Total Synthesis of the Tetracyclic Diquinane *Lycopodium* Alkaloids Magellanine and Magellaninone

Leo A. Paquette,* Dirk Friedrich, Emmanuel Pinard, John P. Williams,[1] Denis St. Laurent, and Brian A. Roden

Evans Chemical Laboratories
The Ohio State University
Columbus, Ohio 43210

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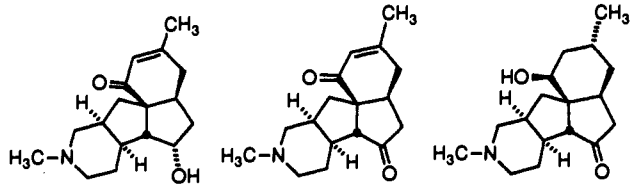
The discovery of a new class of natural products of unusual structure often forms the basis for new thrusts in organic synthesis. The isolation by Castillo, MacLean, and their co-workers of the tetracyclic *Lycopodium* alkaloids magellanine (**1**), magellaninone (**2**), and paniculatine (**3**)[2] has come to be regarded as a development of this magnitude.[3] Early synthetic efforts by a

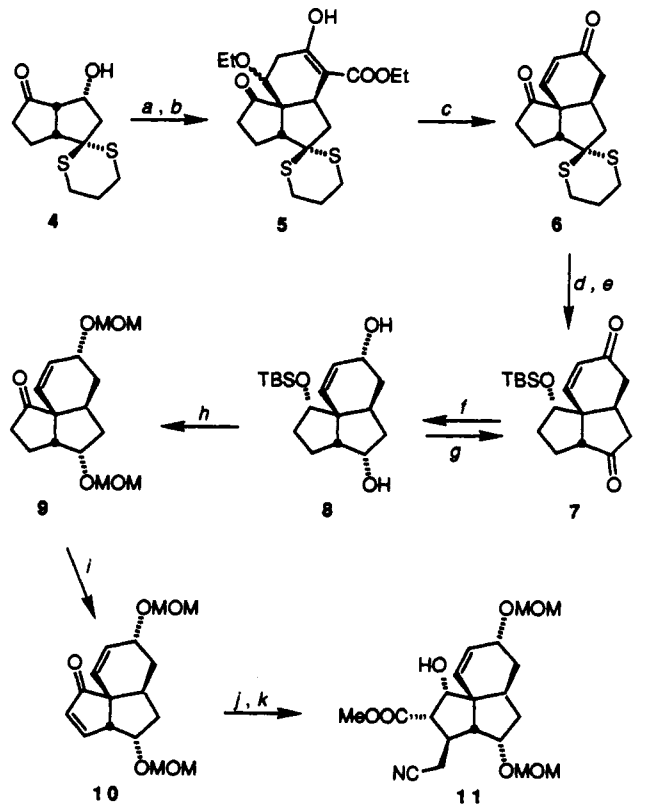


1 **2** **3**

number of research groups served to highlight several of the complexities associated with suitable assembly of these highly condensed diquinane bases.[4] The requirement for strict stereochemical control at six of the eight carbons of the bicyclo[3.3.0]octane core contributes to the challenge of molecular construction. Herein we detail completion of the syntheses of both **1** and **2** by a route which although racemic offers the option of enantioselectivity via kinetic resolution at several stages.[5]

Our synthetic plan takes advantage of the ready availability of **4** and its smooth dehydration to a highly dienophilic α,β-unsaturated ketone.[4a] When the latter was generated *in situ* in the presence of ethyl 5-ethoxy-3-oxo-4-pentenoate[6] and K_2CO_3 in THF–ethanol at room temperature, two sequential Michael reactions took place to deliver the cyclohexannulated product **5** (56%) (Scheme I). Subsequent acid-catalyzed elimination of ethanol and ester cleavage[7] led efficiently to **6**. Controlled exposure of **6** to $NaBH_4$ in ethanol resulted in highly regio- and stereoselective reduction of the cyclopentanone carbonyl (91%). This carbinol was silylated and converted to **7** (65%) by exposure to thallium(III) nitrate.[8]

Scheme I



4 **5** **6** **7** **8** **9** **10** **11**

[a] MsCl, Et_3N. [b] (*E*)-EtOCH=CHC(O)CH_2COOEt, K_2CO_3, Al_2O_3, THF/C_2H_5OH, room temperature. [c] TsOH (cat.), C_6H_6, Δ; NaCl, DMF, Δ. [d] $NaBH_4$, EtOH, CH_2Cl_2, 0 °C; TBSOTf, imid, CH_2Cl_2, room temperature. [e] $Tl(NO_3)_3$, MeOH, THF. [f] Dibal-H, CH_2Cl_2, −78 °C. [g] PCC on Al_2O_3, CH_2Cl_2, room temperature. [h] MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2; $Bu_4N^+F^-$, HMPA, 3-Å sieves, room temperature; PCC on Al_2O_3, CH_2Cl_2. [i] $LiN(SiMe_3)_2$, THF; PhSeCl; H_2O_2, py. [j] $LiCH(CN)SiMe_3$, HMPA, THF; KF, aqueous CH_3CN; LDA, NCCOOMe. [k] $NaBH_4$, MeOH, −20 °.

Diol **8** predominated when **7** was reduced with Dibal-H at −78 °C and was easily purified chromatographically. Since the remaining isomers can be reoxidized quantitatively to **7**, the stage was set for expedient elaboration of the cyclopentenone ring in **10** by application of conventional organoselenium technology. The stereochemical assignments accorded to **7**–**10** were confirmed by high-field NOE analysis of several of these intermediates.

To achieve annulation of the piperidine ring, we favored a scheme that involved conjugate addition to **10** of lithio(trimethylsilyl)acetonitrile[9] followed by C-acylation with methyl cyanoformate.[10] Gratifyingly, this pair of C–C-bond-forming reactions proceeded stereoselectively to provide a β-keto ester, which upon reduction afforded **11** exclusively (41% overall). Subsequent reductive removal of the hydroxyl group by heating of the derived selenocarbonate[11] with tris(trimethylsilyl)silane[12] and AIBN in benzene provided **12** with 87% efficiency over the two steps. The configurations of the newly introduced side chains were established by NOE studies at 300 MHz. Chemoselective reduction of the nitrile functionality was accomplished by means of cobalt(II) chloride-doped sodium borohydride.[13] Without

(1) American Cancer Society Postdoctoral Fellow, 1991–1992.

(2) Unfortunately, an aconite alkaloid has also been named paniculatine (Staehelin, E.; Katz, A. *Pharm. Acta Helv.* **1981**, *55*, 221. Katz, A.; Staehelin, E. *Tetrahedron Lett.* **1982**, *23*, 1155). Herein, our use of the name applies strictly to **3** as defined in ref 3a-d.

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(5) Professor Larry Overman has recently (Dec 10, 1992) informed us that his group has completed an enantioselective approach to **1** and **2** (Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. Submitted for publication).

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(11) (a) Pfenninger, J.; Henberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328. (b) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641. (c) Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B. *J. Chem. Soc., Chem. Commun.* **1990**, 972. (d) Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1621.

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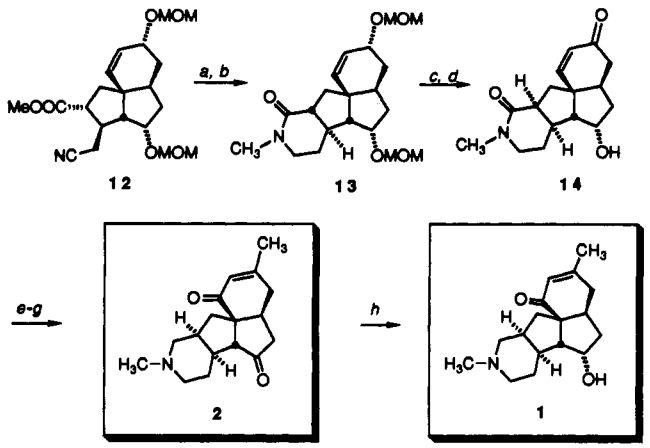
Scheme II



[a] $NaBH_4$, $CoCl_2$, CH_3OH; KOH, CH_3OH; H_3O^+. [b] NaH, CH_3I, THF. [c] LDA, THF, −78 °C → −10 °C; H_2O at −78 °C; HCl, H_2O, THF. [d] MnO_2, $CHCl_3$. [e] CH_3Li, THF, −78 °C. [f] $LiAlH_4$, THF, Δ. [g] Jones oxidation. [h] $NaBH_4$, C_2H_5OH; Ph_3P, DEAD, HCOOH, THF; 10% KOH, CH_3OH.

isolation, cyclization was readily effected upon basification. As expected, progression to the *N*-methyl derivative **13** (54% from **12**) occurred without concomitant epimerization (Scheme II). It was reasoned, however, that the enolate anion of **13** would possess sufficient encumbrance on its β face to exhibit a strong *kinetic* bias for electrophilic capture from the α direction.

Indeed, deprotonation of lactam **13** and quenching of the enolate with H_2O at −78 °C resulted in complete conversion to the cis-fused isomer, sequential acid hydrolysis and MnO_2 oxidation of which furnished **14** (47%). Thus, although the epimerization of **13** conforms also to the greater *thermodynamic* advantage normally associated with cis-fused perhydroindanes, equilibration studies on this heterocyclic congener were not pursued.

Arrival at the targeted alkaloids now required the introduction of a methyl group and proper adjustment of the oxidation levels in three of the constituent rings. The planned regioselective condensation with methyllithium proceeded without event to deliver a single tertiary allylic alcohol, which was directly reduced with $LiAlH_4$ and oxidized with Jones reagent. In this way, it was possible to effect the efficient conversion (67%) to magellaninone (**2**) without making recourse to protecting groups.

As a consequence of steric congestion on the convex surface of the bicyclo[3.3.0]octanone subunit in **2**, its sodium borohydride reduction afforded solely the 5β-alcohol (76%). This stereochemical outcome required that configurational inversion be implemented by means of the Mitsunobu reaction[14] in order to produce magellanine (**1**, 72%). The high-field ^1H and ^{13}C NMR spectra of our end products proved identical to those reported earlier,[3b,d,5] thus permitting the claim of total synthesis to be made with complete confidence.

To sum up, the structurally novel *Lycopodium* alkaloids **1** and **2** have been prepared in stereocontrolled fashion beginning with **4**. Noteworthy tactical elements include a Michael–Michael ring closure to elaborate the highly functionalized six-membered ring in **5**, a new means for constructing a piperidine part structure that has the latitude for epimerization, and economic adjustment of oxidation levels with concomitant incorporation of a methyl group late in the synthetic scheme.

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM-28468).

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(14) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *42*, 335.