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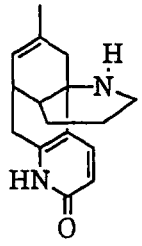
A BRIDGEHEAD ENONE APPROACH TO HUPERZINE A

George A. Kraus* , Jeff Hansen and Danette Vines
Department of Chemistry, Iowa State University, Ames, IA 50011

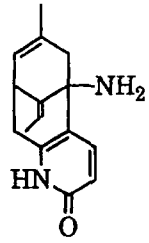
Abstract: The preparation of a bicyclic amino ketone for the synthesis of huperzine has been achieved in only six steps. The key step is the introduction of the primary amine moiety via a bridgehead enone.

Huperzine A was isolated from *Lycopodium serratum* and was characterized by Liu in 1986.[1] As a nootropic agent, it has the ability to enhance memory.[2] On the molecular level, it is a potent inhibitor



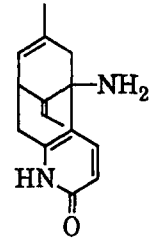
Huperzine B

2



Huperzine A

1



Z- Huperzine A

3

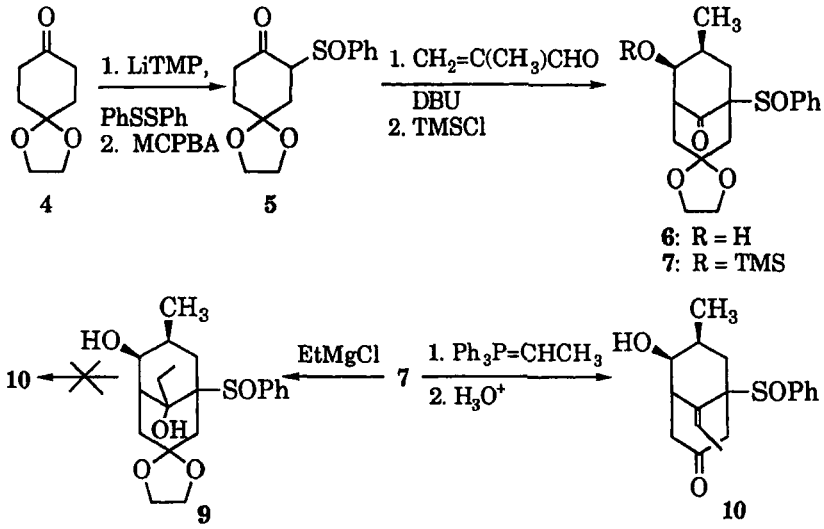
* To whom correspondence should be addressed.

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. Kozikowski has 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] Huperzine B (**2**), a related natural product, and Z-huperzine A (**3**) are both less active than **1**, implying that the primary amine and exocyclic alkene moieties might best be left intact when structural modifications are considered.[4]

Two previous syntheses of huperzine A have been achieved. Both the Ji synthesis[5] and the Kozikowski synthesis of huperzine and selected analogs[4] followed the same basic strategy. Our approach differs from the previous syntheses in that the pyridone ring is installed near the end of the synthesis and the amine is introduced via a bridgehead enone.[6]

Our approach begins with the commercially available mono ketal of 1,4-cyclohexanedione (**4**). Generation the enolate of **4** with lithium tetramethylpiperidide (LiTMP) in THF at -78 °C and trapping of the enolate with diphenyldisulfide provided a keto sulfide which was oxidized to sulfoxide **5** with MCPBA at 0 °C.[7] The bicyclic compound **6** was then constructed 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 is supported by the results of a 2D NOESY experiment on **10**.

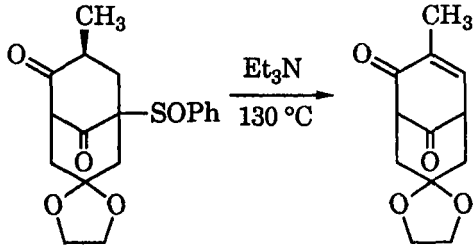
At this point, the hydroxyl group of **6** was protected in order to avoid a retroaldol cleavage during the Wittig reaction. The trimethylsilyl ether **7** was treated with ethylidenetriphenylphosphorane in THF to provide Z-olefin **8**, by analogy with the results obtained by Kozikowski in his synthesis of **1**. Unfortunately, the reaction was not reproducible, providing at best a 50% yield. Since the carbonyl group in **7** is somewhat hindered, it is possible that the Wittig reagent attacked the TMS group, thereby promoting a retroaldol reaction leading to the production of a labile keto aldehyde. In an attempt to circumvent this problem, ketone **7** was reacted with



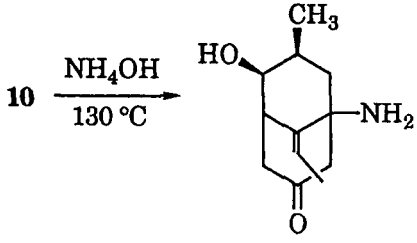
ethyl magnesium chloride to afford the tertiary alcohol **9** in quantitative yield. However, all attempts to convert the tertiary alcohol to keto sulfoxide **10** led to either recovered recovered starting material or to decomposition.

In order to investigate the feasibility of the bridgehead enone chemistry, ketal **8** was hydrolyzed to give **10**. Surprisingly, sulfoxide

10 did not eliminate, even at temperatures as high as 285 °C. This result is in dramatic contrast to our previous findings in the system shown below.[9]



The reluctance of 10 to eliminate under thermal conditions in the presence of primary amines prompted us to explore other ways to replace the bridgehead sulfoxide. We examined sulfoxide elimination using various bases. We discovered that heating bridgehead sulfoxide 10 in concentrated aqueous ammonium hydroxide in a sealable tube at 130 °C for three hours led to amine 11 in 73% yield. This reaction did not proceed in other polar solvents.



11

The synthesis of amino ketone 11 from sulfoxide 10 demonstrated that the amine could be introduced via a bridgehead enone. Completion of the synthesis requires the dehydration of the

secondary alcohol, isomerization of the exocyclic alkene and the regioselective appendage of the pyridone ring. Since both the elimination and the alkene isomerization reactions have close precedents from the Kozikowski synthesis, this direct approach has the potential to supply useful huperzine analogs.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

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 rt over 30 min. 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 min. The solution was slowly warmed to rt over 2 h. The solution was cooled to -15 °C and a solution of diphenyldisulfide in 20 mL of THF was added over a period of 10 min. The solution was stirred at rt for 8 h. 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 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 (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).

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 min. 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 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, 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).

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 min 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 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/z* 351, 368.

9-Ethylidene-7-methyl-1-(phenylsulfinyl)-6-(trimethylsilyl)oxy-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 min 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, 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, 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 min 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 rt for 16 h. 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, 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, 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 min, 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]nonane-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-methyl-bicyclo[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 h. 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, 1700, 1630, 1050 cm^{-1}; MS (NH_3 CI) *m/z* 210, 227.

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7. An alternate preparation which is easier for large scale preparations involves generation of the enol silyl ether with LDA and TMSCl in THF followed by reaction of the enol silyl ether with p-toluenesulfinyl chloride and tin tetrachloride.[8]

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