Experimental Evidence for Nonstatistical Diradical Intermediates:  
Thermal Chemistry of Vinylcyclobutane Derivatives

Submitted by:  
David Charles Powers  
May 1, 2006

Advisor:  
Dr. Phyllis Leber  
Department of Chemistry  
Franklin & Marshall College  
Lancaster PA, 17604-3003

Submitted for Honors to the Franklin & Marshall College Department of Chemistry in partial fulfillment of the requirements of CHM490.

Graduation Date: May 13, 2006
Table of Contents

Prologue 3

Chapter 1: Introduction 10

Chapter 2: Thermal Chemistry of Bicyclic Vinylcyclobutanes 29
  2.1: Thermal Chemistry of Bicyclo[4.2.0]oct-2-ene 29
  Results and Discussion
  Synthesis 29
  Thermal Chemistry 45
  2.2: Thermal Chemistry of 8-Methylbicyclo[4.2.0]oct-2-ene 59
  Results and Discussion
  Synthesis 59
  Thermal Chemistry 62
  2.3: Conclusions 66

Chapter 3: Thermal Chemistry of Tricyclic Vinylcyclobutanes 70
  Introduction 71
  Results and Discussion 81
  Synthesis 81
  Thermal Chemistry 87

Experimental
  Experimental 2.1: Bicyclo[4.2.0]oct-2-ene Syntheses 92
  Experimental 2.2: 8-Methylbicyclo[4.2.0]oct-2-ene Syntheses 107
  Experimental 3: Tricyclicvinylcyclobutane Syntheses 111

Acknowledgements 119

Appendices 119

References 230
Prologue

Cyclobutane has 26.5 kcal/mol of strain energy; due to the significant strain inherent in the four-member ring, the bonds of cyclobutane are susceptible to cleavage under temperatures that are accessible in a laboratory. Two reaction pathways are observed in the thermolysis of 1,2-dideuteriocyclobutane: both stereoisomerization, interconverting the cis- and the trans- isomers, and fragmentation to two equivalents of ethylene are observed. These two disparate pathways are accessed via the same intermediate; when heated, cyclobutane opens to form a tetramethylene diradical. This intermediate can undergo free rotation with reclosure, leading to the observed stereomutation products, or can undergo further bond cleavage to the observed fragmentation products.

The addition of a vinyl substituent on cyclobutane provides the possibility for an additional reaction pathway: a ring expansion reaction. Under thermolysis conditions, vinylcyclobutane is observed to isomerize to cyclohexene via a [1,3] sigmatropic rearrangement. This reactivity can be rationalized energetically using enthalpies of formation of vinylcyclobutane, cyclohexene, and the combination of 1,3-butadiene and ethylene, as well as the activation energies for the respective conversions between these compounds, as shown in Figure 1. The conversion of vinylcyclobutane to cyclohexene is exothermic by 24.8 kcal/mol; the thermodynamic driving force for these reactions is “relief of ring strain.” Cyclohexene is stable under the experimental conditions; fragmentation to butadiene and ethylene has as activation energy of 67.2 kcal/mol and the reverse reaction – reformation of vinylcyclobutane – has activation energy of 72.3 kcal/mol and thus does not occur under typical thermolysis conditions.
The [1,3] sigmatropic reaction was defined by Woodward and Hoffmann as a unimolecular, uncatalyzed reaction in which a sigma bond between carbons with locants 1 and 1' is cleaved and is reformed three carbons removed from the original bonding locus (the new σ bond is between C₁' and C₃; Figure 2). Both vinylcyclopropanes and vinylcyclobutanes have been observed to undergo [1,3] rearrangements, which result in cyclopentene and cyclohexene, respectively (Figure 2). In this rearrangement, a carbon migrates across an allylic π system. Semantically, the 1', 1 sigma bond has migrated to the 1’, 3 position.

**Figure 1:** Energetic Analysis for the Vinylcyclobutane-to-Cyclohexene-to-Butadiene and Ethylene Reaction Sequence. Literature values⁴,⁵ are in units of kcal/mol. Values of ΔH‡ were converted to Eₐ using the equation: Eₐ = ΔH‡ + RT.⁶

![Energetic Analysis Diagram](image)

**Figure 2:** [1,3] Sigmatropic Migration in Vinylcyclopropane and Vinylcyclobutane
Two distinct stereochemical issues must be addressed when examining this reaction: the involvement of the $\pi$ system in the migration, and the stereochemical fate of the migrating carbon atom. The products of [1,3] sigmatropic rearrangements can exhibit formal suprafacial ($s$) migration, in which case the migrating carbon is consistently associated with the same face of the $\pi$ system, or formal antarafacial ($a$) migration, in which case the migrating carbon passes from one face of the $\pi$ system to the other (Figure 3).

![Figure 3. Suprafacial vs. Antarafacial Reaction Pathways](image)

Similarly, two potential stereochemical fates exist for the migrating carbon atom. The products of [1,3] sigmatropic rearrangements can result from net retention ($r$) or inversion ($i$) of stereochemistry. When participation of both the $\pi$ system and the migrating carbon are considered together, four stereochemically distinct options for the [1,3] carbon migration exist: $si$, $sr$, $ai$, and $ar$. Conservation of orbital symmetry predicts that the $si$ and $ar$ products result from symmetry-allowed pathways while the $sr$ and $ai$ products result from symmetry-forbidden pathways.\(^7\)
The orbital symmetry requirements for sigmatropic rearrangements can be understood by analyzing the interactions between the orbitals of the migrating unit and the structure across which it is migrating. In [1,3] rearrangements the appropriate orbitals for consideration are those of the migrating carbon and those of the allylic π system (Figure 4).

![Figure 4. Molecular Orbital Symmetries of Orbitals Significant to [1,3] Carbon Migrations. Symmetry designations A (antisymmetric) and S (symmetric) refer to symmetry with respect to a vertical mirror plane.]

A concerted reaction is one in which both lobes of the migrating orbital are simultaneously and consistently overlapping with both termini of the allylic unit across which migration is occurring. Simply stated, the theory of conservation of orbital symmetry dictates that concerted reactions must proceed with conservation of orbital symmetry; if orbital symmetry is not conserved, the reaction cannot be concerted. Reactions that do not adhere to these laws must proceed with either a diradical or an ionic intermediate. Because $\Psi_2$ is partially filled, it is the lowest energy wavefunction that can interact with the half-filled p-orbital on the migrating carbon unit. When the migrating carbon moves with retention of stereochemistry, one of the terminal lobes of the allylic
wavefunction participates in a bonding interaction while the other participates in an antibonding interaction; in other words, the symmetries of \( \Psi_2 \) and of the migrating p-orbital are not “conserved” when the p-orbital is in this orientation (Figure 5).

![Figure 5. Retention of Configuration (sr)](image)

On the other hand, if the p-orbital on carbon rotates as migration occurs, as would be the case with inversion of stereochemistry, both terminal lobes of the allylic unit can simultaneously participate in bonding interactions (Figure 6). In this configuration, the symmetries of the interacting orbitals are the same with respect to a vertical mirror plane.

![Figure 6. Inversion of Configuration (si)](image)

In the preceding orbital analysis, only suprafacial processes were examined; similar analyses applied to antarafacial processes would show that, according to orbital symmetry considerations, the \( ar \) reaction pathway is orbital-symmetry-allowed while the \( ai \) reaction pathway is orbital-symmetry-forbidden. Antarafacial reactions were omitted
from the preceding discussion because antarafacial utilization of the \( \pi \) system is not accessible to the molecules under investigation herein. The small rings involved in these bicyclic molecules are not sufficiently flexible to allow the migrating carbon to switch faces of the \( \pi \) system; antarafacial processes are geometrically forbidden. More explicitly, the migrating carbon is attached to the ring containing the \( \pi \)-system by a ‘one-carbon tether.’ The link between the migrating carbon and the \( \pi \) system is not long enough to allow the migrating orbital to move to the opposite side of the \( \pi \) system; because of the short length of the tether, antarafacial products are geometrically inaccessible to these molecules.

Two primary types of experimental evidence can be used to probe the mechanistic course of \([1,3]\) sigmatropic rearrangements. First, energetic evidence can be brought to bear. In a diradical mechanism, the activation energy should be similar to the bond dissociation energy because in the formation of a diradical intermediate a bond is cleaved homolytically before any new bonding occurs. Concerted reactions are typified by activation energies that are markedly lower than the bond dissociation energy because some of the energy required for bond cleavage is simultaneously recouped by the formation of a new bond; in concerted reactions the formation of a bond is coupled with the dissociation of a bond, and thus the activation energy is less than the bond dissociation energy. The difference between the activation energy of a concerted reaction and the activation energy that would be expected if the transformation were mediated by a diradical intermediate is referred to as the ‘energy of concert.’ The other type of experimental evidence used in analyzing these rearrangements is stereochemical in nature; the traditional assumption has been that whereas concerted reactions proceed with
stereoselectivity, diradical reactions yield stereorandom products. This generalization can be rationalized by noting that, in order for bond cleavage and formation to occur simultaneously in a concerted reaction, the transition state must have a single geometry. That is, if bond-making and bond-breaking are coupled, the reactive sites of the molecule must be in the configuration that allows these events to occur simultaneously. Diradical reactions, however, do not in principle require a single geometry in the transition state – the reaction events are not coupled and thus a single geometry is not required. Historically, a statistical distribution of products has been expected from such equilibrated intermediates.
Chapter 1: Introduction

Thermally activated carbon migrations have been reported for a number of hydrocarbon systems including vinlylcyclopropanes and vinlylcyclobutanes. Thorough understanding of this prior work is necessary to place in context the data that have been obtained in the course of this study. A [1,3] sigmatropic rearrangement has been observed in both bicyclic vinlylcyclobutanes such as bicyclo[2.1.1]hex-2-enes and bicyclo[3.2.0]hept-2-enes, as well as monocyclic vinlylcyclobutane derivatives. Because these compounds exhibit varying degrees of strain, comparisons between the reactivity of these compounds will reveal the effect of strain on the outcome of the thermal reorganization. In addition, the effect of changing substitution pattern on [1,3] sigmatropic shifts has been examined; specifically, methyl and deuterium have been used as stereochemical probes. Examination of the effects these substituents have on the course of the reaction has allowed insight into the mechanistic course of this rearrangement. The work presented herein, when compared to studies of related systems, will help to answer questions both about the importance of conformational flexibility as well as substitution pattern on the products formed in [1,3] sigmatropic rearrangements.

The first [1,3] sigmatropic rearrangement was observed 12 years prior to the publication of The Conservation of Orbital Symmetry by Woodward and Hoffmann when in 1959 Neureiter reported the thermal isomerization of 1,1-dichloro-2-vinylcyclopropane to 4,4-dichlorocyclopentene at 500°C (Figure 7a). In 1962, the isomerization of syn-cis-bicyclo[3.2.0]hept-2-enyl-6-acetate to exo-5-norbornenyl-2-acetate at 300°C was reported (Figure 7b). The thermal isomerization of isopropenylcyclobutane to 1-
methylcyclohexene at 304 to 348°C was reported in 1963 (Figure 7c). In these thermally induced isomerizations [1,3] carbon migrations occur across allylic π-systems.

![Chemical structures and reactions](image)

**Figure 7. Early Reports of [1,3] Sigmatropic Rearrangements**

In the ensuing discussion of extant studies of [1,3] carbon migrations, results will be presented from a series of compounds in decreasing order of ring strain. The most strained vinylcyclobutane derivative that has been studied is bicyclo[2.1.1]hex-2-ene (1). The first report of the thermal chemistry of this substrate showed that 1 was predominantly converted to bicyclo[3.1.0]hex-2-ene (2) when heated in the gas phase to temperatures between 150-200°C (Fig. 8).

![Chemical structures and reactions](image)

**Figure 8. Rearrangement of Bicyclo[2.1.1]hex-2-ene (1) to Bicyclo[3.1.0]hex-2-ene (2)**
Roth and Friedrich studied the thermally-induced [1,3] sigmatropic rearrangement of both exo- and endo-5-methylbicyclo[2.1.1]hex-2-ene (3 and 4, respectively) to anti- and syn-methylbicyclo[3.1.0]hex-2-enes (5 and 6, respectively). The exo-methyl derivative was observed to rearrange with a great deal of stereospecificity; the product corresponding to the symmetry-allowed pathway was favored over that of the symmetry-forbidden pathway by a factor of 200 (\(si/sr = 98.5 / 0.5 \approx 200\), Table I). The extent of stereospecificity that was observed in this study provided strong evidence for classification of the [1,3] sigmatropic rearrangements as concerted, symmetry-allowed reactions. The endo-methyl derivative (4) rearranged with a slight preference for the symmetry-allowed product (\(si/sr = 56.5 / 25.2 = 2.2\)). The lack of significant compliance with the dictates of orbital symmetry in this reaction was attributed to steric hindrance due to the endo-methyl substituent.

**Table I.** Product Distributions Starting with 3 and 4

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Product 5</th>
<th>Product 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>120°C</td>
<td>98.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>150°C</td>
<td>25.2%</td>
<td>56.5%</td>
</tr>
</tbody>
</table>

*The products reported do not include those made by non-[1,3] pathways*
Following the report of the thermal chemistry of the parent hydrocarbon 1 and the methyl-substituted derivatives 3 and 4, over 15 years elapsed before a report concerning the stereochemical course of the deuterium-substituted derivative was published in 1984.\textsuperscript{15}

Figure 9. Thermal Isomerization of 5-$d$-1 to 6-$d$-2

Carpenter also studied 7 and 9, phenyl-substituted derivatives of 5-$d$-1, which rearrange to compounds 8 and 10, respectively.\textsuperscript{15}

Figure 10. Phenyl-labeled Bicyclo[2.1.1]hex-2-enes Studied by Carpenter\textsuperscript{15}

Carpenter reported that all reactions showed a preference for the suprafacial-inversion product. The ratio of products from the study of 5-$d$-1, however, showed strong
temperature dependence, while the product ratios obtained from the thermolysis of 7 and 9 showed no variation with temperature. This evidence was used to suggest that the reaction of 5-d-1 was mediated by parallel reaction pathways; the lower energy pathway produced the inversion product while the higher energy pathway led to the formation of the retention product.\textsuperscript{15} By invoking two reactions with different activation energies, Carpenter attempted to rationalize the temperature dependence of the product ratio. Because the ratio of products from the other molecules (7 and 9) are invariant with temperature, Carpenter argued that they must be derived from the same intermediate. In this way, both could be produced via pathways with identical activation energies. In a later publication, Carpenter invoked a single intermediate, which could then be partitioned to a variety of products.\textsuperscript{16}

The problem with the biradical mechanism, of course, arises when one tries to explain the stereochemistry of the rearrangement. If the biradical existed long enough to reach complete equilibrium, the product ratio should be very nearly 1:1, since the isomers differ only in the location of the isotopic label. The possibility that the product ratio reflects some hitherto unprecedented isotope effect can be dismissed because experiments conducted with exo labeled reactants were found to give inversion:retention ratios that were indistinguishable from those of the endo epimers. So then, one must conclude that a biradical is involved but that it does not have time to explore all of its region of the potential energy surface before collapsing to products.

As stated previously, bicyclo[2.1.1]hex-2-ene is the most strained substrate that has been subjected to thermolysis conditions. The next-most-strained vinylcyclobutane derivatives that have been studied extensively are the bicyclo[3.2.0]hept-2-enes. Berson’s 1962 report on the thermal chemistry of endo-bicyclo[3.2.0]hept-2-en-6-yl acetate (11) represents the earliest evaluation of the thermal chemistry of bicyclo[3.2.0]-
Berson reported that 11 rearranged to products 12 - 15 as shown in Figure 11.

![Chemical Structure](image)

**Figure 11.** Observed Rearrangement for *endo*-bicyclo[3.2.0]hept-2-en-6-yl acetate (11)

Berson also studied *exo*-7-*d*-bicyclo[3.2.0]-hept-2-en-*endo*-6-yl acetate (16), which rearranged with *si*/sr > 19. The thermal behavior of *exo*-7-methylbicyclo[3.2.0]-hept-2-en-*endo*-6-yl acetate (17) was elucidated and the rearrangement was shown to proceed with *si*/sr of 10. These ratios indicate that both of these reactions proceed with a preference for the symmetry-allowed [1,3] product. These results were originally interpreted as conclusive evidence of a concerted mechanism as both compounds rearranged with at least a ten-fold preference for a single stereochemical pathway.
Figure 12. 6-endo-Acetoxibicyclo[3.2.0]hept-2-enes (16 – 18) Studied by Berson

The same preference for inversion of stereochemistry was, however, not observed in the thermolysis of endo-7-methylbicyclo[3.2.0]hept-2-en-endo-6-yl acetate (18).\textsuperscript{19} This compound was observed to rearrange with $si//sr$ of 0.14, indicating that a preference for retention of stereochemistry was observed. This observation was rationalized by arguing that the endo-methyl substituent sterically inhibited 18 from participating in a concerted reaction, thus forcing rearrangement via a diradical mediated pathway.

In 1971 Cocks and Frey reported that bicyclo[3.2.0]hept-2-ene (19) undergoes [1,3] sigmatropic rearrangement to norbornene (20), fragmentation to cyclopentadiene (21) and ethylene, or cyclobutane ring opening to heptatriene 22 (Figure 13).\textsuperscript{20}

\begin{equation}
\begin{aligned}
k_0 &= k_1 + k_3 + k_4 \\
k_1 &= \text{rate of [1,3] sigmatropic shift} \\
k_2 &= \text{rate of retro Diels Alder Rxn} \\
k_3 &= \text{rate of direct fragmentation} \\
k_4 &= \text{rate of triene formation}
\end{aligned}
\end{equation}

Figure 13. Rearrangement Schematic for Bicyclo[3.2.0]hept-2-ene (19)
Secondary products 23 – 27, presumably formed via the intermediacy of 22, were identified as 5-methylcyclohexa-1,3-diene (23), 2- methylcyclo-hexa-1,3-diene (24), 1-methylcyclohexa-1,3-diene (25), trans, trans-hepta-1,3,5-triene (26), and cis-hepta-1,3,5-triene (27) respectively.

Experimental observations allowed the following rate constants to be determined (Table II).

**Table II. Rate Constants Obtained by Cocks and Frey**

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>$k_0 \times 10^4$ s$^{-1}$</th>
<th>$(k_1 + k_3) \times 10^4$ s$^{-1}$</th>
<th>$k_4 \times 10^4$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>580.8</td>
<td>1.211</td>
<td>1.096</td>
<td>0.115</td>
</tr>
<tr>
<td>588.0</td>
<td>2.035</td>
<td>1.803</td>
<td>0.232</td>
</tr>
<tr>
<td>594.4</td>
<td>3.216</td>
<td>2.756</td>
<td>0.460</td>
</tr>
<tr>
<td>599.3</td>
<td>4.445</td>
<td>3.802</td>
<td>0.643</td>
</tr>
<tr>
<td>603.9</td>
<td>6.327</td>
<td>5.614</td>
<td>0.713</td>
</tr>
<tr>
<td>610.9</td>
<td>10.07</td>
<td>8.744</td>
<td>1.33</td>
</tr>
<tr>
<td>620.1</td>
<td>18.53</td>
<td>16.77</td>
<td>1.68</td>
</tr>
<tr>
<td>626.7</td>
<td>27.87</td>
<td>25.55</td>
<td>2.31</td>
</tr>
</tbody>
</table>

The thermal behavior of 19 should be viewed in light of the isomerizations of both bicyclo[3.2.0]heptane and isopropenylcyclobutane. The activation parameters for bicyclo[3.2.0]hept-2-ene are much closer to those of isopropenylcyclobutane than bicyclo[3.2.0]heptane. These data are evidence of allyl stabilization of the transition state in the rearrangement of 19. The study of this system was complicated because the maximum concentration of norbornene (20) is 1-2% of the product mixture due to the rapid decay of this species to ethene and cyclopentadiene under the experimental conditions necessary to effect the [1,3] migration (Figure 14). This low concentration of 20 made individual determination of $k_1$ and $k_3$ difficult. While these values are suspect due to experimental uncertainties, the overall value of $(k_1 + k_3)$ was not afflicted by similar experimental uncertainty and is consistent with a diradical mechanism.
Figure 14: Relative rates of [1,3] shift (19 20) and retro-[4+2] (20 21) reactions

The results obtained by Cocks and Frey should also be compared with the results of the 6-endo-acetoxybicyclo[3.2.0]hept-2-ene (11) study. Whereas the acetoxy results were originally interpreted as conclusive evidence implicating a concerted mechanism, the results of the Cocks and Frey study do not similarly indicate a concerted over a diradical mechanism. The results of the study by Cocks and Frey were consistent with a two-step mechanism. The authors suggested that perhaps the acetate group made the diradical pathway less favorable without impacting the energetics of the concerted pathway, thus preventing observation of the competitive diradical products. Without a label on the migrating carbon of bicyclo[3.2.0]hept-2-ene, no determination of the stereochemical preferences of this reaction could be made in this study.

In 1988 two groups simultaneously reported results of a stereochemical study of this [1,3] rearrangement. Baldwin studied a series of deuterated compounds at 276°C, and reported 24 ± 4% retention (which corresponds to si/sr of 3, Table III). Clearly, the reaction exhibited preference for stereochemical inversion, but this pathway is not so energetically favorable as to occur to the exclusion of the retention pathway. Baldwin argued that the observation of both si and sr products could not be explained using a single concerted reaction.
Table III. Stereochemical Observations from Baldwin\textsuperscript{21}

<table>
<thead>
<tr>
<th>Reactant (19)</th>
<th>Product (20) exo / endo</th>
<th>[1,3] Shift Retention %</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-d\textsubscript{0}</td>
<td>1.02</td>
<td>---</td>
</tr>
<tr>
<td>19-d\textsubscript{2}</td>
<td>1.34</td>
<td>21</td>
</tr>
<tr>
<td>19-d\textsubscript{3}</td>
<td>1.48</td>
<td>28</td>
</tr>
<tr>
<td>19-d\textsubscript{8}</td>
<td>0.57</td>
<td>27</td>
</tr>
<tr>
<td>19-d\textsubscript{8}</td>
<td>0.43</td>
<td>18</td>
</tr>
<tr>
<td>19-d\textsubscript{8}</td>
<td>0.51</td>
<td>23</td>
</tr>
<tr>
<td>19-d\textsubscript{8}</td>
<td>0.54</td>
<td>25</td>
</tr>
</tbody>
</table>

Klärner studied the same deuterated structures at 312°C.\textsuperscript{22} His group reported that the rearrangement proceeded with 89% inversion of stereochemistry. Further evidence of the stereochemical preference of the reaction was that 82 ± 4% of the deuterated ethene recovered from non-direct-fragmentation pathways was observed to be of the E configuration, which is produced only via the intermediacy of the $si$ pathway (Figure 15).

![Figure 15. Reaction Schematic Elucidated by Klärner et al.\textsuperscript{22}](image-url)
This group concurred with Baldwin that the observed product distribution could not be explained by a single concerted reaction and thus, at the very least, a diradical mechanism must be competing with a concerted reaction.

In each of the above studies, only approximate values of \( k_1 \) and \( k_3 \) could be determined due to the rapid decay of 20. The problem of obtaining reliable values for each of these individual processes was tackled by Baldwin and Belfield using dynamic isotope dilution techniques.\(^{23}\) From the earlier study by Cocks and Frey (see Figure 13), it was known that the quantity \((k_1 + k_3) \gg k_4\) and that \(k_1\) was similar in magnitude to \(k_3\), but neither of these individual rates had been exactly determined. As with Baldwin’s study of the deuterium labeled parent compound, these experiments were carried out at 276°C. From the Cocks and Frey study, it was known that \(k_1 + k_3 = 0.87k_0\), where \(k_0\) is the overall rate of disappearance of 19.\(^{21}\) Utilizing dynamic isotope dilution techniques, Baldwin determined the ratio \(k_1 : k_3\) as 68 : 32, or approximately 2 : 1. In addition, they found that the deuterated ethylene that is produced from \(k_3\) forms in a 1 : 1 mixture of isomers, implicating the intermediacy of an equilibrated diradical (Figure 16). Free rotation of the radical in intermediate 28 would yield the observed stereorandom fragmentation products.

![Figure 16. Free Rotation of Radical Intermediate Expected from 19-\(d_2\)](image-url)
If both Baldwin and Klärner studied the same systems, why were the $si/sr$ ratios different? Carpenter proposed a solution to this apparent conundrum by suggesting that the stereochemical outcome of this reaction was temperature dependent and that the reaction would be more stereospecific at higher temperature. Carpenter challenged the fundamental prediction that biradical intermediates will lead to a stereorandom product distribution.\textsuperscript{24} He argued that dynamic factors, such as conservation of angular momentum, could take a reactant through an intermediate and preferentially to a single product when the reactant, intermediate, and product are on a straight-line path on the potential energy surface. In this argument the fleeting intermediate would not have time to equilibrate and give the ‘classically predicted’ statistical product distribution; dynamic factors would cause short-lived diradical intermediates to form products of a particular stereochemistry preferentially.

Using dynamic modeling calculations, Carpenter investigated both compound 19 and endo- (29) and exo-7-methylbicyclo[3.2.0]hept-2-ene (30).\textsuperscript{25}

![Figure 17. Endo- (29) and Exo-8-Methylbicyclo[4.2.0]oct-2-ene (30)](image)

According to Carpenter’s models compound 19 (with a suitable label such as deuterium) would yield exclusively the inversion product due to conservation of angular momentum. A ‘short-lived’ intermediate exists on the potential energy surface that leads directly from
the reactant to the inversion product due to dynamic factors. For compound 30 Carpenter’s results support the formation of a small amount of retention product generated by a ‘long-lived’ biradical that has time to equilibrate and yield a statistical product distribution. The intermediate that leads directly to the inversion product does not exist on the potential energy surface for the compound 29, which explains the lack of inversion product in the product distribution of the thermolysis of this compound. In short, Carpenter predicted that mostly the si product would be formed from the compound 30, while only the sr product would be produced from compound 29.

Carpenter’s analysis led to the prediction that the si/sr ratio would be temperature dependent. The ‘long-lived’ diradical, which is the only source of retention product, would ‘bleed off’ to fragmentation at higher temperatures, thereby leading to a reduction in the amount of the retention product that would be observed. The elimination of the long-lived, or statistical, diradical intermediate that leads to the retention product would cause the reaction to be more stereospecific, giving more inversion at increased temperature.

The prediction of temperature dependent stereospecificity in this rearrangement was explicitly investigated by the work of Bender et al. By studying compound 30 at temperatures spanning a 50°C range, he determined that there “is no substantive temperature dependence in the si/sr ratio” for this compound. According to Carpenter, the observed temperature independence of this ratio is evidence that there are not two competitive mechanisms responsible for the observed products. Unless the activation energies of the two pathways were coincidentally identical – an unlikely occurrence – two competitive mechanisms could not yield a temperature independent product profile.
In addition to studying the temperature dependence of these systems, Bender et al. also performed rigorous analysis of the thermal behavior of compounds 29 and 30. The authors found that the si/sr ratio for the rearrangement of 30 is 6.8, indicating that the rearrangement of this compound is more stereoselective than the deuterium-labeled parent compound (which had si/sr = 3 at the same temperature according to Baldwin). In accord with Carpenter’s prediction that only the direct retention pathway should be available to 29, the only observed product in the thermolysis of this compound was the retention product. AGC detection limits prevented absolute reporting of an sr/si ratio, but did establish the lower limit for this value to be 38.

In terms of relative strain, the bicyclo[4.2.0]oct-2-enes under investigation herein are intermediate between bicyclo[3.2.0]hept-2-enes and the least-strained vinylcyclobutanes that have been studied: monocyclic vinylcyclobutane derivatives. In 2000, Baldwin and Burrell pursued a rigorous thermal study of both cis- (31) and trans-1-(E)-propenyl-2-methylcyclobutane (32). This study was significant because all four pathways for [1,3] migration – si, sr, ai, and ar – are geometrically available to monocyclic vinylcyclobutanes.

Figure 18. Observed Products in Thermolysis of cis- (31) and trans-1-(E)-propenyl-2-methylcyclobutane (32)
In fact, all four products were observed for both cis- (31) and trans- (32) starting materials (Figure 18); The product distribution from these reactions is outlined in Table IV below.

<table>
<thead>
<tr>
<th>Rearrangement</th>
<th>Product Distribution From 31</th>
<th>Product Distribution From 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>si</td>
<td>18%</td>
<td>58%</td>
</tr>
<tr>
<td>ar</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>sr</td>
<td>51%</td>
<td>33%</td>
</tr>
<tr>
<td>ai</td>
<td>20%</td>
<td>4%</td>
</tr>
</tbody>
</table>

The ratio of ‘allowed’ (si and ar) to ‘forbidden’ products (sr and ai) from the rearrangement of 31 is approximately 3:7 while the same ratio for 32 is approximately 6:4. These reactions, while not completely stereorandom, clearly does not give the product distribution expected of a concerted reaction; that is, the product distribution is not in accord with conservation of orbital symmetry. In both cases, significant amounts of ‘forbidden’ products are observed. Coincidentally, the more thermodynamically stable trans-3,4-dimethylcyclohexene is formed in both cases.

An additional variable to consider in this system is the effect that the methyl group, on the migrating carbon, has on the stereochemical course of the rearrangement. In 31, the suprafacial pathways are favored over antarafacial pathways because steric factors, which are present during antarafacial rearrangements, are minimized during suprafacial migrations. In 32, the suprafacial processes occur to almost the exclusion of antarafacial processes. While the si pathway is the major component of the product mixture, a significant amount of the sr product was observed; the si/sr ratio was 1.8.
Important work is currently ongoing in the Baldwin laboratory involving the study of 2-\textit{d}-1-(\textit{E})-propenylcyclobutanes.\textsuperscript{28} Only preliminary results in this study have been reported; interesting comparisons with existing work will be possible once complete evaluation of reaction stereochemistry has been reported.

**Overview of Background**

Experimental work aimed at understanding the stereochemical and energetic requirements of [1,3] sigmatropic carbon migrations and calculational studies including direct dynamics simulations have been brought to bear on this reaction. Significantly, experiment and theory are now showing good agreement and the mechanistic picture of this reaction is coming into focus.

Concerted reactions possess an ‘energy of concert.’ The transition state of concerted reactions should be lower in energy than a putative diradical intermediate because some of the energy of bond cleavage is simultaneously being recouped by bond formation. If the potential energy of the appropriate diradical is approximated using group additivities, and these energies are compared with ‘experimental values,’ which are obtained by adding the activation energy observed experimentally to the enthalpy of formation of the starting materials, it can be seen that the hypothetical diradical is equal to or lower in energy than the observed transition state for bicyclo[2.1.1]hex-2-ene (1), bicycle[3.2.0]hept-2-ene, and vinylcyclobutane (Figure 19). This analysis clearly indicates that there is no energy of concert in this reaction; in fact, the transition afforded by homolytic bond cleavage of 1 is higher in energy than the corresponding unstrained diradical.\textsuperscript{9}
In a recent review by Houk and Northrop, the state-of-understanding with respect to the vinylcyclobutane-to-cyclohexene was reviewed. The Density Functional Theory (DFT) calculations performed on the ring expansion of vinylcyclobutane showed that the reaction is diradical-mediated; “the rearrangement proceeds through a diradical that exists on a very flat potential energy surface.” Consistent with the proposal of Carpenter that dynamic factors are responsible for the observed product selectivities, Houk found that conformational changes in the transition structure could be invoked to rationalize the observed products. The transition structure leading to the formation of the $si$ product was the lowest energy transition structure found, but the structure leading to the $sr$ product was only slightly higher in energy.
Energetic differences do not explain why the \( sr \) product is not observed in equal amounts to the \( si \) product; instead, conservation of angular momentum must be invoked. The bond cleavage event that leads to the formation of the transition structure involves rotation of the migrating carbon. Continuous rotation of the migrating carbon leads to the \( si \) product, while the \( sr \) product could only be formed if the rotation were to reverse direction at some point along the migration. Carpenter eloquently expressed the idea of dynamic product control:\(^{30}\)

In more picturesque language, one can say that there is a “beam” of trajectories that has the correct combination of R and theta motions to permit [product formation] and this “beam” is pointing roughly in the direction of the inversion product.

The confluence of experimental and theoretical work on [1,3] sigmatropic carbon migrations has led to an understanding of this reaction that is sophisticated enough to allow predictions to be made and tested. In a recapitulation of an earlier review,\(^{9}\) Leber \textit{et al.} articulated three postulates concerning [1,3] sigmatropic carbon migrations.\(^{31}\)

- the \( si/sr \) ratio correlates with the conformational flexibility of the \( \pi \) system
- a methyl substituent on the migrating carbon slows down the rate of rotation relative to a deuterium substituent in a short-lived diradical and thus results in a higher \( si/sr \) ratio
- fragmentation and stereomutation will compete with [1,3] shifts in conformationally labile diradicals.

The effects of increasing vinyl-group-bearing-ring flexibility and exchanging methyl substitution with deuterium substitution are evident in the tabulated data below and will be further tested through thermal investigation of the compounds in Entry 3 (Table V).
Table V. Effects of Carbon Skeleton and Substitution Pattern on $si/sr$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Methyl-Derivative</th>
<th>$si/sr$</th>
<th>Deuterium-Derivative</th>
<th>$si/sr$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Methyl-Derivative" /></td>
<td>200</td>
<td><img src="image2" alt="Deuterium-Derivative" /></td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Methyl-Derivative" /></td>
<td>6.8</td>
<td><img src="image4" alt="Deuterium-Derivative" /></td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Methyl-Derivative" /></td>
<td>This Work</td>
<td><img src="image6" alt="Deuterium-Derivative" /></td>
<td>This Work</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Methyl-Derivative" /></td>
<td>1.8</td>
<td><img src="image8" alt="Deuterium-Derivative" /></td>
<td>Baldwin, unpublished\textsuperscript{28}</td>
</tr>
</tbody>
</table>

Thus, thermal study of bicyclo[4.2.0]oct-2-ene, bearing methyl or deuterium-labeling, will subject the aforementioned predictions to rigorous experimental verification. This effort is undertaken herein.
Chapter 2: Thermal Chemistry of Bicyclic Vinylcyclobutanes

2.1: Bicyclo[4.2.0]oct-2-ene

Bicyclo[4.2.0]oct-2-ene (1) was prepared and the thermal chemistry of this compound was studied at 300°C. The rate constants for the isomerization of this compound to bicyclo[2.2.2]oct-2-ene (2) and fragmentation to 1,3-cyclohexadiene and ethylene were determined. Analogs of this compound with deuterium labels at C7 (7-d-1) and C8 (8-d-1) were prepared to evaluate the participation of two-centered and one-centered epimerization in the thermal manifold of 1 as well as to evaluate the stereochemistry of the rearrangement of 1 to 2.

Results and Discussion

Synthesis

Preparation of Bicyclo[4.2.0]oct-2-ene

Scheme 1. Synthetic Sequence Towards Bicyclo[4.2.0]oct-2-ene (1)

* The experimental details for the preparation of 1 appear in Experimental: Section 2.1.1

The bicyclo[4.2.0]oct-2-ene carbon skeleton (1) was accessed by the ketene cycloaddition of 1,3-cyclohexadiene and dichloroketene, generated by treatment of
trichloroacetyl chloride with a zinc-copper couple. This reaction produced 3 in good yield but only 42% of the theoretical yield was isolated following Kugelrohr distillation. The product, 8,8-dichlorobicyclo[4.2.0]oct-2-en-7-one (3), has been previously reported and characterized and was thus not subjected to rigorous characterization in this investigation.\textsuperscript{32} Data from mass spectrometry indicates that this material was in fact prepared; the ratio of M : M+2 : M+4 was observed to be 9 : 6 : 1 as would be expected for a dichlorinated compound. In addition, the observed molecular ion peak was found at $m/z = 190$, as was expected for 3. Further, the $^{13}$C-NMR spectrum acquired with a DEPT pulse sequence is consistent with the structural assignment.

Compound 3 was converted to bicyclo[4.2.0]oct-2-en-7-one (4) by dechlorination with excess zinc in acetic acid. The crude yield of this conversion was 89%. Flash chromatography was employed to isolate and purify this material, and the resulting pure compound was subjected to thorough structural study. Spectral data, both IR and MS, were as expected for the compound; specifically, a strong IR peak at 1780 cm$^{-1}$, corresponding to the carbonyl stretch, and a molecular ion peak at $m/z = 122$ were observed. $^{1}$H-NMR and $^{13}$C-NMR were obtained for the material. Using an APT pulse sequence $^{13}$C-NMR provided conclusive evidence for the proposed structure.

Compound 4 was converted to the corresponding hydrazone derivative (5) by treatment with hydrazine hydrate and hydrazine sulfate. The reaction mixture was heated at 65°C overnight. Reaction progress was easily monitored by obtaining IR spectra of the organic layer of the reaction mixture; disappearance of the carbonyl stretch was used as evidence that the reaction had gone to completion. This reaction proceeded in 77% yield. IR spectroscopy was the only characterization used on this compound.
Conversion of 5 to compound 1 was effected using a low-temperature Wolff-Kishner reaction involving treatment with potassium tert-butoxide at room temperature.\textsuperscript{33} This reaction proceeded in only 49\% yield. One factor contributing to the low recovery of this material was surely the volatile nature of the product – evaporative loss undoubtedly contributed to the small yield. This material was efficiently isolated and purified by preparative gas chromatography. The four-step synthetic sequence had an overall yield of only 14\%. This low yield is at least in small part due to evaporative loss of material as the synthesis was carried out.

Compound 1 is a known compound but \textsuperscript{13}C-NMR data have not been reported. A DEPT \textsuperscript{13}C-NMR was obtained for 1 and the chemical shift values were consistent with the structure of 1; four carbon resonances were shown to be CH\textsubscript{2} units and four carbons were shown to be CH units. Of the CH units, two resonated in the vinyl region, while the other two resonated in the bridgehead region.

The \textsuperscript{1}H-NMR of a tetradeuterated derivative of 1 has been reported and the spectrum obtained in this work was consistent with reported spectral data.\textsuperscript{34} While \textsuperscript{1}H-NMR chemical shifts have been reported, unambiguous assignments for all the signals in the proton spectrum thus far have not been obtained. Combining existing partial assignments from literature reports,\textsuperscript{34} NMR spectra of deuterium labeled substrates prepared as a part of this study (see ‘Preparation of 7-d-bicyclo[4.2.0]oct-2-ene’ and ‘Preparation of 8-d-bicyclo[4.2.0]oct-2-ene’ in this Results section), and NOE NMR experiments performed on undeuterated 1, unambiguous assignments of most of the relevant proton signals have been made. These assignments have allowed assignment of the relative stereochemistry of deuterium labeled compounds and confirmed the potential
to monitor these reactions by $^2$H-NMR; if the NMR signals of 1 were to overlap with those of 2, analysis of the rearrangement of 1 to 2 by $^2$H NMR would not have provided a useful analysis. The assignments are based on the following numbering scheme.

![Numbering Scheme Diagram]

### Table I: Assignments of Relevant Signals in $^1$H-NMR Spectrum of 1

<table>
<thead>
<tr>
<th>Hydrogen</th>
<th>Chemical Shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.64</td>
</tr>
<tr>
<td>2</td>
<td>5.79</td>
</tr>
<tr>
<td>3</td>
<td>5.73</td>
</tr>
<tr>
<td>6</td>
<td>2.59</td>
</tr>
<tr>
<td>7-exo</td>
<td>1.92</td>
</tr>
<tr>
<td>7-endo</td>
<td>1.77</td>
</tr>
<tr>
<td>8-exo</td>
<td>2.23</td>
</tr>
<tr>
<td>8-endo</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Two vinyl proton signals were observed in the $^1$H-NMR spectrum of 1 ($\delta = 5.73$, 5.79 ppm). In addition to the two vinyl resonances, two bridgehead hydrogen resonances were observed ($\delta = 2.59$ and 2.64 ppm). The more downfield of these signals ($\delta = 2.64$ ppm) is due to the hydrogen on C1; this hydrogen is deshielded by virtue of its allylic position. C6 is more removed from the double bond location and thus the hydrogen at this position is slightly less deshielded ($\delta = 2.59$ ppm).

The $^2$H-NMR spectrum of 7-$d$-bicyclo[4.2.0]oct-2-ene (7-$d$-1) showed two signals ($\delta = 1.77$, 1.92 ppm) due to endo-7- and exo-7- deuterium. Diimide, generated in situ by treatment of hydrazine with hydrogen peroxide, would be expected to add preferentially from the exo-face to avoid the steric crowding of the endo-face.\textsuperscript{35} Attack of diimide from
the \textit{exo}-face would result in more deuterium in the \textit{endo}- position and thus the stronger of the two signals in the $^2$H-NMR should be due to \textit{endo}-deuterium on C7. Based on the intensity of signals, $\delta = 1.77$ ppm was assigned as 7-$\textit{endo}$ while $\delta = 1.92$ ppm was assigned as 7-$\textit{exo}$. The expectation that the stronger $^2$H-NMR peak was due to \textit{endo}-deuterium was proven conclusively by Nuclear Overhauser Enhancement (NOE) experiments. Irradiation of the hydrogen signal in compound 1 at 1.92 caused enhancement of the signal at C6 hydrogen ($\delta = 2.59$), indicating that 1.92 ppm is the C7 exo.

The $^2$H-NMR spectrum of 8-$d$-bicyclo[4.2.0]oct-2-ene (8-$d$-1) also showed two signals ($\delta = 1.63, 2.23$ ppm). Similar arguments about addition of diimide and the resulting resonance intensities in the $^2$H-NMR spectrum allowed the C8 proton assignments to be made; $\delta = 1.63$ ppm was assigned as 8-$\textit{endo}$ and $\delta 2.23$ ppm was assigned as 8-$\textit{exo}$. NOE experiments were employed to confirm these assignments. Irradiation of the signal at $\delta = 2.23$ ppm in the $^1$H-NMR spectrum resulted in enhancement in the C1 proton signal, confirming the assignment that this resonance was due to the 8-$\textit{exo}$ proton. The C8 resonance at $\delta = 1.63$ was therefore assigned as 8-$\textit{endo}$.

The C7 and C8 protons are the signals of particular interest in this study. With the above outlined syntheses and experiments, these important $^1$H-NMR signals were conclusively assigned.
Preparation of Bicyclo[2.2.2]oct-2-ene\textsuperscript{b}

\[ \text{Scheme 2. Synthetic Pathway Towards Bicyclo[2.2.2]oct-2-ene (2)} \]

\textsuperscript{b} The experimental details for the preparation of 2 appear in Experimental 2.1.2

Compound 6 was produced by the Diels-Alder reaction of 1,3-cyclohexadiene and 2-chloroacrylonitrile.\textsuperscript{36} As 6 is a known compound and the procedure employed in producing 6 was identical to a literature report, it was judged that this characterization by IR spectroscopy alone was sufficient.\textsuperscript{37} Compound 6 was not purified due to its reported instability, and thus the IR spectrum was difficult to interpret; i.e. no stretching frequency at \( \sim 2200 \text{ cm}^{-1} \) was observed as was expected for the nitrile and no melting point was obtained. Despite this difficulty, the chemical reactivity of the compound confirmed that the proposed structure was in fact synthesized. Compound 6 was converted by reported methodology to known ketone 7, which was rigorously characterized. Characterization of 7 (outlined below), the product of base-catalyzed hydrolysis, proved unambiguously that 6 had been synthesized.

This base-catalyzed hydrolysis was carried out by treatment with aqueous KOH in DMSO. The product of this reaction crystallized; following drying in a vacuum oven the compound melted at 85 – 88°C. The relatively narrow range over which the compound
melted indicated that the material was fairly pure. Spectral data including IR, MS, \(^1\text{H}-\text{NMR}, \(^{13}\text{C}-\text{NMR},\) and DEPT \(^{13}\text{C}-\text{NMR}\) were obtained for 7. The resulting spectral data were in accord with literature reports of this compound.\(^{38}\) Specifically, the mass spectrum, which showed a strong signal at the M peak \((m/z = 122)\), and \(^{13}\text{C}-\text{NMR}\) data, which were identical with the literature report, gave conclusive structural evidence. The two-step yield for the overall conversion of 1,3-cyclohexadiene and 2-chloroacrylonitrile to 7 was 8%.

Compound 7 was easily reduced to 8 by palladium-catalyzed hydrogenation in 89% yield. The \(^{13}\text{C}-\text{NMR}\) spectrum reflected increased symmetry in this compound relative to 7; only six peaks were observed in the spectrum of 8 while eight peaks were observed in the spectrum of 7. Spectral analysis based on IR, MS, and \(^1\text{H}-\text{NMR}\) was obtained for 8. Compound 8 is a known compound and the spectral data obtained for this compound were in accord with values reported in the literature.\(^{38a,38c,39}\) The melting point of 8 was 169-172°C, indicating that the material was fairly pure.

Upon treatment with \(p\)-toluenesulfonylhydrazide in methanol, 8 was converted to 9 in moderate yield (68%). This less-than-ideal yield is likely due to steric crowding at the carbonyl in 8 due to the two nearby carbon bridges. The product that was isolated was judged to be of high purity based on the very narrow melting point (214-215°C) that was observed. Only IR spectroscopy was utilized to characterize this product since both the synthetic precursor (7) and the compound to which this would be converted (2) have been fully characterized by \(^{13}\text{C}\) NMR data. Further, this tosylhydrazone derivative is a known compound and thus rigorous structure proof was deemed unnecessary.\(^{40}\) The IR of 9 showed the disappearance of the carbonyl stretch (at 1720 cm\(^{-1}\)) that was observed in
the IR of 8 as well as the evolution of peaks corresponding to the functionality of 9 (specifically, peaks at 3210, 2930, 1650, 1320, 1170, and 670 cm$^{-1}$).

Compound 9 was subjected to Shapiro reaction conditions – MeLi in TMEDA – which successfully converted 9 to 2 in 99% crude yield. Compound 9 was characterized by $^1$H-NMR, $^{13}$C-NMR, MS, and IR. NMR data collected on material that had been purified by preparative gas chromatography were in accord with reported values.$^{41}$ Following purification by preparative gas chromatography, the sample of this compound was shown to be 99.2% pure by AGC.
Preparation of 7-\textit{d}-bicyclo[4.2.0]oct-2-ene\textsuperscript{c}

\begin{align*}
  
\text{Cl} & \quad \text{Cl} \\
\text{NaBD}_4 & \quad \text{MeOH} \\
80\% & \\

\text{Cl} & \quad \text{Cl} \\
\text{MsCl} & \quad \text{Et}_3\text{N} \\
83\% & \\

\text{Cl} & \quad \text{Cl} \\
\text{D} & \quad \text{OMs} \\

\text{N} & \quad \text{H}_2\text{O}_2 / \text{N}_2\text{H}_4 \\
76\% & \\

\text{D} & \quad \text{D} \\
12 & \\

\text{H}_2\text{O}_2 / \text{N}_2\text{H}_4 \\
\text{EtOH, \text{-20°C}} \\
52\% & \\

\text{D} & \quad \text{D} \\
\text{7-\textit{d}-1} & \\

\text{Na} / \text{NH}_3(\text{l}) & \\
80\% & \\
83\% & \\
52\% & \\
76\% & \\

\end{align*}

\textbf{Scheme 3.} Synthetic Approach to 7-\textit{d}-1

\textsuperscript{c} The experimental details for the preparation of 7-\textit{d}-1 appear in Experimental 2.1.3.

Deuterated substrate 7-\textit{d}-1 was accessed in four steps starting with 3. Deuterium was introduced at C7 by treatment of 3 with sodium borodeuteride in methanol. Reaction progress was monitored by observing the disappearance of the carbonyl stretch in the IR spectrum of the reaction mixture. This reaction proceeded in 80\% of the theoretical yield. The product 10 was characterized by IR and mass spectrometry. The IR spectrum showed the presence of the stretches expected of an alcoholic compound (3300 \text{ cm}^{-1}) and showed indicated the presence of the desired C-D stretch (2200 \text{ cm}^{-1}). Completely rigorous structure determination was not performed on this compound because an undeuterated analog had previously been reported.\textsuperscript{42}

Compound 10 was then converted to the corresponding methanesulfonate derivative 11. This compound was characterized by IR spectroscopy. The IR spectrum of the product showed the disappearance of the –OH stretch that was present in the starting material and the presence of both symmetric and asymmetric S=O stretches. Mesylate 11 was isolated in 83\% yield. The IR peaks at 1150 and 1350 \text{ cm}^{-1} were evidence that 10 had in fact been completely converted to 11.
Compound 11 was subsequently treated with sodium metal in liquid ammonia leading to the formation of 12 following a procedure adapted by Baldwin$^{43}$ from a procedure developed by Greene.$^{44}$ This reaction proceeded in 52% yield. Preparative gas chromatography was employed to isolate a pure sample of this material for characterization. As 12 is a novel compound, rigorous structure determination was carried out. The mass spectrum obtained for the compound was consistent with the proposed structure of 12; $M^+ = 107$. Further, $^1$H-NMR, $^2$H-NMR, $^{13}$C-NMR, and DEPT $^{13}$C-NMR spectra supported the structural assignment. Deuterium incorporation was judged to be complete based on the $^{13}$C-NMR signal for C7 being split into a 1:1:1 triplet. Further evidence for the total incorporation of deuterium in 12 comes from $^1$H-NMR and $^2$H-NMR spectra that were obtained for the compound. In the proton spectrum of 12, there are signals for nine protons. Notably, there is no proton signal at 6.08 ppm. This is significant because in the $^2$H-NMR of 12 the only signal appears at 6.08 ppm. The absence of a proton signal at 6.08 ppm indicates that the C7 position has been completely deuterated.

Diene 12 was subsequently treated with 30% hydrogen peroxide and anhydrous hydrazine in absolute ethanol at approximately –17°C; reaction progress was monitored by Analytical Gas Chromatography (AGC). Initially, a stoichiometric amount of hydrazine was added to the reaction vessel and hydrogen peroxide was added slowly (in 1 mL aliquots separated by approximately 2 hours). Several products were observed; based on MS evidence these products were proposed to be a doubly reduced structure and a structure in which the undesired double bond was reduced.
Initial slow development of products suggested that diimide – required for this reaction – was being formed but leaving the reaction vessel as a gas before reacting with 12. To probe this possibility, an additional stoichiometric amount of hydrazine was added to the reaction mixture. This addition caused a rapid acceleration in the rate of product formation. Once approximately 80% of the starting material had been consumed, the reaction was quenched. This was done because the selectivity observed in this reaction was being compromised; undesired products were beginning to evolve competitively with 7-d-1. Compound 7-d-1 was isolated by preparative gas chromatography prior to complete structure determination. The mass spectrum of 7-d-1 showed the expected M$^+ = 109$ peak. The $^{13}$C-NMR spectrum obtained for this compound was identical to the spectrum that had been obtained for undeuterated 1, with the exception of the $\delta = 22.1$ ppm signal. Due to the presence of deuterium, this signal was split into a 1:1:1 triplet. Compound 7-d-1 was isolated in 76% yield in this reaction; for the four-step process initiated with 3, compound 7-d-1 was isolated in 26% overall yield.

The proton spectrum of 7-d-1 showed the complete absence of signal assigned for the 7-endo proton, and a slight reduction in the integration of the signal assigned for the 7-exo proton. Both of these proton signals were smaller than the analogous signals in the spectrum of the parent compound because the diimide reduction leading to 7-d-1 did not proceed with exclusively exo- addition. Based on deuterium NMR, the product that was isolated had a deuterium endo / exo ratio of ca. 85 : 5. The $^2$H-NMR spectrum showed two peaks (1.73 and 1.87 ppm). The proton signals are given in Table II and the $^2$H-NMR of this compound is reproduced below (Fig. 1).
Table II: $^1$H-NMR Data for 7-$d$-Bicyclo[4.2.0]oct-2-ene (7-$d$-1)

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.47</td>
<td>M</td>
<td>2H</td>
</tr>
<tr>
<td>1.58</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>1.84</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>1.96</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>2.09</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>2.18</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>2.58</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>2.65</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>5.73</td>
<td>M</td>
<td>1H</td>
</tr>
<tr>
<td>5.79</td>
<td>M</td>
<td>1H</td>
</tr>
</tbody>
</table>

Figure 1. $^2$H-NMR at Time = 0 for 7-$d$-bicyclo[4.2.0]oct-2-ene (7-$d$-1)
Preparation of 8-<em>d</em>-bicyclo[4.2.0]oct-2-ene<sup>d</sup>

![Chemical structures and reactions](image)

**Scheme 4. Synthetic Scheme Towards 8-<em>d</em>-1**

<sup>d</sup>Experimental details for the preparation of 8-<em>d</em>-1 appear in Experimental 2.1.4.

Dichloroketone 3 was selectively dechlorinated by treatment with zinc metal in <em>d</em>-acetic acid. One stoichiometric equivalent of zinc metal was slowly added to a solution of 3 in <em>d</em>-<em>j</em>-acetic acid. The zinc metal was allowed to react completely before additional zinc was added; by maintaining a low concentration of zinc metal in the reaction vessel at all times, the reaction mixture remained at room temperature and double-reduction of 3 was limited. Reaction progress was monitored by mass spectral analysis. When 98% of the starting material was dechlorinated, the reaction was quenched and monochlorinated ketone 13 was extracted. Following isolation, this reaction proceeded in 93% yield. By GC-MS, it was confirmed that 13 was in fact produced; the molecular ion peak that was observed was at <em>m/z</em> = 157.

Ketone 13 was dissolved in <em>d</em>-<em>j</em>-methanol and treated with NaBH<sub>4</sub> to reduce the ketone functionality to the corresponding alcohol 14. Due to concern that the basic conditions of this reaction would promote enolate formation and that subsequent proton abstraction from solvent molecules would remove the deuterium introduced in the
preceeding step, deuterated solvent was used. Under these conditions, enolate formation would simply lead to deuterium-for-deuterium exchange. Reaction progress was monitored by IR; the diappearance of the carbonyl-stretching peak was used to determine when the reaction should be quenched. This reaction proceeded in 74% yield. Following extraction, IR was utilized to characterize 14. In particular, the OH stretching peak at 3400 cm\(^{-1}\) and the C-D stretch at 2220 cm\(^{-1}\) were viewed as diagnostic peaks for the structure of 14.

Alcohol 14 was converted to the corresponding methanesulfonate derivative 15. This transformation was affected by treatment of a solution of 14 in methylene chloride with methanesulfonyl chloride and triethylamine. The reaction mixture became opaque as the reaction proceeded due to the evolution of triethylammonium chloride. This reaction was monitored by IR; the disappearance of the –OH stretching peak and the evolution of peaks corresponding to S=O stretches were used to follow reaction progress. In particular, the loss of the OH stretch, which had been observed at 3400 cm\(^{-1}\) disappeared, and strong peaks at 1180 and 1350 cm\(^{-1}\), diagnostic of symmetrical and unsymmetrical S=O stretches, were observed. This reaction proceeded in 90% yield. IR spectroscopy was used to confirm that 14 had been completely converted to 15.

Mesylate 15 was reduced to deuterated diene 16 by treatment with sodium metal in liquid ammonia. This reaction proceeded in 49% yield. A highly pure sample of the resulting material was secured by preparative gas chromatography; this sample was utilized to secure a \(^2\)H-NMR of 16. Diene 16 differs from the previously prepared diene 12 by only the position of the deuterium label; the spectral data obtained for 16 then would be identical to that which was obtained for 12 except with regard to NMR peaks.
related to the position of the deuterium label. Compound 16 was characterized by $^2$H-NMR; a single resonance was observed at $\delta = 5.92$ ppm. Compound 16 was also characterized by MS, $^1$H-NMR, as well as $^{13}$C-NMR. These spectra were completely consistent with expectations based on previously collected spectral data for 12.

Diene 16 was subsequently treated with 30% hydrogen peroxide and anhydrous hydrazine in absolute ethanol at approximately $-17^\circ$C; reaction progress was monitored by AGC. Initially, a stoichiometric amount of hydrazine was added to the reaction vessel and hydrogen peroxide was added slowly (in 1 mL aliquots separated by approximately 2 hours). Two side products were observed; based on MS evidence these side products were proposed to be a doubly reduced structure and a structure in which the undesired double bond was reduced.

Initial slow development of products suggested that diimide – required for this reaction – was being formed but leaving the reaction vessel as a gas before reacting with 16. To probe this possibility, an additional stoichiometric amount of hydrazine was added to the reaction mixture. This addition caused a rapid acceleration in the rate of product formation. Once approximately 80% of the starting material had been consumed, the reaction was quenched. This was done because the selectivity observed in this reaction was being compromised; undesired products were beginning to evolve competitively with 8-\textit{d}-1. This reaction proceeded in 81% yield. Compound 8-\textit{d}-1 was isolated by preparative gas chromatography prior to complete structure determination. The mass spectrum of 8-\textit{d}-1 showed the expected $M^+ = 109$ peak. The $^{13}$C-NMR spectrum obtained for this compound was identical to the spectrum that had
been obtained for undeuterated $1$, with the exception of the $\delta = 22.1$ ppm signal. Due to the presence of deuterium, this signal was split into a $1:1:1$ triplet.
Thermal Reorganizations

Thermolysis of Bicyclo[4.2.0]oct-2-ene (1)

The thermal chemistry of bicyclo[4.2.0]oct-2-ene (1) was investigated at 300°C. By AGC analysis, the only product observed to evolve with time was identified as bicyclo[2.2.2]oct-2-ene (2) based on AGC co-injection with an authentic sample. AGC elution order of the compounds comprising the thermal product mixture was as follows: 2, 1, and cyclooctane (added as internal standard). Fragmentation products (ethylene and 1,3-cyclohexadiene) were also formed in the thermolysis of 1 but due to the volatility of these compounds, quantitative recovery of these components was impossible. Thus, an internal standard (in this case cyclooctane) was added so that the concentrations of the fragmentation products could be determined by difference.

Figure 1 illustrates the changes in concentration of compounds 1 and 2 with time. The first-order kinetic plot of starting material against time was also prepared; based on this analysis, the first-order rate constant for the disappearance of starting material is (1.37 ± 0.02) x 10^-5 s^-1 (Figure 2).

Thermal studies of 1 were also carried out at 275°C and 315°C to determine the overall rate of disappearance of 1 at these temperatures. The overall rate of decomposition of 1 was 1.7 x 10^-6 s^-1 at 275°C and was 4.4 x 10^-5 s^-1 at 315°C. An Arrhenius plot (Fig. 3) was prepared from these rate constants from which E_a = 52.1 kcal/mol and log(A) = 15.0 for the decomposition of 1.
Figure 1. Concentrations of 1, 2, and Fragments vs. Time at 300°C

Figure 2. First Order Kinetic Plot of 1 at 300°C
Figure 3. Arrhenius Plot of Decomposition of 1

**Thermolysis of Bicyclo[2.2.2]oct-2-ene (2)**

Activation parameters for the retro-Diels-Alder reaction of bicyclo[2.2.2]oct-2-ene have been reported. These data allowed calculation of a rate constant for this reaction at 300°C. Thermolysis of 2 was carried out despite the availability of these data in order to confirm that the experimental techniques employed in this study could reproduce rate data published elsewhere. Further, 2 had already been synthesized to enable independent proof of the observed product in the thermolysis of 1, and thus no additional synthetic work was necessary to allow for this study.

A number of experimental difficulties were experienced in obtaining an accurate rate constant for the decomposition of 2. Fractionation of the thermal sample proved
insurmountable when the internal standard was cyclooctane (which had been used in the study of 1); the ratio of substrate to internal standard when the sample was injected into the vacuum line was not the same as the ratio of substrate to internal standard that was successfully transferred to the thermal bulb. For this reason, a new internal standard was sought which would be more similar in volatility to 2 than cyclooctane; ethylcyclohexane was found to be a suitable standard. In addition to finding an appropriate internal standard, the study was also plagued by the fact that the thermal sample – even after being spiked with internal standard – was solid. This necessitated melting the sample to allow for syringe transfer to the vacuum line. The irreproducibility of the heating used to melt the thermal sample introduced unpredictable errors in the transfer of the thermal sample. To alleviate this issue, the thermal sample was dissolved in pentane. Due to the increased dilution introduced by the addition of pentane, 10 µL of the thermal sample was used in each of the thermal injections. The use of ethylcyclohexane as internal standard and pentane as a bath gas allowed many of the experimental difficulties to be overcome and allowed reasonable rate data to be obtained.

The decomposition of 2 proceeded extremely slowly at 300°C as thus the reaction was not followed to a significant amount of conversion. After 10 days of heating at 300°C, only 10% of the starting material had reacted. The disappearance of 2 and the evolution of fragmentation products with time can be seen in a plot of concentration of these compounds versus time (Figure 4).
Figure 4. Plot of 2 and Fragmentation Products vs. Time

Because there was a literature value for the rate of retro-Diels-Alder reaction of 2, it was deemed unnecessary to follow the reaction to longer times. A rate constant of $(1.3 \pm 0.1) \times 10^{-7} \text{s}^{-1}$ was determined from these data by first order kinetic analysis of 2 (Figure 5). The rate constant that was calculated from activation parameters reported by Huybrechts was $1.85 \times 10^{-7} \text{s}^{-1}$. Considering the experimental difficulties experienced in this thermal study, the observed agreement between the experimental and calculated rate constants is remarkable. Further, this observation confirms that the techniques employed in this study produce reproducible rate constants.
Figure 5. First Order Kinetic Plot of 2

Thermolysis of 7-d-bicyclo[4.2.0]oct-2-ene (7-d-1)

7-Deuteriobicyclo[4.2.0]oct-2-ene (7-d-1) was designed to examine the possibility of a two-centered epimerization reaction competing in the overall thermal manifold of the bicyclo[4.2.0]oct-2-ene system. In this possible reaction, the central C1-C6 bond would cleave leading to the formation of an allylically-stabilized diradical. This intermediate would then undergo a two-centered ring inversion (Figure 6). Reformation of the original carbon skeleton could be detected by inversion of stereochemistry at C7; the substituents on this carbon would be exchanged by two-centered epimerization.
Figure 6. Two-Centered Stereomutation of Bicyclo[4.2.0]oct-2-ene

Interconversion of \textit{endo}-7-\textit{d}-1 with \textit{exo}-7-\textit{d}-1 (Figure 6) would provide conclusive evidence of two-centered stereomutation. In contrast a C8 label could experience stereochemical scrambling by either a two-centered stereomutation (Figure 7a) or by a single centered epimerization following the cleavage of the C1-C8 bond (Figure 7b); thus, analysis of the thermal chemistry of the 8-\textit{d}-1 analog would yield a composite of one-centered and two-centered stereomutation (Figure 7).

Figure 7. Two Mechanisms for C8 Epimerization

To probe for the possibility of two-centered stereomutation, the thermal chemistry of 7-\textit{d}-1 was examined. Since there was significantly more deuterium in the \textit{endo}-
position in the starting material, if two-centered stereomutation were occurring, it would be expected that the ratio of \textit{endo}-7-d-1 to \textit{exo}-7-d-1 would decrease over time; the epimerization should be equally facile regardless of the initial position of the label and thus more \textit{endo}-d would epimerize to \textit{exo}-d than would epimerize in the other direction.

Samples of 7-d-1 were heated in the gas-phase at 300°C for 12, 18, 24, 30, and 36 hours. Analysis of the \textsuperscript{2}H-NMR spectra of the product mixtures indicated that two-centered stereomutation is not occurring. After 30 hours, there is no observable scrambling of the deuterium signal at the C7 position in 7-d-bicyclo[4.2.0]oct-2-ene; the \textit{endo}/\textit{exo} ratio for C7 deuterium in 7-d-1 is invariant over time. Further, the ratio of \textit{exo}-5-d-2 to \textit{endo}-5-d-2 in the bicyclo[2.2.2]oct-2-ene thermal products is equal to the \textit{endo}-to \textit{exo}- deuterium ratio in the starting material within experimental uncertainty (Table III).

\textbf{Table III.} Diasteriomeric Excess of Starting 1 and 2 in Thermolysis of 7-d-1 at 300°C

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% \textit{endo}-1</th>
<th>% \textit{exo}-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>82.3</td>
<td>-----</td>
</tr>
<tr>
<td>600.67</td>
<td>78.6</td>
<td>81.1</td>
</tr>
<tr>
<td>1082.30</td>
<td>83.3</td>
<td>87.4</td>
</tr>
<tr>
<td>1425.06</td>
<td>81.7</td>
<td>83.1</td>
</tr>
<tr>
<td>1770.17</td>
<td>85.4</td>
<td>84.8</td>
</tr>
<tr>
<td>2189.52</td>
<td>85.1</td>
<td>83.2</td>
</tr>
<tr>
<td>Average</td>
<td>83.6 ± 1.7</td>
<td>83.8 ± 2.3</td>
</tr>
</tbody>
</table>

Impurities were present in a number of the thermal samples analyzed by \textsuperscript{2}H-NMR that overlapped the signals of the C7 deuterium-labels in 7-d-1. These impurities were minor and thus did not have a large impact on the resulting integration values. In addition, two samples were secured which contained no observable impurities. The 29.5-hour sample clearly indicated that the stereochemical information of starting material 1
was completely retained in products 2. Specifically in the $^2$H-NMR in Figure 8, the relationships between the stereochemistry of 1 and the stereochemistry of 2 illustrate that there is not C7 stereochemical scrambling during this reaction.

**Table IV.** Stereochemical Data from 29.5 Hour Thermolysis of 7-\textit{d}-1 at 300°C

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>\textit{Exo}-7-\textit{d}-1</th>
<th>\textit{Endo}-7-\textit{d}-1</th>
<th>\textit{Exo}-5-\textit{d}-2</th>
<th>\textit{Endo}-5-\textit{d}-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.5</td>
<td>14.6%</td>
<td>85.4%</td>
<td>84.8%</td>
<td>15.2%</td>
</tr>
</tbody>
</table>
Thermolysis of $8$-$d$-bicyclo[4.2.0]oct-2-ene (8-$d$-1)

The study of 8-$d$-1 was designed to elucidate two separate processes in the thermal manifold of 1. First, deuterium-labeling at C8 allows for the observation of one-centered stereomutation. If the C1-C8 bond were to cleave, yielding an allylic, alkyl diradical; rotation about the C7-C8 bond prior to reclosure to 8-$d$-1 would result in stereochemical scrambling at the C8 position (Figure 7b). Secondly, since C8 is the migrating carbon atom, deuterium-labeling at the position would allow for the evaluation of the stereochemistry of the [1,3] carbon migration in the isomerization of 1 to 2. The thermal processes under investigation utilizing this substrate are illustrated below.
Six samples of 8-\textit{d}-1 were heated in the gas phase at 300°C for periods between 3.5 and 30 hours. The thermal product mixture was dissolved in chloroform and analyzed by $^2$H-NMR. Analysis of the resulting spectra revealed two significant findings. First, one-centered stereomutation is the dominant process in the thermal manifold of 8-\textit{d}-1; the diasteriomeric excess that was observed in the starting material (approximately 85 : 15 in favor of \textit{endo-d}) approaches 50:50 much more quickly than starting material is converted to either \textit{d}_1\textit{-2} or to fragmentation products; the endo-exo equilibration occurs 14 times more quickly than [1,3] carbon migration. This observation is significant primarily because one-centered stereomutation in the cyclobutane moiety cannot be explained without invoking a diradical intermediate. A concerted mechanism thus cannot reasonably be drawn that results in the observed stereomutation. Figure 10 illustrates
that diastereomeric excess decayed much more rapidly than did any skeletal isomerization of 1.

**Figure 10.** Plot of Disappearance of Diastereomeric Excess (de) vs. Time (min)

The second significant observation that was apparent from analyzing the $^2$H-NMR spectra that resulted from the thermal study of 8-\textit{d}-1 was that the \textit{si} product is kinetically favored over the \textit{sr} product by a small amount; \textit{si}/\textit{sr} $\approx$ 1.4. Based on a least-squares exponential fit of that $^2$H-NMR integrations, $k_{si} = 2.46 \times 10^{-6}$ s$^{-1}$ and $k_{sr} = 1.80 \times 10^{-6}$ s$^{-1}$ (Figures 11 and 12).
The observed one-centered stereomutation coupled with the lack of [1,3] carbon migration stereoselectivity is consistent with a diradical intermediate generated by C1-C8.
bond cleavage. The intermediate has sufficient lifetime to explore a significant amount of conformational space.
2.2: Thermal Chemistry of 8-Methylbicyclo[4.2.0]oct-2-ene

8-\textit{Exo}-methylbicyclo[4.2.0]oct-2-ene (18a) is observed to undergo [1,3] sigmatropic rearrangement to 5-methylbicyclo[2.2.2]oct-2-enes at 275-315°C. The symmetry-allowed (\textit{si}) product is observed to be favored over the symmetry-forbidden (\textit{sr}) product by a factor of 2.4; this ratio is independent of temperature. Epimerization and fragmentation processes from 18a are competitive with [1,3] migration. A diradical intermediate can be invoked to rationalize these observations.

Results and Discussion

Synthesis

Preparation of 8-Methylbicyclo[4.2.0]oct-2-ene

\textbf{Scheme 5.} Synthetic Sequence Towards 8-Methylbicyclo[4.2.0]oct-2-ene

\textsuperscript{e} The experimental details for the preparation of 18 appear in Experimental 2.2.
Two approaches were employed to generate the carbon skeleton needed in 8-methylbicyclo[4.2.0]oct-2-ene (18). In the first method, ketene was generated by the reaction of triethylamine with propionyl chloride in the presence of 1,3-cyclohexadiene. The ketene added to the cyclohexadiene to yield 8-methylbicyclo[4.2.0]oct-2-en-7-one (21). This reaction was observed to proceed in exceedingly low yields. In a number of attempts to utilize this cycloaddition reaction, yields of no greater than 5% were achieved.

Due to the extremely low yields in this reaction – mostly attributed to the instability of the ketene that was generated from propionyl chloride – the reaction was also performed using 2-chloropropionyl chloride. The ketene that is generated upon treatment of this compound with triethylamine is much more reactive preferentially toward the 1,3-cyclohexadiene than the aforementioned ketene species, and accordingly this reaction was observed to proceed with 63% yield. The resulting product, 8-chloro-8-methylbicyclo[4.2.0]oct-2-en-7-one (20), was then dechlorinated by treatment with zinc metal in glacial acetic acid; this reaction proceeded in 53% yield. This two-step sequence produced (21) in 33% overall yield, clearly far superior to the single step synthetic approach.

A two-step low temperature Wolff-Kishner reduction was employed to reduce the ketone moiety in 21. The conversion of this ketone to 22 proceeded in good yield. Typically the reaction yielded hydrazone in greater than 80% yield. The product of this reaction was characterized by IR only; disappearance of the peak corresponding to the carbonyl stretching frequency and the evolution of peaks expected for the hydrazone were used as evidence of successful conversion.
The potassium tert-butoxide mediated reduction of 22 was carried out a number of times. The best yield observe from these iterations was 61%. While the vast majority of the methyl ketone was of endo geometry, base-catalyzed epimerization resulted in the hydrocarbon being produced in almost exclusive exo geometry. Thus, the purification of 18a was easily carried out by preparative gas chromatography. Similar purification of 18b was not carried out due to the small amount of it present in the product mixture; purification of this material would have been exceptionally difficult. Both 18a and 18b had previously been characterized rigorously; the samples prepared herein were spectrally identical to authentic samples.

While complete structure proof is outside the scope of this work, the assignment of the stereochemistry of C8 in 18 does merit mention. $^1$H-NMR was utilized to assign the stereochemistry of the methyl group; exo-methyl and endo-methyl exhibit different chemical shifts. The doublet peak – due to the methyl group – that was observed in the $^1$H-NMR of 18a was observed at $\delta = 1.12$ ppm. In contrast, the corresponding peak in the spectrum of 18b was at $\delta = 0.84$ ppm. The endo-methyl group is inside the shielding cone of the carbon-carbon double bond, and thus, the peak corresponding to the methyl protons should be more upfield for endo-methyl versus exo-methyl. This was the primary evidence brought to bear on the structural assignments of 18a and 18b.
Thermal Reorganizations

Thermolysis of 8-Methylbicyclo[4.2.0]oct-2-ene (18a)

Thermolysis reactions were carried out starting with 18a at both 300°C and 315°C using propylcyclohexane as an internal standard. The progress of these reactions was monitored by capillary gas chromatography. The components of the reaction mixture were shown to elute in the following order (Table V).

Table V. GC Elution Order of Products of Thermolysis of 18a

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-endo-methylbicyclo[2.2.2]oct-2-ene</td>
<td>12.9</td>
</tr>
<tr>
<td>5-exo-methylbicyclo[2.2.2]oct-2-ene</td>
<td>13.5</td>
</tr>
<tr>
<td>8-exo-methylbicyclo[4.2.0]oct-2-ene</td>
<td>13.9</td>
</tr>
<tr>
<td>Propylcyclohexane</td>
<td>14.2</td>
</tr>
<tr>
<td>8-endo-methylbicyclo[4.2.0]oct-2-ene</td>
<td>15.3</td>
</tr>
</tbody>
</table>

The plot below illustrates the concentrations each of the reaction mixture constituents as a function of time.
Figure 13. Plot of Concentrations vs. Time in the Thermolysis of 18a (275°C)

Plotting the first-order kinetic analysis of [18a] against time, the overall rate constant for the disappearance of 18a was calculated.
Figure 14. First Order Kinetic Analysis of 18a (275°C)

Figure 14. First Order Kinetic Analysis of 18a (275°C)

Thermolyses of 18a were done at 275, 300, and 315°C. Based on the rate constants measured at these temperatures, activation parameters for both overall disappearance of 18a as well as for the [1,3] carbon migration were calculated. For the overall disappearance of 18a $E_a = 44.3 \pm 1.5$ kcal/mol and log(A) = 12.8 ± 0.6. For the [1,3] sigmatropic rearrangement of 18a $E_a = 46.3 \pm 1.9$ kcal/mol and log(A) = 12.7 ± 0.7. These values were is close agreement to those reported by Berson.¹⁹

The kinetic data observed in the thermolysis of 18a are consistent with a diradical-mediated mechanism. At 300°C, $si/sr = 2.4$; the difference between the rate constants for the formation of the $si$ product and the formation of the $sr$ product translates to an energy difference between the two pathways of less than 1 kcal/mol. This value is very similar to Houk’s calculation for the difference between the two pathways.⁴⁷
In general, [1,3] carbon migration in the thermolysis of 18a was not the process of the overall thermal manifold; fragmentation and stereomutation were competitive processes. Leber et al. have asserted that the fact “that such processes can indeed compete with the [1,3] sigmatropic rearrangement further strengthens the presupposition of an incipient diradical intermediate.”\textsuperscript{31}
2.3 Conclusions Based on Methyl vs. Deuterium Comparisons

A number of important comparisons can be made between the bicyclic vinylcyclobutane work presented herein and work that has previously been reported. Three postulates concerning [1,3] sigmatropic carbon migrations have been articulated.\textsuperscript{9,31}

- the \textit{si/sr} ratio correlates with the conformational flexibility of the $\pi$ system
- a methyl substituent on the migrating carbon slows down the rate of rotation relative to a deuterium substituent in a short-lived diradical and thus results in a higher \textit{si/sr} ratio
- fragmentation and stereomutation will compete with [1,3] shifts in conformationally labile diradicals.

Comparison of similarly substituted systems containing differing carbon skeletons will allow the first of the predictions to be tested. First, the [1,3] migration of bicyclo[4.2.0]oct-2-ene systems is stereorandom as compared to the stereochemistry of the [1,3] migration observed in bicyclo[3.2.0]hept-2-ene. Specifically, deuterium labeled 8-$d_1$-bicyclo[4.2.0]oct-2-ene rearranges with $\textit{si/sr} = 1.4$, while 6,7-$d_2$-bicyclo[3.2.0]hept-2-ene rearranges with $\textit{si/sr} = 3$.\textsuperscript{21} A similar trend is observed with comparing methyl-labeled derivatives; \textit{exo}-8-methylbicyclo[4.2.0]oct-2-ene rearranges with $\textit{si/sr} = 2.4$\textsuperscript{31} while \textit{exo}-7-methylbicyclo[3.2.0]hept-2-ene rearranges with $\textit{si/sr} = 7$.\textsuperscript{26} In both of the aforementioned cases, the smaller ring systems rearranged with greater stereoselectivity than the respective larger ring systems. These differences can be rationalized by comparing the distance between the migration termini.
Table VI. *si*/sr for a Methyl- and Deuterium- Labeled Vinylcyclobutanes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Methyl-Derivative</th>
<th><em>si</em>/sr</th>
<th>Deuterium-Derivative</th>
<th><em>si</em>/sr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Methyl-Derivative 1" /></td>
<td>200</td>
<td><img src="image" alt="Deuterium-Derivative 1" /></td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Methyl-Derivative 2" /></td>
<td>6.8</td>
<td><img src="image" alt="Deuterium-Derivative 2" /></td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Methyl-Derivative 3" /></td>
<td>2.4</td>
<td><img src="image" alt="Deuterium-Derivative 3" /></td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Methyl-Derivative 4" /></td>
<td>1.8</td>
<td><img src="image" alt="Deuterium-Derivative 4" /></td>
<td>Baldwin, unpublished\textsuperscript{28}</td>
</tr>
</tbody>
</table>

The larger the linear distance between the termini of migration, the more time the diradical intermediate has to explore conformational space. Because the distance between termini is larger in bicyclo[4.2.0]oct-2-ene systems, as a result of conformational flexibility, the observed trends in stereoselectivity are consistent with prediction.

Table II. Migration Distances for Various Carbon Skeletons\textsuperscript{48}

<table>
<thead>
<tr>
<th>Carbon Skeleton</th>
<th>Distance Between Migration Termini</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicycle[2.1.1]hex-2-ene</td>
<td>2.444 Å</td>
</tr>
<tr>
<td>Bicyclo[3.2.0]hept-2-ene</td>
<td>3.383 Å</td>
</tr>
<tr>
<td>Bicyclo[4.2.0]oct-2-ene</td>
<td>3.474 Å</td>
</tr>
</tbody>
</table>
When the tabulated stereochemical data in Table I is viewed in light of the inter-termini distances (Table II), it can be seen that as inter-termini distance increases (moving from bicyclo[2.1.1]hex-2-ene to bicyclo[3.2.0]hept-2-ene to bicyclo[4.2.0]oct-2-ene) the stereoselectivity of the rearrangement goes down, with both methyl- and deuterium-labeling. The data presented above support the validity of Postulate 1.

The other major comparison of interest is that between molecules with the same fundamental carbon skeleton but differing in substitution. The observed trend – deuterium-labeled compounds rearrange with less stereoselectivity than do methyl-labeled compounds – can be justified based on dynamic factors. Carpenter’s dynamic simulations of [1,3] rearrangements showed that bond cleavage in strained hydrocarbons requires both bond stretching as well as bond rotation. When bond cleavage is accompanied by rotational motion (which moves any substituents present into to π-face), bonding is maintained for longer and thus the process is lower than energy than if such rotation were not occurring. Once the substituent is under the π-system, a methyl-substituent interferes with free rotation; methyl-labeled vinylcyclobutanes are restricted to product formation following a half of a rotation. Deuterium-labeled analogs are not similarly constrained. There is no steric interference to free rotation and thus product formation is not bound to occur from half-rotation. The differences between the rotational abilities of these substituent groups is reflected in the disparate stereoselectivities that are observed.

In the bicyclo[3.2.0]hept-2-ene systems that have previously been reported, it has been pointed out that this prediction of methyl- vs. deuterium stereoselectivities is in fact observed; the methyl-labeled substrate rearranges with greater stereoselectively than does
the deuterium labeled analog. This trend is again observed in the systems that are reported herein. As seen in Table 1, Entry 3, 8-methylbicyclo[4.2.0]oct-2-ene undergoes \([1,3]\) sigmatropic rearrangement with greater stereochemical preference than does 8-\(d\)-bicyclo[4.2.0]oct-2-ene. In all three of the carbon skeletons that are presented in Table 1, it is observed that methyl-labeled derivatives rearrange with greater stereoselectivity than do the deuterium-labeled analogs. Comparison between the data presented above for methyl and deuterium substituted vinylcyclobutanes supports the validity of Postulate 2.

In addition to Postulates 1 and 2, the observed data also supports the validity of Postulate 3. For instance, stereomutation and fragmentation, together, comprise 50\% of the product distribution in the thermolysis of deuterium-labeled 6,7-\(d_2\)-bicyclo[3.2.0]hept-2-ene. On the other hand, when the thermal chemistry of 8-\(d_1\)-bicyclo[4.2.0]oct-2-ene is examined, stereomutation and fragmentation comprise 90\% of the product distribution. Surprisingly, the portion of the product mixture that is made up of fragmentation does not increase moving from the bicyclo[3.2.0]hept-2-ene skeleton to the bicyclo[4.2.0]oct-2-ene skeleton; however, the sum of fragmentation and stereomutation processes does increase moving towards more flexible carbon skeletons. As conformational flexibility increases, more one-centered stereomutation (epimerization) occurs at the expense of the \([1,3]\) shift.
Chapter 3: Thermal Chemistry of Tricyclic Vinylcyclobutanes

The degree of orbital symmetry control over the [1,3] sigmatropic rearrangement of trans, cis, trans-tricyclo[6.3.0.0²⁷]undec-3-ene (1) is investigated herein. Due to the geometrical constraints present in 1, all [1,3] rearrangement pathways are geometrically forbidden except suprafacial migration with retention of stereochemistry (sr), the symmetry-forbidden product. In previously studied systems, the suprafacial inversion (si) product is known to be favored, but extrasymmetric elements present in 1 prevent this product from being formed. The only observed product in the thermolysis of 1 is the symmetry forbidden 2; hence, \( si/sr = 0 \).

Compound 1 was accessed in three synthetic steps from commercially available materials and was converted to 5 for structure proof (Scheme 1).

\[
\begin{align*}
&\text{Scheme 1. Synthetic Approach Towards 1} \\
1.) &\text{H}_2\text{NNH} \text{Ts} + \text{CH}_3\text{OH (4) } \text{or} \text{H}_2 / \text{Pd (5)}
\end{align*}
\]

Compound 2 was prepared in four synthetic steps from commercially available materials and was reduced to 9 for structure proof (Scheme 2).

\[
\begin{align*}
&\text{Scheme 2. Synthetic Approach Towards 2} \\
1.) &\text{LAH / THF (7) } \\
2.) &\text{MsCl / Et}_3\text{N (8)} \\
3.) &\text{LiEt}_3\text{BH / THF (9)}
\end{align*}
\]
Introduction

Although significant work on monocyclic and bicyclic vinylcyclobutanes has been accomplished thus far, no work has been reported on the investigation of the thermal behavior of analogous tricyclic vinylcyclobutanes. Tricyclic divinylcyclobutanes have, however, been investigated. The chemistry of divinylcyclobutanes will be discussed in order of increasing number of rings. Monocyclic compounds are discussed first, as larger systems should be viewed in light of the results observed in these systems containing one ring. Following the discussion of monocyclic compounds, results from both bicyclic and tricyclic divinylcyclobutanes are presented. Similar to the studies previously presented, the results used to probe these systems are primarily energetic and stereochemical in nature.

The thermal behavior of both cis- (10) and trans-divinylcyclobutane (11) have been reported. A study by Vogel showed that 10 rearranges via a presumably concerted [3,3] sigmatropic pathway to cis-1,5-cyclooctadiene at 120°C (Figure 1).

![Figure 1: Observed Rearrangement of cis-1,2-divinylcyclobutane (10)](image)

Hammond et al. later conducted a study in which the thermal behavior of trans-1,2-divinylcyclobutane was elucidated. Trans-1,2-divinylcyclobutane (11) was shown to yield a mixture of products (Figure 2).
Hammond acknowledged that in this study, it was unclear if 1,5-cyclooctadiene were formed directly from the starting material or via the intermediacy of cis-divinylcyclobutane, which is thermally unstable under the experimental conditions used in this study.

Hammond argued for a “mechanistic discontinuity” between the rearrangements of cis- and trans-divinylcyclobutane; while the cis-isomer rearranges via a concerted pathway, the trans-isomer can not assume the necessary geometry for this mechanism and thus rearranges via a diradical intermediate. Two distinct pieces of evidence provide primary support for this hypothesis. First, a single product is observed in the

Figure 2: Observed Rearrangement of trans-1,2-divinylcyclobutane (11)
rearrangement of the 10 and this result is consistent with a concerted mechanism, while the multitude of products in the study of 11 is consistent with a diradical intermediate. Secondly, the activation parameters are consistent with these mechanistic assignments; the enthalpy of activation ($\Delta H^\ddagger$) for the reaction of 10 is significantly lower than the bond dissociation energy while the $\Delta H^\ddagger$ for the reaction of 11 is similar to the bond dissociation energy. In addition, the entropy of activation ($\Delta S^\ddagger$) for these reactions in also consistent with these proposed mechanisms. The $\Delta S^\ddagger$ for the reaction of 10 is $-11.7$ e.u., which indicates a highly structured transition state as would be expected in a concerted reaction. The $\Delta S^\ddagger$ for the reaction of 11 is $-1.2$ e.u., a value relatively close to zero. This parameter suggests that the transition state is similar in structure to the starting materials, indicating the likely intermediacy of a diradical.

Table I. Activation Parameters for Divinylcyclobutanes

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta H^\ddagger$ (kcal/mol)</th>
<th>$\Delta S^\ddagger$ (e.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>23.1</td>
<td>$-11.7$</td>
</tr>
<tr>
<td>11</td>
<td>34.0</td>
<td>$-1.2$</td>
</tr>
</tbody>
</table>

*Endo-7-methyl-exo-7-vinylbicyclo[3.2.0]hept-2-ene (12) – a more structurally rigid divinylcyclobutane than the aforementioned monocyclic compounds – was studied by Forman and Leber (see Figure 3).*
At $150^\circ$-$166^\circ$C compound 12 rearranges to yield predominantly 16. A plot of the concentration of 15 against time shows a rapid increase in 15 followed by a gradual decrease with longer times. This behavior is consistent with 15 being an intermediate in the eventual production of 16. Minor products 14 and 17 were also observed in the thermolysis mixture. While no 13 was observed, models of 12 indicate that it is not flexible enough to “allow for a stereodistal Cope Rearrangement.” For this reason, it appears that 13 is necessarily an intermediate in the production of 17.

### Table II. Activation Parameters in Rearrangement of 12

<table>
<thead>
<tr>
<th></th>
<th>$\Delta H^\ddagger$ (kcal/mol)</th>
<th>$\Delta S^\ddagger$ (e.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$12 \rightarrow 15$</td>
<td>36.7 ($\pm$3)</td>
<td>+3.9 ($\pm$7)</td>
</tr>
<tr>
<td>$15 \rightarrow 16$</td>
<td>32.9 ($\pm$2)</td>
<td>-2.8 ($\pm$4)</td>
</tr>
<tr>
<td>$13 \rightarrow 17$</td>
<td>21 ($\pm$7)</td>
<td>-22 ($\pm$16)</td>
</tr>
</tbody>
</table>
**Table III.** Rate Constants (k x 10^5 s) for Rearrangement of 12

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>k₁</th>
<th>k₂</th>
<th>k₃</th>
<th>k₄</th>
<th>k₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>150.0</td>
<td>0.032</td>
<td>0.032</td>
<td>0.892</td>
<td>2.52</td>
<td>244</td>
</tr>
<tr>
<td>158.0</td>
<td>0.076</td>
<td>0.076</td>
<td>2.07</td>
<td>5.3</td>
<td>510</td>
</tr>
<tr>
<td>166.0</td>
<td>0.16</td>
<td>0.16</td>
<td>4.53</td>
<td>10.9</td>
<td>626</td>
</tr>
</tbody>
</table>

Based on the activation parameters in Table 2, the [3,3] sigmatropic reaction 13 → 17 was designated a concerted reaction. The other [3,3] migration (15 → 16) is not obviously concerted based on activation parameters but was assigned as such in this study. The si/sr ratio for the rearrangement of 12 was 0.04 based on the relative amounts of the two [1,3] sigmatropic migration products that were produced (see Table III). In this study, as opposed to those previously conducted, epimerization of 12 to 13 accounted for a small portion of the overall rate of rearrangement. Using group additivities, the energy cost for the formation of a bisallylic diradical is estimated to be 32 kcal/mol (84 kcal/mol (C-C bond dissociation energy) – 2(12 kcal/mol) (allylic stabilization energy) – 28 kcal/mol (relief of cyclobutane ring strain). For the 12 → 15 pathway, the ΔH‡ was 36.7 kcal/mol, within the energetic requirement for the formation of an bisallylic stabilized diradical, thus suggesting that this reaction is mediated by a diradical. The experimental activation energies are close but not equal to those predicted for the diradical process, but due to difficulties in estimating the activation energies of these systems, the “energetic criterion of concert fails when observed activation energies approach those estimated for nonconcerted paths.” Finally, the ΔS‡ for the reaction 12 → 15 was +3.7 e.u. compared to the value of +9.9 e.u estimated by Benson for the bisallylic diradical.
Tricyclic divinylcyclobutanes were first studied by Hammond et al. in the investigation of the thermal behavior of tricyclo[6.4.0.0\textsuperscript{2,7}]dodeca-3,4-dienes.\textsuperscript{53} At conditions above 160°C Hammond observed the following [1,3] rearrangements and reported activation parameters for each of the reactions. According to his report, each of these reactions led to a single isomeric product as illustrated (Figures 4 and 5).

\[ \text{Figure 4: anti-tricyclo[6.4.0.0\textsuperscript{2,7}]dodeca-3,4-diene (18)} \]

\[ \text{Figure 5: syn-tricyclo[6.4.0.0\textsuperscript{2,7}]dodeca-3,4-diene (19)} \]

<table>
<thead>
<tr>
<th>Table IV. Activation Parameters for Tricyclic Divinylcyclobutanes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>19</td>
</tr>
</tbody>
</table>

The activation parameters for both of these compounds are similar to those of trans-divinylcyclobutane as well as those of the [1,3] \textit{sr} pathway in the rearrangement of endo-7-methyl-exo-7-vinylbicyclo[3.2.0]hept-2-ene, both of which are believed to involve diradical intermediates (Table IV). These $\Delta H^\ddagger$ values (36.8 and 33.0 kcal/mol,
respectively) are similar to the expected bond dissociation energy, consistent with diradical-mediated reactions. While 18 clearly has the two vinyl groups in the same position as the trans-divinylcyclobutane, and thus would be expected to react similarly, why does 19, which is structurally analogous to cis-divinylcyclobutane, undergo [1,3] rearrangement instead of the [3,3] migration as was observed in the monocyclic compound?

The presence of a three-ring system in these compounds provides a rigid structure in which the two vinyl groups are much more geometrically constrained than in the monocyclic analogs. The transition state in a concerted reaction is highly structured and has a precise geometry. The geometrical rigidity present in these molecules prevents them from adopting the molecular topology that is necessary for a concerted reaction. Because the concerted reaction transition state geometry is precluded in these systems by their restrictive geometry, both of these molecules react via a diradical-mediated mechanism.

In a study directly analogous to Hammond’s work, Doering et al. reported the thermal chemistry of tricyclic divinylcyclobutanes 20 and 21.⁵
The thermal chemistry observed for 20 and 21 is similar to the thermal chemistry of 18 and 19 except that fragmentation reactions were observed in the thermolysis of 20 and 21. Hammond did not explicitly state that fragmentation products were observed. The fragmentation products probably were not observed based on Hammond’s comment that “the reactions [were] shown to go essentially to completion.” In contrast, cyclopentadiene was observed in evolve with time in the thermolysis of both 20 and 21. At 190°C fragmentation of 20 is approximately 1.3 times more favorable than [1,3] sigmatropic rearrangement; at the same temperature, 21 fragments with 2.2 times greater facility than it undergoes [1,3] sigmatropic rearrangement. The difference between the facility with which these structures undergo fragmentation can be rationalized by differences in steric interactions of the five-membered rings. After formation of a diradical intermediate, structure 21 is more likely to lead to fragmentation products than 20 due to steric interactions between the syn-five-membered rings.

**Figure 6.** Observed Thermal Reactions of 20 and 21
Similar to the thermal chemistry of tricyclic divinylcyclobutanes, the thermolysis of 1 is potentially interesting because the only geometrically allowed product is the symmetry-forbidden 2 (Figure 7).

![Figure 7. Geometry-Allowed (sr) Product for 1](image)

Because the migrating carbon is constrained within a ring, the conformational flexibility of any potential intermediate is reduced. If 1 were to rearrange via the $si$ pathway, the cyclopentane ring that contains the migrating carbon would experience significant geometrical distortion (Figure 8).

![Figure 8. Symmetry-Allowed (si) Product for 1](image)

The $sr$ pathway is forbidden by orbital symmetry but the fact that the product resulting from this pathway does not impose gross geometrical contortions in the third ring may make this pathway more favorable.

Because the inversion product is precluded by geometry, thermal studies of these molecules will answer a number of interesting questions. Because both of the orbital-
symmetry allowed reaction pathways are not available to these molecules, will any [1,3] rearrangement occur? Further, if the forbidden product is observed, what portion of the product mixture will it represent? If the forbidden pathway is in fact the only pathway that is realized, is there a significant energy cost for the forbidden rearrangement compared to systems in which the allowed pathway is realized? The distribution of products and the rate of formation of each of them will help to answer these questions and will allow mechanistic conclusions to be drawn.
Results and Discussion

Synthesis

Preparation of cis, anti, cis-tricyclo[6.3.0.0^{2,7}]undec-3-ene (1)

Scheme 1. Synthetic Scheme Towards cis, anti, cis-tricyclo[6.3.0.0^{2,7}]undec-3-ene

\[\text{The experimental details for the preparation of 1 appear in Experimental 3.1}\]

\(\text{Cis, anti, cis-tricyclo[6.3.0.0^{2,7}]undec-3-one (3) – the product of the photoaddition of 2-cyclohexenone and cyclopentene – had been prepared by Bogdan}^{54}\ \text{and was used in the following synthetic work. A }^{13}\text{C-NMR spectrum of this compound showed close agreement with a literature report for the anti-isomer of this ketone and that the predominant isomer of 3 prepared in the aforementioned [2+2] cycloaddition was in fact the anti-isomer.}^{55}\)

\(\text{Without further purification 3 was converted to tosylhydrazone 4 upon treatment with } p\text{-toluenesulfonyl hydrazide. The reaction proceeded in 55-70\% conversion of 3 to 4 in multiple trials. Formation of 4 was extremely slow; 10-12 days were usually required for crystallization to be observed. The long reaction times were attributed to the use of impure 3 as starting material for the reaction – impurities in the ketone likely retarded crystallization. In fact, reactions performed on column-purified material proceeded with similar yields as those reactions starting with impure reactions, although}\)
product formation was observed much more quickly. After being washed and dried under reduced pressure, 4 melted between 130-134°C. This relatively small temperature range indicates that the crystals were fairly pure, and thus no purification of the material was attempted.

Treatment of 4 with methyl lithium yielded two isomers of 1 by GC analysis. The major constituent (later eluting peak) comprised 86% of the product mixture. Not only was the Shapiro reaction clean, but it also gave reasonably good yields of 1; as much as 76% was recovered from this reaction. Coinjection with an authentic sample produced by Bogdan indicated that the product was 1. Compound 1 was easily purified and isolated by preparative gas chromatography.

**Assignment of Geometry for Major Isomer of Compound 1**

The major isomer of 1 was hydrogenated and NMR data was obtained for the resulting saturate hydrocarbon. $^{13}$C NMR chemical shifts have not been reported for 5, but $^{13}$C chemical shifts have been reported for both syn- and anti- isomers of homologous 10 and 12 carbon systems (Table V).[^56]
Table V. $^{13}$C-NMR Data for 10- and 12-Carbon Homologues

<table>
<thead>
<tr>
<th></th>
<th>I.</th>
<th>II.</th>
<th>III.</th>
<th>IV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>33.8</td>
<td>34.3</td>
<td>41.4</td>
<td>37.6</td>
</tr>
<tr>
<td>b.</td>
<td>26.6</td>
<td>22.5</td>
<td>32.7</td>
<td>26.1</td>
</tr>
<tr>
<td>c.</td>
<td>22.6</td>
<td>22.2</td>
<td>24.5</td>
<td>28.0</td>
</tr>
</tbody>
</table>

The chemical shifts reported for these two compounds were compiled and chemical shifts for the 11-carbon system were estimated based on the data from these two systems; it was assumed that solvent effects – Salomon et al. obtained spectra in CCl$_4$ while we obtained spectra in CDCl$_3$ – would be negligible. Estimates were made by assuming that the 5-membered ring of 1 would have similar chemical shifts to the 10-carbon system and that the 6-membered ring of 1 would have similar chemical shifts to the 12-carbon system. Predictions were made for both syn-1 as well as for anti-1 and the experimentally obtained chemical shift values were compared with those predictions. All application shift values and predictions are compiled below (Table VI).
Table VI. Comparison of Predicted and Observed Chemical Shifts

<table>
<thead>
<tr>
<th></th>
<th>V.</th>
<th>VI.</th>
<th>Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>41.4</td>
<td>37.6</td>
<td>43.2</td>
</tr>
<tr>
<td>b.</td>
<td>32.7</td>
<td>26.1</td>
<td>32.2</td>
</tr>
<tr>
<td>c.</td>
<td>24.5</td>
<td>28.0</td>
<td>26.3</td>
</tr>
<tr>
<td>d.</td>
<td>33.8</td>
<td>34.3</td>
<td>35.2</td>
</tr>
<tr>
<td>e.</td>
<td>26.6</td>
<td>22.5</td>
<td>26.6</td>
</tr>
<tr>
<td>f.</td>
<td>22.6</td>
<td>22.2</td>
<td>20.7</td>
</tr>
</tbody>
</table>

The observed shifts were in close agreement with the chemical shifts that were predicted for the *anti*-isomer of the 11 carbon system. Further evidence for the geometrical assignment comes from a homologous synthesis. Bogdan prepared a 12 carbon analog of 1 and showed that the major isomer prepared in that synthesis was also *anti*. The similarity in the approaches used in the syntheses of these two compounds as well as the close agreement between prediction and experiment are conclusive evidence that the major isomer of 1 that was produced is, in fact, the *anti*-conformation.
Preparation of *endo*-Tricyclo[5.2.2.0²,⁶]undec-8-ene (2)°

![Scheme 2. Synthetic Scheme Towards 2](image)

° The experimental details of the preparation of 2 are presented in Experimental 3.2

The Lewis-acid-catalyzed Diels-Alder reaction of cyclohexadiene and 2-cyclopentenone was performed under two sets of conditions. First, the reaction was run using aluminum chloride as a catalyst and using modest heating of the reaction for 144 hours. The reaction solution was dark orange at the conclusion of the reaction, which was likely due to hydrolyzed catalyst. NMR and GC-MS were both consistent with reported data for 6.⁵⁷

A number of preliminary attempts to convert 6 to 2 were unsuccessful; compound 2 was not isolated from a number of Wolff-Kishner reactions nor from the treatment of 6 with *p*-toluenesulfonylhydrazide and sodium cyanoborohydride. The difficulties prompted an attempt to prepare 2 from 6 according to procedures outlined by Masjedizadeh *et al.*⁵⁸ This approach involved the reduction of the ketone moiety, conversion of the resulting alcohol to a mesylate derivative, followed by treatment with lithium aluminum hydride.
Treatment of 6 with sodium borohydride resulted in slow reduction to endo-tricyclo[5.2.2.0²,6]undec-8-en-3-ol (7). Due to the slow rate of reaction, a stronger hydride donor was used. Upon treatment of 6 with lithium aluminum hydride, 6 was completely converted to 7 following 8 hours of reaction. IR analysis showed the absence of a carbonyl peak and the presence of peaks diagnostic of alcohols. The only difficulty experienced with this procedure was that when solid LAH was used, quenching with methanol generated solids from which it was difficult to isolate 7. This minor difficulty was avoided by obtaining a commercial solution of LAH in THF and working up with ethanol and dilute HCl. Thus, flocculate aluminum salts were avoided and 7 was easily isolated from the reaction mixture.

Compound 7 was converted to the corresponding mesylate (8) using methane sulfonyl (mesyl) chloride and triethylamine. The reaction was observed to proceed extremely rapidly, becoming rapidly darker and turning opaque brown as the mesyl chloride was added. The reaction was quenched after stirring overnight, and the product was extracted. IR analysis showed the disappearance of the O-H stretch that was present in the starting materials and the evolution of peaks expected of a mesylate derivative; the broad peak at 3400 cm⁻¹ disappeared and peaks at 1050 and 1350 cm⁻¹ (S=O asymmetric and symmetric stretching) were observed in the IR of 8. This compound was not purified before being used in further reactions.

Compound 8 was reduced to endo-tricyclo[5.2.2.0²,6]undec-2-ene (2) by treatment with lithium triethylborohydride (Superhydride) at 40°C. GC-MS analysis indicated that the desired product was formed in good yield and that none of the potential elimination-reaction-product had been generated. The reaction was also performed using lithium
aluminum hydride, but under these conditions elimination was observed. Two peaks were observed in the AGC trace, with very similar retention times, in a ratio of 3 : 1. These peaks were assigned as the endo- and exo isomers respectively.

Compound 2 was isolated by preparative gas chromatography. The two aforementioned isomers of 2 were inseparable under the GC conditions employed for preparative GC. Due to this difficulty, the two isomers were isolated as a mixture. Since, during thermolysis, each of these isomers will irreversibly yield fragmentation products, the thermal behavior of the desired isomer can be elucidated by performing thermolysis on a mixture of the two isomers without further purification.

A mixture of the two isomers was hydrogenated. GC-MS analysis indicated that hydrogenation caused the product to gain two mass units, consistent with a monounsaturated structure. NMR analysis of 9 was consistent with literature reports of this compound.\textsuperscript{59}

**Thermolysis of cis, anti, cis-Tricyclo[6.3.0.0\textsuperscript{2,7}]undec-3-ene (1)**

Reproducible thermal data could not be obtained for the thermolysis of 1 at Franklin and Marshall College due to fractionation of the reaction mixture; the low volatility of these compounds made vacuum line transfer of the reaction mixture difficult. This experimental difficulty was avoided by performing the study at Syracuse University where vacuum line techniques were not necessary to introduce the reaction mixture to the
thermal bulb. The reaction mixture consisted of 1 and cyclodecane as an internal standard (Figure 9).

**Figure 9.** Chromatogram at Time = 0 Hours (cyclodecane and 1)

Heating of 1 at 315.0°C led to the evolution of a single product peak by AGC analysis (Figure 10). By AGC, cyclodecane eluted first, followed by the observed thermal isomerization product and 1. Based on coinjection with an authentic sample, which had been independently synthesized, the thermal isomerization product was unambiguously assigned as 2.
Figure 10. Chromatogram at Time = 4 Hours (cyclodecane, 2, and 1)

The thermal reaction of 1 was followed at 315.0°C using pentane as bath gas. As was articulated by Powers et al., “the simplest mechanistic explanation for the thermal behavior of 1 is homolytic cleavage of the C1-C2 bond to generate an alkyl, allylic diradical intermediate that partitions itself between potential reformation of 1, formation of the [1,3] sr isomerization product 2, and fragmentation.” Based on six data points extending to approximately 40% disappearance of 1 the overall rate constant for the disappearance of 1 was $4.4 \times 10^6$ s$^{-1}$, with $k_r = 1.4 \times 10^6$ s$^{-1}$ and $k_f = 3.0 \times 10^6$ s$^{-1}$ (Figure 11). Fragmentation products were favored over [1,3] products by a factor of 2.1.
The [1,3] rearrangement pathway in the thermolysis of 1 is significantly more competitive than the [1,3] pathway in the thermal reaction of 8-exo-methylbicyclo[4.2.0]oct-2-ene. The thermolysis of the latter compound gave fragmentation products 4.9 times more frequently than [1,3] products at 315.0°C. In addition, the overall rate of decomposition of 1 is more than forty times slower than the decomposition of 8-exo-methylbicyclo[4.2.0]oct-2-ene (2.0 x 10^{-4} s^{-1} at 315.0°C) (Table VII). This observation can also be rationalized by the proposed diradical-mediated mechanism. In the cleavage of C1-C2 leading to the intermediate, the restrictions to rotation around C1-C8 afforded by the cyclopentane substructure in 1 make this bond cleavage less energetically accessible than the analogous cleavage in the thermal reaction of 8-exo-methylbicyclo[4.2.0]oct-2-ene. This difference in ease of bond cleavage explains the rate difference between these two reactions.
Table VII. Comparison of 1 vs. exo-8-methylbicyclo[4.2.0]oct-2-ene

<table>
<thead>
<tr>
<th>si/sr</th>
<th>$k_d ; (\text{s}^{-1}) ; @ ; 315^\circ \text{C}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Molecule" /></td>
<td>2.4</td>
</tr>
<tr>
<td><img src="image2.png" alt="Molecule" /></td>
<td>0</td>
</tr>
</tbody>
</table>
Preparation of Zinc-Copper Couple.\textsuperscript{61} Approximately 68 g zinc dust were suspended in 100 mL water. Two solutions of 7.7 g copper sulfate (CuSO\textsubscript{4} • 5H\textsubscript{2}O) in 50 mL water were added to the zinc suspension 30 seconds apart; the zinc solution rapidly darkened. The solution was allowed to stir for one minute before being passed through a sintered glass funnel. The solid was washed twice with 50 mL of water, twice with 50 mL of acetone, and once with 50 mL of diethyl ether. The grey solid was dried at 1-2 torr at 50°C for 3 hours before being stored under nitrogen to prevent oxidation.

Preparation of 8,8-dichlorobicyclo[4.2.0]oct-2-en-7-one (3).\textsuperscript{32} A 500 mL three neck round bottom flask was equipped with an over-head stirring device, an addition funnel, and a condenser. This apparatus was oven dried before being flame dried under a stream of nitrogen. Zinc-copper couple (70 g, 0.75 mol) was suspended in a solution of 1,3-cyclohexadiene (25 mL, 0.26 mol) and 200 mL anhydrous ether; this mixture was transferred to the reaction flask. A solution of trichloroacetyl chloride (100 g, 0.550 mol) in 100 mL dimethoxyethane (DME) was added over a period of one hour. The reaction mixture was allowed to stir overnight. Catalyst was removed vacumm filtration through a sintered glass funnel; the catalyst was thoroughly washed with hexanes. The organic
Experimental 2

material was then washed with 0.5 N HCl, 5% NaOH, water, and brine. The reaction solution was passed through a plug of silica gel and charcoal before being dried with magnesium sulfate. Solvent was removed by rotary evaporation and 3 was isolated by kugelrohr distillation at 55-60°C. The purified yield of this reaction was 42%. Spectral data is in accord with literature values.\(^{32}\) IR (cm\(^{-1}\)): 3050 (w), 2950 (w), 2850 (w), 1800 (s), 1650 (w), 705 (S). GC-MS (%): 194 (1), 192 (4), 190 (M, 6), 155 (14), 127 (15), 91 (33), 79 (27), 55 (100). \(^1\)H-NMR (500 MHz, CDCl\(_3\), ppm): 1.61 (1H, m), 2.01 (3H, br m), 3.41 (1H, m), 4.07 (1H, m), 5.84 (1H, m), 6.05 (1H, m). \(^{13}\)C-NMR (125 MHz, CDCl\(_3\), DEPT, ppm): 18.6 (CH\(_2\)), 20.7 (CH\(_2\)), 44.1 (CH), 53.2 (CH), 86.6 (CCl\(_2\)), 122.9 (CH), 132.3 (CH), 196.6 (C=O).

Preparation of Bicyclo[4.2.0]oct-2-en-7-one (4). A 250 mL three neck round bottom flask was fitted with a condenser and addition funnel; the apparatus was oven dried and flame dried under a stream of nitrogen. Zinc dust (12.13 g, 0.186 mol) was suspended in a solution of 60 mL absolute ethanol and 25 mL TMEDA in the reaction flask. Acetic acid (11.8 mL, 0.206 mol) was added over 10 minutes. A solution of 3 (6.00 g, 31.4 mmol) in 12.6 mL (0.219 mol) glacial acetic acid was added. When exothermicity was no longer observed, the reaction vessel was heated to 40°C with a water bath and allowed to stir overnight. Reaction progress was monitored by GCMS. The reaction solution was passed through a sintered glass funnel; water was added to quench the activated zinc before this solid material was rinsed with 50:50 pentane/ether. The organic materials were combined and washed with 1N HCl, saturated NaHCO\(_3\), water, and brine before being dried with magnesium sulfate. Solvent was removed by rotary evaporation. This
Experimental 2

reaction resulted in 3.43 g (28.1 mmol) crude 4 being recovered, representing an 89% yield. IR (cm⁻¹): 3050 (w), 2900 (m), 1780 (s), 1650 (w), 690 (m). GC-MS (%): 122 (0.1), 91 (4), 80 (100), 79 (79), 55 (16), 39 (11). ¹H-NMR (300 MHz, CDCl₃, ppm): 1.51 (1H, m), 1.94 (3H, m), 2.53 (1H, d of t), 2.87 (1H, m), 3.21 (1H, d of q), 3.50 (1H, octet), 5.80 (1H, m), 5.89 (1H, m). ¹³C-NMR (75 MHz, CDCl₃, APT, ppm): 19.4 (CH₂), 22.2 (CH₂), 22.9 (CH), 52.0 (CH₂), 57.3 (CH), 128.3 (CH), 128.8 (CH), 211.7 (C=O).

Preparation of Bicyclo[4.2.0]oct-2-en-7-one Hydrazone (5). A solution of hydrazine sulfate (3.77 g, 29.1 mmol) in 10.5 mL hydrazine hydrate was prepared and transferred to a 100 mL two neck flask that had been fitted with a condenser. Over a period of 15 minutes, 4 (3.43 g, 28.1 mmol) was added to the vessel. The reaction mixture was stirred overnight at 65°C. Reaction progress was monitored by IR. The product was into ether; the combined ethereal extracts were dried with MgSO₄. Solvent was removed by rotary evaporation. The reaction yielded 2.95 g (21.7 mmol) crude 5, representing 77% yield. IR (cm⁻¹): 3460 (w), 3200 (w), 3020 (w), 2930 (m), 1590 (w), 1540 (w), 700 (s).

Preparation of Bicyclo[4.2.0]oct-2-ene (1). A 100 mL two neck round bottom flask was fitted with a condenser; the apparatus was oven dried before being flame dried under a stream of nitrogen. Freshly sublimed potassium tert-butoxide (1.58 g, 14.1 mmol) was dissolved in 25 mL freshly opened anhydrous DMSO. Crude 5 (1.39 g, 9.24 mol) was added to the reaction vessel by volumetric syringe over a period of 5 hours. The reaction was allowed to stir overnight. Ice cold water (5 mL) was added to the reaction vessel and the product was extracted into pentane. Several water washes were used to remove all
residual DMSO before the organic materials were dried with MgSO$_4$. The reaction yielded 0.489 g (4.53 mmol) crude 1 representing a 49% yield. Colorless liquid. IR (cm$^{-1}$): 3010 (w), 2970 (m), 2920 (s), 1650 (w), 700 (s). GC-MS (%): 108 (2), 91 (6), 80 (100), 79 (51), 77 (51), 67 (10), 39 (9). $^1$H-NMR (CDCl$_3$, 500 MHz, ppm): 1.48 (2H, m), 1.61 (1H, septet), 1.73 (1H, quintet), 1.87 (1H, m), 1.97 (1H, m), 2.08 (1H, m), 2.19 (1H, sextet), 2.59 (1H, m), 2.64 (1H, br s), 5.73 (1H, m), 5.79 (1H, m). $^{13}$C-NMR (CDCl$_3$, 125 MHz, DEPT): 21.8 (CH$_2$), 22.6 (CH$_2$), 24.3 (CH$_2$), 28.1 (CH$_2$), 33.0 (CH), 33.2 (CH), 127.1 (=CH), 131.2 (=CH).
Experimental 2.1.2

Preparation of 6-chloro-6-cyanobicyclo[2.2.2]oct-2-ene (6). A 100 mL two neck round bottom flask and spiral condenser were oven dried before being flame dried under a stream of nitrogen. Hydroquinone (~.025 g) was suspended in 1,3-cyclohexadiene (20 mL, 0.176 mol) and dissolved in approximately 40 mL methylene chloride. The solution was transferred to the reaction vessel. 2-Chloroacrylonitrile (10 mL, 0.125 mol) was dried over KOH pellets and added to the reaction vessel. The reaction mixture was refluxed (~60°C) for 24 hours in the dark. Methylene chloride (15 mL) was added to the vessel and the mixture was passed through a silica gel column. Concentration by rotary evaporation yielded a dark brown liquid. Crude 6 (6.90 g, 41.3 mmol) was isolated. The crude yield of this reaction was 33%. IR (cm⁻¹): 3010 (w) 2920 (m), 2850 (m), 1650 (w), 700 (s).

Characterization of Bicyclo[2.2.2]oct-2-en-6-one (7). Crude 6 (6.90 g, 41.3 mmol) was dissolved in 95 mL DMSO in a round bottom flask. KOH (11.60 g) was dissolved in 20 mL distilled water. This solution was added to the reaction flask over a period of 4 hours. The reaction mixture was stirred for 20 hours before being quenched with 100 mL water. The product mixture was extracted five times with pentane. The organic layer
was then washed with brine and dried with magnesium sulfate. Rotary evaporation afforded 7 (1.26 g, 10.3 mmol), a white crystalline solid. This reaction proceeded in 25% yield. mp: 85-88°C. IR (cm\(^{-1}\)): 2950 (m), 2900 (w), 1720 (s), 1610 (w), 700 (s). GC-MS (%): 122 (23), 80 (100), 79 (88), 39 (17). \(^1\)H-NMR (CDCl\(_3\), 500 MHz, ppm): 1.52 (2H, m), 1.67 (2H, m), 1.83 (1H, m), 2.00 (1H, m), 2.96 (1H, octet), 3.10 (1H, br t), 6.17 (1H, t), 6.45 (1H, t). \(^{13}\)C-NMR (CDCl\(_3\), 125 MHz, DEPT, ppm): 22.5 (CH\(_2\)), 24.2 (CH\(_2\)), 32.3 (CH), 40.5 (CH\(_2\)), 48.5 (CH), 128.4 (CH), 137.0 (CH), 213.2 (C=O).

**Preparation of Bicyclo[2.2.2]octan-2-one (8).** A solution of 0.683 g (5.60 mmol) 7 in approximately 50 mL absolute ethanol was prepared and transferred to a thick-walled glass hydrogenation chamber. A catalytic amount of 10% Pd/C (~0.2 g) was added to the vessel. Once loaded in the hydrogenation apparatus, the flask was flushed four times with hydrogen gas before being charged to 50 psi and allowed to mix for two hours. During the mixing time, the chamber was re-pressurized to maintain a fairly constant 50 psi. The catalyst was removed by vacuum filtration, water was added to the reaction solution and the product was extracted into ether. The organic layer was washed with water, dried with MgSO\(_4\), and excess solvent was removed by rotary evaporation. This reaction yielded 0.616 g (5.0 mmol) crude 8, representing 89% yield. Spectral data was in accord with literature values.\(^{38c}\) mp: 169-172°C. IR (cm\(^{-1}\)): 2930 (s), 2870 (m), 1720 (s), 1670 (w). GC-MS (%): 124 (54), 81 (36), 80 (100), 67 (34), 54 (24), 39 (16). \(^1\)H-NMR (CDCl\(_3\), 500 MHz, ppm): 1.58 (2H, m), 1.69 (2H, m), 1.79 (4H, dt), 2.13 (1H, septet), 2.22 (3H, m). \(^{13}\)C-NMR (CDCl\(_3\), 125 MHz, DEPT, ppm): 23.2 (CH\(_2\)), 24.7 (CH\(_2\)), 27.9 (CH), 42.3 (CH), 44.7 (CH\(_2\)), 218.0 (C=O).
Preparation of Bicyclo[2.2.2]octan-2-one Tosylhydrazone (9). A solution of 1.864 g p-toluenesulfonylhydrazide (10.0 mmol) in approximately 50 mL methanol was prepared in a 250 mL Erlenmeyer flask. To this solution, 0.616 g (4.97 mmol) 8 was added. The solution was allowed to sit over night, at which time a significant amount of white crystals were observed. These crystals were isolated by vacuum filtration and washed with a 50-50 solution of pentane and ether. The resulting crystals were dried in a vacuum oven at 1-2 Torr for 90 minutes. This reaction yielded 9 (0.990 g, 3.39 mmol) representing 68% yield. Spectral data was in accord with literature reports. White needles. mp: 214-215°C. IR (cm⁻¹): 3210 (m), 2930 (m), 2860 (w), 1650 (w), 1320 (s), 1170 (s), 670 (s).

Preparation of Bicyclo[2.2.2]oct-2-ene (2). A solution of 0.760 g (2.60 mmol) 9 in 25 mL freshly opened 99.5% TMEDA was prepared and added to a flame dried 100 mL flask. The reaction vessel was placed under an inert atmosphere and cooled with a packed dry ice bath. Over a period of 90 minutes 3.4 mL 1.6 M MeLi in ether was added to the reaction vessel; the reaction vessel was allowed to warm to room temperature following this addition. After stirring over night, the reaction mixture was cooled to approximately -30°C, 20 mL distilled water was added, and the product mixture was extracted four times with pentane. The organic phase was washed sequentially with water, 3 M NaOH, 1 M HCl, water, and brine before being dried with anhydrous MgSO₄. Excess pentane was removed by short-path distillation, 2 was isolated in 99% yield. Spectral data was in accord with literature reports. Colorless, waxy solid. IR (cm⁻¹):
2940 (s), 2860 (m), 1620 (w). GC-MS (%): 108 (17), 80 (100), 79 (47). $^1$H-NMR
(CDCl$_3$, 500 MHz, ppm): 1.21 (4H, br d), 1.48 (4H, br d), 2.46 (br d), 6.23 (2H, sextet).

$^{13}$C-NMR (CDCl$_3$, 125 MHz, DEPT, ppm): 25.7 (CH$_2$), 29.5 (CH), 134.3 (CH).
Preparation of 7-d-8,8-dichlorobicyclo[4.2.0]oct-2-en-7-ol (10). A 100 mL three-neck round bottom flask and spiral condenser were oven dried before being flame dried under a stream of nitrogen. A solution of 3 (4.738 g, 24.9 mmol) in 30 mL MeOH was prepared and transferred to the reaction vessel. The vessel was cooled to 0°C before NaBD₄ (0.90 g, 27 mmol) was added via solid addition funnel over 2 hours. The reaction vessel was allowed to warm and was stirred overnight. The product was extracted into ether before being washed with 1 N HCl, H₂O, saturated NaHCO₃, H₂O, and brine before being dried with MgSO₄. Ether was removed by rotary evaporation. Crude 10 (4.867 g) was isolated and was shown to be 79.4% pure by AGC; based on this information, the reaction yielded 3.864 g 10, representing an 80% yield. IR (cm⁻¹): 3300 (br, w), 3050 (w), 2900 (w), 1650 (w), 860 (s), 710 (m).

Preparation of 7-d-8,8-dichlorobicyclo[4.2.0]oct-2-en-7-ol mesylate (11). A 250 mL three neck flask, a spiral condenser, and an addition funnel were oven dried before being flame dried under a stream of nitrogen. A solution of 10 (3.864 g, 20.0 mmol), triethyl
amine (4 mL), and methylene chloride (~100mL) was prepared and transferred to the flask. The reaction vessel was cooled to 0°C before methane sulfonyl chloride (3.1 mL, 40 mmol) was added over 15 minutes. The reaction vessel was allowed to warm to room temperature and was stirred overnight. The product mixture was extracted into methylene chloride. The organic layers were combined and washed with 1 N HCl, water, saturated sodium bicarbonate, water, and brine before being dried with magnesium sulfate. Rotary evaporation was employed to concentrate the material. The reaction proceeded in 83% yield (3.20 g, 16.6 mmol).

Preparation of 7-d-bicyclo[4.2.0]octa-2,7-diene (12). A 1 L three neck round bottom flask, dry ice condenser, overhead stirrer, and a 250 mL addition funnel were oven dried before being flame dried under a stream of nitrogen. Approximately 500 mL ammonia was condensed. The reaction vessel was cooled to –78°C using a dry ice in acetone bath. Sodium metal (1.84 g, 80 mmol) was rinsed with pentane and dissolved in the ammonia. Compound 11 (3.20 g, 16.6 mmol) was dissolved in approximately 40 mL anhydrous THF. The reaction was allowed to stir for 5 hours at –78°C, at which time the reaction vessel was slowly warmed to approximately –35°C. The reaction vessel was re-cooled to approximately –60°C and ammonium chloride was added to the reaction vessel until the reaction mixture was no longer blue. The reaction vessel was allowed to warm until most of the ammonia had evaporated at which time pentane and water were added. The product mixture was extracted four times with pentane, which was then washed with 1N HCl, water, saturated NaHCO₃, water, and brine before being dried with MgSO₄. Pentane was removed by short path distillation. Compound 12 was isolated in 52% yield.
Experimental 2

(0.923 g, 8.63 mmol). $^1$H-NMR (CDCl$_3$, 500 MHz, ppm): 1.34 (1H, m), 1.76 (1H, d quintet), 1.86 (1H, br m), 2.00 (1H, br m), 3.12 (1H, m), 3.25 (1H, t), 5.83 (2H, m), 5.86 (1H, s). $^{13}$C-NMR (CDCl$_3$, 125 MHz, DEPT, ppm): 21.5 (CH$_2$), 25.8 (CH$_2$), 41.4 (CH), 42.0 (CH), 128.0 (CH), 129.2 (CH), 136.2 (CH), 137.7 (CD). $^2$H-NMR (CHCl$_3$, 92 MHz, ppm): 6.08.

**Preparation of 7-d-bicyclo[4.2.0]oct-2-ene (7-d-1).** A 100 mL three neck round bottom flask was fitted with a spiral condenser. Compound 12 (0.923 g, 8.63 mmol) was dissolved in absolute ethanol and transferred to the reaction vessel. A stoichiometric amount of anhydrous hydrazine was added to the vessel. The reaction was cooled to –17°C using a dry ice in ethylene glycol bath. 30% hydrogen peroxide was added to the reaction mixture in 1 mL aliquots. Reaction progress was monitored by periodic AGC injections. After 6 hours of reaction time, an additional equivalent of hydrazine was added to the vessel. The reaction was allowed to continue until 82% of the starting material had been consumed. Water was added to quench the reaction. 7-d-1 was extracted into pentane and washed several times with cold water. Short path distillation was employed to remove pentane. Isolation afforded 0.715 g 7-d-1 (6.56 mmol), which is 76% yield. $^1$H-NMR (CDCl$_3$, 500 MHz, ppm): 1.47 (2H, m), 1.58 (1H, m), 1.84 (1H, m), 1.96 (1H, m), 2.09 (1H, m), 2.18 (1H, q), 2.58 (1H, m), 2.65 (1H, m), 5.73 (1H, m), 5.79 (1H, m). $^{13}$C-NMR (CDCl$_3$, 125 MHz, DEPT, ppm): 21.5 (CH$_2$), 22.1 (CHD), 24.0 (CH$_2$), 27.7 (CH$_2$), 32.6 (CH), 33.0 (CH), 126.8 (CH), 130.9 (CH). $^2$H-NMR (CHCl$_3$, 92 MHz, ppm): 1.73 (d), 1.87 (d).
Experimental 2.1.4

Preparation of 8-d-8-chlorobicyclo[4.2.0]oct-2-en-7-one (13). A 250 mL three neck round bottom flask was fitted with a condenser. The apparatus was oven dried before being flame dried under nitrogen gas. A solution of 9.22 g 3 (48.5 mmol) in approximately 100 mL d-acetic acid was prepared. While the reaction solution was being stirred, portions of zinc dust were added to the reaction vessel; approximately 3.2 g (49 mmol) Zn were added to the reaction vessel in 0.1 g portions. Zinc metal was allowed to react completely (judged by color change from gray to white) before additional zinc was added. Reaction progress was monitored by GC-MS.

The reaction vessel was cooled at 0°C before ice-water was added to the reaction vessel. The reaction mixture was extracted four times into ether. The ethereal phases were combined and washed several times with water. The organic phase was then washed with saturated sodium bicarbonate, water, 1 N HCl, water, and brine before being dried with anhydrous magnesium sulfate. Rotary evaporation was employed to remove the ether; following concentration, the reaction yielded 7.08 g 13 (45.1 mmol). This reaction proceeded in 93% yield. GC-MS (%): 157 (2), 129 (6), 79 (27), 55 (100).
**Preparation of 8-d-8-chlorobicyclo[4.2.0]oct-2-en-7-ol (14).** A 100 mL three neck round bottom flask was fitted with a spiral condenser and a solid addition funnel. The apparatus was oven dried before being flame dried under a stream of nitrogen. A solution of 5.24 g 13 (33.4 mmol) in approximately 40 mL d-methanol was prepared and transferred to the reaction vessel. The reaction mixture was cooled to 0°C. Sodium borodeuteride (5.58 g, 134 mmol) was added to the reaction vessel over a period of 2 hours. Following the addition, the reaction was allowed to warm to room temperature and was stirred overnight.

The reaction vessel was cooled to 0°C before ice-water was slowly added to the reaction vessel. The product mixture was extracted three times with diethyl ether. The organic phases were combined before being washed with water, saturated sodium bicarbonate, water, 1 N HCl, water, and brine. Anhydrous MgSO₄ was used as a drying agent; rotary evaporation was used to concentrate the product mixture. Compound 14 (3.95 g, 24.7 mmol) was isolated in 74% yield. IR (cm⁻¹): 3400 (br m), 2920 (m), 2220 (w), 1640 (w), 705 (s). GC-MS (%): 159 (1), 103 (16), 80 (100), 57 (31).

**Preparation of 8-d-8-chlorobicyclo[4.2.0]oct-2-en-7-ol mesylate (15).** A 100 mL three neck round bottom flask was fitted with a spiral condenser and an addition funnel. The apparatus was oven dried before being flame dried under a stream of nitrogen. A solution of 14 (3.95 g, 24.7 mmol) in methylene chloride was prepared and transferred to the reaction vessel. Triethylamine (7 mL) was added to the reaction mixture. The reaction mixture was cooled to 0°C before methane sulfonylchloride (7.74 mL, 0.1 mol) was
added via an addition funnel over a period of 1 hour. The reaction vessel was allowed to warm to room temperature following the addition.

The reaction vessel was cooled to 0°C before ice water and methylene chloride was added. The reaction mixture was acidified with 1 N HCl. The product mixture was extracted three times with methylene chloride. The organic phases were combined before being washed with water, saturated NaCO₃, water, 1 N HCl, water, and brine before being dried with MgSO₄. Rotary evaporation was used to concentrate the product. Mesylate 15 (5.24 g, 22.2 mmol) was isolated in 90% yield. IR (cm⁻¹): 2930 (w), 2300 (w), 1350 (s), 1180 (s).

**Preparation of 8-d-bicyclo[4.2.0]octa-2,7-diene (16).** A 500 mL three neck flask was fitted with an overhead stirring device, an addition funnel, and a dry ice condenser. The apparatus was oven dried before being flame dried under a stream of nitrogen. Approximately 200 mL ammonia was condensed in the reaction vessel. Approximately 5 g sodium metal were rinsed with pentane and dissolved in the ammonia. A solution of 5.24 g 15 (22.2 mmol) in approximately 40 mL anhydrous THF was prepared and added to the reaction vessel over a period of 1 hour. The reaction was allowed to stir for 5 hours at –78°C, at which time the reaction vessel was slowly warmed to approximately –35°C. The reaction vessel was re-cooled to approximately –60°C and ammonium chloride was added to the reaction vessel until the reaction mixture became colorless. The reaction vessel was allowed to warm until most of the ammonia had evaporated at which time a mixture of pentane and water was added. The product mixture was extracted four times with pentane, which was then washed with 1N HCl, water, saturated
Experimental 2

NaHCO₃, water, and brine before being dried with MgSO₄. Pentane was removed by short path distillation. Compound 16 was isolated in 49% yield (1.164 g, 10.9 mmol).

$^1$H-NMR (CDCl₃, 500 MHz, ppm): 1.44 (1H, m), 1.85 (1H, d quintet), 1.95 (1H, m), 2.09 (1H, m), 3.21 (1H, br s), 3.34 (1H, m), 5.93 (2H, m), 6.18 (1H, s). $^{13}$C-NMR (CDCl₃, 125 MHz, DEPT, ppm): 21.5 (CH₂), 25.8 (CH₂), 41.3 (CH), 42.1 (CH), 128.0 (=CH), 129.2 (=CH), 136.4 (=CH), 137.6 (=CH). $^2$H-NMR (CHCl₃, 92 MHz, ppm): 5.92 (s).

Preparation of 8-$d$-bicyclo[4.2.0]oct-2-ene (8-$d$-1). A 100 mL three neck round bottom flask was fitted with a spiral condenser. Compound 16 (1.164 g, 10.9 mmol) was dissolved in absolute ethanol and transferred to the reaction vessel. A stoichiometric amount of anhydrous hydrazine was added to the vessel. The reaction was cooled to –17°C using a dry ice in ethylene glycol bath. Hydrogen peroxide (30%) was added to the reaction mixture in 1 mL aliquots. Reaction progress was monitored by periodic AGC injections. After 4 hours of reaction time, an additional equivalent of hydrazine was added to the vessel. The reaction was allowed to continue until 88% of the starting material had been consumed. Water was added to quench the reaction. 8-$d$-1 was extracted into pentane and washed several times with cold water. Short path distillation was employed to remove pentane. Isolation afforded 8-$d$-1 (0.962 g, 8.83 mmol) in 81% yield.
Experimental 2.2:

\[
\begin{align*}
&\text{\text{Experimental 2.2:}} \\
&\text{Preparation of 8-chloro-8-methylbicyclo[4.2.0]oct-2-en-7-one (20). A 500 mL round} \\
&\text{bottom flask was equipped with a condenser, an addition funnel, and an overhead stirring} \\
&\text{device. The entire apparatus was oven dried before being flame dried under a stream of} \\
&\text{nitrogen gas. A solution of 75 mL chloroform, which had been prepared alcohol free, 50} \\
&\text{mL 1,3-cyclohexadiene (0.539 mol), and 31 mL 2-chloropropionyl chloride (0.319 mol) was} \\
&\text{prepared and transferred to the reaction vessel. Approximately 25 mL chloroform} \\
&\text{and 35 mL triethyl amine, which had been distilled from calcium hydride, were placed in} \\
&\text{the addition funnel. This solution was added to the reaction drop-wise over a period of} \\
&\text{six hours. The reaction mixture was allowed to stir overnight.} \\
&\text{Excess chloroform was removed by simple distillation and vacuum filtration was} \\
&\text{employed to remove triethyl amine hydrochloride. Ether was used to wash the solid} \\
&\text{material. The resulting organic extracts were washed twice with water, once with brine,} \\
&\text{and dried with magnesium sulfate. Rotary evaporation was used to remove the ether.} \\
&\text{Kugelrohr distillation was used to remove residual solvent before 20 was distilled at} \\
&\text{approximately 55°C. Following distillation, 26.89 g purified 20 was isolated,}
\end{align*}
\]
Experimental 2

representing 50% yield. IR (cm⁻¹): 3010 (w), 1780 (s), 710 (m), 700 (m). GC-MS (%): 172 (2), 170 (6), 135 (14), 80 (38), 79 (54), 55 (100).

_Preparation of 8-methylbicyclo[4.2.0]oct-2-en-7-one (21)._ A 250 mL three-neck round-bottom flask was oven dried before being flame dried under a stream of nitrogen. Zinc dust (11.6 g, 0.177 mol) was suspended in a solution of 25 mL TMEDA and 60 mL EtOH. Over a period of 10 minutes, 12 mL (0.208 mol) glacial acetic acid was added. A solution of 5.55 g (32.5 mmol) of 20 dissolved in 13 mL (0.226 mol) acetic acid was added. The reaction was heated at approximately 40°C and was allowed to stir overnight.

Taking care to prevent exposing activated zinc to the atmosphere, the reaction mixture was filtered through a sintered glass funnel. The solid material was washed with water to deactivate the zinc and then the material was washed with a 1 : 1 pentane-ether solution. The resulting organic material was washed with 1 N HCl, saturated NaHCO₃, and brine before being dried with anhydrous magnesium sulfate. Solvent was removed by rotary evaporation. Isolated 21 (2.36 g, 17.3 mmol) represented 55.3% yield for the reaction. IR (cm⁻¹): 3020 (w), 1780 (s), 1640 (w), 700 (m). 8-exo-methyl: ¹H-NMR (CDCl₃, 300 MHz, ppm): 1.26 (3H, d). ¹³C-NMR (CDCl₃, 75 MHz, ppm): 14.6 (exo-CH₃), 20.0, 21.4, 31.5, 54.2, 60.3, 128.0, 128.2, 214.0. 8-endo-methyl: ¹H-NMR (CDCl₃, 300 MHz, ppm): 1.00 (3H, d), 1.50 (1H, m), 1.98 (3H, m), 3.00 (1H, br m), 3.41 (1H, ddq), 3.59 (1H, br m), 5.75 (1H, m), 5.94 (1H, m). ¹³C-NMR (CDCl₃, 75 MHz, ppm): 8.8 (endo-CH₃), 18.5, 21.3, 27.6, 55.2, 55.4, 125.5, 130.1, 214.1.
Preparation of 8-methylbicyclo[4.2.0]oct-2-en-7-one hydrazone (22). A 50 mL two-neck round bottom flask was fitted with a condenser. A solution of 2.52 (19.5 mmol) hydrazine sulfate and 7 mL hydrazine hydrate was prepared and transferred to the reaction vessel. To this solution, 2.36 g (17.3 mmol) methyl ketone was added. The reaction mixture was stirred at approximately 65°C overnight. Reaction progress was monitored by taking an aliquot of the organic layer of the reaction mixture and obtaining an IR of the material. The reaction was allowed to run until a carbonyl peak was no longer observed in the IR spectrum.

The reaction mixture was allowed to cool to room temperature before being extracted three times with diethyl ether. The ethereal phases were combined and washed with water and brine before being dried with anhydrous magnesium sulfate. Ether was removed by rotary evaporation to concentrate the product. The reaction yielded 1.73 g (11.5 mmol) of hydrazone representing 66.6% yield. IR (cm⁻¹): 3370 (m), 3260 (m), 3020 (w), 1610 (m), 720 (s).

Sublimation of potassium tert-butoxide. Approximately 3 g commercially obtained potassium tert-butoxide was placed in the well of a sublimation chamber. The sublimation chamber was evacuated using a vacuum pump. Using an oil bath, the bottom of the chamber was heated to 180°-190°C while the cold finger was cooled using ice. After approximately four hours, sufficient potassium tert-butoxide had collected on the cold finger. The sublimation chamber was placed in a nitrogen-flushed glove bag and purified potassium tert-butoxide was transferred to a wide-mouth jar, flushed with nitrogen, and stored in a desiccator.
**Preparation of 8-methylbicyclo[4.2.0]oct-2-ene.** A 50 mL two-neck round bottom flask was fitted with a condenser. The apparatus was oven dried before being flame dried under a stream of nitrogen. Potassium tert-butoxide (2.00 g, 17.8 mmol) was weighed in a glove bag and added to the flask via a solid addition funnel. This material was dissolved in approximately 25 mL freshly-opened anhydrous DMSO. While being efficiently stirred, 1.73 g (11.5 mmol) methyl hydrazone was added to the flask over a period of five hours. The mixture was allowed to mix overnight.

Approximately 5 mL ice-cold water was added to the reaction vessel. The reaction mixture was extracted four times with pentane. The mixture was then washed several times with water until a constant volume of water was recovered, indicating the removal of all the DMSO. Anhydrous magnesium sulfate was used to dry the solution before short path distillation was utilized to remove the pentane. The reaction yielded 0.50 g hydrocarbon (4.1 mmol), representing a 35.6% yield. IR (cm⁻¹): 3015 (w), 700 (s). GC-MS (%): 122 (1), 80 (100), 79 (50). 8-exo-methylbicyclo[4.2.0]oct-2-ene: \(^1\)H-NMR (CDCl₃, 500 MHz, ppm): 1.12 (3H, d), 1.53 (2H, m), 1.59 (1H, m), 1.82 (1H, m), 1.93 (1H, m), 2.01 (2H, dt), 2.20 (1H, br t), 2.50 (1H, sextet), 5.75 (2H, d). \(^{13}\)C-NMR (CDCl₃, 125 MHz, DEPT, ppm): 21.3 (CH₃), 22.1 (CH₂), 25.3 (CH₂), 28.9 (CH), 30.5 (CH₂), 36.8 (CH), 40.4 (CH), 126.8 (CH), 130.1 (CH). 8-endo-methylbicyclo[4.2.0]oct-2-ene: \(^1\)H-NMR (CDCl₃, 300 MHz, ppm): 5.90 (1H, m), 5.66 (1H, br d), 0.84 (3H, d). \(^{13}\)C-NMR (CDCl₃, 75 MHz, ppm): 16.7 (CH₃), 21.2, 22.6, 29.6, 29.9, 33.6, 36.3, 127.8, 128.4.
Experimental 3.1

Scheme 1: Synthetic Scheme Towards cis, anti, cis-tricyclo[6.3.0.0^{2,7}]undec-3-ene (1)

Preparation of cis, anti, cis-tricyclo[6.3.0.0^{2,7}]undec-3-one (3). A Hanovia photochemical reactor equipped with a 450-watt medium pressure mercury lamp, a pyrex sleeve, and a condenser was used for photochemical reactions. The reactor was placed in a large vacuum flask and cooled with an ice bath; aluminum foil was used to insulate the reactor.

A solution of 15 mL 2-cyclohexenone and 150 mL cyclopentene was prepared and transferred to the reaction vessel. The reaction was irradiated for 38 hours, at which time, a large amount of solid residue that was likely due to impurities in cyclohexenone – a conspicuous yellow color was observed in the commercially obtained cyclohexenone; following distillation the material was colorless – was observed on the photoreactor. This material was removed and the reaction was irradiated for an additional 29 hours. At this time, approximately 75% of the cyclohexenone had been consumed. Volatile materials remaining in the reaction mixture were removed by rotary evaporation. The desired monoketone was purified by flash column chromatography on silica gel using pentane,
Experimental 3

95% pentane – 5% ether, and 90% pentane – 10% ether sequentially. NMR data were in accord with literature reports.$^{59}$ IR (cm$^{-1}$): 2900 (m), 2850 (w), 1690 (s), 1620 (w). GC-MS (%): 164 (40), 135 (20), 97 (100), 81 (25), 68 (60). $^1$H-NMR (500 MHz, CDCl$_3$, ppm): 1.65 (4H, br m), 2.12 (8H, br m), 2.39 (2H, m), 2.68 (2H, m). $^{13}$C-NMR (125 MHz, APT, CDCl$_3$, ppm): 20.0 (CH$_2$), 24.9 (CH$_2$), 28.0 (CH$_2$), 32.5 (CH$_2$), 33.1 (CH$_2$), 37.5 (CH), 39.7 (CH$_2$), 41.3 (CH), 41.9 (CH), 47.9 (CH), 215.9 (C=O).

*Preparation of cis, anti, cis-tricyclo[6.3.0.0$^{2,7}$]undec-3-one Tosylhydrazone (4).*$^{64}$ A solution of 4.5 g $p$-toluenesulfonylhydrazide dissolved in 50 mL methanol was prepared in a 250 mL Erlenmeyer flask. Compound 3 (1.97 g, 6.11 mmol) was added to the flask. After four days, crystal formation was observed. The vessel was cooled to 0°C and the crystals were isolated by vacuum filtration. A 50 : 50 solution of pentane and ether was used to wash the crystals, which were then dried under 1-2 Torr in a vacuum oven for approximately 2 hours. Melting point: 130 – 134°C. IR (cm$^{-1}$): 3215 (m), 2920 (m), 1600 (w), 1330 (m), 1170 (s), 800 (m).

*Preparation of cis, anti, cis-tricyclo[6.3.0.0$^{2,7}$]undec-3-ene (1).*$^{64}$ A 100 mL round bottom flask was equipped with a condenser. The apparatus was oven dried before being flame dried under a stream of nitrogen. Crude 4 (1.09 g, 3.3 mmol) was dissolved in 20 mL TMEDA and transferred to the reaction vessel. The reaction vessel was cooled in a dry ice bath before methyl lithium (8.2 mL 1.6 M) was added over two hours by volumetric syringe. The reaction was allowed to warm to room temperature and stirred overnight.
Prior to work-up, the reaction vessel was cooled to –30°C using a bath of dry ice and ethylene glycol. Ice water was added to the reaction vessel until the exothermicity of the base had been quenched. The reaction mixture was extracted three times with pentane; the resulting organic layer was washed with water, 1 N HCl, water, saturated NaHCO₃, water, and brine before being dried with anhydrous magnesium sulfate. The product was concentrated using rotary evaporation. Following concentration, 0.37 g (2.5 mmol) 1 was isolated, representing 76% yield. IR (cm⁻¹): 3010 (w), 2920 (s), 2850 (m), 1650 (w), 680 (s). GC-MS (%): 148 (M⁺, 2), 91 (25), 80 (100). ¹H-NMR (500 MHz, CDCl₃, ppm): 1.47 (5H, br m), 1.61 (1H, q), 1.79 (2H, m), 1.97 (2H, m), 2.10 (2H, br m), 2.20 (1H, quintet), 2.35 (1H, q), 5.80 (2H, m). ¹³C-NMR (CDCl₃, 125 MHz, DEPT, ppm): 21.4 (CH₂), 25.0 (CH₂), 25.6 (CH₂), 32.6 (CH₂), 32.9 (CH₂), 35.2 (CH), 35.8 (CH), 40.5 (CH), 46.0 (CH), 126.8 (=CH), 131.3 (=CH).

Preparation of cis, anti, cis-tricyclo[6.3.0.0²⁷]undecane (5). Approximately 30 microliters of preparative GC purified 1 was dissolved in approximately 50 mL absolute ethanol. Approximately 0.2 g Pd/C was suspended in the solution. The reaction vessel was flushed with hydrogen gas four times before being charged with 50 psi hydrogen gas. The vessel was shaken in the Parr hydrogenation apparatus for 30 minutes. The catalyst was removed from the reaction vessel by vacuum filtration. Ether was added to the reaction mixture and ethanol was removed from the reaction mixture by multiple washes with water. The sample was concentrated by rotary evaporation and 5 was purified by preparative gas chromatography. GC-MS (%): 150 (M⁺, 8), 82 (75), 67 (100), 54 (20), 41 (20). ¹H-NMR (300 MHz, CDCl₃, ppm): 1.52 (15H, br m), 2.33 (3H, m). ¹³C-NMR (75 MHz, CDCl₃, ppm): 20.7, 26.3, 26.6, 32.2, 35.2, 43.2.
Experimental 3.1.2

\[ \text{Scheme 2. Synthetic Scheme Toward 2} \]

Preparation of endo-tricyclo[5.2.2.0^{2,6}]undec-8-en-3-one (6).\textsuperscript{57} A sublimation chamber was oven dried and flame dried under a stream of nitrogen. 1,3-Cyclohexadiene was dried with molecular sieves and toluene was dried with calcium chloride, decanted, and distilled prior to use. Aluminum chloride (2.106 g) was suspended in approximately 100 mL toluene. Cyclopent-2-enone (2.5 mL) was added to the chamber; after stirring for 45 minutes, 17 mL 1,3-cyclohexadiene was added to the chamber. The reaction vessel was flushed with nitrogen and sealed before the reaction mixture was stirred at 40°C for 144 hours.

The reaction mixture was poured into ice water to hydrolyze any remaining active aluminum chloride. The aqueous phase was extracted three times with ether. The toluene and ether layers were combined and washed with water and brine before being dried with MgSO\textsubscript{4}. The product was concentrated by rotary evaporation (to remove ether) and short-path distillation (to remove toluene). Compound 6 was purified by flash column chromatography on silica gel; pentane, 95 : 5 and 90 : 10 pentane ether were
sequentially employed as mobile phase. After isolation 6 was obtained in 66% purified yield (3.28 g 6, 20.2 mmol). IR (cm⁻¹): 3050 (w), 2950 (m), 2870 (w), 1725 (s), 1610 (w), 1170 (m), 710 (s). GC-MS (%): 162 (M⁺, 10), 92 (20), 80 (100). ¹H-NMR (300 MHz, CDCl₃, ppm): 1.25 (2H, m), 1.54 (3H, br m), 2.04 (3H, br m), 2.38 (1H, dd), 2.55 (1H, m), 2.64 (1H, m), 2.94 (1H, m), 6.19 (2H, br m). ¹³C-NMR (125 MHz, DEPT, CDCl₃ ppm): 24.0 (CH₂), 24.8 (CH₂), 26.0 (CH₂), 32.5 (CH), 35.5 (CH), 38.1 (CH₂), 39.6 (CH), 52.4 (CH), 133.6 (=CH), 133.7 (=CH), 222.7 (C=O).

*Preparation of endo-tricyclo[5.2.2.0²⁶]jundec-8-en-3-ol (7).* A 100 mL three-neck round bottom flask was fitted with a condenser; the apparatus was oven dried before being flame dried under a stream of nitrogen. A solution of 6 (1.514 g, 9.35 mmol) in 25 mL anhydrous THF was prepared and transferred to the reaction vessel. The reaction vessel was cooled in an ice-water bath and 15 mL 1 M LAH in THF was added over 30 minutes. After the addition the reaction was warmed to room temperature and stirred overnight.

The reaction vessel was cooled to 0°C and cold absolute ethanol was added to the vessel until the reactivity of excess LAH had been quenched. Cold ammonium chloride was added to the reaction vessel (10 mL) before the reaction solution was acidified with dilute HCl. The reaction solution was extracted three times with ether and the ethereal phase was washed with water, 1 M HCl, water, saturated sodium bicarbonate, water and brine. Magnesium sulfate was used to dry the solution and rotary evaporation was employed to concentrate the product. Compound 7 was isolated in 52% yield (0.719 g, 4.4 mmol). The IR spectrum obtained for this compound was in accord with the literature. IR (cm⁻¹): 3400 (br, m), 2950 (s), 2860 (s), 1620 (w), 710 (s).
Preparation of endo-tricyclo[5.2.2.0²⁶]undec-8-en-3-ol Mesylate (8).44 A 100 mL three-neck round bottom flask and a spiral condenser were oven dried and flame dried under nitrogen. Compound 7 (0.604 g, 3.7 mmol) was dissolved in methylene chloride in the reaction vessel. Triethyl amine (2 mL) was added to the flask, and reaction vessel was cooled in an ice-water bath. Approximately 0.6 mL cold methanesulfonyl chloride was added to the reaction vessel. The reaction was allowed to warm to room temperature and was stirred overnight.

The reaction was cooled to 0°C and a mixture of cold 1N HCl and methylene chloride was added to the vessel until the solution was acidified. The product was extracted three times with methylene chloride. The organic layer was washed with water, 1 N HCl, water, saturated NaHCO₃, water, and brine before being dried with MgSO₄. The product was concentrated by rotary evaporation. Mesylate 8 was isolated in 96% yield (0.85 g). IR (cm⁻¹): 2950 (m), 2900 (w), 1610 (w), 1370 (m), 1350 (m), 1170 (s), 730 (s).

Preparation of endo-tricyclo[5.2.2.0²⁶]undec-8-ene (2).62 A 50 mL round bottom flask was equipped with a spiral condenser and the apparatus was dried both in the oven and with a flame under a stream of nitrogen. A solution of 1.66 (6.9 mmol) crude 8 in 10 mL anhydrous THF was prepared and transferred to the reaction vessel. A volumetric syringe was used to add 14 mL 1 M lithium triethylborohydride to the reaction mixture. After 1 hour, the reaction mixture was heated to approximately 50°C for three hours. The vessel was cooled to 0°C before water was added drop-wise to quench excess hydride.
Experimental 3

Approximately 7 mL 3 M NaOH and 7 mL 30% hydrogen peroxide were added to the vessel. This mixture was refluxed for 90 minutes, after which time the product was extracted three times into pentane. The organic layer was then washed with water and dried with MgSO₄. Pentane was removed by rotary evaporation. IR (cm⁻¹): 2910 (m), 2870 (m), 1615 (w), 710 (s). GC-MS (%): 148 (M⁺, 6), 91 (8), 80 (100), 79 (15).

Preparation of endo-tricyclo[5.2.2.0²⁶]undecane (9). Approximately 30 microliters 2, which had been purified by preparative GC, was dissolved in 50 mL absolute ethanol. A catalytic amount of 10% Pd/C (~0.2 g) was suspended in the solution and the reaction mixture was transferred to a hydrogenation chamber. The reaction vessel was flushed four times with hydrogen gas before being charged with 50 psi hydrogen gas. The contents of the vessel were agitated in the Parr hydrogenation apparatus for 30 minutes. The catalyst was removed from the reaction vessel by vacuum filtration. Ether was added to the reaction mixture and ethanol was removed from the reaction mixture by multiple water washes. Rotary evaporation was utilized to concentrate the sample and preparative GC was employed to purify the material. GC-MS and $^{13}$C-NMR data collected were in accord with literature reports for this 9.$^{63,64}$ GC-MS (%): 150 (M⁺, 100), 122 (90), 93 (45), 80 (60), 67 (45). $^{13}$C-NMR (CDCl₃, 125 MHz, ppm): 20.3, 26.6, 27.2, 28.1, 30.0, 41.0.
**Thermolysis Reactions**

Approximately 4 microliters of each compound to be thermolyzed was dissolved in 2 microliters of the appropriate internal standard. These samples were vaporized and transferred by vacuum-line to the thermal bulb. Each sample was heated for a set amount of time before being removed, diluted in pentane and analyzed by AGC. Each thermal sample provided a single data point.

The only variation in this procedure was for the thermolysis of deuterated substrates. These compounds were thermolyzed without an internal standard and approximately 7 microliters of these compounds were used in each thermal reaction. After heating, these samples were dissolved in chloroform and submitted for NMR analysis. The chloroform used in the NMR experiments had been prepared by treating with concentrated H$_2$SO$_4$, rinsing with water, and distilling from calcium hydride.
Acknowledgements

I have had the great fortune and privilege of working under two fabulous advisors during my undergraduate research career. First and foremost, I would like to thank Dr. Phyllis Leber. Not only was she a fabulous advisor, teacher, and mentor, but she has also been a great friend for the past four years. This work would not have been possible without her constant support. As the consummate teacher-scholar, she has been, and will continue to be a great role model for me. Secondly, Dr. John Baldwin was also instrumental in the preparation of this work. My two weeks in his lab at Syracuse University were both memorable and productive. My experiences working for these two scholars will always be a source of great personal joy.

I would be remiss if I did not acknowledge many of my fellow undergraduate researchers. I had the great fortune to have been trained by Lynne and Drew, to have worked with Liz, Gloria, Xavier, and Ann, and to have taught George. My work would certainly have greatly suffered had I not been surrounded by such excellent and thoughtful coworkers.

I need to thank the funding agencies which have literally made this work possible: the Petroleum Research Fund, the Schappell Scholarship, the Fred A. Snavely Research Award, the John Marshall Scholarship, and the Franklin and Marshall Department of Chemistry.

I would like to thank Carol, Lisa, and Beth for all of the technical assistance, which they have so kindly supplied.

A few of my “non-Leber-lab” friends have had such a profound impact on my time at Franklin and Marshall College that I cannot fail to recognize them. Tamara, Colin, and Jayme – your support and friendship has meant the world to me, I love you all.

Finally, and most importantly, I would like to thank my family. To my parents: Mom and Dad, your unwavering support throughout my life is the reason for all of my successes. It takes an incredibly special pair to have volunteered to read this thesis. I cannot express how significant you have both been, not only in the composition of this work, but in all of my endeavors.
Appendices

Thermal Data

Instructions for Pyrolysis System

Spectra from the Synthesis of:
- Bicyclo[4.2.0]oct-2-ene
- Bicyclo[2.2.2]oct-2-ene
- 7-d-Bicyclo[4.2.0]oct-2-ene
- 8-d-Bicyclo[4.2.0]oct-2-ene

Selected Spectra from Thermolysis of 7-d-Bicyclo[4.2.0]oct-2-ene

Selected Spectra from Thermolysis of 8-d-Bicyclo[4.2.0]oct-2-ene

Spectra from the Synthesis of:
- 8-Methylbicyclo[4.2.0]oct-2-ene
- cis, anti, cis-Tricyclo[6.3.0.02,7]undec-3-ene
- endo-Tricyclo[5.2.2.02,6]undec-8-ene
Table I. Time Dependent Mol Percent Concentrations of Bicyclo[4.2.0]oct-2-ene (1), Bicyclo[2.2.2]oct-2-ene (2) and 1,3-Cyclohexadiene Upon Gas Phase Thermolysis at 275°C.

<table>
<thead>
<tr>
<th>Time (s x 10^{-4})</th>
<th>1</th>
<th>2</th>
<th>1,3-Cyclohexadiene</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5.68</td>
<td>94.0</td>
<td>3.3</td>
<td>2.8</td>
</tr>
<tr>
<td>10.8</td>
<td>80.0</td>
<td>5.7</td>
<td>14.4</td>
</tr>
<tr>
<td>16.9</td>
<td>73.6</td>
<td>8.6</td>
<td>17.8</td>
</tr>
<tr>
<td>24.9</td>
<td>67.6</td>
<td>12.4</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Table II. Time Dependent Mol Percent Concentrations of Bicyclo[4.2.0]oct-2-ene (1), Bicyclo[2.2.2]oct-2-ene (2) and 1,3-Cyclohexadiene Upon Gas Phase Thermolysis at 300°C.

<table>
<thead>
<tr>
<th>Time (s x 10^{-4})</th>
<th>1</th>
<th>2</th>
<th>1,3-Cyclohexadiene</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1.07</td>
<td>80.6</td>
<td>4.3</td>
<td>9.6</td>
</tr>
<tr>
<td>2.11</td>
<td>76.3</td>
<td>8.3</td>
<td>15.5</td>
</tr>
<tr>
<td>3.15</td>
<td>66.8</td>
<td>11.9</td>
<td>21.3</td>
</tr>
<tr>
<td>5.66</td>
<td>45.0</td>
<td>17.0</td>
<td>38.0</td>
</tr>
<tr>
<td>8.49</td>
<td>29.8</td>
<td>20.7</td>
<td>49.5</td>
</tr>
<tr>
<td>13.0</td>
<td>16.5</td>
<td>25.2</td>
<td>58.3</td>
</tr>
<tr>
<td>16.1</td>
<td>11.1</td>
<td>27.5</td>
<td>61.4</td>
</tr>
</tbody>
</table>

Table I. Time Dependent Mol Percent Concentrations of Bicyclo[4.2.0]oct-2-ene (1), Bicyclo[2.2.2]oct-2-ene (2) and 1,3-Cyclohexadiene Upon Gas Phase Thermolysis at 315°C.

<table>
<thead>
<tr>
<th>Time (s x 10^{-4})</th>
<th>1</th>
<th>2</th>
<th>1,3-Cyclohexadiene</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.53</td>
<td>82.2</td>
<td>6.6</td>
<td>11.2</td>
</tr>
<tr>
<td>1.06</td>
<td>61.6</td>
<td>11.5</td>
<td>26.8</td>
</tr>
<tr>
<td>2.18</td>
<td>18.5</td>
<td>37.9</td>
<td>43.6</td>
</tr>
<tr>
<td>4.87</td>
<td>26.5</td>
<td>11.8</td>
<td>61.7</td>
</tr>
</tbody>
</table>
Table IV. Relative $^2$H NMR Integrated Intensities of Deuterium-Labeled Bicyclo[4.2.0]oct-2-enes and Bicyclo[2.2.2]oct-2-enes Following Gas Phase Thermolysis at 300°C of 82.3:17.7 endo:exo-7-d-Bicyclo[4.2.0]oct-2-enes

<table>
<thead>
<tr>
<th>Time (s x $10^{-4}$)</th>
<th>7-x-d-1&lt;sup&gt;a&lt;/sup&gt; δ = 1.91</th>
<th>7-n-d-1 δ = 1.77</th>
<th>5-n-d-2&lt;sup&gt;b&lt;/sup&gt; δ = 1.24</th>
<th>5-x-d-2 δ = 1.51</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>17.7</td>
<td>82.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.60</td>
<td>21.4</td>
<td>78.6</td>
<td>81.1</td>
<td>18.9</td>
</tr>
<tr>
<td>6.49</td>
<td>16.7</td>
<td>83.3</td>
<td>87.4</td>
<td>12.6</td>
</tr>
<tr>
<td>8.55</td>
<td>18.3</td>
<td>81.7</td>
<td>83.1</td>
<td>16.9</td>
</tr>
<tr>
<td>10.62</td>
<td>14.6</td>
<td>85.4</td>
<td>84.8</td>
<td>15.2</td>
</tr>
<tr>
<td>13.14</td>
<td>14.9</td>
<td>85.1</td>
<td>83.2</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>17.3 ± 2.5</td>
<td>82.7 ± 2.5</td>
<td>83.9 ± 2.3</td>
<td>16.1 ± 2.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> With (7-x-d-1) + (7-n-d-1) = 100%.  
<sup>b</sup> With (5-n-d-2) + (5-x-d-2) = 100%.
Table V. Relative $^2$H NMR Integrated Intensities of Deuterium-Labeled Bicyclo[4.2.0]oct-2-enes and Bicyclo[2.2.2]oct-2-ene Following Gas Phase Thermolysis at 300°C of 85.4:14.6 endo:exo-8-d-Bicyclo[4.2.0]oct-2-enes

<table>
<thead>
<tr>
<th>Time (s x $10^{-4}$)</th>
<th>8-n-d-1 $\delta = 1.63$</th>
<th>8-x-d-1 $\delta = 2.23$</th>
<th>5-n-d-2 $\delta = 1.24$</th>
<th>5-x-d-2 $\delta = 1.51$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>85.4</td>
<td>14.6</td>
<td>3.6</td>
<td>3.4</td>
</tr>
<tr>
<td>1.30</td>
<td>61.5</td>
<td>31.5</td>
<td>5.7</td>
<td>5.9</td>
</tr>
<tr>
<td>2.44</td>
<td>50.5</td>
<td>38.0</td>
<td>8.6</td>
<td>7.9</td>
</tr>
<tr>
<td>3.52</td>
<td>45.4</td>
<td>38.1</td>
<td>12.2</td>
<td>10.8</td>
</tr>
<tr>
<td>5.25</td>
<td>40.9</td>
<td>36.1</td>
<td>16.7</td>
<td>15.0</td>
</tr>
<tr>
<td>7.36</td>
<td>33.9</td>
<td>34.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>28.5</td>
<td>24.8</td>
<td>24.0</td>
<td>22.7</td>
</tr>
</tbody>
</table>

Table VI. Time Dependent Mol Percent Concentrations of endo and exo Isomers of 8-d-Bicyclo[4.2.0]oct-2-ene and 5-d-Bicyclo[2.2.2]oct-2-ene in Reaction Mixtures from Gas Phase Thermal Reactions at 300°C

<table>
<thead>
<tr>
<th>Time (s x $10^{-4}$)</th>
<th>8-n-d-1 $\delta = 1.63$</th>
<th>8-x-d-1 $\delta = 2.23$</th>
<th>5-n-d-2 $\delta = 1.24$</th>
<th>5-x-d-2 $\delta = 1.51$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>85.4</td>
<td>14.6</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>1.30</td>
<td>55.2</td>
<td>28.3</td>
<td>2.6</td>
<td>2.4</td>
</tr>
<tr>
<td>2.44</td>
<td>40.6</td>
<td>30.6</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td>3.52</td>
<td>33.3</td>
<td>27.9</td>
<td>6.2</td>
<td>5.7</td>
</tr>
<tr>
<td>5.25</td>
<td>25.6</td>
<td>22.6</td>
<td>8.5</td>
<td>7.4</td>
</tr>
<tr>
<td>7.36</td>
<td>17.9</td>
<td>18.1</td>
<td>10.3</td>
<td>9.3</td>
</tr>
<tr>
<td>10.0</td>
<td>13.3</td>
<td>11.6</td>
<td>11.8</td>
<td>11.2</td>
</tr>
</tbody>
</table>

$a$ (8-n-d-1) + (8-x-d-1) = 100*exp(-1.39 x $10^{-5}$t) and (5-n-d-2) + (5-x-d-2) = 30.67*(1-exp(-1.39x10^{-5}t)), from data of Table I; (8-n-d-1):(8-x-d-1) and (5-n-d-2):(5-x-d-2) from NMR data of Table V.
**Pyrolysis System Sample Injection Procedure**


Check the septa at the injection port and the nitrogen inlet and replace if necessary.

1. Cool main trap with liquid N\(_2\).
2. Close stopcocks A and C.
3. Cool the bottom of the injection port with liquid N\(_2\).
4. Inject the sample through the septum and wait 30 seconds for the sample to collect at the bottom of the injection port.
5. Open stopcock C; wait until the pressure gauge returns to the level it was before stopcock C was opened.
6. Close stopcocks B and C.
7. Remove liquid N\(_2\) from the injection port and allow it to warm.
8. Turn on secondary pump.
9. Open stopcock G and allow trap to pump down.
10. Cool secondary trap with one small dewer of liquid N\(_2\).
11. Close stopcock G and turn off secondary pump.
12. Remove needle assembly from syringed tygon tubing attached to the gaseous N\(_2\) tank and then turn tank on to flush the tube. (Flow rate should be barely audible)
13. Re-insert needle assembly onto the syringe to flush with gaseous nitrogen.
14. Open stopcocks I and L; watch pressure gauge until pressure returns to baseline.
15. Close stopcocks N, K, and H.
16. Insert the syringe attached to the gaseous nitrogen tank into the septum directly above stopcock L and allow the mercury level in the manometer to rise to the top of the clamp (approximately 100-150 torr) then remove the syringe from the septum.
17. Close stopcock L.
18. Turn off the gaseous nitrogen.
19. Heat the injection port with a heating gun until all of the sample is vaporized (several seconds).
20. Sequentially, open stopcock A, then C, then close A and close C. Start the timer.
21. Close stopcock I then slowly open stopcock H.
22. Turn on the secondary pump and then open stopcock G (10 minutes).
23. Open stopcock N and then K and allow the system to pump down to baseline pressure.
24. Close stopcock G and turn off the secondary pump.

**Pyrolysis System Sample Removal Procedure**

1. Close stopcock J. Open stopcocks C and M. Open stopcock D until the pressure gauge registers an increase in pressure.
2. Attach collection tube to either E or F and open corresponding stopcock.
3. Cool collection coil with N\textsubscript{2}.
4. Open stopcock A, stop timer. Let system pump down for 1-2 minutes before proceeding.
5. Close stopcocks D and M. Open stopcock J.
6. Cool collection tube with liquid N\textsubscript{2}. Remove dewer from collection coil. Use heating gun on fan mode to remove frost from collection coil. Heat collection coil with heat gun for at least 1 minute.
7. Close stopcock E or F. Remove sample.
References


46 The work presented in Chapter 2.2 is based on work that has appeared in print. Only that work which was carried out as part of the investigation reported herein will be presented in this thesis; work done by research collaborators — specifically, exhaustive characterization and collection of thermal data at 275°C — will not be explicitly presented.


48 These distances were calculated based on energetically minimized geometries using Spartan '05.


Inamoto, Yoshiaki; Aigami, Koji; Takaishi, Naotake; Fujikura, Yoshiaki; Tsuchihashi, Kiyoshi; Ikeda, Hiroshi. “Pathways of the Trifluoromethanesulfonic Acid Catalyzed Rearrangement of cis-2,3-Trimethylenebicyclo[2.2.2]octane to 4-Homoisotwistane.” *J. Org. Chem.* 1977, 42(24), 3833-3839.


46 The work presented in Chapter 2.2 is based on work that has appeared in print. Only that work which was carried out as part of the investigation reported herein will be presented in this thesis; work done by research collaborators – specifically, exhaustive characterization and collection of thermal data at 275°C – will not be explicitly presented.


48 These distances were calculated based on energetically minimized geometries using Spartan ‘05.


60. Inamoto, Yoshiaki; Aigami, Koji; Takaishi, Naotake; Fujikura, Yoshiaki; Tsukihashi, Kiyoshi; Ikeda, Hiroshi. “Pathways of the Trifluoromethanesulfonic Acid Catalyzed Rearrangement of cis-2,3-Trimethylenebicyclo[2.2.2]octane to 4-Homoisotwistane.” J. Org. Chem. 1977, 42(24), 3833-3839.


