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Synthesis of (±)-Acetylnorloline via Stereoselective Tethered Aminohydroxylation

M. Todd Hovey, Emily J. Eklund, Robert D. Pike, Anshul A. Mainkar, and Jonathan R. Scheerer*

Department of Chemistry, The College of William & Mary, P.O. Box 8795, Williamsburg, Virginia 23187, United States

jrscheerer@wm.edu

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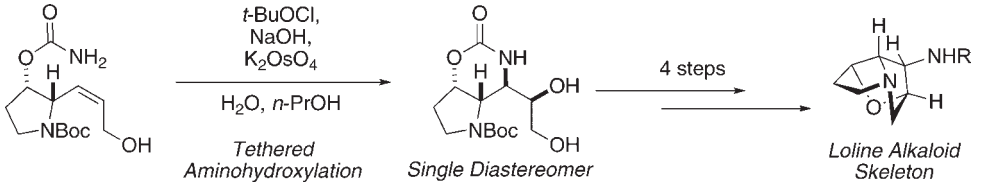
ABSTRACT



Loline alkaloids exhibit a strained ether-bridged pyrrolizidine skeleton and possess insecticidal and insect antifeedant properties. The synthesis of acetylnorloline, a prototypical member of the alkaloid family, is described. Central to the route is a stereoselective tethered aminohydroxylation (TA) of a homoallylic carbamate. Allylic (A1,3) strain is exploited to enforce diastereofacial selectivity during the aminohydroxylation.

Several *Lolium* species of common pasture grasses including fescue and rye are known to harbor mutualistic fungi.[1] In return for nutrients from the plant, these fungal endophytes (mainly *Neotyphodium* and *Epichloe* species) produce loline alkaloids (e.g., **1**−**4**).[2] The alkaloids have potent antifeedant and insecticidal activities that protect the plant from insect herbivory. This mutualistic relationship between specific grasses and fungi is a long-standing natural pest control paradigm, and because of low mammalian toxicity,[3] there is potential to use lolines as natural commercial insecticides. In addition to insecticidal properties, the most abundant alkaloid, loline **1**, also exhibits modest antitumor[4] activity and related derivatives of **1** are muscle relaxants.[5]

The lolines are polycyclic pyrrolizidine alkaloids[6] featuring an *exo* amine at C1 and a strained bridgehead ether connecting C2 and C7. The C1-amine is found with various alkyl and acyl substitutions. Representative lolines **1**−**4** are presented in three perspectives (Figure 1).

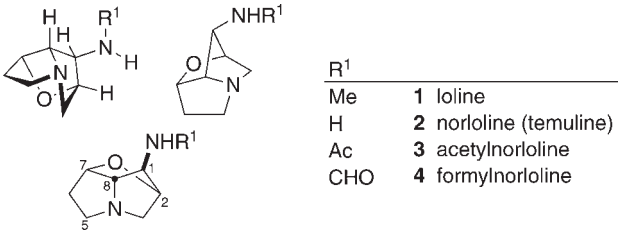


Figure 1. Perspective illustrations of loline alkaloids.

As a result of the challenging and densely functionalized topology and motivating biological profile of the lolines, several synthetic approaches to the core have been explored. Prior to this work, two unsuccessful routes[7] as well as a racemic synthesis featuring a nitrone cycloaddition (by Tufariello and co-workers[8]) and an asymmetric synthesis (by White and co-workers[9]) have been reported.

(1) For a comprehensive review, see: Schardl, C. L.; Grossman, R. B.; Nagabhyru, P.; Faulkner, J. R.; Mallik, U. P. *Phytochemistry* **2007**, *68*, 980–996.

(2) Petroski, R. J.; Yates, S. G.; Weisleder, D.; Powell, R. G. *J. Nat. Prod.* **1989**, *52*, 810–817.

(3) Riedell, W. E.; Kieckhefer, R. E.; Petroski, R. J.; Powell, R. G. *J. Entomol. Sci.* **1991**, *26*, 122–129.

(4) (a) Culvenor, C. C. *J. Pharm. Sci.* **1968**, *57*, 1112–1117. (b) Petroski, R. J.; Powell, R. G.; Sunhil, R.; McLaughlin, J. L. *Int. J. Pharmacogn.* **1994**, *32*, 409–412.

(5) Abdullaez, N. P.; Batirov, E. Kh.; Malikov, V. M.; Shakhidoyatov, Kh. M.; Kadyrov, Ch. Sh.; Yunusov, S. Yu. *Chem. Nat. Compd. (Engl. Transl.)* **1977**, *13*, 313–315.

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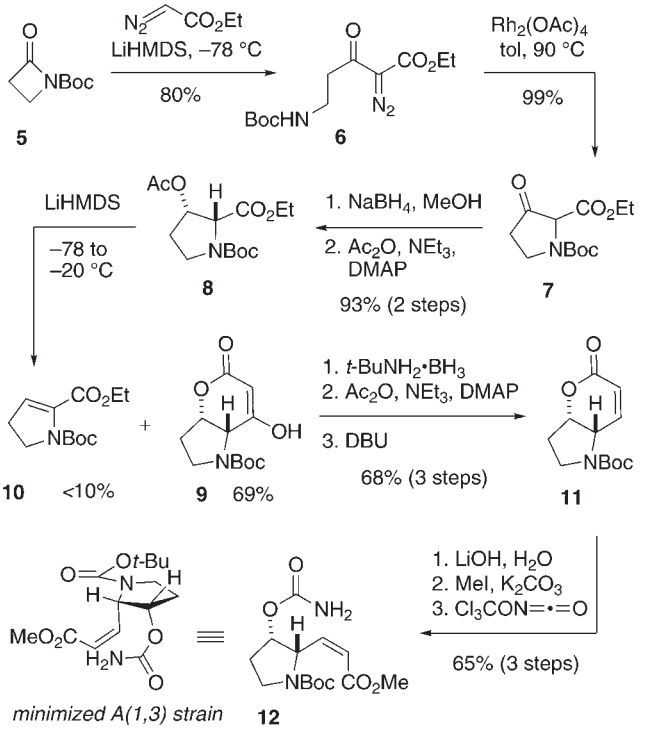
Our synthesis of the lolines initiated from the protected 3-oxo-proline **7**, which can be prepared in three steps from glycine ethyl ester (in 25−48% overall yield[10]) or by a competitive route that we developed starting from *N*-Boc-2-azetidinone[11] (**5**) (Scheme 1). In this newly developed route, lithiation of ethyl diazoacetate in the presence of the β-lactam **5** at −78 °C afforded the Claisen condensation product **6** in 80% yield.[12] Decomposition of the diazocarbonyl function with $Rh_2(OAc)_4$ and subsequent N−H insertion cleanly delivered β-ketoester **7** (99% yield, chomatography not required).[13]

We envisioned that two of the four contiguous stereocenters of loline could be selectively installed by whole-cell bioreduction of β-ketoester **7** using Baker's yeast under nonfermenting conditions.[14] On multigram-scale, we and others found that efficient extraction of the product was not possible and untenable yields of 40% or lower were typically observed.[14b] In the interest of economy and expedience, we decided to pursue the synthesis of loline alkaloids with racemic *cis*-3-hydroxyproline, prepared by reduction of **7** with $NaBH_4$.[15]

Formation of 3-acetoxyproline **8** preceded kinetically controlled enolization with LiHMDS. On warming to −20 °C, Dieckmann condensation ensued delivering the desired enol-lactone cyclization product **9** in respectable yield (69%). The undesired elimination product **10**, a result of deprotonation at the thermodynamically more favorable pyrrolidine ring α-proton and extrusion of acetate, is formed in less than 10% yield and can be easily removed during workup by extraction of **9** into aqueous base. Enolization of **8** at temperatures above −78 °C or by inverse addition of base to substrate produced a greater amount of **10**.

A reduction−elimination sequence emerged as a facile operation to convert enol lactone **9** into the desired α,β-unsaturated lactone **11**. Enol lactone **9** was reduced to the

Scheme 1. Synthesis of Aminohydroxylation Precursor



derived β-hydroxy lactone with a borane-*tert*-butyl amine complex in methanol buffered with citric acid. Following acylation of the resulting 5:1 mixture of hydroxyl diastereomers, elimination was completed with DBU to give the α,β-unsaturated lactone **11**. This overall sequence required two reaction vessels and cleanly provided **11** in 68% yield without the need for purification of intermediates.

Hydrolysis of **11** to the derived carboxylate, followed by esterification with methyl iodide, provided the intermediate *Z*-α,β-unsaturated ester. This material was moderately slow to relactonize, permitting conversion of the hydroxyl function to the primary carbamate **12** with trichloroacetyl isocyanate (65% yield from **11**). Analysis of carbamate **12** reveals the presence of an 1,3-allylic nonbonding interaction enforced from the *Z*-α,β-unsaturated ester moiety (see 3-D illustration, Scheme 1).[16] Minimizing for this interaction, the carbamate in **12** is positioned on the *re* face of the alkene. When we attempted to engage the carbamate in an osmium-catalyzed tethered aminohydroxylation, the oxidative transformation was not observed (Scheme 2).[17,18]

(6) Selected reviews of pyrrolizidine alkaloids: (a) Liddell, J. R. *Nat. Prod. Rep* **2002**, *19*, 773–781. (b) Liddell, J. R. *Nat. Prod. Rep*. **2001**, *18*, 441–447. (c) Liddell, J. R. *Nat. Prod. Rep*. **2000**, *17*, 455–462. (d) Roeder, E. *Curr. Org. Chem*. **1999**, *3*, 557–576. (e) Robins, D. J. *Nat. Prod. Rep*. **1989**, *6*, 577–589.

(7) (a) Glass, R. S.; Deardorff, D. R.; Gains, L. H. *Tetrahedron Lett*. **1978**, *33*, 2965–2968. (b) Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem*. **1981**, *46*, 3887–3891.

(8) Tufariello, J. J.; Meckler, H.; Winzenberg, K. *J. Org. Chem*. **1986**, *51*, 3556–3557.

(9) (a) Blakemore, P. R.; Kim, S. K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831–1845. (b) Blakemore, P. R.; Schulze, V. K.; White, J. D. *Chem. Commun* **2000**, 1263–1264.

(10) (a) Blake, J.; Willson, C. D.; Rapoport, H. *J. Am. Chem. Soc*. **1964**, *86*, 5293–5299. (b) Williams, R. M.; Cao, J. H.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc*. **2003**, *125*, 12172–12178.

(11) *N*-Boc-2-azetidinone is commercially available and easily prepared: Chincholkar, P. M.; Kale, A. S.; Gumaste, V. K.; Deshmukh, A. *Tetrahedron* **2009**, *65*, 2605–2609.

(12) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett*. **1987**, *28*, 5351–5352.

(13) (a) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem*. **1985**, *50*, 5223–5230. (b) For a recent review on diazocarbonyl C−H insertion, see: Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev*. **2010**, *110*, 704–724.

(14) (a) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1313–1317. (b) Porter, E. A.; Wang, X.; Schmitt, M. A.; Gellman, S. H. *Org. Lett*. **2002**, 3317–3319.

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(16) Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841–1860.

(17) For a recent review of aminohydroxylation, see: (a) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem.—Eur. J*. **2011**, *17*, 58–76. (b) Donohoe, T. J.; Johnson, P. D.; Helliwell, M.; Keenan, M. *Chem. Commun*. **2001**, 2078–2079. (c) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc*. **2002**, *124*, 12934–12935. (d) Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem*. **2003**, *1*, 2025–2028.

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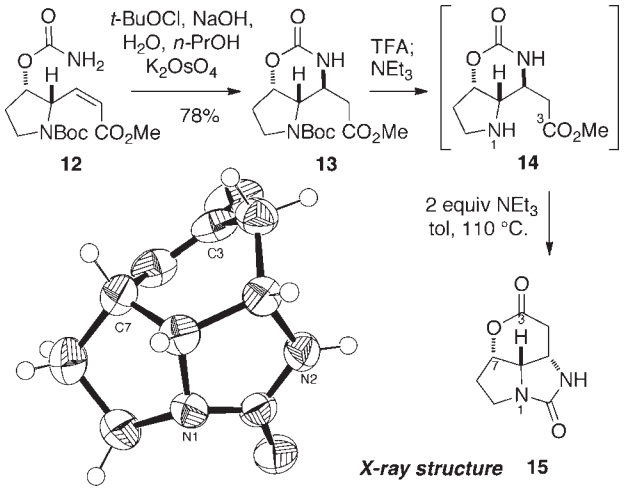
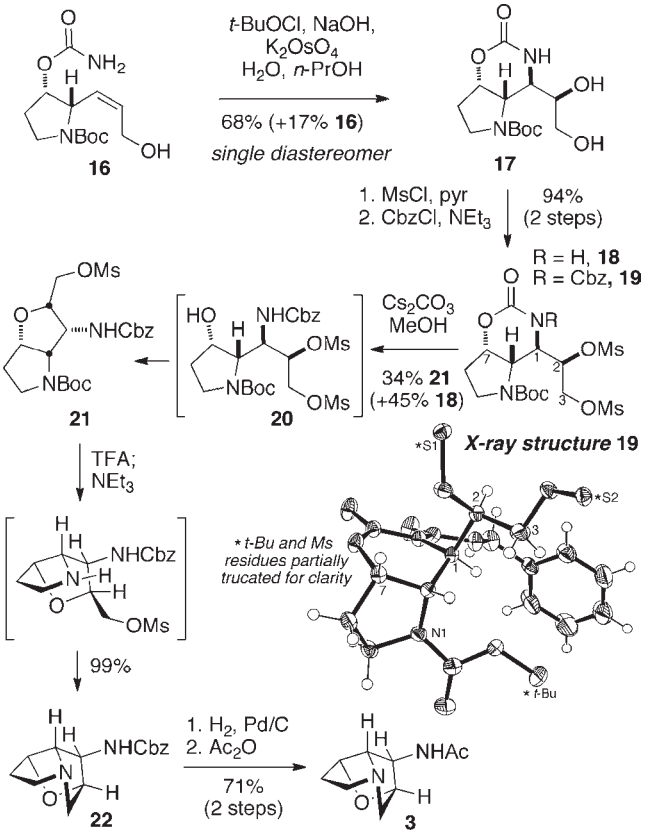
Scheme 2. Attempted Aminohydroxylation of Unsaturated Ester



Rather, heteroconjugate addition occurred to give bicycle **13**. Although conjugate addition was not the desired outcome, the β-amino function was installed with excellent diastereoselectivity (>20:1) in support of our conformational predictions.

The heteroconjugate addition product **13** was used as a model to explore late-stage pyrrolizidine formation. Toward this end, deprotection of the *tert*-butyl carbamate (25% TFA) provided after basification pyrrolidine **14**. The nucleophilic amine in **14** showed no propensity to engage the pendant C3-methyl ester in lactam formation. Under more forcing conditions (refluxing toluene), the amine condensed at the carbamate. Subsequent lactonization gave the observed urea **35**, which was verified by X-ray crystallography. These results established that pyrrolizidine construction would require cleavage of the cyclic carbamate prior to bond formation between N1 and C3. In order to facilitate the desired intramolecular aminohydroxylation in preference to heteroconjugate addition the α,β-unsaturated ester **12** was reduced to allylic alcohol **16**. The required ester reduction was best accomplished with diisobutylaluminum hydride (3.0 equiv, CH_2Cl_2, -78 °C, 73% yield). Tethered aminohydroxylation of allylic alcohol **16** under the original conditions using *tert*-butyl hypochlorite[19] as the stoichiometric oxidant afforded the desired product **17** as a single diastereomer in good yield (68%) as well as a small quantity of unreacted starting material **16** (17%). Tethered aminohydroxylation leading to six-membered cyclic carbamates, while precedented, are retarded relative to the formation of corresponding five-membered carbamate (2-oxazolidone) products and often suffer competing side reactions and low yield.[20] The efficient aminohydroxylation of **16** is noteworthy; the conformation enforced by 1,3-allylic strain may entropically favor productive aminohydroxylation over substrates with less ordered structure.

Scheme 3. Synthesis of Acetylnorloline



With the four stereocenters required for the synthesis of the loline skeleton installed, we turned our attention to formation of the pyrrolizidine core and the strained ether bridge. To achieve these objectives, the two hydroxy functionalities in **17** were primed for displacement by conversion to the bis-mesylate and the cyclic carbamate was reacted with CbzCl and NEt_3 to provide imide **19**. X-ray crystallographic analysis of **19**[21] confirmed our structural assignment and verified the stereochemistry resulting from the aminohydroxylation. Methanolysis (MeOH, Cs_2CO_3) of the imide led to a mixture of endocyclic and exocyclic cleavage,[22] providing both the desired 2° alcohol **20** (34% yield) and returning compound **18** (45% yield) resulting from loss of the Cbz functionality. Intermediate **20** could not be isolated and collapsed through regioselective attack at the 2° mesylate to form

(19) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Col. Vol. 5, p 184.

(20) For discussion on tethered aminohydroxylation of homoallylic carbamates and a direct solution to the experimental limitations of the original (*t*-BuOCl) conditions, see: (a) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515. (b) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725–1728.

(21) *tert*-Butyl carbamate and mesylate residues partially truncated for clarity in the X-ray depiction of **19** (Scheme 3). For the complete crystallographic image, see Supporting Information.

(22) Bodner, R.; Marcellino, B. K.; Severino, A.; Smenton, A. L.; Rojas, C. M. *J. Org. Chem.* **2005**, *70*, 3988–3996.

the ethereal bond in bicycle **21**. The defined topology of **21** reveals a mesylate properly oriented on the concave face for reaction with the pyrrolidine amine. Indeed, cleavage of the Boc residue and basification with NEt_3 led to facile intramolecular alkylation, delivering the loline core as the Cbz-protected norloline derivative **22** in nearly quantitative yield (99%). This key intermediate is poised for conversion to all congeners of the loline alkaloid family. As a representative example, acetylnorloline (**3**) was prepared by hydrogenation and acylation (H_2, Pd/C; Ac_2O, 71% yield). The ^1H and ^{13}C NMR spectra of synthetic acetylnorloline are identical with the natural isolated material.[2]

In summary, we have developed a synthesis of the loline alkaloids, a family of insecticidal and insect antifeedant molecules. Key to the synthesis is an efficient diastereoselective tethered aminohydroxylation (TA), a reaction that circumvents the poor regioselectivity of the intermolecular aminohydroxylation used by White and co-workers in their approach to loline.[9] We hope that this example of the TA reaction will add to the scope of an already powerful alkene functionalization strategy. Developments are underway toward more direct access to the TA precursor, an effort that we anticipate will both enable larger-scale preparation of lolines and streamline research into the insecticidal and antifeedant activities, as well as other properties, of both natural and synthetic derivatives.

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Supporting Information Available. Experimental procedures and spectral data (^1H and ^{13}C NMR, FT-IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.