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

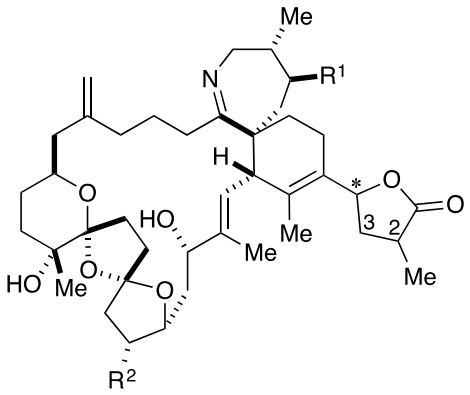
1,2-DCE	1,2-Dichloroethane
BAIB	Bis(acetoxy)iodobenzene
Bn	Benzyl
BOC	*t*-Butyloxycarbonyl
BOX	Bis(oxazoline)
Cy	Cyclohexane
DCM	Dichloromethane
DIAD	Diisopropylazodicarboxylate
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphorylazide
dr	Diastereomeric ratio
EtOAc	Ethyl acetate
ICR	Isomerization/Claisen rearrangement
MIB	3-*exo*-Morpholinoisoborneol
MOM	Methoxymethyl
MPM	4-Methoxybenzyle

Ms	Mesyl
NMR	Nuclear magnetic resonance
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
pyr	Pyridine
RCM	Ring-closing metathesis
TBAF	Tetrabutylammonium fluoride
TBAN3	Tetrabutylammonium azide
TBDPS	*t*-Butyldiphenylsilyl
TBMID	*t*-Butyl methyl iminodicarboxylate
TBS	*t*-Butyldimethylsilyl
TEA	Triethylamine
TEOC	2-(Trimethylsilyl)ethyl carbonate
Tf	Triflate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl

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]



Spirolide A: $\Delta^{2,3}$; R^1 = H; R^2 = Me (**1**) Spirolide C: $\Delta^{2,3}$; R^1 = Me; R^2 = Me (**3**)
Spirolide B: R^1 = H; R^2 = Me (**2**) Spirolide D: R^1 = Me; R^2 = Me (**4**)

Figure 1. Structures of the major spirolide natural products

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-spirocyclic 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 spirocyclic imine is hydrolyzed into its constituent ketone and amine fragments.[4] Although the spirocyclic 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.[5-7]

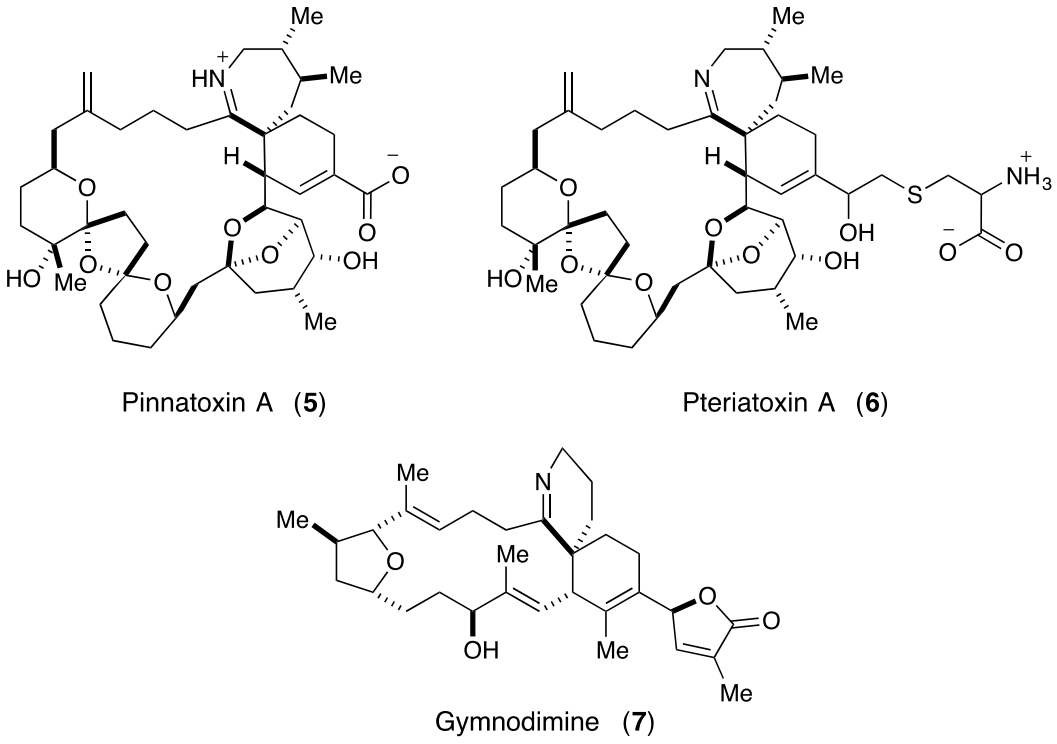
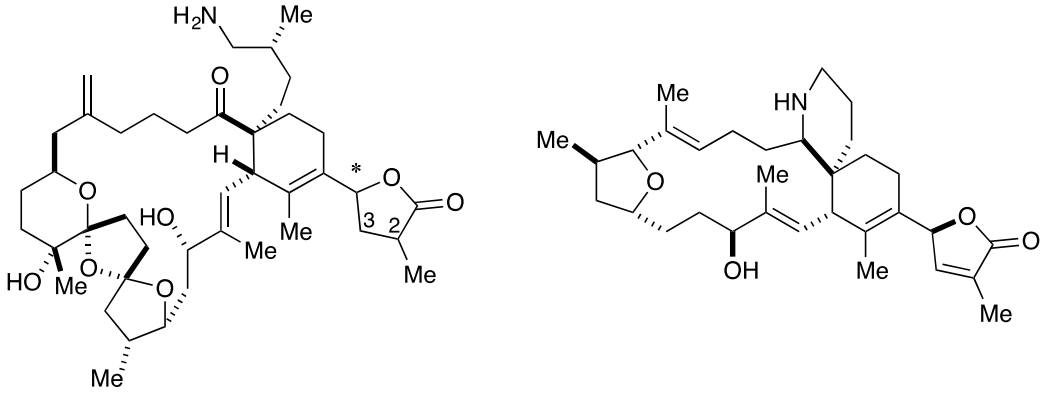


Figure 2. Representatives of families of natural products structurally related to the spirolides

The spirolide family of natural products has continued to expand, and now encompasses named compounds through spirolide I, as well as several naturally occuring hydroxylated or demethylated derivatives of previously discovered spirolides (e.g. 27-oxo-13,19-didesmethyl spirolide C).[8-9] 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.[10] The C4 stereocenter was eventually assigned in 13,19-didesmethyl spirolide C, but remains ambiguous in the rest of the family.[11]

The spirolides behave as a fast acting biotoxin in a mouse assay, causing death within 5 minutes of injection.[1] 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.[1, 12] 13-Desmethyl spirolide C has also been shown to reduce Aβ and hyperphosphorylated Tau protein,

suggesting potential therapeutic applications in Alzheimer's Disease.[13] 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.[4] 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.[14] 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.[8]



Spirolide E: $\Delta^{2,3}$ (**8**)
Spirolide F (**9**)

Gymnodamine (**10**)

Figure 3. Structures of spirolides E and F and gymnodamine

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

and amine substituents, however these conditions are ineffective in hydrolyzing the imine in spirolide C and D.[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.[3]

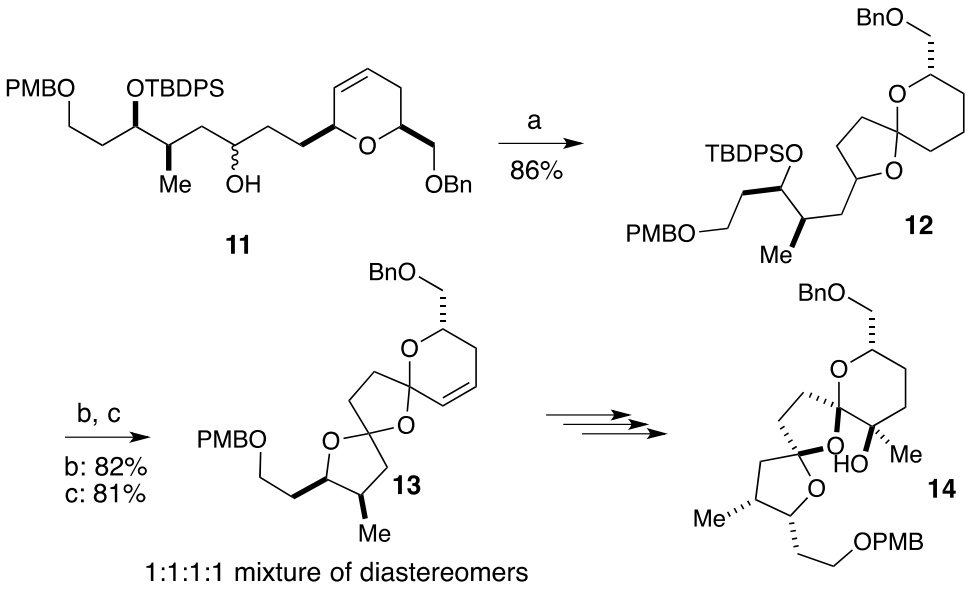
1.2 PREVIOUS FRAGMENT SYNTHESES

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.[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-spirocyclic 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.[20] Eventually, they amended their strategy to use a sequence of multiple oxidative radical cyclizations.[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.[22-24]

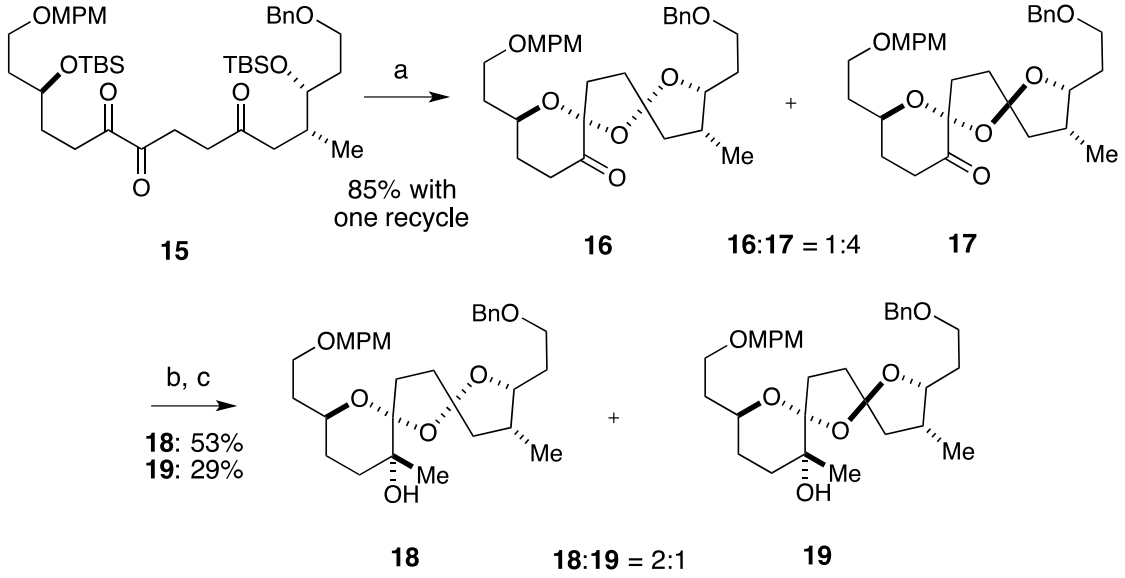
Scheme 1. Brimble's approach to the bis(spiroketal) ring system of the spirolides



Conditions: a) $PhI(OAc)_2$, I_2, hν, cyclohexane, rt. b) TBAF, DMF, 80 ^{o}C. c) $PhI(OAc)_2$, I_2, hν, 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.[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.

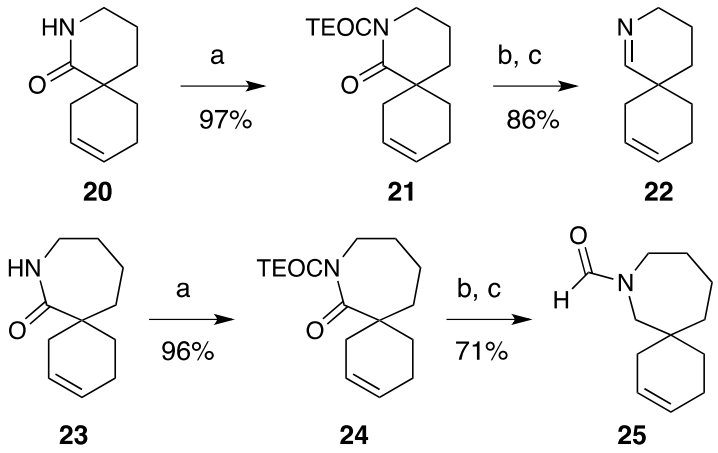
Scheme 2. Ishihara's one step bisketalization for spirolide B bis(spiroketal) system



Conditions: a) HF·pyridine, MeCN, 23 ^{o}C. b) MeLi, THF, -78 ^{o}C. c) TBSOTf, 2,6-lutidine, DCM, 0 ^{o}C to 20 ^{o}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]

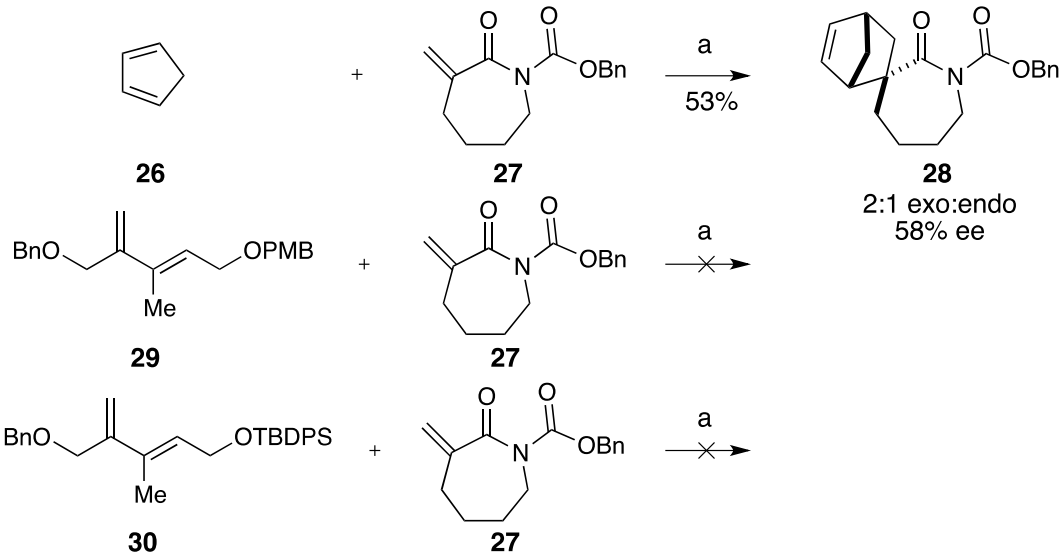
Scheme 3. Brimble's RCM and lactam reduction approach



Conditions: a) *n*-BuLi, THF, -78 ^{o}C; 2-(TMS)ethyl 4-nitrophenyl carbonate, -78 ^{o}C to rt. b) $LiEt_3H$, -78 ^{o}C. c) Bu_4NF, 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.

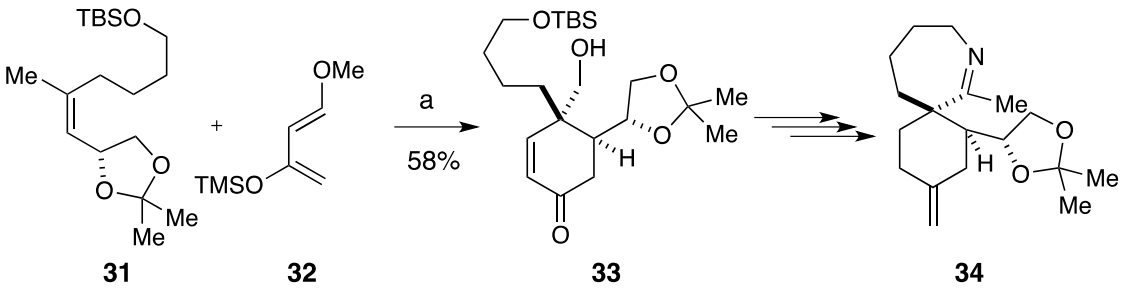
Scheme 4. Brimble's α-methylene lactam Diels-Alder approach



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).[29] Subsequent manipulation of the structure provided 7,6-spirocyclic imine **34**.

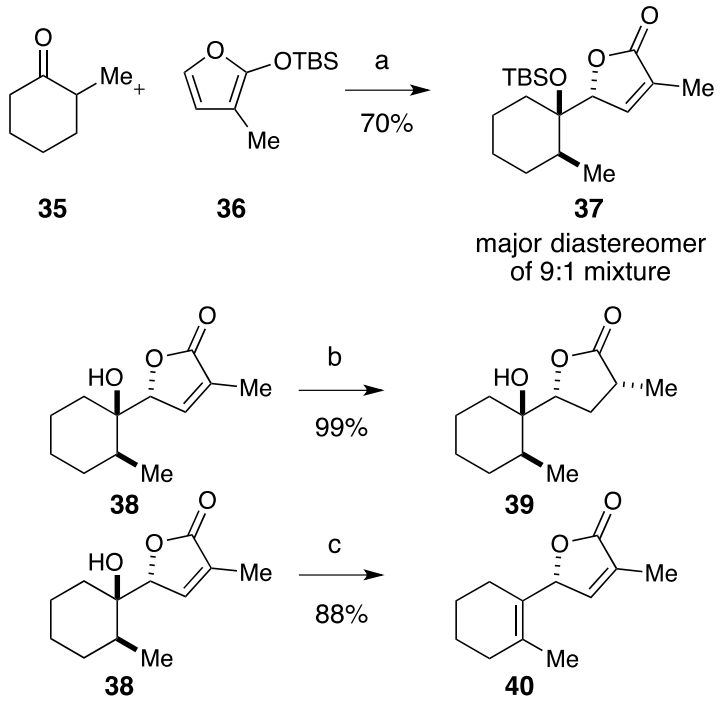
Scheme 5. Brimble's synthesis of a 7,6-spiroimine related to the spirolides



Conditions: a) neat, μν 150 ^{o}C, 48 h.

Romo and coworkers have also contributed to the synthesis of the spirolides. They developed on efficient strategy to append the butenolide fragment of the molecule to the e-ring of the larger macrocycle using a vinylogous Mukaiyama aldol reaction.[30] The reaction proved to have a wide substrate scope, and further manipulation of the resulting tertiary alcohol **38** was not problematic. Two particular reactions of note are the dehydration of **38** to provide tetrasubstituted olefin **40** and the reduction of the butenolide alkene to form saturated lactone **39**. These reactions provide access to substrates analogous to different members of the spirolide family.

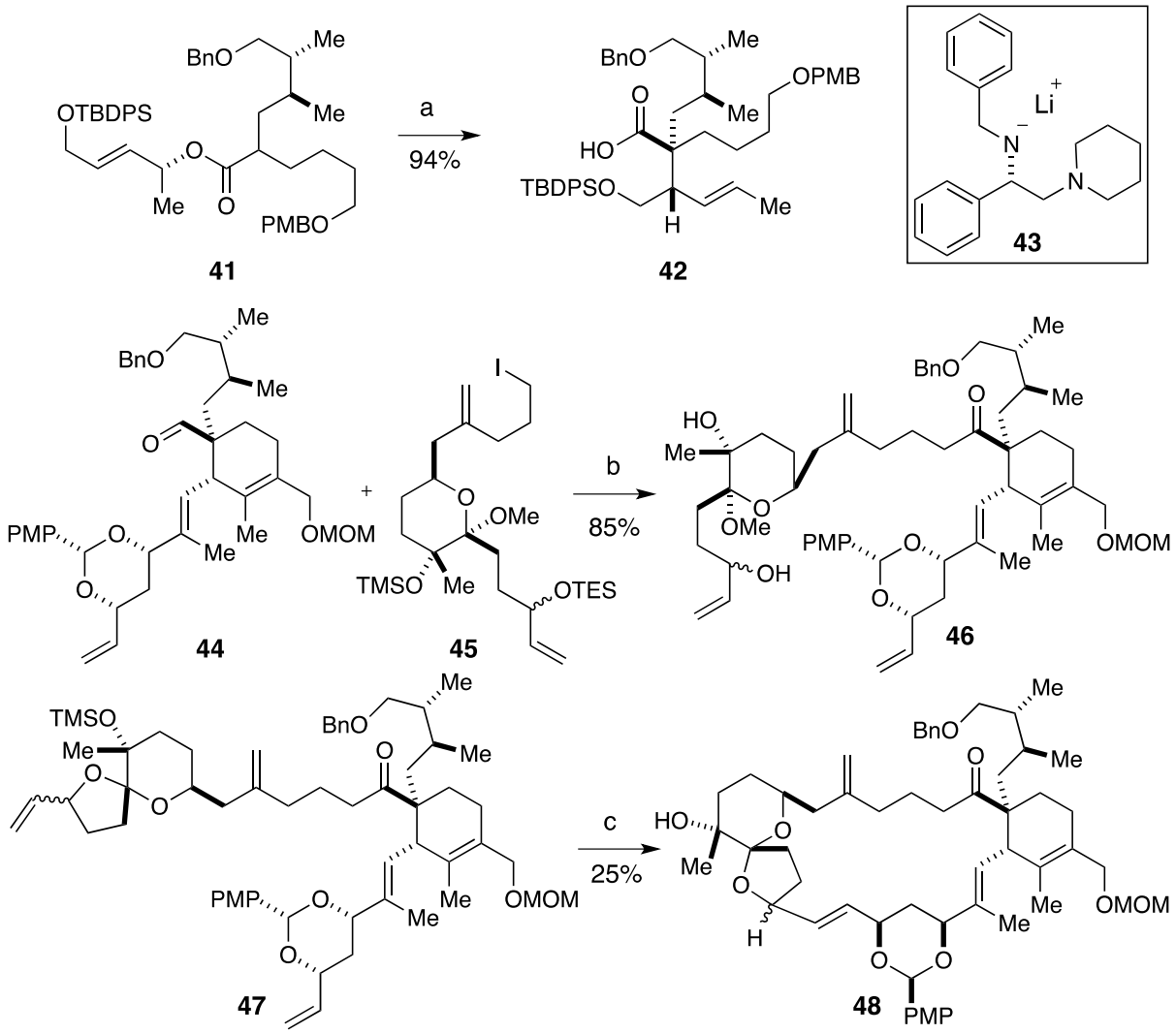
Scheme 6. Romo's butenolide annulation and relevant subsequent transformations



Conditions: a) $TiCl_4$, DCM, -78 ^oC. b) H_2, Pd/C, EtOAc, 25 ^oC. c) $SOCl_2$, pyr, DCM, -50 ^oC.

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.[31] 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.[32] 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



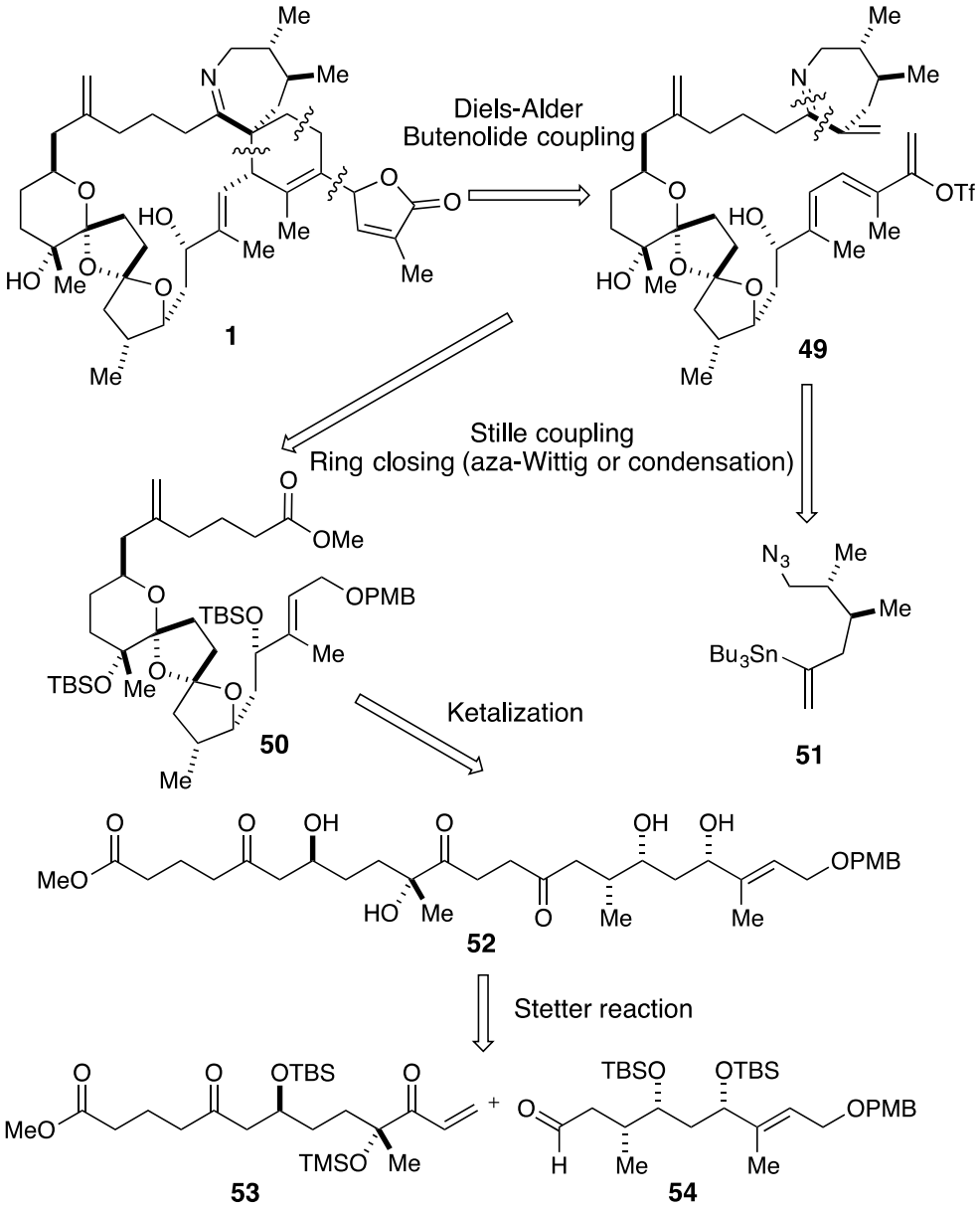
Conditions: a) **43**, THF; Me_3SiCl, -78 ^oC to ambient temperature. b) *t*-BuLi, Et_2O; **43**; DMP, pyr; TBAF, THF. c) Grubbs II 30 mol%, 1,2-DCE, 60 ^oC.

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 α,β-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**)

*

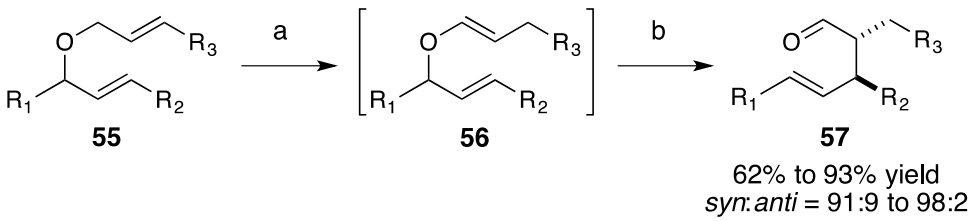


The bottom half of the molecule has been synthesized efficiently via the unprecedented use of a late stage intermolecular Stetter reaction by Binbin Guo.[33] After the screening of various catalysts, it was discovered that Glorious' catalyst promoted the intermolecular coupling of fragments **53** and **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.

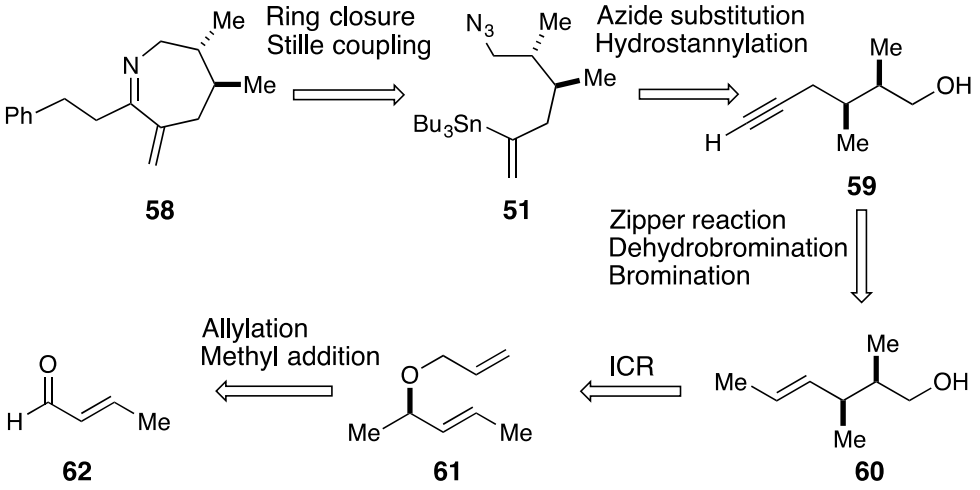
Scheme 9. General ICR reaction and tolerated substitution patterns.



Conditions: a) $[IrCl(COE)_2]_2$, PCy_3, $NaBPh_4$, 1,2-DCE/acetone, rt. b) PPh_3, 60 ^oC.

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.[34]

Scheme 10. First generation retrosynthetic analysis of the desired model system

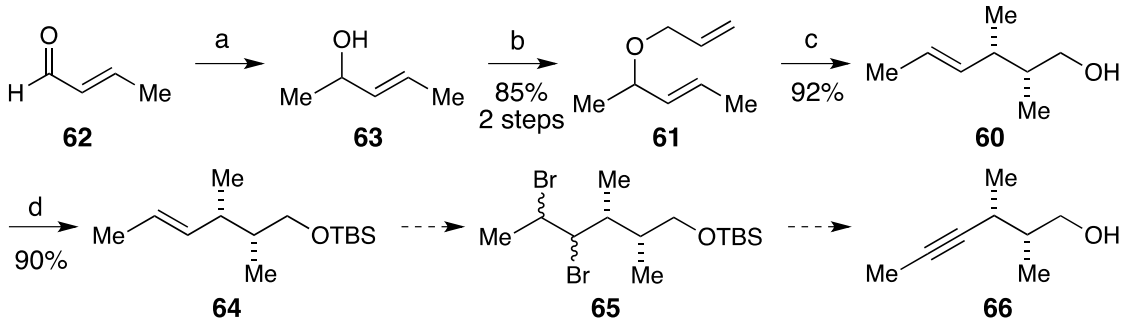


2.0 RESULTS AND DISCUSSION

2.1 FIRST GENERATION APPROACH TO THE 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 *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 TBSCl to give the TBS-ether **64** in 90% yield.

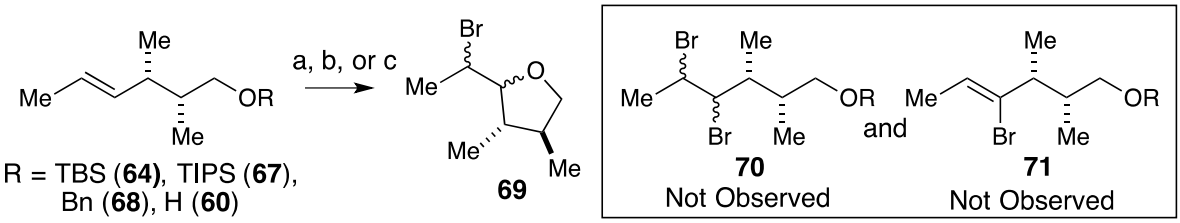
Scheme 11. First generation synthesis of internal alkyne **66**



Conditions: a) MeMgBr, ether, 0 ^{o}C; reflux. b) NaH, 0 ^{o}C to rt; allyl bromide, rt. c) $[IrCl(COE)_2]_2$, $NaBPh_4$, PCy_3, 40:1 1,2-DCE:acetone, rt; PPh_3, reflux; $NaBH_4$, 0 ^{o}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**.[37] 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.[38-39]

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 ^oC. (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 brominium 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. Furthurmore, 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.

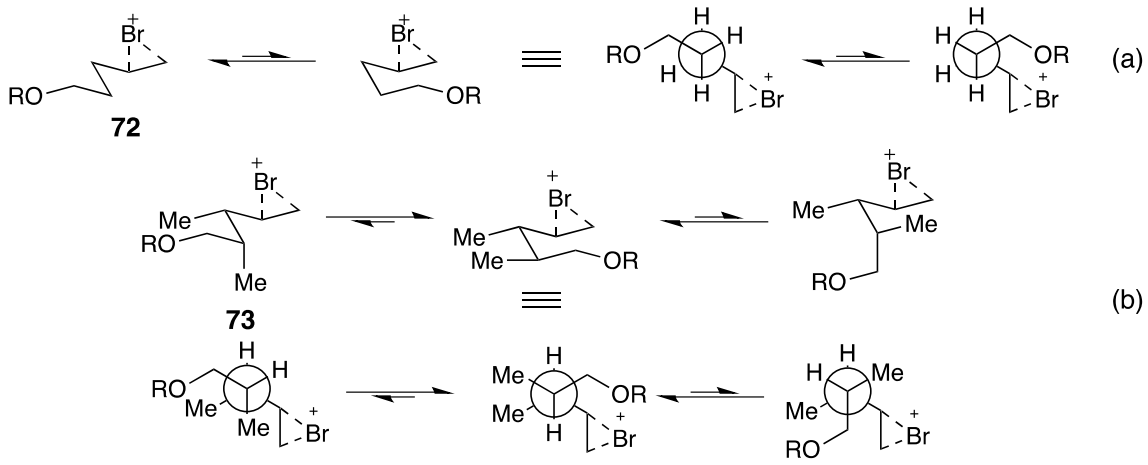


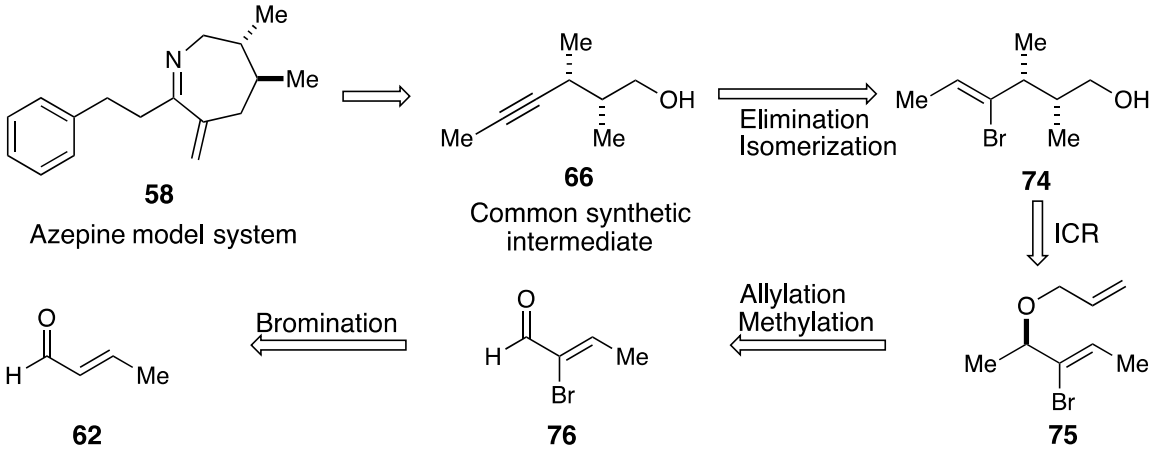
Figure 4. Conformational preferences of bromonium ions

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

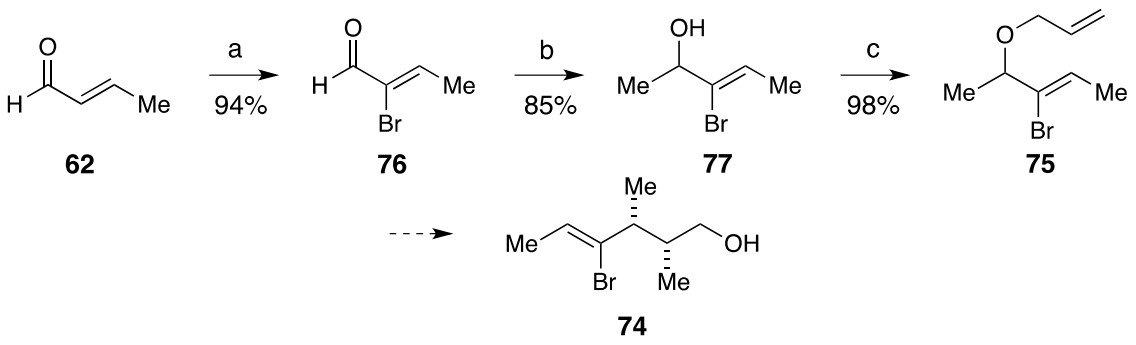
using crotonaldehyde as starting material. Alkyne **66** would be synthesized by the dehydrohalogenation of the vinyl bromide in **74**. In turn, **74** would result from an ICR of **75** that would also set the vicinal methyl stereocenters. The ICR precursor diallyl ether **75** would come from allyation 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 retrosynthesic 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**



a) Br_2, DCM, rt; DMSO, 60 ^oC. b) MeMgBr, ether, 0 ^oC to rt. c) NaH, 0 ^oC to rt; allyl bromide, THF, 0 ^oC to rt.

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.

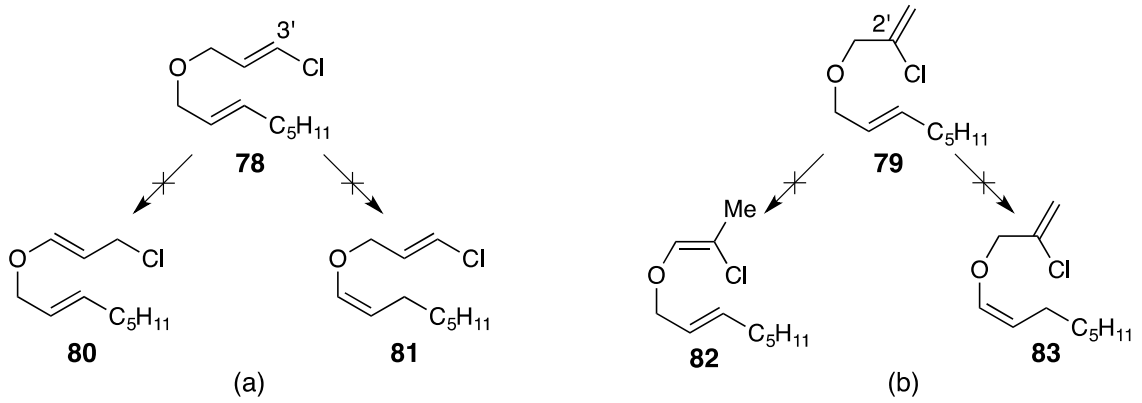
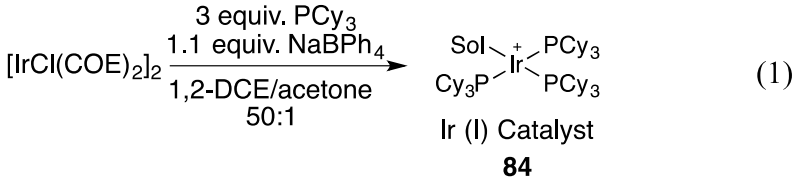


Figure 5. Previous attempted ICR reactions halogen substituted diallyl ethers at the (a) 3' position and the (b) 2' position

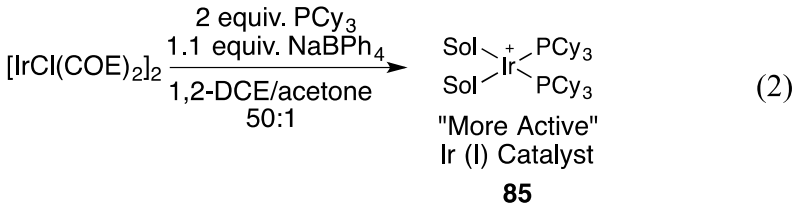
Efforts to effect the ICR reaction of the bromine-containing substrate **75** began with the standard ICR conditions. Unfortunately, the conditions developed for traditional substrates proved ineffective for **75** (Table 1, Entry A). As was seen previously with the other halogen-containing substrates, 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 degredation of the catalyst via insertion across the carbon-bromine bond. Indeed, a similar oxidative insertion for iridium complexes has been observed. [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.



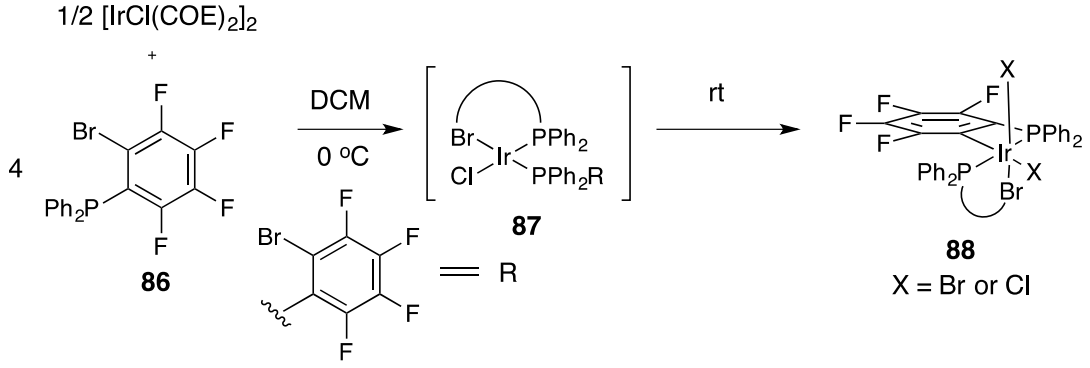
(1)



(2)

One possible mechanism of the decomposition of the iridium catalyst is oxidative insertion of an Ir (I) complex across a Csp^2-Br bond.[42] 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[42]



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.

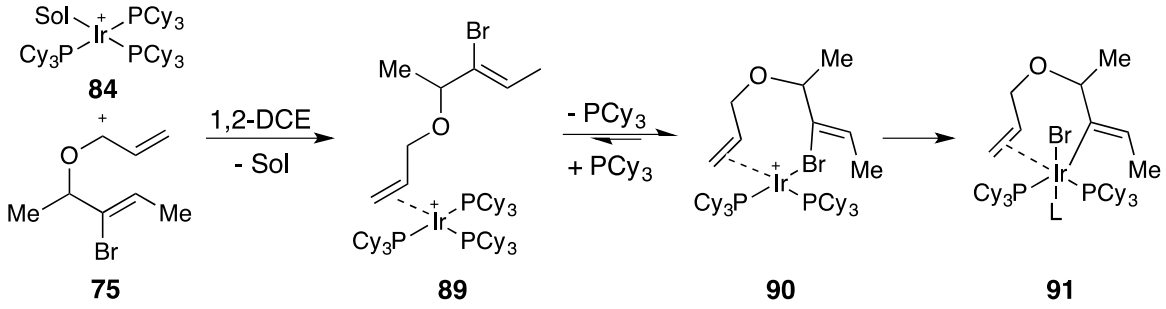


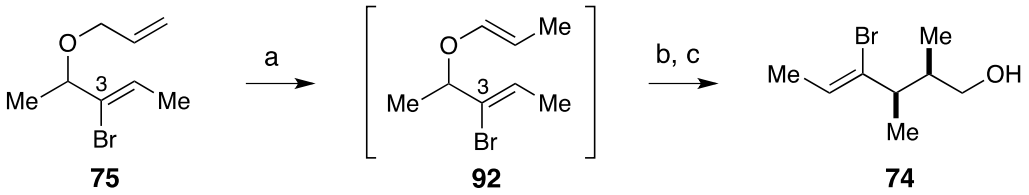
Figure 6. Possible mechanism of decomposition of iridium isomerization catalyst

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**



75 **92** **74**

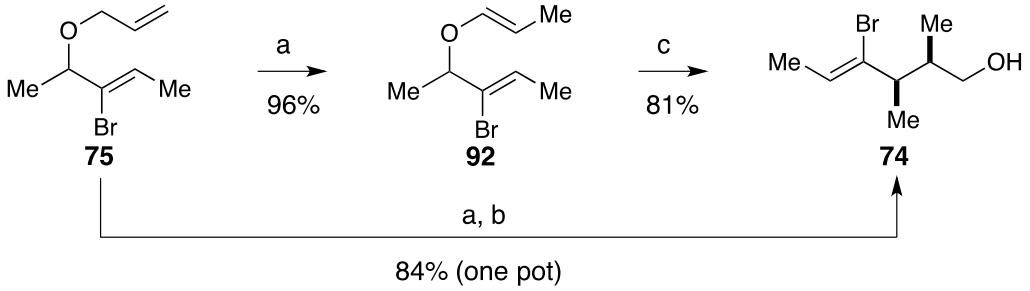
Conditions: a) $[IrCl(COE)_2]_2$, PCy_3, $NaBPh_4$, DCE/acetone, rt. b) PPh_3, 60 ^{o}C. c) $NaBH_4$, MeOH, 0 ^{o}C to rt.

Entry	$[IrCl(COE)_2]_2$ (mol %)	PCy_3 (mol %)	PPh_3 (mol %)	Yield **74**	d.r. (syn:anti)
A	0.5	3	4	-	-
B	0.5	2	4	-	-
C	1.5	9	12	< 50%	1.6:1
D	1.5	9	15	84 %	13:1

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 ^{o}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) $[IrCl(COE)_2]_2$, PCy_3, $NaBPh_4$, DCE/acetone, rt. b) PPh_3, 80 ^{o}C; $NaBH_4$, MeOH, 0 ^{o}C to rt. c) toluene, 110 ^{o}C; $NaBH_4$, MeOH, 0 ^{o}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 α-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]

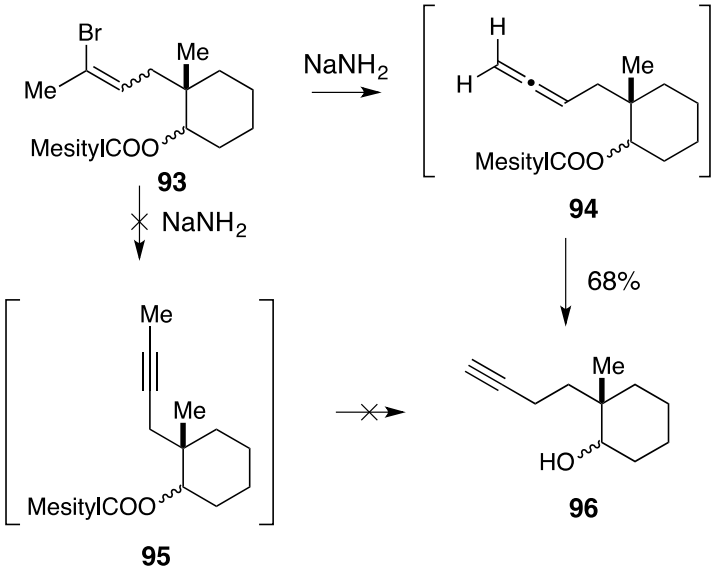
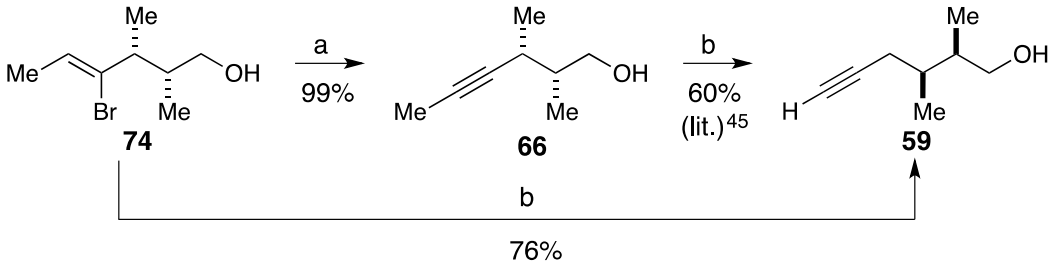


Figure 7. Direct conversion of vinyl bromide to terminal alkyne possibly via an allene

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.[45] 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

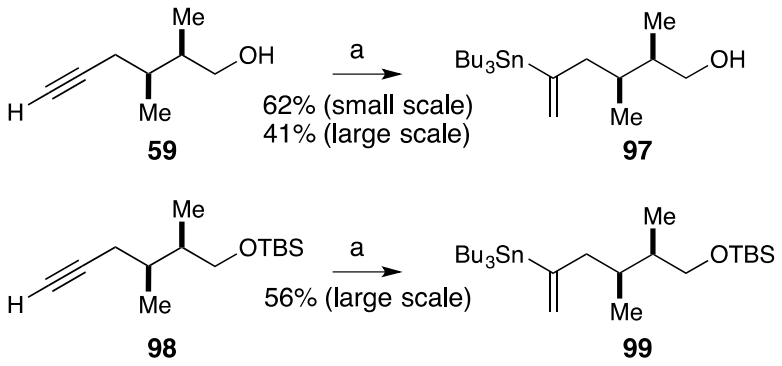


Conditions: a) TBAF•3H_2O, DMF, 60 ^oC, then rt, ether. b) Ethylene diamine, NaH, 60 ^oC.

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.[46] 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

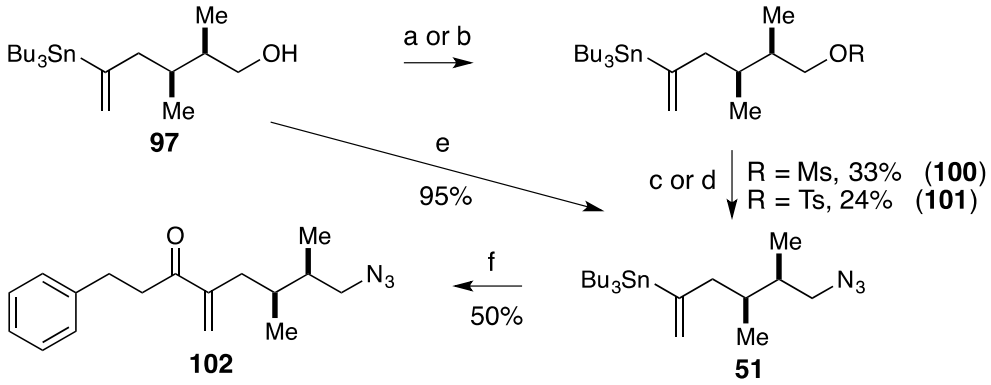


Conditions: a) Bis(tributyltin), *n*-BuLi, -40 ^{o}C; CuCN, -78 ^{o}C.

Completing 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.[47] 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 ^{o}C to rt. b) R = Ts; TsCl, pyr, rt. c) R = Ms; NaN_3, DMF, 50 ^{o}C. d) R = Ts, $TBAN_3$, THF, 60 ^{o}C. e) DIAD, PPh_3, DPPA, 0 ^{o}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′-unsatruated 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,[48] but using trimethylphosphine resulted in degradation of the starting material and no isolation of product. Initial attempts to use a

Staudinger reduction to transform **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 **102**. The terminal end of the olefin in **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 **103**, there is a potential competing 7-*endo*-trig cyclization of the amine on the olefin, and both the desired 7-*exo*-trig and the competing 7-*endo*-trig ring closures are allowed by Baldwin's rules.[40] Despite this complication, there is evidence that the desired mode of cyclization can be promoted using kinetic conditions.[49] Another potential unproductive pathway can occur during the initial exposure of the enone **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 **102** in an intermolecular Rauhut-Currier reaction.[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.

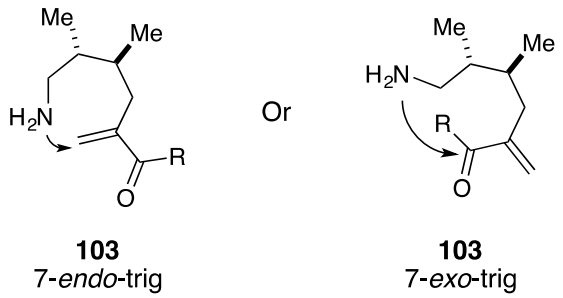


Figure 8. Potential modes of cyclization of free amine **103**

3.0 FUTURE WORK

3.1 EXTENSION OF ICR METHODOLOGY TO INCLUDE VINYL BROMIDES

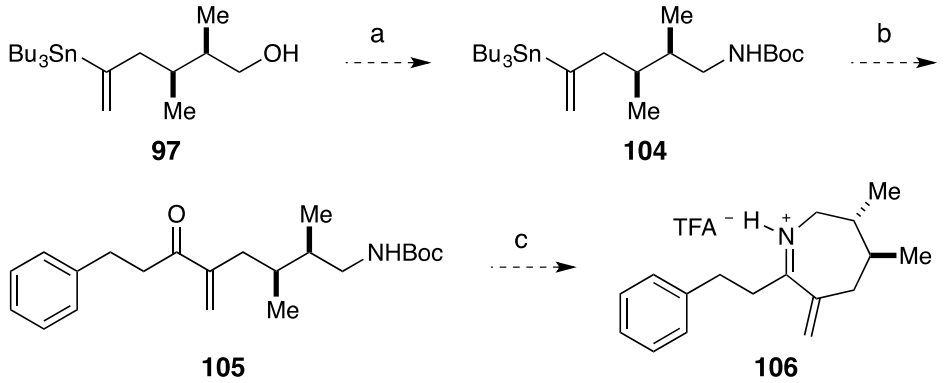
One potential extension of the preceding work is to develop efficient conditions to perform ICR reactions on any vinyl bromide substrate, and the conditions developed in this work (Table 1, Entry D) would serve as a starting point for that development. This would provide a valuable extension to the ICR 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.[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.[55] This protected amine could be carried through the remaining synthesis, and cyclized with TFA using conditions from Evans used to cyclize similar intermediates.[49] 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, PPh_3, THF, TBMID 0 ^oC to rt; KOH, MeOH, rt . b) Hydrocinnamoyl chloride, [allylPdCl], MeCN. c) TFA, DCM, rt; 40 ^oC.

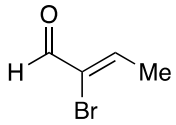
3.3 DIELS-ALDER STUDIES ON ACYCLIC ENONE SUBSTRATE

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.[15] 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.

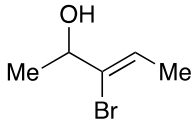
4.0 EXPERIMENTALS

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 repoted relative to residual $CHCl_3$ (7.26 ppm) or D_6-acetone for ^1H NMR and $CDCl_3$ (77.16) for ^{13}C 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 CaH_2. 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).

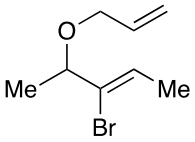


(*Z*)-2-Bromobut-2-enal (76).[41] Freshly distilled crotonaldehyde (5.26 g, 75 mmol) was dissolved in 150 mL of dichloromethane and cooled to 0 ^oC. Neat bromine (12 g, 75 mmol, 1 equiv.) was added dropwise and allowed to stir for 5 min. A 150 mL saturated sodium thiosulfate solution was added to quench 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

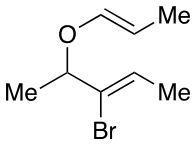
extracts were dried, filtered, and the solvent was removed via rotovap. The residual oil was dissolved in 300 mL of dimethyl sulfoxide and heated to 60 ^{o}C for 2 h. The reaction was cooled 0 ^{o}C and diluted with 300 mL of water. The mixture was then extracted with DCM (5 x 150 mL), and the combined organic layers with washed with brine (300 mL) and water (3 x 150 mL), dried ($MgSO_4$), 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. ^{1}H NMR (300 MHz, $CDCl_3$) 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).[56] 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 ^{o}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 ^{o}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 $MgSO_4$, 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 123.7, 72.6, 22.4, 16.3. Satisfactory mass data could not be obtained for this compound.

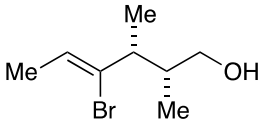


(*Z*)-4-(Allyloxy)-3-bromopent-2-ene (75). A 27.4 mL solution of allyl alcohol **77** (8.04 g, 48.7 mmol, 1.8 M in THF) was added to 27.4 mL of a sodium hydride suspension (2.55 g of 60% in mineral oil, 63.8 mmol, 1.31 equiv., 2.33 M in THF) at 0 ^{o}C. The reaction mixture was allowed to warm to ambient temperature and stir for 20 min, then was cooled back to 0 ^{o}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 $MgSO_4$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.



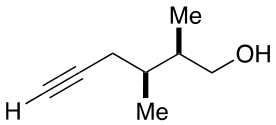
(*Z*)-3-Bromo-4-(((*E*)-prop-1-en-1-yl)oxy)pent-2-ene (92). A mixture of $[IrCl(COE)_2]_2$ (0.203 g, 0.277 mmol, 1.5 mol%), $NaBPh_4$ (0.171 g, 0.500 mmol, 3.3 mol%), and PCy_3 (0.381 g, 1.36 mmol, 9 mol%) was dissolved in 21.6 mL of thoroughly degassed 1,2-DCE and 0.5 mL of degassed acetone and the 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, $CDCl_3$) δ 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, $CDCl_3$) δ 144.2, 130.1, 125.3, 102.4, 79.9, 20.5, 16.3, 12.5; HRMS (*EI*) *m*/*z* calcd for (M^+) $C_8H_{13}OBr$: 204.0150; found: 204.0112.

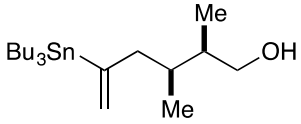


(*Z*)-4-Bromo-(*syn*)-2,3-dimethylhex-4-en-1-ol (74). Allyl vinyl ether **92** (2.83 g, 13.8 mmol) was dissolved in 69 mL of toluene and heated to reflux for 3 h. The reaction mixture was then cooled to 0 ^{o}C. Sodium borohydride (1.05 g, 27.8 mmol, 2.02 equiv.) and methanol (5 mL) were added, and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was cooled to 0 ^{o}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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 135.5, 122.8, 66.5, 45.9, 38.5, 17.3, 16.7, 13.7;

HRMS (*ESI*) *m*/*z* calcd for ([M – OH]$^+$) $C_8H_{14}Br$: 189.02734; found: 189.02664, *m*/*z* calcd for ([M – OH]$^+$) $C_8H_{14}{}^{81}Br$: 191.02529; found: 191.02453, *m*/*z* calcd for ([M – Br]$^+$) $C_8H_{15}O$: 127.11174; found: 127.11137.

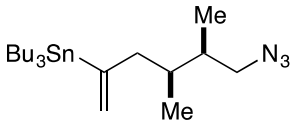


(*syn*)-2,3-Dimethylhex-5-yn-1-ol (59). Sodium hydride (1.20 g, 30.0 mmol, 4.14 equiv.) was added to 11.8 mL of ethylene diamine cooled to 0 ^oC, and the mixture was allowed to warm to ambient temperature and stir for 1 h. The mixture was then heated to 60 ^oC for 1 h, then cooled to 45 ^oC for the dropwise addition vinyl bromide **74** (1.50 g, 7.24 mmol), followed by warming of the reaction mixture back to 60 ^oC for 2 h. The mixture was then slowly cooled to 0 ^oC 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 $MgSO_4$, 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; ^1H 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.5, 69.3, 66.5, 38.7, 33.3, 24.1, 15.0, 11.9; HRMS (*EI*) *m*/*z* calcd for (M^+) $C_8H_{14}O$: 126.1045; found: 126.1069.



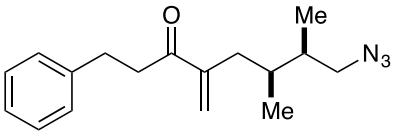
(*syn*)-2,3-Dimethyl-5-(tributylstannyl)hex-5-en-1-ol (97). A 40 mL solution of bis(tributyltin) (19.7 g, 34 mmol, 6.2 equiv., 0.857 M in THF) in THF was cooled to -40 ^oC, and 21.8 mL of *n*-BuLi (33.5 mmol, 6.12 equiv., 1.54 M in hexanes) was added and the solution was stirred for 1 h at -40 ^oC. Copper cyanide (1.51 g, 16.9

mmol, 3.08 equiv) was added and the solution was cooled to -78 ^{o}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 ^{o}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_2SO_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_4H_9]$^{+}$) C16H33OSn: 361.1548; found: 361.2676.



(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 ^{o}C. Diisopropyl azodicarboxylate (0.626 g, 3.10 mmol, 1.5 equiv) was added and the resulting solution was stirred for 20 min. Diphenylphorphoryl 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_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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^+) $C_{20}H_{43}N_3Sn$: 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_2SO_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) δ 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

1. Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Watson-Wright, W. M.; Wright, J. L. C., "Spirolides B and D, Two Novel Macrocycles Isolated from the Digestive Glands of Shellfish," *J. Chem. Soc., Chem. Commun.* **1995**, 2159-2161.

2. Cembella, A. D.; Lewis, N. I.; Quilliam, M. A., "Spirolide Composition of Micro-Extracted Pooled Cells Isolated from Natural Plankton Assemblages and from Cultures of the Dinoflagellate Alexandrium Ostenfeldii," *Nat. Toxins* **1999**, *7*, 197-206.

3. Hu, T.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C., "Characterization of Spirolides a, C, and 13-Desmethyl C, New Marine Toxins Isolated from Toxic Plankton and Contaminated Shellfish," *J. Nat. Prod.* **2001**, *64*, 308-312.

4. Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C., "Characterization of Biologically Inactive Spirolides E and F: Identification of the Spirolide Pharmacophore," *Tetrahedron Lett.* **1996**, *37*, 7671-7674.

5. Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.-z.; Chen, H.-s., "Pinnatoxin A: A Toxic Amphoteric Macrocycle from the Okinawan Bivalve Pinna Muricata," *J. Am. Chem. Soc.* **1995**, *117*, 1155-1156.

6. Takada, N.; Umemura, N.; Suenaga, K.; Uemura, D., "Structural Determination of Pteriatoxins a, B and C, Extremely Potent Toxins from the Bivalve Pteria Penguin," *Tetrahedron Lett.* **2001**, *42*, 3495-3497.

7. Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T., "Gymnodimine, a New Marine Toxin of Unprecedented Structure Isolated from New Zealand Oysters and the Dinoflagellate, Gymnodinium Sp," *Tetrahedron Lett.* **1995**, *36*, 7093-7096.

8. Roach, J. S.; LeBlanc, P.; Lewis, N. I.; Munday, R.; Quilliam, M. A.; MacKinnon, S. L., "Characterization of a Dispiroketal Spirolide Subclass from Alexandrium Ostenfeldii," *J. Nat. Prod.* **2009**, *72*, 1237-1240.

9. Ciminiello, P.; Dell'Aversano, C.; Iacovo, E. D.; Fattorusso, E.; Forino, M.; Grauso, L.; Tartaglione, L.; Guerrini, F.; Pezzolesi, L.; Pistocchi, R., "Characterization of 27-Hydroxy-13-Desmethyl Spirolide C and 27-Oxo-13,19-Didesmethyl Spirolide C. Further Insights into the Complex Adriatic Alexandrium Ostenfeldii Toxin Profile," *Toxicon* **2010**, *56*, 1327-1333.

10. Falk, M.; Burton, I. W.; Hu, T.; Walter, J. A.; Wright, J. L. C., "Assignment of the Relative Stereochemistry of the Spirolides, Macrocyclic Toxins Isolated from Shellfish and from the Cultured Dinoflagellate Alexandrium Ostenfeldii," *Tetrahedron* **2001**, *57*, 8659-8665.

11. Ciminiello, P.; Catalanotti, B.; Dell'Aversano, C.; Fattorusso, C.; Fattorusso, E.; Forino, M.; Grauso, L.; Leo, A.; Tartaglione, L., "Full Relative Stereochemistry Assignment and Conformational Analysis of 13,19-Didesmethyl Spirolide C Via Nmr- and Molecular Modeling-Based Techniques. A Step Towards Understanding Spirolide's Mechanism of Action," *Org. Biomol. Chem.* **2009**, *7*, 3674-3681.

12. Wandscheer, C. B.; Vilariño, N.; Espiña, B. a.; Louzao, M. C.; Botana, L. M., "Human Muscarinic Acetylcholine Receptors Are a Target of the Marine Toxin 13-Desmethyl C Spirolide," *Chem. Res. Toxicol.* **2010**, *23*, 1753-1761.

13. Alonso, E.; Vale, C.; Vieytes, M. R.; Laferla, F. M.; Giménez-Llort, L.; Botana, L. M., "13-Desmethyl Spirolide-C Is Neuroprotective and Reduces Intracellular Aβ and Hyperphosphorylated Tau in Vitro," *Neurochem. Int.* **2011**, *59*, 1056-1065.

14. Stewart, M.; Blunt, J. W.; Munro, M. H.; Robinson, W. T.; Hannah, D. J., "The Absolute Stereochemistry of the New Zealand Shellfish Toxin Gymnodimine," *Tetrahedron Lett.* **1997**, *38*, 4889-4890.

15. McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y., "Total Synthesis of Pinnatoxin A," *J. Am. Chem. Soc.* **1998**, *120*, 7647-7648.

16. Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M., "A Formal Total Synthesis of (+)-Pinnatoxin A," *Angew. Chem., Int. Ed.* **2004**, *43*, 6505-6510.

17. Nakamura, S.; Kikuchi, F.; Hashimoto, S., "Total Synthesis of Pinnatoxin A," *Angew. Chem., Int. Ed.* **2008**, *47*, 7091-7094.

18. Stivala, C. E.; Zakarian, A., "Total Synthesis of (+)-Pinnatoxin A," *J. Am. Chem. Soc.* **2008**, *130*, 3774-3776.

19. Araoz, R.; Servent, D.; Molgó, J.; Iorga, B. I.; Fruchart-Gaillard, C.; Benoit, E.; Gu, Z.; Stivala, C.; Zakarian, A., "Total Synthesis of Pinnatoxins a and G and Revision of the Mode of Action of Pinnatoxin A," *J. Am. Chem. Soc.* **2011**, *133*, 10499-10511.

20. Caprio, V.; Brimble, M. A.; Furkert, D. P., "Synthesis of the Novel 1,7,9-Trioxadispiro[4.1.5.2]-Tetradecane Ring System Present in the Spirolides," *Tetrahedron* **2001**, *57*, 4023-4034.

21. Furkert, D. P.; Brimble, M. A., "Synthesis of the C10−C22 Bis-Spiroacetal Domain of Spirolides B and D Via Iterative Oxidative Radical Cyclization," *Org. Lett.* **2002**, *4*, 3655-3658.

22. Meilert, K.; Brimble, M. A., "Synthesis of the Bis-Spiroacetal Moiety of Spirolides B and D," *Org. Lett.* **2005**, *7*, 3497-3500.

23. Meilert, K.; Brimble, M. A., "Synthesis of the Bis-Spiroacetal Moiety of the Shellfish Toxins Spirolides B and D Using an Iterative Oxidative Radical Cyclization Strategy," *Org. Biomol. Chem.* **2006**, *4*, 2184-2192.

24. Brimble, M. A.; Halim, R., Synthetic Studies toward Shellfish Toxins Containing Spiroacetal Units. In *16th International Conference on Organic Synthesis*, Pure and Applied Chemistry: Merida, Yucatan, Mexico, 2007; Vol. 79, pp 153-162.

25. Ishihara, J.; Ishizaka, T.; Suzuki, T.; Hatakeyama, S., "Enantio- and Stereocontrolled Formation of the Bisspiroacetal Core of Spirolide B," *Tetrahedron Lett.* **2004**, *45*, 7855-7858.

26. Trzoss, M.; Brimble, M. A., "Synthesis of Spirocyclic Imines: Key Pharmacophores in the Shellfish Toxins Spirolides and Gymnodimine," *Synlett* **2003**, *2003*, 2042-2046.

27. Brimble, M. A.; Trzoss, M., "A Double Alkylation—Ring Closing Metathesis Approach to Spiroimines," *Tetrahedron* **2004**, *60*, 5613-5622.

28. Brimble, M. A.; Crimmins, D.; Trzoss, M., "Synthesis of Spirolactams Via Diels-Alder Addition of 1,3-Butadienes to an Alpha-Methylene Lactam," *ARKIVOC* **2005**, *2005*, 39-52.

29. Guéret, S. p. M.; Furkert, D. P.; Brimble, M. A., "Synthesis of a Functionalized 7,6-Bicyclic Spiroimine Ring Fragment of the Spirolides," *Org. Lett.* **2010**, *12*, 5226-5229.

30. Kong, K.; Romo, D., "Diastereoselective, Vinylogous Mukaiyama Aldol Additions of Silyloxy Furans to Cyclic Ketones: Annulation of Butenolides and Γ-Lactones," *Org. Lett.* **2006**, *8*, 2909-2912.

31. Stivala, C. E.; Zakarian, A., "Studies toward the Synthesis of Spirolides: Assembly of the Elaborated E-Ring Fragment," *Organic Lett.* **2009**, *11*, 839-842.

32. Stivala, C. E.; Gu, Z.; Smith, L. L.; Zakarian, A., "Studies toward the Synthesis of Spirolide C: Exploration into the Formation of the 23-Membered All-Carbon Macrocyclic Framework," *Org. Lett.* **2012**, *14*, 804-807.

33. Guo, B. Catalytic Asymmetric Bond Constructions in Complex Molecule Synthesis. An Approach to the Synthesis of Spirolide C and the Development of Enantioselective Enolate Hydroxylation Reactions. University of Pittsburgh, Dietich School of Arts and Sciences, 2012.

34. A. Nugent, W., "Mib: An Advantageous Alternative to Daib for the Addition of Organozinc Reagents to Aldehydes," *Chem. Commun.* **1999**, 1369-1370.

35. Nelson, S. G.; Bungard, C. J.; Wang, K., "Catalyzed Olefin Isomerization Leading to Highly Stereoselective Claisen Rearrangements of Aliphatic Allyl Vinyl Ethers," *J. Am. Chem. Soc.* **2003**, *125*, 13000-13001.

36. Nelson, S. G.; Wang, K., "Asymmetric Claisen Rearrangements Enabled by Catalytic Asymmetric Di(Allyl) Ether Synthesis," *J. Am. Chem. Soc.* **2006**, *128*, 4232-4233.

37. Ngatimin, M.; Gartshore, C. J.; Kindler, J. P.; Naidu, S.; Lupton, D. W., "The A-Halogenation of A,B-Unsaturated Carbonyls and Dihalogenation of Alkenes Using Bisacetoxyiodobenzene/Pyridine Hydrohalides," *Tetrahedron Lett.* **2009**, *50*, 6008-6011.

38. Crombie, L.; Harper, S. H., "346. Stereochemical Studies of Olefinic Compounds. Part Ii. Ring Scission of 2-1[Prime or Minute]-Halogenoalkyltetrahydrofurans and 3-Halogeno-2-Alkyl-Tetrahydropyrans as a Route to Alk-4-En-1-Ols of Known Configuration and as a Method of Chain Extension by Five Methylene Groups," *J. Chem. Soc.* **1950**, 1707-1714.

39. Hill, K. W.; Taunton-Rigby, J.; Carter, J. D.; Kropp, E.; Vagle, K.; Pieken, W.; McGee, D. P. C.; Husar, G. M.; Leuck, M.; Anziano, D. J.; Sebesta, D. P., "Diels−Alder Bioconjugation of Diene-Modified Oligonucleotides," *J. Org. Chem.* **2001**, *66*, 5352-5358.

40. Baldwin, J. E., "Rules for Ring Closure," *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

41. Li, W.; Li, J.; Wan, Z.-K.; Wu, J.; Massefski, W., "Preparation of A-Haloacrylate Derivatives Via Dimethyl Sulfoxide-Mediated Selective Dehydrohalogenation," *Org. Lett.* **2007**, *9*, 4607-4610.

42. Besteiro, J. C.; Lahuerta, P.; Sanatú, M.; Solana, I.; Cotton, F. A.; Llusar, R.; Schwotzer, W., "C—Br Insertion Reactions in Rhodium and Iridium Compounds Containing an Ortho-Halo-Arylphosphine. X-Ray Structures of Two Ortho-Metallated Compounds of Formula Irx2[P(C6f4)Ph2][P(O-Brc6f4)Ph2], (X = Cl, Br)," *Polyhedron* **1988**, *7*, 87-96.

43. Lespieau, R.; Bourguel, M., "3-Cyclohexylpropine," *Org. Synth.* **1926**, *6*, 26-27.

44. Grattan, T. J.; Whitehurst, J. S., "Chiral 2,2-Disubstituted Cyclohexanones; Annulation Via Claisen Rearrangement Products," *J. Chem. Soc., Perkin Trans. 1* **1990**, 11-18.

45. Sui, B.; Yeh, E. A. H.; Curran, D. P., "Assignment of the Structure of Petrocortyne a by Mixture Syntheses of Four Candidate Stereoisomers," *J. Org. Chem.* **2010**, *75*, 2942-2954.

46. Matsubara, S.; Hibino, J.-I.; Morizawa, Y.; Oshima, K.; Nozaki, H., "Regio- and Stereo-Selective Synthesis of Vinylstannanes. Transition-Metal Catalyzed Stannylmetalation of Acetylenes and Conversion of Enol Triflates and Vinyl Iodides into Vinylstannanes," *J. Organomet. Chem.* **1985**, *285*, 163-172.

47. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K., "Diphenylphosphoryl Azide a Novel Reagent for the Stereospecific Synthesis of Azides from Alcohols," *Tetrahedron Lett.* **1977**, *18*, 1977-1980.

48. Pelc, M. J.; Zakarian, A., "An Approach to the Imine Ring System of Pinnatoxins," *Org. Lett.* **2005**, *7*, 1629-1631.

49. Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A., "Effect of Counterion Structure on Rates and Diastereoselectivities in A,B-Unsaturated Iminium-Ion Diels–Alder Reactions," *Org. Lett.* **2011**, *13*, 3758-3761.

50. Rauhut, M. M.; Currier, H. Preparation of Dialkyl 2-Methylene Glutarates. 3074999, 1963.

51. Aroyan, C. E.; Dermenci, A.; Miller, S. J., "The Rauhut–Currier Reaction: A History and Its Synthetic Application," *Tetrahedron* **2009**, *65*, 4069-4084.

52. Okutani, M.; Mori, Y., "Conversion of Bromoalkenes into Alkynes by Wet Tetra-*N*-Butylammonium Fluoride," *J. Org. Chem.* **2008**, *74*, 442-444.

53. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., "Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis," *Angew. Chem., Int. Ed.* **2005**, *44*, 4442-4489.

54. Normant, H., "Recherches Sur Les Magnesiens Vinyliques," *Compt. Rend.* **1955**, *240*, 1435-1437.

55. Sliwinska, A.; Zwierzak, A., "An Expedient Transformation of Alcohols into *N*-Boc-Amines," *Pol. J. Chem.* **2004**, *78*, 2127-2130.

56. Pasto, D. J.; Sugi, K. D., "On the Maximum Rotation and the Solvobromination and -Mercuration of Enantioenriched 1,3-Dimethylallene," *J. Org. Chem.* **1991**, *56*, 4157-4160.