

CHM-4328

Assignment 2

Professor: Dr. Louis Barriault

Student Name(s):

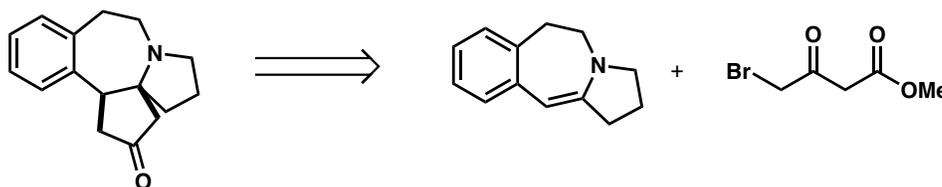
Student Number(s):

Deadline: Electronic submission of the assignment to lbarriau@uottawa.ca subject: CHM-4328 assignment 2, by February 24, 2017 11:59 pm. After the deadline, there will be a penalty of 5 pts per day.

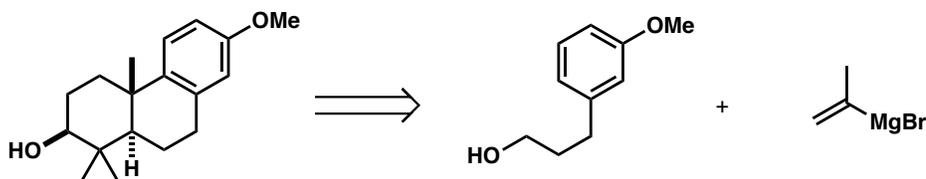
N.B. No more than 4 students per assignment. Please provide all the necessary reference (if needed)

1. By applying the principles of retrosynthetic analysis, show how each of the indicated target molecules could be prepared from the starting material given. No more than 10 separate transformations are necessary in any of the syntheses **(20 pts)**

1.1



1.2



2. Read the attached paper on the total synthesis of (+)-Fastigiatine by Shair et al. Provide the reaction mechanism for each steps display in Scheme 2 and explain the diastereoselectivity when applicable **(80 pts)**

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.

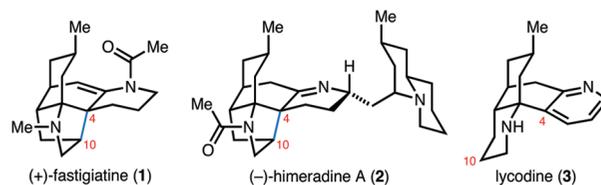
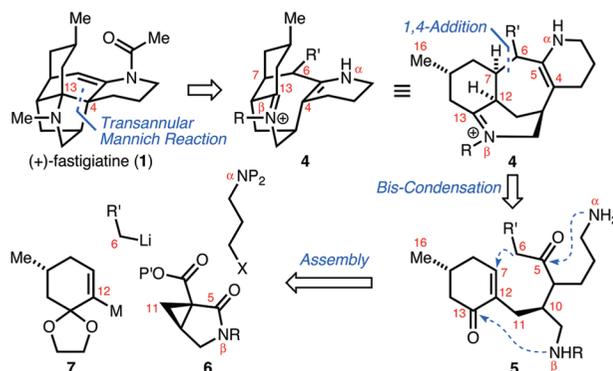


Figure 1. Selected *Lycopodium* alkaloids.

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



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 lycodine,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 structural 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**).

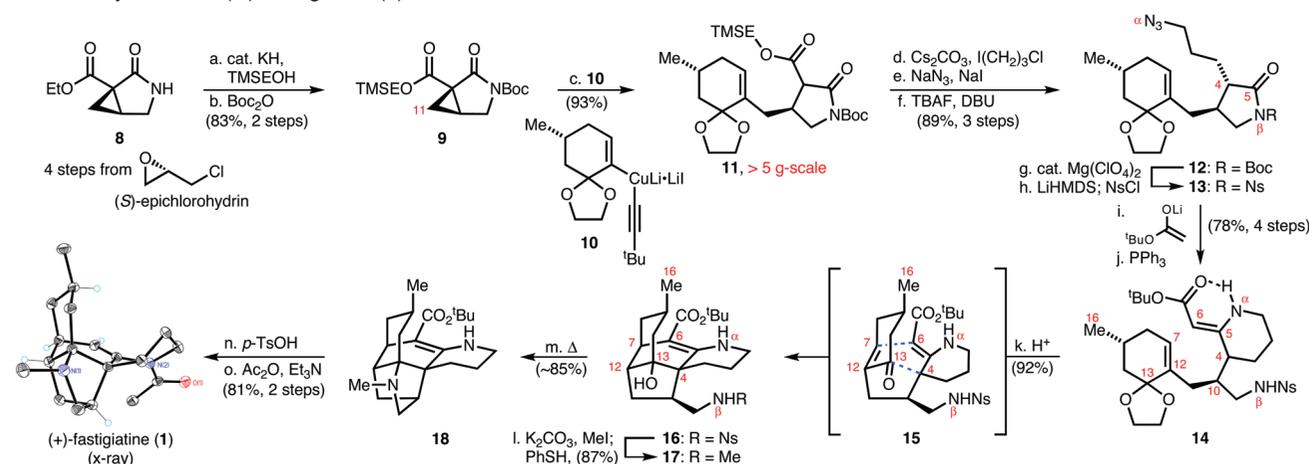
Our retrosynthetic analysis of (+)-fastigiatine (**1**) is outlined in Scheme 1. Inspired by the proposed biosynthesis of lycodine,¹ we envisioned that the core skeleton of **1** could be constructed from tetracycle **4** via a transannular Mannich reaction to form the C4–C13 bond. Tetracycle **4** could be formed from diamine **5** by an intramolecular 1,4-conjugate addition and condensation of N α and N β 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 opening⁷ 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 cleaved⁹ 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 reaction¹⁰ to afford vinylogous urethane (*Z*)-**14** as an inconsequential \sim 3:2 mixture of C4-epimers in 88% overall yield.

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 N β 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–N β bond and form the C5–N α 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]-cycloaddition¹² 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

Scheme 2. Synthesis of (+)-Fastigiatine (1)^a

^a Conditions: (a) 15 mol % KH, 2-(trimethylsilyl)ethanol, THF; (b) Boc₂O, 10 mol % 4-DMAP, Et₃N, CH₂Cl₂, 83% (two steps); (c) 1.4 equiv of **10**, THF, -78 → 0 °C, 93%; (d) Cs₂CO₃, 1-chloro-3-iodopropane, DMF; (e) NaN₃, NaI, DMF, 65 °C; (f) TBAF, 25 mol % DBU, THF, 50 °C, 89% (three steps); (g) 20 mol % Mg(ClO₄)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) PPh₃, PhH, 50 °C, 88% (two steps); (k) HCl, THF/H₂O, 92%; (l) K₂CO₃, MeI, DMF, 0 °C → RT; then PhSH, 0 °C → RT, 87%; (m) CF₃CH₂OH, 80 °C, ~85%; (n) *p*-TsOH·H₂O, PhH, 80 °C, 95%; (o) Ac₂O, Et₃N, CH₂Cl₂, 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 ([α]_D²⁴ = +375 (c 1.4, CHCl₃)).¹⁴ The ¹H and ¹³C 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 ¹³C 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 ([α]_D²³ = +290 (c 1.36, CHCl₃). See ref 3b.

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