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Syntheses of the Optical Isomers of Befunolol·HCl and Their β-Adrenergic Blocking Activities[1)]

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The optical isomers of 2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran hydrochloride (**1a, b**) (befunolol·HCl) were synthesized by using (*S*)-1,2-*O*-isopropylideneglycerol (**4**) as a common chiral building block, and their β-adrenergic blocking activities were examined. The (*S*)-(−)-isomer **1b** was about 300 times more potent than the (*R*)-(+)-isomer **1a** on an atrial preparation.

Keywords——optical isomer; befunolol·HCl; (*S*)-1,2-*O*-isopropylideneglycerol; (*R*)-glycidol; β-adrenergic; atrial preparation; glaucoma; enantioselective; optical purity

Befunolol·HCl, 2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzofuran hydrochloride (**1a,b**), is a potent β-adrenergic blocking agent[2)] and is currently used for the treatment of glaucoma. Previously, we have reported the resolution of racemic **1a,b** and the absolute configuration of the enantiomers.[3)] In the present paper, we wish to report the syntheses of (*R*)-(+)-**1a** and (*S*)-(−)-**1b** and their antiisoproterenol activities on a guinea pig atrial preparation.

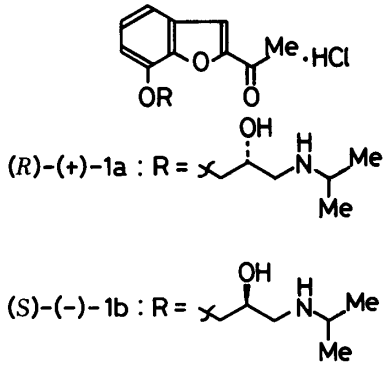

Chart 1

Syntheses of (*R*)-(+)- and (*S*)-(−)-Befunolol·HCl

In the enantioselective synthesis of aryloxypropanolamine-type β-blockers, (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**3**)[4)] or (*S*)-1,2-*O*-isopropylideneglycelol (**4**),[5)] derived from D-mannitol (**2**), is a useful chiral building block. Thus, a number of optical isomers of aryloxypropanolamine-type β-blockers have been synthesized by using **3** or **4**.[6)] In our present syntheses of (*R*)-(+)-**1a** and (*S*)-(−)-**1b**, we chose **4** as a common chiral building block and attempted to obtain the key intermediates, (*R*)-(−)- and (*S*)-(+)-2-acetyl-7-(2,3-epoxypropoxy)benzofurans (**6a, b**), using **4** and 2-acetyl-7-hydroxybenzofuran (**5**).

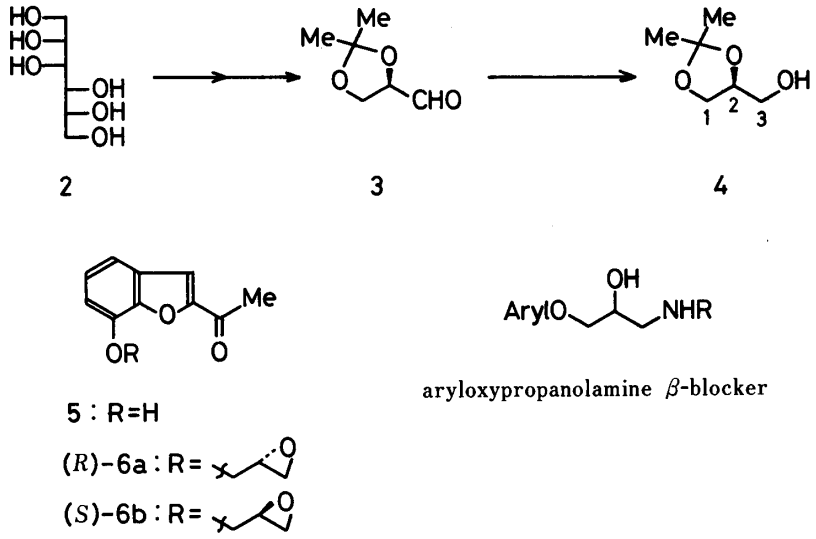

Chart 2

For the synthesis of (*R*)-(+)-**1a**, the phenolic compound **5** and isopropylamine have to be introduced at the C-3 and C-1 positions of **4**, respectively. Firstly, the redox dehydrative condensation (Mitsunobu reaction) of **4** and **5** using diethyl azodicarboxylate and triphenylphosphine[7] was attempted to give an 79.3% yield of (*S*)-(+)-2-acetyl-7-(2,2-dimethyl-1,3-dioxolane-4-ylmethoxy)benzofuran (**7**) which, on treatment with hydrochloric acid, was easily converted to (*R*)-(−)-2-acetyl-7-(2,3-dihydroxypropoxy)benzofuran (**8**). After the regioselective tosylation of the diol (**8**), the obtained (*S*)-(+)-2-acetyl-7-(2-hydroxy-3-tosyloxypropoxy)benzofuran (**9a**) was treated with sodium methoxide (NaOMe) in dry tetrahydrofuran (THF) to give (*R*)-(−)-2-acetyl-7-(2,3-epoxypropoxy)benzofuran (**6a**) in 84.7% yield. The reaction of **6a** with isopropylamine, followed by treatment with hydrochloric acid, gave (*R*)-(+)-befunolol·HCl (**1a**), mp 151 °C (from isopropyl alcohol), $[\alpha]_D$ +15.3° (c = 1.00, MeOH).

In the synthesis of (*S*)-(−)-**1b**, contrary to the above-mentioned case, the phenolic compound **5** and isopropylamine have to be introduced at the C-1 and C-3 positions of **4**, respectively. In order to obtain the enantiomer of the (*S*)-tosylate (**9a**), we tried to introduce

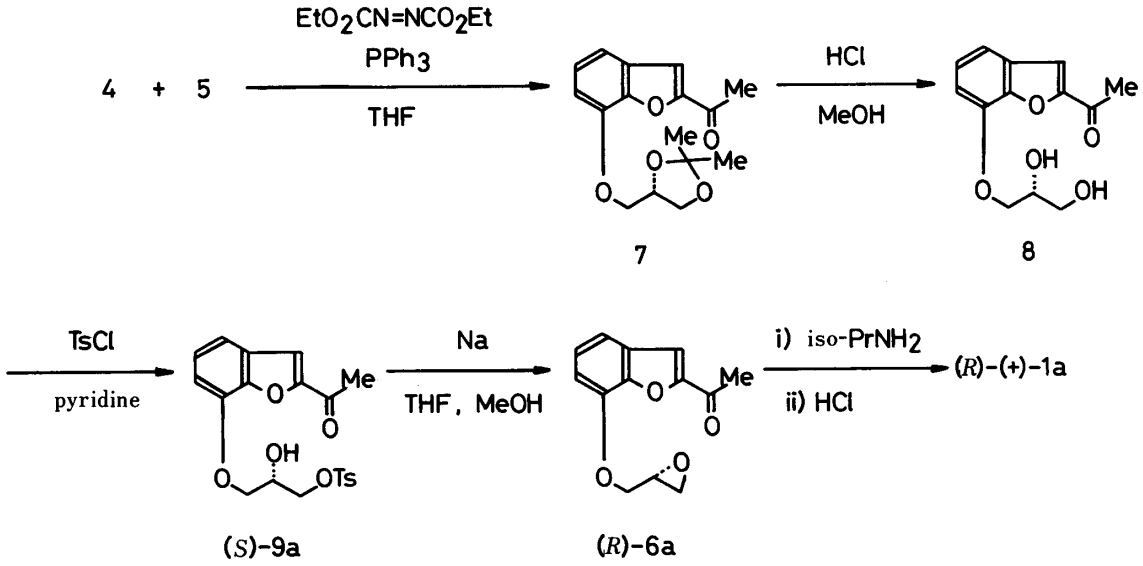

Chart 3

(*R*)-(−)-3-tosyloxy-1,2-propanediol (**10**),[8] readily obtained from **4** in two steps,[9] into **5** under Mitsunobu reaction condition. However, in this reaction, the desired compound (*R*)-**9b** was not produced but only **5** was recovered. We assumed that compound **10** reacted with itself under such condition. Therefore, the tosylate (**10**) was treated with NaOMe in anhydrous ether to give the (*R*)-glycidol (**11**),[9] which was condenced with **5** under Mitsunobu reaction condition. The reaction proceeded with high regioselectivity and gave the (*S*)-(+)-epoxide (**6b**) in 79.7% yield. The obtained (*S*)-(+)-**6b** was converted to (*S*)-(−)-befunolol·HCl (**1b**), mp 151—152 °C (from isopropyl alcohol), $[\alpha]_D$ −15.5° (c=1.00, MeOH), according to the above-mentioned procedure.

The optical purities of (*R*)-(+)-**1a** and (*S*)-(−)-**1b** thus obtained were determined by comparing the peak areas of the diastereoisomers derived from **1a**,**b** and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**12**)[10] which were separated by high-performance liquid chromatography. The calculated optical purities of the synthesized enantiomers are shown in Table I. Both of the synthesized enantiomers had >99% optical purities.

Antiisoproterenol Activity

The antagonistic activities against isoproterenol of (*R*)-(+)-**1a** and (*S*)-(−)-**1b** on an

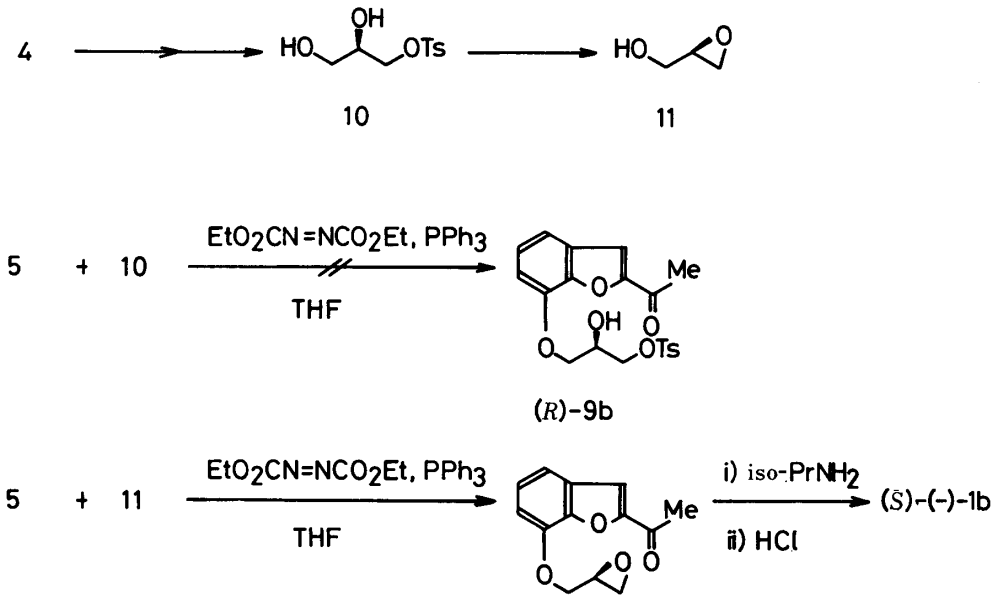

Chart 4

TABLE I. Optical Purities of Synthetic Befunolol·HCl (**1a**, **b**)

Compd.		$[\alpha]_D$ (c=1.00, MeOH)	Optical purity (%)[a]
(*R*)-(+)-**1a**	Synthesized compound	+15.3	99.1
	Resolved[b] compound	+15.0	98.2
(*S*)-(−)-**1b**	Synthesized compound	−15.5	99.4
	Resolved[b] compound	−15.0	98.2

a) See the experimental section. *b*) See reference 3.

TABLE II. pA_2-Values[a] of Befunolol·HCl (**1a**, **b**) on Isolated Guinea-Pig Atria

Compd.	pA_2 (mean±S.E. (n=6))	
	Atrial beats	Atrial contraction
(±)-**1a**, **b**	8.74±0.05	8.84±0.09
(*R*)-(+)-**1a**	6.51±0.05	6.66±0.06
(*S*)-(−)-**1b**	9.11±0.08	9.02±0.07

a) See reference 11.

isolated guinea pig atrial preparation are shown in Table II. The (*S*)-(−)-**1b** was shown to be about 300 times more potent than (*R*)-(+)-**1a** on the atrial preparation.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were taken with a Shimadzu IR 430 spectrometer; proton nuclear magnetic resonance (^{1}H-NMR) were recorded using tetramethylsilane as an internal standard on a JEOL PS-100 spectrometer at 100 MHz; mass spectra (MS) were recorded with a Hitachi M-52 spectrometer. Merck Kieselgel 60 and Merck Kieselgel $60F_{254}$ were employed for column chromatography and thin-layer chromatography (TLC), respectively.

(*S*)-(+)-2-Acetyl-7-(2,2-dimethyl-1,3-dioxolan-4-ylmethoxy)benzofuran (7)——Diethyl azodicarboxylate (11.3 g, 0.065 mol) was gradually added to a solution of (*S*)-1,2-*O*-isopropylideneglycerol (**4**) (8.6 g, 0.065 mol), 2-acetyl-7-hydroxybenzofuran (**5**) (8.8 g, 0.05 mol) and triphenylphosphine (17.0 g, 0.065 mol) in dry THF (80 ml), with stirring under a nitrogen atmosphere at 40 °C. After being stirred at room temperature for 2 h, the solution was concentrated under reduced pressure and ether (100 ml) was added to the resulting mixture. The separated crystals were filtered off and the filtrate was concentrated to give a residue, which was purified by column chromatography (SiO_2 300 g, benzene : AcOEt = 10 : 1 v/v) to give **7** in 79.3% yield (11.5 g). It was recrystallized from hexane–benzene (1 : 3 v/v) to furnish plates, mp 90 °C, $[\alpha]_D$ + 11.6° (c = 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ : 1.39 (3H, s), 1.41 (3H, s), 2.51 (3H, s), 3.75—4.17 (4H, m), 4.29—4.52 (1H, m), 6.69 (1H, dd, J = 8, 2 Hz), 6.85—7.06 (2H, m), 7.17 (1H, s). MS m/z: 290 (M^+), 275, 233, 215, 176.

(*R*)-(−)-2-Acetyl-7-(2,3-dihydroxypropoxy)benzofuran (8)——A solution of **7** (14.5 g, 0.05 mol) in MeOH (100 ml) was stirred with 10 ml of concentrated hydrochloric acid for 15 min at room temperature. The mixture was neutralized with aqueous 10% NaOH solution, and concentrated *in vacuo* to give a residue, which was extracted with CH_2Cl_2. The extract was washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crystalline residue which was recrystallized from AcOEt to give 11.6 g (92.5%) of pale yellow needles **8**, mp 85°C, $[\alpha]_D$ − 14.7° (c = 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3550, 3400, 1675. ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 3.21 (2H, br s), 3.77—3.88 (2H, m), 4.20 (3H, br s), 6.81 (1H, dd, J = 8, 2 Hz), 7.02—7.16 (2H, m), 7.30 (1H, m). MS m/z: 250 (M^+), 219, 189, 176, 161.

(*S*)-(+)-2-Acetyl-7-(2-hydroxy-3-tosyloxypropoxy)benzofuran (9a)——*p*-Toluenesulfonyl chloride (7.7 g, 0.04 mol) was gradually added to a solution of the (**8**) (10 g, 0.04 mol) in dry pyridine (40 ml), with stirring and cooling at 0—10 °C. The reaction mixture was stirred for 4 h, then $CHCl_3$ (200 ml) was added.

The $CHCl_3$ solution was washed with water (100 ml), 10% hydrochloric acid (265 ml, 0.53 mol), and saturated $NaHCO_3$ solution (50 ml), then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crystalline residue, which was recrystallized from AcOEt to give **9a** (8.8 g, 54.5%) as pale yellow prisms, mp 134 °C, $[\alpha]_D$ + 10.8° (c = 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3450, 1685, 1350, 1170. ^{1}H-NMR ($CHCl_3$) δ: 2.34 (3H, s), 2.55 (3H, s), 3.02 (1H, br s), 4.16—4.37 (5H, s), 6.84 (1H, dd, J = 8, 2 Hz), 7.11—7.27 (4H, m), 7.46 (1H, s), 7.71 (2H, d, J = 9 Hz). MS m/z: 404 (M^+), 323, 189, 176, 161, 155.

(*R*)-(−)-2-Acetyl-7-(2,3-epoxypropoxy)benzofuran (6a)——A solution of the tosylate (**9a**) (8.1 g, 0.02 mol) in absolute MeOH (20 ml) and dry THF (40 ml) was treated with Na metal (0.46 g, 0.02 atom), with stirring and cooling at 0 °C. After being stirred for 3 h at 0—10 °C, the solution was neutralized with 10% hydrochloric acid. The separated precipitates were filtered off and the filtrate was concentrated under reduced pressure to give an oily residue, to which $CHCl_3$ (50 ml) was added. The $CHCl_3$ solution was washed with water and dried over $MgSO_4$, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 200 g, benzene: AcOEt = 10 : 1 v/v) to give (*R*)-(−)-**6a**, which was recrystallized from MeOH to give pale yellow needles (3.9 g, 84.7%), mp 74—76 °C, $[\alpha]_D$ − 25.8° (c = 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1680. ^{1}H-NMR ($CDCl_3$)δ: 2.59 (3H, s), 2.78—3.02 (2H, m), 3.36—3.58 (1H, m), 4.11—4.28 (1H, dd, J = 6, 12 Hz), 7.03—7.43 (4H, m). MS m/z: 232 (M^+), 202, 189, 176, 161.

(*S*)-(+)-2-Acetyl-7-(2,3-epoxypropoxy)benzofuran (6b)——Diethyl azodicarboxylate (20.9 g, 0.12 mol) was gradually added to a solution of 2-acetyl-7-hydroxybenzofuran (**5**) (17.6 g, 0.1 mol), (*R*)-glycidol (**11**) (8.9 g, 0.12 mol), and triphenylphosphine (31.4 g, 0.12 mol) in dry THF (150 ml), with stirring under a nitrogen atmosphere at 0—10 °C. After being stirred at room temperature for 3 h, the solution was concentrated under reduced pressure, and ether (100 ml) was added to the resulting mixture. The separated crystals were filtered off and the filtrate was concentrated to give a residue, which was purified by column chromatography (SiO_2 250 g, CH_2Cl_2: hexane: ether = 3 : 3 : 1 v/v) to give (*S*)-**6b** in 79.7% yield (18.5 g). This was recrystallized from MeOH to furnish pale yellow needles, mp 74—76 °C, $[\alpha]_D$ + 25.9° (c = 1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1680. ^{1}H-NMR ($CDCl_3$) δ : 2.59 (3H, s), 2.78—3.02 (2H, m), 3.36—3.58 (1H, m), 4.11—4.28 (1H, dd, J = 6, 12 Hz), 4.45—4.62 (1H, dd, J = 4, 12 Hz), 7.03—7.43 (4H, m). MS m/z: 232 (M^+), 202, 189, 176, 161.

(*R*)-(+)-Befunolol·HCl (1a)——A solution of (*R*)-(−)-2-acetyl-7-(2,3-epoxypropoxy)benzofuran(**6a**) in isopropyl alcohol (60 ml) and isopropylamine (29.5 g, 0.5 mol) was refluxed for 2 h and then evaporated to dryness *in vacuo*. The resulting solid was dissolved in ethanol (100 ml) and treated with concentrated hydrochloric acid (10 ml)

at 25 °C. After being kept for 5 h, the solution was evaporated *in vacuo* to give a solid, which was crystallized from isopropyl alcohol (150 ml). The obtained crystals were recrystallized from isopropyl alcohol (150 ml) to give (*R*)-(+)-**1a** (26.5 g, 81.4%) as pale yellow prisms, mp 151 °C, $[\alpha]_D$ +15.3° (c = 1.00, MeOH). *Anal.* Calcd for $C_{16}H_{21}NO_4 \cdot HCl$: C, 58.62; H, 6.78; N, 4.27. Found: C, 58.40; H, 6.82; N, 4.15. IR ν_{max}^{KBr} cm^{-1}: 3375, 1680. ^{1}H-NMR (D_2O) δ: 1.66 (6H, d, J = 7 Hz), 2.49 (3H, s), 3.44—3.60 (2H, m), 3.82 (1H, sep., J = 7 Hz), 4.29 (2H, br d), 4.45—4.72 (1H, m), 6.94–7.25 (3H, m), 7.30 (1H, s). MS *m/z*: 291, 276, 247, 176, 161, 102, 72.

(*S*)-(−)-Befunolol·HCl (1b)——(*S*)-(+)-2-Acetyl-7-(2,3-epoxypropoxy)benzofuran (**6b**) was treated as described for (*R*)-(+)-befunolol·HCl (**1a**) to give (*S*)-(−)-**1b** (26.4 g, 80.5%) as pale yellow prisms, mp 151—152 °C, $[\alpha]_D$ −15.5° (c = 1.00, MeOH). *Anal.* Calcd for $C_{16}H_{21}NO_4 \cdot HCl$: C, 58.62; H, 6.78; N, 4.27. Found: C, 58.33; H, 6.57; N, 4.04. IR, ^{1}H-NMR and MS of **1b** were identical with those of **1a**.

Determination of the Optical Purities of Befunolol·HCl (1a,b)——i) Preparation of the Diastereomeric Derivatives of **1a, b**: A mixture of 5 mg of test compound and 25 μl of 10% (w/v) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**12**) in *N*,*N*-dimethylformamide (DMF) was allowed to stand at room temperature for 30 min, and then 5 μl of 2% (v/v) hydrazine hydrate DMF solution was added. This mixture was stirred for 10 min at room temperature, and an aliquot was injected directly into the chromatograph.

ii) Separation of the Obtained Diastereomers: A modular high-performance liquid chromatographic system, Waters Associates type 204, which consisted of a 6000-A pump, U6K injector, and 440 ultraviolet (UV) detector, was used. The separation of the obtained mixture was carried out under the following conditions: column, 4.6 × 150 mm; packing, Cosmosil 5C_{18}; mobile phase, 0.01 M phosphate buffer (pH 2.8) : MeOH = 35 : 65 v/v; flow rate, 0.7 ml/min; detector, UV absorption at 254 nm. The diastereoisomers derived from (*R*)-**1a** and (*S*)-**1b** were separated as two peaks and their retention times were 15.42 and 11.38 min, respectively. The optical purity was calculated by comparing the separated peak areas.

Anti-isoproterenol Potency——Hartley male guinea pigs were killed by venesection. The atrial preparation was placed in a 20 ml organ bath filled with Krebs-Hensleit solution at 37 °C and bubbled with carbogen. The responses were recorded by using an isometric transducer and a multipurpose polygraph (Nihon Koden, RM-85) under a tension of 1 g. Isoproterenol was added cumulatively to the bath fluid and the concentration–response curves were obtained. The test compound was added to the bath fluid 10 min before isoproterenol. The activity of the test compound was expressed as pA_2-value, which was calculated from the parallel shifts of the cumulative dose–response curve of isoproterenol.[11]

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References and Notes

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