ASYMMETRIC SYNTHESIS OF (+)- AND (-)-EPTAZOCINE *VIA* AN ENZYMATIC REACTION

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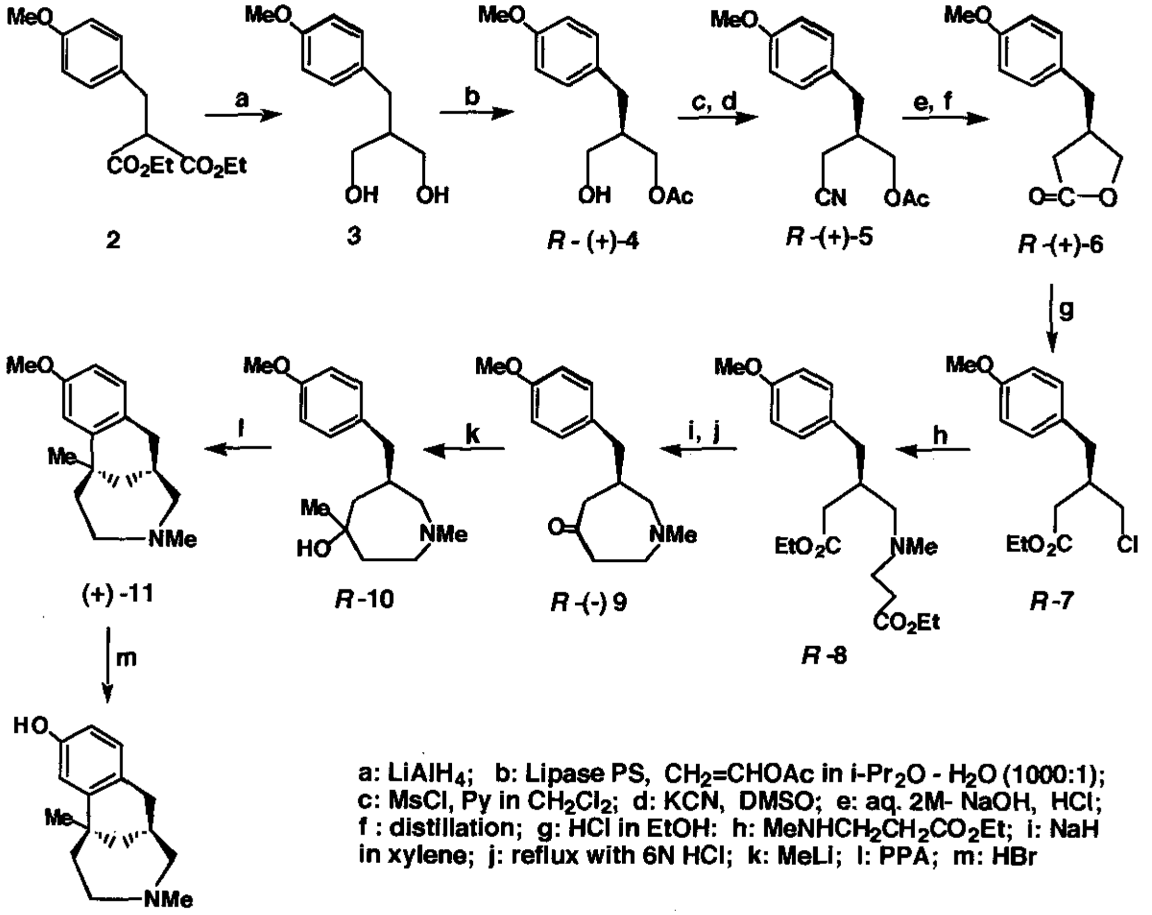
Abstract-Starting from (*R*)-3-hydroxy-2-(*p*-methoxybenzyl)propyl acetate (*R*-(+)-**4**) prepared by enzymatic monoacetylation of 2-(*p*-methoxybenzyl)propane-1,3-diol (**3**) with lipase PS in the presence of vinyl acetate as an acetyl donor, lactones ((+)- and (-)-**6**) were obtained. Using the lactones, (+)- and (-)-eptazocine were synthesized.

Eptazocine ((-)-**1**), an antagonistic analgesic which is currently used for therapeutic purposes, was first synthesized in the racemic form[1] in 1976 and resolved to compare the analgetic and other pharmacological properties of the both enantiomers[2] in 1979. Recently, elegant asymmetric syntheses of chiral 1-hydroxymethyl-1-methyl-7-methoxy-1,2-dihydonaphthalene, a key intermediate for the synthesis of (+)- or (-)-**1** have been reported by four groups. The first relies on the 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.[3] Shibasaki applied an asymmetric intramolecular Heck reaction of appropriately substituted arylolefins with palladium-(0)-(*R*)-BINAP complex catalyst for the introduction of chirality in 1,1-disubstituted 7-methoxytetralin derivatives.[4] Node synthesized the asymmetric tetralin derivatives by the methylation of (*R*)-binaphthyl ester of 7-methoxytetralin-1-carboxylic acid.[5] Meyers has recently reported another route to the asymmetric 1,1-disubstituted 1,2-dihydronaphthalenes, which involves an asymmetric addition to naphthalene derivatives having a chiral oxazoline-substituent at the α-position with lithiosilanes and iodomethane to produce chiral 1,1-disubstituted 7-methoxy-1,2-dihydronaphthalenes.[6]

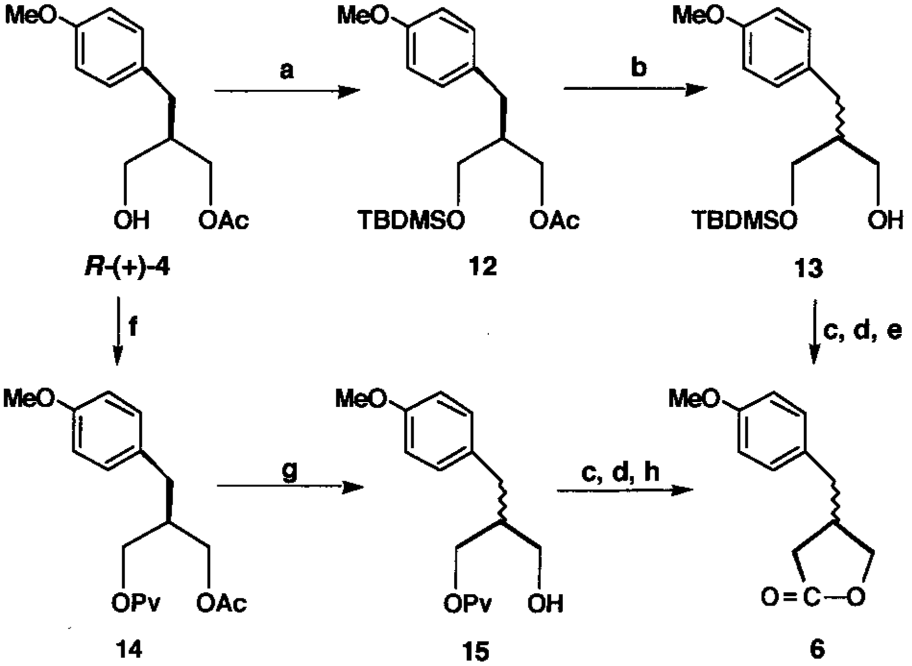
Meanwhile, the enzymatic reaction is now well recognized as an easy and useful means of preparing enantiomerically pure compounds.[7] Recent papers reporting the use of lipase PS for the enantiospecific monoacetylation of 2-benzyl-1,3-propanediol derivatives[8,9] prompted us to use the enzymatic enantiospecific monoacetylation of 2-(*p*-methoxybenzyl)-1,3-propanediol (**3**) for the asymmetric synthesis of (+)- and (-)-**1**. Treatment of the prochiral diol (**3**) with 50 wt% of lipase PS in a mixture of diisopropyl ether and water (1000:1) in the presence of vinyl acetate as an acetyl donor afforded optically pure monoacetate (*R*-(+)-**4**). The hydroxyl group of *R*-(+)-**4** was mesylated and treated with potassium cyanide in dimethyl sulfoxide to give the cyanoacetate (*R*-(+)-**5**).



a: $LiAlH_4$; b: Lipase PS, $CH_2{=}CHOAc$ in i-Pr_2O - H_2O (1000:1); c: MsCl, Py in CH_2Cl_2; d: KCN, DMSO; e: aq. 2M- NaOH, HCl; f : distillation; g: HCl in EtOH: h: $MeNHCH_2CH_2CO_2Et$; i: NaH in xylene; j: reflux with 6N HCl; k: MeLi; l: PPA; m: HBr

Scheme 1.

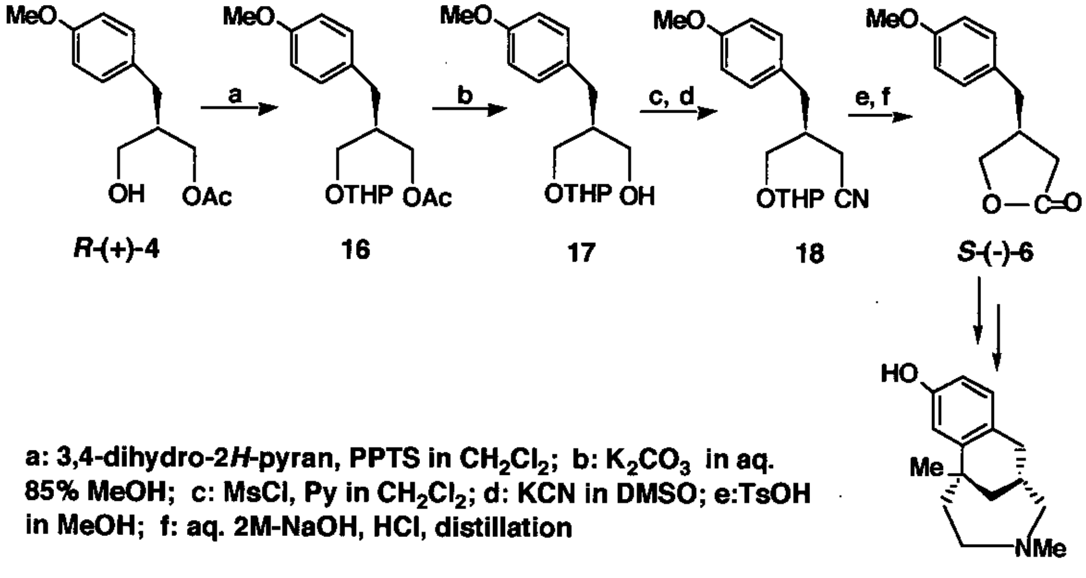
Hydrolysis of compound (*R*-(+)-**5**) with sodium hydroxide followed by acidification and vacuum distillation gave the corresponding lactone (*R*-(+)-**6**) of >98% ee.[10] Compound (*R*-(+)-**6**) was treated with hydrogen chloride in anhydrous ethanol to give ethyl (+)-3-chloromethyl-4-(*p*-methoxybenzyl)butylate (*R*-**7**) in good yield. Refluxing of the chloro compound (*R*-**7**) with ethyl 3-methylaminopropionate[11] in chlorobenzene in the presence of potassium carbonate and a small amount of sodium iodide for 2 days afforded the corresponding diester (*R*-**8**) in 80% yield. The Dieckmann cyclization of the compound (*R*-**8**) with sodium hydride in xylene followed by refluxing with hydrochloric acid gave the perhydroazepinone (*R*-(−)-**9**). Treatment of the ketone *R*-(−)-**9**) with methyllithium afforded the tertiary alcohol ((*R*)-**10**), which was submitted to the Grewe cyclization with polyphosphoric acid to give (+)-*O*-methyleptazocine ((+)-**11**), from which (+)- eptazocine ((+)-**1**) was obtained by heating with hydrobromic acid.[12]



a: TBDMSCl, Py in CH_2Cl_2; b: aq. 2M-NaOH or aq. LiOH; c: MsCl, Py in CH_2Cl_2; d: KCN in DMSO; e: TBAF in THF then reflux with aq. 2M-NaOH, HCl; f: PvCl, Py in CH_2Cl_2; g: guanidine in EtOH or Mg/MeOH; h: reflux with aq. 2M-NaOH, HCl

Scheme 2.

In order to synthesize eptazocine ((−)-**1**), thus, it was required to introduce a cyano group at the acetoxymethylene carbon of the monoacetate (*R*-(+)-**4**). For this purpose, the hydroxyl group in compound (*R*-(+)-**4**) must be masked with an appropriate protective group prior to hydrolysis of the acetoxy function, and three protective groups, *tert*- butyldimethylsilyl (TBDMS), pivaloyl (Pv) and tetrahydropyranyl (THP), were tried to mask the hydroxyl group of *R*-(+)-**4**. TBDMS ether, one of the most favorable protective groups for hydroxy functionality, of compound (*R*-(+)-**4**) was formed easily in high yield to give compound (**12**). However, hydrolysis of the acetoxy group of **12** with lithium hydroxide or sodium hydroxide in aqueous methanol afforded the monosilyl ether (**13**) in excellent chemical yield but resulted in complete or partial racemization, which would be caused by migration of the silyl group under the basic condition.[13] It had been reported that pivaloates are not cleaved with guanidine in ethanol while acetates easily removed,[14] and recently Walker has reported that pivaloates are more stable than acetates to the reductive deacylation with magnesium in methanol.[15] Thus, the pivaloate (**14**) of compound (*R*-(+)-**4**) was prepared and submitted to the deacetylation with guanidine and with magnesium in methanol. In both cases, the acetyl group was selectively removed in high chemical yield to give compound (**15**), but the optical yield of the monopivaloate was almost zero in the former case and very low in the latter. These results would be caused again by migration of the pivaloyl group under basic conditions.



a: 3,4-dihydro-2*H*-pyran, PPTS in CH_2Cl_2; b: K_2CO_3 in aq. 85% MeOH; c: MsCl, Py in CH_2Cl_2; d: KCN in DMSO; e:TsOH in MeOH; f: aq. 2M-NaOH, HCl, distillation

Scheme 3.

Finally, the hydroxyl group of monoacetate (*R*-(+)-**4**) was converted to the THP ether with 3,4-dihydro-2*H*-pyran in the presence of pyridinium *p*-tosylate (PPTS) in dichloromethane[16] to give compound (**16**), the acetoxy group of **16** was selectively hydrolyzed with potassium carbonate in aqueous methanol[17] to afford the mono-THP ether (**17**) in high yield without racemization. Mesylation of the hydroxyl group of **17** followed by treatment with potassium cyanide in DMSO yielded the nitrile (**18**). Deprotection of the THP group with *p*-toluenesulfonic acid[18] and the subsequent hydrolysis of the cyano group with sodium hydroxide yielded the corresponding lactone (*S*-(-)-**6**) in high chemical and optical yield (>92% ee).[10] Eptazocine ((-)-**1**) was synthesized from *S*-(-)-**6** by using the same procedure for the preparation of (+)-eptazocine from *R*-(+)-**6**.

The present work offers a simple and useful method of synthesizing optically pure (+)- and (-)-eptazocine. The use of enzymatic acetylation of prochiral propane-1,3-diol derivatives developed by Itoh[8] and Achiwa[9] made it possible to synthesize the optically pure lactones (+)- and (-)-**6** enantioselectively, which can be used for the asymmetric syntheses of many other natural and unnatural compounds.

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 or JNM-PMX-60 spectrometer in $CDCl_3$ solution unless otherwise stated. Ir specta were taken on a JASCO FT/IR 7300 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. Mass spectra were obtained by using JEOL JMS-OISG-2 spectrometer. All organic extracts were dried over $MgSO_4$.

2-(*p*-Methoxybenzyl)propane-1,3-diol (3). To a stirred mixture of sodium hydride (60% in mineral oil, 2.32 g, 58 mmol) in THF (70 ml) was added a solution of diethyl malonate (12 g, 75 mmol) in THF (20 ml) at room temperature over 30 min and stirring was continued for another 30 min at this temperature. To the mixture was added a THF solution of *p*-methoxybenzyl chloride (7 g, 45 mmol) at 0℃ over 10 min followed by refluxing for 4 h. After evaporation of the most of the solvent, the mixture was acidified with 10% HCl under ice-cooling and extracted with CH_2Cl_2 to give an oily product. Diethyl *p*-methoxybenzylmalonate (**2**) (9.22 g, 74%) was obtained after distillation under reduced pressure (157-159℃ at 0.6 mmHg): ^1H Nmr δ 7.11 (2H, d, J = 8.8 Hz), 6.78 (2H, d, J = 8.8 Hz), 4.14 (2H, q, J = 7.2 Hz), 4.13 (2H, q, J=7.2 Hz), 3.74 (3H, s), 3.60 (1H, t, J = 8.0 Hz), 3.15 (d, J = 8.8 Hz), 1.19 (6H, t, J = 7.2 Hz); ^{13}C nmr δ 168.8(2×C), 158.2, 136.9, 129.6(2×C), 113.6(2×C), 61.0(2×C), 54.8, 53.8, 33.6, 13.7(2×C); ir(neat) 2983, 2938, 1733(C=O), 1514, 1250, 1180, 1036, 824 cm^{-1}.

To a mixture of $LiAlH_4$ (3.75 g, 98.7 mmol) in THF (100 ml) was added a THF (45 ml) solution of the malonate (9.22 g, 33 mmol) at 0℃ over 20 min and the mixture was refluxed for 4 h. The reaction was quenched by addition of MeOH (3.5 ml), and 10% HCl (35 ml) under ice-cooling and the mixture was extracted with $CHCl_3$. Diol (**3**) was obtained by distillation *in vacuo* or recrystallization from ether as colorless needles in 95% yield; mp 67.5-69℃ (bp 130-150℃ (bath temperature) at 0.08 mmHg); ^1H nmr δ 7.07(2H, d, J = 8.8 Hz), 6.81 (2H, d, J = 8.8 Hz), 3.76 (3H, s), 3.72 (2H, dd, J = 3.6, 10.8 Hz), 3.60 (2H, dd, J = 6.8, 10.8 Hz), 3.24 (2H, br s), 2.52 (2H, d, J = 7.6 Hz), 1.96 (1H, ddt, J = 3.6, 6.8, 7.6 Hz); ^{13}C nmr δ 157.8, 131.8, 129.8 (2×C), 113.8(2×C), 64.9, 55.2, 43.9, 33.2; ir(KBr) 3332(OH), 2933, 2837, 1612, 1513, 1300, 1037, 976, 831 cm^{-1}. *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.46; H, 7.93.

(*R*)-3-Hydroxy-2-(*p*-methoxybenzyl)propyl Acetate ((*R*)-(+)-4). To a stirred solution of diol (**3**) (4.2 g, 21 mmol), 2,6-di-*tert*-butyl-*p*-cresole (90 mg, 0.4 mmol, antioxidant) and vinyl acetate (4.9 ml. 53 mmol) in *i*-Pr_2O (300 ml) were added Lipase PS (2 g) and water (0.1 ml) at room temperature. After being stirred for 1.5 h, the mixture was filtered through a sintered glass filter with a Celite pad. The filtrate was evaporated, and the resdidue was chromatographed on a silica gel (400 g) column, hexane/AcOEt (1:1), to give (*R*)-(+)-**4** (4.8 g, 96%) as a colorless oil of bp 140-150℃ at 0.2 mmHg; $[\alpha]^{26}_D$ +23.1° (c=8.96, $CHCl_3$); ^1H nmr δ 7.09 (2H, d, J = 8.4 Hz), 6.83 (2H, d, J = 8.4 Hz), 4.15 (1H, dd, J = 3.8, 11.2 Hz), 4.05 (1H, dd, J = 6.4, 11.2 Hz), 3.78 (3H, s), 3.58 (1H, ddd, J = 5.2, 6.0, 11.2 Hz), 3.49 (1H, ddd, J = 5.6, 6.0, 11.2 Hz), 2.63 (1H, dd, J = 7.6, 13.6 Hz), 2.56 (1H, dd, J = 7.6, 13.6 Hz), 2.31 (1H, t, J = 6.0 Hz), 2.12-2.02 (1H, m), 2.07 (3H, s); ^{13}C nmr δ 171.6, 158.0, 131.2, 129.9(2×C), 113.8(2×C), 63.9, 61.9, 55.2, 42.5, 33.3, 20.8; ir (neat) 3448(OH), 2937, 2838, 1736(C=O), 1613, 1513, 1347, 1180, 1037, 843, 807 cm^{-1}; ms (EI) *m/z* (rel intensity) 238([M^+], 4), 220(4), 178(11), 160(28), 159(13), 147(38), 134(5), 129(8), 121(100), 117(10); HRms calcd for $C_{13}H_{18}O_4$ 238.1204, found 238.1200. *Anal.* Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.80; H, 7.91.

(*R*)-3-(*p*-Methoxybenzyl)butyrolactone ((*R*)-(+)-6). To a solution of (*R*)-(+)-**4** (2.96 g, 12.4 mmol) and pyridine (6 ml, 75 mmol) in CH_2Cl_2 (20 ml) was added a solution of MsCl (2.4 g, 21 mmol) in CH_2Cl_2 (10 ml) at 0℃ under nitrogen. The reaction mixture was stirred for 39 h at room temperature. After addition of ice-water, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. The residual syrup was chromatographed on a silica gel column (240 g), hexane/AcOEt (1:1), to yield the mesylate (3.45 g, 88%) as a colorless oil. A mixture of the mesylate (5.57 g, 17.6 mmol) and powdered KCN (1.95 g, 30 mmol) in DMSO (50 ml) was stirred at 90℃ for 24 h. After being cooled and diluted with water, the mixture was extracted with a mixed solvent (Et_2O/C_6H_6, 1:1) several times. The organic layers were combined, dried and evaporated to give a crude product (4.0 g), which was chromatographed on a silica gel column (400 g), $CHCl_3$/MeOH (99:1), to yield pure sample of the nitrile ((*R*)-**5**) (3.7 g, 85%) as a colorless oil; $[\alpha]^{29}_D$ +0.1° (c=15.3, $CHCl_3$). A mixture of (*R*)-**5** (3.33 g, 13.5 mmol) in aqueous 2M NaOH solution (70 ml, 140 mmol) was refluxed for 3 h. After being cooled, the reaction mixture was extracted with benzene, and the aqueous layer was acidified with 10% HCl, extracted with $CHCl_3$. The residue of the chloroform extract was chromatographed on a silica gel column (300 g), hexane/AcOEt (1:1), to give (*R*)-(+)-**6** (2.37 g, 85%) as a colorless oil (solidified on standing, mp 56.5-59℃), bp 135℃ at 0.3 mmHg; $[\alpha]^{29}_D$ +5.4° (c=6.8, $CHCl_3$); ^1H nmr δ 7.07 (2H, d, J = 8.3 Hz), 6.85 (2H, d, J = 8.3 Hz), 4.32 (1H, dd, J = 7.2, 8.8 Hz), 4.02 (1H, dd, J = 6.0, 8.8 Hz), 3.79 (3H, s), 2.81 (1H, m), 2.72 (1H, dd, J = 8.0, 14.0 Hz), 2.70 (1H, dd, J = 6.8, 14.0 Hz), 2.59 (1H, dd, J = 8.0, 17.6 Hz), 2.27 (1H, dd, J = 6.8, 17.6 Hz); ^{13}C nmr δ 176.8, 158.4, 130.2, 129.6(2×C), 114.1(2×C), 72.6, 55.2, 38.0, 37.3, 34.2; ir (KBr) 3014,2916,2844,1772,1612,1511,1246,1177,1032,1011, 835,816 cm^{-1}; ms (EI) *m/z* (rel intensity) 206([M^+,100),180(10),166(9),147(8), 135(5),122(36),121(98); HRms calcd for $C_{12}H_{14}O_3$ 206.0942, found 206.0945. *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.60; H, 6.75.

(*R*)-1-Methyl-3-(*p*-methoxybenzyl)-5-oxo-2,3,4,5,6,7-hexahydro-1*H*-azepine ((*R*)-(-)-9). Into a solution of (*R*)-(+)-**6** (2.37 g, 11.5 mmol) and $ZnCl_2$ (184 mg, 1.4 mmol) in absolute EtOH (13 ml) was passed HCl gas at 0℃ for 15 min and then at room temperature for 6 h. The reaction mixture was diluted with ice-water and extracted with $CHCl_3$. The chloroform extract was washed with aqueous $NaHCO_3$ solution and water, dried, and evaporated. The crude residue was purified by chromatography on a silica gel column (40 g), hexane/AcOEt (2:1), to give ethyl (*R*)-4-chloro-3-(*p*-methoxybenzyl)butylate ((*R*)-**7**) (3.0 g, 78%). A mixture of (*R*)-**7** (2.43 g, 9 mmol) ethyl 3-(methylamino)propionate (3.07 g, 23.4 mmol), K_2CO_3 (1.38 g, 10 mmol) and NaI (50 mg, 0.3 mmol) in chlorobenzene (40 ml) was refluxed for 44 h. After being cooled, the reaction mixture was washed with water, extracted with 10% HCl. The aqueous layer was basified with 10% NaOH aqueous solution, extracted with $CHCl_3$. The chloroform extract was dried and evaporated to give (*R*)-**8** (2.3 g, 70%) as a pale yellow syrup. A mixture of (*R*)-**8** (630 mg, 1.7 mmol) and NaH (60% in mineral oil, 272 mg, 6.8 mmol) in xylene (19 ml) was stirred and refluxed under nitrogen for 7 h. Then, the reaction mixture was refluxed with 6N HCl (14 ml) for 3 h. After being cooled, the layers were separated, and the organic layer was extracted with 10% HCl. The combined aqueous layers were made alkaline with 10% NaOH solution, extracted with $CHCl_3$. The extract was dried and evaporated to give a crude product (250 mg). The crude product was chromatographed on a silica gel column (25 g), $CHCl_3$/MeOH (99:1), to give pure sample of (*R*)-(-)-**9** (151 mg, 36%) as a pale yellow syrup; $[\alpha]^{31}_D$ -25.3° (c=3.14, $CHCl_3$); ^1H nmr δ 7.06 (2H, d, J = 8.8 Hz), 6.82 (2H, d, J = 8.8 Hz), 3.78 (3H, s), 2.97-2.77 (3H, m), 2.66-2.26 (8H, m),

2.36 (3H, s); ^{13}C nmr δ 211.7, 158.1, 131.1, 130.0(2×C), 113.8(2×C), 65.3, 55.1, 53.3, 48.6, 47.2, 43.8, 40.0, 36.5; ir (neat) 3031, 2941, 2836, 2800, 1702 (C=O), 1612, 1512, 1464, 1247, 1179, 1035, 822 cm^{-1}; ms (EI) *m/z* (rel intensity) 247 ([M$^+$], 36), 147 (27), 126 (65), 121 (57), 112 (46), 108 (38), 71 (95), 70 (57), 58 (29), 57 (33), 43 (100), 42 (56); HRms calcd for $C_{15}H_{21}NO_2$ 247.1571, *found* 247.1568.
Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.90; H, 8.60; N, 5.37.

(1*S*,6*S*)-(+)-1,4-Dimethyl-10-methoxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine ((+)-11). To a solution of (*R*)-(−)-**9** (477 mg, 1.8 mmol) in a mixture of THF (5 ml) and Et_2O (6 ml) was added a solution of MeLi-LiBr in ether (1.5M, 6 ml, 9 mmol) with stirring and ice-cooling under nitrogen. After being stirred for 15 h at room temperature, the reaction mixture was treated with a solution of aqueous 10% NH_4Cl solution. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried, and evaporated to leave 480 mg of crude (*R*)-**10** (ir (neat) 3385 (OH), 2848 (NMe)), which was used for the next step without any purification.
A mixture of the crude (*R*)-**10** (480 mg) and PPA (4 g) was heated on a water bath for 3 h. After being cooled, the reaction mixture was diluted with ice-water, made alkaline with 40% NaOH solution and extracted with $CHCl_3$. After being dried, the solvent was evaporated to leave 380 mg of the crude product, which was purified by chromatography on a silica gel (35 g) column, $CHCl_3$/MeOH (99:1-98:2), to give a pure sample of (+)-**11** (258 mg, 60%) as a colorless oil (bp 130-140℃ (bath temperature) at 0.1 mmHg); $[\alpha]^{30}_D$ +15.3° (c=1.32, $CHCl_3$). The ^{1}H nmr and ir spectra of this sample were identical with those of the sample of (−)-**11** obtained by optical resolution of racemic **11**.[19]

(+)-Eptazocine ((+)-1). A mixture of (+)-**11** (258 mg, 1.05 mmol) in HBr aqueous solution (47%, 6.5 ml) was refluxed for 1 h. The mixture was evaporated to dryness, and the residual solid was recrystallized from MeOH to give (+)-**1·HBr** (192 mg, 80%), mp 260-262℃ (lit.,[2a] 266-270℃); $[\alpha]^{29}_D$ +17.2° (c=2.88, EtOH) (lit.,[2a] $[\alpha]^{20}_D$ +15.0° (c=5.0, H_2O)). The ^{1}H nmr and ir spectra were identical with those of the sample obtained by Shiotani's method.[1,2a]
(*S*)-3-(*tert*-Butyldimethylsilyoxy)-2-(*p*-methoxybenzyl)propyl Acetate (12). To a solution of (*R*)-(+)-**4** (1.28 g, 5.1 mmol) and TBDMSCl (1.3 g, 8.6 mmol) in CH_2Cl_2 (9 ml) was added pyridine (2.2 ml, 27.5 mmol) with stirring and ice-cooling under nitrogen. The mixture was stirred for 24 h at room temperature, and the reaction was quenched with ice- water (20 ml). The reaction mixture was extracted with CH_2Cl_2 (3×10 ml). The combined extracts were washed with water, dried and evaporated to leave 1.83 g of crude residue, which was chromatographed on a silica

gel (90 g) column, hexane/AcOEt (3:1), to give the pure sample of **12** (1.72 g, 96%); ^{1}H nmr δ 7.06 (2H, d, J = 8.4 Hz), 6.80 (2H, d, J = 8.4 Hz), 4.01 (2H, d, J = 5.2 Hz), 3.77 (3H, s), 3.55 (1H, dd, J = 4.4, 10.0 Hz), 3.49 (1H, dd, J = 5.2, 10.0 Hz), 2.63 (1H, dd, J = 7.6, 14.0 Hz), 2.52 (1H, dd, J = 7.6, 14.0 Hz), 2.03 (3H, s), 2.03 (1H, m), 0.88 (9H, s), 0.01 (6H, s); ir(neat) 2955,2927,2858,1743(C=O),1624,1513,1472,1365,1248,1179,1091,1038, 837,777 cm^{-1}.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(*p*-methoxybenzyl)propanol (13). **(a)** To a solution of **12** (1.64 g, 4.65 mmol) in EtOH (20 ml) was added 2M NaOH solution (4.7 ml, 9,3 mmol) at room temperature with stirring. After being stirred for 18 h, most of the solvent was evaporated, and the residue was treated with water and $CHCl_3$. The chloroform extract was dried and evaporated to leave mono-TBDMS ether (**13**) (1.24 g, 86%) as a pale yellow syrup, which was used for the next step without any purification; ir (neat) 3420(OH),2951,2930,2858,1614,1513,1471,1248,1179,1039,837, 777 cm^{-1}.

(b) A mixture of **12** (740 mg, 2.1 mmol), LiOH (110 mg, 2.6 mmol) and water (15 ml) in THF (45 ml) was at room temperature for 15 h under nitrogen. The mixture was diluted with water (10 ml), and extracted with $CHCl_3$. Evaporation of the solvent of the dried chloroform extract gave **13** (660 mg, 89%), which was used for the next step without further purification.

Conversion of 13 to the Lactone (6). To a solution of **13** (1.24 g, 4.0 mmol) obtained by hydrolysis of **12** with NaOH, and pyridine (2.2 ml, 27.5 mmol) in CH_2Cl_2 (10 ml) was added a solution of MsCl (780 mg, 6.8 mmol) in CH_2Cl_2 (3 ml) at 0℃ with stirring under nitrogen. The reaction mixture was stirred for 40 h at room temperature, treated with ice-water, and the organic layer was dried and evaporated to give 3-*tert*-butyldimethylsilyloxy-2-(*p*-methoxybenzyl)propyl mesylate (1.53 g, 98%) as a colorless syrup. A mixture of the mesylate (1.0 g, 2.57 mmol) and KCN (0.27 g, 4.12 mmol) in DMSO (15 ml) was stirred at 80 ℃ for 24 h. After being cooled diluted with water, the mixture was extracted with a mixed solvent (benzene/Et_2O (1:1)) several times. The combined organic extracts were dried and evaporated to give crude 4-*tert*-butyldimethylsilyloxy-3-(*p*-methoxybenzyl)butyronitrile (0.7 g, 89%) as a colorless syrup. To a solution of the nitrile (670 mg, 2.1 mmol) in THF (20 ml) was added a solution of Bu_4NF in THF (1.0M, 4.2 ml, 4.2 mmol) with stirring and ice-cooling. After being stirred for 40 min at room temperature, the mixture was treated with water, and extracted with $CHCl_3$. The residue (430 mg, 100%) of the dried chloroform extract was refluxed with aqueous NaOH solution (2M, 10 ml, 20 mmol) for 3 h. After being cooled, the reaction mixture was washed with benzene, and the aqueous layer was acidified with 10% HCl, extracted with $CHCl_3$, and the extract wasdried and evaporated to leave 400 mg of oily residue, which was distilled under reduced pressure to give lactone (**6**) (347 g, 80%) as a colorless oil (bp 140-150℃ at 0.3 mmHg); $[\alpha]^{26}_D$ -0.8° (c=3.80, $CHCl_3$). The ^1H nmr and ir spectra were identical with those of (*R*)-(+)-**6** and the tlc exhibited single spot (silica gel, hexane/AcOEt (2:1), Rf 0.55). Using the same procedure, compound (**13**) obtained by hydrolysis with LiOH was converted to lactone (**6**); $[\alpha]^{26}_D$ -1.2° (c=3.52, $CHCl_3$).

(*S*)-3-Acetoxy-2-(*p*-methoxybenzyl)propyl Pivaloate (14). To a solution of (*R*)-(+)-**4** (1.2 g, 5.0 mmol), 4-dimethylaminopyridine (140 mg, and pyridine (2 ml) in CH_2Cl_2 (10 ml) was added a solution of PvCl (900 mg, 7.5 mmol) in CH_2Cl_2 (5 ml) with ice-cooling and stirring over a period of 5 min. After being stirred at room temperature for 15 h, the reaction mixture was washed with 10% HCl (50 ml) and with water. The organic layer was dried and evaporated to give compound (**14**) (1.49 g, 91%) as a colorless oil (bp 150℃ at 0.3 mmHg); $[\alpha]^{28}_D$ -1.5° (c=2.28, $CHCl_3$); ^1H nmr(60 MHz, CCl_4) δ 6.95 (2H, d, J = 8.2 Hz), 6.70 (2H, d, J = 8.2 Hz), 3.95 (4H, d, J = 5.0 Hz), 3.73 (3H, s), 2.60 (2H, d, J = 7.5 Hz), 2.40-2.05(1H, m), 1.98 (3H, s),1.18(9H,s); ir(neat) 2972,2951,2937,2837,1733(C=O),1614,1514,1465,1367, 1247,1159,1038 cm^{-1}; ms (EI) (rel intensity) 322([M^+],2),262(4),221(2),220 (6),161(26),160(100),159(32.8),147(19),145(20),134(16),129(16),121(85); HRms calcd for $C_{18}H_{26}O_5$ 322.1779, found 322.1765.
Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.25; H, 8.03.

(*S*)-3-Hydroxy-2-(*p*-methoxybenzyl)propyl Pivaloate(15). (a). Hydrolysis of 14. To a solution of compound (**14**) (322 mg, 1.0 mmol) in EtOH (8 ml) was added a solution of guanidine (0.125M, in EtOH, 8 ml, 1.0 mmol) at room temperature with stirring. After being stirred for 1 h at this temperature, the mixture was evaporated, and the residue was treated with 5% HCl (10 ml) and extracted with CH_2Cl_2. The extract was dried and evaporated to give the monopivaloate (**15**) (261 mg, 93%), which exhibited single spot on the tlc (silica gel, hexane/AcOEt (1:1), Rf 0.48); $[\alpha]^{25}_D$ 0.0° (c=5.22, $CHCl_3$); ^1H nmr (60 MHz, CCl_4) δ 7.03 (2H, d, J = 8.2 Hz), 6.71 (2H, d, J = 8.2 Hz), 4.04 (2H, d, J = 5.2 Hz), 3.72 (3H, s), 3.41 (2H, d, J = 5.0 Hz), 2.74 (1H, s), 2.56 (2H, d, J = 8.0 Hz), 2.26-1.76 (1H, m), 1.20 (9H, s); ir (neat) 3440(OH),2960,2953,2935,2875,1728(C=O),1613,1513,1287,1248, 1163,1037 cm^{-1}; ms(EI) *m/z* (rel intensity) 280([M^+],3),262(7),219(2),206(4), 178(18),160(66),147(55),145(32),129(17),121(100); HRms calcd for $C_{16}H_{24}O_4$ 280.1673, found 280.1665.

(b). Reductive Deacetylation of 14. To a solution of **14** (1.05 g, 3.25 mmol) in dry MeOH (160 ml) was added Mg (turnigs, 105 mg, 4.38 mmol) with ice-cooling. After being stirred for 15 h at room temperature, to the mixture was added 10% HCl (5 ml), and the solvent was evaporated. The residue was dissolved in a mixed solvent (benzene/ Et_2O, 1:1). The solution was washed with water, dried and evaporated the solvent to give compound (**15**) (0.88 g, 97%) as a colorless oil, which exhibited single spot on the tlc (silica gel, hexane/AcOEt (1:1), Rf 0.48); $[\alpha]^{25}_D$ 21.3° (c=2.0, $CHCl_3$). The ^1H nmr and ir spectra of this sample were identical those of the compound (**15**) obtined in the above.

Conversion of 15 to the Lactone (6). To a solution of **15** (210 mg, 0.75 mmol) (prepared by the *reductive deacetylation of* **14** with Mg in MeOH) and pyridine (0.6 ml, 7.5 mmol) in CH_2Cl_2 (3 ml) was added a solution of MsCl (146 mg, 1.28 mmol) in CH_2Cl_2 (3 ml) at 0 ℃ under nitrogen. The reaction mixture was stirred for 40 h at room temperature. After addition of ice-water, the organic layer was separated, washed with 10% HCl, dried and evaporated to leave 265 mg (99%) of the mesylate as a colorless oil.

A *mixture of the mesylate (265 mg,* 0.75 mmol) and powdered KCN (78.5 mg, 1.2 mmol) in DMSO (6 ml) was stirred at 90 ℃ for 24 h. After being cooled and diluted with water, the mixture was extracted with a mixed solvent (Et_2O/benzene, 1:1) several times. The combined organic layers were dried and evaporated to give 191 mg (88%) of 4-pivaloyloxy-3-(*p*-methoxybenzyl)butyronitrile as a pale yellow oil; IR(neat) 2971,2935, 2837,2247(CN),1731,1614,1514,1481,1465,1284,1249,1156,1036,838 cm^{-1}.

A *mixture of the pivaloyloxybutyronitrile* (490 mg, 1.7 mmol) and aqueous NaOH solution (2M, 2 ml, 4 mmol) in EtOH (6 ml) was stirred at room temperature for 18 h. The solvent was evaporated, and the residue was treated with water and $CHCl_3$. The residue (340 mg, 1.66 mmol) of the dried chloroform extract was refluxed with aqueous NaOH solution (2M, 8.3 ml, 16.6 mmol) for 3 h. After being cooled, the reaction mixture was acidified with HCl and extracted with ether. The extract was dried and evaporated to give an oily residue. The residual oil was distilled under reduced pressure to give the lactone (**6**) (290 mg, 85%) as a colorless syrup; $[\alpha]^{25}_D$ -4.5° (c=0.5, $CHCl_3$). The monopivaloate (**15**) prepared by hydrolysis of compound (**14**) with guanidine was converted to the lactone (**6**), using the same procedure described in the above; $[\alpha]^{25}_D$ -0.0° (c=1.0, $CHCl_3$). The ^1H nmr and ir spectra of both the samples were identical with those of **(*R*)-(+)-6**.

(*R*)-3-(2-Tetrahydropyranyloxy)-2-(*p*-methoxybenzyl)propyl Acetate (16). A mixture of *R*-(+)-**4** (1.25 g, 5.25 mmol), 3,4-dihydro-2*H*-pyran (0.88 g, 10.5 mmol) and pyridinium *p*-tosylate (132 mg, 0.52 mmol) in CH_2Cl_2 (75 ml) was stirred at room temperature for 3 h. The mixture was washed with brine, dried and evaporated to leave 1.9 g of a pale yellow oil. Distillation of the residue under reduced pressure afforded the pure sample of **16** (1.65 g, 97%) as a colorless oil (bp 150 ℃ at 0.12

mmHg); $[\alpha]^{25}_{D}$ +6.0° (c=5.1, $CHCl_3$); ^1H nmr δ 7.08 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 8.4 Hz), 6.81 (2H, d, J = 8.4 Hz), 4.55 (0.5H, t, J = 3.2 Hz), 4.53 (0.5H, t, J = 3.2 Hz), 4.14-4.03 (2H, m), 3.83-3.68 (2H, m), 3.75 (3H, s), 3.49-3.45 (1H, m), 3.30 (0.5H, dd, J = 5.2, 9.6 Hz), 3.25 (0.5H, dd, J = 6.0, 9.6 Hz), 2.72-2.53 (2H, m), 2.03 (3H, s), 1.87-1.48(6H, m); ir(neat) 2943,2871,1740(C=O),1614,1513,1467,1454,1442,1384, 1367,1246,1180,1123,1035,813 cm^{-1}; ms(EI) *m/z* (rel intensity) 322($[M^+]$,3), 295(7),238(6),221(15),220(6),178(24),161(13),160(53),147(37),121(28),85 (45),84(18),58(75); HRms calcd for $C_{18}H_{26}O_5$ 322.1779, found 322.1778. *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.96; H, 8.13. Found: C, 66.89; H, 8.08.

(*S*)-3-(Tetrahydro-2*H*-pyranyloxy)-2-(*p*-methoxybenzyl)propanol (17). A mixture of **16** (3.0 g, 9.31 mmol) and K_2CO_3 (0.9 g, 6.65 mmol) in $MeOH/H_2O$ (85%, 100 ml) was stirred at room temperature for 1.5 h. After evaporation of the solvent, the residual mixture was treated with water and CH_2Cl_2. The organic layer was washed with water, dried and evaportaed to give crude **17** (2.4 g), which was chromatographed on a silica gel column (130 g), hexane/AcOEt (1:1), to give the pure sample (2.24 g, 82%) as a colorless oil; $[\alpha]^{28}_{D}$ -16.7° (c=2.8, $CHCl_3$); ^1H nmr δ 7.10 (1H, d, J = 8.8 Hz), 7.09 (1H, d, J = 8.8 Hz), 6.82 (2H, d, J = 8.8 Hz), 4.55-4.52 (1H, m), 3.90-3.82 (2H, m), 3.78 (3H, s), 3.77-3.60 (2H, m), 3.54-3.48 (1.5H, m), 3.38 (0.5H, dd, J = 6.0, 9.6 Hz), 2.74 (1H, br s), 2.65-2.49 (2H, m), 2.13-2.02 (1H, m), 1.83-1.67 (2H, m), 1.60-1.50 (4H, m); ir(neat) 3441(OH),2941,2870,1613,1513,1247,1179,1138,1122,1032,809 cm^{-1}; ms (EI) *m/z* (rel intensity) 280($[M^+]$,7),196(5),178(12),160(6),147(28),122 (11),121(100),85(21); HRms calcd for $C_{16}H_{24}O_4$ 280.1673, found 280.1681. *Anal.* Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.87; H, 8.93.

(*S*)-3-(*p*-Methoxybenzyl)butyrolactone ((*S*)-(-)-6). Compound (**17**) (2.0 g, 7.13 mmol) was converted to the mesylate by stirring with mesyl chloride (1.88 g, 16.4 mmol), 4-dimethylaminopyridine (200 mg, 1.64 mmol) and pyridine (6.5 ml, 81.3 mmol) in CH_2Cl_2 (100 ml) for 15 h in 88% yield. The mesylate (2.26 g, 6.3 mmol) was heated with KCN (660 mg, 10.1 mmol) in DMSO (37 ml) at 80-90℃ for 24 h to give (*S*)-4-(2-tetrahydro-2*H*-pyranyloxy)-3-(*p*-methoxybenzyl)butyronitrile (**18**) (1.57 g, 86%). A mixture of **18** (1.39 g, 4.8 mmol) and TsOH (1.0 g, 5.3 mmol) in MeOH (70 ml) was stirred at room temperature for 1.5 h. After evaporation of the methanol, the residual syrup was treated with water (50 ml) and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ solution and water, and dried. After evaporation of the solvent, the residual oil was distilled *in vacuo* to afford 0.96 g (97%) of (*S*)-4-hydroxy-3-(p-methoxybenzyl)butyronitrile, bp 160-170℃ at 0.05 mmHg; $[\alpha]^{25}_{D}$ +39.5° (c=1.76, $CHCl_3$); ^1H nmr δ 7.10 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 3.79 (3H, s), 3.73 (1H, dt, J = 4.4, 10.8 Hz), 3.60 (1H, ddd, J = 4.8, 6.8, 10.8

Hz), 2.74 (1H, dd, J = 7.2, 14.0 Hz), 2.61 (1H, dd, J = 8.0, 14.0 Hz), 2.46 (1H, dd, J = 5.6, 17.0 Hz), 2.37 (1H, dd, J = 6.0, 17.0 Hz), 2.15 (1H, m), 1.92 (1H, dd, J = 4.4, 4.8 Hz); ^{13}C nmr δ 158.3, 130.2, 129.9(C×2), 118.6, 114.1(C×2), 63.4, 55.2, 39.8, 35.4, 18.3; ir(neat) 3452 (br OH), 2933, 2838, 2249 (CN), 1613, 1414, 1248, 1180, 1036, 839 cm^{-1}; ms (EI) *m/z* (rel intensity) 205 ([M+], 100), 147 (18), 134 (22), 122 (91), 121 (100), 103 (19), 91 (54), 78 (53), 77 (74); HRms calcd for $C_{12}H_{15}NO_2$ 205.1102, found 205.1100. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.96; H, 7.27; N, 6.77.

A mixture of the (*S*)-butyronitrile (0.96 g, 4.67 mmol) in aqueous NaOH solution (2M, 23.4 ml, 46.7 mmol) was stirred and refluxed for 3.5 h. After being cooled, the mixture was acidified with 10% HCl and extracted with $CHCl_3$. The residual oil (0.75 g) from the chloroform extract was chromatographed on a silica gel column (70 g), hexane/ethyl acetate (1:1) to give (*S*)-(−)-**6** (0.77 g, 80%) as a colorless oil; bp 135-140℃ (bath temperature) at 0.3 mmHg; $[\alpha]^{25}_D$ -5.8° (c=2.18, $CHCl_3$). The ^{1}H nmr, ^{13}C nmr, ir and mass spectra were identical with those of (*R*)-(+)-**6**.

(1*R*,6*R*)-(−)-1,4-Dimethyl-10-methoxy-2,3,4,5,6,7-hexahydro-1,6-methano-1H-benzazonine ((−)-11). (*S*)-(−)-**6** (1.7 g, 8.3 mmol) was derived to *O*-methyleptazocine ((−)-**11**) by the same procedure used for the preparation of (+)-eptazocine from (*R*)-(+)-**6**, in 24 % over-all yield. $[\alpha]^{27}_D$ -14.6° (c=3.42, $CHCl_3$)(lit.,[19] $[\alpha]^{20}_D$ -16.9° (c=1.0, EtOH)). The ^{1}H nmr and ir spectra were identical with those of (*R*)-**11** and of the sample obtained by optical resolution of racemic **11**.[19]

Eptazocine ((−)-1). (−)-**11** (171 mg, 0.7 mmol) was refluxed with HBr (aqueous 47%, 5 ml) to give 198 mg (90 %) of (−)-**1**·**HBr**; mp 263-267℃ (lit.,[2a] mp 266-270℃); $[\alpha]^{28}_D$ -20.0° (c=1.9, EtOH) (lit.,[2a] $[\alpha]^{20}_D$ -15.0 (c=5.0, H_2O)).

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10. The ee of (+)- and (-)-**6** was determined by DAICEL CHIRALCEL AS, hexane/2-propanol (9:1).
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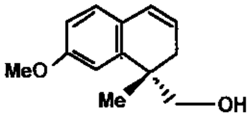
12. When we started this investigation, it was expected that (-)-eptazocine would be obtained from *R*-(+)-lactone (*R*-(+)-**6**) through our synthetic route, because the absolute configuration of (-)-eptazocine was correlated to that of (-)-1-hydroxymethyl-1-methyl-7-methoxy-1,2-dihydronaphthalene ((-)-**A**) which had been assigned by Shibasaki[4a] to be *R* based on what had been reported eariler by Takano.[3b] In addition, the absolute configuration of the monoacetae (*R*-(+)-**4**) and, consequently, that of the lactone (*R*-(+)-**6**), should be same with those of many (*R*)-3-hydroxy-2-arylmethylpropyl acetates whose absolute configurations were established by numerous examples of asymmetric synthesis of natural compounds.[8,9] Our discrepant result, however, was clarified by Meyers' report[6] in which they described the absolute configuration of (-)-A to be *S* and commented that Shibasaki had corrected their error in the absolute configuration of (-)-A from *R* to *S*.[4b] Thus, the absolute configuration of eptazocine ((-)-**1**) has been correctly established to be 1*R*, 6*R*.



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