# Toward a Total Synthesis of Englerin A

A Dissertation
SUBMITTED TO THE FACULTY OF
UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Andrew M. Harned, Advisor

December 2014

**Acknowledgements**

First, I would like to thank my wife, Kate, for her constant love and support. You have been my partner, my best friend and my personal cheerleader. I don't know if I could have done it without you. I look forward to many happy years together.

I would like to thank my family for their enthusiastic support. Especially my parents, Rick and Rose, for your unending love and support in everything that I have done. Your support over the years has shaped who I am today. Also to my in-laws who always had a hot meal and an encouraging word waiting for me when I needed it.

To all of the U of M professors, post-docs, grad students and support staff. Thank you for the countless ways in which you have helped me in my journey here. Especially Profs. Douglas, Barany, and Hoye.

To the Harned group members past and present: thank you for your companionship, friendship and support along the way. I'm lucky to have been able to share a lab and office as well as many conversations both intellectual and frivolous.

Finally to my advisor, Prof. Andrew Harned, I have had the privilege to be the first to join your lab. You have always had an open door and been willing to talk about chemistry whenever I needed. The skills that I have learned in your lab are invaluable and I will always be thankful for the opportunity that I had to learn there.

**Dedication**

To Kate, on our one year anniversary.

…I should have just bought flowers.

**Abstract**

Englerin A is a guiane sesquiterpenoid isolated from the spurred potato-bush *Phyllanthus engleri* that has shown potent and selective activity against renal cancer cell lines. Our approach to the synthesis of englerin A features a Diels-Alder reaction between an axially chiral allene and a 3-siloxyfuran. We have found the oxabicyclo[2.2.1]heptane framework to be a sterically formidable structure and have discovered a novel decomposition pathway of acetyl-oxabicyclo[2.2.1]heptanes to 3(2*H*)-furanones.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| aq. | aqueous |
| BINOL | binaphthol |
| Bu | butyl |
| CBz | carbobenzoyl |
| COSY | COrellation SpectroscopY |
| CSA | camphor sulfonic acid |
| dba | dibenzylidine acetone |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichlormethane |
| DEPT | distortionless enhancement by polarization transfer |
| DIBAL-H | diisobutylaluminum hydride |
| DMAP | *N,N*-dimethylaminopyridine |
| DMDO | dimethyldioxirane |
| DMF | *N,N*-dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMSO | dimethylsulfoxide |
| *dr* | diastereomeric ratio |
| EDA | ethyl diazoacetate |
| EDCI | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| *ee* | enantiomeric excess |

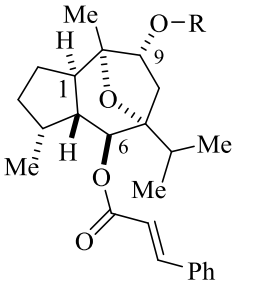
| | |
|---|---|
| en | ethylenediamine |
| Et | ethyl |
| $GI_{50}$ | 50% growth inhibition |
| HMBC | hetronuclear multiple bond correlation |
| HRMS | high-resolution mass spectroscopy |
| HSF1 | heat shock factor 1 |
| HSQC | Heteronuclear Single Quantum Coherence |
| IBX | 2-iodosobenzic acid |
| *i*Pr | isopropyl |
| KHMDS | potassium hexamethyldisilizane |
| LDA | lithium diisopropyl amide |
| LG | leaving group |
| LHMDS | lithium hexamethyldisilizane |
| *m*CPBA | *meta*-chloroperbenzoic acid |
| Me | methyl |
| MMPP | magnesium monoperoxyphalate |
| MOM | methoxymethyl |
| Ms | methanesulfonate |
| NCI | National Cancer Institute |
| nM | nanomolar |
| NMO | *N*-methylmorphline oxide |
| NMR | nuclear magnetic resonance |
| PCC | pyridinium chlorochromate |

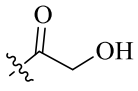
| | |
|---|---|
| Ph | phenyl |
| PIDA | phenyl iodonium diacetate |
| Pr | propyl |
| RCC | renal cell carcinoma |
| SAR | structure-activity relationship |
| sat. | saturated |
| TBAF | tetrabutylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilane |
| TBHP | *tert*-butylhydroperoxide |
| TBME | *tert*-butyl methyl ether |
| TBS | *tert*-butylsilyl |
| TEA | triethylamine |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TLC | thin layer chromatography |
| TPAP | tetrapropylamino perruthenate |
| Ts | *para*-toluenesulfonyl |

# Chapter 1 Syntheses of Englerin A and Derivatives

## 1.1 Introduction

Renal cancer incidence is increasing steadily and accounts for 2-3% of all cancers reported in adults.[1] Renal cell carcinoma (RCC) continues to present a challenge to clinicians as one of the most lethal forms of cancer. The insidious nature of this disease is two-fold. First, the initial diagnosis often is made at an advanced stage. Second, advanced renal cancer does not typically have a durable response to traditional therapies and patients with distant metastases have a 5-year survival rate of less than 10%.[2] First line therapy is surgical; when this option is no longer viable (as in metastatic disease) chemotherapeutics are the standard of care. While chemotherapy can produce some response, typically it only halts progression for a finite period. For this reason renal cancer has been identified as a high priority for new drug development by the National Cancer Institute.




R = 


R = H,

englerin A **1**
englerin B, **2**

*RCC growth inhibition data (Mean $GI_{50}$ in $\mu M$)*

| renal cell line | **1** | Taxol® |
|---|---|---|
| 786-0 | <0.01 | 0.034 |
| A498 | <0.01 | 0.10 |
| ACHN | <0.01 | 0.65 |
| CAKI-1 | 15.5 | 0.35 |
| RXF-393 | 0.011 | 0.041 |
| SN12C | 0.087 | 0.018 |
| TK-10 | 15.5 | 0.11 |
| UO-31 | <0.01 | 0.45 |

Figure 1 The englerins

As part of a program to identify new compounds with activity against renal cancer, Ratnayake and coworkers isolated englerin A (**1)** and B (**2)**, from an East African shrub, *Phyllanthus englerin.*[3] Previous investigations into this plant have found the triterpene phyllanthol which did not show biological activity, and a toxic glycoside which was not well-characterized. Guided by bioassay fractionation, the authors identified the active compound as part of the dichloromethane-methanol extractions of stem bark. The extracts were further separated by silica gel chromatography and HPLC. The structure of the compound isolated was identified by HRMS, $^{1}H$, $^{13}C$, COSY, NOESY, and HMBC NMR. This guaiane sesquiterpene was found to have potent and selective inhibitory activity against six of the eight NCI renal cancer cell lines with $GI_{50}$ values ranging from 1-87 nM. An NCI COMPARE analysis shows englerin A may operate by a novel mechanism. This prompted a study to identify the molecular targets of englerin A to provide new strategies to combat cancer.[4]

The authors of this study used three kidney cancer cell lines that each had an important genetic mutation. Treatment of each of these cell lines with englerin A successfully reduced the number of viable cells. When the wild-type cells were treated (with functions restored) they became insensitive to englerin A.

Comparing the structure of englerin A to structurally similar molecules with known mechanisms suggested protein kinase C (PKC) as a possible target. An assay then showed that englerin A does, in fact, increase PKC activity in a dose-dependent fashion. PKCθ was shown to be the specific target as loss of this protein kinase allowed cells to survive treatment with englerin A. Sapin toxin D is a known binder of PKCθ. Cells pretreated with englerin A showed a significant decrease in binding to this molecule which verified PKCθ as a target.

The authors noted englerin A may cause insulin resistance from downstream effects of PKCθ and so the authors wanted to know if englerin A would raise blood glucose levels. To their surprise, the blood glucose levels of the mice treated with englerin A were actually lower than those of the controls. Previous experiments suggested that such an effect could be explained by elevated levels of heat shock protein 70 (HSP70). The authors found that

HSF1, a regulator of the gene for HSP70 was activated by englerin A. HSF1 is a known tumor promoter and promotes glucose dependence.[5,6] Further experiments showed that englerin works by stimulating insulin resistance by PKCθ while at the same time making the cells more glucose dependent with HSF1. In conclusion, englerin A works by making tumor cells more glucose dependent while simultaneously decreasing glucose availability.

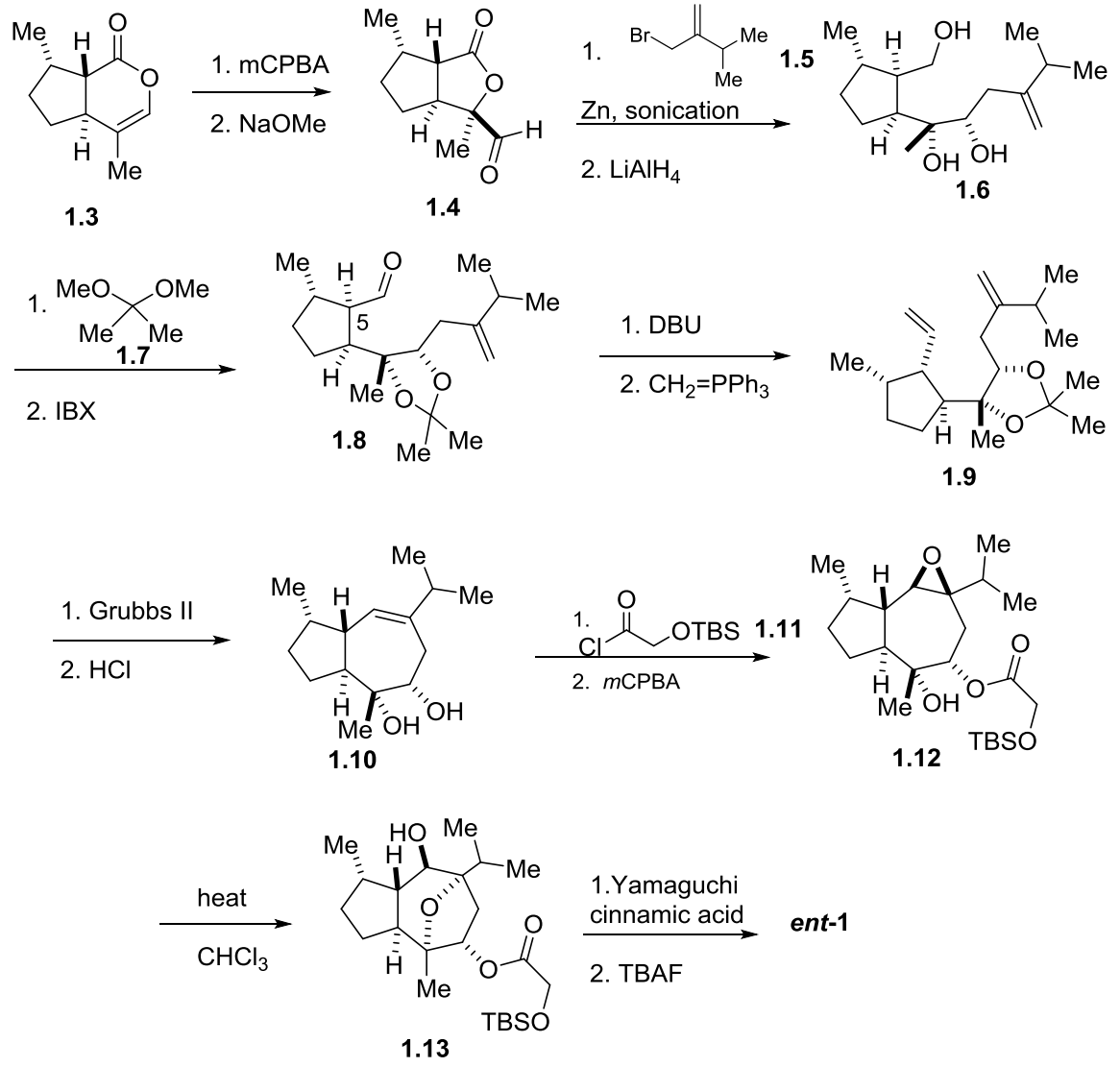
Due to the strong interest in the densely functionalized architecture and selectively potent bioactivity, a number of total syntheses of englerin A have been carried out. It should be noted that at the outset of our synthetic endeavors, no syntheses had yet been disclosed.

## 1.2 Ring-Closing Metathesis/ Transannular Epoxide Opening Strategy

### *1.2.1 Christmann*

In 2009, Mathias Christmann's group published the first total synthesis of the englerins.[7] They chose to start from *cis,trans*-nepetalactone **1.3** which can be obtained by the distillation of catnip.[8] The lactone was epoxidized followed by treatment with sodium methoxide to provide the ring-contracted aldehyde **1.4**. Barbier conditions with the bromide **1.5** followed by reduction with lithium aluminum hydride provided the carbon framework for the rest of the molecule. The diol **1.6** was then protected with acetal **1.7** and the molecule isomerized at C-5. The aldehyde **1.8** was then subjected to Wittig olefination. A ring-closing metathesis with Grubbs second generation catalyst was then used with **1.9** to furnish the guiane skeleton in **1.10**. Acidic deprotection of the acetonide was followed by the formation of glycolate ester with TBS-protected glycolic acid chloride **1.11**. The tertiary olefin was then epoxidized to **1.12** and simply warming the material caused it to undergo the transannular epoxide opening to **1.13**. Yamaguchi conditions were used to append the cinnamyl ester and TBAF deprotection furnished (+) englerin A. This synthesis established the absolute configuration of englerin A to be the opposite of that

synthesized. Unfortunately, nepetalactone is not generally available in the opposite enantiomer.



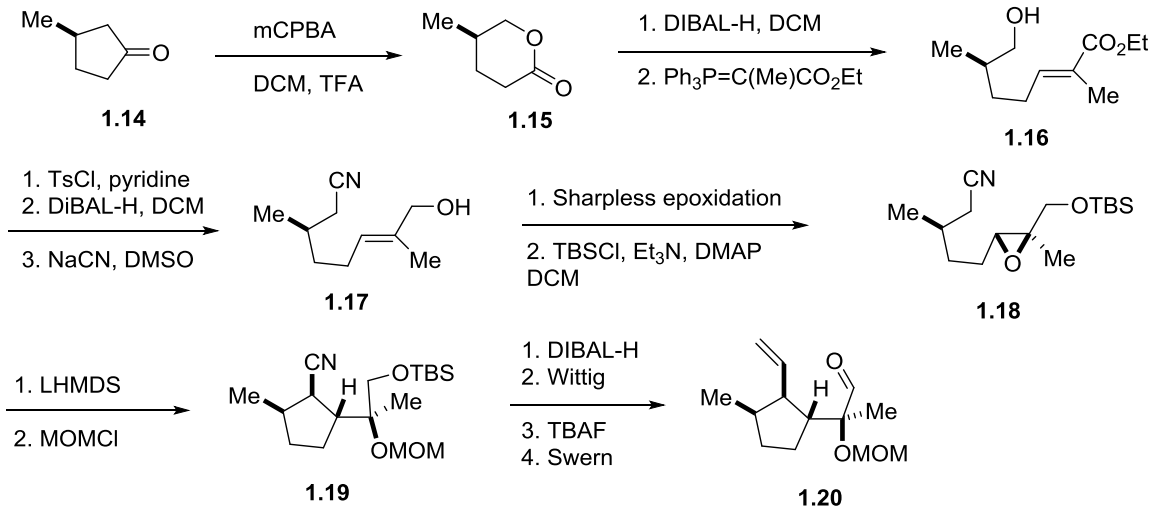

Scheme 1. Christmann's synthesis of englerin

The Christmann group subsequently published a synthesis of the natural enantiomer.[9] Because (−)-*cis,trans*-nepetalactone is not readily available as the (+) enantiomer, it can instead be synthesized from (+)-citronellal following a protocol from

Schreiber.[10] With this material they were able to improve their synthesis of englerin A and produce 32 analogs for SAR *(Vide infra*).

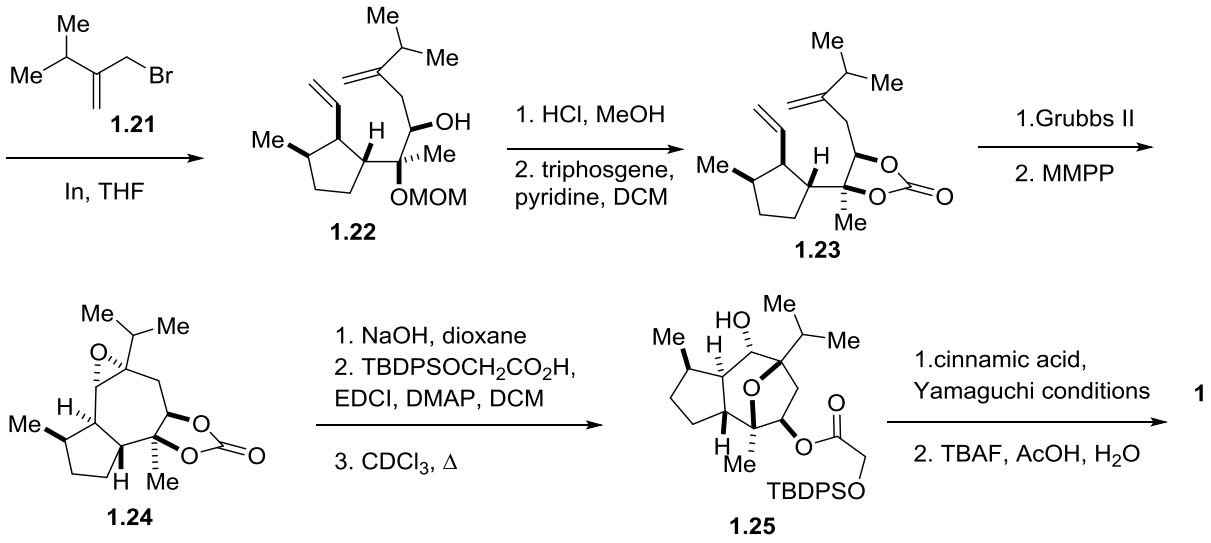
### *1.2.2 Hatakeyama*

Hatakeyama and co-workers published a synthesis that mirrored the original work by Christmann in many ways. Unique to this synthesis was the formation of cyclopentene ring via an epoxynitrile ring closure, a method developed by Stork.[11,12] Chiral ketone **1.14** was chosen as the starting material. Baeyer-Villiger oxidation was used to furnish the lactone **1.15,** which was reduced and treated by the Horner-Emmons reaction. The alcohol **1.16** was then tosylated and displaced with sodium cyanide and the ester reduced to the alpha-beta unsaturated alcohol, **1.17**. Sharpless conditions installed the epoxide diastereoselectively and the alcohol was then protected as the TBS-ether, **1.18**. Base-promoted epoxynitrile cylization was optiomized to a yield of 87%. The free alcohol was orthogonally protected with a MOM group giving **1.19**. The nitrile was reduced with DIBAL and resulting aldehyde was olefinated under Wittig conditions. The primary alcohol was desilylated and Swern oxidation was used to produce the aldehyde **1.20** required for the planned Barbier coupling.




Scheme 2 Hatakayama's synthesis of aldehyde substrate for Barbier coupling

After some experimentation with conditions, a Barbier-type coupling, utilizing indium rather than the traditional zinc was used to couple bromide **1.21** to **1.20** forming the diene, **1.22**. A removal of the MOM group was followed by protection of the 1,2-diol by carbonate formation. The terminal olefins of **1.23** were brought together by ring-closing metathesis. Epoxidation of the resultant tri-substituted olefin was accomplished with magnesium monoperoxyphthalate. The carbonate, **1.24**, was deprotected with sodium hydroxide and the less hindered secondary alcohol was esterified to the *t*-butyldiphenylsilyl-protected glycolate ester with the coupling reagent, EDCI. Simply heating in chloroform yielded the oxygen-bridged **1.25**. Cinnamic acid was coupled under Yamaguchi conditions and glycolate alcohol was deprotected to yield **1**.

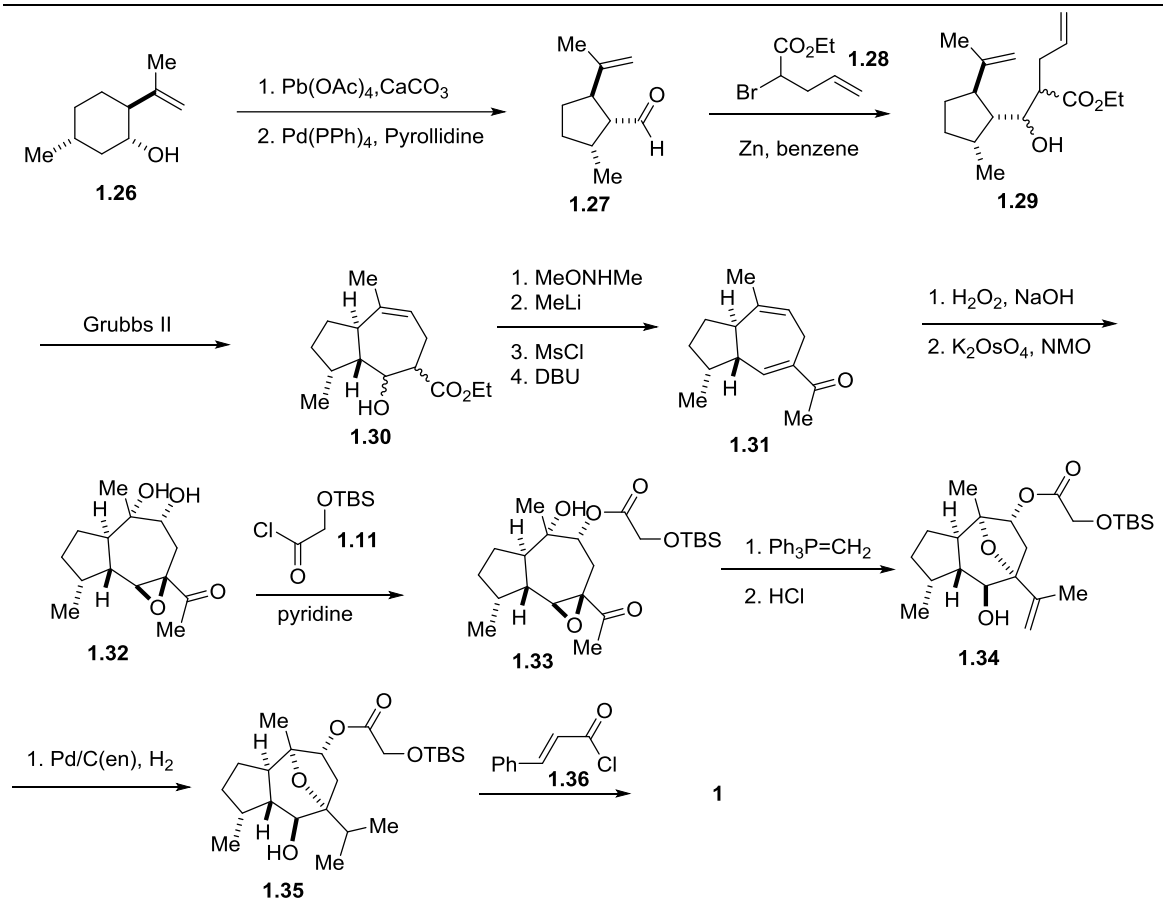



Scheme 3 Hatakeyama's endgame

### *1.2.3 Metz*

In 2013, a total synthesis was reported from the Metz group.[13] Starting from (–)-isopulegol **1.26**, a lead tetraacetate cleavage followed by treatment with palladium/pyrrolidine yielded aldehyde **1.27**. Originally, the authors envisaged a Horner-Emmons reaction to produce a trienol, however these reaction conditions proved too basic

and epimerization of substrate was observed. Reformatsky conditions with **1.28** were used instead to produce dienone **1.29**. Ring closing metathesis produced the bicyclic intermediate **1.30**. The ethyl ester was converted to the methyl ketone via the Weinreb amide and methyl lithium. The free alcohol was mesylated with MsCl and eliminated with DBU to give dienone **1.31**. Epoxidation of the α,β-unsaturated ketone was accomplished with hydrogen peroxide and osmium tetroxide was used to dihydroxylate the remaining olefin to give **1.32**. The secondary alcohol reacted with protected glycolic acid derivative **1.11** to give glycolic ester derivative **1.33**. The ketone was olefinated in a Wittig reaction followed by a hydrochloric acid mediated trans-annular epoxide opening/ ring formation to give **1.34**. Hydrogenation with Pd/C(en)[13] gave **1.35** followed by formation of the cinnamyl ester with cinnamoyl chloride, **1.36** and deprotection completed their synthesis of **1**.



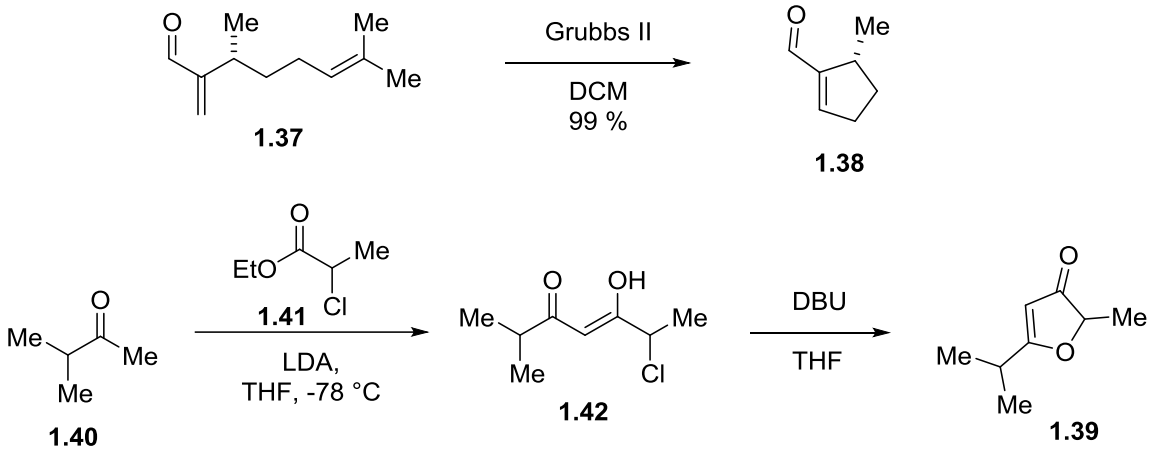

Scheme 4 Metz's synthesis

## 1.3 Samarium Iodide-Mediated Coupling Strategy

### *1.3.1 Chain*

In 2011, Chain and Coworkers reported their synthesis of (−)-englerin A.[14] Citronellal **1.37** (Scheme 5) was used as the starting material to produce unsaturated

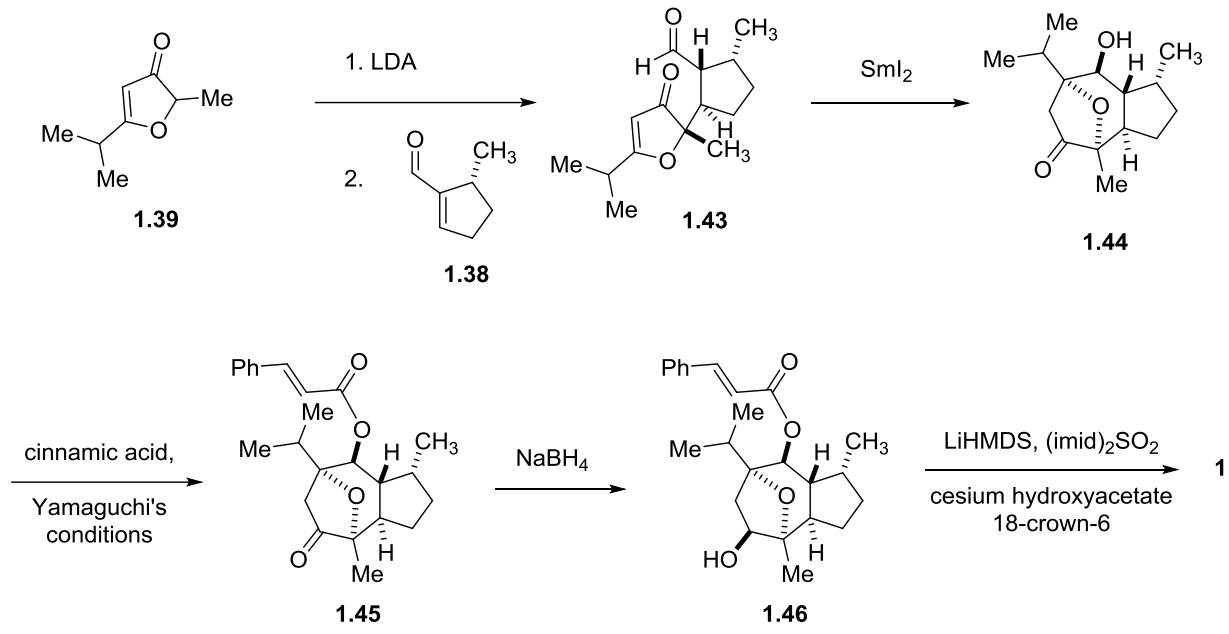
aldehyde **1.38** by ring closing metathesis. Furanone **1.39** was formed by addition of ketone **1.40** to ester **1.41** to give **1.42** followed by condensation with DBU.




Scheme 5. Chain's synthesis of starting materials

A lithium-chelate directed Michael addition into α,β-unsaturated aldehyde, **1.38** (Scheme 6) furnished dicarbonyl compound, **1.43**. The key step of this synthesis was a samarium iodide mediated annulation to form the 7-membered ring in **1.44**. Yamaguchi conditions were then used to place the cinnamic ester in **1.45** followed by sodium borohydride reduction of the ketoester to hydroxyl ester. The newly formed alcohol in **1.46** was converted into the sulfonate imidazole and which was then displaced to invert the

stereocenter at $C_9$ with cesium hydroxyacetate and 18-crown-6 in toluene to furnish **1**. This synthesis has the great advantage of efficiency in steps.




Scheme 6 Chain's synthesis of englerin A

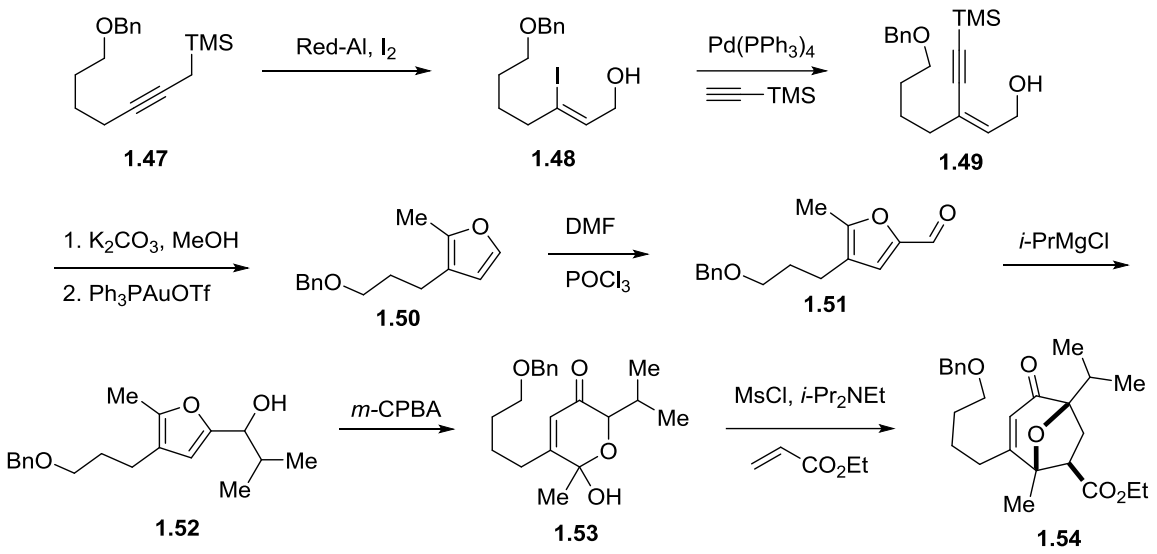
## 1.4 Cycloaddition Strategies

The groups of Nicoloau/Chen and Theadorakis published syntheses of englerin based on cycloaddition to form the oxabicycle followed by cyclopentane formation.

### *1.4.1 Nicoloau/Chen*

The Nicoloau/Chen synthesis hinged upon a [5+2] cycloaddition of an oxopyrillium ion with ethyl acrylate. The synthesis commenced with known compound **1.47**. Reduction with Red-Al and iodine produced vinyl iodide **1.48** which underwent a Heck coupling with TMS acetylene to **1.49**. This ene-yne-ol was then subjected to a gold-catalyzed cyclization producing furan **1.50**. This furan was then formylated to aldehyde **1.51** and alkylated to give furan **1.52**. Treatment by *m*CPBA affected an Achmatowicz rearrangement[15,16] to

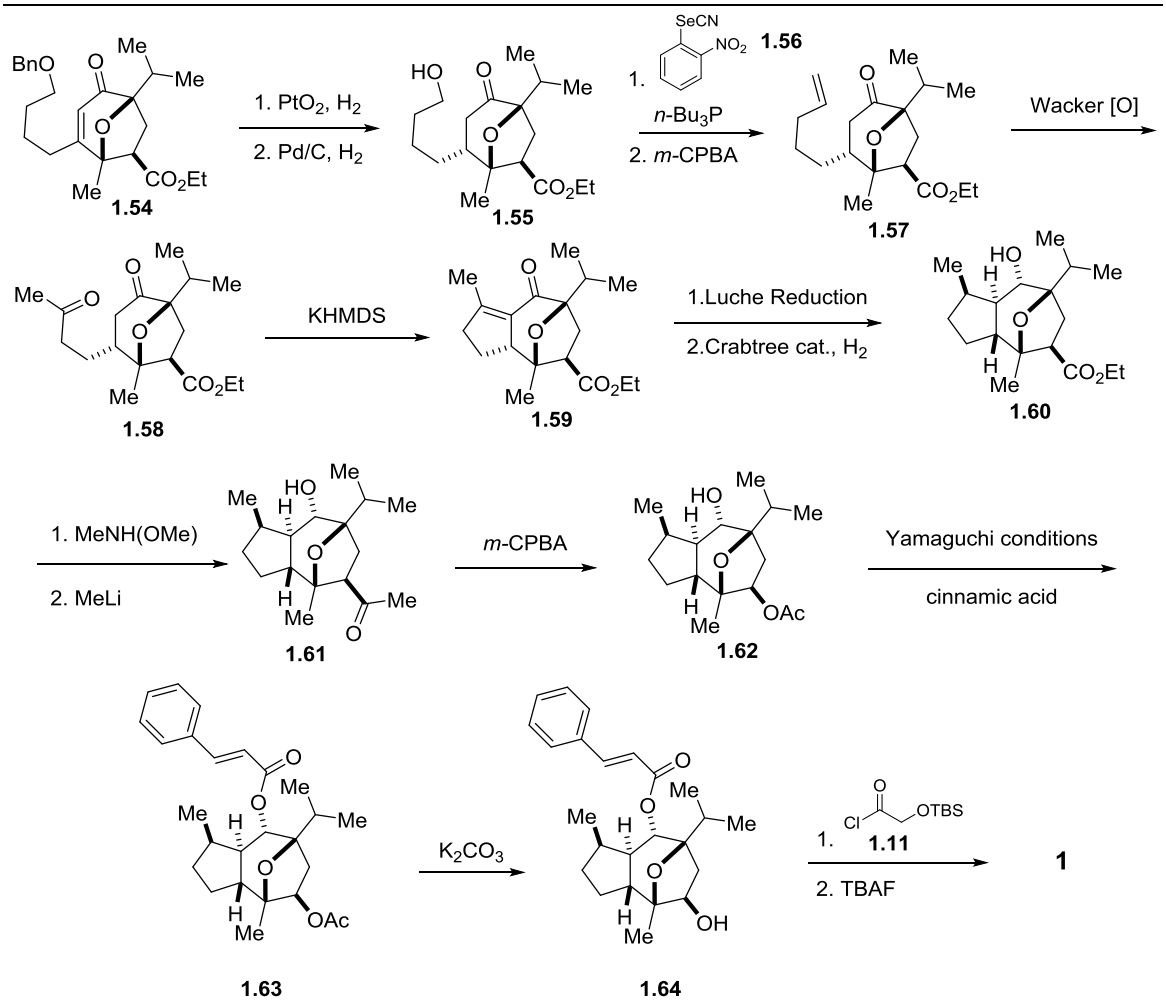
**1.53** setting them up for the key oxopyrillium [5+2] cyclization. Mesylation, elimination and enolization produced the requisite oxopyrillium which cyclized with ethyl acrylate to give 46% yield of the desired product **1.54** in an 8:1 diastereomeric ratio.




Scheme 7 Nicoloau/Chen formation of oxacycle

Sequential reductions of **1.54** with Adam's catalyst followed by palladium on carbon gave hydrogenation of the alkene and removal of the benzyl group, respectively, to form **1.55**. Selenium compound **1.56** was used in the dehydration of **1.55** to give terminal alkene **1.57** and Wacker oxidation gave the methyl ketone **1.58**. The authors then used and aldol-dehydration sequence to close the cyclopentene with KHMDS to **1.59** which underwent stereoselectively reduction of the ketone under Luche conditions. The olefin was reduced utilizing the directing effect of the newly formed hydroxyl group with Crabtree's catalyst to form **1.60**. The ethyl ester was then converted via the Weinreb amide to the methyl ketone, **1.61** and underwent the Baeyer-Villiger reaction to install the oxygen required at $C_9$. The cinnamoyl ester was appended to at $C_6$ of **1.62** via a Yamaguchi esterification to give **1.63**. The acetate was then hydrolyzed and TBS-protected glycolate was appended and unmasked to reveal racemic englerin A. The Nicoloau/Chen strategy could be made asymmetric by tethering the acrylate of the key [5 + 2] cycloaddition to a

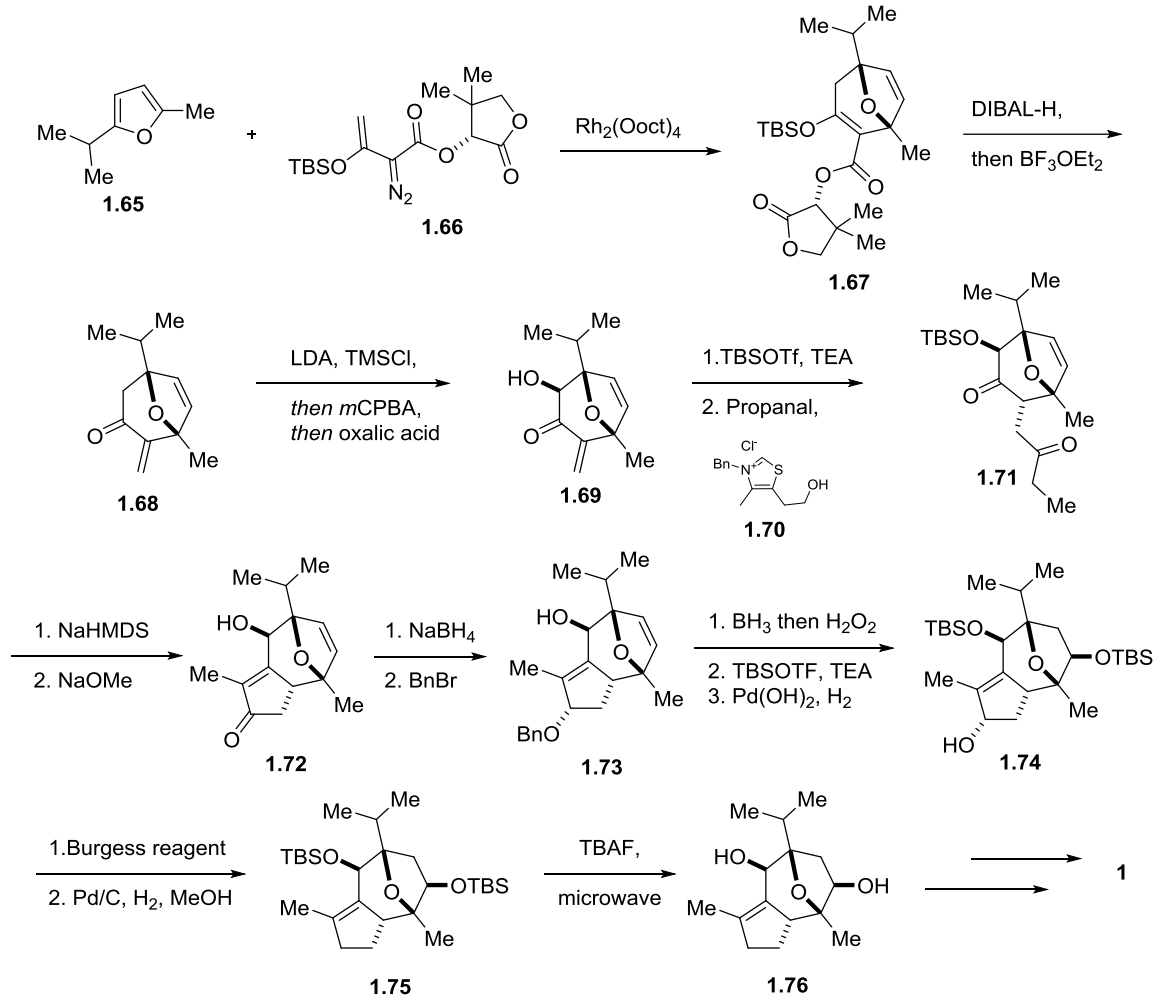
chiral sulfonamide auxiliary. This directed the *exo* addition in a 2:1 fashion favoring the desired product.




Scheme 8 Nicoloau/Chen endgame

### *1.4.2 Theadorakis*

The synthesis out of the Theadorakis group utilized an interesting [4 + 3] strategy for ring formation. The enantioselective reaction between furans and diazoesters was originally reported by Davies and coworkers in 1996. Furan **1.65** which was prepared in 3 steps from 2-methylfuran was cyclized with diazoester **1.66**, which was prepared from (*R*)-pantolactone in 3 steps. This reaction yielded the oxabicycle **1.67** in 90% yield and 3:1 diastereomeric ratio. The chiral auxiliary was then removed with DIBAL-H, and the beta-hydroxyl silyl enol ether underwent a rearrangement with $BF_3$ to furnish ketone **1.68**.



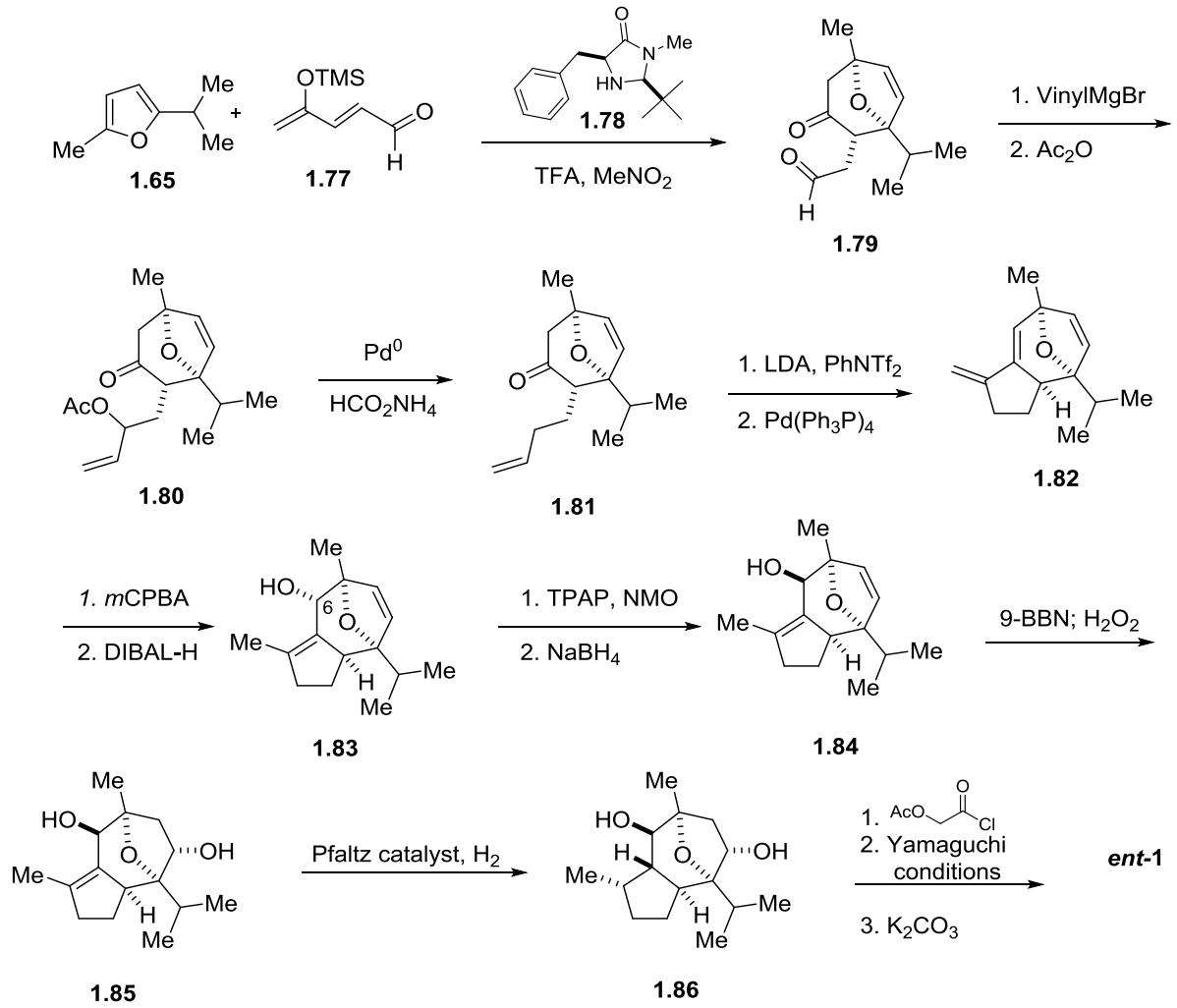

Scheme 9 Theadorakis' synthesis

A Rubottom oxidation gave alpha-hydroxy ketone **1.69**. The alcohol was protected as the silylether and the enone was subjected to 1,4-addition of propanal with the use of Stetter[17] reagent **1.70** gave the ketone **1.71**. The enone **1.72** was formed under aldol conditions followed by reduction of the carbonyl and protection of the resultant alcohol as a benzyl ester in **1.73**. Required oxygenation was installed at C-9 by means of a hyroboration/oxidation. The newly appended alcohol was protected as the TBS-ether and the benzyl group was hydrogenolyzed with Adam's catalyst producing **1.74**. Burgess reagent was then used to eliminate the free alcohol at C-3 and hydrogenation with Pd/C to **1.75** was followed by deprotection with TBAF resulted in the core structure minus the side chains **1.76**, which is part of the total synthesis of englerin reported by Ma and coworkers (*vide infra*).

### *1.4.3 Lin and Sun*

Lin and Sun[18] took an organocatalytic approach to construction of the [5.3.0] bicyclic system. The authors envisaged furan **1.65** and dienal **1.77** (both previously reported compounds) could be combined stereoselectively with the appropriate organocatalyst. The reaction was attempted with Harmata's catalyst but the yield was low. Optimal conditions were found using MacMillan's catalyst **1.78** giving **1.79** in a 2.4:1 ratio.

It was not discovered until completion of the synthesis that that product of the reaction was the opposite enantiomer of the desired target.



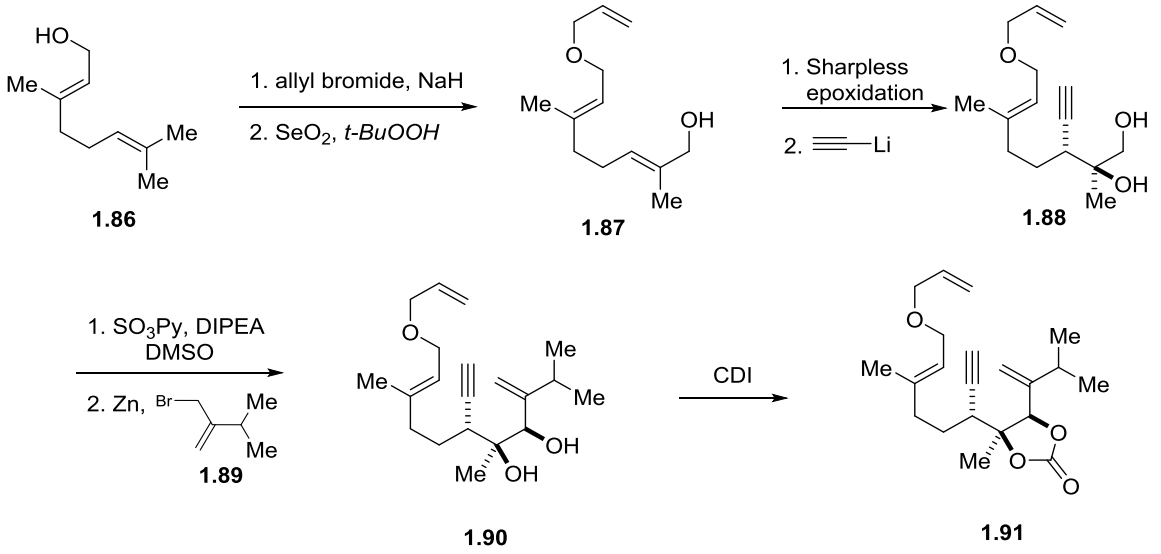

Scheme 10 Lin and Sun's synthesis

The guiane core was formed by extending the side chain with vinyl Grignard followed by an acetylation of the newly formed hydroxyl group giving **1.80.** Removal of acetoxy group was accomplished with palladium black and ammonium formate to give the terminal olefin **1.81**. The 5-membered ring was closed by a palladium-catalyzed Heck reaction of the vinyl triflate formed of the ketone enolate to give the carbon framework in

**1.82**. Epoxidation of the electron–rich double bond followed by conjugate reduction gave alcohol **1.83**. An oxidation-reduction sequence inverted the alcohol stereocenter at C-6 giving **1.84**. Hydroboration-oxidation followed by hydrogenation with Pfaltz catalyst gave diol **1.85**. Side chains were appended and deprotected, completing the synthesis of (+)-englerin A.

### *1.4.4 Parker*

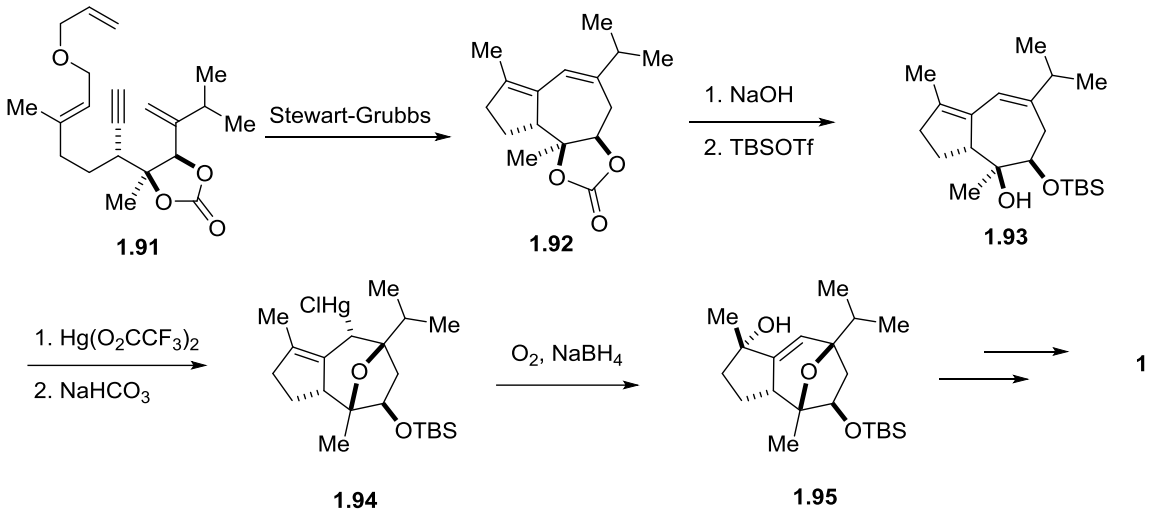
A different metathesis approach was taken by Parker. Retrosynthetically, they considered the core could be formed by a metathesis-based bicyclization of an ene-yne-ene system. The strategy, while hinging upon a ring-closing metathesis, is more reminiscent of the strategies of Ma and Echavarrin, who used a gold-catalyzed cascade to assemble the main structural elements of the molecule (*vide infra*).




Scheme 11 Parker's synthesis of RCM substrate

The ring-closing relay metathesis substrate was produced in 7 steps from geraniol, **1.86**. First the authors allylated the hydroxyl group followed by an allylic oxidation forming a free alcohol at the opposite end of **1.87**. A Sharpless asymmetric epoxidation

followed by epoxide opening with lithium acetylide formed diol **1.88**. Parikh–Doering oxidation gave the aldehyde that was subjected to Reformatsky conditions with bromide **1.89** giving **1.90**. Carbonyldiimidazole was used to protect the diol as the carbonate (**1.91)**. Using the Stewart-Grubbs catalyst, the carbon framework was assembled to give desired **1.92** in 45% yield. After removal of the carbonate and TBS protection of the secondary alcohol gave **1.93**. The oxacycle, **1.94**, was formed by an oxymercuration procedure. The demercuration of **1.94** resulted in alcohol **1.95**, which completes a formal synthesis, with 7-step procedure to **1** being reported in the synthesis by Echavarrin (*vide infra).*

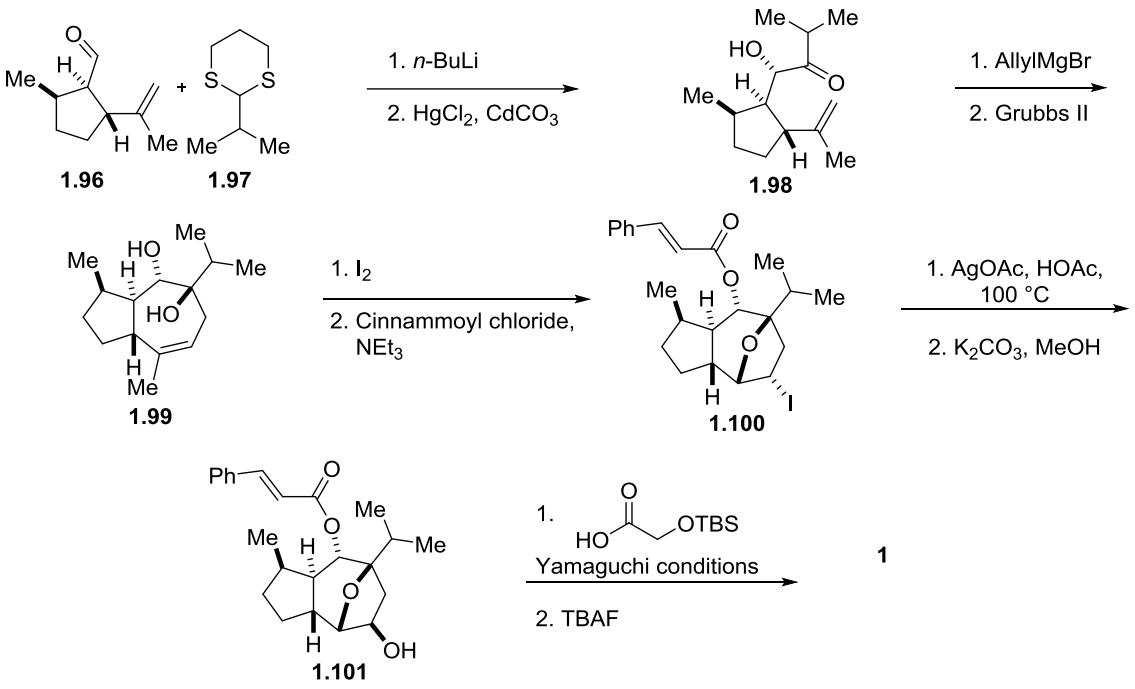



Scheme 12 Parker's endgame

### *1.4.5 Shen*

The synthesis published by the Shen group adapted and combined previous strategies towards the guaianolides.[19] Meyer was able to produce the cyclopentane ring with the appropriate stereochemistry starting with the inexpensive terpenoid (−)-carvone in 13 steps. The Shen group adapted this procedure to cyclopentane **1.96**. This cyclopentane had the isopropyl group appended with the anion of dithiane **1.97** to form **1.98** after deprotection. Like in previous syntheses the cyclohexane was then elaborated to the diene which was set up for a ring-closing metathesis giving **1.99** in this case. The oxabicycle was formed via a transannular iodonium opening and the cinnamoyl side chain

was appended at $C_6$ to produce **1.100**. Displacement of iodine with silver acetate inverted the stereocenter as required and the acetate was cleaved to the alcohol **1.101**. Yamaguchi conditions were used followed by deprotection of the glyocolate alcohol produced **1**.These authors retested englerin A against the renal cancer cell line 786-0. Surprisingly, the authors observed a $GI_{50}$ of 6.57 μM whereas the original isolation of englerin observed a $GI_{50}$ of <0.01 μM. It is unclear what accounts for this difference.



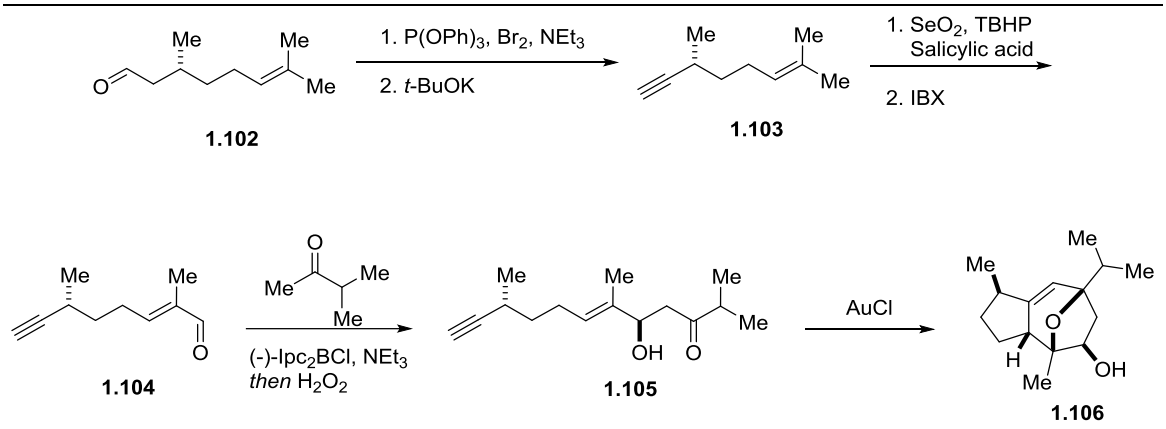

Scheme 13 Shen's synthesis

## 1.5 Gold-Catalyzed Cyclization Strategies

The total synthesis out of the Ma group was published back-to-back with Echavarren's synthesis (*vide infra*). Both syntheses utilize a gold-catalyst to "zip up" the molecular framework of the molecule.

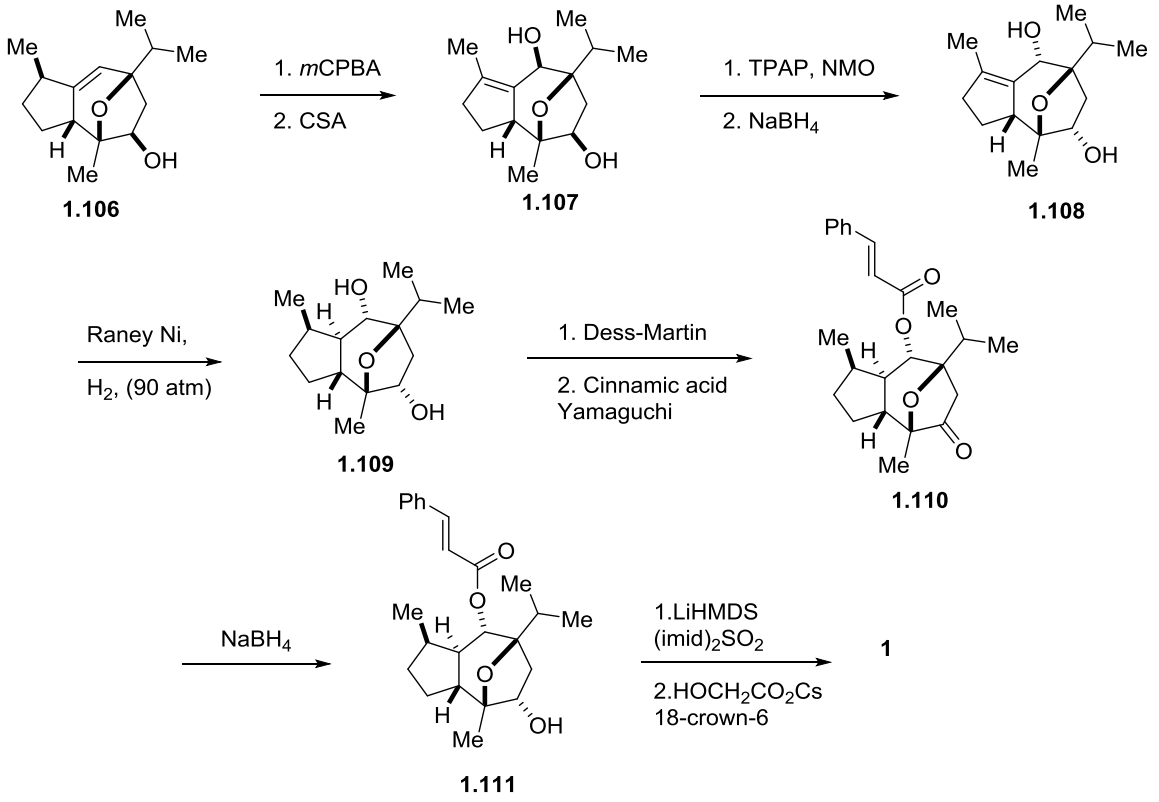
### *1.5.1 Ma*

The Ma synthesis[20] commenced with chiral starting material (*R*)-cintronellal **1.102**. From this they obtained the *gem*-dribromo olefin and eliminated with *t*-BuOK to afford the terminal alkyne **1.103**. Allylic oxidation with $SeO_2$ followed by further oxidation with IBX gave aldehyde **1.104**. This underwent a boron-mediated enantioselective aldol reaction to give **1.105**. Here they treated with **1.105** AuCl to affect the key cyclization wherein the tricyclic framework of the molecule was formed, giving **1.106**.




Scheme 14 Ma's syntheis of enlgerin framework

The alkene was then epoxidized by *m*CPBA and the epoxide opened with CSA to the diol **1.107**. Each of the hydroxyls were inverted by oxidation with TPAP/NMO followed by reduction with $NaBH_4$ to give **1.108**. The group notes extensive experimentation was required to find appropriate conditions for hydrogenation of double bond eventually finding Raney Ni in ethanol at 75 °C with 90 atmospheres of hydrogen to be efficacious. The next step in the synthesis is selective oxidation of the C-9 hydroxy group of **1.109** with DMP to protect it from the following Yamaguchi eterification with cinnamic acid which yielded **1.110**. They then return C-9 to its former hydroxyl group in **1.111** with $NaBH_4$. The free alcohol of **1.111** was first converted to a leaving group and then the cesium salt of glycolic acid is heated in the presence of 18-crown-6 to complete the synthesis.

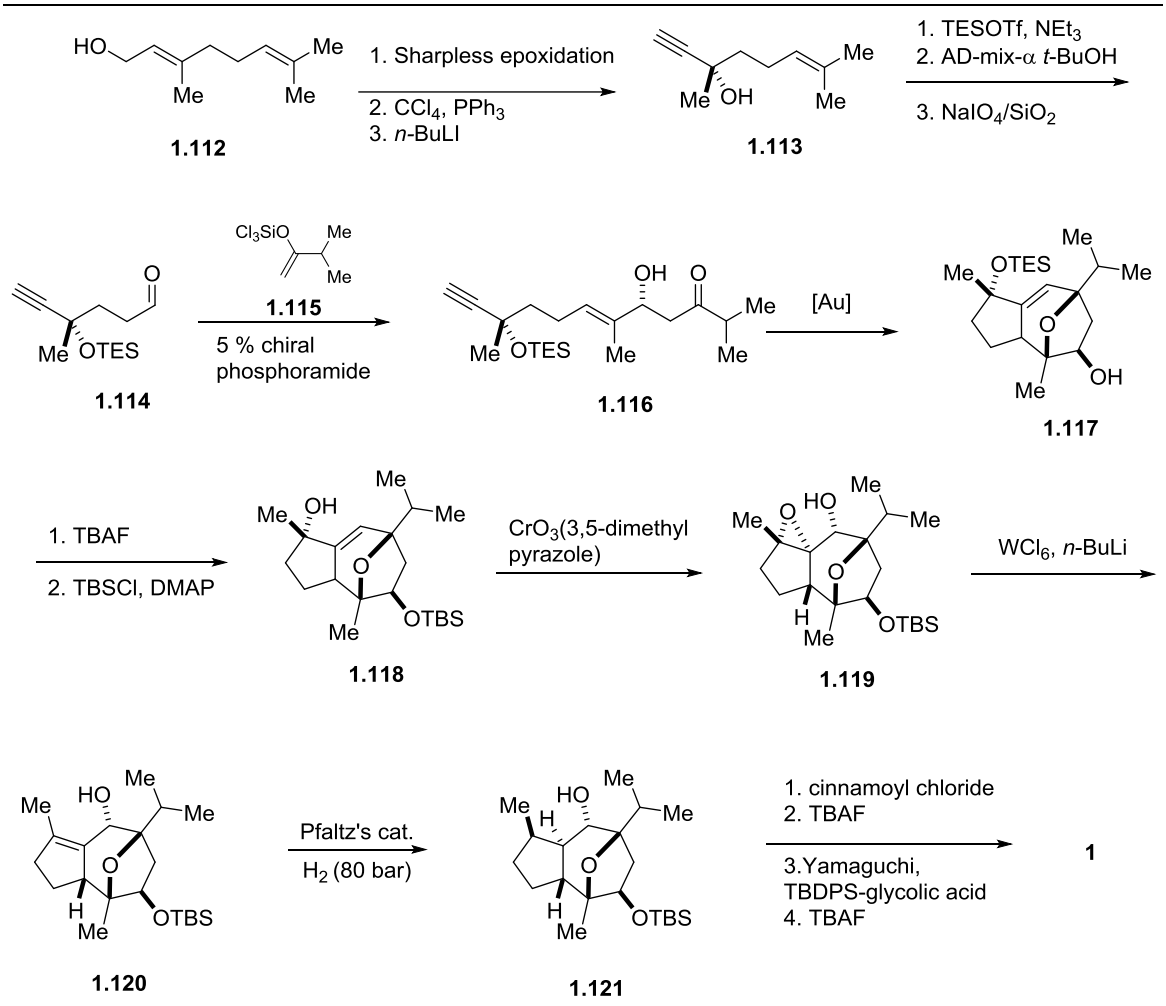



Scheme 15 Ma's endgame

### *1.5.2 Echavarrin*

The synthesis out of the Echavarrin group[21] commenced with the Sharpless asymmetric epoxidation of achiral dienol **1.112**. This was followed by replacement of the hydroxyl group with chloride and reaction with BuLi to give the terminal alkyne, **1.113**. The alcohol was protected as the TES ether and the alkene was oxidatively cleaved to afford the aldehyde **1.114**. This aldehyde underwent a chiral phosphonamide catalyzed stereoselective Denmark aldol with silyl enol ether **1.115**. Multiple protecting groups were tried but the authors reported the unprotected alcohol **1.116** underwent the gold-catalyzed cyclization best affording **1.117**. With the carbon framework assembled, the authors did a protecting group swap to get **1.118** and epoxidized the olefin obtaining **1.119** which was then reduced by $WCl_6$ and *n*-BuLi to afford **1.120**. Hydrogenation was done with Pfaltz's catalyst under 80 bar $H_2$ to give **1.121**. Side chains were appended with cinnamoyl chloride

followed by deprotection with TBAF. Yamaguchi conditions were used to append the protected glycolate ester followed by TBAF deprotection completing the synthesis.



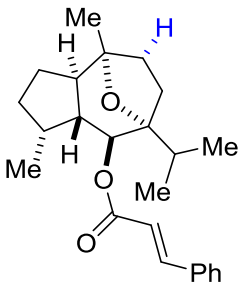

Scheme 16. Echavarren's synthesis

## 1.6 Unnatural Analogs

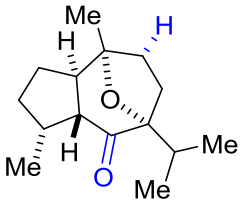
### *1.6.1 Maier Analogs*

The Maier group tested the 9-desoxyenglerin analog and found that replacing the glycolate group with hydrogen caused a slight loss in potency against multiple cell lines.

However, when replacing C-6 cinnamoyl group with a carbonyl, the molecule was essentially inactive.[22]




**1.122**




**1.123**

essentially inactive IC50 > 170 uM

Figure 2 Maier analogs

Table 1. *Cytotoxicity ($IC_{50}$ in μM) of englerin A (**1**) and analog **1.122***

| Compound | L-929 | A-498 | KB-3-1 | MCF-7 | HUVEC |
|---|---|---|---|---|---|
| **1** | 29 | 0.4 | 12 | 18 | 4.3 |
| **1.122** | 65 | 35 | 41 | 41 | 9.8 |

L-929 (mouse fibroblasts), A-498 (renal cancer cell line)

KB-3-1 (HeLa cells), MCF-7 (breast cancer cells)

HUVEC (primary endothel cells). Compound **1.123** was essentially inactive

### *1.6.2 Christmann Analogs*

The Christmann group completed a tour de force SAR study by making substitutions at three different positions.[9] Many variations were made at the cinnamoyl (C in figure 3) and glycolate esters (A in Figure 3). Also substituted were the smaller alkyl

groups for the isopropyl group (B in Figure 3). Most notably, the 3-napthoate produced a 2-fold activity enhancement with better selectivity (>30 μM $IC_{50}$).

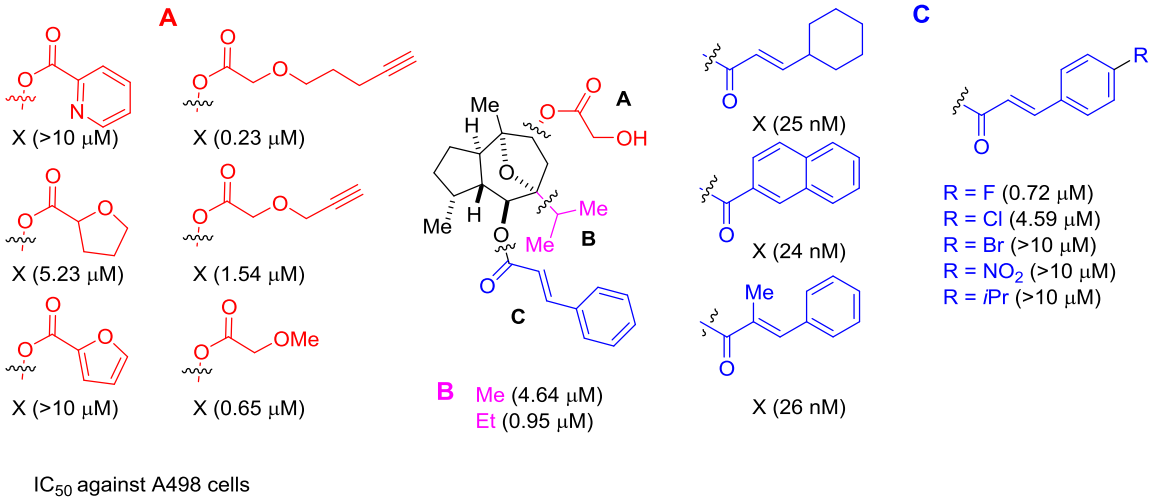
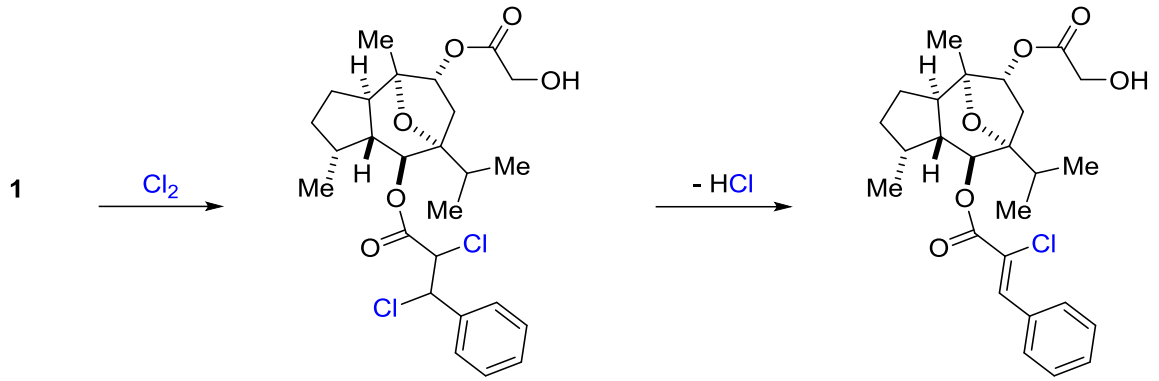



Figure 3 Selected Christmann analogs

### *1.6.3 Beulter Analogs*

Akee and coworkers[23] at the NCI created chlorinated analogs of englerin by the addition of an equivalent of $Cl_2$ across the olefin of the cinnamoyl chain. None of the analogs produced gave better results against renal cancer cell lines than englerin itself, but the authors note that analogously fluorinated or iodinated analogs could be used as tracer compounds with isotopically enriched halogens that may be useful for biological studies of distribution or metabolism.




Scheme 17. Beulter chlorinated analogs

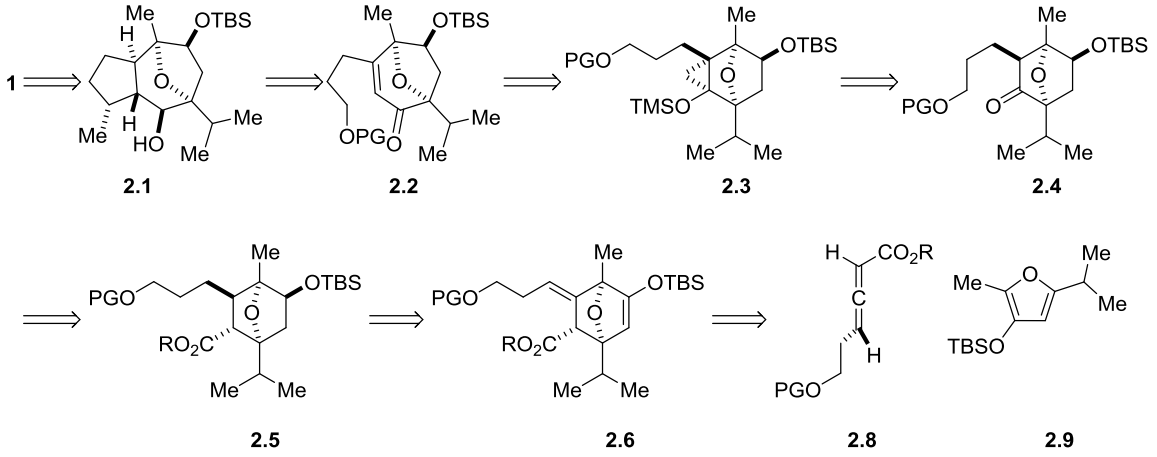
# Chapter 2 Synthetic Efforts Toward a Total Synthesis of Englerin A

### *2.1.1 Introduction*

Our desire to attempt a synthesis of englerin a stemmed from our interest in axially chiral allenes and the ability to deploy them for chirality transfer and rapid complexity building. Already underway were studies on rhodium-catalyzed cycloadditions with allene carboxylates as dipolarophiles.[24] When the report of the isolation and biological activity came out, we were intrigued. We believed using an axially chiral allene would be an excellent strategy for its synthesis and derivatization; its remarkable biological activity made it that much more appealing.

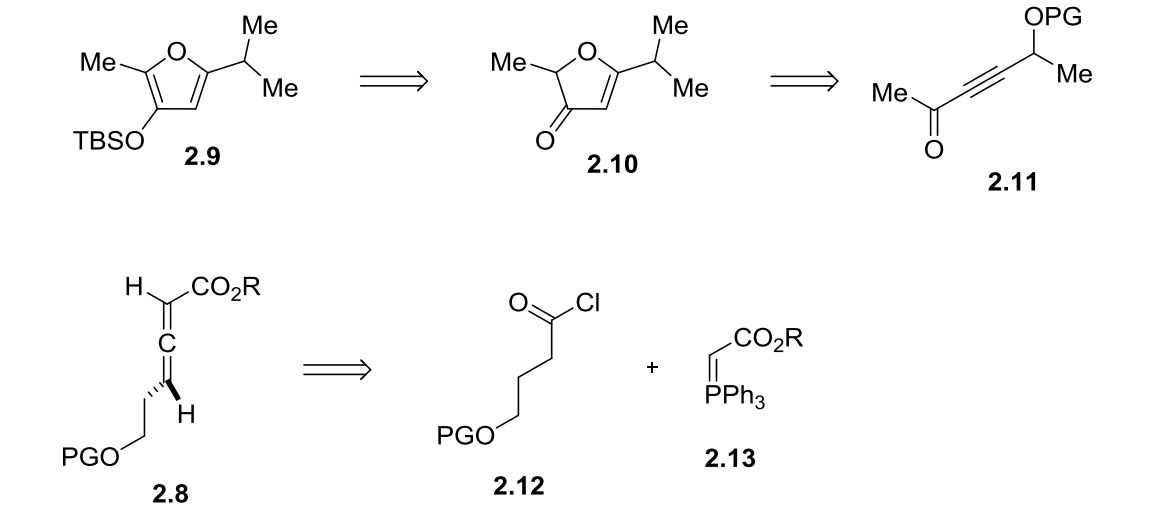
## 2.2 Retrosynthesis I

We believed the glycolate at C-9 and the cinnamoyl ester at C-6 would come from the protected diol **2.1** (Scheme 18), which could be made by the annulation of the side chain branching from C-1. **2.2** would come from the ring expansion of cyclopropane **2.3**.[25] We believed we could access this structure by the cyclopropanation of silyl enol ether of **2.4** which is derived from the ozonolysis of the silyl enol ether of ester **2.5** and hydrogenation of both olefins in **2.6**. This oxacycle is the result of a Diels-Alder reaction between our enantioenriched allene **2.8** and 3-siloxyfuran **2.9**.




Scheme 18 Retrosynthesis I

Our 3-siloxyfuran **2.9** would come from furanone **2.10** (Scheme 19). Furanones of this kind have been shown to be produced readily from alkynones such as **2.11.** Our allene, at least to begin with, would be made in racemic fashion from an acid chloride and a stabilized Wittig reagent, **2.13**.[26]




Scheme 19 Retrosynthesis of furan and allene

Our approach to englerin A utilizes a Diels-Alder reaction between a 3-siloxyfuran and an electron-poor, axially chiral allene. [27–32] We believed this approach was appealing for a few reasons. We believed the Diels-Alder reaction would serve to set two stereocenters directly and those could be used as a template to direct the other five. This reaction should be stereospecific with respect to the approach of the furan as the $R^2$ group will block approach from the opposite face. We decided to see if this approach was commonly used but could only find a few examples in the literature of allene-furan Diels-Alder reactions.[27–32] There was only one single example of allenes being used to direct the stereochemical outcome of the reaction and that reaction is intramolecular.[33]

## 2.3 Allenes

### *2.3.1 Introduction to Allenes*

Allenes are an interesting class of molecules. The defining characteristic is the cumulated α,β-double bonds with their orthogonal π systems. Allenes can be found in more than 150 natural products[34] and are useful for synthesis. Until recently, they were thought of as unstable moieties. The strain of an allene arises from the inflexibility of the cumulated π-π system. While not quite as unstable as their reputation would lead one to believe, they are more reactive than alkenes due to their strain, a fact we noted ourselves in our exploration of the Diels-Alder reaction when switching from allenes to alkenes (*vide infra*). One aspect which makes them particularly useful is their axial chirality. Rather than arising from a point, like a tetrahedral carbon, the four substituents that makes the allene chiral are connected by an axis defined by the 3 cumulated carbons.

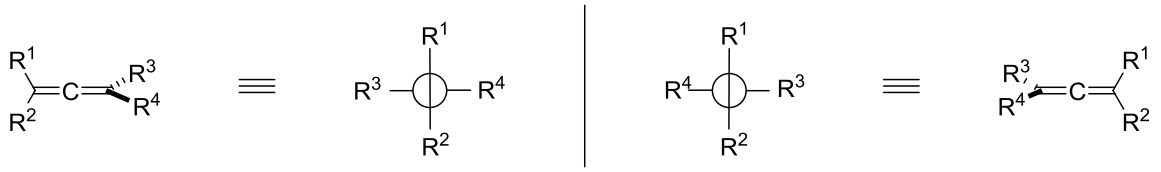
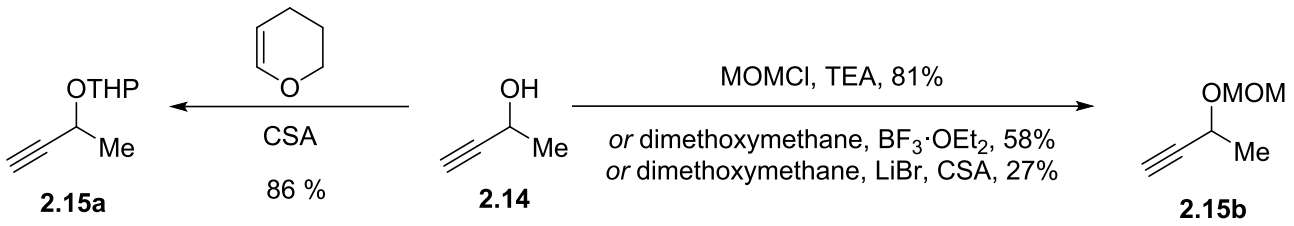


Figure 4 axially chiral allenes

## 2.4 Synthetic endeavors

### *2.4.1 First generation furan synthesis*

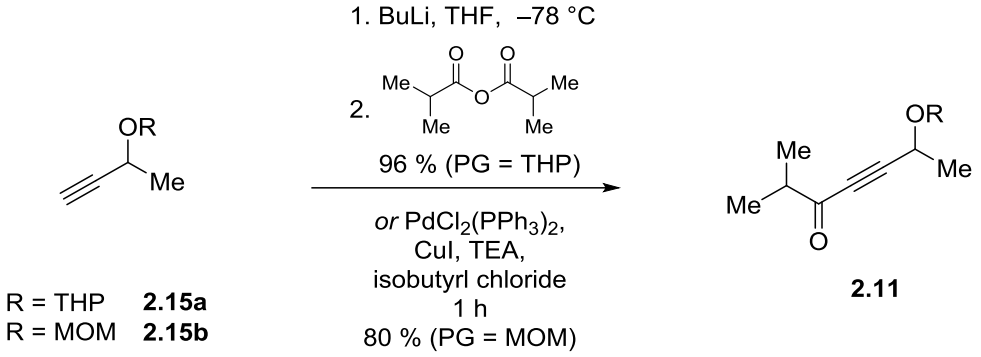
Initially our furan was formed starting with 3-butyn-2-ol, **2.14**. The hydroxyl group was protected as a THP (**2.15**), but this was found to make the spectral interpretation unnecessarily difficult due to the formation of diastereotopic protons. Subsequently, a MOM group was instead used instead, greatly simplifying spectra. MOMCl is a convenient reagent for the introduction of MOM group but suffers the drawback of being highly carcinogenic.




Scheme 20 Protection of 3-butyn-2-ol

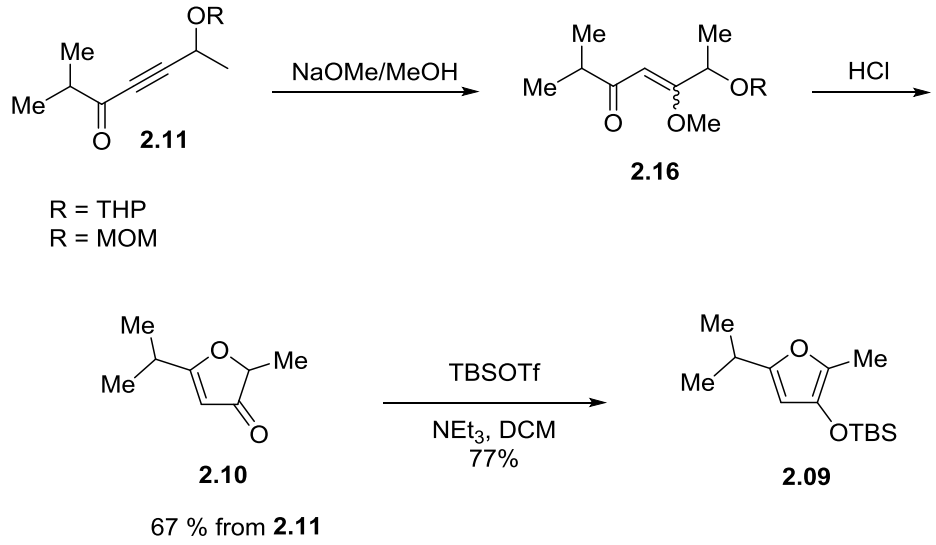
We found a MOM group could be introduced by utilizing dimethoxymethane and zinc bromide and an organic acid. *para*-Toluenesulfonic acid was used in the literature,[35] we found anhydrous camphorsulfonic acid was readily available and worked just as well. Alternatively, we found that stoichiometric $BF_3 \cdot OEt_2$ also catalyzed the reaction. This

method to introduce the MOM protecting group suffered from the drawback of necessitating the use of dimethoxymethane in solvent quantities in order to drive the equilibrium to products.




Scheme 21 Preparation of alkynone **2.11**

Initially, we believed a lithium acetylide addition into isobutyric anhydride would be a good strategy for the production of **2.11**. While this strategy did produce **2.11** in good yield, we later found a more convenient palladium-catalyzed, Sonogashira-type coupling could be utilized to couple our protected alkynol to isobutyryl chloride to produce alkynone **2.11**. This reaction was far more convenient, being run at room temperature, and the reaction only required one hour for complete conversion.

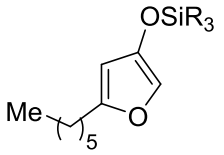



Scheme 22 Synthesis of furanone **2.09**

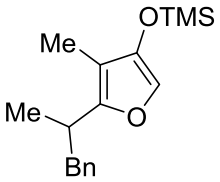
Our next step was to convert the alkyne to a masked enolate **2.16**. At first, we reasoned methanol could be induced into a conjugate addition by activation of the alkynone with a Lewis acid. Where this strategy failed; simply adding **2.11** to a solution of sodium methoxide in methanol succeeded in converting it into the masked enolate **2.16** quite rapidly. In the same pot, concentrated hydrochloric acid hydrolyzed both the protecting group. The methoxy group and the transient dienol then cyclized to form the furanone **2.10**. With this in hand, the furan was ready to be formed. Simply treating **2.10** with TBSCl and TEA did not afford product; the more reactive TBSOTf was required when triethylamine was used as the base. We later found that the use of DBU, a stronger base, would allow us to use the more convenient TBSCl (*vide infra*).

Our early attempts at making this furan often led to impure material; standard silica gel chromatography was not compatible with the substrate. Early on, we simply coped by using impure furan and accepted that the impurities would not be removed until after hydrogenation of the Diels-Alder adduct.

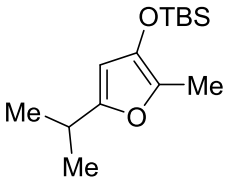
### *2.4.2 Chromatography of 3-Siloxyfurans in the Literature*




**2.17**, R = Me
**2.18**, R= *i*-Pr




**2.19**




**2.10**

Figure 5 3-siloxyfurans

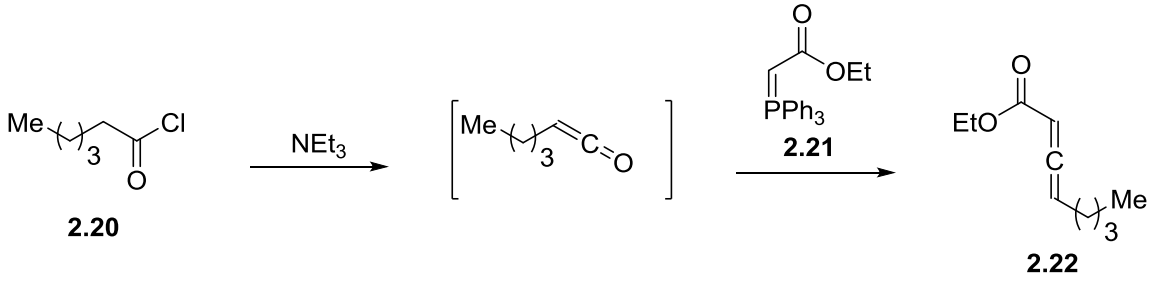
While there is currently no mention in the literature of the instability of siloxyfurans (with small silyl groups) to chromatography with neutral solvents, the literature implies as much.

Winkler[36] and coworkers prepared two 5-hexyl-3-siloxyfurans **2.17** and **2.18** (Figure 5). When the protecting group is triisopropylsilyl **2.18**, the authors used hexanes on silica for purification, yielding product quantitatively. It is not surprising that when the much more labile trimethylsilyl version was synthesized, it was not subjected to similar chromatography but was instead treated with pentane and the product was decanted from the lithium salts from LDA yielding **2.17** 98% yield.

This can be contrasted with the report from Poonoth and Krause[37] who produced a 4,5-substituted trimethylsiloxyfuran **2.19** in just 49% yield after chromatography on silica with 10:1 cyclohexane:ethyl acetate. Our observations generally mirrored those we found in the literature. Treatment of **2.9** by standard silica gel chromatography generally led to decomposition of furan and very poor recovery. We also tried basic alumina and Florisil as stationary phase. The alumina, like the silica gave decomposition. The Florisil gave poor resolution as the furan and silanol often co-eluted. We ran into the same problem using a small percentage of triethyl amine in hexanes; the solvent was too polar and separation was not cleanly achieved. We later found a more elegant solution to this problem which will be discussed later in this chapter (*vide infra*).

## 2.5 Testing the Model System Diels-Alder Reaction

In order to assess the likelihood of success of our synthesis, we needed to set ourselves up to test the key reaction. Rather than expend the time and resources to produce the allene precursor we felt would be required, we believed it prudent to test the reaction on an easily synthesized model system first. Hexanoyl chloride **2.20** was treated with triethylamine to produce the ketene *in situ* by elimination of HCl. Stabilized Wittig reagent **2.21** was allowed to react with the ketene to produce our racemic allene **2.22** after chromatography.




**2.20** **2.22**

Scheme 23 Synthesis of allene **2.22**

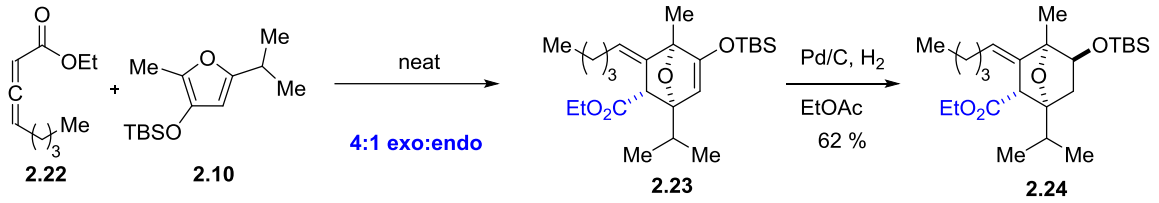
Our next objective was to validate our key step, the Diels-Alder reaction between our 3-siloxyfuran and our electron-poor allene. We reasoned that a polar solvent may promote the reaction and decided ethyl acetate would be a good first choice of solvent. No reaction was seen, however, when mixing the two reagents in ethyl acetate at room temperature or at reflux. Even refluxing toluene failed to produce product in a meaningful yield.

Dramatic rate accelerations of Diels Alder reactions have been seen in lithium perchlorate/ether solutions, likely owing to the high solvent pressure of this system.[38] This system did seem to produce product, unlike our previous attempts, but the rate and conversion was not as good as desired. We found that running the reaction without any solvent at room temperature did produce our Diels-Alder adduct in good yield within about two days. Due to the instability of the TBS enol ether, we opted not to isolate the product

of the Diels-Alder reaction. Instead, we subjected the crude product to hydrogenation conditions.

### *2.5.1 Attempted Hydrogenation of the Diels-Alder adduct*

The adduct **2.23** was subjected to palladium on carbon in ethyl acetate under hydrogen at atmospheric pressure. After one day, **2.24** was isolated in 62% yield in a 4:1 *dr*. Initially, we were surprised at the hydrogenation of only the enol ether and not the exocyclic olefin. We attempted a series of hydrogenation methods and catalysts in order to exhaustively hydrogenate our Diels-Alder adduct. We attempted the reaction at a higher pressure of hydrogen (50 psi) in a Fisher-Porter tube. Unfortunately, after 16 h, this only affected the hydrogenation of the enol ether and not the exocyclic double bond.

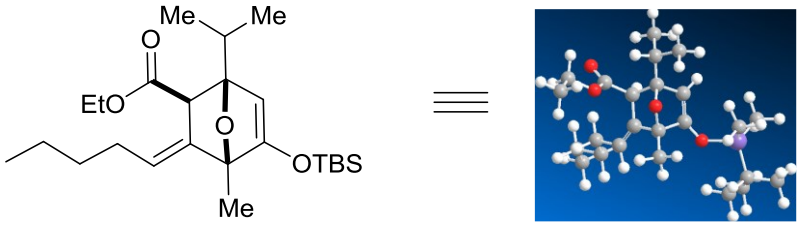



Scheme 24 Diels-Alder with **2.22**

### *2.5.2 Double-Bond Isomerization*

Another strategy was to isomerize the exocyclic double bond into conjugation, then use a hydride donor to do the conjugate reduction. DBU is a strong, non-nucleophilic base that seems to be the choice reagent for basic isomerizations of olefins.[39] By NMR, the reaction did not produce the desired product and only caused some decomposition of starting material.

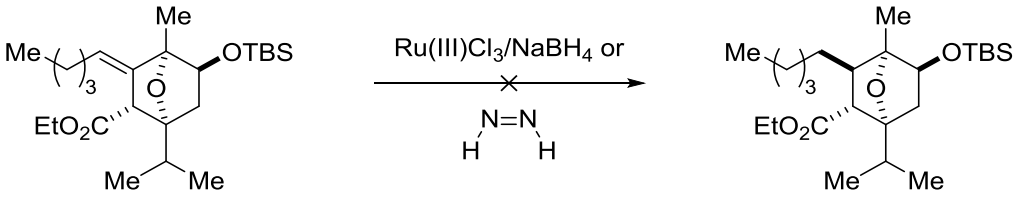
### *2.5.3 Alternate Hydrogenation Attempts*




**2.23**

Figure 6 Steric hinderance of our oxabicycle **2.23**

We hypothesized that this exocyclic double bond was so recalcitrant because of its sterically hindered environment. When viewing a model of **2.23**, in three dimensions both double bonds appear to be quite sterically hindered; there is however free rotation around the O-Si-C bonds that allow for the TBS protecting group to move out of the way of the incoming hydrogenation catalyst. The exocyclic double bond does not have this ability. The methyl group and the ethyl ester both have some free rotation available, but these rotations do not relieve steric congestion, as they are still held in the space over the exocyclic olefin in the approaching path of hydrogenation catalyst. Approach from the bottom face is blocked by the opposite side of the oxacycle. Due to these constraints, we theorized that a homogenous catalyst may be beneficial due to the smaller size of the catalyst and removing the requirement of adsorption onto catalyst surface.

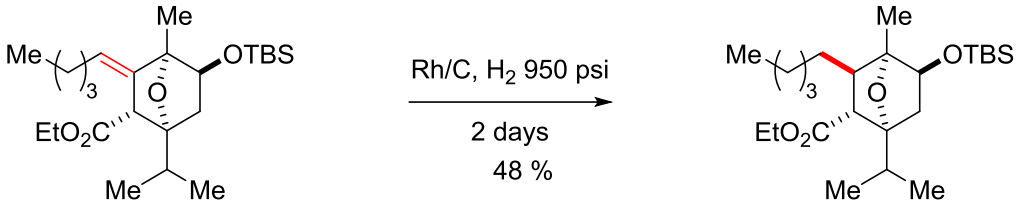



**2.24** **2.25**

Scheme 25 Reduction attempts with some homogeneous reagents

This led us to try ruthenium chloride/sodium borohydride.[40] When this reaction failed to produce the desired product we turned our attention to diimide,[41] ($N_2H_2$) a reducing agent comprised of just 4 atoms that works by transferring an equivalent of hydrogen and giving $N_2$ as a by-product. This strategy also failed despite the sterically unassuming size of the reagent.

### *2.5.4 Hydrogenation with Higher Pressures of Hydrogen*




**2.24** **2.25**

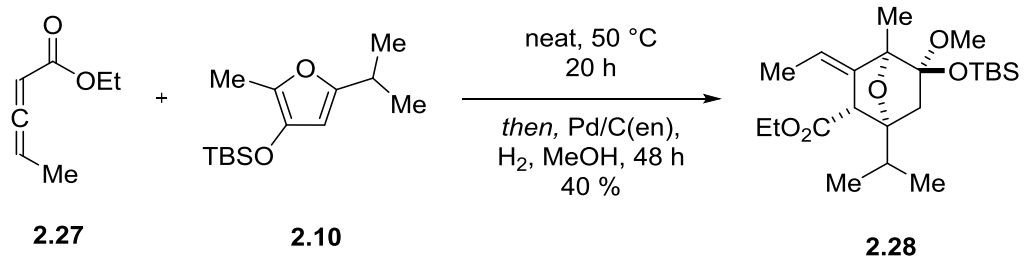
Scheme 26 Successful hydrogenation of **2.24**

At this point we believed the best option was to screen different catalysts at increasing pressures of hydrogen. A Fisher-Porter tube was utilized to apply 40 psi of hydrogen gas over a mixture of **2.24** and one of the following: palladium on carbon, rhodium on carbon, rhodium on alumina, Adam's catalyst (platinum oxide), or Crabtree's catalyst. After one day, only hydrogenation of the silyl enol ether was seen. The same result was seen when the experiment was repeated with 400 psi of hydrogen. It was not until 950 psi of hydrogen was applied for 16 hours did we see evidence of hydrogenation of the exocyclic double bond and this was only with rhodium on carbon as a catalyst. Further experimentation showed two days of hydrogenation with rhodium on carbon would convert **2.24** into **2.25** in moderate yield (Scheme 26).

### *2.5.5 Idiosyncratic behavior of palladium on carbon-ethylene diamine complex*

Palladium coordinated with ethylene diamine (Pd/C(en)) was developed as a chemoselective hydrogenation catalyst that would not cause hydrogenolysis of functional

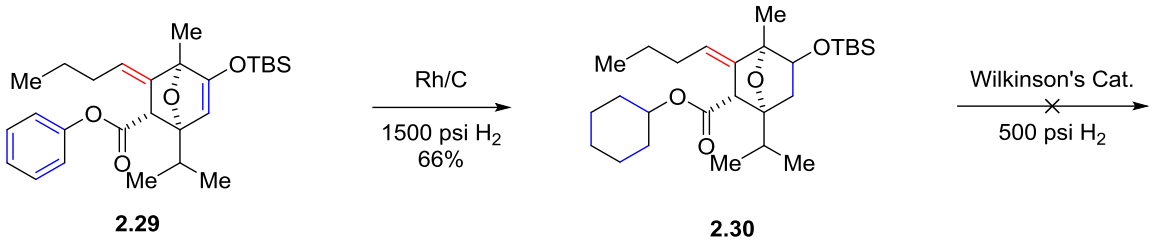
groups like benzyl esters CBz-amines but has found use for hydrogenation where Pd/C would normally cause de-silylation.[42] It was recently used in the Metz synthesis of englerin so as to not affect the TBS ether in **1.34** (Scheme 4). Seeing as de-silylated compounds made up a portion of our reaction products for hydrogenation, we decided to attempt the reaction with Pd/C(en) after the Diels-Alder between **2.27** and **2.10** (Scheme 27). At room temperature with 1 atmosphere hydrogen, we observed a product that no longer bore the enol but had an additional three protons as a singlet. Upon further investigation, we determined that rather than an equivalent of hydrogen adding across our double bond, an equivalent of solvent methanol did. Our main product was **2.28** after column chromatography.




Scheme 27 Addition of methanol across enol

### *2.5.6 Hydrogenation with Phenyl Ester*

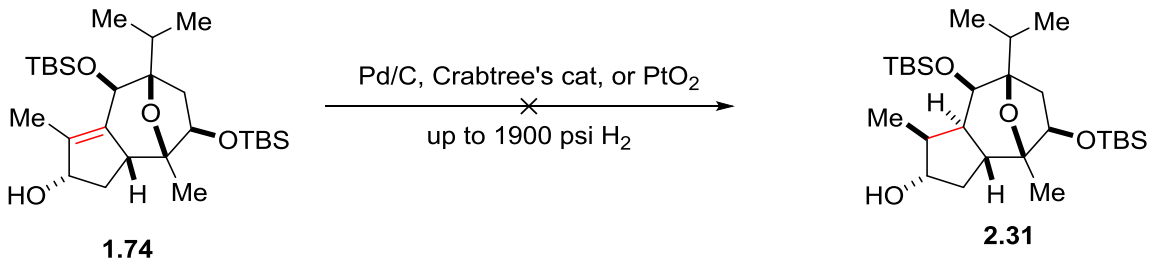
To give the reader an idea of the recalcitrant nature of the exocyclic olefin to hydrogenation, we later attempted hydrogenation of the phenyl ester, **2.29**, with rhodium on carbon and 1500 psi of hydrogen, overnight. The major product took up four equivalents of hydrogen, one on the enol ether, and three in the phenyl group. The exocyclic double bond remained, however. This product was used to test Wilkinson's catalyst, which also failed.




Scheme 28 An unexpected hydrogenation

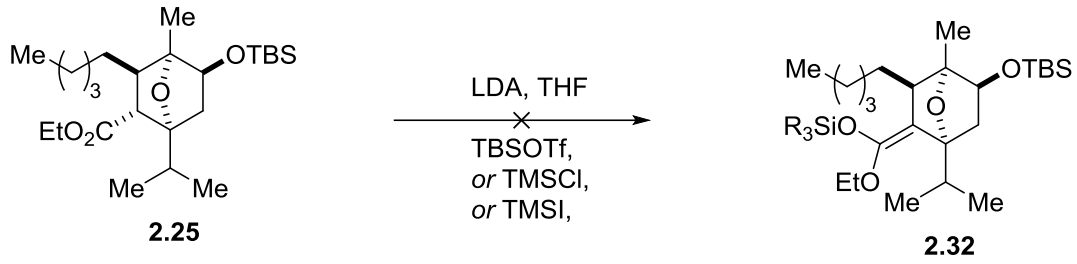
### *2.5.7 Similar Hydrogenation Issues*

We were not surprised to find that the Theadorakis group also reported difficulties hydrogenating a similar system. Their attempts to hydrogenate **1.74** with palladium on carbon, Crabtree's catalyst or Adam's catalyst to obtain **2.31** all failed even with pressures up to 1900 psi.




Scheme 29 Hydrogenation issues from Theadorakis

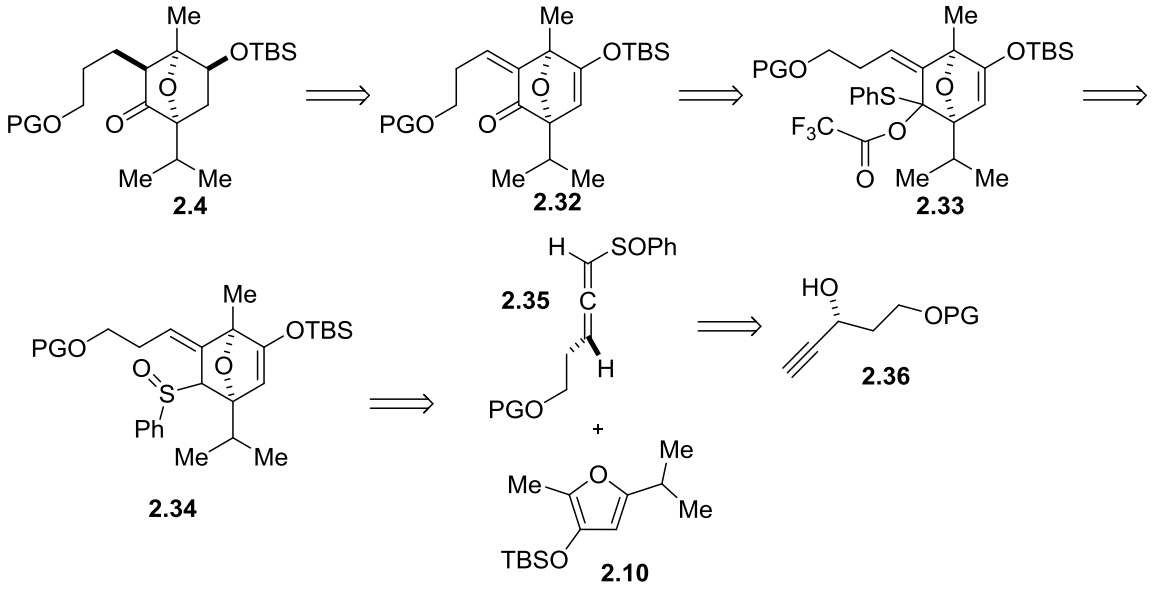
Our next task was to attempt the formation of the silyl enol ether **2.32** (Scheme 30) such that ozonolysis of the enol ether would produce the requisite ketone **2.4**. After our difficulties with hydrogenating the exocyclic double bond it should come as no surprise that the hydrogen alpha to the ester did not appear to be accessible by LDA. Repeated attempts at treating **2.25** with LDA and TBSOTf, TMSCl, or TMSI, failed to give **2.32**, and simply returned starting material. Because we saw the difficulty of deprotonation of ester **2.25**, we decided to attempt an alternative strategy.




Scheme 30 Attempted Silation of **2.25**

## 2.6 Retrosynthesis II

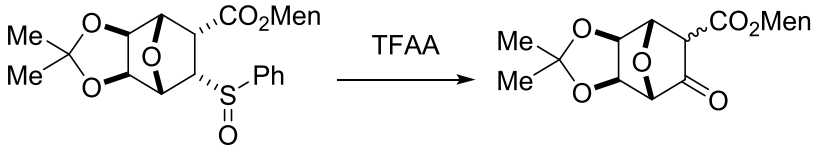
With our failure to deprotonate the ester in mind, we decided to attempt to access ketone **2.4** by the hydrolysis of **2.32** which we believed could be formed from the hydration of the intermediate **2.33** which is formed by a Pummerer rearrangement of sulfoxide **2.34**. The oxacycle could be formed from our siloxyfuran **2.10** and a sulfoxide-substituted allene[43] **2.35** which would come from alkynol **2.36**.




Scheme 31 Retrosynthesis II

We believed this route had many merits. First, we were inspired to see Takahashi and coworkers[44] were able to affect a Pummerer rearrangement on an oxacycle **2.37** to

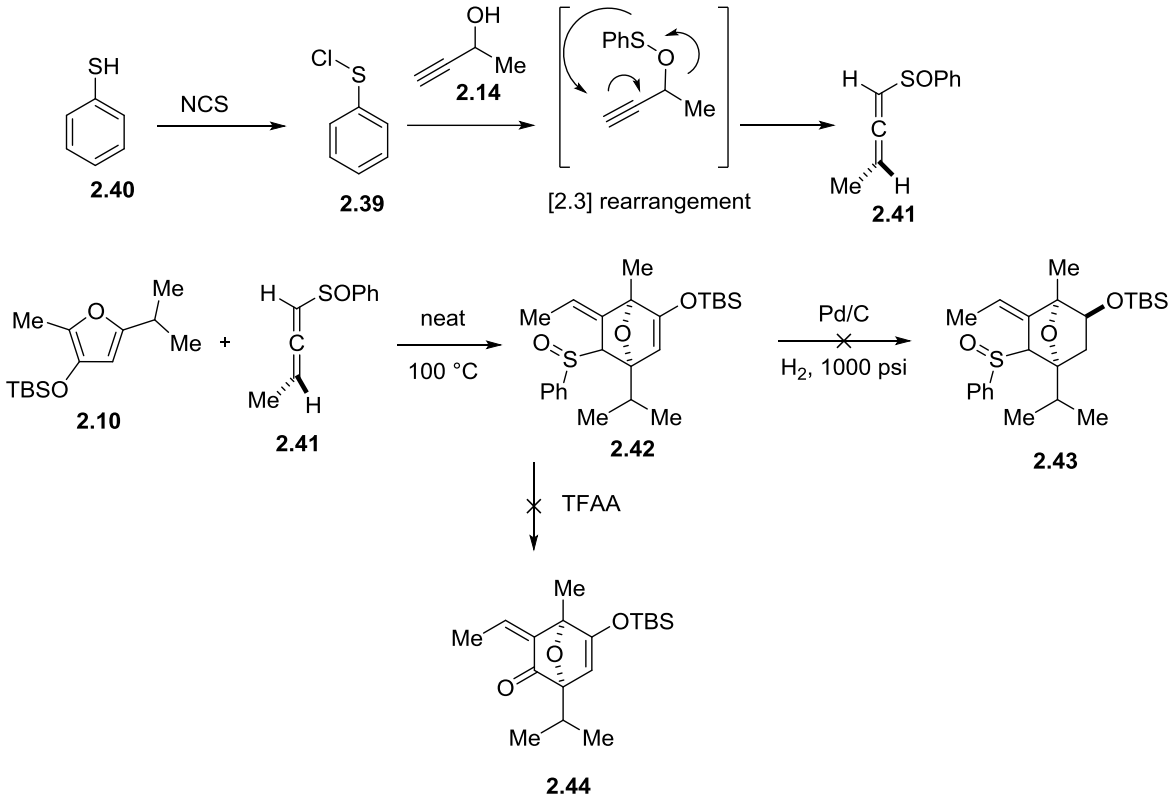
produce **3.38** (scheme 32). Also, it has been shown that sulfoxides can be made stereoselectively by the spontaneous [2,3] rearrangement, formed by the addition of organo-sulfinyl chloride to an alpha, beta alkynol which is greatly to our advantage as we would require one enantiomer of the sulfoxide for an enantioselective synthesis.[45]




**2.37** **2.38**

Scheme 32 Takahiashi's example of Pummerer rearrangement

We began our new synthetic route by synthesizing phenyl sulfinyl choride **2.39** from toluenethiol **2.40** and *N*-chlorosuccinimide by a known procedure (Scheme 33).[46] This reagent was then used in the reaction with 3-alkyn-2-ol **2.14** to give us our racemic sulfoxyallene **2.41**. When we subjected **2.41** to our standard Diels-Alder conditions, neat and room temperature, we did not see product formation, in fact, the siloxyfuran and the allene were not miscible and the mixture was biphasic. When we heated the reaction to 100 °C, we were able to observe a 95% conversion by NMR. Unlike our ester-substituted bicycle, when we attempted hydrogenation of **2.42**, we did not observe, the product of enol ether hydrogenation, **2.43**. Our attempts at hydrogenation of the **2.42** returned starting material, even at high pressures of $H_2$. We attribute this failure to hydrogenate due to poisoning of the catalyst by the sulfoxide. At this point we figured we should attempt the Pummerer rearrangement; sulfoxide **2.42** was then treated with trifluoroacetic anhydride. The crude NMR spectrum of the crude product indicated good conversion of starting material and this new material was subjected to hydrogenation conditions to allow us to isolate a more stable product that does not bear an enol ether. Unfortunately, from the NMR we could tell that this material was not our desired ketone **2.44**. Viewing these results retrospectively, it is likely that this compound underwent a retro-Michael reaction. This retro-Michael mode of reactivity of oxabicycles will be discussed at greater detail later in this chapter.

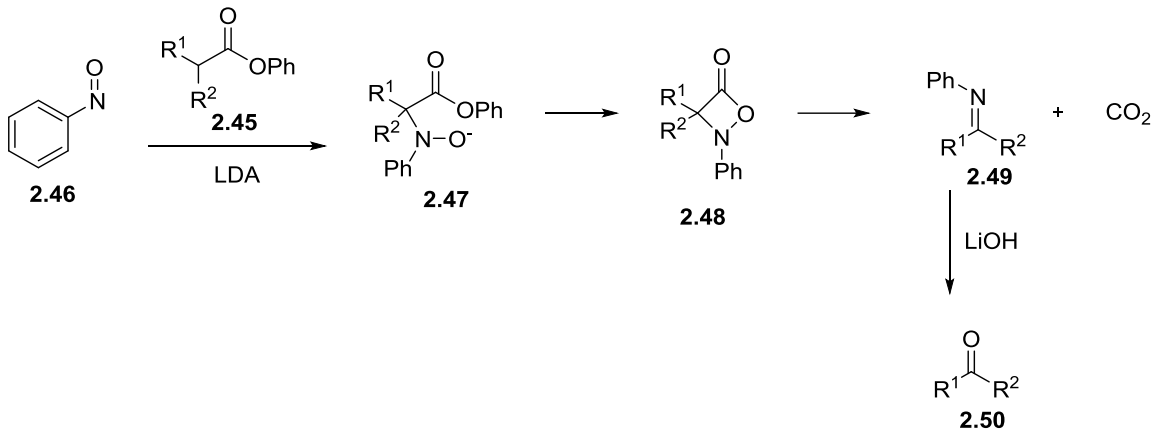



Scheme 33 Attempts with sulfoxides

### *2.6.1 Oxidative Decarboxylation*

At the same time as the above studies, we noticed a publication from the Yamamoto group on oxidative decarboxylations of phenyl esters that we believed may be helpful. The reaction proceeds as follows: a phenyl ester **2.45** is deprotonated with LDA which then attacks nitrosobenzene **2.46**. Newly formed oxyanion of **2.47** then displaces the phenoxide to form oxazetidin-4-one intermediate **2.48** which is unstable and rapidly decomposes to

the imide **2.49** and carbon dioxide. This intermediate is hydrolyzed by aqueous lithium hydroxide and yields the ketone **2.50**.

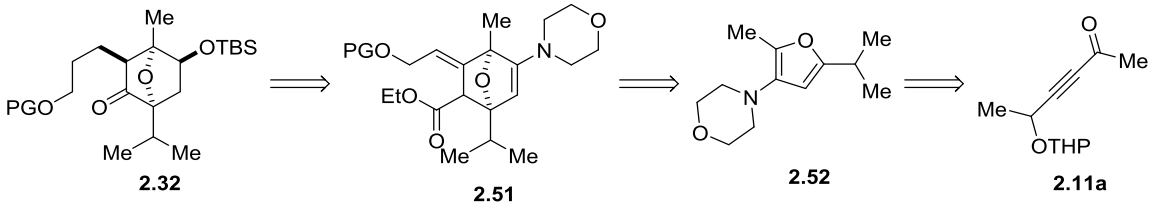



Scheme 34 Yamamoto's oxidative decarboxylation

In order to attempt to test this tactic, we formed the phenyl allenoate via our previous Wittig route. This allene was then used in a Diels-Alder reaction with our siloxyfuran **2.10** to form the oxacycle under our standard conditions. Unfortunately, but somewhat predictably, no product was obtained upon treatment of this species with LDA and nitrosobenzene and only starting material was returned.

Given our difficulty in accessing the α-hydrogen, coupled with the fact that the enol ether of the siloxyfuran appeared to be sensitive, we decided to attempt a slightly different strategy that would not require a bulky silicon protecting group. We wondered if that group was blocking the approach of the base from the bottom face of the oxacycle. With this idea in mind, we designed a route utilizing a morpholine-substituted furan.

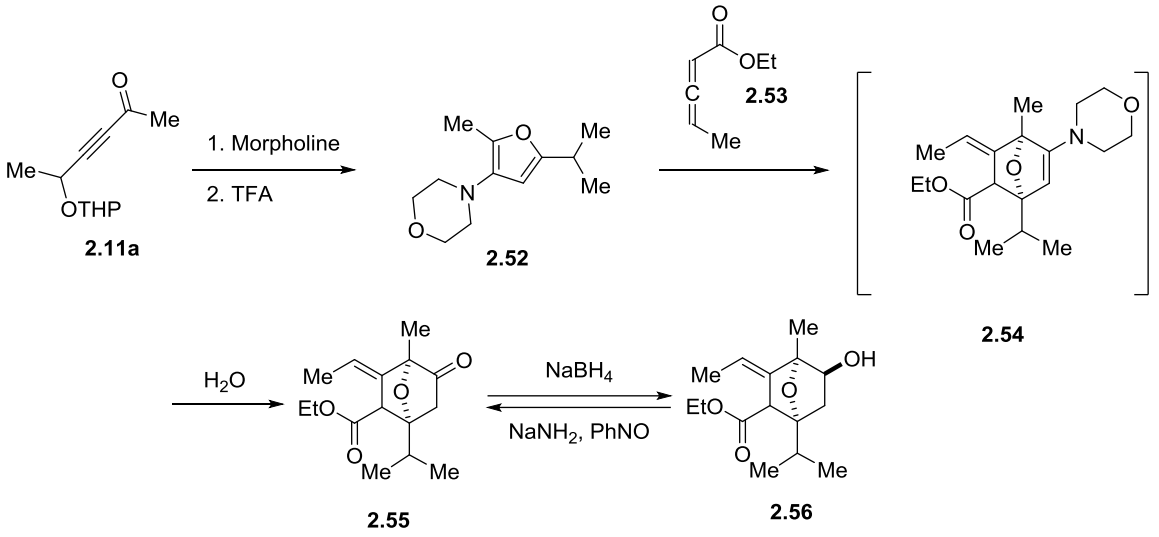
Retrosynthetically, our new route would converge with our old route at **2.32**. This oxacycle would be formed by the hydrogenation of the exocyclic double bond. This ketone would come from the oxidative decarboxylation of **2.51** and reduction/ TBS protection of C-9 ketone. We believed we could obtain **2.51** by the Diels-Alder reaction of the morpholine-substituted furan **2.52** and our allene followed by acidic hydrolysis.[47] Furan **2.52** would come from the addition of morpholine to **2.11a**.




Scheme 35 Morpholino furan retrosynthesis

Our alkynone **2.11a** was treated with morpholine followed by TFA to produce our new furan **2.52**. This was combined neat with allene **2.53** at room temperature to produce **2.54** which was washed with 10% aqueous HCl to afford ketone **2.55**. We then reduced the ketone to afford our new material **2.56** to test the oxidative decarboxylation. With the idea that sterics was a major obstacle to success, we attempted the reaction with sodium amide, rather than LDA, and then added nitrosobenzene. We were surprised to find that the product was identical to the starting material of the previous reaction; we had oxidized the alcohol back to the ketone **2.55**. No more attempts were made to accomplish this transformation as we believed attempting a carboxy-inversion strategy may bear more fruit.

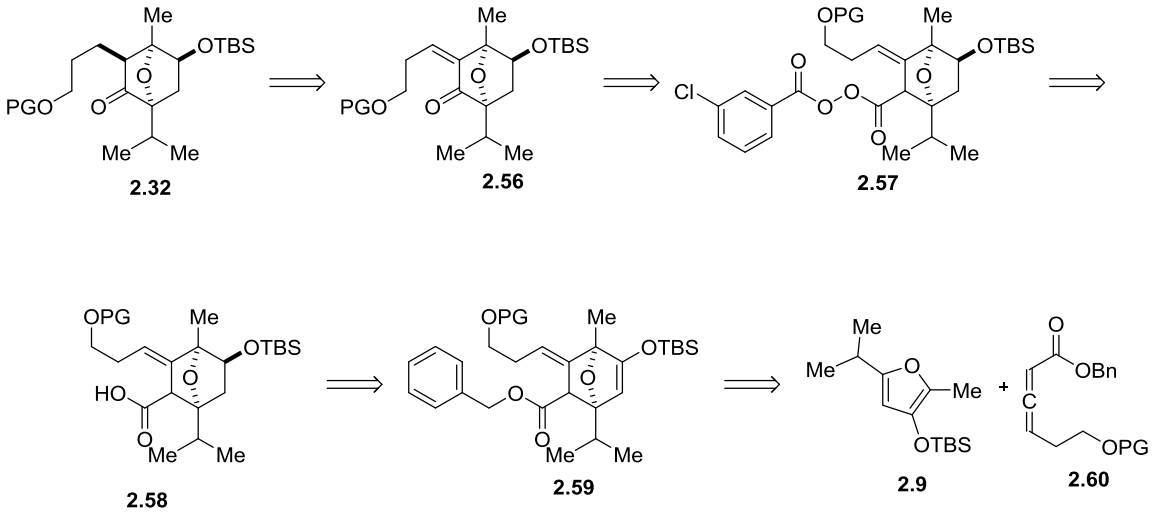
Carboxy-inversion is a transformation that turns a carboxylic acid to an alcohol via a diacyl peroxide.[48] This strategy has been used in multiple syntheses to date.[49–52]




Scheme 36 Attempted oxidative cleavage with nitrosobenzene.

### *2.6.2 Carboxy Inversion Strategy*

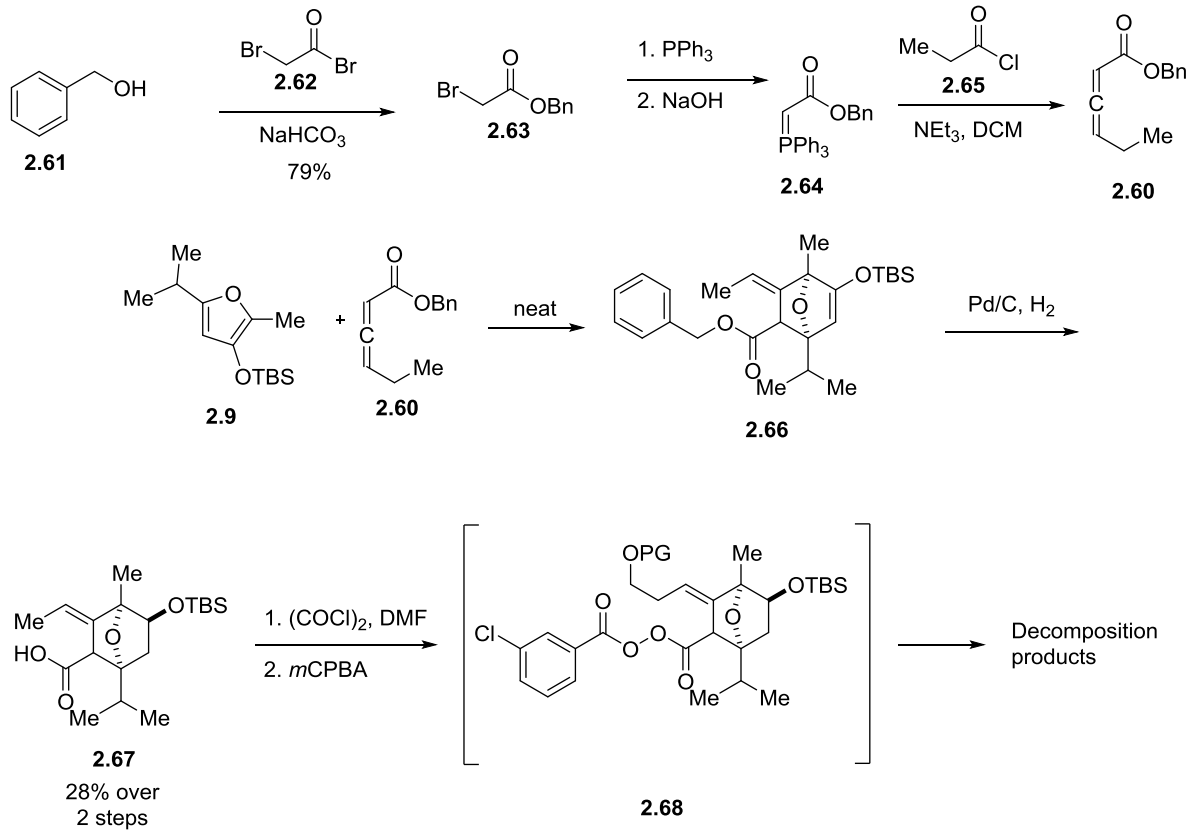
Our strategy to get to ketone **2.56** via diacyl peroxide **2.57** was either via acid **2.57** which would result from the hydrolysis of ester or by the direct hydrogenolysis of benzyl ester **2.58**. We felt that hydrogenolysis of a benzyl ester **2.59** was more advantageous because it would be done concomitantly with the hydrogenation of the silyl enol ether. The oxacycle would be formed as before from the Diels-Alder of **2.10** and our appropriately substituted allene, **2.60.**




Scheme 37 Carboxy-inversion retrosyntheis

To test our new method we needed to produce our benzyl ester allene. Benzyl alcohol was added to bromoacetyl bromide to produce benzyl acetyl bromide **2.63**. This compound was treated with triphenylphosphine followed by aqueous sodium hydroxide resulting in our benzyl Wittig reagent, **2.64**.

The first substrate we tested with this particular Wittig reagent was ethyl-4-oxo-4-chlorobutyrate, as this acid chloride has oxygen functionalization at the appropriate position for our synthesis and was readily available. Despite numerous attempts, we never detected any desired product from this reaction. We think the carboxyl group may be interfering in the reaction by intercepting the ketene intermediate more rapidly that the Wittig reagent.

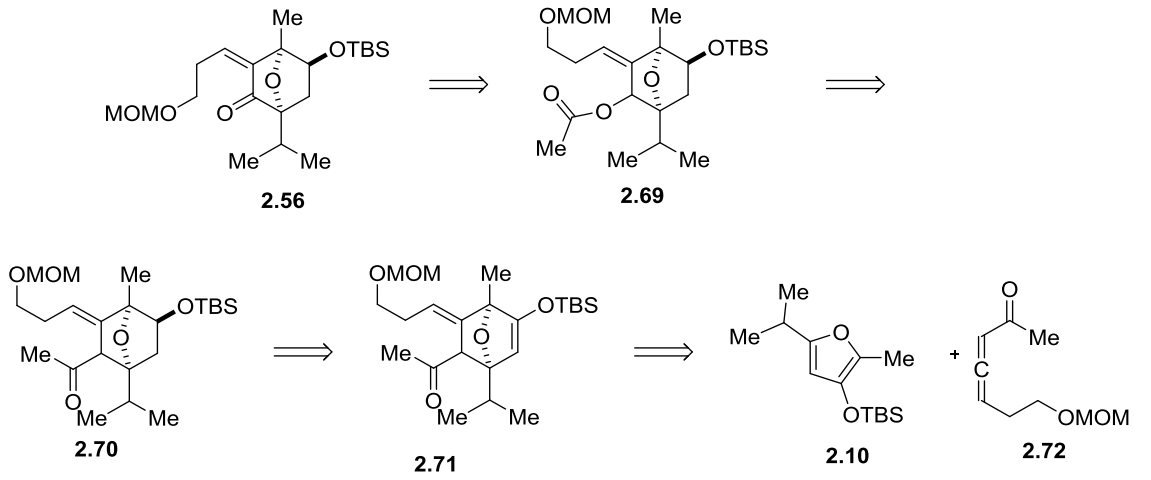



Scheme 38 Attempt at the carboxy-inversion strategy

Finding barriers to our preferred acid chloride, we decided to move to a simpler model system. Benzyl alcohol **2.61** (Scheme 38) was added to bromoactyl bromide **2.62** to produce benzyl bromoacetate **2.63** which was added to triphenyl phosphine and deprotonated to form the benzyl Wittig reagent **2.64**. This was mixed with propionyl chloride **2.65** to produce our allene **2.60**. With this reagent in hand, we then proceeded to our Diels-Alder reaction yielding **2.66** and subsequently hydrogenated the adduct with palladium on carbon to give **2.67**. Frustratingly, this dual-purpose hydrogenation repeatedly gave poor yields. Despite this, we attempted to couple the acid to *m*CPBA and decompose the diacylperoxide to induce the carboxy-inversion. This reaction sequence was difficult to monitor; all of the protons involved were exchangeable in NMR and the reaction did not take place at a carbon center. TLC showed conversion of starting material,

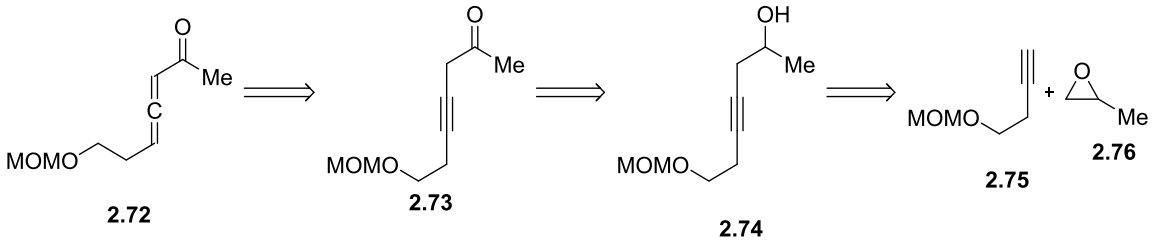
but whether or not the peroxide was coupled with our substrate was not immediately obvious. We ended up attempting to stain our TLC with 1% aqueous sodium iodide which at least showed us which spots contained oxidizing compounds. Repeated experiments showed new compounds that were oxidizing. Unfortunately, these compounds never showed good evidence of being our desired carboxy-inverted product. The low yielding reactions coupled with the uncertainty pushed us to explore other avenues, particularly a Bayer-Villiger strategy to install the requisite oxygenation.

## 2.7 Retrosynthesis III




Scheme 39 Retrosynthesis III

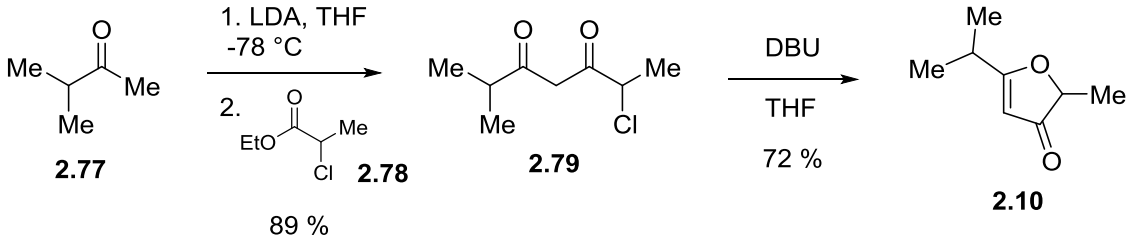
Our new retrosynthetic strategy would get to a carbonyl at C-6 from hydrolysis and oxidation of the ester **2.69** (Scheme 39). We believed that we could arrive at **2.69** by a Baeyer-Villeger reaction of ketone **2.70**. This ketone would come from the Diels-Alder reaction of allenone **2.72** and our siloxyfuran **2.10**. This allenone **2.72** we believed could be produced from the isomerization of **2.73** which would come from the oxidation of alcohol **2.74.** This molecule would be the addition product of alkyne **2.75** and propylene oxide.




Scheme 40 Retrosynthesis of allenone **2.72**

### *2.7.1 Furan Synthesis Re-visited*

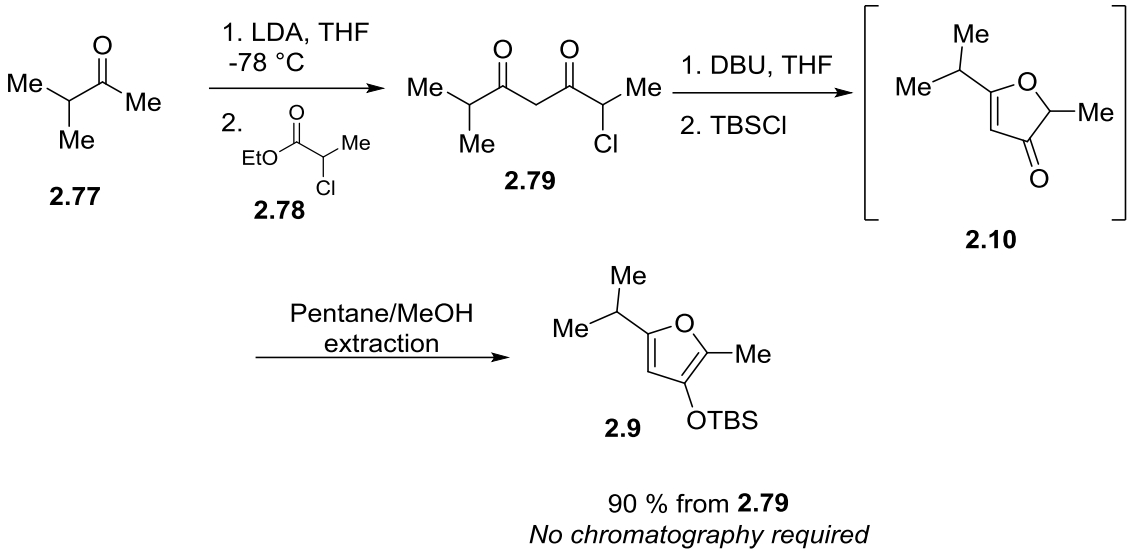
Around this time, we noticed the synthesis of englerin out of the Chain group utilized a shorter path to furanone **2.09** (Scheme 41) and we decided to attempt forming our furan via this path. The first step in their synthesis was the formation of chlorodiketone **2.79**, on multigram scale in 89% yield. Despite many attempts, we were unable to replicate these results. The product of the reaction was reported as a colorless oil. Our product was always orange in color. Chromatographic conditions reported were with 4% ethyl acetate/hexanes. When we attempted this system, the product would drag on the column and decompose. Despite being in contact with Dr. Chain, we were never able to resolve the issues with this reaction. Nonetheless, we pushed forward because of the efficiency that we had created in the next steps.




Scheme 41 Chain's synthesis of furanone **2.10**

The next step of the Chain synthesis is the annulation to the furanone with DBU. Our step beyond this was also utilizing amine base conditions so we saw the opportunity for a two-step, one pot reaction to our siloxyfuran. We attempted this reaction and were pleased to find that using the stronger base DBU (as opposed to TEA) we were able to

move away from the more reactive TBSOTf and use the much more convenient TBSCl. The problem of the furan purification still remained, however.




Scheme 42 Our new synthesis of furan **2.9**

To circumvent the need for chromatography, we invented a new workup procedure taking advantage of the highly non-polar nature of the siloxyfuran. In the reaction we used an excess of TBSCl accordingly we quenched the reaction with methanol and extracted into pentane which forms a biphasic system. This allowed us to separate the siloxyfuran and TBSOMe from the DBU and any other relatively polar species. TBSOMe was removed simply by high vacuum, leaving our desired product in high yield and without the need for chromatography.

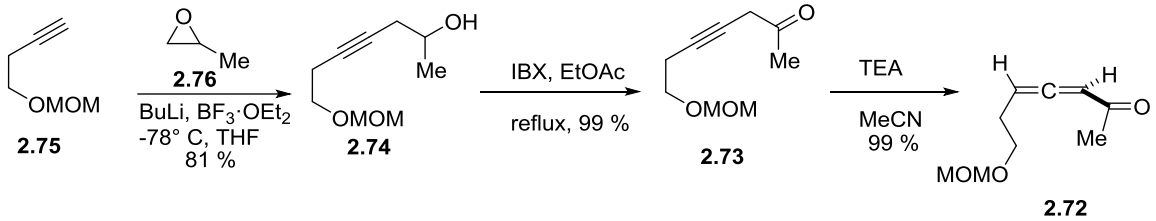
A colleague in the Stoltz lab was having trouble preparing 2,5-siloxyfuran **2.80** (Scheme 43). Seeing a potential use for our new protocol we attempted to apply our original conditions to succinic anhydride **2.81** (DBU, TBSCl) but the reaction produced black precipitate and did not yield desired product. When we attempted our earlier conditions for silation (TBSOTf, TEA) followed by our new pentane/methanol work-up produced the desired product reasonably pure and in good yield, indicating the protocol may be useful for the preparation of a range of highly sensitive molecules.


Scheme 43 Synthesis of **2.80**

## 2.8 Attempts with Allenones

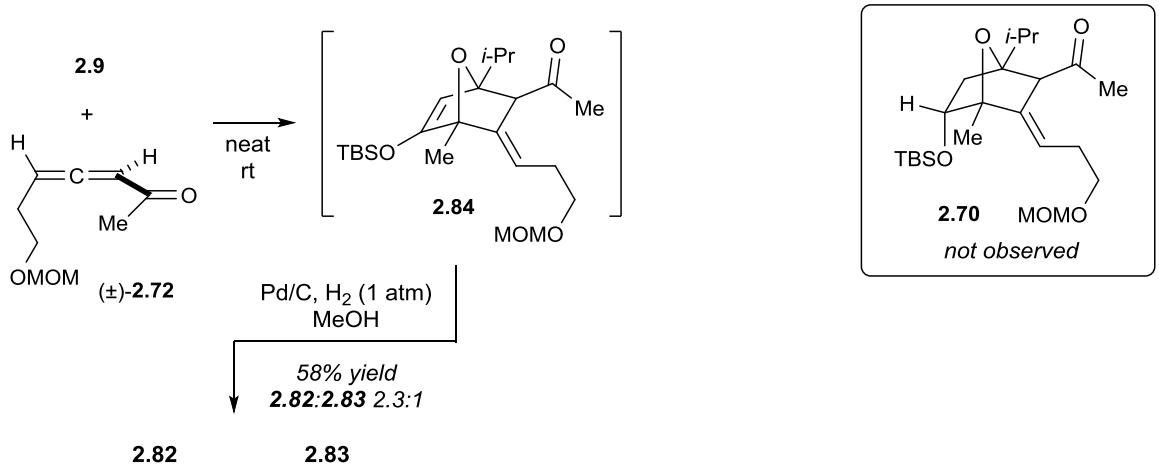
### *2.8.1 Synthesis of allenones*

Our synthesis commenced by the MOM protection of 3-buyn-1-ol as in the synthesis of allenonates. It is unclear as to whether Suarez and coworkers[53] attempted the copper catalyzed coupling of terminal alkynes with diazoketones. Nonetheless, this reaction failed in our hands and a new route was devised. **2.75** was deprotonated with *n*-BuLi and added into propylene oxide **2.76** to produce the alkynol **2.74**. Care had to be taken when oxidizing this compound as the alpha hydrogen is acidic and isomerization occurs readily. Due to this fact, oxidation protocols utilizing basic conditions had to be avoided. IBX is a mild, neutral oxidant. Unfortunately, it is also insoluble in nearly all solvents except DMSO, which has its own drawbacks. To overcome these limitations and unlock the potential of IBX, the reagent can be used in refluxing ethyl acetate.[54] This convenient protocol allows for the filtration of iodine species when the reaction is complete affording our product **2.73** by removal of solvent.




Scheme 44 Synthesis of allenes

Triethylamine in acetonitrile was observed to bring about the desired isomerization in 99% yield to afford the requisite allene in racemic form. The Diels-Alder reaction between our allenone and furan was observed to be rapid. We discovered this when we mixed (co-spotted) the furan and the allenone starting materials on TLC and ran it in 40% ethyl acetate/hexanes. Upon developing the TLC plate, we saw Diels-Alder adduct spots (both *endo*- and *exo*- isomers). The overall reaction, however, still took two days at room temperature which suggests that the reaction is probably reversible and requires the longer reaction time to overcome the reverse reaction.




*selected NMR data for **2.82**:*
$^{1}$H NMR, δ: 5.37 (s, 1H, CH)
$^{13}$C NMR, δ: 204.95 (C), 204.78 (C), 196.91(C), 99.93 (CH), 91.20 (C)

*selected $^{13}$C data for **2.83**:*
$^{1}$H NMR, δ: 5.40 (s, 1H, CH)
$^{13}$C NMR, δ: 203.13 (C), 198.05 (C), 197.35 (C), 100.03 (CH), 91.28 (C)

Scheme 45 Unexpected products.

As with the esters, hydrogenation of the Diels-Alder adduct was our next step. This reaction produced two compounds that were not diastereomoers of each other as was expected. They instead appeared to differ in the location of the trisubstituted double bond. We also noticed the $^{1}$H and $^{13}$C NMR spectra exhibited unusual chemical shifts that we believed indicated a loss of the bicyclic ring system formed by the Diels-Alder reaction.

We were especially puzzled by the appearance of a non-exchangable, uncoupled proton at 5.37 and 5.40 ppm (for **2.82** and **2.83**, respectively) that was attached to a carbon with chemical shift of ~100 ppm. In addition, the $^{13}C$ NMR spectrum for both compounds revealed the presence of three highly deshielded carbon atoms. While the methyl ketone introduced by the allene and hydrolysis of the silyl enol ether in **2.84** would account for two of these carbons, it was not clear how a third ketone moiety would be introduced by these reaction conditions. Furthermore, the IR spectrum for each compound indicated that only two carbonyl groups were present. Through extensive NMR analysis ($^{1}H$ and $^{13}C$ NMR, COSY, DEPT, HMBC, and HSQC) we concluded that products **2.82** and **2.83** both contained a furanone ring, and were assigned the structures shown in Figure 6. These assignments were confirmed by comparing the chemical shifts of known 3(2*H*)-furanones **2.85**,[55] **2.86**,[56] and **2.87**.[56]

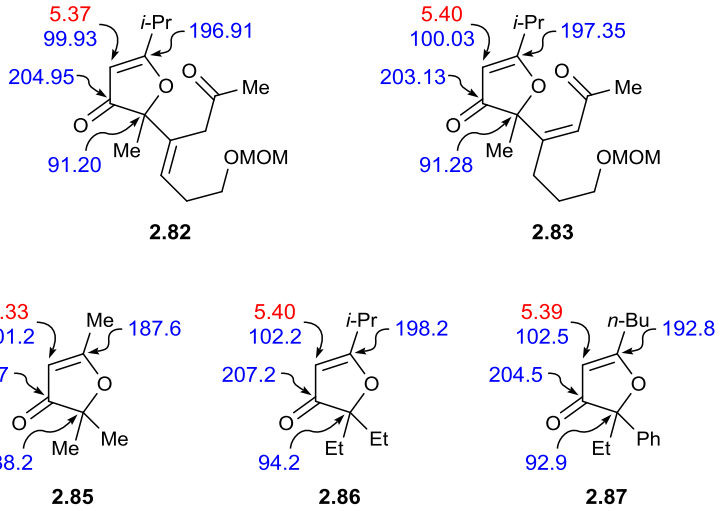
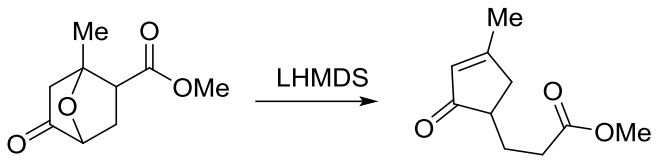



Figure 7 Furanones for comparison.

Surprised by the ring fragmentation experienced by bicyclic ketone **2.84**, we looked to the literature to see if there was any precedence for similar retro-Michael reactions. There have been reports of similar ring fragmentations taking place with oxabicyclo[2.2.1]heptane-2-carboxylates (Scheme 45), but conversion of **2.88** to **2.89** required lithium amide bases to proceed.[57] To the best of our knowledge, analogous retro-

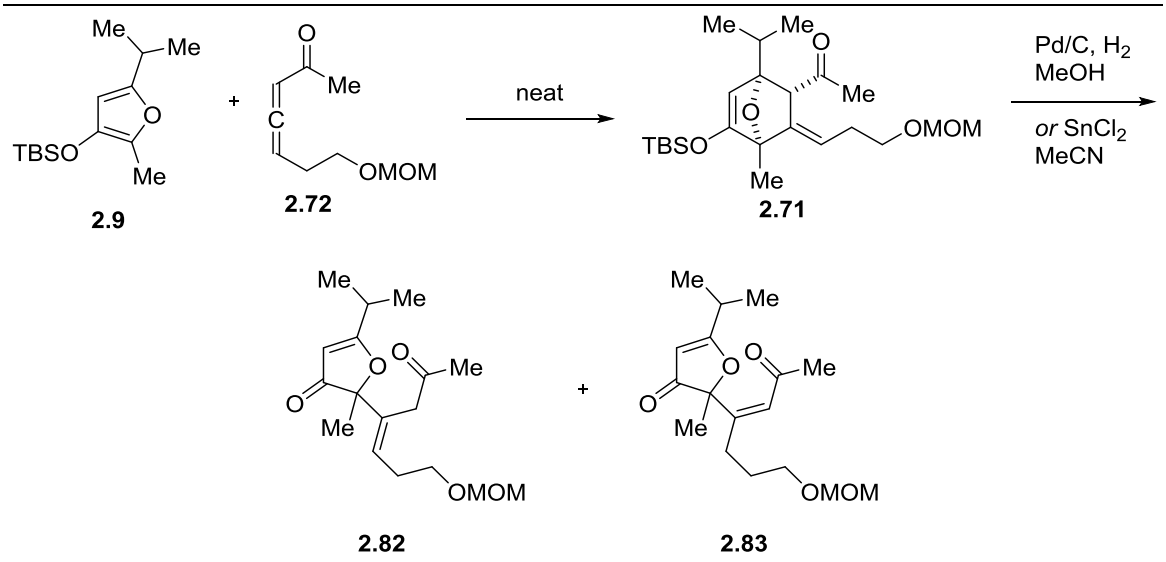
Michael reactions of acetyl-oxabicyclo[2.2.1]heptanes has not been reported. More surprising was the facile nature of this reaction. Simply leaving the reaction mixture containing **2.84** in $CDCl_3$ for a few weeks has proven to be enough to promote the reaction. Decomposition was not seen to a significant degree in control experiments in deuterated benzene, indicating acid catalysis as a possible mechanism of decomposition.




**2.88** **2.89**

Scheme 46 Literature example of retro-Michael

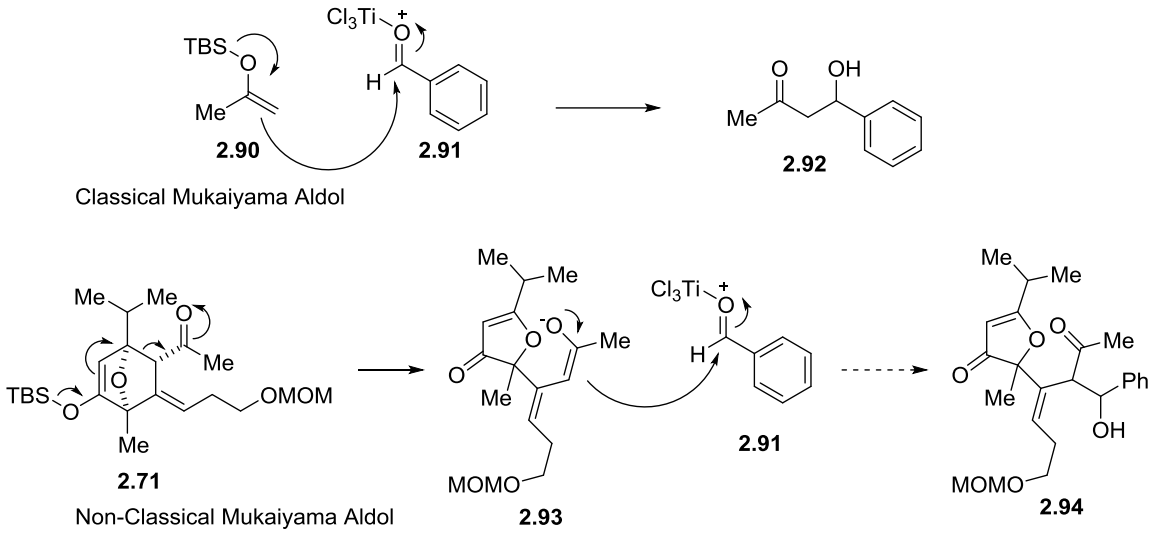
As this cycloaddition/retro-Michael reaction represents a new synthesis of potentially useful functionalized 3(2*H*)-furanones, we sought to identify more attractive conditions for promoting the ring fragmentation. Several Lewis acid promoters ($SnCl_2$, $FeCl_3$, $TiCl_4$, $SiO_2$) were evaluated, as were a few bases ($NEt_3$ and $K_2CO_3$/MeOH). In the end, it was found that simply stirring Diels-Alder adduct **2.84** with catalytic (10 mol%) $SnCl_2 \cdot 2\ H_2O$ in acetonitrile quickly produced decomposition product **2.82** in 75% yield without any observed isomerization of the trisubstitued olefin (Scheme 47).




Scheme 47 Synthesis of substituted furanones

### *2.8.2 Mukaiyama Aldol*

One idea we had to expand the utility of this reaction was to attempt to use the intermediate ketone enolate in an aldol reaction with an aldehyde analogously to a Mukaiyama type aldol reaction.[58] The classical Mukaiyama aldol involves the breakdown of a silyl enol ether such as **2.90** to attack an aldehyde **2.91** activated with a Lewis acid such as $TiCl_4$ to give **2.92**. Our system **2.71** also contains a silyl enol ether decomposition to enolate (by way of C-C bond breaking). We hypothesized that the enolate formation would be promoted by association with the titanium catalyst and thus, the intermediates of the reaction would be substantially similar such that they may react via the same pathway.

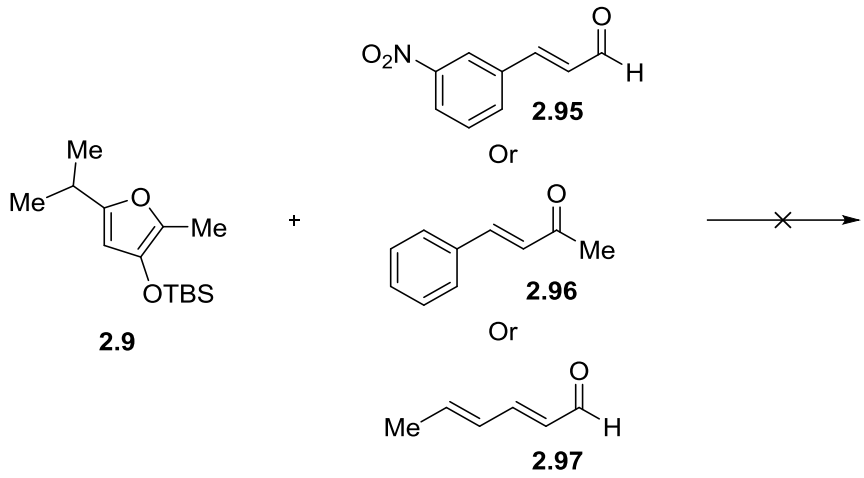



Scheme 48 Classical and proposed non-classical mukaiyamam aldols

When we attempted this reaction under standard Mukayama aldol conditions, we did not obtain any products containing aromatic NMR peaks, indicating that no aldol reaction took place. In fact, under these conditions we actually produced the desilative retro-Michael product without isomerization of the double bond; **2.82** was produced cleanly in 98% yield!

### *2.8.3 Scope and Limitations*

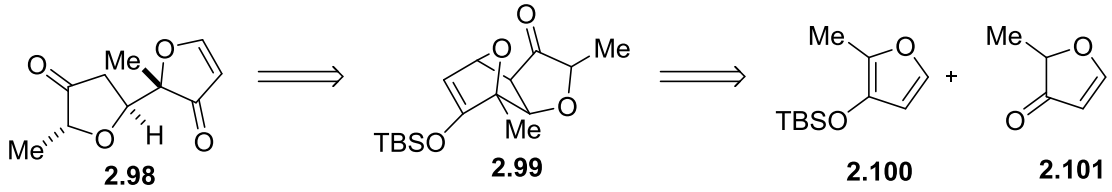
We wanted to test the scope and limitations of this reaction and sought to make a series of Diels-Alder adducts with our 3-siloxyfuran. We tested *o*-nitrocinnamaldahyde, **2.95**, benzylidene acetone **2.96**, and 2,4-hexadienal **2.97**. Even with heating there was very little reaction seen by TLC and reactions returned mostly starting materials. We believe this indicates the utility of using electron-poor allenes as the dienophile with 3-siloxyfurans. Our hypothesis to explain this phenomenon is the cumulated double bond experiences strain release not seen with the alkenes making the reverse reaction unfavorable.




Scheme 49 Attempted Diels-Alder reaction with alkenes

### *2.8.4 Chilenone, a potential application*

One potential use for this new reaction that we saw was the synthesis of the natural product chilenone[59] **2.97**, a racemic molecule isolated from the marine alga *laurencia chilensis*. We believed that the molecule could come (with other stereoisomers) directly from the retro-Michael fragmentation of **2.99**, which we believed we could make from siloxyfuran **2.100** and its direct precursor, **2.101**. We believed we could make this molecule analogously to the method utilized in the englerin synthesis from the Chain group.



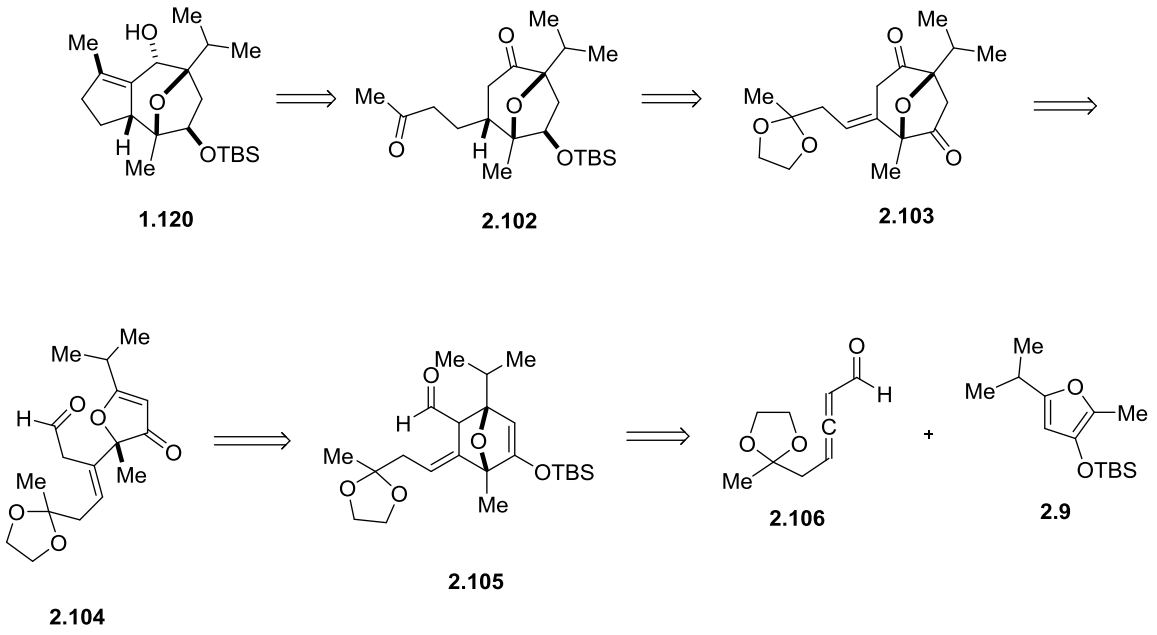

Scheme 50 Chilenone retrosynthesis

Unfortunately, we found furanone **2.101** is not easily obtained. After multiple attempts to synthesize this furanone utilizing a few different methods, we decided to abandon this synthesis.

## 2.9 Retrosynthesis IV

### *2.9.1 Retrosynthetic Plan*

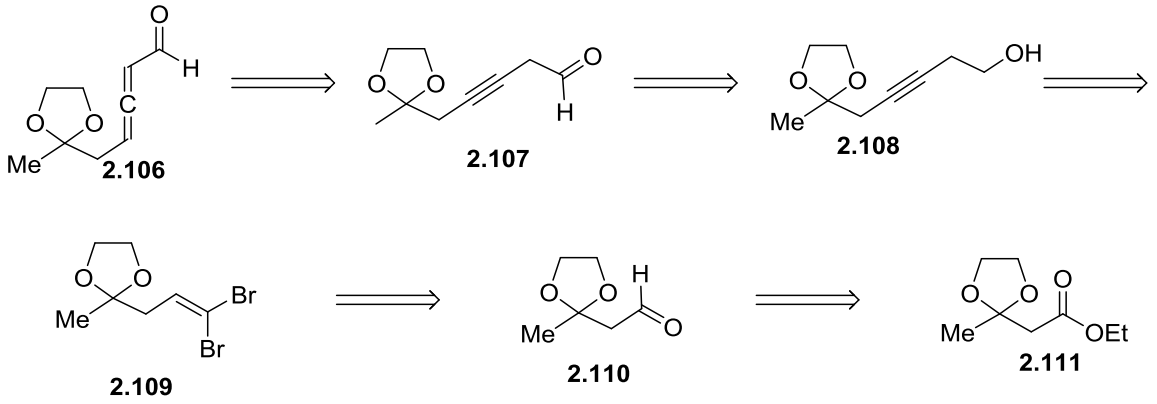
We believed that we could potentially use the newly discovered retro-Michael reaction to our advantage and devised a new strategy for our synthesis of **1**. We believed that we could intercept intermediate **1.120** in the synthesis from the Echavarrin group. This compound we believed could come from an aldol-reduction sequence analogous to that found in the Nicoloau group to give **2.102.** This intermediate would come from a net reduction and protecting group changes on **2.103** which could in turn be formed by a Stetter reaction of **2.104** being the retro-Michael product of our Diels-Alder intermediate **2.105**. The Diels-Alder would take place between our allenal **2.106** and our furan **2.9**.




Scheme 51 Retrosynthesis IV

Our newest retrosynthetic scheme would leave us needing to make a suitably substituted allenal **2.106**. The allenal functionality is quite sensitive to various conditions so one must take great care when preparing them. One strategy that was considered was to unmask the aldehyde functionality directly prior to use in the Diels-Alder. Typical protecting groups for an aldehyde would be as an acetal. Unfortunately the requisite acidic environment required for deprotection of allenyl acetals has been shown to lead to hydration of the allene.[60] A more obvious approach would be via the isomerization analogous to our previous attempts of the alkynal directly after (or even in the same pot as) the oxidation of the homopropargylic alcohol.

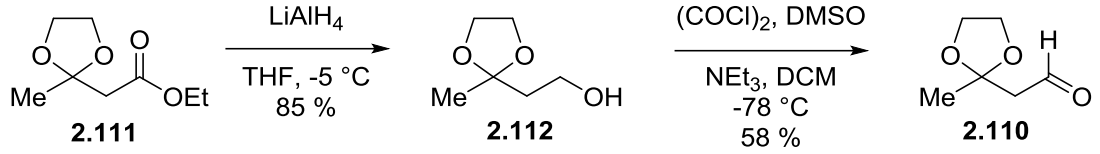
Retrosynthetically, we would form the allenal **2.106** from the 3-alkynal **2.107** which would come from oxidation of alkynol **2.108**. We believed we could form the alkynol from the Corey-Fuchs reaction via dibromoolefin **2.109** from aldehyde **2.110.** Aldehyde **2.110** would be formed from ester **2.111**.




Scheme 52 Allenal retrosynthesis

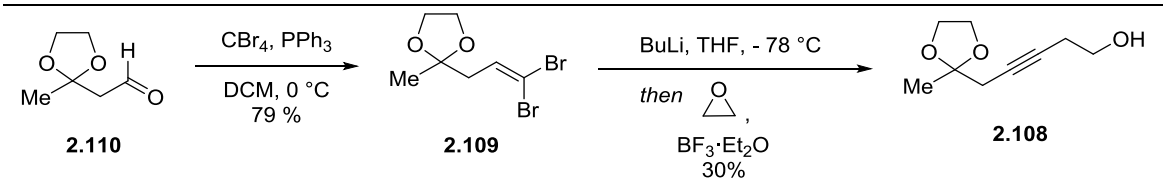
Our synthesis of allenal **2.102** began with the acetal of ethyl acetoacetate 2.**111** which was subjected to reduction with $LiAlH_4$ to **2**.**112** followed by Swern oxidation to the aldehyde **2.110**. Selective reduction of the ester to aldehyde directly was attempted, but in our hands this reaction was plagued by poor yields, both using DIBAL-H at low

temperatures or by the addition of sodium *tert*-butoxide to DIBAL-H at various temperatures (room temperature, 0, or –43 °C).




Scheme 53 Synthesis of **2.110**

With our aldehyde in hand, we treated with Corey-Fuchs conditions first furnishing the dibromo- olefin **2.109** followed by treatment with two equivalents of *n*-BuLi giving the acetylide which was trapped by ethylene oxide and $BF_3 \cdot OEt_2$ to yield **2.108**. Our yields for this reaction seemed to be consistently low, usually around 30%, despite allowing for a longer reaction time and using 10 equivalents of ethylene oxide.



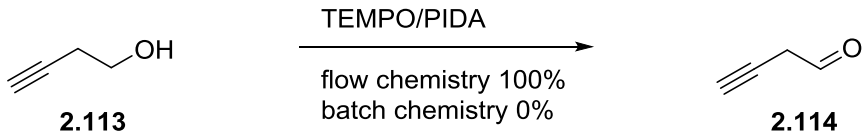

Scheme 54 Synthesis of **2.108**

### *2.9.2 Background for Oxidation of Homopropargylic Alcohol to Homopropargylic Aldehydes*

There are few examples in the literature of oxidation of primary homopropargylic alcohols to aldehydes and none of the examples are on complex substrates. This may indicate the difficulty in this transformation and the sensitivity of the product.

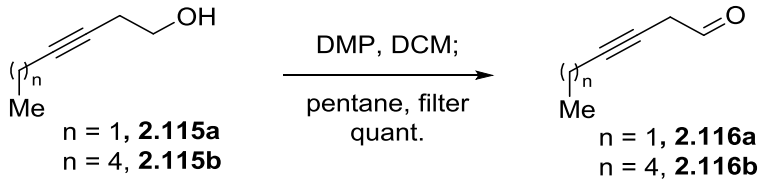
While exploring the flow chemistry with TEMPO/PIDA, Ambreen and coworkers were able to oxidize 3-butyn-1-ol **2.113** to obtain 3-butynal **2.114** in 100% conversion with no isolated yield given. The setup mixed a solution of PIDA and alcohol **2.113** with catalytic TEMPO. The authors cite general advantages to flow chemistry over batch

chemistry, but do not report attempting the reaction of **2.113** batch-wise. Interestingly, in their attempt to make cyanohydrins from primary alcohols, Vugts and co-workers[61] did attempt to use TEMPO/PIDA batch-wise in a 1:1 pentane:DCM mixture to produce **1.114** but reported no conversion.




Scheme 55 Literature oxidation of **2.113**

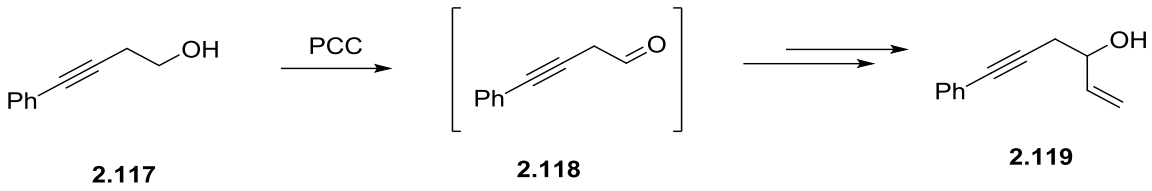
Waverin and Viala[62] reported the use of Dess-Martin periodinane to oxidize homoallylic and homopropargylic into β,γ-unsaturated aldehydes. They note that β,γ-acetylenic aldehydes are highly unstable due to the acidic alpha proton. Waverin and Viala also note the high potential of these molecules in synthesis. These authors were able to produce hex-3-enal from (*Z*)-hex-3-en-1-ol using DMP and azeotropically drying the product with benzene (Scheme 55). The same protocol failed to produce the analogous aldehydes of hex-3-ynol **2.114a** and non-3-ynol **2.114b**. The authors surmised that polycondensation of the allene isomer was probably to blame for the lack of product. The authors then attempted a modified workup, treating with cold pentane precipitated the perionane which was subsequently filtered with silica. Volatiles were removed and again, the product was dried by azeotropic removal with benzene. This new method provided quantitative yields of 3-hexynal **2.116a** and 3-nonynal **2.116b**.




Scheme 56 Oxidation of **2.116** with DMP

Vugts and co-workers[61] also used DMP to produce a variety of γ,δ-unsaturated aldehydes. Citing the drawbacks to DMP, they explored TEMPO/PIDA as an alternative. Six alkenols were oxidized by the TEMPO/PIDA system with quantitative conversion. Alkynols did not fare as well, however as the authors noted 1-butynol did not react under the standard conditions. The one carbon longer analog 3-pentyne-1-ol, however, was reported to convert to 41% in 70 minutes.

A chromium-based oxidant has also been used for 3-alkynal production, but there is only one example. Zhang and coworkers[63] have reported PCC to do the oxidation of 4-phenyl-3-butyn-1-ol **2.117** to **2.118** as part of a two-step synthesis of 7-phenylhept-1-en-6-yn-3-ol **2.119**. The intermediate alkynal was not isolated.




**2.117** **2.118** **2.119**

Scheme 57 Oxidation of **2.117** with PCC

### *2.9.3 Attempted oxidation of our 3-alkyn-ol*

Our efforts to oxidize our particular alkynol **2.108** began analogously to the oxidation of our previous substrate **2.73**. IBX and **2.108** was heated in a sealed vessel at 80 ° C for a few hours. To our surprise the primary alcohol appeared to oxidize much more sluggishly than the secondary alcohol and the reaction mixture was contaminated with side products. Due to the sensitivity of the product, we searched for method that would be mild enough to produce a clean reaction.

It was reasoned that using IBX at high temperature was leading to side products (observed by TLC), therefore we reasoned using IBX at a lower temperature may suppress the side-products formation. Thus, we attempted the reaction at room temperature in DMSO but this reaction failed to convert after long reaction times.

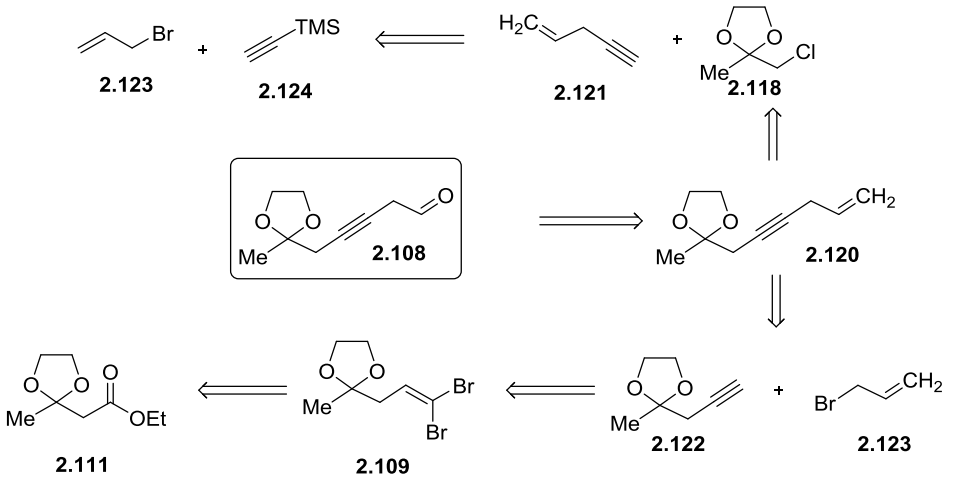
Dess-Martin periodinane was a logical next step. This reagent has been shown to be mild and capable in many reactions. Despite its power as an oxidant, there are some

drawbacks to DMP. The reagent is not commercially available and must be prepared from IBX, a preparation which is not always trivial. The reagent is water sensitive and degrades slowly upon storage. Nevertheless, multiple batches of DMP were prepared and mixed with our alcohol **2.108**. Unfortunately, this reaction also failed to produce **2.107**, returning only starting material.

While there is no precedent of using the Ley oxidation[64] on primary homopropargylic alcohols, we felt this method had a reasonable chance at success as the reaction conditions are mild. The Ley oxidation utilizes a ruthenium catalyst and *N*-methylmorpholine oxide as re-oxidant. When we attempted this reaction, a small amount of product would be rapidly produced (~ ten minutes) but then the reaction would stall out. Additional TPAP did not seem to drive the reaction forward, nor did the addition of acetonitrile, which has been shown to drive some Ley oxidations to completion.[65] The reason for this idiosyncratic action of acetonitrile in the Ley oxidation remains unknown. Some of the failed Ley oxidation seem to have to do with the catalyst being chelated to the substrate, which is conceivable with our acetal.

### *2.9.4 Johnson-Lemieux approach*

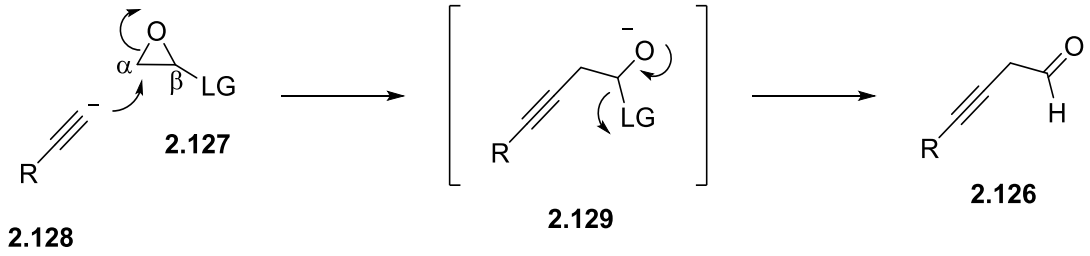
Considering the difficulty with our strategy of oxidation of an alkynol to alkynal, we decided to approach the formation of aldehyde differently. We envisioned the aldehyde **2.108** could be formed via an oxidative cleavage[66] of a diol formed from an alkene **2.120**. This necessitated the formation of a skipped alkeneyne **2.121** to be coupled to chloride **2.122** which would come from allyl bromide **2.123**and TMS acetylene **2.124**. We believed this compound could be alternatively be formed by utilizing our terminal alkyne intermediate **2.125**, in a coupling reaction with allyl bromide **2.123**.




Scheme 58 Alternative retrosynthesis to **2.103**

### *2.9.5 β-Activated Epoxide Strategy*

Another method for the rapid preparation of a 3-alkynal **2.126** (Scheme 59) that we conceived of was by the use of an epoxide bearing a beta group that was "activated" with a leaving group **2.127**. We believed that we could use a nucleophile such as acetylide anion **2.128** to open our epoxide and utilize the alkoxide intermediate **2.129** to expel a leaving group which would form our requisite aldehyde in one step. We were unaware of any one else attempting to use an acetylide to open an epoxide to form an aldehyde directly.

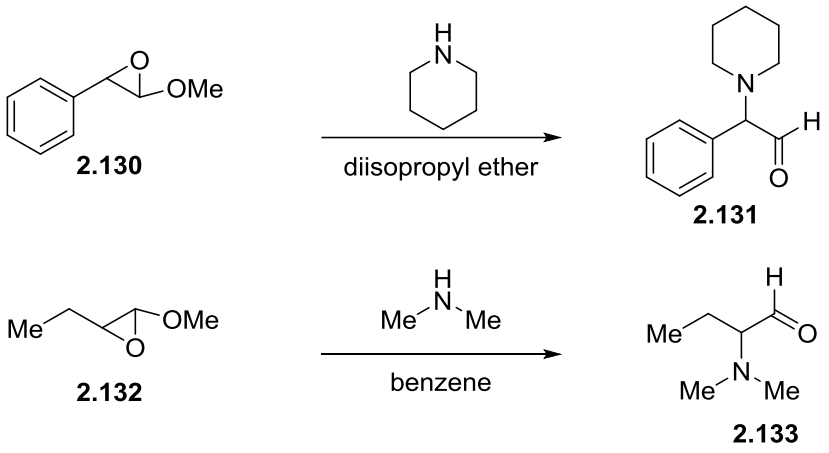



Scheme 59 Proposed epoxide opening to 3-alkynal

In synthetic organic chemistry, leaving groups often are oxygen-based (e.g. alkoxide, tosylate, mesylate, etc.) and such a leaving group would make sense as it should

prove a facile leaving group in our proposed reaction. Another advantage to using oxygen-based leaving groups is the availability of the requisite enol ether starting material. We believe we could use commercial or readily available vinyl ethers and simply epoxidize to get to our target epoxide.

When searching the literature for oxygen-based leaving groups we are only aware of two examples of any incipient nucleophile attacking the alpha position to make an aldehyde, both of the examples involve amine nucleophiles. Epoxide **2.130.** was opened with piperidine to give **2.131**. In the other example **2.132** was opened by the dimethyl amine to give **2.133.**



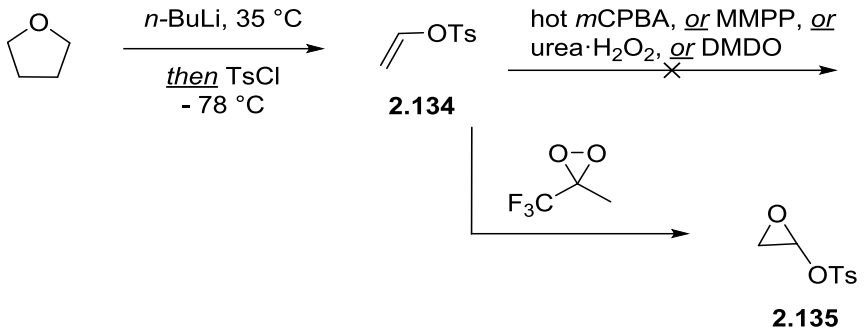

Scheme 60 Literature examples of aldehyde formation via epoxide opening with β-leaving group.

Our initial attempt to make an activated epoxide was by the mixing *m*CPBA with ethyl vinyl ether. Unsurprisingly, as this olefin is highly electron-rich, this reaction failed. We quickly realized that we needed our enol ether to be less electron-rich. It is known that vinyl tosylate can be made by the addition of *n*BuLi to THF at elevated temperature followed by the addition of TsCl. With our vinyl tosylate, we attempted the epoxidation with a variety of reagents. Magnesium monoperoxyphthalate[67], urea hydrogen peroxide,[68] and *m*CPBA at elevated temperature all failed. DMDO, a very

highly active epoxidation agent[69] was used is large excess. After one day, only 5% of product was seen by NMR.

Undaunted, we used an even more active epoxidizing agent, trifluoromethyl methyl dioxirane.[70] This epoxidizing agent produced our desired epoxide in good yield. We attempted to use this epoxide to form our desired aldehyde multiple times.

Unfortunately, we were never able to convert the epoxide to the aldehyde; we also found the epoxide was not shelf-stable, as it readily decomposed in a matter of hours. Somewhat paradoxically, when we exposed our epoxide to acetylide anion −78 °C, we only re-isolated the epoxide.




Scheme 61 Formation of electron-poor enol **2.134** ether and β-activated epoxide **2.135**.

### *2.9.6 Conclusions and future work*

We believe the osmium tetroxide-based strategy holds the best chance for success in the rapid synthesis of the 3-alkynal that can be isomerized to the required enantioenriched allenal. This substrate is highly likely to be a good substrate for the Diels-Alder. Due to the similar electonegativities between a methyl ketone and an aldehyde (as opposed to an ester) one would expect the retro-Michael reaction to take place readily and set us up for the cycloheptane annulation, the last big hurdle in our synthesis.

# Chapter 3 Investigations Into the Stereoselective Isomerization of 3-Alkynes to Allenes

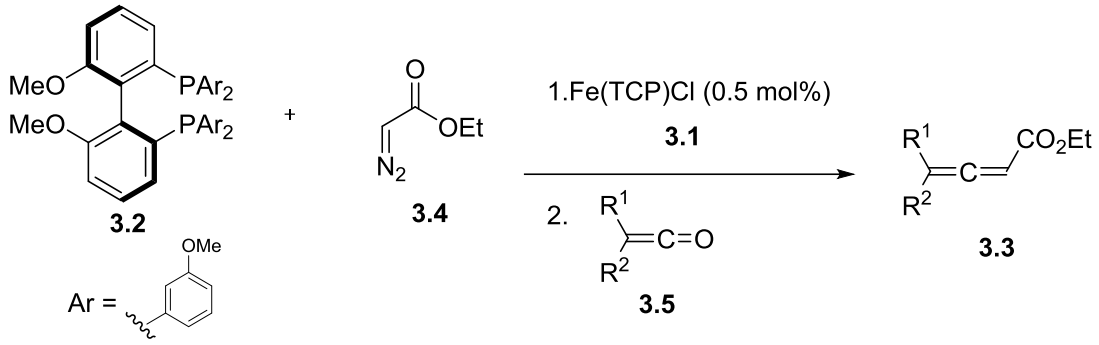
### *3.1.1 Allene Requirements*

The key reaction in our plan to synthesize englerin A requires the use of an enantioenriched allene having an electron withdrawing group at the alpha position. The stereochemistry of this allene will control the stereocenters formed both during the Diels-Alder reaction and to direct future stereocenters (*vide supra*). Initially our group was planning to develop an alkylidene-based strategy to produce enantioenriched allenes based on photolysis of a tungsten complex. This effort did not bear fruit, however. Therefore, we set about to develop a method for the production of enantioenriched, electron-deficient allenes.

### *3.1.2 Background*

Allenes are becoming an important part of modern synthetic chemistry.[71] Their rise in popularity has brought about many new methods for their synthesis.[72–82] While asymmetric methods for allene synthesis have conventionally required stoichiometric chiral reagents, catalytic enantioselective syntheses do exist, but this area is underdeveloped and the methods are few.[72] When one considers the synthesis of electron-deficient allenes, many of these methods fall short or are simply incompatible. Consequently, very few methods have been developed that allow for the asymmetric preparation of chiral electron-deficient allenes from achiral starting materials.

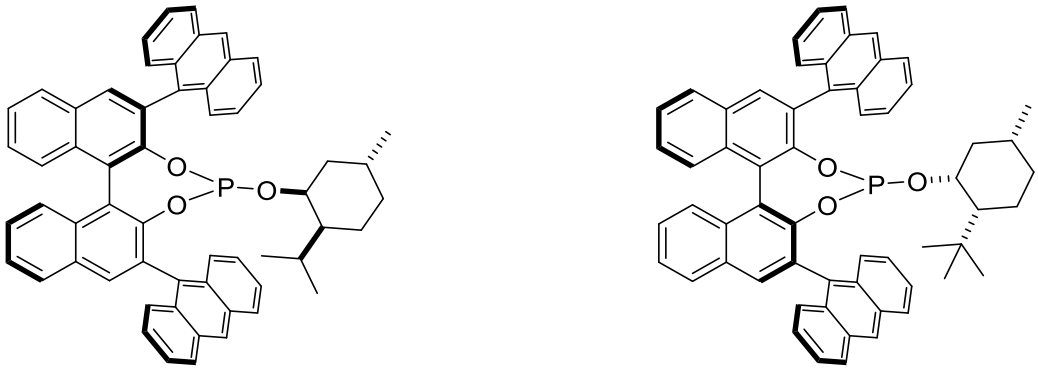
### *3.1.3 Iron Porphyrin-Chiral Phosphine Mediated Asymmetric Allene Synthesis*



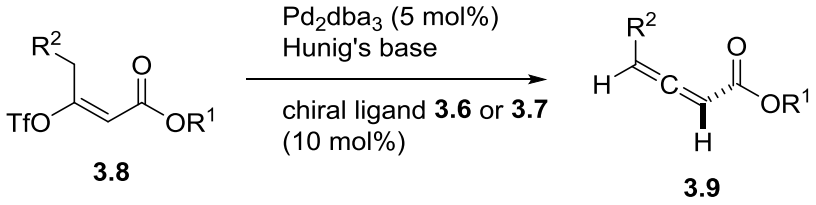

Scheme 62 Li allene synthesis

In 2006 Li and coworkers[82] disclosed a reaction with iron porphyrin **3.1**, chiral phosphine **3.2** system that was able to produce allenoates **3.3** from EDA (**3.4**) and a ketene **3.5**. While the yield and *ee*'s where very good, the EDA to chiral phosphine ratio was 2:1 making this reaction quite expensive to run on a large scale.

### *3.1.4 Asymmetric Allenes by Palladium Catalyzed β-Hydride Elimination*



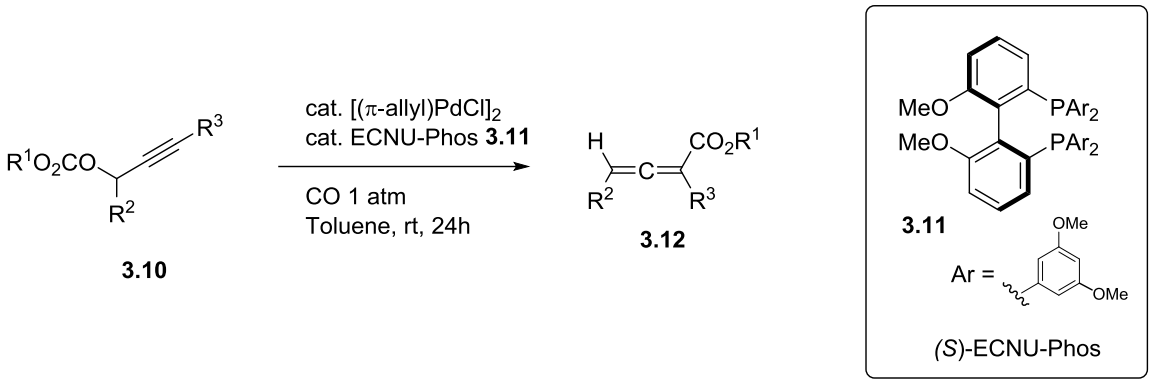
**3.6** **3.7**




Scheme 63 Frantz allene synthesis

Recently, a report from the group of Doug Frantz has made major progress in the synthesis of asymmetric allenoates[83]. A survey of around 60 chiral phosphorus-based ligands was undertaken to evaluate asymmetric beta-hydride elimination as a viable path to chiral allenes. BINOL-based ligands **3.6** and **3.7** were found to give the most promising *ee*'s with menthol-type alcohols attached. With these catalysts in hand, they found the reaction is applicable to a wide range of *E*-enol triflates **3.8** and gives allenes **3.9** in good yields with good to excellent *ee*'s.

### *3.1.5 Dynamic Kinetic Asymmetric Carbonylation*




Scheme 64 Ma allene synthesis

In 2013, the Ma group disclosed a palladium catalyzed carbonylation of alkynyl carbonates **3.10** using the newly designed ECNU-Phos **3.11** to give allenoates **3.12**.[84] This reaction runs at room temperature and has low catalyst loading (1 - 2 mol% palladium). There are no reported examples where $R^3$ = H, a requirement for our synthesis, so it is unclear if this reaction may be helpful to us.

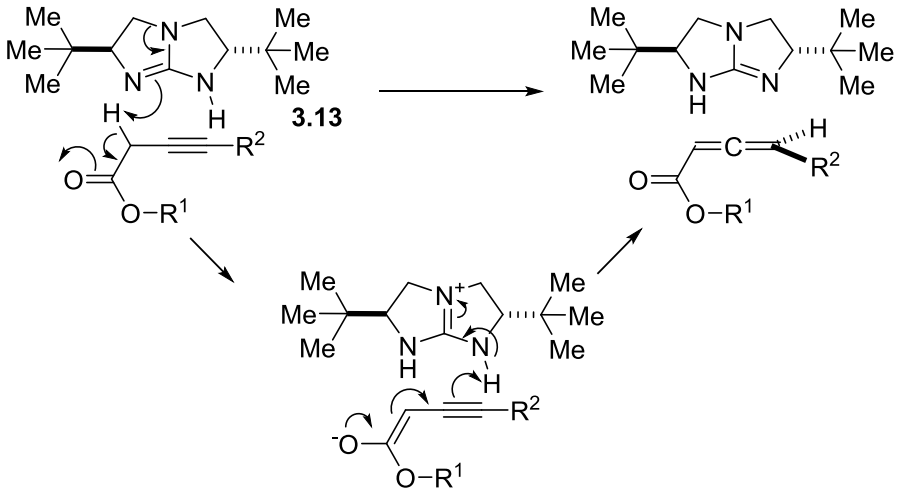
## 3.2 Enantioenriched Allenes by Isomerization of Alkynes

### *3.2.1 Guanidine Catalyst Isomerization*

Liu and cowokers[85] were able to isomerize 3-alkynoates to allenoates using a chiral guanadine-derirved organocatalyst **3.13**. Their method for isomerization takes place in hexane at room temperature or –20 °C and requires 12-34 hours. The *ee* of product formed was generally very good to excellent. While the reported yields are consistently in the high 90's, this is an isolated combined yield of alkynoate and allenoate. This mixture of starting material and product is one of the major drawbacks of this strategy as generally, these two species, as are not separable by standard column chromatography. Another major drawback is the cost. The catalyst is made from *tert*-leucinol, the *S*-enantiomer of which

costs $99 per gram from Sigma-Aldrich at the time of writing. To access the opposite enantiomer the *R*-enantionmer of *tert*-leucinol would be needed and that material is even more expensive at $150 per 100 milligrams.

It is our hypothesis that the mechanism of this reaction may involve deprotonation of the alkynoate by the most basic nitrogen and re-protonation by the beta nitrogen. This mechanism leaves the catalyst in the same electronic state as seen in scheme 65. The importance of this mechanism, where deprotonation and re-protonation occur from different atoms will become more important in our discussion of isomerization by cinchona alkaloids and their derivatives (*vide infra*).

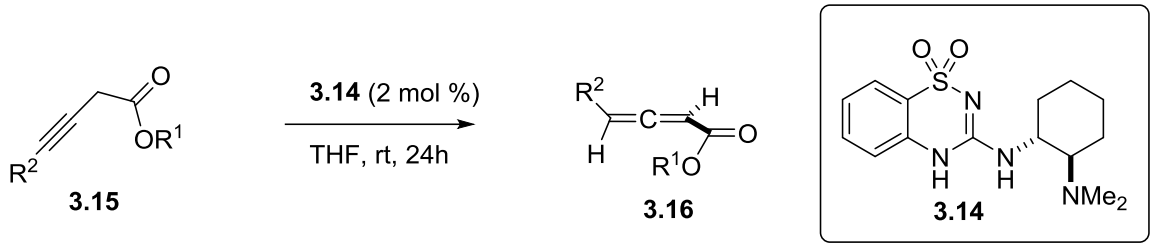



Scheme 65 Theorized mechanism of isomerization by guanidine catalyst

### *3.2.2 Hydrogen-Bond Donor Catalysis*

The Takemoto lab synthesized the hydrogen-bond donor organocatalyst **3.14** and screen its effect in multiple different reactions.[86] One of the reaction types screened was the isomerization of 3-alkynoates **3.15** to the corresponding allenes **3.16**. Their enantioselectivities were generally good to excellent and yields were consistently high. The major limitation to the reactions with this catalyst were incomplete conversion to allene as the products were always recovered as an inseparable mixture. Conversion to product allene was reported 51-77% with the remainder being alkyne. The authors also

subjected an isolated allene to the reaction conditions and did see the appearance of alkyne, indicating that the reaction is reversible.

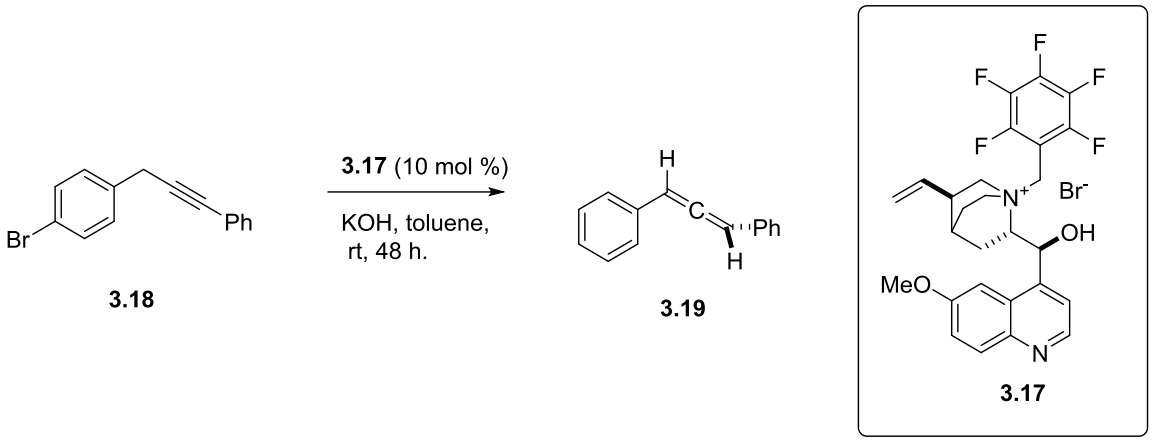



Scheme 66 Takemoto's allene synthesis by isomerization

Takemoto and co-workers followed up this work by using the catalyst to make tri-substituted allenes.[87] Such a reaction allows racemization of a propargyl chiral center followed by preferential isomerization of one enantiomer over the other to form one allene enantiomer over the other (and thus making it a dynamic kinetic resolution). The alpha substituent was found to suppress the reverse reaction, allowing for greater product to starting material ratios.

### *3.2.3 Phase-Transfer Catalysis*

The only other literature report of the formation of an enantioenriched allene by isomerization of a prochiral alkyne was in a brief report by Oku and coworkers who used a cinchona alkaloid-based phase-transfer catalyst **3.17** to isomerize a diaryl alkyne to an allene in a 71% yield with a 35% enantiomeric excess.[88] This was the only example the authors reported.




Scheme 67 Isomerization of alkyne to allene with PTC

## 3.3 Our Attempts at Asymmetric Alkyne/Allene Isomerization

### *3.3.1 Synthetic Goals*

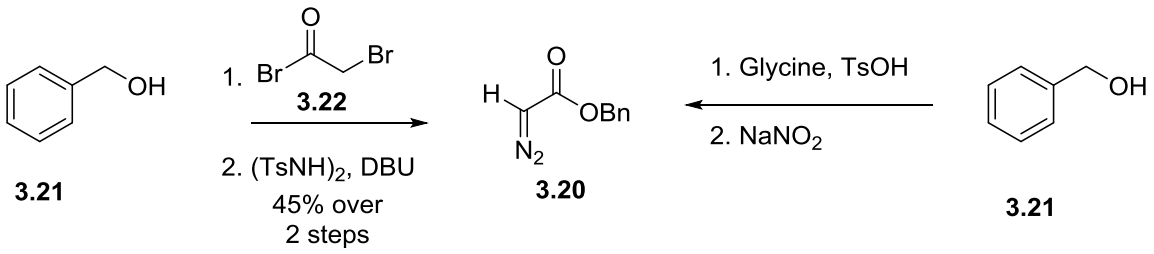
It was our hope to develop a reaction that would produce our required allene by isomerization with the following features.

1. *High conversion to allene*. Liu and coworkers developed an isomerization to allenoates with high enantioselectivity, but conversion was always a problem. Our goal was to create allenes with a high allene:alkyne ratio, especially because the two isomers are not generally separable with standard column chromatography.
2. *Good enantioselectivity*. The enantioselectivity in this reaction would dictate the level of enantioselectivity we would get in the entire synthesis because the allene would be the only source of chirality.
3. *Rapid conversion*. While having a fast reaction is much more convenient, it is not an absolute requirement. Given the requirement for the use of the allene in the synthesis of englerin, we preferred a reaction that would allow for rapid screening of substrates, catalyst

modifications, solvents, temperatures, *etc*. A sluggish reaction would greatly retard the development of a more convenient enantioselective isomerization reaction.

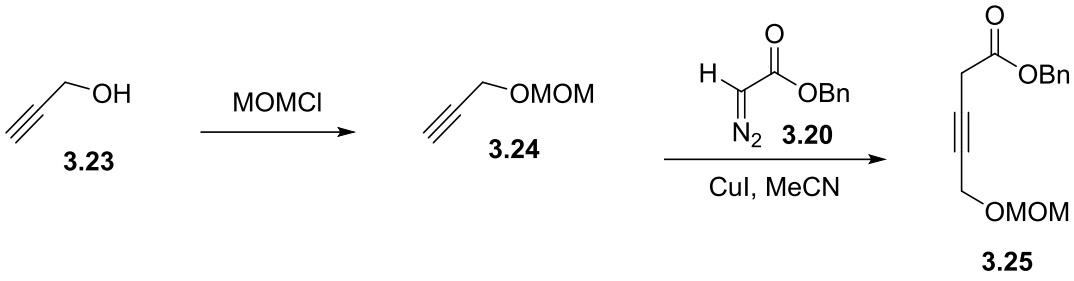
Given the precedent of isomerization of alkynoates but the drawback of the expensive and labor intensive guanidine catalyst we decided to attempt the isomerization of alkynoate with commercially available chiral bases. Like Liu and coworkers, we began by following the protocol by Suarez and Fu.[53] This protocol uses copper iodide, to couple terminal alkynes and diazoesters to produce 3-alkynoates. This method is superior to other methods as it is mild; it avoids going by way of acetylide anions which readily isomerize 3-alkynoates and are not functional group tolerant. The protocol also benefits from simplicity, copper iodide is used without additional ligand. Further, the method is atom efficient as a 1:1 ratio of alkyne and diazo are used.

We began by synthesizing benzyl bromoacetate **3.20** from benzyl alcohol **3.21** and bromoacetyl bromide **3.22**. This was then diazotized by the treatment of ditosylhydrazine and DBU. Ditosylhydrazine is readily prepared by the addition of p-tolylsulfonyl chloride to tosylhyrazine with pyridine. We found that on larger scale, it was far more convenient to prepare the diazo compound first by esterification of glycine and isolation as the amine salt followed by treatment with sodium nitrite.




Scheme 68 Sythesis of **3.20**

We MOM-protected propargyl alcohol **3.23**, a cheap and readily available substance, and used the product **3.24** in our copper-mediated coupling with **3.20**.




Scheme 69 Synthesis of **3.25**

### *3.3.2 Cinchona Alkaloids and Their Derivatives*

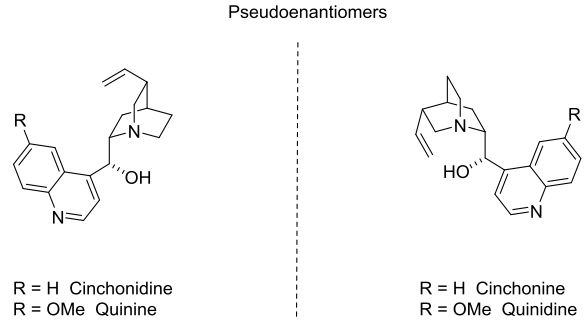
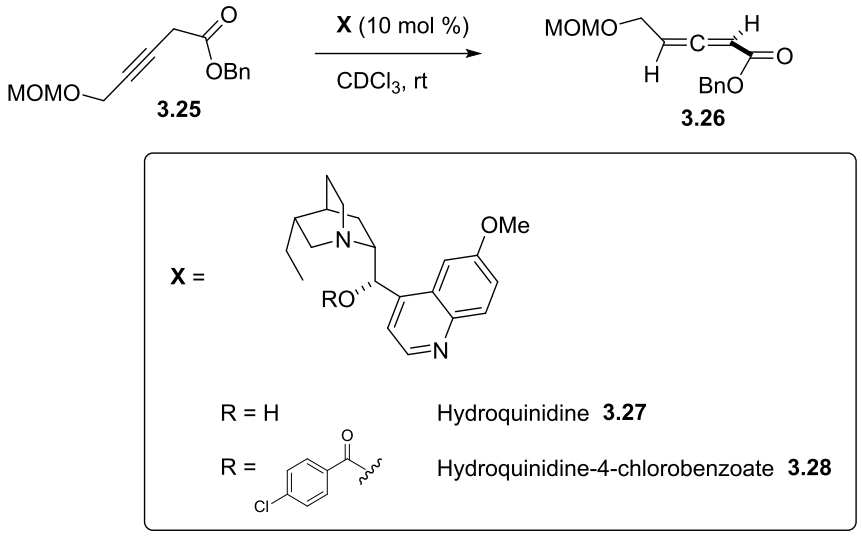



Figure 8 *Cinchona* alkaloids

*Cinchona* alkaloids are considered to be a privileged catalyst[89] meaning that they have found great utility in asymmetric catalysis over a wide range of substrates.[90] *Cinchona* alkaloids have been used to asymmetrically catalyze the Baylis-Hillman reaction, Michael reactions, epoxidations of enones just to name a few. Most importantly, cinchona alkaloids play a key role in asymmetric dihydroxylation. They are readily available in both pseudo-enantiomers meaning chemists have access to both enantiomers of products for a given reaction.




Scheme 70 Isomerization of **3.25**

### *3.3.3 Catalyst Screening*

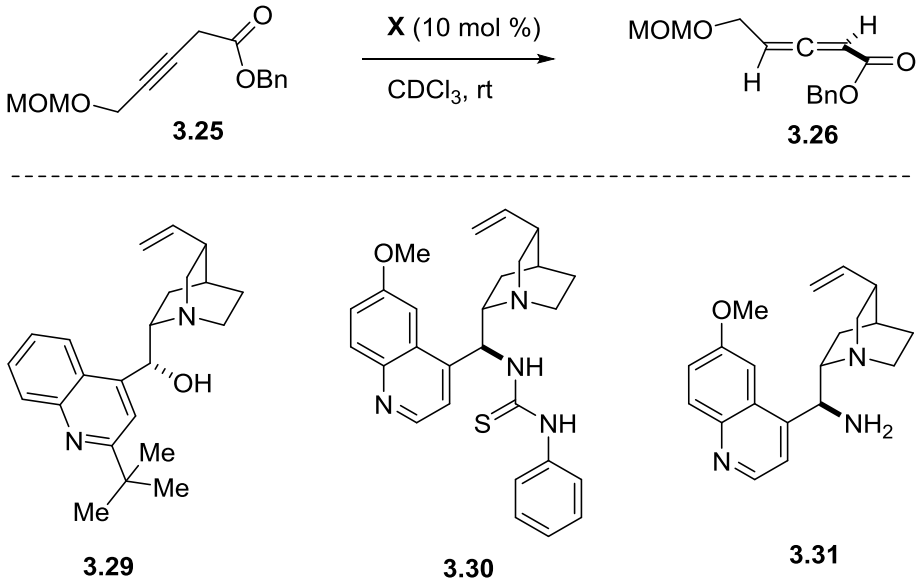
We began by testing a small amount of substrate with 10 mol% of four different catalysts. Cinchonidine, hydroquinidine-4-chlorobenzoate, hydroquinidine and L-proline were screened by watching reaction progress by NMR. It quickly became apparent that L-proline would not serve as an ideal catalyst in $CDCl_3$ as it was insoluble.

Hydroquinidine **3.27** quickly converted our alkyne to allene; 85% conversion was achieved in 55 minutes. HPLC revealed this reaction to have a 13% *ee.* The reaction containing cinchonidine was noted to be nearly complete after 18 h. Unfortunately, this reaction showed no stereoselectivity. Hydroquinidine-4-chlorobenzoate, was monitored over a series of days, and at 13 days the reaction was only 42% complete; orders of magnitude slower than the analogous alcohol.

The slow rate of conversion while using the chlorobenzoate may give clues to the mechanism of the reaction. It is possible that that the 3-alkynoate is being deprotonated by quinuclidine amine and reprotonation is coming from the hydroxyl group. This would be analogous to the postulated mechanism of the guanidinium catalysis (*vide supra*). It is also possible that having then benzyl ester retards the reaction rate simply by providing steric hindrance to quinuclidine.

Hydroquinidine, the most successful of the first catalysts screened was then tested in benzene *d*-6. The reaction was nearly complete within 1 hour. HPLC revealed the *ee* of **3.26** prepared in this solvent to be identical of that in $CDCl_3$, 13%.

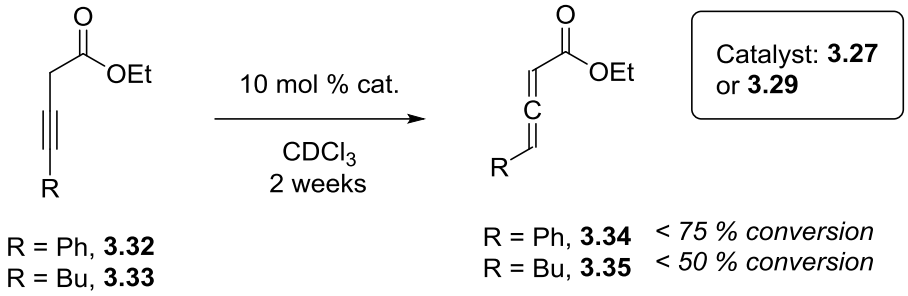
A second set of cinchona alkaloid derivatives were screened using analogous conditions. *t*-Butyl cinchonidine **3.29**, showed promise; the reaction was ~75% complete by NMR at the 250 minute mark. The reaction product showed a moderate 35% *ee.* Switching the solvent to toluene, we found the *ee* went down to 25%. The second cinchona, derivative, a thiourea, **3.30,** is generally used for asymmetric hydrogen-bond catalysis. This mode of catalysis may be a valid way to induce an asymmetric isomerization of our alkynoate. In our screening reaction however, the conversion was slow, only reaching 57% after 8 days at room temperature. Catalyst **3.31** is actually the direct precursor to catalyst **3.30**. The reaction with catalyst **3.31** was slow as well. The reaction was found 46% complete after 48 hours and 72% complete after 8 days.




Scheme 71 *Cinchona* derivatives as alkynoate-allenoate isomerization catalysts

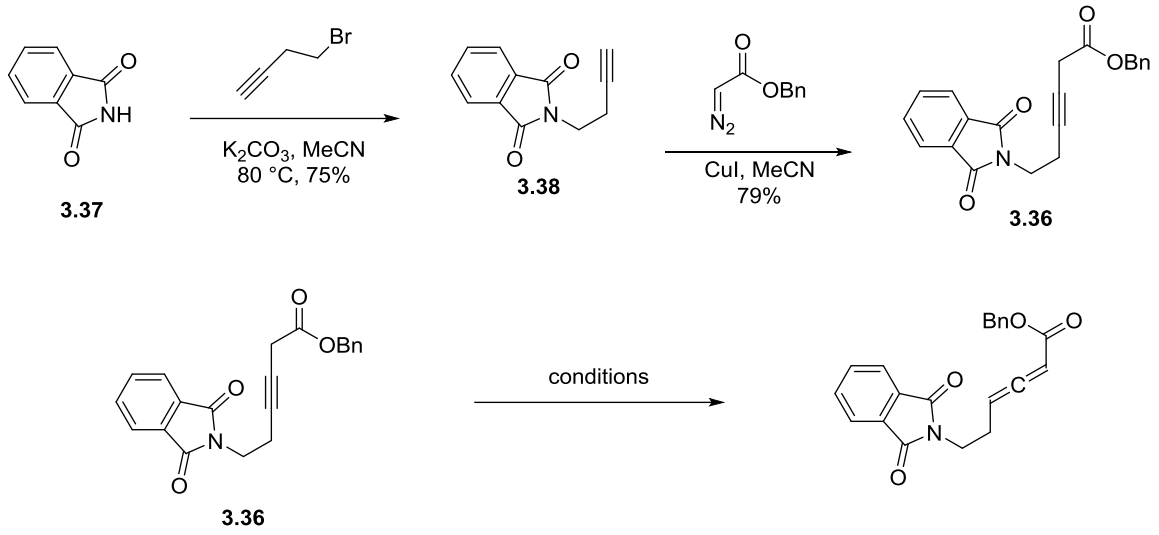
Other 3-alkynoates were prepared to help us get an understanding of the scope of this reaction. Compounds **3.32** and **3.33** were prepared by the standard Wittig method and were tested with hydroquinidine and *t*-butylcinchonidine in $CDCl_3$. The alkyne bearing

only a plain alkyl group was very sluggish to isomerize with either catalyst. After two weeks, neither reaction had progressed past 50%. Regardless of catalyst, the substrate bearing phenyl group, converted to about 75% after 5 days.




Scheme 72 Isomerization of alkyl/aryl substituted alkynes

Liu and coworkers found the thalimido substituted alkyonate gave better conversion to the allene than other substitution patterns (95% vs next best OBn, 79%) and so we were curious if better conversion would also be born out in our system. Thalimido substituted alkynoate **3.36** was synthesized starting from thalimide **3.37**, and propargyl bromide (Scheme 76). This was coupled with benzyl diazoacetate, to yield **3.36**. This was subjected to standard reaction conditions and was complete within 24 hours. The substrate was also tested with cinchonidine and was found to go to completion as well. Hydroquinidine showed the reaction complete within 3 hours. The rapid completion of this reaction was welcomed but the *ee*, 11%, left much to be desired. Changing solvent to acetonitrile caused an increase in reaction rate, despite the poor solubility of cinchonidine. A 1:2 mixture of $CDCl_3$ and acetonitrile led to the fastest rate we observed; the reaction was done within 105 minutes.




Scheme 73 Thalimide-based allene

Our initial catalyst screens showed 9-desoxy-aminoquinine **3.31** giving the best enantioselectivity so we pursued a solvent screen with this catalyst and a substrate that better reflected our needed substrate for our englerin synthesis. Because of the sluggish nature of the reaction with this catalyst we decided to attempt the reaction at elevated temperature. When this substrate was exposed to catalyst **3.31**, at 60 °C 2,2,2-trifluoroethanol, THF and $CDCl_3$, showed no reaction. Reaction in acetonitrile and DMF showed 46 and 50% completion, respectively. Based on these results, we hypothesized that the reaction worked best in polar, aprotic solvents. With this data in hand we switched catalyst to hydroquinidine and screened the reaction in acetonitrile DMSO and acetic acid to confirm our hypothesis. NMR at 17 hours showed no reaction in acetic acid, with the reaction in acetonitrile and DMSO both near 66% complete.

### *3.3.4 Conclusions and Future Work*

While we did not find optimal conditions for the isomerization of 3-alkynoates to allenoates, we were able to identify conditions for moderate *ee.* We were

also able to identify aprotic non-polar solvents being preferred. Reactions in protic solvents did not show any conversion and reactions in non-polar solvents were sluggish. We also determined substrates bearing electronegative atoms worked better than those without. A phenyl group at the 4- position converted faster than a butyl; substrates with heteroatoms on the substituents were generally better than alkyl or aryl. These findings should allow for more productive screening of future catalysts and substrates to produce a quick, convenient, highly selective isomerization of 3-alkynoates to allenes. A full accounting of our work isomerizing 3-alkynoates to allenones can be found in Appendix I.

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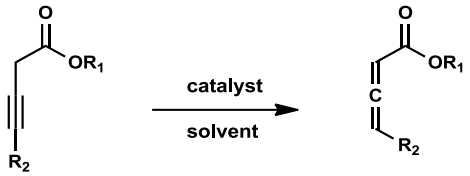
# Appendix I 3-Alkyne isomerizations




| $R_1$ | $R_2$ | Catalyst | Solvent | Time | Temp | %Conversion | % ee |
|---|---|---|---|---|---|---|---|
| **OBn** | $CH_2OMOM$ | HQD | $CDCl_3$ | 1 h | rt | 85 | 13 |
| | | | benzene | 1h | rt | >65[a] | 13 |
| | | AQD | $CDCl_3$ | 8 d | rt | 72 | 50 |
| | | CD | $CDCl_3$ | 18 h | rt | | 0 |
| | | *t*-BuCD | $CDCl_3$ | 250 min | rt | | 34 |
| | | | toluene | 250 min | rt | | 25 |
| | | QN | | 17 h | rt | | 0 |
| | | ATU | $CDCl_3$ | 8 d | rt | 57 | 42 |
| | $CH2CH_2OTIPS$ | HQD[b] | MeCN | 17 h | rt | 67 | |
| | | | AcOH | 17 h | rt | 0 | |
| | | | DMSO | 17 h | rt | 65 | |
| | | AQD | $F_3CCH_2OH$ | 48 h | 60 ° C | 0 | |
| | | | THF | 48 h | 60 ° C | 0 | |
| | | | $CDCl_3$ | 48 h | 60 ° C | 0 | |
| | | | MeCN | 48 h | 60 ° C | 50 | |
| | | | DMF | 48 h | 60 ° C | 46 | |
| | | CD | Phosphate buffer | 30 min | 110° C [c] | 50 | |
| | | *t*-BuCD | $CDCl_3$ | 24 h | rt | 0 | |
| | $CH_2CH_2$*N*-phalimide | HQD[b] | $CDCl_3$ | 1 h | 0 ° C | 100 | |
| | | | $CDCl_3$ | 3 h | rt | 100 | 11 |
| | | CD | MeCN | 105 min | rt | 100 | |
| | | *t*-BuCD | $CDCl_3$ | 24 h | rt | 100 | |
| | CH2CH2OBOC | HQD | $CDCl_3$ | 22 h | rt | 76 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $CH2CH_2OTIPS$ | Ph-gly-OH | MeCN | 8 d | rt | 0 | | |
| | | HQD | MeCN | 8 d | rt | 67 | | |
| | | AQD | MeCN | 8 d | rt | 0 | | |
| | | *t*-BuCD | MeCN | 8 d | rt | 55 | | |
| | | QN | MeCN | 8 d | rt | 52 | | |
| ***t*-BuO** | $CH_2CH_2OMOM$ | HQN | MeCN | 3 d | rt | 39 | | |
| | | | acetone | 3 d | rt | 44 | 0 | |
| | | | nitrobenzene | 3 d | rt | 40 | | |
| | | HQN | neat | 21 h | 50° C | 61[d] | | |
| | | DBU | MeCN | 20 min | rt | 50 | | |

[a]Conversion at 20 minutes, *ee* determination at 1 h.

[b]20 mol% catalyst used

[c]microwave heating

[d] 24 h later still at 61% conversion.

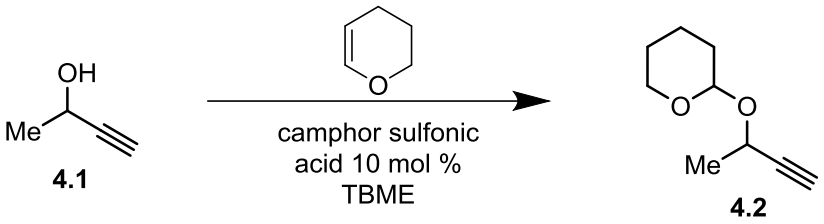
# Appendix II Experimental Procedures

## 3.4 General Procedures

All glassware was either oven or flame-dried and sealed with standard rubber septa under dry nitrogen atmosphere using standard Schlenk technique unless otherwise noted. THF was distilled from sodium and benzophenone under nitrogen. DCM and MeCN was dried by passage through an activated alumina column under nitrogen Thin-layer chromatography (TLC) was performed using plates precoated with silica gel XHL w/UV254 (250 mm) and visualized by UV light, $KMnO_4$, or anisaldehyde stain, followed by heating. All necessary purifications were conducted by flash column chromatography (FCC) using silica gel (particle size 32–63 μm). $^{1}H$ and $^{13}C$ NMR spectra are reported relative to the residual solvent peak (δ 7.27 and δ 77.2 for $^{1}H$ and $^{13}C$, respectively). Data for $^{1}H$ NMR spectra are reported as follows: chemical shift (δ (ppm)) (multiplicity, coupling constant (Hz), integration). Spectra are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet m = multiplet, br = broad. IR samples were prepared on NaCl plates by evaporation from $CHCl_3$ or $CH_2Cl_2$.

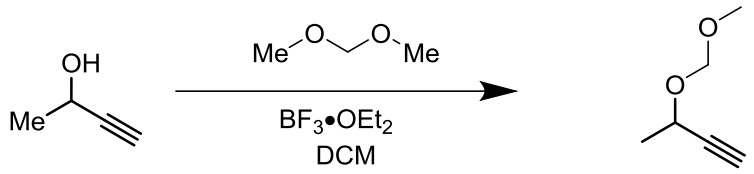
**General Procedure A.**

CuI (60.8 mg, 0.32 mmol) was added to a 1 dram vial containing terminal alkyne (6.47 mmol) and 3.5 mL MeCN. Diazo compound (6.47 mmol) is added over a period of 5 minutes and the vial is capped and stirred overnight. Then MeCN is removed under reduced pressure and the residue passed through a plug of silica with an appropriate ethyl acetate/hexanes ratio to afford crude product.




**2-(but-3-yn-2-yloxy)tetrahydro-2H-pyran**: 3-Butyn-2-ol (2.10 g, 30.0 mmol) was added to a flask containing 300 mL of TBME and and 3,4-dihydro-(2H)-pyran. Camphor sulfonic acid (696 mg, 3.0 mmol, 10 mol%) was added in one portion. The reaction was stirred for 8 h when it was quenched with 50 mL sat. $NaHCO_3$, and was extracted with 100 mL diethyl ether. The organic layer was washed with 50 mL water, and 50 mL brine. The aqueous layer was back-extracted with 50 mL of petroleum ether and pooled with the organic layers which were dried with $MgSO_4$ and concentrated. Crude product was plugged through silica with hexanes and concentrated yielding **4.2** (3.77 g, 82%) as a colorless oil.

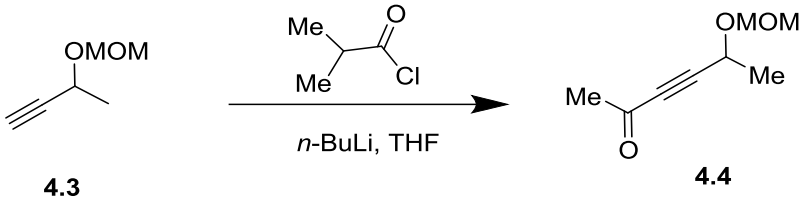
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 5.01 - 4.92 (m, 1 H), 4.78 (t, *J* = 3.2 Hz, 1 H), 4.56 (dq, *J* = 2.0, 6.7 Hz, 1 H), 4.47 (dq, *J* = 2.2, 6.6 Hz, 1 H), 4.00 (ddd, *J* = 2.7, 8.9, 11.4 Hz, 1 H), 3.86 - 3.79 (m, 2 H), 3.58 - 3.50 (m, 3 H), 2.44 (d, *J* = 2.0 Hz, 1 H), 2.38 (d, *J* = 2.0 Hz, 1 H), 1.90 - 1.81 (m, 3 H), 1.79 (t, *J* = 2.9 Hz, 1 H), 1.77 - 1.69 (m, 3 H), 1.67 - 1.51 (m, 14 H), 1.49 (d, *J* = 6.8 Hz, 5 H), 1.45 (d, *J* = 6.3 Hz, 4 H)




**4.1** **4.3**

**2-(methoxymethoxy)-3-butyne:** Dimethoxymethane (1.06 mL, 6.0 mmol) and $BF_3 \cdot OEt_2$ (0.6 mL, 4.8 mmol) was added dropwise simultaneously to a mixture of 3-buyn-2-ol (280 mg, 4.0 mmol) and 6 mL of DCM. The reaction was stirred for 70 minutes, was quenched with 20 mL of saturated aqueous $NH_4Cl$, extracted with 20 mL of DCM and dried with $Na_2SO_4$, and concentrated yielding **4.3** (263 mg 58%) of colorless volatile product.

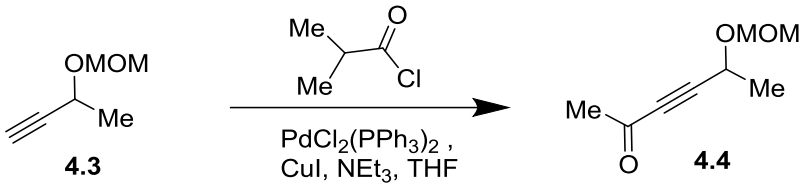
**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 4.93 (d, *J* = 6.6 Hz, 1 H), 4.61 (d, *J* = 7.0 Hz, 1 H), 4.45 (dq, *J* = 1.8, 6.7 Hz, 1 H), 3.39 (s, 3 H), 2.42 (d, *J* = 1.8 Hz, 1 H), 1.48 (d, *J* = 7.0 Hz, 3 H).




**4.3** **4.4**

**5-(methoxymethoxy)hex-3-yn-2-one:**

**Method A:** 2-(Methoxymethyoxy) but3-yne (440 mg, 3.8 mmol) was added to 40 mL of THF. *n*-BuLi (1.52 mL, 3.8 mmol, 2.5 M in hexane) was added dropwise at -78 °C. After 25 minutes, butyryl chloride was added in 5 mL of THF and the mixture was stirred for 1 h then allowed to warm to room temperature. The reaction was then quenched with 20 ml water, and etracted with diethyl ether (2 × 25 mL), washed with 20 ml water and 20 mL brine and dried with $MgSO_4$. The organic layer was concentrated and columned with 20% ethyl acetate/hexanes and concentrated yielding **4.5** (201 mg, 34%) as a colorless oil.

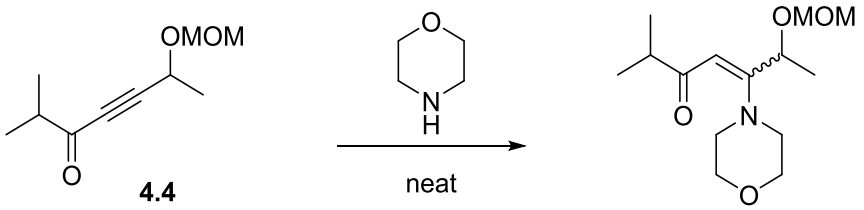



**4.3** **4.4**

**Method B:** 2-(Methoxymethyoxy) but3-yne (4.56 g, 39.9 mmol) and butryryl chloride (4.79 g, 4.71 mL, 45.0 mmol) was added to 80 mL THF followed by $PdCl_2(PPh_3)_2$ (189 mg, 0.270 mmol) and CuI (171 mg, 0.900 mmol). Triethylamine was added dropwise over one minute and the reaction was stirred at room temperature for 50 minutes when it was added to 225 mL of water and 225 mL of diethyl ether. The layers were mixed and

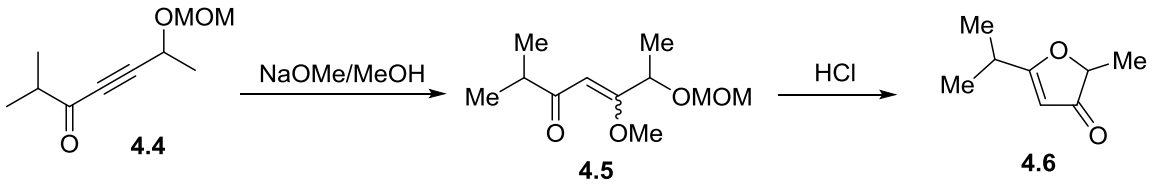
separated and the organic layer was washed with 100 mL water. The aqueous layer was back-extracted with hexanes (2 × 100 mL) and DCM (100 mL) and the pooled organic layers were dried with $Na_2SO_4$ and concentrated. Solids in the concentrate were removed by filtration through a plug of celite with hexanes and concentrating the filtrate. The crude residue was purified with flash column chromatography on $SiO_2$ with 10-50% ethyl ether/hexanes and fractions containing product were concentrated yielding **4.4** (7.35 g,84%) of product as a colorless oil.

**$^1$H NMR:** $^1$H NMR (300MHz ,CHLOROFORM-d) δ = 4.89 (d, *J* = 7.0 Hz, 1 H), 4.70 - 4.55 (m, 2 H), 3.40 (s, 3 H), 2.66 (spt, *J* = 7.0 Hz, 1 H), 1.53 (d, *J* = 7.0 Hz, 3 H), 1.20 (d, *J* = 7.0 Hz, 6 H)



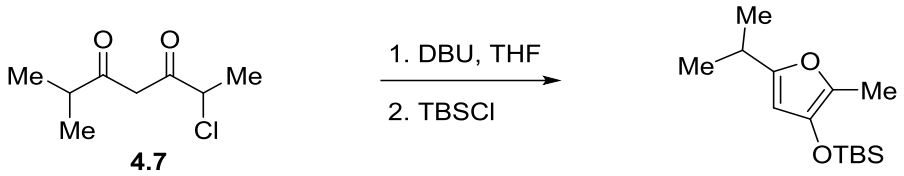

**6-(methoxymethoxy)-2-methyl-5-morpholinohept-4-en-3-one:** Morpholine (41 mg, 0.47 mmol) was added dropwise to a stirred vial containing **4.4** (86 mg, 0.47 mmol) at 0 °C. After the addition the reaction was allowed to warm to rt and was stirred for 3 days yielding **4.5** (127 mg, quantitiative) of product as a yellow oil.

**$^1$H NMR** (500MHz ,CHLOROFORM-d) δ = 6.29 (q, *J* = 7.0 Hz, 1 H), 5.15 (s, 1 H), 4.67 - 4.56 (m, 2 H), 3.87 - 3.67 (m, 6 H), 3.56 (ddd, *J* = 3.4, 6.2, 12.8 Hz, 2 H), 3.37 (s, 3 H), 3.30 (ddd, *J* = 3.2, 6.2, 13.1 Hz, 2 H), 2.63 - 2.45 (m, 2 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.08 (dd, *J* = 4.9, 6.8 Hz, 6 H)




**5-isopropyl-2-methylfuran-3(2H)-one**: Sodium methoxide (2.29 g, 10.6 mmol, 2 equiv. 25% solution in methanol) was added to 5-(methoxymethoxy)hex-3-yn-2-one (983 mg, 5.32 mmol) in 25 mL of methanol. After 1 minute TLC indicated starting material was used up. Concentrated hydrochloric acid was slowly added (20 mL) and the reaction mixture was stirred for 5 minutes. Water was added (50 mL) and the mixture was extracted with dichloromethane (50 mL). The organic layer was washed with 20 mL sat. $NaHCO_3$, and 20 mL of brine. The layer was dried with $MgSO_4$ and concentrated. Resultant crude was chromatographed on silica with 10-15% ethyl acetate/hexanes and concentrated to yield **4.6** (458 mg, 67%) as a colorless oil.

**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 5.39 (s, 1 H), 4.49 (q, *J* = 7.0 Hz, 1 H), 2.71 (spt, *J* = 7.0 Hz, 1 H), 1.43 (d, *J* = 7.3 Hz, 3 H), 1.23 (d, *J* = 7.0 Hz, 6 H).

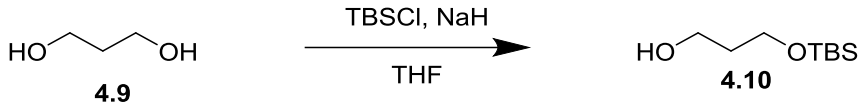



**4.7** **4.8**

**3-(*tert*-butyldimethylsiloxy)-5-isopropyl-2-methylfuran 4.8**: Chlorodiketone **4.7** (177 mg, 1.0 mmol, 1 equiv.) was added to a stirred 4 mL vial containing THF (2.5 mL). DBU (447 μL, 3.0 mmol, 3 equiv.) was added dropwise. Dry $N_2$ was blown over the top and the vial was capped and stirred 3 h. TBSCl (181 mg, 1.2 mmol, 1.2 equiv.) was added and mixture stirred 1 h. At this point the reaction was complete by TLC and 5 mL of MeOH was added and the solvent was removed by rotory evaporation. The residue was taken up in 10 mL of MeOH and extracted with petroleum ether (3 × 20 mL). The petroleum ether layers were pooled and washed with 5 mL of water which was drained into the collected MeOH layer whereupon two phases were formed. TLC showed the presence of product in the top phase and so it was separated and pooled with the other petroleum ether layers. The combined petroleum ether layers were dried with $Na_2SO_4$, decanted, and concentrated yielding siloxyfuran **4.8** in 81% yield with no further purification required.

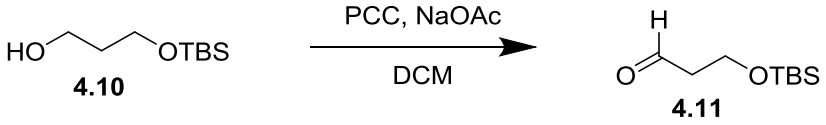
**$^1$H NMR** (500MHz , $CDCl_3$) δ = 5.63 (s, 1 H), 2.78 (spt, *J* = 6.7 Hz, 1 H), 2.14 (s, 3 H), 1.18 (d, *J* = 6.7 Hz, 6 H), 0.97 (s, 9 H), 0.14 (s, 6 H).

**$^{13}$C NMR** (125MHz ,$CDCl_3$) δ = 4.7, 10.3, 18.0, 21.0, 25.6, 28.0, 100.2, 134.6, 137.7, 157.1.




**3-*tert*-butyldimethylsilyloxypropan-1-ol:** 1,3-propanediol (502 mg, 6.6 mmol was added to a stirred suspention of sodium hydride (158 mg, 6.6 mmol) in 13 mL THF. After 1 hr, TBSCl (1.00 g, 6.6 mmol) was added. The reaction was stirred overnight then 30 mL of diethyl ether was added and the mixture was washed with 20 mL of 10% aqueous $K_2CO_3$, 20 mL of brine and was dried with $Na_2SO_4$ and was concentrated. Residue was purified by column chromatography on silica with 20% ethyl acetate/hexanes yielding **4.10** (877 mg, 69%) of colorless oil.

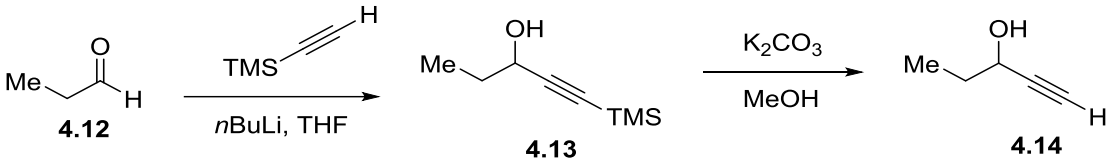
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 3.85 (t, *J* = 5.6 Hz, 2 H), 3.81 (q, *J* = 5.4 Hz, 7 H), 2.57 (t, *J* = 5.4 Hz, 1 H), 1.79 (quin, *J* = 5.5 Hz, 2 H), 0.91 (s, 9 H), 0.08 (s, 6 H)




**3-*tert*-butyldimethylsilyloxypropanal:** Pyridinium chlorochromate (3.80 g, 17.8 mmol was added to a mixture of sodium acetate (582mg, 7.10 mmol) and **4.10** (1.7 g 8.9 mmol) in 36 mL of DCM at 0 °C and the mixture was stirred at that temperature for 1 h. The reaction was allowed to warm to room temperature and was stirred an additional 1.5 h. Reaction was then diluted with 100 mL of diethyl ether and stirred with celite. The mixture was plugged through celite, then through silica. The mixture was washed with 50

mL 10% aqueous NaOH, 50 mL of brine and was dried with $MgSO_4$, and concentrated yielding aldehyde **4.11** as a coloroless oil (873 mg, 52%).

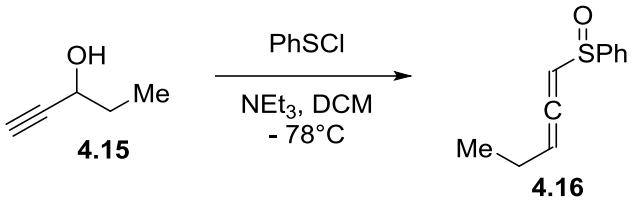
**$^1$H NMR**: (300MHz ,CHLOROFORM-d) δ = 9.99 - 9.62 (m, 1 H), 3.98 (t, *J* = 6.0 Hz, 2 H), 2.60 (dt, *J* = 2.0, 6.0 Hz, 2 H), 0.87 (s, 9 H), 0.06 (s, 6 H)




**Pent-1-yn-3-ol**: Trimethylsilylethyne (3.8 mL, 26.7 mmol) was added to 50 mL of THF followed by *n*-BuLi (2.5 M in hexane, 5.36 mL, 13.4 mmol) dropwise at 0 °C and the reaction was stirred for 20 minutes. Propionaldehyde (0.5 mL, 10.8 mmol) was added dropwise and stirred overnight while allowing the reaction to warm to rt. The reaction was quenched with 20 mL sat. aq. $NH_4Cl$, extracted with diethyl ether (3 × 20 mL), washed with 20 mL water, 20 mL brine and dried with $Na_2SO_4$ and immediately used in the following reaction.

Into the flask containing the reaction intermediate **4.13** was added 20 mL MeOH and a large excess of $K_2CO_3$. The reaction was stirred for 1 h after which the product was extracted with diethyl ether (3 × 20 mL) and dried with $MgSO_4$, concentrated and purified by silica gel column chromatography with DCM containing 2% acetone yielding 322 mg (35% ) of **4.14** as a colorless oil.

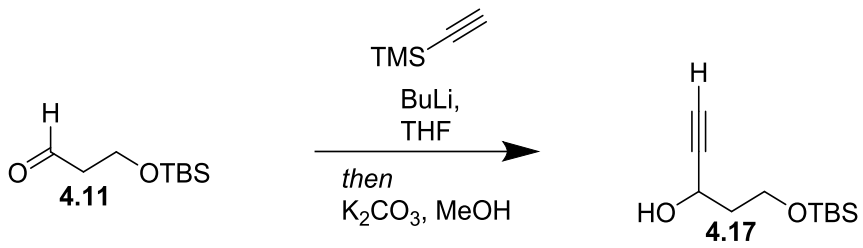
**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 4.33 (br. s., 1 H), 2.47 (d, *J* = 2.2 Hz, 1 H), 1.93 (br. s., 1 H), 1.75 (quin, *J* = 7.1 Hz, 2 H), 1.03 (t, *J* = 7.5 Hz, 3 H)




**4.15** **4.16**

**(Penta-1,2-dien-1-ylsulfinyl)benzene:** Phenylsulfinyl choride was added dropwise to a solution of pent-1-yn-3-ol(322 mg, 3.7 mmol), triethylamine(0.52 mL, 3.7 mmol) and 10 mL of DCM at – 78 °C until the red color was durable. Reaction was allowed to run for 3 h, and was quenched with 10 mL of saturated $NH_4Cl$, and was extracted with 10 mL of DCM followed by 10 mL of $Et_2O$, and the combined organic layers were washed with 10 mL of water. Organic layers were dried with $MgSO_4$ and concentrated this residue was columned on silica with DCM containing 2% acetone and fractions containing prouct collected and concentrated. Fractions were further purified with flash column chromatography on silica with 0 to 20% ethyl acetate/hexanes and fractions containing product were concentrated yielding 99.1 mg of **4.16** containing ethyl acetate.

**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 7.81 - 7.60 (m, 1 H), 7.59 - 7.40 (m, 3 H), 6.08 (td, *J* = 3.0, 6.0 Hz, 1 H), 5.90 - 5.69 (m, 1 H), 2.26 - 2.08 (m, 2 H), 1.14 - 0.95 (m, 3 H)

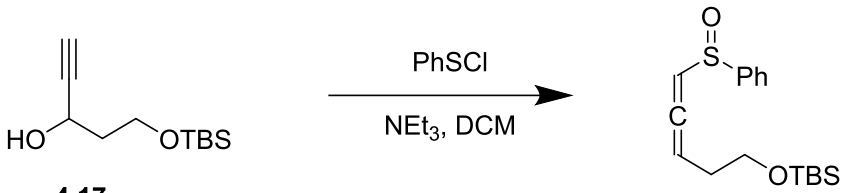



**5-((tert-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol:**

*n*-Buli (2.5M in hexanes, 2.6mL, 0.96mmol) was added dropwise to a solution of trimethylsilylacetylene (667 mg, 6.8 mmol) and THF 10 mL at 0 °C. Mixture was stirred for 30 minutes then cooled to -78 °C. Aldehyde **4.11** (836 mg, 4.40) mmol in 50 mL THF was cannulated into the reaction flask. Reaction was allowed to warm overnight and was then quenched with 50 mL saturated $NH_4Cl$, and extracted with 100 mL diethyl ether. Organic layer was washed with 50 mL brine and dried with $MgSO_4$ and concentrated. The residue was diluted in 20 mL methanol and a large excess of $K_2CO_3$ was added. The reaction was stirred for 30 minutes when TLC indicated the reaction was complete. The mixture was quenched with 20 mL saturated $NH_4Cl$, and extracted with 50 mL diethyl ether. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. Residue obtained was purified by flash column chromatography on silica with hexanes to hexanes containing 12% ethyl acetate and fractions containing product were concentrated yielding 317 mg (34%) of **4.17** as a colorless oil.

**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 4.73 - 4.55 (m, 1 H), 4.07 (ddd, *J* = 3.4, 8.3, 10.3 Hz, 1 H), 3.85 (ddd, *J* = 4.4, 5.9, 10.3 Hz, 1 H), 3.55 (d, *J* = 6.3 Hz, 1 H),

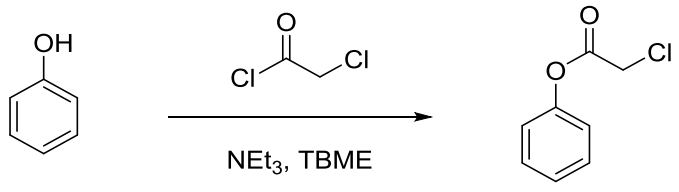
2.47 (d, *J* = 2.0 Hz, 1 H), 2.11 - 1.96 (m, 1 H), 1.88 (dtd, *J* = 3.7, 6.2, 14.3 Hz, 1 H), 0.91 (s, 9 H), 0.10 (d, *J* = 3.9 Hz, 6 H)




**4.17** **4.18**

Compound Name: A mixture of triethylamine (226 μL, 1.6 mmol) and 15 mL of DCM were cooled to -78 °C 3-propyn-2-ol (125 mg, 1.5 mmol) phenylsulfinyl chloride was added until the color was durable (2.5 mL) Reaction was allowed to run for 3 h, and was quenched with 10 mL of saturated $NH_4Cl$, and was extracted with 10 mL of DCM followed by 10 mL of $Et_2O$, and the combined organic layers were washed with 10 mL of water. Organic layers were dried with $MgSO_4$ and concentrated this residue was columned on silica with 20% ethyl acetate/hexanes yielding 143 mg (50%) of light yellow oil **4.18**.

**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 7.80 - 7.59 (m, 2 H), 7.57 - 7.38 (m, 4 H), 6.03 (td, *J* = 2.7, 5.7 Hz, 1 H), 5.86 - 5.60 (m, 1 H), 3.83 - 3.52 (m, 2 H), 2.47 - 2.21 (m, 2 H), 0.98 - 0.81 (m, 9 H), 0.10 - -0.01 (m, 6 H)

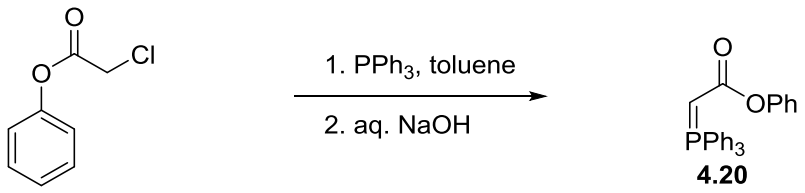



**4.19**

**Phenyl 2-chloroacetate:** Phenol (3.76 g, 40 mmol) and triethylamine (5.6 mL, 40 mmol) were added to TBME. Chloroacetylchloride (3.2 mL, 40 mmol) was then added dropwise and the mixture was stirred for 30 min. The reaction was filtered and concentrated and the crude material was recrystallized from ethanol/water overnight yielding 6.12 g (90%) **4.19** as off-white needles.

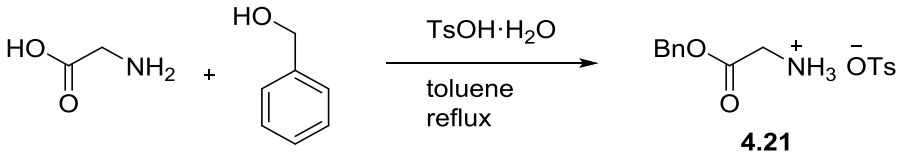
**$^{1}$H NMR:** (300MHz ,CHLOROFORM-d) δ = 7.47 - 7.36 (m, 2 H), 7.32 - 7.21 (m, 1 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 4.31 (s, 2 H).

**$^{13}$C NMR:** (75MHz, CHLOROFORM-d) δ = 165.8, 150.3, 129.6, 126.4, 121.1, 40.9.




4.19 **4.20**

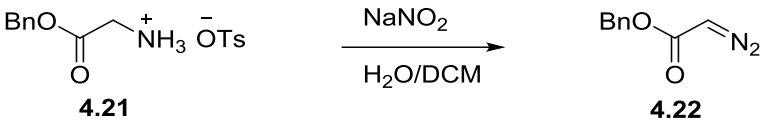
Phenyl chloroacetate (6.12 g, 38.9 mmol) was added to 40 mL of toluene followed by triphenylphosphine (10.2 g, 38.9 mmol) and the mixture was heated to reflux wherein a precipitate was formed and filtered. The filtered material was dissolved in a minimal amount of water and precipitated by the dropwise addition of 15% aqueous NaOH with stirring. NaOH addition was done when a small amount of phenolphthalein indicator showed the reaction medium was basic. The precipitate was then vacuum filtered and washed with water and recrystallized from ethanol yielding 4.92 g (32%) white needles.




**4.21**

**Benzyl glycine *p*-toyluenesulfonic acid complex:** Glycine (13.5 g, 180 mmol) was added to a mixture of 20 g (185 mmol) benzyl alcohol in 370 mL toluene. Para-toluenesulfonic acid ·$H_2O$ (185 mmol, 35.15 g) was added and the mixture was heated to reflux with a Dean-Stark trap attached. The mixture was refluxed for 1 day then removed from heat, capped and cooled to – 40 °C overnight. Reaction mixture was filtered on a Buchner funnel and washed with toluene until the filtrate ran clear (~200 mL). Collected crystals **4.21** were fluffy and butter-cream colored 47.9 g, 79% yield.

**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 8.08 (br. s., 3 H), 7.65 (d, *J* = 8.1 Hz, 2 H), 7.28 - 7.10 (m, 4 H), 6.95 (d, *J* = 8.1 Hz, 2 H), 4.94 (s, 2 H), 4.07 (br. s., 2 H), 3.69 (d, *J* = 5.5 Hz, 2 H), 2.21 (s, 3 H).

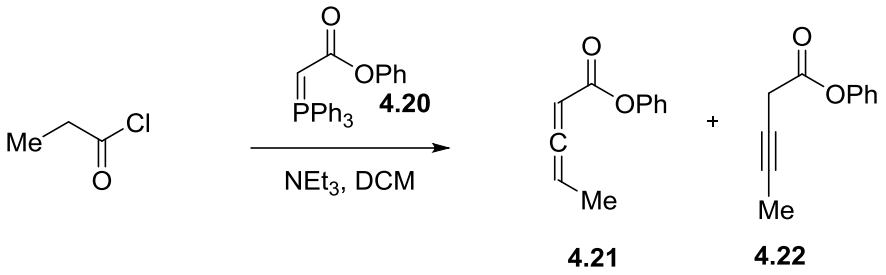



**4.21** **4.22**

**Benzyldiazoacetate:** In a 500 mL Erlenmeyer flask was added benzylglycine-paratoluene sulfonic acid complex followed by 75 mL of water and 75 mL DCM. Sodium nitrite was added portion-wise at 0 °C over 15 minutes. Reaction was stirred an additional 15 minutes and was then poured into a separatory funnel where it was quenched with 50 mL of saturated $NaHCO_3$, and the layers were separated. The aqueous layer was extracted

with 25 mL of DCM and combined organics were dried with $Na_2SO_4$ and concentrated yielding **4.22** (5.54 g, 57%) crude yellow oil.

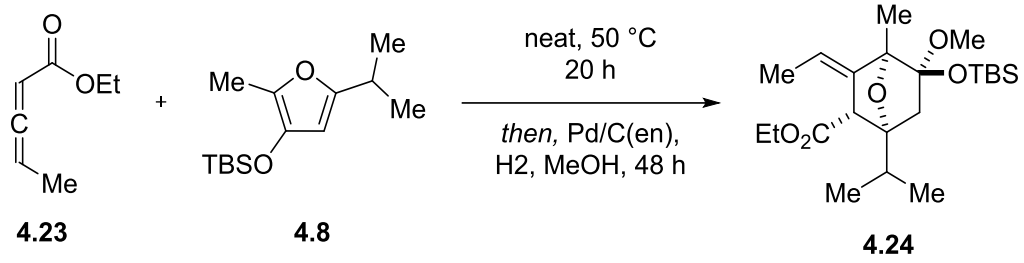
**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 7.38 (s, 5 H), 5.22 (s, 2 H), 4.82 (br. s., 1 H)




**4.21** **4.22**

1 : 1 inseperable mixture

**Phenyl penta-2,3-dienoate/phenyl pent-3-ynoate**: Wittig reagent **4.20** (1.51 g, 3.8 mmol was stirred with triethylamine 354 mg, 3.50 mmol) in 40 mL of DCM. Propionyl choride (1.6 mL, 3.2 mmol) was added dropwise as a 2 M solution in DCM and the reaction was stirred overnight. The mixture was concentrated and eluted through silica with 5% ethyl acetate/hexanes affording 183 mg (33%) of alkyne **4.22** and allene **4.21** as a 1 : 1 inseparable mixture.

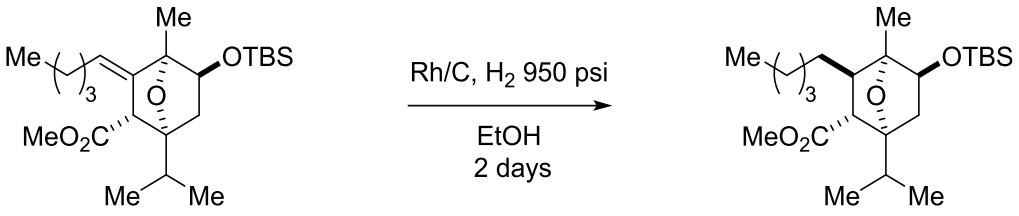



**4.23** **4.8** **4.24**

**Ethyl 5-((tert-butyldimethylsilyl)oxy)-3-ethylidene-1-isopropyl-5-methoxy-4-methyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate:** Into a 1 dram vial was placed 120 mg (0.47 mmol) of furan **4.8** and 60 mg of allene **4.23** and the vial was heated to 50 °C for 20 hours after which $^{1}$H NMR showed the starting material was consumed. Pd/C(en) (21 mg, 0.019 mmol) was added to a flask and the reaction mixture was transferred to the flask with 5 mL MeOH. A hydrogen balloon was attached to the flask and the reaction was allowed to stir for 2 days when the reaction was determined to be complete by TLC. The mixture was filtered through celite and concentrated under vacuum. The residue was purified by flash column chromatography on silica with hexanes to 20% ethyl acetate/hexanes and fractions containing product were concentrated yielding **4.24** (78 mg, 40%) as a clear, colorless oil.

**$^{1}$H NMR**: (500MHz ,CHLOROFORM-d) δ = 5.36 (dq, *J* = 2.9, 6.9 Hz, 1 H), 4.25 - 4.10 (m, 2 H), 3.47 (br. s., 1 H), 3.37 (s, 3 H), 2.50 (d, *J* = 13.1 Hz, 1 H), 2.19 - 2.03 (m, 2 H), 1.57 - 1.51 (m, 3 H), 1.36 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.13 (s, 6 H).

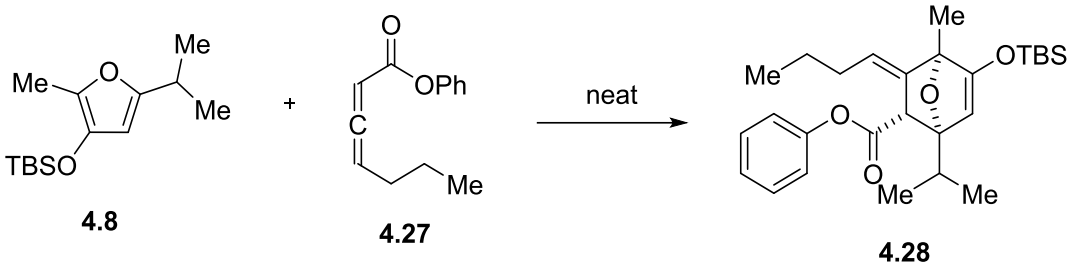
**$^{13}$C NMR** (125 MHz ,CHLOROFORM-d) δ**:** 171.7, 141.9, 118.9, 106.6, 91.0, 89.5, 60.3, 52.6, 51.6, 38.1, 33.3, 25.8, 18.2, 17.7, 17.1, 14.2, 14.1, 13.0, -2.6, -3.5.




**4.25** **4.26**

**Methyl-5-((tert-butyldimethylsilyl)oxy)-1-isopropyl-4-methyl-3-pentyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate:** 5% Rh/C (18.1 mg, 0.0088 mmol) was added to a vial containing **4.25**, (70.0 mg, 0.177 mmol) and 2 mL ethanol. The vial was sealed in hydrogenation vessel and pressurized with hydrogen to 950 psi and was stirred magnetically. The reaction was allowed to run for 2 days, after which the mixture was filtered through celite and concentrated. The crude residue was subjected to silica column chromatography with hexanes to 20% ethyl acetate in hexanes and product fractions were concentrated under vacuum giving 34.2 mg of **4.26** (47%) as a colorless oil.

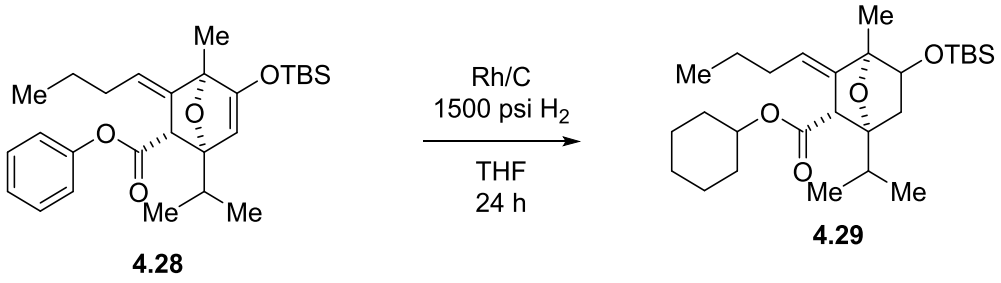
**$^1$H NMR:** (300MHz ,CHLOROFORM-d) $\delta$ = 3.98 - 3.83 (m, 1 H), 3.63 (s, 3 H), 3.06 (dd, *J* = 1.5, 12.1 Hz, 1 H), 2.72 (dd, *J* = 5.1, 12.5 Hz, 1 H), 2.25 - 2.07 (m, 1 H), 2.03 - 1.71 (m, 3 H), 1.69 - 1.49 (m, 1 H), 1.33 (s, 3 H), 1.30 - 0.99 (m, 4 H), 0.91 (s, 9 H), 0.89 - 0.82 (m, 8 H), 0.05 (d, *J* = 8.8 Hz, 6 H).




**phenyl 5-((tert-butyldimethylsilyl)oxy)-3-butylidene-1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate:** Furan **4.8** (0.23 mmol, 185 mg) was mixed with allene **4.27** (0.73 mmol, 148 mg) in a vial and was stirred neat for 15 hours and the mixture was checked by $^{1}$H NMR, and determined to be complete and the *endo*:*exo* ratio was determined to be 5:1 of **4.28**.

**Crude, Major Diastereomer, *exo*:**

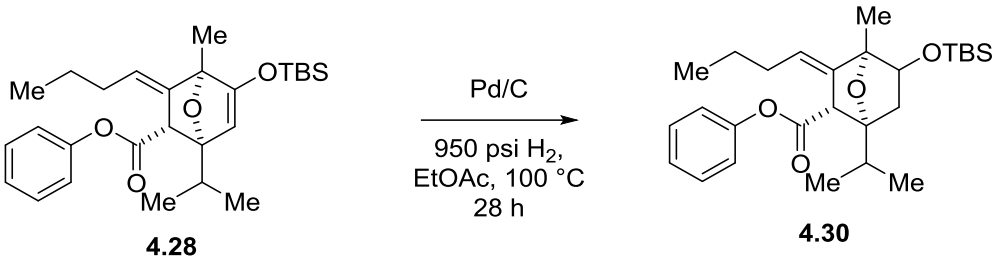
**$^{1}$H NMR:** (500MHz ,CHLOROFORM-d) δ = 7.43 - 7.38 (m, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.04 (d, *J* = 7.8 Hz, 2 H), 5.34 (dt, *J* = 2.2, 7.2 Hz, 1 H), 4.94 (s, 1 H), 3.79 (s, 1 H), 2.36 - 2.26 (m, *J* = 7.1, 13.9 Hz, 2 H), 2.13 - 1.99 (m, 2 H), 1.49 (s, 4 H), 1.14 (dd, *J* = 3.4, 6.8 Hz, 8 H), 0.92 (s, 9 H), 0.19 (s, 3 H), 0.09 (s, 3 H).




**4.28** **4.29**

**Cyclohexyl-5-((tert-butyldimethylsilyl)oxy)-3-butylidene-1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate:** Compound **4.28** was added to 7 mL of THF and 75 mg 5% Rh/C and placed in a sealed hydrogenation bomb. $H_2$ pressure was applied (1500 psi) for 24 h before the reaction mixture was filtered through celite and the solvent removed under vacuum. Mixture was chromatographed on silica with 6% ethyl acetate/hexanes and product fractions concentrated under vacuum yielding 70 mg, (66%) of **4.29** with other unidentified products.

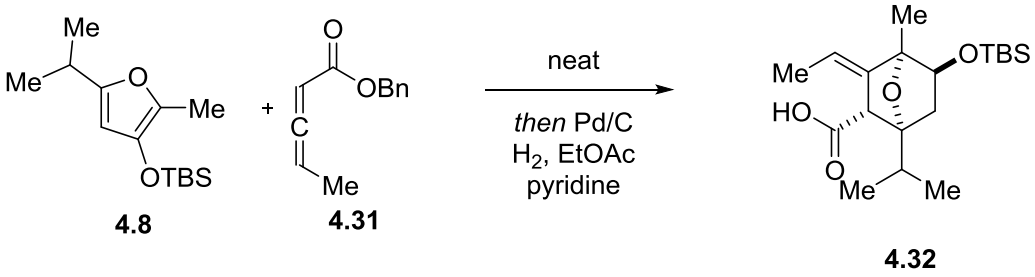
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) $\delta$ = 5.16 (dt, *J* = 2.8, 7.3 Hz, 1 H), 4.86 - 4.77 (m, 1 H), 4.18 (td, *J* = 4.2, 6.5 Hz, 1 H), 3.86 (dd, *J* = 3.9, 10.0 Hz, 1 H), 3.52 - 3.42 (m, 1 H), 2.24 (dd, *J* = 3.9, 12.5 Hz, 1 H), 2.17 (td, *J* = 6.9, 13.2 Hz, 1 H), 2.02 (td, *J* = 6.9, 13.9 Hz, 1 H), 1.98 - 1.67 (m, 11 H), 1.59 - 1.50 (m, 3 H), 1.48 - 1.22 (m, 20 H), 1.19 (d, *J* = 6.3 Hz, 2 H), 1.00 (d, *J* = 6.8 Hz, 4 H), 0.94 (d, *J* = 7.1 Hz, 6 H), 0.92 - 0.83 (m, 26 H), 0.06 - 0.02 (m, 9 H), 0.00 (s, 6 H)




**4.28** **4.30**

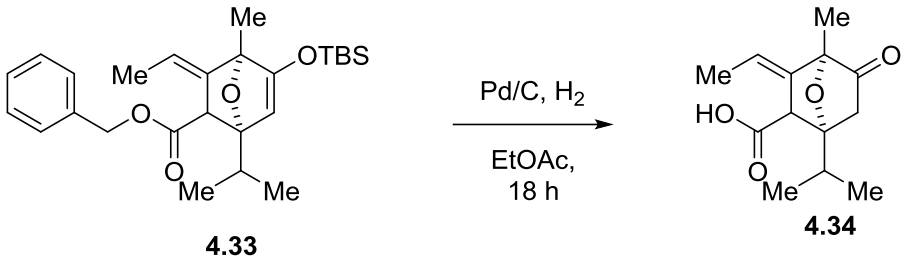
**Phenyl-5-((tert-butyldimethylsilyl)oxy)-3-butylidene-1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate:** **4.28** was added to a vial containing 10 mL of ethyl acetate and 212 mg (0.20 mmol) 10% Pd/C and the vial was sealed in a pressure bomb. 950 psi of $H_2$ gas was added and the vessel was heated to 100 °C for 28 hours. Contents were filtered through celite and concentrated. Crude residue was purified by silica gel chromatography with hexanes to 20% ethyl acetate hexanes yielding **4.30** (335 mg, 35%) as a colorless oil.

**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 7.45 - 7.34 (m, 3 H), 7.25 - 7.19 (m, 1 H), 7.12 - 7.00 (m, 3 H), 5.28 (dt, *J* = 2.9, 7.3 Hz, 1 H), 3.92 (dd, *J* = 3.7, 10.0 Hz, 1 H), 3.76 (br. s., 1 H), 2.61 - 2.52 (m, 1 H), 2.26 (dd, *J* = 3.4, 12.7 Hz, 1 H), 2.14 (tt, *J* = 6.6, 13.2 Hz, 2 H), 2.02 (qd, *J* = 7.2, 14.6 Hz, 1 H), 1.95 - 1.85 (m, 1 H), 1.77 (quin, *J* = 7.6 Hz, 1 H), 1.53 - 1.41 (m, 3 H), 1.39 (s, 3 H), 1.15 - 1.03 (m, 6 H), 0.94 (t, *J* = 7.3 Hz, 6 H), 0.84 (s, 9 H), 0.01 (d, *J* = 12.2 Hz, 6 H)



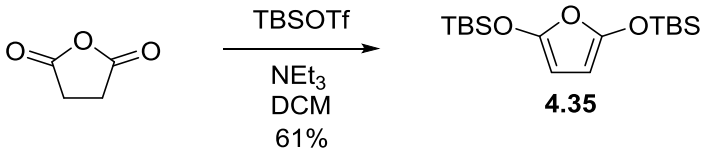

**5-((tert-Butyldimethylsilyl)oxy)-3-ethylidene-1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid:** Furan **4.8** (146 mg 0.57 mmol) and allene **4.31** (107 mg, 0.57 mmol) were placed in a vial and stirred at rt for 2.5 days after which the starting materials were consumed by NMR. 10% Pd/C (60 mg, 0.057 mmol, 10 mol%) and pyridine (9 mg, 0.114 mmol) and 5 mL of ethanol were added to the vial and the vial was sealed in a hydrogenation vessel. 500 psi of hydrogen were applied while stirring and the reaction was run for 5 hours. The reaction mixture was filtered through celite and concentrated under vacuum. The obtained residue was purified with flash column chromatography on silica with hexanes to 50% ethyl aceate/hexanes and fractions containing product were concentrated under vacuum yielding **4.32** (57 mg, 28%) as a colorless oil.

**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 5.48 (dq, *J* = 2.4, 6.8 Hz, 1 H), 4.17 - 4.03 (m, 1 H), 3.69 (br. s., 1 H), 2.16 - 2.05 (m, 2 H), 1.82 (dd, *J* = 1.2, 13.9 Hz, 1 H), 1.65 (dd, *J* = 1.0, 6.8 Hz, 3 H), 1.42 (s, 3 H), 1.09 - 0.98 (m, 7 H), 0.88 (s, 9 H), 0.11 (s, 6H)




**3-Ethylidene-1-isopropyl-4-methyl-5-oxo-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid: 4.33** was mixed with 1.8 mg of 10% Pd/C (0.0017 mmol) in 1 mL of ethyl acetate. A balloon with $H_2$ was affixed and the reaction was stirred for 18 h. The mixture was then filtered through celite and concentrated. The crude product was chromatographed on silica with hexanes to 20% ethyl acetate hexanes. Fractions containing product were concentrated yielding **4.34** (2.1 mg, 52%) as a colorless oil.

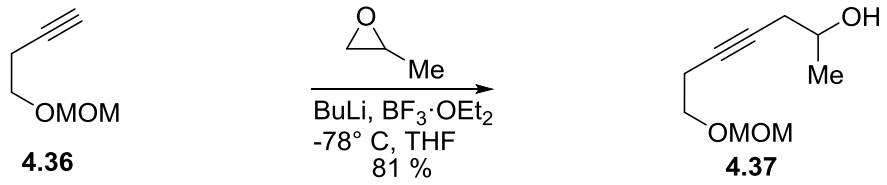
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 5.59 (dq, *J* = 2.4, 7.0 Hz, 1 H), 3.69 (br. s., 1 H), 2.87 (d, *J* = 17.6 Hz, 1 H), 2.34 - 2.21 (m, 2 H), 1.62 (dd, *J* = 1.2, 7.1 Hz, 4 H), 1.45 (s, 3 H), 1.10 (dd, *J* = 6.8, 19.0 Hz, 6 H)




**2,5-bis((*tert*-butyldimethylsilyl)oxy)furan:** Succininc anhydride (200 mg, 2.0 mmol) was stirred with 6 mL triethylamine and 6 mL DCM. TBSOTf (1 mL, 4.4 mmol)

was added dropwise and the mixture was stirred for 45 minutes. The reaction was quenched with 20 mL methanol and extracted with pentane (20 mL × 3), dried with $Na_2SO_4$ and concentrated affording **4.35** as a colorless oil, 400 mg, 61%.

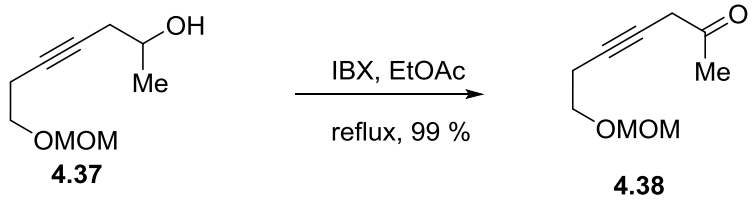
**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 4.88 (s, 2 H), 0.95 (s, 18 H), 0.20 (s, 12 H).




**7-(methoxymethoxy)hepta-3,4-dien-2-ol :** To a solution of alkyne (208 mg, 1.82 mmol) in 18 mL of THF at –78 ºC was added butyllithium in hexanes (2.5 M, 0.77 mL, 1.91 mmol). After 1 h, $BF_3$•$Et_2O$ was added (1.82 mmol, 258 mg, 229 μL) followed by propylene oxide (3.28 mmol, 229 μL). The reaction was stirred for 1 h, at which time TLC indicated complete reaction. The reaction was quenched with 5 mL saturated aq. $NH_4Cl$, followed by 5 mL saturated aq. $NaHCO_3$. The mixture was then extracted with EtOAc (20 mL x 3). The organic layer was dried ($Na_2SO_4$), decanted and concentrated. The pure product was obtained after removal of residual volatiles under high-vacuum (253 mg, 81% yield).

**$^1$H NMR** (500MHz ,$CDCl_3$) δ = 4.66 (s, 2 H), 3.91 (td, *J* = 5.5, 11.4 Hz, 1 H), 3.64 (t, *J* = 6.9 Hz, 2 H), 3.38 (s, 3 H), 2.54–2.45 (m, 2H), 2.41–2.38 (m, 1 H), 2.38–2.34 (m, 1 H), 2.30 (td, *J* = 2.3, 6.7 Hz, 1 H), 2.26 (td, *J* = 2.4, 6.8 Hz, 1 H), 2.14 (d, *J* = 4.3 Hz, 1 H), 1.24 (d, *J* = 6.1 Hz, 3 H).

**HRMS** $C_9H_{16}O_3Na$ $[M + Na]^+$ 195.0992, found 195.0989.

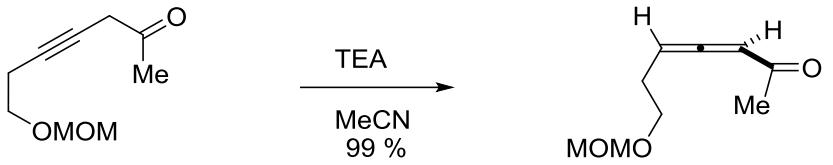



**7-(methoxymethoxy)hepta-3,4-dien-2-one :** Alkynol **4.37** (432 mg, 3.26 mmol) was placed into a pressure tube with teflon cap. Ethyl acetate (12.5 mL) was added followed by IBX (912 mg, 3.26 mmol, 1.3 eq). The vial was flushed with nitrogen and stirred at 85 ºC for 24 h. The reaction mixture was then cooled to rt and filtered over celite with ethyl acetate. The filtrate was then concentrated *in vacuuo* yielding a yellow oil, **4.38** (423 mg, 99% yield) essentially pure by NMR.

**$^1$H NMR** (500MHz ,$CDCl_3$) δ = 4.66 (s, 2 H), 3.65 (t, *J* = 6.9 Hz, 2 H), 3.38 (s, 3 H), 3.24 (br. s., 2 H), 2.53 (t, *J* = 6.6 Hz, 2 H), 2.27 (s, 3 H).

**$^{13}$C NMR** (125MHz ,$CDCl_3$) δ = 20.2, 28.6, 34.8, 55.1, 65.9, 73.4, 81.6, 96.2, 202.9.

**HRMS** (ESI-TOF) m/z calcd for $C_9H_{14}O_3Na$ $[M + Na]^+$ 193.0835, found 193.0835.



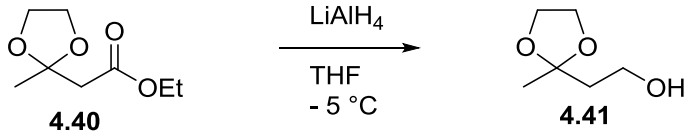

**4.38** **4.39**

**7-(methoxymethoxy)hepta-3,4-dien-2-one 4.39:** Alkyne **4.38** (148 mg, 0.87mmol)was placed in 8.7 mL MeCN and 12 μL of $NEt_3$ was added and the reaction was stirred overnight. The reaction was concentrated under reduced pressure to yield **4.39** as a yellow oil (147 mg, 99%) containing 12% starting material.

**$^1$H NMR** (500MHz ,CHLOROFORM-d) δ = 5.79 - 5.73 (m, 1 H), 5.68 (q, *J* = 7.0 Hz, 1 H), 4.64 (s, 2 H), 3.66 (t, *J* = 6.3 Hz, 2 H), 3.37 (s, 3 H), 2.48 (dq, *J* = 3.1, 6.4 Hz, 2 H), 2.25 (s, 3 H).

**$^{13}$C NMR** (125MHz ,CHLOROFORM-d) δ = 213.6, 198.9, 98.0, 96.5, 92.2, 66.3, 55.3, 28.5, 26.4

**HRMS** (ESI-TOF) m/z calcd for $C_9H_{14}O_3Na$ $[M + Na]^+$ 193.0835 found 193.0839.

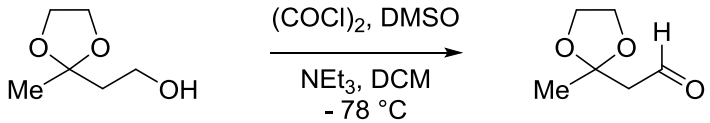



**4.40** **4.41**

**2-(2-hydroxyethyl)-2-methyl-dioxolane**: Ester **4.40** was added dropwise to a suspension of $LiAlH_4$ (1.97 g, 51.7 mmol) in 80 mL of THF at – 5 °C and was stirred for 1.5 hours when it was quenched with 10 mL of saturated aqueous sodium potassium tartrate. The aqeuous layer was separated and extracted with diethyl ether (2 × 50 mL).

The organic layers were combined and washed with 100 mL brine, dried with $Na_2SO_4$ and concentrated under reduced pressure to give 5.8 g (85%) **4.41** as a colorless oil.

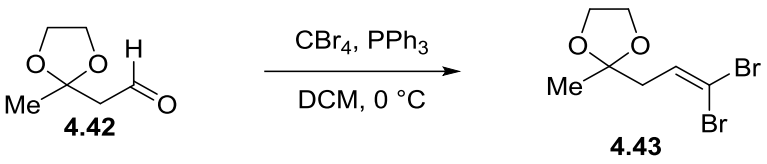
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 4.02 (s, 4 H), 3.79 (q, *J* = 5.6 Hz, 2 H), 2.84 - 2.77 (m, 1 H), 1.9 8 (t, *J* = 5.3 Hz, 2 H), 1.39 (s, 3 H).




**4.41** **4.42**

**2-(2-methyl-1,3-dioxolan-2-yl)acetaldehyde:** DMSO (1.86 mL, 26.3 mmol) was added dropwise to a solution of oxallyl chloride (2.25 mL, 3.33 g, 26.3 mmol) in 11 mL of dry DCM at – 78 °C and the mixture was stirred at this temperature for 15 minutes, then a solution of alcohol X in 11 mL DCM was added dropwise. The resultant solution was stirred for 30 minutes at – 78 °C after which 11.2 mL $NEt_3$ was added and the mixture was stirred for 5 minutes before being allowed to warm to rt. The reaction was washed with 3 × 30 mL sat. aq. $NH_4Cl$ and dried with $Na_2SO_4$ and concentrated under reduced pressure to yield 1.52 g (58%) of aldehyde **4.42** as a yellow oil.

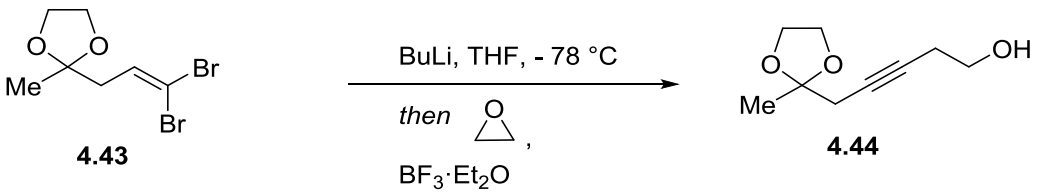
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 9.77 (t, *J* = 2.9 Hz, 1 H), 4.09 - 3.96 (m, 4 H), 2.74 (d, *J* = 2.7 Hz, 2 H), 1.45 (s, 3 H).




**4.42** **4.43**

**2-(3,3-Dibromoallyl)-2-methyl-1,3-dioxolane:** $CBr_4$ (5.15 g 15.6 mmol)was added to a flask followed by 20 mL of DCM. The flask was cooled in an ice bath and $PPh_3$ (8.15 g, 31.12 mmol) in 20 mL of DCM was added dropwise over 30 minutes via a pressure-equalizing addition funnel. The mixture was stirred for 10 minutes then a solution of aldehyde **4.42** (1.35 g, 10.37 mmol) in 15 mL DCM was added dropwise over 10 minutes. The mixture was allowed to stir for 1 hour in an ice bath then was transferred to a separatory funnels and 25 mL of water was added. The mixture was extracted with DCM (3 x 10 mL) and collected organics were washed with 30 mL brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. To this residue, 25 mL diethyl ether was added and the flask sealed and stirred overnight. The mixture was then filtered through a plug of silica, and the plug washed with (3 × 20 mL) of diethyl ether. Collected organics were washed with brine, dried with $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica with 20% ethyl acetate in hexanes and fractions containing product were concentrated under reduced pressure yielding 2.34 g (79%) of **4.43** as a clear, pale yellow oil.

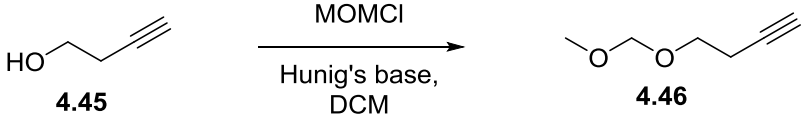
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) $\delta$ = 6.49 (t, $J$ = 7.2 Hz, 1 H), 4.02 - 3.97 (m, 4 H), 2.48 (d, $J$ = 7.0 Hz, 2 H), 1.38 (s, 3 H).




**5-(2-methyl-1,3-dioxolan-2-yl)pent-3-yn-1-ol**: *n*-BuLi (2.5 M in hexanes,0.927 mL, 2.32 mmol) was added dropwise over a period of 1 h to mixture of **4.43** (323 mg, 1.13 mmol) in 11 mL of THF at – 78 °C. The reaction was stirred at that temperature for 10 minutes and then $BF_3 \cdot OEt_2$ (240 mg, 1.70 mmol) was added followed by ethylene oxide (1.73 M solution in THF, 1.95 mL, 3.39 mmol) and the reaction was stirred for 6 hours after which the reaction was quenched with 25 mL saturated $NH_4Cl$, was extracted with EtOAc (3 × 25 mL). Organic layers were collected and washed with 25 mL brine and dried with $Na_2SO_4$ and concentrated under vacuum. The crude residue was purified by silica column chromatography and fractions containing product were collected and concentrated under vacuum yielding 57 mg (30%) of **4.44** as a pale yellow oil.

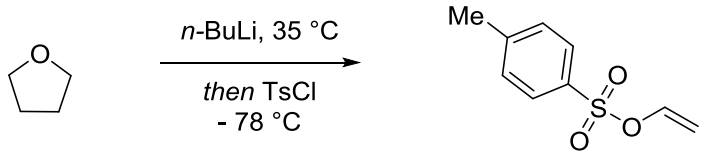
**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 4.01 - 3.96 (m, 4 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 2.51 (t, *J* = 2.2 Hz, 2 H), 2.47 - 2.36 (m, 2 H), 1.44 (s, 3 H).

**$^{13}$C NMR: (500 MHz, CHLOROFORM-d)** 108.7, 78.5, 78.2, 65.1, 61.2, 30.2, 23.7, 23.3.



**4-(methoxymethoxy)but-1-yne:** 3-butyn-1-ol was added to 120 mL DCM followed by *N,N*-diisopropylethylamine (20.97 mL, 120.4 mmol) and the reaction mixture was cooled to 0 °C. Cloromethyl methyl ether was added (8.69 mL, 114.4 mmol) dropwise. After the addition was complete the ice bath was removed and the mixture was allowed to warm to rt overnight. Sat. aq. $NaHCO_3$ (50 mL) was added and the organic phase was separated and washed with 5% HCl (2 × 10 mL) and brine (2 × 10 mL) was dried with $MgSO_4$. The material was concentrated under reduced pressure and subjected to silica column chromatography with 20% ethyl acetate in hexanes and fractions containing product were concentrated under reduced pressure to afford **4.46** (5.85 g, 67%).

**$^1$H NMR**: (300MHz ,CHLOROFORM-d) δ = 4.66 (s, 2 H), 3.66 (t, *J* = 6.8 Hz, 2 H), 3.38 (s, 3 H), 2.49 (dt, *J* = 2.6, 6.8 Hz, 2 H), 2.00 (t, *J* = 2.6 Hz, 1 H)

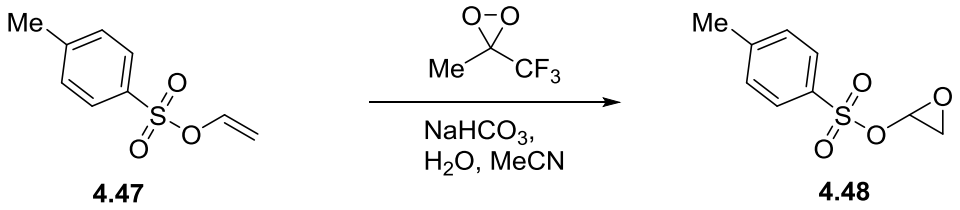



**4.47**

**Vinyl 4-methylbenzenesulfonate:** BuLi (2.5 M in hexanes, 7.8 mL, 19.5 mmol) was added dropwise to 20 mL THF at rt. The reaction mixture was then heated to 35 °C and was stirred at this temperature for 2 hours. The reaction was then cooled to – 78 °C and *p*-toluylsulfonyl chloride (2.86 g, 15 mmol) was added in 20 mL of THF over 15 minutes. The reaction was then warmed to rt, quenched with sat. aq. $NH_4Cl$ and was extracted with 50 mL of ethyl acetate. This was concentrated and purified by running

through a short plug of silica with ethyl acetate and was concentrated under vacuum to yield 556 mg crude product **4.47** that was used as obtained.

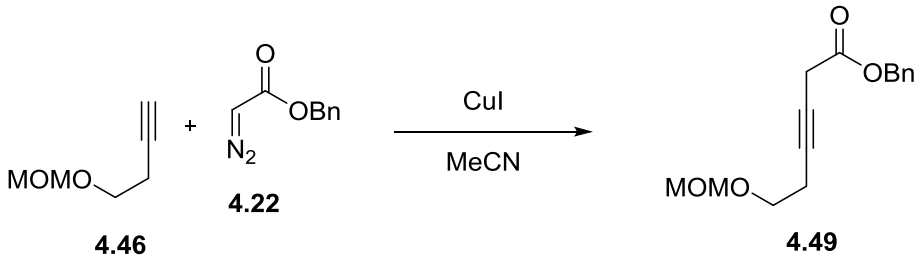
**$^1$H NMR**: (500MHz ,CHLOROFORM-d) δ = 7.87 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 7.9 Hz, 2 H), 5.48 (d, *J* = 1.8 Hz, 1 H), 2.90 (d, *J* = 4.3 Hz, 1 H), 2.79 (dd, *J* = 2.4, 4.3 Hz, 1 H), 2.49 (s, 3 H)




**4.47** **4.48**

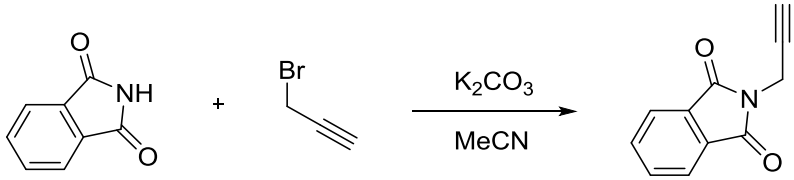
**Oxiran-2-yl 4-methylbenzenesulfonate:** To an amber glass jar was added 2 mL of water and 3 mL of MeCN followed by **4.47** (79 mg, 0.4 mmol), 0.4 mL 1,1,1-trifluoroacetone, oxone (307 mg, 1.0 mmol) $NaHCO_3$. The bottle was swirled, sealed and placed in a – 40 °C freezer. After 2 h, 0.2 mL 1,1,1-trifluoroacetone was added. After another 2.5 h half of the original amounts of $NaHCO_3$ and oxone are added. After 2 more h, the reaction appears nearly done by TLC. The mixture is diluted with 50 mL water and extracted with DCM (3 × 30 mL) and the organics dried with $Na_2SO_4$, and concentrated under vacuum to give 93 mg crude **4.48** as a colorless oil that was used as obtained.

**$^1$H NMR:** (500MHz ,CHLOROFORM-d) δ = 7.87 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 7.9 Hz, 2 H), 5.48 (d, *J* = 1.8 Hz, 1 H), 2.90 (d, *J* = 4.3 Hz, 1 H), 2.79 (dd, *J* = 2.4, 4.3 Hz, 1 H), 2.49 (s, 3 H)




**4.46** **4.22** **4.49**

**Benzyl 6-(methoxymethoxy)hex-3-ynoate:** Produced by general procedure **A** using 20% ethyl acetate in hexanes for the silica plug. 1.38 g of **4.49** obtained as a colorless oil. **$^1$H NMR**: (300MHz ,CHLOROFORM-d) δ = 5.15 (s, 2 H), 4.63 (s, 2 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 3.35 (s, 3 H), 3.33 - 3.28 (m, 2 H), 2.61 - 2.44 (m, 2 H)

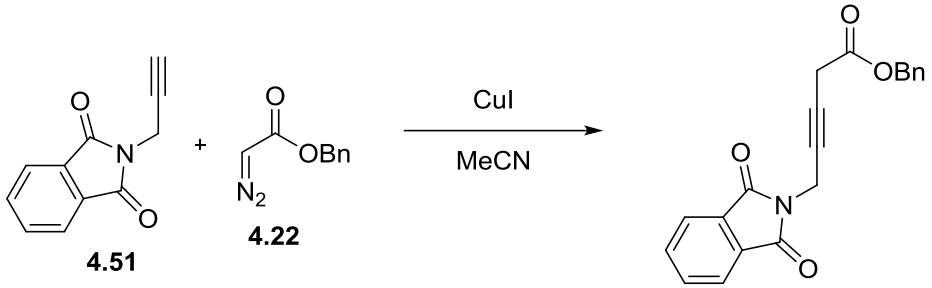



**4.50**

***N*-propargylphalimide:** Phalimide **(**2.0 mmol, 294 mg) was combined with propargyl bromide (250 mg, 2.1 mmol) and $K_2CO_3$, (304 mg, 2.2 mmol) and 6 mL MeCN in a pressure tube. The vessel was sealed and heated to 80 °C for 18 h. Water (50 mL) was added and a precipate was formed. The precipate was vacuum filtered and washed with

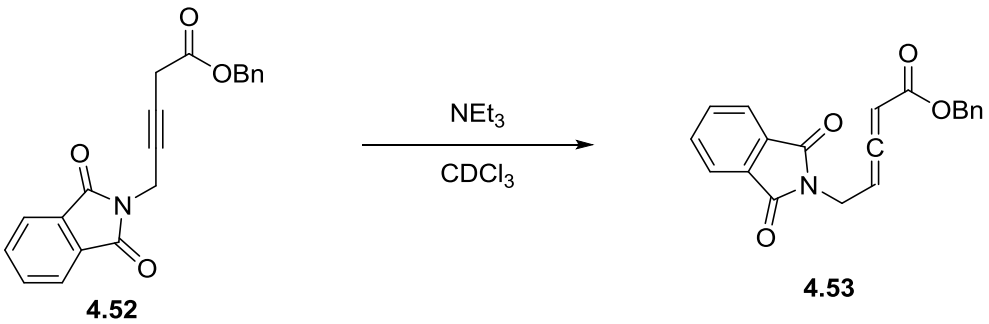
additional water and dried on a vacuum. The product, **4.50** was a yellow solid (278mg, 75%)

**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 7.89 (dd, *J* = 3.1, 5.3 Hz, 2 H), 7.75 (dd, *J* = 2.9, 5.5 Hz, 2 H), 4.46 (d, *J* = 2.6 Hz, 2 H), 2.23 (t, *J* = 2.2 Hz, 1 H)



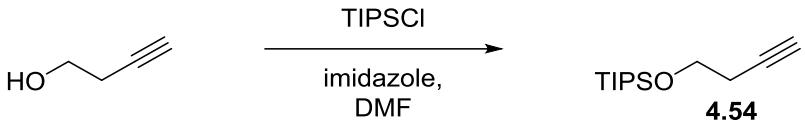

**Benzyl 5-(1,3-dioxoisoindolin-2-yl)pent-3-ynoate:** General procedure **A** was followed on a 0.63 mmol scale. Ethyl acetate was used to filter the crude mixture through a silica plug. A yellow solid (173 mg) **4.52** with ~20% allene and DCM impurities was obtained.

**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 7.95 - 7.80 (m, 2 H), 7.80 - 7.65 (m, 2 H), 7.39 - 7.28 (m, 5 H), 5.14 (s, 2 H), 4.48 (d, *J* = 2.2 Hz, 2 H), 3.30 (d, *J* = 1.8 Hz, 2 H)



**Benzyl 5-(1,3-dioxoisoindolin-2-yl)penta-2,3-dienoate: 4.52** (3.5mg) was added to an NMR tube with 0.8 mL $CDCl_3$. One drop of triethylamine was added and the NMR[1] spectrum was collected showing full conversion to **4.53**.

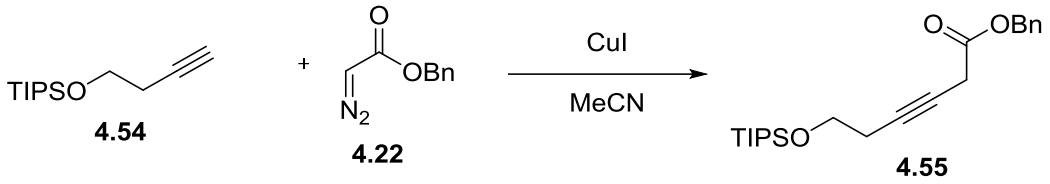
**$^1$H NMR**: (500MHz ,CHLOROFORM-d) δ = 7.84 (dd, *J* = 3.4, 5.4 Hz, 2 H), 7.73 (dd, *J* = 2.9, 5.4 Hz, 2 H), 7.33 (s, 4 H), 5.79 (q, *J* = 6.0 Hz, 1 H), 5.77 - 5.72 (m, 1 H), 5.14 (s, 2 H), 4.45 - 4.39 (m, 2 H)




**1-Triisopropylsiloxy-but-3-yne:** Chlorotriisoproylsilane (964 mg, 5.0 mmol) was added to a mixture of 3-butyn-1-ol (350 mg, 5.0 mmol) and imidazole (374 mg, 5.5 mmol) in 5 mL DMF. The reaction was stirred 40 minutes when TLC indicated the reaction was complete. The reaction was quenched with 20 mL sat. aq. $NH_4Cl$, and extracted with 30 mL hexanes. The organic layer was washed with water (3 × 20mL) and brine (30 mL) and the organic phase was dried with $Na_2SO_4$ and concentrated under reduced pressure to yield (981 mg 87%) of **4.54** as a colorless oil.

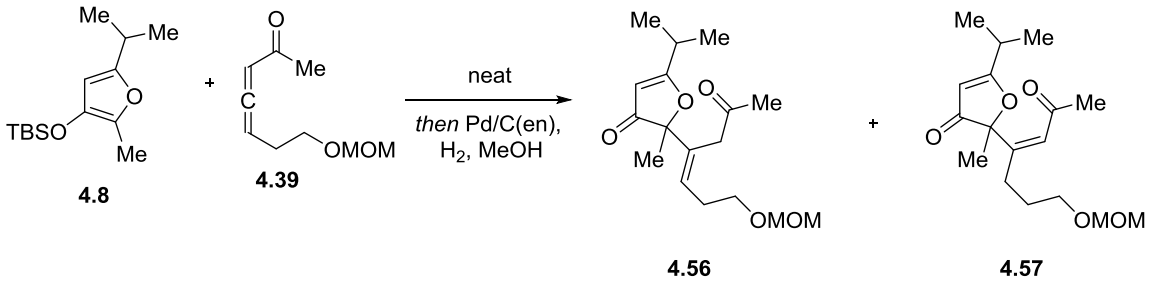
**$^1$H NMR:** (300MHz ,CHLOROFORM-d) δ = 3.82 (t, *J* = 7.3 Hz, 2 H), 2.44 (dt, *J* = 2.6, 7.1 Hz, 2 H), 1.96 (t, *J* = 2.4 Hz, 1 H), 1.10 - 1.01 (m, 21 H).

[1] NMR showed the starting material had been consumed. The spectrum was obscured by strong peaks from triethylamine. The NMR data has been taken from another experiment.




**Benzyl 6-(triisopropylsilyloxy)hex-3-ynoate:** General procedure **A** was followed on a 1.59 mmol scale. 10% Ethyl acetate in hexanes was used to filter the crude mixture through a silica plug. A colorless oil (293 mg, 50%) **4.55** with and additional 103mg of material from mixed fractions.

**$^1$H NMR**: (300MHz ,CHLOROFORM-d) δ = 7.36 (s, 5 H), 5.16 (s, 2 H), 3.78 (t, *J* = 7.5 Hz, 2 H), 3.29 (s, 2 H), 2.51 - 2.37 (m, 2 H), 1.05 (s, 21 H)



**5-isopropyl-2-(1-(methoxymethoxy)-6-oxohept-3-en-4-yl)-2-methylfuran-3(2H)-one and 5-isopropyl-2-(7-(methoxymethoxy)-2-oxohept-3-en-4-yl)-2-methylfuran-3(2H)-one:** **4.8 (**392 mg, 1.54 mmol) was mixed with **4.39**(262 mg, 1.54 mmol) in a sealed vial and the mixture was stirred for 18 h. At that time the mixture was transferred to a round bottom flask with 15 mL MeOH and Pd/C(en) (69 mg, 0.062 mmol) and an $H_2$ balloon was attached. The reaction was allowed to stir for 3.5 h after which the catalyst was filtered over celite and the mixture was concentrated under reduced pressure. The crude mixture was purified by silica flash column chromatography with 20% ethyl acetate/ hexanes and fractions containing product were concentrated under reduced pressure to yield **4.56** (165mg, 35%) and **4.57** (113 mg, 24%), both colorless oils.

**4.56:**

**$^1$H NMR**: (500MHz ,CHLOROFORM-d) δ = 5.93 (t, *J* = 7.2 Hz, 1 H), 5.35 (s, 1 H), 4.60 (s, 2 H), 3.57 (t, *J* = 6.7 Hz, 2 H), 3.38 - 3.31 (m, 4 H), 3.07 (d, *J* = 17.4 Hz, 1 H), 2.70 (spt, *J* = 6.9 Hz, 1 H), 2.28 (q, *J* = 6.7 Hz, 2 H), 2.15 (s, 3 H), 1.46 (s, 3 H), 1.22 (t, *J* = 6.1 Hz, 7 H)

**$^{13}$C NMR:** (125 MHz, CHLOROFORM-d) δ = 205.0, 204.8, 196.9, 131.1, 127.7, 100.0 96.3, 91.2, 66.5, 55.2, 41.9, 30.3, 29.2, 29.0, 21.9, 19.4.

**HRMS** (ESI-TOF) m/z calcd for $C_{17}H_{26}NaO_5$ $[M + Na]^+$ 333.1673 found: 333.1673

**4.57:**

**$^1$H NMR** (500MHz ,CHLOROFORM-d) δ = 6.42 (s, 1 H), 5.41 (s, 1 H), 4.61 (s, 2 H), 3.56 (t, *J* = 6.4 Hz, 2 H), 3.35 (s, 3 H), 2.80 (spt, *J* = 7.0 Hz, 1 H), 2.67 (dt, *J* = 4.9, 11.6

Hz, 1 H), 2.37 (dt, *J* = 4.9, 11.6 Hz, 1 H), 2.24 (s, 3 H), 1.85 - 1.60 (m, 3 H), 1.55 (s, 3 H), 1.29 (dd, *J* = 5.0, 6.9 Hz, 6 H)

$^{13}$**C NMR** (125 MHz, CHLOROFORM-d) δ = 203.1, 198.0, 197.3, 155.2, 123.5, 100.0, 96.2, 91.2, 67.7, 55.1, 32.3, 30.3, 29.7, 25.4, 23.0, 19.5.

**HRMS** (ESI-TOF) m/z calcd for $C_{17}H_{26}NaO_5$ $[M + Na]^+$ 333.1672 found: 333.1673.