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Unified Strategy for the Synthesis of the "Miscellaneous" *Lycopodium* Alkaloids: Total Synthesis of (±)-Lyconadin A

Alakesh Bisai, Scott P. West, and Richmond Sarpong*

Department of Chemistry, University of California, Berkeley, California 94720

Received April 16, 2008; E-mail: rsarpong@berkeley.edu

The *Lycopodium* alkaloids are a diverse group of architecturally complex natural products, which were postulated, principally by Ayer,[1] to originate from the phlegmarine skeleton (see **1**, Figure 1). Several members of this family of alkaloids, exemplified by huperzine A,[2] have been shown to be potent inhibitors of acetylcholinesterase. In addition, biological activity ranging from neurotrophic activity to anticancer properties has been reported for others in this family.[3] Despite the encouraging bioactivity of select congeners, comprehensive biological evaluation for the majority of these compounds has yet to be undertaken. Our interest is in a subset of *Lycopodium* natural products referred to as the "miscellaneous group", which includes **2**−**4** (Figure 1), because they possess unique frameworks that fall outside the distinct structural classes (lycopodine, lycodine, and fawcettimine). A unified strategy for their syntheses would present opportunities to trace their biosynthetic relationships and provide access to significant quantities of the natural products and related derivatives.

We reasoned that the majority of the miscellaneous *Lycopodium* alkaloids could arise synthetically from a common precursor related to the tetracyclic core of **4** on the basis of their close structural resemblance.[4] Importantly, installation of a C11−N bond (dihydrolycolucine numbering) in **4** could lead to lyconadin A (**2**)[5,6] and lyconadin B (**3**).[7] In this Communication, we present initial results that have culminated in a concise total synthesis of lyconadin A using an unprecedented oxidative C−N bond-forming reaction.

Retrosynthetically (Scheme 1), we envisioned **2** arising from tetracycle **5a** via a late-stage proximity-driven oxidative C−N bond-forming reaction. Importantly, **5a** represents a powerful common intermediate that may be utilized in the syntheses of the majority of the miscellaneous *Lycopodium* alkaloids. We imagined tetracycle **5a** arising from pyridine-annulated cycloheptadiene **6**, which could in turn be accessed from a coupling of bromomethoxypicoline **7**[8] and vinylogous ester **8**.[9]

Our synthetic efforts commenced with the preparation of the cycloheptadiene (**6**) as outlined in Scheme 2. Utilizing a Stork−Danheiser sequence,[10] anion **9** (generated upon treatment of methoxypicoline **7** with excess LDA) was coupled with vinylogous ester **8** to afford enone **10** in 64% yield. Cross-metathesis of the allyl group with ethyl acrylate was accomplished using the Grubbs−Hoveyda (Generation II) catalyst (**11**),[11] which provided enoate **12** in 88% yield. Heck cyclization[12] of **12** under standard conditions proceeded with subsequent isomerization of the resulting exocyclic double bond into cross conjugation with the enone moiety to provide the desired cycloheptadiene (**6**) in excellent yield.

In a key development toward the synthesis of **5a**, formal net hydrogenation of **6** provided **13** (Scheme 3), where three stereocenters in the seven-membered-ring are introduced. Although the direct hydrogenation (Pd/C, H_2) of **6** proceeded without event on small scale, large scale reductions to yield **13** were more efficient following initial Luche reduction of **6** and Swern oxidation of the hydrogenation product.[13] The C15 methyl substituent (lyconadin

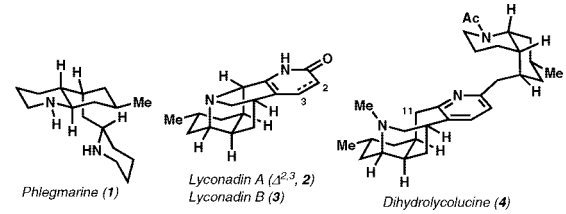
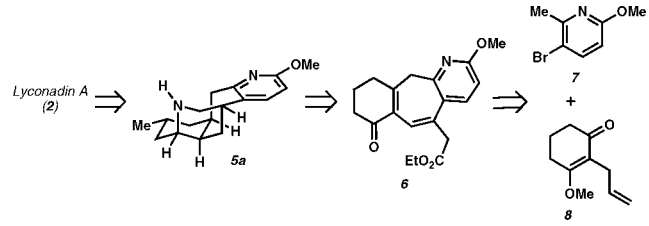
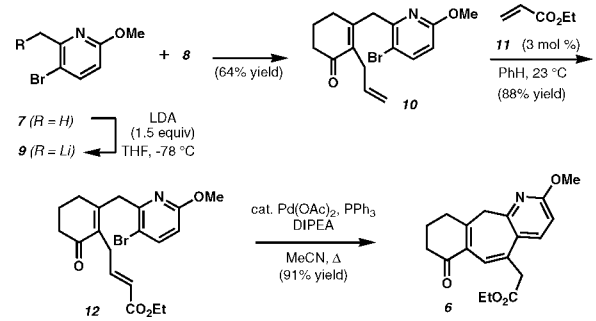


Figure 1. Selected "miscellaneous" *Lycopodium* alkaloids

Scheme 1



Scheme 2



numbering; see **14**) was introduced with high diastereoselectivity (>15:1 dr) in good overall yield by employing a Saegusa−Ito oxidation[14] of **13** followed by conjugate addition to the resultant enone using the Gilman reagent. To saponify the ester group in high yield (see **14**→**15**) and avoid epimerization at C12, it was necessary to reduce and protect the carbonyl group.[15] The three-step sequence for the conversion of **14** to **15** can be routinely performed on a multigram scale without the need for purification of intermediates in 91% overall yield. Curtius rearrangement of **15**,[16] followed by reinstallation of the carbonyl group at C13, proceeds in 62% overall yield. A two-stage reduction of **16** (hydrogenolysis of the Cbz group and hemiaminal reduction) effects a net reductive amination to afford secondary amine **5a**, providing the requisite substrate for the key C−N bond-forming reaction.

Initially, we explored a Hofmann−Löffler−Freytag (HLF) reaction[17] to achieve the desired C−N bond formation using *N*-chloro compound **5b**.[18] Unfortunately, under a variety of conditions known to effect the HLF reaction, a complex mixture of products was

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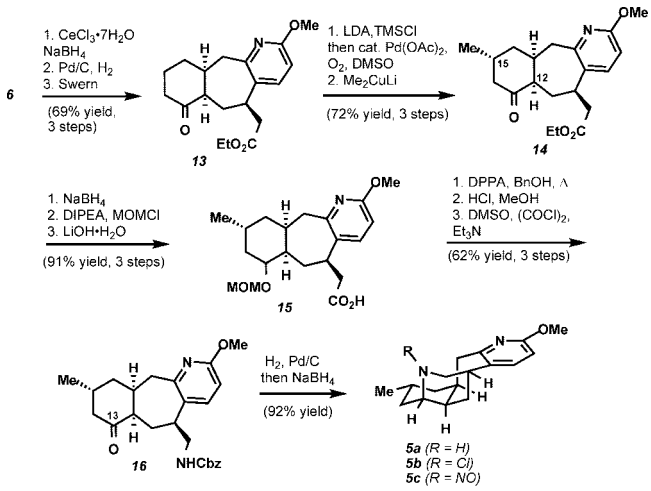
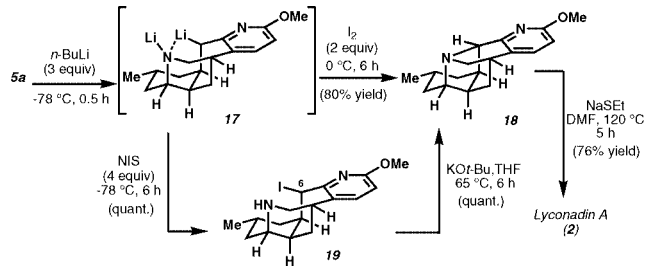
Scheme 3



Scheme 4



obtained. A variant of the Barton nitrite ester oxidation[19] using *N*-nitroso compound **5c**[20] fared equally poorly.

We anticipated that a double deprotonation of **5a** (first of the 2° amine and then of the pseudobenzylic "picolinic" position) could lead to a dianion such as **17** (Scheme 4), which upon treatment with a suitable oxidant could result in oxidative C−N bond formation. We were especially encouraged by the potential for added stabilization of **17** via formation of a six-membered chelate of the nitrogen lone pair with the C6-bound Li.[21] In the event, treatment of **5a** with *n*-BuLi (3 equiv) at −78 °C for 30 min resulted in a bright orange solution, which upon exposure to I_2 (2 equiv) and slow warming to 0 °C over 6 h yielded pentacycle **18** as the sole product following workup in 80% yield.[22] This simple, single-pot protocol provides direct access to the pentacyclic core of lyconadin A in high yield. Alternatively, quenching the reaction at low temperature with *N*-iodosuccinimide (NIS) yields the C6 iodinated compound **19**, which is transformed in quantitative yield to **18** upon exposure to excess KO*t*-Bu in refluxing THF.[23] Cleavage of the methyl ether of **18** using NaSEt furnished lyconadin A in 76% yield. Synthetic (±)-lyconadin A (**2**) prepared in our laboratory provided spectral data consistent with that obtained during its isolation by Kobayashi et al.[5] and its synthesis by Beshore and Smith.[6]

Thus, the total synthesis of lyconadin A was achieved in 18 total steps (via **19**; 10% overall yield) from a readily available picoline derivative (**7**) and vinylogous ester (**8**) as starting material using a unique proximity-driven oxidative C−N bond-forming reaction to craft the caged pentacycle. The application of our general strategy to the total synthesis of other *Lycopodium* alkaloids, as well as the enantioselective total syntheses of lyconadins A, B are well underway and will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Readily prepared from **5a** in 80% yield (*N*-chlorosuccinimide in CH_2Cl_2) as described in the Supporting Information.
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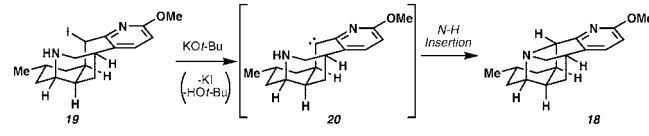
(20) Prepared from **5a** (NOCl, pyridine) in 98% yield. For details, see the Supporting Information.
(21) Li−amide aggregates have been extensively characterized. See: Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259–2268.
(22) Metal salts such as $CuCl_2$ and $FeCl_3$ have thus far proved ineffective.
(23) A mechanism involving carbene formation (see **20**) could be operative for the conversion of **19** to **18**.



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