146.8, 138.0, 131.1, 129.6, 128.0, 126.5, 124.4, 123.9, 116.0, 110.7, 100.6, 48.5 (br), 44.3 (br), 26.6 (br), 25.7 (br), 24.6; HRMS (ESI) calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$ 324.1230, found 324.1226.

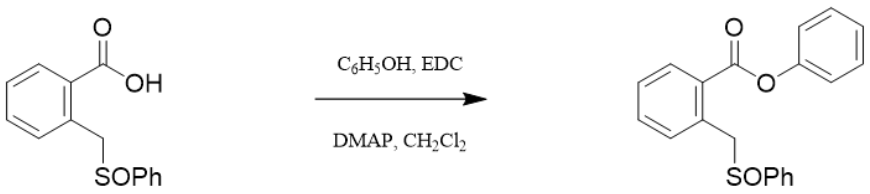
10-Hydroxy-3-(morpholine-4-carbonyl)-1*H*-benzo[*g*]isochromen-1-one (3.12u): Purified using 10%-35% acetone in 66% $CHCl_3$/petroleum ether to give **3.12u** (0.064 g, 67%) as an orange amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 8.47 (*J* = 8.5 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.74 – 7.68 (m, 1H), 7.63 - 7.56 (m, 1H), 7.40 (s, 1H), 7.17 (s, 1H), 3.78 (br s, 8H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 162.2, 161.3, 145.9, 138.0, 131.2, 129.2, 128.0, 126.7, 124.5, 124.1, 116.5, 112.2, 100.4, 67.0 (br), 53.6 (br), 47.5 (br); HRMS (ESI) calcd for $C_{18}H_{16}NO_5$ $[M+H]^+$ 326.1023, found 326.1027.

tert*-Butyl hexyl(10-hydroxy-1-oxo-1H-benzo[g]isochromene-3-carbonyl)carbamate (3.12v*):** Purified using pure $CHCl_3$ followed by another purification using 75%-100% $CHCl_3$/hexanes to give **3.12v (0.046 g, 35%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.12 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.69 (ddd, *J* = 8.6, 6.8, 1.3 Hz, 1H), 7.58 (dt, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (s, 1H), 7.18 (s, 1H), 3.78 – 3.71 (t, *J* = 7.7 Hz, 2H), 1.73 – 1.62 (m, 2H), 1.42 (s, 9H), 1.38 – 1.31 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 164.8, 162.1, 152.6, 146.9, 137.9, 131.1, 129.4, 128.0, 126.7, 124.4, 124.2, 116.8, 111.0, 100.6, 84.0, 46.2, 31.6, 28.8, 27.9, 26.6, 22.7, 14.1; HRMS (ESI) calcd for $C_{25}H_{28}NO_6$ $[M-H]^-$ 438.1922, found 438.1909.

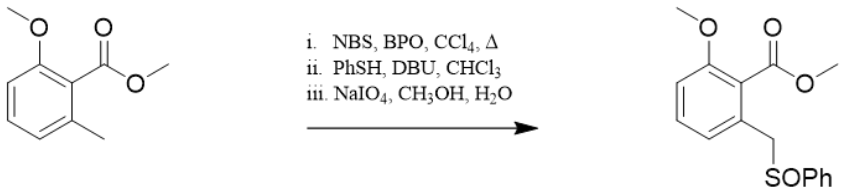
Dimethyl (2*Z*,4*Z*)-2-hydroxyhexa-2,4-dienedioate (3.13): Isolated as an amorphous orange solid (0.008 g, 5%) from isolation optimization trials: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 15.6, 11.7 Hz, 1H), 6.35 (br s, 1H), 6.26 (dd, *J* = 11.7, 0.8 Hz, 1H), 6.03 (dd, *J* = 15.6, 0.9 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 165.3, 143.9, 137.1, 122.9, 108.8, 53.6, 51.8; HRMS (ESI) calcd for $C_8H_{10}O_5Na$ $[M+Na]^+$ 209.0420, found 209.0434.



2-((Phenylsulfinyl)methyl)benzoic acid (3.16): A flask was charged with **3.11** (0.295 g, 1.13 mmol), water (25 mL) and methanol (25 mL). Solid NaOH (0.290 g, 7.13 mmol) was added and the mixture was heated to 50 °C for 4 h. After cooling, the methanol was removed under reduced pressure. Unreacted starting material was removed by washing the aqueous solution with CH_2Cl_2 (2 x 25 mL). The aqueous layer was acidified (pH ~2) using 3 M HCl and **3.16** (0.333 g, 68%) was collected via filtration as a white precipitate: ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 – 8.05 (m, 1H), 7.63 – 7.50 (m, 5H), 7.48 – 7.43 (m, 2H), 7.14 – 7.09 (m, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 169.8, 144.0, 134.4, 133.4, 133.2, 132.67, 132.65, 131.4, 130.3, 129.8, 125.5, 64.0; HRMS (ESI) calcd for $C_{14}H_{13}O_3S$ $[M+H]^+$ 261.0585, found 261.0577



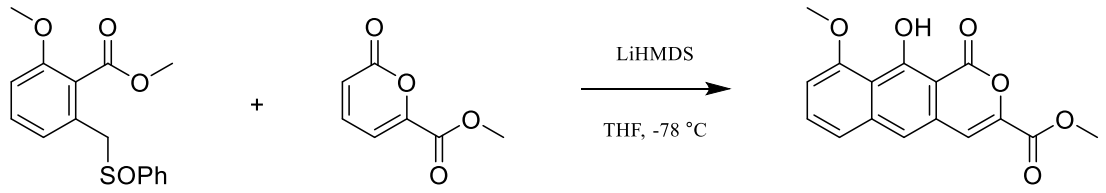
Phenyl 2-((phenylsulfinyl)methyl)benzoate (3.17): To a stirring solution of **3.16** (0.295 g, 1.13 mmol), phenol (0.110 g, 1.17 mmol), and EDC·HCl (0.240 g, 1.25 mmol) dissolved in CH_2Cl_2 (6 mL) was added DMAP (14.0 mg, 0.115 mmol). After stirring at rt for 24 h, the reaction was quenched by the addition of $NaHCO_3$ (3 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic layers were washed with NaOH (0.5 M, 8 mL) and brine (8 mL), dried (Na_2SO_4), and concentrated. The residue purified was using flash chromatography (SiO_2, 33-50% EtOAc/hexanes) to give **3.17** (0.233 g, 61%) as a clear and colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.17 (m, 1H), 7.59-7.41 (m, 9H), 7.33 – 7.28 (m, 1H), 7.25 – 7.21 (m, 3H), 4.92 (d, *J* = 12.1 Hz, 1H), 4.26 (d, *J* = 12.2 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.5, 150.8, 143.8, 133.6, 133.11, 133.10, 131.8, 131.0, 129.7, 129.0, 128.9, 128.7, 126.2, 124.3, 121.9, 63.0; HRMS (ESI) calcd for $C_{20}H_{16}O_3SNa$ $[M+Na]^+$ 359.0718, found 359.0710.



Methyl 2-methoxy-6-((phenylsulfinyl)methyl)benzoate (3.19): The following reaction as carried out in an analogous manner to the published procedure.[8] Methyl methoxytoluate **3.18** (0.195 g, 1.08 mmol), NBS (0.214 g, 1.20 mmol), and AIBN (9.6 mg, 0.0061 mmol) were added to a dried flask. After purging with nitrogen, CCl_4 (12 mL) was added, and the reaction was refluxed for 3.5 h. After cooling to room temperature, the reaction was filtered and was carried onto the next step without further purification.

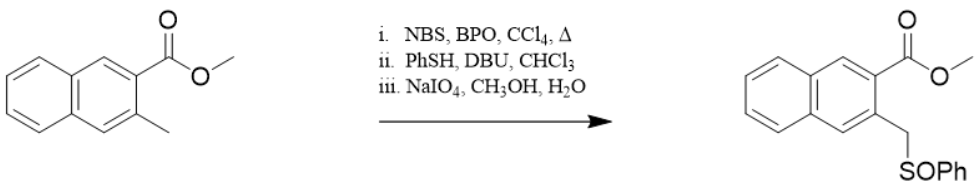
Dried K_2CO_3 (0.299 g, 2.16 mmol) was added to a flame-dried in flask, followed by crude oil and thiophenol (0.124 mL, 1.21 mmol). After purging, acetone (20 mL) was added and the mixture heated at reflux overnight. After cooling to room temperature, Et_2O (25 mL) and 5% aqueous NaOH solution (5 mL) was added and the layers were separated. The aqueous layer was concentrated and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated furnishing a red oil which was carried on without further purification.

Crude was dissolved in methanol (25 mL) and water (5 mL). $NaIO_4$ (0.230 g, 1.08 mmol) was added the reaction was stirred overnight, after which the methanol was removed under reduced pressure. The mixture was extracted with EtOAc (3 x 20 mL), dried (Na_2SO_4), and concentrated. The residue was purified using flash chromatography (SiO_2, 0%-65% EtOAc/hexanes) to yield **3.19** (0.176 g, 53%) as a viscous, off-white oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 5H), 7.24 (t, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8.5 1H), 6.64 (d, *J* = 8.0 1H), 4.17 (d, *J* = 12.7 Hz, 1H), 4.03 (d, *J* = 12.7 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.9, 157.4, 143.5, 131.4, 131.1, 129.8, 129.1, 124.3, 123.8, 123.7, 111.6, 62.5, 56.3, 52.5; HRMS (ESI) calcd for $C_{16}H_{16}O_4SNa$ $[M+Na]^+$ 327.0667, found 327.0660.



<u>Methyl 10-hydroxy-9-methoxy-1-oxo-1*H*-benzo[*g*]isochromene-3-carboxylate (3.20):</u> The material was prepared according to the general procedure for pyrone annulation using **3.7a** (0.098 g, 0.636 mmol), **3.19** (0.079 g, 0.260 mmol), and LiHMDS (0.78 mL, 1 M, 0.78 mmol) in THF (5 mL). Purified using $CHCl_3$ followed by 25%-40% EtOAc/hexanes to yield **3.20** (0.015 g,

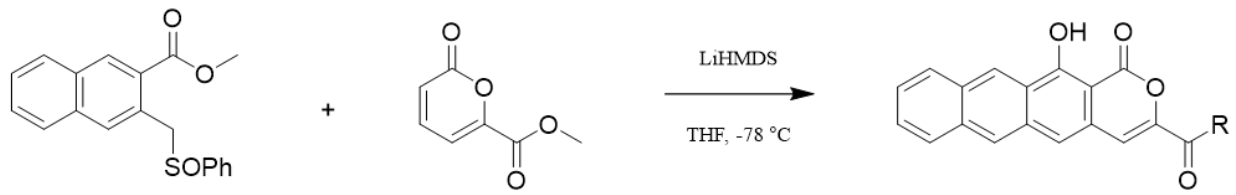
22%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.93 (s, 1H), 7.60 (t, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 0.5 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.37 (s, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 4.06 (s, 3H), 3.97 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.1, 164.3, 160.8, 159.3, 141.5, 140.3, 131.7, 129.4, 120.8, 117.4, 115.9, 114.2, 107.0, 100.9, 56.4, 53.0; HRMS (ESI) calcd for $C_{16}H_{13}O_6$ $[M+H]^+$ 301.0712, found 301.0703.



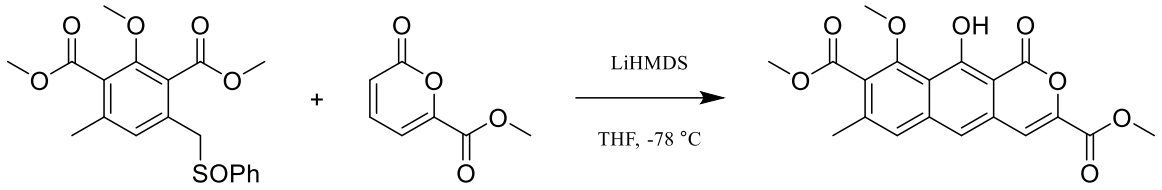
<u>Methyl 3-((phenylsulfinyl)methyl)-2-naphthoate (3.23):</u> The following reaction was carried out in an analogous manner to the published procedure.[9] **Caution!** Carbon tetrachloride is highly toxic and should be handled exclusively in a fume cabinet to avoid vapor exposure. Naphthoate **3.21** (0.518 g, 2.59 mmol) was dissolved in CCl_4 (16 mL). To the stirring mixture was added NBS (0.484 g, 2.73 mmol) and benzoyl peroxide (10.0 mg, 0.0412 mmol). The mixture was heated to reflux and stirred for 6 h, after which the reaction was cooled, filtered, and concentrated to yield an orange oil which was used without further purification. This material was dissolved in $CHCl_3$ (20 mL) and thiophenol (0.277 mL, 2.72 mmol) and Et_3N (0.38 mL, 2.7 mmol) were added. The mixture was stirred at rt overnight, after which solids were filtered away. The filtrate was washed with 1 M NaOH (3 x 10 mL), brine (10 mL), and dried (Na_2SO_4). The material was concentrated and used without further purification.

Crude oil was dissolved in methanol (15 mL) and water (1.5 mL) and after addition of $NaIO_4$ (0.581 g, 2.72 mmol) was stirred overnight. The mixture was concentrated to remove the methanol, diluted with EtOAc (10 mL), and filtered. The filtrate was partitioned with water (20

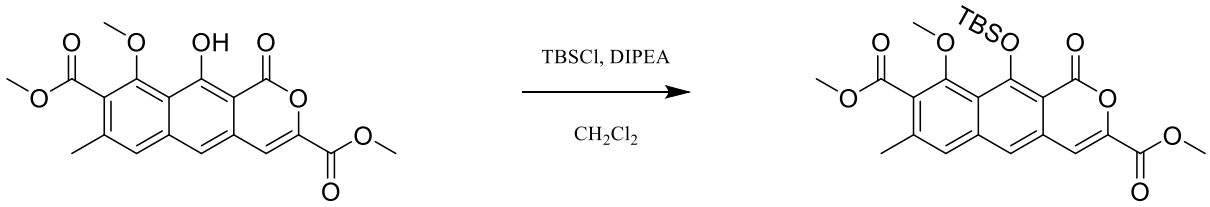
mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated and the residue purified using flash chromatography (SiO_2, 0%-33% EtOAc/$CHCl_3$) to yield **3.23** (0.454 g 54%) as an off-white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.66 – 7.52 (m, 5H), 7.50 – 7.42 (m, 3H), 4.98 (d, *J* = 12.2 Hz, 1H), 4.39 (d, *J* = 12.2 Hz, 1H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 144.2, 134.8, 133.2, 133.0, 132.3, 131.0, 129.1, 129.00, 128.97, 127.9, 127.7, 127.4, 126.6, 124.4, 64.0, 52.4; HRMS (ESI) calcd for $C_{19}H_{17}O_3S$ $[M+H]^+$ 325.0898, found 325.0897.



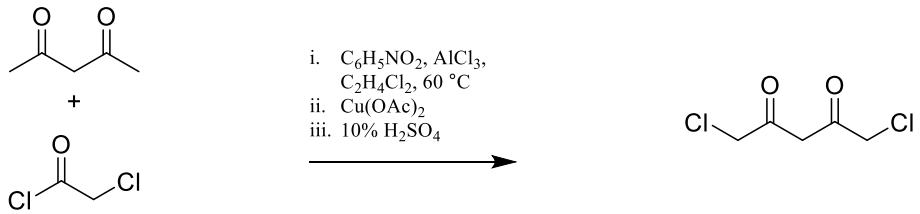
<u>Methyl 12-hydroxy-1-oxo-1*H*-naphtho[2,3-*g*]isochromene-3-carboxylate (3.24):</u> The material was prepared according to the general procedure for pyrone annulation using **3.7a** (0.132 g, 0.856 mmol), **3.23** (0.119 g, 0.367 mmol), and LiHMDS (1.15 mL, 1.15 mmol) in THF (16 mL). Purified using $CHCl_3$ to give **3.24** (0.018 g, 15%) as an orange amorphous solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.53 (s, 1H), 9.12 (s, 1H), 8.43 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.67 – 7.53 (m, 4H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.5, 163.9, 161.0, 140.8, 134.6, 133.6, 131.8, 129.4, 128.2, 128.0, 127.0, 126.9, 126.7, 125.2, 123.0, 117.9, 115.1, 98.6, 53.0; HRMS (ESI) calcd for $C_{19}H_{13}O_5$ $[M+H]^+$ 321.0763, found 325.0752.



<u>Dimethyl 10-hydroxy-9-methoxy-7-methyl-1-oxo-1H-benzo[g]isochromene-3,8-dicarboxylate (4.7):</u> A flask containing THF (2 mL) was added HMDS (2.42 mL, 11.6 mmol) was cooled to 0 °C using a water/ice bath. Once cooled, *n*BuLi (5.2 mL, 2.1 M) was added slowly. After addition, the mixture was warmed to room temperature and cooled to -78 °C using a dry ice/acetone bath. Once cooled, pyrone **2.6** (1.36 g, 8.75 mmol) dissolved in THF (45 mL) and was added slowly. The reaction stirred for 15 minutes, at which point sulfoxide **2.27** (1.40 g, 3.64 mmol) dissolved in THF (16 mL) was added dropwise slowly. After stirring cold for 60 min, the cold bath was removed and the reaction left to stir for an additional 60 min. The reaction was quenched with aqueous HCl (24 mL, 10%) and residual THF was removed under reduced pressure. The resulting residue was diluted with $CHCl_3$ (30 mL) and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification using flash chromatography (SiO_2, 1 → 10% EtOAc:$CHCl_3$) yielded **4.7** (0.46 g, 33%) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 3.99 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 2.46 (s, 3H); 13C NMR (100 MHz, $CDCl_3$) 168.0, 166.4, 163.1, 160.6, 156.1, 141.8, 140.3, 139.1, 130.1, 128.7, 124.9, 117.01, 116.95, 114.1, 101.2, 64.5, 53.1, 52.6, 19.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}O_8$ 373.0923, found 373.0907.



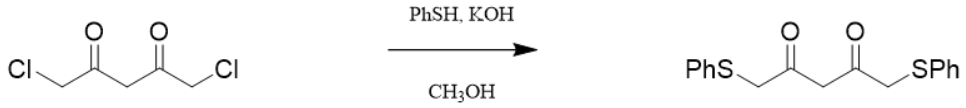
<u>Dimethyl 10-((tert-butyldimethylsilyl)oxy)-9-methoxy-7-methyl-1-oxo-1H-benzo[g] isochromene-3,8-dicarboxylate (4.8):</u> To a flask containing **4.7** (0.024 g, 0.064 mmol) was added CH_2Cl_2 (1.5 mL). Once fully dissolved the reaction was placed in an ice/water bath and DIPEA (0.17 mL, 0.999 mmol) was added dropwise. After stirring for 1 min, TBSCl (0.097 g, 0.642 mmol) was added. After stirring for 5 min, the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL) and the layers were separated. The aqueous was washed with CH_2Cl_2 (3 x 2.5 mL) and the combined organic layers were dried using Na_2SO_4 and concentrated. The residue was purified using flash chromatography (SiO_2, 20% → 50% EtOAc:$CHCl_3$) to yield **4.8** (0.029 g, 95%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.42 (s, 1H) 7.40 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.81 (s, 3H), 2.43 (s, 3H), 1.11 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 161.2, 158.6, 157.9, 155.8, 142.4, 139.4, 137.6, 132.2, 128.0, 124.2, 121.1, 119.6, 112.5, 110.0, 63.6, 52.8, 52.4, 26.2, 19.6, 18.5, -4.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{31}O_8Si$ 487.1788, found 487.1783.



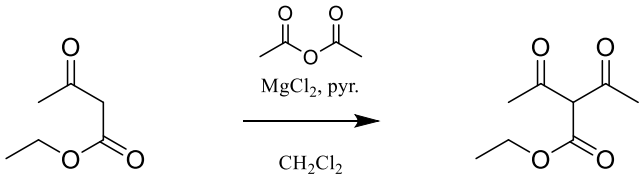
<u>1,5-Dichloropentane-2,4-dione (4.18):</u> To a flame-dried, 2-necked round-bottomed flask was added $AlCl_3$ (6.49 g, 48.8 mmol). An addition funnel was placed in the internal neck, connected

to a nitrogen line, with the other neck being attached to a hose adapter, with the outlet feeding into a bath composed of a saturated $NaHCO_3$ solution (1 L). Once purged with nitrogen, nitrobenzene (8.2 mL, 48.6 mmol) was added slowly via the addition funnel, followed by addition of 1,2-dichloroethane (9.6 mL) via the addition funnel. Once the solids had fully dissolved, which required sonication, the reaction was cooled in a water/ice bath and 2,4-pentanedione was added via the addition funnel over the course of 20 min. Chloroacetyl chloride (8.50 mL, 107 mmol) was added via the addition funnel over 15 min and the mixture was warmed to room temperature. After stirring for 30 min, the addition funnel was exchanged with a short path distillation apparatus outlet and the mixture was heated to 70 °C (oil bath) to remove any remaining acyl chloride. After heating for 1 h, the mixture was cooled and poured into a beaker containing ice (80 g) and concentrated HCl (8 mL) and stirred overnight.

The layers were separated and the aqueous layer washed with Et_2O (3 x 15 mL). The combined organic layers were then added to a saturated solution of $Cu(OAc)_2$ (100 mL) and stirred for 3 h. The resulting gray solid that formed was collected by filtration and rinsed with additional portions of diethyl ether (3 x 15 mL). The isolated solid was added to a solution of H_2SO_4 (50 mL, 10%). Once stirring was initiated, Et_2O (50 mL) was added. The layers were separated and the aqueous washed with additional portions of ether (3 x 15 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated to yield a black-red oil. Purification using flash chromatography (SiO_2, 5% → 10% EtOAc:Hex) resulted in **4.18** (1.17 g, 14%) as a dark red oil. The compound exists as a mixture of tautomers with the rapidly interconverting cyclic enol form dominating in the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.09 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.3, 96.8, 44.1. **Mass could not be obtained due to instability of material.**

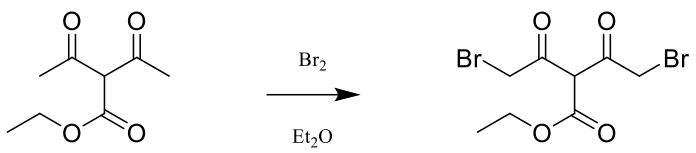


<u>1,5-Bis(phenylthio)pentane-2,4-dione (4.19):</u> To a stirring solution of KOH (2.97 g, 53.0 mmol) in methanol (50 mL) was added thiophenol (5 mL, 49.0 mmol). After stirring for 15 minutes, **4.18** (2.76 g, 16.3 mmol) was added dropwise and the resulting mixture was stirred for 72 h. The mixture was filtered (filter paper, methanol) and the filtrate concentrated. The residue was dissolved in Et_2O (50 mL) and washed with $NaHCO_3$ (50 mL). The aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with $NaHCO_3$ (2 x 50 mL), brine, (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified via column chromatography (SiO_2, 5 → 20% EtOAc:Hex) to give **4.19** (2.22 g, 43%) as an orange oil as a mixture of the tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 12H), 5.89 (s, 1H (enol)), 3.93 (s, 0.4H (tautomer)), 3.85 (s, 0.6H (tautomer)), 3.70 (s, 0.8H (tautomer)), 3.58 (s, 4H (enol)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.X (keto), 189.5 (enol), 134.7 (enol), 130.3 (enol), 129.8 (keto), 129.4 (keto), 129.2 (enol), 127.4 (keto), 127.3 (enol), 98.8 (enol), 51.6 (keto), 44.4 (keto), 40.4 (enol); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}O_2S_2$ 317.0664; found 317.0665.

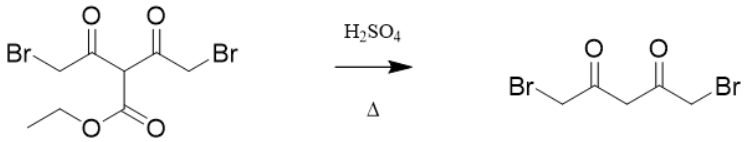


<u>Ethyl 2-acetyl-3-oxobutanoate (4.20):</u> As per the literature precedent,[11] a flask was charged with ethyl acetoacetate (5.99, 46.0 mmol), $MgCl_2$ (4.43 g, 46.5 mmol), and CH_2Cl_2 (50 mL). After purging with nitrogen, acetic anhydride (4.40 mL, 46.5 mmol) was added, followed by

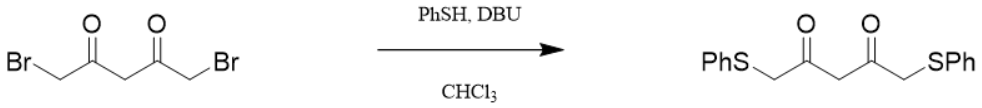
dropwise addition of pyridine (7.5 mL, 94.8 mmol). The mixture stirred overnight, after which it was filtered through filter paper (CH_2Cl_2). The filtrate was washed with water (25 mL), aqueous HCl (1 M, 3 x 40 mL), and brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield **4.20** (6.0 g, 76%) as a clear oil. Spectral data were in accordance with that previously reported.[11]



<u>Ethyl 4-bromo-2-(2-bromoacetyl)-3-oxobutanoate (4.21):</u> To a 2-necked round-bottomed flask equipped with an addition funnel and an outlet to a water bath was added **4.20** (9.99 g, 58.0 mmol) and Et_2O (40 mL). The mixture was cooled in a water/ice bath and bromine (6.00 mL, 117 mmol) was added dropwise over 2 h. The mixture was warmed to room temperature and stirred overnight. After pouring onto ice (50 g), the mixture was diluted with Et_2O (50 mL). The layers were separated and the organic layer was washed with water (2 x 50 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated to give **4.21** (18.7 g, 98%) as an orange oil that solidified upon cooling to an orange-brown amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 4H), 4.35 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 164.9, 106.5, 61.9, 30.0, 14.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_8H_{10}Br_2NaO_4$ 350.8844; found 350.8834.

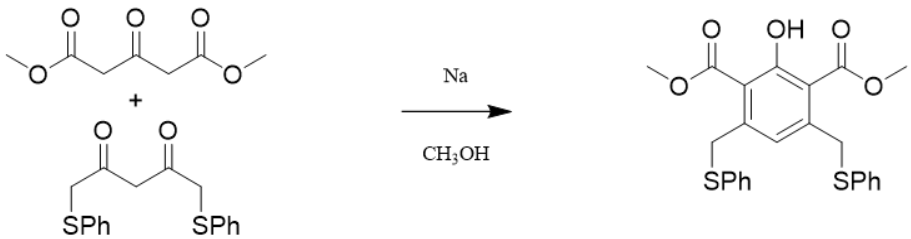


<u>1,5-Dibromopentane-2,4-dione (4.22):</u> Compound **4.21** (28.7 g, 87.0 mmol) was dissolved in conc. H_2SO_4 (40 mL). The mixture was slowly heated to an internal temperature of 85 °C, which was maintained for 15 min (**NOTE**: for small scale decarboxylation use lower internal temperature, 75 °C). The reaction was cooled to room temperature, after which it was poured onto ice-cold water (850 mL). After the ice had melted, the aqueous mixture was extracted with Et_2O (3 x 250 mL). The combined organic layers were washed with brine (250 mL), dried (Na_2SO_4), and concentrated under nitrogen stream. The residue was purified using column chromatography (SiO_2, 8 → 10% EtOAc:Hex) to yield **4.22** (17.0 g, 76%) as a yellow oil that quickly became a black-green oil upon limited exposure to atmosphere with the enol tautomer predominating. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 3.89 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.8, 98.4, 30.1; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_5H_7Br_2O_2$ 256.8813; found 256.8806.

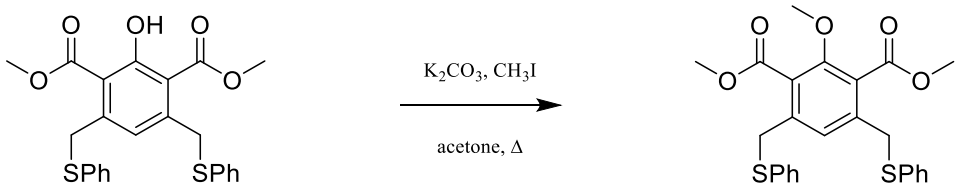


<u>1,5-Bis(phenylthio)pentane-2,4-dione (4.19):</u> To a round-bottomed flask containing $CHCl_3$ (40 mL) was added thiophenol (3.30 mL, 32.4 mmol). The mixture was cooled in an ice/water bath, and after stirring for 15 minutes, DBU (5.30 mL, 35.5 mmol) was added dropwise. After stirring for 5 min, **4.22** (4.18 g, 16.2 mmol) dissolved in $CHCl_3$ (10 mL) was added dropwise. The ice bath was removed and the reaction allowed to warm to room temperature with stirring overnight. The mixture was diluted with $CHCl_3$ (25 mL), washed with water (25 mL), aqueous HCl (1 M, 2 x 25 mL), $NaHCO_3$ (25 mL), and brine (25 mL), dried (Na_2SO_4), and concentrated. The residue

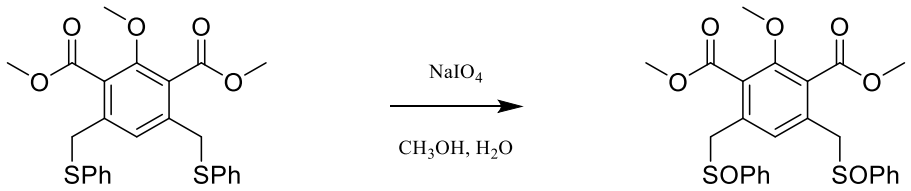
was purified using flash chromatography (SiO_2, 4 → 6% EtOAc:Hex) to yield **4.19** (3.92 g, 77%) as a dark-orange oil. Spectral data were in accord with the material produced from **4.19** above.



<u>Dimethyl 2-hydroxy-4,6-bis((phenylthio)methyl)isophthalate (4.23):</u> To a flame-dried flask was added Na (0.092 g, 3.8 mmol). After purging with nitrogen and cooling in an ice/water bath, CH_3OH (22 mL) was added slowly with proper ventilation for off-gassing hydrogen. Once the metal had dissolved, **4.3** (0.510 mL, 3.53 mmol) was added dropwise. The cooling bath was removed, and the reaction was stirred for 5 min, after which diketone **4.19** (1.06 g, 3.34 mmol) dissolved in CH_3OH (8 mL) was added dropwise. The mixture was stirred for 3.5 days. The mixture was filtered (filter paper, CH_3OH) and the filtrate acidified (pH 1) using aqueous HCl. The mixture was concentrated and the resulting oil dissolved in CH_2Cl_2 (20 mL). Water was added (16 mL) and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, washed with brine (20 mL), and concentrated. Purification using column chromatography (SiO_2, 13→26 % EtOAc:Hex gradient) gave **4.23** (1.06 g, 40%, 56% brsm) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 7.25 – 7.18 (m, 10H), 6.55 (s, 1H), 4.12 (s, 4H), 3.90 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 160.6, 142.5, 135.4, 131.3, 129.1, 127.3, 123.8, 116.6, 52.8, 39.0; ESI calc for $C_{24}H_{23}O_5S_2$ 455.0987, found 455.0967.

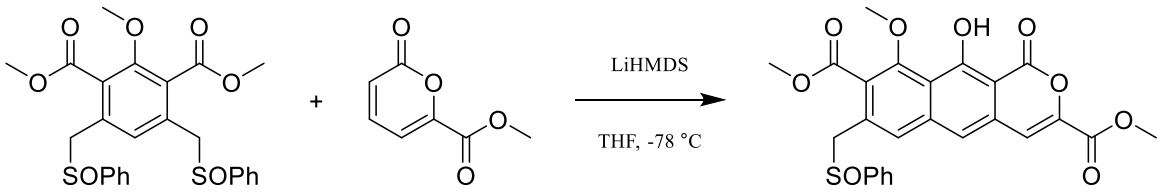


<u>Dimethyl 2-methoxy-4,6-bis((phenylthio)methyl)isophthalate (4.24):</u> K_2CO_3 (0.160 g, 1.13 mmol) was added to a flask and flame dried and purged with nitrogen. Phenol **4.23** (0.29 g, 0.64 mmol) was dissolved in acetone (24 mL) and added to the flask, followed by dropwise addition of CH_3I (0.10 mL, 1.6 mmol). The mixture was refluxed overnight, after which it was cooled to room temperature and concentrated. The residue was suspended in EtOAc (25 mL) with stirring and filtered (filter paper, EtOAc). The filtrate was dried (Na_2SO_4) and concentrated to yield **4.24** (0.296 g, 99.3%) as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.15 (m, 10H), 6.90 (s, 1H), 4.04 (s, 4H), 3.88 (s, 6H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 156.0, 139.1, 135.2, 131.1, 129.1, 127.2, 127.1, 127.0, 63.8, 52.7, 37.1; ESI calcd for $C_{25}H_{25}O_5S_2$ 469.1143; found 469.1124.



<u>Dimethyl 2-methoxy-4,6-bis((phenylsulfinyl)methyl)isophthalate (4.25):</u> Compound **4.24** (1.40 g, 2.99 mmol) was dissolved in a mixture of methanol (70 mL) and water (10 mL). $NaIO_4$ (1.59 g, 7.45 mmol) was added and the mixture was stirred overnight. The mixture was filtered

(filter paper, methanol) and the filtrate was concentrated. The residue was dissolved in EtOAc (60 mL), washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. Purification using flash chromatography (SiO_2, 50→100% EtOAc:Hex) yielded **4.25** (1.30 g, 87%) as a yellow white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 20H), 6.65 (s, 1H), 6.56 (s, 1H), 4.14 (d, J = 12.7 Hz, 2H), 4.07 (s, 4H), 3.99 (d, J = 12.8 Hz, 2H), 3.90 (s, 6H), 3.89 (s, 6H), 3.79 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.7, 156.4, 142.9, 139.4, 134.9, 131.5, 131.4, 131.0, 129.2, 129.0, 128.7, 128.3, 127.2, 124.2, 124.2, 63.7, 61.3, 52.7, 52.7, 36.8; ESI calcd for $C_{25}H_{25}O_5S_2$ 501.1042, found 501.1025.



<u>Dimethyl 10-hydroxy-9-methoxy-1-oxo-7-((phenylsulfinyl)methyl)-1H-benzo[*g*]isochromene-3,8-dicarboxylate (4.26, 5.2):</u> LiHMDS (1 M, 1.2 mL, 1.2 mmol) was added to a flask containing THF (0.4 mL) and cooled to -78 °C using a dry ice/acetone bath. After stirring for 10 min, pyrone **2.6** (0.167 g, 1.08 mmol) dissolved in THF (5 mL) was added dropwise. After stirring for 15 min, bissulfoxide **4.25** (0.224 g, 0.447 mmol) dissolved in THF (XX mL) was added dropwise. The mixture was stirred for 45 min at -78 °C and then warmed to room temperature overnight. The mixture was acidified (pH 1) using aqueous HCl (3.24 M, ~6 mL) and the THF removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Repeated purification of the residue using flash chromatography (SiO_2, 15 → 25 % EtOAc:$CHCl_3$) eventually yielded **4.26** (0.072 g, 32%) as an orange amorphous solid. (600

MHz, $CDCl_3$) ^1H NMR (600 MHz, $CDCl_3$) δ 12.96 (s, 1H), 7.53 – 7.45 (m, 6H), 7.41 (s, 1H), 7.33 (s, 1H), 4.22 (q, J = 13.0 Hz, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.96; 13C NMR (150 MHz, $CDCl_3$) □ ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4, 166.4, 163.2, 160.5, 157.8, 142.7, 142.2, 140.0, 131.7, 131.3, 130.9, 129.4, 127.7, 126.8, 124.3, 118.4, 117.6, 114.0, 102.2, 64.7, 62.3, 53.3, 52.9; ESI calcd for $C_{25}H_{21}O_5S$ 497.0888; found 497.0906.

6.2 References

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Chapter 7: ^{1}H and ^{13}C NMR of Synthesized Molecules

Figure 7.1: ^{1}H NMR of **2.23** (400 MHz, CD_3OD).

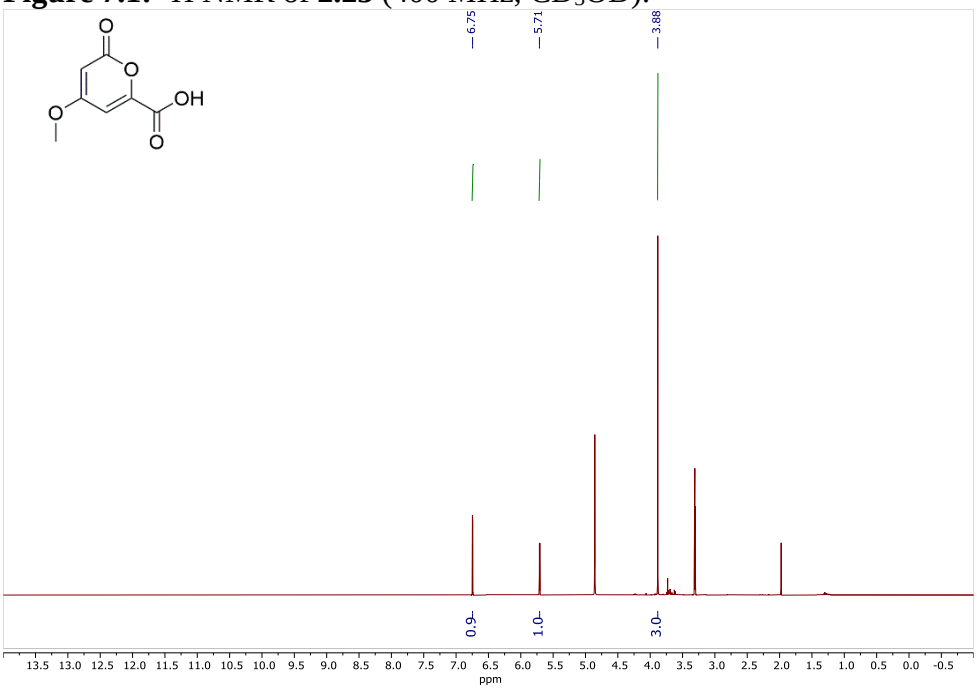

Figure 7.2: ^{13}C{^{1}H} NMR of **2.23** (101 MHz, CD_3OD).

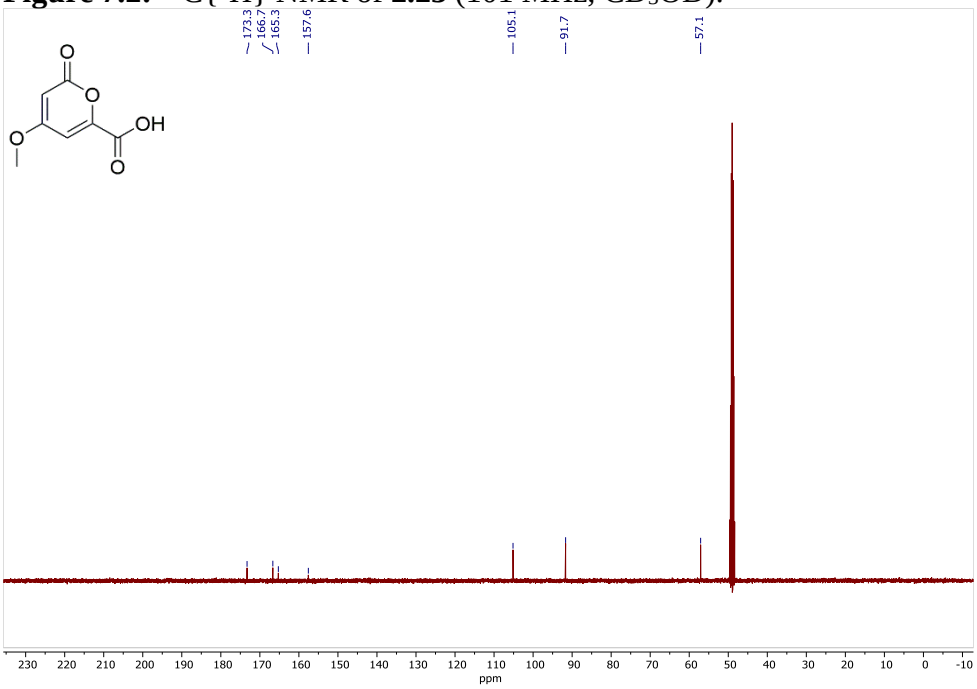

Figure 7.3: ^{1}H NMR of **2.24** (400 MHz, $CDCl_3$).

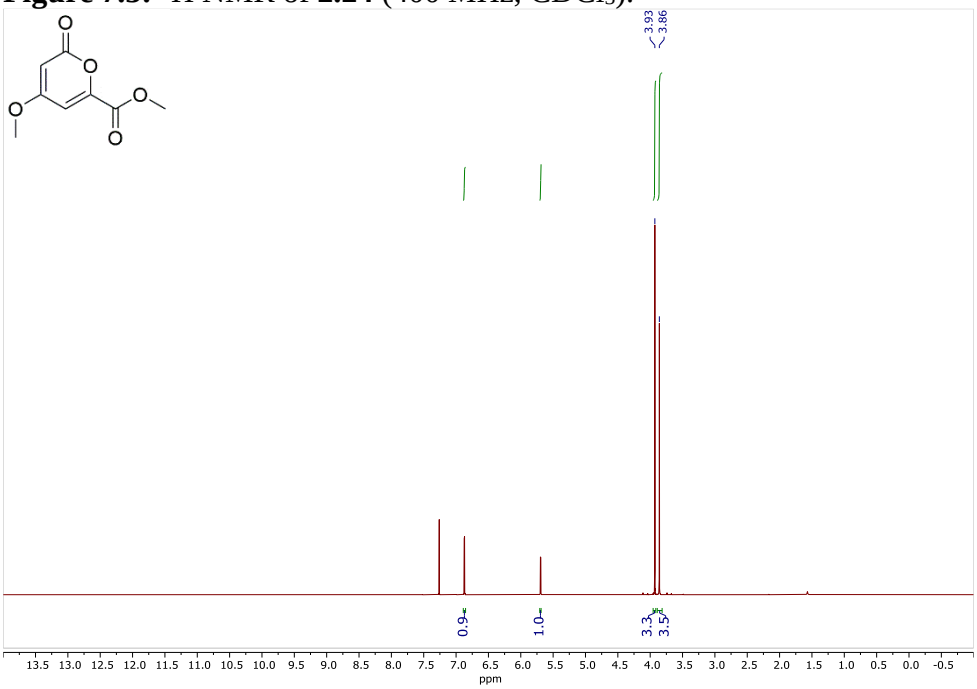

Figure 7.4: ^{13}C{^{1}H} NMR of **2.24** (101 MHz, $CDCl_3$).

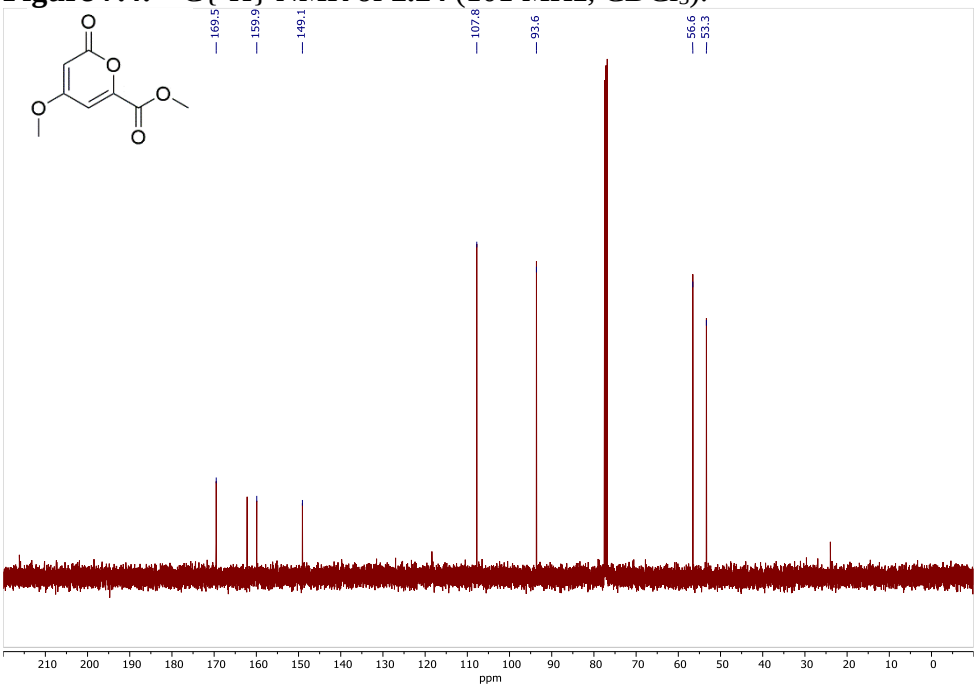

Figure 7.5: ^{1}H NMR of **2.27** (400 MHz, $CDCl_3$).

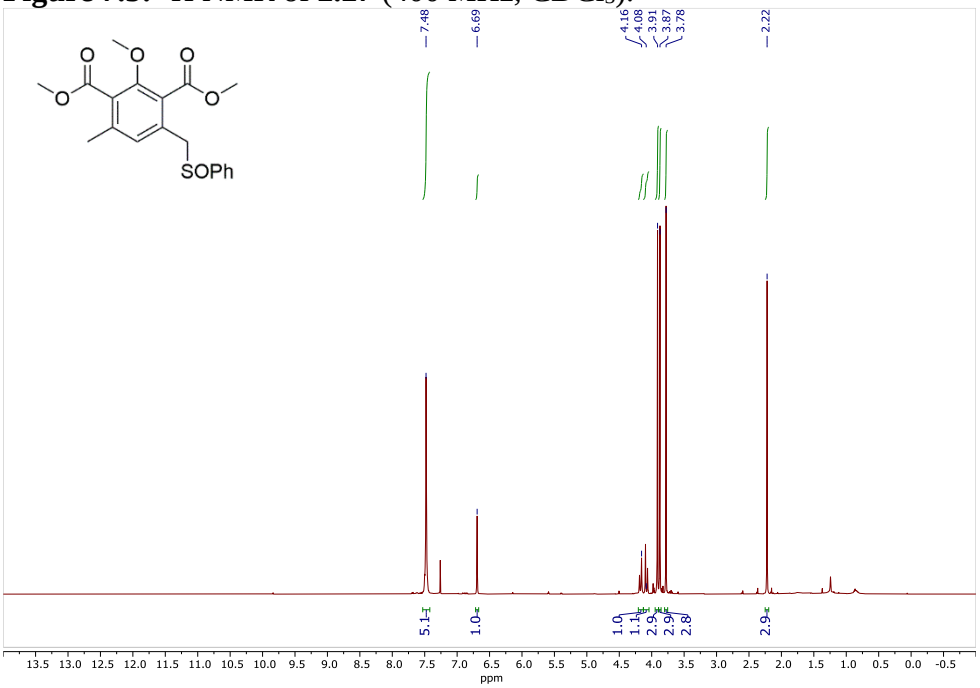

Figure 7.6: ^{13}C{^{1}H} NMR of **2.27** (101 MHz, $CDCl_3$).

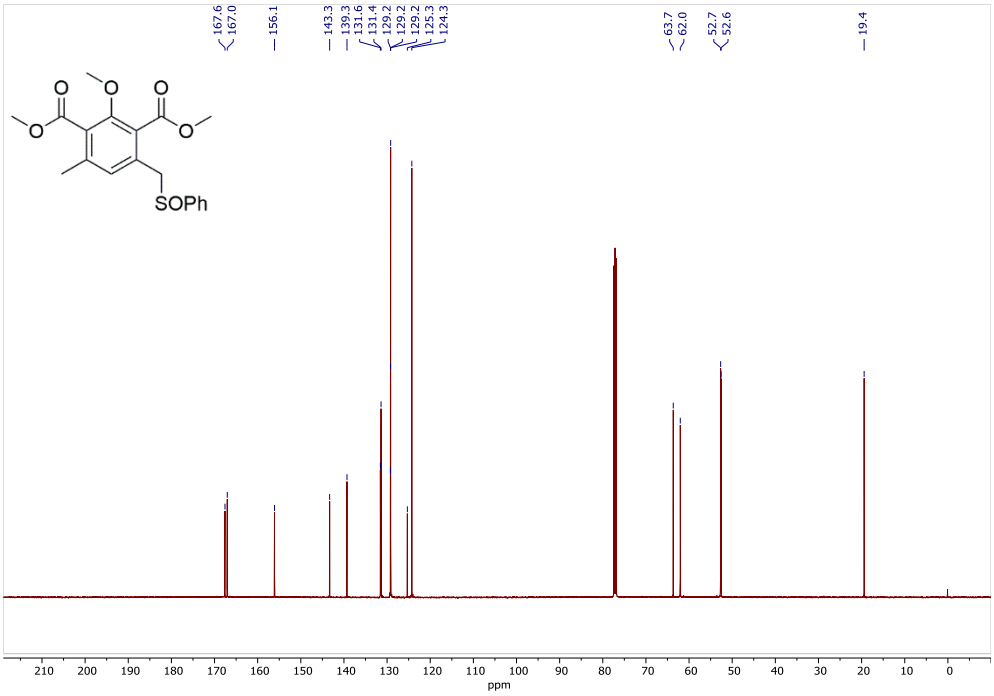

Figure 7.7: ^{1}H NMR of **2.34** (400 MHz, $CDCl_3$).

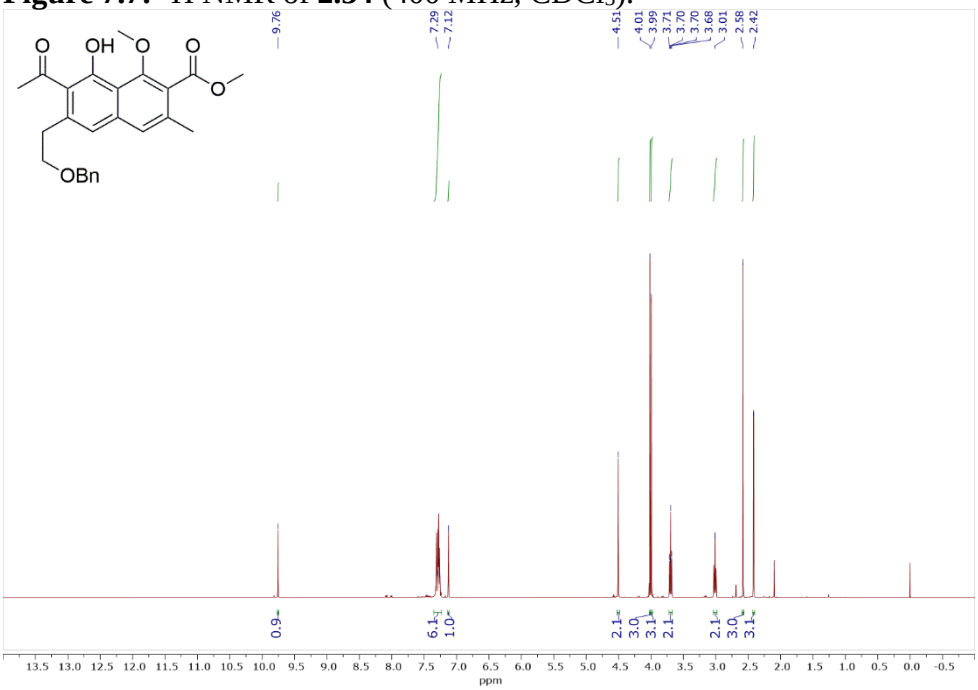

Figure 7.8: ^{13}C{^{1}H} NMR of **2.34** (101 MHz, $CDCl_3$).

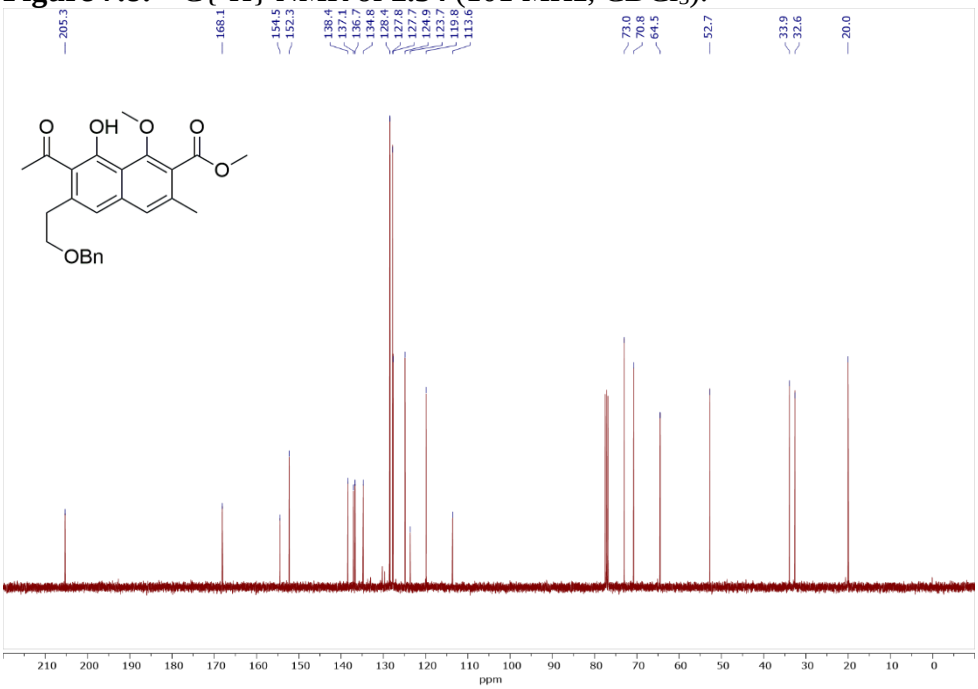

Figure 7.9: ^{1}H NMR of **2.35** (400 MHz, $CDCl_3$).

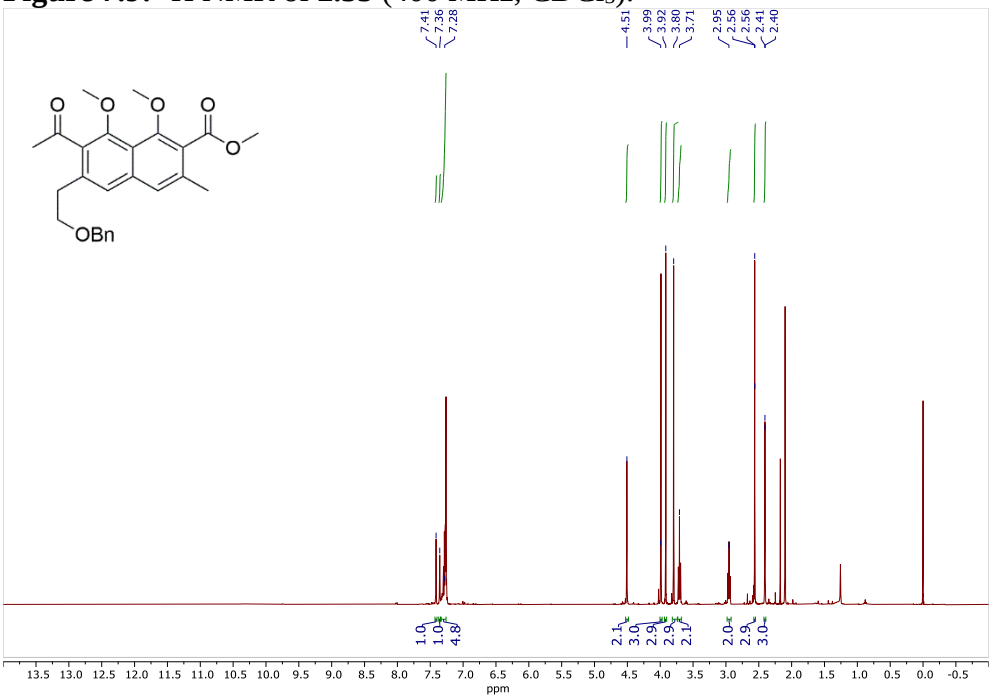

Figure 7.10: ^{13}C{^{1}H} NMR of **2.35** (101 MHz, $CDCl_3$).

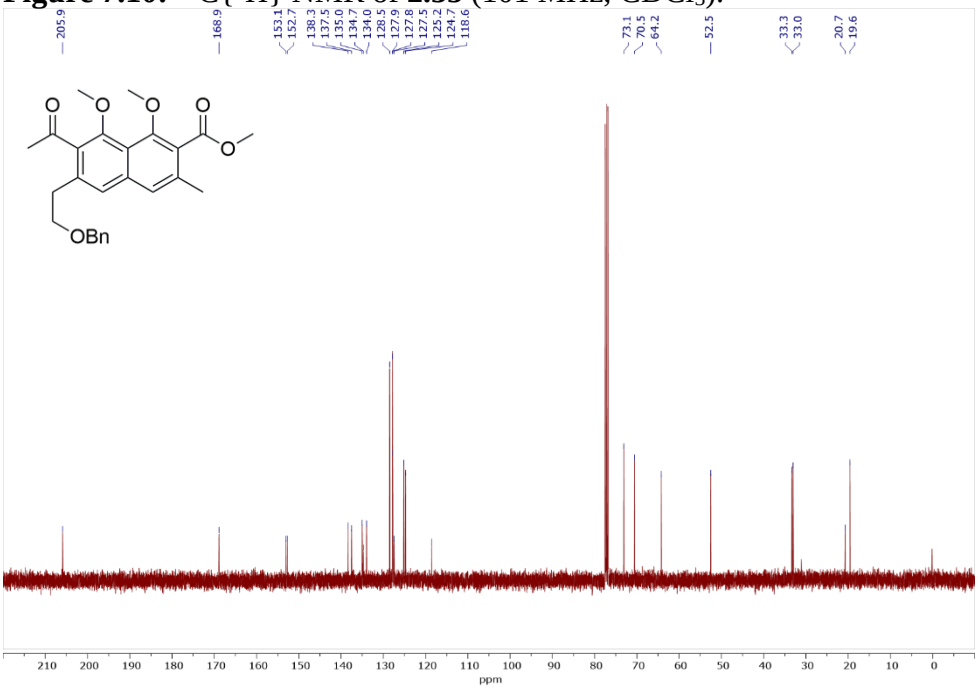

Figure 7.11: ^{1}H NMR of **2.6, 3.7a, 4.6, 5.18** (400 MHz, $CDCl_3$).

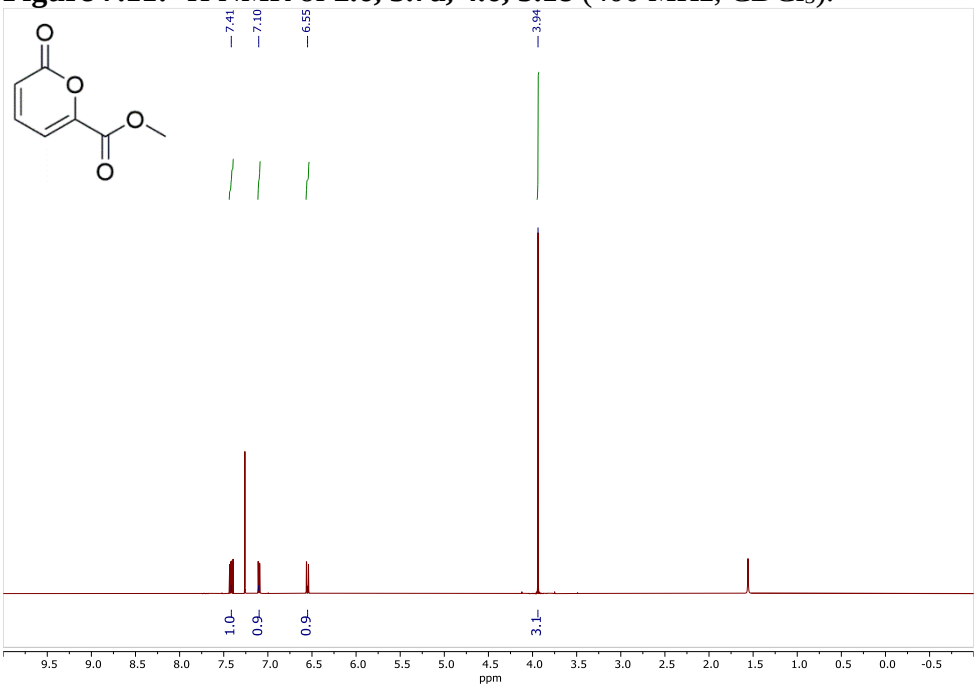

Figure 7.12: ^{13}C{^{1}H} NMR of **2.6, 3.7a, 4.6, 5.18** (101 MHz, $CDCl_3$).

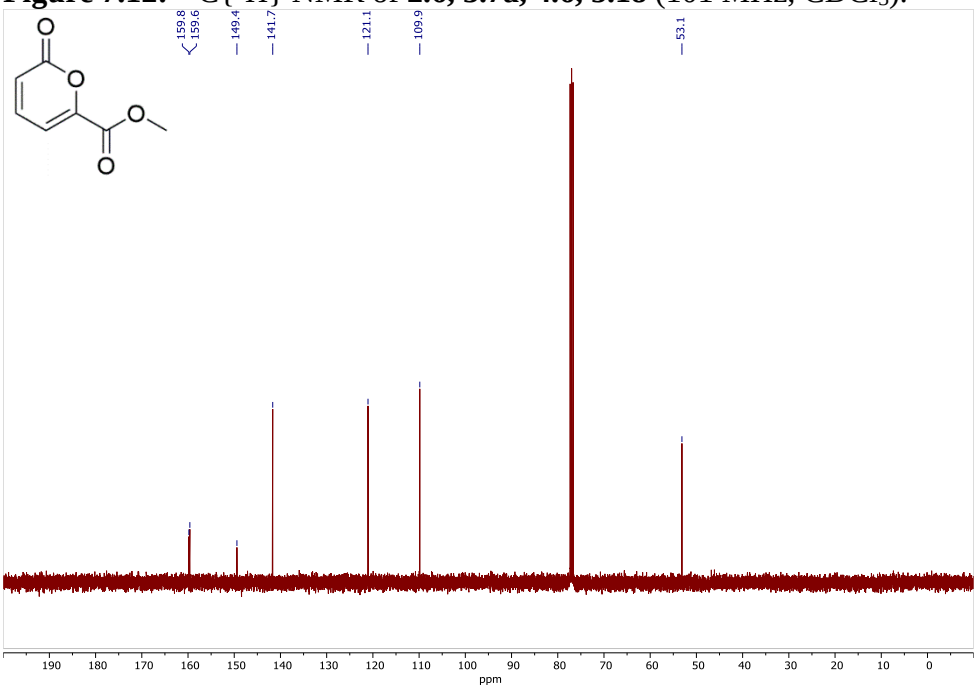

Figure 7.13: ^{1}H NMR of **3.7b** (400 MHz, $CDCl_3$).

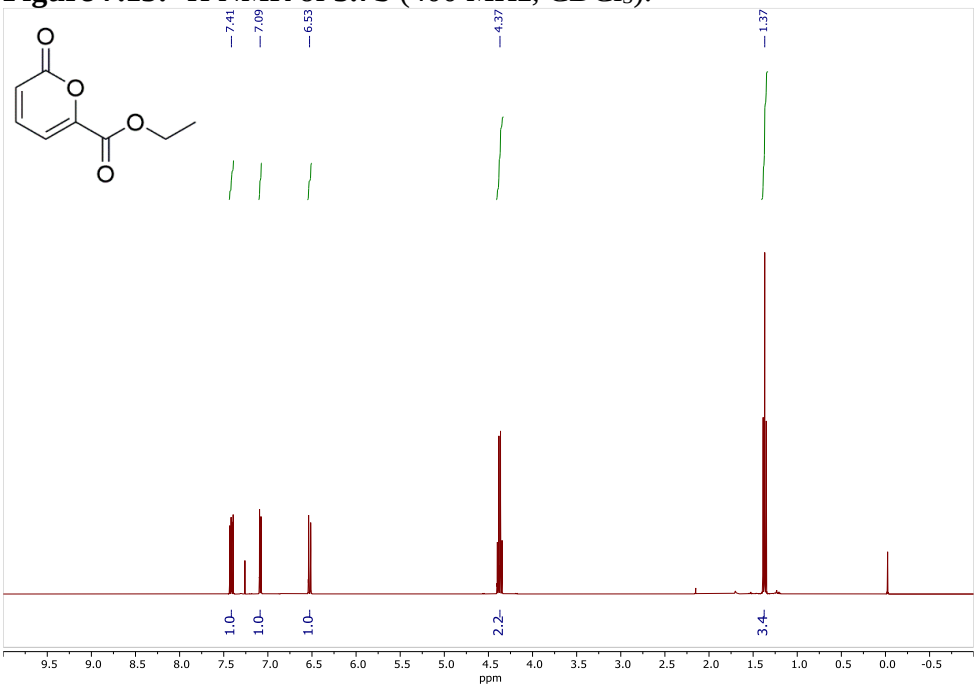

Figure 7.14: ^{13}C{^{1}H} NMR of **3.7b** (101 MHz, $CDCl_3$).

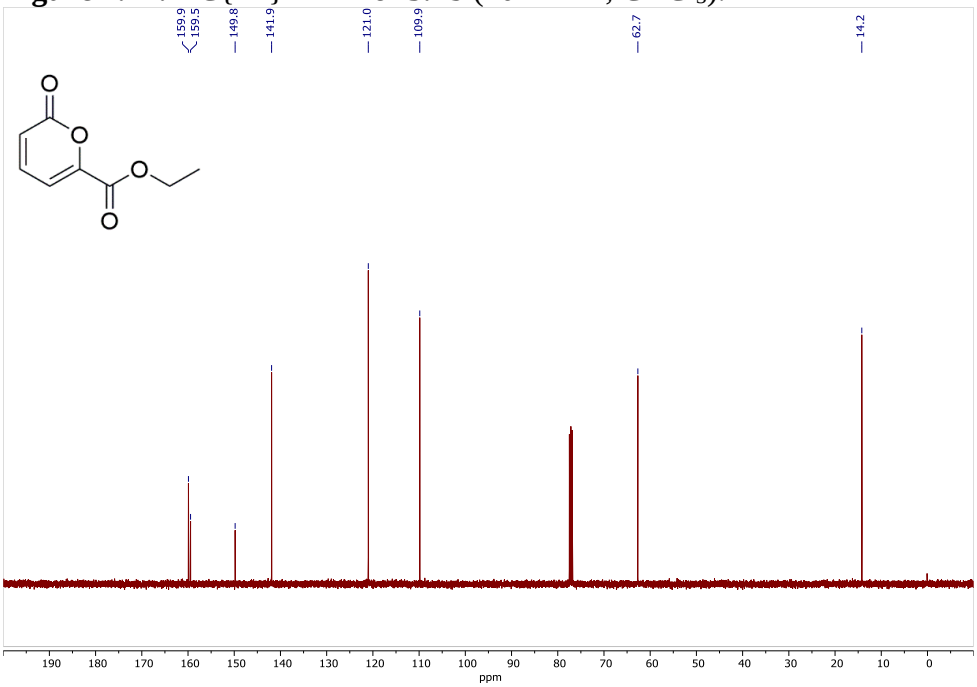

Figure 7.15: ^{1}H NMR of **3.7c** plus CH_2Cl_2 (400 MHz, $CDCl_3$).

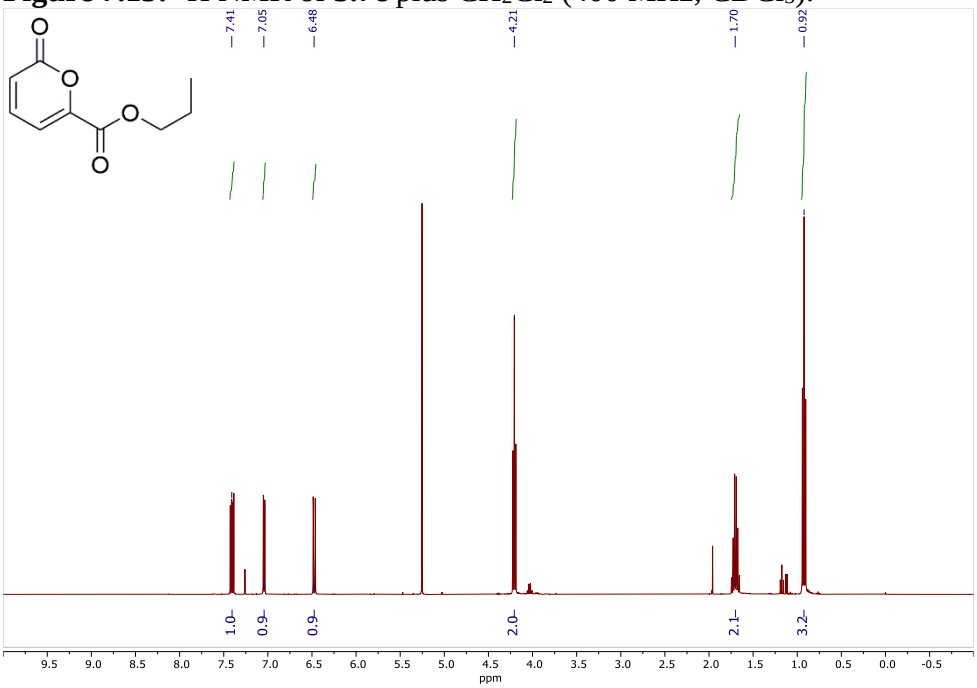

Figure 7.16: $^{13}C\{^{1}H\}$ NMR of **3.7c** (101 MHz, $CDCl_3$).

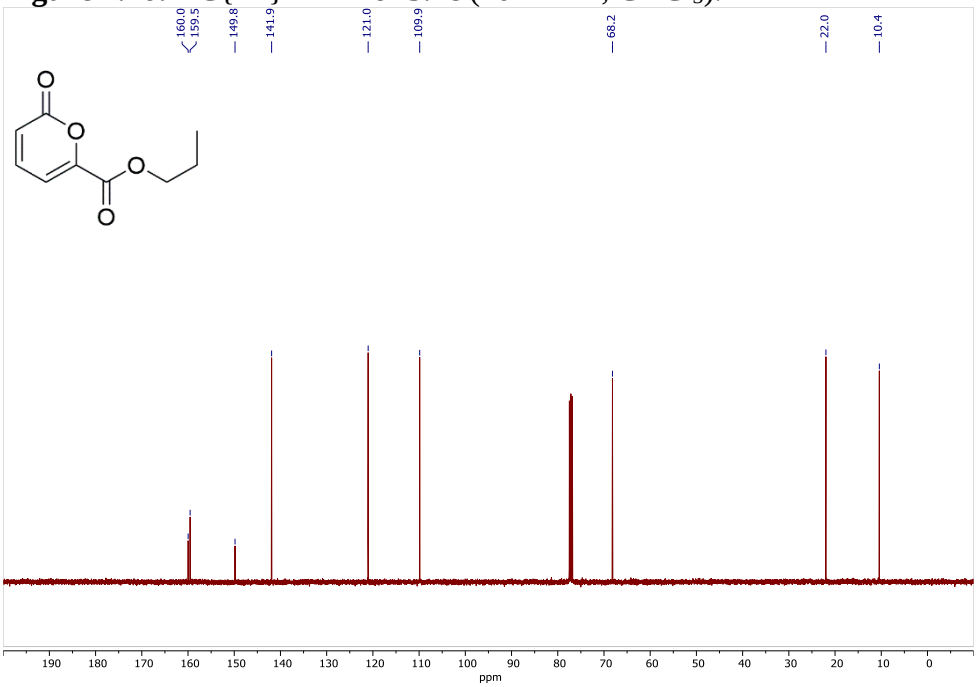

Figure 7.17: ^{1}H NMR of **3.7d** (400 MHz, $CDCl_3$).

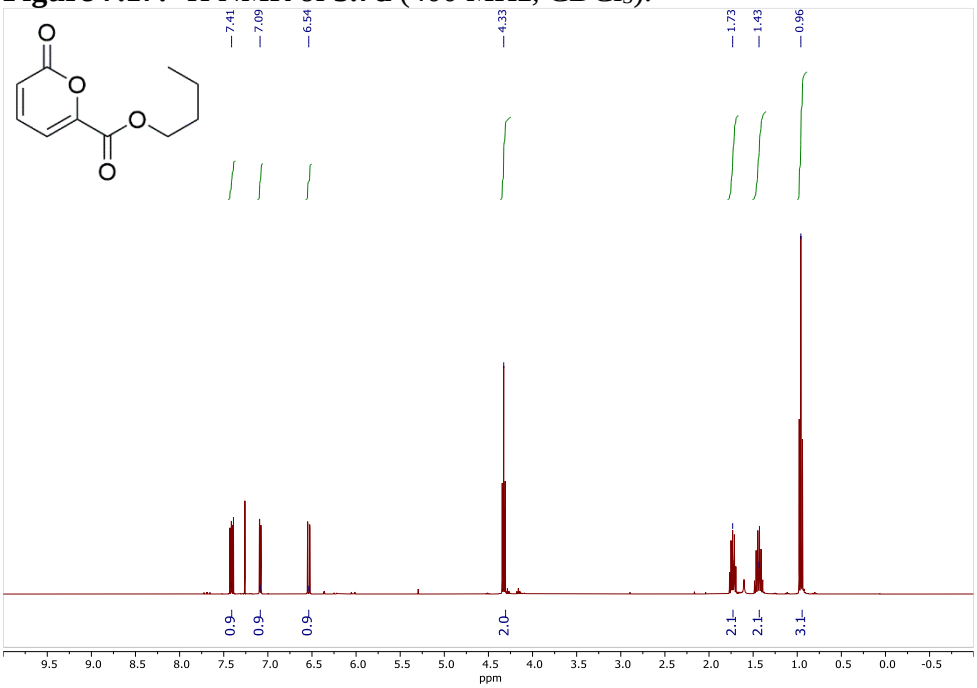

Figure 7.18: ^{13}C{^{1}H} NMR of **3.7d** (101 MHz, $CDCl_3$).

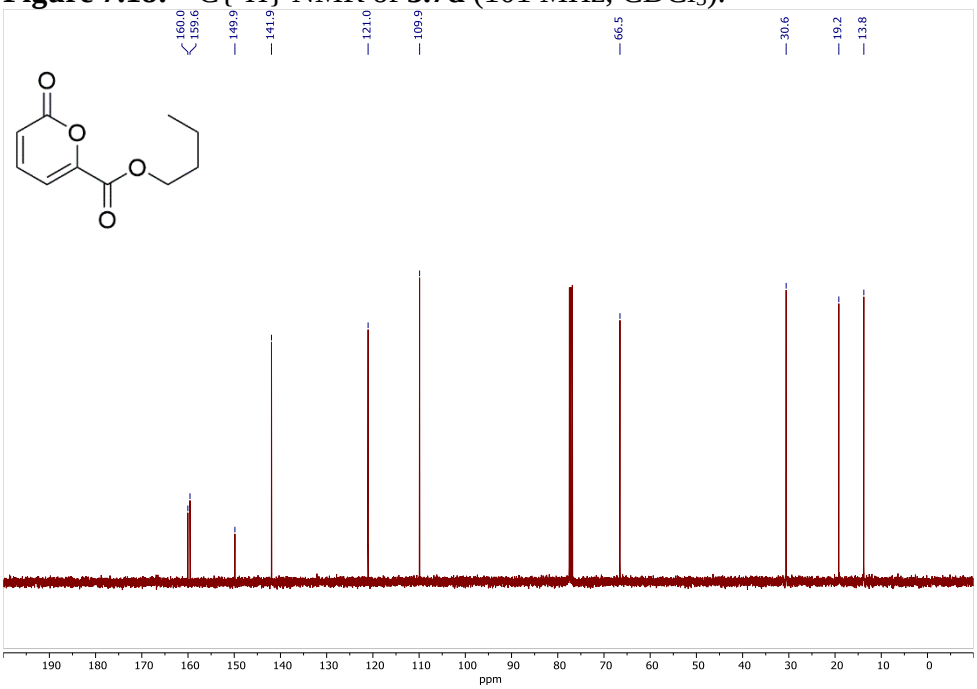

Figure 7.19: ^{1}H NMR of **3.7e** (400 MHz, $CDCl_3$).

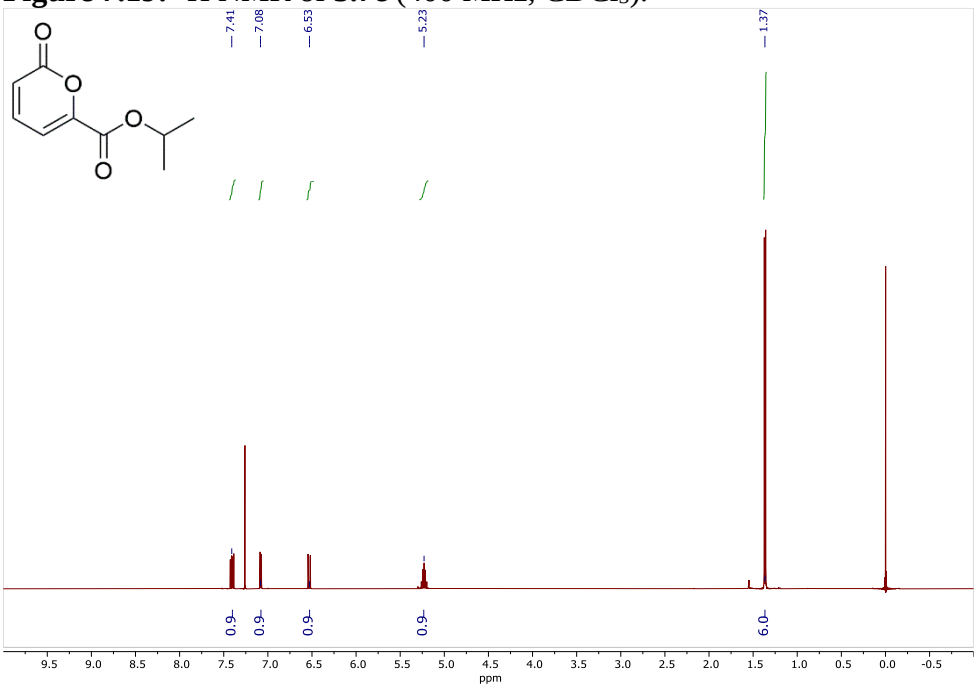

Figure 7.20: ^{13}C{^{1}H} NMR of **3.7e** (126 MHz, $CDCl_3$).

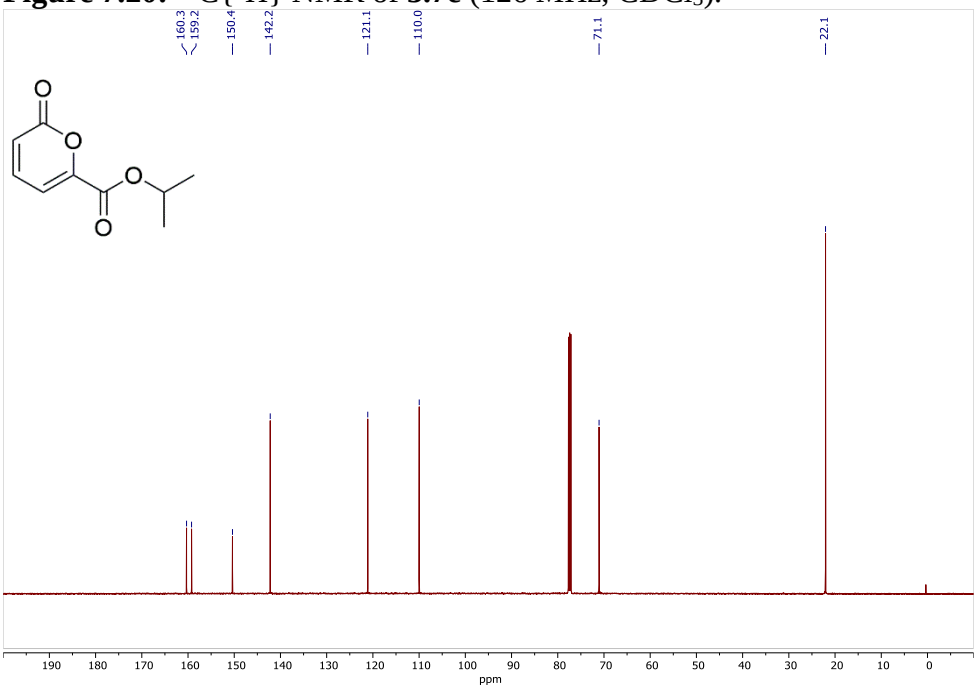

Figure 7.21: ^{1}H NMR of **3.7f** (400 MHz, $CDCl_3$).

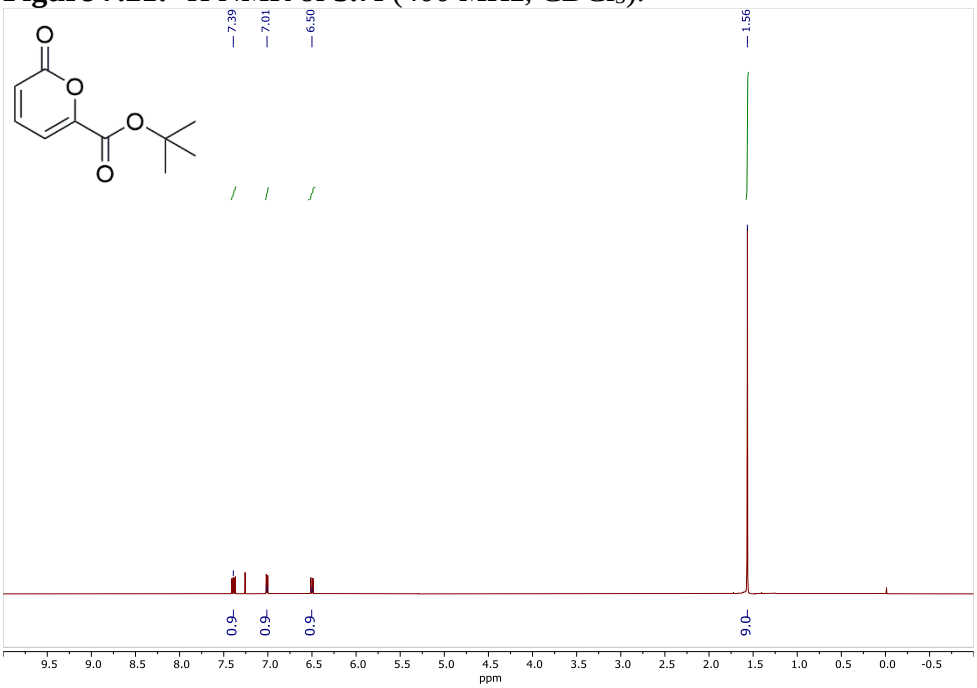

Figure 7.22: ^{13}C{^{1}H} NMR of **3.7f** (101 MHz, $CDCl_3$).

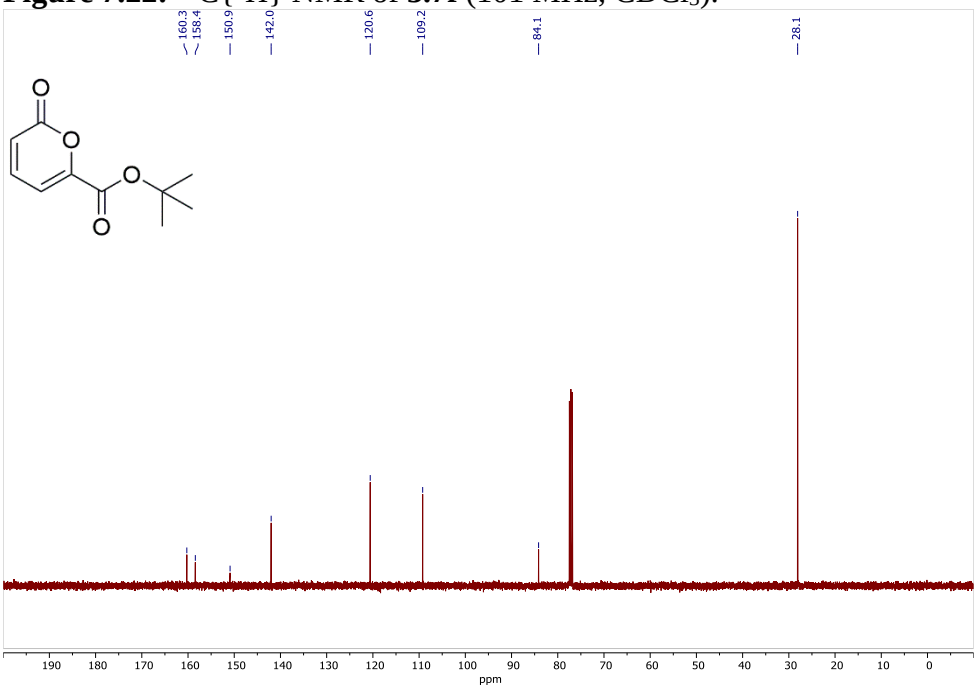

Figure 7.23: ^{1}H NMR of **3.7g** (400 MHz, $CDCl_3$).

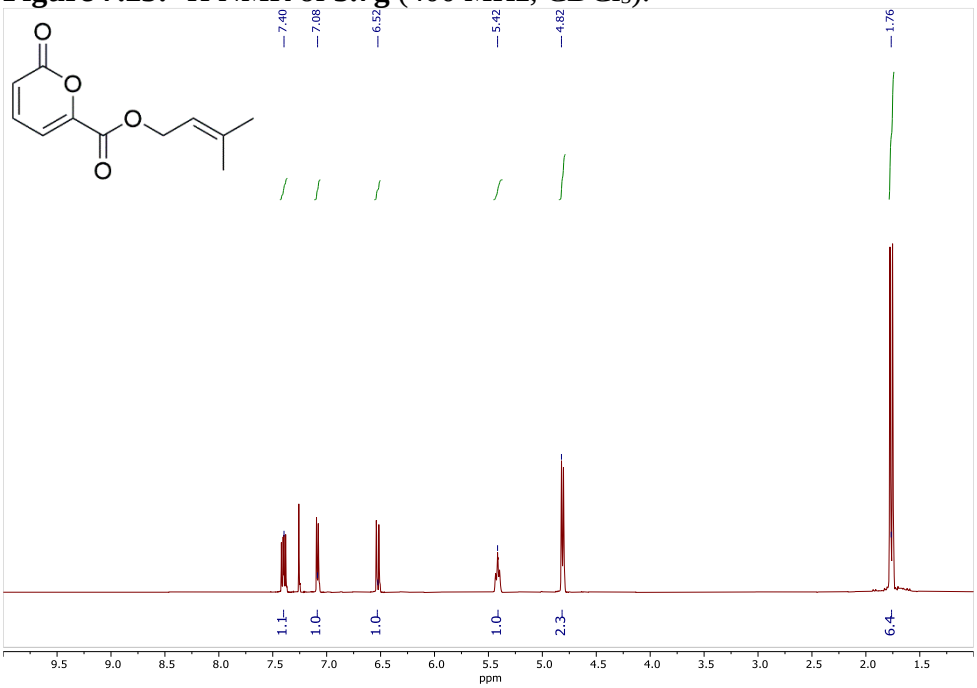

Figure 7.24: ^{13}C{^{1}H} NMR of **3.7g** (101 MHz, $CDCl_3$).

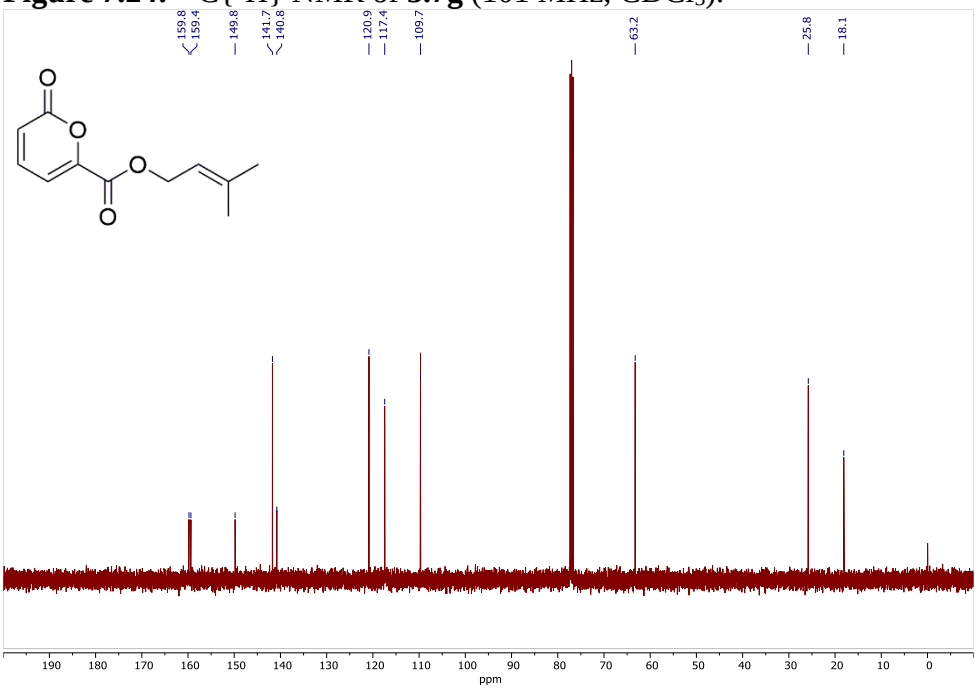

Figure 7.25: ^{1}H NMR of **3.7h** (400 MHz, $CDCl_3$).

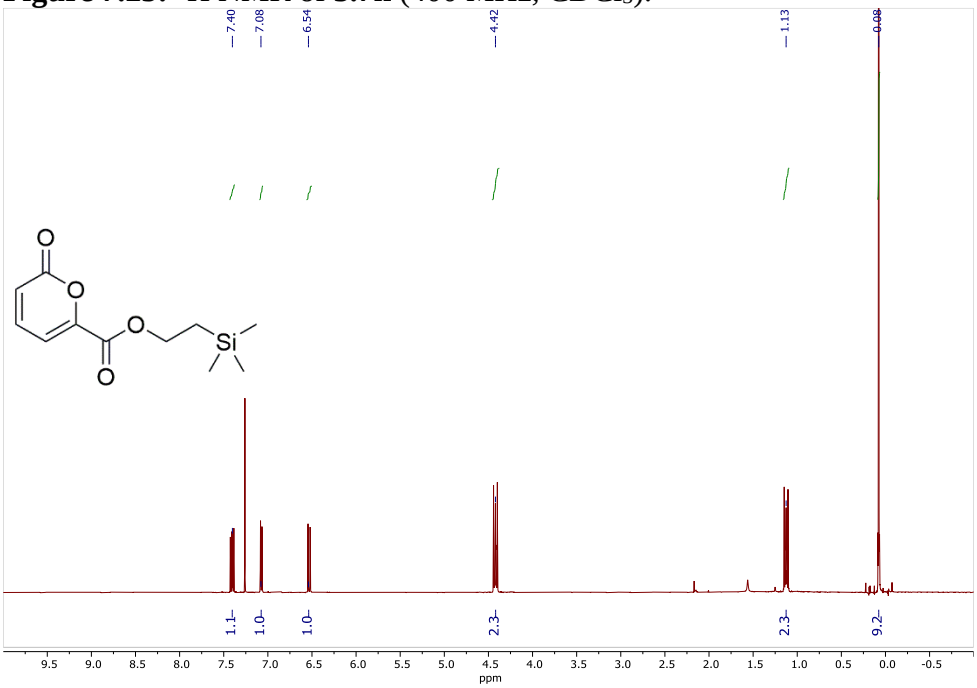

Figure 7.26: ^{13}C{^{1}H} NMR of **3.7h** (101 MHz, $CDCl_3$).

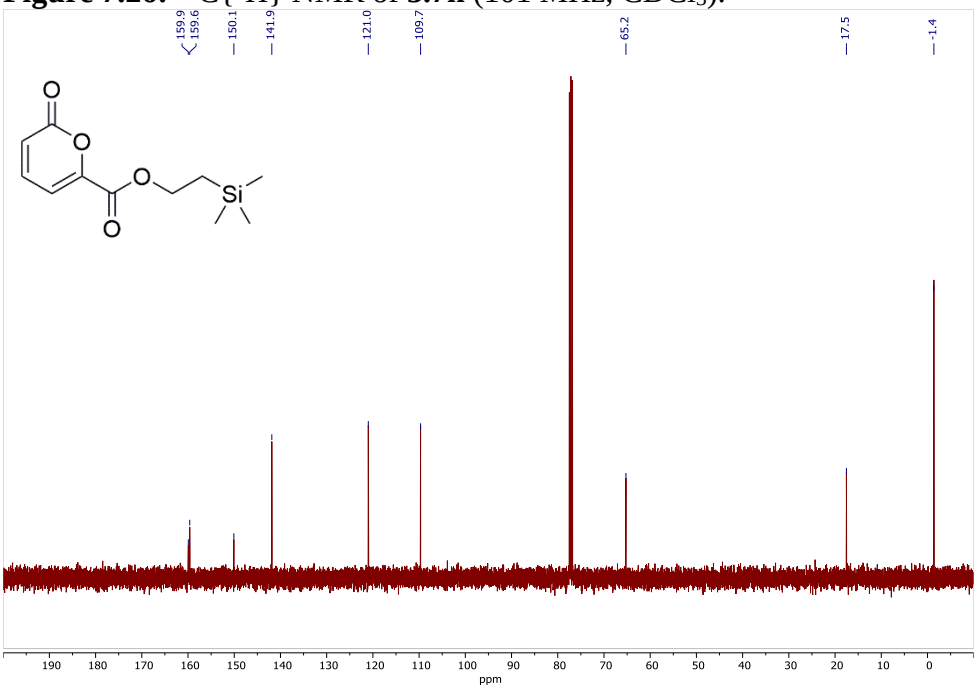

Figure 7.27: ^{1}H NMR of **3.7i** (400 MHz, $CDCl_3$).

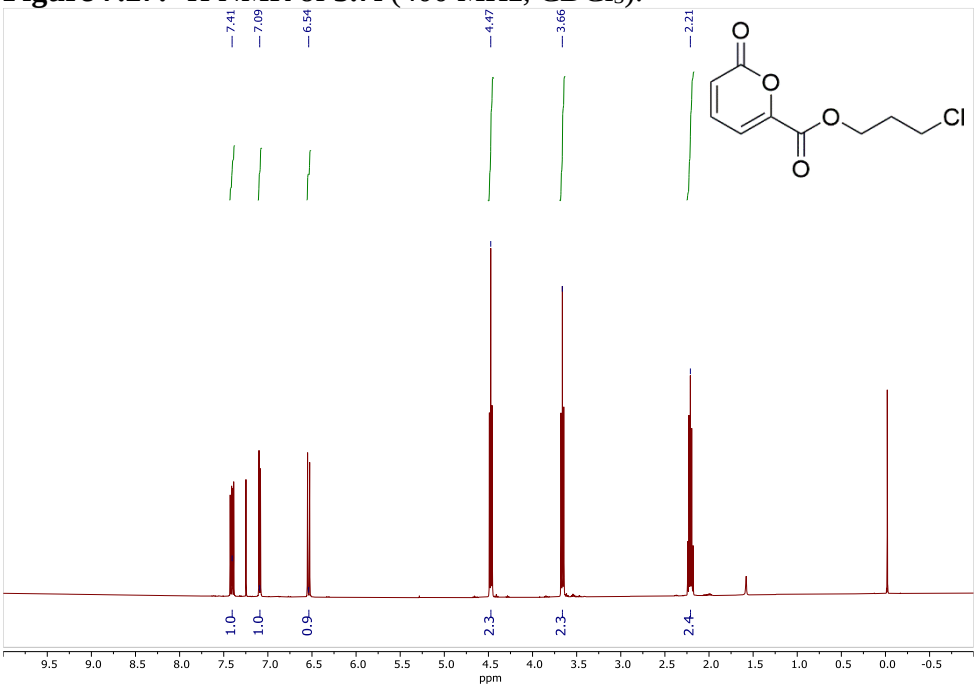

Figure 7.28: ^{13}C{^{1}H} NMR of **3.7i** (101 MHz, $CDCl_3$).

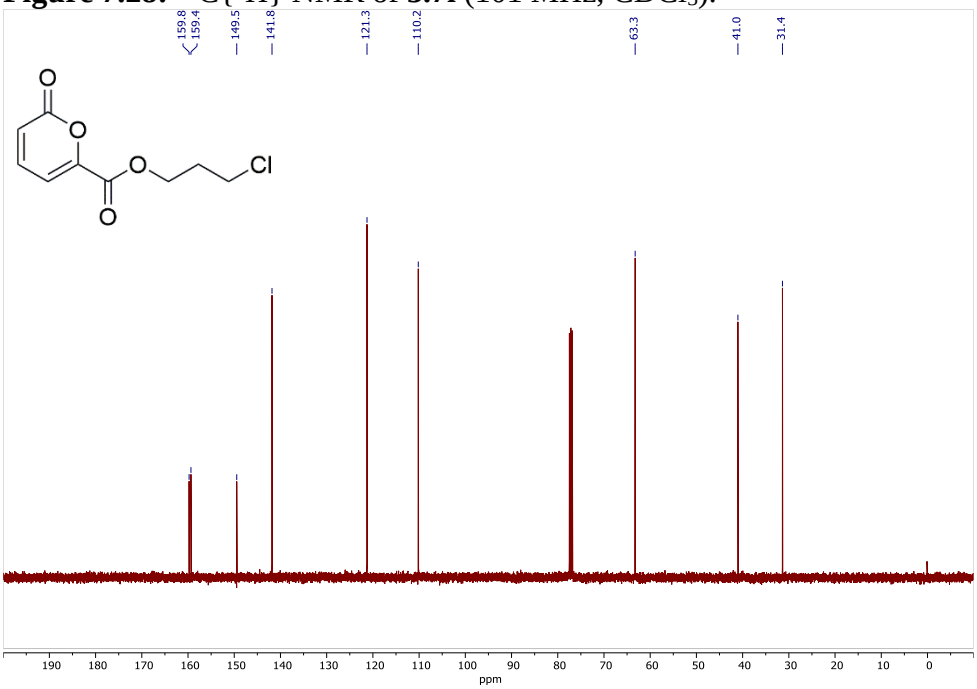

Figure 7.29: ^{1}H NMR of **3.7j** (400 MHz, $CDCl_3$).

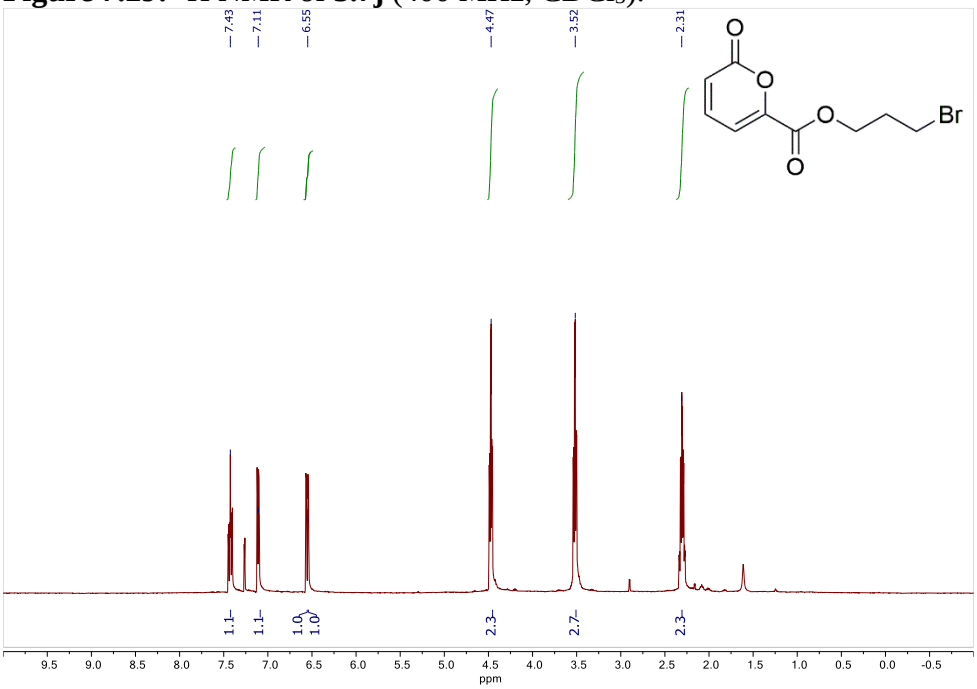

Figure 7.30: ^{13}C{^{1}H} NMR of **3.7j** (126 MHz, $CDCl_3$).

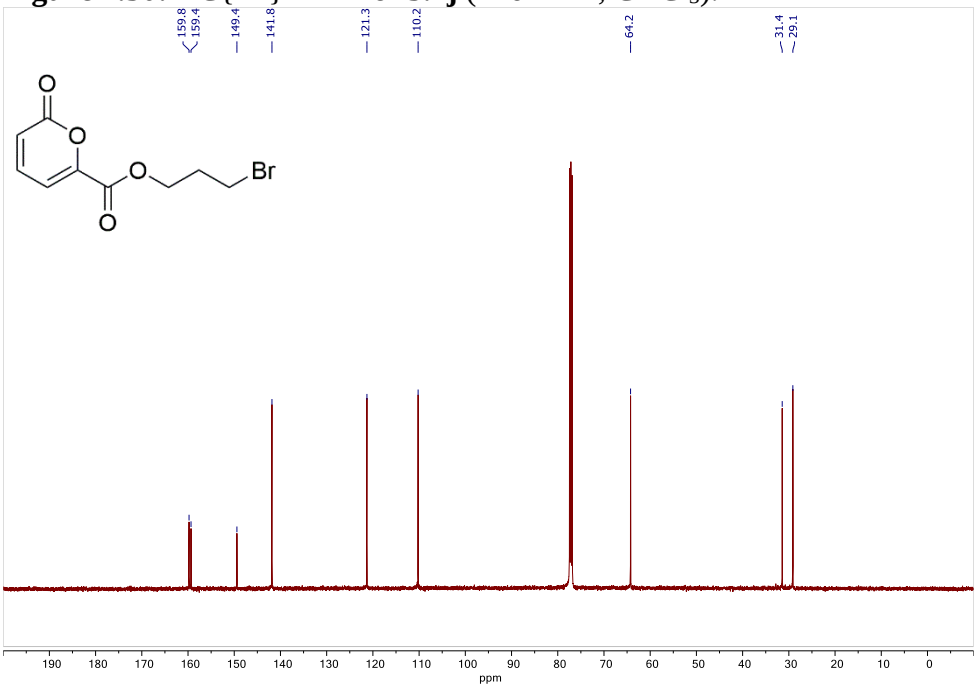

Figure 7.31: ^{1}H NMR of **3.7k** (400 MHz, $CDCl_3$).

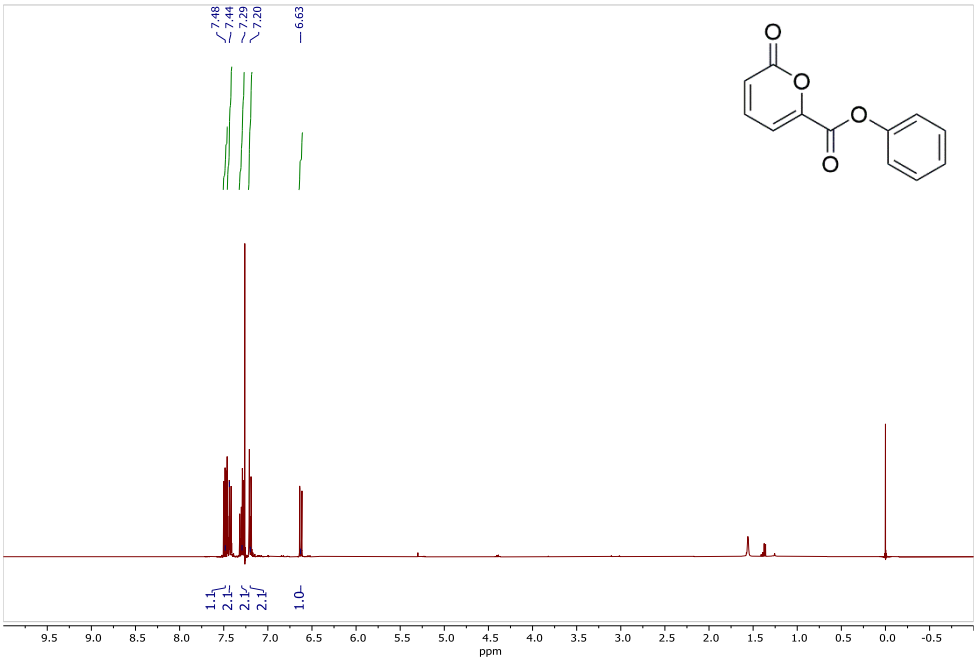

Figure 7.32: ^{13}C{^{1}H} NMR of **3.7k** (101 MHz, $CDCl_3$).

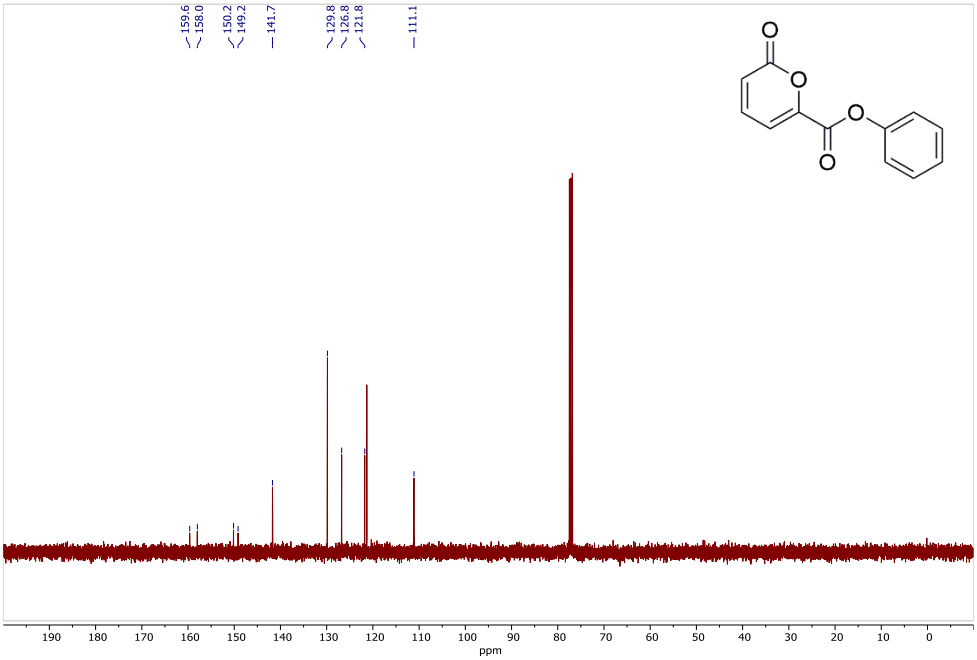

Figure 7.33: ^{1}H NMR of **3.7l** plus trace acetone (400 MHz, $CDCl_3$).

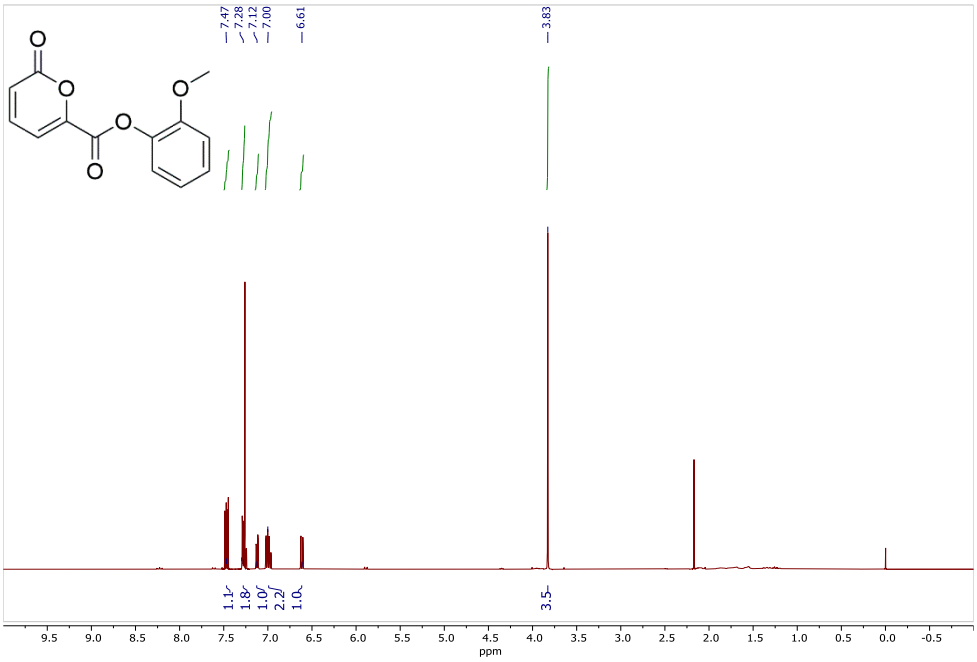

Figure 7.34 $^{13}C\{^{1}H\}$ NMR of **3.7l** (101 MHz, $CDCl_3$).

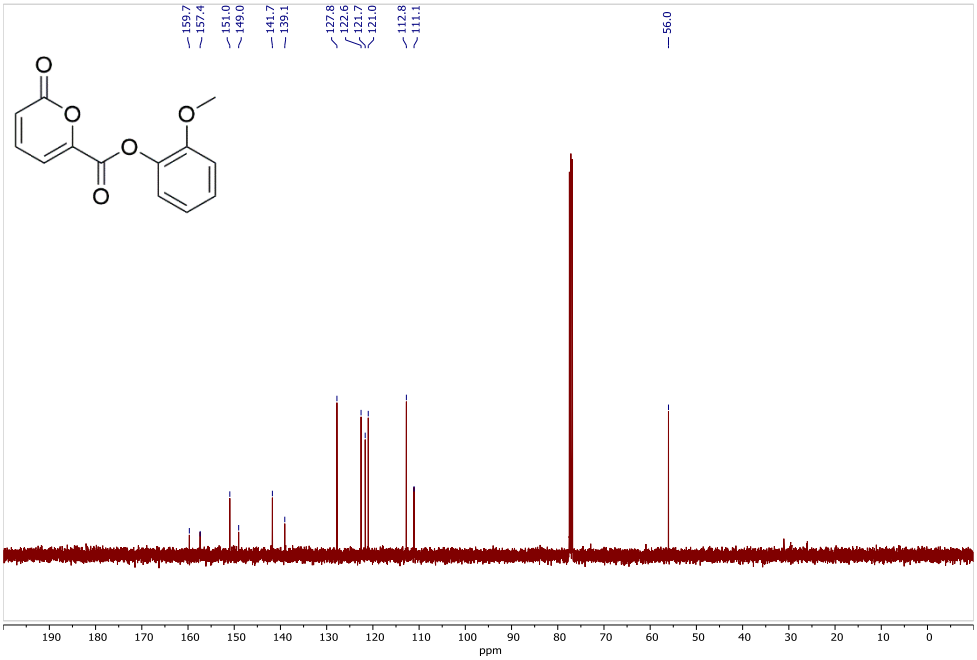

Figure 7.35: ^{1}H NMR of **3.7m** plus trace 4-methoxyphenol (400 MHz, $CDCl_3$).

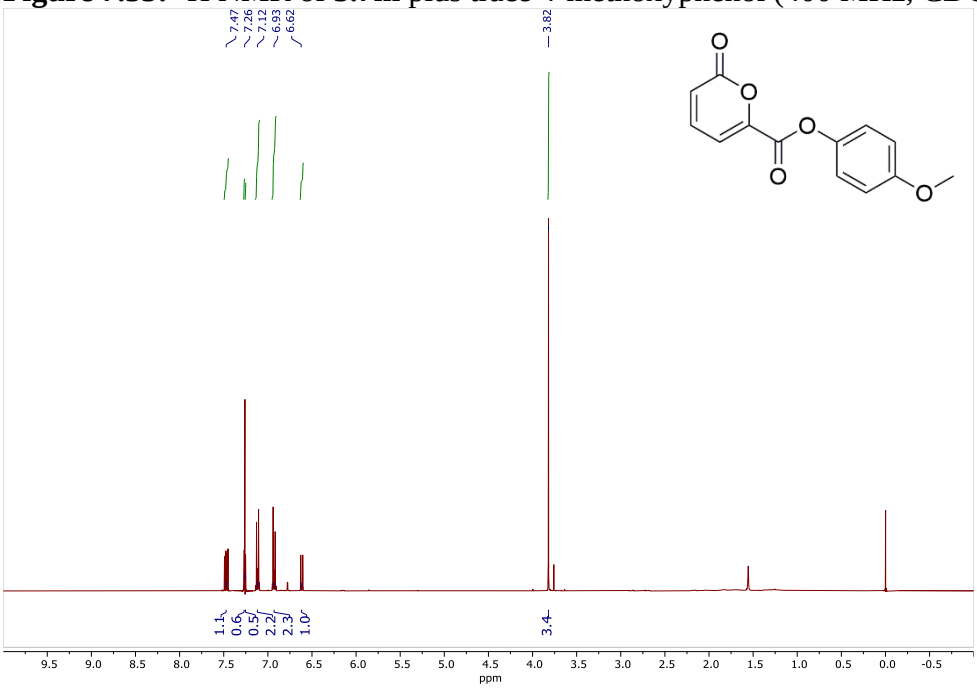

Figure 7.36: ^{13}C{^{1}H} NMR of **3.7m** (101 MHz, $CDCl_3$).

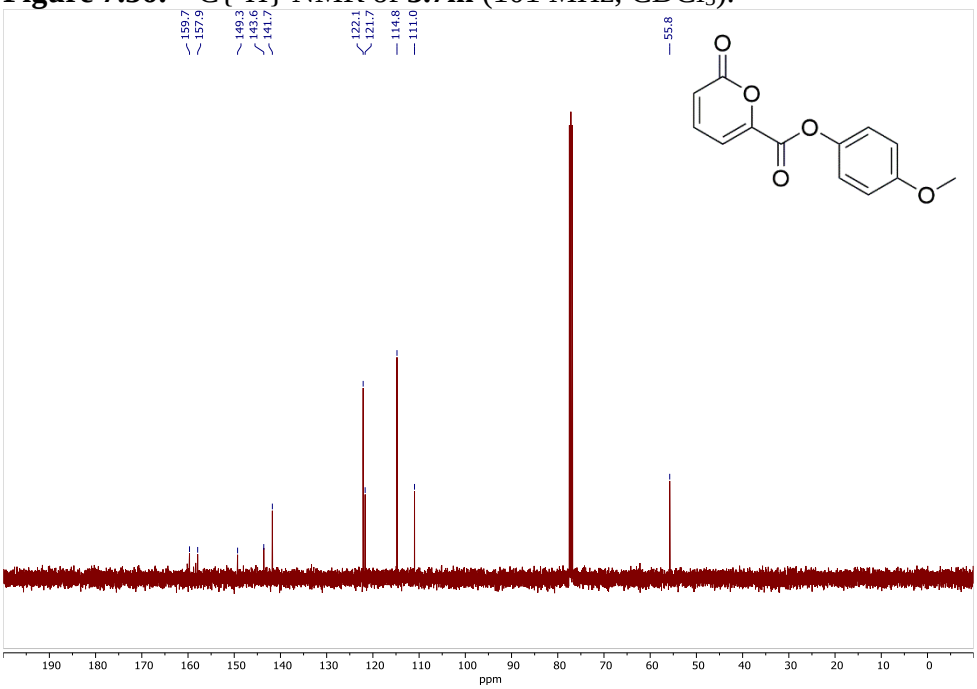

Figure 7.37: ^{1}H NMR of **3.7n** plus trace water (400 MHz, $CDCl_3$).

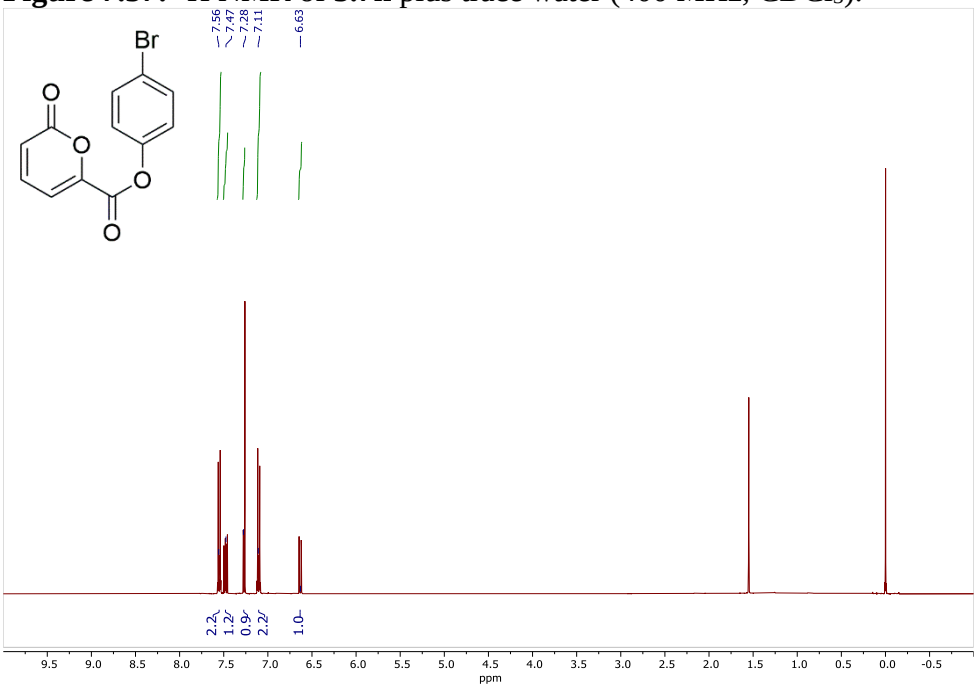

Figure 7.38: ^{13}C{^{1}H} NMR of **3.7n** (101 MHz, $CDCl_3$).

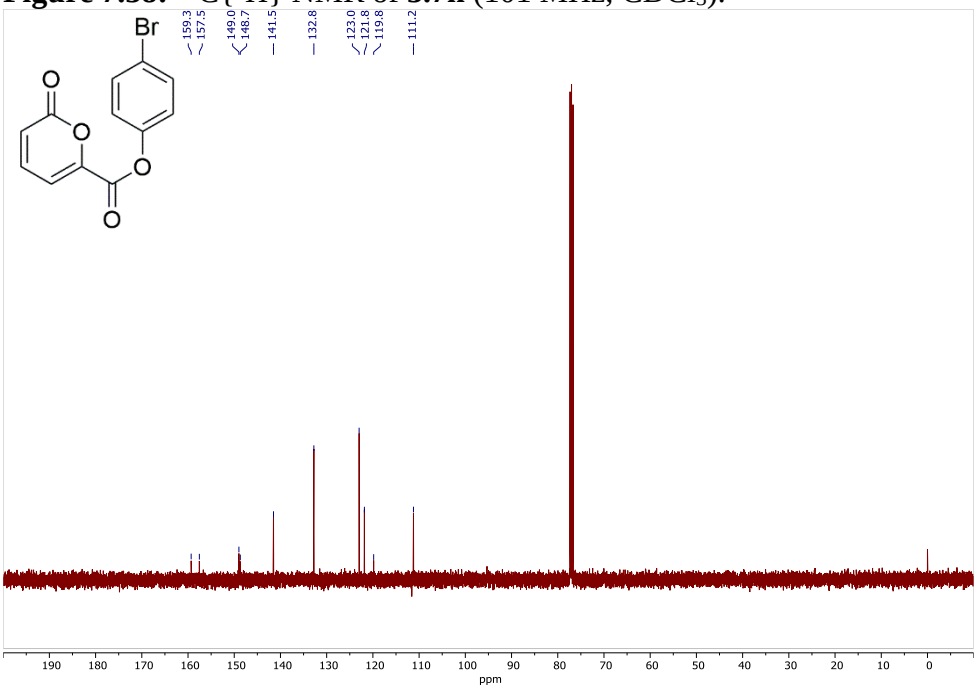

Figure 7.39: ^{1}H NMR of **3.7o** (400 MHz, $CDCl_3$).

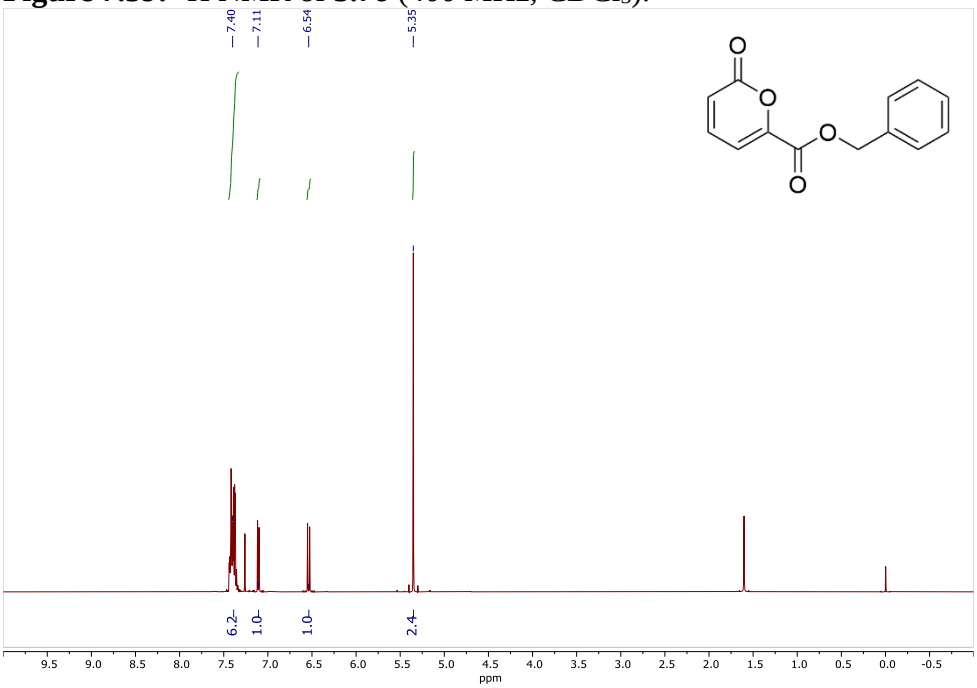

Figure 7.40: ^{13}C{^{1}H} NMR of **3.7o** (101 MHz, $CDCl_3$).

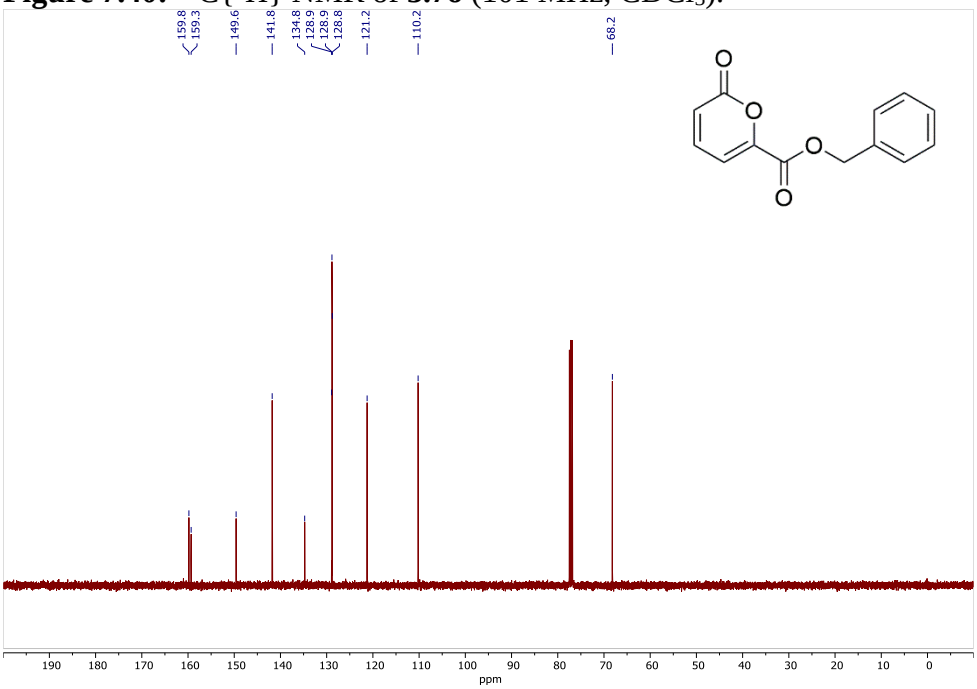

Figure 7.41: ^{1}H NMR of **3.7p** (400 MHz, $CDCl_3$).

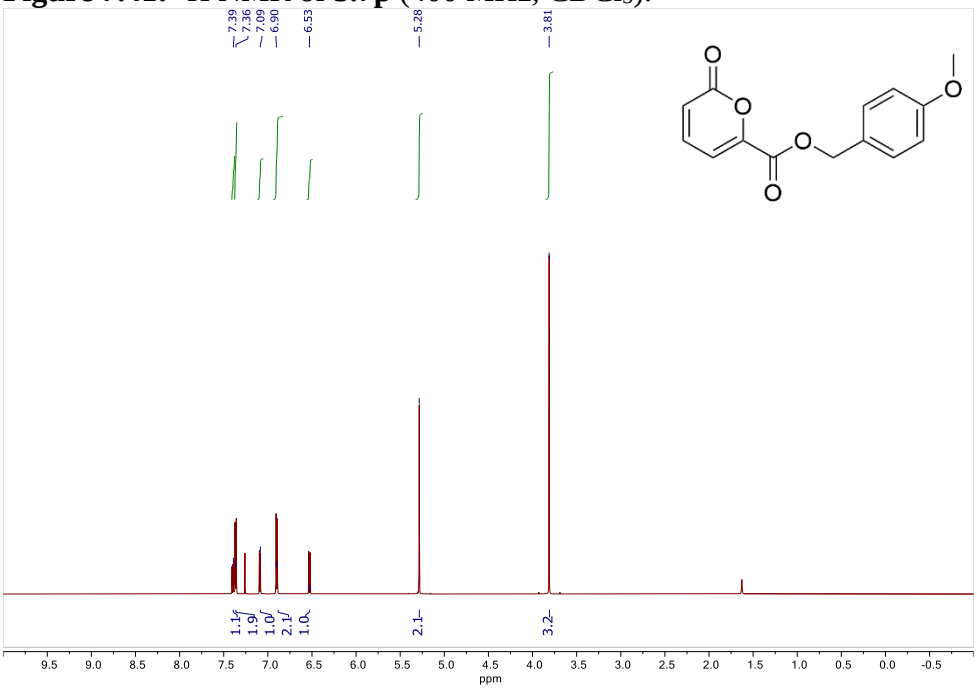

Figure 7.42: ^{13}C{^{1}H} NMR of **3.7p** (151 MHz, $CDCl_3$).

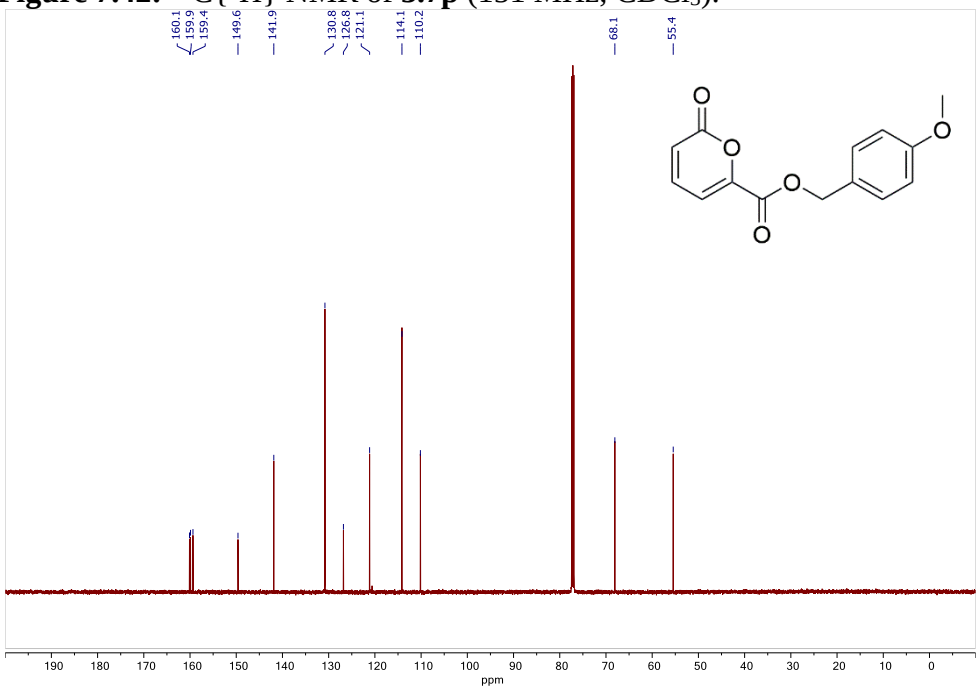

Figure 7.43: ^{1}H NMR of **3.7q** (400 MHz, $CDCl_3$).

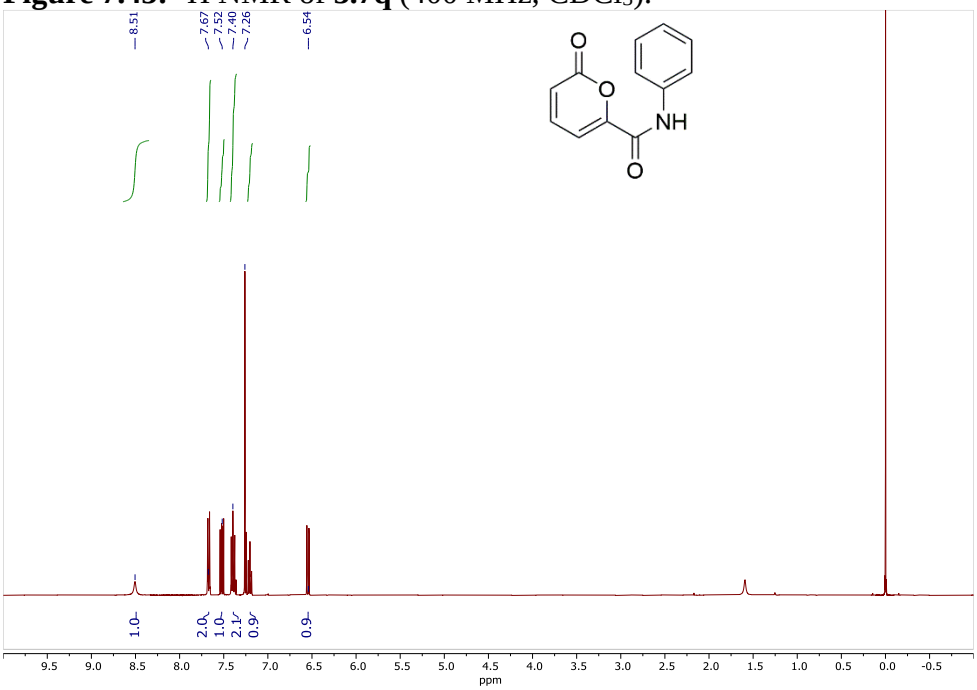

Figure 7.44: ^{13}C{^{1}H} NMR of **3.7q** (126 MHz, $CDCl_3$).

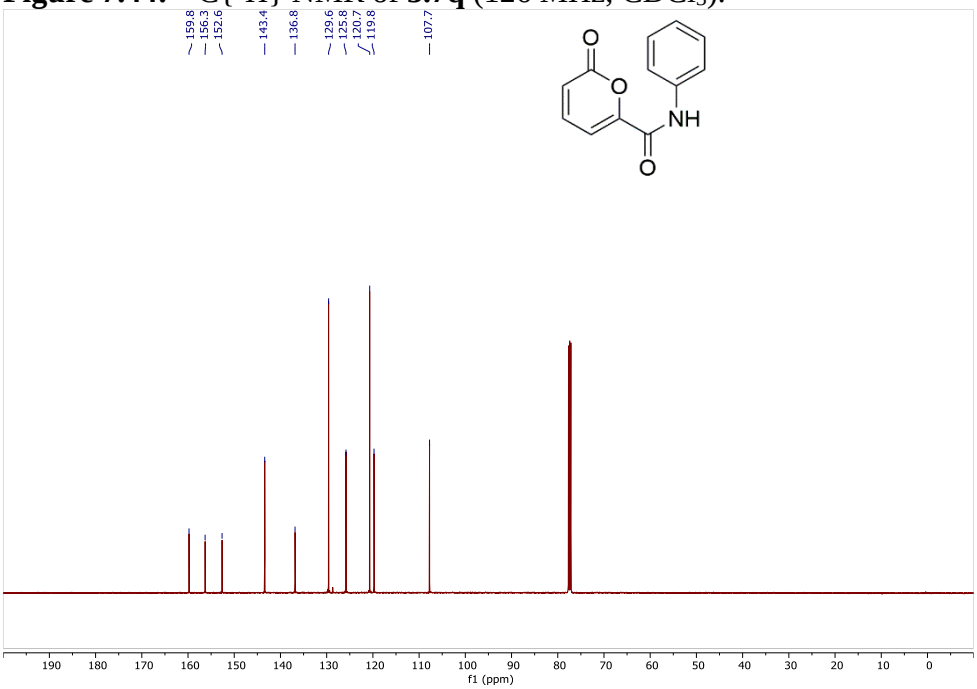

Figure 7.45: ^{1}H NMR of **3.7r** (400 MHz, $CDCl_3$).

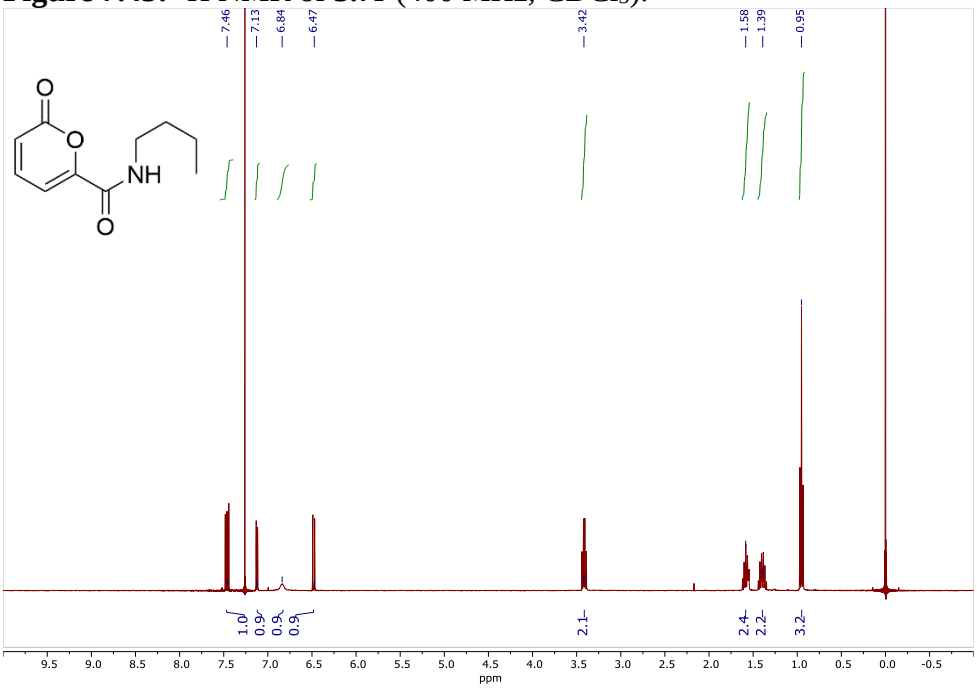

Figure 7.46: ^{13}C{^{1}H} NMR of **3.7r** (126 MHz, $CDCl_3$).

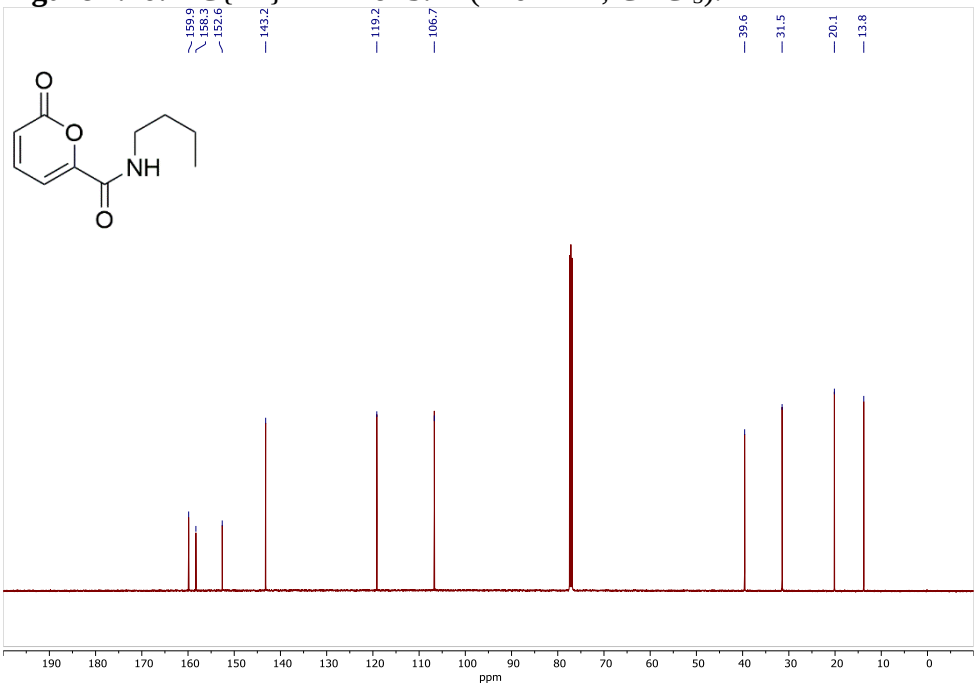

Figure 7.47: ^{1}H NMR of **3.7s** plus trace acetone (400 MHz, $CDCl_3$).

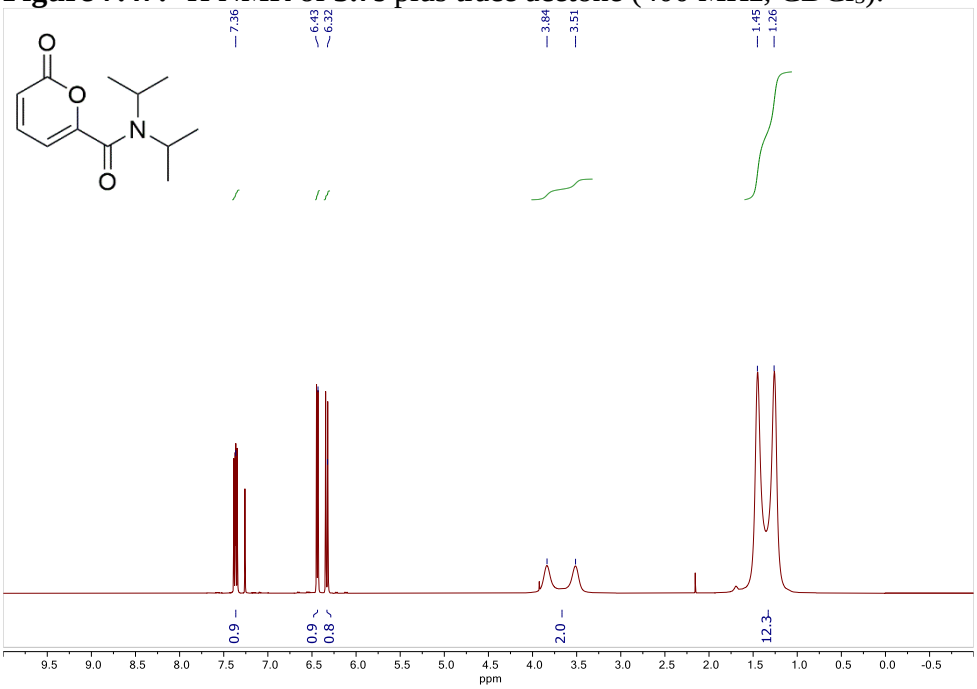

Figure 7.48: ^{13}C{^{1}H} NMR of **3.7s** (126 MHz, $CDCl_3$).

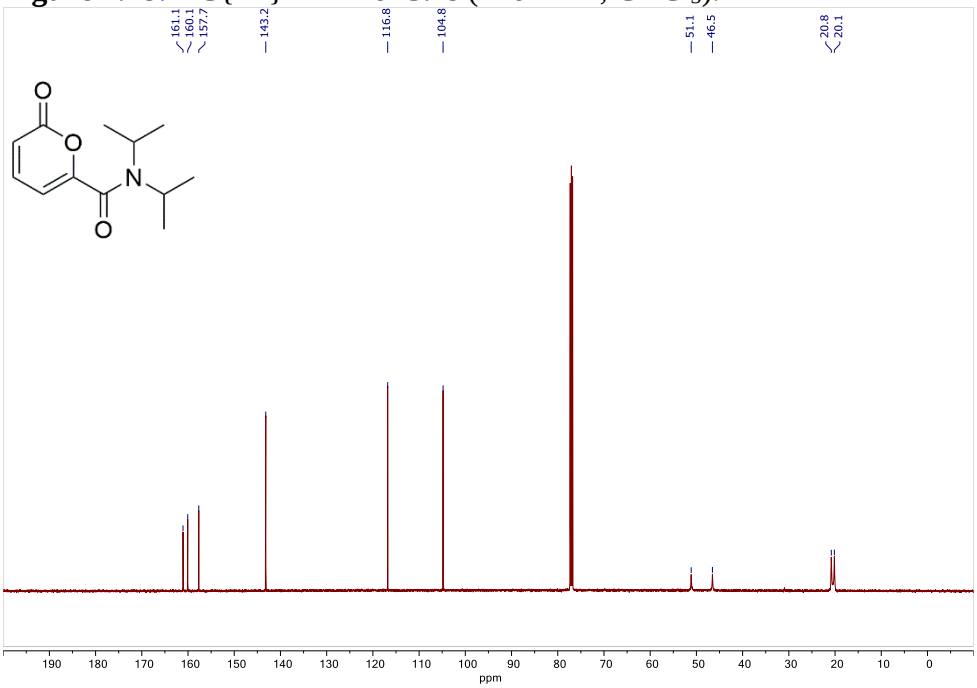

Figure 7.49: ^{1}H NMR of **3.7t** (400 MHz, $CDCl_3$).

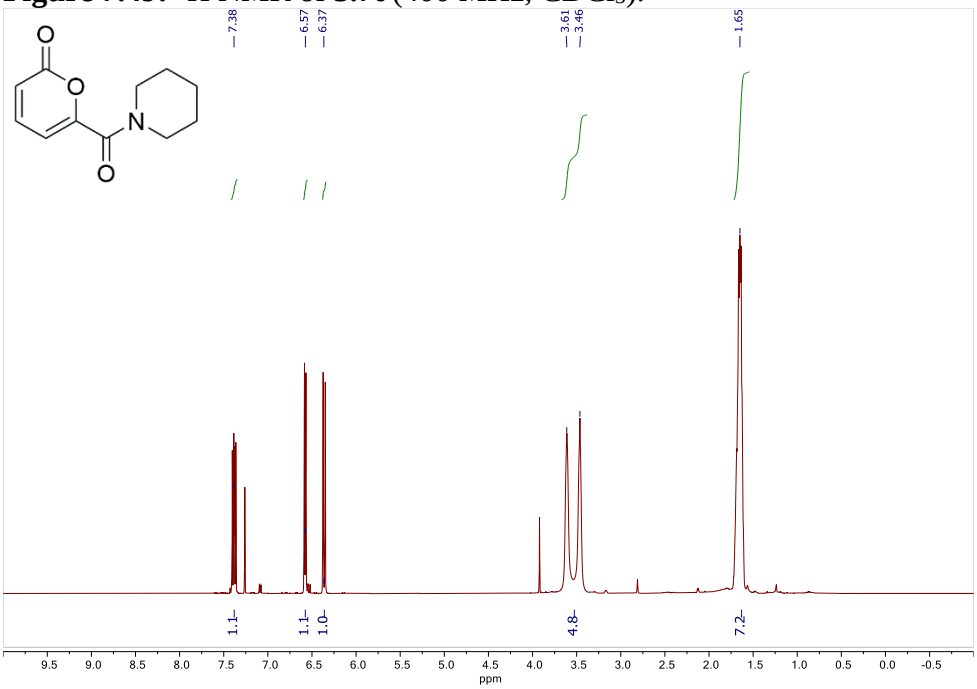

Figure 7.50: ^{13}C{^{1}H} NMR of **3.7t** (126 MHz, $CDCl_3$).

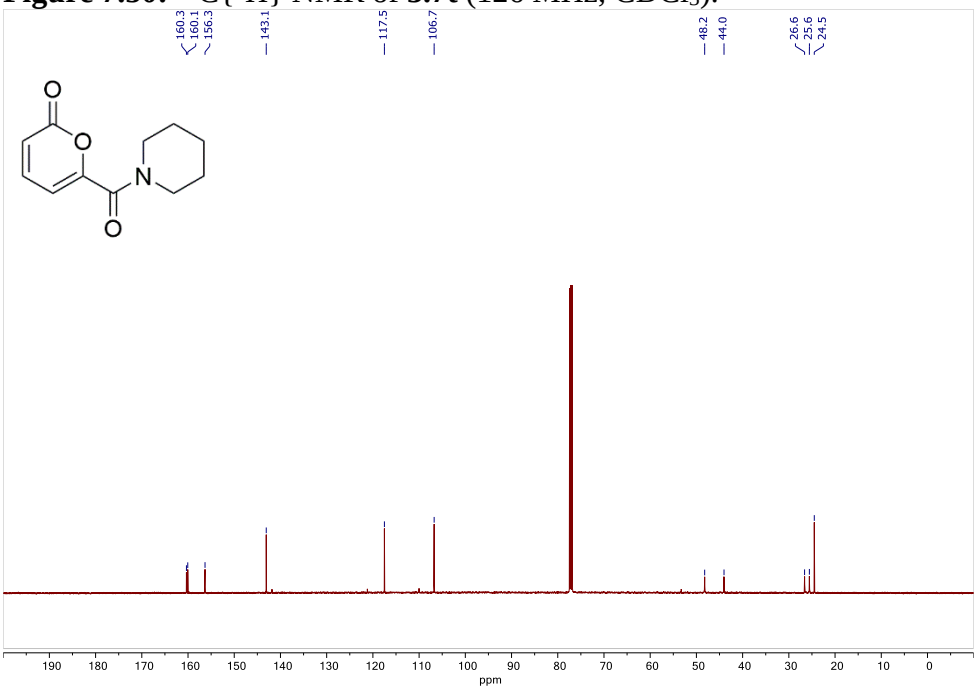

Figure 7.51: ^{1}H NMR of **3.7u** (400 MHz, CD_3OD).

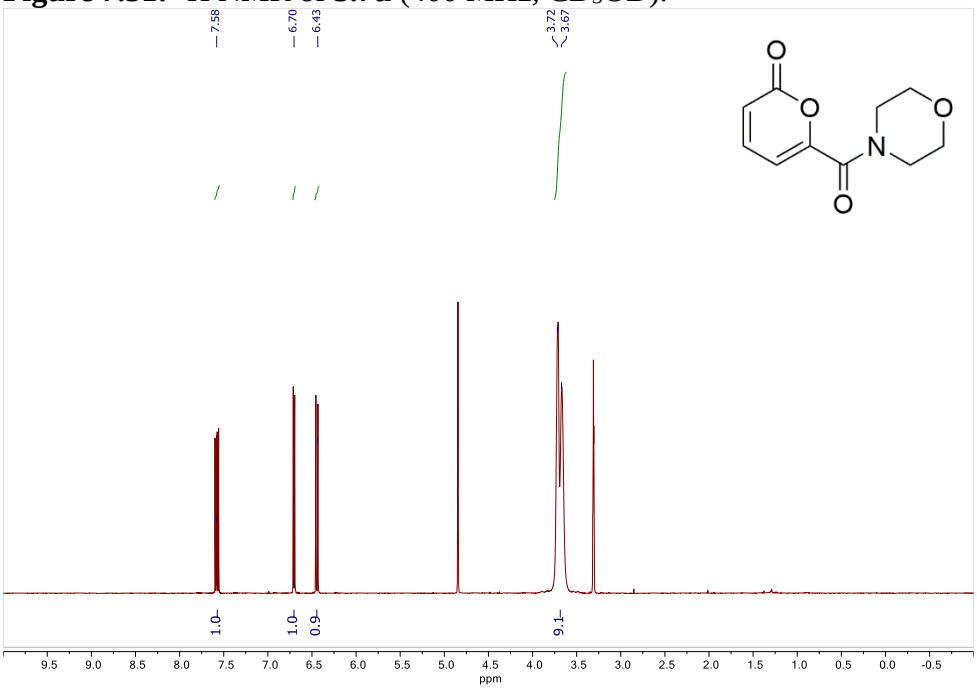

Figure 7.52: ^{13}C{^{1}H} NMR of **3.7u** (151 MHz, CD_3OD).

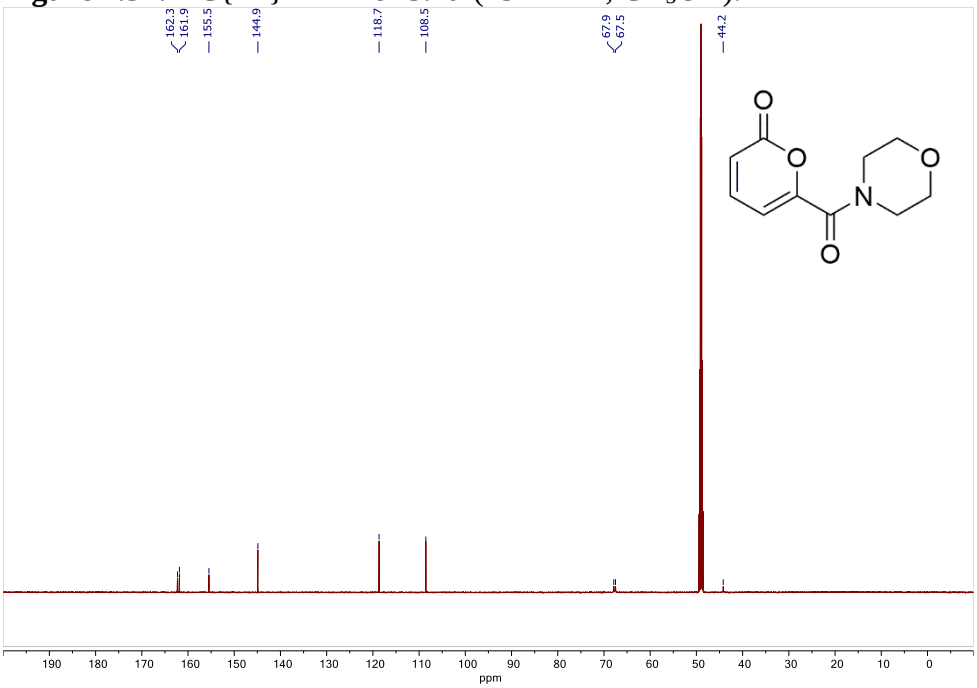

Figure 7.53: ^{1}H NMR of **3.7v** (400 MHz, $CDCl_3$).

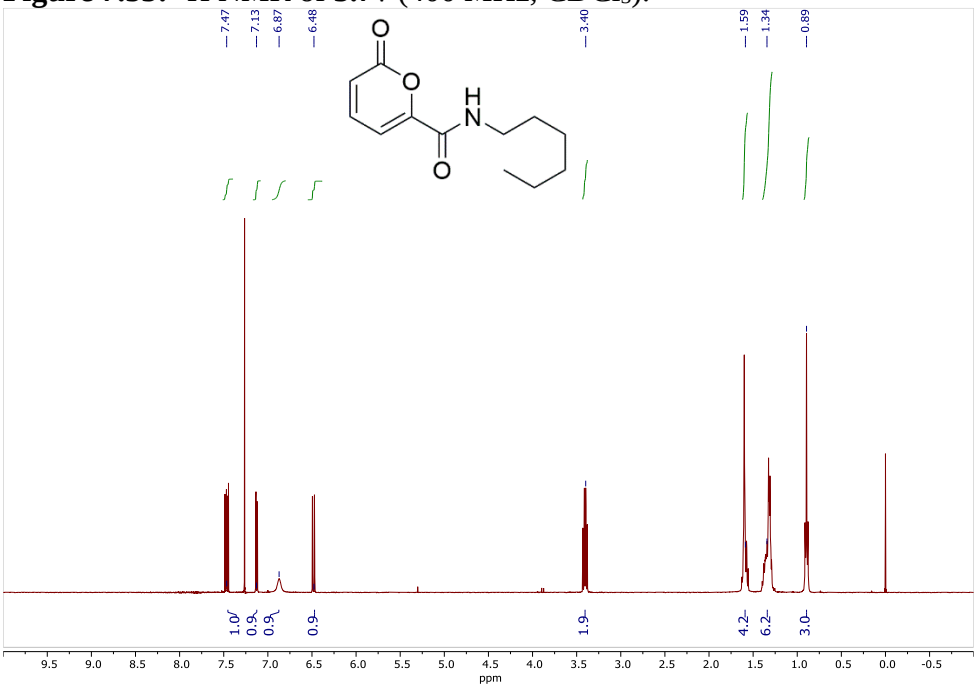

Figure 7.54: ^{13}C{^{1}H} NMR of **3.7v** (101 MHz, $CDCl_3$).

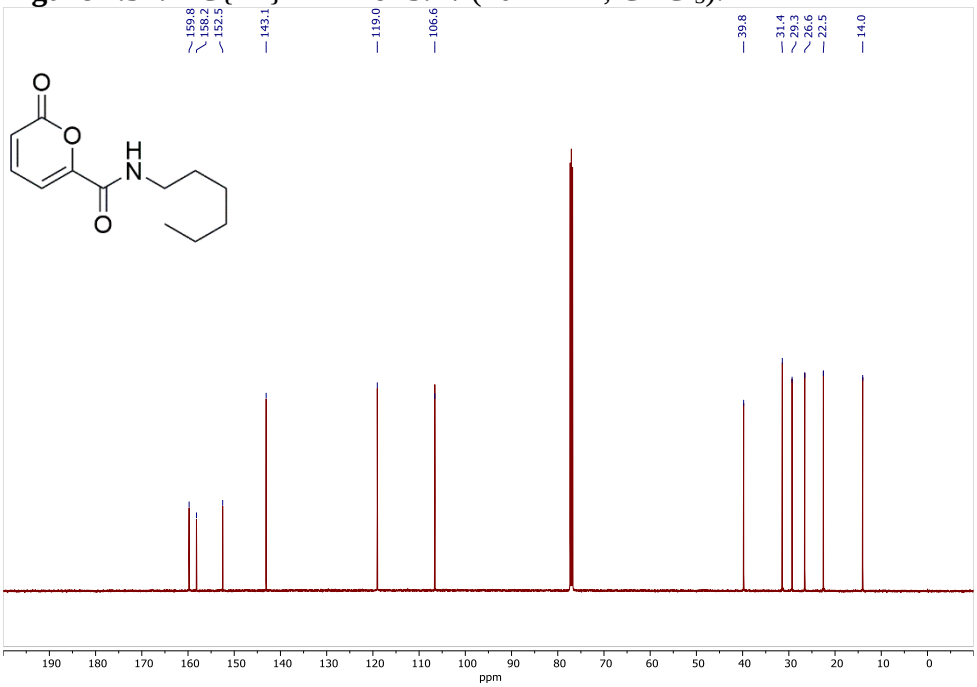

Figure 7.55: ^{1}H NMR of **3.7q*** (400 MHz, $CDCl_3$).

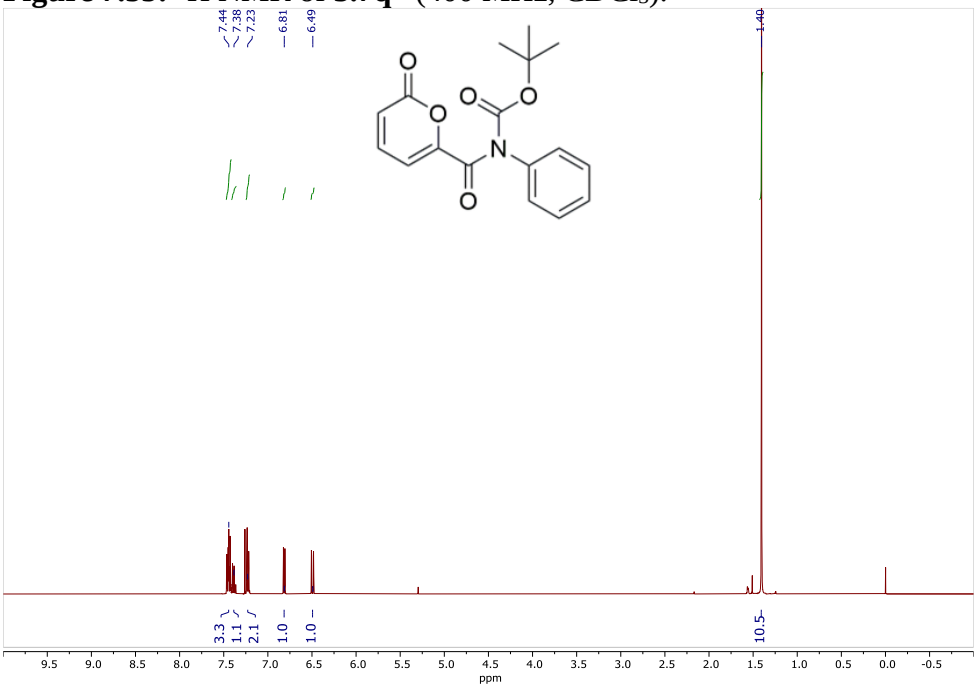

Figure 7.56: ^{13}C{^{1}H} NMR of **3.7q*** (101 MHz, $CDCl_3$).

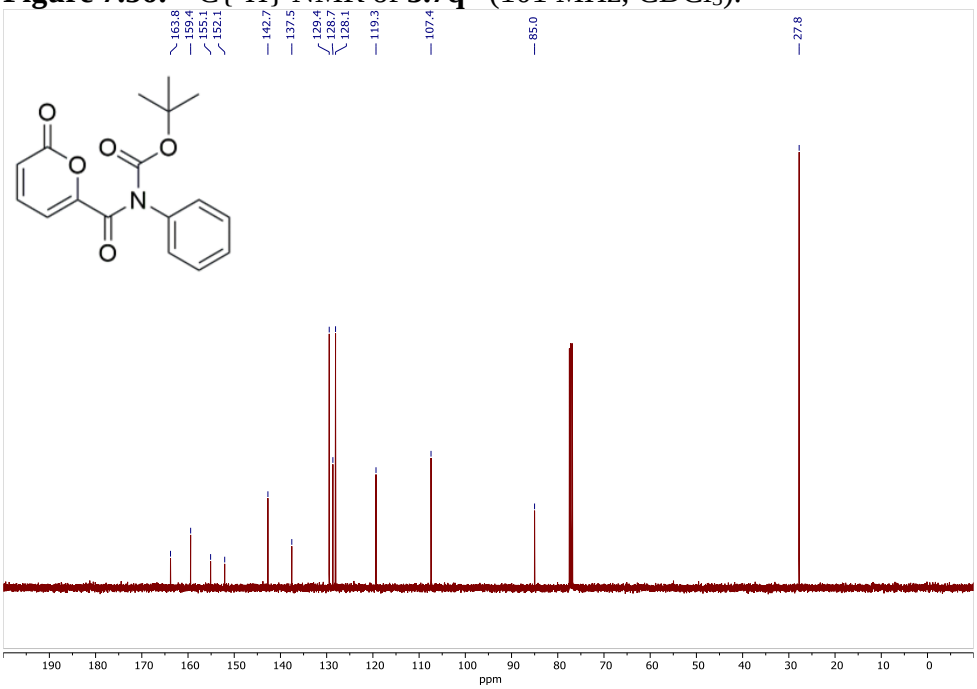

Figure 7.57: ^{1}H NMR of **3.7v*** (400 MHz, $CDCl_3$).

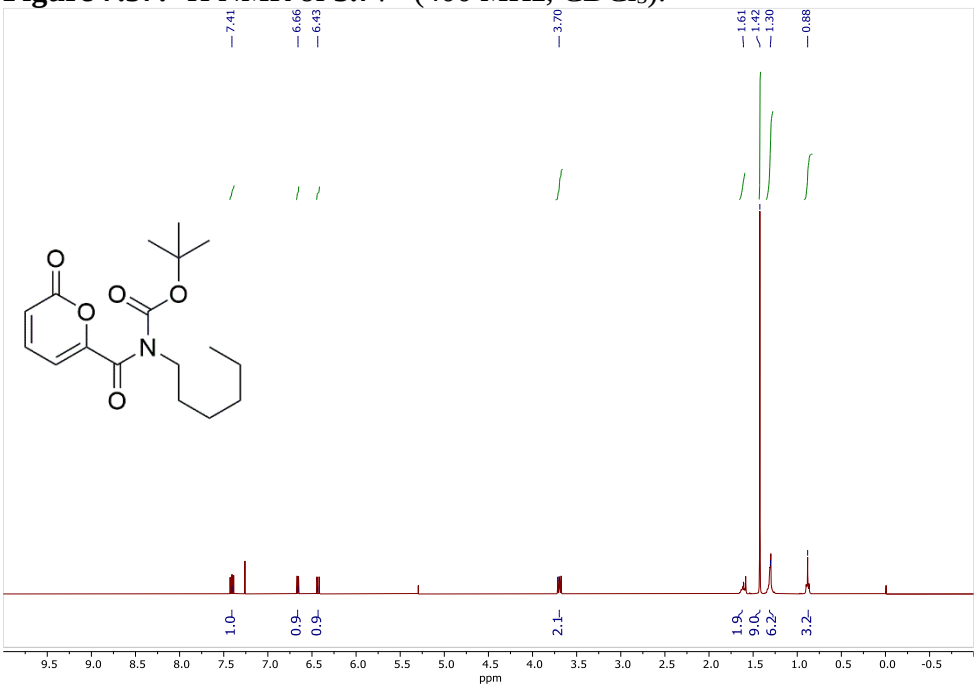

Figure 7.58: ^{13}C{^{1}H} NMR of **3.7v*** (101 MHz, $CDCl_3$).

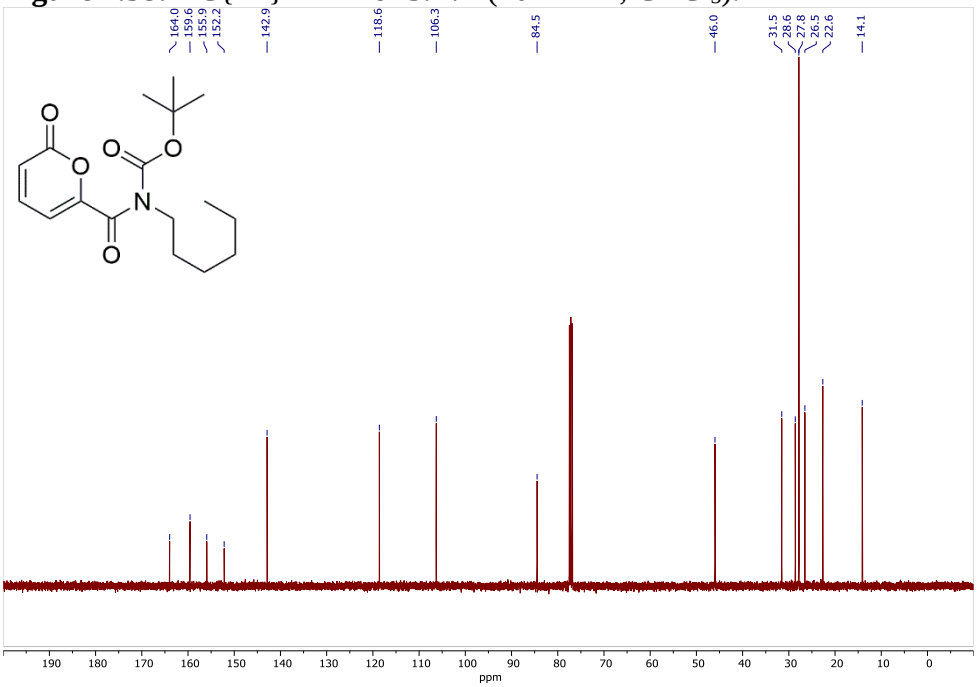

Figure 7.59: ^{1}H NMR of **3.12a** (400 MHz, $CDCl_3$).

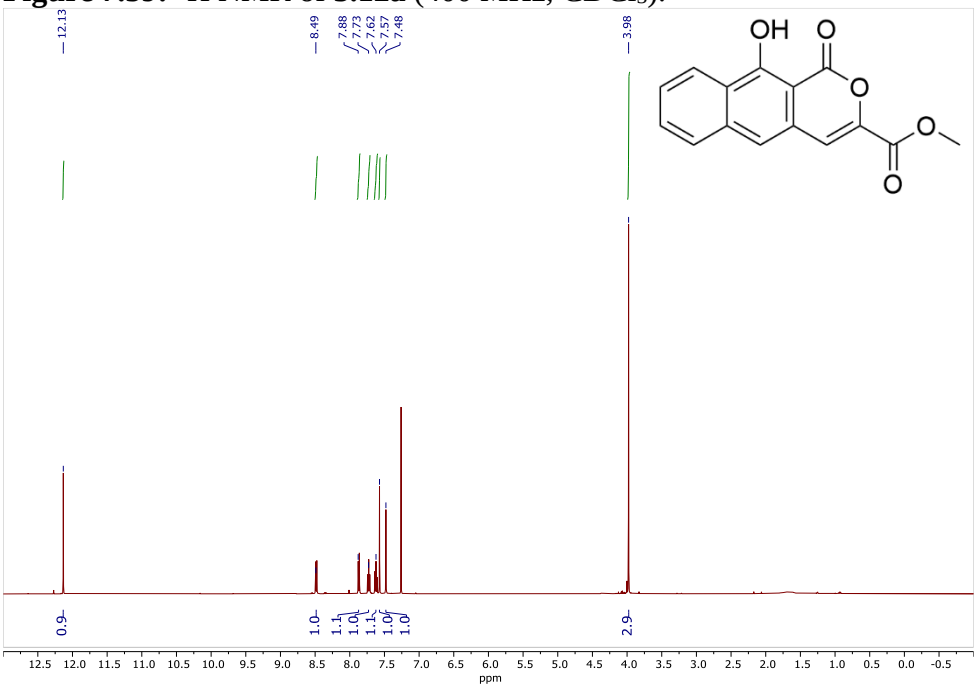

Figure 7.60: ^{13}C{^{1}H} NMR of **3.12a** (126 MHz, $CDCl_3$).

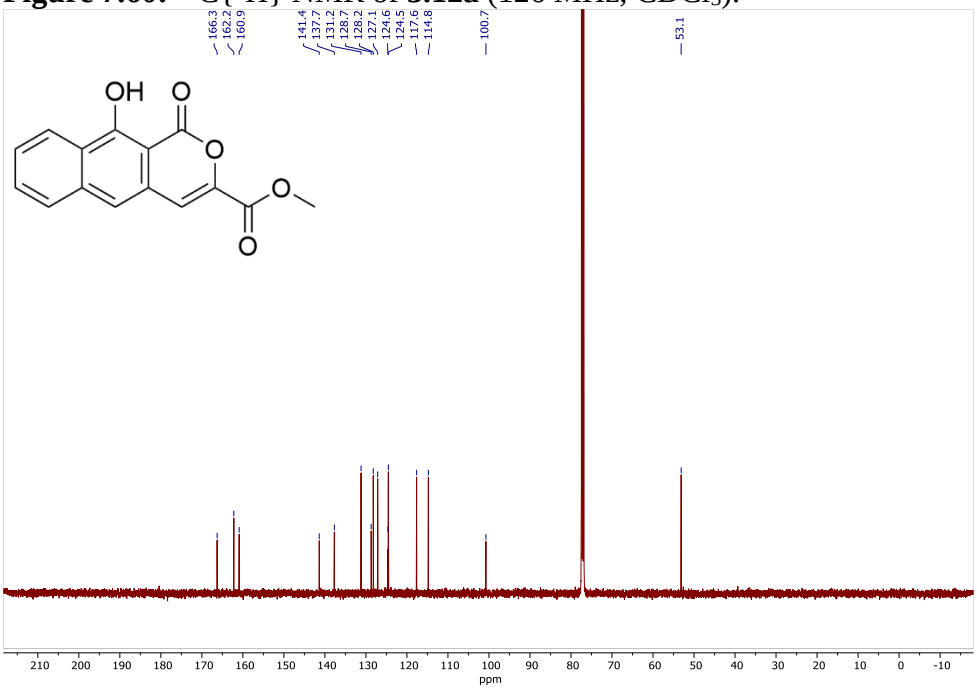

Figure 7.61: ^{1}H NMR of **3.12b** (400 MHz, $CDCl_3$).

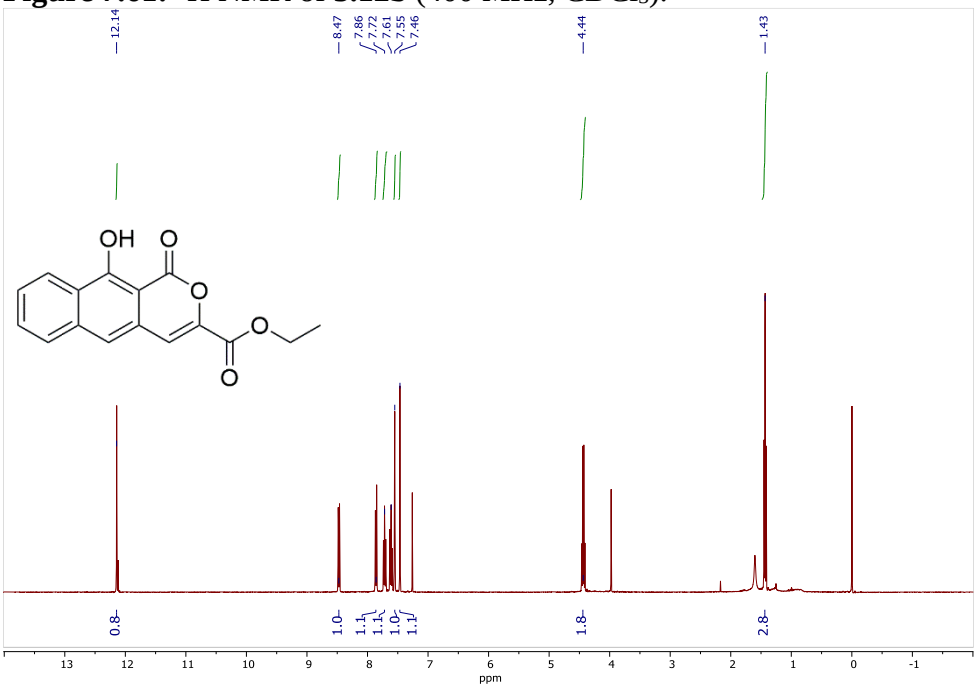

Figure 7.62: ^{13}C{^{1}H} NMR of **3.12b** (101 MHz, $CDCl_3$).

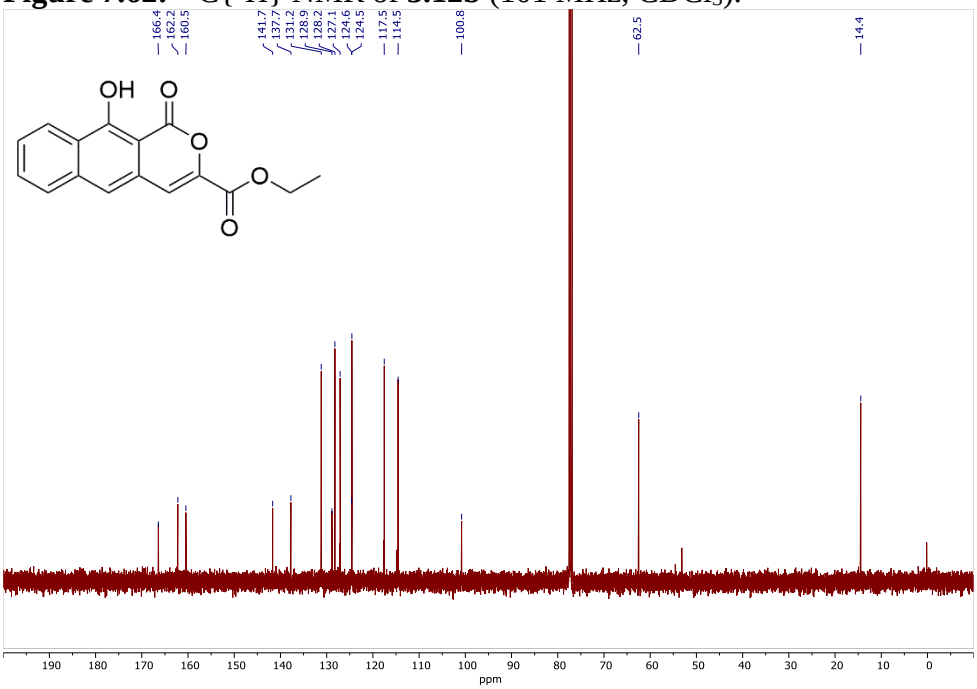

Figure 7.63: ^{1}H NMR of **3.12c** plus grease (400 MHz, $CDCl_3$).

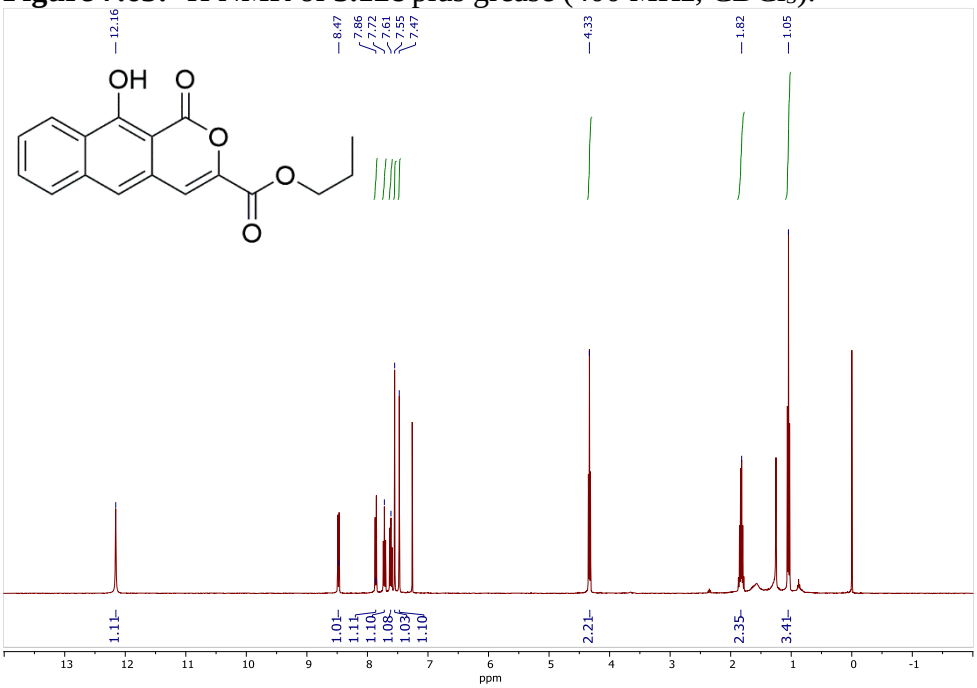

Figure 7.64: ^{13}C{^{1}H} NMR of **3.12c** plus grease (101 MHz, $CDCl_3$).

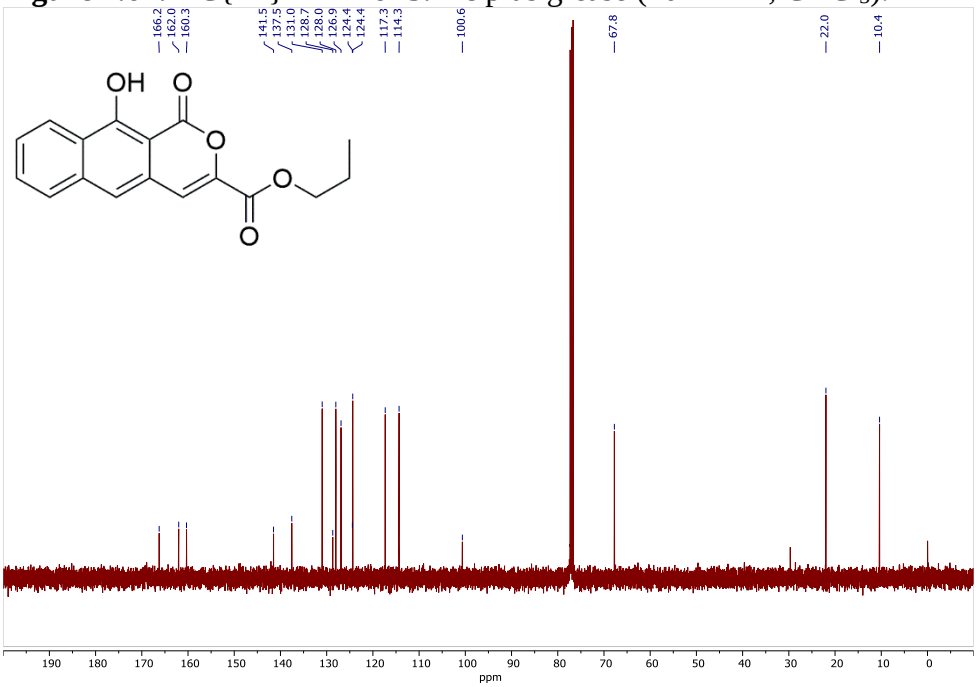

Figure 7.65: ^{1}H NMR of **3.12d** (400 MHz, $CDCl_3$).

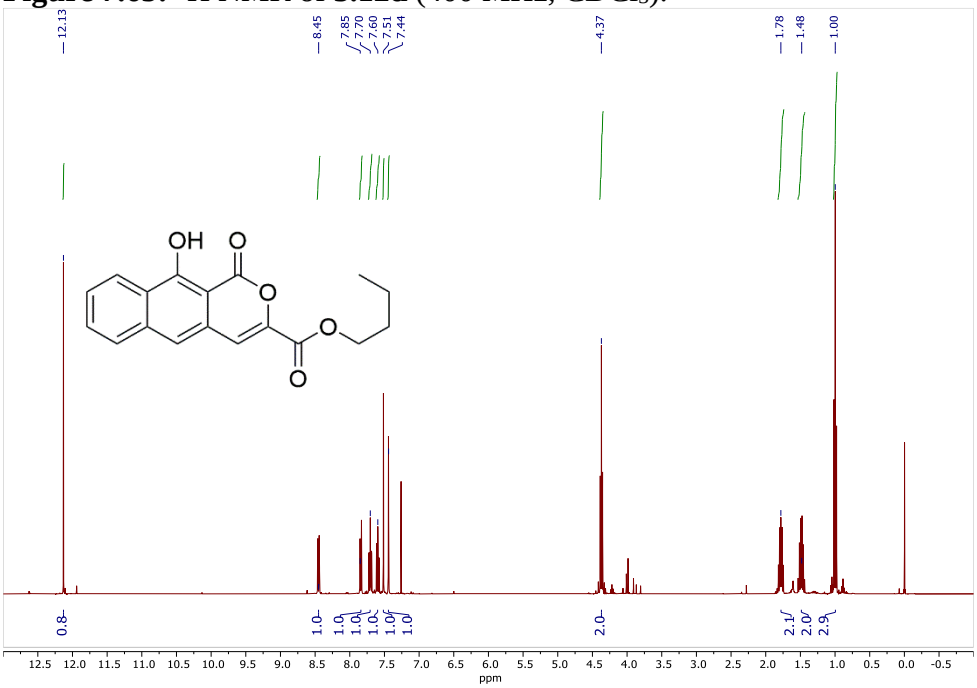

Figure 7.66: ^{13}C{^{1}H} NMR of **3.12d** (101 MHz, $CDCl_3$).

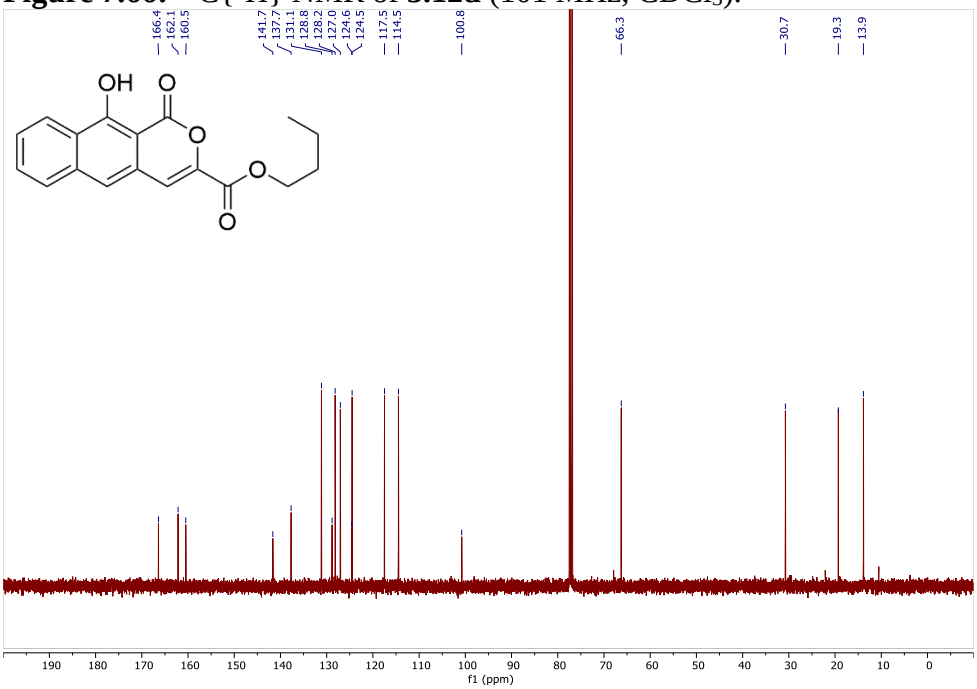

Figure 7.67: ^{1}H NMR of **3.12e** (400 MHz, $CDCl_3$).

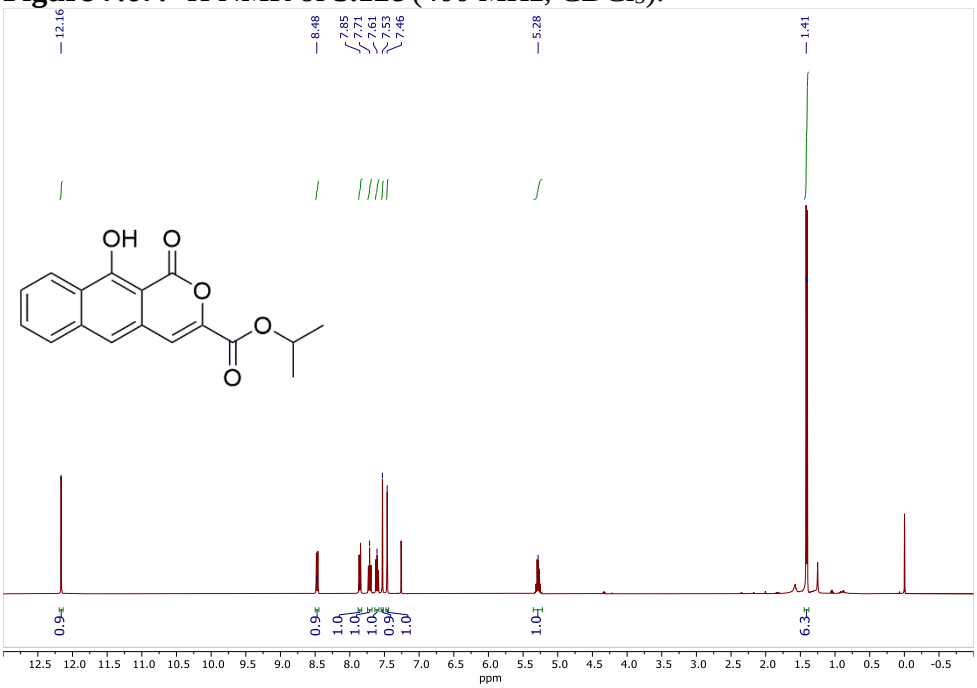

Figure 7.68: ^{13}C{^{1}H} NMR of **3.12e** (101 MHz, $CDCl_3$).

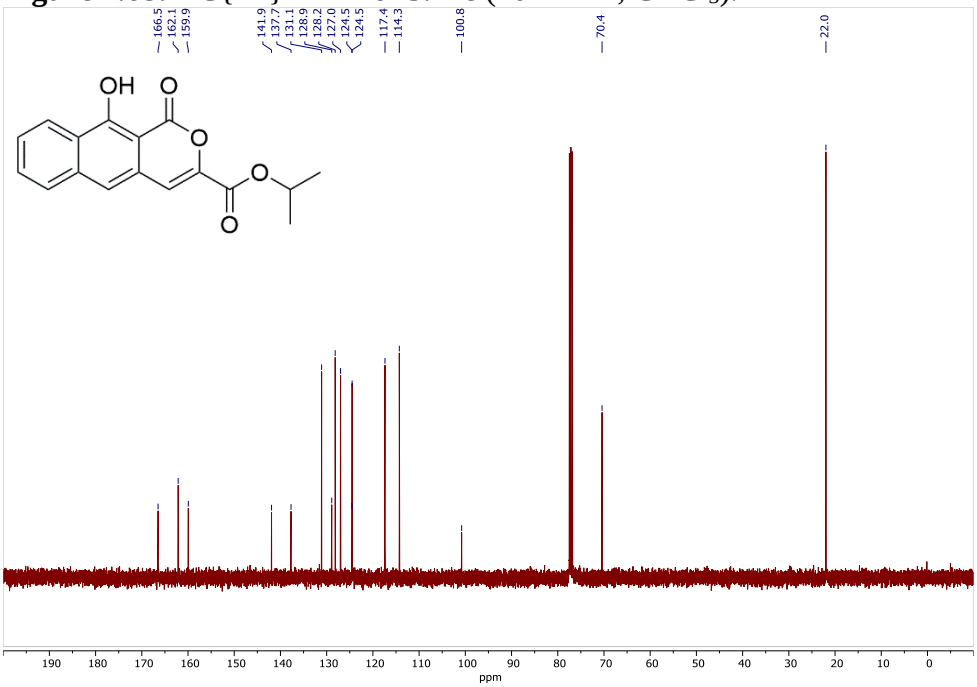

Figure 7.69: ^{1}H NMR of **3.12g** plus grease (400 MHz, $CDCl_3$).

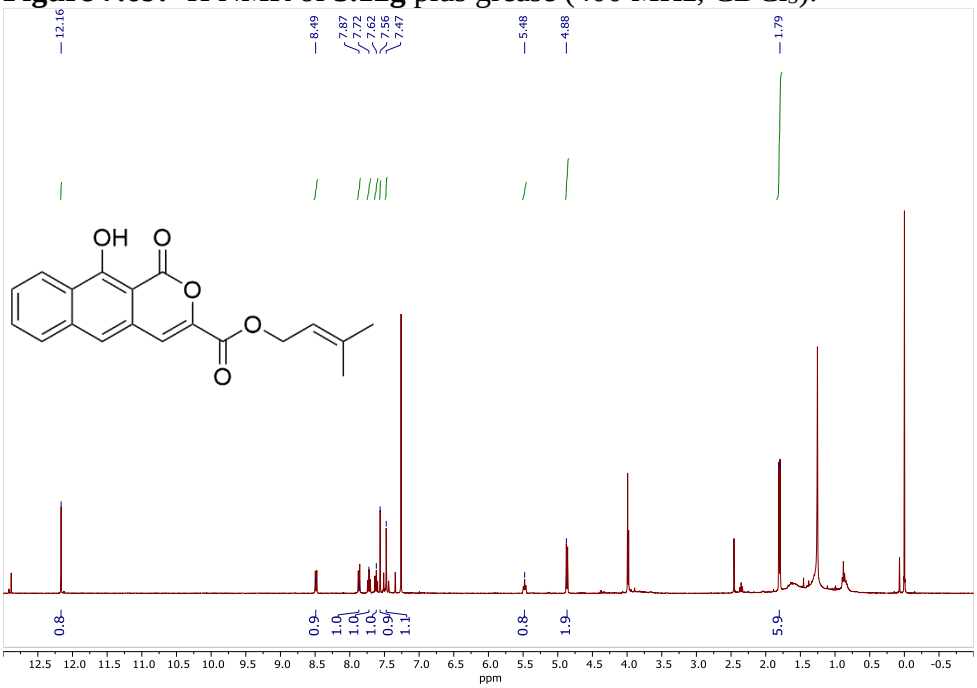

Figure 7.70: ^{13}C{^{1}H} NMR of **3.12g** plus grease (101 MHz, $CDCl_3$).

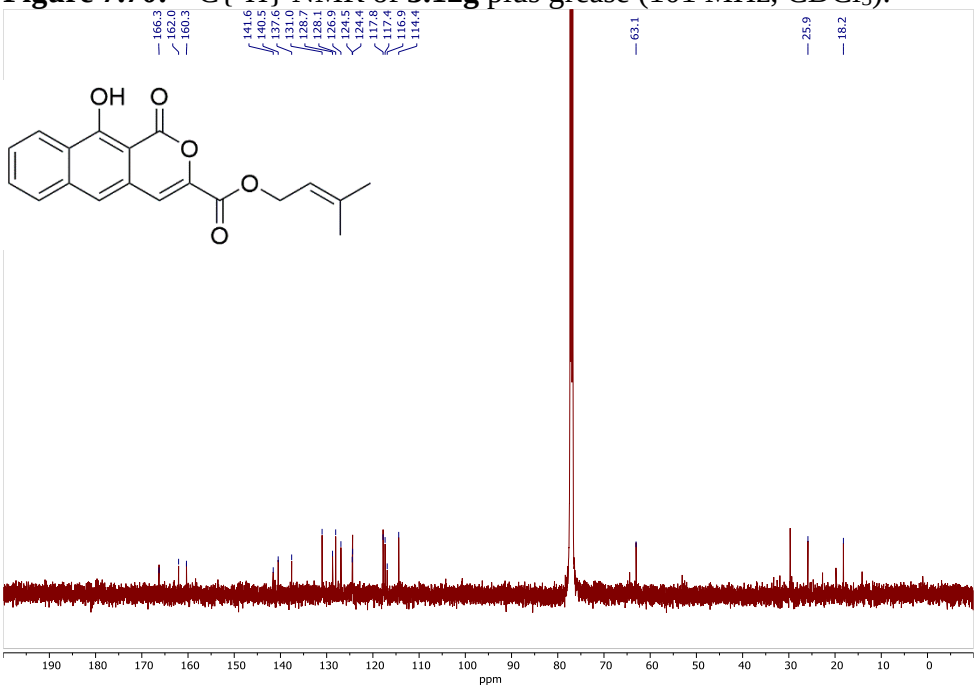

Figure 7.71: ^{1}H NMR of **3.12h** plus grease (400 MHz, $CDCl_3$).

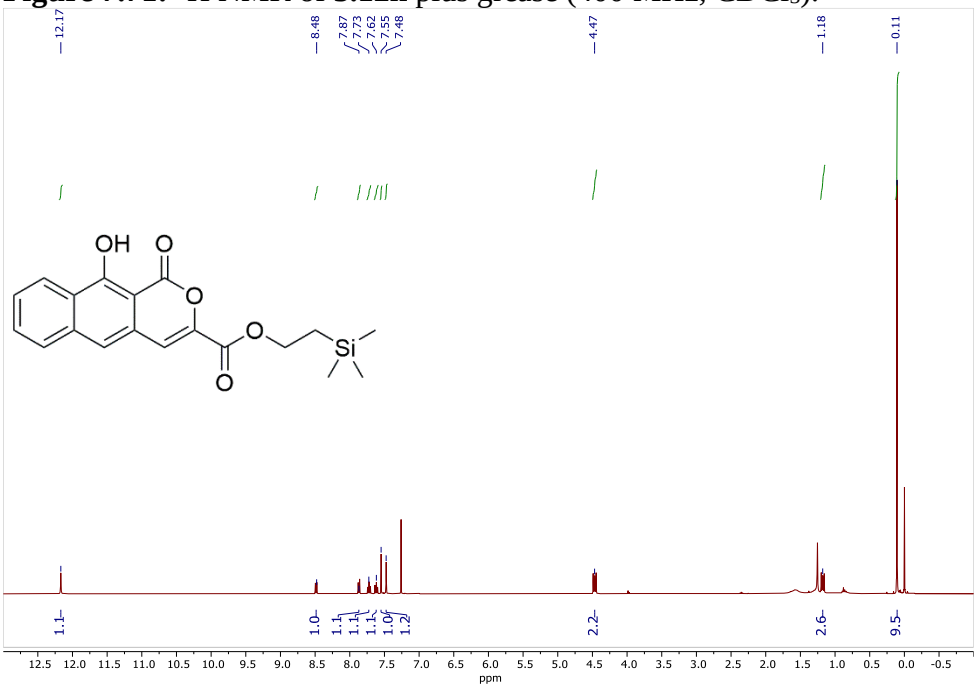

Figure 7.72: ^{13}C{^{1}H} NMR of **3.12h** plus grease (126 MHz, $CDCl_3$).

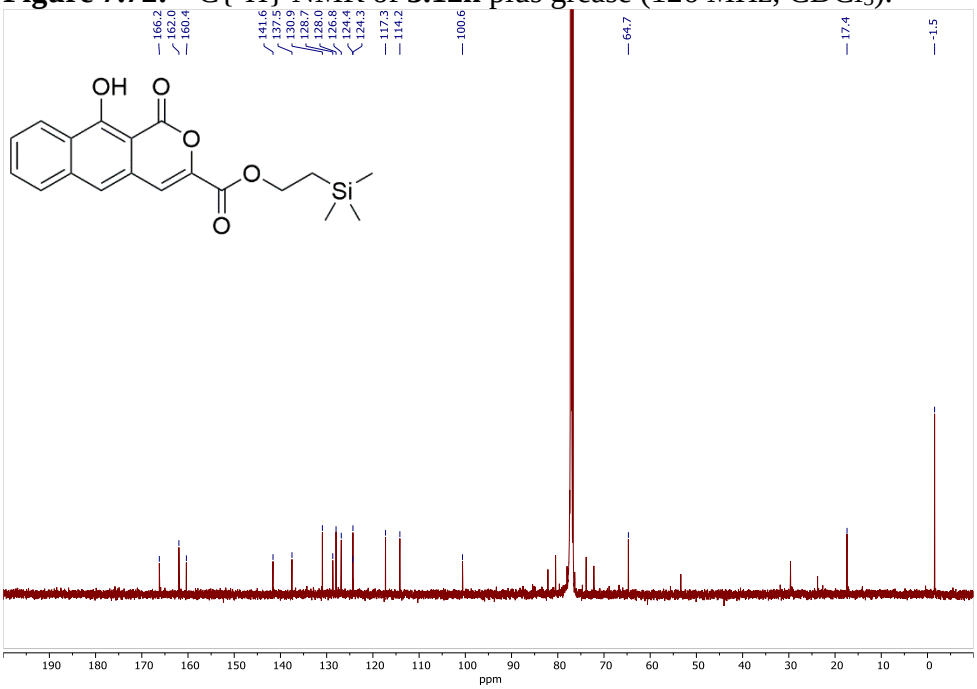

Figure 7.73: ^{1}H NMR of **3.12i** (400 MHz, $CDCl_3$).

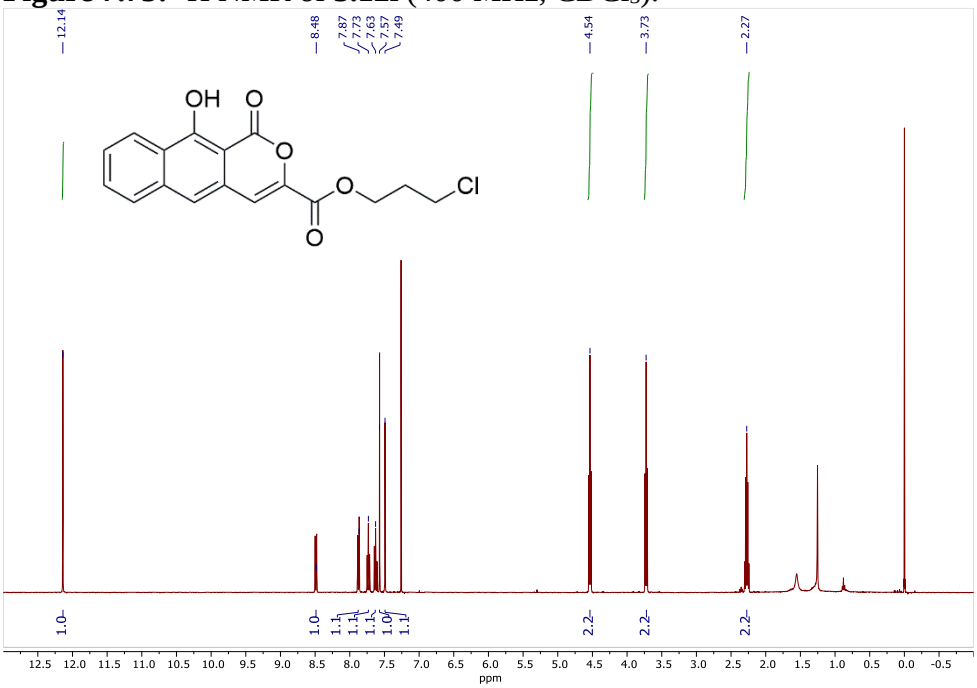

Figure 7.74: ^{13}C{^{1}H} NMR of **3.12i** (101 MHz, $CDCl_3$).

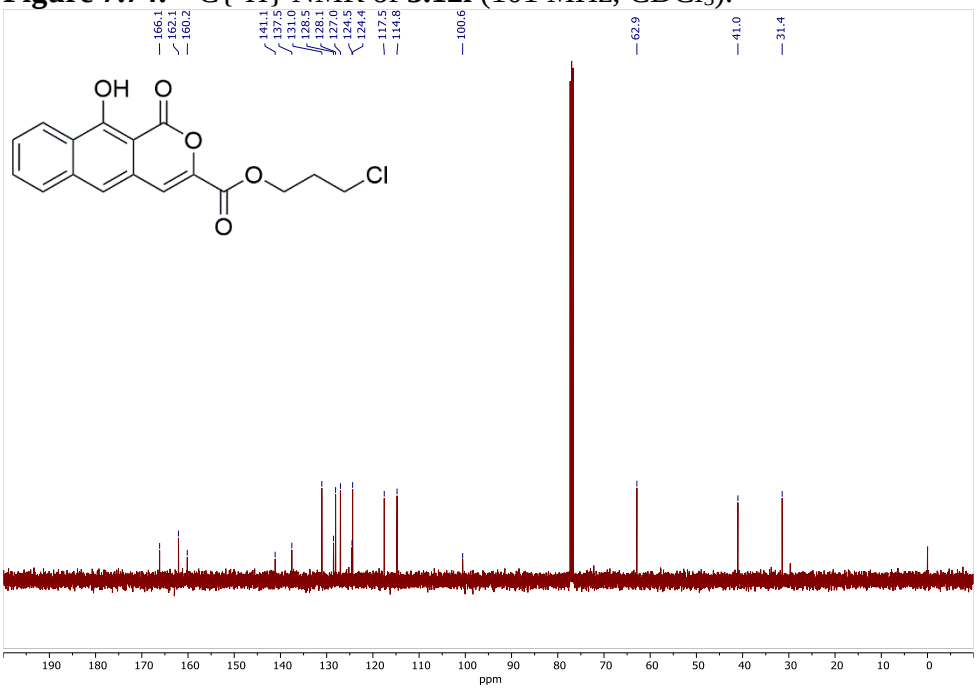

Figure 7.75: ^{1}H NMR of **3.12j** plus grease (500 MHz, $CDCl_3$).

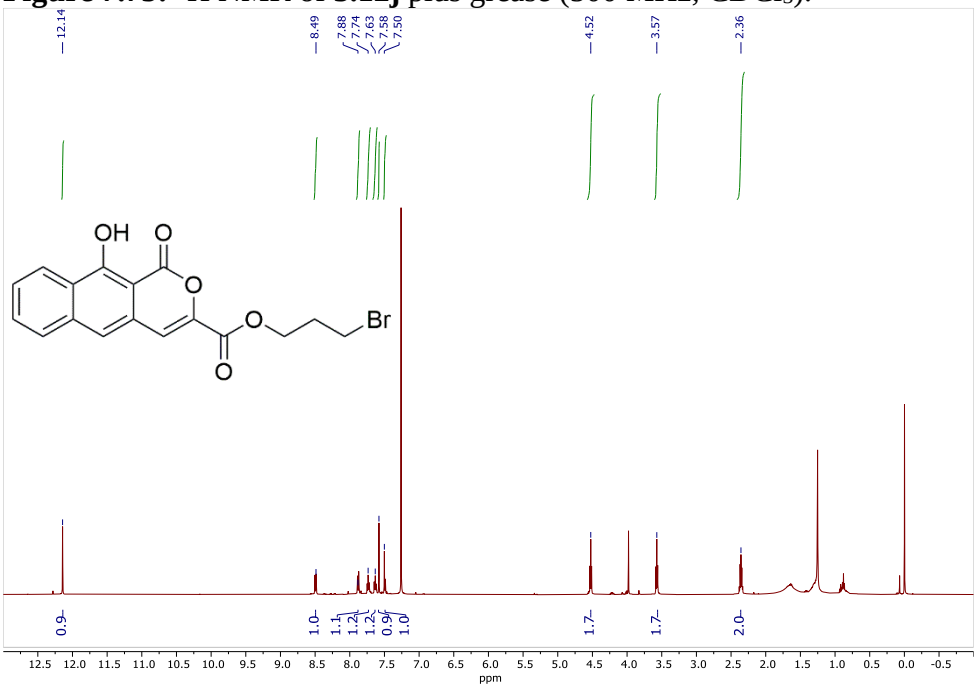

Figure 7.76: ^{13}C{^{1}H} NMR of **3.12j** plus grease (126 MHz, $CDCl_3$).

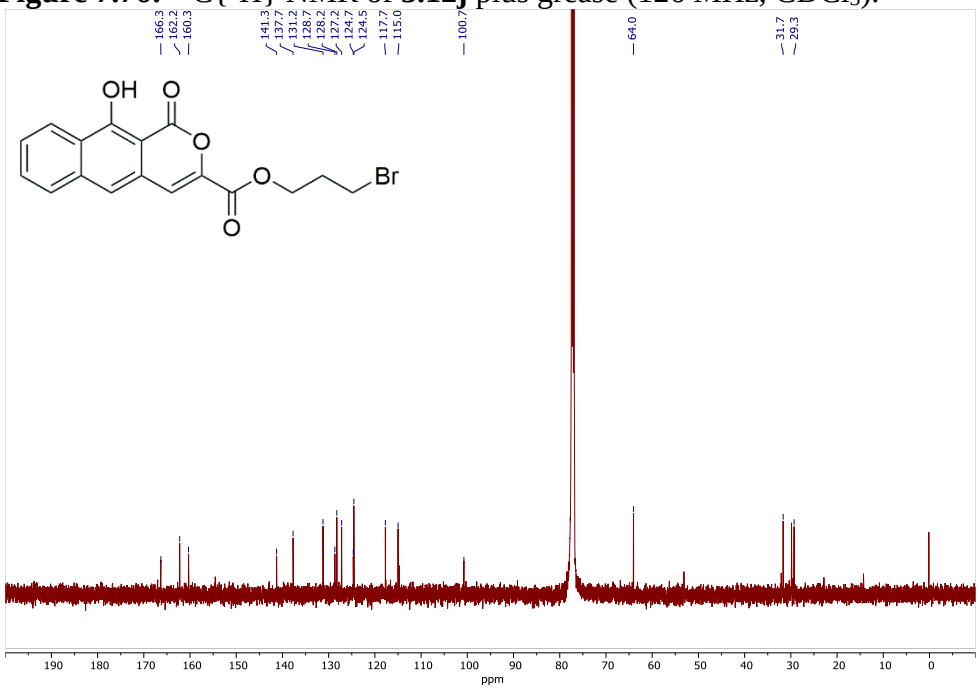

Figure 7.77: ^{1}H NMR of **3.12o** (400 MHz, $CDCl_3$).

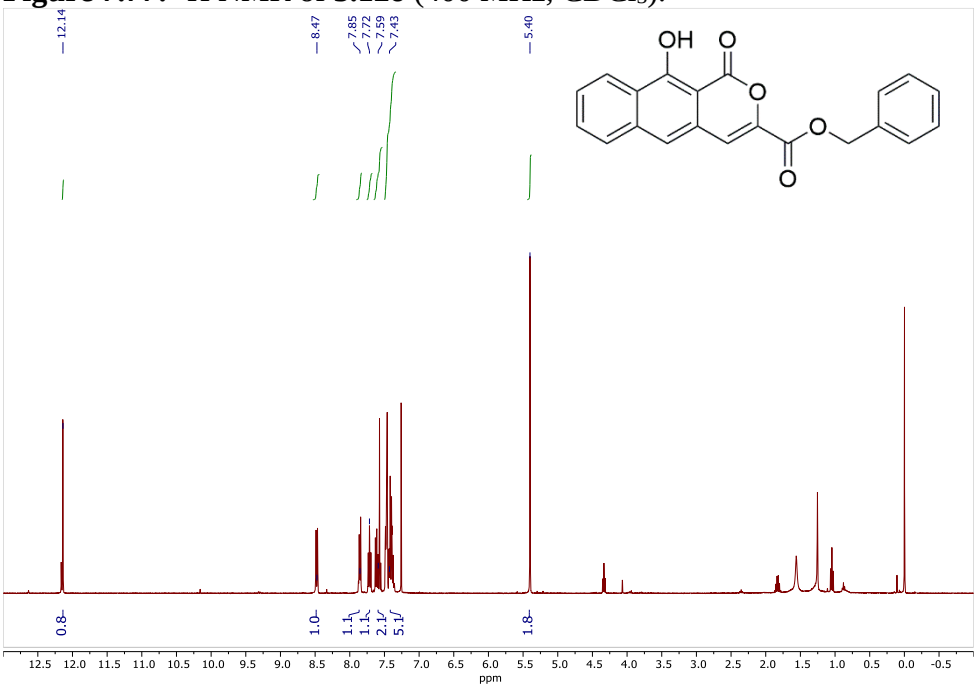

Figure 7.78: ^{13}C{^{1}H} NMR of **3.12o** (101 MHz, $CDCl_3$).

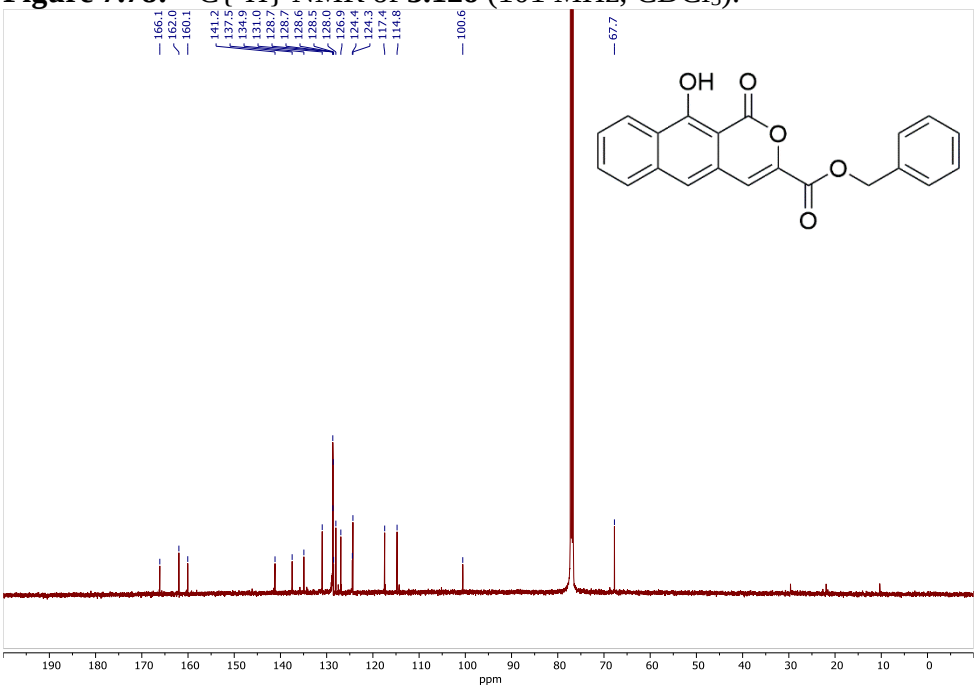

Figure 7.79: ^{1}H NMR of **3.12p** plus grease (400 MHz, $CDCl_3$).

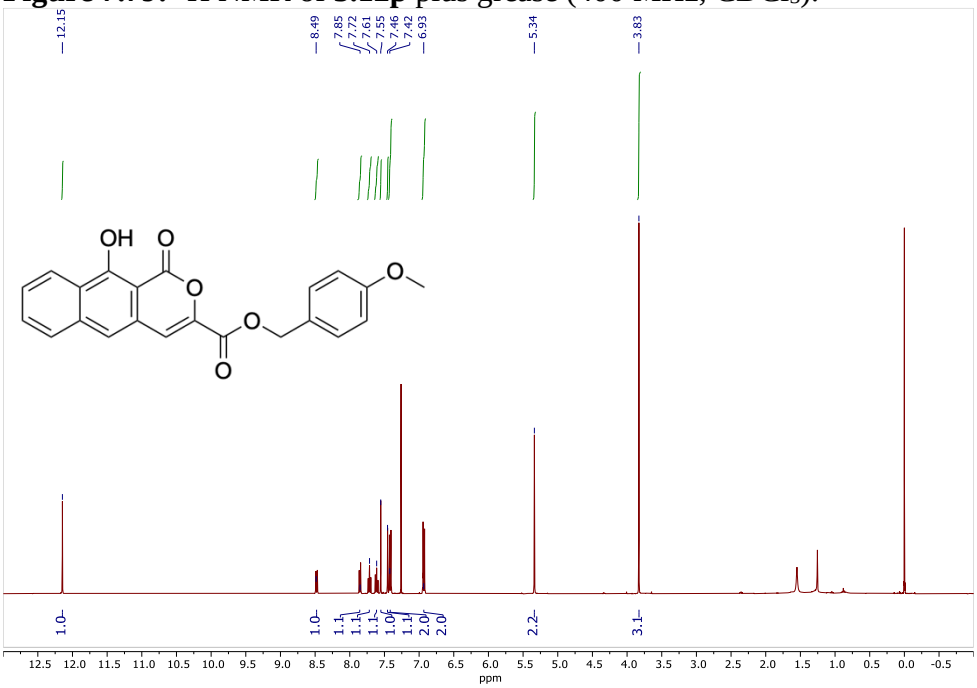

Figure 7.80: ^{13}C{^{1}H} NMR of **3.12p** plus grease (126 MHz, $CDCl_3$).

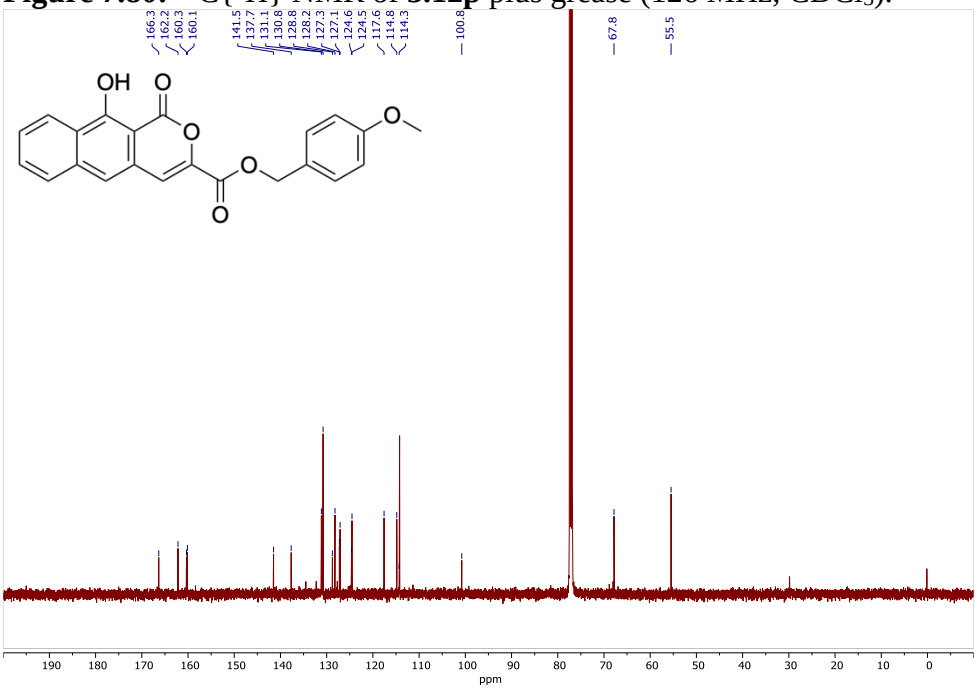

Figure 7.81: ^{1}H NMR of **3.12s** (400 MHz, $CDCl_3$).

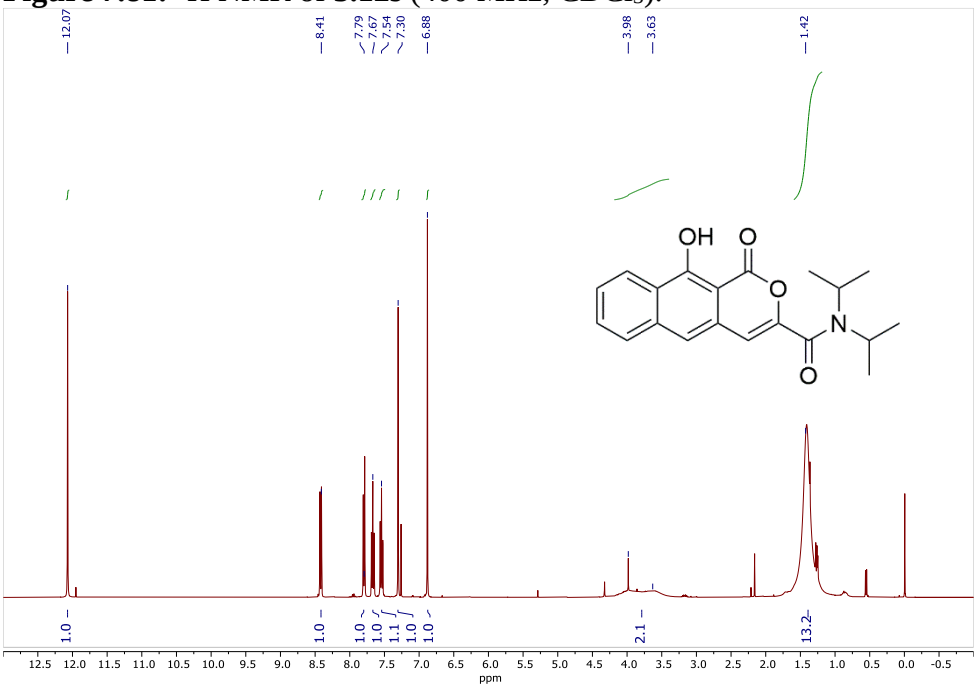

Figure 7.82: ^{13}C{^{1}H} NMR of **3.12s** (101 MHz, $CDCl_3$).

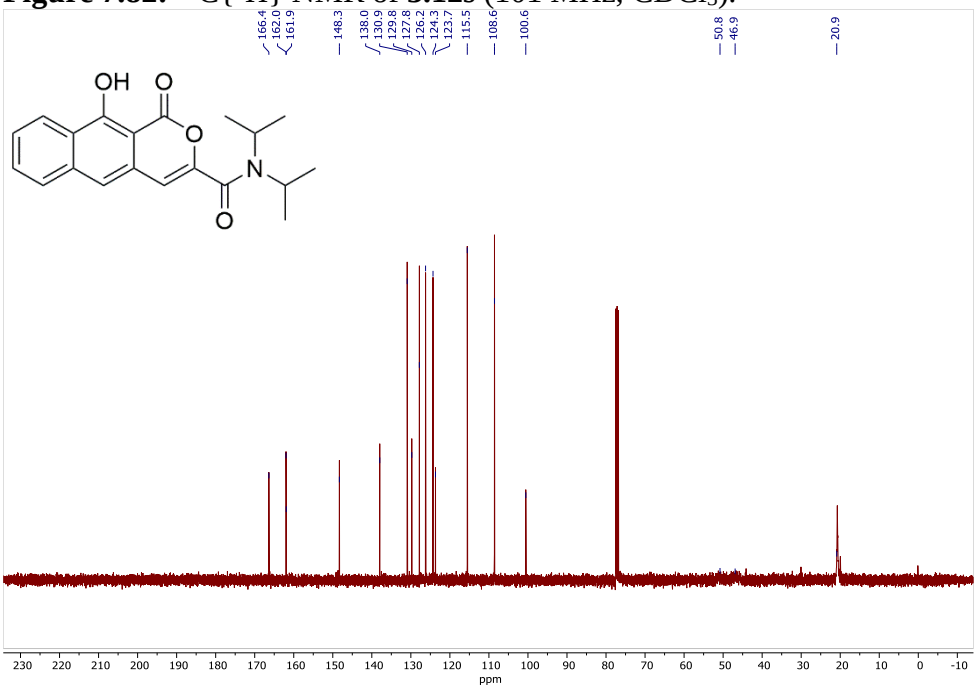

Figure 7.83: ^{1}H NMR of **3.12t** (400 MHz, $CDCl_3$).

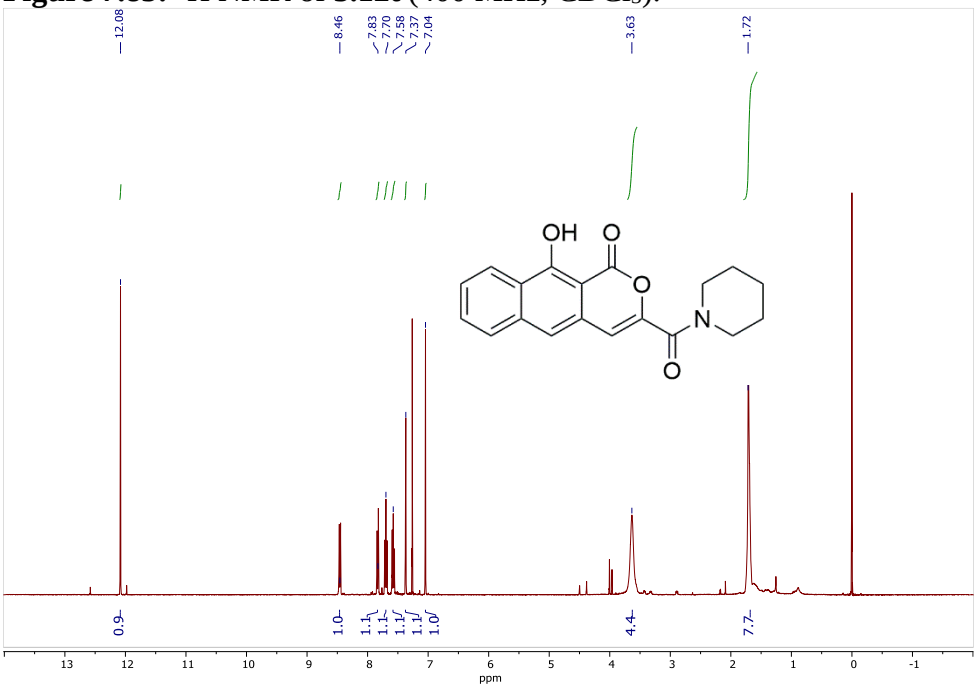

Figure 7.84: ^{13}C{^{1}H} NMR of **3.12t** (100 MHz, $CDCl_3$).

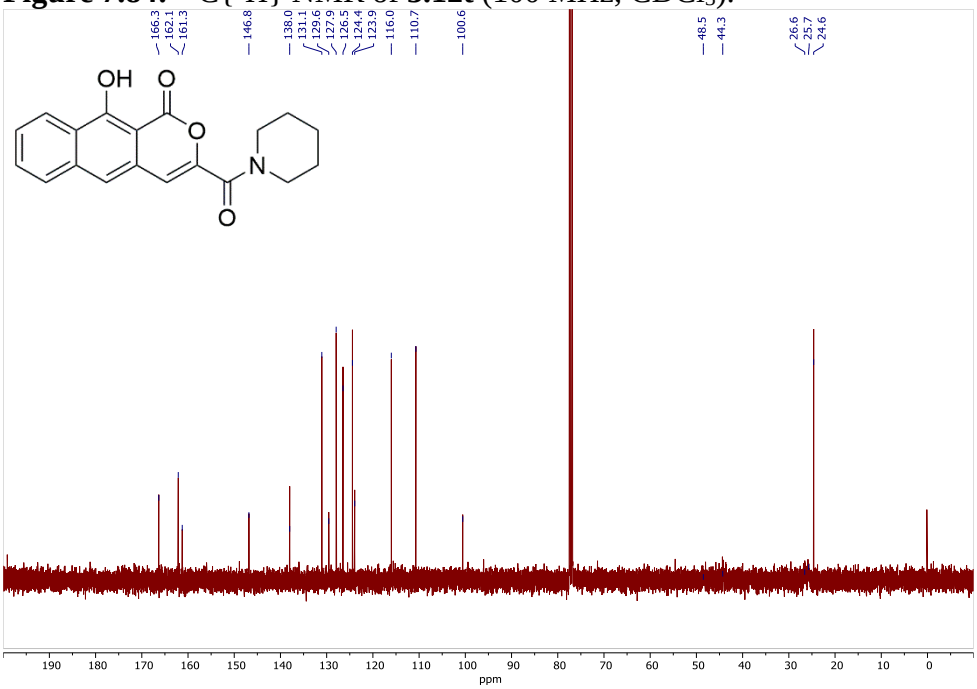

Figure 7.85: ^{1}H NMR of **3.12u** (400 MHz, $CDCl_3$).

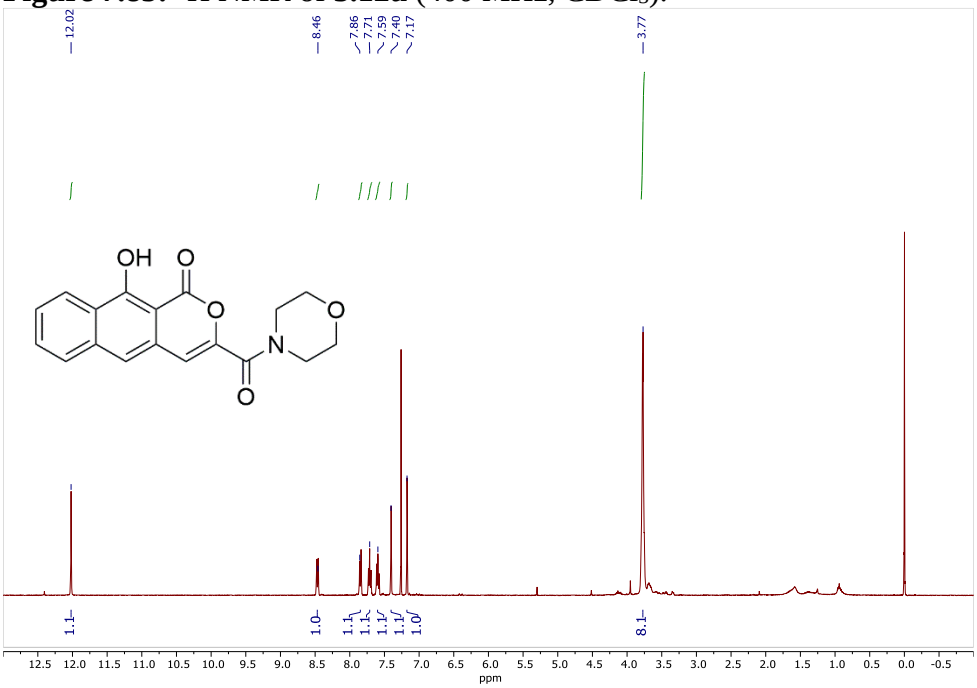

Figure 7.86: ^{13}C{^{1}H} NMR of **3.12u** (101 MHz, $CDCl_3$).

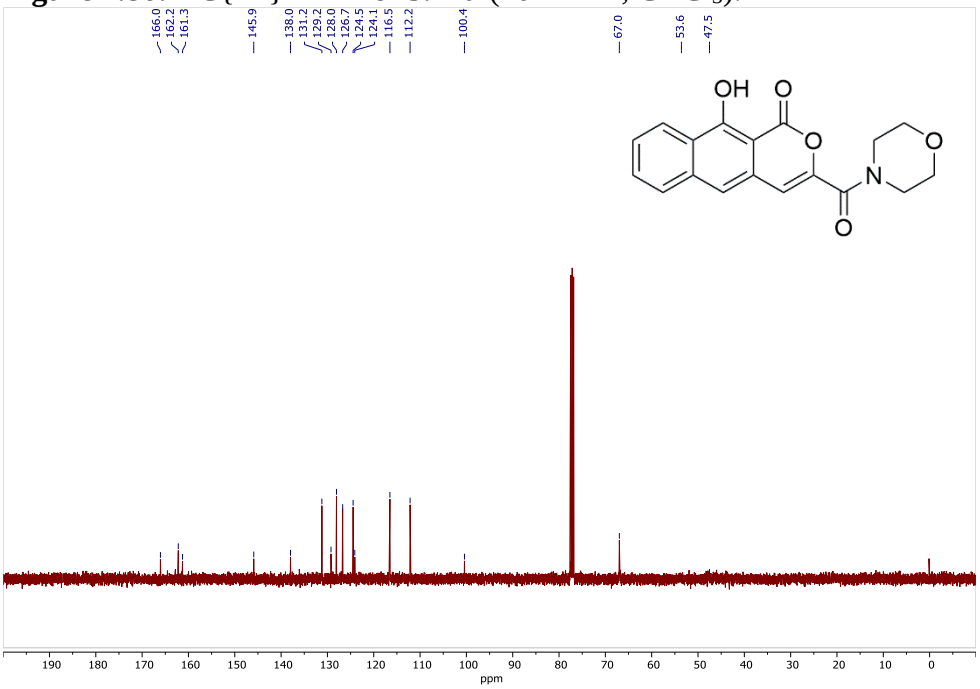

Figure 7.87: ^{1}H NMR of **3.12v*** (400 MHz, $CDCl_3$).

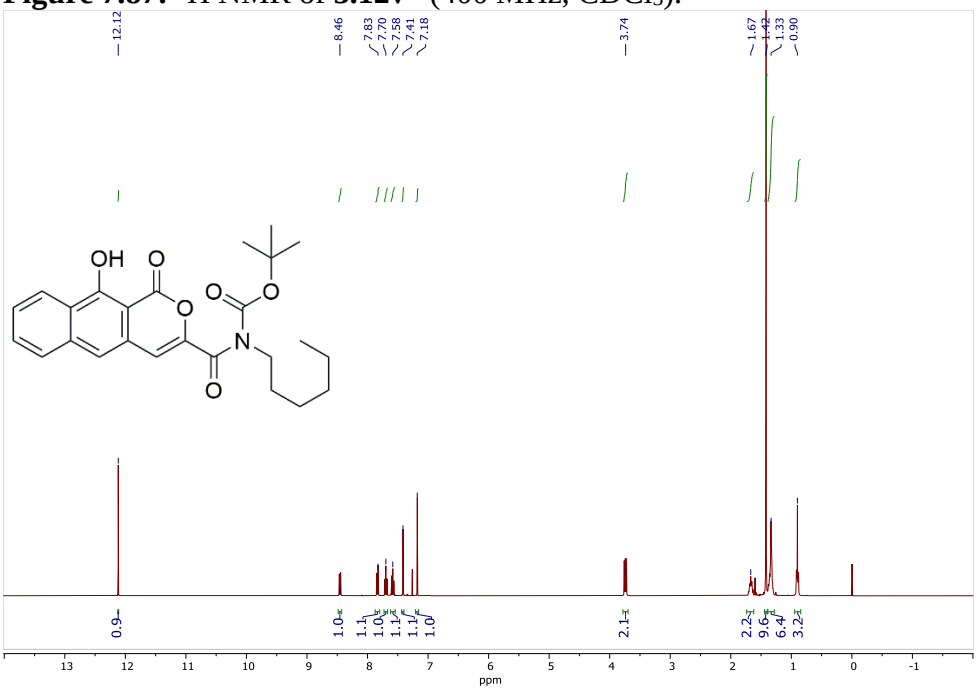

Figure 7.88: ^{13}C{^{1}H} NMR of **3.12v*** (101 MHz, $CDCl_3$).

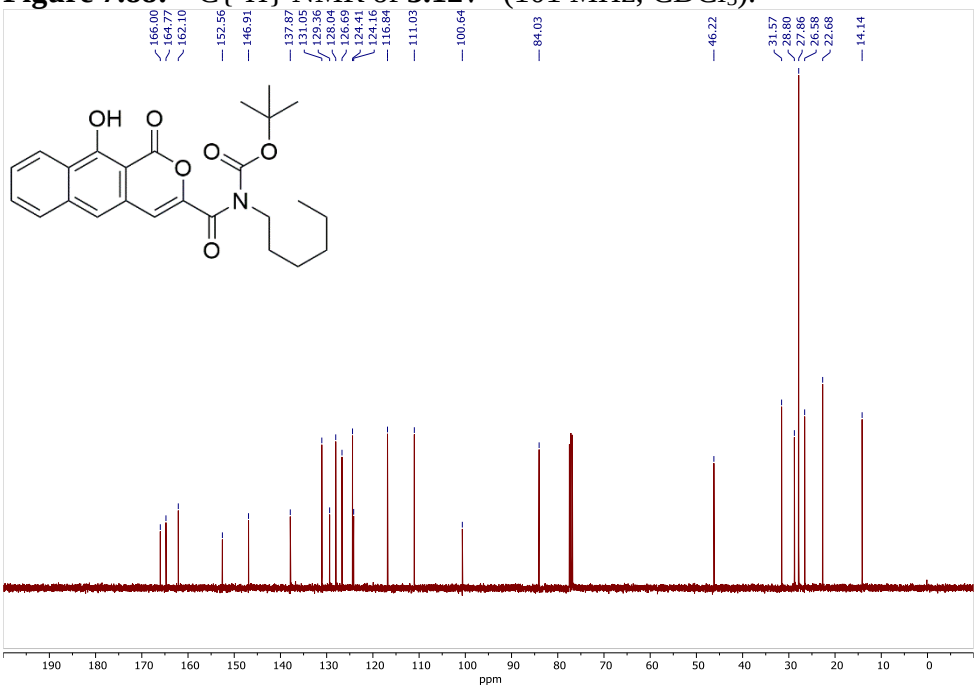

Figure 7.89: ^{1}H NMR of **3.13** (400 MHz, $CDCl_3$).

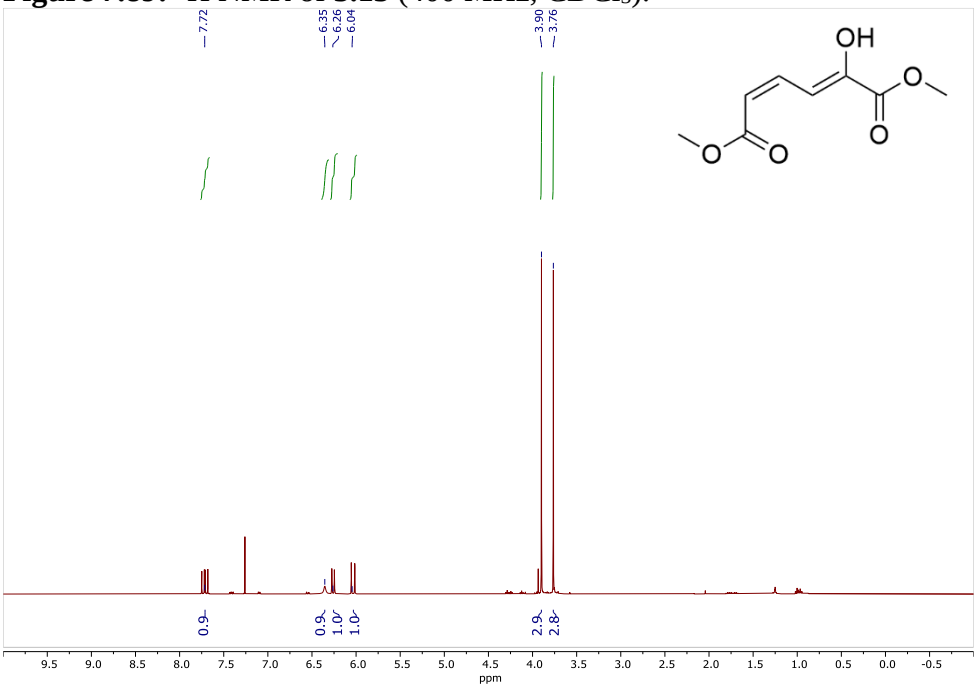

Figure 7.90: ^{13}C{^{1}H} NMR of **3.13** (101 MHz, $CDCl_3$).

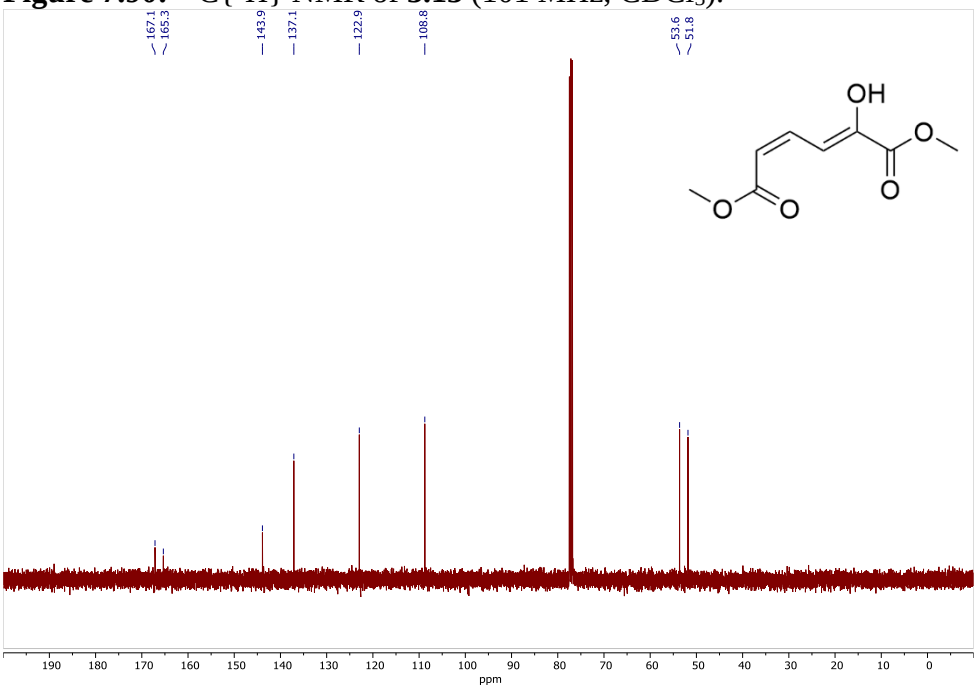

Figure 7.91: ^{1}H NMR of **3.16** (400 MHz, CD_3OD).

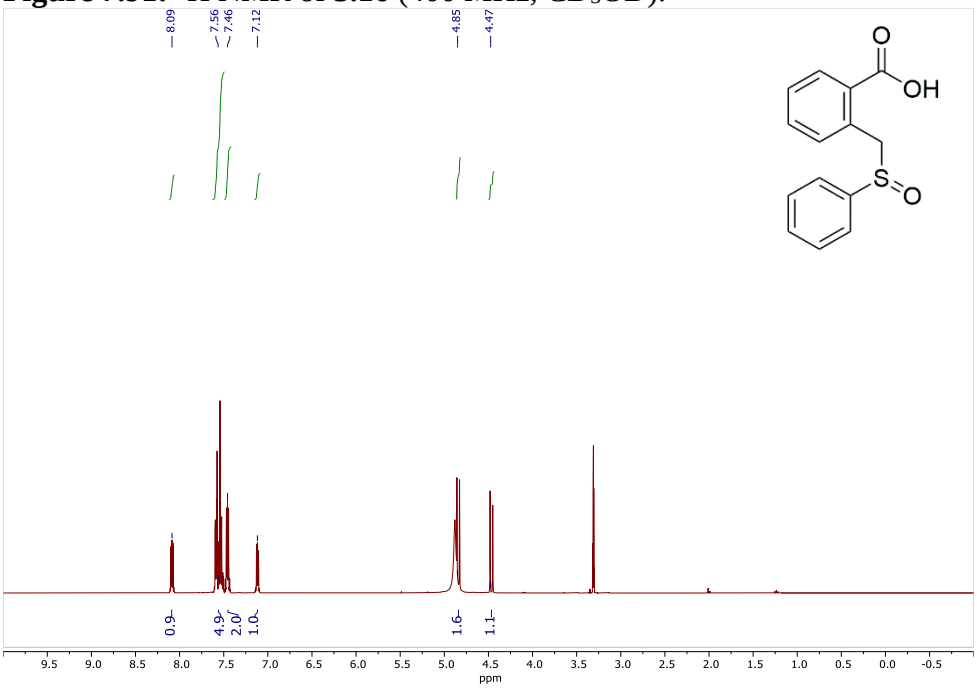

Figure 7.92: ^{13}C{^{1}H} NMR of **3.16** (101 MHz, CD_3OD).

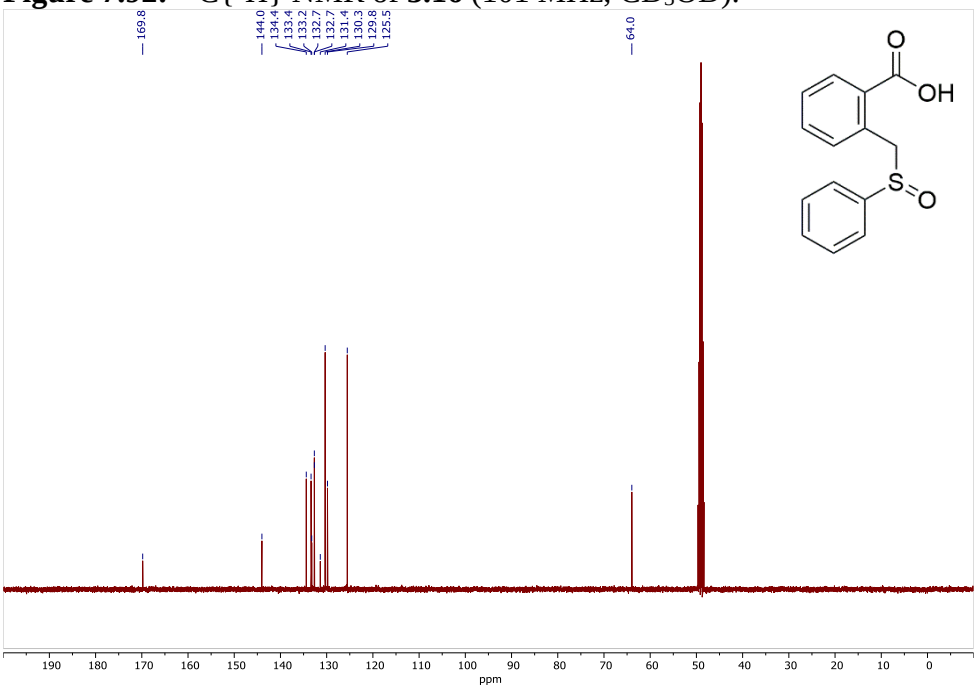

Figure 7.93 ^{1}H NMR of **3.17** (400 MHz, $CDCl_3$).

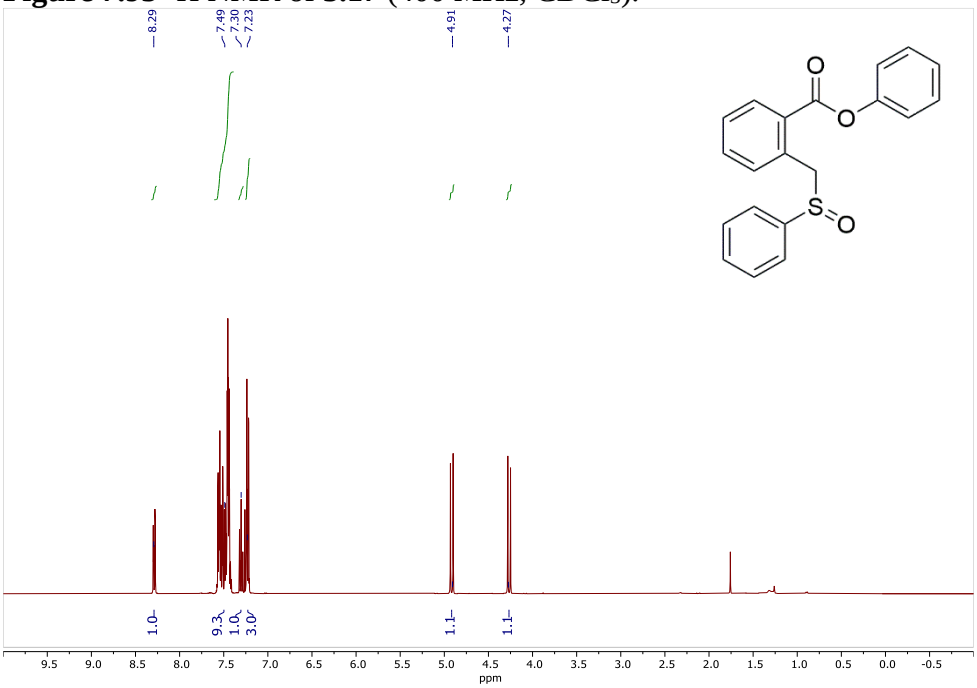

Figure 7.94: ^{13}C{^{1}H} NMR of **3.17** (101 MHz, $CDCl_3$).

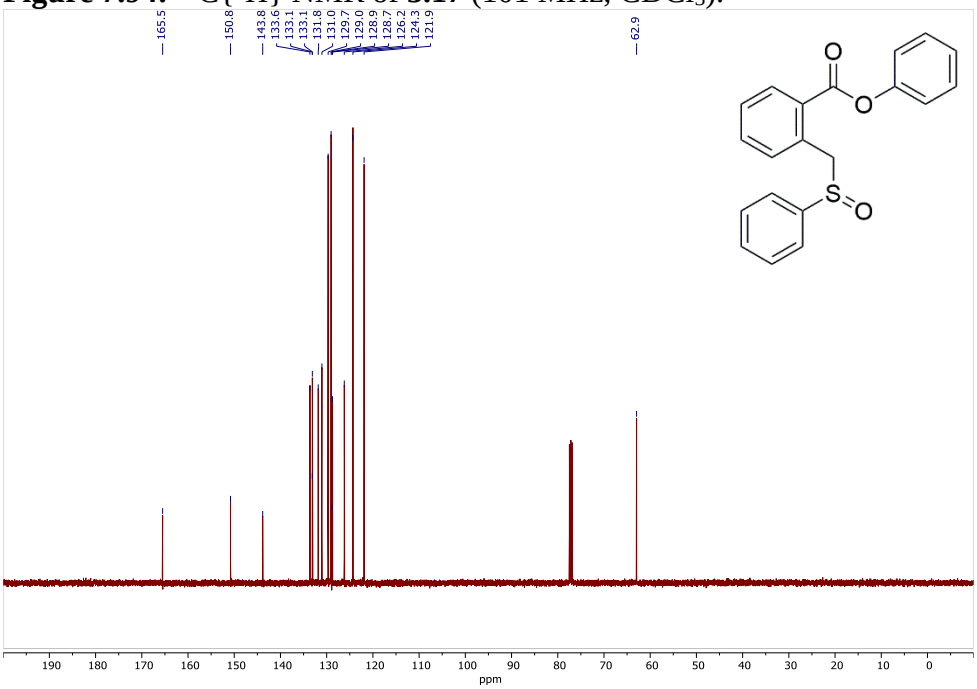

Figure 7.95: ^{1}H NMR of **3.19** plus acetone (400 MHz, $CDCl_3$).

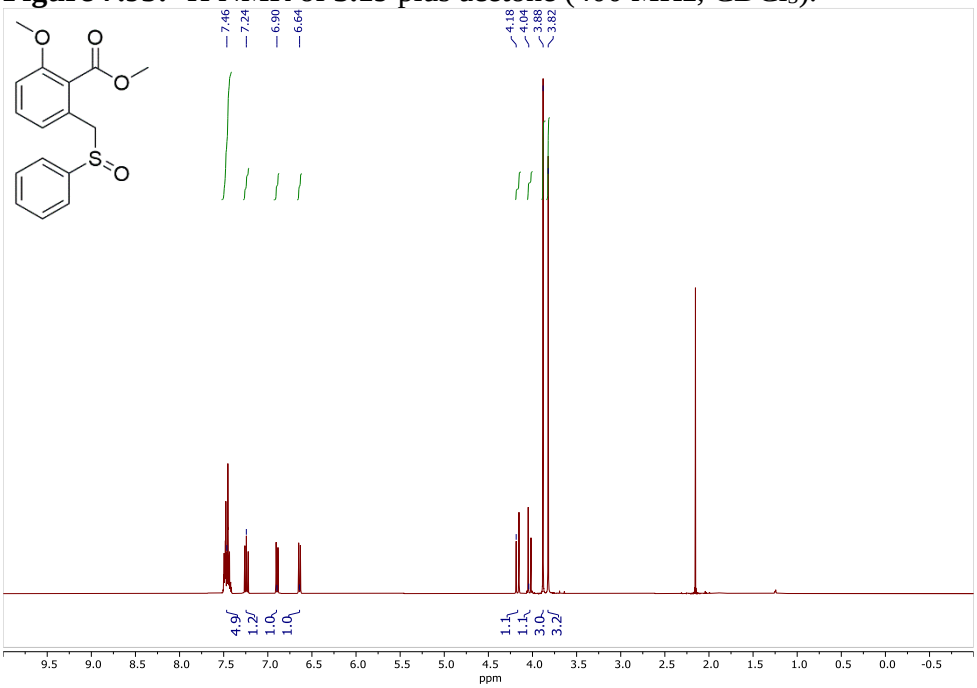

Figure 7.96: ^{13}C{^{1}H} NMR of **3.19** plus acetone (101 MHz, $CDCl_3$).

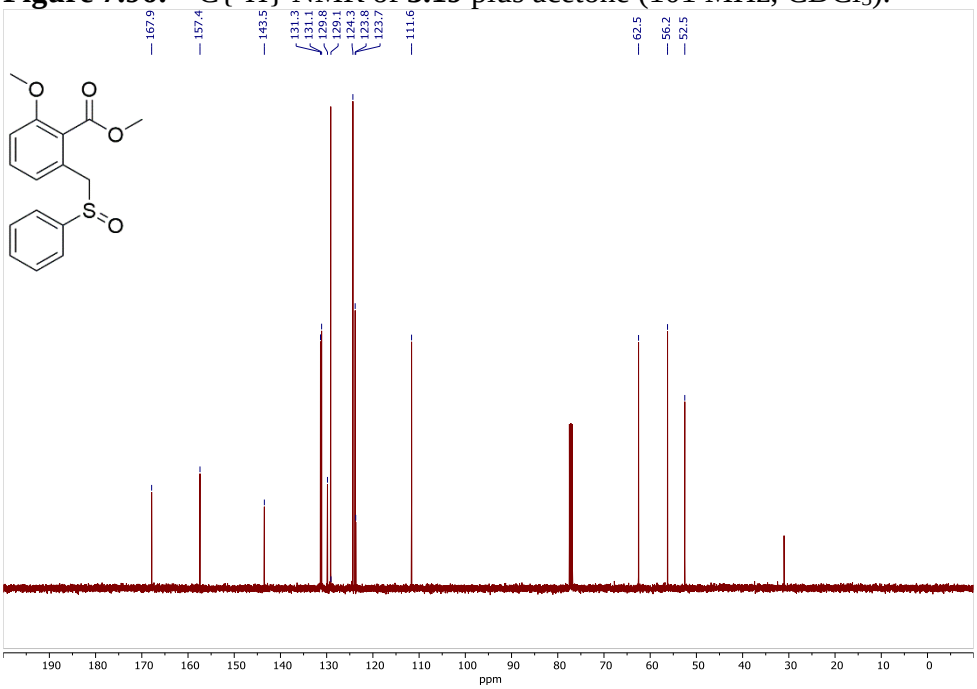

Figure 7.97: ^{1}H NMR of **3.20** plus water (400 MHz, $CDCl_3$).

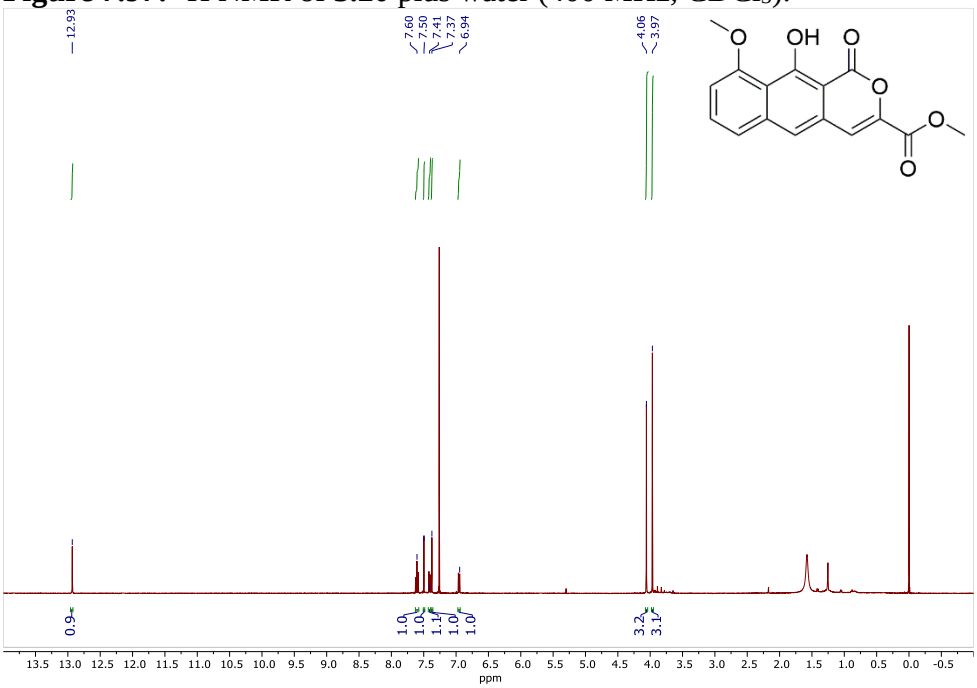

Figure 7.98: ^{13}C{^{1}H} NMR of **3.20** (151 MHz, $CDCl_3$).

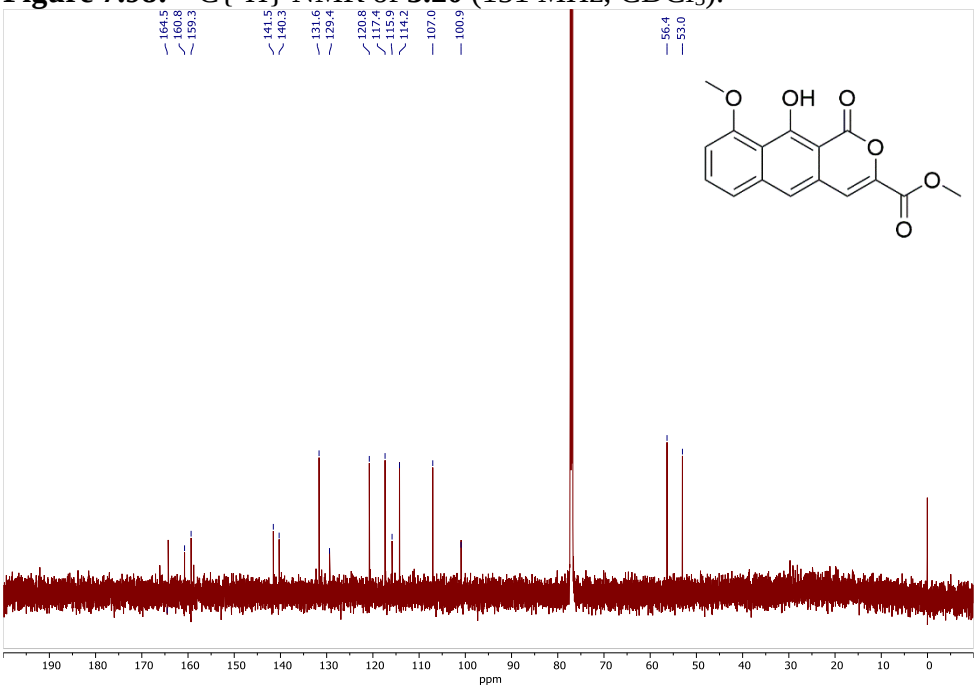

Figure 7.99: ^{1}H NMR of **3.23** plus water (400 MHz, $CDCl_3$).

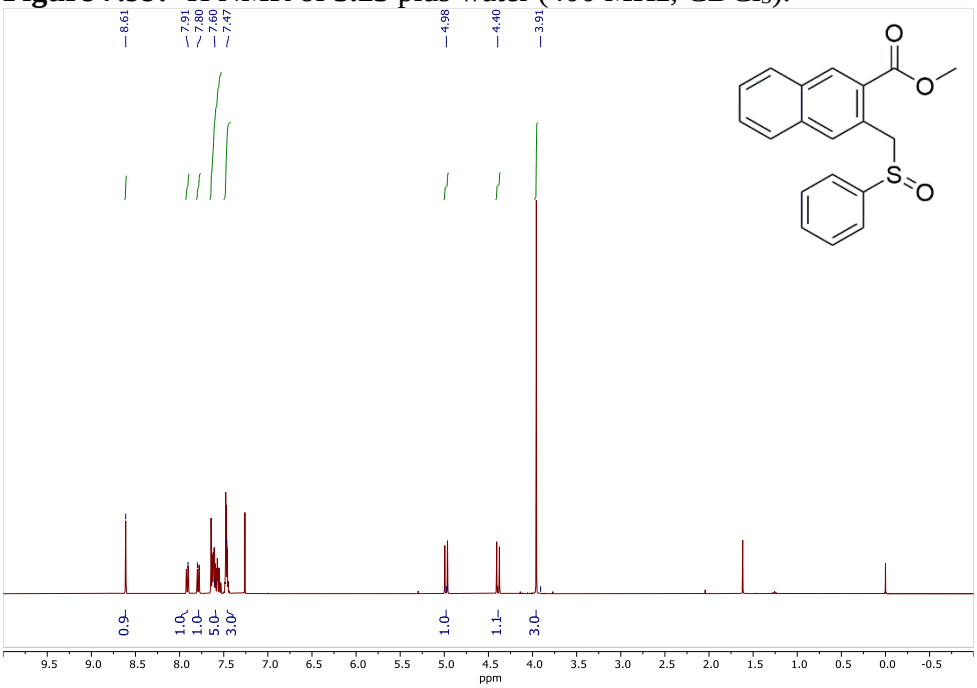

Figure 7.100: ^{13}C{^{1}H} NMR of **3.23** (100 MHz, $CDCl_3$).

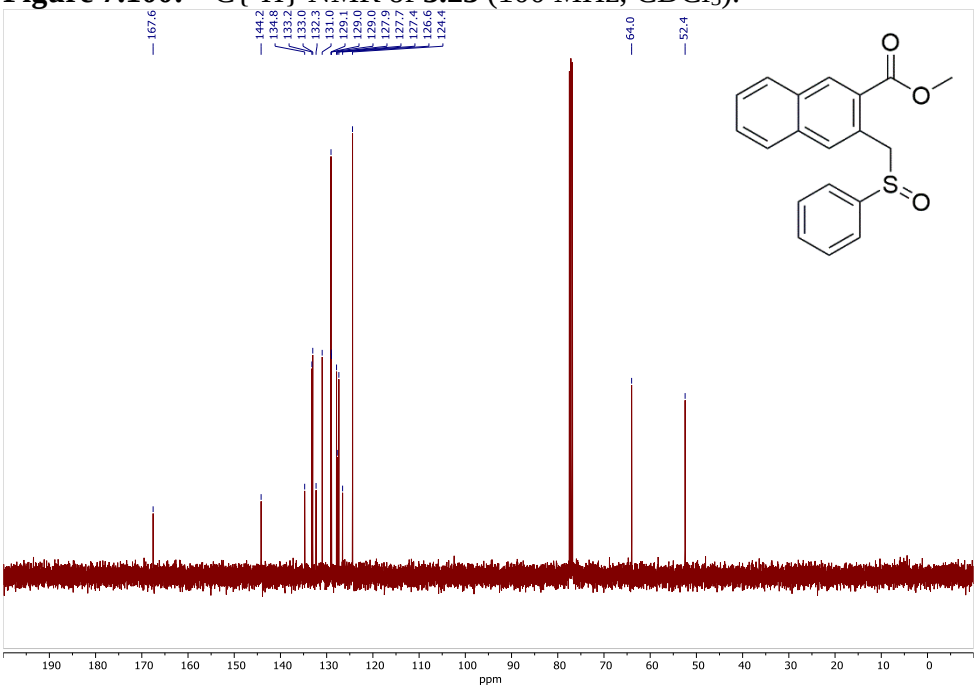

Figure 7.101: ^{1}H NMR of **3.24** plus water (400 MHz, $CDCl_3$).

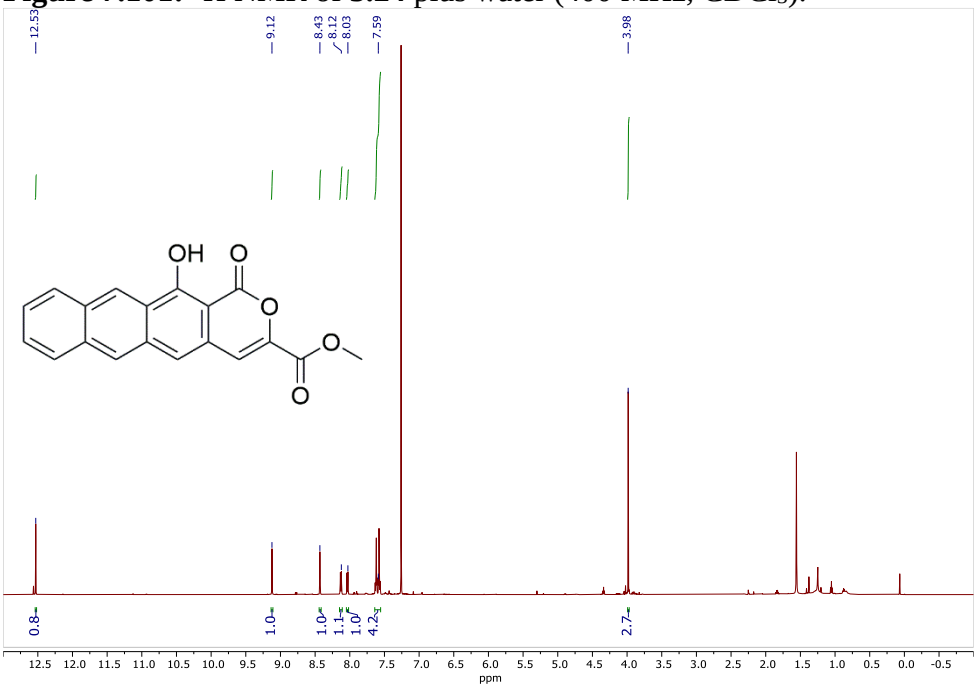

Figure 7.102: ^{13}C{^{1}H} NMR of **3.24** (151 MHz, $CDCl_3$).

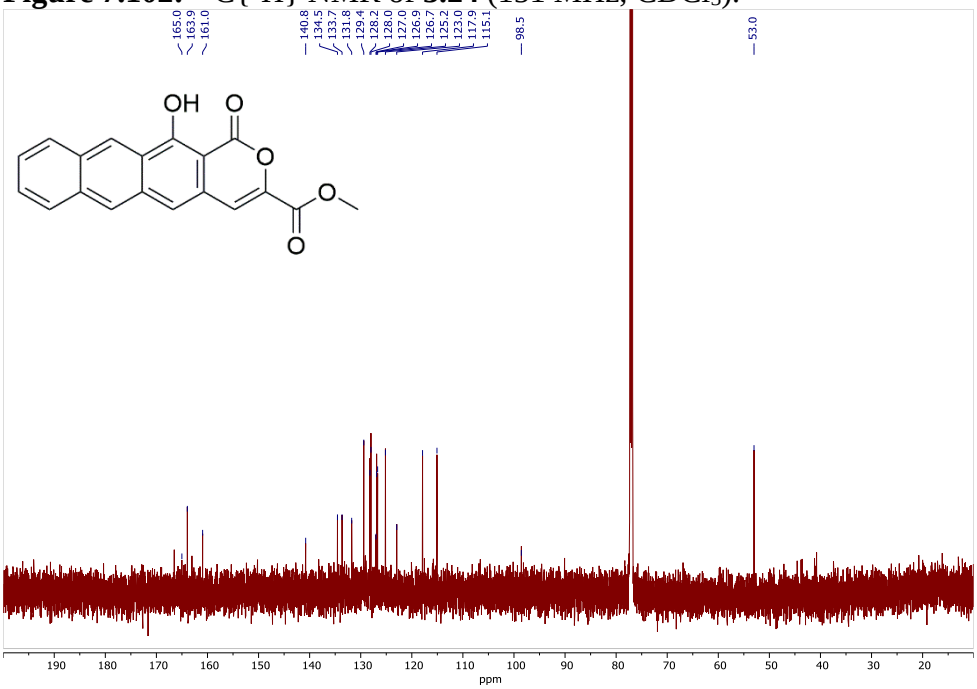

Figure 7.103: ^{1}H NMR of **4.7** (400 MHz, $CDCl_3$)

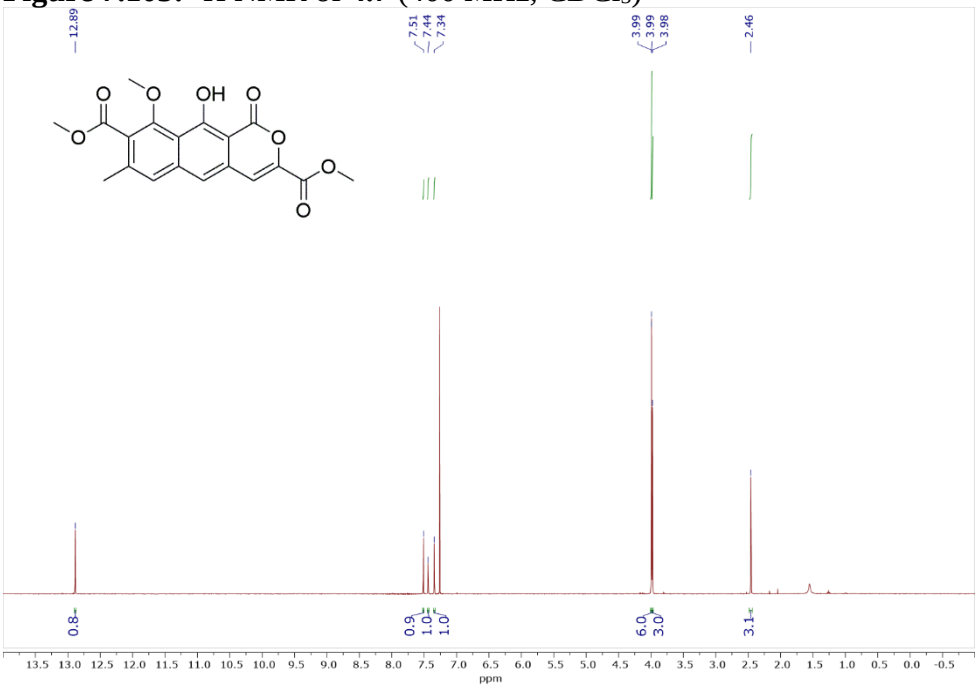

Figure 7.104: ^{13}C{^{1}H} NMR of **4.7** (101 MHz, $CDCl_3$).

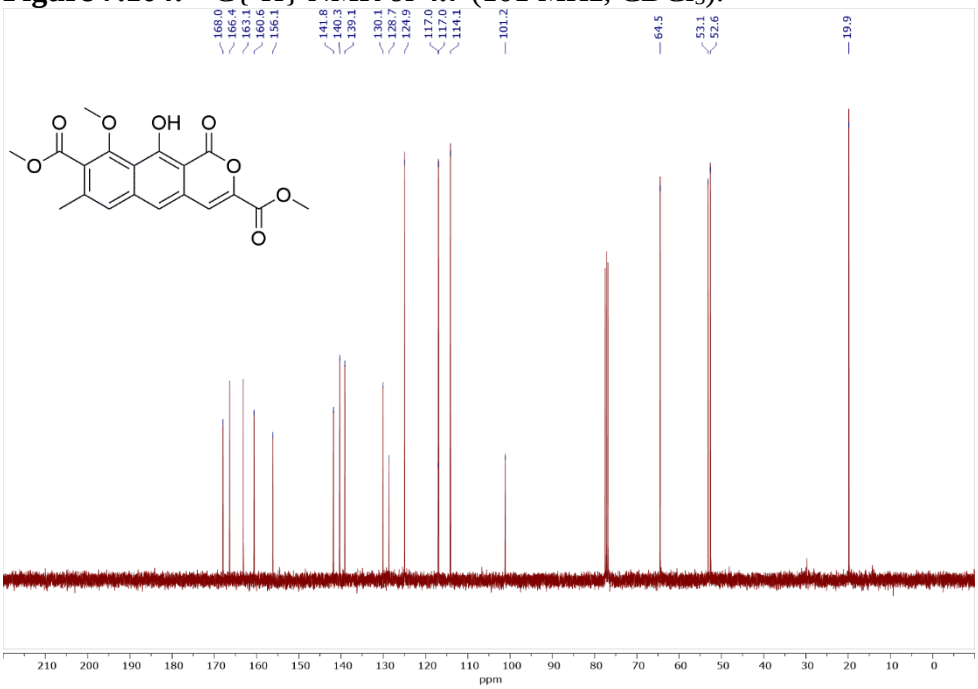

Figure 7.105: ^{1}H NMR of **4.8** plus water (400 MHz, $CDCl_3$)

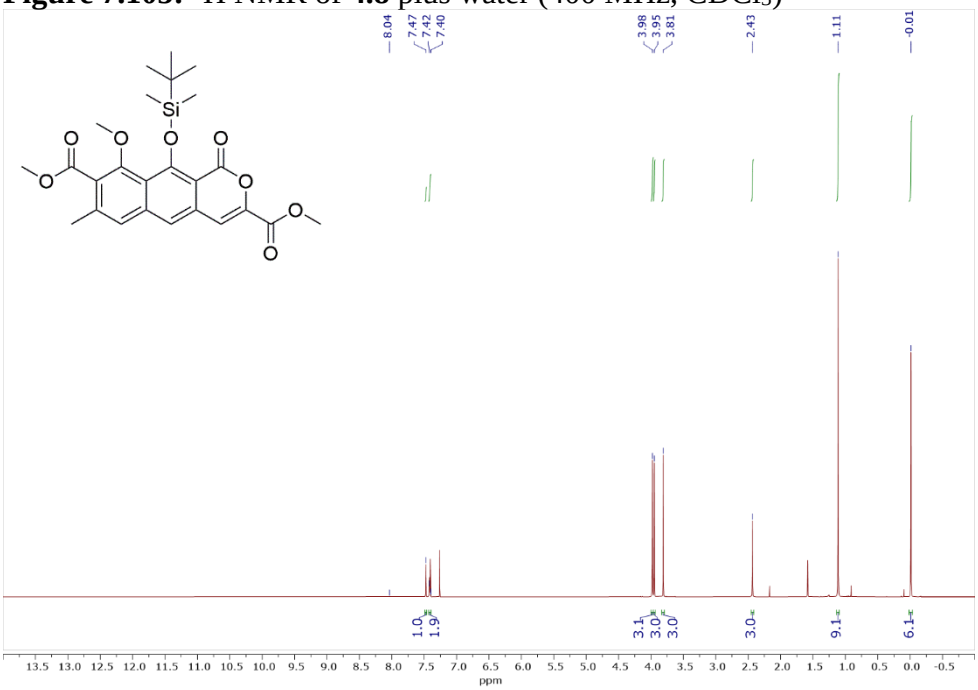

Figure 7.106: ^{13}C{^{1}H} NMR of **4.8** (151 MHz, $CDCl_3$).

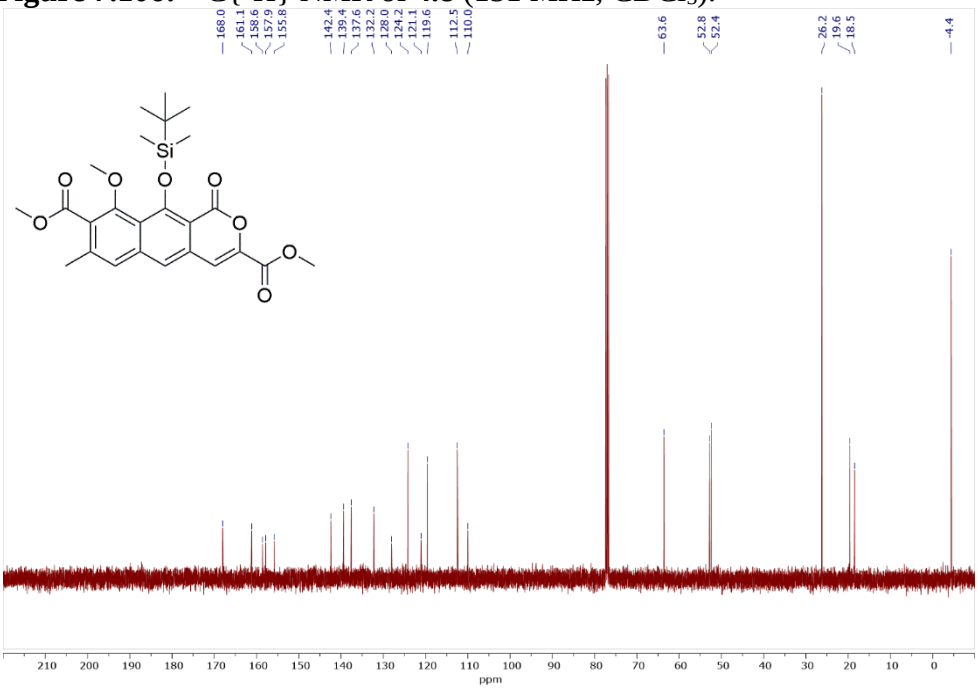

Figure S107: ^{1}H NMR of **4.18** (400 MHz, $CDCl_3$)

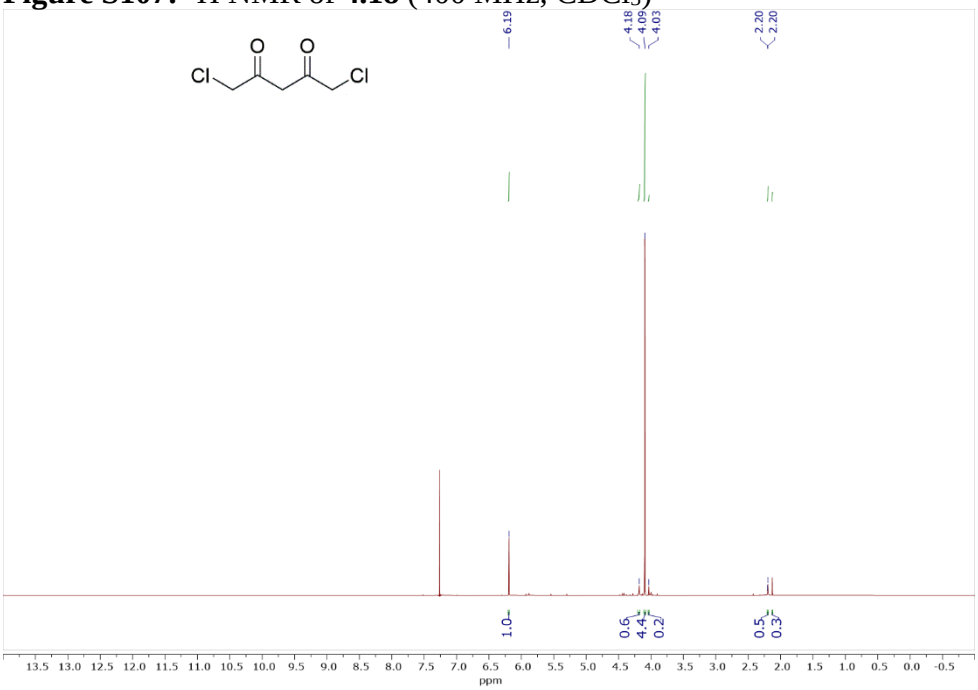

Figure S108: ^{13}C{^{1}H} NMR of **4.18** (101 MHz, $CDCl_3$).

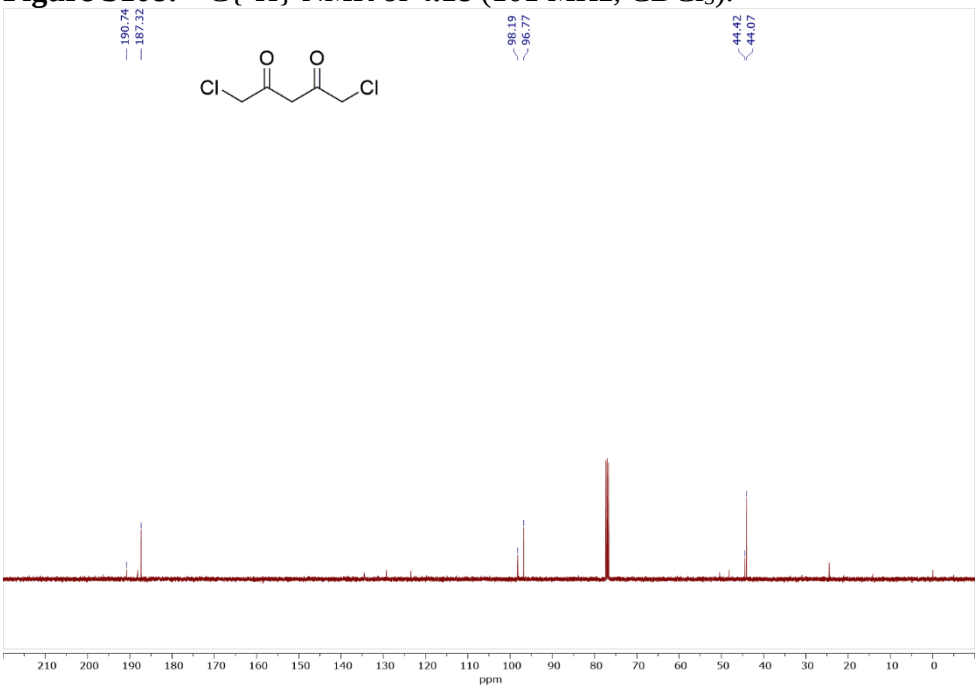

Figure 7.109: ^{1}H NMR of **4.19** (400 MHz, $CDCl_3$)

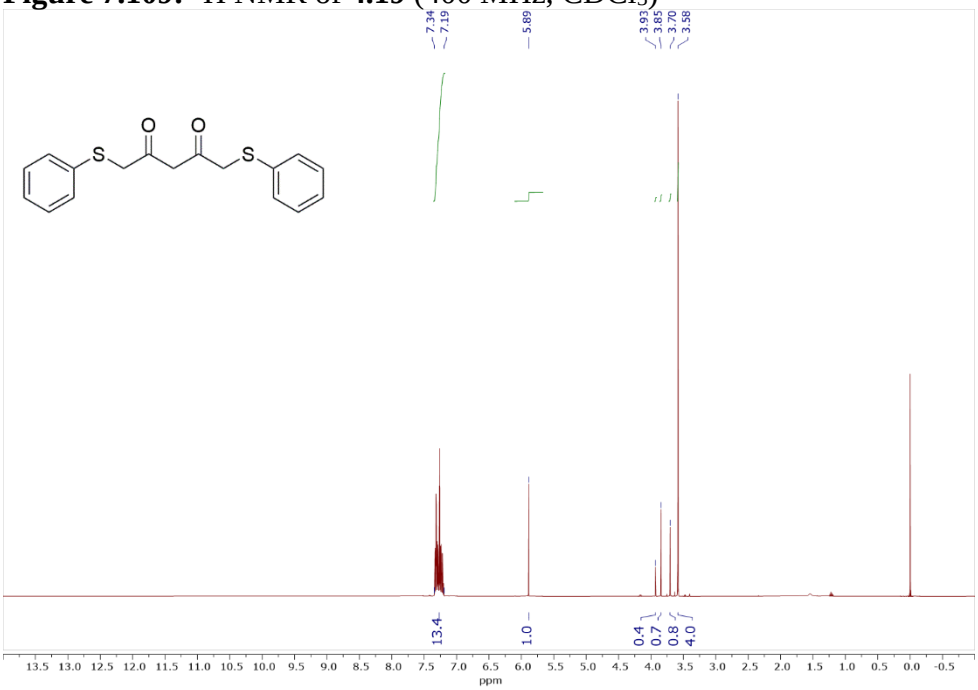

Figure 7.110: ^{13}C{^{1}H} NMR of **4.19** (101 MHz, $CDCl_3$).

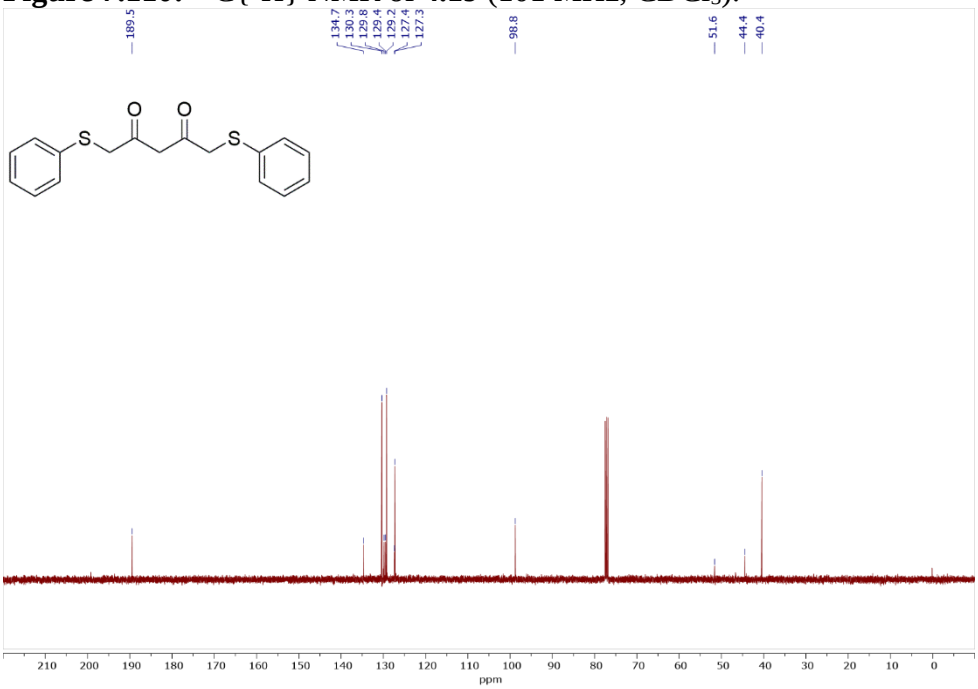

Figure 7.111: ^{1}H NMR of **4.21** (400 MHz, $CDCl_3$)

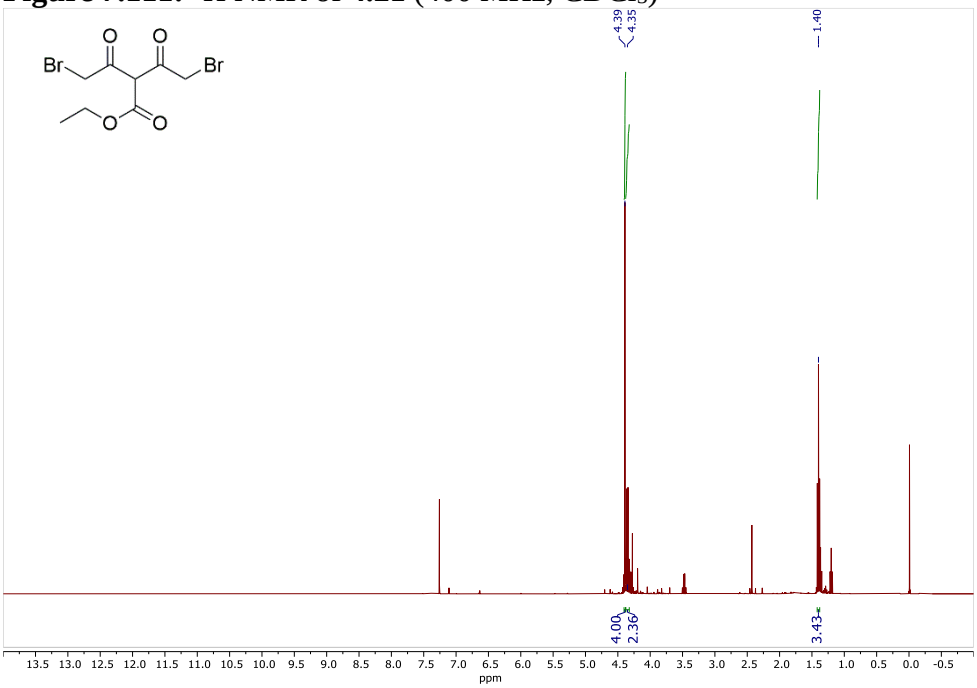

Figure 7.112: ^{13}C{^{1}H} NMR of **4.21** (101 MHz, $CDCl_3$).

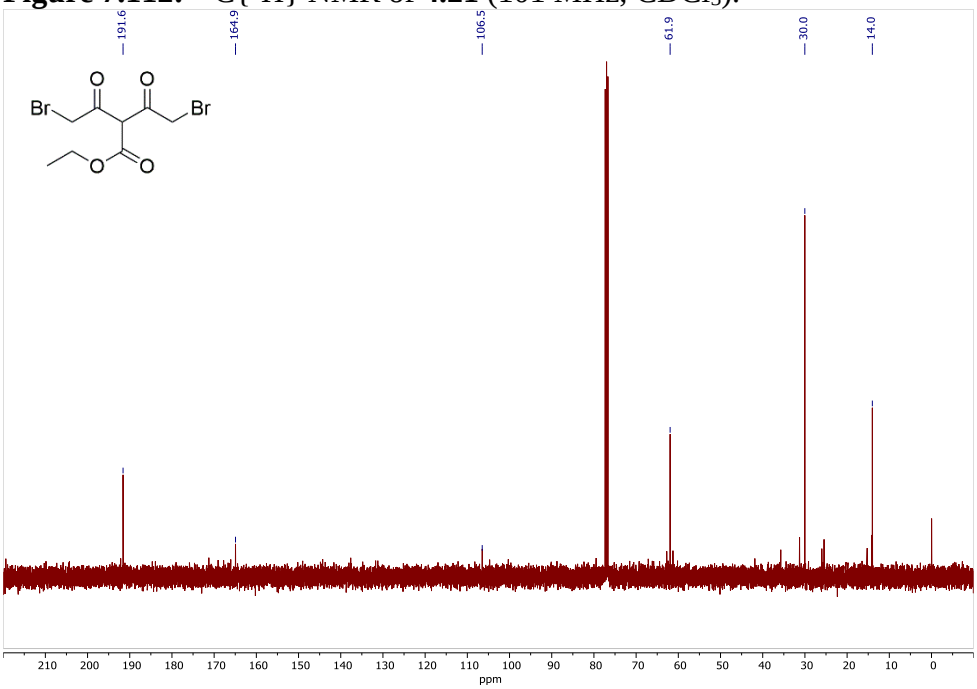

Figure 7.113: ^{1}H NMR of **4.22** (400 MHz, $CDCl_3$)

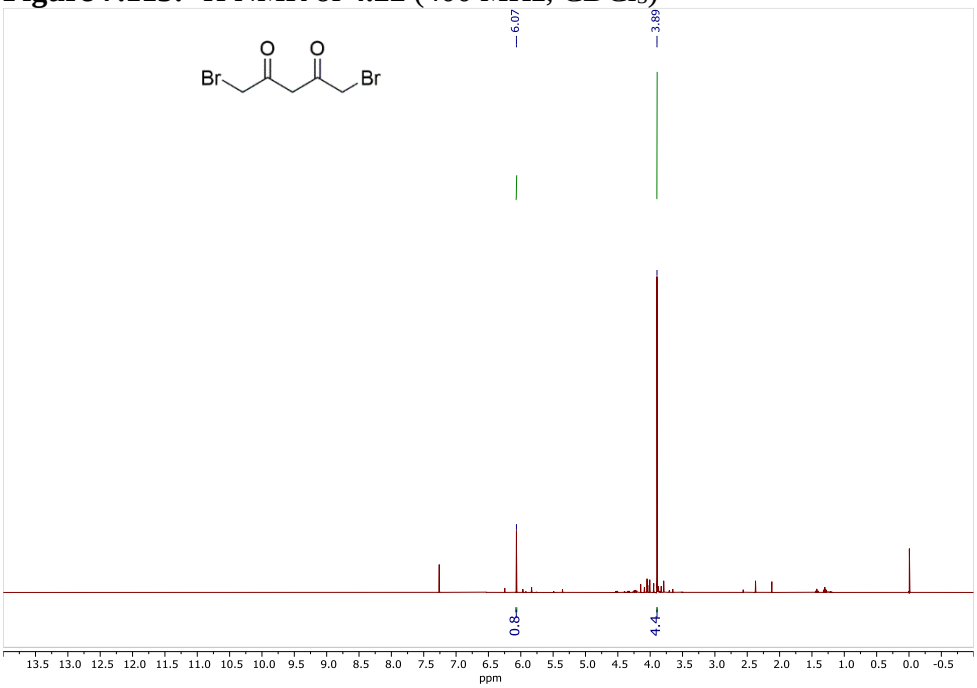

Figure 7.114: ^{13}C{^{1}H} NMR of **4.22** (101 MHz, $CDCl_3$).

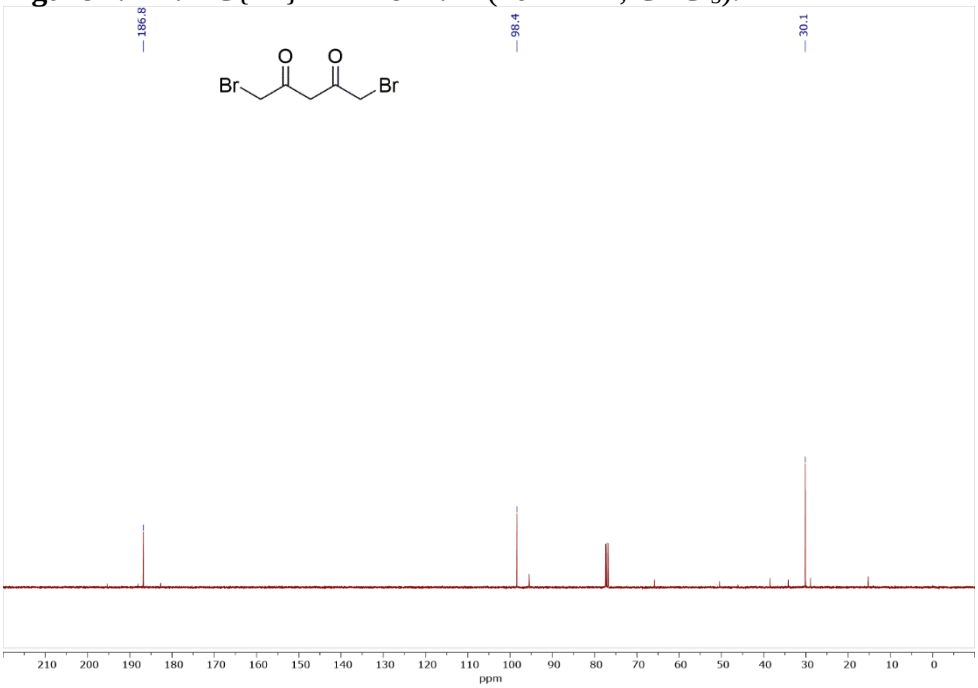

Figure 7.115: ^{1}H NMR of **4.23** (400 MHz, $CDCl_3$)

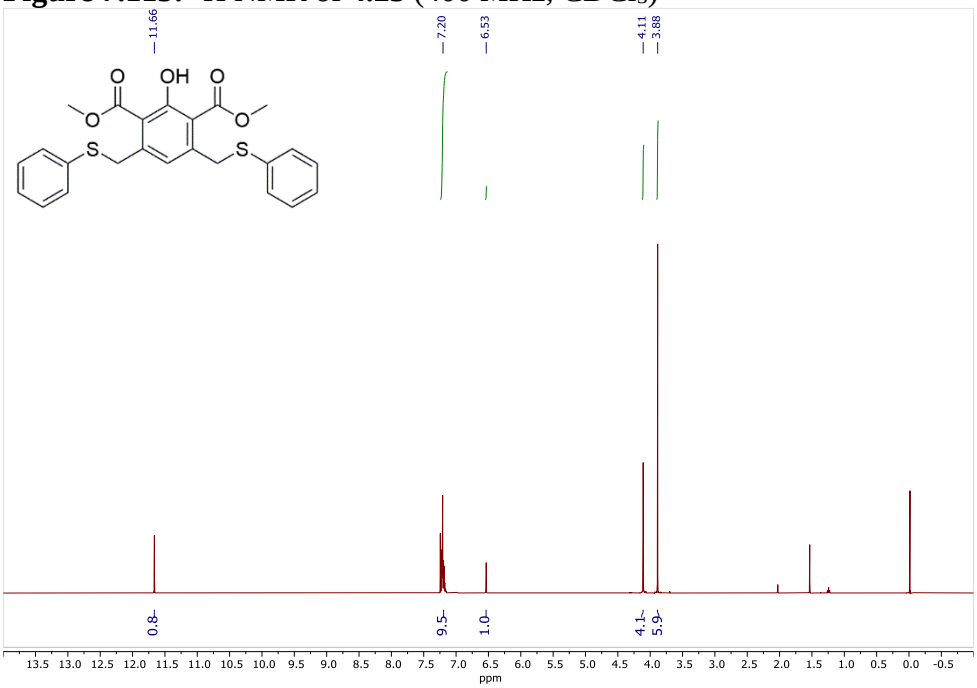

Figure 7.116: ^{13}C{^{1}H} NMR of **4.23** (101 MHz, $CDCl_3$).

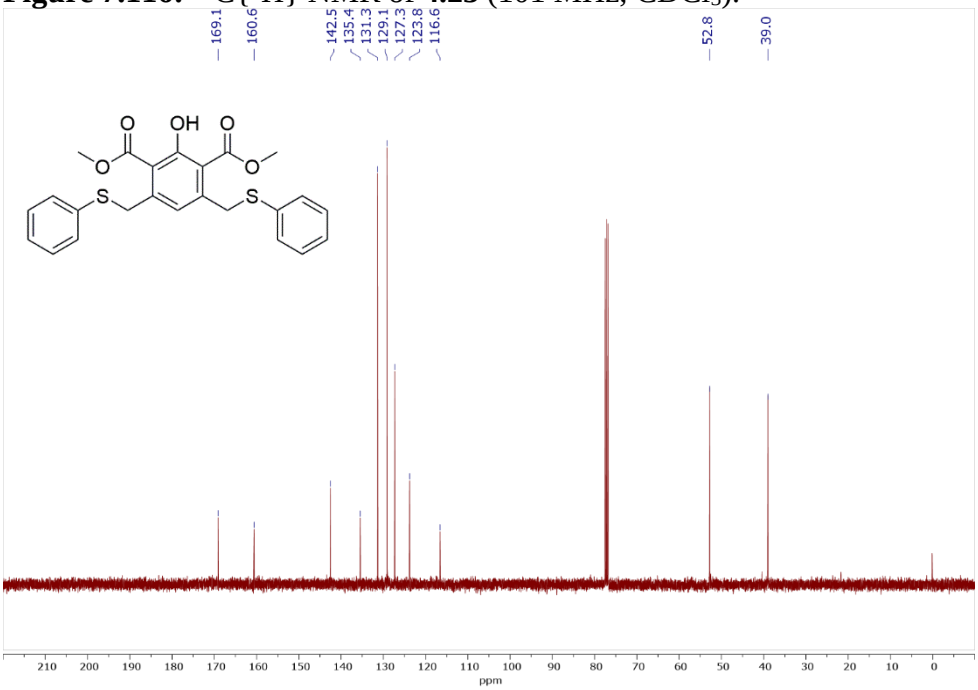

Figure 7.117: ^{1}H NMR of **4.24** (400 MHz, $CDCl_3$)

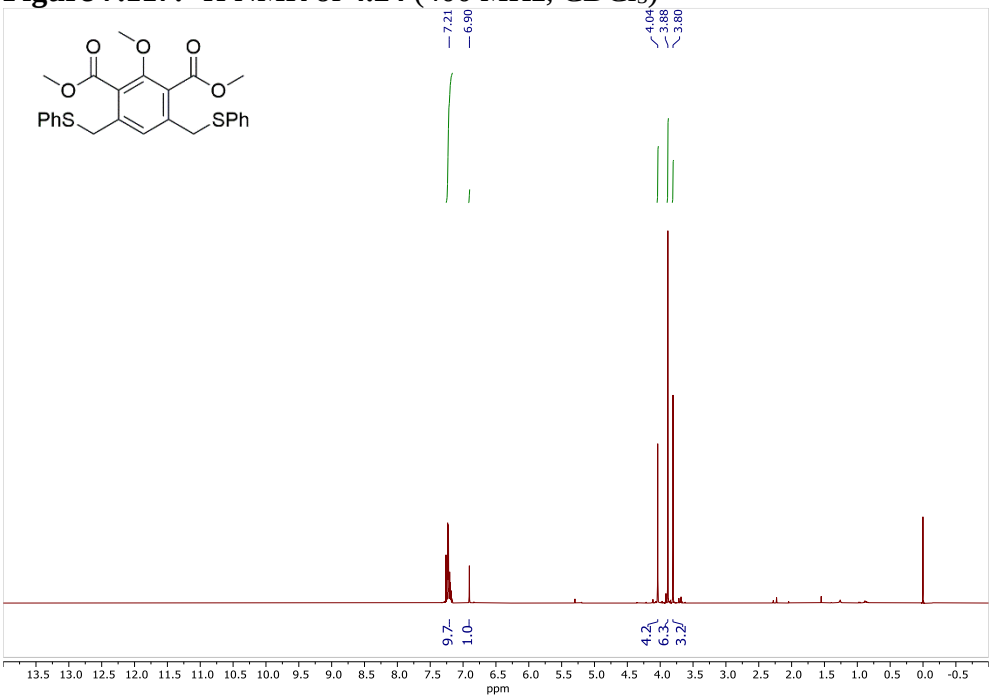

Figure 7.118: ^{13}C{^{1}H} NMR of **4.24** (101 MHz, $CDCl_3$).

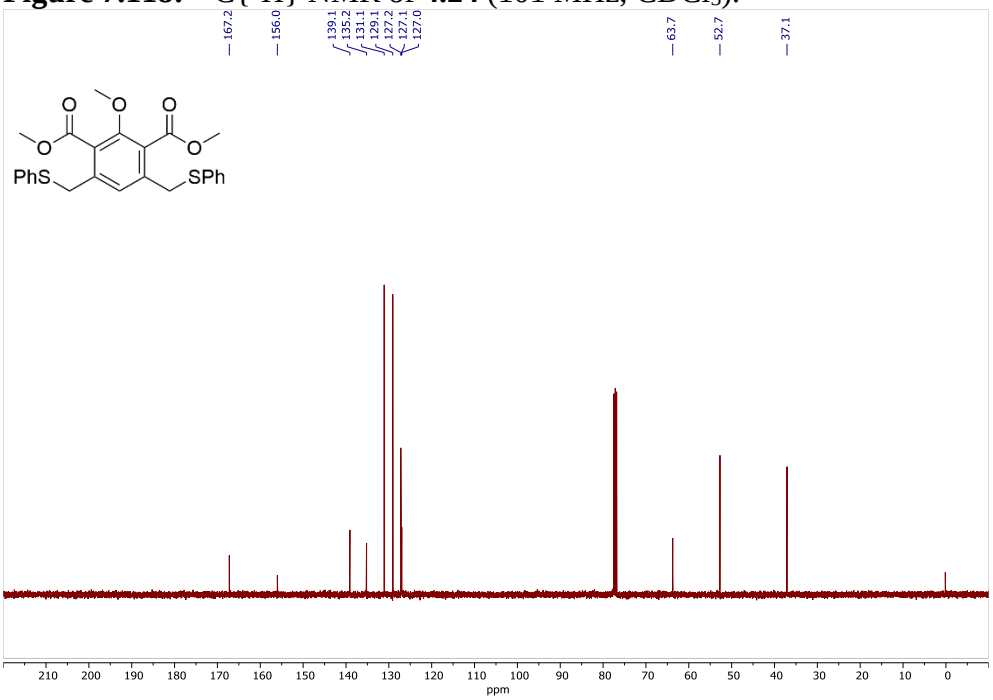

Figure 7.119: ^{1}H NMR of **4.25** (400 MHz, $CDCl_3$)

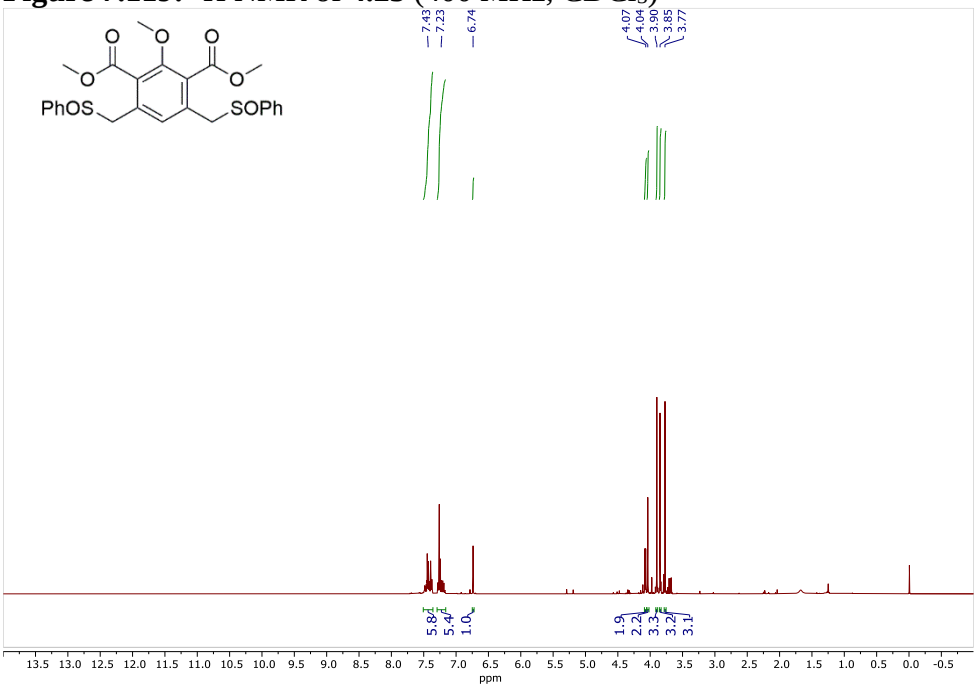

Figure 7.120: ^{13}C{^{1}H} NMR of **4.25** (101 MHz, $CDCl_3$).

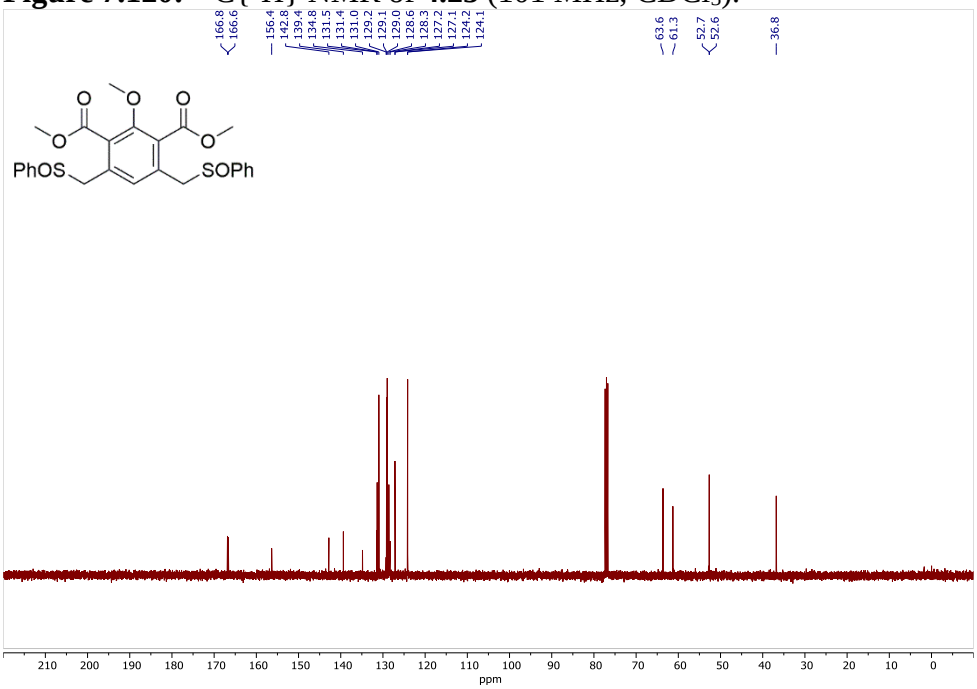

Figure 5.121: ^{1}H NMR of **4.26** (400 MHz, $CDCl_3$)

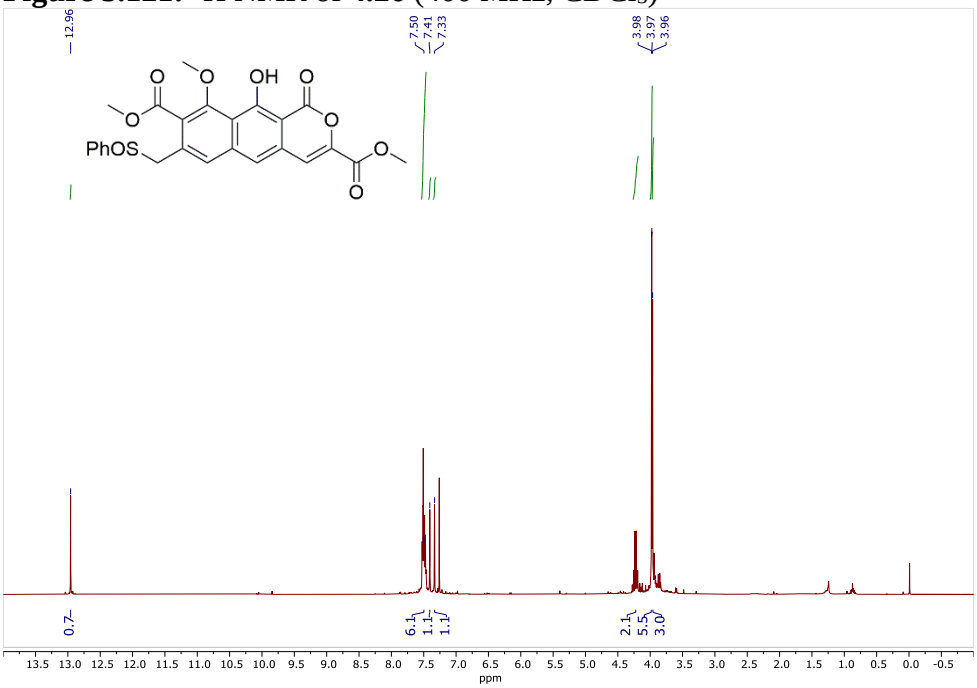
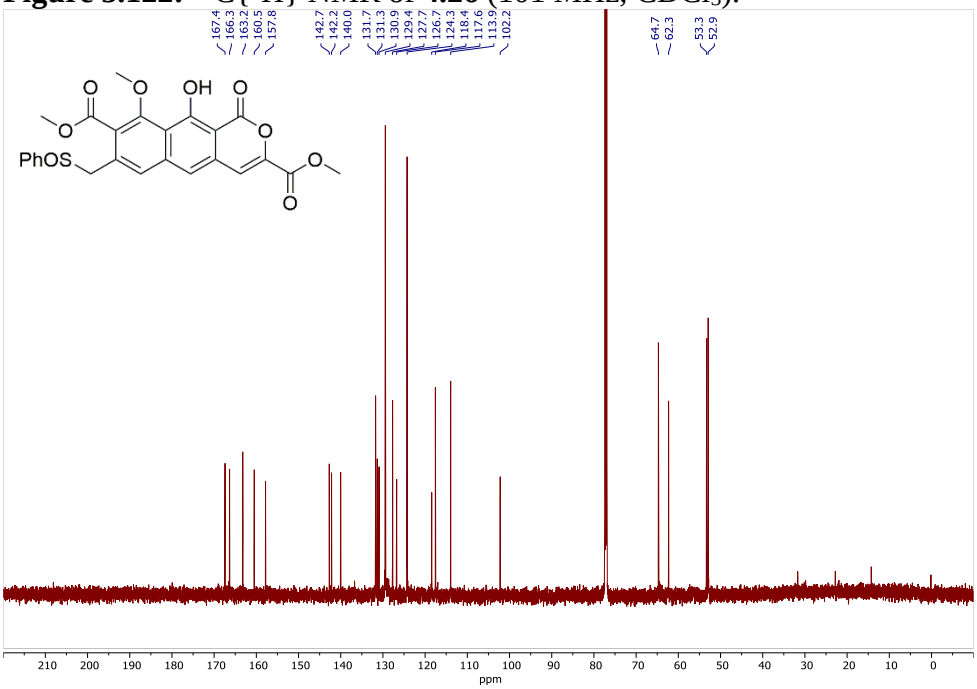
Figure 5.122: ^{13}C{^{1}H} NMR of **4.26** (101 MHz, $CDCl_3$).