Abstract:
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The Diels-Alder cyclization between a phosphonate dienophile and a silyl enol ether diene has been studied. The regio- and stereoselective course of the reaction allowed for isolation of one product. Future work towards phosphonate inositol derivatives has been outlined.
NOVEL SYNTHETIC METHODOLOGIES: RADICAL AND PHOTOCHEMICAL APPROACHES TOWARDS ALKALOIDS. DIELS-ALDER METHODOLOGY TOWARDS INOSITOL DERIVATIVES

by

Jeffrey Stevens Link

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

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A dissertation has been read by each member of the dissertation committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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<td>Sigmatropic 1,3-Acyl Shift</td>
</tr>
<tr>
<td>ADPM</td>
<td>Aza-di-π-methane</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisobutyronitrile</td>
</tr>
<tr>
<td>CNDO</td>
<td>Configuration Neglect of Differential Overlap</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DPM</td>
<td>Di-π-methane</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>hv</td>
<td>light</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamine</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>nOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>ODPM</td>
<td>Oxa-di-π-methane</td>
</tr>
<tr>
<td>sens</td>
<td>Triplet Sensitizer</td>
</tr>
<tr>
<td>SOMO</td>
<td>Singly Occupied Molecular Orbital</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl- or Tetramethyl silane</td>
</tr>
<tr>
<td>TTMSS</td>
<td>Tris(trimethylsilyl) silane</td>
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ABSTRACT

The radical cyclization between an aromatic radical and an imidate ester has been studied. Variations on the functional group situated on the imidate ester have shown that a phenyl group is needed for the cyclization to take place.

The photochemical reactivities of 1-aza and 2-azabicyclo[2.2.2]oct-2-en-5-ones have been studied. There is a strong correlation between the efficiency of the oxa-di-π-methane (ODPM) rearrangement and the degree of electron density in the π system. Efficiency of the 1,3-acyl shift has been shown to be independent on the electronics of the π system. The formal synthesis of petasinecine, trachelanthamidine, isoretronecanol, and supinidine has been completed.

The Diels-Alder cyclization between a phosphonate dienophile and a silyl enol ether diene has been studied. The regio- and stereoselective course of the reaction allowed for isolation of one product. Future work towards phosphonate inositol derivatives has been outlined.
CHAPTER 1

INTRODUCTION

The creation of novel methods towards the syntheses of naturally occurring compounds has been one of the primary goals of organic chemistry since its inception. The environmental impact of isolating biologically active compounds from their natural sources has made the creation of better synthetic methods a critical issue. The best of these methods tend to be general, yielding more than one target compound during the synthetic scheme, and stereospecific, establishing diastereomerically pure stereocenters within a compound. Ideally, these new methods should also be expeditious and high-yielding, thereby reducing the time and chemicals needed to complete the synthetic scheme. This work was undertaken to develop novel synthetic methodologies towards the synthesis of some biologically active naturally occurring compounds.

The objectives of this work are three fold: (1) Investigation into the use of radical chemistry in the formation of carbon-nitrogen bonds towards the synthesis of mitomycin C, 1, (Figure 1) (2) Use of the oxa-di-π-methane photochemical rearrangement of azabicyclo[2.2.2]octenones to synthesize various pyrrolizidine alkaloids such as macronecine, 2, heliotridane, 3, and
Figure 1. Synthetic targets.
xenovenine, 4, (Figure 1) and (3) progress towards the synthesis of myo-inositol derivatives 5 and 6 (Figure 1) using Diels-Alder methodology to construct the six membered ring.

Radical Cyclization Approach Towards Mitomycin C.

The use of radicals in the formation of carbon-carbon bonds under non-ionic conditions has become a standard in the modern synthetic chemist's arsenal. Typically, these reactions involve the addition of a carbon radical into an olefin, resulting in a 5-membered ring being formed according to Baldwin's rules of ring closure. See Scheme 4. Incorporation of a carbon-nitrogen unsaturation in these cyclizations has been limited to azo groups\(^5\), isonitriles\(^6\), and imidate esters.\(^7,^8\) In these examples, the carbon of the unsaturation was attacked by the radical in all cases except in the cases of some aldimines\(^7\) and ketimines\(^8\) where steric hindrance was a factor. See Scheme 2. The purpose of the research described in Chapter 2 is to investigate the 5-exo vs 6-endo cyclization selectivity in the model system illustrated in Scheme 2. That is, can we favor 5-exo cyclization by attack of the radical at the nitrogen end of a carbon-nitrogen double bond?
**Scheme 1.** General radical cyclizations.
Photochemical Rearrangements of Azabicyclo[2.2.2]octenones

The oxa-di-π-methane rearrangement has become an useful method in the synthesis of tricyclic cyclopropyl ketones from β,γ-unsaturated bicyclic ketones (Scheme 3). These cyclopropyl ketones can then be selectively opened to yield highly functionalized bicyclic ketones. The majority of the work done in this area involves carbocyclic systems. Substitution on the olefin has been limited to esters and alkyl groups.
Scheme 3. Example of the oxa-di-π-methane photorearrangement in bicyclic systems. The synthesis of cedrene by Yates and Stevens.\textsuperscript{9g}

The ability of the imine function to add to other multiple bond compounds has been used extensively in the construction of heterocyclic molecules.\textsuperscript{11} Use of the imine functionality in the di-π-methane photorearrangement has been limited to benzobarrelene systems such as 5,6-benzo-2-aza-bicyclo[2.2.2]octadienes in which the imine functionality does not participate in the rearrangement and simple acyclic imidates (Scheme 4).\textsuperscript{12} To our knowledge, incorporation of a nitrogen into the oxa-di-π-methane rearrangement has thus far been unreported in the literature.
Scheme 4. The triplet sensitized photorearrangement of imines and imidates.

The research outlined in Chapter 3 describes our investigations into the photochemical behavior of nitrogen containing bicyclic systems under sensitized (oxa-di-π-methane rearrangement) and non-sensitized (Norrish type I rearrangement) conditions, as shown in Scheme 5. These products will then be further functionalized to synthesize the target molecules macronecine, heliotridane, and xenovenine. Additionally, this research describes the Diels-Alder reactivity of nitriles in the synthesis of the aforementioned bicyclic systems (Scheme 6).
Scheme 5. Photochemical behavior and applications of azabicyclo[2.2.2]octenones.

Scheme 6. Diels-Alder reactivity of nitriles.
Synthetic Studies Towards the Synthesis of Inositol Derivatives.

To date, the synthesis of most inositol analogs has been based on the modification of the readily available myo-inositol and proceed through multiple protection and deprotection steps to produce the desired functional group patterns. The remainder of the syntheses have commenced from cyclohexenol derivatives. Previous work in the McClure group has shown the effectiveness of general phosphonate synthesis using oxaphospholene methodology (Scheme 7).

![Scheme 7. Preparation of phosphonate dienophile.](image)

The research outlined in Chapter 4 describes our efforts towards the synthesis of the myo-inositol derivatives 5 and 6 through a Diels-Alder
cyclization with a phosphonate dienophile. This Diels-Alder product will then be further functionalized so as to establish the stereocenters needed (Scheme 8).

Scheme 8. Synthetic plan towards myo-inositol derivatives 5 and 6.
CHAPTER 2

FORMATION OF A CARBON-NITROGEN BOND VIA A 5-EXO-TRIG RADICAL CYCLIZATION ONTO THE NITROGEN OF AN IMIDATE ESTER

Introduction

Historical Background

In the hundred years since their discovery, carbon radicals have seen increased usage in the formation of carbon-carbon and carbon-heteroatom bonds. First observed in 1900 when Gomberg\textsuperscript{16} studied the reactivity and formation of the triphenylmethyl radical, these reactive species saw their first use in practical synthetic chemistry in 1937 when Hey and Waters\textsuperscript{17} described the phenylation of aromatic compounds by benzoyl peroxide as a radical reaction. Later that same year, Kharasch reported that the anti-Markovnikov addition of HBr to alkenes proceeded via a radical process.\textsuperscript{18} In the last thirty years, radical chemistry in organic synthesis has undergone a metamorphosis with the use of new carbon-heteroatom radical propagators (group IVB and group VIB compounds being the most commonly used)\textsuperscript{19} in the place of heat
and light, and the rapid development in the methodology towards the formation of aromatic and aliphatic carbon-carbon and carbon-heteroatom bonds.

The recent use of radicals in the formation of heterocyclic rings has been well documented in the literature.\textsuperscript{19} These methods have been shown to be effective and elegant ways toward complex heterocyclic frameworks. Radical cyclizations have many advantages over non-radical methods in that they do not generally suffer from racemization problems, can be run in neutral organic solutions, and have the ability to form many rings in one-pot reactions.

Radical cyclization reactions represent a breakthrough for synthetic chemistry.\textsuperscript{19} These reactions exhibit high regio- and stereoselectivities and can be carried out with a variety of functional groups as radical traps. Since the activation entropies are less negative than those of intermolecular reactions\textsuperscript{19a,b}, not only carbon-carbon but also carbon-nitrogen multiple bonds react intramolecularly with radicals. When an olefin is used as the trapping group the resulting radical can react again intramolecularly. Commonly called a tandem radical cyclization, this method has been used by many groups to effectively form two or more rings simultaneously.\textsuperscript{19} The goal of this project is to combine the two effects described above by employing a tandem radical cyclization onto the nitrogen end of an imidate ester followed by subsequent carbon-carbon bond formation with the incipient radical, to produce the mitomycin skeleton, which could be further derived to a variety of mitomycins (Scheme 9).
Scheme 9. Proposed radical cyclization towards the mitomycin skeleton.
The Proposed Application of Radical Chemistry

Nitrogen-carbon unsaturations have been used frequently in radical cyclizations.\(^{20-26}\) These reactions have been applied to oximes\(^{20}\), nitriles\(^{21}\), and imines\(^{22}\). In these examples, the carbon of the unsaturation was always attacked by the radical, producing an aminal radical intermediate (e.g. 6-endo over 5-exo). See Scheme 10. At the time that this work was begun, the examples of a carbon radical adding to the nitrogen of the unsaturation were limited to azo groups\(^{23}\), isonitriles\(^{24}\), ketimines\(^{25,26}\), and aldimines.\(^{25,26}\) However, during the course of this work, the radical cyclizations of aldimines and ketimines have been accomplished.\(^{25,26}\) This work was done by two independant researchers, Warkentin\(^{25}\) and Takano\(^{26}\). Apart from the work described, the cyclization onto an imidate ester remains unreported in the literature.

Scheme 10. Possible ring closure products.
Warkentin and Tomaszewski studied the intramolecular cyclization of a phenyl radical into the C=N group of various aldimines (R¹=H) and ketimines (R¹=Et). See Table 1. The aldimines underwent 6-endo cyclization to yield tetrahydroisoquinolines, 3, as the major products, while the ketimine predominantly underwent debromination with some 5-exo cyclization occurring to yield the dihydroindole, 2.

The preference of the 6-endo product over the 5-exo product was contrary to what was seen in alkene cyclizations. A potential explanation comes by examining the bond energies and geometries of imines compared to alkenes. The resulting C-C bond that is formed in the endocyclic ring closure is 10 kcal/mol stronger than the alternative C-N bond. Examining the geometries of the imines, the C-N=C angle of 119°, is much smaller than the C-C=C angle of 125°. The reduced bond angle in the former case, improves the orbital overlap between the SOMO and the π*-orbital of the imine in the transition state for the 6-endo closure. The results combined to show a definite preference towards 6-endo ring closure.

Kinetic studies by Warkentin, based upon varying concentrations of Bu₃SnH, verified his experimental results. Using deuterated aldimines (R¹=D)
in a large excess of $\text{Bu}_3\text{SnH}$, the rate constants for the 6-endo and 5-exo cyclizations were calculated to be approximately $1.4 \times 10^8 \text{ s}^{-1}$ and $6.0 \times 10^6 \text{ s}^{-1}$, respectively.$^{25}$

![Chemical structure](image)

<table>
<thead>
<tr>
<th>$R$</th>
<th>$R'$</th>
<th>2 (%)</th>
<th>3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>i-Pr</td>
<td>H</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>Et</td>
<td>Et</td>
<td>22</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 1. Results of Warkentin's imine cyclizations.$^{25}$

**Takano's Radical Cyclization Results.$^{26}$**

Takano et al. studied a similar series of radical cyclizations of aldimines and ketimines. In Takano's work, only the aromatic imines cyclized. The cyclization of aldimines resulted, as Warkentin had reported, in a preference for
the 6-endo cyclization. See Table 2. Studies of aromatic ketimines showed a reversal in the regiochemical outcome (Table 2). Takano reasoned that steric congestion forced the cyclization to occur at the nitrogen end of the C=N bond.

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>5 (%)</th>
<th>6 (%)</th>
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</thead>
<tbody>
<tr>
<td>H</td>
<td>3,4-(CH$_3$O)-Ph</td>
<td>9</td>
<td>51</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>59</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Results of Takano’s imine cyclizations.
The chemistry of Warkentin and Takano provided a suitable entry point towards the synthesis of derivatized dihydroindoles. The first attempt at the utilization of this chemistry towards naturally occurring compounds was the synthesis of the mitomycins.

Mitomycins

Mitomycins are a class of antibiotics, isolated from Streptomyces verticillatus, with activity against both gram-positive and gram-negative bacteria, and several types of tumors. They represent the first naturally occurring examples of aziridine ring systems. Mitomycins have as their basic skeleton a pyrrolo[1,2-a]indole ring system. The pyrrolo ring system is made up of a benzoquinone and a pyrroldine ring. To date there are 30 known natural mitomycins, and greater than 500 synthetic variants, which are divided into 3 main types (Figure 2). Types A and B are diastereotopic, differing only in the stereochemistry at C-9, whereas type G has an exocyclic methylene at the C-9 position.

Biological testing of the mitomycin series, revealed four variants that were particularly effective against bacteria and tumors, mitomycins A, B, C, and porfiromycin. Of these, mitomycin C has been shown to be the most effective. Currently marketed by Bristol Myers under the brand name Mutamycin, it has
Figure 2. Mitomycins.\textsuperscript{30}
shown many side effects including toxicity of the blood, kidneys, and bone.\textsuperscript{31} To this end, synthetic efforts have concentrated on the development of potent derivatives that have fewer side effects.\textsuperscript{32,33}

Investigations into the biological effectiveness of mitomycins has shown their ability to alkylate DNA through the aziridine. Activation of the aziridine comes after \textit{in vivo} reduction of the quinone ring to a hydroquinone. Loss of methanol allows the aziridine to open at the C-1 position, allowing nucleophilic attack to occur onto DNA. The free aziridine nitrogen is now capable of a second DNA alkylation. It has been suggested that the formation of those intrahelical, intrastrand DNA-mitomycin C adducts inhibit DNA replication, resulting in a drop of cell division. \textit{In vivo} oxidation of the hydroquinone to a semiquinone radical allows for cleavage of the bound DNA, either on its own or through the formation of other peroxides.\textsuperscript{33,34}

The extension of the work of Warkentin and Takano to the synthesis of the mitomycin skeleton is discussed below.
Results and Discussion

Radical Cyclization Precursors.

We decided to initially investigate the 5-exo cyclization onto the nitrogen of an imidate ester using imidate 15 as the model system. Our synthesis began with commercially available 2-bromophenyl acetonitrile, 10. Reduction of the nitrile with lithium aluminum hydride in the presence of aluminum chloride yielded amine 11 in good yield (Scheme 11).

\[
\text{Scheme 11. Reduction of nitrile.}
\]

Typically, subjection of halogenated compounds to radical forming conditions results in displacement of the halogen. Subsequent quenching of the radical with a proton yields what is commonly known as the reduced product. To this end, phenethylamine, 12, was chosen as the starting amine for the reduced analogs in order to prove their structure.
Table 3. Preparation of amides.

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>13a</td>
<td>Br</td>
<td>Ph</td>
<td>97</td>
</tr>
<tr>
<td>13b</td>
<td>Br</td>
<td>iPr</td>
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<tr>
<td>13c</td>
<td>Br</td>
<td>nBu</td>
<td>99</td>
</tr>
<tr>
<td>13d</td>
<td>Br</td>
<td>CO₂Et</td>
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<tr>
<td>13e</td>
<td>Br</td>
<td>Me</td>
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<td>14a</td>
<td>H</td>
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</tr>
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<td>14b</td>
<td>H</td>
<td>iPr</td>
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</tr>
<tr>
<td>14c</td>
<td>H</td>
<td>nBu</td>
<td>97</td>
</tr>
<tr>
<td>14d</td>
<td>H</td>
<td>CO₂Et</td>
<td>87</td>
</tr>
</tbody>
</table>
Table 4. Preparation of imidates from amides.
Syntheses of imidates 15a-d, for radical cyclization studies followed from amides 13a-d. Both the brominated, 13a-e, and nonbrominated, 14a-d, amides were made in a straightforward manner. The appropriate acid chloride was added to a solution of triethylamine and primary amine 11 or 12, to yield amides 13a-e and 14a-d in excellent yields. See Table 3. Formation of the imidates proceeded cleanly upon treatment with ethyl Meerwein's reagent in non-buffered CH₂Cl₂. Column chromatography on basic alumina yielded imidates 15a-d and 16a-d in good to excellent yields (Table 4). At this point, it was necessary to eliminate the methyl imidate, 15e, from the study as it rapidly decomposed upon isolation.

Radical Cyclization Results.

With the above imidates in hand, the radical cyclization was performed under a variety of conditions. Initial studies were performed using tributyltin hydride and AIBN. A solution of tributyltin hydride (0.01 M) and AIBN (10 mol%) in benzene was added by syringe pump over a period of 18 h to the imidate in refluxing benzene. After the addition was complete, the reaction was allowed stir at reflux until the reaction progress had ended, typically 1 hour. These radical reactions showed marginal success. Cyclization was observed only with the phenyl imidate 15a, with the other imidates producing only the reduction products 16a-d (Table 5).
Table 5. Summary of radical cyclization attempts.

<table>
<thead>
<tr>
<th>R</th>
<th>Rad'</th>
<th>method</th>
<th>temp (°C)</th>
<th>17 (%)</th>
<th>15 (%)</th>
<th>16 (%)</th>
</tr>
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<tbody>
<tr>
<td>Ph</td>
<td>Bu₂SnH, AIBN</td>
<td>A</td>
<td>80</td>
<td>30</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>iPr</td>
<td>Bu₂SnH, AIBN</td>
<td>A</td>
<td>80</td>
<td>0</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Bu</td>
<td>Bu₂SnH, AIBN</td>
<td>A</td>
<td>80</td>
<td>0</td>
<td>20</td>
<td>75</td>
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<tr>
<td>Bu</td>
<td>Bu₂SnH, AIBN</td>
<td>A</td>
<td>140</td>
<td>0</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>Bu₂SnH, AIBN</td>
<td>A</td>
<td>80</td>
<td>0</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Ph</td>
<td>Bu₂SnH, BEt₃</td>
<td>B</td>
<td>23</td>
<td>0</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>Ph</td>
<td>TTMSS, BEt₃</td>
<td>B</td>
<td>23</td>
<td>0</td>
<td>34</td>
<td>53</td>
</tr>
<tr>
<td>Ph</td>
<td>TTMSS, BEt₃</td>
<td>B</td>
<td>80</td>
<td>0</td>
<td>20</td>
<td>63</td>
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<tr>
<td>Ph</td>
<td>TTMSS, AIBN</td>
<td>C</td>
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<tr>
<td>iPr</td>
<td>TTMSS, AIBN</td>
<td>C</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>nBu</td>
<td>TTMSS, AIBN</td>
<td>C</td>
<td>80</td>
<td>0</td>
<td>7</td>
<td>85</td>
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<td>CO₂Et</td>
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<td>C</td>
<td>80</td>
<td>0</td>
<td>13</td>
<td>84</td>
</tr>
</tbody>
</table>
Isolation of the amide and not the expected aminal can be explained in terms of a radical chain reaction. The carbon radical formed after the cyclization step, 18a, undergoes beta fragmentation with loss of ethyl radical to give the amide. The ethyl radical then propagates the chain by hydrogen transfer from tributyltin hydride, see Scheme 12. Fragmentation is driven by formation of the amide. The reduction products were confirmed by comparing spectral data to the previously synthesized reduced imidates, 16a-d.

Developed in 1969, tris(trimethylsilyl)silane (TTMSS) is a less toxic alternative to tributyltin hydride. TTMSS does not suffer from the purification problems of tin reagents and has been shown to reduce the amount of reduction product in radical reactions. Reaction of the imidate in TTMSS showed similar results to the tributyltin hydride. The phenyl imidate, 15a, cyclized effectively to give 53% of the cyclized amide with no reduction observed. The other imidates formed only reduced product.

A mixture of triethylborane and oxygen has been shown to be an effective initiator of radical reactions and can be used at low or room temperature. Use of tributyltin hydride or TTMSS as the radical propagator resulted in only reduced product even at elevated temperatures. It is important to note that in all cases no 6-endo cyclization was seen by any spectroscopic analysis ($^1$H-NMR, GC-MS, IR).
Scheme 12. Radical formation of amide.
Conclusion

Model studies into the phenyl radical's effectiveness have shown that the proposed cyclization to the mitomycin skeleton would not be feasible. Cyclization occurred only when the phenyl imidate, 15a, was subjected to radical forming conditions. Surprisingly, these cyclizations afforded only the 5-exo product. The non-reactivity of the alkyl imidates with the phenyl radical revealed that the electronics of the system would not permit the butene derivative to react, see Scheme 9, thereby eliminating the tandem cyclization route. The predominance of the 5-exo over the 6-endo trig cyclization, not seen by other investigators, prompted us to study the system in greater detail. It has been shown that the intramolecular cyclization of a phenyl radical onto an imidate ester occurs in a regioselective manner, yielding only the 5-exo product. This is not in accordance with the results of Warkentin and Takano. They found that ketimines cyclized to form mixtures of the 5-exo and 6-endo ring closure products. While the generality of the results showed the phenyl substituent would cyclize, the results are important in the fact that this is the first example of a radical cyclization onto the nitrogen end of an imidate ester.
Experimental

General

All experiments were carried out under an atmosphere of dry argon in oven (140°C, >6 h) and/or flame dried glassware. $^1$H, $^{13}$C, $^{31}$P NMR spectra were obtained on a Bruker DPX-300 spectrometer using CDCl$_3$ as solvent unless noted otherwise. Chemical shifts are reported in ppm downfield from the internal reference tetramethylsilane, or phosphoric acid (in the case of $^{31}$P). Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), sept (septet), sext (sextet), and m (multiplet); addition of b indicates a broadened pattern, addition of app indicates an apparent signal i.e. app pent=apparent pentet. Substances for which combustion analyses were not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Infrared spectra were taken on a Bruker IFS25 series FTIR spectrometer as neat oils on NaCl plates or as solid plates with KBr and are reported in cm$^{-1}$. Mass spectra were obtained on a Hewlett Packard model 5970 set at 70 eV. High resolution mass spectra were obtained on a VG70E_HF double-focusing mass spectrometer. Gas chromatography was performed on a Hewlett Packard model 5890A using a 30 m DB-5 column (0.25 mm i.d., 0.25 mm film thickness), He flowrate 30 cm/sec calibrated at 200°C, start 50°C hold 5 min, ramp 10°C/min to 300°C, hold until
complete. Column chromatography was performed using either Aldrich 22,719-6 silica gel or where indicated Acros 18999 activated, basic aluminum oxide. The solvent mixtures used for column chromatography are reported as volume/volume mixtures. \( R_f \) values refer to thin layer chromatography on Analtech 2.5 x 10 cm, 250M analytical plates coated with silica gel GF, or where basic aluminum oxide is needed, on Alltech 4 x 8 cm, ALOX analytical plates. Non-u.v. active compounds were indicated by charring (spray consists of either ethanol/sulfuric acid/anisaldehyde/acetic acid 93.2/3.3/2.5/1, or water/sulfuric acid/ammonium heptamolybdate tetrahydrate/kerium sulfate 84.9/9.4/4.7/0.94). Preparative TLC was performed using Analtech 20 x 20 cm Uniplates coated with silica GF, 2.0 mm thickness. Melting points were taken on a Lab Device Mel-Temp and are uncorrected. CH\(_3\)CN, ClCH\(_2\)CH\(_2\)Cl, and CH\(_2\)Cl\(_2\) were distilled from CaH\(_2\) under argon. THF, benzene, toluene, xylenes, and diethyl ether were distilled from sodium benzophenone ketyl before use.

**Experimental**

**Triethylloxonium tetrafluoroborate\(^{39}\) (1 M):** A tared 50 mL round bottomed flask was charged with boron trifluoride diethyl etherate (14.2 g, 100 mmol) and Et\(_2\)O (25 mL) and heated to reflux. Epichlorohydrin (7.02 g, 75.8 mmol) was added slowly to refluxing mixture and refluxing was continued for an
additional hour. The mixture was allowed to cool to room temperature and after 12 h a gray precipitant was observed. The precipitant was washed anhydrously with ether (4 X 50 mL) and dried under reduced pressure to yield a white solid (11.1 g, 58.5 mmol, 77%). This solid was dissolved with dry CH₂Cl₂ (58.5 mL) and stored in a desiccator at -20°C until needed.

2-(2-bromophenyl)ethylamine (11). A 250 mL round-bottomed flask was charged with LiAlH₄ (1.89 g, 49.8 mmol) and cooled to 0°C. Et₂O (50 mL) was added slowly and the mixture was stirred at 0°C for 30 min. In a separate 100 mL round-bottomed flask was placed AlCl₃ (7.18 g, 53.9 mmol) and cooled to 0°C. Et₂O (70 mL) was added slowly and the mixture was stirred at 0°C until the AlCl₃ was dissolved, approximately 30 min. The AlCl₃/Et₂O solution was transferred to the cooled LiAlH₄/Et₂O solution. After 75 min of stirring at 0°C, 2-bromophenylacetonitrile (8.15 g, 41.6 mmol) in Et₂O (5 mL) was added dropwise. After 10 min of stirring at 0°C the mixture was allowed to warm to room temperature and stirring was continued for 2 h. The mixture was cooled to 0°C, concentrated NH₄OH (80 mL) was added very slowly, and the mixture was stirred overnight. The mixture was filtered and the layers were separated. The aqueous layer was extracted with Et₂O (4 x 40 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced
pressure to yield a yellow oil (9.24 g). Bulb-to-bulb distillation (80-88°C, 3 mm Hg) yielded 11 as a clear oil (7.24 g, 36.2 mmol, 87%).

![Chemical structure](image)

$^1$H-NMR (CDCl₃): 7.46 (d, 1H, $J=8.0$ Hz, H on C3), 7.16-7.15 (m, 2H, H's on C5 and C6), 7.02-6.96 (m, 1H, H on C4), 2.92-2.79 (m, 4H, H's on C7 and C8), 1.02 (s, 2H, H's on N). $^{13}$C-NMR (CDCl₃): 139.0 (C2), 132.8 (C3), 130.7 (C6), 127.8 (C4), 127.3 (C5), 124.5 (C1), 42.0 (C8), 40.2 (C7). Spectral data is consistent with literature values.³³

**General Procedure 1: Preparation of $N$-2-(2-bromophenyl)ethylamides (13a-e) and $N$-2-phenethylamides (14a-d).** A 25 mL round-bottomed flask was charged with 1 equivalent of 2-(2-bromophenyl)ethylamine, 11, (for 13a-e) or 1 equivalent of 2-phenethylamine, 12, (for 14a-d) 2.5 equivalent of NEt₃, and CH₂Cl₂ (10 mL). The mixture was cooled to 0°C and 1.1 equivalents of the appropriate acid chloride was added dropwise with stirring. The mixture was allowed to warm to room temperature.
After stirring at room temperature for 2 h, the mixture was poured into 10% aqueous HCl (20 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic washes were combined, dried with MgSO$_4$, and the solvent was removed under reduced pressure to yield a crude solid. Column chromatography and/or recrystallization yielded pure amide.

Al-2-(2-bromophenyl)ethylbenzamide (13a). As outlined in General Procedure 1, benzoyl chloride (0.540 mL, 4.65 mmol) was added to a 25 mL round-bottomed flask charged with 2-(2-bromophenyl)ethylamine, 11, (0.841 g, 4.21 mmol), NEt$_3$ (1.80 mL, 12.9 mmol), and CH$_2$Cl$_2$ (10 mL) to yield a pink solid (1.56 g). Column chromatography (15% EtOAc/Hex) yielded 13a as a clear oil ($R_f$=0.45, 40% EtOAc/Hex) which solidified on standing (1.240 g, 4.07 mmol, 97%); mp 93.4-94.2°C (toluene).
$^1$H-NMR (CDCl$_3$): 7.71-7.68 (m, 2H, H's on C11 and C15), 7.55 (d, 1H, $J$=7.8 Hz, H on C3), 7.50-7.37 (m, 3H, H's on C12, C13, and C14), 7.27-7.21 (m, 2H, H's on C5 and C6), 7.12-7.06 (m, 1H, H on C4), 6.18 (bs, 1H, H on N), 3.73 (app q, 2H, $J$=6.7 Hz, H's on C8), 3.09 (t, 2H, $J$=6.9 Hz, H's on C7). $^{13}$C-NMR (CDCl$_3$): 167.5 (C9), 138.3 (C1), 134.5 (C10), 133.0 (C3), 131.4 (C13), 131.1 (C6), 128.5 (C11 and C15), 128.3 (C4), 127.7 (C5), 126.8 (C12 and C14), 124.6 (C2), 39.9 (C8), 35.7 (C7). HRMS calculated for C$_{15}$H$_{14}$BrNO: 303.025875, found: 303.024704. GC: Rt=27.4 min. MS 304 (1), 224 (50), 183 (8), 181 (8), 162 (5), 134 (13), 105 (100), 77 (40), 51 (14). IR (KBr, cm$^{-1}$): 3269, 3063, 2966, 1636, 1541, 1491, 1382.

$\text{N-2-(2-bromophenyl)ethyl-2-methylpropanamide (13b).}$ As outlined in General Procedure 1, 2-methylpropanoyl chloride (0.310 mL, 2.86 mmol) was added to a 25 mL round-bottomed flask charged with 2-(2-bromophenyl)ethylamine, 11, (0.405 g, 2.52 mmol), NEt$_3$ (1.20 mL, 8.61 mmol), and CH$_2$Cl$_2$ (10 mL) to yield a yellow oil (0.86 g). Column chromatography (1% MeOH/CH$_2$Cl$_2$) yielded 13b as a clear oil ($R_f$=0.37, 40% EtOAc/Hex) which solidified on standing (0.651 g, 2.41 mmol, 96%); mp 79.5-80.1°C (toluene).
$^1$H-NMR (CDCl$_3$): 7.52 (d, 1H, $J$=8.1 Hz, H on C3), 7.25-7.17 (m, 2H, H's on C4 and C5), 7.10-7.04 (m, 1H, H on C6), 5.55 (bs, 1H, H on N), 3.50 (app q, 2H, $J$=6.8 Hz, H's on C8), 2.95 (t, 2H, $J$=6.9 Hz, H's on C7), 2.76 (sept, 1H, $J$=6.9 Hz, H on C10), 1.09 (d, 6H, $J$=6.9 Hz, H's on C11 and C12). $^{13}$C-NMR (CDCl$_3$): 176.9 (C9), 138.4 (C1), 132.9 (C3), 131.1 (C6), 128.2 (C4), 127.5 (C5), 124.5 (C2), 39.0 (C8), 35.7 (C7), 35.6 (C10), 19.6 (C11 and C12). HRMS calculated for C$_{12}$H$_{16}$BrNO: 269.041525, found: 269.041496. GC: Rt=22.7 min. MS: 270 (1), 268 (1), 190 (56), 183 (19), 181 (20), 100 (34), 90 (10), 71 (100). IR (KBr, cm$^{-1}$): 3288, 3075, 2966, 1653, 1559, 1432, 1244.

$N$-2-(2-bromophenyl)ethylbutanamide (13c). As outlined in General Procedure 1, valeryl chloride (0.440 mL, 3.71 mmol) was added to a 25 mL round-bottomed flask charged with 2-(2-bromophenyl)ethylamine, 11, (0.675 g, 3.37 mmol), NEt$_3$ (1.40 mL, 10.0 mmol), and CH$_2$Cl$_2$ (10 mL) to yield a yellow oil
(1.05 g). Column chromatography (1% MeOH/CH₂Cl₂) yielded 13c as a clear oil (Rᵣ=0.18, 1% MeOH/CH₂Cl₂), (0.946 g, 3.33 mmol, 99%).

[Diagram of the molecule]

¹H-NMR (CDCl₃): 7.50 (d, 1H, J=8.0 Hz, H on C3), 7.24-7.17 (m, 2H, H's on C4 and C5), 7.08-7.02 (m, 1H, H on C6), 5.73 (bs, 1H, H on N), 3.48 (app q, 2H, J=6.6 Hz, H's on C8), 2.93 (t, 2H, J=7.0 Hz, H's on C7), 2.10 (t, 2H, J=7.6 Hz, H's on C10), 1.55 (app pent, 2H, J=7.6 Hz, H's on C11), 1.27 (app sext, 2H, J=7.4 Hz, H's on C12), 0.86 (t, 3H, J=7.2 Hz, H's on C13). ¹³C-NMR (CDCl₃): 173.8 (C9), 138.8 (C1), 133.3 (C3), 131.3 (C6), 128.6 (C4), 128.0 (C5), 125.0 (C2), 39.6 (C8), 36.8 (C7), 36.2 (C10), 28.2 (C11), 22.8 (C12), 14.2 (C13). HRMS calculated for C₁₃H₁₈NOBr: 283.055298, found: 283.057175. GC: Rt=24.1 min. MS: 284 (1), 282 (1), 243 (6), 241 (6), 204 (100), 184 (21), 182 (21), 171 (9), 169 (9), 114 (34), 85 (82), 57 (95). IR (KBr, cm⁻¹): 3290, 3070, 2872, 1645, 1552, 1471, 1440, 1270.
37

*N-2-(2-bromophenyl)ethyloxalamic acid ethyl ester (13d).* As outlined in General Procedure 1, ethyl oxalyl chloride (1.14 mL, 10.2 mmol) was added to a 25 mL round-bottomed flask charged with 2-(2-bromophenyl)ethylamine, 11, (1.683 g, 8.41 mmol), NEt₃ (12.3 mL, 25.1 mmol), and CH₂Cl₂ (10 mL) to yield a yellow oil (2.70 g). Column chromatography (1% MeOH/CH₂Cl₂) yielded 13d as a clear oil (Rf=0.47, 2% MeOH/CH₂Cl₂) which solidified on standing (2.17 g, 7.24 mmol, 86%); mp 63.8-64.7 °C (toluene).

1H-NMR (CDCl₃): 7.54 (d, 1H, J=8.0 Hz, H on C3), 7.28-7.05 (m, 4H, H’s on C4, C5, C6, and N), 4.32 (q, 2H, J=7.1 Hz, H’s on C11), 3.60 (q, 2H, J=6.8 Hz, H’s on C8), 3.01 (t, 2H, J=7.1 Hz, H’s on C7), 1.36 (t, 3H, J=7.1 Hz, H’s on C12).

13C-NMR (CDCl₃): 160.6 (C10), 156.6 (C9), 137.5 (C1), 133.1 (C3), 130.9 (C6), 128.6 (C4), 127.8 (C5), 124.5 (C2), 63.2 (C11), 39.6 (C8), 35.4 (C7), 14.0 (C12).

HRMS calculated for C₁₂H₁₄NO₃Br: 299.015705, found: 299.014847. GC: Rt= 23.3 min. MS: 301 (1), 299 (1), 220 (100), 184 (70), 182 (70), 171 (18), 169
(18), 146 (9), 102 (71), 77 (28), 51 (11). IR (KBr, cm$^{-1}$): 3321, 2988, 1730, 1672, 1535, 1469, 1225, 1017.

$N$-2-(2-bromophenyl)ethylmethanamide (13d). As outlined in General Procedure I, acetyl chloride (0.520 mL, 7.31 mmol) was added to a 25 mL round-bottomed flask charged with 2-(2-bromophenyl)ethylamine, 11, (1.216 g, 6.07 mmol), NEt$_3$ (2.73 mL, 19.4 mmol), and CH$_2$Cl$_2$ (10 mL) to yield a yellow oil (1.60 g). Column chromatography (1% MeOH/CH$_2$Cl$_2$) yielded 13d as a yellow oil ($R_f=0.14$, 1% MeOH/CH$_2$Cl$_2$), (1.32 g, 5.45 mmol, 90%).

$^1$H-NMR (CDCl$_3$): 7.52 (d, 1H, $J=8.0$ Hz, H on C5), 7.26-7.18 (m, 2H, H's on C3 and C4), 7.10-7.04 (m, 1H, H on C6), 5.67 (bs, 1H, H on N), 3.50 (app q, 2H, $J=6.8$ Hz, H's on C8), 2.95 (t, 2H, $J=7.0$ Hz, H's on C7), 1.94 (s, 3H, H's on C10).

$^{13}$C-NMR (CDCl$_3$): 170.2 (C9), 138.3 (C1), 132.9 (C5), 130.9 (C2), 128.3 (C4), 127.6 (C3), 124.6 (C6), 39.4 (C8), 35.7 (C7), 23.2 (C10). HRMS calculated for C$_{10}$H$_{12}$BrNO (M+H$^+$): 242.017452, found: 242.01805. GC: Rt=21.4 min. MS:
243 (1), 241 (1), 184 (34), 182 (34), 162 (100), 119 (14), 90 (36), 72 (83), 63 (26), 51 (17). IR (NaCl, cm\(^{-1}\)): 3416, 3075, 2964, 1637, 1560, 1438, 1364, 1019.

\(N\)-2-phenethylbenzamide (14a). As outlined in General Procedure 1, benzoyl chloride (1.20 mL, 10.3 mmol) was added to a 25 mL round-bottomed flask charged with phenethylamine, 12, (0.965 g, 7.96 mmol), NE\(_3\) (3.50 mL, 25.1 mmol), and CH\(_2\)Cl\(_2\) (10 mL) to yield an orange solid (1.92 g). Recrystallization in toluene yielded 14a as a white solid (1.688 g, 7.49 mmol, 94%); mp 110.6-111.9\(^\circ\)C (Lit. mp 110 -112\(^\circ\)C\(^{40a}\)) (toluene).

\(\text{\(^1\)H-NMR (CDCl}_3\): 7.69-7.19 (m, 10H, H's on C2, C3, C4, C5, C6, C11, C12, C13, C14, and C15), 6.33 (bs, 1H, H on N), 3.68 (app q, 2H, \(J\approx 6.7\) Hz, H's on C8), 2.92 (t, 2H, \(J\approx 6.9\) Hz, H's on C7). \(\text{\(^{13}\)C-NMR (CDCl}_3\): 167.4 (C9), 138.9 (C1), 134.6 (C10), 131.3 (C3 and C5), 129.3 (C13), 128.8 (C4), 128.7 (C11 and
C15), 128.6 (C6), 128.5 (C12), 126.8 (C14), 126.5 (C2), 41.1 (C8), 35.7 (C7).
GC: Rt=23.2 min. MS: 225 (11), 162 (6), 134 (10), 105 (100), 77 (50), 51 (17).
Spectral data is consistent with literature values.40a

**N-2-phenethyl-2-methylpropanamide (14b).** As outlined in General Procedure 1, 2-methylpropanoyl chloride (1.10 mL, 10.5 mmol) was added to a 25 mL round-bottomed flask charged with phenethylamine, 12, (0.965 g, 7.96 mmol), NEt₃ (3.50 mL, 25.1 mmol), and CH₂Cl₂ (10 mL) to yield a pink solid (1.72 g). Recrystallization in toluene yielded 14b as a white solid (1.484 g, 7.76 mmol, 98%); mp 85.4-86.5 °C (Lit. mp 84-86°C40b) (toluene).

![Chemical structure of 14b](image)

**1H-NMR (CDCl₃):** 7.31-7.15 (m, 5H, H's on C2, C3, C4, C5, and C6), 5.44 (bs, 1H, H on N), 3.48 (app q, 2H, J=6.7 Hz, H's on C8), 2.79 (t, 2H, J=6.8 Hz, H's on C7), 2.25 (sept, 1H, J=6.9 Hz, H on C10), 1.08 (d, 6H, J=6.9 Hz, H's on C11 and C12). **13C-NMR (CDCl₃):** 176.8 (C9), 139.0 (C1), 128.8 (C3 and C5), 128.6 (C2
and C6), 126.4 (C4), 40.4 (C8), 35.7 (C7), 35.6 (C10), 19.6 (C11 and C12).
Spectral data is consistent with literature values.\textsuperscript{40b}

**N-2-phenethylbutanamide (14c).** As outlined in General Procedure 1, valeryl chloride (1.25 mL, 10.5 mmol) was added dropwise to a 25 mL round-bottomed flask charged with phenethylamine, 12, (0.965 g, 7.96 mmol), \( \text{NEt}_3 \) (3.50 mL, 25.1 mmol), and \( \text{CH}_2\text{Cl}_2 \) (10 mL) to yield a yellow oily solid (1.72 g). Recrystallization in toluene yielded 14c as a white solid (1.592 g, 37.8 mmol, 97%); mp 42.1-42.6\( ^\circ \)C (Lit. mp 42-43\( ^\circ \)C\textsuperscript{40c}) (toluene).

![Chemical Structure](image)

\( ^1\text{H-NMR (CDCl}_3\): 7.26-7.11 (m, 5H, H’s on C2, C3, C4, C5, and C6), 5.84 (bs, 1H, H on N), 3.43 (app q, 2H, J=6.7 Hz, H’s on C8), 2.75 (t, 2H, J=7.0 Hz, H’s on C7), 2.07 (t, 2H, J=7.5 Hz, H’s on C10), 1.51 (app pent, 2H, J=7.6 Hz, H’s on C11), 1.24 (app sext, 2H, J=7.2 Hz, H’s on C12), 0.83 (t, 2H, J=7.3 Hz, H’s on C13). \( ^{13}\text{C-NMR (CDCl}_3\): 173.1 (C9), 138.9 (C1), 128.6 (C3 and C5), 128.4 (C2
and C6), 126.2 (C4), 40.4 (C8), 36.3 (C7), 35.6 (C10), 27.7 (C11), 22.2 (C12), 13.6 (C13). Spectral data is consistent with literature values.40c

*N-Phenethyloxalamic acid ethyl ester (14d).* As outlined in General Procedure 1, ethyl oxalyl chloride (1.00 mL, 8.94 mmol) was added to a 25 mL round-bottomed flask charged with phenethylamine, 12, (0.965 g, 7.96 mmol), NEt3 (3.50 mL, 25.1 mmol), and CH2Cl2 (10 mL) to yield a yellow oil (1.94 g). Column chromatography (1% MeOH/CH2Cl2) yielded 14d as a clear oil (Rf=0.55, 2% MeOH/CH2Cl2) which solidified on standing (1.53 g, 6.92 mmol, 87%); mp 67.7-68.2°C (toluene).

\[ \text{1H-NMR (CDCl3): } 7.35-7.11 \text{ (m, 5H, } \text{H's on C2, C3, C4, C5, and C6)}, 7.13 \text{ (bs, 1H, H on N)}, 4.30 \text{ (q, 2H, } J=7.1 \text{ Hz, H's on C11)}, 3.58 \text{ (app q, 2H, } J=7.0 \text{ Hz, H's on C8)}, 2.85 \text{ (t, 2H, } J=7.1 \text{ Hz, H's on C7}), 1.35 \text{ (t, 3H, } J=7.1 \text{ Hz, H's on C12}). \]

\[ \text{13C-NMR (CDCl3): } 160.6 \text{ (C10)}, 156.5 \text{ (C9)}, 138.1 \text{ (C1)}, 128.7 \text{ (C3 and C5)}, \]
128.6 (C2 and C6), 126.7 (C4), 63.1 (C11), 41.0 (C8), 35.2 (C7), 13.9 (C12).

HRMS calculated for C_{12}H_{15}NO_{3}: 221.105194, found: 221.105808. GC: Rt=20.6 min. MS: 221 (13), 148 (8), 104 (100), 91 (20), 77 (15), 51 (11). IR (KBr, cm\(^{-1}\)): 3351, 3027, 2931, 1736, 1685, 1534, 1455, 1371, 1281, 1226, 1031.

General Procedure 2: Preparation of Ethyl \(N\)-2-(2-bromophenyl)ethylimidates (15a-d) and Ethyl \(N\)-2-phenethylimidates (16a-d). A 25 mL round-bottomed flask was charged with 1 equivalent of the appropriate \(N\)-2-(2-bromophenyl)ethylamide, 13a-d, (for 15a-d), or the appropriate \(N\)-2-phenethylamide, 14a-d, (for 16a-d) and CH\(_2\)Cl\(_2\) (10 mL). The solution was cooled to \(0^\circ\)C and ethyl Meerwein's reagent (1.5 equivalents, 1.0 M in CH\(_2\)Cl\(_2\)) was added. The mixture was stirred at \(0^\circ\)C for 4 h and then warmed to room temperature. After stirring at room temperature for 36 h, the mixture was poured into 10% aqueous (20 mL) and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The organic washes were combined, dried with MgSO\(_4\), and the solvent was removed under reduced pressure to yield a crude oil. Column chromatography using basic alumina yielded pure imidate.
Ethyl \( N\text{--}2\text{-(2-bromophenyl)ethylbenzimidate} \) (15a). As outlined in General Procedure 2, ethyl Meerwein's reagent (0.750 mL, 1.0 M in \( \text{CH}_2\text{Cl}_2 \)) was added to a 25 mL round-bottomed flask charged with \( \text{N-benzoyl 2-(2-bromophenyl)ethylamine, 13a, (0.137 g, 0.450 mmol)} \) and \( \text{CH}_2\text{Cl}_2 \) (10 mL) to yield a yellow oil (0.21 g). Column chromatography (10% EtOAc/Hex) using basic alumina yielded 15a as a colorless oil (\( R_t=0.51 \), 40% EtOAc/Hex), (0.143 g, 0.430 mmol, 96%).

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{CH}_3
\end{array}
\]

\( \text{H-NMR (CDCl}_3\text{: 7.45 (d, 1H, } J=7.8 \text{ Hz, H on C3), 7.35-7.20 (m, 3H, H's on C11, C13, and C15), 7.19-7.13 (m, 4H, H's on C5, C6, C12, and C14), 7.05-7.01 (m, 1H, H on C4), 4.23 (q, 2H, } J=7.1 \text{ Hz, H's on C16), 3.51 (t, 2H, } J=7.3 \text{ Hz, H's on C8), 2.96 (t, 2H, } J=7.3 \text{ Hz, H's on C7), 1.32 (t, 3H, } J=7.1 \text{ Hz, H's on C17).} \\
\text{\( ^{13}\text{C-NMR (CDCl}_3\text{: 161.5 (C9), 139.6 (C1), 132.6 (C10), 131.3 (C3), 129.1 (C13), 128.2 (C11 and C15), 127.7 (C4 and C6), 127.6 (C12 and C14), 127.1 (C5), 124.7 (C2), 61.1 (C16), 49.6 (C8), 38.4 (C7), 14.4 (C17). \) HRMS}
\]
calculated for $\text{C}_{17}\text{H}_{18}\text{BrNO}$: 331.057231, found: 331.059642. GC: Rt=25.4 min. MS: 333 (11), 331 (11), 252 (37), 224 (10), 183 (5), 162 (52), 118 (68), 105 (100), 77 (66), 51 (20). IR (NaCl, cm$^{-1}$) 3059, 2975, 1630, 1537, 1439, 1367, 1288, 1027.

**Ethyl $N$-2-(2-bromophenyl)ethyl-2-methylpropanimidate (15b).** As outlined in General Procedure 2, ethyl Meerwein's reagent (1.80 mL, 1.0 M in $\text{CH}_2\text{Cl}_2$) was added to a 25 mL round-bottomed flask charged with $N$-2-(2-bromophenyl)ethyl-2-methylpropanamide, 13b, (0.326 g, 1.21 mmol) and $\text{CH}_2\text{Cl}_2$ (10 mL) to yield a yellow oil (0.66 g). Column chromatography (10% EtOAc/Hex) using basic alumina yielded 15b as a colorless oil ($R_f$=0.58, 40% EtOAc/Hex), (0.290 g, 1.01 mmol, 83%).
1H-NMR (CDCl₃): 7.49 (d, 1H, J=7.9 Hz, H on C3), 7.26-7.15 (m, 2H, H's on C4 and C5), 7.08-6.98 (m, 1H, H on C6), 3.99 (q, 2H, J=7.1 Hz, H's on C13), 3.49 (app q, 2H, J=7.2 Hz, H's on C8), 2.94 (t, 2H, J=7.2 Hz, H's on C7), 2.78 (sept, 1H, J=6.8 Hz, H on C10), 1.20 (t, 3H, J=7.1 Hz, H's on C14), 0.95 (d, 6H, J=6.8 Hz, H's on C11 and C12). 13C-NMR (CDCl₃): 167.3 (C9), 139.8 (C1), 132.6 (C3), 131.4 (C6), 127.7 (C4), 127.2 (C5), 124.6 (C2), 59.9 (C13), 47.7 (C8), 38.5 (C7), 27.0 (C10), 19.4 (C11 and C12), 14.2 (C14). HRMS calculated for C₁₄H₂₀NOBr: 297.072826, found: 297.072929. GC: Rt=19.9 min. MS 299 (4), 297 (4), 270 (1), 268 (1), 218 (2), 190 (7), 171 (10), 168 (10), 128 (30), 104 (15), 90 (17), 84 (100), 61 (25), 51 (12). IR (NaCl, cm⁻¹) 3059, 2970, 1668, 1471, 1260, 1088.

Ethyl N-2-(2-bromophenyl)butanamide (15c). As outlined in General Procedure 2, ethyl Meerwein’s reagent (1.20 mL, 1.0 M in CH₂Cl₂) was added to a 25 mL round-bottomed flask charged with N-2-(2-bromophenyl)ethylbutanamide, 13c, (0.133 g, 0.91 mmol) and CH₂Cl₂ (10 mL) to yield a yellow oil (0.150 g). Column chromatography (40% EtOAc/Hex) using basic alumina yielded 15c as a colorless oil (Rf=0.75, 40% EtOAc/Hex), (0.131 g, 0.42 mmol, 90%).
1H-NMR (CDCl3): 7.52 (d, 1H, J=7.9 Hz, H on C3), 7.24-7.17 (m, 2H, H's on C4 and C5), 7.08-7.02 (m, 1H, H on C6), 3.97 (q, 2H, J=7.0 Hz, H's on C14), 3.46 (t, 2H, J=7.0 Hz, H's on C8), 2.92 (t, 2H, J=7.0 Hz, H's on C7), 2.12 (t, 2H, J=7.3 Hz, H's on C10), 1.46-1.30 (m, 2H, H's on C11), 1.29-1.18 (m, 5H, H's on C12 and C15), 0.85 (t, 3H, J=7.1 Hz, H's on C13). 13C-NMR (CDCl3): 179.6 (C9), 136.4 (C1), 132.8 (C3), 131.9 (C6), 128.9 (C4), 127.8 (C5), 127.6 (C2), 70.2 (C14), 42.3 (C8), 34.4 (C7), 30.2 (C10), 27.4 (C11), 14.2 (C12), 13.7 (C13), 13.2 (C15). HRMS calculated for C15H22BrNO: 311.088476, found: 311.088089.

GC: Rt=21.7 min. MS: 313 (3), 311 (3), 271 (11), 269 (11), 200 (10), 198 (10), 185 (10), 183 (10), 162 (9), 142 (100), 114 (15), 98 (60), 85 (32), 57 (52). IR (NaCl, cm⁻¹): 3052, 2959, 1674, 1471, 1260, 1033.

**Ethyl N-2-(2-bromophenyl)-(2-ethylmethionate)imidate (15d).** As outlined in General Procedure 2, ethyl Meerwein's reagent (1.40 mL, 1.0 M in CH₂Cl₂) was added to a 25 mL round-bottomed flask charged with N-2-(2-bromophenyl)ethyloxalamic acid ethyl ester, 13d, (0.262 g, 0.91 mmol) and
CH₂Cl₂ (10 mL) to yield a yellow oil (0.31 g). Column chromatography (10% EtOAc/Hex) using basic alumina yielded 15d as a colorless oil (Rf=0.72, 20% EtOAc/Hex.), (0.271 g, 0.83 mmol, 95%).

H-NMR (CDCl₃): 7.50 (d, 1H, J=7.6 Hz, H on C3), 7.26-7.16 (m, 2H, H's on C4 and C5), 7.08-7.00 (m, 1H, H on C6), 4.24 (q, 2H, J=7.1 Hz, H's on C11), 4.13 (q, 2H, J=7.1 Hz, H's on C13), 3.63 (t, 2H, J=7.4 Hz, H's on C8), 2.99 (t, 2H, J=7.3 Hz, H's on C7), 1.30 (t, 3H, J=7.1 Hz, H's on C12), 1.28 (t, 3H, J=7.1 Hz, H's on C14). ¹³C-NMR (CDCl₃): 159.9 (C10), 151.7 (C9), 139.2 (C1), 132.7 (C3), 131.3 (C6), 127.8 (C4), 127.2 (C5), 124.6 (C2), 62.1 (C11), 61.8 (C13), 48.9 (C8), 38.0 (C7), 14.1 (C12 and C14). HRMS calculated for C₁₄H₁₈NO₃: 327.047005, found: 327.045998. GC: Rt=21.6 min. MS 329 (10), 327 (10), 300 (100), 298 (100), 272 (15), 270 (15), 248 (70), 226 (20), 185 (45), 183 (45), 158 (50), 130 (90), 102 (75), 90 (25), 77 (15), 56 (12). IR (NaCl, cm⁻¹): 3052, 2983, 1739, 1679, 1472, 1372, 1305, 1018.
**Ethyl N-2-phenethylbenzimidate (16a).** As outlined in General Procedure 2, ethyl Meerwein’s reagent (1.20 mL, 1.0 M in CH₂Cl₂) was added to a 25 mL round-bottomed flask charged with N-benzoyl 2-phenethylamine, 14a, (0.181 g, 0.80 mmol) and CH₂Cl₂ (10 mL) to yield a yellow oil (0.21 g). Column chromatography (10% EtOAc/Hex.) using basic alumina yielded 16a as a colorless oil (Rf=0.70, 20% EtOAc/Hex), (0.178 g, 0.70 mmol, 87%).

![Chemical structure of 16a](image)

**1H-NMR (CDCl₃):** 7.65-7.11 (m, 10H, H’s on C2, C3, C4, C5, C6, C11, C12, C13, C14, and C15), 4.26 (q, 2H, J=7.1 Hz, H’s on C16), 3.51 (t, 2H, J=7.3 Hz, H’s on C8), 2.85 (t, 2H, J=7.3 Hz, H’s on C7), 1.34 (t, 3H, J=7.1 Hz, H’s on C17).

**13C-NMR (CDCl₃):** 161.2 (C9), 140.3 (C1), 132.7 (C10), 129.5 (C3), 129.1 (C13), 128.2 (C11 and C15), 128.1 (C4 and C6), 127.6 (C12 and C14), 126.0 (C5), 125.9 (C2), 61.1 (C16), 51.7 (C8), 38.4 (C7), 14.4 (C17). HRMS calculated for C₁₇H₁₉NO (M-H⁻): 252.138839, found: 252.138382. GC: Rt=21.2 min. MS:
As outlined in General Procedure 2, ethyl Meerwein's reagent (1.80 mL, 1.0 M in CH$_2$Cl$_2$) was added to a 25 mL round-bottomed flask charged with $N$-2-phenethyl-2-methylpropanamide, 14b, (0.220 g, 1.15 mmol) and CH$_2$Cl$_2$ (10 mL) to yield a yellow oil (0.28 g). Column chromatography (10% EtOAc/Hex) using basic alumina yielded 16b as a colorless oil ($R_f=0.74$, 20% EtOAc/Hex), (0.232 g, 1.05 mmol, 92%).

$^1$H-NMR (CDCl$_3$): 7.30-7.14 (m, 5H, H's on C2, C3, C4, C5, and C6), 4.02 (q, 2H, $J=7.1$ Hz, H's on C13), 3.49 (t, 2H, $J=7.5$ Hz, H's on C8), 2.82 (t, 2H, $J=7.5$ Hz, H's on C7), 2.74 (sept, 1H, $J=6.8$ Hz, H on C10), 1.22 (t, 3H, $J=7.1$ Hz, H's on C14), 0.96 (d, 6H, $J=6.8$ Hz, H's on C11 and C12). $^{13}$C-NMR (CDCl$_3$): 167.2
(C9), 140.5 (C1), 128.9 (C3 and C5), 128.2 (C2 and C6), 125.9 (C4), 60.1 (C14), 49.7 (C8), 38.4 (C7), 27.0 (C10), 19.3 (C11 and C12), 14.2 (C14). HRMS calculated for C_{14}H_{21}NO: 219.162314, found: 219.162693. GC: Rt=17.2 min. MS 233 (1), 219 (5), 128 (40), 91 (40), 84 (100). IR (NaCl, cm⁻¹) 3026, 2975, 1672, 1454, 1362, 1262, 1088.

**Ethyl \( \text{N-2-phenethylbutanimidate (16c).} \)** As outlined in General Procedure 2, ethyl Meerwein's reagent (1.80 mL, 1.0 M in CH₂Cl₂) was added to a 25 mL round-bottomed flask charged with N-2-phenethylbutanamide, 14c, (0.247 g, 1.20 mmol) and CH₂Cl₂ (10 mL) to yield a yellow oil (0.31 g). Column chromatography (10% EtOAc/Hex) using basic alumina yielded 16c as a colorless oil (Rf=0.72, 20% EtOAc/Hex.), (0.264 g, 1.13 mmol, 94%).

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\begin{align*}
\text{H-NMR (CDCl}_3): & \quad 7.30 - 7.14 (m, 5H, \text{H's on C2, C3, C4, C5, and C6}), 4.02 (q, 2H, J=7.1 Hz, \text{H's on C14}), 3.44 (t, 2H, J=7.6 Hz, \text{H's on C8}), 2.81 (t, 2H, J=7.6 Hz, \text{H's on C14})
\end{align*}
\]
Hz, H's on C7), 2.09 (t, 2H, J=7.6 Hz, H's on C10), 1.46-1.30 (m, 2H, H's on C11), 1.29-1.18 (m, 5H, H's on C12 and C15), 0.85 (t, 3H, J=7.1 Hz, H's on C13). $^{13}$C-NMR (CDCl$_3$): 164.2 (C9), 140.6 (C1), 128.9 (C3 and C5), 128.2 (C2 and C6), 125.9 (C4), 60.1 (C14), 50.6 (C8), 38.4 (C7), 28.3 (C10), 28.2 (C11), 22.6 (C12), 14.3 (C13), 13.8 (C15). HRMS calculated for C$_{15}$H$_{23}$NO: 233.177965, found: 233.177856. GC: Rt=18.8 min. MS: 233 (2), 205 (3), 191 (8), 142 (28), 98 (100), 91 (40), 57 (50). IR (NaCl, cm$^{-1}$): 3026, 2958, 1676, 1453, 1260, 1096, 1033.

**Ethyl N-2-phenethyl(2-ethyl methionate)imidate (16d).** As outlined in General Procedure 2, ethyl Meerwein's reagent (1.80 mL, 1.0 M in CH$_2$Cl$_2$) was added to a 25 mL round-bottomed flask charged N-phenethyloxalamic acid ethyl ester, 14d, (0.252 g, 1.14 mmol) and CH$_2$Cl$_2$ (10 mL) to yield a yellow oil (0.30 g). Column chromatography (10% EtOAc/Hex) using basic alumina yielded 16d as a colorless oil (R$_f$=0.84, 20% EtOAc/Hex.), (0.262 g, 1.05 mmol, 92%).
$^1$H-NMR (CDCl$_3$): 7.34-7.14 (m, 5H, H's on C2, C3, C4, C5, and C6), 4.22 (q, 2H, J=7.1 Hz, H's on C11), 4.13 (q, 2H, J=7.1 Hz, H's on C13), 3.61 (t, 2H, J=7.4 Hz, H's on C8), 2.85 (t, 2H, J=7.4 Hz, H's on C7), 1.30 (t, 3H, J=7.2 Hz, H's on C12), 1.28 (t, 3H, J=7.2 Hz, H's on C14). $^{13}$C-NMR (CDCl$_3$): 159.9 (C10), 151.6 (C9), 140.6 (C1), 128.9 (C3 and C5), 128.2 (C2 and C6), 126.0 (C4), 62.0 (C11), 61.7 (C13), 50.9 (C8), 38.0 (C7), 28.3 (C10), 14.1 (C12 or C14), 14.0 (C14 or C12). HRMS calculated for C$_{14}$H$_{19}$NO: 249.136494, found: 249.135944. GC: Rt=19.0 min. MS 249 (10), 220 (100), 176 (12), 158 (45), 130 (65), 105 (52), 91 (40), 77 (20), 56 (22). IR (NaCl, cm$^{-1}$): 3057, 2983, 1740, 1682, 1496, 1371, 1302, 1029.

**General Procedure 3: Radical Cyclization.**

**Method A.** A 100 mL round bottomed flask was charged with 1 equivalent of the appropriate ethyl imidate, 15a-d, and benzene (25 mL) and degassed under a stream of argon for 2 hours. The solution was brought to reflux as a solution of 0.05 equivalents of AIBN, 1.25 equivalents of radical
propagator, and benzene (10 mL) was added via syringe pump at a rate of 0.6 mL/hr. The solution was allowed to reflux for an additional hour and the solvent was removed under reduced pressure to yield a yellow oil. The oil was diluted in EtOAc (25 mL) and saturated aqueous KF (25 mL). After stirring for 30 min the solution was filtered and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The organic washes were combined, dried with MgSO₄, and the solvent was under reduced pressure to yield a yellow oil. Column chromatography (100% Hex to 20% EtOAc/Hex) yielded indoline 17a (15b,c,d did not cyclize) (Rₐ=0.20, 20% EtOAc/Hex), RCO₂Et (hydrolysis product) (Rₐ=0.3-0.5, 20% EtOAc/Hex), reduced ethyl imidate 16a-d (Rₐ=0.4-0.6, 20% EtOAc/Hex), and ethyl imidate 15a-d (Rₐ=0.6-0.9, 20% EtOAc/Hex).

Method B. A 50 mL round bottomed flask was charged with 1 equivalent of the appropriate ethyl imidate 15a-d, 2 equivalents of tris(trimethylsilyl)silane, 1.5 equivalents of triethylborane, and benzene (50 mL). The flask was equipped with a drying tube filled with CaCl₂ and allowed to stir 18 h. The solvent was removed under reduced pressure to yield a yellow oil. Column chromatography (100% Hex to 20% EtOAc/Hex) yielded RCO₂Et (hydrolysis product) (Rₐ=0.3-0.5, 20% EtOAc/Hex), reduced ethyl imidates 16a-d (Rₐ=0.5-0.7, 20% EtOAc/Hex), and ethyl imidate 15a-d (Rₐ=0.6-0.8, 20% EtOAc/Hex).
Method C. A 100 mL round bottomed flask was charged with 1 equivalent of the appropriate ethyl imidate 15a-d, 1.5 equivalents of radical propagator, and benzene (50 mL). The solution was brought to reflux as a solution of 0.25 equivalents of AIBN and benzene (10 mL) was added via syringe pump at a rate of 0.6 mL/hr. The solution was allowed to reflux for an additional hour and the solvent was removed under reduced pressure to yield a yellow oil. Column chromatography (100% Hex to 20% EtOAc/Hex) yielded indoline 17a (15b,c did not cyclize) (Rf=0.20, 20% EtOAc/Hex), RCO₂Et (hydrolysis product) (Rf=0.3-0.5, 20% EtOAc/Hex), reduced ethyl imidate 16a-d (Rf=0.4-0.6, 20% EtOAc/Hex), and ethyl imidate 15a-d (Rf=0.6-0.9, 20% EtOAc/Hex).

N-Benzoyl indoline (17a):

As outlined in General Procedure 3, Method A, a 100 mL round bottomed flask was charged with phenyl imidate 15a (0.102 g, 0.30 mmol) and benzene (50 mL), degassed under a stream of argon for 2 hours, and heated to reflux. A solution of tributyltin hydride (0.10 mL, 0.35 mmol), AIBN (0.0072 g, 0.044 mmol), and benzene (10 mL) was degassed under a stream of argon for 2 hours, added via syringe pump over 17 h, and allowed to stir at reflux for an additional hour. Column chromatography (100% Hex to 20% EtOAc/Hex) yielded N-benzoyl indoline 17a (Rf=0.21, 20% EtOAc/Hex) as a white solid.
(0.020 g, 0.090 mmol, 30%); mp 99.5-100.6°C (toluene), unreacted starting imidate 15a (Rf=0.55, 20% EtOAc/Hex) as a yellow oil (0.397 g, 0.12 mmol, 40%), and reduced imidate 16a (Rf=0.60, 20% EtOAc/Hex) as a yellow oil (0.015 g, 0.060 mmol, 20%).

As outlined in General Procedure 3, Method B, a 100 mL round bottomed flask was charged with phenyl imidate 15a (0.052 g, 0.16 mmol), TTMSS (0.09 mL, 0.29 mmol) and benzene (50 mL), degassed under a stream of argon for 2 hours, and heated to reflux. A solution of AIBN (0.010 g, 0.062 mmol) in benzene (10 mL) was degassed under a stream of argon for 2 hours, added via syringe pump over 16 h, and allowed to stir at reflux for an additional hour. Column chromatography (100% Hex to 20% EtOAc/Hex) yielded N-benzoylindoline 17a (Rf=0.21, 20% EtOAc/Hex) as a white solid (0.019 g, 0.085 mmol, 53%); mp 99.5-100.6°C (toluene).
$^1$H-NMR (CDCl$_3$): 7.55-7.00 (m, 9H, H’s on C5, C6, C7, C8, C12, C13, C14, C15, and C16), 4.12-3.95 (m, 2H, H’s on C2), 3.10 (t, 2H, $J$=8.2 Hz, H’s on C3).

$^{13}$C-NMR (CDCl$_3$): 168.9 (C10), 130.3 (C4 and C9), 128.5 (C6, C7, C13, C14, and C15), 127.1 (C5 and C8), 124.9 (C12 and C16), 123.9 (C11), 50.0 (C2), 28.0 (C3). HRMS calculated for C$_{15}$H$_{13}$NO: 223.099714, found: 223.099442.

GC: Rt=27.0 min. MS: 224 (52), 184 (12), 171 (6), 134 (17), 105 (100), 77 (50), 51 (17). IR (KBr, cm$^{-1}$): 3062, 2988, 1636, 1595, 1482, 1404, 757, 700.
CHAPTER 3

OXA-DI-π-METHANE REARRANGEMENT OF AZA-5-OXO-BICYCLO[2.2.2]OCT-2-ENES

Introduction

This chapter will outline the utilization of the oxa-di-π-methane photorearrangement, a triplet sensitized sigmatropic 1,2-acyl shift, in the synthesis of petasinecine 7, isoretronecanol, 8, trachelanthamidine, 9, supinidine, 10, and xenovenine, 11. Additionally, the mechanism of the oxa-di-π-methane rearrangement will be examined through the synthesis of a series of β,γ-unsaturated ketones, 1 and 4, see Scheme 13. Lastly, the synthesis of the [6,4] bicyclic amines, 3 and 6, through a light-induced sigmatropic 1,3-acyl shift on the above mentioned β,γ-unsaturated ketones, 1 and 4, will be studied.

Photochemistry has seen an increased amount of use in modern organic synthesis as it enables the chemist to perform highly selective transformations in the presence of chemically sensitive functional groups. In order to discuss the various photoprocesses below, it is first necessary to go into a short introduction of some basic photochemical concepts.
Scheme 13. Proposed utilization of a nitrogen in the 1,3-AS and ODPM rearrangements.
The chronology of a photoreaction can be split into three sections: (1) an absorptive act, which consists of the interaction between a photon and a molecule. This results in the absorption of the photon and formation of an electronically excited molecule; (2) the primary photochemical process of the electronically excited molecule; and (3) the dark process, or secondary photochemical process, in which the intermediates formed from the primary process react. The fact that light absorption, rather than heat, initiates a photoreaction allows for selective transformation, as only light absorbing molecules are activated. This fact also allows for reactions to be run at very low temperatures, thereby minimizing side reactions occurring under thermal conditions.

The Electronic Excitation of Organic Molecules

In the ground state of most molecules any pair of electrons in the same orbital will have opposite spins. When this molecule is excited, one electron is promoted from the HOMO (highest occupied molecular orbital) to the LUMO (lowest unoccupied molecular orbital) (Figure 3). This is called the excited singlet state, and for convenience its various energy levels are designated $S_1$, $S_2$, $S_3$ and so on in order of increasing energy. If the electron which has been promoted to the LUMO undergoes a spin "flip", both of the electrons' spins are oriented in the same direction. This is called the triplet state, and for
convenience, its various energy levels are designated $T_1$, $T_2$, $T_3$ and so on in order of increasing energy.

\[
\begin{align*}
\psi^* & \quad \text{electron jump} \quad \psi^* \\
\psi & \quad \text{Spin-allowed absorption} \\
\psi^* & \quad \text{electron jump} \quad \psi^* \\
\psi & \quad \text{Spin-forbidden absorption}
\end{align*}
\]

Figure 3. Orbital energy level description of absorption.\textsuperscript{41}

The commonly encountered photophysical processes occurring from the $S_x$ state are shown below (Figure 4).\textsuperscript{41}

1. "Allowed" radiative emission to the ground state, called fluorescence ($S_1 \rightarrow S_0 + \nu$), characterized by the rate constant $k_F$. 
2. "Allowed" radiationless transition between states of the same spin, called internal conversion \((S_1 \rightarrow S_0 + \text{heat})\), characterized by the rate constant \(k_{IC}\).
3. "Forbidden" radiationless transition between excited states of different spin, called intersystem crossing ($S_1 \rightarrow T_1 + \text{heat}$), characterized by the rate constant $k_{ST}$.

4. Chemical change, characterized by the rate constant, $k_{R}^{S}$.

The commonly encountered photophysical processes occurring from the $T_x$ state are shown below (Figure 4).

1. "Forbidden" radiative emission to the ground state singlet, called phosphorescence ($T_{1} \rightarrow S_{0} + hv$), characterized by the rate constant $k_{P}$.

2. "Forbidden" radiationless decay to the ground state singlet, also called intersystem crossing ($T_{1} \rightarrow S_{0} + \text{heat}$), characterized by a rate constant, $k_{TS}$.

3. Chemical change, characterized by the rate constant $k_{R}^{T}$.

4. Energy transfer in the presence of an appropriate acceptor, called either triplet sensitization or triplet quenching ($T_{1}(\text{donor}) + S_{0}(\text{acceptor}) \rightarrow S_{0}(\text{donor}) + T_{1}(\text{acceptor})$).

**Collisional Energy Transfer**

Energy transfer can occur by either one of two different pathways, electron exchange by way of physical contact and energy transfer by coulombic interactions. The electron exchange mechanism can be viewed as a collisional
exchange. By collisions it is meant that the electron clouds of the reacting species overlap significantly in space. For example, let us consider a collisional mechanism for the energy process,

\[ M^* + Q \rightarrow M + Q^* \]

where \( M \) is the donor molecule and \( Q \) is the acceptor molecule. As \( M \) and \( Q \) approach each other, while in their ground states, their interactions are repulsive and the energy of the ground state surface rapidly rises. If either \( M \) or \( Q \) is excited as they approach, the energy of the collisional pair, \( M^*Q \) or \( MQ^* \), will usually be lower than that of the separated pairs \( M^* + Q \) and \( M + Q^* \). At some geometry, \( r_c \), the surface of \( M^* + Q \) can be imagined to intersect with that of \( M + Q^* \) and an internal conversion (or intersystem crossing if a triplet is involved) to the lower energy surface may occur. At some crossing point, \( r_c \), an interaction between \( M^* \) and \( Q \) allows a transfer of electronic excitation (Figure 5).\(^{41}\) At the collisional point, \( r_c \), there is a competition between returning to the upper surface and separation of the collisional complex, \( MQ^* \), into separated monomers, \( M + Q^* \). A return to monomers \( M^* \) and \( Q \), requires thermal energy. If the latter option results, then a net electronic energy transfer from \( M^* \) to produce \( Q^* \) has been affected.\(^{41}\)
Figure 5. Schematic surface representation of collisional energy transfer.\textsuperscript{41}
This energy process is analogous to the radiationless transitions of intersystem crossing and internal conversion within a molecule. In the same way that this process can occur within a single molecule, it can also occur between two molecules. This transition, $M^* + Q \rightarrow M + Q + \text{heat}$, can be visualized if there is an intersection between $M^* + Q$ and the ground state, $M + Q$ (Figure 5). This pathway is thought to be how intersystem crossing and intermolecular internal conversion occur.

**Coulombic Energy Transfer**

The second energy transfer mechanism can be visualized by the Coulombic (dipole-dipole) mechanism, where the surfaces $M^*$, $M$, $Q$, and $Q^*$ do not intersect (Figure 6). This is commonly known as a transmitter-antenna mechanism. In this description, an electric field is generated near an electronically excited molecule. This occurs by the back-and-forth motion of the excited electron along the molecular framework of $M^*$, similar to the electric field of a light wave. The resulting charge is radiated and electrostatic forces are felt by the electronic systems of neighboring molecules. If this oscillating field is emitting at the correct frequency, a coupling occurs between the electrons of $Q$ and the oscillating field of $M^*$, and an energy transfer occurs to stimulate $Q$ to its excited form $Q^*$ (Figure 6).
Figure 6. Schematic surface representation of coulombic energy transfer.\textsuperscript{41}
Triplet-Triplet Energy Transfer

The most common and important type of energy transfer is triplet-triplet energy transfer. By triplet-triplet energy transfer it is meant that an electronically excited donor molecule in its triplet state directly produces an electronically excited acceptor in its triplet state.

From theory, it can be seen that there are two possible mechanisms for transfer of triplet to triplet energy exist, collisional and coulombic mechanisms. Experimentally, these two mechanisms can be distinguished by measurements of the rate constants for energy transfer ($k_{ET}$), for diffusion ($k_{DIF}$), and then measuring the rate constant for energy transfer as it relates to solvent viscosity. If energy transfer occurs faster than diffusion, i.e. $k_{ET} > k_{DIF}$, and energy transfer is independent on solvent viscosity, the collisional mechanism can be ruled out and the coulombic mechanism can be confirmed. However, if energy transfer is comparable to, or less than, diffusion and energy transfer is dependent on solvent viscosity then the collisional mechanism can be said to be occurring. Ermolaev and others have shown that triplet-triplet energy transfer generally occurs via the collisional mechanism.

Triplet sensitization is the population of the triplet energy levels (chiefly $T_1$) of an acceptor via an energy transfer from a suitable donor. This donor, also called a triplet sensitizer, must have a fast intersystem crossing rate relative to
Table 6. Important parameters for triplet photosensitizers.\textsuperscript{42a} Energies are in kcal/mol. $\tau =$ maximum lifetime for inert solvents (sec). $\Phi =$ relative rate of intersystem crossing.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$E_S$</th>
<th>$E_T$</th>
<th>$\tau_S$</th>
<th>$\tau_T$</th>
<th>config. $T_1$</th>
<th>$\Phi_{st}$</th>
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<td>benzene</td>
<td>110</td>
<td>84</td>
<td>$\sim10^{-7}$</td>
<td>$10^{-6}$</td>
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<tr>
<td>acetone</td>
<td>$\sim85$</td>
<td>$\sim78$</td>
<td>$10^{-9}$</td>
<td>$10^{-5}$</td>
<td>$n,\pi^*$</td>
<td>1.0</td>
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<tr>
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<td>74</td>
<td>$10^{-10}$</td>
<td>$10^{-4}$</td>
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</tr>
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<td>acetophenone</td>
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<td>$10^{-11}$</td>
<td>$10^{-4}$</td>
<td>$n,\pi^*$</td>
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<td>$10^{-11}$</td>
<td>$10^{-4}$</td>
<td>$n,\pi^*$</td>
<td>1.0</td>
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<td>$\sim65$</td>
<td>$10^{-7}$</td>
<td>$10^{-4}$</td>
<td>$\pi,\pi^*$</td>
<td>0.7</td>
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<td>61</td>
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<td>$10^{-4}$</td>
<td>$\pi,\pi^*$</td>
<td>1.0</td>
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<tr>
<td>2-acetonaphthalene</td>
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<td>59</td>
<td>$10^{-8}$</td>
<td>$10^{-4}$</td>
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<tr>
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<td>$10^{-4}$</td>
<td>$10^{-4}$</td>
<td>$\pi,\pi^*$</td>
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<td>$n,\pi^*$</td>
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<tr>
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<td>47</td>
<td>$\sim10^{-9}$</td>
<td>$10^{-4}$</td>
<td>$\pi,\pi^*$</td>
<td>0.7</td>
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</table>
Table 7. Energies for triplet quenchers.\textsuperscript{42b} Energies are in kcal/mol.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$E_s$</th>
<th>$E_T$</th>
</tr>
</thead>
<tbody>
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<td>but-2-ene</td>
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<td>78</td>
</tr>
<tr>
<td>phenylacetylene</td>
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<tr>
<td>cyclopentadiene</td>
<td>-90</td>
<td>58</td>
</tr>
<tr>
<td>cis-stilbene</td>
<td>-95</td>
<td>57</td>
</tr>
<tr>
<td>1,3-cyclohexadiene</td>
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<td>53</td>
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<tr>
<td>trans-stilbene</td>
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<td>50</td>
</tr>
<tr>
<td>oxygen</td>
<td>-</td>
<td>23</td>
</tr>
</tbody>
</table>

decay to its $S_1$ state, a long triplet lifetime in order to maximize the energy transfer process, and a low chemical reactivity (Table 6). The most important single parameter in the selection of a triplet sensitizer is the energy gap between the triplet energy levels of the donor and acceptor, as the maximum value for $K_{ET}$ is only achieved if the energy transfer from donor to acceptor is exothermic. Triplet sensitization is useful in populating triplet states where intersystem crossing is not efficient. The reverse process, triplet quenching, is
the process of transferring triplet energy from a donor molecule to an acceptor. Common triplet quenchers include olefins, aromatics, and molecular oxygen (Table 7).

**Quenching by Molecular Oxygen**

Molecular oxygen ($^3\Sigma$) is a ground state triplet possessing two low-lying singlet states at energies of $\sim$23 kcal/mol ($\Delta^1$) and $\sim$38 kcal/mol ($^1\Sigma$).\(^{44a}\) Experimentally, both singlet\(^{44b}\) and triplet\(^{44a}\) states are quenched effectively by $^3\text{O}_2$. Additionally, $^3\Sigma$ oxygen is a reactive species in its own right, and is very capable of extracting an electron from or adding to excited states. Thus, experimentally, it is imperative to deoxygenate all samples prior to irradiation in order to avoid unseen complications.

**The Photochemistry of $\beta,\gamma$-Unsaturated Ketones**

The photochemistry of $\beta,\gamma$-unsaturated ketones has been significantly advanced in the past twenty five years. The reviews in 1975 by Dauben\(^{45}\) and Houk\(^{46}\) constituted the first mention of these synthetically useful photoprecursors. Further reviews by Schaffner\(^{47}\) in 1979, Schuster\(^{48}\) in 1980, Demuth and Schaffner\(^{49,50}\) in 1982 and 1986, and again by Demuth\(^{51}\) in 1991,
Figure 7. Examples of natural products photochemically synthesized with the oxa-di-π-methane rearrangement and the sigmatropic 1,3-acyl shift.\textsuperscript{52-54}
enabled other chemists to manipulate β,γ-unsaturated ketones into various cyclopentanoid natural products. Examples of these include the cedranoid sesquiterpenes, 12, by Yates and Stevens\textsuperscript{52}, coriolin, 13, by Demuth and Schaffner\textsuperscript{53}, and the hirsutanes, 14 and 15, by Singh and Porinchu\textsuperscript{54} (Figure 7). β,γ- Unsaturated ketones photochemically react through two major pathways, the sigmatropic 1,3-acyl shift (1,3-AS), commonly called a Norrish Type I reaction, and the sigmatropic 1,2-acyl shift, commonly called the oxa-di-π-methane photoisomerization (ODPM).

The Sigmatropic 1,3-Acyl Shift (1,3-AS)

The sigmatropic 1,3-acyl shift was first reported in 1963 independently by the groups of Schenck\textsuperscript{55a} and Shuster\textsuperscript{55b} when they subjected dehydronorcamphor, 16, to light in a photochemically inert solution. Schenck reported that the quantitative photolytic fragmentation of 16 to ketene and cyclopentadiene occurred in a variety of solvents (i.e. hexanes, ether) at temperatures ranging from -70 to 25°C with a quantum yield of 0.25.\textsuperscript{55a} Schuster found that the 1,3-AS product, 17, was formed rapidly and ketene and cyclopentadiene were formed more slowly (Scheme 14).
The reaction mechanism of the 1,3-AS has been elucidated through studies of cyclopentenyl methyl ketones.\textsuperscript{56} The 1,3-acyl migration is initiated by photolytic $\alpha$-cleavage of the ketone to an acyl/allyl diradical which has the option of either recombining to regenerate starting material or recombining in the alternative allylic position and forming the 1,3-AS product (Schemes 15 and 16). The reaction occurs from the $n,\pi^*$ excited singlet and triplet states of the $\beta,\gamma$-unsaturated ketone, $S_1(n,\pi^*)$ and $T_2(n,\pi^*)$, respectively.

Initially it was thought that the 1,3-AS occurred solely from the $S_1(n,\pi^*)$ state in view of the product selectivity on direct irradiation versus triplet sensitization. This was refuted by studies on the structural dependence of rate constants for reaction and decay of singlet excited states. These experiments show that singlet-triplet intersystem crossing in the $\beta,\gamma$-unsaturated ketone leads to the $T_2(n,\pi^*)$ state which more efficiently undergoes the 1,3-AS than internal...
conversion to the $T_1(\pi,\pi^*)$ state (Figure 8).\textsuperscript{56c,d} The triplet pathway remains a minor contribution, even though the proportion of the $T_2(n,\pi^*)$ radical cleavage increases with decreasing temperature.\textsuperscript{50}

The stereochemical course of the 1,3-AS in (R)-(+)\textsuperscript{-}18 has been shown to be predominantly suprafacial, to enantioselectively form the 1,3-AS (S)-(\textsuperscript{-})-isomer 20, i.e. the predominant reaction can result from recombination of the singlet radical pair, at a faster rate than rotation by 180\(^\circ\) about its in-plane axis, and from the concerted process. Racemization of the (R)-(+)\textsuperscript{-}isomer 18 occurs at a rate of less than 20\% to form the (S)-(\textsuperscript{-})-isomer 19 (Scheme 15).\textsuperscript{50}

In solution, two thermal activation barriers deactivate the $S_1(n,\pi^*)$ states of 22 and 23. The larger ($E_{\text{act}} \sim 13$ kJ/mol in hydrocarbon solution) is associated with the stepwise 1,3-AS (Scheme 16).\textsuperscript{56d} The process contributing to the smaller activation energy ($E_{\text{act}} \sim 3$ kJ/mol in hydrocarbon solution) has yet to be determined. One possibility is that it is associated with the concerted 1,3-AS. Gas phase studies at 1 bar of carbon dioxide show that this pathway is followed about 30\% of the time(Scheme 16).\textsuperscript{56c}
Figure 8. Excited state energies and electronic configurations of various $\beta,\gamma$-unsaturated ketones. Energy range of dark areas was obtained from experimental data, those of white areas are estimated. Correlations of excited states with photoreactions determined experimentally.\textsuperscript{50}
Scheme 15. Mechanistic route for the 1,3-AS starting with (R)-(+) isomer 18.
The concerted enantiospecific reaction and stepwise pathway via $\alpha$-cleavage to
the radical pair.\(^{50}\)
Scheme 16. Orbital symmetry-allowed concerted (top) versus stepwise mechanism (via radical pair, bottom) of the 1,3-acetyl shift of methyl 2-cyclopentenylketones.
The Sigmatropic 1,2-Acyl Shift
or the Oxa-di-π-methane (ODPM) Rearrangement

In the photolysis of β,γ-unsaturated ketones, the 1,3-AS can be viewed as an undesired side reaction which can be avoided by preventing direct light absorption by the β,γ-unsaturated ketone through high dilution, and by choosing a triplet sensitizer with a triplet energy lying between that of the T₁ and T₂ energies (Table 6). Our main interest in this system is with the oxa-di-π-methane (ODPM) rearrangement. The ODPM rearrangement is a sigmatropic 1,2-rearrangement of β,γ-unsaturated ketones under triplet sensitized conditions to yield a cyclopropyl ketone (Scheme 17). β,γ-Unsaturated ketones in which the alkene is further conjugated can undergo ODPM rearrangement under direct irradiation through the singlet state.57

Scheme 17. The oxa-di-π-methane (ODPM) rearrangement.
The reaction mechanism of the ODPM rearrangement has been elucidated through the same study of cyclopentenyl methyl ketones that was responsible for the mechanistic study of the 1,3-AS.\textsuperscript{56} While the 1,3-acyl migration is initiated by photolytic $\alpha$-cleavage of the ketone to an acyl/allyl diradical, the ODPM rearrangement is initiated by photolytic cleavage of the ketone. CNDO-MO calculations confirmed the reactive state as the $T_1(\pi,\pi^*)$, the lowest electronically excited energy level.\textsuperscript{58}

Initially, the ODPM rearrangement was explained by either a fully concerted $[\sigma^2 + \pi^2]$ or a stepwise mechanism. For example, in the ODPM rearrangement of various cyclopentenyl ketones $24\textit{a-d}$ to the diastereomeric cyclopropyl ketones $25\textit{a-d}$ and $26\textit{a-d}$, either of the two mechanisms can be said to be occurring (Scheme 18). In the concerted mechanism the kinetically controlled formation of $25$ and $26$ was thought to occur via parallel doubly antara and suprafacial one step addition routes to give $25$ and $26$, respectively. Conversely, the formation of $25$ and $26$ was thought to transpire via discrete diradical intermediates (Scheme 18).
Scheme 18. ODPM rearrangement of cyclopentenyl methyl ketones.\(^{56}\)

In the late 1970's evidence for the stepwise mechanism was shown in three independent examples in which the reaction paths could only be described by a sequence of discrete diradical intermediates (Scheme 19).\(^{59-61}\)

In the first case, stereochemical scrambling of the isotopically labeled geminal methyls of the products (30a and 30b, 1:1 ratio) during the ODPM rearrangement can only be explained via a stepwise radical process, such as the one involving the diradical intermediates, 28a,b and 29a,b.\(^{100}\)

Furthermore, the ODPM rearrangement products obtained from 31 and 34 demand the occurrence of at least a 29-like intermediate such as 32 and 35 respectively.\(^{60,61}\)
Scheme 19. ODPM examples establishing the stepwise mechanism.\(^{59-61}\)
Limitations on the ODPM Rearrangement

In general, the more geometrically constrained a $\beta,\gamma$-unsaturated ketone is, the more efficiently it undergoes ODPM rearrangement. Acyclic $\beta,\gamma$-unsaturated aldehydes do not undergo ODPM rearrangement and acyclic $\beta,\gamma$-unsaturated ketones only rearrange if the C=C $\pi$ bond is further conjugated.\(^{57,62}\) In all other cases, where the olefin is less favorably substituted, twisting of the C=C bond predominates yielding cis-trans isomerization. This form of energy transfer has been termed the “free rotor effect” for $\beta,\gamma$-unsaturated ketones, appropriating the term used for unconstrained di-$\pi$-methane (DPM) rearrangements.\(^{63}\) This effect is shown very well in Scheme 20. Non-conjugated systems undergo cis-trans isomerization solely\(^{63a}\), singly conjugated systems undergo both isomerization and rearrangement\(^{63b}\), and extensively conjugated systems undergo only rearrangement even in the absence of a triplet sensitizer, albeit only in 7% yield.\(^{63c}\)

Semicyclic $\beta,\gamma$-unsaturated ketones where either the C=C or the C=O bonds are part of a cyclic system are somewhat less substituent dependent than the acyclic cases. As noted previously, efficiency and limitation of the ODPM rearrangement are strongly coupled to the degree of flexibility instilled in the
Scheme 20. ODPM examples of acyclic $\beta,\gamma$-unsaturated ketones.$^{57,62}$
olefin. To put it simply, the greater the flexibility of the C=C \( \pi \) bond, the more twisting is observed. This equals more energy transfer to the cis-trans isomerization process. When the C=C bond is geometrically constrained, as in a 5-membered ring system, the ODPM rearrangement proceeds smoothly (Scheme 21).\(^{62a}\) However, substrates in which the methane carbon is not fully substituted, for example 45 (\( R = H \)), are ODPM unreactive, irregardless of ring size (Scheme 21).\(^{64}\)

**ODPM Rearrangement of Bicyclo[2.2.2]oct-2-en-5-ones**

Generally, the best candidates for ODPM rearrangement are the conformationally rigid [2.2.1] and [2.2.2] bicyclic enones, where twisting of the C=C bond is eliminated. Of particular interest in this research is the ODPM rearrangement of the [2.2.2] bicyclic enones such as 49. Low temperature phosphorescence studies have shown that the \( T_1 \) level for simple \( \beta,\gamma \)-unsaturated [2.2.2] bicyclic enones lies in the range of 70-75 kcal/mol.\(^{58}\) This means that relatively common triplet sensitizers such as acetone (\( E_T \sim 78 \) kcal/mol)\(^{42a}\) or acetophenone (\( E_T = 74 \) kcal/mol)\(^{42a}\) can be used. The ODPM rearrangements of 49 are typically run to 95% conversion yielding photoproduct 50 in yields ranging from 72-91% irregardless of the solvent or sensitizer (Scheme 22). The reaction run in neat acetone, in addition to its
Scheme 21. ODPM examples of cyclic $\beta,\gamma$-unsaturated ketones.$^{62a,64}$
efficiency, provides an attractive synthetic method from a practical viewpoint. Acetone serving as both the solvent and sensitizer renders the work-up and purification facile, as no separation procedure is required. In the cases where acetophenone is the sensitizer, concentrations in the range of 1-5% acetophenone in acetone can be utilized. Concentrations greater than 10% have not been shown to be more effective, and purification is exacerbated due to aromatic by-products from the irradiation of acetophenone. Additionally, removal of the high boiling acetophenone has its own share of problems. Distillation of the acetophenone, even under high vacuum conditions, requires enough heat to initiate a thermal 1,3-AS, thereby converting valuable photoproduct to the less synthetically useful 1,3-AS product.

Reactions are run in concentrations of no greater than 3% enone. High dilution conditions are used to prevent direct absorption of light by the \( \beta,\gamma \)-unsaturated enone which would lead to the corresponding 1,3-AS product. This unwanted side reaction has been seen in yields of up to 20% when concentrations greater than 5% have been used.

The synthesis of many natural products has been accomplished by employing an ODPM rearrangement of a [2.2.2] bicyclic enone as the ring-forming step. Examples of these include the cyclopentanoid derivatives 12-14, shown in Figure 7. As yet unreported, is the ODPM rearrangement on an aza [2.2.2] bicyclic enone. Utilization of these substrates could lead to the tricyclic pyrrolizidine precursors, 52 and 53, depending on the position of the nitrogen in the bicyclic skeleton (Figure 9). These precursors can then be further functionalized by utilizing the cyclopropyl ketones’ reactivity. Previous literature examples have shown that the ring-opening of the cyclopropyl ketone can be effected through either nucleophilic or electrophilic means, or by
hydrogenolysis of the cyclopropane.\textsuperscript{47,49,52-54} We plan to use the hydrogenolysis reaction to enable us to achieve formal synthesis to petanecine, 7, isoretronecanol, 8, trachelanthamide, 9, and supinidine, 10. Additionally, the synthesis of xenovenine, 11, will be attempted from photoproduct 53. To determine if these synthetic methods are feasible the effect of the nitrogen in photochemical rearrangements must be discussed.
The incorporation of a nitrogen into the photoprecursor for the ODPM rearrangement has thus far been unreported, although analogous transformations have been brought about. Of these, there are two that have been shown to be useful synthetically. The first is the di-\(\pi\)-methane (DPM) rearrangement, in which the nitrogen functionality is not in the chromphore (light-absorbing) region of the molecule. This is shown excellently in Scheme 23, in which the rearrangement of benzobarrelene 54 is effected without participation of the imidate ester. Alternatively, an aza containing compound can undergo photorearrangement through the aza-di-\(\pi\)-methane (ADPM) rearrangement. Although unreactive in the ODPM rearrangement, acyclic \(\beta,\gamma\) unsaturated aldehydes and ketones do photochemically rearrange in the presence of a triplet sensitizer when the carbonyl functionality is converted into an imine or imidate ester derivative.\(^{66-68}\) The success of a ADPM rearrangement is very dependent on the substitution at the nitrogen position.
Scheme 23. Examples of the di-π-methane and aza-di-π-methane rearrangements.\textsuperscript{66-68}
Oximes and oxime ethers, 56d, do not react except when in a geometrically constrained system as in 58. The unreactivity of the oxidized derivatives is thought to be due to an alternative reaction path, isomerization around the C=C π and C=N π bonds. This same path predominates in the all carbon systems. In order to bias the ADPM rearrangement to occur, the ionization potential of the imine was increased using oxime acetates, 56a-c, that suppress the electron transfer from the nitrogen lone pair of the imine moiety to the alkene component. The acetophenone sensitized rearrangement of 56a and 56b turns out to be a highly efficient process, yielding the cyclopropanes 57a and 57b in yields of 79% and 76% respectively. The unresponsiveness of 56c can be directly attributed to the substitution on the olefin. As in the case of the all carbon systems, lack of further conjugation on the alkene moiety causes a lack of stability for the carbon radical. This lack of stability in the all carbon system causes an isomerization of the double bond while in the ADPM cases this lack of substitution starts a [2π + 2π] cyclization to occur with acetone. Cyclization between the carbon radical and the acetone yields the substituted oxetane as the sole product. The ADPM path is activated when a higher energy triplet sensitizer, such as neat acetone, is used.
Proposed Work

The goal of this research is to determine the feasibility of an ODPM rearrangement on 1-aza- and 2-azabicyclo[2.2.2]oct-2-en-5-one derivatives, 1 and 4 and their ODPM rearrangement products. These tricyclic photoproducts, 2 and 5, will then be taken onto various pyrrolizidine alkaloids, specifically the formal syntheses of petanecine, 7, isoretronecanol, 8, trachelanthamide, 9, and supinidine, 10, will be discussed. The cyclopropane moiety inherent in the ODPM rearrangement provides us with another position to install functionality. It has been shown that cleavage of the cyclopropyl ketone can be affected with a variety of nucleophiles.$^{69,70}$ The involvement of the nitrogen in this ring opening will be determined through these studies.

Additionally, the direct irradiation, 1,3-AS, of these photoprecursors, 1 and 4 will be studied. Formation of the 6,4 ring system through a single photochemical process could be advantageous in the formation of natural products similar to protoilludanoid A, 15. This is particularly true in the direct irradiation of 4 which would lead to a substituted β-lactam, 6, a common skeletal feature in many bioactive molecules (Scheme 13).$^{71}$
Results and Discussion

Retrosynthetic Analysis for the Formal Syntheses of Petasinecine, 7, Isoretroacol, 8, Trachelanthamidine, 9, and Supinidine, 10.

Our interest in this area was stimulated by the prospect of designing a general method towards the pyrrolizidine alkaloids (Figure 9). In particular, this first section will concentrate on the formal syntheses of various 4,6-substituted pyrrolizidine alkaloids (Figure 9). The Rueger synthesis of (-)-petasinecine, 7, (-)-isoretroacol, 8, (-)-trachelanthamidine, 9, and (-)-supinidine, 10, also starts from the common intermediate 60. Rueger synthesized 60 from (S)-proline in a 34% yield over 12 steps (Scheme 25).\textsuperscript{72}

Our strategy is outlined in the retrosynthetic format depicted in Scheme 24. The key feature of our approach is based upon an oxa-di-π-methane photorearrangement of the bicyclic \( \beta,\gamma \) enone 1 to give the tricyclic photoproduct 2. Regioselective ring opening of the cyclopropyl ketone moiety can then be accomplished by a variety of techniques. Of these, hydrogenolysis of the cyclopropyl ring and transesterification should yield the bicyclic enol 60. The synthesis of the bicyclic \( \beta,\gamma \) enone 1 was envisaged to arise from the azabicyclic compound 61 through the use of selenium chemistry to install the
Scheme 24. Retrosynthetic analysis for the formal syntheses of petasinecine, 7, isoretronecanol, 8, trachelanthamidine, 9, and supinidine, 10.
double bond. Azabicyclic compound 61 has been shown by Snow et al. to be prepared from cinchomeronic acid, 63, through a Dieckmann cyclization on piperidine 62. \(^7^3\) I now wish to report an application of this methodology to the formal syntheses of the above pyrrolizidine alkaloids.

\[
\begin{align*}
\text{(S)-proline} & \rightarrow \text{steps} \rightarrow \text{Cl}^- \\
\text{BrCH}_2\text{CO}_2\text{Et} & \rightarrow \text{BrCH}_2\text{CO}_2\text{Et} \rightarrow \text{1. NaOEt} \Delta_x \rightarrow \text{60 (34\% from (S)-proline)}
\end{align*}
\]

Scheme 25. Rueger's synthesis of 60 from (S)-proline.\(^7^2\)

**Synthesis of the Dieckmann Precursor**

As shown in Scheme 24, the first step in our retrosynthetic plan is the synthesis of the Dieckmann precursor. The synthesis of the N-alkylated piperidine 62 required for our purposes has been carried out according to
Scheme 26. Cinchomeronic acid, 63, was converted to the anhydride, 64, by stirring in refluxing acetic anhydride. Regioselective opening of the resulting anhydride 64 with methanol yielded a 2:1 mixture of the desired, 66, and undesired regioisomers, 65. This regioselectivity can be explained by examining resonance structures of the anhydride, 64a-d (Figure 10). Comparing the electronics at the two carbonyl centers it can be seen that the carbonyl at the 4-position is significantly more electron deficient. This is due to the neighboring carbocation in resonance structure 64c. Thus, the methanol attack at the 4-position is justified. The desired isomer was then obtained by fractional recrystallization from methanol to greater than 98% purity. The ester by product 65 could be easily recycled by hydrolysis to cinchomeronic acid.73a

The preparation of amide 67 commenced from monoester 66 (Scheme 26). Treatment of the monoester with oxalyl chloride produced the corresponding acid chloride, which was quenched in situ with diethyl amine to afford amide 67 in 96% yield over the two steps. To avoid poisoning of the Adams' catalyst during hydrogenation, the amide was converted to its hydrochloride salt using HCl in diethyl ether, yielding the pyridine salt in near quantitative yield. The pyridine salt was then hydrogenated at elevated pressure and temperature to yield cis-piperidine 68 in excellent yield. Alkylation of the secondary amine with methyl bromoacetate under basic conditions proceeded cleanly and efficiently to piperidine 62 in an overall yield
of 52% over 7 steps an improvement over the published yields (Scheme 26).\textsuperscript{73b,c}

![Resonance structures of the pyridine anhydride](image)

Figure 10. Resonance structures of the pyridine anhydride

A more economic route to piperidine 62, a route also used by Snow in analogous transformations\textsuperscript{73b}, involved the "tying up" of the lone pair at nitrogen by alkylating at the nitrogen prior to hydrogenation (Scheme 27). This eliminated the need to form the pyridine HCl salt. The methyl bromoacetate treatment of amide 66 in refluxing methanol yielded pyridine salt 69 in 60% yield.\textsuperscript{73c} Hydrogenation of the pyridine salt produced less than optimal results. Treatment of the salt with Adams' catalyst at elevated pressure and temperature yielded no better than a 1:1 mixture of the saturated piperidine 62 and the
Scheme 27. Synthesis and hydrogenation of the alkylated pyridine salt 69.
monounsaturated piperidine 70. These two compounds were inseparable by common purification methods (i.e. HPLC, distillation, formation and recrystallization of the salt) and could not be further derivatized by successive hydrogenations. Due to lower yields and isolation problems this route was discarded.

Dieckmann Cyclization

The procedure, reported by Snow et al., to form methyl azabicycle 61a from piperidine 62 is a modified Dieckmann cyclization that can be broken down into three steps (Scheme 28). First, the piperidine was treated with a solution of freshly scraped potassium metal and freshly distilled tert-butanol in refluxing toluene to presumably yield the β-keto ester 71. Slow addition of the piperidine to the potassium tert-butoxide solution, mimicking high dilution conditions, is crucial at this stage of the reaction to obtain high yields of the cyclized intermediate. The β-Keto ester was then hydrolyzed and decarboxylated with concentrated aqueous HCl at reflux for 24 hours to yield the keto acid 72. The resulting HCl salt was thoroughly dried and treated with thionyl chloride in an acidic methanol solution to yield the methyl azabicyclic compound 61a in good yield over the three steps (Scheme 28).
variation of Snow's procedure was employed here as trimethyl orthoformate was used to ensure complete ketalization of methyl azabicyclic compound 61a.

**Synthesis of Methyl Photoprecursor**

A shown in Scheme 29, synthesis of the methyl ester photoprecursor, 1a, was completed in a straightforward manner. Enolization of the methyl ester with LDA followed by quenching with phenylselenyl chloride yielded selenide 73a, in acceptable yield, as one stereoisomer. Deprotection of the ketal with perchloric acid yielded ketone 74, which was oxidized to the β,γ enone, 1a, with acidic hydrogen peroxide. Isolation of the β,γ enone proved to be troublesome due to the high volatility of the compound. In order to simplify the process, a transesterification was performed to decrease the volatility of the resulting enone.

**Syntheses of Ethyl and Heptyl Photoprecursors**

To that end, there are three esters that will be investigated as alternatives to the methyl ester. Firstly, examining the target enol, 60, the ethyl ester is an obvious option as additional transesterifications would not be needed later in the synthesis. A concern with the ethyl ester is that the volatility problems inherent in the methyl ester might be present here also. The benzyl ester is also
Scheme 29. Synthesis of the methyl and ethyl photoprecursors, 1a and 1b.
an attractive choice. This is due to the ultraviolet activity of the phenyl group, and utilizing a benzyl ester could incorporate an internal triplet sensitizer into the photoprecursor which would ease the clean-up following the ODPM rearrangement. Lastly, the heptyl ester will be investigated. The heptyl ester allows us a compound that will not suffer from volatility problems and can be used as a control system in the benzyl example.

To lessen the effects on the ketal, the transesterification method of Mori, which involves the use of catalytic KCN, was employed. Following this procedure, transesterification in dry ethanol or heptanol, proceeded very cleanly to yield the ethyl or heptyl esters, 1b and 1c, in excellent yields (Scheme 30). Transesterification to the benzyl ester was more difficult. Conditions included use of titanium and tin catalysts with no better results than those obtained with the cyanide catalyst (60% yield by GC). Problems have also been encountered with the purification of the benzyl ester as it is unstable to chromatographic conditions and was too high boiling to isolate by distillation.

As predicted, the ethyl ester, 61b, suffers from the same volatility problem as the methyl case and, therefore, is impractical in the continuation of the synthesis (Scheme 29). Therefore, due to the difficulty in preparing and purifying the benzyl, ethyl, and methyl derivatives, the heptyl derivative was used exclusively in subsequent steps.
Scheme 30. Transesterification from the methyl to the ethyl and heptyl esters.

With a suitable bicyclic compound readily available, installation of the double bond was performed using a variation of the procedure used by Robins. Treatment of the ester with LDA followed by quenching the enolate with phenylselenyl chloride yielded one isomer of selenide 73c in acceptable yield (Scheme 31).

Derivatization of the selenide was predicted to occur over two steps as with the methyl ester example. That is, deprotection of the ketone with perchloric acid and then oxidation and elimination of the selenium with acidic peroxide. Careful monitoring of the reaction revealed however, that the $\beta,\gamma$ enone 1c was slowly being formed in the presence of perchloric acid (Scheme 31). Extending the reaction time from 30 minutes to 2 hours enabled the $\beta,\gamma$
enone to be formed directly from the selenide in excellent yield. Surprisingly, this was not seen in the methyl case.

Scheme 31. Synthesis of the heptyl photoprecursor 1c.
Unsensitized Irradiation of the Heptyl Enone (1,3-AS).

The photochemical behavior of $\beta,\gamma$ enone 1c was next investigated. To determine possible side products that could be observed during sensitized irradiation, direct irradiation of the $\beta,\gamma$ enone 1c was first investigated. Irradiation of a solution of the $\beta,\gamma$ enone in hexane with a Pyrex ($\lambda_{\text{max}} = 290-330$ nm)\textsuperscript{76} filter yielded only starting material. Incorporation of higher energy light using a Vycor filter ($\lambda_{\text{max}} = 210-240$ nm)\textsuperscript{76} yielded pyridine 78 in acceptable yield (Scheme 32). A similar phenomenon was seen by Demuth during the direct irradiation of bicyclo[2.2.2]octenones (Scheme 13). Demuth observed that direct irradiation of these bicyclo[2.2.2]octenones gave 1,3-acyl shift products, analogous to the azavariant 3c, which upon further irradiation, lost ketene without any detectable reverse 1,3 shift, to yield dihydrobenzene derivatives analogous to azavariant 78 (Scheme 32).\textsuperscript{47}

To investigate the effects of higher energy light on $\beta,\gamma$ enone 1c, direct irradiation in hexane in a quartz ($\lambda_{\text{max}} < 190$ nm)\textsuperscript{76} reaction vessel, yielded a 1:1 mixture of azacyclooctenone 79 and starting $\beta,\gamma$ enone 1c. Extension of the reaction time from 16 hours to 48 hours showed no increase in the amount of azacyclooctenone being formed. Isolation of the azacyclooctenone and
resubmission of the $\beta,\gamma$ enone to the photolysis reaction yielded another 1:1 mixture which was separated and resubmitted. Continuation of this process led to azacyclooctenone 79 in greater than 95% combined yield.

Scheme 32. Photochemistry of the heptyl ester under direct irradiation with a Vycor filter.
Scheme 33. Photochemistry of the heptyl ester under direct irradiation in quartz.

The structure of azacyclooctenone 79 was deduced from spectral and analytical methods. The mass spectrum of the photoproduct showed a molecular ion at 267 m/z, a mass of 2 units greater than that of the starting β,γ enone, indicating loss of one degree of unsaturation. High resolution mass spectrometry confirmed this as the molecular weight. The mass spectrum showed very little in fragmentation patterns, with a minor loss of 28 m/e due to a loss of the ketone carbonyl as CO, and a major loss of 171 m/e due to loss of the ring system leaving the heptyl group charged. This lack of fragmentation indicated a system with little functionality and branching of alkyl groups.77 The
infrared spectrum showed a strong band centered at 3400 cm\(^{-1}\) due to a NH stretch, and 2 strong absorption bands at 1740 and 1732 cm\(^{-1}\). These indicated the presence of 2 carbonyl functions, neither of which are from a cyclobutanone (\(\sim 1775\) cm\(^{-1}\)), as in the expected bicycle 3c. Instead, these could be due to a cyclooctane ketone and an \(\alpha,\beta\) unsaturated ester. Conjugation of both the ketone and ester functionalities does not correspond to the infrared spectrum as a conjugated ketone typically appears in the range of 1680-1660 cm\(^{-1}\).\(^{77}\)

\(^1\)H-NMR analysis, though not conclusive, did show diagnostic signals. A broad singlet at \(\delta\) 5.65, coupled with the IR results, indicated a secondary amine. Additional diagnostic signals include a multiplet centered at \(\delta\) 5.32, indicating a vinyl proton, and a group of signals below \(\delta\) 2.0 inherent to the heptyl group present. In this case the \(^{13}\)C-NMR spectrum of the azacyclococtane, 79, was more conclusive in assigning a structure. Determination of conjugation was clearly shown in the \(^{13}\)C-NMR spectrum. Appearance of the ketone peak at \(\delta\) 205.4 was in range for a non-conjugated ketone on a eight-membered ring (\(\delta\) 217-202).\(^{77}\) Additionally, the ester carbonyl peak was clearly seen at \(\delta\) 166.8, in the range of a conjugated ester. Taking these facts together along with the IR results indicated a system where the ketone is non-conjugated and the ester is in conjugation to the alkene. The remainder of the \(^1\)H and \(^{13}\)C-NMR signals were all between \(\delta\) 3.5-2.7 and \(\delta\) 55-30, respectively, very indicative of a
functionalized large ring system. Due to a lack of material, COSY analysis of the material was not performed, and with the results of the other spectral data was deemed redundant. Through these experiments (GC-MS, IR, $^1$H-NMR, and $^{13}$C-NMR), 1,3-AS product 79 could be shown to correspond well with the proposed structure.

This result can be explained by the mechanism shown in Scheme 33. Direct irradiation of the $\beta,\gamma$ enone causes a 1,3 acyl shift which is stabilized by resonance into the allyl radicals 76 and 77. Recombination of the radicals via structure 76 leads to the starting $\beta,\gamma$ enone 1c which can be irradiated repeatedly. Recombination of the radicals via structure 77 leads to the azabicyclic compound 3c, the expected product (Scheme 23). Homolytic opening of the strained 4-membered ring is well known to occur through irradiation. This ring opening leads to the stable aminyl/allyl diradical azacyclooctenone which, after hydrogen abstraction by the radicals, leads to azacyclooctenone 79, with no side products being observed.

Deviation from the route proposed by Demuth where loss of a ketene predominates can be explained by noting the stability of the aminyl and allylic radicals formed in the ring opening step (Scheme 33). Compounds used by Demuth incorporated either alkyl groups, yielding dihydrobenzene derivatives, or unsaturated systems, yielding aromatic derivatives.
Sensitized Irradiation of the Heptyl Enone (ODPM)

The primary focus of this research is the oxa-di-π-methane rearrangement. Previous literature examples on the all-carbon systems have shown that acetone ($E_T \sim 78$ kcal/mol)\textsuperscript{42a} is a suitable triplet sensitizer for many ODPM rearrangements. Subjection of the $\beta,\gamma$ enone, 1c, to irradiation in acetone yielded mainly starting enone with the remainder of the material being a complex mixture of uncharacterized compounds (Table 8). Incorporation of nitrogen into the $\beta,\gamma$ enone is responsible for the shift in triplet energy of the $\beta,\gamma$ enone and subsequent reactivity in acetone. Lowering of the energy of the triplet sensitizer is warranted to achieve optimal reactivity of the $\beta,\gamma$ enone in the triplet state.

Birks has reported that acetophenone ($E_T=74$ kcal/mol) is an efficient triplet sensitizer for $\beta,\gamma$ enones.\textsuperscript{42a} Acetophenone has been used in conjunction with acetone ($E_T\sim78$ kcal/mol)\textsuperscript{42a} as a suitable solvent for oxa-di-π-methane rearrangements, commonly at concentrations 2-5% acetophenone in acetone.\textsuperscript{51}

Irradiation of the $\beta,\gamma$ enone 1c in a degassed solution of 5% acetophenone/acetone showed efficient conversion of the $\beta,\gamma$ enone 1c to photopродuct 2c. Incomplete conversion lead to a study of different solvent
Table 8. Summary of the irradiation of heptyl ester 1c with various acetophenone/acetone mixtures

<table>
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<td>28</td>
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mixtures in an attempt to optimize the reaction conditions. The solvent mixtures and irradiation results are listed in Table 8.

These reactions were run in concentrations from 1-3% enone. Irradiation of the β,γ enone 1c in concentrations greater than 4% caused the formation of the unsensitized product, 79, in noticeable yields. The dependence of the formation of azacyclooctenone 79 on concentration (1-10% solutions of 1c) points to residual direct absorption due to insufficient light filtering by the acetophenone/acetone solution as the cause of the 1,3-AS.

As shown in Table 8, complete conversion to photoproduct 2c could not be achieved with acetophenone/acetone mixtures. This was proposed to be due to the triplet quenching ability of the photoproduct. Numerous control studies were then performed to examine the course of the reaction. An equilibrium effect was discarded when the isolated photoproduct was irradiated in acetophenone/acetone to yield no photodecomposition products. Next, a mixture of 70% photoproduct, 2c, and 30% starting enone, 1c, was irradiated as to determine if by-products made in the reaction sequence were quenching the reaction’s progress. After irradiation for a sufficient length of time, no change in the ratio of 2c to 1c was observed. A mixture of 10% photoproduct and 90% starting enone was then irradiated. This yielded, after reaction progress had ended, a mixture of 70% photoproduct and 30% starting enone. These results combined point to the theory that the photoproduct 2c when at a
sufficient concentrations, in this case 70%, acts as a triplet quencher, thus stopping the progress of the reaction.

Ideally the concentration of acetophenone must be greater or equal to 5% in acetone to achieve the maximum yield of photoproduct 2c (Table 8). Acetophenone concentrations greater than 10% showed side products arising from the photochemical rearrangement of acetophenone, as shown by control studies. These side products hampered isolation of photoproduct 2c, co-eluting with the photoproduct during flash chromatography with 1% triethylamine in diethyl ether. Decreasing the concentration of acetophenone to 5% eliminated these side products allowing photoproduct 2c to be isolated in greater than 98% purity. Comparing this result to the all-carbon systems studied by Demuth et al., Singh et al., and Yates et al., the structure proposed as photoproduct 2c corresponded well.51-54

The structure of the photoproduct was deduced from its spectral and analytical data. The mass spectrum of the starting β,γ enone and photoproduct both showed a molecular ion at 265 m/z, although the relative intensities were very different. The starting β,γ enone exhibited a molecular ion peak at 265 m/z of less than 1%, while that of the photoproduct was 21%. Both compounds readily lost a fragment of 28 m/z, due to the ketone carbonyl being lost as CO. The peak at 237 m/z was the base peak in the β,γ enone, but had a relative intensity of only 25% in the photoproduct. Apart from these similarities the mass
spectrum of the β,γ enone and photoproduct were very different, with the photoprecursor exhibiting a simple fragmentation pattern, major peaks appearing at 140 m/z (loss of the CO₂C₇H₁₅ ester) and 95 m/z. The product also showed the 95 m/z peak along with major peaks at 222, 167, 149, 139, 122, and 85 (base peak) m/z.

The ¹H-NMR spectrum of the starting β,γ enone, 1c, showed a doublet at δ 7.50, due to the vinyl proton. The signal was farther downfield than that typical for an enone due to the α-nitrogen, which made the moiety essentially a vinylogous carbamate. The ¹H-NMR spectrum of the photoproduct, 2c, did not have the same downfield signal. Therefore, the vinylogous carbamate moiety was no longer present. The ¹H-NMR spectrum of the photoproduct also lacked any other peaks which might have corresponded to an unsaturated system. Apart from the heptyl group, the ¹H-NMR spectrum for β,γ enone 1c and photoproduct 2c showed no similarities, but also could not help in determining the structure of the photoproduct.

To verify the structure of the photoproduct and establish that it was in fact the tricyclic compound 2c, 2D NMR techniques were used. COSY analysis of the photoproduct allowed the connectivity and coupling patterns to be established (Figure 11). The first peaks to be assigned were the protons of the heptyl group. The methyl protons, H₁₆, at the terminus of the heptyl chain were
Figure 11. The COSY NMR spectrum of the photoproduct, 2c.
clearly seen as a signal at $\delta$ 0.86 ($J=6.0$ Hz). These protons were coupled to a multiplet centered at $\delta$ 1.29 and were assigned as H11-H15. Coupled to these was a triplet at $\delta$ 4.09 ($J=6.7$ Hz) assigned as H10. The next set of resonances to be assigned were those due to protons only coupled to one other proton. These were three signals at $\delta$ 4.15, 3.60, and 2.80. The signals at $\delta$ 3.60 ($J=17.7$ Hz) and 2.80 ($J=17.7$ Hz) were coupled only to each other. Their large coupling constant indicated geminal coupling, and their isolation from all other spin systems were consistent with their assignment to protons H2$\alpha$ and H2$\beta$. The signal at $\delta$ 4.15 was coupled only to the proton whose resonance was $\delta$ 3.00. Of the remaining protons H5-H8, only H5 was expected to couple to one other proton, H6. Shift calculations$^{77}$ on H5 indicated that a NMR chemical shift of $\delta$ 4.15 was not unreasonable, as it was $\alpha$ to a nitrogen and part of a rigid ring system.$^{77}$ Taking these facts together, the triplet at $\delta$ 4.15 was assigned as H5.

The triplet assigned as H5 was only coupled to a signal at $\delta$ 3.00, which can be assigned as H6. This assignment was made on the fact that no other protons can couple to H5. Coupled to H6 is a signal at $\delta$ 2.20 ($J=7.2$ Hz). This signal could be attributed to either H7$\alpha$ or H7$\beta$. *Ab initio* calculations on the dihedral angle between H6 and H7$\alpha$ or H7$\beta$, at the 3-21G* level, showed
dihedral angles of -104.6° and 16.6°, respectively. Plotting these angles on the Karplus curve to estimate coupling constants showed that coupling would be minimal (estimated <1 Hz) between H6 and H7α (-104.6°) and can be discarded, leaving the signal at δ 2.20 to be assigned as H7β. Coupled to H7β were two other signals at δ 3.30 (J=9.3 Hz) and 1.94 (J=17.8 Hz). The complex signal at 1.94 (dddd) can be assigned as H7α due to the large coupling constant indicating geminal coupling. The remaining signal in this coupling pattern can be assigned as H8β. This assignment was made due to the fact that only two other protons have yet to be assigned, H8α and H8β. Ab initio calculations on the dihedral angle between H7β and H8α or H8β were performed yielding angles of -91.8° and 31.0°, respectively. Plotting these angles on the Karplus curve to estimate coupling constants showed that coupling would not occur between H7β and H8α (-91.8°) leaving the signal at δ 3.30 to be assigned as H8β. The remaining signal, δ 2.75, can be assigned as H8α as no other protons remain unassigned. Coupling patterns agree with this assignment showing coupling of H8α to H8β (J=12.3 Hz) and H7α (J=6.5 Hz).

nOE experiments were run to determine the stereochemistry of the ring junction, and for additional proof of H7α and H7β assignments. Irradiation of the
signal at $\delta$ 4.15, H5, showed enhancement of the resonance at $\delta$ 3.00, H6, which corresponded well with the proposed structure and cis ring junction. Irradiation of the signal at $\delta$ 3.00 showed enhancement of the resonances at $\delta$ 4.15, as expected, and at $\delta$ 2.21, H7$\beta$, which corresponded well with the proposed assignments by the COSY. Through these experiments (GC-MS, IR, $^1$H-NMR, $^{13}$C-NMR, nOE and COSY), photoproduct 2c could be shown to correspond well with the proposed structure.

**Thermal Activation of the 1,3-AS**

Synthesis of the azacyclooctenone 79 can also be effected by employing the thermal instability of cyclopropyl ketones. First reported in 1981, Demuth noted that ODPM cyclopropyl ketone products from the irradiation of cyclopentenyl ketones (Scheme 17) thermally revert to starting material and the 1,3-AS product.56 This phenomenon is responsible for the relatively late discovery of the ODPM rearrangement as previous ODPM examples were analyzed solely by gas chromatography and therefore escaped detection.79 This was illustrated well in our case. Irregardless of the actual yield of the ODPM rearrangement, the GC/MS trace showed 1:1:3 mixture of starting $\beta,\gamma$ enone, 1c : ODPM product, 2c : 1,3-AS product 79.
To determine the mechanism responsible for the thermal reversion of the photoproduc
2c to the 1,3-AS product 79, a number of control studies were run. First the photoproduc
2c was heated to 120°C for 2 hours in acetophenone. This resulted in the complete decomposi
tion of the tricyclic cyclopropyl ketone to a complex mixture of products. Reducing the heat to 60°C
and extending the reaction time to 6 hours in acetophenone or THF, resulted in yields of 55% for the 1,3-AS product, 79, and 31% for the starting enone, 1c (Scheme 34). Extension of the reaction time to 24 hours resulted in no change in the reaction outcome.

Scheme 34. Thermal activation of the sigmatropic 1,3-acyl shift (1,3-AS).
It was still not clear whether the mixture of products came from two competing mechanisms or one mechanism where either the 1,3-AS product or the starting enone was an intermediate. Experimentally it has been proven that the mixture of thermal products comes from two competing mechanisms. This was done by separately heating both the 1,3-AS product and the starting enone at 60°C in either THF and acetophenone (Scheme 35). In both cases no rearrangement occurred. The thermal stability of both the starting enone and the 1,3-AS product meant that neither could be intermediates in the thermal 1,3-AS mechanism.

Mechanistically, the thermal 1,3-AS is proposed to start with homolytic α-cleavage to yield the stabilized diradical (Scheme 35). Cleavage of the cyclopropyl ring occurs so that the resulting double bond formed is in conjugation with the heptyl ester. Recombination of the radicals then yields the [4.2.0] ring system, 3c. From the [4.2.0] ring system, 3c, routes to both the 1,3-AS product and the starting enone have already been shown in Scheme 33.

Cyclopropyl Ring Opening Strategies

Previous studies of the regioselective ring opening of a cyclopropyl ketone have shown that there are two possible modes of nucleophilic attack. Shown in Scheme 36, the nucleophile can attack at the 6-position to yield the
Scheme 35. Proposed mechanistic pathway for the thermal 1,3-AS on cyclopropyl ketone 2c.
Scheme 36. Possible modes of nucleophilic attack on a cyclopropyl ketone.
[3.3.0] azabicyclic octenone, 80 (path a). Alternatively, the nucleophile can attack at the 5-position to yield the [3.2.1] aza bicyclic octenone, 81 (path b) (Scheme 36). Numerous studies by Demuth on the all-carbon systems have shown that the attack of the nucleophile prefers the path a route, as it provides the greatest overlap between the developing carbanion and both the ketone and the C-4 ester carbonyl to yield [3.3.0] ring system 80.47,49,53

Cyclopropyl ketones can be ring-cleaved in a number of different ways. Geminally double-activated cyclopropyl moieties are readily attacked in a 1,4 fashion52,69; a few monoactivated cyclopropyl derivatives are sufficiently reactive, in the absence of forced catalysis, either owing to extremely powerful nucleophiles or to release of considerable ring strain during reaction80; cyclopropyl ketones add nucleophiles in a cooperative action with strong electrophiles such as Lewis acids, acetyl, SiR₃, and protons69; alternatively, Si-induced cation formation may cause the rearrangement of cyclopropyl ketones to olefinic isomers.70

Demuth et al. have shown that the use of Si(CH₃)₃ coupled with various nucleophiles added these nucleophiles regioselectively and in good yield.69 In this mechanism the Si(CH₃)₃ complexes with the ketone, further activating the cyclopropyl ring to nucleophilic attack. As shown in Scheme 37, addition of the trifluoroacetate proceeded cleanly under electrophilic conditions to yield the 6-
substituted acetate $\text{83}$. Si-cation induced cyclopropyl ring opening with Nafion-TMS yielded the 6,7 olefin $\text{84}$ in good yield.

Scheme 37. Addition products seen by Demuth.$^{69}$

Subjection of photoproduct $\text{2c}$ to these conditions yielded only starting material. To increase the activity of the Nafion-TMS, carbon tetrachloride was employed as the solvent. Carbon tetrachloride has been shown by Olah to swell the Nafion resin thereby increasing the amount of active sites available to the substrate.$^{81}$ Reaction of the photoproduct $\text{2c}$ with Nafion-TMS in refluxing carbon tetrachloride also showed no reaction.
The use of cuprates as cyclopropyl ring opening agents was initiated by the work of Yates and Stevens. In their synthesis of α-cedrol, 12, Yates and Stevens reacted their tricyclic ODPM photoproduct, 85, with lithium dimethylcuprate at 0°C in Et₂O to yield the bicyclic enol, 86, in good yield (Scheme 38). Also observed was the formation of the [3.2.1] bicyclic enol, 87, as a minor product.52

![Scheme 38. Yates' cyclopropyl ring opening results with Me₂CuLi.](image)

Formation of 87 was explained by Yates and Stevens as occurring via the increased nucleophilicity of the organometallic cluster, resulting from improved coordination of the solvent with lithium ions.52 Addition of an electron to the tricyclic system, 85, causes an opening of the ketone to yield the ketonic isomer, 88. Regioselective opening of the cyclopropyl group occurs so that the
bond that is broken has the greatest overlap with the \( \pi \)-orbital of the ketonic group. The presence of the C5 ester group promotes the cleavage of the C4-C5 bond because of the stabilization of the anion radical 89. When the tricyclic ketone 85 was subjected to dissolving metal reduction the [3.2.1] enone was produced in 76% yield (Scheme 39).\(^5\)
Reaction of our photoproduct, 2c, with lithium dimethylcuprate produced results similar to those of Yates and Stevens. After a syringe pump addition of the cyclopropyl ketone, 2c, to a cooled solution of methyl lithium and copper iodide, the bicyclic enol, 90, was recovered in good yield with none of the [3.2.1] minor product observed under any spectroscopic methods (Scheme 40). Stereochemistry of the methyl group was first confirmed by examining coupling constants of the relevant protons and then fully confirmed by nOES studies.

\[
\begin{align*}
\text{H} & \quad \text{CO}_2\text{Hep} \\
\text{Me}_2\text{CuLi} \quad \text{Et}_2\text{O} & \quad \text{H}_3\text{C} \quad \text{CO}_2\text{Hep} \\
\text{2c} & \quad \text{22\%} \\
\text{90} & \quad (77\%) \\
\end{align*}
\]

Scheme 40. Cyclopropyl ring opening results with Me\textsubscript{2}CuLi.

Due to the unresponsiveness of our photoproduct to ring opening by a masked oxygen following Demuth's methods, use of a lithium dialkyl cuprate could provide another method. Use of the silyl cuprate should yield a similar addition result to that of the dimethyl cuprate. Initial efforts into this ring opening have been disappointing, yielding only unreacted starting material. Successful
ring opening with the silyl cuprate will lead to the system shown in Scheme 41.\textsuperscript{82} Oxidation of the silyl group to the corresponding alcohol would then lead to the 6-hydroxyl necine bases of which there are greater than 60 known to exist.\textsuperscript{71}

\begin{center}
\begin{tikzpicture}
  \node (1) at (0,0) {\text{\textbf{2c}}};
  \node (2) at (2,0) {\text{\textbf{91}}};
  \node (3) at (0,-2) {\text{HO}};
  \node (4) at (2,-2) {\text{HO}};
  \node (5) at (2,-1) {\text{R}};
  \node (6) at (2,-1.5) {\text{R}};
  \draw (1) -- (2);
  \draw (2) -- (3);
  \draw (3) -- (4);
  \draw (4) -- (5);
  \draw (5) -- (6);
  \node (7) at (0,1) {\text{(PhMe\textsubscript{2})\textsubscript{2}SiCuLi}};
  \node (8) at (0,0.5) {\text{Et\textsubscript{2}O}};
\end{tikzpicture}
\end{center}

Scheme 41. Proposed installation of a hydroxyl group.

Explanation for the disappearance of the [3.2.1] minor product in the reaction of 2c with lithium dimethylcuprate can be attributed to the lack of a stabilizing group at the C5 position. In the parent system, 45a, reduction of the cyclopropyl ketone with lithium in ammonia was shown to yield the [3.3.0]
bicyclic ketone in 95% yield with only a minor amount of the [3.2.1] bicyclic ketone (<5%) (Scheme 42).  

Scheme 42. Reduction of cyclopropyl ketone with lithium in ammonia.  

Regressive cleavage via the dissolving metal reduction, shown above, is only one of the possible methods for opening of the cyclopropyl ring. Of these alternative procedures, we selected H_2/Pd-C as a reagent for this purpose due to convenience, simplicity and also since it eliminates the formation of the [3.3.1] bicyclic enone. Thus, the tricyclic ketone was stirred with palladium on carbon (10%) in an hydrogen atmosphere for 12 h. Removal of the catalyst followed by chromatography gave the product 92 in excellent yield as a mixture of the keto and enol forms (Scheme 43). The ratio of the keto product to the enol product was determined simply by ^1H-NMR integration; in the keto form, the proton alpha to both the ketone and ester corresponds to a multiplet centered at δ 5.30,
whereas the proton on the oxygen, in the enol form, corresponds to a broad singlet $\delta 5.62$.

Scheme 43. Hydrogenation of the cyclopropyl ketone.

Synthesis of Enol 60.

Once the hydrogenation had been achieved, a transesterification from the heptyl to the ethyl ester (Scheme 44) was all that was needed to complete the formal syntheses, as 60 has been previously converted to (-)-petasinecine, 7, (-)-isoretronacol, 8, (-)-trachelanthamidine, 9, and (-)-supinidine, 10, by Rueger (Scheme 45). At first glance this seems to be an inefficient method for the synthesis of 60. Upon closer examination, this method is advantageous in a number of respects. First and foremost, utilization of the heptyl ester eliminates the problems of volatility observed with the methyl and ethyl esters, thereby simplifying isolation and purification. Additionally, the heptyl selenide
can be converted to the heptyl enone in one high yielding step, whereas the ethyl, like the methyl, requires two steps each averaging 50% yield. Taking these facts together it can be summarized that use of the heptyl ester, followed by a transesterification to the ethyl ester in the last step, is a superior method in the synthesis of enol 60.

Scheme 44. Transesterification to ethyl ester 60.

The \(^1\)H and \(^{13}\)C-NMR spectral data derived from the latter material agree very well with those reported by Rueger.\(^{72}\) Since 60 was previously converted into the target alkaloids (Scheme 45),\(^{72}\) acquisition of this material completes formal total syntheses for petasinecine, 7, isoretronacol, 8, trachelanthamidine, 9, and supinidine, 10.
Scheme 45. Rueger's synthesis of (-)-petasinecine, 7, (-)-isoretrotronecanol, 8, (-)-trachelanthamidine, 9, (-)-supinidine, 10, from enol 60.
Future Work

The opportunities for future work in this area are boundless. Firstly, the ring-opening with the silyl cuprate should be completed (Scheme 41). Successful synthesis of the bicyclic silane would lead to an alternative route to the 4-hydroxyl necine bases. These bases are abundant in nature and medicine, with derivatives including platynecine ($R^1=\text{CH}_2\text{OH}, \ R^2=\text{H}$), croalbinecine ($R^1=\text{CH}_2\text{OH}, \ R^2=\text{OH}$), and heliofoline ($R^1=\text{CH}_2\text{OCOC(CH}_3\text{)CHCH}_3, R^2=\text{OH}$) (Scheme 41).

An alternative method towards the synthesis of the 4-hydroxyl necine bases could come about utilizing Demuth’s TMSTFA ring-opening protocol on the reduced ester derivative, 2d (Figure 12). Examining the successful systems Demuth used in his ring-opening studies, one can see that only electron rich groups on the cyclopropyl ring were used successfully. *Ab initio* calculations at the 3-21G* level were performed on our electron deficient cyclopropyl ketone 2c and Demuth’s electron rich photoproduct 82. Considerable differences in the electron density in the HOMO on the 6-position were found. This could account for the reactivity differences between the two cyclopropyl ketones. When the reduced ester, 2d, was subjected to the same calculations, the electron densities of the 6-position in Demuth’s photoproduct, 82, and the reduced ester were essentially the same. Utilizing the primary alcohol in place
of the ester could allow the TMSTFA to react with our cyclopropyl ketone, thereby installing an oxygen at the 6-position.

![Chemical structure of 2d]

Figure 12. The reduced ester ODPM product.

Additionally, work on the 1,3-AS, both photolytically and thermally, could offer more insight into the 1-azabicyclic system, 2. Work into the study of light filters could allow for the isolation of the expected [6,4] bicyclic ring system, 3.

**Retrosynthetic Analysis for Xenovenine.**

The encouraging results of the ODPM rearrangement on the 1-aza bicyclic system prompted us to study various 2-aza bicyclic systems under photochemical conditions. As shown in Scheme 13, sensitized irradiation of enone 4 would yield the tricyclic photoproduct 5. Derivatization of tricycle 5 at the cyclopropyl ring would lead us to the 2,8-substituted pyrrolizidine alkaloids (Figure 9).
Incorporation of the nitrogen into the chromophoric region of the molecule, although very interesting, presents problems which must be addressed. The presence of a nitrogen in the chromophoric region of the molecule will alter the $T_1$ energy level and could demand the use of alternative triplet sensitizers (Table 6). Additionally, complications would arise with the handling of the acid/water sensitive imine functionality as opposed to the relatively stable alkene.

However, in working with these systems, an obvious disconnect in the photoprecursor has been revealed. The [2.2.2] bicyclic imine could come about through a Diels-Alder cycloaddition of a nitrile and a silyl enol diene. In order to determine the efficacy of the method, a 2,8 substituted pyrrolizidine alkaloid was chosen as the synthetic target.

In 1989, Crouse and Pinder published a four step synthesis of normearsine $4a$ ($R=\text{CH}_3$) starting from cyclohexenone, acetaldehyde, and benzyl amine through a tandem Mannich-1,4 addition followed by installation of the double bond through the Ruschig sequence.\textsuperscript{84} Successful triplet sensitized irradiation of $4a$ would lead us to the synthesis of the tricyclic aziridine, $5a$ (Scheme 46). Regioselective ring-opening of the aziridine with a lithium dialkyl cuprate will allow for the addition of a second alkyl group either at the nitrogen atom leading to the tropane skeleton shown in Scheme 36, or at the 8-position of the resulting bicyclic system.
Scheme 46. Retrosynthetic analysis of xenovenine, 53.

There are a small number of naturally occurring alkaloids with this basic structure. Of these, xenovenine, 11, was particularly attractive due to its anticipated medicinal value. Thus, utilizing a heptyl cuprate in the aziridine ring opening or beginning with the heptyl bicyclic imine, and utilizing the more common methyl cuprate, followed by reduction of the ketone would yield xenovenine, 11 in a relatively few steps (Scheme 46).
Formation of the Azabicyclic Ketone

Following the retrosynthetic strategy outlined in Scheme 46, the first step in the synthesis is the formation of the bicyclic ring system utilizing the tandem Mannich-1,4-addition described by Crouse and Pinder.84

The tandem Mannich-1,4-addition can be viewed as a three step process. The reaction commences with a condensation between the aldehyde and benzyl amine. Attack of the subsequent benzyl imine by the acid-catalyzed enol of cyclohexenone yielded Mannich base 95. The Mannich base then underwent a thermally activated, intramolecular 1,4-addition into the cyclohexenone section of the Mannich base. This cyclization yielded the benzyl amine 93 yields similar to those published by Crouse and Pinder.84 Examination of the remaining reaction mixture indicated that is predominantly unreacted Mannich base 95. Isolation of the Mannich base and attempts at inducing a thermal 1,4-cycloaddition to improve the overall yield have thus far been unsuccessful.

Continuation of Crouse and Pinder's synthesis towards the bicyclic imine 4 was discontinued at this point because of irreproducibility problems. It was stated by them that hydrogenolysis of the benzyl amine under neutral conditions resulted in near quantitative yield of secondary amine 96.84 In our hands however, hydrogenolysis led to the polymeric enamine 97, as the free amine repeatedly attacked the ketone yielding a series of polymeric enamines 97.
Scheme 47. Mannich reaction to synthesize benzyl amine 93.
Scheme 48. Synthesis of polymeric enamine 97.

(Scheme 48). Product ratios showed a 4:2:1 ratio of the three enamines, \( n=1,2,3 \), as detected by gas chromatography.

\[
\begin{align*}
\text{93a} & \quad \text{H}_2 \quad \text{Pd/C} \quad \text{MeOH} \\
\text{96} & \\
\text{97} & \\
\end{align*}
\]

Synthesis and Photochemical Behavior of 2-Aza-3-methyl bicyclic[2,2,2]oct-2-en-5-one. 4a

At this point, it was clear that either the nucleophilicity of the nitrogen or the electrophilicity of the ketone had to be reduced to eliminate this
polymerization. The most obvious and efficient choice was to protect the amine as its hydrochloride salt. This method was chosen due to its ease of formation and regeneration. Work was also done with the 1,3-dioxolane protected variant of 93 but was discontinued due to the difficulty in regenerating the ketone.

Formation of the salt was done quantitatively by stirring in a solution of 1M HCl in diethyl ether. The salt was isolated by filtration and hydrogenated at atmospheric pressure with 10% palladium on carbon in 5-6M HCl in isopropanol to yield the secondary amine 96 as its hydrochloride salt. The imine double bond was then established by a modified Ruschig reaction sequence (Scheme 49). Chlorination of the secondary amine was done with N-chlorosuccinimide yielding chloro amine 98 in 85% yield. Elimination of chlorine as HCl was done using DBU to yield imine 4a in excellent overall yield (Scheme 49).

Similar to the methyl ester case, 1a, in the previous section, the methyl imine suffered from volatility problems. Isolation and purification of the imine was done in a two step sequence, an initial crude separation using basic alumina chromatography and ether as the eluent. After removal of the ether under a stream of argon, fine purification was accomplished by distillation (75-80°C at 29 mm) from the higher boiling contaminants (i.e. unreacted starting material, DBU).
Scheme 49. Preparation of the methyl imine 4a.

Subjection of the methyl imine to ODPM conditions (5% acetophenone/acetone) have yielded encouraging results. GC analysis of the reaction mixture showed the presence of ODPM product 5a (R=CH₃) along with what appears to be the 1,3-AS product, 6a (R=CH₃) (Scheme 13). Isolation efforts were hampered by the high volatility of the photoproduct as it boiled in the same temperature range as acetophenone, thereby eliminating the removal of excess acetophenone by bulb-to-bulb distillation. Column chromatography was also ineffective as the photoproduct 5a co-eluted with acetophene even when hexane was used as the column eluent. Attempts were made to isolate the photoproduct 5a by formation of the HCl salt. Thus, the crude reaction mixture was stirred in 1 M HCl/Et₂O for 30 min, under argon. This resulted in complete decomposition of the presumed photoproduct and starting imine.
Due to difficulty with the methyl imine the heptyl imine was chosen. If the
heptyl could be installed prior to photorearrangement, well-documented ring
opening with the methyl cuprate instead of with the heptyl cuprate followed by
reduction of the ketone would yield xenovenine, 11 (Scheme 46).

Synthesis of the bicyclic heptyl precursor 93b was carried out according
to the Crouse and Pinder procedure used for the synthesis of the methyl bicycle,
93a. Octanal was slowly added to a stirring mixture of benzyl amine and
cyclohexenone in methanol to produce the corresponding Mannich base which
was then heated for 5 days to affect the 1,4-addition in similar yield to the methyl
case (Scheme 47).

Preparation of the heptyl imine 4b, has thus far been hampered by the
ineffectiveness of hydrogenolysis of the benzyl protecting group. Standard
hydrogenolysis conditions, 10% Pd/C in a hydrogen atmosphere, produced
either from bubbling hydrogen gas into the system or by utilizing ammonium
formate, have been unproductive yielding only unreacted starting material.
Marginal success has been achieved using Pearlman’s catalyst (Pd(OH)₂) at
elevated pressures of hydrogen (300 psi) yielding the secondary amine salt in
yields approaching 30%. Subjection of the secondary amine salt to N-
chlorosuccinimide and then with DBU, mimicking the procedure used in the
methyl example, have yielded trivial amounts of heptyl imine 57b, observed only by GC-MS analysis.

Future Work

Optimization of the heptyl imine synthesis will allow for irradiation of the less volatile heptyl imine. This will allow us to investigate the results of the ODPM rearrangement on an electron rich imine as the acetophenone can be removed by reduced pressure distillation, allowing for chromatographic separation of the photoproduct 5b from unreacted starting imine, 4b. Completion of the synthesis then involves regioselective ring opening with methyl cuprate followed by reduction of the ketone using standard literature methods, to yield the pyrrolizidine ant venom xenovenine, 11. Additionally, more work must be performed on the isolation of the methyl photoproduct, 5a, from the reaction mixture.

Examination of this system is crucial as it consists of the first reported ODPM rearrangement on a β,γ imine ketone. Depending upon the result, these examples will also illuminate the effects of an electron donating group situated within the chromophoric region of the molecule. Lastly, the effects of an aziridine on the cyclopropyl ring opening will be examined. It is not clear, presently, if the nucleophilic attack will be at the 8-position of the aziridine or at the nitrogen, both of which will yield interesting synthetic intermediates.
**Diels-Alder Cycloaddition With a Nitrile**

A subsequent set of target molecules to be investigated were the 2-azabicyclo[2.2.2]oct-2-en-5-ones, 4, where an electron withdrawing group is substituted on the imine moiety. Our synthetic strategy towards these photoprecursors incorporates a Diels-Alder cycloaddition between an electron poor nitrile and a silyl enol ether, 99 (Scheme 50).

![Scheme 50. Proposed synthesis of 2-aza-bicyclo[2.2.2]oct-2-en-5-ones.](image)

As shown in Scheme 51, synthesis of silyl enol ether 99 was easily done by enolization of cyclohexenone with LDA followed by *in situ* quenching with trimethylsilyl chloride. The mixture was then quenched with ice-water and purified by reduced pressure distillation to yield silyl enol ether 99 in good
yield. The silyl enol ether was stable at -20°C for up to 6 months and was used without further purification in subsequent reactions.

\[
\text{O} \quad \xrightarrow{\text{LDA, TMSCl}} \quad \text{OTMS} \\
\text{Et}_2\text{O, }0^\circ\text{C}
\]

99 (71 %)

Scheme 51. Synthesis of 2-siloxy-1,3-cyclohexadiene, 99.

Use of the Diels-Alder cycloaddition in the synthesis of bicyclic[2.2.2]octenones has been well documented. Specifically, the use of silyl enol ether 99 has been shown by Holmes, in the synthesis of isoprosopinine B and desoxoprosopinine, to be an effective method towards the synthesis of the bicyclic[2.2.2]octenone skeleton (Scheme 52). Holmes and coworkers performed the cycloaddition between 99 and the imine of ethyl glyoxylate, 101, followed by deprotection under mild acid hydrolysis to yield the bicyclic tosyl amine 102 in good yield. This compound was then further derivatized to the desired targets.
The use of nitriles as dienophiles in the Diels-Alder cycloaddition has been limited to one example. In 1974, Jagt reported that the cycloaddition between tosyl cyanide and cyclopentadiene yielded the tosyl imine 103, which was subsequently hydrolyzed with dilute acetic acid to yield the 2-azabicyclic[2.2.1]hept-3-one, 104, in good yield (Scheme 53).
Our first attempt in the synthesis of these electron deficient imine photoprecursors was directed toward installing an ester on the imine functionality. To that effect, silyl enol ether 99 and ethyl cyanoformate were stirred at 110°C in a sealed tube for 48 days with no cyclization observed by ¹H-NMR and GC/MS spectrometry. Through numerous Lewis Acid studies, MgBr₂:OEt₂ was determined to be a highly effective catalyst for the Diels-Alder reaction, affecting cycloaddition at concentrations of less than 10 mol% catalyst. Suitable yields of the ester-imine, 100a, were then produced by stirring the silyl enol ether and nitrile in ether for 16 h in the presence of 30 mol% MgBr₂:OEt₂ (Scheme 54).

Conversion of the silyl enol ether to the ketone has thus far been unsuccessful. Deprotection conditions included 0.005M HCl, K₂CO₃/methanol,
HF:pyridine, and CsF/CH$_3$CN with only decomposition of the starting material observed. At this point, it was clear that another method must be chosen to produce the $\beta,\gamma$ enone 4c.

Literature reports of the palladium catalyzed conversion of enol triflates to esters prompted us to examine the enol triflate version of 4c.$^{90}$ Enol triflates are easily prepared from the corresponding amides through reaction with triflic anhydride.$^{91}$ Thus, to arrive at ester 4c, we needed to synthesize the ketoamide 105 (Scheme 55).

![Scheme 55. Proposed conversion of amide to imine ester.](image)

Preparation of the amide can be envisaged to arise via a Diels-Alder cycloaddition between the silyl enol ether 99 and tosyl cyanide followed by hydrolysis of the tosyl imine. This was shown well by Jagt in the synthesis of 2-aza-bicyclic[2.2.1]hept-3-one, 104 (Scheme 53).$^{88}$

The Diels-Alder reaction between silyl enol ether 99 and tosyl cyanide under thermal conditions (CHCl₃, 60°C) proceeded quantitatively to yield one regioisomer, which was presumed to be 100b by ¹H-NMR analysis. Isolation of the bicyclic imine proved to be troublesome as the imine decomposed readily upon contact with air. Subsequent attempts at deprotection of the silyl enol ether were unsuccessful as the imine decomposed more rapidly than the silyl enol ether. Hydrolysis of both the imine and silyl enol ether yielded ketoamide 105 (Scheme 56) in good yield, by the reaction pathway shown by Jagt.⁸⁸

![Scheme 56. Preparation of 2-Azabicyclo[2.2.2]octan-3,5-dione, 104.](image-url)
Proof of this regiochemistry came through $^1$H-NMR experiments. One dimensional $^1$H-NMR analysis showed a broad singlet at $\delta$ 7.71, assigned as the amine proton H2, two one proton multiplets at $\delta$ 4.01 and $\delta$ 3.25 which were assigned as protons H1 and H3 respectively, a two proton multiplet centered at $\delta$ 2.38, which was assigned as both H4's, and a four proton multiplet centered $\delta$ 2.04, which was assigned to protons H5 and H6 (Figure 13). These assignments were made in conjunction with calculations done following the procedures of Silverstein and Bassler$^{77}$, but were not conclusive in deciding regioselectivity. Definitive proof of structure 105 was made through interpretation of the COSY spectrum (Figure 14).

Figure 13. Possible Diels-Alder products.
Figure 14. The COSY NMR spectrum of the Diels-Alder product, 105.
COSY analysis confirmed the above shift assignments, clearly showing that H2 was coupled to H1 and that both H1 and H3 were coupled to the H5 and H6 signals. Furthermore, the COSY spectrum showed that H1, and not H3, was coupled to H4, which is only possible in compound 105 (Figure 14). Based on the above observations, it must be concluded that the resulting ketoamide corresponds to structure 105 and not 106.

Synthesis and Photochemical Behavior of 2-Aza-3-trifluoromethanesulfoxycyclo[2.2.2]oct-2-en-5-one, 4d

With ketoamide 105 in hand, the synthesis of triflate 4d was done according to a modified version of the Snieckus procedure. Thus, reaction of ketoamide 105 with triflic anhydride and triethyl amine yielded triflate 4d in good yield by GC/MS analysis of the reaction mixture (Scheme 57). Attempts to isolate the triflate have been unsuccessful due to its instability, leaving the purification of 4d to be minimal. Purification consisted of an aqueous work-up to remove excess triflic acid, yielding the triflate 4d which was found to be 60% pure by GC and $^1$H-NMR analysis.
Due to its availability, it was deemed necessary to examine the effects of sensitized irradiation on triflate 4d. Consequently, irradiation of the triflate in a thoroughly degassed solution of 5% acetophenone/acetone yielded only unreacted starting material and ketoamide 105, resulting from the decomposition of triflate 4d. Studies towards the optimal triplet sensitizer have been performed attempting to induce photorearrangement via the ODPM pathway. Nevertheless, rearrangement of the triflate was not detected using acetophenone ($E_T=74 \text{ kcal/mol}$)\textsuperscript{42a}, acetone ($E_T=-78 \text{ kcal/mol}$)\textsuperscript{42a}, or benzene ($E_T=84 \text{ kcal/mol}$)\textsuperscript{42a} as the triplet sensitizer. Due to the instability of the triflate under the photochemical conditions required, examination of the reactivity in the 1,3-AS route was not performed. Thus, the triflate was taken onto the carbonylation without further purification.
Synthesis and Photochemical Behavior of 2-Aza-3-ethoxycarbonyl bicyclo[2.2.2]oct-2-en-5-one, 4c

Preparation of ethyl ester 4c commenced from triflate 4d, following the method of Ortar (Scheme 58). The crude triflate was stirred in ethanol in the presence of a carbon monoxide atmosphere and palladium catalyst for 4 hours to yield ester 4c in 60% yield by GC analysis.

Attempts at purification of the ester have been unsuccessful. Subjection of the ester to an aqueous work-up to remove the triphenylphoshine and palladium, resulted only in decomposition of the ester. Surprisingly, the presumed less stable triflate endured a rapid aqueous work-up in the previous step. Due to these difficulties, the ester was irradiated without further purification.
Irradiation of the crude ester imine 4c in 5% acetophenone/acetone has yielded exciting results with the tricyclic ketone being isolated in 32% yield from keto amide 105 (Scheme 59).

![Scheme 59. ODPM rearrangement on ester imine 4c.](image)

The structure of photoproduct 5c has been deduced from its spectral and analytical data. The mass spectrum of the starting β,γ enone and photoproduct both showed a molecular ion at 195 m/z, although the relative intensities were different. The starting β,γ enone 4c exhibited a molecular ion peak at 195 m/z of 35%, while that of photoproduct 5c was less than 1%. Both compounds readily lost a fragment of 28 m/z, due to the ketone carbonyl being lost as CO. Apart from these similarities the mass spectrum of the β,γ enone and photoproduct were very different, with the photoprecursor exhibiting a simple fragmentation pattern, with major peaks appearing at 109 m/z and 81 m/z (base
peak). The photoproduct also showed the 109 m/z and 81 m/z peaks, along with major peaks at 139, 97, and 69 (base peak) m/z.

The $^1$H-NMR spectrum of the starting ester imine, 4c, showed a cluster of peaks all in the range of $\delta$ 3.50-2.00, excepting the peaks attributed to OC$_2$H$_5$ group and what appears to be a bridgehead proton at $\delta$ 4.30. Examining the spectrum of the photoproduct, 5c, major differences can be seen. The $^1$H-NMR spectrum of the photoproduct showed an apparent triplet at $\delta$ 4.30 similar to the signal shown on the comparable photoproduct 2c, attributed to the proton in the highly constrained cyclopropyl system, vicinal to the bridgehead nitrogen.

The $^{13}$C-NMR spectrum shows signals at $\delta$ 208.3 and 168.0 which can be attributed to the ketone and ester moieties respectively. These signals would also be present in the starting imine but as the reaction mixture has been subjected to column chromatography no starting imine would be present. Evidence for this is seen in the lack of additional $^{13}$C signals in the unsaturated region. The remaining signals in the $^{13}$C-NMR show the lack of any additional functionalization on the ring system, as a number of the signals are in the $\delta$ 20-40 range. The structure of the photoproduct was definitely determined through COSY measurements which agreed very well with the proposed structure.
Synthesis and Photochemical Behavior of 2-Aza-3-Ethoxybicyclo[2.2.2]oct-2-en-5-one, 4e

Following the results of the enol triflate, 4d, and ester imine, 4c, the photochemical behavior of the more stable imidate was examined. Conversion of the amide to the imidate was done quantitatively by treating the amide, 105, with ethyl Meerwein's reagent\(^\text{92}\) in CH\(_2\)Cl\(_2\) at room temperature (Scheme 60). UV absorption measurements on ethyl imidate 4e showed that it was a suitable candidate for photolysis as its absorption bands corresponded well with the output of the lamp.

\[
\begin{align*}
\text{H} & \quad \text{Et}_3\text{O} \quad \text{BF}_4 \\
\text{O} & \quad \text{CH}_2\text{Cl}_2 \\
\text{105} & \quad \text{4e} (99\%) 
\end{align*}
\]

Scheme 60. Preparation of ethyl imidate 4e.

The photochemical behavior of imidate 4e was next investigated. Direct irradiation in a quartz immersion well of a solution of imidate 4e in degassed hexane showed a very complex mixture of products containing only a small
amount (< 1%) of the 1,3-AS product, 6e, by GC-MS analysis. Examining the UV spectrum of imidate 4e, it can be seen that with a Pyrex filter (UV cutoff=290-330 nm) the “tail-end” of the imidate’s absorption can still be irradiated, thereby decreasing the energy absorbed. Indeed, irradiation in a Pyrex reaction vessel of a solution of imidate 4e in degassed hexane, showed a clean conversion of imidate 4e to β-lactam 6e with only these two compounds being present by GC analysis (Scheme 61). Longer reaction times led only to decomposition of the imidate and β-lactam 6e.

Scheme 61. Light-induced sigmatropic 1,3-acyl shift on imidate 4e.

However, imidate 4e was unresponsive to sensitized irradiation under a variety of triplet sensitizers, yielding only unreacted starting material. The triplet sensitizers used included benzene ($E_T=84$ kcal/mol), acetone ($E_T=78$ kcal/mol), and acetophenone ($E_T=74$ kcal/mol).\textsuperscript{42a} Analogous to the triflate
example, this indicated either the presence of a higher triplet energy for imidate 4e than that of the triplet sensitizer, or that imidate 4e was not electronically capable of undergoing the oxa-di-π-methane rearrangement.

**Synthesis and Photochemical Behavior of 2-Aza-3-Thioethoxybicyclo[2.2.2]oct-2-en-5-one. 4f**

To test the former hypothesis, the lowering of the triplet energy can be achieved through replacement of an oxygen atom with a sulfur. This phenomenon has been reported by Birks, an example of which is xanthone (E_T=74 kcal/mol) versus thioxanthone (E_T=65 kcal/mol) (Table 6). Alternatively, the imidate might be electronically unable to undergo rearrangement, and, in that case, replacement of the oxygen with sulfur should have little to no effect on the rearrangement.

Reaction of ketoamide 105 with Lawesson's reagent in HMPA at 100°C yielded thioamide 107 in good yield, as a very stable solid. The thioamide was then subjected to ethyl Meerwein's reagent in CH₂Cl₂ to give thioimidate 4f in near quantitative yield (Scheme 62).

The photochemical behavior of the thioimidate 4f showed similar results to the irradiation of imidate 4e. Direct irradiation in a quartz immersion well of a solution of thioimidate 4f in degassed hexane also showed a very complex
mixture of products. The UV spectrum of thioimidate 4f showed that absorption could occur through irradiation in Pyrex, as in the imidate example. Irradiation in Pyrex of a solution of thioimidate 4f in degassed hexane showed a clean conversion of thioimidate 4f to β-lactam 6f, with the remaining material being starting imidate 4f (Scheme 63). Longer reaction times led only to decomposition of the imidate and β-lactam.

Scheme 62. Preparation of ethyl thioimidate 4f.
The acetophenone \((E_T=74 \text{ kcal/mol})^{42a}\) sensitized irradiation of thioimidate 4f, in a quartz immersion well, yielded a similar degradation pattern to the direct irradiation results in quartz. This suggested that either the acetophenone is not acting as a suitable triplet sensitizer and direct irradiation to the singlet level is occurring, or more likely, that irradiation to the \(T_2\) level is occurring. The \(T_2\) level, as noted previously, is of the same electronic configuration \(\left(n,\pi^*\right)\) as the \(S_1\) energy level and therefore causes similar rearrangements in the irradiated molecule. To induce an ODPM rearrangement on thioimidate 4f, the sensitizer had to be changed to accommodate a lower triplet energy level. Due to the solubility of the various sensitizers used, acetone was used as the co-solvent.

\[
\text{EtS} \quad \xrightarrow{\text{hv}} \quad \text{EtS} \quad \text{hexanes}
\]

\(4f\)  
\(6f \ (40\%)\)

Scheme 63. Light-induced sigmatropic 1,3-acyl shift of thioimidate 4f.
Control studies on the irradiation of thioimidate 4f in acetone ($E_T=\sim 78$ kcal/mol) showed predictable results, i.e. degradation of the thioimidate similar to that of the direct irradiation. Irradiation, in a quartz immersion well, of thioimidate 4f in 5% benzophenone ($E_T=69$ kcal/mol)/acetone showed a complex mixture of benzophenone by-products which obscured any reaction that occurred with the thioimidate. Dilution of the benzophenone to 1% in acetone eliminated these by-products showing 20% of the starting thioimidate with the remainder of the material decomposing similarly to that of direct irradiation in quartz. Irradiation of the thioimidate in 1% naphthalene ($E_T=61$ kcal/mol)/acetone yielded 80% starting material with the remainder similar to that of direct irradiation in a quartz immersion well. Lastly, irradiation in a quartz immersion well, of thioimidate 4f in 1% benzil ($E_T=54$ kcal/mol)/acetone yielded only starting material with no other compounds being isolated.

These results indicate that a mixing of the energy levels, $T_2$ and $T_1$, occurs between 69 and 54 kcal/mol, with the $T_1$ level of thioimidate 4f lying near 54 kcal/mol. Additionally, due to the electronic similarities between the imidate and thioimidate, we can assume that if the thioimidate is electronically unable to rearrange then it is unlikely that the imidate will be electronically able to rearrange.
Future Work

In order to establish the electronic requirements for the ODPM rearrangement, a series of electronically differing imine systems will be irradiated. These will be grouped according to their reactivity and electronic nature in order to attempt to establish a pattern. The effects can also be studied in the direct irradiation as only electron rich imdates have been examined so far.

Conclusion

The formal syntheses of (-)-petasinecine, 7, (-)-isoretronacol, 8, (-)-trachelanthamidine, 9, and (-)-supinidine, 10, has been completed through the synthesis of the common intermediate, enol 60, in an overall yield of 10% over 17 steps as compared to the Rueger synthesis in which enol 60 was synthesized in an overall yield of 34% yield over 12 steps (Scheme 25).\(^7\)

In route to the synthesis of the above pyrrolizidine alkaloids, the unusual sensitivity of heptyl selenide \(^7\) to oxidation by perchloric acid was discovered. This effect was not seen when the methyl ester, \(^7\), was used. Additionally, it has been shown that the azabicyclic \(\beta,\gamma\) enone 1c undergoes ODPM rearrangement in the presence of sensitized light to yield the tricyclic photoprodut 2c. Also shown is the formation of the expected 1,3-AS product
3c and its subsequent reactions, depending upon the energy of light, to pyridine 78 and azabicyclooctanone 79. The thermal instability of the cyclopropyl ketone 2c has been examined through the thermal rearrangement of 2c to 79.

Cyclopropyl ring opening studies have shown that the aza version utilized above is unreactive towards the electrophilic-nucleophilic ring opening conditions used by Demuth.47,49,53 However, ring opening will occur under methyl cuprate and hydrogenolysis reaction conditions.

The synthesis of methyl imine 4a has been completed in a five step sequence in an overall yield of 12%, due to a very low yielding initial cyclization.

The synthesis of imidates 4c-f have been completed from the common intermediate, keto amide 105. These imidates have been subjected to sensitized irradiation with no ODPM rearrangement observed. Imidates 4e and 4f have also been subjected to direct irradiation to from β-lactams 6e and 6f in reasonable yields.
Purification of Cul:\(^{94}\): A 125 mL Erlenmeyer flask was charged with crude Cul (13.2 g, 69.2 mmol), KI (135 g, 813 mmol), decolorizing carbon (5 g), and \(\text{H}_2\text{O}\) (400 mL) and heated to reflux to dissolve the inorganics. The solution was filtered, the filtrate cooled to 0°C until a grey precipitate formed, and filtered to yield a grey solid (9.1 g). The precipitate was washed with \(\text{H}_2\text{O}\) (4 X 100 mL), acetone (4 X 80 mL), and \(\text{Et}_2\text{O}\) (4 X 80 mL) and dried under reduced pressure (16 h at room temperature then 4 h at 90°C) to yield a grey solid (8.21 g). The Cul was stored under argon in the dark until needed.

(Dimethylphenylsilyl)lithium:\(^{95}\): A 10 mL round bottomed flask was charged with lithium ribbon (0.0048 g, 0.69 mmol) and THF (5 mL). The mixture was cooled to 0°C and chlorodimethylphenyl silane (0.102 g, 0.60 mmol) was slowly added. The mixture was allowed to stir at 0°C for 18 h to yield a dark red solution which was 0.09 M by titration\(^{96}\) (82%).
Methyl 3-carboxypyridine-4-carboxylate (65): A 250 mL round-bottomed flask was charged with chinchomeronic acid, 63, (25.03 g, 0.15 mol) and acetic anhydride (100 mL). The mixture was stirred at reflux for 4 h. Acetic anhydride was then removed by distillation. The flask was then charged with methanol (100 mL) and stirred at reflux for 4.5 h. Methanol was then removed by distillation yielding a oily brown solid (27.54 g). Recrystallization of the solid in methanol yielded 65 as a brown solid (17.09 g, 0.094 mol, 63%), mp 170.2 - 172.4°C (Lit. mp 170-172°C\textsuperscript{73a}) (methanol).

\[
\begin{align*}
\text{CH}_3 & \\
8 & \text{O} \\
7 & \text{O} \\
5 & \text{N} \\
4 & \text{C} \\
9 & \text{OH} \\
\end{align*}
\]

\textsuperscript{1}H-NMR (DMSO-\textit{d}_6): 9.04 (s, 1H, H on C6), 8.88 (s, 1H, H on C2), 7.64 (s, 1H, H on C5), 3.86 (s, 3H, H on C8). \textsuperscript{13}C-NMR (DMSO-\textit{d}_6): 167.7 (C9), 166.9 (C7), 154.0 (C6), 151 (C2), 141.3 (C4), 126 (C3), 122.5 (C5), 53.8 (C8). Spectral data are consistent with literature values.\textsuperscript{73a}
Methyl 3-(Diethylcarbamoyl)pyridine-4-carboxylate (66): A 250 mL round-bottomed flask was charged with the ester-acid, 65, (15.17 g, 0.0837 mol) and CH₂Cl₂ (100 mL). This mixture was cooled to 0°C. To the stirred, cooled mixture was added dropwise a solution of oxalyl chloride (15.71 g, 0.124 mol). The mixture was stirred at 0°C for 2 h, at room temperature for 6 h, and at reflux for 16 h. The mixture was cooled to 0°C as diethylamine (19.09 g, 0.261 mol) was added dropwise. The mixture was stirred at 0°C for 1 h then at room temperature for 3 h. The mixture was cooled to 0°C, 10% Na₂CO₃ (100 mL) was added, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (4 X 50 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield a black oil (20.2 g). Column chromatography (2% MeOH/CH₂Cl₂) yielded 66 as a yellow oil (Rₜ=0.28, 2% MeOH/CH₂Cl₂), (18.92 g, 0.0801 mol, 96%).
$^1$H-NMR (CDCl$_3$): 8.71 (d, 1H, $J=5.1$ Hz, H on C6), 8.58 (s, 1H, H on C2), 7.78 (d, 1H, $J=5.0$ Hz, H on C5), 3.86 (s, 3H, H's on C8), 3.55 (q, 2H, $J=7.1$ Hz, H's on C10 or C12), 3.08 (q, 2H, $J=7.1$ Hz, H's on C12 or C10), 1.25 (t, 3H, $J=7.1$ Hz, H's on C11 or C13), 1.02 (t, 3H, $J=7.1$ Hz, H's on C13 or C11). $^{13}$C-NMR (CDCl$_3$): 167.4 (C7), 164.8 (C9), 150.3 (C2), 148.0 (C6), 134.4 (C3), 132.9 (C4), 123.3 (C5), 52.7 (C8), 42.9 (C10 or C12), 39.0 (C12 or C10), 13.6 (C11 or C13), 12.3 (C13 or C11). GC: Rt=22.6 min. MS: 236 (8), 235 (40), 203 (10), 177 (5), 164 (100), 136 (15), 93 (15), 78 (40), 72 (35), 50 (15). Spectral data are consistent with literature values. $^{73c}$

cis-Methyl-3-(Diethylcarbamoyl)-1-(methoxycarbonylmethyl)piperidine-4-carboxylate (62): A 50 mL round-bottomed flask was charged with piperidine 67, (5.43 g, 0.022 mol), methyl bromoacetate (4.36 g, 0.029 mol), K$_2$CO$_3$ (6.93 g, 0.050 mol), and toluene (20 mL). After stirring at 80°C for 6 h, the reaction was quenched with H$_2$O (50 mL). The layers were separated and the aqueous layer was washed with CH$_2$Cl$_2$ (4 X 30 mL). The organic washes were combined, dried over MgSO$_4$, and the solvent was removed under reduced pressure to yield a brown oil (7.80 g). Column
chromatography (2% MeOH/CH₂Cl₂) yielded 62 as a yellow oil (Rt=0.33, 3% MeOH/CH₂Cl₂), (6.56 g, 0.021 mol, 92%).

![Molecule Diagram]

¹H-NMR (CDCl₃): 3.67 (s, 3H, H's on C9 or C16), 3.62 (s, 3H, H's on Cl6 or C9), 3.42-3.14 (m, 6H, H's on C2, C11, and C13), 3.00-2.60 (m, 6H, H's on C5, C6, and C7), 2.23 (ddd, 1H, J=13.2, 8.2, 4.1 Hz, H on C3), 1.93 (ddd, 1H, J=13.2, 8.8, 4.5 Hz, H on C4), 1.19 (t, 3H, J=7.2 Hz, H's on C12 or C14), 1.06 (t, 3H, J=6.9 Hz, H's on C14 or C12). ¹³C-NMR (CDCl₃): 174.0 (C8 or C15), 171.1 (C15 or C8), 17.8 (C10), 59.3 (C7), 52.6 (C2), 51.6 (C9 or C16), 51.5 (C16 or C9), 50.4 (C3), 41.7 (C11 or C13), 40.4 (C13 or C11), 39.7 (C4 and C6), 26.0 (C5), 14.5 (C12 or C14), 12.9 (C14 or C12). GC: Rt=25.6 min. MS: 314 (12), 283 (130, 255 (100), 214 (18), 182 (5), 154 (55), 126 (5), 86 (22), 72 (24), 55 (20). Spectral data are consistent with literature values.⁷³c
cis-Methyl 3-(Diethylcarbamoyl)pyridine-4-carboxylate (67): A 250 mL flask was charged with ester-amide 66 (6.85 g, 0.029 mol), Et$_2$O (25 mL), and HCl:Et$_2$O (200 mL, 1.0 M). The mixture was allowed to stir for 3 h, the solvent was removed via cannula and reduced pressure to yield the pyridine salt, 66$\cdot$HCl, (7.84 g, 0.029 mol). The salt in methanol (60 mL) was transferred to a 250 mL Parr pressure vessel which was charged with PtO$_2$ (0.165 g, 0.73 mmol). The pressure vessel was charged to 300 psi and purged this was repeated three times. The pressure vessel was charged to 400 psi and heated to 100°C. After stirring at 100°C, 400 psi for 18 h, the mixture was filtered through celite. The methanol washings were combined and concentrated under reduced pressure to yield a brown oil (6.91 g). The oil was diluted in H$_2$O (100 mL), sat K$_2$CO$_3$ (100 mL), and CH$_2$Cl$_2$ (100 mL). The layers were separated and the aqueous layer was washed with CH$_2$Cl$_2$ (4 X 60 mL). The organic washes were combined, dried over MgSO$_4$, and the solvent was removed under reduced pressure to yield 67 as a brown oil (6.56 g, 0.027 mol, 94%), which was > 95% pure by spectroscopy.
N-(methyl ethionate)-methyl 3-(Diethylcarbamoyl)-4-carboxylate pyridinium bromide (69): A 25 mL round-bottomed flask was charged with ester-amide 66 (0.66 g, 2.79 mmol), methyl bromoacetate (0.27 mL, 2.85 mmol), and MeOH (15 mL). After stirring at reflux for 72 h, solvent was removed under reduced pressure to yield an oily brown solid (1.2 g). Recrystalization in
iPrOH yielded 69 as a pale brown solid (0.65 g, 1.67 mmol, 60%), mp 130.2-130.9°C (dec), (Lit. mp 129-130 (dec)\(^{73b}\)) (iPrOH).

\[
\begin{align*}
\text{1H-NMR (CDCl}_3\text{):} & \quad 9.87 (d, 1H, J=8.0 \text{ Hz, } H \text{ on C6}), 9.56 (s, 1H, H \text{ on C2}), 8.43 (d, 1H, J=6.2 \text{ Hz, } H \text{ on C3}), 6.48 (s, 2H, H's \text{ on C7}), 3.96 (s, 3H, H's \text{ on C9}), 3.78 (s, 3H, H's \text{ on C16}), 3.52 (q, 2H, J=7.1 \text{ Hz, } H's \text{ on C11 or C13}), 3.25 (q, 2H, J=7.1 \text{ Hz, } H's \text{ on C13 or C11}), 1.25 (t, 3H, J=7.1 \text{ Hz, } H's \text{ on C12 or C14}), 1.13 (t, 3H, J=7.1 \text{ Hz, } H's \text{ on C14 or C12}).
\end{align*}
\]

\[
\begin{align*}
\text{13C-NMR (CDCl}_3\text{):} & \quad 165.7 (C8), 162.2 (C15), 161.8 (C10), 147.8 (C6), 145.3 (C2), 142.7 (C3), 137.0 (C4), 128.1 (C5), 61.4 (C7), 54.1 (C9 or C16), 53.9 (C16 or C9), 43.9 (C11 or C13), 40.0 (C13 or C11), 13.7 (C12 or C14), 12.2 (C14 or C12).
\end{align*}
\]

Spectral data are consistent with literature values.\(^{73b}\)
1-Aza-5,5-dimethoxy-3-methoxycarbonylbicyclo[2.2.2]octane (61a):
A 250 mL 3-necked round bottomed flask was charged with freshly scraped potassium metal (2.88 g, 73.7 mmol) and toluene (45 mL), and heated to reflux. To the refluxing mixture was added t-butanol (5.58 g, 75.3 mmol) in toluene (5 mL) and the mixture was allowed to stir at reflux for 3.5 h. The piperidine, 62, (3.62 g, 11.5 mmol) in toluene (30 mL) was then added by syringe pump over 135 min. The mixture was stirred at reflux for 8 h and then cooled to 0°C as the mixture was slowly decomposed with concentrated HCl (70 mL). The layers were separated and the organic layer was washed with concentrated HCl (3 X 30 mL). The acid layers were combined, stirred at reflux for 24 h, and then the solvent was removed under reduced pressure to yield an oily black solid (4.21 g). The solid was washed with methanol (10 X 3 mL) yielding a white solid (KCl). The methanol washings were combined, the solvent was removed under reduced pressure, and dried under high vacuum at 70°C for 19 h to yield a brown solid (3.36 g). The solid in methanol (40 mL) was added to a refluxing mixture of trimethyl orthoformate (7.76 g, 73.1 mol), thionyl chloride (9.62 g, 80.9 mol), and methanol (30 mL) and stirred at reflux for 68 h. The mixture was cooled to 0°C and quenched with saturated K₂CO₃ (50 mL). The layers were separated and the aqueous layer was washed with CH₂Cl₂ (4 X 50 mL). The organic washes were combined, dried with MgSO₄, and the solvent was
removed under reduced pressure to yield a black oil (2.82 g). Column chromatography (1% NEt₃/2.5% MeOH/CH₂Cl₂) yielded a brown oil, 61a, as a 1:1 mixture of diastereomers (Rᵣ=0.46, 1% NEt₃/2.5% MeOH/CH₂Cl₂) (Rᵣ=0.24, 1% NEt₃/2.5% MeOH/CH₂Cl₂) both of which were further purified by bulb-to-bulb distillation (90-100°C/0.5 mm Hg) to yield 61a as a colorless oil (Rᵣ=0.46, 0.72 g, 3.14 mmol, 27%), (Rᵣ=0.24, 0.84 g, 3.66 mmol, 32%).

exo isomer:

¹H-NMR (CDCl₃): 3.61 (s, 3H, H's on C12), 3.36 (ddd, 1H, J=12.4, 5.3, 2.1 Hz, H on C3), 3.11 (s, 3H, H's on C9 or C10), 2.99 (s, 3H, H's on C10 or C9), 2.92-2.60 (m, 6H, H's on C2, C6, and C7), 2.44 (ddd, 1H, J=13.3, 6.2, 2.8 Hz, H on C4), 1.75 (dddd, 1H, J= 16.0, 11.2, 9.8, 2.8 Hz, H on C8), 1.42 (dddd, 1H, J= 15.9, 10.1, 6.5, 2.7 Hz, H on C8). ¹³C-NMR (CDCl₃): 174.2 (C11), 99.6 (C5), 58.8 (C6), 51.8 (C12), 48.8 (C10 or C9), 48.3 (C2), 47.7 (C9 or C10), 46.3 (C7), 39.7 (C3), 22.5 (C8). GC: Rt=18.3 min. MS: 229 (4), 214 (100), 198 (25), 166
(16), 139 (12), 96 (14), 55 (14). Spectral data are consistent with literature values.\textsuperscript{73c}

\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

\textbf{endo isomer:}

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 3.65 (s, 3H, H's on C12), 3.36 (ddd, 1H, J=12.4, 5.3, 2.1 Hz, H on C3), 3.15 (s, 3H, H's on C9 or C10), 2.99 (s, 3H, H's on C10 or C9), 2.92-2.60 (m, 6H, H's on C2, C6, and C7), 2.44 (ddd, 1H, J=13.3, 6.2, 2.8 Hz, H on C4), 1.75 (dddd, 1H, J= 16.0, 11.2, 9.8, 2.8 Hz, H on C8), 1.42 (ddddd, 1H, J= 15.9, 10.1, 6.5, 2.7 Hz, H on C8). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): 174.2 (C11), 99.6 (C5), 58.2 (C6), 51.7 (C12), 48.6 (C10 or C9), 48.0 (C2), 47.7 (C9 or C10), 45.9 (C7), 37.2 (C3), 22.5 (C8). GC: Rt=18.5 min. MS: 229 (4), 214 (100), 198 (25), 166 (16), 139 (12), 96 (14), 55 (14). Spectral data are consistent with literature values.\textsuperscript{73c}
1-Aza-5,5-dimethoxy-3-ethoxycarbonylbicyclo[2.2.2]octane (61b): A 100 mL round-bottomed flask was charged with the ketal, 61a, (0.621 g, 2.71 mmol), KCN (0.089 g, 1.36 mmol), and dry ethanol (40 mL). After stirring at 80°C for 72 h, the solvent was removed under reduced pressure to yield an orange oil (0.72 g). The oil was diluted in H₂O (40 mL) and CH₂Cl₂ (30 mL). The layers were separated and the aqueous layer was washed with CH₂Cl₂ (4 X 30 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield a yellow oil (0.69 g). Column chromatography (1% NEt₃/2% MeOH/CH₂Cl₂), yielded 61b as a pale yellow oil as a 1:1 mixture of diastereomers (Rf=0.36, 1% NEt₃/2% MeOH/CH₂Cl₂), (0.263 g, 1.08 mmol, 40%), (Rf=0.29, 1% NEt₃/2% MeOH/CH₂Cl₂), (0.270 g, 1.11 mmol, 41%).
exo isomer:

$^1$H-NMR (CDCl$_3$): 4.10 (q, 2H, $J=7.1$ Hz, H's on C12), 3.32 (dd, 1H, $J=7.0$, 2.9 Hz, H on C3), 3.19 (s, 3H, H's on C9 or C10), 3.11 (s, 3H, H's on C10 or C9), 3.02-2.62 (m, 6H, H's on C2, C6, and C7), 2.45 (dd, 1H, $J=4.2$, 2.9 Hz, H on C4), 1.65-1.56 (m, 2H, H's on C8), 1.18 (t, 3H, $J=7.1$ Hz, H's on C13).  $^{13}$C-NMR (CDCl$_3$): 174.2 (C11), 100.3 (C5), 60.5 (C12), 58.9 (C2), 48.8 (C10), 48.5 (C6), 48.1 (C9), 46.3 (C7), 39.7 (C3), 32.0 (C4), 22.5 (C8), 14.2 (C13). HRMS calculated for C$_{12}$H$_{21}$NO$_4$: 243.147058, found: 243.146571. GC: Rt=20.0 min. MS: 243 (2), 228 (100), 212 (12), 200 (20), 182 (2), 166 (10), 96 (14), 55 (13). IR (NaCl, cm$^{-1}$): 2941, 2850, 1729, 1436, 1363, 1122, 1035.

endo isomer:

$^1$H-NMR (CDCl$_3$): 4.08 (q, 2H, $J=7.1$ Hz, H's on C12), 3.29 (dd, 1H, $J=7.0$, 2.9 Hz, H on C3), 3.19 (s, 3H, H's on C9 or C10), 3.04 (s, 3H, H's on C10 or C9), 3.08-2.72 (m, 6H, H's on C2, C6, and C7), 2.45 (dd, 1H, $J=4.2$, 2.9 Hz, H on C4),
1.65-1.56 (m, 2H, H’s on C8), 1.18 (t, 3H, J=7.1 Hz, H’s on C13). $^{13}$C-NMR (CDCl$_3$): 173.6 (C11), 99.7 (C5), 60.2 (C12), 58.1 (C2), 48.6 (C10), 48.3 (C6), 47.5 (C9), 45.9 (C7), 39.6 (C3), 31.9 (C4), 22.5 (C8), 14.0 (C13). HRMS calculated for C$_{12}$H$_{21}$NO$_4$: 243.147058, found: 243.146591. GC: Rt=20.1 min. MS: 243 (2), 228 (100), 212 (12), 200 (20), 182 (2), 166 (10), 96 (14), 55 (13). IR (NaCl, cm$^{-1}$): 2941, 2872, 1728, 1436, 1362, 1122, 1035.

1-Aza-5,5-dimethoxy-3-heptoxycarbonylbicyclo[2.2.2]octane (61c):

A 100 mL round-bottomed flask was charged with the ketal, 61a, (1.50 g, 6.56 mmol), KCN (0.3583 g, 5.50 mmol), and heptanol (40 mL). After stirring at 130°C for 40 h, the solvent was removed under reduced pressure to yield an orange oil (2.22 g). The oil was diluted in H$_2$O (30 mL) and CH$_2$Cl$_2$ (30 mL). The layers were separated and the aqueous layer was washed with CH$_2$Cl$_2$ (4 X 30 mL). The organic washes were combined, dried with MgSO$_4$, and the solvent was removed under reduced pressure to yield a yellow oil (2.07 g). Column chromatography (1% NEt$_3$/2% MeOH/CH$_2$Cl$_2$), yielded 61c as a pale yellow oil as a 1:1 mixture of diastereomers ($R_f$=0.33, 1% NEt$_3$/2% MeOH/CH$_2$Cl$_2$), (0.97 g, 3.10 mmol, 47%), ($R_f$=0.28, 1% NEt$_3$/2% MeOH/CH$_2$Cl$_2$), (0.93 g, 2.97 mmol, 45%).
exo isomer:

$^1$H-NMR (CDCl$_3$): 4.10 (t, 2H, $J=5.9$ Hz, H's on C12), 3.34 (dd, 1H, $J=4.6$, 2.9 Hz, H on C3), 3.19 (s, 6H, H's on C9 and C10), 3.02-2.62 (m, 6H, H's on C2, C6, and C7), 2.45 (dd, 1H, $J=4.2$, 2.9 Hz, H on C4), 1.65-1.56 (m, 3H, H's on C8 and C13), 1.34-1.22 (m, 8H, H's on C14, C15, C16, and C17), 0.85 (t, 3H, $J=7.0$ Hz, H's on C18). $^{13}$C-NMR (CDCl$_3$): 174.8 (C11), 100.9 (C5), 65.2 (C12), 59.3 (C2), 49.4 (C10), 48.8 (C6), 48.7 (C9), 46.8 (C7), 37.8 (C3), 32.0 (C4), 31.9 (C13), 29.5 (C14), 29.1 (C15), 26.4 (C16), 22.9 (C8), 18.3 (C17), 14.4 (C18).

HRMS calculated for C$_{17}$H$_{31}$NO$_4$: 313.225309, found: 313.224571. GC: Rt=24.8 min. MS: 313 (2), 298 (100), 281 (15), 252 (12), 200 (28), 184 (9), 166 (10), 138 (26), 111 (13), 96 (14), 55 (13). IR (NaCl, cm$^{-1}$): 2933, 2857, 1723, 1466, 1362, 1312, 1190, 1122, 1035, 910, 732.
endo isomer:

$^1$H-NMR (CDCl$_3$): 4.08 (t, 2H, $J$=5.9 Hz, H's on C12), 3.19 (s, 6H, H's on C9 and C10), 3.11 (dd, 1H, $J$=18.2, 4.6 Hz, H on C3), 3.02-2.62 (m, 6H, H's on C2, C6, and C7), 2.43 (dd, 1H, $J$=4.2, 2.9 Hz, H on C4), 1.65-1.56 (m, 3H, H's on C8 and C13), 1.34-1.22 (m, 8H, H's on C14, C15, C16, and C17), 0.85 (t, 3H, $J$=7.0 Hz, H's on C18). $^{13}$C-NMR (CDCl$_3$): 174.8 (C11), 100.9 (C5), 65.0 (C12), 58.7 (C2), 49.1 (C10), 48.7 (C6), 46.5 (C9), 46.8 (C7), 40.3 (C3), 32.1 (C4), 31.9 (C13), 29.5 (C14), 29.1 (C15), 26.3 (C16), 22.9 (C8), 18.3 (C17), 14.4 (C18). HRMS calculated for C$_{17}$H$_{31}$NO$_4$: 313.225309, found: 313.224571. GC: Rt=24.4 min.

MS: 313 (2), 298 (100), 281 (15), 252 (12), 200 (28), 184 (9), 166 (10), 138 (26), 111 (13), 96 (14), 55 (13). IR (NaCl, cm$^{-1}$): 2933, 2857, 1723, 1466, 1362, 1312, 1190, 1122, 1035, 910, 732.

1-Aza-5,5-dimethoxy-3-methoxycarbonyl-3-phenylselenyl-bicyclo[2.2.2]octane (73a): A 50 mL round-bottomed flask was charged
with diisopropyl amine (0.722 g, 7.14 mmol) and THF (10 mL). The flask was cooled to 0°C as n-butyllithium (6.5 mL, 1.1 M in hexanes) was added. After stirring at 0°C for 45 min, ketal 61a (0.692 g, 3.02 mmol) in THF (10 mL) was added by syringe pump over 90 min and allowed to stir at 0°C for 1 h. The flask was charged with phenylselenyl chloride (0.675 g, 3.53 mmol) in THF (10 mL) and allowed to slowly warm to room temperature. After stirring at room temperature for 13 h the mixture was quenched with H₂O (40 mL). The layers were separated and the aqueous layer was washed with Et₂O (3 X 20 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield an orange oil (1.25 g). Column chromatography (1% NEt₃/Et₂O), yielded 73a as a pale yellow oil as a single diastereomer (Rₜ=0.25, 1% NEt₃/Et₂O), (0.638 g, 1.66 mmol, 55%).
$^1$H-NMR (CDCl$_3$): 7.48 (d, 2H, $J$=6.8 Hz, H's on C14 and C18), 7.28-7.06 (m, 3H, H's on C15, C16, and C17), 3.76-3.41 (m, 1H, H on C4), 3.38 (s, 3H, H's on C12), 3.06 (s, 3H, H's on C9 or C10), 2.89 (s, 3H, H's on C10 or C9), 3.21-2.50 (m, 6H, H's on C2, C6, and C7), 2.21-2.05 (m, 1H, H on C8), 1.80-1.64 (m, 1H, H on C8). $^{13}$C-NMR (CDCl$_3$): 173.8 (C11), 137.8 (C14 and C18), 129.1 (C15 and C17), 128.9 (C16), 128.0 (C13), 101.6 (C5), 57.8 (C6), 56.9 (C2), 51.9 (C3), 49.8 (C9, C10, or C12), 49.1 (C10, C12, or C9), 48.3 (C12, C9, or C10), 46.0 (C7), 36.2 (C4), 19.7 (C8). HRMS calculated for C$_{17}$H$_{23}$NO$_4$Se$_7^6$: 382.074543, found: 382.076521. GC: Rt=26.6 min. MS: 385 (6), 370 (25), 354 (12), 228 (100), 212 (15), 196 (17), 154 (62), 101 (11), 77 (19), 51 (14). IR (NaCl, cm$^{-1}$): 3055, 2959, 2873, 1728, 1639, 1438, 1260, 1120, 802, 736.

1-Aza-5,5-dimethoxy-3-heptoxycarbonyl-3-phenylselenyl-bicyclo[2.2.2]octane (73c): A 50 mL round-bottomed flask was charged with diisopropyl amine (0.40 g, 3.92 mmol) and THF (10 mL). The flask was cooled to 0°C as n-butyllithium (2.8 mL, 1.4 M in hexanes) was added. After stirring at 0°C for 45 min, ketal 61c (0.488 g, 1.56 mmol) in THF (10 mL) was added by syringe pump over 90 min and allowed to stir at 0°C for 1 h. The flask was charged with phenylselenyl chloride (0.861 g, 4.50 mmol) in THF (10 mL) and allowed to slowly warm to room temperature. After stirring at room temperature for 13 h the mixture was quenched with H$_2$O (40 mL). The layers
were separated and the aqueous layer was washed with Et$_2$O (3 X 20 mL). The organic washes were combined, dried with MgSO$_4$, and the solvent was removed under reduced pressure to yield an orange oil (0.92 g). Column chromatography (1% NEt$_3$/Et$_2$O), yielded 73c as a pale yellow oil as a single diastereomer (R$_f$=0.30, 1% NEt$_3$/Et$_2$O), (0.391 g, 0.83 mmol, 53%).

$^1$H-NMR (CDCl$_3$): 7.54 (d, 2H, J=7.1 Hz, H's on C20 and C24), 7.38-7.24 (m, 3H, H's on C21, C22, and C23), 4.05-3.54 (m, 3H, H's on C4 and C12), 3.12 (s, 3H, H's on C9 or C10), 2.98 (s, 3H, H's on C10 or C9), 3.42-2.50 (m, 6H, H's on C2, C6, and C7), 2.31-2.14 (m, 1H, H on C8), 1.90-1.76 (m, 1H, H on C8), 1.42-1.34 (m, 2H, H's on C13), 1.28-1.14 (m, 8H, H's on C14, C15, C16, and C17), 0.85 (t, 3H, J=7.0 Hz, H's on C18). $^{13}$C-NMR (CDCl$_3$): 173.3 (C11), 137.2 (C20 and C24), 129.0 (C22), 128.7 (C21 and C23), 101.3 (C5), 64.6 (C12), 57.4 (C6),
56.2 (C2), 48.7 (C9 or C10), 47.6 (C3), 45.5 (C10 or C9), 35.4 (C4), 31.7 (C13), 28.8 (C14), 25.8 (C15), 22.5 (C16), 19.2 (C17), 14.0 (C18). HRMS calculated for \( \text{C}_{23}\text{H}_{36}\text{NO}_{4}\text{Se}\): 465.178496, found: 465.177582. MS: 467 (1), 437 (7), 388 (8), 335 (7), 312 (28), 280 (53), 261 (100), 246 (39), 214 (22), 166 (49), 154 (81), 138 (31), 77 (63). IR (NaCl, cm\(^{-1}\)): 3054, 2968, 2872, 1723, 1639, 1466, 1382, 1206, 1124, 1070, 910, 732.

1-Aza-3-heptoxycarbonylbicyclo[2.2.2]oct-2-en-5-one (1c, \( R=\text{C}_7\text{H}_{15} \)): A 25 mL round-bottomed flask was charged with selenide 73c (0.264 g, 0.56 mmol) and CH\(_2\)Cl\(_2\) (7 mL). The flask was cooled to 0\(^\circ\)C as HClO\(_4\) (7 mL, 70%) was slowly added, the stirring mixture was then slowly warmed to room temperature. After stirring for 90 min at room temperature, the mixture was poured into 10% Na\(_2\)CO\(_3\) (20 mL) and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 \times 30 mL). The organic washes were combined, dried with MgSO\(_4\), and the solvent was removed under reduced pressure to yield a black oil (0.32 g). Column chromatography (1% NEt\(_3\)/Et\(_2\)O) yielded 1c as a pale yellow oil (\( R_f =0.35\), 1% NEt\(_3\)/Et\(_2\)O), (0.137 g, 0.52 mmol, 93%).
$^1$H-NMR (CDCl$_3$): 7.51 (d, 1H, $J$=1.2 Hz, H on C2), 4.16 (t, 2H, $J$=6.5 Hz, H's on C10), 3.80-3.75 (m, 1H, H on C4), 3.29-2.95 (m, 3H, H's on C6, C7), 2.78 (dddd, 1H, $J$=14.2, 9.3, 5.1, 2.4 Hz, H on C8), 2.15 (dddd, 1H, $J$=14.1, 7.5, 5.2, 2.4 Hz, H on C8), 1.95 (ddd, 1H, $J$=18.1, 9.5, 4.4 Hz, H on C7), 1.66 (app pent, 2H, $J$=7.0 Hz, H's on C11), 1.42-1.16 (m, 8H, H's on C12, C13, C14, C15), 0.89-0.83 (t, 3H, $J$=6.5 Hz, H's on C16). $^{13}$C-NMR (CDCl$_3$): 209.0 (C5), 154.0 (C9), 137.4 (C2), 129.2 (C3), 65.4 (C6), 58.1 (C10), 47.7 (C7), 44.7 (C4), 31.7 (C11), 28.9 (C12), 28.5 (C13), 26.4 (C14), 25.9 (C15), 22.6 (C8), 14.0 (C16). HRMS calculated for C$_{15}$H$_{23}$NO$_3$: 265.167794, found: 265.167694. GC: Rt=23.8 min. MS: 266 (1), 237 (85), 208 (10), 194 (18), 150 (20), 140 (42), 122 (26), 95 (100), 67 (40), 55 (35). IR (NaCl, cm$^{-1}$): 2926, 1735, 1719, 1618, 1466, 1300, 1262, 1092, 910, 733. UV: $\lambda_{max}$=204 (log $\varepsilon$=3.24), 218 (log $\varepsilon$=3.40), 260 (log $\varepsilon$=2.68), 300 (log $\varepsilon$=2.20).
Heptyl 3-carboxypyridine (78): A 100 mL cone flask was charged with enone 1c (0.0254 g, 0.094 mmol) and hexane (50 mL). The mixture was transferred to an immersion photowell and irradiated with a Hanovia medium pressure 450 W lamp, equipped with a vycor filter and quartz cooling jacket, for 40 h. The solvent was removed under reduced pressure to yield an orange oil (0.1 g). Column chromatography (1% NEt₃/Et₂O) yielded 78 as a pale yellow oil (Rf=0.16, 1% NEt₃/Et₂O), (0.0062 g, 0.028 mmol, 30%).

\[ \text{\begin{center} \includegraphics[width=0.5\textwidth]{structure.png} \end{center}} \]

\(^1\)H-NMR (CDCl₃): 9.12 (d, 1H, J=1.3 Hz, H on C2), 8.65 (dd, 1H, J=4.7, 1.5 Hz, H on C4), 8.18 (dt, 1H, J=7.9, 1.8 Hz, H on C6), 7.28 (dd, 1H, J=7.9, 4.8 Hz, H on C5), 4.24 (t, 2H, J=6.7 Hz, H's on C8), 1.67 (app pent, 2H, J=6.8 Hz, H's on C9), 1.40-1.12 (m, 8H, H's on C10, C11, C12, and C13), 0.77 (t, 3H, J=6.7 Hz, H's on C14). \(^{13}\)C-NMR (CDCl₃): 165.1 (C7), 153.1 (C2), 150.7 (C6), 136.8 (C4), 126.2 (C3), 123.0 (C5), 63.4 (C8), 31.5 (C9), 28.7 (C10), 28.5 (C11), 25.8 (C12), 22.4 (C13), 13.8 (C14). HRMS calculated for C₁₃H₂₀NO₂: 222.149404 (M+H⁺),
found: 222.149902. GC: Rt=21.2 min. MS: 221 (1), 220 (5), 178 (8), 164 (12), 124 (100), 106 (70), 78 (45), 51 (17). IR (NaCl, cm\(^{-1}\)): 2956, 2929, 1725, 1591, 1468, 1419, 1283, 1113, 1024, 741.

1-Aza-5-heptoxycarbonylcylooct-5-ene-3-one (79):

Photolytic Preparation: A 50 mL cone flask was charged with enone 1c (0.0754 g, 0.28 mmol) and hexane (40 mL). The mixture was transferred to an immersion photowell and irradiated with a Hanovia medium pressure 450 W lamp, equipped with a quartz cooling jacket, for 20 h. The solvent was removed under reduced pressure to yield an orange oil (0.1 g). Column chromatography (1% NEt\(_3\)/2% MeOH/CH\(_2\)Cl\(_2\)) yielded 79 as a pale yellow oil (R\(_f\)=0.10, 1% NEt\(_3\)/2% MeOH/CH\(_2\)Cl\(_2\)), (0.038 g, 0.14 mmol, 50%) and enone 1c (R\(_f\)=0.35, 1% NEt\(_3\)/Et\(_2\)O), (0.034 g, 0.13 mmol, 49%).

Thermal Preparation: A 5 mL cone vial was charged with photoproduct 2c (0.030 g, 0.11 mmol) and acetophenone (1 mL). The mixture was heated to 55°C. After stirring at 55°C for 6 h, the solvent was removed under reduced pressure to yield an orange oil (0.45 g). Column chromatography (1% NEt\(_3\)/2% MeOH/CH\(_2\)Cl\(_2\)) yielded 79 as a pale yellow oil (R\(_f\)=0.10, 1% NEt\(_3\)/2% MeOH/CH\(_2\)Cl\(_2\)), (0.016 g, 0.060 mmol, 53%).
\begin{align*}
^1\text{H-NMR (CDCl}_3\text{):} & \ 5.65 (bs, 1H, H on N), 5.40-5.24 (m, 1H, H on C6), 4.06 (t, 2H, H's on C10), 3.38-3.10 (m, 2H, H's on C2), 3.09-2.97 (m, 4H, H's on C4 and C8), 2.94-2.83 (m, 2H H's on C7), 1.72-1.49 (m, 2H, H's on C10), 1.47-1.15 (m, 10H, H's on C11, C12, C13, C14, and C15), 0.86 (t, 3H, J=7.2 Hz, H's on C16). \\
^13\text{C-NMR (CDCl}_3\text{):} & \ 205.4 (C3), 166.8 (C9), 135.5 (C5), 124.3 (C6), 66.9 (C2), 61.5 (C10), 50.7 (C8), 32.1 (C4), 31.2 (C7), 29.6 (C8), 28.5 (C11), 25.1 (C12), 24.8 (C13), 21.8 (C14), 17.3 (C15), 13.1 (C16). \ HRMS \ calculated \ for \ C_{15}H_{26}NO_3: \ 268.191269, \ found: \ 268.190872. \ GC: \ Rt=23.3 \ min. \ MS: \ 267 (2), 239 (15), 210 (5), 196 (7), 152 (5), 96 (100), 82 (7), 55 (10). \ IR (NaCl, cm^{-1}): 3408, 3012, 2929, 2857, 1740, 1732, 1467, 1261, 1095, 909, 736.
\end{align*}

\textbf{1-Aza-4-heptoxycarbonyl[tricyclo[3.3.0.0^{4,6}]octan-3-one (2c):} \ An 100 mL cone flask was charged with enone 1c (0.168 g, 0.63 mmol), acetophenone
(3 mL), and acetone (60 mL). The mixture was frozen under vacuum and then thawed under argon. This degassing process was repeated three times. The mixture was then irradiated in an immersion photowell with a Hanovia medium pressure 450 W lamp, equipped with a quartz cooling jacket for 20 h. The solvent was removed under reduced pressure to yield an orange oil (0.19 g). Column chromatography (1% NEt$_3$/Et$_2$O) yielded 2c as a pale yellow oil ($R_f$=0.24, 1% NEt$_3$/Et$_2$O), (0.117 g, 0.44 mmol, 70%) and enone 1c ($R_f$=0.35, 1% NEt$_3$/Et$_2$O), (0.047 g, 0.18 mmol, 27%).

$^1$H-NMR (CDCl$_3$): 4.15 (d, 1H, $J$=4.8 Hz, H on C5), 4.09 (t, 2H, $J$=6.7 Hz, H's on C10), 3.60 (d, 1H, $J$=17.7 Hz, H on C2$\alpha$ or $\beta$), 3.29 (dt, 1H, $J$=8.1, 11.1 Hz, H on C8$\alpha$), 3.00 (dt, 1H, $J$=1.1, 7.2 Hz, H on C6), 2.80 (d, 1H, $J$=17.7 Hz, H on C2$\beta$ or $\alpha$), 2.75 (dd, 1H, $J$=6.5, 12.3 Hz, H on C8$\beta$), 2.33-2.08 (m, 1H, H on C7$\beta$), 1.94 (dddd, 1H, $J$=1.7, 6.5, 9.3, 17.8 Hz, H on C7$\alpha$), 1.68-1.56 (m, 2H, H's on C11),
1.37-1.20 (m, 8H, H's on C12, C13, C14, and C15), 0.86 (t, 3H, J=6.0 Hz, H's on C16). $^{13}$C-NMR (CDCl$_3$): 207.4 (C3), 165.9 (C9), 68.3 (C2), 65.7 (C8), 64.0 (C10), 63.0 (C5), 48.2 (C4), 42.7 (C6), 31.6 (C11), 28.8 (C12), 28.4 (C13), 26.1 (C7), 25.7 (C14), 22.5 (C15), 14.0 (C16). HRMS calculated for C$_{15}$H$_{23}$NO$_3$: 265.167794, found: 265.167000. GC: Rt=23.4 min. MS: 265 (21), 236 (25), 222 (15), 208 (8), 194 (13), 181 (14), 166 (34), 149 (28), 139 (60), 122 (54), 111 (15), 95 (75), 82 (100), 67 (36), 55 (44). IR (NaCl, cm$^{-1}$): 2928, 2856, 1744, 1716, 1458, 1354, 1256, 1235, 1142, 1041, 810. UV: $\lambda_{max}$=204 (log $\varepsilon$=3.20), 214 (log $\varepsilon$=3.40), 262 (log $\varepsilon$=2.74).

5-Aza-8-methyl-2-heptoxycarbonylbicyclo[3.3.0]oct-2-ene-3-ol (90):
A 25 mL round-bottomed flask was charged with Cul (0.030 g, 0.16 mmol) and Et$_2$O (7 mL) and cooled to 0°C. After stirring at 0°C for 15 min, MeLi (0.40 mL, 0.85 M) in Et$_2$O (3 mL) was added by syringe pump over a period of 60 min. After stirring at 0°C for 2 h, tricyclic amine 2c (0.0207 g, 0.078 mmol) in Et$_2$O (5 mL) was added by syringe pump over a period of 60 min. After stirring at 0°C for 16 h the mixture was poured into 10% HCl (20 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 X 10 mL). The organic washes were combined, dried with MgSO$_4$, and the solvent was removed under reduced pressure to yield an orange oil (0.028 g). Column
chromatography (3% MeOH/CH₂Cl₂) yielded 90 as a colorless oil (Rᵋ=0.08 3% MeOH/CH₂Cl₂), (0.017 g, 0.060 mmol, 77%).

¹H-NMR (CDCl₃): 5.62 (bs, 0.78 H, H on O (enol form)), 5.36-5.29 (m, 0.22 H, H on C4 (keto form)), 4.15 (dd, 1H, J=6.7, 17.2 Hz, H on C5), 4.06 (t, 2H, J=6.7 Hz, H’s on C10), 3.65 (d, 1H, J=4.5 Hz, H on C2α or β), 3.50-3.18 (m, 3H, H’s on C6 and C8), 2.83-2.67 (m, 1 H, H₂β or α), 2.62-2.10 (m, 1H, H on C7β), 2.05-1.91 (m, 1H, H on C7α), 1.72-1.54 (m, 2H, H’s on C11), 1.37 (d, 3H, J=6.8 Hz, H’s on C17), 1.36-1.05 (m, 8H, H’s on C12, C13, C14, and C15), 0.86 (t, 3H, J=7.2 Hz, H’s on C16). ¹³C-NMR (CDCl₃): 203.9 (C3, keto form), 194.0 (C3, enol form), 176.9 (C9, enol form), 170.6 (C9, keto form), 120.3 (C4, enol form), 77.2 (C2), 68.9 (C4, keto form), 68.3 (C8), 63.3 (C5), 53.0 (C10), 45.8 (C6), 31.7 (C11), 29.7 (C12), 28.8 (C13), 28.5 (C17), 26.2 (C7), 25.8 (C14), 22.5 (C15), 14.0 (C16). HRMS calculated for C₁₆H₂₇NO₃: 281.199094, found: 281.200165. GC:
Rt=23.3 min. MS: 281 (2), 253 (13), 210 (8), 182 (5), 166 (10), 110 (100), 96 (27), 84 (22), 49 (40). IR (NaCl, cm\(^{-1}\)): 3366, 2926, 2855, 1734, 1718, 1654, 1458, 1263, 1078, 737.

**5-Aza-2-heptoxycarbonylbicyclo[3.3.0]oct-2-ene-3-ol (92):** A 25 mL round-bottomed flask was charged with photoproduct 2c (0.018 g, 0.068 mmol), Et\(_2\)O (3 mL) and HCl:Et\(_2\)O (5 mL, 1.0 M). The mixture was allowed to stir for 0.5 h, the solvent was removed via cannula and reduced pressure to yield the tricyclic amine salt (0.020 g). The salt was dissolved in ethanol (5 mL) and Pd/C (10%, 0.015 g) was added. The mixture was stirred under an atmosphere of H\(_2\) for 16 h, filtered through celite, and concentrated under reduced pressure to yield an orange oil (0.021 g). Column chromatography (1% NEt\(_3\)/2% MeOH/CH\(_2\)Cl\(_2\)) yielded 92 as a pale yellow oil (R\(_f\)=0.41 1% NEt\(_3\)/3% MeOH/CH\(_2\)Cl\(_2\)), (0.015 g, 0.056 mmol, 82%).
1H-NMR (CDCl₃): 5.62 (bs, 0.75H, H on O (enol form)), 5.38-5.29 (m, 0.25H, H on C4 (keto form)), 4.16 (dd, 1H, J=11.5, 5.6 Hz, H on C5), 4.05 (t, 2H, J=6.8 Hz, H’s on C10), 3.60 (d, 1H, J=7.1 Hz, H on C2α or β), 3.50-3.10 (m, 2H, H’s on C8), 3.16-3.04 (m, 2H, H’s on C6), 3.02-2.67 (m, 1H, H on C2β or α), 2.12-1.96 (m, 2H, H’s on C7), 1.72-1.58 (m, 2H, H’s on C11), 1.36-1.20 (m, 8H, H’s on C12, C13, C14, and C15), 0.86 (t, 3H, J=6.8 Hz, H’s on C16). 13C-NMR (CDCl₃): 203.9 (C3, keto form), 194.0 (C3, enol form), 176.9 (C9, enol form), 170.6 (C9, keto form), 120.3 (C4, enol form), 77.2 (C2), 68.9 (C4, keto form), 68.3 (C8), 63.3 (C5), 53.0 (C10), 45.8 (C6), 31.7 (C11), 29.7 (C12), 28.8 (C13), 26.2 (C7), 25.8 (C14), 22.5 (C15), 14.0 (C16). HRMS calculated for C₁₅H₂₆NO₃: 268.191269 (M+H⁺), found: 268.190872. GC: Rt=24.7 min. MS: 267 (1), 264 (3), 239 (16), 219 (10), 196 (10), 152 (8), 141 (10), 96 (100), 84 (12), 71 (11), 55 (5). IR (NaCl, cm⁻¹): 3385, 2929, 2857, 1733, 1468, 1397, 1262, 1198, 909, 733.

5-Aza-2-ethoxycarbonylbicyclo[3.3.0]oct-2-ene-3-ol (60): A 50 mL round-bottomed flask was charged with hydrogenated photoproduct 92 (0.048 g, 0.18 mmol), KCN (0.010 g, 0.15 mmol) and freshly distilled ethanol (30 mL). The mixture was allowed to stir for 4 d at reflux, the solvent was removed under reduced pressure to yield a brown oil (0.050 g). The oil was dissolved in H₂O
(20 mL) and organics were extracted with CH$_2$Cl$_2$ (4 X 20 mL) yield an orange oil (0.041 g). Column chromatography (1% NEt$_3$/2% MeOH/CH$_2$Cl$_2$) yielded 60 as a pale yellow oil ($R_I$=0.38 1% NEt$_3$/3% MeOH/CH$_2$Cl$_2$), (0.028 g, 0.14 mmol, 80%).

$^1$H-NMR (CDCl$_3$): 5.72 (bs, 1H, H on OH), 4.05 (t, 2H, $J$=7.1 Hz, H’s on C10), 4.02-3.93 (m, 1H, H on C5), 3.39 (t, 2H, $J$=6.5 Hz, H’s on C2), 2.42-2.29 (m, 2H, H’s on C8), 2.25-2.10 (m, 1H, H on C7$\alpha$ or C7$\beta$), 1.74-1.60 (m, 2H, H’s on C6), 1.52-1.39 (m, 1H, H on C7$\beta$ or C7$\alpha$), 1.13 (t, 3H, $J$=7.1 Hz, H’s on C11). $^{13}$C-NMR (CDCl$_3$): 194.1 (C3), 170.5 (C9), 127.9 (C4), 77.2 (C2), 59.9 (C5), 55.9 (C10), 41.8 (C8), 23.7 (C7), 20.5 (C6), 13.8 (C11). GC: Rt=24.6 min. MS: 196 (10), 177 (20), 149 (100), 121 (12), 105 (15), 93 (10), 76 (10). IR (NaCl, cm$^{-1}$): 3385, 2929, 2857, 1733, 1468, 1397, 1262, 1198, 909, 733.
2-Aza-2-Benzyl-3-methyl-5-oxobicyclo[2.2.2]octane (93a): A 100 mL round-bottomed flask was charged with benzylamine:hydrochloride (10.8 g, 75.2 mmol), 2-cyclohex-1-en-one (7.94 g, 82.6 mmol), and MeOH (50 mL). After stirring at 0°C for 30 min, acetaldehyde (15.8 g, 357.8 mmol) was added and the mixture was allowed to stir at 0°C for an additional 30 min. The mixture was heated to reflux and allowed to stir for 64 h. The solvent was then removed under reduced pressure to yield a brown oil (24.7 g). The oil was dissolved in 10% HCl (30 mL), CH₂Cl₂ (40 mL), and stirred at room temperature overnight. The mixture was neutralized with 20% Na₂CO₃ (50 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (4 X 30 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield a brown oil (23.2 g). Column chromatography (10% EtOAc/Hex) yielded a yellow oil, 93a, as a 1:1 mixture of diastereomers (Rf=0.37, 20% EtOAc/Hex), (1.49 g, 6.50 mmol, 9%). (Rf=0.25, 20% EtOAc/Hex), (1.48 g, 6.49 mmol, 9%).
exo isomer:

$^1$H-NMR (CDCl$_3$): 7.35-7.22 (m, 5H, H's on C12, C13, C14, C15, and C16), 3.79-3.49 (m, 2H, H's on C10), 3.20-3.13 (m, 1H, H on C4), 2.92-2.73 (m, 2H, H's on C6), 2.38-1.24 (m, 6H, H's on C1, C4, C7, and C8), 1.04 (d, 3H, $J$=6.2 Hz, H's on C9). $^{13}$C-NMR (CDCl$_3$): 215.2 (C5), 140.0 (C11), 128.5 (C12 and C16), 128.2 (C13 and C15), 127.0 (C14), 59.4 (C10), 56.5 (C4), 50.4 (C6), 50.2 (C1), 46.9 (C3), 22.4 (C7), 21.9 (C8), 16.3 (C9). GC: Rt=22.3 min. MS: 229 (15), 214 (62), 186 (17), 172 (53), 158 (9), 132 (9), 91 (100), 65 (22). Spectral data are consistent with literature values.$^{84}$
endo isomer:

$^1$H-NMR (CDCl$_3$): 7.35-7.22 (m, 5H, H's on C12, C13, C14, C15, and C16),
3.79-3.49 (m, 2H, H's on C10), 3.20-3.13 (m, 1H, H on C4), 2.92-2.73 (m, 2H,
H's on C6), 2.38-1.24 (m, 6H, H's on C1, C4, C7, and C8), 1.13 (d, 3H, J=6.2 Hz,
H's on C9). $^{13}$C-NMR (CDCl$_3$): 215.2 (C5), 140.0 (C11), 128.5 (C12 and C16),
128.2 (C13 and C15), 127.0 (C14), 59.4 (C10), 56.5 (C4), 50.4 (C6), 50.2 (C1),
46.9 (C3), 22.9 (C7), 21.9 (C8), 17.8 (C9). GC: Rt=22.8 min. MS: 229 (15), 214
(62), 186 (17), 172 (53), 158 (9), 132 (9), 91 (100), 65 (22). Spectral data are
consistent with literature values.$^{84}$

2-Aza-2-Benzyl-3-heptyl-5-oxobicyclo[2.2.2]octane (93b): A 100 mL
round-bottomed flask was charged with benzylamine:hydrochloride (5.59 g,
38.9 mmol), 2-cyclohex-1-en-one (3.77 g, 39.3 mmol), octyl aldehyde (11.0 g,
85.8 mmol), and MeOH (7 mL). The mixture was heated to reflux and allowed to
stir for 120 h. The solvent was then removed under reduced pressure to yield
an orange oil (20.8 g). The oil was dissolved in 10% HCl (20 mL), Et$_2$O (30 mL),
and stirred at room temperature overnight. The mixture was neutralized with
20% Na$_2$CO$_3$ (25 mL) and the layers were separated. The aqueous layer was
extracted with Et$_2$O (3 X 30 mL). The organic washes were combined, dried
with MgSO$_4$, and the solvent was removed under reduced pressure to yield an
orange oil (16.4 g). Column chromatography (50% Et₂O/Hex) yielded an orange oil, 93b, as a 1:1 mixture of diastereomers (R_f=0.37, 33% Et₂O/Hex), (1.23 g, 3.92 mmol, 10%). (R_f=0.25, 33% Et₂O/Hex), (1.30 g, 4.15 mmol, 11%).

exo isomer:

^1^H-NMR (CDCl₃): 7.32-7.18 (m, 5H, H's on C18, C19, C20, C21, and C22), 3.79-3.49 (m, 2H, H's on C10), 3.87-3.54 (m, 2H, H's on C16), 2.60-1.95 (m, 4H, H's on C1, C4, and C6), 1.80-1.52 (m, 5H, H's on C3, C7 and C8), 1.45-1.32 (m, 2H, H's on C9), 1.30-1.08 (m, 10H, H's on C10, C11, C12, C13, and C14), 0.86 (t, 3H, J=6.7 Hz, H's on C15). ^1^C-NMR (CDCl₃): 217.5 (C5), 140.7 (C17), 128.3 (C18 and C22), 128.1 (C19 and C21), 126.9 (C20), 61.2 (C16), 51.3 (C4), 47.1 (C6), 45.2 (C1), 39.4 (C6), 34.1 (C3), 31.6 (C7), 29.4 (C8), 27.6 (C9), 26.1 (C10), 22.6 (C11), 20.8 (C12), 19.0 (C13), 16.2 (C14), 14.0 (C15). HRMS calculated for C_{22}H_{31}NO: 313.240565, found: 313.239433. GC: Rt=28.3 min.
endo isomer:

$^1$H-NMR (CDCl$_3$): 7.32-7.18 (m, 5H, H’s on C18, C19, C20, C21, and C22), 3.79-3.49 (m, 2H, H’s on C10), 3.87-3.54 (m, 2H, H’s on C16), 2.60-1.95 (m, 4H, H’s on C1, C4, and C6), 1.80-1.52 (m, 4H, H’s on C7 and C8), 1.45-1.32 (m, 3H, H’s on C3 and C9), 1.30-1.08 (m, 10H, H’s on C10, C11, C12, C13, and C14), 0.86 (t, 3H, J=6.7 Hz, H’s on C15). $^{13}$C-NMR (CDCl$_3$): 217.5 (C5), 140.7 (C17), 128.3 (C18 and C22), 128.1 (C19 and C21), 126.9 (C20), 61.2 (C16), 51.3 (C4), 47.1 (C6), 45.2 (C1), 39.4 (C6), 34.1 (C3), 31.6 (C7), 29.4 (C8), 27.6 (C9), 26.1 (C10), 22.6 (C11), 20.8 (C12), 19.0 (C13), 16.2 (C14), 14.0 (C15). HRMS calculated for C$_{22}$H$_{31}$NO: 313.240565, found: 313.23853. GC: Rt=28.4 min.

MS: 313 (5), 242 (10), 222 (9), 174 (6), 146 (25), 133 (20), 105 (16), 91 (100), 68 (22). IR (NaCl, cm$^{-1}$): 2926, 2855, 1722, 1455, 1223, 1111, 911, 734.
2-Aza-2-chloro-3-methyl-bicyclo[2.2.2]octan-5-one (98): A 50 mL round-bottomed flask was charged with benzyl amine 93a (0.330 g, 1.40 mmol) and HCl:Et₂O (1.0 M, 20 mL). The solution was allowed to stir for 1 h at room temperature. The Et₂O solution was removed by cannula and the remaining solid was dried under reduced pressure to yield the benzylamine salt (0.38 g). The solid was dissolved in HCl:iPrOH (5-6 M, 10 mL) and Pd/C (10%, 0.134 g) was added. The mixture was stirred under an atmosphere of H₂ for 16 h, filtered through celite, and concentrated under reduced pressure to yield an orange oil (0.24 g). The oil was dissolved in CH₂Cl₂ (20 mL) and N-chlorosuccinimide (0.501 g, 3.8 mmol) was added. The solution was allowed to stir at room temperature for 3 h. The mixture was quenched with H₂O (25 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 X 30 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under a stream of argon to yield an orange oil (0.32 g). Column chromatography (basic alumina) yielded a colorless oil, 98, as a 1:1 mixture of diastereomers (Rf=0.47, Et₂O), (0.102 g, 0.59 mmol, 42%). (Rf=0.41, Et₂O), (0.105 g, 0.61 mmol, 43%)
exo isomer:

$^1$H-NMR (CDCl$_3$): 3.26 (q, 1H, $J=6.7$ Hz, H on C3), 3.07 (bs, 1H, H on C1), 2.30-1.95 (m, 7H, H's on C4, C6, C7, and C8), 1.29 (d, 3H, $J=6.7$ Hz, H's on C9).

$^{13}$C-NMR (CDCl$_3$): 204.5 (C5), 62.8 (C1), 56.1 (C3), 45.7 (C4 and C6), 28.5 (C7), 20.8 (C8), 14.5 (C9). HRMS calculated for C$_8$H$_{12}$NOCl$^{35}$: 171.045092, found: 171.044567. GC: Rt=16.8 min. MS: 173 (22), 171 (66), 143 (24), 136 (60), 130 (81), 116 (40), 108 (76), 100 (63), 88 (38), 67 (89), 55 (100). IR (NaCl, cm$^{-1}$): 2965, 1757, 1462, 1383, 1257, 1227, 1075, 910, 732. Spectral data are consistent with literature values.$^{84}$
endo isomer:

$^1$H-NMR (CDCl$_3$): 3.26 (q, 1H, $J=6.7$ Hz, H on C3), 3.07 (bs, 1H, H on C1), 2.30-1.95 (m, 7H, H's on C4, C6, C7, and C8), 1.27 (d, 3H, $J=6.7$ Hz, H's on C9).

$^{13}$C-NMR (CDCl$_3$): 204.5 (C5), 62.8 (C1), 55.9 (C3), 45.7 (C4 and C6), 28.5 (C7), 20.8 (C8), 14.5 (C9). HRMS calculated for C$_8$H$_{12}$NOCI$_3$: 171.045092, found: 171.044281. GC: Rt=16.9 min. MS: 173 (22), 171 (66), 143 (24), 136 (60), 130 (81), 116 (40), 108 (76), 100 (63), 88 (38), 67 (89), 55 (100). IR (NaCl, cm$^{-1}$): 2965, 1757, 1462, 1383, 1257, 1227, 1075, 910, 732. Spectral data are consistent with literature values.$^{84}$

2-Aza-3-methyl-bicyclo[2.2.2]oct-2-en-5-one (4a, R=CH$_3$): A 50 mL round-bottomed flask was charged with chloro amine 98 (0.207 g, 1.20 mmol), CH$_2$Cl$_2$ (20 mL), and cooled to 0°C. DBU (0.916 g, 6.0 mmol) was added to the stirring mixture and allowed to stir at room temperature for 2 h. The solution was concentrated under reduced pressure to yield an orange oil (0.22 g). Column chromatography (basic alumina) ($R_f=0.52$, 25% Et$_2$O/Hex) followed by bulb-to-bulb distillation (75-80°C/29 mm Hg), yielded 4a as a colorless oil (0.14 g, 1.0 mmol, 69%).
\[^{1}H\text{-NMR (CDCl}\text{)}: 3.26 \text{ (m, 1H, H on C1), 3.07 \text{ (m, 1H, H on C4), 2.25-1.98 \text{ (m, 6H, H's on C6, C7, and C8), 1.41 \text{ (s, 3H, H's on C9).}^{13}C\text{-NMR (CDCl}\text{)}: 207.6 \text{ (C5), 176.1 \text{ (C3), 62.1 \text{ (C1), 54.3 \text{ (C4), 41.7 \text{ (C9), 33.6 \text{ (C6), 31.6 \text{ (C7), 26.4 \text{ (C8).} HRMS calculated for C}_8\text{H}_11\text{NO: 137.084064, found: 137.084679.} GC: Rt=14.3 \text{ min. MS: 137 (100), 108 (20), 94 (33), 82 (60), 67 (85), 54 (70). IR (NaCl, cm}^{-1}: 2960, 1740, 1645, 1446, 1380, 1093. UV: \lambda_{\text{max}}=216 \text{ (log } \varepsilon=3.34), 229 \text{ (log } \varepsilon=2.92), 262 \text{ (log } \varepsilon=2.45). Spectral data are consistent with literature values.}\]^{84} 

**2-Trimethylsiloxyl-1,3-cyclohexadiene (99):** A 250 mL round-bottomed flask was charged with diisopropylamine (6.93 g, 0.069 mol), Et\text{2O (25 mL), and THF (25 mL)} \text{. The mixture was cooled to 0}^\circ\text{C and n-butyllithium (44 mL, 1.54 M) was added dropwise. After stirring at 0}^\circ\text{C for 30 min, 2-cyclohexen-1-one (5.96 g, 0.062 mol) in THF (10 mL) was added over 30 min by syringe pump. After stirring at 0}^\circ\text{C for 90 min the flask was charged with chlorotrimethylsilane (13.0}
mL, 0.102 mol) and NEt₃ (14.0 mL, 0.100 mol). The mixture was allowed to stir at 0°C for 20 min, then at room temperature for 40 min. The reaction was quenched with H₂O (100 mL) and the layers were separated. The aqueous layer was washed with pentane (2 x 100 mL). The organic washes were combined, dried over MgSO₄, and the solvent was removed under reduced pressure to yield a yellow liquid (11.3 g). Bulb-to-bulb distillation (70-80°C, 19 mm Hg) yielded 99 as a colorless liquid (7.40 g, 0.044 mol, 71%).

\[
\begin{align*}
\text{H-NMR (CDCl₃)}: & \quad 5.37-5.81 (m, 1H, H on C1), 5.66 (dd, 1H, J=8.2, 1.6 Hz, H on C3), 4.86 (bs, 1H, H on C4), 2.19-2.06 (m, 4H, H's on C5 and C6), 0.17 (s, 9H, H's on C7).  \\
\text{C-NMR (CDCl₃)}: & \quad 148.0 (C2), 128.9 (C3), 126.4 (C1), 102.4 (C4), 22.6 (C5), 21.7 (C6), 0.14 (C7).  
\end{align*}
\]

Spectral data are consistent with literature values.⁸⁹
2-Aza-3-(carboxylic acid ethyl ester)-5-trimethylsiloxy-bicyclo[2.2.2]octan-2,5-diene (100a): A 25 mL round-bottomed flask was charged with silyl enol ether 99 (0.352 g, 2.09 mmol), ethyl cyanoformate (0.23 mL, 2.39 mmol), magnesium bromide diethyl etherate (0.151 g, 0.584 mmol), and ether (5.00 mL). After stirring at room temperature for 16 h, $^1$H-NMR analysis showed disappearance of silyl enol ether. The solvent was removed under a stream of argon to yield a orange oil (0.62 g). The oil was filtered through celite and concentrated under reduced pressure to yield 100a as a colorless oil (0.402 g, 1.55 mmol, 72%).

$^1$H-NMR (CDCl$_3$): 6.92 (dt, 1H, $J$=12.1, 5.6 Hz, H on C1), 5.96 (t, 1H, $J$=6.4 Hz, H on C4), 4.62-4.02 (m, 3H, H's on C6 and C11), 2.54-1.63 (m, 4H, H's on C7 and C8), 1.23 (t, 3H, $J$=7.2 Hz, H's on C12). $^{13}$C-NMR (CDCl$_3$): 199.4 (C5), 150.4 (C10), 129.9 (C3), 100.7 (C6), 65.3 (C11), 50.5 (C1), 42.0 (C4), 29.6 (C7),
23.3 (C8), 13.9 (C12), 11.0 (C9). HRMS calculated for C₁₃H₂₁NO₃Si: 267.405632, found 267.405328. IR (NaCl, cm⁻¹): 2981, 1750, 1640, 1620, 1250, 800.

2-Aza-3-(4-methylphenylsulfonyl)-5-trimethylsiloxybicyclo[2.2.2]octan-2,5-diene (100b): A 25 mL round-bottomed flask was charged with silyl enol ether 99 (0.0177 g, 0.105 mmol), p-toluenesulfonyl cyanide (0.0191 g, 0.105 mmol), and CDCl₃ (0.50 mL). After stirring at room temperature for 58 h, ¹H-NMR analysis showed disappearance of silyl enol ether. The solvent was removed under a stream of argon to yield 100b as a colorless oil which was >95% pure by ¹H-NMR analysis (0.037 g, 0.105 mmol, 99% crude).
$^1$H-NMR (CDCl$_3$): 7.75 (d, 2H, $J$=8.3 Hz, H's on C12 and C14), 7.33 (d, 2H, $J$=8.0 Hz, H's on C11 and C15), 5.18 (dd, 1H, $J$=5.9, 2.5 Hz, H on C1), 5.06 (dd, 1H, $J$=5.8, 2.2 Hz, H on C6), 4.14 (t, 1H, $J$=2.3 Hz, H on C4), 2.42 (s, 3H, H's on C16), 1.66-1.20 (m, 4H, H's on C7 and C8), 0.12 (s, 9H, H's on C9). $^{13}$C-NMR (CDCl$_3$): 175.6 (C3), 155.9 (C5), 145.8 (C6), 134.0 (C10), 131.3 (C13), 130.2 (C12 and C14), 129.7 (C11 and C15), 103.6 (C1), 61.5 (C4), 43.7 (C16), 25.2 (C7), 23.6 (C8), 0.2 (C9). HRMS calculated for C$_{15}$H$_{18}$NO$_3$SSi (M-C$_2$H$_5^+$): 320.077669, found: 320.077988. MS 320 (I), 306 (5), 257 (39), 242 (23), 194 (65), 149 (12), 139 (10), 121 (9), 91 (13), 73 (100). IR (NaCl, cm$^{-1}$): 2957, 1645, 1598, 1329, 1255, 1204, 1153, 909, 849.

2-Azabicyclo[2.2.2]octan-3,5-dione (105): A 25 mL round-bottomed flask was charged with silyl enol ether 99 (2.38 g, 14.1 mmol), p-tolunesulfonyl cyanide (2.68 g, 10.6 mmol), and CH$_2$Cl$_2$ (10 mL). After stirring at reflux for 24 h, the mixture was cooled to 0°C and the flask was charged with glacial acetic acid (4 mL) and H$_2$O (8 mL). After stirring at 0°C for 3 h, the mixture was neutralized with NaOH and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 40 mL). The organic washes were combined, dried with MgSO$_4$, and the solvent was removed under reduced pressure to yield a oily
yellow solid (2.3 g). Trituration with Et₂O yielded 105 as a pale yellow solid (1.51 g, 10.9 mmol, 77%), mp 143.4-143.7°C (EtOAc:Hex, 1:2).

\[ \text{H-NMR (CDCl}_3\text{: 7.71 (bs, 1H, H on N), 4.01-3.99 (m, 1H, H on C1), 3.26-3.22 (m, 1H, H on C4), 2.49-2.24 (m, 2H, H's on C6), 2.13-1.79 (m, 4H, H's on C7 and C8).} \]

\[ \text{C-NMR (CDCl}_3\text{: 205.7 (C5), 171.2 (C3), 57.4 (C1), 47.4 (C4), 43.3 (C6), 26.7 (C8), 21.1 (C7).} \]

HRMS calculated for C₇H₉NO₂: 139.064022, found: 139.063329. GC: Rt=18.3 min. MS: 139 (39), 97 (57), 69 (100), 55 (92). IR (KBr, cm\(^{-1}\)) 3182, 2796, 1740, 1682, 1450, 1398, 1337, 1309, 1096, 1010.

2-Aza-3-(trifluoroacetoxy)-bicyclo[2.2.2]octan-2-ene-5-one (4d, R=OSO₂CF₃): A 25 mL round-bottomed flask was charged with keto-amide 105 (0.211 g, 1.52 mmol), NEt₃ (0.436 g, 4.31 mol), and CH₂Cl₂ (10 mL). The flask was cooled to 0°C and trifluoroacetic anhydride (0.59 g, 2.83 mmol) was added. After stirring for 2 h at 0°C the flask was warmed to room temperature.
and stirred for an additional 3 hours. The solvent was removed under a stream of argon to yield 4d as an orange oil (0.42 g), which was found to be 60% pure by GC and $^1$H-NMR analysis. The oil was used without further purification.

![Chemical structure](image)

$^1$H-NMR (CDCl$_3$): 4.34 (s, 1H, H on C1), 3.54-3.43 (m, 1H, H on C4), 2.82-1.76 (m, 6H, H’s on C6, C7, and C8). HRMS calculated for C$_8$H$_8$NO$_4$SF$_3$: 271.012614, found: 271.012558. GC: Rt=17.7 min. MS: 271 (30), 229 (45), 201 (100), 160 (5), 123 (5), 96 (10), 68 (78), 55 (46). IR (NaCl, cm$^{-1}$): 2952, 1733, 1683, 1475, 1245, 1169, 1031, 914. UV: $\lambda_{max}$=218 (log $\varepsilon$=3.32), 260 (log $\varepsilon$=2.68), 304 (log $\varepsilon$=2.08).

2-Aza-3-(ethoxycarbonyl)-bicyclo[2.2.2]oct-2-en-5-one (4c, $R$=CO$_2$Et). A 25 mL round-bottomed flask was charged with crude triflate 4d (0.433 g, 1.59 mmol), NEt$_3$ (0.284 g, 2.87 mmol), palladium acetate (0.0191 g,
0.0849 mmol), triphenyl phosphine (0.0459 g, 0.175 mmol), and ethanol (10 mL). The flask was purged with carbon monoxide for 5 min and then equipped with a carbon monoxide filled balloon. After stirring for 3 h the solvent was removed under a stream of argon to to yield 4c as a red oil (0.42 g), which was found to be 60% pure by GC and $^1$H-NMR analysis. The oil was used without further purification.

$^1$H-NMR (CDCl$_3$): 4.04 (q, 2H, $J=6.8$ Hz, H's on C10), 3.65 (m, 2H, H's on C1 and C4), 2.65-1.85 (m, 6H, H's on C6, C7, and C8), 1.12 (t, 3H, $J=6.7$ Hz, H's on C11). HRMS calculated for C$_{10}$H$_{13}$NO$_3$: 195.089543, found: 195.088604. GC: Rt=16.4 min. MS: 195 (35), 154 (7), 126 (13), 109 (27), 94 (15), 81 (100), 68 (15). IR (NaCl, cm$^{-1}$): 2945, 1738, 1715, 1625, 1210, 794.

1-Aza-2-ethoxycarbonyltricyclo[3.3.0.0$^{4,6}$]octan-3-one (2c): An 100 mL cone flask was charged with crude ester 4c (0.32 g, 60%, 1.00 mmol),
acetophenone (3 mL), and acetone (60 mL). The mixture was frozen under vacuum and then thawed under argon. This degassing process was repeated three times. The mixture was then irradiated in an immersion photowell with a Hanovia medium pressure 450 W lamp, equipped with a quartz cooling jacket for 20 h. The solvent was removed under reduced pressure to yield an orange oil (0.19 g). Column chromatography (1% NEt₃/Et₂O) yielded 5c as a pale yellow oil (Rᵣ=0.24, 1% NEt₃/Et₂O), (0.095 g, 0.49 mmol, 32% from 104).

**1H-NMR (CDCl₃):** 4.32 (app t, 1H, J=6.2 Hz, H on C8), 4.09 (q, 2H, J=6.4 Hz, H's on C10), 4.07 (q, 2H, J=6.4 Hz, H's on C10), 3.40-3.10 (m, 1H, H's on C4), 3.16 (dd, 2H, J=7.7, 4.2 Hz, H's on C4), 1.92-1.75 (m, 2H, H's on C7), 1.70-1.48 (m, 2H, H's on C6), 1.15 (t, 3H, J=6.4 Hz, H's on C11). **13C-NMR (CDCl₃):** 208.3 (C3), 168.0 (C9), 61.8 (C2), 53.2 (C10), 50.8 (C5), 45.5 (C8), 40.6 (C4), 24.3 (C6), 21.5 (C7), 14.1 (C11). GC: Rt=15.7 min. MS: 195 (1), 167 (8), 139 (90),
125 (28), 110 (20), 97 (73), 81 (16), 69 (100). IR (NaCl, cm⁻¹): 3420, 2974, 2869, 1734, 1728, 1636, 1380, 1120.

2-Aza-3-ethoxy-bicyclo[2.2.2]octan-2-ene-5-one (4e, R=OEt): A 25 mL round-bottomed flask was charged with keto-amide 105 (0.1112 g, 0.80 mmol) and CH₂Cl₂ (10 mL). The flask was cooled to 0°C and ethyl Meerwein’s reagent ⁹² (1.30 mL, 1.0 M) was added. After stirring for 4 h at 0°C, the mixture was allowed to stir at room temperature for 40 h, the mixture was then poured into 10% NaHCO₃ (15 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield a yellow oil (0.14 g). Column chromatography (basic alumina) (20% EtOAc/Hex) yielded 4e as a colorless oil (Rf=0.15, 20% EtOAc/Hex), (0.1324 g, 0.798 mmol, 99%).
\[^1\text{H}-\text{NMR (CDCl}_3\text{):} \ 4.28 \text{ (d, 1H, } J=7.9 \text{ Hz, H on C1), 4.07 \text{ (q, 2H, } J=7.2 \text{ Hz, H's on C9), 3.13 \text{ (t, 1H, } J=2.8 \text{ Hz, H on C4), 2.11 \text{ (s, 2H, H's on C6), 1.88-1.65 \text{ (m, 4H, H's on C7 and C8), 1.23 \text{ (t, 3H, } J=7.2 \text{ Hz, H's on C10).} \] \[^1\text{C}-\text{NMR (CDCl}_3\text{):} \ 208.2 \text{ (C5), 167.9 \text{ (C3), 61.7 \text{ (C1), 53.1 \text{ (C9), 50.7 \text{ (C4), 40.6 \text{ (C6), 24.3 \text{ (C8), 21.4 \text{ (C7), 14.0 \text{ (C10).} HRMS calculated for C}_9\text{H}_{13}\text{NO}_2: \text{ 167.094629, found: 167.094749.} \] \[\text{GC: } \text{Rt}=15.9 \text{ min. MS: 167 (8), 139 (62), 97 (60), 69 (100), 55 (75). IR (NaCl, cm}^{-1} \text{) 2984, 1736, 1654, 1488, 1374, 1244, 1058. UV: } \lambda_{max}=216 \text{ (log } \varepsilon=3.18), 262 \text{ (log } \varepsilon=2.51).\]

1-Aza-8-ethoxy-bicyclo[4.2.0]octan-7-ene-2-one (6e): A 100 mL round-bottomed flask was charged with imidate 4e (0.271 g, 1.62 mmol) and hexane (50 mL). The mixture was frozen under vacuum and thawed under argon. This degassing process was repeated three times. The mixture was then irradiated in a Pyrex round-bottomed flask for 40 h, under an argon atmosphere. The mixture was concentrated under reduced pressure to yield a yellow oil (0.29 g). Column chromatography (basic alumina) (Hex) yielded 6e as a colorless oil (Rf=0.78, 20% EtOAc/Hex), (0.101 g, 0.60 mmol, 37%).
$^1$H-NMR (CDCl$_3$): 4.19 (q, 2H, $J=7.5$ Hz, H's on C9), 3.73-3.46 (m, 2H, H's on C4 and C7), 1.71-1.15 (m, 6H, H's on C3, C5, and C6), 0.89 (t, 3H, $J=7.5$ Hz, H's on C10). $^{13}$C-NMR (CDCl$_3$): 167.8 (C2), 157.9 (C8), 132.4 (C7), 79.4 (C4), 68.2 (C9), 38.7 (C6), 30.4 (C3), 23.8 (C5), 15.5 (C10). HRMS calculated for C$_9$H$_{13}$NO$_2$: 167.094629, found: 167.094421. GC: Rt=18.1 min. MS: 167 (82), 138 (15), 125 (80), 110 (30), 97 (65), 80 (33), 69 (100), 55 (70). IR (NaCl, cm$^{-1}$): 2961, 2930, 1723, 1464, 1290, 1125, 1074, 910.

2-Azabicyclo[2.2.2]octan-3-thione-5-one (107): A 25 mL round-bottomed flask was charged with keto-amide 105 (0.580 g, 4.16 mmol), Lawesson's reagent (0.864 g, 2.14 mmol), and HMPA (20 mL). The flask was heated to 100°C. After stirring at 100°C for 4 h the mixture was poured into H$_2$O (30 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 X 30 mL). The organic washes were combined, dried with MgSO$_4$, and the solvent was removed under reduced pressure to yield an
orange oil (0.92 g). Column chromatography (80% EtOAc/Hex) yielded 107 as a white solid ($R_f=0.42$, 80% EtOAc/Hex), (0.450 g, 2.90 mmol, 70%), mp 152.4-152.8°C (EtOAc:Hex, 1:1).

![Chemical structure](image)

$^1$H-NMR (CDCl$_3$): 9.44 (bs, 1H, H on N), 4.14 (d, 1H, $J=4.8$ Hz, H on C1), 3.88 (s, 1H, H on C4), 2.50-2.27 (m, 2H, H's on C6), 2.10-1.83 (m, 4H, H's on C7 and C8). $^{13}$C-NMR (CDCl$_3$): 203.9 (C5), 199.7 (C3), 65.1 (C1), 50.8 (C4), 41.4 (C6), 26.4 (C8), 22.4 (C7). HRMS calculated for C$_7$H$_9$NOS: 155.040486, found: 155.039925. GC: Rt=21.3 min. MS: 155 (75), 112 (100), 68 (50), 55 (33). IR (KBr, cm$^{-1}$): 3144, 2882, 1728, 1518, 1332, 1300, 1094, 739.

2-Aza-3-thioethoxy-bicyclo[2.2.2]octan-2-ene-5-one (4f, R=SEt): A 25 mL round-bottomed flask was charged with keto thioamide 107 (0.0629 g, 0.41 mmol) and CH$_2$Cl$_2$ (10 mL). The flask was cooled to 0°C and ethyl Meerwein's reagent$^{92}$ (0.7 mL, 1.0 M) was added. After stirring for 4 h at 0°C,
the mixture was allowed to stir at room temperature for 40 h, the mixture was then poured into 10% NaHCO₃ (20 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 X 20 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield an orange oil (0.11 g). Column chromatography (basic alumina) (20% EtOAc/Hex) yielded 4f as a colorless oil (Rᵣ=0.38, 20% EtOAc/Hex), (0.073 g, 0.40 mmol, 98%).

\[ \text{1H-NMR (CDCl}_3\text{): } 4.57 \text{ (s, 1H, H on C1), 3.18 (s, 1H, H on C4), 2.92 (q, 2H, J=7.4 Hz, H's on C9), 2.91 (q, 2H, J=7.4 Hz, H's on C9), 2.16 (s, 2H, H's on C6), 1.92-1.65 (m, 4H, H's on C7 and C8), 1.26 (t, 3H, J=7.4 Hz, H's on C10), 1.25 (t, 3H, J=7.4 Hz, H's on C10).} \]

\[ \text{13C-NMR (CDCl}_3\text{): } 207.6 \text{ (C5), 170.3 (C3), 56.8 (C1), 55.4 (C4), 40.1 (C9), 24.3 (C6), 23.3 (C8), 21.7 (C7), 13.8 (C10).} \]

HRMS calculated for C₉H₁₃NOS: 183.071786, found: 183.072041. GC: Rt=17.6 min. MS: 183 (20), 155 (100), 140 (20), 125 (30), 113 (80), 94 (30), 80 (25), 68 (35),
54 (90). IR (NaCl, cm⁻¹) 2967, 1730, 1575, 1338, 1069, 907. UV: λₘₐₓ=216 (log ε=3.36), 238 (log ε=3.02).

1-Aza-8-thioethoxy-bicyclo[4.2.0]octan-7-ene-2-one (6f): A 100 mL round-bottomed flask was charged with thioimidate 4f (0.235 g, 1.28 mmol) and hexane (50 mL). The mixture was frozen under vacuum and thawed under argon. This degassing process was repeated three times. The mixture was then irradiated in a the pyrex round-bottomed flask for 40 h, under an argon atmosphere. The mixture was concentrated under reduced pressure to yield a yellow oil (0.28 g). Column chromatography (basic alumina) (20% EtOAc/Hex) yielded 4f as a colorless oil (Rf=0.58, 40% EtOAc/Hex), (0.093 g, 0.51 mmol, 40%).

\[ \text{H}_3\text{C} \quad \text{O} \]
\[ \text{H}_3\text{S} \quad \text{N} \quad \text{O} \]

$^1$H-NMR (CDCl₃): 3.72-3.56 (m, 2H, H's on C4 and C7), 3.53 (q, 2H, J=6.9 Hz, H's on C9), 1.72-1.10 (m, 6H, H's on C3, C5, and C6), 0.84 (t, 3H, J=6.9 Hz, H's
on C10). $^{13}$C-NMR (CDCl$_3$): 173.3 (C2), 160.9 (C8), 127.2 (C7), 78.1 (C4), 69.8
(C9), 43.9 (C6), 29.7 (C3), 15.5 (C5), 15.1 (C10). HRMS calculated for
C$_9$H$_{13}$NOS: 183.071786, found: 183.072025. GC: Rt=20.4 min. MS: 183 (67),
155 (48), 140 (34), 126 (35), 108 (100), 80 (41), 54 (24). IR (NaCl, cm$^{-1}$): 2957,
1732, 1631, 1514, 1463, 1123, 909.
CHAPTER 4

APPLICATION OF OXAPHOSPHOLENE METHODOLOGY TOWARDS THE SYNTHESIS OF EPI-4-DEOXY-5-PHOSPHONO-MYO-INOSITOL

Introduction

Over the past five decades the role of phosphorous as a necessary component of life has been well elucidated. Its importance is shown with the great variety of biological phosphorous compounds found in living organisms. These include ADP, ATP, phospholipids, DNA, carbohydrates, and proteins. In most of these compounds the phosphorous moiety is present as a phosphate group. A phosphate group is characterized by a phosphoryl group attached to the carbon of interest by way of an oxygen atom (Figure 15). The phosphorous-oxygen bond is very labile and cleaved easily in the body during enzyme initiated metabolic processes. Due to this fact, the phosphate functionality is known to be the active site in many metabolic processes.

Phosphate containing compounds have been found to regulate or control energy production and transfer, signal transduction, calcification, and cell proliferation.

In order to investigate various physiological processes centered around a phosphate group it is necessary to replace the labile P-O-C bond with a more
stable bond. This could also create biological analogs that could act as antimetabolites. Antimetabolites are compounds that slow or stop a metabolic processes by inhibition of one or more enzymatic processes.

![Phosphates and phosphonates](image)

**Figure 15. Phosphates and phosphonates.**

**Phosphonates and their Analogs**

For more than 30 years phosphonates have been used as phosphate analogs. A phosphonate group differs from a phosphate in that the phosphonate is attached directly to the carbon atom. See Figure 15. The C-P bond is not readily hydrolyzable and therefore is not easily cleaved during metabolic processes. Phosphonates have been shown to be effective agents...
for the treatment of calcification diseases. They have also shown antiviral, anti-HIV, and antibiotic activity. Examples of biologically active phosphonates are shown in Figure 16.

Fluorophosphonate 1 is a phosphonate isostere which is being used as a substrate for host-cell phosphorylating enzymes. An isostere is an analog of a compound that exhibits similar electrical and steric activity. The difluoromethylene group has been shown to be an effective mimic of an oxygen
atom, thereby creating a less labile phosphate analog. Phosphinate 2 is a phosphonothricin analog which is currently being evaluated for use as a substitute against gram-positive bacteria. Phosphonocholine 3 has an additional methylene group on the phosphonate group to mimic the size of a phosphate group. This analog is being evaluated for its ability to inhibit leukemic cell growth in vivo and in vitro. One of the more important uses of phosphonates is in the investigation of the mechanism for signal transduction across biomembranes.

Development of a general method towards the synthesis of organophosphonates is of great interest. With the discovery of new organophosphates occurring almost daily, development of a relatively simple method for preparing phosphonate analogs would enable scientists to better investigate their biological activities.

**Historical Background: The Preparation of Phosphonates**

The development of methods to generally synthesize phosphonate derivatives has grown considerably (Scheme 64). The most noted one was developed by Arbuzov. Alkyl halides were condensed with trialkoxy phosphites at high temperatures to form phosphonium salts. Dealkylation of the
Scheme 64. Phosphonate preparations.¹⁰⁴
phosphonium salt with the halide counterion produced various phosphonate derivatives in reasonable yields (30-60%). Other reactions that have been used include the Michaelis-Becker reaction, a reaction that utilizes an anionic trivalent phosphorous compound and an alkyl halide, the Abramov reaction, and the Pudovik reaction. The Abramov and Pudovik reactions both involve the electrophilic condensation of the nucleophilic phosphorus with various aldehydes. Each of these methods has a number of limitations related to the structure of the electrophile as well as the structure of the trivalent phosphorus. Due to these limitations it was necessary to use an alternative method for the general preparation of phosphonate derivatives.

Preparation of Phosphonates via Pentacovalent Phosphorus

Due to the various problems attributed to the phosphonate reactions above, it was necessary to develop a general and high yielding method for preparing phosphonates. McClure and co-workers have shown that the condensation of a trialkoxy phosphite with various enones yielded trialkoxy-\(1,2\lambda^5\)-oxaphospholenes (Scheme 65).

The \(1,2\lambda^5\)-oxaphospholene, 4, can be viewed as a cyclic phosphoenol ether with the reactivity of an open enolate/phosphonium species. \(^{31}\text{P}\)-NMR analysis showed that the \(1,2\lambda^5\)-oxaphospholenes clearly exist as cyclic
pentacovalent species, showing a $^{31}\text{P}$-NMR shift of -22 ppm relative to phosphoric acid.$^{105}$

Scheme 65. Preparation of triethyl-1,2,5-oxaphospholene, 4.

In model studies utilizing the pentacoordinated phosphorus (P(V)), 4, many different electrophiles were found to successfully condense to a variety of functionalized phosphonates.$^{124}$ Scheme 66 shows some of the reactions that have been performed utilizing the above methodology. Condensation of P(V) with an oxiziridine yields the β-hydroxy phosphonate, 5, which is currently being taken on to the naturally occurring phosphonotrixin. Condensation of P(V) with various aldehydes under neutral conditions produces β-hydroxy ketones, 6, these contain an α-phosphonomethyl group.
Scheme 66. Use of McClure's organophosphorus methodology.\textsuperscript{105}
These β-hydroxy ketones are currently being used by the McClure group in the synthesis of phosphorylated sugars. Other examples include the condensation of P(V) with azodicarboxylates to produce α-hydrazido β-phosphono ketones, 7, for the synthesis of sphingomylein analogs. The formation of heterocyclic ring systems is possible by condensation of P(V) with 2 equivalents of various aromatic isocyanates to produce the uracil 8. These heterocyclic rings are currently being used in the synthesis of nucleoside analogs. Condensation of the P(V) with a proton yields the non-derivatized keto phosphonate 9. The non-derivatized phosphonate 9 has been very important in the McClure group as it is formed when water is present in the P(V) preparation. Due to the amount isolated, the non-derivatized keto phosphonate 9 has been very useful in model systems to determine the activity of various reactants before use in the “real” systems via standard enolate chemistry.

Preparation of β-Acyl-vinylphosphonates using Electrophilic Bromine

McClure and Grote discovered that the condensation of P(V) with various bromine sources (e.g. bromine, N-bromosuccinimide) yielded the β-bromo phosphonate, 10, in excellent yield (Scheme 67). The β-bromo phosphonate can be readily purified by column chromatography, but is unstable to heat yielding the β-acyl-vinylphosphonate (KVP), 11, quantitatively.
Further examination showed that triethylamine produced the same debrominated results in less time.\textsuperscript{105,106} The 2-D $J$-resolved spectrum indicates that the double bond in KVP has the trans geometry after measurement of coupling constants, $J_{HH}=18.0$ Hz between the two vinyl protons.

Scheme 67. Electrophilic condensations with Br$^+$.\textsuperscript{105a, 106b}

Vinylphosphonates have been synthesized previously by the Arbuzov reaction reacting vinyl halides with trivalent phosphorus compounds in the
presence of a metal catalyst (Scheme 64). This method gave low yields (20-30%) and purification of the vinylphosphonate was difficult. Other methods involve a Horner-Emmons olefination or Peterson elimination on a bisphosphonate.

The preparation of an optically active vinylphosphonate can also be achieved in this manner by use of chiral ligands on the phosphite. This work is in progress in the McClure laboratories presently. These chiral vinylphosphonates could provide a simple strategy for the asymmetric syntheses of various natural products.

The purpose of this project is to synthesize and test mono-phosphonate inositol derivatives. Accomplishing this will further elucidate the biological importance of the 1,4, and 5-phosphate positions on the inositol ring. The synthesis will take place with a Diels-Alder reaction between the KVP, 11, and E-1-acetoxy-1,3-butadiene, 17 as the key ring-forming step. This cyclization will not only form the six-membered ring but also establish three of the five stereocenters required.

Use of Keto Vinylphosphonates as Dienophiles

The first reports of phosphonates and phosphine oxides participating in the Diels-Alder cyclization involved unsubstituted vinylphosphonates, such as 12a, and vinylphosphine oxides, such as 12b. The first involved the thermal
Diels-Alder cyclization between vinylphosphonate, 12a, and cyclopentadiene. Daniewski reported a 1.0 : 1.0 endo/exo ratio.\textsuperscript{108b} Buono and coworkers using the vinylphosphonate 12a in the Lewis acid catalyzed Diels-Alder cyclization with cyclopentadiene, found that aluminum trichloride increased the endo/exo ratio from 1.0 : 1.0 (thermal results)\textsuperscript{108b} to 3.0 : 1.0 (Scheme 68).\textsuperscript{108a} Buono noted that the stereoselectivity notably decreased in relation to the results using acrylic derivatives. This was explained by taking into account the steric bulk of the diethyl phosphonate, forcing the group into the less congested exo configuration. Additionally, it was reported that the larger diphenyl phosphine oxide 12b underwent cyclization with cyclopentadiene to yield the bicyclic phosphine oxide in an endo/exo ratio of 4.5 : 1.0 further verifying the hypothesis of Buono (Scheme 68).\textsuperscript{108a}

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12a: R = OEt
b: R = Ph
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Scheme 68. Use of vinylphosphonates and vinylphosphine oxides as dienophiles.\textsuperscript{108}
Keto vinylphosphonates and keto vinylphosphine oxides have also been used as dienophiles in the Diels-Alder cyclization. Zbiral found that the Diels-Alder cyclization between the triisopropyl keto vinylphosphonate, 13, and cyclopentadiene resulted in an acetyl endo, 14 /acetyl exo, 15 ratio of 3.0 : 1.0 (Scheme 69).\textsuperscript{109}

The use of alternative dienophiles, especially that of \textit{E}-1-acetoxy-1,3-butadiene, 17, was shown by Darling. Darling found that the thermal Diels-Alder cyclization between \textit{E}-1-acetoxy-1,3-butadiene and the diphenyl keto vinylphosphine oxide, 16, resulted in the isolation of only one isomer, 18. This isomer resulted from the phosphine group directing the cyclization process (Scheme 70).\textsuperscript{110}
Previous work in the McClure laboratories has shown KVP to be an excellent dienophile. Studies by McClure, Hansen, and Herzog on the Lewis-acid assisted Diels-Alder reaction between furan and KVP showed a endo preference for the acetyl group with a acetyl endo, 19a / acetyl exo, 19b ratio of up to 3.57 : 1.0.105

Scheme 70. Use of a keto vinylphosphine oxide in the Diels-Alder reaction with E-1-acetoxy-1,3-butadiene.110

Further derivatization to the diols, 20a and 20b, with osmium tetroxide, was needed to confirm the stereochemical assignments as the Diels-Alder products, 19a and 19b, rapidly underwent a retro Diels-Alder reaction back to the starting materials at temperatures greater than 5°C (Scheme 71). The diols are presently being brought on to the inositol derivative, 4-deoxy-D-my o-Inositol
5-phosphonate, 21, by way of a regioselective oxygen and a Baeyer-Villiger oxidation on the acetyl group.

Scheme 71. Diels-Alder cyclization of KVP with furan followed by bis-hydroxylation with OsO₄\(^{105}\).

Additional work by McClure, Hansen, and Herzog has shown that the Lewis-acid assisted Diels-Alder cyclization between \(E\)-1-acetoxy-1,3-butadiene and KVP resulted in the isolation of only one cyclization product, 22, (Scheme
This product shows an opposite regiochemical preference to that shown in Darling’s thermal cyclization.

Scheme 72. Lewis-acid catalyzed Diels-Alder cyclization between KVP and 1-acetoxy-1,3-butadiene. 

**Inositols**

Derivatives of inositols, 1,2,3,4,5,6-hexahydroxycyclohexanes, are widely found in all biological systems, particularly associated with biomembranes. They exist principally as inositol phosphates with one to six phosphates esterified to one inositol. Their biological functions include intracellular communication, phosphate storage and transfer, and they provide the predominant means for covalent anchoring of proteins to membranes. In
biomembranes they exist in inositol phosphatides as one of the few head groups forming the structures of naturally occurring phospholipid bilayers.

Figure 17. D-myo-Inositol 1,4,5-trisphosphate, 23, 4-deoxy-D-myo-Inositol 5-phosphonate, 21, and 1-epi-4-deoxy-D-myo-Inositol-5-phosphonate, 24.

D-myo-Inositol 1,4,5-trisphosphate, 23, the calcium mobilizing intracellular second messenger of the phosphatidylinositol (PI) cycle, is rapidly metabolized in vivo by either of two divergent pathways: (a) initial phosphorylation by a 3-kinase followed by hydrolysis of the C(5)-phosphate, or (b) direct dephosphorylation by a specific 5-phosphatase. Replacement of the 5-phosphate group on 23 with a less labile phosphonate group has the potential of preventing its degradation via the proposed deactivation step. An example of this was shown by Falck when he reported that the 5-methylene phosphonate analog of 23 has been shown to be a long lived agonist of calcium mobilization.
The goal of this research is to investigate the regio- and stereoselectivity of a thermal Diels-Alder cyclization between KVP and 1-acetoxy-1,3-butadiene in order to discern whether it follows the results of Darling or the results of McClure. With the Diels-Alder cyclization product in hand, we plan to complete the synthesis of 4-deoxy-\(\text{D-myositol}\) 5-phosphonate, 21, and 1-epi-4-deoxy-\(\text{D-myositol}\)-5-phosphonate, 24 (Figure 17).

Results and Discussion

Retrosynthetic Analysis

To date, the syntheses of most inositol analogues has been based on the modification of the readily available, \(\text{myo-inositol}\), and proceed through multiple protection and deprotection steps to produce the desired functional group patterns.\textsuperscript{111-115} Several syntheses have also commenced with non-inositol precursors such as benzene, quinic acid, and simpler cyclohexenol derivatives.\textsuperscript{116,117} Of the phosphonate derivatives that have been prepared, the majority of them are methylene phosphonate derivatives, and are generally biologically inactive.\textsuperscript{118a-c} Most of these methylene phosphonate derivatives were synthesized via Homer-Emmons-Wadsworth olefinations with methylbisphosphonate and a cyclohexanone derivative, followed by
hydrogenation of the resulting olefin.\textsuperscript{116b,d} Non-isosteric phosphonate analogs, such as our target molecules, 21 and 24, are scarce.\textsuperscript{117a,b}

Scheme 73. Retrosynthetic analysis towards myo-inositol 21 and 24.
Our interest in this area was stimulated by the prospect of designing a synthesis of inositol derivatives 21 and 24, employing our oxaphospholene methodology. The strategy is outlined in the retrosynthetic format depicted in Scheme 73. Diels-Alder cyclization of KVP and acetoxybutadiene will set 3 stereocenters in the cyclohexene intermediate, 22. Bishydroxylation of the resulting olefin should then set the remaining two stereocenters. Following the preparation of the diol, Baeyer-Villiger oxidation to convert the acetyl group into an acetoxy group should then yield 25 which can then be sequentially deprotected to yield the myo-inositol derivative 21 or 24, depending on the stereochemistry observed in the Diels-Alder cyclization.

**Thermal Diels-Alder Cyclization**

The first goal of this research was to investigate the thermal Diels-Alder cyclization between KVP and acetoxybutadiene. Cyclization using Darling's conditions, 48 hours in a sealed tube at 100°C, with a catalytic amount of radical inhibitor added yielded one regio and stereoisomer, 22, in excellent yield (Scheme 74). The cyclization product was identical to the one obtained by Herzog and Hansen under Lewis acid assisted conditions.\textsuperscript{106} Proof of the regio and stereochemistry of the cyclization product was done using two-dimensional NMR experiments, including HETCOR, COSY, and nOE. These corresponded very well to the known results of the Lewis acid assisted conditions.\textsuperscript{106} It is
important to note here that extended reaction times or exclusion of the radical inhibitor yielded the cyclic diene, 27, in yields up to 50%.

Scheme 74. Thermal Diels-Alder cyclization results.

**Attempted Synthesis of 1-epi-4-deoxy-D-myo-Inositol-5-phosphonate.**

Knowing that the regio and stereoselectivity of the thermal Diels-Alder cyclization was identical to the Lewis acid assisted results, the thermal reaction
was used exclusively due to its ease in preparation and lack of any aqueous work-up.

Scheme 75. Osmylation and acetonide protection of the Diels-Alder product.

Bishydroxlation of the Diels-Alder product, 22, with OsO₄ and 4-methyl morpholine N-oxide (NMO) using known methods¹¹⁹a was stereoselectively directed by the neighboring acetoxy group yielding only one stereoisomer, 28,
in good yield. Masking of the 1,2-diol proceeded using the isopropylidene ketal (acetonide) group. The acetonide protecting group has commonly been used in carbohydrate chemistry to selectively mask the hydroxyls of sugars. Preparation of the acetonide proceeded quantitatively with dimethoxypropane in the presence of an acidic resin to yield acetonide 29 (Scheme 75).

Attempted Baeyer-Villiger oxidations on acetonide 29 to yield the protected inositol derivative, 30, have been unsuccessful, yielding only starting material (Scheme 76).

![Scheme 76. Attempted Baeyer-Villiger oxidation of acetonide 29.](image)

Alternative experimental conditions included elevated temperatures (reflux in ClCH₂CH₂Cl), use of other peracids, mCPBA (meta chloroperoxybenzoic acid) (70-90% active oxygen content), DNPBA (3,5-
dinitroperoxybenzoic acid\textsuperscript{121} (85\% active oxygen content), or TFPAA (peroxytrifluoroacetic acid) (90+\% active oxygen content), or addition of Lewis acids (MgBr\textsubscript{2}:OEt\textsubscript{2}, ZnCl\textsubscript{2}, BF\textsubscript{3}:OEt\textsubscript{2}) produced no better results.

![Scheme 77. Deacetylation using potassium carbonate.](image)

After numerous attempts to perform a Baeyer-Villiger oxidation on 29, it was thought that perhaps there was a steric issue involved, due to the neighboring acetoxy group. Deacetylation of 29, was performed easily using standard literature conditions, potassium carbonate in wet methanol, to produce alcohol 31 in excellent yield (Scheme 77).\textsuperscript{122} Alcohol 31 was then subjected to Baeyer-Villiger conditions identical to those used previously with similar results. As in the case of alcohol 30, only unreacted starting material was recovered from the reaction mixture in all cases, except when reacted at elevated
temperatures. Under these thermal Baeyer-Villiger conditions, decomposition of the alcohol was observed yielding a complex mixture of uncharacterized products.

Scheme 78. Use of a Mitsonobu reaction to reverse hydroxyl stereochemistry.
Attempted Synthesis of 4-deoxy-D-myoinositol-5-phosphonate, 21

Grieco and Hunt have recently published an example of the accelerating effects of a proximal hydroxyl group on the Baeyer-Villiger oxidation of ketones.\textsuperscript{123} This acceleration was explained as being due to the formation of hemiketal between the hydroxyl group and the ketone. Molecular modeling calculations at the 3-21G* level on alcohol 31 showed that reversing the stereochemistry of the alcohol at C-1 would put it in close proximity to the acetyl ketone. Additionally, reversal of the stereochemistry at the hydroxyl position would set up a synthesis of 4-deoxy-D-myoinositol 5-phosphonate, 21, following the synthetic scheme planned for 1-epi-4-deoxy-D-myoinositol-5-phosphonate, 24 (Scheme 73).

Subjection of alcohol 31 to Mitsonobu conditions\textsuperscript{124} using H$_2$O as the nucleophile yielded alcohol 32 in excellent yield (Scheme 78). This high yield can be explained by noting the thermodynamic advantage in converting from the axial to the equatorial hydroxyl group. The stereochemistry of alcohol 32 was verified using the change in coupling constants in the $^1$H-NMR spectrum and by nOE experiments. Baeyer-Villiger oxidation of alcohol 32 with mCPBA in CH$_2$Cl$_2$ has been unsuccessful in preliminary trials.
Future Work

Further attempts include more vigorous reaction conditions in the Baeyer-Villiger oxidation of alcohol 32. These will include the use of stronger oxidants (e.g. DNPBA) and the addition of Lewis acids (e.g. BF$_3$·OEt$_2$ or MgBr$_2$·OEt$_2$) to increase the electrophilicity of the carbonyl carbon.

Scheme 79. Synthetic plan towards myo-inositol derivatives 21 and 24.
An alternative synthetic route is shown in Scheme 79. Thermodynamic enolization of the acetyl group followed by \textit{in situ} quenching with TMSCl should yield silyl enol ether 33. This enol can then be oxidatively cleaved with ozone followed by exhaustive reduction of the resulting ozonide and ketone to yield the protected inositol derivative 34. Depending on the stereochemistry of the starting protected alcohol either 21 or 24 can then be synthesized by multiple deprotection steps. Additionally, other inositol derivatives can be prepared if the diastereomer is formed in the reduction.

![Figure 18. Chiral keto vinyl phosphonate derived from (+)-ephedrine.](image)

Conclusion of this research will be performed by inducing chirality into the synthetic plan. Optimally, chirality will be induced in the cyclization step.
either by use of a chiral Lewis acid or with a chiral phosphonate derivative such as 35 (Figure 18). As noted previously, these chiral phosphonates have been prepared by members of the McClure group, for example, 35 was prepared from methyl vinyl ketone and a aminophosphite, derived from (+)-ephedrine. An alternative method includes the use of Sharpless’ asymmetric dihydroxylation methodology.

Conclusion

It has been shown that the thermal Diels-Alder cyclization between KVP and acetoxy butadiene yields the cis-trans cyclohexene 22, as Hansen and Herzog had predicted in the Lewis acid assisted cyclization, and not 18 as shown by Darling. Further derivatization to the acetonide 29 has been accomplished in good yield over two steps. Presently, Baeyer-Villiger oxidation, towards the synthesis of 24, of acetonide 29 or the deacetylated intermediate, 31, has been unsuccessful using common methods. Additionally, it has been shown that the stereochemistry at the C-1 position can be reversed under Mitsonobu conditions.
**Experimental**

For general experimental information, see the Experimental Section in Chapter 2.

**Diethyl-3-oxo-1-butenephosphonate (11).** A 250 mL round-bottomed flask was charged with triethyl phosphite (11.5 mL, 0.0671 mol). The phosphite was cooled to 0°C and methyl vinyl ketone (5.00 mL, 0.0601 mol) was added dropwise via syringe over 15 min. This mixture was allowed to slowly come to room temperature and stirred for 48 h, forming a small amount of white precipitate in a pale yellow solution. This mixture was then recooled to 0°C and a solution of bromine (10.9 g, 0.0679 mol) in CH₂Cl₂ (100 mL) was added dropwise via an addition funnel over 45 min. The mixture was allowed to slowly come to room temperature and stirred for 6 h. The solvent was then removed from the reaction mixture under reduced pressure to yield an orange oil (13.21 g) which was diluted with Et₂O (40 mL). The solution was then cooled to 0°C and a solution of NEt₃ (24.5 g, 0.244 mol) in Et₂O (100 mL) was added dropwise via an addition funnel over 45 min. The mixture was allowed to slowly come to room temperature and stirred for 12 h, forming a white precipitate in a orange solution. The precipitate was removed by vacuum filtration and the excess solvent was removed under reduced pressure to give an orange oil (14.28 g).
Column chromatography (3% MeOH/Et₂O) yielded 11 as a colorless oil (Rt=0.55, 3% MeOH/Et₂O), (8.65 g, 0.0419 mol, 70%).

![Chemical Structure](image)

**1H-NMR (CDCl₃):** 6.79 (dd, 1H, Jₚ,H=20.0 Hz, J=18.0 Hz, H on C1), 6.56 (dd, J=18.0 Hz, Jₚ,H=17.0 Hz, H on C2), 4.00 (app pent, 4H, J=7.6 Hz, H's on C5 and C7), 2.24 (s, 3H, H's on C4), 1.23 (t, 6H, Jₚ,H=7.3 Hz, H's on C6 and C8).  **13C-NMR (CDCl₃):** 196.4 (d, Jₚ,C=23.8 Hz, C3), 143.3 (d, Jₚ,C=4.0 Hz, C2), 129.4 (d, Jₚ,C=183.7 Hz, C1), 63.4 (d, Jₚ,C=6.0 Hz, C5 and C7), 27.8 (C4), 16.2 (d, Jₚ,C=6.2 Hz, C6 and C8).  **³¹P-NMR (CDCl₃):** 15.8.  **HRMS calculated for C₈H₁₅O₄P:** 206.070798, found 206.070786.  **GC:** Rt=16.3 min.  **MS:** 207 (6), 191 (13), 163 (33), 135 (100), 107 (40), 81 (42), 55 (25).  **IR (NaCl, cm⁻¹):** 2984, 2909, 1686, 1258, 1165, 1052, 972.
1-Acetoxyl-1,3-butadiene (17). A 100 mL round-bottomed jar was charged with potassium acetate (22.0 g, 224 mmol) and acetic anhydride (36 mL). The mixture was brought to reflux and 1-butenal (15.7 g, 225 mmol) was added dropwise over a period of 45 min. The mixture was refluxed further for 1 hour. The mixture was cooled to room temperature, 20% Na₂CO₃ (50 mL) was added, and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 30 mL). The extracts were combined, dried over MgSO₄, and the solvent was removed in vacuo to yield an orange liquid (28.2 g). Distillation (45-52°C, 36 mm Hg) yielded 17 as a colorless liquid (15.65 g, 140 mmol, 62%), (E/Z ratio 68/32).

Z-isomer:

\[ \text{H-NMR (CDCl}_3\text{): 6.94 (d, 1H, J=6.8 Hz, H on C1), 6.59 (dtd, 1H, J=17.1, 10.2, 0.9 Hz, H on C2), 5.92 (dd, 1H, J=17.7, 11.8 Hz, H on C3), 5.41 (dd, 1H, J=11.0, 6.4 Hz, H on C3), 5.13 (dd, 1H, J=17.1, 0.9 Hz, H on C4), 4.99 (dd, 1H, J=9.7, 0.9 Hz, H on C4), 2.03 (s, 3H, H on C6). \] \text{^13C-NMR (CDCl}_3\text{): 167.1 (C5), 133.8} \]
(C1), 128.6 (C2), 117.3 (C4), 113.0 (C3), 20.2 (C6). Spectral data is consistent with literature values.\textsuperscript{107}

$$
\text{E-isomer:}
$$

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 7.28 (d, 1H, J=12.3 Hz, H on C1), 6.16 (dt, 1H, J=16.9, 10.8 Hz, H on C2), 5.92 (dd, 1H, J=17.7, 11.8 Hz, H on C3), 5.03 (dd, 1H, J=16.8, 0.9 Hz, H on C4), 4.96 (dd, 1H, J=10.2, 0.9 Hz, H on C4), 2.10 (s, 3H, H on C6).

\textsuperscript{13}C-NMR (CDCl\textsubscript{3}): 167.4 (C5), 138.5 (C1), 131.5 (C2), 116.8 (C4), 115.7 (C3), 21.7 (C6). Spectral data is consistent with literature values.\textsuperscript{107}

**Diethyl 3-acetoxy-2-(1-oxoethyl)-4-cyclohexen-1-phosphonate (22).**

A 5 mL cone vial was charged with 1-acetoxy-1,3-butadiene, 17 (1.70 g, 15.3 mmol), diethyl-3-oxobut-1-enphosphonate, 11, (2.80 g, 13.6 mmol), and 5-tert-butyl-4-hydroxy-2-methylphenylsulfide (0.015 g, 0.042 mmol) under a stream of argon. The reaction vessel was then sealed and heated to 100\textdegree{}C for 45 h to
yield an orange oil (4.45 g). Column chromatography (3% MeOH/Et$_2$O) yielded 22 as a yellow oil ($R_f$=0.42, 3% MeOH/Et$_2$O), (3.85 g, 12.1 mmol, 89%).

$^1$H-NMR (CDCl$_3$): 6.00-5.90 (m, 1H, H on C4), 5.78-5.68 (m, 1H, H on C5), 5.55-5.47 (m, 1H, H on C3), 4.00 (qd, 4H, $J$=7.4 Hz, $J_{p-H}$=2.1 Hz, H's on C7 and C9), 3.07 (ddd, 1H, $J_{p-H}$=8.9 Hz, $J$=6.1, 2.8 Hz, H on C2), 2.61 (ddd, 1H, $J_{p-H}$=8.2 Hz, $J$=4.9, 1.7 Hz, H on C1), 2.62-2.19 (2H, m, H's on C6), 2.27 (3H, s, H's on C12), 1.93 (s, 3H, H's on C14), 1.24 (td, 6H, $J_{p-H}$=7.1 Hz, $J$=2.7 Hz, H's on C8 and C10). $^{13}$C-NMR (CDCl$_3$): 205.6 (d, $J_{p-C}$=3.6 Hz, C11), 170.1 (C13), 130.9 (d, $J_{p-C}$=14.7 Hz, C5), 123.0 (C4), 63.7 (q, $J_{p-C}$=14.3 Hz, C7 and C9), 49.9 (d, $J_{p-C}$=3.0 Hz, C3), 30.4 (C12), 28.9 (C2), 28.0 (d, $J_{p-C}$=137.2 Hz, C1), 24.6 (d, $J_{p-C}$=4.7 Hz, C6), 20.7 (C14), 16.1 (d, $J_{p-C}$=3.2 Hz, C8 or C10), 15.9 (d, $J_{p-C}$=3.2 Hz, C10 or C8). $^{31}$P-NMR (CDCl$_3$): 31.4 Hz. HRMS calculated for C$_{14}$H$_{24}$O$_6$P:
Diethyl 2-(1-oxoethyl)-2,4-cyclohexadien-1-phosphonate (27): A 5 mL cone vial was charged with 1-acetoxy-1,3-butadiene, 17 (1.70 g, 15.3 mmol) and diethyl-3-oxobut-1-enphosphonate, 11, (2.80 g, 13.6 mmol) under a stream of argon. The reaction vessel was then sealed and heated to 100°C for 95 h to yield a black oil (4.45 g). Column chromatography (3% MeOH/Et₂O) yielded 27 as a yellow oil (Rᵢ=0.32, 3% MeOH/Et₂O), (1.75 g, 6.81 mmol, 50%).

\[^{1}H\text{-NMR (CDCl₃)}\;
\begin{align*}
&{6.96 \text{ (dd, 1H, } J_{P,H}=5.6 \text{ Hz, } J_{H-H}=5.6 \text{ Hz, H on C5}),}\,
&{6.11 \text{ (m, 2H, H's on C3 and C4),}\,
&{4.05 \text{ (q, 4H, } J_{H-H}=7.0 \text{ Hz, H's on C7 or C9),}\,
&{3.94 \text{ (q, 4H, } J_{H-H}=7.0 \text{ Hz, H's on C9 or C7),}\,
&{3.56 \text{ (dd, } J_{P,H}=25.6 \text{ Hz, } J_{H-H}=10.5 \text{ Hz, H on C1),}}
\end{align*}\]
2.86 (dddm (app tdm), 1H, $J_{\text{p-H}}=19.1$ Hz, $J_{\text{H-H}}=19.1$, 5.7 Hz, H on C6), 2.54 (dddm, 1H, $J_{\text{p-H}}=53.0$ Hz, $J_{\text{H-H}}=19.1$, 10.7 Hz, H on C6), 2.32 (s, 3H, H's on C12), 1.20 (t, 6H, $J_{\text{H-H}}=7.0$ Hz, H's on C8 or C10), 1.18 (t, 6H, $J_{\text{H-H}}=7.0$ Hz, H's on C10 or C8). $^{13}$C-NMR (CDCl$_3$): 196.4 (d, $J_{\text{p-C}}=3.3$ Hz, C11), 134.7 (d, $J_{\text{p-C}}=10.1$ Hz, C5), 133.0 (d, $J_{\text{p-C}}=5.7$ Hz, C3 or C4), 132.2 (d, $J_{\text{p-C}}=9.4$ Hz, C4 or C3), 123.7 (d, $J_{\text{p-C}}=4.7$ Hz, C2), 62.0 (d, $J_{\text{p-C}}=5.2$ Hz, C7 or C9), 61.9 (d, $J_{\text{p-C}}=6.6$ Hz, C9 or C7), 28.0 (d, $J_{\text{p-C}}=134.8$ Hz, C1), 25.1 (C12), 23.9 (d, $J_{\text{p-C}}=5.3$ Hz, C6), 16.3 (d, $J_{\text{p-C}}=2.3$ Hz, C8 or C10), 16.2 (d, $J_{\text{p-C}}=2.6$ Hz, C10 or C8). $^{31}$P-NMR (CDCl$_3$): 30.8 Hz. HRMS calculated for C$_{12}$H$_{19}$O$_4$P: 257.931526, found 257.931105. MS: 257 (1), 255 (41), 233 (42), 217 (39), 166 (16), 138 (100), 121 (23), 111 (71), 95 (44), 82 (39). IR (NaCl, cm$^{-1}$): 2983, 2932, 1721, 1640, 1369, 1236, 1027, 966. UV: $\lambda_{\text{max}}=265$ (log $\varepsilon=4.74$).

**Diethyl 3-acetoxy-4,5-dihydroxy-2-(1-oxoethyl)-4-cyclohexan-1-phosphonate (28).** A 50 mL round-bottomed flask was charged with 4-methylmorpholine N-oxide (0.632 g, 5.39 mmol), H$_2$O (3 mL), and acetone (5 mL). OsO$_4$ (0.025 M in acetone, 3.45 mL, 0.086 mmol) was added to the mixture, and cooled to 0°C. The flask was then charged with Diels-Alder product 22 (0.820 g, 2.58 mmol) and acetone (10 mL). The mixture was allowed to slowly come to room temperature and stirred for 15 h. 10% NaHSO$_3$
(10 mL) was added to the solution and stirred for 30 min. The aqueous layer was then saturated with NaCl and the organics were extracted with EtOAc (8 x 40 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield an oily white solid (0.810 g). This solid was recrystallized in EtOAc to yield 28 as a white solid (Rf=0.78, 6% MeOH/Et₂O), (0.685 g, 1.94 mmol, 75%), mp 139.9-140.1°C (EtOAc).

**1H-NMR (CDCl₃):** 5.39 (dd, 1H, J=7.3, 4.1 Hz, H on C3), 4.02 (qd, 4H, J=7.4 Hz, Jₚ,H=2.1 Hz, H's on C7 and C9), 3.87-3.82 (m, 4H, H's on C4, C5, and OH's), 3.30 (ddd, 1H, Jₚ,H=8.9 Hz, J=6.1, 2.8 Hz, H on C2), 2.61 (ddd, 1H, Jₚ,H=8.2 Hz, J=4.9, 1.7 Hz, H on C1), 2.21 (s, 3H, H's on C12), 2.09-1.81 (m, 2H, H's on C6), 1.99 (3H, s, H's on C14), 1.27 (6H, td, J=7.1 Hz, Jₚ,H=2.7 Hz, H's on C8 and C10). **13C-NMR (CDCl₃):** 206.2 (C11), 169.7 (C13), 70.2 (d, Jₚ,C=14.0 Hz, C5),
69.1 (C4), 67.1 (d, \( J_{P,C} = 17.9 \) Hz, H on C3), 62.4 (q, \( J_{P,C} = 4.7 \) Hz, C7 and C9), 46.5 (d, \( J_{P,C} = 2.9 \) Hz, C2), 30.4 (C12), 30.1 (d, \( J_{P,C} = 142.1 \) Hz, C1), 26.4 (d, \( J_{P,C} = 4.6 \) Hz, C6), 20.8 (C14), 16.3 (d, \( J_{P,C} = 5.9 \) Hz, C8 or C10), 16.1 (d, \( J_{P,C} = 5.9 \) Hz, C10 or C8) \(^{31}\)P-NMR (CDCl\(_3\)): 30.0. HRMS calculated for C\(_{14}H_{23}PO_8\): 353.13653 (M+H\(^+\)), found: 353.13744. MS: 353 (1), 275 (15), 264 (8), 249 (41), 233 (16), 221 (22), 207 (34), 193 (9), 175 (27), 165 (45), 147 (17), 138 (100), 121 (19), 111 (82), 95 (61), 83 (47), 65 (34), 55 (18). IR (NaCl, cm\(^{-1}\)): 3474, 3276, 2980, 2962, 1737, 1705, 1375, 1230, 1018, 974.

**Diethyl 3-acetoxy-4,5-dihydroxy-2-(1-oxoethyl)-4-cyclohexan-1-phosphonate O-Acetonide (29).** A 25 ml round-bottomed flask was charged with the diol, 28 (0.133 g, 0.377 mmol), Amberlite IR120 (plus) (0.127 g), dimethoxypropane (4 mL), and CH\(_2\)Cl\(_2\) (2 mL). The mixture was allowed to stir for 16 h at room temperature, filtered, and the solvent was removed under reduced pressure to yield a purple oil (0.160 g). Column chromatography (3% MeOH/Et\(_2\)O) yielded 29 as a yellow oil (R\(_f\)=0.56, 6% MeOH/Et\(_2\)O), (0.147 g, 0.374 mmol, 99%).
$^1$H-NMR (CDCl$_3$): 5.12 (dd, 1H, $J$=5.9, 0.8 Hz, H on C3), 4.34 (qd, 1H, $J_{p,H}$=7.5 Hz, $J$=1.8 Hz, H on C5), 4.08 (t, 1H, $J$=6.9 Hz, H on C4), 4.08-3.90 (m, 4H, H's on C7 and C9), 3.44 (ddd, 1H, $J_{p,H}$= 8.9 Hz, $J$=5.1, 3.7 Hz, H on C2), 2.57 (ddd, 1H, $J_{p,H}$=9.0 Hz, $J$=5.1, 2.6 Hz, H on C1), 2.22-1.82 (m, 2H, H's on C6), 2.18 (s, 3H, H's on C12), 2.03 (s, 3H, H's on C14), 1.44 (s, 3H, H's on C16 or C17), 1.28-1.11 (m, 9H, H's on C8, C10, and C17 or C16). $^{13}$C-NMR (CDCl$_3$): 207.1 (C11), 169.6 (C13), 109.0 (C15), 73.5 (C4), 72.1 (d, $J_{p,C}$=15.5 Hz, C5), 70.2 (d, $J_{p,C}$=10.6 Hz, C3), 62.0 (q, $J_{p,C}$=10.4 Hz, C7 and C9), 45.5 (d, $J_{p,C}$= 3.0 Hz, C2), 31.3 (C12), 29.6 (C16 or C17), 27.6 (C17 or C16), 25.6 (d, $J_{p,C}$=142.2 Hz, C1), 24.0 (d, $J_{p,C}$=23.4 Hz, C6), 20.8 (C14), 16.4 (d, $J_{p,C}$=5.9 Hz, C8 or C10), 16.2 (d, $J_{p,C}$=5.9 Hz, C10 or C8). $^{31}$P-NMR (CDCl$_3$): 30.7. HRMS calculated for C$_{17}$H$_{29}$PO$_8$: 392.161514, found: 392.160007. MS: 393 (1), 377 (78), 317 (10), 289 (64), 275 (61), 249 (11), 215 (17), 203 (16), 175 (45), 165 (15), 155 (18),...
Diethyl 3,4,5-trihydroxy-2-(1-oxoethyl)-4-cyclohexan-1-phosphonate 4,5-O-Acetonide (31). A 25 mL round-bottomed flask was charged with acetonide, 29, (0.310 g, 0.79 mmol), K₂CO₃ (0.174 g, 1.26 mmol), MeOH (15 mL), and H₂O (2.5 mL). The mixture was allowed to stir for 4 h at room temperature, poured into 10% HCl (10 mL), and the layers were separated. The organics were extracted with CH₂Cl₂ (3 X 20 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield an orange oil (0.28 g). Column chromatography (3% MeOH/Et₂O) yielded 31 as a colorless oil (Rf=0.15, 3% MeOH/Et₂O), (0.260 g, 0.74 mmol, 94%).
1H-NMR (CDCl₃): 4.35 (dd, 1H, J=7.3, 4.1 Hz, H on C3), 4.13-4.00 (m, 4H, H's on C7 and C9), 4.08-3.86 (m, 2H, H's on C4 and C5), 3.36 (ddd, 1H, Jp,H=14.4 Hz, J=9.6, 4.2 Hz, H on C2), 2.96 (1H, bs, OH), 2.52 (ddddd, 1H, Jp,H=20.3 Hz, J=11.9, 7.7, 4.7 Hz, H on C1), 2.34 (3H, s, H's on C12), 2.21 (ddddd, 1H, Jp,H=16.8 Hz, J=11.2, 6.4, 5.4 Hz, H on C6), 1.78 (ddddd, 1H, Jp,H=16.5 Hz, J=11.9, 4.9, 3.3 Hz, H on C6), 1.47 (s, 3H, H's on C14 or C15), 1.28 (m, 9H, H's on C8, C10, and C15 or C14). 13C-NMR (CDCl₃): 211.6 (C11), 108.8 (C13), 75.4 (C4), 72.1 (d, Jp,C=17.4 Hz, C5), 70.5 (d, Jp,C=17.7 Hz, C3), 62.2 (d, Jp,C=6.7 Hz, C7 and C9), 46.8 (d, Jp,C=2.8 Hz, C2), 32.7 (C12), 28.5 (d, Jp,C=147.1 Hz, C1), 27.3 (C14 or C15), 25.9 (C15 or C14), 24.8 (d, Jp,C=6.1 Hz, C6), 16.4 (d, Jp,C=4.9 Hz, C8 or C10), 16.2 (d, Jp,C=4.9 Hz, C10 or C8). 31P NMR (CDCl₃): 31.2 Hz. HRMS calculated for C₁₅H₂₈O₇P: 351.157267, found 351.155701. MS 351 (2), 335 (62), 289 (56), 275 (13), 249 (12), 231 (13), 207 (14), 193 (10), 175 (33), 165 (28), 155 (17), 137 (100), 121 (15), 111 (55), 95 (46), 83 (30), 67 (20). IR (NaCl, cm⁻¹): 3346, 2987, 1716, 1383, 1211, 1053, 970.

**Diethyl 3,4,5-trihydroxy-2-(1-oxoethyl)-4-cyclohexan-1-phosphonate 4,5-O-Acetonide (32).** A 25 mL round-bottomed flask was charged with acetonide, 31, (0.023 g, 0.065 mmol), PPh₃ (0.022 g, 0.084 mmol), and THF (8 mL). The mixture was cooled to 0°C and DEAD (0.015g,
0.084 mmol) in THF (2 mL) was added dropwise. The mixture was allowed to
stir at room temperature for 30 min. The mixture was quenched with H₂O (4 mL), allowed to stir at room temperature for an additional 30 min, and the layers were separated. The organics were extracted with CH₂Cl₂ (6 X 10 mL). The organic washes were combined, dried with MgSO₄, and the solvent was removed under reduced pressure to yield a pink oily solid (0.042 g). Column chromatography (3% MeOH/Et₂O) yielded 32 as a colorless oil (Rᵣ=0.16, 3% MeOH/Et₂O), (0.021 g, 0.059 mmol, 91%).

1H-NMR (CDCl₃): 4.35 (dd, 1H, J=14.5, 6.4 Hz, H on C3), 4.13-4.00 (m, 4H, H’s on C7 and C9), 4.04-3.89 (m, 2H, H’s on C4 and C5), 3.37 (ddd, 1H, Jₚₗ=14.4 Hz, J=9.7, 4.2 Hz, H on C2), 2.96 (bs, 1H, OH), 2.52 (dddd, 1H, Jₚₗ=20.3 Hz, J=11.9, 7.7, 4.7 Hz, H on C1), 2.34 (s, 3H, H’s on C12), 2.21 (ddddd, 1H, Jₚₗ=16.8 Hz, J=11.2, 6.4, 5.4 Hz, H on C6), 1.78 (ddddd, 1H, Jₚₗ=16.5 Hz, J=11.9,
4.9, 3.3 Hz, H on C6), 1.47 (s, 3H, H's on C14 or C15), 1.28 (m, 9H, H's on C8, C10, and C15 or C14). $^{13}$C-NMR (CDCl$_3$): 211.6 (C11), 108.8 (C13), 75.4 (C4), 72.1 (d, $J_{p-c}$=17.4 Hz, C5), 70.5 (d, $J_{p-c}$=17.7 Hz, C3), 62.2 (d, $J_{p-c}$=6.7 Hz, C7 and C9), 46.8 (d, $J_{p-c}$=2.8 Hz, C2), 32.7 (C12), 28.5 (d, $J_{p-c}$=147.1 Hz, C1), 27.3 (C14 or C15), 25.9 (C15 or C14), 24.8 (d, $J_{p-c}$=6.1 Hz, C6), 16.3 (d, $J_{p-c}$=4.9 Hz, C8 and C10). $^{31}$P NMR (CDCl$_3$): 31.2 Hz. HRMS calculated for C$_{15}$H$_{28}$O$_7$P: 351.157267, found 351.155698. MS 351 (2), 335 (62), 289 (56), 275 (13), 249 (12), 231 (13), 207 (14), 193 (10), 175 (33), 165 (28), 155 (17), 137 (100), 121 (15), 111 (55), 95 (46), 83 (30), 67 (20). IR (NaCl, cm$^{-1}$): 3346, 2987, 1716, 1383, 1211, 1053, 970.
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