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Solid state properties and effective resolution procedure for guaifenesin, 3-(2-methoxyphenoxy)-1,2-propanediol

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Abstract—Racemic expectorant guaifenesin, 3-(2-methoxyphenoxy)-1,2-propanediol **2** undergoes spontaneous resolution upon crystallization. This fact is confirmed by thermal analysis (single eutectic V-shape binary melting phase diagram, adequate entropy and free energy characteristics). Racemic **2** could be effectively resolved into (*S*)- and (*R*)-**2** by a preferential crystallization procedure. Single enantiomer drugs levomoprolol and levotensin were obtained by starting from enantiomeric **2** through the sulfite route.
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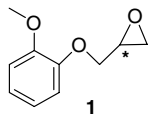
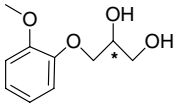
1. Introduction

The problem of an economically effective and environmentally friendly production of single enantiomer compounds is among the main goals of modern organic chemistry. The phenomenon of the spontaneous resolution of racemates is one of the promising ways to reach a desirable aim.[1] However, even in the case of conglomerate forming substances it is not always easy to use the benefits of a spontaneous resolution. We have recently reported the conglomerate nature of a valuable intermediate in chiral drug synthesis of 1,2-epoxy-3-(2-methoxyphenoxy)-propane **1**, but were unable to achieve an effective resolution of this compound by an entrainment procedure.[2] The described situation is not uncommon. Coquerel et al.[3] is of opinion that almost half of conglomerate forming compounds would demonstrate poor entrainment characteristics.

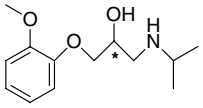
Conceivable tactics to overcome this problem are to determine the reasons for such a behavior and to take rational steps to counteract them, if possible. Another tactic is not to overcome, but get around the obstacles, that is, to find another conglomerate forming compound structurally similar with the initial one. Among the formal derivatives of epoxide **1**, 3-(2-methoxyphenoxy)-1,2-propanediol **2**, expectorant guaifenesin,[4a] attracts our attention. We have already reported preliminary data about conglomerate type of crystallization for this diol based on the depression of melting temperature of racemic **2** as compared with scalemic, and on the coincidence of IR spectra for racemic and scalemic crystalline samples of guaifenesin.[5]



1



2
Guaifenesin



3
Moprolol

The first aim of this report is to extend the scope of the evidence of the guaifenesin conglomerate nature by thermochemical investigations. The second aim is to develop a practical method of direct resolution of (nearly) racemic diol **2**. The last part of this paper deals with the use of diastereomeric cyclic sulfites, epoxide-like derivatives of enantiomeric **2**, in the short synthesis of single enantiomer β-adrenoblocker levomoprolol **3**.[4b]

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2. Results and discussion

2.1. Thermochemical investigations

Thermodynamic data on binary mixtures of enantiomers are useful, for checking the purity (including enantiomeric purity) of chiral compounds, and for obtaining information concerning a particular technique to be used for achieving enantiomeric resolution and/or enrichment. This part of the work deals with binary mixtures of (*R*)- and (*S*)-**2** using differential scanning calorimetry (dsc) as a research method. The temperature data were determined according to the method of Höhne et al.,[6] and were treated as described previously.[1]

The results obtained for the temperature and enthalpy of fusion of the pure enantiomer and the pure racemate, as well as calculated[1,7] values of entropy of mixing for liquid enantiomeric **2**, ΔS_l^m, and free energy of formation for racemic compound in the solid state, ΔG^0, are presented in Table 1.

The entropy of mixing for enantiomeric **2** in the liquid state is equal to 5.15 J K^{-1} mol^{-1}, which is slightly less but close to the ideal value of 5.75 J K^{-1} mol^{-1} ($R\ln 2$) for conglomerates. The near zero value for ΔG^0 also shows the same peculiarity of chiral **2**.[7]

For the right evaluation of the binary phase diagram based on the dsc experiment, the correct information concerning an enantiomeric composition [mole fraction of each enantiomer, n_R and n_S, $(n_R + n_S) = 1$] of the samples investigated is of primary importance. We have used for this purpose the value of optical purity $[\alpha_i]/[\alpha_{max}] = op \approx ee = |(n_R - n_S)|/(n_R + n_S)$. The closer is the value $[\alpha_{max}]$ used in the calculations of to the value of the specific rotation for enantiopure sample, the better is equivalence between the optical purity and the enantiomeric excess.

Using the specific rotation data for quantitative conclusions one must take into account the pronounced solvent dependence of this chiroptical property. In particular, for enantiomeric **2** the value of the specific rotation strongly depends upon the water content in alcohols commonly used for the measurements. Thus for enantiopure (*S*)-**2** $[\alpha]_D^{20} = +11.7$ (*c* 1.0) in anhydrous EtOH, whereas $[\alpha]_D^{20} = +15.0$ (*c* 1.0) in absolute EtOH. The same is true for MeOH as well. For the same sample the value of $[\alpha]_D^{20} = +9.5$ (*c* 1.0, anhydrous MeOH) changes to $[\alpha]_D^{20} = +12.1$ (*c* 1.0) in the MeOH/H_2O 9:1 (v/v) mixture. Notice that for (*S*)-**2** $[\alpha]_D^{20} = +13.7$ (*c* 1.1, H_2O), hence the water influence is not an additive one.

With this fact in mind, we used methanol, freshly distilled from sodium for the quantitative measurements. We believe that enantiopure samples (ee >99%) of (*S*)-**2** are characterized by the value $[\alpha]_D^{20} = +9.5 \pm 0.1$ (*c* 1.0, anhydrous MeOH). The following reasons were taken into account to establish the enantiomeric purity of such a sample. (1) The value of the specific rotation was constant after several consecutive crystallizations; for conglomerate forming substances (only) it is a solid evidence for the enantiomeric purity. (2) The dsc heating curve for this sample has virtually an ideal shape with a base line and a linear front part of the curve that constitutes a nearly perfect angle. (3) This value was close enough to the published value $[\alpha]_D^{25} = -9.4$ (*c* 1.0, MeOH) for (*R*)-**2**, 99.4% ee.[8]

From the dsc data the melting temperature against the composition diagram was drawn as depicted in Figure 1. Experimental points in Figure 1 form an obvious single eutectic V-shape curve typical for a racemic conglomerate.[1] Figure 1 also presents the theoretical solidus and liquidus curves (dashed lines) deduced for conglomerate from the reductive Schröder–Van Laar equation $\ln(n) = (\Delta H_A^f/R)(1/T_A^f - 1/T^f)$. Both experimental and theoretical sets correlate quite well.

2.2. Resolution of guaifenesin by preferential crystallization

Guaifenesin **2** is a popular object for developing and testing of enantioselective preparative approaches. Thus nonracemic **2** has been obtained by multistep synthesis from natural D-mannitol[9] and through one step interaction of guaiacol with scalemic glycidol[8,10] or 3-chloropropane-1,2-diol.[11] Both enantiomers of **2** have been prepared by Sharpless asymmetric dihydroxylation of prochiral 1-allyloxy-2-methoxy-benzene.[12,13] Racemic **2** was resolved via diastereomeric glycosylated derivatives.[14] Kinetic resolution approaches including lipase catalyzed esterification of *rac*-**2**[15] and Jacobsen salen-catalyzed enantioselective

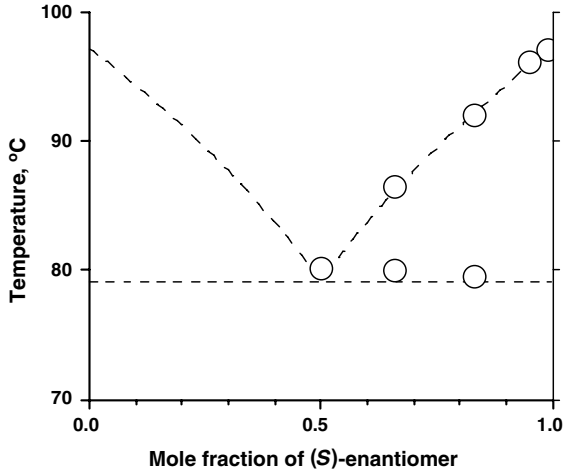


Figure 1. Experimental (○) and calculated (---) melting point phase diagram of **2**.

Table 1. Dsc measured melting point and enthalpy of fusion of racemic (low index *R*) and enantiopure (low index *A*) 3-(2-methoxyphenoxy)-1,2-propanediol **2** and calculated thermodynamic characteristics for the substance

$T_A^{'f}$ (°C)	$T_R^{'f}$ (°C)	ΔH_A^f (J mol^{-1})	ΔH_R^f (J mol^{-1})	ΔS_l^m (J K^{-1} mol^{-1})	ΔG^0 (J mol^{-1})
97.2	80.2	41,800	37,600	5.15	−118

hydrolysis of racemic glycidyl ether of guaiacol[16] were also used for *scal*-**2** production.

The now uncovered conglomerate nature of guaifenesin opens up possibilities for the direct resolution of this valuable substance. As a result we first examined entrainment abilities of guaifenesin during seed induced crystallization of its oversaturated slightly nonracemic solutions. We employed water as a 'green' solvent for the purpose. Mother liquor optical rotation power was used as an indicator quantity. The experimental time dependence for the mother liquor optical rotation power is depicted in Figure 2.

As can be seen from Figure 2, investigated solutions of different concentrations but of equal starting enantiomeric enrichment behave uniformly in the main features. During the crystallization process primary enantiomeric prevalence of solute decreases to zero, changes sign, and mounts to initial absolute value (even exceeds this value for high initial concentrations). The mother liquor enantiomeric composition (and the composition of deposited crystals as well) then asymptotically tends to be racemic. It is apparent that to achieve optimal output of the pure solid enantiomer, the crystallization process must be interrupted not far from the turning point of the curve. In the timescale of a real experiment, this moment is difficult to fix for high starting concentrations (curves 1 and 2). On the other hand, overall cycle times become too long for low concentrations (curves 4 and 5). As a result, the intermediate conditions were selected for the preparative resolution of racemic guaifenesin.

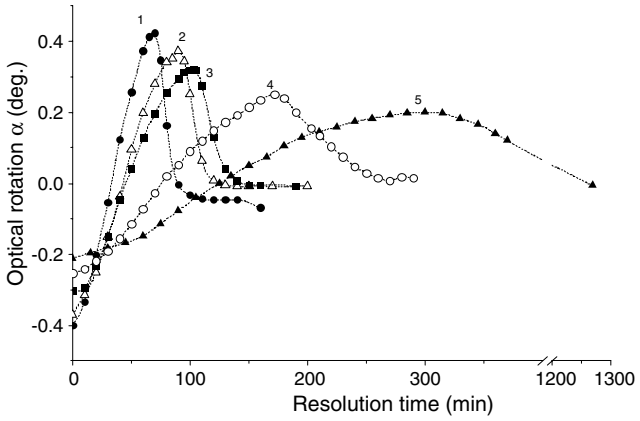


Figure 2. The dynamics of guaifenesin crystallization. Mother liquor optical rotation power ($T = 25$ °C; cell length 100 mm; $\lambda = 436$ nm) time dependence during seed induced crystallization of slightly enantiomerically enriched **2**. Experimental conditions: $T = 22$ °C; 25 mg of powered seed crystals per run; 9 g of *rac*-**2** + 1 g of (*R*)-**2** in 60 (curve 1), 70 (curve 2), 80 (curve 3), 100 (curve 4), and 120 (curve 5) cm^3 of H_2O.

An example of the successful resolution of near racemic **2** is illustrated in Table 2. Over the course of the resolution, a supersaturated solution of *rac*-**2**, including a small excess of (*R*)-**2**, was prepared by heating, and then cooling to 22 °C. A small amount of seed crystals of (*R*)-**2** was added and the stirred solution was allowed to crystallize for about 100 min. The weight of (*R*)-**2** obtained after filtration was more than common weight of the initial excess of the (*R*)-enantiomer and seed added. To the mother liquor, *rac*-**2** was added in order that the overall quantity of **2** in the solution could be recovered. The mixture was heated until the solid was completely dissolved and then cooled to 22 °C. After the solution had been seeded with (*S*)-**2** and stirred for about 100 min, precipitated (*S*)-**2** was collected in a similar manner. The cycle was repeated several times.

As cited in Table 2 values for yield of enantiomer [YE (g)] and degree of resolution [DR (%)] were calculated by analogy with Shiraiwa et al.,[17] according to the following equations:

$$\mathrm{YE\ (g)} = [\mathrm{Yield(g)} \times \mathrm{OP\ (\%)}]/100 - 0.25$$

$$\mathrm{DR\ (\%)} = \mathrm{YE\ (g)} \times 100/[0.5 \times (\mathrm{Amount\ of\ } \textit{rac}\text{-}\mathbf{2}\ \mathrm{(g)} - 34.4)]$$

where OP is the optical purity of the obtained (*S*)- or (*R*)-**2**, 0.25 (g) is the seed weight, and 34.4 (g) is the solubility determined by us of *rac*-**2** in 800 cm^3 water at 22 °C.

As evident from Table 2, three cycles of entrainment resolution using ordinary laboratory equipment and no resolving agents are sufficient enough to obtain (*R*)- and (*S*)-**2**

Table 2. Resolution by entrainment of *rac*-guaifenesin in water (800 cm^3 H_2O, 0.25 g crystal seeds on every run, crystallization temperature 22 ± 0.5 °C)

Run	Added amount of (*R*,*S*)-**2** (g)	Operation amount of (*R*)- and (*S*)-**2**[b] (g)		Resolution time (min)	(*R*)- and (*S*)-**2** obtained			
		(*R*)-**2**	(*S*)-**2**		Yield (g)	OP[c] (%)	YE[d] (g)	DR[e] (%)
1	90.46[a]	55.77	45.23	100	(*R*) 21.26	91	19.10	68.1
2	21.01	45.24	54.76	110	(*S*) 19.11	99	18.67	66.6
3	18.86	54.86	45.40	110	(*R*) 17.53	>99	17.11	60.7
4	17.28	46.02	53.98	115	(*S*) 17.22	84	14.21	49.3
5	16.97	53.08	46.92	120	(*R*) 19.68	87	16.87	56.8
6	19.43	44.68	55.32	125	(*S*) 22.60	89	19.84	72.2

[a] Additional amount of (*R*)-**2** 9.54 g.
[b] The operation amounts in runs 2–6 were calculated based on the results in runs 1–5 respectively.
[c] OP: Optical purity; the optical purities of (*R*)- and (*S*)-**2** obtained, were calculated on the basis of the specific rotation of (*S*)-**2**: $[\alpha]_D^{20} = +9.5$ (*c* 1.0, MeOH).
[d] YE: Yield of enantiomer.
[e] DR: Degree of resolution.

samples of about 50 g each. The quality of each nonracemic specimen is good enough, which single recrystallization is sufficient to obtain (*R*)- and (*S*)-**2** diols suitable for further use.

2.3. Levomoprolol synthesis

Guaifenesin **2** has an obvious structural similarity with the known β-adrenoblocker moprolol **3**, which belongs to an extensive class of 1-alkylamino-3-aryloxypropan-2-ols with cardiovascular activity. Within this class, it has been shown that (*S*)-enantiomers are eutomer components of the racemic drug, whereas (*R*)-enantiomers (distomers) usually display other (often undesirable) activities.[18] The availability of (*S*)-**2** allowed us to obtain single enantiomer drug (*S*)-**3**, also known as levomoprolol and its hydrochloride (*S*)-**3**·HCl known as levotenzine.[4b] We used the well-known cyclic sulfite route[19,20] outlined in Scheme 1.

Due to the appearance of an additional chiral sulfur atom, cyclic sulfites **4** were obtained as an epimer mixture with an (*R*)-configuration at the carbon centre. The mixture was used in the next step without the separation of individual diastereomers. Overall nonoptimized isolated yields of (*S*)-**3** and (*S*)-**3**·HCl were better than 80%.

3. Conclusion

To the best of our knowledge glycerol ether **2**, guaifenesin is the first registered chiral drug resolved by the direct crystallization as itself, not in the form of a derivative of any kind. Guaifenesin belongs to the family of chiral 3-(2-*R*-phenoxy)-1,2-propanediols within the range of which the conglomerate forming representatives are common ones. Thus, based on thermochemical properties we disclosed the conglomerate nature of 2-I-, 2-Br-, and 2-Cl-phenoxypropanediols, whereas 2-F- and unsubstituted ether forms unstable and rather stable racemic compounds, respectively.[21] It could be suggested with a great deal of certainty that 2-CN- and 2-EtO-derivatives are conglomerate forming substances. Among 3-(2-alkylphenoxy)-1,2-propanediols at least 2-Me-substituted compound, another registered drug, muscle relaxant mephenesin[4c] also forms conglomerate upon crystallization.[5] We believe that a more detailed search for conglomerates within this highly potent class of chemicals would lead to more deep understanding of the nature of spontaneous resolution and more intent practical use of this unappreciated phenomenon.

4. Experimental

4.1. General

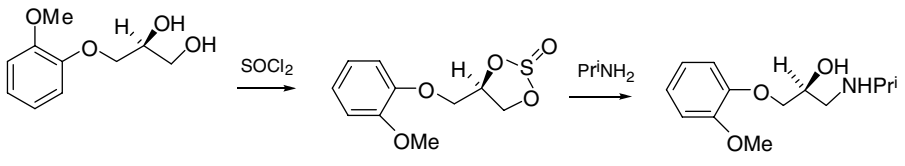
The NMR spectra were recorded on the Bruker WM-250 and the Avance-600 spectrometers in $CDCl_3$ with TMS or the signals of the solvent as the internal standard. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration c is given as g/100 ml). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected.

The melting curves of the samples of 3-(2-methoxyphenoxy)-1,2-propanediol were measured on a Setaram DSC-111 differential scanning calorimeter in stainless steel cells with the rate of heating of 1 °C min^{-1}. Mass of the samples amounted to approximately 2.5 mg. Temperature scale and heat flux were calibrated against the data for α-corundum (sapphire), phenol, and naphthalene. Experimental DSC curves were treated according to Gallis et al.[22]

4.2. Synthesis

Racemic epichlorohydrin, 3-chloropropane-1,2-diol and guaiacol are commercially available. (*R*)- and (*S*)-3-chloro-1,2-propanediol were prepared by the enantioselective partial hydrolysis of racemic epichlorohydrin according to the Jacobsen method without modifications.[23]

4.2.1. Racemic 3-(2-methoxyphenoxy)-propane-1,2-diol, *rac*-guaifenesin, *rac*-2. Racemic 3-(2-methoxyphenoxy)-propane-1,2-diol, *rac*-guaifenesin, *rac*-**2** was prepared following the general procedure of Egri et al.[24] To a solution of guaiacol (83.4 g, 0.67 mol) in ethanol (400 ml), a solution of NaOH (33.6 g, 0.84 mol) in water (135 ml) was added and the resulting mixture stirred and heated at reflux for 30 min. A solution of racemic 3-chloropropane-1,2-diol (111.5 g, 1.01 mol) in ethanol (84 ml) was then added within 30 min and the mixture was further stirred and heated at reflux for 8 h. After cooling, the volume of the resulting mixture was reduced to about one third followed by the addition of water (400 ml) and extraction with CH_2Cl_2 (3×200 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed. Crude diol **2** was purified by distillation (bp 110–120 °C at 0.05 mmHg) and recrystallization from CCl_4. Yield 81.2 g (61%), mp 79–80 °C; lit.[25] mp 78.5–79.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.74$ (br s, 1H, OH), 3.48 (br s, 1H, OH), 3.76–3.81 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 4.04–4.06 (m, 2H, CH_2), 4.13–4.14 (m, 1H, CH), 6.88–6.92 (m, 3H, Ar), 6.95–6.98 (m, 1H, Ar).



(*S*)-**2** (*R*)-**4** (*S*)-**3**

Scheme 1.

4.2.2. (*R*)-3-(2-Methoxyphenoxy)-propane-1,2-diol, (*R*)-2. (*R*)-3-(2-Methoxyphenoxy)-propane-1,2-diol, (*R*)-**2** which was used as the seed was obtained from the (*R*)-3-chloropropane-1,2-diol {13.3 g, 0.12 mol; $[\alpha]_D^{20} = -6.4$ (*c* 5, H_2O)} and guaiacol (12.4 g, 0.1 mol) as described for racemic compound. Crude (*R*)-**2** (16.38 g, 83%) was crystallized from a mixture of CCl_4 (200 ml) and EtOH (12 ml) to give colourless needles {12.23 g (62%); mp 97–98 °C; $[\alpha]_D^{20} = -9.5$ (*c* 1.0, MeOH), $[\alpha]_D^{20} = -11.7$ (*c* 1.0, EtOH), >99% op}; {lit.[8] mp 96.8–99.1 °C, $[\alpha]_D^{25} = -9.4$ (*c* 1.0, MeOH), 99.4% ee}. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.71$ (br s, 1H, OH), 3.47 (br s, 1H, OH), 3.77–3.83 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.06–4.08 (m, 2H, CH_2), 4.13–4.15 (m, 1H, CH), 6.90–6.93 (m, 3H, Ar), 6.96–6.98 (m, 1H, Ar). ^{13}C NMR (150.864 MHz, $CDCl_3$): $\delta = 55.86$ (CH_3), 63.89 (CH_2OH), 70.08 (CH_2O), 72.29 (CH), 111.98 (C^3_{Ar}), 114.95 (C^6_{Ar}), 121.13 (C^4_{Ar}), 122.22 (C^5_{Ar}), 148.07 (C^1_{Ar}), 149.79 (C^2_{Ar}).

4.2.3. (*S*)-3-(2-Methoxyphenoxy)-propane-1, 2-diol, (*S*)-2. (*S*)-3-(2-Methoxyphenoxy)-propane-1,2-diol, (*S*)-**2** which was used as the seed was synthesized analogously from the (*S*)-3-chloropropane-1,2-diol {$[\alpha]_D^{20} = +6.4$ (*c* 4.7, H_2O)}. The colourless needles; yield 63%; mp 97–98 °C; $[\alpha]_D^{20} = +9.4$ (*c* 1.0, MeOH). {lit.[15] $[\alpha]_D^{25} = +11.2$ (*c* 1, EtOH), 88% ee; lit.[5] $[\alpha]_D^{20} = +9.4$ (*c* 1.0, MeOH)}.

4.3. Resolution of racemic 3-(2-methoxyphenoxy)-1,2-propanediol (guaifenesin, *rac*-2) by preferential crystallization (entrainment)

Racemic guaifenesin *rac*-**2** (90.46 g) and (*R*)-**2** (9.54 g) was dissolved in 800 ml of water at 42–45 °C. The solution was cooled to 23 °C and seeded with finely pulverized (*R*)-**2** (0.25 g). After stirring the mixture for 100 min at 22 ± 0.5 °C, precipitated (*R*)-**2** was collected by filtration {21.26 g after drying; $[\alpha]_D^{20} = -8.6$ (*c* 1.1, MeOH), 91% op} (Table 2, run 1). The extra portion of *rac*-**2** (21.01 g) was then dissolved in the mother liquor at 42 °C; the resulting solution was cooled to 23 °C. After the addition of (*S*)-**2** (0.25 g) as seed crystals to the solution, and stirring the mixture for 110 min at 22 ± 0.5 °C, (*S*)-**2** {19.11 g after drying; $[\alpha]_D^{20} = +9.4$ (*c* 1.0, MeOH), 99% op} was collected by filtration (run 2). Further resolution was carried out at 22 ± 0.5 °C by adding amended amounts of *rac*-**2** to the filtrate in a manner similar to that described above. The detailed conditions are given in Table 2. After second cycle, 17.53 g of (*R*)-**2** {$[\alpha]_D^{20} = -9.6$ (*c* 1.0, MeOH), >99% op} and 17.22 g of (*S*)-**2** {$[\alpha]_D^{20} = +7.9$ (*c* 1.0, MeOH), 84% op} were collected. After third cycle, 19.68 g of (*R*)-**2** {$[\alpha]_D^{20} = -8.2$ (*c* 1.0, MeOH), 87% op} and 22.60 g of (*S*)-**2** {$[\alpha]_D^{20} = +8.4$ (*c* 1.1, MeOH), 89% op} were collected. A high degree of enantiomeric purity of collected diols can be achieved by simple recrystallization. For example: a portion of (*R*)-**2** (21.26 g, $[\alpha]_D^{20} = -8.6$ (*c* 1.1, MeOH), 91% op) was dissolved in a boiling mixture of CCl_4 (250 ml) and EtOH (15 ml). After cooling the solution to 5–10 °C, the crystallized (*R*)-**2** was collected by filtration (yield 19.75 g; $[\alpha]_D^{20} = -9.5$ (*c* 1.0, MeOH), >99% op).

4.3.1. (2*RS*,4*R*)-4-(2-Methoxyphenoxy)methyl-1,3,2-dioxathiolane-2-one (2*RS*,4*R*)-4. To a stirred and cooled (0 °C) solution of (*S*)-3-(2-methoxyphenoxy)-propane-1,2-diol (*S*)-**2** (1.0 g, 5 mmol) in CH_2Cl_2 (50 ml), a solution of $SOCl_2$ (0.62 g, 5.2 mmol) in CH_2Cl_2 (10 ml) was added dropwise. The reaction mixture was stirred for an extra 1 h, and the volatile material removed under reduced pressure to afford 1.2 g {solid, mixture of *cis* and *trans* isomers (43:57), mp 63–69 °C, $[\alpha]_D^{20} = +42.3$ (*c* 1.0, CH_2Cl_2)} of (2*RS*,4*R*)-**4**, which was used in the next step without further purification. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.85$ (s, 3H, OCH_3); 3.99–4.19 (m, 1.14H, CH_2OS (*trans*)); 4.25–4.46 (m, 0.86H, CH_2OS (*cis*)); 4.53–4.59, 4.68–4.71, 4.79–4.85 (all m, totally 2H, CH_2OAr (*cis*, *trans*)); 4.90–4.95 (m, 0.43H, CHOS (*cis*)); 5.23–5.32 (m, 0.57H, CHOS (*trans*)); 6.89–7.05 (4H, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 56.17$ (CH_3); 68.84 (CH_2OAr (*trans*)); 69.00 (CH_2OAr (*cis*)); 70.19 (CH_2OS (*trans*)); 70.85 (CH_2OS (*cis*)); 78.13 (CHOS (*trans*)); 80.17 (CHOS (*cis*)); 112.76, 112.81 (C^3_{Ar}); 116.37, 116.60 (C^6_{Ar}); 121.15, 121.17 (C^4_{Ar}); 123.19, 123.36 (C^5_{Ar}); 147.71 (C^1_{Ar}); 150.37, 150.50 (C^2_{Ar}).

4.3.2. (*S*)-1-Isopropylamino-3-(2-methoxyphenoxy)-propane-2-ol, (*S*)-moprolol, levomoprolol, (*S*)-3. A solution of dioxathiolane (2*RS*,4*R*)-**4** (1.08 g, 4.4 mmol) and Pr^iNH_2 (4 g, 68 mmol) in DMF (10 ml) was heated at 60–70 °C for 45 h. After this period, excess amine and DMF were removed in vacuo. A solution of NaOH (35 ml, 1 M) was added, the mixture extracted with AcOEt (3 × 40 ml), and extract was dried with Na_2SO_4. After removal of the solvent in vacuo, the residue (1.1 g, 87%) was crystallized from EtOAc to give (*S*)-**3**, mp 78–80 °C; $[\alpha]_D^{20} = -2.8$ (*c* 2.25, EtOH); lit.[26] mp 80–81 °C, $[\alpha]_D^{20} = -5.6$ (*c* 4.5, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (d, 3H, CH_3), 1.07 (d, 3H, CH_3), 2.20–2.86 (m, 5H, OH, NH, CH_2O, NCH), 3.84 (s, 3H, OCH_3), 3.96–4.06 (m, 3H, CH_2O, CH), 6.87–6.96 (m, 4H, ArH) [cf. lit.[26]]. Solid (*S*)-**3** was dissolved in 30 ml of Et_2O and gaseous HCl was passed through the resulting solution to give 0.95 g (82%) of (2*S*)-1-isopropylamino-3-(2-methoxyphenoxy)-propane-2-ol hydrochloride (levotensin) (*S*)-**3**·HCl, mp 124–125 °C (EtOAc/EtOH); $[\alpha]_D^{20} = -16.5$ (*c* 5.0, EtOH). Lit.[4b] mp 121–123 °C, $[\alpha]_D^{20} = -16.3$ (*c* 5.0, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.54$ (d, $^3J = 6.6$, 3H, CH_3), 1.53 (d, $^3J = 6.6$, 3H, CH_3), 3.26–3.30 (m, 1H, $1N^+CH_2$), 3.44–3.46 (m, 1H, $1N^+CH_2$), 3.51–3.53 (m, 1H, N^+CH), 3.88 (s, 3H, OCH_3), 4.10 (dd, $^2J = 9.8$, $^3J = 5.9$, 1H, $1OCH_2$), 4.22 (dd, $^2J = 9.8$, $^3J = 4.2$, 1H, $1OCH_2$), 4.63–4.67 (m, 1H, OCH), 5.40 (br s, OH), 6.91–7.01 (m, 4H, Ar), 8.69 (br s, N^+H), 9.50 (br s, 1H, N^+H). ^{13}C NMR (150.864 MHz, $CDCl_3$): $\delta = 19.11$ (CH_3), 18.98 (CH_3), 48.45 (CH_2N), 51.43 (CHN), 55.89 (OCH_3), 65.52 (CH), 71.93 (OCH_2), 112.22 (C^3_{Ar}), 115.12 (C^6_{Ar}), 121.17 (C^4_{Ar}), 122.40 (C^5_{Ar}), 147.83 (C^1_{Ar}), 149.76 (C^2_{Ar}).

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