J|A|C|S COMMUNICATIONS

Published on Web 06/22/2010

Total Synthesis of (+)-Fastigiatine

Brian B. Liau and Matthew D. Shair*

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received May 26, 2010; E-mail: shair@chemistry.harvard.edu

Abstract: The first total synthesis of the *Lycopodium* alkaloid (+)-fastigiatine has been accomplished in 15 steps and 30% overall yield from known compounds. Noteworthy transformations include a convergent fragment coupling via a nucleophilic cyclopropane opening, a highly diastereoselective formal [3 + 3]-cycloaddition, and a transannular Mannich reaction to construct the core of the natural product.

The *Lycopodium* alkaloids are a family of complex natural products that have long been synthetic targets in organic chemistry.[1] Since Stork's inaugural synthesis of lycopodine,[2] these diverse alkaloids have continued to attract synthetic interest due to their polycyclic architecture and diverse biological activity. (+)-Fastigiatine (**1**)[3] and (−)-himeradine A (**2**) are unique members of the lycodine stuctural class (Figure 1). Each molecule has an unprecedented pentacyclic core with a C4−C10 bond in contrast to lycodine (**3**). The additional C4−C10 linkage adds considerable strain and complexity to these molecules, creating a densely functionalized pyrrolidine ring and an array of five contiguous stereocenters, two of which are vicinal quaternary carbons. Herein we report the first total synthesis of (+)-fastigiatine (**1**).

Our retrosynthetic analysis of (+)-fastigiatine (**1**) is outlined in Scheme 1. Inspired by the proposed biosynthesis of lycodine,[1] we envisioned that the core skeleton of **1** could be constructed from tetracycle **4** via a transannular Mannich reaction to form the C4−C13 bond. Tetracycle **4** could be formed from diamine **5** by an intramolecular 1,4-conjugate addition and condensation of Nα and Nβ with the C5- and C13-carbonyls, respectively. At this point, the order of bond-forming events was considered flexible. Diamine **5** could then be convergently assembled from several building blocks via nucleophilic opening of cyclopropane **6** with organometallic **7** and subsequent alkylation.

The synthesis began with cyclopropane **8**,[4] which was prepared in four steps from (*S*)-epichlorohydrin on multigram scale according to literature protocol. Transesterification of **8** with 2-(trimethylsilyl)ethanol,[5] followed by *N*-Boc formation, afforded cyclopropane **9** in 83% overall yield (Scheme 2). Upon exposure to mixed cuprate **10**,[6] cyclopropane **9** underwent facile, regioselective opening[7] at C11 to provide imide **11** in 93% yield. Conveniently, this convergent fragment coupling could be conducted on greater than 5-g scale. Imide **11** was then transformed in 89% yield to *N*-Boc-2-pyrrolidinone **12** in three steps: (1) alkylation with 1-chloro-3-iodopropane, (2) displacement of the resultant primary chloride with sodium azide, and (3) cleavage of the 2-(trimethylsilyl)ethyl ester with concomitant decarboxylation,[8] followed by in situ base-catalyzed epimerization to yield a >10:1 mixture of C4-epimers. Although the C4-stereocenter of **12** is ultimately inconsequential, this epimerization facilitated characterization. At this point, the *N*-Boc group of **12** was cleaved[9] and replaced with a 2-nitrobenzenesulfonyl (Ns) group to afford *N*-Ns-2-pyrrolidinone **13** in 89% overall yield. Addition of the lithium enolate of *tert*-butylacetate to **13** at −78 °C cleanly delivered the corresponding β-ketoester, which underwent an intramolecular aza-Wittig reaction[10] to afford vinylogous urethane (*Z*)-**14** as an inconsequential ∼3:2 mixture of C4-epimers in 88% overall yield.

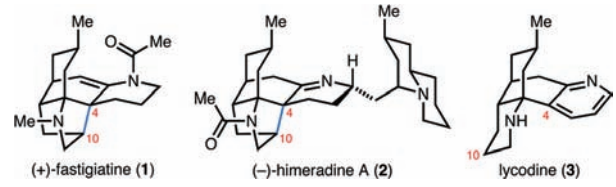
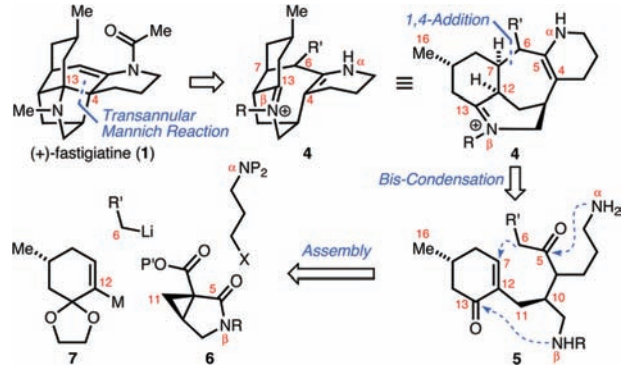


Figure 1. Selected *Lycopodium* alkaloids.

Scheme 1. Retrosynthetic Analysis of (+)-Fastigiatine (**1**)

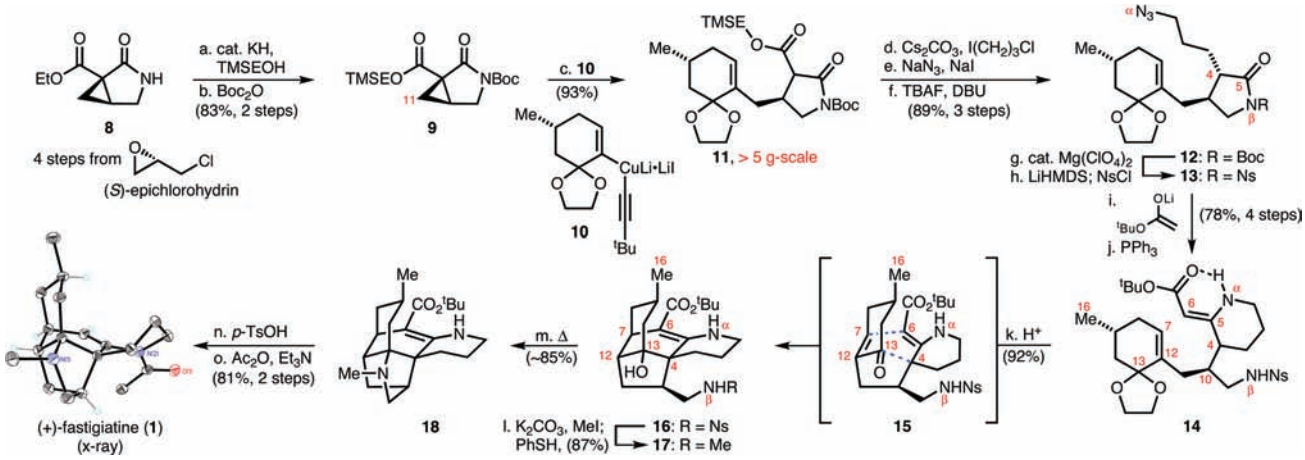


With all of the carbons and nitrogens of the core of (+)-fastigiatine (**1**) in place, we were eager to test the intramolecular 1,4-conjugate addition on **14**. Our initial strategy involved forming the C13-iminium ion with Nβ prior to 1,4-conjugate addition, where the C10-stereocenter would then control the formation of the remaining stereocenters. Unfortunately, removal of the Ns group led to exclusive formation of the five-membered vinylogous urethane. A similar phenomenon was observed with *N*-Boc-2-pyrrolidinone **12**, where attempts to break the C5−Nβ bond and form the C5−Nα bond were ultimately unsuccessful, suggesting a preference for the five-membered ring system. With these results, it became clear that the Ns group was needed to maintain the correct C−N connectivity and should be removed at a later stage.

Consequently, we attempted direct 1,4-conjugate addition to the latent 2-cyclohexenone of **14**.[11] Remarkably, exposure of **14** to aqueous hydrochloric acid led to tetracycle **16** as a single diastereomer in 92% yield. This formal [3+3]-cycloaddition[12] is believed to occur via initial C13-dioxolane cleavage, 7-*endo-trig* intramolecular conjugate addition to form the C6−C7 bond, tautomerization to secure the C12 stereocenter, and finally a transannular aldol reaction to form the C4−C13 bond. The high diastereoselectivity of the initial 7-*endo-trig* cyclization can be rationalized by stereoelectronically favored axial attack *anti* to the C16-methyl group.[11]

10.1021/ja104575h

Scheme 2. Synthesis of (+)-Fastigiatine (**1**)[a]



[a] Conditions: (a) 15 mol % KH, 2-(trimethylsilyl)ethanol, THF; (b) Boc_2O, 10 mol % 4-DMAP, Et_3N, CH_2Cl_2, 83% (two steps); (c) 1.4 equiv of **10**, THF, −78 → 0 °C, 93%; (d) Cs_2CO_3, 1-chloro-3-iodopropane, DMF; (e) NaN_3, NaI, DMF, 65 °C; (f) TBAF, 25 mol % DBU, THF, 50 °C, 89% (three steps); (g) 20 mol % $Mg(ClO_4)_2$, MeCN, 60 °C; (h) LiHMDS, THF; NsCl, 0 °C → RT, 89% (two steps); (i) LDA, *t*-BuOAc, THF, −78 °C; then **13**, −78 °C; (j) PPh_3, PhH, 50 °C, 88% (two steps); (k) HCl, THF/H_2O, 92%; (l) K_2CO_3, MeI, DMF, 0 °C → RT; then PhSH, 0 °C → RT, 87%; (m) CF_3CH_2OH, 80 °C, ~85%; (n) *p*-TsOH·H_2O, PhH, 80 °C, 95%; (o) Ac_2O, Et_3N, CH_2Cl_2, 85%.

Completion of the pentacyclic core required exchanging the C13-hydroxyl with Nβ. To this end, alkylation of **16** with methyl iodide in the presence of potassium carbonate, followed by subsequent addition of thiophenol,[13] yielded tetracyclic *N*-methylamine **17** in 87% yield in a one-pot sequence. Gratifyingly, heating **17** in 2,2,2-trifluoroethanol cleanly afforded pentacycle **18** in ~85% yield. This exchange presumably occurs via initial retro-aldol reaction followed by iminium ion formation to afford intermediate **4**, which then undergoes the pivotal transannular Mannich reaction to afford **18**. The remarkable ease of this transformation may suggest that an intermediate similar to **4** could be involved in the biosynthesis of **1** and **2**, in contrast to what is currently proposed.[1a,c] Treatment of **18** with *p*-toluenesulfonic acid induced facile *tert*-butoxycarbonyl loss to yield the corresponding pentacyclic imine, which upon exposure to acetic anhydride and triethylamine afforded (+)-fastigiatine (**1**) in 82% overall yield ($[\alpha]^{24}_D = +375$ (*c* 1.4, $CHCl_3$)).[14] The ^1H and ^{13}C NMR spectra for synthetic (+)-**1** matched those reported for the natural compound, and the structure of synthetic (+)-**1** was unequivocally established via single crystal X-ray diffraction analysis.

In summary, we have reported the first total synthesis of (+)-fastigiatine (**1**) in 15 steps and ~30% overall yield from cyclopropane **8**. Noteworthy transformations include a convergent fragment coupling via a cyclopropane opening, a highly diastereoselective formal [3+3]-cycloaddition to generate four contiguous stereocenters, and a transannular Mannich reaction to construct the core of (+)-fastigiatine (**1**) and (−)-himeradine A (**2**).

Acknowledgment. B.B.L. is thankful for an NSF predoctoral fellowship. Dr. Shao-Liang Zheng is acknowledged for assistance with X-ray crystallography. Amy S. Lee and Shota Kikuchi are acknowledged for thoughtful discussions.

Supporting Information Available: Experimental procedures, spectroscopic data, copies of ^1H and ^{13}C NMR spectra, and X-ray structure of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews of the *Lycopodium* alkaloids, see: (a) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2005; Vol. 61, pp 1−57. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772. (c) Ayer, W. A.; Trifonov, L. S. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: New York, 1994; Vol. 45, pp 233−266.
(2) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648.
(3) For isolation of (+)-fastigiatine (**1**), see: (a) Gerard, R. V.; MacLean, D. B.; Fagianni, R.; Lock, C. J. *Can. J. Chem.* **1986**, *64*, 943–949. (b) Gerard, R. V.; MacLean, D. B. *Phytochemistry* **1986**, *25*, 1143–1150.
(4) Medda, A. K.; Lee, H.-S. *Synlett* **2009**, *6*, 921–924, and references therein.
(5) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227–10238.
(6) Mixed cuprate **10** was generated from the corresponding vinyl iodide and 3,3-dimethyl-1-butyne by a modified procedure of Majetich, G.; Leigh, A. J.; Condon, S. *Tetrahedron Lett.* **1991**, *32*, 605–608. See Supporting Information for further details.
(7) For a review on electrophilic cyclopropanes, see: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72.
(8) Knobloch, E; Brückner, R. *Synlett* **2008**, *12*, 1865–1869.
(9) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron. Lett.* **1993**, *34*, 7873–7876.
(10) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Org. Chem.* **1985**, *50*, 5352–5356.
(11) For a similar intramolecular 7-*endo-trig* cyclization, see: (a) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149. (b) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2008**, *130*, 13778–13789.
(12) For other examples of formal [3+3]-cycloadditions, see: (a) Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *64*, 883–893, and references therein. (b) Movassaghi, M.; Chen, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 565–568.
(13) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
(14) The reported optical rotation for (+)-fastigiatine (**1**), which contains a minor amount of des-*N*-methylfastigiatine, is ($[\alpha]^{23}_D = +290$ (*c* 1.36, $CHCl_3$). See ref 3b.

JA104575H