The First Asymmetric Synthesis of a Lycorine Alkaloid. Total Synthesis of (+)-1-Deoxylycorine

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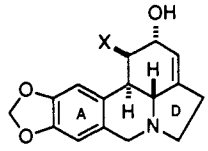
Lycorine (**1a**; unnatural enantiomer shown) and related *Amaryllidaceae* alkaloids exhibit antiviral, antineoplastic, and short-term hypotensive activity.[1] Although several syntheses of racemic lycorine alkaloids have been developed, an asymmetric synthesis has not been reported.[2] We now communicate a highly



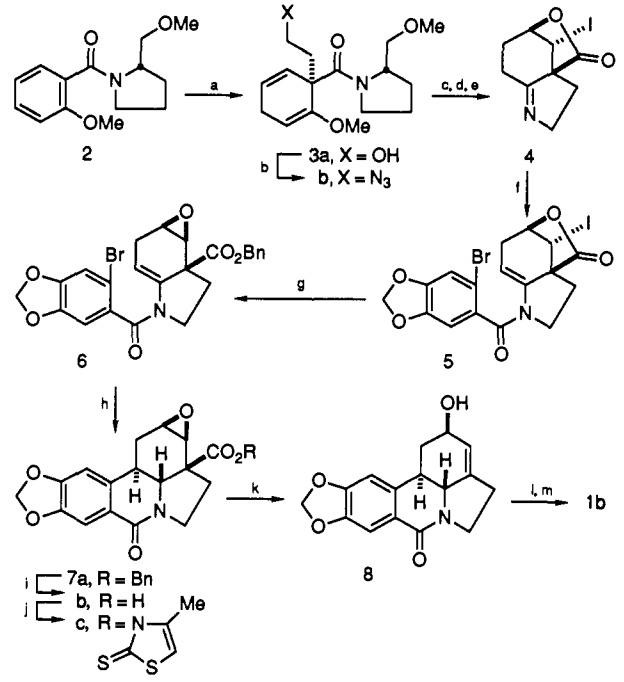
1a, X = OH; *ent*-lycorine
b, X = H; (+)-1-deoxylycorine

enantioselective synthesis of (+)-1-deoxylycorine (**1b**)[3] by a method that is expected to provide convenient access to most of the known lycorine alkaloids in either enantiomeric modification. A particularly noteworthy feature of the synthesis is the complete facial selectivity for the radical cyclization **6** → **7a**.

It has been noted that the stereoselective functionalization of the C ring in **1a** remains a major challenge.[1a] An efficient solution to this problem begins by Birch reduction of the chiral benzamide **2**,[4] followed by alkylation of the resulting enolate with 2-bromoethyl acetate and ester saponification to give the 6-(2-hydroxyethyl)-1-methoxy-1,4-cyclohexadiene **3a** in 96% yield as a single diastereoisomer (Scheme I).[5] This substance was converted to the azide **3b**, which was subjected to enol ether hydrolysis, and then iodolactonization, and finally treatment with triphenylphosphine to give the enantiomerically pure imine **4** (mp 130 °C; ~50% overall yield).

Acylation of **4** gave the enamide **5** (98%). To facilitate the desired radical cyclization to a fully developed lycorane ring system, **5** was converted to the epoxy benzyl ester **6**. On treatment with AIBN and Bu_3SnH in refluxing benzene solution, **6** provided highly crystalline lactam **7a** (mp 203 °C) as the only cyclized product in 53% isolated yield.[6] Although a coupling constant of 12.2 Hz for the protons in **7a** at the BC ring junction was indicative

Scheme I [a]



[a] Reaction conditions: (a) K, NH_3, *t*-BuOH (1 equiv) –78 °C; $BrCH_2CH_2OAc$ (2 equiv) –78 to 25 °C; KOH, MeOH; (b) DEAD, PPh_3, $(PhO)_2P(O)N_3$, THF; (c) HCl, MeOH; (d) I_2, THF, H_2O; (e) PPh_3, THF, reflux; (f) ArCOCl (1 equiv) Et_3N, CH_2Cl_2; (g) BnOH, THF, *n*-BuLi, –78 to 25 °C; (h) AIBN, Bu_3SnH, PhH, reflux; (i) 10% Pd/C, H_2, EtOH (1 atm); (j) DCC, 4-pyrrolidinopyridine, $HONC_4H_4S_2$, CH_2Cl_2; (k) AIBN, Bu_3SnH, PhH, reflux; (l) DEAD, PPh_3, AcOH, THF; (m) $LiAlH_4$, THF, reflux.

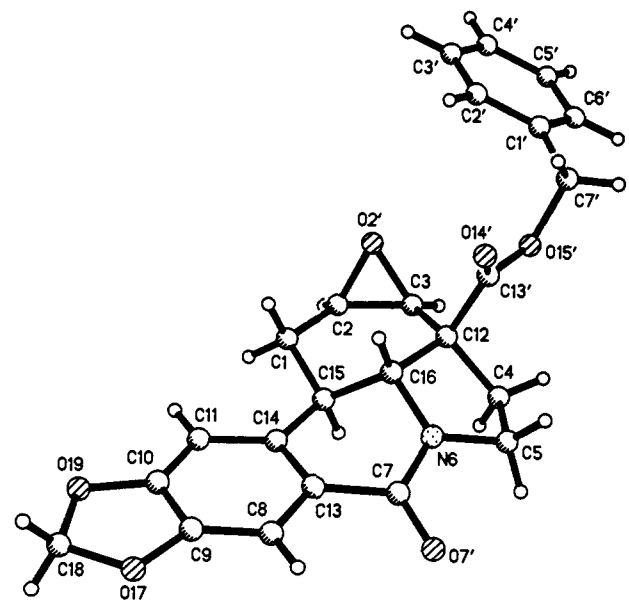


Figure 1. Molecular structure of **7a** (prepared in racemic form via an achiral analogue of benzamide **2**).

of *trans*-dihydro stereochemistry, the facial selectivity of the radical cyclization could not be unambiguously established by NMR spectroscopy.[7] A single-crystal X-ray structure determination provided the molecular structure shown in Figure 1.

Aryl radical addition to give the equatorial C(14)–C(15) bond in **7a** appears to be a result of more favorable orbital overlap at

(1) For recent reviews of the *Amaryllidaceae* alkaloids, see: (a) Martin, S. M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251. (b) Lewis, J. R. *Nat. Prod. Rep.* **1992**, *9*, 183.

(2) A synthesis of nonracemic lycorine has been reported, but the procedure utilized a degradation product of natural lycorine as a relay compound, see: Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Irie, H.; Tanaka, H.; Takagi, S.; Yamaki, M.; Murata, M. *J. Chem. Soc., Chem. Commun.* **1975**, 933.

(3) For a claim to a previous total synthesis of racemic **1b**, see: Baker, J. A. Ph.D. Thesis, Cornell University, Ithaca, NY, 1970. The last step in the synthesis was the reduction of 1-deoxy-2-lycorinone (prepared as described in: Muxfeldt, H.; Bell, J. P.; Baker, J. A.; Cuntze, U. *Tetrahedron Lett.* **1973**, 4587) with $NaBH_4$ in ethanol. However, we find that reduction of (+)-1-deoxy-2-lycorinone (prepared by oxidation of **1b** with MnO_2 in $CHCl_3$) by this method instead gives (+)-1-deoxy-2-*epi*-lycorine in 75% yield with only a trace of **1b**. For other syntheses of 1-deoxy-2-lycorinone, see: (a) Kotera, K. *Tetrahedron* **1961**, *12*, 240. (b) Weller, T.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 935.

(4) (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828. (b) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207. (c) Benzamide **2** is prepared by procedures described in ref 4a or may be purchased from Aldrich Chemical Co. (34,836-8).

(5) All synthetic intermediates were characterized by ^1H and ^{13}C NMR, IR, and low-resolution MS analyses. Products from reactions c, d, e, f, and g gave satisfactory combustion analyses.

(6) The only other material produced in this reaction was the uncyclized reduction product **6** (Br = H).

(7) For the exclusive formation of a trans BC ring junction in a radical cyclization of an achiral substrate related to **6**, see: Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975. It should be noted that the issue of facial selectivity for the aryl radical cyclization was not examined in this study.

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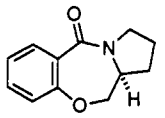
the β-rather than the α-face of the enamide double bond as well as an obvious steric interaction that would result from passage of C(14) near the C(15)–H bond during α-facial attack. Reduction of the intermediate tertiary radical at C(16) by Bu_3-SnH also occurs from the β-face despite the presence of the relatively bulky (benzyloxy)carbonyl group at C(12). This stereoselectivity reflects the greater stability of the product **7a**, which has a trans BC ring fusion and a cis CD ring fusion, compared to the epimer, with cis BC and trans CD ring fusions.[8,9]

The radical cyclization effectively transfers the stereogenicity developed at *pro*-C(12) during reductive alkylation of the chiral benzamide **2** to C(15) of **7a**. With this transfer accomplished, the stage was set for the intended decarboxylative elimination to provide the C(2)–C(3)–C(12) allylic alcohol unit characteristic of the lycorine alkaloids. Hydrogenolysis of **7a** gave the carboxylic acid **7b**, which was immediately converted to either the *N*-hydroxy-2-thiopyridone ester[10a] or the *N*-hydroxy-2-thiazoline thione ester **7c**;[10b] treatment of **7c** with AIBN and Bu_3SnH in refluxing benzene solution provided the crystalline allylic alcohol **8** (50%, mp 231 °C).[11]

The conversion of **8** to (+)-1-deoxylycorine (**1b**) was accomplished by Mitsunobu inversion to give an allylic acetate (94%),[12] followed by reduction with $LiAlH_4$ in refluxing THF (73%).

In summary, the first asymmetric total synthesis of a lycorine alkaloid has been accomplished with near complete stereo- and regiocontrol. It is expected that the C(1) oxygen-substituted alkaloids will be obtained by a modification involving allylic oxidation of **3** or a related substrate; benzoxazepinone **9**[13] will provide lycorine alkaloids with the natural absolute configuration.



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Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates (9 pages). Ordering information is given on any current masthead page.

(8) Molecular modeling (MM2 via MacroModel, Version 3.0) demonstrated that **7a** is more stable than the indicated epimer by ~11 kcal/mol. It is noteworthy that aryl radical addition to the α-face of the enamide double bond followed by reduction of the tertiary radical would probably generate an isomer of **7a** with cis BC and CD ring fusions (overall trans radical addition) rather than the less stable epimer (~6 kcal/mol) required for a lycorine synthesis with trans BC and CD ring fusions. These and other facets of stereoselectivity will be considered in greater detail in the full account of this work.

(9) For earlier examples of the control of ring junction stereochemistry via radical cyclization, see: Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.

(10) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (b) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.

(11) For earlier examples of radical-induced epoxide fragmentations, see: (a) Sabatino, E. C.; Gritter, R. J. *J. Org. Chem.* **1963**, *28*, 3437. (b) Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363. (c) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181. (d) Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106. (e) Rawal, V. H.; Krishnamurthy, V. *Tetrahedron Lett.* **1992**, *33*, 3439. (f) Rawal, V. H.; Iwasa, S. *Tetrahedron Lett.* **1992**, *33*, 4687. (g) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1992**, *33*, 6169.

(12) It was found that the allylic acetate compared favorably (500-MHz ^1H NMR, ^{13}C NMR, solution IR, and low-resolution MS) to a substance prepared by treatment with acetic anhydride/triethylamine of the corresponding racemic allylic alcohol obtained by total synthesis according to: Moller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chim. Scand. B* **1978**, *32*, 98. We thank Professor Torssell for a generous sample of this allylic alcohol (identified as **1b** in the published account).

(13) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915.