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A Unified Strategy for the Synthesis of 7-Membered-Ring-Containing *Lycopodium* Alkaloids

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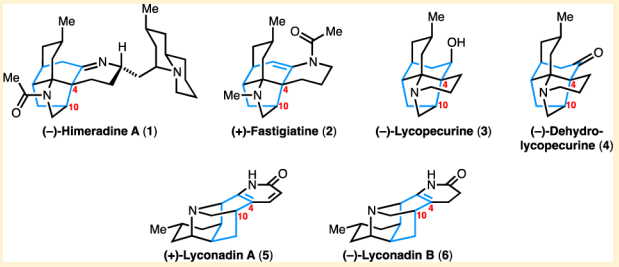
Supporting Information

ABSTRACT: A unique subset of the *Lycopodium* alkaloid natural products share a 7-membered-ring substructure and may potentially arise from a common biosynthetic precursor. To both explore and exploit these structural relationships, we sought to develop a unified biosynthetically inspired strategy to efficiently access these complex polycyclic alkaloids through the use of a cascade sequence. In pursuit of these goals, the first total synthesis of (+)-fastigiatine (**2**) was accomplished via a series of cascade reactions; we describe herein a full account of our efforts. Insight from these endeavors led to critical modifications of our synthetic strategy, which enabled the first total syntheses of (−)-himeradine A (**1**), (−)-lycopecurine (**3**), and (−)-dehydrolycopecurine (**4**), as well as the syntheses of (+)-lyconadin A (**5**) and (−)-lyconadin B (**6**). Our approach features a diastereoselective one-pot sequence for constructing the common 7-membered-ring core system, followed by either a biomimetic transannular Mannich reaction to access himeradine A (**1**), lycopecurine (**3**), and dehydrolycopecurine (**4**) or an imine reduction for lyconadins A (**5**) and B (**6**). This strategy may potentially enable access to all 7-membered-ring-containing *Lycopodium* alkaloids and provides additional insight into their biosynthetic origin.



INTRODUCTION

Background. The *Lycopodium* alkaloids are a diverse family of complex natural products that have garnered long-standing interest in synthetic organic chemistry due to their intricate polycyclic structures.[1] Recently, certain members have been demonstrated to exhibit neurological bioactivity, most notably huperzine A. A subset of the *Lycopodium* alkaloids contains a common 7-membered-ring system, which results in unique polycyclic core structures that distinguish them from other members (Figure 1). Included in this subset are himeradine A (**1**)[2] and fastigiatine (**2**),[3] both of which belong to the lycodine structural class of *Lycopodium* alkaloids. Both **1** and **2** contain an unprecedented pentacyclic core with a C4−C10 linkage,[4] which adds considerable strain and complexity. Additionally, himeradine A (**1**) contains in total 7 rings, 10 stereocenters, 3 potentially basic nitrogens, and a quinolizidine subunit appended to the core via a methylene linker, rendering **1** arguably the most synthetically challenging *Lycopodium* alkaloid. Lycopecurine (**3**)[5] and related alkaloids also contain a strained C4−C10 bond and an analogous core structure to **1** and **2** but differ in that the A ring is rearranged, which is characteristic of members of the lycopodine class. Lyconadins A (**5**) and B (**6**) are members of the miscellaneous class[6] and possess a unique pentacyclic ring system. Despite belonging to different structural classes, the presence of the common C4−C10 bond and resultant 7-membered-ring system in this subset of *Lycopodium* alkaloids raises the question of whether (1) they are derived biosynthetically from a common precursor and subsequently diverge and (2) if a synthetic strategy mirroring this process could be devised to efficiently access all such members from a common intermediate.

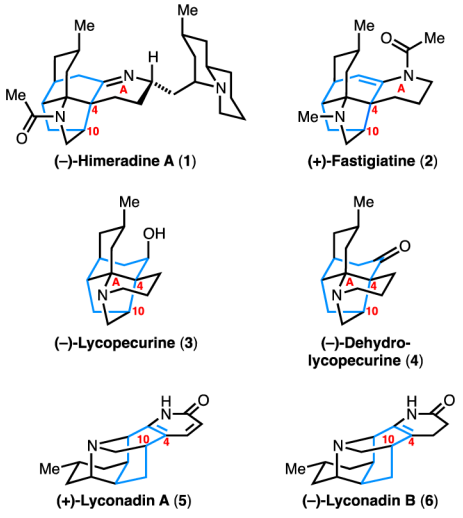


Figure 1. Himeradine A (**1**), fastigiatine (**2**), lycopecurine (**3**), dehydrolycopecurine (**4**), and lyconadins A and B (**5** and **6**).

We describe herein a detailed account of our synthesis of fastigiatine (**2**)[7] and report the first total syntheses of the proposed structure of himeradine A (**1**), lycopecurine (**3**), and

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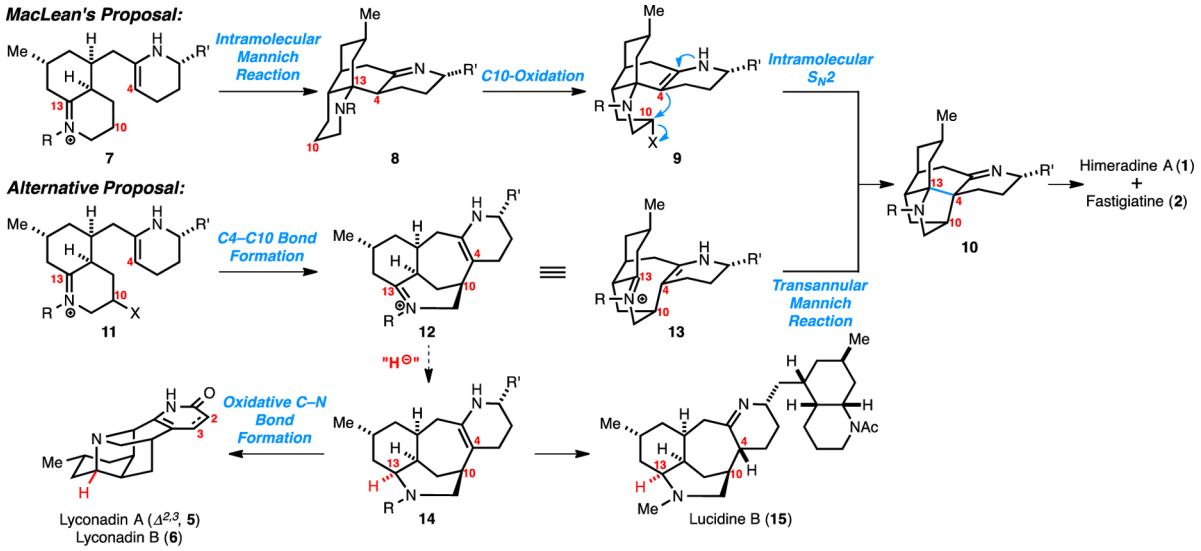
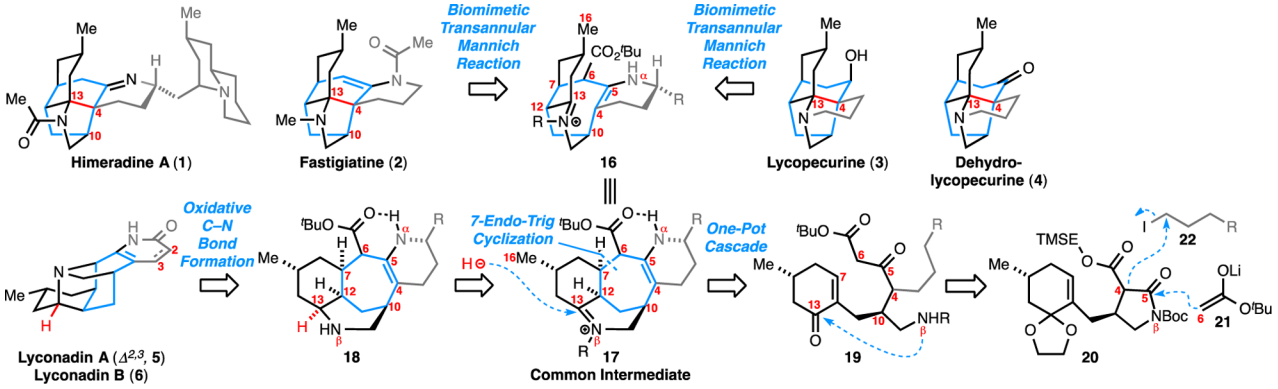
Scheme 1. Proposed Biosynthetic Pathway for 7-Membered-Ring-Containing *Lycopodium* Alkaloids



Scheme 2. Biosynthetically Inspired Retrosynthetic Analysis of 7-Membered-Ring-Containing *Lycopodium* Alkaloids



dehydrolycopecurine (**4**) as well as the syntheses of lyconadins A and B (**5** and **6**) via a unified, biosynthetically inspired strategy for constructing 7-membered-ring-containing *Lycopodium* alkaloids.

Biosynthetic Hypothesis. The proposed biosynthetic pathway for 7-membered-ring-containing *Lycopodium* alkaloids is illustrated in Scheme 1. In MacLean's original proposed biosynthesis of the pentacyclic core of himeradine A (**1**) and fastigiatine (**2**),[3] it was postulated that lycodane skeleton **8**, which could arise from imine **7** via an intramolecular Mannich reaction, could undergo oxidative functionalization at C10 to afford tetracycle **9**. A subsequent intramolecular enamine S_N2 cyclization through a boat-like conformation could then construct the key C4−C10 bond, delivering pentacycle **10**, the core skeleton common to **1** and **2**.

Alternatively, we propose that the 7-membered ring could be constructed via initial cyclization of phlegmarine derivative **11** to form tetracycle **12**. Imine **12** (redrawn as **13**) would then be poised to undergo an intramolecular transannular Mannich reaction to construct the C4−C13 bond in **10**, which could then result in himeradine A (**1**) or fastigiatine (**2**). Alternatively, reduction of the C13-imine in **12** would allow access to the core structures common to the lucidines[8] (e.g., **15**) and lyconadins (e.g., **5** and **6**). In order to access these related alkaloids in MacLean's original hypothesis, a retro-Mannich reaction of **10** to **13** would be necessary, followed by interception of the resultant imine by a hydride equivalent. Our biosynthetic hypothesis could provide an alternative explanation for the possible common origin of other 7-membered-ring-containing *Lycopodium* alkaloids and their divergence from the pentacyclic members **1** and **2**. A biosynthetically inspired strategy based upon our proposed biosynthesis could potentially provide ready access to all such 7-membered-ring-containing members. Hence, we decided to embark on the total syntheses of several 7-membered-ring-containing *Lycopodium* alkaloids, including fastigiatine (**2**), himeradine A (**1**), lycopecurine (**3**), dehydrolycopecurine (**4**), and lyconadins A and B (**5** and **6**).

RESULTS AND DISCUSSION

Biosynthetically Inspired Retrosynthetic Analysis. Our biosynthetically inspired retrosynthetic analysis for himeradine A (**1**), fastigiatine (**2**), lycopecurine (**3**), dehydrolycopecurine (**4**), and lyconadins A and B (**5** and **6**) is outlined in Scheme 2. We envisioned installing the C4−C13 bond in **1**, **2**, and **3** from iminium ion intermediate **16** via a biomimetic transannular Mannich reaction to construct the strained core system. This disconnection would test the plausibility of our proposed biosynthesis, since at the outset it was unknown whether the strained intermediate **16** could readily be accessed. Importantly, **16** (redrawn as **17**) could potentially serve as a common synthetic intermediate for the synthesis of other 7-membered-

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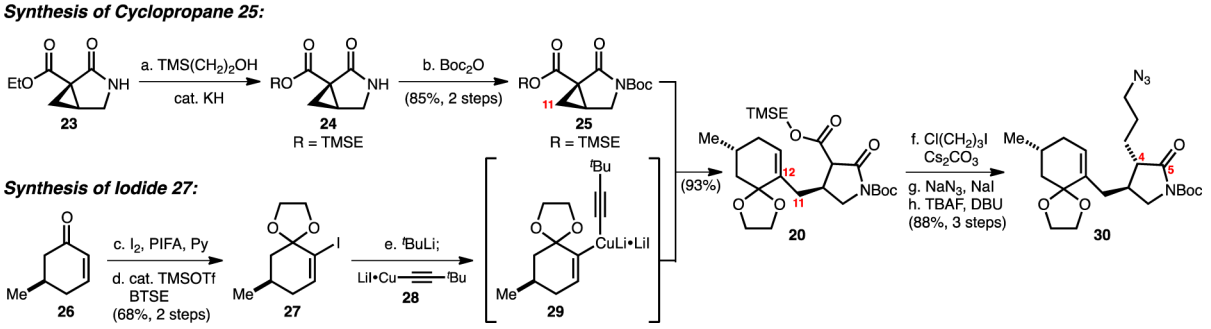
Scheme 3. Convergent Nucleophilic Cyclopropane Opening To Synthesize β-Carboxyimide 20 and Azide 30[a]



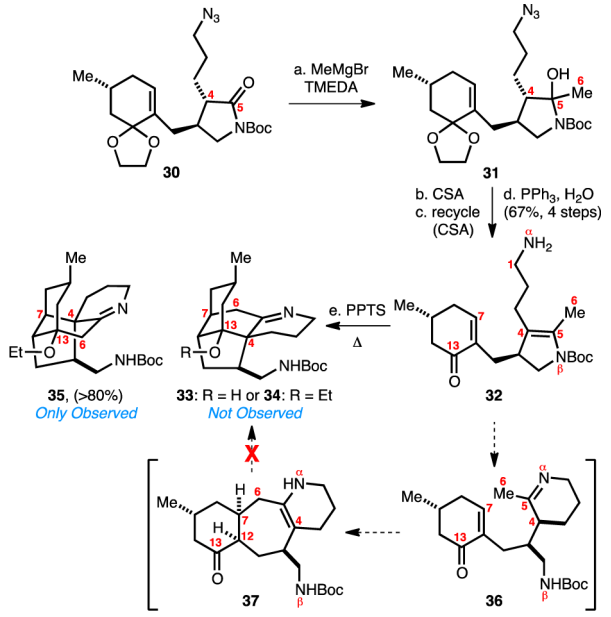
[a]Conditions: (a) cat. KH, 2-(trimethylsilyl)ethanol (TMSEOH), THF; (b) Boc_2O, cat. 4-DMAP, Et_3N, CH_2Cl_2, 85% (2 steps); (c) I_2, PIFA, Py, CH_2Cl_2; (d) cat. TMSOTf, 1,2-bis(trimethylsiloxy)ethane (BTSE), CH_2Cl_2, −78 → −20 °C, 68% (2 steps); (e) *t*-BuLi, Et_2O, −78 °C; then **28**, −78 °C; then **25**, −78 → 0 °C, 93%; (f) Cs_2CO_3, 1-chloro-3-iodopropane, DMF; (g) NaN_3, NaI, DMF, 65 °C; (h) TBAF, DBU, THF, 50 °C, 88% (3 steps).

ring-containing *Lycopodium* alkaloids. For example, reduction of the C13-iminium ion followed by oxidative amination could lead to the lyconadins in a biomimetic fashion.

Enamine **17** could arise from β-ketoester **19** via a diastereoselective 7-*endo-trig* intramolecular 1,4-conjugate addition,[9] forming the C6−C7 bond as well as the C7- and C12-stereocenters. Concomitantly, the Nα−C5 and Nβ−C13 bonds could be introduced via condensation of Nα and Nβ with the C5- and C13-carbonyls, respectively. We anticipated that the stereoselectivity of these transformations would be controlled by topological constraints or by stereoelectronically favored axial attack *anti* to the C16-methyl group.[9,10] At the outset, the order of these potentially tandem bond-forming events was considered flexible depending on judicious selection of nitrogen protecting groups. Our original objective was to achieve a one-pot cascade reaction to construct the pentacyclic core in **1** and **2**, and more importantly, we hoped to later program this sequence to access all 7-membered-ring-containing *Lycopodium* alkaloids. A convergent synthesis of cascade precursor **19** can be accomplished via initial alkylation of β-carboxyimide **20** with iodide **22** and subsequent addition of the lithium enolate of *tert*-butylacetate **21** to the C5-carbonyl. By varying the electrophilic alkylation partner of **20**, a variety of structurally diverse target members could potentially be accessed. To explore our strategy, we initially targeted fastigiatine (**2**), which culminated in its first total synthesis.[7] A detailed account of our efforts toward the synthesis of **2** will first be presented.

Total Synthesis of (+)-Fastigiatine (2). Our synthesis of fastigiatine (**2**) commenced with the syntheses of coupling fragments cyclopropane **25** and vinyl iodide **27** (Scheme 3). Transesterification of ethyl ester **23**, derived in four steps from (*S*)-epichlorohydrin,[11] with 2-(trimethylsilyl)ethanol (TMSEOH),[12] followed by *N*-Boc protection, afforded cyclopropane **25**. Cyclohexenone **26**, derived in four steps from (*R*)-pulegone, was first α-iodinated according to literature protocol[13] and then protected as a dioxolane to afford vinyl iodide **27**. Electrophilic cyclopropanes such as **25** have been demonstrated to undergo nucleophilic opening in the presence of suitable nucleophiles.[14] Exploiting this reactivity, we sought to couple a 2-cyclohexenone anion equivalent[15] derived from **27** to cyclopropane **25**. To this end, we first generated mixed organocuprate **29** from vinyl iodide **27** via lithium−halogen exchange with *tert*-butyllithium followed by transmetalation with copper acetylide **28**, where the acetylide functions as a nontransferable ligand. Subsequent exposure of cyclopropane **25** to **29** led to regioselective nucleophilic opening to afford β-carboxyimide **20** in 93% yield. Carboxyimide **20** underwent efficient alkylation with 1-chloro-3-iodopropane, and the resultant primary chloride was displaced with NaN_3. The corresponding azide was then exposed to TBAF and DBU, resulting in cleavage of the TMSE ester with concomitant decarboxylation and in situ base-catalyzed epimerization at C4 to yield *N*-Boc-2-pyrrolidinone **30**;[16] the use of a TMSE ester proved necessary as other ester derivatives could not be selectively hydrolyzed at this stage. Next, the C6-carbon was successfully introduced via regioselective addition of MeMgBr to the C5-carbonyl of **30**, furnishing hemiaminal **31** (Scheme 4). Dehydration of **31** with CSA occurred with simultaneous ketal deprotection to provide the corresponding dihydro-

Scheme 4. Synthesis of Dihydropyrrole 32 as a Potential Cascade Precursor[a]



[a]Conditions: (a) MeMgBr, TMEDA, THF, −78 → −20 °C; (b) CSA, PhH; (c) recycle (CSA, PhH); (d) PPh_3, THF/H_2O, 60 °C, 67% (4 steps); (e) PPTS, EtOH, 80 °C, 80%.

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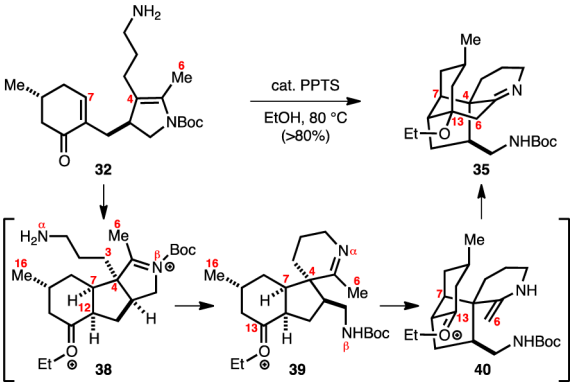
pyrrole. Staudinger reduction of the azide functionality then delivered primary amine **32**.

Although the C−N connectivity in **32** did not correspond to that found in fastigiatine (**2**), we hypothesized that the more nucleophilic Nα-amine could exchange with the Nβ-carbamate to provide imine **36**. Imine **36** could then undergo the desired 7-*endo-trig* cyclization via tautomerization to the corresponding exocyclic enamine, followed by a subsequent transannular aldol reaction to establish the C4−C13 bond of tetracycle **33** or **34**. We originally assumed that **32** could not undergo 5-*endo-trig* cyclization to form the incorrect C4−C7 bond since this would violate Baldwin's rules.[17] However, heating **32** with PPTS in EtOH resulted in exclusive formation of constitutional isomer **35**.

Our proposed mechanism for the formation of **35** is depicted in Scheme 5. Upon exposure to PPTS, formation of the

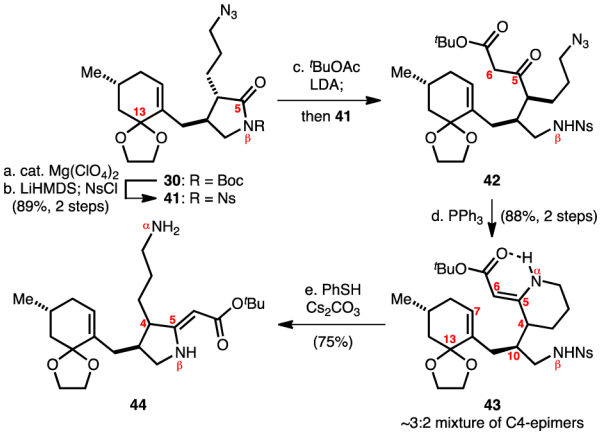
Scheme 5. 5-*Endo-Trig* Cyclization To Form Tetracycle 35



corresponding oxocarbenium ion from **32** would result in 5-*endo-trig* cyclization *anti* to the C16-methyl group to establish the C4−C7 bond in *cis*-5,5-bicyclic iminium ion intermediate **38**. We speculated that formation of a charged oxocarbenium intermediate allowed an exception to Baldwin's rules, which generally disfavors 5-*endo-trig* cyclizations. Next, Nα and Nβ could undergo exchange to provide imine **39**. Tautomerization of **39** to exocyclic enamine **40** followed by a transannular aldol reaction would then yield tetracycle **35**. From these results it was apparent that (1) the correct C−N connectivity was most likely required for the cascade sequence and (2) 5-*endo-trig* cyclization was facile.

Unfortunately, attempts to form the 6-membered imine with the correct Nα−C5 connectivity (e.g., **36**) were largely unsuccessful, primarily due to an apparent strong thermodynamic preference for the 5-membered-ring system containing the incorrect Nβ−C5 bond. In order to reduce the propensity of forming the undesired cyclic 5-membered-ring system, the Nβ-Boc group was replaced with a 2-nitrobenzenesulfonyl (Ns) group, which we speculated would inductively deactivate Nβ and thus prevent Nα and Nβ exchange. This was accomplished via chemoselective cleavage of the *N*-Boc group of **30** with $Mg(ClO_4)_2$[18] followed by *N*-sulfonylation to yield *N*-Ns-2-pyrrolidinone **41** (Scheme 6). Gratifyingly, addition of the lithium enolate of *tert*-butyl acetate to the C5-carbonyl provided β-ketoester **42** with Nβ completely disengaged from C5. Staudinger reaction of **42** afforded vinylogous urethane **43** as an inconsequential ~3:2 mixture of C4-epimers.[19] Of note, the C6-*tert*-butyloxycarbonyl was utilized to induce preferential formation of the exocyclic Nα−C5−C6 enamine over the

Scheme 6. Installation of the Correct Nα−C5 Connectivity via Inductive Deactivation of Nβ[a]



[a]Conditions: (a) cat. $Mg(ClO_4)_2$, MeCN, 60 °C; (b) LiHMDS, THF; NsCl, 0 °C → RT, 89% (2 steps); (c) LDA, *t*-BuOAc, THF, −78 °C; then **41**, −78 °C; (d) PPh_3, PhH, 50 °C, 88% (2 steps); (e) PhSH, Cs_2CO_3, DMF, 75%.

otherwise preferred endocyclic Nα−C5−C4 enamine,[20] thereby suppressing potential undesired 5-*endo-trig* cyclization. Only a few steps remained in order to test the key cascade reaction: (1) cleavage of the Nβ-Ns group, (2) deprotection of the C13-ketal, and (3) condensation of Nβ with the resultant C13-ketone to form the corresponding α,β-unsaturated imine, which we anticipated would initiate the cascade sequence to form the pentacyclic core of **2**. However, upon cleavage of the Nβ-Ns group, Nα and Nβ underwent rapid transamination to afford 5-membered vinylogous urethane **44**. On the basis of these results, it was clear that the Nβ-Ns group would have to be removed at a later stage.

Instead of cleaving the Nβ-Ns group, **43** was directly exposed to aqueous HCl, which resulted in a formal [3+3]-cycloaddition[20,21] to furnish tetracycle **51** as a single diastereomer in 92% yield (Scheme 7). Formation of **51** presumably occurred via initial C13-dioxolane cleavage to provide enone **45**, which then underwent 7-*endo-trig* intramolecular 1,4-conjugate addition to form the C6−C7 bond via stereoelectronically favored axial attack *anti* to the C16-methyl group. Axial attack of the enone *syn* to the C16-methyl group is disfavored due to a developing 1,3-diaxial interaction in the resultant enol intermediate between the C16-methyl group and the newly formed C6−C7 bond. Next, stereoselective protonation of the ensuing C12−C13 enol **49** occurred via stereoelectronically favored axial protonation[22] to provide ketone **50**. Finally, a transannular aldol reaction resulted in formation of the C4−C13 bond to deliver tetracycle **51**. Despite the efficiency of this transformation, which selectively generated four contiguous stereocenters, it was uncertain whether tetracycle **51** could ultimately be converted to fastigiatine (**2**); this would require a formal exchange between the C13-hydroxyl and Nβ in order to access the pentacyclic core.

Nonetheless, only a few steps remained in order to achieve a synthesis of fastigiatine (**2**). To this end, alkylation of **51** with MeI in the presence of K_2CO_3, followed by addition of PhSH, delivered *N*-methylamine **52** (87%). Up until this point, there was no evidence that **52** or other tetracyclic intermediates existed in equilibrium with the corresponding tricyclic retro-aldol isomers. However, submission of **52** to electrospray

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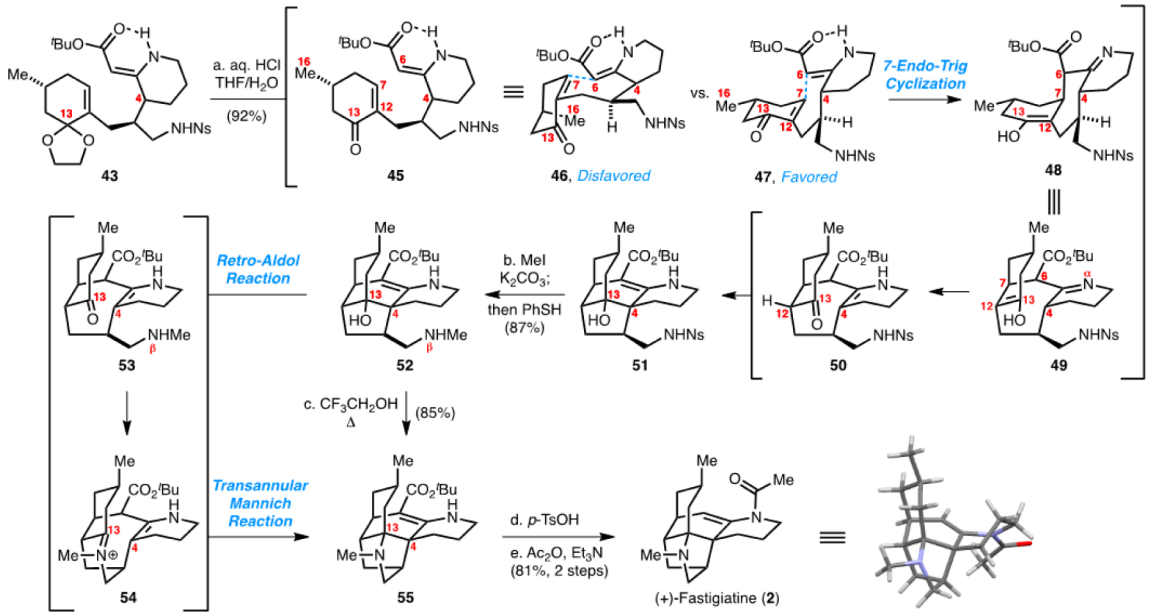
Scheme 7. Completion of the Total Synthesis of (+)-Fastigiatine via a Formal [3+3]-Cycloaddition[a]



[a]Conditions: (a) HCl, THF/H_2O, 92%; (b) K_2CO_3, MeI, DMF, 0 °C → RT; then PhSH, 0 °C → RT, 87%; (c) CF_3CH_2OH, 80 °C, 85%; (d) *p*-TsOH·H_2O, PhH, 80 °C, 95%; (e) Ac_2O, Et_3N, CH_2Cl_2, 85%.

ionization mass spectrometry revealed an ion with mass $[M - H_2O + H]^+$, potentially corresponding to the desired dehydrated product and suggesting that the desired conversion of tetracycle **52** to the pentacyclic core was possible. Gratifyingly, heating **52** in deoxygenated 2,2,2-trifluoroethanol (TFE) yielded pentacycle **55** in 85% yield, presumably via (1) initial retro-aldol reaction to afford ketone **53**, (2) condensation of Nβ with the resultant C13-ketone to form iminium ion **54**, and (3) the key biomimetic transannular Mannich reaction to construct the C4−C13 bond. The use of deoxygenated TFE, a strong hydrogen-bond donor but not a strong acid such that it would protonate Nβ or induce cleavage of the *tert*-butyloxycarbonyl group, as solvent was crucial to the success of this reaction. Other common solvents (e.g., EtOH, DMSO, DMF, MeCN, PhMe, etc.) and additives (e.g., acids) failed to yield **55**. We speculated that under acidic conditions, protonation of Nβ would disfavor formation of the positively charged intermediates involved in the retro-aldol reaction. Finally, heating **55** with *p*-TsOH resulted in removal of the *tert*-butyloxycarbonyl group to furnish the corresponding imine, which was subsequently acetylated to afford (+)-fastigiatine (**2**) in 81% yield over 2 steps ($[\alpha]_D^{24}$ = +375 (*c* 1.4, $CHCl_3$)). This constitutes the first total synthesis of fastigiatine (**2**), the structure of which was unambiguously confirmed by single-crystal X-ray diffraction analysis.

In summary, an efficient synthesis of fastigiatine (**2**) was achieved. Our synthesis featured a convergent fragment coupling via a nucleophilic cyclopropane opening and a diastereoselective formal [3+3]-cycloaddition reaction. Additionally, an unusual retro-aldol, iminium ion formation, and biomimetic transannular Mannich cascade allowed for the construction of the strained pentacyclic core. The ease of the transannular Mannich reaction suggests that imine **13** is a feasible biosynthetic intermediate. However, despite the efficiency of the formal [3+3]-cycloaddition and subsequent retro-aldol−Mannich sequence, this strategy prohibited direct isolation of an imine analog derived from an intermediate such as **13** or **17** and thus prevented our ultimate objective of developing a unified strategy to access other 7-membered-ring-containing *Lycopodium* alkaloids. Indeed, reprogramming the cascade sequence and thereby obviating the need to formally exchange the C13-hydroxyl with Nβ would be necessary toward achieving this goal. This objective was ultimately accomplished in our total synthesis of the proposed structure of himeradine A (**1**), which will be discussed next.

Total Synthesis of the Proposed Structure of (−)-Himeradine A (1). In addition to sharing a pentacyclic core with fastigiatine (**2**), himeradine A (**1**) contains a quinolizidine subunit appended to the core via a methylene linker. A synthesis of **1** has not been reported in the literature to date. As discussed previously, we wanted to accomplish two objectives in a synthesis of **1**: (1) the development of a unifying strategy that could permit access to all 7-membered-ring-containing *Lycopodium* alkaloids and (2) a one-pot sequence for the construction of the strained core system common to **1** and **2**.

Our retrosynthetic analysis of the quinolizidine subunit of himeradine A (**1**) is illustrated in Scheme 8. The desired β-carboxyimide (**20**) alkylation partner **56** could be constructed from allyl *N*-Boc piperidine **57** via a strategy involving a ring-closing metathesis. *N*-Boc piperidine **57** contains four stereocenters; we planned to introduce the C6′-, C10′-, and C17-stereocenters through substrate control. The C6′-stereocenter in **57** could be installed via diastereotopic deprotonation at C6′ in *N*-Boc piperidine **58** followed by alkylation. The C10′- and C17-stereocenters could be introduced by relaying the stereochemical information of the single C8′-stereocenter in *N,O*-methoxyacetal **61** via a diastereoselective *N*-acyliminium ion Mannich reaction followed by a stereoselective ketone reduction.

Our synthesis of himeradine A (**1**) commenced with the lipase-mediated desymmetrization of 3-methylglutaric anhydride with *n*-PrOH,[23] providing carboxylic acid **63** in 98% yield (93% ee) (Scheme 9). Chemoselective reduction of the

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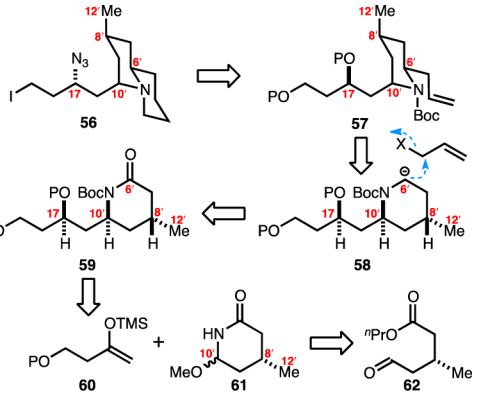
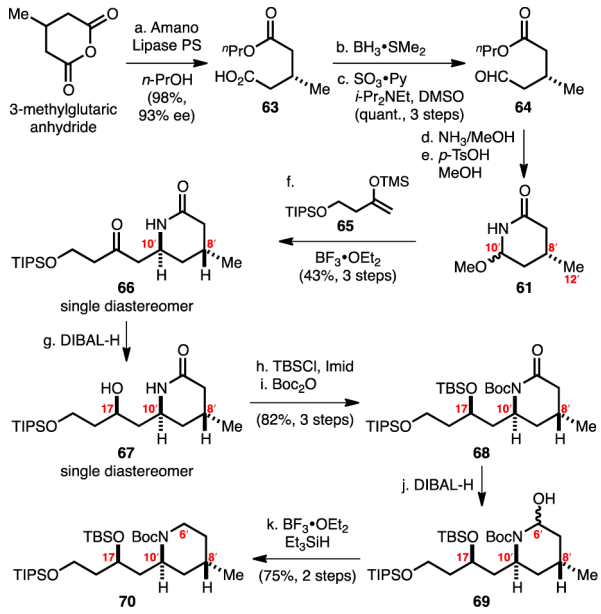
Scheme 8. Retrosynthesis of the Quinolizidine Subunit 56



Scheme 9. Synthesis of *N*-Boc Piperidine 70[a]

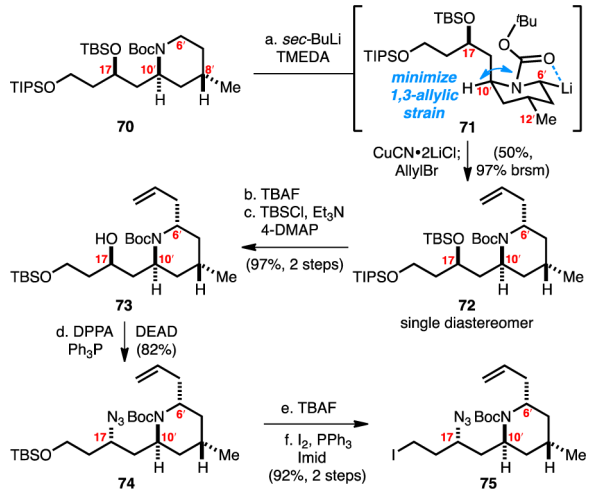


[a]Conditions: (a) Amano Lipase PS, *n*-PrOH, *i*-Pr_2O, 98% (93% ee); (b) BH_3·SMe_2, THF, 0 °C → RT; (c) SO_3·Py, *i*-Pr_2NEt, DMSO, CH_2Cl_2, 0 °C, quant. (3 steps); (d) NH_3/MeOH, 50 °C; (e) *p*-TsOH, MeOH, 50 °C; (f) **65**, BF_3·OEt_2, MeCN, −40 °C → RT, 43% (3 steps); (g) DIBAL-H, THF, −78 °C; (h) TBSCl, Imid, DMF, 98% (2 steps); (i) Boc_2O, 4-DMAP, MeCN, 84%; (j) DIBAL-H, −78 → 0 °C; (k) BF_3·OEt_2, Et_3SiH, CH_2Cl_2, −78 °C, 75% (2 steps).

carboxylic acid in **63** with BH_3·SMe_2, followed by Parikh–Doering oxidation of the resultant primary carbinol, furnished aldehyde **64**. Exposure of **64** to NH_3/MeOH resulted in the formation of a mixture of *N,O*-hydroxy and *N,O*-methoxy acetals, which was subsequently heated with *p*-TsOH in MeOH at 50 °C to afford *N,O*-methoxy acetal **61** as a mixture of diastereomers. Next, exposure of **61** and silyl enol ether **65** to BF_3·OEt_2 afforded lactam **66** as a single diastereomer via an *N*-acyliminium ion Mannich reaction in 43% yield (3 steps).[24] The diastereoselectivity of this reaction was controlled via stereoelectronically favored axial attack by **65** at C10′ of the *N*-acyliminium ion intermediate *anti* to the C12′-methyl group. Next, chelate-controlled 1,3-*syn* reduction[25] of ketone **66** with DIBAL-H afforded alcohol **67** as a single diastereomer, which was converted to *N*-Boc-piperidine **70** in four steps, involving TBS protection of the C17-hydroxyl, Boc protection of the lactam, and a two-step reduction of the C6′-carbonyl to a methylene (62% over 5 steps).

Next, diastereotopic deprotonation of **70** at C6′ was accomplished with *sec*-butyllithium in the presence of TMEDA (Scheme 10).[26] The conformation of lithiated *N*-

Scheme 10. Synthesis of *N*-Boc Piperidine Iodide 75[a]



[a]Conditions: (a) *sec*-BuLi, TMEDA, −78 °C; CuCN·2LiCl, −78 °C; AllylBr, −78 °C → RT, 50% (97% brsm); (b) TBAF, THF, 0 °C → RT, quant.; (c) TBSCl, 4-DMAP, Et_3N, CH_2Cl_2, 97%; (d) DPPA, PPh_3, DEAD, THF, 82%; (e) TBAF, THF, 0 °C → RT, 96%; (f) I_2, PPh_3, Imid, CH_2Cl_2, 96%.

Boc piperidine **71** is rigidly locked due to 1,3-allylic strain minimization between the *N*-Boc group and the C10′-stereocenter, which is further reinforced by the equatorial C12′-methyl group. Equatorial lithiation is favored due to chelation with the *N*-Boc group.[26] Transmetalation with Cu(I), followed by alkylation with allyl bromide, yielded allyl *N*-Boc piperidine **72** as a single diastereomer in 50% yield (97% based on recovered starting material). Attempted alkylation with more functionalized electrophiles (e.g., electrophilic cyclopropanes, substituted allylic halides) was unsuccessful. Global silyl deprotection, followed by selective protection of the resultant primary hydroxyl, afforded TBS ether **73** (97%, 2 steps). Finally, Mitsunobu displacement of the secondary hydroxyl group in **73**, cleavage of the primary TBS ether, and formation of the corresponding iodide yielded the desired alkylation partner, iodide **75**. Of note, attempted synthesis of quinolizidine **56** or the mesylate or tosylate analogs as potential alkylation partners was unsuccessful, presumably due to inter- and intramolecular alkylation by the tertiary amine. We also attempted to protect the quinolizidine tertiary amine as an amide, but downstream efforts to reduce the tertiary amide proved incompatible with the diverse array of functional groups present.

β-Carboxyimide **20** underwent efficient alkylation with iodide **75** to afford coupled product **76** in 94% yield (Scheme 11). Carboxyimide **76** was converted to *β*-ketoester **79** in four steps via (1) cleavage of the TMSE ester with concomitant decarboxylation, (2) chemoselective removal of the *N*-Boc group with $Mg(ClO_4)_2$, (3) protection of the resultant pyrrolidinone with a Ns group,[27] and (4) addition of the lithium enolate of *tert*-butylacetate to *N*-Ns-2-pyrrolidinone **78**. With **79** in hand, the key cascade sequence was next explored.

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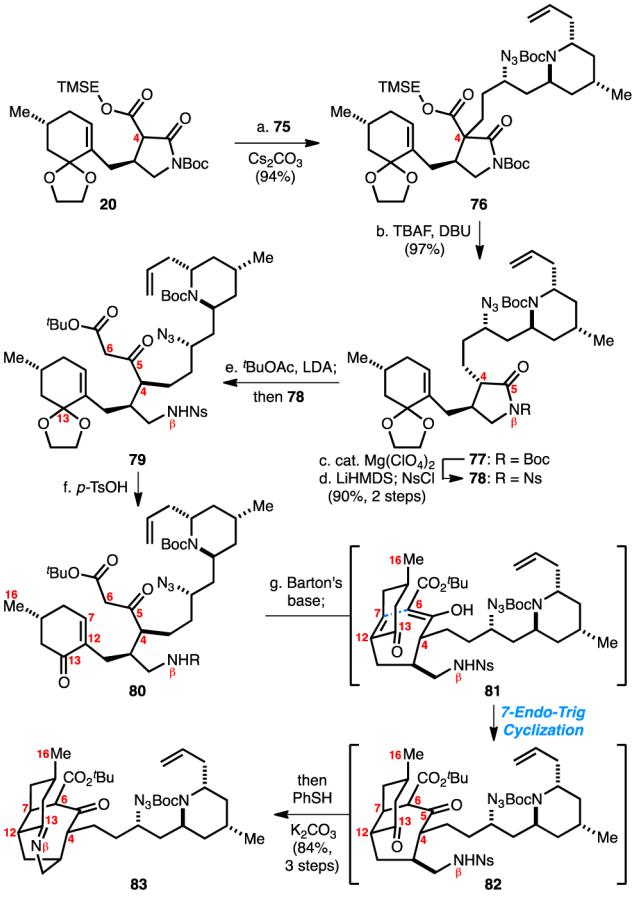
Scheme 11. One-Pot Sequence for the Synthesis of the Tricyclic Core of (−)-Himeradine A (1)[a]



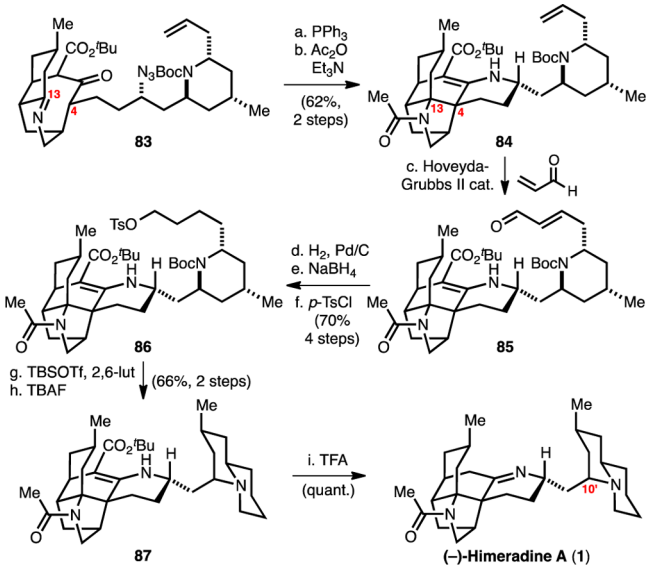
[a]Conditions: (a) **75**, Cs_2CO_3, DMF, 94%; (b) TBAF, DBU, THF, 50 °C, 97%; (c) cat. $Mg(ClO_4)_2$, MeCN, 60 °C; (d) LiHMDS, THF; NsCl, 0 °C → RT, 90% (2 steps); (e) LDA, *t*-BuOAc, THF, −78 °C; then **78**, −78 °C; (f) *p*-TsOH, 8:1 THF/H_2O; (g) 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base), MeCN, 0 °C → RT; then PhSH, K_2CO_3, 0 °C → RT, 84% (3 steps).

As discussed previously, the formal [3+3]-cycloaddition employed in the synthesis of fastigiatine (**2**) could not allow access to an imine intermediate such as **17**. This strategy was thus not readily amenable toward the synthesis of other 7-membered-ring-containing *Lycopodium* alkaloids, which was one of our ultimate objectives.

Instead, a new reaction sequence was developed that enabled the construction of the strained tricyclic core structure in imine **83** in a single pot. Instead of performing a Staudinger reaction on **79** and forming the corresponding vinylogous urethane, the C13-dioxolane was first removed upon exposure to *p*-TsOH to provide enone **80**. Next, **80** was converted to imine **83** in a one-pot sequence involving (1) initial exposure of **80** to Barton's base to induce 7-*endo-trig* intramolecular cyclization to form the C6−C7 bond via axial attack *anti* to the C16-methyl group, (2) tautomerization of the resultant C12−C13 enol to secure the C12-stereocenter through protonation from the convex face, (3) cleavage of the *N*-Ns protecting group upon addition of PhSH and K_2CO_3, and (4) in situ condensation of N*β* with the C13-ketone to form imine **83**. By forming the C6−C7 bond first via the *β*-ketoester prior to cleavage of the *N*-Ns group, we were able to circumvent both undesired formation of the N*β*−C5 bond as well as the transannular aldol reaction. This allowed direct isolation of imine **83**, which would enable access to other 7-membered-ring-containing *Lycopodium* alkaloids (vide infra).

Next, Staudinger reduction of **83** resulted in formation of the corresponding vinylogous urethane, which underwent the key biomimetic transannular Mannich reaction to form the C4−C13 bond in situ, furnishing the corresponding hexacycle in 75% yield (Scheme 12). With the successful construction of the

Scheme 12. Total Synthesis of the Proposed Structure of (−)-Himeradine A (1)[a]



[a]Conditions: (a) PPh_3, 8:1 THF/H_2O, 70 °C, 75%; (b) Ac_2O, Et_3N, CH_2Cl_2, 83%; (c) acrolein, Hoveyda−Grubbs catalyst II, CH_2Cl_2, quant.; (d) H_2, Pd/C, EtOAc; (e) $NaBH_4$, EtOH, 0 °C; (f) *p*-TsCl, Et_3N, 4-DMAP, CH_2Cl_2, 70% (3 steps); (g) TBSOTf, 2,6-lut, CH_2Cl_2, 0 °C → RT; (h) TBAF, THF, 0 °C, 66% (2 steps); (i) 1:1 TFA/CH_2Cl_2, quant.

pentacyclic core realized, the resultant secondary amine was then acetylated to provide amide **84** in 83% yield. Next, the allyl *N*-Boc piperidine moiety in **84** was converted to the desired quinolizidine subunit in a multistep sequence. First, cross metathesis of the allyl group of **84** with acrolein was conducted with Hoveyda−Grubbs catalyst II,[28] which yielded enal **85** (quant.). Hydrogenation of **85**, followed by $NaBH_4$ reduction of the aldehyde intermediate, and sulfonylation of the resultant hydroxyl group, afforded tosylate **86** in 70% yield (3 steps). Two-step cleavage of the *N*-Boc group of **86**, involving initial treatment with TBSOTf followed by TBAF, resulted in in situ cyclization via displacement of the tosylate group by the resultant secondary amine to deliver heptacycle **87** (66%, 2 steps), which now contained the quinolizidine subunit.

Finally, cleavage of the *tert*-butyloxycarbonyl group with concomitant decarboxylation occurred upon exposure to TFA, yielding the proposed structure of (−)-himeradine A (**1**) as the bis-TFA salt (quant., $[\alpha]_D^{23} = -19$ (*c* 0.3, MeOH)). With the exception of the chemical shift of H10′, which is shifted upfield by $\Delta\delta = 0.14$ ppm in synthetic relative to natural himeradine A (**1**), the ^{1}H NMR, ^{13}C NMR, COSY, NOESY, HSQC, and HMBC spectra, as well as the specific rotation, are in excellent agreement with the data reported for the natural product. It is well documented that the protonation state of basic nitrogen atoms can have a significant impact on proton chemical shifts.[29] Hence, we carefully titrated the bis-TFA salt of himeradine A

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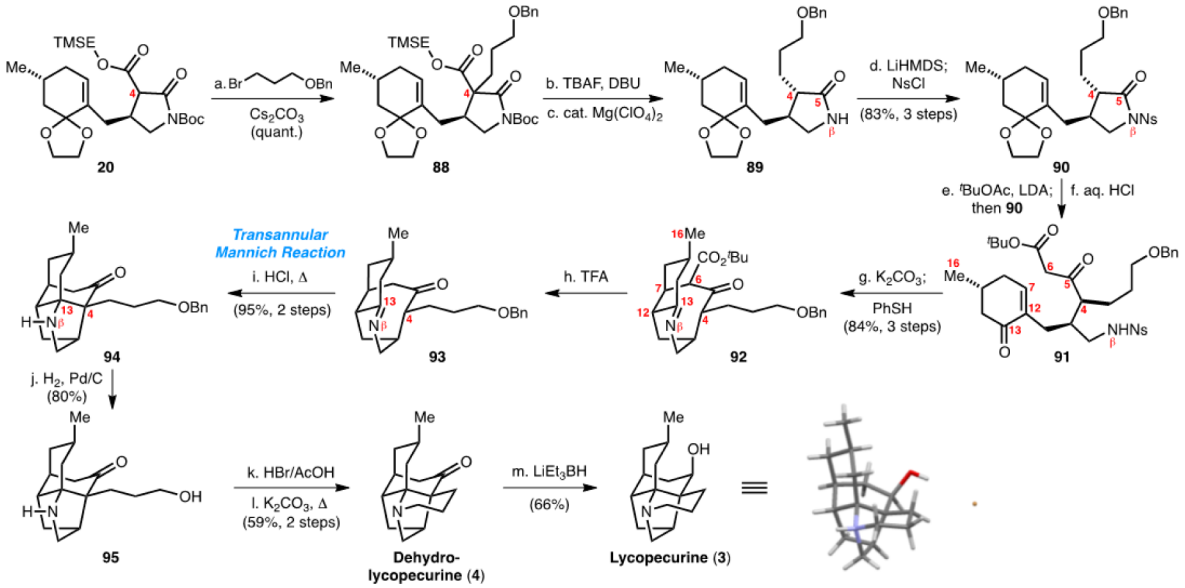
Scheme 13. Total Syntheses of Lycopecurine (3) and Dehydrolycopecurine (4)[a]



[a]Conditions: (a) benzyl 3-bromopropyl ether, Cs_2CO_3, DMF, quant.; (b) TBAF, DBU, 50 °C, 87%; (c) cat. $Mg(ClO_4)_2$, MeCN, 60 °C; (d) LiHMDS, THF; NsCl, 0 °C → RT, 95% (2 steps); (e) LDA, *t*-BuOAc, THF, −78 °C; then **90**, −78 °C; (f) HCl, 8:1 THF/H_2O; (g) K_2CO_3, DMF; then PhSH, 0 °C → RT, 84% (3 steps); (h) 1:1 TFA/CH_2Cl_2; (i) HCl, MeOH, 65 °C, 95% (2 steps); (j) H_2, Pd/C, HCl, EtOH, 80%; (k) 3:1 AcOH/HBr; (l) K_2CO_3, MeCN, 50 °C, 59% (2 steps); (m) $LiEt_3BH$, THF, 0 °C → RT, 66%.

(**1**) with $NaOCD_3$ until the free base was obtained, and then we titrated aliquots of TFA until the bis-TFA salt was reisolated. We were unable to identically replicate the published ^{1}H NMR spectrum of the bis-TFA salt of natural himeradine A, although the ^{1}H NMR spectrum of the free base of synthetic (**1**) and natural himeradine A appeared to match.[30] Varying the concentration and temperature did not affect the proton chemical shift. Without an authentic sample of **1**, we were unable to unambiguously verify that the proposed structure of himeradine A (**1**) corresponded to the correct structure of natural himeradine A. This constitutes the first total synthesis of the proposed structure of himeradine A (**1**).

In summary, a biosynthetically inspired and convergent strategy for the synthesis of himeradine A (**1**) was achieved. Noteworthy transformations include a diastereoselective one-pot sequence for constructing the core system shared by **1** and other *Lycopodium* alkaloids, and a key biomimetic transannular Mannich reaction for accessing the pentacyclic core. As discussed previously, isolation of imine **83** (Scheme 11) could potentially allow access to other 7-membered-ring-containing *Lycopodium* alkaloids through a unifying strategy, which will be the topic of the upcoming sections.

Total Syntheses of (−)-Lycopecurine (3) and (−)-Dehydrolycopecurine (4). We decided to first embark on the syntheses of lycopecurine (**3**) and dehydrolycopecurine (**4**) using our biosynthetically inspired, unifying strategy (Scheme 13). Lycopecurine (**3**) was isolated in 1969 from *Lycopodium alopecuroides*,[5a,b] and dehydrolycopecurine (**4**) was obtained from *Lycopodium inundatum*[5c] in 1971. To date, a synthesis of either **3** or **4** has not been reported in the literature.

To this end, *β*-carboxyimide **20** underwent efficient alkylation with benzyl 3-bromopropyl ether to provide alkylated product **88** (quant.). Next, **88** was converted in five steps to enone **91** by utilizing an analogous reaction sequence employed in our synthesis of himeradine A (**1**). Using a modified protocol for our one-pot sequence involving initial exposure to K_2CO_3 and subsequent addition of PhSH, **91** underwent a 7-*endo-trig* intramolecular cyclization to form the C6−C7 bond with stereoselective C12-protonation, followed by in situ condensation of N*β* with the C13-ketone, to yield imine **92** (69%, 6 steps).

Treatment of **92** with TFA resulted in cleavage of the *tert*-butyloxycarbonyl group with concomitant decarboxylation. Upon heating with HCl in MeOH,[31] ketone **93** underwent a key biomimetic transannular Mannich reaction to establish the C4−C13 bond in tetracycle **94** (95%, 2 steps). Cleavage of the benzyl ether group in **94** via hydrogenolysis afforded alcohol **95**. Alcohol **95** was then treated with 25% HBr in glacial AcOH, resulting in bromination of the hydroxyl group and formation of the corresponding ammonium bromide salt. This intermediate underwent cyclization upon heating with K_2CO_3 via displacement of the bromide by the secondary amine to yield dehydrolycopecurine (**4**) (59%, 2 steps, $[\alpha]_D^{22} = -69$ (*c* 0.34, MeOH)). Diastereoselective reduction of the ketone with $LiEt_3BH$ then delivered lycopecurine (**3**) (66%, $[\alpha]_D^{22} = -19$ (*c* 0.14, MeOH)). The structure of lycopecurine (**3**) was unambiguously confirmed via single-crystal X-ray diffraction analysis of the HBr salt of **3**. Our report constitutes the first total syntheses of lycopecurine (**3**) and dehydrolycopecurine (**4**).

Total Syntheses of (+)-Lyconadin A (5) and (−)-Lyconadin B (6). Lyconadin A (**5**) was isolated in 2001 from the club moss *Lycopodium complanatum* by Kobayashi and coworkers[6a] and exhibited modest cytotoxicity against murine lymphoma L1210 cells (IC_{50} = 0.46 *μ*g/mL) and human epidermoid carcinoma KB cells (IC_{50} = 1.7 *μ*g/mL). Lyconadin A (**5**) contains a pentacyclic core, including a 2-pyridone ring, 6 stereocenters, and a tertiary amine. Lyconadin B (**6**), isolated in 2006, contains a dihydropyridone instead of a pyridone subunit but is otherwise identical to **5**.[6b] Both **5** and **6** have been shown to enhance expression of nerve growth factor (NGF) in 1321N1 human astrocytoma cells. Due to their complex

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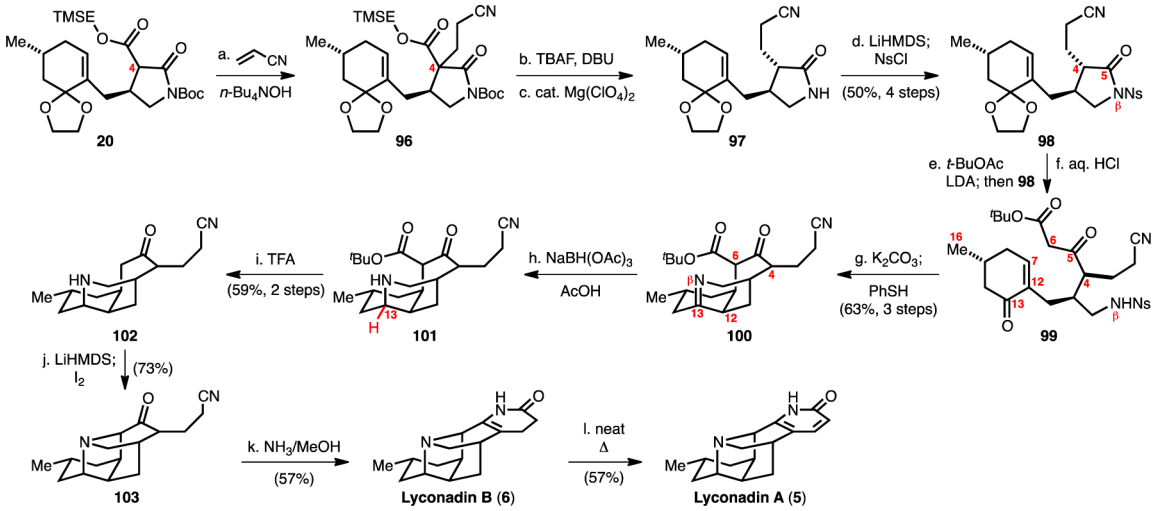
Scheme 14. Total Syntheses of (+)-Lyconadin A (5) and (−)-Lyconadin B (6)[a]



[a]Conditions: (a) acrylonitrile, *n*-Bu_4NOH, MeCN, 0 °C → RT; (b) TBAF, DBU, 50 °C, 78% (2 steps); (c) cat. $Mg(ClO_4)_2$, MeCN, 60 °C; (d) LiHMDS, THF; NsCl, 0 °C → RT, 64% (2 steps); (e) LDA, *t*-BuOAc, THF, −78 °C; then **98**, −78 °C; (f) HCl, 8:1 THF/H_2O; (g) K_2CO_3, DMF; then PhSH, 0 °C → RT, 63% (3 steps); (h) $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 0 °C → RT; (i) 1:1 TFA/CH_2Cl_2, 59% (2 steps); (j) LiHMDS; I_2, THF, −78 → 0 °C, 73%; (k) NH_3/MeOH, 120 °C, 57%; (l) neat, 160 °C, 57%.

polycyclic architecture and promising biological activity, the lyconadins have been the subject of synthetic efforts by various laboratories.[9,32] We envisioned that our unifying strategy could be applied toward the syntheses of lyconadins A (**5**) and B (**6**) via reduction of an iminium ion intermediate such as **17** instead of application of a transannular Mannich reaction.

Our synthesis commenced with the alkylation of *β*-carboxyimide **20** with acrylonitrile to afford nitrile **96** (Scheme 14). Carboxyimide **96** was converted to enone **99** in five steps by employing an analogous reaction sequence utilized in our syntheses of himeradine A (**1**) and lycopecurine (**3**). Successful application of our one-pot protocol involving initial addition of K_2CO_3 followed by PhSH then yielded tricyclic imine **100** in 63% yield (3 steps). Chemoselective reduction of the imine functionality in **100** with $NaBH(OAc)_3$ and AcOH occurred smoothly to furnish amine **101**.

Next, treatment of **101** with TFA resulted in loss of the *tert*-butyloxycarbonyl group with concomitant decarboxylation to provide ketone **102** in 59% yield (2 steps). Formation of the corresponding enolate of **102** via deprotonation by LiHMDS, followed by addition of I_2, directly afforded tertiary amine **103** in 73% yield. In Sarpong's synthesis of lyconadin A (**5**), an analogous transformation was employed for the construction of the C−N bond involving deprotonation with *n*-butyllithium, followed by addition of I_2.[32a,b] Formation of **103** could have occurred via two possible mechanisms: (1) initial *α*-iodination of the ketone from the convex face and subsequent intramolecular S_N2 displacement of the iodide by the secondary amine or (2) oxidative enolate amination to form the C−N bond. Finally, heating nitrile **103** in an NH_3/MeOH solution[33] in a sealed vessel at 120 °C resulted in dihydropyridone formation to deliver (−)-lyconadin B (**6**) (57%, $[\alpha]_D^{21} = -102$ (*c* 0.5, MeOH)). During conversion of **103** to lyconadin B (**6**), we observed the formation of trace quantities of lyconadin A (**5**) in the crude ^1H NMR.[34] The formation of lyconadin A (**5**) presumably occurred via autoxidation in the presence of trace oxygen. Heating lyconadin B (**6**) neat at 160 °C under an atmosphere of air delivered lyconadin A (**5**) in 57% yield ($[\alpha]_D^{22} = +37$ (*c* 0.12, MeOH)). In conclusion, the biomimetic syntheses of lyconadins A (**5**) and B (**6**) have been accomplished via our unified strategy.

CONCLUSION

The successful synthesis of several diverse 7-membered-ring-containing *Lycopodium* alkaloids was accomplished through the development of a unifying, biosynthetically inspired strategy. The first total syntheses of the proposed structure of himeradine A (**1**), fastigiatine (**2**), lycopecurine (**3**), and dehydrolycopecurine (**4**), as well as the syntheses of lyconadins A (**5**) and B (**6**) were achieved. Our efforts commenced with the total synthesis of fastigiatine (**2**) in 2010,[7] a detailed account of which was discussed. A convergent fragment coupling via a nucleophilic cyclopropane opening was developed to form the C11−C12 bond and yield the versatile synthetic intermediate *β*-carboxyimide **20** (vide infra). Problems associated with attaining the correct C−N connectivity were solved with the use of a strongly electron-withdrawing Ns group, which allowed for a successful diastereoselective formal [3+3]-cycloaddition. An unusual retro-aldol, iminium ion formation, and transannular Mannich reaction sequence then furnished the pentacyclic core of **2**. However, despite the high overall efficiency of the cascade sequences developed, the synthetic route for fastigiatine (**2**) was not amenable to the synthesis of other 7-membered-ring-containing *Lycopodium* alkaloids.

A unifying strategy was finally realized in the first total synthesis of the proposed structure of himeradine A (**1**) (Scheme 12), which contains 7 rings and 10 stereocenters. A stereoselective synthesis of the quinolizidine subunit was accomplished via substrate stereocontrol. A one-pot sequence for the construction of the strained core system of **1**, common to other 7-membered-ring-containing *Lycopodium* alkaloids, was achieved. The isolation of imine intermediate of type **83**, the direct product of the one-pot sequence, would eventually allow us to access other *Lycopodium* alkaloid members. A key biomimetic transannular Mannich reaction then provided the pentacyclic core of himeradine A (**1**).

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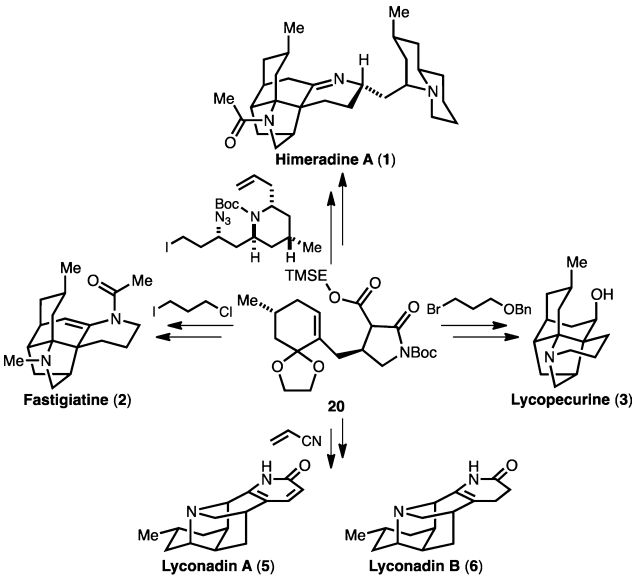
Our unifying strategy was successfully applied toward the first total syntheses of lycopecurine (**3**) and dehydrolycopecurine (**4**), which also featured the key transannular Mannich reaction. Our one-pot sequence was also successfully utilized in the concise syntheses of lyconadins A (**5**) and B (**6**), which involved reduction of an imine intermediate derived from our one-pot sequence instead of an intramolecular Mannich reaction to construct the core system. The plausibility of our biosynthetic hypothesis that 7-membered-ring-containing *Lycopodium* alkaloids can arise from a common imine precursor was further validated by the successful syntheses of **5** and **6**.

In summary, we have developed a unifying, biosynthetically inspired strategy for the synthesis of structurally diverse 7-membered-ring-containing *Lycopodium* alkaloids. Through simple variation of the alkylation partners of versatile intermediate **20**, we were able to divergently access six such members with diverse carbon skeletons (Scheme 15). We envision that this strategy could potentially be readily applied to the synthesis of all such 7-membered-ring-containing *Lycopodium* alkaloids in order to further enable their biological profiling.

Scheme 15. A Unified Biosynthetically Inspired Strategy for the Synthesis of 7-Membered-Ring-Containing *Lycopodium* Alkaloids



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray structure of lycopecurine (**3**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(4) The positional numbering system we employed for himeradine A (**1**) is different from that utilized in the original isolation report (see ref 2) in order to facilitate comparison with related *Lycopodium* alkaloids, which share a common numbering scheme. See Supporting Information for more details.

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