Bridgehead approaches toward polycyclic alkaloids

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Bridgehead approaches toward polycyclic alkaloids

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Iowa State University, 1993
Bridgehead approaches toward polycyclic alkaloids

by

Bradley Jay Andersh

A Dissertation Submitted to the Graduate Faculty in Partial Fulfillment of the Requirements for the Degree of DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

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For the Graduate College

Iowa State University
Ames, Iowa

1993
DEDICATION

This dissertation is dedicated to my wife, Amy, and our son, Jonathon. Throughout my tenure as a graduate student, they have had to make many sacrifices in their lives. Despite this they have always been there for me and have given me more love than one person deserves.
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GENERAL INTRODUCTION

The synthesis of natural products has developed into one of the most active areas of research in organic chemistry in recent years. Although the ultimate goal of natural product research is to prepare the naturally occurring compounds or analogs of these compounds, often-times new methodology is developed in the course of the investigation. This dissertation will deal with both the development of new methodology, as well as synthetic efforts toward the diterpene alkaloids.

Explanation of Dissertation Format

This dissertation is divided into two papers with each paper being preceded by an introduction. The two papers are intended to be separate, publishable articles. The first paper deals with the use of highly functionalized bridgehead radicals in organic synthesis. The second paper deals with applications of bridgehead radical chemistry for the preparation of polycyclic alkaloids. A general summary of both papers follows the second paper.
PAPER I. BRIDGEHEAD RADICALS IN ORGANIC SYNTHESIS
INTRODUCTION

Although radical chemistry can be dated back to 1900,\(^1\) it was not until the 1950's and the 1960's that chemists began to develop an understanding of radical structure and reactivity.\(^2\) Because of this pioneering work, radical chemistry has become a valuable tool for the preparation of both simple and complex molecules.\(^3\) The prominence that radical chemistry has obtained in organic synthesis is largely due to the mild reaction conditions which are employed. Whereas many reactions in organic synthesis involve the use of Lewis acids and Lewis bases, radical reactions are usually performed under neutral conditions. Because of this, a wide variety of functional groups can be tolerated within the substrates, reactants, and products. The prevalence of radical chemistry in organic synthesis can also be explained by the normally high levels of chemoselectivity, regioselectivity, and stereoselectivity which are observed in radical reactions.

Despite all of the synthetic work that has been reported in recent years with alkyl radicals,\(^4\) relatively little attention has been given to the use of bridgehead radicals in synthetic chemistry. Researchers have, however, begun to look closely at the physical properties of bridgehead radicals.\(^5\)

There are two types of bridgehead radicals which have been produced and studied by chemists, those which are produced from fused bicyclic compounds and those which are produced from bridged bicyclic compounds. A general structure for and a member of each of
Figure 1: Examples of the types of bridgehead radicals.

It has been shown experimentally that bridgehead radicals are more reactive and less stable than tertiary radicals. This increased reactivity is due in part to the fact that bridgehead radicals are pyramidal instead of nearly planar like tertiary radicals. Since the bridgehead radicals are pyramidal, the $\beta$-carbons of the radical center are tied back, causing less steric congestion at the radical center. The internal strain which is present in bridgehead radicals also increases their reactivity.

The pyramidal structure of bridgehead radicals also influences the singly occupied molecular orbital (SOMO) of the radical center by ensuring that the SOMO will be a $\sigma$-orbital with high $s$-character. Since the orientation of the SOMO with respect to other bonds in the molecule
is different, orbital overlap in less favorable. This difference in orbital orientation helps to explain why bridgehead radicals are less stable than acyclic tertiary radicals. It has been suggested that most of the increased stability of the tert-butyl radical versus the methyl radical can be attributed to hyperconjugation and inductive effects. Since hyperconjugation and inductive effects are less prevalent with bridgehead radicals, because of poor orbital overlap, it follows that bridgehead radicals are less stable than tertiary radicals. Also, the structures that would have to be produced to allow for hyperconjugation in bridged bicyclic systems would contain energetically unfavorable bridgehead alkenes (see Figure 2).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Figure 2: Hyperconjugation in the tert-butyl radical and a bridged bicyclic radical.

Because of the lower stability of bridgehead radicals, they are more difficult to generate than normal tertiary radicals. It has been found, however, that as the strain of the bicyclic system decreases, the ease of formation of the bridgehead radical increases. Although
bridgehead radicals are harder to form than tertiary radicals, they can still be generated with relative ease. Methods which have been employed for the preparation of bridgehead radicals include perester thermolysis,6 azoalkane thermolysis,7 tin hydride reduction of bridgehead halides,8 the Barton decarboxylation reaction,9 fragmentation of alkoxy radicals,10 hydrogen abstraction,11 and ring closure reactions.12

Electron spin resonance spectroscopy (ESR) has also been used to obtain structural information about bridgehead radicals. It has been shown by ESR that the lifetimes of bridgehead radicals in solution are of the same order of magnitude as other transient alkyl radicals.5 This is surprising because some highly strained bridgehead carbocations cannot be observed by low-temperature NMR, because they react or rearrange too rapidly. ESR spectroscopy has also provided supportive evidence for the theory that bridgehead radicals do not undergo hyperconjugation as readily as other tertiary radicals, because the observed hyperfine splittings with respect to the β-carbons (α(Hβ) values) are much lower for bridgehead radicals than for tert-butyl radicals.5 It has also been shown by ESR spectroscopy that some bridgehead radicals show large long-range hyperfine splittings, thus indicating the presence of through-space and through-bond reenforcements of the bridgehead radical center. These observations help to explain why the bridgehead radicals of bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane are more readily formed than the bridgehead radical of bicyclo[2.2.1]heptane by hydrogen atom abstraction as shown in Scheme I.13
Scheme I

1. \( R^- \rightarrow \) t-BuO⁻ 100 0
   Cl⁻ 50 50

2. \( R^- \rightarrow \) t-BuO⁻ 0 100
   Br⁻ 0 100
   \((\text{Me}_3\text{Si})_2\text{N}^-\) 29 71

3. \( R^- \rightarrow \) Br⁻ 0 100
   \((\text{Me}_3\text{Si})_2\text{N}^-\) 3 97
Although some of the properties of bridgehead radicals are slightly different from those of normal alkyl radicals, bridgehead radicals still undergo most of the reactions which are common for carbon centered radicals. As is true of most carbon-centered radicals, bridgehead radicals are nucleophilic. The high s-character of bridgehead radicals actually makes them more nucleophilic than normal tertiary radicals. Because of their nucleophilic character, conventional abstraction and addition reactions occur readily. Disproportionation reactions, however, are less common in bridgehead systems because the resulting products would be anti-Bredt alkenes. Unimolecular reactions, such as decomposition and rearrangement, are also less common with bridgehead radicals than with alkyl radicals, because there is insufficient orbital overlap between the SOMO of the radical center and the other bonds of the molecule. 

The most widely used bridgehead radical in organic synthesis has been the 1-adamantyl radical. Ohno and coworkers have recently published the results of an extensive study on the reaction of the 1-adamantyl radical with electron-deficient alkenes, alkynes, and allenies. In this study the adamantyl radical was prepared by either treating 1-adamantyl bromide or iodide with tri-n-butyltin hydride and AIBN or by treating 1-adamantyl bromide with a zinc-copper couple in ethanol and water. By these methods they were able to prepare various β-functionalized alkyl and alkenyl adamantyl derivatives. The results from some of these reactions are shown in Scheme II. Although this was not the first use of adamantyl radicals, it is one of the most
Scheme II

\[
\begin{align*}
\text{X} + \text{R}^1\text{R}^2 & \rightarrow \text{R}^1\text{R}^2 \\
\% \text{ Yield} & \\
\text{X} & \text{R}^1 & \text{R}^2 & n\text{-Bu}_3\text{SnH, AIBN} & Zn/Cu \\
\text{Br} & H & CN & 80 & \\
\text{Br} & H & \text{COCH}_3 & 43 & \\
\text{Br} & H & \text{CO}_2\text{CH}_3 & 70 & \\
\text{Br} & \text{CN} & \text{CO}_2\text{CH}_3 & 0 & \\
\text{I} & \text{CN} & \text{CO}_2\text{CH}_3 & 36 & \\
\text{Br} & H & \text{SOPh} & 35 & 41 \\
\text{Br} & -(\text{CH}_2)_3\text{CO}- & & 33 & 91 \\
\end{align*}
\]
extensive studies to be published with respect to bridgehead radical chemistry.

There have also been a number of other reported uses of the 1-adamantyl radical in organic synthesis. Testaferri and coworkers have found that the treatment of adamantane-1-carboxylic acid with ammonium persulfate and silver nitrate in the presence of para-substituted nitrobenzenes gives para-substituted 1-adamantylbenzenes via the intermediacy of the adamantyl radical.\textsuperscript{15} In this reaction it is necessary that the group \textit{para} to the nitro group is an electron-withdrawing group. Aromatic substitution reactions involving the
1-adamantyl radical have also been reported by Barton. He has found that irradiation of a solution of the adamantyl ester of \(N\)-hydroxy-2-thiopyridone and protonated pyridines gives only 2-adamantyl pyridines when the four position of the pyridine is blocked. If, however, there is a hydrogen at the four position of the pyridine, then both 2-adamantyl pyridines and 4-adamantyl pyridines are produced. In both cases, excellent yields of the adamantyl pyridines are obtained for this reaction.

Scheme III

\[
\text{Ad}^* + \begin{array}{c}
\text{NO}_2 \\
X
\end{array} \rightleftharpoons \begin{array}{c}
\text{Ad} \\
\text{NO}_2
\end{array} \rightarrow \begin{array}{c}
\text{Ad} \\
X
\end{array}
\]

\[ \text{Ad}^* = \begin{array}{c}
\text{ adamantyl radical}
\end{array} \]

\[
\text{Ad}^* + \begin{array}{c}
\text{R}^2 \\
\text{R}^3
\end{array} \rightarrow \begin{array}{c}
\text{R}^2 \\
\text{R}^3
\end{array} \text{Ad} + \begin{array}{c}
\text{R}^2 \\
\text{R}^1
\end{array} \text{N}
\]

When \( R^3 = H \)
It has been shown by Baldwin that triphenylprop-2-ynylstannane as well as various allylic stannanes react with the 1-adamantyl radical to give allenic and allylic derivatives of adamantane (see Scheme IV).\textsuperscript{17} Similarly, Barton has shown that the 1-adamantyl radical reacts

Scheme IV

\[ \text{Br} + \text{SnPh}_3 \xrightarrow{\text{AIBN}} \text{H} \xrightarrow{\text{SnPh}_3} \text{C}_2\text{CH}_2 \]

\[ \text{Br} + \text{SnPh}_3 \xrightarrow{\text{AIBN}} \text{H} \xrightarrow{\text{SnPh}_3} \text{C}_2\text{CH}_2 \]

\[ \text{Br} + \text{CO}_2\text{Et} \xrightarrow{\text{AIBN}} \text{CO}_2\text{Et} \xrightarrow{\text{SnBu}_3} \text{CH}_2 \]

\[ \text{Br} + \text{CONH-}t\text{-Bu} \xrightarrow{\text{AIBN}} \text{CONH-}t\text{-Bu} \xrightarrow{\text{SnBu}_3} \text{CH}_2 \]
radical reacts with 2-substituted allylic sulfides giving the corresponding allylic adamantane derivatives (see Scheme V). In these reactions the 1-adamantyl radical was generated from the adamantyl ester of N-hydroxy-2-thiopyridone.

Scheme V

Curran has also shown that allylic transfer occurs with the 1-adamantyl radical. By treating 1-adamantyl bromide with allyl tris(trimethylsilyl)silane in the presence of AIBN, he was able to prepare 1-(2-propenyl)adamantane in 48% yield.
A limited number of publications which do not involve the 1-adamantyl radical have also appeared. Buchi has used bridgehead radical chemistry in his syntheses of β-agarofuran and dihydroagarofuran.\textsuperscript{21} By irradiating a mixture of bromide 1, tri-$n$-butyltin hydride and AIBN in cyclohexane, dihydroagarofuran 2 was prepared in 20% yield via an intramolecular addition of the resulting bridgehead radical to the olefin. Unfortunately, this reaction also gave isodihydroagarofuran (the β-methyl compound) in 47% yield. To overcome this lack of stereoselectivity, Buchi prepared vinyl silane 4 in 72% yield by irradiating a mixture of the acetylenic bromide 3, tri-$n$-butyltin hydride, and AIBN in cyclohexane. As in the first example,
this reaction undoubtedly proceeds through the intermediacy of a bridgehead radical. The resulting tricyclic compound 4 was then converted into both dihydroagarofuran and β-agarofuran. These reactions are particularly noteworthy because they are the first examples of intramolecular cyclizations involving bridgehead radicals, and one of the few examples of the use of functionalized bridgehead radicals in organic synthesis.

Kraus and Hon also have reported an example of an intramolecular cyclization reaction involving a bridgehead radical. They found that when bromide 5 was treated with tri-\(n\)-butyltin hydride and AIBN in boiling benzene tricyclic compound 6 was produced in 50% yield.

They also discovered that, in this system, the electron-withdrawing group on the olefin was essential for cyclization to occur, because treatment of compound 7 with tri-\(n\)-butyltin hydride and AIBN in boiling benzene gave only the reduction product 8.
\[ \text{7} \quad \text{n-Bu}_3\text{SnH, AIBN} \quad \text{Benzene, 80°C} \quad \text{8} \]
RESULTS AND DISCUSSION

As is evident from the previous review of the literature, most of the published work using bridgehead radicals has dealt with unfunctionalized bicyclic systems. In order to show the applicability of bridgehead radical chemistry for other systems, we have begun an investigation into the preparation and use of functionalized bridgehead radicals. Although the ultimate goal of this research is to use the resulting radical adducts for the preparation of polycyclic alkaloids, we have attempted a number of interesting reactions involving bridgehead radicals.23

The bicyclic system that has been the focus of our research is the azabicyclo[3.2.1]nonane derivative 9 which had been previously prepared by Kraus and Shi from ethyl 2-cyclohexanone carboxylate in two steps.24 Kraus and Shi also have shown that treatment of bromide 9 with AIBN and allyltri-n-butyltin gave the corresponding allylic compound 10 in 90% yield via radical 11 (see Scheme VI).25
Since this work was completed, we have discovered a number of other reagents which react with radical 11 in fair to good yield. One of the first goals of this research was to find satisfactory reaction conditions for the reaction of electron-deficient alkenes with radical 11. Based on Eguchi's work with 1-bromoadamantane,\textsuperscript{14} it was assumed that the reaction between bromide 9 and methyl vinyl ketone in the presence of tri-n-butyltin hydride and catalytic AIBN would give diketone 13. Unfortunately, when the reaction conditions of Eguchi were employed, the only product obtained was the reduction product 12. Compound 12 is undoubtedly generated by the abstraction of a
hydrogen atom from tri-\textit{n}-butyltin hydride by radical 11 before addition of the radical to methyl vinyl ketone can take place.

Modifications such as increasing the concentration of methyl vinyl ketone relative to the concentration of tri-\textit{n}-butyltin hydride usually result in the formation of the desired radical adduct.\textsuperscript{4b} Despite numerous attempts with different concentrations of methyl vinyl ketone and tri-\textit{n}-butyltin hydride, however, we only obtained the reduction product 12 or unidentified polymeric materials. Even when the reaction was run at extremely low concentrations of tri-\textit{n}-butyltin hydride (by regenerating tri-\textit{n}-butyltin hydride with sodium cyanoborohydride\textsuperscript{26} or by slowly adding tri-\textit{n}-butyltin hydride and AIBN via a syringe pump), we were unable to obtain compound 13.

Due to the failure of the "tin method" for the introduction of the desired 3-oxo-butane subunit, we then attempted to prepare the bridgehead radical in the presence of methyl vinyl ketone by treating bromide 9 with tri-\textit{n}-hexylborane using the conditions of Oshima.\textsuperscript{27} Again, the only product obtained was the reduction product 12.
Because radical 11 was reluctant to react with methyl vinyl ketone under the aforementioned conditions, we attempted to trap radical 11 with other electron-deficient alkenes. Reactions involving acrylonitrile, methyl methacrylate, or di-tert-butyl methylenemalonate.\textsuperscript{28} and

\begin{center}
\textbf{Scheme VII}
\end{center}

\begin{align*}
\text{Br} & \text{CN} \\
\text{CO}_2\text{Et} & \text{n-Bu}_3\text{SnH, AIBN, Benzene, 80°C} \\
\text{9} & \text{CN} \\
\text{Me} & \text{OMe} \\
\text{CO}_2\text{Et} & \text{n-Bu}_3\text{SnH, AIBN, Benzene, 80°C} \\
\text{9} & \text{OMe} \\
\text{t-BuO} & \text{O-t-Bu} \\
\text{CO}_2\text{Et} & \text{n-Bu}_3\text{SnH, AIBN, Benzene, 80°C}
\end{align*}
bromide 9 in the presence of tri-n-butyltin hydride and AIBN also led to the formation of the reduction product 12 and/or other undesired products.

Because the reduction of bromide 9 continually plagued the reactions involving tri-n-butyltin hydride, we investigated alternative methods for generating the bridgehead radical 11 with a trialkylstannyl radical. It is known that hexaalkylditins undergo homolytic cleavage of the tin-tin bond upon irradiation to generate two equivalents of the trialkylstannyl radical. Curran has also shown that hexaalkylditins serve as excellent reagents for atom transfer reactions. Based on this work we postulated that the treatment of bromide 9 with 0.6 equivalents of hexa-n-butylditin in the presence of excess 2-chloroacrylonitrile would give nitrile 14. Unfortunately, no reaction occurred.

By treating bromide 9 with 0.6 equivalents of hexa-n-butylditin in the presence of excess trichloroethylene, however, we were able to obtain a 20% yield of the dichloroethylene adduct 15 after irradiation of the mixture for 72 hours with a medium pressure Hanovia lamp.
Sixty-five% of the starting bromide 9 was also recovered from the reaction mixture.

A proposed mechanism for the formation of compound 15 is shown in Scheme VIII. Abstraction of the bromine atom from bromide 9 with a tri-\textit{n}-butylstannyl radical gives radical 16. The resulting bridgehead radical then adds to trichloroethylene at the carbon bearing only one chlorine atom, thereby generating the more stable radical 17. Elimination of a chlorine radical from intermediate 17 then gives compound 15.
In an effort to increase the conversion of bromide 9 into adduct 15 we increased the equivalents of hexa-n-butylditin to 1.2, thereby increasing the number of equivalents of the tri-n-butylstannyl radical to 2.4. Irradiation of this mixture for seven days gave the desired compound 15 in 37% yield along with 40% of the starting bromide. Further increases in the number of equivalents of hexa-n-butylditin to 2.4 gave, after irradiation for 48 hours, compound 15 in 72% yield with no recovery of starting bromide 9. We are uncertain at this time why 4.8 equivalents of the tri-n-butylstannyl radical are necessary for the complete conversion of bromide 9 to compound 15. Two of the equivalents are undoubtedly consumed in the formation of tri-n-butyltin bromide and tri-n-butyltin chloride. The rest may have added to trichloroethylene.

Based on the success of the trichloroethylene reaction, we then investigated the potential of other radical trapping agents using the same reaction conditions. Unfortunately, irradiation of a mixture of 1,2-dichloroethylene and bromide 9 with hexa-n-butylditin did not give chloride 18. Bromide 9 was recovered unchanged.
Likewise, irradiation of a mixture of tribromoethylene and bromide 9 with hexa-n-butylditin resulted in the recovery of bromide 9 unchanged. Although tribromoethylene has been shown to trap the thiophenol radical, this reaction may have been plagued by the formation of a vinyl radical of tribromoethylene.

Because the addition of radical 11 to electron deficient olefins was not as successful as we had envisioned, we then investigated the use of more functionalized allylic stannanes as radical traps. Treatment of bromide 9 with 2,3-bis(trimethylstannyl)-propene and a catalytic amount of AIBN in boiling toluene gave vinyl stannane 20 in 50% yield. Shortly after completing this work, Curran reported the first use of this reagent as a radical trapping reagent. He has shown that this reagent...
reacts with a number of different types of carbon centered radicals including the 1-adamantyl radical, but he did not report a yield for that particular reaction.

We have also found that bromide 9, when treated with 2,4-pentadienyltri-n-butylstannane and AIBN in boiling toluene for 48 hours, gave diene 21 in 30% yield. To the best of our knowledge, this is the first use of this reagent in radical chemistry. It is also interesting to note that no addition of the radical to the middle of the dienylstannane was observed and that the resulting diene was at least 95% trans as determined by proton nuclear magnetic resonance (NMR) spectroscopy. In an effort to increase the yield of this reaction, it was repeated under the same conditions, but in boiling benzene. Under these conditions compound 21 was generated in 45% yield.

We have also attempted to treat bromide 9 with cyclopentadienyltrin-butylstannane and a catalytic amount of AIBN in boiling toluene. Although it is known that substituents at the C-1 and C-3 positions of allyl stannanes retard radical reactions, it has been shown
that the tert-butyl radical reacts with cyclopentadienyltri-n-butyl-stannane.\textsuperscript{36} Unfortunately, we were unable to obtain the desired diene 22.

We also found that radical 11 reacted with tetravinyltin.\textsuperscript{37} When bromide 9 was treated with tetravinyl tin and catalytic AIBN in boiling toluene, compound 23 was produced in 27\% yield via addition of radical 11 alpha to the tin atom followed by elimination of the trivinylstannyl radical. The low yields that are observed in this reaction are most likely due to steric hindrance in the addition step because both radical 11 and tetravinyltin are quite sterically hindered.
Since the next planned transformation with compound 23 was an ozonolysis of the olefin, we attempted to form the desired aldehyde directly from bromide 9. It has been shown that halides can be converted into aldehydes directly when treated with carbon monoxide, tri-\textit{n}-butyltin hydride, and catalytic AIBN under high pressure.\textsuperscript{38} Unfortunately, when bromide 9 was treated with carbon monoxide, tri-\textit{n}-butyltin hydride, and catalytic AIBN at 100°C and 1000 psi, the reduction product 12 was obtained in quantitative yield.

\[
\begin{array}{c}
\text{Br} \quad \text{CO, } n\text{-Bu}_3\text{SnH, AIBN} \\
\text{Benzene, 100°C, 1000 psi}
\end{array}
\]

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{9}
\end{array}
\quad \rightarrow \quad \begin{array}{c}
\text{H} \\
\text{CO}_2\text{Et} \\
\text{12}
\end{array}
\]

In an effort to show that other functionalized bridgehead systems also react with allylic stannanes, we have investigated the use of bromide 24\textsuperscript{39} as a radical precursor. We have found that bromide 24 when treated with allyltri-\textit{n}-butylstannane or with 2,4-penta-dienyltri-\textit{n}-butylstannane in the presence of catalytic AIBN in boiling toluene give the desired radical adducts 25 and 26 in 63% and 27% yields respectively (See Scheme IX). In the case of the latter reaction, the yield should be able to be increased by changing the solvent from toluene to benzene, based on the results of a similar reaction with bridgehead bromide 9.
Scheme IX

\[
\begin{align*}
24 & \xrightarrow{\text{Sn(n-Bu)}_3} \text{AIBN, Toluene, } 111^\circ C \rightarrow 25 \\
25 & \xrightarrow{n-\text{Bu}_3\text{Sn}} \text{AIBN, Toluene, } 111^\circ C \rightarrow 26 
\end{align*}
\]
CONCLUSION

We have shown that highly functionalized bridgehead bromides can be converted into bridgehead radicals with trialkylstannyl radicals. Functional groups such as tertiary amines, ketones, esters, and olefins can be tolerated under these reaction conditions. Prior to this work, most bridgehead radical chemistry which had been published dealt with the radicals of hydrocarbon systems. We have also shown that 2,4-pentadienyltrih-\textsubscript{n}butylstannane reacts with carbon centered radicals at the 5-position. To the best of our knowledge this is the first use of this reagent in radical chemistry. It is a reagent, however, which should see continued use due to the prevalence of dienes in organic synthesis.
Unless otherwise noted, materials were obtained from commercial suppliers and were used without additional purification. Benzene was distilled from lithium aluminum hydride. Toluene was distilled from sodium. All reactions were conducted under argon atmosphere and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of nitrogen or dried in a 150 °C oven for 12 h and cooled under a stream of nitrogen. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F254 prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm⁻¹. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicolet NMC-1280 spectrometer and are reported in δ relative to CDCl₃ (77.00 ppm). High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass
spectra were obtained on a Finnegan 4023 mass spectrometer. The purity of all title compounds was judged to be \( \geq 90\% \) by \(^1\)H NMR spectral determination.

**Ethyl 5-(2,2-dichloroethylene)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (15).** A solution of bromoketone 9 (2.45 g, 7.70 mmol), trichloroethylene (40.40 g, 301 mmol), and hexabutylditin (10.80 g, 18.6 mmol) in a pyrex tube was degassed with argon at room temperature for 20 minutes. The colorless solution was irradiated with a Hanovia medium pressure mercury lamp for 48 hours. The resulting yellow-tan solution was then concentrated *in vacuo*, and the remaining oil was diluted with hexane. The hexane layer was extracted with three portions of 1 N hydrochloric acid. To the combined acid extracts was added ether, and the aqueous layer was neutralized with NaHCO₃ (solid). The layers were separated and the aqueous layer was washed with two more portions of ether. The combined ether washings were then washed with saturated sodium chloride solution. The organic layer was then dried and concentrated *in vacuo*. Purification by silica gel chromatography (20:1 H:EA) yielded 71% of 15 (2.57 g, 5.48 mmol): \( RF = 0.26 \) (10:1 H:EA); \(^1\)H NMR (CDCl₃) \( \delta \)

- 6.60 (s, 1 H), 4.22 (q, J=7.2 Hz, 2 H), 3.62 (dd, J=2.1 Hz, J=11 Hz, 1 H),
- 3.15 (dd, J=2.1 Hz, J=11.4 Hz, 1 H), 2.96 (d, J=11.4 Hz, 1 H), 2.76 (m, 2 H), 2.5 (m, 4 H), 2.23 (m, 1 H), 1.99 (m, 1 H), 1.53 (m, 1 H), 1.29 (t, J=7.2 Hz, 3 H), 1.13 (t, J=7.2 Hz, 3 H);
- \(^{13}\)C NMR (CDCl₃) \( \delta \) 207.93, 170.80, 128.58, 122.49, 61.34, 61.18, 58.17, 51.76, 50.80, 37.28, 36.15, 20.37,
14.06, 12.43; IR (neat) 3038, 2971, 2933, 2813, 2776, 1734, 1717, 1616, 1257, 896 cm⁻¹.

**General Procedure for the Reaction of Bridgehead Bromides with Stannanes.** To a solution of bromoketone 9 (1 equiv) in dry toluene or dry degassed benzene (1.0 M) was added the stannane (2 equiv) and AIBN (0.1 equiv). The resulting colorless solution was heated in boiling toluene until no bromoketone remained by TLC. The reaction mixture was then cooled to room temperature and was diluted with hexane. The hexane layer was extracted with three portions of 1 N hydrochloric acid. To the combined acid extracts was added ether, and the aqueous layer was neutralized with NaHCO₃ (solid). The layers were separated and the aqueous layer was washed with two more portions of ether. The combined ether washings were then washed with saturated sodium chloride solution. The organic layer was then dried and concentrated *in vacuo*. The resulting crude product was then purification by silica gel chromatography.

**Ethyl 5-(2-trimethylstannyl-2-propenyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (20).** \( R_F = 0.34 \) (10:1 H:EA); 

\(^1\)H NMR (CDCl₃) \( \delta \) 5.62 (d, \( J=2.7 \) Hz, 1 H), 5.29 (d, \( J=3 \) Hz, 1 H), 4.20 (q, \( J=6.9 \) Hz, 2 H), 3.17 (dd, \( J=2.1 \) Hz, \( J=19.2 \) Hz, 1H), 2.91 (dd, \( J=2.1 \) Hz, \( J=5.4 \) Hz, 2 H), 2.33 (m, 10 H), 1.98 (m, 1 H), 1.78 (m, 1H), 1.48 (m, 1H), 1.28 (t, \( J=7.2 \) Hz, 3 H), 1.08 (t, \( J=7.2 \) Hz, 3 H), 0.12 (s, 9 H); 

\(^{13}\)C NMR (CDCl₃) \( \delta \) 213.01, 171.23, 151.30, 129.85, 65.35, 61.73, 61.03, 58.96, 51.19, 49.67, 45.68, 40.15, 36.92, 20.55, 14.17, 12.73, -7.89; IR (neat) 3034, 2972, 2928, 2862, 1736, 1715, 1258, 922 cm⁻¹.
Ethyl 5-(3,5-pentadienyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (21). $R_F = 0.32$ (10:1 H:EA); $^1$H NMR (CDCl$_3$) $\delta$ 6.30 (dt, J=10.5 Hz, J=17.1 Hz, 1 H), 6.02 (dd, J=7.5 Hz, J=15 Hz, 1 H), 5.68 (m, 1 H), 5.10 (d, J=17.1 Hz, 1 H), 4.98 (d, J=9.9 Hz, 1 H), 4.21 (q, J=7.2 Hz, 2 H), 3.19 (dd, J=2.4 Hz, J=11.4 Hz, 1 H), 3.92 (m, 4H), 2.30 (m, 7 H), 1.87 (m, 1 H), 1.60 (m, 1 H), 1.29 (t, J=7.2 Hz, 3 H), 1.09 (t, J=7.2 Hz, 3 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 212.48, 171.06, 136.74, 134.03, 129.81, 115.37, 64.61, 61.58, 60.95, 58.88, 51.05, 46.35, 39.29, 38.05, 36.77, 20.41; IR (neat) 3083, 2971, 2930, 2809, 1735, 1717, 1257, 1006 cm$^{-1}$.

Ethyl 5-ethenyl-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (23). $R_F = 0.25$ (15:1 H:EA); $^1$H NMR (CDCl$_3$) $\delta$ 6.11 (dd, J=11.1 Hz, J=17.7 Hz, 1 H), 5.15 (d, J = 11.1 Hz, 1 H), 5.03 (dd, J=0.6 Hz, J=18 Hz, 1 H), 4.21 (t, J=7.2 Hz, 2 H), 3.11 (m, 4 H), 2.46 (m, 4 H), 2.20 (m, 2 H), 2.05 (m, 1 H), 1.60 (m, 1 H), 1.28 (t, J=7.2 Hz, 3 H), 1.1 (t, J=7.2 Hz, 3 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 211.17, 171.11, 138.72, 114.24, 64.31, 61.87, 61.21, 58.89, 51.89, 39.92, 38.92, 20.43; MS (Cl-NH$_3$) m/e 226 (M+H), 283 (M+NH$_4$).

Methyl 5-(2-propenyl)-4-methyl-9-oxo-bicyclo[3.3.1]non-3-ene carboxylate (25). $R_F = 0.24$ (10:1 H:EA); $^1$H NMR (CDCl$_3$) $\delta$ 5.77 (m, 2 H), 5.05 (d, J=15.6 Hz, 1 H), 5.01 (d, J=10.5 Hz, 1 H), 3.76 (s, 3 H), 3.30 (m, 1 H), 2.42 (m, 3 H), 2.20 (dd, J=14.7 Hz, J=7.2 Hz, 1 H), 1.85 (m, 4 H), 1.64 (m, 4 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 210.27, 172.56, 135.22, 134.66, 124.06, 116.70, 58.12, 53.39, 52.27, 39.11, 37.33, 37.17, 18.80, 18.36; IR (neat) 3072, 2949, 1737, 1713, 1264, 915 cm$^{-1}$.
Methyl 5-(3,5-pentadienyl)-4-methyl-9-oxo-bicyclo-[3.3.1]non-3-ene carboxylate (26). \( R_F = 0.28 \) (10:1 H:EA); \(^1\text{H} \text{ NMR (CDCl}_3\text{)} \delta 6.27 \) (dt, \( J=10.5 \) Hz, \( J=16.5 \) Hz, 1 H), 6.06 (dd, \( J=9.9 \) Hz, \( J=15 \) Hz, 1 H), 5.71 (m, 2 H), 5.06 (d, \( J=17 \) Hz, 1 H), 4.94 (d, \( J=17.4 \) Hz, 1 H), 3.76 (s, 3 H), 3.29 (m, 1 H), 2.37 (m, 4 H), 1.88 (m, 4 H), 1.65 (m, 4 H); \(^{13}\text{C} \text{ NMR (CDCl}_3\text{)} \delta 210.39, 172.66, 137.21, 134.66, 133.18, 131.57, 124.21, 114.98, 58.21, 53.71, 52.42, 39.14, 37.46, 37.80, 36.14, 18.86, 18.50; IR (neat) 3017, 2927, 2854, 1738, 1714, 1456, 1265, 1005, 738 cm\(^{-1}\).
REFERENCES

1. (a) Gomberg, M. J. Am. Chem. Soc. 1900, 22, 757; (b) Gomberg, M. Chem. Ber. 1900, 33, 3150.


37. To the best of our knowledge this is the first use of this reagent as a radical acceptor.
PAPER II. SYNTHETIC APPROACHES TOWARD DITERPENE ALKALOIDS
INTRODUCTION

The diterpene alkaloids are a large and diverse group of compounds which are found throughout Asia, Europe, and North America. These alkaloids have been isolated from the plants of the Aconitum, Delphinium, Spiraea, Consolida, and Thalictrum species. For centuries these alkaloids have seen use both as traditional medicinal agents, as well as deadly toxins, and because of these observations, researchers today have began to reexamine the usefulness of the diterpene alkaloids as modern medicinal agents. Because our work, as well as most of the work by others, has focused on the closely related alkaloids of the Aconitum and Delphinium species, this paper will deal with alkaloids from these two species of plants.

Traditionally, diterpene alkaloids have been defined as nitrogenous bases whose nitrogen-functionalized skeletons could be identified as being formed from a C20-terpenoid precursor. Although there are many structural variations within this class as a result of this definition, one structural subunit, the 2-azabicyclo[3.3.1]nonane ring system, is common to all naturally occurring diterpene alkaloids. Within the group of alkaloids which are found in the Aconitum and Delphinium species, two different structural frameworks exist; those based on a hexacyclic C19 skeleton and those based on a C20 skeleton. The naming of these compounds as C19 and C20 alkaloids is based upon the number of carbon atoms in the diterpene framework.
The C₁₉ diterpene alkaloids are further divided into two subdivisions, the aconitine-type alkaloids and the lycoctonine-type alkaloids. The basic ring systems of both types and the naturally occurring compounds from which their names were derived are shown below. As can be seen, the only differences between their skeletons is the presence of an oxygen substituent at the C-7 position in the lycoctonine-type alkaloids which is not found in the aconitine-type alkaloids.
The C\textsubscript{20} diterpene alkaloids are also divided into two smaller groups, atisine-type alkaloids and veatchine-type alkaloids.\textsuperscript{1c} In the case of the C\textsubscript{20} diterpene alkaloids, the difference lies in the structure of the C and D rings. In the atisine-type alkaloids, the C and D rings comprise a bicyclo[2.2.2]octane subunit, whereas in the veatchine-type alkaloids the C and D rings comprise a bicyclo[3.2.1]octane subunit.

Another notable difference between the C\textsubscript{19} and C\textsubscript{20} diterpene alkaloids is the lack of an F ring in most of the C\textsubscript{20} compounds. Within the C\textsubscript{20} diterpene subdivision, however, there is a small group of
alkaloids that have an F ring. An example of such a compound is songorine, which contains twenty carbon atoms in its skeleton, as well as the F ring. The other noticeable difference between the C\textsubscript{19} and C\textsubscript{20} alkaloids is the size of the B ring. In the C\textsubscript{19} diterpene alkaloids, the B ring consists of seven carbon atoms, whereas the B ring of the C\textsubscript{20} diterpene alkaloids consists of only six carbons.

This structural diversity, as well as the diversity of the substituents which surround the diterpene skeletons, result in a wide variety of biological activities within the group. As previously stated, it has been known for centuries that diterpene alkaloids can be used as medicinal agents, as well as potent toxins. These alkaloids have been used as cardiotonics, febrifuges, sedatives, anodynes, analgesics, antiinflammatory agents, emetics, and anthelmintics.\textsuperscript{2} There are even reports that some of these compounds may serve as anticancer agents.\textsuperscript{2} Little is known about which compounds exhibit these properties, however, because many of the ancient medicines where prepared directly from the raw plants.
Although there is a lack of knowledge as to which alkaloids are responsible for the observed medicinal properties, there is some understanding as to why other diterpene alkaloids are neurotoxins. Researchers have found that there are two modes of action, aconitiform activity and curariform activity, by which some diterpene alkaloids act as toxins.2

Diterpene alkaloids which possess aconitiform activity effect the cardiovascular system, the skeletal muscle system, and the central nervous system.2 Their activity is believed to be the result of a reversible binding of the alkaloid to a receptor site in the sodium-potassium pump. In doing so, the sodium channels are held open, leading to prolonged depolarization of the membrane. If the alkaloids are present in large enough doses, death usually occurs by respiratory failure or by cardiac arrest. Only the C19 alkaloids aconitine, bikhaconitine, hypaconitine, indaconitine, jesaconitine, mesaconitine, pseudoaconitine, aconifine, and delphinine are known to possess this type of activity. By looking at the substituent patterns of these compounds and their derivatives, researchers have been able to predict the minimum structural requirements for aconitiform activity.2 In comparing compound 1 to aconitine, the only differences are the lack of hydroxyl groups at the C-3 and the C-15 positions and the nature of the R group on the tertiary amine.
Curariform-type activity also is found only in the C_{19} alkaloids. In this case the alkaloids effect skeletal muscles and sympathetic and parasympathetic nerves.\textsuperscript{2} Alkaloids of this type are believed to inhibit acetylcholine at nicotinic sites by a similar mechanism as (+)-tubocurarine chloride. Diterpene alkaloids which exhibit this type of activity include methyllycaconitine, delsemine, anthranoyllcacontine, delphininemethochloride, and delphoninemethochloride. By comparing these compounds' structures and their derivatives, researchers have been able to develop a model (compound 2) for the minimum structural requirements for curariform activity.\textsuperscript{2}
Interest in the biological activities of these compounds as well as the synthetic challenges that their complex structures provide, has resulted in a number of reported synthetic approaches toward the diterpene alkaloids. It was not until the last thirty to forty years, though, that synthetic approaches toward these alkaloids began to appear in the literature. Most of the approaches and subsequent total syntheses to date, however, have dealt with the preparation of the simpler C20 diterpene alkaloids.

In 1963 the first total synthesis of a diterpene alkaloid appeared in the literature. Nagata and coworkers successfully prepared a known precursor of atisine from 6-methoxy-1-tetralone in thirty-four synthetic transformations as shown in Scheme I. Starting with nitrile 3, alkaline hydrolysis followed by ethylation yielded an epimeric mixture of ethoxy lactams. Treatment of this mixture with lithium aluminum hydride gave compound 4 which after Birch reduction and subsequent hydrolysis gave enone 5 as a single diastereomer. With the correct stereochemistry of the A and B rings set, Nagata then converted enone 5 into mesylate 6 in twelve steps. Treatment of mesylate 6 with potassium tert-butoxide resulted in the formation of 7 in 54% yield. Compound 7 was then converted into a known degradation product of atisine which had been previously transformed into the natural product by Pelletier.

Nagata has also published total syntheses of garryine and veatchine (see Scheme II). Using the mesylate of enone 5 from the synthesis of atisine, Nagata was able to prepare compound 9. This was
Scheme I

1) Birch reduction
2) H^+

12 Steps

KOr-Bu
Scheme II

1) HCN
2) ketalization
3) MeLi
4) H^+
5) OH^-
6) Ac_2O, py

5 Steps

1) KOH, Δ
2) Ph_3P=CH_2
3) Birch reduction

5 Steps

dihydroveatchine
accomplished by hydrocyanating enone 8, protecting the resulting ketone as a ketal, adding methyl lithium to the nitrile, and then hydrolyzing both the imine and the ketal. The resulting diketone was then cyclized with dilute alkali, and the newly generated hydroxy-ketone was protected as its acetate. Unfortunately, this route produced the wrong stereochemical configuration of the [3.2.1]bicyclooctane subunit. To correct this problem, compound 9 was converted into the brosylate 10. Treatment of brosylate 10 with potassium hydroxide in boiling methanol gave a ketone which was smoothly converted into the exo-methylene compound with the ylide of methyltriphenylphosphonium bromide. Removal of the mesylate protecting group then gave secondary amine 11. Compound 11 was converted into dihydroveatchine in six additional steps. Since dihydroveatchine had been previously converted into garryine and veatchine, Nagata's work constituted total syntheses of these alkaloids.6

Recently Fukumoto has published an alternative route for the preparation of Nagata's tetracyclic intermediate 4 (see Scheme III).7 Starting with 1-cyano-4-methoxy-benzocyclobutene (12), Fukumoto was able to prepare the aldehyde 13 in eight steps and 41% overall yield. The initial strategy for preparing Diels-Alder adduct 15 involved treating aldehyde 13 with 1-methylallyldiphenylphosphine oxide. This reaction failed, however, and aldehyde 13 had to be converted into silane 14 instead via a four step pathway. Treatment of the silane with mesyl chloride and triethylamine resulted in the production of a
Scheme III

8 Steps

1) MsCl, Et₃N
2) LAH
3) PhCOCl, K₂CO₃
4) LAH

4 Steps

1) CH₂O, AcOH, 150°C
2) H₂, Pd/C

4
tricyclic intermediate in 86% yield by an elimination/Diels-Alder reaction.

The inseparable mixture of diastereomeric nitriles which resulted from the Diels-Alder reaction was then reduced with lithium aluminum hydride. Treatment of the intermediate from this reduction with benzoyl chloride gave two separable isomeric benzoates in 97% yield. The desired trans-adduct constituted only 45% of the isolated product. The trans-benzoate was then reduced with lithium aluminum hydride giving the benzyl-protected amine 15. Heating 15 with 37% aqueous formaldehyde in acetic acid at 150°C, resulted in the generation of a tetracyclic amine via an intramolecular Mannich-type cyclization. Hydrogenation over 10% Pd-C under a hydrogen atmosphere removed the benzyl protecting group and reduced the olefin giving target molecule 4. Although Nagata's synthesis of 4 is shorter (14 steps vs. 18 steps) and proceeds in higher overall yield (14% vs. 8%), Fukumoto's route provides an interesting alternative for the preparation of the E ring of the C20 alkaloids. If, however, a solution could be found for the failed Wittig/Diels-Alder reaction, then Fukumoto's route would prove to be an even more attractive alternative for the preparation of compound 4.

Shortly after Nagata's synthesis of atisine appeared, Masamune reported the first synthesis of dihydroveatchine (see Scheme IV), a precursor to both veatchine and garryine. The starting material for this synthesis, 6-benzyloxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid, was converted into bromide 16 in five steps. Treatment of the
diastereomeric mixture of bromophenols with base followed by acid resulted in the production of the tricyclic intermediate 17 in 30% overall yield from 6-benzyloxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid. Unfortunately, only one of the isomers of compound 16 cyclized, thereby lowering the overall yield of this series of reactions. The tricyclic intermediate 17 was then converted into the tetracyclic intermediate 18 in five steps with the A ring being produced via a Robinson annulation between the corresponding β-keto ester and ethyl

Scheme IV

\[
\begin{align*}
\text{Scheme IV} \\
\text{16} & \xrightarrow{1) \text{ Base}} \xrightarrow{2) \text{ H}^+} \text{17} \\
\text{19} & \xrightarrow{7 \text{ Steps}} \text{18}
\end{align*}
\]
vinyl ketone. Conversion of intermediate 18 into 19 was then completed in seven additional transformations.

Treatment of the acid chloride of 19 with anhydrous hydrazine followed by sequential treatment with ethylene glycol and p-toluene-sulfonic acid and then nitrous acid yielded the unstable azide 21 as shown in Scheme V. Photolysis of azide 21 gave a lactam which was reduced with lithium aluminum hydride. The resulting secondary amine was then acylated with acetic anhydride and pyridine. Deketalization gave compound 22 which was converted into

Scheme V

Dihydroveatchine

22
dihydroveatchine by the previously reported route of Wiesner.\textsuperscript{6a} As stated earlier, dihydroveatchine can be converted into both veatchine and garryine.

Wiesner has reported total syntheses of atisine, veatchine, and garryine. The first total synthesis reported by Wiesner dealt with the preparation of dihydroveatchine (see Scheme VI).\textsuperscript{9} Starting with 6-methoxy-2-tetralone, Wiesner and coworkers were able to prepare acid \textit{23} in three steps. This acid was then converted into compound \textit{24} in another five steps. Oxidation of the olefin \textit{24} with osmium tetroxide in pyridine followed by further oxidation with lead tetraacetate in acetic acid yielded a dialdehyde. Treatment of this dialdehyde with hydroxylamine in boiling pyridine followed by catalytic reduction with platinum oxide in acetic acid yielded amine \textit{25}. Intermediate \textit{25} was then converted into ketone \textit{26} via a six step route.

Alkylation of ketone \textit{26} with allyl bromide and sodium hydride resulted in the generation of a single new ketone. It is believed that the axially attached nitrogen bridge screens the \textit{\alpha}-face of the molecule, and therefore induces high stereoselectivity in this reaction. With the necessary stereochemistry set, the synthesis was then completed in a straightforward manner. Treatment of the product from the alkylation with sodium hydroxide, followed by sodium periodate and osmium tetroxide, gave a ketoaldehyde which was cyclized via treatment with methanolic sulfuric acid. The resulting ketone \textit{27} was then converted into dihydroveatchine in eight additional steps.
Scheme VI

1) PTSA
2) \((\text{CH}_2\text{SH})_2, \text{ZnCl}_2\)
3) Raney Ni
4) BzCl, py
5) 320°C

1) NaH, CH₂=CHCH₂Br
2) NaOH
3) NaIO₄, OsO₄
4) H₂SO₄

1) OsO₄, py
2) \(\text{Pb(OAc)}₄\)
3) NH₂OH
4) Pt, AcOH

Dihydroveatchine
Wiesner latter published an alternative approach toward the C_{20} diterpene alkaloids which resulted in an efficient preparation of an atisine precursor as shown in Scheme VII. Preparation of the nitrogen containing E ring of atisine was accomplished in four steps from acid 28 via the intermediacy of an isocyanate. Subsequent removal of the ketone of compound 29 and reduction of the aromatic ring with lithium and ammonia yielded enone 30 after acid hydrolysis. Irradiation of enone 30 in the presence of excess allene gave pentacyclic intermediate 31, which was then converted into compound 32 in five additional steps. Treatment of the hydroxy ketal 32 with dilute hydrochloric acid gave intermediate 33 which was then easily converted into atisine via known methods.\textsuperscript{4b}

Wiesner has also used this strategy for the preparation of dihydroveatchine (see Scheme VIII). Starting with the ketoamide 31 which was previously prepared in the synthesis of atisine, urethane 34 was prepared in eleven steps. Nitrosation of compound 34 with nitrogen dioxide and sodium acetate gave a nitroso urethane which decomposed upon treatment with sodium ethoxide in boiling ethanol to give intermediate 35. Since Nagata had already shown that 35 could be converted into the target molecule,\textsuperscript{5} its preparation constituted a formal total synthesis of dihydroveatchine.
Scheme VII

1) EtOOC\(_2\)Cl, Et\(_3\)N
2) NaN\(_3\)
3) Benzene, 80°C
4) PTSA

1) (CH\(_2\)SH)\(_2\), BF\(_3\)•Et\(_2\)O
2) Ran-nickel
3) Li, NH\(_3\), t-BuOH
4) H\(^+\)

5 Steps

Ac - N - H
Me

Ac - N - H
Me

Ac - N - H
Me
Scheme VIII

More recently Fukumoto has developed a strategy which has allowed for the completion of an asymmetric total synthesis of atisine.\textsuperscript{12} This is the first asymmetric total synthesis of a diterpene alkaloid to be reported. As shown in Scheme IX, bicyclic amine 37 was prepared from keto diester 36 by a double Mannich reaction with two equivalents of formaldehyde and one equivalent of benzyl amine. The achiral amino diester 37 was then converted into the chiral intermediate 38 in four steps. This was accomplished by first converting the ketone of compound 37 into an \textit{exo}-methylene substituent. Reduction of the
Scheme IX

36

\[
\begin{align*}
&\text{CO}_2\text{Me} \\
&\text{CH}_2\text{O, BnNH}_2 \\
&\text{Bn} \\
&\text{CO}_2\text{Me} \\
&\text{37}
\end{align*}
\]

1) Ph$_3$P=CH$_2$
2) LAH
3) Ac$_2$O, Et$_3$N, DMAP
4) CCL

39

\[
\begin{align*}
&\text{MeO}_2\text{C} \\
&\text{LiHMDS} \\
&\text{Bn} \\
&\text{OH} \\
&\text{OAc} \\
&\text{38}
\end{align*}
\]

40

\[
\begin{align*}
&\text{MeO}_2\text{C} \\
&\text{5 Steps} \\
&\text{Ac} \\
&\text{Me} \\
&\text{41}
\end{align*}
\]

14 Steps
resulting diester with lithium aluminum hydride gave a diol which was protected as the diacetate upon treatment with acetic anhydride, triethylamine, and catalytic 4-dimethylaminopyridine. Enzymatic hydrolysis of the diacetate with *Candida cylindracea* lipase (CCL) on Celite gave (+)monoacetate 38 in 26% yield and 83% enantiomeric excess. This chiral monoacetate was then converted into intermediate 39 in fourteen steps. Treatment of compound 39 with lithium hexamethyldisilylamide gave keto ester 40 in 58% yield via a double Michael reaction. In five additional steps, intermediate 40 was converted into ketone 41, a known precursor of atisine.4

To date, there have only been a few reported synthetic approaches toward the aconitine-type C19 diterpene alkaloids. From these approaches only two total syntheses have been achieved. Both talatisamine13 and chasmanine14 have been prepared by Wiesner and coworkers. Wiesner's approach has been based upon the observation of Johnston and Overton that derivatives of atisine-type alkaloids undergo a Wagner-Meerwein rearrangement to give aconitine-type products.15 Johnston and Overton discovered that when 42 was subjected to gas phase pyrolysis conditions, 43 was produced in 77% yield.
Wiesner latter found that bicyclo[2.2.2]octane derivatives rearranged under much milder conditions.\textsuperscript{13a} For example, when 44 was treated with tetramethylguanidine (TMG) in DMSO at 180°C, compounds 45 and 46 were produced in a 1:1 ratio in 85% yield. Unfortunately only one of the isomers, compound 45, is useful for the completion of a synthesis of an aconitine-type alkaloid.

Despite the limitations of the bicyclo[2.2.2]octane rearrangement approach, Wiesner's initial synthetic strategy toward these alkaloids was designed around this rearrangement (see Scheme X).\textsuperscript{13} The natural product talatisamine was chosen as the first target molecule to test the validity of this approach. The choice of this particular molecule was based solely upon the fact that talatisamine is one of the least
functionalized molecules in this class, and is therefore, an easier molecule to prepare.

Starting with the Diels-Alder adduct of *trans, trans*-1,4-diacetoxy-1,3-butadiene and 1-cyano-6-methoxy-3,4-dihydronaphthalene, compound 47 was prepared in thirty-three steps via a pathway which paralleled Wiesner's earlier route for the preparation of atisine. With compound 47 in hand, Wiesner was then ready to try the crucial rearrangement. He found that when compound 47 was treated with tetramethylguanidine (TMG) in DMSO at 180°C, the desired pentacyclic compound 48 was produced in 40% yield along with an equal amount of the isomeric compound. Although half of the material produced in this reaction was useless for the preparation of talatisamine, sufficiently large quantities of 48 could be produced to finish the synthesis.

The conversion of 48 into talatisamine was then completed in an additional four steps. Reduction of amide 48 with lithium aluminum hydride gave a tertiary amine. Treatment of this amine with aqueous methanolic hydrochloric acid, followed by sodium borohydride, resulted in the stereospecific production of alcohol 49. The stereoselectivity of the sodium borohydride reduction was probably the result of the methoxy group being large enough to hinder attack of the ketone from the opposite face. Now that all of the necessary functional groups were in place, the synthesis was completed by oxidizing 49 with mercuric acetate giving talatismamine in 38 total steps.
Wiesner has also completed a total synthesis of the more substituted aconitine-type diterpene alkaloid chasmanine. Wiesner's initial strategy for preparing chasmanine was to use a similar route to that used in the preparation of talatismamine. Although such a strategy
would most likely have been successful, the problem still remained that half of the material which would be produced in the rearrangement of the bicyclo[2.2.2]octane ring system would not be useable for the preparation of the natural product. To overcome this shortcoming, Wiesner designed a synthesis in which the F ring was prepared prior to the rearrangement of the bicyclo[2.2.2]octane subunit. To test this hypothesis, the model system 50 was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in o-xylene and DMSO at 180°C. As predicted, a single product, compound 51, was produced in 90% yield.16

![Chemical Structures]

Based on the success of the model system, Wiesner and coworkers then began the task of preparing chasmanine via a similar strategy as shown in Scheme XI.14 The tricyclic subunit 52, which was prepared in ten steps, served as the precursor for the generation of the F ring of the chasmanine ring system. Treatment of 52 with azidotrimethylsilane followed by acetic acid and acetic anhydride lead to formation of the acetylziridine 53. Heating compound 53 at 85°C for several days resulted in the formation of rearrangement product 54.
Scheme XI

1) TMSN₃
2) AcOH, Ac₂O

52

53

Δ

41 Steps

R₁, R₂ = OCH₂CH₂O

55

DMSO,  o-xylene
DBN, 180°C

54

1) Hg(OAc)₂
2) NaBH₃CN
3) AcOH, 85°C
4) LAH

R₁, R₂ = OCH₂CH₂O

56

Chasmanine
The rearrangement is believed to have been initiated by the opening of the aziridine carbon-nitrogen bond nearest the methoxy group on the aromatic ring, followed by a Wagner-Meerwein rearrangement. The observed regioselectivity for this reaction is most likely due to the increased migratory aptitude of the bond ortho to the methoxy group, whereas the competing rearrangement is more difficult due to the presence of the ester carbonyl.

Having developed an effective method for the generation of the F ring, Wiesner then prepared compound 55, the precursor for the key rearrangement step. Treatment of the bromide 55, which was prepared from 54 in forty-one steps, with DBN in o-xylene and DMSO at 180°C resulted in the formation of the desired olefin 56 in 85% yield. The synthesis of chasmanine was then completed in three additional transformations. Oxymercuration of olefin 56 gave an alcohol which was subsequently treated with acetic acid at 85°C to remove the ketal. The newly generated keto amide was then reduced with lithium aluminum hydride giving chasmanine in fifty-six total steps. Although this synthesis is quite long, it was an improvement upon the previous strategy,¹³ because a solution was found for the lack of regioselectivity in the rearrangement step.

Three other approaches toward the aconitine-type diterpene alkaloids have recently appeared in the literature. Fukumoto has found that the amine salt 57 undergoes a Mannich reaction upon treatment with 37% aqueous formaldehyde and acetic acid.¹⁷ The product from
this reaction was the tertiary amine 58 which contains the A, E, and F rings of the C19 diterpene alkaloids. Although no total syntheses have resulted from this approach, it does offer an interesting alternative for the formation of the F ring.

An approach toward the ABCD ring system of the C19 diterpene alkaloids was recently reported by van der Baan. In this approach, the seven-membered B ring was prepared by a ring expansion reaction. As shown in Scheme XII, the desired compound 60 was generated from the pyrrolidine enamine of compound 59 via treatment with tert-butyl propiolate in toluene at 85°C. The resulting β-keto ester was then converted into intermediate 61 in fourteen additional steps. Treatment of 61 with sodium methoxide in methanol then gave compound 62 which contains the A, B, C, and D rings of the alkaloids. Although this route has not resulted in a total synthesis of any of the diterpene alkaloids, intermediate 62 is interesting because it contains the necessary functional groups to complete a synthesis of a number of these alkaloids.
Kraus and Shi have reported an approach toward the lycocotine-type alkaloids. Their route was based upon the use of a bridgehead radical. Details of this route will be discussed in the results and discussion section.19
The ultimate goal of our research in bridgehead radical chemistry is to develop a concise synthetic route for the preparation of the basic ring system of the polycyclic diterpene alkaloids. As can be seen from the previous review of the literature, the published routes toward these alkaloids all suffer from the same problem; they involve too many synthetic steps for general use in organic synthesis. In planning our strategy for preparing these compounds, more emphasis has been placed on developing a short and adaptable route than on just making the target molecule. Therefore, some solutions for the problems which we have encountered were avoided, because these solutions would have ultimately led to a long synthesis.

Our general retrosynthetic plan for preparing the diterpene alkaloids is shown in Scheme XIII. There are two potential pathways through which we envisioned preparing polycyclic intermediates of the diterpene alkaloids. Pathway a involves the preparation of polycyclic intermediate 64 by an intramolecular aldol condensation involving diketone 65. This diketone would be prepared by the functionalization of an intermolecular bridgehead radical addition product of bromide 66. Pathway b, in contrast, involves an intramolecular addition of the bridgehead radical generated from bromide 67 to an olefin. This then would give compound 64 which would contain at least four of the rings found in the natural products. Intermediate 67 would be prepared by an addition of a nucleophile to the ketone of bromide 66. As can be
seen, pathway a is quite similar to pathway b except that the order of operations is reversed. In pathway a the radical addition step proceeds the step involving a nucleophilic addition to the ketone, whereas in pathway b these steps are reversed.

As previously stated, Kraus and Shi have reported a synthetic approach toward the lycoctonine-type diterpene alkaloids which
followed the strategy outlined by pathway b from the aforementioned retrosynthetic analysis. In their approach, compound 68 was first converted into aldehyde 69 by treatment with ozone and one equivalent of trifluoroacetic acid in methylene chloride (see Scheme XIV). The resulting aldehyde was then treated with 1-triphenylphosphoranylidenemethyl ester which unexpectedly gave hemiketal 70. Preparation of the desired enone 71 was then effected by the treatment of hemiketal 70 with sulfuric acid. The Diels-Alder reaction of enone 71 with 1-trimethylsilyloxy-1,3-butadiene at 260°C resulted in the preparation of adduct 72 in 71% yield as a mixture of stereoisomers. This mixture was then treated with potassium hexamethyldisilazide resulting in the formation of the tetracyclic intermediate 73 in six steps and in 41% overall yield from bromide 66. This series of reactions is especially promising because the A, B, D, and E rings were prepared in a straightforward and efficient manner. Drawbacks to this route, however, include the lack of reactivity of enone 71 toward dienes, a lack of reactivity which leads to the necessity of employing high temperatures for the Diels-Alder reaction. The Diels-Alder reaction is also a problem because it forms a complex mixture of diastereomers, a mixture which would be difficult to convert into a single compound in a limited number of steps.

To overcome these problems, we envisioned using enone 71 as the diene, rather than the dienophile, in the Diels-Alder reaction. The route of Kraus and Shi was used to prepare enone 71 with one notable
Scheme XIV

\[ \text{68} \xrightarrow{1) \text{CF}_3\text{COOH, } \text{O}_3} \xrightarrow{2) \text{Me}_2\text{S}} \text{69} \]

\[ \text{69} \xrightarrow{\text{Ph}_3\text{P=CHCOCH}_3} \]

\[ \text{70} \xrightarrow{\text{H}_2\text{SO}_4} \text{71} \]

\[ \text{71} \xrightarrow{\text{OTMS}} \xrightarrow{260^\circ\text{C}} \text{72} \xrightarrow{\text{KN(TMS)}_2} \text{73} \]
improvement. It was found that aldehyde 69 could be converted directly into enone 71 in 98% yield when the ylide for the Wittig reaction was carefully dried at 50°C under a vacuum of 0.5 mm of mercury. Enone 71 was then converted into diene 74 in 90-99% yield when treated with tert-butylidimethylsilyl triflate and triethylamine in methylene chloride at -78°C.

With the necessary diene in hand, we then heated diene 74 and methyl vinyl ketone along with a trace amount of bis(trimethylsilyl)-acetamide\textsuperscript{21} at 80°C for thirteen hours. The resulting products from this reaction appeared to be a mixture of the tricyclic enol silyl ethers 75 along with some of enone 71. Treatment of this crude mixture with potassium hexamethyldisilazide did not give tetracyclic compound 76, but rather returned compound 77 after work up.

Because it was believed that an impurity in the crude mixture from the Diels-Alder reaction was impeding the formation of compound 76, we then attempted to purify compound 75. Numerous attempts to purify compound 75 by column chromatography using either silica gel or florisil led to the isolation of compound 77 as the major fraction.
We then attempted to cyclize compound 77 with potassium hexamethyldisilazide in the hope of forming tetracyclic intermediate 76. Unfortunately, this reaction did not yield tetracyclic intermediate 76, but rather a product which we believed was tetracyclic compound 78. Although we did not carefully determine the structure of the product from this reaction, compound 78 is a logical suggestion because five membered ring formation is known to occur more readily than seven membered ring formation. Also, the presence of a singlet at
2.13 ppm in the proton NMR (characteristic of a methyl from an acetyl group), as well as a stretch at 3500 cm\(^{-1}\) in the crude IR (characteristic of a hydroxyl group), indicate that a structure such as 78 is possible.

In an effort to alleviate the potential for the formation of tetracyclic 78, we proposed that the further activation of the methyl of the acetyl group would lead to the selective formation of the tetracyclic intermediate 80 when compound 79 (A = activating group) was treated with base. The activating group which was chosen for this purpose was a phosphonate group because it is well known that ketophosphonates undergo Horner-Emmons reactions with ketones. A phosphonate, unlike most other activating groups which could have been used, was an
attractive choice because no further transformations would be necessary for its removal after the cyclization occurred, because it would eliminate during the course of the reaction.

We believed that the introduction of the phosphonate group would be most efficiently accomplished by preparing dienophile \( \text{81} \). A Diels-Alder reaction between reagent \( \text{81} \) and diene \( \text{74} \) would then give a suitably substituted system for the required cyclization.

Our first attempt at preparing compound \( \text{81} \) involved treating acryloyl chloride with the lithium anion of dimethyl methyl phosphonate.\(^{24} \) Unfortunately, compound \( \text{81} \) did not result from this reaction. We then treated acrolein with the lithium anion of dimethyl methyl phosphonate, resulting in the formation of an alcohol which was oxidized with the Jones reagent giving phosphonate \( \text{81} \) in 70% overall yield over the two steps. With the desired dienophile prepared, we then attempted the Diels-Alder reaction with diene \( \text{74} \). Disappointingly, no reaction occurred below 80°C, and above 80°C diene \( \text{74} \) began to hydrolyze giving enone \( \text{71} \).
Shortly after attempting this reaction, we found that 2,4-pentadienyltri-n-butylstannane<sup>19a</sup> reacted with bromide 66 in the presence of a catalytic amount of AIBN to give diene 84 in 45% yield. Because the tert-butyldimethylsilyloxy group in compound 74 was not necessary for latter transformations, we investigated the potential of diene 84 for the preparation of a tetracyclic intermediate such as 64.

We first attempted to heat diene 84 with methyl vinyl ketone in the hope of forming Diels-Alder adduct 85. At temperatures below 100°C, no reaction occurred. At temperatures above 100°C, it appeared that the methyl vinyl ketone began to polymerize. It is well known that Lewis acids catalyze Diels-Alder reactions and usually much lower
temperatures are needed for a reaction to occur.\textsuperscript{25} Treatment of a mixture of diene \textsuperscript{84} and methyl vinyl ketone with Lewis acids, such as tin tetrachloride or diethylaluminum chloride, in methylene chloride at 0°C resulted in the formation of an insoluble material which could not be identified. It is possible that this material was the salt which resulted from the reaction of the tertiary amine and the Lewis acid. All attempts, however, to neutralize this material failed.

Because the Diels-Alder reactions failed with methyl vinyl ketone, we then looked at more reactive dienophiles. Treatment of diene \textsuperscript{84} with the lithium enolate of ethyl acetate gave alcohol \textsuperscript{86}. The Diels-Alder reaction between this alcohol and dimethyl acetylene-dicarboxylate\textsuperscript{26} then gave 1,4-diene \textsuperscript{87} which was subsequently treated with potassium tert-butoxide in THF at -78°C under an air atmosphere. By this sequence, compound \textsuperscript{88} was prepared in 49% overall yield from diene \textsuperscript{84}. Surprisingly, treatment of triester \textsuperscript{88} with bases such as potassium tert-butoxide or lithium diisopropylamide did not result in the formation of Dieckmann\textsuperscript{27} product \textsuperscript{89}. A potential problem with this strategy is that compound \textsuperscript{89} is a Knoevenagel-type intermediate.\textsuperscript{28} This intermediate, if it did form, may have undergone
Scheme XVI

84 \[\xrightarrow{\text{EtOAc, LDA}}\] 86

\[\xrightarrow{\text{DMAD}}\] 87

\[\xrightarrow{\text{KO-\(t\)-Bu, air}}\] 88

89
a retro-Knoevenagel reaction, thereby, reducing the likelihood of isolating compound 89.

We have also found that diene 84 reacts with 1-phenylsulfonyl buten-3-one upon heating at 100°C for thirty-six hours. Because the crude product 90 was very clean by proton NMR spectroscopic analysis and was unstable to silica gel chromatography, we immediately took the mixture of the crude diketo-sulfones on to the next step. We attempted, initially, to eliminate the phenyl sulfonyl group by treatment with potassium tert-butoxide in THF at 0°C under a nitrogen atmosphere. Such reaction conditions gave a complex mixture of products most likely due to aldol reactions occurring both prior and subsequent to the
elimination of the phenyl sulfonyl group. If the reaction was run under an air atmosphere, then tetracyclic compound 92 was produced in 10% overall yield from diene 84. The formation of compound 92 most likely results from an air oxidation of 1,4-diene 91 followed by an intramolecular aldol reaction. Problems were encountered, however, when we attempted to reproduce these results. If a solution can be found for this lack of reproducibility, this route would be potentially useful, because an intermediate containing the A, B, D, and E rings is produced in only three steps from readily available bromide 66.

We have also attempted to synthesize intermediates for the preparation of the lycoctonine diterpene alkaloids by pathway b as outlined in Scheme XIII. Before attempting this strategy with a complicated molecule such as 67, a model system was designed to test this hypothesis. Our plan was to generate the A, B, C, and D rings of these alkaloids by an intramolecular radical addition reaction of an aryl radical, rather than a bridgehead radical, to a bicyclic system. Based on this idea, compound 93 was chosen as the target molecule for this study due to its ease of preparation.
The preparation of bicyclic compound 93 was accomplished in four steps from 2-bromo-4-methoxybenzoic acid (94) as shown in Scheme XVII. Reduction of acid 94 with the borane-tetrahydrofuran complex gave a benzylic alcohol in 85% yield. Treatment of this alcohol with carbon tetrabromide and triphenylphosphine resulted in the preparation of bromide 95 in 91% yield. Bromide 95 was then treated with allyl magnesium bromide in ether at 0°C giving compound 96 in 95% yield. Subsequent heating of compound 96 and 5,5-dimethoxy-1,2,3,4-tetrachloro-cyclopentadiene at 150°C for twenty hours gave the desired bicyclic compound 93 in 98% yield. With the necessary system prepared, we then attempted the radical cyclization.
Treatment of bromide 93 with tri-\textit{n}-butyltin hydride and AIBN in boiling benzene produced a new compound in 55% yield which was originally believed to be cyclization product 98. Because there were some inconsistencies in the spectral data which were obtained for this compound, we submitted a sample for single crystal x-ray analysis.
Unexpectedly, the structure which was determined for this sample (see Appendix) showed that we had prepared the rearrangement product 97, rather than compound 98.32

A proposed mechanism for the formation of compound 97 is shown in Scheme XVIII. Aryl radical 99 is believed to abstract a hydrogen atom six atoms away, generating tertiary radical 100.33 Radical 100 then undergoes an intramolecular addition to the olefin.
Scheme XVIII

\[ n-\text{Bu}_3\text{SnH} \]

\[ \text{102} \rightarrow \text{97} \]
giving the highly strained radical 101. The resulting cyclopropyl-carbinyl radical, which is stabilized by a chlorine atom, has two pathways by which it can proceed. It can revert to radical 100, or it can break the other bond of the cyclopropyl ring giving radical 102. Radical 102 is then trapped by tri-n-butyltin hydride resulting in the formation of compound 97. It is interesting that with all the intermediates which have to be formed in order for compound 97 to result, this was the only compound isolated besides 35% of the starting bromide 93. Although this is not the first example of a radical rearrangement of a norbornene ring system, to the best of our knowledge, it is the first example of the initiation of such a rearrangement by an atom transfer reaction.

It is also important to note that the stereochemistry of compound 93 is as shown, that is the endo product was prepared by the
Diels-Alder reaction. The supporting evidence for this was obtained from NOESY and COSY 2-D NMR experiments. The lack of an NOE between the hydrogens of methoxy group A and hydrogens Hc and Hd indicated that the 2-(4-methoxyphenyl)ethyl group was endo. This is crucial, because if we had prepared the exo product instead, then the intramolecular addition of aryl radical 99 to the olefin would not have been possible.

We have also attempted to prepare intermediates which could be useful for the preparation of the C20 diterpene alkaloids based on the retrosynthetic synthesis outlined in Scheme XIII. One of the first routes

Scheme XIX

\[
\begin{align*}
\text{103} & \quad \text{CO}_2\text{Et} \\
\text{69} & \quad \text{CO}_2\text{Et}
\end{align*}
\]
that we investigated involved using aldehyde 69 as the starting material to build the A, B, D, and E rings of the C20 diterpene alkaloids. As shown in Scheme XIX our synthetic plan was to prepare compound 103 via an intramolecular aldol reaction from compound 104. Compound 104, it was believed, could be generated by an addition of an acyl anion equivalent to enone 105 which would be obtained from aldehyde 69.

This synthesis began by converting aldehyde 69 into enamine 106 via treatment with morpholine in boiling benzene in the presence of activated molecular sieves.\textsuperscript{35} Under these conditions the best ratio of enamine to aldehyde obtained was 2:1 as determined by proton NMR spectral analysis. This mixture was then treated with excess methyl vinyl ketone in boiling benzene, and the residue which remained after concentration \textit{in vacuo} was taken up in methanol and water (1:1) and heated at 80°C.\textsuperscript{35} From this set of reactions, enone 105 was obtained in 35\% yield as a mixture of diastereomers.
Addition of the cuprate of α-ethoxyvinyl lithium\textsuperscript{36} to enone 105 was then attempted. Unfortunately, this reaction failed. Although this route looks promising, we have not been able to continue to pursue it due to problems with the ozonator. Numerous attempts to prepare aldehyde 69 by an alternative route, such as osmylation, followed by sodium periodate oxidation or mCPBA oxidation, followed by periodic acid oxidation, failed.

Because this route was closed until aldehyde 69 could be obtained, we developed an alternative strategy for the preparation of the A, B, D, and E rings of the C\textsubscript{20} diterpene alkaloids. Kraus and Shi have reported that bromide 66 upon treatment with the lithium enolate
of 1-acetyl cyclohexene undergoes a ring contraction reaction giving compound 107 in 60% yield. Because it was unknown whether the carboethoxy group was necessary for this contraction to occur, we set out to prepare compound 108, a compound which would be capable of undergoing an intramolecular radical addition.

Reduction of compound 66 with lithium aluminum hydride gave diol 109 in 60% yield (see Scheme XX). The primary alcohol of diol 109 was then selectively protected by treatment with chloromethyl methyl ether and diisopropylethylamine resulting in the generation of compound 110 in 61% yield. Oxidation of alcohol 110 was
accomplished by treatment with trifluoroacetic anhydride, DMSO, and triethyl amine in 73% yield. Unfortunately, treatment of ketone 111 with the lithium enolate of acetyl cyclohexene resulted in the formation of compound 112, instead of the desired alcohol 108.
Although this rearrangement was unwanted and produces a compound which is useless for the completion of our synthesis, it does provide some insight into the mechanism of this rearrangement. We believe that there are two possible pathways via which the rearrangement product could be generated from alkoxide 113. If alkoxide 113 underwent a retro-Claisen reaction, anion 114 would result. This compound could then displace the bromide of 114 by an intramolecular displacement reaction giving compound 115.
Alternatively, alkoxide 113 could undergo a concerted reaction to give compound 115 directly. When group R of compound 113 is a carboethoxy group, a retro-Claisen reaction would be possible as shown in the first pathway. When the R group is a protected hydroxymethyl group, however, as in compound 110, the formation of 114 is unlikely because the protected hydroxymethyl group would not be capable of stabilizing the resulting anion and there would be no driving force for the reaction to occur. Therefore, a concerted reaction may be the pathway by which this rearrangement occurs. Although these results do not provide enough evidence to support such a mechanism, they do at least show that such a mechanism is possible.

Kraus and Shi have shown that although the addition of lithium anions to bromide 66 results in the formation of rearrangement product 115, compound 116 can be isolated when magnesium anions are used instead. Based on these findings we envisioned preparing atisine by an intramolecular radical addition reaction involving compound 117, a compound which would be prepared by the addition of the magnesium
Scheme XXII

Atisine

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Me} \\
\text{H} \\
\text{H} \\
\text{OH} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{Me} \\
\text{OH} \\
\text{SO}_2\text{Ph} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{Me} \\
\text{CN} \\
\text{Cl} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Me} \\
\text{OH} \\
\text{SO}_2\text{Ph} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array} \quad \xymatrix{\ar[r] & } \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{Br} \\
\text{CO}_2\text{Et} \\
\end{array}
\]
anion of compound 118 to bromide 66 as shown in our retrosynthetic analysis (Scheme XXII). We chose to use a phenylsulfonyl group as the activating group for the formation of the magnesium anion because an unstablized Grignard (one prepared directly from a halide) would be too reactive to tolerate the functionality found in compound 118.

Before preparing compound 118, we attempted to add another more easily prepared sulfone to bromide 66. We found that treatment of methyl phenyl sulfone with bromomagnesium isopropylcyclohexylamide, followed by bromide 66, gave compound 119 in 58% yield. With the success of this reaction, we then set out to prepare compound 118. Birch reduction of 4-methoxyphenethyl
alcohol with sodium and ammonia in ethanol and THF gave alcohol 120. Initially, we attempted to isomerize compound 120 to the 1,3-diene 121 with potassium tert-butoxide in DMSO at 80°C. Although we were able to generate compound 121, the material isolated from this reaction was a mixture of compounds 121, 120, and 4-methoxyphenethyl alcohol.

Because the base-catalyzed reaction of 120 was not as clean of a reaction as we had hoped, we then looked at alternative methods for the isomerization of 120 to 121. Based on the work of Birch, we treated compound 120 with Wilkinson's catalyst in chloroform. Although Birch has reported numerous examples of similar isomerizations of 1,4-dienes, a complex mixture resulted from this reaction. Birch has also reported the use of dichloromaleic anhydride as a catalyst for this type of reaction. However, when compound 120 was treated with dichloromaleic anhydride, compound 120 was returned unchanged (see Scheme XXIII).
Evans has reported the use of 2-chloroacrylonitrile as both the catalyst and the dienophile for the conversion of the 3,5-dihydroanisoles into bicyclo[2.2.2]octenes. Based on these findings, we treated crude alcohol 120 with chlorotrimethylsilane and pyridine. Heating a solution of the resulting protected alcohol and 2-chloroacrylonitrile in benzene at 100°C gave alcohol 122 after subsequent treatment with 1 N hydrochloric acid. The overall yield of
Compound 122 from 4-methoxyphenethyl alcohol was 52%. Conversion of alcohol 122 into sulfone 118 was then accomplished in 53% yield by treatment with carbon tetrabromide and triphenylphosphine followed by the sodium salt of benzenesulfinic acid.43
Unfortunately, treatment of sulfone 118 with bromomagnesium isopropylcyclohexylamide, followed by bromide 66, only resulted in the recovery of starting material. The lack of reactivity of the magnesium anion of 118 is most likely due to steric hindrance in the transition state of the reaction.

\[ \text{C}_6\text{H}_{11}-\text{iPrNMgBr} \]

\[ \text{CO}_2\text{Et} \]

\[ \text{CO}_2\text{EtSO}_2\text{Ph} \]

\[ \text{OMe} \]

\[ \text{CN} \]

\[ \text{Cl} \]

\[ \text{117} \]
CONCLUSION

We have shown that bridgehead radicals are synthetically useful intermediates for the preparation of complex molecules. By using the bridgehead methodology, we have been able to prepare potentially useful synthetic intermediates of the diterpene alkaloids. We have also discovered a novel method for the initiation of the radical rearrangement of the norbornene system. The overwhelming preference for hydrogen-atom transfer over the intramolecular radical addition to a strained alkene is particularly surprising.
Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Toluene was distilled from sodium metal. Dichloromethane and 1,2 dichloroethane were distilled from calcium hydride. All reactions were conducted under nitrogen atmosphere and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of nitrogen or dried in a 150°C oven for 12 h and cooled under a stream of nitrogen. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F₂₅₄ prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm⁻¹. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ABq (AB quartet), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a
Nicolet NMC-1280 spectrometer and are reported in δ relative to CDCl₃ (77.00 ppm). High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. The purity of all title compounds was judged to be ≥ 90% by ¹H NMR spectral determination.

Ethyl 5-(4-trimethylsiloxy-3,5-pentadienyl)-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (74). To a solution of enone 71 (0.140 g, 0.436 mmol) in 5 ml of dry methylene chloride at -78°C was added triethyl amine (0.080 ml, 0.58 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.13 ml, 0.57 mmol). The resulting colorless solution was stirred at -78°C for 2.5 hours. The reaction mixture was quenched at -78°C with 5 ml of saturated ammonium chloride. The resulting mixture was allowed to warm to 0°C and was then extracted with methylene chloride (3 x 5 ml portions). The organic layer was dried and concentrated in vacuo. The resulting oil was purified by sg chromatography giving diene 74 (0.188 g, 0.432 mmol) as a colorless oil in 99% yield. \( R_F = 0.32 \) (20:1 H:EA); \(^{1}H\) NMR (CDCl₃) δ 5.97 (m, 2 H), 4.37 (m, 4 H), 3.22 (m, 1 H), 2.96 (m, 3 H), 2.30 (m, 8 H), 1.77 (m, 1 H), 1.50 (m, 1H), 1.29 (t, J=6.9 Hz 3 H), 1.08 (t, J=7.2 Hz, 3H), 0.998 (s, 9 H), 0.167 (s, 6 H).

Compound 77. To a sealed tube was added diene 74 (0.161 g, 0.370 mmol) and methyl vinyl ketone (0.31 ml, 3.7 mmol) and 1 drop of bistrimethylsilyl acetamide. The resulting solution was heated at 80°C for thirteen hours. The reaction mixture was then concentrated and the residue was purified by sg chromatography giving compound 77
(0.116 g, 0.236 mmol) in 80% yield. $R_F = 0.55 \ (1:1 \ H:EA)$; $^1H$ NMR (CDCl$_3$) $\delta$ 4.16 (t, $J=7.2$ Hz, 2 H), 2.90 (m, 4 H), 1.90 (m, 19 H), 1.24 (t, $J=7.2$ Hz, 3 H), 1.05 (t, $J=7.2$ Hz, 3 H); IR (neat) 2934, 2812, 2777, 1730, 1714, 1696, 1256 cm$^{-1}$.

**4-Dimethylphosphono-1-buten-3-one (81):** To a solution of dimethyl methyl phosphonate (5.0 ml, 46 mmol) in 80 ml of THF at -78°C was added $n$-butyl lithium (2.5 ml, 6.0 mmol) dropwise over 15 minutes. The resulting white suspension was then stirred at -78°C for an additional 30 minutes. Acrolein (0.60 ml, 9.0 mmol) in 3 ml of THF was then added over a 15 minute period. The resulting colorless solution was stirred at -78°C for 45 minutes and was then warmed to 0°C. Seven ml of hydrochloric acid (1 N) followed by 3 ml of aqueous saturated sodium chloride were added. The mixture was extracted with ethyl acetate (4 x 25 ml) and the combined organic layers were dried and concentrated *in vacuo* giving 8.43 g of a yellow residue. The resulting residue was taken up in 100 ml of acetone. To this solution was added Jones Reagent over 30 minutes. The mixture was stirred for an additional 1 hour and was then filtered through a moistened (acetone) pad of celite. Concentration of the filtrate followed by $sg$ chromatography (EA) gave 81 (5.75 g, 32.3 mmol) in 70% yield. $R_F = 0.3$ (EA); $^1H$ NMR (CDCl$_3$) $\delta$ 6.32 (dd, $J=17.7$ Hz, $J=10.5$ Hz, 1 H), 6.17 (d, $J=10.5$ Hz, 1 H), 3.79 (d, $J=11.4$ Hz, 6 H), 3.27 (d, $J=22.8$ Hz, 2 H); $^{13}C$ NMR (CDCl$_3$) $\delta$ 191.34, 135.75, 130.52, 52.84, 39.15, 37.43; IR (neat) 2957, 2929, 2835, 1731, 1698, 1682, 1256, 1033 cm$^{-1}$. 
Ethyl 5-(3,5-pentadienyl)-3-ethyl-9-oxo-3-azabicyclo-[3.3.1]nonane carboxylate (84). To a solution of bromoketone 83 (3.26 g, 10.2 mmol) in 10 ml of dry benzene was added 2,4-pentadienyltri-n-butylstannane (7.31 g, 19.7 mmol) and AIBN (0.16 g, 0.98 mmol). The resulting colorless solution was heated in boiling benzene for 24 hours. The reaction mixture was then cooled to room temperature and was diluted with hexane. The hexane layer was extracted with three portions of 1 N hydrochloric acid. To the combined acid extracts was added ethyl ether, and the aqueous layer was neutralized with NaHCO₃ (solid). The layers were separated and the aqueous layer was washed with two more portions of ether. The combined ether washings were then washed with saturated sodium chloride solution. The organic layer was then dried and concentrated in vacuo, and the resulting crude product was purified by sg chromatography (20:1 H:EA) giving 84 (1.41 g, 4.62 mmol) in 45% yield. 

\[ R_F = 0.32 \text{ (10:1 H:EA)} \]

\[ ^1H \text{ NMR (CDCl}_3 \text{) } \delta \text{ 6.30 (dt, } J=10.5 \text{ Hz, } J=17.1 \text{ Hz, 1 H), 6.02 (dd, } J=7.5 \text{ Hz, } J=15 \text{ Hz, 1 H), 5.68 (m, 1 H), 5.10 (d, } J=17.1 \text{ Hz, 1 H), 4.98 (d, } J=9.9 \text{ Hz, 1 H), 4.21 (q, } J=7.2 \text{ Hz, 2 H), 3.19 (dd, } J=2.4 \text{ Hz, } J=11.4 \text{ Hz, 1 H), 3.92 (m, 4H), 2.30 (m, 7 H), 1.87 (m, 1 H), 1.60 (m, 1 H), 1.29 (t, } J=7.2 \text{ Hz, 3 H), 1.09 (t, } J=7.2 \text{ Hz, 3 H);} \]

\[ ^13C \text{ NMR (CDCl}_3 \text{) } \delta \text{ 212.48, 171.06, 136.74, 134.03, 129.81, 115.37, 64.61, 61.58, 60.95, 58.88, 51.05, 46.35, 39.29, 38.05, 36.77, 20.41; IR (neat) 3083, 2971, 2930, 2809, 1735, 1717, 1257, 1006 \text{ cm}^{-1}. \]

Compound 92. To a sealed tube was added 1-phenylsulfonyl-3-buten-2-one (0.425 g, 2.02 mmol) and diene 84 (0.620g, 2.03 mmol).
The mixture was heated at 100°C for 36 hours. After cooling, 0.104 g of 90 (2.03 mmol) was diluted with 2 ml of THF. To this solution at 0°C was added potassium tert-butoxide (0.067 g, 0.60 mmol). The red solution was warmed to room temperature over 1 hour. The resulting deep red solution was then stirred at room temperature for an additional 4 hours. Water was then added to the mixture. The resulting mixture was extracted with methylene chloride and the combined extracts were dried and concentrated in vacuo. Purification by sg chromatography (4:1 H:EA) gave 92 (0.0071 g, 0.020 mmol) in 10% yield. Rp = 0.28 (4:1 H:EA); 1H NMR (CDCl3) δ 7.33 (m, 3 H), 7.05 (d, J=8.1 Hz, 1 H), 6.05 (s, 1H), 4.21 (q, J=7.2 Hz, 2 H), 3.55 (m, 2H), 3.40 (d, J=11.4 Hz, 1 H), 2.90 (m, 4H), 2.00 (m, 5 H), 1.85 (m, 1 H), 1.31 (t, J=7.2 Hz, 3 H), 1.04 (t, J=6.9, 3 H).

1-Bromo-2-bromomethyl-5-methoxybenzene (95): To a solution of 2-bromo-4-methoxybenzoic acid (1.00 g, 4.33 mmol) in 2 ml of THF at 0°C was added 5.8 ml of borane/THF complex (1.0 M) over 15 minutes. The reaction mixture was stirred at 0°C for 45 minutes and then at room temperature for 30 minutes. The reaction was carefully quenched with 10 ml of a 1:1 mixture of THF and water. The resulting mixture was extracted with ethyl ether (3 x 25 ml). The combined ethyl ether extracts were washed with brine (10 ml), dried, and concentrated in vacuo. The resulting oil was purified by sg chromatography (4:1 H:EA) giving the corresponding alcohol (0.80 g, 3.69 mmol) in 85% yield. 1H NMR (CDCl3) δ 7.42 (d, J=8.7 Hz, 1 H), 7.06 (d, J=3.0 Hz, 1 H), 6.71 (dd, J=8.7 Hz, J=3.0 Hz, 1 H), 4.71 (br s, 2H),
3.8 (s, 3 H); IR (neat) 3378, 3000, 2956, 2906, 2835, 1594, 1575, 1471, 1238, 1160, 1014 cm⁻¹; MS: m/e 218, 216, 145, 137, 109, 94, 77; HRMS: calculated for C₈H₇O₂Br 215.97859, found 215.97872. To a solution of the resulting alcohol (0.80 g, 3.69 mmol) in 5 ml of ethyl ether at room temperature was added triphenylphosphine (1.04 g, 3.96 mmol) and carbon tetrabromide (1.31 g, 3.95 mmol). The resulting mixture was stirred at room temperature for 45 minutes and was then filtered through a moistened (ethyl ether) pad of celite. The filtrate was concentrated in vacuo, and the resulting orange oil was purified by sg chromatography (15:1 H:EA). Compound 95 (0.94 g, 3.36 mmol) was obtained in 91% yield. ¹H NMR (CDCl₃) δ 7.45 (d, J=9.0 Hz, 1 H), 6.90 (d, J=3.0 Hz, 1 H), 6.74 (dd, J=8.7 Hz, J=3.0 Hz, 1 H) 4.56 (s, 2 H), 3.80 (s, 3H); MS: m/e 201, 199, 120, 90, 77; HRMS: calculated for C₈H₇OBr₂ 277.89418, found 277.89421.

1-Bromo-2-(3-butenyl)-5-methoxybenzene (96): To a solution of bromide 95 (0.82 g, 2.93 mmol) in 5 ml of THF at 0°C was added 4.4 ml of allyl magnesium bromide (1.0 M in ethyl ether) over 30 minutes. The resulting solution was stirred at 0°C for 3 hours. The reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with ethyl ether. The combined ether extracts were washed with brine, dried, and concentrated in vacuo. Purification by sg chromatography (H) of the resulting oil gave 96 (0.67 g, 2.78 mmol) in 95% yield. Rᶠ = 0.37 ( 10:1 H:EA); ¹H NMR (CDCl₃) δ 7.41 (d, J=8.7 Hz, 1 H), 6.77 (d, J=3.0 Hz, 1 H), 6.63 (dd, J=8.7 Hz, J=3.0 Hz, 1 H) 5.88 (m, 1 H), 5.04 (m, 2 H); ¹³C NMR (CDCl₃) δ 158.76, 141.92, 137.51, 133.11,
116.02, 115.13, 114.79, 112.99, 55.30, 35.77, 33.74; MS: m/e 242, 240, 169, 171, 16, 120, 91, 77; HRMS: calculated for C_{11}H_{11}OBr 240.01498, found 240.01500.

5(2-(2-Bromo-4-methoxyphenyl)ethyl-7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-2-ene (93): Compound 96 (0.24 g, 1.00 mmol) and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene were heated in a sealed tube at 150°C for 20 hours. The crude product was purified by sg chromatography (9:1 H:EA) giving compound 93 (0.495 g, 0.98 mmol) in 98% yield. \(^1\)H NMR (CDCl₃) δ 7.40 (d, J=5.4 Hz, 1 H), 6.74 (d, J=1.8 Hz, 1 H), 6.63 (dd, J=1.8 Hz, J=5.1 Hz, 1 H), 3.78 (s, 3 H), 3.60 (s, 3 H), 3.55 (s, 3 H), 2.60 (m, 3 H), 1.90 (m, 1 H), 1.56 (dd, J=2.1 Hz, J=6.9 Hz, 1 H), 1.15 (m, 1 H); \(^1^3\)C NMR (CDCl₃) δ 158.94, 141.42, 133.31, 129.80, 128.56, 115.88, 114.74, 113.75, 111.71, 78.83, 44.68, 55.42, 52.61, 51.53, 47.04, 41.54, 34.00, 29.98; IR (neat) 3001, 2942, 2843, 1602, 1475, 1198, 739 cm⁻¹.

6,6-Dimethoxy-4-(2-(2-bromo-4-methoxyphenyl))ethyl-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-5-ene (97): To a solution of compound 93 (0.107 g, 0.212 mmol) in 6 ml of benzene was added tri-n-butyltin hydride (0.10 ml, 0.372 mmol) and AIBN (0.0038 g, 0.023 mmol). The resulting solution was boiled for 12 hours. After cooling the reaction mixture to room temperature, the solution was concentrated in vacuo. Purification of the crude product by sg chromatography (10:1) (x 2) gave compound 97 (0.050 g, 0.117 mmol) in 55% yield along with 35% of the starting bromide (0.037 g, 0.074 mmol). \(RF = 0.20\) (10:1 H:EA); \(^1\)H NMR (CDCl₃) δ 7.25 (m, 1 H),
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6.79 (m, 3 H), 4.10 (s, 1 H), 3.81 (s, 3 H), 3.57 (s, 3 H), 3.37 (s, 3 H), 2.62 (m, 2 H), 2.30 (m, 3 H), 2.00 (m, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 159.73, 142.35, 135.56, 133.20, 129.56, 120.52, 114.02, 114.47, 104.42, 77.20, 68.11, 56.72, 55.15, 53.80, 52.39, 51.06, 30.92, 30.38; IR (neat) 2994, 2948, 1603, 1260, 1076 cm$^{-1}$. MS: m/e 389, 353, 266, 122; HRMS: calculated for C$_{17}$H$_{17}$Cl$_3$O$_2$ (M-OMe) 394.99511, found 394.99532.

Ethyl 5-(4-(2-cyclohexen-1-one))-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate (105): To a solution of aldehyde 69 (0.101 g, 0.355 mmol) in 2 ml benzene was added activated molecular sieves and morpholine (0.071 ml, 0.80 mmol). The mixture was boiled for 12 hours. NMR spectral analysis of an aliquot showed a 2:1 mixture of an enamine and the starting aldehyde. Heating for an additional 6 hours gave the same ratio of material. The mixture was then filtered through glass wool and concentrated in vacuo. The residue was diluted with 2 ml of benzene and the methyl vinyl ketone (0.035 ml, 0.42 mmol) was added. The resulting solution was boiled for 7 hours. Concentration in vacuo gave a brownish-orange oil, which was diluted with 2 ml of methanol and 2 ml of water. The resulting mixture was heated at 80°C for 10 hours. After cooling to room temperature, 5 ml of water were added. The mixture was extracted with ethyl ether (5 x 25 ml). The combined extracts were washed with brine, dried and concentrated. Purification by sg chromatography (4:1 H:EA) gave 105 (0.041 g, 0.12 mmol) in 35% yield. R$_F$ = 0.32 (4:1 H:EA); $^1$H NMR (CDCl$_3$) $\delta$ 6.85 (m, 1 H), 6.02 (m, 1 H), 4.24 (m, 2 H), 2.3 (m, 17 H), 1.30 (t, J=7.2 Hz, 3 H), 1.10 (m, 3 H).
1-Bromo-3-ethyl-9-hydroxy-5-hydroxymethyl-3-azabicyclo[3.3.1]nonane (109): To a solution of bromide 66 (0.16 g, 0.50 mmol) in 5 ml of THF at 0°C was added lithium aluminum hydride (0.029 g, 0.76 mmol) over 5 minutes. The ice bath was removed and the suspension was stirred at room temperature for 1 hour. To this mixture was added 29 µl of water, 29 µl of 15% aqueous sodium hydroxide, and 87 µl of water. The resulting suspension was filtered through glass wool and the filtrated was concentrated in vacuo. Sg chromatography (3:2 H:EA) of the remaining residue gave compound 109 (0.079 g, 0.30 mmol) in 60% yield. $^1$H NMR (CDCl$_3$) $\delta$ 3.80 (d, J=3.0 Hz, 1 H), 3.46 (m, 4 H), 2.50 (m, 10 H), 1.54 (m, 1 H), 1.32 (m, 1 H), 1.04 (t, J=7.2 Hz, 3 H); IR (neat) 3403, 2971, 2928, 2807, 1079, 746 cm$^{-1}$.

1-Bromo-3-ethyl-5-methoxymethoxymethyl-9-oxo-3-azabicyclo[3.3.1]nonane (111): To a solution of diol 109 (0.477 g, 1.71 mmol) in 3.4 ml of methylene chloride at room temperature was added chloromethyl methyl ether (0.13 ml, 1.71 mmol) and diisopropylethyl amine (0.30 ml, 1.72 mmol). The solution was stirred at room temperature for 36 hours. The reaction mixture was quenched with saturated ammonium chloride, and the resulting mixture was extracted with methylene chloride. The combined methylene chloride extracts were dried and concentrated in vacuo. The crude product was purified by sg chromatography (9:1 H:EA) giving compound 110 (0.338 g, 1.05 mmol) in 61 % yield. To a solution of DMSO (0.135 ml, 1.90 mmol) in 1 ml of methylene chloride at -78°C was added 0.69 ml of trifluoroacetic acid (2.09 M in methylene chloride) over 10 minutes. To the white
suspension was added alcohol 110 (0.322 g, 1.00 mmol) in methylene chloride over 10 minutes. The resulting mixture was stirred at -78°C for 40 minutes. The cold bath was removed and the reaction mixture changed from a white suspension to a yellow solution. After stirring the solution at room temperature for 70 minutes, triethylamine (0.37 ml, 2.66 mmol) was added over 10 minutes. After stirring the reaction mixture for an additional 10 minutes, water was added. The mixture was extracted with methylene chloride. The combined methylene chloride extracts were dried and concentrated in vacuo. Purification of the crude product by sg chromatography (9:1 H:EA) gave compound 111 (0.234 g, 0.73 mmol) in 73% yield. $^1$H NMR (CDCl$_3$) $\delta$ 4.62 (ABq, J=6.9 Hz, 2 H), 3.50 (m, 3 H), 3.36 (s, 3 H), 3.20 (m, 2 H), 2.89 (dd, J=2.1 Hz, J=11.1 Hz, 1H), 2.73 (m, 2 H), 2.54 (m, 1 H), 2.41 (q, J=6.9 Hz, 2 H), 2.27 (m, 1 H), 1.70 (m, 1 H), 1.53 (m, 1 H), 1.10 (t, J=7.2 Hz, 3 H); IR (neat) 2928, 2817, 1733, 1290, 1148, 1112, 1043, 918 cm$^{-1}$.

**Compound 112:** To a solution of diisopropylamine (0.10 ml, 0.71 mmol) in 1 ml of THF at 0°C was added 0.35 ml of n-butyllithium (2.10 M) dropwise. After stirring for 15 minutes the colorless solution was cooled to -78°C. Acetyl cyclohexene (0.071 ml, 0.55 mmol) was added, and the resulting solution was stirred at -78°C for 1.5 hours. Compound 111 (0.138 g, 0.43 mmol) in 2 ml of THF was then added over 10 minutes. The resulting mixture was stirred at -78°C for 1 hour and then was slowly warmed to 0°C over 1 hour. Stirring was continued at 0°C for 2 additional hours. The reaction mixture was then quenched with saturated ammonium chloride, and the resulting mixture was extracted
with methylene chloride. The combined methylene chloride extracts were dried and concentrated in vacuo. The crude product was purified by gc chromatography (EA) giving compound 112 (0.098 g, 0.270 mmol) in 63% yield. $^1$H NMR (CDCl$_3$) $\delta$ 6.88 (m, 1 H), 4.50 (s, 2 H), 3.40 (ABq, $J=6.3$ Hz, 2 H), 3.29 (s, 3 H), 3.10 (m, 1 H), 2.80 (m, 1 H), 2.54 (m, 1 H), 1.7 (m, 11 H), 1.12 (t, $J=7.2$ Hz, 3 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 201.83, 180.19, 135.52, 133.33, 96.65, 94.05, 72.91, 64.61, 62.57, 58.52, 55.12, 49.40, 37.63, 35.83, 25.96, 24.31, 23.64, 22.18, 21.61, 13.84; IR (neat) 2933, 2870, 2792, 1739, 1639, 1588, 1234, 1148, 1108, 1047, 918 cm$^{-1}$; MS: m/e 363, 318, 288, 270, 254, 192, 164, 151, 136; HRMS: calculated for C$_{21}$H$_{33}$O$_4$N 363.24096, found 363.24152.

4-(2-Hydroxyethyl)-1-methoxy-1,4-cyclohexadiene (120): To a two neck flask fitted with a dry ice condensor and a calcium chloride drying tube was added 4-methoxyphenethyl alcohol (9.30 g, 61.2 mmol), 18 ml of ethanol, and 40 ml of THF. The solution was cooled to -78°C and then approximately 500 ml of ammonia was condensed in the reaction vessel. Small pieces of sodium (8.5 g, 369 mmol) were then added over 30 minutes. The ice bath was removed and the reaction was stirred for 4 hours at -33°C. The reaction was then carefully quenched by adding 80 ml of water over 1 hour. The resulting mixture was warmed to room temperature, and then stirred at room temperature for 5 hours. The mixture was then extracted with ethyl ether, and the combined ethyl ether extracts were dried and concentrated in vacuo giving crude 120 (8.01 g, 52.0 mmol) in 85% yield.
2-Chloro-2-cyano-4-(2-hydroxyethyl)-1-methoxy-bicyclo[2.2.2]oct-5-ene (122): To a solution of crude compound 120 (1.54 g, 10.0 mmol) in 20 ml of THF at 0°C was added pyridine (1.0 ml, 12.4 mmol) and chlorotrimethylsilane (1.6 ml, 12.6 mmol). The resulting suspension was stirred at 0°C for 2 hours. Forty ml of hexane were then added to the reaction mixture, and the resulting mixture was then filtered through a moistened (hexane) pad of Celite. The filtrate was concentrated giving the protected alcohol (2.38 g, 10.5 mmol). The resulting compound (2.38 g, 10.5 mmol) and 2-chloroacrylonitrile (1.6 ml, 20 mmol) in 5 ml of dry benzene were then heated at 100°C for 26 hours. The mixture was cooled to room temperature and concentrated. To the resulting oil was added 30 ml of THF and 12.5 ml of hydrochloric acid (1 N). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated sodium bicarbonate and then extracted with ethyl ether. The combined ethyl ether extracts were dried and concentrated in vacuo. The resulting oil was then purified by sg chromatography (3:2 H:EA) giving compound 123 (1.28 g, 5.30 mmol) in 53% yield. R<sub>F</sub> = 0.37 (1:1 H:EA); ¹H NMR (CDCl<sub>3</sub>) δ 6.40 (dd, J=8.7 Hz), 6.26 (dd, J=8.7 Hz), (6.46 and 6.26 equal 2 H), 3.81 (t, J=6.0 Hz, 2 H) 3.53 (s, 3H), 2.5 (m, 1H), 2.05 (m, 3 H), 1.6 (m, 4 H); IR (neat) 3440, 3053, 2939, 2836, 2240, 1374, 1113 cm<sup>-1</sup>.

2-Chloro-2-cyano-1-methoxy-4-(2-phenylsulfonylethyl)-bicyclo[2.2.2]oct-5-ene (118): To a solution of alcohol 123 (0.292 g, 1.21 mmol) in 3.6 ml of ethyl ether at room temperature was added triphenylphosphine (0.306 g, 1.17 mmol) and carbon tetrabromide
(0.386 g, 1.16 mmol). The resulting mixture was stirred at room temperature for 3.5 hours. The reaction mixture was filtered through a moistened (ethyl ether) pad of celite, and the filtrate was concentrated in vacuo. The resulting crude bromide was then diluted with 1.8 ml of methanol. To this solution was added the sodium salt of benzenesulfinic acid (0.40 g, 2.44 mmol). The resulting suspension was then boiled for 28 hours. After cooling to room temperature, the reaction was quenched with water. The resulting mixture was then extracted with methylene chloride. The combined methylene chloride extracts were dried and concentrated in vacuo. Purification by sg chromatography (2:1 H:EA) gave compound 118 (0.232 g, 0.634 mmol) in 52% yield. 

$R_F = 0.57$ (1:1 H:EA); $^1$H NMR (CDCl$_3$) $\delta$ 7.92 (dd, J=1.5 Hz, J=6.9 Hz, 2 H), 7.54 (m, 3 H), 6.46 (d, J=9.0 Hz), 6.29 (d, J=8.7 Hz), (6.46 and 6.29 equal 1 H), 6.16 (d, J=9.0 Hz), 6.08 (d, J=9.0 Hz), (6.16 and 6.08 equal 1 H), 3.51 (s, 3 H), 3.10 (m, 2 H), 2.5 (d, J=14.4 Hz, 1 H), 2.05 (m, 5 H), 1.60 (m, 2 H); IR (neat) 3058, 2942, 2242, 1378, 1303, 1149, 739 cm$^{-1}$. 
### APPENDIX

#### Crystal Data

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<td>range (2θ)</td>
<td></td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>-50(1)</td>
</tr>
<tr>
<td>Scan method</td>
<td>θ - 2θ</td>
</tr>
<tr>
<td>Data col. range, 2θ, deg</td>
<td>4.0 - 50.0</td>
</tr>
<tr>
<td>No. data collected:</td>
<td>7271</td>
</tr>
<tr>
<td>No. unique data, total:</td>
<td>3153</td>
</tr>
<tr>
<td>with Fᵡ &gt; 2.5σ(Fᵡ):</td>
<td>1214</td>
</tr>
<tr>
<td>Number of parameters refined</td>
<td>226</td>
</tr>
<tr>
<td>Trans. factors, max., min. (ψ-scans)</td>
<td>0.999, 0.755</td>
</tr>
<tr>
<td>R*</td>
<td>0.047</td>
</tr>
<tr>
<td>R₂</td>
<td>0.056</td>
</tr>
<tr>
<td>Quality-of-fit indicator</td>
<td>1.21</td>
</tr>
<tr>
<td>Largest shift/esd, final cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>Largest peak, e/Å³</td>
<td>0.31(6)</td>
</tr>
</tbody>
</table>

---

\[ ^*R = \Sigma||F_o| - |F_c||/\Sigma|F_o| \]

\[ ^{R_w} = \left( \Sigma w|(F_o) - |F_c|)^2/\Sigma w|F_o|^2 \right)^{1/2}; w = 1/\sigma^2(|F_o|) \]

\[ ^{\text{Quality-of-fit}} = \left( \Sigma w(|F_o) - |F_c|)^2/(N_{\text{w}} - N_{\text{parameters}}) \right)^{1/2} \]
REFERENCES

1. (a) Yunusov, M. S. *Natural Product Reports* 1991, 499; (b) Pelletier, S. W.; Page, S. W. *Natural Product Reports* 1986, 451; (c) Amiya, T.; Bando, H. *The Alkaloids* 1988, 34, 95.


19. (a) Shi, J. Ph.D. Thesis, Iowa State University, **1990**;

20. Trifluoroacetic acid is added to protect the tertiary amine from oxidation.

21. Bis(trimethylsilyl)acetamide is added to silylate any impurities which may hinder the formation of the Diels-Alder adduct.


43. Sanchez, I. H.; Aguilar, M. A. Synthesis 1981, 55.

The first paper discusses the use of bridgehead radicals in organic synthesis. This paper has shown that bridgehead radicals can be prepared in high functionalized systems. The mild reaction conditions of this chemistry coupled with the tolerance of a broad range of functional groups makes this method particularly attractive for the preparation of complex molecules. This research has also lead to the development of a new method for the preparation of dienes by radical methods.

The second paper deals with the use of the bridgehead radical methodology for the preparation of polycyclic alkaloids. By this method a variety of potentially useful synthetic intermediates for the preparation of diterpene alkaloids have been prepared in an efficient manner. This research has also resulted in the discovery of a novel method of initiation of a radical rearrangement of a norbornene system.
ACKNOWLEDGEMENTS

I would like to thank Dr. George A. Kraus for his guidance during my tenure as a graduate student. The challenging and stimulating atmosphere of his research group as well as the enthusiasm which he brings to research has made my career at Iowa State University an enjoyable one.

I would also like to thank the members of the Kraus group, both past and present for their help and friendship. I would especially like to thank Dan Bougie, Mark Schwinden, Li Chen, and Jackie Applegate for their guidance during the early years of my graduate career.

Finally, I would like to thank my family for their support and encouragement during the last four years.