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Stereoselective Synthesis of the Eastern Quinolizidine Portion of Himeradine A

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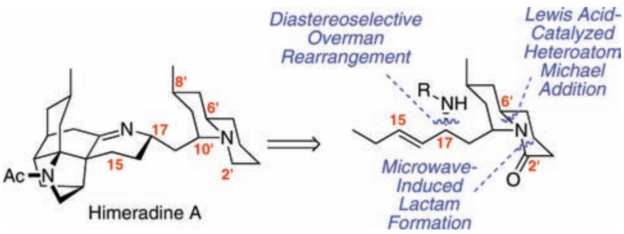
ABSTRACT



The synthesis of the $C_{15}-C_{17}/N_{1'}-C_{11'}$ quinolizidine portion of himeradine A is disclosed. An intramolecular, heteroatom Michael addition was employed to establish the $C_{6'}$ stereogenic center with high diastereoselectivity. The quinolizidine ring was constructed using microwave-induced cyclization at the $N_{1'}-C_{2'}$ position. The C_{17} stereogenic center was introduced through a diastereoselective Overman rearrangement.

In 2003, Kobayashi and co-workers reported the isolation and structural determination of the alkaloid himeradine A (**1**) from the club moss *Lycopodium chinense* in small amounts (2 mg, 0.001%, Figure 1).[1] Polycycle **1** was assigned based on extensive 2D NMR techniques (COSY, HOHAHA, HMQC, HMBC, and HMQC-HOHAHA); however, they were unable to establish the correlation between the eastern and western halves or the absolute stereochemistry of the molecule. Alkaloid **1** showed modest cytotoxicity against murine lymphoma L1210 cells (IC_{50} 10 μg/mL), but a thorough biological screening of the compound has not been reported. Other members of the *Lycopodium* family have shown intriguing biological activity.[2]

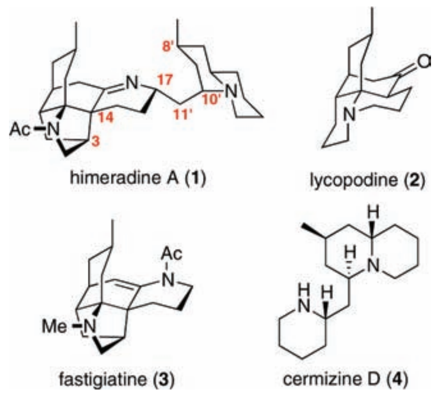


Figure 1. Himeradine A and related *Lycopodium* alkaloids.

The heptacyclic himeradine A (**1**) possesses a challenging array of structural features: ten stereogenic centers including one all-carbon quaternary center, a densely packed pentacyclic western half, the $C_{8'}-C_{10'}$-*trans*-disubstituted quinolizidine, and the challenging sigma linkage at $C_{11'}$ (Figure 1). The carbon framework of the western portion is similar to that found in lycopodine (**2**);[3] however, the

(1) Morita, H.; Hirasawa, Y.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 4563–4566.

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(3) Structure determination: (a) Ayer, W. A.; Iverach, G. G. *Tetrahedron Lett.* **1962**, *3*, 87–92. Enantioselective total syntheses: (b) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239. (c) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929–4938. Racemic total syntheses: (d) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648. (e) Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. *J. Am. Chem. Soc.* **1968**, *90*, 1648–1650. (f) Kim, S.; Bando, Y.; Horii, Z. *Tetrahedron Lett.* **1978**, 2293–2294. (g) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054–1068. (h) Schumann, D.; Mueller, H. J.; Naumann, A. *Liebigs Ann. Chem.* **1982**, 1700–1705. (i) Kraus, G. A.; Hon, Y. S. *Heterocycles* **1987**, *25*, 377–386. (j) Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128–5129. Formal syntheses: (k) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87. (l) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 637–638.

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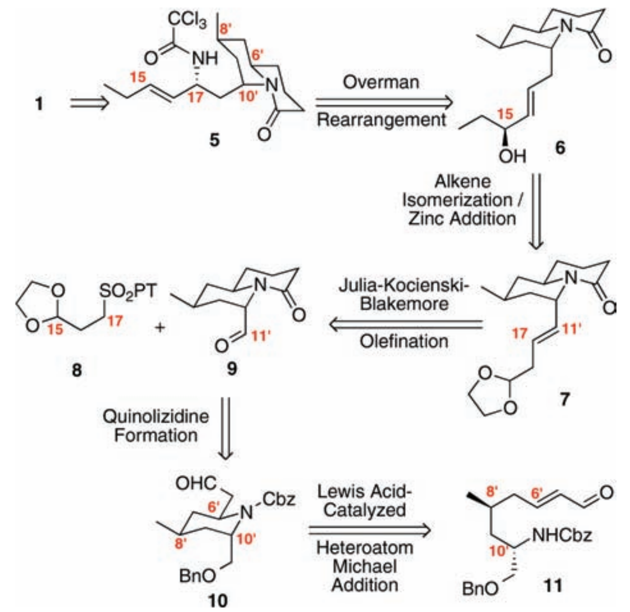
additional challenge of the C_3-C_{14} linkage increases the complexity of any synthetic endeavor. A related structural scaffold can be found in fastigiatine (**3**).[4] The relative stereochemistries of the eastern quinolizidine ring systems are distinct from typical stereochemical combinations found in related natural products such as cermizine D (**4**).[5] In particular, the axially disposed $C_{10'}$ moiety creates added synthetic challenges. To date, no synthetic endeavors have been published toward himeradine A.[6] Herein, we disclose the synthesis of the eastern portion of himeradine A and the development of a viable model coupling strategy for incorporation of the $C_{15}-C_{17}$ carbons including the C_{17} stereogenic center.

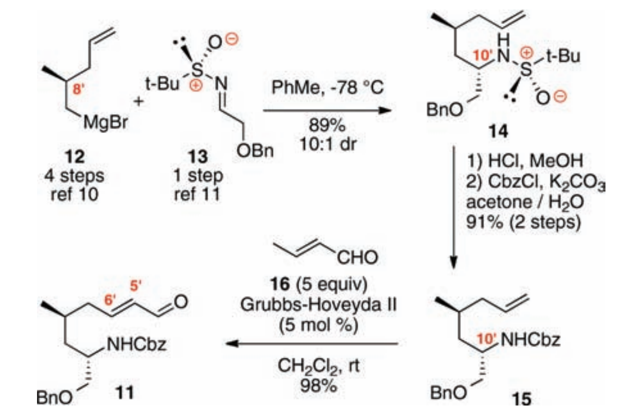


Scheme 1. Retrosynthesis

Our retrosynthetic strategy is shown in Scheme 1. For the polycyclic western portion of himeradine, we intend to adapt our previously developed route to lycopodine for the construction of the carbon framework.[3b,c] Compound **5** will be formed via a diastereoselective Overman rearrangement[7] of the trichloroimidate derived from alcohol **6**. The required C_{15} stereogenic center will be introduced through an organozinc addition to an α,β-unsaturated aldehyde. This aldehyde will be accessible in turn from a Julia–Kocienski–Blakemore olefination[8] with the known 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone **8**[9] and aldehyde **9** followed by acid-catalyzed deacetalization with *in situ* alkene migration. The quinolizidine ring system **9** will be formed via a $N_{1'}-C_{2'}$ lactamization strategy. The piperidine ring system **10** will be constructed from a substrate-controlled, intramolecular heteroatom Michael addition of enal **11**.

Synthesis of cyclization precursor **11** is shown in Scheme 2. The key $C_{10'}$ stereocenter was constructed from a Grignard addition of organomagnesium species **12**[10] with the known Ellman imine **13**[11] in good levels of diastereoselectivity and chemical yield. Removal of the sulfoxamine under acid-catalyzed conditions followed by Cbz protection revealed the carbamate **15**. Cross metathesis of alkene **15** with crotonaldehyde (**16**) cleanly provided the enal **11**. We have previously shown that cross metathesis of monosubstituted alkenes with α,β-unsaturated carbonyl compounds proceeds in higher chemical yield when the unsaturated carbonyl compound contains a β-methyl substitution (e.g., **16**).[3b,c,12]

Scheme 2. Synthesis of Cyclization Precursor



The key Lewis acid catalyzed intramolecular, heteroatom Michael addition is shown in Scheme 3. We had hypothesized that the $C_{8'}$ and $C_{10'}$ stereogenic centers would work in concert to direct facial attack on an α,β-unsaturated oxonium ion, as shown in possible transition state model **17**. The planar carbamate at $C_{10'}$ should force the

(4) Structure determination: (a) Gerard, R. V.; MacLean, D. B.; Fagianni, R.; Lock, C. J. *Can. J. Chem.* **1986**, *64*, 943–949. (b) Gerard, R. V.; MacLean, D. B. *Phytochemistry* **1986**, *25*, 1143–1150. Total synthesis: (c) Liau, B. B; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594–9595.

(5) Structure determination: (a) Morita, H.; Hiraswa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015–7023. Total synthesis: (b) Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987–1990. (c) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608–1617.

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(8) (a) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

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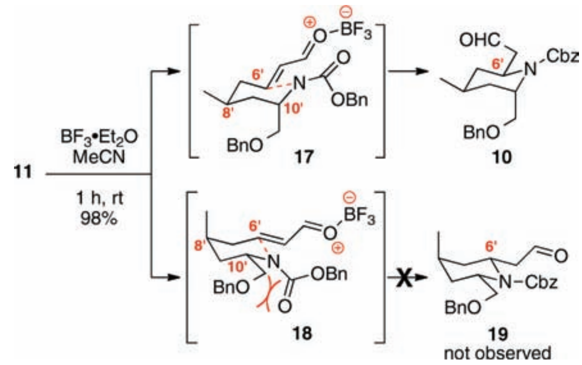
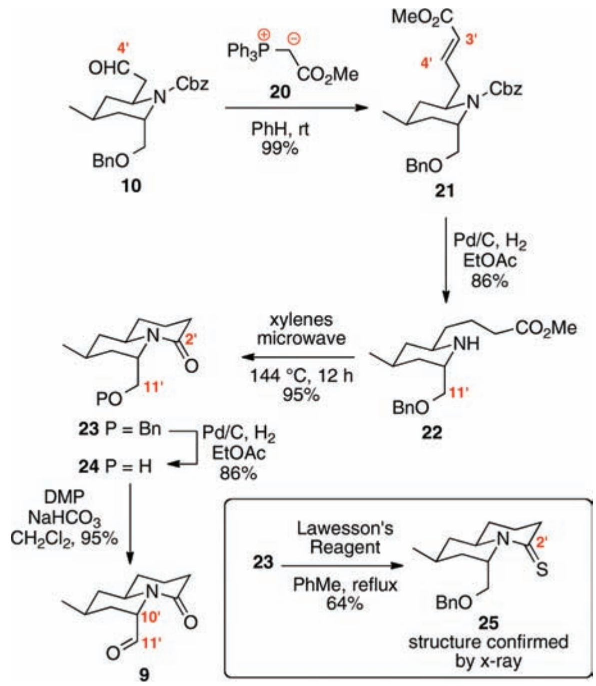
CH_2OBn moiety into a pseudoaxial position in the transition state in order to minimize steric repulsions with the Cbz moiety.[13] We were pleased to see that our hypothesis proved accurate as aldehyde **10** was isolated as the sole diastereomer (> 20:1 dr) in excellent chemical yield (98%).

Scheme 3. Intramolecular Heteroatom Michael Addition



The next hurdle was the construction of the quinolizodine ring system (Scheme 4). Wittig olefination of aldehyde **10** provided the α,β-unsaturated ester **21** in excellent yield. We had anticipated that hydrogenation of **21** would not only reduce the alkene but also induce Cbz deprotection and debenzylation at $C_{11'}$. To our surprise, only two of the three predicted events occurred, delivering the benzyl ether **22** as the sole product in high yield. Lactam formation of **22** (or its corresponding carboxylic acid) under a variety of conditions proved unusually challenging. Fortunately, we ultimately identified that thermolysis under microwave irradiation cleanly induced lactam formation in high yield. The synthetic challenge with this bond formation may be due to the required placement of the $C_{10'}$ substituent in the axial orientation to facilitate $C_{2'}-N_{1'}$ bond formation. Interestingly, heating of amine **22** in refluxing xylenes (approximately 140 °C) using an oil bath provided the product **23** in significantly lower yield (40% conversion after 48 h). Microwave irradiation's ability to provide purely rotational energy transfer[14] may facilitate this transformation more efficiently than standard thermal conditions, thereby inducing rotation of the side arm into close proximity for the 2° amine to attack the $C_{2'}$ ester. Next, hydrogenation of the benzyl ether **23** under essentially the same conditions as employed previously with compound **21** provided the free alcohol **24**. One possible explanation for the divergent reactivity (compounds **21** vs **23**) may be the presence of the free amine in compound **22**, which may poison the catalyst. The stereochemistry of the newly formed quinolizidine ring system was conclusively established by X-ray crystallographic analysis on the thiolactam **25**.[15] Oxidation of 1° alcohol **24** under buffered Dess–Martin conditions revealed the aldehyde **9**. We had feared **9** might be prone to epimerization; however, **9** appeared to be configurationally stable at $C_{10'}$, likely due to the presence of the lactam carbonyl again disfavoring placement of the $C_{10'}$ substituent in an equatorial position due to $A^{1,3}$ strain.[13]

Scheme 4. Synthesis of the Quinolizidine Core



With the aldehyde **9** in hand, we shifted our attention to the incorporation of the $C_{15}-C_{17}$ carbon atoms and the C_{17} stereogenic center (Scheme 5). Olefination of **9** with the known PT sulfone **8**[9] gave the desired β,γ-unsaturated acetal in good yield with an inconsequential 14:1 *E*/*Z* selectivity. Treatment of acetal **7** under aqueous acidic conditions induced both acetal deprotection and alkene isomerization to cleanly provide the desired α,β-unsaturated aldehyde **26** with excellent *E*/*Z* selectivity (> 20:1). *N*-Methyl diphenylprolinol catalyzed addition of Et_2Zn to the aldehyde **26** revealed the allylic alcohol **27** in 10:1 dr.[16,17] Formation of the trichloroacetimidate was accomplished using DBU as the base followed by thermolysis at 90 °C in the presence of K_2CO_3 to cleanly generate the rearranged amide **5**. The presence of the carbonate base

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(15) See Supporting Information of crystallographic information.

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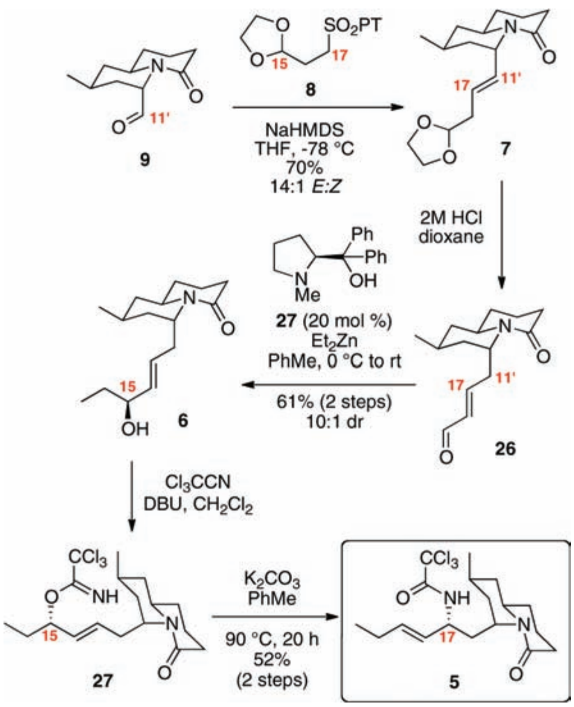
Scheme 5. Incorporation of the $C_{15}-C_{17}$ Portion



appeared to prevent decomposition under the reaction conditions.[18]

In summary, the synthesis of the $C_{15}-C_{17}/N_{1'}-C_{11'}$ quinolizidine core of himeradine A has been accomplished. Key steps in the synthetic sequence include a diastereoselective Overman rearrangement, a substrate-controlled, intramolecular heteroatom Michael addition, and a microwave-induced lactam formation. Further studies toward the total synthesis of himeradine A and other related *Lycopodium* alkaloids will be reported in due course.

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Supporting Information Available. Complete experimental procedures are provided, including ^1H and ^{13}C spectra, of all new compounds. X-ray crystallographic data (CIF) for compound **25** is also provided. This material is available free of charge via the Internet at http://pubs.acs.org.