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Synthesis of the Enantiomer of the Structure Assigned to the Natural Product Nobilisitine A

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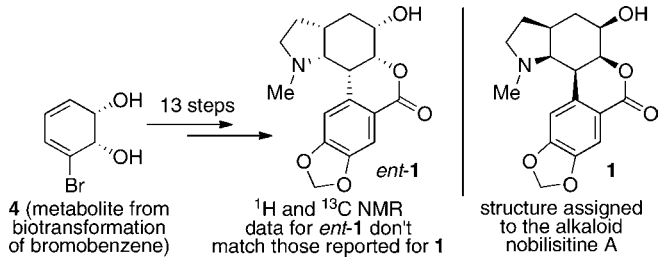
ABSTRACT



The synthesis of the enantiomer of the structure, 1, assigned to the natural product nobilisitine A has been accomplished using the enantiomerically pure *cis*-1,2-dihydrocatechol 4 as starting material. The ^{1}H and ^{13}C NMR spectral data derived from compound *ent*-1 do not match those reported for the natural product, thus suggesting its structure has been incorrectly assigned.

In 1999 Evidente and his colleagues reported on the isolation of the natural product nobilisitine A from the Egyptian ornamental plant *Clivia nobilis*.[1] On the basis of the recorded NMR, infrared, and mass spectral data, they concluded that the compound was a masanane- or lycorenine-type alkaloid possessing structure **1** (Figure 1) in which there is an "all-*cis*" arrangement of non-hydrogen substituents about the cyclohexane C-ring. Structure **1** represents a diastereoisomer of clivonine (**2**),[2] arguably the "signature" member of this small subset of *Amaryllidaecae* alkaloids. Given our interest[3] in the biogenetically and structurally related lycorine alkaloids (e.g., **3**),[4] we sought to develop syntheses of compound **1** and related systems

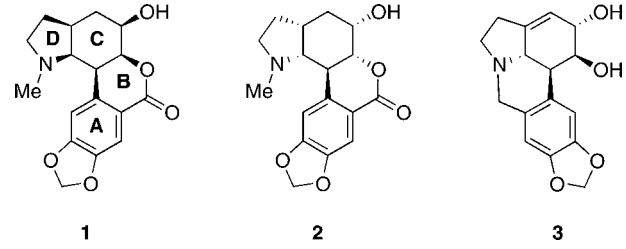


Figure 1. Structures of compounds **1**−**3**.

for the purposes of checking Evidente's structural assignment and to obtain materials for biological evaluation. In this connection, we now describe the first total synthesis of the structure *ent*-**1** and report that the derived spectral data do not match those recorded for nobilisitine A.

The opening stages of our synthesis of compound *ent*-**1** started (Scheme 1) with *cis*-1,2-dihydrocatechol **4**, an enantiomerically pure compound that is available in large

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(4) Mañas, C. G.; Paddock, V. L.; Bochet, C. G.; Spivey, A. C.; White, A. J. P.; Mann, I.; Oppolzer, W. *J. Am. Chem. Soc.* **2010**, *132*, 5176, and references cited therein.

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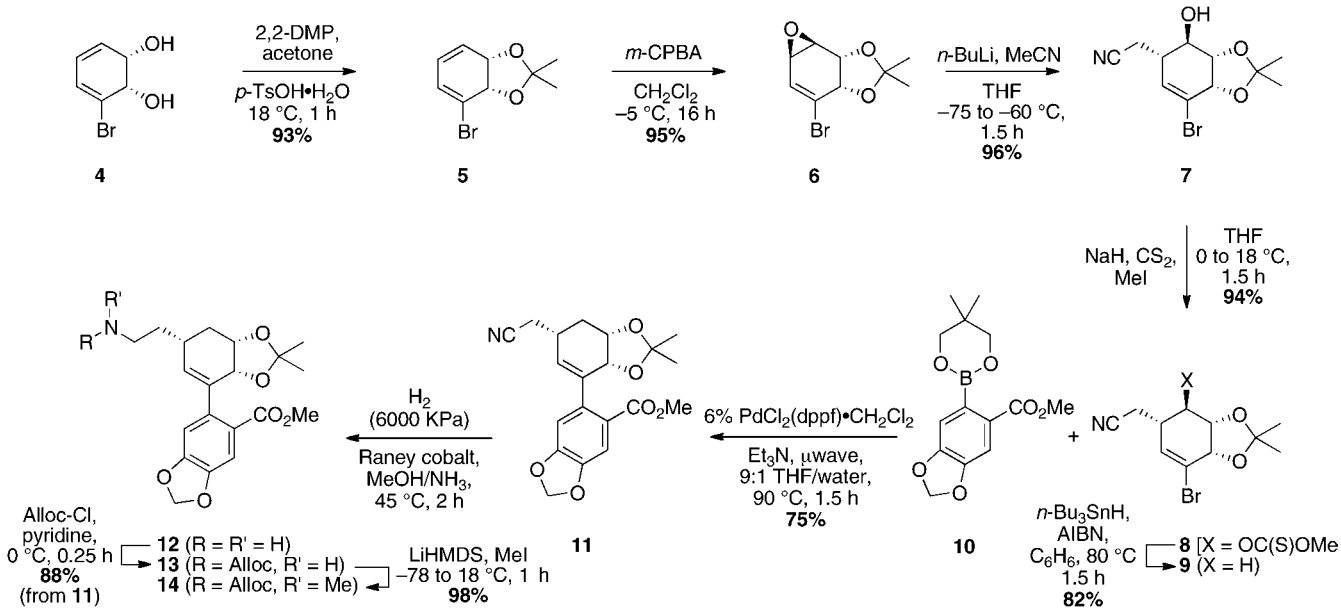
Scheme 1. Synthesis of *N*-Methyl Carbamate **14**

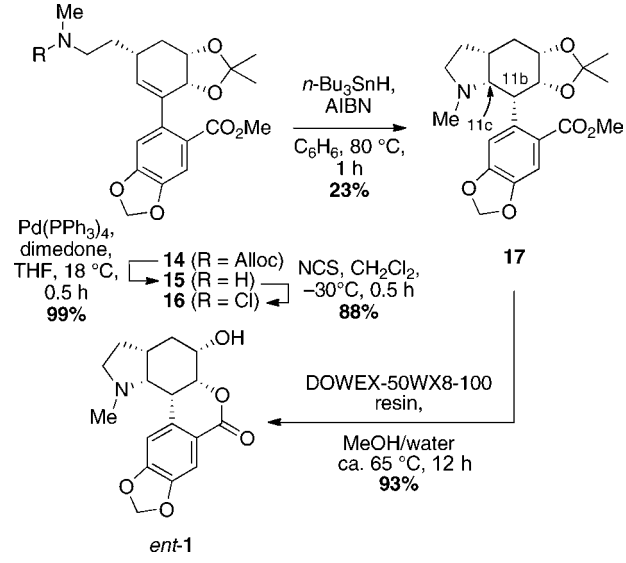


quantities via the whole-cell biotransformation of bromobenzene.[5] Thus, diol **4** was converted, under standard conditions, into the well-known[6] acetonide **5** (93%) that was then subjected to electrophilic epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA). The resulting and previously reported[6] epoxide **6** (95%), which was obtained in a completely regio- and diastereoselective manner, was then treated with the acetonitrile anion, thereby affording the γ-hydroxynitrile **7**[3] (96%) as the only isolable product of reaction. Subjection of the latter compound to a Barton−McCombie deoxygenation reaction sequence[7] provided, via the intermediate xanthate ester **8** (94%), the desired methylene-containing derivative **9**[3] (82% from **8**). Suzuki−Miyaura cross-coupling[8] of compound **9** with the readily available boronate ester **10**[3] then gave the arylated cyclohexene **11**[3] (75%), a key intermediate associated with our recently reported[3] synthesis of a lycorine degradation product.

As a prelude to installing the D-ring and associated methyl group of target *ent*-**1**, the nitrile moiety within compound **11** was reduced, in a completely chemoselective manner, to the corresponding primary amine **12** using dihydrogen in the presence of Raney cobalt.[9] Reaction of the latter compound with Alloc-Cl in the presence of pyridine gave carbamate **13** (88% from **11**) that could be *N*-methylated through its successive treatment with lithium hexamethyldisilazide (LiHMDS) and methyl iodide. Compound **14** was thereby obtained in 98% yield.

The D-ring of target *ent*-**1** was formed using a nitrogen-centered radical cyclization process.[10] The substrate required for this purpose was prepared as shown in Scheme 2. Thus, the Alloc group associated with compound **14** was cleaved

Scheme 2. Completion of the Synthesis of Lactone *ent*-**1**



(5) For reviews on methods for generating compounds such as **4** 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.

(6) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439.

(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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

(9) 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.

by treating it with $Pd(Ph_3P)_4$ in the presence of an excess of dimedone.[11] The resulting secondary amine **15** (99%) was then subjected to chlorination, at nitrogen, using *N*-chlorosuccinimide (NCS), and the *N*-chloroamine **16** so formed (88%) was treated with tri-*n*-butylstannane (*n*-Bu_3SnH, 1.1 mol equiv) and AIBN (5 mol %) in benzene at reflux. This resulted in the coproduction of the chromatographically separable reductive cyclization product **17** (23% or 77% based on recovered **15**) and the direct reduction product **15** (71% recovery).

The initial assignment of stereochemistry to the two new stereogenic centers, C11b and C11c, established within product **17** during the radical cyclization process was based on mechanistic arguments. Thus, in keeping with outcomes observed in analogous cyclization reactions involving carbon-centered radicals,[12] the formation of a *cis*-ring-fused system would be expected. Furthermore, the benzylic radical created as a result of the cyclization process would be expected to react with *n*-Bu_3SnH at the sterically less congested β-face, thereby establishing the illustrated α-orientation of the aryl group at C11b in compound **17**.

The conversion of product **17** into target *ent*-**1** was effected, in 93% yield, by treating the former compound with acidified DOWEX-50WX8-100 ion-exchange resin in water/methanol. All of the spectral data derived from lactone *ent*-**1** were in complete accord with the assigned structure, and final confirmation of the relative stereochemistry followed from a single-crystal X-ray analysis.[13] The ORTEP arising from this analysis is shown in Figure 2, while further details are presented in the Supporting Information, including the full assignment of the ^1H and ^{13}C NMR spectral data recorded for the compound.

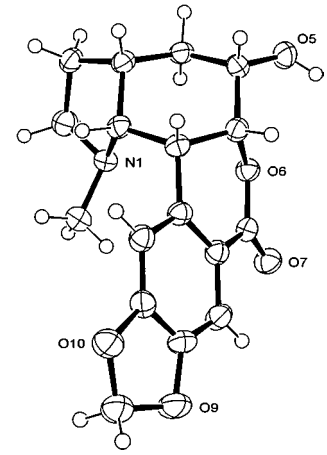


Figure 2. ORTEP derived from the single-crystal X-ray analysis of compound *ent*-**1**. Thermal ellipsoids are drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

A comparison of the ^1H and ^{13}C NMR spectral data derived from lactone *ent*-**1** with those reported[1] for nobilisitine A is presented in Table 1. This quite clearly reveals that the two compounds are different and, therefore, that the structure assigned to the title natural product is incorrect. The large difference in the chemical shifts of the resonances due to the methyl group protons (δ_H 1.45 for *ent*-**1** vs δ_H 2.24 for nobilisitine A) is particularly notable. The high-field nature of the former chemical shift can be attributed to the shielding of the *N*-methyl group in lactone *ent*-**1** by the adjacent *cis*-related arene unit. It is tempting, therefore, to assume that in the natural product a *trans*-relationship exists between the

Table 1. Comparison of the ^{13}C and ^1H NMR Data Recorded for Synthetically-Derived Lactone *ent*-**1** with those Reported for Nobilisitine A

^{13}C NMR (δ_C)		^1H NMR (δ_H)	
lactone *ent*-**1**[a]	nobilisitine A[b]	lactone *ent*-**1**[c]	nobilisitine A[d]
164.7	164.0	7.54, s, 1H	7.53, s, 1H
151.9	152.6	6.70, s, 1H	7.05, s, 1H
147.6	147.2	6.05, m, 2H	6.05, broad s, 2H
137.8	137.3	4.61, app. t, J = 2.5 Hz, 1H	4.65, dd, J = 6.6 and 5.0 Hz, 1H
121.0	118.6	3.74, ddd, J = 11.7, 3.7, and 2.9 Hz, 1H	3.96, ddd, J = 9.9, 6.6, and 5.0 Hz, 1H
109.8	109.7	3.31, td, J = 10.6 and 6.8 Hz, 1H	3.34, dd, J = 5.0 and 5.0 Hz, 1H
106.6	106.5	2.87, dd, J = 4.6 and 3.0 Hz, 1H	3.24, ddd, J = 13.6, 6.6, and 5.0 Hz, 1H
101.9	102.0	2.60, app. t, J = 4.9 Hz, 1H	2.67, dd, J = 5.8 and 5.0 Hz, 1H
78.0	81.4	2.37−2.33, complex m, 1H	2.30, m, 1H
69.7	68.6	2.26−2.22, complex m, 1H	2.24, s, 3H
67.7	66.6	1.95−1.90, complex m, 1H	2.27, m, 1H
55.0	54.9	1.88, app. q, J = 12.4 Hz, 1H	2.02, m, 1H
45.2	41.8	1.78, dt, J = 10.3 and 4.9 Hz, 1H	2.00, m, 1H
41.0	36.6	1.47−1.44, complex m, 1H	1.62, m, 2H
39.4	34.7	1.45, s, 3H	−
30.9	33.7	signal due to OH proton not observed	signal due to OH proton not observed
29.8	30.1	−	−

[a] Data recorded in $CDCl_3$ at 200 MHz. [b] Data obtained from ref 1 and recorded in $CDCl_3$ at unspecified field strength. [c] Data recorded in $CDCl_3$ at 800 MHz. [d] Data obtained from ref 1 and recorded in $CDCl_3$ at unspecified field strength.

equivalent moieties. Certainly, the chemical shift of the *N*-methyl group protons reported for nobilisitine A is more consistent with the presence of a *cis* B/C *anti*, *cis* C/D arrangement[14] of the constituent ring systems (assuming, of course, that the basic lycorenine framework assigned to this natural product is indeed correct). Efforts are now underway to determine the true structure of nobilisitine A.

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Supporting Information Available: Full experimental procedures; data derived from the single-crystal X-ray analysis of compound *ent*-**1**; and ^{1}H and ^{13}C NMR spectra of compounds **12**−**17** and *ent*-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For relevant examples of nitrogen-centered radical cyclization processes, see, for example: (a) Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1783. (b) Banwell, M. G.; Lupton, D. W. *Heterocycles* **2006**, *68*, 71.

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(12) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(13) CCDC 793455 contains the supplementary crystallographic data for compound *ent*-**1**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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