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Chemoenzymatic Approaches to Lycorine-Type *Amaryllidaceae* Alkaloids: Total Syntheses of *ent*-Lycoricidine, 3-*epi*-*ent*-Lycoricidine, and 4-Deoxy-3-*epi*-*ent*-lycoricidine

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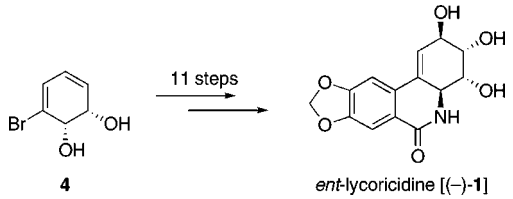
ABSTRACT



4 *ent*-lycoricidine [(−)-**1**]

The readily available and enzymatically derived *cis*-1,2-dihydrocatechol 4 has been elaborated, over 11 steps including an Overman rearrangement, into the non-natural enantiomer, (−)-1, of the alkaloid lycoricidine [(+)-1]. Related chemistries have provided analogues 18, 19, and 26.

The lycorine-type *Amaryllidaceae* alkaloids (+)-lycoricidine [(+)-**1**], (+)-narciclasine [(+)-**2**], and (+)-pancratistatin [(+)-**3**] have been known for many years and have been isolated from, inter alia, plants of the genus *Amaryllidaceae* including the bulbs of narcissi and daffodils.[1] The potent biological properties of such compounds, particularly their carcinostatic and antiviral qualities, have resulted in their being considered for use as therapeutic agents.[2] For example, (+)-pancratistatin and some of its derivatives have been the subject of preclinical development studies as agents for the treatment of certain cancers.[2] This situation, together with the limited availability of certain of these alkaloids from natural sources, has prompted a substantial body of work directed at the development of practical synthetic routes to these compounds and various analogues. The extensive efforts devoted to this matter have been the subject of a number of recent reviews.[3] Work in the area continues unabated.[4]

As part of a continuing program to exploit readily available, microbially derived and enantiomerically pure *cis*-1,2-dihydrocatechols such as **4** as starting materials in chemical synthesis,[5] we have developed and now report efficient synthetic sequences that enable the rather rapid

(1) For reviews dealing with this class of alkaloid, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p 323. (c) Jin, Z. *Nat. Prod. Rep*. **2003**, *20*, 606.

(2) For useful points on entry into the literature concerned with the biological properties of lycorine-type alkaloids and their analogues, see: (a) Pettit, G. R.; Melody, N. *J. Nat. Prod*. **2005**, *68*, 207. (b) McNulty, J.; Larichev, V.; Pandey, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315. (c) Pettit, G. R.; Eastham, S. A.; Melody, N.; Orr, B.; Herald, D. L.; McGregor, J.; Knight, J. C.; Doubek, D. L.; Pettit, G. R., III; Garner, L. C.; Bell, J. A. *J. Nat. Prod*. **2006**, *69*, 7.

(3) (a) Hudlicky, T. *J. Heterocycl. Chem*. **2000**, *37*, 535. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365. (c) Chapleur, Y.; Chrétien, F.; Ibn Ahmed, S.; Khaldi, M. *Curr. Org. Synth*. **2006**, *3*, 341.

(4) For recent synthetic efforts in this area that have not been covered in the above-mentioned reviews,[3] see: (a) Zhang, H.; Padwa, A. *Synlett* **2006**, 2317. (b) Zhang, H.; Padwa, A. *Org. Lett*. **2006**, *8*, 247. (c) Shukla, K. H.; Boehmler, D. J.; Bogacyzk, S.; Duvall, B. R.; Peterson, W. A.; McElroy, W. T.; DeShong, P. *Org. Lett*. **2006**, *8*, 4183. (d) Li, M.; Wu, A.; Zhou, P. *Tetrahedron Lett.* **2006**, *47*, 3707. (e) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830. (f) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed*. **2007**, *46*, 2303. (g) Padwa, A.; Zhang, H. *J. Org. Chem*. **2007**, *72*, 2570.

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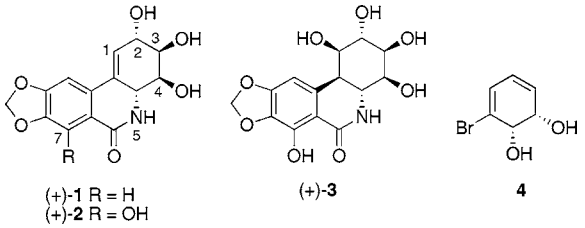
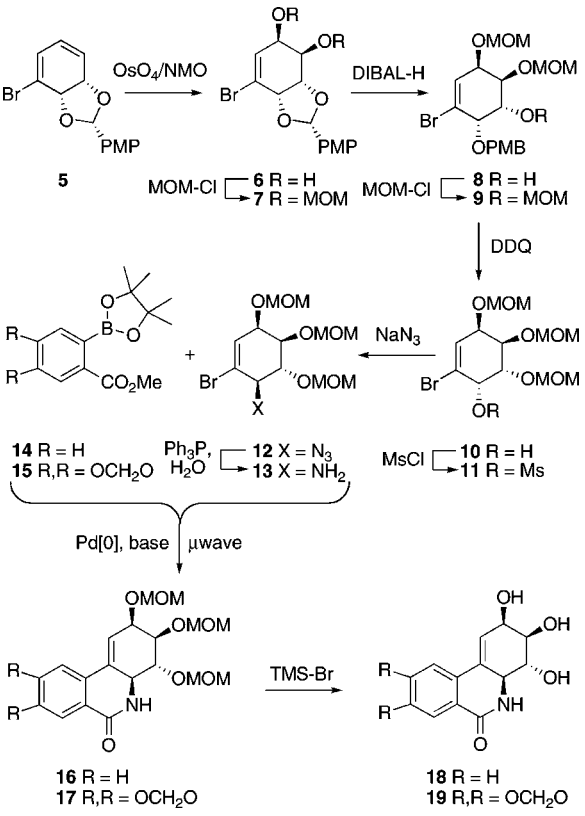
transformation of this material into *ent*-lycoricidine [(−)-**1**] and various congeners. Hudlicky and co-workers have exploited metabolite **4** and its enantiomer in cycloaddition and aziridination protocols culminating in elegant total syntheses of alkaloids **1**−**3** as well as various related (especially deoxygenated) systems.[3] The present work is distinct in that very different protocols have been applied to compound **4** in order to obtain the title compounds.



The syntheses of 3-*epi*-*ent*-lycoricidine and that analogue lacking the methylenedioxy unit are shown in Scheme 1.

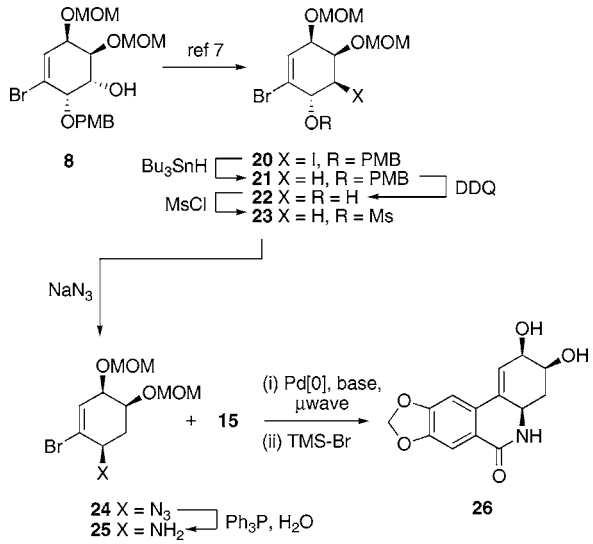
Scheme 1



Thus, *cis*-1,2-dihydroxylation of the readily accessible *p*-methoxybenzylidene acetal derivative **5**[6,7] of metabolite **4** under the UpJohn conditions[8] followed by treatment of the resulting diol (**6**) with MOM-Cl in the presence of base afforded the previously reported[7] compound **7** (59% from **5**). Treatment of this last compound with DIBAL-H resulted in essentially completely regiocontrolled cleavage of the PMP-acetal residue within the substrate and formation of the alcohol **8**[7] (84%) that was immediately protected, using standard conditions, as the corresponding MOM-ether **9** (90%). Oxidative cleavage of the PMB-ether residue within this last compound using DDQ then afforded alcohol **10** (95%), which was immediately converted into the corresponding mesylate **11** using a minor modification of the Crossland−Servis procedure.[9] Reaction of compound **11** with sodium azide afforded the expected S_N2 product **12** (95% from **10**) that was reduced to the corresponding amine **13** (99%) using the Staudinger protocol.[10] Subjection of compound **13** to reaction with the commercially available boronate ester **14** under Suzuki−Miyaura cross-coupling conditions[11] in a microwave reactor then provided the tricyclic compound **16** in 50% yield. Thus far, we have been unable to determine the precise order of events associated with the conversion **13** + **14** → **16** but presume that the cross-coupling reaction precedes the lactamization step. This last step contrasts with most other protocols[3] for establishing the lactam ring of such isocarbostyrils that often involve the application of a modified Bischler−Napieralski cyclization reaction.[3,12] Treatment of compound **16** with trimethylsilyl bromide at −30 °C[13] resulted in cleavage of the MOM-protecting groups and formation of the corresponding triol **18** (43%). Reaction of boronate **15**[14] with compound **13** under the same conditions as just described afforded the coupling product **17** (69%) that then gave 3-*epi*-*ent*-lycoricidine (**19**) (44%) upon exposure to trimethylsilyl bromide.

The synthesis of the 4-deoxy analogue of compound **19** was achieved in a similar manner (Scheme 2). Thus, treatment of alcohol **8**[7] with a mixture of triiodoimidazole, imidazole, and triphenylphosphine gave the iodide **20**[7] (81%) that was immediately reduced with tri-*n*-butyltin hydride to

Scheme 2

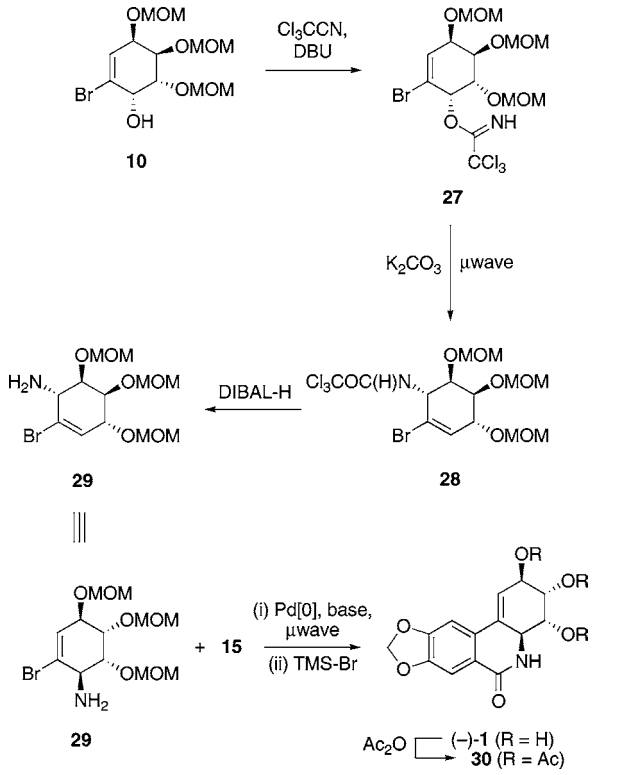


(5) For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35. (b) Banwell, M. G.; Edwards, 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.

give the iodinated system **21**[7] (85%). Subjection of the last compound to treatment with DDQ afforded alcohol **22** (96%) that was immediately converted into the corresponding mesylate **23** under standard conditions. Treatment of compound **23** with sodium azide afforded the expected product **24**[7] (76% from **22**) that was reduced directly to the amine **25**[7] (96%) under Staudinger conditions. Suzuki−Miyaura cross-coupling of this last compound with boronate ester **15** followed by treatment of the product lactam (62%) with trimethylsilyl bromide then gave 4-deoxy-3-*epi*-*ent*-lycoricidine (**26**) in 92% yield.

The synthesis of *ent*-lycoricidine [(−)-**1**] followed very similar lines (Scheme 3) and involved initial reaction of alcohol **10** with trichloroacetonitrile in the presence of DBU to give the acetimidate **27**. Subjection of this last compound to microwave irradiation in the presence of K_2CO_3[15] resulted in an Overman rearrangement[16] and the formation of the acetamide derivative **28** (65% from **10**). To the best of our knowledge the conversion **27** → **28** represents the first example of such a rearrangement that involves a halogenated alkene and that is effected by microwave irradiation. Hydrolysis of amide **28** was achieved using DIBAL-H[17] and provided amine **29** (89%) that could be subjected to a Suzuki−Miyaura cross-coupling reaction with boronate ester **15**. The ensuing lactam (83%) was treated with trimethylsilyl bromide to give *ent*-lycoricidine [(−)-**1**][18] in 62% yield. The NMR, MS, and IR spectral data derived from this material were completely consistent with those reported for both the natural product[18] and its enantiomer.[18] Similarly, the specific rotation of our material {$[\alpha]_D = -141$ (*c* 0.44, pyridine)} was consistent with that reported[18] previously {$[\alpha]_D = -164$ (*c* 0.45, pyridine) for (−)-**1**}. Final confirmation of structure followed a single-crystal X-ray analysis[19] of the derived triacetate **30** (70%): mp = 224−228 °C (lit.[18] mp = 205−210 °C); $[\alpha]_D = -196$ (*c* 0.40, $CHCl_3$) {lit.[18] $[\alpha]_D = -205$ (*c* 0.40, $CHCl_3$)}.

Scheme 3



Given the availability of the enantiomer of starting material **4**,[5] the work detailed above will also provide access to (+)-lycoricidine [(+)-**1**]. Moreover, it seems reasonable to suggest that rather straightforward modifications to these reaction sequences should permit the efficient preparation of other members of the lycorine alkaloid class. Work directed to such ends is now underway in these laboratories and results will be reported in due course.

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Supporting Information Available: Full experimental procedures; crystallographic data and atomic displacement ellipsoid plot for compound **30** (CCDC no. 648758); ^{1}H and/or ^{13}C NMR spectra of compounds **18**, **19**, **26**, **29**, (−)-**1**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Details of this analysis are provided in the Supporting Information.