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Total Synthesis of (+)-Fastigiatine

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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.

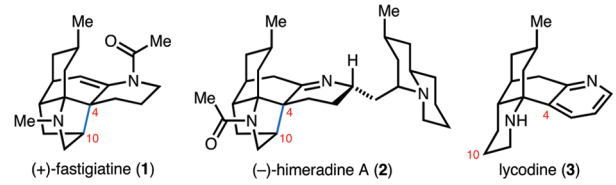
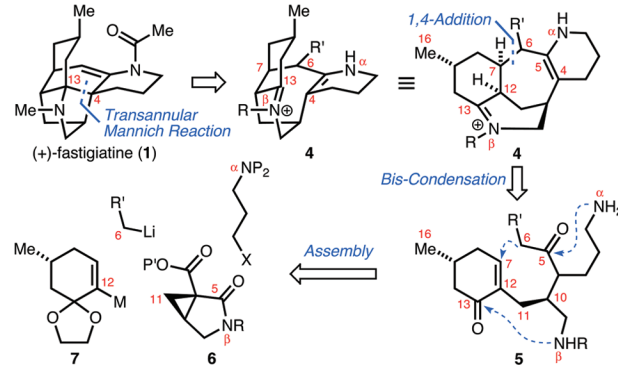


Figure 1. Selected *Lycopodium* alkaloids.

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

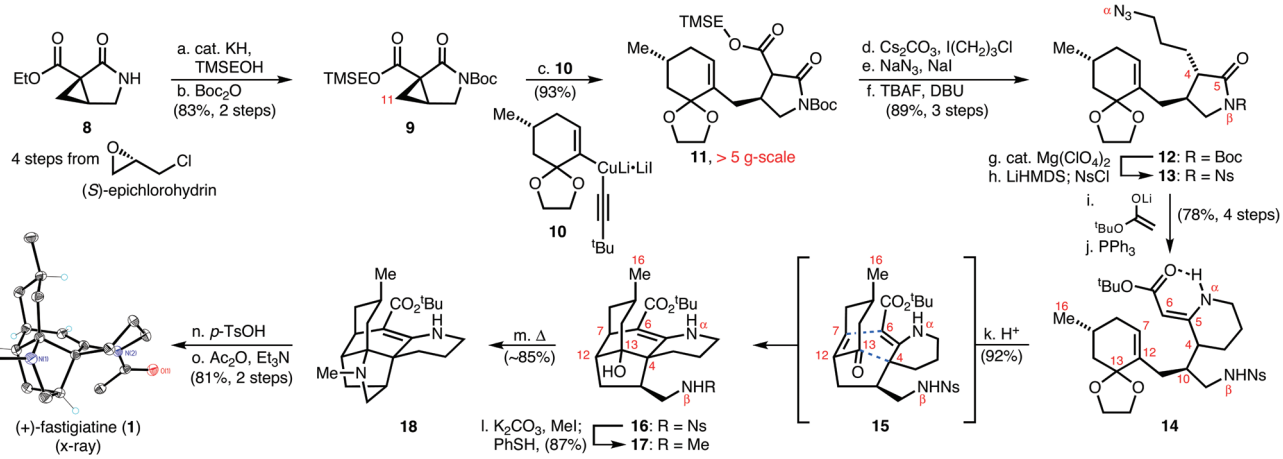


With all of the carbons and nitrogens of the core of (+)-fastigiatine (**1**) in place, we were eager to test the intramolecular 1,4-conjugate addition on **14**. Our initial strategy involved forming the C13-iminium ion with Nβ prior to 1,4-conjugate addition, where the C10-stereocenter would then control 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**).

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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.

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(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.

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