J|A|C|S ARTICLES

Published on Web 07/10/2009

Total Synthesis of (+)-Lyconadin A and Related Compounds via Oxidative C−N Bond Formation

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Abstract: The formation of carbon−nitrogen (C−N) bonds is a fundamental bond construction in organic synthesis and is indispensable for the synthesis of alkaloid natural products. In the context of the synthesis of the architecturally complex *Lycopodium* alkaloid lyconadin A, we have discovered a highly efficient oxidative C−N bond forming reaction that relies on the union of a nitrogen anion and a carbon anion. Empirical evidence amassed during our synthetic studies suggests that the mechanism of the C−N bond forming process encompasses polar as well as radical processes. Herein, we present our study of this novel C−N bond forming reaction and its application to the enantioselective total synthesis of lyconadin A and related derivatives.

Introduction

Since the isolation of the first *Lycopodium* alkaloid natural product (lycopodine (**1**, Figure 1)) by Bödeker in 1881[1] and the structural elucidation of annotinine (**2**) by Wiesner in 1957,[2] synthetic organic chemists have remained fascinated with the architecture of this family of compounds. The majority of these natural products are believed to arise in Nature from the phlegmarine skeleton (see **3**). The reigning postulate for the biosynthesis of these compounds was advanced by Spenser[3] and is well described in the literature.[4,5] Over the past three decades, there has been an increase in the number and diversity of alkaloids identified as constituents of the *Lycopodium* family.[6] Several members, exemplified by huperzine A (**4**),[7] have been shown to be potent inhibitors of acetylcholinesterase and have begun to find use in the treatment of Alzheimer's disease in China.[8] In addition, biological activity ranging from neurotrophic activity to anticancer properties has been reported for others in this family.[9]

Despite the reported bioactivity of select congeners, a comprehensive biological screen of the majority of the *Lycopodium* alkaloids has yet to be undertaken. Total synthesis endeavors can play a critical role in the bioactivity elucidation studies of the *Lycopodium* alkaloids by providing access to significant quantities of the natural products and related derivatives. We have been interested in tracing the connections among a subset *of Lycopodium* alkaloids referred to as the "miscellaneous" group[10] because they possess unique frameworks distinct from the traditional structural classes (i.e., lycopodine, lycodine, and fawcettimine). The development of a unified strategy for the synthesis of the "miscellaneous" group would afford opportunities to study their biosynthetic relationships as well as provide unambiguous structural characterization and satisfactory quantities for biological studies.

On the basis of the structural resemblance between dihydrolycolucine (**5**), lucidine A (**6**), and oxolucidine A (**7**), we reasoned that these compounds could arise synthetically from a common precursor (**8**) related to the tetracyclic core of **5** via a series of hydrogenation and/or oxygenation reactions. Importantly, installation of a C11−N bond (lucidine numbering; see **5**)[11] could offer an opportunity to access lyconadin A (**9**)[12] and related compounds such as lyconadin B (**10**).[13] Moreover, in line with the proposed biogenesis of spirolucidine (**11**) from an oxolucidine relative,[14] ring-contractive rearrangement of the α-hydroxyimine moiety of **7** could form the spirotetracycle of **11**. Additionally, the spirocyclic nankakurine skeleton (see **12**),

(1) Bödeker, K. *Ann. Chem.* **1881**, *208*, 363.
(2) Wiesner, K.; Ayer, W. A.; Fowler, L. R.; Valenta, Z. *Chem. Ind. (London)* **1957**, 564–565.
(3) For leading references, see: (a) Castillo, M.; Gupta, R. N.; MacLean, D. B.; Spenser, I. D. *Can. J. Chem.* **1970**, *48*, 1893–1903. (b) Castillo, M.; Gupta, R. N.; Ho, Y. K.; MacLean, D. B.; Spenser, I. D. *Can. J. Chem.* **1970**, *48*, 2911–2918. (c) Heimscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1993**, *115*, 3020–3021. (d) Heimscheidt, T.; Spenser, I. D. *J. Am. Chem. Soc.* **1996**, *118*, 1799–1800.
(4) Ayer, W. A. *Nat. Prod. Rep.* **1991**, *8*, 455–463.
(5) Ayer, W. A.; Trifonov, L. S. Lycopodium Alkaloids. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press: New York, 1994; Vol. 45, pp 233−266.
(6) For a recent review, see: Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.
(7) (a) Liu, J. S.; Zhu, Y. L.; Yu, C. M.; Zhou, Y. Z.; Han, Y. Y.; Wu, F. W.; Qi, B. F. *Can. J. Chem.* **1986**, *64*, 837–839. (b) For a recent review on huperzine A, see Ma, X.; Tan, C.; Zhu, D.; Gang, D. R.; Xiao, P. *J. Ethnopharmacol.* **2007**, *113*, 15–34.
(8) Jiang, H.; Luo, X.; Bai, D. *Curr. Med. Chem.* **2003**, *10*, 2231–2252.
(9) For a recent review on *Lycopodium* alkaloids, which discusses their biological activity in detail, see: Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.
(10) This word was introduced to describe a subset of *Lycopodium* alkaloids of unclassified biogenesis. See ref 9.
(11) For lucidine numbering, see: **6** (Figure 1) and ref 9.
(12) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901–5904.
(13) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Biorg. Med. Chem.* **2006**, *14*, 5995–6000.
(14) (a) Tori, M.; Shimoji, T.; Takaoka, S.; Nakashima, K.; Sono, M.; Ayer, W. A. *Tetrahedron Lett.* **1999**, *40*, 323–324. (b) Tori, M.; Shimoji, T.; Shimura, E.; Takaoka, S.; Nakashima, K.; Sono, M.; Ayer, W. A. *Phytochemistry* **2000**, *53*, 503–509.

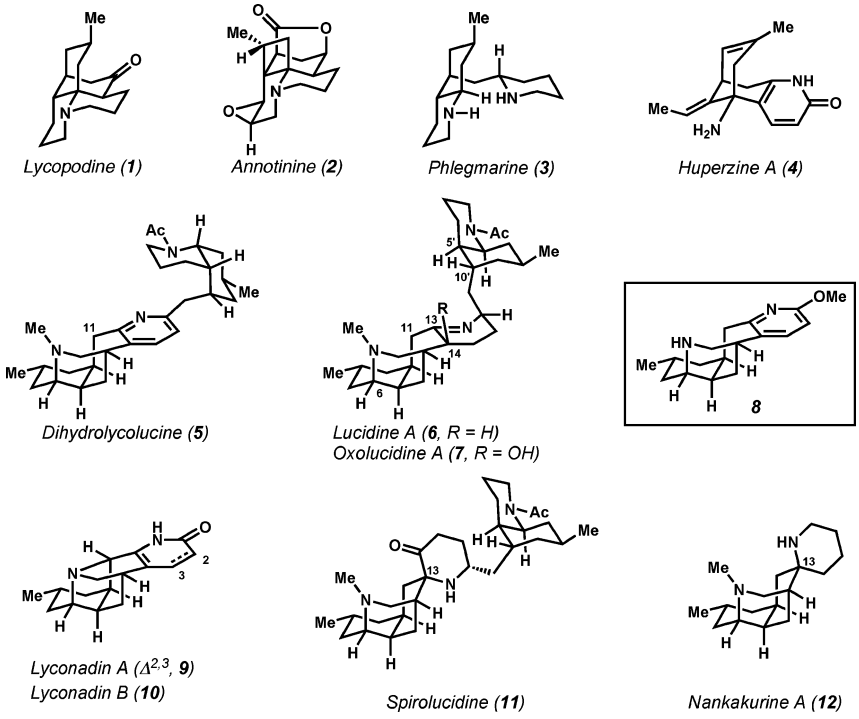


Figure 1. Selected congeners of the *Lycopodium* alkaloid family.

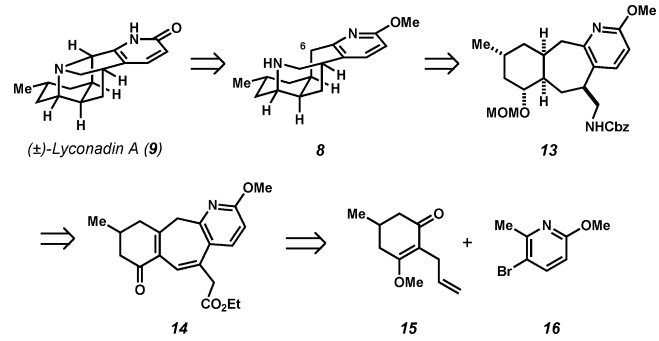
which was recently revised by Kobayashi to be epimeric at C13 with respect to **11**[15] and confirmed by Overman and co-workers via total synthesis,[16] could be constructed by a related α-hydroxyimine rearrangement.

Prior to our initial communication on lyconadin A, only one total synthesis of this *Lycopodium* alkaloid, by Beshore and Smith, had been reported.[17] Smith's elegant approach to the lyconadins also provided a synthesis of (−)-lyconadin B and unambiguously established the absolute configurations of these natural products. In addition, the groups of Castle[18] and Hsung[19] have disclosed creative approaches to the lyconadins.

Our synthetic studies of lyconadin A (**9**), reported herein, have culminated in a concise, enantioselective synthesis of tetracycle **8**, which has been applied to a total synthesis of (+)-lyconadin A using an unprecedented oxidative C−N bond forming reaction.[20] Additionally, we report studies that have enabled us to gain insight into the C−N bond forming process for the synthesis of the lyconadin pentacycle. The general synthetic strategy that was developed for the synthesis of lyconadin A sets the stage for exploring the total syntheses of many of the other *Lycopodium* alkaloids depicted in Figure 1.

Initial Synthetic Plan. Given our focus on the development of a unified synthetic strategy, the initial goal was to achieve a concise synthesis of tetracyclic amine **8**, which could be transformed into a number of different *Lycopodium* alkaloids including lyconadin A. Our retrosynthetic approach to lyconadin A is shown in Scheme 1. We anticipated that late stage C−N bond formation to construct the lyconadin pentacycle could be accomplished via lateral functionalization of the methoxypyridine moiety of **8**. Tetracycle **8** could be accessed from tricycle **13** using standard amination reactions. We imagined tricycle **13** could derive from pyridine-annulated cycloheptadiene **14**.[21] An important, albeit naive, assumption we made at this stage was that the resident lone stereocenter in **14** would correctly direct the installation of the four additional stereocenters present in pyridine-annulated cycloheptane **13**. Thus, the racemic synthesis of **13** was an important milestone that would enable a test of this hypothesis. We envisioned cycloheptadiene **14**

Scheme 1



(15) (a) Hirasawa, Y.; Morita, H.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3389–3391. (b) Hirasawa, Y.; Kobayashi, J.; Obara, Y.; Nakahata, N.; Kawahara, N.; Goda, Y.; Morita, H. *Heterocycles* **2006**, *68*, 2357–2364.

(16) Nilsson, B. L.; Overman, L. E.; de Alaniz, J. R.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297–11299.

(17) (a) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149. (b) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2008**, *130*, 13778–13789.

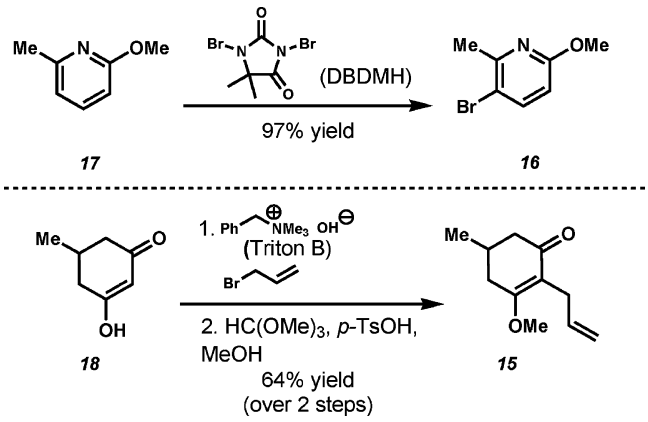
(18) Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867–1870.

(19) Tracey, M. R.; Hsung, R. *Abstract of Papers*, Presented at the 226th National Meeting of the American Chemical Society, New York, September 2003; paper ORGN-721.

(20) For an initial communication, see: Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223.

(21) For other examples of syntheses of natural products that contain a seven-membered ring using cycloheptadiene intermediates from our group, see: (a) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883–2886. (b) Simmons, E. M.; Yen, J. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2705–2708.

Scheme 2



arising from a union of vinylogous ester **15** and bromomethoxypicoline **16**.

Results and Discussion

Construction of the Pyridine-Annulated Cycloheptane 13. Our synthesis of **13** began with the preparation of bromopicoline derivative **16** (Scheme 2) starting from commercially available methoxypicoline **17**. Following literature precedent, bromination of **17** using dibromodimethylhydantoin (DBDMH) gave **16** in 97% yield.[22] The corresponding coupling partner (**15**) was prepared by a sequence that began with allylation of commercially available **18**,[23] followed by formation of the vinylogous ester using trimethyl orthoformate in 64% yield over the two steps.

The union of **15** and **16** (Scheme 3) was accomplished by initial lateral deprotonation of **16** followed by reaction with **15** in a Stork−Danheiser sequence to give **19** in 63% yield.[24] Initially, we investigated the oxidative cleavage of the terminal double bond of **19** to afford an aldehyde followed by a Wittig reaction to install an α,β-unsaturated ester. However, because of the pronounced instability of the requisite intermediate aldehyde, this proved to be a capricious route at best. These stability concerns were obviated by using an alternative route employing cross-metathesis of the allyl group of **19** with ethyl acrylate, which was accomplished using the Grubbs−Hoveyda second generation catalyst.[25] Intramolecular Heck reaction of the intermediate ester and concomitant double bond migration furnished cycloheptadiene **14** in 77% yield over the two steps. Luche reduction of the carbonyl group to the corresponding alcohol (>14:1 dr) and ensuing hydrogenation afforded tricycle **20** as a single diastereomer, setting three stereocenters in a single operation. Unfortunately, X-ray analysis of **24** (Figure 2) revealed that the diastereoselectivity of the reduction (with respect to the C15 stereocenter and the newly introduced hydrogens; see **20**) was *anti*, which is opposite to the relative stereochemistry needed to access the natural product. In an attempt to reverse the diastereoselectivity of the hydrogenation, we sought to utilize the hydroxyl group resulting from carbonyl reduction of **14** as a directing group. A variety of directed hydrogenation conditions employing Brown's,[26] Wilkinson's, or Crabtree's catalysts were unsuccessful in promoting reduction of the diene from the desired face to provide the correct relative stereochemistry for the natural product.[27] We believe that the pseudoequatorial orientation of the C13 hydroxyl group in the diene substrate prevents productive metal−hydride orientation. Additionally, coordination of the methoxypyridine moiety of the substrate to the homogeneous hydrogenation catalysts could lead to reduced activity. These factors most likely account for the lack of directing group effect in the hydrogenation and instead result in sterically controlled reduction of the diene from the face opposite the C15 methyl group to yield **20** as the major product.

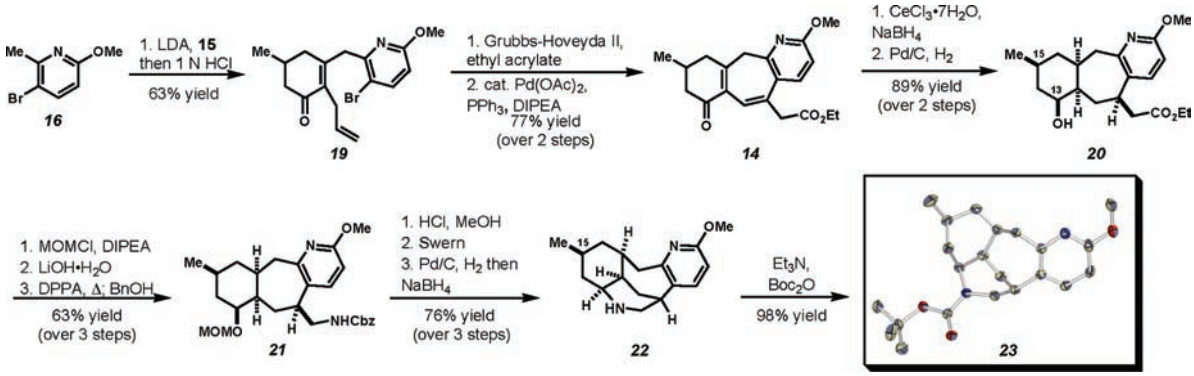
Nonetheless, **20** provided a serviceable model system to investigate the synthesis of the advanced tetracycle of the lyconadins and other related lucidine alkaloids. In this regard, a sequence involving MOM protection of the C13 hydroxyl group of **20**, saponification of the ethyl ester, and Curtius rearrangement using diphenylphosphoryl azide (DPPA)[28] in the presence of benzyl alcohol afforded Cbz-protected amine **21** in 63% overall yield. Cleavage of the MOM ether was followed by Swern oxidation to provide an intermediate ketone, which was subjected to reductive amination conditions to afford tetracycle **22**. Protection of the secondary amine with a Boc group gave **23**, which furnished X-ray quality crystals that enabled an unequivocal assignment of this late stage tetracycle. Secondary amine **22** differed from desired tetracycle **8** (Scheme 1) only in the C15 stereochemistry.

To obtain tetracycle **8** with the desired C15 stereochemistry for the synthesis of lyconadin A, we began with vinylogous ester **25**[29] and bromopicoline **16** (Scheme 4). Following a sequence similar to that previously described in Scheme 3 provided access to alcohol **26**, which was converted to enone **27** by Swern oxidation and subsequent Saegusa−Ito oxidation.[30] Conjugate addition of the Gilman reagent to **27** proceeded from the convex face (α-face) to install the methyl group with the desired stereochemistry at C15 (see **28**). Tricycle **28** was carried on to tetracycle **8** following synthetic steps analogous to those already established for the closely related conversion of **20** to **22** (Scheme 3).

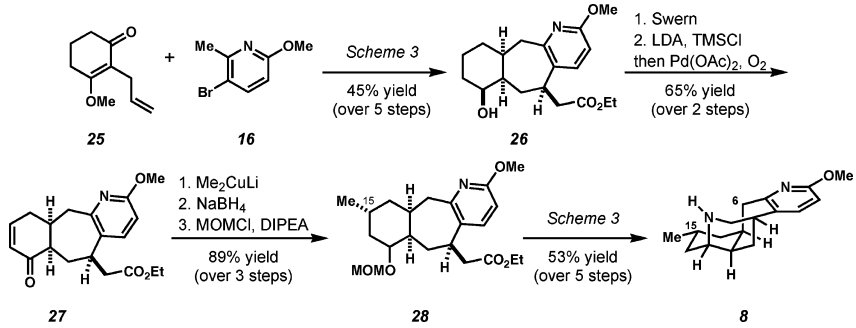
Forging the Key C−N Bond en Route to Lyconadin A. With tetracycle **8** in hand, we initially investigated its conversion to the lyconadin pentacycle by functionalization at C6 using the Boekelheide variant[31] of the Polonovski rearrangement[32] employing the pyridine *N*-oxide of **29** (Scheme 5). Treatment of **29** with *m*-chloroperbenzoic acid generated the *N*-oxide intermediate, but subsequent reaction with trifluoroacetic anhydride (TFAA) or acetic anhydride did not lead to the desired product (**30**) bearing a nucleofuge at C6. Inspired by Shibanuma's examples of building highly caged alkaloid structures,[33] an alternative approach to form pentacycle **32** via a Hofmann−

(22) For a synthesis of bromopicoline **16**, see: Haudrechy, A.; Chassaing, C.; Riche, C.; Langlois, Y. *Tetrahedron* **2000**, *56*, 3181–3187.
(23) Rajamannar, T.; Palani, N.; Balasubramanian, K. K. *Synth. Commun.* **1993**, *23*, 3095–3108.
(24) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.
(25) For a recent review, see: Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45–52.
(26) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866–3868.
(27) For a review on directed hydrogenations, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
(28) For a Curtius rearrangement using DPPA, see: Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
(29) For the synthesis of **25**, see: Patterson, J. W. *Tetrahedron* **1993**, *49*, 4789–4798.
(30) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.
(31) For pertinent accounts of the Boekelheide reaction, see: (a) Traynelis, V. J. In *Mechanisms of Molecular Migrations*; Thyagarjan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp 1−42. (b) Cohen, T.; Deets, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 932–938.
(32) For a review, see: Grierson, D. *Org. React.* **1990**, *39*, 85–295.

Scheme 3



Scheme 4



Löffler−Freytag (HLF) reaction[34] was explored. HLF substrate **31a** was easily prepared by treatment of secondary amine **8** with *N*-chlorosuccinimide (NCS). Unfortunately, under a variety of conditions known to effect the HLF reaction,[35] a complex mixture of products was always obtained. Imine byproducts resulting from elimination of HCl were observed in many cases. Additionally, *N*-nitrosoamine **31b** was synthesized from amine **8** by nitrosation with NOCl and pyridine to pursue a variant of the Barton nitrite ester oxidation.[36] In an attempt to functionalize C6, photolysis of **31b** was conducted and resulted in nonspecific decomposition of the substrate. Alternatively, following the Rabe example in the synthesis of quinine recently revisited by Williams,[37] we envisioned that lateral deprotonation of **31a** followed by intramolecular nucleophilic attack on the chloroamine nitrogen with loss of chloride could provide the desired pentacycle. However, attempted deprotonation of **31a** with a variety of bases (LDA, NaHMDS, NaH, $NaNH_2$, KO*t*-Bu) led to complex mixtures of products. However, we were encouraged to find that treatment of chloroamine **31a** with KOH in refluxing methanol effected the desired transformation to afford pentacycle **32**, albeit in low yield.

Ultimately, we found that the desired C−N bond can be formed cleanly in high yield by a one-pot process that entails deprotonation of **8** using excess *n*-BuLi[38] at low temperature (−78 °C) followed by oxidation of the resulting dianion to deliver pentacycle **32** (Scheme 6). Initially, reductive elimination strategies for C−N bond formation utilizing reagents such as $Pd(OAc)_2$, $FeCl_3$, $Cu(OAc)_2$, or $Cu(OTf)_2$ with excess iodine as an oxidant were attempted from the presumed dianion intermediate **34**.[39] The eventual use of iodine alone as an oxidant was fortuitous and emerged only after control experiments for these reactions revealed that iodine in the absence of metal salts accomplished the desired transformation. Demethylation of **32** using NaSEt proceeded without event to provide (±)-lyconadin A (**9**) in 76% yield.

Investigation of the Key C−N Bond Forming Reaction. Bond forming reactions that rely on the linking of two organolithium anions via oxidative processes are experiencing a renaissance in modern organic synthesis. This powerful "umpolung" tactic serves as an impetus for the design of new strategies in complex molecule synthesis. While many notable examples that feature C−C bond forming oxidative processes have appeared,[40] studies detailing C−N bond formation via oxidation of dianionic intermediates have, to our knowledge, not been pursued.

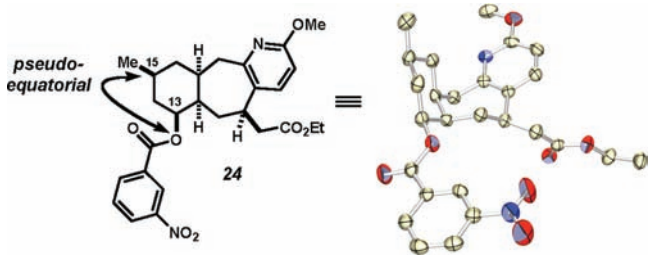
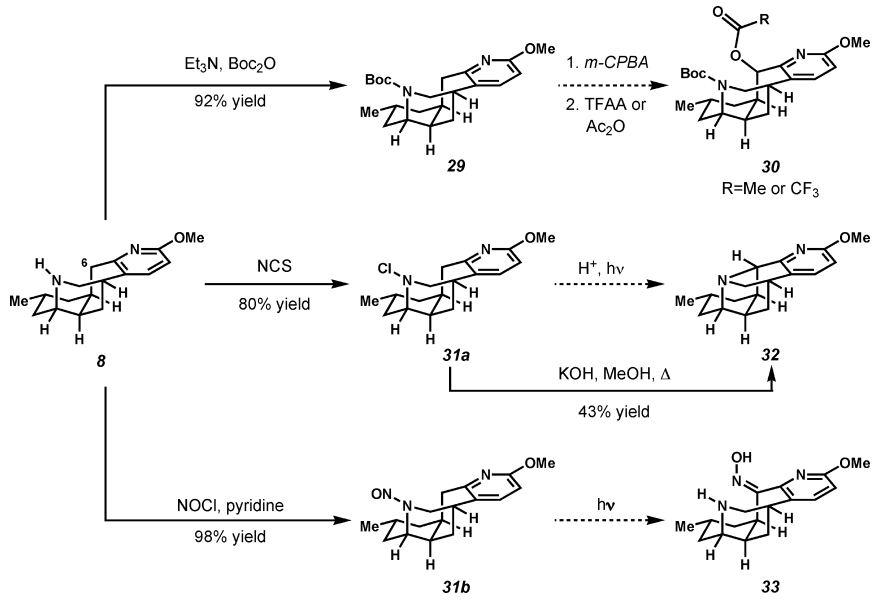


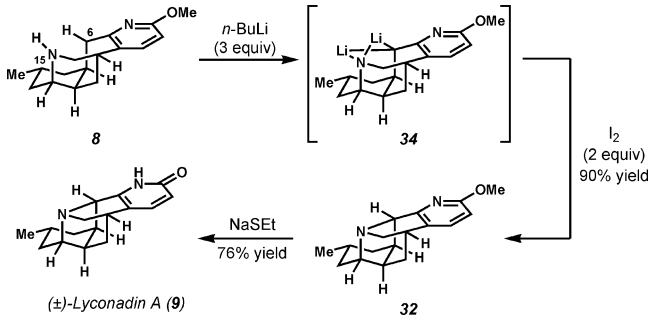
Figure 2. ORTEP representation of **24**.

(33) Shibanuma, Y.; Okamoto, T. *Chem. Pharm. Bull.* **1985**, *33*, 3187–3194.
(34) For pertinent reviews, see: (a) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095–7129. (b) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55–64.
(35) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657–1668.
(36) 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, FL, 2004; pp 101−116.
(37) (a) Rabe, P.; Kindler, K. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 466–467. (b) Smith, A. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1736–1740.
(38) Subsequent optimization studies have shown that these reactions require only 2 equiv of *n*-BuLi.
(39) Dieter, R. K.; Li, S.; Chen, N. *J. Org. Chem.* **2004**, *69*, 2867–2870.

Scheme 5



Scheme 6



In the context of our synthesis of lyconadin A (**9**), we viewed a direct C−N bond forming approach as a powerful simplifying transform. Presumably, upon treatment of secondary amine **8** with *n*-BuLi, the resulting lithium amide anion serves as an intramolecular base to effect lateral deprotonation of the methoxypyridine moiety to ultimately yield dianion **34**.[41] Because of the relative acidity of the picoline pseudobenzylic position ($pK_a \approx 34$ in THF),[42] deprotonation of the secondary amine of **8** might not be viewed as an important requirement for lateral deprotonation of the pseudobenzylic ("picolinic") position. However, our investigations of the direct C−N bond formation suggest that deprotonation of the secondary amine group is indeed a vital component of the overall process. The requisite initial deprotonation of the secondary amine is supported by the observation that protection of the secondary amine group in **8** (with Boc, allyl, Cbz, etc.) followed by attempted lateral deprotonation of the "picolinic" methylene position and trapping with a variety of electrophiles (e.g., D_2O, PhSeCl, I_2) returned only the starting material (Scheme 7). Additionally, we believe that deprotonation to form lithium dianion **34** may be favorable due to the added stabilization provided by formation of a six-membered chelate of the nitrogen lone pair with the C6-bound lithium (see **34**, Scheme 6), in line with earlier examples.[43,44]

Primarily due to its ease of access, model tetracyclic amine **36**[45] (Scheme 8), which lacks the methyl substituent at C15, was used for further investigation of the key C−N bond formation. When **36** is treated with *n*-BuLi (2 equiv), it presumably generates the dianion **37** which is converted to pentacyclic amine **39** upon treatment with iodine (1 equiv). Mechanistically, the C−N bond formation may proceed via C-iodination at the picolinic position of dianion **37** to form iodide **38**, which is rapidly converted to pentacycle **39**. The stereochemistry at C6 upon reaction of **37** with electrophiles deserves further comment. Because of the anticipated configurational stability of dianion **37** at −78 °C, reaction with sterically small, "hard" electrophiles (e.g., D_2O) should yield the products of "endo" addition (see **40**). Indeed, quenching **37** with D_2O did result in deuterium incorporation at the C6 endo position.[46] Subjection of deuterated amine **40a** (72% D) to *n*-BuLi followed by addition of H_2O or D_2O revealed that quenching occurs exclusively at the endo position of the picolinic methylene carbon (see **40a** (72% D) → **40b** (85% D) and **40a** → **36**, Scheme 8). Conversely, the addition of a halogen electrophile (e.g., iodine) likely proceeds with inversion about C6 by virtue of the steric size of the electrophile and its "soft" nature. This potential stereodivergence, based on the electrophile, in the

(40) For pertinent examples, see: (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569. (b) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693. (c) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277–7283. (d) Cohen, T.; McNamara, K.; Kuzenko, M. A.; Ramig, K.; Landi, J. J., Jr.; Dong, Y. *Tetrahedron* **1993**, *49*, 7931–7942.

(41) For a discussion of lateral deprotonation and dianion chemistry, see: (a) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, 1994. (b) Brandsma, L. *Preparative Polar Organometallic Chemistry 2*; Springer-Verlag: Berlin-New York, 1987; p 127. (c) Wheatley, A. E. H. *Eur. J. Inorg. Chem.* **2003**, 3291–3303.

(42) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232–3234.

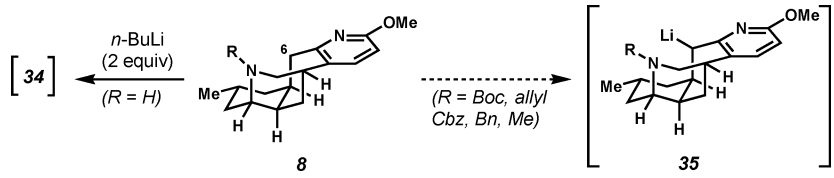
(43) Li-amide aggregates have been extensively characterized. See: Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259–2268.

(44) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716–738.

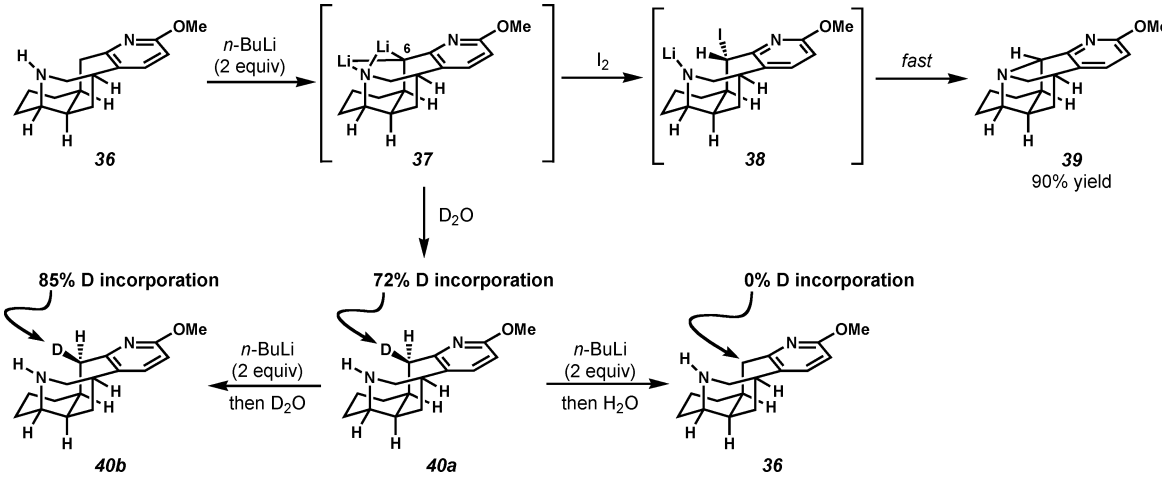
(45) Tetracyclic amine **36** was obtained from alcohol **26** in 46% yield over six steps analogous to the conversion of **20** to **22** (Scheme 3).

(46) Determined on the basis of 2D NMR studies of **36** and **40**. See Supporting Information for details.

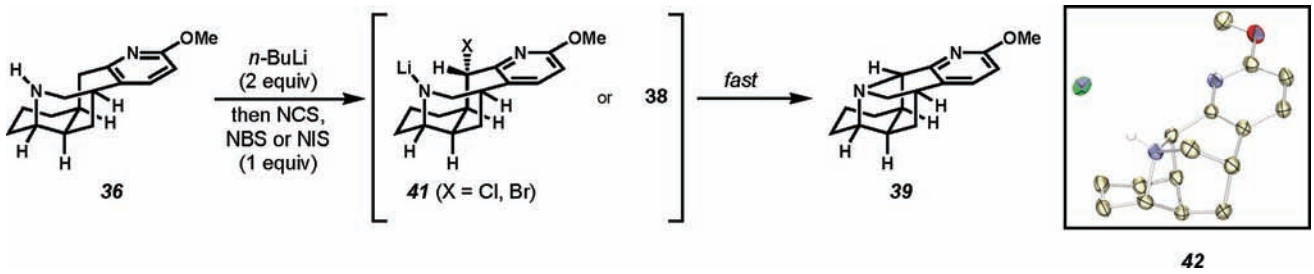
Scheme 7



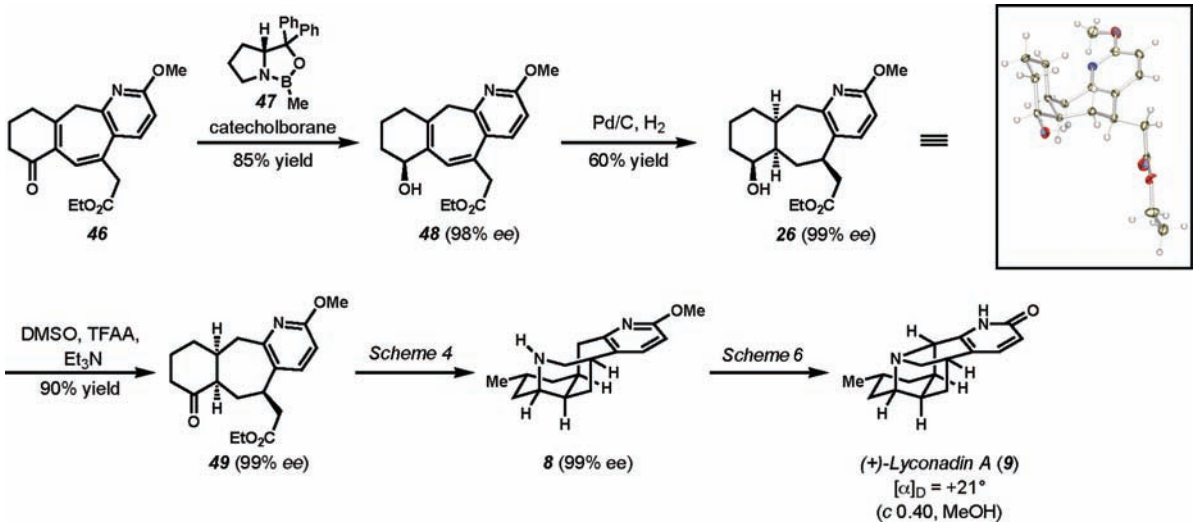
Scheme 8



Scheme 9



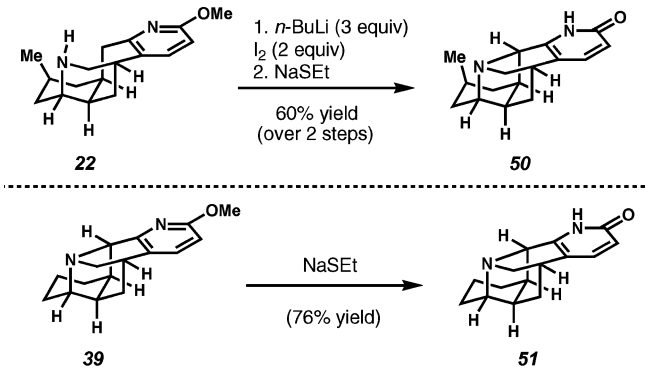
Scheme 10



reactions of sterically encumbered lithium anions is supported by observations made in the 1960s by Applequist[47] and Glaze.[48] Additionally, the studies on the "conducted tour mechanism" for epimerization of heteroatom stabilized carbanions first suggested by Cram and Gosser[49] also support reaction with inversion using halogen electrophiles.[50]

In addition to iodine, other oxidants such as NCS, NBS, NIS, and (diacetoxyiodo)benzene (PIDA; Scheme 9) can effect the

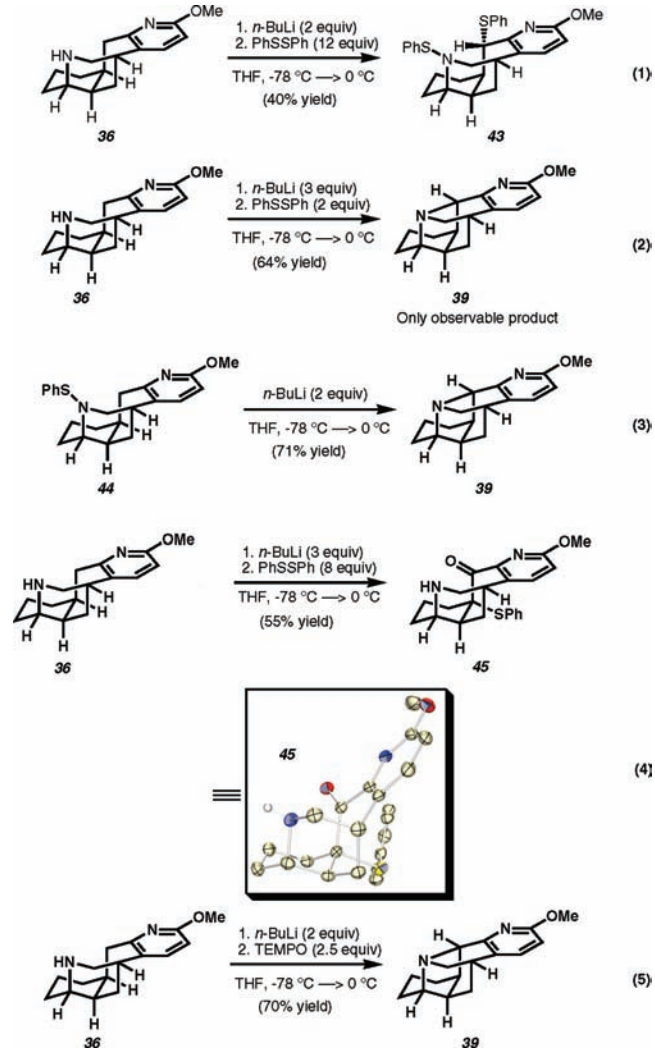
Scheme 11



desired C−N bond formation to provide **39** in comparable yield (65% yield for PIDA, 80−90% yield for NBS, NCS, and NIS).[51] Recrystallization of the HCl salt of tertiary amine pentacycle **39** provided crystals suitable for X-ray analysis (see **42**), providing unambiguous support for the connectivity of **39**.

To gain further insight into the electrophilic trapping of carbanion **37**, studies with diphenyl disulfide were conducted (eqs 1−4). Treatment of **36** with 2 equiv of *n*-BuLi followed by 12 equiv of PhSSPh yielded disulfide **43**[52] in 40% yield (eq 1), whereby reaction with inversion of the carbanion was observed.[53] Along with **43**, 22% of pentacycle **39** and trace amounts of **45** (eq 4) were recovered. Conversely, generation of dianion **37** using 3 equiv of *n*-BuLi and trapping with 2 equiv of PhSSPh yielded desired pentacycle **39** as the major product in 64% yield (eq 2) along with trace amounts of **45**. To better understand the C−N bond formation using PhSSPh, we independently prepared *N*-sulfide **44** (eq 3),[54] which upon treatment with *n*-BuLi yielded pentacycle **39** in 71% yield. This preliminary observation lends support to **44** as a potential precursor to the C−N bond-forming event.[55] In an interesting development, treating **36** with 3 equiv of *n*-BuLi followed by addition of 8 equiv of PhSSPh yielded ketosulfide **45** (eq 4) as the major product in 55% yield following aqueous workup. The structure of **45** was unambiguously established by X-ray crystallography as illustrated by the ORTEP picture in eq 4.[56]

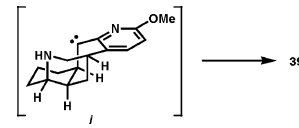
Although the observations associated with the reaction of dianion **37** using PhSSPh as an electrophile are suggestive of a polar process, the possibility of single electron transfer (SET) processes cannot be ruled out. The SET reactions of metalated organic compounds have been well documented and appear to have some dependency on the nature of the electrophile.[57] On the basis of this existing precedent, we decided to test the likelihood of SET processes in the C−N bond formation from dianion **37**. In the key test, subjecting **36** to 2 equiv of *n*-BuLi at −78 °C followed by treatment with TEMPO (2.5 equiv) led to clean formation of pentacycle **39** in 70% yield (eq 5). These observations (eqs 1−5) taken together support a complementary polar and radical nature to the C−N bond forming process and accentuate the continuum of reactivity that is possible with these dianion intermediates depending on the choice of electrophile/oxidant.



Enantioselective Total Synthesis of (+)-Lyconadin A. We designed the synthesis of lyconadin A to highlight a unified approach to the "miscellaneous" group of *Lycopodium* alkaloids. Furthermore, to initiate highly convergent syntheses of dihydrolycolucine (**5**) and spirolucidine (**11**) via fragment coupling of two enantioenriched pieces, we targeted the enantioselective synthesis of the common tetracyclic intermediate **8** (Scheme 10). This exercise commenced with the Corey−Bakshi−Shibata (CBS) reduction[58] of the previously prepared cycloheptadienone **46** (from **16** and **25**) to afford allylic alcohol **48** in 85% yield and 98% ee. Cycloheptadienol **48** served as a substrate for hydrogenation using Pd/C and H_2 (1 atm) to afford pyridine-annulated cycloheptane **26** as the major diastereomer (8:1 dr). A screen of various hydrogenation catalysts and solvents did not lead to any improvement in the diastereocontrol.[59] However, recrystallization of the product mixture provided **26** as a single diastereomer in 60% yield and 99% ee.

(47) Applequist, D. E.; Chmurny, G. N. *J. Am. Chem. Soc.* **1967**, *89*, 875–880.
(48) Glaze, W. H.; Selman, C. M.; Ball, A. L.; Bray, L. E. *J. Org. Chem.* **1969**, *34*, 641–644.
(49) Cram, D. J.; Gosser, L. *J. Am. Chem. Soc.* **1964**, *86*, 2950–2952.
(50) For a pertinent example, see: Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763–5769.

(51) A mechanism involving the formation of a carbene intermediate (**i**) followed by N−H insertion to form **39** cannot be discounted.



i

(52) Stereochemistry was determined by NOESY measurements.

The absolute and relative stereochemistry of alcohol **26** was confirmed by X-ray crystallographic analysis.[60,61] Swern oxidation of **26** proceeded without event to afford ketone **49**.[62] With **49** in hand, the enantioselective synthesis of (+)-lyconadin A was achieved by a sequence analogous to that described in Schemes 4 and 6. Spectral data for synthetic (+)-lyconadin A (**9**) were in agreement with spectroscopic (^{1}H, ^{13}C, IR, MS) and chiroptical data obtained for natural (+)-lyconadin A (**9**) as well as the synthetic material prepared by Smith and Beshore.

Synthesis of C15-*epi*-lyconadin A and C15-nor-Me-lyconadin A. As a further testament to the generality of our approach to lyconadin A, we have applied an analogous synthetic protocol to the preparation of analogues of lyconadin A that differ at the C15 position (Scheme 11).[63] Tetracycle **22**, prepared as detailed in Scheme 3, smoothly underwent C−N bond formation and was advanced to C15-*epi*-lyconadin A (**50**). Cleavage of the methyl ether of pentacycle **39** (Scheme 11) provided C15-nor-Me-lyconadin A (**51**). These compounds will be evaluated alongside lyconadin A in a comprehensive screen for neurotrophic biological activity.

Conclusion

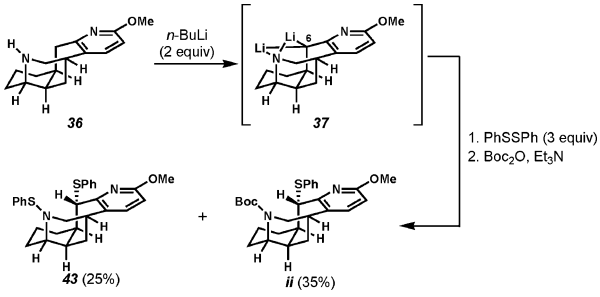
In summary, an enantioselective total synthesis of the structurally complex *Lycopodium* alkaloid (+)-lyconadin A has been achieved in 17 steps. A key aspect of this synthesis was the development of an operationally simple C−N bond-forming reaction to efficiently forge the pentacyclic core of the lyconadins. Empirical evidence amassed during our synthetic studies suggests the C−N bond formation may proceed via polar or SET mechanisms. The route to (+)-lyconadin A features a highly enantioselective Corey−Bakshi−Shibata reduction and a diastereoselective hydrogenation which sets three stereocenters in a single operation. Our approach lays the foundation for the enantioselective total syntheses of many other "miscellaneous" *Lycopodium* alkaloids including dihydrolycolucine, spirolucidine, and the nankakurines. These efforts are currently underway in our laboratories.

Acknowledgment. The authors are grateful to UC Berkeley, Abbott Laboratories, Eli Lilly, GlaxoSmithKline and Johnson and Johnson for generous, unrestricted financial support. The authors thank Materia (Pasadena, CA) for a gift of the Grubbs−Hoveyda Generation II catalyst and BristolMyersSquibb (Dr. Rodney Parsons) for a gift of cyclohexanedione starting material. The authors are indebted to Dr. Fred Hollander and Dr. Antonio DiPasquale for crystallographic data. R.S. is a 2009 Alfred P. Sloan Fellow and a 2009 Camille Dreyfus Teacher-Scholar.

Supporting Information Available: Experimental details and characterization data for select compounds, in addition to spectral comparison of synthetic and natural (+)-lyconadin A. This material is available free of charge via the Internet at http://pubs.acs.org.

JA903868N

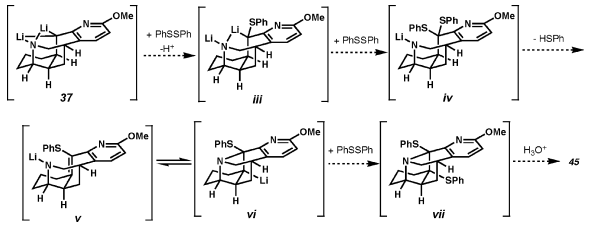
(53) The formation of **ii** along with **43** upon treatment of **36** with *n*-BuLi (2 equiv) followed by the addition of PhSSPh (3 equiv) and subsequent reaction of the crude product mixture with Boc_2O supports initial reaction of electrophiles with the carbanionic position of dianion **37**.



(54) For the preparation of **44**, see the Supporting Information.

(55) This is consistent with our initial observations regarding the reaction of **31a** to give **32** (Scheme 5).

(56) A proposed mechanism for the formation of **45** may proceed via **iii**-**vii** as intermediates.



(57) For pertinent examples, see: (a) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. (b) Maji, M. S.; Pfeifer, T.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9547–9550.

(58) (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.

(59) The diastereomers resulting from hydrogenation would lead to enantiomers in subsequent oxidation steps, which would diminish the overall ee of the final compound.

(60) Cu radiation was used to determine the absolute stereochemistry of alcohol **26**.

(61) (a) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881. (b) Bernardinelli, G.; Flack, H. D. *Acta Crystallogr., Sect. A* **1985**, *41*, 500–511.

(62) If alcohol **26** is not recrystallized, Swern oxidation of the diastereomeric mixture of alcohols from the hydrogenation led to ketone **51** in a diminished 77% ee.

(63) For details, see the Supporting Information.