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An Efficient Total Synthesis of (−)-Huperzine A‡

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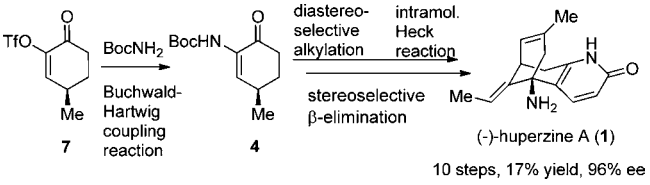
ABSTRACT



The total synthesis of *Lycopodium* alkaloid (−)-huperzine A has been accomplished in 10 steps with 17% overall yield from commercially abundant (*R*)-pulegone. The synthetic route features an efficient synthesis of 4 via a Buchwald−Hartwig coupling reaction, a dianion-mediated highly stereoselective alkylation of 4, and a rare example of an intramolecular Heck reaction of an enamine-type substrate. The stereoselective *β*-elimination and the accompanying Wagner−Meerwein rearrangement are of particular interest.

As a neurodegenerative disease, Alzheimer's disease (AD) constitutes a major public health concern due to its devastating psychosocial and financial impact on family.[1] Although the detailed pathogenic mechanism of AD is not fully understood, reduced synthesis of the neurotransmitter acetylcholine is believed to probably contribute to the onset of the disease.[2] Accordingly several acetylcholinesterase (AChE) inhibitors have been invented for the treatment of AD.

In this context, (−)-huperzine A (**1**, Figure 1), a *Lycopodium* alkaloid isolated in 1986 from the club moss *Huperzia serrata*,[3] has drawn considerable attention after it was revealed to be a potent, selective, and reversible AChE inhibitor.[4] Additionally, huperzine A is an NMDA (*N*-methyl-D-aspartate) receptor antagonist and an antioxidant, rendering it an effective neuroprotective agent.[5] Clinical trials have demonstrated that huperzine A may compare favorably to current AChE inhibitors in symptomatic treatment of AD.[6] In addition, huperzine A has been proposed to be a potential pretreatment of exposure to organophosphate nerve agents, such as sarin and VX.[7]

Despite the biological significance of huperzine A, the supply has long been suffering from its very low content in natural sources. Moreover, these plants are not abundant and grow extremely slowly, and so far no successful mass production by cultivation has been reported.[8] To this end, the total synthesis of **1** has been an enduring topic among the synthetic community for decades,[9] including the pioneering work by Ji[9a] and Kozikowski,[9b−d] modifications to the Kozikowski route,[9e−h,j,l,r] and partial,[9m,o,11b] formal,[9i,k,n] and completed syntheses.[9p,q] In this paper, we report the efficient total synthesis of (−)-huperzine A.

The highlights of our strategic bond disconnections are illustrated in Scheme 1. Initial disconnections reduce **1** to

‡ Dedicated to the late Professor Wei-Shan Zhou, who passed away on August 10, 2012.

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(2) (a) Francis, P. T.; Palmer, A. M.; Snape, M.; Wilcock, G. K. *J. Neurol. Neurosurg. Psychiatr.* **1999**, *66*, 137–147. (b) Bai, D. L.; Tang, X. C.; He, X. C. *Curr. Med. Chem.* **2000**, *7*, 355–374. (c) Gravitz, L. *Nature* **2011**, *475*, S9–S11.

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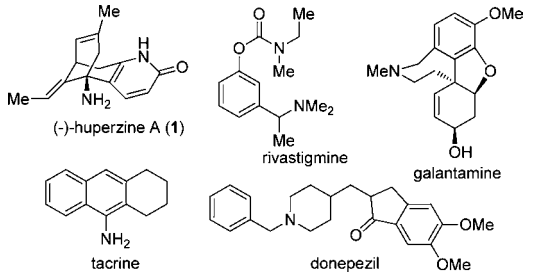
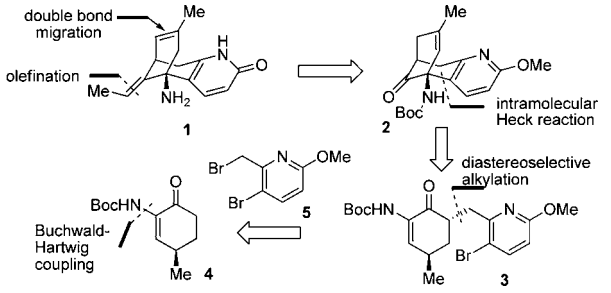


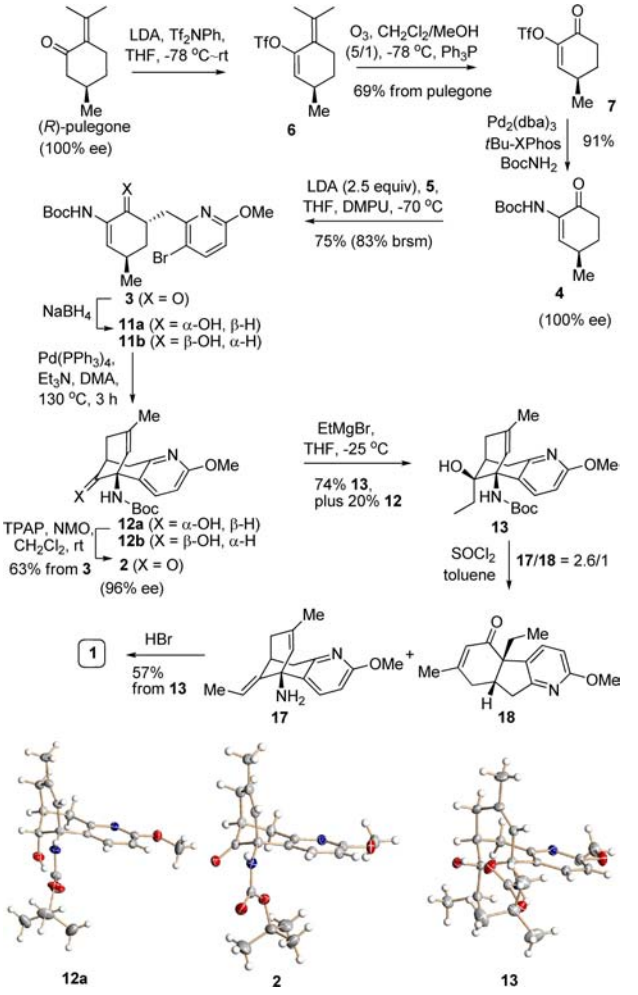
Figure 1. Huperzine A (**1**) and clinically used AChE inhibitors.

Scheme 1. Strategic Bond Disconnections of Huperzine A (**1**)



the key precursor **2**. The subsequent bond disconnection would allow **2** to be produced from **3** via an intramolecular Heck reaction,[9n,10] which entails a *trans* relative stereochemistry in **3**. This defined stereochemistry could be created via diastereoselective alkylation of α-amido-γ-methylcyclohexenone **4** with bromide **5**.[11] Lastly, compound **4** would stem from (*R*)-pulegone via a Buchwald–Hartwig coupling reaction.[12]

Scheme 2. Total Synthesis of (−)-Huperzine A (**1**)



The successful implementation of the above strategy is shown in Scheme 2, commencing with an efficient synthesis of **4**. Starting with optically pure (*R*)-pulegone, we were able to obtain **4** in decagram scale with excellent optical purity. Thus, (*R*)-pulegone was triflated with LDA/Tf_2NPh to deliver **6**, which was subjected to ozonolysis to generate **7** in 63% overall yield. The Buchwald–Hartwig coupling reaction of **7** with $BocNH_2$ catalyzed by $Pd_2(dba)_3$/*t*Bu-XPhos was then effected to establish the key C–N bond. With anhydrous K_2CO_3 being chosen as the base and toluene as the solvent, **4** was generated in 91% yield and 100% ee, while the same product with diminished yield (83%) and enantioselectivity (94% ee) was obtained with Cs_2CO_3 as the base. The ligand *t*Bu-XPhos could be mostly recovered (ca. 90%) and reused. Notably, this represents the first example of a Buchwald–Hartwig coupling reaction with a simple α-trifloxy enone substrate. This practical synthesis of the useful chiral building block of **4** should find applications in asymmetric synthesis.

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The alkylation reaction between **4** and bromide **5** was next investigated. It was observed that the stoichiometry of the base being ca. 2.5 equiv versus substrate **4** was important for achieving a good yield of alkylation product, an evidence pointing to the involvement of an intermediary dianion.[13] Particular attention was paid to the racemization problem. Under optimal conditions, **4** was exposed to 2.5 equiv of LDA at −70 °C to react with **5** for 18 h to afford **3** in 75% yield (83% b.r.s.m.) with >20/1 dr and >94% ee.[14]

Despite the fact that the intramolecular Heck reaction has gained widespread acceptance in the total synthesis of a myriad of natural products,[10] including Mann's formal synthesis of (±)-**1**,[9n] there were only a few examples where it was applied to enamine-type substrates to access tertiary carbinamines.[15] Actually, such a reaction proved challenging, and none of the attempted substrates **8**, **9a**−**b**, and **10a**−**e** could give any desired cyclization product (Figure 2).

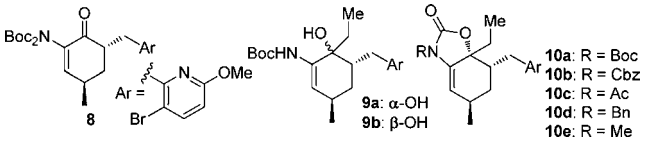
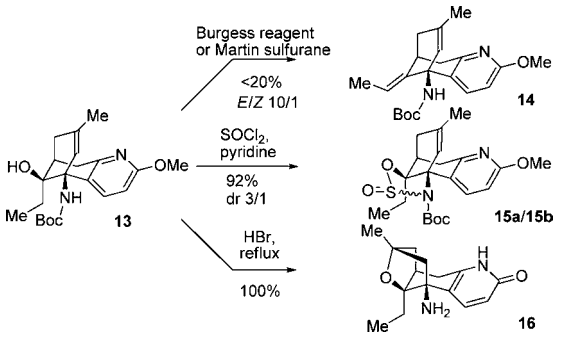


Figure 2. Attempted substrates **8**, **9a**−**b**, and **10a**−**e** for the intramolecular Heck reaction.

Ketone **3** was subsequently reduced to give a 1/1 mixture of allylic alcohols **11a**/**11b** in quantitative yield. To our delight, both **11a** and **11b** underwent the intramolecular Heck reaction to furnish **12a**/**12b** in yields of ca. 40%. The [3.3.1] bicyclic framework along with the stereochemistry of **12a** was established through X-ray crystallographic analysis (Scheme 2).[20] Further, both **12a** and **12b** were found to undergo Ley−Griffith oxidation[16] to afford **2** in nearly quantitative yield.[20] Notably, crude **11** and **12** could be used directly in the sequence to produce **2**. Under optimal conditions (Et_3N, DMA, 130 °C, 0.005 M), ketone **2** could be isolated in 63% yield and 96% ee over three steps from **3**. This procedure allowed the multigram scale operation to offer **2** in consistent yields, cementing the pivotal role of the intramolecular Heck reaction in the construction of cyclic tertiary carbinamines.[15]

Despite appearing deceptively simple, the construction of the exocyclic C=C bond proved nontrivial. After attempted Wittig and Julia olefination reactions failed, we turned to an addition−elimination based protocol to meet the challenge. Thus, an addition reaction of **2** with ethylmagnesium bromide furnished **13** in a yield of 74% with 7/1 dr, along with a 20% yield of **12** which could be completely recycled by Ley−Griffith oxidation. The structure of **13** was confirmed by X-ray crystallographic analysis (Scheme 2).[20]

Scheme 3. Attempted Dehydration of **13**



The formal dehydration of **13** was realized with limited success (Scheme 3). Exposure of **13** to Burgess reagent or Martin sulfurane generated olefine **14** in low yields. Treatment of **13** with $SOCl_2$ in the presence of pyridine furnished cyclic imides **15a**/**15b**, which failed to produce **14** under various conditions. Intriguingly, when **13** was exposed to concentrated HBr in refluxing toluene, a facile annulation proceeded to furnish the tetracyclic cage-like molecule **16** in quantitative yield. Biological evaluations of this compound would be interesting.

Despite the above setbacks, eventually we were exhilarated to discover that $SOCl_2$, in the absence of pyridine, could effect a slow dehydration of **13** to form **17** as the sole isomer, along with trace amounts of **14** and **18** (Table 1). In toluene, the ratio of **17**/**18** was 2.6/1, while, in DMF or DMA, **18** could be isolated as the major product. The structure of **18** was deduced from extensive spectroscopic studies and further validated by the isolation of **19**, which exhibited a high propensity toward hydrolysis to give **18**. The Boc protecting group was found necessary for the reaction to proceed.

Based on these data, a formative scenario for both **14** (**17**) and **18** (**19**) was proposed (Table 1). In the absence of pyridine, **14** reacted with $SOCl_2$ to give the putative intermediate carbocation **20**, and β-elimination (path A) and Wagner−Meerwein rearrangement (path B) then followed to generate **14** (**17**) and **18** (**19**), respectively.

Eventually, in light of these crucial observations, a one-pot sequence was developed (Scheme 2). In the event, **13** was exposed to $SOCl_2$ at room temperature for 36 h followed by refluxing with 1.0 mol/L aqueous HBr for 10 h to effect demethylation and concomitant double bond transposition, providing **1** in 57% yield. The spectroscopic

(13) For examples of *N,C*-dianion alkylations, see: (a) Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700–1703. (b) Watanabe, H.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 4278–4279.

(14) In the chiral HPLC chromatogram of **3**, there was an impurity mixed with the minor peak. The optical purity of **3** should be equal to that of **2**, which was 96% ee.

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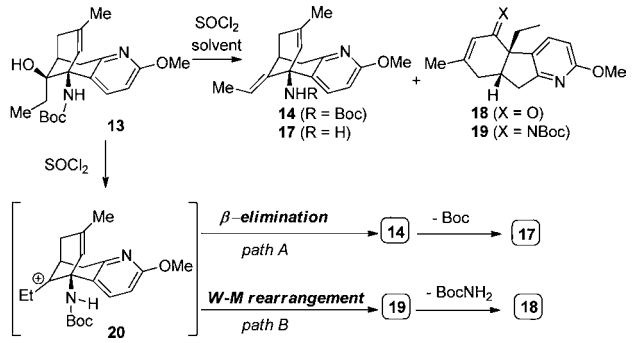
Table 1. Transformation of **13** to **14** (**17**) and **18** (**19**)



entry	solvent	temp	product (yield [%])[a]
1	toluene	rt	**14/17** (59), **18** (23)
2	DMF	rt	**14**(37), **18/19** (50)
3	DMA	rt	**14**(43), **18/19** (48)
4	DMA	60 °C	**14**(32), **18/19** (55)

[a] Yields were determined by crude ^{1}H NMR.

data of synthetic **1** matched those reported for the natural sample of **1** in all respects.

In conclusion, the total synthesis of (−)-huperzine A has been accomplished in 10 steps with a 17% overall yield from commercially abundant (*R*)-pulegone. This forms a new basis for further development of an efficient industrial process aiming to eliminate the supply problem of (−)-huperzine A.[17] The disclosed rearrangement of **13** to **18** (**19**) is of particular interest, which provides support for the biosynthetic proposals of fawcettimine-type alkaloids[18] and holds good potential in cultivating *de novo* biomimetic total syntheses of these natural products.[19] Endeavors along these lines are currently being actively pursued in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data for new compounds, and selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) All the steps leading to **2** have been operated on multigram scales (see Supporting Information). Due to the high activity and skin permeability of huperzine A, the last three steps leading to **1** were operated on subgram scales.

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(20) CCDC 863191 (**12a**), 884493 (**13**), and 884495 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The authors declare no competing financial interest.