ASYMMETRIC SYNTHESIS OF BENZYLIC QUATERNARY CARBON CENTER *VIA* AN ENZYMATIC REACTION[1]

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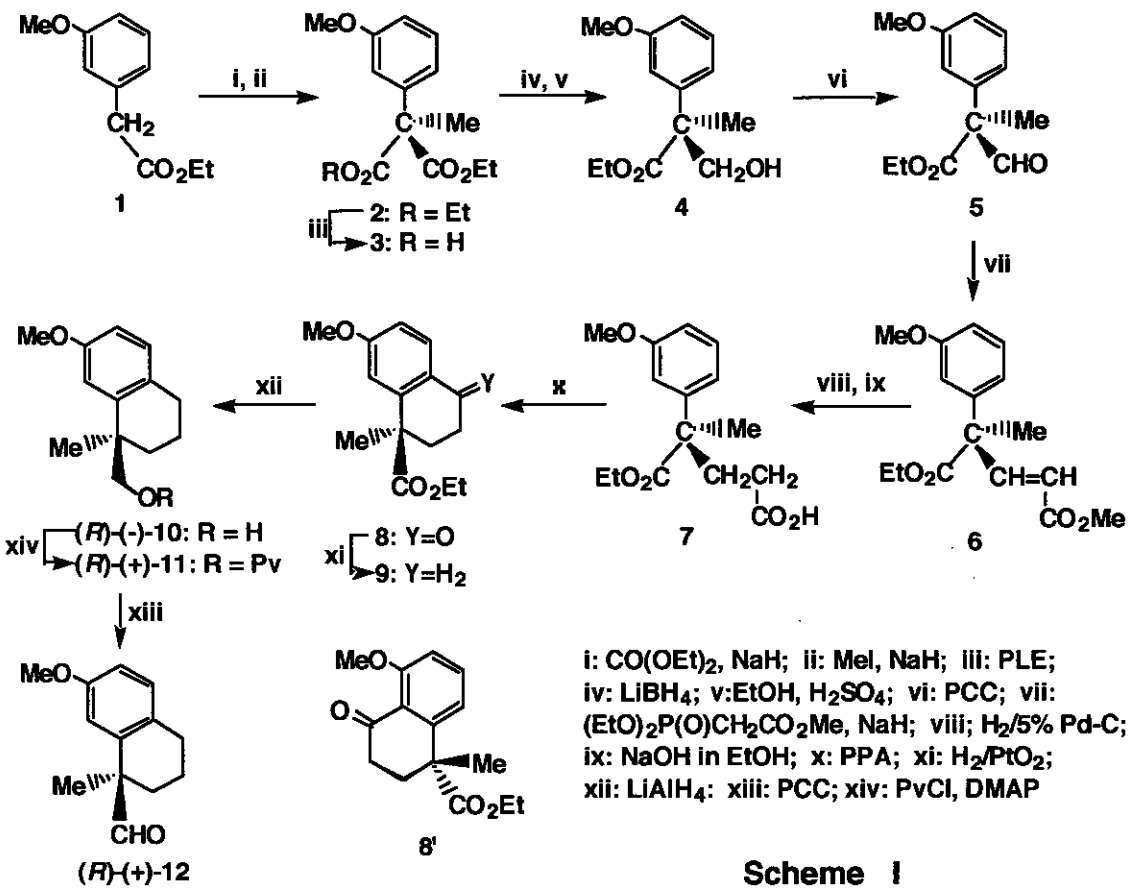
Abstract - (*R*)-(+)- ((*R*)-(+)-**12**) and(*S*)-(-)-1-formyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene((*S*)-(-)-**12**) were synthesized based on enantioselective PLE hydrolysis of diethyl 2-(*m*-methoxyphenyl)-2-methylmalonate. From (*R*)-(+)-**12**, (+)-*O*-Methylaphanorphine (**16**) and (-)-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] pentazocine[2b] and aphanorphine[2c] exhibit potent pharmacological activities, and the construction of such centers in a enantioselective manner has been reported from several groups. Elegant asymmetric syntheses of chiral 1-hydroxymethyl-1-methyl-7-methoxy-1,2-dihydronaphthalene, 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 Grewe 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]

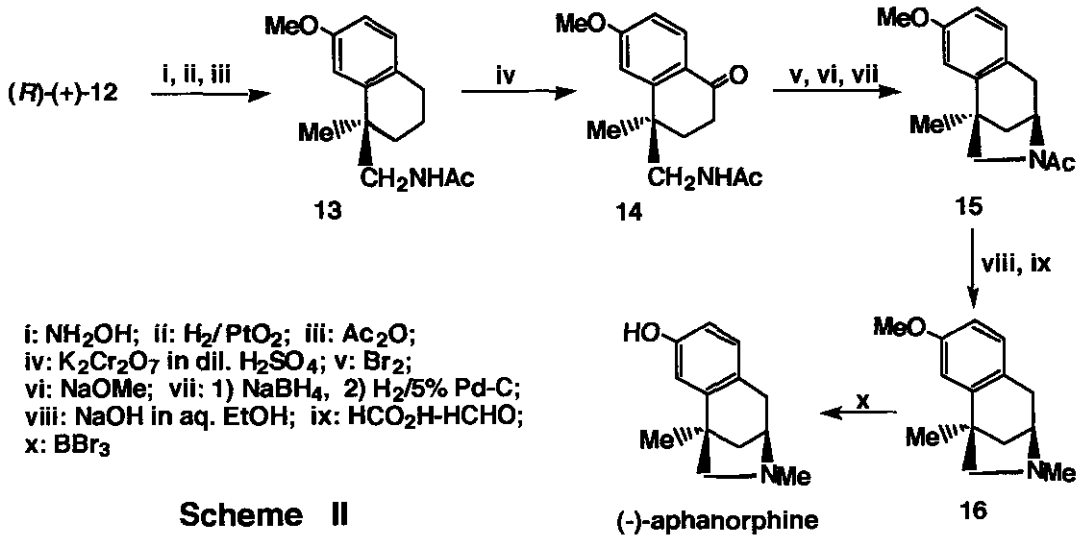


Scheme I

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 hydroxymethyl 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-methoxytetralone (**8**) and 5-methoxy isomer (**8'**) (4:1), which was isolated by column

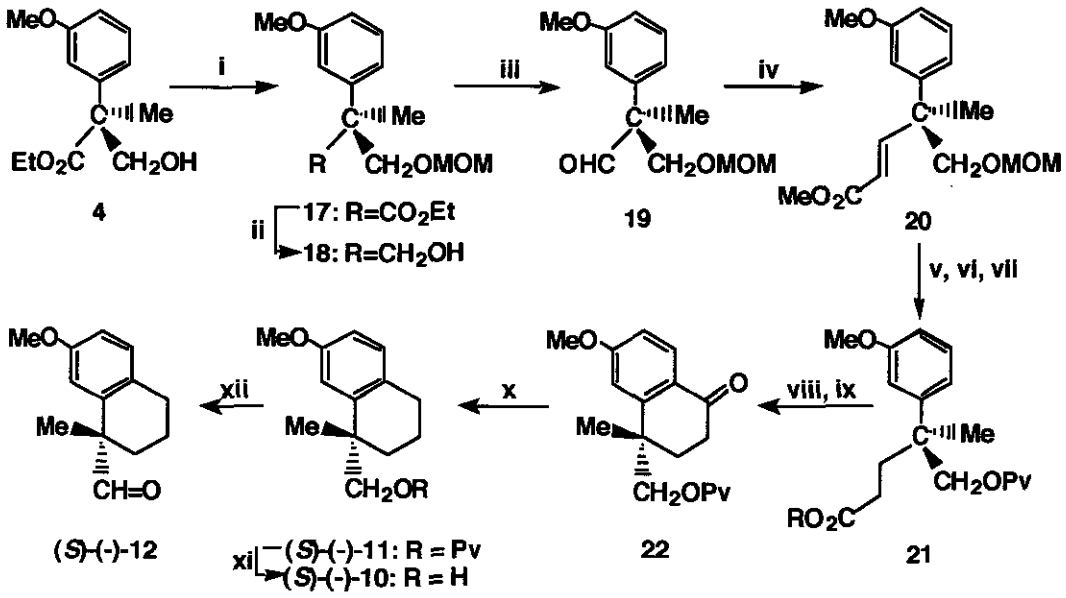
chromatography. On hydrogenating over PtO_2 in ethanol containing a few amount of hydrochloric acid the carbonyl group of **8** was easily reduced to give the tetralin derivative (**9**). Compound (**9**) was reduced with lithium aluminum hydride to give the hydroxymethyl compound ((*R*)- (-)-**10**), which was converted to the pivalate ((*R*)-(+)-**11**) and its optical yield was determined to be >95% ee.[12] Oxidation of (*R*)-(-)-**10** with PCC yielded the aldehyde ((*R*)-(+)-**12**), whose absolute value of the specific rotation ($[\alpha]_D^{24}$+16.0° (c=1.32, $CHCl_3$) was in good agreement with Meyer's data[5] ($[\alpha]_D^{20}$ -18.0° (c=2.3, $CHCl_3$)) but the sign was opposite.

The formyl derivative ((*R*)-(+)-**12**) was converted to *O*-methylaphanorphine (**16**) by applying the method for the synthesis of desmethylaphanorphine previously reported by one of these author.[13] The oxime of (*R*)-(+)-**12** was catalytically hydrogenated over PtO_2, followed by acetylation with acetic anhydride to give the acetamide (**13**). Oxidation of the benzylic methylene 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 methylene by reduction with sodium borohydride and the subsequent catalytic deoxygenenation over 5%-Pd/C to give compound (**15**). (+)-*O*-Methylaphanorphine (**16**) ($[\alpha]_D^{21}$ +10.4° (c=1.24, $CHCl_3$)) (lit.,[3b] $[\alpha]_D^{29}$ +8.46° (c=0.915, $CHCl_3$)) was obtained from **15** by hydrolysis of the *N*-acetyl group and *N*-methylation with HCOOH-HCHO. Treatment of (+)-*O*-methylaphanorphine with BBr_3 afforded (-)-aphanorphine.[3b,14]



Scheme II

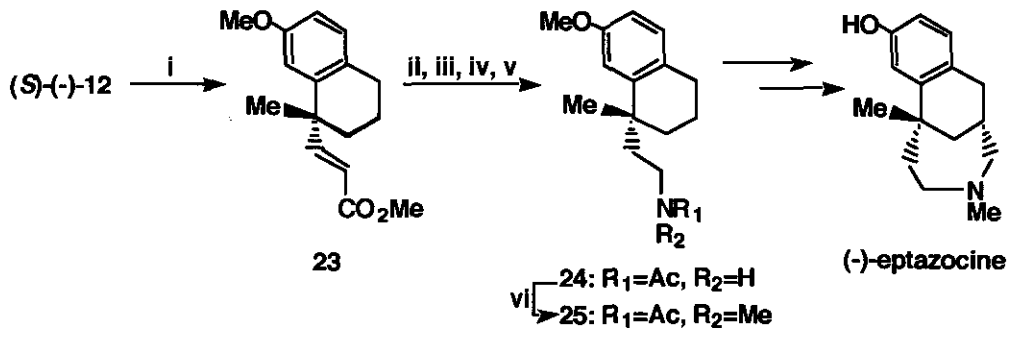
In order to synthesize (*S*)-(-)-**12**, the hydroxy group in **4** was protected by conversion to the methoxymethyl (MOM) ether (**17**), and the ester group was reduced with $LiAlH_4$ to give 2-(*m*-methoxyphenyl)- 2-methyl-3-methoxymethoxypropane-1-ol (**18**). Oxidation of the hydroxymethyl group 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**).[15] Hydrolysis of the methyl ester



i: MOMCl, DMAP; ii: $LiAlH_4$; iii: PCC; iv: $(EtO)_2P(O)CH_2CO_2Me$, NaH; v: HCl in aq. EtOH; vi: PvCl, Py; vii: H_2/5% Pd-C; viii: K_2CO_3 in aq. MeOH; ix; PPA; x: H_2/PtO_2; xi: $LiAlH_4$; xii: PCC

Scheme III

group of **21** and the subsequent cyclization with PPA afforded the tetralone (**22**). Hydrogenlysis of the carbonyl group of **22** yielded the tetralin compound (*S*)-(-)-**11** (>95% ee).[12] Reductive elimination of the pivaloyl group with $LiAlH_4$ yielded (*S*)-(+)-**10**, from which the aldehyde ((*S*)-(-)-**12**)($[\alpha]_D^{28}$ -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



i: $(EtO)_2P(O)CH_2CO_2Me$, NaH; ii: H_2/5% Pd-C; iii: NaOH in aq. MeOH; iv: $ClCO_2Et$, NaN_3; v: Ac_2O; vi: MeI, NaH

Scheme IV

in complete agreement with Shibasaki's published data,[4] including the sign and magnitude of specific rotation ($[\alpha]_D^{24}$ +24.9° (c=2.30, $CHCl_3$)) (*lit.*, $[\alpha]_D^{24}$ +23.2° (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 FT/IR 7300 spectrophotometer. Optical rotations were determined by using JASCO DIP-370 polarimeter. Mass spectra were obtained by using JEOL JMS-OISG-2 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 g, 60% in mineral oil, 0.4 mol) and diethyl carbonate (63.3 g, 0.54 mol) in benzene (350 ml) was added a solution of ethyl *m*-methoxyphenylacetate (**1**) (26.0 g, 0.134 mol) in benzene (60 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 g (72%) of diethyl 2-(*m*-methoxyphenyl)malonate, bp 142-145°C (0.32 mmHg), as a colorless oil; ^{1}H-nmr δ 7.27 (t, J = 8.0 Hz, 1H), 6.97 (dt, J = 8.0, 1.2 Hz, 1H), 6.97 (dd, J = 2.4, 1.2 Hz, 1H), 6.87 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 4.58 (s, 1H), 4.24 (q of AB, J = 7.2, 10.8 Hz, 2H), 4.20 (q of AB, J = 7.2, 10.8 Hz, 2H), 1.26 (t, J = 7.2 Hz, 6H); ms m/z 266 (M^+, 67), 193 (48), 165 (58), 148 (100), 121(58), 109 (73); HRms calcd for $C_{14}H_{18}O_5$: 266.1153: found 266.1154. To a suspension of NaH (1.13 g, 60% in mineral oil, 28.2 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; ^{1}H-nmr δ 7.26 (t, J = 8.0 Hz, 1H), 6.95 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 6.94 (t, J = 1.2 Hz, 1H), 6.83 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.85 (s, 3H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C-nmr δ 171.3 (2×C), 159.3, 139.8, 129.0, 119.8, 113.9, 112.6, 61.7 (2×C), 58.8, 55.2, 22.4, 13.9 (2×C); ir (neat): 2984, 2838, 1732, 1603, 1585, 1493, 1465, 1252, 1109, 1046, 868 cm^{-1}; ms m/z 280 (M^+, 52), 207 (59), 179(36), 162(68), 161(29), 151(22), 135 (22), 134 (34), 133 (92); HRms calcd for $C_{15}H_{20}O_5$: 280.1310: found 280.1308; *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.23; H, 7.19. Found: C, 64.60; H, 7.10.

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 $NaHCO_3$ 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 $LiBH_4$ (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 (1.150g, 7.13 mmol), sulfuric acid (0.1 ml) and benzene (25 ml) in EtOH (50 ml) was refluxed with a water separater for 45 h. After evaporation of the solvents, the residual oil was treated with water, basified with $NaHCO_3$, 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); $[\alpha]_D^{26}$ -30.0° (c=3.22, $CHCl_3$); ^{1}H-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); ^{13}C-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 $C_{13}H_{18}O_4$: 238.1204: found 238.1207; *Anal.* Calcd for $C_{13}H_{18}O_4$: 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 CH_2Cl_2 (25 ml) was added a solution of **4** (390 mg, 1.64 mmol) in CH_2Cl_2 (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 diethylphosphonoacetate (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

chromatographed on a silica gel (40 g) column eluting with hexane-ethyl acetate (3:1). The second fraction gave the pure sample of **6** (383 mg, 80% from **4**); $[\alpha]_D^{28}$ -8.6° (c=4.74, $CHCl_3$); ^{1}H-nmr δ 7.47 (d, J = 16.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.83 - 6.77 (m, 3H), 5.82 (d, J = 16.0, 1H), 4.22 (q of AB, J = 7.2, 10.8 Hz, 1H), 4.18 (q of AB, J = 7.2, 10.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 1.68 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C-nmr δ 173.2, 166.8, 159.7, 150.5, 143.2, 129.6, 120.9, 118.8, 112.9, 112.2, 61.6, 55.2, 53.2, 51.7, 23.1, 14.0; ir (neat) 1729, 1653 cm^{-1}; ms m/z 292 (M^+, 8), 218 (7), 181 (6), 165 (16), 161 (12), 160 (19), 159 (100), 131 (10), 119 (11); HRms calcd for $C_{16}H_{20}O_5$: 292.1309: found 292.1302; *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.80; H, 6.78.

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); $[\alpha]_D^{26}$ -12.4° (c=1.26, $CHCl_3$); ^{1}H-nmr δ 7.24 (t, J = 8.0 Hz, 1H), 6.89 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 6.84 (t, J = 2.0 Hz, 1H), 6.78 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 4.15 (q, J = 7.2 Hz, 1H), 4.14 (q, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 2.33 - 2.19 (m, 4H), 1.54 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C-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 calcd for $C_{16}H_{22}O_5$: 294.1466: found: 294.1463; *Anal.* Calcd for $C_{16}H_{22}O_5$: 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 $CHCl_3$. 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 $CHCl_3$. 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); $[\alpha]_D^{29}$ -9.0° (c=1.26, $CHCl_3$); ^{1}H-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); ^{13}C-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 calcd for $C_{15}H_{18}O_4$: 262.1204: found: 262.1205; *Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.65; H, 6.95. **8'**; bp 150°C (bath temperature, 0.1 mmHg); $[\alpha]_D^{27}$ +78.2°; ^{1}H-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 (ddd, J = 5.6, 6.8, 13.6 Hz, 1H), 1.96 (ddd, J = 5.6, 9.6, 13.6 Hz, 1H), 1.56 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C-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

262 (M^+, 55), 234 (27), 206 (25), 189 (100), 188 (39), 177 (59), 161 (75), 148 (25), 115 (25); HRms calcd for $C_{15}H_{18}O_4$: 262.1204: found: 262.1203.

(*R*)-(-)-1-Hydroxymethyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene ((*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 PtO_2 (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 $CHCl_3$, 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 tetralin-1-carboxylate derivative (**9**), bp 135-140°C (bath temperature, 0.45 mmHg); ^{1}H-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); ^{13}C-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 m/z 248 (M^+, 15), 176 (14), 175 (100), 174 (11), 57 (9); HRms calcd for $C_{15}H_{20}O_3$: 248.1411: found: 248.1411.

A mixture of **9** (278 mg, 1.12 mmol) and $LiAlH_4$ (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; $[\alpha]_D^{26}$ -16.5° (c=0.36, $CHCl_3$); ^{1}H-nmr δ 7.01 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 2.4 H, 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), 1.23 (s, 3H), 1.04 (s, 1H); ^{13}C-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 $C_{13}H_{18}O_2$: 206.1306: found: 206.1282; *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.56; H, 8.97.

A mixture of (*R*)-(-)-**10** (19 mg, 0.92 mmol), PvCl (33 mg, 0.28 mmol) and DMAP (33 mg, 0.27 mmol) in CH_2Cl_2 (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% $NaHCO_3$ solution, and dried. Evaporation of the solvents gave 29 mg of oily residue, which was chromatographed on a silica gel (6 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); ($[\alpha]_D^{26}$ +4.4° (c=1.25, $CHCl_3$). The ^{1}H-nmr, ^{13}C-nmr, ir and mass spectra were identical with those of (*S*)-(-)-**11** ($[\alpha]_D^{25}$ -5.3° (c=1.18, $CHCl_3$)).

(*R*)-(+)-1-Formyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene ((*R*)-(+)-12). To a suspension of PCC (520 mg, 2.4 mmol) and Celite (520 mg) in CH_2Cl_2 (20 ml) was added a solution of **10** (247 mg, 1.2 mmol) in CH_2Cl_2 (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**; $[\alpha]_D^{24}$ +16.0 ° (c=1.32, $CHCl_3$) (lit.,[5] for (*S*)-(-)-isomer; $[\alpha]_D^{20}$ -18.0°(c=2.3, $CHCl_3$); ^{1}H-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); ^{13}C-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 $C_{13}H_{16}O_2$: 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), $H_2NOH\cdot HCl$ (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; $[\alpha]_D^{26}$ +8.0° (c=3.14, $CHCl_3$); ^{1}H-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), 1.95-1.89 (m, 1H), 1.86-1.80 (m, 2H), 1.74-1.66 (m, 1H), 1.46 (s, 3H); ^{13}C-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 $C_{13}H_{17}NO_2$: 219.1258: found: 219.1256.

A solution of the oxime (228 mg, 1.04 mmol) in AcOH (5 ml) was shaken with PtO_2 (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 $CHCl_3$. 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 Ac_2O (1 ml, 10.6 mmol) was refluxed for 4 h. After evaporation of the excess AcOH and Ac_2O, the residue was dissolved in $CHCl_3$. 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); $[\alpha]_D^{23}$ -68.5° (c=0.65, $CHCl_3$); ^{1}H-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 (br s, 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); ^{13}C-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 $C_{15}H_{21}NO_2$: 247.1571: found: 247.1570; *Anal.* Calcd for $C_{15}H_{21}NO_2$: 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-dihydronaphthalen-1(2*H*)-one (14).

To a solution of **13** (270 mg, 1.1 mmol) in AcOH (5 ml) was added a solution of $K_2Cr_2O_7$ (645 mg, 2.2 mmol) in 1*N* H_2SO_4 (3 ml) with ice cooling and stirring during 10 min, and then added 10*N* H_2SO_4 (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 $CHCl_3$. The chloroform extract was washed with 5% $NaHCO_3$ 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); $[\alpha]_D^{23}$ -8.6° (c=1.35, $CHCl_3$); ^{1}H-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); ^{13}C-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) 1661 cm^{-1}; ms m/z 261 (M^+, 2), 191 (13), 190 (100), 189 (13), 175 (39), 161 (10); HRms calcd for $C_{15}H_{19}NO_3$: 261.1364: found: 261.1368; *Anal.* Calcd for $C_{15}H_{19}NO_3$: 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-1*H*-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 Br_2 (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 $CHCl_3$ and water. The residual syrup from the dried chloroform solution was chromatographed on a silica gel (12 g) column. Elution with $CHCl_3$ gave 65 mg (85%) of 2,3,4,5-tetrahydro-1,4-methano-1*H*-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 $NaBH_4$ (75 mg, 2.0 mmol) during 20 min with ice cooling. After stirring was continued at room temperature for 2 h, the solvent was evaporated. The colorless residue was treated with $CHCl_3$ 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 $HClO_4$ (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 $CHCl_3$, and the solution was washed with 5% $NaHCO_3$ 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; $[\alpha]_D^{25}$ -200.5° (c=0.505, $CHCl_3$); ^{1}H-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 (97:3) afforded the pure sample of **16** (30 mg, 80% from **15**), bp 110-120°C (bath temperature, 0.08 mmHg); $[\alpha]_D^{21}$ +10.4° (c=1.24, $CHCl_3$) (lit.,[3b] $[\alpha]_D^{29}$ +8.46° (c=0.35, $CHCl_3$)); ^{1}H-nmr δ 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); ^{13}C-nmr δ 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); $[\alpha]_D^{23}$ - 24.0° (c=0.33, MeOH) (lit.,[3b] $[\alpha]_D^{22}$ -46.3° (c=0.22, HCl salt in H_2O)). The ^{1}H-nmr and ir spectra were identical with those kindly provided by Professor K. Ogasawara.

Ethyl (*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** (2.27g, 95%), bp 120°C (bath temperature, 0.08 mmHg); $[\alpha]_D^{23}$ - 23.7° (c=1.22, $CHCl_3$); ^{1}H-nmr δ 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}; ms m/z 282 (M^+, 3), 221 (9), 220 (59), 192 (20), 177 (13), 176 (11), 162 (22), 149 (10), 134 (9), 133 (20), 45 (199); 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 dried and evaporated to give 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 $C_{13}H_{20}O_4$: 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_2Cl_2 (70 ml) was added a solution of **18** (1.95 g, 8.13 mmol) in CH_2Cl_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,

111.4, 96.6, 74.3, 55.4, 55.2, 51.5, 45.4, 22.8; ir (neat) 1724 cm^{-1}; ms m/z 294 (M^+, 2), 264 (19), 188 (73), 173 (36), 160 (34), 159 (89), 45 (100); HRms calcd for $C_{16}H_{22}O_5$: 294.1466: found 294.1461; *Anal.* Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.37; H, 7.25.

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 $CHCl_3$, washed with aqueous 5% $NaHCO_3$ 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 (1.66g, 6.64 mmol) in dichloromethane (40 ml) was added a solution of pivaloyl chloride (1.2 g, 9.96 mmol) in CH_2Cl_2 (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% $NaHCO_3$ 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); $[\alpha]_D^{23}$ - 3.5° (c=1.60, $CHCl_3$); ^{1}H-nmr δ 7.24 (t, 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); ^{13}C-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 $C_{19}H_{28}O_5$: 336.1935: found: 336.1927; *Anal.* Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.38. Found: C, 68.12; H, 8.15.

(*S*)-(-)-6-Methoxy-4-methyl-4-pivaloyloxy-3,4-dihydronaphthalen-1(2*H*)-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 $CHCl_3$. 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 $CHCl_3$. The chloroform solution was washed with water, dried and evaporated to give 1.4g 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); $[\alpha]_D^{26}$ -19.0 ° (c=1.30, $CHCl_3$); ^{1}H-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); ^{13}C-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 $CHCl_3$, 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 δ 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), 1.60 (dd of AB, J = 12.8, 8.4, 2.8 Hz, 1H), 1.30 (s, 3H), 1.14 (s, 9H); ^{13}C-nmr δ 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(3×C), 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: 290.1887; *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); $[\alpha]_D^{24}$ +16.6° (c=3.40, $CHCl_3$). The ^{1}H-nmr and ir spectra were identical with those of (*R*)-(-) isomer. *Anal.* Calcd for $C_{13}H_{18}O_2$: 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_2Cl_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 diethylphosphonoacetate (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; $[\alpha]_D^{27}$ +32.6° (c=1.04, $CHCl_3$); ^{1}H-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); ^{13}C-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), 200 (13), 186 (26), 185 (100), 174 (36), 173 (46), 159 (33), 158 (19); HRms calcd for $C_{16}H_{20}O_3$: 260.1411: found: 260.1409; *Anal.* Calcd for $C_{16}H_{20}O_3$: 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; $[\alpha]_D^{27}$ -12.1° (c=1.18, $CHCl_3$); ^{1}H-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); ^{13}C-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 $C_{16}H_{22}O_3$: 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 Et_3N (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 NaN_3 (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 $CHCl_3$ (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 $CHCl_3$. The chloroform solution was dried over K_2CO_3 and evaporated to give 175 mg of the primary amine as a slightly brown oil, which was heated with Ac_2O (1 ml, 10.6 mmol) and AcOH (1 ml, 17.7 mmol) on a water bath for 4 h. After evaporation of the excess Ac_2O and AcOH, the residual syrup was dissolved in $CHCl_3$, 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 δ 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 δ 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^+, 32), 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° (c=2.30, $CHCl_3$) (lit.,[4] $[\alpha]_D^{24}$ +23.20° (c=1.60, EtOH)); ^{1}H-nmr δ 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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