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Rapid and Enantioselective Assembly of the Lycorine Framework Using Chemoenzymatic Techniques

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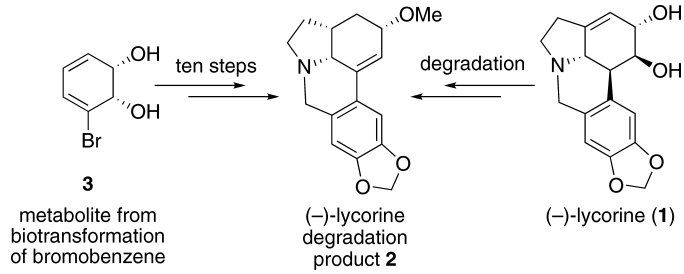
ABSTRACT



The pentacyclic framework associated with the alkaloid (−)-lycorine (1) can be assembled in as few as six steps from the enantiomerically pure *cis*-1,2-dihydrocatechol 3 which is itself readily available on a large scale through the whole-cell biotransformation of bromobenzene. The methodology has been used in developing the first synthesis of compound 2, a derivative of lycorine.

The alkaloid lycorine (**1**, Figure 1) constitutes up to 1% of the dry weight of daffodil bulbs and is considered to be the most abundant of the nitrogen bases of the *Amaryllidaceae*.[1] The determination of the structure of this compound rests, in large measure, on the outstanding efforts of several Japanese groups started in the mid-1930s and which included degradation work whereby lycorine was converted into derivative **2**.[2] The structural proposals arising from these studies were confirmed through the single-crystal X-ray analysis of the hydrobromide salt of dihydrolycorine, the product of hydrogenation of compound **1**.[3]

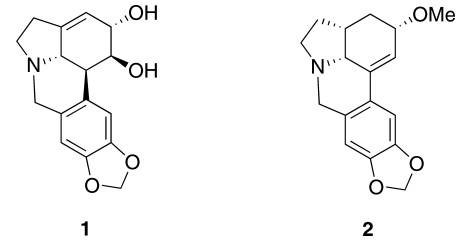


Figure 1. Alkaloid (−)-lycorine (**1**) and a degradation product **2**.

Lycorine displays a remarkable range of biological properties.[4,5] During its initial isolation,[1] it was recognized as a

(1) (a) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1952; Vol. *2*, p 331. (b) Dalton, D. R. *The Alkaloids: The Fundamental Chemistry - A Biogenetic Approach*; Marcel Dekker: New York, 1979; p 2.

(2) (a) Kondo, H.; Uyeo, S. *Chem. Ber.* **1935**, *68*, 1756. (b) Humber, L. G.; Kondo, H.; Kotera, K.; Takagi, S.; Takeda, K.; Taylor, W. I.; Thomas, B. R.; Tsuda, Y.; Tsukamoto, K.; Uyeo, S.; Yajima, H.; Yanaihara, N. *J. Chem. Soc.* **1954**, 4622. (c) Takagi, S.; Taylor, W. I.; Uyeo, S.; Yajima, H. *J. Chem. Soc.* **1955**, 4003. (d) Takeda, K.; Kotera, K. *Chem. Pharm. Bull.* **1957**, *5*, 234. (e) Nakagawa, Y.; Uyeo, S. *J. Chem. Soc.* **1959**, 3736. (f) Kotera, K.; Hamada, Y.; Tori, K.; Aono, K.; Kuriyama, K. *Tetrahedron Lett.* **1966**, *7*, 2009.

(3) Shiro, M.; Sato, T.; Koyama, H. *Chem. Ind.* **1966**, 1229.

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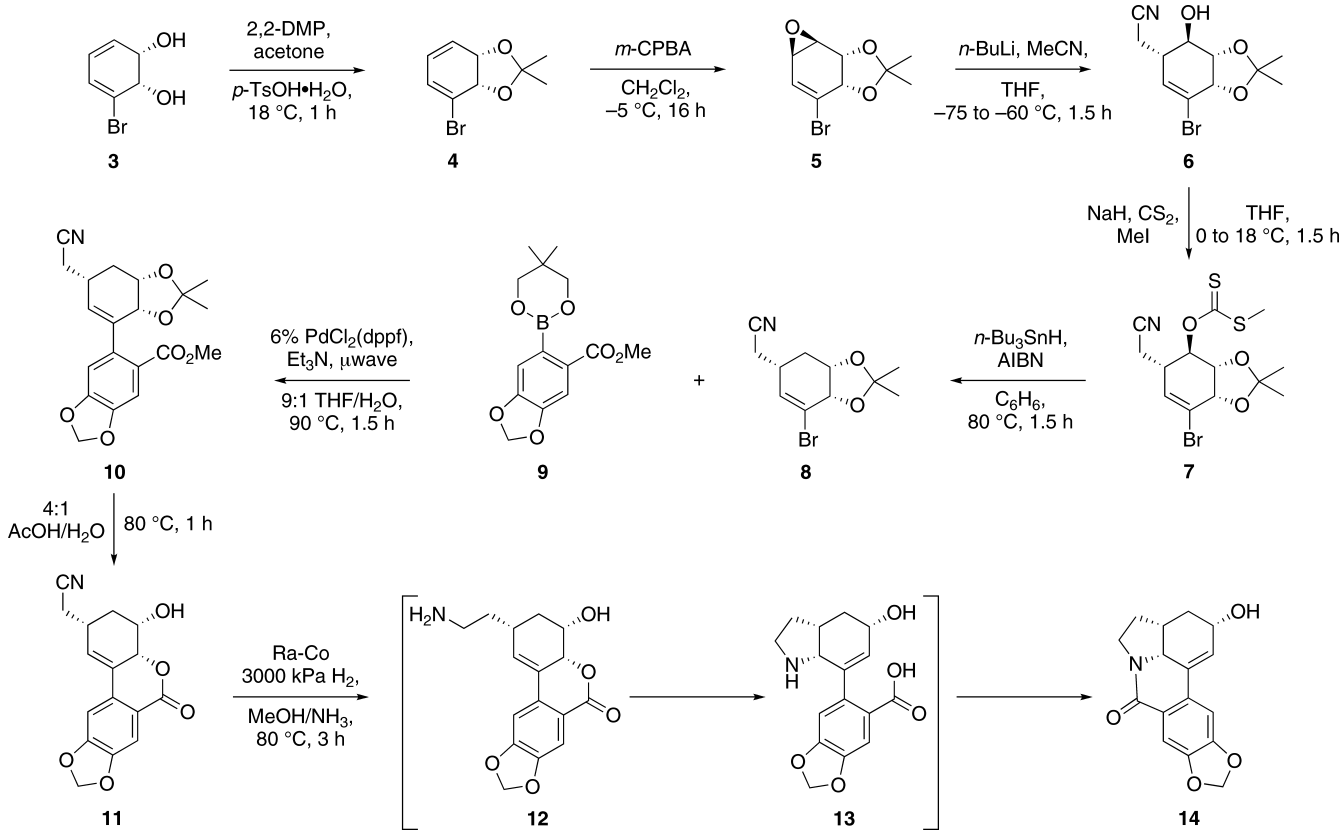
Scheme 1



potent emetic. It is also a strong inhibitor of growth and cell division in higher plants, algae, and yeast and has been shown to inhibit protein and DNA synthesis in murine cells as well as impacting on the in vivo growth of a murine-transplantable ascite tumor. Potent antiviral and immunosuppressive properties have also been attributed to lycorine.[4,5]

Various studies directed toward the synthesis of lycorine have been carried out[6−8] with most of these leading to the racemic modification of the alkaloid.[7] A relay synthesis of the natural product was described by Tsuda and co-workers in 1975,[7a] while in 1993, Schultz and co-workers reported[8a] the preparation of *ent*-lycorine and *ent*-1-deoxylycorine in 13 to 14 steps using the Birch-reductive alkylation of a chiral benzamide as a key transformation. Very recently (2009) Tomioka and co-workers described[8b] the first asymmetric total synthesis of (−)-lycorine using a chiral ligand-controlled cascade conjugate addition reaction. It is against this background that we now describe an abbreviated and chemoenzymatic synthesis of the natural enantiomeric form of the lycorine framework that has allowed for the ready assembly of degradation product **2** as well as a more heavily functionalized system that is an isomer of lycorine. This isomer may serve as a precursor to the natural product itself.

The essential features of the present synthesis of the lycorine framework are shown in Scheme 1. The reaction sequence starts with the enantiomerically pure *cis*-1,2-dihydrocatechol **3** which is available in large quantity through the whole-cell biotransformation of bromobenzene.[9] Thus, conversion of diol **3** into the corresponding and well-known

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(6) Synthetic approaches: (a) Hill, R. K.; Joule, J. A.; Loeffler, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 4951. (b) Hendrickson, J. B.; Alder, R. W.; Dalton, D. R.; Hey, D. G. *J. Org. Chem.* **1969**, *34*, 2667. (c) Landeryou, V. A.; Grabowski, E. J. J.; Autrey, R. L. *Tetrahedron* **1969**, *25*, 4307. (d) Irie, H.; Nishitani, Y.; Sugita, M.; Uyeo, S. *Chem. Commun.* **1970**, 1313. (e) Ganem, B. *Tetrahedron Lett.* **1971**, *12*, 4105. (f) Dyke, S. F.; Sainsbury, M.; Evans, J. R. *Tetrahedron* **1973**, *29*, 213. (g) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1974**, 499. (h) Kissel, W. S.; Padwa, A. *Tetrahedron Lett.* **1999**, *40*, 4003. (i) Ishizaki, M.; Kai, Y.; Hoshino, O. *Heterocycles* **2002**, *57*, 2279.

(7) Total syntheses or formal total syntheses of (±)-lycorine: (a) 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. (b) Møller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chem. Scand. B* **1978**, *32*, 98. (c) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K. *Heterocycles* **1979**, *12*, 1475. (d) Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634. (e) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (f) Hoshino, O.; Ishizaki, M.; Kamei, K.; Taguchi, M.; Nagao, T.; Iwaoka, K.; Sawaki, S.; Umezawa, B.; Iitaka, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 571.

(8) Total synthesis of (+)- or (−)-lycorine: (a) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210. [(+)-lycorine]. (b) Yamada, K.-i.; Yamashita, M.; Sumiyoshi, T.; Nishimura, K.; Tomioka, K. *Org. Lett.* **2009**, *11*, 1631. [(−)-lycorine].

acetonide **4** (93%)[10] is followed by treatment of the latter compound with *m*-CPBA to give the previously reported[10] epoxide **5** in 95% yield. Reaction of compound **5** with the anion derived from acetonitrile then gave, as the exclusive product of reaction, the γ-hydroxynitrile **6** (96%) arising from attack of the nucleophile at the allylic carbon of the epoxide ring of the former compound.[11] Removal of the hydroxy group within compound **6** was achieved using the Barton−McCombie protocol[12] although some care was required in forming the intermediate xanthate ester **7** because the use of an excess of carbon disulfide in this step led to dramatically diminished yields of this product. Under the best conditions identified so far (and leading to a 94% yield of **7**), a close to 1:1:1 molar ratio of substrate, CS_2, and MeI was used. Reductive cleavage of ester **7** was readily achieved with 2.1 mol equiv of *n*-Bu_3SnH in refluxing benzene and using AIBN as initiator. Under such conditions, the nitrile **8** was obtained in yields ranging from 67 to 82%. It was critical to subject this compound to rigorous chromatographic purification to remove coproduced carbonyl sulfide[13] which, when present, adversely affects the efficiency of the Suzuki−Miyaura cross-coupling[14] that is the next step in the reaction sequence. So, when a mixture of a carbonyl sulfide-free sample of compound **8**, aryl boronate **9**,[15] 6 mol % $PdCl_2$(dppf), and triethylamine was subjected to microwave irradiation at 90 °C for 1.5 h, then the expected product, arylcyclohexene **10**, was obtained in 75% yield. Hydrolysis of the acetonide residue within compound **10** was readily achieved using a 4:1 v/v mixture of acetic acid and water at 80 °C, and the allylic alcohol so-revealed engaged in a spontaneous lactonization reaction with the adjacent aryl ester residue and thus forming the isolable lactone **11** in 89% yield.

In the most demanding and unusual step of the reaction sequence, the nitrile moiety within compound **11** was selectively reduced with dihydrogen, at 80 °C in the presence of Raney-cobalt and using ammoniacal methanol as solvent.[16] In this manner, the lactam **14** was obtained in 65% yield. Presumably, the primary amine **12** is the initially formed product of reaction, but this then undergoes an S_N' reaction[17] with the pendant allylic lactone residue to give the amino acid **13** which, in turn, lactamizes to give the observed product **14**. The structure of compound **14** was confirmed through a single-crystal X-ray analysis of the readily generated *p*-nitrobenzoate derivative. The resulting ORTEP plot is shown in Figure 2, while other details of this analysis are provided in the Supporting Information (SI).

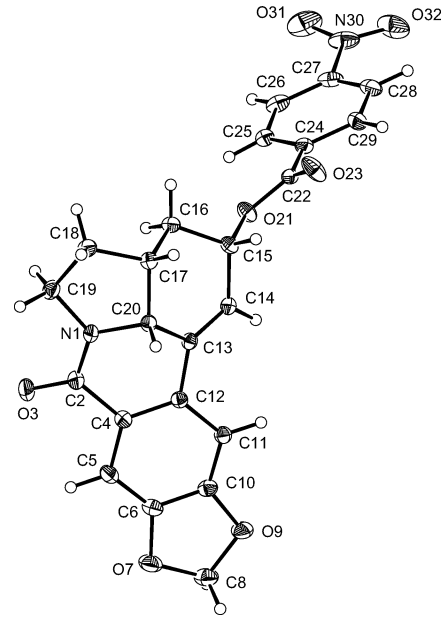
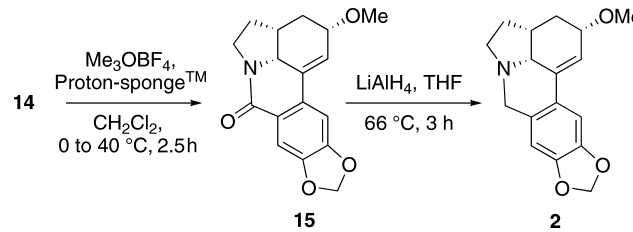


Figure 2. ORTEP plot derived from the single-crystal X-ray analysis of the *p*-nitrobenzoate of alcohol **14**. Only the major sites of disordered atoms are shown. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

The conversion of compound **14** into the dihydrolycorine degradation product **2** was achieved in a straightforward manner by the pathway shown in Scheme 2. Thus, *O*-methylation of the former compound using trimethyloxonium tetrafluoroborate in the presence of Proton-sponge[18] gave the ether **15** (95%), and the lactam carbonyl within this product

Scheme 2



(9) Compound **3** can be obtained from the Aldrich Chemical Co. (Catalogue Number 489492) or from Questor, Queen's University of Belfast, Northern Ireland. Questor Centre Contact Page: http://questor.qub.ac.uk/newsite/contact.htm (accessed July 2, 2009). For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35. (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.* **2003**, *75*, 223. (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117. (d) Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685.

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(11) For related examples of this type of epoxide ring-opening process, see: Banwell, M. G.; Haddad, N.; Hudlicky, T.; Nugent, T. C.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1779.

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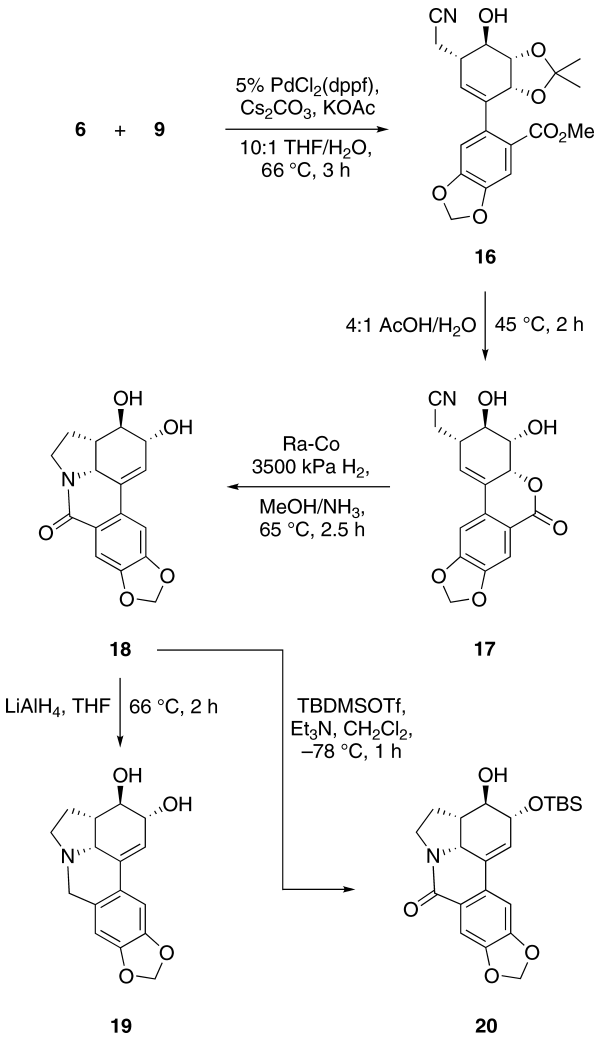
(13) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 3991.

(14) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

(15) In keeping with expectations (Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655) the 2,2-dimethyl-1,3-propanediol derived boronate **9**, which was readily prepared by the methods defined in the Supporting Information, proved a more effective coupling partner than its pinacol-derived equivalent (Matveenko, M.; Kokas, O. J.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 3683).

(16) For a related reduction process involving Raney-cobalt see: Janey, J. M.; Orella, C. J.; Njolito, E.; Baxter, J. M.; Rosen, J. D.; Palucki, M.; Sidler, R. R.; Li, W.; Kowal, J. J.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 3212.

Scheme 3



was readily removed using $LiAlH_4$ in THF and thereby affording the target **2** in 89% yield as a crystalline solid that was also subjected to single-crystal X-ray analysis (see SI for details). The melting point (mp 154−157 °C), specific rotation {$[\alpha]_D$ −64 (*c* 0.9, EtOH)}, and UV spectrum (see SI) of our sample of ether **2** were in good agreement with those recorded by Takeda and Kotera {mp 155−156 °C, $[\alpha]_D$ −80 (*c* 1.0, EtOH)}[2d] for the compound (assigned structure **2**) they obtained by manipulating dihydrolycorine.

The adaptation of the above-mentioned chemistry to the synthesis of an isomer of lycorine (and a potential precursor to the natural product) is shown in Scheme 3. Thus, Suzuki−Miyaura cross-coupling of diol **6** with boronate **9**, under conditions similar to those used for the conversion **8** + **9** → **10**, gave the expected arylcyclohexene **16** in 79% yield. Treatment of this last compound with acetic acid/water then gave lactone **17** (65−82%), and exposure of this to dihydrogen in the presence of Raney-cobalt afforded, in 51% yield, lactam **18**. Reaction of compound **18** with $LiAlH_4$ in THF then gave amine **19** (78%), the targeted isomer of lycorine.

Interestingly, reaction of diol **18** with one molar equivalent of *tert*-butyldimethylsilyl triflate (TBDMSOTf) in the presence of triethylamine gave, in 48% yield, the monosilyl ether **20** which may represent a useful intermediate en route to lycorine itself. The structure of compound **20** was confirmed by a single-crystal X-ray analysis, details of which will be described elsewhere.

The reaction sequences reported here provide ready access to the lycorine framework and should enable the preparation of a wide range of analogues of the natural product as well as compound **1**. Work directed toward the latter end is now underway, and results will be reported in due course. Since the *cis*-1,2-dihydrocatechol *ent*-**3** is readily available,[19] the present work should also provide access to the non-natural enantiomeric forms of members of the lycorine class of alkaloid.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for financial support.

Supporting Information Available: Preparative procedures and product characterization for compounds **2**, **6**−**11**, and **14**−**20** are provided together with the data derived from the single-crystal X-ray analyses of compound **2** and the *p*-nitrobenzoate of alcohol **14** (CCDC numbers 735464 and 735465, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For a review of this type of process, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(18) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171.

(19) Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1995**, 117.