2011

Studies toward the total synthesis of Trocheliophorolide A

Stephanie Dorn

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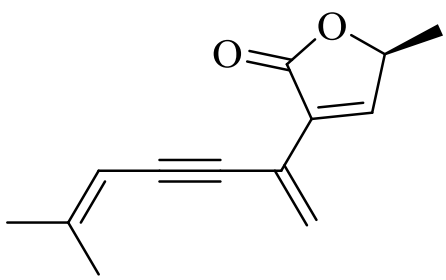

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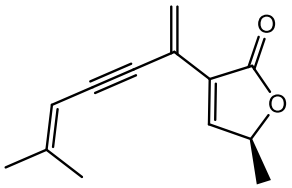
Thank you all very much for your contribution and participation in this important chapter of my life.

Abstract

Transition metal-mediated carbon-carbon bond forming reactions are among the most synthetically useful chemical transformations in modern organic synthesis. The most expedient routes toward many natural products and compounds of pharmacological interest involve such reactions. Our research focuses on the development of a novel synthetic route towards the total synthesis of the novel antibacterial natural product trocheliophorolide A using such transition metal-mediated reactions. Specifically, trocheliophorolide A was envisioned to be synthesized *via* a Stille coupling between a butenolide and an unsaturated sidechain. The butenolide synthesis was optimized and several routes to synthesize the sidechain were investigated. This thesis will detail the ongoing synthesis of trocheliophorolide A using a Wittig reaction rather than the previously envisioned Corey-Fuchs reaction, as well as suggestions towards the completion of the total synthesis.



Trocheliophorolide A

Abbreviations

^{1}H-NMR.....proton NMR

^{13}C-NMR.....carbon-13 NMR

Ac.....acyl

AcOH.....acetic acid

Boc.....*tert*-butyloxycarbonyl

Bu.....butyl

Bu_3SnH.....tributyltin hydride

C.....Celsius

DHP.....dihydropyran

DIBAL-H.....diisobutylaluminum hydride

DMAP.....4-dimethylaminopyridine

DMF.....dimethylformamide

DMSO.....dimethylsulfoxide

Et.....ethyl

Et_3N.....triethylamine

EtO_2CCl.....ethyl chloroformate

EtOAc.....ethyl acetate

eq.....equivalent(s)

g.....gram(s)

GC-MS.....gas chromatography – mass spectrometry

h.....hour(s)

Hex.....hexanes

HF-pyr.....hydrogen fluoride – pyridine complex

Hz.....hertz

L.....ligand

LC-MS.....liquid chromatography – mass spectrometry

LDA.....lithium diisopropylamide

mp.....melting point

Me.....methyl

MHz.....megahertz

min .....minute(s)

mL .....milliliter

mol .....mole

NaHMDS .....sodium hexamethyldisilazide

n-BuLi .....*n*-butyllithium

NMR .....nuclear magnetic resonance

PCC .....pyridinium chlorochromate

$Pd(PPh_3)_4$.....tetrakis(triphenylphosphine)palladium(0)

$Pd(PPh_3)Cl_2$ .....dichlorobis(triphenylphosphine)palladium(II)

Ph .....phenyl

PPh_3.....triphenylphosphane

p-TsCl .....*para*-toluenesulfonyl chloride

p-TsOH .....*para*-toluenesulfonic acid

RT .....room temperature

Sat .....saturated

TBS .....*tert*-butyldimethylsilyl

Tf.....trifluoromethanesulfonyl (CF_3SO_2)

THF.....tetrahydrofuran

THP.....tetrahydropyran

TLC.....thin layer chromatography

TMS .....trimethylsilyl

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1.0 Introduction and Background

Soft corals produce novel and structurally intriguing natural products. Chemists are interested in synthesizing these natural products, particularly if the compound is beneficial to society. It is often more practical to synthesize the compound in the lab rather than to isolate it from our limited natural resources.

The objective of this project is to synthesize the natural product trocheliophorolide A (Figure 1). Our collaborator, Dr. Michael Savka of the RIT Biology Department, studies plant-produced lactones. Upon the synthesis of trocheliophorolide A, the Savka group will be given the final product for further biological evaluation.

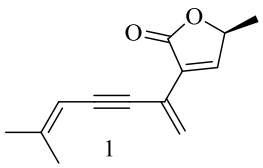


Figure 1. Molecular structure of trocheliophorolide A

1.1 Isolation and Biological Activity

Soft corals have yielded many natural compounds of interest to chemists, specifically steroids and their derivatives.[1,2] For example, three cytoxic steroids were isolated from the coral *Leptogorgia sarmentosa,* located in Spain.[3] Butenolides have been studied since they were isolated in the 1960's from the soft corals *Pterogorgia anceps* and *Pterogoria guadalupensis* (Figure 2).[2,4,5,6] In 2001, Rezanka and coworkers isolated and characterized the structure of six compounds A-F. The compounds were named trocheliophorolide A-F (**1**-**6** respectively, Figure 2). The six butenolide and butanolide lipids were isolated from two soft corals in the Red Sea, near Sarcophyton, Israel. Compounds **1-4** were isolated from the soft coral *Sarcophyton (S.) trocheliophorum*, while compounds **5** and **6** were isolated from the soft coral *Lithophyton (L.) arboretum.*[7]

Evaluation of the butenolides and butanolides indicated biological activity against *Staphylococcus aureus* and *Bacillus subtilis* (Table 1). The γ-lactones were also tested against *Eschericha coli* and *Saccharomyces cerevisae* but gave no response in these

cases. This indicated that the lactones were only active against Gram-positive bacteria, and inactive against Gram-negative bacteria and yeast.[6]

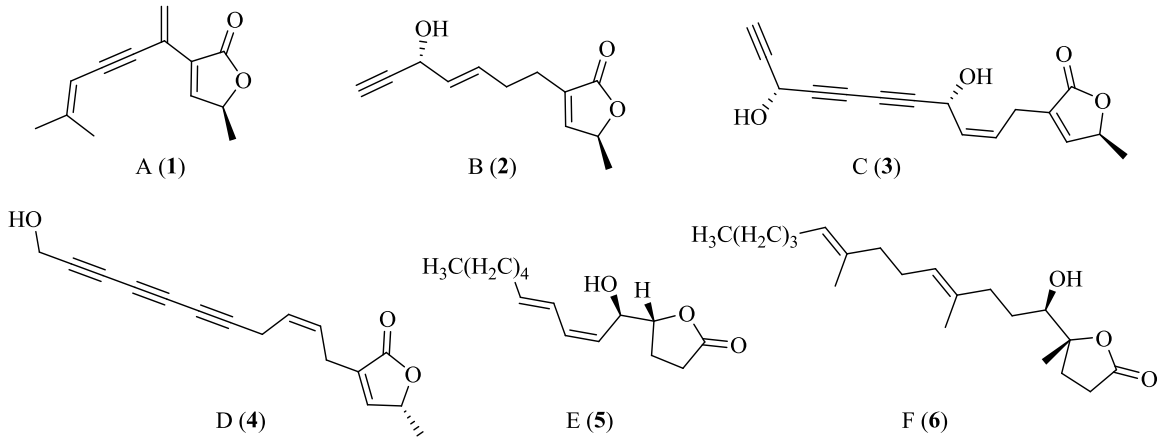


Figure 2. Structures of butenolides and butanolides isolated from *S. trocheliophorum* (A-D) and *L. arboretum* (E-F)

Table 1. Bioactivities of trocheliophorolides A-F (**1**-**6**)

Test Organism	A (**1**)	B (**2**)	C (**3**)	D (**4**)	E (**5**)	F (**6**)
*Staphylococcus aureus**	11.5	13.2	8.5	10.3	7.8	18.6
*Bacillus subtilis**	13.0	14.9	7.6	13.9	5.6	14.7

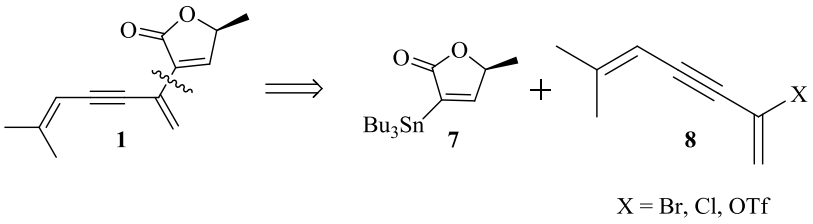
* Samples (10 μg) were applied on 50.8 mm paper disks, values are diameters (mm) of inhibitory zones

1.2 Retrosynthesis

We chose to synthesize trocheliophorolide A because of its challenging and very novel unsaturated sidechain (Figure 1).

The construction of trocheliophorolide A was envisioned from butenolide **7** and unsaturated sidechain **8** as a vinyl halide, joining *via* a Stille cross-coupling (Scheme 1). Butenolide **7** is a known compound, having been synthesized previously using different routes (Section 1.3). Sidechain **8** is not known, but highly conjugated unsaturated sidechains are both challenging and common in natural products. The synthesis of

sidechain **8** would contribute to the literature, as it would aid in the synthesis of this and many other natural products.[8,1]



Scheme 1. Retrosynthesis of trocheliophorolide A

1.3 Biological significance of (*S*)-*β*-angelica lactone of natural products

A butenolide (Figure 3, **9**) is a γ-lactone possessing an additional degree of unsaturation. Specifically, the butenolide moiety in trocheliophorolide A is (*S*)-*β*-angelica lactone **10** (Figure 3).

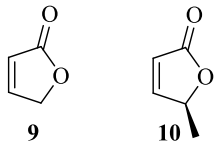


Figure 3. Skeletal structure of a butenolide **9** and (*S*)-*β*-angelica lactone **10**

Butenolides have been found in several natural products, many of which have exhibited biological activity (Figure 4). For example, four lactones were isolated from *Streptomyces antiobiticus* and indicated antibiotic activity against *Pseudomonas aeruginosa*, the bacteria that causes ear infections as well as other common illnesses.[9] Similarly, the plant *Dicentra spectabilis* had been used in central Africa to treat the bacterial infection of dysentery,[10] which provoked scientists to study the plant further. Indeed, butenolides (menisdaurilide and aquilegiolide) isolated from this plant were found to induce apoptosis in lymphoma and colon carcinoma cancer cells.[11] In Vietnam, leaves, twigs and flowerbud samples were examined from the plant *Litsea verticillata*

Hance, and several of the butenolides isolated from this sampling were found to inhibit HIV-1 replication.[12]

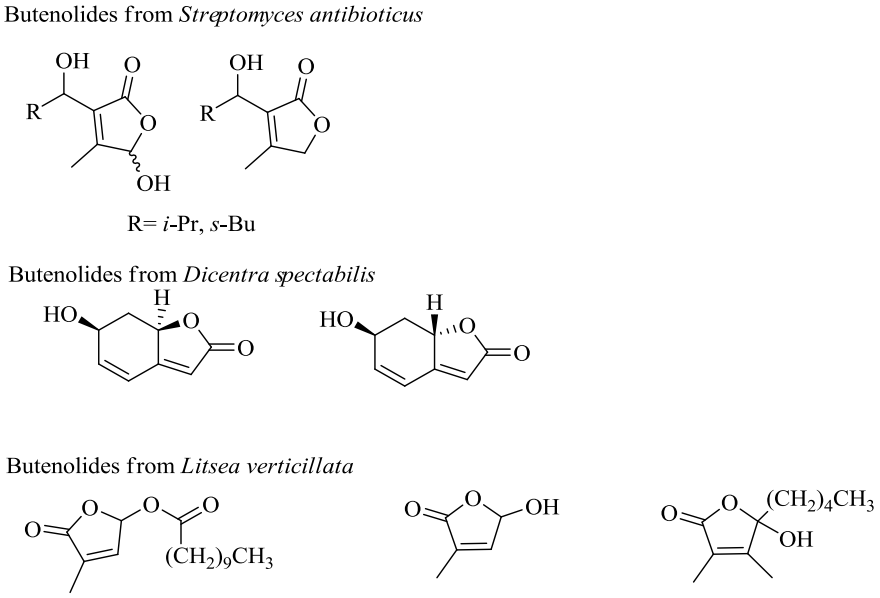


Figure 4. Selected biologically active butenolides isolated from natural products

1.3.1 Previous syntheses of (*S*)-*β*-angelica lactone of natural products in the literature

The butenolide moeity **10** (Figure 3) is a substructure of compounds found in many different natural products, and has been synthesized by many different routes in the past several years. [13,14] William Spencer, a previous Master's student in the Collison Group, reviewed several syntheses of compounds containing the butenolide similar to the butenolide moiety in trocheliophorolide A.[15] The compounds reviewed by Spencer included asimicin,[16] hamabiwalactone B,[17] giganticin,[18] blastomycin,[19] muconin,[20] pyranicin,[21] membranacin,[22] mucocin,[23] and a derivative of himbacine[24] (Figure 5).

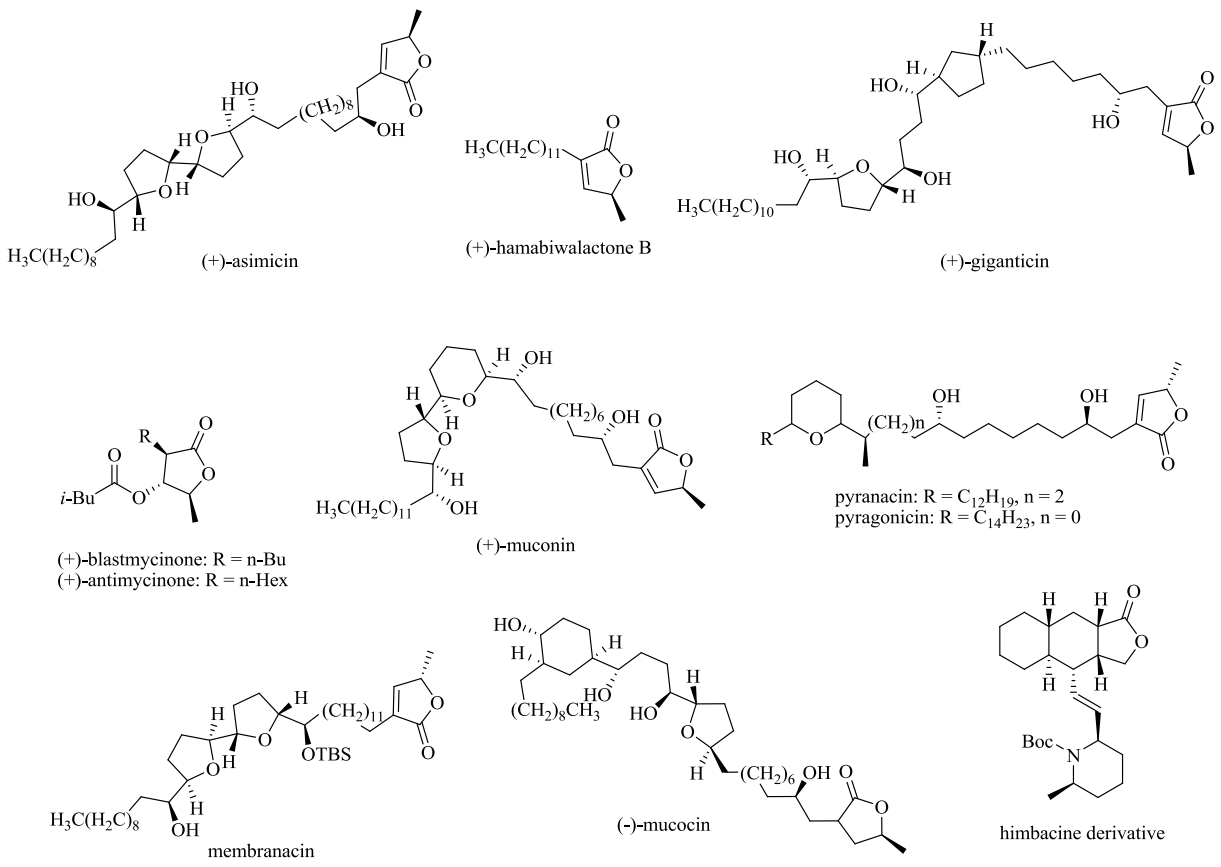
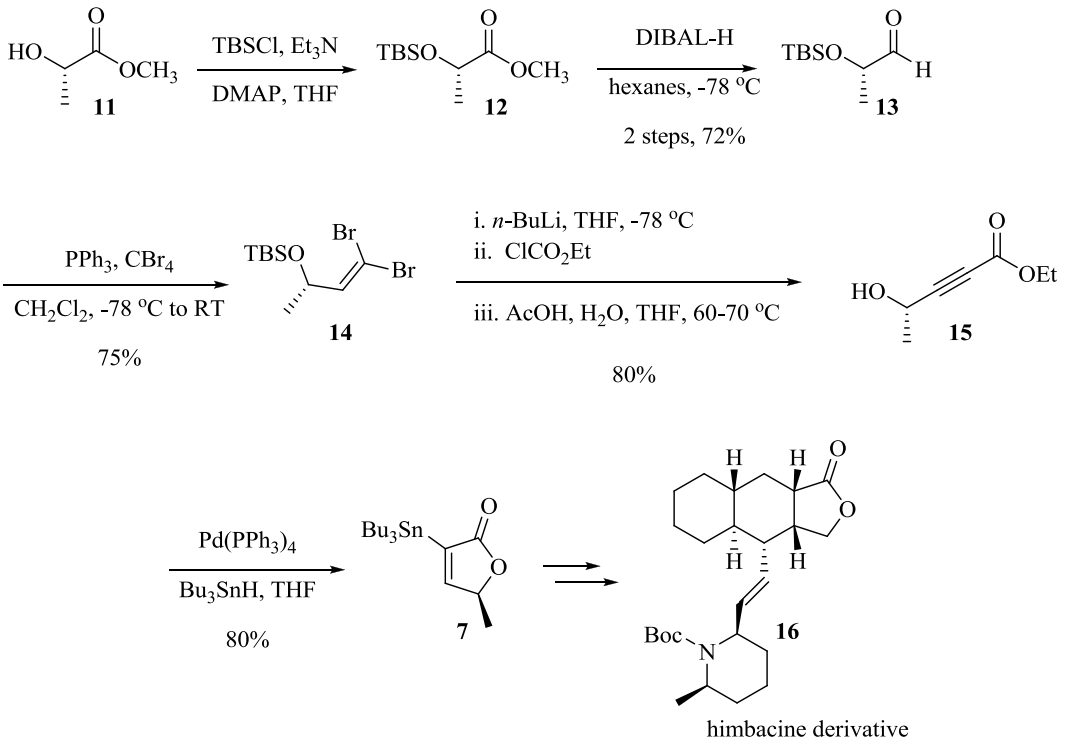


Figure 5. Structures of butenolides reviewed by William Spencer

The synthesis of the butenolide in the himbacine derivative was used as a template for the synthesis of the butenolide in our synthesis of trocheliophorolide A (Scheme 2). Hofman and coworkers[18] started with commercially available (*S*)-ethyl lactate **11**. Alcohol **11** was then protected to make silyl ether **12**. Ether **12** was then reduced to aldehyde **13** using DIBAL-H, with a 72% yield over the two steps. A Corey-Fuchs olefination was performed on aldehyde **13** to obtain dibromide **14** in a 75% yield. Dibromide **14** was converted to the alkyne, first using *n*-butyllithium to form the anion which was quenched with with ethyl chloroformate to afford alkynoate **15**. The silyl ether was then deprotected using acetic acid in THF, affording alkynoate **15** in 80% yield from dibromide **14**. A hydrostannation was then performed on alkynoate **15**, using tetrakis(triphenylphosphine)palladium(0) as a catalyst with tributyltin hydride to form butenolide **7** in 80% yield. The himbacine derivative was afforded several steps later.



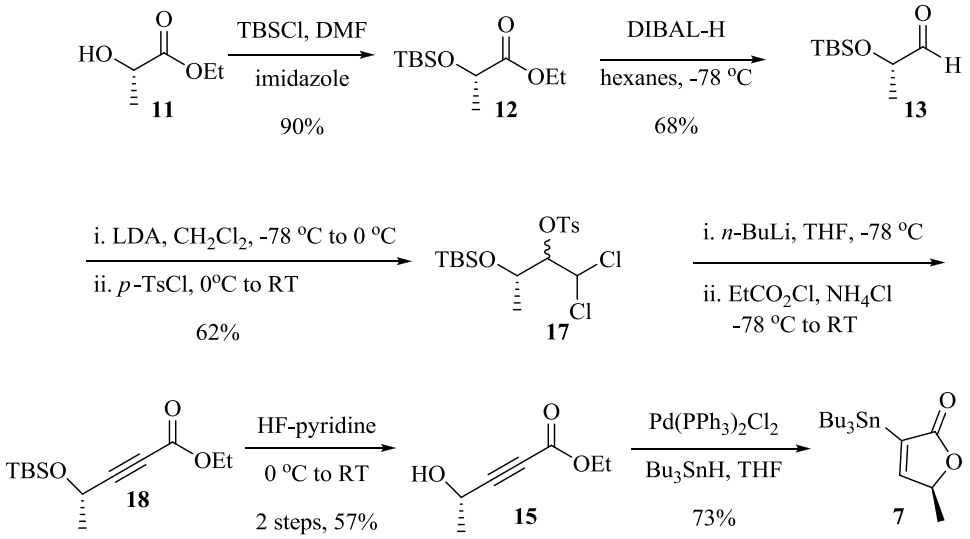
Scheme 2. Hofman's route to butenolide **7** in the himbacine derivative

The major drawback with Hofman's route is that dibromide **14** is extremely unstable and light-sensitive, with decomposition occuring very quickly. As such, work in the Collison group adopted a synthetic strategy to avoid the dibromide.

1.3.2 Previous work in the Collison Group on the butenolide moiety

In order to avoid dibromide **14** in Hofman's route,[25] our synthesis involved forming tosylate **17** from aldehyde **13** rather than performing the Corey-Fuchs reaction (Scheme 3).

Spencer commenced the synthesis of the butenolide by keeping the first two steps of our synthesis of butenolide **7** identical to Hofman's Route.[25] He used commercially available (*S*)-ethyl lactate, protecting the alcohol to make silyl ether **12**, and reduced ester **12** to aldeyde **13** under DIBAL-H conditions.



Scheme 3. Preparation of butenolide **7** in our synthesis of trocheliophorolide A

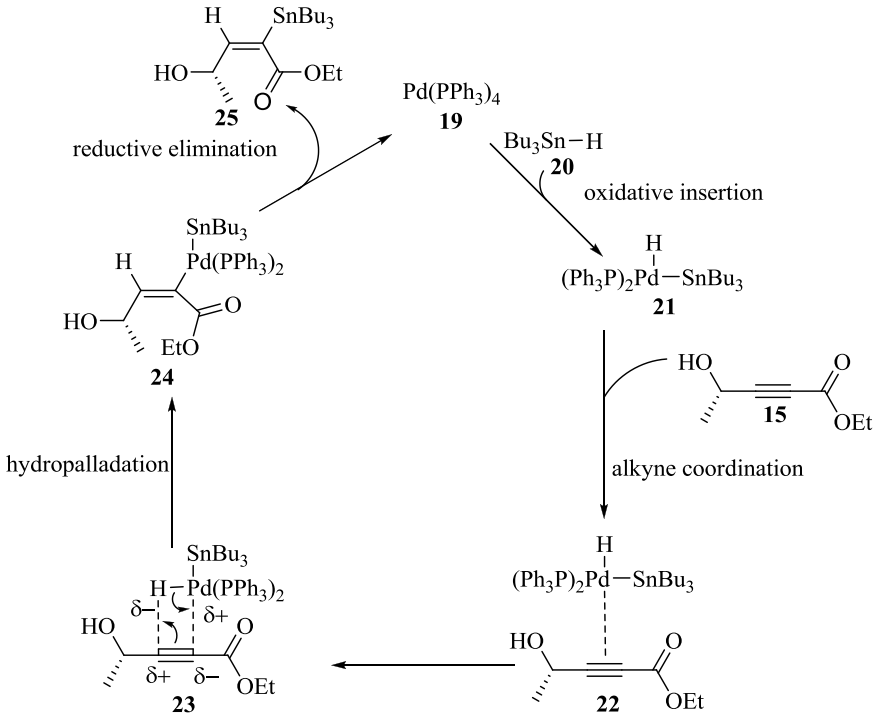
The significant alteration in our synthesis of the butenolide is the formation of tosylate **17** instead of dibromide **14**. The synthesis of tosylate **17** was prepared using LDA and dichloromethane as conducted by Marshall and coworkers.[25] Tosylate intermediate **17** is much more stable than the dibromide intermediate **14** in the synthesis toward himbacine derivative due to the presence of vinyl chlorines rather than vinyl bromides (Scheme 2). Large quantities (~75 g) of the tosylate were stored in the refrigerator for well over a year without substantial degradation. The diastereoselectivity of tosylate **17** was not significant since the center would be destroyed in a subsequent step.

Alkynoate **18** was made using three equivalents of *n*-butyllithium (Scheme 3). Two equivalents of *n*-butyllithium perform the E2 elimination of the tosylate and then the chlorine, forming an alkyne. The other equivalent of *n*-butyllithium is utilized for the lithium-halogen exchange to create the anion, which is reacted with ethyl chloroformate leading to alkynoate **18**.

In order for the Stille coupling with the vinyl halide to occur, tributyltin needed to be placed on the butenolide. This group was added *via* a palladium-catalyzed hydrostannylation reaction (Scheme 4).

Trost and Ball described the mechanism for the hydrostannylation.[26] The Pd(0) catalyst oxidatively inserts between the tin-hydride bond to form complex **21**. Alkyne **15**

then coordinates to the palladium to form complex **22**. In order to obtain the desired regioselectivity, the palladium-hydrogen bond undergoes a *syn*-addition across the π-bond of the alkyne to give complex **23**. The partially positive palladium aligns to the α-carbon of the alkynoate, and the partially positive *β*-carbon with the partially negative hydride ligand. Lastly, reductive elimination ensues to give vinyl stannane **25** and regeneration of the Pd(0) catalyst (Scheme 4).



Scheme 4. Proposed mechanism of hydrostannylation to produce alkene **25** precursor to butenolide **7**

Under the same conditions, lactonization then occurs to produce butenolide **7** (Scheme 3). Spencer was the first student on the project to be successful in synthesizing butenolide **7**. His first attempt at the hydrostannylation/lactonization afforded butenolide **7** in a 68% yield. However, he noticed that his yields for butenolide **7** decreased with each attempt. In section 3.0 describes my research and efforts to develop a more robust procedure.

1.4 Previous routes towards unsaturated sidechain 8 in the literature

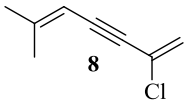
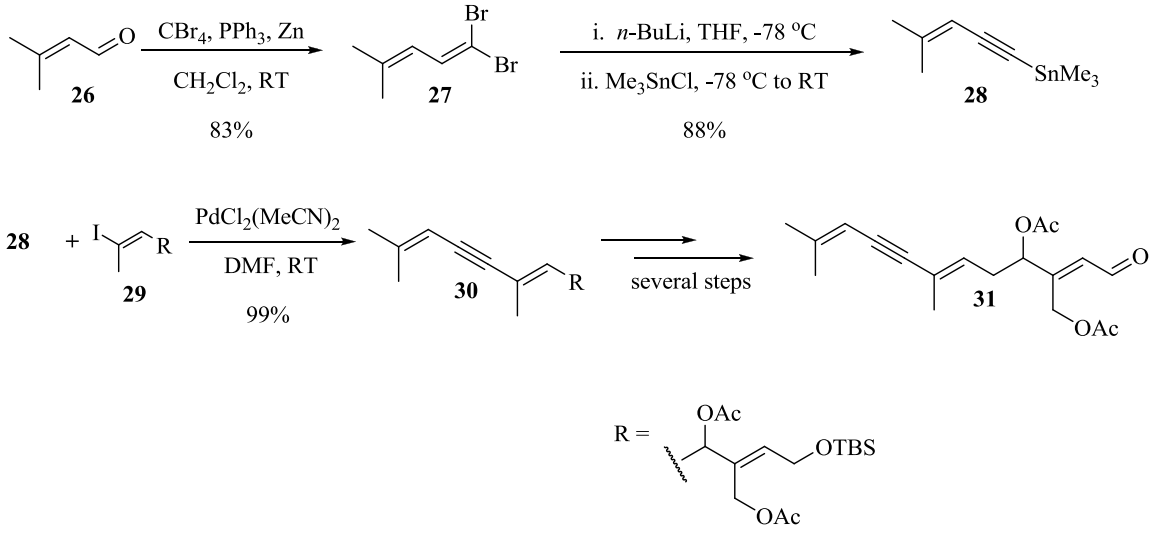


Figure 6. Molecular structure of vinyl halide coupling partner **8**

The unsaturated sidechain **8** proposed in the retrosynthesis is not known in the literature. However, compounds with sidechains of similar unsaturation patterns have been reported. One such compound bearing a similar unsaturation pattern is taxifolial A. Commeiras synthesis[27] of (±)-taxifolial A (Scheme 5) commenced with commercially available aldehyde **26**, upon which the Corey-Fuchs olefination was performed to afford *gem*-dibromide **27** in 83% yield. Dibromide **27** underwent elimination and lithium-halogen exchange using *n*-BuLi in THF, and trimethyltin chloride was used to quench the anion to form stannane **28**. A Stille coupling was then performed on stannane **28** using a Pd(II) catalyst to afford triene **30** in 99% yield. Several steps later (±)-taxifolial A **31** was synthesized.



Scheme 5. Commeiras synthesis of the ynediene appendage of (±)-taxifolial A

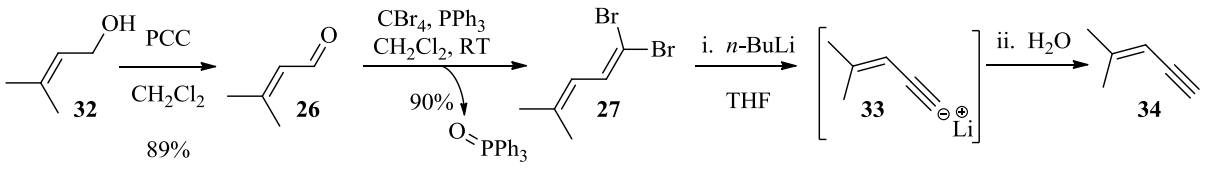
1.4.1 Previous synthetic approaches to sidechain 8 in Collison Group (O. Augusto)

The synthesis of the unsaturated sidechain **8** is arguably the most challenging part of this synthetic project. As such, there has been copious work towards its synthesis in

the Collison Group. The first student to work on sidechain **8** was Olukorede Augusto.[28] The synthesis began with commercially available 3-methyl-2-buten-1-ol **32**, which was oxidized to aldehyde **26** using pyridinium chlorochromate to afford aldehyde **26** in 89% pure yield (Scheme 6). Upon removal of the chromium(IV) salt with a plug of silica gel, aldehyde **26** was concentrated *via* distillation. Aldehyde **26** was determined to be of acceptable purity for the next reaction. While aldehyde **26** is also commercially available, it had to be purified *via* distillation prior to use, therefore the less expensive alcohol **32** was purchased.

Then similar to Commeiras synthesis of taxifolial, aldehyde **26** underwent a Corey-Fuchs olefination to yield dibromide **27** (Scheme 5).[29] Zinc is traditionally used and serves several roles; it produces zinc(II) bromide which allows for the regeneration of the triphenylphosphine. This ultimately reducing the equivalents of triphenylphosphine required for the reaction.[30] However, Augusto found that the use of zinc decreased yields. Therefore zinc was not used in later trials; instead excess triphenylphopshine afforded the highest yields.

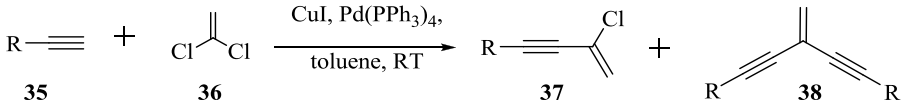
Dibromide **27** was then subjected to two equivalents of *n*-butyllithium; one equivalent for lithium-halogen exchange and the second equivalent for elimination. This afforded anion **33**, which was quenched with water to produce terminal alkyne **34**. While neither anion **33** nor alkyne **34** were recovered, likely due to its volatility, anion **33** was later confirmed (section 1.4.2).



Scheme 6. Attempted synthesis of alkyne sidechain **34**

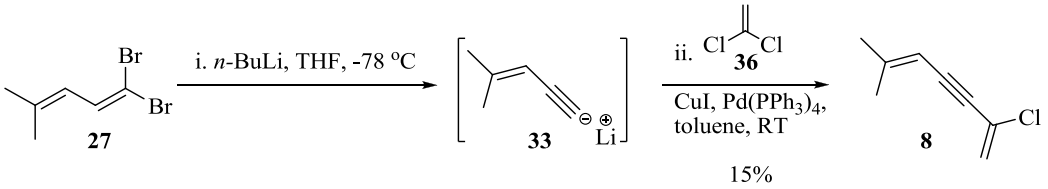
Augsto then focused on circumventing the isolation of alkyne **34**. She adapted work by Negishi and coworkers who completed a methodology project on the synthesis of vinyl chlorides with terminal alkynes and vinylidine dichloride **36** (Table 2).[31]

Table 2. Summary of Negishi's synthesis of vinyl halides from terminal alkynes



Alkyne	R group	% Yield **37a-c**	% Yield **38a-c**
35a	*n*-Hexane	**37a** – 66%	**38a** – 5%
35b	Ph	**37b** – 82%	**38b** - <1%
35c	Me_3Si	**37c** – 69%	**38c** – 4%

Alkynes **35a-c** were most analogous to our alkyne **8**, and therefore the similar conditions were used. To avoid volatile terminal alkyne **34**, Augusto used an *in situ* approach. The elimination-Sonogashira coupling route was performed with anion **33** and commercially available dichloride **36** to yield vinyl chloride **8** in 15% yield (Scheme 8).

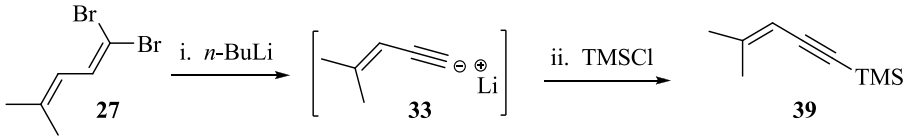


Scheme 7. Synthesis of chloroynediene **8** *via* Sonogashira coupling

Unfortunately, this route afforded for an unfavorable 15% pure yield and was not reproducible. As chlorides are not as labile as bromine for oxidative addition, vinyl dibromide could have been used to produce a brominated form of sidechain **8**. However, vinyl dibromide is not commercially available and is extremely sensitive. Thus an alternative route was sought.

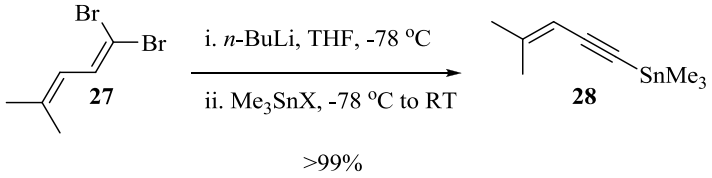
1.4.2 Previous synthetic approaches to sidechain 8 in Collison Group (W. Spencer)

William Spencer continued Augusto's work on the synthesis of sidechain **8**.[16] In order to determine that anion **33** was indeed being made, Spencer quenched anion **33** with TMSCl (Scheme 8). This reaction did afford silane **39** in moderate yields, confirming anion **33** is formed.



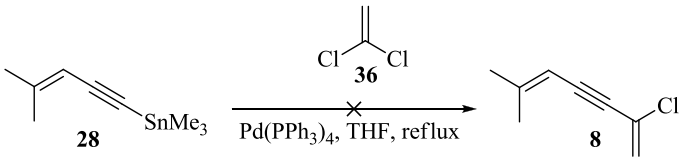
Scheme 8. Synthesis of silane **39**, confirming anion **33** is formed

A similar route leading to vinyl chloride **8** was attempted with the synthesis of stannane **28** as an intermediate (Scheme 9), as performed in the synthesis of taxifolial A by Commeiras.[28] Spencer increased the yields obtained by Commeiras, which was originally 88% yield, to greater than 99% yield.



Scheme 9. Synthesis of stannane intermediate **34**

While crude yields of stannane **28** were high, decomposition occurred during column chromatography. It was therefore brought forward without purification. A Stille coupling was performed on stannane **28** and vinyl dichloride **36**, using a Pd(0) catalyst (Scheme 10). No vinyl chloride **8** was observed and the reagents were consumed (observed by ^{1}H-NMR).

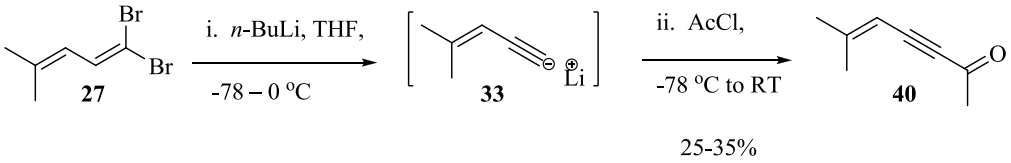


Scheme 10. Attempted synthesis of vinyl chloride **8**

Due to the difficulty of making vinyl chloride **8**, the coupling partner was altered to bear a more reactive triflate instead of the chloride. Starting with *gem*-dibromide **27**, ketone **40** was envisioned to form. The enolate would then be formed and trapped to produce triflate **41** (Scheme 11).

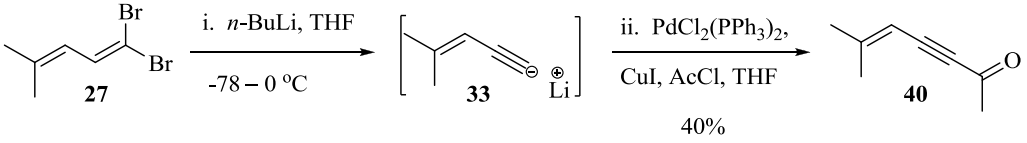
Scheme 11. Envisioned synthesis route with triflate as the leaving group

Several routes were attempted to form ketone **40**. The first route Spencer attempted was quenching the resulting anion **33** with acetyl chloride, which resulted with yields between 25 and 35 % (Scheme 12).



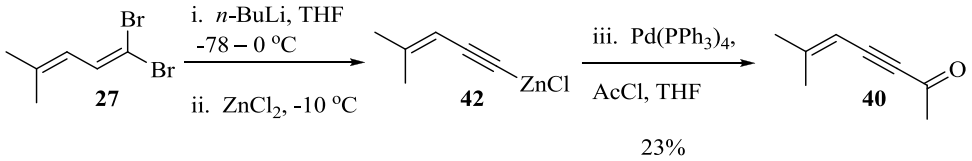
Scheme 12. Elimination and acyl substitution to afford ketone **40**

Spencer next attempted a Sonogashira coupling to afford ketone **40** (Scheme 13). Using a Pd(II) catalyst, copper iodide, and acetyl chloride in THF resulted in a 40% yield, a slight improvement over quenching with acetyl chloride.



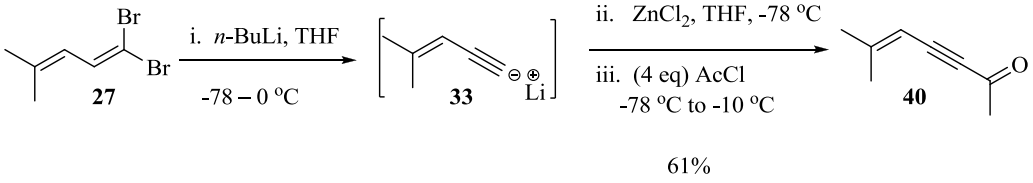
Scheme 13. Elimination and Sonogashira coupling to afford ketone **40**

A Negishi coupling of acetyl chloride and alkynyl zinc chloride **42** was then attempted. While this is a novel route and very unprecedented, this only resulted in a 23% yield of ketone **40** (Scheme 14).



Scheme 14. Elimination and Negishi coupling to afford ketone **40**

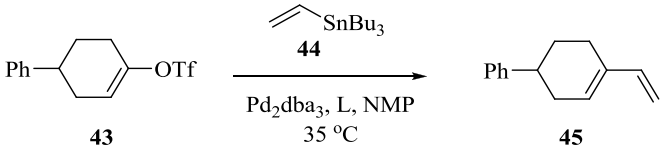
The final route that was attempted involved two equivalents of *n*-butyllithium forming the anion. Anion **33** was quenched with zinc(II) chloride and acyl chloride to afford ketone **40** in 61% yield (Scheme 15). The zinc exchanges with the lithium, as the zinc is an alternative nucleophilic partner compared to the lithium.[32]



Scheme 15. Elimination and quench with acyl chloride.

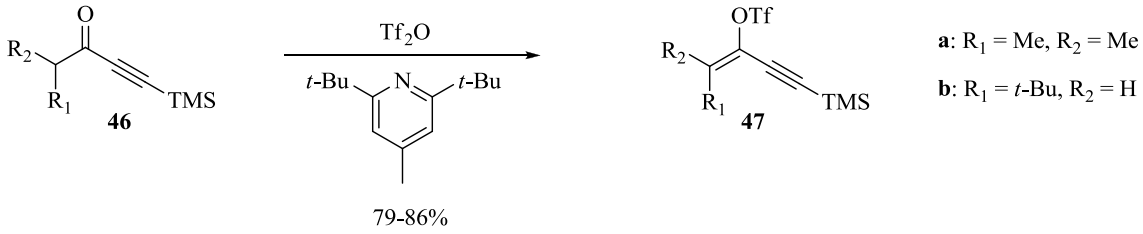
Vinyl triflates have been widely used as coupling partners with stannanes.[33] For example, Farina and Krishnan successfully performed a Stille coupling with vinyl triflate **43** and vinyl stannane **44** (Table 3). Farina and Krishnan found that vinyl triflates coupling with stannanes required slightly different reaction conditions (including LiCl, different temperatures with different catalysts) but that vinyl riflates were comparable with vinyl halides (Table 3).

Table 3. Farina and Krishnan's investigation on the coupling of vinyl triflates with stannanes



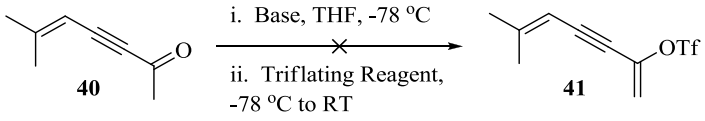
Triflate **43**	Ligand	% yield **45**
a	PPh_3	>95
b	$(2\text{-furyl})_3P$	>95
c	AsPh	>95
d	$Ph_2P(CH_2)PPh_2$	<2
e	$(2\text{-furyl})_3P$	>95
f	$(2\text{-furyl})_3P$	>95

Similarly, Stang and Fisk studied isomeric 1-(ethynyl)-vinyl compounds using sterically hindered and non-nucleophilic 2,6-di-*t*-butyl-4-methylpyridine to afford the desired triflate **47** with yields in the mid-80%s (Scheme 16).[34]



Scheme 16. Triflation of ethynyl vinyl compound **46**, using a bulky base.

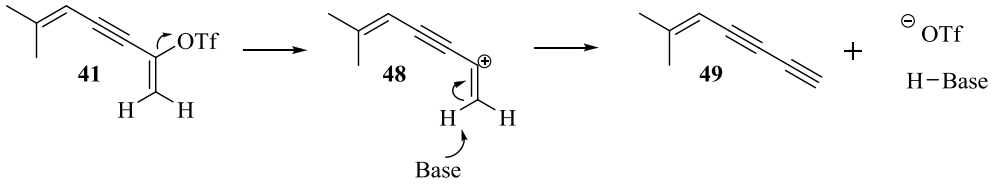
Given Stang's and Fisk's success with vinyl triflations, Spencer attempted to convert ketone **40** to triflate **41** (Scheme 17).



Scheme 17. General scheme for attempted generation of triflate **41**

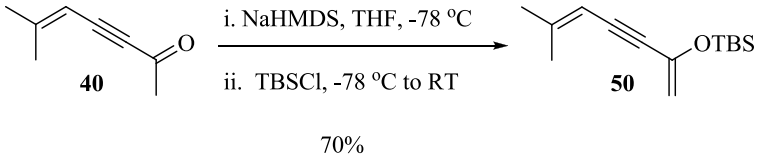
For the enolate trapping, Spencer used various bases including LDA, LiHMDS, NaHMDS, and sodium hydride, along with the different triflating reagents of triflic anhydride and *N*,*N*-bis(trifluoromethylsulfonyl)aniline. The reactions afforded only starting materials and unidentified side products. He also attempted soft enolization by first reacting ketone **40** with triflic anhydride followed by triethylamine, only to afford starting materials and the same unidentified products.

Spencer hypothesized that the enol triflate had various resonance structures[16,35,35] and was undergoing an S_N1 solvolysis with water during the work-up. Another hypothesized reaction that could have been occurring was an E1 elimination. Upon the addition of excess base, the result would be diynene **49** which we presume to be highly volatile and thus difficult to isolate and observe (Scheme 18).



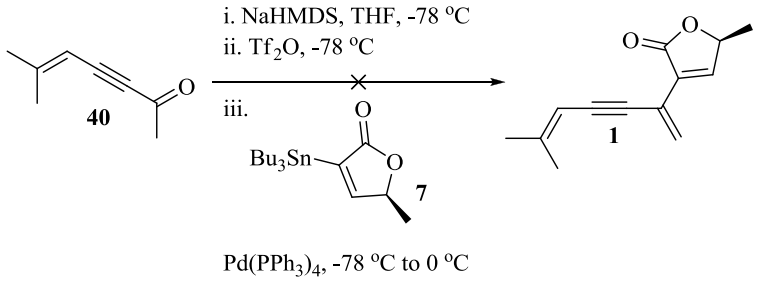
Scheme 18. Proposed mechanism of E1 elimination of triflate **41** to form byproduct **49**

To determine if the problem with forming vinyl triflate **41** was stabilization of the enolate, ketone **40** was treated with sodium hexamethyl disilazide, and the anion was quenched with *t*-butyldimethylsilyl chloride (Scheme 19). This reaction produced protected enolate **50** in 70% yield, indicating that enolization was not the problem, but perhaps triflate **41** was unstable.



Scheme 19. Protection of ketone **40** with TBSCl

Spencer next attempted the triflation followed by the coupling with the butenolide *in situ* in an effort to prevent the triflated alkyne from undergoing hydrolysis. This reaction was unsuccessful, but there was no ketone **40** remaining (confirmed by ^{1}H-NMR, Scheme 20).



Scheme 20. Attempted triflation of ketone **40** and coupling with butenolide **7** *in situ*

Given the work completed by Augusto and Spencer, it was clear that three goals needed to be met by my research:

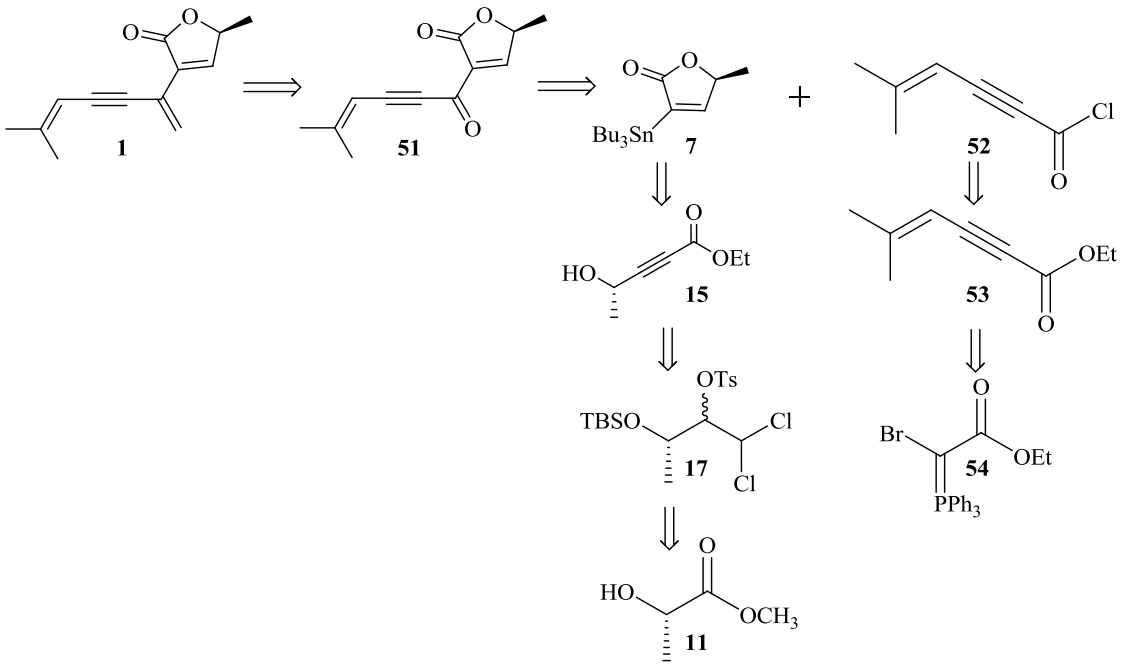
1. Optimization of the hydrostannylation/lactonization

2. Design of an alternative route to prepare the unsaturated sidechain fragment
3. Execution of the synthesis for the sidechain fragment

2.0 Synthetic Design

As depicted in Scheme 21, trochliophorolide A (**1**) possesses a butenolide moiety and a sidechain with unique unsaturation. For this reason, the synthesis of trocheliphorolide A was envisioned as the coupling of butenolide **7** and a vinyl halide **8** (Scheme 21).

Our new retrosynthetic design (Scheme 21) contains a convergent synthesis between butenolide **7** and the sidechain **52**, which were synthesized separately; therefore, if other trocheliophorolide compounds are attempted, only the sidechain functionality will need altering. Butenolide **7** is a known compound, and its synthesis has been optimized by the Collison group as compared to the Hofman[25] synthesis, by using the tosylate intermediate instead of the unstable dibromide.[16]



Scheme 21. Retrosynthetic analysis for trocheliophorolide A

Presently, a revised retrosynthesis has been designed. The lactone moiety remains unmodified; however the route to the unsaturated sidechain fragment has been dramatically altered. The sidechain now incorporates acid chloride **52** as a coupling partner. The acid chloride will be synthesized from ester **53** which has more precedence than the previously envisioned vinyl chloride **8**. Acid chlorides have been used in the

literature as coupling partners in Stille reactions.[36] Finally, a Wittig reaction would be employed to complete the synthesis of Trocheliophorolide A.

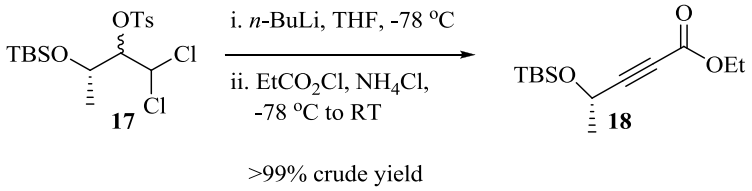
3.0 Results

3.1 Synthesis and optimization of butenolide 6

Following the retrosynthetic design (Scheme 21), the synthesis of butenolide **7** was continued from the tosylate intermediate **17**, which William Spencer had produced in mass quantities and stored for future use. The task was then to optimize the hydrostanation-cyclization toward the final coupling partner.

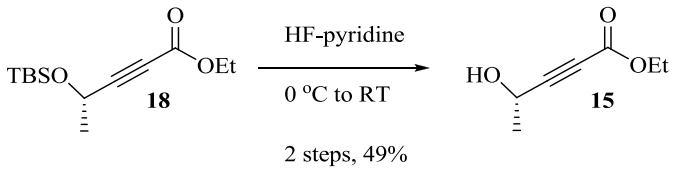
3.1.1 Synthesis of alkyne 14 from tosylate 16

Spencer prepared nearly 75 grams of tosylate **17** for our use. Tosylate **17** was converted to the ester **18** (Scheme 22), through elimination and subsequent lithium-halogen exchange using 3.3 equivalents of *n*-butyllithium, quenching the anion with ethyl acetate to afford ester **18** in >99% crude yield. It was determined to be of acceptable purity by ^{1}H-NMR for the deprotection.



Scheme 22. Synthesis of ester **18**

In order to perform the lactonization in the final steps, we next had to remove the silyl protecting group (Scheme 23). Crude ester **18** was deprotected using HF-pyridine, and purified *via* chromatography with silica, affording alcohol **15** in 49% pure yield from tosylate **17**. There was no effect on the percent yield when using pure ester **18**.

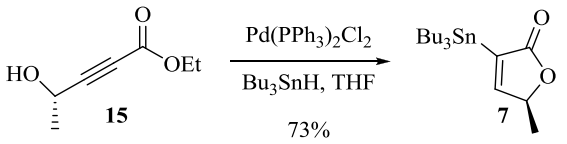


Scheme 23. Synthesis of alkynyl ester **15**

3.1.2 Cyclization and lactonization of alcohol 14 to afford butenolide 6

The final step in the synthesis of butenolide **7** was the hydrostannation and lactonization. Alcohol **14** and tributyltin hydride were added to freshly prepared

tetrakis(triphenylphosphine)palladium(0) in anhydrous THF. Although Spencer had successfully completed the synthesis of butenolide **7**, the yield was relatively low (65%) and was only successful once, most likely due to the purity of the tributyltin hydride. It was found that the tribultyl tin hydride degraded quickly (confirmed by ^{1}H-NMR), with the loss of the necessary hydride and was therefore analyzed before each reaction. Jennifer Swartzenberg, a current member of the Collison Group, and I worked on the optimization of the cyclization. Another catalyst was tried, bis(triphenylphosphine)palladium(II) chloride (Scheme 24). Using the new catalyst and a fresh bottle of tributyltin hydride, butenolide **7** was afforded in 73% pure yield. Optical rotation afforded **$[\alpha]_D^{20}$ = +22.7, as compared to $[\alpha]_D^{23}$ = +27.9 from the literature.[37] This value remained unchanged with storage.



Scheme 24. Synthesis of butenolide **7**

3.2 Synthesis of acid chloride coupling partner

The Collison group has attempted several syntheses of unsaturated sidechain **8**. The earliest routes were aimed at the synthesis of vinyl chloride **8**, but current studies are focused on synthesizing acid chloride **52**.

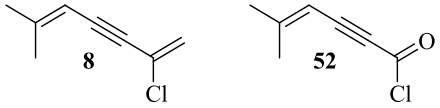


Figure 7. Coupling partners, vinyl chloride **8** and acid chloride **52**

Three different strategies were investigated in order to afford acid chloride **52**:

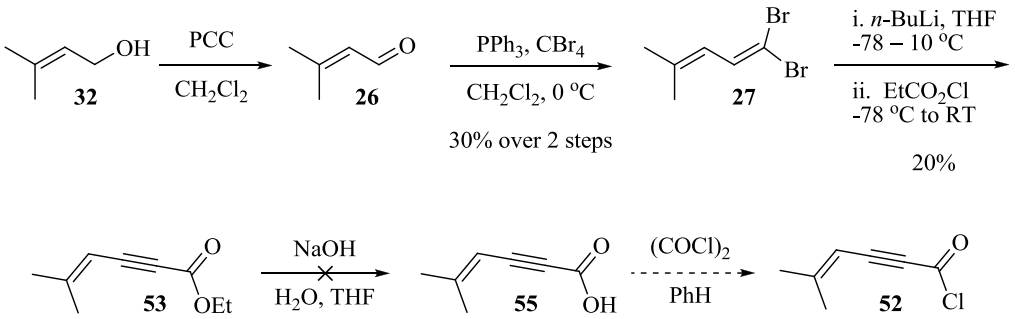
1. Corey Fuchs strategy,
2. Tandem elimination/deprotonation strategy,
3. Wittig strategy.

Our efforts in employing these three routes are discussed in the following sections.

3.2.1 Synthesis of coupling partner 52 *via* dibromide (Corey-Fuchs strategy)

The synthesis of coupling partner **52** (Scheme 25) began with commercially available and inexpensive 3-methylbut-2-en-1-ol **32**, which was oxidized to aldehyde **26** using PCC in CH_2Cl_2. Aldehyde **26** was filtered with Celite under argon pressure and then concentrated by distilling off the dichloromethane, to afford an 89% pure yield. Aldehyde **26** was concentrated by distillation instead of *in vacuo* due to the volatility of the aldehyde. In past experiences, Augusto and Spencer had noticed loss of aldehyde during concentration *in vacuo*, thus distillation was used instead for concentration. Aldehyde **26** was determined pure enough (confirmed by ^{1}H-NMR).

Aldehyde **26** undergoes a Corey-Fuchs olefination forming *gem*-dibromide **27.** Aldehyde **26** was added to a solution of triphenylphosphine and carbon tetrachloride in dichloromethane at 0 ^{o}C. It was purified *via* silica gel flash chromatography to afford a yellow oil in 30% yield over 2 steps. *Gem*-dibromide **27** was stored in light sensitive container, purged under argon, and was used within 24 hours to avoid decomposition.



Scheme 25. Route for synthesis of acid chloride **52**

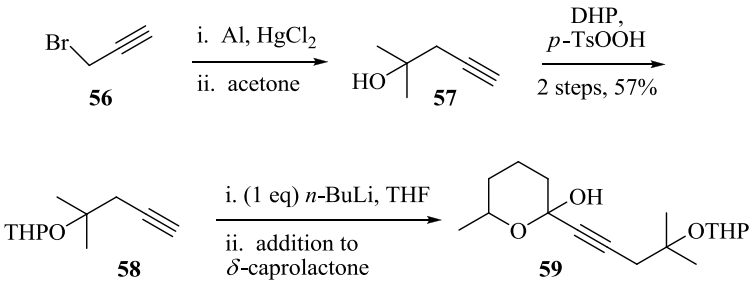
Dibromide **27** was then converted to ester **53** (Scheme 25) using two equivalents of *n*-butyllithium in THF and quenching the anion with ethyl chloroformate to afford ester **53**. Ester **53** was purified *via* chromatography to afford ester **53** in a suboptimal yield (20%).

The synthesis of ester **53** was not able to be reproduced, and therefore other routes to ester **53** were attempted. It is believed that dibromide **27** was not stable enough to undergo purification *via* column chromatography, and was reacting with itself by radical chemistry. Anion **33** could have been quenched with water, air, or other dibromide species. Also, ^{1}H-NMR indicated that the *n*-butyllithium was attacking the ethyl chloroformate producing ethyl pentanoate.

Once ester **53** was made, saponification was attempted using sodium hydroxide, diethyl ether, water and benzyl triethylammonium chloride as a phase transfer catalyst (Scheme 25). Acid **55** was not observed and starting materials were consumed (confirmed by ^{1}H-NMR).

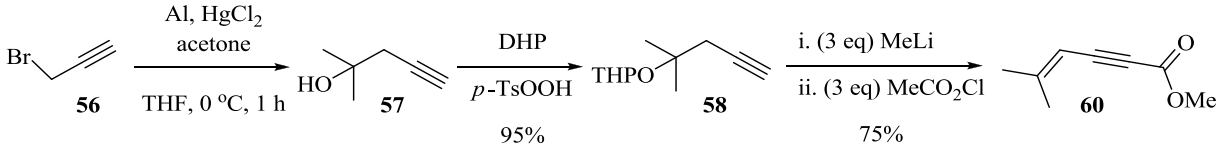
3.2.2 Synthesis of coupling partner *via* (tandem elimination/deprotonation)

Due to the instability of dibromide **27**, an alternate synthesis towards ester **53** was attempted. This synthesis was inspired by Yong and coworkers[38] who began with commercially available propargyl bromide **56**, and converted the resulting alcohol **57** into a good leaving group using DHP. Then deprotonation was achieved using *n*-butyllithium and the anion was quenched with *δ*-caprolactone to afford hemiacetal **59** (Scheme 26).



Scheme 26. Yong's synthesis of OTHP intermediate **58**

Neumann, Buchecker and coworkers[39] also commenced with the reagents of aluminum, mercury(II) chloride, and acetone to ultimately afford alcohol **57**. Alcohol **57** was protected using DHP and acid to afford protected alcohol **58** in 95% yield. Neumann and coworkers took protected intermediate **58** and treated it with three equivalents of methyllithium base in order to perform an elimination and also deprotonate the terminal alkyne. This was then treated with methyl chloroformate to form methyl ester **60** in 75% yield (Scheme 27).

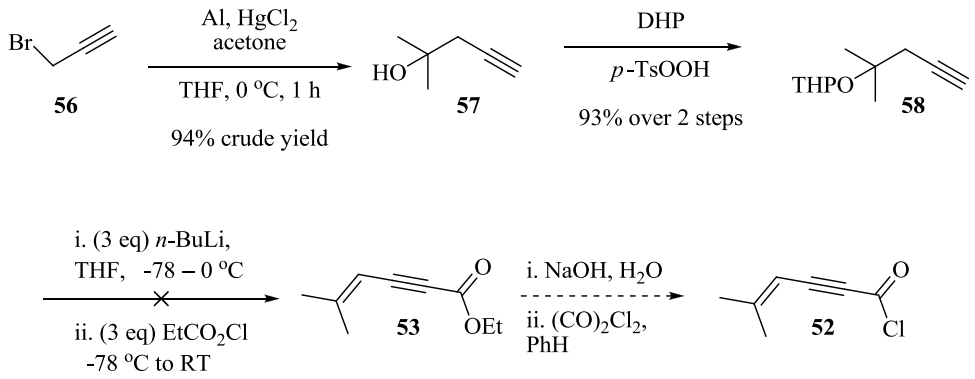


Scheme 27. Neumann's synthesis of methyl ester **60**

To commence our synthesis of ethyl ester **53**, aluminum flakes, mercury(II) chloride and propargyl bromide **56** were combined to form an amalgam in dry THF. Acetone was added, affording alcohol **57** in 94% crude yield (Scheme 28).

Alcohol **57** was then converted to a good leaving group using dihydropyran (Scheme 28). Alcohol **57** and *p*-toluenesulfonic acid were added to dichloromethane. Dihydropyran was added slowly to the solution, and the resulting oil was purified *via* column chromatography. This afforded ether **58** in 93% pure yield from propargyl bromide **56**.

We then subjected ether **58** to *n*-butyllithium instead of methyllithium as Neumann and coworkers had performed. We attempted to quench our resulting anion with ethyl chloroformate, however we were unsuccessful (Scheme 28).



Scheme 28. Synthesis of coupling partner **52** *via* mercury-aluminum amalgam

Excess *n*-butyllithium was used as some of the equivalents may have reacted with the ethyl chloroformate instead of performing the elimination or deprotonation. Ester **53** was never produced using this method, though starting materials had been consumed (confirmed by ^{1}H-NMR). It was believed that a similar problem was occurring as with the original route making the ester, in which anion **33** (Scheme 25) was being quenched with another proton source, and not with the ethyl chloroformate. We focused new attention on alternate routes due to this lack of success.

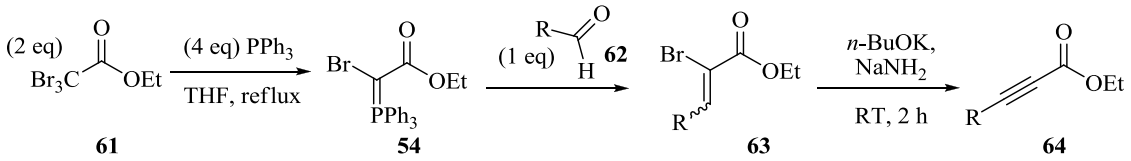
3.2.3 Synthesis of coupling partner *via* Wittig Reaction

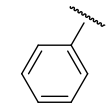
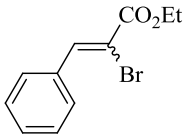
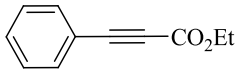
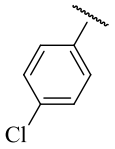
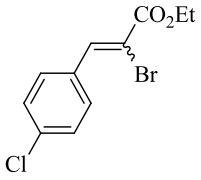
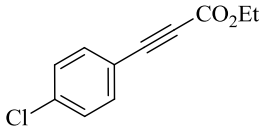
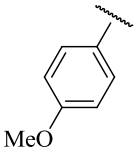
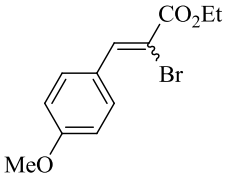
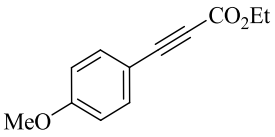
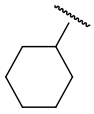
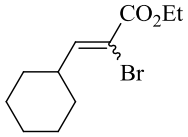
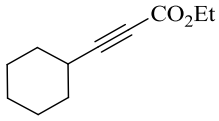
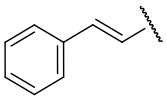
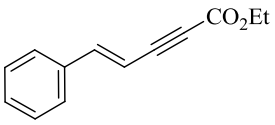
A method to synthesize ester **53** that circumvents the use of *n*-butyllithium and ethyl chloroformate is the employment of the Wittig reaction. Kim and coworkers studied the synthesis of conjugated acetylenic carboxylates, including conjugated and vinyl aldehydes.[40]

Kim's syntheses of acetylenic carboxylates involved commercially available tribromide **72** being reacted with triphenylphosphine to make brominated ylide **61**. A Wittig reaction was then performed with ylide **61** and alehydes **35a-f** to form alkenes **73a-f** (Table 4).

Kim's work demonstrated that the α-bromoacrylates were stable, with electron-withdrawing groups (**63b**), electron-donating substitutents on the ring (**63c**,**63e**), and aliphatic substituents (**63d**). Therefore Kim continued with the α-bromoacrylates to afford conjugated acetylenic carboxylates (Table 4).

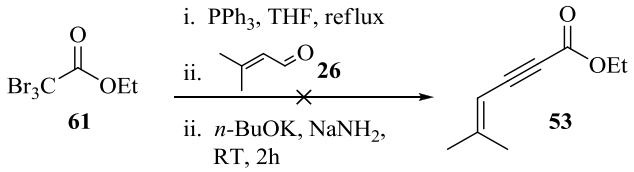
Table 4. Kim's analysis of Wittig reactions with aldehydes and the preparation of alkynoates



Entry **61**	R substituent on Aldehyde **62**	Wittig Product **63**	Wittig % Yield	Alkynoate Product **64**	Isolated % Yield
a			83		76
b			90		80
c			68		60
d			74		59
e		NA	NA		85

Kim concluded that aromatic aldehydes with electron withdrawing groups at the para- or ortho-postions of the ring results in higher percent yields, while aldehydes with electron donating groups resulted in percent yields in the range of 60-70%. Wittig reaction with aliphatic aldehydes resulted in only moderate yields (Table 4).

Our aim was to attempt the one-pot synthesis of alkynoate **53** using Kim's procedure. Kim's cinnamaldehyde **62e** is most analogous to our aldehyde **26** which is also conjugated. Therefore we used the same conditions as Kim used to make cinnamaldehyde-alkynoate **64e** (Scheme 29).



Scheme 29. One-pot synthesis of ester **53** *via* brominated ylide **54**

During the first step, triphenylphosphine was reacted with tribromide **61** in THF to afford brominated ylide **54**. This ylide is stabilized by the bromine and the carbonyl group. The second step of this reaction involved reacting the brominated ylide *in situ* with aldehyde **35** to afford brominated diene. The third step in Kim's reaction was reacting brominated ylide with potassium *n*-butoxide and sodium amide (Scheme 29). The butoxide acts as a base for the elimination of the bromine and formation of the alkyne. Kim had found that using *t*-butyllithium resulted in undesirable yields (5%) and that using excess potassium *tert*-butoxide resulted in mildly better yields (34%). The optimal base was a 1:1 equivalent ratio of sodium amide and potassium *tert*-butoxide.

Kim[41] observed primarily the *Z*-brominated alkene, which is due to the polarity of the THF solvent. In a nonpolar solvent (Figure 8a), no solvolysis occurs, and therefore the opposite olefin geometry is observed (Figure 8). In a polar solvent (Figure 8b), the ylide and aldehyde approach in a gauche alignment, while in a nonpolar solvent the ylide and aldehyde align anti. Following Kim's work, we chose THF as our solvent to obtain the *Z*-brominated alkene.

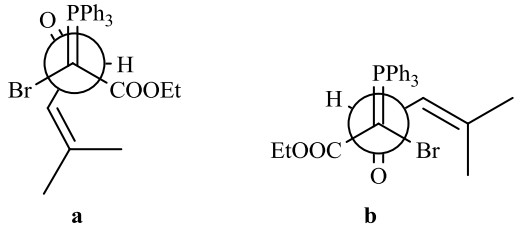
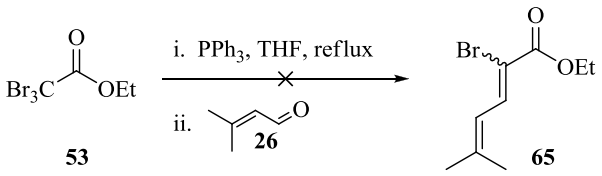


Figure 8. Olefin geometry of product from Wittig reaction (Scheme 29); alkene geometry obtained was *Z* in a nonpolar solvent, *E* in a polar solvent.

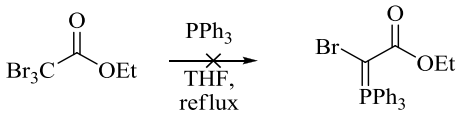
Kim's method to produce the ester was attempted three times. The first attempt was *in situ* to obtain the alkyne **60** as suggested (Scheme 29). Triphenylphosphine was reacted with tribromide **72** in THF to afford brominated ylide **61**. Aldehyde **26** was then added to the flask when the first reaction was completed (monitored by TLC). When the aldehyde had all been reacted (monitored by TLC), potassium butoxide and sodium amide were added to the flask. Unfortunately, ester **53** was not observed and reagents had been consumed (confirmed by ^{1}H-NMR). As it was unclear which steps were problematic, the following attempts were aimed at isolating the intermediates.



Scheme 30. Second attempt of *in situ* attempt of forming brominated diene **65**

The second attempt involved isolating brominated diene **65** (Scheme 30). Triphenylphosphine was reacted with tribromide **53** in THF to afford brominated ylide. Aldehyde **26** was then added to the flask when the first reaction was completed

(monitored by TLC). Unfortunately, brominated diene **65** was not observed and reagents had been consumed (confirmed by ^{1}H-NMR).



53 **54**

Scheme 31. Third attempt, isolating bromintaed ylide **54**

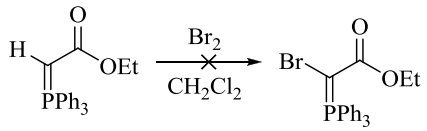
The third attempt involved isolated brominated ylide **54** (Scheme 31). Triphenylphosphine was reacted with tribromide **53** in THF to afford brominated ylide **54**. Unfortunately, brominated ylide **54** was not observed and reagents had been consumed (confirmed by ^{1}H-NMR).

Tribromide **53** was determined to have degraded (confirmed by ^{1}H-NMR). [41] Due to the cost of tribromide **53**, the synthesis of brominated ylide **54** was attempted using alternative methods.

3.2.3.1 Synthesis of halogenated ylide by Br_2

Given the difficulty in handling the tribromide starting material **53**, a bromination of an ylide was next attempted.

Denney and Ross synthesized brominated ylide **54** in their study to prepare stable halophosphoranes.[42] Bromine was added to ylide **80** in dichloromethane to afford vinyl bromide **54** (Scheme 32)



66 **54**

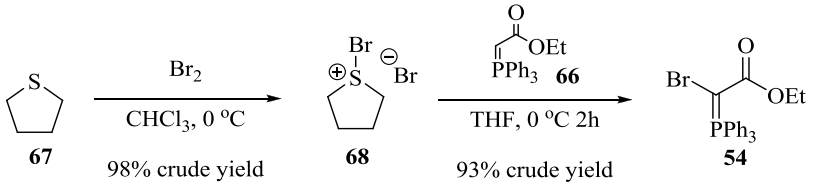
Scheme 32. Synthesis of brominated ylide **54** *via* bromine in dichloromethane

LC-MS analysis of brominated ylide **54** (Scheme 32) indicated that it was actually brominated twice. The melting point taken of the yellow solid was approximately 170-171 ^{o}C which is 10 degrees higher than the expected melting point (157-158 ^{o}C literature[42]) of monobrominated ylide **54**, thus confirming the undesired product.

3.2.3.2 Synthesis of Halogenated Ylide using thiophene

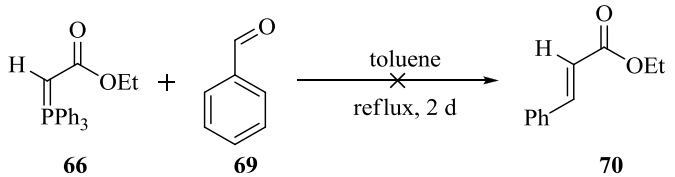
In 1955 Runge and coworkers[43] published a method converting thiophene **67** to its brominated species **68** in chloroform and bromine with a reported melting point of 79°C (Scheme 33). Using the same procedure thiophene **67** was converted to brominated species **68** obtaining a 98% yield. The orange solid had a melting point of 74-75 °C experimental, and was determined to be of acceptable purity. ^{1}H-NMR spectroscopy wasn't used to confirm the structure as the chemical shifts would be nearly identical for thiophene **67** and brominated thiophene **68**.[44]

With the brominated thiophene **68** in hand, we then followed the procedure by Magdesieva and coworkers for the bromination of the ylide.[45] Commercially available ylide **66** was reacted with brominated thiophene **68** in THF at 0 °C for two hours, affording brominated ylide **54** in 93% crude yield, and was confirmed with a melting point of 153-154 °C (Scheme 33). ^{1}H-NMR spectroscopy wasn't used to confirm the structure as there were no spectra for comparison in the literature (154-156 °C literature[46]).



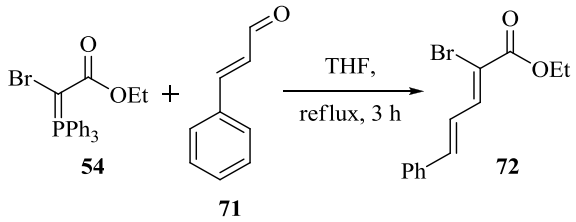
Scheme 33. Synthesis of brominated ylide **54** *via* thiophene **67.**

In order to determine if the Wittig reaction would occur in our hands, a known Wittig reaction was completed using Kim's procedure with benzaldehyde **69** and the commercially available ylide **66** affording ethyl cinnamate **70** in toluene at reflux (Scheme 34).[41] Ester **70** was not observed, though reagents had been consumed (confirmed by ^{1}H-NMR).



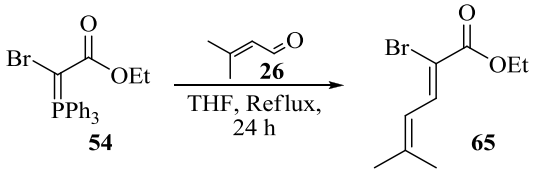
Scheme 34. Determination of conditions for Wittig reaction in the preparation of ethyl cinnamate from benzaldehyde and ylide **70**

Returning to Kim's methodology on Wittig reactions,[41] it appeared that a variety of reaction conditions were used when using brominated ylide **54**, one of which involved overnight heating. It also appeared that benzaldehyde **69** may have been a poor choice in aldehydes due to purity issues. Cinnamaldehyde **71** would thus be more analogous to our aldehyde **26** than benzaldehyde **69**. So, we performed the Wittig reaction with cinnamaldehyde **71** and the brominated ylide **54** (Scheme 40). GC-MS results indicated that dienyl ester **72** was indeed produced, however in limited quantity.



Scheme 35. Wittig reaction using brominated ylide **54** and cinnamaladehyde **71**

Using similar conditions aldehyde **26** was reacted with borminated ylide **54** (Scheme 36). Because our aldehyde **26** is very volatile and the reaction ran at ~70 ^{o}C, a sealed vessel was used instead of a reflux condenser for 24 hours, then cooled for 24 hours. While diene **65** was not observed (GC-MS analysis), and aldehyde was used in excess, the resulting solution indicated aldehydic protons still present (confirmed by ^{1}H-NMR). This indicated that at this temperature, the aldehyde **26** is not polymerizing, but not reacting with brominated ylide **54** either. Perhaps higher temperatures would allow the reaction to proceed forward.



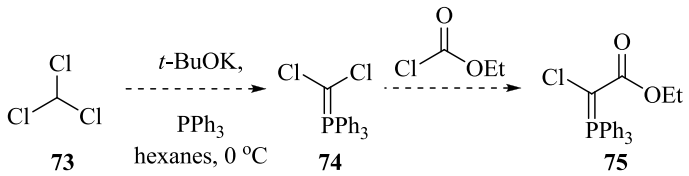
Scheme 36. Synthesis of brominated dienyl ester **65** using brominated ylide **54**

3.3 Future Work

Given the work completed to date, the Wittig reaction appears to be the most potential of the three strategies investigated. It is particularly attractive because it avoides sensitive anion chemistry. Nevertheless, other routes are being considered.

3.3.1 Potential synthesis of chlorinated ylide

Speziale and Ratts[48] produced chlorinated ylide **75** using commercially available triphenylphosphine, chloroform **73**, potassium *t*-butoxide, and ethyl chloroformate (Scheme 37).

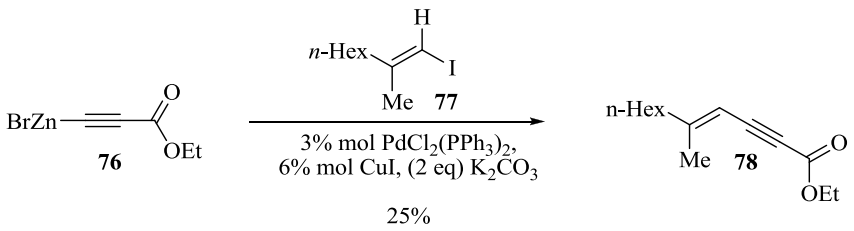


Scheme 37. Synthesis of chlorinated ylide **75** *via* triphenyl phosphine and chloroform

While this reaction was not performed due the further investigation of other routes, this would allow an alternate synthesis of a halogenated ylide. Bromoform could also be used instead of chloroform to afford brominated ylide **54** instead of chlorinated ylide **75**. This might provide an inexpensive and alternative option.

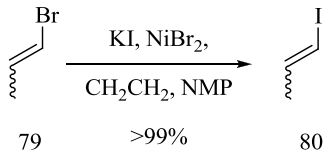
3.3.2 Potential synthesis of sidechain *via* Sonogashira coupling

Negishi and coworkers have much experience in making unsaturated chains similar to the one we aim to construct in trocheliophorlide A.[47] Negishi studied the coupling of alkenyl halides and alkynes using a palladium catalyst (Scheme 38).



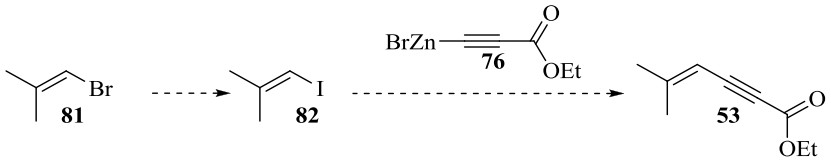
Scheme 38. Negishi's synthesis of alkynoate **78** by Sonogashira coupling

While the yield achieved by Negishi and coworkes was quite low, the substituents on our olefin **82** are less sterically hindered and thus ours may prove more efficient (Scheme 40.l;). Meyer and coworkers prepared a similar iodoolefin **80** to Negishi in >99% yield starting from commercially available bromo olefin **79** (Scheme 39).[48]



Scheme 39. Meyer's preparation of iodoolefin **80**

It would thus be extrapolated that combining Meyer's synthesis of an iodoolefin with a commercially available vinyl bromide **81**, in a Sonogashira coupling similar to Negishi's could afford the alkynoate **53** (Scheme 43).



Scheme 40. Potential route to sidechain **53** *via* Sonogashira coupling

4.0 Conclusions

Trocheliophorolide A is a challenging synthetic project due largely to the complexity of the unsaturated sidechain. My studies have accomplished the following points: (1) The synthesis of butenolide **6** has been optimized, utilizing an alternate catalyst of palladium(II) during the cyclization step and freshly purchased tin hydride. (2) A variety of alternate routes to synthesize the sidechain have been designed.

The investigation of the alternate unsaturated sidechain routes lead us to further pursue the Wittig strategy. Anion chemistry was determined to be very difficult to control given the unconditioned laboratory environment and the challenges associated with avoiding humidity when running reactions.

Although the total synthesis has not been completed, a promising route for the sidechain has been designed and preliminary results have been obtained.

General Procedures

All non-aqueous reactions were carried out using flame-dried glassware under argon. All reagents were added into the argon atmosphere *via* syringe or cannula through a rubber septum. Temperatures in the schemes indicate the temperature of the bath. Distillations were performed under argon atmosphere, under reduced pressure if noted (*via* water aspirator, 10-20 mmHg).

Concentration was performed *in vacuo* using a rotary evaporator. A Büchi rotary-evaporator, used reduced pressure to remove solvent (*via* water aspirator, 10-20 mm Hg).

Chromatography

Purification by chromatography was performed (as noted) using EM reagent silica gel 60 (230-400 mesh). Thin layer chromatography was performed using EM silica gel 60 F-254 pre-coated glass plates (0.25 mm) and TLC Silica gel 60 F-254 pre-coated plastic sheets with the solvent system as noted. The plates were visualized using short-wave UV illumination (254 nm) or by dipping the plate into a potassium permanganate stain followed by heating on a hot plate (glass plates) or heating with a heat gun (plastic plates). The potassium permanganate stain was prepared by mixing potassium permanganate (6 g), potassium carbonate (40 g), sodium hydroxide (5%, 10 mL), and diluting the solution to 1 L.

Reagents and Solvents

Commercially available solvents were used without further purification for extractions, work-up procedures, and reactions unless otherwise noted. Deionized water was used for all aqueous reactions, work-up procedures, and preparation of all aqueous solutions (e.g. brine). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl; dichloromethane was distilled from calcium hydride.

Spectroscopic Measurements

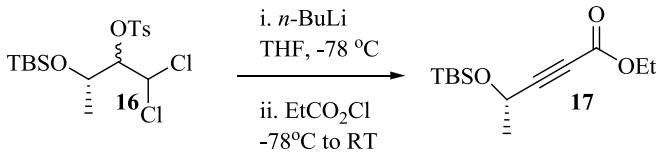
Proton (^{1}H) and carbon-13 (^{13}C) nuclear magnetic resonance (NMR) spectra were acquired using either a Bruker DRX-300 or AMX-400 NMR. Chemical shifts in ^{1}H-NMR spectra are reported in relation to the resonance of residual $CHCl_3$ (δ 7.26 ppm).

Chemical shifts in ^{13}C-NMR spectra are reported in relation to the resonance of $CDCl_3$ (δ 77.2 ppm). All coupling constants are reported in Hz.

Melting points were acquired using a Mel-Temp 50/60 cycles, 110-120 Volts and are uncorrected.

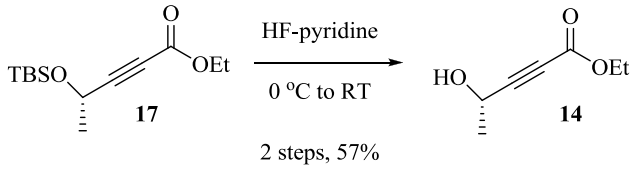
LC-MS specra were acquired using an Applied Biosystems – Q Trap 3200 Liquid Chromatograph – Mass Spectrometer on solutions in 1% acetic acid in methanol.

Experimentals



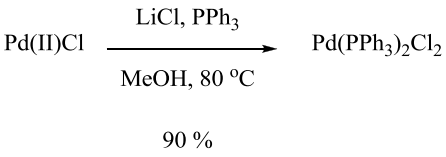
A 100 mL round bottom flask was charged with purified tosylate (2.241 g, 5.24 mmol). Anhydrous THF (25 mL) was added at -78 °C. To the solution, *n*-butyllithium (7.9 mL, 2.20M) was added and stirred at -78 °C for 30 min. The solution was then allowed to warm to 0 °C for 45 min. The solution was cooled back to -78 °C and ethyl chloroformate (0.6 mL, 6.29 mmol) was added dropwise over 20 min. The solution was to stirred at -78 °C for 1 h. The reaction was monitored by TLC (4:1 hex:EtOAc) and when finished was quenched with aqueous ammonium chloride (80 mL), brine (75 mL), and water (30 mL). The solution was extracted with ether (2 × 50 mL), dichloromethane (4 × 50 mL) and the combined organics were dried over anhydrous magnesium sulfate. Solution was concentrated *in vacuo*, to afford ester **17** as a brown oil with >99% crude yield.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.61 (q, *J* = 6.5 Hz, 1H), 4.22 (q, *J* = 4.3 Hz, 2 H), 1.66 (d, *J* = 6.6 Hz, 3H), 1.31 (m, 9 H), 0.94, (t, *J* = 2.1 Hz, 3H), 0.01 (s, 6H)

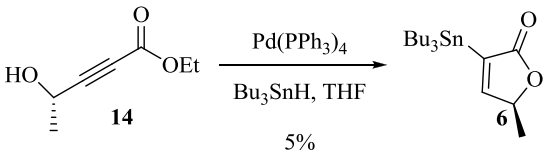


A 250 mL round bottom flask was charged with anhydrous THF (7.8 mL) and ether **17** (0.474 g, 1.85 mmol) at 0 °C. To the solution, HF-pyridine (0.95 mL, 37.0 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, then was allowed to warm to RT over 1.2 h. The reaction was monitored by TLC (4:1 hex:EtOAc), and when finished the reaction was quenched with aqueous saturated sodium bicarbonate (100 mL), and extracted with ether (40 mL), and dichloromethane (2 × 35 mL). The organics were washed with saturated aqueous copper(II) sulfate (30 mL) and saturated brine (30 mL). Solution was filtered to remove excess copper (II) sulfate and then extracted. Organics were dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Purification *via* column chromatography was performed using 100:0-0:100 hex:EtOAc, to afford alcohol **14** as a brown oil in 57% yield over 2 steps (1.45 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.54 (q, *J* = 6.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.82 (s, 1H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H)

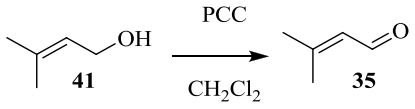


A solution of palladium(II) chloride (0.1263g, 0.712 mmol), lithium chloride (0.0605 g, 1.42mmol), methanol (2 mL), and triphenylphosphine (0.4109 g, 1.57 mmol) was allowed to reflux at 80-85 °C for 30-40 min. Flask was allowed to cool to RT for 1 h. Solution was filtered, washed with distilled methanol, and pushed through with argon pressure. Solid was dried under argon pressure overnight to yield yellow solid Pd(II) catalyst (0.452g, 90% yield). Solid was stored in dessicator in foil covering.[49]



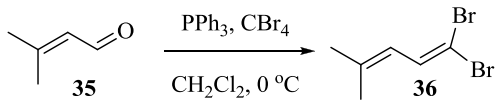
A solution of purified ester **14** (57 mg, 0.400 mmol) and Pd(0) catalyst (46.7 mg, 0.040 mmol) and anhydrous (and degassed) THF (1 mL), was stirred for 10 min in a 50 mL round bottom flask. To the solution, tributyltin hydride (0.12 mL, 0.440 mmol) was added dropwise over 40 min *via* cannula. The solution was stirred in the dark for 70 min at RT. Solution was concentrated *in situ*, then diluted with pentanes (20 mL, 0 ^{o}C) and stirred for 1 hr in the dark at 0 ^{o}C. Solution was filtered, washed with pentanes, and concentrated to afford butenolide **6**. The crude product was purified *via* column chromatography with a gradient elution of 100:0-90:10 pentanes/ethyl acetate to afford butenolide **6** (7 mg, 5% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 1.4 Hz, 1H), 5.07 (q, *J* = 6.9 Hz, 1H), 1.52 (m, 6H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.32 (m, 6H), 1.08 (m, 6H), 0.89 (t, *J* = 7.3 Hz, 9H)



A 100 mL round bottom flask was charged with PCC (3.3411 g, 15.5 mmol) and pre-distilled dichloromethane (40 mL). Reaction was stirred at RT for 10 minutes. Alcohol **41** (1 mL, 10.7 mmol) was added, causing the solution to turn black in color. Solution was stirred at RT for 3 h. Aldehyde **35** was concentrated by distilling off excess dichloromethane until 1 g solution remained, to afford aldehyde **35** as a black liquid with yellow tint, not purified.

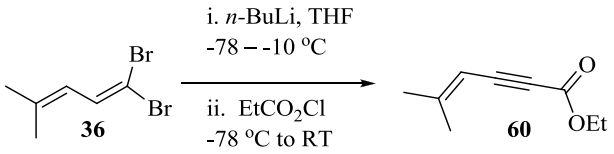
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.96 (d, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 8.0 Hz, 1H), 2.17 (s, 3H), 1.98 (s, 3H).



30% over 2 steps

A round bottom flask was charged with triphenyl phosphine (3.74 g, 14.3 mmol) and carbon tetrabromide (2.37 g, 7.14 mmol). Dichloromethane (26 mL) and aldehyde **35** (0.4 g, 4.76 mmol) were added, and solution was stirred at 0 °C for 1.5 h. When the reaction was complete (monitored by TLC, 10:1 hex:EtOAc), cold pentanes (40 mL) was added, and the solution was stirred for 1 h. The solution was sonicated and filtered through a Büchner funnel with 2 filter papers. Solution was concentrated *in vacuo*, to afford dibromide **36** as a greenish yellow liquid. Purification was performed *via* column chromatography with a gradient solution of 0:100 – 100:0 hex:EtOAc, to afford dibromide **36** (0.342 g, 30% yield over 2 steps) as a brown oil, which was stored at 0 °C in a flask covered in foil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 10.6 Hz, 1H), 5.85 (d, *J* = 10.6 Hz, 1H), 1.80 (s, 3H), 1.75 (s, 3H)

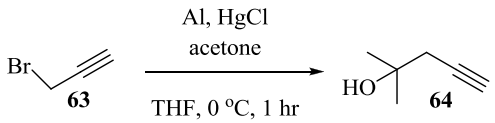


20%

A round bottom flask was placed in a -78 °C dry ice/acetone bathand was charged with *n*-butyllithium (2.3 M, 1.04 mL, 2.39 mmol) and dry THF (4 mL). To a second flask containing dibromide **36** (.262 g, 1.09 mmol), dry THF (2 mL) was added. The dibromide/THF solution was cannulated to the original flask at -78 °C and stirred for 30 min. The solution was then allowed to warm to -10 °C and stirred for 45 min. After cooling the solution back to -78 °C, ethyl chloroformate (1.25 mL, 13.1 mmol) was added along with THF (2 mL). The solution was stirred until the reaction was complete (3 h, monitored by TLC, 10:1 hex:EtOAc). The solution was quenched with saturated aqueous

ammonium chloride (30 mL), saturated brine (30 mL), and distilled water (15 mL). The solution was extracted with diethyl ether (3 × 30 mL) and dichloromethane (3 × 30 mL), and the combined organics were dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified *via* column chromatography with a gradient solvent system of 100:0 – 0:100 hex:EtOAc, to afford a yellow oil, ester **60** (32.6 mg, 20% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.36 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.99 (s, 3H), 1.88 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H)

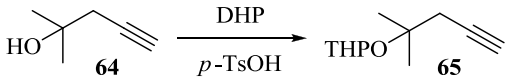


60%

A 20 mL round bottom flask was charged with mercury dichloride (16 mg, 0.059 mmol) and aluminum flakes (.17g, 6.30 mmol). Dry THF (distilled, 2 mL) was added and solution was stirred for 10 min. Propargyl bromide (1 mL, 6.4 mmol) and THF (distilled, 1 mL) was added to the flask, and the solution was stirred at 40 °C for 30 min. The solution was then cooled to 0 °C, and acetone (.6 mL, 7.7 mmol) was added. The solution was stired again for 30 min at 40 °C.

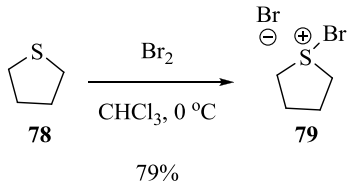
The solution was quenched by adding ice water (100 mL) and saturated aqueous ammonium chloride (40 mL). The solution was attempted to be separated using THF and ether, but the aluminum caused difficulty. The solution was therefore filtered through a fritted funnel to remove the aluminum flakes, and then extracted with diethyl ether (3 × 100 mL). The combined organics were dried over magnesium sulfate and concentrated, to afford alcohol **64** as an oil matching literature properties[50] (380 mg, 60% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.38 (d, *J* = 2.4 Hz, 2H), 2.09 (t, *J* = 2.5 Hz, 1H), 1.32 (s, 6H)



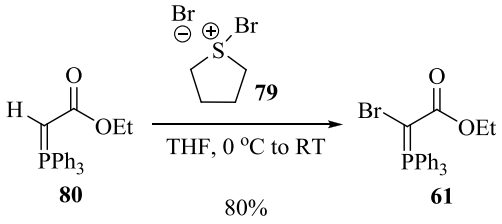
A round bottom flask was charged with alcohol **64** and *p*-toluene sulfonic acid (0.0198 g, 0.115 mmol). Dichloromethane was added to the flask at 0 ^{o}C. DHP (0.52 mL, 6.2 mmol) was added slowly, and reaction was stirred. After 1.5 h, the reaction was quenched with saturated aqueous sodium carbonate (60 mL), and the solution was extracted with dichloromethane (3 × 40 mL). The combined organics were dried over magnesium sulfate and concentrated *in vacuo*. Oil was purified *via* column chromatography, using gradient eluent system of 100:0 – 0:100 hex:EtOAc., to afford ether **65** as a brown oil in 93% yield (0.61 g).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.81 (m, 1H), 4.03 (m, 1H), 3.55 (m, 1H), 2.17 (s, 6H), 1.79 (m, 4H), 1.55 (m, 4H).



A 5 mL round bottom flask was charged chloroform (dried with moleculer sieves, 3.0mL) at 0 ^{o}C. Tetrahydrothiophene (0.2 mL, 227 mmol) was added dropwise to the flask, then bromine (.12 mL, 227 mmol) was added. Immediately a red solid formed. Solution was filtered through a fritted funnel *via* vacuum filtration, and washed with 1mL cold chloroform, to afford brominated thiophene **79** (426 mg, 79% yield) as a red and yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.49 (m, 4H), 2.39 (m, 4H).
mp: 74-75 ^{o}C.



A round bottom flask was charged triphenylphosphine methylene ethylacetate (538 mg, 1.55 mmol). At 0 °C, distilled THF (5 mL) was added to the solution. To the flask containing thiophene dibromide **79** (from previous experiment), distilled THF (5 mL) was added. The dibromide/THF solution was cannulated to the first flask, and using more distilled THF (10 mL) to ensure complete transfer of reagents. The solution was stirred overnight at RT under argon, and white solid precipitated. The solution was filtered through a fritted funnel to afford brominated ylide **61** as a white solid (262 mg, 80% yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.92 (m, 6H), 7.79 (m, 3H), 7.68 (m, 6H), 4.04 (q, 7.2 *J* = Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 3H)

mp: 150-151 °C

MS: m/z = 426

MS (EI): *m/z* calc. for [$C_{22}H_{20}BrO_2P$] 426.0, found: 426.0.

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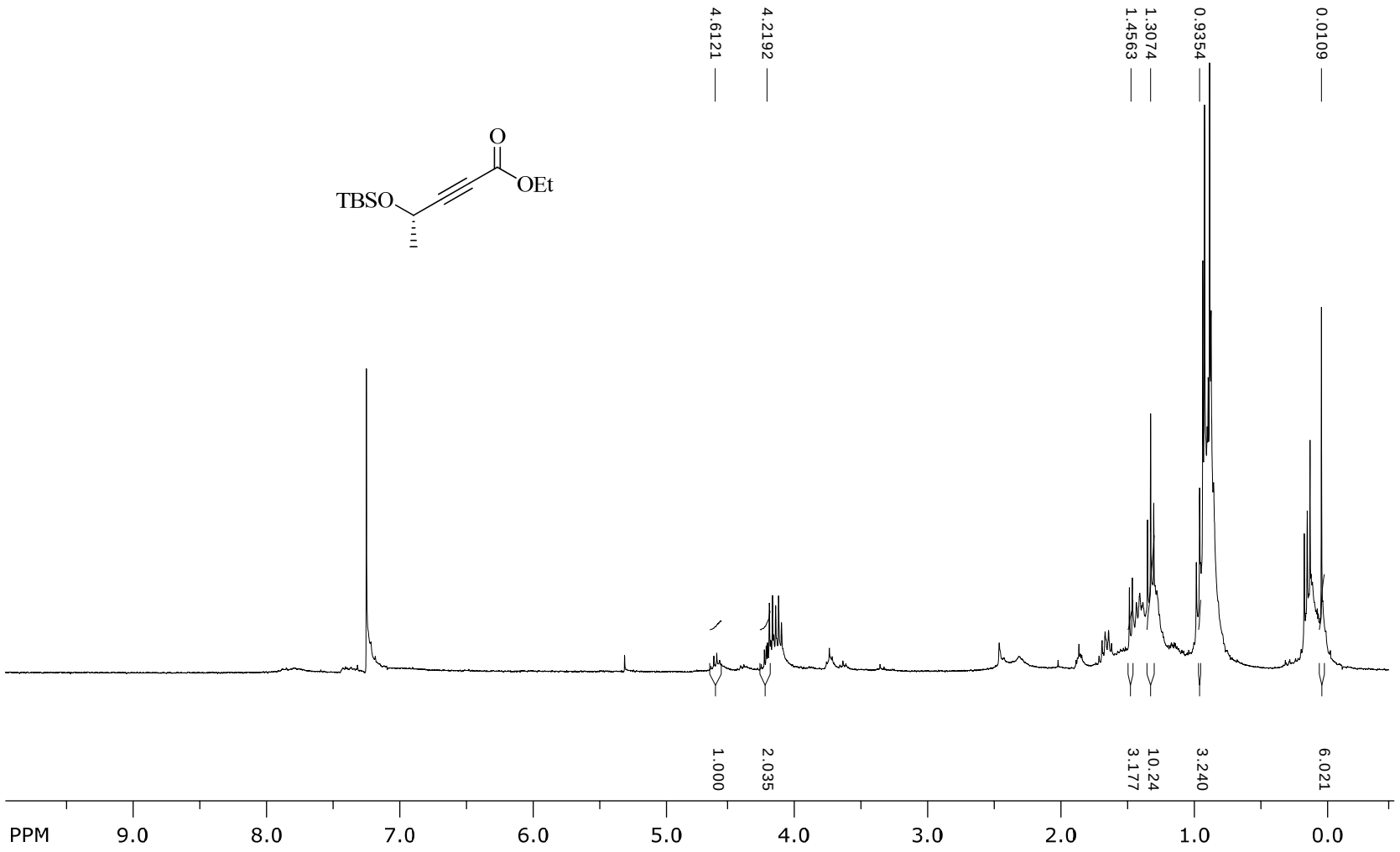
Spectra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3.240
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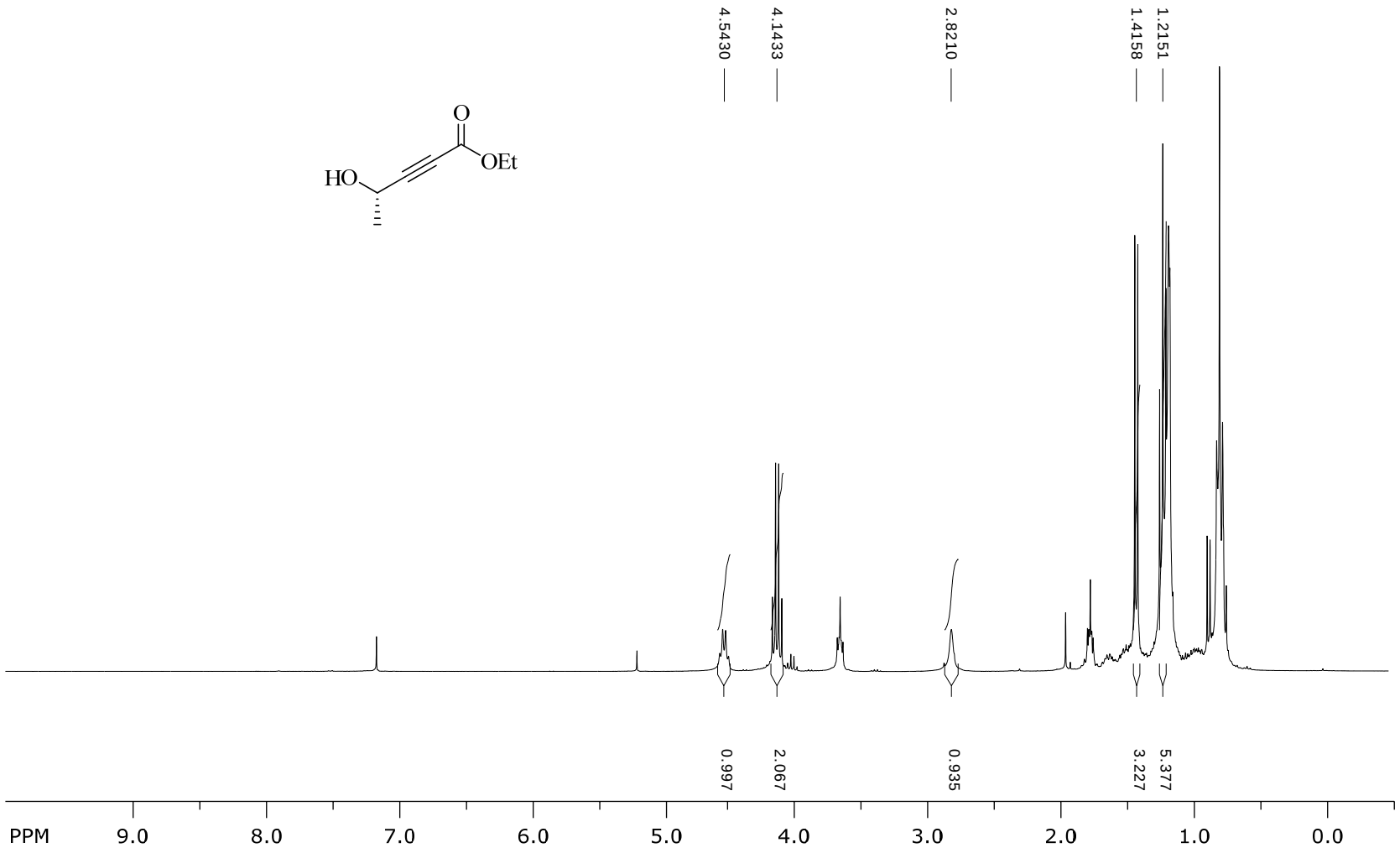
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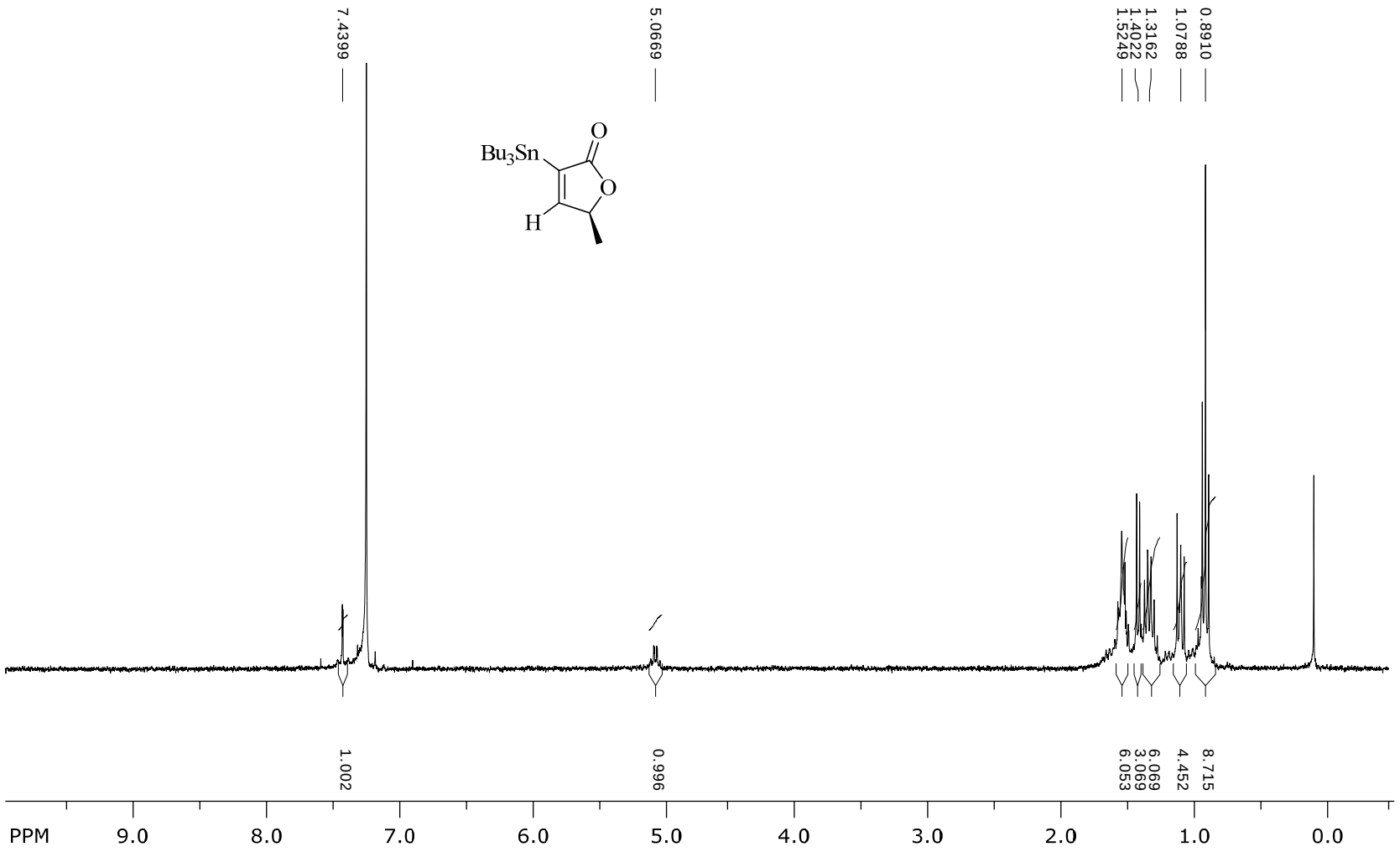
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6.069
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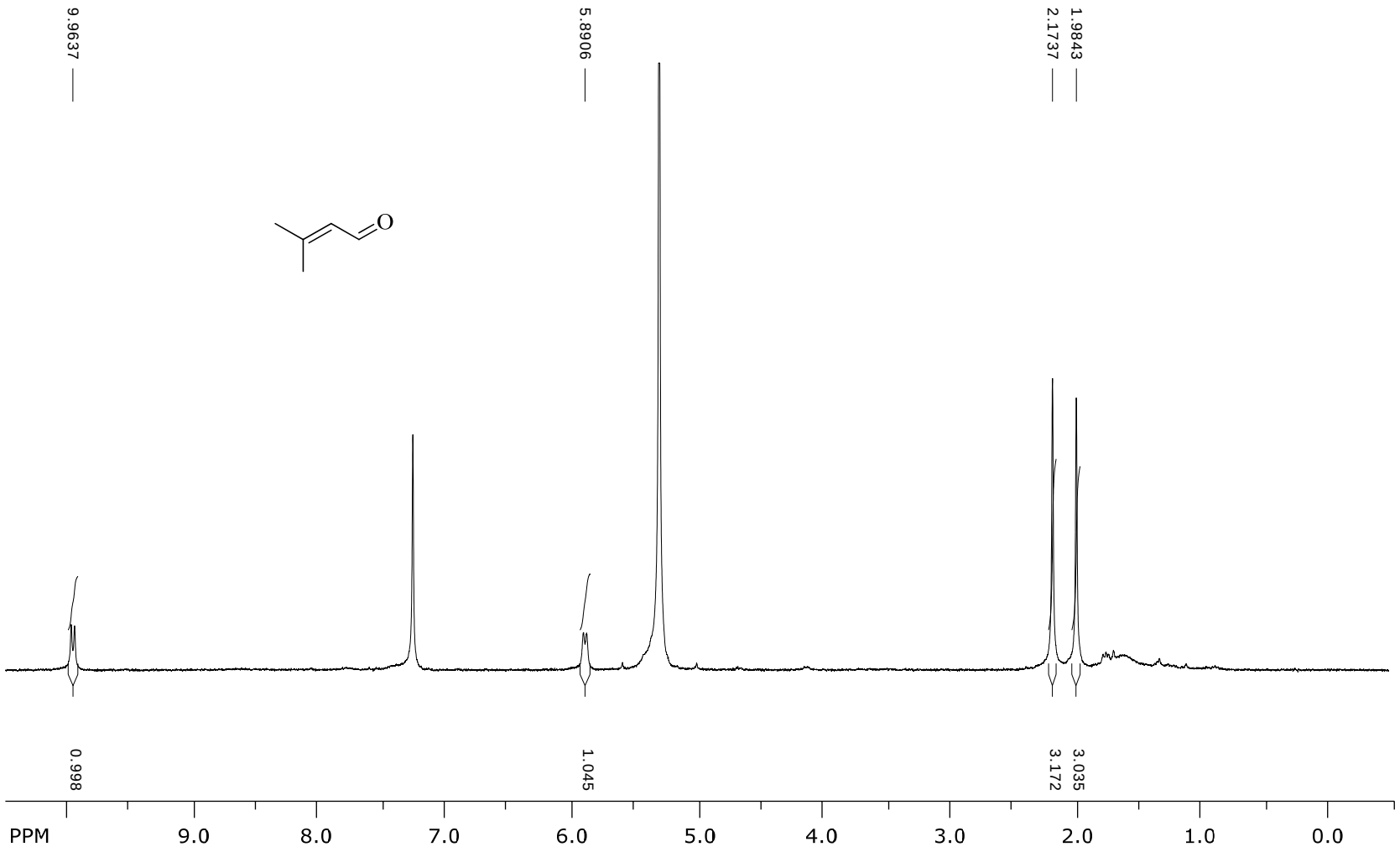
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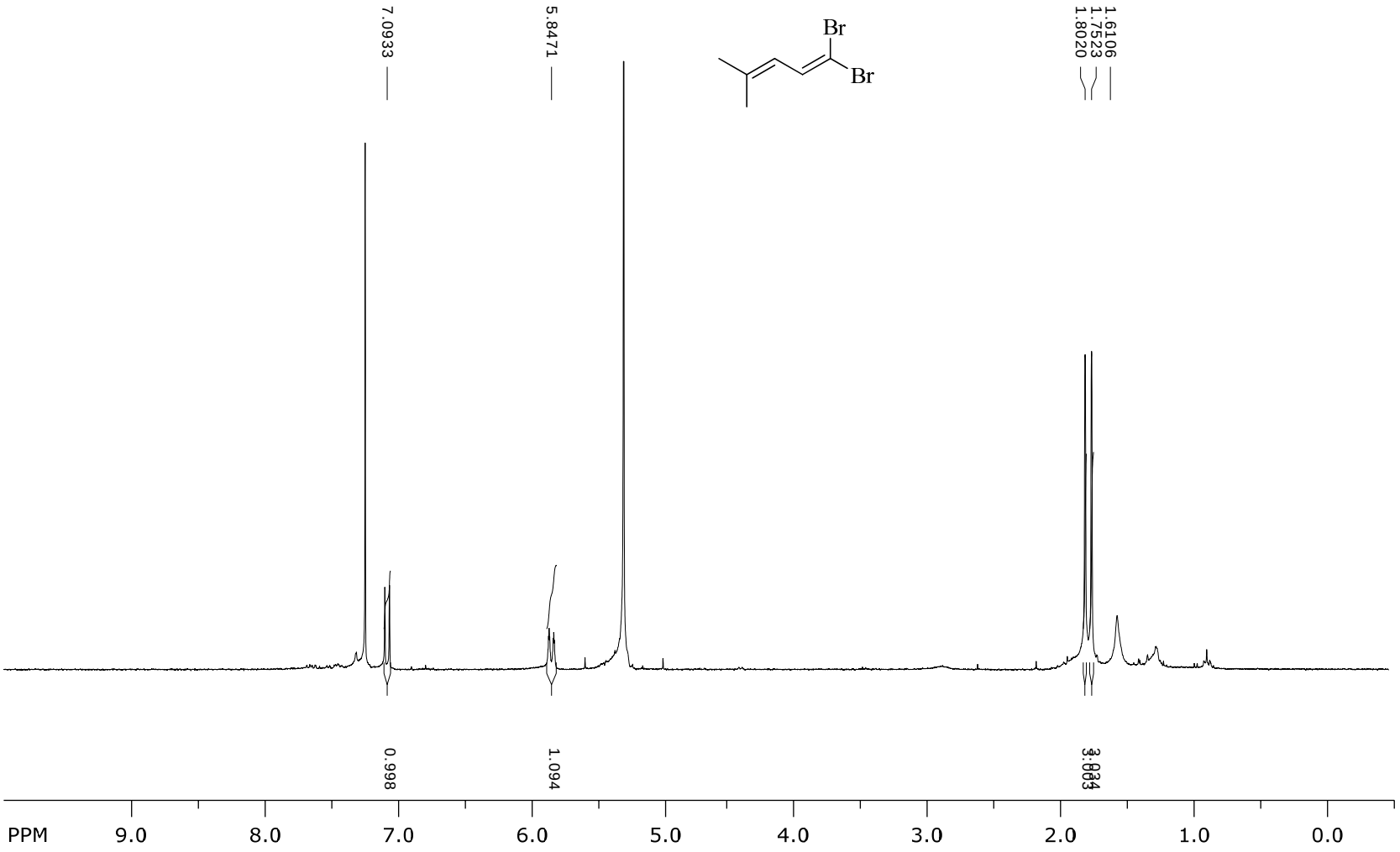
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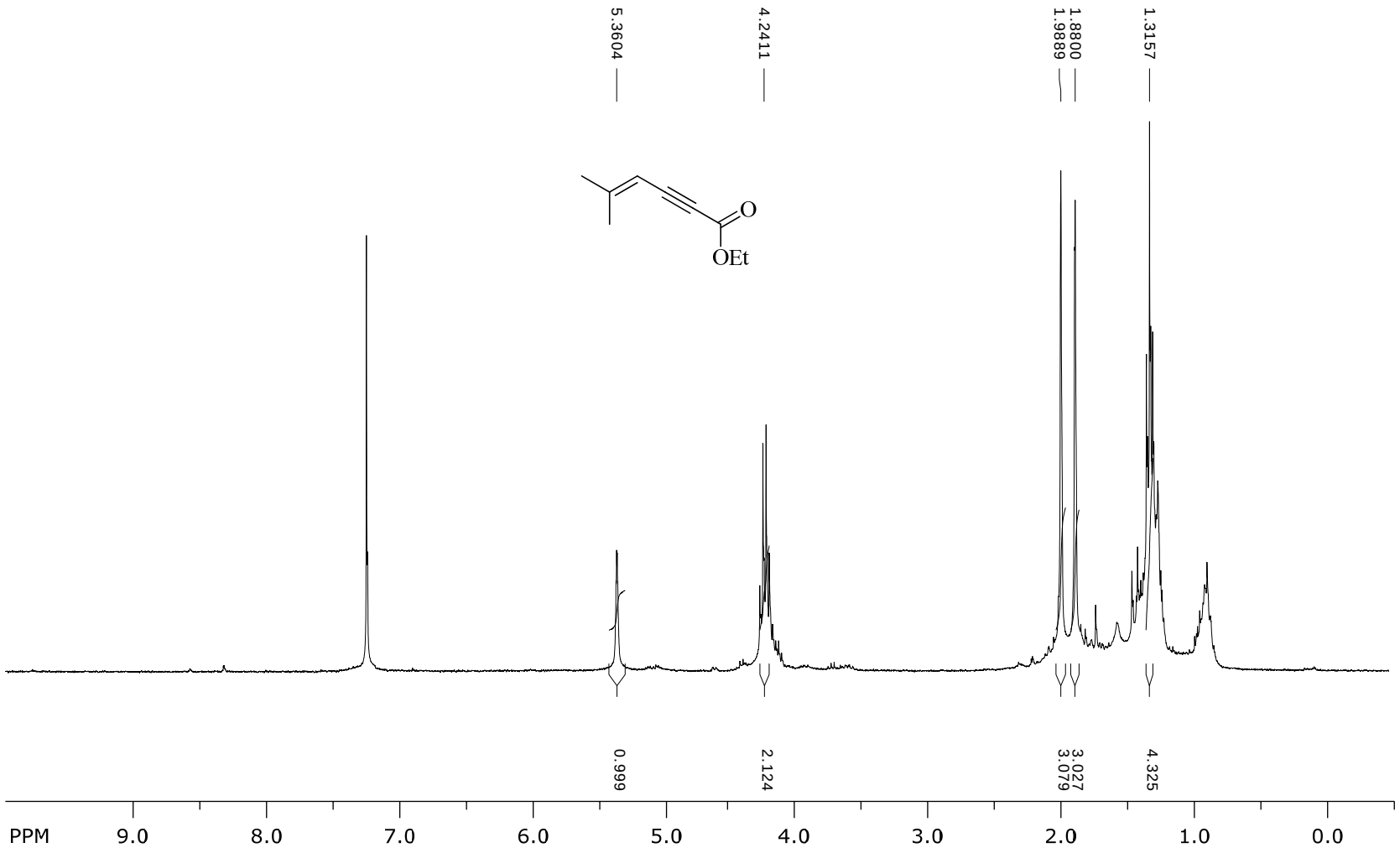
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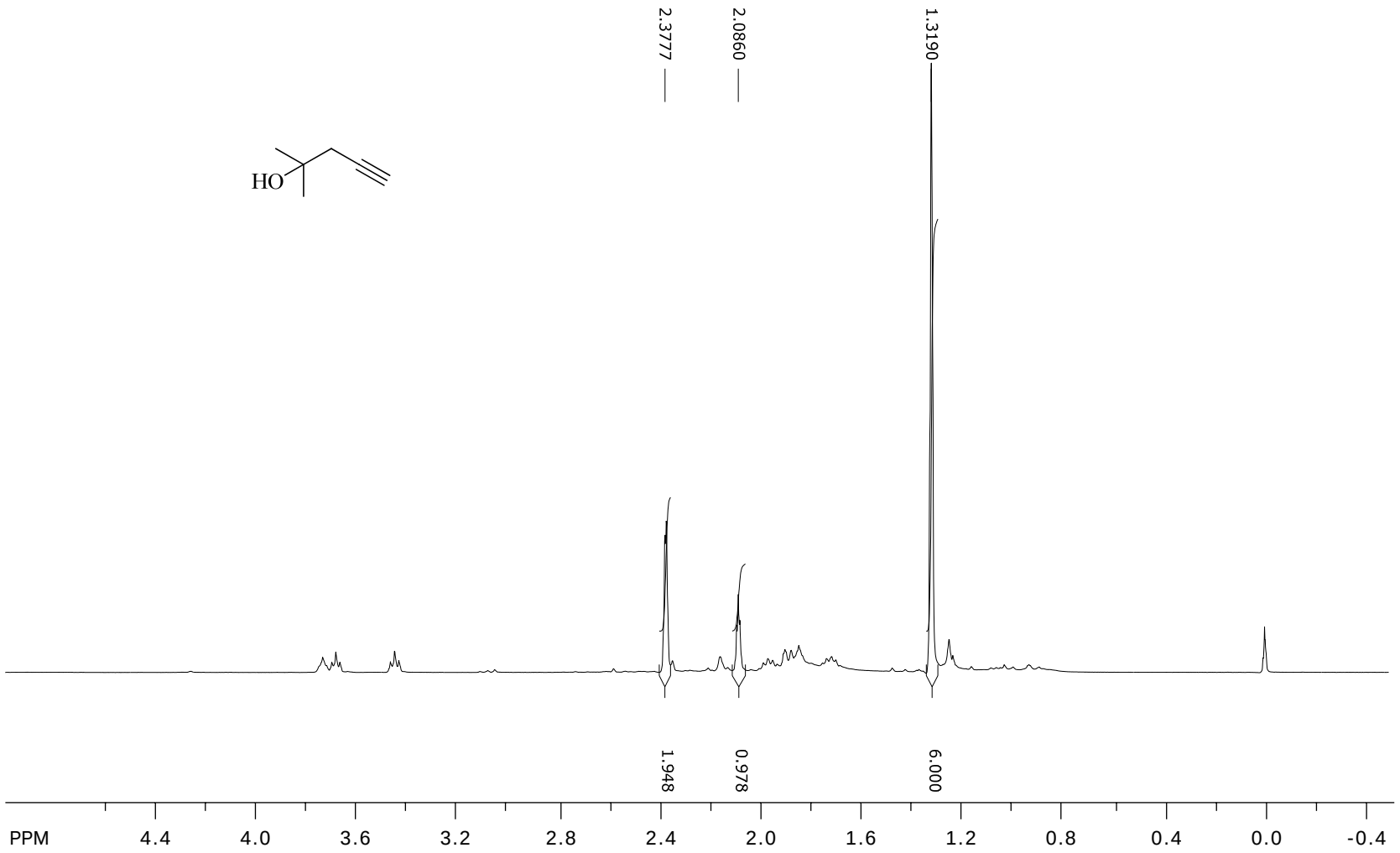
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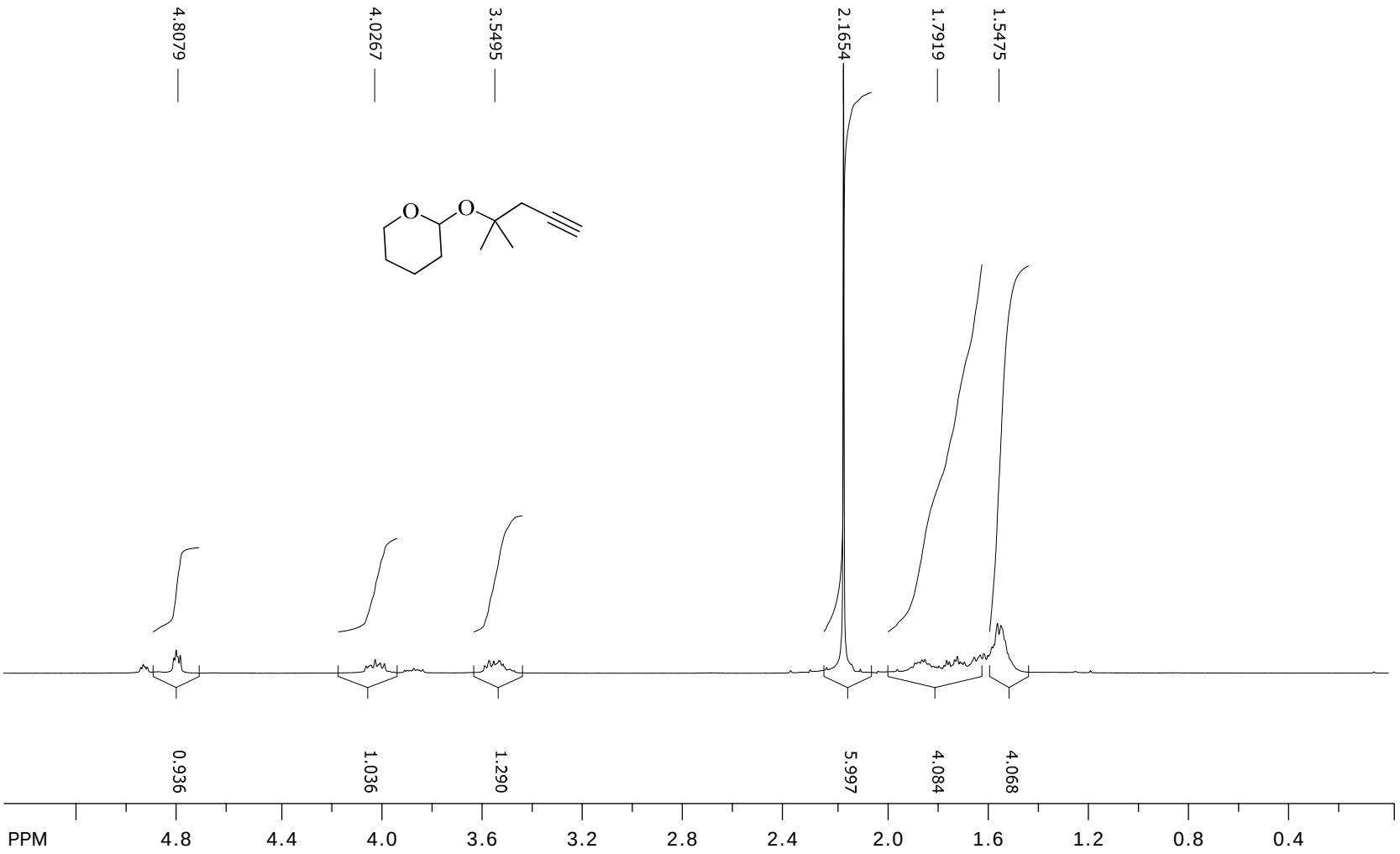
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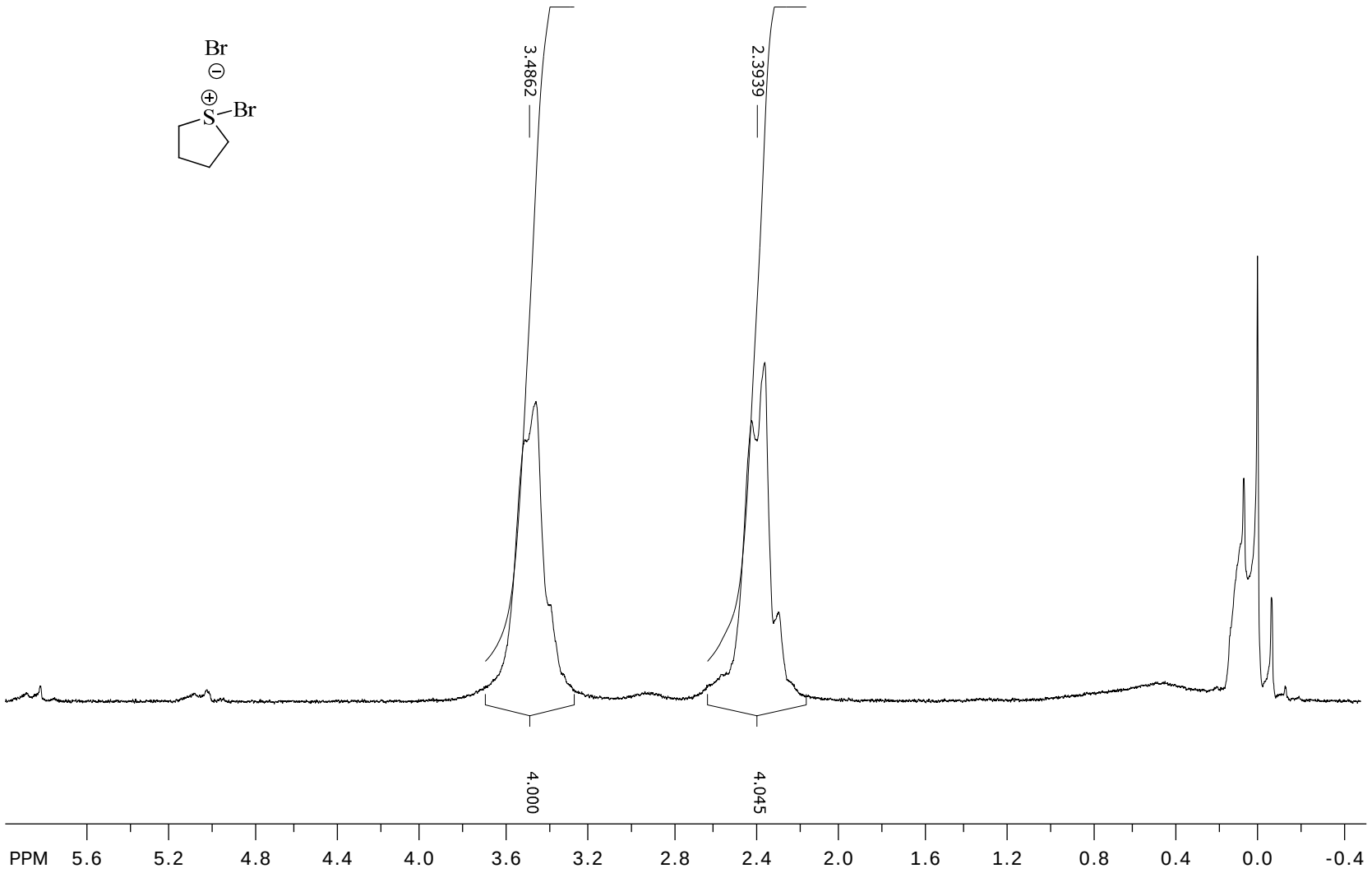
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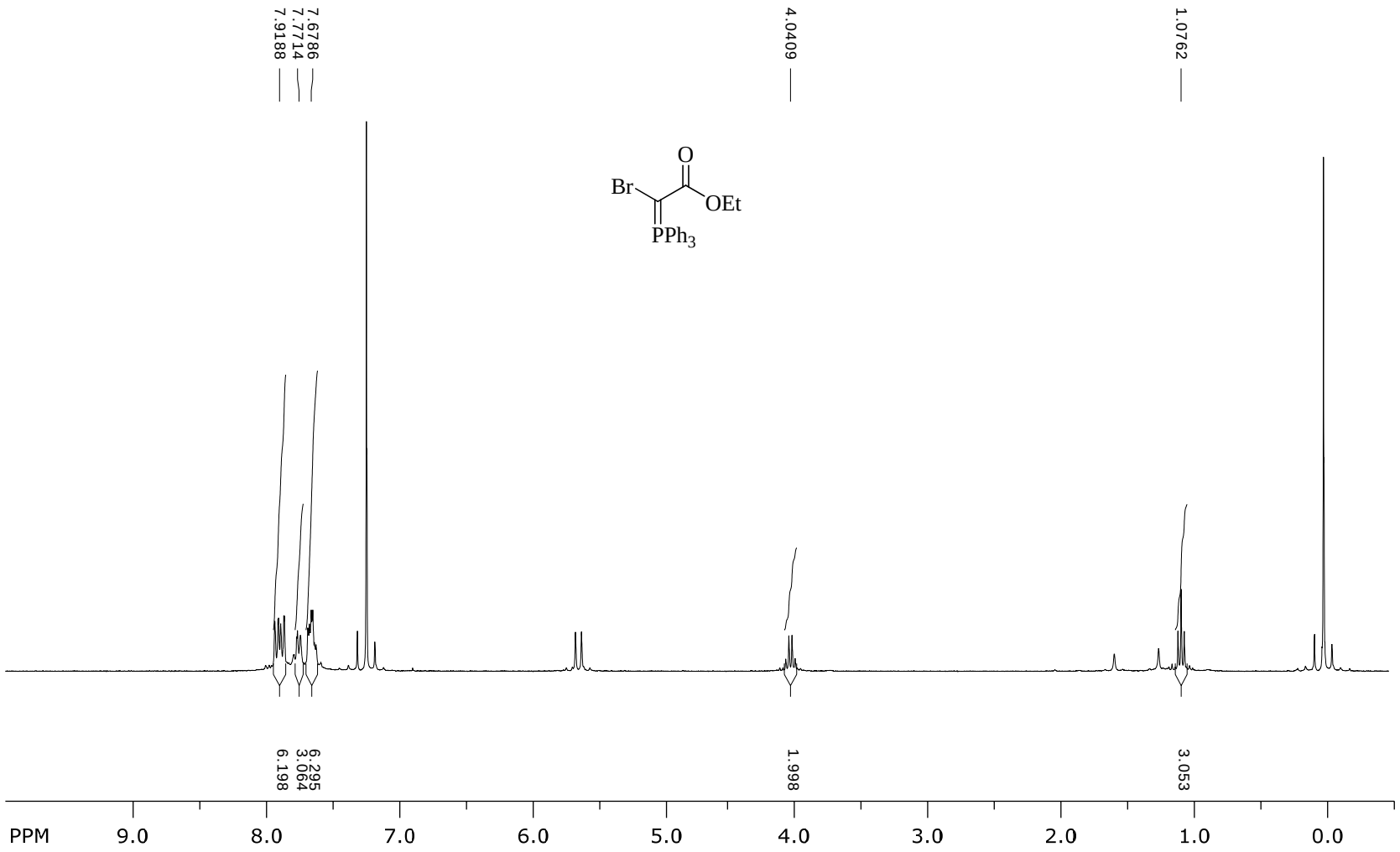
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