(1988-1990) and a Henry and Camille Dreyfus Teacher-Scholar Award (1988-1993).

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, and bond distances and angles for **3** (2 pages); table of final observed and calculated structure factors for **3** (6 pages). Ordering information is given on any current masthead page.

A Practical Synthesis of the Chinese "Nootropic" Agent Huperzine A: A Possible Lead in the Treatment of Alzheimer's Disease

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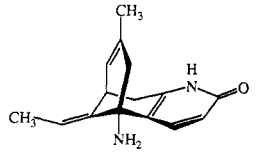
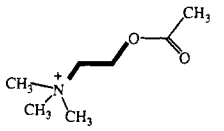
In this article we report the first total synthesis of the alkaloid huperzine A.[1] This tricyclic system represents one of nature's own contributions of a nootropic agent to mankind.[2] In studies carried out in China, huperzine A was found to improve memory and learning in animal models.[3] Of substantial interest was the finding that huperzine A could, in fact, improve memory in aged individuals suffering from various forms of memory impairment.[4] Pharmacologically, huperzine A functions as a potent inhibitor of the degradative enzyme, acetylcholinesterase, with a PI_{50} on acetylcholinesterase from erythrocyte membrane of 7.2.[5] In molecular graphics comparisons, the heteroatoms of acetylcholine in its completely extended {180°, 180°} conformation overlay well with those of huperzine A. This extended conformation is believed to be the one which is operative during hydrolysis by acetylcholinesterase.[6] Huperzine A is, in fact, more active than other well-documented acetylcholinesterase inhibitors such as physostigmine and neostigmine. Furthermore, the memory facilitating effects of huperzine A in higher order primates have been confirmed in studies carried out in the U.S. and Switzerland.



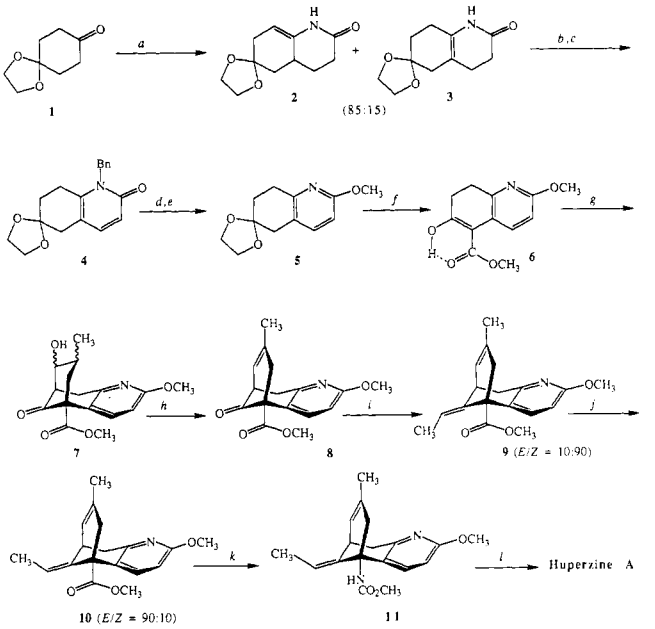
Huperzine A



Acetylcholine

In our program aimed at improving upon nature's original contribution of a nootropic agent, we have designed a short and practical route to this molecule. This route described below is sufficiently flexible to allow for the production of a variety of structural analogues.[7]

Scheme I.[a] Synthesis of Huperzine A



[a] (a) Pyrrolidine, PhH, *p*-TsOH (catalyst), reflux; acrylamide, dioxane, reflux; H_2O, dioxane, reflux (70% overall); (b) KH, BnCl, THF, room temperature (100%); (c) LDA, PhSeCl, THF, −78 °C; $NaIO_4$; Et_3N, MeOH, reflux (80%); (d) H_2, $Pd(OH)_2/C$, HOAc, room temperature (80%); (e) Ag_2CO_3, MeI, $CHCl_3$, room temperature (92%); (f) 5% HCl, acetone, reflux (85%); KH, $(MeO)_2CO$, reflux (87%); (g) methacrolein, tetramethylguanidine, CH_2Cl_2, room temperature (93%); (h) MsCl, Et_3N, DMAP, CH_2Cl_2 (96%); NaOAc, HOAc, 110 °C, 24 h (50%); (i) $Ph_3P{=}CHCH_3$, THF, 0 °C to room temperature (73%); (j) PhSH, AIBN, 170 °C, 24 h (100%); (k) 20% NaOH, THF, MeOH, reflux, 2 days (78% based on *E* ester); $SOCl_2$, toluene, 80 °C, 2 h; NaN_3, 80 °C; MeOH, reflux (80% overall); (l) TMSI, $CHCl_3$, reflux (92%).

The synthesis (Scheme I) begins by annealing a pyridone ring to the monoethylene ketal of 1,4-cyclohexanedione. This is done by reacting the pyrrolidine enamine of **1** with acrylamide in dioxane followed by refluxing with aqueous dioxane.[8] A mixture of the double bond regioisomers **2** and **3** (**2**/**3** = 85/15) is isolated in 70% yield. The ring nitrogen is next protected by *N*-benzylation and dehydrogenation to the pyridone system **4** brought about by α-selenenylation followed by oxidative elimination and base-catalyzed isomerization.[9] While a variety of logical transformations were subsequently examined using this N-protected pyridone, these all proved problematic as a consequence presumably of the instability of the pyridone ring. On several occasions aromatization of the cyclohexane ring was found to take place. Far better results were achieved on protecting the pyridone ring system on oxygen rather than nitrogen and carrying the fully aromatic methoxypyridine derivative on in the synthesis. Accordingly, pyridone **4** was debenzylated using palladium hydroxide in acetic acid and O-methylation brought about with silver carbonate and methyl iodide. Next, the ketal group of **5** was removed by aqueous acid hydrolysis, and the free ketone was then carbomethoxylated at its doubly activated site by heating with potassium hydride and dimethyl carbonate.[10]

While several methods were studied to introduce the unsaturated carbon bridge, we were most pleased to find that methacrolein could be added across the β-keto ester **6** in a single pot reaction

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if 1,1,3,3-tetramethylguanidine (TMG) was employed as the catalyst.[11] The yield of stereoisomeric bridged products was >90%. Elimination of the hydroxyl group could be effected in reasonable yield by refluxing the derived mesylate in acetic acid with sodium acetate for 1 day.[12] Olefin **8** was isolated in ~50% yield in addition to some of the unreacted mesylate possessing equatorial methyl and mesylate groups.

A Wittig reaction with ethylidenetriphenylphosphorane proceeded readily to afford the trisubstituted olefin **9** of predominantly *Z* stereochemistry, a stereochemical result reminiscent of that found for α-oxygenated cyclohexanones.[13] The *Z*/*E* mixture was isomerized to a mixture **10** comprised predominantly of the *E* olefin (90:10 ratio) by heating with thiophenol and AIBN.[14] Interestingly, hydrolysis of the *E*/*Z* mixture of esters could be carried out to provide solely the acid of *E* stereochemistry in addition to the unreacted, more sterically encumbered ester of *Z* olefin stereochemistry.

The acid was treated sequentially with thionyl chloride, sodium azide, and methanol to provide the urethane **11** through the Curtius rearrangement.[15] Lastly, trimethylsilyl iodide was employed to effect both N- and O-deprotection.[16] Huperzine A, isolated in racemic form, was identical with the natural material by 300 MHz NMR, IR, and mass spectral analysis.[17,18] Furthermore, racemic huperzine A was found to be nearly equipotent to natural huperzine A in its inhibition of rat brain acetylcholinesterase.[19]

In summary, the synthesis developed for this important natural product is relatively efficient, an accomplishment dependent upon the remarkable ability of TMG to catalyze the tandem Michael/aldol sequence. Current efforts are aimed at improving upon the biological profile of this nootropic agent through computer aided structural modification of the huperzine A molecule. Efforts to identify more effective anticholinesterase-based therapies for the palliative treatment of Alzheimer's dementia lie at the heart of these efforts.

Acknowledgment. We are indebted to Professor J.-S. Liu of the Shanghai Institute of Materia Medica for a sample of natural huperzine A. We thank the National Institute on Aging (Grant No. IR01AG07591) for their generous support of our program. Y. Xia thanks the University of Pittsburgh for an Andrew Mellon Predoctoral Fellowship (1986–1988).

Supplementary Material Available: R_f, IR, NMR, and mass spectral data for compounds **2–11** and huperzine A (5 pages). Ordering information is given on any current masthead page.

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(17) Satisfactory spectroscopic data (including ^{1}H NMR, IR, high resolution MS, and/or ^{13}C NMR) were obtained for all intermediates.

(18) Dr. D. W. Armstrong of the University of Missouri-Rolla has found that a cyclodextrin-bonded phase column can be used to separate racemic huperzine A into its enantiomers on an analytical scale. We thank him and H. L. Jin for carrying out these studies. Efforts to resolve huperzine A by classical methods of diastereomeric salt formation have so far proven unsuccessful.

(19) The cholinesterase studies were conducted by Dr. Israel Hanin of Loyola University Stritch School of Medicine on a subcontract from NIA Grant No. 1R01AG07591. Huperzine A has also been found to have an action at the NMDA receptor complex by Dr. German Barrionuevo of the Behavioral Neuroscience Department of the University of Pittsburgh. A full report on the biological activity of huperzine A and its analogues will be published separately.

Reactions of the (η^3-Allyl)iron Tricarbonyl Anion with Carbon Electrophiles

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Numerous synthetically useful carbon–carbon bond-forming reactions are based on the fact that unsaturated hydrocarbon ligands bound to neutral or cationic metal carbonyl moieties are activated toward addition of nucleophiles.[1] Recently, several reports have described the complementary approach: activation of unsaturated hydrocarbons toward electrophilic attack by complexation with anionic metal carbonyl fragments. Examples of such anionic complexes which form carbon–carbon bonds upon reaction with carbon electrophiles include diene-$Mn(CO)_3^-$,[2] cyclohexadienyl-$Cr(CO)_3^-$,[3] cycloheptadienyl-$Fe(CO)_2^-$,[4] (arene)$Mn(CO)_2^-$,[5] $Cr(CO)_2(arene)^{2-}$,[6] and η^4-$C_8H_8Mn(CO)_3^-$.[2e,f] Attack of the electrophile is usually endo[2-5] suggesting the intermediacy of metal alkyl complexes which have been observed in certain cases.[5] Acyl products are isolated in some systems indicating CO insertion prior to metal-to-ligand migration.[3-5] We report here a synthetic and mechanistic study of the reaction of the simple anionic allyl complex, η^3-$C_3H_5Fe(CO)_3^-$, **1**, with alkyl halides which leads to α,β- or β,γ-unsaturated ketones.

Treatment of η^3-$C_3H_5Fe(CO)_3^-Na^+$ (**1**)[7] with alkyl halides in THF (0 °C, 10–20 min) followed by addition PPh_3 (2 equiv, 25 °C, 2–6 h) gives α,β-unsaturated ketone complexes, (η^4-enone)-$Fe(CO)_2(PPh_3)$, **2** (see Scheme I).[8] Results using several alkyl halides are summarized in Table I. The complexes obtained with PPh_3 are exclusively the trans isomers (≥95%); yields are good for both primary and secondary halides.

Substantial evidence has been obtained for the reaction pathway shown in Scheme I. Thermally unstable allyliron tricarbonyl alkyl complexes **3a,b** have been obtained and spectroscopically char-

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(8) All new compounds were characterized by ^{1}H and ^{13}C NMR and IR spectroscopy and combustion analysis. Details are given in Supplementary Material. Some spectropic data for selected compounds are as follows: η^4-[CH_3CH=$CHCOCH_3$]$Fe(CO)_2PPh_3$, **2a**; IR ν_{max} (THF) 1990, 1930, 1835, 1475, 1435 cm^{-1}; ^{1}H NMR (C_6D_6, δ) 7.78–7.65 (m, 5 H, Ph), 7.10–6.95 (m, 10 H, 2 Ph), 4.82 (dd, J_{H-P} = 2.3 Hz, J = 8.2 Hz, 1 H, =C*H*CO), 2.10 (d, J_{H-P} = 2.5 Hz, 3 H, $COCH_3$), 1.62–1.50 (m, 1 H, CH_3CH=), 1.10 (dd, J = 1.8, 6.4 Hz, 3 H, CH_3CH=); ^{13}C NMR (C_6D_6, δ, decoupled) 17.1 (CH_3CH=), 21.1 ($COCH_3$), 55.2 (CH_3CH=), 84.2 (=*C*HCO). Anal. Calcd for $C_{25}H_{23}O_3FeP$: C, 65.52; H, 5.06. Found: C, 65.59; H, 5.37. η^4-[CH_3CH=$CHCOCH_2Ph$]$Fe(CO)_2PPh_3$, **2b**: IR ν_{max} (THF) 1990, 1925, 1470, 1430 cm^{-1}; ^{1}H NMR (C_6D_6, δ) 7.78–7.68 (m, 5 H, Ph), 7.11–6.98 (m, 15 H, 3Ph), 4.95 (dd, J_{H-P} = 2.0 Hz, J = 8.4 Hz, 1 H, =C*H*CO), 4.04, 3.69 (ABq, J_{H-P} = 1.7 Hz, J = 14.8 Hz, 2 H, CH_2Ph), 1.52 (dq, J = 2.0, 7.3 Hz, 1 H, CH_3CH=), 0.99 (dd, J = 0.6, 7.3 Hz, 3 H, CH_3CH=); ^{13}C NMR ($CDCl_3$, δ, decoupled) 17.6 (CH_3CH=), 42.4 ($COCH_2Ph$), 56.5 (CH_3CH=), 85.0(=*C*HCO). Anal. Calcd for $C_{31}H_{27}O_3FeP$: C, 69.67; H, 5.09. Found: C, 69.80; H, 5.12.

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