First Total Synthesis of *Lycopodium* Alkaloids of the Magellanane Group. Enantioselective Total Syntheses of (-)-Magellanine and (+)-Magellaninone

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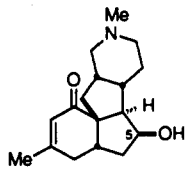
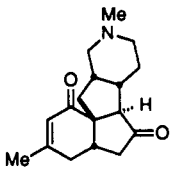
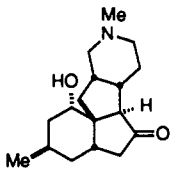
A strikingly diverse array of polycyclic alkaloids are found in club moss (genus *Lycopodium*), and these structures have long served to stimulate innovations in organic synthesis.[1,2] Some years ago investigations of *Lycopodium paniculatum* and *Lycopodium magellanicum* revealed the presence of three new alkaloids having a unique tetracyclic skeleton: magellanine (**1**), magellaninone (**2**), and lycopaniculatine (paniculatine) (**3**).[3,4] The structures of **2** and **3** were secured by X-ray crystallography,[3] while absolute configurations were assigned by optical methods.[4] In this communication we report the first total syntheses of *Lycopodium* alkaloids having the magellanane skeleton.[5-7] These total syntheses highlight the power of pinacol-terminated cationic cyclizations for assembling angularly-fused polycyclics.[6c,8]



magellanine (**1**)



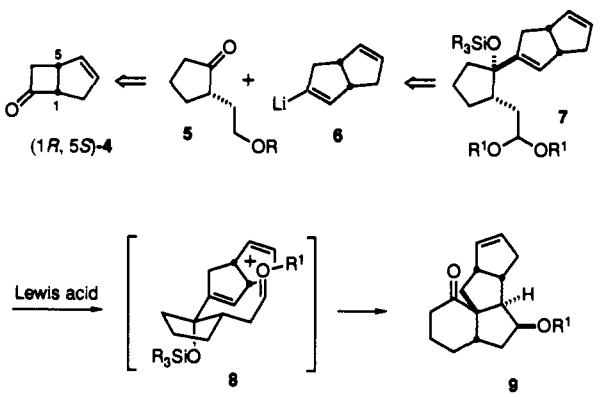
magellaninone (**2**)



paniculatine (**3**)

The angularly-fused carbotetracycle 9 was envisaged as the immediate precursor of the magellanane skeleton (Scheme I). The heart of our plan was the formation of this late intermediate by Prins-pinacol rearrangement of the dienyl acetal **7**. Central to the design of this strategy was the expectation that the desired stereochemical outcome would result if Prins cyclization took place from the convex face of the cis-fused bicyclooctadiene fragment as illustrated in cyclization conformer **8**.[6c,8] The readily available enantiopure (1*R*,5*S*)-bicyclo[3.2.0]heptenone **4**[9] would

Scheme I



serve as the common precursor of **5** and **6**, the direct progenitors of the cyclization substrate **7**.

The *cis*-bicyclo[3.3.0]octadienyl iodide **12** was prepared from **4** as summarized in Scheme II. Treatment of (+)-**4** with [bis(methylthio)methyl]lithium, followed by reaction of the resulting alcohol with $Cu(OTf)_2 \cdot C_6H_6$, as described by Cohen,[10] produced the ring-expanded α-sulfenyl ketone **10** in 70% yield and >10:1 regioselectivity.[11,12] The methylthio substituent in **10** was subsequently exploited to introduce selectively the required second unsaturation in the bicyclo[3.3.0]octane fragment. Sequential treatment of **10** with Li-NH_3, Me_3SiCl, MeLi, and *N*-phenyltriflamide[13] provided vinyl triflate **11** in 49% yield. This intermediate was then treated in turn with $Pd(Ph_3P)_4$ and hexamethylditin[14] and then *N*-iodosuccinimide[15] to afford iodide **12** in good yield. This overall sequence allowed vinyl iodide **12** to be prepared in enantiopure fashion in 27% overall yield from (+)-**4**.

Addition of the vinyllithium reagent **6** derived from **12** to the (*S*)-cyclopentanone **5**[15-17] was plagued by the propensity of cyclopentanone **5** to enolize. Enolization was minimized when this addition was carried out in Et_2O at -110 °C, conditions that afforded diol **13** and its stereoisomer (ds = 8:1) in 71% yield after desilylation. Conversion of this mixture to the bis(triethylsilyl) ethers followed by selective Swern oxidation of the primary silyl ethers[17,18] provided aldehydes **14**, which were converted to the dimethyl acetals **15** (an 8:1 mixture of stereoisomers, 72% overall yield from **13**) by treatment with trimethyl orthoformate and pyridinium *p*-toluenesulfonate in CH_2Cl_2.[19] The critical rearrangement of **15** was effected by exposure to this intermediate to 1.1 equiv of $SnCl_4$ in CH_2Cl_2 (-78 → -20 °C) to give the tetracyclic ethers **16** and **17** in a 2:1 ratio and 57% yield, together

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(1) MacLean, D. B. *Alkaloids* (*Academic Press*) **1985**, *26*, 241 and earlier reviews in this series.

(2) Blumenkopf, T. A.; Heathcock, C. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 185-240.

(3) (a) Castillo, M.; Morales, G.; Loyola, L. A.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1975**, *53*, 2513. (b) Castillo, M.; Loyola, L. A.; Morales, G.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2893. (c) Castillo, M.; Morales, G.; Loyola, L. A.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2900.

(4) Loyola, L. A.; Morales, G.; Castillo, M. *Phytochemistry* **1979**, *18*, 1721.

(5) Approaches to these alkaloids[6] and the synthesis of the tetracyclic magellanane skeleton[7] have been described.

(6) (a) St. Laurent, D. R.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 3861. (b) Mehta, G.; Rao, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1578. (c) Hirst, G. C.; Howard, P. N.; Overman, L. E. *J. Am. Chem. Soc.* **1989**, *111*, 1514. (d) Crimmins, M. T.; Watson, P. S. *Tetrahedron Lett.* **1993**, *34*, 199.

(7) Mehta, G.; Reddy, M. S. *Tetrahedron Lett.* **1990**, *31*, 2039.

(8) For brief reviews, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (b) Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; NATO ASSI Series 289; Schinzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; pp 1-20.

(9) Collington, E. W.; Wallis, C. J.; Waterhouse, I. *Tetrahedron Lett.* **1983**, *24*, 3125 and footnote 15 therein.

(10) Abraham, W. D.; Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1987**, *28*, 2203. Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 4749.

(11) All intermediates were fully characterized by ^1H and ^{13}C NMR, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. All yields refer to isolated, purified products.

(12) The abbreviations used for standard reagents can be found in the following: *J. Org. Chem.* **1992**, *57*, 14A.

(13) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

(14) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

(15) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133.

(16) Prepared from (1*R*,5*S*)-**4** by sequential treatment with (a) H_2, Pd-C, (b) *m*-CPBA, TFA, CH_2Cl_2, (c) $LiAlH_4$, (d) *tert*-butyldiphenylsilyl chloride and pyridine, and (e) the Swern reagent.[17]

(17) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(18) Mahrowald, R.; Schick, H.; Vasil'eva, L. L.; Pivnitsky, K. K.; Weber, G.; Schwartz, S. *J. Prakt. Chem.* **1990**, *332*, 169.

(19) Miyasha, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

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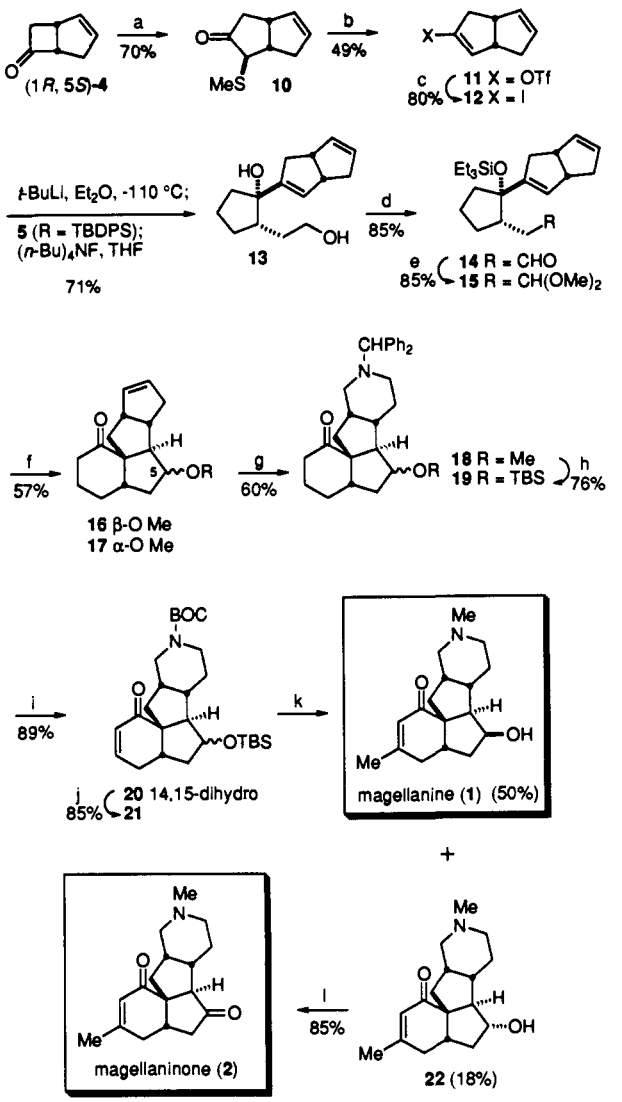
Scheme II[a]



[a] Reaction conditions: (a) $LiCH(SMe)_2$, THF, 0 °C; $Cu(OTf)_2$·PhH, $(i\text{-}Pr)_2NEt$, PhH, 50 °C. (b) Li, NH_3–THF, -40 °C; TMSCl, THF; MeLi, THF, -78 → 0 °C; $PhN(Tf)_2$, -78 → 23 °C. (c) $(Me_3Sn)_2$, $Pd(Ph_3P)_4$, LiCl, THF, 60 °C; *N*-iodosuccinimide, THF, 0 °C. (d) Et_3SiCl, imidazole, DMAP, DMF, 50 °C; Swern oxidation. (e) $(MeO)_3CH$, PPTS, CH_2Cl_2, 23 °C. (f) 1.1 equiv of $SnCl_4$, CH_2Cl_2, -78 → -23 °C. (g) OsO_4 (cat.), $NaIO_4$, dioxane–H_2O, 23 °C; Ph_2CHNH_3Cl, $NaBH_3CN$, *i*-PrOH, 23 °C. (h) Cl_3SiMe, NaI, MeCN, 80 °C; TBSCl, imidazole, DMF, 23 °C. (i) H_2, $Pd(OH)_2$, EtOAc, 23 °C; $(BOC)_2O$, Et_3N, DMAP, MeCN, 23 °C. (j) LDA, Me_3SiCl, THF, -78 °C; $Pd(OAc)_2$, MeCN, 80 °C. (k) $LiMe_2Cu$, TMEDA, Me_3SiCl, -78 → 0 °C; $Pd(OAc)_2$, MeCN, 80 °C; CF_3CO_2-H, 23 °C, concentrate; HCHO, $NaBH_3CN$, MeCN, 23 °C; HF, CH_3CN. (l) Jones oxidation, 23 °C.

with 5–15% of the corresponding C(5) alcohols.[20] This pivotal conversion establishes five of the six stereocenters of magellanine with complete stereocontrol.

Although the ether epimers **16** and **17** could be resolved on silica gel, for convenience we carried this mixture forward to the final stage of the synthesis, at which time the epimers were diverted to different natural product targets. Oxidative cleavage[21] of the cyclopentane ring followed by double reductive amination[22,23] furnished the azatetracycles **18** in 60% overall yield from the mixture of epimers **16** and **17**. Adjustment of the ether protecting group[24] to give **19** followed by cleavage of the benzhydryl group[25] and N-carbamoylation afforded **20** in 67% overall yield from **18**. The A-ring functionality was then developed in a conventional fashion. Dehydrogenation[26] provided **21**, which was treated with $LiMe_2Cu$–Me_3SiCl and $Pd(OAc)_2$[26] to afford the corresponding β-methyl enone. This intermediate was then exposed to CF_3CO_2H to cleave the BOC protecting group, the resulting secondary amine was reductively methylated, and the silyl protecting group was removed with HF in acetonitrile. Resolution on basic alumina gave (–)-magellanine (**1**), mp 162–164 °C, and C(5)-epimagellanine **22** in 50% and 18% yields, respectively. Epimagellanine **22** was then oxidized with Jones reagent to provide (+)-magellaninone (**2**) in 85% yield. Spectral data for magellanine and magellaninone closely matched literature data.[3b,4,27] Since samples of the natural isolates were not available, the structure of **1** was confirmed by single-crystal X-ray analysis of its methiodide derivative.

In summary, the first total syntheses of *Lycopodium* alkaloids of the magellanane class have been accomplished. The enantioselective total syntheses of magellanine (**1**) and magellaninone (**2**) are fully stereocontrolled and proceed in 25–26 steps from the (1*R*,5*S*)-bicyclo[3.2.0]heptenone **4**. The key strategic feature is the use of a Prins-pinacol rearrangement to assemble, with complete stereocontrol, the angular tetracyclic core of the alkaloid targets.

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Supplementary Material Available: Details of the single-crystal X-ray analysis of synthetic magellanine methiodide (**1**) (11 pages). Ordering information is given on any current masthead page.

(20) The 8:1 mixture of diastereomeric acetals was used in the rearrangement step. The four components of the product mixture were chemically converged, to establish their common carbon skeleton, by catalytic hydrogenation followed by treatment with RuO_4 which produced a single diketone. The relative stereochemistry of the methoxy epimers **16** and **17** was determined by ^1H NOE experiments.

(21) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(22) The reaction was carried out in 2-propanol instead of methanol, to minimize formation of acetals.[23]
(23) Danheiser, R. L.; Morin, J. M., Jr.; Salaski, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 8066.
(24) Olah, G. A.; Husain, A.; Balaram Gupta, B. G.; Narang, S. C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 690.
(25) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* **1988**, *27*, 1167.
(26) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(27) That synthetic **1** was enantiopure, within the limits of detection by ^1H NMR analysis at 500 MHz, was established by ^1H NMR analysis of the Mosher ester prepared from (*R*)-(–)-MPTA-Cl.[28] This derivative prepared from **1** and *rac*-MPTA-Cl showed clearly resolved signals for the methoxy groups of the two diastereomeric esters (δ 3.48 and 3.57). Comparisons of rotation data with those of the natural isolate are of limited use, since concentration was not reported for the measured rotation of **1**, M^{25}_D = –64.8° or $[\alpha]^{25}_D$ = –23.6° ($CHCl_3$),[4] and no rotation data are reported for natural **2**. Optical rotation data measured for synthetic **1** and **2** are as follows. **1**: $[\alpha]^{25}_D$ = –11.5 °, $[\alpha]^{25}_{577}$ = –15.7°, $[\alpha]^{25}_{546}$ = –19.3° (*c* = 0.47, $CHCl_3$); $[\alpha]^{25}_{577}$ = –21.7° (*c* = 0.16, $CHCl_3$). **2**: $[\alpha]^{25}_D$ = 95.0°, $[\alpha]^{25}_{577}$ = 50.6°, $[\alpha]^{25}_{546}$ = 69.8° (*c* = 0.10, $CHCl_3$).
(28) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.