Progress Towards the Total Synthesis of 3α-Hydroxy-15-Rippertene

by

Adam J Rosenberg

B.S. Chemistry, University of Rochester, 2006

Submitted to the Graduate Faculty of
Arts & Sciences in partial fulfillment
of the requirements for the degree of

Master of Science

University of Pittsburgh

2009
This thesis was presented

by

Adam J Rosenberg

It was defended on
May 26th, 2009

and approved by
Professor Dennis P. Curran
Professor Paul E. Floreancig

Thesis Advisor: Professor Kay M. Brummond
The Rh(I)-catalyzed allenic cyclocarbonylation reaction is a formal [2 + 2 + 1] cyclocarbonylation process that has been used to gain access to 4-alkylidene cyclopentenones. Inclusion of a six-membered ring on the tether between the allene and the alkyne components allows access to a variety of [6-7-5] ring structures found in the core-skeletons of natural products such as rippertene. This thesis describes a synthetic approach to the carbocyclic skeleton of 3α-hydroxy-15-rippertene, utilizing the Rh(I)-catalyzed allenic cyclocarbonylation reaction. Starting from 2-butyne-1-ol the [6-7-5] carbocyclic core of rippertene was synthesized in 1.9% over 10 steps.
# TABLE OF CONTENTS

LIST OF TABLES.................................................................................................................................... VII
LIST OF FIGURES ................................................................................................................................... VIII
LIST OF SCHEMES ................................................................................................................................ IX
ABBREVIATIONS.................................................................................................................................... XI

1.0 INTRODUCTION.................................................................................................................................. 1
  1.1 TRANSITION-METAL CATALYZED CYCLOCARBONYLATION REACTIONS TO PREPARE CYCLOPENTENOINES .................................................................................................................. 1
  1.2 CYCLOCARBONYLATION OF ALLENE-YNES............................................................................. 2
  1.3 3α-HYDROXY-15-RIPPETENE ................................................................................................. 6
    1.3.1 Isolation, Characterization & Biological Activity of 3α-Hydroxy-15-Rippertene and Structurally Related Compounds ................................................................. 6
    1.3.2 Previous Synthetic Explorations of Rippertene and Analogs................................. 8

2.0 RESULTS AND DISCUSSION ........................................................................................................... 13
  2.1 AN ALLENIC CYCLOCARBONYLATION APPROACH TO RIPPETENE: A RETROSYNTHETIC ANALYSIS .................................................................................................................... 13
  2.2 PRELIMINARY RESULTS AND FEASIBILITY STUDIES REPORTED BY CHEN/BRUMMOND ................................................................................................................................. 14
  2.3 GENERATION OF ALLENYL IODIDE 58 ............................................................................. 15
2.4 INSTALLATION OF THE ALLENE COMPONENT VIA AN ALKYLLATION OF ALLENYL IODIDE 58 WITH BETA-KETOESTER 57 .......... 16
2.5 INSTALLATION OF THE ALKYNE COMPONENT: A CROSS-COUPLING STRATEGY ................................................................. 20
2.6 INSTALLATION OF THE ALKYNE: AN ORGANOMETALLIC ADDITION TO THE KETONE ................................................................. 27
2.7 SYNTHESIS OF CYCLOCARBONYLATION PRECURSOR 55: SAPONIFICATION AND DEHYDRATIVE DECARBOXYLATION ....................... 28
2.8 RHODIUM CATALYZED CYCLOCARBONYLATION .................................................. 32
2.9 ATTEMPTS AT HYDROGENATION ........................................................................ 36
3.0 CONCLUSIONS ................................................................................................... 38
4.0 EXPERIMENTAL .................................................................................................. 39
5.0 BIBLIOGRAPHY ................................................................................................. 51
6.0 SPECTRA ........................................................................................................... 55
LIST OF TABLES

Table 2.1: Preliminary Results ........................................................................................................ 15
Table 2.2: Tentative $^1$H NMR Assignments for Compound 75 .................................................. 25
Table 2.3: Tentative $^{13}$C Assignments for Compound 75 ......................................................... 26
Table 2.4: $^1$H NMR Assignments for Cyclocarbonylation Product 54 ........................................ 34
Table 2.5: $^{13}$C NMR Assignments for Cyclocarbonylation Product 54 ....................................... 35
Table 2.6: Hydrogenation Results ................................................................................................. 37
LIST OF FIGURES

Figure 1.1 Rippertene Structures .................................................................................................... 7
Figure 2.1: Dianion Conformations .............................................................................................. 17
Figure 2.2: 65a (MM3 Modeling) ................................................................................................. 18
Figure 2.3: 65b (MM3 Modeling) ................................................................................................. 19
Figure 2.4: Expansion of $^1$H NMR Showing the Methyl Doublets of 56 ............................ 20
Figure 2.5: CF$_3$ Quartet in the $^{13}$C NMR Spectrum of 70 ..................................................... 21
Figure 2.6: β-Lactone 78 ............................................................................................................. 28
Figure 2.7: Carbocycle 55 ............................................................................................................. 31
Figure 2.8: Cyclopentenone 54, Least Energy Conformer (MM3) ............................................. 33
LIST OF SCHEMES

Scheme 1.1: The Pauson-Khand Reaction ................................................................. 1
Scheme 1.2: Modes of Reactivity for the Cyclocarbonylation of Allene-ynes ........... 2
Scheme 1.3: Cyclocarbonylation of Allene-yne 4 towards the formation of HMAF .... 3
Scheme 1.4: Regioselectivity via Reagent Control ..................................................... 3
Scheme 1.5: Formation of [7-5] Bicycles using Co$_2$(CO)$_8$ ...................................... 4
Scheme 1.6: Rh(I)-Catalyzed Cyclocarbonylation of Allene-ynes ............................. 4
Scheme 1.7: Cyclocarbonylation in the Synthesis of Guanacastepene A .................... 5
Scheme 1.8: Formation of Alternate [6-7-5] Ring Systems ...................................... 6
Scheme 1.9: Proposed Biosynthetic Pathway ............................................................. 7
Scheme 1.10: Metz's First Generation Approach$^{24}$ ................................................. 9
Scheme 1.11: Second Generation Approach $^{26}$ ....................................................... 10
Scheme 1.12: Proposed Completion ......................................................................... 11
Scheme 1.13: Synthesis of 4-desmethyl-3α-hydroxy-15-rippertene$^{25}$ ..................... 12
Scheme 2.1: Retrosynthetic Analysis of Rippertene .................................................. 14
Scheme 2.2: Preparation of Allenyl Iodide 58 ........................................................... 16
Scheme 2.3: Dianion Alkylation ................................................................................. 17
Scheme 2.4: Cross-Coupling Disconnection ............................................................. 20
Scheme 2.5: Buchwald's Silane to Stannane Conversion .......................................... 22
Scheme 2.6: Model System ........................................................................................................... 22
Scheme 2.7: Potential Mechanisms .............................................................................................. 24
Scheme 2.9: Formation of Alcohol 77 .......................................................................................... 28
Scheme 2.10: Saponification and Elimination .............................................................................. 29
Scheme 2.11: Decarboxylation Mechanism ................................................................................. 31
Scheme 2.12: Cyclocarbonylation ............................................................................................... 32
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH</td>
<td>Acetic Acid</td>
</tr>
<tr>
<td>BQ</td>
<td>1,4-Benzoquinone</td>
</tr>
<tr>
<td>COD</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>DIBAl-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMA</td>
<td>$N,N$-Dimethylacetamide</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium Aluminum Hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium Hexamethyldisilazide</td>
</tr>
<tr>
<td>MsCl</td>
<td>Methanesulfonyl Chloride</td>
</tr>
<tr>
<td>NMO</td>
<td>$N$-Methylmorpholine-$N$-Oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Rochelle’s Salt</td>
<td>Sodium Potassium Tartrate</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Tf$_2$O</td>
<td>Trifluoromethanesulfonic Anhydride</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluoromethanesulfonic Acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>Toluene</td>
</tr>
<tr>
<td>TsCl</td>
<td>$p$-Toluenesulfonyl Chloride</td>
</tr>
<tr>
<td>TsOH</td>
<td>$p$-Toluenesulfonic Acid</td>
</tr>
</tbody>
</table>
1.0 INTRODUCTION

1.1 TRANSITION-METAL CATALYZED CYCLOCARBONYLATION REACTIONS TO PREPARE CYCLOPENTENONES

The Pauson-Khand reaction, a [2+2+1] cyclocarbonylation, was first reported in 1971 by I.U. Khand. The reaction between an alkyne, olefin, and carbon monoxide to form a cyclopentenone can be carried out in either an intra- or inter-molecular fashion. (Scheme 1.1) Subsequently the Pauson-Khand reaction, as well as closely related cyclocarbonylation reactions, have been widely used for the formation of cyclopentenones in total synthesis. The originally discovered reaction is mediated by Co$_2$(CO)$_8$; however, the reaction is stoichiometric in dicobalt-octacarbonyl and is therefore problematic on larger scales as well as in waste-disposal due to the large amount of the reduced metal.

![Scheme 1.1: The Pauson-Khand Reaction](image)
There have been numerous modifications of the Pauson-Khand reaction over the intervening years. The modification that has had the greatest impact, is the development of reaction conditions where the transition-metal is used catalytically.

1.2 CYCLOCARBONYLATION OF ALLENE-YNES

Replacement of the olefin present in the standard Pauson-Khand reaction with an allene provides for the construction of cyclopentenones that possess a higher degree of molecular complexity. This allene-yne starting material possesses two distinct modes of reactivity, either with the proximal or distal double bonds present in the allene. Reaction with the distal double bond of allene-yne 1 provides 4-alkylidene cyclopentenone 2 (Scheme 1.2, pathway a), while reaction with the proximal double bond provides α-methylene cyclopentenone 3 (Scheme 1.2, pathway b).

![Scheme 1.2: Modes of Reactivity for the Cyclocarbonylation of Allene-ynes](image)

Brummond and co-workers were the first to report cyclocarbonylation of allene-ynes using Mo(CO)$_6$ to prepare α-methylene cyclopentenones. This protocol can be applied to produce bicyclo[3.3.0] and bicyclo[4.3.0] ring systems, depending upon the length of the linker in the starting material. However, when the allene is additionally substituted on the proximal
double bond, the selectivity is reversed (b to a), yielding exclusively the 4-alkylidene cyclopentenone product. This methodology was utilized as a key step in the synthesis of the natural product hydroxymethylacylfulvene (HMAF). (Scheme 1.3)²,¹⁴

Scheme 1.3: Cyclocarbonylation of Allene-yne 4 towards the formation of HMAF

Subsequently, it was discovered that modification of the reaction conditions could produce a change in the selectivity that was not substrate, but reagent dependent.¹⁵,¹⁶ Using Rh(I)-catalyzed conditions developed by Narasaka,¹⁷ Brummond and co-workers achieved selective reaction with the distal double bond present in allene-yne 6, yielding exclusively the 4-alkylidene cyclopentenone 7.¹⁶ (Scheme 1.4)

Scheme 1.4: Regioselectivity via Reagent Control

One of the greatest advantages of the incorporation of an allene in the [2+2+1] cyclocarbonylation reaction is that it allows the formation of seven-membered rings. This development vastly increases the utility of the reaction as seven-membered rings are present in a great deal of natural products that are of biological interest. In 1997 Cazes and co-workers
developed cobalt catalyzed conditions that produced a [7-5] bicycle; however, the reaction, while successful in producing the seven-membered ring, gave either a poor yield of 11a or low selectivity of 12a vs. 12b.\(^\text{18}\) (Scheme 1.5)

\[
\begin{align*}
\text{Me}_2C & \quad \text{R}_1 \quad \text{Me}_2C \\
\text{Me}_2C & \quad \text{R}_2 \quad \text{Me}_2C \\
\text{9} & \quad \text{Co}_2(\text{CO})_8, \text{NMO} \\
\text{CH}_2\text{Cl}_2, -78{^\circ}\text{C} \text{to } \text{rt} & \quad \text{Me}_2C \\
\text{Me}_2C & \quad \text{R}_1 \quad \text{Me}_2C \\
& \quad \text{R}_2 \quad \text{Me}_2C \\
\text{11/12a} & \quad \text{Me}_2C \\
\text{11/12b} & \quad \text{Me}_2C \\
\text{9} & \quad \text{R}_1 = \text{Me}, \text{R}_2 = \text{H} \quad 10\% \quad 100:0 (11a:11b) \\
\text{10} & \quad \text{R}_1 = \text{H}, \text{R}_2 = \text{Me} \quad 50\% \quad 45:55 (12a:12b)
\end{align*}
\]

Scheme 1.5: Formation of [7-5] Bicycles using Co\(_2\)(CO)\(_8\)

In their development of the Rh(I)-catalyzed cyclocarbonylation reaction, Brummond and co-workers demonstrated that [7-5] ring systems could be accessed under Rh(I) conditions.\(^\text{16}\) (Scheme 1.6) This method allows for the selective formation of the [7-5] ring system without any steric or other substrate control.

\[
\begin{align*}
\text{EtO}_2C & \quad \text{Pr} \\
\text{EtO}_2C & \quad \text{Pr} \\
\text{13} & \quad 5 \text{mol}\% \quad [\text{Rh(CO)}_2\text{Cl}]_2 \\
\text{1 atm CO, toluene} & \quad 77\% \\
\text{14} & \quad \text{EtO}_2C \\
\end{align*}
\]

Scheme 1.6: Rh(I)-Catalyzed Cyclocarbonylation of Allene-ynes

This cyclocarbonylation reaction to form [7-5] ring systems was later utilized as a key step in the synthesis of the core of guanacastepene A.\(^\text{19}\) (Scheme 1.7)
The Rh(I)-catalyzed cyclocarbonylation has also been applied to make allene-yne scaffolds in the pursuit of [6-7-5] tricyclic natural products. Modification of the placement of the allene and alkyne on the six-membered ring can yield a variety of [6-7-5] ring systems. For example, reaction of allene-yne 17 affords the linear [6-7-5] tricyclic ring system 18, which contains the basic skeleton of grayanotoxin III. Reaction of allene-yne 19 affords the angular tricycle 20, which can be used to quickly generate the core of resiniferatoxin. Particularly inspiring, is the rapid access to the carbocyclic core of rippertene from reaction of allene-yne 21 to give angular [6-7-5] ring system 22. This transformation establishes the [6-7-5] core as well as introduces synthetic handles for further functionalization.
Scheme 1.8: Formation of Alternate [6-7-5] Ring Systems

1.3 3A-HYDROXY-15-RIPPERTENE

1.3.1 Isolation, Characterization & Biological Activity of 3α-Hydroxy-15-Rippertene and Structurally Related Compounds

The defense secretions of termite soldiers contain terpene-derived natural products with interesting molecular architecture. In 1980 Prestwich and co-workers isolated several structurally
unique tri- and tetracyclic diterpenes from *Nasutitermes rippertii* and *N. ephratae*.\textsuperscript{21} 3α-Hydroxy-15-rippertene, originally assigned as structure (24)\textsuperscript{22, 23} was later identified as 23, (Figure 1.1) determined from an x-ray crystal structure of functionalized derivative 25.\textsuperscript{21}

![Figure 1.1 Rippertene Structures](image)

Biosynthetically the rippertene skeleton may arise via a 1,2-methyl migration from a tetracyclic intermediate such as 26, in turn derived from proton-induced intramolecular cyclization of a tricycle such as 25. (Scheme 1.9) Modeling studies show that unfavorable steric interactions resulting from the two boat-like fused six-membered rings and the axial C(10)-C(11) bond are alleviated by this migration and by the subsequent flattening of the convex dome cap by proton loss to the tetrasubstituted olefin.\textsuperscript{21} Attempts to investigate the biosynthesis via feeding the termites \textsuperscript{14}C-impregnated wood did not provide labeled rippertene.

![Scheme 1.9 Proposed Biosynthetic Pathway](image)
1.3.2 Previous Synthetic Explorations of Rippertene and Analogs.

To date, there has not been a successful total synthesis of 3α-hydroxy-15-rippertene; however, Metz and coworkers have published three explorative syntheses.24-26 The first generation approach was published in 1993, and demonstrated the synthesis of the rippertene core.24 (Scheme 1.10) Starting with commercially available (-)α-santonin 27 as the chiral source, he quickly established the B and C rings though a photolytic transformation of 27 to give 28. Elimination of the acetate and reductive ring opening of lactone 29 provided unsaturated acid 30. The acid was then elaborated to ring-closure precursor aldehyde 31. The A ring was closed through a stereoselective vinylogous aldol under basic conditions to provided tricyclic alcohol 32. To set the key C7 stereocenter as well as form the second olefin required for the upcoming [4+2] cycloaddition, alcohol 32 was mesylated and then subjected to heating with lithium bromide in DMF to provide an isomeric mixture of dienones. Rhodium-catalyzed isomerization of the crude mixture enhanced the desired ratio from 82:18 to 93:7. Concomitant with the elimination of the mesylate, the hydrogen present at C7 epimerized to the desired (S) configuration. Stereoselective reduction of the ketone and subsequent O-alkylation with propargyl bromide provided alkyne 34, setting the stage for the key intramolecular [4+2] cycloaddition. Following the methodology of Kanematsu27, 28 the alkyne was isomerized in situ to allene 35 and under the reaction conditions then cyclized to generate tetracyclic enol ether 36. This product contains the entire core ring structure of 23; however, it lacks the methyl substitution at C1.
Scheme 1.10: Metz's First Generation Approach

The second generation approach of 23 proceeded through an alternate disconnection strategy. Metz proposed a domino Heck cyclization of enol-triflate 44 to generate the A and D rings. To generate Heck-precursor 44, the synthesis proceeded from (-)-isopulegol 38. The B ring
was generated through a regioselective ring-expansion of ketone 39 using TMS-diazomethane to provide substituted-cycloheptanone 40. (Scheme 1.11) Further elaboration through a Saegusa-Ito oxidation, conjugate addition, deprotection, and an aldol condensation provided 43a. Following these transformations, the synthetic plan calls for a diastereoselective conjugate addition and enol-triflate formation to obtain the precursor for the domino-Heck cyclization, triflate 44. (Scheme 1.12) Studies toward completion of the synthesis according to this strategy are reported to be in progress.

Scheme 1.11: Second Generation Approach 26
The most recent synthetic approach was pressed to completion as a close analog of 3α-hydroxy-15-rippertene (23), 4-desmethyl-3α-hydroxy-15-rippertene (51). The synthetic strategy had a similar end-game as the previous attempts, but the core synthesis was based upon an aldol strategy. Cyclohexanone 39 was elaborated to diketone 46, condensed and alkylation to provide bicycle 47. Wacker oxidation followed by a second aldol reaction to close the C ring provided the core [6-7-5] ring structure present in 48. Diastereoselective reduction and O-alkylation provided the cycloaddition precursor 49. In situ isomerization followed by a [4+2] cycloaddition under basic microwave conditions formed the D ring in 83% yield. This was then elaborated to the desmethyl natural product 51 through a series of oxidation/reduction steps. The synthesis was 19 steps with an overall yield of 1.6% along the shortest linear sequence starting from cyclohexanone 39. However, this is not a commercially available compound and is synthesized from (-)-isopulegol in 77% over a four-step sequence.
Scheme 1.13: Synthesis of 4-desmethyl-3α-hydroxy-15-rippertene\textsuperscript{25}
2.0 RESULTS AND DISCUSSION

2.1 AN ALLENIC CYCLOCARBONYLATION APPROACH TO RIPPERTENE: A RETROSYNTHETIC ANALYSIS

We envision a total synthesis of 3α-hydroxy-15-rippertene (23) using a Rh(I)-catalyzed allenic cyclocarbonylation reaction of allene-yne 55 to give [6-7-5] tricycle 54. (Scheme 2.1) Cyclocarbonylation affords the B and C rings of the rippertene core and places the ketone and olefins in strategic locations for the further introduction of functionality and stereochemistry. Ketone 54 can be elaborated to the desired natural product 23 through a [4+2] intramolecular cycloaddition of the distal double bond of an allene tethered to the core structure with a diene component. The resulting enol-ether can be transformed to the natural product through a series of oxidation/reduction functional group manipulations, as has been demonstrated by Metz on a closely related compound.24, 25 We envision generating the allene-yne cyclocarbonylation precursor 55 from β-ketoester 56, which in turn can be constructed through a diastereoselective dianion alkylation from methyl 4-methyl-2-oxocyclohexanecarboxylate (57) and 5-iodo-3-methylpenta-1,2-diene (58). This strategy would provide tricycle 54 in a rapid and concise manner, and allow for straightforward derivatization. While it uses a similar end-game strategy to Metz,25 it reaches the convergent point with fewer chemical transformations.
2.2  PRELIMINARY RESULTS AND FEASIBILITY STUDIES REPORTED BY CHEN/BRUMMOND

Studies directed at exploring the scope of the Rh(I)-catalyzed cyclocarbonylation of allene-ynes, have shown that the angular structure present in rippertene can be generated in a model system. Preliminary results show that the cyclocarbonylation of 60a (R1=R2=H) gives 61a in 85% yield in 100 min. (Table 2.1) Cyclocarbonylation of 60b (R1=H, R2=Me) and 60c (R1=Me, R2=H) afford the more substituted dienones 61b and 61c in lower yields of 67% and 56%, respectively. Finally, reaction of 60d (R1=R2=Me) with [Rh(CO)2Cl]2 affords 61d in 58% yield in 20 h. The extended reaction time for this reaction is attributed to the developing A(1,3) strain between R1 and R2. This ring strain also hinders rotation along the C15-C16 bond leading to potential atropisomers (not observed), further increasing the stereo-complexity of the
molecule. Although this stereo-complexity was not explored, it may prove an interesting point for further explorations of this molecular architecture.

Table 2.1: Preliminary Results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R¹</th>
<th>R²</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60a</td>
<td>H</td>
<td>H</td>
<td>100 min</td>
<td>85</td>
<td>61a</td>
</tr>
<tr>
<td>2</td>
<td>60b</td>
<td>H</td>
<td>Me</td>
<td>130 min</td>
<td>67</td>
<td>61b</td>
</tr>
<tr>
<td>3</td>
<td>60c</td>
<td>Me</td>
<td>H</td>
<td>70 min</td>
<td>56</td>
<td>61c</td>
</tr>
<tr>
<td>4</td>
<td>60d</td>
<td>Me</td>
<td>Me</td>
<td>20 h</td>
<td>58</td>
<td>61d</td>
</tr>
</tbody>
</table>

These preliminary results demonstrate that the rhodium(I)-catalyzed cyclocarbonylation reaction is amenable to generating the A, B, and C rings of rippertene.

2.3 GENERATION OF ALLENYL IODIDE 58

Allenyl Iodide 58 was prepared using a 4-step reaction sequence following a procedure analogous to that reported previously.20 (Scheme 2.2) 2-Butyne-1-ol was subjected to an acid
catalyzed Johnson-Claisen rearrangement to give ester 63, which was immediately reduced to alcohol 64 with LiAlH₄ in 85% yield. Alcohol 64 was then converted to the mesylate and subjected to Finkelstein reaction conditions to give allenyl iodide 58 in 38% yield over two steps. Attempts were made to effect a more direct conversion of alcohol 64 to iodide 58 using PPh₃ / I₂ conditions, however, removal of the triphenylphosphine oxide proved problematic.

\[
\begin{align*}
\text{Scheme 2.2: Preparation of Allenyl Iodide 58}
\end{align*}
\]

### 2.4 INSTALLATION OF THE ALLENE COMPONENT VIA AN ALKYLATION OF ALLENYL IODIDE 58 WITH BETA-KETOESTER 57

To install the allene side chain in a regio and stereo-selective manner we choose to utilize the methodology of Weiler and co-workers. This methodology has been previously utilized by Corey in a stereoselective manner in his synthesis of Desogestrel. Deprotonation of β-ketoester 57 with 2.1 equiv of LDA gives a dianion. Alkylation with iodide 58 gives allene 56 in 64% yield. (Scheme 2.3)
Determining the diastereoselectivity for this reaction is difficult due to the keto/enol tautomerization. However, later in the synthetic sequence this problem is resolved due to the removal of all other stereogenic centers. While the cis-diastereomer is represented, it was not definitively confirmed. It is predicted that the cis-diastereomer will be obtained for stereo-electronic reasons. As seen in figure 2.1, there are two predominant configurations the dianion may adopt. Both configurations contain a six-membered ring through coordination between the lithium and oxyanions, thereby stabilizing the intermediate. It is known that enolate alkylations have an early transition state, and therefore the diastereoselectivity depends on the relative populations of the enolate configurations. If the electrophile approaches from a pseudo-axial position, 65a would generate the cis product, and 65b would generate the trans product. Since an equatorial approach would necessitate a boat or twist-boat transition state, and thereby disrupt the coordination of the oxygens and lithium, it was theorized that the equatorial approach would have a minimal impact on the stereochemical result.
When comparing \textbf{65a} to \textbf{65b}, the most important difference is the conformation of the methyl group; in \textbf{65a} the methyl group is equatorial, while in \textbf{65b} it is axial. This difference would normally result in a 1.8 kcal/mol energy difference in a methyl-substituted cyclohexane in the ground state,\textsuperscript{34} while in the case of \textbf{65} the energy difference will be modified. A 1.8 kcal/mol energy difference would result in a 21:1 ratio of diasteromeric products; however, the experimental ratio (determined in section 2.7) is 19:1 (an energy difference of 1.74 kcal/mol). This disparity can be explained by the fact that only one proton, H\textsubscript{a}, is present to interfere with the ideal conformation as well as the constrained nature of the ring. Therefore, alkylation product \textbf{65} is conditionally assigned as cis.

![Figure 2.2: 65a (MM3 Modeling)](image_url)
In the $^1$H NMR spectrum of 56, there are three methyl doublets present. (Figure 2.4) These doublets represent the keto-enol tautomerization of 56. The major tautomer in solution is the enol tautomer, identified by the resonance at 12.27 ppm which is indicative of an enol proton. This corresponds to the resonance at 0.94 ppm with an integration of 2.26. The other two doublets can result from the two epimers of the methyl ester in the keto form, which would provide two diastereomers. The ratio of the enol tautomer to the keto tautomer was roughly 3:2 based upon the ratio of methyl resonances.
2.5 INSTALLATION OF THE ALKYNE COMPONENT: A CROSS-COUPLING STRATEGY

Scheme 2.4: Cross-Coupling Disconnection
Two different strategies were considered for the introduction of the alkyne component into the cyclocarbonylation precursor. The first involves the enol tautomer of 56, its conversion into the corresponding enol triflate 67 and subsequent cross-coupling with an alkynyl component to give ene-yne 66. (Scheme 2.4) The second strategy involves the direct addition of an acetylide anion to the ketone and then a dehydrative decarboxylation to afford 55.

Because neither of these approaches is well-precedented, the feasibility of a cross-coupling route to allene-yne 55 was investigated through a model system. Vinyl triflate 70 was produced from β-keto ester 57 using triflic anhydride and sodium hydride and taken on crude to the cross-coupling. Formation of the triflate was confirmed through $^{13}$C NMR analysis, where the quartet resulting from the CF$_3$ ($\delta=118.3$ ppm) was clearly present with a $J_{CF} = 320$ Hz coupling constant. (Figure 2.5)

With triflate 70 in hand, a number of coupling protocols were tested including Kumada conditions and the silver-mediated direct coupling of TMS-protected alkynes.$^{36}$ The Stille coupling proved to be the optimal way to synthesize the ene-yne, giving 71 in 74% yield over 2
steps. (Scheme 2.6) However, the procurement of the required stannane proved interesting. In 1994 Buchwald and co-workers developed a catalytic method of converting silanes to stannanes, which allowed production of stannane 69 in a straightforward manner.\(^{37}\) (Scheme 2.5)

![Scheme 2.5: Buchwald's Silane to Stannane Conversion](image)

Following cross-coupling, reduction of the ester was effected with DIBAl-H in 97% yield to give alcohol 72. Deoxygenation was planned via tosylation of the alcohol, followed by \(S_N2\) displacement with either DIBAl-H\(^{38}\) or NaBH\(_4\).\(^{39, 40}\) (Scheme 2.6)

![Scheme 2.6: Model System](image)

Once the cross-coupling was successfully carried out on the model system, work began on the system with the appendant allene. \(\beta\)-Ketoester 56 was converted to the corresponding vinyl triflate using \(N\)-phenyl-bis(trifluoromethanesulfonylimide) and sodium hydride to give the
expected vinyl triflate. The formation of the triflate was confirmed by $^{13}$C NMR, which showed a quartet at 118.3 ppm with a coupling constant of $J_{CF} = 320$ Hz.

Enol triflate 67 was then subjected to the cross-coupling conditions developed for the model system. Unfortunately, instead of the cross-coupling to give the desired ene-yne (Scheme 2.7, Cycle A) an intramolecular carboxylation of the allene occurred, giving bicycle 75 in 47% yield. (Scheme 2.7, Cycle B) The structure of 75 was tentatively assigned through the presence of vinyl protons (δ= 5.65, 4.96, 4.91) and supported by the appearance of new olefinic carbon resonances at the appropriate resonances. (Tables 2.2 & 2.3)
Scheme 2.7: Potential Mechanisms
<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity, Coupling Constant (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H_a</td>
<td>2.25-1.88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>m</td>
</tr>
<tr>
<td>H_b</td>
<td>1.78-1.63&lt;sup&gt;b&lt;/sup&gt;</td>
<td>m</td>
</tr>
<tr>
<td>H_c</td>
<td>1.78-1.63&lt;sup&gt;b&lt;/sup&gt;</td>
<td>m</td>
</tr>
<tr>
<td>H_d</td>
<td>1.01</td>
<td>d, 6.3</td>
</tr>
<tr>
<td>H_e</td>
<td>2.25-1.88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>m</td>
</tr>
<tr>
<td>H_f</td>
<td>2.25-1.88&lt;sup&gt;a&lt;/sup&gt;</td>
<td>m</td>
</tr>
<tr>
<td>H_g</td>
<td>5.66</td>
<td>d, 4.5</td>
</tr>
<tr>
<td>H_h</td>
<td>1.84-1.82</td>
<td>m</td>
</tr>
<tr>
<td>H_i</td>
<td>4.91</td>
<td>s</td>
</tr>
<tr>
<td>H_j</td>
<td>4.96</td>
<td>s</td>
</tr>
<tr>
<td>OMe</td>
<td>3.63</td>
<td>s</td>
</tr>
</tbody>
</table>

<sup>a</sup> These assignments may be interchangeable, <sup>b</sup> These assignments may be interchangeable

Table 2.2: Tentative <sup>1</sup>H NMR Assignments for Compound 75
<table>
<thead>
<tr>
<th>Carbon</th>
<th>Chemical Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126.8</td>
</tr>
<tr>
<td>2</td>
<td>27.8</td>
</tr>
<tr>
<td>3</td>
<td>29.8</td>
</tr>
<tr>
<td>4</td>
<td>35.9</td>
</tr>
<tr>
<td>5</td>
<td>43.9</td>
</tr>
<tr>
<td>6</td>
<td>145.5</td>
</tr>
<tr>
<td>7</td>
<td>143.6</td>
</tr>
<tr>
<td>8</td>
<td>133.0</td>
</tr>
<tr>
<td>9</td>
<td>127.1</td>
</tr>
<tr>
<td>10</td>
<td>34.3</td>
</tr>
<tr>
<td>11</td>
<td>19.8</td>
</tr>
<tr>
<td>12</td>
<td>20.5</td>
</tr>
<tr>
<td>13</td>
<td>110.7</td>
</tr>
<tr>
<td>14</td>
<td>173.0</td>
</tr>
<tr>
<td>15</td>
<td>52.3</td>
</tr>
</tbody>
</table>

Table 2.3: Tentative $^{13}$C Assignments for Compound 75
This type of allenic carbopalladation has been observed previously by Negishi and co-workers to form medium to large rings.\textsuperscript{42, 43} In 1990 Negishi and co-workers encountered a similar problem with intra vs. intermolecular coupling.\textsuperscript{44} In his attempts at performing a tandem carbopalladation and subsequent cross-coupling. They noted that when organozincs were used in the Pd-catalyzed reaction, they underwent the transmetallation step much faster than those containing Al, B, Cu, Sn and Zr. When they substituted the Zn for Sn, they were able to affect the carbopalladation step prior to the cross-coupling. We sought to take advantage of this effect in reverse, by substituting the Sn for Zn. However, when enol triflate 67 was subjected to Pd-catalyzed cross-coupling using the organozinc propyne, no cross-coupling product was detected via NMR.

2.6 INSTALLATION OF THE ALKYNE: AN ORGANOMETALLIC ADDITION TO THE KETONE

The secondary strategy explored to install the alkyne functionality, was a 1,2 addition of the acetylide to the ketone of β-ketoester \textsuperscript{56}. Standard Grignard and organolithium additions of propyne failed to produce the desired reactivity, and more involved methods such as the organocerium were also unsuccessful.\textsuperscript{45} This was most likely due to the poor electrophilicy of the desired ketone, due to its predominate enol tautomer, and the basicity of the organometallic reagents. β-Ketoester \textsuperscript{56} was α-methylated using cesium carbonate and methyl iodide to give ketone \textsuperscript{76} in 85% yield; thus eliminating the keto-enol equilibrium. (Scheme 2.9) Addition of 1-
propynyl lithium\textsuperscript{46} gave alcohol 77 in yields ranging from 46 – 62\%. The addition was confirmed by the loss of the ketone resonance (210.5 ppm) and appearance of the propynyl-methyl resonance (3.5 ppm) in the \textsuperscript{13}C NMR.

Scheme 2.8: Formation of Alcohol 77

2.7 SYNTHESIS OF CYCLOCARBONYLATION PRECURSOR 55: 
SAPONIFICATION AND DEHYDRATIVE DECARBOXYLATION

In order to form the ene-yne present in the cyclocarbonylation precursor 55, the ester and the β-hydroxyl group needed to be converted to an olefin. Our first plan for this transformation was to form the β-lactone 78 (Figure 2.6) and under thermal conditions it would undergo a retro [2+2] cycloreversion to form 55.\textsuperscript{47} However, the formation of the β-lactone was complicated by expected lack of stereo-control at the two pertinent carbons, and therefore difficulty in the lactonization.

Figure 2.6: β-Lactone 78
Alternatively, when β-hydroxy acid 79 is treated with an acetal of N,N-dimethylformamide a dehydrative decarboxylation can occur and yield the required olefin. This methodology, originally pioneered by Nozaki and co-workers\textsuperscript{48} and later explored by Mulzer\textsuperscript{49,50} is not commonly used, but proved ideal for our purposes. Carbocyclic acid 79 was generated through anhydrous saponification conditions using potassium trimethylsilanolate.\textsuperscript{51} (Scheme 2.10) Using these conditions, acid 79 was produced from ester 77 in 67% yield. Standard LiOH•H₂O conditions were explored but proved unsuccessful, most likely due to the poor solubility of ester 77 in aqueous solutions.

Dehydrative decarboxylation with dimethylformamide dineopentyl acetal gave ene-yne 55 in 78% yield. The neopentyl acetal was necessary due to the methyl ester being reformed with the dimethyl acetal. This was due to methanol, produced in situ, reacting with the activated carbonyl group and producing methyl ester 77 as the primary product. Mulzer noted this effect as well and used the neopentyl acetal to avoid this, due to the decreased nucleophilicity of neopentanol with respect to methanol.

Scheme 2.9: Saponification and Elimination

![Scheme 2.9: Saponification and Elimination](image-url)
The mechanism for this elimination is not fully understood, but it has been explored by Mulzer.\textsuperscript{50} Two of the most promising mechanisms are displayed in Scheme 2.10. In both mechanisms the first step is the loss of R'OH and formation of zwitterionic intermediate 80, followed by attack of the alcohol onto the iminium carbon and loss of another equivalent of R'OH to give zwitterionic intermediate 82. From here two possibilities emerge, either formation of six-membered lactone 83 and subsequent cycloreversion (Scheme 2.11, eq. 1.), or it could undergo an elimination reaction (either E1 or E2) (Scheme 2.11, eq. 2.). The results of Mulzer’s experimentation show that the pathway shown in eq. 1 is unlikely as they obtain a mixture of E and Z isomers from the reaction. The alternate mechanism also has two possibilities for the elimination, E1 or E2 type elimination. Mulzer discovered that both modes of elimination appear to be operative; however, by controlling the steric interactions the E1 pathway can become the dominant or even the exclusive pathway.
Scheme 2.10: Decarboxylation Mechanism

With this elimination successfully carried out, the spectra were greatly simplified, due to the reduced number of stereogenic centers and it was possible to determine the diastereoselectivity the alkylation of the allenyl side chain. (Figure 2.7) From the ratio of methyl doublets of C-20 present in the $^1$H NMR, a diasteromeric ratio of 19:1 was deduced. Unfortunately, it was not possible to determine the relative configuration of the two stereocenters as the relevant proton resonances for C-11 and C-12 were unresolved in the $^1$H NMR spectrum.

Figure 2.7: Carbocycle 55
2.8 RHODIUM CATALYZED CYCLOCARBONYLATION

The key step in the synthetic plan for rippertene is the Rh(I)-catalyzed cyclocarbonylation of allene-yne 55 to give tricycle 54. The reaction occurred as expected under the conditions used by Brummond and co-workers to give cyclopentenone 54 in 34% yield.20 (Scheme 2.12) Changing the catalyst to the one formed in situ from [Rh(COD)Cl]$_2$ and dppp$^{52}$ did not show improvement in reaction time or yield for this reaction. In our experience, longer reaction times result in decreased yields for the Rh(I)-catalyzed cyclocarbonylation reaction and therefore the extended reaction time causes a diminished yield, although in Brummond’s previously reported example of 61d (Table 2.1) the yield was not as greatly reduced. The long reaction time observed for this system is most likely caused by the developing A(1,3) steric strain between carbons 17 and 18. This strain can be seen in the model of cyclopentenone 54 in Figure 2.8.

![Scheme 2.11: Cyclocarbonylation](image-url)
Figure 2.8: Cyclopentenone 54, Least Energy Conformer (MM3)
Table 2.4: $^1$H NMR Assignments for Cyclocarbonylation Product 54

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity, Coupling Constant (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_a$</td>
<td>2.88, 2.82</td>
<td>2 x 1/2 AB q, (21)</td>
</tr>
<tr>
<td>$H_b$</td>
<td>1.79</td>
<td>s</td>
</tr>
<tr>
<td>$H_c$</td>
<td>1.87-1.83, 1.66-1.58</td>
<td>2 x m</td>
</tr>
<tr>
<td>$H_d$</td>
<td>1.87-1.83, 1.66-1.58</td>
<td>2 x m</td>
</tr>
<tr>
<td>$H_e$</td>
<td>2.49-2.43</td>
<td>m</td>
</tr>
<tr>
<td>$H_f$</td>
<td>0.9</td>
<td>d, (6.5)</td>
</tr>
<tr>
<td>$H_g$</td>
<td>1.95-1.88</td>
<td>m</td>
</tr>
<tr>
<td>$H_h$</td>
<td>1.87-1.81</td>
<td>m</td>
</tr>
<tr>
<td>$H_i$</td>
<td>1.36</td>
<td>ddd, (6.5, 7, 7)</td>
</tr>
<tr>
<td>$H_j$</td>
<td>2.12-2.04</td>
<td>m</td>
</tr>
<tr>
<td>$H_k$</td>
<td>2.04-1.95</td>
<td>m</td>
</tr>
<tr>
<td>$H_l$</td>
<td>1.47</td>
<td>s</td>
</tr>
<tr>
<td>$H_m$</td>
<td>1.58</td>
<td>s</td>
</tr>
<tr>
<td>Carbon</td>
<td>Chemical Shift (ppm)</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>132.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>136.4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>205.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>39.0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>130.9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>137.6</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>31.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>33.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>42.4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>28.4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>128.2</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>169.0</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>19.3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> These assignments may be interchangeable

Table 2.5: <sup>13</sup>C NMR Assignments for Cyclocarbonylation Product 54
2.9 ATTEMPTS AT HYDROGENATION

The goal for the next step in the synthesis was to regioselectively and stereoselectively hydrogenate the C7-C8 olefin. In Metz’s 1993 partial synthesis, he was able to affect this type of transformation using Pd/BaSO₄ or Pd/C catalysis with substrate control. Although not perfectly selective, this reaction demonstrated the possibility of this transformation. Initially conditions that were demonstrated to be tolerant of α,β-unsaturated ketones were explored (Table 2.6, entries 1 & 3); however, these failed to provide 84. More forcing conditions were also attempted (entry 5); however, while these proved to consume the starting material, it did not affect the desired transformation. We were unable to identify conditions for the regioselective hydrogenation of triene 54.
Table 2.6: Hydrogenation Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Conditions</th>
<th>Reaction Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol % Pd/BaSO₄ EtOAc</td>
<td>1.5 h</td>
<td>Partial reduction of unknown olefin (by ¹H NMR analysis)</td>
</tr>
<tr>
<td>2</td>
<td>10 mol% Pd/C EtOAc</td>
<td>1h</td>
<td>Partial Reduction, regioselectivity unclear (LC/MS monitoring)</td>
</tr>
<tr>
<td>3</td>
<td>10 mol% Pd/BaSO₄ EtOH</td>
<td>5 d</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>10 mol % Pd/C THF</td>
<td>2 h</td>
<td>No Reaction</td>
</tr>
<tr>
<td>5</td>
<td>10 mol % Pd/C THF, reflux</td>
<td>20 h</td>
<td>Messy, SM consumed by LC/MS</td>
</tr>
</tbody>
</table>

2 peaks by LC/MS, unidentifiable by NMR
3.0 CONCLUSIONS

Our proposed synthetic plan required that we construct carbocyclic allene-yne 55, and carry out the key Rh(I)-catalyzed cyclocarbonylation reaction. We synthesized the desired intermediate in a diastereoselective manner in six steps from 3-methylcyclohexanone. Since 3-methylcyclohexanone is commercially available in its enantiomerically enriched form it is possible to construct allene-yne 55 in its enantiomerically enriched form. The key cyclocarbonylation reaction was performed successfully and the product fully characterized, providing insights for future attempts at the synthesis. This carbocycle (54), represents the A, B, and C rings present in 3α-hydroxy-15-rippertene (23) and contains much of the necessary stereochemistry present in the natural product.
4.0 EXPERIMENTAL

**General methods and Chromatography:** Unless otherwise specified, all reactions were carried out in glassware that was flame-dried under vacuum, and allowed to cool under an atmosphere of dry nitrogen. Liquids and solutions were transferred via syringe or by stainless steel cannula. Stirring of reaction vessels was accomplished with Teflon™ coated magnetic stir bars. Elevated temperatures were maintained in variac-controlled oil baths. Thin layer chromatography plates (0.25 mm, silica gel 60, F254, glass-backed) were visualized by ultraviolet light or treatment with the appropriate stain followed by gentle heating. Chromatographic purification of products was accomplished by flash chromatography, as described by Still and co-workers\(^1\). Silica gel 60, 230-400 mesh was purchased from EM Science. Toluene and Acetonitrile were purchased from Mallinckrodt Chemicals and distilled from CaH\(_2\) before use. Dichloromethane (DCM) and diethyl ether (Et\(_2\)O) were purchased from Mallinckrodt Chemicals and were purified through a Soltek column purification apparatus before use. Tetrahydrofuran (THF) was purchased from Aldrich and purified through a Soltek column purification apparatus before use. All other chemicals were used as received.

1H and 13C NMR spectra were obtained on Bruker 300 or 500 MHz instruments. All chemical shifts (δ) are reported in ppm. \(^1\)H NMR spectra were calibrated to the residual CHCl\(_3\)

peak at δ 7.26; $^{13}$C NMR spectra were referenced to the CDCl$_3$ resonance at δ 77.16. The following abbreviations are used to denote the indicated splitting pattern 1H NMR spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; abbreviations are used in combination to indicate more complex splitting (e.g., dtd = doublet of triplets of doublets). Infrared spectra were obtained on a Nicolet Avatar E. S. P. 360 FT-IR.

![Chemical structure](image)

3-Methylpenta-3,4-dien-1-ol (64)

2-Butyn-1-ol (5.34 mL, 71.4 mmol), triethyl orthoacetate (17 mL, 93 mmol) and propionic acid (0.3 mL, 4 mmol) were combined in a 50 mL round-bottom flask equipped with a Dean-Stark trap and heated to 130 °C under an atmosphere of N$_2$ for 24 h. The reaction was then cooled to rt, diluted with Et$_2$O, quenched with 10% aq HCl, and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with Et$_2$O (2X). The combined organic layers were washed with sat’d aq NaHCO$_3$, brine, dried over MgSO$_4$, and concentrated in vacuo. The crude product was applied to a silica gel plug, eluted with 10% EtOAc / hexanes, concentrated in vacuo, and taken on to the next step crude. LiAlH$_4$ (4.23 g, 95%, 106 mmol) was suspended in 180 mL Et$_2$O and cooled to 0 °C. The crude product was dissolved in 24 mL Et$_2$O and added to this suspension slowly via cannula. Upon completion of the addition, the mixture was warmed to rt and stirred for 4 h at which time TLC analysis showed consumption of the starting material. The mixture was cooled to 0 °C and quenched slowly with sat’d aq Rochelle’s Salt solution. The precipitate was filtered off and the resulting solution was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The crude
product was passed through a silica gel plug, eluting with 30% EtOAc/hexanes, and concentrated in vacuo to give 3-methylpenta-3,4-dien-1-ol (64) (5.96 g, 85%) as a colorless oil.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta = 4.74-4.69\) (m, 2H), 3.80-3.74 (m, 2H), 2.28-2.20 (m, 2H), 1.76 (t, \(J = 3\) Hz, 3H).

\[
\begin{align*}
\text{HO-} & \quad \text{I} \\
\text{5-Iodo-3-methylpenta-1,2-diene (58)}
\end{align*}
\]

To a solution of alcohol 64 (2.00 g, 20.4 mmol) in 68 mL CH\(_2\)Cl\(_2\) at -78 °C was added triethylamine (3.97 mL, 28.5 mmol) and methanesulfonyl chloride (1.89 mL, 24.5 mmol). The mixture was stirred for 1 h before warming to 0 °C whereupon it was stirred for 3 h at which time the reaction was complete as shown by TLC analysis. The reaction mixture was diluted with CH\(_2\)Cl\(_2\), and washed with 1M aq HCl, sat’d aq NaHCO\(_3\), and brine. The combined organic layers were dried over MgSO\(_4\), concentrated in vacuo and dissolved in 102 mL dry acetone. Sodium iodide (4.58 g, 30.6 mmol) was added and the reaction was heated to reflux overnight (16 h). The reaction was then cooled to rt, diluted with Et\(_2\)O and H\(_2\)O. The layers were separated, and the aqueous was extracted with Et\(_2\)O (2X). The combined organic layers were washed with sat’d aq sodium thiosulfate (2X), brine, dried over MgSO\(_4\), and concentrated carefully in vacuo (keeping rotovap water bath below 10 °C). The crude product was purified on a silica gel column, eluted with pentane to give iodide 58 (1.63 g, 38% over 2 steps) as a clear oil.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta = 4.72-4.66\) (m, 2H), 3.19 (t, \(J = 7.5\) Hz, 2H), 2.51-2.46 (m, 2H), 1.70-1.66 (m, 3H).
Methyl 2-hydroxy-4-methyl-3-(3-methylpenta-3,4-dienyl)cyclohex-1-enecarboxylate (56)

To a solution of diisopropylamine (0.37 mL, 2.64 mmol) in 6.5 mL THF at -78 °C was added 1.54 mL n-BuLi (1.6 M in hexanes, 2.46 mmol) slowly. The solution was allowed to warm to -20 °C and β-Ketoester 57 (200 mg, 1.17 mmol) was added as a solution in 1.2 mL THF. The mixture was stirred for 30 min while warming to 0 °C. Allenyl iodide 58 (256 mg, 1.23 mmol) was added as a solution in 1.2 mL THF. The reaction mixture was allowed to stir for 4 h while warming to room temperature. When the starting material was consumed as shown by TLC analysis, the reaction was quenched by the addition of sat’d aq NH₄Cl, and further diluted with Et₂O and H₂O. The layers were separated and the aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo giving crude 56 (261 mg). The crude product was purified on a silica gel column eluted with 10% EtOAc / hexanes to give 56 (186 mg, 64%) as a mixture of keto/enol tautomers.

**1H NMR** (300 MHz, CDCl₃) δ = 12.27 (br s, 0.5 H), 4.60 – 4.52 (m, 2H), 3.71 (s, 3H), 3.70 (s, 0.4 H), 2.50 – 1.70 (m, 8H), 1.70 – 1.63 (m, 3H), 1.35 – 1.15 (m, 2H), 1.05 (d, J = 6.3 Hz, 0.71H), 1.00 (d, J = 6.3 Hz, 0.46H), 0.94 (d, J = 6.6 Hz, 1.8H)

**13C NMR** (75.5 MHz, CDCl₃) δ = 207.0, 206.1, 174.1, 173.1, 170.5, 98.3, 97.2, 74.6, 74.4, 74.2, 57.5, 56.8, 55.7, 55.3, 52.2, 52.0, 51.4, 45.1, 39.5, 38.1, 33.2, 30.7, 30.6, 30.5, 29.1, 28.7, 27.1, 25.2, 23.6, 20.6, 20.2, 19.6, 18.8

**FT-IR** (NaCl, thin film) ν = 2952, 2930, 2857, 1960, 1748, 1713, 1655, 1614, 1441 cm⁻¹
**General Procedure for the Preparation of**

Tributyl(prop-1-ynyl)stannane (69)

To a solution of 1-trimethylsilyl propyne (0.66 mL, 96%, 4.5 mmol) in 11.1 mL THF was added bis(tributyltin) oxide (1.13 mL, 2.13 mmol) and TBAF (1M in THF, 0.089 mL, 0.089 mmol). The reaction was heated in a 60 °C oil-bath for 2.5 h, cooled to rt, concentrated in vacuo and used without further purification.

Methyl 4-methyl-2-(prop-1-ynyl)cyclohex-1-enecarboxylate (71)

Sodium hydride (60% in mineral oil, 223 mg, 5.57 mmol) was washed with hexanes, suspended in 11 mL CH₂Cl₂ and cooled in an ice-water bath. Enol 57 (631 mg, 3.71 mmol) was added as a solution in 5 mL CH₂Cl₂. The reaction was stirred for 10 min, trifluoromethanesulfonic anhydride (1.25 ml, 7.42 mmol) was added and the reaction was stirred for a further 10 min when the starting material was consumed via TLC analysis. The reaction was quenched through the addition of sat’d aq NH₄Cl and diluted with Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was added to a solution of tributyl(prop-1-ynyl)stannane (4.5 mmol) in 5 mL THF. Palladium tetrakis-triphenylphosphine (427 mg, 0.37 mmol) was added to the reaction mixture and it was heated in a 60 °C oil-bath for 1.5 h at which time TLC analysis showed consumption of starting material. The reaction was cooled to rt,
concentrated in vacuo, and purified on a silica gel column which was eluted with 7.5% EtOAc / hexanes to provide ene-yne 71 (527 mg, 74%)

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3 \delta = 3.73 \text{ (s, 3H), 2.58-2.10 (m, 4H), 2.05 \text{ (s, 3H), 1.80-1.50 (m, 3H), 0.95 (d, } J = 6.6 \text{ Hz, 3H)} \]

\[ \text{\textsuperscript{13}C NMR (75.5 MHz, CDCl}_3 \delta = 167.8, 132.2, 129.5, 93.7, 79.9, 51.5, 50.0, 30.0, 27.8, 26.1, 20.0, 4.8} \]

\[ \text{FT-IR (NaCl, thin film) } \nu = 2950, 2221, 1723, 1613, 1434 \text{ cm}^{-1} \]

\[ \text{HRMS (EI\textsuperscript{+}) Calc (C\textsubscript{12}H\textsubscript{16}O\textsubscript{2}): 192.1150, Found: 192.1144} \]

To a solution of ester 71 (200 mg, 1.04 mmol) in 2.1 mL CH\textsubscript{2}Cl\textsubscript{2} at - 78 °C was added DIBAL-H (1 M in hexanes, 2.3 mL, 2.3 mmol) slowly. The reaction was stirred for 15 min at which time TLC analysis showed consumption of the starting material. The reaction was warmed to 0 °C and quenched through the addition of sat’d aq Rochelle’s salt and a few drops of 10% aq HCl. The mixture was stirred for 30 min, filtered through celite, and diluted with H\textsubscript{2}O. The layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (5X). The combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, and concentrated in vacuo to provide crude alcohol 72 (165 mg, 97%).

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3 \delta = 4.21 \text{ (1/2 AB q, } J = 5.7 \text{ Hz, 1H), 4.19 \text{ (1/2 AB q, } J = 5.7 \text{ Hz, 1H), 2.45-2.00 (m, 4H), 1.91 \text{ (s, 3H), 1.80-1.40 (m, 3H), 0.89 (d, } J = 6.3 \text{ Hz, 3H)} \]

\[ \text{(4-Methyl-2-(prop-1-ynyl)cyclohex-1-enyl)methanol} \]

\[ \text{(72)} \]

\[ \text{\textsuperscript{2} Contaminated with Silicon or Tin based impurities} \]
$^{13}$C NMR (75.5 MHz, CDCl$_3$) δ= 142.0, 117.0, 88.4, 78.9, 64.7, 38.7, 30.4, 28.3, 26.8, 21.3, 4.2

FT-IR (NaCl, thin film) ν= 3342, 2949, 2917, 2870, 1454 cm$^{-1}$

HRMS (EI+) Calc (C$_{11}$H$_{16}$O): 164.1201, Found: 164.1198

4,7-dimethyl-8-methylene-2,3,4,4a,5,8-hexahydronaphthalene-1-carboxylate (75)

To a solution of enol 56 (50 mg, 0.20 mmol) in 2 mL THF at 0 °C was added NaH (60% in mineral oil, 12 mg, 0.30 mmol) and N-phenyl-bis(trifluoromethanesulfonimide) (79 mg, 0.22 mmol). The reaction was stirred for 3.5 h at which time TLC analysis showed consumption of starting material. The reaction was cooled to 0 °C, quenched with H$_2$O and diluted with Et$_2$O. The layers were separated and the aqueous layer was extracted with Et$_2$O (3X). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo to give the intermediate vinyl triflate 67 (76 mg, 99%).

Separately, to a solution of 1-trimethylsilyl propyne (0.16 mL, 0.11 mmol) 0.3 mL THF was added bis(tributyltin) oxide (0.28 mL, 0.055 mmol) and TBAF (1M in THF, 0.002 mL, 0.002 mmol). The reaction was heated in a 60 °C oil-bath for 2.5 h, at which time it was cooled to 50 °C. Vinyl triflate 67 was added as a solution in 0.2 mL THF. Palladium tetrakis(triphenylphosphine) (10.4 mg, 0.009 mmol) was added and the reaction was stirred for 1.5 h and concentrated in vacuo. The mixture was applied to a silica gel column which was eluted with 10% EtOAc / hexanes to provide 75 (22 mg, 47%)
\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ = 5.65 (d, $J$ = 4.5 Hz, 1H), 4.96 (s, 1H), 4.91 (s, 1H), 3.63 (s, 3H), 2.64-2.50 (m, 2H), 2.20-1.90 (m, 4H), 1.84-1.80 (m, 3H), 1.78-1.62 (m, 2H), 1.01 (d, $J$ = 6.3 Hz, 3H)

\textbf{13C NMR} (75.5 MHz, CDCl$_3$) $\delta$ = 173.0, 145.5, 143.6, 133.0, 127.1, 126.8, 110.7, 52.3, 43.9, 35.9, 34.3, 29.8, 27.8, 20.5, 19.8,

\textbf{Methyl 1,4-dimethyl-3-(3-methylpenta-3,4-dienyl)-2-oxocyclohexanecarboxylate (76)}

To a solution of enol 56 (787 mg, 3.15 mmol) in 31.5 mL MeCN was added cesium carbonate (5.13 g, 15.7 mmol) and methyl iodide (0.98 mL, 15.7 mmol). The resulting suspension was stirred for 6 h, quenched through the addition of H$_2$O and stirred until the precipitate was dissolved. The reaction mixture was diluted with Et$_2$O, and the layers were separated. The aqueous layer was extracted with Et$_2$O (3X) and the combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo to provide 76 (707 mg, 85%) as a complex mixture of diastereomers.

\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ = 4.54-4.48 (m, 2H), 3.70-3.60 (m, 3H), 2.52-1.61 (m, 8H), 1.59 (t, $J$ = 3 Hz, 3H), 1.58-1.48 (m, 2H), 1.37* (s, 2.2H), 1.20** (s, 0.8 H), 1.07* (d, $J$ = 6.6 Hz, 0.3H), 0.99** (d, $J$ = 6.3 Hz, 2H), 0.93*** (d, $J$ = 6.3 Hz, 1.2H), 0.80**** (d, $J$ = 6.9 Hz, 0.35H)

\textbf{13C NMR} (75.5 MHz, CDCl$_3$) $\delta$ = 210.5, 206.1, 173.5, 98.2, 74.3, 57.2, 53.0, 52.1, 49.0, 38.1, 37.2, 25.2, 33.9, 21.4, 30.8, 28.9, 24.7, 22.2, 21.1, 20.6, 18.7

\textbf{FT-IR} (NaCl, thin film) $\nu$ = 2951, 2870, 1959, 1741, 1710, 1455 cm$^{-1}$

\textbf{HRMS} (EI+) Calc: 264.1727, Found: 264.1729
Methyl 2-hydroxy-1,4-dimethyl-3-(3-methylpenta-3,4-dienyl)-2-(prop-1-yny1)cyclohexanecarboxylate (77)

To a solution of (E/Z)-1-bromo-1-propene (83 μL, 0.97 mmol) in 0.65 mL THF at -78 °C was added n-BuLi (1.6 M in hexanes, 0.89 mL, 1.4 mmol). The mixture was stirred for 2 h at -78 °C at which time ketone 76 (145 mg, 0.55 mmol) was added in 0.55 mL THF. The mixture was allowed to warm to room temperature overnight at which time the no starting material was observed via TLC. The reaction was quenched through the addition of sat’d aq NH₄Cl and diluted with Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo giving crude 77 (131 mg). The crude product was purified in a silica gel column that was eluted with 10% EtOAc / hexanes to provide alcohol 77 (77 mg, 46%) as a mixture of diastereomers. No attempt was made to separate the diastereomers.

**H NMR** (300 MHz, CDCl₃) δ= 4.60-4.50 (m, 2H), 3.74* (s, 0.18H), 3.73** (s, 0.15H), 3.71*** (s, 1.17H), 3.71**** (s, 1.48H), 2.15-1.85 (m, 5H), 1.84* (s, 0.7H), 1.79-1.78**/*** (2 x s, 2.3H), 1.77-1.70 (m, 1H), 1.69-1.65 (m, 3H), 1.64-1.40 (m, 4H), 1.40* (s, 1.2H), 1.36** (s, .75H), 1.23*** (s, 1.1H), 0.95-0.88 (m, 3H)

**C NMR** (75.5 MHz, CDCl₃) δ= 206.6, 206.3, 179.1, 178.7, 99.0*, 98.8**, 98.7***, 82.5, 81.7, 81.6, 80.5, 80.2, 78.6, 78.0, 75.3, 74.5, 73.7, 73.5, 52.2, 52.0, 51.5, 51.4, 47.5, 47.2, 36.4, 35.3,
To a solution of ester 77 (200 mg, 0.66 mmol) in 6.6 mL MeCN was added potassium trimethylsilanolate (281 mg, 90% purity, 2.0 mmol). The mixture was stirred for 2 d at which time TLC analysis showed consumption of the starting ester. The reaction was diluted with Et₂O and quenched by adding 10% aq HCl. The layers were separated and the aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to give crude acid 79 (181 mg). The crude product was purified on a silica gel column that was eluted with EtOAc : hexanes : AcOH (70:30:1) to provide carboxylic acid 79 (128 mg, 67%).

**¹H NMR** (300 MHz, CDCl₃) δ= 4.60-4.50 (m, 2H), 2.07-2.00 (m, 2H), 2.00-1.85 (m, 1H), 1.84 (s, 0.6H), 1.79 (2 x s, 2.4H), 1.69-1.64 (m, 3H), 1.61-1.44 (m, 3H), 1.44 (s, 0.6H), 1.39 (s, 1.1 H), 1.29 (s, 1.3H), 1.27-1.13 (m, 2H), 0.95-0.85 (m, 3H)

**¹³C NMR** (75 MHz, CDCl₃) δ= 206.3, 183.8, 99.0, 98.7, 83.5, 82.5, 81.0, 80.9, 79.9, 75.3, 74.5, 73.8, 73.6, 36.3, 35.4, 34.7, 34.6, 34.2, 31.8, 30.6, 30.2, 29.7, 29.3, 28.5, 27.6, 20.2, 20.1, 20.0, 18.7, 18.6, 16.8, 4.6

**HRMS:** Pending
To a solution of β-hydroxy acid 79 (250 mg, 0.86 mmol) in 17 mL of freshly distilled CHCl₃ was added N,N-dimethyl formamide dineopentyl acetal (0.72 mL, 99%, 2.6 mmol). The reaction was stirred for 1 h at rt and then refluxed for 2 h, at which time TLC analysis of the reaction mixture indicated consumption of starting material. The reaction was cooled to rt, diluted with H₂O and CH₂Cl₂. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2X). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to give the crude product (318 mg). Purification of the crude product on a silica gel column, eluted with 1% Et₂O / pentanes provided 55 (153 mg, 78%) as a pale oil.

**1H NMR** (300 MHz, CDCl₃) δ = 4.60-4.55 (m, 2H), 1.98 (s, 3H), 1.97-1.88 (m, 2H), 1.85 (s, 3H), 1.84-1.72 (m, 3H), 1.70 (t, J = 3.3 Hz, 3H), 1.68-1.58 (m, 3H), 1.35-1.22 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H)

**13C NMR** (75 MHz, CDCl₃) δ = 206.4, 139.9, 118.0, 98.9, 87.4, 80.2, 73.8, 45.1, 30.7, 30.6, 29.6, 29.0, 26.7, 22.3, 19.7, 18.8, 4.5

**HRMS (EI+):** Calc (C₁₇H₂₄): 228.1878; Found: 228.1884

**Rf:** (10% Et₂O / pentanes) 0.6
To a 25mL round-bottom flask was added [Rh(CO)₂Cl]₂ (52 mg, 0.13 mmol). The flask was placed under vacuum and then filled with CO gas (1 ATM). The flask was then evacuated and refilled with CO gas twice more. A solution of allene-yne 55 (304 mg, 1.33 mmol) in 13.3 mL toluene was added to the flask which was then placed in an oil-bath pre-heated to 90 °C and the reaction mixture was allowed to stir for 11.5 h, at which time TLC analysis showed no detectable starting material. The reaction was cooled to room temperature, passed through a silica gel plug, eluting with 10% EtOAc / hexanes, and concentrated in vacuo to provide crude 54 (250 mg). The crude product was purified on a silica gel column, eluting with 10% EtOAc / hexanes to provide cyclopentenone 54 (114 mg, 34%).

**1H NMR** (500 MHz, CDCl₃) δ= 2.90 (½ AB q, J= 20.5 Hz), 2.82 (½ AB q, J= 21 Hz), 2.50-2.40 (m, 1H), 2.15-1.80 (m, 5H), 1.80 (s, 3H), 1.79-1.74 (m, 1H), 1.67-1.60 (m, 1H), 1.59 (s, 3H), 1.57-1.48 (m, 1H), 1.47 (s, 3H), 1.40-1.32 (m, 1H), 0.90 (d, J= 6.5 Hz, 3H)

**13C NMR** (126 MHz, CDCl₃) δ= 205.6, 169.0, 137.6, 136.4, 132.0, 130.9, 128.2, 42.3, 39.0, 33.7, 32.2, 31.2, 28.4, 25.7, 23.4, 21.0, 19.3, 9.3

**FT-IR** (NaCl, thin film) ν= 2924, 1690, 1577, 1439 cm⁻¹

**HRMS** (TOF MS ES+): Calc (C₁₈H₂₄ONa⁺): 279.1725; Found: 279.1702

**R_f**: (10% EtOAc / hexanes) 0.4
5.0 BIBLIOGRAPHY


6.0 SPECTRA
AJR-2-189
Post Column (multiple spots)
Current Data Parameters
NAME AJR-2-106
EXPGC 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20070523
Time 14:46
INSTROM spect
PROBBD 5 mm DUL 1H-13
FURPROG zg
TD 65536
SOLVENT CDC13
NS 1
DS 16
SW 2
NPH 6218.905 Hz
FIDRES 0.094993 Hz
AQ 5.269145 sec
DG 16
DW 80.400 usec
dE 6.00 usec
TE 300.0 K
DI 2.00000000 sec
TD0 1

-------- CHANNEL f1 --------
NUC1 1H
F1 9.00 usec
PB 1.00 dB
SF01 300.3818550 MHz

F2 - Processing parameters
SI 32768
SF 300.3799993 MHz
MDW 10
SSB 0
LB 0.30 Hz
GB 0
PC 1.00