Title
Progress Towards the Total Synthesis of Rugulosone and Methodologies of Alkene Isomerization and Formation of Substituted Adamantanones

Permalink
https://escholarship.org/uc/item/1hw3z1ct

Author
Lee, Gloria S.

Publication Date
2014

Peer reviewed|Thesis/dissertation
Progress Towards the Total Synthesis of Rugulosone

and

Methodologies of Alkene Isomerization and Formation of Substituted Adamantanones

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Chemistry

by

Gloria Shen Lee

2014
ABSTRACT OF THE DISSERTATION

Progress Towards the Total Synthesis of Rugulosone

and

Methodologies of Alkene Isomerization and Formation of Substituted Adamantanones

by

Gloria Shen Lee

Doctor of Philosophy in Chemistry

University of California, Los Angeles

2014

Professor Michael E. Jung, Committee Chair

In Chapter 1, potential strategies toward the synthesis of rugulosone were investigated. Although initial efforts towards forming the bicyclo[3.3.1]nonane core via a Michael addition – Dieckmann condensation reaction sequence did not prove useful for our investigations, the synthesis of the core was accomplished via a highly efficient tetraalkylation of commercially available starting materials. Using our developed methodology, we were able to isomerize unactivated alkenes to form the C₂ symmetric core necessary for the natural product. Studies toward the addition of the northern side chain were conducted, and proved to be promising.
Synthesis of a protected southern side chain was accomplished, and may be used in the future to couple with the functionalized core to facilitate a highly divergent synthesis of the natural product.

For our work towards the synthesis of the core of rugulosone, we developed a methodology to isomerize exo-methylene groups to their corresponding tri-substituted internal alkenes. The exo-methylene groups of 2,6-disubstituted bicyclo[3.3.1]nonan-9-ones were readily isomerized over a palladium catalyst under an atmosphere of hydrogen to form predominantly the isomer with C₂ symmetry with very little formation of the analogous product with C₅ symmetry. A hydrogen source was essential to effect the rearrangement.

The third and last chapter outlines formation of highly substituted adamantanones. Adamantane-based small molecules are useful in the treatment of a variety of conditions, ranging from neurodegenerative disorders such as Parkinson’s and Alzheimer’s disease, to viral infections such as HIV. We thus desired to efficiently construct substituted adamantanones, potential precursors to the corresponding adamantanes. Trifluoromethanesulfonic acid facilitated formation of the adamantanone core from 1,5-dialkyl-3,7-dimethylenebicyclo[3.3.1]nonan-2-one, which was easily obtained in one step from commercially available starting materials. The resulting adamantyl cation was trapped with a variety of nucleophiles to form tetrasubstituted adamantanones. Aromatic and heteroaromatic nucleophiles have proven to be successful, and oxygen and nitrogen nucleophiles provide access to a wide variety of functionality at the newly formed tertiary position.
The dissertation of Gloria Shen Lee is approved.

Kendall N. Houk

Jing Huang

Michael E. Jung, Committee Chair

University of California, Los Angeles

2014
To my loving parents, Mr. and Mrs. Philip and Teresa Lee.
# TABLE OF CONTENTS

**CHAPTER 1: Progress Towards the Total Synthesis of Rugulosone**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>Results and Discussion</td>
<td>6</td>
</tr>
<tr>
<td>Conclusion</td>
<td>35</td>
</tr>
<tr>
<td>Experimental</td>
<td>36</td>
</tr>
<tr>
<td>References</td>
<td>59</td>
</tr>
</tbody>
</table>

**CHAPTER 2: Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di-(exo)methylenes to Endocyclic Dienes**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>62</td>
</tr>
<tr>
<td>Results and Discussion</td>
<td>65</td>
</tr>
<tr>
<td>Conclusion</td>
<td>80</td>
</tr>
<tr>
<td>Experimental</td>
<td>81</td>
</tr>
<tr>
<td>References</td>
<td>89</td>
</tr>
</tbody>
</table>
**CHAPTER 3**: Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonanes

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>93</td>
</tr>
<tr>
<td>Results and Discussion</td>
<td>98</td>
</tr>
<tr>
<td>Conclusion</td>
<td>114</td>
</tr>
<tr>
<td>Experimental</td>
<td>115</td>
</tr>
<tr>
<td>References</td>
<td>137</td>
</tr>
</tbody>
</table>
LIST OF SCHEMES

CHAPTER 1: Progress Towards the Total Synthesis of Rugulosone

Scheme 1-1. Selected methods of forming bicyclo[3.3.1]nonanone core 4

Scheme 1-2. Progress towards Gymnastatin G 5

Scheme 1-3. Original retrosynthetic analysis for rugulosone 6

Scheme 1-4. Proposed forward synthesis to make cyclohexane 29 6

Scheme 1-5. Formation of Feringa’s ligand 36 7

Scheme 1-6. Formation of 3-methyl-4-methoxyphenol 38 8

Scheme 1-7. Alternative proposed synthesis of 29 9

Scheme 1-8. Michael addition – Dieckmann condensation to give bicyclo[3.3.1]nonanone 45 9

Scheme 1-9. Michael addition of 46 to methyl bromomethacrylate 30 to form ketoester 47 10

Scheme 1-10. Attempted formation of Dieckmann condensation to form dione 48 11

Scheme 1-11. Reported example of light activated E/Z isomerization of alkenes 11

Scheme 1-12. nOE correlation of E-isomer 47 and Z-isomer 51 13

Scheme 1-13. Attempts to perform Dieckmann condensation to form bicyclodione 48 13

Scheme 1-14. Attempt to perform Michael addition – Dieckmann condensation to form bicyclodione 54 14

Scheme 1-15. Michael addition of 53 with potassium tert-butoxide to form bicyclodione 55 14

Scheme 1-16. Application to our system 15

Scheme 1-17. Retrosynthesis to make trimethyl cyclohexenone 43 16
Scheme 1-18. Oxidation to ketone 59

Scheme 1-19. Desired Dieckmann condensation of enone 43 and methylmethacrylate 56 18

Scheme 1-20. Formation of bicyclo[2.2.2]octanes 67 and 70 18

Scheme 1-21. New approach to form bicyclo[3.3.1]nonane core 74 19

Scheme 1-22. Revised retrosynthesis 19

Scheme 1-23. Formation of allyl dichloride 72 20

Scheme 1-24. Isomerization of bicycle 73 to give two isomers, 74 and 80 21

Scheme 1-25. Isomerization of bicycloketone 73 with catalytic palladium on charcoal 22

Scheme 1-26. Approach to install the northern side chain 24

Scheme 1-27. Application of dianion chemistry to our system 25

Scheme 1-28. Dianion addition control experiment 25

Scheme 1-29. Reaction of 94 with cyclohexanone 26

Scheme 1-30. Reaction of dianion substrates with bicycle 74 27

Scheme 1-31. Forward synthesis of northern side chain 27

Scheme 1-32. Formation of epoxide 102 from diene 74 28

Scheme 1-33. Revised synthesis of methyl ketone 104 29

Scheme 1-34. Hindered Horner reaction to form methyl ketone 104 30

Scheme 1-35. Conversion of aldehyde 103 to methyl ketone 104 31

Scheme 1-36. Heck coupling to install northern side chain 31

Scheme 1-37. Model system for Heck coupling 31

Scheme 1-38. Attempted Heck coupling to form northern side chain 32

Scheme 1-39. Attempted Shapiro reaction 33

Scheme 1-40. Proposed synthesis of the southern side chain 33
Scheme 1-41. Formation of diols 125, 126, 127, and 128

Scheme 1-42. Selective protections of diol 125 to give compound 130

CHAPTER 2: Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di-(exo)methylene to Endocyclic Dienes

Scheme 2-1. E/Z isomerization of alkenes

Scheme 2-2. Isomerization of oct-1-ene 131 to isomers 132-136

Scheme 2-3. Two potential mechanistic pathways of alkene isomerization

Scheme 2-4. Hydrogenation conditions with palladium on charcoal

Scheme 2-5. Reported isomerization of allylic alcohol 139

Scheme 2-6. Formation of dienone 73

Scheme 2-7. Chemdraw representation and molecular ball-and-stick models of isomerization of 73 to give 74 and/or 80

Scheme 2-8. Epoxidation of bicycle 73 to give diepoxide 141

Scheme 2-9. Isomerization of 73 to give 74 and other products

Scheme 2-10. Formation of bicyclo[3.3.1]nonane analogues

Scheme 2-11. Isomerization of alkenes 150 and 151

Scheme 2-12. Attempt to make bicycle 156

Scheme 2-13. Attempt to make ketodiester 159

Scheme 2-14. Treatment of 160 with deuterium gas

Scheme 2-15. Proposed mechanism for the isomerization of 163
CHAPTER 3: Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonanes

**Scheme 3-1.** von Tague Schleyer’s adamantane synthesis 93

**Scheme 3-2.** Commercial synthesis of amantadine 173 94

**Scheme 3-3.** Commercial production of memantine 177 94

**Scheme 3-4.** Two methods of formation of substituted adamantanes 96

**Scheme 3-5.** Formation of bicyclononane 73 98

**Scheme 3-6.** Cyclization of analogues 146-148 to give adamantanones 185-187 101

**Scheme 3-7.** Attempts to cross-couple haloadamantanone 213 109

**Scheme 3-8.** Mechanism of formation of the adamantanone core 109

**Scheme 3-9.** Hydrolysis of 210 to give the memantine analog 220 110

**Scheme 3-10.** Attempts to reduce ketone 73 113
LIST OF FIGURES

CHAPTER 1: Progress Towards the Total Synthesis of Rugulosone

Figure 1-1. Structure of Rugulosone 1 2
Figure 1-2. Natural products bearing a bicyclo[3.3.1]nonane core 3
Figure 1-3. Constitutional isomer and analogues 43 9
Figure 1-4. Model substrate for Michael addition – Dieckmann condensation 10
Figure 1-5. Side product 79 21
Figure 1-6. 3D structures of isomers 74 and 80 by Max Kopelevich 22
Figure 1-7. Overoxidized trione 82 24

CHAPTER 2: Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di-(exo)methylenes to Endocyclic Dienes

Figure 2-1. Examples of common transition metal isomerization catalyst 62
Figure 2-2. Rugulosone 1 65
Figure 2-3. Structures of the C2 and Cs dienes 74 and 80 66
Figure 2-4. The monoisomerized and C2 and Cs bis-isomerized optimized structures 78
CHAPTER 3: Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonanes

Figure 3-1. Laube’s crystal structure of 3,5,7-trimethyl-1-adamantyl cation Sb$_2$F$_{11}$

and adamantane numbering scheme 97

Figure 3-2. Rugulosone 1 98

Figure 3-3. 5-Methoxy-1,3,7-trimethyladamantan-2-one 183 100

Figure 3-4. Compound 225 112
LIST OF TABLES

CHAPTER 1: Progress Towards the Total Synthesis of Rugulosone

Table 1-1. Attempted 1,4-additions to cyclohexadienone 32
Table 1-2. E/Z isomerization of alkene 47
Table 1-3. Reduction of 1,3,5-trimethylphenol 61
Table 1-4. Oxidation to enone 43
Table 1-5. Formation of cyclohexanone 29 and bicycle 73
Table 1-6. Attempted allylic oxidation of bicycle 74
Table 1-7. Opening of epoxide 102
Table 1-8. Horner reaction for formation of aldehyde 103

CHAPTER 2: Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di-(exo)methylenes to Endocyclic Dienes

Table 2-1. Attempts to isomerize bicyclodiene 73
Table 2-2. Attempts to open diepoxide 141
Table 2-3. Control experiments to demonstrate need for hydrogen gas
Table 2-4. Solvent effects on conversion of 73 to 74, 80, 144, 145
Table 2-5. Free energy calculations for C2 and C5 isomers
CHAPTER 3: Synthesis of Highly Substituted Adamantanones from Bicyclo[3.3.1]nonanes

Table 3-1. Attempts at isomerization of bicyclodiene 73  
Table 3-2. Conversion of diene 73 to phenyladamantane 184  
Table 3-3. Reduction of 73 with aromatic rings 188-191 to give 192-196  
Table 3-4. Reactions of 73 with heterocyclic nucleophiles to give 197  
Table 3-5. Reactions of 73 with oxygen and non-aryl carbon nucleophiles to give 197  
Table 3-6. Trapping of 73 with non-aryl C and N nucleophiles  
Table 3-7. Reactions of 73 with both electrophiles and nucleophiles to give 211  
Table 3-8. Attempts to trap acrylate electrophiles onto mercuric salt 216  
Table 3-9. Attempts to reduce ketone 184
ACKNOWLEDGEMENTS

I would like to start by thanking my advisor, Professor Michael. E. Jung, for all of his time, guidance, and patience through the years. Even with an extremely packed schedule, his office door was always open to discuss the intriguing NMR spectrum or the annoying reaction side products. I surely would not have become the individual that I am today without his knowledge and support. Thank you!

To my committee members, Dr. Kendall Houk, Dr. Steven Clarke, Dr. Jing Huang, and Dr. Benhur Lee, for their time to serve on my committee.

I would like to thank all previous and current Jung lab members, for their time and willingness to help me, their knowledge and expertise in chemistry, and their jokes and laughter through tough times. I will surely miss the good ‘ol Jung lab!

A big thank you to my friends and colleagues in other labs at UCLA. Whether it was to grab lunch or to run out for a quick coffee, those breaks were much needed and appreciated.

And finally, I would like to thank my family for all their love and support through the years. No matter how crazy and seemingly out of control my world got, they assured me that with a little time, patience, and hard work, everything would be okay. Turns out, they were right.
VITA

2001 – 2005  B.S., Biochemistry/Chemistry (ACS Certified)

University of California, San Diego

2009 – 2014  Graduate Research Assistant

University of California, Los Angeles

2013 – 2014  Technology Transfer Fellow

UCLA Office of Intellectual Property and Industry Sponsored Research

PUBLICATIONS AND PRESENTATIONS


CHAPTER 1

Progress Towards the Total Synthesis of Rugulosone
INTRODUCTION

Figure 1-1. Structure of Rugulosone (1).

Rugulosone 1 (Figure 1-1) is a secondary metabolite which was first isolated by Moosophon and coworkers in 2009 from the fungal strain *Emericella rugulosa* in 2009. Previous natural products isolated from the fungal genus have sparked much interest in the scientific community, possessing properties of being cytotoxic against cancer cell lines, sesterterpenes with unusual tricyclic and pentacyclic skeletons, and prenylated polyketides.

Rugulosone has shown significant biological activity, including *in vitro* antimalarial activity against *Plasmodium falciparum* with an IC$_{50}$ value of 1.9 µg/mL, antimycobacterial activity against *Mycobacterium tuberculosis* with a MIC value of 12.5 µg/mL. In addition, rugulosone was also cytotoxic against the BC1, KB, and NCI-H187 cancer cell lines, with IC$_{50}$ values of 1.3, 2.6, and 1.3 µg/mL, respectively.

Rugulosone has a bicyclo[3.3.1]nonane core that is present in a number of natural products (Figure 1-2), most notably a class of polyprenylated acylphlorogluconols (PPAPs) that bear a highly substituted and oxygenated bicyclo[3.3.1]nonane-2,4,9-trione framework. A number of total syntheses of this class of molecules have been accomplished, including garsubellin A,
hyperforin, and guttiferone A, to name a few. Also, many groups have focused their efforts on developing stereocontrolled syntheses of the intriguing bicyclononane core. A number of general reviews on the formation of the bicyclo[3.3.1]nonane core have been published. However, the bicyclo[3.3.1]nona-2,6-diene core of rugulosone is the first derivative of its kind to be obtained from a natural source. The highly symmetric bicyclic framework presents a great challenge for synthetic organic chemists. No synthesis of rugulosone has been reported to date.

![Gymnastatin G](image1.png) ![Garsubellin A](image2.png) ![Guttiferone B](image3.png) ![Papuaforin A](image4.png)

**Figure 1-2.** Natural products bearing a bicyclo[3.3.1]nonane core.

A number of routes are used to form the bicyclo[3.3.1]nonane core present in natural products (Scheme 1-1). The most commonly used methods are:

1. Michael addition – intramolecular aldol
2. Annulations of β-keto esters
3. Pd-catalyzed cyclization with acetyloxymethallyl acetate
4. Cycloalkylations
Scheme 1-1. Selected methods of forming bicyclo[3.3.1]nonanone core.
5. Ring cleavage of adamantane derivatives
6. Ring closing metathesis
7. Annulations of cyclooctane derivatives

Previously in our lab, in a proposed synthesis of Gymnastatin G, one of the key steps of the synthesis was the formation of the bicyclo[3.3.1]nonane core, which relied on the tandem Michael-aldol reaction shown in Scheme 1-2. First, Michael addition of the chlorodiketone 21 to acrolein gave the intermediate 22, which then underwent a 1,6-hydrogen shift, or a simple deprotonation/reprotonation, that was then perfectly set up for an intramolecular aldol reaction to close the second ring, giving a mixture of the alcohols 25.

Scheme 1-2. Progress towards Gymnastatin G.

Our synthetic approach towards the synthesis of rugulosone relied on reported tandem reactions to form the bicyclic core, through reactions of either Michael addition – aldol condensation or Michael addition – Dieckmann condensation. We will now describe our efforts for the synthesis of the bicyclo[3.3.1]nonadienone core of rugulosone and its conversion to the natural product.
RESULTS AND DISCUSSION

Scheme 1-3. Original retrosynthetic analysis for rugulosone 1.

Our original retrosynthetic analysis of Rugulosone 1 is shown in Scheme 1-3. We envisioned completion of the natural product by appending the southern side chain 28 with the central fragment 26 in a highly convergent total synthesis. Fragment 26 would arise from the bicyclo[3.3.1]nonane core 27 that, in turn, would be formed from a tandem Michael addition – Dieckmann cyclization sequence starting with the cyclohexanone 29 and the methyl bromomethacrylate 30.

Scheme 1-4. Proposed forward synthesis to make cyclohexane 29.
Our forward synthesis began with the formation of 2,6-dimethyl-4-methylene-cyclohexanone 29 (Scheme 1-4). The synthesis commenced with 4-hydroxyanisole 31,

![Scheme 1-5](image)

**Scheme 1-5.** Formation of Feringa’s ligand 36.

**Table 1-1.** Attempted 1,4-additions to cyclohexadienone 32.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂CuLi</td>
<td>Formed 4-methoxyphenol</td>
</tr>
<tr>
<td>2</td>
<td>Me₂Zn</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl₂, MeMgBr</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Me₄Zn, Cu(OTf)₂, R-BINOL, Et₃N</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>MeLi, CuBr·Me₂S, TMSCl, -78 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>CuBr·Me₂S, HMPA, TMSCl</td>
<td>Formed 3-methyl-4-methoxyphenol 38</td>
</tr>
</tbody>
</table>
which was oxidized with phenyliodine diacetate (PIDA) in methanol to give the enone 32. Next, it was envisioned that one could perform two cuprate additions to the enone 32. However, attempts to use Feringa’s ligand 36, prepared as shown in Scheme 1-5, failed to give cuprate addition to the enone. Table 1-1 shows conditions attempted for the cuprate addition. Simple reaction with lithium dimethylcopper reformed the previous starting material, 4-methoxyphenol (entry 1). No reaction was observed when enone 32 was treated with a solution of dimethylzinc. Similarly, treatment with dimethylzinc or a mixture of zinc chloride and methylmagnesium bromide gave no reaction. In addition, treatment of zincate reagents with a copper source, as in entries 4 and 5, gave no reaction. Although treatment of the enone 32 with copper bromide dimethyl sulfide complex in HMPA as an additive did not return starting material, we instead isolated 3-methyl-4-methoxyphenol 38, the rearomatized product after addition of methyl cuprate.

Scheme 1-6. Formation of 3-methyl-4-methoxyphenol 38.

Subsequently, we turned our attention to an alternative proposed forward synthesis (Scheme 1-7). Starting with cyclohexane-1,4-dione 39, monoprotection with ethylene glycol then subsequent Wittig reaction formed the methylene ketal which could then be deprotected to give the ketone 41. However, treatment with methyl iodide under a variety of basic conditions gave mixtures of mono-, di-, and trimethylated products. Thus, we were unable to prepare 2,6-dimethyl-4-methylene cyclohexanone 29 selectively.
Scheme 1-7. Alternative proposed synthesis of 29.

Since we were unable to synthesize the ketone 29, we set out to make the constitutional isomer ketone 43 (Figure 1-3), which should be able to undergo our desired Michael addition – Dieckmann condensation sequence (Scheme 1-8). 7

Figure 1-3. Constitutional isomer and analogue 43.

Scheme 1-8. Michael addition – Dieckmann condensation to give bicyclo[3.3.1]nonadienone 45.

Before attempting to perform the Michael addition – Dieckmann condensation reaction sequence on the enone 43, a model system was used first. Thus, a mixture of 2,6-dimethylcyclohexanone diastereomers 46 was selected as the model substrate. Treatment of 2,6-
Figure 1-4. Model substrate for Michael addition – Dieckmann condensation.

dimethylcyclohexanone 46 with methyl bromomethacrylate 30 under basic conditions using potassium tert-butoxide furnished the Michael adduct 47 in an unoptimized yield of 55% (Scheme 1-9). No formation of the Michael addition – Dieckmann condensation product was observed when this reaction was carried out. Further treatment of the ketoester 47 with base did not result in ring closure to form the bicyclic compound 48 (Scheme 1-10). However, upon closer inspection, the alkene that was formed was the E-isomer, and therefore it would be impossible to form a 6-membered ring with this geometry. Thus, we had to first isomerize the double bond to the Z-isomer.

Scheme 1-9. Michael addition of 46 to methyl bromomethacrylate 30 to form ketoester 47.
Scheme 1-10. Attempted formation of Dieckmann condensation to form dione 48.

![Scheme 1-10](image)

Scheme 1-11. Reported example of light activated E/Z isomerization of alkenes.

There are a number of literature procedures reported for the E/Z isomerization of alkenes.\(^8\) One example by Garcia-Exposito and coworkers is shown in Scheme 1-11, where the alkene is trisubstituted, a methyl group and ester group are on one carbon, and a large bulky substituent and hydrogen are on the other side. Under activation with ultraviolet light, an equilibrium could be effected between the two isomers. In this case, after 60 minutes in acetone, a 1:1 ratio of E- and Z-isomers was observed. Thus, we set out to isomerize our E isomer as the presumably thermodynamic isomer to the less stable Z-isomer. A number of conditions were attempted, with mixed results (Table 1-2).

A number of entries used deuterated solvent in an NMR tube for easy analysis by NMR spectroscopy. Thus, under a handheld UV lamp, a new vinyl proton appeared, but was slow to convert to product, even under prolonged reaction time. Using a strong ultraviolet lamp in
acetonitrile, slow conversion was again observed. After 6 hours at very dilute concentration in a quartz reaction flask, only 20% conversion was observed.

**Table 1-2.** *E/Z* isomerization of alkene 47.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Time</th>
<th>Molarity</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Handheld UV lamp, NMR tube</td>
<td>Acetone-d6</td>
<td>1 h</td>
<td>0.63 M</td>
<td>See new vinyl proton</td>
</tr>
<tr>
<td>2</td>
<td>Handheld UV lamp, NMR tube</td>
<td>Acetone-d6</td>
<td>12 h</td>
<td>0.63 M</td>
<td>See <em>Z</em>-isomer formation</td>
</tr>
<tr>
<td>3</td>
<td>Handheld UV lamp, NMR tube</td>
<td>Acetone-d6</td>
<td>12 h</td>
<td>0.05 M</td>
<td>Slow conversion</td>
</tr>
<tr>
<td>4</td>
<td>450W lamp, NMR tube</td>
<td>Acetonitrile-d3</td>
<td>0.5 h</td>
<td>0.05 M</td>
<td>See new vinyl proton</td>
</tr>
<tr>
<td>5</td>
<td>450W lamp, Quartz reaction flask</td>
<td>Acetone</td>
<td>6 h</td>
<td>0.05 M</td>
<td>Only 20% conversion</td>
</tr>
</tbody>
</table>

We were able to distinguish the two isomers in the 2D-NMR using nOE correlation (Scheme 1-12). The methyl ester of the *E*-isomer showed an nOE with the vinyl proton, while in the *Z*-isomer, the methyl ester is now flipped and thus there is no nOE with the vinyl proton.
The small amount of Z-isomer 51 that was isolated was used in an attempt to effect a Dieckman condensation (Scheme 1-13). However, treatment with mild basic conditions of sodium methoxide and potassium tert-butoxide gave unidentifiable products.

Scheme 1-12. nOE correlation of E-isomer 47 and Z-isomer 51.

Another possible method to form the bicyclo[3.3.1]nonane ring system is shown in Scheme 1-14. Treatment of 2,6-dimethylcyclohexanone 46 with methyl 2-(bromomethyl)acrylate 52 would undergo either an SN2 or SN2’ reaction to give 53. Ring closure to give the bicyclo[3.3.1]nonane 54, followed by final isomerization of the resulting methylene would provide access to our unsaturated natural product core. However, after the first alkylation to give 53, treatment with potassium tert-butoxide did not result in a Dieckman condensation but rather an intramolecular Michael addition to form the bicyclo[3.3.1]nonane ester 55 (Scheme 1-15).

Scheme 1-14. Attempt to perform Michael addition – Dieckmann condensation to form the bicyclicdione 54.

Scheme 1-15. Michael addition of 53 with potassium tert-butoxide to form bicyclicdione 55.

We then set out to perform a Michael addition – aldol condensation sequence with methyl methacrylate 56 instead of either methyl bromomethacrylate 30 or methyl 2-(bromomethyl)acrylate 52 to avoid the formation of the resulting E-alkene or the unexpected bicyclononane ester. Via this method, after the first Michael addition to form 57, there is free rotation around the C-C single bond so that the subsequent aldol reaction can occur to form the
bicycle 58 (Scheme 1-16). To make our desired bicyclo[3.3.1]nonane core, we would then oxidize bicycle 58 to afford the desired unsaturation of intermediate 48. This annulation/oxidation reaction sequence was used previously in efforts towards the total synthesis of hyperforin, a bicyclo[3.3.1]nonane containing natural product.10

Scheme 1-16. Application to our system.

Thus, we set out to follow Scheme 1-16 as a model system for the annulation and oxidation sequence. Since 2,6-dimethylcyclohexanone 46 was commercially available and we could quickly test this annulation-oxidation concept sequence, we started with the Michael addition with methyl methacrylate to form the ketoester 57 in 84% yield. Then, gratifyingly, treatment of 57 with potassium tert-butoxide yielded bicyclo[3.3.1]nonane 58 in 98% yield. Then, oxidation under Saegusa-Ito conditions with trimethylsilyl chloride followed by palladium acetate and oxygen then gave the dione 48 in 86% yield over two steps. Thus, we were able to prove the concept of performing this multi-step Michael – aldol sequence. With the dione 48 in hand, we had established in this model system that it was possible to do the Michael – aldol sequence. Now, we needed to carry out this sequence on a trimethylated cyclohexenone substrate.

Retrosynthetic analysis of the 2,4,6-trimethylcyclohexenone 43 is shown in Scheme 1-17. We envisioned the formation of the enone 43 via oxidation of the trimethylcyclohexanone 59
which, in turn, would come from the corresponding alcohol. The alcohol would come from complete hydrogenation of the aromatic precursor, 1,3,5-trimethylphenol \(61\).

![Scheme 1-17. Retrosynthesis to make trimethyl cyclohexenone 43.]

Table 1-3. Reduction of 1,3,5-trimethylphenol \(61\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Raney Ni-Al, KOH, H(_2)O, 90 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Raney Ni-Al, H(_2), 80 °C, 65atm, 2 d</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Raney Ni-Al, H(_2), 135 °C, 110atm, 2 d</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Rh/Al(_2)O(_3), H(_2), 40 bar, 4 d</td>
<td>Quantitative yield</td>
</tr>
</tbody>
</table>

Thus, hydrogenation of the aromatic ring of \(61\) with Raney Ni-Al\(^{11}\) was attempted (Table 1-3). However, no reaction was observed under basic conditions with potassium hydroxide, elevated temperature, or increased pressure for long periods of time under an atmosphere of hydrogen (entries 1-3). It was then found that the conditions of rhodium on alumina and high pressure of hydrogen for 4 days\(^{12}\) produced the desired secondary alcohol in quantitative yield.
Subsequent oxidation with DMP gave the corresponding ketone 59 in 75% yield (Scheme 1-18). Oxidation of the ketone 59 to the isomeric enones 43 and 62 is shown in Table 1-4. Under Saegusa-Ito conditions, the desired product 43 was isolated in 20% yield, whereas first making the phenylselenide then oxidation with hydrogen peroxide gave the desired enone 43 in 33% (entries 1-2). It was then found that instead of forming phenylselenium bromide *in situ*, using the commercially available PhSeBr reagent followed by oxidative elimination gave a mixture of the two enones 43 and 62 in a combined yield of 70%, which can be subjected to toluenesulfonic acid in refluxing benzene to obtain only enone 43.

**Table 1-4. Oxidation to enone 43.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Combined Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA, TMSCl; Pd(OAc)₂, O₂</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>LDA, HMPA, PhSeSePh, Br₂; H₂O₂</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>LDA, HMPA, PhSeBr; H₂O₂</td>
<td>70</td>
</tr>
</tbody>
</table>
With enone \(43\) in hand, we were ready to attempt the Michael – Dieckmann sequence (Scheme 1-19). When we reacted the trimethylcyclohexenone \(43\) with methyl methacrylate \(56\), we obtained very little of our desired Michael product \(63\). However, resubjecting the Michael product \(63\) to potassium tert-butoxide did not afford the expected Michael – Dieckmann product \(64\), but we instead observed formation of another bicyclic compound, namely, a bicyclo[2.2.2]octanone product. This was determined to be a result of a Michael reaction. The proposed formation of the two bicyclo[2.2.2]octanones \(67\) and \(70\) are shown in Scheme 1-20. Instead of the desired Michael – Dieckmann sequence, we observed a double Michael and/or a Michael – aldol reaction sequence.
to produce the bicyclooctanones 67 and 70. This double Michael reaction sequence has been reported previously.\textsuperscript{13} Other compounds were also formed but their structures were not identified at this time.

Because of this result, we decided to revisit our retrosynthetic analysis to make the bicyclononane core. We recognized the symmetry present in the bicyclo[3.3.1]nona-2,6-diene core. Thus, we came up with a new approach, namely, could we effect the tetraalkylation of 3-pentanone 71 with two equivalents of the readily available 3-chloro-2-(chloromethyl)prop-1-ene 72 to give the bicycle 73 (Scheme 1-21).\textsuperscript{14} Our revised retrosynthesis is shown in Scheme 1-22.


Scheme 1-22. Revised retrosynthesis.
Scheme 1-23. Formation of allyl dichloride 72.

Table 1-5. Formation of cyclohexanone 29 and bicycle 73.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃, rt, 3d</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>LDA, rt, 3d</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>LHMDS, rt, 3d</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>NaH, 90 – 100 °C, 3d</td>
<td>Multiple products</td>
</tr>
<tr>
<td>5</td>
<td>NaH, 110 °C, 12 h</td>
<td>90% yield of 73</td>
</tr>
</tbody>
</table>

First, the allyl dichloride 72 was synthesized from pentaerythritol 75 according to the literature procedure (Scheme 1-23).¹⁵ Then, treatment of 3-pentanone 71 with the allyl dichloride 72 with excess base of potassium carbonate, LDA, and LHMDS gave no reaction (Table 1-5).
Presumably, the conditions were either not strongly basic enough or due to steric hindrance, the quaternary centers were unable to be formed effectively. In toluene at 90 – 100 °C using four equivalents of sodium hydride, a multitude of products were formed. One of the byproducts that we observed was the O-alkylated product 79. At the higher temperature of refluxing toluene, we were able to effect the highly efficient tetraalkylation to form the bicycle 73 in 90% isolated yield.

![Figure 1-5. Side product 79.](image)

With the bicyclo[3.3.1]nonane 73 in hand, we then turned our attention to the isomerization of the exo-methylenes to the internal, trisubstituted alkenes. However, upon closer inspection, one realizes there are two possible isomers that can form, namely, the C2 isomer 74, with an axis of symmetry going through the carbonyl, or the C5 isomer 80, with a plane of symmetry again going through the carbonyl.

![Scheme 1-24. Isomerization of bicycle 73 to give two isomers, 74 and 80.](image)
through the carbonyl. Our initial inspection using Dreiding models led us to the prediction that the C2 isomer would be favored, as the Cs isomer has two interacting allylic protons (Scheme 1-24). We decided to investigate the stability of the two structures computationally.

The initial calculations were done by Max Koepelevich, using B3LYP/6-31G calculations (Figure 1-6). He found that the C2 isomer was more stable than the Cs isomer by 3.3 kcal/mol. We then collaborated with Hung Pham in the laboratory of Professor Ken Houk and developed a methodology of palladium hydride promoted stereoselective isomerization of unactivated di(exo)methylenes to endocyclic dienes (Scheme 1-25; also, see Chapter 2 of this dissertation).

**Figure 1-6.** 3D structures of isomers 74 and 80 by Max Kopelevich.

**Scheme 1-25.** Isomerization of bicycoketone 73 with catalytic palladium on charcoal.
With the bicyclo[3.3.1]nonane C₂ isomer 74 in hand, we then set out to functionalize the symmetric bicycle with a functional handle in order to attached our southern side chain. Allylic oxidation conditions were tried to effect a mono-allylic oxidation of the completely symmetric compound. Thus, only slightly more than one equivalent of reagent was used in all the cases (Table 1-6). Manganese oxide and palladium acetate under acetic acid conditions returned predominantly starting material. Treatment with selenium oxide under a variety of conditions gave starting material and possibly traces of other product. In one case, under tert-butanol conditions, we observed via GCMS the possible formation of the overoxidized trione 82 but could not confirm the structure via NMR. Attempts to form the allylic bromide were made using reagents such as NBS and bromine, but a mixture of compounds were formed.

Table 1-6. Attempted allylic oxidation of bicycle 74.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂, MnO₂, AcOH</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>SeO₂, DMSO</td>
<td>Mixture</td>
</tr>
<tr>
<td>3</td>
<td>SeO₂, tBuOOH</td>
<td>Mixture</td>
</tr>
<tr>
<td>4</td>
<td>SeO₂, tBuOH</td>
<td>Product + trione 82</td>
</tr>
<tr>
<td>5</td>
<td>SeO₂, DMSO</td>
<td>Mixture</td>
</tr>
<tr>
<td>6</td>
<td>NBS or Br₂</td>
<td>Mixture</td>
</tr>
</tbody>
</table>
Figure 1-7. Overoxidized trione 82.

We then turned our attention to installing the northern side chain first. We thought of a way to make an “aldol equivalent” as shown in Scheme 1-26. The addition of dianions to sterically congested carbonyls has been reported by Kowalski and coworkers\textsuperscript{16} and it seemed applicable to our neopentyl ketone system to install the northern side chain in a single step.

Scheme 1-26. Approach to install the northern side chain.

Application of the dianion concept to our system is shown in Scheme 1-27. First, the bromo enol acetate 85 was treated with methyllithium and two equivalents of tert-butyl lithium to form the dilithiate 86, which could then add to the bicyclic ketone 74 to form intermediate 87. Tautomerization to 88 and β-elimination would form 89. Either 89 could have been isolated and later isomerized, or the compound might have isomerized \textit{in situ} to the more stable isomer 84.
Before applying this idea to the real system, a few preliminary reactions were carried out (Scheme 1-28). First, to reproduce the literature results, acetophenone 90 was treated with bromine, followed by LDA and acetic anhydride to form the bromo enol acetate (Scheme 1-28). Treatment of this intermediate with methyllithium and tert-butyllithium formed the dianion in situ,

\[ \text{dianion addition control experiment.} \]

and it was able to add to cyclohexanone 92 to form the ketoalcohol 93, as reported. Next, another control experiment was carried out using our real dianion nucleophile that has an additional methyl group with cyclohexanone. However, the bromo enol acetate 94 and cyclohexanone gave a product that had a molecular weight two less than the expected product. We believe what occurred is shown in Scheme 1-29. After forming the first lithiate, instead of undergoing a metal-halogen exchange,
tert-butyllithium instead deprotonated the terminal proton to form the allenoate 99, which then added to cyclohexanone to form the ketoalcohol 100, which has a molecular weight two less than the desired and expected product 96.

![Scheme 1-29. Reaction of 94 with cyclohexanone.](image)

Even though this was the case, we decided to try this method on our system. However, using the bromo enol acetate 94 with our bicyclo[3.3.1]nonanone 74, only formation of the tert-butyllithium adduct of the ketone, namely the alcohol 101, was observed (Scheme 1-30). This is surprising in that not only did neither the dianion nor the allenoate add to the ketone, but instead tert-butyllithium added as a very hindered nucleophile to the very hindered ketone. This result might be because of the steric hindrance of our substrate, and thus only a very harsh nucleophile such as tert-butyllithium was able to add, even though it is extremely hindered. When the bromo
trimethylsilyl enol 102 was used, no reaction was observed. When we used the iodo analogue 103, again we saw only addition of the tert-butyl group to give the alcohol 101.

**Scheme 1-30.** Reaction of dianion substrates with bicycle 74.

We decided next to adopt a stepwise approach to forming the northern side chain. Thus, the epoxide 102 would be formed, followed by ring opening to form the aldehyde 103, addition of methyllithium and oxidation to form the ketone 104. Treatment with phenyl triflate to form the enol triflate 105, and then a final Heck coupling would form the northern side chain (Scheme 1-31).
Scheme 1-32. Formation of epoxide 102 from diene 74.

Table 1-7. Opening of epoxide 102.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsOH</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>H₃PO₄: DMSO</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Ti(OiPr)₄</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Ti(OiPr)₄, Mg, TMSCl</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃, reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>Et₂AlCl</td>
<td>Decomposition</td>
</tr>
<tr>
<td>8</td>
<td>BF₃.OEt₂</td>
<td>13 spots!</td>
</tr>
</tbody>
</table>

The forward synthesis started with the epoxidation of the bicycle 74 with Corey’s reagent which afforded the epoxide 102 in quantitative yield (along with grease from the sodium hydride). However, a variety of conditions were tried to effect epoxide rearrangement, all to no avail (Table 1-7). Acids such as tosic acid and phosphoric acid gave no reaction (entries 1-2). Milder Lewis
acidic conditions such as treatment with titanium isopropoxide, chloroform, diethylaluminum chloride or tin tetrachloride also gave no conversion to product. Treatment with boron trifluoride etherate gave a multitude of spots.

**Scheme 1-33.** Revised synthesis of methyl ketone 104.

At this point, a different approach was considered, namely using a Wittig olefination or a Horner reaction to form the methyl ketone 104 (Scheme 1-33). There were only two examples of a highly substituted Horner reaction using substituted diphenylphosphine oxide 107 in the literature. Since the additional methyl substituent is already there, this sequence would only require two steps from the ketone to make the methyl ketone functionality of 104. However, under a variety of conditions, the hindered Horner reaction did not produce high yields, with the best conditions producing only a 25% conversion to the enol ether 108 by GCMS (Scheme 1-34). Hydrolysis of the enol ether 108 gave a quantitative yield of the methyl ketone 104.

Thus, a longer, four-step sequence was used instead to introduce the methyl ketone to the bicyclononane ketone from which the northern side chain could be built (Table 1-8). Using methoxymethyltriphenylphosphonium chloride with phenyllithium or sodium hydride, we observed a complicated mixture of products. No reaction was observed when we attempted a Peterson olefination using the trimethylsilyl analogue. Finally, after making the methoxymethylphosphine
Scheme 1-34. Hindered Horner reaction to the form methyl ketone 104.

oxide from the corresponding methoxymethyltriphenylphosphonium chloride, treatment of the phosphine oxide with LDA in the presence of the ketone 74 gave 40% yield of the methyl enol ether 109. Hydrolysis gave the aldehyde 103 in quantitative yield.

Table 1-8. Horner reaction for formation of aldehyde 103.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃PCH₂OCH₃Cl, PhLi</td>
<td>Mixture (works well with cyclohexanone)</td>
</tr>
<tr>
<td>2</td>
<td>Ph₃PCH₂OCH₃Cl, NaH, DMSO</td>
<td>Mixture</td>
</tr>
<tr>
<td>3</td>
<td>TMSCH₂OMe, sBuLi</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Ph₂POCH₂OCH₃, LDA</td>
<td>40%</td>
</tr>
</tbody>
</table>

Conversion of the aldehyde 103 to the methyl ketone 104 was uneventful. Treatment with methyllithium and subsequent Dess-Martin oxidation proceeded in 85% over two steps to give methyl ketone 104 (Scheme 1-35).
Scheme 1-35. Conversion of aldehyde 103 to methyl ketone 104.

Scheme 1-36. Heck coupling to install northern side chain.

With the methyl ketone 104 in hand, we then attempted to install the northern side chain via a Heck coupling, as shown in Scheme 1-36. Formation of the enol triflate 105 and treatment with ethoxypropene 106 with palladium would furnish ketone 84.

Scheme 1-37. Model system for Heck coupling.

First, we performed the reaction sequence on a model system, as shown in Scheme 1-37. Treatment of methyl isopropyl ketone 110 with lithium bis(trimethylsilyl)amide and N-phenyltriflimide selectively formed the less substituted enol triflate 111. Addition of
ethoxypropene 106 and tetrakis- (triphenylphosphine)palladium and triethylamine furnished the Heck coupling product 112 in trace amounts.

With this proof-of-concept reaction in hand, we then applied the approach to our system (Scheme 1-38). However, treatment of the enol triflate 105 with ethoxypropene 106 under identical conditions to those previously used in our model system did not furnish any desired product and instead gave a multitude of products. One of the side products isolated was the alkyne 113, the result of the β-elimination of the highly reactive enol triflate.

Scheme 1-38. Attempted Heck coupling to form northern side chain.

Our next approach to installing the northern side chain was to perform a Shapiro reaction, and the application to the same model system is shown in Scheme 1-39. Hydrazone 115 was first synthesized from the corresponding ketone 110 and p-toluenesulfonyl hydrazine 114. However, reaction with the Weinreb amide 116 did not furnish the expected alkene products 117 or 118. Instead, a cyclization occurred and the hydroxyl dihydropyrazole 119 was isolated.
Scheme 1-39. Attempted Shapiro reaction.

With the failure to install the northern side chain, we then turned our attention to forming the southern side chain by making the selectively protected diol 124 (Scheme 1-40). Synthesis of the southern side chain was based on literature precedent,20 starting with the Prins reaction of cyclopentadiene and formaldehyde to form the diol 122. Selective primary tosylation would give intermediate 123, then TBS protection would furnish the protected diol 124.

Scheme 1-40. Proposed synthesis of the southern side chain.
The Prins reaction of cyclopentadiene and formic acid gave a mixture of all four stereoisomers (Scheme 1-41). Although all four products 125, 126, 127, and 128 are very close stereoisomers, we were able to separate the compounds on silica gel chromatography, using a 1:100 product: silica gel ratio in a 19:1 dichloromethane:methanol solvent system.

\[
\text{Scheme 1-41. Formation of diols 125, 126, 127, and 128.}
\]

Thus, we decided to protect the diol diastereomer necessary for our natural product, 125, with silyl protecting groups. Selective tosylation of the diol 125 was achieved in a moderate yield of 38% to give the alcohol 129 (Scheme 1-42). Secondary alcohol protection with TBSCl gave 124 in 89% yield.

\[
\text{Scheme 1-42. Selective protections of diol 125 to give compound 124.}
\]

Even though we were able to prepare the protected tosylate 124, we did not pursue the attachment of the southern side chain due to time constraints.
CONCLUSION

A potential strategy toward the synthesis of rugulosone has been investigated. Although initial efforts towards forming the bicyclo[3.3.1]nonane core via a Michael addition – Dieckmann condensation reaction sequence did not prove successful, the synthesis of the core was accomplished via a highly efficient tetraalkylation of commercially available starting materials. This methodology of isomerization of unactivated alkenes produced the C2 symmetric core. Studies toward the addition of the northern side chain have been conducted, and look promising. Synthesis of southern side chain has been accomplished, and is ready to be coupled with the functionalized core to facilitate a highly divergent synthesis of the natural product.
EXPERIMENTAL

General

All reactions were carried out under an argon atmosphere unless otherwise specified. Methylene chloride was distilled from calcium hydride under an argon atmosphere. All other solvents or reagents were purified according to literature procedures. $^1$H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), integration, multiplicity and coupling constant (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. $^{13}$C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). HPLC purification was conducted on a Shimadzu HPLC system with a refractive index detector RID-10A and one Luna 5 μm C18(2) column with acetonitrile and water as an eluent. High resolution mass spectrometry was taken on a Thermo Fisher Scientific Exactive Plus mass spectrometer equipped with an IonSense ID-CUBE DART ion source.

Methyl (E)-3-(1,3-dimethyl-2-oxocyclohexyl)-2-methylpropenoate, 47.

To a suspension of potassium tert-butoxide (2.02 g, 18.0 mmol) in THF (15 mL) was added 2,6-dimethylcyclohexanone (0.822 mL, 6.0 mmol) in THF (20 mL) at -78 °C. The reaction was stirred for 1.5 h. A solution of methyl bromomethacrylate (1.45 mL, 12.0 mmol) in THF (10 mL) was added and the reaction continued to stir at -78 °C for 3 h. The solution was then quenched with a saturated solution of NH$_4$Cl (30 mL), extracted with diethyl ether (3 x 30 mL), washed with
brine (30 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester 47 (0.74 g, 3.29 mmol, 55%) as a light yellow oil.

$^1$H NMR (400 MHz, CDCl₃) δ:

6.91 (s, 1H)

3.71 (s, 3H)

2.59 (ddq, $J = 17.8, 6.4, 6.4$ Hz, 1H)

2.04 (dq, $J = 14.0, 3.2$ Hz, 1H)

1.99 (m, 1H)

1.81 (dddd, $J = 13.5, 13.5, 13.5, 3.5$ Hz, 1H)

1.64 (m, 1H)

1.59 (s, 3H)

1.48 (ddd, $J = 13.6, 13.6, 3.6$ Hz, 1H)

1.29 (dddd, $J = 12.8, 12.8, 12.8, 3.6$ Hz, 1H)

1.12 (s, 3H)

0.95 (d, $J = 6.4$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl₃) δ 215.3, 168.4, 146.3, 129.5, 51.9, 51.6, 44.5, 42.9, 38.0, 22.4, 21.8, 14.7, 12.4.

GCMS ($m/z$): 224.2.
**1,3,5-Trimethylbicyclo[3.3.1]non-3-ene-2,9-dione, 48.**

To a solution of diisopropylamine (0.35 mL, 2.5 mmol) in THF (5 mL) was added n-butyllithium (2.5 M in hexanes, 1.0 mL, 2.5 mmol) at -78 °C. The reaction flask was warmed to 0 °C for 30 min, and a solution of dione 58 (0.194 g, 1.0 mmol) in THF (3 mL) was added. The flask was cooled to -78 °C, a solution of TMSCl (0.50 mL, 4.0 mmol) in THF (1 mL) was added, then warmed to 0 °C and let stir for 2 h. The reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (3 X 10 mL), washed with brine (30 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated *in vacuo* to give an oil. The crude mixture was then dissolved in DMSO (3 mL). Palladium acetate was added (0.112 g, 5.0 mmol) and the reaction mixture was left to stir overnight under an atmosphere of oxygen. The reaction was quenched with water (5 mL), and extracted with ethyl acetate (3 X 10 mL), washed with brine (30 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated *in vacuo* to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dione 48 (0.167 g, 0.86 mmol, 86%) as a light yellow oil.

**1H NMR (500 MHz, CDCl₃) δ:**

6.50 (bq, *J* = 1.5 Hz, 1H)
1.97 (m, 1H)
1.90 (s, 3H)
1.79 (bd, *J* = 12.5 Hz, 1H)
1.69 (m, 2H)
1.57 (m, 2H)
1.27 (s, 3H)
1.23 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 210.6, 200.9, 148.0, 138.4, 61.7, 49.5, 41.8, 38.4, 21.4, 18.9, 16.2, 15.6.

GCMS ($m/z$): 192.0.

**Methyl (Z)-3-(1,3-dimethyl-2-oxocyclohexyl)-2-methylpropenoate, 51.**

A solution of ketoester 47 (0.100 g, 4.46 mmol) in acetone (9 mL) was added to a quartz reaction flask, then subjected to a 450W mercury UV lamp for 6 h. The solution was then concentrated *in vacuo*. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester 51 (0.020 g, 0.892 mmol, 20%) as a light yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$:

6.01 (q, $J$ = 1.6 Hz, 1H)

3.61 (s, 3H)

2.75 (ddq, $J$ = 12.8, 6.4, 6.4 Hz, 1H)

2.00 – 1.90 (m, 1H)

1.97 (d, $J$ = 1.6 Hz, 3H)

1.75 (dddd, $J$ = 13.6, 13.6, 13.6, 3.6 Hz, 1H)

1.61 (m, 2H)

1.50 (td, $J$ = 13.6, 4.0 Hz, 1H)

1.35 – 1.25 (m, 1H)
1.15 (s, 3H)
0.95 (d, $J = 6.4$ Hz, 3H).

**Methyl 2-((1,3-dimethyl-2-oxocyclohexyl)methyl)acrylate, 53.**

To a suspension of potassium tert-butoxide (0.067 g, 0.60 mmol) in THF (3 mL) was added 2,6-dimethylcyclohexanone (0.068 mL, 0.50 mmol) in THF (2 mL). The reaction was cooled to -78 °C, then a solution of methyl bromomethylacrylate 52 (0.09 mL, 0.50 mmol) in THF (2 mL) was added dropwise. The reaction was stirred for 1.5 h, then quenched with a saturated solution of NH₄Cl (10 mL), extracted with ethyl acetate (3 × 15 mL), washed with brine (15 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester 53 (0.082 g, 0.44 mmol, 73%) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl₃) $\delta$:

6.18 (d, $J = 1.0$ Hz, 1H)

5.47 (bs, 1H)

3.69 (s, 3H)

3.04 (d, $J = 14.0$ Hz, 1H)

2.91 (ddq, $J = 13.0, 6.5, 6.5$ Hz, 1H)

2.36 (d, $J = 14.0$ Hz, 1H)

2.05 (m, 1H)

1.97 (qt, $J = 13.5, 3.7$ Hz, 1H)

1.86 (dq, $J = 13.7, 3.0$ Hz, 1H)
1.63 (bd, $J = 13.6$ Hz, 1H)
1.54 (td, $J = 13.5$, 4.0 Hz, 1H)
1.32 (qd, $J = 13.0$, 4.0 Hz, 1H)
0.99 (d, $J = 6.5$ Hz, 3H)
0.93 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 216.3, 167.7, 136.8, 128.2, 51.9, 48.6, 41.7, 41.4, 39.5, 36.6, 22.5, 21.2, 15.0.

GCMS ($m/z$): 224.1.

Methyl 3-(1,3-dimethyl-2-oxocyclohexyl)-2-methylpropanoate, 57.

To a suspension of potassium tert-butoxide (3.36 g, 30.0 mmol) in THF (30 mL) was added 2,6-dimethylcyclohexanone (1.37 mL, 10.0 mmol) in THF (10 mL) at -78 °C and stirred for 0.5 h. A solution of methylmethacrylate (1.60 mL, 15.0 mmol) in THF (20 mL) was added and the reaction continued to stir at -78 °C for 4 h. The solution was then quenched with a saturated solution of NH$_4$Cl (30 mL), extracted with diethyl ether (3 X 30 mL), washed with brine (30 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester 57 (1.90 g, 8.4 mmol, 84%) as a light yellow oil. The product is a mixture of at least diastereomers. The proton NMR is of the major diastereomer.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$:

3.65 (s, 3H)
2.57 (m, 1H)
2.42 (m, 1H)
1.99 (m, 2H)
1.84 (m, 1H)
1.75 – 1.47 (m, 4H)
1.38 – 1.24 (m, 1H)
1.19 (d, $J$ = 6.9 Hz, 3H)
1.14 (d, $J$ = 4.8 Hz, 3H)
0.97 (d, $J$ = 6.6 Hz, 3H).

The $^{13}$C data is for the mixture of diastereomers.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 216.7, 216.6, 216.4, 178.4, 178.3, 176.9, 51.7, 51.6, 51.5, 48.6, 43.0, 42.5, 41.2, 40.9, 40.8, 39.4, 37.9, 36.8, 36.6, 36.3, 36.2, 35.9, 35.4, 24.1.

**1,3,5-Trimethylbicyclo[3.3.1]nonane-2,9-dione, 58.**

To a suspension of potassium tert-butoxide (1.50 g, 13.3 mmol) in THF (20 mL) was added ketoester 57 (2.0 g, 4.4 mmol) in THF (10 mL) at -78 °C and slowly warmed to 21 °C and stirred for 1 h. The solution was then cooled to -78 °C, quenched with a saturated solution of NH$_4$Cl (30 mL), extracted with diethyl ether (3 X 30 mL), washed with brine (30 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give a crude oil.
Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dione 58 (0.83 g, 4.3 mmol, 98%) as a light yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.34 (bd, $J = 11.0$ Hz, 1H) 2.19 (m, 1H) 1.89 – 1.87 (m, 2H) 1.62 (dd, $J = 15.5$, 4.0 Hz, 1H) 1.57 (tdd, $J = 13.0$, 13.0 Hz, 1H) 1.50 (bd, $J = 12.5$ Hz, 2H) 1.43 (m, 1H) 1.21 (s, 3H) 1.11 (s, 3H) 1.08 (d, $J = 6.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 214.7, 214.1, 60.8, 46.2, 44.6, 43.9, 42.7, 38.2, 24.8, 19.7, 17.9, 13.2.

GCMS ($m/z$): 194.1.

**Methyl 2-methyl-3-(1,3,5-trimethyl-2-oxocyclohex-3-en-1-yl)propanoate, 63.**

To a suspension of potassium tert-butoxide (0.17 g, 1.52 mmol) in THF (5 mL) was added 2,4,6-trimethylcyclohex-2-en-1-one 43 (0.07 g, 0.51 mmol) in THF (2 mL) at -78 °C and stirred for 0.5 h. A solution of methyl methacrylate (0.08 mL, 0.76 mmol) in THF (2 mL) was added and
the reaction continued to stir at -78 °C for 3 h. The solution was then quenched with a saturated solution of NH₄Cl (20 mL), extracted with ethyl acetate (3 X 20 mL), washed with brine (20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the ketoester 63 (0.004 g, 0.017 mmol, 6%) as a light yellow oil as a mixture of mostly two diastereomers. The NMR data is for the mixture of diastereomers.

¹H NMR (500 MHz, CDCl₃) δ:

- 6.78 (s, 1H)
- 3.69 (s, 1.8H)
- 3.65 (s, 1.2H)
- 2.52 (m, 1H)
- 2.40 (m, 1H)
- 2.21 (s, 3H)
- 2.07 (m, 2H)
- 1.92 – 1.77 (m, 2H)
- 1.38 (d, J = 4.4 Hz, 3H)
- 1.25 (d, J = 7.2 Hz, 3H)
- 1.08 (d, J = 7.2 Hz, 3H)
- 0.98 (d, J = 7.2 Hz, 3H).


To a suspension of potassium tert-butoxide (0.17 g, 1.52 mmol) in THF (5 mL) was added 2,4,6-trimethylcyclohex-2-en-1-one 63 (0.07 g, 0.51 mmol) in THF (2 mL) at -78 °C and stirred
for 0.5 h. A solution of methyl methacrylate (0.08 mL, 0.76 mmol) in THF (2 mL) was added and the reaction continued to stir at -78 °C for 3 h. The solution was then quenched with a saturated solution of NH₄Cl (20 mL), extracted with ethyl acetate (3 X 20 mL), washed with brine (20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the bicyclo[2.2.2]octane 67 (0.019 g, 0.085 mmol, 27%) as a light yellow oil.

¹H NMR (500 MHz, CDCl₃) δ:
3.64 (s, 3H)
2.55 (m, 2H)
2.51 (m, 1H)
2.01 (bs, 1H)
1.81 (dd, J = 17.0, 13.0 Hz, 1H)
1.37 (s, 3H)
1.25 (d, J = 18.0 Hz, 1H)
1.08 (ddd, J = 15.5, 7.5, 3.5 Hz, 1H)
1.04 (d, J = 9.0 Hz, 3H)
0.97 (d, J = 9.5 Hz, 3H)
0.95 (s, 3H).

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one, 73.

To a suspension of 60% NaH in mineral oil (0.176 g, 4.40 mmol) (washed three times with hexanes) in toluene (5 mL) was added dropwise 3-pentanone (0.086 g, 1.00 mmol) in toluene (2
mL). A solution of 1-chloro-2-(chloromethyl)-2-propene (0.254 g, 2.20 mmol) in toluene (2 mL) was added dropwise and the reaction was refluxed overnight. The solution was then cooled to room temperature and quenched with a saturated solution of NH₄Cl (20 mL). The mixture was extracted with ethyl acetate (3 X 20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the bicyclononanone 73 (0.171 g, 0.90 mmol, 90%) as a light yellow oil.

1H NMR (500 MHz, CDCl₃) δ
4.73 (s, 4H)
2.57 (d, J = 15.0 Hz, 4H)
2.42 (d, J = 15.0 Hz, 4H)
1.03 (s, 6H).

13C NMR (125 MHz, CDCl₃) δ 218.5, 141.8, 112.7, 49.7, 45.3, 23.5.


(±) (1R,5R)-1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-dien-9-one, 74.

To a solution of the bicyclononanone 73 (0.050 g, 2.63 mmol) in ethyl acetate (5 mL) was added palladium (10 wt. % on activated carbon) (0.011 g, 0.11 mmol). The reaction vessel was then purged with a hydrogen balloon for 5 min, then allowed to stir at ambient temperature and pressure for 1 h. The mixture was then filtered over Celite, washed with ethyl acetate (15 mL),
then concentrated in vacuo to give diene 74 and other products (0.50 g, 2.63 mmol, 100%) as a light yellow oil. The crude mixture was then purified via HPLC.

\[^1^H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta\]

5.14 (2H, s)
2.27 (2H, d, \(J = 17.0 \text{ Hz}\))
2.22 (2H, d, \(J = 17.0 \text{ Hz}\))
1.65 (6H, s)
1.07 (6H, s).

\[^{13}C \text{NMR} (125 \text{ MHz, CDCl}_3) \delta\]

216.6, 132.8, 130.9, 48.5, 45.5, 22.3, 21.1.

HRMS (ESI, \(m/z\)): 191.1425, calculated for \([\text{C}_{13}\text{H}_{19}\text{O}] \) 191.1436.

(\pm)(1^R,5^R)-9-[(1,1-Dimethylethyl)-1,3,5,7-tetramethylbicyclo[3.3.1]nona-2,6-dien-9-ol, 101.

To 2,2'-bipyridyl (0.010 g, 0.64 mmol) was added methyllithium (1.4M in diethyl ether, 0.36 mL, 0.52 mmol) at -78 °C. The solution was warmed to room temperature to remove the diethyl ether. Dimethoxyethane (2 mL) was added at 0 °C, warmed to room temperature for 6 min, then cooled to -78 °C. Tert-butyllithium (1.7 M solution in pentane, 0.34 mL, 0.2 mmol) was added and stirred for 10 min. The bicycle 74 (0.05 g, 0.26 mmol) was then added to the mixture and stirred for 2 h. The reaction was then quenched with 1M HCl (10 mL), extracted with ethyl ether (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO4, filtered and concentrated in vacuo to give an oil. Purification by flash column
chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the bicycle 101 (0.006 g, 0.023 mmol, 9%) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

4.97 (s, 1H)
4.75 (s, 1H)
2.25 (d, $J$ = 17.0 Hz, 1H)
2.20 (d, $J$ = 17.5 Hz, 1H)
1.80 (d, $J$ = 18.0 Hz, 1H)
1.59 (s, 3H)
1.57 (s, 3H)
1.42 (d, $J$ = 17.5 Hz, 1H)
1.26 (s, 3H),
1.21 (s, 3H),
1.15 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 136.0, 132.9, 131.9, 131.8, 45.5, 44.9, 43.8, 43.0, 41.3, 32.0, 31.5, 27.2, 26.9, 22.7, 22.4.

(±)(1R,5R)-1,3,5,7-Tetramethylspiro[bicyclo[3.3.1]nonane-9,2'-oxirane]-2,6-diene

To a solution of the bicycle 74 (1.0 g, 5.3 mmol) in THF (20 mL) was added a solution of NaH (0.32 g, 7.8 mmol) and trimethylsulfoxonium iodide (1.7 g, 7.8 mmol) in DMSO (10 mL). The reaction was stirred overnight. The reaction was then quenched with water (20 mL), extracted
with ethyl acetate (5 X 20 mL), washed with brine (20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated *in vacuo* to give epoxide **102** (1.1 g, 5.5 mmol, 100%) as a crude yellow oil that was used without further purification.

**1H NMR (500 MHz, CDCl₃) δ:**

- 5.12 (s, 1H)
- 5.05 (s, 1H)
- 2.77 (s, 2H)
- 2.17 – 2.05 (m, 4H)
- 1.65 (s, 3H)
- 1.63 (s, 3H)
- 0.85 (s, 3H)
- 0.80 (s, 3H).

**13C NMR (125 MHz, CDCl₃) δ:**

132.4, 131.9, 130.7, 129.6, 64.2, 46.3, 45.4, 42.5, 36.1, 35.4, 23.0, 22.8, 21.4, 20.8.

**GCMS (m/z):** 204.2.

**1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-diene-9-carbaldehyde, 103.**

To a solution of the enol ether **109** (0.44 g, 2.0 mmol) in THF (20 mL) was added a solution of 2M HCl (10 mL). The reaction was stirred at 21 °C for 3 h. The reaction was then extracted with ethyl acetate (3 X 40 mL), washed with brine (50 mL) and the combined organic extracts
were dried with MgSO₄, filtered and concentrated in vacuo to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the aldehyde 103 (0.41 g, 2.0 mmol, 99%) as a light yellow oil.

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3) \delta: \\
9.55 (\text{d, } J = 6.5 \text{ Hz, 1H}) \\
5.18 (\text{s, 1H}) \\
5.07 (\text{s, 1H}) \\
1.96 (\text{d, } J = 18.5 \text{ Hz, 1H}) \\
1.86 (\text{d, } J = 6.5 \text{ Hz, 1H}) \\
1.85 (\text{d, } J = 16.5 \text{ Hz, 1H}) \\
1.77 (\text{d, } J = 18.0 \text{ Hz, 1H}) \\
1.68 (\text{d, } J = 17.0 \text{ Hz, 1H}) \\
1.67 (\text{s, 3H}) \\
1.60 (\text{s, 3H}) \\
1.03 (\text{s, 3H}) \\
1.01 (\text{s, 3H}).
\end{align*}
\]

\[
\begin{align*}
\text{C NMR (125 MHz, CDCl}_3) \delta 208.5, 132.5, 131.7, 131.5, 128.3, 81.1, 44.8, 40.4, 35.6, 34.6, 26.8, 26.4, 23.0, 22.8.
\end{align*}
\]

HRMS (ESI, \text{m/z}): 204.1590, calculated for C_{14}H_{21}O (M+H)^+ 204.1514.
1-(1,3,5,7-Tetramethylbicyclo[3.3.1]nona-2,6-dien-9-yl)ethan-1-one, 104.

To a solution of the aldehyde 109 (0.2 g, 0.979 mmol) in THF (2 mL) was added methylmagnesium bromide (3M solution in diethyl ether, 4.4 mL, 1.47 mmol) at 0 °C. The reaction was stirred for 3 h, then quenched with a solution of Na2S2O3 (5 mL), extracted with ethyl acetate (3 X 10 mL), washed with brine (50 mL) and the combined organic extracts were dried with MgSO4, filtered and concentrated in vacuo to give an oil. The crude oil was the redissolved in dry ethyl acetate (5 mL) and IBX was added (0.82 g, 2.9 mmol). The solution was heated to 80 °C for 2 h. The solution was cooled to room temperature, excess IBX was filtered off, then concentrated in vacuo to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the methyl ketone 104 (0.18 g, 0.83 mmol, 85%) as a light yellow oil.

1H NMR (500 MHz, CDCl3) δ:

5.07 (s, 1H)
4.94 (s, 1H)
2.54 (s, 1H)
2.15 (s, 3H)
2.09 (d, J = 17.5 Hz, 1H)
1.93 (d, J = 17.5 Hz, 1H)
1.69 (d, J = 17.5 Hz, 1H)
1.65 (s, 3H)
1.57 (s, 3H)
1.53 (d, J = 17.0 Hz, 1H)
1.00 (s, 3H)
0.99 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.3, 133.3, 132.7, 131.2, 126.3, 61.1, 46.4, 39.8, 35.8, 35.7, 34.8, 26.8, 25.5, 23.1, 22.8.

HRMS (ESI, $m/z$): 219.1739, calculated for C$_{15}$H$_{23}$O (M+H)$^+$ 219.1749.

**9-(Methoxymethylene)-1,3,5,7-tetramethylbicyclo[3.3.1]nona-2,6-diene, 109.**

To a solution of diisopropylamine (2.43 mL, 17.0 mmol) in THF (30 mL) was added $n$-butyllithium (2.0 M in hexanes, 8.31 mL, 16.8 mmol) at -78 °C. The reaction flask was warmed to 0 °C for 30 min then cooled back to -78 °C. Diphenyl(methoxymethyl)phosphine oxide (4.53 g, 18.4 mmol) was added, followed by a solution of the bicycle 74 (1.0 g, 5.3 mmol) in THF (10 mL). The reaction mixture was stirred for 4 h. After disappearance of all starting material by TLC, the reaction was quenched with water (20 mL), extracted with ethyl acetate (3 X 50 mL), washed with brine (50 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo to give an oil. The crude oil in THF (10 mL) was then added to a solution of washed NaH (2.1 g, 52.6 mmol) in THF (30 mL) and let stir for 16 h. The solution was then cooled to 0 °C, quenched with water (30 mL), extracted with ethyl acetate (3 X 50 mL), washed with brine (50 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dione 109 (0.45 g, 2.1 mmol, 40%) as a light yellow oil.
1H NMR (500 MHz, CDCl3) δ:
5.69 (s, 1H)
5.07 (s, 1H)
4.97 (s, 1H)
3.48 (s, 3H)
2.13 (bd, \(J = 17.0\) Hz, 1H)
1.92 (bd, \(J = 17.0\) Hz, 1H)
1.79 (bd, \(J = 17.0\) Hz, 1H)
1.70 (bd, \(J = 17.0\) Hz, 1H)
1.58 (s, 6H)
1.42 (s, 3H)
1.10 (s, 3H).

(±)(1\text{R,5R})-9-Ethynyl-1,3,5,7-tetramethylbicyclo[3.3.1]nona-2,6-diene, 113.

To a solution of the methyl ketone 104 (0.16 g, 0.73 mmol) in THF (2 mL) was added lithium bis(trimethylsilyl)amide (LHMDS, 0.9 M solution in THF, 0.9 mL, 0.81 mmol) at -78 °C. The reaction was warmed to 0 °C for 0.25 h, then cooled to -78 °C. N-Phenyl-bis(trifluoromethanesulfonimide) (0.29 g, 0.81 mmol) in THF (1 mL) was added slowly, then the reaction was warmed to 0 °C and continued to stir for 2 h. The solution was quenched with a saturated solution of NaHCO₃ (10 mL), extracted with diethyl ether (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated.
in vacuo to give the crude enol triflate 105 as a light yellow oil. The crude enol triflate 105 was then dissolved in DMSO (1.6 mL) in a screw cap flask, to which the ethoxy propene 106 (0.32 g, 3.6 mmol), palladium (II) acetate (0.005 g, 0.022 mmol), and triethylamine (0.15 mL, 1.1 mmol) were added. The reaction mixture was heated to 60 °C for 3 h. The reaction was then quenched with dropwise addition of water (5 mL), extracted with hexanes (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give the alkyne 113 in trace amounts as a light yellow oil.

\[ \text{1H NMR (400 MHz, CDCl3)} \delta: \]

5.09 (bs, 1H)
4.97 (bs, 1H)
2.17 (d, \( J = 3.5 \) Hz, 1H)
1.89 (bd, \( J = 21.0 \) Hz, 1H)
1.70 (d, \( J = 21.0 \) Hz, 1H)
1.64 (d, \( J = 23.0 \) Hz, 1H)
1.63 (s, 3H)
1.59 (s, 3H)
1.50 (d, \( J = 21.5 \) Hz, 1H)
1.19 (s, 3H)
1.14 (s, 3H)
1.00 (d, \( J = 3.5 \) Hz, 1H).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 132.6, 131.2, 130.5, 127.5, 84.2, 70.8, 44.4, 43.6, 39.7, 35.8, 35.5, 27.2, 26.9, 23.2, 22.9.

HRMS (ESI, $m/z$): 201.1628, calculated for C$_{15}$H$_{21}$ (M+H)$^+$ 201.1643.

5-Ethyl-3-isopropyl-1-(4-methylphenylsulfonyl)-4,5-dihydro-1$H$-pyrazol-5-ol, 119.

To a solution of hydrazone 115 (0.20 g, 0.78 mmol) in hexane (2 mL) and TMEDA (2 mL) was added sec-butyllithium (0.87 M solution in cyclohexane, 2.0 mL, 1.7 mmol) at -55 °C. The solution was stirred at this temperature for 2 h, then at 0 °C for 0.5 h. A solution of the Weinreb amide 116 (0.11 g, 0.94 mmol) in hexane (2 mL) was added and the reaction mixture was allow to warm to 21 °C and stirred overnight. The reaction was quenched with a saturated solution of NaHCO$_3$ (5 mL), extracted with hexane (3 X 10 mL), washed with water (5 X 10 mL) and 1M HCl (1 X 10 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the dihydropyrazole 119 in trace amounts.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

7.83 (bd, $J$ = 7.0 Hz, 2H)
7.26 (bd, $J$ = 8.0 Hz, 2H)
2.83 (d, $J$ = 17.5 Hz, 1H)
2.67 (d, $J$ = 18.0 Hz, 1H)
2.57 (sep, $J$ = 7.0 Hz, 1H)
2.39 (s, 3H)
2.26 (dq, $J = 14.4, 7.2$ Hz, 1H)
2.23 (s, 1H)
2.15 (dq, $J = 14.4, 7.2$ Hz, 1H)
1.08 (d, $J = 7.0$ Hz, 3H)
1.06 (d, $J = 7.0$ Hz, 3H)
0.97 (t, $J = 7.5$ Hz, 3H).

$(\pm)$((1S,4R)-4-Hydroxycyclopent-2-en-1-yl)methyl 4-methylbenzenesulfonate, 129.

To a solution of diol 125 (0.12 g, 0.45 mmol) in dichloromethane (2 mL) and pyridine (2 mL) was added $p$-toluenesulfonyl chloride (0.10 g, 0.53 mmol) at 21 °C and the reaction was stirred overnight. The reaction was then extracted with dichloromethane (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO4, filtered and concentrated in vacuo to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the alcohol 129 (0.045 g, 0.17 mmol, 38%) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl3) δ:
7.78 (d, $J = 8.0$ Hz, 2H)
7.34 (d, $J = 8.0$ Hz, 2H)
5.91 (m, 1H)
5.75 (bd, $J = 5.0$ Hz, 1H)
4.76 (bs, 1H)
3.99 (m, 2H)
2.91 (m, 1H)
2.45 (s, 3H)
2.40 (dt, $J = 14.2, 7.8$ Hz, 1H)
1.65 (bs, 1H)
1.36 (dt, $J = 14.0, 4.0$ Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.9, 136.3, 133.3, 132.8, 129.9, 127.9, 76.5, 72.7, 43.8, 36.4, 21.6.

(±)((1S,4R)-4-((1,1-Dimethylethyldimethylsilyl)oxy)cyclopent-2-en-1-yl)methyl 4-methylbenzenesulfonate, 130.

To a solution of the alcohol 129 (0.10 g, 0.37 mmol) in dimethylformamide (DMF, 2 mL) and pyridine (0.014 mL, 0.66 mmol) was added tert-butyldimethylsilyl triflate (0.10 mL, 0.44 mmol) at room temperature and the reaction was stirred overnight. The reaction was then extracted with dichloromethane (3 X 10 mL), washed with brine (10 mL) and the combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo to give an oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the cyclopentene xx (0.126g, 3.31 mmol, 89%) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$:

7.75 (d, $J = 8.5$ Hz, 2H)
7.31 (d, $J = 8.0$ Hz, 2H)
5.75 (bd, $J = 6.0$ Hz, 1H)
5.67 (bd, $J = 5.5$ Hz, 1H)
4.75 (m, 1H)
3.93 (dd, $J = 9.0, 7.0$ Hz, 1H)
3.87 (dd, $J = 9.0, 7.5$ Hz, 1H)
2.41 (s, 3H)
2.26 (ddd, $J = 13.5, 6.0, 6.0$ Hz, 1H)
1.24 (m, 2H)
0.89 (s, 9H)
0.06 (s, 6H).
REFERENCES


9. Please see Appendix A for nOE of compounds 47 and 51.


CHAPTER 2

Palladium Hydride Promoted Stereoselective Isomerization of
Unactivated Di-(exo)methylene to Endocyclic Dienes
INTRODUCTION

Isomerization of alkenes with transition metals and their complexes under catalytic conditions has been well studied.\(^1\) A range of metals has been used, including Ir, Ni, Rh, Pd, and Co, to make catalysts used for the isomerization of a range of functional groups (Figure 2-1).

![Figure 2-1. Examples of common transition metal isomerization catalysts, 130a-d.](image)

Allyl arenes can be converted into the alkyl styrene isomers, and allyl alcohols can be converted into the corresponding ketone after tautomerization.\(^2\) In addition, an equilibrium can be effected between \(E\) and \(Z\) alkene isomers.\(^3\)

![Scheme 2-1. \(E/Z\) isomerization of alkenes.](image)

However, there has been little research on the isomerization of unfunctionalized alkenes. Of the few accounts reported, many use large transition metal complexes, numerous additives, high temperatures and long reaction times.\(^4\)
Scheme 2-2. Isomerization of oct-1-ene 131 to isomers 132-136.

One example is the isomerization of straight chain olefinic hydrocarbons with rhodium (Scheme 2-2).\textsuperscript{5} Morrill and coworkers found that treatment of oct-1-ene 131 with rhodium trichloride and borane-THF complex gave a mixture of the isomers 132-136 as well as recovered starting material. Two pathways were possible to produce the products (Scheme 2-3): addition/elimination reactions of metal hydride complexes (eq. 1) or a rearrangement through a $\pi$-allyl complex, consisting of coordination of the metal with alkene, followed by a reversible hydrogen transfer to generate the $\pi$-allyl M-H complex (eq. 2). In this report, deuterium labeling studies were conducted and it was determined that the isomerization pathway most likely goes through the metal hydride addition/elimination mechanism, instead of the $\pi$-allyl complex.

\begin{align*}
\text{RC} = \text{CH} = \text{CH} = \text{CH}2 & \xrightarrow{\text{cat. RhCl3-H2O B} = \text{H}2-\text{THF}} \text{R} = \text{CH} = \text{CH} = \text{CH}3 + \text{RC} \text{= CH} = \text{CH} = \text{CH}2 \\
\text{R} = \text{CH}2 \text{= CH}2 & \xrightarrow{\text{M-H}} \text{R} = \text{CH} = \text{CH} = \text{CH}3 + \text{R} = \text{CH}2 \text{= CH}2
\end{align*}

Scheme 2-3. Two potential mechanistic pathways of alkene isomerization.
In general, palladium on charcoal, written as Pd/C, is used to hydrogenate alkenes\(^6\) with, in many cases, high facial selectivity (Scheme 2-4).\(^7\)

![Scheme 2-4. Hydrogenation conditions with palladium on charcoal.]

An unexpected report showed that using 3 mol% Pd/C and hydrogen (1 bar) in isopropyl alcohol as solvent gave predominantly the isomerized product instead of the expected hydrogenated product. Fordred, et al., then developed a methodology with Pd(OH)\(_2\)/C and hydrogen in acetonitrile to isomerize alkenes.\(^8\) However, this methodology was only used for allylic alcohols, not unactivated alkenes (Scheme 2-5).

![Scheme 2-5. Reported isomerization of allylic alcohol 139.]

In this chapter, we describe the study of the isomerization of a novel bicyclic di-(exo)methylene system to the internal dienes.
RESULTS AND DISCUSSION

Figure 2-2. Rugulosone 1.

For our efforts towards the total synthesis of the natural product rugulosone, 1,9 we needed a simple and efficient way to construct the bicyclo[3.3.1]nona-2,6-diene core. Our approach began by first obtaining the simple analogue 1,5-dimethyl-3,7-bis(methylene)bicyclo[3.3.1]nonan-9-one 73 in one step by the tetraalkylation of 3-pentanone 71 with 1-chloro-2-(chloromethyl)-2-propene 72 (Scheme 2-6). We then needed to isomerize the di-(exo)methylene of the diene 73 to the internal, trisubstituted alkenes.

Scheme 2-6. Formation of dienone 73.

Before attempting any experiments, a closer examination proved that the transformation might not have been as simple as it appears. Two possible isomers could form from the rearrangement of the diene 73. Namely, the C2 isomer 74, with an axis of symmetry going through the carbonyl, and/or the C5 isomer 80, with a place of symmetry going through the carbonyl, could
be formed (Scheme 2-7). The C2 isomer 74 was the one required for the synthesis of the natural product rugulosone.

Scheme 2-7. Chemdraw representation and molecular ball-and-stick models of isomerization of 73 to give 74 and/or 80.

In addition, we believed that the C2 isomer 74 would be more stable than C5 isomer 80 due to the steric non-bonded interaction of the indicated allylic hydrogens present in 80 but not in the C2 isomer 74 (Figure 2-3).

Figure 2-3. Structures of the C2 and C5 dienes 74 and 80.
Initial attempts to directly isomerize the diene 73 with transition metal catalysts such as Wilkinson’s or Crabtree’s catalyst failed to yield either 74 or 80; only starting material was recovered. Similarly, reaction with palladium (II) acetate or palladium (II) chloride gave no reaction. Under either basic 4-dimethylaminopyridine (DMAP) or slightly acidic (silver perchlorate) or microwave conditions with or without silica gel, again no reaction was observed. The uniquely strained and/or hindered structure of the bicyclononane core may cause this lack of reactivity.

Table 2-1. Attempts to isomerize bicyclodiene 73.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wilkinson’s catalyst (RhCl(PPh₃)₃)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>H₂, Crabtree’s catalyst [Ir(cod)(PCy₃)(py)]PF₆</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂, benzene reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>DMAP</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂</td>
<td>Completely saturated product</td>
</tr>
<tr>
<td>6</td>
<td>AgClO₄</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>MW, various temperatures, times, w/ or w/o silica gel</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
Since we were unable to directly isomerize the olefins, we decided upon a longer and more complicated process. After the initial formation of the diepoxide, if it could be opened to either the tertiary alcohol or the allylic alcohol, then cleavage of either alcohol would form the desired internal olefins.

Epoxidation of 73 with meta-chloroperoxybenzoic acid (mCPBA) or oxone gave a mixture of products. Treatment of 73 with dimethyldioxirane (DMDO) at room temperature for three hours afforded the single diepoxide 141 in 71% yield. We have assigned the structure as the bis(exo)epoxide 141 due to steric hinderance.

Scheme 2-8. Epoxidation of bicycle 73 to give diepoxide 141.

Many conditions were used in an attempt to promote ring opening of the diepoxide to either the allylic alcohol or the tertiary alcohol (Table 2-2). Conditions such as Super Hydride, LiEt₃BH,¹¹ LiEt₂N,¹² chloroform,¹³ and magnesium isopropylcyclohexylamine (MICA)¹⁴ either only returned starting material or gave a complex mixture of products. It is presumed that the lack of activity is due to the uniquely structured bicyclononane ring system.

The desired isomerization of the diene 73 was, however, effected by the use of an activated palladium catalyst mixed with hydrogen gas. Thus, treatment of 73 in methanol with 4 mol% Pd/C under a balloon of hydrogen afforded the desired C₂ isomer 74 along with the monoreduced and direduced products 144 and 145 (Scheme 2-9).
Table 2-2. Attempts to open diepoxide 141.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LAH, reflux, 1 day</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>LAH, Fieser workup</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄, LiCl</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>LiEt₃BH</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>LiNEt₂</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>TMSOTf, DBU</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Al(OiPr)₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>9</td>
<td>TsOH, CHCl₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>10</td>
<td>nBu₃SnH, AIBN, NaI</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>11</td>
<td>MICA</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>
It was surprising to us that under these conditions, the predominant products were the C₂ and C₅ isomers 74 and 80, respectively, and not the hydrogenated products as one typically expects from these hydrogenation conditions. Thus, a number of control experiments were conducted to demonstrate that hydrogen was required for this isomerization (Table 2-3). Although there initially appeared to be a temperature effect on the ratios of C₂ and C₅ isomers, multiple runs later proved it was within experimental error (entry 2). Under an argon atmosphere, instead of hydrogen, no reaction was observed. To eliminate the possibility of hydrogen being needed to reduce potential palladium oxide that formed on the surface and to regenerate active palladium (0), the catalyst was pretreated with hydrogen gas and then the flask was purged with argon. This procedure also gave no isomerization. The addition of excess cyclohexene (to remove all the hydrogen gas) before the addition of 73 was also unsuccessful. However, the use of ammonium formate, which generates hydrogen gas in situ for transfer hydrogenation, also produced the expected isomerization. Therefore, it seems that the reaction requires a small amount of hydrogen to initiate the isomerization.

Scheme 2-9. Isomerization of 73 to give 74 and other products.
Table 2-3. Control experiments to demonstrate need for hydrogen gas.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂, Pd/C, 25 °C</td>
<td>70% yield, mixture of C₂, Cs, mono-, and di-reduced products</td>
</tr>
<tr>
<td>2</td>
<td>H₂, Pd/C at 0 and 35 °C</td>
<td>Slightly different ratio of C₂ and Cs</td>
</tr>
<tr>
<td>3</td>
<td>Pd/C, argon</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>“activated” Pd/C, then flush with argon</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Pd/C, HCO₂NH₄, argon</td>
<td>Product formation</td>
</tr>
<tr>
<td>6</td>
<td>H₂, Pd/C</td>
<td>90% (1g scale)</td>
</tr>
</tbody>
</table>

Being able to obtain the desired C₂ isomer 74, we then sought to increase the relative yields of the isomeric products. It is known that solvent effects can play a large role in hydrogenation rates. Therefore, we believed that if we could slow down the hydrogenation pathway via a change of solvent, then the alkene isomerization pathway might be favored. Table 2-4 shows a variety of solvent systems there were screened to see if solvent effects could improve the yield of the isomerization.

It was found that polar, protic solvents such as methanol and isopropanol gave large amounts of the monoreduced product 144 and some of the fully reduced material 145. Reaction in
ethyl acetate gave the desired C₂ product 74 in high yield (87%), along with the first observation of the formation of the Cs isomer 80 and the monoreduced product 144. This was our first observation of a lack of formation of the di-reduced product 145. Other polar, aprotic solvents, such as acetone, dioxane and THF, also produced predominantly the desired C₂ product 74 along with small amounts of the Cs isomer 80 and the monoreduced compound 144. Again, no fully reduced product 148 was observed. Using a non-polar solvent such as hexane afforded isomerization with similar results. Thus, we were able to obtain a more desirable ratio between the C₂ isomer, the Cs isomer, the mono-reduced, and the di-reduced products by a change in solvent.

Table 2-4. Solvent effects on conversion of 73 to 74, 80, 144, and 145.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time</th>
<th>74</th>
<th>80</th>
<th>144</th>
<th>145</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>1h</td>
<td>68</td>
<td>0</td>
<td>28</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>iPrOH</td>
<td>1h</td>
<td>68</td>
<td>0</td>
<td>26</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>EtOAc</td>
<td>1h</td>
<td>87</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Hexane</td>
<td>1h</td>
<td>81</td>
<td>7</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>1h</td>
<td>79</td>
<td>6</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Dioxane</td>
<td>1h</td>
<td>64</td>
<td>6</td>
<td>11</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>1h</td>
<td>77</td>
<td>9</td>
<td>13</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
We then explored whether the isomerization to the C₂ isomer in great preference to the C₅ isomer was general. Thus, the additional bis(exo-methylene) compounds, 146-149, were prepared from the corresponding substituted ketones and the bis(chloromethyl)ethylene 72. The structures and yields are given in Scheme 2-10.

Scheme 2-10. Formation of bicyclo[3.3.1]nonane analogues.

Treatment of both 146 and 147 under the conditions described above, namely Pd/C under an atmosphere of hydrogen gas, afforded predominately the C₂ products 150 and 151 in preference to the possible C₅ product (Scheme 2-11). However, the diphenyl-substituted analogue 148 gave only starting material under these conditions with no production of any isomeric or reduction products. It is postulated that although palladium can certainly coordinate to the exo-methylene of the starting material, after hydride addition, it is difficult to eliminate the β-hydride to effect the isomerization, presumably because of the steric interaction with the large diphenyl substituents. Thus, we decided to synthesize the diisopropyl-substituted analogue 149 since phenyl and isopropyl groups are comparable in size. If isomerization could be effected, then we would conclude that there must be another reason other than steric hinderance that is causing the diphenyl to give no reaction. However, under our normal conditions, the diisopropyl analogue 149 gave a bad mixture of products. Thus, this preference for the C₂ product rather than the C₅ product occurs for most alkyl substituents at the bridgehead carbons.
We attempted to make the parent compound, \( 156 \), where \( R = H \) in \( 146 \), but simple reaction of acetone with the allyl dichloride \( 72 \) failed to give any of the desired product. A longer route was attempted (Scheme 2-12), beginning with 1,4-cyclohexanedione monoketal \( 152 \), followed by Wittig reaction to produce the exo-methelene group of intermediate \( 153 \) and then deprotection to form the ketone \( 154 \). Under various basic conditions, reaction of the ketone \( 154 \) with the allyl dichloride \( 72 \) gave only trace amounts of the parent bicyclo[3.3.1]nonanone \( 156 \).

In addition, attempts were made to synthesize the ketodiester \( 159 \) (Scheme 2-13). Simple reaction of dimethyl 1,3-acetonedicarboxylate \( 157 \) with the allyl dichloride \( 72 \) furnished very little of the desired bicycle. And although we were able to form the cyclohexanone \( 158 \) via the dialkylolation, all attempts to form the bicyclononane \( 159 \) were unsuccessful.
Scheme 2-13. Attempt to make ketodiester 159.

We also attempted to make 2,2,6,6-tetramethyl-4-methylene cyclohexanone 162 for deuterium studies. We wanted to see if the orientation of the bicycle had any influence on the slow hydrogenation pathway over the isomerization pathway. Thus, in this monocyclic model, we could probe to see which of the two pathways are favored without the steric influence. Simple inspection of the NMR would be able to distinguish between the two possible deuterated products 161 and 162. Attempted polyalkylation of 4-methylene cyclohexan-1-one 154 with methyl iodide gave many products. We obtained very little of the desired cyclohexanone 160 after 9 days at 40°C in benzene (Scheme 2-14). With only a small amount of cyclohexanone 160 in hand, experiments using deuterium gas were inconclusive.

Scheme 2-14. Treatment of 160 with deuterium gas.

The proposed mechanism for the isomerization is shown in Scheme 2-15. We believe the isomerization proceeds via a metal hydride addition/elimination sequence, instead of proceeding
Scheme 2-15. Proposed mechanism for the isomerization of 163.

through a π-allyl complex.\textsuperscript{10} Thus, coordination of the bis(exo-methylene) 163 with palladium would give A, followed by hydride addition to form B, subsequent β-hydride elimination to afford
C, and then decomplexation to give the monoisomerized product D, which has never been observed. The same type of process can convert D, via the intermediates E–G, to either the C₂ isomer 164 or the C₅ isomer 165 and can interconvert between these intermediates as well.

It is important to note that all these processes are reversible and the product ratio is most likely determined by thermodynamic stabilities. It is presumed that the thermodynamic equilibrium lies completely on the side of the C₂ isomer. Using our conditions, however, it is difficult to arrive at the thermodynamic equilibrium because although most processes are reversible, the process of an alkene being hydrogenated is probably not reversible.

In collaboration with the Houk laboratories, Hung Pham determined the energies of each of the isomers by calculating the structure and energies of reactants, the mono-isomerized species and the isomeric di-isomerized species with density functional theory. Using Gaussian 09, optimizations were performed using B3LYP/6-31G(d), followed by M06-2X/6-311+G(d,p) single point calculations to account properly for dispersion effects. The results are shown in Table 2-5. The parent unsubstituted system 163 (R = H) shows a 2.9 kcal/mol preference for the C₂ diene isomer over the C₅ diene. All of the trisubstituted alkenes were significantly more stable, e.g., 7-9 kcal/mol, than the disubstituted alkene starting materials. Methyl and larger alkyl substituents at the bridgehead carbons led to a greater preference for the C₂ isomer. This is in good agreement with the fact that under all conditions the C₂ diene 164 is the predominant product.

We set out to investigate the source of the preference for the C₂ isomer. As mentioned before, the examination of molecular models revealed a possible unfavorable steric interaction involving the two allylic hydrogen atoms in 165 as shown in Figure 2-3. Inspection of the optimized geometries
Table 2-5. Free energy calculations for C₂ and Cs isomers

<table>
<thead>
<tr>
<th>R</th>
<th>Exo (SM)</th>
<th>C₂</th>
<th>C₅</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.0</td>
<td>-8.0</td>
<td>-5.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Me</td>
<td>0.0</td>
<td>-7.1</td>
<td>-3.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Et</td>
<td>0.0</td>
<td>-9.0</td>
<td>-5.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Pr</td>
<td>0.0</td>
<td>-8.7</td>
<td>-4.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Ph</td>
<td>0.0</td>
<td>-9.2</td>
<td>-6.4</td>
<td>2.8</td>
</tr>
</tbody>
</table>

*aGas phase calculations were carried out using M06-2X/6-311+G(d,p)/B3LYP/6-31G(d) and are quoted in kcal/mol.

Figure 2-4. The monoisomerized and C₂ and C₅ bis-isomerized optimized structures.

Free energies calculated using M06-2X/6-311+G(d,p)/B3LYP/6-31G(d) are relative to 73.
reveals that, although the decrease in H---H distance correlates well with an increase in stability across the isomers (Figure 2-4), a 2.28 Å distance is not sufficient to conclude that the 3-4 kcal/mol thermodynamic preference is dominated by steric repulsion. Interestingly, a twisting of the bicyclo[3.3.1]nonadienone core in 74, which is not observed in the less stable 80, points towards ring strain induced by non-bonding interactions as being another component of the energy difference. This slight rotation relieves some of the unfavorable eclipsing interactions and translates to an increase in the endo hydrogen distance.
CONCLUSION

In summary, the facile isomerization of the bis(exo)-methylene bicyclo[3.1.1]nonane systems gives rise predominately to the C₂ products rather than the possible C₅ products. Theoretical calculations reveal that the origin of this preference stems from thermodynamic effects, involving transannular hydrogen-hydrogen interactions and ring strain induced by these interactions. Many of these results have been published recently.¹⁹
EXPERIMENTAL

General

All reactions were carried out under an argon atmosphere unless otherwise specified. Dichloromethane was distilled from calcium hydride under an argon atmosphere. All other solvents or reagents were purified according to literature procedures. $^1$H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), integration, multiplicity and coupling constant (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. $^{13}$C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). HPLC purification was conducted on a Shimadzu HPLC system with a refractive index detector RID-10A and one Luna 5 μm C18(2) column with acetonitrile and water as an eluent. High resolution mass spectrometry was taken on a Thermo Fisher Scientific Exactive Plus mass spectrometer equipped with an IonSense ID-CUBE DART ion source.

General procedure for formation of di-(exo)methylene

To a suspension of 60% sodium hydride in mineral oil (0.176 g, 4.40 mmol) (washed three times with hexanes) in toluene (5 mL) was added dropwise 3-pentanone (0.086g, 1.00 mmol) in toluene (2 mL). A solution of 1-chloro-2-(chloromethyl)-2-propene (0.254 g, 2.20 mmol) in toluene (2 mL) was added dropwise and the reaction was refluxed overnight. The solution was then cooled to room temperature and quenched with a saturated solution of NH₄Cl (20 mL). The
mixture was extracted with ethyl acetate (3 X 20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the bicyclononanone 73 (0.171 g, 0.90 mmol, 90%) as a light yellow oil.

Compounds 146 and 147 were prepared in an analogous manner.

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one, 73.

1H NMR (500 MHz, CDCl₃) δ

4.73 (s, 4H)
2.57 (d, J = 15.0 Hz, 4H)
2.42 (d, J = 15.0 Hz, 4H)
1.03 (s, 6H).

13C NMR (125 MHz, CDCl₃) δ 218.5, 141.8, 112.7, 49.7, 45.3, 23.5.


General procedure for the palladium hydride promoted isomerization

To a solution of the bicyclononanone 73 (0.050 g, 2.63 mmol) in ethyl acetate (5 mL) was added palladium (10 wt. % on activated carbon) (0.011 g, 0.11 mmol). The reaction vessel was then purged with a hydrogen balloon for 5 min, then allowed to stir at ambient temperature and pressure for 1 h. The mixture was then filtered over Celite, washed with ethyl acetate (15 mL),
then concentrated in vacuo to give diene 74 and other products (0.50 g, 2.63 mmol, 100%) as a light yellow oil. The crude mixture was then purified via HPLC.

Compounds 150 and 151 were prepared and purified in an analogous manner.

\((\pm)(1 R,5 R)-1,3,5,7\)-Tetramethylbicyclo[3.3.1]nona-2,6-dien-9-one, 74.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)
- 5.14 (s, 2H)
- 2.27 (d, \(J = 17.0\) Hz, 2H)
- 2.22 (d, \(J = 17.0\) Hz, 2H)
- 1.65 (s, 6H)
- 1.07 (s, 6H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\)
- 216.6, 132.8, 130.9, 48.5, 45.5, 22.3, 21.1.

HRMS (ESI, \(m/z\)): 191.1425, calculated for [C\(_{13}\)H\(_{19}\)O] 191.1436.

1',5'-Dimethylspiro[oxirane-2,3'-bicyclo[3.3.1]nonane-7',2''-oxiran]-9'-one, 141.

To a solution of freshly prepared dimethylidioxirane (DMDO) in acetone (9.26 mL, 0.78 mmol) was added the bicyclonanone 73 (0.050 g, 2.63 mmol) in acetone (2 mL). The reaction was allowed to stir at 21 °C for 1 h, then dried with MgSO\(_4\) and concentrated in vacuo to give the diepoxide 141 (0.052 g, 89%) as white crystals.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)
2.95 (s, 4H)  
2.31 (d, $J = 14.5$ Hz, 4H)  
1.64 (d, $J = 14.5$ Hz, 4H)  
1.08 (s, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 215.1, 59.7, 54.7, 47.1, 45.5, 23.8.

HRMS (ESI, $m/z$): 223.1324, calculated for [C$_{13}$H$_{19}$O$_3$] 223.1334.

1,5-Diethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one, 146.

$^1$H NMR (500 MHz, CDCl$_3$) δ  
4.74 (t, $J = 2$ Hz, 4H)  
2.57 (d, $J = 14.8$ Hz, 4H)  
2.33 (d, $J = 14.8$ Hz, 4H)  
1.50 (q, $J = 7.6$ Hz, 4H)  
0.86 (t, $J = 7.6$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 218.5, 142.0, 113.1, 47.8, 46.6, 29.2, 8.0.

HRMS (ESI, $m/z$): 219.1738, calculated for [C$_{15}$H$_{23}$O] 219.1749.

3,7-Dimethylene-1,5-dipropylbicyclo[3.3.1]nonan-9-one, 147.

$^1$H NMR (500 MHz, CDCl$_3$) δ
4.73 (t, $J = 2$ Hz, 4H)
2.58 (d, $J = 15.0$ Hz, 4H)
2.39 (d, $J = 15.0$ Hz, 4H)
1.44 – 1.40 (m, 2H)
1.29-1.25 (m, 6H)
0.93 (t, $J = 7.5$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl₃) δ 218.4, 142.0, 112.8, 47.8, 47.1, 39.0, 16.8, 14.9.


± (1$R$,5$R$)-1,5-Diethyl-3,7-dimethylbicyclo[3.3.1]nona-2,6-dien-9-one, 150.

$^1$H NMR (500 MHz, CDCl₃) δ

5.17 (s, 2H)
2.24 (d, $J = 17.0$ Hz, 2H)
2.15 (d, $J = 17.0$ Hz, 2H)
1.73-1.66 (m, 2H)
1.67 (s, 6H)
1.35 (q, $J = 7.0$ Hz, 1H)
1.32 (q, $J = 7.0$ Hz, 1H)
0.85 (t, $J = 7$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl₃) δ 215.9, 133.5, 128.7, 49.1, 46.6, 27.2, 22.6, 8.5.
HRMS (ESI, m/z): 219.1737, calculated for [C_{15}H_{23}O] 219.1749.

(±) (1R,5R)-3,7-Dimethyl-1,5-dipropylbicyclo[3.3.1]nona-2,6-dien-9-one, 151.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$

5.17 (s, 2H)
2.24 (d, $J = 17.0$ Hz, 2H)
2.14 (d, $J = 17.0$ Hz, 2H)
1.66 (s, 6H)
1.65-1.60 (m, 2H)
1.38-1.29 (m, 2H)
1.29-1.18 (m, 4H)
0.90 (t, $J = 7.0$ Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 215.9, 133.1, 129.0, 48.9, 46.9, 37.1, 22.5, 17.4, 14.9.

HRMS (ESI, m/z): 247.0877, calculated for [C$_{17}$H$_{27}$O] 247.2062.

3,7-Dimethylenebicyclo[3.3.1]nonan-9-one, 156.

To a solution of sodium hydride (0.18 g, 4.5 mmol) in benzene (5 mL) was added 4-methylenecyclohexan-1-one 154 (0.2 g, 1.82 mmol) in benzene (5 ml) followed by a solution of allyl chloride 72 (0.25 g, 2.0 mmol) in benzene (2 mL). The reaction mixture was refluxed overnight, then quenched with dropwise addition of aqueous NH$_4$Cl (10 mL), extracted with ethyl
acetate (3 x 10 mL), and washed with brine (10 mL). The combined organic extracts were dried with MgSO₄, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the bicyclic dienone 156 (0.010 g, 0.06 mmol, 3%) as a light yellow oil.

1H NMR (500 MHz, CDCl₃) δ:
4.78 (t, *J* = 2.0 Hz, 4H)
2.72 (bd, *J* = 14.0 Hz, 4H)
2.67 (bd, *J* = 15.0 Hz, 4H)
2.47 (bs, 2H).

13C NMR (125 MHz, CDCl₃) δ 217.9, 141.4, 113.7, 47.3, 42.1.

2,2,6,6-Tetramethyl-4-methylenecyclohexan-1-one, 160.

To a solution of 4-methylenecyclohexan-1-one 154 (0.1 g, 0.91 mmol) in toluene (5 ml) was added sodium hydride (0.43 g, 10.8 mmol) and methyl iodide (0.57 mL, 0.91 mmol). The solution was stirred at 40 °C for 9 d. The reaction mixture was quenched by the dropwise addition of water (5 mL), extracted with ethyl acetate (3 x 10 mL) and washed with brine (10 mL). The combined organic extracts were dried with MgSO₄, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the cyclohexanone 160 (0.015 g, 0.09 mmol, 10%) as a light yellow oil.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$:

4.90 (pentet, $J = 1.2$ Hz, 2H)

2.36 (t, $J = 1.2$ Hz, 4H)

1.11 (s, 12H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 219.2, 141.9, 112.1, 46.8, 45.1, 27.1.

GCMS ($m/z$): 166.1.
REFERENCES


6. For recent reviews, please see: (a) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001. (b) Hudlicky,


Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken,
V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.;
Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.;
Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.


CHAPTER 3

Synthesis of Highly Substituted Adamantanones

from Bicyclo[3.3.1]nonan-9-ones
INTRODUCTION

The unique, caged structure of adamantane has interested chemists for nearly a century. Even before its isolation in 1933 from petroleum,\(^1\) chemists sought to synthesize this smallest unit cage structure of the diamond crystal lattice. The first attempted laboratory synthesis was in 1924 when Hans Meerwin reacted formaldehyde with diethyl malonate under basic conditions.\(^2\) However, instead of adamantane, Meerwein obtained 1,3,5,7-tetracarbomethoxy-bicyclo[3.3.1]nona-2,6-dione instead; this compound was later named Meerwein’s ester.

The first synthesis of adamantane was accomplished by Vladimir Prelog in 1941 in five steps from Meerwein’s ester, with an overall yield of less than 1%.\(^3\) Then, in 1957, Paul von Rague Schleyer accidentally synthesized adamantane \(169\) by first hydrogenating dicyclopentadiene \(167\) with platinum (II) oxide, then heating the product \(168\) with aluminum (III) chloride to 150 °C.\(^4\) This method has been improved upon (from 30% to 60% yield) and is the current method of synthesizing adamantane today (Scheme 3-1).

![Scheme 3-1. von Rague Schleyer’s adamantane synthesis.](image)

Adamantane possesses unique structural and physical properties with practical applications in drugs, polymeric materials, and lubricants. Studies have shown that adamantane is the most stable of the \(C_{10}H_{16}\) isomers with an unusually high melting point of 270 °C. In addition, as the simplest diamondoid, adamantane consists of four connected cyclohexane rings all in a “chair” conformation. Almost contradictory, the structure is both extremely rigid but yet almost strain-free.
The first instance of the adamantane structure in medicinal chemistry involved 1-aminoadamantane 173, commonly referred to as amantadine (Scheme 3-2). Developed by Du Pont, the selective antiviral agent was approved in 1966 for use against influenza. Today, amantadine is no longer prescribed as an antiviral agent. Instead, it may be prescribed for the treatment of mild to moderate Parkinson’s disease.

Scheme 3-2. Commercial synthesis of amantadine 173.

A number of other adamantane-containing small molecules have been approved for the treatment of various diseases, including adapalene, dopamantin, rimantadine, and tromantadine, to name a few. Today, the most common derivative is 3,5-dimethyl-1-aminoadamantane, or memantine, which has been approved for the treatment of Alzheimer’s disease. The current commercial synthesis involves bromination of 1,3-dimethyladamantane, then treatment with

Scheme 3-3. Commercial production of memantine 177.
sulfuric acid in acetonitrile as solvent to form the acetamide 176. Hydrolysis and treatment with HCl forms the hydrochloric salt of memantine (Scheme 3-3).

Although there are a number of adamantane drugs on the market, the biological mechanism of action of the adamantane derivatives is still unclear. One hypothesis is that the size and shape of the adamantane core disrupts the transmembrane flow of protons within a helical viral matrix protein tetramer. Another idea suggests that the adamantane unit binds between the membrane and the protein.

The medicinal properties of the adamantane core have been investigated and found to possess four functions:

1. To change the Absorption, Distribution, Metabolism, or Excretion (ADME) properties of a small molecule.
2. To bind to an enzyme and inhibit viral replication.
3. To act as antagonists and prevent binding of a natural mediator.
4. To act as a rigid scaffold in the spatial positioning of functional groups.

Thus, adamantane is an important structural moiety in medicinal chemistry. In the literature, two methods are employed to form functionalized adamantanes (Scheme 3-4).

The first method is a one-step procedure that starts with the bicycle, 3,7-dimethylene-bicyclo[3.3.1]nonane, 178, and carries out an electrophilic cyclization. It has been shown that reaction with a few reagents such as sulfuric acid, mercury acetate in water, and bromine produce the corresponding substituted adamantanes.
Scheme 3-4. Two methods of formation of substituted adamantanes.

The second method is a two-step procedure that involves starting with a parent adamantane, treating with bromine or chlorine to prepare the mono-, di-, or polyhalogenated adamantane, e.g. 180, and then effecting subsequent functionalization to afford the desired products, e.g., 181. Often times, harsh conditions such as high temperature, long reaction times, and high pressure mercury lamps are used.\(^\text{13}\)

Examples of Friedel-Crafts alkylation of aromatics with the adamantane core are limited. Inamoto, et al., has shown that phenol and o-, m-, and p-cresol were able to undergo adamantylation with 1-bromoadamantane under sulfuric acid conditions.\(^\text{14}\) Olah and coworkers have reported a boron tris(triflate)-catalyzed adamantylation of benzene and toluene with haloadamantanes.\(^\text{15}\) Although the yields of the reaction are moderate (50-70%), a large amount of adamantane is recovered. In addition, only two aromatics, benzene and toluene, were studied.\(^\text{16}\)

Both methods go through the same adamantyl carbocation intermediate. The adamantyl carbocation has a unique structure as the caged system of the molecule renders the carbocation non-
planar. Compared to even its tertiary counterpart, the adamantyl carbocation is unusually stable. The crystal structure of 3,5,7-trimethyl-1-adamantyl cation Sb$_2$F$_{11}$ 182 was obtained by Laube in 1986 (Figure 3-1).$^{17}$ The cationic center C1 is clearly flattened with bonds from C1 having an average length of 1.44 Å. Small C-C-C bond angles around the carbocation of 99° show that the atoms around C1 are more sp$^2$ hybridized than one would expect. This reflects that fact that the 1-adamantyl cation is stabilized by carbon-carbon hyperconjugation.$^{18}$

![Laube's crystal structure of 3,5,7-trimethyl-1-adamantyl cation Sb$_2$F$_{11}$ 182 and adamantane numbering scheme.](image)

**Figure 3-1.** Laube’s crystal structure of 3,5,7-trimethyl-1-adamantyl cation Sb$_2$F$_{11}$ 182 and adamantane numbering scheme.

To our knowledge, no systematic study of the Friedel-Crafts alkylation and trapping of nucleophiles with adamantanes has been carried out. Thus, we were interested to see if one could efficiently construct substituted adamantanones, potential precursors to the corresponding adamantanes. In addition to lengthy syntheses and harsh conditions, limited reactions scope prompted us to investigate a more efficient way of rapidly constructing substituted adamantanes. If we were able to construct a large variety of substituted adamantanones in a highly efficient and simple manner, the resulting biological testing might point us in the right direction to investigate the mechanism of action of this structurally unique class of compounds.
RESULTS AND DISCUSSION

Initially, for our work towards the synthesis of rugulosone, 1 (Figure 3-2), we sought to construct the C₂ symmetric bicyclo[3.3.1]nonane core.¹⁹ Thus, we prepared 1,5-dimethyl-3,7-dimethylene-bicyclo[3.3.1]nonan-9-one 73 by the very efficient quadruple alkylation of 3-pentanone 71 with 1,1-bis(chloromethyl)ethylene 72, a reaction that proceeded in 90% yield (Scheme 3-5).²⁰

![Figure 3-2. Rugulosone 1.](image)

In our efforts to isomerize the exo-methylene groups of the bicyclononane 73 to the internal, trisubstituted alkenes, we tried a number of conventional transition metal catalysts. Wilkinson’s Rh-based catalyst, as well as Crabtree’s Ir-based catalyst, returned only starting material with no formation of isomerized product.²¹ Similarly, reaction with palladium (II) acetate gave no reaction. Treatment with palladium (II) chloride under an atmosphere of hydrogen gave

![Scheme 3-5. Formation of bicyclononane 73.](image)
the completely saturated product. Under either basic, 4-(dimethylamino)pyridine, or slightly acidic, silver perchlorate, or microwave conditions with or without silica gel, again no reaction was observed.

**Table 3-1.** Attempts at isomerization of bicyclodiene 73.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wilkinson’s catalyst (RhCl(PPh3)3)</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>H2, Crabtree’s catalyst [Ir(cod)(PCy3)(py)]PF6</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)2, benzene reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>DMAP</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>H2, PdCl2</td>
<td>Completely saturated product</td>
</tr>
<tr>
<td>6</td>
<td>AgClO4</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>MW, various temperatures, times, w/ or w/o silica gel</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>RhCl3·H2O (10 mol%), MeOH</td>
<td>40% side product</td>
</tr>
</tbody>
</table>

Finally, it was found that treatment with RhCl3·H2O in a 1:1 ratio of CHCl3:MeOH gave 40% of an unexpected product. This was determined to be the adamantanone methyl ether 183.
We believe that this resulted from formation of the adamantyl cation followed by trapping by the methanolic solvent. However, we hypothesize that slight traces of HCl in the RhCl₃ catalyst, instead of the Rh metal, triggered the formation of the cation, since Wilkinson’s catalyst did not produce even trace amounts of product.²²

Thus, we set out to develop a methodology to provide rapid access to the functionalized adamantanone core. Starting from the 3,7-dimethylenebicyclo[3.3.1]nonan-9-one core, we envisioned forming the adamantyl cation with acid, followed by trapping with various nucleophiles to obtain 5-substituted adamantan-2-ones.

We first screened various acidic conditions for the formation of the desired adamantanone product, 1,3,7-trimethyl-5-phenyladamantan-2-one 184 from 73 (Table 2-2). Without the presence of an added nucleophile, the cation can be quenched by the benzene solvent. Thus, treatment of the diene 73 with trimethylsilyl triflate in benzene afforded the 5-phenyl-substituted adamantanone 184 in 65% yield. Other Lewis acids, such as boron trifluoride etherate and aluminum (III) chloride, gave rise to 184 in moderate yields. Protic acids such as sulfuric acid and trifluoroacetic acid also gave the desired adamantanone core in yields of 21% and 59%, respectfully. Trifluoromethanesulfonic acid, triflic acid, was the best acid of those tested, resulting in a 90% isolated yield of 184. Some Lewis acid catalysts, such as cupric triflate, did not provide any product but only returned starting material, as did the reaction without an additive.
Table 3-2. Conversion of diene 73 to phenyladamantane 184.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·OEt₂</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>H₂SO₄</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>TFA</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>TfOH</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)₂</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

To expand our substrate scope, we prepared the additional compounds 146, 147, and 148 by the reaction of the corresponding commercially available ketones 4-heptanone, 5-nonanone, and 1,3-diphenylpropan-2-one with 3-chloro-2-(chloromethyl)prop-1-ene 72, under conditions similar to those used before, to form the bicyclic analogues 146-148 (Scheme 3-6). Treatment of these dienes with triflic acid in benzene as the nucleophilic solvent gave the corresponding adamantanes 185, 186, and 187 in moderate yields.

Scheme 3-6. Cyclization of analogues 146-148 to give adamantanes 185-187.
Next, we investigated the nucleophilic substrate scope of our reaction with 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonane 73 using the mild conditions of triflic acid at room temperature (Table 3-3). Various aromatic rings with electron-donating groups 188-191 reacted as good nucleophiles to produce the substituted adamantanones 192-196 in moderate yields. Toluene 188 gave a 76% combined yield of a 3:1 mixture of the 4-methyl and 2-methyl products, 192 and 193. 

*p*-Xylene 189 gave the expected product 194 in 47% isolated yield; similarly, *m*-dimethoxybenzene 190 afforded the expected product 195 in 47% yield. The more hindered 1,3,5-trimethoxybenzene 191 gave the expected product 196 in only 21% yield, perhaps due to the steric hindrance of the only available aromatic position. Some other aromatic nucleophiles, such as anthracene, failed to yield any product. Not surprisingly, chlorobenzene did not trap, presumably due to its electron deficient nature.

Table 3-3. Reaction of 73 with aromatic rings 188-191 to give 192-196.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>188</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>192, 57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>193, 19</td>
</tr>
<tr>
<td>2</td>
<td>189</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>194, 47</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>195, 47</td>
</tr>
<tr>
<td>4</td>
<td>191</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>196, 21</td>
</tr>
</tbody>
</table>
Again, there have been scattered reports of the trapping of adamantyl cations with benzenoid nucleophiles but no systematic study has been reported.\textsuperscript{23}

To our knowledge, no heterocycles have ever been used to trap an adamantyl cation under acidic conditions. Therefore, we attempted to use several 5- and 6-membered heterocycles as nucleophiles for the non-planar carbocation generated \textit{in situ}. Furan and \textit{N}-methylindole gave poor results, generating a number of unidentified products. Morpholine and pyrrole only returned starting material under these conditions, presumably since protonation of the nitrogen atoms renders the substrate non-nucleophilic.

The reaction of 73 in the presence of triflic acid with \textit{N}-methylpyrrole gave a mixture of the 2- and 3-substituted pyrrole products, 198 and 199, in yields of 33\% and 17\% respectively. The assignment of the structures was based on the pattern of the absorptions in the proton NMR spectrum which matched literature data.\textsuperscript{24} In this case, the ratio of the trapping at C2 vs C3 (1.9:1) is somewhat surprising, given that the reported ratio of trapping of a \textit{tert}-butyl cation with \textit{N}-methylpyrrole is 1:1.4 (C2:C3).\textsuperscript{25} Similarly, reaction of 73 with thiophene in the presence of triflic acid afforded the 2- and 3-substituted products, 200 and 201, in a 1.2:1 ratio in yields of 26\% and 21\%. The assignment was made by comparing the coupling constants for the three aromatic protons and by analogy to literature data.\textsuperscript{26}

In addition to trapping the adamantyl cation with aromatic nucleophiles, we also investigated trapping with oxygen nucleophiles. There have been reports of similar nucleophilic trapping in the literature, but no systematic study has been carried out. Good yields of the expected trapping product were obtained using methanol and acetic acid as nucleophilic solvents, giving 202 and 203 in yields of 52\% and 88\%, respectively. In an attempt to obtain the tertiary alcohol
Table 3-4. Reactions of 73 with heterocyclic nucleophiles to give 197.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nuc</th>
<th>R</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\] | \[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\] | 198, 33 |
|       | \[
\begin{array}{c}
\text{Me}
\end{array}
\] | \[
\begin{array}{c}
\text{Me}
\end{array}
\] | 199, 17 |
| 2     | \[
\begin{array}{c}
\text{Me}
\end{array}
\] | \[
\begin{array}{c}
\text{Me}
\end{array}
\] | 200, 26 |
|       | \[
\begin{array}{c}
\text{Me}
\end{array}
\] | \[
\begin{array}{c}
\text{Me}
\end{array}
\] | 201, 21 |

204, we tried simple addition of water to triflic acid but that resulted in inactivation of the acid and no reaction was observed. We also attempted to hydrolyze the acetate 203 to afford the tertiary alcohol, but many harsh conditions such as strong acid, strong base, and heat, simply returned starting material. Finally, concentrated sulfuric acid was used as the solvent to obtain the desired alcohol product 204 in 74% yield. The initial product was probably the corresponding sulfate, but upon aqueous workup, it fell apart to the alcohol. Propargyl alcohol also trapped on oxygen to give the progargyl ether 205 in 35% yield. However, similar primary alcohols such as furfuryl alcohol and cinnamyl alcohol failed to give the corresponding ethers. Perhaps these substrates were unstable to the strongly acidic conditions.
Table 3-5. Reactions of 73 with oxygen and non-aryl carbon nucleophiles to give 197.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nuc</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HOMe</td>
<td>OMe</td>
<td>202, 52</td>
</tr>
<tr>
<td>2</td>
<td>HOAc</td>
<td>OAc</td>
<td>203, 88</td>
</tr>
<tr>
<td>3</td>
<td>H2O</td>
<td>OH</td>
<td>204, 74</td>
</tr>
<tr>
<td>4</td>
<td>HOCH\textsubscript{2}CCH</td>
<td>OCH\textsubscript{2}C\equiv CH</td>
<td>205, 35</td>
</tr>
<tr>
<td>5</td>
<td>HOPh</td>
<td>OPh</td>
<td>206, 36</td>
</tr>
<tr>
<td>6</td>
<td>HOTf</td>
<td>OSO\textsubscript{2}CF\textsubscript{3}</td>
<td>207, trace</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>208, trace</td>
</tr>
</tbody>
</table>

Somewhat surprisingly, phenol gave only trapping on the oxygen atom to give 206 in 36% yield. No trapping on carbon, either C4 or C2, was observed. Pyridin-4-ol failed to trap at either O or N. In the absence of any external trapping agent, one obtains trace amounts of the triflate 207 and the symmetrical bis(ether) 208.

A few thiols were attempted as nucleophiles, such as 2-propanethiol and ethanethiol. However, it is believed that under acid conditions, the thiol forms a thioketal from the ketone faster than trapping the adamantyl cation.

Next, we attempted to trap with hydride as our nucleophile. Thus, we tried to use BH\textsubscript{3}∙THF and Et\textsubscript{3}SiH to afford hydride trapping, but no product formation was observed by GCMS.
We then moved on to non-aromatic carbon nucleophiles. Treatment with tetramethylsilane did not afford the tetramethylated adamantane. Vinyl silane and allyl silane failed to produce trapping at the tertiary carbocation. Also, the preformed trimethylsilyl enol ether of acetophenone did not trap and simply returned acetophenone. Simple cyclohexene also failed to trap to give the cyclohexyl moiety. A possible reason for the failure of these reactions is that the trapping agents, especially the alkenes, may react preferentially with the strong acid. Finally, we were able to obtain C-C bond formation of a non-aromatic substrate, namely trimethylsilyl acetylene, to give the acetylene product in 44% yield (Table 3-6).

One can also carry out a Ritter reaction, namely treatment of with triflic acid in acetonitrile as solvent, to generate the acetamide in 88% yield. This trapping would be useful for preparing analogues of memantine.

We also examined the addition of electrophiles other than proton to one of the exocyclic methylenes of with the idea of triggering the cyclization to produce the adamantyl cation, which could then be trapped with simple nucleophiles. Reports of such dual addition of electrophiles and nucleophiles to similar dienes have appeared in the literature, but here again no systematic study

---

**Table 3-6. Trapping of 73 with non-aryl C and N nucleophiles.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nuc</th>
<th>R</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS-C≡CH</td>
<td>C≡CH</td>
<td>209, 44</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CN</td>
<td>NHCOMe</td>
<td>210, 88</td>
</tr>
</tbody>
</table>

---

27 Vinyl silane and allyl silane failed to produce trapping at the tertiary carbocation.
28 Simple cyclohexene also failed to trap to give the cyclohexyl moiety. A possible reason for the failure of these reactions is that the trapping agents, especially the alkenes, may react preferentially with the strong acid.
29 Finally, we were able to obtain C-C bond formation of a non-aromatic substrate, namely trimethylsilyl acetylene, to give the acetylene product in 44% yield (Table 3-6).
30 This trapping would be useful for preparing analogues of memantine.
31 Reports of such dual addition of electrophiles and nucleophiles to similar dienes have appeared in the literature, but here again no systematic study.
has been carried out. Thus treatment of the diene 73 with N-bromosuccinimide (NBS) in aqueous DMSO or in methanol gave the bromomethyl alcohol and methyl ether, 212 and 213, in 66% and 89% yields, respectively (Table 3-9). Addition of either bromine or iodine to 73 in dichloromethane gave the dihalo products, 214 and 215, in yields of 88% and 77%, respectively.

**Table 3-7. Reactions of 73 with both electrophiles and nucleophiles to give 211.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>R₁</th>
<th>R₂</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NBS, aq. DMSO</td>
<td>Br</td>
<td>OH</td>
<td>212, 66</td>
</tr>
<tr>
<td>2</td>
<td>NBS, MeOH</td>
<td>Br</td>
<td>OMe</td>
<td>213, 89</td>
</tr>
<tr>
<td>3</td>
<td>Br₂, CH₂Cl₂</td>
<td>Br</td>
<td>Br</td>
<td>214, 88</td>
</tr>
<tr>
<td>4</td>
<td>I₂, CH₂Cl₂</td>
<td>I</td>
<td>I</td>
<td>215, 77</td>
</tr>
<tr>
<td>5</td>
<td>Hg(OAc)₂, MeOH; aq. NaCl</td>
<td>HgCl</td>
<td>OMe</td>
<td>216, 26</td>
</tr>
</tbody>
</table>

Non-halogenated electrophiles could also be used. Thus addition of mercuric acetate to 73 in methanol provided the acetoxymercurio ether, which, for ease of isolation, was converted into the chloromercurio ether by addition of NaCl to give 216 in 26% yield.

Many attempts were tried to utilize the mercury chloride salt as a functional handle to trap electrophiles, such as methyl methacrylate, acrylonitrile, and acrolein (Table 3-8).\(^{32}\) Conditions attempted included radical conditions, trialkysilanes, or KI in the dark. Though some product formation was observed by GCMS, all attempt to isolate the products proved futile.
Table 3-8. Attempts to trap acrylate electrophiles onto mercuric salt 216.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methyl methacrylate</td>
<td>NaBH₄ in diglyme, DCM</td>
<td>1:1 ratio of desired product with Me-Ad-OMe</td>
</tr>
<tr>
<td>2</td>
<td>Acrylonitrile</td>
<td>NaBH₄ in diglyme, DCM</td>
<td>Mess</td>
</tr>
<tr>
<td>3</td>
<td>Acrolein</td>
<td>NaBH₄ in diglyme, DCM</td>
<td>Me-Ad-OMe</td>
</tr>
<tr>
<td>4</td>
<td>Acrylonitrile</td>
<td>KI, DMSO</td>
<td>Product formation; could not isolate</td>
</tr>
<tr>
<td>5</td>
<td>Methacrylate</td>
<td>KI, DMSO</td>
<td>Could not isolate</td>
</tr>
<tr>
<td>6</td>
<td>Acrylonitrile</td>
<td>KI, NH₄Br, DMSO</td>
<td>Mess</td>
</tr>
<tr>
<td>7</td>
<td>Methyl methacrylate</td>
<td>Et₃SiH, DMSO (w/ and w/o KI)</td>
<td>Small amount of product with Et₃SiH and Et₃SiOH</td>
</tr>
<tr>
<td>8</td>
<td>Methyl acrylate</td>
<td>Et₃SiH, DMSO (w/ and w/o KI)</td>
<td>Could not isolate</td>
</tr>
<tr>
<td>9</td>
<td>Methyl methacrylate</td>
<td>Ph₃SiH, DMSO (w/ and w/o KI)</td>
<td>Product formation; could not isolate</td>
</tr>
<tr>
<td>10</td>
<td>Methyl acrylate</td>
<td>Ph₃SiH, DMSO (w/ and w/o KI)</td>
<td>Could not isolate</td>
</tr>
</tbody>
</table>

We also attempted to react the resulting primary halide via cross-coupling conditions. However, treatment of the bromomethyl adamantyl methyl ether 213 and methyl methacrylate
with triethylsilane or triphenylsilane failed to give rise to any product. Similarly, reaction with an organoborane and a palladium catalyst did not yield the expectant Suzuki cross-coupled product (Scheme 3-7).

Scheme 3-7. Attempts to cross-couple haloadamantanone 213.

We believe the mechanism of this process (Scheme 3-8) involves the addition of an electrophile, E+ (H+, X+) to one of the two identical alkenes of 73 from the exo face to generate the tertiary carbocation A. Cyclization of the other alkene on this carbocation would then generate the adamantyl cation B, despite the instability inherent in a non-planar cation. Attack of the

Scheme 3-8. Mechanism of formation of the adamantane core.
nucleophile on B, with loss of a proton, would afford the observed products 211. Though the formation of adamantyl cations is well known,33 they are often formed from adamantyl halides and not from bicyclo[3.3.1]diene systems.

Memantine, 3,5-dimethyladamantan-1-amine, was approved by the FDA in 2003 for the treatment of Alzheimer’s disease under the trade name Namenda, marketed by Forest Labs, Inc. With over $1.7 billion in sales revenue, it was ranked the 29th top selling drug in the United States in 2012.

We decided to utilize our developed methodology to make an analogue of memantine. Thus, the acetamide 210, obtained from 73 by the Ritter reaction, was subjected to a variety of hydrolysis conditions in order to produce the amine 220. Quite harsh conditions were applied, such as a 1:1 v/v ratio of concentrated HCl:water, refluxing with potassium hydroxide in toluene, and catalytic palladium on charcoal, all of which gave no reaction. Finally, concentrated HCl in ethanol in a sealed tube at 100 °C for 3 days produced the primary amine 220 in 97% yield.

\[
\text{NHCOCH}_3 \xrightarrow{c. \text{HCl, EtOH, } 100 \, ^\circ\text{C, 3 days, 97\%}} \text{NH}_2
\]

Scheme 3-9. Hydrolysis of 210 to give the memantine analog 220.

We attempted to reduce the ketone of 220 to the methylene derivative under a variety of conditions, as shown in Table 3-9. Entries 1-3 attempted to fully reduce the ketone to the methylene in a one-step procedure. As far as we can tell, there are references for a Wolff-Kishner reaction of very hindered ketones, but never a substituted adamantane.34 Thus, treatment of ketone 184
Table 3-9. Attempts to reduce ketone 184.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH, NH₂NH₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>PtO₂, H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Zn/Hg/Cl</td>
<td>30% conversion to unknown</td>
</tr>
<tr>
<td>4</td>
<td>PCl₃</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>PCl₃:PCl₅</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>WCl₆</td>
<td>Full conversion to tentative structure 225</td>
</tr>
<tr>
<td>7</td>
<td>LiAlH₄</td>
<td>Multiple products</td>
</tr>
<tr>
<td>8</td>
<td>NaBH₄</td>
<td>Reduction to alcohols 223 and 223’</td>
</tr>
<tr>
<td>9</td>
<td>Ac₂O on 223, 223’</td>
<td>Formation of acetate 224 and 224’ (R = Ac)</td>
</tr>
<tr>
<td>10</td>
<td>Na on 224, 224’</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
with NaOH and hydrazine at high temperature gave no conversion to product. Reduction with platinum oxide under a hydrogen atmosphere also failed.\textsuperscript{35} An attempted Clemmensen reduction with zinc amalgam and hydrochloric acid gave a 30\% conversion to an unknown product, that might have been the fully reduced product, as its NMR had broad doublets that are characteristic of adamantanes.\textsuperscript{36} However, this unknown product was never isolated in a pure state.

Entries 4-6 attempted to convert the ketone to the dichloride. However, treatment with phosphorus trichloride alone or in combination with phosphorus pentachloride gave no reaction.\textsuperscript{37} Reaction with tungsten hexachloride\textsuperscript{38} gave full conversion to an unknown product that appears to have two stereocenters, as observed from the unique coupling pattern in its proton NMR. We have tentatively assigned the structure 225 to this compound.

![Figure 3-4. Compound 225.](image)

In a longer approach, we attempted reduction to the alcohol first (entry 8). Although lithium aluminum hydride gave a mixture of products, reduction with sodium borohydride gave approximately a 1:1 mixture of diastereomeric alcohols 223 and 223’. Reaction of this mixture with 1,1’-thiocarbonyldiimidazole (TCDI), MeI and CS\textsubscript{2} in THF, and phenyl chlorodithioformate gave no reaction, presumably because of the steric hindrance around this neopentyl secondary alcohol. Although treatment with acetic anhydride easily gave the corresponding mixture of acetates 224 and 224’, treatment with sodium metal did not furnish the fully reduced bicycle.
Attempts were then made on the bicyclic dienone 73 (Scheme 3-10). If reduction was to occur, then one could then trap the corresponding hydrocarbon with any nucleophile and produce a whole range of adamantane analogues in two simple steps. However, after reducing the ketone 73 to the alcohol 226 and reaction with carbon disulfide and methyl diiodide to form dithioate 227, we were unable to reduce 227 to the hydrocarbon 228 under the normal radical conditions.

Although we were unable to effect the reduction of either the bicyclic ketone 73 or the adamantanone 184, we believe that under the right conditions, the reaction could be made to occur.
CONCLUSION

In conclusion, we have shown that the readily available 1,5-dimethyl-3,7-dimethylenecyclo[3.3.1]nonan-2-one 73 can be easily converted into a wide variety of adamantanone derivatives by treatment with various electrophiles, especially proton, in the presence of a trapping agent. Aromatic and heteroaromatic nucleophiles have proven to be successful, and oxygen and nitrogen nucleophiles can provide access to a wide variety of functionality at the newly formed tertiary position. Many of these results have been published recently.39
EXPERIMENTAL

General

All reactions were carried out under an argon atmosphere unless otherwise specified. Methylene chloride was distilled from calcium hydride under an argon atmosphere. Trifluoromethanesulfonic acid was purchased from Acros Organics in 99% purity. All other solvents or reagents were purified according to literature procedures. $^1$H NMR spectra were recorded on Bruker spectrometers (at 500 MHz) and are reported relative to deuterated solvent signals. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad. $^{13}$C NMR spectra were recorded on Bruker Spectrometers (at 125 MHz). Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). Thin-layer chromatography (TLC) was carried out using pre-coated silica gel sheets (Merck 60 F254). Visual detection was performed using phosphomolybdic acid or iodine. Flash chromatography was performed using SilicaFlash™ P60 (60 Å, 40-63 µm) silica gel from SiliCycle Inc. with compressed air. High resolution mass spectrometry was taken on a Thermo Fisher Scientific Exactive Plus mass spectrometer equipped with an IonSense ID-CUBE DART ion source.

General Procedure for Acid Promoted Cyclization in Benzene

To a solution of diene 73 (0.200 g, 1.05 mmol) in benzene (5 mL) was added trifluoromethanesulfonic acid (0.111 mL, 1.26 mmol) at 0 °C. The reaction was let warm to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of NaHCO$_3$ (10 mL). The
mixture was extracted with hexanes (3 X 20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the phenyladamantanone 184 (0.253 g, 0.94 mmol, 90%) as a light yellow oil.

**General Procedure for the Triflic Acid Promoted Cyclization and Trapping of Nucleophiles**

To a solution of diene 73 (0.200 g, 1.05 mmol) in dichloromethane (5 mL) was added m-dimethoxybenzene 190 (0.030 mL, 5.25 mmol) then trifluoromethanesulfonic acid (0.11 mL, 1.26 mmol) at 0 °C. The reaction was let warm to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of NaHCO₃ (10 mL). The mixture was extracted with dichloromethane (3 X 20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give a crude light yellow oil. Purification by flash column chromatography on silica gel (19:1 hexanes/ethyl acetate) afforded the 2,4-dimethoxyphenyladamantanone 195 (0.162 g, 0.49 mmol, 47%) as a light yellow oil.

**General Procedure for the Addition of Various Electrophiles and Subsequent Trapping of Nucleophiles**

To a solution of the diene 73 (0.100 g, 0.525 mmol) in 1:1 methanol:dichloromethane (6 mL) was added NBS (0.121 g, 0.068 mmol) at 0 °C. The reaction was warmed to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of NaHCO₃ (10 mL). The mixture was extracted with dichloromethane (3 X 15 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated in vacuo to give crude bromomethyl methoxyadamantanone 213 (0.140 g, 89%) as a light yellow oil.
1,3,5-Trimethyl-7-phenyladamantan-2-one, 184.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 
7.38 – 7.31 (m, 4H) 
7.23 (bt, $J = 7.0$ Hz, 1H) 
1.98 (bd, $J = 12.0$ Hz, 2H) 
1.88-1.85 (m, 4H) 
1.64 (bd, $J = 12.5$ Hz, 2H) 
1.57-1.54 (m, 2H) 
1.01 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 218.5, 147.7, 128.3, 126.2, 124.9, 52.5, 51.5, 48.1, 45.9, 38.4, 32.1, 28.8, 22.6.

HRMS (ESI, $m/z$): 269.1895, calculated for C$_{19}$H$_{25}$O (M+H)$^+$ 269.1905.

1,3-Diethyl-5-methyl-7-phenyladamantan-2-one, 185.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 
7.39 (bd, $J = 8.4$ Hz, 2H) 
7.34 (bt, $J = 7.6$ Hz, 2H) 
7.22 (bt, $J = 6.8$ Hz, 1H) 
1.94 (bd, $J = 12$ Hz, 2H) 
1.87 (s, 2H) 
1.84 (bd, $J = 12.4$ Hz, 2H)
1.56 (m, 4H)
1.48 (q, J = 7.2 Hz, 2H)
1.47 (q, J = 7.2 Hz, 2H)
1.04 (s, 3H)
0.85 (t, J = 7.6 Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 218.0, 147.9, 128.2, 126.1, 124.8, 49.3, 48.6, 48.55, 48.50, 37.9, 31.6, 29.1, 28.3, 7.8.

HRMS (ESI, m/z): 297.2209, calculated for C$_{21}$H$_{29}$O (M+H)$^+$ 297.2218.

5-Methyl-7-phenyl-1,3-dipropyladamantan-2-one, 186.

$^1$H NMR (500 MHz, CDCl$_3$) δ

7.38 (bd, J = 8.0 Hz, 2H)
7.34 (bt, J = 7.5 Hz, 2H)
7.23 (bt, J = 7.0 Hz, 1H)
1.95 (bd, J = 12.5 Hz, 2H)
1.86 (s, 2H)
1.85 (d, J = 12.0 Hz, 2H)
1.60 (d, J = 12.5 Hz, 2H)
1.55 (d, J = 12.5 Hz, 2H)
1.38 (m, 4H)
1.28 (m, 4H)
1.02 (s, 3H)
0.92 (t, \(J = 7.0\) Hz, 6H).

\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 218.1, 148.0, 128.4, 126.2, 124.9, 50.0, 49.1, 48.8, 48.6, 38.4, 38.0, 31.8, 29.3, 16.7, 15.0.

HRMS (ESI, m/z): 325.2522, calculated for C\(_{23}\)H\(_{33}\)O (M+H)+ 325.2531.

5-Methyl-1,3,7-triphenyladamantan-2-one, 187.

\(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\)

7.51 (d, \(J = 7.0\) Hz, 2H)

7.42-7.20 (m, 13H)

2.81 (d, \(J = 12.0\) Hz, 2H)

2.45 (d, \(J = 12.5\) Hz, 2H)

2.38 (d, \(J = 12.5\) Hz, 2H)

2.09 (d, \(J = 12.5\) Hz, 2H)

2.05 (s, 2H)

1.24 (s, 3H).

\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 212.7, 147.4, 142.8, 128.9, 128.8, 128.6, 128.1, 127.1, 126.6, 54.0, 50.7, 49.8, 48.2, 38.6, 32.4, 29.7.

HRMS (ESI, m/z): 393.2204, calculated for C\(_{29}\)H\(_{29}\)O (M+H)+ 393.2218.

1,3,5-Trimethyl-7-(4-methylphenyl)adamantan-2-one, 192, 193.
$^1$H NMR (500 MHz, CDCl$_3$) δ:

7.25 (d, $J = 8.0$ Hz, 2H)
7.16 (d, $J = 8.0$ Hz, 2H)
2.33 (s, 3H)
1.96 (m, 2H)
1.85 (m, 4H)
1.65 (bd, $J = 12.5$ Hz, 2H)
1.54 (m, 2H)
1.00 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 218.6, 144.7, 135.7, 129.1, 124.8, 52.5, 51.5, 48.1, 45.9, 38.5, 32.1, 28.8, 22.8, 20.9.

HRMS (ESI, m/z): 283.2051, calculated for C$_{20}$H$_{27}$O (M+H)$^+$ 283.2062.

5-(2,5-Dimethylphenyl)-1,3,7-trimethyladamantan-2-one, 194.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

7.13 (s, 1H)
7.03 (d, $J = 8.0$ Hz, 1H)
6.95 (d, $J = 7.5$ Hz, 1H)
2.55 (s, 3H)
2.32 (s, 3H)
2.07 (m, 4H)
1.99 (s, 2H)
1.64 (d, J = 12.0 Hz, 2H)
1.56 (d, J = 12.0 Hz, 2H)
1.03 (s, 6H)
1.02 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 218.6, 144.1, 135.4, 133.4, 132.7, 127.0, 126.9, 52.4, 49.8, 46.2, 45.9, 39.9, 32.2, 29.0, 23.2, 22.8, 21.2.

HRMS (ESI, m/z): 297.2197, calculated for C$_{21}$H$_{29}$O (M+H)$^+$ 297.2218.

1,3,5-Trimethyl-7-(2,4-dimethoxyphenyl)adamantan-2-one, 195.

$^1$H NMR (500 MHz, CDCl$_3$) δ:
6.46 (s, 1H)
6.44 (m, 2H)
3.80 (s, 3H)
3.79 (s, 3H)
2.15 (d, J = 11.5 Hz, 2H)
1.97 (d, J = 9.0 Hz, 2H)
1.55 (m, 6H)
0.98 (s, 9H).
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 219.4, 159.4, 159.2, 127.5, 126.9, 103.6, 99.7, 55.2, 54.9, 52.7, 49.2, 45.9, 45.8, 38.4, 32.0, 29.0, 22.8.

HRMS (ESI, $m$/z): 329.2100, calculated for C$_{21}$H$_{29}$O$_3$ (M+H)$^+$ 329.2117.

1,3,5-Trimethyl-7-(2,4,6-trimethoxyphenyl)adamantan-2-one, 196.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 6.13 (s, 2H) 3.78 (s, 3H) 3.74 (s, 6H) 2.36 (bd, $J$ = 12.5 Hz, 2H) 2.25 (bd, $J$ = 12 Hz, 2H) 2.16 (s, 2H) 1.53 (s, 4H) 0.95 (s, 6H) 0.92 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 219.9, 160.5, 158.9, 115.4, 93.1, 55.8, 55.1, 52.5, 50.4, 46.1, 45.8, 41.1, 31.9, 29.3, 23.0.

HRMS (ESI, $m$/z): 359.2210, calculated for C$_{22}$H$_{31}$O$_4$ (M+H)$^+$ 359.2222.
1,3,5-Trimethyl-7-(1-methyl-1H-pyrrol-2-yl)adamantan-2-one, 198.

1,3,5-Trimethyl-7-(1-methyl-1H-pyrrol-3-yl)adamantan-2-one, 199.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$:

6.53 (t, $J = 2.5$ Hz, 1H)
6.48 (t, $J = 2.5$ Hz, 1.9H)
6.40 (t, $J = 2.0$ Hz, 1H)
6.04 (t, $J = 2.0$ Hz, 1H)
6.01 (t, $J = 2.5$ Hz, 1.9H)
5.94 (t, $J = 2$ Hz, 1.9H)
3.76 (s, 5.7H)
3.60 (s, 3H)
2.05 (d, $J = 12.0$ Hz, 4H)
1.95 – 1.87 (m, 10H)
1.77 (m, 4H)
1.62 (d, $J = 12.5$ Hz, 4H)
1.60 – 1.50 (m, 8H)
0.99 (s, 18H)
0.96 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 219.1, 218.2, 138.0, 132.6, 124.4, 121.6, 116.8, 106.1, 105.9, 105.1, 52.7, 52.4, 49.8, 49.1, 46.5, 45.9, 45.6, 37.2, 36.4, 36.1, 34.6, 32.0, 31.8, 28.8, 28.7, 22.65, 22.60.
HRMS (ESI, m/z): 272.2005, calculated for C_{18}H_{26}NO (M+H)^+ 272.2014.

1,3,5-Trimethyl-7-(thiophen-2-yl)adamantan-2-one, 200.

1,3,5-Trimethyl-7-(thiophen-3-yl)adamantan-2-one, 201.

$^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$:

7.28 (dd, $J = 5.0, 3.0$ Hz, 1H)
7.16 (dd, $J = 5.0, 1.0$ Hz, 1H)
7.07 (dd, $J = 5.0, 1.5$ Hz, 1H)
6.98 (dd, $J = 3.0, 1.5$ Hz, 1H)
6.94 (m, 1H)
6.84 (dd, $J = 3.5, 1.5$ Hz, 1H)
2.02 (d, $J = 12.0$ Hz, 2H)
1.97 (d, $J = 12.0$ Hz, 2H)
1.90 (m, 4H)
1.83 (m, 4H)
1.62 (d, $J = 12$ Hz, 4H)
1.56 (m, 4H)
1.00 (s, 18H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 218.3, 217.8, 153.8, 149.8, 126.5, 125.6, 125.3, 122.6, 121.2, 118.2, 52.7, 52.5, 52.4, 51.6, 49.7, 48.4, 46.0, 45.9, 38.1, 37.3, 32.3, 32.0, 28.7, 28.5, 22.5, 22.4.

HRMS (ESI, m/z): 275.1460, calculated for C$_{17}$H$_{23}$OS (M+H)$^+$ 275.1470.
5-Methoxy-1,3,7-trimethyladamantan-2-one, 202.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

3.25 (s, 3H)
1.77 (bd, $J = 15.0$ Hz, 2H)
1.68-1.65 (m, 4H)
1.53 (bd, $J = 15.0$ Hz, 2H)
1.47-1.43 (m, 2H)
0.98 (s, 3H)
0.97 (s, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 217.3, 72.5, 52.5, 48.8, 47.7, 46.1, 45.4, 33.5, 28.2, 22.2.

HRMS (ESI, $m/z$): 223.1689, calculated for C$_{14}$H$_{23}$O$_2$ (M+H)$^+$ 223.1698.

3,5,7-Trimethyl-4-oxoadamantan-1-yl acetate, 203.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

2.13 – 2.02 (m, 6H)
1.97 (s, 3H)
1.52 (s, 4H)
0.96 (bs, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 216 4, 170.1, 79.2, 52.1, 47.7, 46.3, 45.2, 33.8, 28.0, 22.0, 21.9.
HRMS (ESI, m/z): 251.1638, calculated for C_{18}H_{26}NO (M+H)^+ 251.1647.

5-Hydroxy-1,3,7-trimethyladamantan-2-one, 204.

To a solution of the diene 2 (0.050 g, 0.26 mmol) in DMSO (1 mL) was added conc. H_2SO_4 (1 mL) and water (0.1 mL) at 0 °C. The reaction was let warm to 21 °C and stirred for 3 h. The solution was quenched with a saturated solution of NaHCO_3 (10 mL), extracted with dichloromethane (3 X 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried with MgSO_4, filtered and concentrated in vacuo to give the hydroxyadamantanone 204 (0.041 g, 0.20 mmol, 74%) as a light yellow oil.

^1H NMR (500 MHz, CDCl_3) δ:
1.77 (m, 2H)
1.65 (m, 4H)
1.49 (m, 4H)
1.23 (s, 1H)
0.97 (s, 3H)
0.95 (s, 6H).

^13C NMR (125 MHz, CDCl_3) δ 217.4, 69.0, 52.3, 51.8, 49.8, 46.4, 33.9, 28.1, 22.1.

HRMS (ESI, m/z): 209.1538, calculated for C_{13}H_{21}O_2 (M+H)^+ 209.1542.
1,3,5-Trimethyl-7-(prop-2-yn-1-yloxy)adamantan-2-one, 205.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

4.14 (d, $J = 2.5$ Hz, 2H)

2.39 (t, $J = 2$ Hz, 1H)

1.83 (bd, $J = 11.0$ Hz, 2H)

1.73 (s, 2H)

1.75-1.72 (m, 2H)

1.52 (bd, $J = 12.5$ Hz, 2H)

1.46 (bd, $J = 10.0$ Hz, 2H)

0.98 (s, 3H)

0.97 (s, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 217.0, 81.2, 74.4, 73.6, 52.2, 49.8, 48.1, 46.3, 45.9, 33.7, 28.2, 22.2.

HRMS (ESI, $m/z$): 247.1686, calculated for C$_{16}$H$_{23}$O$_2$ (M+H)$^+$ 247.1698.

1,3,5-Trimethyl-7-phenoxyadamantan-2-one, 206.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

7.28 (bt, $J = 8.5$ Hz, 2H)

7.13 (bt, $J = 7.5$ Hz, 1H)

6.98 (bd, $J = 8.5$ Hz, 2H)

1.91 (bd, $J = 10.5$ Hz, 2H)
1.81 (s, 2H)
1.79-1.78 (m, 2H)
1.52 (bd, $J = 12.5$ Hz, 2H)
1.47-1.44 (m, 2H)
0.98 (s, 3H)
0.97 (s, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 217.0, 153.8, 129.0, 124.7, 124.2, 77.5, 52.3, 49.3, 47.2, 46.4, 33.9, 28.2, 22.2.

HRMS (ESI, $m/z$): 285.1849, calculated for C$_{19}$H$_{25}$O$_2$ (M+H)$^+$ 285.1855.

3,5,7-Trimethyl-4-oxoadamantan-1-yl trifluoromethanesulfonate, 207.

$^1$H NMR (500 MHz, CDCl$_3$) δ:
1.79 (m, 2H)
1.70 (bs, 2H)
1.77 (bd, $J = 13.0$ Hz, 2H)
1.52 (bd, $J = 15.0$ Hz, 2H)
1.47 (m, 2H)
0.99 (s, 3H)
0.96 (s, 6H).
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 217.1, 69.3, 52.2, 51.5, 49.6, 46.3, 33.9, 27.9, 21.8 (one low-field carbon not observed).

GCMS (EI+) found 340.1, calculated for C$_{14}$H$_{19}$F$_3$O$_4$S 340.0.

7,7'-Oxybis(1,3,5-trimethyladamantan-2-one), 208.

$^1$H NMR (500 MHz, CDCl$_3$) δ:
1.89 (d, $J = 11.5$ Hz, 4H)
1.78 (m, 4H)
1.56 (s, 4H)
1.48 (m, 8H)
0.97 (s, 6H)
0.96 (s, 12H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 217.5, 75.2, 52.3, 52.2, 50.1, 46.6, 33.9, 28.5, 22.4.

GCMS (EI+) found 398.4, calculated for C$_{26}$H$_{38}$O$_3$ 398.3.

5-Ethynyl-1,3,7-trimethyladamantan-2-one, 209.

$^1$H NMR (500 MHz, CDCl$_3$) δ:
2.13 (s, 1H)
1.91 (bd, $J = 12.5$ Hz, 2H)
1.83-1.80 (m, 4H)
1.52-1.47 (m, 4H)
0.95 (s, 6H)
0.94 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 217.1, 89.4, 68.0, 52.2, 50.5, 47.5, 45.5, 31.5, 31.3, 28.5, 22.3.

HRMS (ESI, $m/z$): 217.1581, calculated for C$_{15}$H$_{22}$O (M+H)$^+$ 217.1592.

N-(3,5,7-Trimethyl-4-oxoadamantan-1-yl)acetamide, 210.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$:
5.41 (bs, 1H)
1.97 (s, 4H)
1.94 (s, 2H)
1.90 (s, 3H)
1.51 (s, 4H)
0.94 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 217.2, 169.8, 52.9, 52.3, 48.5, 45.9, 45.8, 32.7, 28.2, 24.5, 22.2.

HRMS (ESI, $m/z$): 250.1799, calculated for C$_{15}$H$_{24}$NO$_2$ (M+H)$^+$ 250.1807.
5-(Bromomethyl)-7-hydroxy-1,3-dimethyladamantan-2-one, 212.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 
3.27 (s, 2H) 
2.60 (s, 1H) 
1.79 (m, 4H) 
1.69 (m, 2H) 
1.59 (s, 4H) 
0.99 (s, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 216.1, 68.8, 51.7, 48.3, 46.1, 45.9, 43.5, 37.7, 22.0.

HRMS (ESI, $m/z$): 287.0628, calculated for C$_{13}$H$_{20}$BrO$_2$ (M+H)$^+$ 287.0647.

5-(Bromomethyl)-7-methoxy-1,3-dimethyladamantan-2-one, 213.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 
3.27 (s, 2H) 
3.25 (s, 3H) 
1.78 – 1.70 (m, 6H) 
1.62 – 1.56 (m, 4H) 
1.00 (s, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 216.2, 72.5, 49.1, 48.5, 47.7, 45.7, 43.7, 41.9, 37.3, 22.2.
HRMS (ESI, m/z): 301.0785, calculated for C\textsubscript{14}H\textsubscript{22}BrO\textsubscript{2} (M+H)\textsuperscript{+} 301.0803.

**5-Bromo-7-(bromomethyl)-1,3-dimethyladamantan-2-one, 214.**

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) δ:

3.23 (s, 2H)
2.33 (m, 4H)
2.21 (m, 2H)
1.67 (s, 4H)
0.99 (s, 6H).

\(^1\)C NMR (125 MHz, CDCl\textsubscript{3}) δ: 214.2, 59.1, 55.5, 49.5, 48.0, 47.6, 42.9, 38.7, 21.8.

HRMS (ESI, m/z): 348.9797, calculated for C\textsubscript{13}H\textsubscript{19}Br\textsubscript{2}O (M+H)\textsuperscript{+} 348.9803.

**5-Iodo-7-(iodomethyl)-1,3-dimethyladamantan-2-one, 215.**

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) δ:

3.06 (s, 2H)
2.52 (s, 2H)
2.51 (d, \(J = 11.0\) Hz, 2H)
2.41 (d, \(J = 12.5\) Hz, 2H)
1.75 (d, \(J = 12.0\) Hz, 2H)
1.68 (d, \(J = 11.5\) Hz, 2H)
0.98 (s, 6H).
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 214.2, 58.8, 53.7, 49.0, 48.6, 39.9, 37.5, 21.6, 19.1.

HRMS (ESI, $m/z$): 444.9519, calculated for C$_{13}$H$_{19}$I$_2$O (M+H)$^+$ 444.9525.

(7-Methoxy-3,5-dimethyl-4-oxoadamantan-1-yl)methylmercury(II) chloride, 216.

$^1$H NMR (400 MHz, CDCl$_3$) δ:

3.16 (s, 3H)
2.05 (s, 2H)
1.67 (m, 4H)
1.55 (m, 4H)
1.44 (m, 2H)
0.89 (s, 6H).

5-Amino-1,3,7-trimethyladamantan-2-one, 220.

To a solution of the acetamide 210 (0.087 g, 0.35 mmol) and ethanol (2 mL) was added conc. HCl (0.5 mL) and water (0.1 mL) in a sealed tube. The vessel was heated to 100 °C for 3 d. The solution was then cooled to 0 °C and quenched with a saturated solution of NaHCO$_3$ (20 mL). The mixture was extracted with dichloromethane (3 X 20 mL), and washed with brine (20 mL). The combined organic extracts were dried with MgSO$_4$, filtered and concentrated in vacuo to give the crude 5-aminoadamantanone 220 (0.070 g, 0.34 mmol, 97%) as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ:

1.65 (d, $J = 11.5$ Hz, 2H)
1.53 (m, 4H)
1.43 (d, \( J = 11.5 \) Hz, 2H)
1.24 (s, 2H)
0.96 (s, 3H)
0.94 (s, 6H).

\(^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 218.0, 53.3, 52.4, 50.8, 49.1, 46.0, 33.1, 28.2, 22.2.

HRMS (ESI, \( m/z \)): 208.1691, calculated for C\(_{13}\)H\(_{22}\)NO (M+H\(^+\)) 208.1701.

1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-ol, 226.

To a solution of the bicycle 73 (0.50 g, 2.62 mmol) in 1:1 MeOH:THF (16 mL) was added NaBH\(_4\) (0.20 g, 5.24 mmol) and the reaction stirred for 1 h. The solution was then quenched with a saturated solution of NaHCO\(_3\) (20 mL), extracted with dichloromethane (3 X 30 mL) and washed with brine (30 mL). The combined organic extracts were dried with MgSO\(_4\), filtered and concentrated \textit{in vacuo} to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the alcohol 226 (0.45 g, 2.33 mmol, 89\%) as a light yellow oil.

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta:

4.52 (q, \( J = 2.5 \) Hz, 4H)
3.25 (s, 1H)
2.36 (d, \( J = 15.0 \) Hz, 2H)
2.21 (d, \( J = 15.0 \) Hz, 2H)
2.10 (d, $J = 15.0$ Hz, 2H)
1.96 (d, $J = 15.0$ Hz, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 145.0, 144.1, 110.3, 109.4, 47.8, 40.6, 36.3, 27.1.

HRMS (ESI, $m/z$): 193.1587, calculated for C$_{13}$H$_{21}$O (M+H)$^+$ 193.1592.

**O-1,5-Dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-yl) S-methyl carbonodithioate, 227.**

To a solution of the alcohol 55 (0.16 g, 0.84 mmol) in 1:1 THF:CS$_2$ (20 mL) was added sodium hydride (0.10 g, 2.5 mmol) and the reaction stirred for 3 h. The solution was then quenched with a saturated solution of NaHCO$_3$ (20 mL), extracted with dichloromethane (3 X 30 mL) and washed with brine (30 mL). The combined organic extracts were dried with MgSO$_4$, filtered and concentrated *in vacuo* to give a crude yellow oil. Purification by flash column chromatography on silica gel (9:1 hexanes/ethyl acetate) afforded the carbonodithioate 227 (0.07 g, 0.25 mmol, 30%) as a light yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ:
5.85 (s, 1H)
4.59 (m, 4H)
2.57 (s, 3H)
2.39 (d, $J = 15.0$ Hz, 2H)
2.28 (s, 4H)
2.09 (d, $J = 15.0$ Hz, 2H)
0.91 (s, 6H).
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 216.8, 144.1, 142.7, 111.3, 110.3, 90.7, 47.6, 42.2, 36.9, 26.7.

HRMS (ESI, $m/z$): 283.1185, calculated for C$_{15}$H$_{23}$OS$_2$ (M+H)$^+$ 283.1190.
REFERENCES


24. The 2-substituted isomer has one absorption at low field, $\delta$ 6.7, and two absorptions at higher field, $\delta$ 6.1 and 6.0, while the pattern for the 3-substituted isomer was the opposite, namely two absorptions at low field, $\delta$ 6.8 and 6.9, and one absorption at higher field, $\delta$ 6.15. For similar examples, see: von der Saal, W.; Reinhardt, R.; Stawitz, J.; Quast, H. Eur. J. Org. Chem. 1998, 1645.


