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Stereochemical Studies. XXVII.[1] Total Synthesis of (+)-Mesembrine with Asymmetric Synthesis using Proline Derivative[2]

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Asymmetric synthesis of 4,4-disubstituted 2-cyclohexenone with enamine alkylation was successfully applied to the total synthesis of (+)-mesembrine. The assignment of the absolute configuration for synthetic (+)-mesembrine was consistent with the configuration of natural (−)-mesembrine determined by X-ray crystallography.

An earlier paper[1] dealing with the asymmetric synthesis of 4,4-disubstituted 2-cyclohexenone (IV) by the alkylation of enamines (III) obtained from disubstituted acetaldehyde (I) and L-proline pyrrolidide (II), with methyl vinyl ketone, showed that all the cyclohexenones obtained were optically active and that their absolute configurations could be determined.

The present investigation was undertaken to apply this method to the synthesis of optically active natural compounds. Although applications of asymmetric synthesis to obtain optically active natural compound have been reported,[4–9] no readily available method for the synthesis of optically active complicated compounds except for amino acids[8] has been published.

Mesembrine was chosen as the compound to be synthesized. Total syntheses of (±)-mesembrine have been reported by several authors.[10] Of these the total synthesis by M. Shamma and H.R. Rodriguez[11] included the 4,4-disubstituted 2-cyclohexenone derivative, racemic X, as an intermediate. The total synthesis of optically active mesembrine was expected to be achieved by the asymmetric synthesis of 4,4-disubstituted 2-cyclohexenone (X).

When this work started, the two opposite absolute configurations had been independently assigned to natural (−)-mesembrine by two separate groups on the basis of spectral data. M. Shamma and his co-workers[12] made the reasonable assumption of a preferred conformation and on the basis of its optical rotatory dispersion (ORD) curve they represented the absolute configuration as structure XI. Recently P.W. Jeffs and his co-workers[13] reassigned the absolute configuration structure XII on the basis of detailed studies of infrared (IR) and nuclear magnetic resonance (NMR) spectral data of the alkaloid and its related compounds.

1) Part XXVI: G. Otani and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2125 (1973).
2) This work was the subject of a preliminary report: S. Yamada and G. Otani, *Tetrahedron Letters*, **1971**, 1133.
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4) A. McKenzie and H.B. Thompson, *J. Chem. Soc.*, **1905**, 1004; V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).
5) H.C. Brown, N.R. Ayyangar, and G. Zweifel, *J. Am. Chem. Soc.*, **86**, 397 (1964).
6) R.M. Bowman and M.F. Grundon, *J. Chem. Soc.* (*C*), **1967**, 2368; R.M. Bowman, J.F. Collis, and M.F. Grundon, *ibid.*, **1967**, 1131.
7) S.I. Goldberg and I. Ragade, *J. Org. Chem.*, **32**, 1046 (1967).
8) E.J. Corey, R.J. McCaully, and H.S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2476 (1970), and cited therein.
9) For a recent review, see D.R. Boyd and M.A. McKervey, *Quart. Rev.* (London), **22**, 95 (1968).
10) T. Oh-ishi and H. Kugita, *Chem. Pharm. Bull.* (Tokyo), **18**, 299 (1970), and cited therein.
11) M. Shamma and H.R. Rodriguez, *Tetrahedron*, **24**, 6583 (1968).
12) E. Smith, N. Hosansky, M. Shamma, and J.B. Moss, *Chem. Ind.* (London), **1961**, 402.
13) P.W. Jeffs, R.J. Hawks, and D.S. Farrier, *J. Am. Chem. Soc.*, **91**, 3831 (1969).

The assignment of the absolute configuration may be achieved by the total synthesis of optically active mesembrine, whose absolute configuration would be determined, by this asymmetric synthesis.

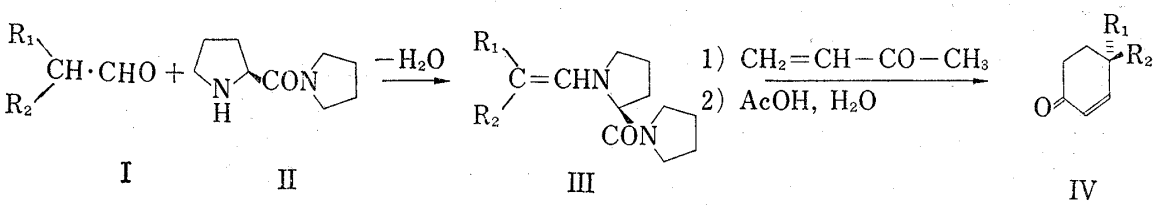

Chart 1

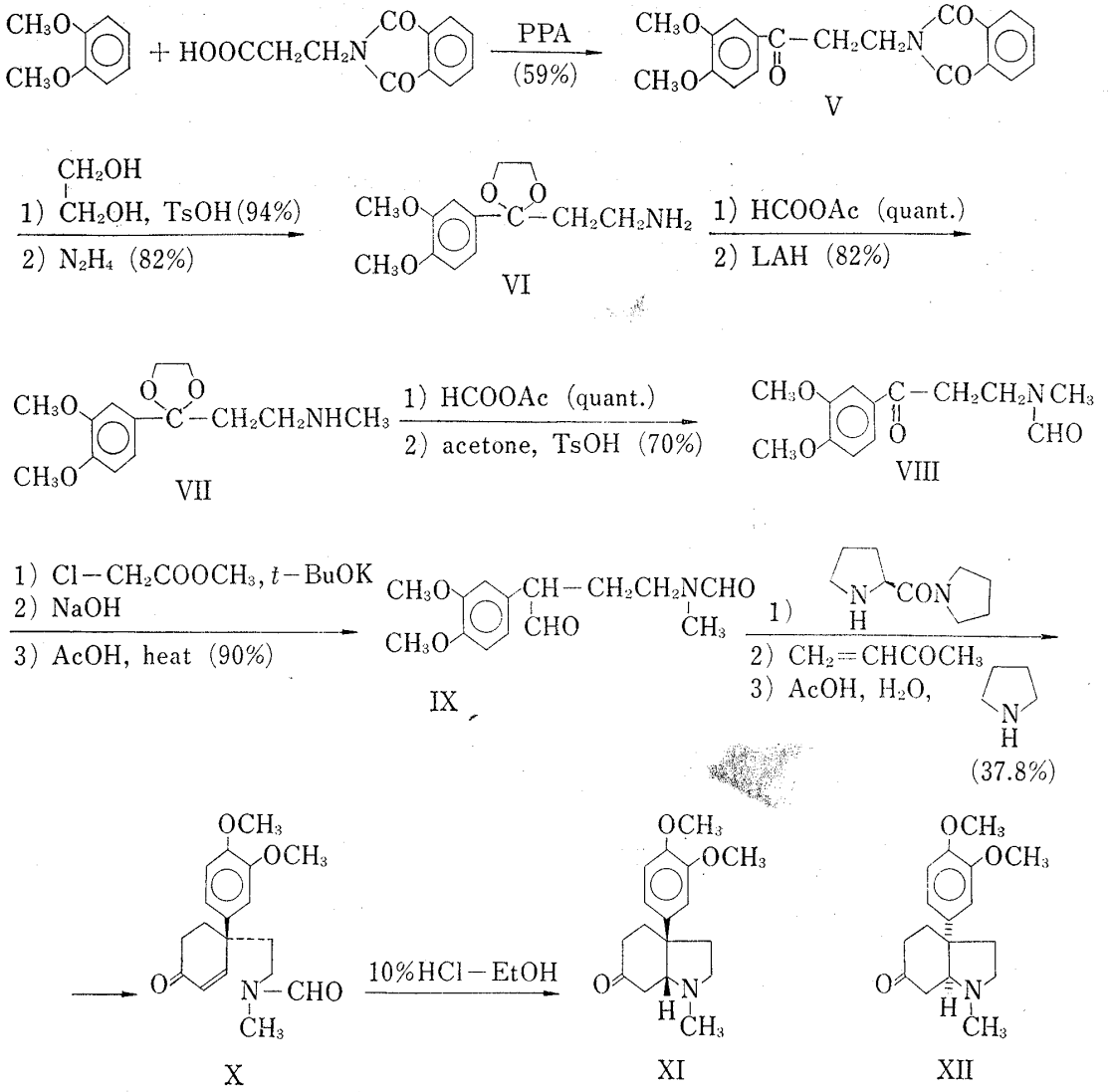

Chart 2

The key intermediate, disubstituted acetaldehyde IX, for this asymmetric synthesis was prepared as follows (Chart 2). 1,2-Dimethoxybenzene and β-phthaloylaminopropionic acid were condensed to phthaloylaminopropiophenone V, in the presence of polyphosphoric acid. The ketone group was protected by ketalization with ethylene glycol, then the phthaloyl group was removed with hydrazine hydrate to give amine VI. Amine VI was formylated and reduced with LAH to the secondary amine VII. After further formylation of the secondary amine VII, ketone VIII was obtained by hydrolysis of the protection group for ketone

group. Conversion of ketone VIII to the required aldehyde IX was accomplished with the modified Darzens method. The aldehyde IX obtained was used successively for asymmetric synthesis without purification, since it was unstable. Its structure and purity were confirmed by its IR and NMR spectra, by thin-layer chromatography (TLC) and by elemental analysis of its semicarbazone.

Asymmetric synthesis of optically active cyclohexenone X from aldehyde IX was performed using a previously reported method.[1] The solution of aldehyde IX and L-proline pyrrolidide in benzene was heated to remove the water produced by azeotropic distillation until the distillate became clear. Then the benzene was evaporated under reduced pressure and the residual enamine was successively used for enamine alkylation. Methyl vinyl ketone was added to a 10% solution of the enamine in methanol. The reaction mixture was allowed to stand for 44 hours at room temperature (10—20°). After enamine alkylation, the neutral fraction was extracted and heated in methanol containing acetic acid, water and pyrrolidine for cyclization. The crude product was chromatographed on silica gel and the optically active cyclohexenone X, $[\alpha]_D^{20}$ +12.7° (c=1.48, MeOH), was obtained in a 38% yield. It exhibited a positive Cotton effect, $[M]_{max}$ +770° (364 mμ) and $[\theta]_{max}$ +43° (351 mμ) in methanol (Fig. 1). Following the results of an earlier report,[1] its absolute configuration was assigned as structure X, since the conformation energy of the dimethoxyphenyl group is undoubtedly larger than that of the formylmethylaminoethyl group.[14]

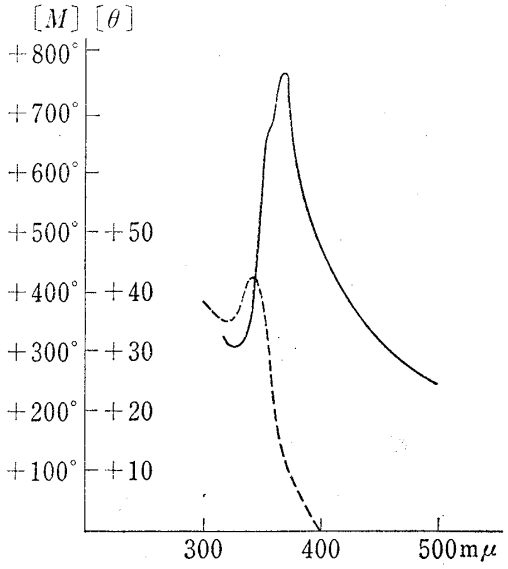

Fig. 1. ORD and CD Curves of (+)-4-(3′,4′-Dimethoxyphenyl)-4-(N-formyl-β-methylaminoethyl)-2-cyclohexenone (X)

ORD: ——
CD : ----

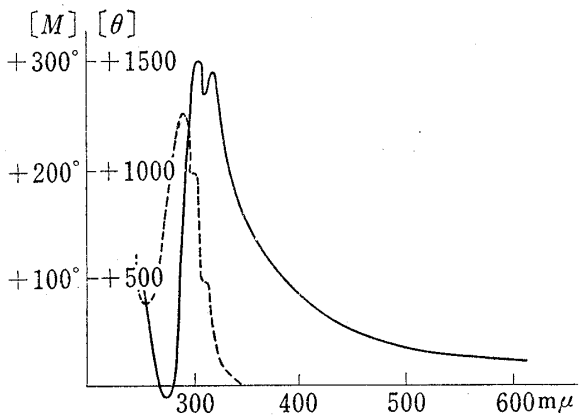

Fig. 2. ORD and CD Curves of Synthetic (+)-Mesembrine

ORD: ——
CD : ----

The transformation of cyclohexenone X to mesembrine in a 70% yield was easily carried out with ethanolic hydrochloric acid by reference to the synthesis of (±)-mesembrine by M. Shamma and H.R. Rodoriguez.[11] Except for the optical rotation, synthetic mesembrine

14) As with the reported conformation energies,[14a] the dimethylamino group (2.1 kcal/mole) and even the tertiary butyl group (over 4 kcal/mole) fall to 2.0 kcal/mole when the methylene group is inserted (-$CH_2C(CH_3)_3$). Therefore, the conformation energy of the N-formyl-2-methylaminoethyl group is not larger than 2.0 kcal/mole. The conformation energy of the dimethoxyphenyl group may be almost equal to that of phenyl group (3.0 kcal/mole); *a*) J.A. Hirsch, "Table of Conformational Energies-1967," in "Topics in Stereochemistry," Vol. 1, ed. by N.L. Allinger and E.L. Eliel Interscience Publishers, Inc., New York, p. 199.

was identical with natural (−)-mesembrine in its IR ($CHCl_3$) and NMR ($CDCl_3$) and TLC values. Synthetic mesembrine exhibited partial optical activity, $[\alpha]_D^{20}$ +16.1° (MeOH),[15] and the opposite optical rotation sign to natural (−)-mesembrine.

Partially optically active (+)-mesembrine hydrochloride was repeatedly recrystallized from isopropanol and was separated into two types of crystals, prisms and less soluble needles, whose IR spectra (KBr) differed. The IR spectrum (KBr) of the needles was identical with that (KBr) of natural (−)-mesembrine hydrochloride. The needles were almost optically pure, $[\alpha]_D^{20}$ +7.3±0.5° (MeOH),[16] and the prisms were racemic. Furthermore, synthtic optically active (+)-mesembrine exhibited a positive Cotton effect, with a pattern antipodal to that of natural (−)-mesembrine (Fig. 2).

Clearly the (+)-mesembrine derived from (+)-cyclohexenone X, possesses the absolute configuration represented by structure XI. Thus, the absolute cnofiguration of natural (−)-mesembrine, as proposed by P.W. Jeffs and his co-workers rather than the one proposed by M. Shamma and his co-workers, that is antipodal to XI, has been assigned. This is consistent with the most recent report of the X-ray analysis of 6-epimesembranol methiodide.[17]

So far as is known, this is the first paper to report the successful synthesis of an optically active and complicated alkaoid by asymmetric synthesis.

Experimental[18]

3,4-Dimethoxy-β-phthaloylaminopropiophenone (V)——A mixture of 1,2-dimethoxybenzene (25 g), β-phthaloylaminopropionic acid[19] (59 g), and polyphosphoric acid (400 g), was heated with stirring at 120° for 4 hr. The cooled dark red mixture was poured onto ice (1 kg), then was extracted with methylene chloride. The extract was washed with water, 10% aqueous sodium carbonate solution and water, successively and dried over sodium sulfate. After the solution was evaporated to a volume of 200 ml, methanol (100 ml) was added to the residue. White needles (35 g, 59%) was precipitated and were filtered. Recrystallization from chloroform–methanol did not alter the mp. *Anal.* Calcd. for $C_{19}H_{17}O_5N$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.48; H, 5.01; N, 4.03. IR ν_{max}^{KBr} cm^{-1}: 1775, 1719, 1667. NMR ($CDCl_3$) τ: 2.25 (4H, multiplet), 2.47 (1H, doublet, J=8 cps), 2.54 (1H, singlet), 3.16 (1H, doublet, J=8 cps), 5.86 (2H, triplet), 6.07 (6H, singlet), 6.64 (2H, triplet).

3,4-Dimethoxy-β-phthloylaminopropiophenone Ethylene Ketal——3,4-Dimethoxy-β-phthaloylaminopropiophenone (V) (17 g), ethylene glycol (20 g), and *p*-toluenesulfonic acid (0.5 g) were added to benzene (300 ml), then the mixture was heated under reflux for 12 hr with a Dean–Stark apparatus to remove the water produced. The cooled reaction mixture was washed with 10% aqueous sodium carbonate solution (50 ml) and water, then it was dried over sodium sulfate and evporated to a volume of 50 ml. *n*-Hexane (20 ml) was added to the residue and the solution was allowed to stand. A white powder precipitated. Recrystallization from benzene–*n*-hexane (2:1) gave ethylene ketal (18 g, 94%), mp 129—133°. *Anal.* Calcd. for $C_{21}H_{21}O_6N$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.90; H, 5.57; N, 3.80. IR ν_{max}^{KBr} cm^{-1}: 1771, 1722. NMR ($CDCl_3$) τ: 2.35 (4H, multiplet), 3.0—3.4 (3H, multiplet), 5.9—6.3 (12H, multiplet), 7.7 (2H, triplet).

3,4-Dimethoxy-β-aminopropiophenone Ethylene Ketal (VI)——3,4-Dimethoxy-β-phthaloylaminopropiophenone ethylene ketal (20.7 g) and 80% hydrazine hydrate (8.45 g) were dissolved in ethanol (250 ml) and the solution was heated under reflux for an hour. Crystals precipitated and were filtered off after cooling, then they were washed with ethanol. The filtrate and washings were collected and evaporated. Aqueous sodium carbonate solution (10%) was added to the residue to make the pH 11, after which the solution was extracted with chloroform. The extract was dried over sodium sulfate and evaporated. Distillation of the residue gave 3,4-dimethoxy-β-aminopropiophenone ethylene ketal (VI) (11.15 g, 81.6%), bp 178—180°

15) The optical rotation of natural mesembrine, $[\alpha]_D^{20}$ −55.4±0.5° (MeOH), has been reported. A. Popelak, E. Haack, G. Lettenbauer, and H. Spingler, *Naturwissenschaften*, **47**, 156 (1960).

16) The optical rotation of natural mesembrine hydrochloride, $[\alpha]_D^{20}$ −8.4±0.5° (MeOH), has been reported.[15]

17) P. Coggon, D.S. Farrier, P.W. Jeffs, and A.T. McPhail, *J. Chem. Soc.* (*B*), **1970**, 1267.

18) All melting and boiling points are uncorrected. Optical rotations were measured with a Yanagimoto Model OR-10 polarimeter. ORD and Circular dichroism (CD) curves were recorded on a Nippon Bunko Model ORD/UV-5 spectropolarimeter. IR spectra were obtained with Nippon Bunko Models IR-S and DS-403G spectrophotometers. NMR spectra were recorded at 60 Mc on a Japan Electron Optics Model JNM C-60 NMR spectrometer. Gas–liquid chromatography (GLC) analyses were carried out on Shimazu Model GC-1 and Perkin-Elmer Model 800 gaschromatographs with dual flame ionization detectors.

19) Y. Ando, S. Takemura, H. Kamiya, M. Kimura, and T. Kita, *Yakugaku Kenkyu*, **33**, 74 (1961).

(3 mmHg), as a colorless liquid. NMR ($CDCl_3$) τ: 3.1 (3H, multiplet), 5.9—6.3 (10H, multiplet), 7.25 (2H, triplet), 7.97 (2H, triplet), 8.5 (2H, singlet, NH_2).

Its picrate, mp 140—142°, as yellow prisms, was recrystallized from ethanol–ether. *Anal.* Calcd. for $C_{19}H_{22}O_{11}N_4$: C, 47.30; H, 4.60; N, 11.62. Found: C, 47.15; H, 4.37; N, 11.46.

3,4-Dimethoxy-β-formylaminopropiophenone Ethylene Ketal——Acetic formic anhydride (0.057 mole) was added to the solution of 3,4-dimethoxy-β-aminopropiophenone ethylene ketal (VI) (12.8 g, 0.0506 mole) in chloroform (30 ml) dropwise over 5 min with stirring under ice cooling. Then the solution was stirred for 3 hr at room temperature, after which it was washed repeatedly with 10% aqueous sodium carbonate solution, then with water and finally was dried over sodium sulfate. Evaporation gave a pale yellow oil (1.42 g, quantitative), which exhibited only one spot on TLC (alumina, $CHCl_3$: AcOEt=1:1). This was used for the next reaction without purification. NMR ($CDCl_3$) τ: 1.87 (1H, singlet, N-CHO), 3.1 (3H, multiplet), 3.7 (1H, broad singlet), 5.9—6.25 (10H, multiplet), 6.6 (2H, multiplet), 8.0 (2H, multiplet). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1684.

3,4-Dimethoxy-β-methylaminopropiophenone Ethylene Ketal (VII)——A solution of 3,4-dimethoxy-β-formylaminopropiophenone ethylene ketal (11.5 g, 0.041 mole) in dry tetrahydrofuran (50 ml) was added dropwise over 30 min to a suspension of lithium aluminum hydride (2.33 g, 0.061 mole) in dry ether (40 ml) with stirring under ice cooling. The mixture was heated under reflux for 5 hr, then with ice cooling a 10% aqueous sodium hydroxide solution (7 ml) was carefully added dropwise with stirring. The gray precipitate changed to a white color and was then filtered and washed with ether. The filtrate and washings were collected and evaporated. Distillation of the residue gave 3,4-dimethoxy-β-methylaminopropiophenone ethylene ketal (VII) (9.0 g, 82%), bp 160° (3 mmHg), as a colorless liquid. NMR ($CDCl_3$) τ: 3.1 (3H, multiplet), 5.9—6.2 (10H, multiplet), 7.4 (2H, multiplet), 7.62 (3H, singlet, N-CH_3), 7.9 (2H, triplet), 8.2 (1H, singlet, NH).

Its picrate, mp 138—140°, as yellow prisms, was recrystallized from methanol. *Anal.* Calcd. for $C_{21}H_{24}O_{11}N_4$: C, 48.39; H, 4.87; N, 11.29. Found: C, 48.41; H, 4.91; N, 11.31.

N-Formyl-3,4-dimethoxy-β-methylaminopropiophenone (VIII)——Acetic formic anhydride (0.043 mole) was added dropwise with stirring under ice cooling to a solution of 3,4-dimethoxy-β-methylaminopropiophenone ethylene ketal (VII) (10.5 g, 0.0393 mole) in chloroform (40 ml), then the solution was stirred for 1.5 hr at room temperature. The solution was washed with 10% aqueous sodium carbonate solution and water, then dried over sodium sulfate. Evaporation gave N-formyl-3,4-dimethoxy-β-methylaminopropiophenone ethylene ketal (11.6 g, quantitative), pale yellow liquid. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. NMR ($CDCl_3$) τ: 2.0 (1H, doublet, N-CHO).

N-Formyl-3,4-dimethoxy-β-methylaminopropiophenone ethylene ketal (11.6 g) and *p*-toluenesulfonic acid (0.5 g) were dissolved in acetone (100 ml) and heated under reflux for 3 hr. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in chloroform, washed twice with water, then dried over sodium sulfate. The solution was evaporated and the residue was recrystallized from benzene–ether to give N-formyl-3,4-dimethoxy-β-methylaminopropiophenone (VIII) (6.9 g, 70%), mp 105—108°, as white prisms. *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.35; H, 6.60; N, 5.39. IR ν_{max}^{KBr} cm^{-1}: 1673. NMR ($CDCl_3$) τ: 1.88 (1H, doublet), 2.40 (1H, quartet, J=2 and 8 cps), 2.48 (1H, doublet, J=2 cps), 3.10 (1H, doublet, J=8 cps), 6.05 (6H, singlet), 6.3 (2H, multiplet), 6.7 (2H, multiplet), 7.04 (3H, doublet).

N-Formyl-2-(3′,4′-dimethoxyphenyl)-4-methylaminobutyraldehyde (IX)——A solution of potassium *t*-butoxide in *t*-butanol (potassium 0.036 atom, *t*-butanol 50 ml) was added dropwise for an hour with stirring under ice cooling to a solution of N-formyl-3,4-dimethoxy-β-methylaminopropiophenone (6.0 g, 0.024 mole) and methyl chloroacetate (3.9 g, 0.036 mole) in dry tetrahydrofuran (25 ml). Then, for another hour the reaction mixture was stirred at room temperature, after which it was allowed to stand overnight. The mixture was evaporated under reduced pressure. Water was added to the residue and extraction with chloroform followed. The extract was washed with water and dried over sodium sulfate and evaporated. A solution of sodium ethoxide in ethanol (sodium 0.84 g, 0.036 atom, in ethanol 25 ml) was added to a solution of the residual orange oil in ethanol (25 ml), then water (0.5 ml) was added and the mixture was allowed to stand overnight. The mixture was evaporated under reduced pressure and the residue was dissolved in water (20 ml). Insoluble material was removed by extraction with chloroform. Acetic acid was added to the aqueous solution to make the pH 5. Then chloroform (20 ml) was added and the mixture was heated under reflux for 20 min till the evolution of carbon dioxide gas had almost ceased. After cooling, the organic layer was separated and the aqueous layer was extracted with chloroform. The organic layer and the extract were collected and washed with 10% aqueous sodium carbonate solution and water then were dried over sodium sulfate. Evaporation gave a pale yellow oil (5.7 g, 90%). TLC (silica gel, $CHCl_3$: AcOEt=1:1) *Rf* 0.4, one spot. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1670. NMR ($CDCl_3$) τ: 0.32 (1H, singlet, C-CHO), 2.0 (1H, doublet, N-CHO), 3.1—3.4 (3H, multiplet), 6.1 (6H, singlet), 6.3—6.9 (3H, multiplet), 7.1 (3H, doublet), 7.5—7.9 (2H, multiplet).

Its semicarbazone, mp 136—139°, as a white powder, was prepared as usual and was recrystallized from ethanol. *Anal.* Calcd. for $C_{15}H_{22}O_2N_4$: C, 55.88; H, 6.88; N, 17.38. Found: C, 55.91; H, 6.56; N, 17.06.

Asymmetric Synthesis of (+)-4-(3′,4′-Dimethoxyphenyl)-4-(N-formyl-β-methylaminoethyl)-2-cyclohexenone (X)——A solution of N-formyl-2-(3′,4′-dimethoxyphenyl)-4-methylaminobutyraldehyde (IX) (1.8 g, 6.8 mmoles) and L-proline pyrrolidide (1.0 g, 6.8 mmoles) in benzene (20 ml), was heated under reflux for 15 min with a Dean–Stark apparatus to remove water by azeotropic distillation. The solution was evaporated under reduced pressure. Methyl vinyl ketone (1.0 g, 0.012 mmoles) was added to the solution of the residual yellow oil in methanol (20 ml) and the reaction mixture was allowed to stand at room temperature (10—20°) for 44 hr. Then, 33% aqueous acetic acid (3 ml) was added and the mixture was evaporated under reduced pressure. Dilute hydrochloric acid (10%) was added to the residue and the mixture was extracted with chloroform. The extract was washed with water and dried over sodium sulfate and evaporated to give a reddish brown oil (2.8 g). This oil was dissolved in methanol (20 ml), then 33% aqueous acetic acid (1 ml) and pyrrolidine (0.3 ml) were added and the whole was heated under reflux for 2 hr. The mixture was evaporated, after which the residue was dissolved in chloroform and was successively washed with 10% hydrochloric acid and 10% aqueous sodium carbonate solution and water. The solution was dried over sodium sulfate and evaporated. The residual reddish brown oil (2.8 g) was chromatographed on silica gel, twice, giving a pale yellow oil (0.70 g, 32.5%). TLC (silical gel, AcOEt: EtOH=9: 1) *Rf* 0.4, one spot. $[\alpha]_D^{20}$ +14.6° (*c*=4.08, MeOH). ORD (*c*=4.1, MeOH) $[M]^{25}$ (mμ): +38.6° (700), +60° (589), +770° (364) (peak), +570° (352) (shoulder), +310° (332) (trough), +850° (300). CD (*c*=4.1, MeOH) $[\theta]^{25}$ (mμ): +43 (351) (positive maximum). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1688. NMR ($CDCl_3$) τ: 2.05 (1H, doublet), 2.94 (1H, doublet, *J*=10.5 cps), 3.14 (3H, singlet), 3.78 (1H, doublet, *J*=10 .5cps), 6.1 (6H, singlet), 6.6—7.0 (2H, multiplet), 7.1 (3H, doublet), 7.7—8.2 (6H, multiplet).

The same reaction was carried out twice more producing the following: 33.8% and 37.8% yields; $[\alpha]_D^{20}$ +15.8° (*c*=4.11, MeOH) and $[\alpha]_D^{20}$ +12.7° (*c*=1.48, MeOH).

(+)-Mesembrine (XI)——A solution of (+)-4-(3′,4′-dimethoxyphenyl)-4-(N-formyl-β-methylaminoethyl)-2-cyclohexenone (X) (2.35 g, 7.4 mmoles), $[\alpha]_D^{20}$ +12.7° (*c*=1.48, MeOH), and 10% hydrochloric acid (9 ml) in ethanol (30 ml), was heated under reflux for 2 hr. The reaction mixture was evaporated and the residue dissolved in water (30 ml). The water-insoluble material was extracted with chloroform. The aqueous solution was made alkaline with 10% aqueous sodium hydroxide, then it was extracted with chloroform. The extract was dried over potassium carbonate and evaporated under reduced pressure. The residual yellow oil (2.1 g) was chromatographed on alumina (200 g) with chloroform to give a pale yellow oil (1.50 g, 70%), $[\alpha]_D^{20}$ +16.1° (*c*=1.32, MeOH). Its IR spectrum (CCl_4) was identical with that of natural (−)-mesembrine and that of (±)-mesembrine.[10] Its NMR spectrum ($CDCl_3$) was identical with that of (±)-mesembrine.[10]

The partially optically active (+)-mesembrine was dissolved in isopropanol, then the calculated amount of hydrochloric acid was added and the mixture was evaporated to dryness. The hydrochloride produced was repeatedly recrystallized from isopropanol. Needles which were insoluble and prisms were separated.

The needles, $[\alpha]_D^{20}$ +5.8±0.5° (*c*=0.535, MeOH), were repeatedly recrystallized from isopropanol. The optical rotation reached an almost constant value, $[\alpha]_D^{20}$ +7.3±0.5° (*c*=0.465, MeOH). The IR spectrum (KBr) was identical with that of natural (−)-mesembrine hydrochloride. The sample melted at 208—210.5° (decomp.). A mixture of the sample and natural mesembrine hydrochloride, mp 206.5—208° (decomp.), melted at 185—187° (decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_3NCl$: C, 62.66; H, 7.42; N, 4.30. Found: C, 62.64; H, 7.37; N, 4.08.

From synthetic (+)-mesembrine hydrochloride, the (+)-mesembrine base was released and its ORD curve was recorded. ORD (*c*=4.0, dioxane) $[M]^{25}$ (mμ): +17.3° (700), +23.1° (589), +293° (316) (peak), +267° (311) (trough), +303° (306) (peak), −14° (275) (through), +108° (247). CD $[\theta]^{25}$ (mμ): 0 (330), +495 (310) (shoulder), +990 (300) (shoulder), +1270 (291) (positive maximum), +365 (257).

For a comparison, the ORD curve of natural (−)-mesembrine was also recorded. ORD (*c*=5.0, dioxane) $[M]^{25}$ (mμ): −17.4° (700), −25.4° (589), −319° (316) (though), −289 (311) (peak), −329° (306) (through), +15° (275) (peak), −110° (248). CD $[\theta]^{25}$ (mμ): 0 (330), −527 (310) (shoulder), −1120 (300) (shoulder), −1300 (291) (negative maximum), −387 (257).