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Spontaneous resolution among chiral glycerol derivatives: crystallization features of *ortho*-alkoxysubstituted phenyl glycerol ethers

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Abstract—Five chiral arylglycerol ethers 2-R-C_6H_4-O-$CH_2CH(OH)CH_2OH$ (R = OMe, OEt, OPr^n, OPr^i, OBu^t) have been prepared in racemic and enantiopure form. The melting points and enthalpies of fusion of every species were measured by differential scanning calorimetry. Binary phase diagrams were reconstructed for the whole family, the entropies of the mixing of the enantiomers in the liquid state, and Gibbs free energy of formation of the racemic compound, as well as Pettersson *i*-values were derived from the thermal data. The differences in the phase behavior of the investigated compounds were associated with the conformations of the alkoxy fragments.

1. Introduction

The increasing demand for enantiopure chemicals has promoted the development of different optical resolution methods among which crystallization based ones play an exceptional role.[1] Such separations are most often performed by the formation and crystallization of diastereomeric derivatives, also direct resolution methods (e.g., preferential crystallization[2]) could be less expensive and simpler. The last methods, however, can only be applied to racemates that form a conglomerate, that is, a mechanical mixture of enantiopure crystals.[3] The phenomenon of conglomerate formation, referred to as the spontaneous resolution of racemates upon crystallization, or simply spontaneous resolution, has attracted considerable interest as evidenced by the substantial number of the reviews published on the subject over the last year.[2,4–6]

With regards to spontaneous resolution, all reviewers are in agreement that the understanding of the factors controlling the two enantiomers' behavior in solution or melt upon crystallization is rather limited. Perez-Garcia and Amabilino have finished their review, thus 'the understanding and prediction of spontaneous resolution—an apparently modest goal when compared with other contemporary ends—remains one of the true challenges for science in the 21st century'.[5]

The modern level of theory has given no way to solve the problem 'from the first principles'. Occasional attempts to predict a chiral substance crystallization type have proven to be very abstract[7] or rather vulnerable with regards to their axiomatization.[8] We believe that a less sophisticated but also more practical way of thinking about empirical models linking the crystal structure changes with the chemical structure variations in the series of closely related compounds would be of great use. The members of such a series must be selected in such a way that every compound would have minimal but regular distinctions from each other. In addition, it would be desirable to have not only two qualitative categories 'conglomerate' and 'racemic compound' for the characterization of crystalline type, but to introduce a quantitative measure allowing us to rank the observed properties.

This measure is not easy to introduce for conglomerate forming substances, while for the racemic compound forming substances, one can use at least two numeric values.

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The relative stability of a racemic compound can be evaluated based on the melting phase diagram of a chiral substance using that introduced by Pettersson dimensionless units i according to the equation

$$i = (T_m^R - T_m^E)/(T_m^A - T_m^E) \quad (1)$$

where T_m are the melting temperatures of the racemate (upper index R), pure enantiomer (index A), and the eutectic (index E). According to Pettersson[9,3] the values $i < 0.5$ characterize unstable racemic compounds, $0.5 \leqslant i \leqslant 1.5$ are indicative of their moderate stability, and $i > 1.5$ are typical of chiral compounds that form stable racemic compounds with a 1:1 composition. For all conglomerates $T_m^R = T_m^E$, hence the i value is always equal to zero. Another way to evaluate the relative stability of racemic compound is to estimate the Gibbs free energy changes accompanied by the reaction of the racemic compound formation from the enantiopure components. Based on a thermodynamic cycle involving the solid and liquid phases of the enantiomers and racemic species, formulas for the ΔG^0 calculations were proposed by Grant et al.[10]

$$\Delta G^0_{T^f_R} = -\frac{(T^f_R - T^f_A)\Delta H^f_A}{T^f_A} - T^f_R R \ln 2 \quad (\text{if } T^f_R - T^f_A < 0) \quad (2a)$$

$$\Delta G^0_{T^f_A} = -\frac{(T^f_R - T^f_A)\Delta H^f_R}{T^f_R} - T^f_A R \ln 2 \quad (\text{if } T^f_R - T^f_A > 0) \quad (2b)$$

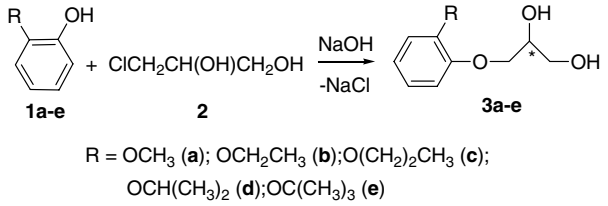
Here T^f_R, T^f_A, ΔH^f_R, ΔH^f_A are the melting point temperatures and fusion enthalpies of the racemate and pure enantiomer, respectively. The Gibbs free energy of formation is always negative for a racemic compound, if it can exist, while for a racemic conglomerate, this value must be (but not always is) close to zero.

Recently, we disclosed the conglomerate nature and developed an effective direct resolution procedure of 3-(2-methoxyphenoxy)-1,2-propanediol, the popular chiral drug guaifenesin.[11] The purposes of this work are to obtain a series of chiral *o*-alkoxysubstituted phenyl glycerol ethers as racemates and as enantiomers; to compare in pairs the solid state IR spectra of the samples; to investigate the melting of the aryl glycerol ethers as enantiomers, as racemates, and in some cases as mixtures of intermediate compositions by means of differential scanning calorimetry; to evaluate the stabilities of racemic compounds under experiment; and to compare the crystallization peculiarities with the substitution pattern.

2. Results

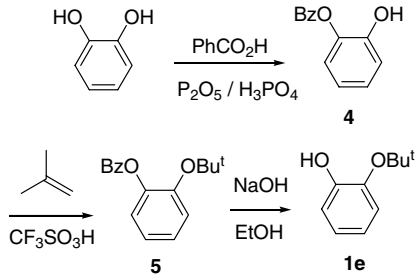
2.1. Chemistry

The availability of both enantiomers of 3-chloro-2,3-propanediol **2** by Jacobsen kinetic hydrolytic resolution of a racemic epichlorohydrin[12] makes it possible to obtain all the series of aryloxypropanediols **3a**–**e** through the use of a single process:



(*S*)-Diols were obtained from (*S*)-chloropropane-1,2-diol and (*R*)-chloropropane-1,2-diol gave (*R*)-diols.

tert-Butoxy substituted phenol **1e** was obtained by following the scheme of Main et al.[13]



2.2. IR spectroscopy

To investigate the type of crystallization for our compounds, we compared the IR spectra of the racemic and highly enantiomerically enriched crystalline samples of **3a**–**e** in KBr pellets, since the IR spectra of the optically active and the racemic form should be identical for the conglomerate formation and different for racemic compounds.

To substantiate this comparison, the spectra were subjected to a procedure of normalization and baseline correction, as described in our previous paper.[14] For this purpose, coefficients that minimize the difference $A_s - [a_0 + a_1 v + A_r(a_2 + a_3 v)]$, where A_s and A_r are the molar absorption coefficients of the scalemic and racemic samples, respectively; v is the IR radiation frequency corresponding to A, and a_n are the desired regression coefficients, were selected by the least-squares method. It was reasonable to introduce the regression terms $a_1 v$ and $A_r a_3 v$ to correct the spectral differences caused by the nonspecific (not related to particular absorption bands) interaction of IR radiation with matter (probably, by radiation scatter on heterogeneities of the sample). It should be noted that the use of polynomials of higher powers (quadratic and cubic) for the generation of differential spectra does not improve the statistical parameters characterizing regression. The ratio between the mean-square deviation of the differential curves and the mean-square deviation of spectral curves for the racemate, that is, the ratio of error to variation (%), was used as a quantitative characteristic for differential curves.

Figure 1 shows good coincidence between the pairs of spectra for compounds **3a** and **3d** under visual comparison; the same is almost true for the normal propoxy derivative **3c**, whereas the spectra of racemic and enantiopure crystalline samples for *tert*-butoxy compound **3e**, and especially for

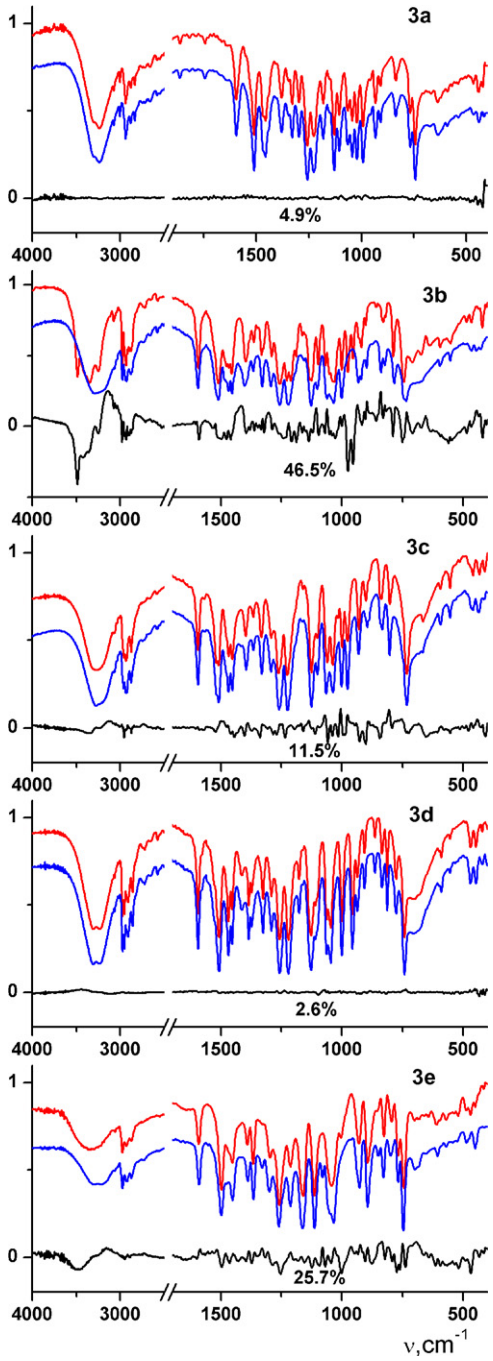


Figure 1. IR spectra of the crystalline samples **3a**–**e**. Red curves—racemates, blue curves—scalemates, black curves are differential curves (see text).

the ethoxy substituted one, differ noticeably. A similar pattern can be observed for the differential curves: for compounds **3a** and **3d**, and to a greater or lesser extent for compound **3c**, differences between the spectra of the racemate and enantioenriched sample are about the same level as instrumental background. At the same time, they are rather substantial for compound **3e** and dramatic for compound **3b**. This is in agreement with the assumption that the racemic compounds are formed upon crystallization of racemic ethoxy, and *tert*-butoxy *ortho*-substituted phenyl glycerol ethers. At the same time, the IR-test confirms the conglomerate nature of guaifenesin **3a**. There is a great probability that a racemic conglomerate is also formed by isopropoxy derivative **3d**. The question of a crystalline type for compound **3c** cannot be solved on this basis.

2.3. Thermochemical investigations

This part of the work deals with the binary mixtures of (*R*)- and (*S*)-compounds **3a**–**e** using differential scanning calorimetry (d.s.c.) as a research method. The temperature data were determined according to the method of Höhne et al.,[15] and were treated as described previously.[16]

The results obtained for the temperature and the enthalpy of fusion of the pure enantiomers and the pure racemates, as well as the calculated[3,10] values of entropy of mixing for the liquid enantiomeric compounds, ΔS_l^m, and the free energy of formation of racemic compounds in the solid state, ΔG^0, are presented in Table 1. The calculated and experimentally obtained eutectic melting temperatures and eutectic compositions, as well as Pettersson's *i*-values calculated according to Eq. 1 are presented in the same table.

According to the *i*-values all but one (compound **3e**) of the racemic compounds in the series studied are very unstable, if they exist at all. It is not feasible to draw a precise line of distinction between compounds **3a**–**d** with only this criterion in mind as the experimental accuracy of the T_{eu}^f determination may amount to 0.5 degree. As a result, other criteria with a more distinct physical sense must be used to attribute the crystalline type of chiral compound in the boundary cases.

Thus, the entropy of mixing for enantiomers **3a** and **3d** in the liquid state is equal to 5.31 and 5.45 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 points to the same peculiarity of chiral **3a** and **3d**.[10] The relatively high negative value for ΔG^0 for *tert*-butoxy derivative **3e** is a good diagnostic for a stable racemic compound formation in the crystalline state.[10] The intermediate ΔS_l^m and especially ΔG^0 values for ethoxy and propoxy diols **3b** and **3c** preclude conglomerate formation, and are compatible with the assumption of a rather unstable racemic compound formation.

From the d.s.c. data, the idealized melting temperatures against the composition diagrams were reconstructed and are depicted in Figure 2. The binary phase diagrams for compounds **3a** and **3d** have an obvious single eutectic V-shape typical for a racemic conglomerate.[3] It follows that the eutectic ee for guaifenesin **3a** (already known) and for the isopropoxyphenyl ether **3d** are equal to zero. The phase diagram for **3e** is very typical for a racemic compound. The eutectic ee in this case found as mutual point(s) for Schröder–Van Laar and Prigogine–Defay curves branches is equal to 57%, that is, a sample with about 79% or more of one enantiomer which could only be enantioenriched by crystallization. The phase diagrams for **3b** and **3d** repre-

Table 1. D.s.c. measured melting point (T^f) and enthalpy of fusion (ΔH^f) of racemic (low index R) and enantiopure (low index A) compounds **3a**–**e** and calculated thermodynamic characteristics for these substances, calculated and measured eutectic (low index eu) fusion temperature and eutectic enantiomeric composition, along with Pettersson's *i*-values (see text)

Compd	T^f_A (°C)	T^f_R (°C)	ΔH^f_A (kJ mol^{-1})	ΔH^f_R (kJ mol^{-1})	T^f_{eu}, calcd (°C)	T^f_{eu}, exp (°C)	ee_{eu} (%)	ΔS^m_I (J K^{-1} mol^{-1})	ΔG^0 (J mol^{-1})	*i*-Value
3a	97.2	79.9	43.0	36.9	79.7	79.7	0	5.31	−15	0.0
3b	78.7	65.6	36.5	36.2	65.1	65.1	22	3.99	−595	0.04
3c	88.8	73.4	38.6	37.9	73.2	73.0	12	4.70	−353	0.02
3d	80.8	62.6	37.9	33.4	62.7	62.6	0	5.45	14	0.0
3e	54.7	53.1	29.0	30.5	47.4	47.4	57	0.46	−1732	0.77

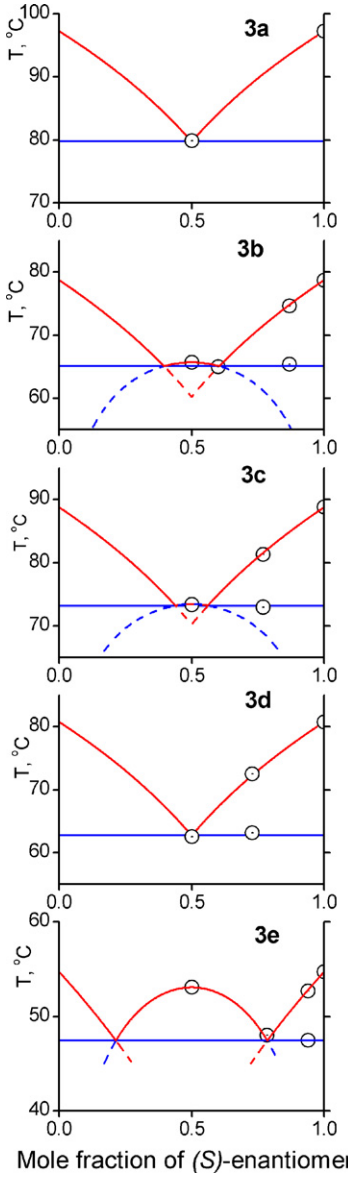


Figure 2. Experimental (circles) points and calculated (solid lines) binary melting phase diagrams for compounds **3a**–**e**.

sent rather conglomerate-like curves with very shallow plateaus in the racemate region. The theoretical eutectic ee for compound **3b** is about 22%, an even smaller value of 12% characterizes the eutectic for propoxy substituted ether **3c**.

3. Discussion

There are no monotone phase behavior changes (e.g., the smooth rise of a racemic compound stability) in the series of alkoxy substituted glycerol ethers with the monotonously changing substituents. In as much as the molecular structures of compounds **3a**–**e** are substantially the same, the differences in the crystal structure are bound to the alkoxy fragment structure in the solid state.

Until now only the published crystallographic information on the family has been available for guaifenesin *rac*-**3a**.[17] As has been established in our earlier work,[18] conglomerate racemic guaifenesin crystallizes in the chiral space group $P2_12_12_1$. As it can be evaluated from the cif-file[17] (refcode PANKUL, available free of charge from the Cambridge Crystallographic Data Centre), the main supramolecular pattern in the homochiral crystal lattice is the endless 3D 'wall' formed by the intermolecular hydrogen bonds between glycerol moieties. Each glycerol hydroxyl is simultaneously a donor (H) and an acceptor (O) for two hydrogen bonds with two different molecules. The tightly hydrogen bonded region positions itself in the central part of every wall. The physical bonding between the walls occurs through hydrophobic interactions of the peripheral phenyl and alkoxy groups. The thus formed crystal packing is stable enough to exclude racemic compound formation. One can try to evaluate the factors destabilizing (or stabilizing) this homochiral mode of packing in the case of other alkoxy substituted compounds **3b**–**e**.

The statistics of the crystal structures for methoxysubstituted benzenes[19,20] shows that the mean torsion angle $\tau_1 = C_{Ar}–C_{Ar}–O–C_{Me}$ is close to zero, if at least one of the *ortho*-positions is free of anything but H substituents. We have analyzed the Cambridge Crystallographic Database[21] (CCD) information for all organic molecules having another alkoxysubstituted (Alk = Et, *n*-Pr, *i*-Pr, *tert*-Bu) phenyl ring with at least one near alkoxy group unsubstituted position. The torsion angles nearest to an aromatic, that is, $\tau_1 = C_{Ar}–C_{Ar}–O–C_{Alk}$, as well as torsions $\tau_2 = C_{Ar}–O–C_{Alk}–C_{Alk}$ for ethoxy and propoxy derivatives, and $\tau'_2 = C_{Ar}–O–C_{Alk}–H$ for isopropoxy substituted aromatics were analyzed. Some results are summarized in Table 2.

From Table 2 it follows that the methoxy, ethoxy, propoxy, and isopropoxy substituted aromatics can be characterized as near planar within the $C_{Ar}C_{Ar}OC_{Alk}$ fragment. CCD contains structure information about only two organic

Table 2. The Cambridge Crystallographic Database[a] statistics for some torsion angles in the alkoxy substituted aromatics Ar–OR with at least one near alkoxy group unsubstituted position

R in Ar–O–R	Number of entries	$\tau_1 = C_{Ar}–C_{Ar}–O–C_{Alk}$ (°)	$\tau_2 = C_{Ar}–O–C_{Alk}–C_{Alk}$ (°)	$\tau'_2 = C_{Ar}–O–C_{Alk}–H$ (°)
a, Me[b]		~0		
b, Et	248	0.7 ± 1.0	178.6 ± 1.0	
c, Pr	62	0.5 ± 2.8	179.0 ± 2.3	
d, Pr^i	133	5.7 ± 3.7		±43.0 ± 3.2
e, Bu^t	2	~90		

[a] Ref. 21.
[b] For details see Refs. 19 and 20.

compounds having *tert*-butoxy substituted phenyl rings, namely two short peptides with the *O*-*tert*-butyltyrosyl moieties. Both have the $(CH_3)_3C–O$ bond orthogonal to the aromatic plane, $\tau_1 \sim 90°$. We believe that the bulky *tert*-butoxy substituent located from only one side of phenyl ring hinders the two **3e** molecules approaching each other, thereby not allowing homochiral hydrogen bonded wall (HHBW) formation. This is probably the reason for the substantial differences in the phase diagram for compound **3e** when compared with the other members of the series.

The reasons for a pairwise similarity in the phase behavior between compounds **3a**,**d** and **3b**,**c**, and on the contrary for a pairwise distinction between the above mentioned pairs could be concealed in the conformation of the alkyl part of the alkoxy substituents. For the ethoxy and normal propoxy aromatics, the fragment $C_{Ar}–O–C_{Alk}–C_{Alk}$ is near planar *trans*, so one would expect a near planar organization of the alkoxyaromatic fragment for compounds **3a**–**c**. One additional feature needs to be noted. The ethyl and propyl fragments are more extended when compared to the methyl group. This is not important for hydrogen bonding patterned after **3a**, but it is important for peripheral hydrophobic bonding. The shortest C/C distance between the carbon atoms of the OCH_3 groups amounts to as much as 4.98 Å within the HHBW, and only 3.59 Å for the neighboring walls in the **3a** crystal lattice, hence there is no way to put an additional pair of CH_2 (even more so for CH_2CH_2) moieties toward one another from opposite directions conserving alkoxy group planarity. This will lead either to a change in the optimum conformation of the alkoxy substituent within the homochiral packing or, as it is realized for racemic **3b** and **3c**, for changing the homochiral packing patterned after **3a** to a heterochiral one.

As for the isopropoxy derivative, the CCD statistics allows us to make rough estimates of the two τ_2 values as $\tau'_2 \pm 120°$. For positive τ'_2 this means 163 and −77°; that is, no C–CH_3 bond lies in the plane of molecule **3d**, and the optimal conformation for **3d** is compatible with the crystal lattice of the guaifenesin type. Moreover, excess CH_3 groups located in the hollows of HHBW could enlarge the hydrophobicity of the walls periphery, and for this reason to stabilize the homochiral packing.

4. Conclusion

In conclusion, we are able to say that the investigated series of chiral *o*-alkoxysubstituted phenyl glycerol ethers fall into two groups. The first, consisting of only one representative (*tert*-BuO, compound **3e**), demonstrates the formation in the solid state of a molecular racemic compound of moderate stability. The representatives of the second group, compounds **3a**–**d**, form very unstable molecular racemic compounds **3b** and **3c**, or undergo spontaneous resolution, crystallizing as racemic conglomerates, that is, form no racemic compound at all (**3a** and **3d**). We believe that the main difference between the two groups is related to the conformation of an alkoxy substituent in the solid state: the expected value of the dihedral angle $C_{Ar}–C_{Ar}–O–C_{Alk}$ is about 90° for the *tert*-butoxy derivative and close to zero for all other alkoxysubstituted phenyl glycerol ethers. The fine structural differences between the alkyl fragments could be the reason for controlling the crystallization type within the second group.

5. Experimental

5.1. General

The NMR spectra were recorded on a Bruker Avance-600 spectrometer in $CDCl_3$ with TMS or the signals of the solvent as the internal standard. The IR spectra of the polycrystalline samples of *rac*- and *scal*-compounds under investigations in KBr pellets 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.

Melting curves were measured on a Perkin–Elmer Diamond DSC differential scanning calorimeter in aluminum pans with a 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). All experiments except in the case of compound **10** were run with column temperature 40 °C; eluent hexane/isopropanol/diethylamine = 80:20:0.1; and flow rate 1.0 ml/min.

5.2. Synthesis

Racemic epichlorohydrin (99%), guaiacol **1a** (98%), 2-ethoxyphenol **1b** (98%), 2-isopropoxyphenol **1d** (97%), and *rac*-guaifenesin *rac*-**3a** were purchased from Alfa Aesar®; *rac*-3-chloropropane-1,2-diol *rac*-**2** (99+%) was purchased from Acros Organics®. (*R*)- and (*S*)-3-chloro-1,2-propanediol (*R*)-**2** and (*S*)-**2** were prepared through Jacobsen kinetic hydrolytic resolution of *rac*-**2** without modifications.[12]

5.2.1. 2-*n*-Propoxyphenol, 1c. A solution of NaOH (2.8 g, 0.07 mol) in water (11 ml) was added to a solution of pyrocatechol (7.7 g, 0.07 mol) in ethanol (50 ml), and the resulting mixture was stirred and heated at reflux for 45 min. A solution of 1-bromopropane (9 g, 0.07 mol) was then added dropwise within 1 h, and the mixture was further stirred and heated at reflux for 6 h. After removal of the solvent in vacuo, the residue was purified by distillation. Yield 7.0 g (65%); bp 81–84 °C (0.5 Torr); n_D^{20} 1.5120; {lit.[22] bp 80–83 °C (4 Torr)}. ^{1}H NMR (600 MHz) δ 1.05 (t, $J = 7.6$ Hz, 3H, CH_3), 1.85 (m, 2H, CH_2CH_3), 4.01 (t, $J = 6.6$ Hz, 2H, OCH_2), 5.70 (s, 1H, OH), 6.95–6.79 (m, 4H, Ar).

5.2.2. 2-*tert*-Butoxyphenol, 1e. This was obtained following the published scheme.[13] Through acylation of pyrocatechol by benzoic acid in polyphosphoric acid 2-hydroxyphenyl benzoate **4** was obtained. Yield 55%; mp 132–133 °C; (lit.[13] mp 130 °C). ^{1}H NMR (600 MHz) δ 5.5 (br s, 1H, IH), 7.0 (dt, $J = 7.8$, 1.3 Hz, 1H), 7.1 (dd, $J = 8.1$, 1.1 Hz, 1H), 7.21 (m, 2H), 7.55 (t, $J = 7.8$ Hz, 2H), 7.7 (t, $J = 7.6$ Hz, 1H), 8.2 (d, $J = 7.3$ Hz, 2H); (cf. lit.[13]). Trifluoromethanesulfonic acid catalyzed addition of **4** to isobutene has led to 2-*tert*-butoxyphenyl benzoate, **5**. Yield 70%; mp 62 °C. ^{1}H NMR (600 MHz) δ 1.33 (s, 9H), 7.12–7.15 (m, 1H), 7.19–7.22 (m, 2H), 7.54 (t, $J = 7.4$, 7.9 Hz, 2H), 7.65 (t, $J = 7.4$ Hz, 1H), 8.25 (d, $J = 7.4$ Hz, 2H). Saponification of **5** by aqueous NaOH followed by distillation of the crude product allows us to obtain 2-*tert*-butoxyphenol, **1e**. Yield 60%; bp 60 °C (0.4 Torr); {lit.[13] bp 60 °C (0.4 Torr)}. ^{1}H NMR (600 MHz) δ 1.44 (s, 9H), 5.77 (s, 1H), 6.78–6.81 (m, 1H), 6.96–6.99 (m, 2H), 7.04 (d, $J = 7.9$ Hz, 1H); (cf. lit.[13]).

Racemic diols **3b**–**e** and enantiomeric diols **3a**–**e** were synthesized by analogy with a published procedure[23] from racemic or enantiomeric 3-chloropropane-1,2-diols and corresponding phenol; (*S*)-aryloxypropanediols were obtained from (*S*)-chloropropane-1,2-diol, and vice versa. Only the (*S*)-enantiomers are reported.

5.2.3. (*S*)-3-(2-Methoxyphenoxy)-propane-1,2-diol, (*S*)-3a. The yield was 77%, mp 98–99 °C (lit.:[11] mp 98–99 °C); $[\alpha]_D^{20} = +9.5$ (*c* 1.0, MeOH); 99.9% ee [chiral HPLC analysis; $t_R = 10.3$ (minor), 17.3 min (major)].

5.2.4. *rac*-3-(2-Ethoxyphenoxy)-propane-1,2-diol, *rac*-3b. Yield 76%, mp 64–65 °C. ^{1}H NMR (600 MHz) δ 1.45 (t, $J = 7.1$ Hz, 3H, CH_3), 2.59 (t, $J = 6.0$, 6.6 Hz, 1H, OH), 3.28 (d, $J = 5.5$ Hz, 1H, OH), 3.79–3.84 (m, 2H, CH_2O), 4.00–4.04 (m, 1H, CH), 4.05–4.09 (m, 2H, CH_2CH_3 and 1H, CH_2O), 4.18 (dd, $J = 9.7$, 3.1 Hz, 1H, CH_2I), 6.88–6.97 (m, 4H, Ar). ^{13}C NMR (150.864 MHz) δ 14.77 (CH_3), 64.03 (CH_2CH_3), 64.32 (CH_2OH), 69.80 (CH), 73.46 (CH_2O), 113.10 (C^3_{Ar}), 115.99 (C^6_{Ar}), 121.08 (C^4_{Ar}), 122.64 (C^5_{Ar}), 148.18 (C^1_{Ar}), 149.38 (C^2_{Ar}).

5.2.5. (*S*)-3-(2-Ethoxyphenoxy)-propane-1,2-diol, (*S*)-3b. Yield 68%, mp 78–79 °C; $[\alpha]_D^{20} = +8.8$ (*c* 1, hexane/EtOH 4:1), $[\alpha]_D^{20} = +11.7$ (*c* 1, EtOH); {lit.:[24] $[\alpha]_D^{20} = +3.9$ (*c* 1, acetone)}. 99.2% ee [chiral HPLC analysis; $t_R = 16.5$ (minor), 19.3 min (major)]. NMR spectra were identical with that cited above for *rac*-**7**.

5.2.6. *rac*-3-(2-Propoxyphenoxy)-propane-1,2-diol, *rac*-3c. Yield 74%, mp 73–74 °C (hexane). ^{1}H NMR (600 MHz) δ 1.04 (t, $J = 7.3$ Hz, 3H, CH_3), 1.81–1.87 (m, 2H, CH_2CH_3), 2.75 (t, $J = 5.8$, 6.0 Hz, 1H, OH), 3.40 (d, $J = 5.2$ Hz, 1H, OH), 3.77–3.83 (m, 2H, CH_2IH), 3.94 (t, $J = 6.6$ Hz, 2H, CH_2CH_2), 4.01–4.03 (m, 1H, CH), 4.05 (dd, $J = 9.4$, 5.8 Hz, 1H, CH_2O), 4.16 (dd, $J = 9.4$, 3.2 Hz, 1H, CH_2O), 6.87–6.96 (m, 4H, Ar). ^{13}C NMR (150.864 MHz) δ 10.46 (CH_3), 22.57 (CH_2), 64.03 (OCH_2), 69.87 (CH_2O), 70.44 (CH), 73.17 (CH_2O), 113.22 (C^3_{Ar}), 115.82 (C^6_{Ar}), 121.03 (C^4_{Ar}), 122.55 (C^5_{Ar}), 148.23 (C^1_{Ar}), 149.52 (C^2_{Ar}).

5.2.7. (*S*)-3-(2-Propoxyphenoxy)-propane-1,2-diol, (*S*)-3c. The yield was 74%, mp 88–90 °C (hexane); $[\alpha]_D^{20} = +3.1$ (*c* 1, hexane/EtOH 4:1); $[\alpha]_D^{20} = +6.8$ (*c* 1, EtOH); 99.8% ee [chiral HPLC analysis; $t_R = 14.9$ min (minor), 16.9 (major)]. NMR spectra were identical with that cited above for *rac*-**3c**.

5.2.8. *rac*-3-(2-Isopropoxyphenoxy)-propane-1,2-diol, *rac*-3d. The yield was 88%, mp 63–64 °C (hexane). ^{1}H NMR (600 MHz) δ 1.35 (d, $J = 4.2$ Hz, 6H, CH_3), 2.79 (br s, 1H, OH), 3.48 (br s, 1H, OH), 3.75–3.81 (m, 2H, CH_2IH), 3.99–4.02 (m, 1H, CH), 4.04 (dd, $J = 9.4$, 5.9 Hz, 1H, CH_2O), 4.14 (dd, $J = 9.4$, 2.9 Hz, 1H, CH_2O), 4.50–4.54 (m, 1H, CH), 6.88–6.95 (m, 4H, Ar). ^{13}C NMR (150.864 MHz) δ 22.08 (CH_3), 64.00 (OCH_2), 69.86 (CH), 71.57 (CH), 73.39 (CH_2O), 115.85 (C^3_{Ar}), 116.41 (C^6_{Ar}), 121.47 (C^4_{Ar}), 122.58 (C^5_{Ar}), 148.23(C^1_{Ar}) , 149.27 (C^2_{Ar}).

5.2.9. (*S*)-3-(2-Isopropoxyphenoxy)-propane-1,2-diol, (*S*)-3d. The yield was 79%, mp 81–82 °C (light petroleum); $[\alpha]_D^{20} = +7.8$ (*c* 1, EtOH); $[\alpha]_D^{20} = +6.6$ (*c* 1, hexane/EtOH 4:1); 99.3% ee [chiral HPLC analysis; $t_R = 26.3$ (minor), 27.7 min (major)]. NMR spectra were identical with cited above for *rac*-**3d**.

5.2.10. *rac*-3-(2-*tert*-Buthoxyphenoxy)-propane-1,2-diol, *rac*-3e. The yield was 65%, mp 50–52 °C (pentane). ^{13}C NMR (150.864 MHz) δ 27.90 (CH_3), 62.96 (OCH_2), 69.51 (CH), 70.73 (CH_2O), 79.73 (CMe_3), 114.49 (C^3_{Ar}), 120.74 (C^6_{Ar}), 123.75 (C^4_{Ar}), 124.71 (C^5_{Ar}), 144.15(C^1_{Ar}) , 152.21 (C^2_{Ar}).

5.2.11. (*S*)-3-(2-*tert*-Buthoxyphenoxy)-propane-1,2-diol, (*S*)-3e. The yield was 60%, mp 47–52 °C (pentane); $[\alpha]_D^{20} = +8.8$ (*c* 1, EtOH); 87.8% ee [chiral HPLC analysis;

column temperature 27 °C; eluent: hexane/isopropanol/diethylamine = 95:5:0.1; $t_R = 21.1$ min (minor), 22.8 (major)]. ^{1}H NMR (600 MHz) δ 1.39 (s, 9H, CH_3), 2.47 (t, $J = 6.0$, 6.3 Hz, 1H, IH), 3.48 (d, $J = 4.7$ Hz, 1H, IH), 3.73–3.76 (m, 1H, ICH_2), 3.79–3.82 (m, 1H, ICH_2), 3.99–4.02 (m, 1H, CH), 4.04 (dd, $J = 9.6$, 6.4 Hz, 1H, CH_2O), 4.14 (dd, $J = 9.6$, 3.3 Hz, 1H, CH_2O), 6.92–6.97 (m, 2H, Ar), 7.04–7.07 (m, 2H, Ar).

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