Total Syntheses of (−)-Mesembrane and (−)-Mesembrine *via* Palladium-Catalyzed Enantioselective Allylic Substitution and Zirconium-Promoted Cyclization

Miwako Mori,* Shinji Kuroda, Chang-Shan Zhang, and Yoshihiro Sato

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Received January 22, 1997[⊗]

4-Arylhexahydroindole derivatives **5** were synthesized from 2-arylcyclohexenyl allylamine derivatives **4**, which have a large protecting group on nitrogen, using zirconium-promoted cyclization. Reaction of **4e** with Cp_2ZrBu_2, followed by treatment with MeMgBr and then O_2, gave **2a** in 63% yield by a one-pot reaction, since the approach of O_2 to zirconium was prevented by the aryl group. The total syntheses of (±)-mesembrane and (±)-mesembrine were achieved starting from **2a**. To synthesize these natural products in a chiral form, the starting allylamine derivative **24** (80% yield, 86% ee, recrystallized from MeOH, 99% ee with 79% recovery) was prepared from allyl carbonate **22a** and *N*-tosylallylamine **23** using palladium-catalyzed asymmetric amination in the presence of (*S*)-BINAPO as a chiral ligand. (−)-Mesembrane and (−)-mesembrine were synthesized from this allylamine **24**.

Zirconium-promoted diyne, enyne, and diene cyclizations are very useful in synthetic organic chemistry because regio- and stereocontrolled carbon−carbon bonds can be formed between these multiple bonds.[1] This procedure is very attractive for the synthesis of natural products.[2,3a,d] Recently, we reported the synthesis of perhydroindole derivatives using zirconium-promoted[3a] or zirconium-catalyzed[3e] cyclization.

Since many alkaloids have a *cis*-3a-aryloctahydroindole skeleton, zirconium-promoted diene cyclization should be useful in their synthesis. Typical alkaloids with a *cis*-3a-aryloctahydroindole skeleton are shown in Figure 1.

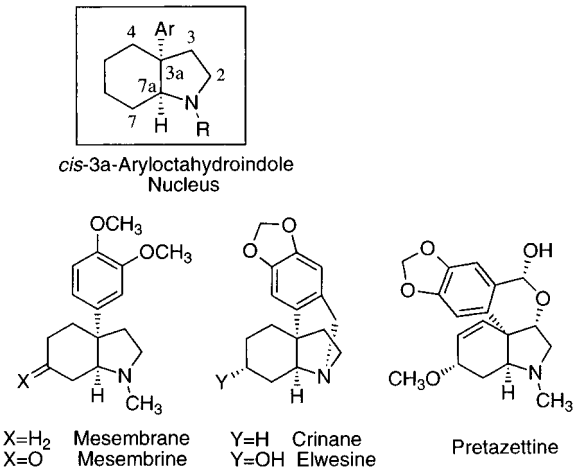


Figure 1.

Our retrosynthetic study of (−)-mesembrane and (−)-mesembrine is shown in Scheme 1.

In this plan, an important problem is whether dienes with large substituents on the alkene can be cyclized by Cp_2ZrBu_2. Another is how to prepare the chiral starting diene **3**. We report here the total syntheses of (−)-mesembrane (**1a**) and (−)-mesembrine (**1b**)[4] using palladium-catalyzed enantioselective allylic substitution and zirconium-promoted cyclization as the key steps.

Synthesis of *cis*-Octahydroindole Derivatives Using Zirconium-Promoted Cyclization

Cyclization of diene **4a**, which has a phenyl group on the alkene, was tried first. To a THF solution of Cp_2ZrBu_2 prepared from Cp_2ZrCl_2 and BuLi[5] was added a THF solution of **4a** at −78 °C, and the solution was stirred at room temperature for 4 h. After hydrolysis of the reaction mixture, hexahydroindole derivative **5a** was obtained in 26% yield along with deallylation product **6a** (47% yield) (Scheme 2).

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.

(1) (a) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. Taber, *D. F.*; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 9457, references are cited therein. (b) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568. Negishi, E.-i.; Choueirry, D.; Nguyen, T. B.; Swanson, D. R.; Suzuki, N.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 9751. (c) For reviews, see: Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.

(2) (a) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (b) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956. (c) Wender, P. A.; McDonald, F. E. *Tetrahedron Lett.* **1990**, *31*, 3691. (d) Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 7424. (e) Agnel, G.; Owczarczyk, Z.; Negishi, E. *Tetrahedron Lett.* **1991**, *32*, 1543. (f) Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5469.

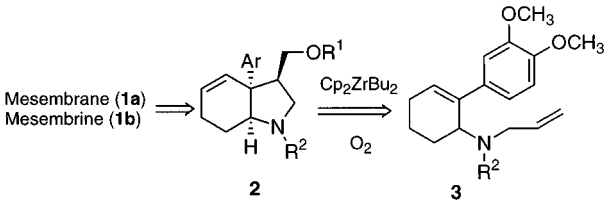
(3) (a) Mori, M.; Uesaka, N.; Shibasaki, M. *J. Org. Chem.* **1992**, *57*, 3519. (b) Mori, M.; Saitoh, F.; Uesaka, N.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4993. Saitoh, F.; Mori, M.; Okamura, K.; Date, T. *Tetrahedron* **1995**, *51*, 4439. (c) Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643. (d) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633. (e) Uesaka, N.; Mori, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4542. (f) Mori, M.; Imai, A. E.; Uesaka, N. *Heterocycles* **1995**, *40*, 551.

(4) (a) Jeffs, P. W. In *The Alkaloids*; Rodrigo, R., Ed.; Academic Press, Inc.: New York, 1981; Vol. 19; p 1. (b) Capps, T. M.; Hargrave, K. D.; Jeffs, P. W.; McPhail, A. T. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1098. Nagashima, H.; Ara, K.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1985**, 518. (c) Stevens, R. V.; Wentland, P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (d) For a total synthesis of (−)-mesembrane, see Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. Meyers, A. I.; Hanreich, R.; Hanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron Asymmetry* **1993**, *4*, 1409. Nemoto, H.; Tababe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785 (references of a total synthesis of (±)-mesembrine are cited therein).

(5) Neigishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

S0022-3263(97)00118-7 CCC: $14.00

Scheme 1. Retrosynthetic Study



Scheme 2

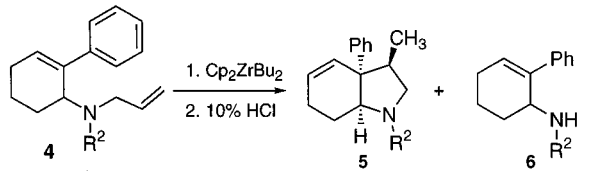
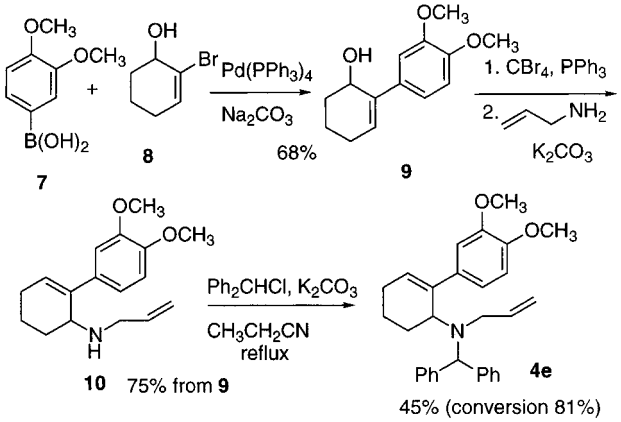


Table 1. Effects of the Nitrogen Substituent

					yields (%)	
run	R^1	R^2	substrate	time (h)	**5**	**6**
1	H	CH_2Ph	**4a**	4	26	47
2	H	H[a]	**4b**	4	–	50
3	H	CH_3	**4c**	2	–	56
4	H	$CHPh_2$	**4d**	4	58	17

[a] BuLi (1 equiv) was added to the substrate.

Scheme 3

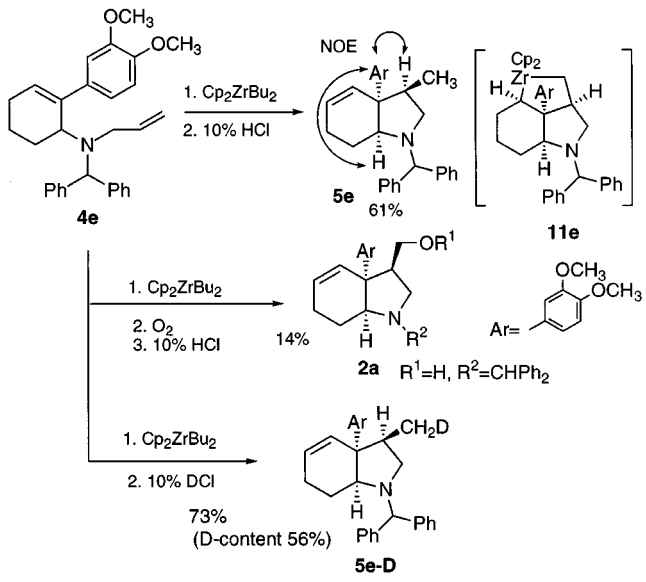


To improve the yield of the desired cyclized product **5**, the effects of the substituent on nitrogen were investigated, and the results are shown in Table 1. While small substituents, such as H or Me, did not give the cyclized product (runs 2 and 3), good results were obtained with large substituents (runs 1 and 4). For the syntheses of mesembrane (**1a**) and mesembrine (**1b**), we tried to react diene **4e** with Cp_2ZrBu_2. The starting allylamine **4e** was prepared as shown in Scheme 3.

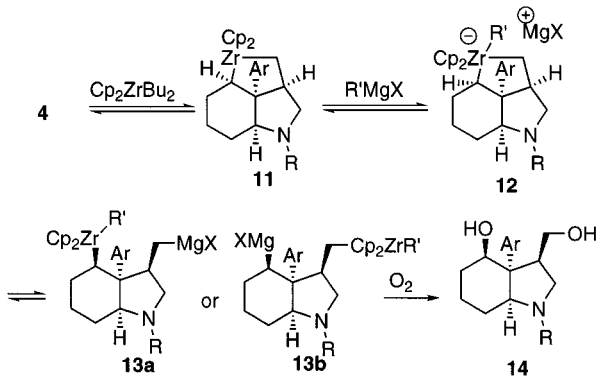
Suzuki–Miyaura coupling[6] of 3,4-dimethoxyphenylboric acid (**7**) and 2-bromo-2-cyclohexen-1-ol **8** proceeded smoothly in the presence of $Pd(PPh_3)_4$ and Na_2CO_3. Allyl alcohol **9** was treated with CBr_4 and PPh_3 and then allylamine to give **10**. Nitrogen was protected with diphenylmethyl chloride in the presence of K_2CO_3 in CH_3CH_2CN to provide **4e**. The reaction of diene **4e** with Cp_2ZrBu_2, was carried out in a similar manner to give the cyclized product **5e** in 61% yield (Scheme 4). NOE experiments with the cyclized product **5e** indicated that the ring junction of **5e** is *cis*, which means that the ring junction of the 5,5-membered ring of the zirconacycle **11e**

(6) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

Scheme 4



Scheme 5



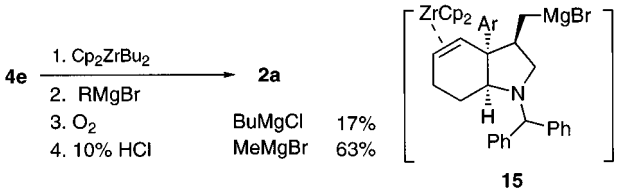
formed from **4e** is also *cis*.[2b] To synthesize mesembrane (**1a**) and mesembrine (**1b**), zirconacycle **11e** was then treated with O_2, since the hydroxymethyl group at the 3-position could be easily removed.

However, the desired product **2a** was obtained in only 14% yield. Zirconacycle **11e** was treated with 10% DCl–D_2O to give **5e-D** in 73% yield, with a D-content of 56%, which indicates that the carbon–zirconium bond of **11e** is retained until it is reacted with O_2 and the approach of O_2 to zirconium is prevented by the large aryl group. To overcome this problem, we attempted the transmetalation of zirconium to magnesium.[7] Our idea is shown in Scheme 5.

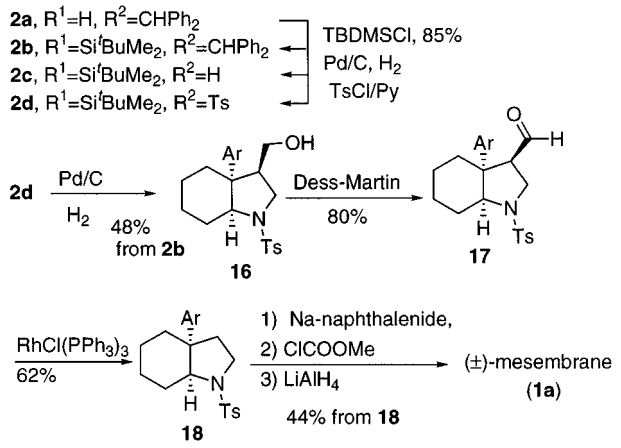
Zirconacycle **11** is treated with Grignard reagent to give complex **12**, which is in a state of equilibrium with **13a** or **13b**, treatment of which with O_2 should afford diol **14**. Thus, diene **4e** was treated with Cp_2ZrBu_2 and the solution was stirred at room temperature for 2 h. To

(7) (a) Dzhemilev, U. M.; Vastrikova, O. S.; Tolstikov, G. A. *J. Organomet. Chem.* **1986**, *304*, 17. (b) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E.-i. *J. Am. Chem. Soc.* **1991**, *113*, 6266. Suzuki, N.; Kondakov, D. Y.; Takahashi, T. *J. Am. Chem. Soc.* **1993**, *115*, 8485. (c) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079. Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950. Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692. Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614. Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997. Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.* **1993**, *58*, 4237. (d) Lewis, D. L.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6769. (e) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. Wischmeyer, U.; Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735.

Scheme 6



Scheme 7



this solution was added a THF solution of BuMgCl (5 equiv), and the solution was stirred at room temperature for 5 h. The atmosphere of argon was then changed to oxygen and the solution was stirred at room temperature overnight. After hydrolysis with 10% HCl, alcohol **2a** was obtained in 17% yield. Since it was considered that BuMgCl was too large, MeMgBr was used for this reaction to give **2a** in 63% yield. In this case, the intermediate magnesium complex should be **15** *via* magnesium complex **13a** (Scheme 6).

Total Synthesis of (±)-Mesembrane and (±)-Mesembrine

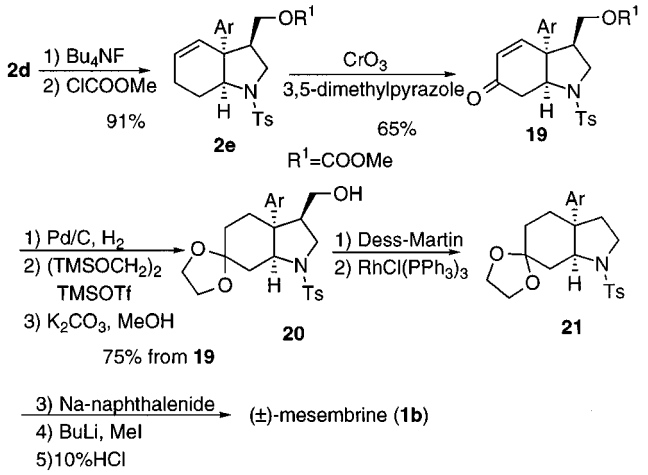
To synthesize mesembrane (**1a**), alcohol **2a** was converted into **16**[8] in the usual manner, which was then oxidized to aldehyde **17**. Deformylation of **17** with RhCl(PPh$_3$)$_3$ gave perhydroindole **18** in 62% yield. The tosyl group of **18** was converted into a methyl group, and we could obtain **1a**, whose spectral data agreed with those reported for mesembrane[3c] (Scheme 7).

On the other hand, the protecting group of **2d** was converted into the methoxycarbonyl group, and then allylic oxidation of **2e** with CrO_3 gave enone **19**, which was subjected to hydrogenation and ketalization to give **20**. Using a treatment similar to that for the synthesis of mesembrane from **16**, we synthesized (±)-mesembrine (**1b**)[4d] from **20** (Scheme 8). The spectral data of **1b** agreed with those reported in the literature.[4d]

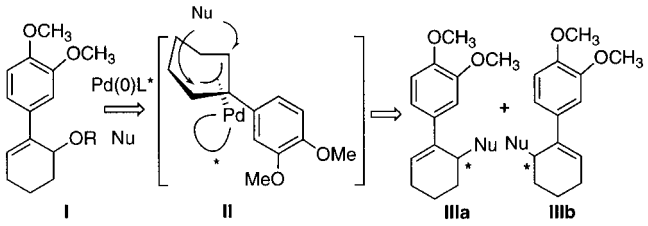
Palladium-Catalyzed Asymmetric Synthesis of a Key Intermediate of (−)-Mesembrane and (−)-Mesembrine

Although we succeeded in the total syntheses of mesembrane and mesembrine, they are racemic forms.

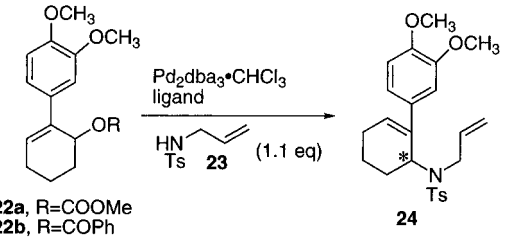
Scheme 8



Scheme 9



Scheme 10



Thus, we next tried to synthesize (−)-mesembrane and (−)-mesembrine. For that purpose, the optically active diene **4e** was required.

Our plan for the palladium-catalyzed asymmetric synthesis is shown in Scheme 9. Palladium-catalyzed alkylation or amination of compound **I** should give compound **III** *via* π-allylpalladium complex **II**. If a chiral ligand is used for this reaction, optically active **IIIa** or **IIIb** should be formed from racemic **I**.

When a DMSO solution of allyl carbonate **22a**, which was prepared from **9**, and *N*-tosylallylamine **23** was warmed in the presence of Pd_2dba_3•$CHCl_3$ (2.8 mol %) and dppb (5.6 mol %) as a ligand at 50 °C for 13 h, the desired tosylamide **24** was obtained in 36% yield (Table 2, run 1). The same reaction was carried out in the presence of (*S*)-BINAP[9] or (+)-**25**[10] as a chiral ligand, but the reaction rate was lower and good results were not obtained (runs 2 and 3). We were very surprised to find that when the reaction was carried out in the presence of palladium catalyst and (*S*)-BINAPO,[11] the reaction proceeded smoothly at room temperature for 3 h and the desired product **24** was obtained in 51% yield with 70% ee (run 4). Use of **22b** as a substrate did not affect the ee (run 5), but the reaction rate was lower. With regard to the solvent, nonpolar solvent gave good results. When

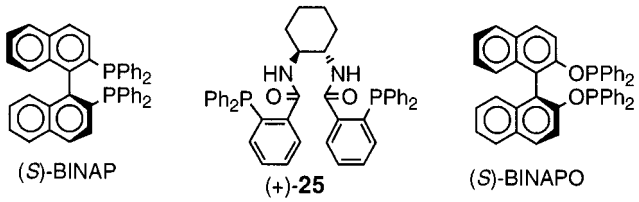
(8) Hydrogenation of compound **2b** with 10% Pd/C for a short reaction time gave **2c**, which was unstable under hydrogenation. Thus, the nitrogen of **2c** was protected with a tosyl group and further hydrogenation was carried out to give **2d**.

(9) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(10) Trost, B. M.; Van Vranken, D. L.; Gingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(11) (a) Grubbs, R. H.; DeVries, R. A. *Tetrahedron Lett.* **1977**, 1879. (b) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.

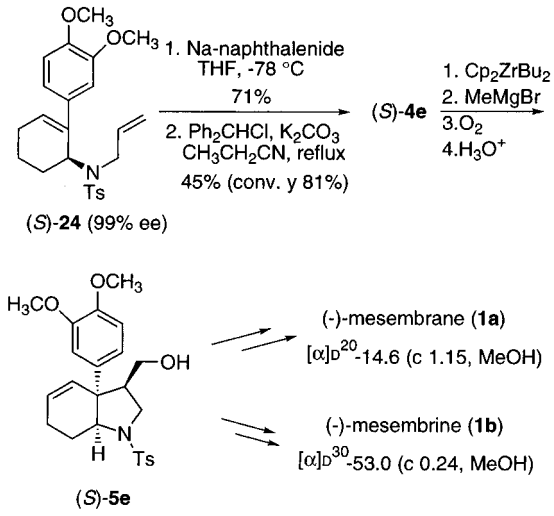
Table 2. Reaction of 22 with 23 under Various Conditions[a]



run	substrate	ligand	solvent	temp (°C)	time (h)	yield (%)	ee[b] (%)
1	**22a**	dppb	DMSO	50	13	36	–
2	**22a**	(*S*)-BINAP	DMSO	60–75	50	12	9
3	**22a**	(+)-**25**	THF	50	98	0	–
4	**22a**	(*S*)-BINAPO	DMSO	rt	3	51	70
5	**22b**[d]	(*S*)-BINAPO	DMSO	rt	27	64	68
6	**22a**	(*S*)-BINAPO	DMF	rt	3	70	71
7	**22a**	(*S*)-BINAPO	toluene	rt	31	76	80
8	**22a**	(*S*)-BINAPO	CH_3CN	rt	4	68	66
9	**22a**	(*S*)-BINAPO	CH_2Cl_2	rt	2	75	73
10	**22a**	(*S*)-BINAPO	THF	rt	19	80	86[e]
11	**22a**	(*S*)-BINAPO	THF	0	216	53	87

[a] All of the reactions (except for run 10) were carried out in the presence of **23** (1.1 equiv), Pd_2dba_3·$CHCl_3$ (2.8 mol %), and (*S*)-BINAPO (5.6 mol %). The reaction in run 10 was carried out in the presence of **23** (1.1 equiv), Pd_2dba_3·$CHCl_3$ (1.0 mol %), and (*S*)-BINAPO (2.0 mol %). [b] The ees were determined by HPLC analysis. (DAICEL CHIRALCEL OJ, hexane/^{i}PrOH, 9/1). [c] The starting material was recovered in 89% yield. [d] NaH was used as a base. [e] Recrystallized from MeOH, **24** was obtained in 99% ee (79% recovery).

Scheme 11



the reaction was carried out in THF at room temperature for 19 h, we obtained chiral diene **24** in 80% yield with 86% ee (run 10), which was recrystallized from MeOH to give **24** with 99% ee (79% recovery).

Total Synthesis of (−)-Mesembrane and (−)-Mesembrine

Detosylation of **24** with sodium naphthalenide proceeded smoothly to give amine in 71% yield, which was converted into diene **4e**. From **4e**, we succeeded in the total synthesis of (−)-mesembrane (**1a**). The melting point and the $[\alpha]_D$ value of **1a** agreed with those of the natural product reported previously.[3a] Moreover, we also achieved the total synthesis of (−)-mesembrine[12] from (*S*)-**5e**.

In conclusion, zirconium-promoted cyclization is useful for the synthesis of *cis*-3a-aryloctahydroindole derivatives. In this reaction, diene with a large aryl group on the alkene gave cyclized products in good yields when the substrate had a large protecting group on the nitrogen. The reaction of zirconacycle with O_2 proceeded using the transmetalation of zirconium to magnesium. This procedure could be useful for further carbon−carbon bond formation by the reaction of magnesium complex **15** with the carbon nucleophile. To synthesize the chiral natural products, we obtained the chiral amine **4e** by palladium-catalyzed asymmetric amination. As a result, we succeeded in the total synthesis of (−)-mesembrane and (−)-mesembrine.

Experimental Section

General. All manipulations were performed under an argon atmosphere unless otherwise mentioned. Solvents were distilled under an argon atmosphere from sodium−benzophenone (THF, Et_2O, toluene, and benzene), CaH_2 (CH_2Cl_2, CH_3CN, CH_3CH_2CN), or sodium (EtOH). All other solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (Merck, 70−230 or 230−400 mesh) using the indicated solvent.

***N*-Allyl-*N*-benzyl-2-phenyl-2-cyclohexen-1-ylamine (4a).** To a solution of 2-phenyl-2-cyclohexen-1-ol[13] (98.8 mg, 0.567 mmol) and CBr_4 (241 mg, 0.726 mmol) in CH_2Cl_2 (1 mL) was added PPh_3 (229 mg, 0.860 mmol) at 0 °C and the solution was stirred at room temperature for 2.5 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 20/1) to give 3-bromo-2-phenylcyclohexene, which was dissolved in CH_3CN (6.0 mL). To this solution were added K_2CO_3 (166 mg, 1.20 mmol) and benzylamine (0.19 mL, 1.70 mmol), and the solution was stirred at room temperature for 15 h. Water was added at 0 °C and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 6/1) to give a colorless oil, *N*-benzyl-2-phenyl-2-cyclohexen-1-ylamine (127 mg, 85%): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.46 (bs, 1 H), 1.58−1.88 (m, 3 H), 1.98 (m, 1 H), 2.09−2.28 (m, 2 H), 3.68 (d, J = 13.2 Hz, 1 H), 3.73 (bs, 1 H), 3.81 (d, J = 13.2 Hz, 1 H), 6.06 (dd, J = 3.9 Hz, 3.9 Hz, 1 H), 7.15−7.30 (m, 10 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 17.8, 26.2, 27.4, 51.3, 51.9, 126.1, 126.7, 126.8, 128.2, 128.3, 128.5, 139.6, 140.5, 141.0; IR (neat) ν 3335, 1642, 1599 cm^{-1}; EI-MS m/z 263 (M^+), 172, 156, 91, 77; HRMS calcd for $C_{19}H_{21}N$ 263.1674, found 263.1699. To a solution of the above amine (388 mg, 1.47 mmol) in CH_3CN (10.0 mL) were added K_2CO_3 (630 mg, 4.56 mmol) and allyl bromide (0.25 mL, 2.89 mmol) at 0 °C, and the solution was stirred at room temperature for 44 h. After removal of the solvent, water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 50/1) to give a colorless oil, **4a** (435 mg, 97%): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.56−2.00 (m, 4 H), 2.16 (m, 2 H), 2.90 (dd, J = 8.7, 13.8 Hz, 1 H), 3.05 (m, 1 H), 3.25 (d, J = 13.5 Hz, 1 H), 3.67 (d, J = 13.5 Hz, 1 H), 3.98 (m, 1 H), 4.96−5.07 (m, 2 H), 5.47−5.62 (m, 1 H), 6.06 (m, 1 H), 6.80 (m, 2 H), 7.11−7.13 (m, 3 H), 7.18−7.30 (m, 5 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.3, 21.3, 26.0, 52.6, 53.2, 54.7, 116.2, 126.1, 126.4, 127.3, 127.4, 127.7, 128.8, 130.2, 137.6, 140.5, 141.5, 142.2; IR (neat) ν 1640, 1600 cm^{-1}; EI-MS m/z 303 (M^+), 212, 156, 91, 77; HRMS calcd for $C_{22}H_{25}N_3O_3$ 303.1987, found 303.1982.

***N*-Allyl-2-phenyl-2-cyclohexen-1-ylamine (4b).** To a solution of the crude 3-bromo-2-phenylcyclohexene in CH_3CN (20 mL), prepared from 2-phenyl-2-cyclohexen-1-ol (654 mg, 3.75 mmol), CBr_4 (1.76 g, 5.31 mmol), and PPh_3 (1.57 g, 5.99

(12) The absolute configuration of **24** was determined to be *S* by the syntheses of (−)-mesembrane and (−)-mesembrine.

(13) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114.

mmol), were added K_2CO_3 (1.04 g, 7.52 mmol) and allylamine (0.85 mL, 11.3 mmol), and the solution was stirred at room temperature for 15 h. Water was added at 0 °C and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 10/1 ∼ 1/1) to give **4b** (716 mg, 89%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.23 (bs, 1 H), 1.62 (m, 1 H), 1.67−1.82 (m, 2 H), 1.91 (m, 1 H), 2.11−2.25 (m, 2 H), 3.15 (dd, J = 6.8, 13.9 Hz, 1 H), 3.26 (dd, J = 5.5, 13.9 Hz, 1 H), 3.74 (dd, J = 3.8, 3.8 Hz, 1 H), 5.01 (dd, J = 1.3, 10.1 Hz, 1 H), 5.07 (dd, J = 1.3, 17.1 Hz, 1 H), 5.79 (dddd, J = 5.5, 6.8, 10.1, 17.1 Hz, 1 H), 6.04 (dd, J = 3.9, 3.9 Hz, 1 H), 7.23 (dd, J = 7.5, 7.5 Hz, 1 H), 7.31 (dd, J = 7.5, 7.5 Hz, 2 H), 7.37 (d, J = 7.5 Hz, 2 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 17.58, 26.03, 27.53, 50.03, 51.96, 115.61, 126.02, 126.71, 128.23, 128.28, 137.11, 139.56, 141.14; IR (neat) ν 3336, 1642, 1598 cm^{-1}; EI-MS m/z 213 (M^+), 212, 156 (bp), 136, 77; HRMS calcd for $C_{15}H_{19}N$ 213.1518, found 213.1533.

***N*-Allyl-*N*-(2-phenyl-2-cyclohexenyl)diphenylmethylamine (4d).** A solution of **4b** (306 mg, 1.43 mmol), K_2CO_3 (774 mg, 5.60 mmol), and diphenylmethyl chloride (0.50 mL, 2.82 mmol) in CH_3CN (7 mL) was refluxed for 10 days. After usual workup, the residue was purified by column chromatography on silica gel (hexane/EtOAc, 50/1) to give **4d** (318 mg, 60%) and the starting amine (25%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.40 (m, 1 H), 1.61−1.67 (m, 2 H), 1.80 (m, 1 H), 2.05−2.12 (m, 2H), 3.18 (dd, J = 7.4, 15.0 Hz, 1 H), 3.23 (dd, J = 5.9, 15.0 Hz, 1 H), 4.07 (bs, 1 H), 4.67 (dd, J = 1.0, 17.2 Hz, 1 H), 4.73 (dd, J = 1.0, 10.0 Hz, 1 H), 4.90 (s, 1 H), 5.56 (dddd, J = 5.9, 7.4, 10.0, 17.2 Hz, 1 H), 5.99 (dd, J = 4.5, 5.1 Hz, 1 H), 6.91−6.93 (m, 2H), 7.03−7.07 (m, 3 H), 7.19−7.35 (m, 10 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.6, 24.7, 25.9, 50.4, 56.0, 61.4, 68.8, 115.0, 126.2, 126.3, 126.8, 127.3, 127.6, 127.6, 128.1, 128.4, 129.3, 130.9, 138.4, 141.9, 142.9, 143.1, 143.5. IR (neat) ν 1638, 1598 cm^{-1}; MS m/z 379 (M^+), 302, 224, 212, 167, 77; HRMS calcd for $C_{28}H_{29}N$ 379.2300, found 379.2318.

2-(3,4-Dimethoxyphenyl)-2-cyclohexen-1-ol (9). To a solution of 2-bromo-2-cyclohexenol (**8**)[14] (890 mg, 5.03 mmol) and $Pd(PPh_3)_4$ (289 mg 0.250 mmol) in benzene (36 mL) was added a 2 M solution of Na_2CO_3 (5 mL, 10.0 mL). To this solution was added a solution of 3,4-dimethoxyphenylboric acid (**7**)[15] (965 mg, 5.33 mmol) in EtOH (24 mL), and the mixture was warmed at 80 °C for 1.3 h under argon. After cooling, H_2O_2 (1.6 mL) was added at 0 °C and the solution was stirred at room temperature for 1 h. Water was added and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3/1) to give a colorless oil, 2-(3,4-dimethoxyphenyl)-2-cyclohexen-1-ol (798 mg, 68%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.63 (d, J = 5.3 Hz, 1 H), 1.68 (m, 1 H), 1.74−1.89 (m, 2 H), 1.97 (m, 1 H), 2.16 (m, 1 H), 2.26 (ddd, J = 4.5, 9.1, 18.5 Hz, 1 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 4.68 (bd, J = 4.1 Hz, 1 H), 6.09 (dd, J = 3.9, 3.9 Hz, 1 H), 6.85 (d, J = 8.9 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H), 7.02 (dd, J = 2.0, 8.9 Hz, 1 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 17.81, 26.47, 32.01, 56.32, 56.37, 66.09, 110.03, 111.68, 118.69, 128.00, 133.68, 139.23, 148.88, 149.45; IR (neat) ν 3416 cm^{-1}; MS m/z 234 (M^+), 216, 151; HRMS m/z calcd for $C_{14}H_{18}NO_3$ 234.1254, found 234.1229.

***N*-Allyl-2-(3,4-dimethoxyphenyl)-2-cyclohexen-1-ylamine (10).** To a solution of **9** (783 mg, 3.34 mmol) and CBr_4 (2.20 g, 6.63 mmol) in CH_2Cl_2 (20 mL) was added PPh_3 (3.47 g, 13.2 mmol) at 0 °C and the solution was stirred at the same temperature for 2 h. After the usual workup, the residue was purified by column chromatography on silica gel (hexane/AcOEt, 2/1) to give *N*-allyl-2-(3,4-dimethoxyphenyl)-2-cyclohexen-1-ylamine (682 mg, 75%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24 (bs, 1 H), 1.60−1.79 (m, 3 H), 1.91 (m, 1H), 2.12−2.23 (m, 2H), 3.16 (dd, J = 6.8, 13.9 Hz, 1H), 3.30 (dd, J = 5.4, 13.9 Hz, 1H), 3.68 (bs, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 5.03 (dd, J = 1.0, 9.9 Hz, 1H), 5.10 (dd, J = 1.0, 17.0 Hz, 1H), 5.80 (dddd, J = 5.4, 6.8, 9.9, 17.0 Hz, 1H), 5.98 (dd, J = 3.8, 3.8 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.93 (dd, J = 1.7, 8.2 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H); ^{13}C-NMR (126MHz, $CDCl_3$) d: 17.60, 26.06, 27.52, 50.21, 52.20, 55.76, 55.86, 109.77, 111.13, 115.74, 118.26, 127.25, 134.31, 137.22, 139.25, 148.12, 148.77; IR (neat) ν 3334, 1642, 1602 cm^{-1}; MS m/z 273 (M^+), 216; HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1718.

***N*-Allyl-*N*-[2-(3,4-dimethoxyphenyl)-2-cyclohexenyl]-diphenylmethylamine (4e).** A solution of **10** (682 mg, 2.49 mmol), K_2CO_3 (1.38 g, 9.98 mmol), and diphenylmethyl chloride (0.880 mg, 4.96 mmol) in CH_3CH_2CN (10 mL) was warmed at 90 °C for 9 days. After the usual workup, the residue was purified by column chromatography on silica gel (hexane/AcOEt, 2/1) to give **4e** (490 mg, 45%), and the starting material was recovered in 44% yield: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.42 (m, 1 H), 1.64−1.71 (m, 2 H), 1.80 (m, 1 H), 2.06−2.07 (m, 2 H), 3.19 (dd, J = 7.4, 15.0 Hz, 1 H), 3.27 (dd, J = 5.7, 15.0 Hz, 1 H), 3.90 (s, 3 H), 3.93 (s, 3 H), 4.03 (bs, 1 H), 4.67 (d, J = 17.2 Hz, 1 H), 4.72 (d, J = 9.9 Hz, 1 H), 4.92 (s, 1 H), 5.57 (dddd, J = 5.7, 7.4, 9.9, 17.2 Hz, 1 H), 5.95 (bs, 1 H), 6.84−6.85 (m, 3 H), 6.96−6.98 (m, 2 H), 7.04−7.09 (m, 3 H), 7.19−7.31 (m, 5 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.4, 24.9, 25.8, 50.6, 55.9, 56.0, 56.1, 68.9, 110.7, 111.0, 114.8, 119.7, 126.3, 126.8, 127.6, 127.9, 128.1, 128.4, 129.2, 130.3, 136.1, 138.5, 141.5, 143.2, 143.5, 147.7, 148.2; IR (neat) ν 1638, 1600, 1582 cm^{-1}; MS m/z 439 (M^+), 362, 272, 167; HRMS m/z calcd for $C_{30}H_{33}NO_2$ 439.2511, found 439.2524. For (*S*)-**4e**, $[\alpha]^{29}_D$ −41.1 (*c* 1.05, CH_3OH) (99% ee).

The General Procedure for the Cyclization Using Cp_2ZrBu_2. To a THF solution of Cp_2ZrCl_2 (1.3 equiv) was added BuLi (*ca*. 1.6 M in hexane, 2.6 equiv) at −78 °C, and the solution was stirred at the same temperature for 1 h. To this solution was added the diene (1 equiv) at −78 °C and the solution was stirred at room temperature. After 10% HCl was added to this solution at 0 °C, the mixture was stirred for 1 h, and the aqueous layer was made basic by K_2CO_3, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give the cyclized product.

(3*S,3a*R**,7a*R**)-1-Benzyl-3-methyl-3a-phenyl-2,3,3a,6,7,7a-hexahydroindole (5a).** A crude product, which was prepared from Cp_2ZrCl_2 (62.3 mg, 0.213 mmol), BuLi (1.69 M in hexane, 0.240 mL, 0.406 mmol), and **4a** (49.2 mg, 0.162 mmol), was purified by column chromatography on silica gel (hexane/AcOEt, 50/1−20/1) to give **5a** (13.3 mg, 27%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.74 (d, J = 5.7 Hz, 3 H), 1.32 (m, 1 H), 1.52 (m, 1 H), 1.82 (ddd, J = 5.3, 5.3, 17.3 Hz, 1 H), 2.35 (m, 1 H), 2.66 (bs, 3 H), 2.96 (bs, 1 H), 3.49 (d, J = 13.7 Hz, 1 H), 3.91 (d, J = 13.7 Hz, 1 H), 5.62 (dd, J = 1.1, 10.0 Hz, 1 H), 5.97 (dd, J = 4.9, 10.0 Hz, 1 H), 7.12−7.36 (m, 10 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.7, 20.8, 22.0, 41.1, 52.3, 59.2, 59.5, 71.0, 125.9, 126.5, 126.7, 127.6, 128.1, 128.1, 128.4, 129.5, 140.9, 145.4; IR (neat) ν 1598 cm^{-1}; MS m/z 303 (M^+), 212, 91, 77; HRMS calcd for $C_{22}H_{25}N$ 303.1987, found 303.1980.

(3*S,3a*R**,7a*R**)-1-(Diphenylmethyl)-3-methyl-3a-phenyl-2,3,3a,6,7,7a-hexahydroindole (5d).** A crude product, which was prepared from Cp_2ZrCl_2 (55.3 mg, 0.189 mmol), BuLi (1.69 M in hexane, 0.210 mL, 0.355 mmol), and **4d** (52.7 mg, 0.139 mmol), was purified by column chromatography on silica gel (hexane/CH_2Cl_2, 20/1−1/1) to give **5d** (30.7 mg, 58%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.71 (d, J = 6.8 Hz, 3 H), 1.11 (m, 1 H), 1.19 (dddd, J = 1.7, 4.9, 11.6, 11.6 Hz, 1 H), 1.81 (bd, J = 17.4 Hz, 1 H), 2.41−2.47 (m, 2 H), 2.77 (dd, J = 10.6, 10.6 Hz, 1 H), 2.93 (dd, J = 7.7, 10.6 Hz, 1 H), 3.22 (bd, J = 3.0 Hz, 1 H), 4.97 (s, 1 H), 5.65 (d, J = 10.3 Hz, 1 H), 6.12 (ddd, J = 1.7, 5.0, 10.3 Hz, 1 H), 7.14−7.37 (m, 15 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 11.7, 21.2, 21.4, 40.7, 52.9, 56.9, 68.6, 71.1, 125.9, 126.7, 126.8, 127.6, 127.9, 128.0, 128.2, 128.7, 128.7, 130.4, 143.0, 143.6, 145.3; IR (neat) ν 1653, 1598 cm^{-1}; MS m/z 379 (M^+), 302, 212, 167, 91, 77; HRMS m/z: calcd for $C_{28}H_{29}N$ 379.2300, found 379.2292.

(3*R,3a*S**,7a*S**)-1-(Diphenylmethyl)-3-methyl-3a-(3,4-dimethoxyphenyl)-2,3,3a,6,7,7a-hexahydroindole (5e).** A crude product, which was prepared from Cp_2ZrCl_2 (42.5 mg, 0.146 mmol), BuLi (1.71 M in hexane, 0.160 mL, 0.274 mmol),

(14) Sonnenberg, J.; Winstein, S. *J. Org. Chem.* **1962**, *27*, 748.
(15) Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 715. Huber, M. L.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 721.

and **4e** (49.3 mg, 0.112 mmol), was purified by column chromatography on silica gel (hexane/CH_2Cl_2, 1/3−1/10) to give **5e** (10.8 mg, 61%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.71 (d, J = 6.8 Hz, 3 H), 1.21−1.23 (m, 2 H), 1.83 (dd, J = 3.2, 16.5 Hz, 1 H), 2.30 (ddd, J = 6.8, 7.6, 10.7 Hz, 1 H), 2.46 (m, 1 H), 2.77 (dd, J = 10.7, 10.7 Hz, 1 H), 2.97 (dd, J = 7.6, 10.7 Hz, 1 H), 3.21 (bs, 1 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.99 (s, 1 H), 5.64 (d, J = 10.2 Hz, 1 H), 6.13 (ddd, J = 2.0, 5.1, 10.2 Hz, 1 H), 6.78 (d, J = 2.0 Hz, 1 H), 6.79 (d, J = 8.3 Hz, 1 H), 6.85 (dd, J = 2.0, 8.3 Hz, 1 H), 7.17−7.39 (m, 10 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 11.6, 21.2, 21.3, 41.0, 52.4, 55.8, 55.8, 56.4, 68.3, 70.5, 110.6, 111.0, 119.9, 126.6, 126.8, 127.9, 128.2, 128.7, 128.8, 130.4, 137.9, 142.6, 143.6, 147.2, 148.5; IR (neat) ν 1734, 1654, 1600 cm^{-1}; MS m/z 439 (M^+), 362, 272, 167, 91; HRMS calcd for $C_{30}H_{33}NO_2$ 439.2511, found 439.2491.

(3*R*,3a*S*,7a*S*)-1-(Diphenylmethyl)-3-(hydroxymethyl)-3a-(3,4-dimethoxyphenyl)-2,3,3a,6,7,7a-hexahydroindole (2a). To a stirred solution of **4e** (496 mg, 1.13 mmol), Cp_2ZrCl_2 (497 mg, 1.70 mmol) in THF (15 mL) was added BuLi (1.58 M in hexane, 2.1 mL, 3.32 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h and then at room temperature for 3.2 h. To the resultant solution was added MeMgBr (0.87 M in THF, 12.0 mL, 10.4 mmol) at −78 °C, and the mixture was stirred at room temperature for 3 h. The argon atmosphere in the reaction vessel was exchanged to oxygen, and the mixture was stirred for 10 h under oxygen. After 10% HCl was added to this solution at 0 °C, the mixture was stirred for 1 h, and the aqueous layer was made basic by K_2CO_3. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give **2a** (324 mg, 63%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.24−1.37 (m, 2 H), 1.54 (bs, 1 H), 1.82 (m, 1 H), 2.38 (m, 1 H), 2.57 (m, 1 H), 2.88 (dd, J = 10.1, 10.1 Hz, 1 H), 3.06 (dd, J = 8.0, 10.1 Hz, 1 H), 3.17 (bd, J = 2.8 Hz, 1 H), 3.51 (dd, J = 7.7, 10.6 Hz, 1 H), 3.62 (dd, J = 5.8, 10.6 Hz, 1 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.99 (s, 1 H), 5.67 (d, J = 10.2 Hz, 1 H), 6.12 (ddd, J = 2.6, 4.8, 10.2 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.85 (d, J = 2.1 Hz, 1 H), 6.89 (dd, J = 2.1, 8.4 Hz, 1 H), 7.17−7.39 (m, 10H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 11.4, 20.5, 21.0, 49.3, 51.4, 52.7, 55.8, 55.8, 62.9, 68.2, 69.6, 110.6, 110.6, 119.5, 126.7, 126.9, 127.1, 128.0, 128.2, 128.4, 128.8, 130.5, 138.6, 141.6, 143.2, 147.3, 148.5; IR (neat) ν 3494, 1600 cm^{-1}; MS m/z 455 (M^+), 424, 378, 288, 216, 167; HRMS calcd for $C_{30}H_{33}NO_3$ 455.2461, found 455.2475; $[\alpha]^{30}_D$ + 13.6 (c 1.01, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(Diphenylmethyl)-3-[((*tert*-butyldimethylsilyl)oxy)methyl]-3a-(3,4-dimethoxyphenyl)-2,3,3a,6,7,7a-hexahydroindole (2b). A solution of **2a** (210 mg, 0.461 mmol), imidazole (68.0 mg, 1.00 mmol), and *tert*-butyldimethylsilyl chloride (104 mg, 0.690 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 3 h. After usual workup, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 20/1) to give **2b** (239 mg, 85%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 3 H), −0.13 (s, 3 H), 0.74 (s, 9 H), 1.28 (m, 1 H), 1.38 (m, 1 H), 1.81 (dd, J = 3.6, 17.2 Hz, 1 H), 2.35−2.46 (m, 2 H), 2.84 (dd, J = 10.2, 10.2 Hz, 1 H), 3.05 (dd, J = 7.9, 10.2 Hz, 1 H), 3.17 (bd, J = 2.9 Hz, 1 H), 3.41 (dd, J = 9.7, 9.7 Hz, 1 H), 3.52 (dd, J = 5.3, 9.7 Hz, 1 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 4.98 (s, 1 H), 5.58 (d, J = 10.2 Hz, 1 H), 6.06 (ddd, J = 2.5, 4.9, 10.2 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 1 H), 6.79 (d, J = 1.9 Hz, 1 H), 6.85 (dd, J = 1.9, 8.4 Hz, 1 H), 7.18−7.40 (m, 10 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ −5.5, −5.4, 18.1, 20.7, 21.1, 25.8, 49.5, 51.6, 52.6, 55.8, 55.9, 63.0, 68.2, 69.3, 110.7, 110.8, 119.8, 126.6, 126.9, 127.6, 128.0, 128.1, 128.4, 129.1, 129.8, 139.0, 141.6, 143.5, 147.2, 148.5; IR (Nujol) ν 1600, 1586 cm^{-1}; MS m/z 569 (M^+), 167; HRMS calcd for $C_{36}H_{47}NO_3Si$ 569.3326, found 569.3309; $[\alpha]^{27}_D$ +19.6 (c 1.06, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-(hydroxymethyl)-3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindole (16). A suspension of **2b** (98.8 mg, 0.173 mmol) and 10% Pd on charcoal (93.2 mg) in methanol (3 mL) was stirred at room temperature for 9 h under an atmosphere of hydrogen. After the catalyst was filtered off, the solvent was evaporated to give the crude **2c**, which was dissolved in CH_2Cl_2. To this solution were added pyridine (0.025 mL, 0.307 mmol) and *p*-toluenesulfonyl chloride (45.8 mg, 0.240 mmol), and the mixture was stirred at room temperature for 12 h. After usual workup, the crude **2d** was obtained. A suspension of the crude **2d** and 10% Pd on charcoal (53.3 mg) in methanol (3 mL) was stirred at room temperature for 10 h under an atmosphere of hydrogen. After the catalyst was filtered off, the solvent was evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1−1/2) to give **16** (36.2 mg, 48% from **2b**): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.00 (bs, 1 H), 1.26 (m, 1 H), 1.35−1.49 (m, 2 H), 1.59−1.76 (m, 4 H), 1.84−2.08 (m, 2 H), 2.47 (s, 3 H), 3.41−3.45 (m, 2 H), 3.45 (dd, J = 11.2, 11.2 Hz, 1 H), 3.65 (bs, 1 H), 3.76 (s, 3 H), 3.84 (dd, J = 9.0, 11.2 Hz, 1 H), 3.84 (s, 3 H), 6.56 (d, J = 2.2 Hz, 1 H), 6.73 (dd, J = 2.2, 8.5 Hz, 1 H), 6.79 (d, J = 8.5 Hz, 1 H), 7.39 (d, J = 8.1 Hz, 2 H), 7.79 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 19.7, 21.5, 21.9, 24.7, 25.2, 48.7, 52.0, 52.1, 55.7, 60.5, 66.7, 109.9, 111.1, 119.3, 127.7, 129.7, 133.4, 133.8, 143.5, 147.6, 148.9; IR (Nujol) ν 3397 cm^{-1}; MS m/z 445 (M^+), 290, 162; HRMS calcd for $C_{24}H_{31}NO_5S$ 445.1923, found 445.1945; $[\alpha]^{30}_D$ +88.0 (c 1.04, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-formyl-3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindole (17). To a solution of **9** (24.2 mg, 0.050 mmol) in CH_2Cl_2 (1.7 mL) was added Dess−Martin reagent (60.4 mg, 0.140 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 min and then at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give **17** (19.6 mg, 80%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.25−1.44 (m, 4 H), 1.55−1.77 (m, 4 H), 2.47 (s, 3 H), 2.66 (dd, J = 9.9, 11.3 Hz, 1 H), 3.65 (dd, J = 9.9, 11.3 Hz, 1 H), 3.80 (s, 3 H), 3.83−3.84 (m, 1 H), 3.87 (s, 3 H), 3.96 (dd, J = 11.3, 11.3 Hz, 1 H), 6.67 (s, 1 H), 6.83 (s, 2 H), 7.34 (d, J = 7.9 Hz, 2 H), 7.78 (d, J = 7.9 Hz, 2 H), 9.36 (s, 1 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 19.4, 21.5, 21.8, 25.2, 26.5, 29.7, 46.9, 50.0, 55.9, 60.8, 66.1, 109.9, 111.4, 119.2, 127.6, 129.8, 132.5, 133.9, 143.8, 148.2, 149.2, 199.6; IR (Nujol) ν 1716 cm^{-1}; MS m/z 443 (M^+), 288; HRMS calcd for $C_{24}H_{29}NO_5S$ 443.1767, found 443.1752; $[\alpha]^{30}_D$ +93.8 (c 1.00, CH_3OH) (99% ee).

(3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindole (18). A solution of **17** (29.1 mg, 0.060 mmol) and $RhCl(PPh_3)_3$ (55.5 mg, 0.060 mmol) in CH_3CH_2CN (4.0 mL) was refluxed for 24 h. After being cooled to room temperature, the mixture was diluted with EtOH and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 5/1) to give **18** (17.1 mg, 62%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33−1.48 (m, 3 H), 1.69−1.91 (m, 5 H), 2.02 (m, 1 H), 2.18 (ddd, J = 7.8, 7.8, 12.7 Hz, 1 H), 2.38 (s, 3 H), 3.30 (ddd, J = 7.8, 7.8, 9.8 Hz, 1 H), 3.55 (ddd, J = 4.9, 7.8, 9.8 Hz, 1 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.90 (dd, J = 5.4, 7.8 Hz, 1 H), 6.61 (d, J = 2.4 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 6.69 (dd, J = 2.4, 8.3 Hz, 1 H), 7.12 (d, J = 8.1 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 21.4, 22.0, 22.5, 29.7, 30.0, 33.8, 35.5, 45.7, 48.3, 55.7, 64.0, 109.7, 110.6, 117.8, 127.0, 129.2, 135.6, 138.1, 142.8, 147.4, 148.6; IR (Nujol) ν 1598, 1464, 1336 cm^{-1}; MS m/z 415 (M^+), 260, 122; HRMS calcd for $C_{23}H_{29}NO_4S$ 415.1818, found 415.1796; $[\alpha]^{31}_D$ +54.0 (c 1.02, CH_3OH) (99% ee).

(3a*S*,7a*S*)-1-(Methoxycarbonyl)-3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindole. To a solution of **18** (16.1 mg, 0.030 mmol) in THF (1.0 mL) was added soldium naphthalenide (0.14 M solution in THF, 3.5 mL, 0.490 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min. After the reaction mixture was quenched by the addition of water, the mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, to the residue in CH_2Cl_2 (2.0 mL) were added K_2CO_3 (139 mg, 1.00 mmol) and methyl chloroformate (0.05 mL, 0.647 mmol), and the mixture was stirred at room temperature for 19 h. After the usual workup, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give the desired (methoxycarbonyl)indole derivative (7.2 mg, 59%): ^{1}H-NMR (400 MHz, $CDCl_3$,

at 55 °C) δ 1.27−1.69 (m, 6 H), 1.94 (m, 1 H), 2.05 (m, 1 H), 2.14 (bs, 1 H), 2.34 (ddd, J = 9.3, 9.3, 12.8 Hz, 1 H), 3.15 (m, 1 H), 3.39 (m, 1 H), 3.66 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.21 (bs, 1 H), 6.79−5.86 (m, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.4, 23.4, 35.9, 43.6, 52.1, 56.1, 56.2, 59.9, 110.1, 111.8, 118.0, 140.5, 147.7, 149.2, 155.4; IR (neat) ν 1694 cm^{-1}; MS m/z 319 (M^+), 304, 288, 260; HRMS calcd for $C_{18}H_{25}NO_4$ 319.1784, found 319.1758.

(3a*S*,7a*S*)-1-Methyl-3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindole ((−)-Mesembrane, 1a). To a solution of the above (methoxycarbonyl)indole (7.2 mg, 0.023 mmol) in Et_2O (1.0 mL) was added $LiAlH_4$ (4.2 mg, 0.111 mmol) at 0 °C, and the mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched by the addition of Na_2SO_4·10H_2O, and the solution was stirred at room temperature for 1 h. The mixture was diluted with Et_2O and filtered. The filtrate was concentrated to give the crude product, which was purified by column chromatography on aluminum oxide (hexane/ethyl acetate, 20/1) to give (−)-mesembrane (**1a**) (4.8 mg, 74%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.47−1.63 (m, 5 H), 1.77−1.91 (m, 3 H), 1.92−1.95 (m, 2 H), 2.29 (m, 1 H), 2.32 (s, 3 H), 2.58 (bs, 1 H), 3.24 (ddd, J = 4.5, 9.1, 9.1 Hz, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 6.81 (d, J = 8.3 Hz, 1 H), 6.90 (d, J = 2.1 Hz, 1 H), 6.92 (dd, J = 2.1, 8.3 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 22.9, 23.7, 36.0, 40.7, 41.0, 47.6, 54.4, 55.9, 56.0, 68.7, 110.7, 110.8, 118.9, 140.3, 146.9, 148.6; IR (neat) ν 1588, 1520 cm^{-1}; MS m/z 275 (M^+), 274, 260, 232; HRMS calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1878; $[\alpha]^{20}_D$ −14.6 (*c* 1.15, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-(hydroxymethyl)-3a-(3,4-dimethoxyphenyl)-2,3,3a,6,7,7a-hexahydroindole. To a solution of **2d** (178 mg, 0.319 mmol) in THF (3.0 mL) was added Bu_4NF (1.0 M in THF, 0.64 mL, 0.64 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1) to give the alcohol (143 mg, 100%): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.29−1.65 (m, 2 H), 1.98 (m, 1 H), 2.12−2.24 (m, 2 H), 2.38 (m, 1 H), 2.47 (s, 3 H), 3.22 (dd, J = 11.5, 11.5 Hz, 1 H), 3.37−3.50 (m, 2 H), 3.63 (bs, 1 H), 3.73 (s, 3 H), 3.84 (s, 3 H), 3.92 (dd, J = 7.2, 11.5 Hz, 1 H), 5.46 (ddd, J = 1.4, 1.4, 10.4 Hz, 1 H), 6.21 (dd, J = 4.9, 10.4 Hz, 1 H), 6.49 (d, J = 2.2 Hz, 1 H), 6.63 (dd, J = 2.2, 8.4 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 2 H), 7.80 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 20.4, 22.0, 23.0, 49.4, 52.0, 52.7, 56.2, 56.3, 61.4, 68.0, 110.4, 111.4, 120.3, 125.2, 128.1, 130.2, 133.1, 135.0, 135.2, 143.9, 148.5, 149.3; IR (neat) ν 3526, 1654, 1598 cm^{-1}; MS m/z 443 (M^+), 288; HRMS calcd for $C_{24}H_{29}NO_5S$ 443.1767, found 443.1782; $[\alpha]^{30}_D$ +193.9 (*c* 1.04, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-[((methoxycarbonyl)oxy)methyl]-3a-(3,4-dimethoxyphenyl)-2,3,3a,6,7,7a-hexahydroindole (2e). A solution of the above alcohol (104 mg, 0.235 mmol), pyridine (0.17 mL, 2.10 mmol), and methyl chloroformate (0.09 mL, 1.2 mmol) in CH_2Cl_2 (2.0 mL) was stirred at room temperature for 6 h. After the usual workup, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give **2e** (105 mg, 91%): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.47 (m, 1 H), 1.99 (m, 1 H), 2.17 (m, 1 H), 2.31−2.44 (m, 2 H), 2.47 (s, 3 H), 3.25 (dd, J = 11.6, 11.6 Hz, 1 H), 3.63 (bs, 1 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 3.84 (s, 3 H), 3.87−3.95 (m, 3 H), 5.46 (ddd, J = 1.3, 1.3, 10.4 Hz, 1 H), 6.24 (dd, J = 4.9, 10.4 Hz, 1 H), 6.48 (d, J = 2.2 Hz, 1 H), 6.63 (dd, J = 2.2, 8.5 Hz, 1 H), 6.75 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 19.9, 21.5, 22.5, 45.2, 51.7, 51.8, 54.8, 55.7, 55.9, 65.9, 67.2, 109.8, 111.0, 119.9, 124.4, 127.6, 129.8, 133.1, 133.6, 134.8, 143.5, 148.1, 148.9, 155.3; IR (neat) ν 1742, 1518, 1456 cm^{-1}; MS m/z 501 (M^+), 346; HRMS calcd for $C_{26}H_{31}NO_7S$ 501.1821, found 501.1841; $[\alpha]^{27}_D$ +164.8 (*c* 1.00, CH_2Cl_2) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-[((methoxycarbonyl)oxy)methyl)-3a-(3,4-dimethoxyphenyl)-6-oxo-2,3,-3a,6,7,7a-hexahydroindole (19). To a solution of CrO_3 (485 mg, 4.85 mmol) in CH_2Cl_2 (5 mL) was added 3,5-dimethylpyrazole (478 mg, 4.97 mmol) at −10 °C, and the mixture was stirred at the same temperature for 30 min. To the resulting solution was added a solution of **2e** (49.4 mg, 0.099 mmol) in CH_2Cl_2 (2.0 mL), and the mixture was stirred at the same temperature for 20 h. The reaction mixture was diluted with Et_2O, and filtered through Florisil. The filtrate was concentrated, the residue was dissolved in ethyl acetate, and the solution was washed with 10% HCl, saturated aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2/1) to give **19** (32.8 mg, 65%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3 H), 2.50 (dd, J = 3.1, 16.8 Hz, 1 H), 2.69 (m, 1 H), 3.08 (dd, J = 11.6, 11.6 Hz, 1 H), 3.16 (dd, J = 2.9, 16.8 Hz, 1 H), 3.68 (s, 3 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 3.96 (dd, J = 7.1, 11.6 Hz, 1 H), 4.02 (dd, J = 8.6, 11.3 Hz, 1 H), 4.08 (bs, 1 H), 4.13 (dd, J = 5.0, 11.3 Hz, 1 H), 6.40 (d, J = 10.4 Hz, 1 H), 6.57 (d, J = 2.1 Hz, 1 H), 6.69 (dd, J = 1.7, 10.4 Hz, 1 H), 6.71 (dd, J = 2.1, 8.3 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.74 (d, J = 8.1 Hz, 2 H). ^{13}C-NMR (126 MHz, $CDCl_3$), δ 21.5, 38.3, 46.4, 51.2, 52.6, 54.9, 55.8, 55.9, 64.5, 67.0, 109.1, 111.4, 119.6, 127.6, 128.7, 129.9, 132.6, 134.7, 144.1, 144.3, 149.1, 149.6, 155.2, 195.9; IR (Nujol) ν 1748, 1692 cm^{-1}; MS m/z 515 (M^+), 360; HRMS calcd for $C_{26}H_{31}NO_8S$ 515.1615, found 515.1616; $[\alpha]^{26}_D$ +138.0 (*c* 0.97, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-[((methoxycarbonyl)oxy)methyl]-3a-(3,4-dimethoxyphenyl)-6-oxo-2,3,3a,4,5,6,7,7a-octahydroindole. A suspension of **19** (68.2 mg, 0.132 mmol) and 10% Pd on charcoal (71.2 mg) in CH_2Cl_2 (2 mL) was stirred at room temperature for 3.5 h under an atmosphere of hydrogen. After the catalyst was filtered off, the solvent was evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1) to give the indolinone (58.0 mg, 79%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.22 (m, 1 H), 2.34−2.43 (m, 5 H), 2.47 (s, 3 H), 3.23 (dd, J = 2.5, 15.8 Hz, 1 H), 3.33 (dd, J = 11.0, 11.0 Hz, 1 H), 3.68 (s, 3 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.87 (dd, J = 9.3, 11.0 Hz, 1 H), 4.00, (d, J = 6.9 Hz, 2 H), 4.32 (bs, 1 H), 6.72 (s, 1 H), 6.84 (s, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 7.76 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.5, 24.7, 36.7, 41.0, 48.2, 49.1, 50.8, 54.9, 55.9, 56.1, 65.5, 67.8, 109.6, 111.6, 118.8, 127.7, 129.9, 131.1, 134.3, 144.1, 148.6, 149.6, 155.2, 207.4; IR (Nujol) ν 1748, 1717 cm^{-1}; MS m/z 517 (M^+), 362; HRMS calcd for $C_{26}H_{31}NO_8S$ 517.1771, found 517.1745.

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-[((methoxycarbonyl)oxy)methyl]-3a-(3,4-dimethoxyphenyl)-6,6-(ethylenedioxy)-2,3,3a,4,5,6,7,7a-octahydroindole. To a solution of the above indolinone (54.1 mg. 0.105 mmol) in CH_2Cl_2 (1.5 mL) were added TMSOTf (1.0 μL, 5.2 μmol) and 1,2-bis-(trimethylsiloxy)ethane (0.050 mL, 0.204 mmol) at −30 °C, and the mixture was stirred at the same temperature for 6 h. To the mixture was added saturated aqueous $NaHCO_3$ at −30 °C, the mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1) to give the ethylene ketal (55.1 mg, 98%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.46 (dd, J = 4.0, 15.0 Hz, 1 H), 1.76−1.82 (m, 2 H), 2.08−2.15 (m, 3 H), 2.46 (s, 3 H), 2.75 (d, J = 15.0 Hz, 1 H), 3.42 (dd, J = 11.4, 11.4 Hz, 1 H), 3.66 (s, 3 H), 3.76 (s, 3 H), 3.81−3.87 (m, 3 H), 3.85 (s, 3 H), 3.91−4.02 (m, 3 H), 4.03 (bs, 1 H), 4.10 (dd, J = 7.1, 14.7, Hz, 1 H), 6.54 (d, J = 2.1 Hz, 1 H), 6.73 (dd, J = 2.1, 8.6 Hz, 1 H), 6.78 (d, J = 8.6 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 2 H), 7.83 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.5, 22.9, 31.2, 32.6, 48.5, 48.7, 51.1, 54.8, 55.8, 55.8, 63.9, 64.4, 65.6, 66.6, 107.0, 109.6, 111.2, 119.1, 127.7, 129.7, 131.7, 134.4, 143.5, 148.0, 149.0, 155.2; IR (Nujol) ν 1750 cm^{-1}; MS m/z 561 (M^+), 406, 99; HRMS calcd for $C_{28}H_{35}NO_9S$ 561.2033, found 561.2008; $[\alpha]^{30}_D$ +59.4 (*c* 0.88, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-(hydroxymethyl)-3a-(3,4-dimethoxyphenyl)-6,6-(ethylenedioxy)-2,3,3a,4,5,6,7,7a-octahydroindole (20). To a solution of the above ethylene ketal (53.2 mg, 0.095 mmol) in CH_2Cl_2 (1.0 mL) were added MeOH (1.0 mL) and K_2CO_3 (41.3 mg, 0.299 mmol), and the mixture was stirred at room temperature for 2 h. After

the usual workup, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/2) to give **20** (46.1 mg, 97%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.94 (bs, 1 H), 1.45 (dd, J = 4.1, 14.9 Hz, 1 H), 1.76−1.80 (m, 2 H), 1.97 (m, 1 H), 2.09−2.12 (m, 2 H), 2.46 (s, 3 H), 2.75 (d, J = 14.9 Hz, 1 H), 3.41 (dd, J = 11.3, 11.3 Hz, 1 H), 3.44 (bs, 1 H), 3.75 (s, 3 H), 3.82−3.87 (m, 2 H), 3.85 (s, 3 H), 3.93 (dd, J = 7.0, 12.2 Hz, 1 H), 4.00 (m, 2 H), 4.02 (bs, 1 H), 4.12 (dd, J = 7.2, 14.7 Hz, 1 H), 6.56 (d, J = 1.7 Hz, 1 H), 6.74 (dd, J = 1.7, 8.6 Hz, 1 H), 6.77 (d, J = 8.6 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 2 H), 7.84 (d, J = 8.1 Hz, 2 H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 21.5, 23.0, 31.3, 32.7, 48.5, 51.6, 52.2, 55.8, 60.5, 63.9, 64.3, 66.9, 107.2, 109.6, 111.2, 119.0, 127.8, 129.7, 132.6, 134.3, 143.5, 147.9, 149.1; IR (Nujol) ν 3508 cm^{-1}; MS m/z 503 (M^+), 348, 99; HRMS calcd for $C_{26}H_{33}NO_7S$ 503.1978, found 503.1984; $[\alpha]^{28}_D$ +85.6 (c 1.15, CH_3OH) (99% ee).

(3*R*,3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3-formyl-3a-(3,4-dimethoxyphenyl)-6,6-(ethylenedioxy)-2,3,3a,4,5,6,7,7a-octahydroindole. To a solution of **20** (42.9 mg, 0.085 mmol) in CH_2Cl_2 (2.5 mL) was added Dess−Martin reagent (72.3 mg, 0.170 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1) to give the aldehyde (39.0 mg, 91%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.65 (dd, J = 4.3, 14.8 Hz, 1 H), 1.68−1.78 (m, 2 H), 2.11 (m, 2 H), 2.21 (m, 1 H), 2.45 (s, 3 H), 2.62 (d, J = 14.8 Hz, 1 H), 2.77 (dd, J = 8.6, 8.6 Hz, 1 H), 3.64 (dd, J = 8.6, 11.8 Hz, 1 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 3.82−4.00 (m, 4 H), 4.06 (dd, J = 6.6, 14.1 Hz, 1 H) 4.22 (bs, 1 H), 6.68 (s, 1 H), 6.79−6.81 (m, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.80 (d, J = 8.1 Hz, 2 H), 9.47 (s, 1 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 21.5, 25.5, 31.1, 33.6, 46.6, 49.8, 55.9, 55.9, 60.4, 64.0, 64.4, 66.1, 106.8, 109.6, 111.3, 118.8, 127.7, 129.7, 132.4, 134.5, 143.7, 148.4, 149.3, 199.6; IR (Nujol) ν 1718 cm^{-1}; MS m/z 501 (M^+), 346, 99; HRMS calcd for $C_{26}H_{31}NO_7S$ 501.1825, found 501,1827; $[\alpha]^{30}_D$ +78.6 (c 1.08, CH_3OH) (99% ee).

(3a*S*,7a*S*)-1-(*p*-Tolylsulfonyl)-3a-(3,4-dimethoxyphenyl)-6,6-(ethylenedioxy)-2,3,3a,4,5,6,7,7a-octahydroindole (21). A solution of the above aldehyde (37.0 mg, 0.074 mmol) and $RhCl(PPh_3)_3$ (95.9 mg, 0.104 mmol) in CH_3CH_2CN (3.0 mL) was refluxed for 24 h. After being cooled to room temperature, the mixture was diluted with ethanol and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1) to give **21** (27.6 mg, 79%): ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.56−1.65 (m, 2 H), 1.69−1.88 (m, 3 H), 1.98−2.22 (m, 2 H), 2.36 (s, 3 H), 2.40 (m, 1 H), 3.23 (ddd, J = 7.3, 10.0, 10.0 Hz, 1 H), 3.59 (ddd, J = 1.8, 8.9, 8.9 Hz, 1 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 3.85−3.93 (m, 4 H), 4.25 (dd, J = 6.5, 10.0 Hz, 1 H), 6.55 (d, J = 8.4 Hz, 1 H), 6.62 (d, J = 2.3 Hz, 1 H), 6.66 (dd, J = 2.3, 8.4 Hz, 1 H), 7.00 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.2 Hz, 2 H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 11.4, 21.3, 30.8, 34.0, 39.8, 45.2, 47.8, 55.6, 55.6, 64.4, 64.5, 64.7, 108.0, 109.5, 110.3, 117.6, 126.6, 129.0, 135.6, 137.8, 147.6, 147.6, 148.6; IR (Nujol) ν 1508, 1456 cm^{-1}; MS m/z 473 (M^+)m 318, 99; HRMS calcd for $C_{25}H_{31}NO_6S$ 473.1873, found 473.1898; $[\alpha]^{30}_D$ +58.5 (c 0.99, CH_2Cl_2) (99% ee).

(3a*S*,7a*S*)-1-Methyl-3a-(3,4-dimethoxyphenyl)-6-oxo-2,3,3a,4,5,6,7,7a-octahydroindole ((−)-Mesembrine, 1b). To a solution of **21** (4.9 mg, 0.010 mmol) in THF (0.5 mL) was added sodium naphthalenide (0.15 M solution in THF, 1.2 mL, 0.180 mmol) at −78 °C, and the mixture was stirred at −78 °C for 15 min. After the reaction mixture was quenched by the addition of water, the aqueous layer was extracted with ethyl acetate, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in THF (0.5 mL), and BuLi (1.69 M in hexane, 0.020 mL, 0.034 mmol) was added to this solution at −78 °C. To this solution was added MeI (1.0 μL, 16.1 μmol) at −78 °C, and the solution was stirred at the same temperature for 1 h. The reaction mixture was quenched by the addition of water, and the resulting mixture was extracted with ethyl acetate. After removal of the solvent, the residue was dissolved in 10% HCl and the aqueous solution was stirred at room temperature for 18 h. The reaction mixture was made basic by the addition of K_2CO_3, and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by preparative TLC to give (−)-mesembrine (**1b**) (1.0 mg, 35%): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.04−1.61 (m, 3 H), 1.94−2.20 (m, 3 H), 2.26 (s, 3 H), 2.35 (m, 1 H), 2.54 (m, 2 H), 2.89 (m, 1 H), 3.08 (m, 1 H), 3.81 (s, 3 H), 3.88 (s, 3 H), 6.75−6.91 (m, 3 H); IR (neat) ν 1722, 1520 cm^{-1}; MS m/z 289 (M^+), 274, 218, 70; HRMS calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1699; $[\alpha]^{30}_D$ −53.0 (c 0.24, CH_3OH) (99% ee).

2-(3,4-Dimethoxyphenyl)-3-[(methoxycarbonyl)oxy]-1-cyclohexene (22a). To a stirred solution of **9** (261 mg, 1.12 mmol) and pyridine (0.36 mL, 4.46 mmol) in CH_2Cl_2 (6 mL) was added methyl chloroformate (0.17 mL, 2.23 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. Water was added to the reaction mixture, and the mixture was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3/1) to give **22a** (323.2 mg, 99%) as a colorless solid: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.64−1.94 (m, 3 H), 2.06−2.40 (m, 3 H), 3.71 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 5.72−5.78 (m, 1 H), 6.25 (dd, J = 4.8, 3.2 Hz, 1 H), 6.82 (brd, J = 9.1 Hz, 1 H), 6.88−6.94 (m, 2 H); IR (Nujol) ν 1742, 1602, 1580, 1518, 1464, 1448, 1242, 1170, 1148, 1022 cm^{-1}; MS m/z 292 (M^+), 216. 201, 185, 151, 115, 91, 79. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.55; H, 6.89.

Typical Procedure for Palladium-Catalyzed Enantioselective Allylic Substitution of 22a (Table 2, Run 10). A solution of Pd_2dba_3·$CHCl_3$ (6.8 mg, 6.5 μmol), (*S*)-BINAPO (9.0 mg, 13.7 μmol), **22a** (191 mg, 0.65 mmol), and **23** (152 mg, 0.72 mmol) in THF (6.5 mL) was stirred at room temperature for 19 h. After removal of the solvent, the residue was dissolved in Et_2O, and the organic layer was washed with 10% aqueous NaOH (three times), saturated aqueous NH_4Cl, and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 5/1) to give **24** (223 mg, 80%, 86% ee) as a colorless solid. A single recrystallization of **24** (4.35 g, 86% ee) from MeOH afforded the nearly enantiomerically pure **24** (3.44 g, 99% ee, 79% recovery): mp 88−90 °C; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.56−1.98 (m, 4 H), 2.08−2.20 (m, 2 H), 2.40 (s, 3 H), 3.51 (dddd, J = 16.2, 6.7, 1.2, 1.2 Hz, 1 H), 3.61 (dddd, J = 16.2, 5.9, 1.2, 1.2 Hz, 1 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 4.86 (ddd, J = 10.1, 1.6, 1.2 Hz, 1 H), 4.96 (ddd, J = 17.2, 1.6, 1.2 Hz, 1 H), 5.14−5.25 (m, 1 H), 5.31 (dddd, J = 17.2, 10.1, 6.7, 5.9 Hz, 1 H), 6.12 (ddd, J = 4.0, 3.9, 1.8 Hz, 1 H), 6.71 (d, J = 8.3 Hz, 1 H), 6.79 (dd, J = 8.3, 2.0 Hz, 1 H), 6.94 (d, J = 2.0 Hz, 1 H), 7.20 (d, J = 8.1 Hz 2 H), 7.60 (d, J = 8.1 Hz, 2 H); IR (Nujol) ν 1638, 1600, 1582, 1518, 1466, 1342, 1330, 1250, 1164, 1024 cm^{-1}; MS m/z 427 (M^+), 272, 216, 201, 190, 185, 151, 115, 91, 79; $[\alpha]^{30}_D$ −27.2 (c 1.02, CH_3OH) (99% ee). Anal. Calcd for $C_{24}H_{29}NO_4S$: C, 67.42; H, 6.84; N, 3.28; S, 7.50. Found: C, 67.31; H, 6.84; N, 3.23; S, 7.57.

Synthesis of (*S*)-10 from (*S*)-24. To a sodium naphthalenide solution in THF [ca. 0.17 M, prepared from sodium (739 mg, 32.1 mg atom) and naphthalene (4.53 g, 35.3 mmol) in THF (190 mL)] was added a solution of (***S***)-**24** (3.44 g, 8.04 mmol) in THF (20 mL) at −78 °C, and the mixture was stirred at the same temperature for 50 min. Water was added to the reaction mixture at −78 °C, and the solution was warmed to room temperature. The aqueous layer was extracted with Et_2O, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 10/1−5/1−1/2) to give (***S***)-**10** (1.57 g, 71%): $[\alpha]^{28}_D$ −128.0 (c 1.00, CH_3OH) (99% ee).

Supporting Information Available: Complete spectroscopic characterization, including reproduction of the ^{1}H or ^{13}C NMR spectra of the compounds discussed (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9701187