Studies on Agents with Vasodilator and β-Blocking Activities. III.[1] Synthesis and Activity of Optical Isomers of TZC-1370

Toshimi SEKI,* Takayuki TAKEZAKI, Rikio OHUCHI, Morinobu SAITOH, Tsutomu ISHIMORI, and Kikuo YASUDA

Research Division, Teikoku Hormone Manufacturing Co., Ltd., 1604 Shimosakunobe Takatsu-ku, Kawasaki, Kanagawa 213, Japan. Received April 11, 1995; accepted June 20, 1995

Optical isomers of TZC-1370 (1) were prepared from (*R*)- and (*S*)-1-(2-chlorophenoxy)-2,3-epoxypropane. When given intravenously to anesthetized rats, the (*S*)-isomer was about 40 times more potent in terms of β-blocking activity than the (*R*)-isomer, while their hypotensive activities were equipotent with that of the racemic compound, TZC-1370.

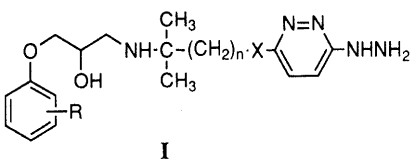
Key words phenoxypropanolamine; optical isomer; antihypertensive agent; hydrazinopyridazine; β-blocking activity; hypotensive activity

Most vasodilators cause tachycardia. To overcome this unfavorable effect, we have tried to hybridize a vasodilator with a β-blocker. In our previous study, a series of novel aryloxypropanolamine derivatives (I) having a hydrazinopyridazinyl moiety on the *N*-alkyl group was synthesized in the hope that they would exhibit both hypotensive and β-blocking activities. TZC-1370 (**1**) was revealed to have the most potent dual activities among them (equipotent hypotensive activity to hydralazine and 2.7-fold more potent β-blocking activity than propranolol) and was selected for further study as a candidate antihypertensive agent.[1] In the present study, the two optical isomers of **1** were synthesized to investigate their dual activities.

Chemistry

Several β-blockers have been resolved into their optical isomers by the use of a chiral acid such as *O*,*O*′-di-*p*-toluoyltartaric acid.[2] The resolution of **1** by this method, however, could not be achieved, probably due to the instability of the hydrazino group on the pyridazine ring. Thus, enantioselective synthesis of **1** was attempted using chiral C_3 building blocks, namely chiral glycidyl arenesulfonate (**4**) or glycerol-1,2-acetonide.

Various enantioselective syntheses of the aryloxypropanolamine β-blockers have been developed, for instance, using chiral glycerol-1,2-acetonide (**7**)[3] or chiral glycidol.[4] High optical purity was obtained with glycidyl arenesulfonate (**2a**)[5] or epichlorohydrin (**2b**).[6] A phenoxide anion, however, has access to the chiral reagent (**2**) either at C-1 or C-3. The attack at C-1 causes direct displacement of X (path a), and that at C-3 causes epoxide ring opening, followed by internal displacement of the leaving group X (path b) as shown in Chart 2. Consequently, path b results in the opposite configuration to path a.[5,7]



I

1 (TZC-1370): R=2-Cl, n=1, X=O

Chart 1

We therefore synthesized the optical isomers of TZC-1370 (**1**) as follows. The (*R*)- and (*S*)-glycidyl ethers (**6**), key intermediates for the synthesis of optically active **1**, were prepared by two different methods, as shown in Chart 3.

Reaction of (*S*)-glycidyl 3-nitrobenzenesulfonate [(*S*)-**4**],[5] an excellent regioselective agent, with 2-chlorophenol (**5**) in the presence of equimolar sodium hydride afforded the (*S*)-glycidyl ether [(*S*)-**6**] through direct displacement of the arenesulfonate group with the phenoxide anion (method A). The optical purity of (*S*)-**6** was determined as 96.5% enantiomeric excess (ee) on the basis of high-performance liquid chromatography (HPLC) using a chiral stationary phase (Fig. 1a). This result indicates that a competitive attack of the phenoxide anion on the epoxide hardly occurred, as was expected from the result of Klunder *et al.*[5]

In order to assign the configuration at the C-2 position of the glycidyl ether (**6**) obtained by method A, an alternative classical method using chiral glycerol-1,2-acetonide (**7**) as described below was carried out. Compound (*R*)-**7** was prepared from L-tartaric acid according to the literature.[8] Tosylation of (*R*)-**7** gave (*S*)-tosyloxy-1,2-propanediol acetonide [(*S*)-**8**]. Compound (*S*)-**8** was treated with phenol (**5**) in the presence of sodium hydride to afford the phenoxy compound [(*R*)-**9**]. Deprotection of the ketal group of (*R*)-**9** gave the diol [(*S*)-**10**]. Selective monotosylation of the primary hydroxy group of (*S*)-**10** with *p*-toluenesulfonyl chloride

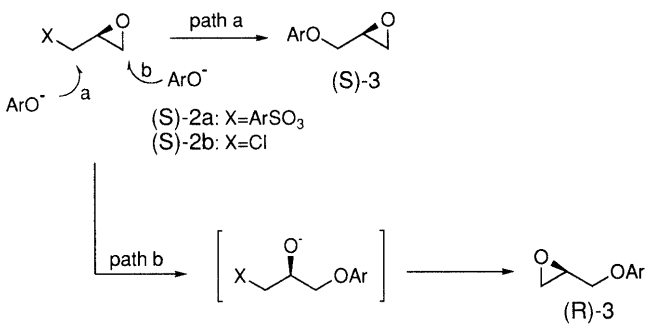


Chart 2

* To whom correspondence should be addressed.

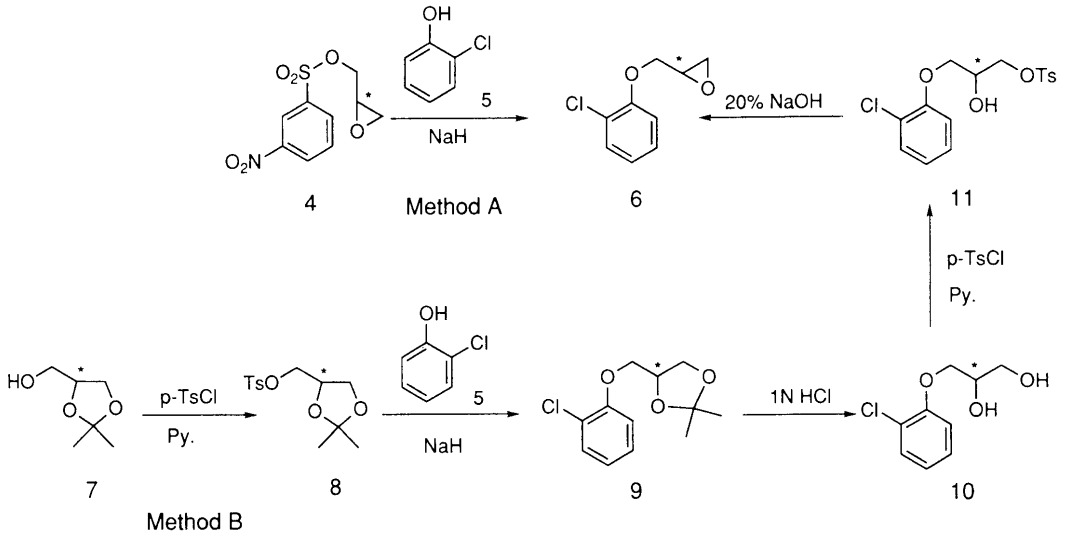


Chart 3

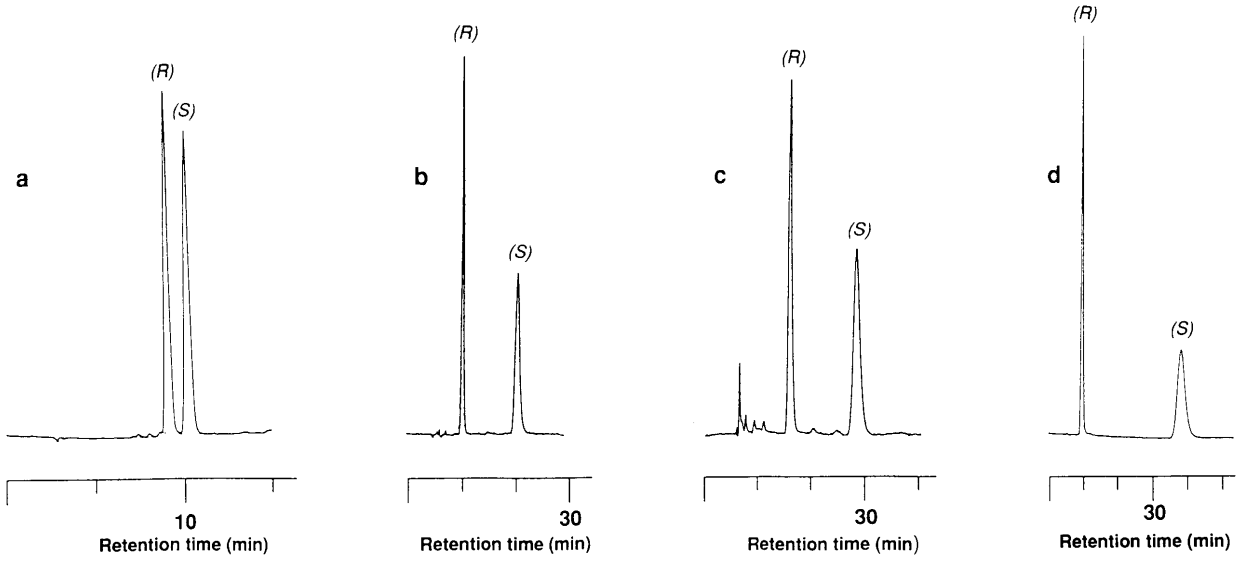


Fig. 1. Elution Patterns of (a) (±)-Glycidyl Ether (**6**), (b) (±)-Chloropyridazine (**13**), (c) (±)-Methylthiopyridazine (**15**) and (±)-Hydrazonopyridazine (**16**)

Chromatographic conditions were as described in Experimental.

in pyridine, followed by ring closure with sodium hydroxide gave the glycidyl ether of *S*-configuration [(*S*)-**6**] with 89.2% ee (method B). The low optical purity of (*S*)-**6** was probably due to partial racemization of the starting material [(*R*)-**7**] itself, as reported by Baldwin *et al.*[6] A single recrystallization from ethanol gave a high enantiomeric excess of (*S*)-**6**, as was expected from the finding of Klunder *et al.* that optical purification could be attained if an enantiomer-enriched form had a melting point higher than that of its racemic form.[5]

In the same way, the (*R*)-glycidyl ether [(*R*)-**6**] was derived from (*R*)-glycidyl arenesulfonate [(*R*)-**4**] or (*S*)-glycerol acetonide [(*S*)-**7**] with 92.7% ee or 89.2% ee, respectively. Compound (*S*)-**7** was synthesized from D-mannitol according to the literature.[3,9] Recrystallization of (*R*)-**6** from ethanol similarly improved its optical purity (98.8% ee). Since the configuration of the starting material [(*S*)-**7**] in method B would be retained as in the case of the above-mentioned (*S*)-**6**, the configuration at the C-2 position was assigned as *R*. On HPLC, the major peak of (*R*)-**6** appeared at 9.4 min and the minor peak of the (*S*)-isomer appeared at 10.6 min.

Conversion of each chiral glycidyl ether (**6**) to the corresponding optical isomer of **1** is shown in Chart 4. The retention of steric configuration in the intermediates (**13**, **14**) and the final compounds (**1**) was confirmed by HPLC using a chiral stationary phase (Fig. 1b—d). Ring opening of the (*S*)-glycidyl ether [(*S*)-**6**] with the amine (**12**), followed by treatment with hydrogen chloride, gave the (*S*)-propanolamine [(*S*)-**13**] as a crystalline hydrochloride with 99.4% ee. The chloride [(*S*)-**13**] was treated with thiourea, followed by hydrolysis of the thiuronium salt with sodium carbonate to the thioxo derivative [(*S*)-**14**]. Compound **14** was treated with iodomethane to give the *S*-methyl compound (**15**), whose optical purity was 98.8% ee based upon HPLC. Reaction

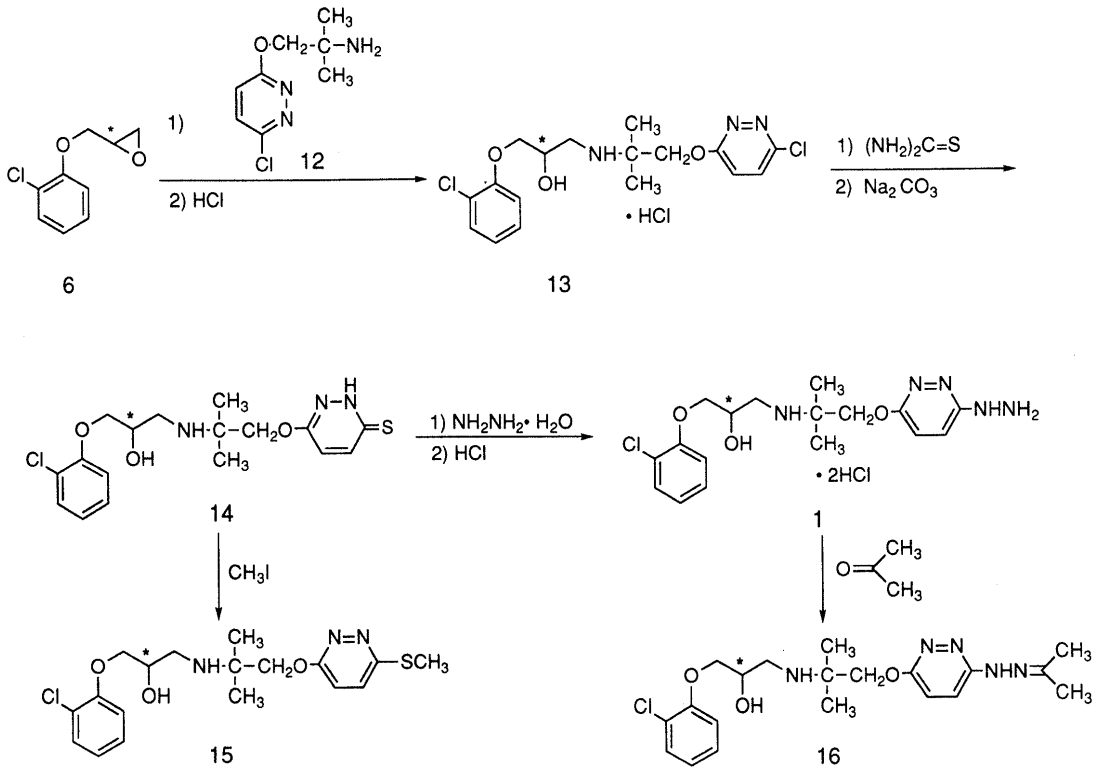


Chart 4

of (*S*)-**14** with excess hydrazine hydrate gave the desired hydrazino compound [(*S*)-**1**], which was then converted to the isopropylidenehydrazone (**16**). HPLC indicated an optical purity of 98.8% ee. Thus, the (*S*)-hydrazino compound [(*S*)-**1**] was obtained from the (*S*)-glycidyl ether [(*S*)-**6**] with no detectable racemization, as was expected.

Similarly, synthesis of (*R*)-**1** (98.6% ee) was achieved through the reaction of the (*R*)-glycidyl ether [(*R*)-**6**] with the amine (**12**).

Pharmacology

The hypotensive and β-blocking activities of racemic **1** and its optical isomers were evaluated in anesthetized rats using the procedures previously described.[10] The results are shown in Table 1.

It is known that *S* configuration at the C-2 position in an aryloxypropanolamine is essential for β-blocking activity.[11] In accordance with this, we found that the β_1-blocking activity of the (*S*)-isomer [(*S*)-**1**] was about 40 times more potent than that of the (*R*)-isomer. On the other hand, as regards hypotensive activity, each optical isomer had the same potency as the racemic compound. There seemed to be no significant contribution of the configuration at the asymmetric carbon to the hypotensive activity.

In our previous study, the more potent was the β-blocking activity, the more potent was the hypotensive activity.[1] However, in the case of the (*R*)-isomer of **1**, irrespective of its low β-blocking activity, the hypotensive activity was equal to that of the (*S*)-isomer.

In a study relating to the vasodilator action of β-blockers in our laboratory,[12] it was recognized that the vasodilation caused by alprenolol was due to a direct action on vascular smooth muscle and the potency of the (*R*)-isomer was equal to that of the racemic compound. These results imply that the vasodilation caused by alprenolol was apparently not affected by the β-blocking activity. Furthermore, in an experiment on the vasodilator activity of a number of racemic β-blockers,[13] it was observed that their vasodilating potencies seemed to vary in proportion to their β-blocking activities. We consider that the hypotensive activity of **1** may be mediated not by the β-blocking activity, but by direct vasodilator activity, probably involving the hydrazinopyridazinyloxy group.

Table 1. Pharmacological Activities of TZC-1370 (**1**) and Its Optical Isomers

Compound No.	β_1-Blocking activity[a]	β_2-Blocking activity[b]	Hypotensive activity[c]
	Mean ± S.E. (*n*)	Mean ± S.E. (*n*)	Mean (*n*)
Racemic **1**	7.5 ± 2.10 (3)	−3.9 ± 5.78 (3)	0.55 (3)
(*S*)-**1**	7.8 ± 2.64 (5)	18.0 ± 5.86 (5)	0.55 (3)
(*R*)-**1**	300 (2)	60 (2)	0.55 (3)

Each compound was injected intravenously into anesthetized rats. β-Blocking activities were evaluated as antagonism of isoproterenol (0.1 μg/kg i.v.)-induced tachycardia and hypotension. *a*) Dose (μg/kg i.v.) giving 50% inhibition of tachycardia. *b*) Inhibition (%) of hypotension by **1** at a dose causing 50% inhibition of tachycardia induced by isoproterenol. *c*) Dose (mg/kg i.v.) causing 40 mmHg hypotension. *n*, number of experiments.

Experimental

Melting points were determined with a Mettler FP-2 melting point apparatus and are uncorrected. NMR spectra were taken at 60 MHz on a Hitachi R-20A spectrometer with tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. Mass spectra were determined with a Shimadzu GCMS-QP 1000 instrument. Elemental analysis results were within ±0.3% of the theo-

retical values. Specific rotations were measured on a JASCO DPI-140 digital polarimeter. HPLC was performed on a Hitachi HPLC instrument (L-6000 pump, L-3000 photo diode array detector and D-2500 chromato-integrator) using the following conditions unless otherwise stated: mobile phase, *n*-hexane–iso-PrOH–Et_2NH (500 : 500 : 1); flow rate, 0.5 ml/min; detector, UV absorption at 280 nm; room temperature.

Determination of Optical Purity Analysis of optical purities in these experiments was carried out by HPLC using a chiral stationary phase (Chiralcel OD, Daicel Chemical Industry) and optical purity was calculated from the peak area ratio between (*R*)- and (*S*)-isomer.

(*S*)-(+)-1-(2-Chlorophenoxy)-2,3-epoxypropane [(*S*)-6] Method A: A solution of **5** (1.43 g, 11.1 mmol) in dry *N*,*N*-dimethylformamide (DMF) (5 ml) was added dropwise to an ice-cooled mixture of 60% NaH (468 mg, 11.7 mmol) and dry DMF (15 ml) with stirring. Stirring was continued for 30 min, then (*S*)-**4**[14] (2.59 g, 10 mmol) was added to the mixture. The whole was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was dissolved in AcOEt. The solution was washed with 5% NaOH. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give (*S*)-**6** (1.755 g, 95.1%) as colorless crystals. HPLC t_R 10.6 min, 96.5% ee [mobile phase, *n*-hexane–iso-PrOH (95 : 5); flow rate, 1.0 ml/min; detector, UV 270 nm].

Method B: (*R*)-**7** was derived from L-tartaric acid according to the literature method,[8] bp 101—103 °C (35 mmHg). $[\alpha]_D^{20}$ −11.2° (*c* = 1.00, MeOH). [lit.[8] bp 110—130 °C (bath temp.) (2 mmHg). $[\alpha]_D^{20}$ −11.0° (*c* = 1.72, MeOH)].

p-TsCl (8.8 g, 46.2 mmol) was added in portions to a solution of (*R*)-**7** (5.0 g, 37.9 mmol) in pyridine (10 ml) with stirring at ice-cooling. Stirring was continued overnight, then Et_2O was added to the reaction mixture. The whole was washed with H_2O and 1 N HCl. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give (*S*)-**8** (10.71 g, 98.9%) as a colorless oily material.

A solution of **5** (6.69 g, 52.1 mmol) in dry DMF (15 ml) was added dropwise to an ice-cooled mixture of 60% NaH in oil (2.27 g, 56.8 mmol) and dry DMF (35 ml) with stirring. Stirring was continued for 30 min, then a solution of (*S*)-**8** (13.6 g, 47.6 mmol) in dry DMF (15 ml) was added dropwise. The whole was stirred for 3 h at 100 °C, poured into ice-water and extracted with Et_2O (100 ml × 3). The combined organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by distillation to give (*R*)-**9** (10.63 g, 92.4%) as a colorless oil, bp 117—120 °C (0.8 mmHg). NMR ($CDCl_3$) δ: 1.39 (3H, s), 1.45 (3H, s), 3.75—4.75 (5H, m), 6.70—7.50 (4H, m). $[\alpha]_D^{20}$ −26.1° (*c* = 1.00, EtOH).

A mixture of (*R*)-**9** (10.6 g, 43.7 mmol) and 1 N HCl (106 ml) was stirred for 1 h at 70 °C. After cooling, the resulting precipitates were collected by filtration to give (*S*)-**10** (6.95 g, 78.5%) as colorless crystals, mp 87—89 °C. NMR ($CDCl_3$) δ: 2.60 (1H, br s), 3.15 (1H, br s), 3.50—4.35 (5H, m), 6.70—7.50 (4H, m). $[\alpha]_D^{20}$ −3.0° (*c* = 1.00, MeOH).

A solution of *p*-TsCl (7 g, 36.7 mmol) in dry C_6H_6 (50 ml) was added dropwise to an ice-cooled solution of (*S*)-**10** (6.85 g, 33.8 mmol) in dry pyridine (20 ml) with stirring. Stirring was continued for 65 h at room temperature, then the reaction mixture was diluted with C_6H_6 (200 ml). The whole was washed with 1 N HCl (120 ml × 3) and H_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (*R*)-**11** (9.63 g, 80.3%) as a colorless oil. NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.80—4.43 (6H, m), 6.70—7.50 (6H, m), 7.77 (2H, d, *J* = 9 Hz). $[\alpha]_D^{20}$ −18.6° (*c* = 1.00, EtOH).

A 20% NaOH solution (3 ml) was added dropwise to a solution of (*R*)-**11** (3.0 g, 8.4 mmol) in dimethyl sulfoxide (6 ml) with stirring at room temperature. Stirring was continued for 1 h at room temperature, then the whole was poured into ice-water and extracted with Et_2O. The organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by distillation to give (*S*)-**6** (987 mg, 63.6%) as colorless crystals. bp 102—104 °C (0.6 mmHg). HPLC conditions were as described above. 89.2% ee. Recrystallization from EtOH gave optically pure (*S*)-**6** as colorless needles, mp 41—43 °C. NMR ($CDCl_3$) δ: 2.70—3.00 (2H, m), 3.20—3.55 (1H, m), 3.85—4.45 (2H, m), 6.70—7.50 (4H, m). MS *m/z*: 184 (M^+), 128 (base peak). $[\alpha]_D^{20}$ +10.3° (*c* = 1.00, EtOH). *Anal.* Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91. Found: C, 58.26; H, 4.83. HPLC t_R 10.6 min, 98.4% ee.

3-(2-Amino-2-methylpropoxy)-6-chloropyridazine (12) According to the method described previously,[1] **12** was obtained from 3,6-dichloropyridazine and 2-amino-2-methyl-1-propanol in the presence of NaH.

(*S*)-(−)-1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-chloro-6-pyridazinyloxy)ethylamino]-2-propanol Hydrochloride [(*S*)-13] A solution of (*S*)-**6** (800 mg, 4.31 mmol) and **12** (1.05 g, 5.21 mmol) in *tert*-BuOH (20 ml) was stirred overnight at 60 °C. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give (*S*)-**13** (1.56 g) as a colorless oily free base. The free base was treated with an excess of 20% methanolic HCl and the solvent was removed under reduced pressure. The residue was dissolved in acetone and kept overnight in a refrigerator. The resulting precipitates were collected by filtration to give (*S*)-**13** (1.322 g, 72.1%) as a colorless hydrochloride, mp 135—137 °C. NMR (CD_3OD) δ: 1.58 (6H, s), 3.27—3.60 (2H, m), 4.00—4.55 (3H, m), 4.64 (2H, s), 6.80—7.60 (4H, m), 7.29 (1H, d, *J* = 9 Hz), 7.69 (1H, d, *J* = 9 Hz). MS *m/z*: 386 ($M^+ + 1$), 242 (base peak). $[\alpha]_D^{26}$ −20.6° (*c* = 1.00, MeOH). *Anal.* Calcd for $C_{17}H_{21}Cl_2N_3O_3 \cdot HCl$: C, 48.30; H, 5.25; N, 9.94. Found: C, 48.55; H, 5.31; N, 9.91. HPLC t_R 19.8 min, 99.4% ee.

(*S*)-(−)-1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-[3(2*H*)-thioxo-6-pyridazinyloxy]ethylamino]-2-propanol [(*S*)-14] A solution of (*S*)-**13** (1.0 g, 2.37 mmol) and thiourea (720 mg, 9.46 mmol) in EtOH (10 ml) was stirred at 50 °C for 3 h. The solvent was removed under reduced pressure. Then, 5% Na_2CO_3 was added to the residue. The whole was stirred for 3 h at room temperature. The resulting precipitates were collected by filtration and recrystallized from $CHCl_3$–C_6H_6 to give (*S*)-**14** (388 mg, 85.5%) as yellow crystals, mp 131—133 °C. NMR ($CDCl_3$) δ: 1.24 (6H, s), 2.86—3.10 (2H, m), 4.10 (5H, br s), 6.02 (3H, s), 6.73 (1H, d, *J* = 9 Hz), 6.80—7.50 (4H, m), 7.54 (1H, d, *J* = 9 Hz). MS *m/z*: 383 (M^+), 242 (base peak). $[\alpha]_D^{26}$ −14.9° (*c* = 1.00, MeOH). *Anal.* Calcd for $C_{17}H_{22}ClN_3O_3S$: C, 53.18; H, 5.78; N, 10.95. Found: C, 53.21; H, 5.94; N, 11.08. (*S*)-**14** (10 μmol) was added to a solution of 0.1% (v/v) CH_3I in EtOH (1.25 ml, 20 μmol) and the whole was stirred at room temperature for 48 h. After removal of the solvent, the residue was purified by preparative thin-layer chromatography to give **15**, which was then subjected to HPLC. t_R 30.2 min, 98.8% ee.

(*S*)-(−)-1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-hydrazino-6-pyridazinyloxy)ethylamino]-2-propanol Dihydrochloride [(*S*)-1] A solution of (*S*)-**14** (500 mg, 1.31 mmol) and hydrazine hydrate (2.5 ml) in EtOH (5 ml) was stirred for 3 h at reflux temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed twice with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in EtOH and treated with an excess of 20% ethanolic HCl. The solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give (*S*)-**1** (372 mg, 62.5%) as colorless crystals, mp 174—176 °C. NMR (D_2O) δ: 1.58 (6H, s), 3.33—3.60 (2H, m), 4.10—4.60 (3H, m), 4.46 (2H, s), 6.85—7.53 (4H, m), 7.22 (2H, s). MS *m/z*: 381 (M^+), 242 (base peak). $[\alpha]_D^{26}$ −17.6° (*c* = 1.00, MeOH). *Anal.* Calcd for $C_{17}H_{24}ClN_5O_3 \cdot 2HCl$: C, 44.89; H, 5.76; N, 15.40. Found: C, 44.79; H, 5.84; N, 15.68.

A solution of (*S*)-**1** (10 μmol) in acetone (1 ml) and MeOH (1 ml) was stirred for 2 h at room temperature to give **16** and the solution was directly subjected to HPLC without purification. t_R 37.0 min, 98.8% ee.

(*R*)-(−)-1-(2-Chlorophenoxy)-2,3-epoxypropane [(*R*)-6] Method A: In the same manner as described for (*S*)-**6**, (*R*)-**6** (331 mg, 99.7%) was prepared from (*R*)-glycidyl arenesulfonate [(*R*)-**4**][14] (467 mg, 1.8 mmol) and phenol (**5**) (257 mg, 2.0 mmol). HPLC t_R 9.4 min, 92.7% ee.

Method B: (*S*)-**7** was derived from D-mannitol according to the literature,[9] bp 93—95 °C (23 mmHg). $[\alpha]_D^{20}$ +11.5° (*c* = 1.00, MeOH). [lit.[9] bp 86—87 °C (16 mmHg). $[\alpha]_D$ +11.4° (*c* = 5.29, MeOH)].

In the same way as described for the synthesis of (*S*)-**6**, (*S*)-**7** was converted to the (*R*)-glycidyl ether [(*R*)-**6**]. Overall yield; 37.0% (89.2% ee). Recrystallization from EtOH gave optically pure (*R*)-**6** as colorless needles, mp 42—43 °C. NMR ($CDCl_3$) δ: 2.70—3.00 (2H, m), 3.20—3.55 (1H, m), 3.85—4.45 (2H, m), 6.70—7.50 (4H, m). $[\alpha]_D^{22}$ −10.0° (*c* = 1.00, EtOH). *Anal.* Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91. Found: C, 58.30; H, 4.83. HPLC t_R 9.4 min, 98.8% ee.

(*R*)-(+)-1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-chloro-6-pyridazinyloxy)ethylamino]-2-propanol Hydrochloride [(*R*)-13] In the same manner as described for (*S*)-**13**, (*R*)-**6** (800 mg, 4.34 mmol) was treated with **12** (1.05 g, 5.21 mmol) to give (*R*)-**13** (1.168 g, 63.7%) as colorless crystals, mp 136—138 °C. $[\alpha]_D^{26}$ +20.6° (*c* = 1.00, MeOH). *Anal.* Calcd for $C_{17}H_{21}Cl_2N_3O_3 \cdot HCl$: C, 48.30; H, 5.25; N, 9.94. Found: C, 48.04;

H, 5.18; N, 9.91. HPLC t_R 10.4 min, 99.1% ee. The NMR and MS spectra of (*R*)-**13** were identical with those of (*S*)-**13**.

(*R*)-(+)-1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-[3(2*H*)-thioxo-6-pyridazinyloxy]ethylamino]-2-propanol [(*R*)-14] In the same manner as described for (*S*)-**14**, (*R*)-**13** (1.014 g, 2.39 mmol) was treated with thiourea (720 mg, 9.46 mmol) to give (*R*)-**14** (804 mg, 87.4%) as yellow crystals, mp 131—133 °C. $[\alpha]_D^{26}$ +14.9° (*c*=1.00, MeOH). *Anal.* Calcd for $C_{17}H_{22}ClN_3O_3S$: C, 53.18; H, 5.78; N, 10.95. Found: C, 53.41; H, 5.88; N, 10.88. HPLC t_R 16.6 min, 98.8% ee. The NMR and MS spectra of (*R*)-**14** were identical with those of (*S*)-**14**.

(*R*)-(+)-1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-hydrazino-6-pyridazinyloxy)ethylamino]-2-propanol Dihydrochloride [(*R*)-1] In the same manner as described for (*S*)-**1**, (*R*)-**14** (500 mg, 1.31 mmol) was treated with hydrazine hydrate (2.5 ml) to give (*R*)-**1** (335 mg, 56.7%) as colorless crystals, mp 174—177 °C. $[\alpha]_D^{26}$ +17.3° (*c*=1.00, MeOH). *Anal.* Calcd for $C_{17}H_{24}ClN_5O_3 \cdot 2HCl$: C, 44.89; H, 5.76; N, 15.40. Found: C, 44.85; H, 5.87; N, 15.69. HPLC t_R 9.8 min, 98.6% ee. The NMR and MS spectra of (*R*)-**1** were identical with those of (*S*)-**1**.

1-(2-Chlorophenoxy)-3-[1,1-dimethyl-2-(3-methylthio-6-pyridazinyloxy)ethylamino]-2-propanol (15) A solution of **14** (100 mg, 0.26 mmol) and CH_3I (74 mg, 0.52 mmol) in EtOH (3 ml) was stirred for 24 h at room temperature, then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give **15** (96 mg, 92.3%) as a colorless oil. NMR ($CDCl_3$) δ: 1.22 (6H, s), 2.68 (3H, s), 2.80—3.00 (2H, m), 4.03 (3H, br s), 4.32 (2H, s), 6.80—7.55 (4H, m), 6.78 (1H, d, *J*=9 Hz), 7.18 (1H, d, *J*=9 Hz). MS *m/z*: 397 (M^+), 242 (base peak). An analytical sample was purified as the oxalate, mp 163—165 °C. *Anal.* Calcd for $C_{18}H_{24}ClN_3O_3S \cdot 0.5\ (CO_2H)_2$: C, 51.52; H, 5.69; N, 9.49. Found: C, 51.33; H, 5.69; N, 9.50. By a similar method to that described for (±)-**15**, (*R*)- and (*S*)-**14** were treated with CH_3I to give the corresponding chiral **15**. The specific rotations and optical purities were follows: (*R*)-**15** $[\alpha]_D^{27}$ +12.1° (*c*=1.00, MeOH). HPLC t_R 16.6 min, 99.3% ee, (*S*)-**15** $[\alpha]_D^{27}$ −12.1° (*c*=1.00, MeOH). HPLC t_R 30.2 min, 100% ee.

References and Notes

1) Seki T., Takezaki T., Ohuchi R., Ohuyabu H., Tanimoto Y., Yamaguchi Y., Saitoh M., Ishimori T., Yasuda K., *Chem. Pharm. Bull.*, **43**, 247 (1995).
2) Howe R., Rao B. S., *J. Med. Chem.*, **11**, 1118 (1968); Itoh K., Igarashi T., Ikemoto M., Nagahara M., Nakanishi T., *Yakugaku Zasshi*, **98**, 297 (1978); Honma S., Ito T., Kambegawa A., *Chem. Pharm. Bull.*, **33**, 760 (1985).
3) Danilewicz J. C., Kemp J. E. G., *J. Med. Chem.*, **16**, 168 (1973); Nelson W. L., Wennerstrom J. E., Sankar S. R., *J. Org. Chem.*, **42**, 1006 (1977); Nelson W. L., Burke T. R., Jr., *ibid.*, **43**, 3641 (1978); Jung M. E., Shaw T. J., *J. Amer. Chem. Soc.*, **102**, 6304 (1980); Leclerc G., Amlaiky N., Rouot B., *Eur. J. Med. Chem.*, **17**, 69 (1982).
4) Klunder J. M., Ko S. Y., Sharpless K. B., *J. Org. Chem.*, **51**, 3710 (1986); Ko S. Y., Sharpless K. B., *ibid.*, **51**, 5413 (1986).
5) Klunder J. M., Onami T., Sharpless K. B., *J. Org. Chem.*, **54**, 1295 (1989).
6) Baldwin J. J., Raab A. W., Mensler K., Arison B. H., McClure D. E., *J. Org. Chem.*, **43**, 4876 (1978); Kasai N., Sakaguchi K., *Yuki Gosei Kagaku Kyokai Shi*, **51**, 388 (1993).
7) McClure D. E., Arison B. H., Baldwin J. J., *J. Amer. Chem. Soc.*, **101**, 3666 (1979).
8) Ohno M., Fujita K., Nakai H., Kobayashi S., Inoue K., Nojima S., *Chem. Pharm. Bull.*, **33**, 572 (1985).
9) Takano S., Goto E., Hirama M., Ogasawara K., *Heterocycles*, **16**, 381 (1981).
10) Seki T., Takezaki T., Ohuchi R., Ohuyabu H., Ishimori T., Yasuda K., *Chem. Pharm. Bull.*, **42**, 1609 (1994).
11) Dukes M., Smith L. H., *J. Med. Chem.*, **14**, 326 (1971); Price B. J., Roberts S. M., "Medicinal Chemistry, The Role of Organic Chemistry in Drug Research," Academic Press, 1985 Chapter 5; Ruffolo R. R., Jr., *Tetrahedron*, **47**, 9953 (1991).
12) Himori N., Izumi A., Ishimori T., *Eur. J. Pharmacol.*, **47**, 341 (1978).
13) *a*) Himori N., Ishimori T., Taira N., *Arch. Int. Pharmacodyn. Ther.*, **242**, 115 (1979); *b*) Himori N., *Jpn. J. Pharmacol.*, **30**, 255 (1980); *c*) Unpublished data.
14) (*R*)- and (*S*)-glycidyl 3-nitrobenzenesulfonate (**4**) were purchased from Nagase Fine Chemical Ltd. and their optical rotations were as follows: (*R*)-**4** $[\alpha]_D^{21}$ −22.8° (*c*=1.00, $CHCl_3$), (*S*)-**4** $[\alpha]_D^{26}$ +21.9° (*c*=1.00, $CHCl_3$), [lit.[4]) $[\alpha]_D$ +23.0° (*c*=2.14, $CHCl_3$)].