ASYMMETRIC SYNTHESIS OF BENZYLIC QUATERNARY CARBON CENTER VIA AN ENZYMATIC REACTION

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Abstract - (R)-(+)-(R)-(+)12 and (S)-(−)-1-formyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene(S)-(−)-12 were synthesized based on enantioselective PLE hydrolysis of diethyl 2-(m-methoxyphenyl)-2-methylmalonate. From (R)-(+)12, (+)-O-Methylaphanorphine (16) and (-)-aphanorphine were synthesized. (S)-(+)1-(N-Acetyl-N-methylaminoethyl)-1-methyl-7-methoxytetralin (25) was synthesized from (S)-(−)-12. This transformation constitutes a formal synthesis of (-)-eptazocine.

Compounds having a benzylic quaternary carbon center such as eptazocine,2a pentazocine2b and aphanorphine2c exhibit potent pharmacological activities, and the construction of such centers in an enantioselective manner has been reported from several groups. Elegant asymmetric syntheses of chiral 1-hydroxymethyl-1-methyl-7-methoxy-1,2-dihyronaphthalene, a key intermediate for the synthesis of eptazocine and aphanorphine, have been reported by four groups. Takano et al. applied a stereoselective Grignard addition of m-methoxyphenylmagnesium bromide in the presence of copper(I) bromide to a dienone obtained from cyclopentadiene dimer to give optically active 4-(m-methoxyphenyl)-4-methylcyclopentenone.3b Shibasaki et al. reported synthesis of the 1,1-disubstituted 1,2-dihydro- and 1,2,3,4-tetrahydronaphthalenes using asymmetric Heck reaction.4 Node has synthesized the asymmetric 1-methyl-7-methoxytetralin-1-carboxylic acid by the methylation of (R)-binaphthyl ester of 7-methoxytetralin-1-carboxylic acid.5 Meyers has recently reported another route to the chiral 1,1-disubstituted 1,2-dihydro- and 1,2,3,4-tetrahydronaphthalenes, which involve an asymmetric addition to naphthalene derivatives having a chiral oxazoline-substituent at the α-position with lithiosilanes and iodomethane.6 Marazano et al. synthesized (+)-normetazocine by a stereocontrolled alkylation of chiral pyridinium salts with Grignard reagents and the subsequent Grew cyclization.7 Recently, we have reported the synthesis of (+)- and (-)-eptazocine based on the enantioselective monoacetylation of 2-(p-methoxybenzyl)propane-1,3-diol with lipase PS.8 Methyl and tert-butyl esters of chiral 2-methyl-2-phenyl-3-oxobutanoic acid had been synthesized by an asymmetric Claisen type acylation.9 Meanwhile, chiral 2-aryl-2-alkylmalonic monoesters or monoacylated 2-aryl-2-alkylpropane-1,3-diols would be versatile building blocks for the synthesis of biologically active compounds having a benzylic
quaternary carbon, including eptazocine, pentazocine, aphanorphine and various morphinan alkaloids. For the preparation of chiral monoesters of dicarboxylic acids or monoacylated diols, porcine liver esterase (PLE) catalyzed asymmetric hydrolysis of prochiral dicarboxylic acid diesters and diacetylated diols has been often used.10 We now wish to report the stereoselective and efficient PLE catalyzed asymmetric hydrolysis of diethyl 2-(m-methoxyphenyl)-2-methylmalonate (2) to give (R)-2-(m-methoxyphenyl)-2-methylmalonic monoester (3) and its application to the synthesis of eptazocine and aphanorphine.11

Diethyl 2-(m-methoxyphenyl)-2-methylmalonate (2) was prepared by ethoxycarbonylation of ethyl (m-methoxyphenyl)acetate (1) with diethyl carbonate and sodium hydride, and the subsequent methylation with iodomethane and sodium hydride. The diester (2) was hydrolyzed with PLE in phosphate buffer solution at pH 8.04 to give the chiral monoester (3) in 70% crude yield. Reduction of the ester group of 3 with lithium borohydride in THF and the subsequent esterification of the carboxyl group afforded the hydroxy-methyl carboxylic acid ester (4) in excellent yield. Compound (4) was converted to the aldehyde (5) by oxidizing with pyridinium chlorochromate (PCC), which was subjected to a Wittig-Horner reaction with methyl diethylphosphonoacetate to afford an α,β-unsaturated ester (6). Hydrogenation of compound (6) over 5%-Pd/C and the subsequent alkaline hydrolysis of the methoxycarbonyl group at room temperature afforded the monoester (7). Cyclization of the monoester (7) with polyphosphoric acid (PPA) afforded a mixture of 7-methoxystetralone (8) and 5-methoxy isomer (8') (4:1), which was isolated by column

\[
\begin{align*}
\text{1} & \quad \text{MeO} - \quad \text{CO}_2\text{Et} \\
\text{CH}_2 & \quad \text{i, ii} \\
\text{MeO} & \quad \text{MeO} \\
\text{CO}_2\text{Et} & \quad \text{i, ii} \\
\text{RO}_2\text{C} & \quad \text{C}_\text{III}\text{Me} \\
\text{3: R = H} & \quad \text{iv, v} \\
\text{EtO}_2\text{C} & \quad \text{C}_\text{III}\text{Me} \\
\text{CH}_2\text{CH}_2 & \quad \text{vi} \\
\text{CHO} & \quad \text{vii} \\
\text{10: R = H} & \quad \text{viii, ix} \\
\text{11: R = Pv} & \quad \text{x} \\
\text{CO}_2\text{Et} & \quad \text{xii: LiAIH}_4 \\
\text{CHO} & \quad \text{xiii: PCC} \\
\text{(R)-(+)12} & \quad \text{xiv: PCl}_3, \text{DMAP} \\
\end{align*}
\]

\[\text{i: CO(OEt)}_2, \text{NaH; ii: Mel, NaH; iii: PLE; iv: LiBH}_4; \text{v: EtOH, H}_2\text{SO}_4; \text{vi: PCC; vii: (EtO)}_2\text{P(O)(O)}CH_2\text{CO}_2\text{Me, NaH; viii: H}_2\text{SO}_4/5\% \text{ Pd-C; ix: NaOH in EtOH; x: PPA; xi: H}_2\text{PO}_4; xii: LiAIH}_4; xiii: \text{PCC; xiv: PCl}_3, \text{DMAP}\]
chromatography. On hydrogenating over PtO₂ in ethanol containing a few amount of hydrochloric acid the carbonyl group of 8 was easily reduced to give the tetralin derivative (9). Compound (9) was reduced with lithium aluminum hydride to give the hydroxymethyl compound ((R)-(-)-10), which was converted to the pivalate ((R)-(-)-11) and its optical yield was determined to be >95% ee. Oxidation of (R)-(-)-10 with PCC yielded the aldehyde ((R)-(-)-12), whose absolute value of the specific rotation ([α]₂₀⁺16.0° (c=1.32, CHCl₃) was in good agreement with Meyer's data ([α]₂₀⁻18.0° (c=2.3, CHCl₃)) but the sign was opposite.

The formyl derivative ((R)-(-)-12) was converted to O-methylapanorphine (16) by applying the method for the synthesis of desmethylenchaphanorphine previously reported by one of these author. The oxime of (R)-(-)-12 was catalytically hydrogenated over PtO₂, followed by acetylation with acetic anhydride to give the acetamide (13). Oxidation of the benzylmethylene of 13 with potassium dichromate gave the tetralone derivative (14). Compound (14) was brominated with molecular bromine in THF, and the resulting bromo ketone was treated with sodium methoxide to give a tricyclic ketone, the carbonyl group of which was converted to the methyl group by reduction with sodium borohydride and the subsequent catalytic deoxygenation over 5%-Pd/C to give compound (15). (+)-O-Methylapanorphine (16) ([α]₂₀⁺21+10.4° (c=1.24, CHCl₃) (lit., [α]₂₀⁺8.46° (c=0.915, CHCl₃)) was obtained from 15 by hydrolysis of the N-acetyl group and N-methylation with HCOOH-HCHO. Treatment of (+)-O-methylapanorphine with BBr₃ afforded (-)-apanorphine,²³b,⁴

(Scheme II)

In order to synthesize (S)-(-)-12, the hydroxy group in 4 was protected by conversion to the methoxymethyl (MOM) ether (17), and the ester group was reduced with LiAlH₄ to give 2-(m-methoxyphenyl)-2-methyl-3-methoxymethoxypropane-1-ol (18). Oxidation of the hydroxymethyl group of 18 with PCC afforded the aldehyde (19), which was derived to the α,β-unsaturated carboxylate (20) by the Wittig-Horner reaction with methyl diethylphosphonoacetate. Compound (20) was treated with hydrochloric acid in methanol, followed by pivaloylation with pivaloyl chloride and pyridine and hydrogenation of the olefinic double bond, to give compound (21).
The MOMCl, DMAP; ii: LIAH₄; iii: PCC; iv: (EtO)₂P(O)CH₂CO₂Me, NaH; v: HCl in aq. EtOH; vi: PvcI, Py; vii: H₂/5% Pd-C; viii: K₂CO₃ in aq. MeOH; ix: PPA; x: H₂/PtO₂; xi: LiAIH₄; xii: PCC. The oligomycin group of 21 and the subsequent cyclization with PPA afforded the tetralone (22). Hydrogenolysis of the carbonyl group of 22 yielded the tetralin compound (S)-(−)-11 (>95% ee). Reductive elimination of the pivaloyl group with LiAIH₄ yielded (S)-(+)−10, from which the aldehyde ((S)-(−)-12) (α → β, 28° - 18.7°) was obtained by oxidation with PCC. The Wittig-Horner reaction of (S)-(−)-12 with methyl diethylphosphonoacetate afforded an α, β-unsaturated ester (23). The olefinic double bond of 23 was hydrogenated over 5%-Pd/C to give the saturated ester, which was subjected to Curtius rearrangement to give the corresponding primary amine. The amine was acetylated with acetic anhydride to give the N-methyl acetamide (24). The N-acetyl derivative (24) was methylated with iodomethane in the presence of sodium hydride to give the N-methylacetamide (25). The spectroscopic data for compound (25) were found to be

(−)-eptazocine

i: (EtO)₂P(O)CH₂CO₂Me, NaH; ii: H₂/5% Pd-C; iii: NaOH in aq. MeOH; iv: ClCO₂Et, NaN₃; v: Ac₂O; vi: Mel, NaH

Scheme IV
in complete agreement with Shibasaki's published data, including the sign and magnitude of specific rotation \([\alpha]_D^{24} = +24.9^\circ (c=2.30, \text{CHCl}_3)\) \(\text{(lit., } [\alpha]_D^{24} = +23.2^\circ \text{ (c=1.60, CHCl}_3)\) This transformation constitutes a formal synthesis of (-)-eptazocine.

**EXPERIMENTAL**

All melting points were determined by using Yanagimoto micro melting point apparatus and are uncorrected. Nmr spectra were measured on a JEOL A-400 spectrometer in CDCl\(_3\) solution. Ir spectra were recorded with a JASCO FTIR 7300 spectrophotometer. Optical rotations were determined by using JASCO DIP-370 polarimeter. Mass spectra were obtained by using JEOL JMS-Q1050 spectrometer. All organic extracts were dried over anhydrous MgSO\(_4\). Column chromatography was conducted on Silica gel 60 (70-230 mesh, Merck) or Aluminium oxide 90 active, neutral (activity I, 70-230 mesh, Merck).

**Diethyl 2-(m-Methoxyphenyl)-2-methylmalonate (2).** To a refluxing mixture of NaH \((16.1 \text{ g, 60% in mineral oil, } 0.4 \text{ mol})\) and diethyl carbonate \((63.3 \text{ g, } 0.54 \text{ mol})\) in benzene \((350 \text{ ml})\) was added a solution of ethyl \(m\)-methoxyphenylacetate \((1) (26.0 \text{ g, } 0.134 \text{ mol})\) in benzene \((60 \text{ ml})\) during 2 h under nitrogen atmosphere. After being refluxed for 2.5 h, the reaction mixture was cooled, treated with ice-water and washed with water. The organic layer was dried and evaporated to give a slightly yellow oily residue. Distillation of the crude oil afforded \(25.3 \text{ g (72%) of diethyl 2-(m-methoxyphenyl)malonate, bp 142-145^\circ \text{C} (0.32 \text{mmHg)}, \text{a colorless oil; } ^1H\text{-nmr} \delta 7.27 (t, J = 8.0 \text{ Hz, } 1\text{H}), 6.97 (dt, J = 8.0, 1.2 \text{ Hz, } 1\text{H}), 6.97 (dd, J = 2.4, 1.2 \text{ Hz, } 1\text{H}), 6.87 (ddd, J = 8.0, 2.4, 1.2 \text{ Hz, } 1\text{H}), 4.58 (s, 1\text{H}), 4.24 (q of AB, J = 7.2, 10.8 \text{ Hz, } 2\text{H}), 4.20 (q of AB, J = 7.2, 10.8 \text{ Hz, } 2\text{H}), 1.26 (t, J = 7.2 \text{ Hz, } 6\text{H}); ^13C\text{-nmr} \delta 171.3 (2\times C), 159.3, 139.8, 129.0, 113.9, 112.6, 61.7 (2\times C), 58.8, 55.2, 22.4, 13.9 (2\times C); \text{ir (neat): } 2984, 2838, 1732, 1603, 1585, 1493, 1465, 1252, 1109, 1046, 868 \text{cm}^{-1}; \text{ms m/z 266 (M}^+\text{, 67), 193 (48), 165 (58), 148 (100), 121(58), 109 (73); HRms calcd for C\text{}_{15}\text{H}_{18}\text{O}_5: 266.1153: found 266.1154. \text{To a suspension of NaH (1.13 g, 60% in mineral oil, } 28.2 \text{ mmol) in 1,2-dimethoxyethane (30 ml) was added a solution of diethyl 2-(m-methoxyphenyl)malonate (5.0 g, 18.8 mmol) in 1,2-dimethoxyethane (20 ml) during 10 min with stirring under nitrogen. After being stirred for 40 min at room temperature, to this mixture was added MeI (4.0 g, 28.2 mmol), and the reaction mixture was stirred for 18 h at room temperature. The mixture was treated with ice-water and benzene. The organic layer was dried and evaporated. Purification of the residue by distillation gave 6.7 g (90%) of 2, bp 140°C (0.2 mmHg), a colorless oil; \( ^1H\text{-nmr} \delta 7.26 (t, J = 8.0 \text{ Hz, } 1\text{H}), 6.95 (ddd, J = 8.0, 2.4, 1.2 \text{ Hz, } 1\text{H}), 6.94 (t, J = 1.2 \text{ Hz, } 1\text{H}), 6.83 (ddd, J = 8.0, 2.4, 1.2 \text{ Hz, } 1\text{H}), 4.24 (q, J = 7.2 \text{ Hz, } 2\text{H}), 4.23 (q, J = 7.2 \text{ Hz, } 2\text{H}), 3.79 (s, 3H), 1.85 (s, 3H), 1.26 (t, J = 7.2 \text{ Hz, } 6\text{H}); ^13C\text{-nmr} \delta 171.3 (2\times C), 159.3, 139.8, 129.0, 119.8, 113.9, 112.6, 61.7 (2\times C), 58.8, 55.2, 22.4, 13.9 (2\times C); \text{ir (neat): } 2984, 2838, 1732, 1603, 1585, 1493, 1465, 1252, 1109, 1046, 868 \text{cm}^{-1}; \text{ms m/z 280 (M}^+\text{, 52), 207 (59), 179(36), 162(68), 161(29), 151(22), 135 (22), 134 (34), 133 (92); HRms calcd for C\text{}_{15}\text{H}_{20}\text{O}_5: 280.1310: found 280.1308; \text{Anal. Calcd for C\text{}_{15}\text{H}_{20}\text{O}_5: C, 64.23; H, 7.19. Found: C, 64.60; H, 7.10.} \text{Ethyl (S)-(3-Hydroxy-2-(m-methoxyphenyl)-2-methylpropionate (4). To a mixture of PLE (2.0 g, lyophilized powder, purchased from Sigma Co.) in phosphate buffer solution (pH 8.04, 85 ml) was}
added a solution of diester (2) (3.0 g, 10.7 mmol) in acetone (15 ml) at room temperature with slow stirring. After being stirred for 10 h, the mixture was filtered through a sintered glass filter with a Celite pad. The filtrate was acidified with 10% hydrochloric acid and extracted with ethyl acetate several times. The extracts were combined, dried and evaporated. The oily residue was treated with NaHCO₃ solution (5%, 50 ml) and benzene. The alkaline aqueous layer was acidified with 10% hydrochloric acid and extracted with ethyl acetate. Evaporation of the dried solution gave 1.86 g (70%) of crude monoester (3), which was used for the next step without further purification. From the benzene layer, 0.74 g (30%) of starting 2 (bp 140°C, 0.1 mmHg) was recovered. To a suspension of LiBH₄ (321 mg, 14.8 mmol) in THF (35 ml) was added a solution of 3 (1.86 g, 7.38 mmol) in THF (15 ml) at 55°C with stirring under nitrogen. After being stirred for 1 h at this temperature, the reaction mixture was cooled, treated with ice-water (5 ml) and evaporated the solvent. The residue was treated with water (30 ml) and benzene. The aqueous layer was acidified with 10% HCl and extracted with ethyl acetate. After being dried, the ethyl acetate solution was evaporated to give 1.50 g (96%) of crude (S)-3-hydroxy-(m-methoxyphenyl)-2-methylpropionic acid, which was used for the next step without any purification. A solution of the hydroxypropionic acid (1.150 g, 7.13 mmol), sulfuric acid (0.1 ml) and benzene (25 ml) in EtOH (50 ml) was refluxed with a water separator for 45 h. After evaporation of the solvents, the residual oil was treated with water, basified with NaHCO₃, extracted with benzene. The dried benzene extract was evaporated to afford a pale yellow oil, which was distilled to give 1.32 g (78%) of pure 4 as a colorless oil, bp 150°C (bath temperature, 0.2 mmHg); [α]D₂⁰ -30.0° (c=3.22, CHCl₃); ¹H-nmr δ 7.26 (t, J = 8.0 Hz, 1H), 6.87 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 8.84 (dd, J = 2.8, 2.0 Hz, 1H), 6.81 (ddd, J = 8.0, 2.8, 0.8 Hz, 1H), 4.20 (q of AB, J = 7.2, 10.8 Hz, 1H), 4.18 (q of AB, J = 7.2, 10.8 Hz, 1H), 4.05 (d, J = 10.8 Hz, 1H), 3.79 (s, 3H), 3.62 (d, J = 10.8 Hz, 1H), 1.64 (s, 3H), 1.23 (t, J = 7.2 Hz, 6H); ¹³C-nmr δ 175.9, 159.7, 142.1, 129.5, 118.6, 112.7, 112.0, 69.7, 61.1, 55.1, 52.5, 20.0, 14.0; ir (neat) 3494 (broad), 1725 cm⁻¹; ms m/z 238 (M⁺, 12), 208 (16), 165 (29), 162 (41), 135 (29), 97 (19), 85 (35), 69 (69), 57 (100); HRms calcd for C₁₃H₁₈O₄; 238.1204: found 238.1207; Anal. Calcd for C₁₃H₁₈O₄: C, 65.53; H, 7.61. Found: C, 65.89; H, 7.53.

**Methyl (R)-(−)-4-Ethoxycarbonyl-4-(m-methoxyphenyl)-4-methyl-2-butenoate (6).** To a suspension of PCC (840 mg, 3.9 mmol) and Celite (840 mg) in CH₂Cl₂ (25 ml) was added a solution of 4 (390 mg, 1.64 mmol) in CH₂Cl₂ (15 ml) with stirring under nitrogen. Stirring was continued for 4 h at room temperature. The mixture was filtered through a sintered glass filter with a Celite pad, and the filtrate was washed with 10% NaOH solution and water. After being dried, the dichloromethane solution was evaporated to leave 290 mg of crude 5, which was used for the next step without purification. To a suspension of NaH (77 mg, 60% in mineral oil, 1.9 mmol) in THF (10 ml) was added methyl diethylphosphonooacetate (507 mg, 2.4 mmol) with stirring and ice cooling under nitrogen. After being stirred for 40 min at room temperature, the mixture was cooled with ice bath, and to this mixture was added a solution of 5 (270 mg, 1.14 mmol) in THF (10 ml) with stirring. After being stirred for 14 h at room temperature, the solvent was evaporated, and the residue was dissolved in hexane. The hexane solution was washed with water, dried and evaporated to give 320 mg of a colorless syrup, which was
Ethyl (R)-(−)-7-Methoxy-1-methyl-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (8). A solution of 6 (860 mg, 2.94 mmol) in MeOH (20 ml) was shaken in hydrogen with 5% Pd/C (250 mg) until hydrogen uptake was ceased (20 h). After removal of the catalyst, the solution was evaporated to leave a colorless oil, 860 mg, which was distilled to give pure sample of the saturated diester (840 mg, 97%), bp 155-165°C (bath temperature, 0.15 mmHg); [α]D26°-12.4° (c=1.26, CHCl3); 1H-nmr δ 7.24 (t, J = 8.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.84 (t, J = 2.0 Hz, 1H), 6.78 (dd, J = 8.0, 2.0, 0.8 Hz, 1H), 7.41 (q, J = 7.2 Hz, 1H), 3.14 (q, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 2.23 - 1.91 (m, 4H), 1.54 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); 13C-nmr δ 175.4, 173.8, 159.6, 144.3, 129.5, 129.4, 118.4, 112.5, 111.7, 60.9, 55.1, 51.6, 49.6, 34.2, 29.9, 22.5, 14.1, 14.0; ir (neat) 1731 cm⁻¹; ms m/z 294 (M⁺, 30), 221 (31), 189 (85), 161 (100), 147 (28); HRms calc'd for C₁₆H₂₂O₅: 294.1466; found: 294.1463; Anal. Calcd for C₁₆H₂₂O₅: C, 65.29; H, 7.53. Found: C, 65.41; H, 7.68. A solution of the saturated diester (810 mg, 2.75 mmol) and NaOH (132 mg, 4.4 mmol) in EtOH (10 ml) was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in water (10 ml), acidified with 10% HCl, extracted with CHCl₃. The residue (7) (770 mg) of the dried chloroform solution was heated with PPA (8.0 g) at 100°C for 1 h. After being cooled, the mixture was treated with cold water and CHCl₃. The chloroform layer was dried and evaporated to give 650 mg of a brown syrup. Column chromatography on silica gel (65 g) eluting with hexane-ethyl acetate (3:1) afforded 395 mg (56%) of 8 and 100 mg (14%) of 8'. 8; bp150-160°C (bath temperature, 0.1 mmHg); [α]D29°-9.0° (c=1.26, CHCl3); 1H-nmr δ 8.05 (d, J = 8.8 Hz, 1H), 6.88 (dd, J = 8.8, 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.81 - 2.57 (m, 3H), 2.12 - 2.04 (m, 1H), 1.66 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); 13C-nmr δ 196.0, 174.9, 163.8, 147.8, 129.9, 125.4, 113.1, 112.3, 61.3, 55.4, 46.2, 34.9, 33.7, 25.7, 14.1; ir (neat) 2980, 2942, 2874, 2841, 1727, 1682, 1601, 1464, 1333, 1286, 1261, 1240, 1184, 1100, 1054, 1019, 827 cm⁻¹; ms m/z 262 (M⁺, 25), 234 (19), 189 (71), 177 (15), 161 (49), 119 (13), 69 (45); HRms calc'd for C₁₅H₁₈O₄: 262.1204: found: 262.1205; Anal. Calcd for C₁₅H₁₈O₄: C, 68.68; H, 6.92. Found: C, 68.65; H, 6.95. 8'; bp 150°C (bath temperature, 0.1 mmHg); [α]D27°+78.2°; 1H-nmr δ 7.37 (t, J = 8.0 Hz, 1H), 6.83 (dd, J = 8.0, 0.8 Hz, 2H), 4.08 (q of AB, J = 7.2, 10.8 Hz, 1H), 4.04 (q of AB, J = 7.2, 10.8 Hz, 1H), 3.83 (s, 3H), 2.68 (dd of AB, J = 5.6, 9.6, 17.2 Hz, 1H), 2.59 (dd of AB, J = 5.6, 6.8, 17.2 Hz, 1H), 2.47 (dd, J = 5.6, 6.8, 13.6 Hz, 1H), 1.96 (dd, J = 5.6, 9.6, 13.6 Hz, 1H), 1.56 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); 13C-nmr δ 196.5, 175.0, 159.8, 147.9, 133.9, 121.8, 118.9, 110.9, 61.2, 56.0, 46.6, 36.8, 33.2, 25.7, 13.9; ir (neat) 1726, 1683 cm⁻¹; ms m/z
(R)-(−)-1-Hydroxymethyl-1-methyl-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene ((R)-(−)-10) and Its Pivalate ((R)-(+)−(11). A solution of 8 (348 mg, 1.33 mmol) in EtOH (10 ml) containing 0.1 ml of 10% HCl was shaken with PtO2 (100 mg) in hydrogen atmosphere until hydrogen uptake was ceased (4 h). After removal of the catalyst and the solvent, the residual oil was dissolved in CHCl3, and the chloroform solution was washed with water, dried and evaporated to leave a colorless oil, which was distilled to give the pure sample of ethyl terephthalate derivative (9). bp 135-140°C (bath temperature, 0.45 mmHg); 1H-nmr δ 6.99 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.72 (dd, J = 8.4, 2.8 Hz, 1H), 4.14 (q of AB, J=7.2, 10.8 Hz, 1H), 4.12 (q of AB, J=7.2, 10.8 Hz, 1H), 2.83-2.66 (m, 2H), 2.29 (ddd, J = 13.2, 9.2, 3.2 Hz, 1H), 1.90-1.36 (m, 3H), 1.53 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); 13C-nmr δ 177.1, 157.6, 140.2, 130.0, 128.6, 112.8, 112.6, 60.8, 55.2, 46.4, 35.0, 29.0, 27.6, 19.8, 14.1; ir (neat) 1727 cm−1; ms mlz 248 (M+ , 19), 176 (14), 175 (100), 174 (11), 57 (9); HRms calcd for C15H20O4: 248.141: found: 248.141 1.

A mixture of 9 (278 mg, 1.12 mmol) and LiAlH4 (212 mg, 5.6 mmol) in THF (15 ml) was refluxed under nitrogen for 2 h. After being cooled, to the reaction mixture was added water (0.2 ml) and ethyl acetate, and the mixture was filtered with a Celite pad. The organic layer was dried and evaporated to give 220 mg of an oily residue, which was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (2:1) to give 205 mg (89%) of (R)-(−)-10 as a colorless oil; [α]D26 = −16.5° (c=0.36, CHCl3); 1H-nmr δ 7.01 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 8.8, 2.4 Hz, 1H), 3.78 (s, 3H), 3.77 (d, J = 13.2 Hz, 1H), 3.51 (d, J = 13.2 Hz, 1H), 2.03-1.33 (complex m, 6H), 1.04 (s, 1H); 13C-nmr δ 157.8, 142.2, 130.4, 130.2, 112.2, 111.5, 71.7, 55.2, 41.8, 33.4, 29.8, 26.6, 19.6; ms m/z 206 (M+ , 2), 188(51), 175(18), 173(39), 160(35), 159(35), 158(26), 129(23), 128(26); HRms calcd for C13H18O2: 248.1411; found: 248.1411.

A mixture of (R)-(−)-10 (19 mg, 0.92 mmol), P2Cl3 (33 mg, 0.28 mmol) and DMAP (33 mg, 0.27 mmol) in CH2Cl2 (3 ml) was stirred at room temperature under nitrogen for 24 h. The reaction mixture was diluted with ethyl acetate (5 ml), washed with 1% HCl solution and 3% NaHCO3 solution, and dried. Evaporation of the solvents gave 29 mg of oily residue, which was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (5:1) to afford 24 mg (90%) of (R)-(+)−11 as a colorless oil, bp 110-120°C (bath temperature, 0.06 mmHg); [α]D26 +4.4° (c=1.25, CHCl3). The 1H-nmr, 13C-nmr, ir and mass spectra were identical with those of (S)-(−)-11 ([α]D25 -5.3° (c=1.18, CHCl3)).

(R)-(++)-1-Formyl-1-methyl-7-methoxy-1, 2, 3, 4-tetrahydrophenanthrene ((R)-(++)-12). To a suspension of PCC (520 mg, 2.4 mmol) and Celite (520 mg) in CH2Cl2 (20 ml) was added a solution of 10 (247 mg, 1.2 mmol) in CH2Cl2 (5 ml) with stirring under nitrogen. After being stirred for 4 h at room temperature, the mixture was diluted with ether (30 ml) and filtered through a sintered glass filter with a Celite pad. The filtrate was washed with 5% NaOH and water, and dried. Evaporation of the solvents...
afforded 217 mg of pale yellow oil, which was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (2:1) to give (220 mg, 90%) of pure (R)-(+) 12; [α]D 24 +16.0° (c=1.32, CHCl3) lit., 5 for (S)-(−)-isomer; [α]D 20 -18.0° (c=2.3, CHCl3); 1H-nmr δ 9.51 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.4 Hz, 1H), 6.58 (d, J = 2.8 Hz, 1H), 3.77 (s, 3H), 2.80-2.68 (m, 2H), 2.11-2.04 (m, 1H), 1.88-1.81 (m, 2H), 1.64-1.56 (m, 1H), 1.41 (s, 3H); 13C-nmr δ 158.0, 136.9, 130.6, 129.7, 113.4, 113.1, 77.6, 55.3, 50.6, 31.0, 29.0, 23.7, 19.2; ir (neat) 2706, 1721 cm−1; ms m/z 204 (M+, 11), 176 (14), 175 (100); HRms calcd for C13H16O: 204.1149; found: 204.1147.

(R)-(−)-1-Acetamidomethyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (13). A mixture of (R)-(−)-12 (239 mg, 1.17 mmol), H2NOH·HCl (405 mg, 5.85 mmol), AcONa (960 mg, 11.7 mmol) and water (2 ml) in ethanol (4 ml) was stirred at room temperature for 40 h. After evaporation of the solvent, the residue was treated with chloroform and water. The chloroform layer was dried and evaporated to give 280 mg of light brown syrup, which was chromatographed on a silica gel (30 g) column eluting with hexane-ethyl acetate (3:1) to yield the oxime (228 mg, 89%) as a viscous syrup; [α]D 26 +8.0° (c=3.14, CHCl3); 1H-nmr δ 7.98 (s, 1H), 7.44 (s, 1H), 7.01 (dd, J = 8.0, 0.8 Hz, 1H), 6.73-6.70 (m, 2H), 3.77 (s, 3H), 2.73 (t, J = 6.0 Hz, 2H), 1.95-1.9 (m, 1H), 1.86-1.80 (m, 2H), 1.74-1.66 (m, 1H), 1.46 (s, 3H); 13C-nmr δ 158.4, 157.7, 140.6, 130.3, 128.7, 113.4, 112.6, 77.2, 55.3, 40.7, 35.4, 29.1, 26.8, 19.2; ms m/z 219 (M+, 1), 201 (34), 174 (62), 159 (51), 144 (22), 134 (43), 129 (23), 128 (23), 115 (27); HRms calcd for C13H17NO2: 219.1258; found: 219.1256.

A solution of the oxime (228 mg, 1.04 mmol) in AcOH (5 ml) was shaken with PtO2 (120 mg) in hydrogen for 17 h at room temperature. After removal of the catalyst and solvent, the residue was treated with water, basified with 10% NaOH solution and extracted with CHCl3. The chloroform solution was washed with water, dried and evaporated to leave 172 mg of the amine as a colorless oil, which was used for the next step without purification.

A mixture of the amine (157 mg, 0.76 mmol), AcOH (1 ml) and Ac2O (1 ml, 10.6 mmol) was refluxed for 4 h. After evaporation of the excess AcOH and Ac2O, the residue was dissolved in CHCl3. The chloroform solution was washed with 10% NaOH solution and water, dried and evaporated to give 198 mg of crude acetamide (12) as a colorless syrup. Chromatography of the crude sample on an alumina (30 g) column eluting with hexane-ethyl acetate (1:1) gave 147 mg (93%) of the pure sample of 13 as a colorless syrup, bp 165°C (bath temperature, 0.08 mmHg); [α]D 23 -68.5° (c=0.65, CHCl3); 1H-nmr δ 7.01 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 8.0, 2.4 Hz, 1H), 5.22 (brs, 1H), 3.79 (s, 3H), 3.62 (dd, J = 13.6, 8.0 Hz, 1H), 3.37 (dd, J = 13.6, 4.4 Hz, 1H), 2.70-2.66 (m, 2H), 1.91 (s, 3H), 1.83-1.72 (complex m, 4H), 1.25 (s, 3H); 13C-nmr δ 170.2, 157.9, 142.4, 130.4, 130.0, 111.8, 111.7, 55.3, 49.4, 38.3, 34.0, 29.6, 28.4, 23.4, 19.4; ir (neat) 3300 (br), 1652 cm−1; ms m/z 247 (M+, 4), 189 (3), 188 (21), 176 (13), 175 (100), 174 (3), 160 (9), 159 (4); HRms calcd for C15H21NO2: 247.1571; found: 247.1570; Anal. Calcd for C15H21NO2: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.53; H, 8.66; N, 5.46.

(R)-(−)-4-Acetamidomethyl-4-methyl-6-methoxy-3,4-dihyronaphthalen-1(2H)-one (14).
To a solution of 13 (270 mg, 1.1 mmol) in AcOH (5 ml) was added a solution of K₂Cr₂O₇ (645 mg, 2.2 mmol) in 1N H₂SO₄ (3 ml) with ice cooling and stirring during 10 min, and then added 10N H₂SO₄ (6 ml) over a period of 2 h. After being stirred for 15 h at room temperature, the reaction mixture was diluted with water (20 ml) and extracted with CHCl₃. The chloroform extract was washed with 5% NaHCO₃ solution and water, and dried. Evaporation of the solvent yielded 170 mg of a yellow oil, which was chromatographed on an alumina (12 g) column eluting with hexane-ethyl acetate (1:5) to give 147 mg (52%) of pure 14 as a viscous syrup, bp 190°C (bath temperature, 0.07 mmHg); [α]D 23 -8.6° (c=1.35, CHCl₃); ¹H-nmr δ 8.06 (d, J = 8.4 Hz, 1H), 6.87 (dd, J = 8.4, 2.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 3.87 (s, 3H), 5.50 (br s, 1H), 3.65 (d of AB, J = 14.0, 5.6 Hz, 1H), 3.52 (d of AB, J = 14.0, 7.2 Hz, 1H), 2.75 (dd of AB, J = 18.0, 7.6, 5.2 Hz, 1H), 2.67 (dd of AB, J = 18.0, 8.8, 5.6 Hz, 1H), 2.14 (dd of AB, J = 14.0, 8.8, 5.2 Hz, 1H), 1.95 (s, 3H), 1.93 (dd of AB, J = 14.0, 7.6, 5.6 Hz, 1H), 1.36 (s, 3H); ¹³C-nmr δ 196.4, 170.3, 164.1, 150.3, 130.5, 125.8, 112.4, 111.0, 55.5, 47.7, 38.5, 34.3, 32.4, 25.8, 23.4; ir (neat) 3308 (br) cm⁻¹; ms m/z 261 (M⁺, 2), 191 (13), 190 (100), 189 (13), 175 (39), 161 (10); HRms calcd for C₁₅H₁₉N₂O₃: 261.1364; found: 261.1368; Anal. Calcd for C₁₅H₁₉N₂O₃: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.73; H, 7.21; N, 5.29.

(R)-(−)-3-Acetyl-8-methoxy-1-methyl-2,3,4,5-tetrahydro-1,4-methano-1H-3-benzazepine (15). To a stirred solution of 14 (77 mg, 0.29 mmol) in benzene (10 ml) and THF (2.5 ml) was added Br₂ (47 mg, 0.29 mmol) in THF (2.5 ml) at room temperature during 10 min. After being stirred (2 h) and evaporation of the solvent, the residual syrup was mixed with a solution of NaOMe (162 mg, 3.0 mmol) in MeOH (10 ml), and the mixture was refluxed for 5 h. After evaporation of the solvent, the residue was treated with CHCl₃ and water. The residual syrup from the dried chloroform solution was chromatographed on a silica gel (12 g) column. Elution with CHCl₃ gave 65 mg (85%) of 2,3,4,5-tetrahydro-1,4-methano-1H-3-benzazepinone derivative as a colorless syrup, which solidified on standing and was used without further purification.

To a stirred solution of the benzazepinone (65 mg, 0.26 mmol) in MeOH (7 ml) was added NaBH₄ (75 mg, 2.0 mmol) during 20 min with ice cooling. After being stirred for 1 h at room temperature, the solvent was evaporated. The colorless residue was treated with CHCl₃ and water. The chloroform layer was washed with water, dried and evaporated. The solid mass (60 mg) was used for the next step without purification.

A mixture of the solid mass (60 mg, 0.23 mmol), 5% Pd/C (60 mg) and HClO₄ (60%, 0.02 ml, 0.02 mmol) in AcOH (1 ml) was shaken in hydrogen at 60°C and atmosphere pressure for 15 h. After removal of the catalyst and the solvent, the residual solid mass was dissolved in CHCl₃, and the solution was washed with 5% NaHCO₃ solution and dried. Evaporation of the solvent gave 55 mg of crude 15, which was recrystallized from acetone-ether to give 52 mg (72% form 14), mp 141.5-143°C; [α]D 25 -200.5° (c=0.505, CHCl₃); ¹H-nmr δ 7.02, 7.02 (d, J = 8.0 Hz, 1H), 6.84, 6.83 (d, J = 2.4 Hz, 1H), 6.75, 6.73 (dd, J = 8.0, 2.4 Hz, 1H), 4.72-4.69, 4.38-4.35 (m, 1H), 3.80, 3.79 (s, 3H), 3.56-3.28 (m, 2H), 3.23-2.88 (m, 2H), 2.17-1.79 (m, 2H), 1.94 (s, 3H), 1.55, 1.54 (s, 3H); ir (neat) 1644, 1621 cm⁻¹; ms m/z 245 (M⁺, 11), 202 (8), 174 (14), 173 (74), 172 (7), 159 (15), 158 (23), 115 (11), 73 (100); HRms...
calcd for C_{15}H_{19}NO_2: 245.1415; found: 245.1409; Anal. Calcd for C_{15}H_{19}NO_2: C, 73.44%; H, 7.81%; N, 5.71. Found: C, 73.22%; H, 7.54%; N, 5.81.

(+) -O-Methylaphanorphine (16) and (-) -Aphanorphine. A mixture of 15 (42 mg, 0.17 mmol) and 10% NaOH solution (5 ml, 12.5 mmol) in EtOH (5 ml) was refluxed for 75 h. After evaporation of the solvent, the residue was treated with CHCl_3 and water. The chloroform layer was washed with water, dried and evaporated to give 33 mg of the deacetyl derivative, which was successively heated with formalin (37%, 0.2 ml, 2.5 mmol) and formic acid (0.3 ml, 8 mmol) at 100°C for 1.5 h. After evaporation of the excess formalin and formic acid, the residue was dissolved in water, basified with 10% NaOH solution and extracted with CHCl_3. The chloroform solution was washed with water, dried and evaporated to give 35 mg of crude 16. Chromatography on an alumina (3 g) column eluting with CHCl_3-MeOH (9:3) afforded the pure sample of 16 (30 mg, 80% from 15). bp 110-120°C (bath temperature, 0.08 mmHg); [a]_D^{25} -10.4' (c=1.24, CHCl_3) (lit., 3b [a]_D^{25} +8.46' (c=0.35, CHCl_3)); 1H-nmr 6 7.02 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 8.4, 2.4 Hz, 1H), 3.78 (s, 3H), 3.37 (m, 1H), 3.01 (br AB, J = 16.4 Hz, 1H), 2.83 (d of AB, J = 16.4, 3.2 Hz, 1H), 2.82 (d of AB, J = 8.8, 1.2 Hz, 1H), 2.72 (AB, J = 8.8 Hz, 1H), 2.46 (s, 3H), 2.00 (dd of AB, J = 10.8, 5.6, 1.2 Hz, 1H), 1.84 (AB, J = 10.8 Hz, 1H), 1.47 (s, 3H); 13C-nmr 6 157.7, 148.1, 130.2, 126.1, 110.8, 109.4, 71.4, 61.3, 55.2, 43.2, 41.8, 41.5, 35.8, 21.5; ir (neat) 2780 cm^{-1}; ms m/z 217 (M+; 28), 203 (15), 202 (100), 174 (26), 173 (11), 172 (13), 160 (13), 159 (48); HRms calcd for C_{14}H_{19}NO: 217.1465; found: 217.1469.

To a solution of 16 (59 mg, 0.27 mmol) in dry CH_2Cl_2 (2 ml) was added a solution of boron tribromide (150 mg, 0.6 mmol) in dry CH_2Cl_2 (1 ml) at -30°C with stirring. The reaction mixture was allowed to attain 0°C (2 h). The mixture was treated with water (0.5 ml) and basified with NaHCO_3. The organic layer was dried and evaporated to leave a colorless viscous syrup, which was warmed with 10% NaOH solution (2 ml) at 100°C for 5 min. The alkaline solution was acidified with 10% HCl, again basified with NaHCO_3 and extracted with CHCl_3. The chloroform extracted was dried and evaporated to give 50 mg of a slightly yellow crystalline mass. The crude mass was recrystallized from acetone to give 42 mg (76%) of (-)-aphanorphine, mp 223-228°C (lit., 3b mp 215-222°C); [a]_D^{23} -24.0' (c=0.33, MeOH) (lit., 3b [a]_D^{23} -46.3' (c=0.22, HCl salt in H_2O)). The 1H-nmr and ir spectra were identical with those kindly provided by Professor K. Ogasawara.

Ethyl (S)-(S)-3-Methoxymethoxy-2-(m-methoxyphenyl)-2-methylpropionate (17). To a solution of 4 (2.01 g, 8.44 mmol) in CH_2Cl_2 (20 ml) was added a solution of diisopropylethylamine (3.27 g, 25.3 mmol) in THF (10 ml) with stirring at room temperature. To this mixture was added chloromethyl methyl ether (1.70 g, 21.1 mmol) dropwise over a period of 15 min with ice-cooling and stirring. After being stirred for 20 h at room temperature, the mixture was stirred with water (3 ml) for 5 min and diluted with ethyl acetate (70 ml). The organic layer was washed with brine, dried and evaporated to leave a slightly yellow oil (2.38 g) of the methoxymethyl ether, which was distilled to give the pure sample of 17 (2.27 g, 95%), bp 120°C (bath temperature, 0.08 mmHg); [a]_D^{23} -23.7' (c=1.22, CHCl_3); 1H-nmr 6 7.25 (t, J = 8.0 Hz, 1H), 6.91 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.88 (dd, J = 2.8, 2.0 Hz, 1H),
6.80 (ddd, J = 8.0, 2.8, 0.8 Hz, 1H), 4.65 and 4.61 (AB-q, J = 6.4 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.11 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 3.73 (d, J = 8.8 Hz, 1H), 3.32 (s, 3H), 1.65 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); \(^{13}\)C-nmr δ 174.3, 159.6, 142.8, 129.4, 118.4, 112.4, 112.0, 96.7, 73.4, 60.9, 55.20, 55.17, 51.1, 21.1, 14.0; ir (neat) 1732 cm\(^{-1}\); m/s 282 (M\(^{+}\), 3), 221 (9), 220 (59), 192 (20), 177 (13), 176 (11), 162 (22), 149 (10), 134 (9), 133 (20), 45 (19); HRms calcd for C\(_{15}\)H\(_{22}\)O\(_5\): 282.1466: found 282.1463; Anal. Calcd for C\(_{15}\)H\(_{22}\)O\(_5\): C, 63.81; H, 7.85. Found: C, 63.80; H, 7.85.

**Methoxymethyl (R)-(−)-3-Hydroxy-2-(m-methoxyphenyl)propyl Ether (18).** A solution of 17 (2.27 g, 8.05 mmol) in THF (30 ml) was added to a suspension of LiAlH\(_4\) (370 mg, 9.7 mmol) in THF (70 ml) at -10°C with stirring. After being stirred for 3.5 h at this temperature, to the mixture was added water (2 ml) and ethyl acetate, and then filtered with a Celite pad. The organic layer was washed with saturated NaOH solution and water, and dried. Evaporation of the solvent gave 1.95 g of crude 18, which was chromatographed on a silica gel (200 g) column eluting with hexane-ethyl acetate (2:1) to give a pure sample of 18 (1.84 g, 95%); [\(\alpha\)]\(_D\)\(^{28}\) = −4.0° (c=0.9, CHCl\(_3\)); \(^1\)H-nmr δ 7.27 (t, J = 8.0 Hz, 1H), 7.00 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.98 (dd, J = 2.8, 2.0 Hz, 1H), 6.79 (ddd, J = 8.0, 2.8, 0.8 Hz, 1H), 4.63 (s, 2H), 3.88 (d, J = 9.6 Hz, 1H), 3.87 (br d, J = 10.2, 1H), 3.81 (s, 3H), 3.78 (br d, J = 10.2 Hz, 1H), 3.72 (d, J = 9.6 Hz, 1H), 3.34 (s, 3H), 1.34 (s, 3H); \(^{13}\)C-nmr δ 159.7, 145.2, 129.4, 118.9, 113.3, 111.1, 96.8, 74.3, 69.6, 55.4, 55.1, 43.9, 21.0; ms m/z 240 (M\(^{+}\), 8), 165 (19), 162 (8), 149 (15), 148 (100), 123 (9), 121 (12), 91 (10); HRms calcd for C\(_{15}\)H\(_{22}\)O\(_4\): 240.1360: found 240.1363.

**Methyl (S)-(−)-5-Methoxymethoxy-4-(m-methoxyphenyl)-4-methyl-2-pentenoate (20).** To a suspension of PCC (3.5 g, 16.2 mmol) and Celite (3 g) in CH\(_2\)Cl\(_2\) (70 ml) was added a solution of 19 (1.95 g, 8.13 mmol) in CH\(_2\)Cl\(_2\) (30 ml) with stirring under nitrogen at room temperature. After being stirred for 4 h at room temperature, the mixture was filtered through a sintered glass filter with a Celite pad, and the filtrate was washed with 10% NaOH solution and water, and dried. Evaporation of the solvent gave 1.90 g of crude 19 ([\(\alpha\)]\(_D\)\(^{28}\) = +3.7° (c=1.84, CHCl\(_3\)); the \(^1\)H-nmr spectrum exhibited the signal of aldehyde proton at δ 9.60 as a singlet), which was used for the next step without purification.

To a suspension of NaH (384 mg, 60% in mineral oil, 7.58 mmol) in THF (50 ml) was added dropwise methyl diethylphosphonoacetate (2.52 g, 12.0 mmol) during 20 min with stirring and ice cooling under nitrogen. After being stirred for 1 h at room temperature, the mixture was cooled with ice bath, and to this mixture was added a solution of 19 (1.90 g, 8.0 mmol) in THF (50 ml) with stirring. After being stirred at room temperature for 20 h, the solvent was evaporated. The residual syrup was dissolved in hexane, and the solution was washed with water, dried and evaporated to give 2.4 g of slightly yellow oil. Chromatography of the crude oil on a silica gel (250 g) column eluting with hexane-ethyl acetate (3:1) afforded 2.20 g (92% from 18) of pure 20 as a colorless oil of bp 140-150°C (bath temperature, 0.05 mmHg); [\(\alpha\)]\(_D\)\(^{23}\) = 5.6° (c=1.44, CHCl\(_3\)); \(^1\)H-nmr δ 7.25 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 15.6 Hz, 1H), 6.90 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.86 (dd, J = 2.8, 2.0 Hz, 1H), 6.78 (ddd, J = 8.0, 2.8, 0.8 Hz, 1H), 5.88 (d, J = 15.6 Hz, 1H), 4.59 (s, 2H), 3.80 (s, 3H), 3.80 and 3.70 (AB-q, J = 9.2 Hz, 2H), 3.74 (s, 3H), 3.29 (s, 3H), 1.50 (s, 3H); \(^{13}\)C-nmr δ 167.2, 159.6, 153.7, 144.9, 129.3, 119.9, 119.1, 113.5,
Methyl (S)-(−)-5-Pivaloyloxy-4-(m-methoxyphenyl)-4-methylpentanoate (21). A solution of 20 (1.95 g, 6.63 mmol) in MeOH (50 ml) containing 35%-HCl (0.5 ml) was stirred at 50°C for 3 h. After evaporation of the solvent, the residue was dissolved in CHCl₃, washed with aqueous 5% NaHCO₃ solution and water. Evaporation of the dried chloroform solution yielded 1.66 g of colorless syrup. To a mixture of 4-N,N-dimethylaminopyridine (810 mg, 6.64 mmol), pyridine (1.58 g, 19.9 mmol) and the above residue (1.66 g, 6.64 mmol) in dichloromethane (40 ml) was added a solution of pivaloyl chloride (1.2 g, 9.96 mmol) in CH₂Cl₂ (10 ml) with stirring and ice cooling under nitrogen. After being stirred at room temperature for 20 h at room temperature, the reaction mixture was washed with 5% HCl, 5% NaHCO₃ solution and water. The residual oil (2.51 g) of the dried dichloromethane solution was chromatographed on a silica gel (250 g) column eluting with hexane-ethyl acetate (5:1) to give 1.95 g (96%) of the pivaloyloxy derivative.

A solution of the pivaloyloxy derivative (1.95 g, 6.37 mmol) in MeOH (40 ml) was shaken with 5% Pd/C (600 mg) in hydrogen atmosphere. After the hydrogen up-take was ceased (ca. 4 h), the catalyst and the solvent were removed, and the residue (1.95 g) was purified by chromatography on a silica gel (200 g) column eluting with hexane-ethyl acetate (3:1) to give compound (21) (1.94 g, 99%) as a colorless oil, bp 160°C (bath temperature, 0.06 mmHg); [α]D₂₃ -3.5° (c=1.60, CHCl₃); ¹H-nmr δ 7.24 (f, J=8.0 Hz, 1H), 6.90 (dd, J=8.0, 0.8 Hz, 1H), 6.90 (dd, J=2.0, 0.8 Hz, 1H), 6.76 (dd, J=8.0, 2.0 Hz, 1H), 4.18 and 4.08 (AB-q, J=6.8 Hz, 2H), 3.80 (s, 3H), 3.61 (s, 3H), 2.17-1.95 (m, 4H), 1.36 (s, 3H), 1.13 (s, 9H); ¹³C-nmr δ 178.2, 174.0, 159.6, 145.1, 129.3, 118.7, 113.0, 111.1, 71.7, 55.1, 51.5, 41.3, 38.8, 33.5, 29.1, 27.1, 22.4; ir (neat) 1732 cm⁻¹; ms m/z 336 (M⁺, 81), 222 (16), 221 (100), 189 (79), 161 (21); HRms calcd for C₁₉H₂₈O₅: 336.1935; found: 336.1927; Anal. Calcd for C₁₉H₂₈O₅: C, 67.83; H, 8.38. Found: C, 68.12; H, 8.15.

(S)-(−)-6-Methoxy-4-methyl-4-pivaloyloxy-3,4-dihydronaphthalen-1(2H)-one (22). A mixture of 21 (1.61 g, 4.79 mmol) and 10% aqueous NaOH solution (2.5 ml, 6.25 mmol) in MeOH (60 ml) was stirred at 50°C for 2 h. After evaporation of the solvent, the pale yellow residue was dissolved in water, acidified with HCl, extracted with CHCl₃. The chloroform layer was dried and evaporated the solvent to give 1.55 g of crude carboxylic acid, which was heated with 16 g of PPA on a water bath for 1 h. After being cooled, the reaction mixture was diluted with ice-water and extracted with CHCl₃. The chloroform solution was washed with water, dried and evaporated to give 1.4 g of light brown syrup, which was chromatographed on a silica gel (140 g) column eluting with hexane-ethyl acetate (3:1) to give the pure sample of 22 (970 mg, 66.5%), mp 84-85°C (from hexane); [α]D₂₆ -19.0° (c=1.30, CHCl₃); ¹H-nmr δ 8.05 (dd, J=9.6, 0.8 Hz, 1H), 6.87-6.84 (m, 2H), 4.36 (d, J=11.2 Hz, 1H), 4.06 (d, J=11.2 Hz, 1H), 3.86 (s, 3H), 2.77-2.63 (m, 2H), 2.27-2.01 (m, 1H), 2.04-1.97 (m, 1H), 1.41 (s, 3H), 1.13 (s, 9H); ¹³C-nmr δ 196.2, 177.9, 163.8, 149.5, 130.0, 125.6, 112.6, 111.1, 76.7, 70.0, 55.3, 38.7, 37.8,
34.2, 32.4, 26.9, 26.8, 24.6; ir (KBr) 1728, 1677 cm\(^{-1}\); ms m/z 304 (M\(^{+}\), 14), 190 (43), 189 (27), 161 (201), 85 (16), 57 (100); HRms calcd for C\(_{18}\)H\(_{24}\)O\(_4\): 304.1673; found 304.1678; Anal. Calcd for C\(_{18}\)H\(_{24}\)O\(_4\): C, 71.03; H, 7.95. Found: C, 71.24, H, 7.86.

(S)-(-)-1-Pivaloyloxymethyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene ((S)-(-)-11). A mixture of the ketone (21) (480 mg, 1.52 mmol) 10% HCl (0.1 ml) and PtO\(_2\) (100 mg) in MeOH (20 ml) was shaken in a hydrogen atmosphere for 5 h. After removal of the catalyst and the solvent, the residue was dissolved in CH\(_2\)Cl\(_2\), and the chloroform solution was washed with aqueous 5% NaHCO\(_3\) solution and water, dried and evaporated to give 450 mg of the tetralin compound (S)-(-)-11; [\(\alpha\)]\(_D\)\(^{25}\) -5.3° (c=1.18, CHCl\(_3\)); \(^1\)H-nmr \(\delta\) 6.98 (d, \(J = 8.4\) Hz, 1H), 6.83 (d, \(J = 2.8\) Hz, 1H), 6.69 (dd, \(J = 8.4, 2.8\) Hz, 1H), 4.22 and 4.01 (AB-q, \(J = 10.8\), 2H), 3.77 (s, 3H), 2.70 (t, \(J = 6.4\) Hz, 1H), 1.88 (dd of AB, J = 12.8, 8.4, 3.6 Hz, 1H), 1.93-1.75 (m, 2H), 1.40 (s, 9H); \(^{13}\)C-nmr \(\delta\) 178.3, 157.7, 141.9, 130.0, 129.4, 112.2, 112.0, 71.6, 55.2, 38.9, 37.9, 34.0, 29.7, 27.1 (3xCH), 26.5, 19.4; ir (neat) 1729 cm\(^{-1}\); ms m/z 290 (M\(^{+}\), 8), 189 (7), 188 (21), 176 (13), 175 (100), 173 (15), 160 (40), 159 (14); HRms calcd for C\(_{18}\)H\(_{26}\)O\(_3\): 290.1881; found: 290.1881; Anal. Calcd for C\(_{18}\)H\(_{26}\)O\(_3\): C, 74.45; H, 9.02. Found: C, 74.64; H, 9.12.

(S)-(+)-1-Hydroxymethyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene ((S)-(+) -10). To a suspension of LiAlH\(_4\) (160 mg, 4.2 mmol) in ether (10 ml) was added a solution of the tetralin compound ((S)-(+) -11) (407 mg, 1.4 mmol) in ether (30 ml) dropwise with stirring at -15°C. After being stirred at 0°C for 3 h, to the reaction mixture was slowly added ethyl acetate (1 ml) and water (1 ml). The mixture was filtered through a sintered glass filter with Celite pad. The dried filtrate was evaporated to leave a colorless syrup, which was distilled to yield 310 mg (95%) of the pure sample of (S)-(+) -10 as a colorless oil of bp 120-130°C (bath temperature, 0.3 mmHg); [\(\alpha\)]\(_D\)\(^{28}\) +16.6° (c=3.40, CHCl\(_3\)). The \(^1\)H-nmr and ir spectra were identical with those of (R)-(+) isomer. Anal. Calcd for C\(_{13}\)H\(_{15}\)O\(_2\): C, 75.69; H, 8.79; Found: C, 75.71; H, 8.89.

(S)-(-)-1-Formyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene ((S)-(-)-12). A mixture of the 1-hydroxymethyl-1-methyl-7-methoxytetralin (386 mg, 1.87 mmol), PCC (810 mg, 3.75 mmol) and Celite (810 mg) in CH\(_2\)Cl\(_2\) (20 ml) was stirred at room temperature for 2 h. After filtration through a sintered glass filter with a Celite pad, the filtrate was evaporated to give 360 mg of an almost colorless oil, which was chromatographed on a silica gel (10 g) column eluting with hexane-ethyl acetate (2:1) to give 336 mg (88%) of the pure sample of (S)-(-)-12; [\(\alpha\)]\(_D\)\(^{28}\) -18.7° (c=4.64, CHCl\(_3\)) (lit., \(^{5}\) [\(\alpha\)]\(_D\)\(^{28}\) -18.6° (c=2.3, CHCl\(_3\))). The \(^1\)H-nmr and ir spectra were identical with those of (R)-(+) isomer.

Methyl (R)-(++)-3-(7-methoxy-1-methyl-1,2,3,4-tetrahydro-1-naphthyl)acrylate (23). To a suspension of NaH (86 mg, 60% in mineral oil, 2.1 mmol) in THF (3 ml) was added methyl diethyl-phosphonoacetate (450 mg, 2.1 mmol) with stirring and ice cooling. After being stirred at room temperature for 1 h, to the mixture was added a solution of (S)-(-)-12 (336 mg, 1.65 mmol) in THF (10
ml) with ice cooling and stirring, and the mixture was stirred at room temperature for 18 h. After evaporation of the solvent, the residue was treated with hexane and water. The organic layer was washed with water, dried and evaporated the hexane to leave 400 mg of colorless syrup, which was chromatographed on a silica gel column (40 g) column. The second fraction eluted with hexane-ethyl acetate (2:1) gave 380 mg (89%) of 23 as a colorless syrup of bp 130-140°C (bath temperature, 0.07 mmHg; [α]D27 +32.6° (c=1.04, CHCl3); 1H-nmr δ 7.05 (d, J = 16.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.71 (dd, J = 8.4, 2.8 Hz, 1H), 6.65 (d, J = 2.8 Hz, 1H), 5.60 (d, J = 16.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.71 (t, J = 6.0 Hz, 2H), 1.87-1.65 (complex m, 4H), 1.44 (s, 3H); 13C-nmr δ 167.4, 158.1, 157.6, 141.4, 130.1, 128.7, 119.0, 113.5, 112.1, 55.2, 51.4, 41.0, 36.9, 29.2, 28.0, 19.3; ir (neat) 1724, 1648 cm⁻¹; ms m/z 260 (M⁺, 55), 232 (12), 201 (20), 186 (26), 185 (100), 174 (36), 173 (46), 159 (33), 158 (19); HRms calcd for C₁₆H₂₀O₃: 260.1411; found: 260.1409; Anal. Calcd for C₁₆H₂₀O₃: C, 73.82; H, 7.74. Found: C, 73.62; H, 7.45.

(R)-1-Acetamidethyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (24). A solution of 23 (379 mg, 1.46 mmol) in MeOH (15 ml) was shaken with 5% Pd/C (300 mg) in hydrogen for 14 h. After removal of the catalyst and the solvent, the residual oil (380 mg) was chromatographed eluting with hexane-ethyl acetate (1:1) to give 364 mg (95%) of methyl 3-(7-methoxy-1-methyl-1,2,3,4-tetrahydro-1-naphthyl)propionate; [α]D27 -12.1° (c=1.18, CHCl3); 1H-nmr δ 6.96 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.66 (dd, J = 8.0, 2.8 Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 2.68-2.64 (m, 2H), 2.30-2.21 (m, 1H), 2.15-2.05 (m, 2H), 1.91-1.66 (complex m, 5H), 1.27 (s, 3H); 13C-nmr δ 174.5, 157.8, 144.6, 130.0, 129.1, 112.0, 111.3, 55.2, 51.5, 37.8, 36.7, 35.1, 30.4, 29.8, 29.7, 19.6; ir (neat) 1739 cm⁻¹; ms m/z 262 (M⁺, 13), 176 (16), 175 (100), 145 (9), 134 (14), 115 (8); HRms calcd for C₁₆H₂₂O₃: 262.1568; found: 262.1568.

A mixture of the hydrogenated ester (251 mg, 0.96 mmol) and NaOH (190 mg, 4.8 mmol) and water (1.9 ml) in EtOH (20 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in water, acidified with 10% HCl and extracted with chloroform. The residual syrup (230 mg, 0.92 mmol) of the dried chloroform solution was dissolved in acetone (15 ml). To this solution was added water (0.4 ml) and Et₃N (230 mg, 2.3 mmol) at 0°C with stirring. After being stirred for 30 min at 0°C, to the mixture was added ethyl chloroformate (300 mg, 2.76 mmol) in acetone (1.0 ml). After being stirred for 1.5 h at 0°C, to the mixture was added a solution of NaN₃ (240 mg, 3.7 mmol) in water (1 ml), then the mixture was stirred for 2 h at 0°C. The reaction mixture was diluted with CHCl₃ (30 ml) and dried, and the solvents were evaporated to leave a pale yellow syrup. The syrup was dissolved in toluene (20 ml) and the solution was heated on a water bath for 45 min. Then, the solvent was evaporated and the residue was dissolved in 10% HCl (20 ml) and the solution was refluxed for 16 h. After being cooled, the aqueous solution was made alkaline with 10% NaOH solution and extracted with CHCl₃. The chloroform solution was dried over K₂CO₃ and evaporated to give 175 mg of the primary amine as a slightly brown oil, which was heated with Ac₂O (1 ml, 10.6 mmol) and AcOH (1 ml, 17.7 mmol) on a water bath for 4 h. After evaporation of the excess Ac₂O and AcOH, the residual syrup was dissolved in CHCl₃, and the chloroform solution was washed with 10% NaOH solution and water, and dried. The residue (200 mg) of the chloroform solution
was chromatographed on an alumina (20 g) column eluting with hexane-ethyl acetate (1:2) to give 180 mg (72% from the hydrogenated ester) of 24 as colorless crystals of mp 95-98°C (from acetone-ether); $^1$H-nmr $\delta$ 6.97 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.66 (dd, J = 8.4, 2.8 Hz, 1H), 5.26 (br s, 1H), 3.78 (s, 3H), 3.35-3.26 (m, 1H), 3.10-3.01 (m, 1H), 2.67 (t, J = 6.0 Hz, 2H), 1.99-1.92 (m, 1H), 1.86 (s, 3H), 1.82-1.70 (complex m, 4H), 1.59-1.54 (m, 1H), 1.20 (s, 3H); $^{13}$C-nmr $\delta$ 169.8, 157.8, 144.9, 130.1, 129.1, 112.1, 111.2, 55.2, 42.7, 36.4, 36.1, 35.3, 30.8, 29.7, 23.2, 19.7; ir (KBr) 1659, 1632 cm$^{-1}$; ms m/z 261 (M+, 18), 187 (14), 177 (19), 176 (93), 175 (100), 134 (34), 87 (13), 86 (27); HRms calcd for $C_{16}H_{23}NO_2$: 261.1727; found: 261.1729; Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.67; H, 8.87; N, 5.35.

(R)-(+)-1-(N-Acetyl-N-methylaminoethyl)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (25). To a suspension of NaH (5 mg, 60% in mineral oil, 0.12 mmol) in THF (1 ml) was added a solution of 24 (25 mg, 0.1 mmol) in THF (1 ml) with stirring and ice cooling under nitrogen. After being stirred for 1 h at room temperature, to this mixture was added MeI (40 mg, 0.29 mmol) with stirring and ice cooling. Stirring was continued for 16 h at room temperature. After evaporation of the solvent, the residue was dissolved in CHCl$_3$, and the chloroform solution was washed with 10% NaOH solution and water. The residual oil (23 mg) of the dried chloroform solution was chromatographed on an alumina (10 g) column eluting with hexane-ethyl acetate (1:1) to give 18 mg (70%) of 25 as a colorless oil; $[\alpha]_D^{24} +24.9^\circ$ (c=2.30, CHCl$_3$) (lit.,$^4$ $[\alpha]_D^{24} +23.20^\circ$ (c=1.60, EtOH)); $^1$H-nmr $\delta$ 6.99, 6.96 (d, J = 8.4 Hz, 1H), 6.84, 6.79 (d, J = 2.8 Hz, 1H), 6.69, 6.66 (dd, J = 8.4, 2.8 Hz, 1H), 3.79, 3.78 (s, 3H), 3.50, 3.46 (dd, J = 11.6, 5.2 Hz, 0.5H), 3.23, 3.19 (dd, J = 11.6, 5.2 Hz, 0.5H), 3.06-2.97 (m, 1H), 2.89, 2.87 (s, 3H), 2.71-2.66 (m, 2H), 2.03-1.92 (m, 1H), 2.01, 1.99 (s, 3H), 1.88-1.69 (complex m, 4H), 1.63-1.55 (m, 1H), 1.31, 1.29 (s, 3H) (lit.,$^3$ 7.02-6.92 (m, 1H), 6.84-6.75 (m, 1H), 6.71-6.61 (m, 1H), 3.79, 3.77 (s, 3H), 3.55-2.93 (m, 2H), 2.89, 2.86 (s, 3H), 2.71-2.62 (m, 2H), 2.01, 1.98 (s, 3H), 2.04-1.51 (m, 6H), 1.30, 1.28 (s, 3H)); ir (neat) 1645 cm$^{-1}$; ms m/z 276 (10), 275 (M+, 46), 177 (14), 176 (100), 175 (47), 134 (14), 101 (17), 100 (66); HRms calcd for $C_{17}H_{25}NO_2$: 275.1884; found: 275.1882.

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REFERENCES AND NOTES
1. A part of this work has been presented in a preliminary form: H. Okada, T. Yamamoto, and S. Shiotani, Abstracts of Papers, the Hokuriku Seminar on Synthetic Organic Chemistry in 1994, Toyama (Japan), October 1994, p. 52.


11. During the preparation of this paper, there appeared two papers concerning the asymmetric synthesis of 1-hydroxymethyl-1-methyl-7-methoxy-1,2-dihydronaphthalene via enantioselective hydrolysis of malonic diester structure using PLE.16

12. The ee of (+)- and (-)-11 was determined by DAICEL CHIRALCEL OJ, hexane/2-propanol (97:3).


14. Based on this result, it was confirmed that the absolute configuration around the carbon at 1-position of (-)-aphanorphine is opposite to that of (-)-eptazocine.8

15. When the double bond of 20 was hydrogenated prior to deprotection of the methoxymethyl group, the corresponding six-membered lactone was formed as a major product on treatment the hydrogenated methoxymethyl ether with acid. Treatment of the lactone with PPA did not afford the tetralone compound.


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