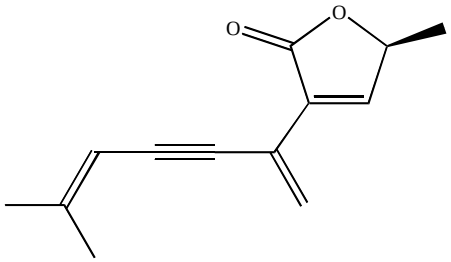
2013

Studies toward the total synthesis of Trocheliophorolide A

Jennifer Swartzenberg

Studies Toward the Total Synthesis of Trocheliophorolide A



Jennifer L. Swartzenberg

Submitted in Partial Fulfillment of the Requirements for the

Master of Science in Chemistry

School of Chemistry and Materials Science

College of Science

Rochester Institute of Technology

2013

Approved by:

Christina Goudreau Collison, Ph. D. _____
Project Advisor

Paul Craig, Ph. D. _____
Department Chair

Michael G. Coleman _____
Committee Member

Jeremy A. Cody _____
Committee Member

Suzanne O'Handley _____
Committee Member

Copyright Release Form

Studies Toward the Total Synthesis of Trocheliophorolide A

I, Jennifer L. Swartzenberg, hereby grant permission to the Wallace Memorial Library of Rochester Institute of Technology, to reproduce my thesis in whole or in part. Any use will not be for commercial use or for profit.

_____

Signature

_____

Date

Acknowledgements

First and foremost I would like to thank my research advisor, Dr. Christina Goudreau-Collison for her professional guidance and mentorship throughout my time at RIT, not only as a graduate student, but also as an undergraduate. You have taught me so much over the last five years and helped inspire my love for Organic Chemistry. For that I thank you from the bottom of my heart!

I would also like to take this opportunity to thank my committee members: Dr. Michael Coleman, Dr. Jeremy Cody and Dr. Suzanne O'Handley. Each one of you has been an inspiration to me. Thank you to each of you for supporting me through this educational journey through guidance in writing my thesis, professional wisdom and for the outstanding examples you set every day.

Special thanks to the Chemistry Department, the College of Science and the Merck Scholars Program for the funding that was supplied to me in the form of stipends and teaching assistantships while I was completing my research here at RIT as both a graduate and an undergraduate student. My sincere appreciation is also extended to David Lake in the Stockroom for all of your help in the lab move last year and for always going the extra mile to make sure we have what we need in the laboratory.

To Bill Spencer, Stephanie Dorn and Anthony Carestia, thank you for the incredible amount of work you have all put into this project. Most of all, thank you to each one of you for the very special friendship we have. People like you make the world a better place and I am blessed to know you.

Sincere thanks also are expressed to Brenda Mastrangelo and Dr. Paul Rosenberg in the Chemistry Department Office. I still remember the first time I met you two at the transfer open house as an undergraduate student. You two truly were the deciding factor for me on whether or not to come to RIT. Both of you welcomed me in and have encouraged, supported and inspired me throughout my entire time at RIT. I am a better person for knowing both of you. Thank you!

Last but certainly not least, I would like to thank my family. Thank you for all of your love, support and encouragement over the years. Mom, thank you for being such a great example and encouraging me to go back to school. Dad, thanks for always making me laugh no matter how tired or stressed I am. To my dearest daughter Felicia, you are my hope, my inspiration and my love in life. Thank you for always being my biggest fan and always convincing me that I could do it even when I wasn't sure myself. To my brother, Eric, and my sisters, Kim and Lacey, thank you for always encouraging me to keep going. Finally to my good friend Cheryl, thank you so much for the endless hours of using your dining room table as a hide out to write and perfect this thesis. I love you guys always!

Abstract

Soft sea corals generate a plethora of natural products including steroids and metabolites. As such, they have been of keen interest to biologists and synthetic organic chemists. Recently the soft corals *Sarcophyton trocheliophorum* and *Lithophyton arboretum*, which were isolated from the Gulf of Aqaba in the Red Sea, have been found to produce six butenolide lipids and butenolides with unusual substitution and unsaturation patterns. The purpose of this research is to achieve the total synthesis of the gamma-lactone **1**, Trocheliophorolide A, one of the six butenolide natural products. Trocheliophorolide A is composed of a lactone ring and a unique unsaturated side chain. This thesis will describe the previous successful synthesis of the lactone ring portion of Trocheliophorolide A, followed by the previously explored routes for synthesizing the unsaturated side chain that were not successful. This thesis specifically discusses the successful synthesis of the acid chloride side chain in a five-step, efficient route with satisfactory overall yields. Additionally, both model study cross-coupling reactions and the actual final cross-coupling reaction are explored and discussed.

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

Pen……..pentane

PCC .....pyridinium chlorochromate

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

$Pd(PPh_3)Cl$……dichlorobis(triphenylphosphine)palladium(II)

Ph .....phenyl

PPh_3.....triphenylphosphane

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

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

rt .....room temperature

Sat .....saturated

$SOCl_2$ ……thionyl chloride

TBS .....*tert*-butyldimethylsilyl

TBSCl .....*tert*-butyldimethylsilyl chloride

Tf.....trifluoromethanesulfonyl (CF_3SO_2)

THF .....tetrahydrofuran

THP .....tetrahydropyran

TLC .....thin layer chromatography

TMS .....trimethylsilyl

Table of Contents

List of Schemes

List of Figures

List of Tables

1.0 Isolation and Biological Activity

Soft sea corals are known for the production of many natural products of interest to synthetic organic chemists and biologists. Most notable are the diverse groups of steroids and steroid derivatives.[1,2] Two particular soft sea corals, *Pterogorgia anceps* and *Pterogoria guadalupensis*, produced the first isolated butenolides in the 1960's and since then these butenolides have been sought after.[2-5] In 2001 Rezanka *et al* isolated and characterized six different butenolides now known as Trocheliophorolides A-F (Figure 1). These butenolides are characterized by their unusual substitution and unsaturation patterns and were isolated from *Sarcophyton trocheliophorum* and *Lithophyton arboretum*, located in the Gulf of Aqaba in the Red Sea.[6] Several natural products contain these butenolide elements. [7-8]

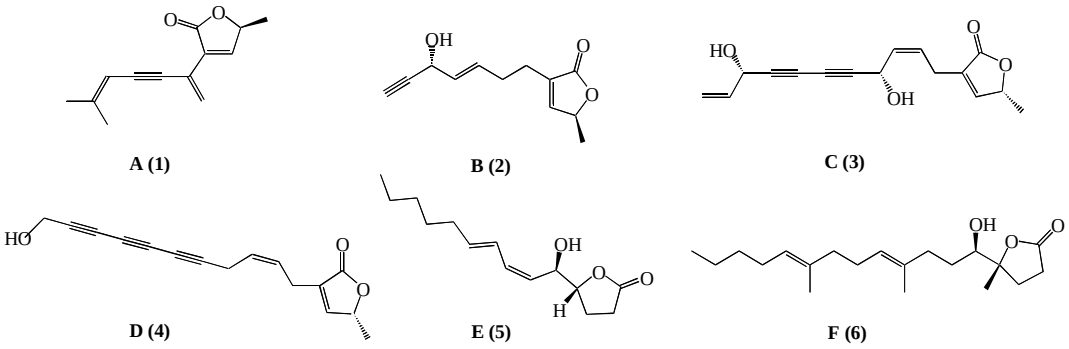


Figure 1: Trocheliophorolides A-F **(1-6)**. Trocheliophorolides A-D **(1-4)** are isolated from *Sarcophyton trocheliophorum*, whereas Trocheliophorolides E-F **(5-6)** are isolated from *Lithophyton arboretum.*

Biological assays confirm that Trocheliophorolides A-F show evidence of considerable inhibition of bacterial cell growth in *Staphylococcus aureus* and *Bacillus subtilis* and toxicity toward the brine shrimp *Artemia salina.* Since both *S. aureus* and *B. subtilis* are problematic resistant strains of bacteria, promising new antibiotic targets are very valuable. Further analysis showed that these butenolides were only biologically active against gram-positive strains of bacteria.[6]

In Table 1, the zones of inhibition of bacterial growth in millimeters for Trocheliophorolides A-F (1-6) are shown. Each of these values is representative of impregnated wafers of the Trocheliophorolide of interest, which are placed into an incubation chamber with the bacteria of interest. The bacteria are allowed to grow overnight and the bacteria closest to the disk are killed while the surviving bacteria can still be seen proliferating. The size of the equidistant circle of inhibited bacteria growth around the impregnated wafer is a measure of how effective that species is at killing those particular bacterial strains.

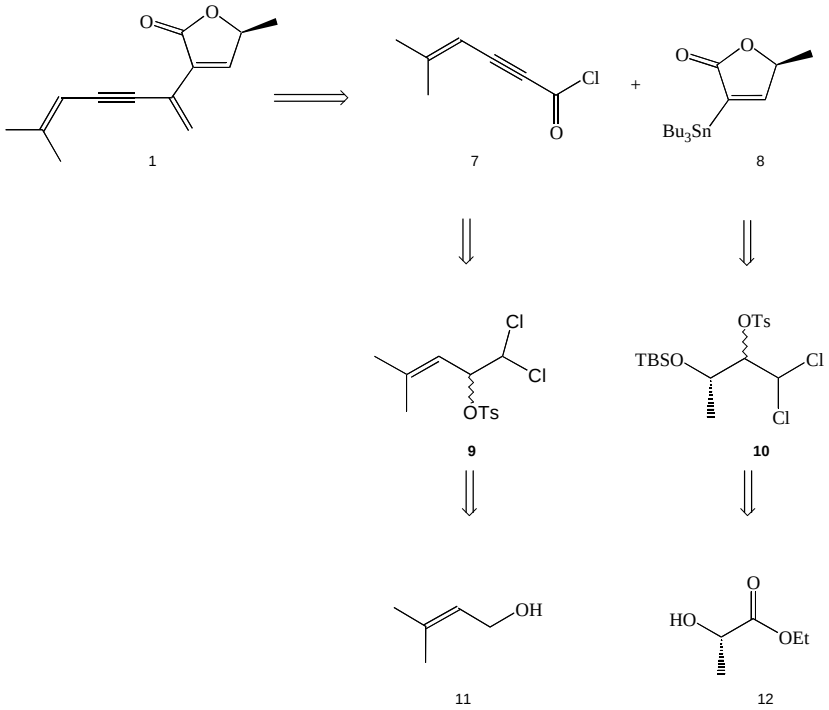
Table 1: The zones of inhibition for Trocheliophorolides A-F **(1-6)** measured in millimeters with respect to *S. aureus* and *B. subtilis.*

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

Given the zone of inhibition for Trocheliophorolide A against *S. aureus* and the appealing structure of the novel unsaturated side chain, butenolide **1** became the synthetic focus of the Collison group. Development of a synthetic strategy for Trocheliophorolide A would also provide an entry toward the rest of the Trocheliophorolide family. Lastly, since only μg quantities of Trocheliophorolide A can be extracted from 500g wet coral, it is important that we find a more sustainable synthetic way of making this compound.[1-2]

1.1 Retrosynthetic Analysis

We envisioned that Trocheliophorolide A (**1**) would be assembled via a convergent synthesis using a palladium-catalyzed coupling reaction between acid chloride **7** and (*S*)-β- lactone **8** (Scheme 1). The synthesis of acid chloride **7** was envisioned to come from tosylate **9** which could be achieved via a series of reactions starting with commercially available 3-methyl-2-buten-1-ol **(11)**. The synthesis of the (*S*)-β- lactone **8** was envisioned to come from tosylate **10** which could be could be achieved via a series of reactions starting with commercially available (*S*)-ethyl lactate **12**. The desired stereocenter in the product is conveniently obtained from the starting material since (*S*)-ethyl lactate **(12)** is derived from a natural amino acid. We decided to turn our attention to the (*S*)-β- lactone **8** first.



Scheme 1: Retrosynthetic analysis of Trocheliophorolide A **(1).**

1. 2 Previous Syntheses of (*S*)-*β*- Lactones

(*S*)-*β*- lactones are a common structural motif in many natural products and as such, have been synthesized via several routes. [9-20] William T. Spencer, a former graduate student in the Collison Group, did an extensive review of the literature with respect to previous syntheses of (*S*)-*β*- lactones (Figure 2).[11]

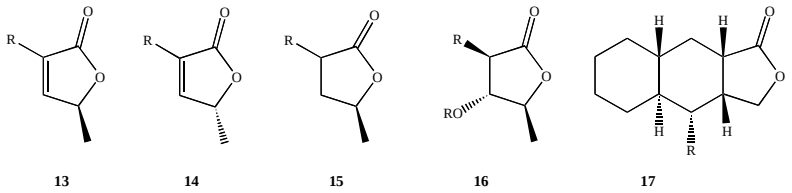
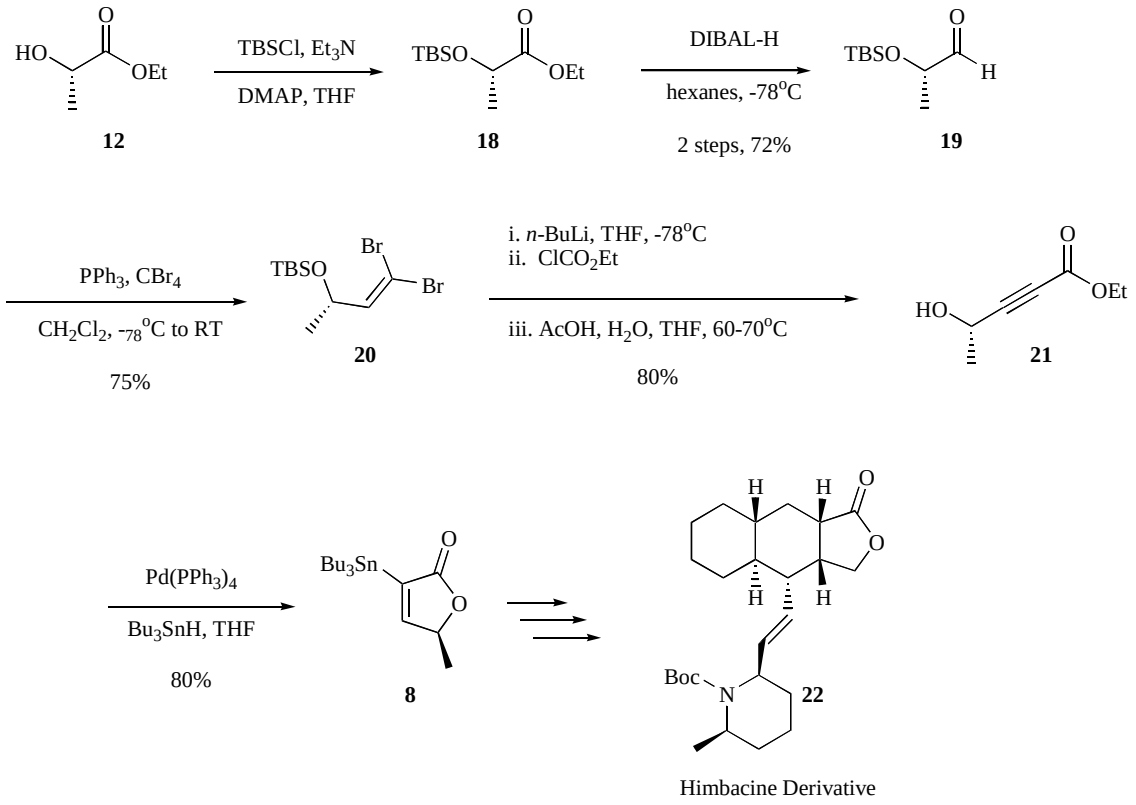


Figure 2: (*S*)-*β*-Angelica lactone syntheses reviewed by Spencer [11]

The Himbacine derivative **22** synthesis by Hofman *et al* was utilized as a partial model for our synthesis of stannylfuranone **8** in Trocheliophorolide A (Scheme 2).[20] The Hofman group began their synthesis by means of commercially available (*S*)-ethyl lactate **(12)** and protecting it using TBSCl and imidazole in *N*,*N*-dimethylformamide to form silyl ether **18**. Silyl ether **18** was then reduced with DIBAL-H to form aldehyde **19** in a 72% yield over two steps. Next a Corey-Fuchs Olefination was run on aldehyde **19** to form dibromide species **20** in a 75% yield. Dibromide **20** then underwent a double elimination reaction followed by a lithium-halogen exchange where the resultant anion was quenched with ethylchloroformate. The silyl ester was then deprotected using a mild reflux with acetic acid to form alcohol **21** in an 80% overall yield. Alcohol **21** then underwent a hydrostannation reaction using tetrakis(triphenylphosphine)palladium(0) and tributyltin hydride to form stannylfuranone **8** in 80% yield. The chief shortcoming of this synthesis is that dibromide species **20** is both light sensitive and thermally unstable to a large temperature range thereby requiring quick use or else suffer rapid decomposition. Given Hofman's work in synthesizing stannylfuranone **8**, we pursued a similar pathway while avoiding the synthesis of the dibromide species **20**.

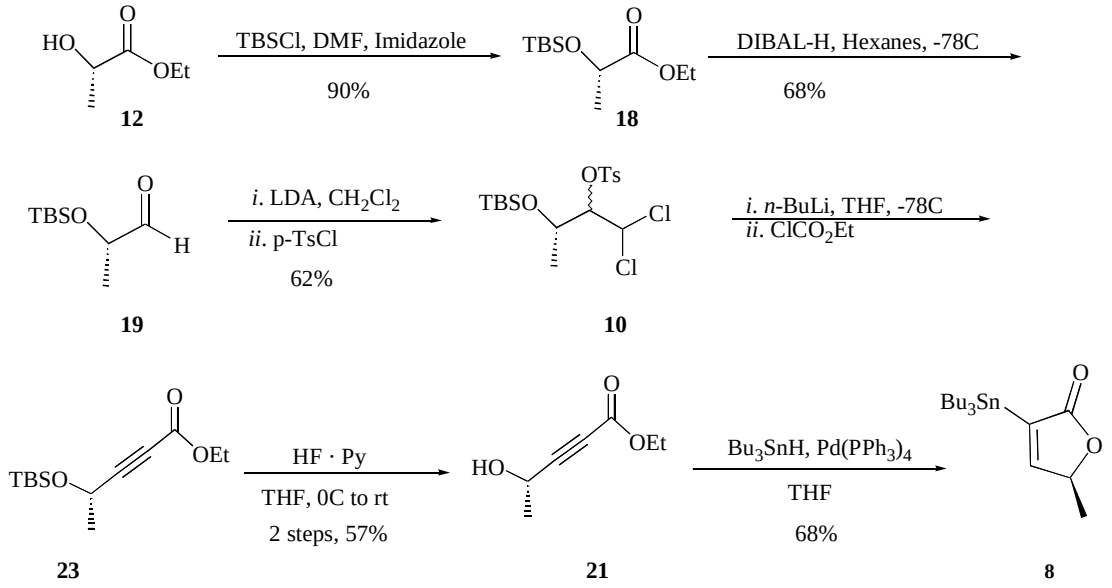


Scheme 2: Synthetic pathway of Hofman *et al* for stannylfuranone **8**. [20]

1.2.1 Synthesis of the Lactone Moiety - Previous Work in the Collison Group

William Spencer of the Collison lab began work towards stannylfuranone **8**. The major modification to Hofman's synthesis of stannylfuranone **8** was the avoidance of the sensitive dibromo species **20** (Scheme 3). Spencer's synthesis began with a protection of *(S)*-ethyl lactate **(12)** using *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide to give silyl ester **18** in a 90% yield. Next ester **18** was reduced with diisobutylaluminum hydride (DIBAL-H) yielding aldehyde **19** in a 68% yield. These first two steps being identical to the synthesis by Hoffman *et al*.[20] Next Spencer elegantly utilized a procedure by Marshall *et al* to avoid production of dibromo species **20**.[21-22] This was done by reacting Aldehyde **19** with a dichloromethane anion and further quenching with *p*-toluenesulfonyl chloride generating tosylate **10** in a 62% yield**.** Since tosylate **10** was silica sensitive it was used in the next reaction without purification

to avoid any decomposition. The crude tosylate **10** underwent a double elimination reaction followed by a lithium-halogen exchange using n-butyllithium. The resultant anion was quenched with ethylchloroformate generating alkynoate **23**. Removal of the silyl protecting group from alkynoate **23** with HF pyridine gave alcohol **21** in a 57% yield after purification over the two steps. During optimization it was noted that no detrimental effects were incurred by not purifying the silyl protected alcohol before deprotection. Finally, purified alkyne **21** was reacted in a palladium-catalyzed hydrostannation using tributyltin hydride and tetrakis(triphenylphosphine)palladium(0) affording stannylfuranone **8** in a 68% yield. [11]



Scheme 3: Spencer's synthesis of stannylfuranone **8.** [11]

One of the minor products Spencer obtained was the β-stannylated lactone. He discovered that if the Pd-catalyst was generated in-situ before the tributyltin hydride and alkyne **21** were added that the yields of the desired product plummeted to 12%. It is postulated that during the hydrostannation mechanism, alkyne **21** coordinates with the palladium to form a complex. In this complex, the partially positive palladium is paired

with the partial negative α-carbon of alkyne **21** and the partially negative hydrido ligand is paired with the partially positive β-carbon of alkyne **21** (Figure 3).[11]

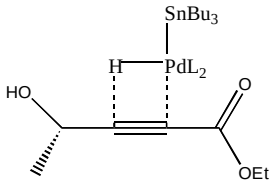
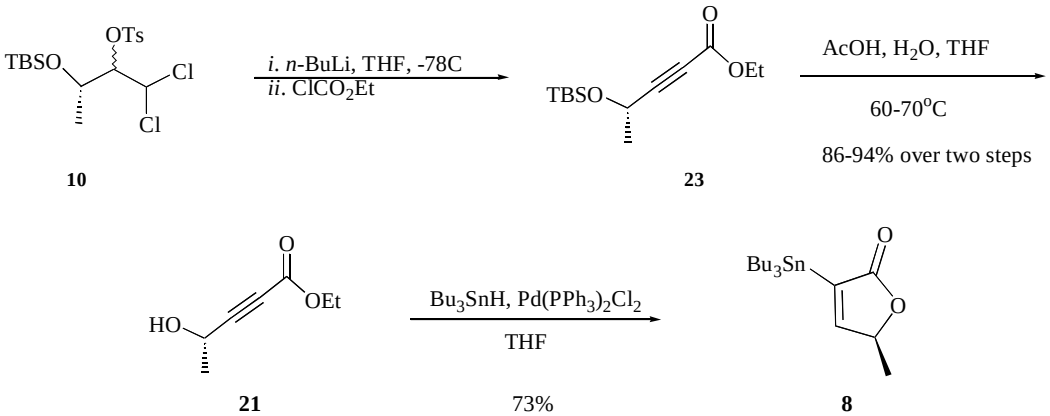


Figure 3: Spencer's postulated configuration of alcohol **21** and Pd-catalyst complex.[11]

1.2.2 Synthesis of the Lactone Moiety - Optimization

As an undergraduate student in the Collison lab, I was tasked with optimizing Spencer's synthesis of stannylfuranone **8**. Spencer completed the synthesis of stannylfuranone **8** with an initial 68% pure yield but each time the reaction was run, the yields diminished and the original result was not satisfactorily reproduced. Another limitation with Spencer's synthesis was that HF pyridine is a toxic reagent. In an effort to circumvent the use of HF pyridine, we elected to find an alternative route to deprotect silyl ether **23**. Since Spencer had stockpiled well over 75 grams of tosylate **10**, optimization studies began from this intermediate (Scheme 4).



Scheme 4: Optimized synthesis of stannylfuranone **8.** [23]

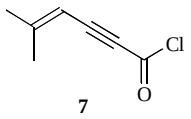
In the optimized synthesis, removal of the silyl protecting group from silyl ether **23** was accomplished via mild acetic acid reflux to give alcohol **21** in 86-94% yield after purification over the two steps. Finally, purified alcohol **21** was reacted in a palladium-catalyzed hydrostannation via dichlorobis(triphenylphosphine)palladium(II) and

tributyltin hydride affording stannylfuranone **8** in a 73% yield. Stannylfuranone **8** proved to be storage stable. Epimerization was not detected after many months in the freezer. Optical rotation was used to assess the fidelity of the stereocenter both pre- and post-storage. The optical rotation results for our stannylfuranone **8** in chloroform at 20°C and using a sodium D line were +22.7° before and after storage. The known literature value for stannylfuranone **8** is +27.9° in chloroform at 23°C and using a sodium D line.[19] The differences in temperature between the experimental sample and the literature value sample may be the reason for the lack of precision between the two optical rotation values. Additionally, there was a small concentration difference between the experimental sample and the literature sample. The results and experimentals for these optimizations were previously published in Stephanie Dorn's thesis.[23]

With vinyl stannane **8** in hand, work commenced on the new coupling partner, acid chloride **7**. The unsaturated side chain, although vacant of stereocenters, has proven to be the most challenging portion of the total synthesis of Trocheliophorolide A. The following sections address the strategies developed towards acid chloride coupling partner **7**.

1.3 Previous Literature Syntheses of Similar Unsaturated Side Chain

The unique unsaturated side chain **7** discussed in the retrosynthesis is not a known compound; although compounds with similar unsaturated side chain motifs exist (Figure 4).

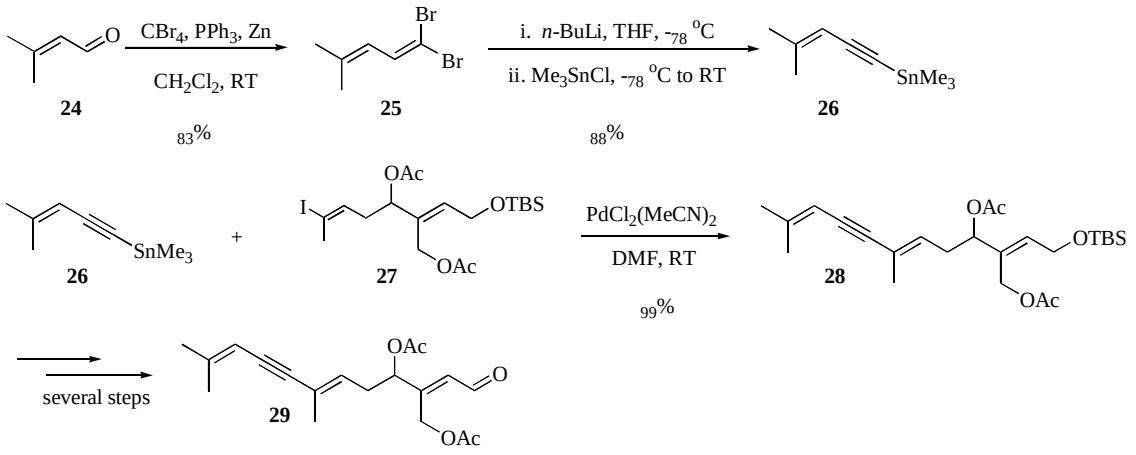


7

Figure 4: Unsaturated side chain **7**.

An example is that of Taxifolial A **29** which was synthesized via Commeiras *et al* in 2001 (Scheme 5).[24] Commeiras' synthesis began using commercially available aldehyde **24** in a Corey-Fuchs olefination yielding *gem*-dibromide **25** in an 83% yield. Next, *gem*-dibromide **25** underwent a double elimination followed by a lithium-halogen

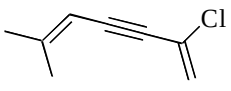
exchange via the use of *n*-BuLi. The resultant anion was quenched with trimethyltin chloride affording stannane **26** in an 88% yield. Stannane **26** was then reacted with vinyl iodine **27** in a Stille Cross Coupling reaction by means of a dichlorobis(acetonitrile)palladium(II) catalyst to afford triene **28** in a 99% yield. After several more steps Taxifolial A **29** was achieved.



Scheme 5: Partial synthesis of Taxifolial A **25** by Commeiras *et al.* [24]

1.3.1 Synthesis of the Unsaturated Side Chain - Previous Work in the Collison Group

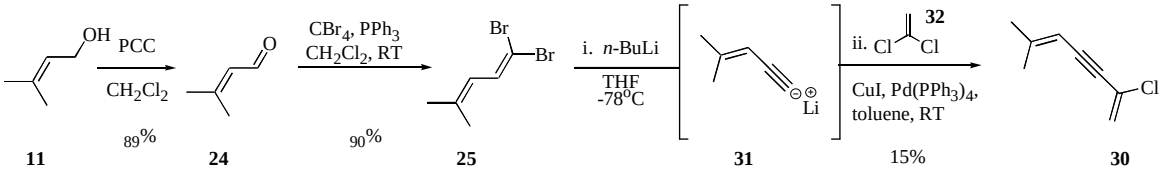
The successful synthesis of the unsaturated side chain has been undoubtedly the main hurdle in the complete synthesis of Trocheliophorolide A (**1**). Several students in the Collison Group have undertaken this task, the first of whom were Olukorede Agusto and William Spencer III.[11, 25] They originally started the side chain with the goal of synthesizing vinyl chloride **30** (Figure 5).



30

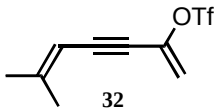
Figure 5: Original vinyl chloride coupling partner **30**.[11, 25]

There were several stumbling blocks along the way to synthesizing vinyl chloride **30** (Scheme 6).[11, 25] First, the terminal alkyne generated in their synthesis was not able to be isolated due to volatility problems and as a result, this route required an *in-situ* Sonagashira Cross-Coupling to circumvent isolation of the terminal alkyne. This route was not reproducible and had a poor yield of only 15%.



Scheme 6: Synthetic route of Spencer and Agusto for vinyl chloride **30** coupling partner.[17, 31]

Due to the problems associated with the previous synthesis of the vinyl chloride **30** coupling partner, Spencer attempted to synthesize vinyl triflate **32** as a more robust coupling partner (Figure 6). Unfortunately this route resulted in low yields of 25–35%, with rapid decomposition of the product and column chromatography resulted in poor purity.[11]

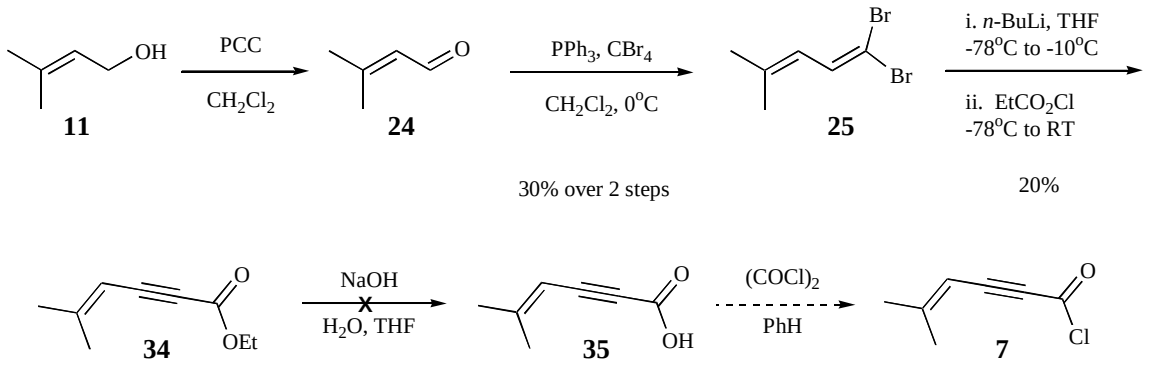


32

Figure 6: Vinyl triflate **32** synthesized by Spencer as alternative coupling partner for lactone **8**.

Given the limitations in constructing the vinyl chloride **30,** Stephanie Dorn attempted to synthesize a new coupling partner, acid chloride **7**. It's been shown in the literature that acid chlorides have been used in Stille Cross-Couplings.[26] Acid chloride **7** was chosen as the new coupling target.

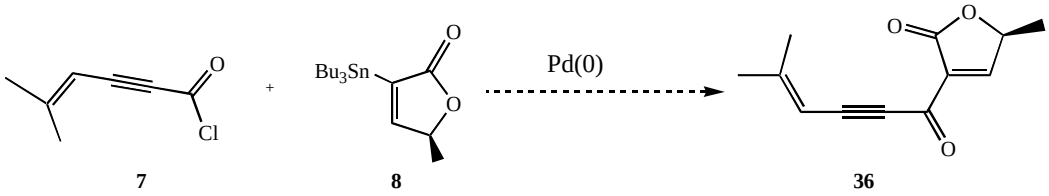
Dorn tried three different approaches to synthesizing acid chloride **7.** Only the first route will be discussed since the intermediates in this route are the same as the ones used in this thesis in synthesizing acid chloride **7**. Dorn's Corey Fuchs method began with commercially available 3-methyl-2-buten-1-ol **(11)**, which was oxidized via pyridinium chlorochromate to yield aldehyde **24** (Scheme 7)**.** Due to volatility issues, aldehyde **24** was filtered through a Celite plug under argon, and then the dichloromethane was carefully distilled away from aldehyde **24** as opposed to concentrating the oil *in vacuo*. Aldehyde **24** was then reacted in a Corey-Fuchs olefination yielding *gem*-dibromide **25** in a 30% pure yield over two steps. Next *gem*-dibromide **25** underwent a double elimination followed by a lithium-halogen exchange via the use of *n*-BuLi. The resultant anion **31** was quenched with ethylchloroformate giving ester **34** in a disappointing 20% pure yield**.** She attempted the subsequent saponification of ester **34**, but ^{1}H-NMR showed the disappearance of starting material and no desired carboxylic acid **35**. It was suspected that instability of dibromide **25** was the cause for future problems with this route as it was sensitive to silica, making purification difficult, and it readily decomposed lending to storage problems. [23]



Scheme 7: Corey-Fuchs method towards acid chloride **7**. [23]

2.0 Results and Discussion

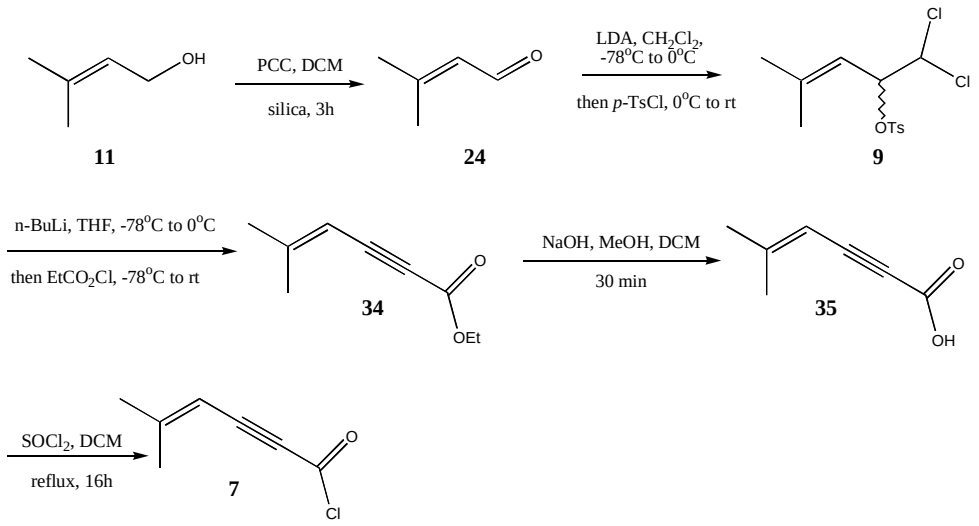
As the project has evolved, it is now envisioned that Trocheliophorolide A (**1**) will be assembled via a palladium-catalyzed coupling reaction between acid chloride **7** and (*S*)-β- lactone **8** (Scheme 8). Acid chlorides are common coupling partners in Stille reactions .[26]



Scheme 8: Final Stille Coupling reaction as envisioned by Collison group.

The newly proposed synthetic route for acid chloride **7** is shown in Scheme 9. Considering the fact that the tosylation method utilized in the lactone synthesis worked so well, this same tosylation method is being applied to the acid chloride route of the synthesis. The benefits to this route are that it avoids both unstable terminal alkyne **31** and dibromo species **25** that were so problematic in the previous routes explored. Once

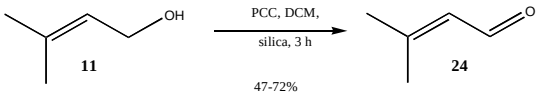
the coupling is accomplished, a Wittig reaction can be used to complete the total synthesis of Trocheliophorolide A.



Scheme 9: Synthetic pathway toward acid chloride **7**.

This synthetic pathway begins with commercially available 3-methyl-2-buten-1-ol **(11)**, which can be oxidized via pyridinium chlorochromate to yield aldehyde **24.** Next, aldehyde **24** can be reacted with a dichloromethane anion and further quenched with *p*-toluenesulfonyl chloride to generate tosylate **9.** Tosylate **9** can then undergo a double elimination reaction followed by a lithium-halogen exchange using n-butyllithium. The resultant anion can then be quenched with ethylchloroformate to generate alkynoate **34**. Saponification of alkynoate **40** can easily be done to afford carboxylic acid **35**; which can then be refluxed with thionyl chloride to afford acid chloride **7**.

2.1 Synthesis of Aldehyde 24



Scheme 10: Synthesis of aldehyde **24**.

The synthesis of acid chloride **7** begins with commercially available 3-methyl-2-buten-1-ol **(11)**, which was oxidized via pyridinium chlorochromate (PCC) to yield aldehyde **24** in a 47-72% pure yield **(**Scheme 10**).** Due to the volatility of aldehyde **24**, its isolation and purification have presented a major hurdle by all students who have worked on this project.

Aldehyde **24** was first synthesized by Augsto in an 89% yield following precedented work by Li *et al*.[25, 27] She synthesized aldehyde **24** using PCC in DCM at room temperature. After three hours she ran the reaction flask contents through a silica plug and concentrated aldehyde **24** *in vacuo*. Since Agusto's attempts, both Spencer and Dorn followed her work and were never able to reproduce the high yields she reported. Following Agusto's same reaction conditions, the average yields for Dorn and Spencer were 40-70%. The differences in the yields correlated with the variations in their work up and purification conditions. [11, 23]

Spencer experimented with Celite, silica and Florisil for purification followed by concentration of aldehyde **24** *in vacuo* and was able to achieve higher purity, but still saw very low yields. Spencer postulated that aldehyde **24** was likely volatile which is why his yields were so low.

In an effort to circumvent the volatility problem, Dorn altered the work up by running the reaction flask contents through a Celite plug followed by distillation of the DCM away from aldehyde **24**. This way she would avoid the rotary evaporation step that

she suspected was causing so much of aldehyde **24** to be lost. She did see higher yields but lower purity.[23]

It was noted that aldehyde **24**, which should be pale yellow oil, was often obtained as a brown, gritty tar. It was suspected that one of the reasons that some of the routes previously attempted were not working was due to chromium salt impurities that may not have been apparent by ^{1}H-NMR. In an effort to increase the yields, and ensure that the chromium salts were removed from the product, an experimental protocol investigation for this oxidation was pursued (Table 2).

Table 2: Experimental protocol optimizations utilized for the synthesis of aldehyde **24**.

Method	**Yield**	**Purity**
Florisil and silica gel plug purification	LOW	HIGH
Extraction purification	HIGH	LOW
Grind PCC & silica gel together to run reaction, then Florisil and silica gel Plug Purification	GOOD	HIGH

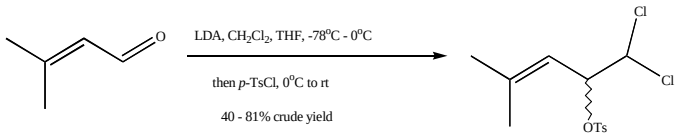
First a plug of florisil and silica gel was utilized in purifying the aldehyde after the reaction was complete. Once the solvent was distilled away from the aldehyde, this technique gave excellent purity but the yields were very low (Table 2).

Next an extraction technique was tried in purifying the aldehyde instead of the traditional silica, florisil or Celite plug. It was hypothesized that since PCC salts were water soluble, this would allow for successful removal of all the chromium salts achieving better purity. Once the solvent was distilled away from the aldehyde, this technique gave good purity, but once again the yields were very low (Table 2).

In a final attempt to optimize the reaction conditions precedent work by Luzzio *et al* was used.[28] This time the PCC was ground with silica gel using a mortar and pestle and

added to the reaction flask along with the dichloromethane solvent and alcohol **11**. This method proved to be the highest yielding and gave the highest level of purity as seen by both ^{1}H-NMR and visual characteristics of the product (Table 2).

2.2 Synthesis of Tosylate 9



24 **9**

Scheme 11: Synthesis of tosylate **9**.

With the procedure to synthesize aldehyde **24** in hand, the next step in the synthesis was attempted, again using precedent work by Marshall *et al*.[21-22] *(*Scheme 11). Tosylate **9** proved to be silica sensitive and therefore was carried on without purification to the next reaction.

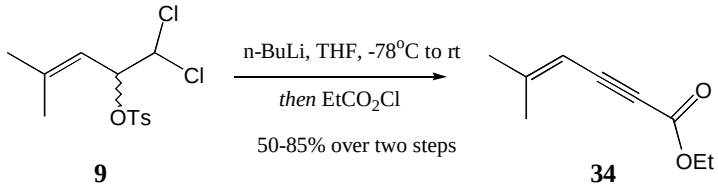
This tosylation step was attempted using four different methods of addition. The first method involved adding the LDA solution drop-wise to a solution of aldehyde dissolved in dichloromethane and THF (LDA into aldehyde, Table 3). The second method involved adding the aldehyde, dichloromethane and THF solution drop-wise to a solution of LDA (Aldehyde into LDA, Table 3). The third and fourth methods involved generating the dichloromethane anion via the LDA first and then either adding it to the aldehyde and THF solution (DCM Anion into Aldehyde, Table 3), or adding the aldehyde and THF solution to it (Aldehyde into DCM Anion, Table 3).

Table 3: Reaction condition results for tosylation reaction.

Method of Addition	Crude Yield	Purity by ^{1}H-NMR
LDA into Aldehyde	65%	Very Good
Aldehyde into LDA	63%	Fair
DCM Anion into Aldehyde	70%	Very Poor
Aldehyde into DCM Anion	59%	Poor

Although the method of generating the DCM anion and then adding that to the aldehyde and THF solution gives a greater crude mass; the method of adding the LDA into the aldehyde has much greater purity for the crude material by ^{1}H-NMR. Each of the respective products was taken onto the next reaction in their crude form to see if better information could be obtained by this experiment. Those results will be discussed in the next section.

2.3 Synthesis of Ester 34



9 **34**

Scheme 12: Synthesis of ester **34**.

With the optimized synthesis of tosylate **9** complete, my attention was focused on synthesizing ester **34**. In this reaction, much like the tosylation seen in the synthesis of lactone **8**, crude tosylate **9** underwent a double elimination reaction followed by a

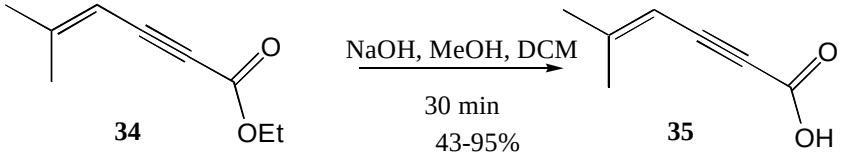
lithium-halogen exchange using n-butyllithium. The resultant anion was quenched with ethylchloroformate generating ester **34** in a 50% initial yield. As the reaction conditions were optimized, pure yields in the 80-85% range have been achieved over the two steps from aldehyde **24** to ester **34**.

As a continuation of my experiment in section 2.2 (Synthesis of Tosylate **9**), results were compiled as to the purified yields of the resultant ester products for each of the methods of addition (Table 4). Since the tosylate is silica sensitive, the crude products of those reactions were carried on to this reaction step without purification. Looking solely at the purified yields, it can be seen that the method of adding the LDA solution into the solution of aldehyde **24**, DCM and THF is the superior method of addition. Resultant spectra for the purified products all had equally pure results upon ^{1}H-NMR analysis.

Table 4: Results for the synthesis of ester **34** based on different tosylation routes examined.

Method of Addition	**Pure Yield**
LDA into Aldehyde	74%
Aldehyde into LDA	54%
DCM Anion into Aldehyde	0%
Aldehyde into DCM Anion	17%

2.4 Synthesis of Carboxylic Acid 35



Scheme 13: Synthesis of carboxylic acid **35**.

With ester **34** in hand, the saponification reaction was attempted using precedent work by Theodorou *et al*.[29] Ester **34** was dissolved in a 9:1 DCM:MeOH solvent pair and enough 3.0 N methanolic NaOH was added to bring the total concentration to about 0.1N NaOH. After 30 minutes the reaction generally showed completion via TLC. Initially the yield was a mere 43%, but after optimizing the work up, the yields rose to the 90-95% semi-purified range.

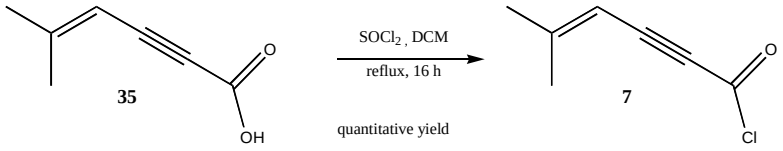
Carboxylic acid **35** is commercially available through select companies. ^{1}H-NMR spectral results are equivalent to what is reported in the literature. Carboxylic acid **35** was purified as well as was able by extraction; however some impurities were still visible by ^{1}H-NMR. IR analysis was used to confirm the carboxylic acid functionality.

Since carboxylic acid **35** is isolated as an oil with some solid crystalline particulate, additional purification by column chromatography was attempted. Unfortunately, no matter the polarity of the solvent or whether flash column chromatography was used, none of the carboxylic acid product was able to be isolated. Two-dimensional TLC techniques confirmed its decomposition on silica (Figure 7). A two-dimensional TLC without decomposition would have all of the spots on the diagonal line.

A **B**

Figure 7: A) The two-dimensional TLC of carboxylic acid **35** (left). B) An example of a two-dimensional TLC without decomposition (right).

2.5 Synthesis of Acid Chloride 7



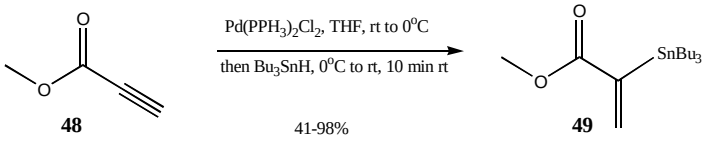
Scheme 14: Synthesis of acid chloride **7**.

Using precedent work by Becker *et al*, extraction purified carboxylic acid **35** was refluxed with thionyl chloride in DCM for 16 hours affording acid chloride **7** in quantitative yield.[30] The beauty of this reaction is two-fold; first, both the thionyl chloride and the DCM were used straight from the bottle requiring no previous purification. Secondly, the work up consists of merely cooling the reaction flask and then concentrating the product *in vacuo*. Since DCM and thionyl chloride are low boiling, they come off in the concentration process. The byproducts of this reaction, sulfur dioxide and HCl are gaseous so they escape from the reaction via the argon out line. The ^{1}H-NMR spectra of the crude reaction product shows good purity. Absence of the

carboxylic acid functionality was quickly confirmed via IR since the ^{1}H-NMR spectra are nearly identical.

2.6 Model Reactions for Final Stille Coupling

In an effort to prepare for the coupling of our lactone **8** and soon to be completed acid chloride **7**, some model conditions were examined. The synthesis of model vinyl stannane **49** was performed to be used in the model coupling reaction to follow in section (2.6.2) using precedent work by Nielsen *et al* (Scheme 15).[31] Model vinyl stannane **49** was chosen because it had an analogous structure to our lactone **8**, it was readily synthesized in high yield from methyl propiolate **(48)**, which is an inexpensive starting material.

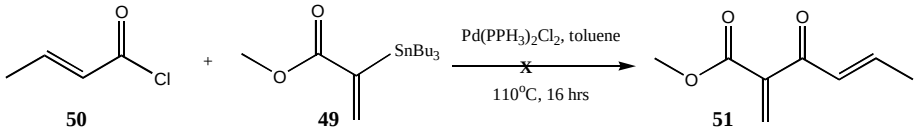


Scheme 15: Synthesis of model vinyl stannane **49**.

In this reaction methyl propiolate **(48)** was mixed with dichlorobis(triphenylphosphine)palladium(II) in THF at 0°C, then tributyltin hydride was added dropwise. In approximately ten minutes reaction completion was seen via TLC and the reaction was worked up. Initial pure yields were in the 40-50% range, but with optimization, a new bottle for tributyltin hydride and less humid lab conditions, pure yields were generally in the range of 85-98%.

2.6.2 Model Coupling Reaction Between Crotonyl Chloride (50) and Vinyl Stannane 54.

With model vinyl stannane **49** in hand, the model coupling reaction between commercially available crotonyl chloride **(48)** and vinyl stannane **49** was attempted (Scheme 16). Crotonyl chloride **(50)** was chosen as the model coupling partner because it has a similar structure to our unsaturated side chain and it is inexpensive and commercially available.



50 **49** **51**

Scheme 16: Model coupling reaction between commercially available acid chloride **(48)** vinyl stannane **49**.

Using precedented work by Cherry *et al* crotonyl chloride **(50)** and vinyl stannane **49** were dissolved in toluene with a catalytic amount of dichlorobis(triphenylphosphine)palladium(II) and refluxed for 16 hours at 110°C.[32] It appeared that there could be some product by the crude ^{1}H-NMR, but after purification the diagnostic protons were absent in the ^{1}H-NMR spectra. Some starting materials were recovered along with ditin species **52** (Figures 8 and 9).

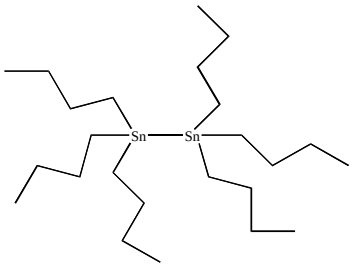


Figure 8: Ditin Species **52**

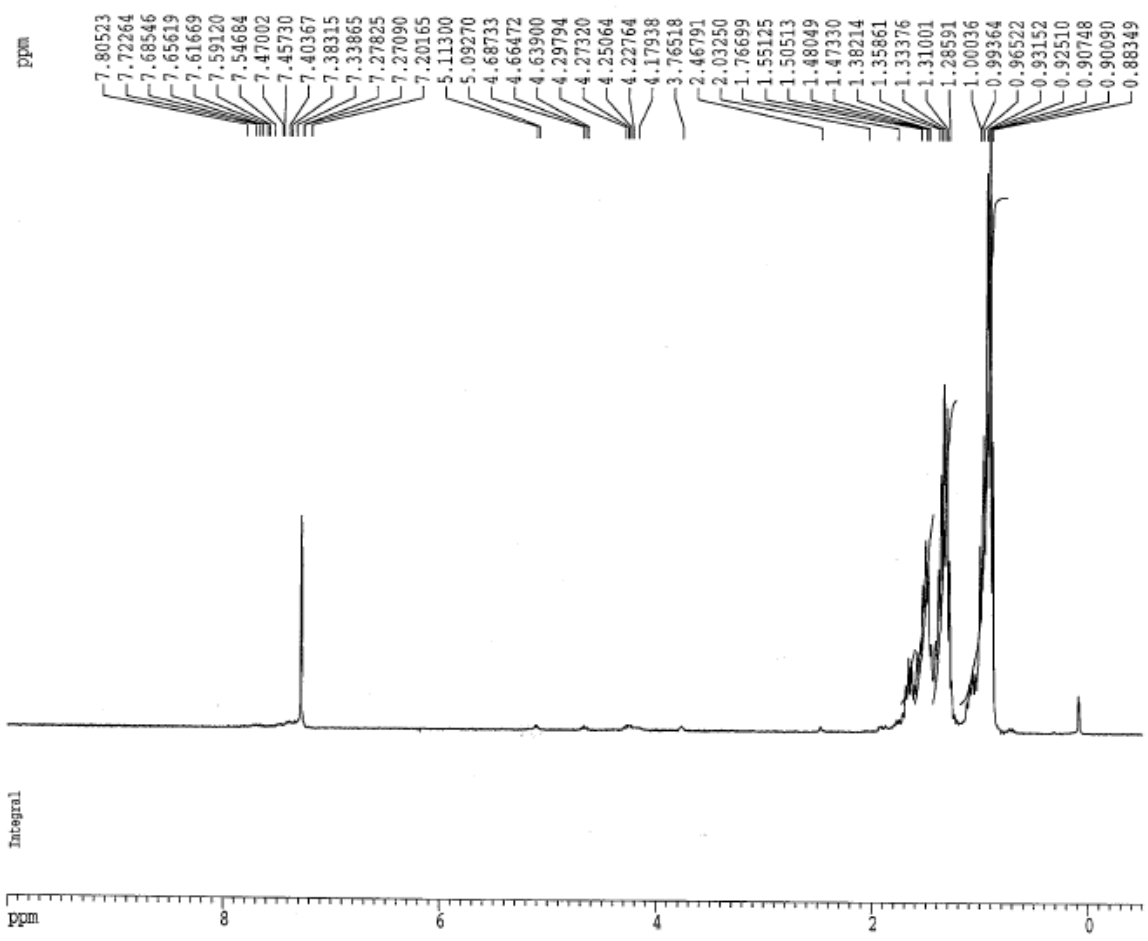
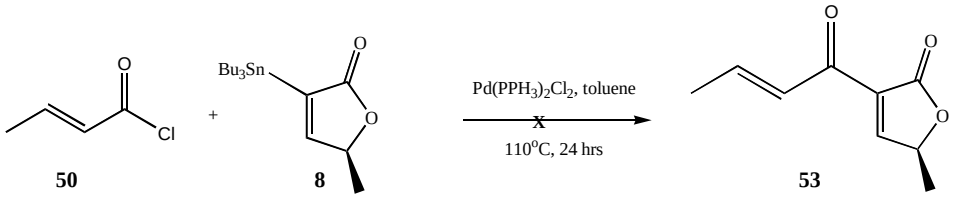


Figure 9: ^{1}H-NMR (300 MHz, $CDCl_3$) of ditin species **52**.

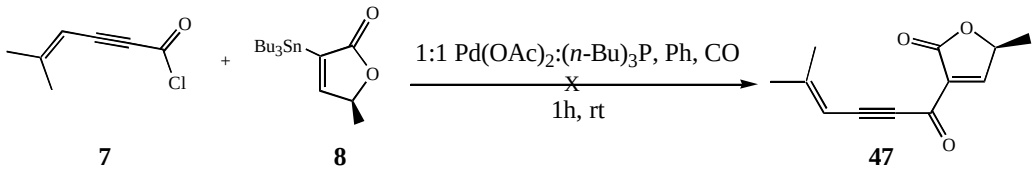


Scheme 17: Model coupling between crotonyl cloride **(50)** and lactone **8**.

When success was not encountered using the model reaction in last section (2.6.2), it was tried with our lactone **8** to see if it might work with less volatile and more robust systems (Scheme 17). Unfortunately, similar results to our model study were

obtained using lactone **8**. When the reaction did not show progression via TLC after 16 hours, the reflux time was increased to 24 hours and more catalyst was added to the reaction, but all that was recovered was unreacted starting materials.

2.7 Coupling of Lactone 8 and Acid Chloride 7



7 **8** **47**

Scheme 18: Stille coupling of lactone **8** and acid chloride **7**.

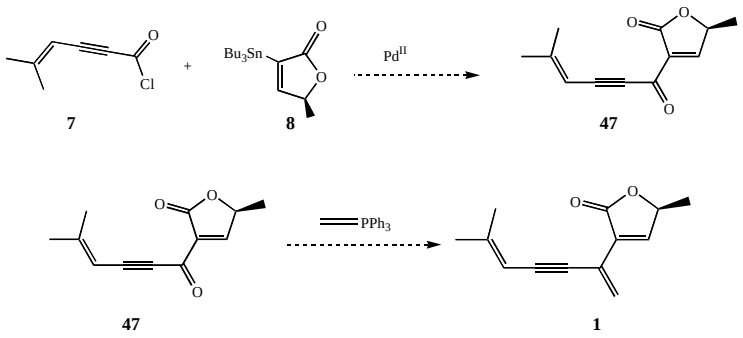
Since the previous coupling reaction was not working, a new procedure was attempted using precedented work by Ichige *et al*.[33] This new procedure involves bubbling CO gas through the reaction vessel to prevent decarbonylation from occurring in the final product. This reaction was attempted using acid chloride 7 which was dissolved in dry benzene and degassed with CO. Then a 0.1M solution of 1:1 $Pd(OAc)_2$:(*n*-$Bu)_3P$ (0.1 mole %) in dry benzene was added in one portion to the flask. The flask was left to stir at room temperature under a CO atmosphere for one hour. After one hour, no new product spots were seen via TLC and the starting material spot was of the same intensity. At that time another 0.5 mole % of the 0.1M solution of 1:1 $Pd(OAc)_2$:(*n*-$Bu)_3P$ in dry benzene was added in one portion to the flask and the flask was allowed to stir at room temperature under a CO atmosphere for another hour. When another TLC was done, it showed that there was an absence of starting material and two new spots; one UV-active and one just a yellow spot. Both of the resultant compounds were purified and analyzed via NMR but no identifiable products were seen. The only

thing seen in the NMR for one of the isolated compounds (the yellow spot) was tri-n-butylphosphine.

3.0 Future Work

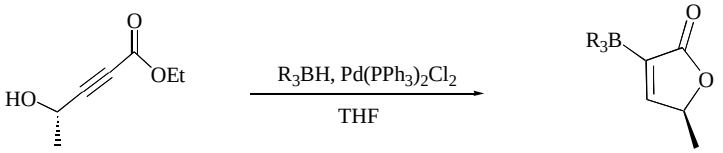
Future studies toward the total synthesis of Trocheliophorolide A will focus on the cross-coupling reaction between lactone **8** and acid chloride **7** and then on the final Wittig reaction (Scheme 19). The final Wittig reaction that will complete the total synthesis of Trocheliophorolide A **(1)** is a classic reaction with well-established precedent chemistry. Other major advantages include: the excellent regioselectivity, mild reaction conditions associated with the reaction, lack of byproducts and consistent yields.[34]

Due to the lack of success so far with the Stille coupling reaction the following considerations are suggested: exploration of other Pd catalysts such as $Pd_2(dba)_3$, $PdC1_2(CH_3CN)_2$, $(dppf)PdC1_2$ and $Pd(PPh_3)_4$, exploration of ligands, co-catalysts and additives such as CuI, CsF, LiCl, $AsPh_3$ and other phosphine compounds, exploration of different solvents such as tetrahydrofuran, dimethylformamide, *N*-methylpyrrolidinone or *N*,*N*-dimethylacetamide and alteration of reaction temperature conditions. [26, 35]



Scheme 19: The End Game.

Another consideration would be to utilize boron chemistry as opposed to the tin chemistry currently being employed in lactone **8** (Scheme 20).[36] This would require slight modification to the synthesis of lactone **8**, but since the metal is not introduced until the last step in the lactone synthesis, it won't require modification of the entire route. Further, tin compounds tend to be toxic, so using boron would present a pathway to 'greener' chemistry in this new route. Since we have had limited success with Stille couplings, this would provide an alternate and promising synthetic route without having to change the synthesis of acid chloride **7** which we have completed and optimized already. The reaction conditions that we have already optimized for lactone **8** may work for the new boron containing lactone **54** too. .



21 **54**

Scheme 20: Proposed synthetic route for boron containing lactone **54**.

4.0 Conclusions

This research toward the total synthesis of trocheliophorolide **(1)** A has been significantly advanced. Thus far both the acid chloride side chain **7** and the lactone **8** have been successfully synthesized and optimized. Specifically the research captured in this thesis describes the synthesis of the acid chloride side chain **7** in a five-step, efficient route with satisfactory overall yields. Additionally, model cross-couplings and actual cross-coupling reactions were attempted. Trocheliophorolide A **(1)** has never been synthesized and once it is completed it will be one of the first reported syntheses of the members of the trocheliophorolide family of biologically active *(S)*-β-lactone natural products.

General Procedures

Each non-aqueous reaction was run in flame-dried glassware under an inert argon atmosphere. All reagents were added either *via* syringe or cannula. All non-room temperature reactions have their respective temperatures within their respective schemes. Each distillation was done under an inert argon atmosphere. Rotary evaporation was completed using a Büchi rotary-evaporator under a reduced pressure of approximately 10-20 mm Hg.

Chromatography

All chromatographic purifications were carried out on EM reagent silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on EM silica gel 60 F-254 pre-coated glass plates or TLC Silica gel 60 F-254 pre-coated plastic sheets. Eluent systems are noted in the respective experimentals. All TLC plates were visualized via short-wave UV illumination (254 nm) or by developing with potassium permanganate stain and heat. Potassium permanganate stain was prepared by diluting potassium permanganate (6 g), potassium carbonate (40 g), and sodium hydroxide (5%, 10 mL) to 1 L with water.

Reagents and Solvents

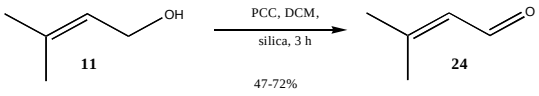
Solvents were obtained commercially and were used without purification unless otherwise noted in experimentals. Distilled water was utilized for every aqueous reaction, work-up procedure, and in the preparation of every aqueous solution used in the work-up. Tetrahydrofuran (THF) distilled after drying with sodium metal and benzophenone. Dichloromethane was distilled after drying with calcium hydride.

Spectroscopic Measurements

Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were obtained via Bruker DRX-300. The chemical shifts in the ^{1}H-NMR spectra are stated with respect to the

resonance of residual $CHCl_3$ at δ 7.26 ppm. Infrared (IR) spectra were recorded via a Shimadzu IRAffinity-1 FTIR.

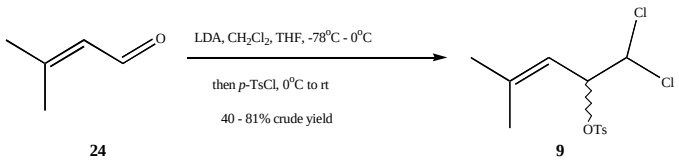
Experimentals



11 **24**

PCC (25.65g, 119 mmol) was ground with silica gel (10g) using a mortar and pestle and added to a flame dried flask along with freshly distilled DCM (278mL) and the flask was argon purged. Alcohol **11** (6.05mL, 59.5 mmol) was added all in one portion via syringe and the once orange suspension immediately turned black. After being stirred for approximately three hours, the reaction was complete as monitored by TLC (4:1 Hex:EtOAc, non-fluorescent silica, $KMnO_4$ stain, developed with heat). The amassed silica gel and PCC salts were then vacuum filtered through a silica and celite pad away from the mother liquor containing aldehyde **24** using DCM as an eluent. The mother liquor was added to a separatory funnel and washed with distilled water and brine to remove any other chromium salts. Finally the mother liquor was dried with anhydrous magnesium sulfate, filtered, and aldehyde **24** was concentrated by distillation. Aldehyde **24** exists as a pale, clear yellow oil. In some cases aldehyde **24** appears to have a greenish tint post-purification. Attempts at using the impure aldehyde samples showed significantly affected yields in the next reaction step (in the cases that the next reaction even worked). It was noted that although distillation does help to lessen the loss in yield due to volatility of the aldehyde; the aldehyde was consistently present in the distilled solvent when analyzed by ^{1}H-NMR. Dichloromethane was used due to its low boiling point to try and circumvent this problem. This is a known compound and the spectral data agrees with the known data published.[27]

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



24 **9**

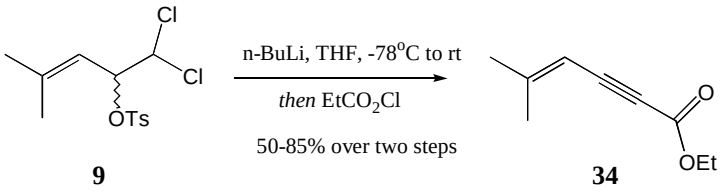
Two double neck round bottom flasks, a 250mL and 100mL and two addition funnels were flame dried and argon purged. The 100mL round bottom was charged with freshly distilled diisopropylamine (5.97mL, 42.3 mmol) and freshly distilled THF (17.54mL, 216 mmol). The contents of this flask were set to stir and submerged in a -78°C dry ice and acetone bath. Once equilibrated, n-butyllithium solution (1.45M, 17.48mL, 25.4 mmol) was added dropwise via addition funnel. The resultant LDA solution was left to stir at -78°C for 45 minutes.

While waiting for the LDA to stir the 250mL double neck round bottom flask was charged with aldehyde **24** (1.62mL, 169 mmol), freshly distilled THF (35.10mL, 433 mmol) and freshly distilled DCM (5.41mL, 845 mmol). This reaction flask was set to stir, submerged in a 0°C and allowed to equilibrate over about 30 minutes. After 30 minutes the flask was submerged in a -78°C dry ice and acetone bath and allowed to equilibrate for another 15 minutes.

The LDA solution, now pale yellow in color, was cannulated from its own round bottom flask into the addition funnel attached to the 250mL round bottom flask. The LDA solution was added to the flask at -78°C dropwise over the course of the next 25-30 minutes. Upon complete addition the reaction was left to stir at -78°C for an additional 30 minutes, at which time it was submerged in a 0°C ice bath for 30 minutes. Next, p-toluenesulfonyl chloride (3.87g, 203 mmol) was added to the flask in one portion, the addition funnel was replaced by a rubber septum, and the flask was argon purged and allowed to stir at 0°C for an additional 10 minutes. Finally, the reaction was removed from the bath and allowed to equilibrate to room temperature over the next 1.5 hours. TLC confirmed reaction completion (4:1 Hex:EtOAc, fluorescent silica) so the reaction was quenched with 20mL of distilled water and allowed to stir at room temperature for 15 minutes.

The contents of the round bottom flask were added to a separatory funnel with 50mL diethyl ether. The layers were partitioned and the organic layer was then washed with 50mL of 0.1N HCl followed by 50mL of 1M NaOH. The aqueous layers were combined and back extracted with 2x10 mL of diethyl ether. Finally the combined organics were washed with 50mL of brine, dried with anhydrous magnesium sulfate, filtered through a celite pad and concentrated *in vacuo* to afford tosylate **9** as a dark brown oil (4.06g, 81% crude yield). Two-dimensional TLC as well as trial and error have shown that tosylate **9** is silica sensitive. As such it is carried onto the next reaction without purification. Tosylate **9** is not a known compound so characterization was done via ^{1}H-NMR and compared to the spectral characteristics of simulated ^{1}H-NMR software.

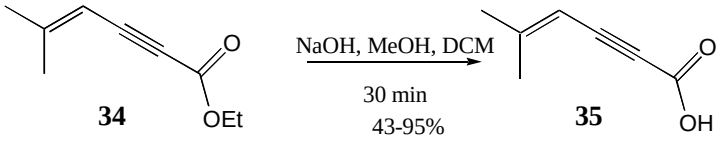
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, 2H), 7.35 (d, 2H), 6.70 (d, 1H), 6.20 (d, 1H), 6.10 (d, 1H), 2.45 (s, 3H), 1.75 (s, 6H).



9 **34**

A 250mL double neck round bottom flask and an addition funnel were flame dried and argon purged. The round bottom was charged with tosylate **9** (4.174g, 14.1 mmol) and freshly distilled THF (51.46mL, 635 mmol). The contents of this flask were set to stir and submerged in a -78°C dry ice and acetone bath. Once equilibrated, n-butyllithium solution (1.45M, 32.10mL, 46.5 mmol) was added dropwise via addition funnel over the course of approximately 20 minutes. Upon complete addition, the reaction flask was left to stir at -78°C for 30 minutes. Next it was submerged in a 0°C ice bath for 30 minutes, then resubmerged in the -78°C dry ice and acetone bath and allowed to equilibrate. Upon temperature equilibration, ethyl chloroformate (2.02mL, 21.2 mmol) was added via syringe in a dropwise fashion over a few minutes time. Upon complete addition the reaction flask was removed from the -78°C bath and allowed to stir at room temperature for 30 minutes. At that time TLC showed reaction completion (4:1 Hex:EtOAc, fluorescent silica) so the solution was allowed to continue equilibration to room temperature over the next 45 minutes and was then quenched with a mixture of 25mL ammonium chloride, 20mL of brine and 15mL distilled water. The contents of the flask were then added to a separatory funnel along with 50mL of diethyl ether. The layers were partitioned and the aqueous layer back extracted with 25mL of diethyl ether then 25mL DCM. Finally the combined organics were washed with 50mL of brine, dried with anhydrous magnesium sulfate, filtered through a celite pad and concentrated *in vacuo* to afford crude ester **34** as a brown oil. Ester **34** was purified by column chromatography, eluting with 10:1 Hex:Et_2O, yielding a pale yellow oil (1.82g, 85% yield). Et_2O was used as the polar eluent instead of EtOAc because they have about the same polarity and EtOAc proved problematic to remove *in vacuo*. This is a known compound and the spectral data agrees with the known data published.[37]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.35 (s, 1H), 4.20 (q, 2H), 1.98 (s, 3H), 1.85 (s, 3H), 1.30 (t, 3H).

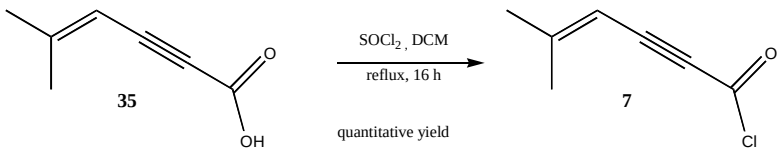


34 **35**

A 25mL round bottom flask was flame dried, charged with ester **34** (0.324g, 2.13 mmol), 9:1 DCM:MeOH (10mL) and 3M methanolic NaOH (4mL) and argon purged. The reaction flask was stirred at room temperature under an argon atmosphere for 20 minutes. At this time TLC was done (4:1 Hex:Et_2O, fluorescent silica) showing reaction completion. The contents of the reaction flask were added to a separatory funnel along with 15mL of Et_2O and 15mL of distilled water. The layers were partitioned and the aqueous layer was washed four times with10mL portions of Et_2O to ensure any unwanted organics were removed. It is easiest for storage purposes to concentrate the sodium salt from the aqueous layer *in vacuo*. It can be carried on to the next reaction as a salt with no detrimental effects. If carboxylic acid **35** is desired, simply acidify the aqueous layer to pH 1-2 (litmus paper turns red) using 3M HCl and extract carboxylic acid **35** into 10-15mL of Et_2O. The organic layer can then be dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford carboxylic acid **35** (0.252g, 95% yield) as a brown oil with solid crystalline particulate. Carboxylic acid **35** was not purified further before being brought onto the next reaction as it proved to be silica sensitive via 2-D TLC techniques.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.39 (s, 1H), 2.05 (s, 3H), 1.95 (s, 3H).

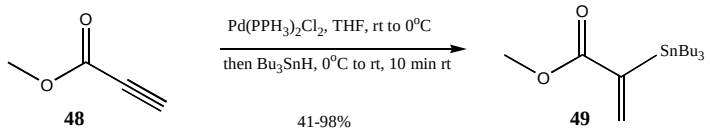
IR (cm^{-1}): 3024, 2956.87 - 2736.99, 2150.63, 1649.14, 1276.88 – 1193.94.



A 10 mL round bottom flask and reflux condenser were flame dried. The round bottom flask was charged with carboxylic acid **35** (0.01g, 0.0806 mmol), thionyl chloride (0.03mL, 0.413 mmol) and DCM (5mL), then argon purged. The reaction flask was refluxed for 16 hours, then cooled and the contents of the flask concentrated *in vacuo* affording acid chloride **7** in quantitative yield. The ^{1}H-NMR spectra of the crude reaction product shows good purity. Absence of the carboxylic acid functionality was quickly confirmed via IR since the ^{1}H-NMR spectra are nearly identical. Acid chloride **7** is not a known compound so ^{1}H-NMR data was also compared to the spectral characteristics of simulated ^{1}H-NMR software.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.50 (s, 1H), 2.10 (s, 3H), 1.95 (s, 3H).

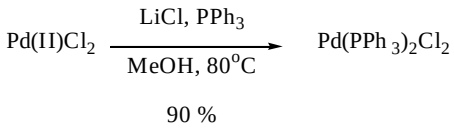
IR (cm^{-1}): 2958.80-2854.65, 2181.49, 1734.01.



A 25mL round bottom flask was flame dried and argon purged. To the flask was added methyl propiolate **(48)** (0.25mL, 3.01 mmol), freshly distilled and degassed THF (12.04mL) and freshly prepared $Pd(PPh_3)_2Cl_2$ (0.65g, 0.926 mmol). The round bottom flask was submerged in a 0°C ice bath and allowed to equilibrate, and then tributyltin hydride (0.89mL, 3.31 mmol) was added dropwise over several minutes. Upon complete addition the reaction flask was removed from the ice bath and allowed to stir at room temperature for 15 minutes. At that time TLC analysis was done (94:6 Pen:EtOAc, fluorescent silica) showing reaction completion so the contents of the flask were concentrated *in vacuo*, then diluted with 20mL of pentane and left to stir at room temperature for about 30 minutes. Finally the solid catalyst was filtered away from the pentane and the pentane was added to a separatory funnel and washed with 25mL of distilled water, followed by 25mL of brine. The organics were then dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford crude model vinyl stannane **49**. Purification was carried out using column chromatography on silica using a gradient elution with a pentane and ethyl acetate solvent system. This is a known compound and the spectral data agrees with the known data published.[30]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.70 (d, 1H), 5.93 (d, 1H), 3.75 (s, 3H), 1.47 (t, 2H), 1.33 (m, 2H), 0.99 (m, 2H), 0.97 (t, 3H).

$Pd(PPh_3)_2Cl_2$ Catalyst



An oven dried pressure vial was charged with palladium(II)chloride (0.126g, 0.712 mmol), lithium chloride (0.060g, 1.42mmol), triphenylphosphine (0.410g, 1.57 mmol) and methanol (2 mL). The reaction vial was refluxed in a sand bath and in the dark due to light sensitivity, at approximately 80-85^{o}C for 30-40 minutes, then the vial was cooled to room temperature. The catalyst was filtered through glass frits under argon rinsing with freshly distilled and degassed methanol, and then the solid catalyst was dried overnight in a septum covered vial under argon yielding $Pd(PPh_3)_2Cl_2$ as a bright yellow solid (0.452g, 90% yield). $Pd(PPh_3)_2Cl_2$ was kept wrapped in aluminum foil in the desiccator between uses to avoid light and moisture exposure. When black flecks begin to appear in the catalyst, recrystallization from methanol is helpful. If the catalyst is not recrystallized, it will require the use of excess catalyst in reactions to compensate for its degradation.[38]

References

1. Faulkner, D.J. *Nat. Prod. Rep.* **2001,** 18, 1-49.

2. Ciereszko, L.S.; Kraus, T.K. Comparitive Biochemistry of Coral Reef Coelenterates. *Biology and Geology of Coral Reefs;* Jones, O.A., Endean, R., Eds.; Academic: New York; **1973**; Vol. 2, pp. 183-203.

3. Schmitz, F.; Krans, K.W.; Ciereszko, L.S.; Sifford, D.H.; Weinheimer, A.J. *Tetrahedron Lett.* **1966**, 97-104.

4. Schmitz, F.; Lorance, E.D.; Cierszko, L.S. *J. Org. Chem.* **1969**, 34, 1989-1990.

5. Schmitz, F.; Lorance, E.D. *J. Org. Chem.* **1971**, 36, 917-925.

6. Rezanka, T.; Dembitsky, V.M. *Tetrahedron*. **2001**, 57, 8743-8749.

7. Pattenden, G. *Prog. Chem. Org. Nat. Prod.* **1978**, 35, 133.

8. Ohlaff, G.; Flament, I. *Prog. Chem. Org. Nat. Prod.* **1979**, 36, 231.

9. Alali, F.; Liu, X.; McLaughlin, J. *J. Nat. Prod.* **1999**, 74, 259.

10. Hoppe, R.; Scharf, H.D. *Synthesis.* **1995**, 12, 1447.

11. Spencer, W. *Thesis: Studies Toward the Synthesis of Trocheliophorolide A.* **2008**.

12. Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, 8, 3557-3560.

13. Richecoeur, A., Sweeney, J.B. *Tetrahedron,* **2000**, 56, 389-395.

14. Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, 126, 12790-12791.

15. Berkenbusch, T., Bruckner, R.; *Tetrahedron.* **1998**, 54, 11461-11470.

16. Yang, W., Kitahara, T. *Tetrahedron.* **2000**, 56, 1451-1461.

17. Strand, D.; Norby, PO.; Reinn, T. *J. Org. Chem.* **2006**, 71, 1879-1891.

18. Head, G.D.; Whittingham, W.G.; Brown, R.C.D. *Synlett.* **2004**, *1437-1439.*

19. Takahashi, S., Nakata, T. *J. Org. Chem.* **2002**, 67, 5739–5752.

20. Hofman, S.; et al. *Eur. J. Org. Chem.* **2001**, 2851-2860.

21. Marshall, J.A.; Yanik, M.M.; Adams, N.D.; Ellis, K.C.; Chobanian, H.R. *Organic Syntheses.* **2005**, 81, 157-170.

22. Danheiser, R.L. Ed. *Organic Synthesis*; V. 81; Organic Synthesis, Inc.: New York, NY, **2004**.

23. Dorn, S. C. M. *Thesis: Studies Toward the Synthesis of Trocheliophorolide A.* **2010**.

24. Commeiras, L.; Santelli, M.; Parrain, J. L. *Org. Lett.* **2001**, 3, 1713-1715.

25. Augsto, O. *Thesis: Studies Toward the Synthesis of Trocheliophorolide A.* **2006**.

26. Kells, K.W.; Chong, J.M. *J. Am. Chem. Soc.* **2004**, 126, 15666-15667.

27. Li, Y.; Lu, B.; Li, C.; Li, Y. *Synthetic Communications.* **2003**, *33*, 1417-1423.

28. Luzzio, F. A.; Fitch, R. W.; Moore, W. J.; Mudd, K. J. *J. Chem. Edu.* **1999**, 76, 974-975.

29. Theodorou, V.; Skobridis, K.; Tzakos, A. G.; Ragoussis, V. *Tetrahedron Lett*. **2007**, 48, 8230-8233.

30. Becker, W.; Eller, G. A.; Holzer, W. *Synthesis.* **2005**, 15, 2583- 2589.

31. Nielsen, T. E.; Le Quement, S.; Juhl, M.; Tanner, D. *Tetrahedron*. **2005**, 61, 8013-8024.

32. Cherry, K.; Lebegue, N.; Leclerc, V.; Carato, P.; Yous, S.; Berthelot, P. *Tetrahedron Lett*. **2007**, *48*, 5751-5753.

33. Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Org. Chem.* **2009**, *74*, 230–243.

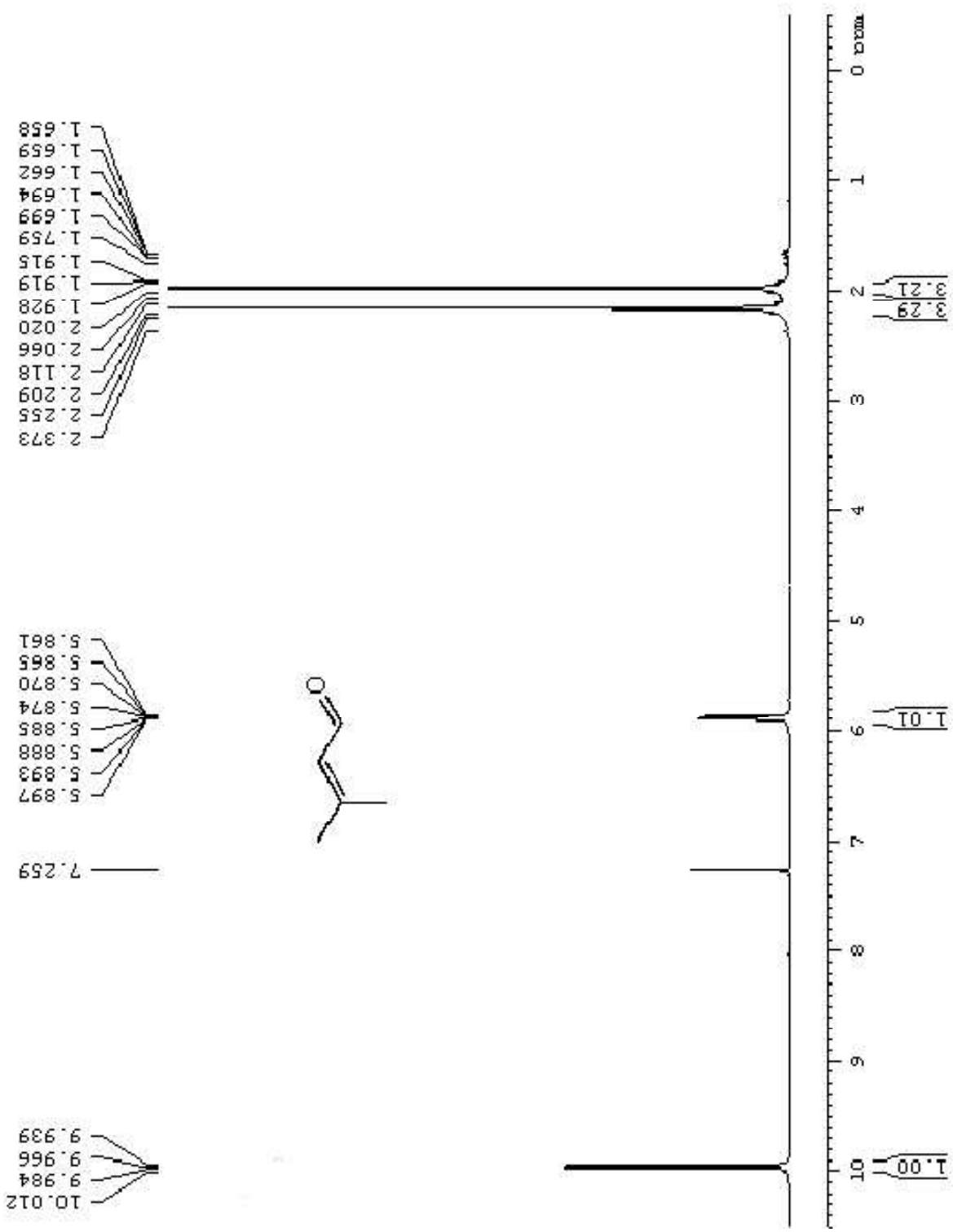
34. Tang, B.; Bray, C. D., Pattenden, G. *Org. Biomol. Chem.* **2009**, 7, 4448-4457.

35. Nantz, M. H.; Zweifel, G. S. "Modern Organic Synthesis an Introduction" W. H. Freeman. **2007**, 372-381.

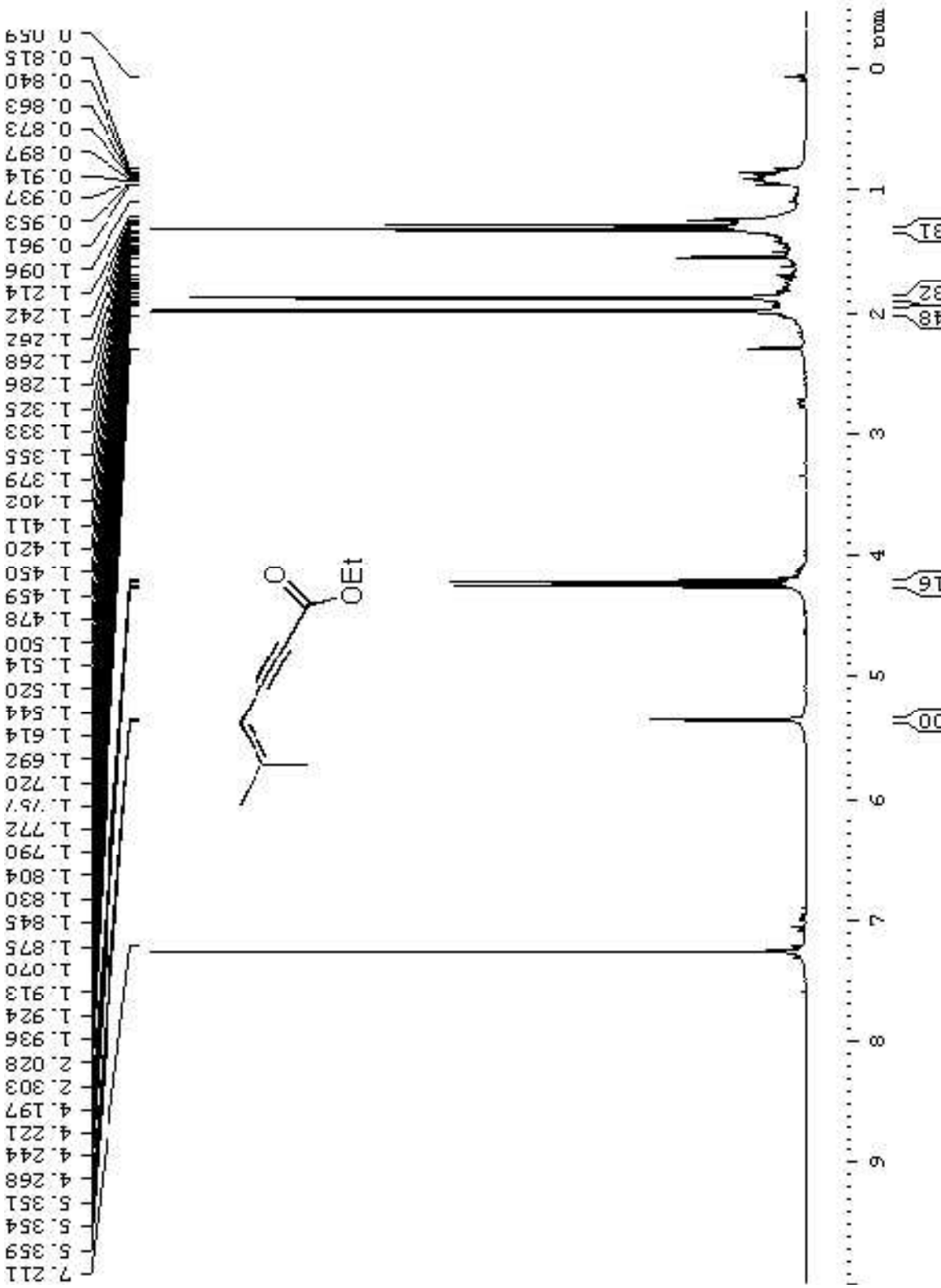
36. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457-2483.

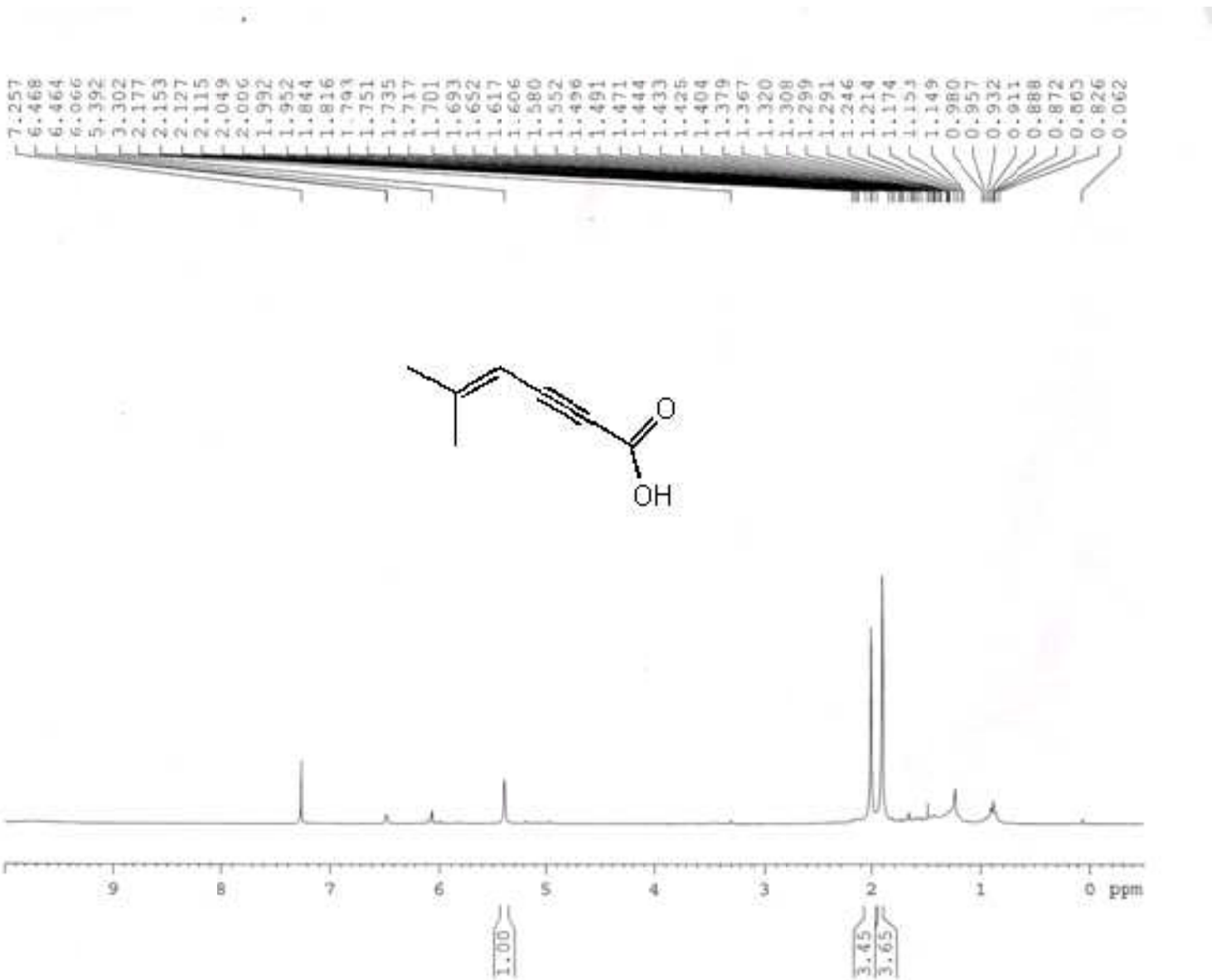
37. Dai, M; Sarlah, D.; Yu, M.; Danishefsky, S. *J. Am. Chem. Soc.* **2007**, 129, 645-657.

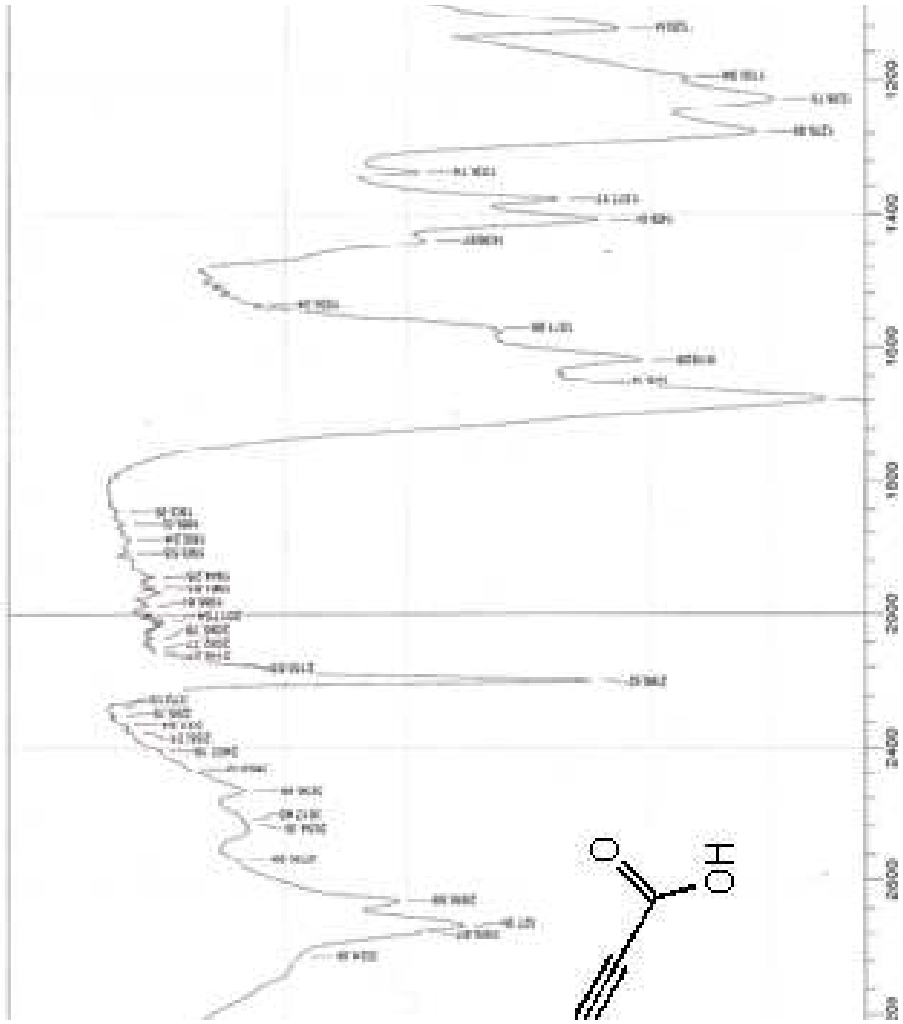
38. Oskooie, H. A.; Heravi, M. M.; Behbahani, F. K. *Molecules.* **2007**, 12, 1438-1446.


10.012
9.984
9.966
9.939
7.259
5.897
5.893
5.888
5.885
5.874
5.870
5.865
5.861
2.373
2.255
2.209
2.118
2.066
2.020
1.928
1.919
1.915
1.759
1.699
1.694
1.662
1.659
1.658
1.00
1.01
3.29
3.21
ppm 0 1 2 3 4 5 6 7 8 9 10

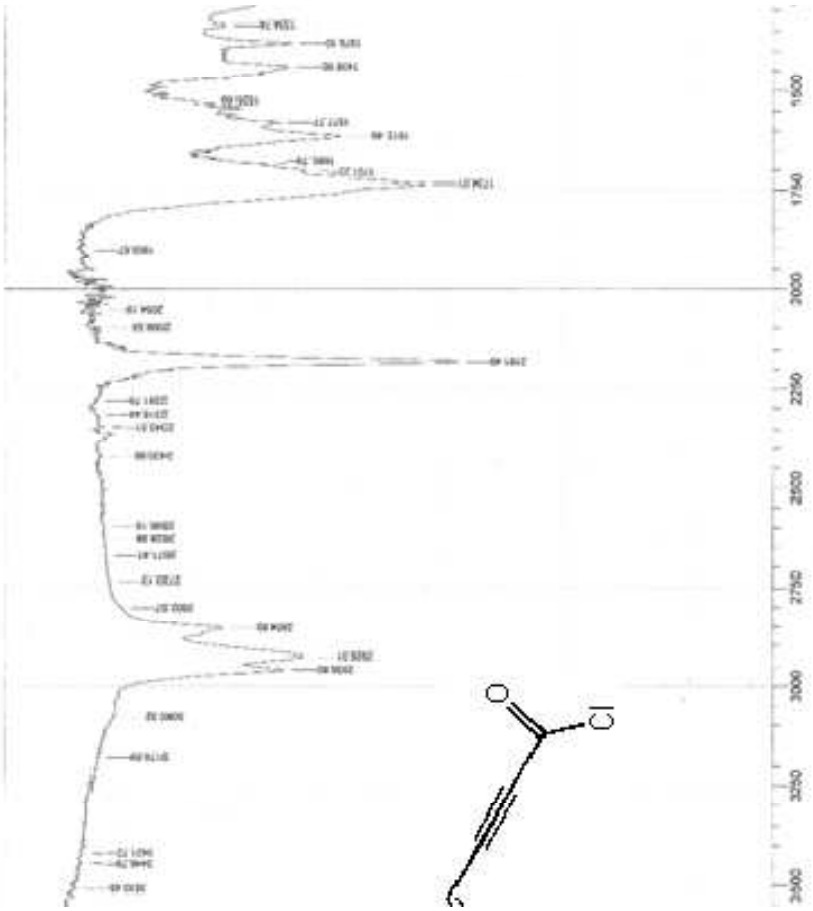
0.062
0.918
0.975
1.035
1.060
1.081
1.097
1.146
1.157
1.168
1.183
1.220
1.246
1.267
1.297
1.312
1.329
1.335
1.353
1.369
1.414
1.429
1.437
1.446
1.468
1.496
1.563
1.620
1.673
1.677
1.690
1.725
1.762
1.776
1.802
1.813
1.828
1.841
2.422
2.452
4.075
4.115
6.006
6.008
6.013
6.033
6.169
6.189
6.211
7.302
7.344
7.370
7.795
7.823
Cl
Cl
OTs
ppm
0
1
2
3
4
5
6
7
8
9
11.24
9.16
4.37
3.08
1.00

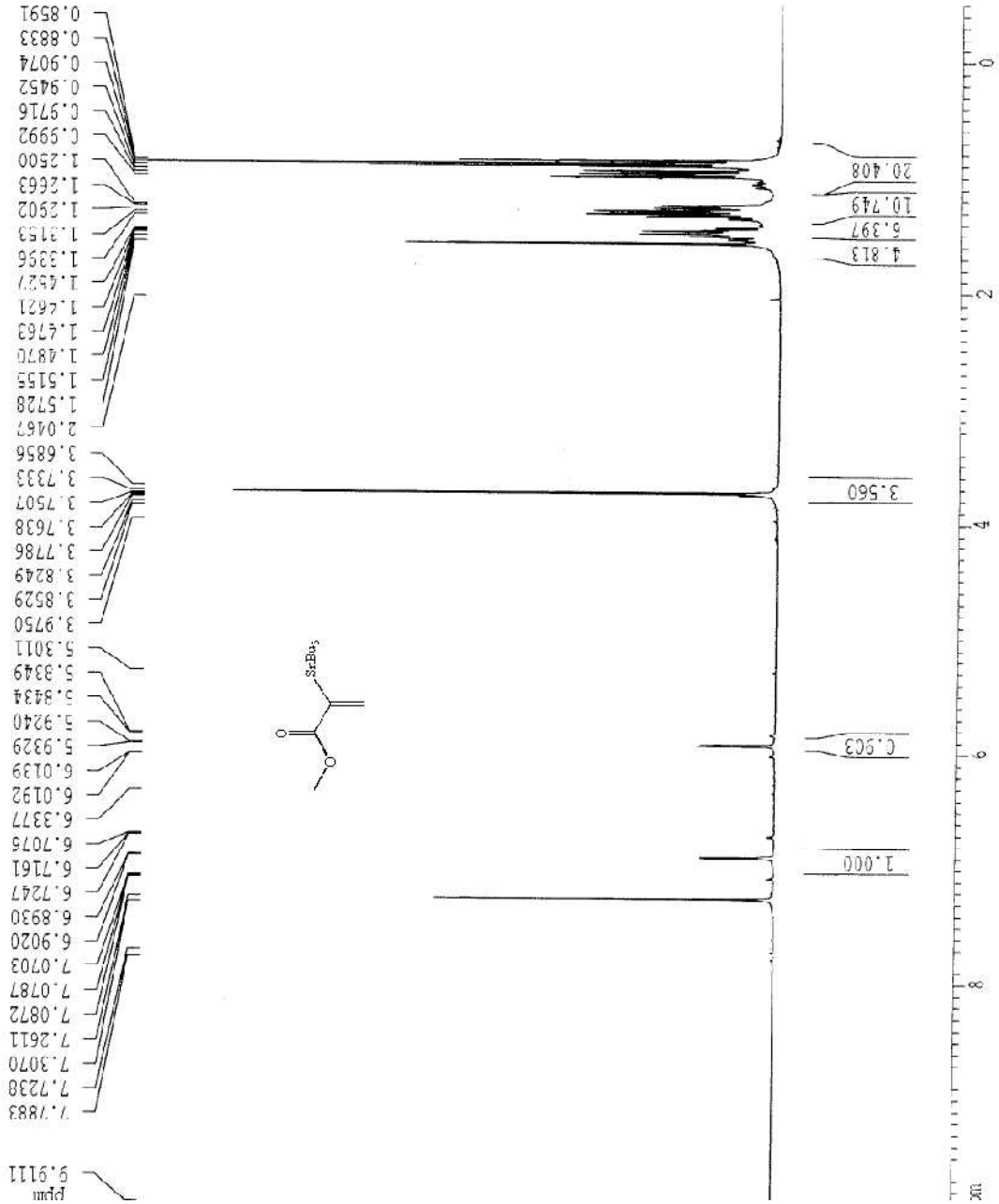

O
OEt


7.257
6.468
6.464
6.066
5.392
3.302
2.177
2.153
2.127
2.115
2.049
2.006
1.992
1.952
1.844
1.816
1.793
1.751
1.735
1.717
1.701
1.693
1.652
1.617
1.606
1.580
1.552
1.496
1.491
1.471
1.444
1.433
1.425
1.404
1.379
1.367
1.320
1.308
1.299
1.291
1.246
1.214
1.174
1.153
1.149
0.980
0.957
0.932
0.911
0.888
0.872
0.865
0.826
0.062
O
OH
9
8
7
6
5
4
3
2
1
0 ppm
1.00
3.45
3.65


O
OH

7.295
7.268
7.248
6.342
5.484
2.040
2.008
1.959
1.942
1.924
1.658
1.642
1.620
1.578
1.489
1.387
1.327
1.240
O
Cl
1.00
3.29
3.73
ppm


O
Cl


9.9111
7.7883
7.7238
7.3070
7.2611
7.0872
7.0787
7.0703
6.9020
6.8930
6.7247
6.7161
6.7075
6.3377
6.0192
6.0139
5.9329
5.9240
5.8434
5.3349
5.3011
3.9750
3.8529
3.8249
3.7786
3.7638
3.7507
3.7333
3.6856
2.0467
1.5728
1.5155
1.4870
1.4763
1.4621
1.4527
1.3356
1.3153
1.2502
1.2663
1.2500
0.9992
0.9716
0.9452
0.9074
0.8833
0.8591
20.408
10.749
6.397
4.813
3.560
1.000
ppm