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Total Synthesis of (−)-Huperzine A

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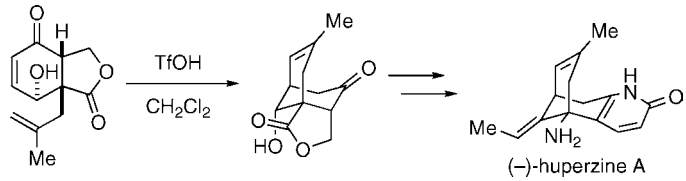
ABSTRACT



The total synthesis of (−)-huperzine A was accomplished in 23 steps from a commercially available anhydride. Our synthetic route features a facile construction of the bicyclo[3.3.1] skeleton equipped with proper functionalities to introduce the remaining substructures.

Huperzine A (**1**) was isolated from *Huperzia serrata* by Liu and co-workers.[1] It was found to exhibit a potent, selective, and reversible inhibitory activity against acetylcholinesterase (AchE). Because of this notable profile, huperzine A has drawn considerable attention as a promising therapeutic agent for Alzheimer's disease and is currently undergoing extensive clinical trials.[2] It is also interesting to note that huperzine A has recently been reported to show neuroprotective properties against glutamate-induced cell death.[3] From the synthetic point of view, the structure of huperzine A is quite fascinating in that it contains a bicyclo[3.3.1] skeleton fused with a pyridone moiety as well as an ethylidene moiety. Thus, considerable attention has been focused on the total synthesis of this closely packed molecule. Kozikowski and co-workers have established two synthetic routes, featuring either a tandem Michael-aldol reaction or a palladium-catalyzed annulation as the key step to build the bicyclo[3.3.1] skeleton.[4,5] Several research groups have applied these two strategies to asymmetric synthesis using chiral catalysts or reagents.[6] More recent syntheses involving a manganese-mediated cyclization and an intramolecular Heck reaction have been developed to assemble the bicyclo[3.3.1] skeleton.[7,8] Herein we report the total synthesis of (−)-huperzine A, featuring a unique construction of the bicyclo[3.3.1] skeleton.

Our retrosynthetic analysis of huperzine A (**1**) is shown in Scheme 1. We envisaged that the ethylidene and the

(1) (a) Liu, J.-S.; Zhu, Y.-L.; Yu, C.-M.; Zhou, Y.-Z.; Han, Y.-Y.; Wu, F.-W.; Qi, B.-F. *Can. J. Chem.* **1986**, *64*, 837. (b) Ayer, W. A.; Browne, L. M.; Orszanska, H.; Valenta, Z.; Liu, J.-S. *Can. J. Chem.* **1989**, *67*, 1538.

(2) For reviews of huperzine A, see: (a) Kozikowski, A. P.; Tückmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641. (b) Bai, D. *Pure Appl. Chem.* **2007**, *79*, 469.

(3) (a) Peng, Y.; Jiang, L.; Lee, D.-Y. W.; Schachter, S.-C.; Ma, Z.; Lemere, C. A. *J. Neurosci. Res.* **2006**, *84*, 903. (b) Wang, R.; Tang, X. C. *Neurosignals* **2005**, *14*, 71. (c) Zhang, H. Y.; Yan, H.; Tang, X. C. *Neurosci. Lett.* **2004**, *360*, 21. (d) Zhang, H. Y.; Liang, Y. Q.; Tang, X. C.; He, X. C.; Bai, D. L. *Neurosci. Lett.* **2002**, *317*, 143. (e) Gordon, R. K.; Nigam, S. V.; Weitz, J. A.; Dave, J. R.; Doctor, B. P.; Ved, H. S. *J. Appl. Toxicol.* **2001**, *21*, S47.

(4) (a) Xia, Y.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1989**, *111*, 4116. (b) Kozikowski, A. P.; Campiani, G.; Aagaard, P.; McKinney, M. *J. Chem. Soc., Chem. Commun.* **1993**, 860.

(5) Independently, Qian and Ji disclosed the synthesis of huperzine A, which is almost the same as that reported by the Kozikowski group in 1989. Qian, L.; Ji, R. *Tetrahedron Lett.* **1989**, *30*, 2089.

(6) Asymmetric syntheses using the tandem Michel-aldol reaction: (a) Yamada, F.; Kozikowski, A. P.; Reddy, E. R.; Pang, Y.-P.; Miller, J. H.; McKinney, M. *J. Am. Chem. Soc.* **1991**, *113*, 4695. (b) Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Heterocycles* **1997**, *46*, 27. (c) Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron* **1998**, *54*, 5471. (d) Pan, Q.-B.; Ma, D.-W. *Chin. J. Chem.* **2003**, *21*, 793. Asymmetric syntheses using the palladium-catalyzed annulation: (e) Kaneko, S.; Yoshino, T.; Katoh, T.; Terashima, S. *Tetrahedron: Asymmetry* **1997**, *8*, 829. (f) Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 8805. (g) Haudrechy, A.; Chassaing, C.; Riche, C.; Langlois, Y. *Tetrahedron* **2000**, *56*, 3181. (h) He, X.-C.; Wang, B.; Yu, G.; Bai, D. *Tetrahedron: Asymmetry* **2001**, *12*, 3213.

(7) (a) Lee, I. Y. C.; Jung, M. H.; Lee, H. W.; Yang, J. Y. *Tetrahedron Lett.* **2002**, *43*, 2407. (b) Lucey, C.; Kelly, S. A.; Mann, J. *Org. Biomol. Chem.* **2007**, *5*, 301.

(8) A radical-mediated construction of the bicyclo[3.3.1] skeleton has also been reported: (a) Ward, J.; Caprio, V. *Tetrahedron Lett.* **2006**, *47*, 553. (b) Ward, J.; Caprio, V. *Heterocycles* **2009**, *79*, 791.

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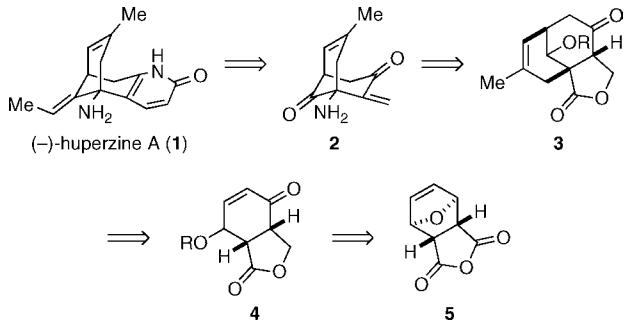
Scheme 1. Retrosynthesis

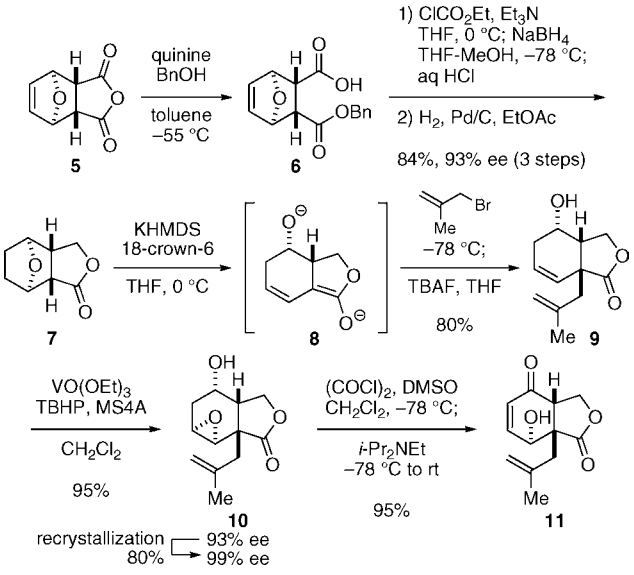


pyridone moieties could be constructed by elaborating the ketone moieties of **2**. The amino group of **2** could be introduced via a Curtius rearrangement of the corresponding carboxylic acid. Connection between the carboxylic acid and the *exo*-methylene would lead to key intermediate **3**. Construction of the bicyclo[3.3.1] skeleton in **3** could be achieved via stereoselective alkylation at the α-position of the lactone and/or conjugate addition of an alkyl group into the enone from the convex face of bicyclic system **4**, which could in turn be derived from commercially available anhydride **5**.

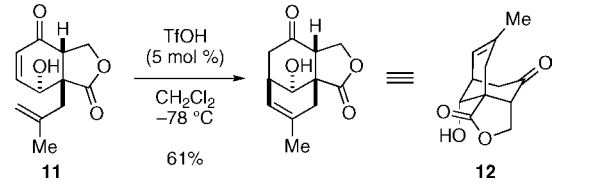
Our synthesis commenced with a desymmetrization of anhydride **5** (Scheme 2). According to the Bolm's procedure,[9] **5** was treated with quinine and benzyl alcohol to give carboxylic acid **6** in good optical purity (93% ee). Selective reduction of the carboxylic acid in **6** via a mixed anhydride afforded a lactone, which was hydrogenated to provide **7**. Treatment of **7** with 2 equiv of KHMDS in the presence of 18-crown-6 (1 equiv) induced cleavage of the tetrahydrofuran ring to form dienolate **8**, which was regio- and stereoselectively reacted with methallyl bromide at the α-position of the lactone from the convex face to give homoallylic alcohol **9**. Since formation of the TMS ether occurred concomitantly in this step, **9** was isolated after treatment with TBAF. Stereoselective epoxidation of **9** using a catalytic amount of $VO(OEt)_3$ afforded epoxide **10** with complete diastereoselectivity.[10] Recrystallization at this stage raised the optical purity of **10** (80% yield and >99% ee). Swern oxidation of **10** caused cleavage of the epoxide to furnish hydroxyenone **11** in good yield.

Initially we planned to construct the bicyclo[3.3.1] skeleton via a ring-closing metathesis between the methallyl moiety and a vinyl group that would be introduced at the *β*-position of the enone. During the course of the protection of the hydroxy group of **11**, we unexpectedly found that treatment of **11** with TBSOTf and 2,6-lutidine in dichloromethane at 0 °C caused a cation-olefin cyclization to afford **12** in moderate yield after cleavage of the corresponding silyl enol ether with TBAF. Since other olefinic regioisomers were obtained as minor products in this transformation, further investigation was conducted to establish the optimal conditions to construct the bicyclo[3.3.1] skeleton. It was eventually found that, using a catalytic amount of TfOH in dichloromethane at −78 °C, **12** was obtained in 61% yield (Scheme 3).[11]

Scheme 2



Scheme 3



With the requisite bicyclo[3.3.1] skeleton **12** in hand, we next focused on elaboration of this core skeleton (Scheme 4). After protection of the secondary hydroxy group, the lactone was cleaved with phenylthiolate to give carboxylic acid **13**. The crucial Curtius rearrangement of **13** using DPPA proceeded smoothly to produce methyl carbamate **14** in 89% yield.[12] Oxidation of the sulfide of **14** and subsequent elimination of the resulting sulfoxide proceeded to give **15** in good yield. Upon treatment of **15** with sulfinylamide **16**

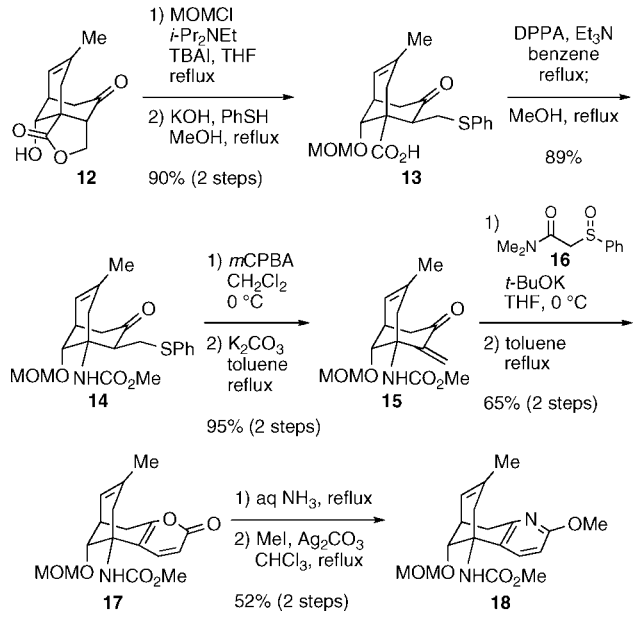
(9) (a) Bolm, C.; Atodiresei, I.; Schiffers, I. *Org. Synth.* **2005**, *82*, 120. (b) Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455. (c) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984.

(10) (a) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429. (b) Nicolaou, K. C.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3256. (c) Evans, J. M.; Kallmerten, J. *Synlett* **1992**, 269. Recently an asymmetric epoxidation of homopallylic alcohols using $VO(Oi\text{-}Pr)_3$ and a chiral ligand was reported: (d) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286.

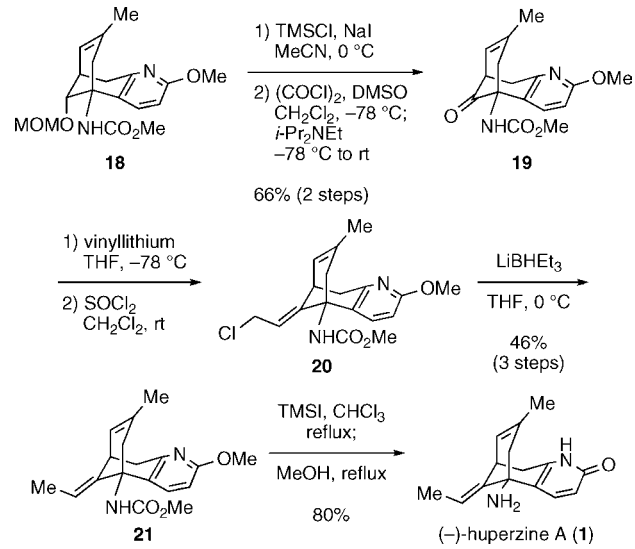
(11) For related reactions, see: (a) Gallen, M. J.; Williams, C. M. *Org. Lett.* **2008**, *10*, 713. (b) Grundl, M. A.; Kaster, A.; Beaulieu, E. D.; Trauner, D. *Org. Lett.* **2006**, *8*, 5429.

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

Scheme 4



Scheme 5



in the presence of a catalytic amount of *t*-BuOK, a Michael addition occurred to furnish *δ*-ketoamide as a mixture of diastereomers, which was refluxed in toluene to induce cyclization and desulfination to afford pyrone **17** in moderate yield.[13] By heating with aqueous NH_3, pyrone **17** was converted into the corresponding pyridone, which was then protected as its 2-methoxypyridine using MeI and Ag_2CO_3 to furnish **18** in 52% yield over two steps.

Removal of the MOM group in **18** using TMSI and subsequent Swern oxidation of the resulting alcohol afforded ketone **19** (Scheme 5). The ketone of **19** was then converted into the ethylidene moiety. In previous syntheses,[4−6] construction of the ethylidene moiety has been achieved via a Wittig olefination; however, here this resulted in formation of the undesired *Z*-isomer as the predominant product.[14] After exploring a variety of methods, we established a highly reliable and versatile procedure to construct the desired isomer. The addition of vinyllithium to the ketone of **19** afforded a 5:1 diastereomeric mixture of allyl alcohols, which was treated with $SOCl_2$ to give the rearranged allyl chloride **20** as the sole isomer. The S_N2' reaction of the chloride ion might proceed by way of the favorable conformer which avoids steric repulsion between the vinyl group and the amino substituent at the bridgehead position. Reduction of the allyl chloride **20** with $LiBHEt_3$ furnished **21**. Finally, deprotection of **21** with TMSI furnished (−)-huperzine A (**1**).

In summary, the total synthesis of (−)-huperzine A (**1**) was accomplished in 23 steps and 1.8% overall yield from a commercially available anhydride. Our synthetic route features a facile construction of the bicyclo[3.3.1] skeleton equipped with proper functionalities to introduce the remaining substructures.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A pyrone synthesis via a Michael addition of phenylthioacetate has been reported. Hoppe, H. W.; Kaiser, M.; Müller, D.; Welzel, P. *Tetrahedron* **1987**, *43*, 2045.

(14) Attempted Wittig olefination of **19** did not proceed, presumably because deprotonation of NH in the carbamate might deactivate the ketone.