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Jeffrey Alan Hansen
Iowa State University

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Hansen, Jeffrey Alan, Ph.D.

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U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

The utilization of bridgehead intermediates in organic synthesis

by

Jeffrey Alan Hansen

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GENERAL INTRODUCTION

The synthesis of natural products has been and continues to be an important and active area of research. In addition, development of new methodology for the direct and efficient synthesis of complicated polycyclic compounds is of great value. In recent years many interesting and useful strategies for the construction of cyclic compounds have been reported. Bond formation to a bridgehead carbon is a strategy that has received little attention from the synthetic chemist until recently. This strategy has been shown to be very useful for the synthesis of some natural products which contain bicyclic ring systems. The goal of the research reported here has been to extend the usefulness of this strategy by developing new methods for the formation of bridgehead intermediates. This has always been approached with the ultimate goal of natural product synthesis in mind.

Explanation of Dissertation Format

This dissertation is divided into two parts preceded by an introduction. The introduction reviews some of the previous contributions in both physical organic and synthetic organic chemistry and provides an overview of bridgehead chemistry. Each of the sections is related to the others in that they are concerned with bridgehead intermediates. The two parts are intended to be separate, publishable articles. The first part deals with the formation

and reaction of bridgehead oxonium ions. The second part deals with the generation of bridgehead intermediates from a bridgehead sulfoxide and an attempt to use this chemistry to synthesize huperzine A.

INTRODUCTION TO BRIDGEHEAD INTERMEDIATES

The occurrence of bicyclic frameworks in natural products abounds. Many of these natural products have intriguing biological activities. Consequently, new methodology for constructing bicyclic systems is of interest.

In the past, these systems have often been prepared by an approach in which bonds to bridgehead carbons are formed prior to synthesis of the bicyclic system. A different approach would be to prepare the bicyclic system first. This approach would require methods for forming bonds to bridgehead carbons.

A number of researchers have investigated the formation and reactions of bridgehead intermediates. The majority of these studies have had a physical organic emphasis. Relatively little had been done from the synthetic viewpoint prior to 1983. Indeed, this area is still largely unexplored with only a handful of syntheses reported which utilize a bridgehead intermediate.[1]

The work done in this area to date can be divided into two categories: bridgehead carbocations and bridgehead enones.

Bridgehead Carbocations

Bridgehead carbocations have been of interest to physical organic chemists for many years. Vogel[2], Schleyer[3] and Warner[4] have provided valuable information on the structure of these intermediates. Much of this information has been collected into a fine review by Fort.[5]

The structure of carbocations is normally planar. Deviation from planarity tends to decrease the stability of the carbocation. The constraints of a bicyclic system do not allow the bridgehead carbons to be planar unless one of the rings is large. As ring size decreases, the bridgehead carbon is forced further from planarity. This results in a higher energy, more reactive, carbocation as can be seen by comparing relative rates of solvolysis of various bridgehead compounds (Figure 1).[5]

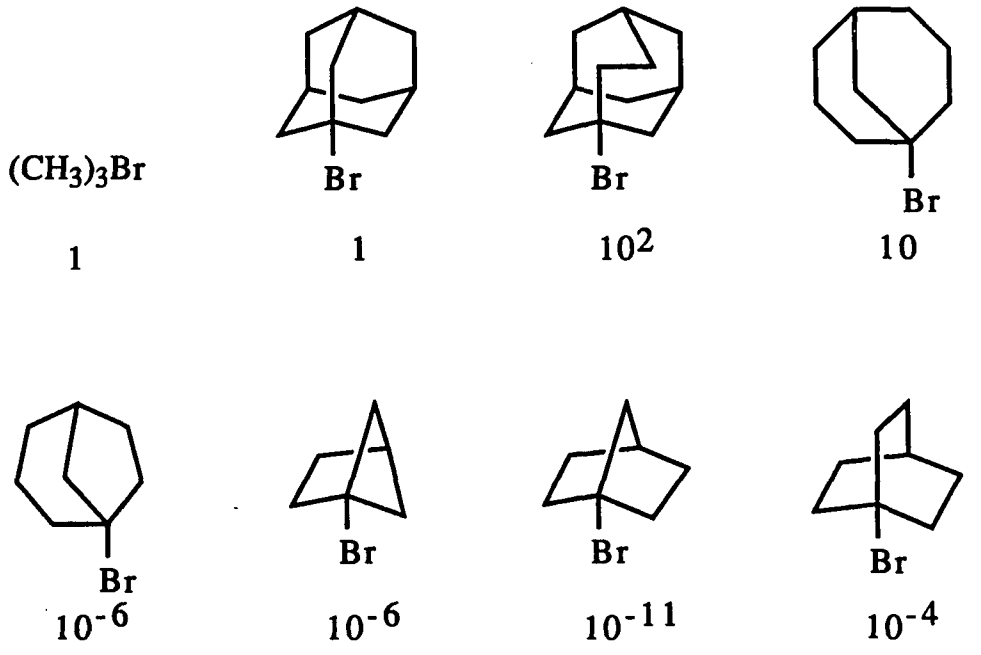


Figure 1. Relative rates of solvolysis of bridgehead compounds

Carbocations have long been useful intermediates in organic synthesis. However, the usefulness of carbocations is diminished by their tendency to undergo unwanted side reactions such as rearrangements and elimination. Conversely, bridgehead carbocations are not prone to do either of these reactions. This feature, coupled with their high reactivity, makes them attractive synthetic intermediates. Consequently, once formed they react cleanly with nucleophiles under mild conditions (Figure 2).[6]

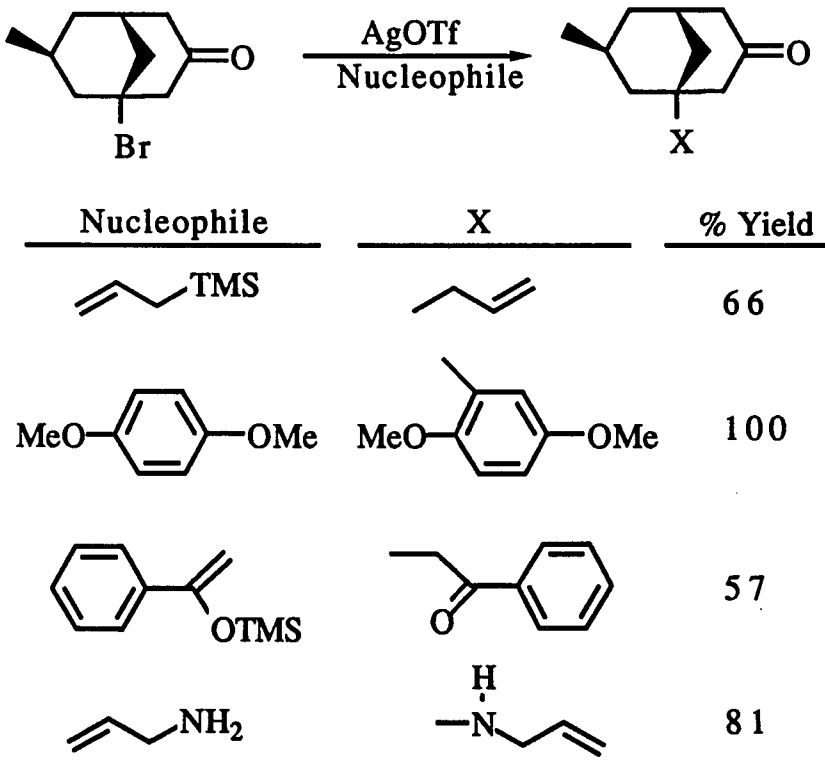
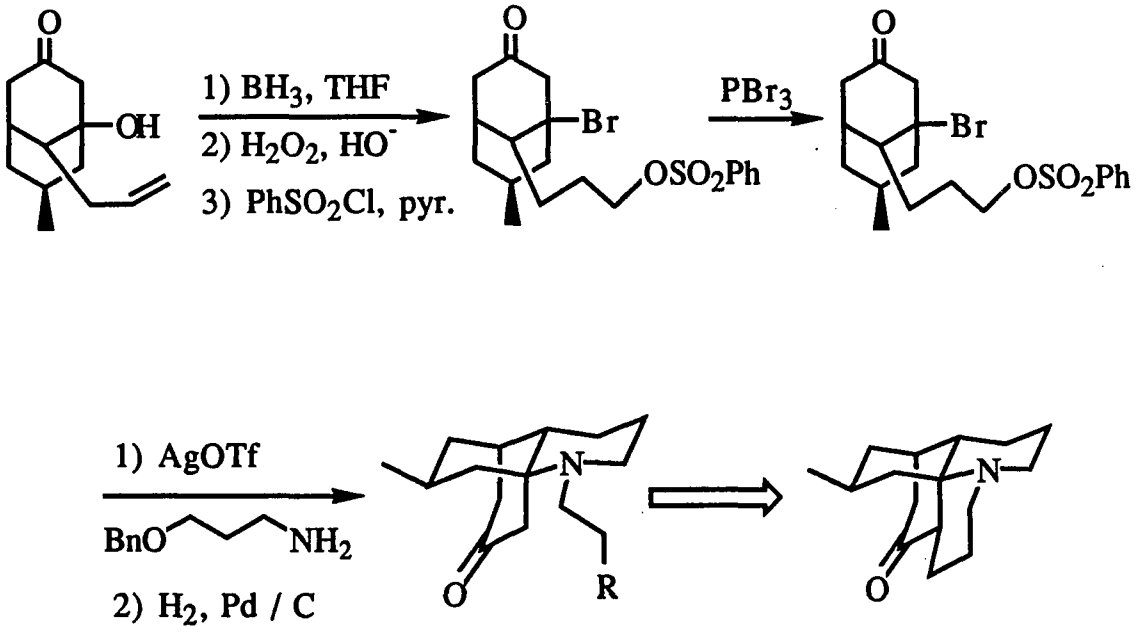


Figure 2. Reactions of bridgehead carbocations with nucleophiles

Bridgehead carbocations have only recently been used synthetically. Heathcock proposed the possibility of a bridgehead carbocation in an elegant synthesis of lycopodine.[7] Kraus and Hon contributed an efficient synthesis of lycopodine using a bridgehead carbocation (Scheme I).[7]

Scheme I



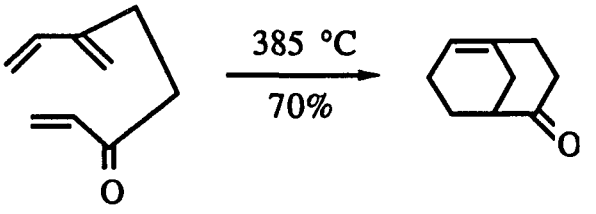
Bridgehead Enones

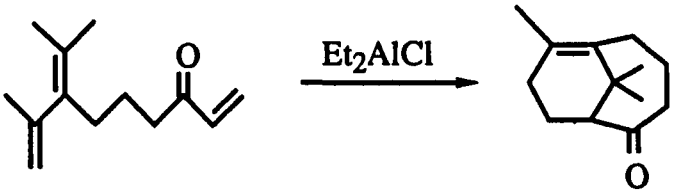
A large body of work has been done on the preparation, structure and stability of bridgehead alkenes.[8] Around 1924 Bredt formulated his famous rule that bicyclic molecules tend not to form double bonds involving bridgehead carbons.[9] Over the years the

limitations of the rule have been more clearly delineated. Most notably, Wiseman has proposed that the stability of a bridgehead alkene closely parallels the stability of the analogous *trans*-cycloalkene.[10] For example, bicyclo[3.3.1]non-1-ene should be similar in stability to trans-cyclooctene. Experimental evidence suggests that Wiseman's proposal is a useful predictor of the relative stabilities of various bridgehead alkenes.

Shea has used an intramolecular Diels-Alder reaction to generate bridgehead alkenes under both thermal and Lewis acid catalyzed conditions (Scheme II).[11,12]

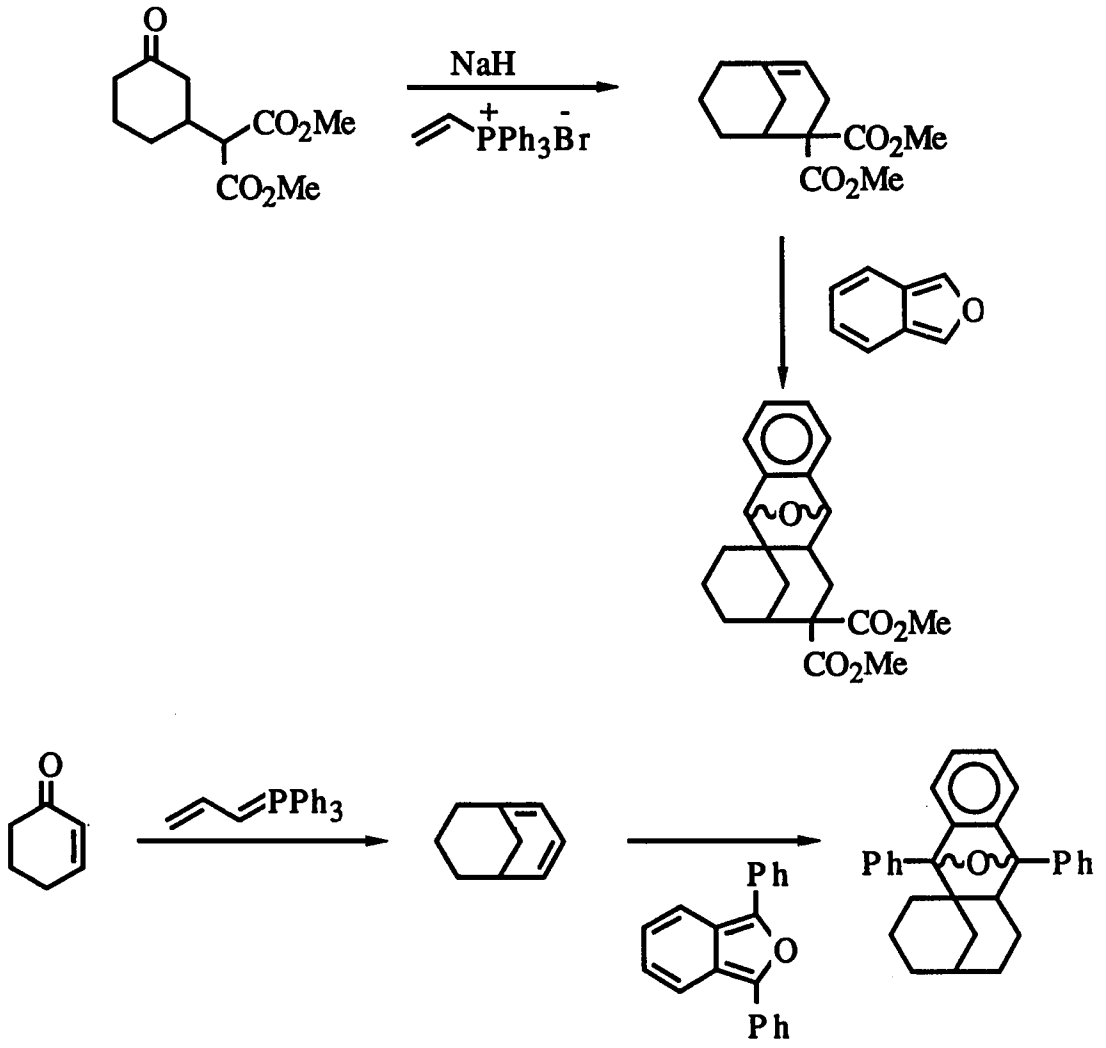
Scheme II





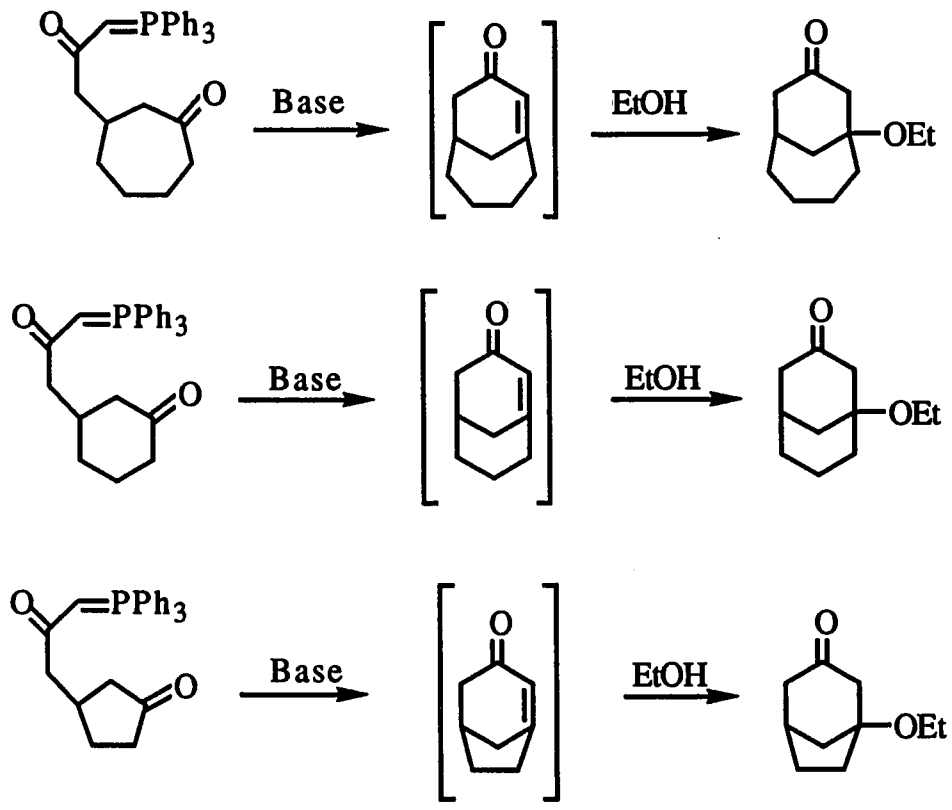
Dauben used an intramolecular Wittig reaction to make bridgehead olefins (Scheme III).[13,14]

Scheme III


O
CO2Me
CO2Me
NaH
+
PPh3Br
-
CO2Me
CO2Me
O
O
CO2Me
CO2Me
O
PPh3
Ph
O
Ph
Ph
O
Ph

Bestmann has used an intramolecular Wittig reaction to make bridgehead enones (Scheme IV).[15]

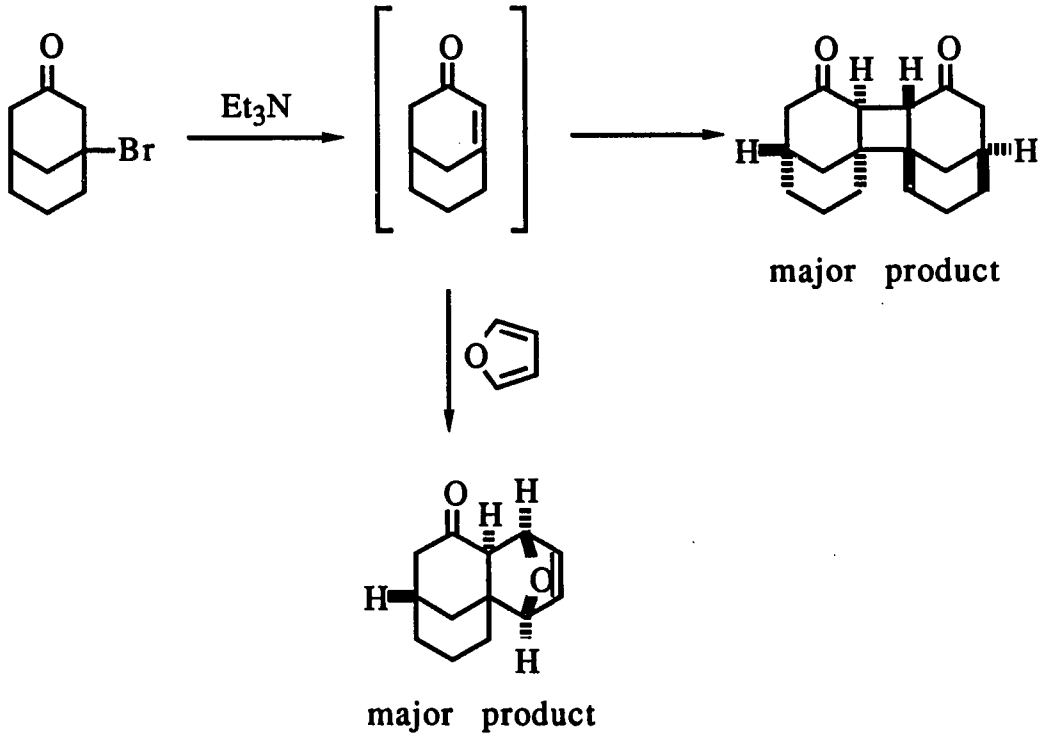
Scheme IV



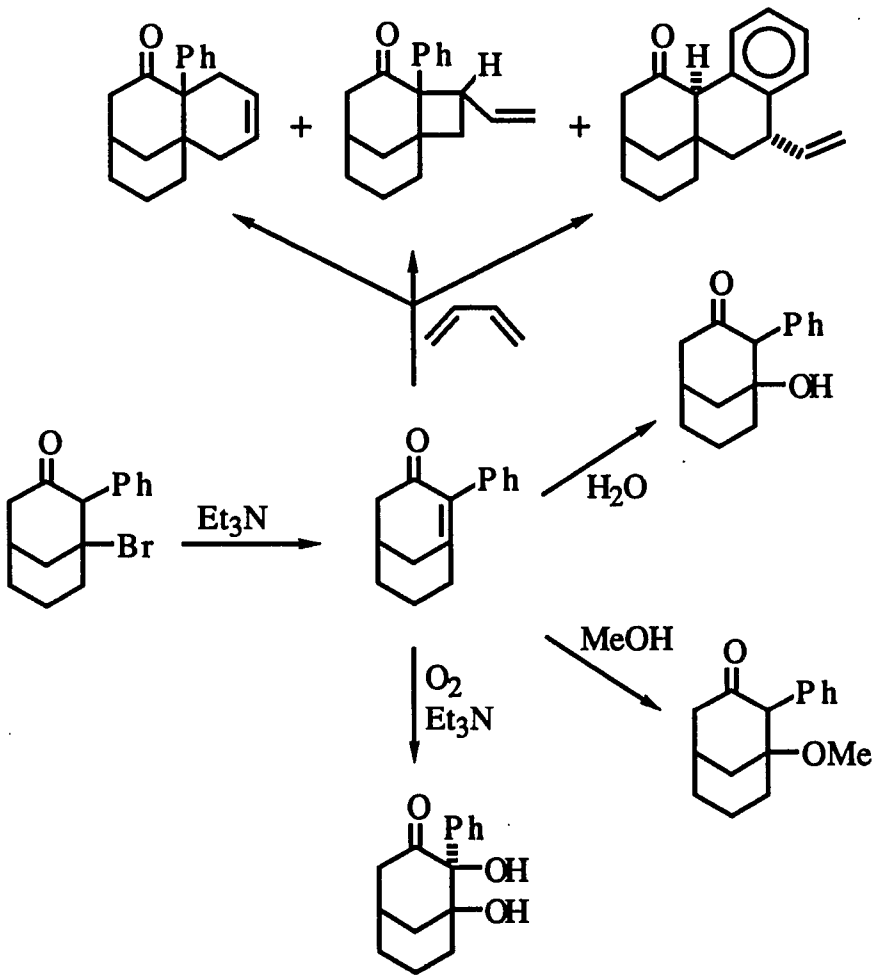
House provided a classic study on the stability of bicyclo[3.3.1]nonen-3-ones.[16] The bridgehead enones were generated by base promoted elimination of bridgehead bromides. The unsubstituted bicyclo[3.3.1]nonen-3-one either dimerized at

sub-ambient temperatures or was trapped by a Diels-Alder reaction with furan (Scheme V). The α-phenyl enone could be isolated and reacted readily with methanol, water, oxygen, and butadiene (Scheme VI).

Scheme V



Scheme VI

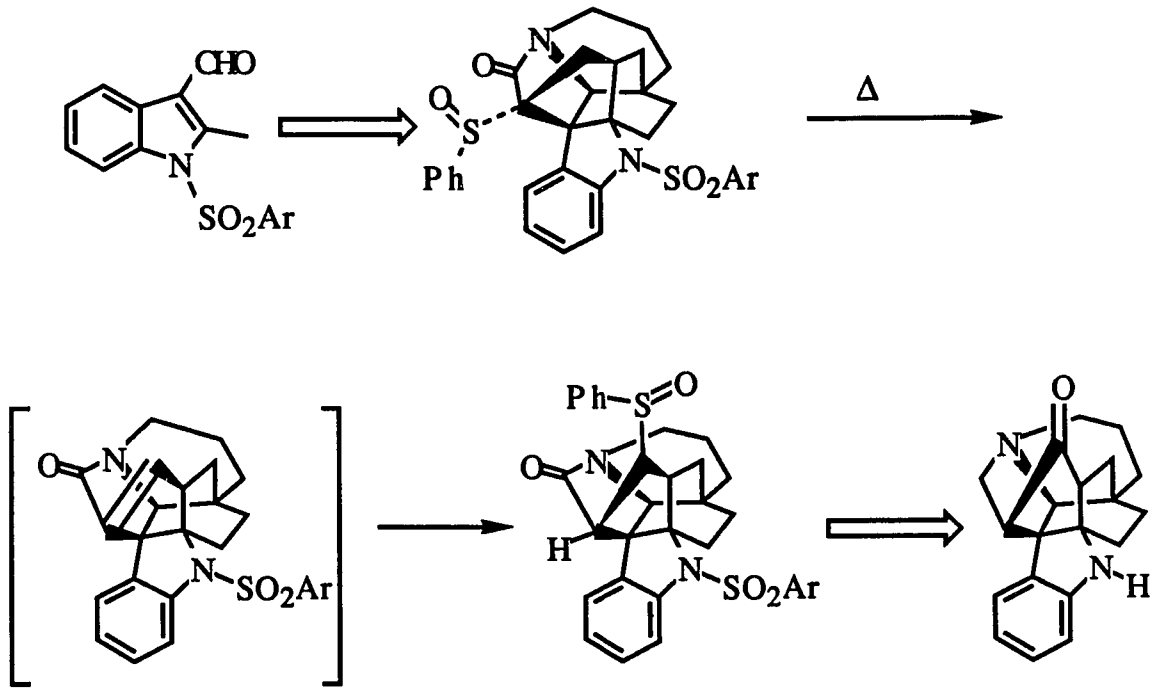


As can be seen from the above examples, once they are formed the bridgehead enones are very reactive. Nucleophiles add rapidly and dienes react to give Diels-Alder adducts at relatively low temperatures. An idea of the reactivity of bridgehead enones can be

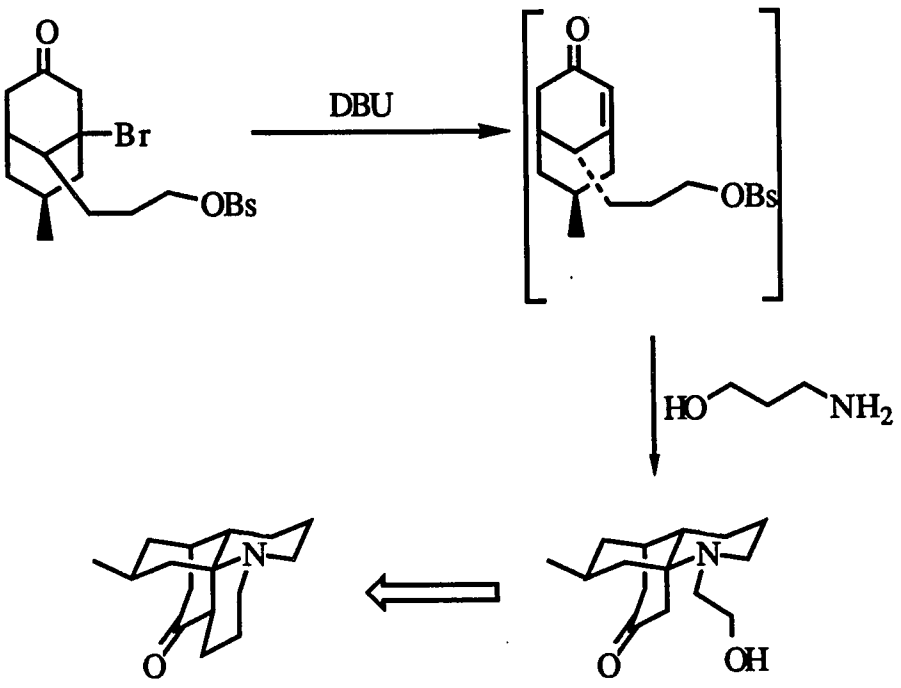
obtained by comparison with cyclohexenone. Bridgehead enones in the [3.3.1] series react with weak nucleophiles such as water and methanol very rapidly at sub-ambient temperatures. Cyclohexenone reacts with these nucleophiles very little or not at all. In the Diels-Alder reaction, bridgehead enones react with unactivated dienes at 0 °C, while cyclohexenone requires temperatures of over 100 °C.

Two total syntheses have been reported which involve bridgehead enone intermediates. The first was by Magnus[17] in his synthesis of kopsanone. He generated the bridgehead enone by a sulfoxide elimination (Scheme VII). The second was by Kraus and Hon in a synthesis of lycopodine.[7] The bridgehead enone was generated by base promoted elimination of a bridgehead bromide (Scheme VIII).

Scheme VII



Scheme VIII



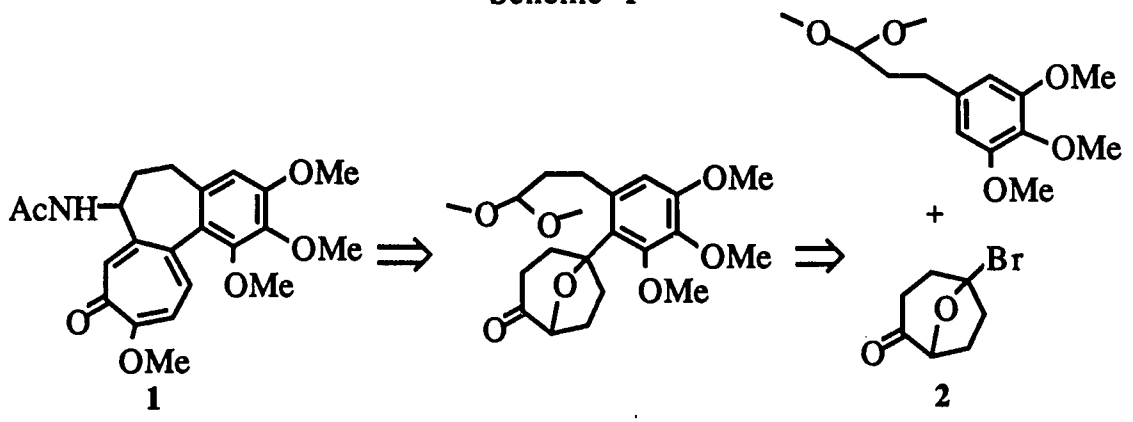
PART I: REACTIONS OF BRIDGEHEAD OXONIUM IONS

HISTORICAL

The usefulness of bridgehead intermediates for the synthesis of natural products containing bridged rings has recently been demonstrated.[1,2] However, the use of bridgehead intermediates for the synthesis of bridged intermediates which could be taken on to fused or spirocyclic ring systems has not been explored. One potential application of this concept could be directed toward the synthesis of the natural product colchicine (**1**). Colchicine has received much attention because of its ability to disrupt a cell's ability to multiply. It exerts this effect by binding to tubulin and preventing microtubule formation that is essential to mitosis.[3] A number of groups have reported syntheses of colchicine.[4]

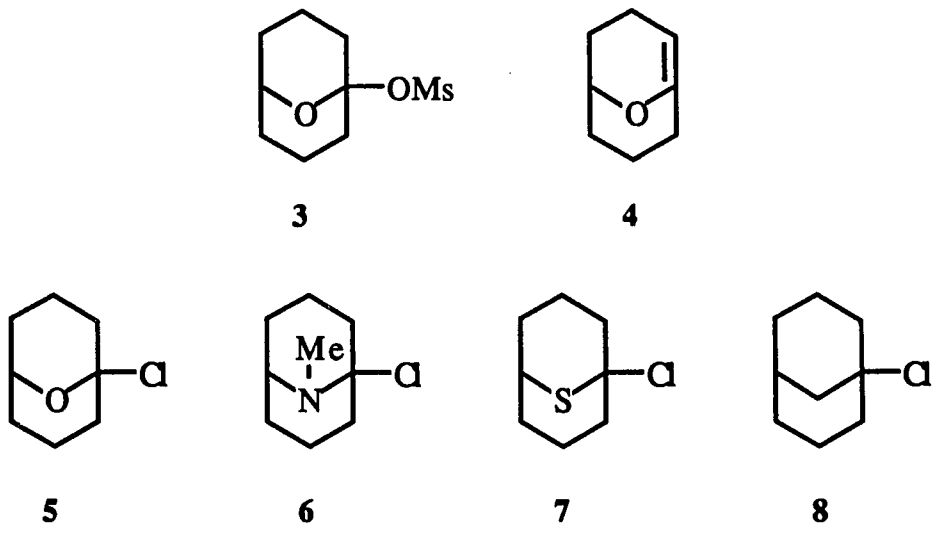
Our approach to colchicine is outlined in Scheme I. The key feature of this route is a Friedel-Crafts alkylation of an appropriately substituted aromatic ring by a bridgehead carbocation derived from the bridged ether **2**.

Scheme I



1 **2**

The chemistry of oxygen bridged compounds, such as **2**, had not been thoroughly studied. Wiseman had prepared the bridgehead mesylate **3** in his synthesis of 9-oxabicyclo[3.3.1]non-1-ene (**4**).[5] He also determined the relative rates of solvolysis of the series of bridgehead chlorides **5-8** (Figure 1).[6] The oxygen bridged chloride **5** was found to solvolyze slower than the all carbon compound **8** by a factor of 3. Wiseman attributed the rate retardation of **5** to the inductive effect of the oxygen which was offset slightly by a small resonance effect. Kirby suggested a slightly different argument based on the stereoelectronic effect.[7]



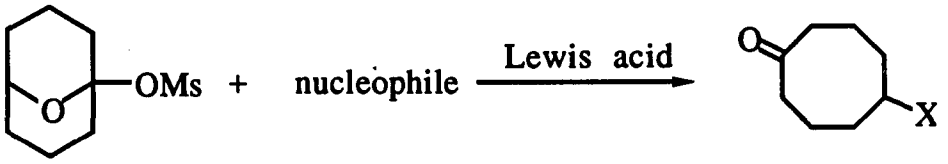
3 **4** **5** **6** **7** **8**

Figure 1. Heteroatom bridgehead compounds

DISCUSSION AND RESULTS

Our work began with bridgehead mesylate **3** which was readily available from 1,5-cyclooctanediol by Wiseman's procedure.[5] Compound **3** was reacted with a variety of substituted benzenes in dichloromethane in the presence of Lewis acids.[8] Optimal conditions were worked out using 1,3-dimethoxybenzene as the nucleophile. Several Lewis acids were used, with titanium tetrachloride giving the best results (Table 1). Other nucleophiles such as allyltrimethylsilane and enol silyl ethers failed in the reaction.

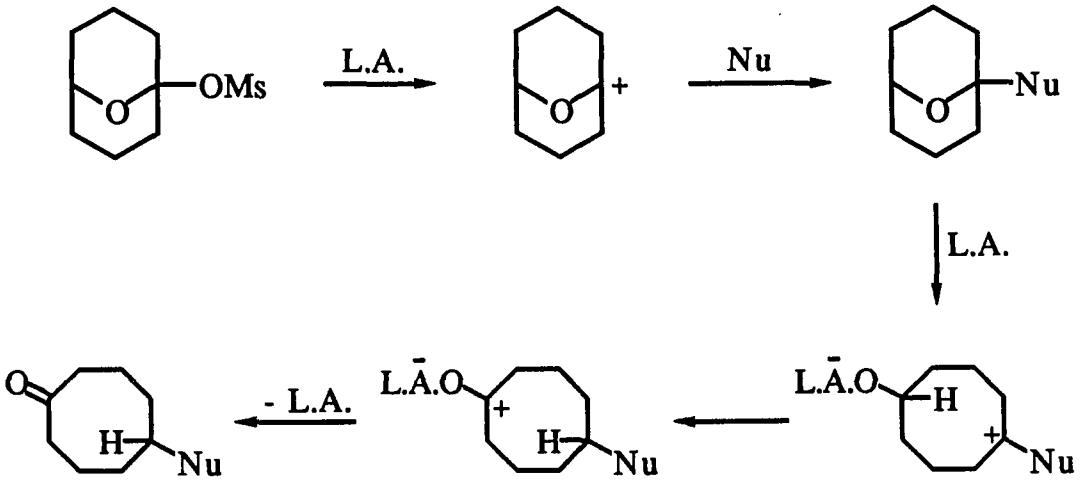
Table 1. Reactions of mesylate **3** with substituted benzenes



Lewis acid	nucleophile	T(°C)	% yield
$TiCl_4$	1,3-di$OMeC_6H_4$	0	45
$BF_3 \cdot Et_2O$	1,3-di$OMeC_6H_4$	0	25
$TiCl_4$	1,3-di$OMeC_6H_4$	-78	73
$TiCl_4$	1,4-di$OMeC_6H_4$	-78	61
$TiCl_4$	3,4,5-tri$OMeC_6H_2CHO$	-78	--
$TiCl_4$	1,3,5-tri$OMeC_6H_3$	-78	56
$TiCl_4$	4-Me anisole	-78	82
$TiCl_4$	1,2,4-tri$OMeC_6H_3$	-78	28

The substituted cyclooctanone products were somewhat unexpected. The products arise by formation of the bridgehead carbocation with subsequent trapping by the nucleophile. The resulting ether is cleaved by the Lewis acid, providing a tertiary benzylic carbocation. A 1,5-hydride transfer gives the cyclooctanone product (Scheme II).

Scheme II



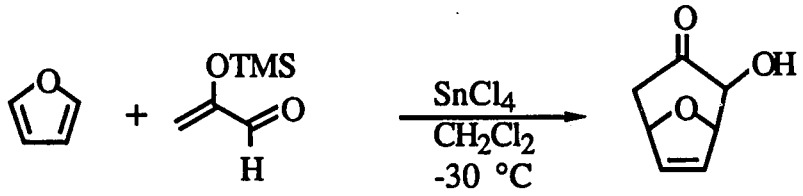
L.A. = Lewis acid
Nu = Nucleophile

The results in the [3.3.1] system prompted us to investigate the analogous [3.2.1] system. Synthesis of the oxabicyclo[3.2.1] bridgehead mesylate or halide proved to be more difficult than the corresponding [3.3.1] compound. While 5-hydroxycyclooctanone

readily closes to the hemiacetal, 4-hydroxycycloheptanone prefers to remain in the open form.

A survey of the literature revealed that a cationic 4+3 cycloaddition reaction has been used to prepare oxabicyclo[3.2.1] compounds (Scheme III).[9]

Scheme III



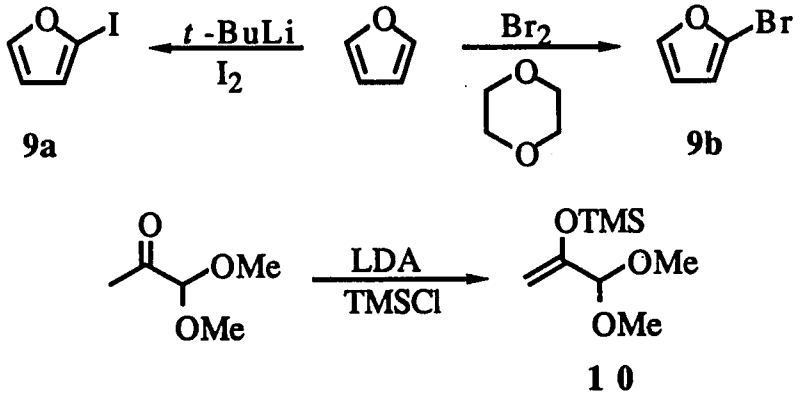
43%

For our purposes the halofuran **9** was needed. Compound **9b** had been made previously according to the procedure of Burness.[10] More conveniently, lithiation of furan with *t*-butyllithium followed by addition of iodine gave **9a** in 60% yield (Scheme IV). The requisite allylic cation precursor **10** was prepared from pyruvaldehyde dimethyl acetal by reaction with LDA and TMSCl.

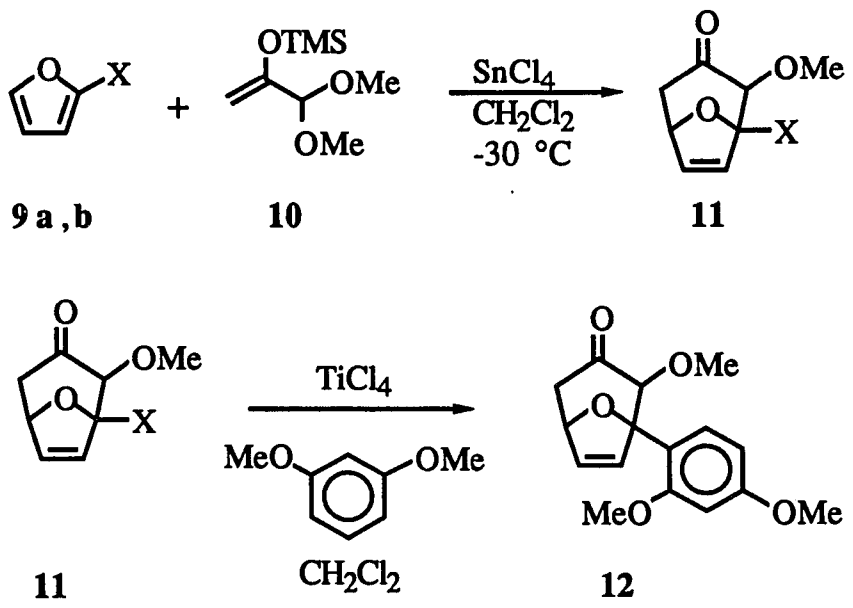
Reaction of **9a** or **9b** and **10** with tin(IV) chloride in dichloromethane at -30°C according to the method of Sasaki gave the bridgehead halides **11a** or **11b** in low yield.[9] Only one regioisomer was observed by proton NMR spectroscopy. The bridgehead halides reacted with titanium(IV) chloride and 1,3-dimethoxybenzene in dichloromethane to give a mixture of products which by proton NMR

spectroscopy contained a product which had incorporated the dimethoxybenzene while leaving the bridgehead ether intact. Interestingly, the bridging ether was apparently not opened under these conditions (Scheme V).

Scheme IV



Scheme V


OTMS
OMe
OMe
X
+
SnCl4
CH2Cl2
-30 °C
O
OMe
X
9 a , b
10
11
TiCl4
MeO
OMe
CH2Cl2
12

CONCLUSION

This chemistry has provided an interesting method for the synthesis of 5-arylcyclooctanones. The chemistry of bridgehead carbocations has been extended to include oxygen bridged species. Furthermore, this reaction has been extended to the analogous bicyclo[3.2.1] system. An improved synthesis of the oxabicyclo[3.2.1] bridgehead halide could lead to an efficient synthesis of colchicine and other biologically active 4-aryltropolones.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane and acetonitrile 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 was 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 F_{254} 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 $CDCl_3$ (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. Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was judged to be $\geq$ 90% by ^1H NMR spectral determinations.

General Procedure for reaction of 3 with substituted benzenes: To a solution of **3** (1 mmol) and substituted benzene (6 mmol) in 2 mL of dichloromethane at -78 °C was added titanium(IV) chloride (1 mmol) dropwise via syringe. The mixture immediately turned brown. The mixture was stirred for 2 hours at -78 °C, then 3 hours at room temperature. The solution was poured into 25 mL saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried and concentrated. The residue was chromatographed on silica gel. Products were generally isolated as colorless oils.

4-(5-Oxocyclooctyl)-1,3-dimethoxybenzene: R_F 0.43 (1:1-H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.6-2.7 (m, 13H), 3.767 (s, 3H), 3.773 (s, 3H), 6.4 (dd, J=3, 8 Hz, 1H), 6.41 (s, 1H), 6.97 (d, J=8 Hz, 1H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 25.50, 34.85, 36.35, 42.17, 55.2, 98.59, 103.67, 127.19, 129.93, 157.26, 158.70, 217.51; IR (neat) 3000, 2940, 2860, 1695, 1610, 1585, 1500, 1205 cm^{-1}; MS *m/e*

calc'd for $C_{16}H_{22}O_3$: 262.15689, found 262.15732; 91, 121, 151, 164, 177, 191, 203, 234, 262.

3-(5-Oxocyclooctyl)-1,4-dimethoxybenzene: R_F 0.41 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.7-2.75 (m, 13H), 3.745 (s, 3H), 3.748 (s, 3H), 6.65 (dd, J=3, 8 Hz, 1H), 6.67 (s, 1H), 6.74 (d, J=8 Hz, 1H); IR (CCl_4) 2940, 2860, 1690, 1605, 1585, 1500, 1220 cm^{-1}; MS *m/e* calc'd for $C_{16}H_{22}O_3$: 262.15689, found 262.15662; 71, 91, 121, 137, 151, 164, 177, 191, 234, 262; Analysis calc'd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; found: C, 73.78; H, 8.57.

2-(5-Oxocyclooctyl)-1,3,5-trimethoxybenzene: R_F 0.20 (3:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45-1.60 (m, 2H), 1.65-1.80 (m, 2H), 2.0-2.15 (m, 4H), 2.25-2.35 (m, 2H), 2.5-2.65 (m, 2H), 2.9-3.0 (m, 1H), 3.74 (s, 6H), 3.78 (s, 3H), 6.08 (s, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 26.14, 32.07, 33.55, 42.25, 55.17, 55.80, 91.04, 118.00, 158.88, 217.81; IR (CCl_4) 3000, 2935, 2855, 2835, 1695, 1605, 1590, 1210, 1200, 1150, 1125 cm^{-1}; MS *m/e* calc'd for $C_{17}H_{24}O_4$: 292.16746, found 292.16694; 77, 91, 121, 151, 179, 181, 194, 207, 221, 264, 292.

2-(5-Oxocyclooctyl)-1-methoxy-4-methylbenzene: R_F 0.57 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-2.7 (m, 16H), 2.24 (s, 3H), 3.75 (s, 3H), 6.7 (d, J=8 Hz, 1H), 6.88 (s, 1H), 6.91 (dd, J=2, 8 Hz, 1H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 25.48, 25.85, 34.67, 37.05, 42.10, 55.35, 110.52, 126.75, 127.94, 129.38, 137.12, 154.24, 217.52; IR (neat) 2930, 2850, 1695, 1610, 1500, 1465, 1445, 1240, 1030 cm^{-1}.

4-(5-Oxocyclooctyl)-1,2,5-trimethoxybenzene: R_F 0.36 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.7-2.7 (m, 13H), 3.77 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.48 (s, 1H), 6.63 (s, 1H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 25.52, 35.01, 36.84, 42.18, 56.18, 56.44, 56.74, 89.09, 98.10, 111.97, 129.41, 142.83, 150.44, 217.48; IR (neat) 2995, 2930, 2850, 1695, 1605, 1500, 1450, 1200, 1035 cm^{-1}.

2-Iodofuran (9a): To a solution of furan (1.36 g, 20 mmol) in 10 mL of Et_2O at 0 °C was added *n*-BuLi (4 mL of 2.5 M sol in hexanes). The solution was stirred at room temperature for 3 hours and was then cooled to -40 °C. A solution of iodine (2.49 g, 9.8 mmol) in 10 mL of Et_2O was added. The solution was stirred for 5 minutes and then was warmed to room temperature and stirred for an additional 5 minutes. The reaction was quenched by adding 20 mL of 10% sodium sulfite solution. The layers were separated and the organic layer was washed with water and saturated sodium chloride solution. The solution was dried and concentrated. The residue was passed through a short column of florisil eluting with Et_2O. The eluent was concentrated to give 1.16 g (60%) of an orange liquid.: ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (AB q, J=1.8, 3 Hz, 1H), 6.53 (d, 3H), 7.52 (d, 1.8H).

[(3,3-Dimethoxy-1-propen-2-yl)oxy]trimethyl silane (10): To a solution of diisopropylamine (1.21 g, 12 mmol) in 10 mL of THF at -78 °C was added *n*-BuLi (4.4 mL of 2.5 M in hexanes). The solution was stirred for 30 minutes, then pyruvaldehyde dimethyl acetal (1.18 g, 10 mmol) in 5 mL of THF was added. The solution was

stirred at -78 °C for 30 minutes and chlorotrimethylsilane (1.30 g, 12 mmol) was added. Stirring was continued while the solution was slowly warmed to room temperature over a period of 1.5 hours. The solvent was removed under a stream of dry nitrogen. The residue was dissolved in hexanes and filtered through a short column of florisil. The solvent was removed and the residue was dissolved in hexanes and filtered again. Removal of the solvent gave 1.75 g (92%) of a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 9H), 3.34 (s, 6H), 4.35 (d, J=1.3 Hz, 1H), 4.53 (br s, 1H), 4.55 (d, J=1.3 Hz, 1H).

1-Iodo-7-methoxy-8-oxabicyclo[3.2.1]non-2-en-6-one (11a): To a solution of **9a** (0.87 g, 4.5 mmol) and **10** (0.58 g, 3.05 mmol) in 10 mL of CH_2Cl_2 at -78 °C was added $SnCl_4$ (3 mL of a 1 M solution in CH_2Cl_2). The solution was stirred for 10 minutes, then poured into saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, concentrated and chromatographed on silica gel with CH_2Cl_2. The product (0.19 g, 22%) was obtained as a brown oil or orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (d, J=18 Hz, 1H), 2.86 (dd, J=5.5, 18 Hz, 1H), 3.71 (s, 3H), 4.0 (s, 1H), 5.08 (br d, J=5.5 Hz, 1H), 6.10 (dd, J=1.8, 6.5 Hz, 1H), 6.50 (d, J=6.5 Hz, 1H).

1-Bromo-7-methoxy-8-oxabicyclo[3.2.1]non-2-en-6-one (11b): Compound **9b** was submitted to the conditions described above for **11a**, providing **11b** in 22% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (d, J=18 Hz, 1H), 2.87 (dd, J=5.7, 18 Hz, 1H), 3.73

(s, 3H), 4.00 (s, 1H), 5.15 (br d, J=5.7 Hz, 1H), 6.26 (dd, J=1.8, 6.5 Hz, 1H), 6.39 (d, J=6.5 Hz, 1H).

1-[7-Methoxy-6-oxo-8-oxabicyclo[3.2.1]non-2-en-1-yl]-2,4-dimethoxybenzene (12). To a solution of **11b** (28 mg, 0.10 mmol) and 1,3-dimethoxybenzene (30 mg, 0.20 mmol) in 0.5 mL of CH_2Cl_2 at -78 °C was added $TiCl_4$ (20 mg, 0.11 mmol). The mixture was stirred while warming to 15 °C for 45 minutes. The mixture was warmed to room temperature and was stirred for 1.5 hours and then was poured into saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. Chromatography with 3:1 H:EA afforded **12** in 25 % yield: ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (d, J=18 Hz, 1H), 2.87 (dd, J=6, 18 Hz, 1H), 3.72 (s, 3H), 3.79 (s, 6H), 5.17 (br d, J=12 Hz, 1H), 6.25-6.55 (m, 4H), 7.23 (d, J=9 Hz, 1H).

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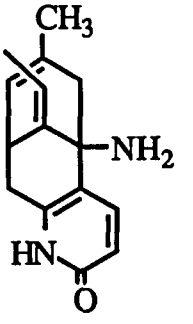
PART II: A BRIDGEHEAD ENONE APPROACH TO HUPERZINE A

HISTORICAL

Huperzine A (1) is as an interesting target for the synthetic chemist. Huperzine was isolated from Lycopodium serratum and characterized by Liu in 1986.[1] It has been found to possess activity as a nootropic agent.[2] That is to say, it has the ability to enhance memory. On the molecular level, it is an inhibitor of acetylcholinesterase.[3] In Alzheimer's disease a decrease in the quantity of acetylcholine in the brain occurs. Consequently, huperzine A has attracted considerable interest as a potential treatment for Alzheimer's patients. A drawback to huperzine A is its hepatotoxicity.



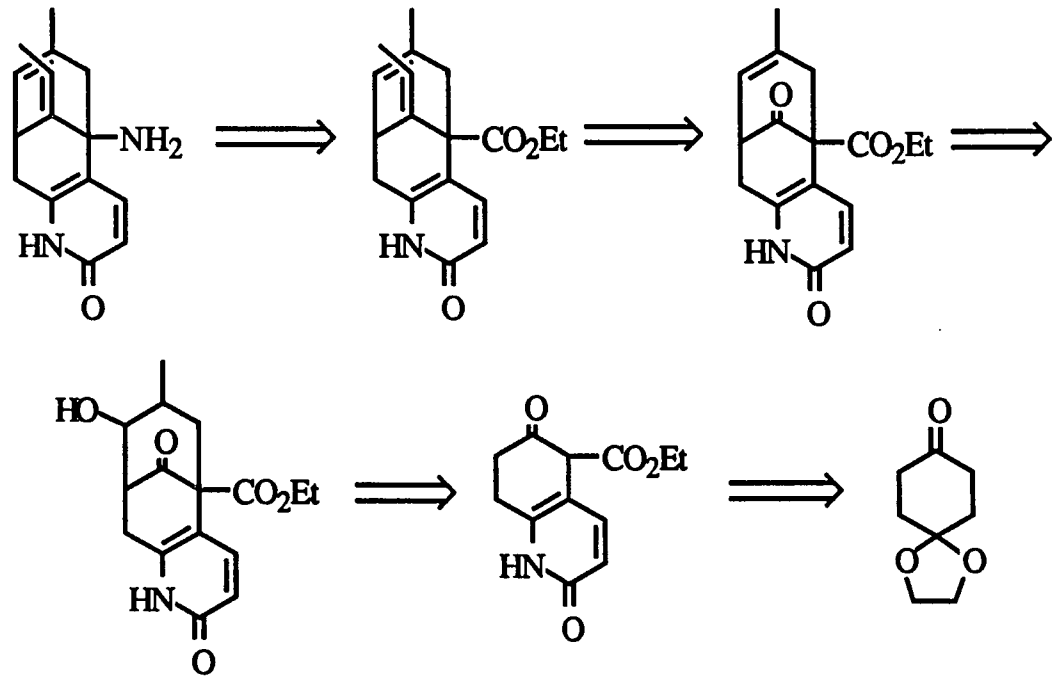
1

The goal of this project was to accomplish the total synthesis of huperzine A or analogs of huperzine A. It was desired to use a strategy that would allow for the synthesis of a variety of analogs so that structure- activity relationships could be determined. It has been suggested that the activity of huperzine A arises from a

similarity in the spatial arrangement of its heteroatoms to the arrangement of heteroatoms in the completely extended conformation of acetylcholine.[4] A rational approach to the synthesis of analogs might therefore be to leave the pyridone ring and bridgehead amine intact while altering the olefinic portion of the molecule in some way. Also, the pyridone ring could be changed to a similar arrangement of heteroatoms that might still retain the desired biological activity. Finally, the bridgehead amine could be changed to a hydroxyl group or other heteroatom.

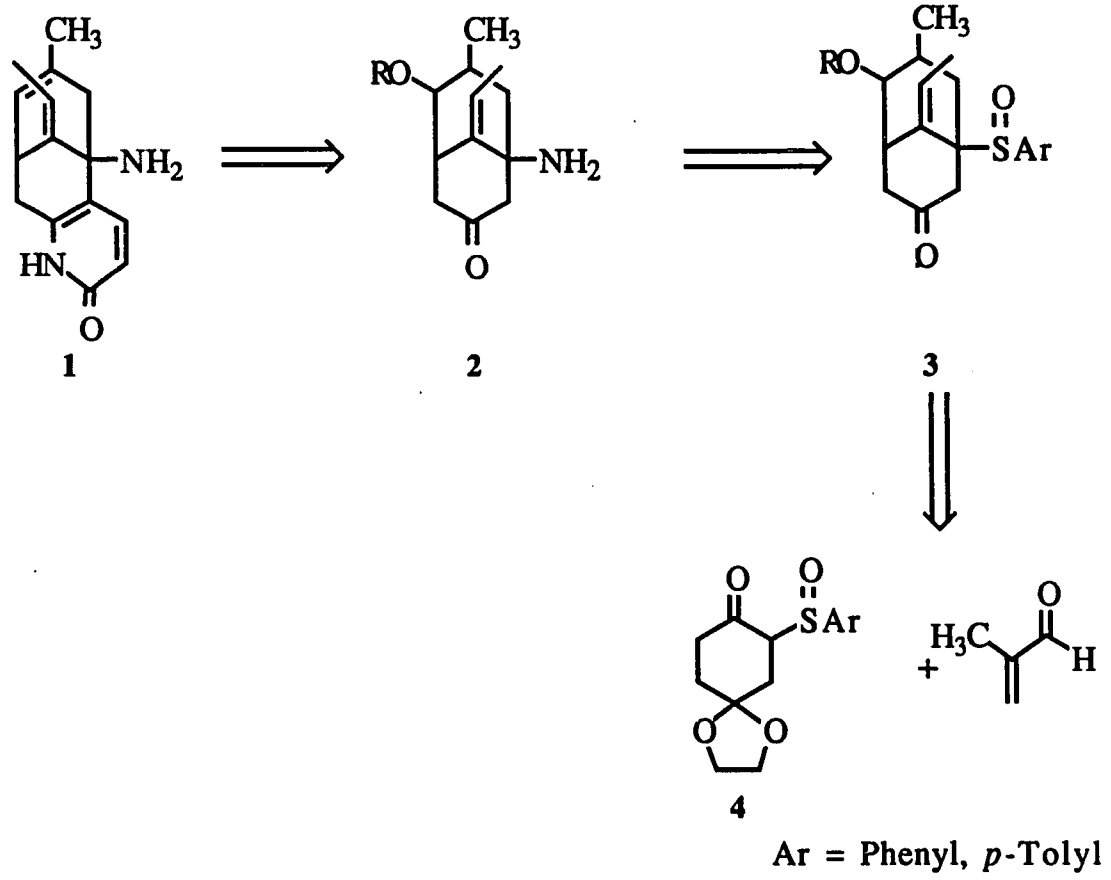
Two previous syntheses of huperzine A have been achieved. The first was by Qian and Ji[5], the second by Kozikowski.[4] Both syntheses followed the same basic strategy (Scheme I).

Scheme I



Scheme II outlines our synthetic strategy. The bridgehead amine **2** arises from elimination of the bridgehead sulfoxide **3**, followed by addition of ammonia to the bridgehead enone. A Wittig reaction is used to introduce the exocyclic double bond on the one carbon bridge. The bicyclic structure is formed by a Michael-Aldol protocol from the readily available keto sulfoxide **4** and methacrolein.

Scheme II



Our approach differs from the previous syntheses in two main ways. The first is the timing of the introduction of the pyridone ring. Previously, the pyridone ring was introduced early in the synthesis. Our route calls for appending the pyridone ring or similar functionality at the end. The second difference is in how the bridgehead amine group is formed. Both of the previous syntheses used a Curtius rearrangement. Our strategy puts the amine in by addition of ammonia to a bridgehead enone. By introducing the pyridone late in the synthesis, we are allowing for a wide variety of analogous functional groups. In addition, the conjugate addition to the bridgehead enone can accommodate a number of different nucleophiles, further adding to the variety of analogs that might be synthesized.

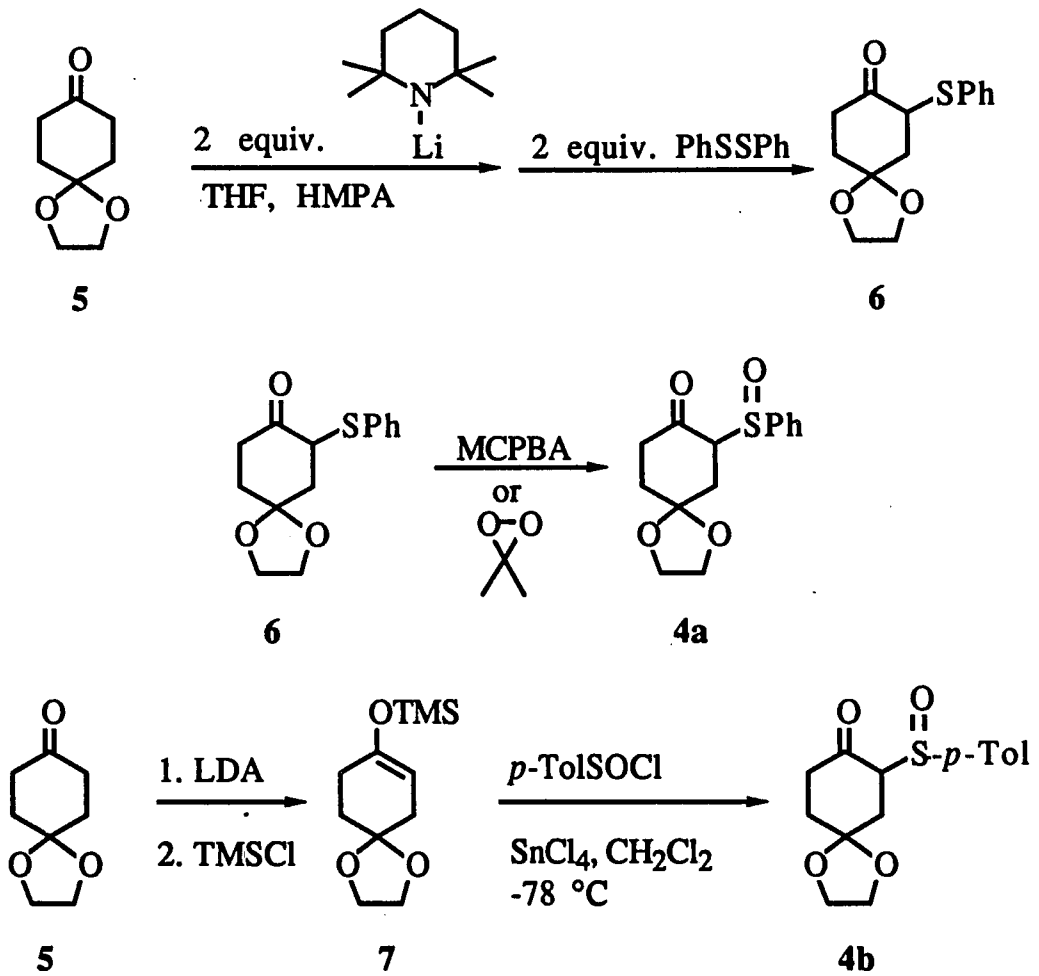
DISCUSSION AND RESULTS

The synthesis begins with commercially available 1,4-cyclohexanedione mono-ethylene ketal (**5**). Two methods were developed for the synthesis of keto sulfoxide **4** (Scheme III). In the first method, the lithium enolate of **5** is generated with lithium tetramethylpiperidide (LiTMP). The enolate is reacted with diphenyl disulfide in the presence of hexamethylphosphoramide (HMPA) to give keto sulfide **6** in 80% yield. Oxidation of **6** with *m*-chloroperoxybenzoic acid (MCPBA) or dimethyldioxirane[6] provided **4a** (Ar = phenyl) in 69% or quantitative yield, respectively. The second method involved formation of the enolate with lithium diisopropylamide (LDA). Trapping the enolate with chlorotrimethylsilane (TMSCl) provided enol silyl ether **7** in 88% yield. Reaction of **7** with *p*-toluenesulfinyl chloride[7] and tin(IV) chloride in dichloromethane at -78° C according to the method of Johnson[8] gave **4b** (Ar = *p*-tolyl) in 45-55% yield. The first method obviously proceeded in better yield. However, it required large amounts of the toxic compound HMPA to scale up, so the second method was used to prepare larger quantities of **4b**.

The bicyclic compound **8** could be made in greater than 90% yield by reacting **4** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry acetonitrile followed by addition of methacrolein (Scheme IV). At this point, the alcohol group of **8** needed to be protected in some manner in order to prevent ring opening and destruction of the

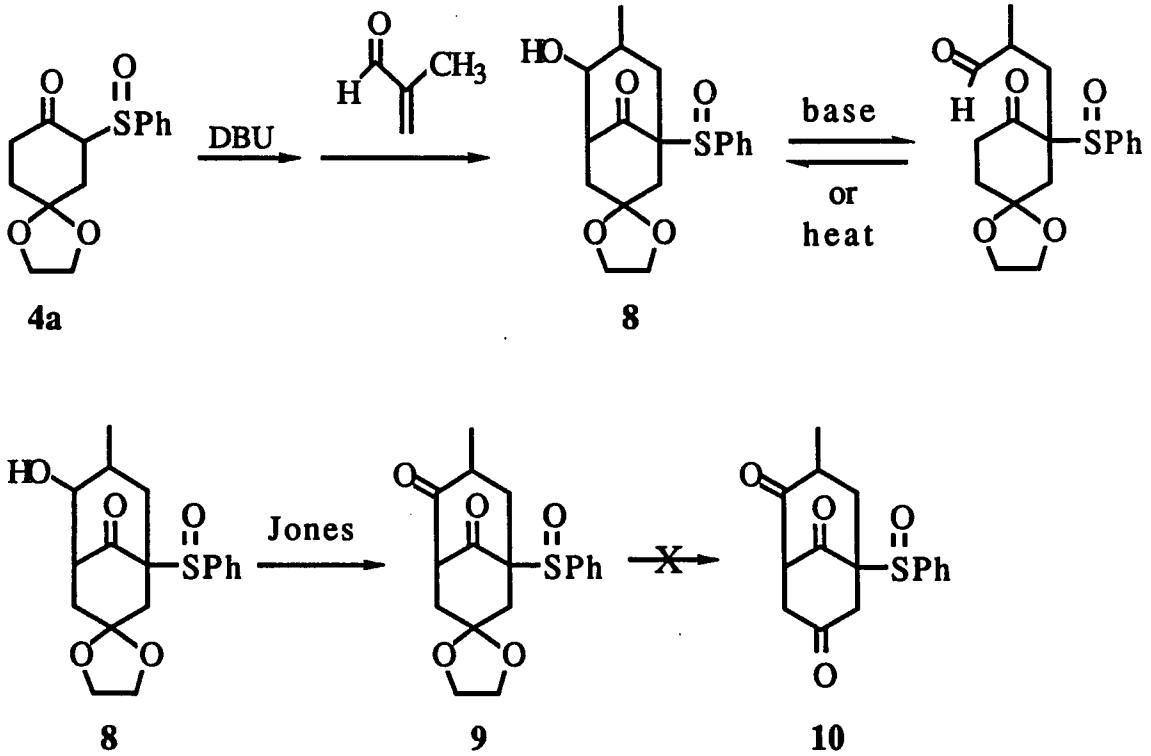
bicyclic framework by a retro-aldol reaction. Furthermore, since it is well known that the sulfoxide elimination proceeds more readily towards an allylic position or a carbon α to a carbonyl, it was desired to unmask the ketone at carbon 13. To accomplish this, the alcohol was oxidized to the diketone **9**. However, numerous attempts to hydrolyze the acetal failed.

Scheme III



5 **6** **6** **4a** **5** **7** **4b**

Scheme IV



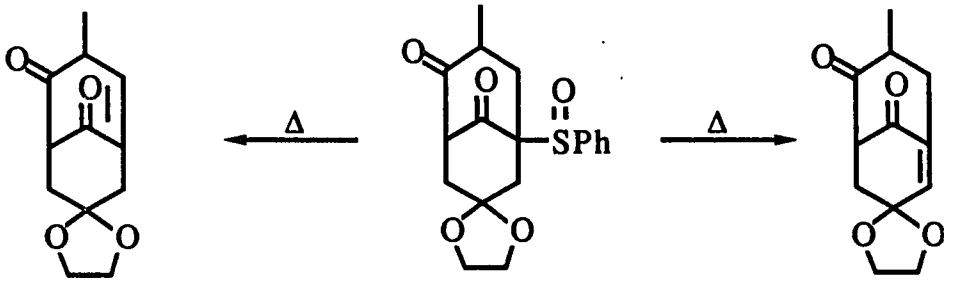
4a 8 8 9 10

While it would be best to do the sulfoxide elimination on triketone **10**, this did not prove to be feasible. Instead, the thermal elimination of the ketal **9** was investigated. In Magnus' synthesis of kopsanone, he performed a similar sulfoxide elimination.[9] That reaction required a temperature of 215 °C to proceed. The elimination of **9** was expected to go under similar conditions to give a mixture of bridgehead olefins **11** and **12** (Scheme V).

The reaction was performed in a sealed tube using toluene as solvent. An excess of *t* -butylamine was added to trap both the

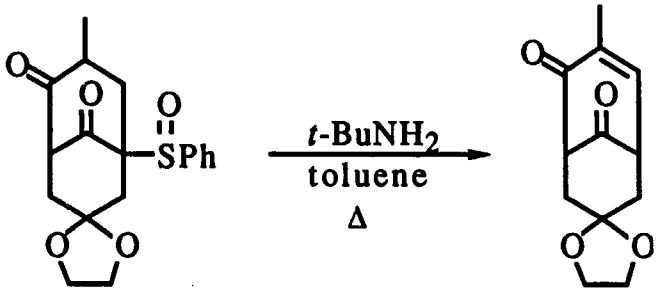
bridgehead olefin and the benzenesulfinic acid. Surprisingly, the only product isolated (63% yield) was the enone **13** (Scheme VI).[10] The product could have been formed through the intermediate **11**, but not **12**. However, the reason for the regioselectivity of this reaction was not obvious. Furthermore, the reaction proceeded at temperatures below 150 °C. This low reaction temperature suggested some sort of activation for the elimination reaction.

Scheme V



11 **9** **12**

Scheme VI

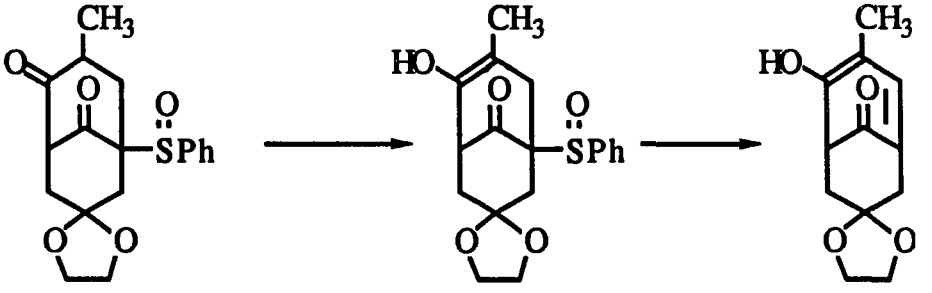


9 **13**

Several more experiments were performed to investigate this interesting reaction. Using other amines gave similar results. In each case the yield of **13** was greater than 50%. Initially, we felt that the reaction might be proceeding through an intermediate enamine. However, when no amine was used and trimethylphosphite was used to trap the benzenesulfinic acid, the results were the same. Indeed, the reaction proceeded with no additional reagents.

To explain these results, we propose an enol intermediate **14** (Scheme VII). The enol provides an allylic site to facilitate the elimination. At this point, two possibilities exist to complete the mechanism. The first is essentially tautomerization, which would require some proton source to protonate the bridgehead carbon. The other is readdition of benzenesulfinic acid to provide a sulfoxide β to the ketone which would then eliminate readily to give the product.

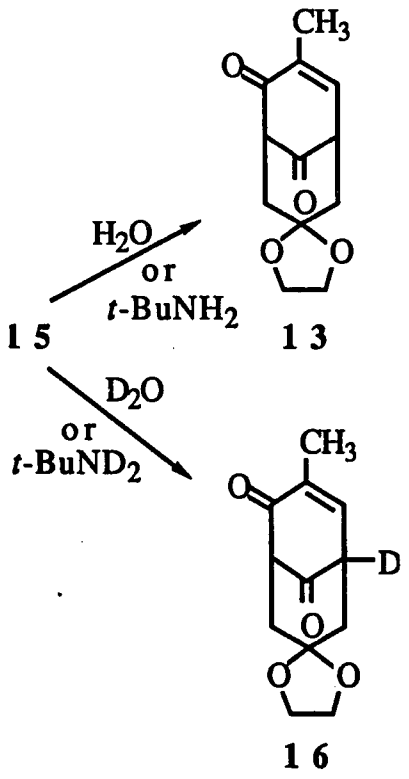
Scheme VII



9 **14** **15**

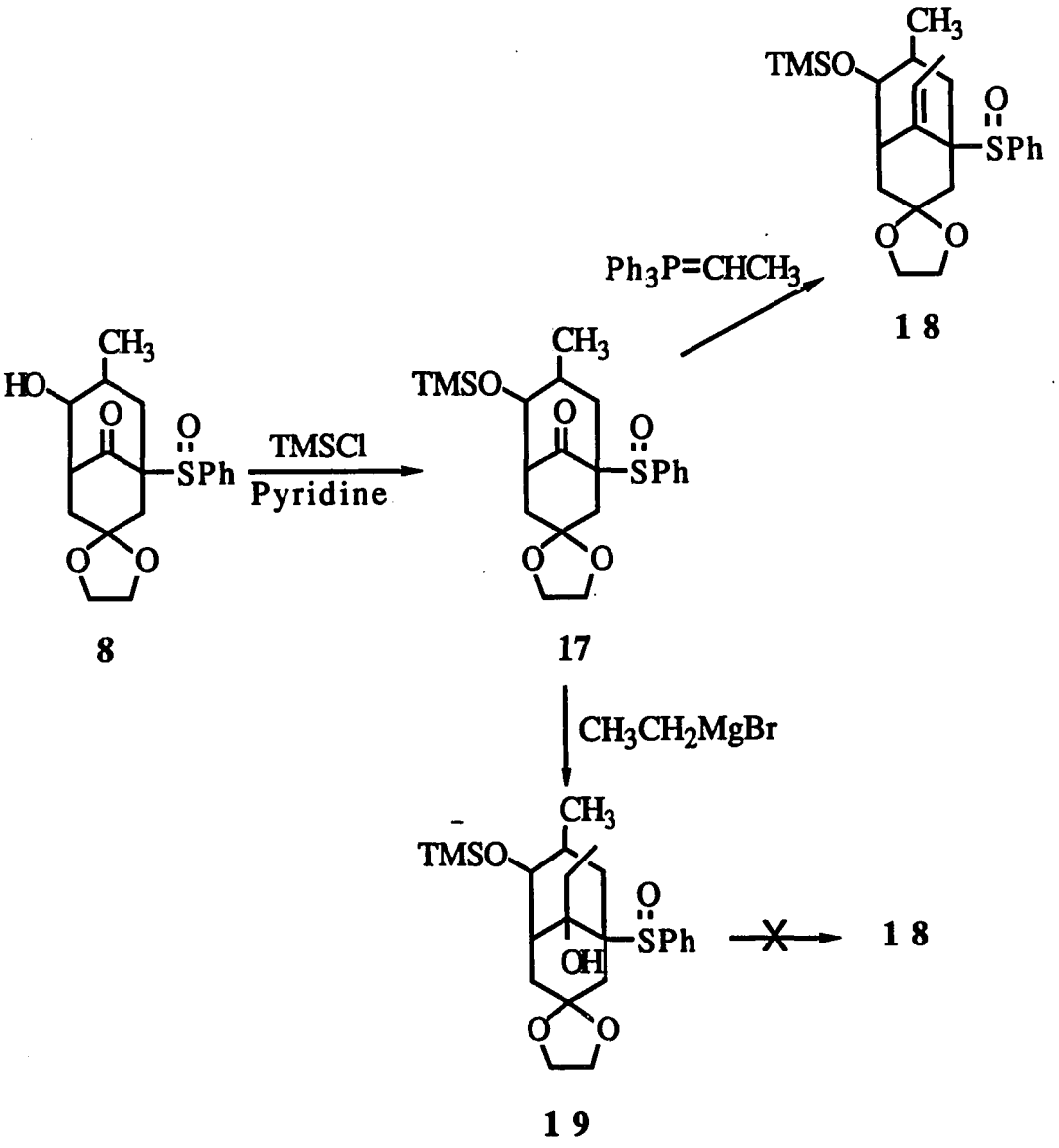
To distinguish between these two possibilities, the reaction was performed in the presence of deuterated *t*-butylamine or deuterium oxide (Scheme VIII). Under these conditions only product **16** with deuterium at the bridgehead carbon was formed. If the reaction proceeds through the elimination-addition-elimination mechanism, at best a mixture of hydrogen and deuterium at the bridgehead would be expected. It is more likely that the amine or deuterium oxide acts as a proton donor to promote the tautomerization.

Scheme VIII



Although this reaction is very interesting, it does not allow introduction of a nitrogen atom at the bridgehead carbon. To accomplish this task, the hydroxyl group of **8** was protected as its trimethylsilyl ether **17** using chlorotrimethylsilane and pyridine (Scheme IX).

Scheme IX



The trimethylsilyl ether **17** was then reacted with ethylidenetriphenylphosphorane to give olefin **18**. Unfortunately, the yield of **18** was only slightly greater than 50%. In an attempt to circumvent this problem, **17** was reacted with ethyl magnesium chloride providing the tertiary alcohol **19** in quantitative yield. However, all attempts to eliminate the tertiary alcohol gave recovered starting material or decomposition.

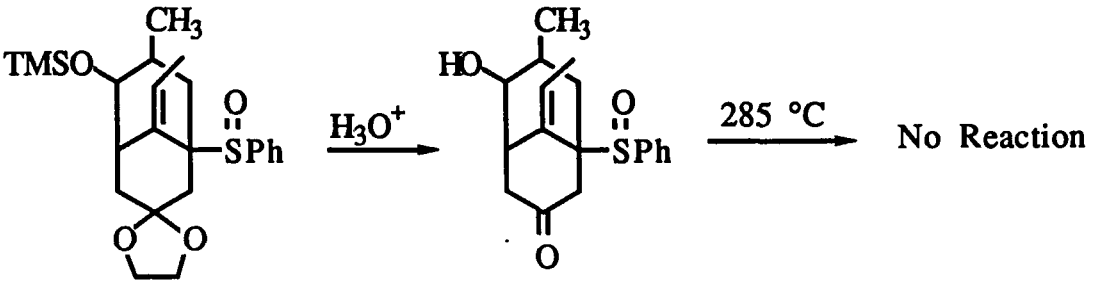
The low yield of the Wittig reaction seemed to be a result of instability of the silyl ether to the reaction conditions. This hypothesis was backed up by isolation of a side product containing only triphenylphosphine and trimethylsilyl signals in the proton NMR spectrum. Elimination of the hydroxyl group of **8** would overcome the problems of the Wittig reaction. However, all attempts to eliminate the alcohol were unsuccessful.

In order to investigate the feasibility of the rest of the synthesis, the Wittig product **18** was hydrolyzed to give **20** (Scheme X). Surprisingly, **20** did not eliminate even at temperatures up to 285 °C.

The reluctance of **20** to eliminate under thermal conditions prompted us to explore other ways to remove the bridgehead sulfoxide. One possible solution was the Pummerer rearrangement. The normal Pummerer proceeds as shown in Scheme XI.[12] Reacting the bridgehead sulfoxide **20** under typical conditions of acetic anhydride and acetic acid gave no reaction. However, reaction with

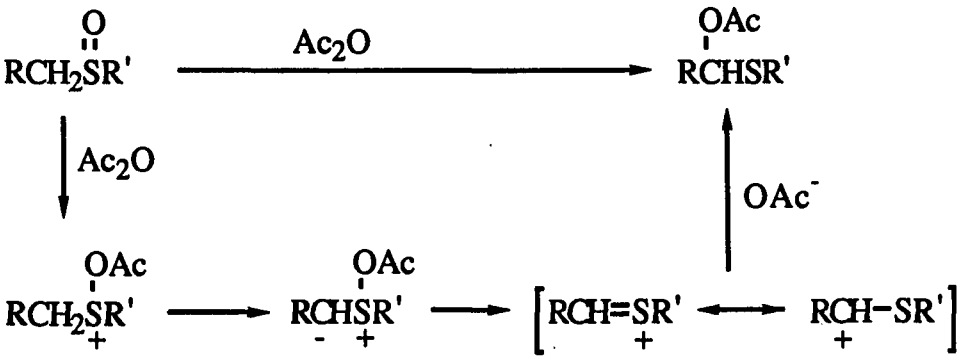
trifluoroacetic anhydride at 130 °C gave the bis-trifluoroacetate **21** in 54% yield (Scheme XII).

Scheme X



18 **20**

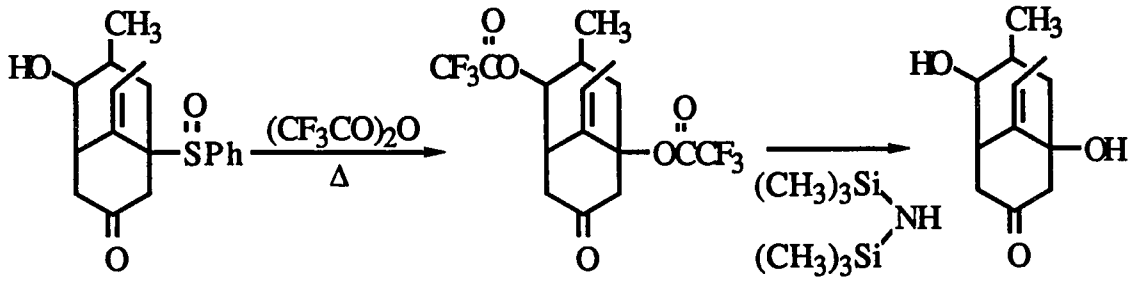
Scheme XI



Compound **21** was reacted with hexamethyldisilazane in dichloromethane in an attempt to eliminate the bridgehead trifluoroacetate and add the hexamethyldisilazane to the resulting bridgehead enone. Unfortunately, the product obtained was the diol

22. Even though this route did not allow us to complete the synthesis, it constitutes the first example of a bridgehead Pummerer reaction.

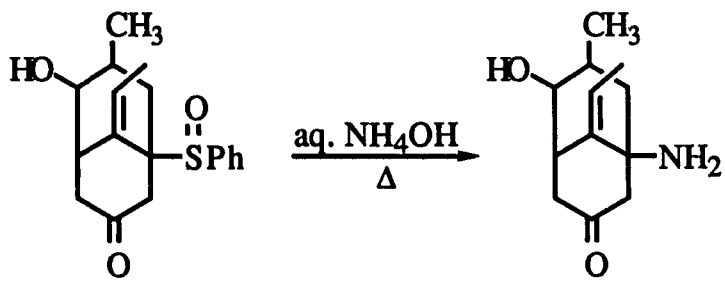
Scheme XII



20 21 22

Next we attempted to eliminate the bridgehead sulfoxide under basic conditions. The sulfoxide **20** was suspended in saturated aqueous ammonium hydroxide and heated in a sealed tube to 120 °C for three and a half hours. Gratifyingly, the bridgehead amine **23** was isolated in 73% yield (Scheme XIII).

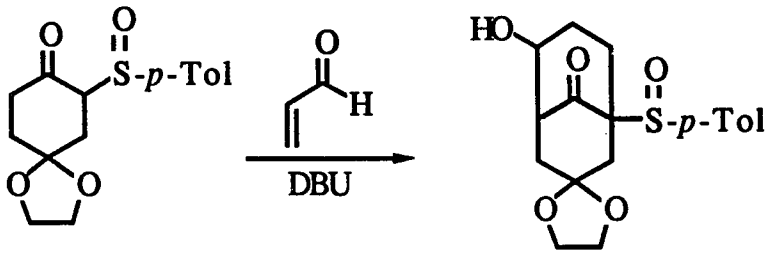
Scheme XIII



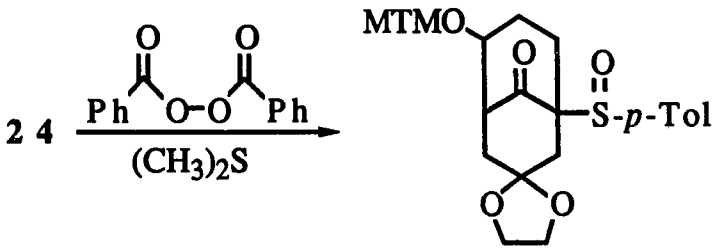
20 **23**

At this point we attempted to improve the yield of the troublesome Wittig reaction. The keto sulfoxide **4b** was reacted with acrolein and DBU to give the bicyclic compound **24** (Scheme XIV). It was hoped that lack of a methyl group at carbon 7 would decrease steric congestion around the ketone without ultimately affecting the biological activity of the final product. Also, the labile trimethylsilyl group was replaced with the heartier methylthiomethyl (MTM) group.

Scheme XIV



4b **24**



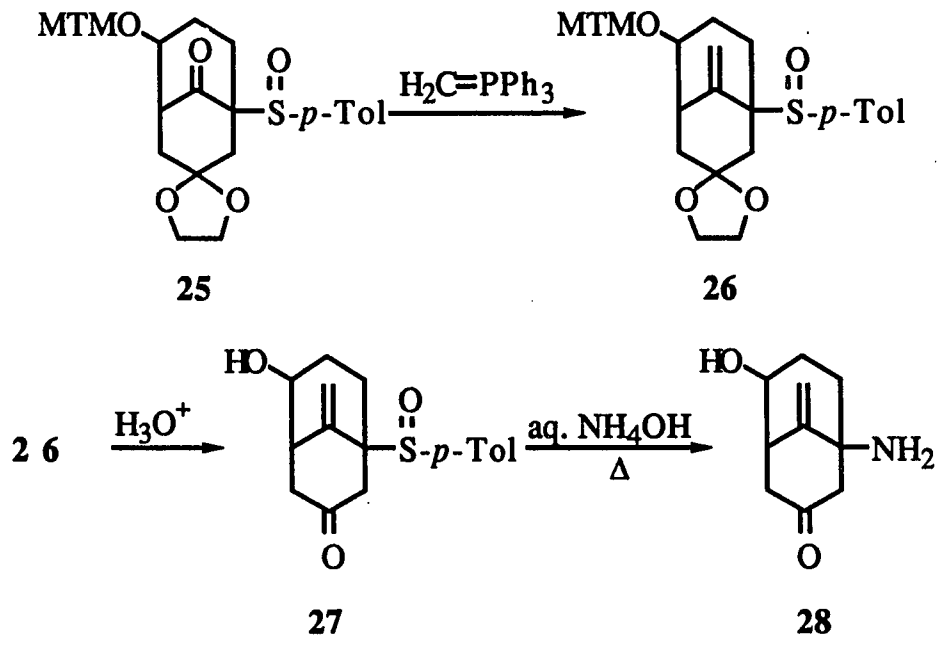
25

This was accomplished by reaction of **24** with dimethyl sulfide and benzoyl peroxide according to the method of Kyler.[12] The MTM protected sulfoxide **25** was submitted to the Wittig conditions using methylidenetriphenylphosphorane, but gave little

methylidenetriphenylphosphorane, but gave little better results than obtained previously.

Nevertheless, compound **26** was obtained and submitted to the hydrolysis and elimination conditions described earlier (Scheme XV). It was desired that the MTM protecting group would survive the hydrolysis conditions. However, the hydrolysis conditions used previously afforded the deprotected compound **27**. The bridgehead amine **28** was obtained from **27** in 46% yield by reaction with aqueous ammonium hydroxide at 120 °C.

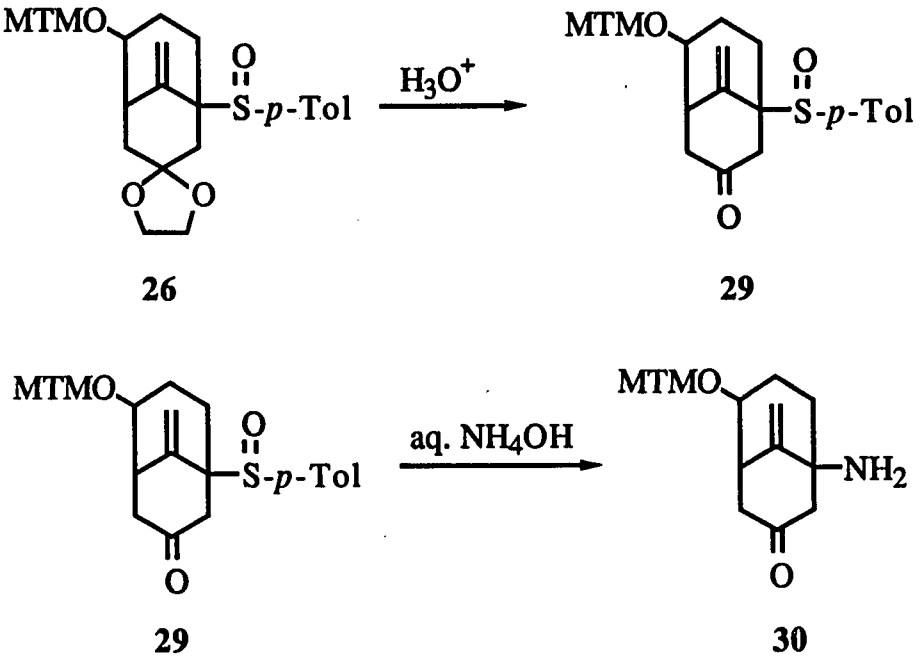
Scheme XV



Submission of **26** to slightly milder hydrolysis conditions provided the MTM protected compound **29** (Scheme XVI).

Compound **29** was reacted with ammonium hydroxide to afford the bridgehead amine **30**.

Scheme XVI

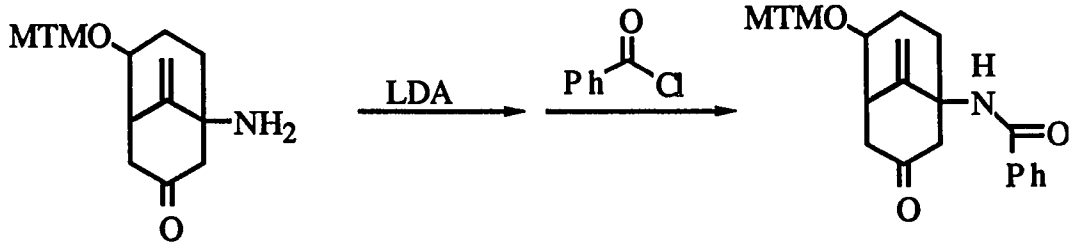


26 **29**

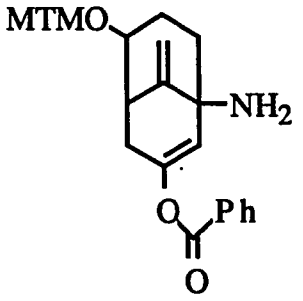
29 **30**

Compound **30** was reacted with LDA and benzoyl chloride with the intention of forming the enol benzoate **31** (Scheme XVII). Unfortunately, the benzamide **32** was isolated instead.

Scheme XVII



30 32



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CONCLUSION

The efficient synthesis of huperzine A and its analogs continues to be an important goal for the synthetic chemist. This work has provided a new method for the construction of the bicyclic core of huperzine A. The major benefits of this route are the low number of steps and the flexibility to prepare a variety of analogs. The major impediment in this work and the previous two syntheses of huperzine A is the elimination of the secondary alcohol which resulted from the Michael-Aldol cyclization reaction.

This research has provided some unexpected and very interesting sidelights. The sulfoxide elimination-tautomerization reaction is an unusual example of elimination toward an enol. The regioselectivity of this reaction is remarkable. Also, the first example of a bridgehead Pummerer reaction was realized.

This work has provided new methodology for the introduction of the bridgehead amine of huperzine A. Ongoing studies are addressing the problems encountered in the synthesis of the bicyclic framework of the molecule.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane and acetonitrile were distilled from calcium hydride. All reactions were conducted under nitrogen atmosphere and all extracts were dried over anhydrous sodium sulfate. The apparatus for experiments requiring anhydrous conditions was 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 F_{254} 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); 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 $CDCl_3$ (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. Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was judged to be ≥ 90% by ^1H NMR spectral determinations.

7-(Phenylthio)-1,4-dioxaspiro[4.5]decan-8-one (6): To a solution of 2,2,6,6-tetramethylpiperidine (6.36 g, 45 mmol) in 25 mL of THF at -40 °C was added *n*-BuLi (23.3 mL of a 1.93 M solution in hexanes). The solution was stirred while warming to room temperature over 30 minutes. The solution was cooled to -40 °C and a solution of 1,4-cyclohexanedione mono-ethylene ketal (**5**) in 7 mL of THF and 30 mL of HMPA was added over 15 minutes. The solution was stirred while slowly warming to room temperature over 2 hours. The solution was cooled to -15 °C and a solution of diphenyldisulfide in 20 mL of THF was added over a period of 10 minutes. The solution was stirred at room temperature for 8 hours. The reaction was quenched by adding 1 N HCl until the pH was below 7. The mixture was extracted 3 times with Et_2O. The combined Et_2O solutions were washed with water and saturated aqueous NaCl solution, dried, and concentrated . The residue was placed on a silica gel column and eluted with hexanes to remove unreacted diphenyldisulfide. Elution with 10:1 H:EA, then with 3:1 H:EA, provided 4.32 g (82%) of a yellow solid: R_F 0.67 (1:3 H:EA); ^1H NMR

(300 MHz, $CDCl_3$) δ 2.0-2.85 (m, 7H), 3.9-4.15 (m, 4H), 7.2-7.45 (m, 5H).

7-(Phenylsulfinyl)-1,4-dioxaspiro[4.5]decan-8-one (4a): To a solution of **6** (3.67 g, 13.9 mmol) in 65 mL of CH_2Cl_2 at 0 °C was added MCPBA (3.11 g, 15.3 mmol) in portions over a 5 minute period. The mixture was stirred at 0 °C for 30 minutes. Saturated $NaHCO_3$ solution was added and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2 and the combined organic layers were washed twice with saturated $NaHCO_3$ solution and once with saturated NaCl solution. The solution was dried and concentrated. The residue was placed on a silica gel column and eluted with 100 mL of 1:1 H:EA then 200 mL 1:3 H:EA and finally with EtOAc. Removal of solvent gave 2.67 g (69%) of a white powder: R_F 0.43 (1:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.8-1.9 (m, 1H), 2.0-2.1 (m, 2H), 2.45-2.75 (m, 3H), 3.60 (dd, J=7.7, 13.3 Hz, 1H), 3.85-4.05 (m, 4H), 7.47-7.65 (m, 5H).

[[4-(1,3-Dioxolan)-1-cyclohexen-1-yl]oxy]trimethylsilane (7): To a solution of diisopropylamine (0.76 g, 7.5 mmol) in 10 mL of THF at -78 °C was added *n*-BuLi (3.2 mL of 2.35 M in hexanes). The solution was stirred for 30 minutes and 1,4-cyclohexanedione mono-ethylene ketal (**5**) (0.79 g, 5 mmol) in 5 mL of THF was added dropwise. Stirring was continued for 1 hour and freshly distilled TMSCl (0.83 g, 7.5 mmol) was added. The solution was stirred and warmed to room temperature over a period of 30 minutes and then was poured into hexanes and suction

filtered through Celite. The filtrate was concentrated and distilled (b.p. 81-87 °C at 1 mm Hg) to give 1.00 g (88%) of a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (t, J=7.3 Hz, 2H), 2.18-2.28 (m, 4H), 3.94-3.98 (m, 4H), 3.72 (tt, J=1, 4.3 Hz, 1H).

7-(4-Methylphenylsulfinyl)-1,4-dioxaspiro[4.5]decan-8-one (4b): To a solution of 7 (685 mg, 3 mmol) in 15 mL of dry CH_2Cl_2 at -78 °C was added a solution of *p*-toluenesulfinyl chloride (524 mg, 3 mmol) in 10 mL of CH_2Cl_2 (precooled to -78 °C). To this solution was added $SnCl_4$ dropwise. The green solution was stirred at -78 °C for 30 minutes and then was poured into 15 mL of H_2O. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were extracted 4 times with a 10% NaOH solution. The combined aqueous extracts were acidified with 2 N HCl and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and saturated NaCl solutions. The solution was dried and concentrated to give 0.48 g (54%) of a tan solid: m.p. 120-122 °C; R_F 0.43 (EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.7-2.3 (m, 4H), 2.40 (s, 3H), 2.42-2.75 (m, 2H), 3.57 (dd, J=7, 13 Hz, 1H), 3.85-4.15 (m, 4H), 7.29 (overlapping doublets, J=9 Hz, 2H), 7.47 (d, J=9 Hz, 2H), 7.55 (d, J=9 Hz, 2H); MS *m/e* 55, 83, 91, 111, 125, 139, 155, 294.

6-Hydroxy-7-methyl-1-(phenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane]-9-one (8): To a solution of **4a** (1.48 g, 5.28 mmol) in 50 mL of CH_3CN (freshly distilled from CaH_2) was added DBU (0.88 g, 5.8 mmol). A solution of

methacrolein (1.40 g, 20 mmol) in 10 mL of dry CH_3CN was added dropwise. The solution was stirred for 30 minutes and then was concentrated. The residue was flash chromatographed on silica gel with 1:1 H:EA then 1:4 H:EA and finally with EA to give 1.68 g (91%) of a white solid: R_F 0.30 (1:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ diastereomers, 1.18 (d, J=7.7 Hz), 1.20 (d, J=7 Hz) total of 1H, 1.7-2.5 (m, 4H), 2.87-2.95 (m, 1H), 3.25-3.35 (m, 2H), 3.55-4.0 (m, 5H), 7.45-7.55 (m, 3H), 7.8-7.85 (m, 2H); IR ($CDCl_3$) 3370, 3045, 2950, 2880, 1715, 1440, 1150, 1080, 1030 cm^{-1}; MS (NH_3 CI) *m/e* 351, 368.

7-Methyl-1-(phenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane]-6,9-dione (9): To a solution of **8** (2.89 g, 8.25 mmol) in 165 mL of acetone was added Jones reagent (0.90 g CrO_3, 0.75 mL H_2SO_4 in 6 mL of H_2O) in 0.5 mL portions. The mixture was stirred for 30 minutes, then was diluted with saturated NaCl solution and extracted 3 times with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and NaCl solutions and dried. The solution was filtered through a short pad of silica gel and concentrated to give 2.38 g (83%) of a tan solid: R_F 0.36 (1:4 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J=8 Hz, 3H), 1.23 (p, J=7 Hz, 1H), 1.61 (s, 1H), 1.71 (dd, J=3.3, 15.3 Hz, 1H), 2.15-2.52 (m, 4H), 3.0-3.2 (m, 1H), 3.30 (dd, J=3.3, 7 Hz, 1H), 3.49 (ABq, J=6.7 Hz, 1H), 3.7-3.9 (m, 4H), 7.50-7.55 (m, 3H), 7.65-7.70 (m, 2H); IR ($CDCl_3$) 3030, 2970, 2920, 2900, 1740, 1715, 1475, 1440, 1090, 1025 cm^{-1}.

7-Methyl-spiro[bicyclo[3.3.1]non-7-ene-3,2'-[1,3]dioxolane]-6,9-dione (13): A solution of **9** (0.17 g, 0.5 mmol) and *t*-$BuNH_2$ (0.14 g, 2.0 mmol) in 6 mL of toluene was heated in a teflon capped culture tube to 130-140 °C for 16 hours. The solution was cooled and solvent was removed. The residue was flash chromatographed with 1:1 H:EA to give 69 mg (63%) of a brown solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.12-2.5 (m, 4H), 3.24-3.33 (m, 2H), 3.74-3.95 (m, 4H), 6.89 (dq, J=1.4, 6.7 Hz, 1H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 15.58, 40.32, 42.88, 47.24, 60.06, 63.55, 64.98, 105.48, 139.01, 142.08, 198.59, 206.21; IR ($CDCl_3$) 2955, 2920, 2880, 1735, 1675, 1425, 1360, 1065 cm^{-1}; MS (NH_3 CI) *m/e* 223, 240, 257.

7-Methyl-spiro[bicyclo[3.3.1]non-7-ene-3,2'-[1,3]dioxolane]-6,9-dione-1-d (16): The reaction was performed as for **13**, except that *t*-$BuND_2$ was used instead of *t*-$BuNH_2$. Alternatively, 5 drops of D_2O was added in place of *t*-$BuNH_2$: R_F 0.51 (1:4 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.1-2.5 (m, 4H), 3.3 (m, 1H), 3.7-3.9 (m, 5H), 6.88 (br s, 1H); MS *m/e* calc'd for $C_{12}H_{13}O_4D$: 223.09548, found 223.09570; 55, 86, 109, 127, 140.

7-Methyl-1-(phenylsulfinyl)-6-(trimethylsilyl)oxy-spiro[bicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane]-9-one (17): To a solution of **8** (70 mg, 0.2 mmol) in 1 mL of pyridine was added TMSCl (44 mg, 0.4 mmol). The solution was stirred for 30 minutes and then poured into 20 mL of Et_2O. The mixture was filtered and

washed with 20 mL of Et_2O. Solvent was removed and the residue was dissolved in benzene. The mixture was decanted and solvent and pyridine were removed to give 78.3 mg (93%) of a yellowish solid: R_F 0.35 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.0 (d, 7.3H), 1.80-2.95 (m, 2H), 2.0-2.35 (m, 6H), 2.45-2.6 (m, 2H), 3.15-3.25 (m, 1H), 3.45-3.60 (m, 3H), 3.8-3.9 (m, 1H), 7.40-7.45 (m, 3H), 7.8-7.85 (m, 2H); IR ($CDCl_3$) 3025, 2945, 2880, 1720, 1580, 1440, 1250, 1100 (broad) cm^{-1}.

9-Ethylidene-7-methyl-1-(phenylsulfinyl)-6-(trimethylsilyl)oxy-spiro[bicyclo[3.3.1]nonane-3,2'-[1, 3]dioxolane] (18): To ethyltriphenylphosphonium bromide (4.7 g, 12.5 mmol) in a 50 mL roundbottom flask was added 30 mL of benzene. The benzene was distilled off to remove any water present. The flask was allowed to cool and 10 mL of THF was added. To the suspension of the phosphonium salt in THF was added *n*-BuLi (5.2 mL of 1.93 M). The solution was stirred for 10 minutes then was cooled to 0 °C. A solution of **17** (2.11 g, 5 mmol) in 10 mL of THF was added dropwise and the solution was stirred at room temperature for 16 hours. The solution was poured into 400 mL of 3:1 pentane:Et_2O. A small amount of acetone was added to quench any unreacted ylid. The mixture was filtered through Celite and the solvent was removed. The residue was flash chromatographed with 3:1 H:EA to give 1.15 g (53%) of a white solid: R_F 0.47 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 0.95 (d, J=7.0 Hz, 3H), 1.7-2.5 (m, 8H), 1.78 (d, J=7.3 Hz, 3H), 2.80-2.87 (m, 1H), 3.5-3.85 (m, 4H),

6.12 (q, J=7.3 Hz, 1H), 7.5-7.9 (m, 5H); IR ($CDCl_3$) 3055, 2950, 1720, 1580, 1440, 1250, 1080 cm^{-1}.

9-Ethyl-6,9-dihydroxy-7-methyl-1-(phenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-dioxolane] (19): To a solution of **17** (0.42 g, 1.0 mmol) and TMSCl (0.02 g, 0.2 mmol) in 5 mL of THF at -78 °C was added ethylmagnesium bromide (0.83 mL of a 3 M solution in Et_2O) dropwise. After 15 minutes, acetic acid (0.14 mL, 2.5 mmol) was added and the solution was poured into brine. The mixture was extracted with Et_2O and the organic phase was dried and concentrated to give 0.45 g (100%) of a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J=7 Hz, 3H), 1.16 (t, J=8 Hz, 3H), 1.9-2.5 (m, 6H), 2.67 (d, J=19.7 Hz, 2H), 2.86 (d, J=21 Hz, 2H), 3.97 (dd, J=5, 12 Hz, 1H), 4.73 (s, 1H), 7.47-7.55 (m, 5H).

9-Ethylidene-6-hydroxy-7-methyl-1-(phenylsulfinyl)-bicyclo[3.3.1]nonane-3-one (20): To a solution of **18** (0.43 g, 1 mmol) in 10 mL of THF was added 1 mL of H_2O and 10 drops of H_2SO_4. The solution was stirred for 1 hour and saturated $NaHCO_3$ solution was added. The aqueous layer was saturated with NaCl and the mixture was extracted twice with Et_2O. The combined extracts were dried and concentrated to give 0.22 g (69%) of a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J=6.7 Hz, 3H), 1.24-1.51 (m, 2H), 1.83-2.05 (m, 2H), 1.87 (d, J=7.5 Hz, 3H), 2.24-2.45 (m, 2H), 2.96 (d, J=19 Hz, 1H), 3.33-3.45 (m, 2H), 6.36 (q, J=7.5 Hz, 1H), 7.5-7.62 (m, 5H); MS (NH_3 CI) *m/e* 363, 380.

9-Ethylidene-7-methyl-1,6-bis(trifluoroacetoxy)-bicyclo[3.3.1]nonane-3-one (21): A solution of **20** (32 mg, 0.1 mmol) in 0.5 mL of trifluoroacetic anhydride was heated in a teflon capped culture tube to 134-139 °C for 2 hours and 15 minutes. The solution was diluted with hexanes and evaporated. The residue was placed on a column of florisil and eluted with hexanes, then 16:1 H:EA, to give 21.9 mg (54%) of an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J=7 Hz, 3H), 1.4-2.1 (m, 3H), 1.82 (d, J=7.7 Hz, 3H), 2.35-2.45 (m, 1H), 2.7-2.9 (m, 2H), 3.55-3.7 (m, 2H), 4.68 (dd, J=5, 12 Hz, 1H), 5.46 (q, J=7.7 Hz, 1H); MS *m/e* 3060, 2965, 2925, 1785, 1715, 1580, 1550, 1460, 1370, 1130-1240.

9-Ethylidene-1,6-dihydroxy-7-methyl-bicyclo[3.3.1]nonan-3-one (22): To a solution of **21** (14.9 mg, 37 μmol) in 0.5 mL CH_2Cl_2 at 0 °C was added hexamethyldisilazane (25 mg, 0.15 mmol). The solution was stirred for 2 hours, then was concentrated to give 22: ^{1}H NMR (300 MHz, $CDCl_3$) δ diastereomer A, 0.98 (d, J=7 Hz, 3H), 1.2-1.35 (m, 2H), 1.7-2.0 (m, 6H), 1.74 (d, J=7.6 Hz, 3H), 2.24 (dd, J=7.3, 19 Hz, 1H), 2.49 (dd, J=1.7, 17.5 Hz, 1H), 2.72 (dd, J=2, 17.5 Hz, 1H), 2.91 (d, 19H), 3.25-3.35 (m, 2H), 5.80 (q, J=7.6 Hz, 1H); diastereomer B, 0.98 (d, J=6.3 Hz, 3H), 1.5-1.65 (m, 1H), 1.79 (d, J=9 Hz, 1H), 1.98 (d, J=8.3 Hz, 1H), 2.28 (dd, J=7.7, 19 Hz, 1H), 2.55-2.9 (m, 5H), 3.37 (m, 1H), 5.53 (q, J=8 Hz, 1H); MS (NH_3 CI) *m/e* 210, 228, 245.

1-Amino-9-ethylidene-6-hydroxy-7-methyl-bicyclo[3.3.1]nonan-3-one (23): A suspension of **20** (75 mg,

0.24 mmol) in 2 mL of saturated aqueous NH_4OH solution was heated to 120 °C in a teflon capped culture tube for 3 hours. The mixture was cooled, diluted with saturated NaCl solution and extracted 3 times with CH_2Cl_2. The combined extracts were dried and concentrated. The residue was placed on a short column of silica gel and eluted with EtOAc to remove side products. Eluting with MeOH provided 36.3 mg (73%) of a brown solid: ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J=6.2 Hz, 3H), 1.14 (td, J=1.7, 14 Hz, 1H), 1.5-1.8 (m, 2H), 1.74 (d, J=6.8 Hz, 3H), 2.04 (dd, J=8, 19 Hz, 1H), 2.15-2.35 (m, 2H), 2.91 (br d, J=19 Hz, 1H), 3.23-3.35 (m, 2H), 5.73 (q, J=6.8 Hz, 1H); IR ($CDCl_3$) 3615, 3375, 3060, 2960, 2920, 1700, 1630, 1580, 1450, 1050 cm^{-1}; MS (NH_3 CI) *m/e* 210, 227.

6-Hydroxy-1-(4-methylphenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-dioxolane]-9-one (24): Compound **24** was prepared in 91% yield by the procedure used for **8**, substituting acrolein for methacrolein and **4b** for **4a**: R_F 0.19 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.73-1.84 (m, 1H), 1.95-2.6 (m, 5H), 2.40 (s, 3H), 2.65-2.75 (m, 1H), 2.94-3.0 (m, 1H), 3.32-3.4 (m, 2H), 3.63-4.32 (m, 4H), 7.31 (d, J=9 Hz, 2H), 7.71 (t, J=9 Hz, 2H); MS *m/e* 55, 67, 79, 93, 111, 121, 139, 149, 165, 183, 193, 211, 350.

6-[(Methylthio)methoxy]-1-(4-methylphenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-dioxolane]-9-one (25): To a solution of **24** (2.63 g, 7.5 mmol) in 50 mL of dry CH_3CN over activated 4 Å molecular sieves at 0 °C was added Me_2S (4.66 g, 75 mmol), followed by portionwise addition of benzoylperoxide (7.5 g,

30 mmol). The solution was stirred at room temperature for 1 hour, then poured into saturated $NaHCO_3$ solution. The mixture was extracted 3 times with CH_2Cl_2 and the combined extracts were dried. The solution was concentrated and chromatographed with 3:1 H:EA to give 2.24 g (73%) of a light yellow solid: m.p. 58-60°; R_F 0.66 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.5-2.7 (m, 7H), 2.14 (s, 3H), 2.17 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 2.8-3.2 (m, 3H), 3.3-4.1 (m, 4H), 4.59 (ABq, J=13, 24 Hz, 2H), 4.68 (s, 2H), 7.31 (d, J=9.3 Hz, 2H), 7.73 (ABq, J=9.3, 12.7 Hz, 2H); MS *m/e* 61, 75, 105, 125, 139, 165, 193, 209, 271, 410.

9-Methylidene-6-[(methylthio)methoxy]-1-(4-methylphenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-dioxolane] (26): Methyltriphenylphosphonium bromide (893 mg, 2.5 mmol) was dried by azeotroping with benzene and then was suspended in 5 mL of THF. To this suspension was added *n*-BuLi (1.06 mL of 2.35 M in hexanes). The solution was stirred for 10 minutes. A solution of **25** (250 mg, 0.61 mmol) in 5 mL of THF was added and the solution was stirred for 15 minutes. The solution was poured into Et_2O and acetone was added to quench any excess ylid. The mixture was filtered through a short pad of silica gel and washed with EtOAc. The filtrate was concentrated and flash chromatographed with 1:1 H:EA to give 130 mg (52%) of a colorless oil: R_F 0.70 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32-1.51 (m, 3H), 1.82-2.0 (m, 3H), 2.15-2.25 (m, 2H), 2.15 (s, 3H), 2.41 (s, 3H), 2.99 (br t, J=7 Hz, 1H), 3.57-3.67 (m, 1H), 3.71-3.9 (m, 4H), 4.63 (ABq, J=13,

15 Hz, 2H), 5.23 (s, 0.18H), 5.28 (s, 0.82H), 5.55 (s, 1H), 7.29 (d, J=9 Hz, 2H), 7.53 (t, J=9 Hz, 2H); IR ($CDCl_3$) 2920, 1600, 1060 cm^{-1}.

6-Hydroxy-9-methylidene-1-(4-methylphenylsulfinyl)-bicyclo[3.3.1]nonan-3-one (27): To a solution of **26** (273 mg, 0.66 mmol) in 20 mL of THF was added 1 mL of H_2O and 0.5 mL of H_2SO_4. The solution was stirred for 3 hours. The reaction was quenched by addition of saturated $NaHCO_3$ solution. The mixture was extracted 3 times with CH_2Cl_2. The combined extracts were dried and concentrated to give 202 mg (100%) of a tan solid: m.p. 197-207 °C; R_F 0.43 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.45 (m, 2H), 1.85-2.5 (m, 5H), 2.43 (s, 3H), 2.93-3.1 (m, 2H), 3.85-3.97 (m, 1H), 5.44 (s, 1H), 5.75 (s, 1H), 7.31 (d, J=9 Hz, 2H), 7.47 (d, J=9 Hz, 2H); MS *m/e* 41, 55, 61, 77, 91, 105, 119, 140, 147, 165, 304.

1-Amino-6-hydroxy-9-methylidene-bicyclo[3.3.1]nonan-3-one (28): A suspension of **27** (25.5 mg, 84 μmol) in 2 mL of saturated NH_4OH was heated to 120 °C in a sealed tube for 7 hours. The mixture was cooled to room temperature and was saturated with K_2CO_3. The mixture was extracted 5 times with CH_2Cl_2, dried, and concentrated. The residue was taken up in MeOH and filtered through silica gel, washing with additional MeOH to give 7.0 mg (46 %) of **28**: R_F 0.11 (2:1 EA:MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.7-1.9 (m, 3H), 2.33 (dd, J=7.5, 18 Hz, 2H), 2.61 (dd, J=2, 18 Hz, 2H), 2.9-3.0 (m, 3H), 3.83-3.9 (m, 1H), 5.07 (s, 1H), 5.16 (s, 1H).

9-Methylidene-6-[(methylthio)methoxy]-1-(4-methylphenylsulfinyl)-bicyclo[3.3.1]nonan-3-one (29): To a solution of **26** (96.1 mg, 0.235 mmol) in 15 mL of THF was added 15 drops of H_2O, followed by 10 drops of H_2SO_4. The solution was stirred overnight, then 1 mL of saturated aqueous $NaHCO_3$ was added. To this mixture was added solid K_2CO_3.. The phases were separated and the organic phase was washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give 80.2 mg (94 %) of **29**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.25-1.46 (m, 2H), 1.82-1.89 (m, 3H), 2.13 (s, 3H), 2.35-2.5 (m, 2H), 2.42 (s, 3H), 2.89 (d, J=19 Hz, 1H), 3.13-3.18 (m, 1H), 3.8-3.9 (m, 1H), 4.61 (s, 2H), 5.46 (s, 1H), 5.75 (s, 1H), 7.31 (d, J=9 Hz, 2H), 7.47 (d, J=9 Hz, 2H); IR ($CDCl_3$) 3080, 2950, 2920, 2880, 1705, 1642, 1595, 1490, 1060 cm^{-1}.

1-Amino-9-methylidene-6-[(methylthio)methoxy]-bicyclo[3.3.1]nonan-3-one (30): Compound **29** (48.0 mg, 0.13 mmol) was submitted to the conditions used for the synthesis of **28** to provide 14.7 mg (46 %) of **30**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.43-1.50 (m, 2H), 1.7-1.95 (m, 2H), 2.15 (s, 3H), 2.26-2.39 (m, 2H), 2.62 (dd, J=2.2, 16.3 Hz, 1H), 2.88 (d, J=17 Hz, 1H), 3.12 (t, J=6.3 Hz, 1H), 3.73-3.87 (m, 1H), 4.63 (s, 2H), 5.08 (s, 1H), 5.17 (s, 1H); IR ($CDCl_3$) 3460, 2920, 2850, 1700, 1100 cm^{-1}.

N-[9-Methylidene-6-[(methylthio)methoxy]-bicyclo[3.3.1]nonan-3-one-1-yl]benzamide (32): To a solution of **30** in THF (0.15 mL of 0.12 M) at -78 °C was added 22 μL of a 1 M solution of LDA. The solution was stirred at -78 °C for 30 minutes

then 20 μL of a 1 M solution of benzoyl chloride was added. The solution was stirred for 2 hours while warming slowly to room temperature. The solution was diluted with Et_2O and filtered through a short column of neutral alumina and washed with ethyl acetate to give **32**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.5-1.66 (m, 1H), 1.76-1.89 (m, 1H), 1.94-2.05 (m, 1H), 2.10-2.18 (m, 1H), 2.16 (s, 3H), 2.49 (dd, J=6.5, 16.8 Hz, 1H), 2.74 (dd, J=2.2, 5.6 Hz, 1H), 2.90 (d, J=16.8 Hz, 1H), 3.16 (t, J=6 Hz, 1H), 3.81-3.93 (m, 2H), 4.65 (ABq, J=13, 15 Hz, 2H), 5.03 (s, 1H), 5.19 (s, 1H), 6.03 (br s, 1H,); IR ($CDCl_3$) 3535, 2920, 2850, 1700, 1665, 1615, 1600, 1575, 1510, 1480, 1060 cm^{-1}.

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GENERAL CONCLUSION

The area of bridgehead intermediates has shown great promise for the synthesis of natural products. This research has continued the exploration of this strategy for natural product synthesis. The extension of bridgehead carbocation chemistry to include bridgehead oxonium ions has been accomplished. This chemistry has been demonstrated to work well in the 9-oxabicyclo[3.3.1] series and has shown promise of being effective in the 8-oxabicyclo[3.2.1] series. Development of an efficient synthesis of the necessary 8-oxabicyclo[3.2.1] bridgehead halides could lead to a convergent synthesis of colchicine.

The facile synthesis of bridgehead sulfoxides makes them attractive precursors to bridgehead intermediates. Indeed, they have been shown to provide bridgehead intermediates under a variety of conditions. Thermal conditions lead to an interesting elimination-rearrangement reaction. Reaction with trifluoroacetic anhydride provided the first example of a bridgehead Pummerer reaction. Base promoted elimination provided a bridgehead enone which reacted with ammonia to afford a bridgehead amine. This latter reaction provide an advanced intermediate for the synthesis of huperzine A analogs. Adaptation of this latter strategy may lead to the synthesis of huperzine A and analogs thereof.

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