TOTAL SYNTHESIS OF SPIROALANFURANTONE A

By

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University Honors

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Abstract

Spiroalanfurantone A is an eudesmanolide-furan sesquiterpenoid adduct biosynthesized by *Inula helenium*, a plant occurring throughout Asia, Africa, and North America. Its medicinal properties are potentially highly valuable; specifically, spiroalanfurantone A is an inhibitor of nitric oxide production, which has implications in reducing the severity of memory loss and combating migraine headaches. Accessing this and related natural products must come from chemical synthesis because their isolation from the natural source is extremely low yielding and impractical. Importantly, the ability to synthesize these compounds enables further exploration of their nitric oxide synthase inhibition. This class of complex natural products has never been synthesized. Thus, developing a synthesis of spiroalanfurantone A is critical for future biomedical and chemical innovation. This project involves a seventeen-step synthesis employing two novel chemical reactions developed in the Kou lab: (1) a type-1 intramolecular Diels-Alder reaction of furan (IMDAF) to form a quaternary carbon center and (2) an oxabicycle ring-opening reaction to create the tricyclic lactone core structure. Currently, thirteen of the seventeen synthetic reactions have been completed, accessing natural products alantolactone, alloalantolactone, isoalantodiene, and epoxyalantolactone, which are biosynthetic precursors to spiroalanfurantone derivatives. My specific contributions focused on optimization of the first eight steps of the synthetic route, plus the large scale, five-step synthesis of the Weinreb amide fragment, an important reactant that is not commercially available, thus allowing access to the four aforementioned natural products. Additionally, I have experimental extensively on the optimization of an alternate Diels-Alder cycloaddition that could improve the overall synthesis. Ongoing studies will involve advancing the synthetic route to access spiroalanfurantone A, as well as access other derivatives of the pool of natural products we are targeting. The completion

of spiroalanfurantone A would enhance accessibility of these complex natural products across the world, which I expect to be highly beneficial for future biochemical and biomedical evaluations.

Acknowledgements

I would like to thank Dr. Kevin Kou for his attention and mentorship throughout the past two years. His role has been instrumental in my future career in both academia and beyond. I would also like to thank graduate students Julio Manuel Larach and Sarosh Abraham for being invested in my development as a training chemist.

I would also like to thank my friends and family for supporting me through my undergraduate career and providing me with inspiration and motivation to work hard and give my best effort.

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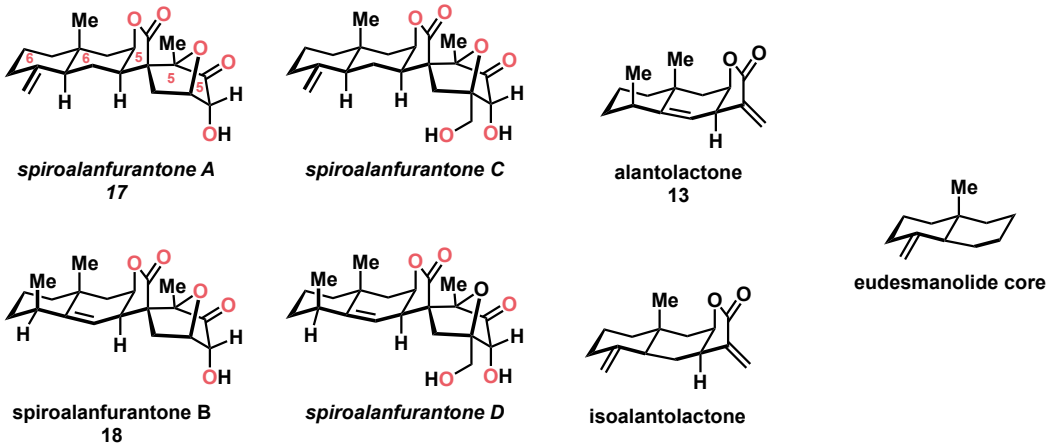
Introduction

Organic chemistry is crucially responsible for our current understanding of atoms and the molecules they make up. Specifically, the study of organic chemistry allows for intricate manipulation of chemical compounds and has led to the development of pharmaceutical compounds which have saved millions of lives over a century plus of research. Pioneers in the field such as Professors Stephen Buchwald, John Hartwig, and Ikira Suzuki have developed revolutionary chemical reactions to assemble functional groups together into molecules that benefit society. In organic chemistry, the subtopic that is responsible in the development of biologically active molecules is natural product total synthesis. In this field, scientists like Richmond Sarpong and Hans Renata have leveraged synthetic organic chemistry and enzymology to synthesize medicinally relevant natural products. Natural products such as penicillin (anti-bacterial), paclitaxel (chemotherapeutic), and artemisinin (anti-malarial) are routinely synthesized on kilogram and ton scales to provide important medications across the world.[1] Although these molecules come from nature (*e.g.*, plants or microorganisms), it is highly important that chemists can recreate these molecules exactly how they're found in nature. This is accomplished by transforming readily accessible chemicals into more complex molecules through a series of chemical reactions.

In natural product synthesis, an important role to play is advancing the starting material. This work consists of taking the initial starting material through the early stages of the synthesis in order for the final key steps to be investigated. Large amounts of these starting materials are required (*e.g.*, >20 grams), which must be purified using silica gel chromatography. Once the majority of the synthetic route is realized, other areas can be focused, such as alternate reagent development, reaction optimization, and side projects that may benefit the overall goal and

impact of the synthesis. Analysis of each intermediate via thin-layer chromatography, nuclear magnetic resonance spectroscopy, infrared spectroscopy, and mass spectrometry is also a highly important aspect in the role of synthetic development and reaction optimization.

Scheme 1. Bioactive terpenoid natural products targeted in this study.



Spiroalanfurantone A **(17)** (Scheme 1) is a eudesmanolide-furan sesquiterpenoid natural product isolated from *Inula helenium*, a plant species found in several continents, but native to Europe.[2] The occurrence of sesquiterpenoid-furan adducts is quite rare in nature, its chemical structure is unique and never been synthesized, and they exhibit important medicinal properties, thus making spiroalanfurantone A a compelling target for chemical synthesis. Spiroalanfurantone A is a secondary metabolite, indicating that the plant likely utilizes it for antibiotic, pigment, or toxin purposes.

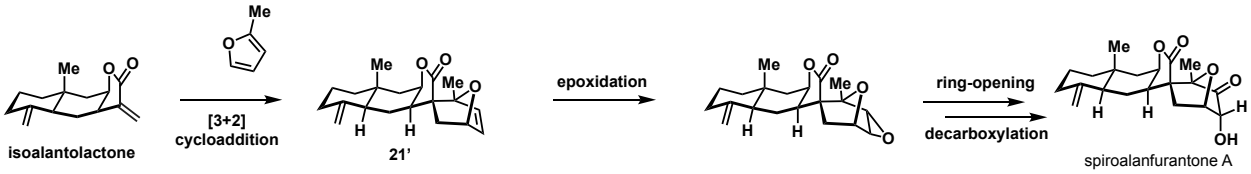
Eudesmanolide refers to the bicyclic core (Scheme 1) of the molecule, indicated by the two leftmost fused cyclohexane rings.[3] Spiroalanfurantones A-D and their biosynthetic precursors, alantolactone and isoalantolactone, all share the same bicyclic core; therefore, the key hypothesis is that the complex spiroalanfurantones A-D can be obtained by diversifying alanto- and isoalantolactone. All of these molecules are eudesmanolide terpenoids. Terpenoids are a class of natural product compounds, which consist of mostly carbons and hydrogens, and are biosynthesized from isoprene.

Apart from being an important chemical target that requires chemical innovation to construct the unprecedented complex structure, biological impact is also important when performing a synthesis. In terms of the biological relevance, spiroalanfurantone A displays nitric oxide inhibition activity again lipopolysaccharide-stimulated RAW264.7 macrophages.[2] Nitric oxide synthase inhibitors are currently developing to become important in therapeutical settings as they are suspected can lead to treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. To elaborate, generally, nitric oxide is an important small molecule in biochemistry for the control of blood vessel pressure. Nitric oxide is released upon conversion of arginine (an amino acid) to citrulline by nitric oxide synthase. With lack of exercise or old age, nitric oxide can become overexpressed, which is no longer beneficial, and can then lead to harmful neuronal degeneration.[4] Nitric oxide is a radical species, specifically a reactive nitrogen species (RNS), so as humans age, it becomes more harmful to the natural flow of biochemistry. The synthesis of spiroalanfurantone A would be key in developing NOS inhibitors and neurodegenerative therapies. When tested, the IC_{50} value was 17.3 μM.[2] Although not the most outstanding IC_{50} value, a pathway to synthesize the molecule in a laboratory setting would vastly improve our capability to examine and understand more about spiroalanfurantone A's biological activity.

An intermediate in the total synthesis of spiroalanfurantone A is alantolactone **(13)**, an intentional target in my synthesis for its anticancer, antifungal, and antibacterial properties. Most excitingly, alantolactone has demonstrated inhibition of multiple target cell lines, including hepatocellular carcinoma in HepG2 cells.[5] Therefore, access to alantolactone as an intermediate to spiroalanfurantone A is a promising target for future biomedical innovation. An isomer of alantolactone, called isoalantolactone, may be capable of similar biological activity and our

synthesis of this pool of natural products will allow biochemists to explore the bioactivity of all of the synthesized natural products.

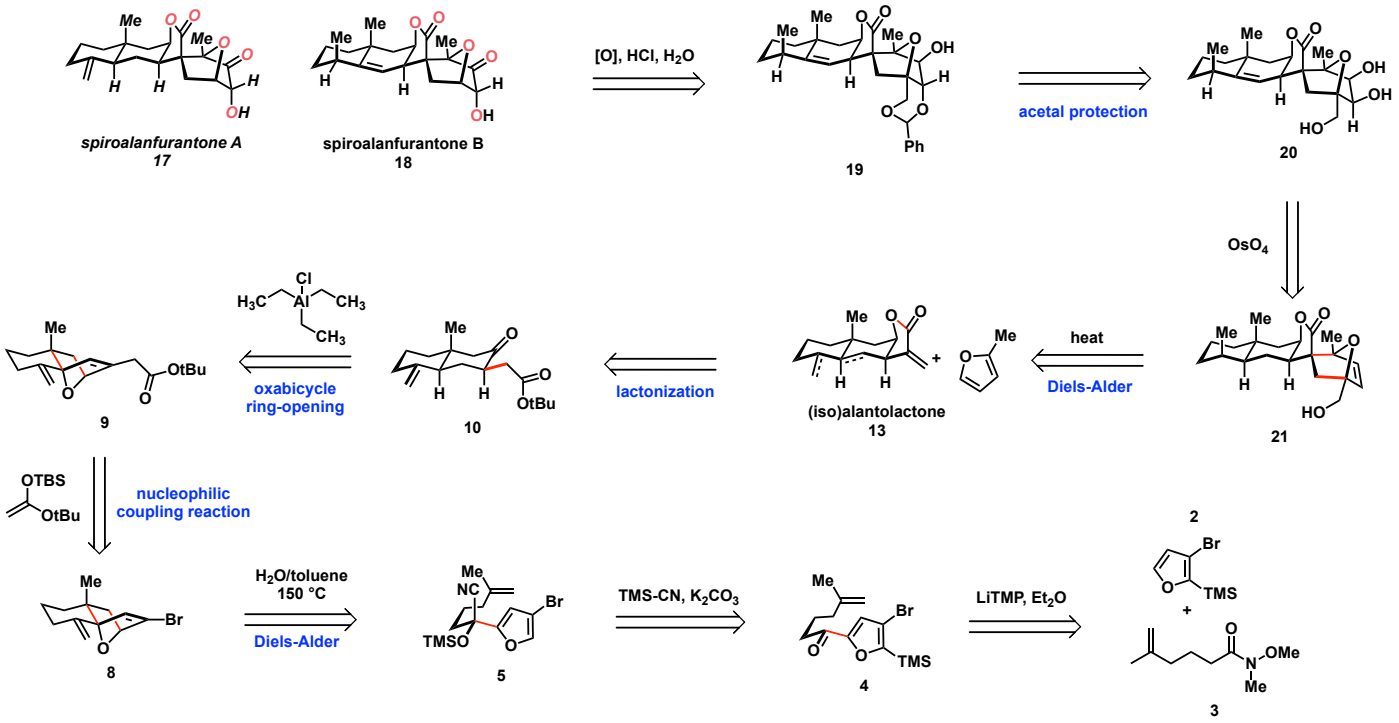
Scheme 2. Proposed biosynthesis of spiroalanfurantone A from synthetic precursor.



The synthetic route developed is biomimetic, meaning that the cycloaddition between precursors such as (iso)alantolactone and naturally abundant furan molecules enable access to the spiroalanfurantone natural product family in the plant, and we are following the biosynthetic route of the plant to access the molecules ourselves. Cao and coworkers propose that the secondary metabolite isoalantolactone undergoes cycloaddition with 2-methylfuran to form pentacyclic **21'** (Scheme 2). From cycloadduct **21'**, epoxide ring-opening and a cascade of oxidation and decarboxylation provide access to spiroalanfurantone A. Our initial synthetic strategy was inspired by the proposed biosynthesis. However, graduate student Julio Manuel Larach found that the proposed biosynthesis pathway was difficult to implement, indicating that the proposed biosynthesis may be challenging to execute in a purely chemical setting or may be incorrect.

Retrosynthesis is a helpful tool in natural product synthesis to rationalize the development of complex chemical targets. Visualizing a commercial starting material for spiroalanfurantone A just by observing its structure would be quite daunting, and would lead to inefficient laboratory time and long synthetic routes. Therefore, the overwhelming majority of chemists utilize retrosynthesis, a strategy to make one bond disconnection at a time. This way, the molecule is broken down to a less complex precursor each time, until the theoretical precursor is commercially available. Retrosynthesis allows for a roadmap, where chemists can now follow what was once a theoretically retrosynthetic route with an experimental forward synthesis.

Scheme 3. Retrosynthetic analysis for spiroalanfurantones and (iso)alantolactone.

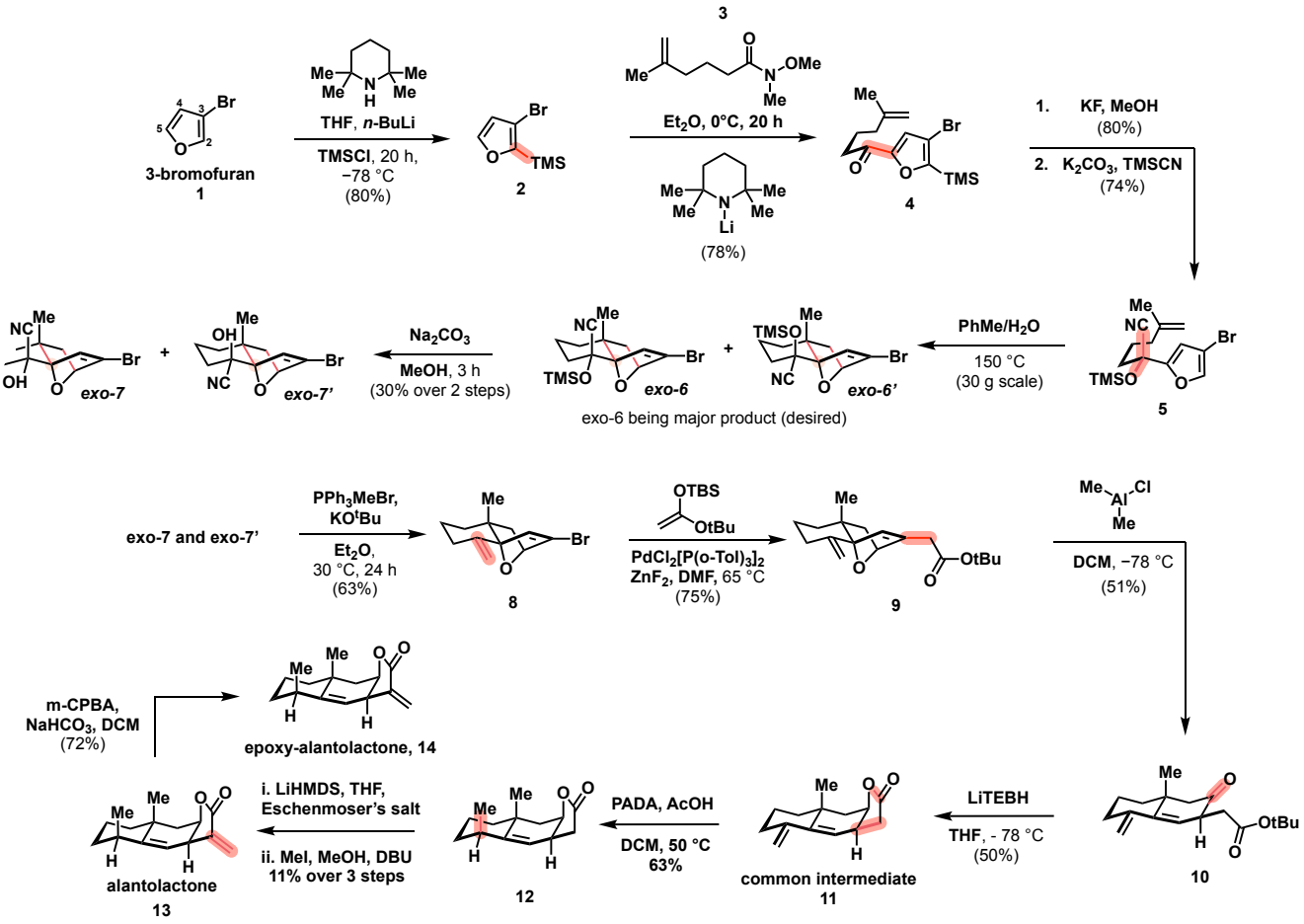


For the retrosynthesis specific to the target molecules for this project, as illustrated in Scheme 3, spiroalanfurantones A and B were imagined to be derived from protected diol **19**. This protected diol would permit selective oxidation of the exposed alcohol. This protected diol would arise from the corresponding unprotected diol **20**, which would be imagined to come from alkene **21** that was dihydroxylated using osmium tetroxide. The pentacyclic alkene would come from a Diels-Alder cycloaddition between a commercially available 2-methylfuran, and the intermediate alantolactone, which is also naturally occurring. Retrosynthetically, to yield a roadmap for alantolactone, it was broken down theoretically to bicyclic ester **10** and would be developed via lactonization. The bicyclic ester would arise from ester oxabicycle **9**, which would be accessed via Lewis acid catalyzed ring-opening. The oxabicycle with ester linkage would then be synthesized via nucleophilic cross coupling between the silyl ketene acetal and a vinyl bromide. This vinyl bromide within the oxabicycle would be accessed via a Diels-Alder cycloaddition, which is a

strong way to make hydrocarbon based (terpene) core structures. The Diels-Alder starting material was imagined to be disubstitued furan **5**, which would be developed from a cyanosilylation of corresponding ketone **4**. Ketone **4** would be synthesized in two steps using lithium chemistry, including the formation of a C-Si bond to protect regioselectivity, followed by subsequent acylation at the 5-position of the furan (Scheme 3).

Results and Discussion

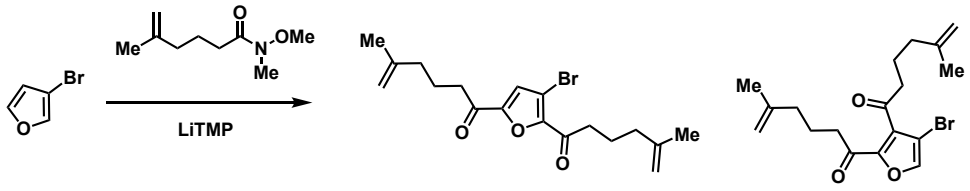
Scheme 4. Total synthesis of alantolactone and epoxyalantolactone.



The synthetic route (Scheme 4) commences with 3-bromofuran (**1**), which is commercially available. Commercial availability is one of the most important considerations when choosing a starting material for a synthesis. Due to our accessible starting material,

laboratories around the world can also utilize this route to access these natural products for their desired uses. This furan is also a useful starting material because it is a cyclic diene, which is important for a future Diels-Alder cycloaddition. The bromine specifically was chosen because of its capability to be utilizes in the late-stage nucleophilic cross coupling reaction as well.[6] 3-Bromofuran (**1**) is silylated at the 2-position, using LiTMP and TMSCl (trimethyl silyl chloride) to access silylated furan 2. This reaction utilizes a strong base, n-BuLi, to deprotonate the 2 position of 3-bromofuran to form the lithiated intermediate nucleophile. Then, the lithiate is replaced with the trimethyl silyl group from TMSCl. This silylation reaction is important to control the regioselectivity of the reaction (Scheme 5). Without the first reaction, we observe acylation at various different carbons in the furan, but selective acylation of the 5 position is necessary to access the desired product.

Scheme 5. Potential outcomes when treating 3-bromofuran **(1)** with Weinreb amide **2** without silylation.



As previously alluded to, the subsequent acylation reaction to access trisubstitued furan **4** is accomplished using a similar procedure to the initial silylation. The acylation begins with lithiation at the 5-position, and subsequent nucleophilic attack of Weinreb amide **3** to access the desired product.

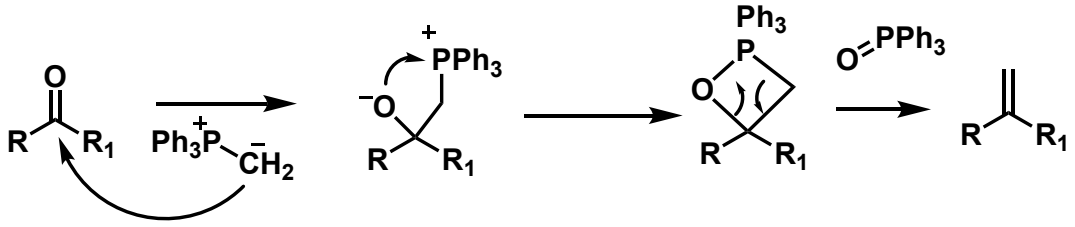
Following acylation of the furan, the trimethylsilyl group which forms a C-Si bond is cleaved using potassium fluoride (i.e., KF), which takes advantage of the fluoride ion binding extremely strongly to the silicon atom to cleave the C-Si bond. To recall, the silyl group was initially added to guide the acyl group to the correct position, however the silyl group is not found in the natural product structure.

From furan **4**, desilylation and subsequent cyanosilylation of the ketone using the nitrile of TMSCN as the nucleophile to form silylated cyanohydrin **5** and subsequent IMDAF (intramolecular furan Diels-Alder) yield a mixture of products **6** and **6**'. High heat (e.g., 150–160 ºC was required to drive the reaction, despite the intramolecular nature). The Diels-Alder cycloaddition is an extremely valuable tool in organic chemistry to create complicated, substituted cyclic products which are often seen in terpene-based natural product structures, such as alantolactone and the spiroalanfurantone family. Generally, manipulating C-C and C-H bonds on a system that has several similar chemical environments (like on cyclohexanone) would be quite difficult. The Diels-Alder cycloaddition requires challenging planning but can lead to exciting transformations and development of compounds that are difficult to access otherwise.

The cyanosilylated cycloadducts are then reformed into ketones/cyanohydrins using sodium carbonate as a base to access and cyanohydrins **7** and **7**', which structures were confirmed using X-ray crystallography. Despite the mixture of products following the IMDAF and desilylation, the products of these reactions all undergo a Wittig reaction to forge the same oxabicyclic alkene **8**. The Wittig reaction is another highly regarded reaction which forms olefins (alkenes). The Wittig reaction utilizes an ylide derived from methyltriphenylphosphonium bromide to generate a nucleophilic carbon atom, which attacks into the ketone of the substrate (Scheme 6). From the nucleophilic attack, the newly formed negatively charged oxygen can establish a single bond to the phosphorus atom, generating the oxaphosphetane intermediate. Among formation of the reactive oxaphosphetane, a retro [2+2] occurs to form a phosphorus oxygen double bond, and the olefinated product.[7] The driving force of the reaction stems from

two reactive intermediates (illustrated in scheme 6), followed by the formation of the strong P=O bond to yield the desired product.

Scheme 6. Mechanism of Wittig olefination reaction; ylide attacks to form oxaphosphetane intermediate and then undergoes retro [2+2] to yield olefin product.



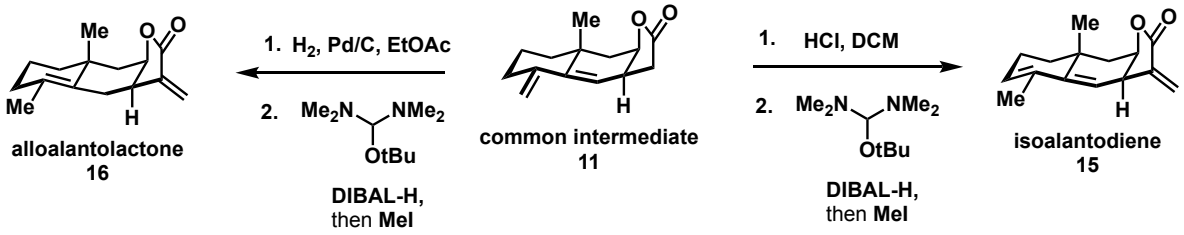
Once oxabicyclic alkene **8** is synthesized, a nucleophilic cross-coupling reaction is performed using a silyl ketene acetal to form ester **9**. Typically, the coupling of a vinyl bromide would be completed using a boronic acid/ester (Suzuki reaction), or a zincate (Negishi reaction). However, on the specific system in the development of alantolactone, these commonly used conditions have quite low yields of desired product. Therefore, the utilization of a silyl ketene acetal as the coupling partner for the vinyl bromide on the oxabicycle was another option. This reaction works generally like most of the other cross-coupling reactions do. A distinct difference is that zinc fluoride is used to form a zinc enolate with the ketene acetal.

Oxabicyclic ester **9** is then subjected to Lewis acid (diethyl aluminum chloride) to undergo a ring-opening. A Lewis acid is a compound with an available empty P-orbital for coordination chemistry. In this example, the Aluminum Lewis acid coordinates to the electron-rich ether linkage. As a result of ring strain, the ether linkage breaks, forms an unstable carbocation intermediate, and this terminates with the isomerization of the internal alkene. Bicyclic ester **10** is then epimerized through silica gel column chromatography (SiO_2) and reduced using LiTEBH to form tricyclic intermediate **11**. LiTEBH is a boron-based hydride source. In this reaction, the ketone is reduced to the alcohol, and this triggers the lactonization

event where the alcohol attacks into the tert-butyl ester, ejecting tert-butoxide as a byproduct. At this point, the pool of natural products is in range from a single tricyclic intermediate, compound **11**. From the intermediate, most of the necessary core functional groups are in place for the desired natural product structures, so all that's required to access alantolactone and similar compounds from this divergent point are a few chemical reactions per natural product target.

From tricyclic intermediate **11**, four natural products can be accessed. Isoalaodiene (**15**) was prepared by HCl-catalyzed isomerization of the diene, followed by a two-step methylenation sequence called the Hoffman elimination (Scheme 7).[8] This occurs with the aminoalkylation of the α position, followed by elimination to yield the methylene group. Through a secondary pathway beginning with intermediate **11**, palladium-on-carbon-catalyzed hydrogenation and subsequent methylenation yields alloalantolactone **(16)**. For the third pathway, hydrogenation of the external alkene followed by methylenation yield alantolactone (**13**, Scheme 4). *m*-CPBA epoxidation forms the epoxide on the internal alkene of alantolactone, yielding 5a-6a-epoxyalantolactone (**14)**. Fortunately, *m*-CPBA is the most common epoxidation reagent in organic chemistry, and is a success in the development of epoxy-alantolactone. The epoxidation is feasible due to a relatively stable five-membered transition state, which is one of the most stable and favorable intermediates in chemistry.

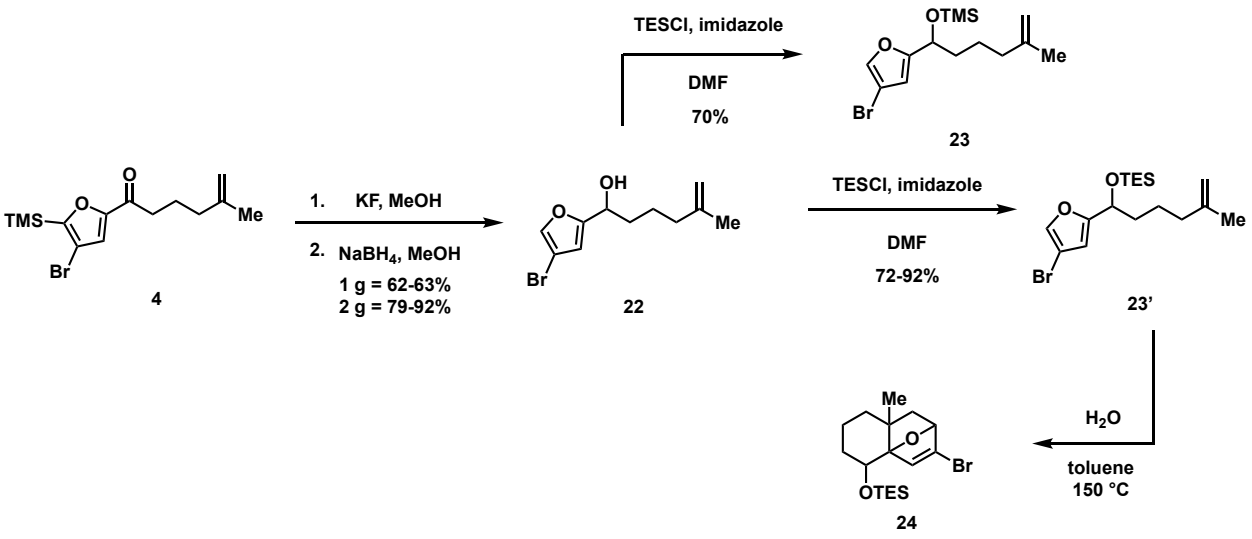
Scheme 7. Divergent synthetic route from the common tricyclic intermediate to isoalantodiene **(15)** and alloalantolactone **(16)**.



During this project, several side projects have been targeted which aim to assist the main synthesis in bolstering the yield, increasing the probability that this synthesis will be useful for

developing a medication in the future. My first side project, and what I worked on most extensively as a side project, is to inflict enantioselectivity on the molecules (Scheme 8). Enantioselectivity controls how a given chemical reaction will install a functional group. In the side project for this work, it is imagined that a enantioenriched alcohol can be synthesized, which can then be converted to a silyl alcohol. After the silyl alcohol formation, the molecule can undergo an intramolecular Diels-Alder of furan. If the starting material is enantioenriched, then the cycloadduct can also be enriched, potentially leading to a total synthesis that is no longer racemic. In general, racemic syntheses are still scientific and reasonable but provide much less value to the industrial application of the molecule. Two enantiomers can react entirely differently in the body, despite having all of the same chemical functional groups and same molecular formula. Therefore, the development of this side project is impactful to make the syntheses of alantolactone and spiroalanfurantones A-D as biologically useful as possible. Although the enantioenrichment is important, proof of concept was necessary to begin with, which does not require stereochemical consideration. This is where I decided to begin on the project as displayed in scheme 8.

Scheme 8. Progress and optimization toward a non-racemic route for alantolactone and spiroalanfurantones.

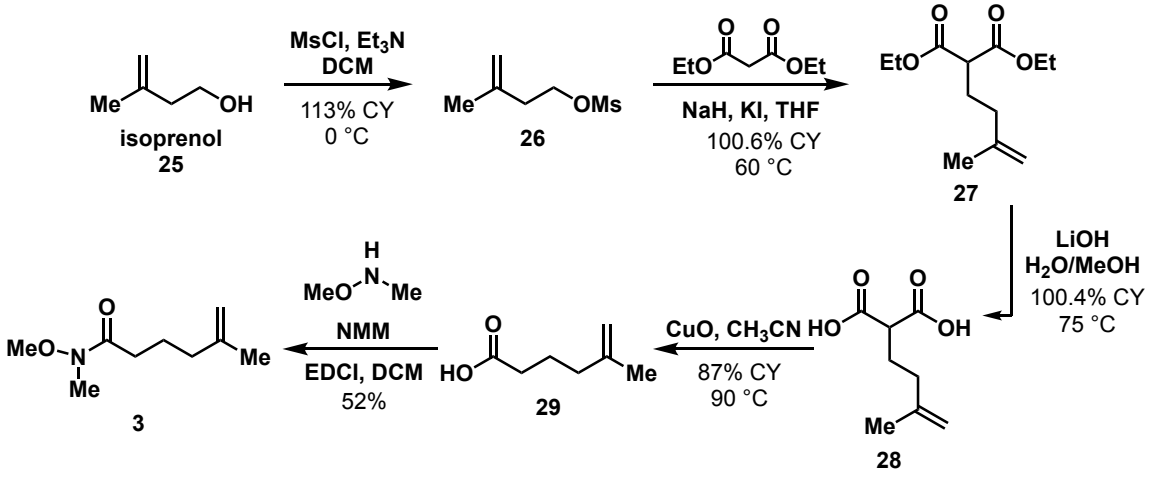


As shown in scheme 8, 3-bromofuran is advanced to ketofuran **4**, which is then treated with sodium borohydride in methanol to yield keto alcohol **22**. From there, the keto alcohol is advanced to silyl alcohol **23** and **23'** using either TMS or TES chloride with a base, either TMS or TES protected. TES (triethylsilane) is generally more favorable for its stability during silica-based column chromatography. Either way, this silyl alcohol furan undergoes the IMDAF reaction in a variety of conditions (Table 1). One set of conditions includes a Lewis acid with toluene as the solvent, as the other set of conditions includes just water and toluene. Temperature, solvent, and Lewis acid additive were varied, but the only successful condition was Lewis acid-free with water and toluene at 150 degree Celsius for 72 hours. Although minor product formation was seen, issues with reproducibility terminated this route before true optimization could commence. The issues of this side project were accompanied with a separate methodology to access an enantioenriched cycloadduct, leading to the synthesis to have enantioenriched capabilities.

Table 1. Progress and optimization table of silyl alcohol IMDAF reactions.

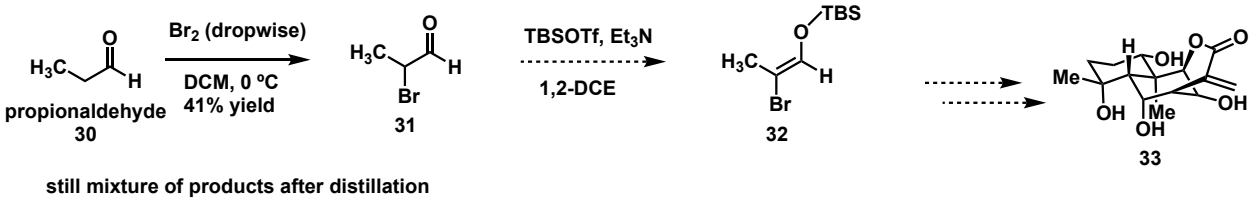
lewis acid	solvent	temperature	yield (%)	silyl group
TESCl	toluene	85 °C	0	TES
AlCl3	toluene	85 °C	0	TES
BF3OEt2	toluene	85 °C	0	TES
N/A	water/toluene	85 °C	0	TES
N/A	water/toluene	150 °C	<5	TES
AlCl3	toluene	150 °C	0	TES
ZnCl2	toluene	150 °C	0	TES
N/A	water/toluene	90 °C	0	TES
N/A	water	90 °C	0	TES
N/A	water/toluene	90 °C	0	TMS
N/A	water	90 °C	0	TMS
N/A	water/toluene	150 °C	0	TES

Scheme 9. Synthetic route of Weinreb amide **3**.



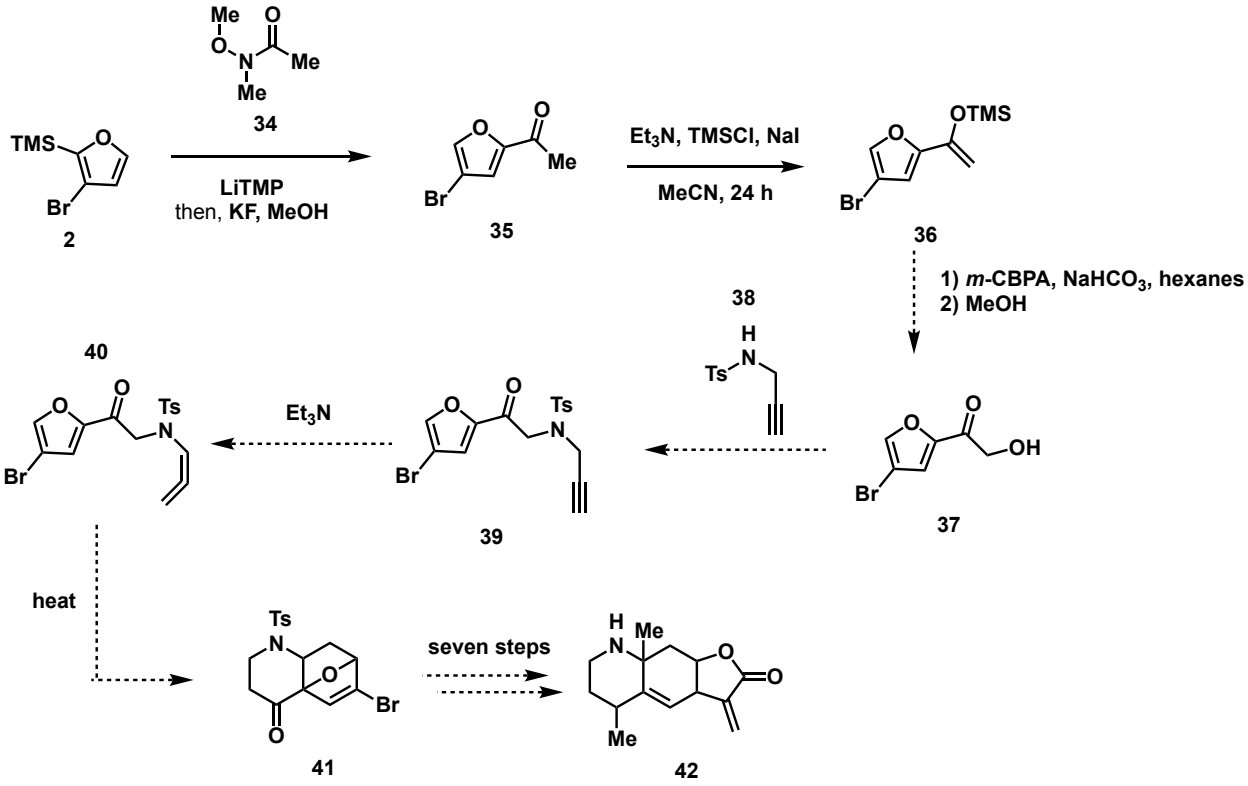
Another large aspect of the synthesis, and one I worked on extensively, is the formation of the Weinreb amide which is used in the acylation step of the synthesis (the second step in the synthetic route of alantolactone and spiroalanfurantones). This is a project that requires synthetic rigor for five large scale chemical reactions, with a final purification to yield 20-30 grams of product. For the Weinreb synthesis, isoprenol **(25)** is converted to mesyl alcohol **26** using mesyl chloride and triethylamine. In this reaction, the isoprenol hydroxyl proton is deprotonated with triethylamine base, and then attacks into MsCl to install the mesyl group as a good leaving group. Then, an alpha-alkylation of diethyl malonate is performed, with the mesylate being the leaving group and attaching an alkyl chain to the malonate to yield diester **27**. Subsequent hydroxylation with LiOH and decarboxylation with Copper (I) oxide furnishes carboxylic acid precursor **29** to the Weinreb amide. From the acid, N-methyl morpholine EDCI, and N,O-dimethyl hydroxylamine convert this substrate to the final amide product.[6] EDCI is used as a coupling intermediate to enable the amine to attack into the Weinreb amide, as without an assisting-reagent, Weinreb amides are not electrophilic enough to undergo attack.

Scheme 10. Attempts at bromoaldehyde fragment for higher order natural products.



Another side project that I developed was a short synthesis of a brominated aldehyde fragment to access higher order natural products (Scheme 10). In this project, propionaldehyde **(30)** underwent mono-alpha bromination to yield corresponding bromoaldehyde **31**. In this reaction, simply adding Br_2 does not suffice. Through optimization, it was found that the Br_2 must be added to a separate round bottom flask of DCM (solvent) and then transferred to the main flask at low temperatures to observe the desired product. Although this reaction was successful based on NMR analysis, the subsequent reaction was unsuccessful. If this can be solved, the resulting fragment has the potential to save 3-4 steps in the synthesis of complex

Scheme 11. Development of heterocyclic natural product derivatives for biochemical evaluation.



natural products (right molecule). This is a fragment that is continuing to undergo development and optimization between myself and graduate student Ruby Chen.

Lastly, I focused on unlocking access to heterocyclic natural product derivatives of alantolactone (Scheme 11). Heteroatoms, specifically nitrogen and oxygen, can be highly valuable for biological interaction. If access to heteroatomic alantolactone derivates can be accessed, then medicinal chemistry-like experimentation can be done to analyze how the heteroatom in various places within the molecule compare to the biological activity of alantolactone and similar natural products. Fortunately, the route developed to access alantolactone includes a series of initial reactions which enable modification between the components of the reagents. For example, rather than the 9-carbon Weinreb amide utilized in the main synthesis, a four-carbon methyl amide (**compound 34**, Scheme 11) can be used in place of the larger fragment. Once acylated sillylated and acylated with the methyl amide, the ketofuran can be converted into corresponding silyl enol ether **36**. From the silyl enol ether, the alkene can be epoxidized and then opened using methanol as a nucleophile to form primary alcohol **37** via Rubottom oxidation. From the primary alcohol, a substitution reaction with a tosyl-amine can provide access to an intramolecular Diels-Alder starting material (compound **39**). At this point, the alkyne can be transformed into an allene, which is more reactive and undergoes the IMDAF to yield a heteroatomic oxabicycle. From the oxabicycle with the heteroatom included, the remainer of the steps are planned to be exactly the same as the main synthesis, yielding access to natural product derivatives to use for biochemical evaluation and optimization (Scheme 11).

Future Directions

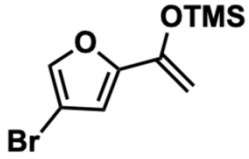
The current goal is to continue the development of spiroalanfurantone A. Although approximately eighty percent of the way through the synthesis of spiroalanfurantones A-D, it is anticipated to be completed in the coming months and will allow novel access to a natural product with important NOS inhibition. Once spiroalanfurantones A-D are completed, myself as well as the rest of my research team will leverage our synthetic strategy to access additional complex eudesmanolide natural products that are otherwise inaccessible.

Conclusion

Overall, this project enabled access to four natural products, which are synthesized biologically in *Inula helenium*. These four natural products are biologically important and improve the pool of synthetic chemistry knowledge for future synthesis projects. My specific contributions include the development of the first eight steps of the synthesis towards the natural products and the synthesis of the Weinreb amide which is utilized in the second step of the synthesis. I also developed a synthetic route to access heteroatomic natural product structures, as well as explored a Diels-Alder cycloaddition to inflict chirality in the natural products. These contributions are highly important for the completion of several biologically active natural products and their derivatives and will allow these molecules to be investigated for their pharmacological utility.

Supporting Information

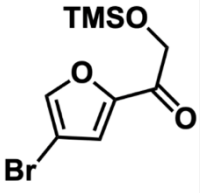
Experimental Procedures and Characterization Data



Sodium iodide (1.95 g) in acetonitrile (19 mL) was added at room temperature to a solution of ketone (1.64 g), triethylamine (1.8 mL) and chlorotrimethylsilane (1.6 mL) successively introduced to the reaction flask under N_2 atmosphere. This solution was vigorously stirred overnight and the reaction was monitored by TLC.

After the reaction was completed, ice-water (10 mL) and cold pentane (10 mL) were successively added. After decantation, the aqueous layer was extracted with pentane (2 × 10 mL). The combined organic layers were dried over Na2SO4 and concentrated under vacuum to give the crude trimethylsilyl enol ether. Repeatedly, high vacuum was shortly applied to remove the volatiles. After distillation, the product was a clear oil (72% yield, 1.64 g).

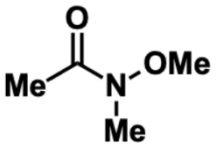
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33, 6.43, 4.89, 4.40, 0.26.



$NaHCO_3$ (0.32 g, 3.83 mmol) and *m*-CBPA (0.43 g, 1.91 mmol) were added to create a stirred solution with hexanes (27 mL, 0.07 M). Then, silly enol ether (0.5 g, 1.91 mmol) was added to the solution at –78 °C. After 15 minutes, the dry ice bath was removed and the reaction mixture was stirred at room temperature for three hours.

After the reaction was completed, the solids were filtered off using a Büchner funnel and the filtrate was concentrated in vacuo. The product was a clear oil (55% yield, 0.29 g).

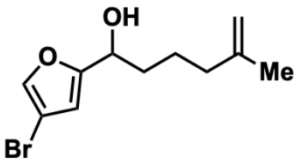
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58, 7.32, 4.68, 0.19.



To a 500 mL N2 filled RBF at 0 °C, methyl amine HCl (6.50 g) was added to create a stirred solution with DCM (175 mL, 400 mM). Then, triethyl amine (19.5 mL, 140.1 mmol) was added. Subsequently, acetyl chloride (5.00 mL, 70.07 mmol) was added to the reaction mixture and was let warm to room temperature overnight.

The solution was then allowed to warm to room temperature and stirred for one hour before quenching the reaction with saturated aqueous NaHCO3 solution (50 ml). The two layers were separated and the organic phase was washed with 1M HCl (50 ml) and brine (50 ml) and dried over Na_2SO_4 before being concentrated in vacuo.

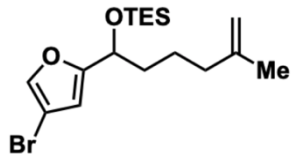
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26, 3.69, 3.18, 2.13.



To a flame-dried and N_2 filled 10 mL round bottom flask equipped with a stir bar, ketofuran (1.00 g, 3.89 mmol) was added to create a stirred solution with methanol (4.3 mL) at 0 °C. Sodium borohydride (.295 g, 7.78 mmol) was then added to the reaction mixture and set to stir at room temperature under N2 while being monitored by thin-layer chromatography (TLC) analysis.

Once complete, the reaction was quenched with H_2O (10 mL). The quenched reaction mixture was then extracted with EtOAc (3 x 10 mL), and then concentrated *in vacuo*. The crude material was purified by flash column chromatography (100% hexane *to* 30% EtOAc / 70% hexane). (63%, 0.64 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37, 6.30, 4.71, 4.67, 1.86 - 1.78, 1.70, 1.61 - 1.54.

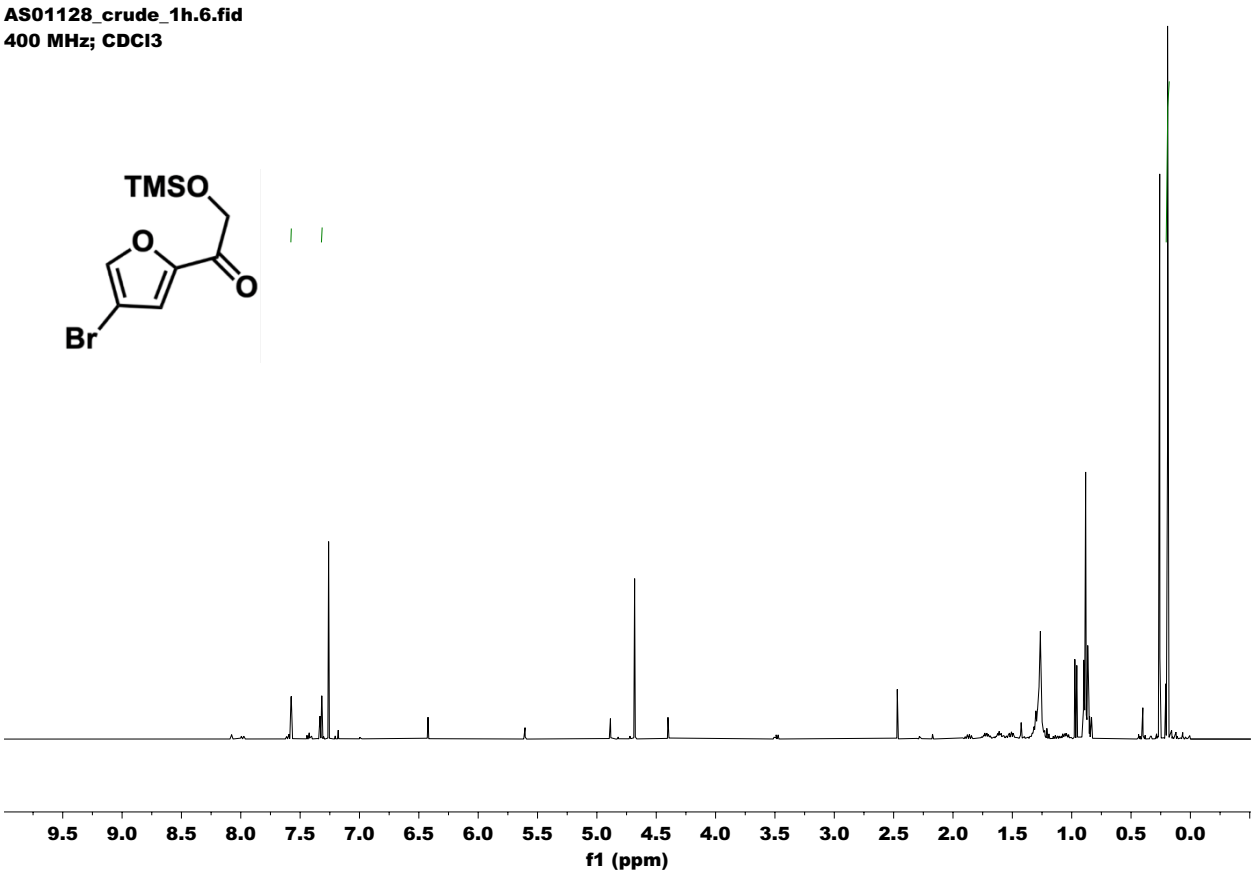


To a flame-dried and N_2 filled 25 mL round bottom flask equipped with a stir bar, imidazole (0.42 g, 6.17 mmol) was added to create a stirred solution with DMF (10 mL). Hydroxyfuran (0.64 g, 2.47 mmol) was then added to the reaction mixture. Then, TESCl (0.5 mL, 2.96 mmol) was added to the reaction mixture and set to stir at room temperature under N_2 while being monitored by thin-layer chromatography (TLC) analysis.

Once complete, the reaction was quenched with H_2O (100 mL). The quenched reaction mixture was then extracted with EtOAc (3 x 10 mL), washed with brine and then concentrated *in vacuo*. The crude material was purified by flash column chromatography (20% Et_2Oin hexanes) (80% yield, 0.74 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33, 6.23, 4.70 - 4.61, 2.02, 1.78- 1.76, 1.69, 0.92, 0.55.

NMR Spectra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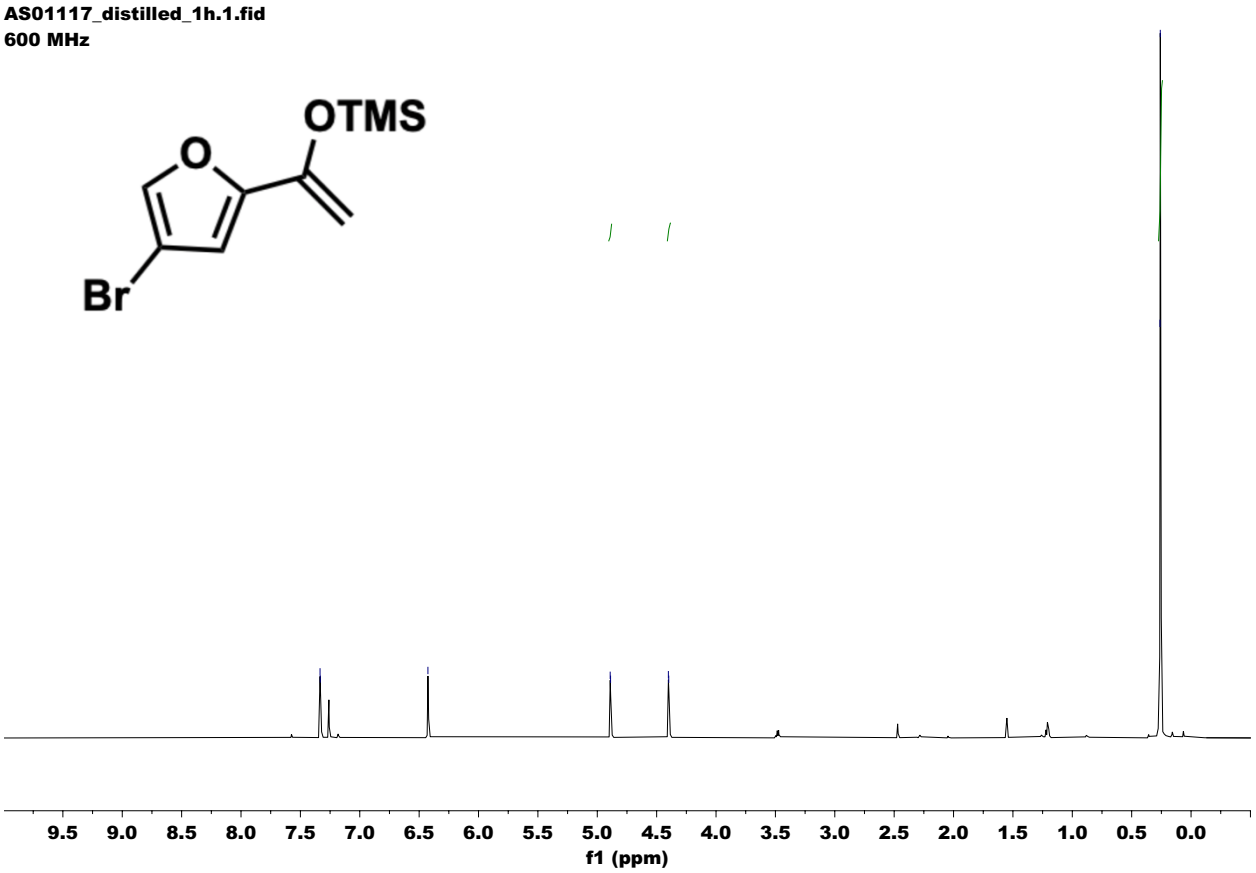
400 MHz; CDCl3
TMSO
O
O
Br
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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600 MHz
OTMS
O
Br
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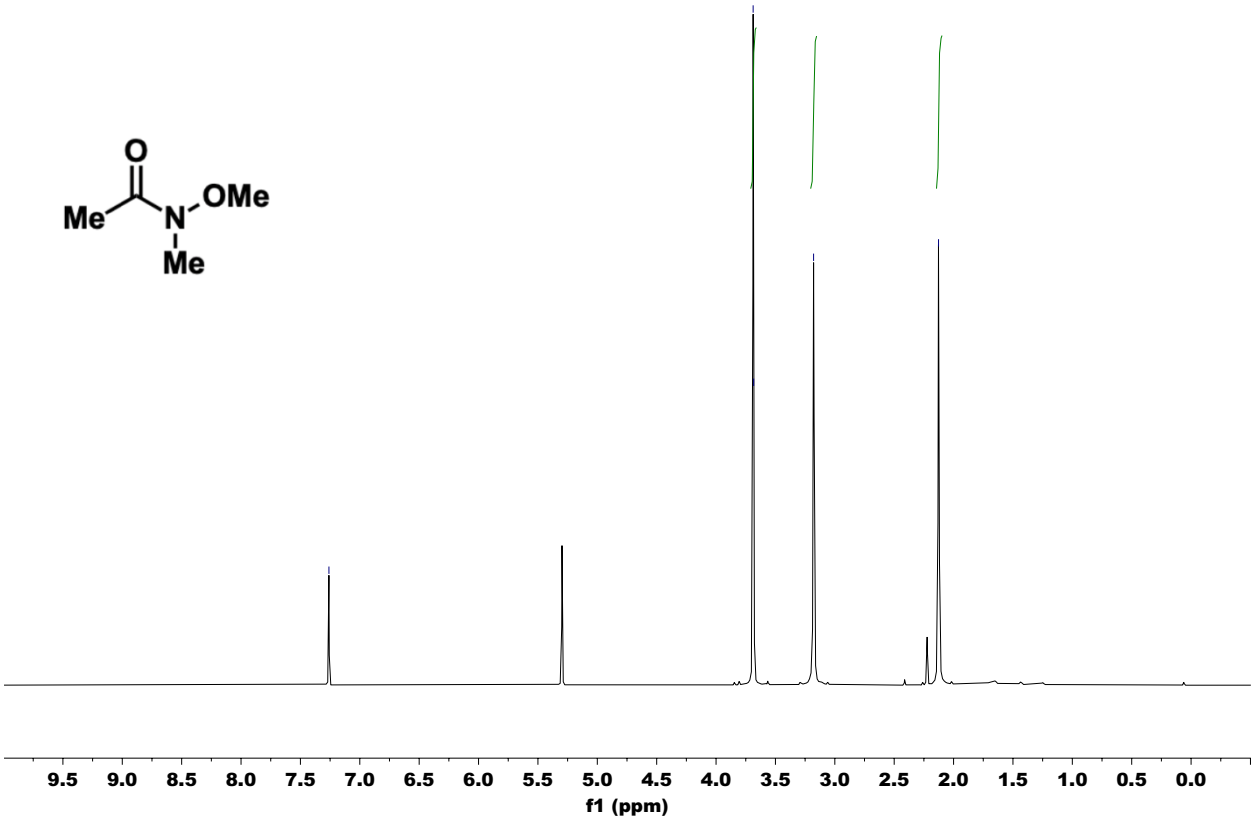
f1 (ppm)

AS01118_crude_1h.1.fid
600 MHz; CDCl3



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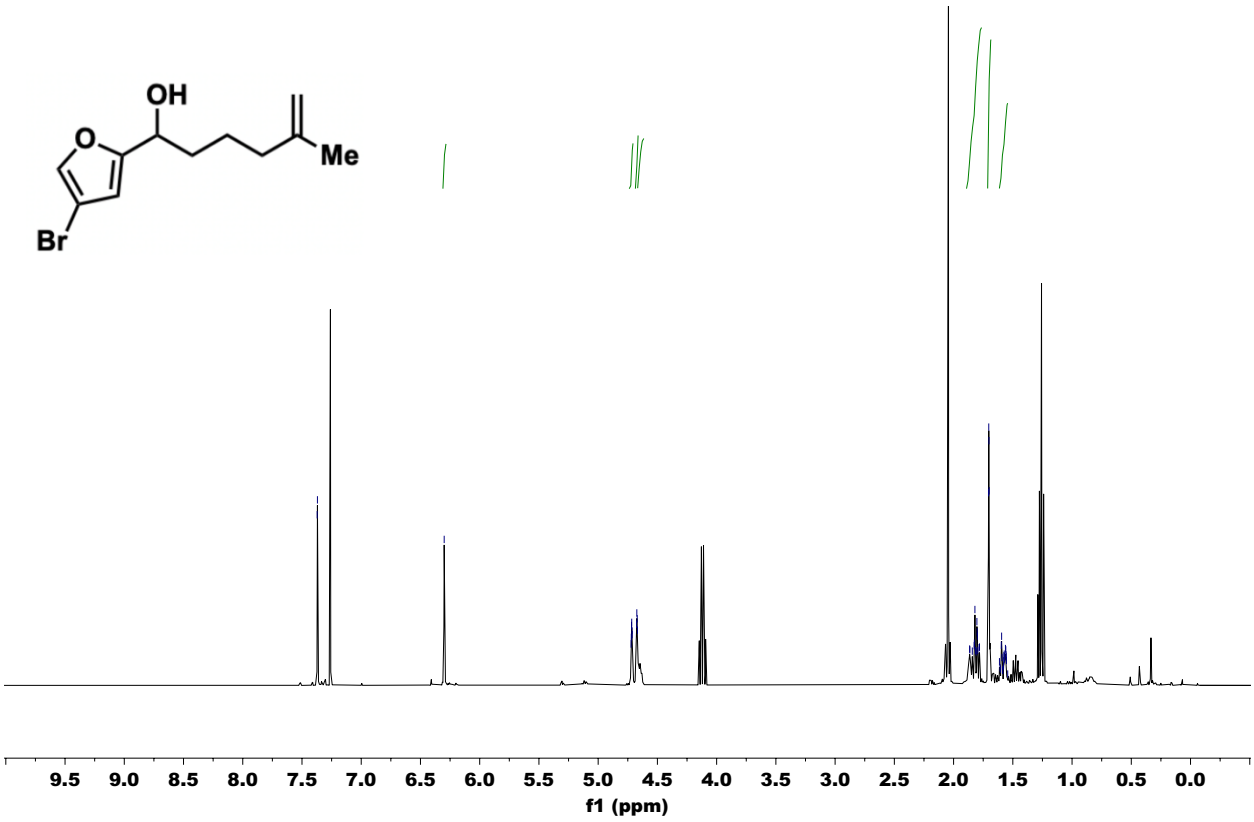

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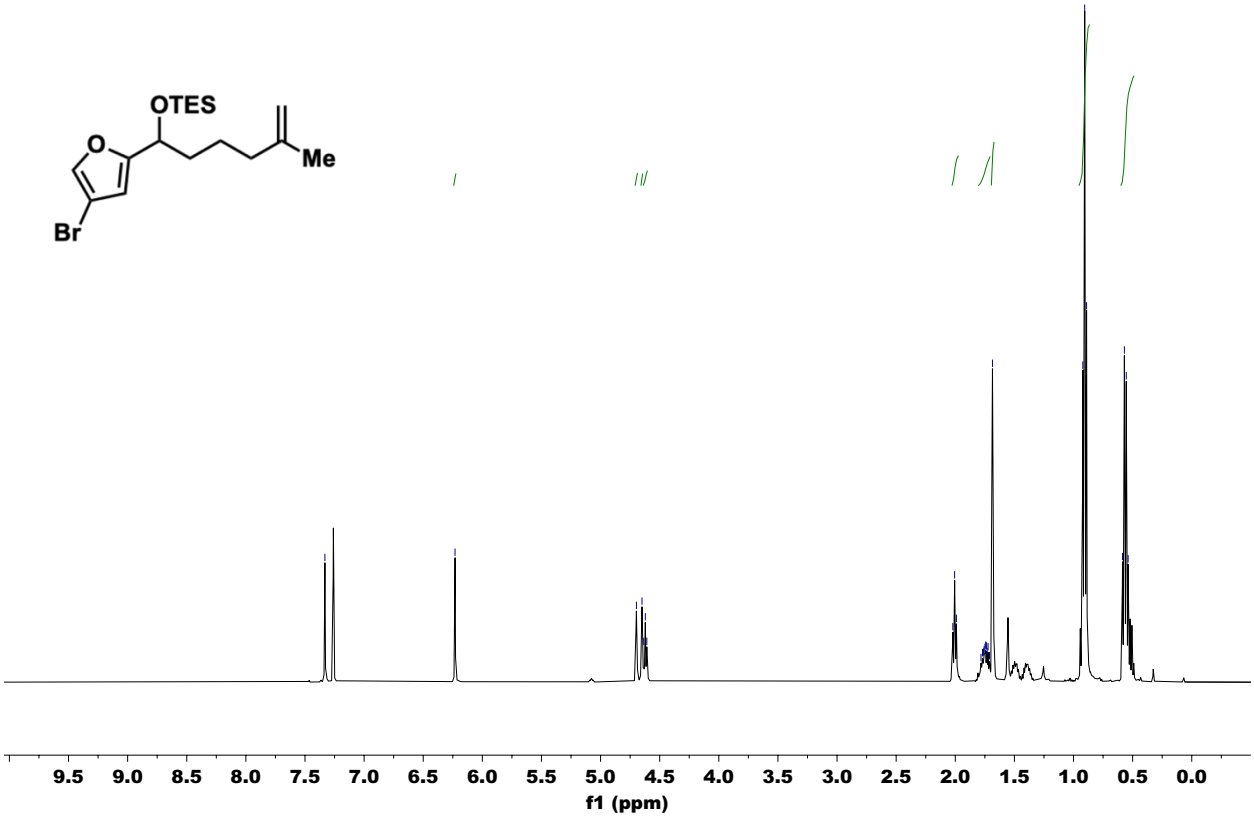
500 MHz; CDCl3



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