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Spontaneous resolution amongst chiral *ortho*-cyanophenyl glycerol derivatives: an effective preferential crystallization approach to a single enantiomer of the β-adrenoblocker bunitrolol

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ABSTRACT

The β-adrenoblocker bunitrolol **1** as well as intermediate cyclic sulfate **6** and glycidyl ether **8** have been prepared in enantiopure form by starting from enantiopure *o*-cyanophenyl glycerol ether **2** by an entrainment resolution procedure. Thermal investigations reveal that **1**·HCl forms a moderately stable racemic compound, whereas **2**, **6** and **8** are conglomerate forming substances potentially capable of entrainment resolution. Some chemical and chiroptical characteristics for bunitrolol and possible intermediates in its synthesis were corrected, and configurations were verified with the configuration of **1**·HCl.

1. Introduction

For the family of β-adrenergic blockers with general formula $ArOCH_2CH(OH)CH_2NHAlk$, it has been shown that (*S*)-enantiomers are eutomer components of the racemic drug, whereas (*R*)-enantiomers (distomers) usually display other (often undesirable) activities.[1] The β-adrenoblocker bunitrolol, 1-(2-cyanophenoxy)-2-hydroxy-3-*tert*-butylaminopropane **1** is no exception. Its enantiomers demonstrate different activities[2] and different rates of metabolic oxidation[3] in specially organized in vitro experiments. Bunitrolol is registered as a racemate.[4] Bearing in mind a general tendency for the replacement of racemic drugs by their single enantiomer analogues,[5] we wanted to report herein the synthesis and properties of scalemic **1**, as well as of some valuable intermediates and related compounds.

Our interest in this problem was for several reasons. First of all we were hopeful of finding a new application of the spontaneous resolution in obtaining practically important products.

The second reason is less general. During the progress of this work, we have found that an essential part of published physical and chiroptical properties for bunitrolol itself and for the main intermediates are discrepant or erroneous. Recently, we established the absolute configuration of bunitrolol hydrochloride by a direct Bijvoet method,[6] meaning that we had a reliable reference point for the chiroptical correlations. The chemical transformations studied in this work are outlined by Scheme 1.

The final part of our work is devoted to thermochemical analysis of the melting (and hence the crystallization) peculiarities of the key chiral substances studied. We share the opinion that the binary melting phase diagram is a 'roadmap' for those concerned with chiral substance resolution and/or purification. Thus, we have tried to reconstruct the phase diagrams for bunitrolol (as its hydrochloride) and for its main precursors.

2. Results and discussion

Many approaches to non-racemic β-adrenoblocker compounds have been described in the literature,[7] one of which starts from the scalemic aryl glycerol ethers. In the case of bunitrolol, the starting material would be 3-(2-cyanophenoxy)-propane-1,2-diol **2**. Compound (*S*)-**2** was obtained through a Sharpless asymmetric dihydroxylation of the corresponding aryl allyl ether by Wang et al.[8] The synthesis was repeated by Sayyed et al.[9] For obtaining this intermediate in racemic and scalemic forms we have used the reaction of 2-cyanophenol **3** and *rac*- or *scal*-3-chloro-1,2-propanediol **4**.

At this point, discrepancies between the published and our observed characteristics began. For a sample of 28% ee, Wang et al. reported the value of $[\alpha]_D^{20} = +9.4$ (*c* 0.5, EtOH).[8] The value of $[\alpha]_D^{20} = +21.8$ (*c* 0.5, EtOH) for the sample of 65% ee was reported by Sayyed et al.[9] It can be seen that these numbers correspond to one another and should be in compliance with the value of $[\alpha]_D^{20} = +33.6$ for the enantiopure sample (9.4:28 = 21.8:65 = 33.6:100). The last work also reports the melting point 140–142 °C for the same sample. For the very pure sample of (*S*)-**2** (overall purity was higher than 99.2% by differential scanning calorimetry, enantiomeric purity was higher than 99.4% by chiral HPLC) we have found mp 72–74 °C and $[\alpha]_D^{20} = +3.1$ (*c* 1.0, EtOH).

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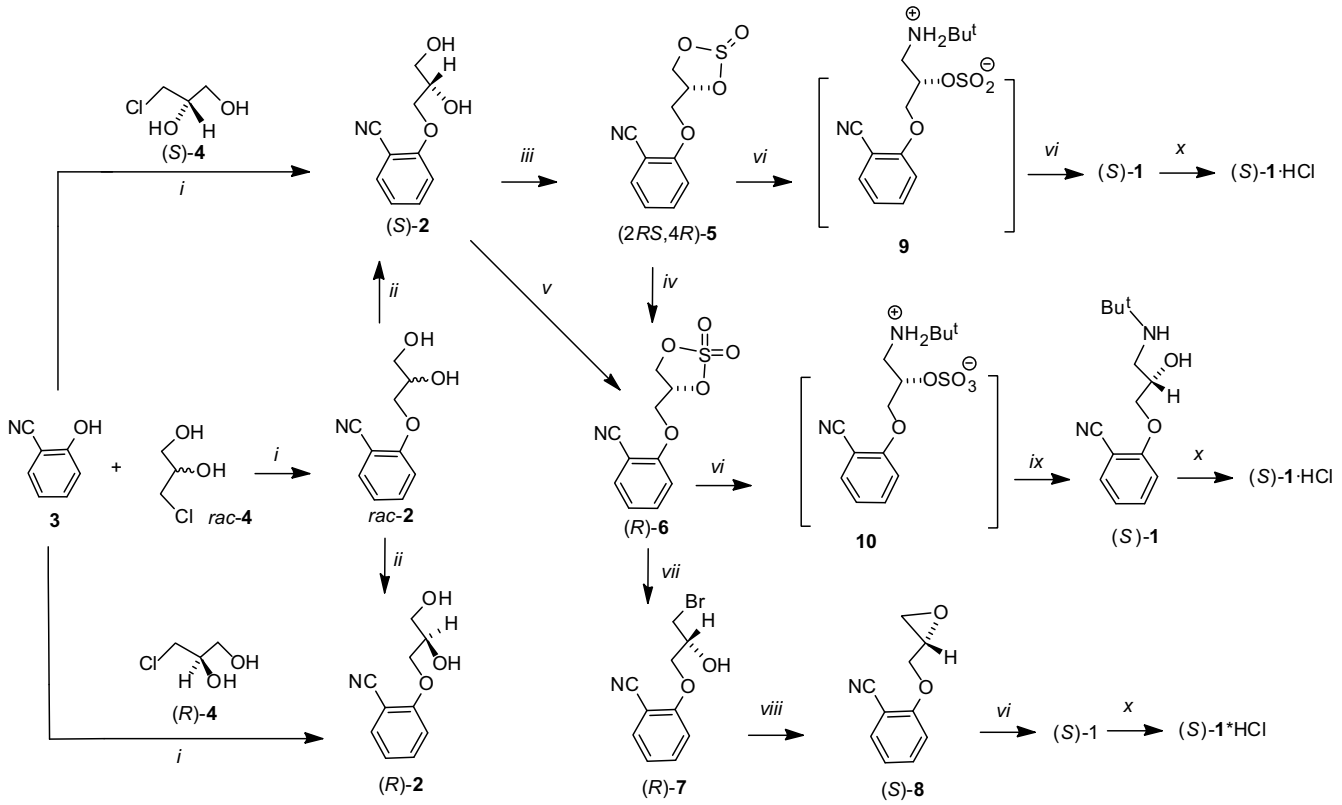

Scheme 1. Reagents and conditions: (i) NaOH, EtOH, reflux; (ii) spontaneous resolution; (iii) $SOCl_2$, CH_2Cl_2, 0 °C; (iv) $NaIO_4$, $RuCl_3·H_2O$, CH_3CN; (v) SO_2Cl_2, AcOEt, NEt_3, 0 °C; (vi) Bu^tNH_2; (vii) LiBr, THF; (viii) K_2CO_3, MeOH; (ix) (a) H_2SO_4; (b) NaOH; (x) HCl.

From the results of Wang et al. it follows that aryl allyl ethers bearing *ortho*-substituents are unsuitable substrates for Sharpless asymmetric dihydroxylation, and the corresponding diols are obtainable with poor enantiomeric excesses.[8] Conversely, it was shown that some phenyl glycerol ethers bearing *ortho*-substituents demonstrate the ability for spontaneous resolution.[10,11] This group contains *o*-Cl-, *o*-Br- and *o*-I-phenyl glycerol ethers;[12] the compounds which closely resemble the *o*-CN-phenyl glycerol ether **2**. Bearing this in mind, we quantitatively investigated the melting properties of chiral compound **2** by means of differential scanning calorimetry (d.s.c.).

The results obtained for the temperature and the enthalpy of fusion of the pure enantiomer and the pure racemate of diol **2**, as well as the calculated[13] values of the entropy of enantiomer mixing for liquid racemate, ΔS_l^m, and free energy of formation of racemic compound in the solid state, ΔG^0, are presented in Table 1. From the d.s.c. data, the idealized melting temperatures against the composition diagram for compound **2** were reconstructed and are shown in Figure 1a. The binary phase diagram for the compound has an obvious single eutectic V-shape typical of a racemic conglomerate.[14] The entropy of mixing for the enantiomers of **2** in the liquid state is equal to 5.56 J K^{-1} mol^{-1}, which is slightly less but very close to the ideal value of 5.75 J $K^{-1}mol^{-1}$ (Rln2) for conglomerates. The near zero positive value for ΔG^0 also points to the same peculiarity for chiral **2**.[13] From all this information it follows that the chiral diol **2** displays a property of spontaneous resolution and could be potentially resolved by direct methods.

Direct methods of racemate resolution, especially operating an entrainment effect, that is, the preferential crystallization of an enantioenriched crop induced by seeding with enantiopure crystals a supersaturated solution of a conglomerate forming (almost) racemic chiral compound, is a gratifying labour for synthetic chemists, since in the event of success, it allows us to obtain both enantiomers easily without resorting to any enantiopure auxiliaries. Even in the case of conglomerate forming substances it is not always easy to use the benefits of spontaneous resolution. Coquerel is of opinion that almost half of conglomerate forming compounds would demonstrate poor entrainment characteristics.[15,16]

As evident from Section 4, racemic diol **2** is a member of the better part of the conglomerate family: for this compound we were able to demonstrate an entrainment effect, which is the preferential crystallization of an enantioenriched crop induced by seeding with enantiopure crystals of the oversaturated racemate solution. Six runs (three cycles) were sufficient enough to resolve about 4 g of the racemate, obtaining the (*R*)- and (*S*)-**2** samples of about 2 g each. The quality of both specimens is good enough, and mak-

Table 1
D.s.c. measured melting point and enthalpy of fusion of racemic (low index *R*) and enantiopure (low index *A*) compounds **1**, **2**, **6** and **8** and calculated thermodynamic characteristics for these substances

Compound	T_A^f (°C)	T_R^f (°C)	ΔH_A^f (kJ mol^{-1})	ΔH_R^f (kJ mol^{-1})	ΔS_l^m (J K^{-1} mol^{-1})	ΔG^0 (J mol^{-1})
2	72.6	51.1	27.7	36.9	5.56	19.2
6	118.6	87.4	26.3	22.2	5.33	15.2
8	90.5	65.7	27.7	25.4	5.32	−68.4
1·HCl	184.5	162.6	41.6	40.1	4.50	−516

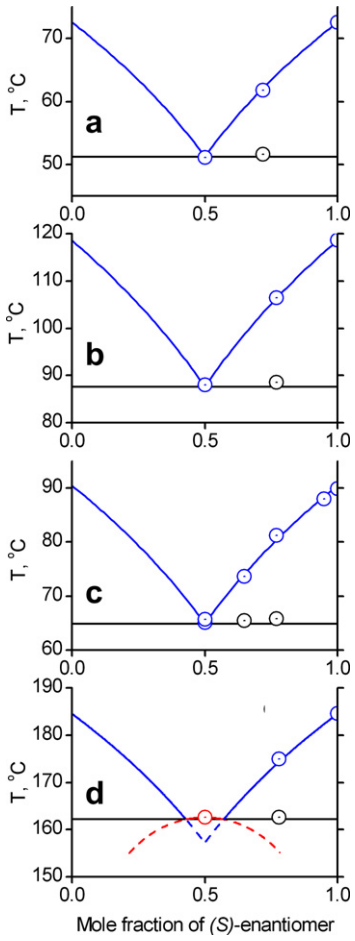

Figure 1. Experimental (circles) points and calculated (solid lines) binary melting phase diagrams for compounds **2** (a), **6** (b), **8** (c) and **1**·HCl (d).

ing sure that the compound **2** is amenable to preferential crystallization we made no attempts to improve the crop enantiopurity or to optimize experimental conditions for the resolution.

The so-established availability of both enantiomers of diol **2** allowed us to compare different routes to free enantiomeric forms of bunitrolol hydrochloride **1**·HCl and free **1**. The general approach to obtain a vicinal amino alcohol starting from a vicinal diol moiety involves the formation of an intermediate cyclic fragment easily capable of subsequent opening with an amine. The most frequently used cyclic moieties, namely sulfite, sulfate and oxirane, could be obtained from one another in this sequence. Scheme 1 shows such a transformation, as applied to diol **2**. Special attention must be given to formal change of the configurational descriptor(s), while the real configuration of the central carbon atom remains constant.

Cyclic sulfites **5** are obtainable through the reaction of **2** with thionyl chloride with quantitative yield. Due to the appearance of an additional chiral sulfur atom, cyclic sulfites **5** were obtained from enantiopure (*S*)-**2** as an epimer mixture (*cis*/*trans* ratio of about 2:3) with an (*R*)-configuration at the carbon centre. The mixture was used in all the next steps without separation of the individual diastereomers. For this reason, sulfites **5** were not investigated by d.s.c.

In this work, the cyclic sulfates **6** were obtained firstly through the well known Sharpless ruthenium-catalyzed oxidation of the sulfite to sulfate with periodate.[17] We have investigated the chiral sulfate **6** thermochemically. D.s.c. measured as well as calculated thermodynamic characteristics for this compound are presented in Table 1. Reconstructed from the d.s.c. data, the idealized binary phase diagram for compound **6** is depicted in Figure 1b. Once again the phase diagram and calculated thermodynamic parameters are close to those typical for a racemic conglomerate.

In the work reported by Sayyed et al.,[9] sulfate (*R*)-**6** [depicted in the original work as the compound **5d** and mistakenly named as (2*R*)-1-(2-cyanophenoxy)-1,3,2-dioxathiolane-2,2-dioxide] has been described as a gum, $[\alpha]_D^{20} = +8.6$ (*c* 2.0, EtOH). In reality it is a very crystalline solid, melting at 118–120 °C, $[\alpha]_D^{20} = +17.0$ (*c* 0.6, EtOH). The phase diagram (Fig. 1b) shows that even a sample with an enantiomeric purity of 50.6% (100 × 8.6/17.0) must fuse between 88 °C (eutectic line) and 107 °C (liquidus line).

The conglomerate forming abilities of sulfate **6** give rise to the potential possibility of using this intermediate in a symmetry braking step. Demonstration experiments performed by us have shown that racemic **6** could be resolved to enantiomers through an entrainment procedure. After optimization and scaling-up of this stage, racemic cyclic sulfate **6** could be a promising starting material in the single enantiomer bunitrilol production. If that is the case, it is desirable to change the usual two-step sequence of sulfite formation/ruthenium oxidation, comfortable for laboratory purposes, to another one, which is shorter, less expensive and which features a simpler work-up, and does not require the use of environmentally unfriendly heavy metals. An alternative approach consists in direct action of sulfuryl chloride on the corresponding diol **2**. Recently Alonso and Riera have drawn attention to this scarcely used synthetic route.[18] Following the general recommendations of this work, we were able to obtain *rac*- as well as *scal*-**6** with moderate to good yields by the direct procedure.

Both sulfites **5** and sulfates **6** react with *tert*-butylamine, and allow us to obtain the target bunitrolol **1** with moderate (sulfites) to low (sulfates) yield. The main difference between these starting materials consists of the intermediate betaines stability. The intermediate internal salt of alkylsulfurous acid **9** is quite labile and easily destroyed by excess amine present. Hence the 'sulfite route' to the target bunitrolol **1** could be organized as a one-pot process. At the same time the intermediate internal salt of alkylsulfuric acid **10** is sufficiently stable and could be destroyed only in more drastic conditions.

Some years ago Bittman et al. reported a highly effective method of transformation of a cyclic sulfate to an epoxide.[19] Following this approach, sulfate **6** was opened by LiBr in THF to provide vicinal bromohydrin **7**. Subsequent cyclization of **7** in methanolic K_2CO_3 solution led to glycidol ether **8** (Scheme 1).

The thermochemistry of chiral epoxide **8** obtained by an alternative route was studied earlier,[6] and for the sake of completeness we reproduce the thermodynamic properties and phase diagram of this compound in Table 1 and Figure 1c. As was established in our previous work, chiral epoxide **8** is a conglomerate forming compound with poor entrainment abilities.[6]

The enantiomeric glycidol ether (*S*)-**8** has been obtained by two groups. Nicola et al. described this compound as a solid mp 88–89 °C, with a positive sign for its specific rotation in ethanol, $[\alpha]_D^{25} = +17.7$ (*c* 1, EtOH).[20] Sayyed et al. declared that (*S*)-**8** is a gum with a positive sign for specific rotation, but in chloroform, $[\alpha]_D^{25} = +2.3$ (*c* 2.3, $CHCl_3$).[9] The sample of **8** obtained from sulfate (*R*)-**6** (Scheme 1) was a white solid, mp 90–91 °C, $[\alpha]_D^{20} = +18.5$ (*c* 0.5, EtOH). We have found that epoxide **8** (as well as diol **2**) belongs to an uncommon group of compounds whose specific rotation sign can change with a change of solvent. The sample of enantiomeric **8** with $[\alpha]_D^{20} = +18.1$ (*c* 1.0, EtOH) manifests $[\alpha]_D^{20} = -5.0$ (*c* 1.0, $CHCl_3$) or $[\alpha]_D^{20} = -14.5$ (*c* 0.65, CCl_4).

To establish the absolute configuration for glycidol ethers **8**, we transformed both enantiomers of the compound into β-blocker bunitrolol **1** (Scheme 1). Levorotary (in ethanol) bunitrolol hydrochloride (−)-**1**·HCl was obtained from the dextrorotary (in ethanol)

epoxide, as well as dextrorotary (+)-**1**·HCl derivatives from levorotary **8**. For the (+)-**1**·HCl the (*R*)-configuration was established unambiguously by the Bijvoet method.[6] The epoxide opening by simple amines is known to be stereospecific and proceeds with a retention of configuration for the carbon stereogenic centre. Thus, the epoxide with an (*S*)-absolute configuration, (*S*)-**8**, must display a *positive* specific rotation in ethanol and *negative* one in chloroform and carbon tetrachloride.

Non-racemic bunitrolol (*S*)-**1** as a free base is low melting, poorly soluble in water compound, characterized by a solvent dependable specific rotation {mp 30–32 °C; $[\alpha]_D^{20} = -9.0$ (*c* 0.8, EtOH); $[\alpha]_D^{20} = +12.3$ (*c* 0.38, H_2O)}. In no part does it resemble its description in the Sayyed et al. paper {(*S*)-bunitrolol: mp 162 °C; $[\alpha]_D^{20} = -10.0$ (*c* 1.4, H_2O), 60% ee}.[9] The low melting point precludes an ordinary d.s.c. investigations of the bunitrolol base.

On the other hand, hydrochloride **1**·HCl is quite suitable for these purposes. D.s.c. measured as well as calculated thermodynamic characteristics for this compound is presented in Table 1. Reconstructed from the d.s.c. data the idealized binary phase diagram for **1**·HCl is depicted in Figure 1d. This time the phase diagram is typical for a racemic compound forming substance, and the calculated substantial negative Gibbs free energy, ΔG^0, is in agreement with a moderate stability of such a solid state racemic compound.

3. Conclusion

In conclusion, we have modified the known synthetic route to a single enantiomer β-adrenoblocker bunitrolol using the spontaneous resolution of *rac*-3-(2-cyanophenoxy)-propane-1,2-diol, *rac*-**2** as a symmetry breaking step. During the progress of this work we have corrected an essential part of published physical and chiroptical properties for bunitrolol itself and for main intermediates en-route for this compound.

We have shown thermochemically also that not only diol *rac*-**2**, but also its reactive cyclic sulfate **6** and epoxide **8** derivatives manifests the same property of spontaneous resolution in racemic form. Thus, other symmetry breaking points based upon this quality are possible in the same synthetic sequence. At least, all of the mentioned intermediates could be enantioenriched to a desirable degree by simple recrystallization. As for the bunitrolol itself, it could also be enantioenriched by crystallization in the hydrochloride form, starting from samples with a rather low ee $\geqslant$ 14% (binary phase diagram eutectic point).

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker Avance-600 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS or the signals of the solvent as the internal standard. The IR spectra were recorded on a Bruker IFS-66v Fourier-transform spectrometer. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration *c* is given as g/100 ml). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected.

The melting curves were measured on a Perkin–Elmer Diamond DSC differential scanning calorimeter in aluminium pans with the rate of heating of 10 °C min^{-1}. The mass of the samples amounted to approximately 2.5 mg. Temperature scale and heat flux were calibrated against the data for indium, phenol and naphthalene.

HPLC analyses were performed on a Shimadzu LC-20AD system controller, and UV monitor 275 nm was used as a detector. The column used, from Daicel, Inc., was Chiralcel OD (0.46 × 25 cm).

4.2. Synthesis

Racemic epichlorohydrin (99%) was purchased from Alfa Aesar®; *rac*-3-chloropropane-1,2-diol (99+%) and 2-cyanophenol (99%) were purchased from Acros Organics®; methyl-*tert*-butyl ether (MTBE, 99.5%) was from Fisher Scientific. (*R*)- and (*S*)-3-chloro-1,2-propanediol, (*R*)-**4** and (*S*)-**4** were prepared through Jacobsen kinetic hydrolytic resolution of *rac*-epichlorohydrin without modifications.[21]

4.2.1. *rac*-3-(2-Cyanophenoxy)-propane-1,2-diol *rac*-2

Compound *rac*-**2** was synthesized by analogy with our early works.[10,11] To a solution of 2-cyanophenol **3** (6.5 g, 0.055 mol) in ethanol (37 ml), a solution of NaOH (3.1 g, 0.077 mol) in water (12 ml) was added and the resulting mixture was stirred and heated at reflux for 30 min. Then a solution of racemic 3-chloropropane-1,2-diol *rac*-**4** (7.3 g, 0.066 mol) in ethanol (6 ml) was added within 30 min, and the mixture was further stirred and heated at reflux for 3 h. After cooling, the volume of the resulting mixture was reduced to about one third followed by the addition water (40 ml) and extraction with CH_2Cl_2 (3 × 60 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed. The crude diol *rac*-**2** was purified by distillation (bp 154–160 °C at 0.05 mm Hg). Yield 9.1 g (86%); viscous oil, crystallizing upon standing. White solid was washed with ether. Mp 50–52 °C (hexane/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.20 (dd, *J* = 5.9, 6.6 Hz, 1H, IH), 2.90 (d, *J* = 4.4 Hz, 1H, IH), 3.83 (dd, *J* = 11.2, 5.0 Hz, 1H, OCH_2), 3.90 (dd, *J* = 11.2, 3.5 Hz, 1H, OCH_2), 4.15–4.22 (m, 3H, CHO, CH_2O), 7.01 (d, *J* = 8.6 Hz, 1H, Ar), 7.05 (t, *J* = 7.6 Hz, 1H, Ar), 7.53–7.56 (m, 2H, Ar). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.73; N, 7.25. Found: C, 62.31; H, 5.77; N, 7.42.

4.2.2. (*R*)-3-(2-Cyanophenoxy)-propane-1,2-diol (*R*)-2

Compound (*R*)-**2** was prepared from (*R*)-3-chloro-1,2-propanediol (*R*)-**4** {0.73 g, 6.6 mmol; $[\alpha]_D^{20} = -6.4$ (*c* 5, H_2O)} and 2-cyanophenol **3** (0.65 g, 5.5 mmol) as described for *rac*-**2**. Crude diol (*R*)-**2** (0.93 g, 89%) was crystallized from a mixture of light petroleum/EtOAc 1:1 to give (*R*)-**2** (0.64 g, 61%); mp 72–74 °C; $[\alpha]_D^{20} = -3.0$ (*c* 0.9, EtOH); $[\alpha]_D^{20} = +9.5$ (*c* 1.0, MTBE); 99.9% ee [chiral HPLC analysis of the diacetate derivative; column temperature 27 °C; eluent: hexane/isopropanol = 95/5; t_R = 23.3 min (major)] IR (KBr, cm^{-1}): 3262 (broad, O–H), 2227 (CN), 1599, 1496 (Ar). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.90 (br s, 2H, IH), 3.83 (dd, *J* = 11.0, 4.7 Hz, 1H, OCH_2), 3.90 (dd, *J* = 11.0, 2.9 Hz, 1H, OCH_2), 4.14–4.20 (m, 3H, CHO, CH_2O), 7.01 (d, *J* = 8.9 Hz, 1H, Ar), 7.04 (t, *J* = 7.3 Hz, 1H, Ar), 7.53–7.56 (m, 2H, Ar). ^{13}C NMR (150.864 MHz, $CDCl_3$) δ 63.3 (CH_2IH), 70.0 (CH), 70.2 (OCH_2), 102.1 (C^2_{Ar}), 112.5 (C^6_{Ar}), 116.5 (CN), 121.3 (C^4_{Ar}), 133.6 (C^3_{Ar}), 134.5 (C^5_{Ar}), 160.3 (C^1_{Ar}). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.73; N, 7.25. Found: C, 62.05; H, 5.69; N, 7.14.

4.2.3. (*S*)-3-(2-Cyanophenoxy)-propane-1,2-diol (*S*)-2

Compound (*S*)-**2** was synthesized analogously from the (*S*)-3-chloropropane-1,2-diol (*S*)-**4** {0.73 g, 6.6 mmol; $[\alpha]_D^{20} = +6.1$ (*c* 4.8, H_2O)}. Yield: 0.68 g (65%). Mp 72–74 °C; $[\alpha]_D^{20} = +3.1$ (*c* 1.0, EtOH); $[\alpha]_D^{20} = +14.3$ (*c* 0.5, H_2O); $[\alpha]_D^{20} = -9.5$ (*c* 1.0, MTBE); 99.4% ee [chiral HPLC analysis of the diacetate derivative; column temperature 27 °C; eluent: hexane/isopropanol = 95:5; t_R = 21.1 min (major)] {cf. lit.[9] mp 140–142 °C; $[\alpha]_D^{20} = +21.8$ (*c* 0.5, EtOH) for 65% ee; lit.[8] $[\alpha]_D^{20} = +9.4$ (*c* 0.5, EtOH) for 28% ee}. NMR spectra were close to above-described for the (*R*)-enantiomer and racemate.

4.2.4. Resolution of racemic 3-(2-cyanophenoxy)-1,2-propanediol, *rac*-2 by preferential crystallization (entrainment)

Racemic **2** (5.8 g) and (*R*)-**2** (0.6 g) were dissolved in 85 ml of MTBE at 40 °C. The solution was cooled to 12 °C and seeded with

finely-pulverized (*R*)-**2** (16 mg, 99% ee). During 45 min of stirring the temperature was lowered to 8 °C; after stirring the mixture for 80 min at 8–9 °C, precipitated (*R*)-**2** was collected by filtration {1.04 g after drying; $[\alpha]_D^{20} = +8.3$ (*c* 0.65, MTBE), 87% ee}. The extra portion of *rac*-**2** (1.02 g) was then dissolved in the mother liquor at 40 °C; the resulting solution was cooled to 10 °C. After the addition to a solution of (*S*)-**2** (16 mg, 99% ee) as seed crystals, and stirring the mixture for 85 min at 7–8 °C, (*S*)-**2** {0.80 g after drying; $[\alpha]_D^{20} = -7.9$ (*c* 0.7, MTBE), 83% ee} was collected by filtration. Further resolution was carried out at 7–8 °C by adding amended amounts of *rac*-**2** to the filtrate in a manner similar to that described above. After a second cycle, 0.66 g of (*R*)-**2** {$[\alpha]_D^{20} = +8.2$ (*c* 0.6, MTBE), 86% ee} and 0.60 g of (*S*)-**2** {$[\alpha]_D^{20} = -7.9$ (*c* 1.0, MTBE), 84% ee} were collected. After third cycle, 0.58 g of (*R*)-**2** {$[\alpha]_D^{20} = +8.2$ (*c* 0.6, MTBE), 87% ee} and 0.62 g of (*S*)-**2** {$[\alpha]_D^{20} = -7.5$ (*c* 1.1, MTBE), 80% ee} were collected. A high degree of enantiomeric purity of collected diols can be achieved by simple recrystallization from MTBE. For example, a portion of (*R*)-**2** (1.04 g, 87% ee) was dissolved in boiling MTBE (45 ml). After cooling the solution to 0–5 °C for 24 h the crystallized (*R*)-**2** was collected by filtration {yield 0.87 g; $[\alpha]_D^{20} = +9.5$ (*c* 0.8, MTBE), >99% ee}.

4.2.5. (2*RS*,4*R*)-4-(2-Cyanophenoxymethyl)-1,3,2-dioxathiolane-2-oxide, (2*RS*,4*R*)-5

To a stirred and cooled (0 °C) solution of (*S*)-3-(2-cyanophenoxy)-propane-1,2-diol (*S*)-**2** (1.93 g, 0.01 mol) in CH_2Cl_2 (25 ml) a solution of $SOCl_2$ (1.31 g, 0.011 mol) in CH_2Cl_2 (10 ml) was added dropwise. The reaction mixture was stirred for an extra 1 h, and the volatile material was removed under reduced pressure to afford a viscous oil, which crystallized upon standing. The mixture of *cis* and *trans* isomers, (2*R*,4*R*)-**5** and (2*S*,4*R*)-**5**, (38:62) was used in the next step without further purification; quantitative yield, mp 70–80 °C, $[\alpha]_D^{20} = +24.3$ (*c* 1.0, CH_2Cl_2)}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.15 (dd, *J* = 10.0, 6.3 Hz; 1H, CH_2OS-*trans*,); 4.28 (dd, *J* = 10.0, 4.2 Hz; 1H, CH_2OS-*trans*), 4.39 (dd,*J* = 9.1, 7.6 Hz; 0.6H, CH_2OS–*cis*), 4.54 (dd, *J* = 9.1, 5.2 Hz; 0.6H, CH_2OS-*cis*), 4.63 (dd, *J* = 8.9, 4.4 Hz; 1.0H, C*H*$_2$OAr-*trans*), 4.76 (d, *J* = 6.8 Hz, 1.2 H, C*H*$_2$OAr-*cis*), 4.90 (dd, *J* = 8.9, 6.5 Hz; 1.0H, C*H*$_2$OAr-*trans*), 4.97–5.02 (m, 0.6H, CHOS-*cis*), 5.30–5.33 (m, 1.0H, CHOS-*trans*), 7.00 (d, *J* = 8.6 Hz, 1.0H, C^6_{Ar}H-*trans*), 7.03 (d, *J* = 8.6 Hz, 0.6H, C^6_{Ar}H-*cis*), 7.09–7.12 (m, 1.6H, C^4_{Ar}H-*cis*/*trans*), 7.56–7.60 (m, 3.2H, C^5_{Ar}H-*cis*/*trans*, C^3_{Ar}H-*cis*/*trans*). ^{13}C NMR (150.864 MHz, $CDCl_3$) δ 67.28 (*C*H$_2$OAr-*trans*); 68.69 (CH_2OS-*trans*); 69.43 (*C*H$_2$OAr-*cis*); 70.20 (CH_2OS-*cis*); 77.32 (CHOS-*trans*); 79.06 (CHOS-*cis*); 102.51, 102.71 (C^2_{Ar}), 112.74, 112.82 (C^6_{Ar}); 115.76, 115.90 (CN), 122.12, 122.20 (C^4_{Ar}); 133.90, 134.00 (C^3_{Ar}); 134.51, 134.58 (C^5_{Ar}); 159.40 (C^1_{Ar}).

4.2.6. (*R*)-4-(2-Cyanophenoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide, (*R*)-6

4.2.6.1. Method A. Sulfate **6** was obtained by ruthenium-catalyzed oxidation of sulfites **5** by analogy with the published procedures.[17,19] To the crude mixture of (2*RS*,4*R*)-**5**, obtained from 1.93 g (0.01 mol) of diol (*S*)-**2**, CCl_4 (30 ml) was added and the resulting solution was refluxed for 30 min to remove the traces of gaseous HCl. After evaporation of solvent under reduced pressure and cooling to 0 °C, the mixture of CH_3CN (11 ml) and H_2O (1.3 ml), $NaIO_4$ (3.2 g, 0.015 mol) and $RuCl_3{\cdot}H_2O$ (4 mg, 0.017 mmol) was added to the residue. The resulting mixture was stirred for 5–6 h (monitored by TLC). After the reaction was completed, the solvent was evaporated under reduced pressure, and residue was diluted with AcOEt (70 ml) and H_2O (2 ml). The organic layer was washed with water (4 ml), saturated aqueous $NaHCO_3$ (2 × 2 ml), and brine (4 ml). After drying over $MgSO_4$, the solution was filtered through a small pad of silica gel. The filtrate was then concentrated to afford (*R*)-**6** as a white solid. Yield: 2.2 g (86%); mp 118–120 °C (CCl_4); $[\alpha]_D^{20} = +17.0$ (*c* 0.6, EtOH); 99.9% ee [chiral HPLC; column temperature 29 °C; eluent: hexane/isopropanol = 60:40; t_R = 13.0 min (major), t_R = 14.6 min (minor).] Cf. lit.[9] gum, $[\alpha]_D^{20} = +8.6$ (*c* 2.0, EtOH). IR (KBr, cm^{-1}): 3074, 3044 (C_{Ar}–H); 2947 (C–H); 2233 (CN); 1581, 1600, 1494 (Ar); 1375, 1206 [S(=O)$_2$]; 1060, 977, 834, 756 (S–O–C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.39 (dd, *J* = 10.2, 6.8 Hz; 1H, OCH_2), 4.48 (dd, *J* = 10.2, 5.0 Hz; 1H, OCH_2), 4.82 (dd, *J* = 9.0, 5.7 Hz; 1H, CH_2IS), 4.93 (dd, *J* = 9.0, 6.4 Hz; 1H, CH_2OS) 5.29–5.33 (m, 1H, CHOS), 7.02 (d, *J* = 8.32 Hz, 1H, C^6_{Ar}H), 7.13 (dd, *J* = 7.4, 7.6 Hz; 1H, C^4_{Ar}H), 7.6 (m, 2H, $C^{3,5}_{Ar}$H). ^{13}C NMR (150.864 MHz, $CDCl_3$) δ 66.8 (CH_2OS), 69.7 (OCH_2), 77.8 (CHOS), 102.9 (C^2_{Ar}), 113.0 (C^6_{Ar}), 115.5 (CN), 122.7 (C^4_{Ar}), 134.0 (C^3_{Ar}), 134.6 (C^5_{Ar}), 158.8 (C^1_{Ar}). Anal. Calcd for $C_{10}H_9NSO_5$: C, 47.05; H, 3.55; N, 5.48; S, 12.55. Found: C, 47.14; H, 3.48; N, 5.56; S, 12.54.

4.2.6.2. Method B. Sulfate (*R*)-**6** was obtained from diol (*S*)-**2** and SO_2Cl_2 following a slightly modified published procedure.[18] Diol (*S*)-**2** (0.58 g, 3 mmol) was dissolved in AcOEt under a nitrogen atmosphere. NEt_3 (4.8 ml, 36 mmol) was then added and the mixture cooled to 0–2 °C. SO_2Cl_2 (1.2 ml, 15 mmol) in AcOEt (1 ml) was added dropwise over a period of 3 h. The reaction mixture was stirred at this temperature for 30 min. Water (45 ml) was added and the layers separated and the organic one was washed twice with water and brine. After drying over $MgSO_4$, the solution was filtered through a small pad of silica gel. The filtrate was then concentrated by rotary evaporation (*i*-PrOH was used to remove the residual H_2O) and further dried under vacuum, washed with ether to yield 0.67 g of a crude solid (*R*)-**6** (87% yield), which was crystallized from CCl_4 to give a pure (*R*)-**6**; mp 118–120 °C (CCl_4); $[\alpha]_D^{20} = +16.5$ (*c* 0.6, EtOH).

4.2.7. (*S*)-4-(2-Cyanophenoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide, (*S*)-6

Compound (*S*)-**6** was obtained from (*R*)-**2** and SO_2Cl_2 following the above-mentioned procedure (method B); mp 118–120 °C, $[\alpha]_D^{20} = -16.9$ (*c* 0.5, EtOH).

4.2.8. *rac*-4-(2-Cyanophenoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide, *rac*-6

Compound *rac*-**6** was synthesized by two-step sequence of sulfite formation/ruthenium oxidation analogously with the above-described (Sections 4.2.5 and 4.2.6.1) methods from the *rac*-3-(2-cyanophenoxy)-propane-1,2-diol, *rac*-**2** (1.5 g, 7.8 mmol). Yield: 1.69 g (85%); white solid; mp 87–89 °C (CCl_4); Anal. Calcd for $C_{10}H_9NSO_5$: C, 47.05; H, 3.55; N, 5.48; S, 12.55. Found: C, 47.38; H, 3.44; N, 5.40; S, 12.41. Other portion of *rac*-**6**, 0.56 g from 0.58 g of *rac*-**2** and 2.4 g SO_2Cl_2 were obtained analogously with Section 4.2.6.2; mp 86–88 °C.

4.2.9. Resolution of *rac*-4-(2-cyanophenoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide, *rac*-6 by preferential crystallization (entrainment)

Racemic **6** (660 mg) and (*R*)-**6** (34 mg) were dissolved in 19 ml of EtOH at 50 °C. The solution was cooled to 15 °C and seeded with finely-pulverized (*R*)-**6** (2 mg). After stirring the mixture for 60 min at 11–12 °C, precipitated (*R*)-**6** was collected by filtration {52 mg after drying; $[\alpha]_D^{20} = +14.5$ (*c* 0.5, EtOH), 84% op}. The extra portion of *rac*-**6** (50 mg) was then dissolved in the mother liquor at 50 °C; the resulting solution was cooled to 15 °C. After the addition to a solution of (*S*)-**6** (2 mg) as seed crystals, and stirring the mixture for 85 min at 10–11 °C, (*S*)-**6** {40 mg after drying; $[\alpha]_D^{20} = -11.6$ (*c* 0.5, EtOH), 67% op} was collected by filtration.

4.2.10. (*S*)-1,2-Epoxy-3-(2-cyanophenoxy)-propane, (*S*)-8

Compound (*S*)-**8** was obtained by analogy with a published procedure.[19] To a solution of 0.63 g (2.5 mmol) of cyclic sulfate (*R*)-**6** in

15 ml of dry THF was added 1.04 g (12 mmol) of anhydrous LiBr. The suspension was stirred at room temperature for 2–3 h (monitored by TLC for the disappearance of cyclic sulfate). After the solvent was removed under vacuum, in the resulting residue, 25 ml of ether and 25 ml of 20% aqueous H_2SO_4 were added. The heterogeneous solution was stirred at 25 °C overnight. After completion of the reaction, the two layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 15 ml). The combined ether layer was washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated to give 0.62 g of (*R*)-3-(2-cyanophenoxy)-1-bromo-2-propanol, (*R*)-**7**, as a slightly yellow oil. To a solution of crude bromoalcohol (*R*)-**7** in 20 ml of MeOH anhydrous K_2CO_3 (1.10 g, 8 mmol) was added at 0 °C. The heterogeneous solution was stirred at this temperature for 2 h (monitored by TLC), and then 10 ml of saturated NH_4Cl aqueous solution was added, followed by extraction with CH_2Cl_2 (4 × 15 ml). The extracts were washed with water and brine, dried over Na_2SO_4 and concentrated to give 0.38 g (86% on the basic of **6**) of crude (*S*)-1,2-epoxy-3-(2-cyanophenoxy)-propane, (*S*)-**8**, as a white solid; mp 90–91 °C (diethyl ether/methanol), $[\alpha]_D^{20} = +18.5$ (*c* 0.5, EtOH), $[\alpha]_D^{20} = -5.0$ (*c* 1.0, $CHCl_3$) {lit.[20] mp 88–89 °C, $[\alpha]_D^{25} = +17.7$ (*c* 1, EtOH); lit.[9] gum, $[\alpha]_D^{25} = +2.3$ (*c* 2.3, $CHCl_3$)}.

4.2.11. (*S*)-1-(2-Cyanophenoxy)-2-hydroxy-3-*tert*-butylaminopropane hydrochloride; (*S*)-bunitrolol hydrochloride; (*S*)-1·HCl

4.2.11.1. Method A. A solution of dioxathiolane (2*RS*,4*R*)-**5** (0.9 g, 3.8 mmol) and Bu^tNH_2 (2.8 g, 38 mmol) in DMF (5 ml) was heated at 60–70 °C for 45 h. After this period, excess amine and DMF were removed in vacuo, 40 ml of a 1 M solution of NaOH was added, the mixture was extracted with AcOEt (3 × 40 ml), and extract was dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was dissolved in 15 ml of ether and gaseous HCl was passed through the resulting solution to give 0.59 g (55%) (*S*)-**1**·HCl, mp 184–186 °C (EtOH); $[\alpha]_D^{20} = -29.7$ (*c* 0.6, EtOH). IR (KBr, cm^{-1}): 3260 (br, OH); 2927, 2874 (NH_2^+); 2227 (CN); 1599, 1580, 1496 (Ar). ^1H NMR (600 MHz, $CDCl_3$): δ 1.54 (s, 9H, CH_3), 3.29 (dd, *J* = 18.5, 9.5 Hz; 1H, CH_2N), 3.40 (dd, *J* = 18.5, 8.6 Hz; 1H, CH_2N), 4.25 (dd, *J* = 9.5, 5.1 Hz, 1H, CH_2O), 4.29 (dd, *J* = 9.5, 4.0 Hz, 1H, $1CH_2O$), 4.72 (m, 1H, CH), 5.50 (s, 1H, OH), 7.03–7.06 (m, $C^4_{Ar}H$, $C^6_{Ar}H$), 7.53–7.56 (m, $C^3_{Ar}H$, $C^5_{Ar}H$), 8.29 (s, 1H, NH), 9.62 (s, 1H, NH). ^{13}C NMR (150.864 MHz, $CDCl_3$): δ 25.91 (CH_3), 45.28 (NCH_2), 58.01 (CMe_3), 65.58 (CHOH), 70.82 (OCH_2), 102.36 (C^2_{Ar}), 113.04 (C^6_{Ar}), 116.27 (CN), 121.50 (C^4_{Ar}), 133.43 (C^3_{Ar}), 134.50 (C^5_{Ar}), 160.14 (C^1_{Ar}). Anal. Calcd for $C_{14}H_{21}ClN_2O_2$: C, 59.89; H, 7.49; N, 9.98; Cl, 12.48. Found: C, 60.07; H, 7.74; N, 9.76; Cl, 12.8.

4.2.11.2. Method B. The cyclic sulfate opening with *tert*-butyl amine was conducted by analogy with a published procedure.[22] A solution of cyclic sulfate (*R*)-**6** (255 mg, 1.0 mmol) and Bu^tNH_2 (0.11 g, 0.16 ml, 1.5 mmol) in 5 ml THF was stirred at room temperature for 24 h until the disappearance of **6** (TLC). The solution was then concentrated, and the residue was stirred with 20% aqueous H_2SO_4 (9 ml) and ether (20 ml) for 12 h. Sodium hydroxide pellets were added to the ice-cooled reaction mixture slowly until the pH >12 was reached. The layers were separated, and the aqueous layer was extracted with three more portions of AcOEt (30 ml each) and combined extract was dried over Na_2SO_4. After the removal of solvent, the residue was dissolved in Pr^iOH (minimal amount), and 0.2 ml of concd aqueous HCl was added. White crystals slowly precipitate during standing. After filtering off and ether rinsing out 71 mg (25%) of (*S*)-bunitrolol hydrochloride, (*S*)-**1**·HCl was collected. Mp 184–186 °C (EtOH), $[\alpha]_D^{20} = -29.1$ (*c* 0.9, EtOH).

4.2.11.3. Method C. (*S*)-1,2-Epoxy-3-(2-cyanophenoxy)-propane, (*S*)-**8** (0.38 g, 2.15 mmol) and 2.3 ml (21 mmol) of Bu^tNH_2 were heated at reflux for 5–7 h. The reaction was monitored by TLC. After the disappearance of the starting epoxide the mixture was evaporated to dryness and the residual viscous oil was crystallized upon standing giving (*S*)-1-(2-cyanophenoxy)-2-hydroxy-3-*tert*-butylaminopropane; (*S*)-bunitrolol (*S*)-**1** as a free base. Mp 30–32 °C; $[\alpha]_D^{20} = -9.0$ (*c* 0.8, EtOH); $[\alpha]_D^{20} = +12.3$ (*c* 0.38, H_2O) [cf. lit.[9] for (*S*)-bunitrolol: mp 162 °C; $[\alpha]_D^{20} = -10.0$ (*c* 1.4, H_2O), 60% ee]. ^1H NMR (600 MHz, $CDCl_3$) δ 1.13 (s, 9H, CH_3), 2.49 (br s, 2H, OH, NH), 2.79 (dd, *J* = 12.1, 6.6 Hz; 1H, CH_2N), 2.93 (dd, *J* = 12.1, 4.4 Hz; 1H, CH_2N), 3.97–4.01 (m, 1H, CH), 4.12 (d, *J* = 4.8 Hz, 2H, CH_2O), 7.00–7.02 (m, 2H, Ar), 7.51–7.56 (m, 2H, Ar). ^{13}C NMR (150.864 MHz, $CDCl_3$): δ 30.54 (CH_3), 45.75 (NCH_2), 51.97 (CMe_3), 69.40 (CHOH), 73.22 (OCH_2), 103.75 (C^2_{Ar}), 114.04 (C^6_{Ar}), 117.80 (CN), 122.55 (C^4_{Ar}), 135.12 (C^3_{Ar}), 135.77 (C^5_{Ar}), 162.03 (C^1_{Ar}) [cf. lit.[9]]. The thus obtained (*S*)-**1** was dissolved in ether, and dry HCl was passed through the solution until saturation was achieved. The solid hydrochloride was filtered out (yield 87%); after two successive crystallizations from EtOH, (*S*)-**1**·HCl was isolated in a yield of 66%; mp 184–186 °C, $[\alpha]_D^{20} = -29.6$ (*c* 0.9, EtOH); $[\alpha]_D^{20} = -14.7$ (*c* 0.8, H_2O).

(*R*)-**1**·HCl was obtained from (*R*)-**8** and Bu^tNH_2 following the above-mentioned procedure. (*R*)-**1**·HCl: mp 187–189 °C, $[\alpha]_D^{20} = +29.2$ (*c* 0.7, EtOH).

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