(d), 111.8 (s), 54.1 (q), 50.77 (t), 46.6 (t). Anal. Calcd for $C_{15}H_{11}O_6Br$: C, 49.07; H, 3.02; Br, 21.76. Found: C, 49.35; H, 3.14; Br, 22.27.

2,2-Dimethyl-6-[(2-bromo-5-hydroxy-1,4-dioxonaphth-3-yl)methyl]-1,3-dioxen-4-one (21). Method A. In a 250-mL 3-necked round-bottom flask, naphthoquinone **1** (1.0 g, 4 mmol) was dissolved in THF (75 mL), placed under nitrogen, and cooled to −78 °C. The diene **4** (2.6 g, 12 mmol) was added via syringe, and the reaction mixture was allowed to stir for 12 h. To effect desilylation, 6 N HCl (10 mL) was added at −78 °C and stirred for 2 h while allowing the solution to warm to room temperature. The solvent was removed under reduced pressure, and the residue was diluted with dichloromethane (125 mL). The solution was washed with water (3 × 50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography (hexane–acetone, 5:1) afforded **21** (1.2 g, 77%) **Method B.** In a 250-mL round-bottom flask were placed THF (50 mL) and diisopropylamine (1.7 mL, 12 mmol) under nitrogen. The solution was cooled to −78 °C, and maintained at that temperature throughout the reaction. Added dropwise to this solution was 4.75 mL of *n*-butyllithium (12 mmol). The solution was allowed to stir for 10 min. 2,2,6-Trimethyl-1,3-dioxen-4-one (1.6 mL, 12 mmol) was added via syringe, and the solution was allowed to stir for 1 h. Naphthoquinone **1** (1.0 g, 4 mmol) dissolved in THF (40 mL) was added slowly through a dropping funnel. The reaction mixture was allowed to stir for 4 h and was treated with 6 N HCl (15 mL) at −78 °C followed by stirring for 2 h while allowing the solution to warm to room temperature. The reaction was subjected to the same procedure as described in method A, affording **21** (1.0 g, 68%): mp 115 °C; ^1H NMR 11.77 (1 H, s), 7.74–7.38 (3 H, m), 5.30 (1 H, s), 3.86 (2 H, s), 1.69 (6 H, s); IR 1710, 1690, 1640, 1580 cm^{-1}; ^{13}C NMR 185.3, 176.4, 171.5, 165.2, 158.1, 144.0, 141.9, 137.2, 135.0, 125.2, 121.7, 114.3, 98.2, 92.5, 47.8, 19.1. Anal. Calcd for $C_{17}H_{13}O_6Br$: C, 51.93; H, 3.33; Br, 20.32. Found: C, 51.45; H, 3.54; Br, 20.01.

2-Bromo-5-hydroxy-3-[2-hydroxy-1-(methoxycarbonyl)-1-propenyl]-1,4-naphthoquinone (25). In a 250-mL 3-necked round-bottom flask were placed THF (30 mL) and NaH (0.6 g, 10 mmol) under nitrogen. The solution was cooled to −78 °C and maintained at that temperature throughout the reaction. Methyl acetoacetate (1.1 mL, 10 mmol) was added via syringe, and resulting solution was allowed to stir for 10 min. Added dropwise to this solution was 4.2 mL of *n*-butyllithium (11 mmol), and the mixture was allowed to stir for 10 min. Naphthoquinone **1** (2.0 g, 8 mmol) dissolved in THF (50 mL) was added via a dropping funnel, and the reaction mixture was allowed to stir for 30 min. The solution was permitted to warm to room temperature and stirred for an additional 15 min. The mixture was cooled to −78 °C and 6 N HCl (7 mL) was added and stirred for 5 min. The reaction mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residue was diluted with dichloromethane (125 mL), washed with water (2 × 50 mL), and dried over $MgSO_4$. Flash chromatography (hexane–ethyl acetate, 10:1) afforded **25** (2.6 g, 88%): mp 134–135 °C; IR 1678, 1656, 1636 cm^{-1}; ^1H NMR 13.06 (1 H, s), 11.93 (1 H, s), 7.76–7.27 (3 H, m), 3.72 (3 H, s), 1.93 (3 H, s); ^{13}C NMR 186.5 (s), 175.3 (s), 170.1 (s), 162.1 (s), 145.7 (s), 143.7 (s), 140.1 (s), 136.6 (d), 129.0 (s), 125.1 (d), 120.8 (d), 118.5 (s), 98.3 (s), 52.2 (q), 20.1 (q). Anal. Calcd for $C_{15}H_{11}O_6Br$: C, 49.07; H, 3.02; Br, 21.76. Found: C, 48.91; H, 3.15; Br, 21.65.

Acknowledgment. We are grateful to the National Science Foundation for a Grant (CHE-8418897) (A.K.) used to purchase the CAD-4 X-ray diffractometer system.

Registry No. **1**, 69008-03-3; **2**, 52431-65-9; **3**, 130573-42-1; **4**, 130573-43-2; **5**, 605-89-0; **6**, 6566-25-2; **7**, 77189-69-6; **8**, 77197-58-1; **10**, 2065-37-4; **11**, 110362-29-3; **12**, 130573-44-3; **13**, 117-10-2; **15**, 74590-73-1; **16**, 52431-74-0; **17**, 52431-73-9; **18**, 130573-45-4; **19**, 130573-46-5; **20**, 130573-47-6; **21**, 130573-48-7; **25**, 130573-49-8; $MeCOCH_2CO_2Me$, 105-45-3; Cl_2SiMe_2, 75-78-5; MeCH/dbdCHCO$_2$Me, 18707-60-3; 1,6-diacetoxynaphthalene, 59335-81-8; 2-bromo-6-acetoxy-1,4-naphthoquinone, 130573-50-1; 1,7-diacetoxynaphthalene, 51850-49-8; 3-bromo-6-acetoxy-1,4-naphthoquinone, 130573-51-2; 2-ethyl-1-hydroxynaphthalene, 30159-69-4; 2-ethyl-1,4-naphoquinone, 5409-32-5; 1,4-diacetoxy-2-methylnaphthalene, 573-20-6; 2-bromo-3-methyl-1,4-naphthoquinone, 3129-39-3; 1-hydroxynaphthalene, 90-15-3; 2,2,6-trimethyl-1,3-dioxen-4-one, 5394-63-8.

Supplementary Material Available: Tables of final atomic fractional coordinates, anisotropic displacement parameters, and selected bond distances and angles and an ORTEP diagram for **12** (4 pages); observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

Radical Cyclization of *N*-(Cyclohex-2-enyl)-α,α-dichloroacetamides. Stereoselective Syntheses of (±)-Mesembranol and (±)-Elwesine

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Received March 28, 1990 (Revised Manuscript Received July 17, 1990)

Stereoselective syntheses of the *Sceletium* alkaloid (±)-mesembranol (**2**) and the *Amaryllidaceae* alkaloid (±)-elwesine (**3**) have been achieved. A key step in the syntheses involves the Bu_3SnH-mediated radical cyclization of the dichloroacetamides **34** and **46**, which provides the *cis*-3a-aryloctahydroindolones **36** and **47**, respectively. The amides **34** and **46** were prepared in a highly stereocontrolled manner from the corresponding 1-arylcyclohexenes **29** and **41** along the lines: **29** → **30a** → **31** → **32** → **33** → **34** and **41** → **42a** → **44a** → **45a** → **46**. Transformation of **36** into (±)-mesembranol was readily accomplished by reduction with diborane and subsequent removal of the *O*-benzyl protecting group by hydrogenolysis over Pd/C. On the other hand, debenzylation of **36** with Raney Ni afforded a mixture of the 6α- and 6β-alcohols **39a** and **39b**, which was then reduced by alane to give a separable mixture of (±)-mesembranol and (±)-6-epimesembranol (**40**). Reduction of **47** with diborane followed by catalytic hydrogenolysis over Pd/C afforded the amino alcohol **50**, which has already been converted into (±)-elwesine by Pictet–Spengler cyclization.

Sceletium alkaloids such as mesembrine (**1**) and mesembranol (**2**), which possess a *cis*-3a-arylhydroindole nucleus as the basic structural element, have remained attractive target molecules for total synthesis.[1] This may

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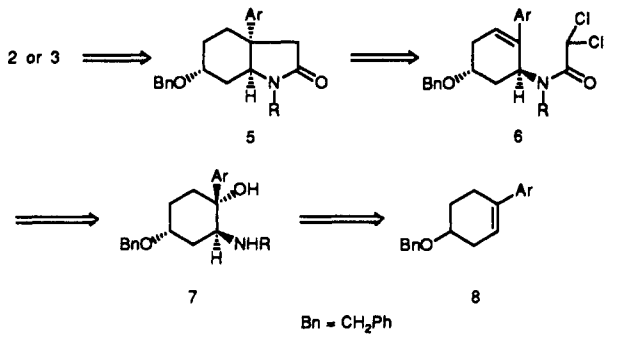
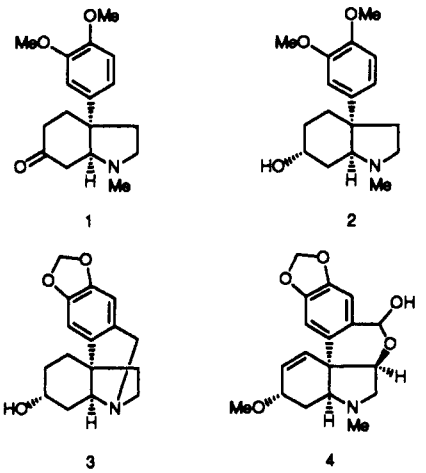
Scheme I



reflect not only the potential central nervous system activity of mesembrine[2] but also the close structural relationship with the more complex *Amaryllidaceae* alkaloids elwesine (**3**) and pretazettine (**4**).[3]

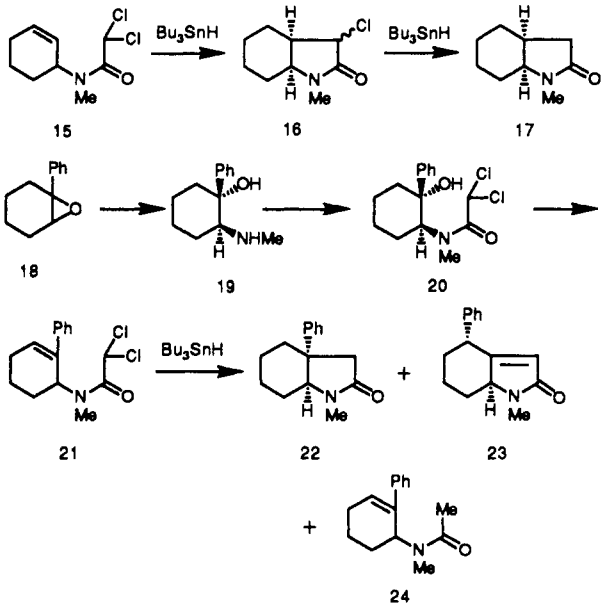


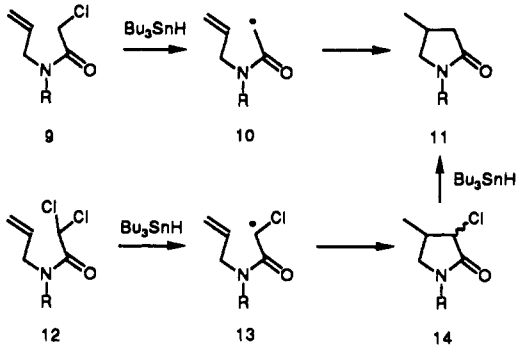
Our interest in this area was stimulated by the prospect of designing a stereoselective entry to this class of alkaloids according to the strategy outlined in retrosynthetic format depicted in Scheme I. The key feature of our approach is based upon a tributyltin hydride (Bu_3SnH) mediated radical cyclization of the α,α-dichloroacetamides **6** to give the *cis*-3a-aryloctahydroindolones **5**.[4] The synthesis of the amides **6** having a relative stereochemistry characteristic of the six-membered ring in **2** or **3** was envisaged to arise from the amino alcohols **7**, which in turn were prepared from the cyclohexenes **8** via a stereoselective epoxidation followed by ring opening with the appropriate amines. We now wish to report an application of this methodology to the total synthesis of (±)-mesembranol (**2**) and the formal total synthesis of (±)-elwesine (**3**).[5]

Synthesis of (±)-Mesembranol (2)

Our previous studies[6] on the Bu_3SnH-mediated radical cyclization of *N*-allyl-α-chloroacetamides have revealed that the carbamoylmethyl radicals **10** derived from α-chloroacetamides **9** give only a minute amount of the γ-butyro lactams **11**, whereas the cyclization of the monochloro-substituted carbamoylmethyl radicals **13** from dichloroacetamides **12** proceeded smoothly to give the α-chloro lactams **14** in good yields. The chloro lactams **14** can readily be converted into the dechlorinated lactams **11** if desired, by treatment with an additional equivalent of Bu_3SnH.

Scheme II





With this information in hand, we began our investigations by examining the cyclization of *N*-(cyclohex-2-en-1-yl)-*N*-methyl-α,α-dichloroacetamide (**15**). Thus, a mixture of Bu_3SnH (1 equiv) and a catalytic amount of azobis(isobutyronitrile) (AIBN) in toluene was added to a boiling solution of **15** (6.5×10^{-3} M) in toluene over a period of 1 h, and the mixture was refluxed for a further hour. At this stage, the chloro lactam **16** might be formed. Further Bu_3SnH (1.1 equiv) and AIBN in toluene were then added before the solution was heated again under reflux for 2 h. Evaporation of the solvent followed by chromatography on silica gel afforded the dechlorinated cis-bicyclic lactam **17** in 92% yield.

Next, the phenyl-substituted compound **21**, which was prepared from 1-phenylcyclohexene oxide (**18**) in 3 steps (Scheme II), was treated with Bu_3SnH (2.1 equiv) and AIBN to give the *cis*-3a-phenylhydroindolone **22** and an unexpected product **23** in 43 and 6% yields, respectively, along with the reduction product **24** (28%). The ^1H NMR spectrum of the rearranged product **23** exhibited a singlet at δ 6.03 due to the olefinic proton at C3. The protons at C4 and C7a appeared as a doublet (J = 4.7 Hz) at δ 4.25 and a doublet of doublets (J = 11.5, 6.3 Hz) at δ 3.78, respectively.

(1) For a review of the chemistry of the *Sceletium* alkaloids, see: Jeffs, P. W. In *The Alkaloids*; Rodrigo, R. G. A., Ed., Academic Press: New York, 1981; Vol. 19, pp 1–80.

(2) Ohishi, A.; Kugita, H. Japan. Patent 1971, 71 43,539 [*Chem. Abstr.* **1972**, 76, 59443u].

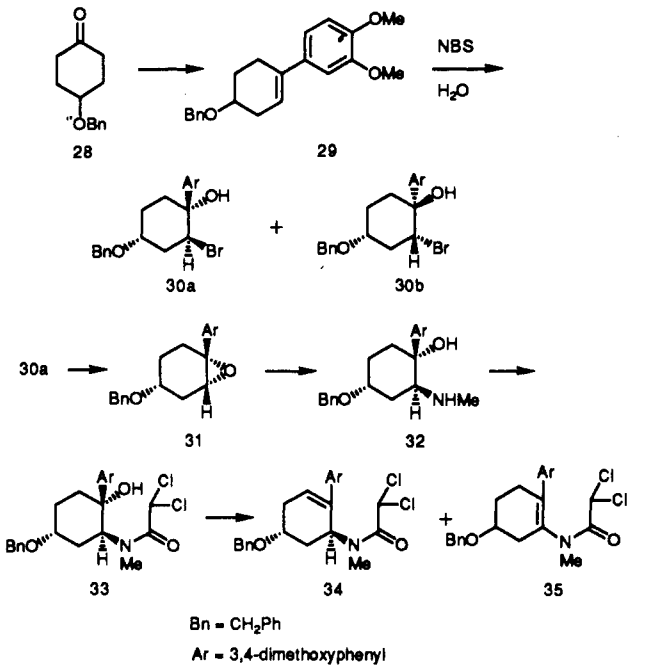
(3) For a review of the *Amaryllidaceae* alkaloids, see: Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251–376.

(4) For other approaches to octahydroindoles via a radical process, see: (a) Nagashima, H.; Ara, K.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1985**, 518. (b) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (c) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.

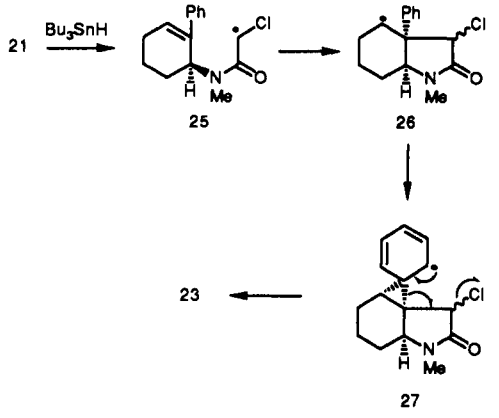
(5) For a preliminary account of a portion of this work, see: Ishibashi, H.; So, T. S.; Sato, T.; Kuroda, K.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1989**, 762.

(6) Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 879.

Scheme III

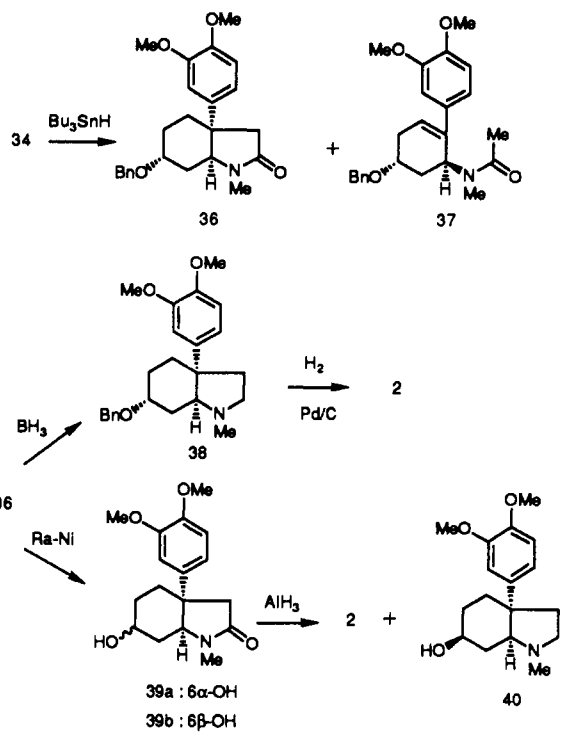


Formation of **22** and **23** can be explained in terms of the common intermediate **26** generated by a cyclization of the carbamoylmethyl radical **25**. The attack of Bu_3SnH on the radical center of **26** would afford the normal product **22** via a reductive dechlorination. On the other hand, when the radical center of **26** attacks the angular phenyl group intramolecularly, a new radical (**27**) might result. This step is then followed by elimination of the chlorine atom, with concomitant 1,2-aryl migration, to lead to **23**.



In planning the synthesis of mesembranol (**2**), the dichloroacetamide **34**, in which the benzyloxy and the acylamino groups are trans to each other is needed. This compound was prepared from 4-(benzyloxy)cyclohexanone (**28**) in a highly stereocontrolled manner (Scheme III). Thus, Grignard coupling of **28** with (3,4-dimethoxyphenyl)magnesium bromide followed by dehydration of the resultant carbinol with *p*-toluenesulfonic acid afforded the cyclohexene **29**. Treatment of **29** with *N*-bromosuccinimide in aqueous acetonitrile provided two bromohydrins **30a** and **30b** in 83 and 10% yields, respectively, after chromatographic separation.[7] The ^1H NMR spectral properties of **30a**, which showed the equatorial nature (dd, J = 5.0, 3.0 Hz) of H-2 (CHBr) and the axial disposition

Scheme IV



(double t, J = 10.0, 4.5 Hz) of H-4 (CHOBn), established the trans relationship of the benzyloxy group and the bromine atom. The 1,3-diaxial nature of H-2 (dd, J = 10.5, 4.9 Hz) and H-4 (double t, J = 8.5, 4.2 Hz) of **30b** indicated the cis relationship of the benzyloxy group and the bromine atom.

Exposure of the major bromohydrin **30a** with potassium carbonate afforded the epoxide **31**,[8] which was then heated with methanolic methylamine in a sealed tube at 100 °C to give, in 78% yield, the amino alcohol **32**. The trans relationship of the benzyloxy group and the methylamino group of **32** was established by its ^1H NMR spectrum (see Experimental Section). Practically, it is not necessary to isolate the epoxide **31**: on heating of the bromohydrin **30a** with methylamine under the same conditions as above, the same amino alcohol **32** was obtained in 83% yield. N-Acylation of **32** with dichloroacetyl chloride afforded the amide **33** in 79% yield together with a small amount (8%) of the requisite amide **34**. Dehydration of **33** was effected with *p*-toluenesulfonic acid in boiling benzene to give the amide **34** (80%) along with the enamide **35** (15%).

Radical cyclization of the dichloroacetamide **34** was performed under essentially the same conditions as those described above, and the expected lactam **36** was obtained in 51% yield along with the reduction product **37** (26%). In this instance, such a rearrangement product as **23** observed for **21** could not be isolated (Scheme IV).

Jeffs and co-workers[9] have reported the synthesis of (±)-mesembranol (**2**) and (±)-6-epimesembranol (**40**) from the mixture of the 6α-benzyl ether **36** and its 6β-epimer via reduction with diborane, catalytic hydrogenolysis under medium pressure, and then chromatographic separation. According to this procedure, the compound **36** was reduced with diborane in tetrahydrofuran (THF) to afford, in 81%

(7) A similar result has been reported for the reaction of 4-*tert*-butyl-1-(3-chlorophenyl)cyclohexene with *N*-bromoacetamide, see: Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463.

(8) A direct epoxidation of the cyclohexene **29** with peracid is presumed to afford a ca. 1:1 mixture of the epoxide **31** and its diastereomer, see: Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron* **1968**, *24*, 1755.

(9) Jeffs, P. W.; Cortese, N. A.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3881. No additional example of the synthesis of (±)-mesembranol has been reported so far.

yield, the hydroindole **38**, which was then subjected to the catalytic hydrogenolysis over 5% Pd–C at 4 kg/cm^2 in ethanol containing hydrochloric acid for 24 h to furnish (±)-mesembranol (**2**) in 68% yield as colorless needles (mp 121–122 °C). On the other hand, hydrogenolysis of the benzyl ether **36** with Raney nickel (W-2) in refluxing ethanol afforded a mixture of the 6α- and 6β-alcohols **39a,b** in a ratio of 3.7:1 (by ^{1}H NMR). This result can be explained by a partial epimerization of the initially formed 6α-alcohol **39a** to the corresponding 6β-isomer **39b** with Raney nickel.[10] The mixture of the alcohols **39a,b** was then reduced by combined $LiAlH_4$ and $AlCl_3$ to give (±)-mesembranol (**2**) and oily (±)-6-epimesembranol (**40**) in 71 and 19% yields, respectively, after chromatographic separation.

The ^{1}H NMR spectrum (100 MHz, in benzene-d_6) with (±)-mesembranol (**2**) herein obtained was in excellent agreement with that of (−)-mesembranol depicted in the literature.[11] However, the melting point (121–122 °C) of our racemic mixture of mesembranol was considerably distinct from that (154–156 °C) of (±)-mesembranol synthesized by Jeffs.[9] Therefore, it forced us to prepare an authentic sample. Thus, reduction of (±)-mesembrine (**1**), synthesized by the reported procedure,[12a] with sodium borohydride gave (±)-mesembranol (**2**) and (±)-6-epimesembranol (**40**) in 20 and 68% yields, respectively. Thus obtained, (±)-mesembranol had mp 122–123.5 °C, thereby confirming the structure of our own.

Jones oxidation of (±)-mesembranol (**2**) afforded (±)-mesembrine (**1**) in 62% yield. This means that the whole sequence of the reactions described above offers also the total synthesis of (±)-mesembrine.

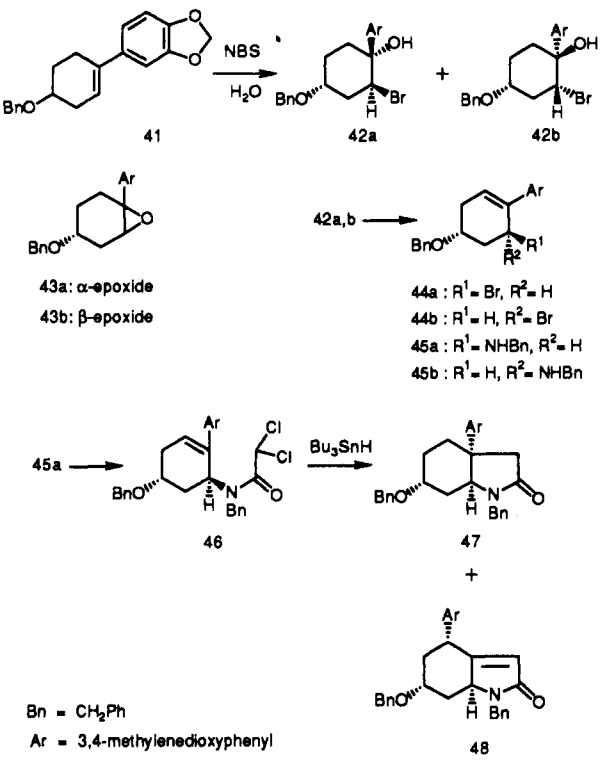
Synthesis of (±)-Elwesine (3)

Our attention was next focused on the synthesis of (±)-elwesine (**3**). The overall strategy followed closely that used for the synthesis of (±)-mesembranol. However, some modifications have been made for the preparation of the key dichloroacetamide **46** having an *N*-benzyl protecting group.

Treatment of the cyclohexene **41**, prepared from **28**, with *N*-bromosuccinimide in aqueous acetonitrile gave an inseparable mixture of two bromohydrins **42a** and **42b** in a ratio of 82:18 (by ^{1}H NMR) (Scheme V). This mixture was then treated with potassium carbonate and the resultant mixture of the epoxides **43a,b** was heated with methanolic benzylamine (1 equiv) in a sealed tube at 100 °C: this, however, gave no desired amino alcohol like **32**. The steric bulk of benzylamine might prevent the S_N2-type ring opening of the epoxide **43**.

This result led us to examine an alternate method for the introduction of a benzylamino group into **42**, and we

Scheme V



decided to adopt a nucleophilic substitution of the allylic bromide **44** with benzylamine. Thus, the mixture of the bromohydrins **42a,b** was treated with *p*-toluenesulfonic acid and the resultant mixture of **44a,b** was allowed to react with benzylamine in the presence of triethylamine to give the expected allylic amines **45a,b**, which were easily separated by chromatography on silica gel to give **45a** and **45b** in 81 and 18% yields, respectively.

The ^{1}H NMR spectrum of the major amine **45a**, which exhibits the signals at δ 3.81 (br s) due to the pseudoequatorial H-6 (CHN) and at δ 3.99 (dddd, J = 11.2, 9.0, 5.2, 3.0 Hz) ascribable to the pseudoaxial H-4 (CHOBn), established the trans relationship of the benzyloxy group and the benzylamino group. The retention of configuration in the displacement of the bromides **44a,b** with benzylamine can be explained in terms of the syn-S_N2' mechanism.

N-Acylation of the major amine **45a** with dichloroacetyl chloride afforded the key dichloroacetamide **46**, which was then treated with 2 molar equiv of Bu_3SnH to give the lactam **47** in 51% yield along with the rearrangement product **48** (30% yield).[13] The ^{1}H NMR spectrum of **48** exhibited a singlet at δ 6.05 due to the olefinic proton at C3. The protons at C4 and C6 appeared as a broad singlet at δ 4.22 and a quintet (J = 3 Hz) at δ 3.84, respectively, clearly indicative of both equatorial hydrogens.

The most remarkable feature of the cyclization of **46** is that no reduction product such as **37**, which is observed for the corresponding *N*-methyl derivative **34**, was detected in the crude reaction mixture. This result was consistent with our previous findings that the use of such large substituents as phenyl group in place of methyl on the nitrogen of **12** resulted in a decrease in the amount of the

(10) Epimerization (attended by dehydrogenation) of some substituted cyclohexanols with Raney nickel has been reported, see: (a) Peppiatt, E. G.; Wicker, R. J. *J. Chem. Soc.* **1955**, 3122. (b) Eliel, E. L.; Schroeter, S. H. *J. Am. Chem. Soc.* **1965**, *87*, 5031. (c) Ishibashi, H.; Sato, K.; Ikeda, M.; Maeda, H.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 605.

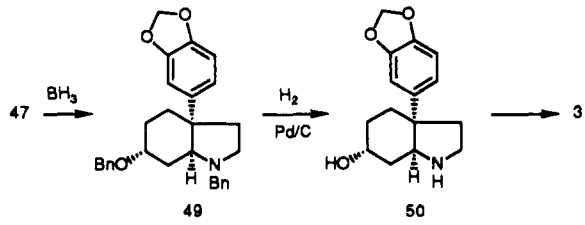
(11) Jeffs, P. W.; Hawks, R. L.; Farrier, D. S. *J. Am. Chem. Soc.* **1969**, *91*, 3831.

(12) For syntheses of (±)-mesembrine, see: (a) Stevens, R. V.; Lesko, P. M.; Lapalme, R. *J. Org. Chem.* **1975**, *40*, 3495. (b) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *Ibid.* **1979**, *44*, 3391. (c) Sanchez, I. H.; Tallabs, F. R. *Chem. Lett.* **1981**, 891. (d) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302. (e) Jeffs, P. W.; Redfearn, R.; Wolfram, J. *Ibid.* **1983**, *48*, 3861. (f) Kochhar, K. S.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *48* 3861. (g) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831 and references cited therein. For a synthesis of (−)-mesembrine, see: (h) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. For a synthesis of (+)-mesembrine, see: (i) Meyers, A. I.; Hanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776.

(13) Further studies on the cyclizations of the dichloroacetamides **21** having other N substituents have revealed that they usually led to an increase in yield of the rearrangement product of type **23** [22% for *N*-ethyl, 27% for *N*-(cyclohexylmethyl), 16% for *N*-phenyl, 27% for *N*-benzyl, and 27% for *N*-(2-phenylethyl) substituents, respectively]. The reason why simple replacement of an *N*-methyl group with other substituents should encourage this rearrangement is not clear at the moment.

reduction product with an increase of the cyclization product **14**.[14]

The lactam **47** was reduced with diborane in THF to give the hydroindole **49** in 74% yield. Removal of two benzyl protecting groups was performed by catalytic hydrogenolysis over 10% Pd–C at 6 kg/cm^2 in ethanol containing 6 N HCl to give the amino alcohol **50** in 58% yield. The spectral properties of **50** herein obtained closely resembled those of (±)-mesembranol (**2**). Thus, the ^{1}H NMR spectrum of **50** exhibited a broad singlet at δ 2.83 ($W_{1/2}$ = 8 Hz) due to the equatorial proton at C7a [δ 2.73 (t, J = 3 Hz) for **2**]. The axial proton at C6 appeared as double triplets (J = 11.0, 4.4 Hz) at δ 4.06 [δ 4.04 (double t, J = 11.0, 4.5 Hz) for **2**]. The ^{13}C NMR spectrum of **50** exhibited signals at δ 66.45 (66.84 for **2**) and 70.40 (70.20 for **2**) due to the C7a and C6, respectively. Further confirmation of the structure of **50** has been made by a comparison of the melting point [240–242 °C dec] of its hydrochloride salt with that [241.5–242 °C dec] described in the literature.[15] Since the amine **50** has already been converted into (±)-elwesine (**3**) via the Pictet–Spengler reaction,[15] the present synthesis of **50** constitutes in a formal sense a total synthesis of (±)-elwesine.[16]



Experimental Section

Melting points are uncorrected. IR spectra were recorded with a JASCO IRA-1 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined with a JEOL JNM-PMX 60 or a Varian XL-300 spectrometer using tetramethylsilane as an internal standard. High resolution mass spectra were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on silica gel 60 PF_{254} (Merck) under pressure.

α,α-Dichloro-*N*-(cyclohex-2-en-1-yl)-*N*-methylacetamide (15). 3-Bromocyclohexene (600 mg, 3.73 mmol) was added to anhydrous methylamine (10 mL) at −78 °C, and the mixture was allowed to stand at room temperature in a sealed tube for 15 h. The reaction vessel was cooled to −78 °C, the stopper was removed, and the reaction mixture was allowed to warm to room temperature to remove any excess methylamine. Water (20 mL) was added to the residue, and the whole was extracted with ethyl ether; then the extract was dried over NaOH pellets. The solvent and the remaining methylamine were evaporated off, and the residue was dissolved again in ethyl ether (20 mL). Pyridine (295 mg, 3.73 mmol) and dichloroacetyl chloride (550 mg, 3.73 mmol) were added successively to the solution containing *N*-(cyclohex-2-en-1-yl)-*N*-methylamine at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water and then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 3:1) to give amide **15** (650 mg, 79%): mp 67.5–68.5 °C (from light petroleum ether); IR (CCl_4) ν 1680 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.15–2.35 (m, 6 H), 2.83, 3.02 (both s, total 3 H), 4.5–5.25 (m, 1 H), 5.4–5.7 (m, 1 H), 5.8–6.2 (m, 1 H), 6.30 (s, 1 H). Anal. Calcd for $C_9H_{13}Cl_2NO$: C, 48.67; H, 5.90; N, 6.31. Found: C, 48.65; H, 5.70; N, 6.36.

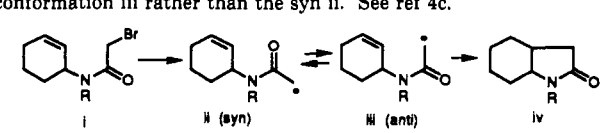
***cis*-Octahydro-1-methylindol-2-one (17).** A mixture of Bu_3SnH (189 mg, 0.65 mmol) and AIBN (11 mg, 0.065 mmol) in dry toluene (45 mL) was added to a boiling solution of **15** (144 mg, 0.65 mmol) in toluene (20 mL) over a period of 1 h, and the mixture was refluxed for a further hour. A mixture of Bu_3SnH (208 mg, 0.72 mmol) and AIBN (12 mg, 0.072 mmol) in toluene (5 mL) was added to the mixture at once, and the whole was heated under reflux for 2 h. After cooling, the solvent was evaporated off and the residue was chromatographed on silica gel (benzene/AcOEt, 1:5) to give the lactam **17**[17] (92 mg, 92%) as an oil: IR (CCl_4) ν 1695 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.1–2.8 (m, 11 H), 2.76 (s, 3 H), 3.43 (t, J = 5 Hz, 1 H).

(1*R,2*S**)-2-(Methylamino)-1-phenylcyclohexan-1-ol (19).** 1-Phenyl-1-cyclohexene (2.0 g, 12.6 mmol) was added by portions to a stirred solution of *m*-chloroperbenzoic acid (3.27 g, 15.2 mmol) in chloroform (60 mL) at 0 °C, and the mixture was stirred at room temperature for 15 h. The reaction mixture was washed with 10% NaOH and dried over $MgSO_4$. The solvent was evaporated off to give quantitatively 1-phenyl-1-cyclohexene oxide (**18**),[18] which was used without further purification in the next stage. The epoxide **18** was dissolved in 40% methylamine in methanol (15 mL), and the mixture was heated in a sealed tube at 100 °C for 7 h. After cooling, the solvent and the excess methylamine were evaporated off and the residue was recrystallized from hexane/benzene to give the amino alcohol **19** (1.61 g, 62%): mp 129–130.5 °C [lit.[19] mp 135–136 °C]; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.1–2.3 (m, 10 H), 2.09 (s, 3 H), 2.67 (t, J = 4 Hz, 1 H), 7.05–7.85 (m, 5 H); exact mass calcd for $C_{13}H_{19}NO$ 205.1465, found 205.1487.

α,α-Dichloro-*N*-methyl-*N*-(2-phenylcyclohex-2-en-1-yl)-acetamide (21). A solution of dichloroacetyl chloride (258 mg, 2.68 mmol) in dichloromethane (2 mL) was added by portions to a stirred solution of **19** (500 mg, 2.44 mmol) and triethylamine (271 mg, 2.68 mmol) in dichloromethane (30 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off, the resultant crude amide **20** was dissolved in benzene (10 mL) containing *p*-toluenesulfonic acid monohydrate (5 mg), and the mixture was heated under reflux for 1 h. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene) to give **21** (677 mg, 93% based on **19**): mp 71.5–73.5 °C (light petroleum ether/AcOEt); IR (CCl_4) ν 1680 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.45–2.5 (m, 6 H), 2.68 (s, 3 H), 5.75 (br s, 1 H), 6.15–6.4 (m, 1 H), 6.03 (s, 1 H), 7.21 (s, 5 H). Anal. Calcd for $C_{15}H_{17}Cl_2NO$: C, 60.42; H, 5.75; N, 4.97. Found: C, 60.38; H, 5.74; N, 5.08.

***cis*-Octahydro-1-methyl-3a-phenylindol-2-one (22), (4*R**,7a*S**)-1-Methyl-4-phenyl-2,4,5,6,7,7a-hexahydroindol-2-one (23), and *N*-Methyl-*N*-(2-phenylcyclohex-2-en-1-yl)-acetamide (24).** Using a procedure similar to that described for the preparation of **17**, the dichloroacetamide **21** (185 mg, 0.62 mmol) was treated with Bu_3SnH (360 mg, 1.24 mmol) and AIBN (20 mg, 0.14 mmol). After usual workup, the crude products were chromatographed on silica gel (hexane/AcOEt, 2:3). The first eluate gave **24** (40 mg, 28%) as an oil: IR (CCl_4) ν 1645 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.65–2.5 (m, 6 H), 1.90 (s, 3 H), 2.50 (s, 3 H), 5.65–6.0 (m, 1 H), 6.1–6.4 (m, 1 H), 7.24 (s, 5 H); exact mass calcd for $C_{15}H_{19}NO$ 229.1465, found 229.1491. The second eluate gave **22**[17] (61 mg, 43%) as an oil: IR (CCl_4) ν 1700 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.1–2.3 (m, 8 H), 2.36 (s, 2 H), 2.76

(14) A similar result has recently been reported by Stork et al., i.e., the bromoacetamides i having a large substituent (R) such as *tert*-butyl or trifluoroacetyl group give good yields of the cyclization products iv. They suggested that the effectiveness of the cyclization might be ascribed to a preference of the initially generated radical to exist largely in the anti conformation iii rather than the syn ii. See ref 4c.



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(s, 3 H), 3.90 (t, J = 3 Hz, 1 H), 7.23 (br s, 5 H). The third eluate gave **23** (8 mg, 6%), which contained a small quantity of the tin residue: IR (CCl_4) ν 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.1–1.85 (m, 4 H), 2.35–2.46 (m, 1 H), 2.54–2.63 (m, 1 H), 2.95 (s, 3 H), 3.78 (dd, J = 11.5, 6.3 Hz, 1 H), 4.25 (d, J = 4.7 Hz, 1 H), 6.03 (s, 1 H), 7.2–7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.01, 26.65, 31.29, 33.56, 41.14, 61.24, 121.22, 126.51, 127.31, 127.39, 127.93, 128.68, 128.82, 140.37, 162.82; this compound was not further purified, owing to the small quantity obtained.

4-(Benzyloxy)-1-(3,4-dimethoxyphenyl)cyclohex-1-ene (29). 1-Bromo-3,4-dimethoxybenzene (1.19 g, 5.5 mmol) was added to a stirred suspension of magnesium turnings (134 mg, 5.5 mmol) in dry THF (10 mL) at room temperature, and the mixture was heated under reflux for 3 h. After the reaction subsided, a solution of 4-(benzyloxy)cyclohexanone (**28**)[9] (1.02 g, 5 mmol) in THF (5 mL) was added dropwise to the solution, and the mixture was heated under reflux for an additional 2 h. After the reaction was quenched with 10% HCl (30 mL), the mixture was stirred at room temperature for 1 h. The mixture was extracted with ethyl ether and the extract was dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene/AcOEt, 40:1) to give **29** (1.17 g, 72%): mp 74.0–74.5 °C (light petroleum ether) [lit.[9] mp 79–80 °C]; ^1H NMR (60 MHz, $CDCl_3$) δ 1.8–2.7 (m, 6 H), 3.35–3.9 (m, 1 H), 3.85 (s, 6 H), 4.58 (s, 2 H), 5.7–6.05 (m, 1 H), 6.75–6.95 (m, 3 H), 7.29 (s, 5 H).

(1*R,2*S**,4*R**)- and (1*S**,2*R**,4*R**)-4-(Benzyloxy)-2-bromo-1-(3,4-dimethoxyphenyl)cyclohexan-1-ol (30a and 30b).** *N*-Bromosuccinimide (267 mg, 1.5 mmol) was added by portions to a stirred solution of **29** (487 mg, 1.5 mmol) in acetonitrile (8 mL) and water (2 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Water (15 mL) was added to the reaction mixture and the whole was extracted with ethyl ether. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene/AcOEt, 5:1). The first eluate gave **30b** (62 mg, 10%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) 1.45–1.58 (m, 1 H), 1.71–1.81 (m, 1 H), 1.98–2.09 (m, 1 H), 2.50–2.63 (m, 3 H), 2.71–2.80 (m, 1 H), 3.65 (double t, J = 8.5, 4.2 Hz, 1 H), 3.87, 3.89 (both s, 3 H each), 4.36 (dd, J = 10.5, 4.9 Hz, 1 H), 4.51, 4.61 (AB q, J = 11.8 Hz, 1 H each), 6.82 (d, J = 8.5 Hz, 1 H), 7.20 (d, J = 2.3 Hz, 1 H), 7.24 (dd, J = 8.5, 2.3 Hz, 1 H), 7.26–7.36 (m, 5 H). The second eluate gave **30a** (523 mg, 83%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.85–2.05 (m, 3 H), 2.28–2.44 (m, 2 H), 2.49 (ddd, J = 13.4, 9.9, 3.5 Hz, 1 H), 2.61 (td, J = 13.4, 4.2 Hz, 1 H), 3.83, 3.85 (both s, 3 H each), 3.91 (double t, J = 10.0, 4.5 Hz, 1 H), 4.44 (dd, J = 5.0, 3.0 Hz, 1 H), 4.55 (s, 2 H), 6.78 (d, J = 8.3 Hz, 1 H), 6.97 (dd, J = 8.3, 2.2 Hz, 1 H), 7.00 (d, J = 2.2 Hz, 1 H), 7.23–7.36 (m, 5 H). This compound was gradually dehydrated when allowed to stand at room temperature.

(1*R,2*S**,4*R**)-4-(Benzyloxy)-1-(3,4-dimethoxyphenyl)-2-(methylamino)cyclohexan-1-ol (32). Method A.** Potassium carbonate (61 mg, 0.44 mmol) was added to a solution of **30a** (138 mg, 0.33 mmol) in methanol (5 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. After the solvent was evaporated off, water was added to the residue and the whole was extracted with dichloromethane. The extract was dried over $MgSO_4$ and the solvent was evaporated off to give quantitatively (1*R**,2*S**,4*R**)-4-(benzyloxy)-1,2-epoxy-1-(3,4-dimethoxyphenyl)cyclohexane (**31**): ^1H NMR (60 MHz, $CDCl_3$) δ 1.5–2.7 (m, 6 H), 3.04 (d, J = 6 Hz, 1 H), 3.85–4.0 (m, 1 H), 3.86 (s, 6 H), 4.53 (s, 2 H), 6.7–7.1 (m, 3 H), 7.32 (s, 5 H). The crude epoxide **31** thus obtained was dissolved in 40% methylamine in methanol (5 mL), and the resulting mixture was heated in a sealed tube at 100 °C for 7 h and then cooled to room temperature. After the solvent and excess methylamine were evaporated off, 10% NaOH (10 mL) was added to the residue and the whole was extracted with ethyl ether. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (AcOEt) to give **32** (96 mg, 78%): mp 117.0–118.5 °C (hexane/AcOEt); IR (CCl_4) ν 3600, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94–1.36 (br s, 1 H), 1.70–2.10 (m, 5 H), 2.11–2.20 (m, 1 H), 2.14 (s, 3 H), 2.49 (td, J = 13.2, 4.1 Hz, 1 H, H-6), 2.82 (br s, $W_{1/2}$ = 7 Hz, 1 H, H-2), 3.76 (double t, J = 11.0, 4.5 Hz, 1 H, H-4), 3.87 3.88 (both s, 3 H each), 4.56, 4.61 (AB q, J = 12 Hz, 1 H each), 6.81 (d, J = 8.3 Hz, 1 H), 6.98 (dd, J = 8.3, 1.8 Hz, 1 H), 7.10 (d, J = 1.8 Hz, 1 H), 7.25–7.40 (m, 5 H). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.97; H, 7.92; N, 3.71.

Method B. The bromohydrin **30a** (1.94 g, 4.6 mmol) was dissolved in 40% methylamine in methanol (40 mL), and the mixture was heated in a sealed tube at 100 °C for 7 h. A similar workup to that described above afforded **32** (1.42 g, 83%).

(1*S,2*R**,5*R**)-*N*-[5-(Benzyloxy)-2-hydroxy-2-(3,4-dimethoxyphenyl)cyclohex-1-yl]-α,α-dichloro-*N*-methylacetamide (33).** A solution of dichloroacetyl chloride (616 mg, 4.18 mmol) in dichloromethane (3 mL) was added dropwise to a solution of **32** (1.41 g, 3.8 mmol) and triethylamine (423 mg, 4.18 mmol) in dichloromethane (15 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with water and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene/AcOEt, 5:1). The first eluate gave **34** (147 mg, 8%), whose physical data are shown in the following section. The second eluate gave **33** (1.45 g, 79%): mp 132–133 °C (hexane/AcOEt); IR (CCl_4) ν 3600, 1675 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.0–2.5 (m, 6 H), 2.18, 2.33 (both s, total 3 H), 3.7–4.2 (m, 1 H), 3.85 (s, 6 H), 4.5–5.3 (m, 2 H), 4.59 (s, 2 H), 6.14 (s, 1 H), 6.7–7.1 (m, 3 H), 7.35 (s, 5 H). Anal. Calcd for $C_{24}H_{29}Cl_2NO_5$: C, 59.76; H, 6.06; N, 2.90. Found: C, 59.58; H, 5.88; N, 3.04.

(1*S,5*R**)-*N*-[5-(Benzyloxy)-2-(3,4-dimethoxyphenyl)-cyclohex-2-en-1-yl]-α,α-dichloro-*N*-methylacetamide (34) and *N*-[5-(Benzyloxy)-2-(3,4-dimethoxyphenyl)cyclohex-1-en-1-yl]-α,α-dichloro-*N*-methylacetamide (35).** The alcohol **33** (1.38 g, 2.86 mmol) was dissolved in benzene (20 mL) containing *p*-toluenesulfonic acid monohydrate (10 mg), and the mixture was heated under reflux for 1 h and then cooled. After the solvent was evaporated off, water was added to the residue, and the whole was extracted with dichloromethane. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene/AcOEt, 9:1). The first eluate gave **34** (1.07 g, 80%): mp 126.5–127.5 °C (hexane–AcOEt); IR ($CHCl_3$) ν 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90 (ddd, J = 13.5, 8.1, 2.5 Hz, 1 H), 2.26 (dt, J = 13.5, 6.7 Hz, 1 H), 2.42–2.58 (m, 2 H), 2.69 (s, 3 H), 3.85 (s, 6 H), 3.88–3.95 (m, 1 H), 4.58, 4.70 (AB q, J = 12.0 Hz, 1 H each), 5.90–5.99 (m, 1 H), 6.09 (s, 1 H), 6.10–6.14 (m, 1 H), 6.78 (d, J = 2.0 Hz, 1 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.85 (dd, J = 8.4, 2.0 Hz, 1 H), 7.25–7.41 (m, 5 H). Anal. Calcd for $C_{24}H_{27}Cl_2NO_4$: C, 62.08; H, 5.86; N, 3.02. Found: C, 61.72; H, 5.78; N, 3.34. The second eluate gave **35** (194 mg, 15%) as an oil: IR (CCl_4) ν 1690 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.65–2.8 (m, 6 H), 2.95, 2.98 (both s, total 3 H), 3.55–4.2 (m, 1 H), 3.80 (s, 6 H) 4.63 (br s, 2 H), 6.29 (s, 1 H), 6.5–6.9 (m, 3 H), 7.31 (s, 5 H); exact mass calcd for $C_{24}H_{27}Cl_2NO_4$ 463.1315, found 463.1300.

(3a*R,6*R**,7a*S**)-6-(Benzyloxy)octahydro-3a-(3,4-dimethoxyphenyl)-1-methylindol-2-one (36) and (1*S**,5*R**)-*N*-[5-(Benzyloxy)-2-(3,4-dimethoxyphenyl)cyclohex-2-en-1-yl]-*N*-methylacetamide (37).** Using a procedure similar to that described for the preparation of **17**, the amide **34** (302 mg, 0.65 mmol) was treated with Bu_3SnH (397 mg, 1.37 mmol) and AIBN (23 mg, 0.137 mmol). After usual workup, the crude products were purified by chromatography on silica gel (benzene/AcOEt, 1:2). The first eluate gave **37** (68 mg, 26%) as an oil: IR (CCl_4) ν 1645 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.1–2.6 (m, 4 H), 1.93 (s, 3 H), 2.51 (s, 3 H), 3.5–4.1 (m, 1 H), 3.83 (s, 6 H), 4.53, 4.70 (AB q, J = 12 Hz, 1 H each), 5.9–6.2 (m, 2 H), 6.5–7.0 (m, 3 H), 7.0–7.55 (br s, 5 H); exact mass calcd for $C_{24}H_{29}NO_4$ 395.2090, found 395.2092. The second eluate gave **36** (131 mg, 51%) as an oil: IR (CCl_4) ν 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36–1.50 (m, 1 H), 1.69–1.81 (m, 1 H), 1.83–1.95 (m, 2 H), 2.11–2.29 (m, 2 H), 2.52 (s, 2 H, H-3), 2.78 (s, 3 H), 3.47 (double t, J = 10.0, 3.7 Hz, 1 H, H-6), 3.85, 3.86 (both s, 3 H each), 4.06 (t, J = 3.9 Hz, 1 H, H-7a), 4.50, 4.60 (AB q, J = 11.9 Hz, 1 H each), 6.82 (d, J = 8.5 Hz, 1 H), 6.83 (d, J = 2.2 Hz, 1 H), 6.90 (dd, J = 8.5, 2.2 Hz, 1 H), 7.26–7.36 (m, 5 H); exact mass calcd for $C_{24}H_{29}NO_4$ 395.2090, found 395.2094.

(3a*R,6*R**,7a*S**)-6-(Benzyloxy)octahydro-3a-(3,4-dimethoxyphenyl)-1-methylindole (38).** A 1.0 M solution of boran–THF complex in THF (0.45 mL, 0.45 mmol) was added dropwise to a stirred solution of **36** (63 mg, 0.16 mmol) in THF

(1 mL) at 0 °C, and the mixture was heated under reflux for 1 h and then cooled. A 6 N HCl (1 mL) was added to the mixture to destroy any excess boran–THF complex, and the solvent was removed by evaporation. The aqueous phase was saturated with NaOH pellets and the resultant slurry was extracted with ethyl ether; then the extract was dried over NaOH pellets. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene/AcOEt, 1:2) to give **38**[9] (50 mg, 81%) an an oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.5–2.5 (m, 9 H), 2.33 (s, 3 H), 2.65–2.9 (m, 1 H), 3.0–3.5 (m, 1 H), 3.5–4.0 (m, 1 H), 3.87 (s, 6 H), 4.53 (s, 2 H), 6.75–7.0 (m, 3 H), 7.3 (s, 5 H).

(±)-Mesembranol (2). The compound **38** (53 mg, 0.13 mmol) was hydrogenolyzed in ethanol (1 mL) containing concentrated HCl (1 mL) over 5% Pd/C (100 mg) in a Paar apparatus at 4 kg/cm^2 of pressure for 24 h. The catalyst was filtered off, the solvent was removed by evaporation, and the residue was chromatographed on silica gel ($CHCl_3$/MeOH, 9:1) to give (±)-mesembranol (**2**) (26 mg, 68%): mp 121–122 °C (hexane/AcOEt); IR (CCl_4) ν 3625, 3360 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.28 (m, 1 H), 1.52 (ddd, J = 13.2, 11.2, 3.6 Hz, 1 H), 1.55–1.75 (br, 1 H), 1.70–1.80 (m, 1 H), 1.80 (ddd, J = 12.7, 10.9, 4.8 Hz, 1 H), 1.91 (ddd, J = 12.7, 8.8, 6.7 Hz, 1 H), 2.01–2.08 (m, 2 H), 2.17 (ddt, J = 13.0, 4.3, 2.2 Hz, 1 H), 2.27 (ddd, J = 10.9, 9.6, 6.7 Hz, 1 H), 2.35 (s, 3 H), 2.73 (t, J = 3 Hz, 1 H), 3.20 (ddd, J = 9.6, 8.8, 4.8 Hz, 1 H), 3.87, 3.89 (both s, 3 H each), 3.98 (double t, J = 11.0, 4.5 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 6.87 (d, J = 2.2 Hz, 1 H), 6.92 (dd, J = 8.3, 2.2 Hz, 1 H); ^{1}H NMR (100 MHz, C_6D_6) δ 1.10–1.19 (m, 6 H), 1.90–2.30 (m, 4 H), 2.21 (s, 3 H), 2.70 (t, J = 3 Hz, 1 H), 2.95–3.20 (m, 1 H), 3.48, 3.49 (both s, 3 H each), 4.04 (double t, J = 11.0, 4.5 Hz, 1 H), 6.60 (d, J = 9 Hz, 1 H), 6.75–6.90 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.87, 33.18, 34.91, 40.23 (C3, C4, C5, C7), 40.56 (NMe), 47.03 (C3a), 54.36 (C2), 55.94 (OMe), 56.00 (OMe), 66.84 (C7a), 70.02 (C6), 110.58, 110.85, 118.78 (C2′, C5′, C6′), 139.22 (C1′), 147.10, 148.77 (C3′, C4′). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found; C, 69.63; H, 8.69; N, 4.90.

(3a*R,6*R**,7a*S**)- and (3a*R**,6*S**,7a*R**)-Octahydro-6-hydroxy-3a-(3,4-dimethoxyphenyl)-1-methylindol-2-one (39a and 39b).** Raney nickel (W-2) (ca. 1 g) was added to a solution of **36** (127 mg, 0.32 mmol) in ethanol (2 mL), and the mixture was heated under reflux for 1 h and then cooled. The Raney nickel was removed by filtration, and the solvent was evaporated off to give a mixture of **39a** and **39b** as an oil, which, without further purification, was used in the next stage: IR ($CHCl_3$) ν 3660, 3600, 3400, 1670 cm^{-1}; ^{1}H NMR for **39a** (300 MHz, $CDCl_3$) δ 1.25–1.42 (m, 2 H), 1.72–1.79 (m, 3 H), 2.27–2.36 (m, 2 H), 2.51 (s, 2 H), 2.88 (s, 3 H), 3.72 (double t, J = 11.0, 4.0 Hz, 1 H), 3.875, 3.887 (both s, 3 H each), 4.11 (t, J = 3.5 Hz, 1 H), 6.83 (d, J = 2.1 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 6.90 (dd, J = 8.4, 2.1 Hz, 1 H) [the spectrum also exhibited two small singlets at δ 3.866 and 3.880, which are assignable as two methoxy groups of **39b**]; exact mass calcd for $C_{17}H_{23}NO_4$ 305.1625, found 305.1616.

Preparation of (±)-Mesembranol (2) and (±)-6-Epimesembranol (40) from 39a,b. A solution of $AlCl_3$ (727 mg, 5.45 mmol) in dry ethyl ether (4 mL) was added dropwise to a suspension of $LiAlH_4$ (217 mg, 5.73 mmol) in dry THF at −20 °C, and the mixture was stirred at room temperature for 30 min. Then 5 mL of the resultant mixture was added to a solution of **39a,b** (108 mg, 0.354 mmol) in dry THF (4 mL) at room temperature, and the mixture was stirred at the same temperature for 1 h. Ethyl ether (30 mL) was added to the reaction mixture and the whole was made alkaline with a 5% aqueous NH_4OH solution. The resultant precipitates were removed by filtration, the solvent was evaporated off, and the residue was chromatographed on alumina ($CHCl_3$/MeOH, 120:1). The first eluate gave (±)-6-epimesembranol (**40**) (20 mg, 19%) as an oil: IR (CCl_4) ν 3350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.48 (m, 1 H), 1.59–1.98 (m, 5 H), 2.11–2.20 (m, 1 H), 2.25–2.41 (m, 3 H), 2.47 (s, 3 H), 2.89 (m, $W_{1/2}$ = 6 Hz, 1 H), 3.31–3.41 (m, 1 H), 3.87, 3.89 (both s, 3 H each), 3.93 (t, J = 2.9 Hz, 1 H), 6.81 (d, J = 8.1 Hz, 1 H), 6.87 (d, J = 2.2 Hz, 1 H), 6.90 (dd, J = 8.1, 2.2 Hz, 1 H); ^{1}H NMR (100 MHz, C_6D_6) δ 1.10–2.50 (m, 9 H), 2.17 (s, 3 H), 2.67 (m, $W_{1/2}$ = 6 Hz, 1 H), 2.80–3.15 (m, 1 H), 3.47, 3.49 (both s, 3 H each), 3.74 (br s, 1 H), 4.02 (m, $W_{1/2}$ = 8 Hz, 1 H), 7.53–7.83 (m, 3 H); exact mass calcd for $C_{17}H_{25}NO_3$ 291.1833, found 291.1804. The second eluate gave (±)-mesembranol (**2**) (73 mg, 71%).

Reduction of (±)-Mesembrine (1) with $NaBH_4$. A solution of $NaBH_4$ (200 mg, 5.2 mmol) in methanol (2 mL) was added dropwise to a stirred solution of (±)-mesembrine[12] (126 mg, 0.44 mmol) in methanol (10 mL), and the mixture was heated under reflux for 1 h and then cooled. A 10% NaOH (5 mL) was added to the reaction mixture, and the methanol was removed by evaporation. The residual aqueous phase was extracted with ethyl ether and the extract was dried over Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on alumina ($CHCl_3$/MeOH, 120:1). The first eluate gave (±)-6-epimesembranol (**40**) (87 mg, 68%) as an oil. The second eluate gave (±)-mesembranol (**2**) (25 mg, 20%): mp 122–123.5 °C (hexane/AcOEt).

Oxidation of (±)-Mesembranol (2) to (±)-Mesembrine (1). (±)-Mesembranol (**2**) (70 mg, 0.24 mmol) in acetone (10 mL) was treated with Jones reagent (0.1 mL) at 0 °C, and the mixture was stirred at room temperature for 10 min. Water (3 mL) was added to the reaction mixture and acetone was removed by evaporation. The residual aqueous phase was made alkaline with saturated Na_2CO_3 and the whole was extracted with ethyl ether. The extract was dried over Na_2SO_4, the solvent was evaporated off, and the residue was chromatographed on silica gel ($CHCl_3$/MeOH, 25:1) to give (±)-mesembrine (**1**) (43 mg, 62%) as an oil, which was identical in all respects with an authentic sample.

4-(Benzyloxy)-1-(1,3-benzodioxol-5-yl)cyclohex-1-ene (41). Using a procedure similar to that described for the preparation of compound **29**, 4-(benzyloxy)cyclohexanone (**28**) (1.42 g, 6.95 mmol) was allowed to react with (1,3-benzodioxol-5-yl)magnesium bromide [prepared from 5-bromo-1,3-benzodioxole (1.4 g, 6.95 mmol) and magnesium turnings (169 mg)], and the resultant carbinol was dehydrated with *p*-toluenesulfonic acid to give **41** (1.57 g, 73%): mp 61–62 °C (hexane); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.5–3.0 (m, 6 H), 3.6–4.0 (m, 1 H), 4.60 (s, 2 H), 5.8–6.0 (m, 1 H), 5.90 (s, 2 H), 6.75–7.0 (m, 3 H), 7.37 (m, 5 H). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.81; H, 6.51.

(1*R,2*S**,4*R**)- and (1*S**,2*R**,4*R**)-1-(1,3-Benzodioxol-5-yl)-4-(benzyloxy)-2-bromocyclohexan-1-ol (42a and 42b).** Using a procedure similar to that described for the preparation of **30a,b**, compound **41** (1 g, 3.24 mmol) was treated with *N*-bromosuccinimide (529 mg, 3.24 mmol) in aqueous acetonitrile to give a mixture of **42a** and **42b** (1.28 g, 98%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84–2.10 (m, 4 H), 2.38–2.66 (m, 3 H), 3.60–3.68 (m, 0.18 H, H-4 for **42b**), 3.92 (double t, J = 9.8, 5.2 Hz, 0.82 H, H-4 for **42a**), 4.31 (dd, J = 10.5, 5.0 Hz, 0.18 H, H-2 for **42b**), 4.42 (dd, J = 5.6, 3.7 Hz, 0.82 H, H-2 for **42a**), 4.58 (s, 1.64 H, $PhCH_2$ for **42a**), 4.66 (s, 0.36 H, $PhCH_2$ for **42b**), 5.94 (s, 2 H), 6.76 (d, J = 8 Hz, 1 H), 6.94 (dd, J = 8.0, 2.0 Hz, 1 H), 6.98 (d, J = 2.0 Hz, 1 H), 7.25–7.40 (m, 5 H). This mixture was used immediately in the next step.

(4*R,6*S**)- and (4*R**,6*R**)-1-(1,3-Benzodioxol-5-yl)-4-(benzyloxy)-6-bromocyclohex-1-ene (44a and 44b).** A solution of the mixture of **42a,b** (441 mg, 1.1 mmol) in benzene (10 mL) containing *p*-toluenesulfonic acid monohydrate (19 mg, 0.22 mmol) was heated under reflux for 1 h and then cooled. Water (10 mL) was added to the mixture, and the organic layer was separated. The aqueous layer was further extracted with benzene and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane/AcOEt, 9:1) to give a mixture of **44a** and **44b** (325 mg, 77%): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.9–3.0 (m, 4 H), 3.9–4.5 (m, 1 H), 4.63 (s, 2 H), 5.1–5.35 (m, 1 H), 5.85–6.05 (m, 1 H), 5.93 (s, 2 H), 6.75–7.0 (m, 3 H), 7.34 (s, 5 H). Recrystallization of the mixture afforded pure **44a**: mp 91–92 °C (hexane/AcOEt). Anal. Calcd for $C_{20}H_{19}BrO_3$: C, 62.03; H, 4.94. Found: C, 61.99; H, 5.04.

(4*R,6*S**)- and (4*R**,6*R**)-1-(1,3-Benzodioxol-5-yl)-6-(benzylamino)-4-(benzyloxy)cyclohex-1-ene (45a and 45b).** A solution of the mixture of **44a,b** (325 mg, 0.84 mmol) in dry dichloromethane (1 mL) was added to a solution of benzylamine (90 mg, 0.84 mmol) and triethylamine (85 mg, 0.84 mmol) in dry dichloromethane (10 mL) at 0 °C, and the mixture was stirred at room temperature for 15 h. Water (10 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was further extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$. The sovlent was evaporated off and the residue was chromatographed on silica

gel (hexane/AcOEt, 2:1). The first eluate gave **45a** (281 mg, 81%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (br s, 1 H), 1.65 (ddd, J = 12.8, 11.2, 4.5 Hz, 1 H), 2.20 (dddd, J = 17.5, 9.0, 2.7, 1.5 Hz, 1 H), 2.35 (br d, J = 12.9 Hz, 1 H), 2.63 (dt, J = 17.5, 5.2 Hz, 1 H), 3.68, 3.82 (AB q, J = 13.2 Hz, 1 H each), 3.81 (br s, 1 H), 3.99 (dddd, J = 11.2, 9.0, 5.2, 3.0 Hz, 1 H), 4.59 (s, 2 H), 5.84 (dd, J = 5.2, 2.7 Hz, 1 H), 5.92 (s, 2 H), 6.70 (s, 2 H), 6.76 (s, 1 H), 7.15–7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.06, 33.87 (C3, C5), 50.20 (NCH_2), 53.06 (C6), 70.25 (OCH_2), 73.05 (C4), 100.85 (OCH_2O), 107.12, 108.04 (C1, C2), 119.60, 123.87, 126.78, 127.45, 127.48, 128.20, 128.30, 128.33, 134.82, 138.69, 140.21, 140.25, 146.52, 147.59; exact mass calcd for $C_{27}H_{27}NO_3$ 413.1989, found 413.2010. The second eluate gave **45b** (62 mg, 18%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (br s, 1 H), 1.96 (ddd, J = 12.7, 9.8, 8.1 Hz, 1 H), 2.24–3.38 (m, 2 H), 2.51 (br dt, J = 17.0, 5.5 Hz, 1 H), 3.64, 3.74 (AB q, J = 12.8 Hz, 1 H each), 3.68–3.79 (m, 2 H), 4.57 (s, 2 H), 5.74–5.78 (m, 1 H), 5.87 (s, 2 H), 6.71 (s, 2 H), 6.76 (s, 1 H), 7.1–7.4 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.09, 33.88 (C3, C5), 50.20 (NCH_2), 53.09 (C6), 70.31 (OCH_2), 73.06 (C4), 100.90 (OCH_2O), 107.14, 108.08 (C1, C2), 119.63, 124.04, 126.85, 127.49, 127.54, 127.71, 128.12, 128.24, 128.36, 134.83, 138.68, 140.09, 140.17, 146.55, 147.63; exact mass calcd for $C_{27}H_{27}NO_3$ 413.1989, found 413.2001.

***N*-[(4*R**,6*S**)-1-(1,3-Benzodioxol-5-yl)-4-(benzyloxy)cyclohex-1-en-6-yl]-*N*-benzyl-α,α-dichloroacetamide (46).** Using a procedure similar to that described for the preparation of **33**, compound **45a** (159 mg, 0.385 mmol) was acylated with dichloroacetyl chloride (57 mg, 0.385 mmol) to give **46** (189 mg, 94%) as an oil: IR (CCl_4) ν 1680 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.9–2.6 (m, 4 H), 3.5–3.8 (m, 1 H), 4.26 (br s, 2 H), 4.30, 4.52 (AB q, J = 12 Hz, 1 H each), 5.80 (s, 1 H), 5.85–6.3 (m, 2 H), 5.90 (s, 2 H), 6.75–6.9 (m, 3 H), 7.29 (br s, 10 H); exact mass calcd for $C_{29}H_{27}Cl_2NO_4$ 523.1346, found 523.1316.

(3a*R,6*R**,7a*S**)-1-Benzyl-6-(benzyloxy)octahydro-3a-(1,3-benzodioxol-5-yl)indol-2-one (47) and (4*R**,6*R**,7a*S**)-1-Benzyl-6-(benzyloxy)-4-(1,3-benzodioxol-5-yl)-2,4,5,6,7,7a-hexahydroindol-2-one (48).** Using a procedure similar to that described for the preparation of **17**, compound **46** (343 mg, 0.654 mmol) was treated with Bu_3SnH (0.4 g, 1.374 mmol) and AIBN (23 mg, 0.14 mmol), and the crude products were purified by chromatography on silica gel (benzene/AcOEt, 5:1). The first eluate gave **47** (153 mg, 51%): mp 129.5–131.0 °C (hexane/AcOEt); IR (CCl_4) ν 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30–1.40 (m, 1 H), 1.70–1.84 (m, 3 H), 2.03–2.23 (m, 2 H), 2.55, 2.60 (AB q, J = 16.1 Hz, 1 H each), 3.26 (double t, J = 10.0, 3.7 Hz, 1 H), 4.00 (t, J = 3.8 Hz, 1 H), 4.06 (d, J = 15.1 Hz, 1 H), 4.28, 4.38 (AB q, J = 11.7 Hz, 1 H each), 4.82 (d, J = 15.1 Hz, 1 H), 5.92 (s, 2 H), 6.72 (br s, 2 H), 6.75 (br s, 1 H), 7.17–7.38 (m, 10 H). Anal. Calcd for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.07; H, 6.50; N, 2.92. The second eluate gave **48** (41 mg, 30%) as an oil: IR (CCl_4) ν 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (td, J = 12.8, 3.0 Hz, 1 H), 1.87 (ddd, J = 14.7, 6.8, 3.0 Hz, 1 H), 2.42–2.52 (m, 1 H), 2.67 (br d, J = 14.7 Hz, 1 H), 3.84 (quint, J = 3 Hz, 1 H), 4.17, 4.21 (AB q, J = 11.8 Hz, 1 H each), 4.22 (br s, 1 H), 4.40 (dd, J = 11.7, 5.9 Hz, 1 H), 4.53, 4.70 (AB q, J = 15.4 Hz, 1 H each), 5.85, 5.87 (AB q, J = 1.5 Hz, 1 H each), 6.05 (s, 1 H), 6.60–6.75 (m, 3 H), 6.84–6.92 (m, 2 H), 7.15–7.35 (m, 8 H); exact mass calcd for $C_{29}H_{27}NO_4$ 453.1938, found 453.1963.

(3a*R,6*R**,7a*S**)-1-Benzyl-6-(benzyloxy)-3a-(1,3-benzodioxol-5-yl)octahydroindole (49).** Using a procedure similar to that described for the preparation of **38**, compound **47** (84 mg, 0.184 mmol) was reduced with diboran in THF to give **49** (60 mg, 74%) as an oil: IR (CCl_4) ν 1610 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.0–2.5 (m, 9 H), 2.8–3.2 (m, 2 H), 3.20 (d, J = 13 Hz, 1 H), 3.5–4.1 (m, 1 H), 4.07 (d, J = 13 Hz, 1 H), 4.46 (s, 2 H), 5.88 (s, 2 H), 6.7–7.0 (m, 3 H), 7.24 (br s, 10 H); exact mass calcd for $C_{29}H_{31}NO_3$ 441.2292, found 441.2301.

(3a*R,6*R**,7a*S**)-3a-(1,3-Benzodioxol-5-yl)octahydroindol-6-ol (50).** Compound **49** (61 mg, 0.138 mmol) was hydrogenolyzed in ethanol (1 mL) and THF (0.2 mL) containing concentrated HCl (0.05 mL) over 10% Pd/C (50 mg) in a Paar apparatus at 6 kg/cm^2 of pressure for 48 h. The catalyst was filtered off and the solvent was removed by evaporation. A 10% Na_2CO_3 solution was added to the residue, and the whole was extracted with ethyl ether and then the extract was dried over K_2CO_3. The solvent was evaporated off and the residue was chromatographed on silica gel ($CHCl_3$/MeOH, 9:1) to give **50** (21 mg, 58%): IR (CCl_4) ν 3660, 3600, 3400 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14–1.29 (m, 1 H), 1.56 (ddd, J = 14.1, 11.2, 3.7 Hz, 1 H), 1.70–1.80 (m, 1 H), 1.82 (ddd, J = 12.9, 11.0, 5.1 Hz, 1 H), 1.93 (ddd, J = 12.9, 8.8, 6.6 Hz, 1 H), 2.0–2.12 (m, 2 H), 2.19 (ddt, J = 13.9, 4.8, 2.4 Hz, 1 H), 2.35 (ddd, J = 11.0, 9.3, 6.6 Hz, 1 H), 2.42 (s, 2 H), 2.83 (br s, $W_{1/2}$ = 8 Hz, 1 H, H-7a), 3.33 (ddd, J = 9.3, 8.8, 5.1 Hz, 1 H), 4.06 (double t, J = 11.0, 4.4 Hz, 1 H, H-6), 5.94 (s, 2 H), 6.76 (d, J = 8.3 Hz, 1 H), 6.81 (dd, J = 8.3, 1.9 Hz, 1 H), 6.85 (d, J = 1.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.46, 32.76, 34.60, 39.93 (C3, C4, C5, C7), 47.26 (C3a), 54.21 (C2), 66.45 (C7a), 70.40 (C6), 100.95 (OCH_2O), 107.43, 107.86, 119.39 (C2′, C5′, C6′), 140.01 (C1′), 145.51, 147.82 (C3′, C4′). HCl salt of **50**: mp 240–242 °C dec [lit.[15] mp 241.5–242 °C dec]; ^{1}H NMR (300 MHz, D_2O) δ 1.30–1.43 (m, 1 H), 1.69–1.88 (m, 2 H), 1.97 (ddd, J = 14.7, 9.1, 5.3 Hz, 1 H), 2.12–2.29 (m, 3 H), 2.40 (ddd, J = 14.0, 8.7, 5.4 Hz, 1 H), 3.34–3.58 (m, 2 H), 4.08 (double t, J = 8.6, 4.2 Hz, 1 H, H-6), 4.26 (t, J = 5.2, Hz, 1 H, H-7a), 4.78 (s, HDO), 5.99 (s, 2 H), 6.92 (d, J = 8.3 Hz, 1 H), 6.96 (dd, J = 8.3, 1.7 Hz, 1 H), 7.04 (d, J = 1.7 Hz, 1 H).

Acknowledgment. We are indebted to the Takeda Science Foundation for financial support of this research program.

Registry No. (±)-**1**, 6023-73-0; (±)-**2**, 82769-19-5; (±)-**3**, 33531-72-5; (±)-**15**, 129920-33-8; (±)-**17**, 116725-60-1; (±)-**18**, 122210-64-4; (±)-**19**, 129920-34-9; (±)-**20**, 129920-35-0; (±)-**21**, 125032-11-3; (±)-**22**, 35119-53-0; (±)-**23**, 129920-36-1; (±)-**24**, 125032-04-4; **28**, 2987-06-6; (±)-**29**, 82732-16-9; (±)-**30a**, 125032-05-5; (±)-**30b**, 125032-12-4; (±)-**31**, 129920-37-2; (±)-**32**, 125032-06-6; (±)-**33**, 125032-07-7; (±)-**34**, 125032-08-8; (±)-**35**, 125032-09-9; (±)-**36**, 82732-18-1; (±)-**37**, 125032-10-2; (±)-**38**, 82732-19-2; (±)-**39a**, 129920-38-3; (±)-**39b**, 80516-00-3; (±)-**40**, 82769-20-8; (±)-**41**, 129920-39-4; (±)-**42a**, 129920-40-7; (±)-**42b**, 129920-31-6; (±)-**44a**, 129920-41-8; (±)-**44b**, 129920-32-7; (±)-**45a**, 129920-42-9; (±)-**45b**, 129942-61-6; (±)-**46**, 129920-43-0; (±)-**47**, 129920-44-1; (±)-**48**, 129920-45-2; (±)-**49**, 129920-46-3; (±)-**50**, 33531-78-1; (±)-3-bromocyclohexene, 108055-90-9; 1-phenylcyclohexene, 771-98-2; 1-bromo-3,4-dimethoxybenzene, 2859-78-1; 5-bromo-1,3-benzodioxole, 2635-13-4.