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Effective synthesis of non-racemic prenalterol based on spontaneous resolution of 3-(4-hydroxyphenoxy)propane-1,2-diol

Zemfira A. Bredikhina, Alexey V. Kurenkov and Alexander A. Bredikhin*

A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 843 273 1872; e-mail: baa@iopc.ru

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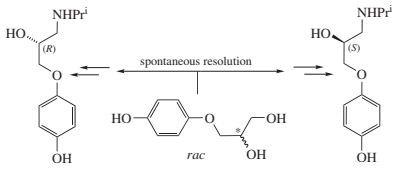
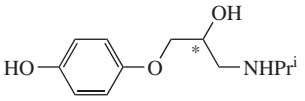
Spontaneous resolution of *rac*-3-(4-hydroxyphenoxy)propane-1,2-diol has been successfully used in the synthesis of both enantiomers of chiral drug prenalterol.



Access to enantiomerically pure intermediates is essential for obtaining pharmaceutically active products.[1] Stereoselective crystallization is increasingly employed in the preparation of enantiopure organic compounds[2–4] since it offers particular practical benefits.[5] A good example among such preparations can be the prenalterol **1** [(*S*)-1-(4-hydroxyphenoxy)-3-(2-propylamino)-propan-2-ol],[6] a partial adrenergic agonist with functional β_1-receptor specificity.[7,8] It is effective in the treatment of acute cardiac failure, postmyocardial infarction low-output syndrome, shock, and is useful in the treatment of β-blocker overdosage.[8,9]



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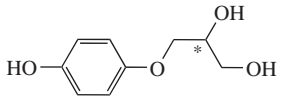

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In the available literature for the synthesis of compound **1**, the natural raw materials (Chiral Pool) are reported as primary sources of chirality. With this, the synthetic schemes are multistep and involve the use of protective groups.[10–13] Investigating the phase behavior of chiral aromatic glycerol ethers, we found that the members of this chemotype often prone to spontaneous resolution during crystallization.[5,14] In particular, we have shown that an *ortho*-substituted analogue of diol **2** crystallizes from a racemic substrate as a conglomerate, a mechanical mixture of enantiopure crystals.[15] In turn, compound **2** can serve as a precursor of potential drug **1**.

Preliminary information on the crystallization nature of a chiral compound can be obtained from comparison between the melting points of its enantiopure and racemic samples.[14] According to the published data, the melting point of amino alcohol *rac*-**1** is higher than that of the enantiomer by 29 °C.[13,16] In contrast, diol *rac*-**2** melts 21 °C below the enantiopure sample.[12,17] Judging from these data, prenalterol itself should form a racemic compound in the crystalline state. However, in the case of diol **2** the formation of conglomerate may be anticipated. Comparison of vibrational spectra and X-ray powder diffraction patterns of racemic and enantiomeric crystalline samples of diol **2** has revealed that this compound can form racemic conglomerate in the solid phase.[18] Here we proved this hypothesis by direct resolution of *rac*-**2** into individual enantiomers using the entrainment method.

In this study, we used O-protected diol **2**, 3-(4-methoxyphenoxy)propane-1,2-diol **3**, whose synthesis was previously described.[19] Removal of the protective *O*-methyl group was performed according to the patent data,[20] by hydrolysis with concentrated HBr. In this manner, *rac*-**2** required for further work, as well as its enantiomers (used then as crystalline seeds), were obtained in overall yields of ~65%.

As already mentioned, *rac*-**2** was resolved by the entrainment approach when crystallization of the enantiomer from supersaturated solutions of racemate was provoked by introducing the enantiopure crystalline seed. Diol **2** is highly soluble in methanol, slightly worse in acetone and poorly soluble in chloroform, dichloromethane, benzene, diethyl ether and ethyl acetate. We have found water to be the most convenient solvent for the separation of diol **2** enantiomers. Quantitatively, the solubility of *rac*-**2** at 23.5 °C in water was 25 mg ml^{-1}, and at 45.5 °C these values for *rac*-**2** and (*R*)-**2** were 81 and 27 mg ml^{-1}, respectively. Varying initial concentration, temperature gap and crystallization time, we have adopted the conditions for the satisfactory resolution of *rac*-**2** (Table 1). The separation process was monitored by chiral HPLC (Figure S1, Online Supplementary Materials).

The first resolution run provided moderate results (see Table 1) when enantiomeric excess for the crystalline *R*-precipitate was ~39% and that for the (*S*)-**2** mother liquor was ~3.8%. In subsequent cycles, the mother liquors were enriched with the opposite enantiomer (after the last completed run the mother liquor *ee* was 10.5%, see Figure S1), the enantiomeric excess of the crystalline precipitate rose to ~80%. At the same time, the one-time crop of the enantiomer also increased from 7.5 to ~23%. Obviously, the enantiomeric purity of non-racemic samples can be improved by recrystallization. In total, for three cycles (6 runs) from 5.28 g of *rac*-**2**, 1.03 g (19.4%) of (*S*)-**2** and 0.87 g (16.5%) of (*R*)-**2** were obtained, counting on pure enantiomers.[†] If necessary, the procedure can be continued until the racemic feedstock is consumed.

[†] *(S)-3-(4-Hydroxyphenoxy)propane-1,2-diol* (*S*)-**2**. Mp 150–151 °C (EtOAc), $[\alpha]_D^{20}$ +8.0 (*c* 1, MeOH) {lit.,[12] 149.5–151 °C (MeOH–$CHCl_3$), $[\alpha]_D^{20}$ +8.01 (*c* 1.0, MeOH)}, 99% *ee* (HPLC).

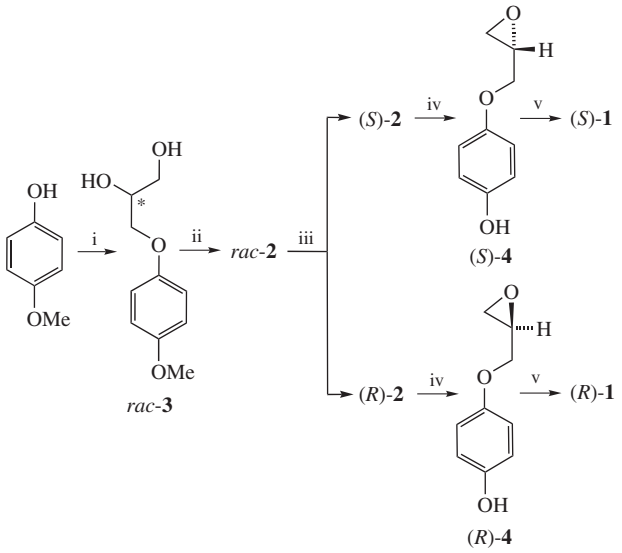
(R)-3-(4-Hydroxyphenoxy)propane-1,2-diol (*R*)-**2**. Mp 149–151 °C (EtOAc), $[\alpha]_D^{20}$ –8.1 (*c* 1.0, MeOH), 98% *ee* (HPLC).

For experimental details, see Online Supplementary Materials.

Table 1 Resolution by entrainment of *rac*-3-(4-hydroxyphenoxy)propane-1,2-diol (*rac*-**2**) in water (50 ml, 8 mg of crystal seeds on every run).

Run	Amount of *rac*-**2** added/g	Operation amount of enantiomers/g		Resolution time/min	*T*/°C	(*R*)-**2** and (*S*)-**2** obtained				Mother liquor *ee* (%)
		(*R*)-**2**	(*S*)-**2**			Yield/g	*ee*[a] (%)	YE[b]/g	YE[c] (%)	
1	3.000	1.500	1.500	150	23–24	(*R*) 0.310	39	0.113	7.5	3.8 (*S*)
2	0.302	1.444	1.556	215	27	(*S*) 0.519	57	0.288	18.5	7.7 (*R*)
3	0.512	1.588	1.413	390	27–28	(*R*) 0.516	74	0.374	23.6	8.4 (*S*)
4	0.508	1.401	1.600	305	27–28	(*S*) 0.451	84	0.371	23.2	9.8 (*R*)
5	0.442	1.586	1.414	480	26–27	(*R*) 0.519	76	0.386	24.3	9.4 (*S*)
6	0.512	1.393	1.608	350	27	(*S*) 0.445	84	0.366	22.8	10.4 (*R*)

[a] *ee* is enantiomeric excess (HPLC). [b] YE is the yield of enantiomer. YE (g) = [Yield (g) × *ee* (%)]/100 – 0.008 (seed weight). [c] YE (%) = [YE (g) × 100]/Operation amount of (*R*)-**2** or (*S*)-**2** (g).



Scheme 1 *Reagents and conditions*: i, *rac*-$ClCH_2CH(OH)CH_2OH$, NaOH, EtOH, reflux; ii, HBr (45% aq.), 50 °C; iii, resolution by entrainment; iv, PPh_3, DEAD, THF, reflux; v, Pr^iNH_2, reflux.

Based on successful spontaneous resolution of compound **2** as a source of chirality, we suggest a new original scheme for the preparation of enantiopure prenalterol **1** (Scheme 1), in which the direct resolution of the racemic diol **2** by an entrainment procedure was the key step. Conversion of thus obtained enantiomers of diol **2** into the target compounds **1** has been carried in two steps. Initially, the intramolecular Mitsunobu etherification of diols **2** to enantiomeric epoxides **4** was performed.‡ The cyclization proceeds in a high yield (up to 97%) and with a little loss of enantiomeric purity (from 98 to 92–93% *ee*). By analogy with similar cyclization,[21] we assume that the initial configuration of the chiral center is retained. Individual enantiomers of (*S*)-**1** and (*R*)-**1** were obtained by reflux of (*S*)-**4** and (*R*)-**4** with excess isopropylamine in the presence of minimum water.§

Samples of *rac*-**1** and *rac*-**4** were obtained similarly from racemic diol **2**. Note that according to patent data,[22] synthesis of *rac*-**4** by the reaction between epichlorohydrin and hydroquinone occurs in a low yield (23%) and is accompanied by contamination of the product.

Thus, both enantiomers of chiral drug prenalterol were obtained based on spontaneous resolution of racemic 3-(4-hydroxyphenoxy)propane-1,2-diol upon crystallization from water. The proposed scheme favorably competes with the 'Chiral Pool' concept due to smaller number of stages and the use of racemic raw materials.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.028.

‡ *(S)-4-(2,3-Epoxypropoxy)phenol* (*S*)-**4**. Yield 97%, mp 81–83.5 °C (hexane–EtOAc), $[\alpha]_D^{20}$ +12.8 (*c* 1.0, MeOH), 93% *ee* (HPLC).

(R)-4-(2,3-Epoxypropoxy)phenol (*R*)-**4**. Yield 95%, mp 81–84 °C (hexane–EtOAc), $[\alpha]_D^{20}$ –13.5 (*c* 1.0, MeOH), 92% *ee* (HPLC).

§ *(S)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol* (*S*)-**1**. Yield 89%, mp 125–127 °C (EtOAc), $[\alpha]_D^{20}$ –1.9 (*c* 1.0, MeOH), $[\alpha]_D^{20}$ –21.0 (*c* 1.0, 0.1 N HCl) {lit.,[6] mp 127–128 °C (EtOAc), $[\alpha]_D^{20}$ = –1±1 (*c* 0.94, MeOH); lit.,[13] $[\alpha]_D^{25}$ –20.67 (*c* 1.0, 0.1 N HCl)}, 98% ee (HPLC).

(R)-1-(4-Hydroxyphenoxy)-3-isopropylaminopropan-2-ol (*R*)-**1**. Yield 94%, mp 124–126 °C (EtOAc), $[\alpha]_D^{20}$ +2.4 (*c* 1.0, MeOH), $[\alpha]_D^{20}$ = +18.4 (*c* 1.0, 0.1 N HCl) {lit.,[13] mp 126–127 °C (acetone), $[\alpha]_D^{25}$ = +20.85 (*c* 1.0, 0.1 N HCl)}, 95% *ee* (HPLC).

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