Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Synthesis, crystal structure, and absolute configuration of the enantiomers of chiral drug xibenolol hydrochloride

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ARTICLE INFO

*Article history:*
Received 27 July 2017
Revised 8 August 2017
Accepted 16 August 2017
Available online xxxx

ABSTRACT

Based on the features of its crystallization, racemic 3-(2,3-dimethylphenoxy)propane-1,2-diol **2**, the synthetic precursor of the chiral drug xibenolol **1**, was resolved into pure enantiomers by the direct method of entrainment. The enantiomers of diol **2** through a Mitsunobu reaction were converted into the nonracemic 1,2-epoxy-3-(2,3-dimethylphenoxy)propanes (*S*)- and (*R*)-**3**, and then into the xibenolol enantiomers. Single crystals of (+)- and (−)-**1**·HCl were studied by X-ray diffraction. On the basis of the Flack parameter, the absolute (*R*)- and (*S*)-configurations were assigned to these compounds and to the other intermediate chiral substances.



## 1. Introduction

Xibenolol **1** is the common name for 1-(*tert*-butylamino)-3-(2,3-dimethylphenoxy)-2-propanol (Chart 1) and is a selective β-adrenergic blocker.[1] Its hydrochloric salt, xibenolol hydrochloride, in its racemic form is present on the market as an antiarrhythmic remedy under the trade names Selapin and Rhythminal.

In general, the stereoselectivity of the physiological action of β-blockers and antiarrhythmic agents is well known.[2,3] A series of papers demonstrated the stereoselectivity of the metabolism and pharmacokinetics of xibenolol and showed that the pharmacological activity belonged predominantly to the (−)-enantiomer and its metabolites.[4,5] In the cited works, however, there are no assignments of the xibenolol enantiomers to a certain absolute configuration. At present, there is a tendency to replace racemic active pharmaceutical ingredients with single enantiomeric ones. Therefore, the preparation of non-racemic xibenolol with a particular configuration is of practical interest.

Different approaches have been used to obtain single-enantiomeric β-blockers.[6] In particular, there are several examples in the literature for obtaining non-racemic xibenolol. The resolution of racemic deuterated xibenolol analogues using (+)- and (−)-di-(*p*-toluyl)tartaric acids as the resolving agents.[4] For hydrochloride salts of xibenolol, the following characteristics are: (−)-**1**-$d_5$·HCl, mp 147–148 °C, $[\alpha]_D^{20} = -25.5$ (*c* 1, EtOH); (+)-**1**-$d_5$·HCl, mp 147–148 °C, $[\alpha]_D^{20} = +25.7$ (*c* 1, EtOH).

The multistage synthesis of (*S*)-xibenolol, in which (*S*)-3-(2,3-dimethylphenoxy)propane-1,2-diol, (Chart 1, (*S*)-**2**) was used as the chirality source has been described.[7] In its turn the diol was obtained by Sharpless asymmetric dihydroxylation of the corresponding aryl allyl ether. To produce the target xibenolol, the diol was converted into the corresponding epoxide (*S*)-**3** (Chart 1) using a three-step procedure. Isolated (*S*)-xibenolol (67% *ee*) was obtained as an oil with a specific rotation $[\alpha]_D^{20} = -17.6$ (*c* 1.0, $CHCl_3$). The (*S*)-configuration was assigned to the obtained product by comparison of the observed specific rotation with the literature data $[\alpha]_D^{20} = -25.4$ (c 1.0, $CHCl_3$).[4] In the cited work,[4] the value for specific rotation was given not for the xibenolol base, but for its hydrochloride; it was also measured in ethanol, not in chloroform. Therefore, the comparison of such data is invalid. In addition, as it described in the work,[7] the key intermediate in the xibenolol synthesis, namely, the epoxide (*S*)-**3** was characterized by specific rotation of $[\alpha]_D^{20} = -6.5$ (*c* 2.3, $CHCl_3$), which is in conflict with another published value for the same parameter: $[\alpha]_D^{27} = +13.8$ (*c* 1.0, EtOH), 96.6% *ee*.[8] To eliminate the above discrepancies in the literature data, we synthesized xibenolol **1** and its precursor oxirane **3** in both enantiomeric forms and determined the absolute configuration of enantiomeric xibenolol hydrochlorides by the single crystal XRD relying on the Flack parameter. As a source of chirality, we used enantiopure samples of 3-(2,3-dimethylphenoxy) propane-1,2-diol **2** obtained by direct resolution of its racemate through an entrainment procedure.

In a recent study we found that depending on the crystallization conditions, racemic diol **2** forms three relatively stable crystalline phases: two polymorphic racemic compounds and the normal racemic conglomerate.[9] Two more metastable racemic phases are

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http://dx.doi.org/10.1016/j.tetasy.2017.08.013
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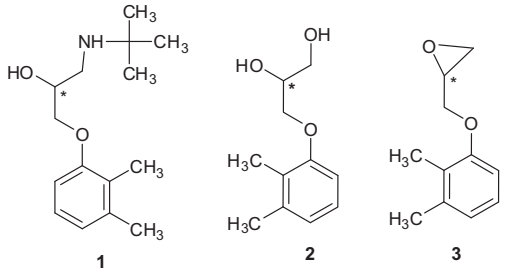


**Chart 1.** Xibenolol **1**, 3-(2,3-dimethylphenoxy)propane-1,2-diol **2** and 1,2-epoxy-3-(2,3-dimethylphenoxy)propane **3**.

formed by the crystallization of *rac*-**2** from the melt. On the one hand, the crystallization of a chiral substance in the form of a normal racemic conglomerate opens up the possibility of its resolution into individual enantiomers by direct methods, which are increasingly used for the preparation of practically important single enantiomeric compounds.[10,11] On the other hand, the complex phase behavior of a chiral substance and, in particular, the presence of several energy-close (meta)stable crystalline racemic compounds, as a rule, adversely affects the results of direct resolution.[12,13] However in the case of diol **2**, the racemic conglomerate, at least above room temperature, is thermodynamically more stable than all other crystalline phases. In addition, it is this form that crystallizes primarily under the conditions of even a slight enantiomeric enrichment of the initial sample. We have shown that taking these features into account allows us in principal to separate racemic **2** into individual enantiomers through an entrainment procedure.[9] Herein this technique is improved and used as the basis for obtaining pure enantiomeric **2** as a starting material for the synthesis of non-racemic xibenolol.

## 2. Results and discussion

### 2.1. Resolution by entrainment of racemic 3-(2,3-dimethylphenoxy)propane-1,2-diol, *rac*-2

As stated above, the source of chirality of the final and intermediate products was the spontaneous resolution of racemic 3-(2,3-dimethylphenoxy)propane-1,2-diol **2**. The starting *rac*-**2** was obtained by the interaction of sodium 2,3-dimethylphenolate with racemic 3-chloropropane-1,2-diol (Scheme 1, step *i*). To obtain enantiopure seeds, we used the same approach with commercially available enantiomeric (*R*)- and (*S*)-3-chloropropane-1,2-diols.[9]

Earlier we showed that for the stable polycyclic resolution of diol **2** in water, after separation of the enantiomeric precipitate, a small amount of *scal*-**2** must be added to the mother liquor, along with the missing racemate, to maintain the initial enantiomeric enrichment of the resolvable mixture of about 10% *ee*.[9] The use of water as a working solvent is inconvenient for preparative purposes, since the solubility of diol **2** is low, for the racemate it is $C_{sat}$ = 10.7 mg/ml at 52 °C.[9] Herein, we preferred to work with a medium in which the solubility of diols **2** is significantly higher. In MTBE the solubility is $C_{sat}$ = 60 mg/ml at 33.5 °C for *rac*-**2** and $C_{sat}$ = 25 mg/ml at 34 °C for (*R*)-**2**. Therefore, we used MTBE as the solvent for the racemic diol resolution. By varying the initial concentration, temperature gap, and crystallization time, we adopted the conditions for the satisfactory resolution of *rac*-**2**.

An example of a successful resolution of near racemic **2** is illustrated in Table 1. In the large scale experiment on the resolution of 3-(2,3-dimethylphenoxy)propane-1,2-diol **2**, the initial concentration of slightly enriched (~10% *ee*) *rac*-**2** was approximately 56 mg/ml. Over the course of resolution a supersaturated solution of *rac*-**2** (1.836 g), including a moderate excess of (*R*)-**2** (0.203 g), was prepared by heating the mixture in 36 ml of MTBE at 45 °C. The solution was cooled to ~23 °C and a small amount (8 mg) of finely pulverized seed crystals of (*R*)-**2** was added. The stirred solution was allowed to crystallize for about 30 min at 23 ± 1 °C.

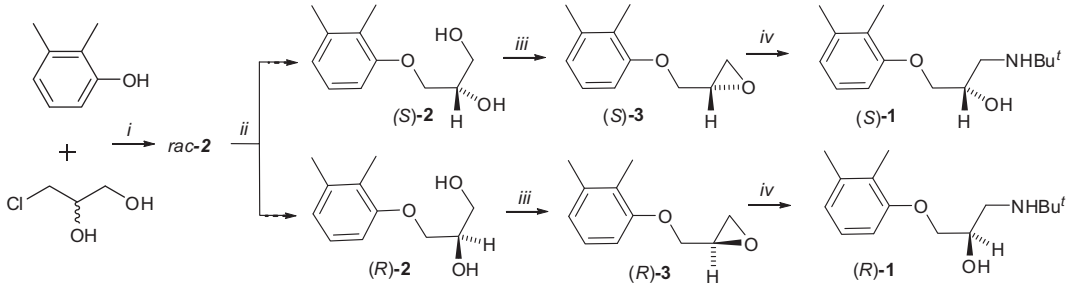
As can be seen from Table 1, for a successful separation in MTBE (as well as in water), after separation of the precipitate, along with a racemic diol, a small amount of a scalemic diol must also be added each time into the mother liquor to create its minor enantiomeric enrichment, otherwise the crystallization of supersaturated racemic solutions is complicated by the formation of racemic polymorphs, which in turn leads to precipitates with a low (about 20%) enantiomeric excess. The scalemate added to the mother liquor need not necessarily have a high enantiomeric purity, it is sufficient to use the raw crystalline samples obtained in the previous resolution runs.

The enantiomeric purity of scalemic samples can be increased to any desired value through simple recrystallization.

### 2.2. Synthesis of enantiopure xibenolol, 1-(*tert*-butylamino)-3-(2,3-dimethylphenoxy)-2-propanol

The general approach we used to obtain the individual enantiomers of xibenolol **1** is shown in Scheme 1. Racemic diol **2** was obtained in good yield by the reaction of sodium 2,3-dimethylphenolate with racemic 3-chloropropane-1,2-diol. The key step in our approach, *ii*, is the direct resolution of the racemic diol **2** by an entrainment procedure, which is described above.

Conversion of the obtained enantiomers of **2** into the target compounds **1** was carried in two steps. Initially, we used an intramolecular Mitsunobu etherification of diols **2** to give enantiomeric epoxides **3**.[14,15] The reaction proceeds with a slight loss of enantiomeric purity (from 98 to 96% *ee*). By analogy with similar cyclizations,[16,17] we assume that the initial configuration of the stereogenic center is conserved. It is noteworthy that the value of the specific rotation for (*S*)-**3** obtained by us does not coincide either in magnitude or in sign with the data of Sayyed et al.,[7] but are in good agreement with the data of Kong et al.[8]



**Scheme 1.** Reagents and conditions: (*i*) NaOH, EtOH, reflux; (*ii*) resolution by entrainment; (*iii*) $PPh_3$, DIAD, THF, reflux; (*iv*) *t*-$BuNH_2$, reflux.

**Table 1**
Resolution by entrainment of *rac*-3-(2,3-dimethylphenoxy)propane-1,2-diol, *rac*-**2** in MTBE (36 ml, 8 mg of crystal seeds on every run; crystallization temperature 23 ± 1 °C)

| Run | Added amount of *rac*-**2**, g | Enantiomeric composition of the added scal-**2**, g | | Operation amount of enantiomers, g | | Resol. time, min | (*R*)-**2** and (*S*)-**2** obtained | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | (*R*)-**2** | (*S*)-**2** | (*R*)-**2** | (*S*)-**2** | | Yield, g | ee[a],% | YE [b] | |
| | | | | | | | | | (g) | (%) |
| 1 | 1.836 | 0.203 | 0 | 1.121 | 0.918 | 30 | (*R*) 0.349 | 79.7 | 0.270 | 24.1 |
| 2 | 0.249 | 0 | 0.141 | 0.940 | 1.148 | 30 | (*S*) 0.366 | 80.9 | 0.288 | 25.1 |
| 3 | 0.102 | 0.151 | 0.017 | 1.100 | 0.900 | 30 | (*R*) 0.394 | 83.8 | 0.322 | 29.3 |
| 4 | 0.189 | 0.046 | 0.151 | 0.900 | 1.100 | 30 | (*S*) 0.381 | 89.4 | 0.333 | 30.3 |
| 5 | 0.275 | 0.088 | 0.010 | 1.100 | 0.900 | 30 | (*R*) 0.388 | 88.0 | 0.333 | 30.3 |
| 6 | 0.179 | 0.066 | 0.135 | 0.900 | 1.100 | 30 | (*S*) 0.395 | 84.7 | 0.327 | 29.7 |
| 7 | 0.297 | 0.082 | 0.008 | 1.101 | 0.899 | 30 | (*R*) 0.400 | 81.5 | 0.318 | 28.9 |
| 8 | 0.281 | 0.011 | 0.100 | 0.900 | 1.100 | 30 | (*S*) 0.379 | 83.8 | 0.310 | 28.2 |

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

Individual enantiomers of xibenolol (*S*)-**1** and (*R*)-**1** were obtained by reflux of (*S*)-**3** and (*R*)-**3** with an excess of *tert*-butylamine in the presence of a minor amount of water. It was stated[7] that (*S*)-xibenolol with an enantiomeric purity of 67% *ee* was characterized by $[\alpha]_D^{20} = -17.6$ (*c* 1.0, $CHCl_3$). Our (*S*)-**1** sample (96.4% *ee*) was characterized by a specific rotation value of $[\alpha]_D^{20} = -15.6$ (*c* 1.1, $CHCl_3$), which is poorly consistent with the data of the cited work.

In the final stage, the resulting amino alcohols **1** were converted into hydrochlorides by passing gaseous HCl through ether solutions of the base. The literature does not contain the characteristics of enantiomers **1**·HCl, but there are data for some deuterated analogues of (−)-xibenolol hydrochloride.[4] Our data for (*S*)-**1**·HCl were in good agreement with the literature.

### 2.3. Single-crystal X-ray investigation

To accurately determine the absolute configuration of the enantiomers of xibenolol and, as a consequence, to remove the abovementioned contradictions, we performed an X-ray diffraction analysis of the individual enantiomers for (−)-**1**·HCl {mp 146–149 °C; $[\alpha]_D^{20} = -27.0$ (*c* 1.0, EtOH), 99.2% *ee*} and (+)-**1**·HCl {mp 144–146 °C; $[\alpha]_D^{20} = +26.0$ (*c* 1.0, EtOH), 96.9% *ee*}. Single crystals for XRD experiments were grown from these samples by slow evaporation of solutions in a mixture of $Et_2O$/MeOH.

Although the growth conditions of both crystals were close, there is a noticeable difference in their habit. As can be seen from the micrographs (Fig. 1) of the single crystals studied, the crystal (−)-**1**·HCl (Fig. 1a) is represented by a prism with commensurate parameters. The crystals (+)-**1**·HCl (Fig. 1b) are characterized by considerable anisometry and are extremely thin plates, the smallest dimension of which is practically at the boundary of the value permissible for X-ray diffraction analysis. This factor depletes the experimental diffraction pattern and complicates its decoding.

It can be assumed that the differences in the crystal habit are related to the different enantiomeric purities of the feeding medium in which they were formed. However, a study of the xybenolol hydrochloride phase behavior was out of the objectives of the present work. Therefore, we have no grounds to judge the details of such influence. The indexing of the faces of the investigated crystals revealed another interesting circumstance: in both cases the largest (and, consequently, the slowest in the growth rate) faces of the crystal correspond to the 0 0 1 planes i.e., regardless of the crystal quality, in both cases the crystals growth in the crystallographic direction 0 0 1 is impeded by some common factor.

Despite the difference in the shape of the crystals, according to X-ray diffraction data, both compounds crystallize as a normal salt and contain one independent "cation–anion" pair in the asymmetric unit of the orthorhombic unit cell $P2_12_12_1$. The parameters of the X-ray experiment are shown in Table 2. There are no anomalous values of bond lengths or valence angles in the studied molecules. The conformation of an independent molecule (or to put it more precisely, the organic cation) in (−)-**1**·HCl crystal is shown in Fig. 2a. The structure of the inverted cation in the (+)-**1**·HCl crystal coincides with this structure up to the experimental errors (Fig. 2b), as it should be for a pair of enantiomers forming the same unit cells (see Table 2).

The absolute structure of the investigated single crystal (−)-**1**·HCl was determined based on the Flack parameter.[18,19] The experimental value -0.01(3) allows us to reliably attribute the (*S*)-configuration to the xybenolol molecules forming this crystal. In turn, this completely confirms the correctness of our configuration assignments made during the synthesis of the target products.

The determination of the absolute configuration by means of an anomalous X-ray scattering analysis is facilitated by the presence of a relatively heavy atom, e.g., chlorine in our case. However, as we noted earlier,[20] with high quality crystals of organic compounds containing only light atoms (up to oxygen inclusive), it is possible to confidently establish the absolute configuration of molecules, even using earlier tests of Hamilton and Rogers.[21,22] This was only possible with close to perfect crystals and is very problematic for crystals such as (+)-**1**·HCl (Fig. 1b). The Flack parameter turned out to be workable even in this situation. The absolute structure of this crystal and, consequently, the absolute configuration of its chiral constituents, (*R*)-**1** molecules, were established by us on this basis. Although it should be noted that in this case, the parameter value [−0.1(2), Table 2] was not so convincing.

The main crystal formative intermolecular interactions in the investigated crystals are the trifurcate hydrogen bonds O—H···Cl and N—H···Cl between the chlorine anion and the hydrogen atoms of the hydroxyl and amino groups. Table 3 shows the parameters of these H-bonds for (*S*)-(−)-**1**·HCl. These interactions are realized between molecules bonded by a screw axis of the second order, and lead to the formation of one-dimensional supramolecular structures, namely, infinite ribbons spread along the crystallographic axis *0b* (Fig. 3).

Taken as a whole, the crystal structure is characterized by the parallel hexagonal packing of similar 1D-supramolecular structures (Fig. 4). At such a mutual arrangement of the molecules, the density of the crystalline packing suffers: the calculated packing index for the crystals of both enantiomers is 64.4%, which is close to the lower limit of the values that are characteristic for crystalline organic matter (65–75%).

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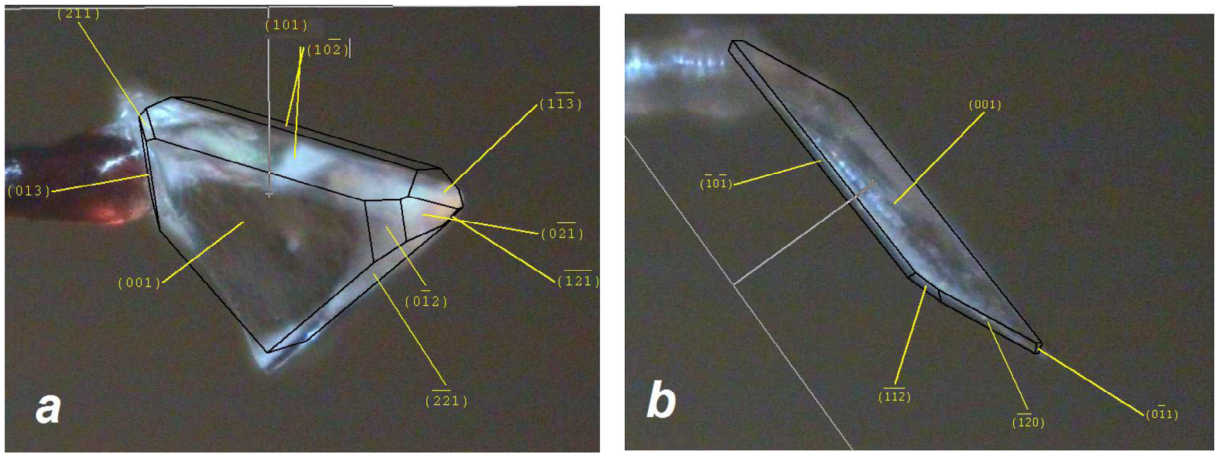


**Figure 1.** Microscopic pictures of (−)-**1**·HCl (**a**) and (+)-**1**·HCl (**b**) crystals with indexed crystal planes.

**Table 2**
Crystallographic data for (*S*)-Xibenolol hydrochloride and (*R*)-Xibenolol hydrochloride

| Compound, sample | (*S*)-(−)-**1**·HCl, (*S*)-xibenolol hydrochloride | (*R*)-(+)-**1**·HCl (*R*)-xibenolol hydrochloride |
|---|---|---|
| Formula | $C_{15}H_{25}NO_2$·HCl | $C_{15}H_{25}NO_2$·HCl |
| *M* (g/mol) | 287.82 | 287.82 |
| Temperature, K | 296(2) | 296(2) |
| Crystal class | Orthorhombic | Orthorhombic |
| Space group | $P2_12_12_1$ | $P2_12_12_1$ |
| Crystal size ($mm^3$) | 0.67 × 0.49 × 0.38 | 0.67 × 0.38 × 0.03 |
| *Z*, *Z*′ | 4, 1 | 4, 1 |
| Cell parameters | *a* = 7.7817(8) Å, | *a* = 7.818(5) Å, |
| | *b* = 8.5131(7) Å, | *b* = 8.514(5) Å, |
| | *c* = 25.181(2) Å | *c* = 25.164(17) Å |
| *V*, $Å^3$ | 1668.2(3) | 1675(1) |
| *F*(000) | 624 | 624 |
| $\rho_{calc}$ g/$cm^3$ | 1.146 | 1.141 |
| $\mu$, $mm^{-1}$ | 0.228 | 0.227 |
| $\theta$ range, deg | 1.617–31.594 | 3.410–26.719 |
| Reflections measured | 24021 | 5185 |
| Independent reflections/*R*(int) | 5326/0.0449 | 3358/0.1275 |
| Number of parameters/restraints | 189/0 | 189/3 |
| Reflections [$I > 2\sigma(I)$] | 3501 | 757 |
| $R_1/wR_2$ [$I > 2\sigma(I)$] | 0.0489/0.1176 | 0.0585/0.0631 |
| $R_1/wR_2$ (all reflections) | 0.0865/0.1442 | 0.3118/0.1163 |
| Goodness-of-fit on $F^2$ | 1.013 | 0.661 |
| $\rho_{max}/\rho_{min}$ (e $Å^{-3}$) | 0.242/−0.252 | 0.155/−0.160 |
| Flack parameter | −0.01(3) | −0.1(2) |

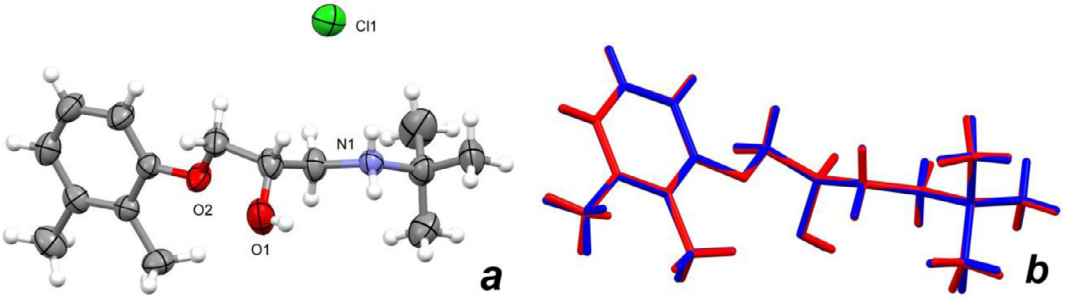


**Figure 2.** (**a**) Asymmetric unit of the unit cell in (−)-**1**·HCl crystals. Non-hydrogen atoms are represented by probability ellipsoids of thermal vibrations (*p* = 50%), hydrogen atoms – by spheres of arbitrary radii. (**b**) Conditional superposition of organic cations in crystals of enantiomeric xibenolol hydrochlorides. Blue color indicates a molecule in (−)-**1**·HCl crystals, red color indicates an inverted molecule in (+)-**1**·HCl crystals.

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**Table 3**
Parameters of hydrogen bonds in the crystal of (*S*)-(−)-**1**·HCl

| Contact | d(D—H),Å | d(H···A), Å | d(D···A), Å | ∠(D–H···A), ° | Symmetry operation |
|---|---|---|---|---|---|
| N1—H1···Cl1* | 0.83(4) | 2.31(4) | 3.134(2) | 173(3) | 1−x, −1/2 + y,1/2−z |
| N1—H2···Cl1** | 0.91(3) | 2.26(3) | 3.154(3) | 167(3) | x, −1 + y,z |
| O1—H21···Cl1** | 0.77(4) | 2.43(4) | 3.172(3) | 164(3) | x, −1 + y,z |

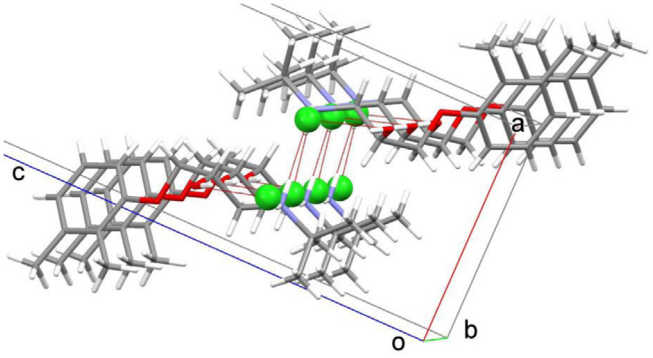


**Figure 3.** Detail of the crystal packing for (*S*)-(−)-**1**·HCl: 1D ribbon along *0b* direction, H-bonds are shown by red dashed lines.

It can be seen from another projection of the same packing (Fig. 5), that it is characterized by the formation of antiparallel (from the point of view of the directivity of intermolecular interactions) layers composed of translations of 1D supramolecular structures along the crystallographic *0a* direction. The antiparallel layers themselves alternate along the crystallographic *0c* direction and turn out to be connected mainly by hydrophobic interactions of peripheral aromatic fragments of adjacent molecules.

As illustrated by the example of the (*S*)-enantiomers, the growth of homochiral **1**·HCl crystals has a common mechanism. This is probably associated with the formation of 1D supramolecular structures (due to strong intermolecular interactions) and their subsequent binding (due to secondary interactions) into 2D layers parallel to *0ab*. Finally, the association of layered structures, due to the hydrophobic effect, leads to the three-dimensional crystal. The last of the three processes proved to be the least effective, and, as was noted above during the discussion of Figure 1, crystal growth in the crystallographic 001 direction slows down.

## 3. Conclusion

An original scheme for the synthesis of chiral drug xibenolol **1** in both enantiomeric forms is proposed. It is based on the stereoselective crystallization of the intermediate 3-(2,3-dimethylphenoxy)propane-1,2-diol **2** followed by Mitsunobu intramolecular etherification into the enantiomeric 1,2-epoxy-3-(2,3-dimethylphenoxy)propanes (*R*)- and (*S*)-**3**. A special feature of the realized approach is the use of the potential of spontaneous resolution of diol **2**, the crystallization of which in the form of a racemic conglomerate is complicated by the formation of polymorphic racemic modifications.

The single crystals of enantiomeric xibenolol hydrochlorides grown from samples with different enantiomeric purities differ in their habit, but have a common crystal structure. Despite the different qualities of the single crystals, the absolute configuration of both homochiral hydrochlorides of amine **1** was reliably determined by the X-ray diffraction method using the Flack parameter. The stereoselective character of the realized synthetic operations made it possible to confirm the absolute configuration of all the chiral substances obtained herein and to eliminate some literature contradictions.

## 4. Experimental

### 4.1. General

The NMR spectra were recorded on a Bruker Avance-400 spectrometer (399.9 MHz for $^{1}$H and 100.5 MHz for $^{13}$C) or a Bruker

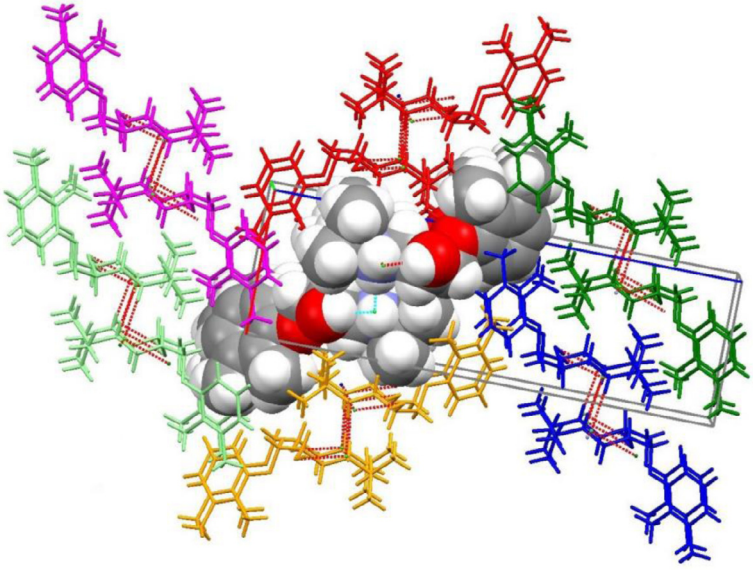

**Figure 4.** Fragment of hexagonal type of 1D ribbons packing in the crystal of (*S*)-(−)-**1**·HCl; view along 0*b* direction. Central ribbon is displayed in "spacefill" style, neighboring ribbons are shown by different colors.

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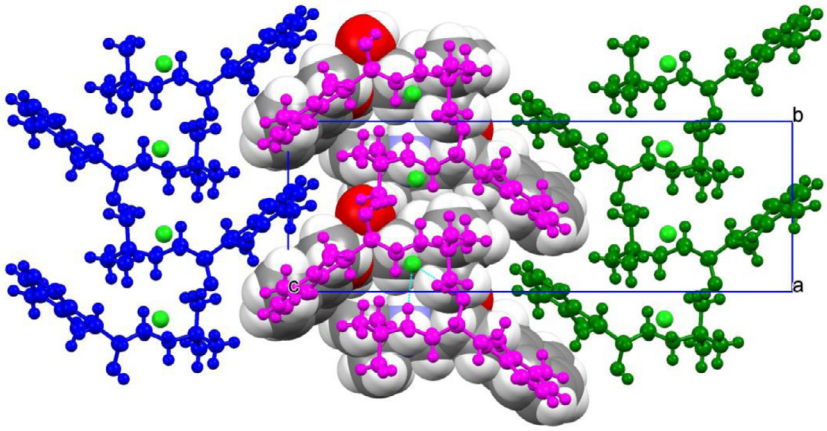


**Figure 5.** Fragment of 1D ribbons packing in (*S*)-(−)-**1**·HCl crystal; view along *0a* direction. Different 1D associates are shown by different style or colors.

Avance-500 (500.13 MHz for 1 H and 125.75 MHz for $^{13}C$) in $CDCl_3$ with the signals of the solvent as the internal standard. Infrared spectra were recorded on a Bruker Tensor 27 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. Thin-layer chromatography was performed on Silufol UV-254 plates using hexane/EtOAc (6:4) as eluent; TLC plates were visualized under UV irradiation or by treatment with iodine vapor. HPLC analyses were performed on a Shimadzu LC-20AD system controller, UV monitor 275 nm was used as detector. The column used, from Daicel Inc., was Chiralcel OD (0.46 × 25 cm); column temperature 20 °C; flow rate: 1 mL/min.

### 4.2. Compounds

Racemic 3-chloropropane-1,2-diol (99%) and *tert*-butylamine (99%) were purchased from Acros Organics. 2,3-Dimethylphenol (99%), (*R*)-3-chloropropane-1,2-diol (97%, 98% *ee*), (*S*)-3-chloropropane-1,2-diol (98%, 98% *ee*), diisopropyl azodicarboxylate (94%), and triphenylphosphine (99%) were purchased from Alfa Aesar. Racemic and enantiopure 3-(2,3-dimethylphenoxy)propane-1,2-diol, *rac*-**2** and (*R*)- or (*S*)-**2**, used as seed, were prepared from *rac*- and (*R*)- or (*S*)-3-chloropropane-1,2-diol as described in our earlier work.[9]

#### 4.2.1. Racemic 3-(2,3-dimethylphenoxy)propane-1,2-diol *rac*-2

Racemic diol *rac*-**2** was prepared by analogy with published procedure.[9] Mp 81.5–90 °C.

#### 4.2.1.1. (*R*)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (*R*)-2.

Non-racemic (*R*)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (*R*)-**2** used as seed was obtained from (*R*)-3-chloropropane-1,2-diol and 2,3-dimethylphenol as described in our preceding work.[9] Mp 101–102.5 °C (light petroleum ether/EtOAc); $R_f$ = 0.1; $[\alpha]_D^{20}$ = +13.4 (*c* 1.1, MTBE); $[\alpha]_D^{20}$ = +1.4 (*c* 1.0, EtOH) {lit.[8] $[\alpha]_D^{25}$ = +1.44 (*c* 1.0, EtOH) 96.6% *ee*}; 99.3% *ee* [chiral HPLC analysis; eluent: hexane/2-propanol (8:2); $t_R$ = 11.2 min]. $^1H$ NMR (400 MHz, $CDCl_3$/$CD_3OD$) δ: 2.11 (s, 3H, 2′-$CH_3$), 2.22 (s, 3H, 3′-$CH_3$), 3.68 (ddd, *J* = 11.5, 6.2, 1.4 Hz; 1H, C*H*$_2$OH), 3.78 (m, *J* = 11.5, 5.0, 1.8 Hz; 1H, C*H*$_2$OH), 3.95 (d, *J* = 5.4 Hz, 2H, $OCH_2$), 4.02–4.07 (m, 1H, C*H*OH), 6.68 (d, *J* = 8.0 Hz; 1H, $C^6_{Ar}H$), 6.75 (d, *J* = 7.3 Hz; 1H, $C^4_{Ar}H$), 6.99 (t, *J* = 7.8 Hz, 1H, $C^5_{Ar}H$). $^{13}C$ NMR (100.5 MHz, $CDCl_3$/$CD_3OD$) δ: 11.4 (2-$CH_3$), 19.9 (3-$CH_3$), 63.7 ($CH_2OH$), 69.3 ($OCH_2$), 70.6 (CHOH), 109.2 ($C^6_{Ar}$), 122.7 ($C^4_{Ar}$), 125.2 ($C^2_{Ar}$-ipso), 125.8 ($C^5_{Ar}$), 137.9 ($C^3_{Ar}$-ipso), 156.4 ($C^1_{Ar}$-ipso).

#### 4.2.1.2. (*S*)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (*S*)-2.

Non-racemic (*S*)-3-(2,3-Dimethylphenoxy)propane-1,2-diol (*S*)-**2** used as seed was synthesized analogously from the (*S*)-3-chloropropane-1,2-diol.[9] Mp 101.5–103 °C; $R_f$ = 0.1; $[\alpha]_D^{20}$ = −13.5 (*c* 1.0, MTBE), 99.9% *ee* [chiral HPLC analysis; $t_R$ = 13.0 min]. NMR spectra were identical with those cited above for (*R*)-**2**.

#### 4.2.2. Resolution of racemic 3-(2,3-dimethylphenoxy)propane-1,2-diol *rac*-2 by preferential crystallization (resolution by entrainment)

Racemic diol *rac*-**2** (1.836 g) and (*R*)-**2** (0.203 g) were dissolved in 36 ml of MTBE at 45 °C. The solution was cooled to 23 °C and then seeded with finely pulverized (*R*)-**1** (0.008 g). After stirring the mixture for 30 min at 23 ± 1 °C, precipitated (*R*)-**2** was collected by filtration {0.349 g after drying; 79.7% ee} (Table 1, run 1). The extra portion of *rac*-**2** (0.138 g) и (*S*)-**2** (0.164 g) was then dissolved in the mother liquor at 45 °C; the resulting solution was cooled to 23 °C. After the addition of (*S*)-**2** (0.008 g) as seed crystals to the solution, and stirring the mixture for 30 min at 23 °C, (*S*)-**2** {0.366 g after drying; 80.9% *ee*} was collected by filtration (run 2). The extra portions of *rac*-**2** (0.102 g) and (*R*)-**2** (0.168 g, 79.7% *ee*) were then dissolved in the mother liquor at 45 °C [corresponding column of Table 1 indicates the enantiomeric content of the added scalemic diol, in this case 0.151 g of (*R*)-**2** and 0.017 g of (*S*)-**2**]. The resulting solution was cooled to 23 °C. After the addition of (*R*)-**2** (0.008 g) as seed crystals to the solution, and stirring the mixture for 30 min at 23 °C, (*R*)-**2** {0.394 g after drying; 83.8% *ee*} was collected by filtration (run 3). Further resolution was carried out at 23 ± 1 °C by adding amended amounts of *rac*-**2** and *scal*-**2** to the filtrate in a manner similar to that described above. The detailed conditions are given in Table 1. A high degree of enantiomeric purity of collected diols can be achieved by simple recrystallization. For example: a portion of (*S*)-**2** (1.288 g, 85.3% *ee*) was dissolved in the boiling mixture (70 ml) of light petroleum ether/EtOAc 2:1. After cooling the solution to 20–25 °C, the crystallized (*S*)-**2** was collected by filtration: yield 0.909 g; mp 101.5–102 °C; $[\alpha]_D^{20}$ = −13.2 (*c* 1.0, MTBE), 98.2% *ee*. Similarly, after recrystallization of combined portions of (*R*)-enantiomer (1.448 g, 85.8% *ee*), pure (*R*)-**2** was received: yield 1.015 g; mp 101–102.5 °C; $[\alpha]_D^{20}$ = +13.1 (*c* 1.0, MTBE), 97.8% *ee*.

#### 4.2.3. (*R*)-1,2-Epoxy-3-(2,3-dimethylphenoxy)propane (*R*)-3

To a stirred solution of triphenylphosphine (1.61 g, 6.1 mmol) in dry THF (5 ml) under an argon atmosphere, a solution of diisopropyl azodicarboxylate (1.24 g, 6.1 mmol) in THF (10 ml) was added dropwise for 30 min at +4 °C. Then to a stirred mixture

was added dropwise a solution of diol (*R*)-**2** (1.0 g, 5.1 mmol) in THF (10 ml). The resulting solution was refluxed for 24 h under an argon atmosphere. The solvent was removed in vacuum. The oily residue was dissolved in ether, kept for 24 h in refrigerator, and the precipitated triphenylphosphine oxide was filtered off. After evaporation of the filtrate, the residue was purified by column chromatography (silica gel, eluent: light petroleum ether/$CH_2Cl_2$/EtOAc = 6:2:1) to afford epoxide (*R*)-**3** as a colorless oil. Yield 0.41 g, 45%; $R_f$ = 0.5 (light petroleum ether/$CH_2Cl_2$/EtOAc = 4:2:1); $[\alpha]_D^{20}$ = −16.9 (*c* 1.3, EtOH), $[\alpha]_{365}^{20}$ = −42.9 (*c* 1.3, EtOH), $[\alpha]_D^{20}$ = −7.1 (*c* 2.1, $CHCl_3$), $[\alpha]_{365}^{20}$ = −11.4 (*c* 2.1, $CHCl_3$); 96% *ee* [chiral HPLC analysis; eluent: hexane/2-propanol (8:2); $t_R$ = 7.1 min]. $^1$H NMR (500 MHz) *δ*: 2.19 (s, 3H, 2′-$CH_3$), 2.29 (s, 3H, 3′-$CH_3$), 2.79 (dd, *J* = 5.0, 2.7 Hz; 1H, $CH_2$), 2.91 (t, *J* = 5.0 Hz, 1H, $CH_2$), 3.36–3.39 (m, 1H, CH), 3.98 (dd, *J* = 11.0, 5.4 Hz; 1H, $OCH_2$), 4.21 (dd, *J* = 11.0, 3.2 Hz, 1H, $OCH_2$), 6.71 (d, *J* = 8.1 Hz, 1H, $C^6_{Ar}H$), 6.82 (d, *J* = 7.6 Hz, 1H, $C^4_{Ar}H$), 7.05 (t, *J* = 7.9 Hz, 1H, $C^5_{Ar}H$). $^{13}$C NMR (100.5 MHz) *δ*: 11.7 (2-$CH_3$), 20.1 (3-$CH_3$), 44.7 ($CH_2$), 50.4 (CH), 69.1 ($OCH_2$), 109.4 ($C^6_{Ar}$), 122.9 ($C^4_{Ar}$), 125.6 ($C^2_{Ar}$-ipso), 125.8 ($C^5_{Ar}$), 138.1 ($C^3_{Ar}$-ipso), 156.5 ($C^1_{Ar}$-ipso).

**4.2.3.1. (*S*)-1,2-Epoxy-3-(2,3-dimethylphenoxy)propane (*S*)-3.** (*S*)-1,2-Epoxy-3-(2,3-dimethylphenoxy)propane (*S*)-**3** was synthesized analogously from (*S*)-**2**. A colorless oil, yield 0.43 g, 47%; $R_f$ = 0.5; $[\alpha]_D^{20}$ = +16.4 (*c* 1.1, EtOH), $[\alpha]_{365}^{20}$ = +40.8 (*c* 1.1, EtOH), $[\alpha]_D^{20}$ = +6.7 (*c* 1.1, $CHCl_3$), $[\alpha]_{365}^{20}$ = +10.5 (*c* 1.1, $CHCl_3$); 96.4% *ee* (chiral HPLC analysis; $t_R$ = 9.5 min);{cf. lit.[8] $[\alpha]_D^{27}$ = +13.8 (*c* 1.0, EtOH), 96.6% *ee*; lit.[7] $[\alpha]_D^{20}$ = −6.52 (c 2.3, $CHCl_3$)}.

**4.2.4. (*R*)-1-(*tert*-Butylamino)-3-(2,3-dimethylphenoxy)-2-propanol, (*R*)-xibenolol (*R*)-1**

A mixture of 1,2-epoxy-3-(2,3-dimethylphenoxy)propane (*R*)-**3** (0.12 g, 0.67 mmol), *t*-Bu-$NH_2$ (0.14 ml, 1.35 mmol) and water (0.05 ml) was refluxed for 1–2 h. The excess amine was removed under reduced pressure to afford (*R*)-**1** as a colorless oil. With prolonged standing, the oil crystallizes. Yield 0.168 g, 99%; mp 35–39 °C; $[\alpha]_D^{20}$ = +11.0 (*c* 1.1, EtOH), $[\alpha]_{365}^{20}$ = +25.5 (*c* 1.1, EtOH), $[\alpha]_D^{20}$ = +15.4 (*c* 1.1, $CHCl_3$), $[\alpha]_{365}^{20}$ = +45.9 (*c* 1.1, $CHCl_3$); 94.2% *ee* [chiral HPLC analysis; eluent: hexane/2-propanol/diethyl amine (6:4:0.1); $t_R$ = 5.2 min]. IR (KBr, $cm^{-1}$): 3336, 3244 (OH, NH); 2972, 2873 ($CH_3$, $CH_2$); 1585, 1465 (Ar); 1364 ($CH_3$), 1266, 1215 ($C(CH_3)_3$); 1091, 1026 (C—O—C). $^1$H NMR (400 MHz) *δ*: 1.13 (s, 9H, $CH_3$), 2.17 (s, 3H, 2′-$CH_3$), 2.28 (s, 3H, 3′-$CH_3$), 2.34 (br. s, 2H, NH, OH), 2.75 (dd, *J* = 11.9, 6.8 Hz; 1H, $CH_2N$), 2.89 (dd, *J* = 11.9, 3.9 Hz; 1H, $CH_2N$), 3.93–4.04 (m, 3H, $OCH_2$, *CH*OH), 6.73 (d, *J* = 8.1 Hz, 1H, $C^6_{Ar}H$), 6.80 (d, *J* = 7.6 Hz, 1H, $C^4_{Ar}H$), 7.05 (t, *J* = 7.9 Hz, 1H, $C^5_{Ar}H$). $^{13}$C NMR (125.75 MHz) *δ*: 11.7 (2′-$CH_3$), 20.1 (3′-$CH_3$), 29.2 ($C(CH_3)_3$), 44.9 ($CH_2N$), 50.3 (*C*Me$_3$), 68.9 (CH), 71.1 ($OCH_2$), 109.2 ($C^6_{Ar}$), 122.6 ($C^4_{Ar}$), 125.2 ($C^2_{Ar}$-ipso), 125.9 ($C^5_{Ar}$), 138.0 ($C^3_{Ar}$-ipso), 156.7 ($C^1_{Ar}$-ipso).

**4.2.4.1. (*S*)-Xibenolol (*S*)-1.** (*S*)-Xibenolol (*S*)-**1** was obtained analogously from oxirane (*S*)-**3**. An oil, yield 0.167 g, 98%; $[\alpha]_D^{20}$ = −10.8 (*c* 1.1, EtOH), $[\alpha]_{365}^{20}$ = −25.3 (*c* 1.1, EtOH), $[\alpha]_D^{20}$ = −15.6 (*c* 1.1, $CHCl_3$), $[\alpha]_{365}^{20}$ = −46.8 (*c* 1.1, $CHCl_3$); 96.4% *ee* [chiral HPLC analysis, conditions were the same as for (*R*)-**1**; $t_R$ = 15.7 min]. Cf. lit.[7]: $[\alpha]_D^{20}$ = −17.58 (c 1.0, $CHCl_3$); 67% *ee*. NMR spectra were identical with those cited above for (*R*)-**1**.

**4.2.5. (*R*)-Xibenolol hydrochloride (*R*)-1·HCl**

The (*R*)-xibenolol (*R*)-**1** (0.120 g) was dissolved in ether and dry HCl gas was passed through it for 15 min, the solvent was removed under reduced pressure and resulting solid recrystallized from $Et_2O$ to afford xibenolol as its hydrochloride salt. Yield 0.114 g, 83%; Mp 144–146 °C ($Et_2O$/MeOH); $[\alpha]_D^{20}$ = +26.0 (*c* 1.0, EtOH), $[\alpha]_{365}^{20}$ = +79.3 (*c* 1.0, EtOH); $[\alpha]_D^{20}$ = +13.0 (*c* 1.0, $CHCl_3$), $[\alpha]_{365}^{20}$ = +36.7 (*c* 1.0, $CHCl_3$); 96.9% *ee* [chiral HPLC analysis; Chiralcel OD-H (0.46 × 25 cm); column temperature 23 °C; flow rate: 0.85 ml/min; eluent: hexane/2-propanol/diethyl amine (62:38:0.05); $t_R$ = 5.7 min]; {Cf. lit.[4] for (+)-**1**-$d_5$·HCl: mp 147–148 °C; $[\alpha]_D^{20}$ = +25.7 (*c* 1, EtOH)}. IR (KBr, $cm^{-1}$): 3371 (OH), 2986, 2882 ($CH_3$, $CH_2$); 2795, 2720, 2679, 2633, 2544, 2513, 2405 ($NH_2^+$); 1585, 1480, 1460 (Ar); 1382 ($CH_3$), 1258 ($C(CH_3)_3$); 1135, 1103 (C—O—C). $^1$H NMR (400 MHz) *δ*: 1.52 (s, 9H, $CH_3$), 2.15 (s, 3H, 2′-$CH_3$), 2.25 (s, 3H, 3′-$CH_3$), 3.11–3.18 (m, 1H, *CH*$_2$N), 3.34–3.39 (m, 1H, *CH*$_2$N), 3.97 (dd, *J* = 9.5, 6.4 Hz; 1H, O*CH*$_2$), 4.10 (dd, *J* = 9.5, 4.4 Hz; 1H, O*CH*$_2$), 4.64–4.71 (m, 1H, CH), 5.35 (br. s, 1H, OH), 6.66 (d, *J* = 8.1 Hz, 1H, $C^6_{Ar}H$), 6.79 (d, *J* = 7.6 Hz, 1H, $C^4_{Ar}H$), 7.02 (t, *J* = 7.9 Hz, 1H, $C^5_{Ar}H$), 8.35 (br. s, 1H, $NH_2^+$), 9.71 (br. s, 1H, $NH_2^+$). $^{13}$C NMR (125.75 MHz) *δ*: 11.8 (2′-$CH_2$), 20.0 (3′-$CH_3$), 25.9 ($C(CH_3)_3$), 45.8 ($CH_2N^+$), 57.6 (*C*Me$_3$), 66.0 (CH), 70.0 ($OCH_2$), 109.2 ($C^6_{Ar}$), 122.9 ($C^4_{Ar}$), 125.2 ($C^2_{Ar}$-ipso), 126.0 ($C^5_{Ar}$), 138.0 ($C^3_{Ar}$-ipso), 156.2 ($C^1_{Ar}$-ipso).

**4.2.5.1. (*S*)-Xibenolol hydrochloride (*S*)-1.** HCl was obtained analogously from the (*S*)-**1** as described for (*R*)-**1**·HCl. Yield 0.127 g, 92%; Mp 146–148 °C ($Et_2O$/MeOH); $[\alpha]_D^{20}$ = −27.0 (*c* 1.0, EtOH), $[\alpha]_{365}^{20}$ = −81.6 (*c* 1.0, EtOH); 99.2% *ee* [chiral HPLC analysis; conditions were the same as for (*R*)-**1**·HCl; $t_R$ = 16.2 min]. {Cf. lit.[4] for (−)-**1**-$d_5$·HCl: mp 147–148 °C; $[\alpha]_D^{20}$ = −25.5 (*c* 1, EtOH)}. NMR spectra were identical with those cited above for (*R*)-**1**·HCl

### 4.3. X-ray analysis

The X-ray diffraction data of the investigated (*S*)-(−)-**1**·HCl and (*R*)-(+)-**1**·HCl crystals were collected on a Bruker AXS Smart Apex II CCD diffractometer in the ω-scan modes using graphite monochromated Mo$K_\alpha$ (*λ* 0.71073 Å) radiation. The crystal data, data collection, and the refinement parameters are given in Table 2. Data were corrected for the absorption effect using SADABS program.[23] The structures were solved by direct method using SHELXS[24] and refined by the full matrix least-squares using SHELXL-2014[25] and WinGX[26] programs. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted at calculated positions and refined as riding atoms except the hydrogen atoms of OH and $NH_2$ groups which were located from difference maps and refined isotropically. During data collections the images were indexed, integrated, and scaled using the APEX2 data reduction package.[27]

The Flack parameters for both investigated crystals were calculated both by the classical procedure[18] and by the modified Parson's method.[19] For (*S*)-(−)-**1**·HCl crystal the corresponding results were as follows: −0.050(97) by classical fit to all intensities and −0.013(25) from 1127 selected quotients (Parsons' method); for (*R*)-(+)-**1**·HCl crystal: −0.054(216) and −0.138(264) from 129 selected quotients, respectively. Table 2 shows the values with better statistical characteristics, and they are discussed in the text.

Crystallographic data for (*S*)-**1**·HCl and (R)-**1**·HCl has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1561629–1561630 respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax:+44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

### Acknowledgments

The authors thank the Russian Fund of Basic Research and the Government of the Republic of Tatarstan for partial financial support (Grant No. 15-43-02238). The authors also thank Dr. A.V. Pashagin and D.V. Zakharychev for valuable assistance with chiral HPLC analysis and Dr. D.B. Krivolapov for valuable help with the X-ray data.

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Please cite this article in press as: Bredikhin, A. A.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2017.08.013