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Total Synthesis of Cadlinolide A and Efforts Towards the Synthesis of Darwinolide

A Thesis submitted in partial satisfaction of the requirements for the degree Master of Science in Chemistry

by

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June 2022

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To Zarina, Brad, and Megan; none of this would be possible without all of you

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Jacob Levin

Natural products have always been a classic source of new treatments against diseases. Recently, the *Darwinellidae* family of Antarctic sea sponges have yielded a family of molecules with high potency against diseases with poor or no current treatment.[1] Darwinolide has been shown to penetrate MRSA bacterial biofilms, while the six-membered ring variants have been shown to be active against Leishmaniasis and Malaria.[1] These compounds can revolutionize treatments, but are difficult to make individually.

A single, robust pathway toward the entire family will allow for the synthesis of related structures that can be tested for similar disease efficacy. The synthetic efforts described in this thesis will enable rapid construction of the common core structure and subsequent access to all family members as well as bioactive analogues.

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I: Bioactivity of Rearranged Spongian Diterpenes

A: Introduction[1]

The family of natural products discussed in this thesis have been studied for their unique and potent bioactivities. These molecules have been studied as potential treatments for many important disease states facing the world. This section will discuss three of the most pressing infections: Leishmaniasis, Malaria, and MRSA bacterial infections. This section will also discuss the molecules that are active against them, and their origin. The list of discussed molecules are shown in **Figure 1.**

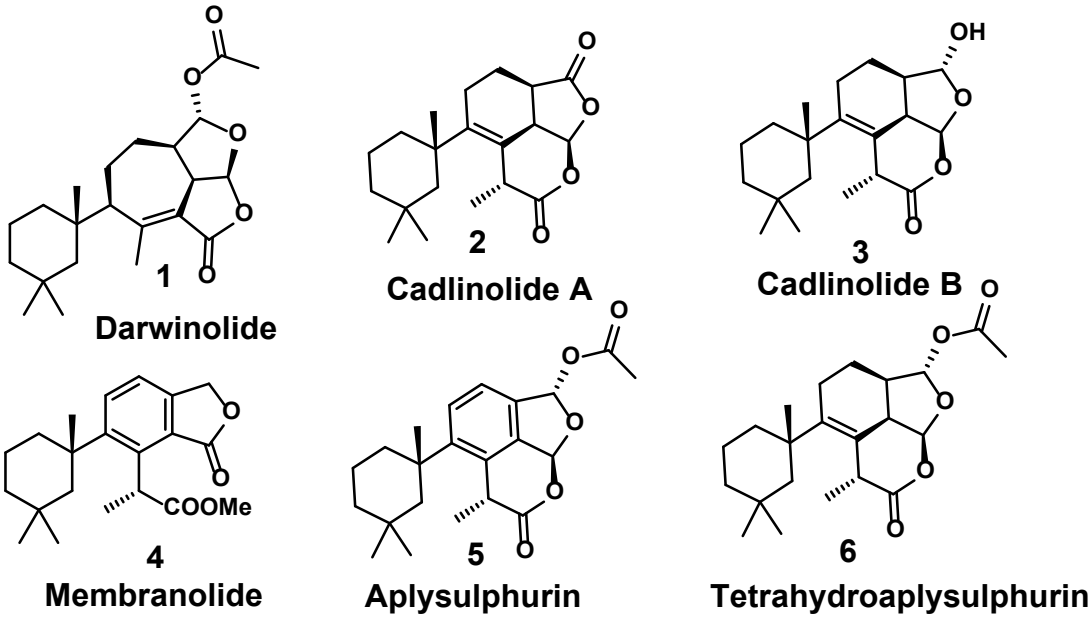


Figure 1: Rearranged Spongian Diterpenes

B. Natural Origin of Rearranged Spongian Diterpenes[2,3]

Natural products from sea sponges are some of the most diverse and interesting chemical compounds found in nature. Their nonribosomal peptide natural products have liberal amounts of carbon bromine bonds because enzymes that

assemble them in microorganisms are able to brominate tyrosine, histidine, and tryptophan residues. However, while those natural products are distinct due to their carbon halogen bonds, terpene derived natural products from sponges are completely unique in their structure.

The spongian derived terpenes have the basic structure of a [6,6,6,5] fused ring system similar in shape to the structure of cholesterol's main ring system. The five membered ring, however, is a tetrahydrofuran ring fused to the next six membered ring at the 3rd and 4th position. The majority of the basic spongian diterpenes differs only in the oxidation around that 5 membered ring, although some oxidation differences occur on the six membered ring at the other side of the structure.

These natural products pale in comparison to the diversity of the rearranged skeleton products. Due to the different rearrangement, oxidation, and derivatization reactions that can be done to the core spongian terpene skeleton, it becomes difficult to see individually how some of these natural products can come from the same family of organisms. While there are many sub families to talk about, this thesis focuses on the rearranged skeletons that form a unique fused ring system with an acylal backbone, and the efforts towards synthesizing this family with one synthetic pathway.

C: Structural Similarities in the Natural Product Family

This natural product family has distinct structural similarities among every member. These shared similarities are shown in **Figure 2.** The 1,3,3-trimethylcyclohexyl ring is an interesting shared feature, providing a large, bulky aliphatic substituent with a chiral center that directly connects to the fused ring

system. This chiral center is critical to the synthetic production of this family, but will be discussed in a following chapter. Almost all family members have a fused three ring system with the outer backbone being made of an acylal moiety. Most ring systems are composed of a 6,6,5-fused tricyclic core, although darwinolide has a unique 7,5,5-fused ring system.

Additionally, a study from 2020 showed that upon exposure to methanolysis conditions, aplysulphurin was degraded into a multitude of semisynthetic derivatives. These derivatives still kept many of the structural features of the natural product family while having unique features to themselves.[5] The bioactivity studies in the same paper showed many of the derivatives having equal or better efficacy against the same disease states as the parent molecule. That study shows the sheer importance of this common scaffold and the need to study it further. Aplysulphurin is the only natural product in the family that is known to undergo methanolysis degradation.[5] Similar products to these “membranoids” in other natural products could have interesting bioactivities. However, there has not yet been a total synthesis that is tunable enough to be capable of synthesizing these compounds.

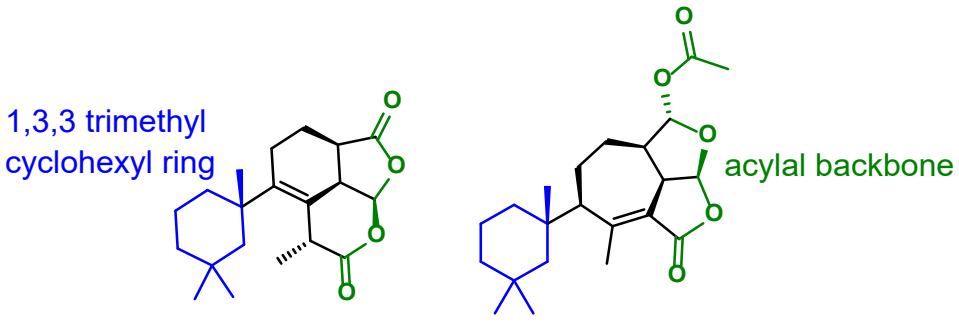


Figure 2: Structural Similarities of Cadlinolide A and Darwinolide

D: Leishmaniasis[1,4]

Among many neglected tropical diseases, Leishmaniasis remains a huge problem for the world. The disease caused by the parasitic protozoa *Leishmania donovani* causes painful ulcers that can prove deadly if the patient is not given adequate medical care. There is currently no known drug to treat this disease without causing irreparable damage to the patient's organs, namely their spleen and kidneys. Leishmaniasis infects millions each year, and causes the deaths of tens of thousands each year.

Both tetrahydroaplysulphurin and aplysulphurin showed an LD_{50} and cytotoxicity conducive with a safe and effective treatment for this disease. Additionally, many semisynthetic derivative formed from the degradation of aplysulphurin in methanol showed similar or even greater treatment potential than the natural products.[5]

E: Malaria[1]

Malaria is a disease that has received worldwide attention for its devastating effects across the world. As such, new treatments are always being researched and newly isolated natural products are tested for bioactivity against it. Membranolide is a rearranged spongian diterpene that has shown bioactivity against malaria and further shows the bioactive diversity of this family.

F: MRSA bacterial infections[6]

Antibiotic resistance is a growing problem for the world. As bacteria develop tools to destroy or disable current antibiotics, the world faces a coming catastrophe once bacteria emerge that can evade all current antibiotic treatments. One issue with

all current antibiotics is they target mechanisms in the individual cells but not the overall biofilms. Biofilms are colonies of the same bacteria that communicate and work together for protection and energy production. Many of the issues we face with antibiotic resistance come from the protections biofilms grant bacteria. Biofilms allow only a few bacteria to create the energy intensive enzymes or natural products needed to counteract antibiotics and protect the entire colony with them. While no current treatment targets biofilms directly, Darwinolide, another member of the title family, has been shown in studies to wipe out methicillin resistant *Staphylococcus aureus* (MRSA) bacterial biofilms.

This is by no means an exhaustive list of the bioactivities of this family, but it does give good evidence of the diverse bioactivities of this family.

G: Conclusions[1,6]

In every isolation and bioactivity paper discussing this family, none to our knowledge mention these natural products as potential treatments. Instead, they recommend modifications to the native structures to develop highly effective treatments that are easy to synthesize. However, there have only been two total syntheses of individual family members (Membranolide and Darwinolide).[7,8] Both syntheses, while impressive, can only be used to make that specific natural product and are not useful for the development of the scaffold as a drug target.

Additionally, the bioactivity study on the membranoid derivatives is a great reason for a more tunable synthesis of this family. While aplysulphurin can undergo methanolysis, it yields many different products with only some of the compounds produced in that reaction having bioactivity. A more efficient method would be

synthesizing these derivatives synthetically. Synthesizing these bioactive derivatives would allow for further understanding of the bioactivity and biological synthesis of this family, allowing for a new generation of therapeutics to be developed from this scaffold.

As such, this thesis focuses on the development of a divergent synthesis for this family of natural products, using Cadlinolide A as an initial target. This synthesis is followed by the experiments and progress related to the synthesis of Darwinolide using a common intermediate in the synthesis of Cadlinolide A.

II: Total Synthesis of Cadlinolide A

A: Retrosynthetic Analysis[9]

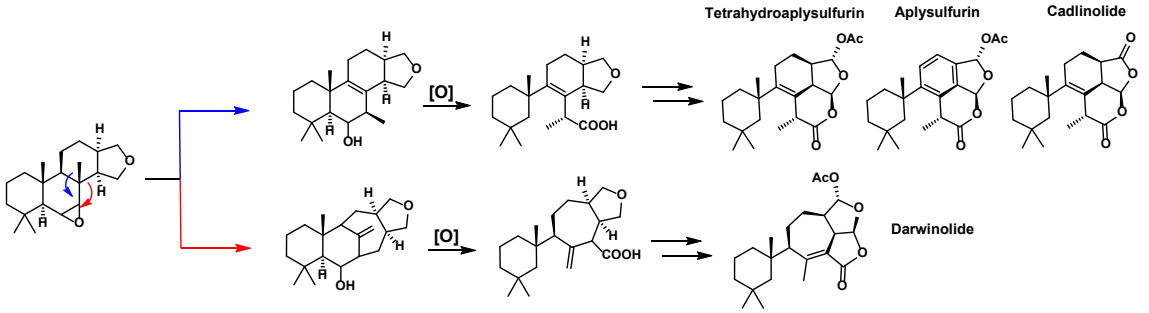


Figure 3:Biosynthetic Pathway of Rearranged Spongian Diterpenes

In the biosynthesis of these natural products, there is a point at which the synthesis of the [6,6,5] and [7,5,5] natural products diverge. This is dependent on the regiochemistry of the rearrangement that opens the epoxide of the common intermediate for this family. The resultant products are oxidized by P-450 enzymes and further derivatized to yield the natural products of the family. This pathway is summarized in **Figure 3**.

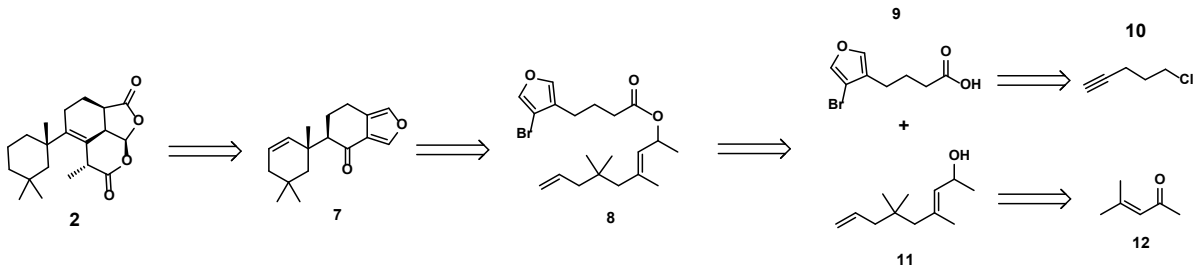
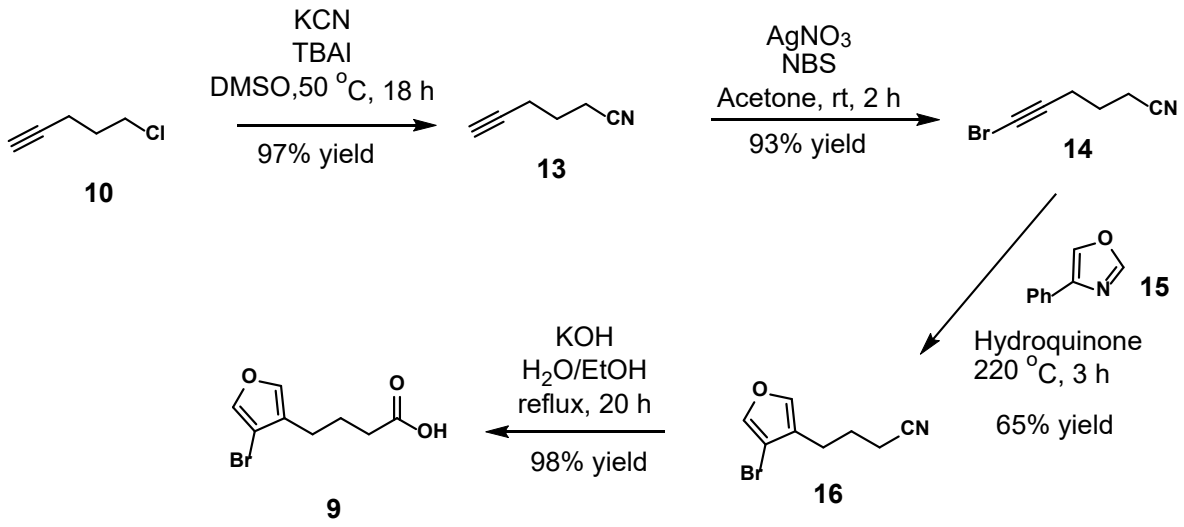


Figure 4: Retrosynthetic Analysis of Cadlinolide A

Like the biosynthesis, a common intermediate was envisioned for the total synthesis of this family of natural products. The furyl ketone **7** was planned as the common intermediate for the synthesis, and a key intermediate for Cadlinolide A, as

well as the other natural products in the family. Cadlinolide A was used as the first synthesis, as it has not been synthesized before, and is a simpler structure compared to other members of the family. Cadlinolide A would be synthesized from this intermediate by utilizing an enolate addition into the furyl ketone, followed by oxidation of the furan, reduction of the olefinic bonds, and elimination of the resulting tertiary alcohol. The final reaction will consist of a cyclization to form the acylal moiety, yielding Cadlinolide A. The furyl ketone will be made from the acyclic allylic ester **8.** A diastereoselective Ireland-Claisen rearrangement, followed by a ring closing metathesis and lithium halogen exchange ring closing reactions will comprise that specific section of the synthesis. The allylic ester will be made from the allylic alcohol **11** and furyl butanoic acid **9**, which will both be synthesized from commercially available starting materials **10** and **12**. The retrosynthetic analysis is summarized in **Figure 4**.

B: Synthesis of the furyl butanoic acid



Scheme 1: Synthesis of the Furyl Butanoic Acid Fragment

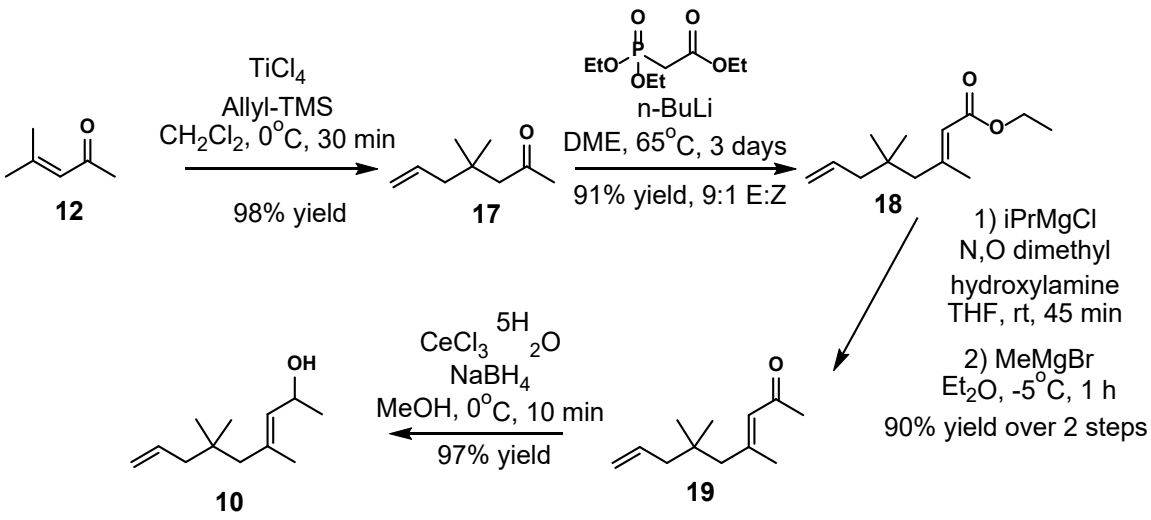
Starting from the commercially available 1-chloro-4-pentyne **10**, an S_N2 reaction followed by bromination of the terminal alkyne allowed for an efficient synthesis of 6-bromo-5-hexynonitrile **14** at decagram scales.

The following reaction attempted to form the furan moiety by undergoing a Diels-Alder/retro Diels-Alder with 4-phenyloxazole (**15**) at elevated temperatures in a sealed microwave vial (benzonitrile as the leaving group). **15** was made in house at hectogram scale by reacting 2-bromo acetophenone with formamide. The purest material came from purifying the heterocycle first by a silica plug and then by vacuum distillation (the material was then stored under argon and treated similarly to any liquid sensitive to moisture and oxygen). Although used in large quantities, **15** can be easily recovered from the purification of the reaction mixture via column chromatography.

The lower yield for this reaction is due to a competing side product that is isolated during the purification of the reaction mixture. The likely identity of this side product is created from the product of the reaction reacting with another alkyne starting material in a second cycloaddition. The more equivalents of oxazole used, the higher the yield of the desired product and the lower the yield of the byproduct. When scaling up this reaction, a decision had to be made to maximize yield and minimize the amount of time to move through the material, as vessel size was a limiting factor for this reaction.

Once **16** was made in high quantities, it could be cleanly converted via hydrolysis to the furyl butanoic acid **9**, that could be staged in decagram quantities for the next steps of the synthesis. The overview of this stage of the synthesis is summarized in **Scheme 1**.

C: Synthesis of the allylic alcohol



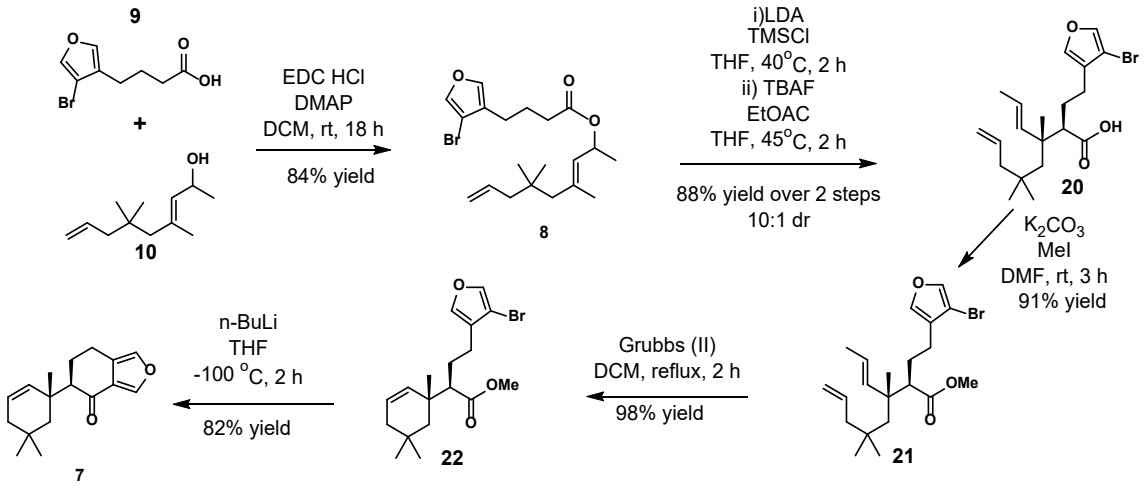
Scheme 2: Synthesis of the Allylic Alcohol Fragment

Starting with commercially available mesityl oxide **12**, a known Sakurai 1,4-allylation could be performed at a large scale to yield large quantities of the ketone **17**. The initial route for this synthesis utilized a Horner-Wadsworth-Emmons olefination to form the unsaturated ester **18**. Initial attempts at this reaction were refluxed in glyme to give middling yields (50-60%) despite full conversion by TLC and NMR. Surprisingly, lowering the reaction temperature and allowing the reaction to run for longer to compensate gave a much cleaner reaction and higher yield of the product. This result is explained by the thermal instability of the starting ketone (found by failed distillations of this intermediate).

To form the unsaturated enone **19**, **18** was converted to the corresponding Weinreb amide. The Weinreb amide allowed for the separation of *E* and *Z* isomers from the olefination as well as a clean conversion to the enone **19**. **19** was converted via Luche reduction to the allylic alcohol **10**. The summary of this section of the

synthesis is outlined in **Scheme 2**. It should be noted that improvements to this synthesis in enantioselectivity, scalability, and step count were carried out. However, these topics are more appropriate for the efforts towards Darwinolide chapter and are detailed there.

D:Synthesis of the furyl ketone[8]



Scheme 3: Synthesis of the Furyl Ketone Intermediate

The allylic alcohol **10** and furylbutanoic acid **9** were combined by esterification to form the allylic ester **8**. This allylic ester was utilized to investigate the Ireland-Claisen rearrangement to form the key stereocenters for this synthesis. In Christmann's synthesis of Darwinolide, they utilize a cyclic Ireland-Claisen rearrangement to set the same stereocenters that were being set in this reaction. However, due to the starting material's cyclic nature, the reaction required being heated at high temperatures in toluene for long periods of time, resulting in a thermodynamic diastereomer that was not the same stereochemistry as Darwinolide. This issue was salvaged with a selective epimerization reaction later in the synthesis, but this still caused 40% of the material to be discarded.

In this synthesis, our acyclic allylic ester allowed for control over the major diastereomer created in the reaction. When 4 equivalents of LDA were used as the base, we created the desired diastereomer in a 9:1 ratio. However, when 3 equivalents of KHMDS were used as the base, we created the **undesired** diastereomer in a 14:1 ratio. The kinetic nature of this reaction with the acyclic rearrangement allowed for another point of flexibility in this synthesis; even if the theory of which diastereomers were being synthesized was wrong compared to reality, the synthesis could still be completed.

In theory, a lithium base would allow for the Ireland transition state to select for the (Z)-silyl ketene acetal to limit the steric clash of the two large groups of the molecule. This preference can be seen in **Figure 5**. Once created, the two enantiomers of the silyl ketene acetal would each produce two enantiomers of the rearranged acid product due to the Claisen transition state. These transition states can be seen in **Figure 6**. Together, they show that a lithium base with an *S* configuration enantioenriched allylic ester would yield the correct enantiomer for all natural products in the family.

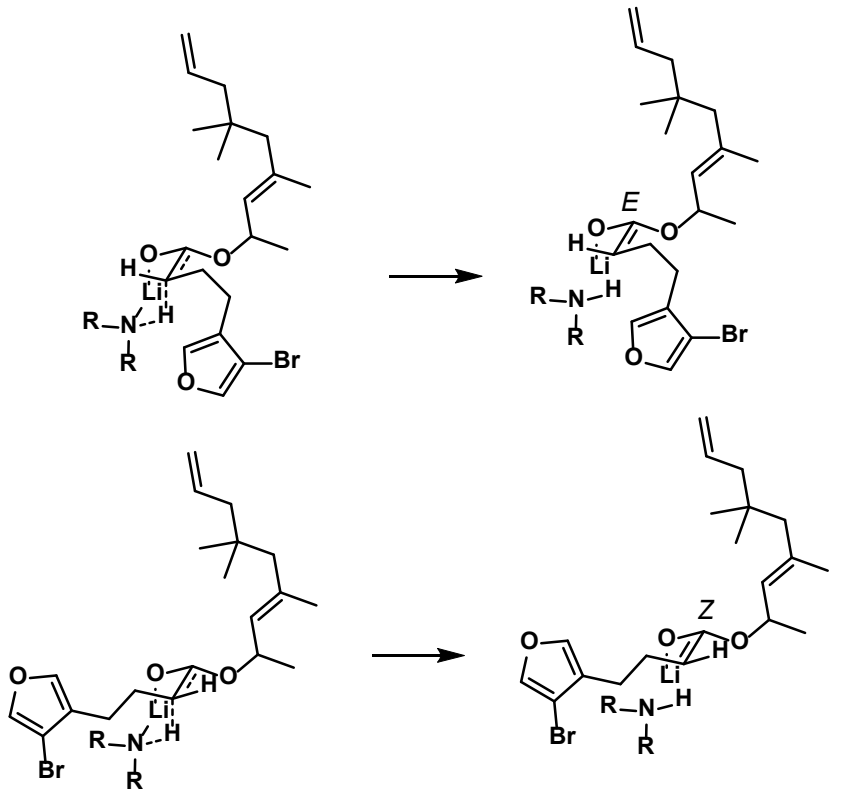


Figure 5: Ireland Transition States

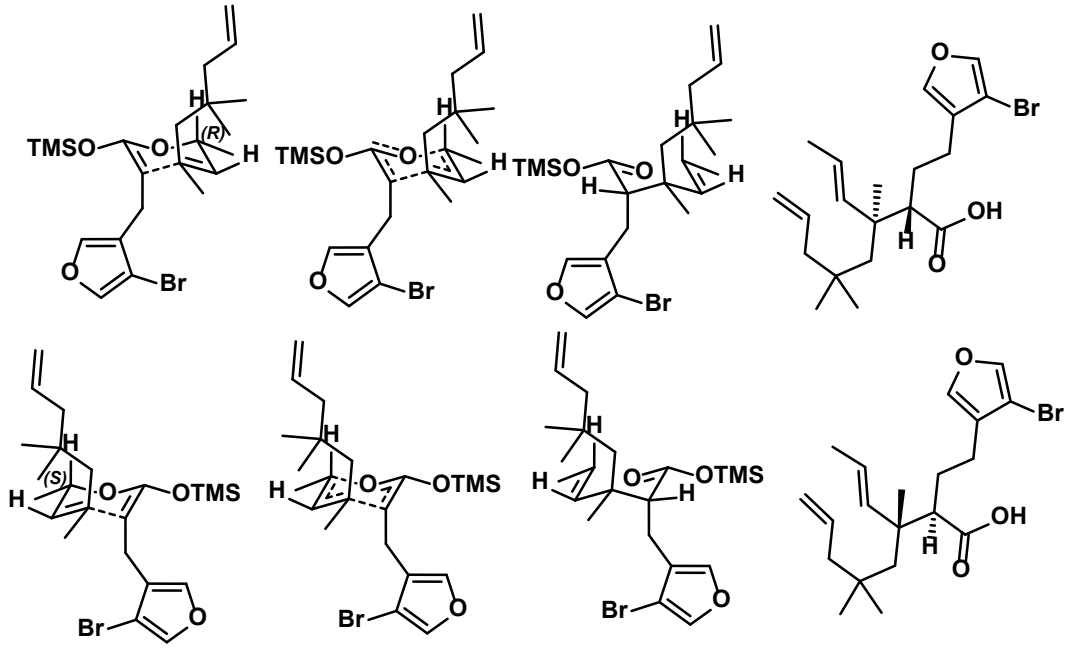


Figure 6: Claisen Transition States for Silyl Ketene Acetal

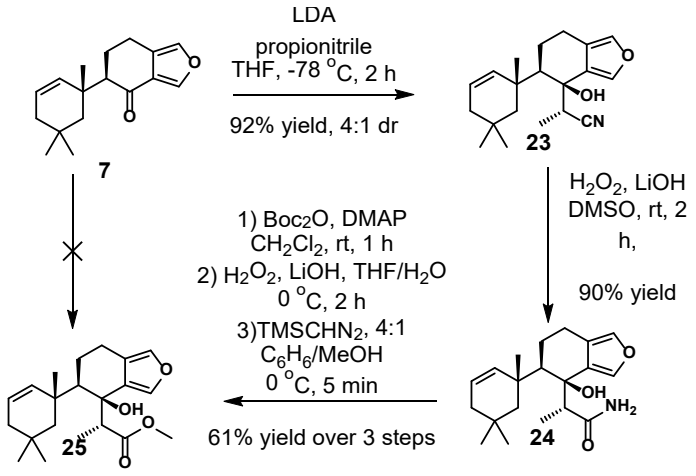
The diastereomers created by these reactions were proven first by NOE experiments with a fused ring system derivative made from the rearrangement product, and later by multiple X-ray crystal structures. The theorized major diastereomers were indeed the major products of the rearrangements.

An interesting note of this rearrangement is the larger than expected equivalents of LDA used in the reaction. The reason for this is that both protons in the furan in our starting material were deprotonated and silyated during the reaction. These TMS groups could be easily removed by submitting the crude material after the rearrangement to a TBAF desilyation reaction. That second reaction also allowed for any side product C-silyation material to be desilyated and recycled during the synthesis. LiHMDS could also be used to perform the rearrangement. In THF it gave lower yields and lower diastereoselectivity, but in toluene it gave slightly lower yields with a large increase in diastereoselectivity (~80% yield, 25:1 dr). Those conditions do allow bypassing the silane deprotection, but also formed side products that were difficult to control for.

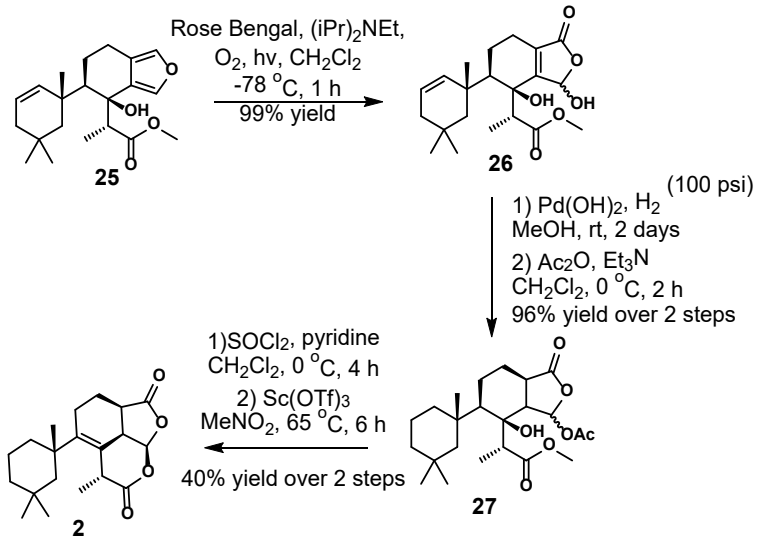
After methylating the rearranged acid **20** to form the methyl ester **21**, a ring closing metathesis with Grubbs' second generation catalyst was used to close the ring of the 1,3,3 trimethyl cyclohexyl ring. The olefin remaining on the ring would be hydrogenated later in the synthesis. **22** was then submitted to a lithium halogen exchange with *n*-BuLi to form the furyl ketone intermediate **7**. An interesting note of this reaction is that it only requires 1 equivalent of lithium, instead of the 2 equivalents normal for this sort of reaction. This is likely due to the methoxide leaving group is being utilized for the deprotonation of *n*-butyl bromide that normally pushes the

equilibrium forward for lithium halogen exchange reactions. This section of the synthesis is summarized in **Scheme 3.**

E: Synthesis of Cadlinolide A



Scheme 4: Addition of Propionitrile



Scheme 5:Synthesis of Cadlinolide A

Most of the reactions in this section of the synthesis were investigated by Brad Reid. This section will discuss these reactions, but his Ph.D dissertation is a much better resource for information on these reactions.

Having synthesized multiple grams of **7,** the next investigation was centered on adding nucleophiles into this cyclic ketone. Due to the bulky 1,3,3-trimethylcyclohexenyl group and the propensity of any addition product to perform a retro aldol reaction, the addition reactions on this ketone were incredibly selective and sensitive. In fact, only three nucleophiles were able to add into this ketone during the course of the investigation: ethyl acetate, chloro-acetic acid, and propionitrile.

Ethyl acetate allowed for a diastereoselective addition into the ketone, and allowed for investigations to yield des-methyl cadlinolide A. Chloro-acetic acid was used for attempts at a semi pinacol rearrangement to form the seven membered ring of Darwinolide. Finally, propionitrile was the only nucleophile with the appropriate amount of carbons to add cleanly enough in a 4:1 diastereomeric ratio (of the carbon next to the addition site; the addition site was completely diastereoselective) to form **23**. Many other enolates and nucleophiles were screened for this bond formation but either led to no reaction or the decomposition of the starting material.

Having added propionitrile to the ketone, the new challenge was to convert the nitrile group into an alkyl ester **25**. As mentioned in the previous paragraph, the addition products can undergo a retro aldol reaction to reform the furyl ketone. As such, a very mild approach was needed to convert the nitrile to the methyl ester. After converting to the amide **24**, the boc protected amide, the acid, and finally methyl ester **25**, the most laborious section of the synthesis was complete. Most of the yield loss was due to retro aldol reactions that occurred (which can be recycled in the synthesis).

The intermediate **25** underwent singlet oxygen oxidation of the furan ring to form the gamma hydroxy butanolide **26**. A dual hydrogenation of both olefin bonds was performed in a bomb reactor at 400 psi of H_2. The tertiary alcohol of intermediate **27** was then eliminated, and the subsequent product was put into cyclization conditions with scandium triflate to yield Cadlinolide A. **Schemes 4 and 5** highlight the reactions for the last section of this synthesis.

F: Conclusion

The synthesis of cadlinolide A was completed in 18 steps with an overall yield of 6%. More importantly, this synthesis has the potential to be tweaked and diverted at key points in order to make more members of this bioactive family. A current issue with this synthesis is that it is racemic, and ideally this pathway would be enantioselective. The ideal point for creation of chirality is the allylic alcohol, and the formation of the enantioenriched allylic alcohol is detailed in chapter 3.

III: Efforts towards the synthesis of darwinolide

The following chapter's title is a bit misleading; although everything in this chapter has the intention of being applied to the eventual synthesis of darwinolide, many of the experiments detailed can and will be applied to the whole family. As has been mentioned before, the key difference between darwinolide and the other members of the family is its unique 7,5,5 fused ring structure. As such, a huge change in the synthesis pathway was needed while still following a common intermediate to the cadlinolide A synthesis. The flexibility, scalability, and enantioselectivity of the synthesis is what is truly being discussed in this chapter.

A: Installation of the 1,3,3-trimethylcyclohexyl ring

In the synthesis of membranolide and darwinolide, as well as the SAR study done by Romo related to the synthesis of this family, huge issues in diastereoselectivity were present when installing the 1,3,3-trimethylcyclohexyl ring.[5,6,8]

Yi's synthesis of membranolide utilized a cuprate addition followed by Wolff-Kishner reduction to attach the cyclohexyl ring to the center aromatic ring of membranolide. However, this reaction resulted in racemic material, that lead to a racemic synthesis of membranolide.[7]

In Romo's paper, a zinc nucleophile was used to attempt a diastereoselective synthesis of the core structure. When the geminal dimethyl carbons were absent from the ring, they saw high diastereoselectivity (19:1 dr). However, when the actual ring needed was used in the same reaction, they saw only racemic material (1:1 dr).

Romo's study shows that control of the stereocenters is partially difficult due to the nature of this unique ring system.[9]

Christmann's synthesis of darwinolide again executes this previous point, as his cyclic Ireland-Claisen rearrangement produces enantioenriched material, but of the wrong diastereomer where the seven membered ring would end up.[8]

Table 1: Effect of Base and Solvent on Ireland-Claisen Rearrangement

Base	Solvent	Yield[a]	Diastereomeric ratio[b]
LDA[c]	THF	88%[d]	10:1
KHMDS	THF	70%	1:14
LiHMDS[e]	THF	66%	3:1
LiHMDS[e]	Toluene	84%	>25:1

a: Isolated yield

b: Inseparable diasteromers. Ratios determined by selected peaks in the isolated acid as well as methyl ester H-NMR

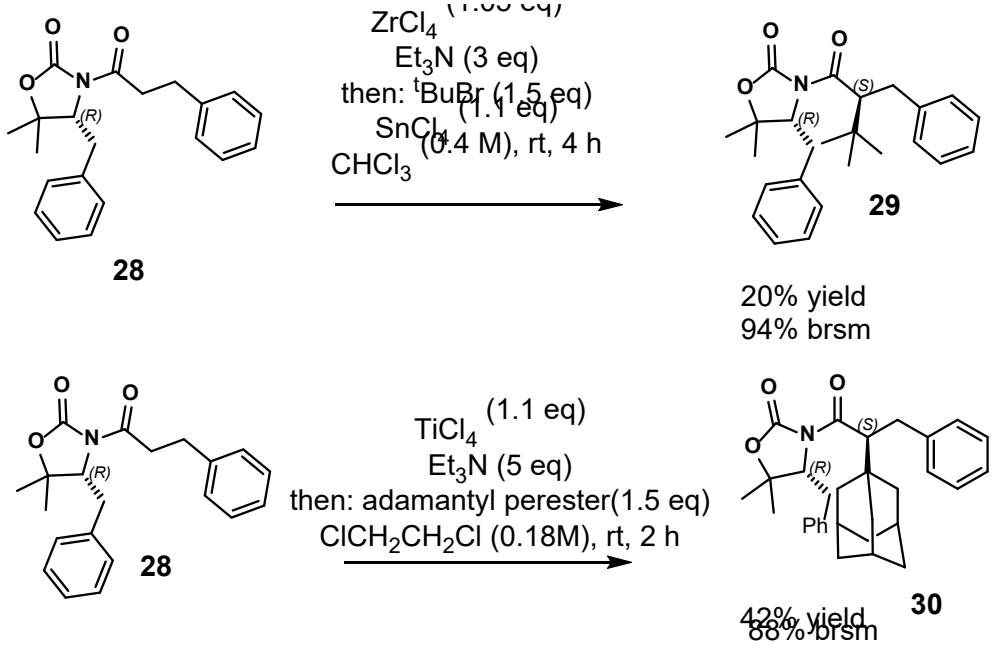
c: Made from *in situ* reaction of diisopropylamine and *n*-Butyl Lithium

d: Yield over two steps due to needed desilyation of furan

e: Made from *in situ* reaction of hexamethyldisilazane and *n*-Butyl Lithium

In the synthesis of cadlinolide A, the acyclic Ireland-Claisen rearrangement gave complete control of these stereocenters. This is illustrated in **Table 1**, where the use of base in the reaction allows for a change in the diastereomer created in the reaction. LDA or LiHMDS conditions were selective for the desired diastereomer, while KHMDS conditions were selective for the undesired diastereomer. By making

an enantioenriched allylic alcohol (detailed in an upcoming section), the resulting acid would be enantioenriched as well.

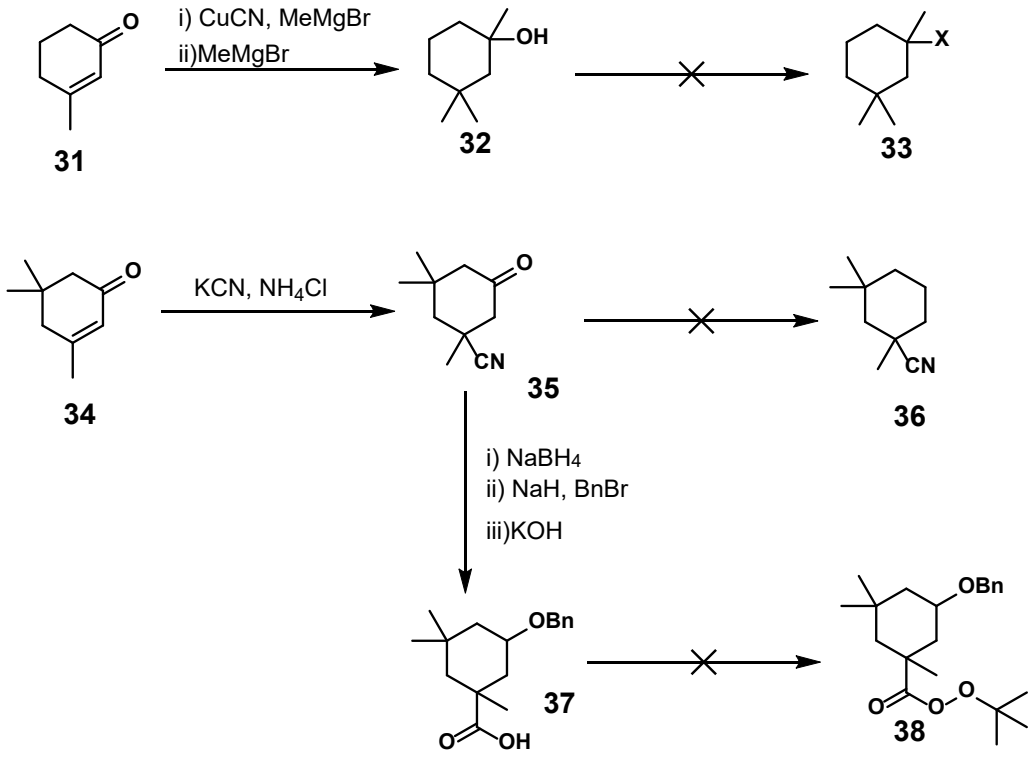


Scheme 6:Radical Alkylation with Chiral Oxazolidinone Auxiliaries

Because of these examples in literature and our own efforts, the first step for expanding the natural products made in this synthesis pathway was making sure that the current method of installing the first two stereocenters in the ring was indeed the best method possible. Two methods developed recently show potential for direct enantioselective radical addition of tertiary centers.[11,12] These reactions utilize an oxazolidinone chiral auxiliary and the titanium or zirconium radical enolate that is produced from their interaction.

Both methods were first reproduced with hydrocinnamic acid and can be seen in **Scheme 6**. It should be noted that although the reactions are low yielding, they

produce no side products and the leftover starting material can be easily recovered and recycled in subsequent reactions.



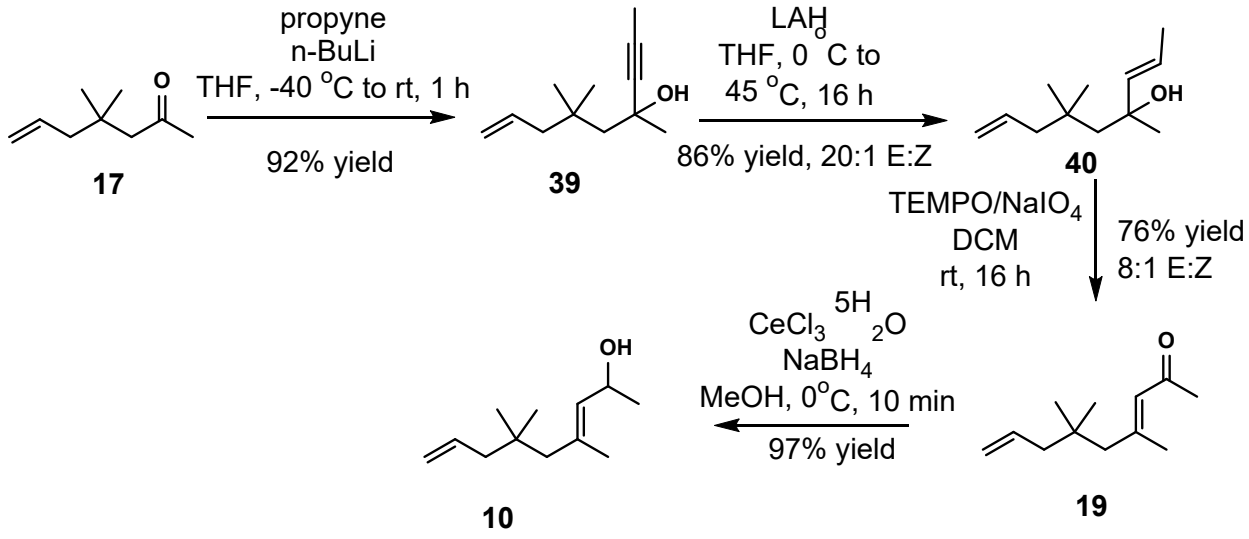
Scheme 7: Attempted Synthesis of radical acceptors

With the reactions reproduced, an investigation to create the radical acceptors was started. The chloro, bromo, or perester of the 1,3,3, trimethyl cyclohexyl unit were chosen as the potential test subjects for the reaction. However, synthesizing these molecules has thus far been unsuccessful. For the halogens, any attempt to substitute a halide in for an alcohol to form **33** resulted in elimination products forming. Even very mild conditions resulted in no reaction, or complete elimination. The perester **38** had a completely different problem. The potential pathway consisted of a conjugate addition of cyanide into isophorone, followed by Wolff- Kishner reduction. The nitrile would then be hydrolyzed and the resulting acid turned into the wanted

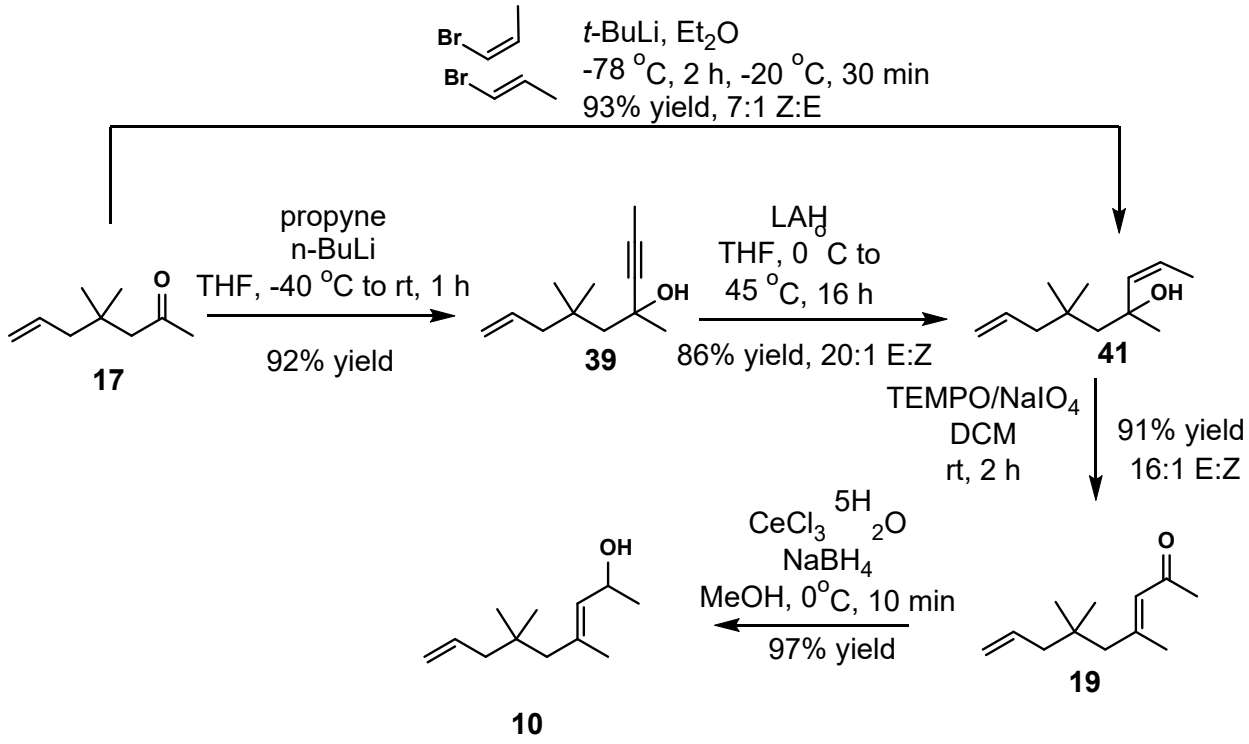
perester. The nitrile addition proceeded easily, however any attempt to remove ketone made the product invisible to TLC visualization on any common stain available, making purification nearly impossible by column chromatography. Reduction of the ketone and capping with a benzyl group allowed for visualization on TLC after hydrolysis, but any attempt to make the perester from the carboxylic acid was met with degradation of the starting material. Although this pathway could work in the future, the current tools available are not sufficient to synthesize these radical acceptors efficiently. The overview of these attempts can be seen in **Scheme 7**

B: Redesigning the synthesis of the allylic alcohol

Having exhausted current ideas for that potential pathway, the focus of the project turned to improving the scalability and ease of the allylic alcohol synthesis, including enantioenriched material. The initial route for the reaction had a 3-day bottleneck in the olefination reaction, as well as scalability issues due to the use of isopropyl magnesium chloride in the Weinreb amide formation.



Scheme 8: Synthesis of the Allylic Alcohol via Propyne



Scheme 9: Synthesis of the Allylic Alcohol Via 1-Lithio-1-Propene

The new routes are shown in **Schemes 8 and 9.** Initially, the lithium acetylide derived from the deprotonation of propyne gas by *n*-BuLi was utilized to form the propargylic alcohol **39**, which was reduced by lithium aluminum hydride to form the E isomer of the allylic alcohol **40** selectively. A oxidative transposition with TEMPO/$NaIO_4$ of this allylic alcohol allowed access to the enone **19** in fair isomer selectivity. However, this was improved futher by adding Z-1-lithio-1-propene derived from Z-1-bromo-1-propene and *t*-BuLi. The Z isomer of this reaction gave higher yield and greater isomer selectivity of the enone **19** than the E isomer under the same reaction conditions and the original route. This new route allowed for quicker access to the allylic alcohol in fewer steps and higher overall yield.

C: Synthesis of the enantioenriched allylic alcohol

With the allylic alcohol synthesis redesigned, the next goal was to synthesis enantioenriched allylic alcohol. Initial reactions such as alkyl zinc addition, CBS reduction, and Noyori reduction all resulted in either no reaction or low %ee of the allylic alcohol.

While chemical methods proved unsuccessful, enzymatic kinetic resolutions proved fruitful. A screening of lipases utilizing vinyl acetate as the acyl donor all produced higher %ee than any of the reactive chemical methods. The best resolution occurred with a lipase derived from *Pseudomonas fluroescens*, yielding both the alcohol and acetate in over 90 %ee. The leftover alcohol (now enriched) is utilized as per the normal synthesis pathway. The acetate first undergoes methanolysis conditions and then the furyl butanoic acid is attached while inverting the stereocenter in a Mitsunobu reaction.

This resolution can go even futher, however, as literature has shown that a specialized vanadium catalyst can be used with tertiary allylic alcohols to transpose and acylate in a dynamic kinetic resolution for over 50% yield of the acetate. The details of the development of this method are detailed in the following section. The Mitsunobu conditions would then be utilized as normal for the acetate to yield enantioenriched pre-Ireland-Claisen allylic ester in 5 steps from commercial sources. These efforts represent a huge improvement in efficiency of the synthesis, even if only applied to cadlinolide A.

D: Development of a dynamic kinetic resolution with rhenium (VII) oxide

While rhenium (VII) oxide has been reported on before for its use in allylic alcohol transpositions, it has never been explored (to our knowledge) in dynamic kinetic resolutions of allylic alcohols. Specialized vanadium catalysts have been used in more limited cases for the required transposition, although most examples utilizing it are on substrates near aromatic systems where the product is favored due to conjugation stability.[13]

When Grubbs and his group first looked into rhenium catalyzed alcohol transpositions, they noticed two potential side products that could form; an elimination product and an ether product.[14] It should be noted that the ether side product was isolated in optimization studies in the dynamic kinetic resolution with vanadium.[13] Regardless, the ratio of these side products and the desired product were highly dependent on the solvent used. As such, a solvent screening took place. In dichloromethane, elimination took place within a few minutes. This is likely due to the

solvation of the rhenium in the solvent, as in toluene the elimination product was significantly lowered, giving a 1:5:1 ratio of elimination, ether, and desired secondary alcohol. Furthermore, when starting with enantioenriched secondary allylic alcohol, the alcohol became racemic, showing that the transposition was occurring with the rhenium catalyst.

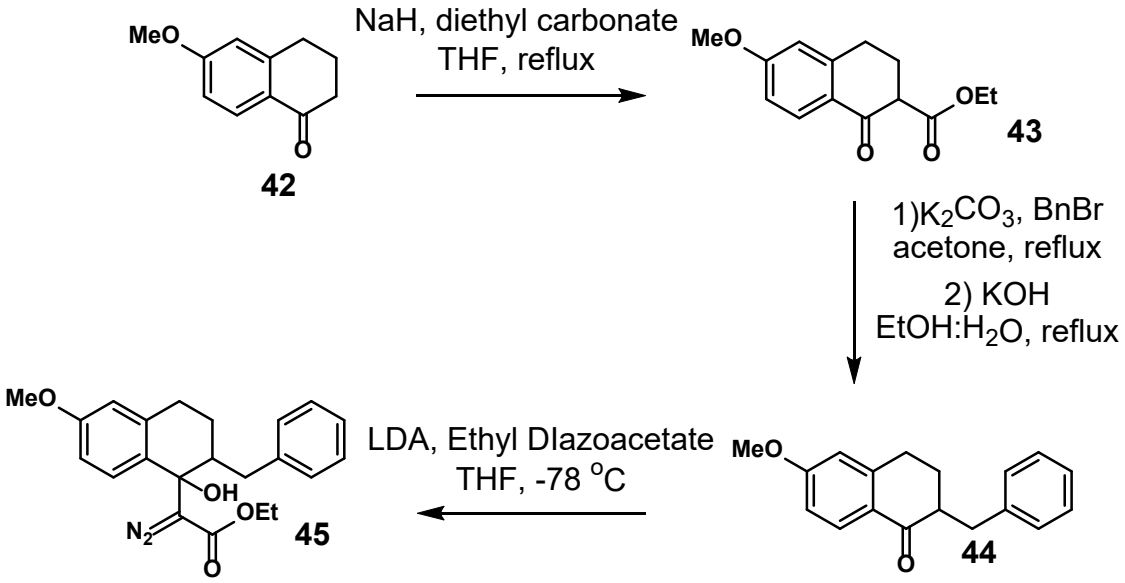
The best results came by performing the reaction in a hexanes solvent, which completely eliminated the elimination products and gave a 1:1 mixture of ether to secondary alcohol. The ether products was further suppressed by dilution, and completely absent once an enzyme was added to the solution. These results are similar to the optimization that the previous vanadium catalyst paper saw.[13]

As of the writing of this thesis, the best results with the lipase CAL-B are 35% ee and 58% yield. The current issue is that the enzyme is not specific enough and the reaction slows down the longer it goes, potentially caused by the build up of acetic acid from vinyl acetate over time. Future studies on this reaction should attempt to screen other enzymes, especially *Pseudomonas fluorescens*. Additionally, other acyl donors such as 4-chlorophenyl acetate should be screened to speed up the reaction by eliminating acetic acid build up.

E: Seven membered ring formation: semi pinacol rearrangement

The initial strategy for expanding to a divergent synthesis was to use the furyl ketone **X** as the common intermediate of the synthesis. By adding an enolate with a specific functional group on the alpha position, such as a diazo or halide, a semi pinacol rearrangement could be performed to yield the desired seven membered ring of darwinolide.

To begin this investigation, a model substrate was synthesized in order to explore reactivity and conserve precious materials. An α-diazo β-hydroxy ester derived from an α-benzyl substituted 6-methoxy tetralone was envisioned as the model substrate. This model is similar to the wanted structure derived from **7** as it has a electron donating aromatic ring on one side of the tertiary alcohol and a bulky group on the other. The diazo was chosen as the first potential leaving group because of the different ways in which it can be activated.



Scheme 10: Synthesis of the Model Substrate

The synthesis of this model substrate was facile: An acetoacetic-type synthesis was performed, where the beta keto ester was first formed from the tetralone, followed by benzyl substitution and a decarboxylation to yield the α-benzyl substituted tetralone. From there, the enolate derived from ethyl diazo acetate was added into the ketone, forming the model substrate. A few grams of the ketone before

enolate addition were synthesized to fully explore this chemistry. This synthesis can be seen in **Scheme 10**.

With the diazo in place, the exploration began with Bronsted acid activation methods. Carbons with diazo functional groups are closer in reactivity to a Shrock carbene: the diazo group is weakly basic/nucleophilic first, and the resulting N_2 leaving group then makes the carbon center a highly electrophilic stabilized carbocation.[15]

Bronsted acids are the simplest way of activating these functional groups, and trifluoroacetic acid was used as the additive first. Even when controlled, this reaction produced an equal molar ratio of both alkyl and phenyl shift regioisomers of the rearrangement as well as the retro aldol product. This same behavior was seen with other Bronsted acids, so other activators were attempted.

Another source of diazo activation comes from electrophilic reagents. One such reagent is DBDMH (see **Scheme 11**), which along with a DABCO catalyst, activates the diazo for a semi pinacol rearrangement.[16] When the model substrate underwent this reaction, the resulting seven membered ring contained a bromine where the shift occured, which was removed with zinc metal to yield the phenyl shift regioisomer in 82% yield over 2 steps. This product's identity was confirmed by reducing the enol-keto tautomer with sodium borohydride and performing homo decoupling HNMR experiments. This regioisomer would yield the core structure of darwinolide if used on the real intermediate

The final method of activating diazo compounds involves lewis acidic metals. A review of their reactivity with diazo compounds in inducing these rearrangements

cited palladium, rhodium, copper, cobalt, zinc, and other metals as capable and facile, if stoichiometric.[17] Zinc was chosen first as the paper mentioning it only forming the desired regioisomer. Surprisingly, an equivalent of zinc bromide with the model substrate in DCM underwent a completely novel transformation, forming an alkyl shift regioisomer with a vinyl bromide instead of the expected β-keto ester (in enol form). This specific product was difficult to determine, requiring a crystal structure that can be seen in **Figure 7**. Absolute stereochemistry of the sample is not shown, but is noted to make it easier to understand the crystal structure.

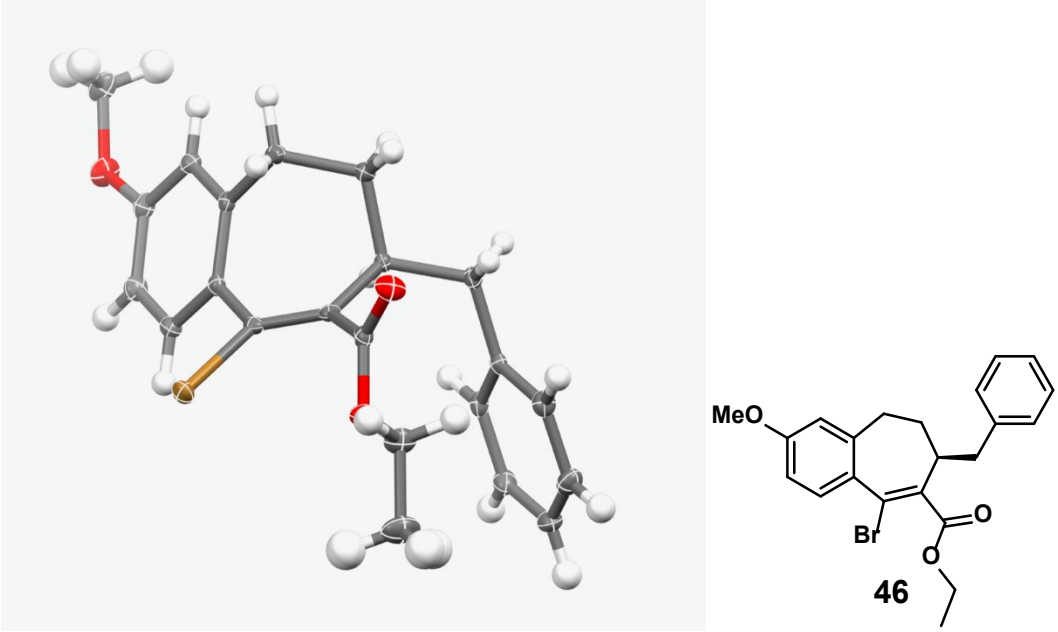
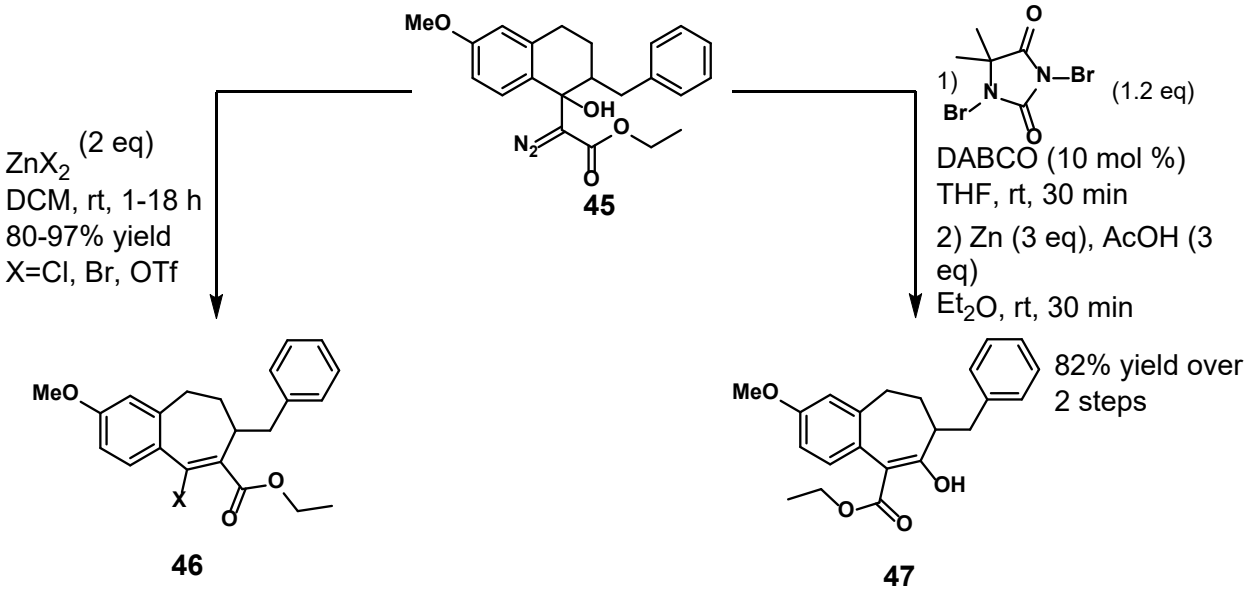


Figure 7: Crystal Structure of Zinc-Mediated Rearrangement Product

A brief investigation into this reaction showed that it could be done at room temperature in an hour with 2 equivalents of zinc bromide or zinc chloride to give the novel product in over 90% yield. If a zinc II salt was reactive, the anion of the salt became the attachment where the carbon-diazo bond was located. Zinc triflate

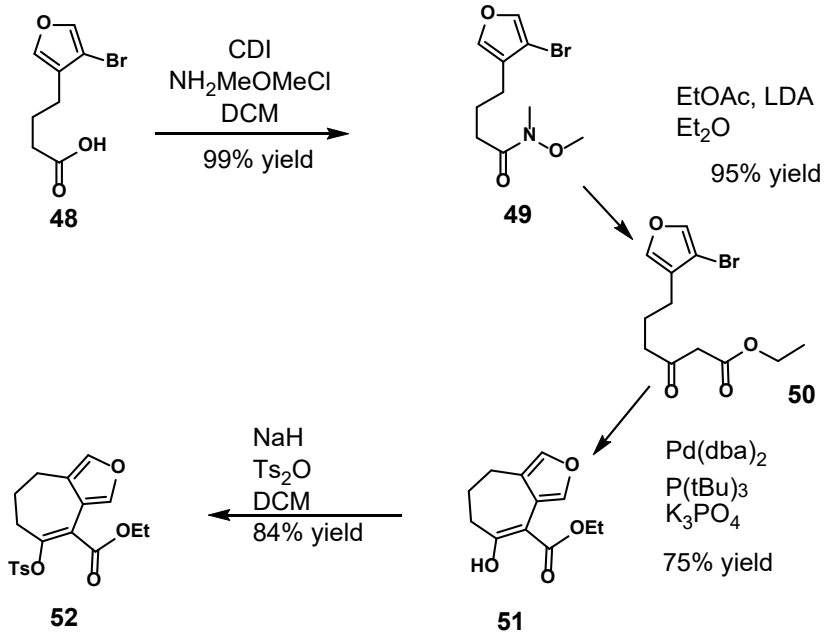
reacted to form the corresponding vinyl triflate, although the reaction was significantly slower, requiring an overnight reaction. A lower yield was observed compared to the halide salts due to partial hydrolysis of the triflate. The summary of the work on this model substrate can be seen in **Scheme 11**. Note that the mechanism of this reaction is unknown but is likely going through a zinc carbene intermediate, as zinc II salts are known to form carbenes when in the presence of a diazo compound. Whether the alcohol is substituted for a halide before or after the rearrangement is unknown.



Scheme 11: Summary of Diazo Rearrangements

Despite these exciting results, these reactions could not be tested on the true intermediate, as efforts to add the lithium enolate of ethyl diazoacetate proved unsuccessful. Halo acetic acids also proved difficult to add in, and rearrangements utilizing those products were much lower yielding on the model substrate. As such, this route to the seven membered ring was not further explored.

F: Seven membered ring formation: alpha arylation



Scheme 12: Seven-Membered Ring Formation Via α-Arylation

Another potential route was to use an earlier intermediate as the point of divergence. The acid after Ireland-Claisen was chosen, as it allowed for a two-carbon extension of the carbon scaffold and subsequent α-arylation explorations to occur. Starting from the acid **48**, an investigation was started to make the seven membered ring without the 1,3,3 trimethyl cyclohexyl group (leading to simpler spectra for analyses). Weinreb amide **49** was made from the acid quantitatively, and ethyl acetate was added into that amide in high yield to form the beta keto ester **50** needed for α-arylation. After looking into two common bases, KO^tBu and K_3PO_4, the phosphate base allowed the palladium catalyzed α-arylation to occur in full conversion.

The material that is currently lost is thought to be from purification, as the keto-enol tautomerization could cause a large amount of material to be lost on the column. A potential technique to alleviate this is to submit the crude material to tosylation or triflation to form the enol tosylate/triflate, as the tosylate **52** made from pure material is not lost on column. Mass spec, proton NMR, and carbon NMR give good evidence that the seven membered ring was made from this method. These results are summarized in **Scheme 12**. Methylation with either an iron/palladium cross coupling or cuprate addition is the next step, but has not yet been attempted.

G: Future studies and Conclusions

The efforts towards improving this synthesis and extending it to the entire family of bioactive natural products are ongoing. The core synthetic plans conceived in this project have the potential to make the entire family, but it is the job of future researchers to achieve that goal.

For darwinolide, the *alpha*-arylation reaction should be attempted on post Ireland-Claisen material with the 1,3,3-trimethylcyclohexyl unit attached with appropriate stereochemistry. Following that and a successful methylation of the enol tosylate or triflate, oxidation of the furan will bring the intermediate very closely aligned to the cadlinolide A synthesis. The one reaction that will need to be changed is the hydrogenation, as two out of the three alkene bonds need to be reduced. The likely candidate for this selectivity are nickel borohydrides, but work must be done in order to achieve this reaction. After that, a similar cyclization as in the cadlinolide A synthesis followed by a regioselective reduction and subsequent acylation will produce darwinolide.

Once darwinolide is synthesized by this pathway, the floodgates can open and many smaller projects can begin. A regioselective reduction followed by acylation can produce cadlinolide B and tetrahydroaplysulphurin. If the central 6-membered ring can be aromatized, potential syntheses of aplysulphurin and many of its semisynthetic membranoids can be attempted. There can then be further SAR studies on different parts of the scaffold and how those changes affect the bioactivities seen in the natural products. The work presented in this thesis is just the beginning of a wide variety of projects that can help jumpstart the next generation of therapeutics with this molecular scaffold. It is up to the readers of this work and its associated publication(s) to continue this goal.

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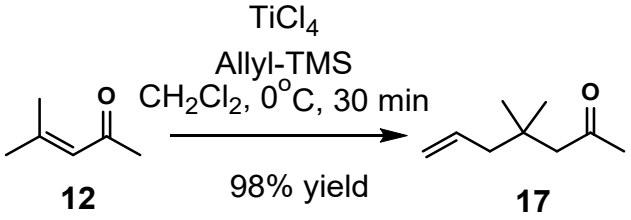
Appendix: Supporting Information

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware unless the reaction procedure states otherwise. Tetrahydrofuran (THF), and diethyl ether (Et_2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dimethoxyethane (DME) was distilled from sodium-benzophenone under an atmosphere of argon. Toluene was distilled from sodium in a continuous still under an atmosphere of argon. Dichloromethane, di-iso-propylamine, triethylamine, and acetonitrile were distilled from calcium hydride in a continuous still under an atmosphere of argon. Reaction temperature was controlled by IKA ETS-D4 fuzzy thermo couples. Analytical normal-phase thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F254 (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), and potassium permanganate staining. Normal-phase flash column chromatography was performed using 40-63 μm silica gel (EMD, Geduran, no. 1.11567.9026) as the stationary phase. Analytical reverse-phase thin-layer

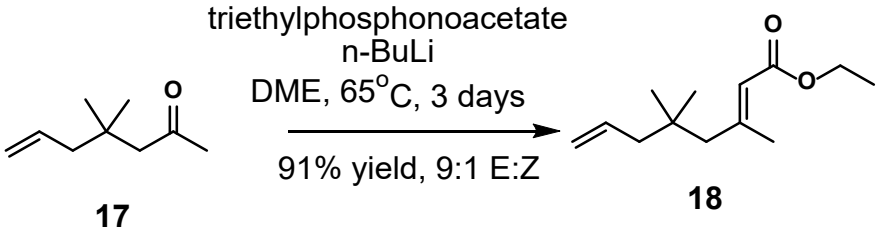
chromatography was performed using pre-coated TLC plates with Silica gel 60 RP-18 F254s (Merck, no. 1.15685.0001). Proton nuclear magnetic resonance spectra were recorded at 500 MHz on a Bruker Avance NEO spectrometer. Carbon nuclear magnetic resonance spectra were recorded at, 125 MHz on a Bruker Avance NEO spectrometer. All chemical shifts were reported in units relative to tetramethylsilane. X-ray crystallographic data were obtained by the X-ray Analytical Facility at the University of California, Santa Barbara. High-resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Irvine



12 **17**

4,4-dimethylhept-6-en-2-one: An oven-dried, two neck round bottom flask equipped with thermometer and addition funnel was charged with mesityl oxide (10 g, 102mmol) in CH_2Cl_2 (170 mL). The flask was cooled to -78 °C, and $TiCl_4$ (11.7 mL, 107 mmol) was added dropwise. After 10 minutes, a bright yellow suspension formed and the flask was warmed to 0 °C. An addition funnel was charged with allyl trimethyl silane (15.12 g, 132 mmol) dissolved in CH_2Cl_2 (170 mL), attached to the apparatus, and added at a rate slow enough for a stable temperature to be maintained. The flask was warmed to room temperature after the addition of the allyl trimethyl silane was complete. The reaction was quenched after 30 minutes with water (350 mL) and diluted with 1:1 ether: pentanes (350 mL). The layers were separated, and the aqueous layer was extracted with 1:1 ether: pentanes (3 x 100 mL). The organic layer was washed with sodium bicarbonate, and brine, dried over

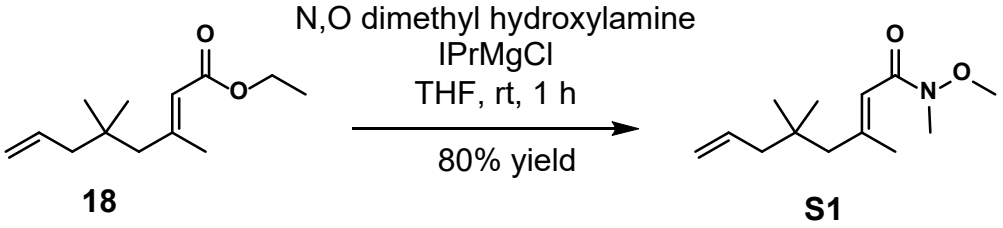
sodium sulfate, and concentrated *in vacuo* at 0°C. The crude residue was purified via column chromatography (1% Ether/Pentane) to afford the ketone **17** (14.24 g, 98% yield, 101.4 mmol) as a colorless oil. For best results, all concentrations should be done at 0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.9, 10.2, 7.5 Hz, 1H), 5.07 – 4.98 (m, 2H), 2.32 (s, 2H), 2.12 (s, 3H), 2.09 (d, *J* = 7.5 Hz, 2H), 1.00 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 134.9, 117.5, 53.3, 46.4, 33.5, 32.4, 27.1.



17 **18**

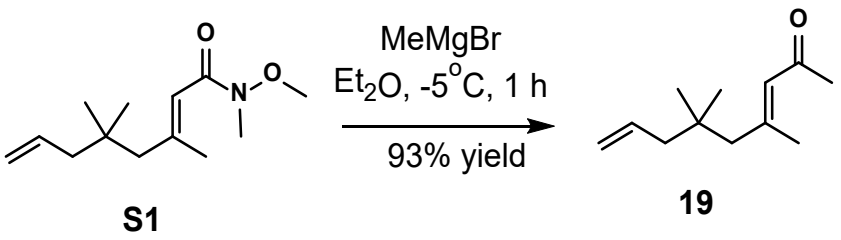
Ethyl (*E*)-3,5,5-trimethylocta-2,7-dienoate: *n*-Butyllithium (2.5 M in hexanes, 11.6 mL, 29.1 mmol)was added dropwise to a solution of triethyl phosphonoacetate (6.98 g, 31.1 mmol in glyme (24 mL) at 0 °C.. After 10 minutes the reaction was warmed up to room temperature, and a solution of ketone **17** (2.91 g, 20.75 mmol) in glyme (6 mL) was added. The reaction was heated to 65 °C for 3 days. The majority of DME was distilled away from the reaction flask under vacuum. The remaining crude mixture was diluted with ether(50 mL) and quenched with saturated aqueous ammonium chloride (50 mL).The layers were separated, and the aqueous layer was extracted with pentanes (3 x 50 mL). The organic layer was washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude oil was purified via column chromatography (1% ether/pentanes) to afford the vinyl ester **18** as a colorless oil (9:1 E:Z) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 – 5.76 (m, 1H), 5.61 (d, *J* = 1.2 Hz, 1H), 5.09 – 4.98 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.19 (d, *J* = 1.3

Hz, 3H), 2.06 (s, 2H), 1.99 (d, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 158.0, 135.0, 118.9, 117.4, 59.4, 52.8, 47.4, 27.1, 21.9, 14.3.



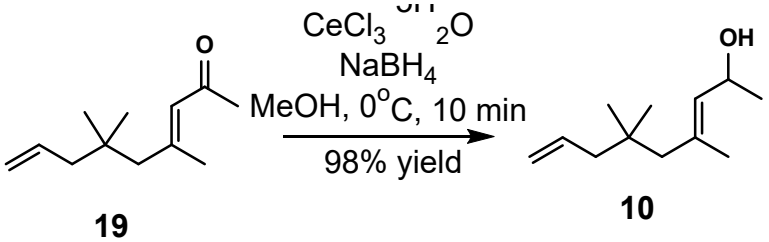
18 **S1**

(*E*)-*N*-Methoxy-N,3,5,5-tetramethylocta-2,7-dienamide: N,O, dimethyl hydroxylamine hydrochloride (9.9 g, 101 mmol) was added to a solution of vinyl ester **18** (10.7 g, 51 mmol) in THF(137 mL). The flask was cooled to 0 °C, and isopropyl magnesium chloride (2M in diethyl ether, 99 mL, 197 mmol) was added dropwise over 10 minutes. The reaction was then warmed to room temperature. After 45 minutes, the reaction was quenched with ammonium chloride (100 mL) and extracted with ethyl acetate (3 x 100 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude oil was purified and separated from the minor diastereomer via column chromatography (10% ethyl acetate/hexanes) to afford the vinyl amide **S1** (9.17 g, 80% yield, 40.7 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.83 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.08 – 4.97 (m, 2H), 3.66 (s, 3H), 3.20 (s, 3H), 2.16 (d, *J* = 1.4 Hz, 3H), 2.08 (s, 2H), 2.01 (d, *J* = 7.5 Hz, 2H), 0.92 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 154.5, 135.3, 117.4, 61.5, 53.0, 47.4, 34.9, 27.3, 21.9.



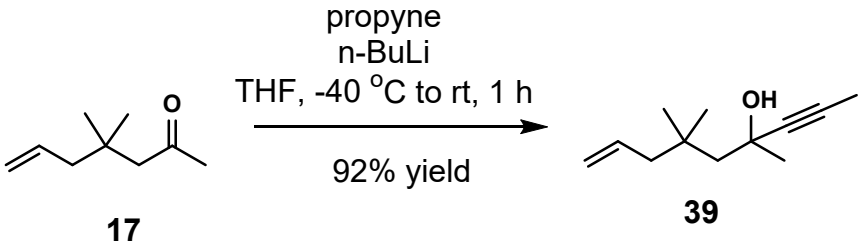
S1 **19**

(*E*)-4,6,6-trimethylnona-3,8-dien-2-one: Methyl magnesium bromide (3.0 M in diethyl ether, 25.4 mL, 76.2 mmol) was added dropwise to a solution of **S1** (5.72 g, 25.4 mmol) diethyl ether (85 mL) at -30 °C. After the addition was complete, the reaction was warmed to -5 °C. After 1 h, the reaction was quenched with concentrated ammonium chloride (50 mL), diluted with ether (50 mL), and extracted with 1:1 ether:hexanes (3 x 50 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude oil was purified via column chromatography (5% ether/pentanes) to afford the enone **19** (4.25 g, 93% yield, 23.6 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.10 – 4.96 (m, 2H), 2.17 (s, 3H), 2.16 (d, *J* = 1.3 Hz, 3H), 2.05 (d, *J* = 0.8 Hz, 2H), 1.99 (d, *J* = 7.4 Hz, 2H), 0.91 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.7, 135.0, 126.8, 117.4, 53.1, 47.4, 34.8, 31.9, 27.1, 22.5.



19 **10**

(E)-4,6,6-trimethylnona-3,8-dien-2-ol: Cerium chloride heptahydrate (10.4 g, 27.9mmol) was added to a solution of Enone **19** (5.00 g, 27.9 mmol) methanol (70 mL) at 0 °C and stirred until fully dissolved. Sodium borohydride (1.06 g, 27.9 mmol) was then added in 3 parts. After 10 minutes, the reaction was quenched with saturated ammonium chloride (50 mL) and diluted with 1:1 ether hexanes (50 mL). The layers were separated, and the aqueous layer was extracted with 1:1 ether:hexanes (3x 50 mL). The organic layer was washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified over a plug of silica (20% ethyl acetate/hexanes) to afford the allylic alcohol **10** (5.01 g, 98% yield, 27.4 mmol), as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.78 (m, 1H), 5.21 – 5.15 (m, 1H), 5.04 – 4.95 (m, 2H), 4.61 – 4.51 (m, 1H), 1.97 – 1.88 (m, 4H), 1.72 (s, 3H), 1.48 (s, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 2.8 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 134.9, 133.4, 64.8, 51.3, 47.3, 34.3, 27.2, 27.1, 23.5, 19.1.

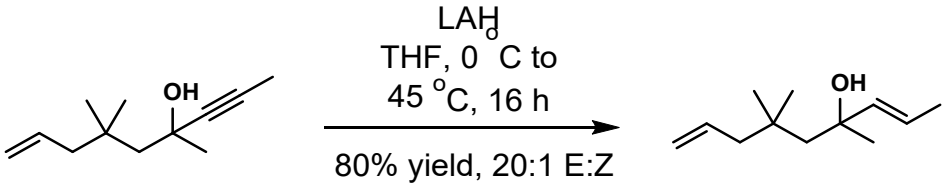


17 **39**

4,6,6-trimethylnon-8-en-2-yn-4-ol: *n*-Butyllithium (2.5 M in hexane, 71 mL, 178 mmol) was added to THF (110 mL) at -78° C under argon. A stream of propyne gas was blown over the surface of the solution for 10 minutes at a rate such that the indentation of the gas hitting the surface is observed (yellow color of the *n*-BuLi

solution fades and solution becomes cloudy). Addition of the gas was then stopped and the solution was stirred at the same temperature for a further 20 minutes. A solution of ketone **17** (10 g, 71.3 mmol) in THF (30 mL) was added dropwise to the solution at -78 °C. After 20 minutes, the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated ammonium chloride, diluted with ether, and extracted with 1:1 ether:hexanes (3x 100 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified via silica gel chromatography (10% ether/pentanes) to afford the propargylic alcohol **39** as a colorless oil (12.1 g, 94% yield, 67.1 mmol).

^{1}H NMR (500 MHz, CDCl 3) δ 5.86 (ddt, J = 16.8, 10.2, 7.4 Hz, 1H), 5.07 – 4.97 (m, 2H), 2.15 (ddt, J = 7.5, 6.4, 1.2 Hz, 2H), 1.83 (s, 1H), 1.82 (s, 3H), 1.63 (d, J = 1.5 Hz, 2H), 1.48 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H). 13 C NMR (126 MHz, $CDCl_3$) δ 135.8, 116.9, 83.9, 80.3, 67.5, 52.7, 48.0, 33.9, 28.1, 28.0, 3.5.

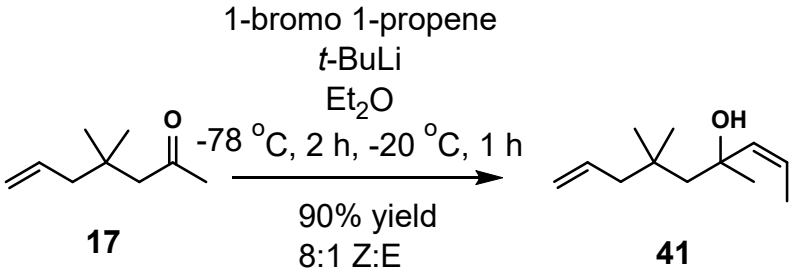


39 **40**

(E)-4,6,6-trimethylnona-2,8-dien-4-ol: A solution of the propargylic alcohol **39** (11.2 g, 61.9 mmol) in THF (40 mL) was added to a suspension of lithium aluminum hydride (2.3 g, 61.9 mmol) in THF (80 mL) at 0 °C, at such a rate to control effervescence. The ice water bath was removed and the reaction mixture was warmed naturally to room temperature. The reaction mixture was then heated to 45

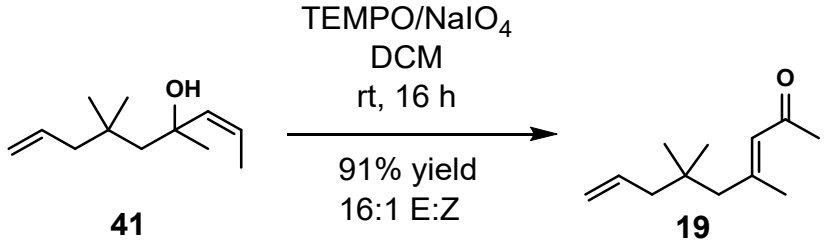
°C for 16 h. The reaction was cooled to 0°C, and diluted with ether (200 mL). Water (2.3 mL) was slowly added, followed by 3 M NaOH (2.3 mL), and again with water (6.9 mL) (careful, violent release of gas and exotherm). The flask was warmed to room temperature and stirred for 15 minutes. Magnesium sulfate was then added, and the flask was stirred for an additional 15 minutes. The resulting solids were filtered, washed with diethyl ether, and the filtrate was concentrated under vacuum. The crude oil was purified via column chromatography (10% diethyl ether/hexanes to 20% diethyl ether/hexanes) to afford the tertiary allylic alcohol **40** as a colorless oil (7.9 g, 71% yield, E/Z > 20:1, 43.8 mmol).

^{1}H NMR (500 MHz, CDCl 3) δ 5.83 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.63 – 5.53 (m, 2H), 5.05 – 4.95 (m, 2H), 2.06 – 2.01 (m, 2H), 1.70 (d, J = 4.8 Hz, 3H), 1.59 – 1.51 (m, 2H), 1.40 (s, 1H), 1.28 (s, 3H), 0.96 (d, J = 1.4 Hz, 6H). ^{13}C NMR (126 MHz, CDCl 3) δ 139.4, 135.9, 120.7, 116.8, 73.9, 52.7, 48.4, 34.1, 31.6, 28.5, 28.4, 17.5.



(Z)-4,6,6-trimethylnona-2,8-dien-4-ol: *t*-BuLi (1.5 M in pentanes, 17.1 mL, 25.7 mmol) was added slowly to a solution of 1-bromo-1 propene (9:1 *Z:E* mixture of isomers,1.10 mL, 12.8 mmol) in diethyl ether (16 mL) at -78 °C. After 2 h, the solution was warmed to 0 °C. After 30 minutes, the solution was cooled to -78 °C,

and ketone **17** (1.00 g, 7.13 mmol) was added dropwise. After 2 h, the solution was warmed to -20 ^{o}C. After an h, the solution was quenched with saturated sodium bicarbonate (30 mL), diluted with 1:1 hexanes:ether (30 mL), and extracted with 1:1 ether:hexanes (3x 30 mL). The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude oil was purified via column chromatography (3% ether/hexanes) to afford the allylic alcohol **41** as a pair of diastereomers: Z (1.09 g, 84% yield 5.98 mmols), E (0.17 g, 13% yield, 0.93 mmol). ^{1}H NMR (500 MHz, CDCl3) δ 5.84 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.47 (dd, J = 11.9, 1.8 Hz, 1H), 5.36 (dq, J = 11.9, 7.1 Hz, 1H), 5.05 – 4.97 (m, 2H), 2.08 (h, J = 6.8 Hz, 2H), 1.84 (dd, J = 7.2, 1.7 Hz, 3H), 1.68 – 1.56 (m, 2H), 1.36 (s, 3H), 1.01 (d, J = 5.2 Hz, 6H).^{13}C NMR (126 MHz, CDCl3) δ 138.2, 136.0, 123.2, 116.9, 75.7, 53.2, 48.7, 34.2, 32.3, 28.6, 28.6, 14.0.



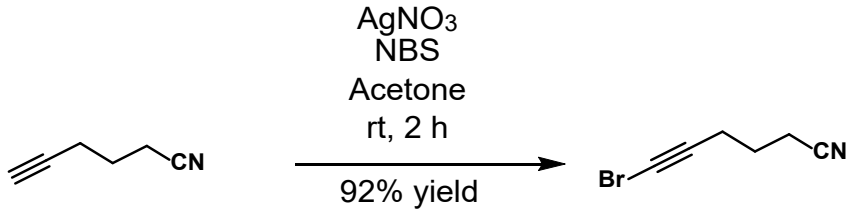
41 **19**

(*E*)-4,6,6-trimethylnona-3,8-dien-2-one: $NaIO_4$-SiO_2 (1.53g/mmol, 36.6 g, 23.99 mmol) was added to a stirring solution of the *Z*-tertiary allylic alcohol **41** (1.09 g, 5.98 mmol) in dichloromethane (51.0 mL) followed by TEMPO (0.0930 g, 0.598 mmol) and the resulting slurry was stirred vigorously for 48 hr. The solids were filtered off and washed thoroughly with diethyl ether, and the filtrate was concentrated. The crude oil contained a mixture of diastereomers (15:1 *E/Z*), and

the *E*-isomer was isolated via silica gel chromatography (2% ether/hexanes) to give ketone **19** (0.992 g, 92% yield, 5.50 mmol).

(E)-4,6,6-trimethylnona-3,8-dien-2-one: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.10 – 4.96 (m, 2H), 2.17 (s, 3H), 2.16 (d, *J* = 1.3 Hz, 3H), 2.05 (d, *J* = 0.8 Hz, 2H), 1.99 (d, *J* = 7.4 Hz, 2H), 0.91 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.7, 135.0, 126.8, 117.4, 53.1, 47.4, 34.8, 31.9, 27.1, 22.5.

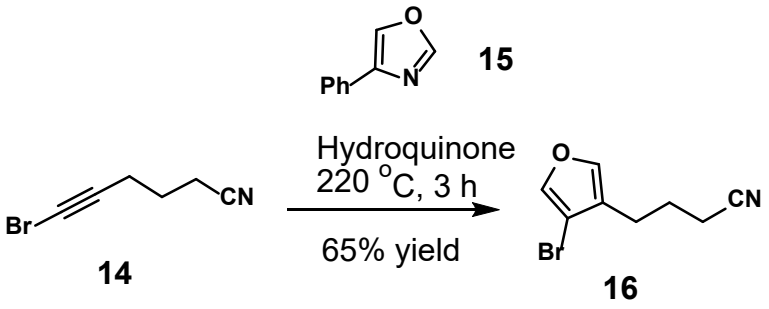
(Z)-4,6,6-trimethylnona-3,8-dien-2-one: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.95 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 6.15 – 6.07 (m, 2H), 3.73 (s, 2H), 3.23 (s, 3H), 3.13 (d, *J* = 7.4 Hz, 2H), 3.00 (s, 3H), 2.00 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 156.6, 135.5, 126.7, 117.1, 48.2, 43.7, 35.6, 32.1, 28.1, 27.3.



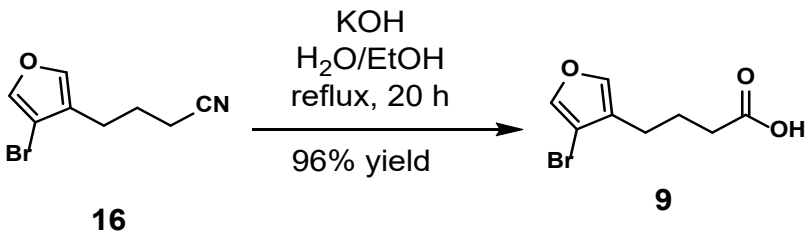
13 **14**

6-bromohex-5-ynenitrile: N-bromo succinimide (19.3 g, 108.24 mmol) and silver nitrate (1.53 g, 9.02 mmol) were added in quick succession to a solution of **13** (8.4 g, 90.2 mmol) in acetone (104 mL), and the reaction was stirred for 2 h. Upon completion of the reaction validated by H-NMR, the reaction was concentrated to half the volume *in vacuo* and filtered over celite. The resulting solution was concentrated *in vacuo*, and dissolved in 1:1 ether hexanes (100 mL) and water (100 mL). The aqueous solution was extracted with 1:1 ether:hexanes (3x 100 mL). The mixture was washed brine, dried over sodium sulfate, and concentrated *in vacuo*.

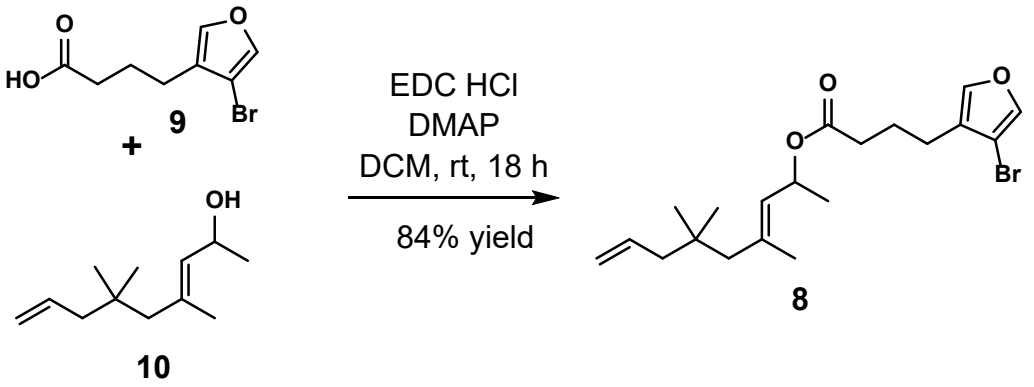
The residue was purified via column chromatography (15% ethyl acetate/hexanes) to afford the brominated cyano alkyne **14** (14.2 g, 92% yield, 82.5 mmol) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (t, *J* = 7.1 Hz, 2H), 2.41 (t, *J* = 6.7 Hz, 2H), 1.88 (p, *J* = 6.9 Hz, 2H).^{13}C NMR (126 MHz, CDCl3) δ 118.8, 77.4, 40.2, 24.1, 18.7, 16.0.



4-(4-bromofuran-3-yl)butanenitrile: Bromo-alkyne **14** (3.50 g, 20.4 mmol), 4-phenyl oxazole **15** (13.3 mL, 102 mmol), and hydroquinone (0.230 mg, 2.00 mmol) were added to a microwave vial. The vial was sparged with argon for 20 minutes, covered with aluminum foil, and heated in a dark hood at 220 °C for 3 h. Once cooled, the resulting black oil was purified via column chromatography (0.5% ethyl acetate/hexanes) to afford the brominated furan **16** (2.87 g, 65% yield, 13.4 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.25 (m, 1H), 2.61 – 2.55 (m, 2H), 2.37 (t, *J* = 7.1 Hz, 2H), 1.95 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 141.4, 140.0, 122.8, 119.1, 102.1, 24.5, 22.5, 16.3.

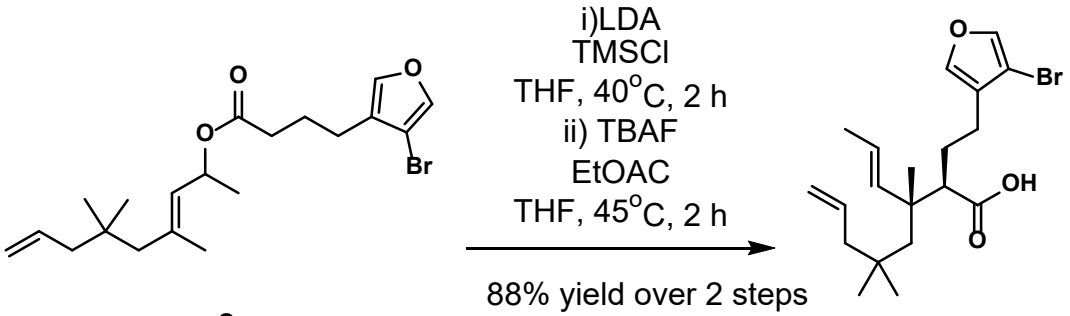


4-(4-bromofuran-3-yl)butanoic acid: . KOH (6.30 g, 112 mmol) was added to a solution of **16** (4.00 g, 18.6 mmol) in 1:1 EtOH:H_2O (94 mL), and the reaction was heated at reflux for 20 h. Upon completion of the reaction, the basic solution was extracted with ether (3x 100 mL). The resulting basic aqueous layer was quenched with concentrated HCL (~10 mL) in an ice bath until the pH was 1-2. The aqeuous solution was extracted with ethyl acetate (4x 100 mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude oil or solid was purified via column chromatography (20% ethyl acetate/hexanes w/ 0.1% acetic acid) or recrystallized from hexanes to afford the furyl acid **9** (4.15 g, 96% yield, 17.8 mmol) as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.91 (bs, 1H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.93 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 179.6, 141.0, 139.7, 124.1, 102.4, 33.1, 23.8, 22.9.



(S,E)-4,6,6-trimethylnona-3,8-dien-2-yl 4-(4-bromofuran-3-yl)butanoate: N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (8.82 g, 46 mmol) was added to a solution of acid **9** (5.36 g, 23 mmol) in CH_2Cl_2 (75 mL). A solution of allylic alcohol **10** (4.97 g, 27.26 mmol) in CH_2Cl_2 (75 mL) was then added to the flask, followed by 4-Dimethylaminopyridine (0.843 g , 6.9 mmol). After 18 h, the

reaction was diluted with CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x 50 mL). The aqueous layer was washed with water, brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude oil was purified via column chromatography (5% ethyl acetate/hexanes) to afford the ester **8** (7.68 g, 84% yield, 19.3 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.7 Hz, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 7.4 Hz, 1H), 5.59 (dq, *J* = 8.9, 6.4 Hz, 1H), 5.14 – 5.10 (m, 1H), 5.05 – 4.96 (m, 2H), 2.44 – 2.40 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.95 (dt, *J* = 7.5, 1.2 Hz, 2H), 1.93 – 1.90 (m, 2H), 1.88 (t, *J* = 7.5 Hz, 2H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 140.9, 139.7, 137.0, 135.6, 128.8, 124.4, 117.0, 102.5, 68.2, 51.3, 47.3, 34.4, 33.8, 27.2, 27.2, 24.2, 23.0, 20.8, 19.4.



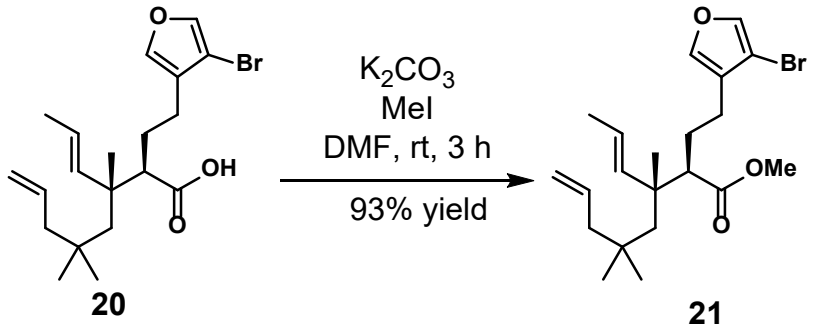
8 **20**

Acid 20: n-BuLi (2.6 M in hexane, 8.60 mL, 22.5 mmol) was added dropwise to a solution of HMDS (4.9 mL, 23.2 mmol) in toluene (60.0 mL) at 0 °C and stirred at the same temperature for 10 min before cooling the mixture to -78 °C. A solution of ester **8** (2.976 g, 7.490 mmol) in toluene (15.0 mL) was added dropwise to the solution of LiHMDS over 10 min at -78 °C and stirred at this temperature for 0.5 hr. TMSCl (2.90 mL, 22.5 mmol) was added to the reaction mixture over 5 min at -78

°C and stirred for a further 0.5 hr at the same temperature. The reaction mixture was then warmed to 0 °C and stirred for 1 hr, then warmed to 23 °C and stirred for a further 1 hr. The reaction was diluted with diethyl ether (75.0 mL) and quenched with sat. aq. $NaHCO_3$ (75.0 mL). The pH of the aqueous layer was adjusted to pH = 2, and extracted with ethyl acetate (3x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by silica gel chromatography (5% EtOAc/Hex to 0.1% AcOH/10% EtOAc/Hex) to afford acid **20** (2.497 g, 84% yield, 6.284 mmol) as a > 25:1 ratio of diastereomers.

^{1}H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 1.7 Hz, 1H), 5.78 (ddt, J = 17.4, 10.2, 7.4 Hz, 1H), 5.35 (dq, J = 15.7, 6.2 Hz, 1H), 5.23 (dd, J = 15.6, 1.7 Hz, 1H), 5.04 – 4.91 (m, 2H), 2.42 (ddd, J = 14.5, 8.4, 5.7 Hz, 1H), 2.25 (dt, J = 15.2, 8.1 Hz, 1H), 2.15 (dd, J = 9.9, 4.0 Hz, 1H), 1.96 (d, J = 7.5 Hz, 2H), 1.80 – 1.67 (m, 2H), 1.70 (d, J = 6.2 Hz, 1H), 1.54 (d, J = 14.5 Hz, 1H), 1.36 (d, J = 14.3 Hz, 1H), 1.20 (s, 3H), 0.89 (s, 6H).

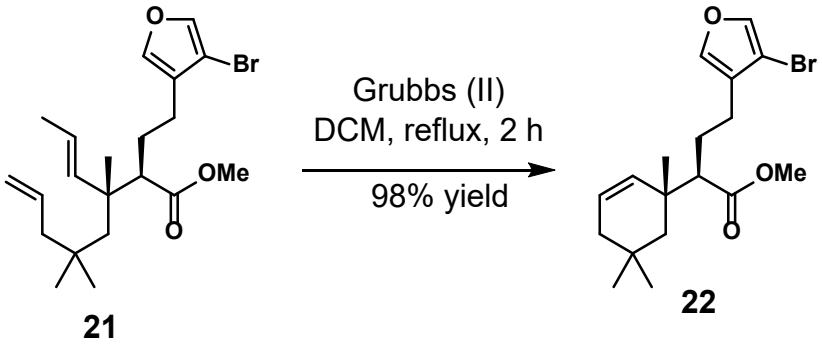
^{13}C NMR (126 MHz, CDCl3) δ 180.94, 180.93, 141.15, 140.09, 138.74, 135.87, 124.31, 123.51, 117.14, 102.59, 56.63, 50.84, 49.42, 42.90, 35.18, 28.98, 28.92, 26.71, 22.56, 19.26, 18.24.



20 **21**

Diene 21: Potassium Carbonate (0.280 g, 2 mmol) was added to a stirring solution of acid **20** (0.800 g, 2 mmol) in DMF (20 mL) at room temperature with a drying tube. Methyl Iodide (0.150 mL, 2.4 mmol) was then added dropwise. After 3 h the solution was diluted with Hexane (30 mL) and water (30 mL). The layers were separated, and the aqueous layer was extracted with hexanes (3x 30 mL). The organic layer was washed with water (3x 30 mL), brine, dried with sodium sulfate, and concentrated *in vacuo*. The crude oil was purified via column chromatography (5% ethyl acetate/hexanes) to afford the ester **21** (0.768 g, 93% yield, 1.87 mmol) as a colorless oil.

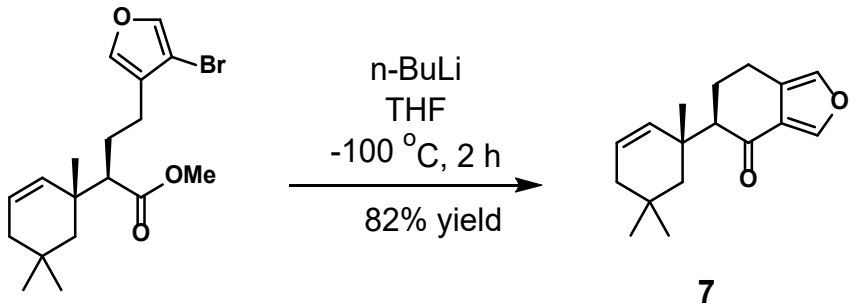
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.8 Hz, 1H), 7.14 (d, *J* = 1.6 Hz, 1H), 5.77 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.33 (dq, *J* = 15.7, 6.3 Hz, 1H), 5.21 (dq, *J* = 15.4, 1.5 Hz, 1H), 5.03 – 4.91 (m, 2H), 3.67 (s, 3H), 2.34 – 2.27 (m, 1H), 2.20 – 2.11 (m, 2H), 1.93 (dt, *J* = 7.4, 1.2 Hz, 2H), 1.81 – 1.65 (m, 2H), 1.69 (m, 3H), 1.46 (d, *J* = 14.5 Hz, 1H), 1.20 (d, *J* = 14.4 Hz, 1H), 1.16 (s, 3H), 0.88 (s, 6H). 13C NMR (126 MHz, CDCl3) δ 175.67, 141.07, 139.96, 139.01, 135.97, 124.45, 123.16, 116.99, 102.64, 56.71, 51.22, 50.80, 49.69, 43.12, 35.10, 28.97, 28.88, 26.73, 22.61, 19.15, 18.22.



21 **22**

Methyl Ester 22: Ester **21** (1.34g, 3.26 mmol) was dissolved in DCM (130 mL) and sparged with argon for 1 h. Grubbs II (0.135 g, 0.163 mmol) was then added and the solution was stirred at reflux. After 2 h, the solution was concentrated under vacuum and purified via column chromatography (1% ethyl acetate/hexanes) to afford the ester **22** (1.20g, 99% yield, 3.26 mmol) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.8 Hz, 1H), 7.17 (s, 0H), 5.62 (ddd, *J* = 10.2, 5.8, 2.2 Hz, 1H), 5.57 – 5.50 (m, 1H), 3.64 (s, 3H), 2.39 – 2.29 (m, 1H), 2.26 – 2.16 (m, 2H), 1.90 (dddd, *J* = 13.8, 11.6, 9.0, 5.1 Hz, 1H), 1.76 (ddt, *J* = 6.8, 4.2, 2.7 Hz, 1H), 1.73 – 1.61 (m, 2H), 1.15 (ddd, *J* = 13.8, 2.4, 1.2 Hz, 1H), 1.07 (s, 3H), 0.94 (s, 7H). ^{13}C NMR (126 MHz, CDCl3) δ 175.17, 140.96, 139.81, 132.25, 125.24, 124.28, 102.41, 56.64, 50.97, 44.66, 38.12, 37.74, 32.65, 29.89, 27.89, 26.52, 25.81, 22.62.



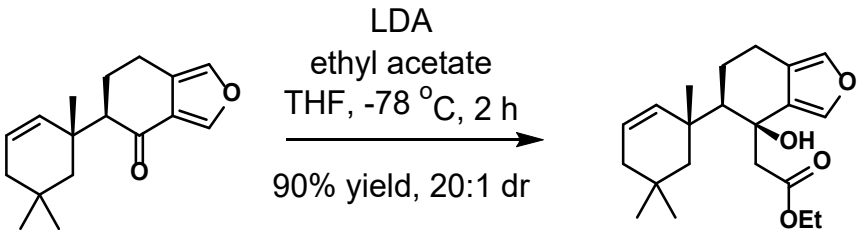
22 **7**

Ketone 7: *n*-BuLi (2.5 M in hexane, 1.45 mL, 3.63 mmol) was added dropwise to a solution of ester **22** (0.659g, 1.78 mmol) in THF (120 mL) over 20 min while maintaining the internal temperature of the solution between -90 °C and -100 °C. After stirring the solution for 30 min at -100 °C, the reaction mixture was warmed to -80 °C and quenched with acetic acid (0.107 mL, 1.78 mmol). The mixture was

warmed to 23 °C and saturated aqueous sodium bicarbonate (50 mL) was added. The aqueous layer was extracted with ethyl acetate (3x50 mL) and the organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography (0.5% EtOAc/Hex to 5% EtOAc/Hex) to give ketone **7** (0.346 g, 75% yield, 1.34 mmol) as a single diastereomer.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J*= 1.5 Hz, 1H), 7.21 (m, 1H), 5.65 (ddd *J*= 10.1, 5.3, 2.7, 1H), 5.57 (ddt J= 10.2, 2.5, 1.1 Hz, 1H), 2.86 (dt *J*= 15.9, 4.8 Hz, 1H), 2.59 (dddd *J*= 15.8, 10.7, 4.8, 1.8 Hz, 1H), 2.39 (dd *J*= 10.7, 3.7 Hz, 1H), 2.27 (ddt *J*=13.5, 4.9, 3.7 Hz, 1H), 1.97 (ddt *J*= 13.4, 10.6, 4.4 Hz, 1H), 1.86 (dt *J*=16.8, 2.8 Hz, 1H), 1.80 (d *J*= 14.0 Hz, 1H), 1.76-1.70 (m, 1H), 1.59 (ddd *J*= 14.0, 2.0, 1.0 Hz, 1 H), 1.14 (s, 3H), 0.98 (s, 3H) 0.96 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ

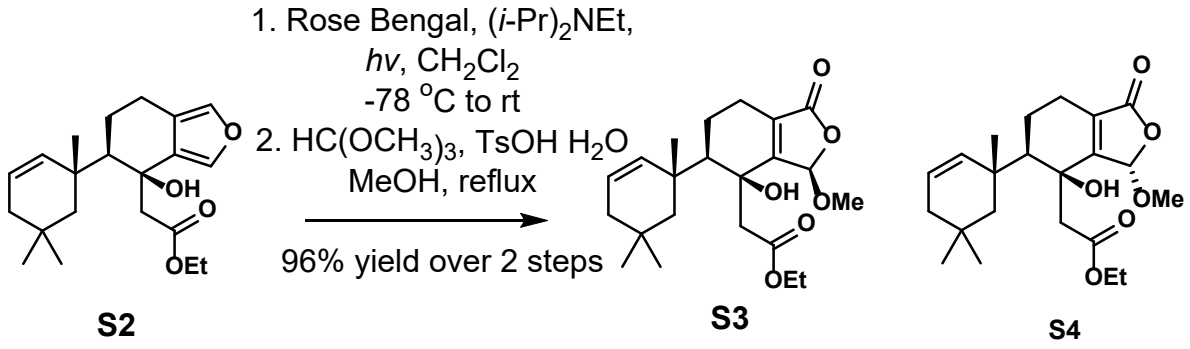


7 **S2**

Ethyl ester S2: *n*-BuLi (2.5 M in hexane, 3.7 mL, 9.35 mmol) was added to a stirring solution of diisopropylamine (1.32 mL, 9.35 mmol) in THF (40 mL) at 0 °C and stirred for 10 min before cooling the mixture to -78 °C. Ethyl acetate (0.913 mL) was added dropwise to the solution of LDA at -78 °C and stirred for 0.5 hr. A solution of ketone **7** (0.345 g, 1.335 mmol) in THF (10.0 mL) was added to the

lithiated ethyl acetate at -78 °C and stirred for 4 hr. The reaction mixture was quenched with AcOH (1.10 mL, 18.7 mmol) at -78 °C. Water was added (40 mL) and the mixture was extracted with EtOAc (3x30 mL). The organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over sodium sulfate and concentrated. The crude product was purified by silica gel chromatography (1% EtOAc/Hex to 10% EtOAc/Hex) to give ethyl ester **S2** (416.0 mg, 90% yield, 0.120 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 1.5 Hz, 1H), 5.73 (dd, J = 10.2, 2.8 Hz, 1H), 5.68 (ddd, J = 10.1, 5.9, 2.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.69 (s, 1H), 3.00 (d, J = 15.5 Hz, 1H), 2.89 (d, J = 15.5 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.40 (dddd, J = 15.8, 7.3, 5.2, 1.6 Hz, 1H), 2.09 (d, J = 13.9 Hz, 1H), 2.00 – 1.92 (m, 2H), 1.87 – 1.79 (m, 2H), 1.68 (ddd, J = 16.7, 6.0, 2.3 Hz, 1H), 1.22 (t, J = 7.1 Hz, 4H), 1.17 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H). LRMS (ESI) calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.20, found 369.2



S2 **S3** **S4**

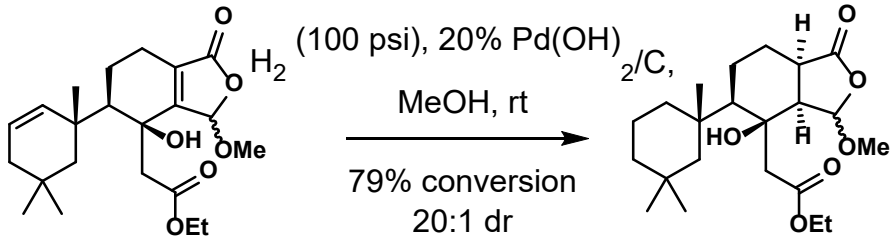
γ-methoxy butenolide S3 and S4: Rose Bengal (7.0 mg, 0.00720 mmol) was added to a solution of methyl ester **S2** (50.0 mg, 0.144 mmol) in CH_2Cl_2 (15.0 ml) followed by *i*-Pr_2NEt (0.250 mL, 1.44 mmol) and the suspension was cooled to -78 °C. Oxygen was bubbled through the solution for 5 min, then the suspension was

irradiated (Kessel Lamp, 100% white/100% intensity) for 20 min while continuing to bubble oxygen through the solution. Oxygen delivery and irradiation were halted and the solution was allowed to warm to 23 °C and stir for 20 min at this temperature. Aqueous $NaHSO_4$ (2 M, 15 mL) was added followed by EtOAc (30 mL). The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography (40% EtOAc/Hex) to give an inseparable, 2:1 mixture of γ-hydroxy butenolide epimers (54.0 mg, 99% yield, 0.143 mmol).

A solution of the γ-hydroxy butenolide (54.0 mg, 0.143 mmol), $TsOH•H_2O$ (27.0 mg, 0.143 mmol), and trimethyl orthoformate (34 µL, 0.315 mmol) in CH_3OH (14.0 mL) was heated to reflux for 4 hr. The reaction mixture was cooled to 23 °C then concentrated and resuspended in EtOAc (20 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (2x20 mL), brine, dried over Na_2SO_4 and concentrated. The crude residue contained a 3:2 mixture of epimers which were separated and purified by silica gel chromatography to give γ-methoxy butenolide **S3** (34.0 mg, 60% yield, 0.0866 mmol) and γ-methoxy butenolide **S4** (20.0 mg, 36% yield, 0.0510 mmol).

γ-methoxy butenolide S3: ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (d, J = 2.4 Hz, 1H), 5.84 – 5.79 (m, 1H), 5.72 – 5.64 (m, 1H), 4.16 – 4.05 (m, 2H), 3.71 (d, J = 14.9 Hz, 1H), 3.64 (s, 3H), 2.88 (d, J = 1.2 Hz, 1H), 2.63 (d, J = 14.9 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.17 (d, J = 13.9 Hz, 2H), 2.06 – 1.96 (m, 1H), 1.94 – 1.87 (m, 1H), 1.83 (d, J = 17.3 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.61 (d, J = 11.4 Hz, 1H), 1.25 – 1.21 (m, 5H), 1.15 (d, J = 12.1 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{32}O_6Na$ $[M+Na]^+$ 415.21, found 415.3

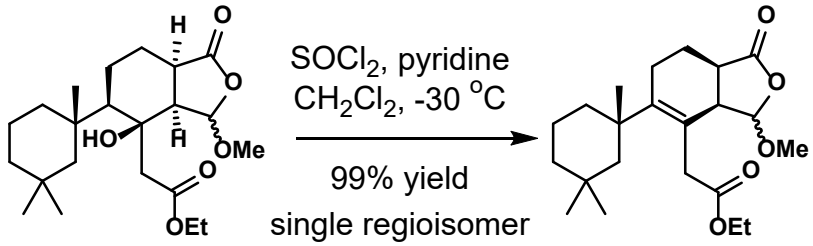
γ-methoxy butenolide S4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.83 (m, 1H), 5.67 (td, J = 7.2, 3.5 Hz, 1H), 5.59 (d, J = 10.2 Hz, 1H), 4.37 (s, 1H), 4.21 – 4.15 (m, 2H), 3.63 (s, 3H), 3.09 (d, J = 16.7 Hz, 1H), 2.78 (d, J = 16.7 Hz, 1H), 2.31 – 2.14 (m, 3H), 1.99 (t, J = 4.4 Hz, 1H), 1.91 (d, J = 13.6 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.68 (dd, J = 16.7, 5.9 Hz, 1H), 1.32 – 1.20 (m, 1H), 1.30 (t, J = 6.9, 3H), 1.13 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{32}O_6Na$ $[M+Na]^+$ 415.21, found 415.3



Tertiary alcohol S6: A suspension of γ-methoxy butenolide **S5** (20.0 mg, 0.0510 mmol) and 20% $Pd(OH)_2/C$ (20.0 mg, 100 wt%) in CH_3OH (1.7 mL) was placed under an atmosphere of H_2 (100 psi) and stirred vigorously at 23 °C for 48 hr. The solid was separated from the solution by filtration with a syringe PTFE filter and the filtrate was concentrated to give a clean sample of tertiary alcohol **S6** (16.0 mg, 79% yield, 0.0404 mmol) as a single diastereomer which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (d, J = 2.4 Hz, 1H), 4.26 – 4.10 (m, 2H), 3.48 (s, 3H), 3.21 (s, 1H), 2.89 (d, J = 17.4 Hz, 1H), 2.86 – 2.80 (m, 1H), 2.75 (d, J = 17.4 Hz, 1H), 2.72 – 2.67 (m, 1H), 2.14 (dt, J = 13.5, 4.5 Hz, 1H), 1.72 (m, 2H), 1.63 (m, 1H), 1.57 (m, 2H), 1.49 – 1.38 (m, 2H), 1.37 – 1.27 (m, 5H), 1.17 (d, J = 13.3

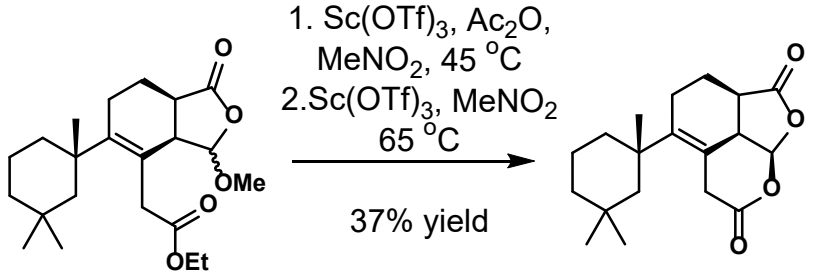
Hz, 1H), 1.09 (s, 3H), 1.01 (m, 2H), 0.96 (s, 3H), 0.85 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{36}O_6Na$ $[M+Na]^+$ 419.51, found 419.3



S6 **S7**

Methoxylactone S7: Thionyl chloride (73.0 µL, 1.010 mmol) was added dropwise to a stirring solution of pyridine (0.330 mL, 4.04 mmol) and tertiary alcohol **S6** (16.0 mg, 0.404 mmol) in CH_2Cl_2 (4.0 mL) at -30 °C and stirred for 2 hr at the same temperature. The reaction was quenched with methanol (41.0 µL, 1.01 mmol) and diluted with hexane (20 mL). The solution was washed with aqueous $NaHSO_4$ (pH = 3, 2x10 mL), brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (5% EtOAc/Hex to 7% EtOAc/Hex) to give methoxylactone **S7** (15.0 mg, 99% yield, 0.0396 mmol) as a single regioisomer.

^1H NMR (600 MHz, $CDCl_3$) δ 5.03 (d, J = 1.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.70 (d, J = 16.8 Hz, 1H), 3.49 (s, 3H), 3.02 (m, 1H), 2.98 (m, 1H), 2.93 (d, J = 16.6 Hz, 1H), 2.24 – 2.12 (m, 2H), 2.07 (dq, J = 12.4, 4.0 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.61 – 1.42 (m, 3H), 1.32 – 1.24 (m, 4H), 1.21 – 1.15 (m, 2H), 1.00 (s, 3H), 0.99 (d, J = 16.6, 1H), 0.85 (s, 3H), 0.78 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.3

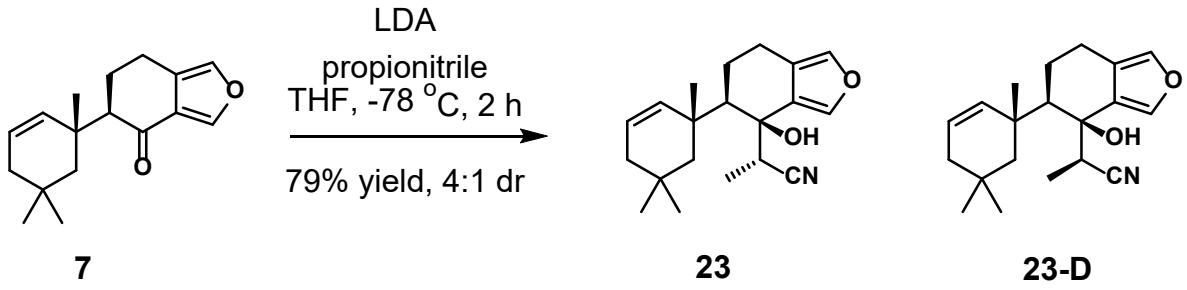


S7 **S8**

(±)-desmethyl cadlinolide A: $Sc(OTf)_3$ (33.0 mg, 0.0677 mmol) was added to a stirring solution of methoxylactone **S7** (16.0 mg, 0.0423 mmol) and Ac_2O (0.20 mL, 2.12 mmol) in nitromethane (5.3 mL) at 23 °C. The reaction mixture was warmed to 45 °C and stirred for 1.5 hr. The mixture was cooled to 23 °C and concentrated. The crude residue was redissolved in EtOAc/Hexane (3:7 v/v, 10 mL) and washed with H_2O (2x 10 mL), brine, dried over Na_2SO_4 and concentrated.

The crude product was redissolved in nitromethane (5.3 mL) and $Sc(OTf)_3$ (33.0 mg, 0.0677 mmol) was added. The reaction mixture was heated to 65 °C for 3 hr. The mixture was cooled to 23 °C and concentrated. The crude product was isolated by silica gel chromatography to give (±)-desmethyl cadlinolide A (5.0 mg, 37% yield, 0.0157 mmol).

^1H NMR (600 MHz, $CDCl_3$) δ 6.12 (d, J = 5.2 Hz, 1H), 4.17 (d, J = 17.1 Hz, 1H), 3.20 (dp, J = 7.3, 1.9 Hz, 1H), 3.08 (dt, J = 7.1, 4.4 Hz, 1H), 2.92 (dtd, J = 17.1, 2.8, 1.4 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.23 – 2.11 (m, 2H), 1.87 (dt, J = 9.0, 5.1 Hz, 1H), 1.75 (d, J = 14.0 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.61 – 1.45 (m, 2H), 1.34 – 1.16 (m, 4H), 1.14 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H). LRMS (ESI) calcd for $C_{19}H_{25}O_4$ $[M-H]^-$ 317.18 and $C_{20}H_{30}NaO_5$ $[M+CH_3OH+Na]^+$ 373.2, found 317.3 and 373.3.



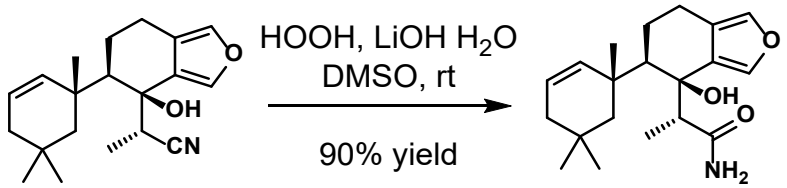
7 **23** **23-D**

Nitrile 23 and 23-D: *n*-BuLi (2.5 M in hexane, 1.50 mL, 3.87 mmol) was added to a stirring solution of diisopropylamine (0.550 mL, 3.87 mmol) in THF (34 mL) at 0 °C and stirred for 10 min before cooling the mixture to -78 °C. Propionitrile (0.270 mL) was added dropwise to the solution of LDA at -78 °C and stirred for 0.5 hr. A solution of ketone **7** (0.200 g, 0.774 mmol) in THF (6.0 mL) was added to the lithiated propionitrile at -78 °C and stirred for 10 min. The reaction mixture was warmed to 0 °C and quenched with AcOH (0.45 mL, 7.74 mmol). Water was added and the mixture was extracted with EtOAc (3x20 mL). The organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude product contained a 4:1 mixture of diastereomers which were separated and purified by silica gel chromatography (3% EtOAc/Hex to 5% EtOAc/Hex) to give nitrile **23** (153.0 mg, 63% yield, 0.488 mmol) and nitrile **23-D** (40.0 mg, 16% yield, 0.127 mmol)

Nitrile 23: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 1.5 Hz, 1H), 7.15 (d, J = 1.4 Hz, 1H), 5.85 (ddd, J = 10.2, 6.2, 1.9 Hz, 1H), 5.79 (ddd, J = 10.2, 3.0, 1.3 Hz, 1H), 3.60 (s, 1H), 3.19 (q, J = 7.1 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.35 (dddd, J = 15.9, 7.2, 5.5, 1.5 Hz, 1H), 2.05 (dd, J = 7.2, 4.5 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.85 (d, J = 17.1 Hz, 1H), 1.74 (ddd, J = 17.1, 6.3, 2.5 Hz, 1H), 1.22 (m, 6H), 1.14 (dt, J = 13.9,

1.9 Hz, 1H), 0.93 (s, 3H), 0.83 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{27}NO_2Na$ $[M+Na]^+$ 336.19, found 336.3

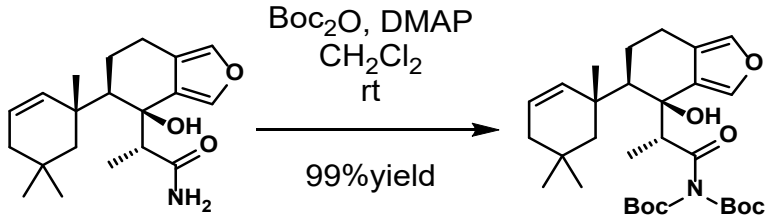
Nitrile **23-D:** ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 1.5 Hz, 1H), 7.18 – 7.15 (m, 1H), 5.86 (ddd, J = 10.1, 5.7, 2.2 Hz, 1H), 5.81 (dt, J = 10.2, 1.5 Hz, 1H), 3.34 (s, 1H), 3.15 (q, J = 7.0 Hz, 1H), 2.66 (ddd, J = 15.5, 6.9, 4.4 Hz, 1H), 2.47 (dddd, J = 15.4, 9.3, 4.5, 1.6 Hz, 1H), 2.10 – 2.00 (m, 2H), 1.93 (ddt, J = 14.0, 6.9, 4.3 Hz, 1H), 1.78 (m, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.27 (s, 3H), 1.22 – 1.18 (m, 1H), 0.94 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{27}NO_2Na$ $[M+Na]^+$ 336.19, found 336.3



23 **24**

Amide 24: $LiOH•H_2O$ (0.109 g, 2.60 mmol) was added to an aqueous solution of hydrogen peroxide (30% $H_2O_{2\,(aq)}$ 5.5 mL, 48.5 mmol) at 23 °C and stirred for 5 min. A solution of nitrile **23** (153 mg, 0.488 mmol) in DMSO (50.0 mL) was added dropwise while stirring to the basic solution of hydrogen peroxide at 23 °C and stirred for 30 min. The reaction was then diluted with EtOAc (50 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (3x50 mL) and the organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified by silica gel chromatography (30% EtOAc/Hex) to give amide **24** (145 mg, 90% yield, 0.438 mmol).

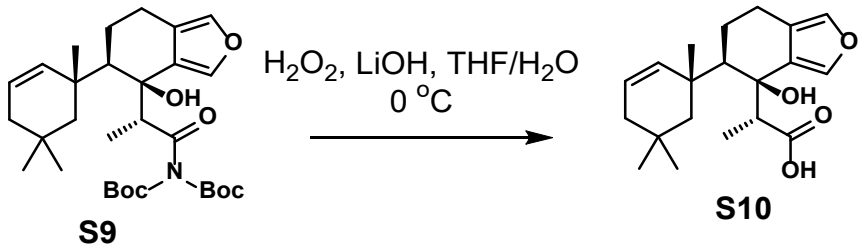
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 6.18 (bs, 1H), 5.65 (m, 2H), 5.31 (bs, 1H), 4.17 (s, 1H), 2.67 (q, J = 7.1 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.16 (ddt, J = 15.1, 6.6, 3.4 Hz, 1H), 2.07 – 2.03 (m, 1H), 1.98 (dtd, J = 15.0, 7.3, 3.7 Hz, 1H), 1.83 (d, J = 14.0 Hz, 1H), 1.75 (d, J = 16.9 Hz, 1H), 1.71 – 1.65 (m, 1H), 1.23 – 1.19 (m, 4H), 1.12 (s, 3H), 0.92 (s, 3H), 0.78 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{29}NO_3Na$ $[M+Na]^+$ 354.20, found 354.4



24 **S9**

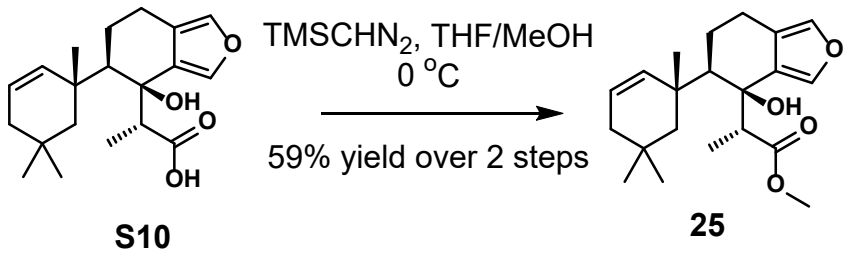
***N,N*-bisBoc amide S9:** DMAP (28.0 mg, 0.230 mmol) was added to a stirring solution of amide **24** (70.0 mg, 0.209 mmol) and Boc_2O (100.0 mg, 0.460 mmol) in CH_2Cl_2 (10.0 mL) at 23 °C and stirred for 30 min. Additional Boc_2O (100.0 mg, 0.460 mmol) and DMAP (28.0 mg, 0.230 mmol) were added and the solution was stirred for an additional 2 hr. The mixture was then concentrated and purified by silica gel chromatography (1% EtOAc/Hexane to 5% EtOAc/Hexane) to give *N,N*-bisBoc amide **S9** (114.0 mg, 99% yield).

1H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 1.6 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 5.57 (ddd, J = 10.1, 5.6, 2.2 Hz, 1H), 5.53 (dd, J = 10.0, 2.6 Hz, 1H), 4.03 (s, 1H), 3.82 (q, J = 6.9 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.49 (dt, J = 11.8, 5.6 Hz, 1H), 2.09 (dq, J = 14.2, 4.6 Hz, 1H), 1.94 (t, J = 4.5 Hz, 1H), 1.90 – 1.80 (m, 3H), 1.64 – 1.58 (m, 1H), 1.53 (s, 18H), 1.24 (m, 4H), 1.05 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{45}NO_7Na$ $[M+Na]^+$ 554.31, found 554.1



S9 **S10**

Acid S10: LiOH•H_2O (5.0 mg, 0.119 mmol) was added to an aqueous solution of hydrogen peroxide (30% $H_2O_{2\,(aq)}$ 0.28 mL, 2.47 mmol). This solution of basic hydrogen peroxide was added to a solution of *N,N*-bisBoc amide **S9** (13.0 mg, 0.0245 mmol) in THF (2.5 mL) at 0 °C and stirred for 1 hr. After 1 hr, the same amount of the basic hydrogen peroxide solution (containing the same amount of LiOH•H_2O and hydrogen peroxide) was added to the reaction mixture at 0 °C and stirred for an additional h. The reaction mixture was then diluted with ethyl acetate (3 mL) and aqueous $NaHSO_4$ (pH = 3, 5 mL). The aqueous layer was extracted with ethyl acetate (3x3 mL) and the organic layers were washed with brine and the acid **S10** was used immediately in the next step.

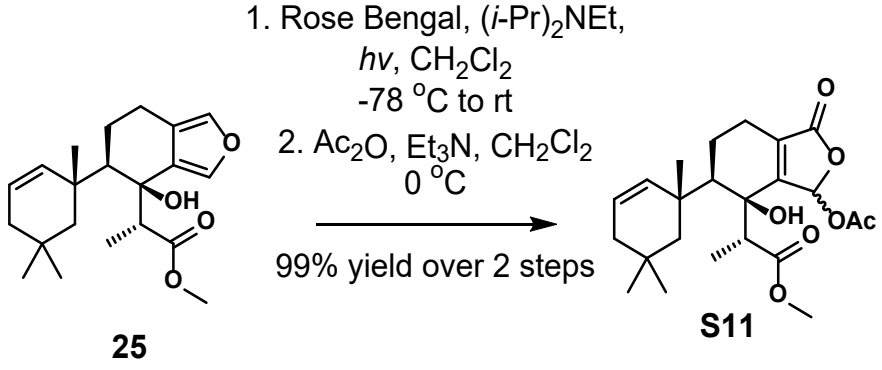


S10 **25**

Methyl Ester 25: Methanol (1 mL) was added to the crude, unconcentrated organic layers from the previous reaction at 23 °C. $TMSCHN_2$ (2M in Et_2O, 50 µL, 0.1 mmol) was added to the organic layers and stirred at 23 °C for 1 hr. The reaction mixture was then concentrated and purified by silica gel chromatography

(1% EtOAc/Hex to 5% EtOAc/Hex to 10% EtOAc/Hex) to give methyl ester **25** (5 mg, 59% yield, 0.0144 mmol).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 5.64 (ddd, J = 10.1, 5.8, 2.5 Hz, 1H), 5.57 – 5.52 (m, 1H), 3.78 (s, 1H), 3.74 (s, 3H), 2.91 (q, J = 7.0 Hz, 1H), 2.58 (dddd, J = 16.4, 10.9, 5.6, 1.5 Hz, 1H), 2.44 (dddd, J = 16.1, 6.1, 4.7, 1.4 Hz, 1H), 2.03 (dq, J = 14.7, 5.3 Hz, 1H), 1.95 (d, J = 13.8 Hz, 1H), 1.88 (dddd, J = 15.0, 10.7, 6.0, 4.4 Hz, 1H), 1.82 (dt, J = 16.7, 2.7 Hz, 1H), 1.78 (dd, J = 5.5, 4.4 Hz, 1H), 1.64 (dddd, J = 16.5, 5.8, 2.1, 0.9 Hz, 1H), 1.19 (ddd, J = 13.7, 2.2, 1.1 Hz, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.07 (s, 3H), 0.91 (s, 3H), 0.82 (s, 3H). LRMS (ESI) calcd for $C_{20}H_{30}O_4Na$ $[M+Na]^+$ 369.20, found 369.3



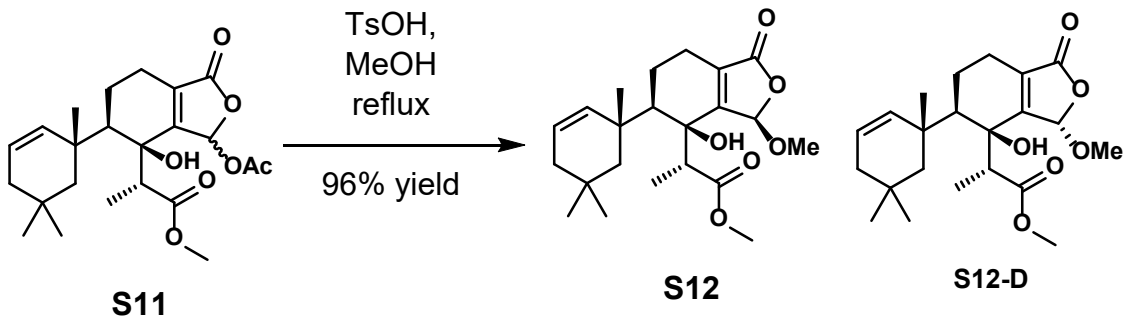
25 S11

γ-acetoxy butenolide S11: Rose Bengal (6.0 mg, 0.00650 mmol) was added to a solution of methyl ester **25** (45.0 mg, 0.130 mmol) in CH_2Cl_2 (13.0 ml) followed by *i*-Pr_2NEt (0.230 mL, 1.30 mmol) and the suspension was cooled to -78 °C. Oxygen was bubbled through the solution for 5 min, then the suspension was irradiated (Kessel Lamp, 100% white/100% intensity) for 20 min while continuing to bubble oxygen through the solution. Oxygen delivery and irradiation were halted and the solution was allowed to warm to 23 °C and stir for 20 min at this temperature. Aqueous $NaHSO_4$ (2 M, 13 mL) was added followed by EtOAc (30 mL). The layers

were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated.

The crude residue from the previous reaction was resuspended in CH_2Cl_2 (13.0 mL). Ac_2O (26 µL, 0.276 mmol) was added to the CH_2Cl_2 solution followed by *i*-Pr_2NEt (65 µL, 0.374 mmol) and the solution was stirred at 23 °C for 1 hr. The reaction mixture was then diluted with EtOAc (13 mL) and washed with aqueous $NaHSO_4$ (pH = 3), brine, dried over Na_2SO_4 and concentrated. The product was then isolated by silica gel chromatography (5% EtOAc/Hex to 10% EtOAc/Hex to 20% EtOAc/Hex) to give γ-acetoxy butenolide **S11** (48.0 mg, 88% yield, 0.114 mmol) as a single regioisomer and epimer.

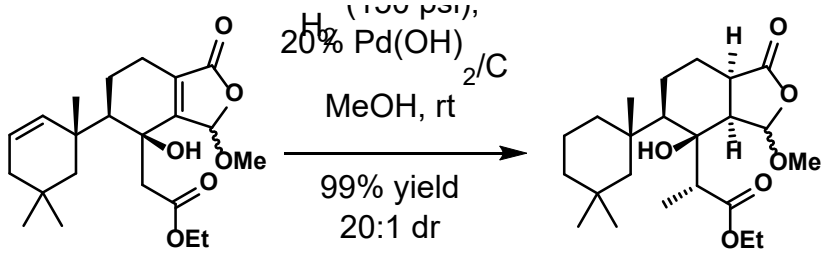
^1H NMR (600 MHz, $CDCl_3$) δ 7.21 (dd, J = 2.3, 1.2 Hz, 1H), 5.68 (ddd, J = 10.1, 6.1, 2.3 Hz, 1H), 5.52 (dd, J = 10.1, 2.9 Hz, 1H), 4.15 (s, 1H), 3.71 (s, 3H), 3.19 (q, J = 7.1 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.23 – 2.17 (m, 1H), 2.15 – 2.06 (m, 5H), 1.92 – 1.78 (m, 3H), 1.69 (ddd, J = 16.3, 6.1, 2.0 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H), 1.17 (m, 4H), 0.94 (s, 3H), 0.93 (s, 3H). LRMS (ESI) calcd for $C_{23}H_{32}O_7Cl$ $[M+Cl]^-$ 455.18, found 455.1



γ-methoxy butenolide S12 and S12-D: A solution of γ-acetoxy butenolide **S11** (47.0 mg, 0.112 mmol) and TsOH•H_2O (70.0 mg, 0.367 mmol) in CH_3OH (22.0 mL) was heated to reflux for 4 hr. The reaction mixture was cooled to 23 °C then concentrated and resuspended in EtOAc (20 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (2x20 mL), brine, dried over Na_2SO_4 and concentrated. The crude residue contained a 2:1 mixture of epimers which were separated and purified by silica gel chromatography to give γ-methoxy butenolide **S12** (29.0 mg, 66% yield, 0.0739 mmol) and γ-methoxy butenolide **S12-D** (13.0 mg, 30% yield, 0.0331 mmol).

γ-methoxy butenolide S12: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.11 – 6.05 (m, 1H), 5.67 (d, J = 3.6 Hz, 2H), 3.82 (d, J = 0.7 Hz, 1H), 3.73 (s, 3H), 3.63 (t, J = 7.2 Hz, 1H), 3.59 (s, 3H), 2.41 (dt, J = 17.7, 4.6 Hz, 1H), 2.10 (d, J = 13.8 Hz, 1H), 1.98 (dddd, J = 17.6, 9.9, 5.0, 2.4 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.76 (dtd, J = 14.4, 10.0, 4.6 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.59 (dd, J = 10.1, 3.3 Hz, 1H), 1.27 (s, 3H), 1.20 – 1.14 (m, 1H), 1.05 (d, J = 7.2 Hz, 3H), 0.95 (s, 3H), 0.92 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{32}O_6$ $[M+Na]^+$ 415.21, found 415.3

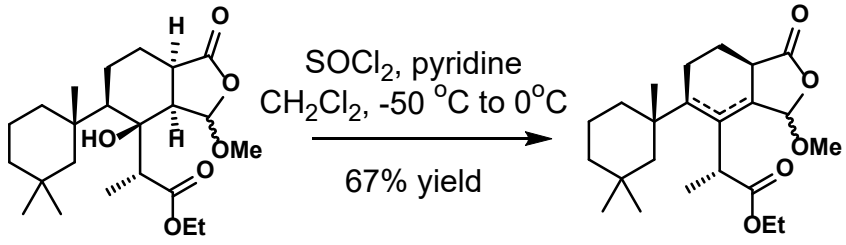
γ-methoxy butenolide S12-D: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 – 5.70 (m, 1H), 5.70 – 5.65 (m, 1H), 5.64 (s, 1H), 5.59 (dd, J = 10.0, 2.7 Hz, 1H), 3.73 (s, 3H), 3.66 (q, J = 7.1 Hz, 1H), 3.51 (s, 3H), 2.39 – 2.32 (m, 1H), 2.16 (d, J = 13.7 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.91 – 1.82 (m, 3H), 1.73 – 1.64 (m, 2H), 1.22 – 1.16 (m, 6H), 1.13 (dd, J = 13.5, 2.2 Hz, 1H), 0.92 (d, J = 6.8 Hz, 6H). LRMS (ESI) calcd for $C_{22}H_{32}O_6Na$ $[M+Na]^+$ 415.21, found 415.3



S12 **S13**

Tertiary alcohol S13: A suspension of γ-methoxy butenolide **S12** (6.0 mg, 0.0513 mmol) and 20% $Pd(OH)_2/C$ (24.0 mg, 400 wt%) in CH_3OH (2.0 mL) was placed under an atmosphere of H_2 (150 psi) and stirred vigorously at 23 °C for 48 hr. The solid was separated from the solution by filtration with a syringe PTFE filter and the filtrate was concentrated to give a clean sample of tertiary alcohol **S13** (6.0 mg, 99% yield, 0.0153 mmol) as a single diastereomer which was used without further purification.

^1H NMR (600 MHz, $CDCl_3$) δ 5.42 (d, J = 4.5 Hz, 1H), 3.81 (s, 1H), 3.76 (s, 3H), 3.52 (s, 3H), 3.15 (q, J = 7.3 Hz, 1H), 2.85 – 2.76 (m, 2H), 2.04 (ddt, J = 14.2, 6.0, 3.2 Hz, 1H), 1.79 – 1.71 (m, 2H), 1.68 – 1.59 (m, 2H), 1.53 – 1.42 (m, 2H), 1.35 – 1.22 (m, 4H), 1.23 (d, J = 8.9 Hz, 3H), 1.17 (s, 3H), 1.15 (m, 1H), 1.07 – 0.97 (m, 1H), 0.98 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{36}O_6Na$ $[M+Na]^+$ 419.24, found 419.

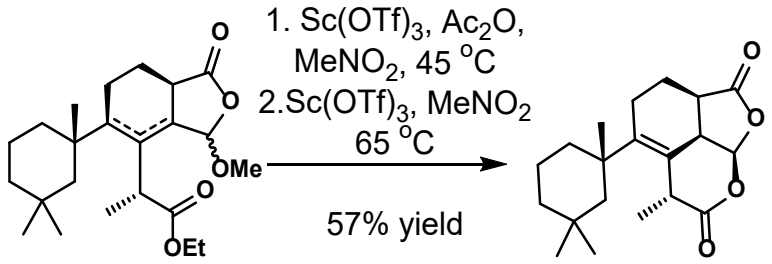


S13 **S14**

Methoxylactone S14: Thionyl chloride (100.0 µL, 1.378 mmol) was added dropwise to a stirring solution of pyridine (0.450 mL, 5.514 mmol) and the tertiary alcohol **S13** (6.0 mg, 0.0151 mmol) in CH_2Cl_2 (5.0 mL) at -50 °C and stirred for 1 hr at the same temperature. The reaction was then warmed to 0 °C and stirred for 1 hr. The reaction was quenched with methanol (56.0 µL, 1.38 mmol) and diluted with 1:1 EtOAc/hexane (20 mL). The solution was washed with aqueous $NaHSO_4$ (pH = 3, 2x10 mL), brine, dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to give methoxylactone **S14** (4.0 mg, 70% yield, 0.0106 mmol) as a 2:5 mixture of regioisomers.

Methoxylactone **S14** (selected signals): ^{1}HNMR (600 MHz, $CDCl_3$) δ 5.75 (m, 1H), 3.76 (s, 3H), 3.43 (s, 3H), 3.27 (q, J = 7.5 Hz, 1H), 1.31 (d, J = 7.4 Hz, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.

Methoxylactone **S14** (selected signals): ^{1}HNMR (600 MHz, $CDCl_3$) δ 5.01 (d, J = 3.5 Hz, 1H), 4.27 (q, J = 7.4 Hz, 1H), 3.70 (s, 1H), 3.42 (s, 1H), 2.97 (dd, J = 3.5 Hz, 10.0 Hz, 1H), 2.89 (dddd, J = 10.0, 7.3, 2.6, 1.3 Hz, 1H), 1.20 (d, J = 7.4 Hz, 3H), 1.06 (s, 3H), 0.88 (s, 3H), 0.88 (s, 3H). LRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.23, found 401.



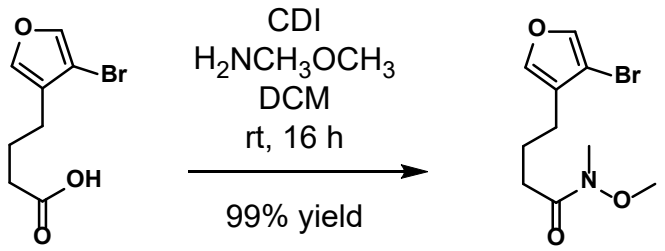
S14 **2**

(±)-cadlinolide A: Ac_2O (0.38 mL, 3.98 mmol) was added to a stirring solution of acetal **S14** (4.0 mg, 0.0106 mmol) and $Sc(OTf)_3$ (26 mg, 0.0530 mmol) in nitromethane (2.0 mL) and heated to 35°C for 3 hr. The reaction mixture was then cooled to 23 °C and diluted with EtOAc/Hex (1:1 v/v, 10 mL). The organic mixture was washed with water (2x 5 mL), brine, dried over Na_2SO_4 and concentrated.

The crude mixture was resuspended in nitromethane (2.0 mL). $Sc(OTf)_3$ (26 mg, 0.0530 mmol) was added to the solution and it was heated to 65°C for 20 min. The reaction mixture was then concentrated and the title product was isolated by silica gel chromatography (20% EtOAc/Hexane to 30% EtOAc/Hexane) to give (±)-cadlinolide A (2.0 mg, 57% yield, 0.006 mmol)

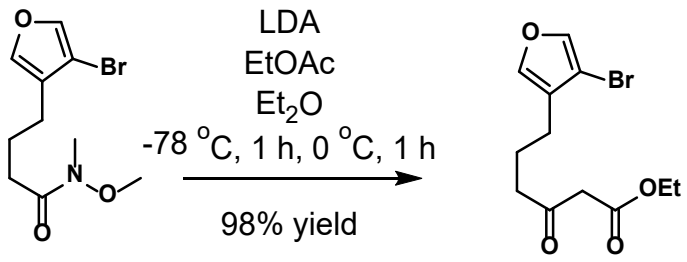
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.13 (d, J = 5.2 Hz, 1H), 4.31 (q, J = 7.4 Hz, 1H), 3.43 (td, J = 5.5, 2.7 Hz, 1H), 3.08 (dt, J = 8.4, 4.6 Hz, 1H), 2.36 (d, J = 17.9 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.12 (dq, J = 13.6, 4.9 Hz, 1H), 1.88 (d, J = 14.4 Hz, 1H), 1.75 (d, J = 14.6 Hz, 1H), 1.70 (m, 1H), 1.61 – 1.50 (m, 2H), 1.49 (d, J = 7.4 Hz, 3H), 1.31 – 1.14 (m, 4H), 1.14 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 173.27, 170.12, 148.14, 118.87, 99.58, 50.50, 40.21, 40.13, 39.49, 39.40, 38.49, 35.49, 32.09, 31.64, 29.86, 28.56, 23.55, 20.87, 20.27, 17.13. LRMS

(ESI) calcd for $C_{20}H_{27}O_4$ $[M-H]^-$ 331.19 and $C_{20}H_{28}ClO_4$ $[M+Cl]^-$ 367.17 and $C_{22}H_{31}NNaO_4$ $[M+CH_3CN+Na]^+$ 396.22, found 331.1 and 367.1 and 396.0



48 **49**

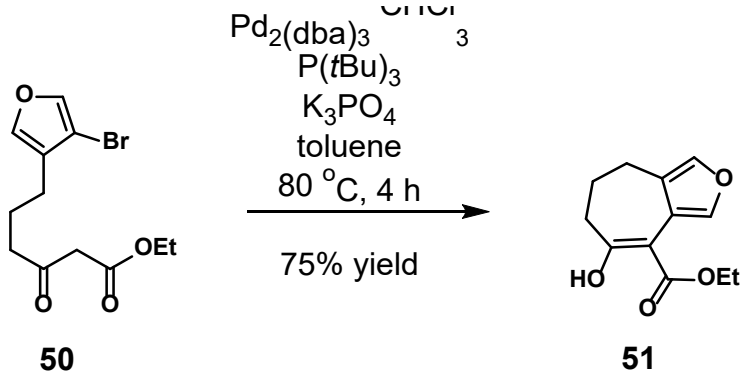
Weinreb Amide 49: Carbonyl diimidazole (0.904 g, 5.58 mmol) was quickly added to a solution of **48** (1.000 g, 4.291 mmol) in CH_2Cl_2 (11 mL). After 1 h, N,O, dimethyl hydroxylamine hydrochloride (0.837 g, 8.58 mmol) was added. The solution was stirred overnight and quenched at 0 °C with 1 M HCl (40 mL) and stirred for 20 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (40% ethyl acetate/ hexanes) to afford the Weinreb amide **49** (1.181 g, 99% yield, 4.277 mmol) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 1.7 Hz, 1H), 7.21 (s, 1H), 3.65 (s, 3H), 3.17 (s, 3H), 2.44 (m, 4H), 1.91 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 174.1, 140.9, 139.7, 124.7, 102.6, 61.2, 32.1, 31.1, 23.7, 23.3.



49 **50**

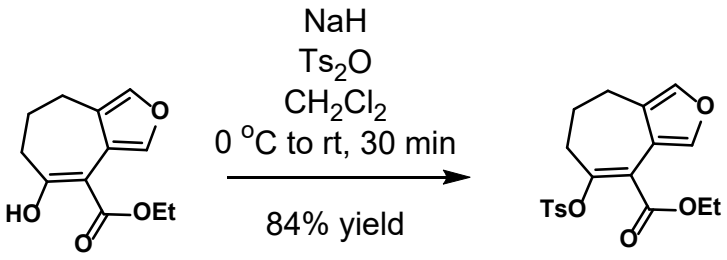
Beta keto ester 50: *n*-BuLi (2.5 M, 2.71 mL, 6.78 mmol) was added slowly to a stirring solution of diisopropylamine (1.00 mL, 7.05 mmol) in diethyl ether (22 mL) at -10 °C. After 20 minutes, the solution was cooled to -78 °C and ethyl acetate (0.690 mL, 7.05 mmol) was added over 10 minutes. After 30 minutes, a solution of **49** (0.748 g, 2.71 mmol) in diethyl ether (6 mL) was added dropwise. After 1 h, the solution was warmed to 0 °C. After another hour, the solution was quenched with saturated aqueous ammonium chloride (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (10% ethyl acetate/ hexanes) to afford the beta keto ester **50** (0.802 g, 98% yield, 2.64 mmol, 14:1 keto:enol) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 7.38 (d, J = 1.8 Hz, 1H), 7.19 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.42 (s, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.43 – 2.38 (m, 2H), 1.88 (p, J = 7.3 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 202.3, 167.1, 141.0, 139.7, 124.3, 102.5, 61.4, 49.3, 42.0, 22.8, 22.5,

14.1.



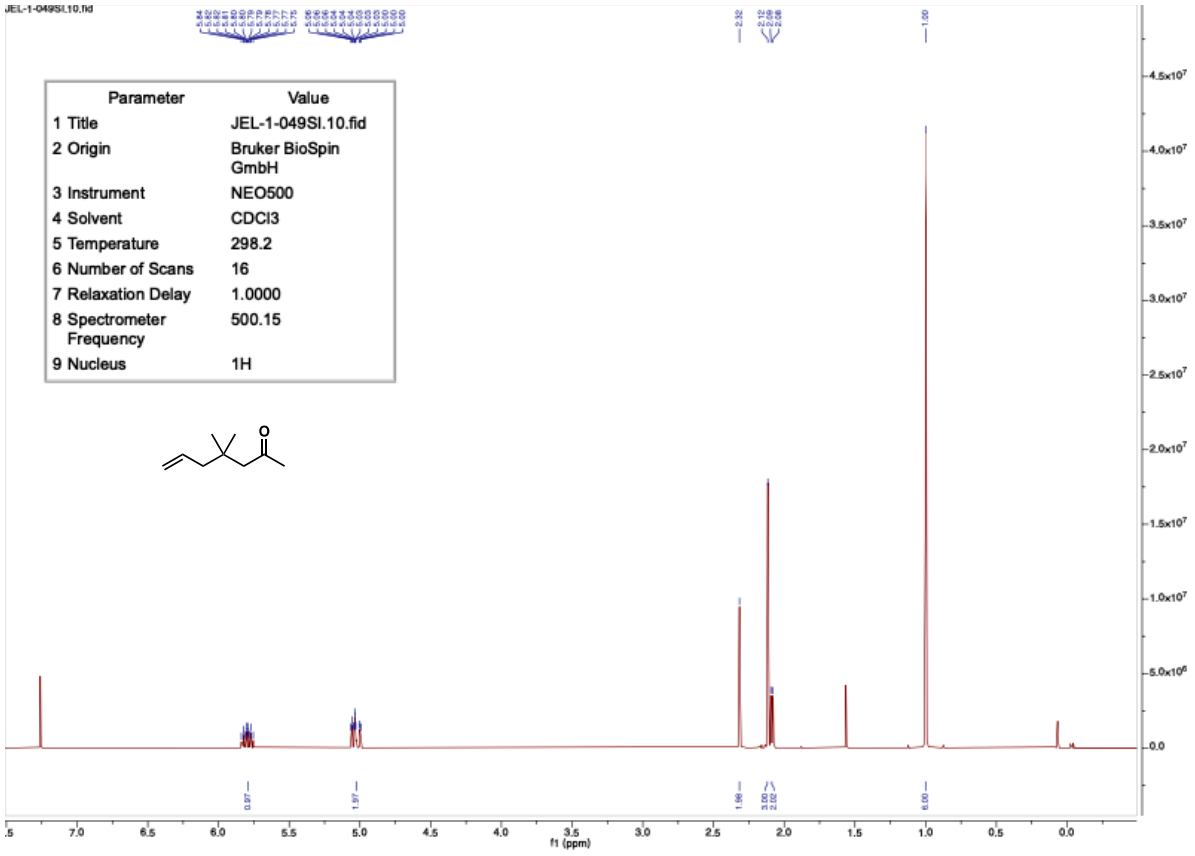
50 **51**

Beta keto ester 51: Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (8.6 mg, 0.0083 mmol) and tritertbutyl phosphine (14 mg, 0.066 mmol) were added to a microwave vial containing tribasic potassium phosphate (210 mg, 0.991 mmol) in the glove box. The vial was removed from the glove box, and a solution of **50** (100 mg, 0.330 mmol) in degassed toluene (5 mL) was added to the vial under argon. The vial was sealed and heated to 80 °C for 4 h. The suspension was cooled to room temperature, diluted with ether, and 1.00 mL of 1M HCl was added. The solution was extracted with ether (3 x 3 mL), dried over sodium sulfate, and concentrated. The crude oil was purified via column chromatography (5% ethyl acetate/hexanes) to afford **51** (54 mg, 75% yield, 0.24 mmol, 10:1 enol:keto tautomers) as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 12.95 (s, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.21 (d, J = 0.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.58 – 2.51 (m, 2H), 2.39 (td, J = 7.0, 0.9 Hz, 2H), 2.08 (p, J = 7.2 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 140.4, 137.3, 123.3, 119.1, 95.2, 60.8, 32.2, 27.1, 20.3, 14.2.



51 **52**

Enol tosylate 52: Sodium hydride (60% wt in mineral oil, 7 mg, 0.175 mmol) was added to a solution of **51** (12 mg, 0.054 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 30 minutes, tosyl anhydride (57 mg, 0.175 mmol) was added. The suspension was stirred for 30 minutes and quenched with saturated aqueous ammonium chloride (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (10% ethyl acetate/ hexanes) to afford the enol tosylate **52** (16 mg, 84% yield, 0.0425 mmol) as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ 7.84 (d, J = 8.4 Hz, 2H), 7.35 (m, 3H), 7.16 (d, J = 1.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.76 – 2.70 (m, 2H), 2.67 – 2.61 (m, 2H), 2.46 (s, 3H), 1.90 (p, J = 6.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 165.8, 147.8, 145.2, 142.6, 139.1, 134.2, 129.7, 128.0, 123.7, 120.1, 117.5, 61.6, 35.2, 23.8, 23.5, 21.7, 13.9.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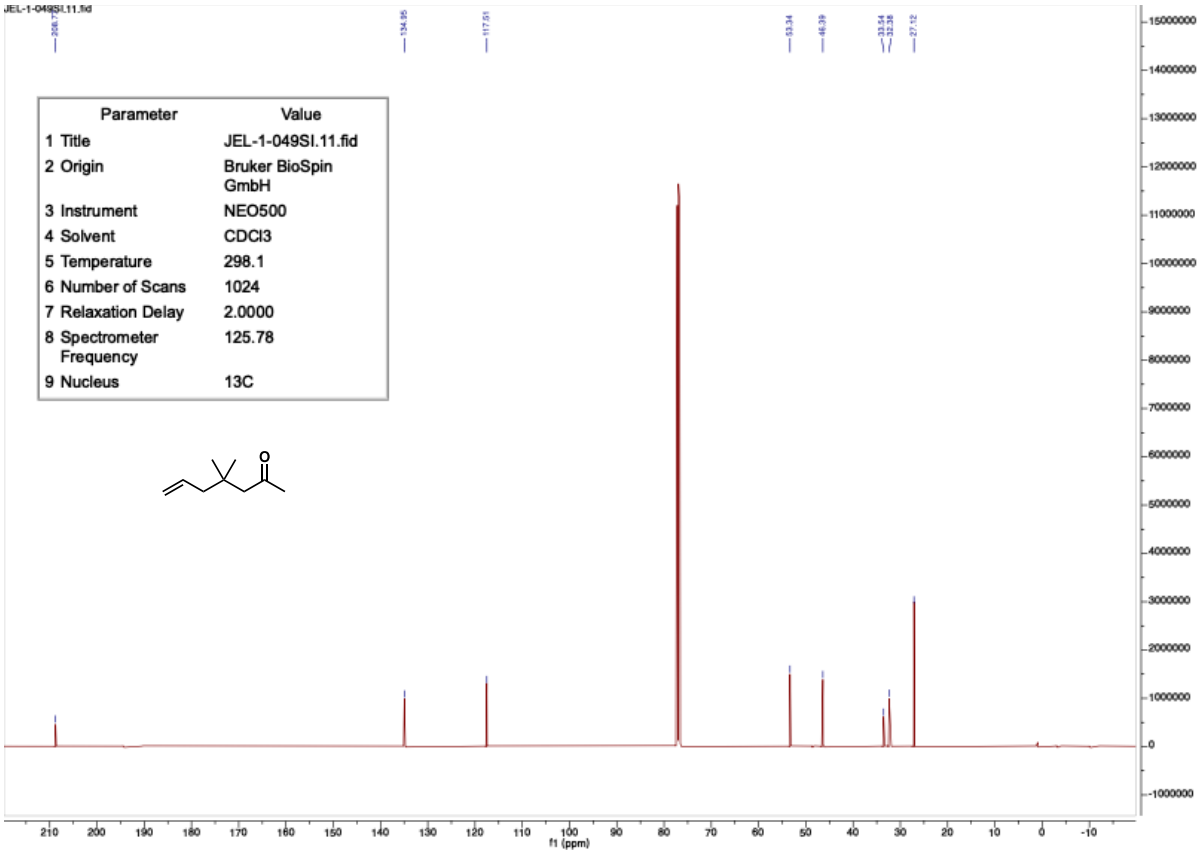
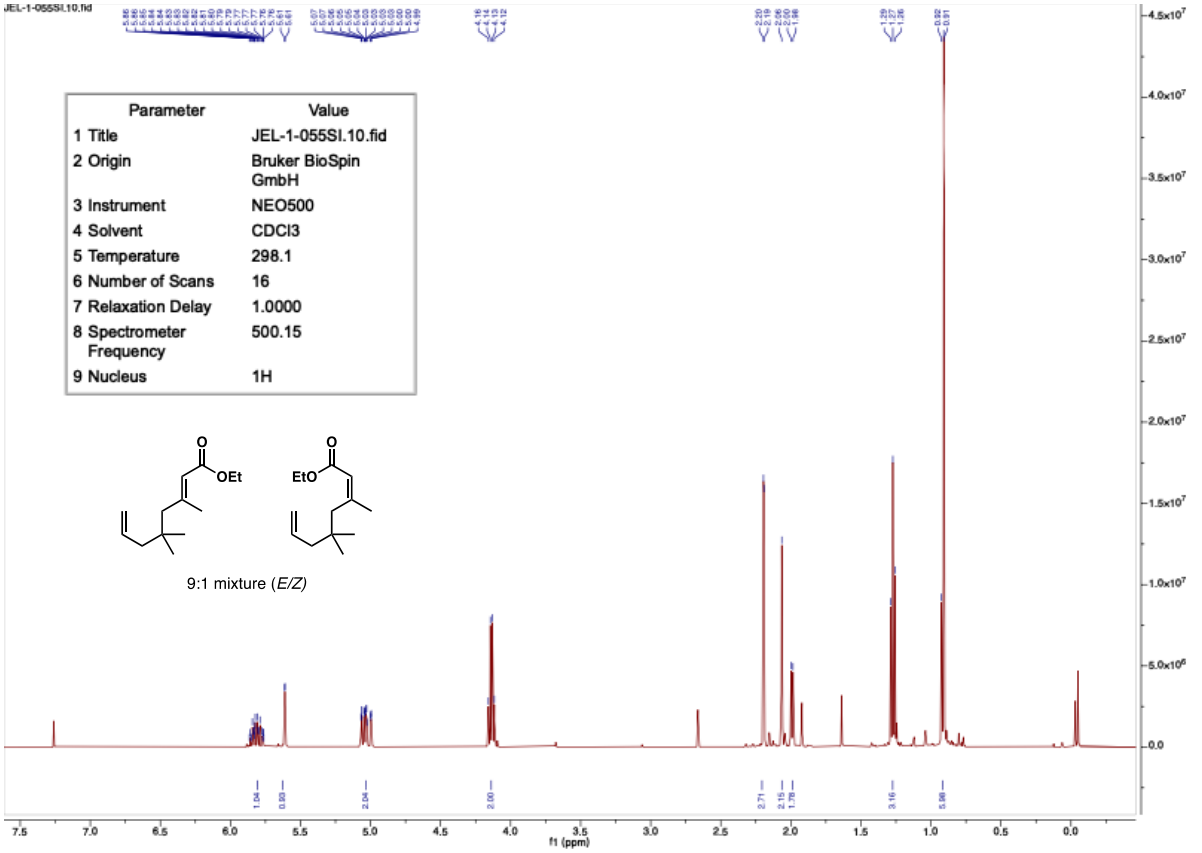
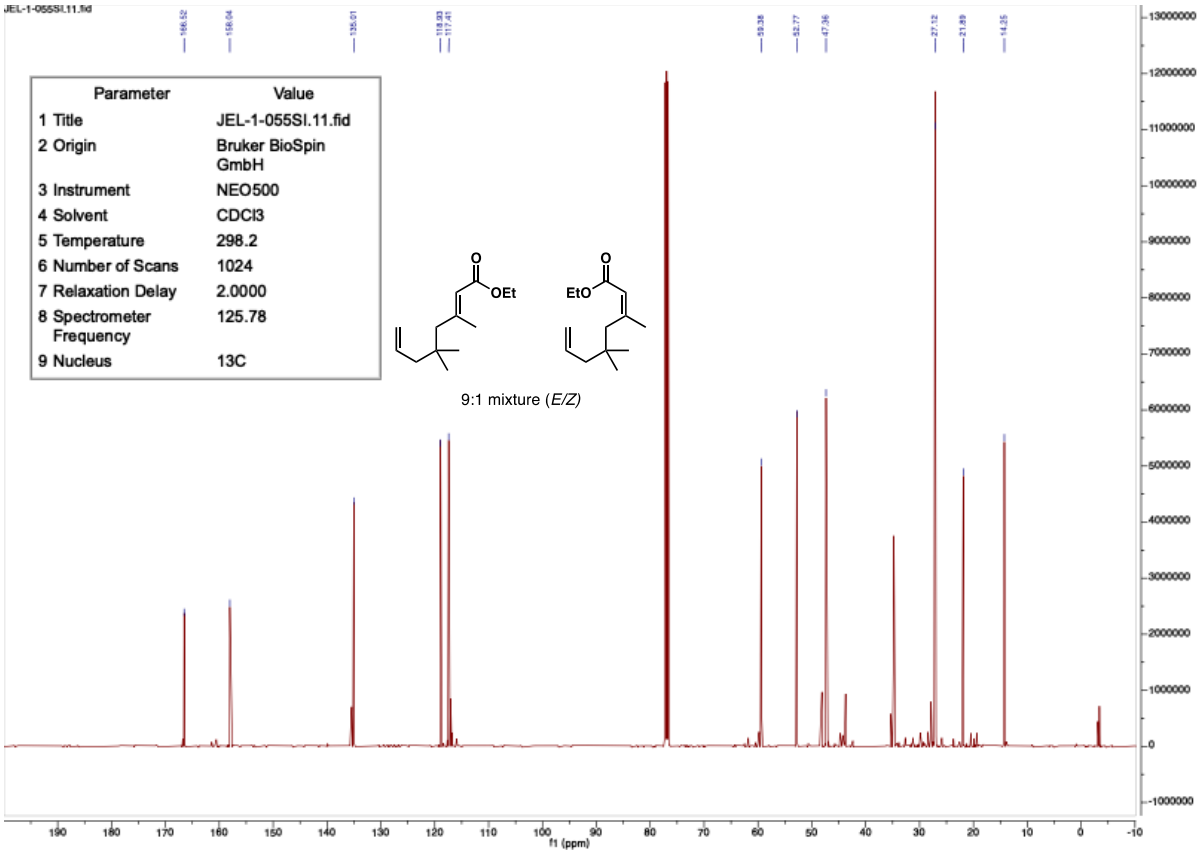




9:1 mixture (*E/Z*)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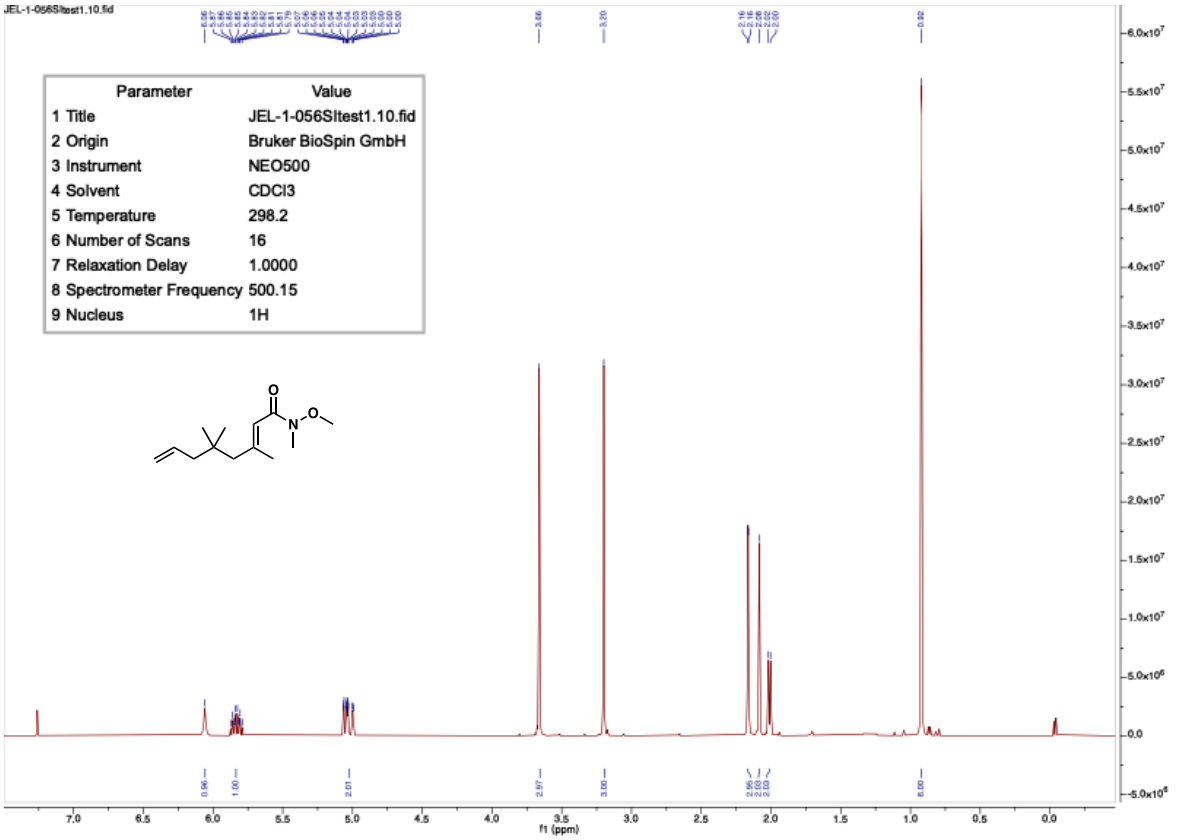
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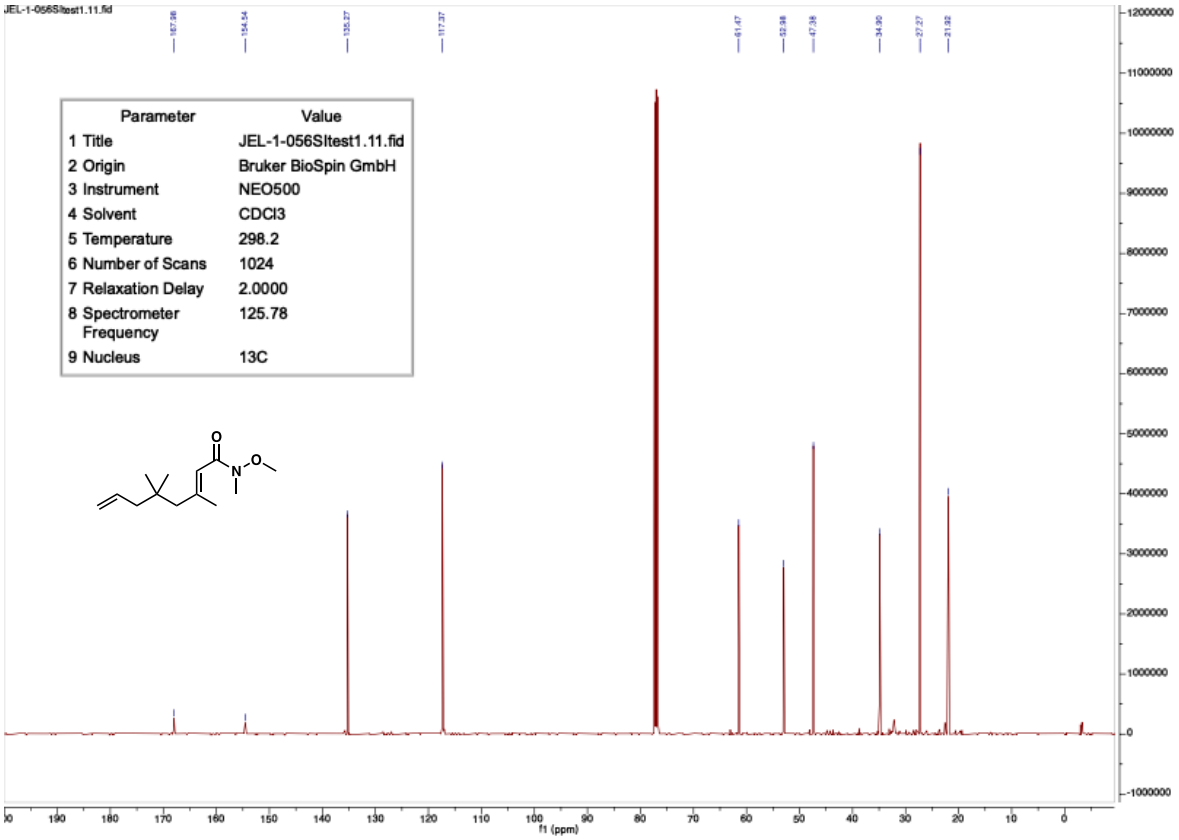
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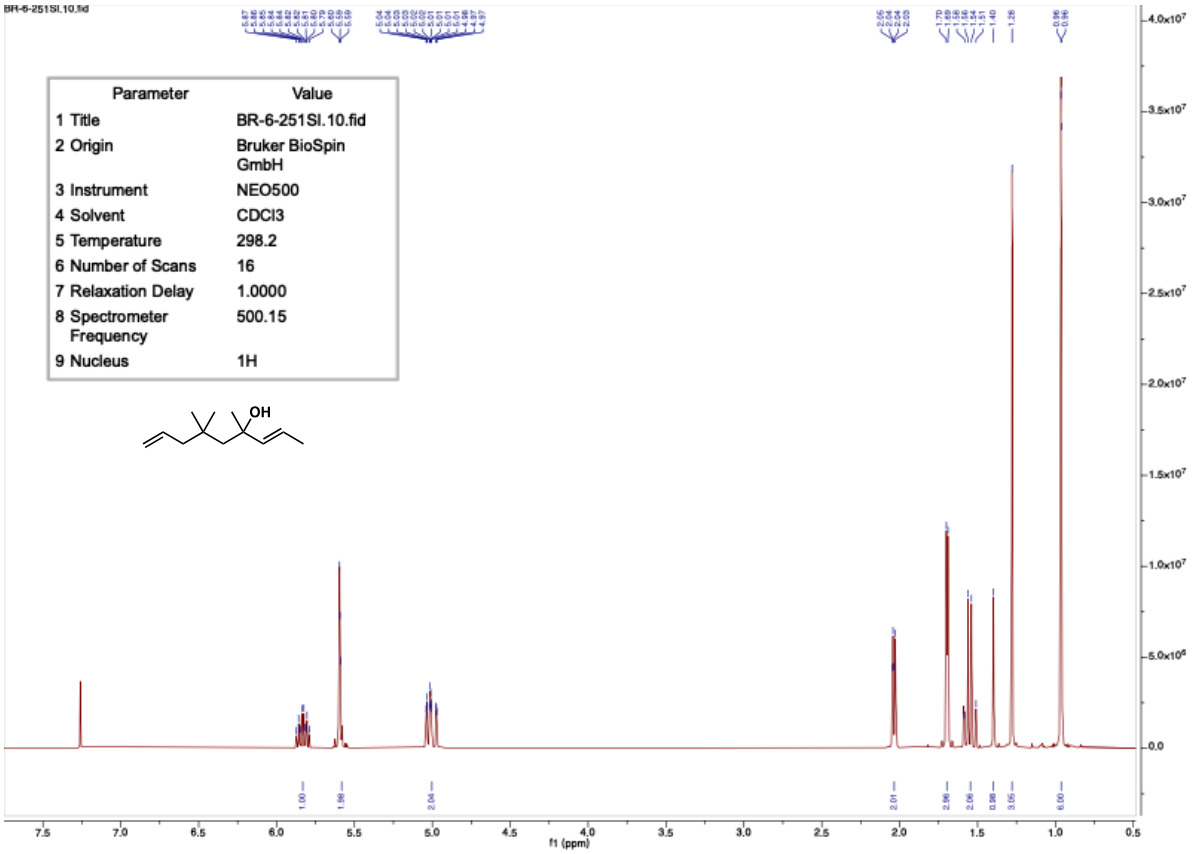
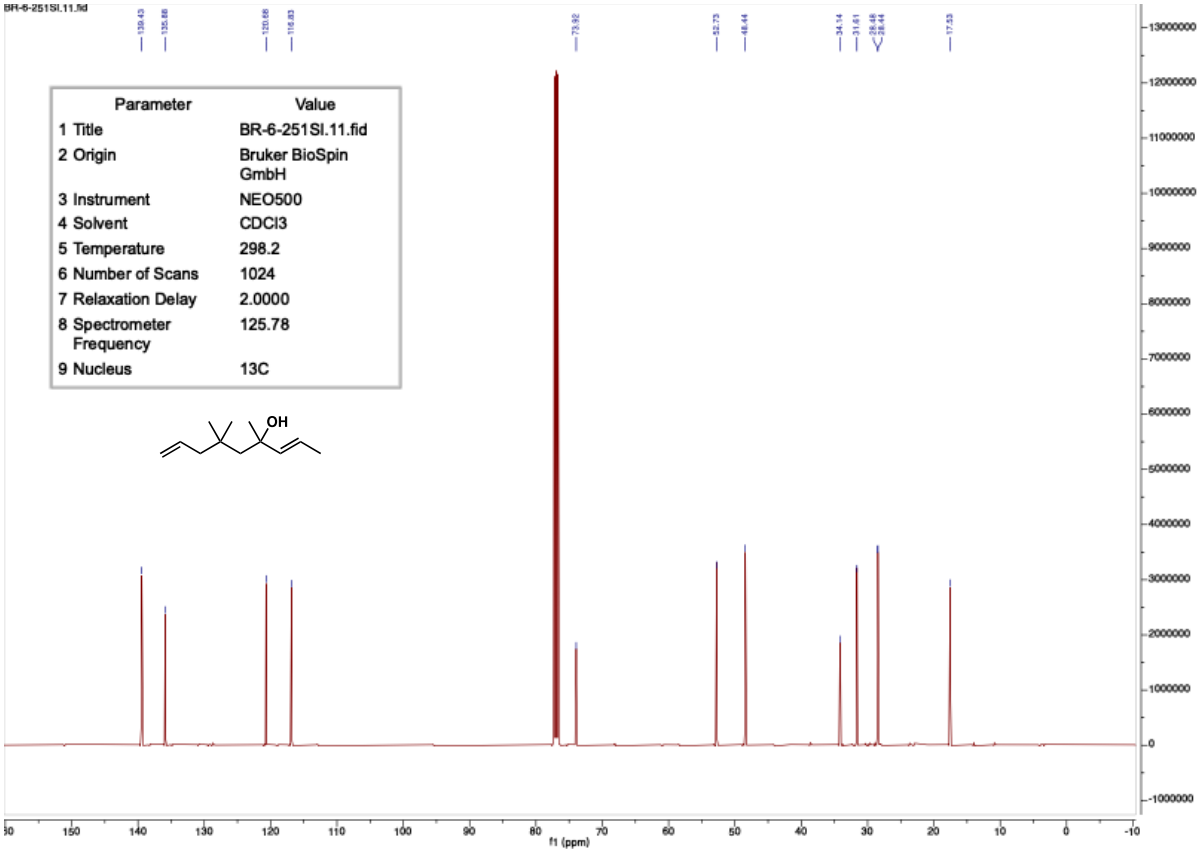
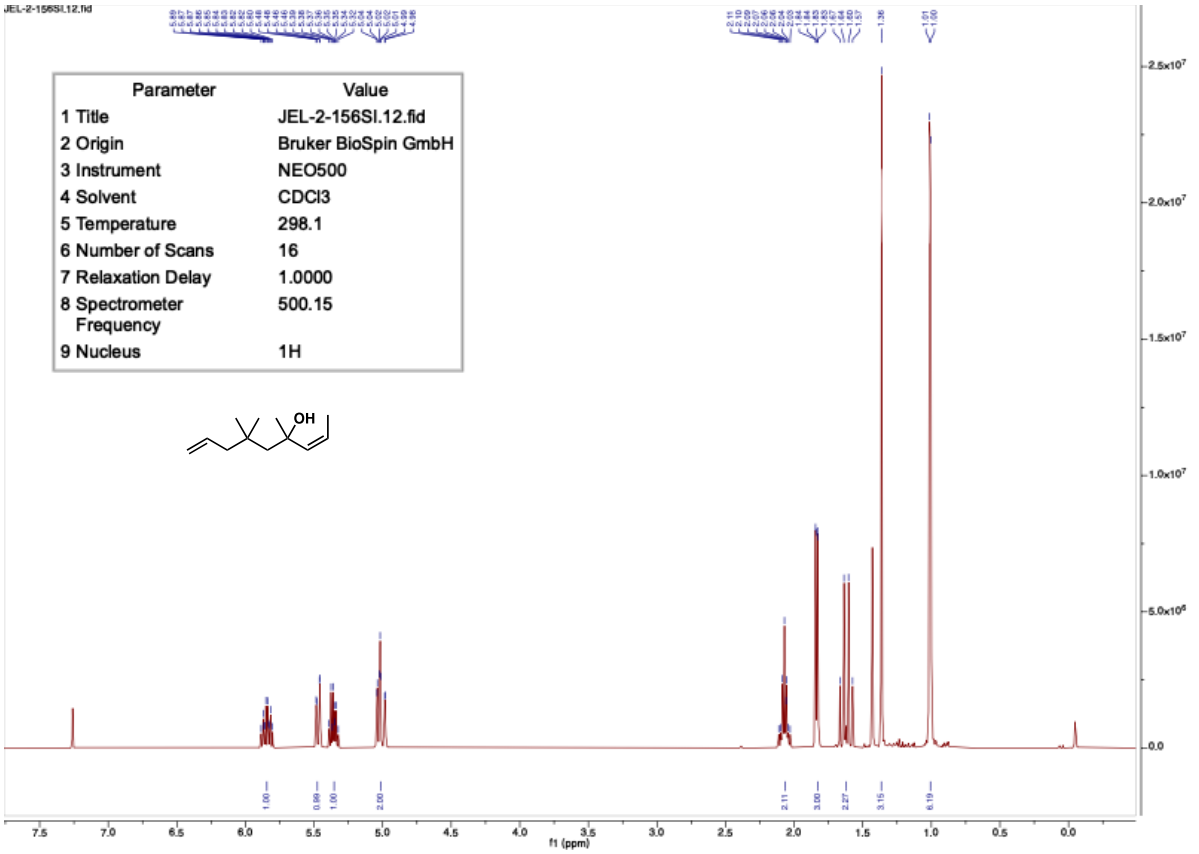
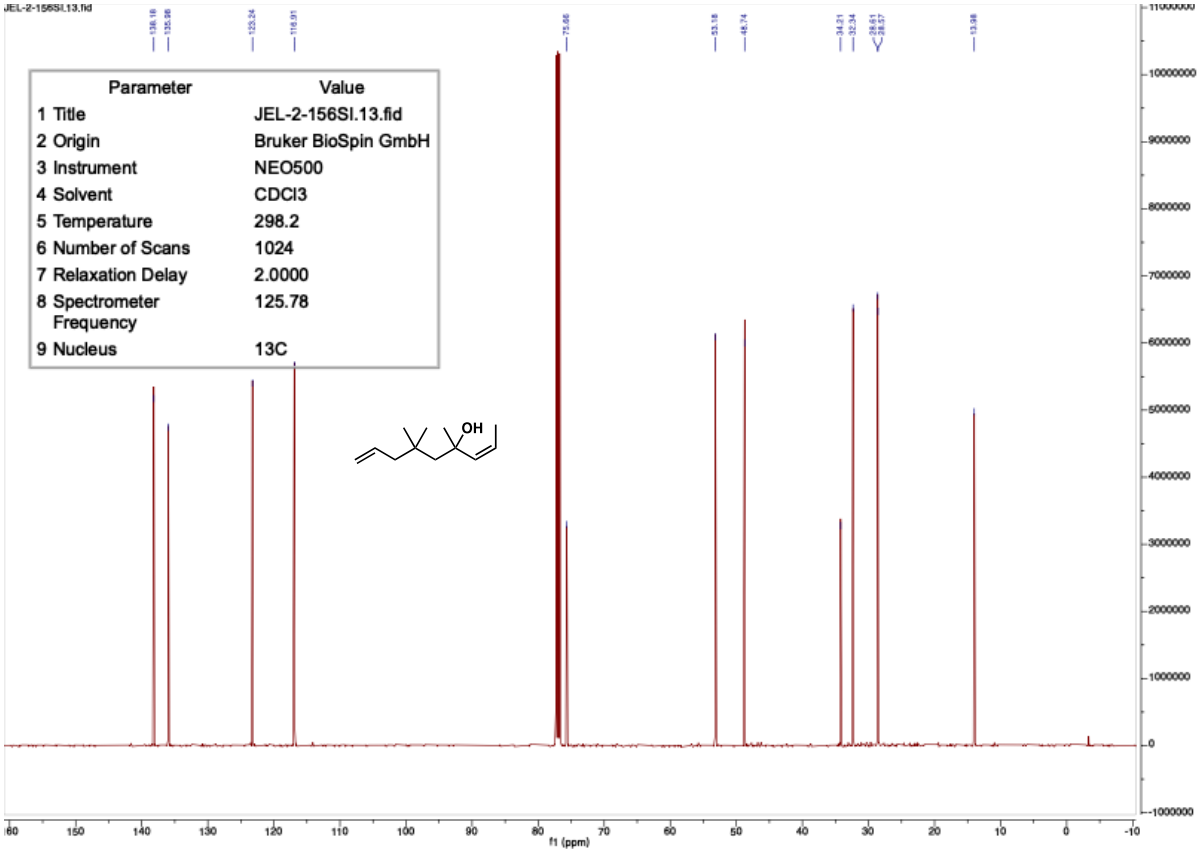
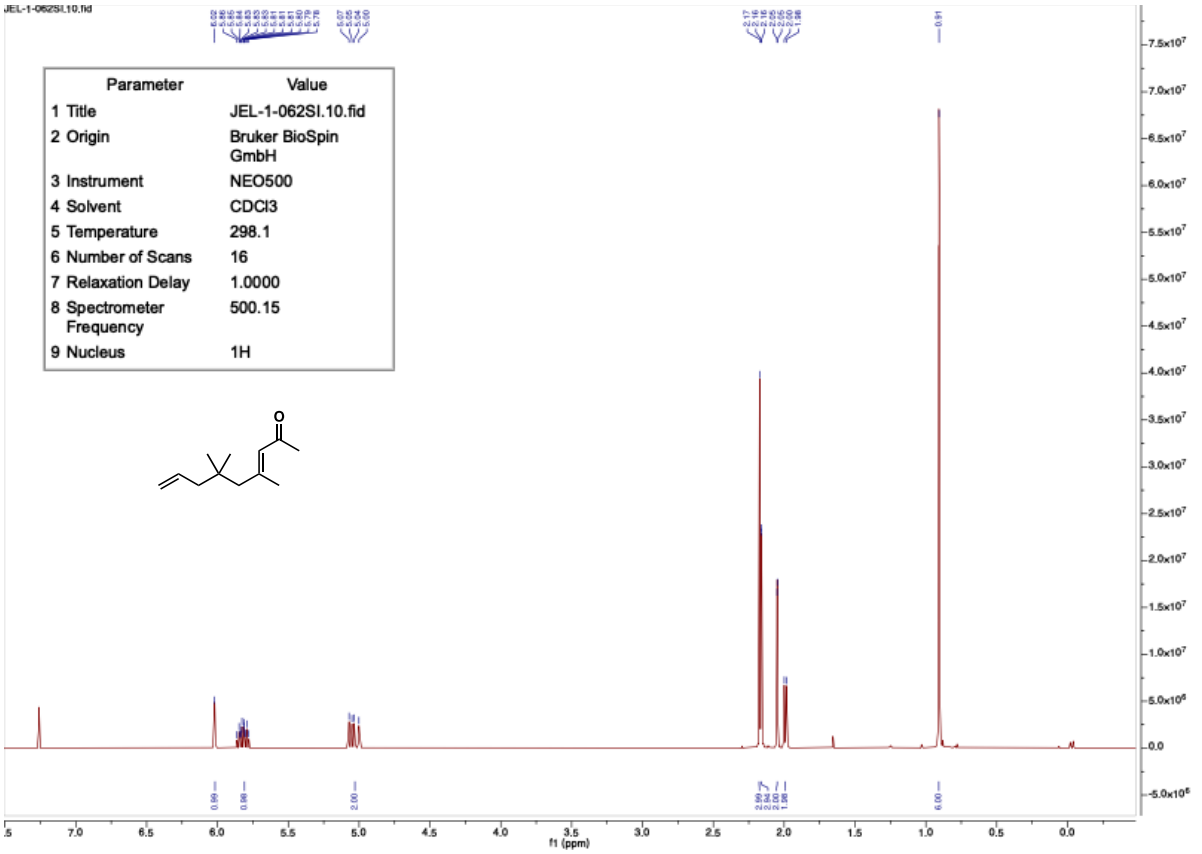
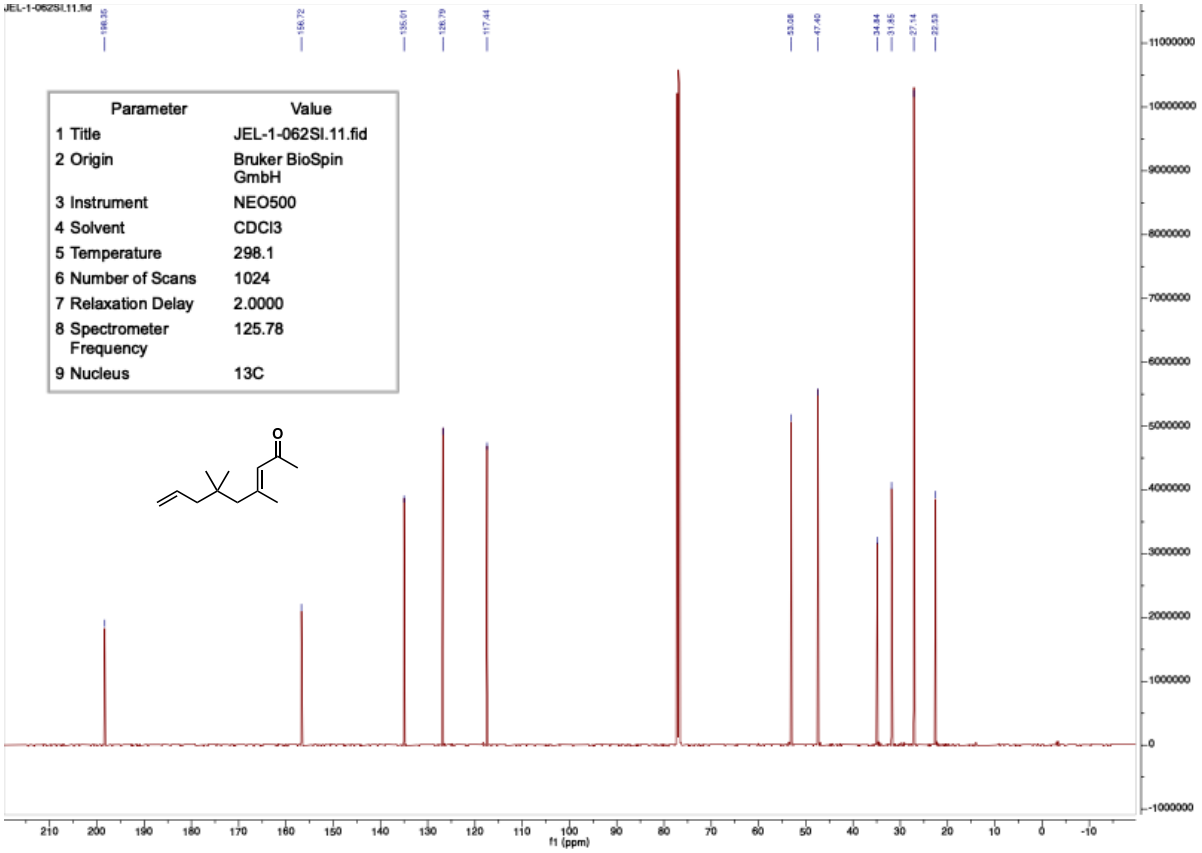

BR-6-251SI.10.fid
Parameter Value
1 Title BR-6-251SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
OH
f1 (ppm)

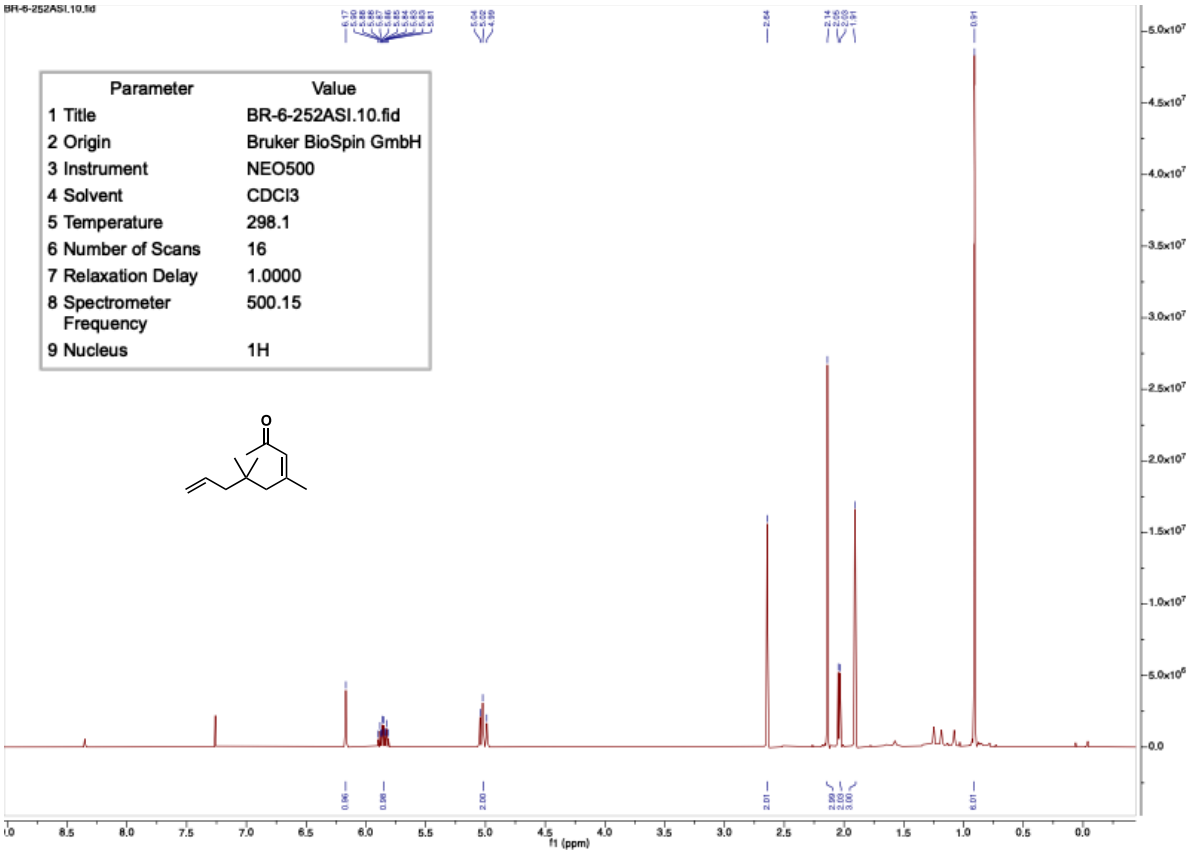

BR-6-251SI.11.fid
Parameter Value
1 Title BR-6-251SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
OH
f1 (ppm)

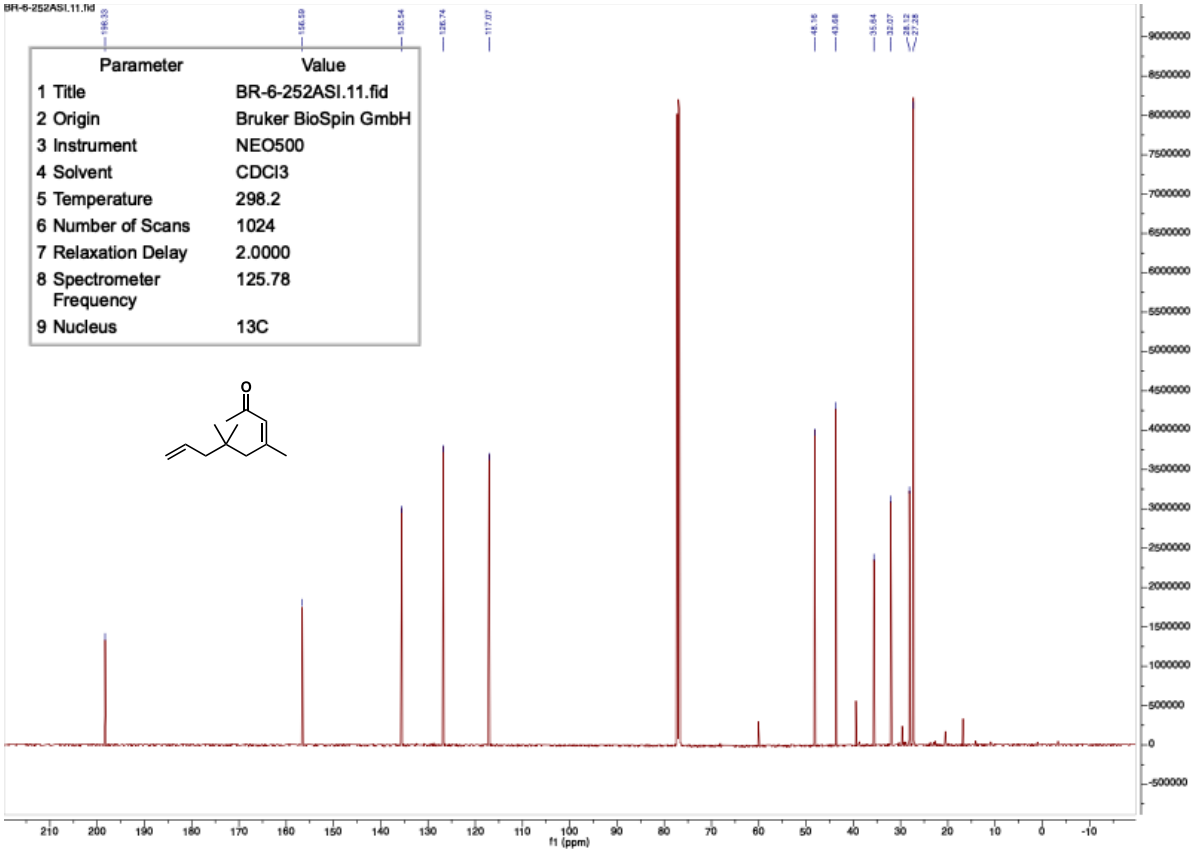

JEL-2-156SI.12.fid
Parameter Value
1 Title JEL-2-156SI.12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
OH
f1 (ppm)

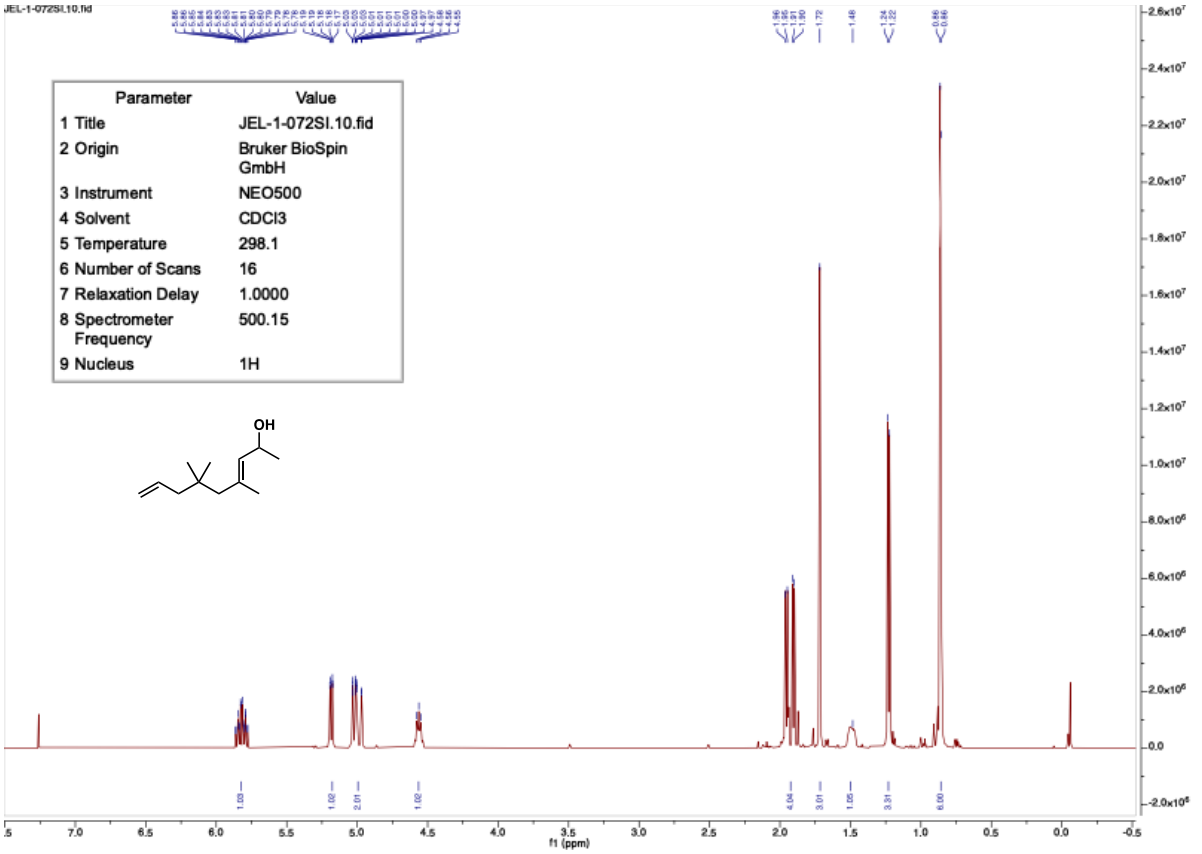

JEL-2-156SI.13.fid
Parameter Value
1 Title JEL-2-156SI.13.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
OH
f1 (ppm)

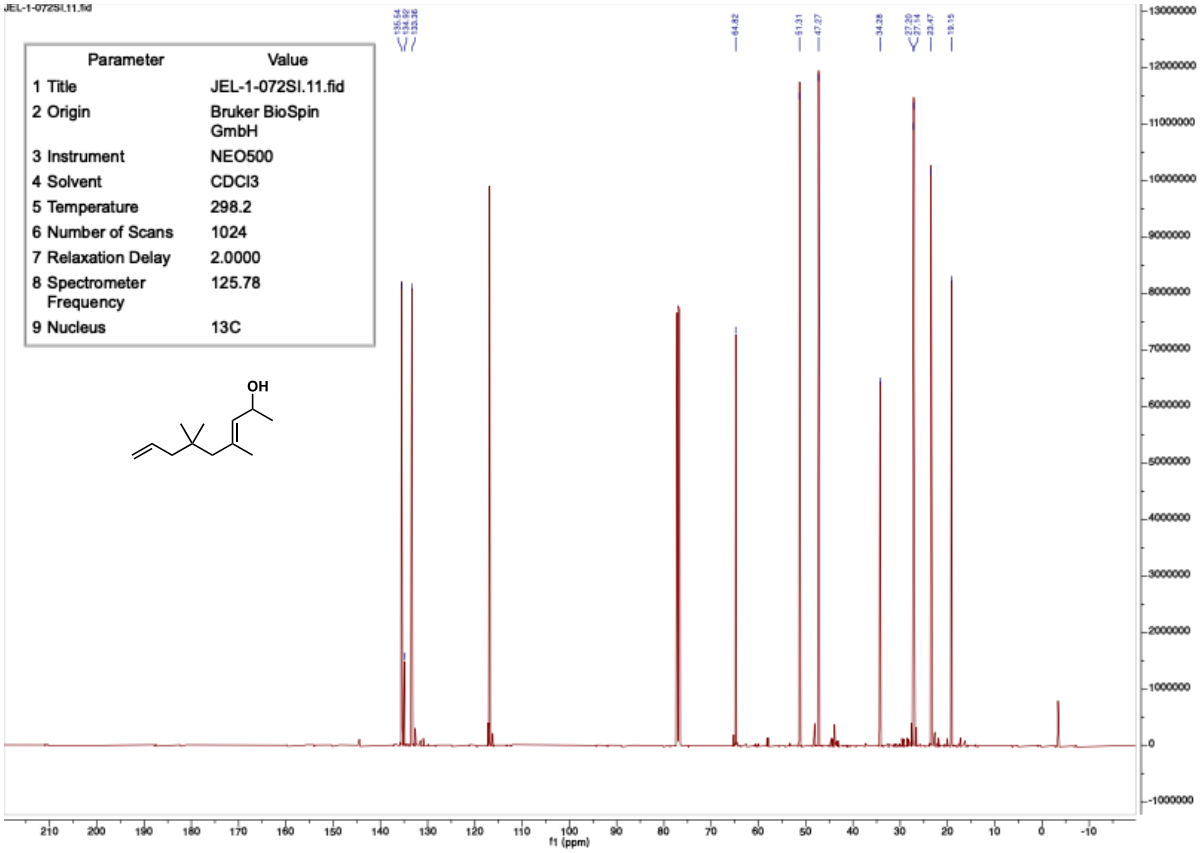

JEL-1-062SI.10.fid
Parameter Value
1 Title JEL-1-062SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
O
f1 (ppm)

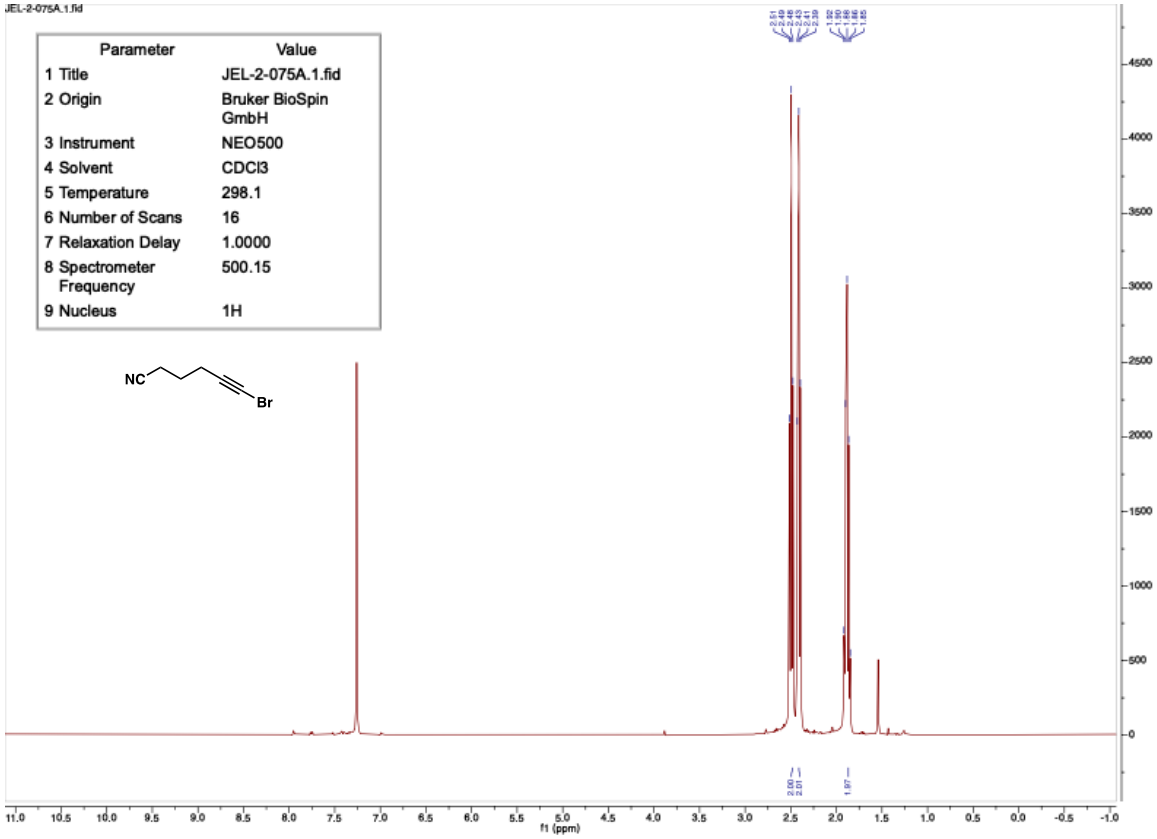

JEL-1-062SI.11.fid
Parameter Value
1 Title JEL-1-062SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
O
f1 (ppm)

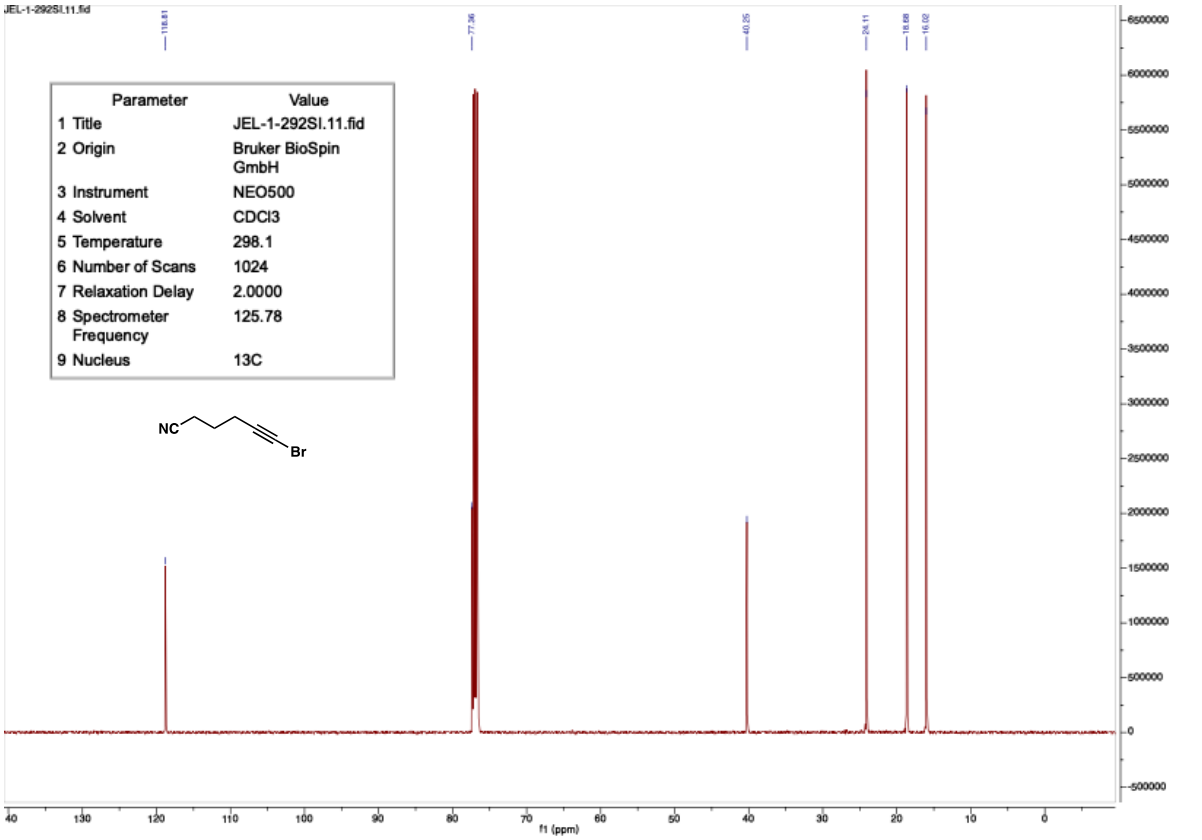

BR-6-252ASI.10.fid
Parameter Value
1 Title BR-6-252ASI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
f1 (ppm)

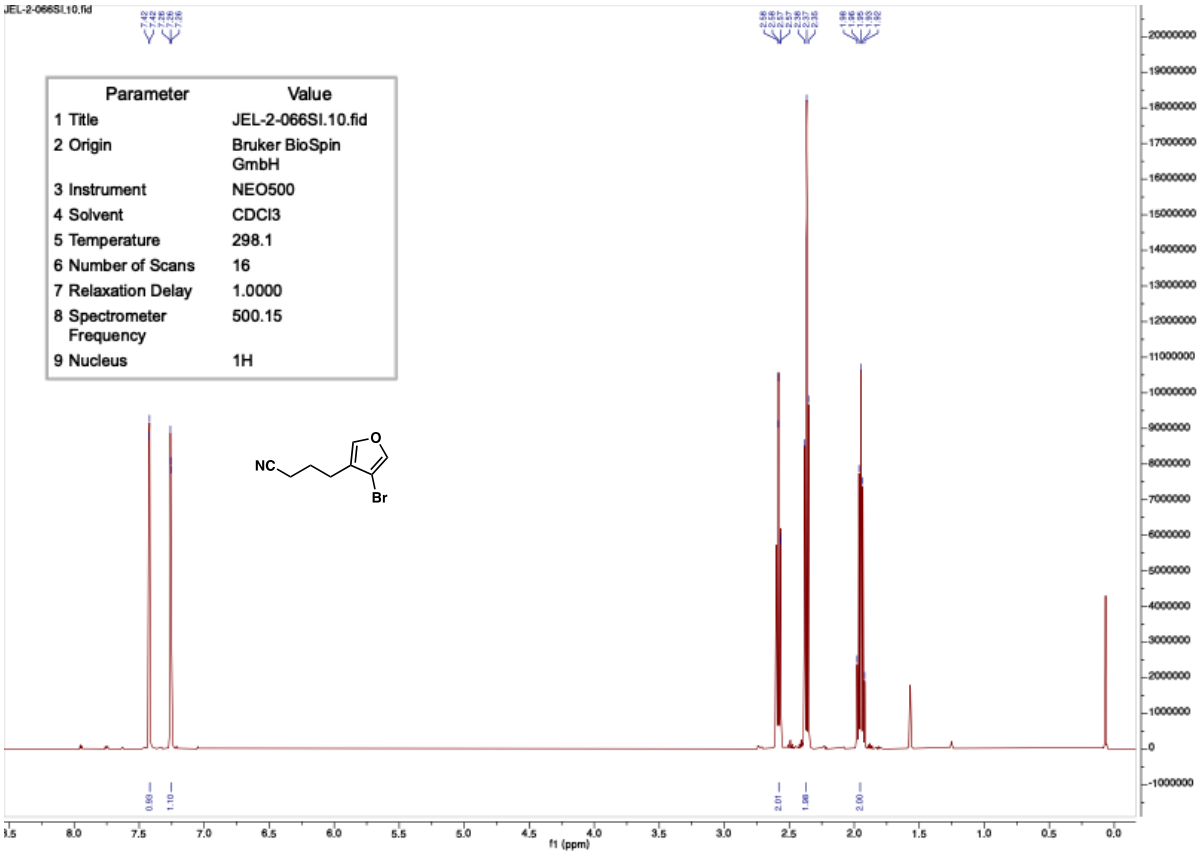

BR-6-252ASI.11.fid
Parameter Value
1 Title BR-6-252ASI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
f1 (ppm)

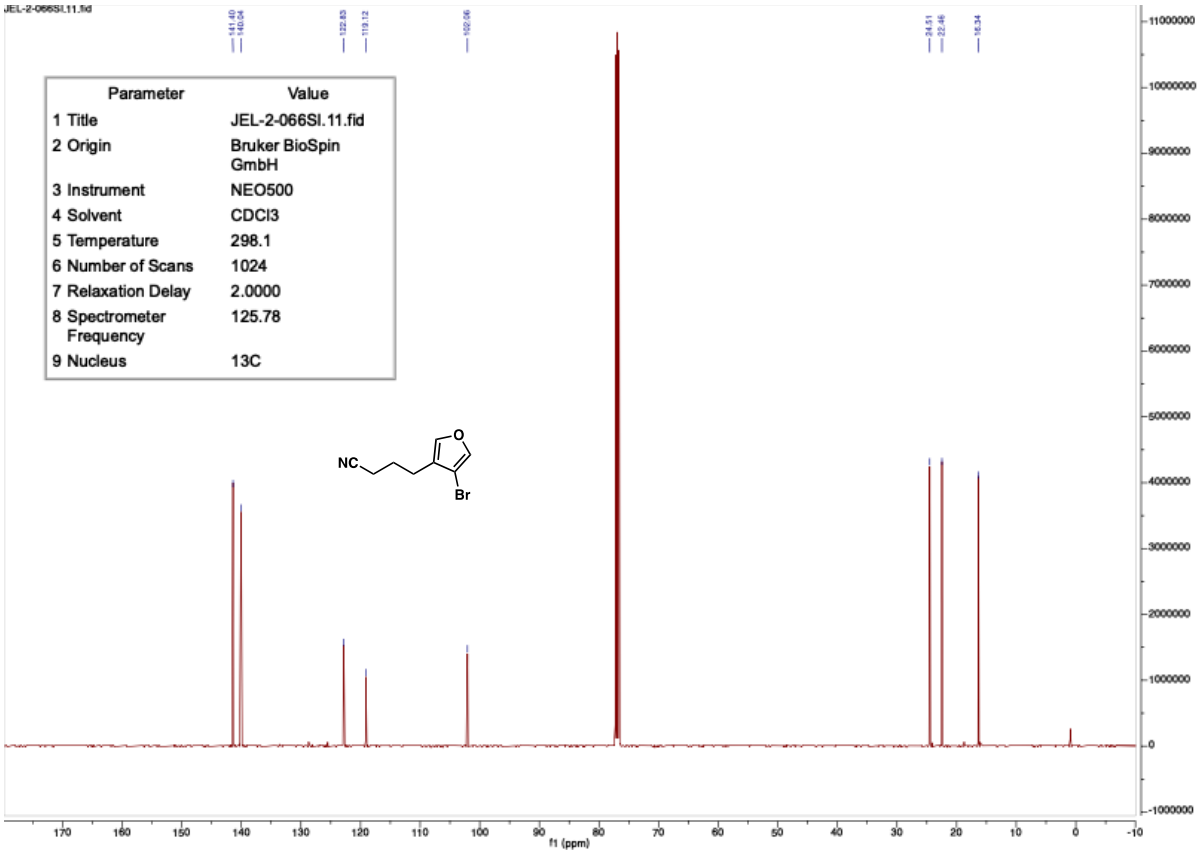

JEL-1-072SI.10.fid
Parameter Value
1 Title JEL-1-072SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
OH
f1 (ppm)

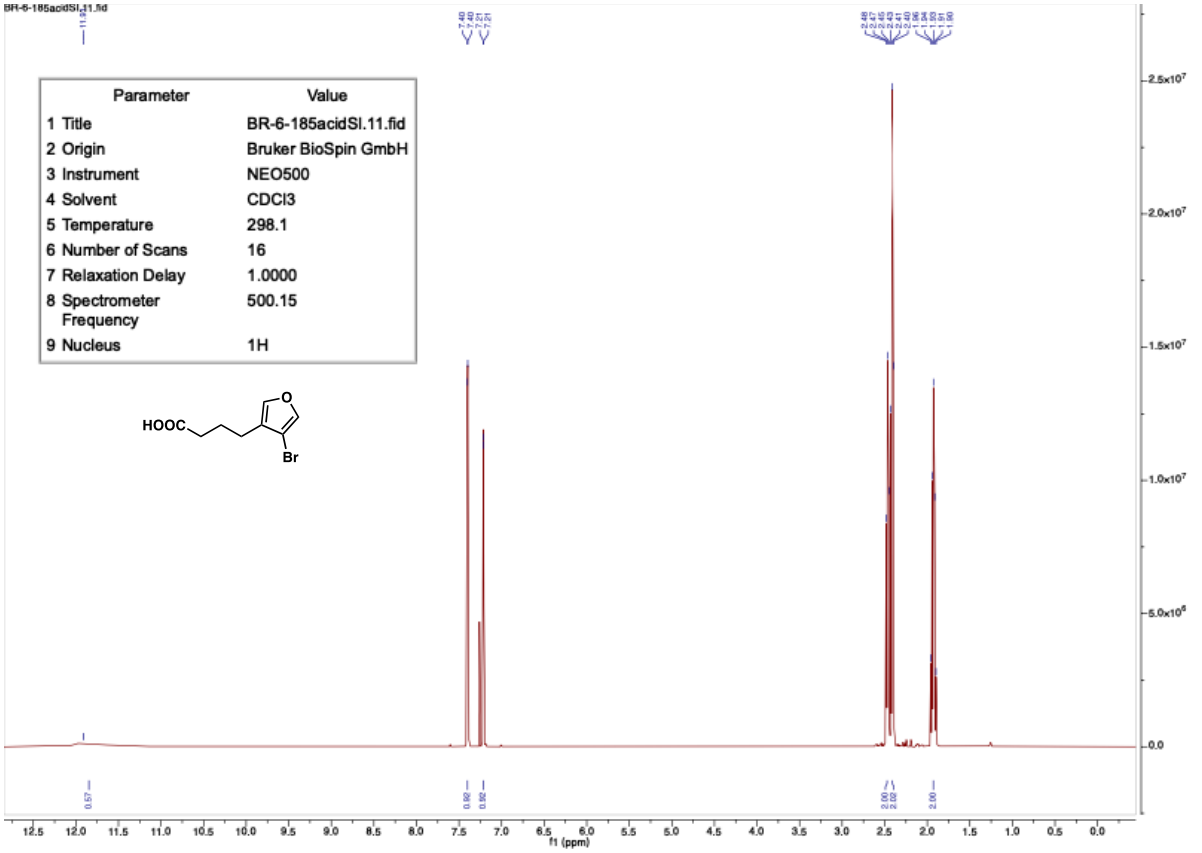

JEL-1-072SI.11.fid
Parameter Value
1 Title JEL-1-072SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
OH
f1 (ppm)

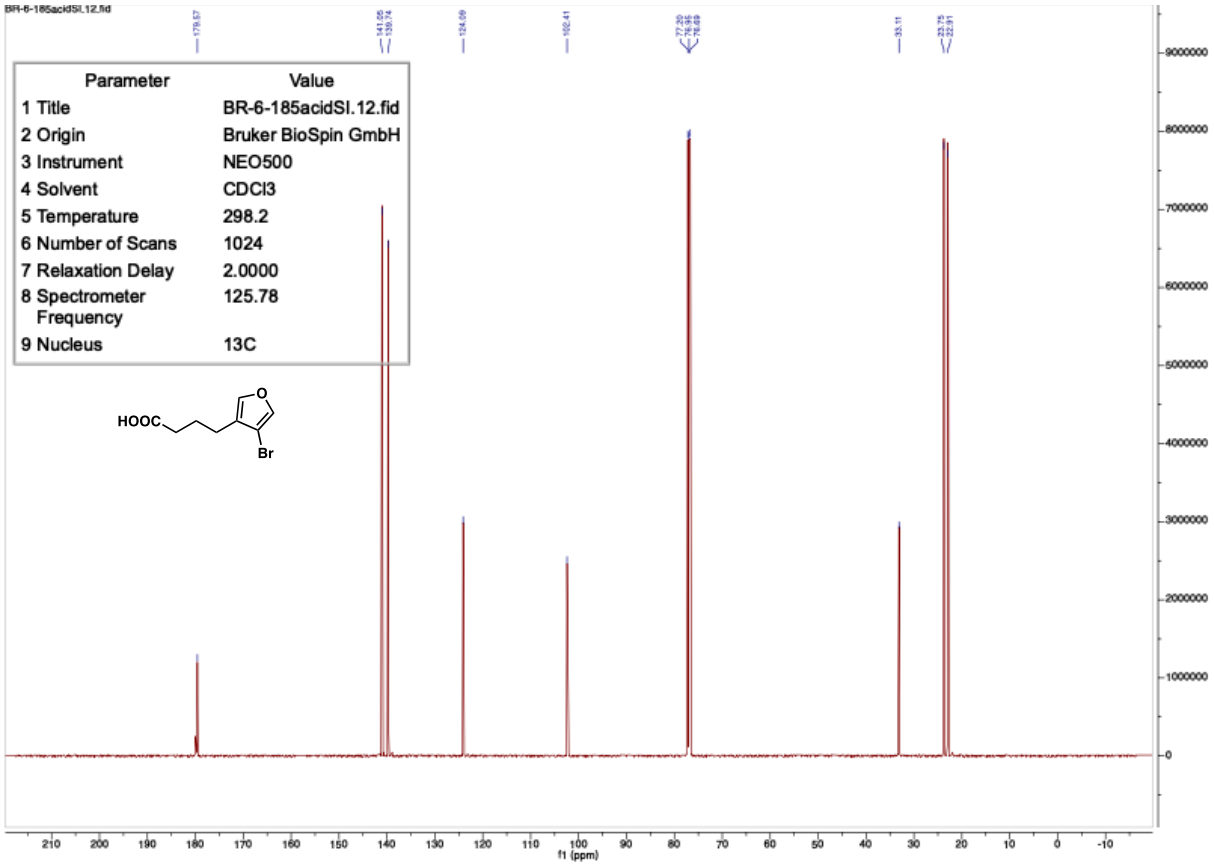

JEL-2-075A.1.fid
Parameter Value
1 Title JEL-2-075A.1.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
NC
Br
f1 (ppm)

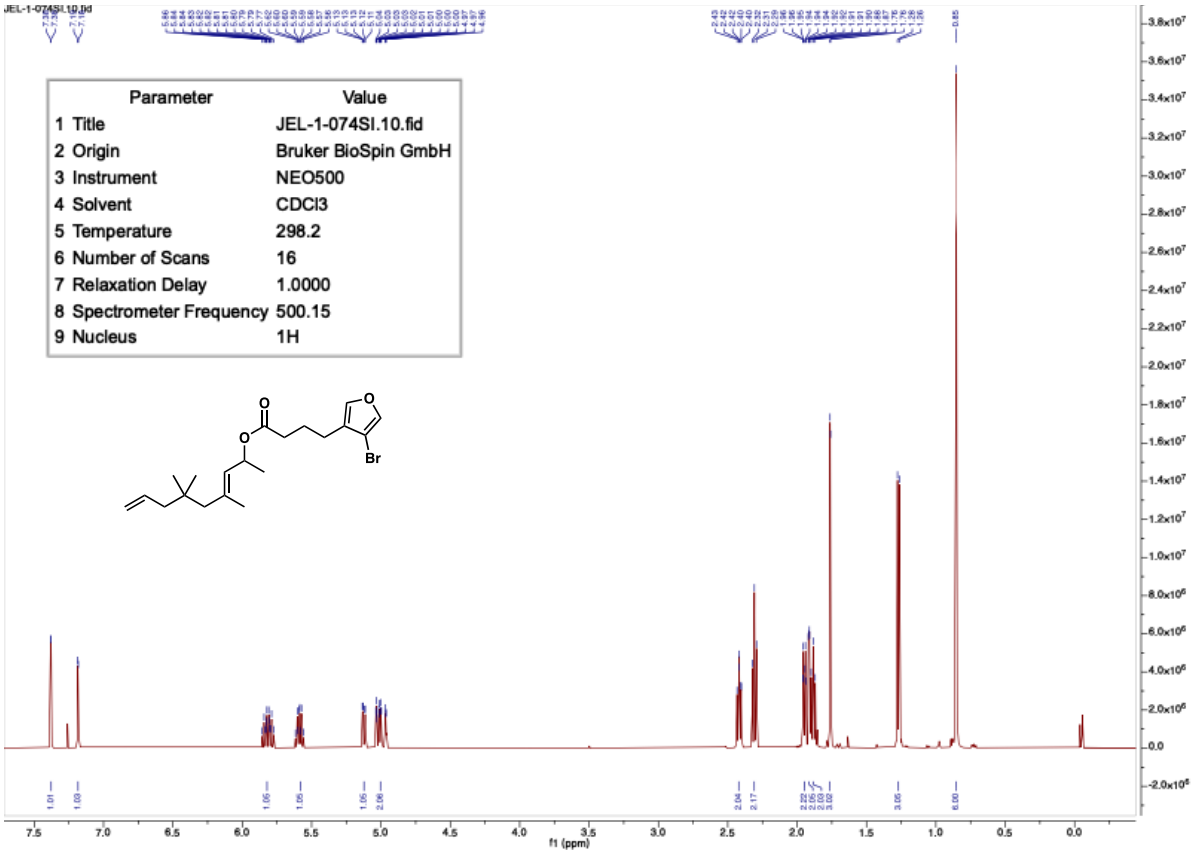

JEL-1-292SI.11.fid
118.81
77.36
40.25
24.11
18.68
16.02
Parameter Value
1 Title JEL-1-292SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
NC
Br
f1 (ppm)

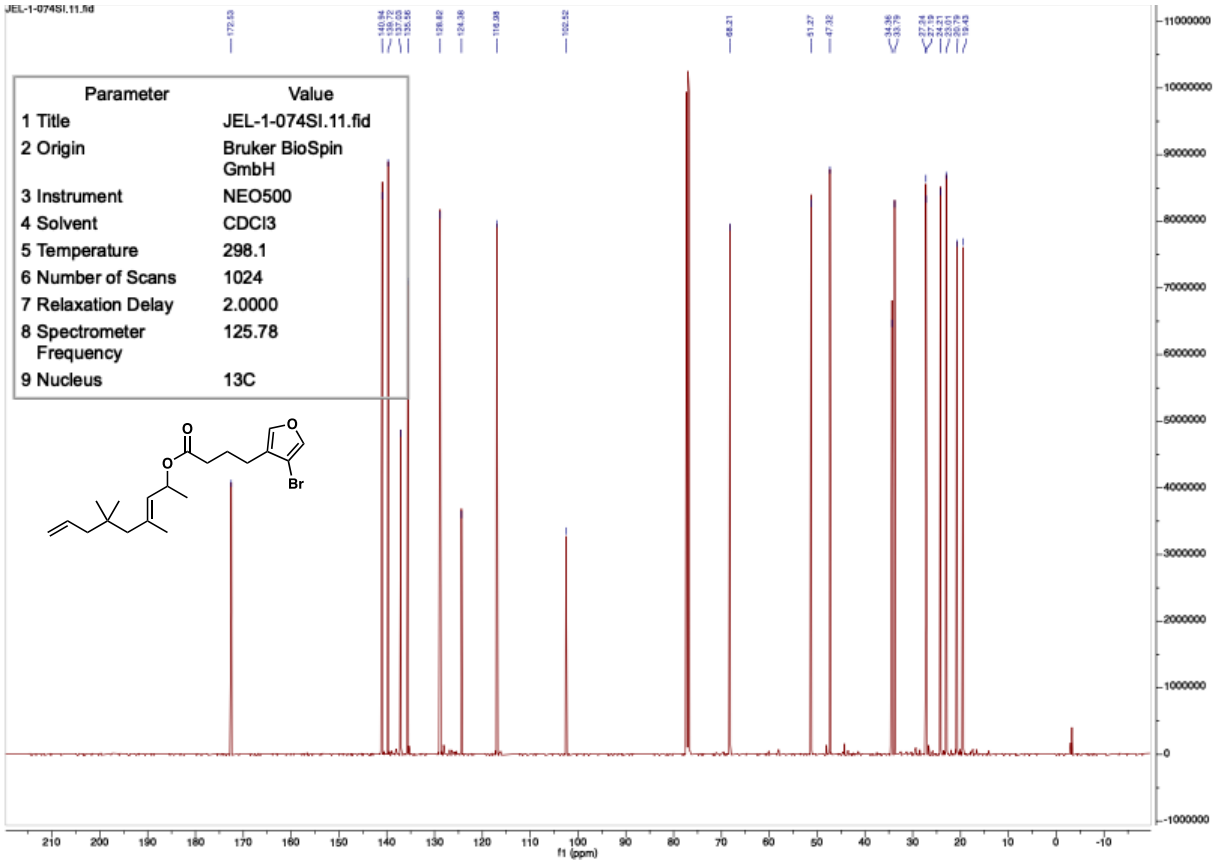

JEL-2-066SI.10.fid
Parameter Value
1 Title JEL-2-066SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
NC
O
Br
f1 (ppm)

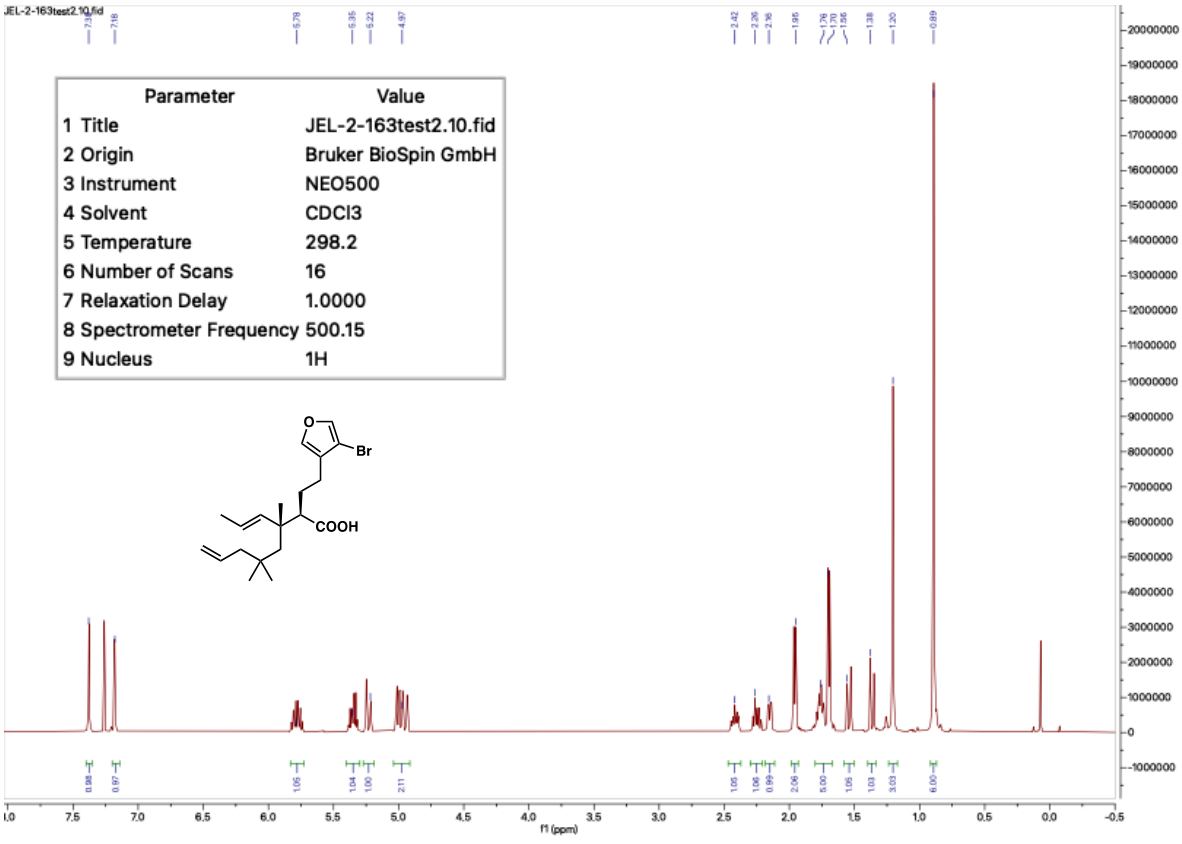

JEL-2-066Sl.11.fid
141.40
140.04
122.83
119.12
102.06
34.51
22.46
18.34
Parameter Value
1 Title JEL-2-066Sl.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
NC
O
Br
f1 (ppm)

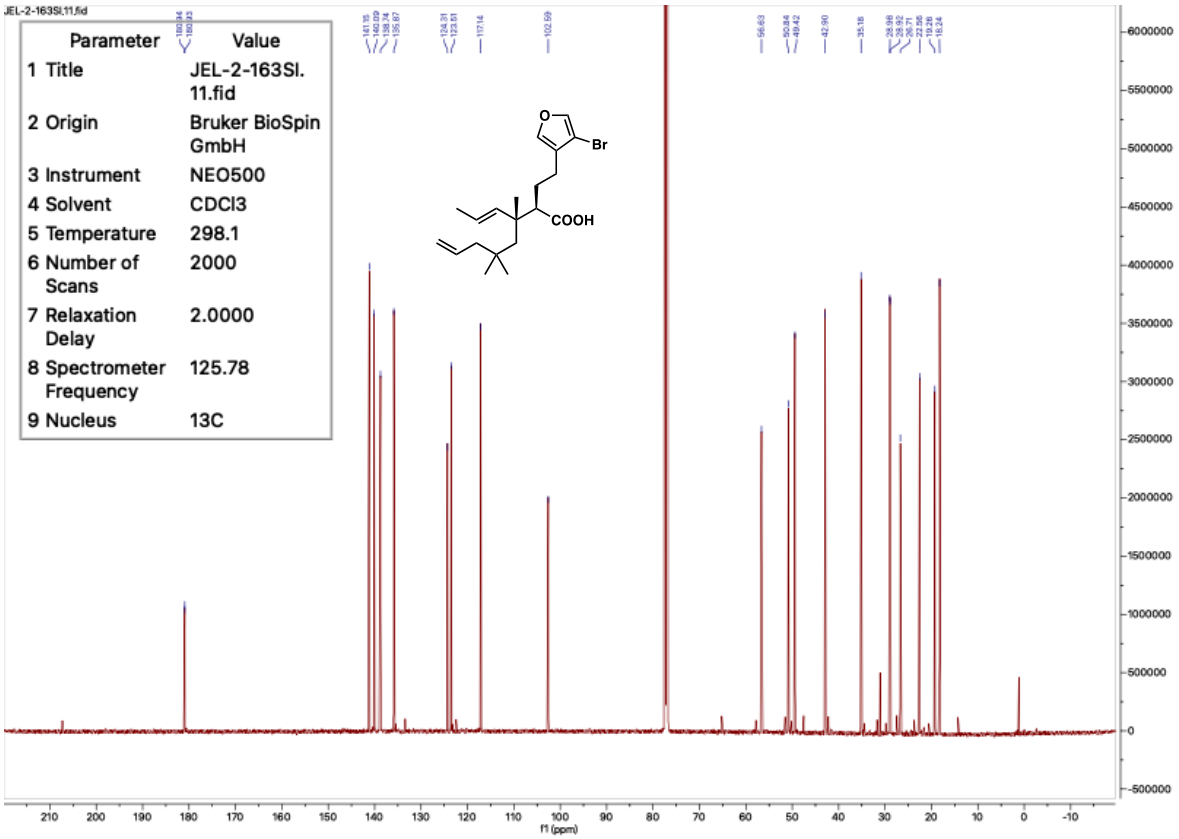

BR-6-185acidSI.11.fid
11.82
7.40
7.40
7.21
7.21
Parameter Value
1 Title BR-6-185acidSI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
HOOC
O
Br
0.57
0.92
0.92
2.00
2.00
f1 (ppm)

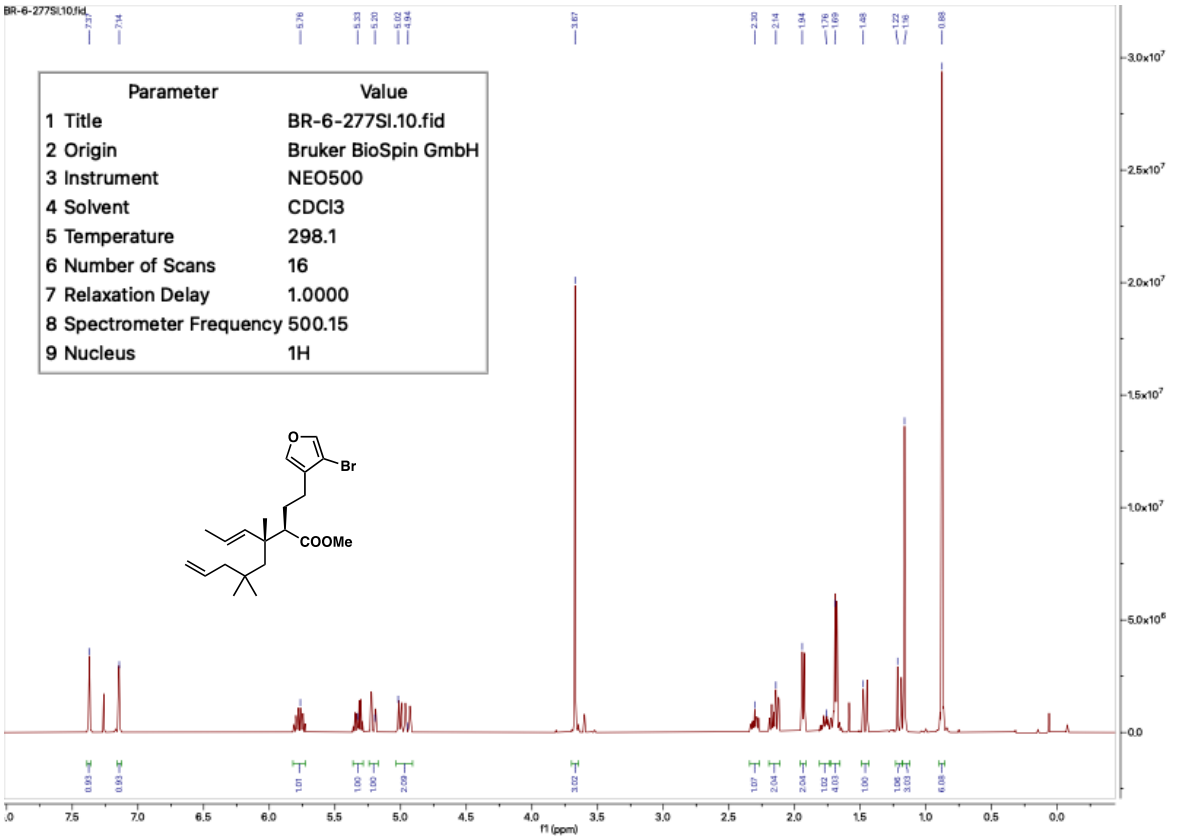

BR-6-185acidSI.12.fid
179.57
141.05
139.74
124.09
102.41
77.20
76.95
76.69
33.11
23.75
22.91
Parameter Value
1 Title BR-6-185acidSI.12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
HOOC
O
Br
f1 (ppm)

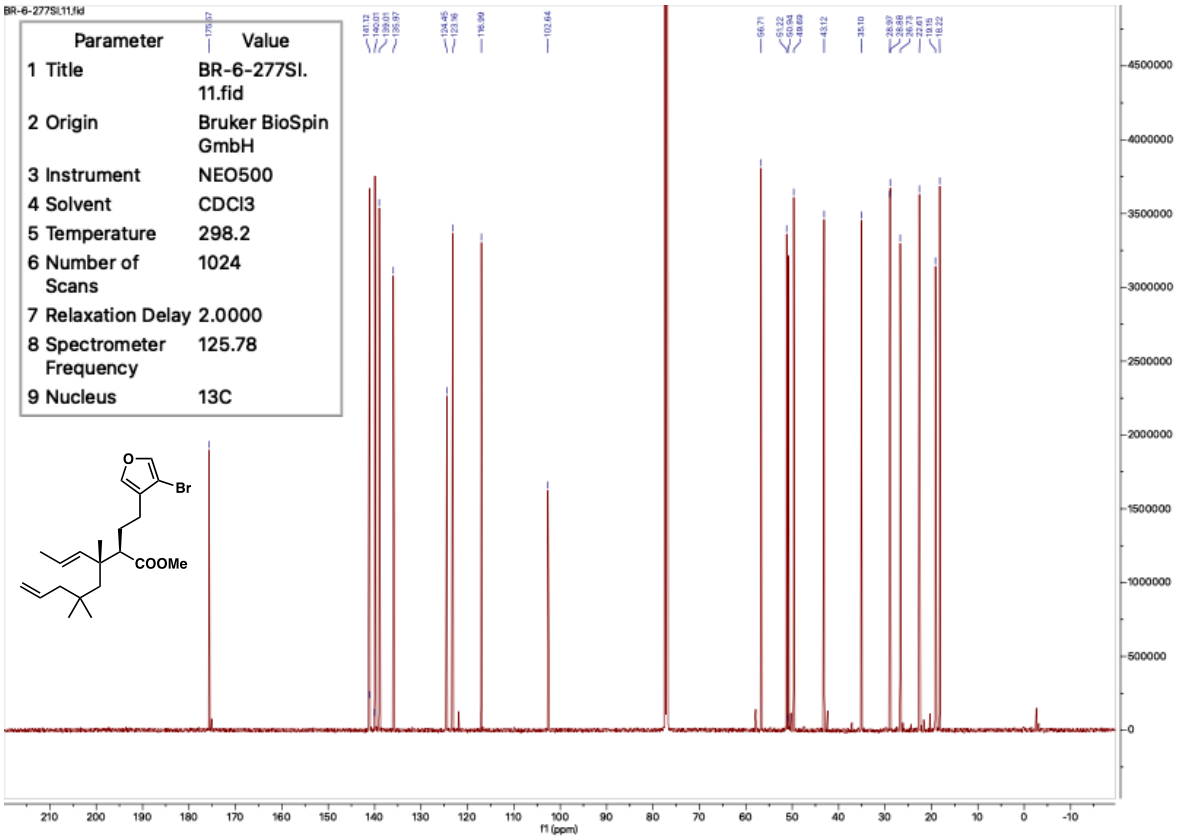

JEL-1-074SI.10.fid
Parameter Value
1 Title JEL-1-074SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
O
O
O
Br
f1 (ppm)

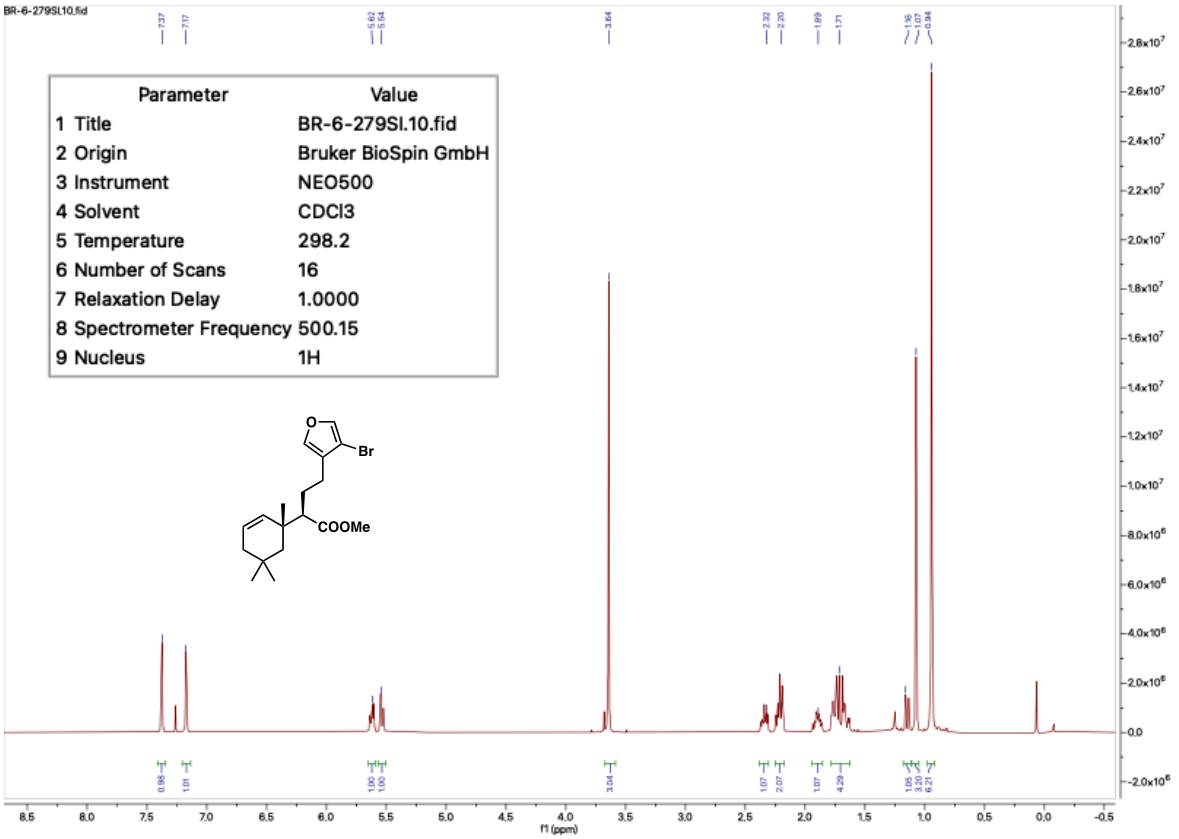

JEL-1-074SI.11.fid
Parameter Value
1 Title JEL-1-074SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
f1 (ppm)

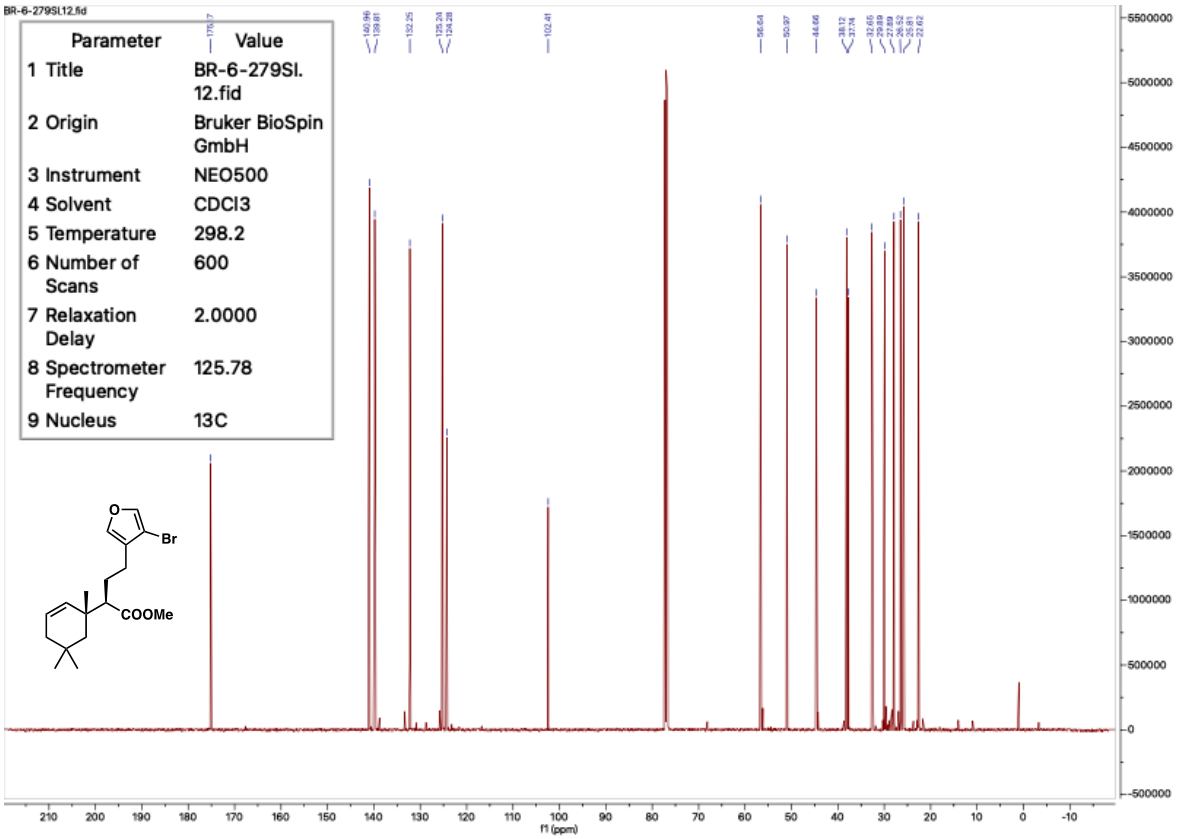

JEL-2-163test2.10.fid
Parameter Value
1 Title JEL-2-163test2.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
COOH
f1 (ppm)

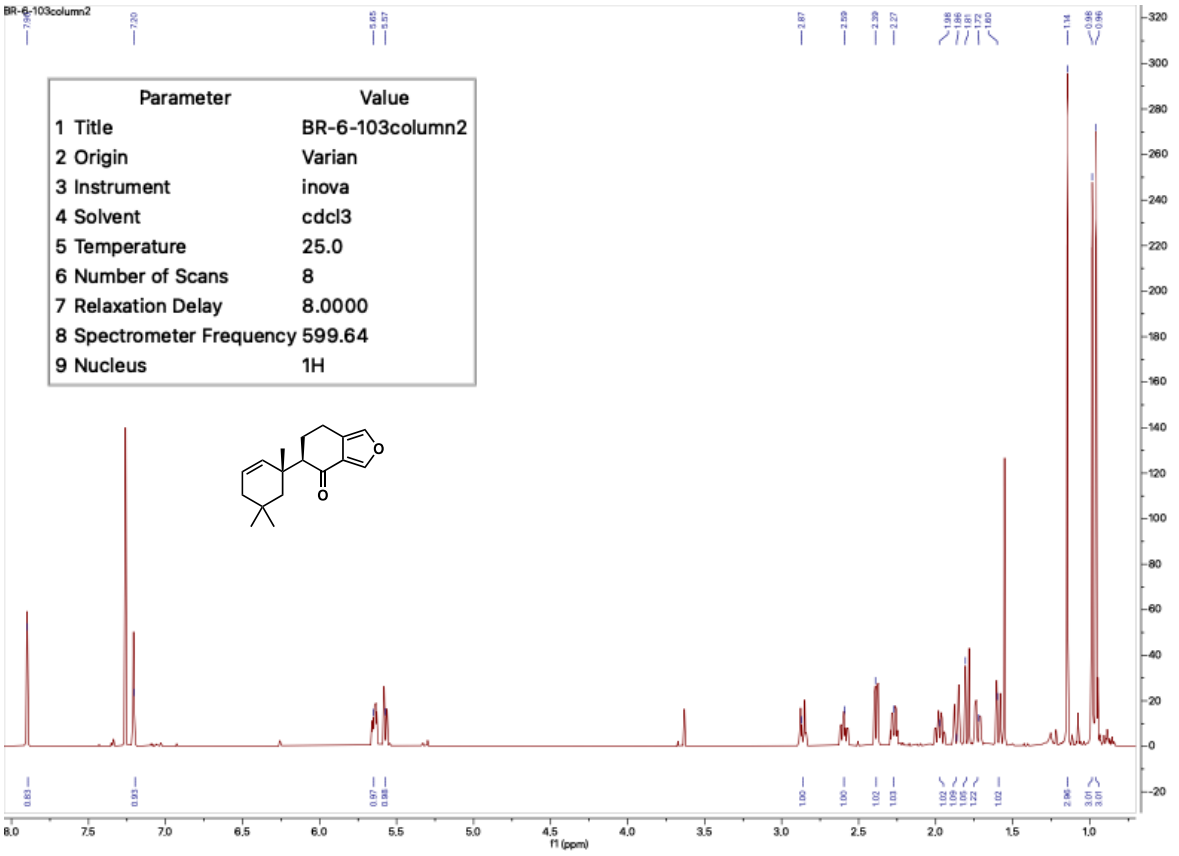

JEL-2-163Sl.11.fid
Parameter Value
1 Title JEL-2-163Sl. 11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 2000
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
COOH
f1 (ppm)

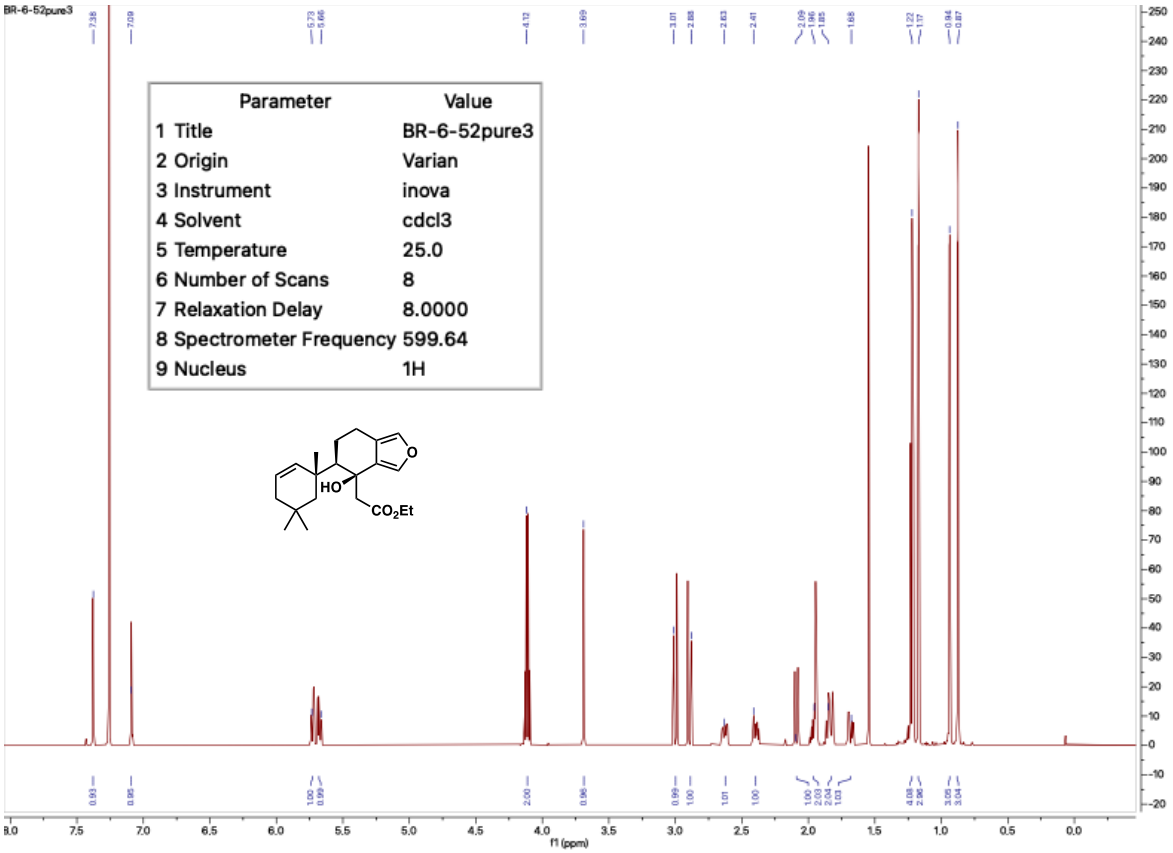

BR-6-277Sl.10.fid
Parameter Value
1 Title BR-6-277Sl.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
COOMe
f1 (ppm)

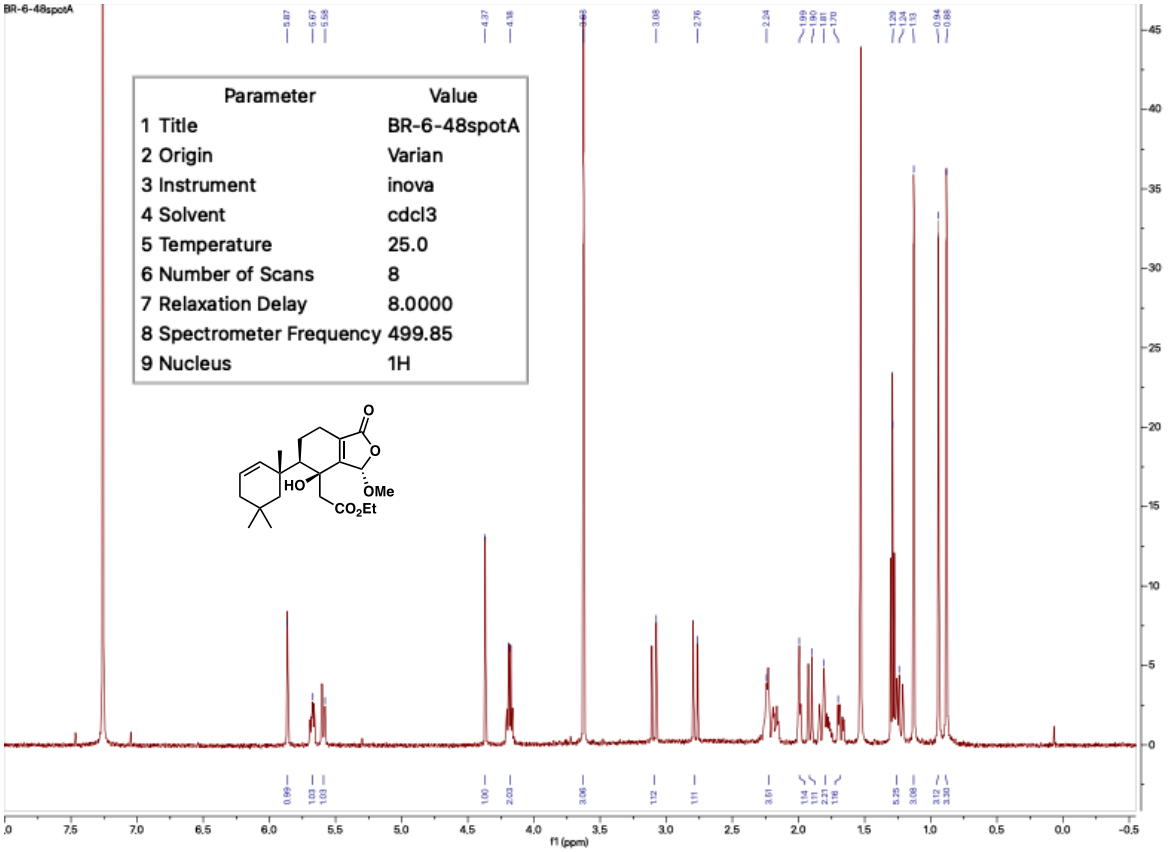

BR-6-277SI.11.fid
Parameter Value
1 Title BR-6-277SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
COOMe
f1 (ppm)

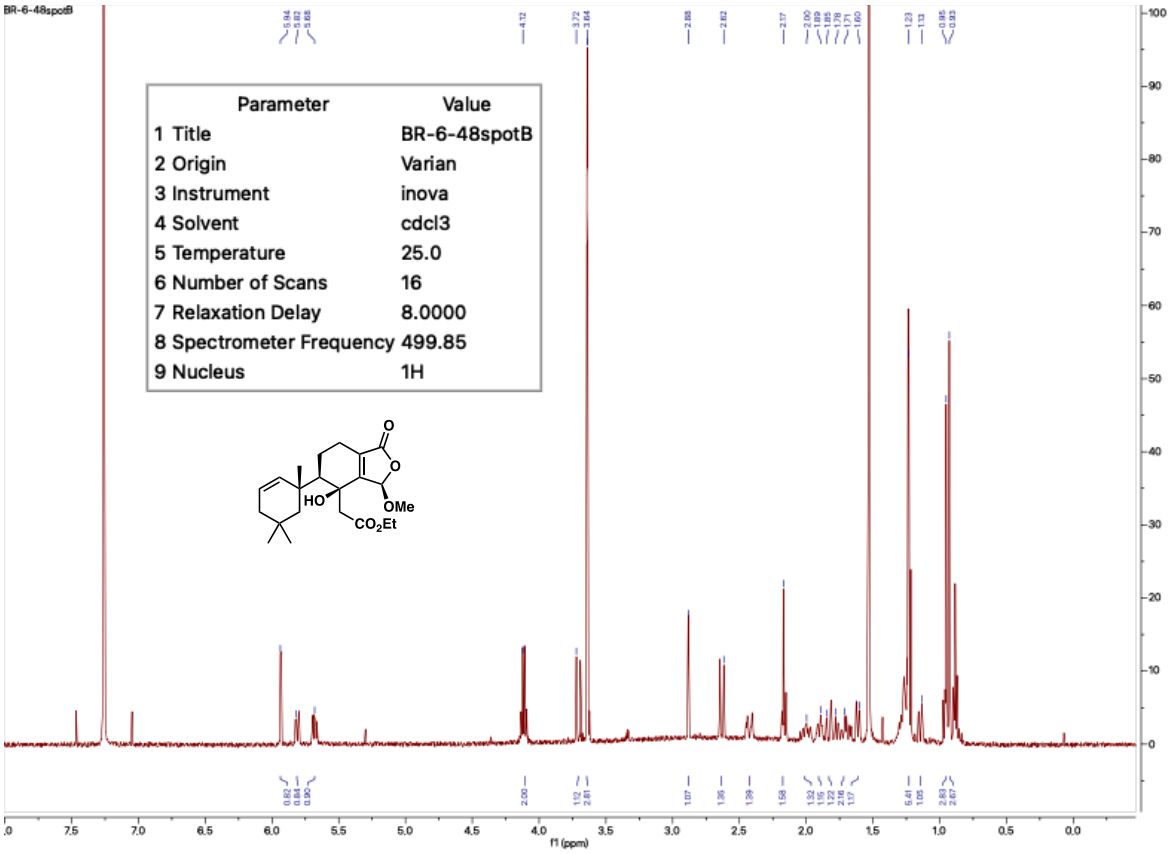

BR-6-279SI.10.fid
Parameter Value
1 Title BR-6-279SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
COOMe
f1 (ppm)

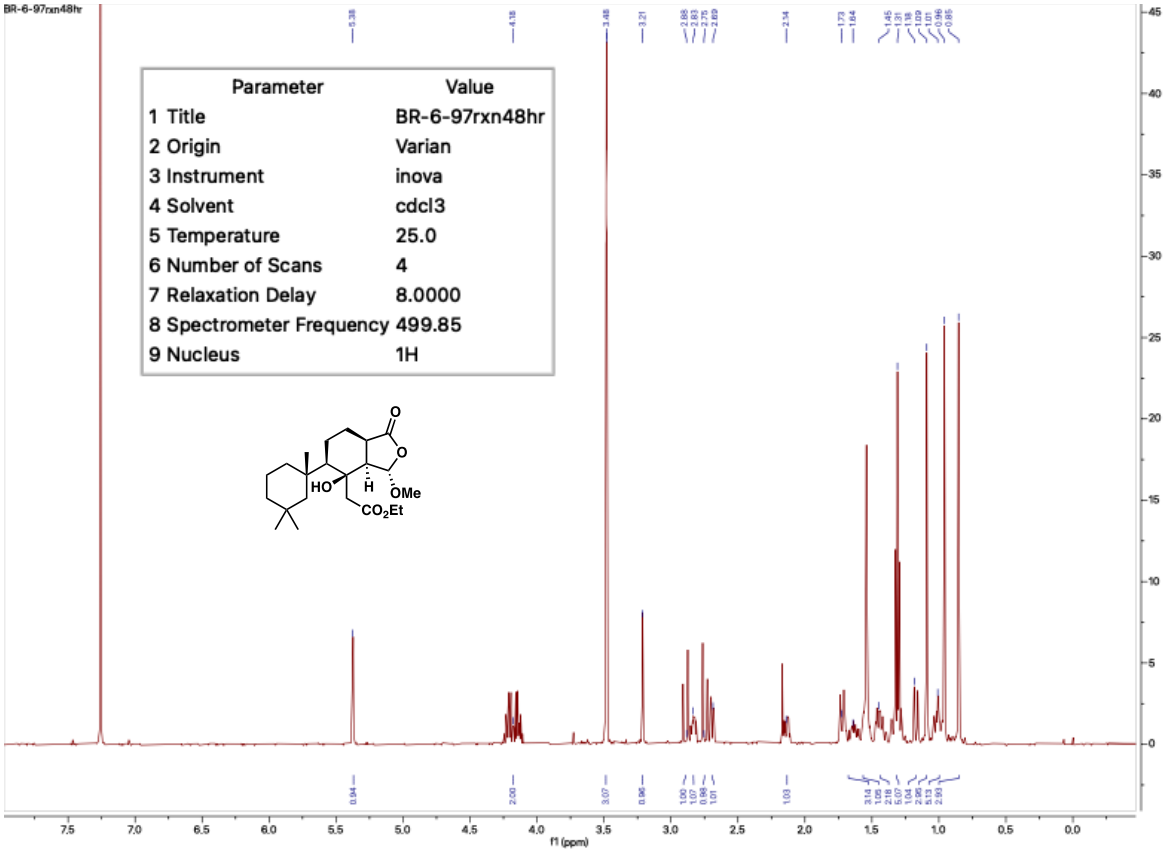

BR-6-279Sl.12.fid
Parameter Value
1 Title BR-6-279Sl. 12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 600
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
COOMe
f1 (ppm)

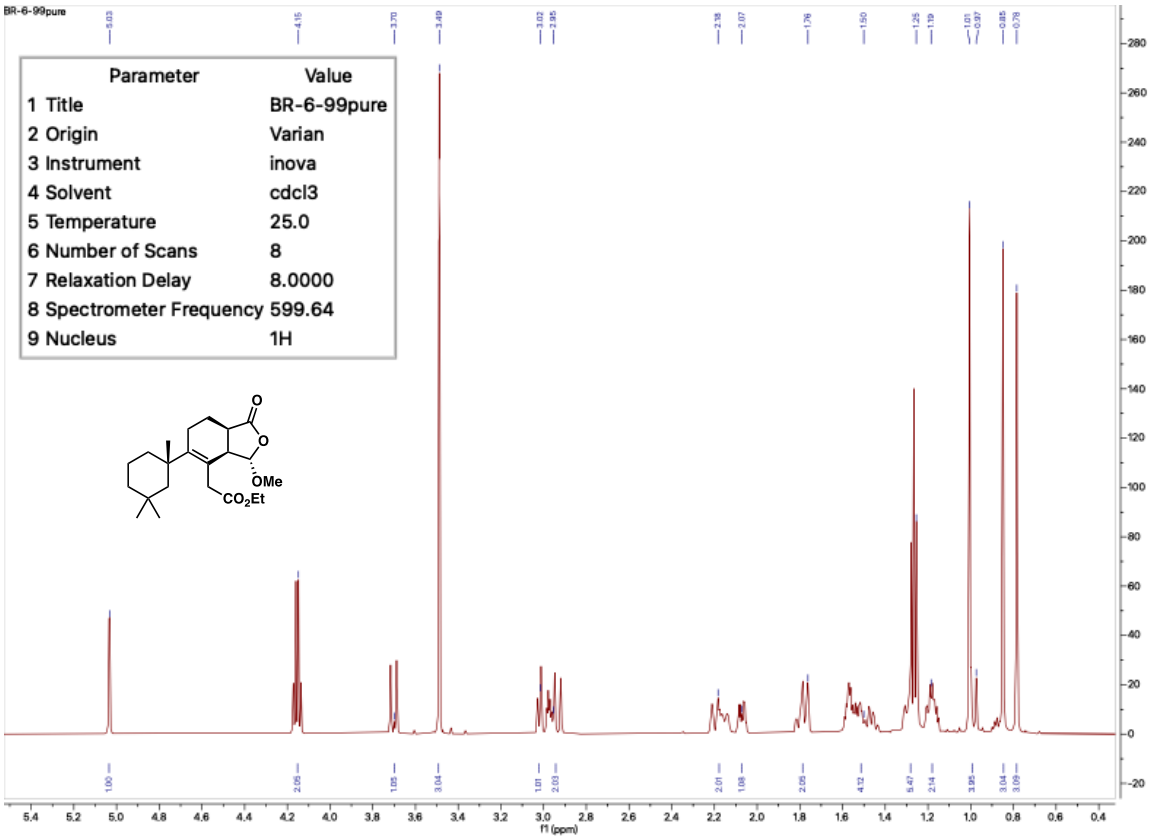

BR-6-103column2
Parameter Value
1 Title BR-6-103column2
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
O
O
f1 (ppm)

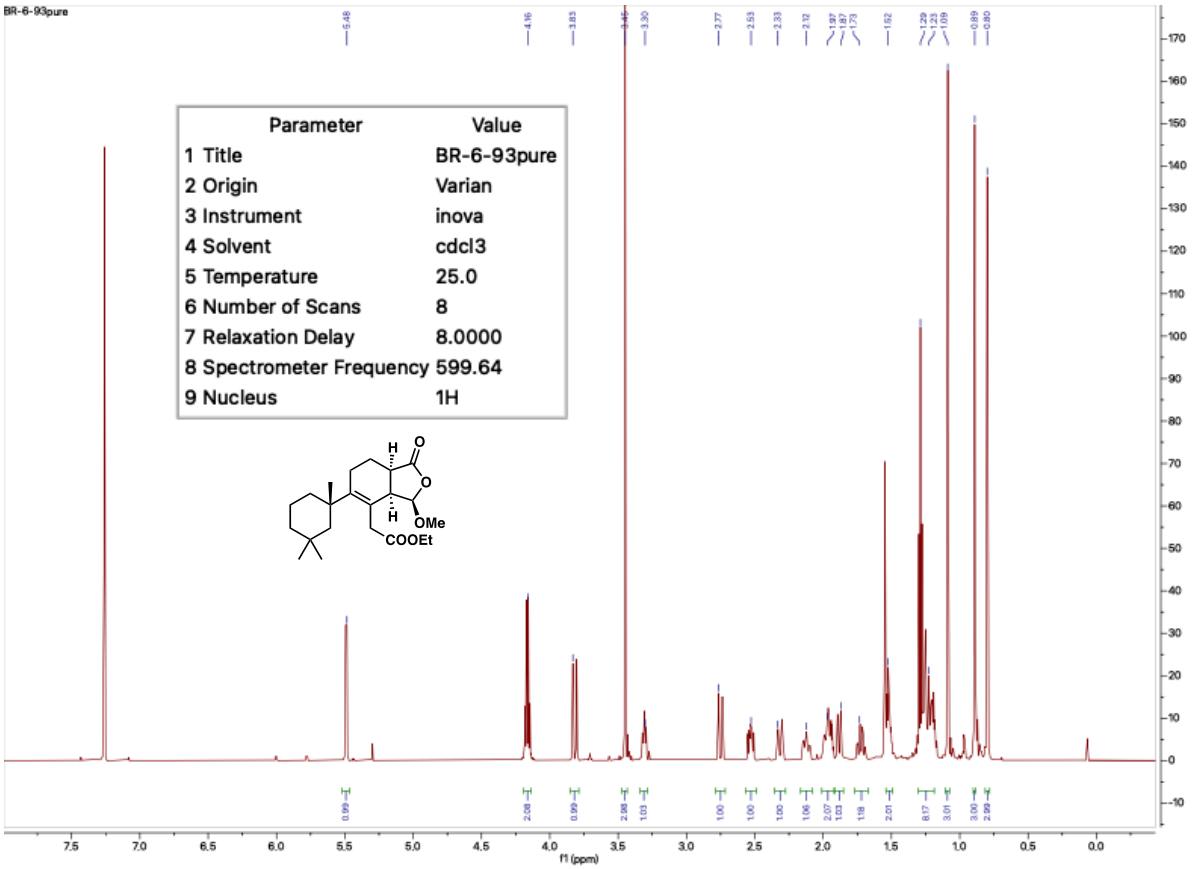

BR-6-52pure3
Parameter Value
1 Title BR-6-52pure3
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
O
CO2Et
f1 (ppm)

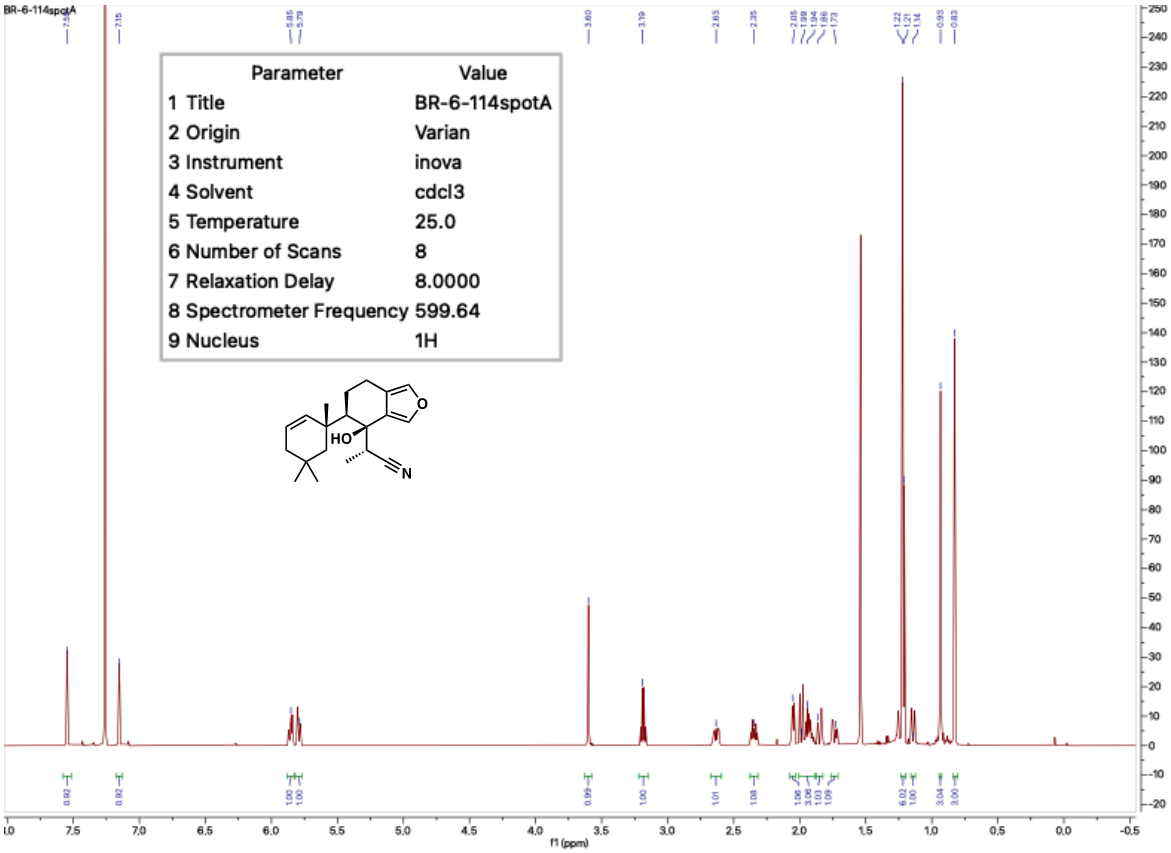

BR-6-48spotA
Parameter Value
1 Title BR-6-48spotA
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
O
OMe
CO2Et
f1 (ppm)

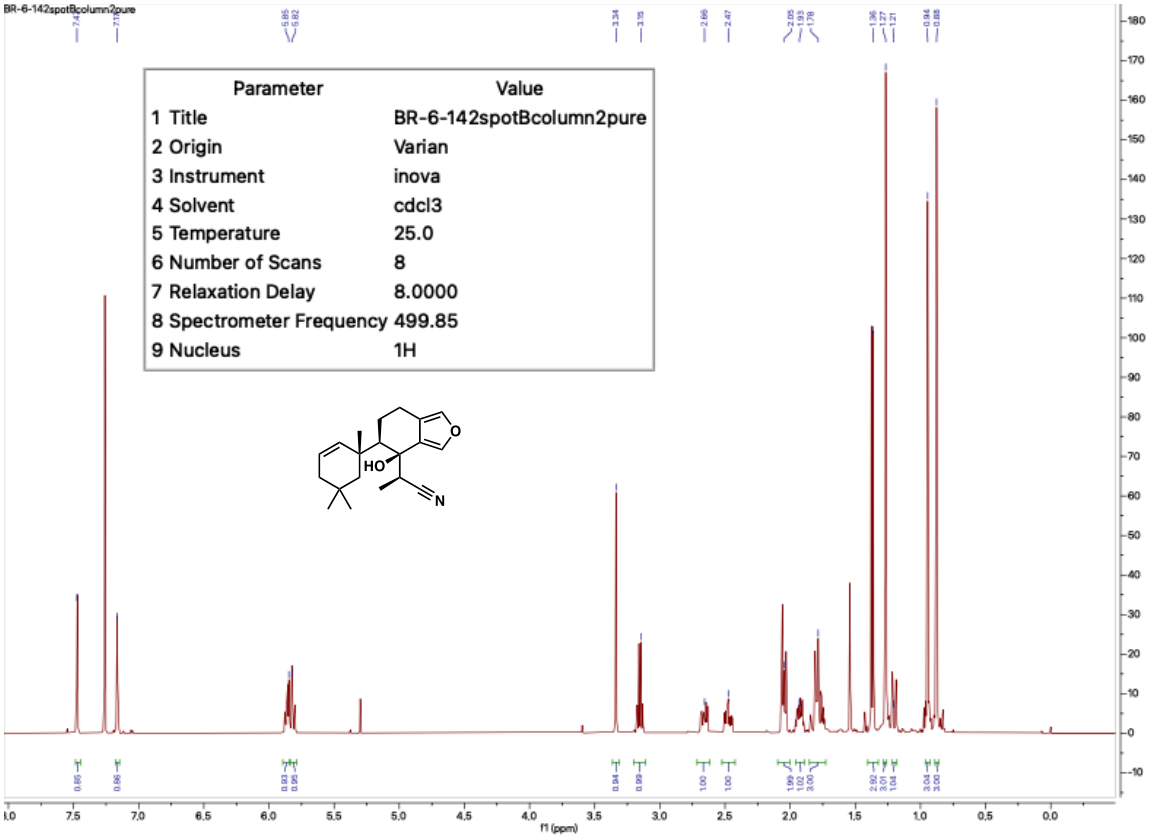

BR-6-48spotB
Parameter Value
1 Title BR-6-48spotB
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 16
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
OMe
CO2Et
f1 (ppm)

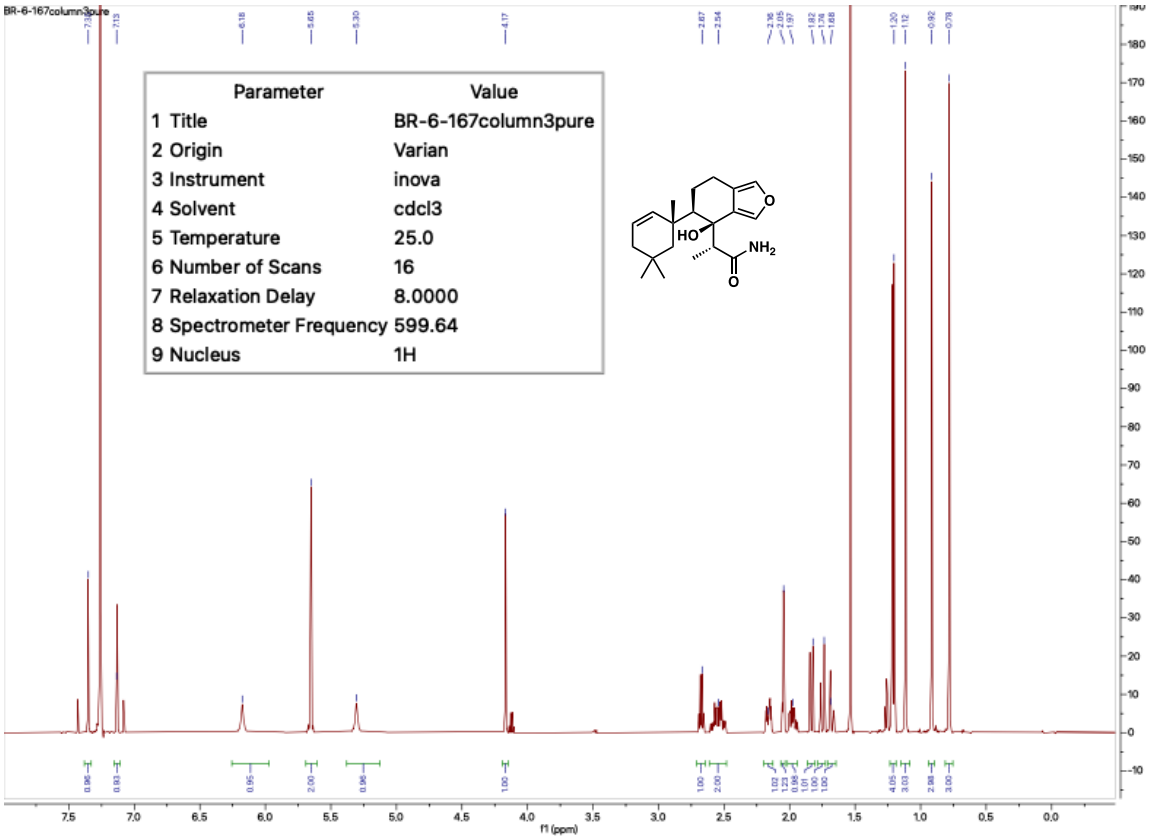

BR-6-97rxn48hr
Parameter Value
1 Title BR-6-97rxn48hr
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 4
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
H
OMe
CO2Et
f1 (ppm)

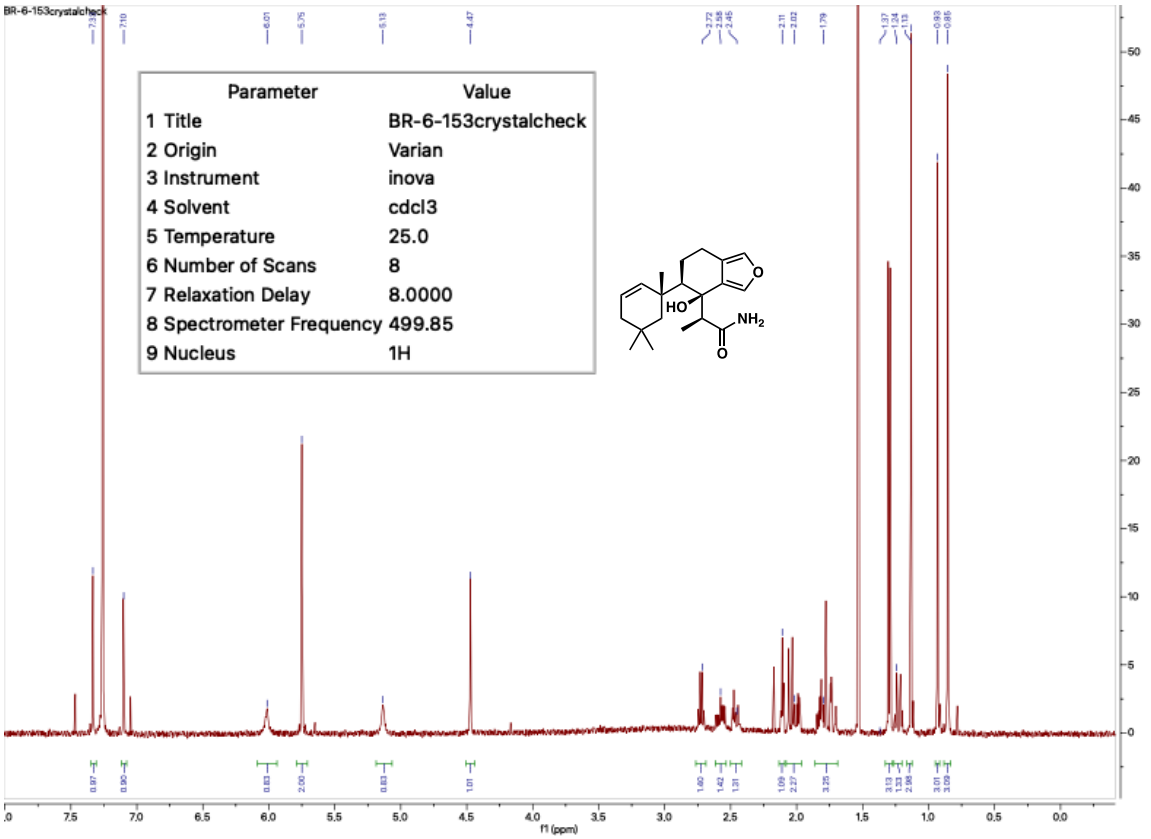

BR-6-99pure
Parameter Value
1 Title BR-6-99pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
OMe
CO2Et
f1 (ppm)

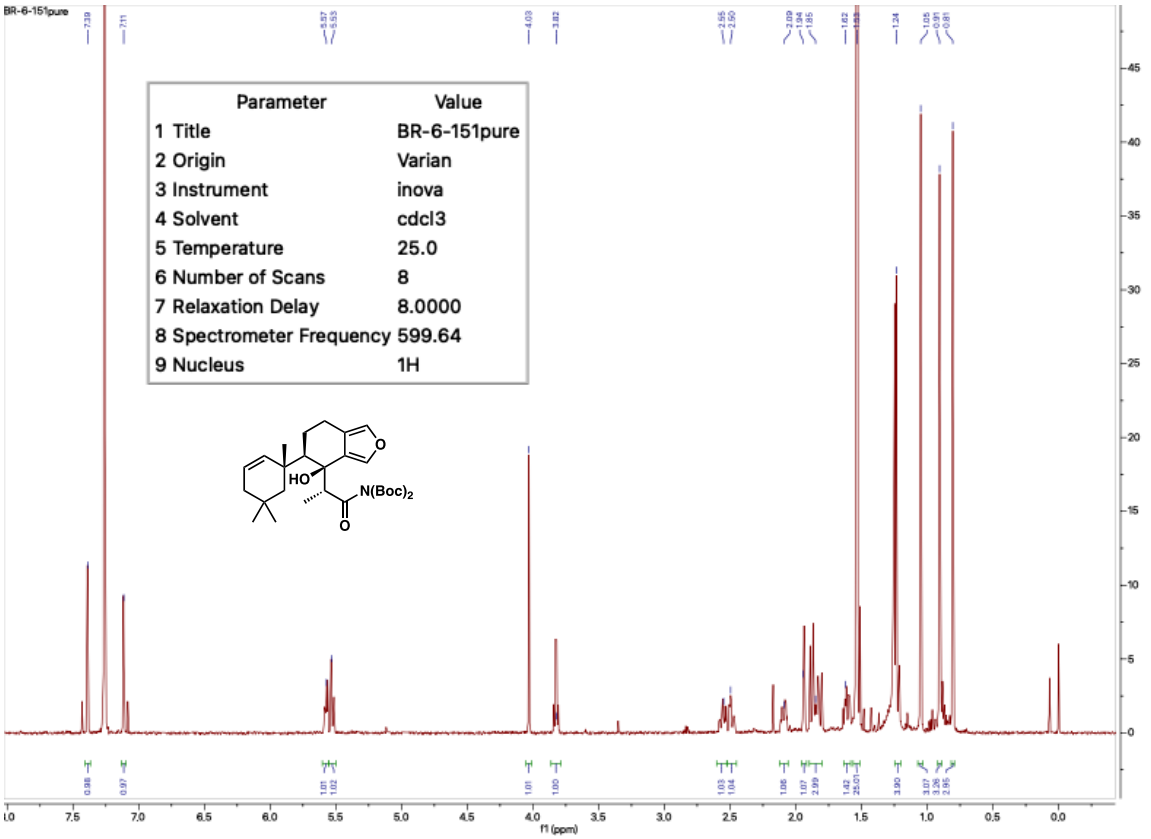

BR-6-93pure
Parameter Value
1 Title BR-6-93pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
H
H
OMe
COOEt
f1 (ppm)

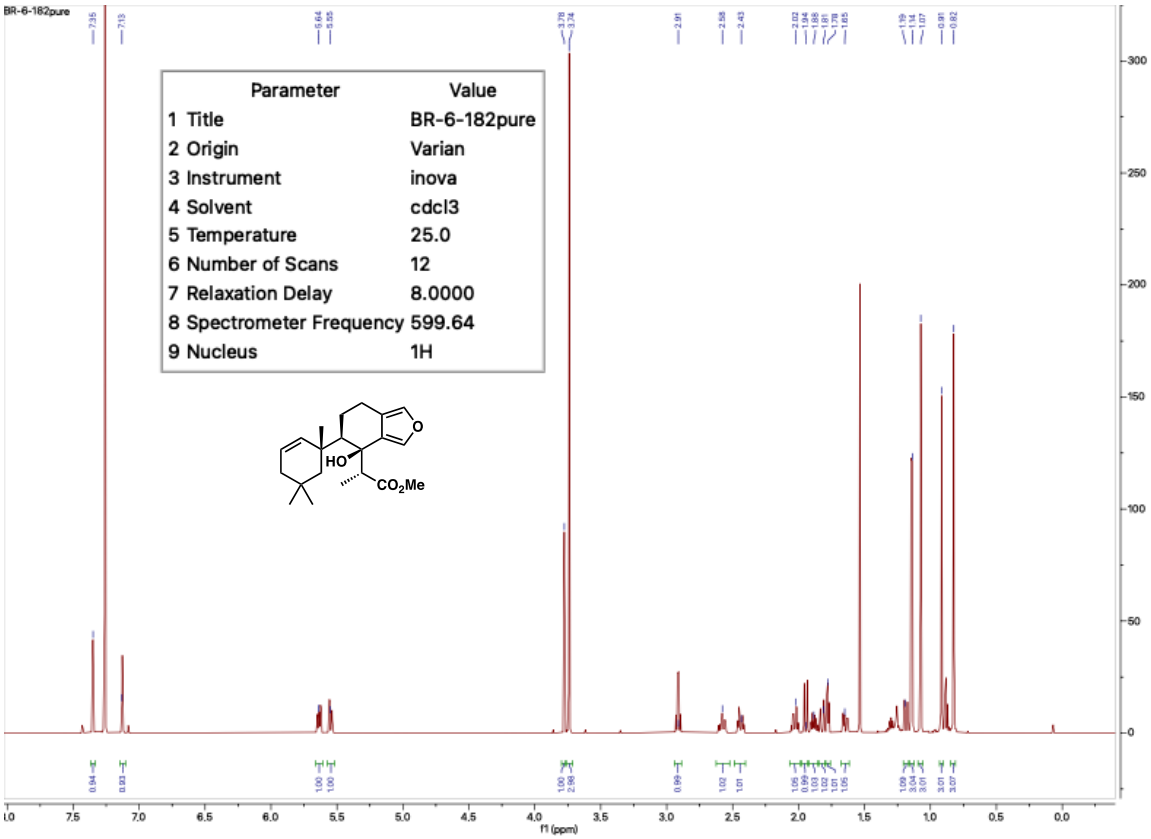

BR-6-114spotA
Parameter Value
1 Title BR-6-114spotA
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
O
N
f1 (ppm)

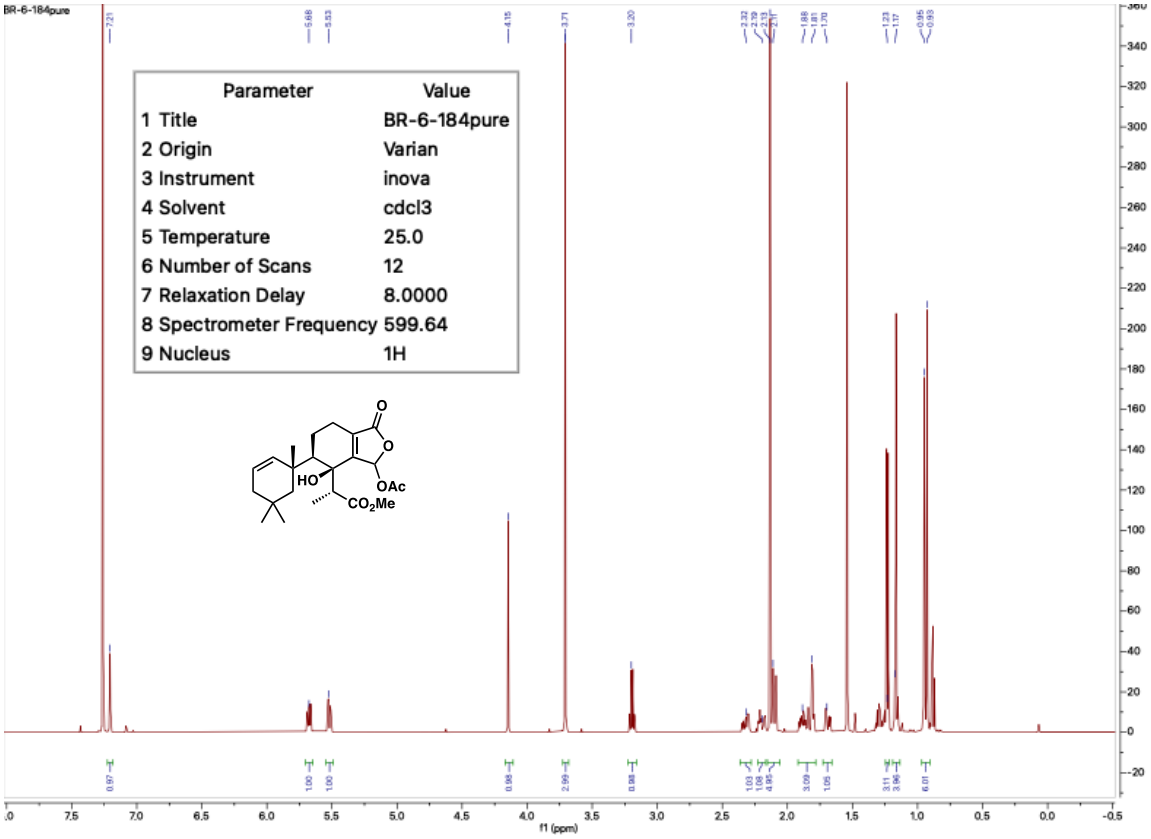

BR-6-142spotBcolumn2pure
Parameter Value
1 Title BR-6-142spotBcolumn2pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
O
N
f1 (ppm)

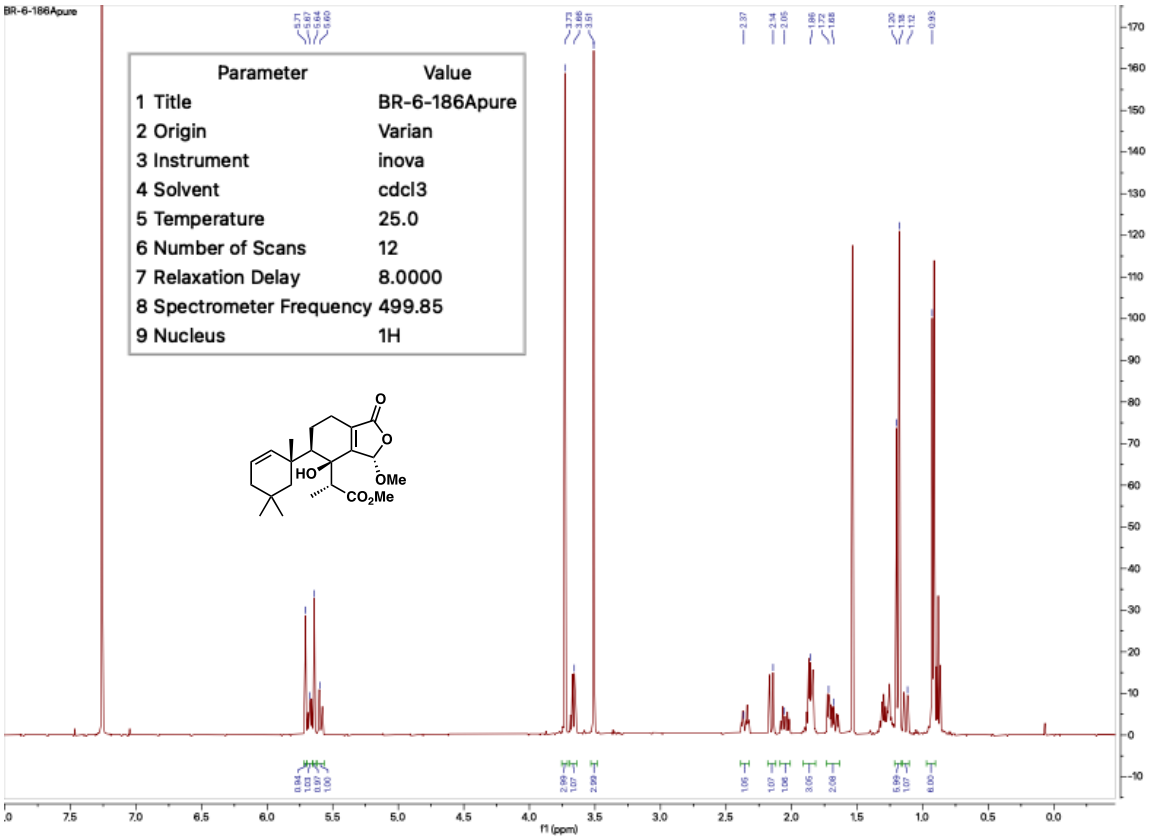

BR-6-167column3pure
Parameter Value
1 Title BR-6-167column3pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 16
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
NH2
O
f1 (ppm)

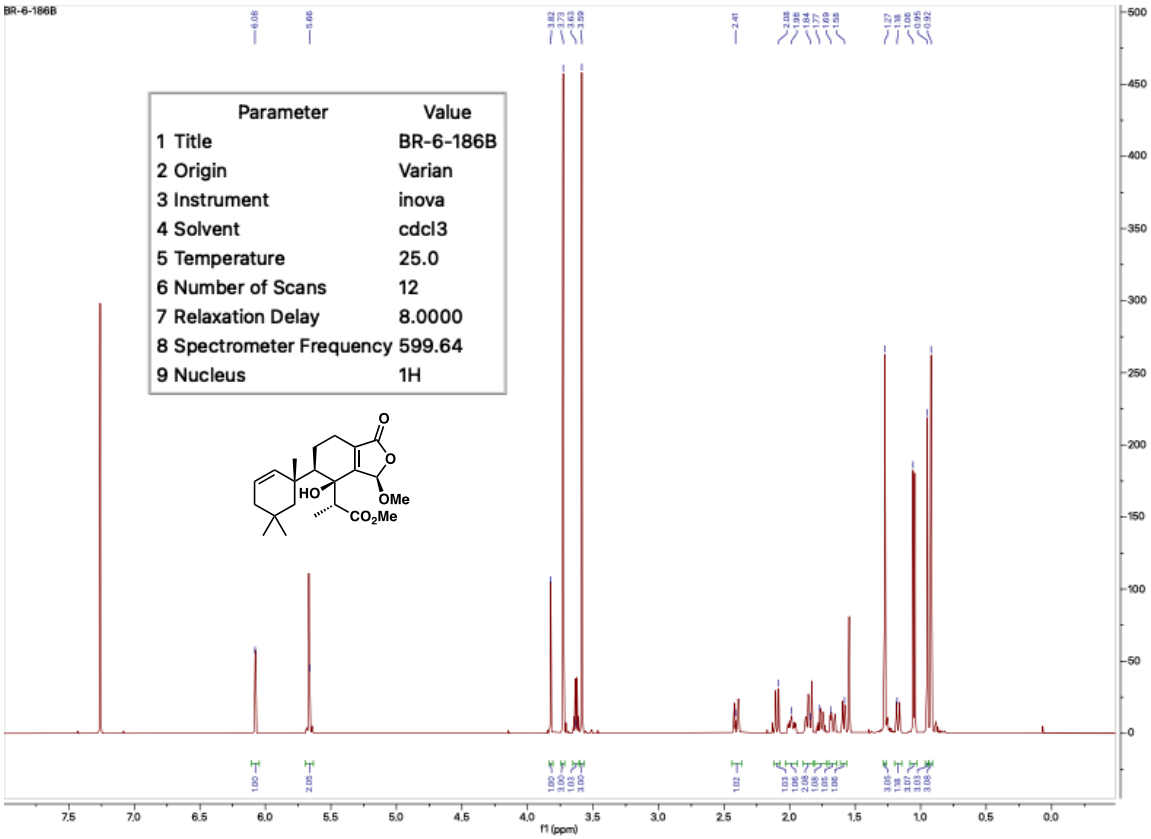

BR-6-153crystalcheck
Parameter Value
1 Title BR-6-153crystalcheck
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
NH2
O
f1 (ppm)

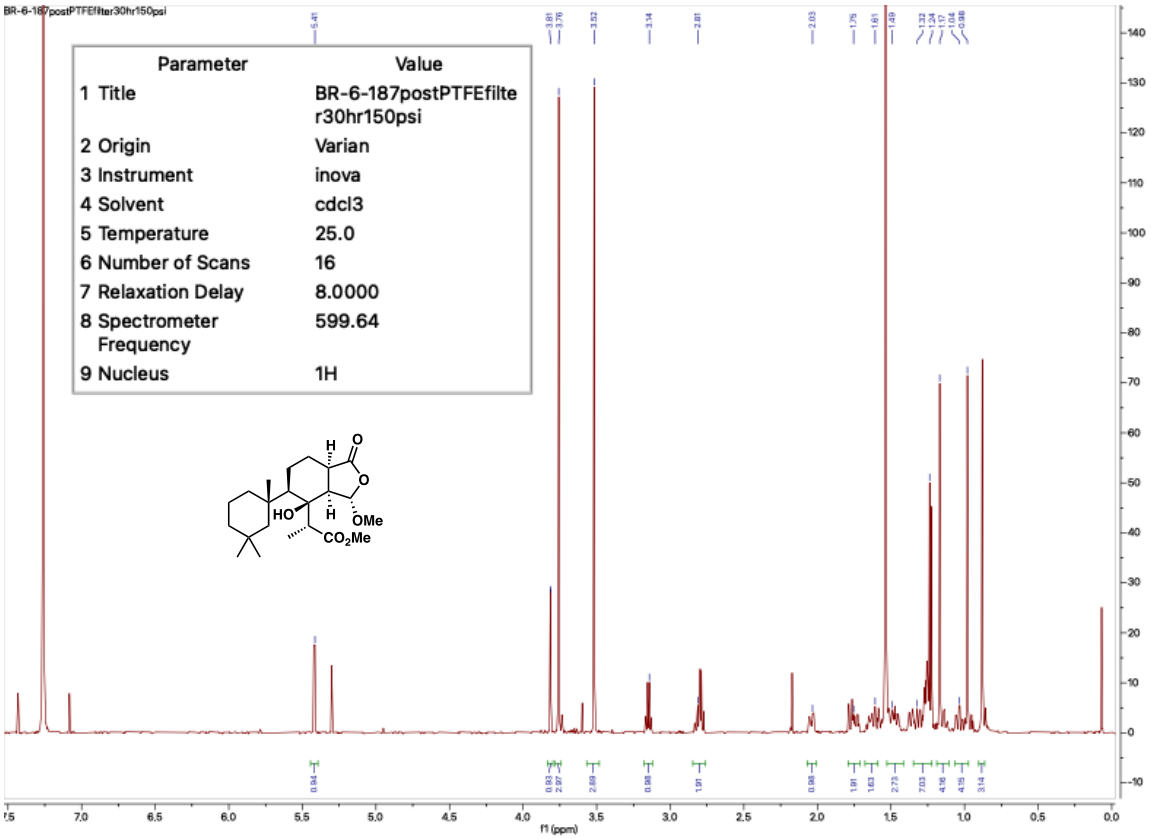

BR-6-151pure
Parameter Value
1 Title BR-6-151pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
O
N(Boc)2
O
f1 (ppm)

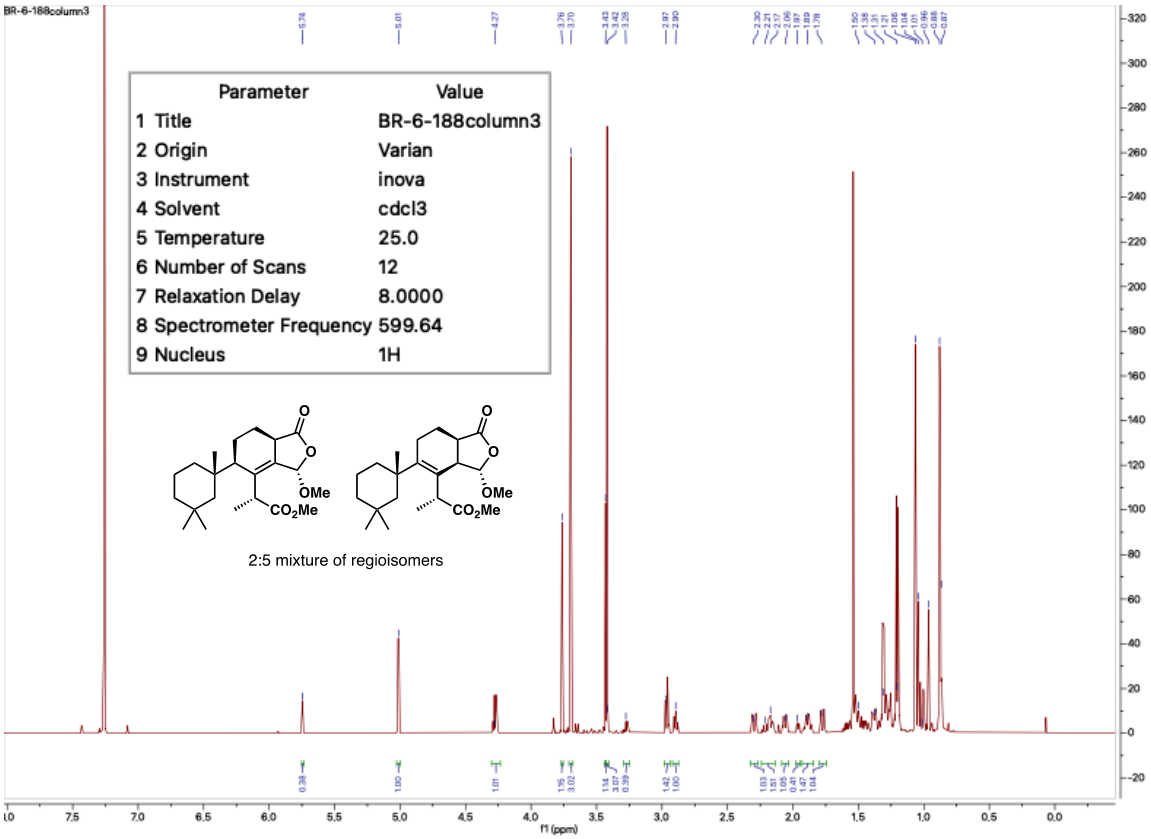

BR-6-182pure
Parameter Value
1 Title BR-6-182pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
O
CO2Me
f1 (ppm)


BR-6-184pure
Parameter Value
1 Title BR-6-184pure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
OAc
CO2Me
f1 (ppm)

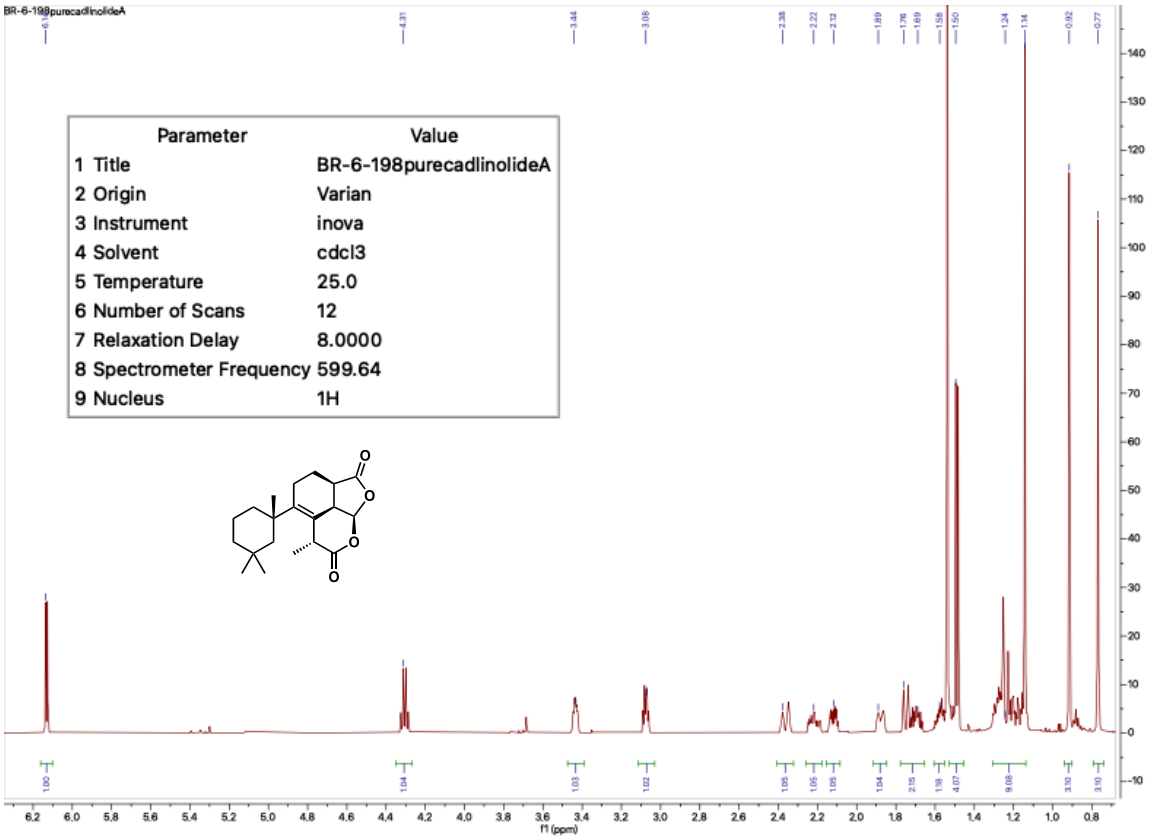

BR-6-186Apure
Parameter Value
1 Title BR-6-186Apure
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
HO
OMe
CO2Me
f1 (ppm)

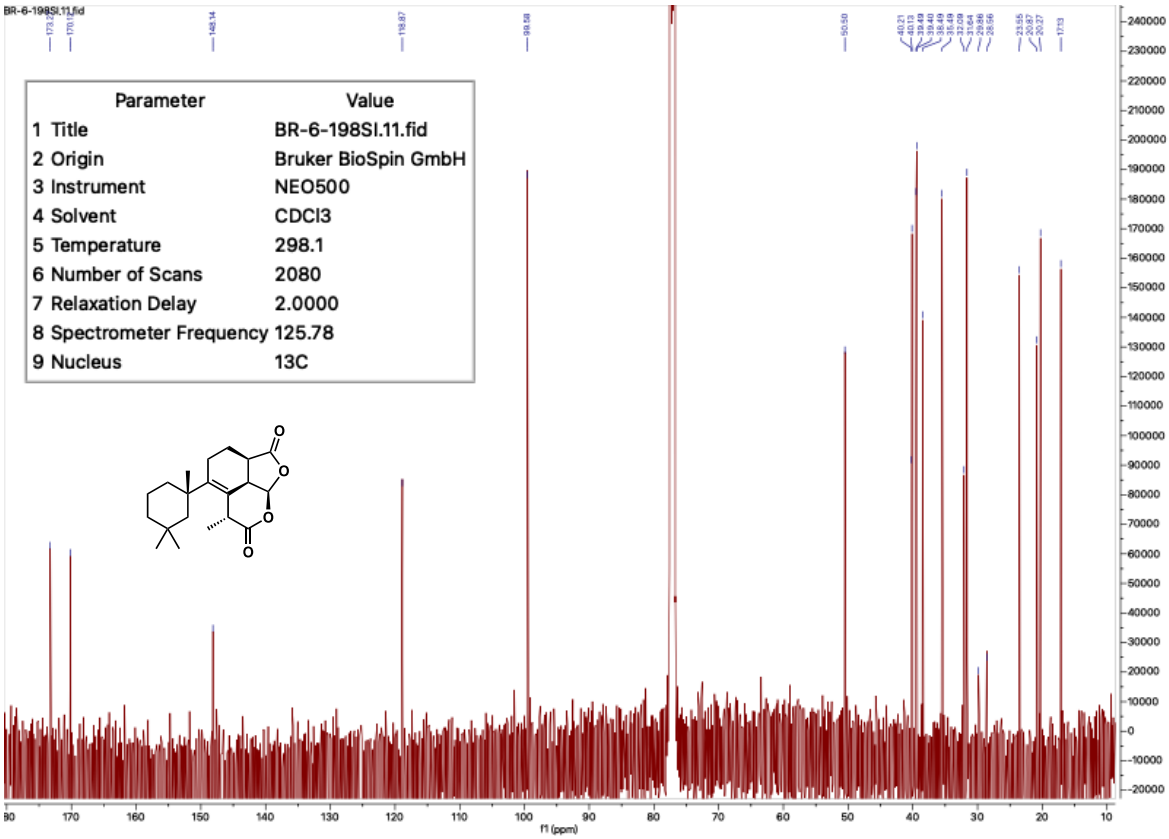

BR-6-186B
Parameter Value
1 Title BR-6-186B
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
HO
OMe
CO2Me
f1 (ppm)

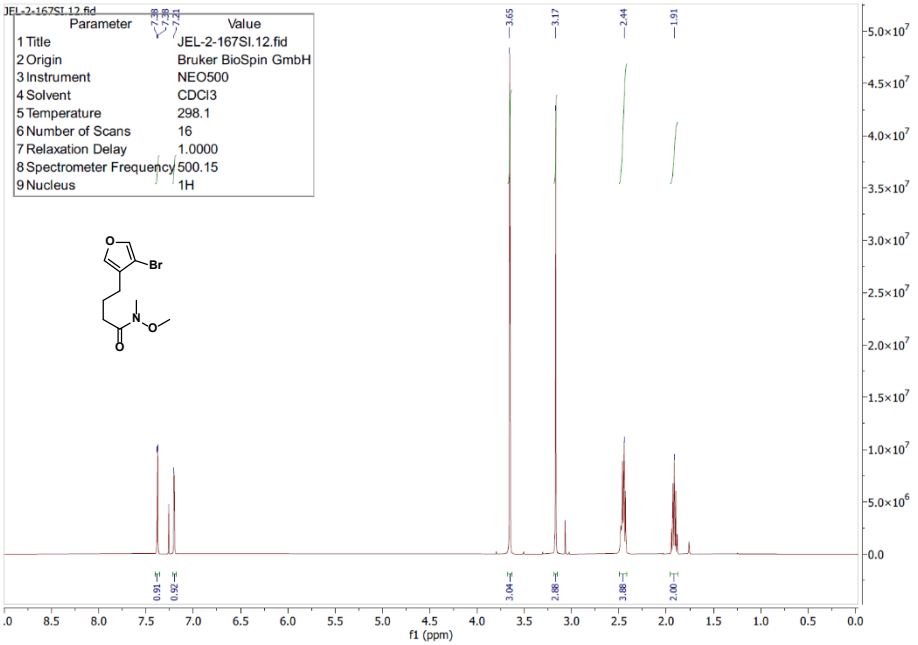


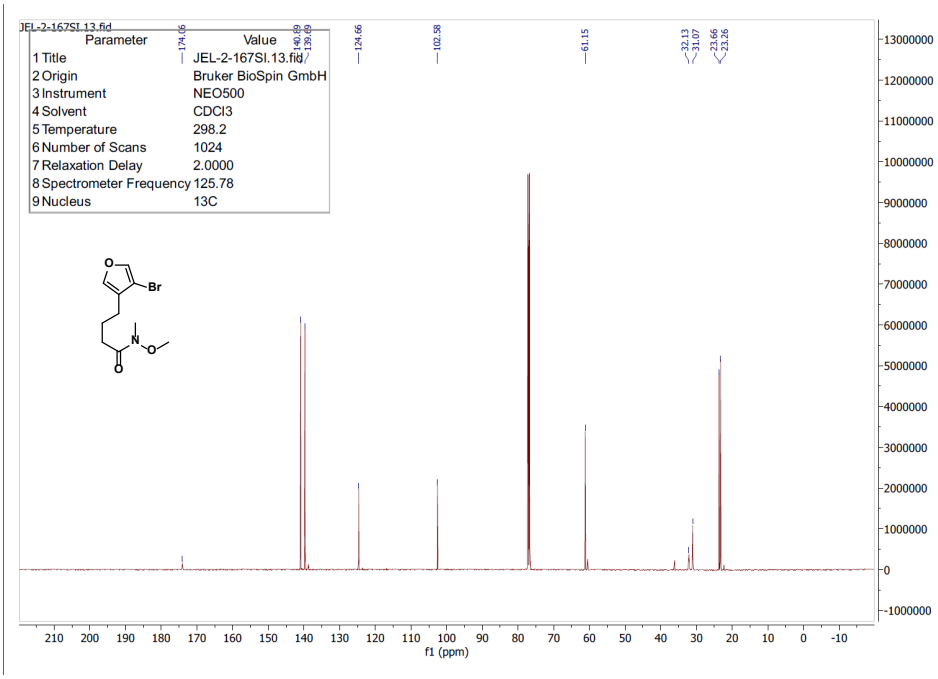


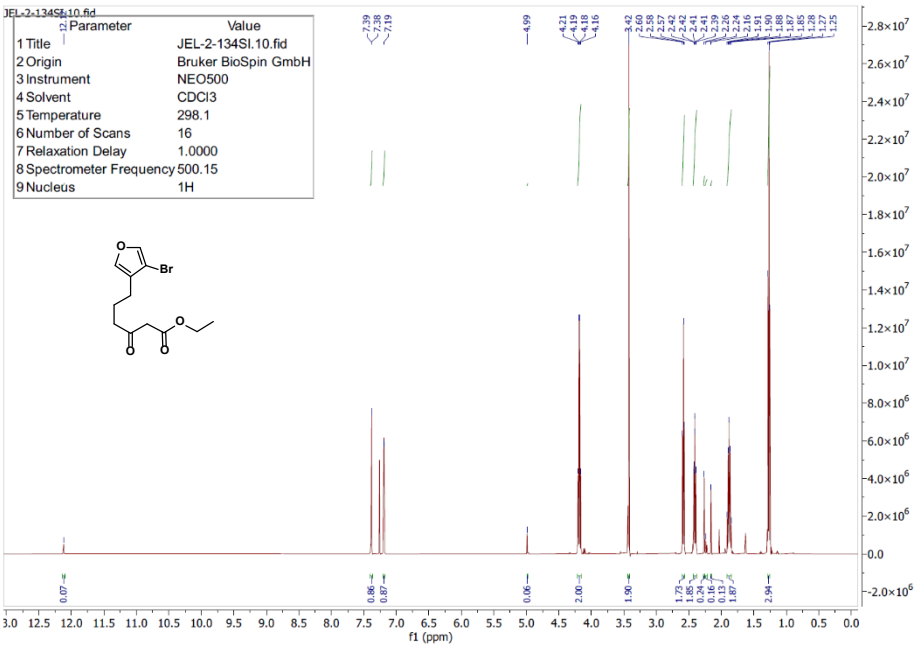
2:5 mixture of regioisomers

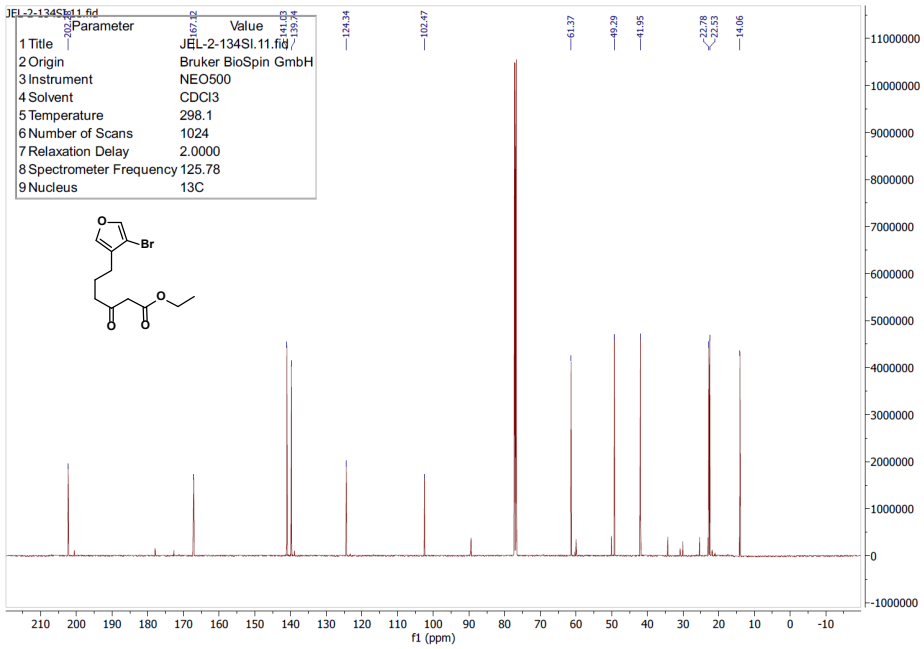

BR-6-198purecadlinolideA
Parameter Value
1 Title BR-6-198purecadlinolideA
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 12
7 Relaxation Delay 8.0000
8 Spectrometer Frequency 599.64
9 Nucleus 1H
f1 (ppm)

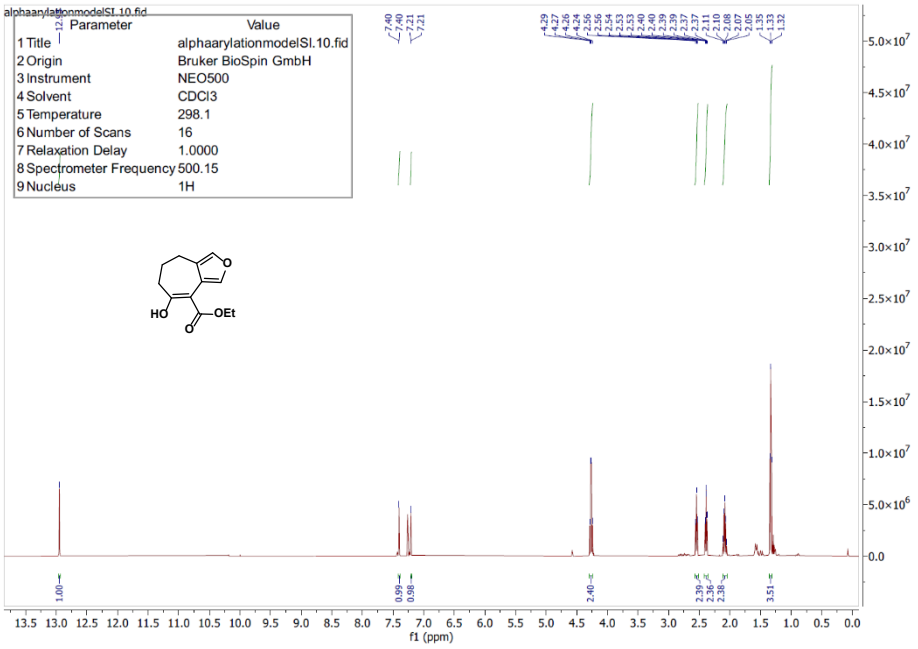

BR-6-198SI.11.fid
Parameter Value
1 Title BR-6-198SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 2080
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
f1 (ppm)

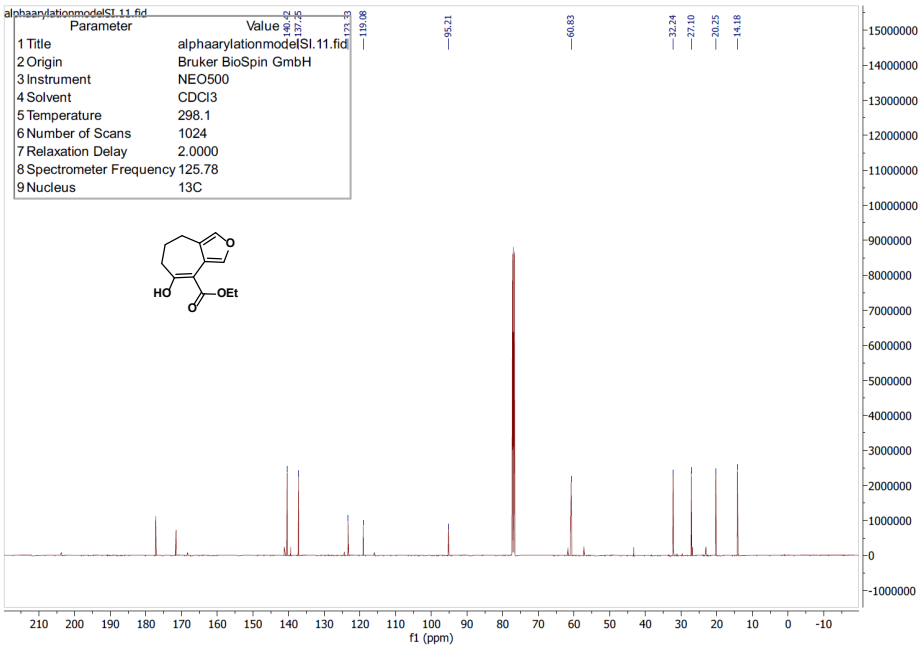

JEL-2-167SI.12.fid
Parameter Value
1 Title JEL-2-167SI.12.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
7.39
7.39
7.21
3.65
3.17
2.44
1.91
Br
O
N
O
O
0.91
0.92
3.04
2.88
3.88
2.00
f1 (ppm)

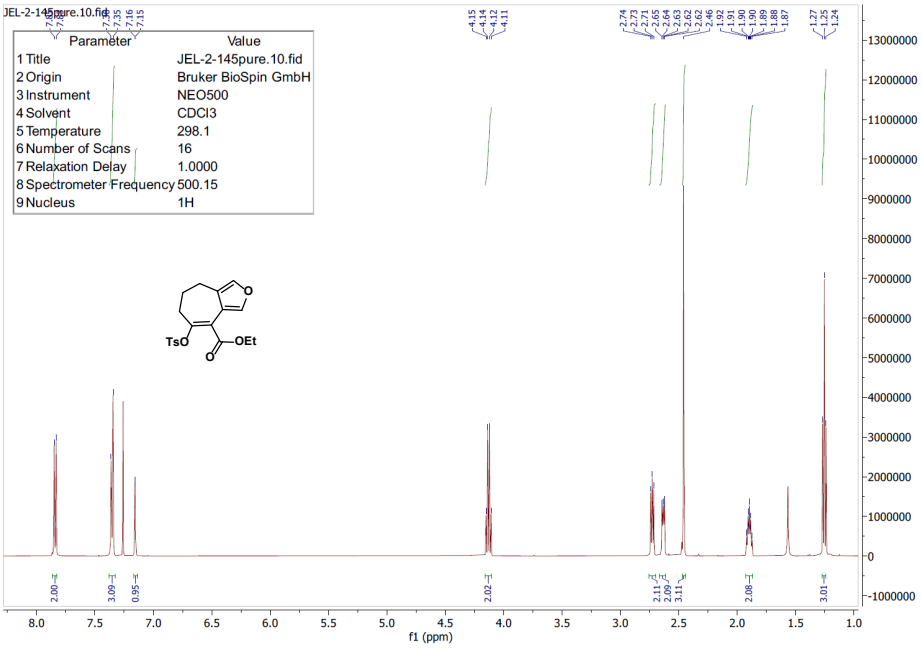

JEL-2-167SI.13.fid
Parameter Value
1 Title JEL-2-167SI.13.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
174.46
140.69
139.69
124.66
102.58
61.15
32.13
31.07
23.66
23.26
Br
O
N
O
O
f1 (ppm)

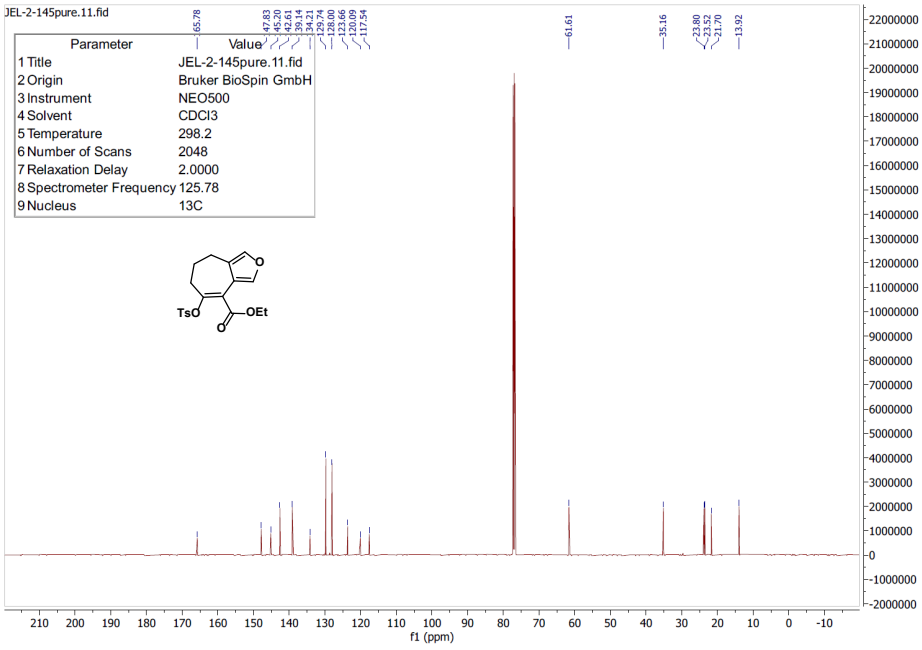

JEL-2-134SI.10.fid
Parameter Value
1 Title JEL-2-134SI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
Br
O
O
O
f1 (ppm)


JEL-2-134SI.11.fid
Parameter Value
1 Title JEL-2-134SI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
Br
O
O
O
f1 (ppm)


alphaarylationmodelSI.10.fid
Parameter Value
1 Title alphaarylationmodelSI.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
HO
O
OEt
O
f1 (ppm)


alphaarylationmodelSI.11.fid
Parameter Value
1 Title alphaarylationmodelSI.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 1024
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
HO
O
OEt
f1 (ppm)


JEL-2-145pure.10.fid
Parameter Value
1 Title JEL-2-145pure.10.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.1
6 Number of Scans 16
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 500.15
9 Nucleus 1H
TsO
OEt
O
f1 (ppm)


JEL-2-145pure.11.fid
Parameter Value
1 Title JEL-2-145pure.11.fid
2 Origin Bruker BioSpin GmbH
3 Instrument NEO500
4 Solvent CDCl3
5 Temperature 298.2
6 Number of Scans 2048
7 Relaxation Delay 2.0000
8 Spectrometer Frequency 125.78
9 Nucleus 13C
TsO
OEt
O
f1 (ppm)