# Stereoselective Total Syntheses of Three *Lycopodium* Alkaloids, (−)-Magellanine, (+)-Magellaninone, and (+)-Paniculatine, Based on Two Pauson−Khand Reactions

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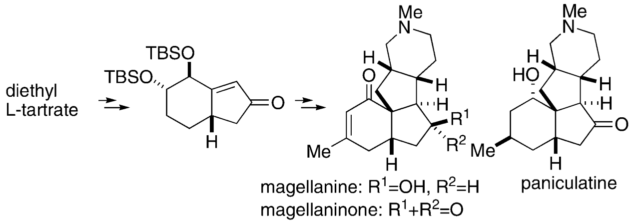
*Received October 1, 2007*

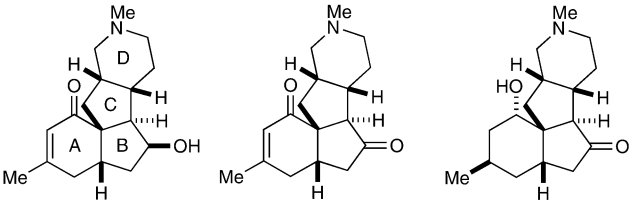


The total syntheses of (−)-magellanine, (+)-magellaninone, and (+)-paniculatine were completed from diethyl L-tartrate via the common intermediate in a stereoselective manner. The crucial steps in these syntheses involved two intramolecular Pauson−Khand reactions of enynes: the first Pauson−Khand reaction constructed the bicyclo[4.3.0] carbon framework, the corresponding A and B rings of these alkaloids in a highly stereoselective manner, whereas the second Pauson−Khand reaction stereoselectively produced the bicyclo[3.3.0]skeleton, which could be converted into the C and D rings of the target natural products.

## Introduction

Three alkaloids, magellanine (**1**),[1] magellaninone (**2**),[2] and paniculatine (**3**),[3] which have a 6-5-5-6 tetracyclic framework with five to seven stereogenic centers as a common structural feature, were isolated from *Lycopodium paniculatum* and *Lycopodium magellanicum* in the mid to late 1970s (Scheme 1). Because of their unique and challenging structures, several studies[4] on the construction of the core tetracyclic skeleton of these alkaloids have been reported. In 1994, Overman[5] completed the first total synthesis of (−)-magellanine (**1**) and (+)-magellaninone (**2**) possessing contiguous six and five stereogenic centers, respectively, via a Prins-pinacol rearrangement, whereas the total synthesis, based on a tandem Michael−Michael addition, of both alkaloids in a racemic form was accomplished by Paquette[6] in the same year.[6a] The masked *o*-benzoquinone Diels−Alder protocol enabled Liao[7] to complete the total synthesis of (±)-**1**. Recently, Ishizaki[8] completed the formal

**SCHEME 1. Structure of Magellanine (1), Megellaninone (2), and Paniculatine (3)**



magellanine (**1**) magellaninone (**2**) paniculatine (**3**)

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[1] Castillo, M.; Loyola, L. A.; Morales, G.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2893−2899.

[2] Loyola, L. A.; Morales, G.; Castillo, M. *Phytochemistry* **1979**, *18*, 1721−1723.

[3] (a) Castillo, M.; Morales, G.; Loyola, L. A.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1975**, *53*, 2513−2514. (b) Castillo, M.; Morales, G.; Loyola, L. A.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2900−2908.

[4] (a) Mehta, G.; Reddy, M. S. *Tetrahedron Lett.* **1990**, *31*, 2039−2042. (b) Sandham, D. A.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2511−2512. (c) Mehta, G.; Reddy, M. S.; Thomas, A. *Tetrahedron* **1998**, *54*, 7865−7882.

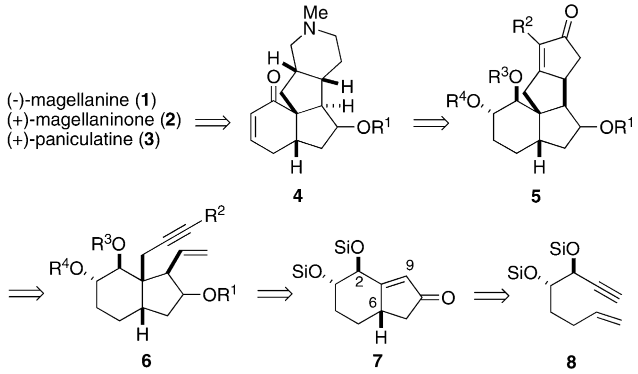
[5] Hirst, G. C.; Johnson, T. O., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992−2993.

[6] (a) Paquette, L. A.; Friedrich, D.; Pinard, E.; Williams, J. P.; St. Laurent, D.; Roden, B. A. *J. Am. Chem. Soc.* **1993**, *115*, 4377−4378. (b) Williams, J. P.; St. Laurent, D. R.; Friedrich, D.; Pinard, E.; Roden, B. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 4689−4696.

[7] Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090−4093.

10.1021/jo702136b CCC: $37.00

**SCHEME 2. Retrosynthesis of Magellanine (1), Magellaninone (2), and Paniculatine (3)**



total synthesis of (±)-magellanine (**1**) based on the intramolecular Pauson−Khand reaction (PKR) for the preparation of the two five-membered rings (B and C rings). In addition, the first total synthesis of (+)-paniculatine (**3**) having seven chiral centers was achieved by the tandem radical cyclization of α-carbonyl radicals by Sha's group.[9]

We have recently been involved in the investigation of not only the stereoselective $Co_2(CO)_8$-mediated intramolecular PKR of enynes resulting in the efficient formation of the bicyclo[3.3.0]octenone and bicyclo[4.3.0]nonenone frameworks[10] but also the Rh(I)-catalyzed intramolecular Pauson−Khand-type reaction of allenynes,[11] which led to the development of a novel method for the construction of the bicyclo[6.3.0] as well as the bicyclo[5.3.0] skeletons. As an extension of our work in this area, we now describe the stereoselective total syntheses of (−)-magellanine (**1**), (+)-magellaninone (**2**), and (+)-paniculatine (**3**), which involve a significantly different strategy (the two PKR as the crucial steps) for the construction of the core tetracyclic skeleton from those of the previously reported ones.[5−9] Our retrosynthetic analysis is depicted in Scheme 2. The 6-5-5-6 tetracyclic enone **4** was envisioned as the common synthetic intermediate for the transformation into the three target alkaloids. The piperidine ring containing tetracyclic framework **4** would be derived from the angularly fused 6-5-5-5 carbotetracycle **5**, which might be assembled by the intramolecular PKR (the second PKR) of the bicyclic compound **6**. The enyne **6** might be derived from the bicyclo[4.3.0]nonenone **7** via the stereoselective introduction of the angular propynyl side chain as well as a vinyl functionality at the $C_9$-position by taking advantage of the $C_2$-hydroxyl functionality. The first PKR of the enyne **8**,[10e] derived from diethyl L-tartrate, could provide the bicyclo[4.3.0] derivative **7** in a stereoselective manner.

## Results and Discussion

Our work began with the improvement of the stereoselectivity in the PKR of **9**, which previously provided the desired bicyclo[4.3.0] compound **10** in 75% yield along with its isomer in 10% yield (88:12) under thermal conditions.[10e] After screening various PKR conditions, Sugihara's procedure ($Me_2S$, $(CH_2Cl)_2$, 45 °C)[12] was found to be the best one for the enyne **9** giving rise to the highly preferential production of **10** (89%) over that of its isomer (3%).[13] The efficient and stereoselective construction of the quaternary stereogenic center at the $C_1$-position of **10** was the next subject for our synthesis. We first examined the direct introduction of alkyl appendages at the $C_1$-position of **10** by the Michael addition under various conditions, but no desired products could be obtained. On the other hand, the simultaneous and stereoselective introduction of the essential alkyl appendages at not only the $C_1$-position but also the $C_9$-position was realized by the Ueno−Stork reaction.[14] Selective deprotection of the $C_2$-siloxy group of **10** with TBAF furnished **11** in 99% yield. The allyl alcohol **11** was treated with ethyl 2-bromovinyl ether under the acidic conditions, and the resulting bromoacetal derivative was subsequently exposed to the conventional radical condition (AIBN in refluxing benzene) in the presence of allyltributyltin to give the tricyclic compound with the quaternary carbon center at the $C_1$-position and an allyl group at the $C_9$-position, respectively. Chemical transformation of thus formed five-membered acetal moiety into the γ-lactone functionality was achieved by exposure to *m*CPBA and $BF_3{\cdot}OEt_2$[15] to yield the corresponding *cis*-fused γ-lactone derivative **12**[16] in 65% overall yield. Thus, we succeeded in the stereoselective introduction of carbon appendages at both $C_1$- and $C_9$-positions from a convex face by taking advantage of the $C_2$-hydroxyl functionality. Stereoselective reduction of **12** with $NaBH_4$ was followed by protection with the MOM group[17] to exclusively afford **13** in 90% yield. The allyl group at the $C_9$-position of **13** was transformed into a vinyl group by successive ozonolysis,

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(8) (a) Ishizaki, M.; Niimi, Y.; Hoshino, O. *Terahedron Lett.* **2003**, *44*, 6029−6031. (b) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, Y. *Tetrahedron* **2005**, *61*, 4053−4065.

(9) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875−9876.

(10) (a) Mukai, C.; Uchiyama, M.; Hanaoka, M. *J. Chem. Soc., Chem. Commun*. **1992**, 1014−1015. (b) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761−5764. (c) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903−2915. (d) Mukai, C.; Kim, J. S.; Uchiyama, M.; Hanaoka, M. *Tetrahedron Lett.* **1998**, *39*, 7909−7912. (e) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem*. **1999**, *64*, 6822−6832. (f) Mukai, C.; Sonobe, H.; Kim, J. S.; Hanaoka, M. *J. Org. Chem*. **2000**, *65*, 6654−6659. (g) Mukai, C.; Kobayashi, M.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225−5230. (h) Mukai, C.; Kozaka, T.; Suzuki, Y.; Kim, I. J. *Tetrahedron Lett.* **2002**, *43*, 8575−8578. (i) Nomura, I.; Mukai, C. *Org. Lett*. **2002**, *4*, 4301−4304. (j) Mukai, C.; Kozaka, T.; Suzuki, Y.; Kim, I. J. *Tetrahedron* **2004**, *60*, 2497−2507. (k) Nomura, I.; Mukai, C. *J. Org. Chem*. **2004**, *69*, 1803−1812.

(11) (a) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755−1758. (b) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem*. **2003**, *68*, 1376−1385. (c) Mukai, C.; Inagaki, F.; Yoshida, T.; Kitagaki, S. *Tetrahedron Lett.* **2004**, *45*, 4117−4121. (d) Mukai, C.; Inagaki, F.; Yoshida, T.; Yoshitani, K.; Hara, Y.; Kitagaki, S. *J. Org. Chem*. **2005**, *70*, 7159−7171. (e) Mukai, C.; Hirose, T.; Teramoto, S.; Kitagaki, S. *Tetrahedron* **2005**, *61*, 10983−10994. (f) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett*. **2006**, *8*, 83−86. (g) Inagaki, F.; Mukai, C. *Org. Lett*. **2006**, *8*, 1217−1220. (h) Inagaki, F.; Kawamura, T.; Mukai, C. *Tetrahedron* **2007**, *63*, 5154−5160.

(12) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771−773.

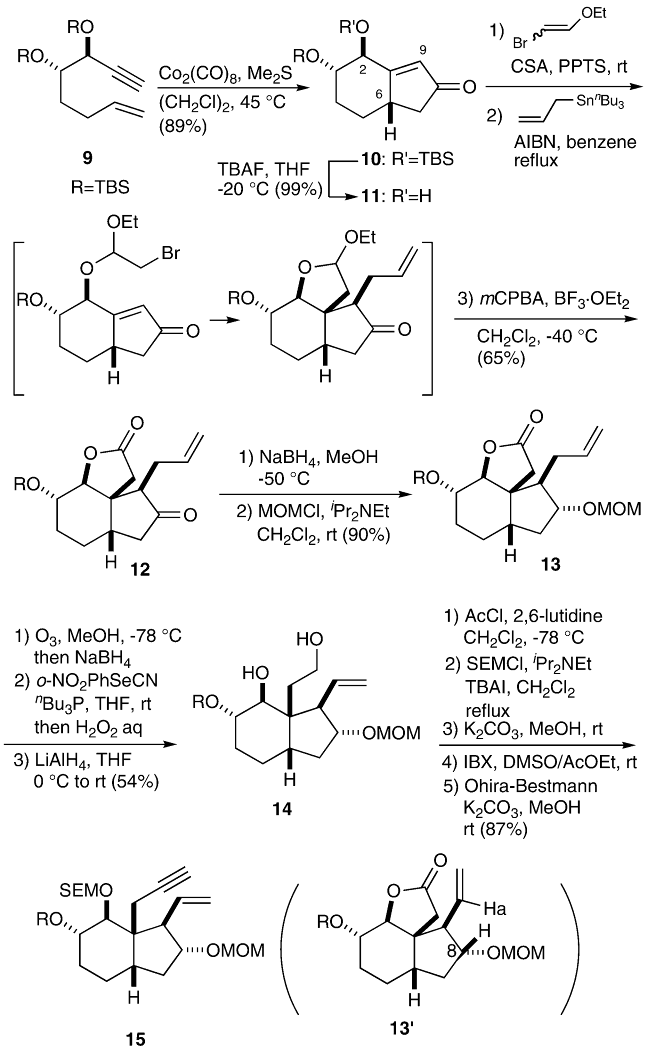
(13) The product ratio of **10** to its epimer was markedly improved to 97:3.

(14) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. (b) Wakamatsu, T.; Hara, H.; Ban, Y. *J. Org. Chem.* **1985**, *50*, 108−112. (c) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351−1356. (d) Stork, G.; Mook, Jr., R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. (e) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304. (f) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384−6385. (g) Stork, G. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 149−154. (h) Stork, G. *Bull. Soc. Chim. Fr.* **1990**, *127*, 675−680. (i) For review; Salom-Roig, X. J.; Dénès, F.; Renaud, P. *Synthesis* **2004**, 1903−1928.

(15) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *19*, 419−420.

(16) The newly generated stereogenic centers ($C_1$ and $C_9$) of compound **12** were confirmed by an NOE experiment. Thus, irradiation of the $C_2$-H of **12** produced a 3.3% enhancement of the $C_9$-H.

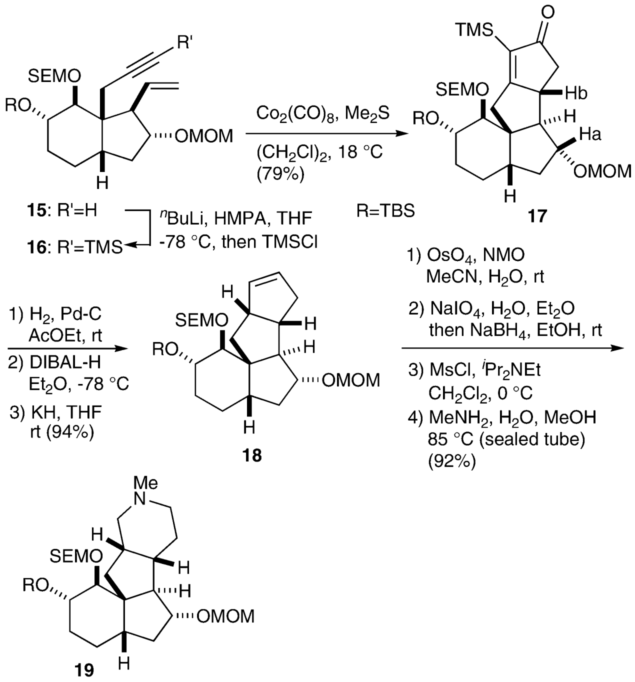
**SCHEME 3. Synthesis of Enyne Precursor 15 to the Second PKR**



reduction, and Grieco olefination,[18] followed by $LiAlH_4$ reduction, to produce the diol derivative **14** in 54% yield. The propargyl functionality at the $C_1$-position, which is essential for the second PKR, was prepared by manipulation involving protection of the secondary hydroxyl group of **14**, oxidation of the primary alcohol into the aldehyde, and treatment with Ohira−Bestmann reagent[19] to give the desired enyne **15** in 87% overall yield (Scheme 3).

With the enyne **15** in hand, our endeavor focused on the second PKR, which should provide a 6-5-5-5 carbotetracycle, a precursor for the core 6-5-5-6 tetracyclic ring system of the target natural products. Prior to carrying out the second PKR, a TMS group was introduced at the triple bond terminus of **15** by taking into account the Peterson olefination[20] for the regioselective introduction of a double bond during a subsequent stage. The resulting TMS derivative **16** again underwent Sugihara's conditions[12] to stereoselectively produce the tetracyclic compound **17** with the proper stereochemistry[21] in 79% yield from **15** along with its epimer (16%).[22] Other conventional Pauson−Khand conditions afforded **17** with a rather low selectivity. The hydrogenation of **17** was followed by reduction of the carbonyl group to provide the secondary hydroxyl compound, the Peterson olefination[20] of which with KH easily proceeded to provide **18** in 94% yield as anticipated. The next phase of this synthesis was confronting the construction of the piperidine ring (D ring). According to the precedents,[5,7] the dihydroxylation of **18** with $OsO_4$, followed by treatment with $NaIO_4$ and $NaBH_4$, gave the tricyclic diol derivative, which was then exposed to mesyl chloride and methylamine to produce the piperidine derivative **19** in 92% overall yield (Scheme 4).

**SCHEME 4. Synthesis of Piperidine Derivative 19**



Finally, elaboration of the required functionalities on both the A and B rings remained before completing the total synthesis. First, introduction of the double bond was achieved by (i) selective removal of the TBS group of **19** by TBAF, (ii) activation of the resulting hydroxyl group as a mesylate, and (iii) E2-type elimination by treatment with DBU to give **20** in 80% yield. Cesium fluoride at 170 °C in DMF effected the removal of the 2-(trimethylsilyl)ethoxymethyl group of **20** to furnish the allyl alcohol, which was oxidized with Dess-Martin periodinane (DMP) affording **21** in 65% yield. Thus, the plausible common synthetic intermediate **21** in our protocol was stereoselectively prepared. The α,*β*-unsaturated compound **21**

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(17) The stereochemical assignment of the secondary hydroxyl moiety was established by an NOE experiment of compound **13′**, which is an intermediate during the conversion of **13** to **14**. Thus, irradiation of the $C_8$-H produced a 4.5% enhancement of the Ha on a vinyl moiety.

(18) (a) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947−949. (b) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486. (c) Reich, H.J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697−1705.

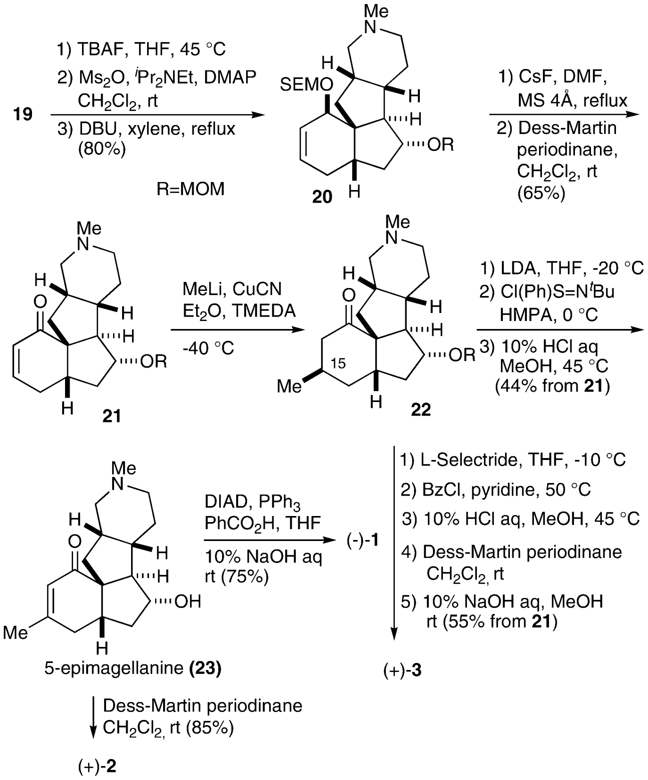
(19) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522. (c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59−62.

(20) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784. (b) Subburaj, K.; Okamoto, S.; Sato, F. *J. Org. Chem.* **2002**, *67*, 1024−1026.

(21) An NOE experiment of **17** revealed a 9.4% enhancement between Ha and Hb, strongly indicating that the newly generated stereogenic center must be (*R*). The stereoselective formation of **17** might be tentatively rationalized on the basis of the mechanistic hypothesis for the intramolecular PKR proposed by Magnus, the same as the interpretation for the stereoselective construction of compound **10**;[10e] see: (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854. (b) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861−5869.

(22) The ratio between compound **17** and its epimer is 83 to 17.

**SCHEME 5. Completion of Total Synthesis of (−)-Magellanine (1), (+)-Magellaninone (2), and (+)-Paniculatine (3)**



was susceptible to the highly stereoselective 1,4-conjugate addition with $Me_2Cu(CN)Li_2$ to furnish **22**,[23] which was then oxidized with *N*-*tert*-butylbenzenesulfinimidoyl chloride[24] to produce, after removal of the MOM group, 5-epimagellanine (**23**)[25] in 44% yield from **21**.[26] The standard Mitsunobu reaction of **23**, followed by basic hydrolysis, provided (−)-magellanine (**1**) in 75% yield, whereas the oxidation of **23** with DMP produced (+)-magellaninone (**2**) in 85% yield.[27,28] On the other hand, compound **22** was transformed into (+)-paniculatine (**3**) as follows. The stereoselective reduction of **22**[23] with L-Selectride gave the corresponding alcohol with the desired stereochemistry, which was subsequently protected with a benzoyl group.[29] The MOM group on the secondary hydroxyl group of the B ring was then removed by acid treatment, and the resulting hydroxyl derivative was successively oxidized with DMP to afford, after removal of the benzoyl group, (+)-**3**[30] in 55% overall yield (Scheme 5).

In conclusion, we have completed the total syntheses of three *Lycopodium* alkaloids, (−)-magellanine (**1**), (+)-magellaninone (**2**), and (+)-paniculatine (**3**), from diethyl L-tartrate in a stereoselective manner (**1**, 43 steps, 1.7% overall yield; **2**, 43 steps, 1.9% overall yield; **3**, 45 steps, 2.8% overall yield). The noteworthy tactical feature of our synthesis involves the two PKR of enynes, which enabled us to accomplish the new total synthesis of these three alkaloids.

## Experimental Section

**(2*S*,3*S*,6*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)bicyclo[4.3.0]non-1(9)-en-8-one ((−)-10).** To a solution of (−)-**9** (937 mg, 2.54 mmol) in 1,2-dichloroethane (51 mL) was added $Co_2(CO)_8$ (1.04 g, 3.05 mmol) at room temperature. After being stirred for 30 min at the same temperature, dimethyl sulfide (1.9 mL, 25 mmol) was added to the reaction mixture and stirred for additional 12 h at 45 °C. The reaction mixture was passed through a short pad of silica gel with hexane−AcOEt (2:1), and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (10:1) to give (−)-**10**[10e] (896 mg, 89%) as a colorless oil and the (+)-epimer[10e] of (−)-**10** (32.8 mg, 3%) as colorless solids.

**(2*S*,3*S*,6*S*)-3-*tert*-Butyldimethylsilyloxy-2-hydroxybicyclo[4.3.0]non-1(9)-en-8-one ((−)-11).** To a solution of (−)-**10** (656 mg, 1.65 mmol) in THF (1.7 mL) was added dropwise TBAF (1.0M in THF; 2.0 mL, 2.0 mmol) at −20 °C. The reaction mixture was stirred for 12 h at the same temperature, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (4:1) to give (−)-**11** (461 mg, 99%) as colorless needles: mp 95.5−96.0 °C (hexane); $[\alpha]^{26}_{D}$ −188.5 (*c* 1.74, $CHCl_3$); IR 1705, 1632 cm$^{-1}$; $^1$H NMR $\delta$ 5.94 (d, 1H, $J = 1.2$ Hz), 4.44 (d, 1H, $J = 3.1$ Hz), 4.08−4.05 (m, 1H), 3.11 (s, 1H), 3.06−2.99 (m, 1H), 2.51 (dd, 1H, $J = 18.9$, 6.1 Hz), 2.08−2.00 (m, 1H), 1.97 (dd, 1H, $J = 18.9$, 1.8 Hz), 1.89−1.84 (m, 1H), 1.62−1.57 (m, 1H), 1.56−1.46 (m, 1H), 0.81 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR $\delta$ 209.9, 182.2, 129.9, 71.7, 70.1, 42.2, 37.2, 28.8, 27.3, 25.6, 17.9, −4.9, −5.0; FAB MS *m*/*z* 283 (M$^+$ + 1, 25.5). FAB HRMS calcd for $C_{15}H_{27}O_3Si$ 283.1730, found 283.1726. Anal. Calcd for $C_{15}H_{26}O_3Si$: C, 63.78; H, 9.28. Found: C, 63.65; H, 9.34.

**(1*S*,5*S*,6*S*,9*S*,12*R*)-6-*tert*-Butyldimethylsilyloxy-12-(2-propenyl)-4-oxatricyclo[7.3.0.0$^{1,5}$]dodecane-3,11-dione ((−)-12).** To a suspension of (−)-**11** (5.93 g, 21.0 mmol) and ethyl 2-bromovinyl ether (6.34 g, 42.0 mmol) were added PPTS (527 mg, 2.10 mmol) and camphorsulfonic acid (487 mg, 2.10 mmol) at room temperature. The reaction mixture was stirred for 6 h at the same temperature, quenched by addition of $Et_3N$ and saturated aqueous

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(23) Compound **22** was obtained as an inseparable mixture with its epimer in the ratio of 93:7 (by $^1$H NMR analysis). This mixture was used for further reactions.

(24) Mukaiyama, T.; Matsuo, J.; Kitagawa, H. *Chem. Lett.* **2000**, 1250−1251.

(25) The structure of synthetic (−)-5-epimagellanine (**23**) was confirmed by comparison with $^1$H and $^{13}$C NMR spectral data of the racemic **23**.[6]

(26) A mixture of **22** and its epimer (93:7) was recovered in 16% yield after exposure to the Matsuo's reagent. Thus, the chemical yield of **23** might be described to be 52% overall yield from **21** based on the recovery of the starting material.

(27) The synthetic (−)-magellanine (**1**) was a colorless solid, mp 160−161°C (AcOEt), and revealed $[\alpha]^{30}_{D}$ −20.3 (*c* 0.14, $CHCl_3$) [natural product[1] was a colorless solid, mp 165−166°C (AcOEt), and revealed $M^{25}_{D}$ −64.8 (specific rotation was not reported); Overman's product[5] was a solid, mp 162−164°C, and revealed $[\alpha]^{25}_{D}$ −11.5 (*c* 0.47, $CHCl_3$)]. The structure of synthetic magellanine was confirmed by comparison not only with spectral data but also with $^1$H and $^{13}$C NMR spectra of natural (−)-magellanine.

(28) The synthetic (+)-magellaninone (**2**) was an oil and revealed $[\alpha]^{30}_{D}$ +82.6 (*c* 0.16, $CHCl_3$) [natural product[2] was an oil and specific rotation was not reported; Overman's product[5] was an oil and revealed $[\alpha]^{25}_{D}$ +95.0 (*c* 0.10, $CHCl_3$)]. The structure of synthetic magellaninone was confirmed by comparison with spectral of natural (+)-magellaninone.

(29) The benzoyloxy derivative could be isolated as a single isomer by passing through a short pad of alumina with AcOEt. The $C_{15}$-methyl carbon resonated at $\delta$ 22.3 in the $^{13}$C NMR spectrum, indicating that the methyl group should take an equatorial position rather than an axial position (see Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 6612−6622). Furthermore, the stereochemistry of the newly generated stereogenic center by L-Selectride reduction could be deduced on the basis of the literature precedent[9] and finally confirmed by conversion into paniculatine.

(30) The synthetic (+)-paniculatine (**3**) was a colorless solid, mp 178−179°C (acetone), and revealed $[\alpha]^{30}_{D}$ +75.1 (*c* 0.17, $CHCl_3$) [natural product[3] was a colorless solid, mp 180−181°C (acetone), and revealed $M_D$ +159.8 (specific rotation was not reported); Sha's product[9] was a solid, mp 117−118°C, and revealed $[\alpha]^{26}_{D}$ +66.0 (*c* 0.20, $CHCl_3$)]. The structure of synthetic paniculatine was confirmed by comparison not only with spectral data but also with $^1$H and $^{13}$C NMR spectra of natural (+)-paniculatine.

$NaHCO_3$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (10:1) to give the crude bromoacetal. To a solution of the crude bromoacetal in benzene (210 mL) were added allyltributyltin (6.53 mL, 63.0 mmol) and AIBN (218 mg, 2.10 mmol) at room temperature. The reaction mixture was refluxed for 12 h. After evaporation of the solvent, the residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to afford the crude acetal. To a solution of the crude acetal in $CH_2Cl_2$ (100 mL) were added *m*CPBA (7.00 g, 40.6 mmol) and $BF_3{\cdot}OEt_2$ (5.20 mL, 40.6 mmol) at −40 °C. The reaction mixture was stirred for 1 h at the same temperature, quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with 1 N aqueous NaOH, water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (5:1) to give (−)-**12** (4.98 g, 65% from (−)-**11**) as a colorless oil: $[\alpha]^{28}_{D}$ −19.4 (*c* 2.69, $CHCl_3$); IR 1788, 1763, 1740, 1641 $cm^{-1}$; $^1H$ NMR $\delta$ 5.91−5.82 (m, 1H), 5.15−5.07 (m, 2H), 4.43 (d, 1H, *J* = 2.7 Hz), 4.28−4.25 (m, 1H), 3.03−2.99 (m, 1H), 2.71, 2.12 (ABq, 2H, *J* = 16.6 Hz), 2.63−2.56 (m, 1H), 2.42 (dd, 1H, *J* = 19.3, 8.3 Hz), 2.16−1.97 (m, 3H), 1.79−1.61 (m, 3H), 1.51−1.45 (m, 1H), 0.88 (s, 9H), 0.093 (s, 3H), 0.087 (s, 3H); $^{13}C$ NMR $\delta$ 215.9, 174.3, 135.8, 117.2, 80.1, 66.2, 48.4, 48.1, 42.3, 37.3, 36.6, 30.8, 26.7, 25.7, 21.9, 17.8, −5.0, −5.3; FAB MS *m*/*z* 365 ($M^+$ + 1, 27.2). FAB HRMS calcd for $C_{20}H_{33}O_4Si$ 365.2148, found 365.2149.

**(1*S*,5*S*,6*S*,9*S*,11*R*,12*R*)-6-*tert*-Butyldimethylsilyloxy-11-methoxymethoxy-12-(2-propenyl)-4-oxatricyclo[7.3.0.0$^{1,5}$]dodecan-3-one ((+)-13).** To a solution of (−)-**12** (204 mg, 0.559 mmol) in MeOH (5.6 mL) was added $NaBH_4$ (106 mg, 2.80 mmol) at −50 °C. The reaction mixture was stirred for 1 h at the same temperature, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with water and brine, dried, and concentrated to afford the crude alcohol. To a solution of the crude alcohol in $CH_2Cl_2$ (5.0 mL) were added $^iPr_2NEt$ (0.30 mL, 1.7 mmol) and MOMCl (0.08 mL, 1.1 mmol) at room temperature. The reaction mixture was stirred for 14 h at the same temperature, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (10:1) to give (+)-**13** (206 mg, 90% from (−)-**12**) as a colorless oil: $[\alpha]^{29}_{D}$ +0.67 (*c* 9.93, $CHCl_3$); IR 1782, 1763, 1641 $cm^{-1}$; $^1H$ NMR $\delta$ 5.83−5.73 (m, 1H), 5.04−4.92 (m, 2H), 4.51, 4.48 (ABq, 2H, *J* = 6.6 Hz), 4.24 (d, 1H, *J* = 2.9 Hz), 4.08−4.06 (m, 1H), 3.66−3.61 (m, 1H), 3.26 (s, 3H), 2.64−2.58 (m, 1H), 2.49, 1.96 (ABq, 2H, *J* = 16.6 Hz), 2.22−2.06 (m, 3H), 1.88−1.79 (m, 1H), 1.67−1.62 (m, 1H), 1.56−1.53 (m, 2H), 1.47−1.40 (m, 1H), 1.35−1.29 (m, 1H), 0.84 (s, 9H), 0.02 (s, 6H); $^{13}C$ NMR $\delta$ 175.1, 136.9, 115.8, 95.6, 82.4, 81.2, 66.7, 55.3, 50.1, 45.9, 41.0, 37.3, 35.7, 34.4, 27.1, 25.6, 22.5, 17.7, −5.2, −5.3; FAB MS *m*/*z* 411 ($M^+$ + 1, 11.0). FAB HRMS calcd for $C_{22}H_{39}O_5Si$ 411.2567, found 411.2575.

**(1*S*,2*S*,3*S*,6*S*,8*R*,9*R*)-3-*tert*-Butyldimethylsilyloxy-9-ethenyl-1-(2-hydroxyethyl)-8-methoxymethoxybicyclo[4.3.0]nonan-2-ol ((+)-14).** Ozone was bubbled through a solution of (+)-**13** (138 mg, 0.337 mmol) in MeOH (5.0 mL) at −78 °C till the pale blue color persisted. Excess ozone was flushed off with nitrogen. To the reaction mixture was added $NaBH_4$ (102 mg, 2.70 mmol) at −78 °C. The reaction mixture was stirred for 30 min at the same temperature, quenched by addition of water, extracted with AcOEt, washed with water and brine, dried, and concentrated to afford the crude alcohol. To a solution of the crude alcohol in THF (1.5 mL) were added *o*-$NO_2$PhSeCN (197 mg, 0.866 mmol) and $^nBu_3P$ (0.21 mL, 0.87 mmol) at room temperature. After being stirred for 10 h at the same temperature, a solution of 30% aqueous $H_2O_2$ (0.50 mL, 4.9 mmol) in THF (3.0 mL) was added to the reaction mixture at 0 °C. After the reaction mixture was stirred for 15 min at the same temperature, the reaction mixture was allowed to warm to room temperature, stirred for additional 4 h, quenched by addition of saturated aqueous $NaHCO_3$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to afford the crude lactone. To a suspension of $LiAlH_4$ (21.9 mg, 0.577 mmol) in THF (2.5 mL) was added the crude lactone in THF (1.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at room temperature, quenched by addition of water, passed through a short pad of Celite with AcOEt, and concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (10:1) to give (+)-**14** (72.5 mg, 54% from (+)-**13**) as a colorless oil: $[\alpha]^{29}_{D}$ +49.7 (*c* 2.73, $CHCl_3$); IR 3421 $cm^{-1}$; $^1H$ NMR $\delta$ 5.65 (ddd, 1H, *J* = 17.1, 10.3, 10.3 Hz), 5.10−5.02 (m, 2H), 4.63, 4.59 (ABq, 2H, *J* = 6.6 Hz), 4.00−3.96 (m, 1H), 3.83−3.71 (m, 3H), 3.51−3.46 (m, 1H), 3.33 (s, 3H), 3.14−3.11 (m, 1H), 2.15−2.08 (m, 1H), 1.89−1.72 (m, 4H), 1.69−1.46 (m, 4H), 0.87 (s, 9H), 0.069 (s, 3H), 0.065 (s, 3H); $^{13}C$ NMR $\delta$ 138.3, 115.9, 95.6, 82.9, 76.7, 72.2, 59.6, 56.5, 55.2, 50.6, 44.1, 36.2, 35.9, 29.5, 25.8, 21.7, 17.9, −4.3, −4.7; FAB MS *m*/*z* 401 ($M^+$ + 1, 13.2). FAB HRMS calcd for $C_{21}H_{41}O_5Si$ 401.2723, found 401.2724.

**(1*S*,2*S*,3*S*,6*S*,8*R*,9*R*)-3-*tert*-Butyldimethylsilyloxy-9-ethenyl-8-methoxymethoxy-1-(2-propynyl)-2-(2-trimethylsilylethoxymethoxy)bicyclo[4.3.0]nonane ((−)-15).** To a solution of (+)-**14** (226 mg, 0.563 mmol) and 2,6-lutidine (0.13 mL, 1.1 mmol) in $CH_2Cl_2$ (5.6 mL) was added AcCl (0.05 mL, 0.68 mmol) at −78 °C. The reaction mixture was stirred for 40 min at the same temperature, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with water and brine, dried, and concentrated to dryness. To a solution of the residue in $CH_2Cl_2$ (5.6 mL) were added $^iPr_2NEt$ (0.30 mL, 1.7 mmol), SEMCl (0.20 mL, 1.1 mmol) and TBAI (229 mg, 0.620 mmol) at room temperature. The reaction mixture was refluxed for 4 h, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with water and brine, dried, and concentrated to dryness. To a solution of the residue in MeOH (5.6 mL) was added $K_2CO_3$ (156 mg, 1.13 mmol) at room temperature. The reaction mixture was stirred for 4 h at the same temperature, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (10:1) to afford the crude alcohol. To a mixture of the crude alcohol and IBX (316 mg, 1.13 mmol) in AcOEt (4.0 mL) was added dropwise DMSO (4.0 mL) at room temperature. The reaction mixture was stirred for 30 min at the same temperature, quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with AcOEt, washed with water and brine, dried and concentrated to afford the crude aldehyde. To a solution of the crude aldehyde in MeOH (5.0 mL) were added dimethyl 1-diazo-2-oxopropylphosphonate (217 mg, 1.13 mmol) and $K_2CO_3$ (312 mg, 2.25 mmol) at room temperature. The reaction mixture was stirred for 3 h at the same temperature, quenched by addition of saturated aqueous $NaHCO_3$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (10:1) to give (−)-**15** (258 mg, 87% from (+)-**14**) as a colorless oil: $[\alpha]^{29}_{D}$ −28.1 (*c* 3.55, $CHCl_3$); IR 3306, 2114, 1637 $cm^{-1}$; $^1H$ NMR $\delta$ 6.04−5.96 (m, 1H), 5.15−5.05 (m, 2H), 4.82, 4.76 (ABq, 2H, *J* = 6.6 Hz), 4.66, 4.58 (ABq, 2H, *J* = 6.6 Hz), 4.08−4.03 (m, 1H), 3.88−3.83 (m, 1H), 3.76−3.70 (m, 1H), 3.56−3.47 (m, 2H), 3.33 (s, 3H), 3.12 (dd, 1H, *J* = 9.3, 5.1 Hz), 2.40−2.24 (m, 3H), 2.12 (dt, 1H, *J* = 13.2, 7.6 Hz), 1.97 (t, 1H, *J* = 2.7 Hz), 1.80−1.53 (m, 5H), 0.95 (dd, 2H, *J* = 9.0, 7.8 Hz), 0.88 (s, 9H), 0.06 (s, 6H), 0.01 (s, 9H); $^{13}C$ NMR $\delta$ 138.9, 116.1, 97.6, 95.2, 84.6, 83.6, 81.3, 72.4, 70.9, 65.7, 57.0, 55.2, 50.3, 39.9, 35.9, 29.1, 25.9, 22.6, 22.0, 18.1, 18.0, −1.4, −4.5, −4.7; FAB MS *m*/*z* 525 ($M^+$ + 1, 3.7). FAB HRMS calcd for $C_{28}H_{53}O_5Si_2$ 525.3432, found 525.3436.

**(1*S*,2*S*,3*S*,6*S*,8*R*,9*R*,10*R*)-3-*tert*-Butyldimethylsilyloxy-8-methoxymethoxy-13-trimethylsilyl-2-(2-trimethylsilylethoxymethoxy)tetracyclo[7.6.0.0$^{1,6}$.0$^{10,14}$]pentadec-13-en-12-one ((−)-17).** To a solution of (−)-**15** (65.0 mg, 0.124 mmol) in THF (1.2 mL) were added $^n$BuLi (1.35 M in hexane; 0.11 mL, 0.15 mmol) and HMPA (0.1 mL) at −78 °C. After being stirred for 1 h at the same temperature, TMSCl (0.03 mL, 0.25 mmol) was added dropwise to the reaction mixture. Then, the reaction mixture was allowed to warm gradually to room temperature, stirred for additional 1 h, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. To a solution of the crude enyne in 1,2-dichloroethane (2.4 mL) was added $Co_2(CO)_8$ (50.8 mg, 0.149 mmol) at room temperature. After being stirred for 30 min at the same temperature, dimethyl sulfide (0.09 mL, 1.2 mmol) was added to the reaction mixture. The reaction mixture was stirred for an additional 4 days at 18 °C and passed through a short pad of silica gel with hexane−AcOEt (2:1), and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (10:1) to give (−)-**17** (61.3 mg, 79% from (−)-**15**) as a colorless oil and (−)-epimer of (−)-**17** (12.7 mg, 16% from (−)-**15**) as a colorless oil. Compound (−)-**17**: $[\alpha]^{30}_{D}$ −70.8 (*c* 0.51, $CHCl_3$); IR 1686, 1607 cm$^{-1}$; $^1H$ NMR $\delta$ 4.85, 4.60 (ABq, 2H, $J$ = 7.1 Hz), 4.60 (s, 2H), 4.16 (td, 1H, $J$ = 7.3, 2.2 Hz), 3.52 (td, 1H, $J$ = 9.8, 5.9 Hz), 3.48−3.39 (m, 2H), 3.33 (s, 3H), 3.22 (td, 1H, $J$ = 9.8, 6.6 Hz), 3.01 (d, 1H, $J$ = 17.1 Hz), 2.77−2.71 (m, 1H), 2.60 (dd, 1H, $J$ = 17.3, 6.6 Hz), 2.26 (dd, 1H, $J$ = 11.0, 2.2 Hz), 2.19−1.97 (m, 5H), 1.72−1.67 (m, 1H), 1.64−1.54 (m, 3H), 0.87 (s, 9H), 0.85−0.74 (m, 2H), 0.17 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), −0.05 (s, 9H); $^{13}C$ NMR $\delta$ 213.4, 197.7, 134.5, 97.2, 95.2, 83.5, 81.2, 75.0, 65.4, 59.7, 58.6, 55.2, 51.4, 45.1, 42.7, 38.5, 35.3, 29.8, 25.8, 22.1, 17.9, −1.2, −1.4, −4.7 (2 × C); FAB MS *m/z* 625 ($M^+ + 1$, 24.7). FAB HRMS calcd for $C_{32}H_{61}O_6Si_3$ 625.3776, found 625.3761. (−)-Epimer of (−)-**17**: $[\alpha]^{30}_{D}$ −17.5 (*c* 3.48, $CHCl_3$); IR 1686, 1609 cm$^{-1}$; $^1H$ NMR $\delta$ 5.06, 4.71 (ABq, 2H, $J$ = 7.1 Hz), 4.59, 4.53 (ABq, 2H, $J$ = 6.8 Hz), 3.81−3.75 (m, 1H), 3.58 (d, 1H, $J$ = 9.3 Hz), 3.49−3.42 (m, 3H), 3.31 (s, 3H), 3.13−3.08 (m, 1H), 2.84 (d, 1H, $J$ = 15.4 Hz), 2.60 (dd, 1H, $J$ = 10.7, 7.3 Hz), 2.41 (dd, 1H, $J$ = 18.3, 7.1 Hz), 2.29−2.21 (m, 2H), 1.81−1.60 (m, 4H), 1.57−1.45 (m, 2H), 1.33−1.29 (m ,1H), 1.00−0.92 (m, 2H), 0.87 (s, 9H), 0.17 (s, 9H), 0.06 (s, 6H), −0.02 (s, 9H); $^{13}C$ NMR $\delta$ 214.7, 195.9, 136.3, 96.8, 95.4, 83.5, 77.6, 74.3, 65.7, 58.1, 55.4, 52.5, 47.3, 41.9, 38.1, 34.9, 34.1, 30.9, 25.8, 22.6, 18.1, 17.9, −0.8, −1.5, −4.7 (2 × C); FAB MS *m/z* 625 ($M^+ + 1$, 19.9). FAB HRMS calcd for $C_{32}H_{61}O_6Si_3$ 625.3776, found 625.3776.

**(1*S*,2*S*,3*S*,6*S*,8*R*,9*R*,10*S*,14*R*)-3-*tert*-Butyldimethylsilyloxy-8-methoxymethoxy-2-(2-trimethylsilylethoxymethoxy)tetracyclo-[7.6.0.0$^{1,6}$.0$^{10,14}$]pentadec-12-ene ((−)-18)**. A mixture of (−)-**17** (357 mg, 0.571 mmol) and Pd−C (35.7 mg) in AcOEt (5.7 mL) was stirred under hydrogen atmosphere (1 atm) for 3 h at room temperature. The reaction mixture was passed through a short pad of Celite, and the filtrate was concentrated to afford the crude ketone. To a solution of the crude ketone in $Et_2O$ (5.7 mL) was added DIBAL-H (1.0 M in hexane; 0.69 mL, 0.69 mmol) at −78 °C. The reaction mixture was stirred for 30 min at the same temperature, quenched by addition of water, and passed through a short pad of Celite with AcOEt. After evaporation of the solvent, the filtrate was concentrated to afford the crude alcohol. To a suspension of KH (45.8 mg, 1.14 mmol; the oil was washed off with hexane prior to use) in THF (4.0 mL) was added dropwise a solution of the crude alcohol obtained above in THF (1.7 mL) at room temperature. The reaction mixture was stirred for 1 h at the same temperature, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with hexane−AcOEt (10:1) to give (−)-**18** (289 mg, 94% from (−)-**17**) as a colorless oil: $[\alpha]^{28}_{D}$ −61.2 (*c* 0.51, $CHCl_3$); $^1H$ NMR $\delta$ 5.63−5.61 (m, 1H), 5.50−5.48 (m, 1H), 4.80, 4.73 (ABq, 2H, $J$ = 6.8 Hz), 4.67, 4.58 (ABq, 2H, $J$ = 6.8 Hz), 4.14−4.10 (m, 1H), 3.71−3.65 (m, 1H), 3.49 (d, 1H, $J$ = 9.5 Hz), 3.43−3.36 (m, 2H), 3.35 (s, 3H), 3.13−3.11 (m, 1H), 2.56−2.50 (m, 1H), 2.31−2.15 (m, 4H), 1.94−1.78 (m, 3H), 1.67−1.52 (m, 5H), 0.94−0.82 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H), 0.00 (s, 9H); $^{13}C$ NMR $\delta$ 135.9, 127.0, 97.5, 94.6, 82.3, 81.3, 74.7, 65.4, 60.3, 59.6, 55.1, 49.9, 46.8, 42.7, 38.3, 36.9, 34.2, 30.0, 25.9, 22.0, 18.0 (2 × C), −1.4, −4.6 (2 × C); FAB MS *m/z* 539 ($M^+ + 1$, 1.6). FAB HRMS calcd for $C_{29}H_{55}O_5Si_2$ 539.3588, found 539.3576.

**(1*S*,3*S*,8*S*,9*R*,10*R*,12*S*,15*S*,16*S*)-15-*tert*-Butyldimethylsilyloxy-10-methoxymethoxy-5-methyl-16-(2-trimethylsilylethoxymethoxy)-5-azatetracyclo[7.7.0.0$^{3,8}$.0$^{1,12}$]hexadecane ((−)-19).** To a solution of (−)-**18** (78.3 mg, 0.145 mmol) in MeCN (1.5 mL) were added NMO (34.0 mg, 0.291 mmol) and 4% aqueous $OsO_4$ (0.18 mL, $2.9 \times 10^{-2}$ mmol) at room temperature. The reaction mixture was stirred for 2 h at the same temperature, quenched by addition of saturated aqueous $Na_2SO_3$, stirred for 30 min, extracted with AcOEt, washed with water and brine, dried, and concentrated to afford crude 1,2-diol. To a solution of the crude 1,2-diol in $Et_2O$ (1.5 mL) and $H_2O$ (1.5 mL) was added $NaIO_4$ (62.2 mg, 0.291 mmol) at room temperature. The reaction mixture was stirred for 2 h at the same temperature, extracted with $Et_2O$, washed with water and brine, dried, and concentrated to afford the crude dialdehyde. To a solution of the crude dialdehyde was added $NaBH_4$ (11.0 mg, 0.291 mmol) at room temperature. The reaction mixture was stirred for 30 min at the same temperature, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with water and brine, dried, and concentrated to afford crude diol. To a solution of the crude diol in $CH_2Cl_2$ (1.4 mL) were added $^iPr_2NEt$ (0.12 mL, 0.67 mmol) and MsCl (0.03 mL, 0.33 mmol) at 0 °C. The reaction mixture was stirred for 15 min at the same temperature, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with water and brine, dried, and concentrated to afford the crude dimesylate. A mixture of the crude dimesylate and 40% aqueous $MeNH_2$ (1.0 mL, 12 mmol) in MeOH (1.4 mL) was stirred for 12 h at 85 °C in a sealed tube. The reaction mixture was extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on $Al_2O_3$ with hexane−AcOEt (5:1) to give (−)-**19** (76.2 mg, 92% from (−)-**18**) as a colorless oil: $[\alpha]^{29}_{D}$ −40.8 (*c* 1.74, $CHCl_3$); $^1H$ NMR $\delta$ 5.01, 4.74 (ABq, 2H, $J$ = 6.6 Hz), 4.61, 4.59 (ABq, 2H, $J$ = 6.6 Hz), 3.86−3.78 (m, 2H), 3.56−3.50 (m, 1H), 3.45−3.37 (m, 2H), 3.33 (s, 3H), 2.56 (dd, 1H, $J$ = 11.5, 4.9 Hz), 2.51−2.45 (m, 1H), 2.23−1.76 (m, 9H), 2.19 (s, 3H), 1.66−1.45 (m, 6H), 1.17 (1H, dd, $J$ = 12.5, 6.6 Hz), 0.93 (t, 2H, $J$ = 8.5 Hz), 0.86 (s, 9H), 0.03 (s, 6H), −0.01 (s, 9H); $^{13}C$ NMR $\delta$ 97.4, 95.1, 83.1, 81.9, 75.2, 66.5, 57.6, 57.3, 57.2, 55.1, 54.4, 47.0, 42.6, 41.4, 38.6, 36.6, 32.0, 31.0, 26.7, 25.9, 22.3, 18.4, 17.9, −1.4, −4.5, −4.7; EI MS *m/z* 569 ($M^+$, 5.5). EI HRMS calcd for $C_{30}H_{59}NO_5Si_2$ 569.3932, found 569.3928.

**(1*S*,3*S*,8*S*,9*R*,10*R*,12*S*,16*R*)-10-Methoxymethoxy-5-methyl-16-(2-trimethylsilylethoxymethoxy)-5-azatetracyclo[7.7.0.0$^{3,8}$.0$^{1,12}$]-hexadec-14-ene ((−)-20).** To a solution of (−)-**19** (2.44 g, 4.28 mmol) in THF (4.3 mL) was added TBAF (1.0M in THF; 4.71 mL, 4.71 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at 45 °C, quenched by addition of saturated aqueous $NH_4Cl$, extracted with AcOEt, washed with water and brine, dried, and concentrated to afford the crude alcohol. To a solution of the crude alcohol in $CH_2Cl_2$ (21.4 mL) were added $^iPr_2NEt$ (3.7 mL, 21 mmol), DMAP (cat.), and $Ms_2O$ (1.49 g, 8.57 mmol) at room temperature. The reaction mixture was stirred for 1.5 h at the same temperature, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with water and brine, dried, and concentrated to afford the crude mesylate. A mixture of the crude mesylate and DBU (1.92 mL, 12.8 mmol) in xylene (43 mL) was refluxed for 12 h, quenched by addition of saturated aqueous $NaHCO_3$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on $Al_2O_3$ with hexane−AcOEt (5:1) to give (−)-**20** (1.50 g, 80% from (−)-**19**) as a colorless oil: $[\alpha]^{27}_{D}$ −68.7 (*c* 0.65, $CHCl_3$); $^1H$ NMR $\delta$ 5.81−5.77 (m, 1H), 5.70−5.65 (m, 1H), 4.86, 4.76 (ABq, 2H, $J$ = 6.8 Hz), 4.63, 4.61 (ABq, 2H, $J$ = 6.8 Hz), 4.04−4.01 (m, 1H), 3.79−3.74 (m, 1H), 3.69 (t, 2H, *J* = 8.5 Hz), 3.34 (s, 3H), 2.57−2.50 (m, 2H), 2.37−2.30 (m, 1H), 2.19 (s, 3H), 2.17−2.08 (m, 3H), 2.00−1.80 (m, 6H), 1.72−1.66 (m, 1H), 1.57−1.47 (m, 2H), 1.09 (dd, 1H, *J* = 12.7, 6.6 Hz), 0.98−0.91 (m, 2H), 0.02 (s, 9H); $^{13}$C NMR δ 130.7, 126.8, 95.4, 94.4, 82.7, 75.6, 65.3, 57.8, 57.2, 55.7, 55.2, 54.7, 47.1, 41.6, 40.7, 39.9, 37.7, 33.1, 26.6, 26.1, 18.1, −1.4; EI MS *m*/*z* 437 ($M^+$, 19.9). EI HRMS calcd for $C_{24}H_{43}NO_4Si$ 437.2961, found 437.2956.

**(1*S*,3*S*,8*S*,9*R*,10*R*,12*S*)-10-Methoxymethoxy-5-methyl-5-azatetracyclo[7.7.0.0$^{3,8}$.0$^{1,12}$]hexadec-14-en-16-on ((−)-21).** A mixture of (−)-**20** (700 mg, 1.60 mmol), CsF (1.21 g, 8.00 mmol), and MS4Å in DMF (20 mL) was refluxed for 12 h and passed through a short pad of Celite with AcOEt to remove MS4Å, and the filtrate was concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (2:1) to give the crude alcohol. To a solution of the crude alcohol in $CH_2Cl_2$ (20 mL) was added Dess-Martin periodinane (919 mg, 2.17 mL) at room temperature. The reaction mixture was stirred for 30 min at the same temperature, quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on $Al_2O_3$ with hexane−AcOEt (5:1) to give (−)-**21** (319 mg, 65% from (−)-**20**) as a colorless oil: $[\alpha]^{29}_D$ −40.0 (*c* 1.08, $CHCl_3$); IR 1661 cm$^{-1}$; $^1$H NMR δ 6.77−6.72 (m, 1H), 6.01−5.97 (m, 1H), 4.58 (s, 2H), 3.67 (dt, 1H, *J* = 9.5, 5.9 Hz), 3.30 (s, 3H), 2.63−2.55 (m, 3H), 2.52−2.49 (m, 1H), 2.32 (dd, 1H, *J* = 19.8, 5.9 Hz), 2.24−2.11 (m, 3H), 2.18 (s, 3H), 2.03−1.95 (m, 3H), 1.85−1.76 (m, 2H), 1.68−1.59 (m, 3H); $^{13}$C NMR δ 202.4, 145.9, 128.6, 95.6, 82.4, 60.8, 60.0, 56.5, 55.2, 54.5, 46.8, 42.4, 40.2, 39.8, 38.5, 38.0, 26.4, 25.0; EI MS *m*/*z* 305 ($M^+$, 97.3). EI HRMS calcd for $C_{18}H_{27}O_3N$ 305.1991, found 305.1992.

**(−)-5-Epimagellanine ((−)-23).** To a suspension of CuCN (66.0 mg, 0.737 mmol) in $Et_2O$ (10 mL) was added MeLi (1.0 M in $Et_2O$; 1.3 mL, 1.3 mmol) at 0 °C. The reaction mixture was stirred for 15 min at the same temperature. To the reaction mixture were added a solution of (−)-**21** (45.0 mg, 0.147 mmol) in $Et_2O$ (5.0 mL) and TMEDA (0.1 mL) at −40 °C. The reaction mixture was stirred for 12 h at the same temperature, quenched by addition of saturated aqueous $NH_4Cl$, and passed through a short pad of Celite with AcOEt. The filtrate was extracted with $Et_2O$, washed with water and brine, dried, and concentrated to afford the crude ketone **22**. To a solution of the crude ketone **22** in THF (1.0 mL) were added LDA (0.4 M in THF; 0.5 mL, 0.2 mmol) and HMPA (0.1 mL) at −20 °C. The reaction mixture was stirred for 1 h at the same temperature. To the reaction mixture was added a solution of *N-tert*-butylbenzenesulfinimidoyl chloride (95.4 mg, 0.442 mmol) in THF (0.5 mL) at −20 °C. The reaction mixture was stirred for 3 h at −20 °C, allowed to warm gradually to 0 °C, stirred for additional 1 h at 0 °C, quenched by addition of saturated aqueous $NH_4Cl$, extracted with $Et_2O$, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on a short pad of silica gel with AcOEt−MeOH (1:1) to recover the ketone (7.4 mg, recovered yield 16%) and with MeOH to give the crude α,*β*-unsaturated ketone. To a solution of α,*β*-unsaturated ketone in MeOH (1.5 mL) was added 10% aqueous HCl at room temperature. The reaction mixture was stirred for 2 h at 45 °C, quenched by addition of saturated aqueous $NaHCO_3$, extracted with AcOEt, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on $Al_2O_3$ with AcOEt−MeOH (10:1) to give (−)-**23** (17.7 mg, 44% from (−)-**21**) as a colorless oil: $[\alpha]^{30}_D$ −15.9 (*c* 0.23, $CHCl_3$); IR 3421, 1651 cm$^{-1}$; $^1$H NMR δ 5.88 (s, 1H), 3.80 (ddd, 1H, *J* = 9.5, 5.9, 5.9 Hz), 2.70−2.53 (m, 3H), 2.39−2.34 (m, 1H), 2.26−1.79 (m, 9H), 2.21 (s, 3H), 1.93 (s, 3H), 1.69−1.60 (m, 2H), 1.54 (ddd, 1H, *J* = 13.7, 11.7, 9.8 Hz); $^{13}$C NMR δ 202.8, 157.8, 125.3, 77.9, 62.9, 60.0, 56.5, 54.5, 46.7, 42.2, 41.3, 40.9, 39.8, 38.2, 30.3, 26.5, 24.5; EI MS *m*/*z* 275 ($M^+$, 100). EI HRMS calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1885.

**(−)-Magellanine ((−)-1).** To a solution of (−)-**23** (8.0 mg, 2.9 × 10$^{-2}$ mmol) in THF (0.3 mL) were added $PPh_3$ (76.2 mg, 0.291 mmol), benzoic acid (71.0 mg, 0.581 mmol), and DIAD (0.06 mL, 0.29 mL) at room temperature. The reaction mixture was stirred for 10 h at the same temperature. To the reaction mixture was added a solution of concentrated aqueous NaOH. The reaction mixture was stirred for 3 h at room temperature, extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$−MeOH (1:1) to give (−)-**1** (6.0 mg, 75%) as colorless solids: mp 160−161 °C (AcOEt); $[\alpha]^{30}_D$ −20.3 (*c* 0.14, $CHCl_3$); IR 3418, 1651 cm$^{-1}$; $^1$H NMR δ 5.87 (s, 1H), 4.23−4.19 (m, 1H), 2.77−2.60 (m, 4H), 2.51 (ddd, 1H, *J* = 12.7, 6.3, 6.3 Hz), 2.32−1.88 (m, 7H), 2.20 (s, 3H), 1.93 (s, 3H), 1.71−1.52 (m, 4H); $^{13}$C NMR δ 203.3, 158.0, 125.7, 72.0, 61.0, 59.6, 56.5, 55.4, 46.9, 41.9, 41.4, 40.3, 37.3, 37.0, 30.4, 27.0, 24.5; EI MS *m*/*z* 275 ($M^+$, 100). EI HRMS calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1886.

**(+)-Magellaninone ((+)-2).** To a solution of (−)-**23** (18.2 mg, 6.61 × 10$^{-2}$ mmol) in $CH_2Cl_2$ (0.7 mL) was added Dess-Martin periodinane (56.1 mg, 0.132 mmol) at room temperature. The reaction mixture was stirred for 1 h at the same temperature, quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on $Al_2O_3$ with hexane−AcOEt (1:1) to give (+)-**2** (15.3 mg, 85%) as a colorless oil: $[\alpha]^{30}_D$ +82.6 (*c* 0.16, $CHCl_3$); IR 1734, 1655 cm$^{-1}$; $^1$H NMR δ 6.00 (s, 1H), 3.02 (d, 1H, *J* = 6.6 Hz), 2.77 (dddd, 1H, *J* = 19.1, 6.4, 2.5, 1.2 Hz), 2.64−1.71 (m, 14H), 2.24 (s, 3H), 1.99 (s, 3H); $^{13}$C NMR δ 216.4, 200.7, 158.1, 125.7, 60.4, 58.5, 56.5, 52.9, 46.6, 44.8, 40.6 39.8, 39.6, 39.2, 29.8, 26.2, 24.6; EI MS *m*/*z* 273 ($M^+$, 100). EI HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1729.

(+)-**Paniculatine** ((+)-**3**): According to the procedure described for preparation of (−)-**23** from (−)-**21**, the crude $C_{14}$-methylated ketone **22** was obtained from (−)-**21** (24.6 mg, 7.65 × 10$^{-2}$ mmol). To a solution of the crude ketone **22** in THF (0.8 mL) was added dropwise L-Selectride (1.0 M in THF; 0.38 mL, 0.38 mmol) at −10 °C. The reaction mixture was stirred for 3 h at the same temperature, quenched by addition of water, extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of $Al_2O_3$ with AcOEt to give the crude alcohol. To a solution of the crude alcohol in pyridine (0.5 mL) was added benzoyl chloride (0.02 mL, 0.16 mmol) at room temperature. The reaction mixture was stirred for 10 h at 50 °C, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to give crude benzoate. The mixture of the crude benzoate and 10% aqueous HCl (0.10 mL, 0.27 mmol) in MeOH (0.5 mL) was stirred for 17 h at 45 °C, quenched by addition of saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with $CHCl_3$−MeOH (10:1) to give crude alcohol. To a solution of the crude alcohol in $CH_2Cl_2$ (0.5 mL) was added Dess-Martin periodinane (46.2 mg, 0.109 mmol) at room temperature. The reaction mixture was stirred for 40 min at the same temperature, quenched by addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to give crude ketone. The mixture of the crude ketone and conc. aqueous NaOH (0.1 mL) in MeOH (0.5 mL) was stirred for 1.5 h at room temperature. The reaction mixture was extracted with $CHCl_3$, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed on $Al_2O_3$ with $CHCl_3$−MeOH (5:1) to give (+)-**3** (11.6 mg, 55% from (−)-**20**) as colorless solids: mp 178−179 °C (acetone); $[\alpha]^{30}_D$ +75.1 (*c* 0.17, $CHCl_3$); IR 3408, 1722 cm$^{-1}$; $^1$H NMR δ 3.83 (br s, 1H), 2.81−2.71 (m, 2H), 2.56−1.68 (m, 13H), 2.31 (s, 3H), 1.34−1.22(m, 4H), 0.93 (d, 3H, *J* =

6.6 Hz); $^{13}$C NMR $\delta$ 220.4, 75.5, 58.5, 57.5, 53.4, 51.9, 46.3, 44.0, 41.2, 40.2, 39.7, 39.4, 38.0, 32.3, 25.6, 22.1, 19.1; EI MS *m*/*z* 277 ($M^+$, 90.1). EI HRMS calcd for $C_{17}H_{27}NO_2$ 277.2042, found 277.2042.

**Acknowledgment.** This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are grateful.

**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for compounds **1**−**3**, **11**−**15**, **17**−**21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702136B