A Palladium-Catalyzed Route to Huperzine A and Its Analogues and Their Anticholinesterase Activity

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Huperzine A is an alkaloid isolated from *Huperzia serrata* (Thunb.) Trev., a Chinese club moss the extracts of which have been used in Chinese folklore medicine to treat a variety of maladies including memory disorders. Recently, this molecule has attracted widespread attention because of its possible use in the treatment of Alzheimer's disease (AD). We describe herein a palladium-catalyzed bicycloannulation route to this molecule which makes huperzine A available in 40% overall yield. The application of this methodology to seven other huperzine A analogues together with their biological activity in the inhibition of rat cortex acetylcholinesterase (AChE) is detailed herein. None of these new compounds was more potent than the parent structure as AChE inhibitors.

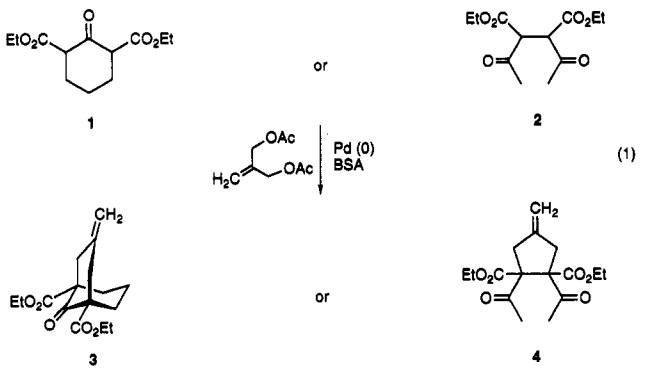
Introduction

Alzheimer's disease (AD) is the most common cause of dementia in middle and late life.[1] The disease is characterized by a gradual and progressive mental deterioration with memory impairment. At present there exists a considerable body of evidence indicating that basal forebrain cholinergic neurons degenerate in AD and that some aspects of the memory deficits observed in AD patients are due to the impairment of cholinergic neurotransmission. In the cholinergic system, acetylcholinesterase (AChE) is the enzyme responsible for the rapid degradation of the neurotransmitter acetylcholine to choline and acetate ion. Since one of the major deficits in AD patients involves the cholinergic system, the use of reversible inhibitors of acetylcholinesterase to increase the level of the neurotransmitter in the central nervous system (CNS) is considered to be one viable therapeutic approach to the disease. While the AChE inhibitor physostigmine has been investigated for use in the treatment of AD, its use has been limited by its short duration of action. Recently, tetrahydroaminoacridine (THA, or tacrine) has been approved for wider use in the treatment of AD patients; however, this compound exhibits toxic side effects (elevation of liver enzymes). To the extent that AChE inhibitors can serve as useful adjuncts in the treatment of AD, several clinical reports indicate huperzine A to be capable of facilitating cholinergic neurotransmission by increasing the concentration of acetylcholine in the CNS.[2] Moreover, its pharmacological profile has been shown to be superior to both physostigmine and THA. In fact, huperzine A is one of the most potent reversible AChE-inhibitors known, and its toxicity is considerably lower than that of other inhibitors. Huperzine A thus appears to be an important psychotherapeutic agent that has good potential for improving cognitive function in Alzheimer's patients by enhancement of central cholinergic tone.[3,4]

In order to produce the quantities of huperzine A needed to support the ongoing preclinical studies required to bring this molecule to clinical trials, we have engaged in efforts to develop a more efficient synthetic route to this compound.[5] In this report we detail a novel total synthesis of huperzine A that furnishes the natural product in 40% overall yield. Additionally, using variations of this new route, syntheses of seven new huperzine A analogues are described together with their action on isolated rat brain AChE.

Chemistry. A New Synthesis of Huperzine A

In order to improve synthetic accessibility to huperzine A we chose to investigate the bicycloannulation methodology reported by Huang and Lu in 1988.[6] These investigators described the reaction of bifunctional allylic alkylating agents with 1,2- and 1,3-bis-nucleophiles under palladium catalysis to form methylenecyclohexane and methylenecyclopentane derivatives (eq 1).



On the basis of this report, we examined related chemistry employing our previously described methoxypyridine **5** as the bis-nucleophile.[7a,b] As shown in Scheme I, the palladium-catalyzed bicycloannulation reaction of β-keto ester **5** using 1,1,3,3-tetramethylguanidine (TMG) as a base (to generate the 5,7-dicarbanion equivalent) and

† Neurochemistry Research.
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(1) Shoenberg, B. S.; Kokmen, E.; Okazaki, H. *Ann. Neurol.* **1987**, *22*, 724.
(2) Tang, X.-C.; De Sarno, P.; Sugaya, K.; Giacobini, E. *J. Neurosci. Res.* **1989**, *24*, 276.
(3) (a) Quinn, D. M. *Chem. Rev.* **1987**, *87*, 955. (b) Brossi, A. *J. Med. Chem.* **1990**, *33*, 724.
(4) (a) Tang, X.-C.; Han, Y. F.; Chen, X. P.; Zhu, X. D. *Acta Pharm. Sin.* **1986**, *7*(6), 507. (b) Vincent, G. P.; Rumennik, L.; Cumin, R.; Martin, J.; Sepinwall, J. *Soc. Neurosci. Abstr.* **1987**, *13*(2), 844. (c) Zhang, S. L. *New Drugs Clin. Rem.* **1986**, *5*(5), 260. (d) Cheng, Z. S. et al. *Ibid.* **1986**, *5*(4), 197.
(5) Kozikowski, A. P.; Campiani, G.; Aagaard, P.; McKinney, M. *J. Chem. Soc., Chem. Commun.* **1993**, *10*, 860.
(6) Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663.

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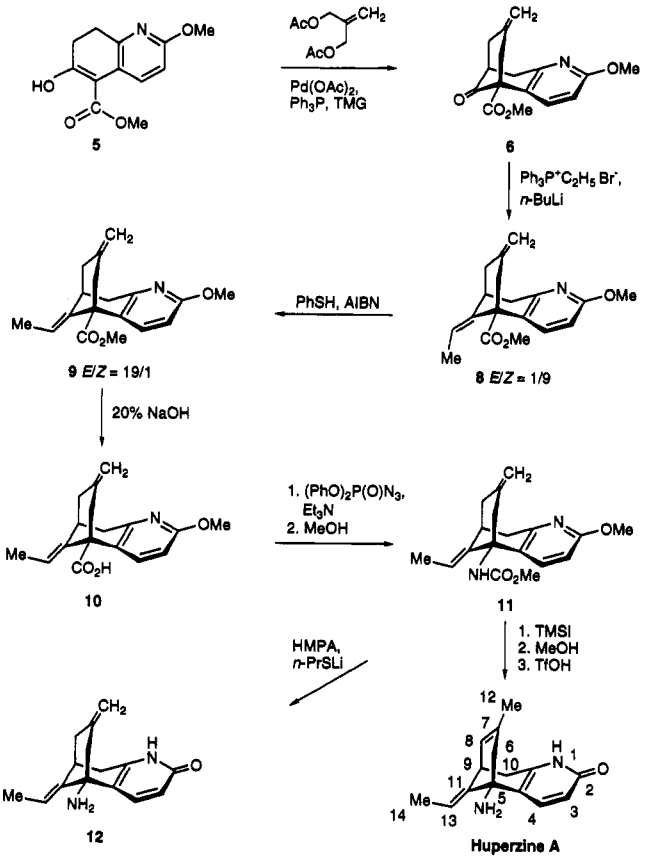
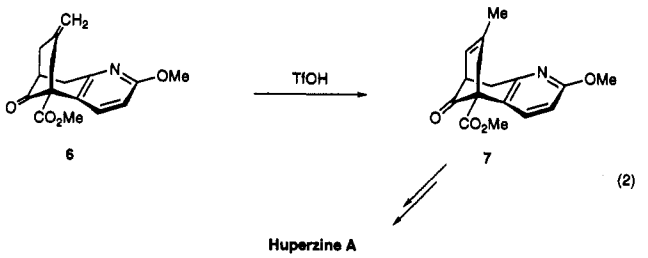
Scheme I. Palladium-Catalyzed Route to Huperzine A and Its Methylene Analogue 12

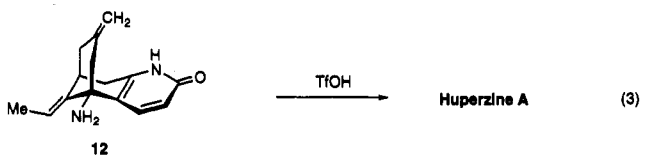


2-methylene-1,3-propanediol diacetate as the bis-electrophile in the presence of tetrakis(triphenylphosphine)-palladium(0) in refluxing dioxane afforded the methylene-bridged structure **6** in 92% yield.[8]

In our first reported route to huperzine A the synthesis of a key intermediate **7** was described.[7a,b] Olefin **7** was obtained by dehydration of an alcohol precursor through a two-step process involving mesylate formation followed by NaOAc/HOAc-induced elimination. The elimination step proved to be the lowest yielding step in this earlier synthesis. The opportunity now existed to bypass this step if a way could be found to isomerize the exo-olefin **6** to its endo-counterpart **7**. After examination of several methods for olefin isomerization,[8,9] we found that exposure of compound **6** to triflic acid in dioxane at 93 °C afforded the endocyclic olefin **7** in 90% yield (81% overall yield from **5**, eq 2).



This endocyclic olefin also proved to be a versatile intermediate for the synthesis of some C-11 modified analogues. Since the double-bond isomerization step can be deferred to the last stage of the synthesis, we decided to carry out the remaining steps of the synthesis starting from **6** as detailed in Scheme I. Thus, the Wittig reaction of **6** with ethylidenetriphenylphosphorane in THF at 0 °C to room temperature[7b] provided a 9:1 mixture of (*Z*)- and (*E*)-alkenes **8** in 83% yield. As the reaction product consists largely of the incorrect isomer, the mixture of *Z*- and *E*-isomers was subjected to an isomerization reaction with thiophenol and azobisisobutyronitrile (AIBN)[10] in toluene at 85 °C leading to a 95:5 mixture of (*E*)- and (*Z*)-alkenes **9** in 92% yield. Conversion of the ester group of **9** to an amine was carried out by a two-step protocol involving alkaline hydrolysis of **9** in THF–methanol under reflux to afford **10** in 83% yield. Under these conditions only the *E*-isomer of **9** was converted to the *E*-acid **10** while the *Z*-isomer was recovered unreacted. Next, Curtius rearrangement of the acid **10** by diphenyl phosphorazidate/triethylamine treatment[11] followed by methanolysis of the resulting isocyanate provided the carbamate **11** (82% yield). Trimethylsilyl iodide (TMSI) mediated deprotection of **11** in refluxing chloroform proceeded uneventfully, although partial isomerization of the exocyclic double bond to the endocyclic olefin, promoted presumably by adventitious hydriodic acid, was observed. Treatment of the mixture with triflic acid in dioxane at 93 °C afforded huperzine A as the sole product in 84% yield (40% overall yield from **5**). Use of lithium *n*-propyl mercaptide[12] as the deprotection agent in HMPA at 90 °C in lieu of TMSI led to the isolation of pyridone **12**, a positional isomer of huperzine A. Exposure of **12** to triflic acid in dioxane furnished huperzine A in 80% yield (eq 3).



As detailed below, this modified route to huperzine A readily lends itself to the preparation of a variety of new analogues.

Synthesis of Huperzine A Analogues Functionalized at Positions 7 and 11. From extensive computer-based modelling studies, we have been able to identify possible binding sites for huperzine A in AChE.[13] In order to explore these possible binding sites more fully, analogues of huperzine A were chosen for synthesis which contain additional hydrogen bond donor or acceptor groups thus allowing the possibility of forming additional H-bond interactions to certain amino acid residues present in these binding sites. Additionally, we were interested in the possibility of introducing one additional amino group into the molecule in order to examine the effect of increased positive charge on the kinetics of interaction with AChE. The choice of the locus of these new structural alterations was in part dictated by the constraints of synthesis in

(7) For the synthesis of huperzine A, see: (a) Xia, Y.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1989**, *111*, 4116. (b) Kozikowski, A. P.; Xia, Y.; Reddy, E. R.; Tückmantel, W.; Hanin, I.; Tang, X.-C. *J. Org. Chem.* **1991**, *56*, 4636.

(8) Other attempts to obtain the bicycloannulation product **6** employing different conditions such as those reported by Gravel *et al.*[a,b] for analogous β-keto esters (K_2CO_3 or acetic acid in toluene, or in the complete absence of any enolizing or deprotonating agents) failed: (a) Gravel, D.; Benoit, S.; Kumanovic, S.; Sivaramakrishnam, H. *Tetrahedron Lett.* **1992**, *33*, 1403; (b) **1992**, *33*, 1407.

(9) Paquette, L. A.; Saver, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375.

(10) Bhalerao, V. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835.

(11) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(12) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.

(13) Kozikowski, A. P.; Pang, Y.-P. In *Trends in QSAR and Molecular Modelling '92*. Proceedings of the 9th European Symposium on Structure–Activity Relationships: QSAR and Molecular Modelling, Wermuth, C.-G., Ed.; ESCOM Science Publishers: Leiden, The Netherlands, 1993.

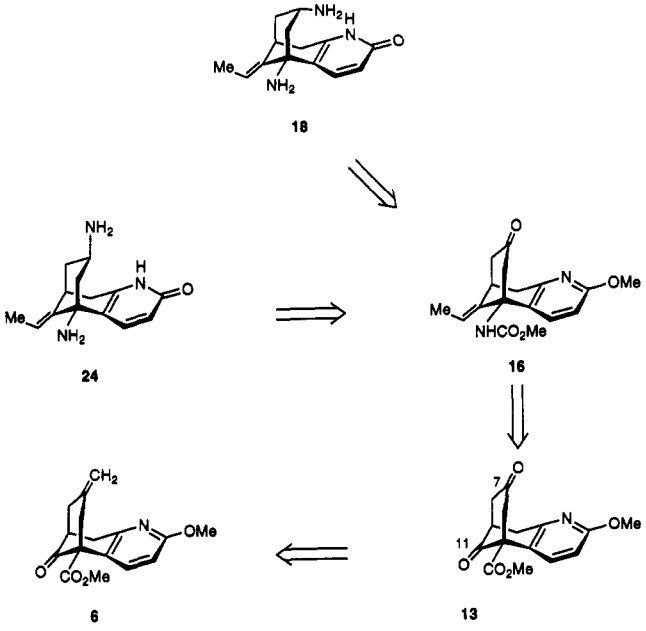


Figure 1. Retrosynthetic analysis of diamines **18** and **24**.

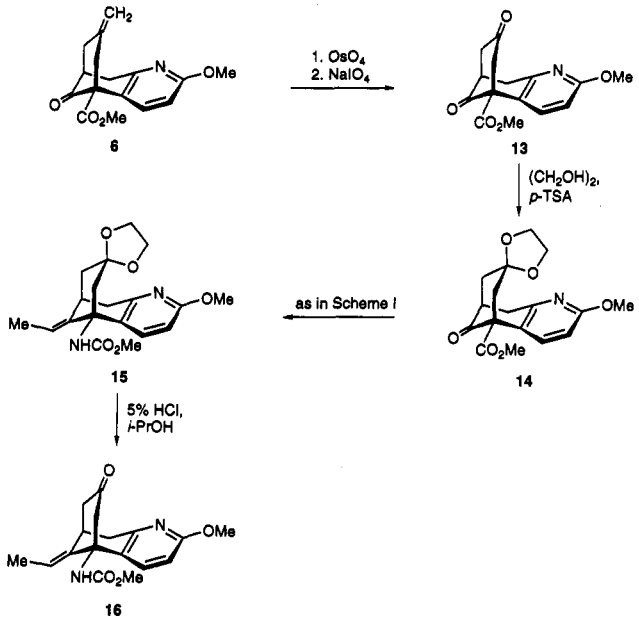
combination with the results of the molecular modeling studies. Accordingly, we chose to replace the C-12 methyl group by an amino group, which therefore required removal of the C-7, C-8 double bond. Both the axial and equatorial amines, **18** and **24**, respectively, were prepared. We also envisioned substituting the lipophilic C-14 methyl group by the more polar methoxycarbonyl, hydroxymethyl, and cyano functions. Lastly, the ethylidene appendage was replaced by an equatorial aminomethyl group.

Our retrosynthetic analysis of compounds **18** and **24** is shown in Figure 1. The exocyclic olefin **6** prepared during the course of the huperzine A synthesis serves as an appropriate precursor to the diketone **13**, which can be selectively ketalized at C-7 (huperzine numbering scheme) leaving the C-11 carbonyl group available for the introduction of the ethylidene group by Wittig reaction. The methoxycarbonyl group of **13** would then be transformed to carbamate in the usual way. Thus, the main task to be accomplished in this synthesis is the discovery of stereoselective methods for introducing an axial or equatorial amino group at C-7 of **16**.

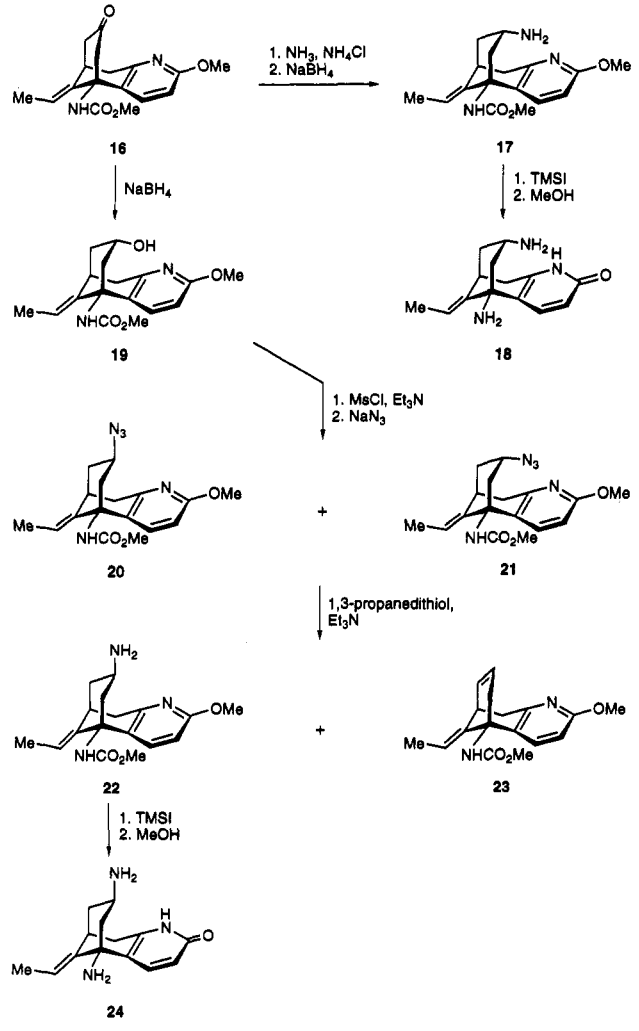
Thus, olefin **6** was first oxidized to the diketone **13** in 89% yield using osmium tetraoxide–sodium periodate in aqueous acetic acid.[14] Diketone **13** was selectively monoketalized[15] at the less hindered C-7 carbonyl group to afford **14** in 94% yield. A Wittig reaction was then carried out at the other carbonyl group, and the resulting 9:1 *Z*/*E* mixture was isomerized to a 1:19 mixture of *Z*- and *E*-olefins with thiophenol and AIBN in toluene. Saponification of the ester yielded, as in the case of the huperzine A synthesis, only the *E*-acid. Curtius rearrangement followed by deketalization with 5% HCl in *i*-PrOH gave the key intermediate **16** (Scheme II).

Regioselective reductive amination[16] of ketone **16** using saturated methanolic ammonia in the presence of anhydrous ammonium chloride, followed by sodium borohydride reduction of the resulting imine, afforded exclusively the axially oriented amino epimer **17** in 84% yield. This

Scheme II. Synthesis of Intermediate 16



Scheme III. Synthesis of the Axial and Equatorial Amino Analogues 18 and 24

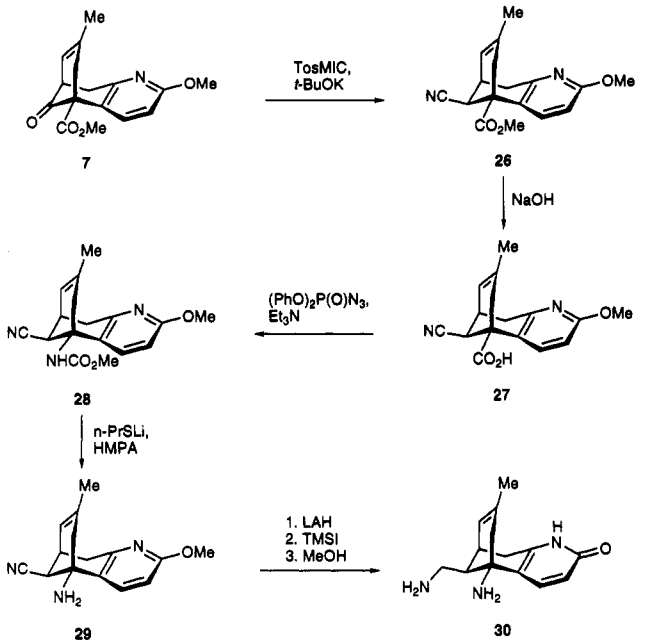


is consistent with the approach of the hydride ion from the less hindered face. TMSI-promoted deprotection gave the desired axial amino analogue **18** in 82% yield.

To obtain the other amine diastereomer, stereoselective reduction of the ketone **16** with sodium borohydride was carried out first to produce the axial alcohol **19** in 85%

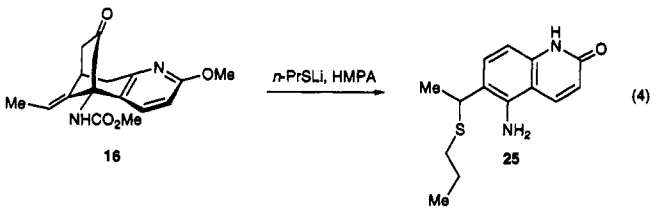
(14) Dvornik, D.; Edwards, O. E. *Can. J. Chem.* **1957**, *35*, 860.
(15) Daignault, R. A.; Eliel, E. L. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 303.
(16) Campiani, G.; Nacci, V.; Garofalo, A.; Botta, M.; Fiorini, I.; Tafi, A.; Peres, A.; Bertollini, L. *Bioorg. Med. Chem. Lett.* **1992**, *57*, 5990.

Scheme IV. Synthesis of an Aminomethyl Analogue 30



yield. Mesylation (93%) of **19** followed by displacement with sodium azide in HMPA[17] at room temperature afforded an inseparable mixture of azide derivatives **20** and **21** in a 78:22 ratio as ascertained by ^{1}H NMR. Since the reagents commonly employed for the reduction of azides (e.g., $LiAlH_4$ or H_2/catalyst) are relatively nonchemoselective (our substrate contains both a carbamate group and an olefin), we were pleased to find that the azide group could be selectively reduced in the presence of the double bond and the carbamate group by the use of propanedithiol–triethylamine[18] in methanol. Surprisingly, under these conditions only the equatorial azide **20** was reduced while the axial azide **21** underwent elimination to the olefin **23**. These products were easily separated by chromatography on silica gel. Other methods for azide reduction such as PPh_3/THF–H_2O[19] or tributyltin hydride led to a mixture of axial and equatorial amine derivatives. Deprotection of **22** with TMSI provided the equatorial amino analogue **24** of huperzine A in 78% yield.

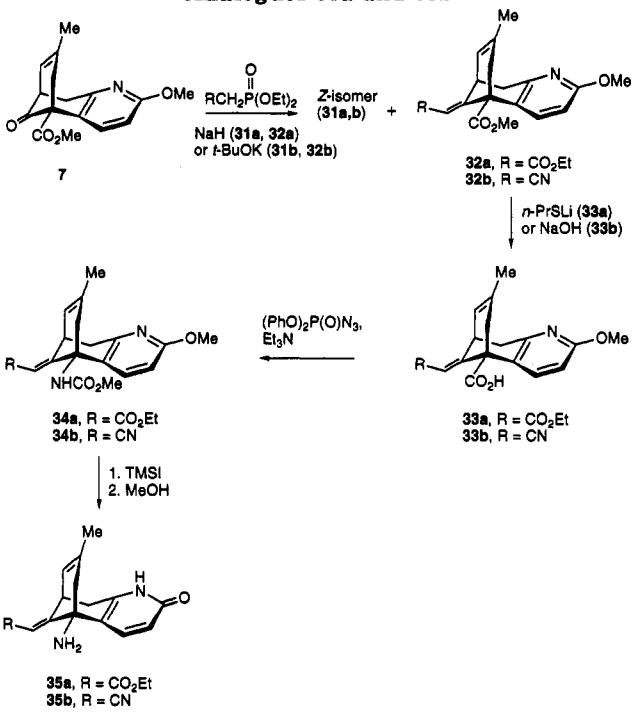
It is also of some interest to note here that attempts were made to deprotect **16** in order to procure an analogue bearing a ketone group in place of the C-12 methyl group of huperzine A. Interestingly, the attempted *n*-PrSLi-promoted deprotection led to the formation of the fragmentation product **25** in 57% yield along with the formation of other side products (eq 4).



(4)

The analogue **30** bearing an aminomethyl group in place of huperzine A's ethylidene appendage was obtained from the β-keto ester **7** in the following manner (Scheme IV).

Scheme V. Synthesis of the Ester and Cyano Analogues 35a and 35b



Reductive cyanation[20] with tosylmethyl isocyanide (TosMIC) and potassium *tert*-butoxide in methanol afforded in 39% yield the β-cyano derivative **26** which was saponified to the acid **27** using NaOH in THF–MeOH. This acid was converted in turn to **30** through a sequence of steps involving (i) methanolysis of the isocyanate obtained from the Curtius rearrangement of **27**, (ii) deprotection of the carbamate function of **28** with lithium *n*-propyl mercaptide in HMPA[12] at rt, (iii) LAH reduction of the cyano group to the amine **29**, and (iv) TMSI-promoted deprotection.

The bridged β-keto ester **7** also served as a convenient starting point for the synthesis of the analogues **35a** and **35b** bearing an ester function or a cyano group, respectively, in place of the C-14 methyl group (Scheme V). These compounds were prepared through a sequence of reactions similar to those described above for huperzine A (Scheme I) using the anions prepared from diethyl (cyanomethyl)-phosphonate[21] or triethyl phosphonoacetate[22] in place of the ethylidenetriphenylphosphorane. The resulting *Z*- and *E*-isomers **31** and **32** were separated by chromatography on silica gel. Treatment of the diester **32a** with lithium *n*-propyl mercaptide in HMPA at room temperature and of the cyanoester **32b** with aqueous NaOH in THF–methanol solution gave acid–ester **33a** (93% yield) and cyano acid **33b** (94% yield). Urethane formation followed by TMSI-promoted deprotection of the corresponding carbamates **34a,b** provided the ester and the cyano analogues of huperzine A in 72% and 68% overall yield, respectively, from **33a** and **33b**.

Lastly, DIBALH reduction[23] of the ethoxycarbonyl

(17) Taber, D. F.; Deker, B. P.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990.
(18) Bayley, H.; Standring, D. M.; Knowles, J. R. *Tetrahedron Lett.* **1978**, *39*, 3633.
(19) Knouzi, N.; Vaultier, M.; Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, 815.
(20) Oldenziel, O. H.; Wildeman, J.; van Leusen, A. M. *Organic Syntheses*; Wiley; New York, 1988; Collect. Vol. VI, p 41.
(21) Chida, N.; Yamada, K.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1131.
(22) Wei-Shan, Z.; Hui-Qiang, Z.; Zhi-Qin, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2281.
(23) Meyers, A. I.; Schmidt, W.; McKennon, M. J. *Synthesis* **1993**, 250.
(24) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863.

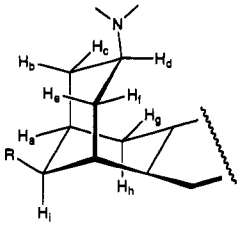


Figure 2. General structure with proton assignments.

Scheme VI. Synthesis of the 11-Hydroxyethylidene Analogue 36

35a 36

group of **35a** furnished the hydroxyethylidene analogue **36** in 82% yield (Scheme VI).

Stereochemical Assignments

The stereochemistry of the amino group in the epimeric amino analogues of huperzine A, **18** and **24**, was assigned from ^{1}H NMR COSY experiments (Figure 2). The benzylic protons g and h were determined by their diagnostic chemical shifts (^{1}H NMR in D_2O shows a dd at 2.90 ppm for g and a d at 2.57 ppm for h). In the COSY spectrum a correlation between protons g and a was observed. The resonance of H_a at 3.33 ppm is also characteristic for this series. No coupling was observed between H_a and H_h due to a dihedral angle of about 80° consistent with molecular modeling. Proton e was observed as a triplet at 1.2 ppm with J = 11.4 Hz. This is consistent with a geminal coupling to H_f and a trans-diaxial coupling to H_d.

The resonance due to H_f was observed as a doublet of doublets at 1.76 ppm and showed the typical geminal coupling constant ($J_{e,f}$ = 11 Hz) as well as a small equatorial–axial coupling ($J_{d,e}$ = 4 Hz). Further examination of the spectral data indicated that H_b appeared at 1.2 ppm as a doublet of a triplet; the smaller coupling showed the expected coupling constant ($J_{a,b}$ = 4 Hz) while the triplet splitting was caused by coupling between H_b and H_c (geminal coupling in the order of 11 Hz) and between H_b and H_d (axial–axial interaction in the order of 11 Hz). H_c was not completely resolved and from the foregoing arguments would likely consist of a doublet of doublet of doublets with J values of about 4 and 11 Hz. The stereochemistry of H_d was deduced primarily by the trans-diaxial coupling constant observed between it and H_e indicating an equatorial orientation of the amino group. A similar analysis was carried out for the axial analogue **18**.

The stereochemistry of the cyano group in intermediate **26** and of the aminomethyl group of analogue **30** was assigned on the basis of ^{1}H NMR COSY experiments. Their ^{1}H NMR spectra showed a coupling constant between H_i and H_a of 4 Hz in agreement with an equatorial–axial coupling.

Biological Testing

The ability of all new analogues reported herein to inhibit acetylcholinesterase isolated from rat brain cortex was measured, and these data are presented as IC_{50} values in Table I. As is apparent, none of these new analogues is able to rival the activity of huperzine A. Further discussions of the structure–activity relationships of these new analogues will be presented elsewhere in conjunction with more detailed molecular modeling studies involving the docking of these compounds to *Torpedo* acetylcholinesterase.

Table I. Extent of AChE Inhibition by the Compounds Tested[a]

compd no.	IC_{50} (μM)	n
(±)-huperzine A	0.196 ± 0.022	11
12	4.28 ± 0.53	4
18	8.14 ● 0.76	3
24	467 ± 41	3
30	17.2 ± 0.41	4
35a	400 ● 46	3
35b	489 ± 105	3
36	8.10 ● 0.46	3

[a] Rat cortical homogenate was assayed for acetylcholinesterase activity in the presence of 10 μM ethopropazine to inhibit pseudocholinesterase activity. Concentrations of huperzine A analogues in the range of 1–100 μM were tested for blockade of acetylcholinesterase hydrolysis of 800 μM acetylcholine. Data were fitted with a logistic model to determine the IC_{50} values.

Conclusions

The palladium-catalyzed bicycloannulation approach to huperzine A detailed herein provides an important advance in the preparation of this therapeutically valuable natural product. The palladium methodology effectively replaces the low-yielding, two-step elimination protocol used in our first total synthesis to introduce the unsaturation present in huperzine's three-carbon bridge. The modified synthesis proceeds in 40% overall yield, and this high overall yield combined with the simplicity of the chemistry will aid greatly in the advancement of huperzine A to the clinic. During the course of this work seven new analogues of huperzine A were assembled. Unfortunately, none of these new compounds was able to rival huperzine A in terms of its ability to inhibit rat brain AChE.

Experimental Section

For general experimental information, see ref 22. Infrared spectra were obtained on a Mattson Galaxy 2020 FT-IR instrument. GC–MS analyses were performed on a Hewlett-Packard 5890 II instrument.

(±)-7,8,9,10-Tetrahydro-2-methoxy-7-methylene-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (6). Palladium diacetate (47 mg, 0.21 mmol) and triphenylphosphine (0.22 g, 0.84 mmol) were stirred at rt in dry dioxane (20 mL) under argon for 30 min. A solution of the β-keto ester **5** (1 g, 4.2 mmol), 1,1,3,3-tetramethylguanidine (0.6 mL, 4.7 mmol), and 2-methylene-1,3-propanediol diacetate (0.68 mL, 4.2 mmol) in dry dioxane (20 mL) was added dropwise to the complex thus obtained over a period of 10 min. After the mixture was stirred for 20 min at rt, a solution of TMG (0.46 mL, 3.7 mmol) in dry dioxane (3 mL) was added dropwise. After being stirred at rt for 20 min, the mixture was refluxed for 5 h and then stirred at rt for 12 h. Concentration and flash chromatography (30% ethyl acetate in hexanes) gave 1.11 g (92%) of the methylene-bridged adduct **6** as colorless prisms: mp 82–83 °C (from hexanes); R_f = 0.39 (30% ethyl acetate in hexanes); IR (neat) 3055, 1741, 1728, 1635, 1479, 1116, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.97 (d, 1 H, J = 8.6 Hz), 6.57 (d, 1 H, J = 8.5 Hz), 4.83 (m, 1 H), 4.49 (m, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.45 (dd, 1 H, J = 18.3, 6.7 Hz), 3.19–3.05 (m, 2 H), 2.96 (m, 1 H), 2.85–2.70 (m, 1 H), 2.62–2.52 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 40.5, 43.9, 45.7, 47.8, 52.6, 53.4, 62.0, 109.5, 116.3, 124.4, 137.6, 138.9, 151.4, 162.9, 171.3, 208.2; MS m/z 287 (100, M$^+$), 270, 258, 255, 244, 228, 212, 200, 184; HRMS calcd for $C_{16}H_{17}NO_4$ 287.1153, found 287.1139.

(11*Z*)-(±)-11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (8). To a suspension of ethyltriphenylphosphonium bromide (4.97 g, 13.4 mmol) in dry THF (48.5 mL) was added *n*-BuLi (6.24 mL, 11.4 mmol, 2.5 M in hexane) within 10 min. The resulting orange-colored suspension was stirred at rt for 70 min. After the mixture was cooled to 0 °C, a solution of β-keto ester **6** (0.822 g, 2.86 mmol) in dry THF (12.1 mL) was slowly added over a period of 15 min. The resulting mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was quenched with water, the THF removed by rotary evaporation, and the aqueous residue extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (10% ethyl acetate in hexanes) gave 0.705 g (83%) of olefin **8** which on standing solidified (*E*/*Z* = 10/90): mp 86–87 °C (from hexanes); R_f = 0.28 (10% ethyl acetate in hexanes); IR (neat) 2945, 1730, 1661, 1601, 1578 cm^{-1}; ^1H NMR (*Z*-olefin, $CDCl_3$) δ 6.93 (d, 1 H, *J* = 8.6 Hz), 6.50 (d, 1 H, *J* = 8.6 Hz), 5.59 (q, 1 H, *J* = 7.3 Hz), 4.59 (m, 1 H), 4.27 (m, 1 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 3.22 (dd, 1 H, *J* = 17.9, 6.6 Hz), 2.83 (m, 2 H), 2.72 (d, 1 H, *J* = 18.0 Hz), 2.40 (m, 3 H), 1.55 (d, 3 H, *J* = 7.2 Hz); MS *m*/*z* 299 (40, M^+), 270, 244 (100), 240, 212, 184.

(11*E*)-(±)-11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (9). To a solution of the olefin mixture **8** (*E*/*Z* = 10/90, 55 mg, 0.18 mmol) in dry toluene (0.4 mL) were added AIBN (22 mg, 0.13 mmol) and thiophenol (28 μL, 0.27 mmol). The resulting solution was heated at 85 °C for 21.5 h. Evaporation of the solvent afforded a residue which was dissolved in dichloromethane, washed with brine, and dried ($MgSO_4$). After concentration, the crude product was chromatographed (10% ethyl acetate in hexanes) to afford 51 mg (92%) of **9** which by ^1H NMR and GC analysis consisted of a 95/5 mixture of the (*E*)- and (*Z*)-alkenes: ^1H NMR (*E*-olefin, $CDCl_3$) δ 6.95 (d, 1 H, *J* = 8.4 Hz), 6.48 (d, 1 H, *J* = 8.4 Hz), 5.18 (q, 1 H, *J* = 6.7 Hz), 4.63 (m, 1 H), 4.30 (m, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.40 (m, 1 H), 3.14 (dd, 1 H, *J* = 17.8, 6.6 Hz), 2.87 (d, 1 H, *J* = 12.6 Hz), 2.78 (d, 1 H, *J* = 17.8 Hz), 2.39 (m, 3H), 1.73 (d, 3 H, *J* = 6.7 Hz); MS *m*/*z* 299 (38, M^+), 284, 240 (100), 212, 172, 154.

(11*E*)-(±)-11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid (10). Ester **9** (90 mg, 0.3 mmol, *E*/*Z* = 95/5) was dissolved in 0.72 mL of methanol/THF (2:1), and 20% NaOH (0.24 mL) was added. The mixture was heated under reflux under argon for 26 h. After cooling, the solution was adjusted to pH 5–6 with 5% HCl, and methanol and THF were evaporated. The aqueous residue was extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (ethyl acetate) to give 71 mg (83%) of the acid **10** as colorless prisms: mp 189–190 °C (from ethyl acetate and hexanes); R_f = 0.58 (ethyl acetate); IR (KBr) 2941, 1726, 1599, 1425, 1273, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, 1 H, *J* = 8.6 Hz), 6.53 (d, 1 H, *J* = 8.5 Hz), 5.45 (q, 1 H, *J* = 6.7 Hz), 4.65 (m, 1 H), 4.32 (m, 1 H), 3.87 (s, 3 H), 3.43 (m, 1 H), 3.15 (dd, 1 H, *J* = 17.8, 6.6 Hz), 2.84 (m, 2 H), 2.42 (m, 3 H), 1.77 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 12.8, 31.8, 39.4, 42.9, 48.0, 53.3, 56.4, 108.1, 113.3, 116.2, 125.8, 137.3, 138.0, 142.0, 153.5, 162.3, 178.3; MS *m*/*z* 285 (22, M^+), 240, 230, 212, 160, 128; HRMS calcd for $C_{17}H_{19}NO_3$ 285.1360, found 285.1356.

(11*E*)-(±)-[11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic Acid Methyl Ester (11). A mixture of acid **10** (20 mg, 0.07 mmol), dry triethylamine (9.6 μL, 0.07 mmol), diphenyl phosphorazidate (14.9 μL, 0.07 mmol), and dry toluene (0.25 mL) was heated at 85 °C for 3 h. After the mixture was cooled, the solvent was removed by rotary evaporation, and the residue was dissolved in dry methanol (0.25 mL). The resulting solution was heated under reflux for 18 h. Evaporation and silica gel flash chromatography (10% ethyl acetate in dichloromethane) gave the urethane **11** (18 mg, 82%) as a colorless solid: mp 146–147 °C (from hexanes); R_f = 0.29 (10% ethyl acetate in dichloromethane); IR (KBr) 3325, 1712, 1599, 1531, 1475, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (d, 1 H, *J* = 8.6 Hz), 6.52 (d, 1 H, *J* = 8.6 Hz), 5.46 (q, 1 H, *J* = 6.5 Hz), 4.95 (s, carbamate NH), 4.65 (m, 1 H), 4.30 (m, 1 H), 3.85 (s, 3 H), 3.65 (s, 3 H), 3.41 (m, 1 H), 3.14 (dd, 1 H, *J* = 17.9, 6.5 Hz), 2.71 (m, 2 H), 2.32 (m, 3 H), 1.74 (d, 3 H, *J* = 6.7 Hz); MS *m*/*z* 314 (34, M^+), 299, 259, 224 (100), 201, 184, 156.

Huperzine A. Iodotrimethylsilane (90 μL, 0.62 mmol) was added to a solution of carbamate **11** (20 mg, 0.06 mmol) in dry chloroform (1.5 mL) under argon at rt, and the solution was refluxed for 5.5 h. After cooling and evaporation, the residue was dissolved in methanol (1.5 mL) and the solution refluxed for 18 h. The solvent was removed by rotary evaporation, the residue was dissolved in dry dioxane (1 mL), and trifluoromethanesulfonic acid (20 μL, 0.22 mmol) was added. The solution was heated at 93 °C for 24 h. Evaporation of the solvent afforded a residue which was partitioned between 10% $NaHCO_3$ solution and chloroform. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (15% methanol in chloroform) gave 13 mg (84%) of huperzine A as a colorless solid whose spectroscopic data are identical with those reported previously.[7]

(11*E*)-(±)-5-Amino-11-ethylidene-5,6,7,8,9,10-hexahydro-7-methylene-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one (12). To a solution of carbamate **11** (18 mg, 0.057 mmol) in dry HMPA (0.8 mL) was added lithium *n*-propyl mercaptide in HMPA (0.5 mL, 1.6 mmol) (3.2 M solution) at rt under argon. The resulting mixture was heated at 90 °C for 6 h. After cooling, the mixture was treated at 0 °C with water and then extracted with 5% methanol in ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (15% methanol in chloroform) to afford **12** (12 mg) in 87% yield as colorless prisms: mp 295 °C dec (from ethyl acetate); R_f = 0.6 (15% methanol in chloroform); IR (KBr) 3480–3395, 2911, 1660, 1610, 1558, 893 cm^{-1}; ^1H NMR (CD_3OD) δ 7.69 (d, 1 H, *J* = 9.4 Hz), 6.24 (d, 1 H, *J* = 9.4 Hz), 5.59 (q, 1 H, *J* = 6.7 Hz), 4.62 (m, 1 H), 4.33 (m, 1 H), 3.37 (m, 1 H), 2.77 (dd, 1 H, *J* = 18.2, 6.9 Hz), 2.43 (d, 1 H, *J* = 18.1 Hz), 2.24–2.11 (m, 4 H), 1.65 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR (CD_3OD) δ 13.5, 33.3, 36.4, 44.7, 53.9, 57.8, 114.3, 115.4, 118.5, 124.9, 141.7, 143.9, 145.7, 145.9, 165.4; MS *m*/*z* 242 (38, M^+), 227, 213, 187, 149, 118 (100), 105; HRMS calcd for $C_{15}H_{18}N_2O$ 242.1414, found 242.1418.

(±)-9,10-Dihydro-2-methoxy-7-methyl-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (7). A mixture of β-keto ester **6** (20 mg, 0.069 mmol), trifluoromethanesulfonic acid (9 μL, 0.1 mmol), and dry dioxane (0.5 mL) was heated at 93 °C in a resealable tube under argon for 12 h. The solvent was removed, and the residue was partitioned between aqueous $NaHCO_3$ and ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and filtered. Concentration and flash chromatography (30% ethyl acetate in hexanes) gave 18 mg (90%) of compound **7** as a colorless solid whose spectroscopic data are identical with those reported previously.[7]

(±)-7,8,9,10-Tetrahydro-2-methoxy-7,11-dioxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (13). The β-keto ester **6** (20 mg, 69 mmol) was dissolved in 80% acetic acid (1.8 mL) and stirred for 5 h with osmium tetraoxide (1.72 mg) until maximum darkness of the solution was reached. The solution was cooled to 4 °C, sodium periodate (13.8 mg) was added, and stirring was continued for 12 h. More sodium periodate (13.8 mg) was added, and the reaction mixture was stirred for 24 h at 4 °C, warmed to rt, and stirred for an additional 1 h. The white precipitate was filtered off and washed with 80% acetic acid, and the filtrate was evaporated at 40 °C. The residue was partitioned between aqueous $NaHCO_3$ and chloroform and the organic phase washed with brine, dried ($MgSO_4$), and filtered. Concentration and flash chromatography (35% ethyl acetate in hexanes) afforded 18 mg (89%) of the diketone **13** as a colorless liquid which on standing solidified: mp 56–57 °C (from hexanes–dichloromethane); R_f = 0.28 (35% ethyl acetate in hexane); IR (neat) 2953, 1747, 1730, 1604, 1114, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04 (d, 1 H, *J* = 8.7 Hz), 6.65 (d, 1 H, *J* = 8.6 Hz), 3.89 (s, 3 H), 3.81 (s, 3 H), 3.55 (dd, 1 H, *J* = 17.8, 5.6 Hz), 3.45 (d, 1 H, *J* = 15.2 Hz), 3.28 (m, 1 H), 3.20 (dd, 1 H, *J* = 17.9, 1.3 Hz), 3.05 (dd, 1 H, *J* = 16.5, 7.0 Hz), 2.91 (dd, 1 H, *J* = 15.1, 3.4 Hz), 2.70 (ddd, 1 H, *J* = 16.5, 3.3, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 41.2, 44.5, 48.0, 52.6, 53.0, 53.5, 59.8, 111.1, 123.7, 138.1, 148.3, 163.6, 169.8, 203.0, 205.5; MS *m*/*z* 289 (100, M^+),

261, 230, 218, 202, 160, 130; HRMS calcd for $C_{15}H_{15}NO_5$ 289.0946, found 289.0938.

(±)-7-(Ethylenedioxy)-7,8,9,10-tetrahydro-2-methoxy-11-oxo-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (14). To a solution of diketone **13** (800 mg, 2.76 mmol) in dry benzene (70 mL) were added *p*-toluenesulfonic acid monohydrate (582 mg, 3.04 mmol) and ethylene glycol (177 μL, 3.17 mmol), and the mixture was refluxed for 3.5 h. Evaporation of the solvent afforded a residue which was directly purified by flash chromatography (20% ethyl acetate in hexanes) to yield 0.870 g (94%) of **14** as colorless prisms: mp 102–104 °C (from hexanes); R_f = 0.53 (20% ethyl acetate in hexanes); IR (KBr) 2953, 1741, 1732, 1601, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (d, 1 H, *J* = 8.6 Hz), 6.57 (d, 1 H, *J* = 8.6 Hz), 3.91 (s, 3 H), 3.85–3.70 (m, 6 H), 3.65–3.57 (m, 1 H), 3.47 (dd, 1 H, *J* = 18.0, 7.3 Hz), 3.26 (d, 1 H, *J* = 18.0 Hz), 2.97 (m, 1 H), 2.79 (d, 1 H, *J* = 14.1 Hz), 2.40 (dd, 1 H, *J* = 14.2, 5.8 Hz), 2.29 (dd, 1 H, *J* = 14.2, 3.6 Hz), 2.20 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 40.1, 43.5, 43.7, 46.2, 52.6, 53.4, 59.8, 63.4, 64.8, 106.2, 108.9, 124.7, 137.8, 151.5, 162.9, 171.2, 208.2; MS *m/z* 333 (100, M^+), 301, 274, 246, 233, 202, 174, 130; HRMS calcd for $C_{17}H_{19}NO_6$ 333.1207, found 333.1209.

(11*E*)-(±)-7-(Ethylenedioxy)-11-ethylidene-7,8,9,10-tetrahydro-2-methoxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester. To a suspension of ethyltriphenylphosphonium bromide (9.05 g, 24.4 mmol) in dry THF (87 mL) was added *n*-BuLi (8.2 mL, 20.5 mmol, 2.5 M in hexane) within 10 min. The resulting orange-colored suspension was stirred at rt for 70 min. After the suspension was cooled to 0 °C, a solution of β-keto ester **14** (1.732 g, 5.2 mmol) in dry THF (238 mL) was slowly added over a period of 15 min. The resulting mixture was allowed to warm to rt and stirred for 4 h. Then the reaction was quenched with water, the THF was evaporated, and the aqueous residue was extracted with ethyl acetate (3 × 50 mL). The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (34% ethyl acetate in hexanes) afforded 1.575 g (88%) of the title compound as an oil which by ^1H NMR and GC analysis consisted of a 20/80 mixture of (*Z*)- and (*E*)-alkenes: R_f = 0.37 (34% ethyl acetate in hexanes); IR (neat) 2945, 1730, 1601, 1479, 734 cm^{-1}; ^1H NMR (*Z*-olefin, $CDCl_3$) δ 6.94 (d, 1 H, *J* = 8.6 Hz), 6.49 (d, 1 H, *J* = 8.5 Hz), 5.57 (q, 1 H, *J* = 7.3 Hz), 3.89 (s, 3 H), 3.72 (s, 3 H), 3.69–3.60 (m, 3 H), 3.48 (m, 1 H), 3.27 (dd, 1 H, *J* = 17.8, 7.4 Hz), 2.87 (m, 2 H), 2.35 (d, 1 H, *J* = 13.4 Hz), 2.15 (dd, 1 H, *J* = 13.5, 2.9 Hz), 2.05 (dd, 1 H, *J* = 13.6, 5.8 Hz), 1.93 (m, 1 H), 1.51 (d, 3 H, *J* = 7.4 Hz); MS *m/z* 345 (20, M^+), 300, 286, 244, 212, 200, 172, 128, 115.

To a solution of the above product (572 mg, 1.65 mmol, *E*/*Z* = 20/80) in dry toluene (4.5 mL) were added AIBN (283 mg, 1.65 mmol) and thiophenol (343 μL, 3.3 mmol), and the mixture was heated at 85 °C for 22 h. Evaporation of the solvent afforded a residue which was dissolved in dichloromethane, washed with brine, and dried ($MgSO_4$). Concentration followed by chromatography (40% ethyl acetate in hexanes) afforded 545 mg (95%) of the product which by ^1H NMR and GC analysis consisted of a 95/5 mixture of (*E*)- and (*Z*)-alkenes: ^1H NMR (*E*-olefin, $CDCl_3$) δ 6.96 (d, 1 H, *J* = 8.6 Hz), 6.47 (d, 1 H, *J* = 8.5 Hz), 5.13 (q, 1 H, *J* = 6.7 Hz), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.70 (m, 3 H), 3.47 (m, 2 H), 3.18 (dd, 1 H, *J* = 17.9, 7.5 Hz), 2.91 (d, 1 H, *J* = 17.9 Hz), 2.38 (d, 1 H, *J* = 13.6 Hz), 2.08 (d, 1 H, *J* = 12.3 Hz), 1.96 (m, 2 H), 1.71 (d, 3 H, *J* = 6.7 Hz); MS *m/z* 345 (18, M^+), 286, 244, 212, 200, 172; HRMS calcd for $C_{19}H_{23}NO_5$ 345.1570, found 345.1575.

(11*E*)-(±)-7-(Ethylenedioxy)-11-ethylidene-7,8,9,10-tetrahydro-2-methoxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid. The above olefin mixture (240 mg, 0.695 mmol, *E*/*Z* = 90/10) was dissolved in THF (0.7 mL), and 20% aqueous NaOH (0.556 mL) was added, followed by methanol (1.2 mL). The reaction mixture was heated with stirring to reflux under Ar for 26 h. After cooling, the pH was adjusted to 5–6 with 15% HCl, and the solvents were evaporated. The residue was dissolved in ethyl acetate, the phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography (ethyl acetate) of the residue afforded the desired acid (185 mg) in 81% yield as a white solid: mp 217–218 °C (from 5% ethyl acetate in hexanes); R_f = 0.51 (ethyl acetate); IR (KBr) 2941, 2607, 1716, 1475, 1124, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, 1 H, *J* = 8.6 Hz), 6.52 (d, 1 H, *J* = 8.5 Hz), 5.43 (q, 1 H, *J* = 6.6 Hz), 3.90 (s, 3 H), 3.76–3.65 (m, 3 H), 3.56–3.43 (m, 2 H), 3.20 (dd, 1 H, *J* = 17.9, 7.4 Hz), 2.94 (d, 1 H, *J* = 17.9 Hz), 2.37 (d, 1 H, *J* = 13.5 Hz), 2.11 (dd, 1 H, *J* = 13.6, 1.2 Hz), 1.98 (m, 2 H), 1.74 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 12.8, 30.3, 38.8, 42.5, 45.9, 53.4, 54.8, 63.0, 64.5, 107.3, 107.9, 116.4, 126.3, 137.4, 137.5, 153.9, 162.3, 179.0; HRMS calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1414.

(11*E*)-(±)-[7-(Ethylenedioxy)-11-ethylidene-7,8,9,10-tetrahydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic Acid Methyl Ester (15). To a solution of the above intermediate (185 mg, 0.556 mmol) and dry triethylamine (77 μL, 0.556 mmol) in dry toluene (2.6 mL) was added diphenyl phosphorazidate (120 μL, 0.556 mmol). The reaction mixture was heated under Ar at 85 °C for 3 h. The solvent was evaporated, dry methanol (2.6 mL) was added, and the resulting solution was refluxed for 16 h. After cooling and evaporation, the residue was directly purified by flash column chromatography (10% ethyl acetate in chloroform) to afford 162 mg (81%) of carbamate **15** as colorless prisms: mp 91–92 °C (from chloroform); R_f = 0.32 (10% ethyl acetate in chloroform); IR (KBr) 3329, 2945, 1716, 1599, 1315, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (d, 1 H, *J* = 8.5 Hz), 6.50 (d, 1 H, *J* = 8.5 Hz), 5.44 (q, 1 H, *J* = 6.8 Hz), 4.86 (s, carbamate NH), 3.88 (s, 3 H), 3.76–3.65 (m, 3 H), 3.64 (s, 3 H), 3.60–3.44 (m, 2 H), 3.18 (dd, 1 H, *J* = 17.9, 7.3 Hz), 2.87 (d, 1 H, *J* = 17.9 Hz), 2.24 (m, 1 H), 2.06–1.92 (m, 3 H), 1.73 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5, 30.1, 38.8, 42.5, 49.6, 51.9, 53.3, 59.0, 63.1, 64.5, 107.4, 108.2, 113.5, 128.8, 129.7, 134.5, 137.3, 154.1, 162.2; MS *m/z* 360 (65, M^+), 315, 274 (100), 259, 227, 199, 143; HRMS calcd for $C_{19}H_{24}N_2O_5$ 360.1679, found 360.1663.

(11*E*)-(±)-[11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-oxo-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic Acid Methyl Ester (16). A solution of ketal **15** (18 mg, 0.05 mmol) in *i*-PrOH (0.61 mL) and 5% HCl (154 μL) was heated at 70 °C under argon for 2.5 h. After cooling, the mixture was evaporated, neutralized, and extracted with ethyl acetate. The organic layers were washed with brine and dried ($MgSO_4$). Evaporation and flash chromatography of the residue (ethyl acetate/dichloromethane (1:1)) gave 15 mg (94%) of ketone **16** as a white solid: mp 89–90 °C (from ethyl acetate); R_f = 0.62 (ethyl acetate/dichloromethane (1:1)); IR (KBr) 3319, 2951, 1714, 1685, 1601, 1475, 1265, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (d, 1 H, *J* = 8.7 Hz), 6.56 (d, 1 H, *J* = 8.6 Hz), 5.67 (q, 1 H, *J* = 7.5 Hz), 5.05 (s, carbamate NH), 3.84 (s, 3 H), 3.69 (m, 4 H), 3.18 (m, 2 H), 2.81 (d, 1 H, *J* = 17.6 Hz), 2.62 (m, 2 H), 2.49 (d, 1 H, *J* = 15.9 Hz), 1.82 (d, 3 H, *J* = 6.8 Hz); MS *m/z* 316 (62, M^+), 301, 246, 227 (100), 199, 184, 156, 115; HRMS calcd for $C_{17}H_{20}N_2O_4$ 316.1418, found 316.1419.

(5*SR*,7*SR*,9*SR*,11*E*)-Amino Carbamate 17. A mixture of ketone **16** (25 mg, 79 mmol), anhydrous NH_4Cl (3.75 mg), and concentrated methanolic ammonia (1.25 mL, 8 M solution) was heated at 71 °C in a resealable tube under argon for 80 min. After the mixture was cooled to 0 °C, sodium borohydride (5 mg, 135 mmol) was added, and the mixture was stirred at 0 °C for 1 h and then warmed to rt and stirred for 20 min. After the reaction was quenched with water (1 mL), the pH was adjusted to 8 with 15% HCl, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated in vacuo. The crude product was purified by flash chromatography (15% methanol in chloroform) to afford the amine **17** in 84% yield (21 mg) as an oil which solidified on standing. Colorless prisms: mp 82–83 °C (from 5% ethyl acetate in hexanes); R_f = 0.37 (15% methanol in chloroform); IR (neat) 3308, 2930, 1716, 1599, 1263, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (d, 1 H, *J* = 8.6 Hz), 6.57 (d, 1 H, *J* = 8.6 Hz), 5.38 (q, 1 H, *J* = 6.8 Hz), 4.86 (s, carbamate NH), 3.87 (s, 3 H), 3.62 (s, 3 H), 3.43 (m, 1 H), 3.26–3.14 (m, 2 H), 2.90 (d, 1 H, *J* = 17.5 Hz), 2.18–2.00 (m, 2 H), 1.90 (dd, 1 H, *J* = 12.4, 2.7 Hz), 1.70 (m, 4 H), 1.25 (br s, NH_2); MS *m/z* 317 (100, M^+), 274, 259, 227, 199, 184, 138, 115; HRMS calcd for $C_{17}H_{23}N_3O_3$ 317.1734, found 317.1735.

(5*RS*,7*SR*,9*SR*,11*E*)-5,7-Diamino-11-ethylidene-5,6,7,8,9,-10-hexahydro-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one (18). To a solution of carbamate **17** (90 mg, 0.284 mmol) in dry chloroform (8.9 mL) was slowly added TMSI (0.563 mL, 3.98 mmol) under argon at rt. The yellow-colored solution was refluxed for 5.5 h. After cooling and evaporation, the residue was dissolved in absolute methanol (8.9 mL), and the resulting solution was refluxed under argon for 16 h. Concentration and

flash chromatography on silica gel half-saturated with ammonia using 30% methanol in chloroform as eluent gave the huperzine A analogue **18** in 87% yield (57 mg) as white crystals: mp 200 °C dec (from ethyl acetate); R_f = 0.22 (30% methanol in chloroform); IR (Nujol) 3395, 1656, 1607, 1450, 830 cm^{-1}; ^{1}H NMR (D_2O) δ 7.72 (d, 1 H, J = 9.4 Hz), 6.34 (d, 1 H, J = 9.4 Hz), 5.37 (q, 1 H, J = 6.7 Hz), 3.31 (m, 1 H), 2.87–2.75 (m, 2 H), 2.54 (d, 1 H, J = 18.0 Hz), 1.92 (dt, 1 H, J = 14.6, 6.2 Hz), 1.73 (dd, 1 H, J = 13.3, 6.4 Hz), 1.62 (dd, 1 H, J = 13.4, 5.1 Hz), 1.50 (d, 3 H, J = 6.7 Hz), 1.40 (dt, 1 H, J = 14.0, 4.0 Hz); ^{13}C NMR (D_2O) δ 14.0, 31.1, 37.6, 40.0, 47.4, 50.7, 55.4, 116.4, 119.2, 128.8, 143.2, 143.6, 145.7, 167.0; MS m/z 245 (23, M$^+$), 228, 213, 187 (100), 173, 161, 143; HRMS calcd for $C_{14}H_{19}N_3O$ 245.1524, found 245.1530.

(5*RS*,7*SR*,9*SR*,11*E*)-Hydroxy Carbamate 19. Sodium borohydride (36.6 mg, 0.969 mmol) was added to a solution of ketone **16** (300 mg, 0.949 mmol) in dry methanol (7 mL) cooled to 0 °C. The mixture was stirred at 5 °C under argon for 3 h, quenched with water (1 mL), and concentrated in vacuo. The aqueous mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to dryness. Purification by flash chromatography (ethyl acetate/dichloromethane (1:1)) provided alcohol **19** in 85% yield (254 mg) as colorless prisms: mp 206–207 °C (from 10% ethyl acetate in hexanes); R_f = 0.29 (ethyl acetate/dichloromethane (1:1)); IR (KBr) 3308, 2918, 1716, 1473, 1109, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1 H, J = 8.6 Hz), 6.56 (d, 1 H, J = 8.5 Hz), 5.40 (q, 1 H, J = 7.1 Hz), 4.87 (s, carbamate NH), 4.12 (m, 1 H), 3.87 (s, 3 H), 3.64 (s, 3 H), 3.46 (m, 1 H), 3.24 (dd, 1 H, J = 17.9, 6.9 Hz), 2.97 (d, 1 H, J = 17.9 Hz), 2.24 (br s, OH), 2.14–2.01 (m, 3 H), 1.72–1.65 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 12.4, 30.3, 39.5, 40.8, 49.4, 51.9, 53.3, 58.2, 66.8, 108.5, 112.9, 129.7, 135.1, 137.9, 153.5, 154.6, 162.5; MS m/z 318 (80, M$^+$), 299, 285, 246, 227 (100), 199, 173, 130; HRMS calcd for $C_{17}H_{22}N_2O_4$ 318.1574, found 318.1588.

(11*E*)-(±)-[7-Azido-11-ethylidene-7,8,9,10-tetrahydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic Acid Methyl Ester (20 and 21). Methanesulfonyl chloride (0.126 mL, 1.68 mmol) was added dropwise to an ice-cooled solution of alcohol **19** (267 mg, 0.84 mmol) and triethylamine (0.35 mL, 2.52 mmol) in 12 mL of dry THF/diethyl ether (5:1) under argon. The reaction mixture was stirred for 2 h at 0 °C and then warmed to 10 °C and stirred for an additional 1 h. After quenching with ice, the solvent was evaporated and the residue extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography (40% hexanes in ethyl acetate) to afford the mesylate in 93% yield (0.309 g) as a colorless oil: R_f = 0.33 (40% hexanes in ethyl acetate); IR (neat) 3321, 2943, 1716, 1599, 1475, 1170, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54 (d, 1 H, J = 8.6 Hz), 6.56 (d, 1 H, J = 8.5 Hz), 5.45 (q, 1 H, J = 6.7 Hz), 5.15 (m, 1 H), 4.86 (s, carbamate NH), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.50 (m, 1 H), 3.24 (dd, 1 H, J = 18.0, 7.1 Hz), 2.95 (d, 1 H, J = 17.9 Hz), 2.46 (s, 3 H), 2.39–2.27 (m, 2 H), 2.10 (m, 1 H), 1.72 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 12.4, 30.0, 38.1, 38.5, 39.1, 46.2, 52.0, 53.4, 58.0, 75.1, 108.0, 114.0, 129.2, 135.2, 136.5, 154.2, 154.9, 162.4; MS m/z 396 (20, M$^+$), 317, 300, 259, 225, 210, 201, 184; HRMS calcd for $C_{18}H_{24}N_2O_6S$ 396.1349, found 396.1340.

To a solution of the mesylate (310 mg, 0.78 mmol) in dry HMPA (3.9 mL) was added sodium azide (509 mg, 7.8 mmol), and the mixture was stirred at rt under argon for 96 h. Insoluble material was filtered off, and the filtrate was partitioned between brine and ethyl acetate and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated, and the crude product was purified by flash chromatography (hexanes/ethyl acetate (1:1)) to yield 233 mg (88%) of a sample which by ^{1}H NMR and GC analysis consisted of a 78/22 mixture of the equatorial (**20**) and axial (**21**) azides: R_f = 0.62 (hexanes/ethyl acetate (1:1)); IR ($CHCl_3$) 3325, 2096, 1716, 1475, 1255, 731 cm^{-1}. This mixture was used directly in the next step without further purification.

(5*RS*,7*RS*,9*SR*,11*E*)-Amino Carbamate 22. To a solution of the azides **20** and **21** (233 mg, 0.67 mmol, eq/ax = 78/22) and triethylamine (0.279 mL, 2 mmol) in dry methanol (3.2 mL) was added 1,3-propanedithiol (0.251 mL, 2.5 mmol). The mixture was stirred at rt under argon for 96 h, and then the white solid was filtered off and the solution evaporated in vacuo. The crude residue was directly chromatographed on silica gel half-saturated with ammonia using 14% methanol in ethyl acetate as eluent to afford the equatorial amine **22** in 68% yield (144 mg) as a white solid: mp 87–88 °C (from hexanes); R_f = 0.38 (30% methanol in ethyl acetate). A small amount of olefin **23** (20%) was obtained in addition as colorless prisms: mp 150–151 °C (from hexanes); R_f = 0.63 (20% methanol in ethyl acetate). Compound **22**: IR (neat) 3308, 2930, 1715, 1599, 1475, 1318, 1260, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1 H, J = 8.5 Hz), 6.53 (d, 1 H, J = 8.6 Hz), 5.40 (q, 1 H, J = 6.7 Hz), 4.97 (s, carbamate NH), 3.86 (s, 3 H), 3.63 (s, 3 H), 3.40 (m, 1 H), 3.19 (dd, 1 H, J = 18.0, 6.7 Hz), 2.80 (d, 1 H, J = 18.1 Hz), 2.72 (m, 1 H), 2.10–1.87 (m, 2 H), 1.83 (br s, NH_2), 1.71 (m, 4 H), 1.42 (dt, 1 H, J = 12.4, 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ 12.4, 30.9, 39.2, 44.3, 44.9, 51.6, 51.9, 53.3, 59.3, 108.5, 113.0, 129.5, 134.9, 137.6, 154.0, 154.7, 162.3; MS m/z 317 (100, M$^+$), 273, 259, 227, 199, 175, 115; HRMS calcd for $C_{17}H_{23}N_3O_3$ 317.1734, found 317.1751. Compound **23**: IR (KBr) 3327, 1714, 1475, 1257, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1 H, J = 8.6 Hz), 6.55 (d, 1 H, J = 8.6 Hz), 5.77–5.72 (m, 1 H), 5.46–5.42 (m, 1 H), 5.37 (q, 1 H, J = 6.7 Hz), 5.10 (s, carbamate, NH), 3.86 (s, 3 H), 3.71 (m, 1 H), 3.60 (s, 3 H), 3.10 (dd, 1 H, J = 16.8, 4.1 Hz), 2.84 (dd, 1 H, J = 16.9, 1.8 Hz), 2.55 (m, 1 H), 2.35 (dd, 1 H, J = 15.9, 5.0 Hz), 1.72 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 12.4, 34.2, 38.9, 44.6, 51.8, 53.2, 58.6, 108.5, 111.9, 124.0, 129.7, 131.4, 135.3, 136.4, 152.9, 154.5, 162.4; MS m/z 300 (10, M$^+$), 253, 225, 210, 196, 167, 128, 91; HRMS calcd for $C_{17}H_{20}N_2O_3$ 300.1475, found 300.1458.

(5*RS*,7*RS*,9*SR*,11*E*)-5,7-Diamino-11-ethylidene-5,6,7,8,9,-10-hexahydro-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one (24). Iodotrimethylsilane (0.444 mL, 3.1 mmol) was added dropwise to a solution of carbamate **22** (71 mg, 0.224 mmol) in dry chloroform (7 mL) under argon at rt, and the yellow-colored solution was refluxed for 5.5 h. The solvent was evaporated, the crude product dissolved in dry methanol (7 mL), and the mixture refluxed for 16 h under argon. Concentration and flash chromatography on silica gel half-saturated with ammonia using 30% methanol in ethyl acetate as eluent gave the huperzine A analogue **24** in 78% yield (43 mg) as a white solid: mp 180 °C dec (from ethyl acetate); R_f = 0.24 (30% methanol in ethyl acetate); ^{1}H NMR (D_2O) δ 7.61 (d, 1 H, J = 9.3 Hz), 6.27 (d, 1 H, J = 9.4 Hz), 5.38 (q, 1 H, J = 6.7 Hz), 3.33 (m, 1 H), 2.86 (dd, 1 H, J = 18.5, 7.2 Hz), 2.64 (m, 1 H), 2.54 (d, 1 H, J = 18.5 Hz), 1.85 (m, 1 H), 1.77 (dd, 1 H, J = 11.7, 4.1 Hz), 1.52 (d, 3 H, J = 6.7 Hz), 1.23 (dt, 1 H, J = 12.5, 4.4 Hz), 1.17 (t, 1 H, J = 11.7 Hz); ^{13}C NMR (D_2O) δ 14.2, 31.8, 36.3, 43.5, 46.9, 51.9, 56.2, 116.0, 118.5, 126.3, 142.7, 143.0, 147.2, 166.8; MS m/z 245 (18, M$^+$), 230, 228 (100), 213, 202, 188, 173, 161; HRMS calcd for $C_{14}H_{19}N_3O$ 245.1524, found 245.1523.

(5*RS*,9*SR*,11*RS*)-Cyano Ester 26. Ketone **7** (345 mg, 1.2 mmol) and (*p*-toluenesulfonyl)methyl isocyanide (306 mg, 1.56 mmol) were dissolved in dry methanol (4 mL) and 1,2-dimethoxyethane (4.2 mL). The stirred solution was cooled to 5 °C, and potassium *tert*-butoxide (336 mg, 3 mmol) was added in portions at such a rate that the temperature was kept between 5 and 10 °C. After the addition was complete, the ice bath was removed, and stirring was continued for 30 min. The reaction mixture was heated for 2 h at 35–40 °C, quenched with water, and extracted with ethyl acetate. The organic layers were washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography (25% and then 33% ethyl acetate in hexanes) gave 140 mg (39%) of nitrile **26** as a white solid: mp 154–155 °C (from ethyl acetate); R_f = 0.53 (30% ethyl acetate in hexanes); IR (KBr) 2935, 2916, 2243, 1734, 1599, 1477, 1295 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1 H, J = 8.7 Hz), 6.55 (d, 1 H, J = 8.7 Hz), 5.45–5.44 (m, 1 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.54 (s, 1 H), 3.15–3.08 (m, 2 H), 2.98 (d, 1 H, J = 18.6 Hz), 2.88 (dd, 1 H, J = 19.3, 7.3 Hz), 2.25 (d, 1 H, J = 18.0 Hz), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 23.0, 33.0, 33.2, 38.0, 38.7, 47.3, 53.0, 53.4, 109.4, 119.5, 120.8, 124.1, 132.8, 136.4, 150.8, 163.1, 173.0; MS m/z 298 (30, M$^+$), 257, 239, 123 (100); HRMS calcd for $C_{17}H_{18}N_2O_3$ 298.1317, found 298.1302. Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.73; H, 6.11; N, 9.40.

(5*RS*,9*SR*,11*RS*)-Cyano Acid 27. A mixture of nitrile **26** (150 mg, 0.5 mmol), THF (1 mL), methanol (1 mL), and 1 N NaOH (1 mL) was stirred for 24 h at rt. The organic solvents were removed by rotary evaporation, and the aqueous residue was neutralized with 5% HCl. Extraction with ethyl acetate, drying ($MgSO_4$), and concentration gave the crude acid which

was purified by flash column chromatography (20% hexanes in ethyl acetate, then ethyl acetate) to afford 131 mg (92%) of acid **27**: R_f = 0.45 (25% methanol in ethyl acetate); IR (neat) 2917, 2857, 2245, 1728, 1479, 1269, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.30 (br s, 1 H), 7.56 (d, 1 H, J = 8.7 Hz), 6.70 (d, 1 H, J = 8.7 Hz), 5.45 (m, 1 H), 3.88 (s, 3 H), 3.54 (s, 1 H), 3.19–3.15 (m, 2 H), 3.02 (d, 1 H, J = 18.1 Hz), 2.84 (d, 1 H, J = 15.9 Hz), 2.25 (d, 1 H, J = 18.0 Hz), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 23.0, 32.9, 33.1, 37.6, 38.5, 47.4, 53.7, 109.2, 119.4, 120.8, 123.9, 132.8, 137.0, 151.0, 163.3, 177.5.

(5*RS*,9*SR*,11*RS*)-Cyano Carbamate 28. To the carboxylic acid **27** (82 mg, 0.29 mmol) in 4 mL of dry toluene were added triethylamine (40 μL, 0.29 mmol) and diphenyl phosphorazidate (63 μL, 0.29 mmol). The mixture was heated at 85 °C under argon for 3 h. After cooling, the solvent was removed, 5 mL of dry methanol was added, and the mixture was refluxed under argon for 18 h. After cooling and evaporation, the residue was directly chromatographed on silica gel (10% and then 20% ethyl acetate in dichloromethane) to afford 60 mg (67%) of urethane **28**: R_f = 0.36 (10% ethyl acetate in dichloromethane); IR (neat) 3337, 2941, 2243, 1714, 1477, 1263, 1222 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1 H, J = 8.6 Hz), 6.57 (d, 1 H, J = 8.6 Hz), 5.52 (m, 1 H), 5.38 (br s, 1 H), 4.10 (m,1 H), 3.87 (s, 3 H), 3.60 (s, 3 H), 3.20–3.10 (m, 2 H), 2.78 (dd, 1 H, J = 18.9, 3.3 Hz), 2.63 (d, 1 H, J = 17.5 Hz), 2.20 (d, 1 H, J = 17.6 Hz), 1.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 22.9, 34.3, 34.6, 37.7, 43.3, 52.3, 53.5, 54.4, 109.6, 119.9, 122.5, 127.2, 131.5, 135.2, 151.3, 154.6, 163.1; MS m/z 313 (60, M$^+$), 288, 266, 239 (100), 123.

(5*RS*,9*SR*,11*RS*)-Cyano Amine 29. To a solution of urethane **28** (100 mg, 0.32 mmol) in 4 mL of HMPA was added under argon lithium *n*-propyl mercaptide (1.6 mL, 3 M in HMPA). The mixture was stirred at rt for 18 h and then quenched by addition of ice and extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (20% and then 50% ethyl acetate in dichloromethane as eluent) gave 50 mg (61%) of amine **29**: R_f = 0.20 (10% ethyl acetate in dichloromethane); IR (neat) 3374, 2930, 2241, 1595, 1475, 1260, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 8.6 Hz), 6.66 (d, 1 H, J = 8.6 Hz), 5.46–5.42 (m, 1H), 3.88 (s, 3 H), 3.14–3.01 (m, 2 H), 2.89 (s, 1 H), 2.79 (d, 1 H, J = 17.0 Hz), 2.52 (d, 1 H, J = 18.1 Hz), 2.02 (d, 1 H, J = 17.5 Hz), 1.63 (br s, 2 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 22.8, 34.8, 38.0, 42.5, 44.4, 51.9, 53.4, 109.1, 120.7, 121.1, 129.6, 133.9, 136.9, 151.1, 163.0; MS m/z 255 (20, M$^+$), 240, 215 (100), 200; HRMS calcd for $C_{15}H_{17}N_3O$ 255.1372, found 255.1364. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.79; H, 6.72; N, 16.63.

(5*RS*,9*SR*,11*RS*)-5-Amino-11-(aminomethyl)-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one (30). To a solution of amine **29** (41 mg, 0.16 mmol) in 4 mL of dry THF was added LAH (41 mg, 1.08 mmol) at rt under argon. After the solution was stirred for 2 h at rt, 2 mL of 15% NaOH was added. Extraction with chloroform, washing with brine, drying ($MgSO_4$), and concentration gave a residue which was dissolved in 5 mL of dry chloroform under Ar. Iodotrimethylsilane (0.4 mL, 2.8 mmol) was added, and the solution was refluxed for 6 h. After cooling and evaporation, 8 mL of methanol was added, and the solution was refluxed again for 18 h. Concentration followed by column chromatography on Amberlite IRA-400 (OH^- form, water as eluent) afforded 34 mg (87%) of diamine **30**: R_f = 0.40 (SiO_2, 20% NH_3 (aq) in MeOH); IR (neat) 3422, 1655, 1606, 1458, 1385 cm^{-1}; ^{1}H NMR (D_2O) δ 7.69 (d, 1 H, J = 9.5 Hz), 6.31 (d, 1 H, J = 9.5 Hz), 5.23–5.21 (m, 1 H), 3.09 (dd, 1 H, J = 13.1, 7.8 Hz), 2.86–2.74 (m, 2 H), 2.49 (m, 1 H), 2.41 (d, 1 H, J = 17.6 Hz), 2.10 (d, 1 H, J = 17.9 Hz), 1.91–1.78 (m, 2 H), 1.36 (s, 3 H); ^{13}C NMR (D_2O) δ 24.3, 34.9, 35.8, 42.4, 42.5, 42.7, 54.4, 119.0, 123.6, 136.3, 143.7, 144.9, 167.1; MS m/z 245 (70, M$^+$), 228, 215 (100), 198, 173, 160; HRMS calcd for $C_{14}H_{19}N_3O$ 245.1528, found 245.1515.

(±)-11-[(Ethoxycarbonyl)methylene]-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (31a and 32a). NaH (60% in oil, 80 mg, 2 mmol) was suspended in dry THF (5 mL), and triethyl phosphonoacetate (0.436 mL, 2.2 mmol) was added at rt under nitrogen. The mixture was stirred for 1 h at rt, and the ketone **7** (287 mg, 1 mmol) in 2 mL of dry THF was added dropwise. After being stirred at rt for 2 h, the reaction was quenched with water, the THF was evaporated, and the aqueous residue was extracted with ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the crude residue (12% ethyl acetate in hexanes as eluent) gave 194 mg (54%) of the ester **32a** and 150 mg (30%) of ester **31a**. **32a**: R_f = 0.63 (42% ethyl acetate in hexanes); IR (neat) 2980, 1734, 1716, 1655, 1601, 1180, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.09 (d, 1 H, J = 8.5 Hz), 6.56 (d, 1 H, J = 8.5 Hz), 5.47 (s, 1 H), 5.37–5.39 (m, 1 H), 4.89 (m, 1 H), 4.18 (m, 2 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.20 (dd, 1 H, J = 17.3, 5.4 Hz), 3.13 (d, 1 H, J = 17.1 Hz), 2.98 (dd, 1 H, J = 17.3, 2.0 Hz), 2.30 (d, 1 H, J = 17.1 Hz), 1.56 (s, 3 H), 1.29 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.3, 33.8, 39.7, 46.2, 52.4, 53.3, 55.1, 60.1, 108.9, 111.7, 124.3, 126.6, 132.2, 137.2, 152.2, 158.6, 162.8, 165.8, 174.1; MS m/z 357 (60, M$^+$), 298, 268, 224 (100); HRMS calcd for $C_{20}H_{23}NO_5$ 357.1576, found 357.1567. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.22; H, 6.37; N, 4.09. **31a**: R_f = 0.53 (30% ethyl acetate in hexanes); IR (neat) 2980, 1740, 1719, 1653, 1601, 1217, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 1 H, J = 8.7 Hz), 6.54 (d, 1 H, J = 8.5 Hz), 5.94 (s, 1 H), 5.39 (m, 1 H), 4.10 (m, 2 H), 3.88 (s, 3 H), 3.59 (s, 3 H), 3.27–3.20 (m, 2 H), 3.12 (d, 1 H, J = 17.1 Hz), 2.90 (dd, 1 H, J = 18.5, 3.3 Hz), 2.49 (d, 1 H, J = 17.1 Hz), 1.55 (s, 3 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 22.5, 39.0, 43.6, 46.0, 51.8, 51.9, 53.4, 60.3, 109.2, 113.3, 125.1, 126.4, 133.9, 136.4, 151.6, 153.6, 162.8, 166.1, 173.0; MS m/z 357 (45, M$^+$), 325, 268, 252, 224 (100); HRMS calcd for $C_{20}H_{23}NO_5$ 357.1576, found 357.1582. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.25; H, 6.50; N, 4.02.

(11*E*)-(±)-11-[(Ethoxycarbonyl)methylene]-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid (33a). To a solution of ester **32a** (107 mg, 0.3 mmol) in dry HMPA (4mL) was added lithium *n*-propyl mercaptide (0.2 mL, 3 M solution in HMPA), and the mixture was stirred at rt under argon for 1 h. The reaction was quenched with water, and the pH was adjusted to 7 with 5% HCl. Extraction with ethyl acetate, drying ($MgSO_4$), concentration, and chromatography (20% ethyl acetate in hexanes and then ethyl acetate) gave 96 mg (93%) of acid **33a**: R_f = 0.46 (ethyl acetate); IR (KBr) 2935, 2583, 1715, 1651, 1487, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (d, 1 H, J = 8.6 Hz), 6.61 (d, 1 H, J = 8.6 Hz), 5.74 (s, 1 H), 5.39–5.37 (m, 1 H), 4.91 (m, 1 H), 4.20 (t, 2 H, J = 7.1 Hz), 3.90 (s, 3 H), 3.22 (dd, 1 H, J = 17.4, 4.9 Hz), 3.09 (d, 1 H, J = 17.2 Hz), 2.97 (dd, 1 H, J = 17.3, 1.6 Hz), 2.32 (d, 1 H, J = 17.2 Hz), 1.55 (s, 3 H), 1.30 (q, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 22.4, 33.8, 39.6, 46.0, 53.6, 55.1, 60.3, 108.8, 112.1, 124.3, 126.3, 132.2, 137.7, 152.5, 157.9, 163.0, 166.0, 177.9.

(11*E*)-(±)-[11-[(Ethoxycarbonyl)methylene]-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic Acid Methyl Ester (34a). To the carboxylic acid **33a** (250 mg, 0.73 mmol) in dry toluene (6 mL) were added triethylamine (0.102 mL, 0.73 mmol) and diphenyl phosphorazidate (0.158 mL, 0.73 mmol). The mixture was heated to 85 °C and stirred under argon for 3 h. After cooling, the solvent was removed, and dry methanol (6 mL) was added. The mixture was again refluxed under argon for 18 h. After cooling and evaporation, the residue was directly chromatographed on silica gel (10% ethyl acetate in dichloromethane) to afford 215 mg (79%) of urethane **34a**: R_f = 0.33 (ethyl acetate in dichloromethane); IR (neat) 3336, 2901, 1715, 1599, 1259, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 1 H, J = 8.6 Hz), 6.57 (d, 1 H, J = 8.6 Hz), 5.80 (s, 1 H), 5.43–5.41 (m, 1 H), 5.18 (s, 1 H), 4.94 (m,1 H), 4.18 (m, 2 H), 3.87 (s, 3 H), 3.62 (s, 3 H), 3.09 (d, 1 H, J = 17.2 Hz), 2.91 (dd, 1 H, J = 17.2, 1.9 Hz), 2.65–2.58 (m, 1 H), 2.27 (d, 1 H, J = 15.7 Hz), 1.51 (s, 3 H), 1.26 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 22.1, 34.7, 39.4, 49.8, 52.1, 53.3, 59.0, 60.0, 108.9, 109.6, 125.6, 128.7, 131.1, 135.0, 152.8, 154.2, 158.7, 162.7, 166.4; MS m/z 267 (15, M$^+$), 224, 209.

(11*E*)-(±)-5-Amino-11-[(ethoxycarbonyl)methylene]-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one (35a). Iodotrimethylsilane (0.84 mL, 5.9 mmol) was added dropwise to a solution of the carbamate **34a** (219 mg, 0.59 mmol) in chloroform (20 mL) under nitrogen at rt. The solution was then refluxed for 6 h. After cooling and evaporation, 20 mL of methanol was added, and the solution was refluxed for 18 h. Concentration and flash chromotagraphy on silica gel half-saturated with ammonia using 10% methanol in dichloromethane as eluent gave 159 mg (90%) of **35a**: R_f = 0.40 (10% methanol

in dichloromethane); IR (KBr) 3385, 2985, 1966, 1664, 1595, 1179, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86 (d, 1 H, J = 9.4 Hz), 6.43 (d, 1 H, J = 9.4 Hz), 5.98 (s, 1 H), 5.39–5.37 (m, 1 H), 4.82 (br s, 1 H), 4.16 (q, 2 H, J = 7.1 Hz), 3.05 (dd, 1 H, J = 17.2, 5.1 Hz), 2.82 (d, 1 H, J = 17.2 Hz), 2.23 (s, 2 H), 1.55 (s, 3 H), 1.37 (br s, 2 H), 1.30 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.2, 33.7, 35.6, 49.4, 55.3, 60.0, 109.3, 117.6, 121.3, 124.1, 133.5, 140.0, 142.8, 164.0, 165.4, 166.3; MS m/z 300 (38, M^+), 285, 243, 227, 131 (100); HRMS calcd for $C_{17}H_{20}N_2O_3$ 300.1474, found 300.1466.

(±)-11-(Cyanomethylene)-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid Methyl Ester (31b and 32b). To a stirred solution of the ketone **7** (720 mg, 2.51 mmol) and diethyl (cyanomethyl)phosphonate (2.03 mL, 12.5 mmol) in dry toluene (15 mL) was added at rt under argon potassium *tert*-butoxide (704 mg, 6.28 mmol), and the resulting mixture was stirred at rt for 6 h. The reaction mixture was then diluted with ethyl acetate, washed with brine, and dried ($MgSO_4$). After evaporation, the residue was chromatographed on silica gel (12% and then 20% ethyl acetate in hexanes) to give 107 mg (13.8%) of nitrile **32b** and 643 mg (82.6%) of nitrile **31b**. Nitrile **32b**: R_f = 0.50 (30% ethyl acetate in hexanes); IR (neat) 2918, 2222, 1734, 1605, 1325, 1254 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (d, 1 H, J = 8.5 Hz), 6.56 (d, 1 H, J = 8.5 Hz), 5.46 (s, 1 H), 5.43–5.39 (m, 1 H), 3.89 (s, 4 H), 3.78 (s, 3 H), 3.15 (dd, 1 H, J = 17.3, 5.1 Hz), 3.02 (d, 1 H, J = 17.8 Hz), 2.95 (dd, 1 H, J = 17.3, 1.7 Hz), 2.29 (d, 1 H, J = 17.3 Hz), 1.56 (s, 3 H); MS m/z 310 (35, M^+), 278, 251, 224 (100). Nitrile **31b**: R_f = 0.40 (30% ethyl acetate in hexanes); IR (neat) 2914, 2220, 1740,1637, 1601, 1323, 1259, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, 1 H, J = 8.6 Hz), 6.57 (d, 1 H, J = 8.6 Hz), 5.46 (s, 1 H), 5.34–5.33 (m, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.24–3.08 (m, 3 H), 2.94 (dd, 1 H, J = 17.1, 1.4 Hz), 2.38 (d, 1 H, J = 17.4 Hz), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 39.4, 42.8, 46.5, 52.4, 53.2, 53.3, 90.4, 109.6, 114.6, 123.7, 125.8, 133.3, 136.5, 150.9, 162.2, 162.7, 172.6; MS m/z 310 (40, M^+), 278, 251, 224 (100).

(11*E*)-(±)-11-(Cyanomethylene)-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-carboxylic Acid (33b). A mixture of nitrile **32b** (65 mg, 0.22 mmol), THF (0.44 mL), methanol (0.44 mL), and 1 N NaOH solution (0.44 mL, 0.44 mmol) was stirred for 24 h at rt. THF and methanol were removed by rotary evaporation, and the pH was adjusted to 7 with 5% HCl. Extraction with ethyl acetate, drying ($MgSO_4$), and concentration gave the acid **33b** (58 mg, 94%) which was filtered over silica gel (20% hexane in ethyl acetate and then ethyl acetate; R_f = 0.26 (30% methanol in ethyl acetate)) and used in the next step without further purification .

(11*E*)-(±)-[11-(Cyanomethylene)-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic Acid Methyl Ester (34b). To a solution of **33b** (148 mg, 0.5 mmol) in 6 mL of dry toluene were added triethylamine (70 mL, 0.5 mmol) and diphenyl phosphorazidate (0.108 mL, 0.5 mmol). The mixture was heated to 85 °C for 3 h under argon. After cooling, the solvent was removed, and 6 mL of dry methanol was added. The mixture was again refluxed under argon for 18 h. After cooling and evaporation, the residue was directly chromatographed on silica gel (10% ethyl acetate in dichloromethane) to afford 130 mg (80%) of urethane **34b**: R_f = 0.35 (10% ethyl acetate in dichloromethane); IR (neat) 3325, 2916, 2220, 1712, 1529, 1477 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (d, 1 H, J = 8.6 Hz), 6.59 (d, 1 H, J = 8.6 Hz), 5.48–5.46 (m, 1 H), 5.30 (s, 1 H), 5.13 (br s, 1 H), 3.97 (m, 1 H), 3.89 (s, 3 H), 3.63 (s, 3 H), 3.26–3.19 (m, 1 H), 2.98 (dd, 1 H, J = 17.2, 1.8 Hz), 2.60 (m, 1 H), 2.29 (d, 1 H, J = 15.7 Hz), 1.55 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 39.1, 39.5, 49.6, 52.3, 53.4, 59.0, 89.4, 109.5, 116.3, 124.4, 127.8, 131.7, 134.6, 152.1, 154.0, 163.0, 164.5; MS m/z 325 (35, M^+), 278, 250.

(11*E*)-(±)-5-Amino-11-(cyanomethylene)-5,6,9,10-tetrahydro-7-methyl-5,9-methanocycloocta[*b*]pyridin-2(1*H*)-one (35b). Iodotrimethylsilane (0.228 mL, 1.3 mmol) was added to a solution of the carbamate **34b** (42 mg, 0.13 mmol) in 5 mL of chloroform at rt under nitrogen, and the solution was refluxed for 6 h. After cooling and evaporation, 5 mL of methanol was added, and the solution was refluxed for 18 h. Concentration and flash chromotagraphy on silica gel half-saturated with ammonia using 3% and then 10% of methanol in dichloromethane gave 28 mg (85%) of **35b**: R_f = 0.39 (10% methanol in dichloromethane); IR (neat) 3369, 3305, 2914, 2220, 1664, 1615, 1556, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.2 (br s, 1 H), 7.79 (d, 1 H, J = 9.5 Hz), 6.59 (d, 1 H, J = 9.5 Hz), 5.58 (s, 1 H), 5.44–5.42 (m, 1 H), 3.91 (m, 1 H), 3.06 (dd, 1 H, J = 17.5, 5.0 Hz), 2.90 (d, 1 H, J = 15.9 Hz), 2.27 (s, 2 H), 1.58 (s, 3 H), 1.44 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.2, 35.6, 37.8, 49.4, 55.4, 89.3, 116.2, 118.4, 120.6, 123.1, 134.3, 139.4, 141.9, 165.2, 169.7; MS m/z 253 (100, M^+), 238, 213, 160; HRMS calcd for $C_{15}H_{15}N_3O$ 253.1215, found 253.1229.

(±)-14-Hydroxyhuperzine A (36). To a solution of **35a** (99 mg, 0.33 mmol) in dry THF (10 mL) was added DIBALH (3.3 mL, 3.3 mmol, 1.0 M in hexanes) dropwise at −78 °C under argon, and the mixture was stirred for 1 h. Saturated sodium tartrate solution was added at −78 °C, the temperature was raised to rt, and stirring was continued for 4 h. After extraction with chloroform, the organic layers were dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography (THF and then 20% methanol in THF) gave 75 mg (82%) of **36**: R_f = 0.33 (20% methanol in THF); IR (KBr) 3432, 2918, 1655, 1647, 1606, 1384, 1062 cm^{-1}; ^1H NMR (CD_3OD) δ 7.85 (d, 1 H, J = 9.5 Hz), 6.29 (d, 1 H, J = 9.5 Hz), 5.61 (t, 1 H, J = 6.8 Hz), 5.34 (m, 1 H), 4.11 (d, 2 H, J = 6.8 Hz), 3.57 (m, 1 H), 2.78 (dd, 1 H, J = 17.0, 4.7 Hz), 2.53 (d, 1 H, J = 17.1 Hz), 2.18 (d, 1 H, J = 16.6 Hz), 2.08 (d, 1 H, J = 16.7 Hz),1.47 (s, 3 H); ^{13}C NMR (CD_3OD) δ 22.6, 34.6, 36.8, 49.9, 55.1, 58.5, 118.0, 118.3, 124.6, 125.1, 135.4, 141.8, 144.2, 144.8, 165.8; MS m/z 258 (20, M^+), 227 (100), 203, 185, 158; HRMS calcd for $C_{15}H_{18}N_2O_2$ 258.1368, found 258.1354.

Determination of AChE Activity. Male Sprague–Dawley rats (125–150 g) were sacrificed by decapitation, and the cortex was rapidly dissected on an ice-cold aluminum block and immersed in an ice-cold sodium–potassium phosphate buffer (pH 7.4). The acetylcholinesterase assay was a modification of the protocol of Wilson *et al.*[25] as previously described.[26] Rat cortical tissue was homogenized at a 1:400 dilution in 50 mM Tris–HCl, pH 7.4, 0.2% Triton X-100. Assays were performed in duplicate. The total assay volume was 50 μL and contained 15 μg equiv wet weight tissue, 10 μM ethopropazine to inhibit butyrylcholinesterase, concentrations of anticholinesterase agents in the range of 1–100 μM, and [^{14}C]acetylcholine (800 μM). Nonenzymatic activity was defined as hydrolysis occurring in the presence of both 10 μM ethopropazine and 10 μM BW284C51, a specific inhibitor of AChE. The incubation was conducted for 20 min at 37 °C. The reactions were terminated by vortexing vigorously with 100 μL of 50 mg/mL sodium tetraphenylborate in 3-heptanone and placing the tubes on ice. A sample of the aqueous phase was counted. Concentration–inhibition curves were fitted with a four-parameter logistic model using the program ALLFIT[27] in order to obtain IC_{50} values.

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Supplementary Material Available: ^{13}C NMR spectra of all new compounds and ^1H NMR spectra of **12** and (±)-[11-ethylidene-7,8,9,10-tetrahydro-7-[(methanesulfonyl)oxy]-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl]carbamic acid methyl ester (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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