PROGRESS IN THE TOTAL SYNTHESIS OF SPIROLIDE C AND A MODEL SYSTEM OF A KEY DIELS-ALDER MACROCYCLIZATION

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Spirolode C is a macrocyclic marine toxin produced by the dinoflagellate *Alexandrium ostenfeldii* that has attracted significant synthetic interest due in particular to its rare spirocyclic imine fragment. The work presented herein details progress made in the synthesis of a model system that will be used to optimize reaction conditions for a biomimetic macrocycle closing Diels-Alder reaction in our planned total synthesis. The synthesis of the model system required an extension of our isomerization/Claisen rearrangement (ICR) to be compatible with new vinyl bromide-containing substrates. New conditions to affect the ICR of these challenging substrates were successfully developed, and this led to significant progress in the synthesis of the desired model system.
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LIST OF ABBREVIATIONS

1,2-DCE  1,2-Dichloroethane
BAIB    Bis(acetoxy)iodobenzene
Bn      Benzyl
BOC     t-Butyloxycarbonyl
BOX     Bis(oxazoline)
Cy      Cyclohexane
DCM     Dichloromethane
DIAD    Diisopropylazodicarboxylate
DMF     N,N-Dimethylformamide
DMP     Dess-Martin periodinane
DMSO    Dimethylsulfoxide
DPPA    Diphenylphosphorylazide
dr      Diastereomeric ratio
EtOAc   Ethyl acetate
ICR     Isomerization/Claisen rearrangement
MIB     3-exo-Morpholinoisoborneol
MOM     Methoxymethyl
MPM     4-Methoxybenzyle
<table>
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<tr>
<td>Ms</td>
<td>Mesyl</td>
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<tr>
<td>NMR</td>
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<tr>
<td>PMB</td>
<td>$p$-Methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>$p$-Methoxyphenyl</td>
</tr>
<tr>
<td>pyr</td>
<td>Pyridine</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring-closing metathesis</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAN3</td>
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<tr>
<td>TBDPS</td>
<td>$t$-Butyldiphenylsilyl</td>
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<td>TBMID</td>
<td>$t$-Butyl methyl iminodicarboxylate</td>
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<td>TBS</td>
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<tr>
<td>TEA</td>
<td>Triethylamine</td>
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<tr>
<td>TEOC</td>
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1.0 INTRODUCTION

1.1 ISOLATION OF SPIROLIDE FAMILY OF COMPOUNDS

The spirolides are a family of natural products that were first isolated from the digestive glands of mussels and scallops in Nova Scotia by Hu, et al., and were reported in 1995.¹ It was suspected that the shellfish were not the organisms ultimately responsible for the production of these toxins, and the dinoflagellate *Alexandrium ostenfeldii* was eventually implicated as the producing species of the natural products.² Spirolides B and D were the first members of the family to have their structure elucidated.¹ A culture sample of *Alexandrium ostenfeldii* allowed enough material to be isolated to assign the structure of spirolides A, C, and 13-desmethyl spirolide C.³
Most of the spirolides contain a 5,5,6-bis(spiroketal) system in a 23-membered carbon macrocycle. Most members of the family also contain a 7,6-spiroyclic imine, except for spirolides E and F. Spirolides E and F appear to be a metabolite of the natural products produced by the shellfish in which the spiroyclic imine is hydrolyzed into its constituent ketone and amine fragments. Although the spiroyclic imine fragment is not a common motif in natural products, it is also present in similar marine toxin families, such as the pinnatoxins, pteriatoxins, and gymnodimine.
The spirolide family of natural products has continued to expand, and now encompasses named compounds through spirolide I, as well as several naturally occurring hydroxylated or demethylated derivatives of previously discovered spirolides (e.g. 27-oxo-13,19-didesmethyl spirolide C). The absolute stereochemistry of the spirolides has not yet been established; the relative stereochemistry of the spirolides, with the exception of the attachment of the butenolide fragment at C4, was determined in 2001. The C4 stereocenter was eventually assigned in 13,19-didesmethyl spirolide C, but remains ambiguous in the rest of the family.

The spirolides behave as a fast acting biotoxin in a mouse assay, causing death within 5 minutes of injection. The exact mode of action of the spirolides is unknown, but they have been implicated as Ca\(^{2+}\) ion channel inhibitors as well as acetylcholine receptor modulators. Desmethyl spirolide C has also been shown to reduce A\(\beta\) and hyperphosphorylated Tau protein,
suggesting potential therapeutic applications in Alzheimer’s Disease. The spirocyclic imine fragment has been shown to be critical for the spirolides toxic activity. Spirolides E and F, in which the spirocyclic imine is cleaved into its ketone and amine components, show no activity in the mouse bioassay used to first identify the family of toxins. Furthermore, when the structurally similar imine subunit in the toxin gymnodimine is reduced to the amine, giving the compound gymnodamine, there is a significant loss of toxic activity. Likewise, the bis(spiroketal) moiety may also play an important role in the pronounced biological activity of the majority of the members of the spirolide family. Spirolides H and I, which contain only a single spiroketal ring system, show a greatly diminished effectiveness as a toxin.

The stability of the spiroimine ring could also have a strong effect on the overall toxicity of the spirolides. Spirolides C and D contain an additional methyl group at C32 relative to spirolides A and B, which may have a pronounced impact on the stability of the imine functionality. Treatment of spirolide A and B with oxalic acid cleaves the imine to the ketone.

Figure 3. Structures of spirolides E and F and gymnodamine
and amine substituents, however these conditions are ineffective in hydrolyzing the imine in spirolide C and D.\textsuperscript{3} For this reason, it has been hypothesized that spirolides C and D may have a longer lifetime in biological systems and therefore enhanced toxicity compared to their monomethylated counterparts.\textsuperscript{3}

\section*{1.2 PREVIOUS FRAGMENT SYNTHESSES}

Although there have been several syntheses of the structurally related pinnatoxins, there has not been a total synthesis of any member of the spirolide family.\textsuperscript{15-19} Most of the activity directed towards synthesis of the spirolides is focused on either the bis(spiroketal) ring system or the 7,6-spiroyclic imine. While some progress has been made toward the efficient synthesis of these systems, much work remains to be done.

Synthesis of the bis(spiroketal) ring system was undertaken by Brimble and coworkers. They initially approached the bis(spiroketal) system as the product of an oxidative radical cyclization after an initial ketalization.\textsuperscript{20} Eventually, they amended their strategy to use a sequence of multiple oxidative radical cyclizations.\textsuperscript{21-24} Spiroketal 12 is synthesized by oxidative radical cyclization of compound 11. Following deprotection and subsequent oxidative radical cyclization of 12, bis(spiroketal) system 13 is produced as a 1:1:1:1 mixture of diastereomers. Subsequent transformations to introduce the methyl and hydroxyl groups to the same carbon yield the product 14 as a single diastereomer. While the thermodynamically favored diastereomer of the product has the incorrect configuration at the 5,5-spiroketal center relative to
the natural configuration of the spirolides, equilibration of the stereocenter to the natural
diastereomer may occur once the ring system is incorporated into the larger macrocycle.\textsuperscript{22-24}

\textbf{Scheme 1.} Brimble’s approach to the bis(spiroketal) ring system of the spirolides

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1}
\caption{Brimble’s approach to the bis(spiroketal) ring system of the spirolides}
\end{figure}

Conditions: a) PhI(OAc)\textsubscript{2}, I\textsubscript{2}, hv, cyclohexane, rt. b) TBAF, DMF, 80 °C. c) PhI(OAc)\textsubscript{2}, I\textsubscript{2}, hv, cyclohexane, rt.

Eschewing an iterative approach to synthesize the ring system, Ishihara and coworkers assembled the bis(spiroketal) system in a single step from an acyclic precursor.\textsuperscript{25} The initial cyclization of 15 with HF-pyridine in acetonitrile gave 16 and 17 in a 1:4 mixture of diastereomers at C15, with the undesired diastereomer 17 being preferred. However, after methylation of the C19 ketone and subsequent TBS-protection of the resulting alcohol, isomerization of the C15 stereocenter occurred and 18 and 19 were isolated in a 2:1 mixture of diastereomers with the desired diastereomer 18 being preferred.
Scheme 2. Ishihara’s one step bisketalization for spirolide B bis(spiroketal) system

Conditions: a) HF-pyridine, MeCN, 23 °C. b) MeLi, THF, -78 °C. c) TBSOTf, 2,6-lutidine, DCM, 0 °C to 20 °C.

Brimble and coworkers also made significant progress towards the completion of the spirocyclic imine ring system of the spirolides. The initial strategy used to synthesize the desired ring system was double alkylation of lactams, followed by ring closing metathesis (RCM) to provide a spiro-fused ring system (20, 23).26 Deprotection and reduction of the lactams to the corresponding imines worked well, except in the cases of the seven membered lactam 23. In these cases, reduction of the carbamate protecting group was preferred to formation of the desired imine. The methodology was eventually extended to incorporate an allyl group at the carbon alpha to the spirocenter to provide a functional handle, as is required for synthesis of the spirolides and other related natural products, however, reduction to the imine was still not achieved in the case of the seven membered lactams.27
Scheme 3. Brimble’s RCM and lactam reduction approach

Conditions: a) n-BuLi, THF, -78 °C; 2-(TMS)ethyl 4-nitrophenyl carbonate, -78 °C to rt. b) LiEt₃H, -78 °C. c) Bu₄NF, THF, rt.

Additionally, Brimble and coworkers have explored the use of Diels-Alder reactions to access the 7,6 spirocyclic imine ring system. Their initial efforts were directed towards an alpha-methylene lactam as the dienophile in the cyclizations.²⁸ While simple test reactions catalyzed by Cu^{II} BOX complexes proceeded in moderate yield and with moderate exo selectivity, reactions with dienes more closely modeled after the natural product, such as 29 and 30, provided no product.
Scheme 4. Brimble’s α-methylene lactam Diels-Alder approach

Conditions: a) 20 mol% [(S,S)-t-Bu-BOX]Cu(OTf)₂, DCM, ambient temperature.

Their next generation Diels-Alder approach involved reaction of Danishefsky’s diene with acyclic α,β-unsaturated ester 31 to form the cyclohexene ring of the spirocycle (Scheme 5). Subsequent manipulation of the structure provided 7,6-spirocyclic imine 34.

Scheme 5. Brimble’s synthesis of a 7,6-spiroimine related to the spirolides

Conditions: a) neat, μν 150 °C, 48 h.
Romo and coworkers have also contributed to the synthesis of the spirolides. They developed an efficient strategy to append the butenolide fragment of the molecule to the e-ring of the larger macrocycle using a vinylogous Mukaiyama aldol reaction. The reaction proved to have a wide substrate scope, and further manipulation of the resulting tertiary alcohol was not problematic. Two particular reactions of note are the dehydration of to provide tetrasubstituted olefin and the reduction of the butenolide alkene to form saturated lactone . These reactions provide access to substrates analogous to different members of the spirolide family.

**Scheme 6.** Romo’s butenolide annulation and relevant subsequent transformations

Conditions: a) TiCl₄, DCM, -78 °C. b) H₂, Pd/C, EtOAc, 25 °C. c) SOCl₂, pyr, DCM, -50 °C.
Zakarian and coworkers have made the most significant progress reported in the literature so far towards the completion of spirolide C. The synthesis of the e-ring decorated with sufficient functionality to allow for further elaboration was completed in an enantioselective fashion using a diastereoselective Ireland-Claisen rearrangement to set the adjacent tertiary and quaternary stereocenters. Ring closure and further manipulation of 42 provided the chiral advanced coupling partner 44. This compound was eventually coupled to bis(spiroketal) precursor 45 using an organolithium addition reaction. Many RCM conditions were used to close the resulting complex intermediate 47 into the macrocycle, but all conditions provided the desired product in modest yields. Using a more conformationally rigid substrate provided the best yield for the reaction, albeit in a still a very modest yield of 25%. Despite the modest yields, 48 represents the most advanced synthesis of the spirolides to date and has allowed for material to be produced and used in subsequent spiroketalization studies to complete the macrocycle of spirolide C.
Scheme 7. Important transformations in Zakarian’s synthesis of the macrocycle of the spirolides

Conditions: a) 43, THF; Me$_3$SiCl, -78 °C to ambient temperature. b) t-BuLi, Et$_2$O; 43; DMP, pyr; TBAF, THF. c) Grubbs II 30 mol%, 1,2-DCE, 60 °C.
1.3 STUDIES TOWARDS THE TOTAL SYNTHESIS OF SPIROLIDE C

With no reported total synthesis of spirolide C, we propose to undertake this endeavor via the following retrosynthetic analysis. The butenolide fragment will be appended to the macrocycle last through the use of a coupling reaction. The macrocycle itself can be formed by an intramolecular Diels-Alder reaction between an \( \alpha,\beta \)-unsaturated imine and diene fragment of 49. We envision a Stille coupling reaction to append the spiroimine precursor 51 to the bis(spiroketal) fragment 50. The bis(spiroketal) ring system can be formed from the ketalization of 52, which arises from the Stetter coupling of advanced enone 53 and aldehyde 54.
Scheme 8. Retrosynthetic analysis of spirolide C (1)
The bottom half of the molecule has been synthesized efficiently via the unprecedented use of a late stage intermolecular Stetter reaction by Binbin Guo. After the screening of various catalysts, it was discovered that Glorious’ catalyst promoted the intermolecular coupling of fragments 53 and 54 in quantitative yield. The bis(spiroketal) ring system was closed via ketalization and after subsequent functional group transformations, the Stille coupling precursor 50 was isolated in a 1.5:1 ratio of diastereomers.

The azepine unit of spirolide C would be initially installed as the vinylstannane 51. Thus, a Stille coupling with an acid chloride would give an enone, followed by an aza-Wittig ring closure to construct the azepine ring in 49. Closing of the macrocycle using a biomimetic Diels-Alder reaction would take place after the fragment was coupled to the lower half of the molecule. Given the complex environment in which these reactions take place, we elected to develop reliable conditions for the Diels-Alder reaction on a simplified exo-methylene azepine 58 (Scheme 10) as a model dienophile. In addition, the synthesis of 58 would provide a test bed for the methodology we would ultimately use in preparing the azepine synthon required by our synthetic strategy.

The isomerization/Claisen rearrangement (ICR) previously developed in our group inspired our plan to synthesize the model system 58. The ICR methodology provides easy access to vicinal-dialkyl substituted aldehyde derivatives (Scheme 9). The starting materials for these reactions are easily synthesized diallyl ethers. Exposure of suitable diallyl ethers to an Ir (I) catalyst effects an isomerization of the diallyl ether to an allyl vinyl ether. After quenching the iridium catalyst, the allyl vinyl ether undergoes a thermal Claisen rearrangement to provide the vicinally disubstituted aldehyde derivatives with both high yields and diastereoselectivities.
Scheme 9. General ICR reaction and tolerated substitution patterns.

\[
\begin{align*}
\text{55} & \xrightarrow{a} \text{56} & \quad \text{b} \quad 57 \\
\text{R}_1 = \text{alkyl, aromatic, H}; \text{R}_2 = \text{alkyl, aromatic, H}; \text{R}_3 = \text{alkyl, H} \\
\end{align*}
\]

Conditions: a) [IrCl(COE)\textsubscript{2}], PCy\textsubscript{3}, NaBPh\textsubscript{4}, 1,2-DCE/acetone, rt. b) PPh\textsubscript{3}, 60 °C.

To effect the synthesis of model system 58, the imine ring system would be closed by an aza-Wittig reaction, with the necessary enone being the result of a Stille coupling between an acid chloride and 1,1-disubstituted vinylstannane 51. Hydrostannylation of the terminal alkyne in 59 gives 51, and the terminal alkyne comes from a bromination/didehydrobromination sequence of the internal alkene in 60. An iridium-catalyzed isomerization/Claisen rearrangement of 61 would be used to set the stereochemistry of the geminal methyl groups as well as provide the alkene functional handle necessary for the synthesis of the vinylstannane from 59. The necessary diallyl ether 61 could be produced simply in racemic form from the reaction of crotonaldehyde and methylmagnesium bromide, or in enantiopure form by using dimethyl zinc under MIB catalysis.\textsuperscript{34}
Scheme 10. First generation retrosynthetic analysis of the desired model system
Implementing the first generation approach to the azepine model system began with the synthesis of internal alkyne $66$. Adding methylmagnesium bromide to crotonaldehyde proceeded to produce secondary alcohol $63$, which was carried on crude. Extensive purification and removal of solvent was not pursued for this reaction due to concerns about the volatility of the product. Transformation of the secondary alcohol to an allyl ether using NaH and allyl bromide converted the allyl alcohol to the isomerization-Claisen rearrangement (ICR) substrate $61$ in 85% yield over two steps. Chemoselective iridium-catalyzed isomerization, followed by a Claisen rearrangement and \textit{in situ} reduction of the resulting aldehyde produced alkene $60$ using the previously developed one-pot isomerization-Claisen rearrangement procedure in 92% yield.$^{35-36}$ The resulting primary alcohol was protected using TBSCI to give the TBS-ether $64$ in 90% yield.
Scheme 11. First generation synthesis of internal alkyne 66

Conditions: a) MeMgBr, ether, 0 °C; reflux. b) NaH, 0 °C to rt; allyl bromide, rt. c) [IrCl(COE)$_2$)$_2$, NaBPh$_4$, PC$_3$, 40:1 1,2-DCE:acetone, rt; PPh$_3$, reflux; NaBH$_4$, 0 °C to rt. d) imidazole, TBSCl, rt.

Efforts to convert alkene 64 into internal alkyne 65 began with dibromination of the alkene. Unfortunately, all attempts to brominate alkene 64 were unsuccessful, and the major product of the reaction was tetrahydrofuran 69. Instead of the desired dibromination, the silyl ether oxygen intramolecularly trapped the intermediate bromonium ion after the initial attack on Br$_2$ by the olefin. Changing the protecting group to a triisopropylsilyl ether (67) or a benzyl ether (68) had no effect, and attempts to perform the dibromination at lower temperature also proved fruitless. A procedure that allowed for dibromination of an alkene in the presence of an unprotected alcohol using HBr·pyridine also failed to provide the desired dibromide 71 from 60. These results suggest that there is a large preference for the intramolecular oxygen capture of the initial bromonium ion instead of intermolecular attack by bromide in solution, even though similar dibrominations have been previously performed on alkenes in the presence of a free alcohol or a TBS-ether.  

37
Scheme 12. Expected and observed reaction products of bromination of 64

Conditions: a) R = TBS, TIPS, Bn, H; Br\(_2\), DCM, rt. (b) R = TBS; Br\(_2\), DCM, -78 °C. (c) R = H; BAIB, HBr•pyridine, DCM, rt.

The overwhelming preference for formation of tetryahydrofuran 69 rather than dibromination can be rationalized by the conformational preference of the vicinally disubstituted alkene 73. With an alkene lacking methyl substituents, such as 72, the gauche conformation about the vicinally disubstituted bond that is required for cyclization is disfavored and less populated. This renders the rate of the cyclization negligible compared to trapping of the bromonium ion by *in situ* bromide (Figure 4, entry a). In alkene 73, the vicinal dimethyl groups in between the alkene and alcohol change the preferred conformation of the alkenyl alcohol in order to minimize gauche interactions about the vicinally disubstituted bond (Figure 4, entry b). The conformation that gives an *anti* relationship between the alkene and the siloxy substituents is disfavored. Instead, the preferred conformation arrays the alkene and the siloxy substituents in a gauche conformation. This causes the molecule to spend more time in a U shape, which brings the alkene and siloxy substituents in close proximity. As a result, the rate of intramolecular capture of the bromonium ion with the ether oxygen to be fast compared to the rate of intermolecular capture with bromide, and the tetrahydrofuran product predominates. Furthermore, this is a 5-exo-tet cyclization, which is favorable and fast.\(^{40}\) While there are some other potential solutions to the problem, such as increasing the concentration of bromide ion in
solution to speed up the rate of intermolecular capture or using either larger or more electron withdrawing protecting groups to reduce the nucleophilicity of the oxygen, a more streamlined route to the model system was preferred.

![Chemical structures and reactions](image)

**Figure 4.** Conformational preferences of bromonium ions

### 2.2 SECOND GENERATION APPROACH TO THE MODEL SYSTEM

In order to avoid the problematic tetrahydrofuran formation, a new synthetic pathway to terminal alkyne 66 was devised. In this new route, a functional group that could be used as a masked alkyne and could be installed early in the synthesis was needed. This would remove the need to brominate a vicinally-disubstuted alkene substrate and would eliminate the problematic intramolecular trapping of the intermediate bromonium ion. For this purpose, we envisioned a vinyl bromide that could be generated in the first step of the route and carried through the synthetic pathway up to the necessary unveiling of the alkyne. Accordingly, alkyne 66, the earliest common synthetic intermediate with the previous route, was targeted for preparation.
using crotonaldehyde as starting material. Alkyne 66 would be synthesized by the dehydrohalogenation of the vinyl bromide in 74. In turn, 74 would result from an ICR of 75 that would also set the vicinal methyl stereocenters. The ICR precursor diallyl ether 75 would come from allylation of the corresponding alcohol, which itself would be the product of methyl Grignard addition to the α-bromoenal 76. Bromination of crotonaldehyde and subsequent elimination of HBr provide the needed α-bromoenal. The synthesis could be modified to provide enantioenriched 77 (Scheme 14) by using a dimethyl zinc addition catalyzed by MIB in place of the Grignard addition.34

Scheme 13. Second generation retrosynthetic analysis of model system 58

With a synthetic plan in place, synthesis of model system 58 began. Bromoenal 76 was obtained from a bromination/elimination sequence of crotonaldehyde in 94% yield.41 Methyl Grignard addition to α-bromoenal 76 gave the allyl alcohol 77 in 85% yield, and subsequent allylation using allyl bromide and sodium hydride also proceeded to give diallyl ether 75 in 98% yield.
Scheme 14. Synthesis of ICR precursor 74

An ICR reaction was envisioned to give the vicinally-disubstituted alcohol 74 from diallyl ether 75. Unfortunately, a key component of the impending ICR of 75 was unprecedented in previous group research. Unpublished research in our group by Richard Liberatore had shown ICR reactions attempted on substrates with halogen substitution at any position in the olefins of the test substrates results in an unsuccessful initial isomerization reaction (Figure 5). Chlorine substitution at C3' of 78 (Figure 5, entry a) resulted in a reaction that gave no observable reaction products of either olefin isomerization. An ICR that was attempted on 79 with chlorine substitution at C2' (Figure 5, entry b) only slowly isomerized the starting material and eventually stalled with minimal conversion to only 83. It was unknown whether halogen substitution at C3 of diallyl ether 74, which is alpha to a tertiary sp3 center, would have the same effect. While the increased steric hindrance may prevent any interaction between the bromine and the iridium catalyst, it seemed likely it would still be an issue. Extending the methodology to tolerate halogens at the C3 position was not only necessary for this project, but would also be potentially very valuable in situations beyond the scope of this synthesis.
Efforts to effect the ICR reaction of the bromine-containing substrate 75 began with the standard ICR conditions. Unfortunately, the conditions developed for traditional substrates proved ineffective for 75 (Table 1, Entry A). As was seen previously with the other halogen-containing substrates, only a small fraction of starting material was isomerized to the allyl vinyl ether product. Starting material could be recovered from the reaction mixture, and the ratio of starting material to isomerization product, which lay heavily in favor of starting material, was unchanged by TLC from a period of 1 hour after the start of the reaction through observance overnight. This evidence suggested that consumption of the starting material by another reaction pathway was not a major concern. Two possible explanations for the inactivity of the catalyst were thought to be lower reactivity of the diallyl ether or accelerated degradation of the catalyst via insertion across the carbon-bromine bond. Indeed, a similar oxidative insertion for iridium complexes has been observed.\textsuperscript{42}

In an attempt to increase the conversion of the starting material in the initial isomerization, a more reactive catalyst was examined. Previous experiments in our group suggested that decreasing the phosphine load of the reaction results in a more reactive catalyst.
The increased activity of the catalyst is most likely due to a new open coordination site on iridium (Equations 1 and 2). Performing the reaction with two equivalents instead of three equivalents of tricyclohexylphosphine was, however, ultimately unsuccessful in increasing the conversion of 75 to the desired allyl vinyl ether 92. The same low conversion and premature stalling of the previous reactions characterized this reaction (Table 1, Entry B). These results suggested that a potential lower reactivity or higher energetic barrier to the isomerization of the starting material is not responsible for the low conversion. Because the reaction stalled after approximately 60 minutes and no further catalytic activity was observed, degradation of the catalyst was most likely the culprit.

One possible mechanism of the decomposition of the iridium catalyst is oxidative insertion of an Ir (I) complex across a Csp^2-Br bond. After stirring [IrCl(COE)$_2$]$_2$ with four equivalents of diphenyl(o-bromotetrafluorophenyl)phosphine in DCM (Scheme 15), Cotton and coworkers observed a bidentate chelating interaction by one of the phosphine ligands in solution by NMR as part of complex 87. Upon warming of the reaction mixture to ambient temperature, they isolated the octahedral Ir (III) complex 88, characterized by x-ray crystallography, which is the product of oxidative insertion across the o-bromine bond with carbon. This reaction takes place under conditions very similar to ICR reactions.
Scheme 15. Cotton’s observed oxidative insertion of a cationic Ir (I) complex

The unsuccessful ICR reaction of diallyl ether 75 could be explained by catalyst decomposition via an oxidative insertion similar to the one described by Cotton. I propose that initial coordination of iridium by terminally substituted olefin to give complex 89 is followed by chelation of the iridium by the bromide of the vinyl bromide moiety to give chelate 90 (Figure 6). Following bidentate chelation of iridium, oxidative insertion across the Csp2-Br bond can occur, giving the octahedral Ir (III) complex 91. While there were no attempts to verify this decomposition pathway, this mechanism provides one possible explanation for the poor performance of vinyl bromide 75 in the ICR reactions.

Figure 6. Possible mechanism of decomposition of iridium isomerization catalyst
To compensate for the catalyst degradation, the catalyst load was increased from 0.5 mol% to 1.5 mol%, and the standard three equivalents of tricyclohexylphosphine were kept (Table 1, Entry C). The reaction proceeded with full conversion to the allyl vinyl ether 92. While catalyst degradation was undoubtedly still a problem, increasing the concentration of iridium catalyst allowed for all of the starting material to be isomerized before the catalyst was fully decomposed. Subsequent addition of triphenylphosphine was meant to quench the iridium catalyst and prevent the now unnecessary Lewis acidic catalyst from interfering with the thermal Claisen rearrangement. Unfortunately, after addition of triphenyl phosphine the ensuing Claisen rearrangement and reduction proceeded only in less than 50% yield and with poor diastereoselectivity.

Steps needed to be taken in order to improve the performance of the thermal Claisen rearrangement because of its poor diastereoselectivity and yield. The higher concentration of iridium during the Claisen rearrangement was a possible cause of the poor yield and diastereoselectivity due to Lewis-acid promoted aldehyde enolization resulting from the additional iridium salts present in the mixture. While the ratio of iridium catalyst to triphenylphosphine was maintained, there are several reasons this ratio may no longer be sufficient to quench the catalyst. If the catalyst does undergo the proposed oxidative insertion to give octahedral complex 91 (Figure 6), there would be more active coordination sites on the iridium atom that would need to be filled before the metal could be fully quenched. Also, there is a higher concentration of unquenched iridium catalyst by virtue of diffusion of a phosphine ligand away from the metal and into the solvent (an equilibrium that will always be present) simply because of the increase in the concentration of catalyst. To quench the apparent higher concentration of active iridium in the reaction mixture, more equivalents of triphenylphosphine
were added (Table 1, Entry D). The increased concentration of triphenylphosphine would more effectively complex the iridium catalyst and would prevent iridium from interfering with the thermal Claisen rearrangement. Increasing the amount of triphenylphosphine added after the initial isomerization allowed for the Claisen rearrangement to proceed without interference, and the desired primary alcohol 74 was isolated in 84% yield and with typically 13:1 d.r. as determined by $^1$H NMR. Although similarly-functionalized substrates have yet to be tested, this method represents a potential set of conditions to extend the utility of the ICR methodology to be compatible with a wide range of vinyl halides. At the very least, these conditions act as a valuable starting point for studies of the expansion of the methodology.

**Table 1. Various conditions tested for the ICR of diallyl ether 75**

<table>
<thead>
<tr>
<th>Entry</th>
<th>$[\text{IrCl(COE)}]_2$ (mol %)</th>
<th>PCy$_3$ (mol %)</th>
<th>PPh$_3$ (mol %)</th>
<th>Yield 74</th>
<th>d.r. (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.5</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>0.5</td>
<td>2</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>1.5</td>
<td>9</td>
<td>12</td>
<td>&lt; 50%</td>
<td>1.6:1</td>
</tr>
<tr>
<td>D</td>
<td>1.5</td>
<td>9</td>
<td>15</td>
<td>84 %</td>
<td>13:1</td>
</tr>
</tbody>
</table>

Although a successful procedure for performing ICR reactions on substrates containing halogens was developed, due to the long reaction times (~3 days) of the Claisen rearrangement at 80 °C in the 1,2-DCE/acetone solvent mixture it was desirable to modify the procedure to reduce the reaction time. Thus, an alternate solvent was sought that would allow the Claisen
rearrangement to be performed at higher temperatures. In order to test different solvents for the Claisen rearrangement, the allyl vinyl ether product of the iridium-catalyzed isomerization had to be isolated. The reaction was worked up after the initial isomerization, providing the isomerized allyl vinyl ether 92 in 96% yield. After purification, the resulting Claisen precursor was dissolved in toluene. The Claisen rearrangement proceeded markedly faster in refluxing toluene relative to the 1,2-DCE/acetone mixture, and was completed in 2 hours. After a reductive sodium borohydride workup, primary alcohol 74 was obtained in 81% yield and a 13:1 d.r. as found by $^1$H NMR. This slightly modified procedure allowed the entire reaction sequence to be completed in one day, and for this reason was used primarily in this synthesis despite increasing the number of steps in the sequence.

**Scheme 16.** Alteration of ICR conditions for time considerations

Conditions: a) [IrCl(COE)$_2$], PCy$_3$, NaBPh$_4$, DCE/acetone, rt. b) PPh$_3$, 80 °C; NaBH$_4$, MeOH, 0 °C to rt. c) toluene, 110 °C; NaBH$_4$, MeOH, 0 °C to rt.

With the synthesis of primary alcohol 74 complete, the synthesis of model system 58 could be continued. Fluoride mediated E2 elimination of the vinyl bromide in 74 provided the internal alkyne 66 in 99% yield (Scheme 17). Internal-to-terminal alkyne isomerization was achieved by an alkyne zipper reaction using ethylene diamine and sodium hydride, and gave the
terminal alkyne 59 without epimerization of the \( \alpha \)-stereocenter. I hypothesized that exposure of vinyl bromide 74 directly to the ethylene diamine/sodium hydride conditions could effect both the E2 elimination and the alkyne isomerization. The use of sodium amide to facilitate the elimination of HBr from vinyl bromides is known, and in one case sodium amide itself also facilitated the isomerization of an internal vinyl bromide directly into the corresponding terminal alkyne, although I propose this occurs through an allene intermediate without a preceding internal alkyne.\(^{43-44}\)

**Figure 7.** Direct conversion of vinyl bromide to terminal alkyne possibly via an allene

This evidence suggested that another strong amide base could also perform the necessary dehydrobromination of vinyl bromide 74. Although the active base in the zipper reaction is not as strong as sodium amide, if the base could perform the initial elimination, excess base in the reaction mixture would isomerize the resulting internal alkyne in one pot. The zipper reaction conditions successfully effected the transformation of vinyl bromide 74 directly to terminal
alkyne 59 in 76% yield, which is comparable with typical alkyne isomerizations using this procedure. This result makes the two-step elimination/isomerization process unfavorable when compared to the one-pot process because of the extra work-up and purification step.

**Scheme 17.** One step elimination/isomerization reaction

Conditions: a) TBAF•3H₂O, DMF, 60 °C, then rt, ether. b) Ethylene diamine, NaH, 60 °C.

In order to provide a functional handle for an ensuing Stille coupling, it was necessary to hydrostannylate terminal alkyne 59 to form a 1,1-disubstituted alkene. Conditions utilizing bis(tributyltin) and CuCN successfully provided 1,1-disubstituted vinylstannane 97 in 61% yield. While small scale reactions were reproducible using theses conditions, attempts to scale up the reaction from submillimolar (~0.7) amounts of starting material to millimolar (~4) amounts resulted in greatly diminished yields, with a maximum of 41%. The free alcohol of 97 was protected as a TBS-ether to give 98 in order to determine whether the free alcohol was adversely affecting the yield of the reaction. Protection of the alcohol had no positive effect on the yield of the reaction and 99 was isolated in 56% yield, although this was done on a slightly larger scale (2 mmol). While these conditions provided 97 and allowed for synthetic studies to continue, these conditions are not yet satisfactory. This transformation represents the biggest bottleneck of the synthetic route, and further experimentation is needed to develop conditions to perform this transformation with higher yields and the ability to successfully scale up the
reaction for the synthesis of the natural product. The reaction with the silyl ether 99 do present one option for scale-up studies. Although the yields of the reaction were similar to those obtained with different conditions, these reactions tended to have a cleaner reaction mixture and were easier to work-up, suggesting a potentially less problematic scale up.

**Scheme 18.** Hydrostannylation of terminal alkynes

Completion of the synthesis of model system 58 required the displacement of a primary alcohol with an azide, followed by a Stille coupling to set up the final aza-Wittig ring closing reaction. The conversion of the primary alcohol of vinyl stannane 97 to an azide was first attempted via simple $S_N2$ displacement of the derived sulfonate ester. Initial attempts to effect the azide mediated substitution of the primary mesylate or tosylate derived from 97 gave the desired primary azides 100 and 101 in 33% or 24% yield, respectively. Fortunately, subjecting 97 to Mitsunobu conditions successfully promoted the displacement in 95% yield using diisopropyl azodicarboxylate, triphenylphosphine and diphenylphosphoryl azide. The resulting azide 51 was used in a Stille coupling reaction between a vinyl stannane and an acid chloride. Coupling of 51 and hydrocinnamoyl chloride mediated by allyl palladium chloride dimer
provided the cyclization precursor 102 in a 50% yield, which is the pentultimate product of the model system synthesis.

Scheme 19. Synthesis of cyclization precursor 102

Conditions: a) R = Ms; MsCl, TEA, DCM, 0 °C to rt. b) R = Ts; pyr, rt. c) R = Ms; NaN₃, DMF, 50 °C. d) R = Ts, TBAN, THF, 60 °C. e) DIAD, PPh₃, DPPA, 0 °C to rt. f) Hydrocinnamoyl chloride, [allylPdCl]₂, MeCN.

Synthesis of the 7-membered imine ring in the target 58 required cyclization of the terminal azide onto the ketone of the α,β'-unsaturated enone 102. Because of the presence of a potential Micheal acceptor in the enone of 102, this ring closure is not a straightforward transformation, and has proven difficult. Subjecting the azide to aza-Wittig conditions using triphenylphosphine resulted in consumption of the starting material, but no product. Initial reaction of the azide with triphenylphosphine provides a very polar product by TLC, thought to be the free amine resulting from hydrolysis of the azaphospha-ylide either in air or on the TLC plate based on its high polarity. After heating, however, neither the resulting aza-Wittig product nor starting material is found in the final reaction mixture. Trimethylphosphine has been shown to promote the ring closure of similar systems, but using trimethylphosphine resulted in degradation of the starting material and no isolation of product. Initial attempts to use a
Staudinger reduction to transform \textbf{102} to an amine and isolate it, followed by condensation of the resulting amine and ketone were inconclusive due to the small quantities used in the initial reaction and the moderate yield of any amine products. A half of an equivalent of triphenylphosphine was isolated after the reaction, suggesting formation of at least some of the free amine, although its isolation has proven difficult.

There are several potential complications in closing the imine ring resulting from the presence of a Michael acceptor in enone \textbf{102}. The terminal end of the olefin in \textbf{102} provides an opportunity for a variety of conjugate additions to take place, all of which compete with the desired cyclization pathway. In the case of free amine \textbf{103}, there is a potential competing 7-\textit{endo}-trig cyclization of the amine on the olefin, and both the desired 7-\textit{exo}-trig and the competing 7-\textit{endo}-trig ring closures are allowed by Baldwin’s rules.\textsuperscript{40} Despite this complication, there is evidence that the desired mode of cyclization can be promoted using kinetic conditions.\textsuperscript{49} Another potential unproductive pathway can occur during the initial exposure of the enone \textbf{102} to any organophosphines. The addition of a phosphine into the enone can provide an enolate, which can then react via a conjugate addition to another molecule of \textbf{102} in an intermolecular Rauhut-Currier reaction.\textsuperscript{50-51} Further experimentation is necessary to find conditions to effect the difficult cyclization or to develop a route which can overcome the current difficulties.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Potential modes of cyclization of free amine \textbf{103}}
\end{figure}
3.0 FUTURE WORK

3.1 EXTENSION OF ICR METHODOLOGY TO INCLUDE VINYL BROMIDES

One potential extension of the preceding work is to develop efficient conditions to perform ICR reactions on any vinyl bromide substrate, and the conditions developed in this work (Table 1, Entry D) would serve as a starting point for that development. This would provide a valuable extension to the ICR methodology because the vinyl bromide products of the reaction have a unique synthetic utility relative to the typical alkene products of the reactions. The resulting vinyl halide is a useful functional handle that could be easily used to provide internal alkynes, could be used in palladium catalyzed cross coupling reactions, or serve as starting materials to synthesize Grignard reagents.\textsuperscript{52-54}

While continuing to manipulate the amounts of some of the reactions components is one potential optimization strategy, a better strategy may be the development of a new ligand for the iridium isomerization complex. The oxidative insertion pathway that is proposed as a possible mechanism of decomposition of the iridium isomerization complex can be eliminated if the bidentate chelation of the vinyl bromide is prevented. A tridentate iridium ligand should allow the coordination of the first olefin, but without another open site on the iridium ligand, the bidentate chelation should be impeded. This would allow the reaction to proceed with fewer equivalents of catalyst, ligand, and triphenylphosphine.
3.2 COMPLETION OF CYCLIC IMINE RING

In order to avoid the potential of a problematic Rauhut-Currier reaction in the aza-Wittig cyclization of enone 102, an alternate route to generating free amine 103 can be envisioned. Instead of displacing the primary alcohol of 97 with azide in a Mitsunobu reaction, the alcohol could be displaced with a protected amine precursor. For example, under similar Mitsunobu conditions, t-butyl methyl iminodicarboxylate (TBMID) can displace the primary alcohol and be partially deprotected to give the BOC-protected amine. This protected amine could be carried through the remaining synthesis, and cyclized with TFA using conditions from Evans used to cyclize similar intermediates. This represents a possible change in route that could be utilized to synthesize model system 58 despite the complications caused by the enone functional group in 102.

Scheme 20. Alternate route to model system 58

Conditions: a) DIAD, PPh₃, THF, TBMID 0 °C to rt; KOH, MeOH, rt. b) Hydrocinnamoyl chloride, [allylPdCl], MeCN. c) TFA, DCM, rt; 40 °C.
3.3 DIELS-ALDER STUDIES ON ACYCLIC ENONE SUBSTRATE

Another way forward from the current stage of the previous research is to study the Diels-Alder reaction on acyclic substrate 102. By performing the Diels-Alder reaction before the ring closure reaction, several problematic pathways associated with the ring closing reaction of 102 can be eliminated. After the Diels-Alder reaction, there is no potential disruptive conjugate addition pathway for either cyclization with a free amine or addition by phosphine for a Rauhut-Currier reaction in the case of an attempted Staudinger reduction or aza-Wittig cyclization.

The main drawback of this pathway is the loss of any measure of substrate control of the Diels-Alder reaction that could be gained by performing the reaction on the closed cyclic imine substrate. In fact, this pathway is similar to the pathway used by Kishi in a synthesis of (ent)-pinnatoxin A, and the diastereoselectivity is only 1.0:0.9:0.4 desired exo:undesired exo: endo, with the desired diastereomer being outnumbering the undesired products in a 1.3:1 ratio. The structures of the macrocycles in pinnatoxin A and spirolide C are different and a different product ratio would be expected, although there is no way to know a priori whether the geometry of the natural product would be more or less favorable than that of pinnatoxin A for the desired exo approach.
4.0 EXPERIMENTALS

General Information: Infrared spectra were recorded on a Thermo Scientific Nicolet IR 200FT-IR. NMR spectra were recorded on a Bruker Avance-300 (300 MHz) spectrometer, a Bruker Avance-400 (400 MHz) spectrometer, or a Bruker Avance-500 (500 MHz) with chemical shifts reported relative to residual CHCl₃ (7.26 ppm) or D₆-acetone for ¹H NMR and CDCl₃ (77.16) for ¹³C NMR. Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous DCM, THF, DMF, diethyl ether, pentane, and toluene were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. Triethylamine was distilled under nitrogen from CaH₂. Acetone and 1,2-DCE used in ICR reactions was thoroughly degassed by bubbling nitrogen gas through the solvent for 2 h. Flash chromatography was performed on EM silica gel 60 (230-240 mesh).

(Z)-2-Bromobut-2-enal (76). Freshly distilled crotonaldehyde (5.26 g, 75 mmol) was dissolved in 150 mL of dichloromethane and cooled to 0 °C. Neat bromine (12 g, 75 mmol, 1 equiv.) was added dropwise and allowed to stir for 5 min. A 150 mL saturated sodium thiosulfate solution was added to quench the reaction and the mixture was allowed to stir and warm to room temp until the organic layer became clear. The layers were separated, and the aqueous layer was extracted with DCM (3 x 150 mL). The combined organic
extracts were dried, filtered, and the solvent was removed via rotovap. The residual oil was dissolved in 300 mL of dimethyl sulfoxide and heated to 60 °C for 2 h. The reaction was cooled 0 °C and diluted with 300 mL of water. The mixture was then extracted with DCM (5 x 150 mL), and the combined organic layers with washed with brine (300 mL) and water (3 x 150 mL), dried (MgSO₄), and the solvent was removed via rotovap to give 10.4 g (93%) of the crude product as a yellow oil. The product was used crude without further purification. ¹H NMR (300 MHz, CDCl₃) δ 9.22 (s, 1H), 7.24 (q, J = 6.9 Hz, 1H), 2.15 (d, J = 6.9 Hz, 3H).

(Z)-3-Bromopent-3-en-2-ol (77). To a solution of methylmagnesium bromide (24 mL, 72 mmol, 1.03 equiv, 3 M in diethyl ether) in 24 mL of ether at 0 °C, a solution of (Z)-2-bromobut-2-enal (76, 10.42 g, 69.9 mmol, 10 M in diethyl ether) in 7 mL of ether was added slowly. The reaction mixture was allowed to warm to ambient temperature and stir for 20 min, then cooled back 0 °C and was quenched by addition of a saturated ammonium chloride solution. The mixture was allowed to warm to ambient temperature and stir until the organic layer became clear. The layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were dried with MgSO₄, filtered, and the solvent was removed via rotovap. The resulting residue was purified by column chromatography (50% ether/pentane on silica gel) to provide 9.1 g (79%) of the product as a pale yellow oil. IR (neat): 3400, 2981, 2924, 1656; ¹H NMR (300 MHz, CDCl₃) δ 6.06 (q, J = 6.6 Hz, 1H), 4.32 (p, J = 6 Hz, 1H), 1.85 (d, J = 6 Hz, 1H), 1.77 (d, J = 6.6 Hz, 3H), 1.37 (d, J = 6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 133.8, 123.7, 72.6, 22.4, 16.3. Satisfactory mass data could not be obtained for this compound.
A 27.4 mL solution of allyl alcohol 77 (8.04 g, 48.7 mmol, 1.8 M in THF) was added to 27.4 mL of a sodium hydride suspension (2.55 g of 60% in mineral oil, 63.8 mmol, 1.31 equiv., 2.33 M in THF) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stir for 20 min, then was cooled back to 0 °C. When the mixture was cooled, 5.1 mL of freshly distilled allyl bromide (7.1 g, 59 mmol, 1.2 equiv.) was added and the reaction mixture was allowed to warm back to ambient temperature and stir overnight. Water was added to quench the reaction, the layers were separated, and the aqueous layer was extracted with ether (3 x 50mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent was removed via rotovap. Column chromatography (2% ether/pentane on silica gel) provided 8.3 g (83%) of the product as a pale yellow oil. IR (solution in DCM): 2986, 2926, 2685; ¹H NMR (400 MHz, CDCl₃) δ 6.03 (q, J = 6.8 Hz, 1H), 5.91 (dddd, J = 17.2 Hz, 10.4 Hz, 6.4 Hz, 5.2 Hz, 1H), 5.26 (dd, J = 17.6 Hz, J = 1.6, 1H), 5.17 (dd, J = 10.4 Hz, 1.2 Hz, 1H), 4.01 (dddd, J = 12.8 Hz, J = 5.2 Hz, J = 1.6 Hz, J = 1.2 Hz, 1H), 3.95 (q, J = 6.4 Hz, 1H), 3.77 (br dd, J = 12.8 Hz, J = 6.4 Hz, 1H), 1.79 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 134.6, 131.5, 125.5, 117.1, 78.8, 69.0, 21.0, 16.3. Satisfactory mass data could not be obtained for this compound.

A mixture of [IrCl(COE)₂]₂ (0.203 g, 0.277 mmol, 1.5 mol%), NaBPh₄ (0.171 g, 0.500 mmol, 3.3 mol%), and PCy₃ (0.381 g, 1.36 mmol, 9 mol%) was dissolved in 21.6 mL of thoroughly degassed 1,2-DCE and 0.5 mL of degassed acetone and the mixture was allowed to stir for 5 min. Neat diallyl ether 75 (3.10 g, 15.1 mmol) was added and the reaction was allowed to stir for 1 h. The reaction mixture was quenched by addition of water, the layers
were separated, and the aqueous layer was extracted with DCM (4 x 30 ml). The combined organic layers were dried over MgSO$_4$, filtered, and the solvent was removed via rotovap. Column chromatography (2% ether/pentane on silica gel) provided 2.98 g (96%) of the product as a pale yellow oil. IR (neat): 3039, 2985, 2922, 2887, 2859, 1675, 1656, 1440; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.04 (q, J = 6.5 Hz, 1H), 6.02 (dq, J = 13.5 Hz, 1 Hz, 1H), 4.96 (dq, J = 13.5 Hz, 7 Hz, 1H), 4.20 (q, J = 6 Hz, 1H), 1.78 (d, J = 6.5 Hz, 3H), 1.53 (dd, (J = 7 Hz, J = 1 Hz, 3H), 1.38 (d, J = 6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.2, 130.1, 125.3, 102.4, 79.9, 20.5, 16.3, 12.5; HRMS (EI) m/z calcd for (M$^+$) C$_8$H$_{13}$OBr: 204.0150; found: 204.0112.

(74). Allyl vinyl ether 92 (2.83 g, 13.8 mmol) was dissolved in 69 mL of toluene and heated to reflux for 3 h. The reaction mixture was then cooled to 0 °C. Sodium borohydride (1.05 g, 27.8 mmol, 2.02 equiv.) and methanol (5 mL) were added, and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was cooled to 0 °C and was quenched by the addition of water. The layers were separated, and the aqueous layer was extracted with ether (3 x 100 mL). The combined organic layers were dried (Na$_2$SO$_4$) and filtered. The volatile ether was removed by rotovap, and the remaining high boiling toluene was removed via azeotrope with methanol. Column chromatography (5% ether/hexanes on silica gel) provided 1.95 g (68%) of the product as a clear yellow oil. IR (neat): 3340, 2970, 2922, 2876, 1654, 1451; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.78 (q, J = 6.4 Hz, 1H), 3.56 (dt, J = 10 Hz, 4.8 Hz, 1H), 3.45 (dt, J = 10.8 Hz, 4.8 Hz, 1H), 2.35 (dq, $J_d$ = 8.4 Hz, $J_q$ = 6.8 Hz, 1H), 1.90 - 1.81 (m, 1H), 1.73 (d, J = 6.4 Hz, 3H), 1.23 (dd, J = 6 Hz, J = 6 Hz, 1H), 1.08 (d, J = 6.4, 3H), 0.95 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.5, 122.8, 66.5, 45.9, 38.5, 17.3, 16.7, 13.7;

(syn)-2,3-Dimethylhex-5-yn-1-ol (59). Sodium hydride (1.20 g, 30.0 mmol, 4.14 equiv.) was added to 11.8 mL of ethylene diamine cooled to 0 °C, and the mixture was allowed to warm to ambient temperature and stir for 1 h. The mixture was then heated to 60 °C for 1 h, then cooled to 45 °C for the dropwise addition vinyl bromide 74 (1.50 g, 7.24 mmol), followed by warming of the reaction mixture back to 60 °C for 2 h. The mixture was then slowly cooled to 0 °C and was quenched with 8.9 mL of 1 M HCl. The layers were separated and the aqueous layer was extracted with ether (5 x 20 mL). The combined organic layers dried over MgSO₄, filtered, and the solvent was removed via rotovap. Column chromatography (50% ether/hexanes on silica gel) provided 0.692 g (76%) of the product as a clear oil. IR (neat): 3308, 2962, 2923, 2116, 1455, 1382, 1032; ^1^H NMR 3.59 – 3.50 (m, 2H) δ 2.19 (dd, J = 7 Hz, J = 2.5 Hz, 2H), 1.97 (t, J = 2.5 Hz, 1H), 1.91 – 1.78 (m, 2H), 1.28 (t, J = 6 Hz, 1H), 0.93 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H); ^1^C NMR (125 MHz, CDCl₃) δ 83.5, 69.3, 66.5, 38.7, 33.3, 24.1, 15.0, 11.9; HRMS (EI) m/z calcd for (M⁺) C₈H₁₄O: 126.1045; found: 126.1069.

(syn)-2,3-Dimethyl-5-(tributylstannyl)hex-5-en-1-ol (97). A 40 mL solution of bis(tributyltin) (19.7 g, 34 mmol, 6.2 equiv., 0.857 M in THF) in THF was cooled to -40 °C, and 21.8 mL of n-BuLi (33.5 mmol, 6.12 equiv., 1.54 M in hexanes) was added and the solution was stirred for 1 h at -40 °C. Copper cyanide (1.51 g, 16.9
mmol, 3.08 equiv) was added and the solution was cooled to -78 °C. A 10.9mL THF solution of terminal alkyne 59 (0.692g, 5.48 mmol, 0.5 M in THF) was added and the reaction mixture was stirred at -78 °C for 2.5 h. The reaction mixture was quenched with water and the mixture was warmed to ambient temperature. The layers were separated, and the aqueous layer was extracted with ether (4 x 100 mL). The combined organic layers were washed with saturated KF and brine, dried over Na$_2$SO$_4$, filtered, and the solvent was removed via rotovap. Column chromatography (10% EtOAc/hexanes on silica gel) provided 0.934 g (41%) of the product as a clear oil. IR (neat): 3337, 3030, 2929, 1462, 1418; $^1$H NMR (500 MHz, CDCl$_3$) δ 5.65 – 5.64 (m, 1H), 5.15 (d, J = 3 Hz, 1H), 3.56 (dt, J = 11 Hz, 6 Hz, 1H), 3.46 (dt, J = 10.5 Hz, 6.5 Hz, 1H), 2.32 (dd, J = 13.5 Hz, 5.5 Hz, 1H), 2.07 (dd, J = 13.5 Hz, 8 Hz, 1H), 1.70 – 1.63 (m, 2H), 1.52 – 1.45 (m, 6H), 1.36 – 1.27 (m, 6H), 1.13 (t, J = 5.5 Hz, 1H), 0.89 (t, J = 7.5 Hz, 9H), 0.90 – 0.87 (m, 6H) 0.83 (d, J = 6.5 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.8, 126.3, 67.2, 47.2, 39.5, 33.3, 29.3, 27.6, 14.4, 13.8, 11.5, 9.8; MS (ES) m/z calcd for ([M – C$_4$H$_9$]$^+$) C16H33OSn: 361.1548; found: 361.2676.

![Bu$_3$Sn](image)

(6-Azido-(syn)-4,5-dimethylhex-1-en-2-yl)tributylstannane (51).

Alcohol 97 (0.862 g, 2.07 mmol) and triphenyl phosphine (0.651 g, 2.48 mmol, 1.2 equiv.) were dissolved in 10.35 mL of THF and cooled to 0 °C. Diisopropyl azodicarboxylate (0.626 g, 3.10 mmol, 1.5 equiv) was added and the resulting solution was stirred for 20 min. Diphenylphosphoryl azide (0.854 g, 3.10 mmol, 1.5 equiv.) was added and the mixture warmed to ambient temperature and stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc (3 x 20). The combined organic layers were dried with Na$_2$SO$_4$, filtered, and the solvent was removed via rotovap. Column chromatography (10%
EtOAc/hexanes on silica gel) provided 0.710 g (78%) of the product as a clear oil. IR (neat): 3429, 2957, 2927, 2097, 1462, 1418; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.65–5.64 (m, 1H), 5.16 (d, J = 3 Hz, 1H), 3.24 (dd, J = 12 Hz, 7 Hz, 1H), 3.14 (dd, J = 12 Hz, 7.5 Hz, 1H), 2.30 (dd, J = 13.5 Hz, 6 Hz, 1 H), 2.06 (dd, J = 13.5 Hz, 8.5 Hz, 1H), 1.76 (dddq, J = 7.5 Hz, 7 Hz, 7 Hz, 3.5 Hz,1H), 1.68 – 1.60 (m, 1H), 1.52 – 1.46 (m, 6H), 1.36 – 1.28 (m, 6H), 0.92 – 0.87 (m, 15H), 0.85, (d, J = 7 Hz, 3H), 0.74 (d, J = 7 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.4, 126.6, 56.6, 47.1, 36.9, 34.0, 29.3, 27.6, 13.9, 13.8, 12.4, 9.8; HRMS (ASAP) m/z calcd for (M$^+$) C$_{20}$H$_{43}$N$_3$Sn: 445.2479; found: 445.2463.

8-Azido-(syn)-6,7-dimethyl-4-methylene-1-phenyloctan-3-one (102). Vinyl stannane 51 (0.100 g, 0.226 mmol) and hydrocinnamoyl chloride (0.040g, 0.236 mmol, 1.04 equiv) were dissolved in 0.56 mL of dry acetonitrile under nitrogen. Allylpalladium chloride dimer (.0050 g, 0.0137 mmol, 6.1 mol%) was added to the solution, which quickly turned black. The reaction was monitored by TLC, and once it was completed 1 mL of a saturated KF solution was added, and the mixture was stirred vigorously overnight. The layers were separated, and the aqueous layer was extracted with ether(3 x 3 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and the solved was removed via rotovap. The crude product was dissolved in ethyl acetate and the precipitated tin fluoride was removed by filtration. The solvent was again removed via rotovap, and column chromatography (10% EtOAc/hexanes on silica gel) provided .0325 mg (50%) of the product as a clear yellow oil. $^1$H NMR (300 MHz, d-acetone) $\delta$ 7.30 – 7.21 (m, 4H), 7.19 – 7.13 (m, 1H), 6.17 (s, 1H), 5.8 (d, J = 0.3 Hz, 1H), 3.29 (dd, J = 12.3 Hz, J = 6.6 Hz, 1H), 3.21 (dd, J = 12.3 Hz, J = 7.2 Hz, 1H), 3.11 – 3.03 (m, 2H), 2.93 – 2.85 (m, 2H), 2.37 (ddd, J = 13.2 Hz, 6 Hz, 0.9
Hz, 1 H), 2.11 (ddd, $J = 13.2$ Hz, 8.1 Hz, 0.9 Hz, 1H), 1.79 – 1.63 (m, 2H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H).
BIBLIOGRAPHY


