A Practical Synthesis of Optically Active Atenolol from Chiral Epichlorohydrin

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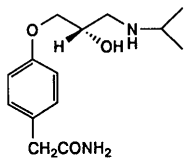
The synthesis of (*R*)- and (*S*)-atenolol (1) was achieved in two steps starting from *p*-hydroxyphenylacetamide (2). Both enantiomers of the glycidyl ether 4 were synthesized from 2 and (*R*)- and (*S*)-epichlorohydrin (3) using an alkali metal hydroxide and/or BTA (benzyltrimethylammonium chloride), respectively. Subsequent treatment of 4 with isopropylamine afforded atenolol (1) with excellent enantiomeric excess (>98% ee).

Key words optically active atenolol; optically active epichlorohydrin; benzyltrimethylammonium chloride; β-adrenergic blocking agent

Since the intrinsic biological activity in a racemic drug often resides in a single enantiomer, synthesizing such drugs in enantiomerically pure form is of great interest.[1,2] For instance, racemic atenolol is one of the top five best-selling drugs in the world today[3] for the treatment of hypertension and angina and has shown promise in the treatment of post myocardial infarction, yet the use of the *S* isomer would make it possible to avoid the side effect of lowered heart rate which is sometimes encountered when using the racemate.[4] We report here the expeditious synthesis of (*R*)- and (*S*)-atenolol (**1**).

Optically active β-adrenergic blocking agents are usually prepared by optical resolution of a racemic compound[5] or by using (*R*)- and (*S*)-3-tosyloxy-1,2-propanediol acetonides[6,7] as chiral building blocks. In general, the former method is tedious, and the latter requires a number of steps in the preparation of the chiral building blocks from D-mannitol.[8] Racemic atenolol and its analogs are prepared by reacting compound **2** with an excess of racemic epichlorohydrin in the presence of a catalytic amount of piperidine at 95 to 100 °C to obtain the glycidyl ether **4**, followed by reaction with the amine compound.[9] However, in this process, even if chiral epichlorohydrin is used, racemization occurs and hence the optical purity of the glycidyl ether **4** becomes less than 70% ee. Moreover, the process requires a large amount of chiral epichlorohydrin, and even when the excess epichlorohydrin is recovered, it can not be re-used because of its decreased optical purity. Accordingly, the above process is not suitable as an industrial process for producing the desired optically active atenolol. In this context, we were intrigued by a novel process using (*R*)- and (*S*)-epichlorohydrins, which have recently become industrially available by means of bio-technology, as the chiral building blocks.[10]



(*S*)-atenolol 1

Fig. 1. Structure of (*S*)-Atenolol

Compound **2** was treated with 1.1 molar eq of (*R*)-epichlorohydrin (**3**) in the presence of 1.0 molar eq of alkali metal hydroxide to afford a mixture of (*S*)-1-[*p*-(carbamoylmethyl)phenoxy]-2,3-epoxypropane (**4**) and (*R*)-1-[*p*-(carbamoylmethyl)phenoxy]-3-chloropropan-2-ol (**5**) (Chart 1).

The mixture, without separation, was reacted with an

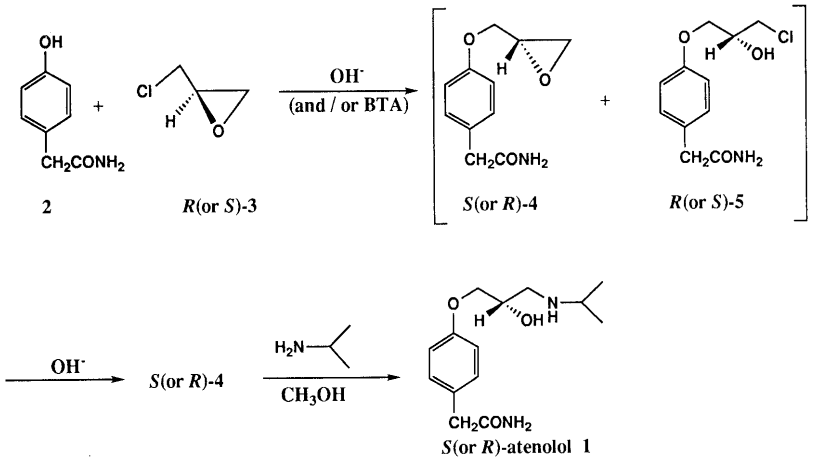


Chart 1

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Table 1. Preparation of the Glycidyl Ethers **4**

Entry	**3**	Conditions				**4**			
		Base	Temp. (°C)	Time (h)		Yield (%)	Crude % ee[a]	Yield (%)[b]	% ee[a,b]
1	*R*	NaOH	45	5	*S*	80	77.0	50	80.3
2	*R*	NaOH	17	8	*S*	67	91.0	59	98.1
3	*R*	NaOH	5	24	*S*	78	96.1	60	99.2
4	*S*	NaOH	5	24	*R*	75	96.0	63	99.0
5	*R*	NaOH, BTA	5	28	*S*	95	96.8	75	99.4
6	*S*	NaOH, BTA	5	30	*R*	93	96.3	72	99.2
7	*R*	KOH	5	24	*S*	70	93.8	58	98.6
8	*R*	KOH, BTA	5	30	*S*	83	94.0	70	98.8
9	*R*	LiOH	5	24	*S*	73	96.2	62	98.6
10	*R*	LiOH, BTA	5	30	*S*	80	96.2	70	98.8

a) As atenolol based on HPLC on a Daicel Chiralcel OD column with hexane–EtOH–Et_2NH (90:10:0.1), 1.0 ml/min; retention times, 14.0, 17.9 min. *b*) After recrystallization. BTA: benzyltrimethylammonium chloride.

additional 0.3 molar eq of alkali metal hydroxide to give (*S*)-**4** in 67 to 78% yield (Table 1). As the reaction proceeds, **4** is precipitated, and the precipitated crystals have an optical purity of 91 to 96% ee.

Enantiomerically pure **4** was obtained by recrystallization from methanol (3 times) to provide 98% ee or higher. During the reaction of **2** with (*S*)-epichlorohydrin (**3**) under the same conditions, (*R*)-1-[*p*-(carbamoylmethyl)-phenoxy]-2,3-epoxypropane (**4**) was obtained in 75% yield. Moreover, employment of phase-transfer conditions by adding BTA (benzyltrimethylammonium chloride) resulted in yields of 80 to 95%. When the reaction temperature was higher than 5 °C, racemization occured and **4** reacted with the alkali metal salt of the starting **2** to produce side reaction products.

The intermediate glycidyl ether **4** thus obtained can be easily converted into the desired enantiomerically pure atenolol (**1**) by reaction with 24 molar eq of isopropylamine in 90% yield and more than 98% ee.

Experimental

Melting points were determined with a Mettler FP-61 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM-GSX-270 NMR spectrometer with tetramethylsilane as an internal standard. HRMS were recorded on a JEOL JMS-AX505W. Optical rotations were measured on a JASCO DIP-370 at 21 °C. All reactions were monitored by HPLC. HPLC analyses were performed on a Daiso Pack SP-120-5-ODS-AP column (4.6 mm i.d. × 150 mm) using a Shimadzu LC-5A system equipped with an SPD-6A UV detector (eluent, MeOH–H_2O containing 2 mM 1-octanesulfonic acid sodium salt, 7:3, v/v; flow rate, 1.0 ml/min; detection, UV at 228 nm; temperature, 40 °C). Enantiomeric excesses were determined by HPLC on a Chiralcel OD column (4.6 mm i.d. × 250 mm, eluent, hexane–EtOH–Et_2NH, 90:10:0.1 v/v; flow rate, 1.0 ml/min; UV at 228 nm; temperature, 30 °C).

Preparation of (*S*)-1-[*p*-(Carbamoylmethyl)phenoxy]-2,3-epoxypropane (4) A mixture of (*R*)-epichlorohydrin (**3**) (24.4 g, 0.26 mol, 98.9% ee) and H_2O (21 ml) was stirred under cooling at 5 °C. To this mixture was added dropwise a solution of **2** (35.7 g, 0.24 mol), benzyltrimethylammonium chloride (0.18 g) and NaOH (9.6 g, 0.24 mol) in H_2O (158 ml) over a period of 1 h. The mixture was stirred at 5 °C for 20 h. Then NaOH (2.9 g, 0.072 mol) in H_2O (48 ml) was then added at 5 °C and the whole was stirred at room temperature for 8 h. After having been neutralized with 3.5% HCl, the reaction mixture was evaporated. The residue was dissolved in AcOEt, washed with H_2O and evaporated to afford crude crystals of (*S*)-**4** (50.4 g). Recrystallization from MeOH gave (*S*)-**4** (37.26 g, 75%) as colorless prisms. mp 167.3—168.6 °C, $[\alpha]_D^{21} = +10.8°$ (*c* 0.5, MeOH), lit.[8] $[\alpha]_D^{21} = +4.8°$ (*c* 1.0, MeOH). ^{1}H-NMR (DMSO-d_6) δ: 2.69 (m, 1H, CH), 2.83 (dt, 1H, J=1.1, 5.1 Hz, CH), 3.29 (s, 2H, CH_2), 3.33 (m, 1H, CH), 3.80 (ddd, 1H, J=−11.4, 1.1, 6.6 Hz, CH_2), 4.29 (ddd, 1H, J=−11.4, 1.1, 2.6 Hz, CH_2), 6.82 (br s, 1H, NH), 6.89 (d, 2H, J=7.7 Hz, ArH), 7.71 (d, 2H, J=7.7 Hz, ArH), 7.39 (br s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 41.33, 43.74, 49.75, 68.90, 114.20, 130.06, 156.81, 172.51. HR-MS *m/z*: 207.0895 (Calcd for $C_{11}H_{13}NO_3$: 207.0894).

Preparation of (*S*)-Atenolol (1) (*S*)-**4** (30.0 g, 0.14 mol) was added to a mixture of MeOH (280 g) and isopropylamine (198 g, 3.36 mol), and the solution was stirred at room temperature for 12 h, then distilled under reduced pressure to remove the solvent. The residue was recrystallized from MeOH to give (*S*)-atenolol (**1**) (33.52 g, 90%, 99.4% ee) as colorless prisms. mp 153.0—154.4 °C, $[\alpha]_D^{21} = -17.3°$ (*c* 1.0, 1 N HCl), lit.[8] $[\alpha]_D^{21} = -13.6°$ (*c* 1.0, 1 N HCl). ^{1}H-NMR (DMSO-d_6) δ: 0.99 (d, 6H, J=6.2 Hz, CH_2), 2.67 (m, 2H, CH_2), 3.28 (s, 2H, CH_2), 3.35 (m, 1H, CH), 3.86 (m, 3H, CH_2, CH), 6.80 (br s, 1H, NH), 6.86 (d, 2H, J=7.7 Hz, ArH), 7.17 (d, 2H, J=7.7 Hz, ArH), 7.37 (br s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 22.90, 22.93, 41.48, 48.29, 49.98, 68.47, 71.08, 114.60, 128.53, 130.29, 157.62, 173.36. HR-MS *m/z*: 266.1630 (Calcd for $C_{14}H_{22}N_2O_3$: 266.1629).

Preparation of (*R*)-1-[*p*-(Carbamoylmethyl)phenoxy])-2,3-epoxypropane (4) (*R*)-**4**, colorless prisms, was synthesized from (*S*)-epichlorohydrin (**3**) in 72% yield by a procedure similar to that used for (*S*)-**4**. mp 166.2—167.9 °C, $[\alpha]_D^{21} = -10.6°$ (*c* 0.5, MeOH). HR-MS *m/z*: 207.0895 (Calcd for $C_{11}H_{13}NO_3$: 207.0894).

Preparation of (*R*)-Atenolol (1) (*R*)-Atenolol **1**, colorless prisms, was synthesized from (*R*)-**4** in 89% yield by a procedure similar to that used for (*S*)-**1**. 99.2% ee, mp 153.3—154.7 °C, $[\alpha]_D^{21} = +17.0°$ (*c* 1.0, 1 N HCl). HR-MS *m/z*: 266.1628 (Calcd for $C_{14}H_{22}N_2O_3$: 266.1629).

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