1994

Synthetic approaches to huperzine A

Danette René Vines
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Synthetic approaches to huperzine A

Vines, Danette René, Ph.D.

Iowa State University, 1994

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Synthetic approaches to huperzine A

by

Danette René Vines

A Dissertation Submitted to the
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DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

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For the Major Department

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For the Graduate College

Iowa State University
Ames, Iowa

1994

DEDICATION

This dissertation is dedicated to my father and mother, Donald and Dolores Vines. Throughout my life, they have loved me unconditionally. When I have needed advice, they have given me wise counsel. When I have needed a shoulder, they have been my best friends. They taught me to value education and to trust in God. For that, I am truly grateful.

TABLE OF CONTENTS

GENERAL INTRODUCTION

Since the beginning of time, man has utilized alkaloids as medicines. The term alkaloid or "alkali-like" is used to describe nitrogen-containing compounds of plant origin. Most of these compounds have complex molecular structures, and possess significant pharmacological activities. Huperzine A is a new lycopodium alkaloid extracted from *Huperzia serrata,* a club moss in China. It has been employed as a traditional medicine in China for the improvement of memory in the elderly. Because of its ability to enhance memory, it has attracted considerable interest as a potential treatment for Alzheimer's disease.

As a consequence of the promise of huperzine A as a nootropic agent for the use in Alzheimer's disease, there is considerable interest in synthesizing this molecule and improved analogs for pharmacological testing. Previously, two syntheses of huperzine A have been reported. However, both routes offer low yields and similar strategies.

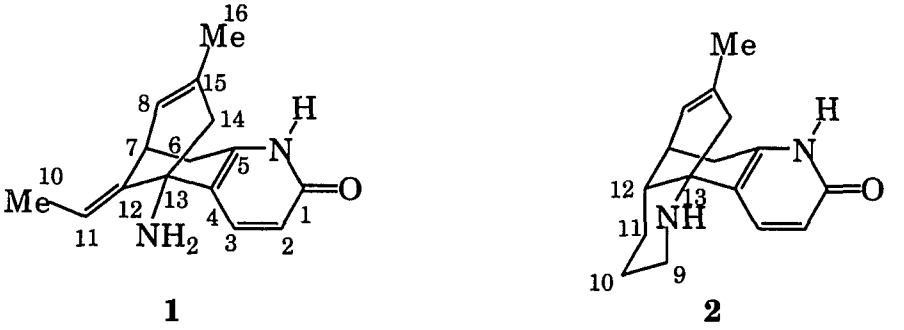
The goal of this research was to synthesize huperzine A and analogs of huperzine A. An extremely efficient synthetic pathway has been devised. In addition, a convergent route to functionalized pyridones, structural subunits of huperzine A, has been developed which offers flexibility and a convenient route to improved analogs. This research will not only help to identify a region of the huperzine skeleton which may offer improved activity, but it will also make available multigram quantities of these useful compounds.

Explanation of Dissertation Format

This dissertation is composed of two papers preceded by an introduction to huperzine A and a review of some previous synthetic routes to huperzine A. The second and third sections contain published and publishable articles, respectively. The first paper, published in *Synthetic Communications*, describes an efficient synthesis of huperzine A. The second paper outlines a route to functionalized pyridones, structural subunits of huperzine A. Following the second paper is a general conclusions chapter.

INTRODUCTION TO HUPERZINE A

Huperzine A (**1**) and a related isomer huperzine B (**2**) were first isolated and characterized by Liu in 1986.[1] The two new Lycopodium alkaloids were extracted from *Huperzia serrata* (Thunb.) Trev., a club moss found in China. The structures of **1** and **2** were determined by spectroscopic studies (Figure 1).



1 **2**

Figure 1. Huperzine A (**1**) and huperzine B (**2**) are two alkaloids isolated from the extracts of a Chinese club moss and used in Chinese folklore medicine.

Both of these alkaloids have been found to exhibit potent anticholinesterase activity. The negative logarithm of the molar concentration causing 50% inhibition of cholinesterase, pI_{50}, of huperzine A when measured on erythrocyte membrane acetylcholinesterase was 7.2; the pI_{50} of huperzine B when measured under the same conditions was 6.1.[2] Therefore, huperzine A is more potent than huperzine B. Furthermore, it was determined that huperzine A has an antiacetylcholinesterase effect approximately three-fold that of physostigmine, another acetylcholinesterase inhibitor. The pI_{50} of physostigmine measured on erythrocyte membrane acetylcholinesterase was 6.7.

In a recent report by doctors at the Walter Reed Army Institute of Research, it was noted that huperzine A inhibited acetylcholinesterase in a

$$E + \text{Hup–A} \underset{K_{off}}{\overset{K_{on}}{\rightleftharpoons}} [E][\text{Hup–A}]$$

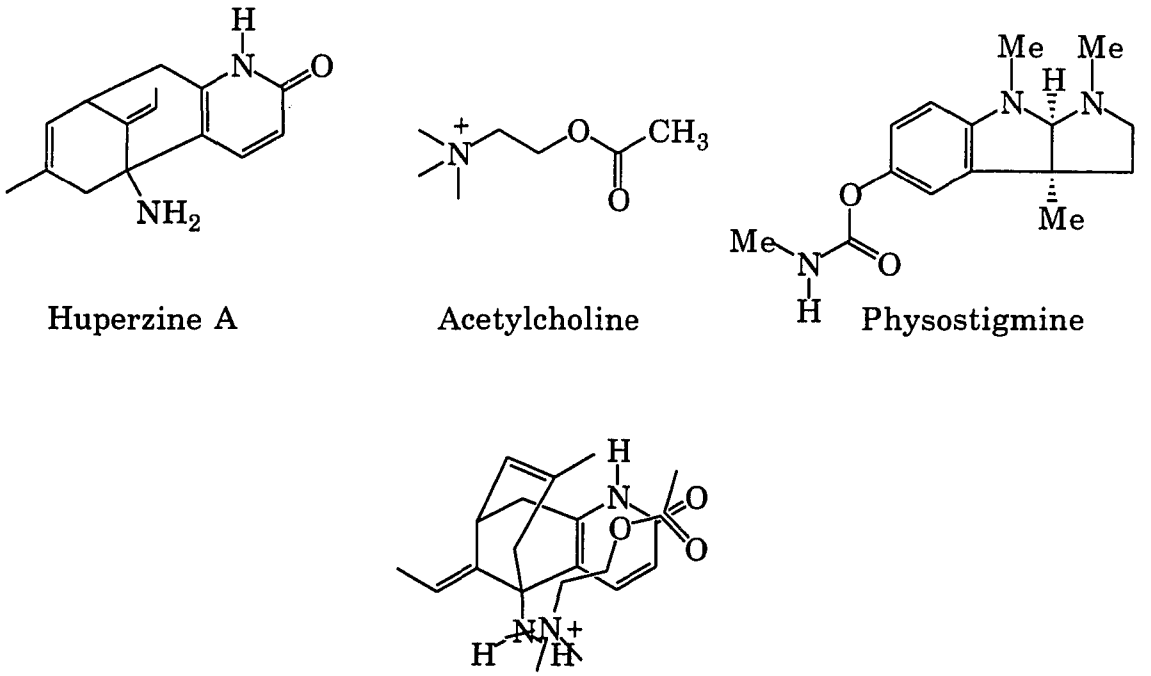
Figure 2. The ratio k_{off}/k_{on} is the dissociation constant k_1 of the enzyme-inhibitor complex. Huperzine A was reported to inhibit AChE in a time-dependent manner ($k_1 = 1 \times 10^6\ M^{-1}\ min^{-1}$). The inhibitor-enzyme constant dissociated slowly ($t_{0.5} = 35$ min).

time-dependent manner and that the inhibitor-enzyme complex dissociated slowly. Physostigmine, however, has a rapid on-and-off rate (Figure 2).[3]

Kozikowski measured the IC_{50} (concentration that inhibited 50% of the acetylcholinesterase activity) of synthetic (±)-huperzine A and compared this result to natural (-)-huperzine A.[4] He found that synthetic (±)-huperzine A was one-half as potent as (-)-huperzine A. This would be expected as racemic huperzine A contains an equal quantity of the inactive (+) isomer.

Because huperzine A possesses anticholinesterase activity, it is considered to be a potential treatment for Alzheimer's disease. In Alzheimer's disease, there is a significant decline in the function of cholinergic neurons in the brain and a resulting decrease in the quantity of acetylcholine.[5] Acetylcholinesterase is the enzyme that breaks down acetylcholine into acetate and choline. Therefore, a possible therapeutic approach to Alzheimer's disease may be to compensate for the loss of cholinergic neurons by increasing the activity of the remaining cells with acetylcholinesterase inhibitors.

Kozikowski has suggested that the heteroatoms of acetylcholine in its extended conformation overlay well with the heteroatoms of huperzine A (Figure 3).[4] This extended conformation is believed to be the one which is operative during hydrolysis. The amino group of huperzine A should be



Huperzine A Acetylcholine Physostigmine

Figure 3. Huperzine A and physostigmine are two acetylcholinesterase inhibitors. Acetylcholine is the neurotransmitter that is hydrolyzed by the enzyme AChE. An overlay of huperzine A and the extended form of acetylcholine is shown.

protonated at physiological pH, and is thus similar to the Me_3N^+ group of acetylcholine.

Quinn *et al.* have described the acetylcholinesterase-inhibitor complex.[6] The enzyme is an ellipsoid with dimensions 65 x 55 x 40 Å. In its middle is a 20 Å deep hydrophobic cleft which contains a hydrogen-bonded triad at the bottom that consists of the side chains of S200, H440 and E327. This triad functions as an acid-base unit to split the ester bond of acetylcholine.[7] In a model of the tetrahedral intermediate involved in the mechanism of acetylcholinesterase, the residue, S200, is joined to the carbonyl carbon of acetylcholine. The side chain of E199 is situated about 4.9 Å from S200. This

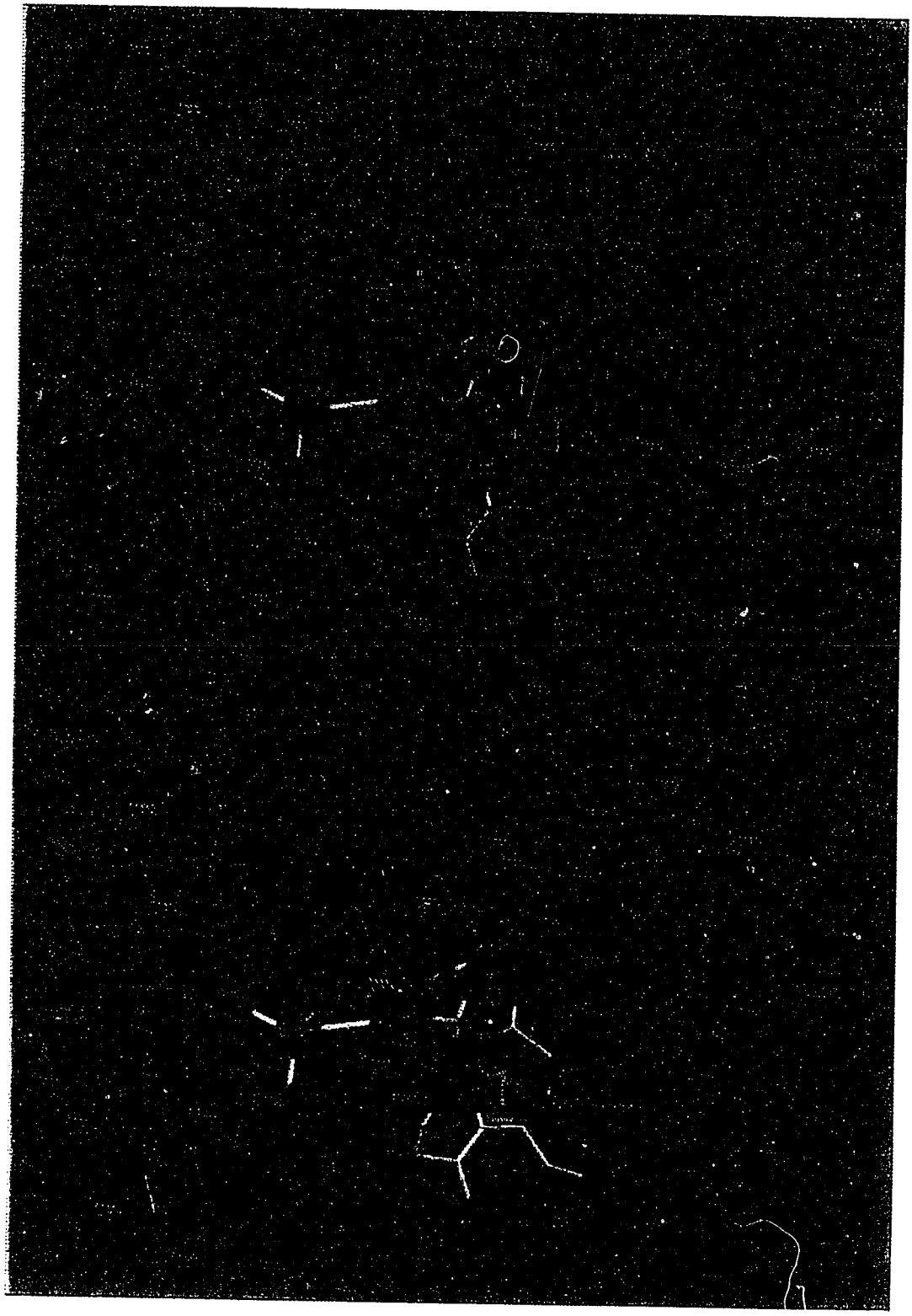
side chain interacts with the quarternary ammonium moiety of acetylcholine. The carbonyl oxyanion of the acetylcholine tetrahedral intermediate is stabilized by hydrogen bonding to the peptide NH residues. These residues form an oxyanion hole (Figure 4).

The distance between the pyridone and exocyclic amino moieties in huperzine A closely resemble the 5 Å distance in acetylcholinesterase between the oxyanion hole and the carboxylate side chain of E199. The similarity between huperzine A and the enzyme, as well as the similarity between huperzine A and acetylcholine (Figure 3) suggest that huperzine A is a constrained analog. Consequently, an improved analog of huperzine A might be one in which the pyridone to amine distance is no longer constrained. For example, a more flexible amino-substituted pyridone may possess enhanced acetylcholinesterase inhibitory activity (Figure 5).

As a slow, reversible inhibitor of acetylcholinesterase that crosses the blood-brain barrier, huperzine A has been demonstrated to be superior for its anti-cholinesterase potency.[8] Consequently, investigators have suggested that huperzine A might be superior to other anti-cholinesterase drugs for the management of memory impairment associated with Alzheimer's disease. Recently, Grunwald *et al.* have reported that huperzine A may provide a safe treatment against nerve agent toxicity.[9]

To date, a number of analogs of huperzine A have been prepared. However, none of these compounds have shown acetylcholinesterase inhibitory activity rivaling that of huperzine A. From the above described studies, it is evident that structural modifications might leave the heteroaromatic ring and the bridgehead amine intact. In addition, huperzine

Figure 4. A model of the tetrahedral intermediate involved in the catalytic mechanism of acetylcholinesterase is shown. The model demonstrates several important contacts between the enzyme and the substrate. The carbonyl oxyanion of the acetylcholine intermediate is stabilized by hydrogen bonding to the peptide amino residues. The side chains of several residues (F288, F290, F331, and W233) form a hydrophobic nest in which the acyl methyl group of acetylcholine is located.



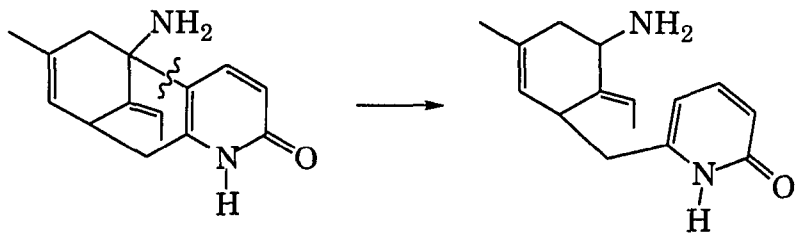


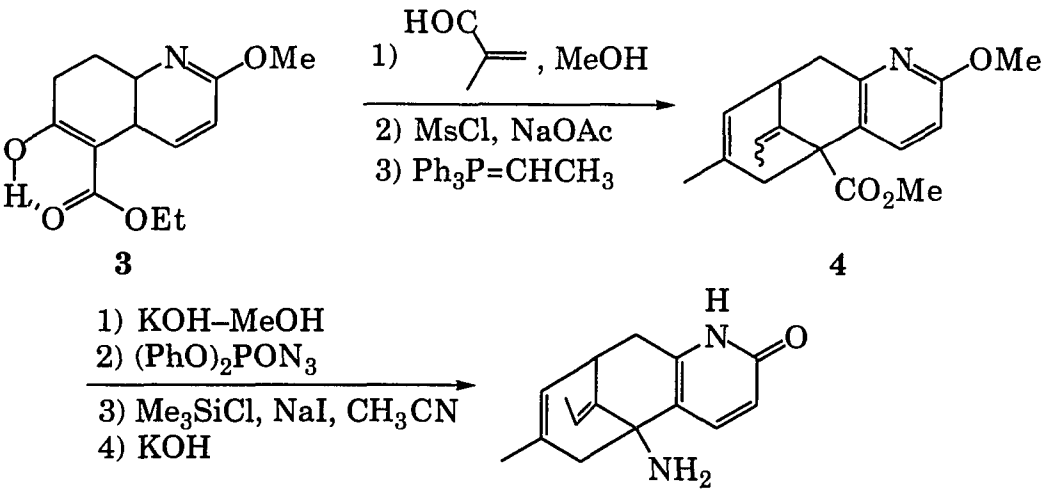
Figure 5. Disconnection of the bond between C_{13} and C_4 may provide an analog of huperzine A with enhanced acetylcholinesterase activity

A is much more potent than its related natural product huperzine B. This implies that not only the primary amine, but also the exocyclic alkene may be important moieties necessary for biological activity.

Although, structural modifications to produce improved analogs are important, clearly an efficient synthesis of huperzine A is the primary goal. Two previous syntheses of huperzine A have been reported. Both the Qian and Ji synthesis[10] and the Kozikowski synthesis[11] followed similar routes.

The Qian and Ji synthesis started with the β-keto ester (**3**) which they prepared from 5-ethoxycarbonyl-6-methyl-2-pyridone in several steps (39% yield). The β-keto ester (**3**) was treated with methacrolein in methanol to give the cyclic ketol. The ketol was dehydrated by mesylation, followed by elimination of the resulting mesylate to the olefin. Wittig reaction with ethylidenetriphenylphosphorane gave (**4**) as a mixture of Z and E isomers. The mixture was treated with KOH in methanol which preferentially hydrolyzed the E-isomer. The corresponding acid was then converted into the urethane using a modified Curtius reaction. Cleavage of the methyl ether and hydrolysis of the urethane to the amine gave racemic huperzine A (Scheme I).

Scheme I

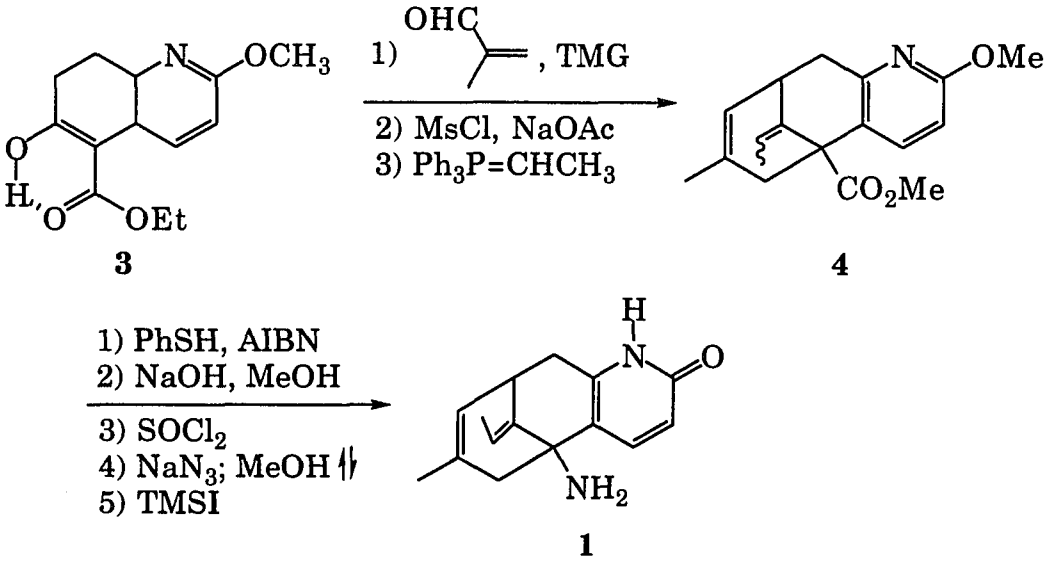


This synthesis produced huperzine A in 0.18% overall yield. The olefination step gave the incorrect isomer as the major product (5:95, E:Z) which was not isomerized to the correct isomer. This tremendously hurt the overall yield of the synthesis. Furthermore, the starting material, which is the same starting material used in the Kozikowski synthesis, is difficult to synthesize and offers at best a 39% yield. A more simplified route starting from readily available materials would offer many advantages toward the synthesis of huperzine A.

The Kozikowski synthesis began with Ji's β-keto ester (**3**) which he prepared in seven steps (27% yield) from the monoethylene-ketal of 1,4-cyclohexanedione. The reaction of the β-keto ester (**3**) with methacrolein using tetramethylguanidine (TMG) gave the cyclic ketol by a Michael/aldol process. Again, dehydration, followed by Wittig olefination with ethylidenetriphenylphosphorane gave the (Z)- and (E)-alkenes (**4**). However, Kozikowski isomerized the incorrect isomer by treating the mixture with AIBN and thiophenol. The last operations offered no surprises, conversion of

the ester group to the amino group by a Curtius rearrangement and cleavage of the O-methylether to the pyridone ring. (±)-Huperzine A was obtained in a 3% overall yield (Scheme II).

Scheme II

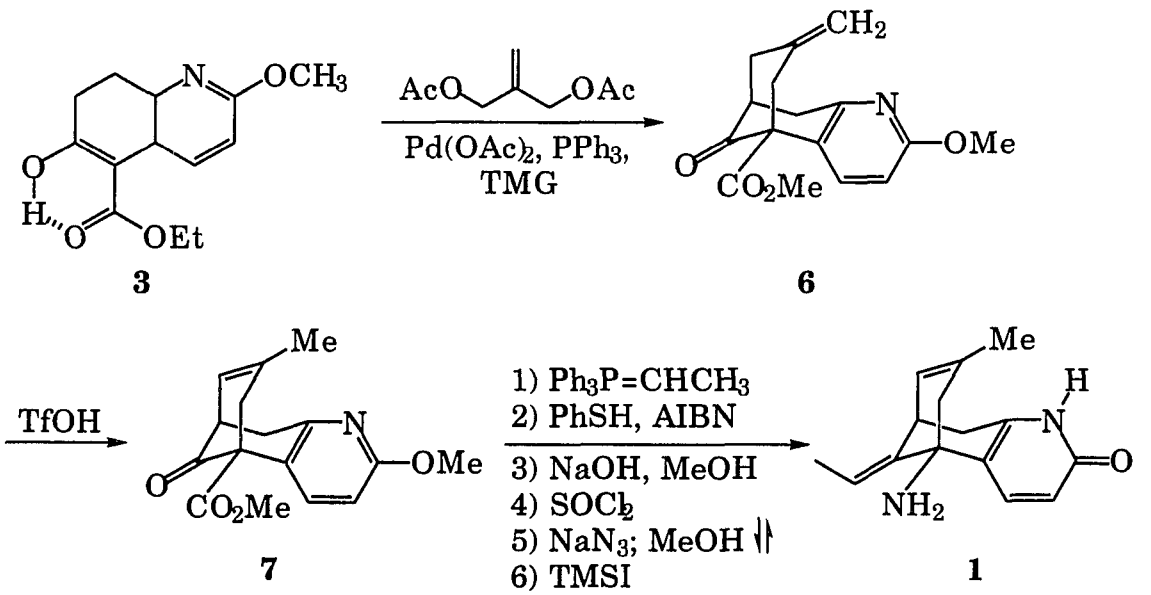


This strategy contained several steps and offered a modest yield. The dehydration of the alcohol to form the endocyclic alkene proceeded in low yield.

Recently, Kozikowski has reported an improved synthesis of huperzine A. The key step involved a palladium-catalyzed alkylation of a bifunctional alkylating agent, **5**, with the β-keto ester **3**, to give **6** in 92% yield. Treatment with triflic acid in dioxane gave the isomerized product, **7**, in a 90% yield. The rest of the synthesis followed that previously reported (Scheme III).

This route significantly improved the yield because it omitted the dehydration step to the endocyclic olefin which at best gave a 31% yield. In this report, he also synthesized two analogs (**9** and **12**) which were tested for

Scheme III

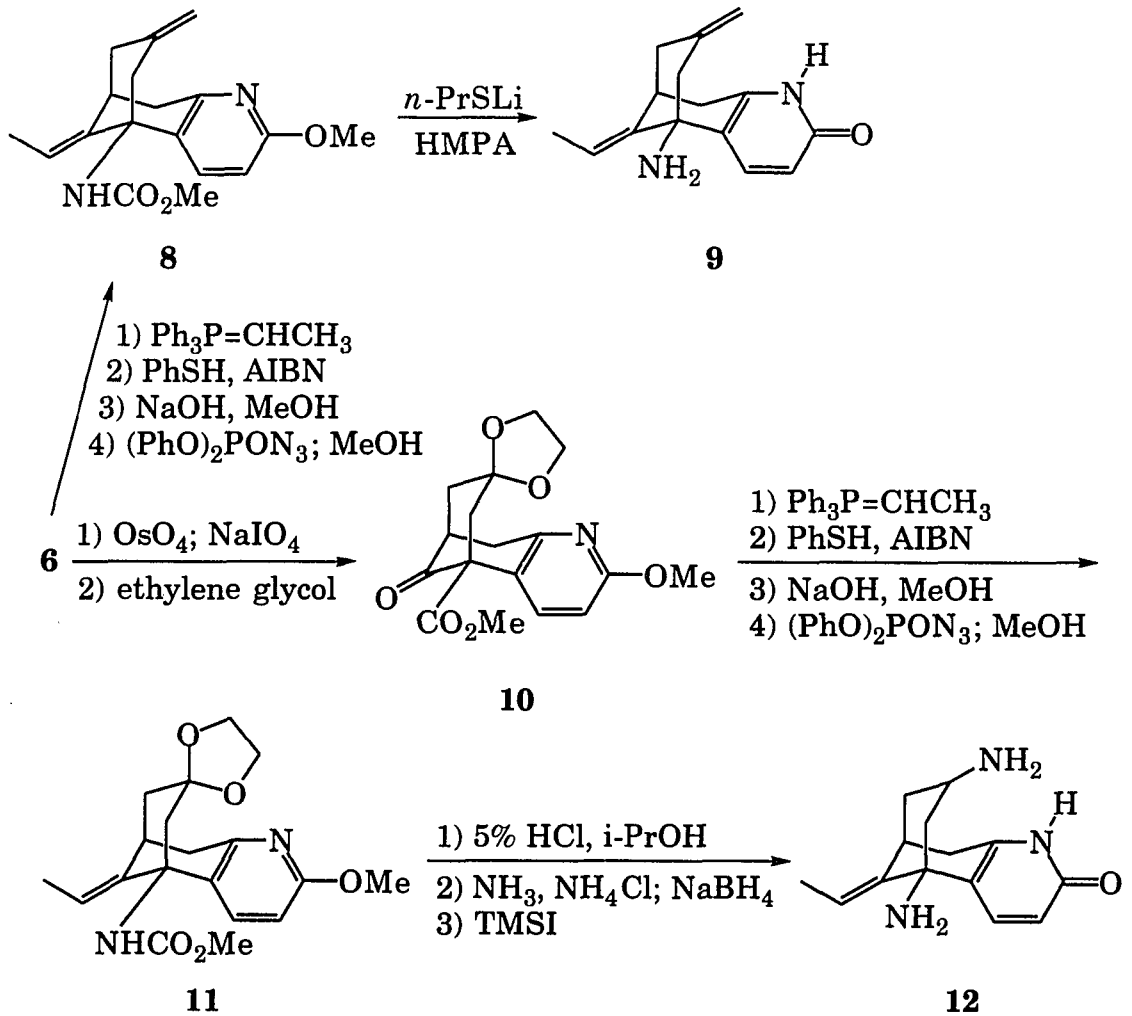


their ability to inhibit acetylcholinesterase enzyme from rat cortex (Scheme IV).

By treatment of **8** with lithium *n*-propanethiolate in HMPA, he obtained the unrearranged aminopyridone, methylene analog **9**. This analog tested less potent than huperzine A, with an IC_{50} of 4.9 ± 1.5 μmol dn^{-3}.

In order to synthesize the diamino analog **12**, the methylene intermediate **6** was reacted with osmium tetroxide-sodium periodate to produce the diketone which was selectively transformed to the monoethylene ketal, **10**. Then, the ethylidene group was installed, the ester was hydrolyzed to the acid, and the acid was converted to the urethane, **11**, by the usual Curtius rearrangement. Ketal hydrolysis, reductive amination and deprotection, resulted in the diamino analog, **12**. Analog **12** had an IC_{50} value of 8.1 ± 1.3 μmol dn^{-3}, which means it had an activity 110 times less active than huperzine A.

Scheme IV



These results may suggest that the endocyclic double bond in the bridged system may be important for its biological activity. Quinn has suggested that modeling shows a π–π interaction between huperzine A and aromatic residues of the enzyme.[6] What effect does the double bond have and is the methyl substituent important for biological activity?

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PAPER I: A BRIDGEHEAD ENONE APPROACH TO HUPERZINE A

Published by *Synthetic Communications* **1992**, *22*, 2625-2634

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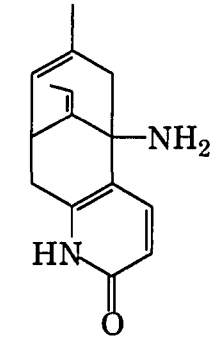
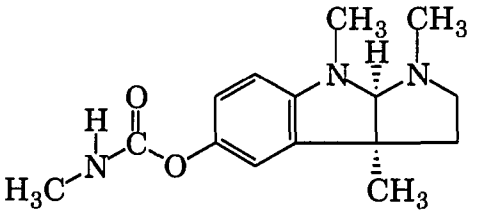
BACKGROUND

Huperzine A has recently attracted considerable interest as a target for the synthetic chemist. It was first isolated from *Lycopodium serratum* and characterized by Liu in 1986.[1] Huperzine A is a potent nootropic agent.[2] In other words, it has the ability to improve memory. Huperzine A is one of the most potent reversible inhibitors of acetylcholinesterase.[3] In the cholinergic system, acetylcholinesterase is the enzyme responsible for the breakdown of acetylcholine to choline and acetate ion. In Alzheimer's disease, a deficiency in the quantity of acetylcholine in the brain is observed. The cholinergic neurons degenerate and it is believed that memory impairment is due to this decrease in cholinergic neurotransmission. The use of reversible inhibitors of acetylcholinesterase, therefore, is considered to be a viable therapeutic approach to the disease. The acetylcholinesterase inhibitor, physostigmine, has been limited by its short duration of action. Recently, tacrine (tetrahydroaminoacridine) has been approved by the FDA as a treatment for Alzheimer's disease. This acetylcholinesterase inhibitor, however, has toxic side effects, such as hepatotoxicity. Huperzine A has demonstrated superiority to both physostigmine and tacrine. Not only does it have fewer side effects than other inhibitors, but it also has a longer duration of action. Consequently, huperzine A has attracted considerable interest as a treatment for Alzheimer's disease (Figure 1).

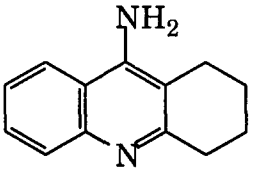
Kozikowski has suggested that the activity of huperzine A is due to the similarity in the arrangement of its heteroatoms to the heteroatoms in the completely extended conformation of acetylcholine.[4] Huperzine B (**2**) and Z-huperzine A (**3**), two related natural products, are both less active than



Huperzine A



Physostigmine

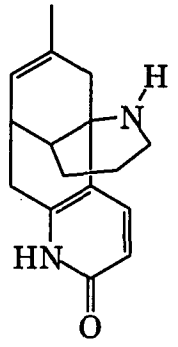


Tacrine

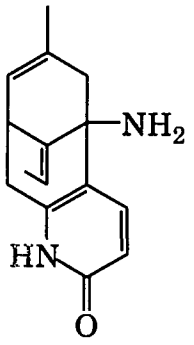
Figure 1. The structures of huperzine A, physostigmine, and tacrine are shown. All are potent acetylcholinesterase inhibitors.

huperzine A (**1**). This implies that the primary amine and the exocyclic alkene moieties might best be left intact when structural modifications are designed (Figure 2).[4]

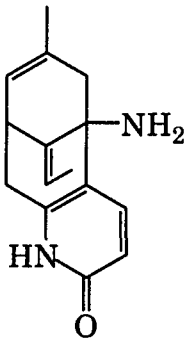
Two previous syntheses of huperzine A have been accomplished. Both the Ji synthesis[5] (path a) and the Kozikowski synthesis (path b) of huperzine and selected analogs[4] followed the same strategy (Scheme I). Recently,



Huperzine B
(**2**)



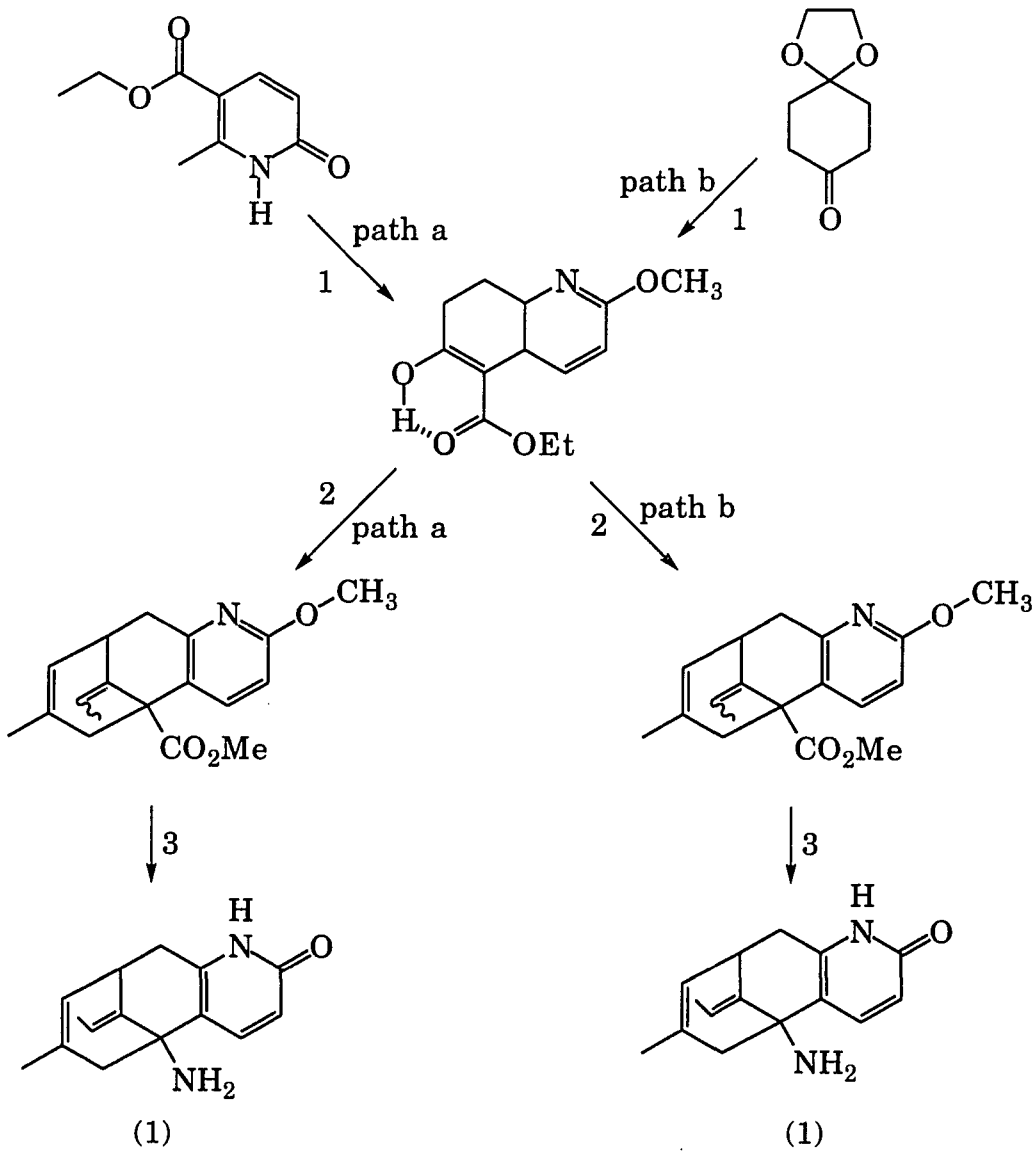
Huperzine A
(**1**)



Z-Huperzine A
(**3**)

Figure 2. The structures of the alkaloids, huperzine B, huperzine A, and Z-huperzine A.

Scheme I



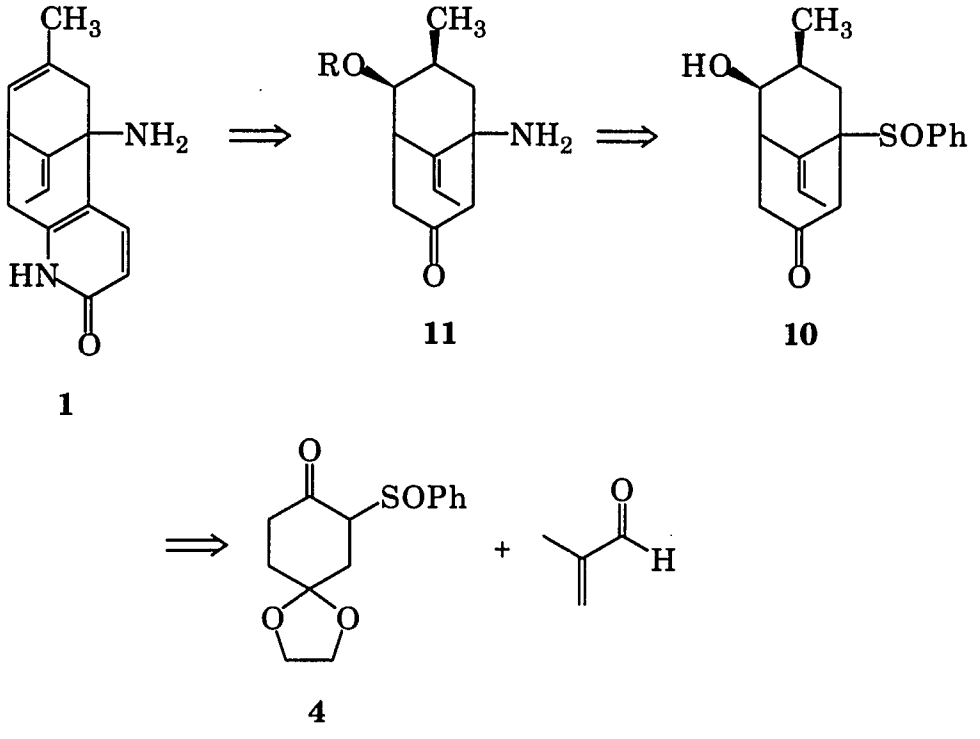
path a 1) i. MeI/Ag_2CO_3/THF; ii. LAH/ether; iii. PhLi/HCHO/ether; iv. $SOCl_2$/$CHCl_3$; v. NaCN/DMSO; vi. MeOH/HCl; vii. NaH/THF. 2) i. methacrolein, MeOH; ii. MsCl, NaOAc; iii. ethylidenetriphenylphosphorane. 3) i. KOH/MeOH, ii. $(PhO)_2PON_3$; iii. Me_3SiCl/NaI/CH_3CN; iv. KOH.

path b 1) i. pyrrolidine; ii. acrylamide; iii. H_2O, iv. KH, BnCl; v. LDA/PhSeCl/$NaIO_4$; vi. H_2, $Pd(OH)_2$/C, AcOH; vii. MeI, Ag_2CO_3; viii. H_3O^+; ix. KH, $(MeO)_2CO$. 2) i. methacrolein, TMG; ii. MsCl/NaOAc; iii. ethylidenetriphenylphosphorane. 3) i. PhSH/AIBN; ii. NaOH/MeOH; iii. $SOCl_2$; iv. NaN_3/MeOH; v. TMSI.

Kozikowski has improved his route by utilizing a palladium-catalyzed bicycloannulation.[6] Our approach differs from these routes in that the amine is introduced via a bridgehead enone.[7]

Scheme II outlines the retrosynthetic analysis of our approach. The bicyclic framework is formed by a Michael-aldol process from the keto sulfoxide and methacrolein. A Wittig reaction is used to introduce the exocyclic ethylidene moiety. The key step involves elimination of the bridgehead sulfoxide to give the reactive bridgehead enone intermediate which reacts with a molecule of ammonia to yield the bridgehead amine.[6]

Scheme II



Our approach differs from the previous syntheses. The synthesis starts from the readily available monoketal of 1,4-cyclohexanedione (**4**). The

intermediate β-keto ester that is common to both the Kozikowski and Qian and Ji syntheses is not used. This intermediate is difficult to prepare and at best offers a yield of 39%. Also, our route introduces the bridgehead amine by a unique bridgehead enone reaction. Both of the previous routes used a Curtius rearrangement to introduce the bridgehead amine. This reaction, the conjugate addition to a bridgehead enone, can accommodate a number of different nucleophiles which would allow for a variety of new analogs.

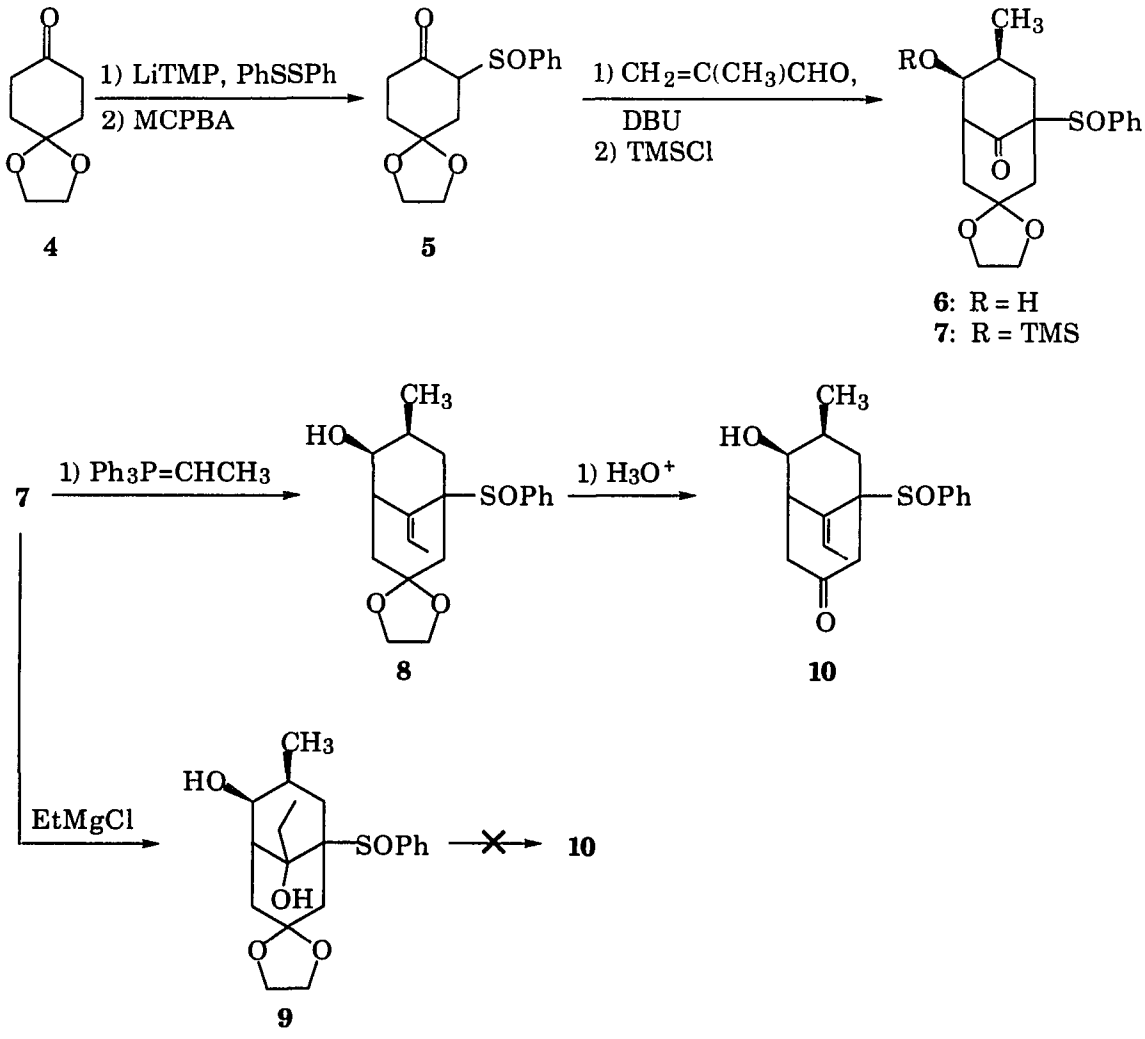
Before our synthetic pathway is discussed, it is worthwhile to review bridgehead enones. House and coworkers contributed to the study of bridgehead enone stability.[8] Magnus was the first to utilize a bridgehead enone generated by a sulfoxide elimination in the synthesis of Kopsane alkaloids.[9] Kraus prepared an important intermediate in the synthesis of lycopodine by a bridgehead enone prepared from the bridgehead bromide and 3-amino-1-propanol and DBU.[10] Bridgehead enones, as demonstrated in the following synthesis, have proven to be useful tools in the synthesis of natural products.

DISCUSSION AND RESULTS

Our approach starts with the commercially available mono ketal of 1,4-cyclohexanedione (**4**). Generation of the enolate of **4** with lithium tetramethylpiperidide (LiTMP) in THF at -78 °C and trapping of the enolate with diphenyldisulfide resulted in the formation of a keto sulfide which was oxidized to the sulfoxide **5** with MCPBA at 0 °C. Another route to the ketosulfoxide, **5**, involved generation of the lithium enolate with lithium diisopropylamide (LDA) and trapping of the enolate with chlorotrimethylsilane (TMSCl). This provided the enol silyl ether in 88% yield. Reaction of the enol silyl ether with *p*-toluenesulfinyl chloride and tin tetrachloride gave the sulfoxide in 45-55% yield.[11] The first method was preferred because it proceeded in a better yield (55% overall yield).

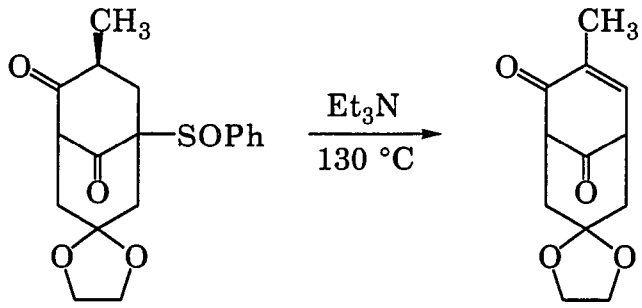
The bicyclic compound **6** was prepared in 90% yield by the addition of methacrolein to a solution of **5** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. The cis stereochemistry shown was determined by a 2D NOESY experiment on **10**. Next, the hydroxyl group was protected in order to prevent a retroaldol cleavage during the Wittig reaction. The trimethylsilyl ether **7** was reacted with ethylidenetriphenylphosphorane in THF to afford *Z*-olefin **8**. Unfortunately, the reaction provided a yield which was no greater than 50%. In an attempt to improve the yield, ketone **7** was treated with ethyl magnesium chloride to afford the tertiary alcohol **9** in quantitative yield. However, all attempts to eliminate the alcohol led to recovered starting material or decomposition.

Scheme III



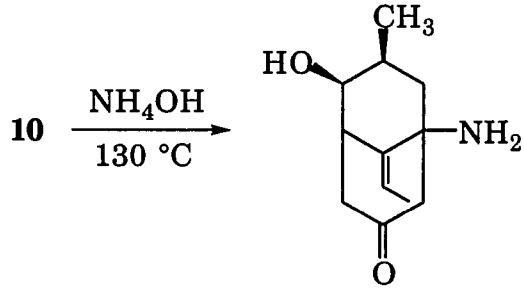
In order to investigate the proposed bridgehead enone reaction, ketal **8** was hydrolyzed to give **10**. However, the sulfoxide did not eliminate even at temperatures as high as 285 °C. This result conflicted with our previous findings (Scheme IV).[12]

Scheme IV



Because **10** was reluctant to eliminate under thermal conditions, we decided to explore other avenues to the bridgehead enone. We discovered that the sulfoxide **10** when heated in a sealed tube in aqueous ammonium hydroxide at 130 °C for three hours was converted into amine **11** in 75% yield (Scheme V).

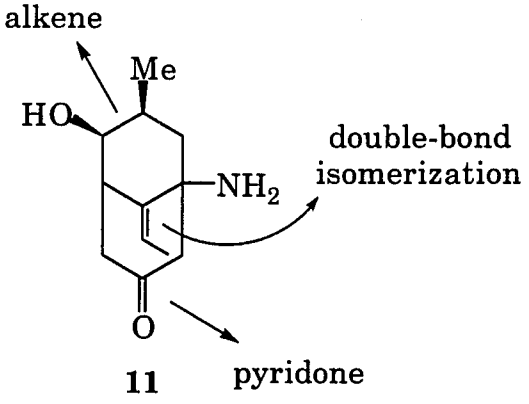
Scheme V



11

The synthesis of the amino ketone **11** from the sulfoxide **10** proved that the amine could be introduced by a bridgehead enone. Completion of the synthesis involves the dehydration of the secondary alcohol and isomerization of the exocyclic alkene. Then, regioselective appendage of the pyridone ring would yield huperzine A. Since both the elimination and

isomerization have precedent from the Kozikowski synthesis, this offers a direct approach to huperzine A and improved analogs (Figure 3).



11

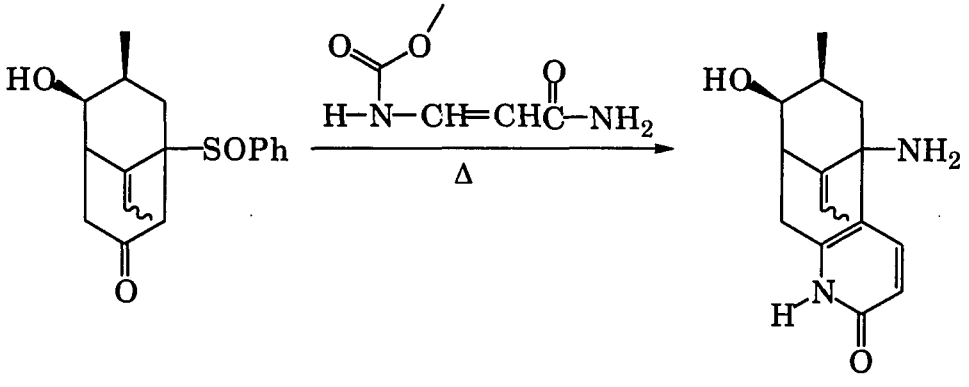
Figure 3. Double-bond isomerization, dehydration to the endocyclic olefin, and pyridone appendage would give huperzine A

CONCLUSION

Huperzine A and its analogs continue to be attractive synthetic targets. An efficient and simplified synthesis would make available this useful natural product for experimentation as a potential treatment for cholinergic disorders. Moreover, the synthesis of analogs would permit the determination of structural modifications necessary for enhanced biological activity.

This study has provided an efficient and creative route to the bicyclic core of huperzine A. It has simplified the synthesis significantly since it starts from readily available materials and consists of few steps. Furthermore, utilization of the bridgehead enone yields a flexible route to improved analogs. In the future, it may lead to a very direct route that would allow for concomitant addition of the amine and regioselective appendage of the pyridone ring in one step (Scheme VI).

Scheme VI



EXPERIMENTAL

All materials were obtained from commercial suppliers and used without purification, unless specified otherwise. The solvents, diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled after drying over lithium aluminum hydride. Both dichloromethane and acetonitrile were distilled over calcium hydride. The reactions were performed under nitrogen atmosphere. During the workups, all extracts were dried over sodium sulfate. Apparati for the experiments were flame-dried under a stream of nitrogen. EM Science Kieselgel F_{254} prepared plates with thicknesses of 0.25 mm were used during thin-layer chromatography. The eluents used were appropriate mixtures of hexanes (H) and ethyl acetate (EA). A Perkin Elmer 1320 spectrophotometer (300 MHz) was used to obtain infrared spectra. The data were reported in cm^{-1}. A Nicolet Magnetics Corporation NMC-1280 spectrometer was used to obtain proton nuclear magnetic resonance spectra (300 MHz). All chemical shifts were reported in ppm relative to tetramethylsilane. The splitting patterns were reported as s for singlet, d for doublet, t for triplet, q for quartet, and dd for double of doublets. The AB quartet was designated as AB_q, and the multiplet as m. The abbreviation br was used to indicate a broadened pattern. The Nicolet NMC-1280 spectrometer was used to obtain Carbon-13 NMR spectra (75.46 MHz). The values were reported in δ relative to $CDCl_3$ (77.0 ppm). The mass spectrometer used was a Finnegan 4023 mass spectrometer. The spectra obtained were high resolution mass spectra. Galbraith laboratories performed all elemental analyses. The compounds were judged to be $\geq$ 90% pure by ^1H NMR spectral determinations.

7-(Phenylsulfinyl)-1,4-dioxaspiro[4.5]decan-8-one (5): 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 warmed to room temperature over 30 minutes. The solution was cooled to -40 °C and a solution of 1,4-cyclohexanedione monoethylene ketal (**4**) in 7 mL of THF and 30 mL of HMPA was added over 15 minutes. The solution was slowly warmed 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 three times with Et_2O. The combined Et_2O solutions were washed with water and saturated aqueous NaCl solution, dried, and concentrated. The residue was purified by sgc. Elution with hexanes removed unreacted diphenyldisulfide. Elution with 10:1 H:EA, then with 3:1 H:EA, provided 4.32 g (82%) of an amorphous solid: R_F 0.67 (3:1 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).

To a solution of the keto sulfide (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 three 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 purified by sgc 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, lH), 2.0-2.1 (m, 2H), 2.45-2.75 (m, 3H), 3.60 (dd, J = 7.7, 13.3 Hz, lH), 3.85-4.05 (m, 4H), 7.47-7.65 (m, 5H).

6-Hydroxy-7-methyl-1-(phenylsulfinyl)spiro[bicyclo[3.3.1]-nonane-3,2'-[1,3]dioxolane]-9-one (6): To a solution of **5** (1.48 g, 5.28 mmol) and DBU (0.88 g, 5.8 mmol) in 50 mL of CH_3CN (freshly distilled from CaH_2) was added dropwise a solution of methacrolein (1.40 g, 20 mmol) in 10 mL of CH_3CN. The solution was stirred for 30 minutes and was concentrated. The residue was purified by sgc with 1:1 H:EA, 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 lH), 1.7-2.5 (m, 4H), 2.87-2.95 (m, lH), 3.25-3.35 (m, 2H), 3.55-4.0 (m, 5H), 7.46-7.66 (m, 3H), 7.8-7.86 (m, 2H); IR ($CDCl_3$) 3370, 3046, 2960, 2880, 1716, 1440, 1160, 1080, 1030 cm^{-1}; MS (NH_3 CI) *m/z* 351, 368.

9-Ethylidene-7-methyl-1-(phenylsulfinyl)-6-(trimethylsilyloxy)-spiro[bicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane] (8): To a solution of **6** (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 **7**: 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, lH), 3.45-3.60 (m, 3H), 3.8-3.9 (m, lH), 7.40-7.45 (m, 3H), 7.8-7.85 (m, 2H); IR ($CDCl_3$) 3025, 2945, 2880, 1720, cm^{-1}. To ethyltriphenylphosphonium bromide (4.7 g, 12.5 mmol) in a 50

mL 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 **7** (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 ylide. The mixture was filtered through Celite and the solvent was removed. The residue was purified by sgc 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, lH), 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, 1250, 1080 cm^{-1}.

9-Ethyl-6,9-dihydroxy-7-methyl-1-(phenylsulfinyl)-spiro[bicyclo[3.3.1]nonane-3,2'-dioxolane] (9): To a solution of **6** (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 diol **9**: ^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]nonan-3-one (10): To a solution of **8** (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/z* 363, 380.

1-Amino-9-ethylidene-6-hydroxy-7-methylbicyclo[3.3.1]nonan-3-one (11): A suspension of **10** (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 three 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, 1700, 1630, 1050 cm^{-1}; MS (NH_3 CI) *m/z* 210, 227.

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PAPER II: A DIRECT ROUTE TO FUNCTIONALIZED PYRIDONES

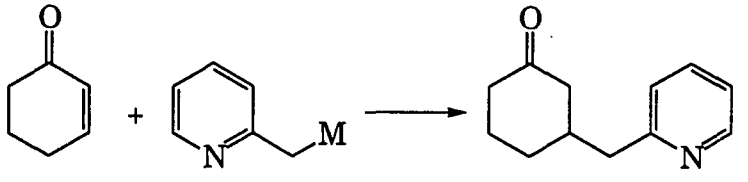
BACKGROUND

It has been well established that huperzine A is a promising acetylcholinesterase (AChE) inhibitor.[1] The current working hypothesis is that AChE inhibitors will improve cognitive function. Today, most industrial scientists believe that AChE inhibitors will have a significant impact on Alzheimer's disease. Recently, tacrine (an AChE inhibitor) has been approved by the FDA as a therapeutic drug for the treatment of Alzheimer's disease.

Huperzine A is a reversible inhibitor of acetylcholinesterase. The discovery of the remarkable anti-acetylcholinesterase activity of huperzine A has prompted considerable attention from both pharmacologists and synthetic chemists.[2]

As part of a study designed to identify analogs of huperzine A with improved AChE inhibitory activity,[3] we required a direct synthesis of 6-substituted pyridones. A direct route to these compounds would involve the conjugate addition of a side-chain metallated pyridine with an α,β-unsaturated ketone (Scheme I).

Scheme I

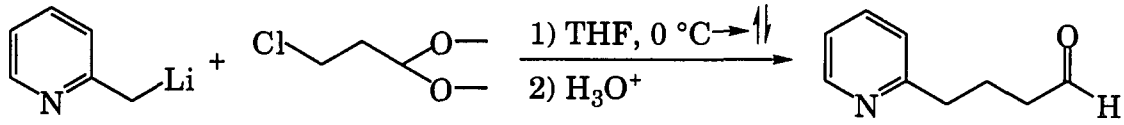


M = metal

It has been well documented that 2-methylpyridine anions undergo aldol[4] and alkylation[5] reactions. Danishefsky and Cain prepared

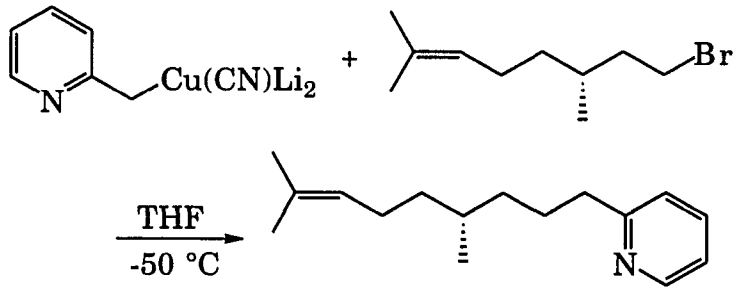
picolylbutyraldehyde by reaction of 2,6-lutidine with phenyllithium and treatment of the resulting anion with 3-chloropropionaldehyde diethylacetal (Scheme II).[6]

Scheme II



Lipshutz prepared the higher order cuprate of 2-picoline by treatment with two equivalents of *n*-BuLi and one equivalent of copper(I) cyanide.[7] He used this reagent in an alkylation reaction with a primary bromide to give the coupled product (Scheme III).

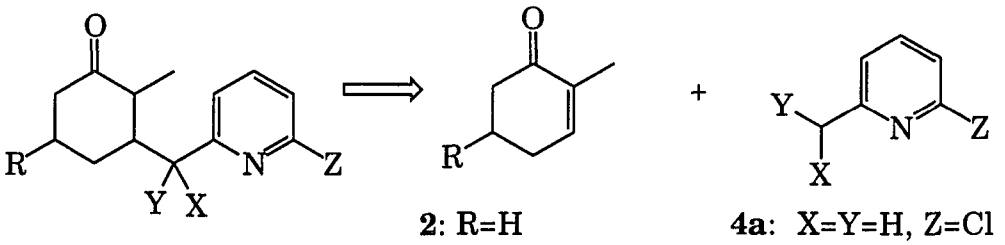
Scheme III



93%

To the best of our knowledge, the use of these anions as donors in conjugate addition reactions has no precedent.[8] Enones **2** and **3** and pyridones **4a-e** were used to explore this pathway (Scheme IV).

Scheme IV



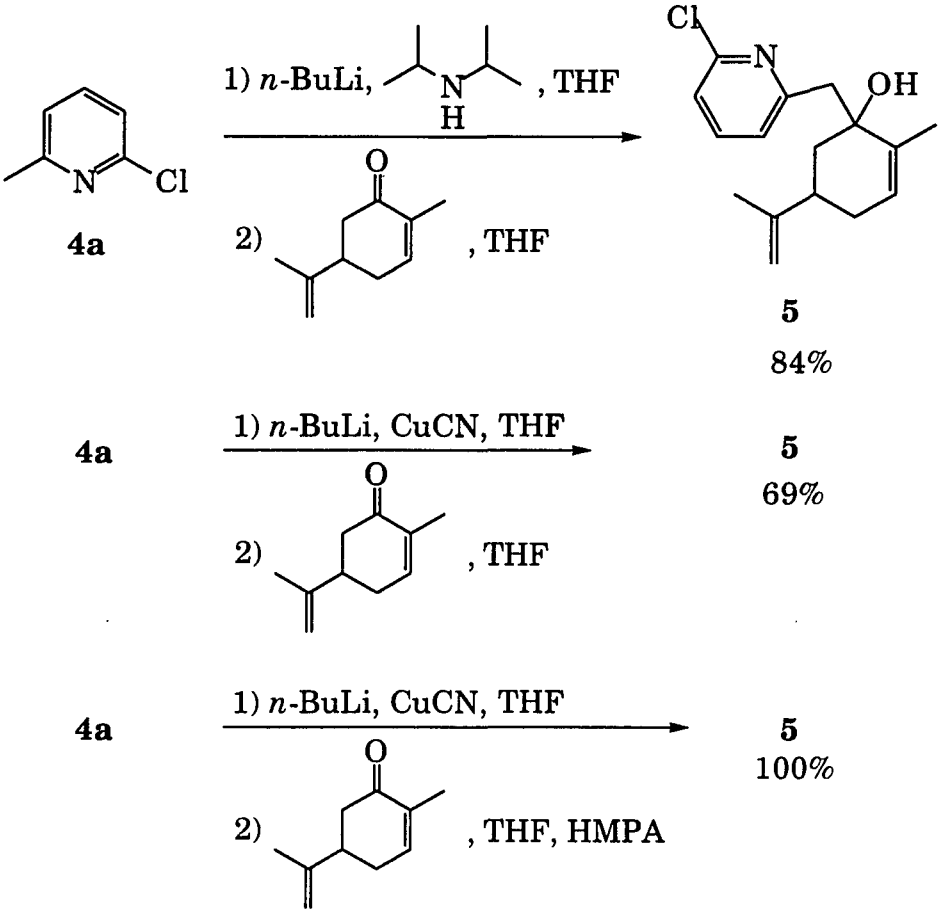
2: R=H
3: R=CMe=CH_2

4a: X=Y=H, Z=Cl
4b: X=H, Y=CO_2Me, Z=Cl
4c: X=Y=SMe, Z=Cl
4d: X=Y=SMe, Z=OMe
4e: X=Y=SMe, Z=OCH_2Ph

DISCUSSION AND RESULTS

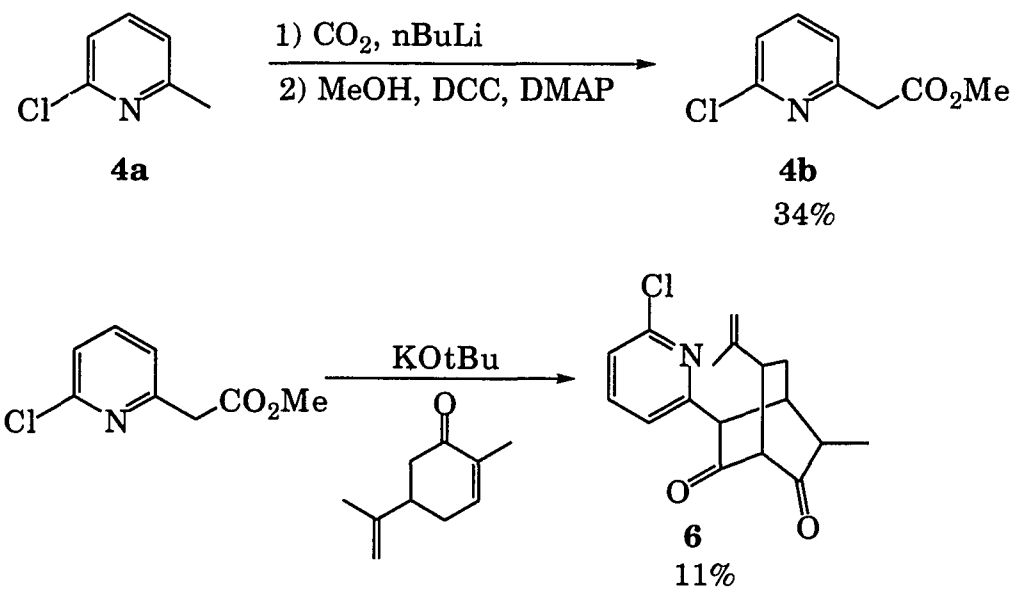
Pyridine **4a** was deprotonated using LDA in THF at 0 °C. The resulting anion was reacted at -78 °C with *l*-carvone to yield alcohol **5** in 84% yield. We did not observe any product resulting from 1,4-addition. Although many options exist for securing 1,4-addition via organocuprates or higher order cuprates, the addition of CuCN, or CuCN-HMPA did not change the regioselectivity (Scheme V).

Scheme V



We next elected to increase the acidity of the anion. Therefore, ester **4b** was prepared by reaction of the anion of **4a** with carbon dioxide followed by DCC-mediated esterification (34% overall yield). Although the lithium anion was not reactive, the potassium anion formed with potassium tert-butoxide provided the unexpected bicyclic adduct **6** (Scheme VI).

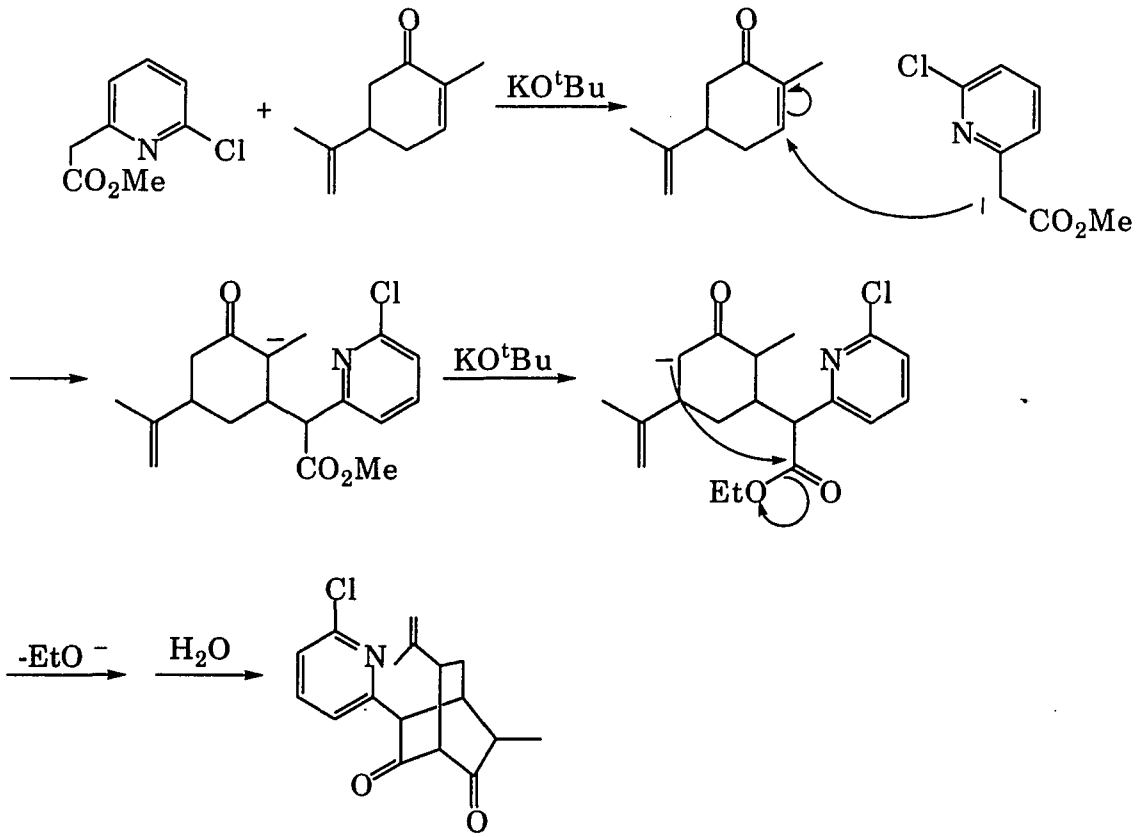
Scheme VI



A likely mechanism would involve Michael addition followed by internal nucleophilic attack on the ester by the enolate (Scheme VII).

The reaction of the lithium anion of **4a** with dimethyl disulfide and subsequent addition of a second equivalent of *n*-BuLi and dimethyl disulfide generated pyridine **4c** in 81% overall yield. The dithiane, **4c**, was then deprotonated with *n*-butyl lithium and reacted with *l*-carvone in the presence of HMPA to yield the ketone, **7**, in a 52% overall yield as a single diastereomer. The yield of **7** was improved to 98% by the addition of CuI. Unfortunately, we

Scheme VII

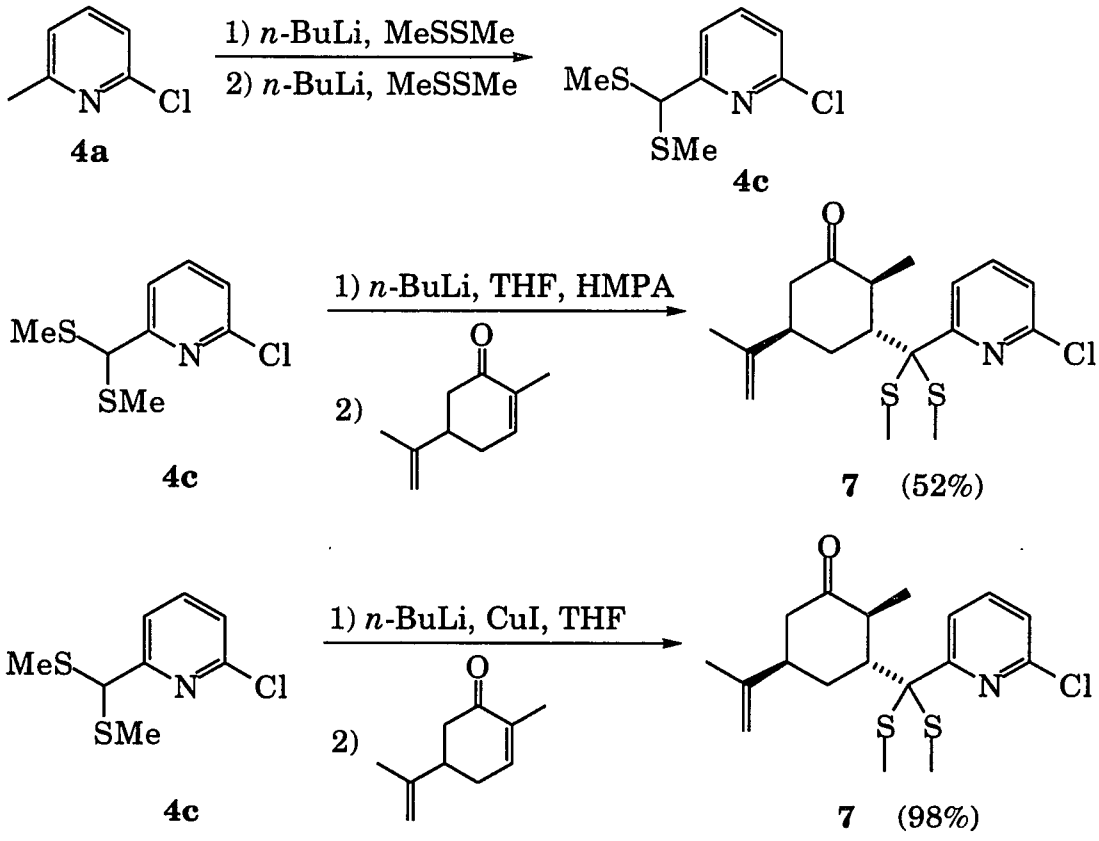


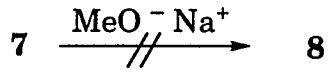
were unable to transform **7** into a pyridone by nucleophilic displacement of the chloride. Perhaps, competing aldol condensations occurred (Scheme VIII).

Our next objective was to introduce an oxygen substituent prior to the conjugate addition step. The reaction of **4a** with sodium methoxide in methanol[9] followed by introduction of the methylthio groups with *n*-BuLi and dimethyl disulfide afforded pyridine **4d** in 30% yield. The yield was increased to 58% by reversing the order of the steps. Thus, **4c** was heated in a sealed tube at 120 °C in a sodium methoxide solution. The resulting methyl ether was deprotonated with *n*-butyllithium and the corresponding anion was

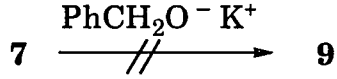
reacted with *l*-carvone in the presence of HMPA to afford the ketone **8** in 61% yield. Unfortunately, attempts to liberate the pyridone by treating the

Scheme VIII





7 → **8**

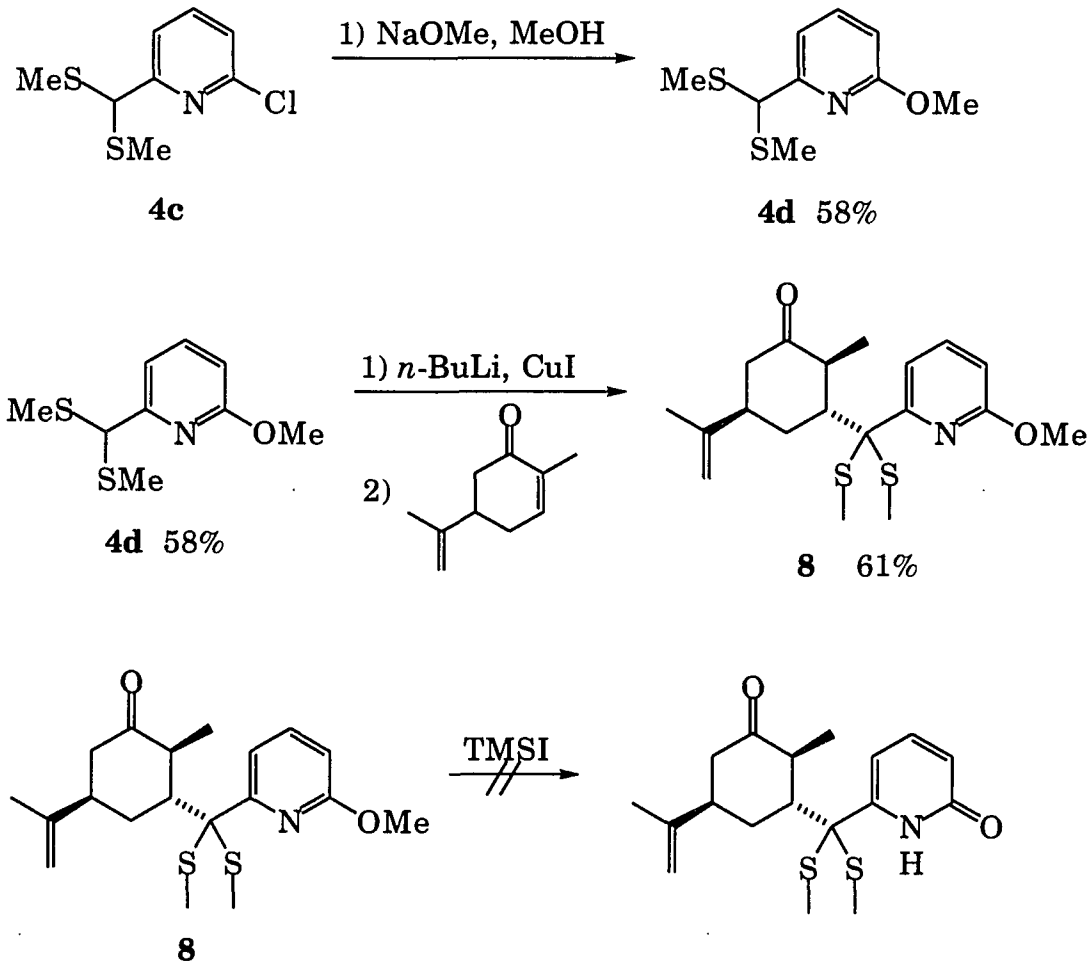


7 → **9**

methyl ether with Lewis acids failed.[10] Consequently, a more labile protecting group was investigated (Scheme IX).

Pyridine **4e** was prepared from **4c** by displacement of the chloride using sodium benzyloxide in benzyl alcohol. Generation of the anion of **4e** by treatment with *n*-BuLi at -78 °C in THF, followed by addition of HMPA and

Scheme IX



l-carvone furnished the ketone **9** in 9% overall yield. The yield of **9** was improved to 99% by the addition of CuI (Scheme X).

The transformation of **9** into the pyridone **10** was the next objective. The reaction of **9** with TMSI failed to give the desired pyridone. Attempted deprotection using catalytic hydrogenation (Pd/C, H_2) gave starting material

only.[11] Fortunately, treatment of **9** with Raney nickel[12] provided pyridone **10** in 85% yield (Scheme XI).

Scheme X

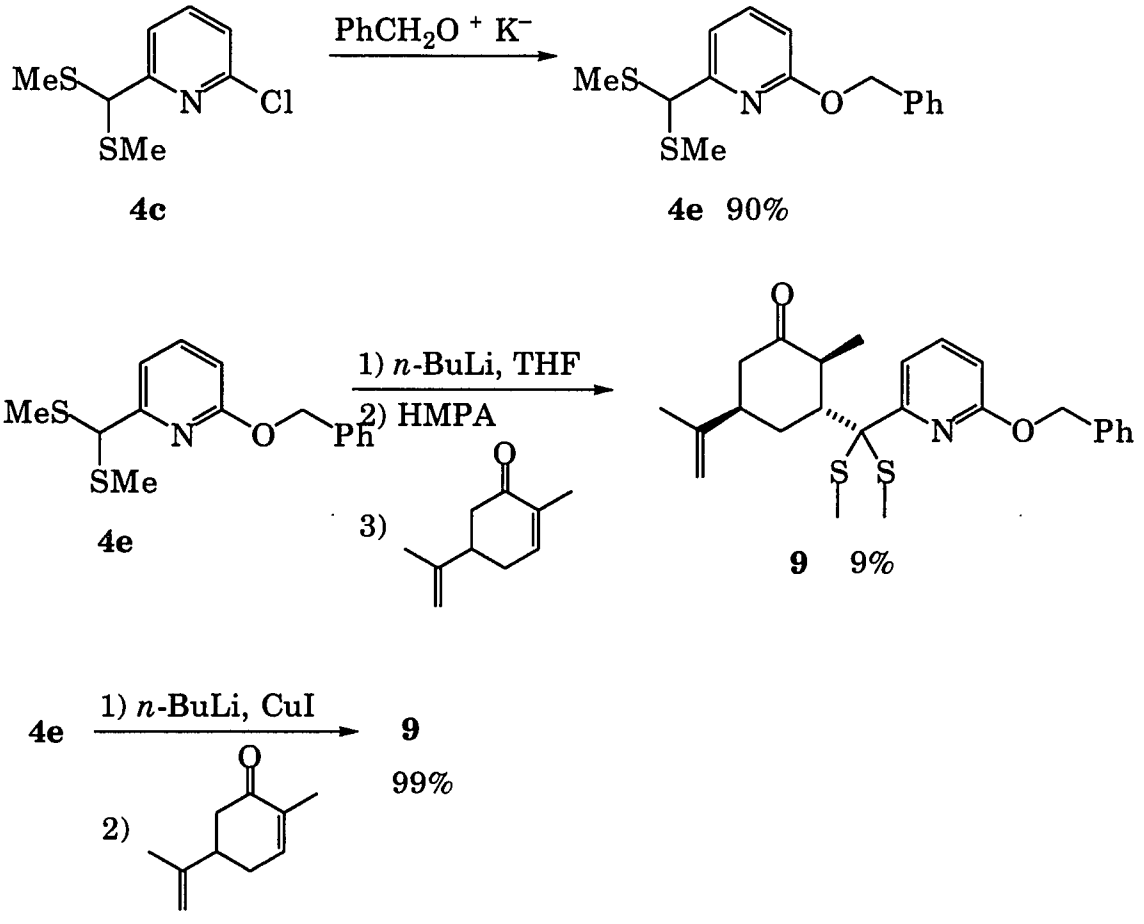


Table I summarizes our results. In order to test the reliability of the conjugate addition, the anions of **4a** and **4c** were reacted with 2-cyclohexene-1-one. As expected, the anion formed by deprotonation of 6-chloro-2-picoline with lithium diisopropylamide upon treatment with the ketone gave the corresponding allylic alcohol (64% yield). Finally,

deprotonation of **4c** with *n*-BuLi and addition of CuI followed by reaction with 2-cyclohexene-1-one gave the 1,4-addition product in quantitative yield.

Scheme XI

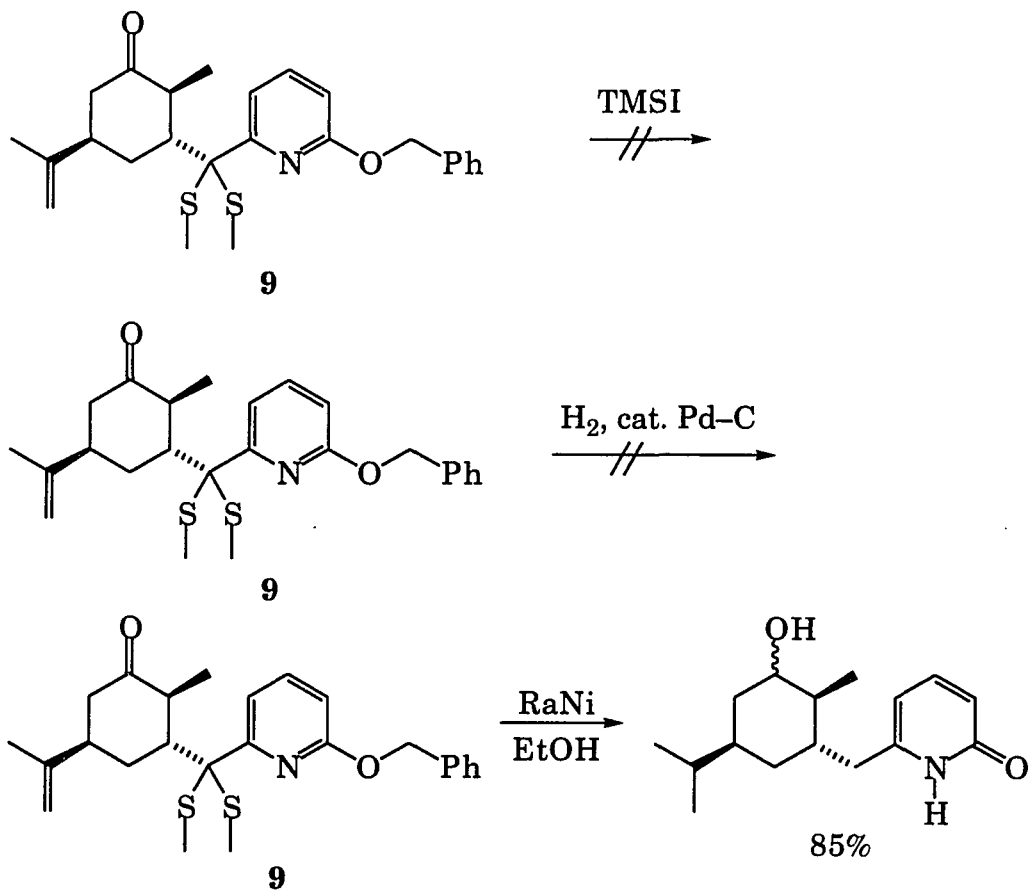
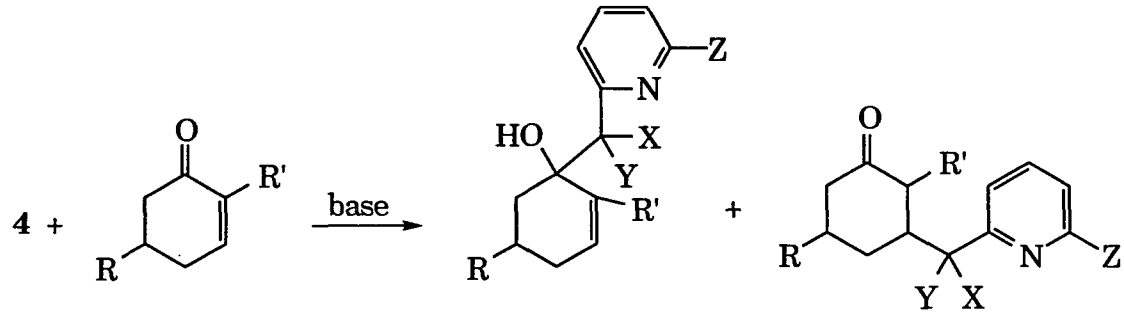


Table I. The reaction of pyridyl anions with carvone



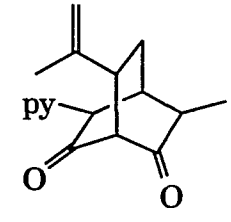
	R	R'	X	Y	Z	Base	Product	% Yield	Compound
1	$C(Me)CH_2$	Me	H	H	Cl	LDA	1, 2	84	**5**
2	$C(Me)CH_2$	Me	H	H	Cl	*n*-BuLi, CuCN	1, 2	69	**5**
3	$C(Me)CH_2$	Me	H	H	Cl	*n*-BuLi, CuCN HMPA	1, 2	100	**5**
4	$C(Me)CH_2$	Me	H	CO_2Me	Cl	t-BuOK		11	**6**
5	$C(Me)CH_2$	Me	SMe	SMe	Cl	*n*-BuLi, HMPA	1, 4	52	**7**
6	$C(Me)CH_2$	Me	SMe	SMe	Cl	*n*-BuLi, CuI	1, 4	98	**7**

Table I. Continued

	R	R'	X	Y	Z	Base	Product	% Yield	Compound
7	$C(Me)CH_2$	Me	SMe	SMe	OMe	*n*-BuLi, HMPA	1, 4	61	**8**
8	$C(Me)CH_2$	Me	SMe	SMe	OCH_2Ph	*n*-BuLi	1, 4	9	**9**
9	$C(Me)CH_2$	Me	SMe	SMe	OCH_2Ph	*n*-BuLi, CuI	1, 4	99	**9**
10	H	H	H	H	Cl	LDA	1, 2	64	
11	H	H	SMe	SMe	Cl	*n*-BuLi/CuI	1, 4	100	

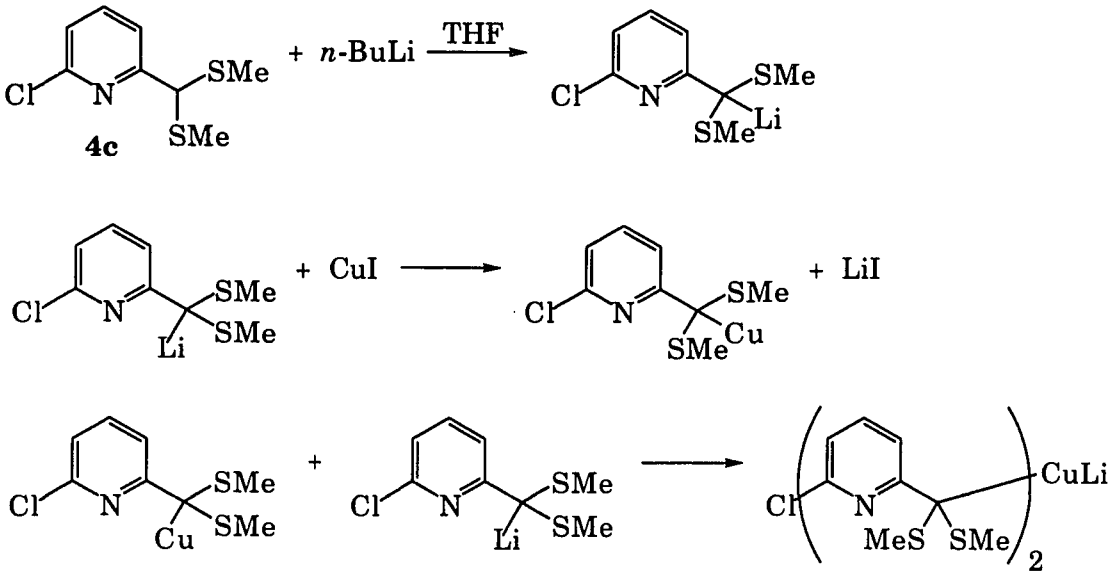
CONCLUSION

In conclusion, it was demonstrated that the conjugate addition of metallated alkylpyridines to enones occurs with high regioselectivities and yields. Two methods were used to secure this transformation.

First, acidity of the Michael donor was increased by adding anion-stabilizing groups. The dithiane, **4c**, was found to be the most successful and has a pK_a of approximately 30. This acyl anion equivalent was readily reduced with raney nickel. Although there are numerous examples of conjugate additions of alkyl dithianes, we are unaware of any derived from 2-picoline.

Second, the addition of one-half equivalent of CuI to the lithiated heteroaromatic species resulted in all cases in improved yields (Scheme XII).

Scheme XII



Two reviews have been written covering substitution and conjugate addition reactions in organocopper chemistry well over a decade ago.[13] These reagents have proven to be of tremendous value to the synthetic organic chemist. In fact, it is indeed rare to find a journal that does not contain a copper-mediated carbon-carbon bond transformation. This study demonstrated the great utility of these reagents and to the best of our knowledge illustrated one of the first methods utilizing the "heteroaromatic Gilman reagent" in a 1,4-conjugate addition.

Lipshutz and Sengupta wrote, "The true measure of the value of an organotransition metal reagent lies in the extent to which it is successfully employed, allowing a transformation to be realized which might otherwise require multiple steps to achieve."[14] This strategy has clearly done just that. The direct synthesis of the pyridone **10** showed that our conjugate addition/deprotection strategy is a reliable one. The two step pathway proceeds in good yields with complete regioselectivity.

Finally, since pyridones are common structural subunits in huperzine A, this route should have great utility. It offers simplicity as well as flexibility toward the synthesis of huperzine A and improved analogs.

EXPERIMENTAL

All materials were obtained from commercial suppliers and used without purification, unless specified otherwise. The solvents, diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled over lithium aluminum hydride. Both dichloromethane and acetonitrile were distilled over calcium hydride. Most of the reactions were performed under nitrogen atmosphere; however, argon gas was used in most of the conjugate addition reactions. The CuI was purified prior to use.[15] The activated raney nickel was prepared from W_2 raney nickel.[16] All apparati for the experiments were flame-dried under a stream of nitrogen. EM Science Kieselgel F_{254} prepared plates with thicknesses of 0.25 mm were used during thin-layer chromatography. The eluents used were appropriate mixtures of hexanes (H) and ethyl acetate (EA). A DigiLab FTS-7 (FT-IR spectrometer) and an IBM/Bruker IR-98 (FT-IR spectrometer) were used to obtain infrared spectra. A Nicolet Magnetics Corporation NMC-1280 spectrometer was used to obtain proton nuclear magnetic resonance spectra (300 MHz). All chemical shifts were reported in ppm relative to tetramethylsilane. The splitting patterns are reported by the following designations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ABq, AB quartet; and m, multiplet. The Nicolet NMC-1280 spectrometer was used to obtain Carbon-13 NMR spectra (75.46 MHz). The values were reported in δ ppm relative to $CDCl_3$ (77.0 ppm). The mass spectrometer used was a Finnegan 4023 mass spectrometer. The compounds were judged to be $\geq$ 90% pure by ^1H NMR spectral determinations.

1-(6-Chloro-2-methylpyridyl)-2-methyl-5-isopropenylcyclohex-2-enol (5): To a solution of LDA, freshly prepared from n-BuLi (2.17 M in hexane; 0.74 mL, 1.6 mmol) and *N,N*-diisopropylamine (0.16 g, 1.6 mmol) in dry THF (32 mL) was added 6-chloro-2-picoline (0.20 g, 1.6 mmol) at 0 ºC. After stirring for 30 minutes, the solution was cooled to -78 °C and l-carvone (0.24 g, 1.6 mmol) in THF (2 mL) was added dropwise. The solution was stirred for two hours and then poured into ice water and extracted with diethyl ether (3 X 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The residue was purified by silica gel chromatography (hexane: AcOEt, 8:1) to give alcohol, **5**, in 84% yield.

IR (film) 3415, 3081, 2921, 1645, 1550, 1408, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 5.49-5.47 (s, 1H), 4.66 (s, 2 H), 3.24 (d, J = 14.4 Hz, 1H), 2.94 (d, J = 14.4 Hz, 1H), 2.44-2.27 (m, 2H), 2.19-1.89 (m, 4H), 1.76 (s, 3H), 1.65 (s, 3H) ; MS (CI, NH_3) m/e 277; HRMS (EI) calcd for $C_{16}H_{20}ClNO$ (M^+) 277.12276, found (M^+) 277.12334; CMR ($CDCl_3$) δ17.3, 20.3, 30.7, 39.6, 40.3, 44.1, 74.2, 108.9, 122.0, 123.1, 123.6, 138.2, 139.1, 148.5, 150.3, 160.0; TLC (4:1, H:EA) R_f = 0.39.

2-Methyl-8-isopropylene-6-(6-chloro-2-pyridyl)-bicyclo[2.2.2]-octan-3,5-dione (6): To a solution of potassium tert-butoxide (0.65 mmol) in THF was added 2-methylethanoate-6-chloropyridine (0.59 mmol) at 0°. The solution was stirred for 30 minutes. L-carvone (0.65 mmol) was added and the mixture was stirred overnight at room temperature. Then, the temperature was raised and the mixture was refluxed for 12 hours. The crude mixture was poured into ice water and extracted with ether. The combined extracts were dried over $MgSO_4$. The residue was purified by silica gel

chromatography (hexane:AcOEt, 12:1) to give the [2.2.2]bicyclo adduct in 11% yield.

IR (film) 3055, 2988, 1701, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.5 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 5.00 (s, 1H), 4.82 (s, 1H), 4.16-4.08 (m, 1H), 2.90-2.40 (m, 4H), 1.91 (s, 3H), 1.88-1.65 (m, 2H), 1.01 (d, J = 6.6 Hz, 3H), R_f = 0.53 (3:1, H:EA).

2-Methyl-5-isopropenyl-3-[(6-chloro-2-pyridyl)bis-methylthio-methyl]cyclohexanone (7): To a stirred solution of **4c** (143 mg, 0.65 mmol) in THF (5 mL) was added n-BuLi (0.30 mL, 0.65 mmol) at -78 °C under an Ar atm. The mixture was stirred for one hour. Cuprous iodide (63 mg, 0.33 mmol) was then added and the mixture stirred for an additional hour at -78 °C. Then l-carvone (50 mg, 0.33 mmol) in 0.1 mL of THF was added slowly at -78 °C and the mixture was stirred at -78 °C for three hours. The reaction mixture was quenched by the addition of H_2O and allowed to reach room temperature. The precipitate was filtered off and the crude mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by silica gel chromatography (hexane:AcOEt, 30:1) to give **7** (98% yield).

IR (film) 2915, 2872, 1708, 1558, 1427 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.5 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 4.81 (s, 1H), 4.77 (s, 1H), 2.94-2.81 (m, 1H), 2.46-1.83 (m, 6H), 2.03 (s, 3H), 1.93 (s, 3H), 1.78 (s, 3H), 0.61 (d, J = 6.6 Hz, 3H); MS (CI, NH_3) m/e 322, 370, 387; CMR ($CDCl_3$) δ 12.8, 13.6, 20.6, 28.1, 42.1, 44.5, 47.6, 48.2, 71.3, 110.1, 122.1, 122.8, 138.5, 147.0, 149.7, 160.4, 213.2; TLC (4:1, H:EA) R_f = 0.57.

2-Methyl-5-isopropenyl-3[(6-methoxy-2-pyridyl)bis-(methylthio)methyl]cyclohexanone (8): To a stirred solution of **4d** (67 mg, 0.31 mmol) in 3 mL of THF was added *n*-BuLi (0.16 mL, 0.34 mmol) at -78 °C. The solution was stirred for one hour at -78 °C and then the temperature was raised to 0 °C and HMPA (0.06 mL, 0.34 mmol) was added. The temperature was lowered to -78 °C and l-carvone (51 mg, 0.34 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for three hours. The reaction mixture was quenched by the addition of water and allowed to reach room temperature. The aqueous solution was extracted with Et_2O, washed successively with H_2O and brine, and dried ($MgSO_4$). Silica gel chromatography (70:1, H:EA) of the residue afforded **8** in 61% yield.

IR (film) 2924, 1711, 1587, 1466, 1263, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 4.83-4.71 (m, 2H), 3.93 (s, 3H), 2.99-2.88 (m, 1H), 2.50-1.22 (m, 6H), 2.02 (s, 3H), 1.92 (s, 3H), 1.78 (s, 3H), 0.91 (d, J = 7.2 Hz, 3H); MS (CI, NH_3) m/e 208, 320, 366; HRMS (EI) calcd for $C_{19}H_{27}NO_2S_2$ (M^+) 365.1483, found (M^+) 365.1484; CMR ($CDCl_3$) δ 18.4, 20.5, 28.4, 42.1, 44.6, 47.6, 48.2, 53.5, 72.5, 109.3, 109.9, 116.4, 123.0, 127.1, 138.5, 147.1, 156.4, 162.8, 213.6; TLC (7:1, H:EA) R_f = 0.71.

2-Methyl-5-isopropenyl-3[(6-benzyloxy-2-pyridyl)bis-methylthiomethyl]cyclohexanone (9): This compound was prepared following the procedure for the preparation of **7**. The product was purified by silica gel chromatography (30:1, H:EA) to give **9a** and **9b** (4:1-99:1, **9a:9b**).

9a (trans isomer): IR (film) 2915, 1708, 1574, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (t, J = 7.8 Hz, 1H), 7.50-7.23 (m, 6H), 6.67 (d, J = 8.4 Hz,

1H), 5.39 (AB quartet, J = 12.3 Hz, 2H), 4.79 (s, 1H), 4.76 (s, 1H), 2.93-2.91 (m, 1H), 2.46-1.71 (m, 6H), 2.01 (s, 3H), 1.89 (s, 3H), 1.76 (s, 3H), 0.73 (d, J = 7.2 Hz, 3H); MS (CI, NH_3) m/e 382, 396, 442; CMR ($CDCl_3$) δ 12.8, 13.5, 20.5, 28.1, 40.0, 42.1, 44.8, 47.6, 48.3, 67.6, 72.8, 109.5, 110.0, 118.8, 127.7, 128.0, 128.3, 137.3, 138.7, 147.2, 156.5, 161.7, 219.6; TLC (30:1, H:EA) R_f = 0.25.

9b (cis isomer): IR (film) 3086, 1708, 1574, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (t, J = 7.8 Hz, 1H), 7.49-7.25 (m, 6H), 6.67 (d, J = 7.8 Hz, 1H), 5.41 (s, 2H), 4.91 (s, 1H), 4.70 (s, 1H), 2.91-2.89 (m, 1H), 2.70 (m, 1H), 2.52-2.42 (m, 4H), 2.02-1.98 (m, 1H), 1.95 (s, 3H), 1.88 (s, 3H), 1.80 (s, 3H), 0.69 (d, J = 7.2 Hz, 3H); MS (CI, NH_3) m/e 396, 442; CMR ($CDCl_3$) δ 12.5, 13.2, 22.3, 24.5, 31.1, 40.0, 40.7, 42.7, 48.0, 67.5, 72.7, 108.4, 112.9, 116.7, 127.8, 127.9, 128.3, 137.5, 138.8, 146.4, 158.8, 161.6, 214.2; TLC (30:1, H:EA) R_f = 0.10.

2-Methyl-3-[(2-pyridone)methyl]-5-isopropylcyclohexanol (10): The sulfide (0.26 mmol) and raney nickel (1 g) were refluxed in 10 mL of ethanol for two hours. The crude solution was filtered carefully. The filtrate was concentrated in vacuo to afford the pyridone in 85% yield. The pyridone could be purified by flash chromatography on silica gel half saturated with ammonia.

10 (pyridone): IR (film) 3377, 3279, 2957, 2870, 1651, 1616, 1457, 1264, 1006 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, J = 6.9 Hz, 1H), 6.41 (d, J = 6.9 Hz, 1H), 6.05 (d, J = 6.9 Hz, 1H), 3.62-3.55 (m, 1H), 2.56-2.45 (m, 2H), 1.93-0.97 (m, 9H), 0.85 (d, J = 6.3 Hz, 6H), 0.79 (d, J = 6.9 Hz, 3H) ; MS (CI, NH_3) m/e 110, 127, 248, 264, 281; CMR ($CDCl_3$) δ 20.0, 21.2, 30.0, 32.2, 33.3, 34.0, 38.2, 39.0, 39.9, 41.6, 73.3, 108.1, 117.2, 143.1, 150.0, 166.6; TLC (10:1, EA: MeOH) R_f = 0.46.

1-(6-Chloro-2-methylpyridyl)cyclohex-2-enol: To a solution of LDA, freshly prepared from *n*-BuLi (2.17 M in hexane; 0.74 mL, 1.6 mmol) and *N,N*-diisopropylamine (0.16 g, 1.6 mmol) in dry THF (32 mL) was added 6-chloro-2-picoline at 0 °C (0.20 g, 1.6 mmol). After stirring for 30 minutes, the solution was cooled to -78 °C and 2-cyclohexen-1-one (0.15 g, 1.6 mmol) in THF (2 mL) was added dropwise. The solution was stirred for two hours and then poured into ice water and extracted with diethyl ether (3 X 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The residue was purified by silica gel chromatography (hexane: AcOEt, 8:1) to give the allylic alcohol in 64% yield.

IR (film) 3410, 2935, 1587, 1558, 1441, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 5.82-5.76 (m, 1H), 5.55 (d, J = 9.9 Hz, 1H), 4.36 (s, 1H), 3.74-3.70 (m, 1H), 3.55-3.15 (m, 1H), 2.96 (AB quartet, J = 11.1 Hz, 2H), 2.37-1.18 (m, 4H); MS (EI) m/e 79.1, 97.1, 129.0, 177.0, 204.1, 223.1; HRMS (EI) calcd for $C_{12}H_{14}ClNO$ (M^+) 223.0764, found (M^+) 223.0760; CMR ($CDCl_3$) δ 18.8, 24.9, 35.8, 47.8, 69.5, 121.8, 126.1, 129.3, 131.7, 138.8, 149.9, 159.6; TLC (5:1 H:EA) R_f = 0.19.

3-[(6-Chloro-2-pyridyl)bis-(methylthio)methyl]cyclohexanone: To a stirred solution of **4c** (200 mg, 0.91 mmol) in THF (8 mL) was added *n*-BuLi (2.22 M in hexane, 0.41 mL, 0.91 mmol) at -78 °C under an Ar atm. The mixture was stirred for one hour. Cuprous iodide (87 mg, 0.45 mmol) was then added and the mixture stirred for an additional hour at -78 °C. Then, 2-cyclohexen-1-one (43 mg, 0.45 mmol) in 0.5 mL of THF was added slowly at -78 °C and the mixture was stirred at -78 °C for three hours. The reaction mixture was quenched by the addition of H_2O and allowed to reach room

temperature. The precipitate was filtered and the crude mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by silica gel chromatography (hexane:AcOEt, 25:1) to give the ketone (100% yield).

IR (film) 2916, 1699, 1574, 1553, 1423, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 2.66-2.08 (m, 5H), 2.04 (s, 3 H), 1.97 (s, 3H), 1.66-1.28 (m, 4H); MS (CI, NH_3) m/e 268, 316, 333; CMR ($CDCl_3$) δ 13.2, 13.5, 24.8, 27.8, 41.0, 44.3, 47.7, 71.8, 121.7, 122.9, 138.7, 150.2, 159.9, 210.7; TLC (2:1, H:EA) R_f = 0.49.

2-Methylethanoate-6-chloropyridine (4b): To a solution of 6-chloro-2-picoline (0.76 g, 6 mmol) in THF (30 mL) at 0° was added *n*-BuLi (2.35 M in hexane, 6.6 mmol, 2.81 mL). The temperature was lowered to -78 °C and carbon dioxide was bubbled through the reaction mixture. The mixture was allowed to warm to 0 °C and then to room temperature. The mixture was quenched by the addition of 0.50 mL of trifluoroacetic acid. The mixture was diluted with THF, filtered through a pad of celite, and concentrated. To a solution of the crude acid in methylene chloride (0.1 M) was added 4-dimethyl-aminopyridine (73 mg, 0.6 mmol) and methanol (384 mg, 12 mmol). The mixture was cooled to 0 °C and 1,3-dicyclohexylcarbodiimide (1.24 g, 6 mmol) in methylene chloride was added. The mixture was stirred for two days at room temperature. The residue was purified by silica gel chromatography (hexane: AcOEt, 10:1) to give the methyl ester in a 34% overall yield.

IR (film) 2951, 2254, 1740, 1559, 1471, 1340, 1268 cm^{-1}; ^1H NMR (330 MHz, $CDCl_3$) δ 7.63 (t, J = 7.8 Hz, 1H); 7.24 (d, J = 7.5 Hz, 2H); 3.88 (s, 2H); 3.72 (s, 3H); MS (CI, NH_3) m/e 186; HRMS (EI) calcd for $C_8H_8ClNO_2$ (M^+) 185.0244,

found (M^+)185.0246; CMR ($CDCl_3$) δ 42.6, 51.7, 122.1, 122.3, 138.8, 150.1, 154.5, 169.8; TLC (4:1, H:EA) R_f = 0.67.

2-Chloro-6-[bis-(methylthio)methyl]pyridine (4c): To a stirred solution of 6-chloro-2-picoline (2 g, 15.7 mmol) in 100 mL of THF was added *n*-BuLi (2.38 M in hexane, 17.3 mmol, 7.3 mL) at 0 °C. The mixture was stirred for 30 minutes. The temperature was lowered to -78 °C and dimethyl disulfide (1.63 g, 17.3 mmol) was added and the mixture was stirred at -78 °C for five hours. The crude mixture was poured into water and extracted with ether. The combined extracts were washed with saturated sodium chloride and dried over $MgSO_4$. The mixture was concentrated in vacuo. To a solution of the crude sulfide in THF (100 mL) was added n-BuLi (2.38 M in hexanes, 17.3 mmol, 7.3 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then the temperature was lowered to -78 °C and dimethyl disulfide (1.63 g, 17.3 mmol) was added. The mixture was stirred for five hours. The mixture was worked up as described above. The residue was purified by silica gel chromatography (30:1, H:EA) to give **4c** in 81% overall yield.

IR (film) 3399, 1617, 1558, 1405, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 4.85 (s, 1H), 2.15 (s, 6H); MS (CI, NH_3) m/e 141, 220; CMR ($CDCl_3$) δ 14.2, 56.9, 118.7, 122.7, 139.2, 149.8, 159.8; TLC (10:1, H:EA) Rf = 0.50.

2-Methoxy-6-[bis(methylthio)methyl]pyridine (4d): The bis-sulfide, **4c**, (429 mg., 2.0 mmol,) was heated in a sealed tube in a sodium methoxide solution (16 mmol, 1M in methanol) for three days at 120 °C. The crude mixture was concentrated in vacuo. The crude product was taken up in

water and neutralized. Then, the aqueous solution was extracted with methylene chloride, and dried over $MgSO_4$ to give the pure product in 57% yield.

IR (film) 2978, 1558, 1411, 1313, 1270 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 4.81 (s, 1H), 3.93 (s, 3H), 2.17 (s, 6H); MS (CI, NH_3) m/e 137, 168, 216; HRMS (EI) calcd for $C_9H_{13}NOS_2$ (M^+) 215.04386, found (M^+) 215.04348; CMR ($CDCl_3$) δ 13.7, 52.8, 57.5, 109.0, 113.4, 138.6, 156.3, 162.8; TLC (20:1, H:EA) Rf = 0.34.

2-Benzyloxy-6-[bis-(methylthio)methyl]pyridine (4e): The bis-sulfide, **4c**, (7.3 mmol, 1.61 g.) was placed in *tert*-butanol (7.3 mL). Benzyl alcohol (1.58 g, 14.6 mmol) and potassium t-butoxide (1.64 g, 14.6 mmol) were added and the mixture was heated in a sealed tube at 120 °C for two days. The mixture was concentrated in vacuo and the residue was taken up in water. The aqueous solution was neutralized by the addition of dilute HCl, and extracted with methylene chloride. The combined extracts were concentrated in vacuo. The crude product was purified by silica gel chromatography (70:1, H:EA) to give the benzyl ether in a 90% overall yield.

IR (film) 3063, 2914, 1699, 1559, 1456, 1266, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, J = 7.5 Hz, 1H), 7.49-7.46 (m, 2H), 7.38-7.29 (m, 3H), 6.96 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.38 (s, 2H), 4.81 (s, 1H), 2.13 (s, 6H); MS (CI, NH_3, negative ion) m/e 290; HRMS (EI) calcd for $C_{15}H_{17}NOS_2$ (M^+) 291.0752, found (M^+) 291.0755; CMR ($CDCl_3$) δ 14.0, 57.9, 67.4, 109.8, 114.0, 127.6, 128.0, 128.2, 137.2, 139.1, 156.5, 162.6; TLC (20:1, H:EA) R_f = 0.40.

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GENERAL CONCLUSION

The first section provides an introduction to huperzine A. It details the history and isolation of this new natural product. It describes its pharmacological properties and its potential therapeutic usage as a treatment for cholinergic disorders, such as Alzheimer's disease. Finally, it outlines the synthetic routes to this alkaloid. This section has shown that huperzine A is an interesting synthetic target and has been synthesized in moderate yield.

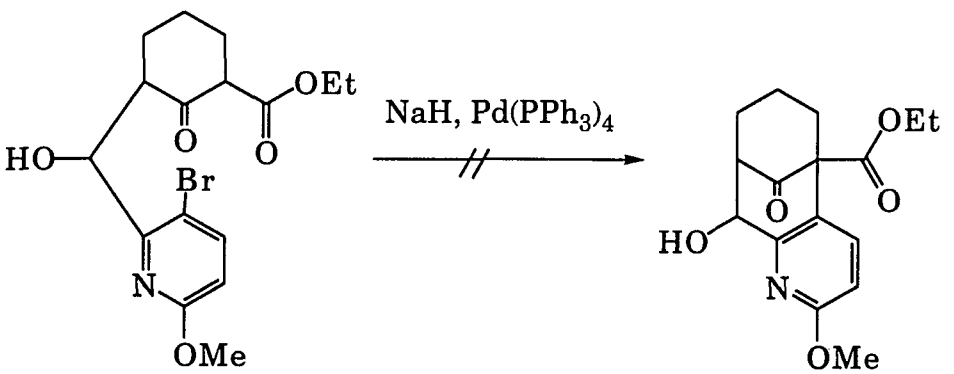
The first paper describes the use of a bridgehead enone methodology to prepare the natural product, huperzine A. By this method, the bicyclic framework can be prepared in six steps. Most of the compounds in this section were prepared by Jeff Hansen. My contribution involved spectral determinations, including 2D NOESY, IR, NMR, and MS.

The second paper describes a direct route to functionalized pyridones, which are structural subunits of huperzine A. By the conjugate addition of metallated alkyl pyridines, the synthesis of a pyridone compound is accomplished in two steps. This research has resulted in the discovery of a novel method of 1,4-addition using a side-chain metallated pyridine.

Throughout my research, I have explored many interesting and synthetically challenging routes to analogs of huperzine A. An alternative route not reported herein, but noteworthy nonetheless, involved the synthesis of the tricyclic core of huperzine A in one step from a functionalized β-keto ester (**I**). The cyclization was first attempted on the bromopyridine (**I**). The compound was reacted with sodium hydride and palladium tetrakistriphenyl-phosphine. The mechanism is thought to proceed by displacement of the

bromide by the palladium to form the heteroaromatic-palladium complex, which is subsequently attacked by the nucleophile of the enolate to form the cyclized product. However, this did not occur in our case. We obtained the product which resulted from retro-aldol cleavage (Scheme I).

Scheme I

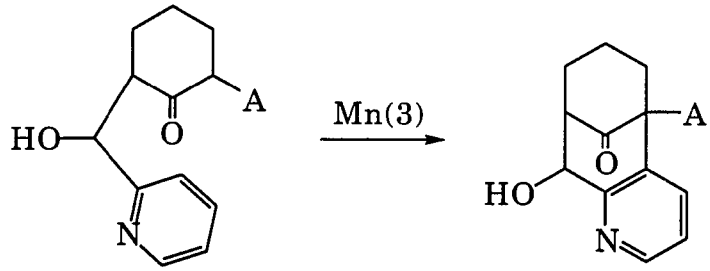


I

We next attempted the cyclization on the β-keto ester (**II**). The compound was reacted with manganese (III) acetate in acetic acid. The mechanism is thought to proceed through a manganese enolate which yields an enol radical. The radical formed attacks the pyridine nucleus to yield a pyridyl radical which is oxidized by manganese (III) acetate to the cation. Then, loss of a proton yields the pyridine ring. This reaction worked and gave the desired tricyclic compound in 50% yield (Scheme II).

Although this route gave us the tricyclic core to huperzine A, we needed a handle to introduce the endocyclic double bond. Furthermore, we were unable to improve the yield. Therefore, we focused our efforts on the conjugate addition series which would allow functionalization, such as an isopropylene moiety in the position of the endocyclic olefin. This would not

Scheme II



II

A = CO_2Et

only give us a unique analog to huperzine A, but also give us one in which the activity might be enhanced due to π-π interactions with aromatic residues in the active site of acetylcholinesterase.

For many years organic chemists have discussed and surmounted problems such as these. It is only through research involving many hours of experimental work that discoveries and insights are obtained. The preparation of this dissertation was based on those laborious and gratifying hours.

The future still holds many new strategies and methods of synthesis waiting to be discovered. If this work is helpful to fellow chemists in their pursuit of new knowledge, the main goal of this dissertation has been achieved.

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