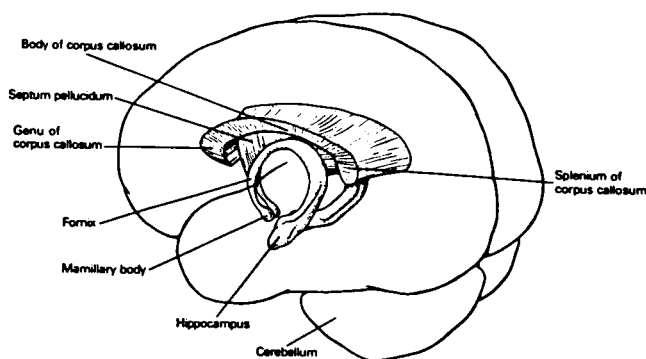


Alan P. Kozikowski

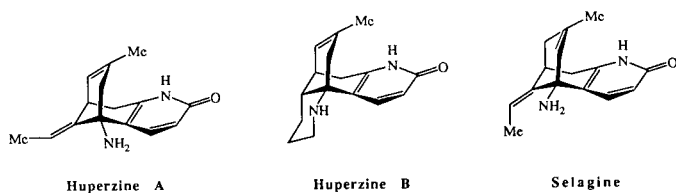
Departments of Chemistry and Behavioral Neuroscience, University of Pittsburgh,
Pittsburgh, PA 15260*J. Heterocyclic Chem.*, **27**, 97 (1990).

In recent years we have begun a program of the synthesis of molecules for use either in facilitating learning and memory processes in man, or for use as molecular probes in trying to better understand the mechanisms of memory processing in the brain [1]. The hippocampal formation, the seahorse shaped structure of the brain (Figure 1), serves as one of the primary conduits in memory processing, and later I shall mention this brain region again when I turn to the involvement of protein kinase C in the phenomenon of long term potentiation (LTP), one of the best models of memory currently available [2].

FIGURE 1. THE BRAIN

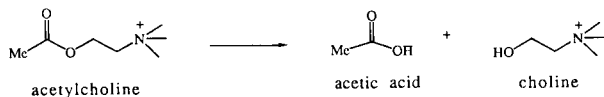


SCHEME 1. HUPERZINE A AND B



Lycopodium alkaloids isolated from *Huperzia serrata* (Thunb.)
Trev. = *Lycopodium serratum* Thunb., a Chinese folklore medicine

Huperzine functions as a cholinesterase inhibitor



activity: huperzine A > physostigmine > neostigmine > huperzine B

Huperzine A has been shown to improve memory and learning in animal models and to improve memory of aged individuals.

The first molecule I would like to talk about is a natural product isolated by workers at the Shanghai Institute of Materia Medica which is known as huperzine A [3]. The structures of huperzine A and its congener huperzine B are shown in Scheme 1. These compounds were isolated from a clubmoss (Figure 2) indigenous to China known as *Huperzia serrata*

FIGURE 2. THE CHINESE CLUBMOSS CONTAINING HUPERZINE A.



(Thunb.) Trev. = *Lycopodium serratum* Thunb., a Chinese folk medicine, Qian Ceng Ta, known to have certain memory restorative properties. In biological studies carried out in China, huperzine A was shown to improve animal performance in Y-maze experiments, to be useful in treating myasthenia gravis in humans, and to help alleviate the memory problems of aged individuals and those afflicted with Alzheimer's dementia [4]. A compilation of the Chinese studies is presented in Scheme 2, while a summary of the biological findings on huperzine A in studies carried out at Hoffmann-LaRoche is presented in Scheme 3 [5]. Huperzine A is a close structural relative of another pyridone bearing alkaloid, selagine, whose structure is displayed in Scheme 1.

Pharmacologically, huperzine A has been found to function as a very potent inhibitor of the brain enzyme, acetylcholinesterase. Structurally, huperzine A shows some resemblance to other known cholinesterase inhibitors, such as neostigmine, physostigmine, and pyridostigmine shown in Scheme 4. These latter three inhibitors are capable of carbamylating

SCHEME 2. CHINESE STUDIES

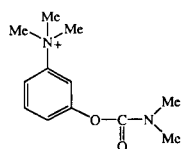
1. **Structure Determination**, Liu *et al.*, *Can. J. Chem.*, **64**, 837-839 (1986).
2. **Anticholinesterase Action**, 3X physostigmine, Tang *et al.*, *Acta Pharm. Sin.*, **7**, 110-113 (1986).
3. **Y-maze**---facilitation of learning and retrieval in rats by administration of 167 $\mu\text{g/kg}$ i.p. 20 min before training, Wang *et al.*, *Acta Pharm. Sin.*, **7**, 507-511 (1986).
4. **100 aged individuals** (46-82 years) suffering from memory impairment including Alzheimer's disease showed improvement 1-4 h after injection with improvement being sustained for 8 h; therapeutic dose is 30 mg, hydergine is 600 mg; Zhang, *New Drugs and Clinical Remedies*, **5**, 2560 (1986).
5. **128 cases of patients** with myasthenia gravis were treated with Hup A instead of prostigmine, 99% had the clinical manifestations of their disease controlled; Hup A duration of action 7 ± 6 h, while prostigmine was 4 ± 5 h. Side effects, dizziness, sweating, blurring of vision were less than observed with prostigmine, *New Drugs and Clinical Remedies*, **5**, 197-199 (1986).

SCHEME 3. HOFFMANN-LAROCHE DATA

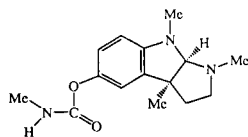
Huperzine A: 3 X potency of physostigmine

1. In CFl mice, Hup-A protected against electro-brain-shock disruption in retrieval of an active avoidance response:
active at doses of 0.001 - 0.01 mg/kg i.p.
physostigmine active at 0.1mg/kg i.p.
hup A also active orally at dose of 0.003 mg/kg and only at a 60 min pretreatment time.
2. Hup A also reverses scopolamine (1 mg/kg) induced amnesia for the retention of a passive avoidance response:
active at 0.00003 - 0.001 mg/kg s.c., also active orally from 0.1 - 1 mg/kg; therapeutic window of physostigmine is narrower, from 0.005 - 0.001 mg/kg
3. Hup A also improved accuracy of retention by 5-13% at doses of 0.003 - 0.03 mg/kg i.m. in squirrel monkeys on a delayed match-to-sample procedure.

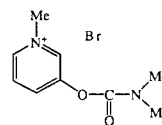
SCHEME 4. OTHER ACETYLCHOLINESTERASE INHIBITORS



Neostigmine (prostigmine)



Physostigmine

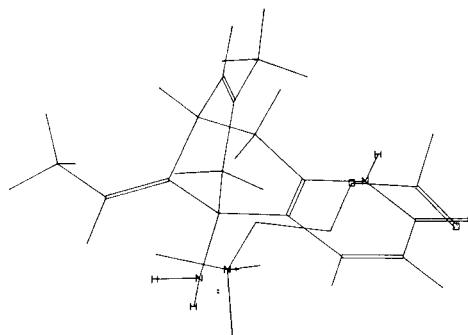


Pyridostigmine Bromide

the serine hydroxyl group present in the active site of the cholinesterase enzyme. The carbamylated enzyme undergoes hydrolysis much more slowly than does the (acetylcholine) acetylated form [6]. While one might suggest a similar role for huperzine A in regard to its ability to bond covalently to the enzyme, this is somewhat unlikely given the general lack of susceptibility of the pyridone ring to nucleophilic attack [7]. No irreversible inhibition of acetylcholinesterase by huperzine A was, in fact, observed in our biological experiments.

The ability of huperzine A to function as a potent inhibitor of the cholinesterase enzyme (3x physostigmine) is not surprising, for a computer-generated overlay of this natural product with the fully extended conformation of acetylcholine, the conformation believed to be relevant to recognition by this degradative enzyme [8], shows a good coincidence of the key heteroatoms (Figure 3). Since some of the machinery responsible for the production of acetylcholine in the brain is lost or damaged in the Alzheimer's afflicted individual, the study of inhibitors of acetylcholinesterase as palliative agents in the treatment of this disease has captured the attention of many pharmaceutical researchers [9]. By inhibiting the degradation of acetylcholine to acetate ion and choline in the Alzheimer's brain, higher local concentrations of this neurotransmitter can be achieved, thus permitting appropriate activation of postsynaptic receptors and the initiation of intracellular signaling events. The inhibition of acetylcholinesterase can also allow for the removal of acetylcholine from the synaptic cleft by reuptake mechanisms, processes which in effect allow for the recycling of the acetylcholine.

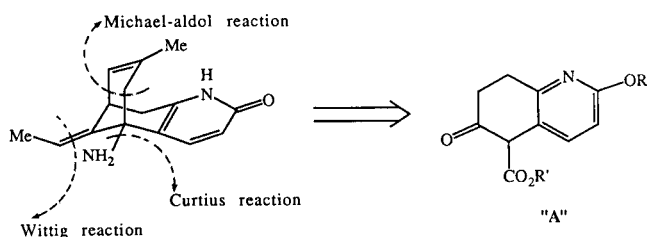
FIGURE 3. A MACROMODEL GENERATED SUPERPOSITION OF ACETYLCHOLINE AND HUPERZINE A.



In order to make huperzine A more widely available for biological evaluation, as well as to rapidly construct analogues of it to discover whether one can further optimize its enzyme inhibitory action, we have devised a method for preparing the compound in the laboratory. A synthesis of huperzine A is important, for the compound can be obtained from the Chinese clubmoss in but limited amounts. In conceptualizing an approach to huperzine A, we decided to build a fused ring pyri-

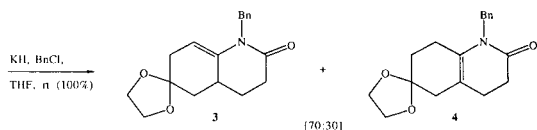
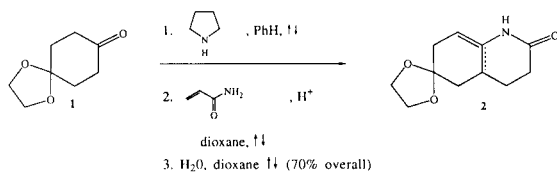
dine structure "A" first, and then to construct the unsaturated carbon bridge, possibly through a combined Michael/aldol process (Scheme 5). The synthesis of the fused ring pyridone

SCHEME 5. A RETROSYNTHETIC ANALYSIS

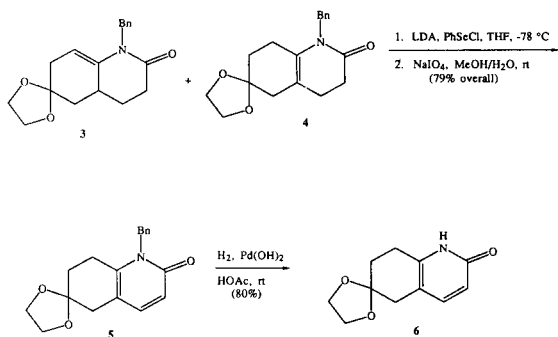


is presented in Schemes 6-8 starting from commercially available 1,4-cyclohexanedione monoethylene ketal. The selenylation/selenoxide elimination reaction used to adjust the oxidation state of the lactam ring was found to proceed best if the lactam nitrogen was protected by prior benzylation. While many experiments to employ the *N*-protected pyridone 5 of Scheme 7 in further reactions were made, we discovered that this intermediate was more easily handled in its fully aromatic pyridine form. Accordingly, the benzyl group of 5 was cleaved by hydrogenolysis, and the free pyridone methylated on oxygen by the use of methyl iodide and silver carbonate.

SCHEME 6. GENERATION OF THE PYRIDONE RING

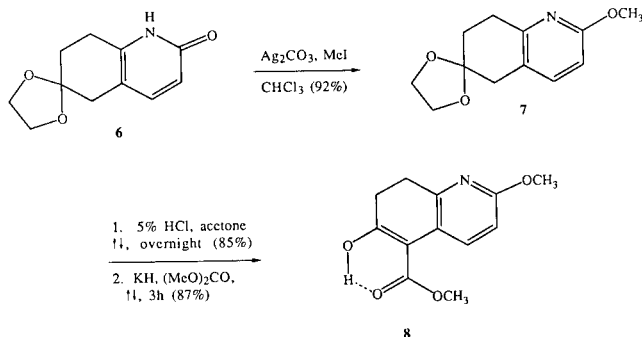


SCHEME 7



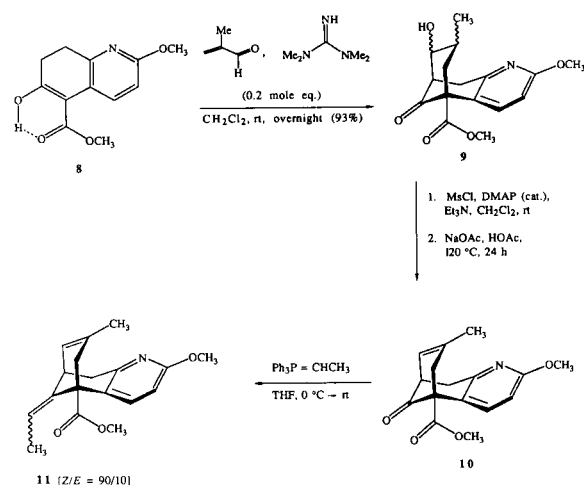
In contrast to the *N*-benzylpyridone 5, the methoxypyridone 7 underwent a facile α -carbomethoxylation reaction to provide intermediate 8 (Scheme 8). This carbomethoxy group

SCHEME 8



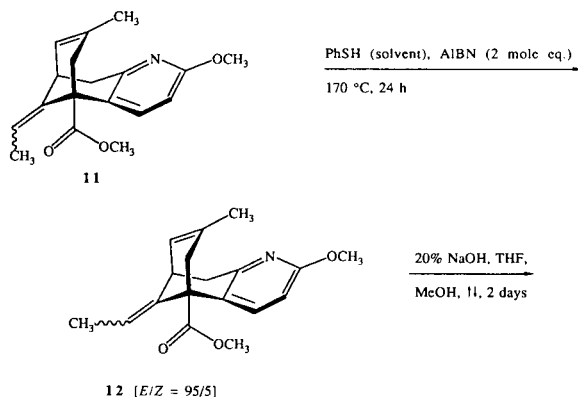
was to serve not only as an important handle for introducing the exocyclic amino group of huperzine A, but it would also facilitate introduction of the carbon bridge. Initial efforts to carry out the Michael/aldol reaction between keto ester 8 and methacrolein using triethylamine, sodium methoxide, tetrabutylammonium fluoride, zinc chloride, or acetic acid as catalysts failed, and several multistep processes for accomplishing the introduction of this four-carbon unit were devised. However, when the combined Michael/aldol sequence was given another try employing 1,1,3,3-tetramethylguanidine (TMG) as the base catalyst [10], the desired reaction (8 \rightarrow 9, Scheme 9) was found to proceed in >90% yield. Certainly, the TMG catalyzed reaction must owe some of its success to the higher basicity of the guanidine in comparison to the basicity of triethylamine. The charge delocalized character of the conjugate acid of TMG may also provide an intermediate suitable for pairing with and stabilizing the enolate anion formed in the Michael addition step.

SCHEME 9. INTRODUCTION OF THE BRIDGE



At this stage, completion of the huperzine A synthesis required the execution of some fairly routine chemical steps. A Wittig reaction was carried out with ethylenetriphenylphosphorane to afford primarily the alkene 11 of incorrect *Z*-stereochemistry (Scheme 9). The olefin was then readily isomerized by heating with AIBN in thiophenol to provide primarily the desired *E*-isomer 12 (Scheme 10). Lastly, the ester

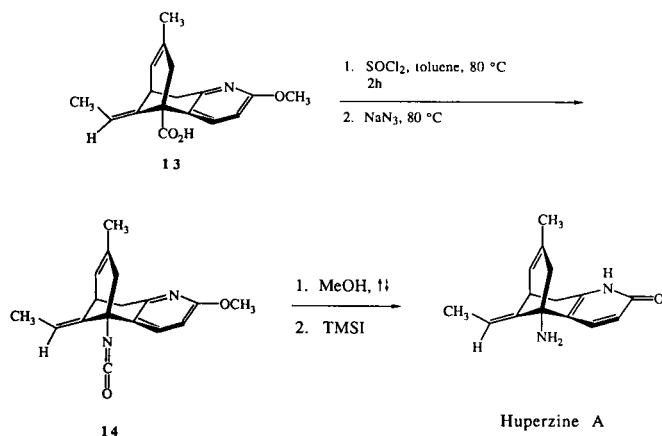
SCHEME 10. EXO-OLEFIN ISOMERIZATION



13 all E; Z-ester is recovered
and recycled

was hydrolyzed, converted to its acid chloride, and reacted with sodium azide and then methanol to provide the urethane derived from the isocyanate **14** (Scheme 11). Notably, the ester of incorrect olefin geometry for conversion to huperzine A failed to undergo hydrolysis to the acid under these reaction conditions, thus providing a simple means for removing the undesired product from the reaction gemisch. Racemic huperzine A was readily obtained from the urethane by trimethylsilyl iodide treatment. The synthetic material was fully identical spectroscopically with the natural product obtained as a gift from Dr. J.-S. Liu of the Shanghai Institute of Materia Medica.

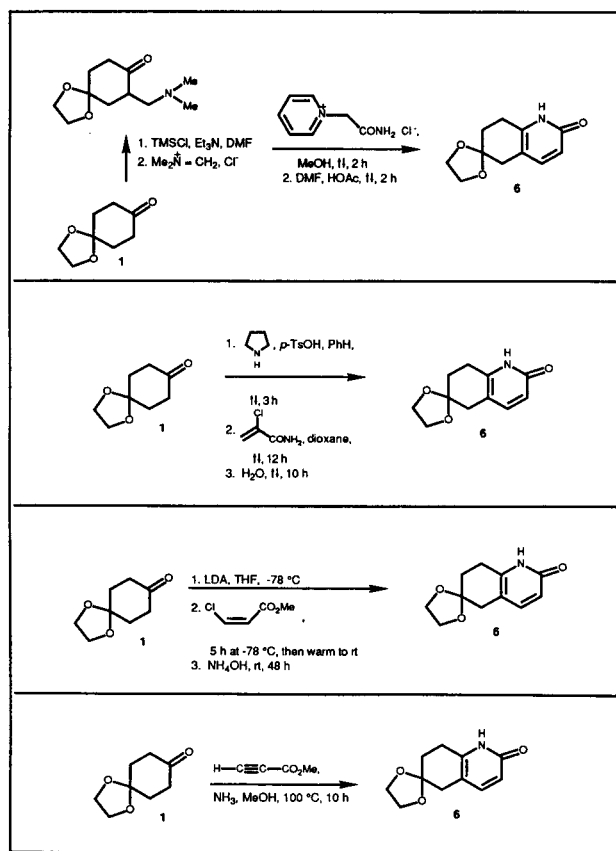
SCHEME 11. COMPLETION OF THE SYNTHESIS



While our synthesis is fairly efficient, 12-13 synthetic steps, we felt that further improvements could be made. In particular, the chemistry used to produce the ring fused pyridone **6** was awkward, and involved the use of expensive reagents,

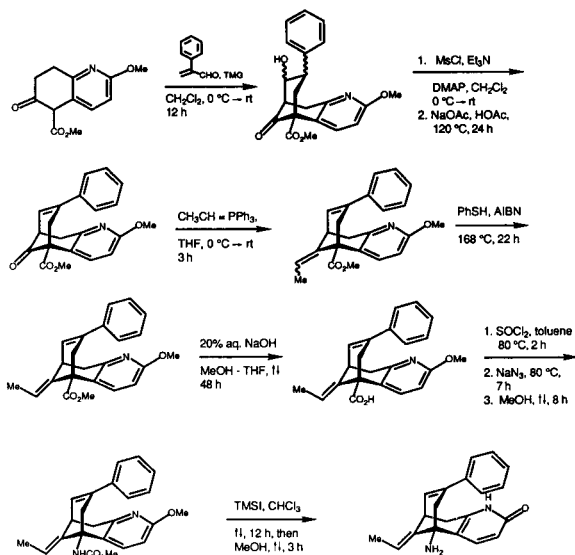
phenylselenenyl chloride and palladium hydroxide. Accordingly, simpler methods for procuring this valuable starting template were needed. Some of the chemistry which we tried is presented in Scheme 12. Of the four processes displayed, the last method, a one-pot, three-component condensation reaction was the best. It can be carried out in 70% yield by simply admixing the 1,4-cyclohexanedione monoethylene ketal and methyl propiolate in ammonia-saturated methanol in a Parr reactor and heating to 100°C for 10 hours. The reaction appears to be general for cyclic ketones as shown by its application to cyclopentanone, cycloheptanone, and α -tetralone. In summation, this pyridone ring forming process, which bears some resemblance to an earlier method reported by Speckamp which starts from an enamino ketone [11], considerably shortens the overall huperzine synthesis, for four of the original steps of the synthesis are replaced by a single, easy to carry out, one pot process [12].

SCHEME 12. ALTERNATIVE ROUTES TO THE PYRIDONE 6



In view of the brevity of the present synthesis, the preparation of analogues of huperzine A can be readily accomplished. While an enantioselective version of the synthesis is currently under study, we have already prepared over a dozen analogues of this natural product, and have or are currently examining the activity of these materials on the inhibition of rat brain acetylcholinesterase. A synthesis of the phenyl bearing analogue is presented in Scheme 13 [13]. Some of the other analogues of huperzine A prepared to date are drawn in Scheme 14. A dose response curve of the inhibition of acetylcholinesterase by synthetic and racemic huperzine A and several of

SCHEME 13. SYNTHESIS OF A PHENYL ANALOGUE OF HUPERZINE A



SCHEME 14. SOME ANALOGUES OF HUPERZINE A

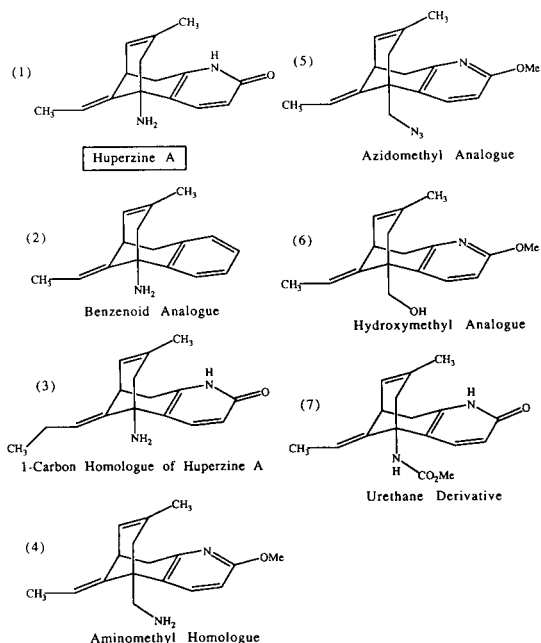
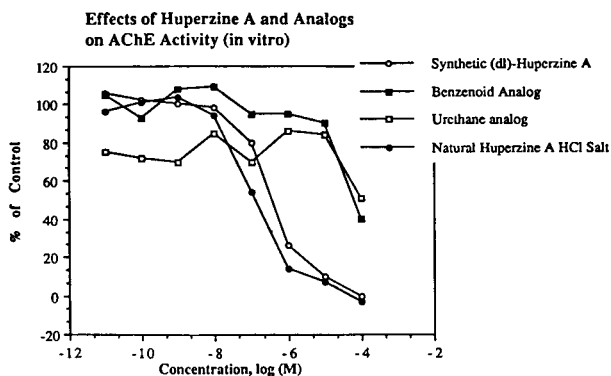


FIGURE 4



the other analogues is shown in Figure 4. Additionally, a compilation of the EC_{50} 's of several of the analogues is presented in Table 1 [14]. As can be discerned, none of the new analogues are better cholinesterase inhibitors than huperzine A itself. While we have not yet been able to improve upon Nature's contribution of a nootropic agent to mankind, we remain optimistic that this may still be possible.

TABLE 1. EXTENT OF CHOLINESTERASE INHIBITION BY THE COMPOUNDS TESTED

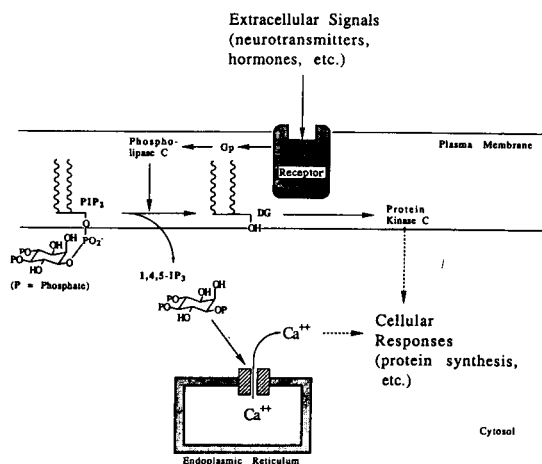
| Compound Number | Structural Name | M.W. | IC_{50} | $\text{IC}_{50}/\text{IC}_{50}$ Synthesized Huperzine A* |
|-----------------|-------------------------|------|----------------------------|--|
| 0 | Natural Huperzine A | 242 | 10^{-7}M | - |
| 1 | Synthesized Huperzine A | 242 | $6 \times 10^{-7}\text{M}$ | 1.0 |
| 2 | Benzenoid Analogue | 225 | $8 \times 10^{-5}\text{M}$ | 133.3 |
| 3 | 1-Carbon Homologue | 256 | 10^{-4}M | 166.6 |
| 4 | Aminomethyl Homologue | 270 | No Activity | ∞ |
| 5 | Azidomethyl Analogue | 296 | No Activity | ∞ |
| 6 | Hydroxymethyl Analogue | 271 | Not tested | - |
| 7 | Urethane Derivative | 300 | $2 \times 10^{-4}\text{M}$ | 333.3 |

*The smaller this number, the more potent the compound.

The synthetic huperzine A is presently being studied in Pittsburgh and at the Loyola University School of Medicine in various animal memory paradigms. It is our hope that huperzine A will continue to show promise as a memory enhancer, for agents capable of alleviating some of the symptoms of Alzheimer's dementia can ease the tremendous human and monetary burden associated with the care of afflicted individuals [15].

Let us now turn to another area of neuroscience, that of trying to understand the nature of the intracellular processes involved in, if you will, the laying down of memory traces. Once a neurotransmitter like acetylcholine binds to its receptor, the external binding event must be transduced through the cellular membrane to provide for an internal signal, which, for example, leads to the transcription and translation of DNA and the production of new proteins products such as nerve growth factor, or even more acetylcholine receptors. In recent years, the phosphatidylinositol cascade has been shown to

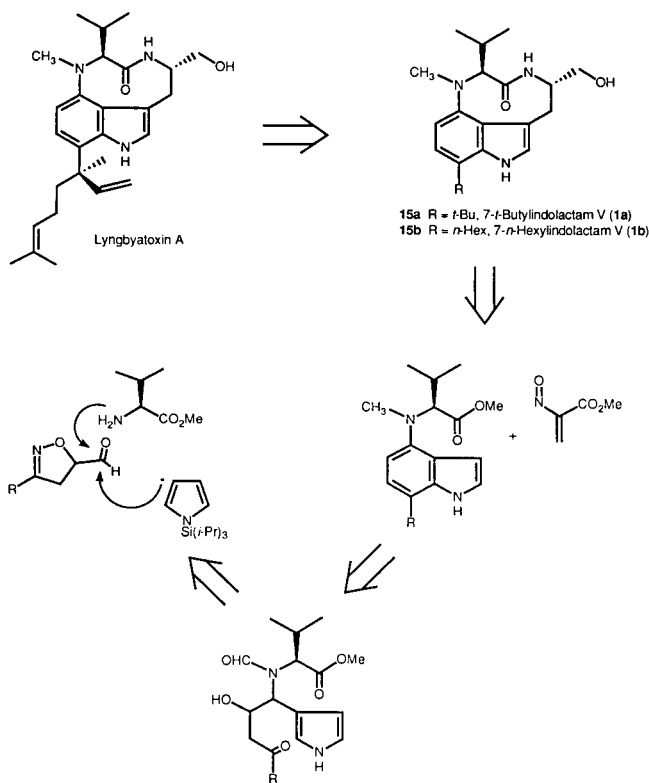
SCHEME 15. MECHANISM OF CELLULAR SIGNAL TRANSDUCTION BY THE INOSITOL PHOSPHATE PATHWAY



play a major role in processes related to hormone, peptide, or neurotransmitter stimulated cell signaling events. The phosphatidylinositol cascade is triggered by the action of a phospholipase C, which degrades membrane phosphoinositides to form inositol polyphosphates and diacylglycerol. The first of these second messenger molecules is known to mobilize intracellular calcium pools, while the second activates protein kinase C (PKC), an enzyme which phosphorylates specific protein targets (Scheme 15) [16]. Recent electrophysiological evidence also substantiates the involvement of protein kinase C, at least in the hippocampus, in the phenomenon of long term potentiation (LTP), a process involving a sustained increase in synaptic efficacy as the consequence of the tetanic stimulation of an afferent input. LTP is currently considered to provide one of the best models of memory available. In the past few years considerable effort has been expended in examining the effects of activators (*e.g.* tumor promoters such as the phorbol esters) and inhibitors (*e.g.* sphingosine, melittin, polymixin B and K-252b) of PKC on the development of LTP, and evidence has been garnered which suggests that PKC activation is crucial to the development of the late, non-decremental phase of LTP [17]. The early, decremental phase of LTP, in fact, appears to require activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, a class of brain receptors recognized to play a key role in learning and memory processes [18]. However, in spite of many sophisticated experiments, the involvement of PKC in memory still remains somewhat controversial, for many concerns exist as to the pharmacological specificity of the agents used in these studies.

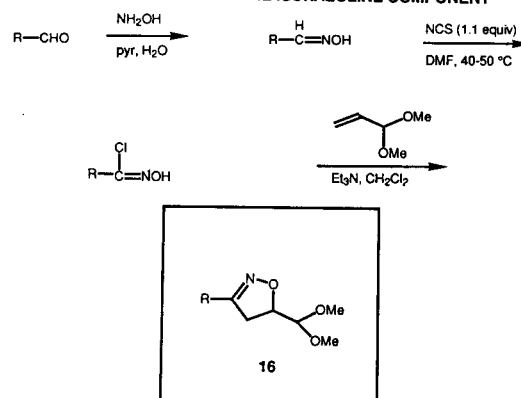
Accordingly, we have undertaken a program to discover new modulators of PKC which are based on the structure of

SCHEME 16. SIMPLIFICATION OF THE LYNGBYATOXIN A STRUCTURE

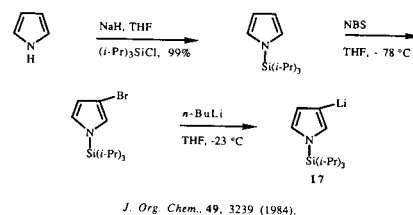


lyngbyatoxin A, a natural product first described by Moore which is known to be a potent tumor promoting agent and a very strong activator of this kinase [19]. New modulators of PKC would be of value not only as tools for the studying the links between PKC and LTP, but, moreover, may provide new leads in cancer therapy as well [16]. In order to produce such compounds in the laboratory efficiently, we chose to modify the lyngbyatoxin structure by replacing its more complex linalyl group by a *n*-hexyl or *t*-butyl group. Our initial targets thus became the structures 15a and 15b, for which a retrosynthetic analysis is detailed in Scheme 16. As diagrammed in Schemes 17-19, the methyl ester of valine is condensed with an isoxazolinecarbaldehyde 16, formed in a dipolar cycloaddition reaction of nitrile oxide with acrolein dimethyl acetyl, and the resulting imine treated with the β -lithiopyrrole 17 to afford 18. Appropriate processing of this intermediate by *N*-formylation, desilylation, Raney nickel hydrogenolysis and aromatic annelation then provides the optically

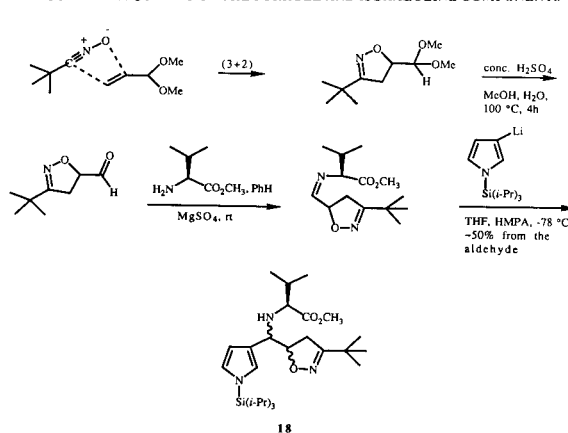
SCHEME 17. PREPARATION OF THE ISOXAZOLINE COMPONENT



SCHEME 18. PREPARATION OF *N*-(TRIISOPROPYLSILYL)- β -LITHIOPYRROLE

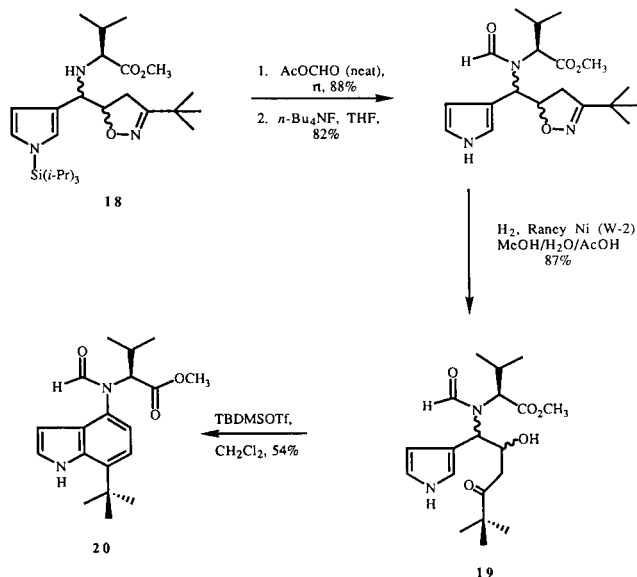


SCHEME 19. JOINING OF THE PYRROLE AND ISOXAZOLINE COMPONENTS

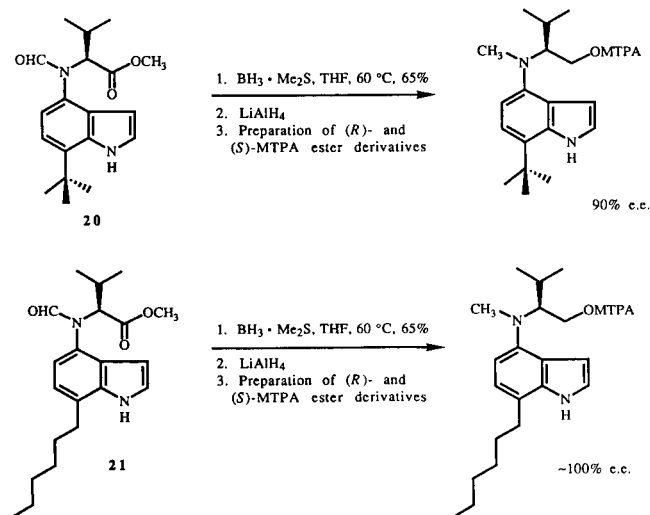


active indole **20** (Scheme 20). The optical purity of these indoles was checked by NMR analysis of the MTPA ester derivatives of their derived alcohols (Scheme 21). Completion of

SCHEME 20. PREPARATION OF THE KEY 4-AMINO-7-ALKYL SUBSTITUTED INDOLE

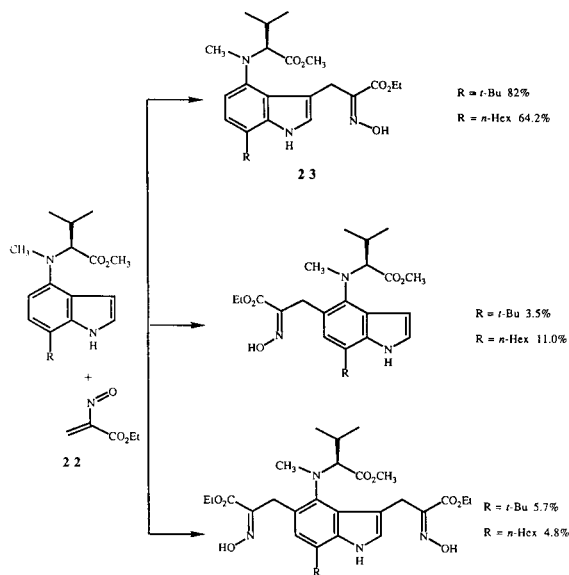


SCHEME 21. DETERMINATION OF OPTICAL PURITY

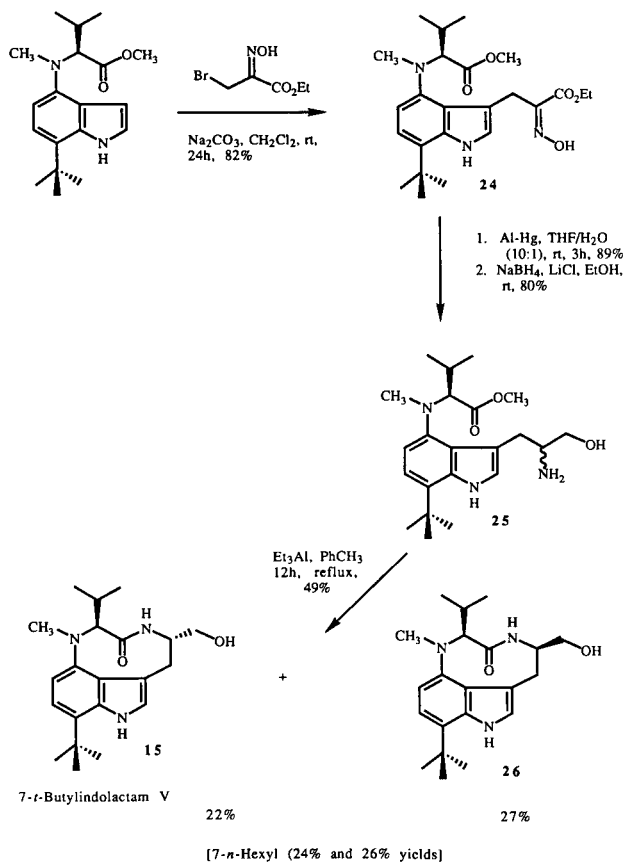


the synthesis required introduction of the indole C-3 amino alcohol appendage, and this was best accomplished by use of Gilchrist's reagent, the α -nitrosoacrylate **22** (Scheme 22). After oxime and ester reduction, lactamization was brought about by simply heating the amino ester with triethylaluminum at reflux in toluene. An easily separable mixture of the 7-alkylindolactam **15** of natural stereochemistry was isolated along with an equivalent amount of the C-9 epimer **26** (Scheme 23). While attempts to improve upon our synthetic scheme by controlling the absolute stereochemistry of the C-9 center of **15** through introduction of the amino alcohol

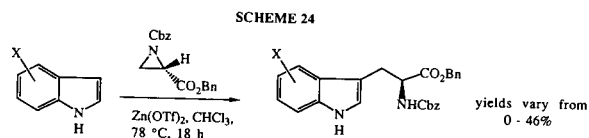
SCHEME 22. SIDE PRODUCTS IN C-3 FUNCTIONALIZATION STEP



SCHEME 23. COMPLETION OF THE SYNTHESIS









side chain by use of optically active aziridine esters were made (Scheme 24), the yields achievable by such methods were disappointing. The Gilchrist reagent provides, for the moment, the best way of introducing functionality at the indole 3-position.



In collaboration with Dr. J. Lazo of the University of Pittsburgh pharmacology department we have examined the ability of these new analogues and some of the intermediates to activate protein kinase C [22]. As anticipated the analogue **15b**, like lyngbyatoxin A itself, is a potent activator of the enzyme (Table 2). The simple amide derivatives **27** and **28** as well as the amino alcohols **25b** and **25b'** failed to activate the enzyme. Clearly, the lactam ring structure is critical for biological activity. Surprisingly, while it had been reported previously that (-)-epi-indolactam **V** was inactive in various biological studies, the epi-compound **26b** functions as a fairly good activator of PKC [23]. Presumably the presence of the hydrophobic *n*-hexyl group is responsible for the heightened biological effect of this analogue, for this group may help to anchor the molecule to the cellular membrane, readying it for interaction with PKC upon translocation of the enzyme from the cytosol to the cellular membrane.

TABLE 2. EFFECTS OF VARIOUS SYNTHETIC ANALOGUES AND INTERMEDIATES OF LYNGBYATOXIN A ON THE ACTIVATION OF PROTEIN KINASE C.

| Compound added | Protein kinase C activity ^a cpm/min/mg protein $\times 10^{-3}$ |
|--|---|
| none | 722 |
| TPA ^b | 1940 |
| Lyngbyatoxin A | 1825 |
|  27 | 731 |
|  28 | 797 |
|  25b (C-9 natural stereochemistry) | 821 |
|  25b' (C-9 epi stereochemistry) | 699 |
|  15b | 1713 |
|  26b | 1209 |

^a The results were representative of three experiments.

^b TPA = 12-O-tetradecanoyl phorbol-13-acetate.

^c These amides were prepared from the corresponding esters by reaction with dimethylaluminum amide.

In view of the relatively efficient approach to lyngbyatoxin structures which is made possible by this isoxazoline-based approach to indoles, we are in a good position to con-

struct carefully selected analogues of this molecule. These compounds may eventually prove useful in further sorting out the links between PKC activation and LTP.

In summary, the synthetic chemistry outlined in this lecture represents the beginnings of a modest effort to arrive at molecules which can either facilitate memory processing in man, or at least serve to unravel some of the mechanisms by which memory is encoded in the brain. A further important effort currently underway in our research group which was not discussed here involves the construction of molecules for use in isolating the NMDA receptor. Perhaps by learning more about the structure of this "memory receptor" at the molecular level, chemists may someday more wisely be able to craft agents capable of facilitating cognitive processes.

Acknowledgements.

I am indebted to the National Institute on Aging (Grant No. 1R01AG07591), the National Cancer Institute (Grant No. 1R01CA50175), the National Institute on Drug Abuse (Grant No. DA05587), and the Fidia Research Foundation for their support of our research. The studies described herein were carried out by a talented group of co-workers which includes Dr. Y. Xia, Dr. E. R. Reddy, Dr. K. Sato, Dr. A. H. Fauq, and Mr. C. P. Miller.

REFERENCES

- [1] A. P. Kozikowski, *Annals of the New Academy of Sciences*, in the press.
- [2] T. V. P. Bliss and T. Lomo, *J. Physiol.*, **232**, 331 (1973); G. Lynch, *Synapses, Circuits and the Beginning of Memory*, MIT Press, Cambridge, 1986.
- [3] J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F. W. Wu, and B. F. Qi, *Can J. Chem.*, **64**, 837 (1986).
- [4] S.-L. Zhang, *New Drugs Clinical Remedies*, **5**, 260 (1986); H. Xu and X.-C. Tang, *Acta Pharm. Sin.*, **8**, 18 (1987); Y. Wang, D.-X. Yue, and X.-C. Tang, *Acta Pharm. Sin.*, **7**, 110 (1986).
- [5] G. P. Vincent, L. Rumennik, R. Cumin, J. Martin, and J. Sepinwall, *Society for Neuroscience Abstracts*, **13**, 844 (1987).
- [6] C. R. Craig and R. E. Stitzel, "Modern Pharmacology", Little Brown and Company, Boston, 1982, pp 167-173.
- [7] A. R. Katritzky, "Handbook of Heterocyclic Chemistry", Pergamon Press, Oxford, 1985, p 168.
- [8] D. L. Beveridge and R. J. Radna, *J. Am. Chem. Soc.*, **98**, 3759 (1971).
- [9] J. W. Ashford, K. A. Sherman, and V. Kumar, *Neurobiology of Aging*, **10**, 99 (1989); D. M. Bowen, *Monogr. Dev. Biol.*, **17**, 42 (1984); W. K. Summers, L. V. Majovski, G. M. Marsh, K. Tachiki, and A. Kling, *N. Engl. J. Med.*, **315**, 1241 (1986).
- [10] G. P. Pollini, A. Barco, and G. DeGiuli, *Synthesis*, 44 (1972).
- [11] M. A. T. Dubas-Sluyter, W. N. Speckamp, and H. O. Huisman, *Rec. Trav. Chim.*, **91**, 157 (1972).
- [12] A. P. Kozikowski, E. R. Reddy, and C. P. Miller, *J. Chem. Soc., Chem. Commun., Perkin Trans. I*, in press.
- [13] E. R. Reddy, unpublished results, University of Pittsburgh, 1989; Y. Xia, E. R. Reddy, and A. P. Kozikowski, *Tetrahedron Letters*, **30**, 3291 (1989).
- [14] The cholinesterase studies are being conducted in collaboration with Dr. Israel Hanin of Loyola University, Stritch School of Medicine on a subcontract from NIA Grant No. 1R01AG07591.
- [15] R. D. Porcilt, *Trends Pharmacol. Sci.*, **10**, 3 (1989).
- [16] "Inositol Lipids in Cell Signaling", R. H. Michell, A. H. Drummond, and C. P. Downes, eds, Academic Press, London, 1989.
- [17] R. Anwyl, *Trends Pharmacol. Sci.*, **10**, 236 (1989).
- [18] H. McLennan, *Progr. Neurobiol.*, **20**, 151 (1983); J. C. Watkins and H. J. Olverman, *Trends Neurosci.*, **10**, 265 (1987).
- [19] J. H. Cardelina, F. J. Marner, and R. E. Moore, *Science*, **204**, 193 (1979).

[20] T. L. Gilchrist, D. A. Lingham, and T. G. Roberts, *J. Chem. Soc., Chem. Commun.*, 1089 (1979).

[21] A. P. Kozikowski and K. Sato, *Tetrahedron Letters*, **30**, 4073 (1989).

[22] A. P. Kozikowski, K. Sato, A. Basu, and J. S. Lazo, *J. Am. Chem. Soc.*, **111**, 6228 (1989).

[23] H. Fujika, M. Suganuma, M. Nakayasu, T. Tahira, Y. Endo, K. Shudo, and T. Sugimura, *Gann*, **75**, 866 (1984).