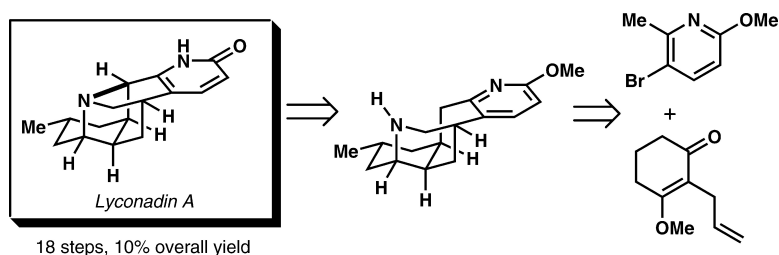Communication

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

Alakesh Bisai, Scott P. West, and Richmond Sarpong

Lyconadin A

18 steps, 10% overall yield

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

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, H₂) 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
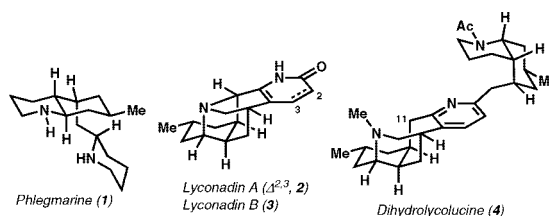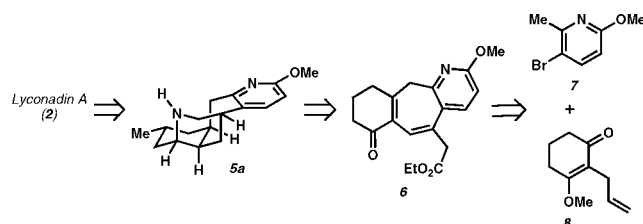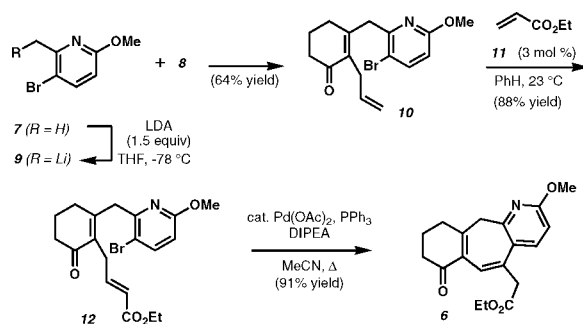

Figure 1. Selected "miscellaneous" *Lycopodium* alkaloids
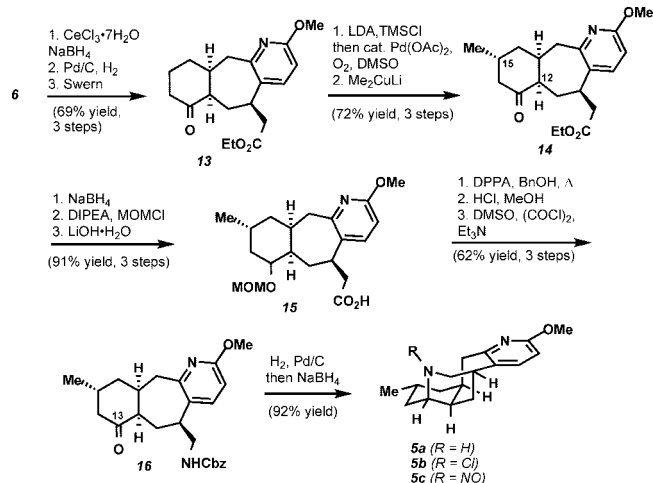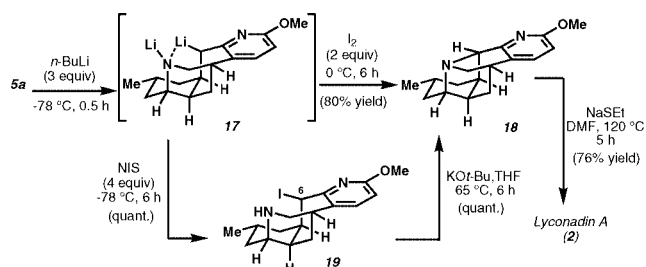
Scheme 1

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
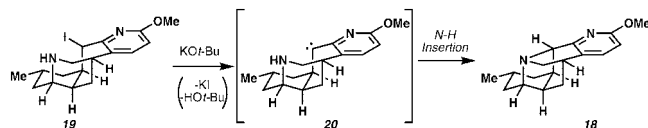
Scheme 3

Scheme 4

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.

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.

References

(1) Ayer, W. A.; Trifonov, L. S. Lycopodium Alkaloids. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: New York, 1994; Vol. 45, p 233–266..
(2) For a review on huperzine A, see: Ma, X.; Tan, C.; Zhu, D.; Gang, D. R.; Xiao, P. *J. Ethnopharmacol.* **2007**, *113*, 15–34.
(3) For a review on *Lycopodium* alkaloids, see: Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.
(4) For a figure illustrating the "miscellaneous" *Lycopodium* alkaloids, see the Supporting Information.
(5) For the isolation of lyconadin A, see: Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901–5904.
(6) For recent total syntheses of (+)-**2** and (−)-**3**, see: Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149.
(7) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Biorg. Med. Chem.* **2006**, *14*, 5995–6000.
(8) For the synthesis of bromopicoline **7**, see: Haudrechy, A.; Chassaing, C.; Riche, C.; Langlois, Y. *Tetrahedron* **2000**, *56*, 3181–3187.
(9) For the synthesis of **8**, see: Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789–4798.
(10) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.
(11) For a pertinent discussion of cross metathesis, see: Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
(12) For a recent review, see: Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5.
(13) An enantioselective variant of this transformation is currently under development.
(14) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013. (b) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044–9045.
(15) Ketal protection of the carbonyl group was also explored but led to significantly diminished yields in the subsequent steps.
(16) For a recent example, see: Nagumo, S.; Nishida, A.; Yamazaki, C.; Matoba, A.; Murashige, K.; Kawahara, N. *Tetrahedron* **2002**, *58*, 4917–4924.
(17) For a review see: Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55–64.
(18) Readily prepared from **5a** in 80% yield (*N*-chlorosuccinimide in CH$_2$Cl$_2$) as described in the Supporting Information.
(19) For a recent review, see: Suginome, H. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, 2004; p 101–116.
(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**.

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