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Methoxypyridines in the Synthesis of *Lycopodium* Alkaloids: Total Synthesis of (±)-Lycoposerramine R

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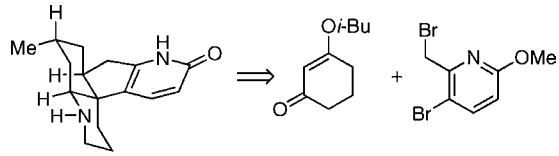
ABSTRACT



A methoxypyridine serves as a masked pyridone in a concise synthesis of the *Lycopodium* alkaloid lycoposerramine R, which has been prepared for the first time. The key step of the synthesis is the use of an Eschenmoser Claisen rearrangement to forge a key quaternary carbon center.

The *Lycopodium* alkaloid family boasts over 200 members, which possess an array of architecturally complex frameworks. The construction of these molecules has presented synthetic challenges that have inspired highly innovative strategic and tactical solutions.[1] The emergence of the *Lycopodium* alkaloid huperzine A as a potential treatment for Alzheimer's disease has further heightened synthetic interest in this family of natural products.[2] Through detailed studies that began in 1942 with the work of Manske and, later, Wiesner, MacLean, Conroy, McMaster and more recently Kobayashi and Takayama, the biosynthetic connections between many of these alkaloids continues to be uncovered.[3] As a result, synthetic strategies to the *Lycopodium* alkaloids that exploit their structural connections are beginning to offer effective and concise avenues to a wide array of these natural products.

As a part of a program to exploit methoxypyridines in the synthesis of various alkaloids, we have reported the total syntheses of the *Lycopodium* alkaloid lyconadin A[4] and the *Galbulimima* alkaloid GB 13.[5] The methoxypyridine group is uniquely effective as a masked pyridone because the methoxy group significantly mitigates the basicity of the pyridine nitrogen via an inductive electron-withdrawing effect.[6] This obviates the need for reversed-phase chromatographic purification, which is often associated with the synthesis of related alkaloids. Building upon our earlier studies, we have embarked on the syntheses of the *Lycopodium* alkaloids lycopladine A (**1**, Figure 1),[7] lycoposerramine R (**2**),[8] and lannotinidine B (**3**)[9] with the intention of accessing all three natural products from a common intermediate.[10]

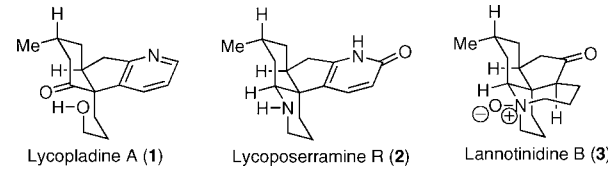


Figure 1. Selected *Lycopodium* alkaloids.

(1) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.

(2) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(3) Hudlicky, T., Reed, J. W. Lycopodium alkaloids. In *The Way of Synthesis*, 1st ed.; Wiley-VCH: Weinheim, 2007; pp 573−602.

(4) (a) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223. (b) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187–11194.

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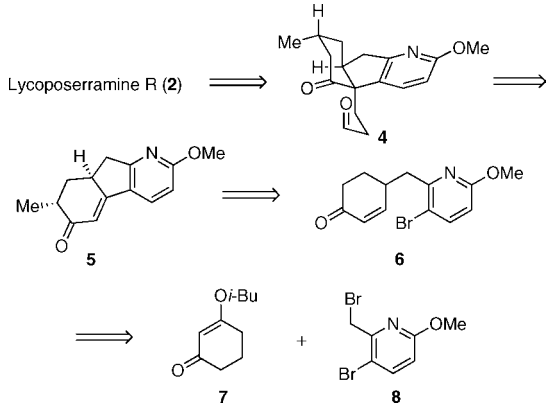
Key to our unified synthetic strategy is the use of a common methoxypyridine intermediate (see **4**, Scheme 1).

Scheme 1. Retrosynthetic Analysis of **2**



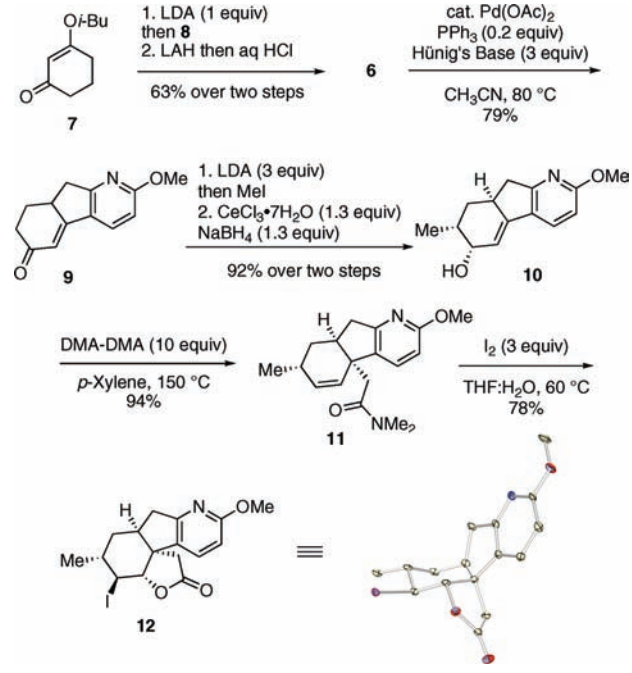
The methoxy group of the methoxypyridine moiety in **4** may be removed en route to **1**,[11] demethylated to unveil the pyridone in **2**, or the methoxypyridine may be unraveled at a late stage to provide **3**. This communication describes our initial studies toward this overall goal, which has culminated in a concise first total synthesis of lycoposerramine R.

Retrosynthetically, we envisioned the tetracyclic framework of **2** (Scheme 1) arising from a late-stage reductive amination of ketoaldehyde **4**, which is closely related to **1**. Tricycle **4** could in turn derive from enone **5** by exploiting a stereospecific pericyclic rearrangement to forge the all-carbon quaternary center. Enone **5** presented several opportunities for the diastereocontrolled intallation of the potentially challenging quaternary center (e.g., oxy-Cope, Claisen, or 2,3-Wittig rearrangements). In turn, tricycle **5** could be obtained from **6** via an intramolecular Heck reaction. The potential Heck precursor **6** could arise from a union of readily available vinylogous ester **7** and dibromide **8**[12] via a Stork−Danheiser sequence.[13]

Our synthesis commenced with the coupling of the enolate of vinylogous ester **7** and picolinyl bromide **8**. This was followed by reduction of the vinylogous ester of the adduct and acidic workup to give **6** in 63% yield over the two steps. Intramolecular Heck reaction of **6** proceeded without event to afford tricyclic enone **9** in 79% yield. The α-methylation of enone **9** and subsequent Luche reduction[14] proceeded with excellent diastereocontrol to give **10** in 92% yield. At this stage, several variants of the Claisen rearrangement were explored. Ultimately, the Eschenmoser Claisen rearrangement[15] utilizing the dimethyl acetal of *N*,*N*-dimethylacetamide (DMA-DMA) proved to be most effective, affording **11** in 94% yield. Iodolactonization of **11** yielded fused lactone **12** in 78% yield.

The structure and relative stereochemistry of iodolactone **12** was confirmed by X-ray analysis of a single crystal (see ORTEP in Scheme 2). With a robust route to tetracycle **12** secured, we next explored the installation of the piperidine ring to complete the synthesis of **2**. LAH reduction of the lactone also effected cleavage of the C−I bond leading to diol **13** (Scheme 3) in 72% yield. Oxidation of **13** under Swern conditions proceeded without event to yield ketoaldehyde **14** in quantitative yield. Two routes for the selective homologation of the aldehyde group of **14** to afford **4** were explored (Scheme 4). The first approach entailed selective Wittig reaction of the aldehyde group using the reagent derived from methoxymethylene phosphonium chloride, followed by hydrolysis of the resulting methyl enol ether to afford **4**. Although this reaction worked well on small scale, the yields proved to be irreproducible on larger scale. After investigating several alternative homologation strategies, it

Scheme 2. Synthesis of Lactone **12**



(5) Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244–13245.

(6) This is supported by a comparison of pK_a's of protonated pyridine and protonated methoxypyridine; see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd.: Cambridge, 2000; pp 71−120.

(7) Ishiuchi, K.; Kubota, T.; Morita, H.; Kobayashi, J. *Tetrahedron Lett.* **2006**, *47*, 3287–3289.

(8) Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Helv. Chim. Acta* **2009**, *92*, 445–452.

(9) Koyama, K.; Morita, H.; Hirasawa, Y.; Yoshinaga, M.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2005**, *61*, 3681–3690.

(10) Lannotinidine B is especially interesting from a biological perspective because it has been shown to enhance mRNA expression for nerve growth factor (NGF) in human glial cells.[9]

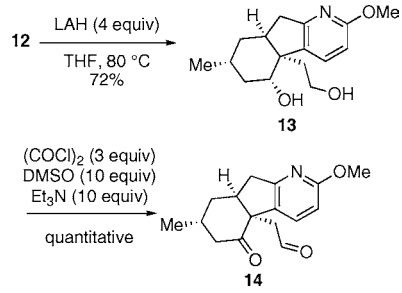
(11) For previous syntheses of **1**, see: (a) Staben, S. T.; Kennedy-Smith, J.; Huang, D.; Corekey, B. K.; LaLonde, R.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991–5994. (b) DeLorbe, J. E.; Lotz, M. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 1576–1579.

(12) Kelly, S. A.; Foricher, Y.; Mann, J.; Bentley, J. M. *Org. Biomol. Chem.* **2003**, *1*, 2865–2876.

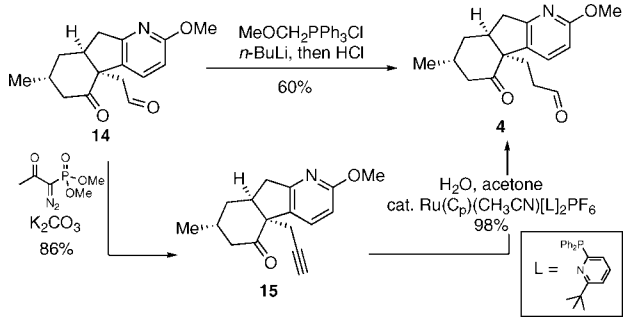
(13) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775–1776.

(14) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.

Scheme 3. Synthesis of Ketoaldehyde **4**



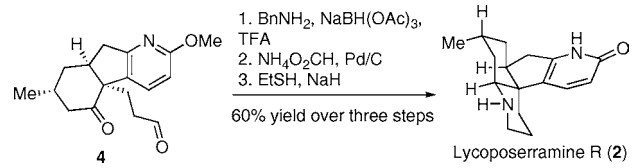
Scheme 4. Homologation of Ketoaldehyde **14**



was found that **4** could be obtained in consistently high yields from **14** using the Ohira−Bestmann reaction to install a triple bond (see **15**) followed by anti-Markovnikov hydration using the procedure introduced by Grotjahn.[16]

At this stage, several direct reductive amination possibilities to forge the piperidine ring in **2** were investigated. However, these were found to be low yielding. Ultimately, the piperidine moiety was best installed using benzylamine (Scheme 5) followed by hydrogenolytic cleavage of the benzyl group. A concluding methyl ether cleavage (NaSEt) gave lycoposerramine R (**2**). Synthetic lycoposerramine R

Scheme 5. Completion of the Synthesis of **2**



gave spectral data (^{1}H and ^{13}C NMR, IR, MS) fully consistent with that reported by Takayama et al. following its isolation.[17]

The synthesis of **2** proceeds in a total of 13 steps (12% overall yield) from **7** and **8**. Key to the completion of the synthesis is the use of a methoxypyridine as a masked pyridone as well as an Eschenmoser Claisen reaction to install a key quaternary carbon center. Our application of these synthetic studies to the enantioselective synthesis of **2** as well as the related fawcettimine-type alkaloid **3** will be reported in due course.

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

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(16) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232–12233.

(17) We are grateful to Prof. Hiromitsu Takayama (Chiba University) for copies of ^{1}H and ^{13}C NMR spectra of **2**.