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Synthesis of 5-Substituted Analogues of Huperzine A

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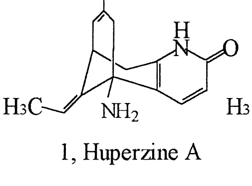
Abstract—Three 5-isosteres of huperzine A (**2**–**4**) were first synthesized. The key intermediate **10** was prepared by the reaction of acid **13** with LTA. The compounds **2** and **3** had 50% inhibition by 35 and 47 μM, respectively, which still retained anti-acetylcholinesterase activity. © 2000 Elsevier Science Ltd. All rights reserved.

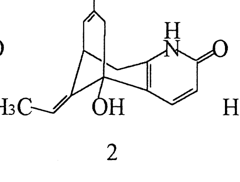
Huperzine A (**1**),[1,2] a Lycopodium alkaloid isolated from Chinese folk remedy *Huperzia serrata*, is a nootropic agent which has been found to be a potent and reversible acetylcholinesterase (AChE) inhibitor and is capable of ameliorating the memory deficits in patients suffering from neurodegenerative diseases such as Alzheimer's and improving cognitive function in AD by enhancement of central cholinergic tone in the CNS.[3–6] It has attracted widespread attention because of its considerable duration of action, its potency and lack of side effects.[5,7] In the course of studies of structure–activity relationship and potent analogues of **1**, many derivatives and analogues of **1** have been synthesized but most of them do not have comparable AChE inhibitory activity to that of (−)-**1**.[8,9]

We report herein our investigations on the synthesis of 5-substituted analogues of huperzine A (**2**–**4**). The hydroxyl group, fluoro group and amino group have the same number of electrons (isosteres) and the hydroxyl group and amino group also are similar in polarity but the hydroxyl group has much lower basicity than the amino group, so we feel that the 5-hydroxyl analogue of **1** (**2**) can not only retain the properties of particular interaction of AChE with **1** but also is easier to penetrate the blood–brain barrier than **1** because it has a much lower potency to ionization. We envisaged that **2** and perhaps 5-fluoro and 5-acetoxyl substituted analogues of **1** (**3** and **4**) have comparable and even better AChE inhibitory potency than **1**.

First, ester **5**,[8,9] after $LiAlH_4$ reduction, Swern oxidation,[10] Grignard reaction and PCC oxidation, gave methyl ketone (**9**). In methodology, we explored Baeyer–Villiger rearrangement of **9** selectively to an acetate ester (**10**). Unfortunately, no desired product **10** was formed and only the epoxide compound **11** was formed under the condition of $mCPBA/NaHCO_3$ which was a successful method in ref 11. Then, we investigated application of the Dakin method ($NaOH/H_2O_2$) for this aim,[12,13] but no reaction took place to provide compound **10** and/or compound **12** (see Scheme 1).

After initial attempts failed, we had to change our strategy to employ lead tetraacetate (LTA) oxidation reaction[14] to pursue the synthesis of the compound **10** (Scheme 2). Reaction of acid **13**[8,9] with LTA in benzene under bubbles of argon to remove ensuing carbon dioxide successfully led to acetate ester **10**. Deprotection of acetate ester **10** with $TMSI/CHCl_3$ only yielded


1, Huperzine A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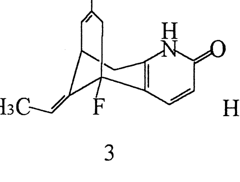
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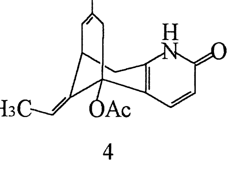
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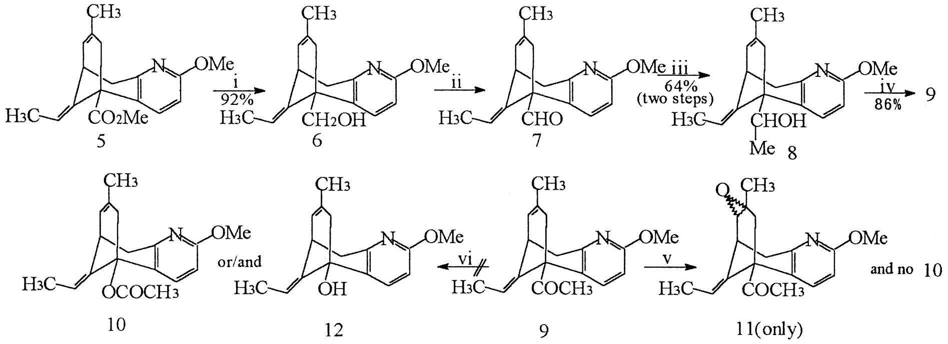
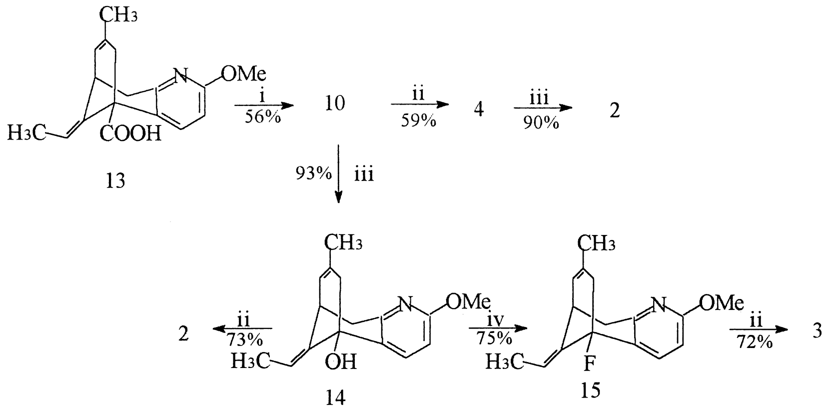


Scheme 1. Reagents and conditions: (i) $LiAlH_4$/THF, 92%; (ii) $(COCl)_2$/DMSO, then Et_3N; (iii) MeMgI/THF, 64% (two steps from **6**); (iv) PCC/CH_2Cl_2, 86%; (v) mCPBA/$NaHCO_3$; (vi) NaOH/H_2O_2.



Scheme 2. Reagents and conditions: (i) LTA/benzene, argon bubbles; (ii) TMSI/$CHCl_3$; (iii) 20% NaOH, MeOH; (iv) DAST/CH_2Cl_2,−78 °C.

deprotected acetate ester **4**[15] which did not ester exchange with MeOH but could be hydrolyzed to the product **2**[16] by 20% NaOH in MeOH. Also, hydrolysis of acetate ester **10** provided alcohol **14** and then deprotection of alcohol **14** with TMSI/$CHCl_3$ gave the product **2**.

After treatment with diethylaminosulfur trifluoride (DAST),[17] **14** could be transformed into **15**. Finally, deprotection of **15** with TMSI gave rise to another target compound **3**[18] (Scheme 2).

With the accomplishment of the synthesis, in vitro AChE inhibitory activity of the analogues was assessed according to the method of Ellman et al.[19] The results listed in Table 1 disclosed that the activity of these analogues is inferior to that of (−)-**1**. These findings suggest that the C-5 amino group plays an important role in holding significant AChE inhibitory activity.

The important reason that the substitution of amino group by hydroxy group makes the activity decrease sharply is that in the physiological condition, the amino group can form quaternary ammonium to imitate the function of acetylcholine and combine the active site of AChE, but the hydroxy group can not act in this way. On the other hand, **2** and **3** exhibit comparable activity indicating that except for the tendency to form the cation, the polarity has less influence on inhibitory activity. Compound **4** has no tendency to form the cation and large hindrance, so has almost no activity.

Table 1. Inhibitory activity against AChE

Compound	Concentration (μM)/ inhibition rate (%)
Compound **2**	35/50
Compound **3**	47/50
Compound **4**	88/6.36

Further exploratory work on this topic is being conducted in our laboratory.

References and Notes

1. Liu, J.-S.; Yu, C.-M.; Zhou, Y.-Z. et al. *Acta Chimica Sinica* **1986**, *44*, 1035.
2. Liu, J.-S.; Zhu, Y.-L.; Yu, C.-M. et al. *Can. J. Chem.* **1986**, *64*, 837.
3. Tang, X.-C.; Han, Y.-F.; Chen, X.-P.; Zhu, X.-D. *Acta Pharm. Sin.* **1986**, *7*, 507.
4. Zhang, S.-L. *New Drugs Clinical Remedies* **1986**, *5*, 260.
5. Wang, Y.; Yue, D.-X.; Tang, X.-C. *Acta Pharm. Sin.* **1986**, *7*, 110.
6. Tang, X.-C.; De Sarno, P.; Sugaya, K.; Giacobini, E. *J. Neurosci. Res.* **1989**, *24*, 276.
7. Kozikowki, A. P.; Thiels, E.; Tang, X.-C.; Hanin, I. In *Advances in Medicinal Chemistry*, Vol. 1; Maryanoff, B. E., Maryanoff, C. A., Ed.; JAI: Greenwich, CT, 1992; pp 172–205.
8. Kozikowski, A. P.; Tuckmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641 (and references cited therein).

9. Kaneko, S.; Nayajima, N.; Shikano, M. et al. *Tetrahedron* **1998**, *54*, 5485 (and references cited therein).

10. Mancnso, A. I.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

11. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

12. Dakin, H. D. *Org. Synth., Coll. Vol. 1* **1932**, *149*.

13. Sakai, K.; Yamashita, M.; Shibata, Y. *Chem. Lett.* **1986**, *353*.

14. Beckwith, A. L. J.; Cross, R. T.; Gream, G. E. *Aust. J. Chem.* **1974**, *27*, 1673.

15. IR, ^{1}H NMR, EI-MS and HR-MS (EI) of compound **4**: IR (KBr) cm^{-1}: 3421, 3010, 2906, 1749, 1660, 1619, 1587, 1228, 1031; ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 7.33 (d, 1H, $J=$ 8.8 Hz), 6.20 (d, 1H, $J=8.8$ Hz), 5.30 (m, 1H), 4.99 (q, 1H, $J=7.1$ Hz), 3.54 (m, 1H), 2.70 (dd, 1H, $J=4.6$, 12.4 Hz), 2.44 (m, 2H), 2.16 (d, $J=16.1$ Hz), 1.97 (s, 3H), 1.51 (d, 3H), 1.41 (s, 3H); EI-MS (*m*/*z*): 285 (M^+), 243, 228 (100%), 210; HR-MS (EI): $C_{17}H_{19}NO_3$ found 285.1371, calcd 285.1366.

16. IR, ^{1}H NMR, EI-MS and HR-MS (EI) of compound **2**: IR (KBr) cm^{-1}: 3500, 3131, 1651, 1604, 1087, 838, 748; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.30 (s, 1H), 7.55 (d, 1H, $J=9.4$ Hz), 6.15 (d, 1H, $J=9.4$ Hz), 5.45 (q, 1H, $J=$ 6.8 Hz), 5.39 (m, 1H), 5.23 (s, 1H), 3.55 (m, 1H), 2.62 (dd, 1H, $J=5.1$, 12.3 Hz), 2.45 (m, 1H), 2.23 (d, 1H, $J=16.5$ Hz), 2.05 (d, 1H, $J=16.5$ Hz), 1.60 (d, 3H, $J=8.9$ Hz), 1.50 (s, 3H); EI-MS (*m*/*z*): 243 (M^+), 228, 214, 200, 188; HR-MS (EI): $C_{15}H_{17}NO_2$ found 243.1239, calcd 243.1260.

17. (a) Markovskii, L. N.; Pashrnnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787. (b) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574

18. IR, ^{1}H NMR, EI-MS and HR-MS (EI) of compound **3**: IR (KBr) cm^{-1}: 3430, 1658, 1620, 1562, 1461, 1423, 1278, 1110, 829; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.55 (s, 1H), 7.45 (d, 1H, $J=9.4$ Hz), 6.21 (d, 1H, $J=9.4$ Hz), 5.43 (m, 1H), 5.40 (q, 1H, $J=6.9$ Hz), 3.66 (m, 1H), 2.73 (m, 1H), 2.53 (m, 1H), 2.50 (m, 1H), 2.37 (d, 1H, $J=16.0$ Hz), 1.64 (d, 3H, $J=$ 6.9 Hz), 1.56 (s, 3H); EI-MS (*m*/*z*): 245 (M^+), 230, 216, 202, 190; HR-MS (EI): $C_{15}H_{16}NOF$ found 245.1208, calcd 245.1216.

19. Ellman, G. L.; Courtney, D.; Andres, V.; Featherstone, R. M. *Biochem. Pharmacol.* **1961**, *7*, 88.