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Stereoselective synthesis of cis and trans-fused 3a-aryloctahydroindoles using cyclization of *N*-vinylic α-(methylthio)acetamides: synthesis of (−)-mesembrane

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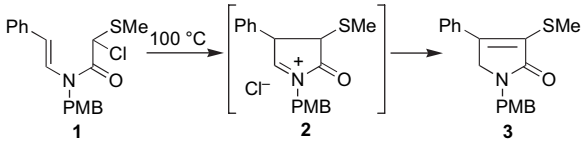
Abstract—Treatment of *N*-(2-arylcyclohex-1-en-1-yl)-α-(methylthio)acetamides with *N*-chlorosuccinimide (NCS) gave 3a-aryl-2,3,3a,4,5,6-hexahydro-3-(methylthio)indol-2-ones. Desulfurization of the cyclization products followed by a catalytic hydrogenation of the resulting hexahydroindol-2-ones gave predominantly or exclusively trans-fused octahydroindol-2-ones. On the other hand, reduction of the desulfurization products with Et_3SiH in CF_3CO_2H exclusively provided cis-fused octahydroindol-2-ones. A chiral induction of *N*-[2-(3,4-dimethoxy)-phenylcyclohex-1-en-1-yl]-α-(methylthio)acetamide having an (*R*)-1-(1-naphthyl)ethyl group on the nitrogen atom led to the synthesis of (−)-mesembrane and (−)-*trans*-mesembrane.

1. Introduction

Carbon–carbon bond-forming reactions of α-chlorosulfides with external or internal alkenic bonds, which are generally performed in the presence of Lewis acid, have emerged as a valuable tool in organic synthesis.[1] For example, α-chlorosulfides gave ene reaction products and [3⁺+2], [4⁺+2], and [2⁺+4] polar cycloaddition products with external alkenes, and olefin cyclization products with internal alkenic bonds. We previously reported that *N*-vinylic α-chloro-α-(methylthio)acetamide **1** underwent cyclization at 100 °C in the absence of Lewis acid to give the product **3** in 30% yield (Scheme 1).[2] This cyclization can be explained in terms of a high nucleophilic nature of the alkenic bond of enamide **1** giving the intermediacy of acyliminium ion **2**. Dehydrochlorination of **2** followed by migration of the alkenic bond would afford **3**.



Scheme 1.

We have been interested in the application of this method to the synthesis of 3a-aryloctahydroindoles such as (±)-mesembrane (*cis*-**13**) using the cyclization of α-chlorosulfide **8** giving **10**. We report here that α-(methylthio)acetamide **6**, when treated with *N*-chlorosuccinimide (NCS), gives no α-chlorosulfide **8** but directly affords the desired cyclization product, 3a-arylhexahydroindol-2-one **10**, the reduction of which provides a new method for the synthesis of (±)-mesembrane (*cis*-**13**) and its isomer *trans*-**13**. Stereoselective synthesis of (−)-mesembrane (**29**) and (−)-*trans*-mesembrane (**33**) using cyclization of enamide **22** having a chiral auxiliary on the nitrogen atom is also described.[3]

2. Results and discussion

2.1. Synthesis of (±)-mesembrane and (±)-*trans*-mesembrane

We began our investigation by examining the cyclization of *N*-(2-arylcyclohex-1-en-1-yl)-α-chloro-α-(methylthio)acetamide **8** (Scheme 2). The requisite α-(methylthio)acetamide **6** was prepared in 52% yield by condensation of 2-(3,4-dimethoxyphenyl)cyclohexanone[4] and methylamine followed by acylation of the resulting imine **4** with (methylthio)acetyl chloride (**5**).[5]

Treatment of sulfide **6** with *N*-chlorosuccinimide (NCS) in CCl_4 at room temperature gave the cyclization product, 3-(methylthio)hexahydroindol-2-one **10**, in 48% yield as a single stereoisomer. No expected α-chlorosulfide **8** was

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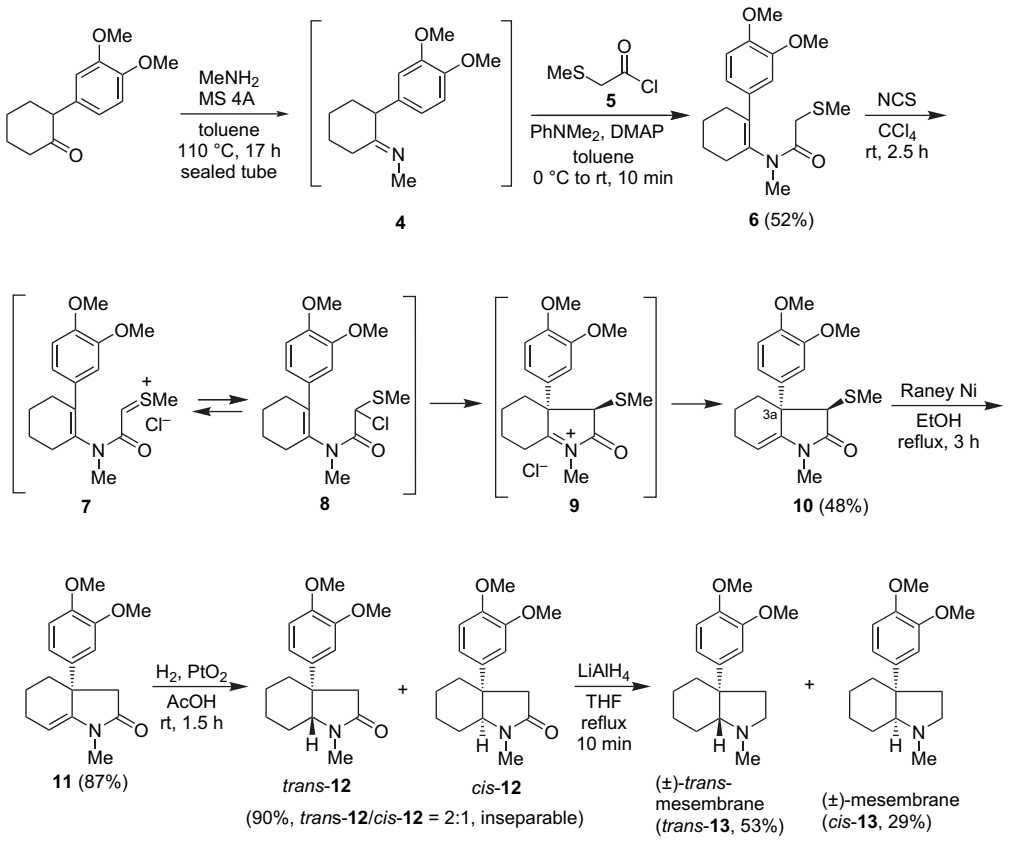


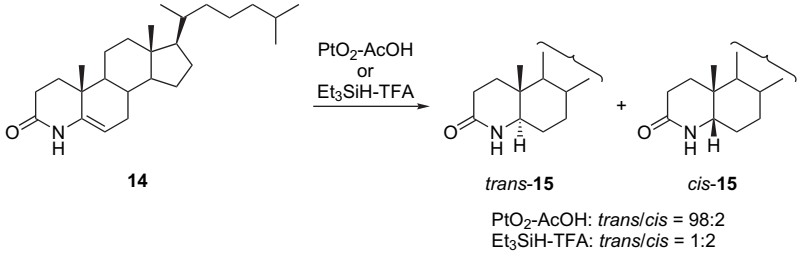
Scheme 2.

obtained. The cyclization of **6** to **10** can be best explained by rapid intramolecular nucleophilic attack of an electron-rich alkenic bond of **7** on the thionium ion, which is an intermediate for the formation of α-chlorosulfide **8** from **6**. Deprotonation of the resulting iminium ion **9** would afford **10**. An alternative mechanism for the formation of **9** may involve a rapid intramolecular S_N2-type substitution of α-chlorosulfide **8**. Stereochemistry of the MeS group of **10** was tentatively assigned to be trans to the neighboring 3,4-dimethoxyphenyl group as depicted in Scheme 2.[6] Desulfurization of compound **10** with Raney nickel gave **11** in 87% yield. A subsequent catalytic hydrogenation of compound **11** in the presence of PtO_2 in acetic acid gave an inseparable ca. 2:1 mixture of trans-fused octahydroindol-2-one *trans*-**12** and its isomer *cis*-**12** in 90% combined yield. A subsequent $LiAlH_4$ reduction of the mixture gave (±)-*trans*-mesembrane (*trans*-**13**)[7d] and (±)-mesembrane (*cis*-**13**)[7] in 53% and 29% yields, respectively.

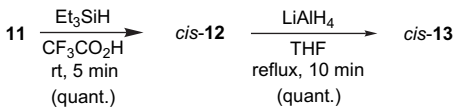
Miller and his co-workers[8] reported that catalytic hydrogenation of compound **14** with PtO_2 in acetic acid gave almost exclusively trans-fused compound *trans*-**15a** as a result of steric hindrance of an angular methyl group of **14**, which caused the metal to preferentially bind to the opposite face of the methyl group (Scheme 3). They also reported that treatment of **14** with Et_3SiH in CF_3CO_2H (TFA) predominantly gave cis-fused compound *cis*-**15** together with trans-fused compound *trans*-**15** in a ratio of ca. 2:1.

We then treated **11** with Et_3SiH in TFA to give cis-fused 3a-aryloctahydroindol-2-one *cis*-**12** as a sole product (Scheme 4). A subsequent reduction of *cis*-**12** with $LiAlH_4$ gave (±)-mesembrane (*cis*-**13**).

The stereochemical outcome of the catalytic hydrogenation of **11** can be explained in a manner similar to that described for **14**. Binding of the metal to the opposite face of the aryl

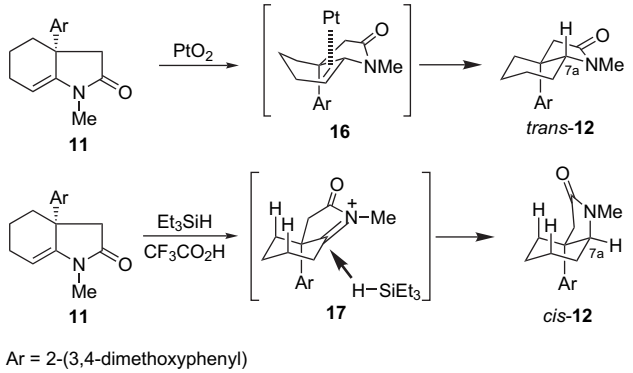


Scheme 3.



Scheme 4.

group at C_{3a} so as to form **16** gave trans-fused compound *trans*-**12** (Scheme 5).



Scheme 5.

On the other hand, the reactive intermediate for the reduction of Et_3SiH in TFA might be the acyliminium ion **17** (Scheme 5). The literature[8] indicated that reduction of **14** with sterically more demanding di-*tert*-butylmethylsilane increased the amount of *cis*-**15** (*trans*-**15**/*cis*-**15**, 1:57) more than in the case of reduction with triethylsilane (*trans*-**15**/*cis*-**15**, 1:2), and we therefore speculated that an equatorial attack of hydride of silane onto the acyliminium ion **17** occurred to give cis-fused compound *cis*-**12** in order to avoid 1,3-diaxial interaction in a chair conformation of **17**.

2.2. Studies on chiral induction

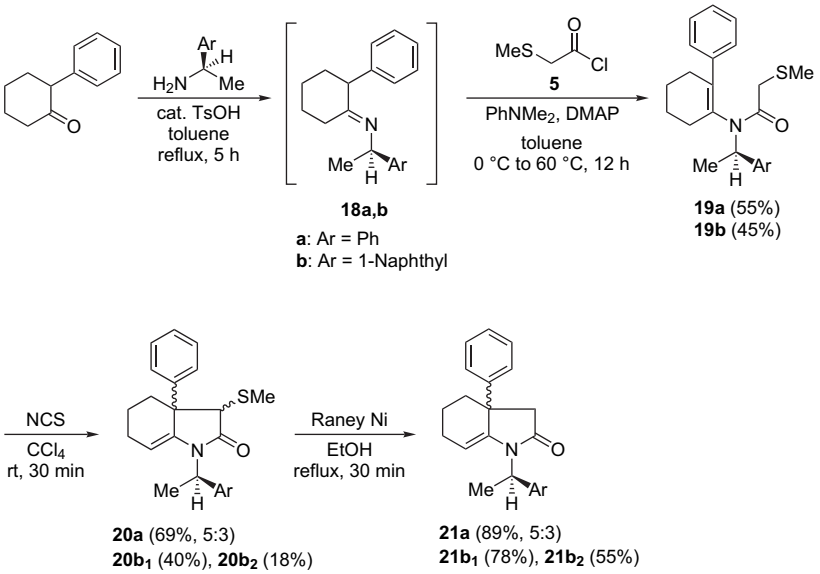
Being encouraged by the success of obtaining (±)-mesembrane (*cis*-**13**) using cyclization of **6**, we next examined synthesis of (−)-mesembrane (**29**) exploiting a chiral induction of compound having a chiral auxiliary on the nitrogen atom.

α-(Methylthio)acetamide **19a** having an (*R*)-1-phenylethyl group was prepared in 55% yield by condensation of 2-phenylcyclohexanone and (*R*)-1-phenylethylamine followed by acylation of the resulting imine **18a** with acid chloride **5** (Scheme 6). When compound **19a** was treated with NCS, compound **20a** was obtained in 69% yield as a ca. 5:3 mixture of two stereoisomers of over four possible diastereoisomers. The MeS groups of the mixture of **20a** were probably trans to the phenyl group in a manner similar to that shown in Scheme 2. This result indicated that the chiral induction of enamide **19a**, having a 1-phenylethyl group on the nitrogen atom, was ca. 5:3. Desulfurization of **20a** gave a ca. 5:3 mixture of two diastereoisomers of **21a** in 89% yield.

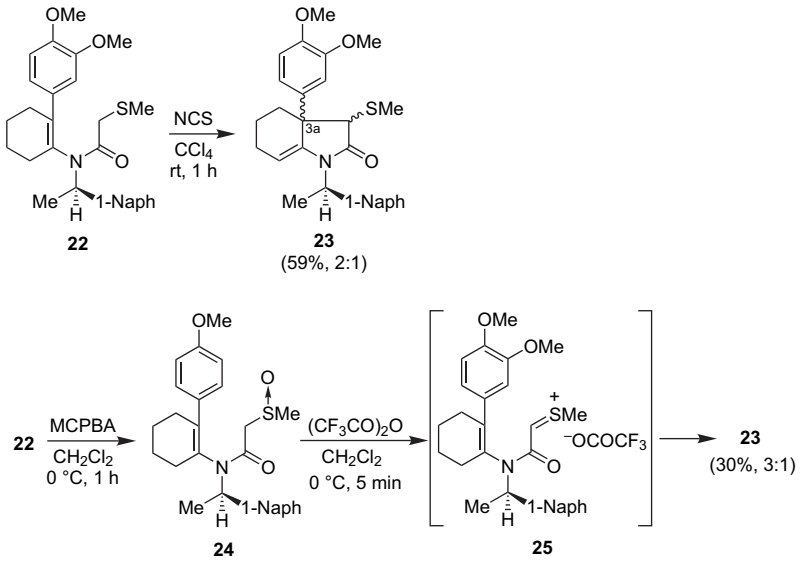
Our attention was next turned to enamide **19b** having an (*R*)-1-(1-naphthyl)ethyl group on the nitrogen atom. Treatment of **19b** with NCS gave two products, $\mathbf{20b_1}$ and $\mathbf{20b_2}$, in 40% and 18% yields, respectively. This result showed that the chiral induction of **19b** was ca. 2:1, indicating that the 1-(1-naphthyl)ethyl group was preferable to the 1-phenylethyl group as a chiral auxiliary on the nitrogen atom. Desulfurization of $\mathbf{20b_1}$ and $\mathbf{20b_2}$ gave diastereomeric isomers $\mathbf{21b_1}$ and $\mathbf{21b_2}$ in 78% and 55% yields, respectively.

2.3. Synthesis of (−)-mesembrane and (−)-*trans*-mesembrane

We then examined the cyclization of compound **22** having an 1-(1-naphthyl)ethyl group on the nitrogen atom for the synthesis of (−)-mesembrane. Treatment of **22** with NCS gave an inseparable ca. 2:1 mixture of the cyclization products **23** in 59% yield (Scheme 7). As mentioned above, formation of **23** from **22** can be considered to proceed, in formal sense, through the thionium ion such as **7** (Scheme 2), and therefore, Pummerer rearrangement of sulfoxide **24** via the intermediacy of thionium ion **25** was next examined. Sulfide **22**



Scheme 6.

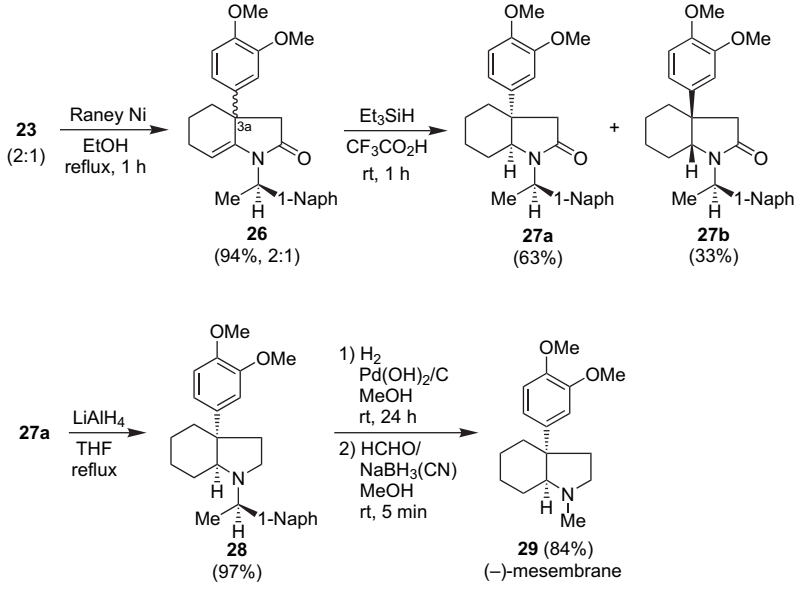


Scheme 7.

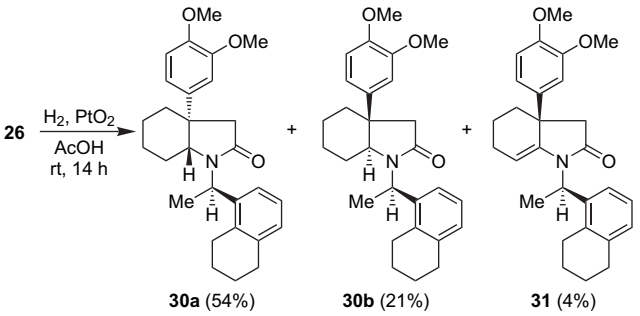
was oxidized with *m*-chloroperbenzoic acid (MCPBA) and the resulting sulfoxide **24** was treated with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at 0 °C to give **23** as a mixture of two diastereoisomers in a ratio of 3:1 and in 30% yield based on **22**. The major isomer of **23** was identical with that obtained by the treatment of **22** with NCS. The diastereoselectivity for the formation of **23** by Pummerer reaction of sulfoxide **24** was slightly improved more than that by treatment of sulfide **22** with NCS. This was probably due to the reaction temperature employed. The reaction of sulfoxide **24** with TFAA could be carried out at 0 °C,[9] whereas the cyclization of **22** by treatment with NCS did not occur at 0 °C.

Desulfurization of **23** gave a diastereoisomeric mixture of hexahydroindol-2-ones **26** in 94% yield (Scheme 8). A subsequent reduction of **26** with Et_3SiH gave octahydroindol-2-one **27a** as a major product and its isomer **27b** as a minor product. The absolute configurations of **27a** and **27b** were confirmed by transforming **27a** to (−)-mesembrane (**29**). The major isomer **27a** was reduced with $LiAlH_4$ to give amine **28** in 97% yield. Hydrogenolysis of amine **28** in the presence of $Pd(OH)_2/C$ followed by *N*-methylation with $HCHO/NaBH_3(CN)$ gave (−)-mesembrane (**29**)[10] {$[\alpha]_D$ −15.6, lit.[11] $[\alpha]_D$ −15.2} in 84% yield. Therefore, the absolute stereochemistry of the aryl group at the C_{3a}-position of the major isomer of **23** (or **26**) was found to be *S*-configuration.

On the other hand, catalytic hydrogenation of **26** in the presence of PtO_2 in acetic acid gave trans-fused octahydroindol-2-one **30a** as a major product and its isomer **30b** as a minor product, together with a small quantity of compound **31**, whose naphthalene rings were partially reduced (Scheme 9).

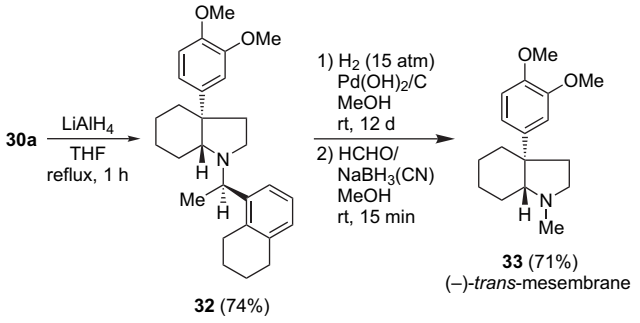


Scheme 8.



Scheme 9.

The trans-stereochemistry of the major isomer **30a** was confirmed by the following conversion into (−)-*trans*-mesembrane (**33**). $LiAlH_4$ reduction of **30a** gave amine **32** in 74% yield (Scheme 10). Hydrogenolysis of **32** in the presence of $Pd(OH)_2/C$ followed by *N*-methylation of the resulting amine gave (−)-*trans*-mesembrane (**33**) in 71% yield based on **32**. The spectral data of enantiopure (−)-*trans*-mesembrane thus obtained were in accord with those reported for (±)-*trans*-mesembrane.[7d]



Scheme 10.

The trans-stereochemistry of another isomer **30b** was deduced from a comparison of the coupling constants (J=13.2, 3.4 Hz) of the 7a-hydrogen atom with that (J=12.7, 2.9 Hz) of trans-isomer **30a**. The cis-compounds **27a** and **27b** have the coupling constants J=8.6, 5.5 Hz and 9.0, 5.9 Hz, respectively. An absolute configuration of **31** was tentatively assigned as shown in Scheme 9.

Catalytic hydrogenation of **11** (Scheme 2) gave a ca. 2:1 mixture of trans and cis-fused compounds *trans*-**12** and *cis*-**12**, whereas a similar hydrogenation of **26** (Scheme 9) gave only trans-fused compounds **30a** and **30b**. It seemed that the bulkiness of the 1-(1-naphthylethyl) group of **26** prevents binding of the metal to the same face of the aryl group at C_{3a}.

3. Conclusion

We revealed that *N*-(2-arylcyclohex-1-en-1-yl)-α-(methylthio)acetamides, when treated with *N*-chlorosuccinimide, underwent cyclization to afford 1,2,3a,4,5,6-hexahydro-3a-aryl-3-(methylthio)indol-2-ones. Stereoselective synthesis of cis and trans-fused octahydroindol-2-ones was performed by reduction of desulfurized hexahydroindol-2-ones with Et_3SiH and by catalytic hydrogenation, respectively. The method was applied to the chiral induction of *N*-[2-(3,4-dimethoxy)phenylcyclohex-1-en-1-yl]-α-(methylthio)acetamide having a 1-(1-naphthyl)ethyl group on the nitrogen atom, which led to the synthesis of (−)-mesembrane and (−)-*trans*-mesembrane.

4. Experimental

4.1. General

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured with a JEOL JNM-GSX 500 or a JEOL JNM-EX 270 spectrometer. δ values quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX-102A mass spectrometer. Column chromatography was performed using silica gel 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm). Thin layer chromatography was carried out on silica gel Wakogel B-5F.

4.1.1. *N*-[2-(3,4-Dimethoxyphenyl)cyclohexen-1-yl]-*N*-methyl-α-(methylthio)acetamide (6). Gaseous methylamine was bubbled to a solution of 2-(3,4-dimethoxyphenyl)cyclohexanone (500 mg, 2.13 mmol) in toluene (4 ml) containing MS 4 Å (ca. 1 g) at −78 °C for 5 min, and the mixture was heated in a sealed tube at 110 °C for 17 h. After removal of excess methylamine, *N*,*N*-dimethylaniline (774 mg, 6.39 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol) were added to the residual solution, and a solution of α-(methylthio)acetyl chloride (399 mg, 3.2 mmol) in toluene (5 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 10 min, and the reaction mixture was washed with a saturated NH_4Cl solution and brine. The organic layer was dried ($MgSO_4$) and concentrated, and the crude material was purified by column chromatography on silica gel (hexane/AcOEt, 10:1→5:1→2:1) to give **6** (371 mg, 52%) as a colorless oil. IR ($CHCl_3$) ν 1636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.74–1.90 (4H, m), 2.05–2.59 (4H, m), 2.13 (3H, s), 2.85 (1H, d, J=14.3 Hz), 2.97 (3H, s), 3.29 (1H, d, J=14.3 Hz), 3.85 (6H, s), 6.63–6.82 (3H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 16.4, 22.6, 22.8, 28.6, 31.1, 34.7, 35.0, 55.7, 55.9, 110.4, 111.1, 119.2, 132.7, 135.1, 135.4, 148.2, 148.7, 168.6; HRMS calcd for $C_{18}H_{25}NO_3S$: 335.1555, found: 335.1555.

4.1.2. (3*R,3a*R**)-2,3,3a,4,5,6-Hexahydro-3a-(3,4-dimethoxyphenyl)-1-methyl-3-(methylthio)indol-2-one (10).** *N*-Chlorosuccinimide (124 mg, 0.93 mmol) was added by portions to a solution of **6** (300 mg, 0.89 mmol) in CCl_4 (10 mL) at 0 °C, and the mixture was stirred at room temperature for 2.5 h. The precipitated succinimide was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 10:1→5:1→2:1) to give **10** (124 mg, 48%) as a colorless oil. IR ($CHCl_3$) ν 1719, 1682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24–1.36 (1H, m), 1.64–1.76 (2H, m), 1.82 (3H, s), 2.12–2.18 (2H, m), 2.67 (1H, dt, J=12.8, 3.1 Hz), 3.09 (3H, s), 3.52 (1H, s), 3.85 (3H, s), 3.86 (3H, s), 5.07 (1H, t, J=3.4 Hz), 6.72 (1H, dd, J=2.4, 8.5 Hz), 6.76 (1H, d, J=8.6 Hz), 6.76 (1H, d, J=1.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.8, 18.4, 22.9, 26.4, 34.0, 49.1, 55.7, 55.8,

59.0, 100.1, 110.5, 111.6, 120.5, 132.5, 143.4, 148.1, 148.3, 171.1; HRMS calcd for $C_{18}H_{23}NO_3S$: 333.1399, found: 333.1401.

4.1.3. 2,3,3a,4,5,6-Hexahydro-3a-(3,4-dimethoxyphenyl)-1-methylindol-2-one (11). Raney nickel (W-2) (ca. 500 mg) was added to a solution of **10** (120 mg, 0.36 mmol) in EtOH (2.5 mL), and the mixture was heated under reflux for 3 h. The Raney nickel was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 10:1→5:1→2:1) to give **11** (90 mg, 87%) as a colorless oil. IR ($CHCl_3$) ν 1717, 1678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16–1.30 (1H, m), 1.56–1.66 (1H, m), 1.79 (1H, td, J=13.3, 2.7 Hz), 2.11–2.25 (3H, m), 2.64 (1H, d, J=16.2 Hz), 2.77 (1H, d, J=16.2 Hz), 2.99 (3H, s), 3.85 (6H, s), 5.13 (1H, t, J=3.7 Hz), 6.77 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 22.6, 26.0, 35.7, 45.6, 46.9, 55.8, 55.9, 100.0, 110.3, 110.8, 119.3, 137.9, 144.1, 147.7, 148.8, 173.0; HRMS calcd for $C_{17}H_{21}NO_3$: 287.1522, found: 287.1524.

4.1.4. (3a*R,7a*S**)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindole [(±)-*trans*-mesembrane] (*trans*-13) and (3a*R**,7a*R**)-3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindole [(±)-mesembrane] (*cis*-13).** A mixture of **11** (20 mg, 0.07 mmol) and platinum dioxide (2.5 mg, 0.01 mmol) in acetic acid (0.5 mL) was stirred at room temperature for 1.5 h under a hydrogen atmosphere. The catalyst was filtered off, the filtrate was concentrated, and the residue was purified by thin layer chromatography on silica gel (hexane/AcOEt, 1:4) to give an inseparable mixture of (3a*R**,7a*S**)-3a-(3,4-dimethoxyphenyl)-1-methyloctahydroindol-2-one (*trans*-**12**) and its (3a*R**,7a*R**)-isomer (*cis*-**12**) (18 mg, 90%) in a ratio of 2:1 (determined by ^1H NMR spectroscopy) as a colorless oil. IR ($CHCl_3$) ν 1682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26–2.15 (22/3H, m, for *trans*-**12** and *cis*-**12**), 2.34 (1H×2/3, d, J=15.3 Hz, for *trans*-**12**), 2.42 (1H×2/3, d, J=15.3 Hz, for *trans*-**12**), 2.48 (1H×1/3, d, J=16.4 Hz, for *cis*-**12**), 2.51 (1H×1/3, d, J=16.4 Hz, for *cis*-**12**), 2.58 (1H×2/3, br d, J=13.4 Hz, for *trans*-**12**), 2.85 (3H×1/3, s, for *cis*-**12**), 2.90 (3H×2/3, s, for *trans*-**12**), 3.53 (1H×2/3, dd, J=13.3, 3.3 Hz, for *trans*-**12**), 3.83 (3H×2/3, s, for *trans*-**12**), 3.85 (3H×2/3, s, for *trans*-**12**), 3.88 (3H×1/3, s, for *cis*-**12**), 3.89 (3H×1/3, s, for *cis*-**12**), 3.91 (1H×1/3, t, J=3.7 Hz, for *cis*-**12**), 6.77–6.91 (3H, m, for *trans*-**12** and *cis*-**12**); HRMS calcd for $C_{17}H_{23}NO_3$: 289.1678, found: 289.1674.

A solution of the mixture of *trans*-**12** and *cis*-**12** (18 mg, 0.062 mmol) obtained above in dry THF (1 mL) was added dropwise to a solution of $LiAlH_4$ (14 mg, 0.37 mmol) in dry THF (0.3 mL) at 0 °C, and the mixture was heated under reflux for 10 min. The reaction mixture was quenched by the successive addition of water (14 μL), aqueous NaOH solution (15%) (14 μL), water (28 μL), and THF (1 mL). After filtration, the filtrate was concentrated, and the residue was purified by thin layer chromatography on silica gel ($CHCl_3$/MeOH/isopropylamine, 80:1:2). The first eluent gave *trans*-**13** (9 mg, 53%) as a colorless oil. IR ($CHCl_3$) ν 1514 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12–1.77 (9H, m), 2.17 (1H, dd, J=10.7, 4.4 Hz), 2.26 (1H, td, J=10.2, 2.9 Hz), 2.36 (3H, s), 2.55–2.60 (1H, m), 3.08 (1H, dt, J=10.1, 8.1 Hz), 3.85 (3H, s), 3.86 (3H, s), 6.79 (1H, d, J=8.6 Hz), 7.28 (1H, dd, J=2.1, 8.6 Hz), 7.59 (1H, d, J=2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 24.2, 25.7, 38.0, 40.0, 41.5, 48.9, 53.3, 55.7, 55.9, 76.8, 110.6, 113.2, 120.9, 138.2, 146.4, 148.3; HRMS calcd for $C_{17}H_{25}NO_2$: 275.1885, found: 275.1883.

The second eluent gave *cis*-**13** (5 mg, 29%) as a colorless oil. IR ($CHCl_3$) ν 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12–1.96 (10H, m), 2.25–2.37 (1H, m), 2.33 (3H, s), 2.59 (1H, br s), 3.26 (1H, td, J=9.1, 4.8 Hz), 3.87 (3H, s), 3.89 (3H, s), 6.81 (1H, d, J=8.2 Hz), 6.89–6.94 (2H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 22.9, 23.6, 36.0, 40.6, 41.0, 47.5, 54.3, 55.8, 55.9, 68.7, 110.7, 110.8, 118.9, 140.2, 146.9, 148.6; HRMS calcd for $C_{17}H_{25}NO_2$: 275.1885, found: 275.1888.

4.1.5. (3a*R,7a*R**)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindol-2-one (*cis*-12): reduction of 11 with Et_3SiH.** A mixture of **11** (20 mg, 0.07 mmol) and triethylsilane (16 mg, 0.14 mmol) in trifluoroacetic acid (0.3 mL) was stirred at room temperature for 5 min. The reaction mixture was concentrated, and the residue was purified by thin layer chromatography on silica gel (hexane/AcOEt, 1:4) to give *cis*-**12** (20 mg, quant.) as a colorless oil. IR ($CHCl_3$) ν 1678 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26–2.05 (8H, m), 2.50 (2H, br s), 2.86 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 3.92 (1H, t, J=3.7 Hz), 6.81–6.73 (3H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.3, 21.6, 24.6, 26.9, 34.8, 42.8, 48.1, 55.9, 56.0, 62.2, 110.3, 111.0, 118.7, 137.1, 147.6, 148.9, 174.3; HRMS calcd for $C_{17}H_{23}NO_3$: 289.1678, found: 289.1680.

4.1.6. (3a*R,7a*R**)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindole [(±)-mesembrane] (*cis*-13).** To a solution of $LiAlH_4$ (14 mg, 0.37 mmol) in dry THF (0.3 mL) was added dropwise a solution of *cis*-**12** (18 mg, 0.062 mmol) in dry THF (1 mL) at 0 °C, and the mixture was heated under reflux for 10 min. After work-up as described above for the preparation of *trans*-**13** and *cis*-**13** from the mixture of *trans*-**12** and *cis*-**12** (Section 4.1.4), the crude material was purified by thin layer chromatography on silica gel ($CHCl_3$/MeOH/isopropylamine, 80:1:2) to give *cis*-**13** (17 mg, quant.) as a colorless oil. The spectral data of this compound were in accord with those of (±)-mesembrane obtained above (Section 4.1.4).

4.1.7. *N*-[2-(3,4-Dimethoxyphenyl)cyclohexen-1-yl]-α-(methylthio)-*N*-[(*R*)-1-(1-naphthyl)ethyl]acetamide (22). A mixture of 2-(3,4-dimethoxyphenyl)cyclohexanone (1 g, 4.3 mmol), (*R*)-1-naphthylethylamine (805 mg, 4.7 mmol), and *p*-toluenesulfonic acid monohydrate (82 mg, 0.43 mmol) in toluene (15 mL) was heated under reflux with azeotropic removal of water for 6 h. After cooling the reaction mixture, *N*,*N*-dimethylaniline (1.56 g, 12.9 mmol), 4-dimethylaminopyridine (53 mg, 0.43 mmol), and a solution of α-(methylthio)acetyl chloride (959 mg, 7.7 mmol) in toluene (30 mL) were added at 0 °C, and the mixture was stirred at 60 °C for 13 h. The reaction mixture was washed with a saturated NH_4Cl solution, brine, dried ($MgSO_4$), and concentrated. The crude material was purified by column chromatography on silica gel (hexane/AcOEt, 7:1) to give **22** (1.05 g, 52%) as a yellow amorphous. IR ($CHCl_3$) ν 1730, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.7–2.6

(8H, m), 1.02 (3H×3/8, d, J=7.1 Hz), 1.61 (3H×5/8, d, J=7.1 Hz), 2.33 (3H×5/8, s), 2.45 (3H×3/8, s), 3.39 (1H×5/8, d, J=13.9 Hz), 3.50 (1H×3/8, d, J=13.9 Hz), 3.55 (1H×5/8, d, J=13.9 Hz), 3.62 (3H×3/8, s), 3.63 (1H×3/8, d, J=13.9 Hz), 3.67 (3H×3/8, s), 3.91 (3H×5/8, s), 3.93 (3H×5/8, s), 5.79 (1H×3/8, d, J=2.0 Hz), 5.87 (1H×3/8, dd, J=8.3, 2.0 Hz), 6.02 (1H×3/8, d, J=8.3 Hz), 6.37 (1H×5/8, q, J=7.1 Hz), 6.48 (1H×3/8, q, J=7.1 Hz), 6.77 (1H×5/8, d, J=2.0 Hz), 6.83 (1H×5/8, dd, J=8.3, 2.0 Hz), 6.89 (1H×5/8, d, J=8.3 Hz), 7.20–8.05 (7H, m). Anal. Calcd for $C_{29}H_{33}NO_3S$: C, 73.23; H, 6.99; N, 2.94. Found: C, 72.96; H, 7.12; N, 2.86.

4.1.8. 2,3,3a,4,5,6-Hexahydro-3a-(3,4-dimethoxyphenyl)-3-methylthio-1-[(*R*)-1-(1-naphthyl)ethyl]indol-2-one (23): by reaction of 22 and NCS. *N*-Chlorosuccinimide (294 mg, 2.2 mmol) was added by portions to a solution of **22** (1 g, 2.2 mmol) in CCl_4 (40 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The precipitated succinimide was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 6:1) to give a ca. 2:1 mixture of two diastereoisomers of **23** (610 mg, 59%) as a yellow amorphous. IR ($CHCl_3$) 1713, 1673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.9–1.9 (6H, m), 1.86 (3H×1/3, s), 1.96 (3H×2/3, s), 2.05 (3H×2/3, d, J=7.1 Hz), 2.52 (1H×1/3, dt, J=12.3, 3.2 Hz), 2.57 (1H×2/3, dt, J=12.7, 3.4 Hz), 3.51 (1H×2/3, s), 3.52 (3H×1/3, s), 3.59 (1H×1/3, s), 3.67 (3H×1/3, s), 3.73 (3H×2/3, s), 3.83 (3H×2/3, s), 4.97 (1H×2/3, t, J=3.8 Hz), 5.21 (1H×1/3, t, J=3.9 Hz), 5.70 (1H×1/3, d, J=8.3 Hz), 5.85 (1H×1/3, d, J=8.3 Hz), 6.29 (1H×2/3, q, J=7.0 Hz), 6.40 (1H×1/3, q, J=7.1 Hz), 6.69 (1H×2/3, d, J=8.5 Hz), 6.76 (1H×1/3, d, J=2.2 Hz), 6.86 (1H×2/3, dd, J=8.5, 2.2 Hz), 6.92 (1H×2/3, d, J=2.2 Hz), 7.37–7.55 (3H, m), 7.74–7.92 (3 H, m), 8.00 (1H×1/3, d J=8.5 Hz), 8.09 (1H×2/3, d, J=8.3 Hz). Anal. Calcd for $C_{29}H_{31}NO_3S$: C, 73.54; H, 6.60; N, 2.96. Found: C, 73.51; H, 6.94; N, 2.88.

4.1.9. Compound 23 by the reaction of 24 and TFAA. *m*-Chloroperbenzoic acid (65%) (56 mg, 0.21 mmol) was added to a solution of **22** (100 mg, 0.21 mmol) in CH_2Cl_2 (6 mL) at 0 °C over 1 h, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was washed with aqueous 10% $Na_2S_2O_3$ solution and aqueous $NaHCO_3$ solution and dried. Trifluoroacetic anhydride (TFAA) (88 mg, 0.42 mmol) was added to a solution of thus obtained crude **24** in CH_2Cl_2 (3.2 mL) at 0 °C, and the mixture was stirred at the same temperature for 5 min. The reaction mixture was washed with aqueous $NaHCO_3$ solution, dried, concentrated, and the crude material was purified by column chromatography on silica gel (hexane/AcOEt, 3:2) to give **23** (30 mg, 30%) as a ca. 3:1 mixture of the diastereoisomers.

4.1.10. 2,3,3a,4,5,6-Hexahydro-3a-(3,4-dimethoxyphenyl)-1-[(*R*)-1-(1-naphthyl)ethyl]indol-2-one (26). Raney nickel (W-2) (ca. 1.5 g) was added to a solution of a 2:1 diastereoisomeric mixture of **23** (300 mg, 0.63 mmol) in EtOH (7 mL), and the mixture was heated under reflux for 1 h. The Raney nickel was filtered off, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1) to give a 2:1 diastereoisomeric mixture of **26** (280 mg, 94%) as a white amorphous. IR ($CHCl_3$) ν 1709, 1667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83–2.10 (6H, m), 1.90 (3H, d, J=7.1 Hz), 2.65 (1H×2/3, d, J=15.6 Hz), 2.69 (1H×1/3, d, J=16.1 Hz), 2.86 (1H×2/3, d, J=15.6 Hz), 2.91 (1H×1/3, d, J=16.1 Hz), 3.34 (3H×1/3, s), 3.70 (3H×1/3, s), 3.81 (3H×2/3, s), 3.86 (3H×2/3, s), 4.91 (1H×2/3, t, J=9.6 Hz), 5.19 (1H×1/3, t, J=9.6 Hz), 5.75 (1H×1/3, dd, J=8.2, 2.3 Hz), 5.98 (1H×1/3, d, J=8.2 Hz), 6.20 (1H×2/3, q, J=7.2 Hz), 6.26 (1H×1/3, q, J=6.0 Hz), 6.28 (1H×1/3, d, J=2.4 Hz), 6.78 (1H×2/3, d, J=8.3 Hz), 6.83 (1H×2/3, d, J=2.0 Hz), 6.86 (1H×2/3, dd, J=8.3, 2.2 Hz), 7.13–8.12 (7H, m); HRMS calcd for $C_{28}H_{29}NO_3$: 427.2148, found: 427.2144.

4.1.11. (3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-1-[(*R*)-1-(1-naphthyl)ethyl]octahydroindol-2-one (27a) and (3a*R*,7a*R*)-3a-(3,4-dimethoxyphenyl)-1-[(*R*)-1-(1-naphthyl)ethyl]octahydroindol-2-one (27b). Triethylsilane (16 mg, 0.14 mmol) was added to a solution of a 2:1 diastereoisomeric mixture of **26** (30 mg, 0.07 mmol) in trifluoroacetic acid (0.3 mL) at room temperature, and the stirring was continued for 1 h. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (hexane/AcOEt, 10:1→5:1→3:1→1:1). The first eluent gave **27a** (19 mg, 63%) as a white amorphous. $[\alpha]_D^{26}$ +65.6 (c 2.19, $CHCl_3$); IR ($CHCl_3$) ν 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.47–0.52 (1H, m), 0.68–0.94 (3H, m), 1.1–1.2 (1H, m), 1.12 (3H, d, J=6.7 Hz), 1.37–1.42 (1H, m), 1.66–1.80 (2H, m), 2.62 (1H, d, J=16.5 Hz), 2.80 (1H, d, J=16.5 Hz), 3.55 (1H, dd, J=8.6, 5.5 Hz), 3.89 (3H, s), 3.93 (3H, s), 6.07 (1H, q, J=6.9 Hz), 6.85 (1H, d, J=8.5 Hz), 6.91 (1H, d, J=1.8 Hz), 6.98 (1H, dd, J=8.5, 2.4 Hz), 7.39–7.58 (4H, m), 7.78–7.84, (2H, m), 8.22 (1H, d, J=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7, 21.6, 22.1, 29.0, 35.5, 39.8, 45.26, 45.29, 55.9, 56.2, 61.6, 110.2, 110.9, 118.6, 123.6, 124.0, 124.8, 125.8, 126.7, 128.5, 128.6, 132.3, 133.4, 136.5, 139.2, 147.8, 148.8, 173.1; HRMS calcd for $C_{28}H_{31}NO_3$: 429.2304, found: 429.2302.

The second eluent gave **27b** (10 mg, 33%) as a white amorphous. $[\alpha]_D^{25}$ −73.0 (c 0.78, $CHCl_3$); IR ($CHCl_3$) ν 1663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15–1.23 (1H, m), 1.38–1.73 (6H, m), 1.72 (3H, d, J=7.1 Hz), 2.00–2.07 (1H, m), 2.67 (1H, d, J=16.4 Hz), 2.81 (1H, d, J=16.4 Hz), 2.97 (1H, dd, J=9.0, 5.9 Hz), 3.45 (3H, s), 3.76 (3H, s), 5.99 (1H, q, J=7.1 Hz), 6.11 (1H, d, J=2.4 Hz), 6.26 (1H, d, J=8.3 Hz), 6.36 (1H, dd, J=8.3, 2.4 Hz), 7.01–7.04 (1H, m), 7.30–7.45 (3H, m), 7.54 (1H, d, J=7.1 Hz), 7.72 (1H, d, J=8.3 Hz), 7.76 (1H, d, J=8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 21.8, 22.5, 30.9, 36.4, 39.7, 44.5, 46.3, 55.3, 55.4, 61.5, 108.8, 109.9, 117.2, 122.9, 123.7, 124.3, 125.4, 126.1, 127.8, 128.6, 131.5, 133.3, 134.4, 138.2, 147.1, 148.1, 173.1. Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.26; H, 7.36; N, 3.21.

4.1.12. (3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-1-[(*R*)-1-(1-naphthyl)ethyl]octahydroindole (28). To a solution of $LiAlH_4$ (87 mg, 0.42 mmol) in dry THF (2 mL) was added dropwise a solution of **27a** (165 mg, 2.28 mmol) in dry THF (7 mL) at 0 °C, and the mixture was heated under reflux for 1 h. After work-up as described above for the preparation

of *trans*-**13** and *cis*-**13**, the crude material was purified by column chromatography on silica gel (hexane/AcOEt/isopropylamine, 90:9:1→75:24:1) to give **28** (153 mg, 97%) as a colorless oil. $[\alpha]_D^{26}$ −4.9 (*c* 0.47, MeOH); IR ($CHCl_3$) ν 1518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97–1.05 (1H, m), 1.37–1.76 (7H, m), 1.39 (3H, d, *J*=6.7 Hz), 2.11–2.20 (2H, m), 2.88–2.94 (1H, m), 3.05–3.08 (1H, m), 3.20 (1H, dd, *J*=15.3, 9.2 Hz), 3.74 (3H, s), 3.91 (3H, s), 4.42 (1H, q, *J*=6.7 Hz), 6.80–6.84 (2H, m), 6.94 (1H, dd, *J*=2.4, 8.5 Hz), 7.23–7.25 (1H, m), 7.32–7.41 (3H, m), 7.68 (1H, d, *J*=7.9 Hz), 7.79 (1H, d, *J*=8.5 Hz), 8.19 (1H, d, *J*=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.4, 23.0, 23.7, 32.0, 36.3, 47.4, 48.8, 55.8, 55.9, 63.1, 110.3, 110.4, 118.1, 124.4, 124.5, 125.0, 125.1, 125.2, 127.0, 128.4, 131.3, 134.0, 141.4, 142.4, 146.8, 148.4; HRMS calcd for $C_{28}H_{33}NO_2$: 415.2511, found: 415.2515.

4.1.13. (3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindole [(−)-mesembrane] (29). A mixture of **28** (149 mg, 0.35 mmol) and $Pd(OH)_2$/C (33 mg) in MeOH (5.5 mL) was stirred at room temperature for 24 h under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated to give (3a*S*,7a*S*)-3a-(3,4-dimethoxyphenyl)octahydroindole. A mixture of this material and aqueous HCHO solution (37%, 0.33 mL, 4.08 mmol) and $NaBH_3(CN)$ (214 mg, 3.4 mmol) in MeOH (8 mL) was stirred at room temperature for 5 min, and the reaction mixture was concentrated. The residue was purified by thin layer chromatography on silica gel (CH_2Cl_2/MeOH/isopropylamine, 80:1:2) to give **29** (83 mg, 84%) as a colorless oil. $[\alpha]_D^{28}$ −15.6 (*c* 1.15, MeOH); IR ($CHCl_3$) ν 1520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12–1.21 (1H, m), 1.34–1.61 (4H, m), 1.76–1.95 (5H, m), 2.27–2.32 (1H, m), 2.32 (3H, s), 2.57 (1H, br s), 3.25 (1H, dt, *J*=9.2, 4.9 Hz), 3.87 (3H, s), 3.89 (3H, s), 6.81 (1H, *J*=8.5 Hz), 6.90 (1H, d, *J*=2.4 Hz), 6.92 (1H, dd, *J*=2.1, 8.2 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.3, 22.9, 23.7, 36.0, 40.6, 41.0, 47.5, 54.3, 55.8, 55.9, 68.6, 110.7, 110.8, 118.9, 140.2, 146.8, 148.6; HRMS calcd for $C_{17}H_{25}NO_2$: 275.1885, found: 275.1888.

4.1.14. (3a*S*,7a*R*)-3a-(3,4-Dimethoxyphenyl)-1-[(*R*)-1-(1,2,3,4-tetrahydronaphthalen-5-yl)ethyl]octahydroindol-2-one (30a), (3a*R*,7a*S*)-3a-(3,4-dimethoxyphenyl)-1-[(*R*)-1-(1,2,3,4-tetrahydronaphthalen-5-yl)ethyl]octahydroindol-2-one (30b), and (*R*)-2,3,3a,4,5,6-hexahydro-3a-(3,4-dimethoxyphenyl)-1-[(*R*)-1-(1,2,3,4-tetrahydronaphthalen-5-yl)ethyl]indol-2-one (31). Platinum dioxide (5 mg, 0.02 mmol) was added to a solution of a 2:1 diastereoisomeric mixture of **26** (40 mg, 0.094 mmol) in acetic acid (1 mL) at room temperature under a hydrogen atmosphere, and the stirring was continued for 14 h. The catalyst was filtered off, the filtrate was concentrated, and the residue was purified by thin layer chromatography on silica gel (hexane/AcOEt, 3:1). The first eluent gave **31** (1.6 mg, 4%) as a colorless oil. $[\alpha]_D^{26}$ +170.9 (*c* 0.27, MeOH); IR ($CHCl_3$) ν 1709, 1667 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88–2.16 (11H, m), 1.72 (3H, d, *J*=7.3 Hz), 2.50 (1H, dt, *J*=17.2, 5.6 Hz), 2.66 (1H, d, *J*=16.2 Hz), 2.75–2.83 (2H, m), 2.95 (1H, d, *J*=16.2 Hz), 3.61 (3H, s), 3.82 (H, s), 5.27 (1H, t, *J*=3.6 Hz), 5.63 (1H, q, *J*=7.7 Hz), 6.36 (1H, dd, *J*=2.1, 8.3 Hz), 6.54 (1H, d, *J*=2.1 Hz), 6.62 (1H, d, *J*=8.2 Hz), 7.04–7.21 (2H, m), 7.39 (1H, d, *J*=7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 17.3, 22.3, 22.8, 25.3, 30.3, 36.6, 45.0, 46.2, 47.0, 55.5, 55.8, 55.9, 103.6, 110.5, 110.6, 119.5, 124.5, 125.3, 128.9, 136.0, 137.25, 137.32, 137.7, 140.7, 147.5, 148.4, 172.5. HRMS calcd for $C_{28}H_{33}NO_3$: 431.2461, found: 431.2464.

The second eluent gave **30a** (22 mg, 54%) as a white amorphous. $[\alpha]_D^{25}$ −92.4 (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) ν 1673 cm^{-1}; ^1H NMR δ 0.95–2.20 (12H, m), 2.81 (3H, d, *J*=7.1 Hz), 2.35 (1H, d, *J*=15.1 Hz), 2.40 (1H, d, *J*=15.1 Hz), 2.52 (1H, br d, *J*=13.4 Hz), 2.75 (1H, dt, *J*=16.6, 4.5 Hz), 2.80–2.88 (2H, m), 3.09 (1H, dd, *J*=12.7, 2.9 Hz), 3.85 (3H, s), 3.86 (3H, s), 5.56 (1H, q, *J*=7.1 Hz), 6.80 (1H, d, *J*=8.5 Hz), 7.00–7.15 (4H, m), 7.33 (1H, d, *J*=7.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.1, 21.7, 22.8, 23.2, 24.4, 25.3, 26.3, 30.2, 36.1, 45.6, 47.5, 48.8, 55.8, 56.2, 67.9, 111.2, 111.5, 120.1, 124.9, 125.0, 129.0, 135.8, 136.6, 136.7, 137.6, 147.2, 148.7, 174.5; HRMS calcd for $C_{28}H_{35}NO_3$: 433.2617, found: 433.2616.

The third eluent gave **30b** (8.6 mg, 21%) as a colorless crystal. $[\alpha]_D^{26}$ +102.4 (*c* 0.30, $CHCl_3$); mp 199.5–200 °C (hexane/AcOEt); IR ($CHCl_3$) ν 1674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94–1.04 (1H, m), 1.32–1.43 (2H, m), 1.56–1.78 (7H, m), 1.69 (3H, d, *J*=7.1 Hz), 1.98–2.01 (1H, m), 2.41 (1H, d, *J*=15.5 Hz), 2.45–2.50 (1H, m), 2.46 (1H, d, *J*=15.1 Hz), 2.62–2.68 (1H, m), 2.77–2.87 (3H, m), 3.63 (1H, dd, *J*=13.2, 3.4 Hz), 3.73 (3H, s), 3.81 (3H, s), 5.53 (1H, q, *J*=7.1 Hz), 6.58 (2H, d, *J*=1.0 Hz), 6.77 (1H, s), 7.05–7.16 (2H, m), 7.30 (1H, d, *J*=7.3 Hz); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 16.8, 21.5, 22.6, 23.2, 24.2, 25.5, 25.8, 30.5, 37.2, 45.4, 47.4, 49.9, 55.7, 56.1, 67.0, 110.3, 111.9, 121.3, 124.7, 124.8, 128.8, 135.5, 136.5, 137.7, 138.5, 147.1, 148.9, 175.0. Anal. Calcd for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14; N, 3.23. Found: C, 77.40; H, 8.17; N, 3.25.

4.1.15. (3a*S*,7a*R*)-3a-(3,4-Dimethoxyphenyl)-1-[(*R*)-1-(1,2,3,4-tetrahydronaphthalen-5-yl)ethyl]octahydroindole (32). To a solution of $LiAlH_4$ (96 mg, 0.42 mmol) in dry THF (2 mL) was added dropwise a solution of **30a** (180 mg, 0.42 mmol) in dry THF (8 mL) at 0 °C, and the mixture was heated under reflux for 1 h. After work-up as described above for the preparation of *trans*-**13** and *cis*-**13**, the crude material was purified by column chromatography on silica gel (hexane/AcOEt, 20:1) to give **32** (130 mg, 74%) as a colorless oil. $[\alpha]_D^{26}$ −138.7 (*c* 0.33, MeOH); IR ($CHCl_3$) ν 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15–1.87 (13H, m), 1.32 (3H, d, *J*=6.6 Hz), 2.56–2.64 (2H, m), 2.71 (1H, dd, *J*=11.6, 3.5 Hz), 2.76–2.84 (4H, m), 3.09 (1H, dt, *J*=10.2, 5.9 Hz), 3.76 (3H, s), 3.84 (3H, s), 4.20 (1H, q, *J*=6.5 Hz), 6.75 (1H, d, *J*=8.5 Hz), 6.94 (1H, d, *J*=7.3 Hz), 7.05 (1H, t, *J*=7.6 Hz), 7.24 (1H, dd, *J*=2.2, 8.5 Hz), 7.29 (1H, d, *J*=7.5 Hz), 7.62 (1H, d, *J*=2.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 22.3, 22.8, 23.5, 25.0, 25.7, 25.9, 30.4, 37.9, 40.3, 44.5, 48.7, 53.0, 55.7, 55.9, 72.6, 110.5, 113.5, 120.6, 124.1, 124.7, 127.6, 134.4, 137.0, 138.1, 143.5, 146.3, 148.0. HRMS calcd for $C_{28}H_{37}NO_2$: 419.2824, found: 419.2829.

4.1.16. (3a*S*,7a*R*)-3a-(3,4-Dimethoxyphenyl)octahydroindole [(−)-*trans*-mesembrane] (33). A mixture of **32** (60 mg, 0.14 mmol) and $Pd(OH)_2$/C (15 mg) in MeOH (1.5 mL) was stirred at room temperature for 12 days under a hydrogen atmosphere. The catalyst was filtered off, and the

filtrate was concentrated to give (3a*S*,7a*S*)-3a-(3,4-dimethoxyphenyl)octahydroindole. A mixture of this material, aqueous HCHO solution (37%, 0.094 mL, 1.15 mmol), and $NaBH_3(CN)$ (60 mg, 0.96 mmol) in MeOH (8 mL) was stirred at room temperature for 15 min. The mixture was concentrated, and the residue was purified by thin layer chromatography on silica gel ($CHCl_3$/MeOH/isopropylamine, 80:1:2) to give **33** (23 mg, 71%) as a colorless oil. $[\alpha]_D^{28}$ −105.8 (*c* 0.32, MeOH); IR ($CHCl_3$) ν 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13–1.79 (9H, m), 2.17 (1H, dd, *J*=11.6, 3.7 Hz), 2.25 (1H, td, *J*=10.4, 2.4 Hz), 2.37 (3H, s), 2.57–2.62 (1H, m), 3.08 (1H, dd, *J*=18.3, 7.9 Hz), 3.84 (3H, s), 3.85 (3H, s), 6.79 (1H, d, *J*=8.6 Hz), 7.28 (1H, dd, *J*=8.5, 2.4 Hz), 7.59 (1H, d, *J*=2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 24.2, 25.7, 38.0, 40.0, 41.5, 48.9, 53.3, 55.7, 55.9, 76.8, 110.6, 113.2, 120.9, 138.1, 146.4, 148.3; HRMS calcd for $C_{17}H_{25}NO_2$: 275.1885, found: 275.1884.

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Supplementary data

Experimental procedure for the preparation of **19a**, **20a**, **21a**, **19b**, **20b$_1$**, **20b$_2$**, **21b$_1$**, and **21b$_2$**; ^1H NMR spectra of **29** and **33**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.153.

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