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Solid state properties of 1,2-epoxy-3-(2-methoxyphenyloxy)-propane—valuable intermediate in non-racemic drug synthesis

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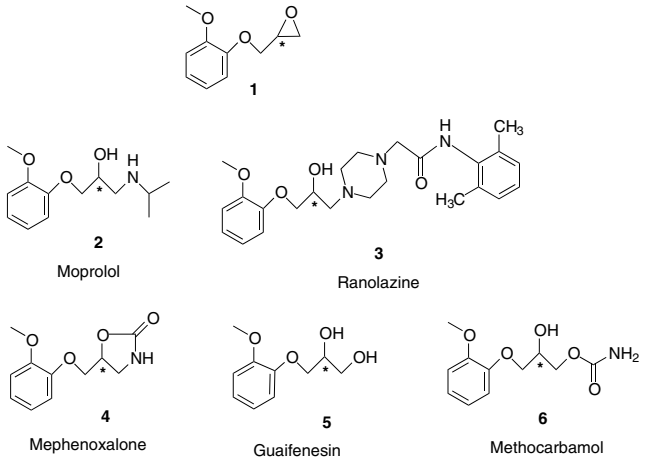
Abstract—Racemic 1,2-epoxy-3-(2-methoxyphenyloxy)-propane **1** undergoes spontaneous resolution upon crystallization. This fact is confirmed by coincidence of the IR spectra of racemic and scalemic crystalline samples of **1**, by thermal analysis (single eutectic V-shape binary melting phase diagram), and X-ray analysis (space group $P2_12_12_1$, $Z = 4$). Racemic **1** could be resolved into (*S*)-(+)- and (*R*)-(−)-**1** by a preferential crystallization procedure.

1. Introduction

Chiral epoxides are versatile building blocks for modern enantioselective synthesis due to their regio- and stereochemically controlled reactivity with a broad range of nucleophiles.[1] Among these, aryl glycidyl ethers have been widely used for the production of non-racemic drugs with β-adrenergic activities.[1a,2]

1,2-Epoxy-3-(2-methoxyphenyloxy)-propane, glycidyl ether **1** has an obvious structural similarity with, and can be used as an intermediate in the synthesis of the β-adrenoblocker moprolol **2**, antianginal remedy ranolazine **3**, anxiolytic mephenoxalone **4**, expectorant guaifenesin **5**, and skeletal muscle relaxant methocarbamol **6**. For the whole of the family of β-adrenoblockers, it has been shown that the (*S*)-enantiomers are eutomer components of the racemic drug, whereas the (*R*)-enantiomers (distomers) usually display other (often undesirable) activity.[3] There is evidence that in the case of methocarbamol **6** one enantiomer is more active in vivo than the other or the racemate.[4] From the standpoint of the modern tendency to replace racemic drugs by enantiopure version it is desirable to have a precise knowledge about the properties of scalemic **1**, and to outline the direct access to both its enantiomeric forms.



A number of different approaches have been developed for obtaining scalemic aryl glycidyl ethers including syntheses from chiral natural products or nucleophilic substitution of activated enantioenriched epoxypropanes. For the present, a wide assortment of kinetic resolutions of racemic aryl glycidyl ethers exists, assisted by catalysts of synthetic or biological nature. Most of the existing approaches can be illustrated by the preparation of enantioenriched epoxide **1**. For the first time both enantiomers of this compound were obtained with low to moderate yield during multistep synthesis from natural D-mannitol.[5] Some years later (*R*)-**1** was resynthesized from the same starting material, whereas (*S*)-**1**

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was obtained from (*R*)-epichlorohydrin via nucleophilic reaction with guaiacol.[6] Enantioenriched (*S*)-**1** was prepared from the corresponding scalemic 1-chloro-3-(2-methoxyphenyloxy)-propane-2-ol, which was in its turn obtained through lipase catalyzed hydrolysis of the chlorohydrin esters.[7] Racemic **1** was kinetically resolved during enantioselective ring opening of epoxide with trimethylsilylazide or isopropylamine in the presence of β-cyclodextrin; (*R*)-enantiomer with ee 59–90% was recovered.[8] Recently (*R*)-**1** was obtained by partial enantioselective hydrolysis of *rac*-**1** in the presence of the Jacobsen (salen)-Co(III) chiral catalyst.[9]

The reports by Schneider et al. and Kamal et al.[7,8] contain no experimental details about the epoxides obtained, and there are some discrepancies among characteristics of non-racemic epoxides **1** mentioned in other sources. According to Nelson et al.[5] the mp values for both enantiomers are equal to 56–57 °C. Caroon et al.[6] reports the values of mp 52–54 °C and $[\alpha]_D = -11.7$ (*c* 0.995, MeOH) for (*R*)-**1** (ee 98 ± 1%, NMR); and mp 43–47 °C and $[\alpha]_D = +13.6$ (*c* 0.997, MeOH) for (*S*)-**1** (ee 98 ± 1%, NMR). Bredikhin et al.[9] report the value $[\alpha]_D^{20} = -11.9$ (*c* 0.87, EtOH) for liquid (*R*)-**1** (ee 89%, NMR).

2. Results and discussion

Here we present the results of our IR, thermochemical, and X-ray investigations revealing the conglomerate nature of chiral epoxide **1**. The crystallization of a chiral substance as a racemic conglomerate makes it possible to resolve it without resorting to enantiopure chiral reagents and/or auxiliaries. We have found that *rac*-**1** is capable on spontaneous resolution upon crystallization and can be resolved by the entrainment technique.[10,11]

2.1. IR spectroscopy

To investigate the type of crystallization we compared the IR spectra of racemic and highly enantiomerically enriched crystalline samples of **1** in KBr pellets, since the IR spectra of the optically active and the racemic form should be identical for conglomerate formation and different for racemic compounds. Figure 1 shows almost complete coincidence of the two spectra.

This is a good diagnostic for racemic conglomerate formation for the compounds with the pronounced H-bonding groups, but for the compounds possessing no classical H-donors (such as **1**), the similarity of the IR spectra must be treated with caution.[12]

2.2. Thermochemical investigations

This part of the work deals with binary mixtures of (*R*)- and (*S*)-**1** using differential scanning calorimetry as a research method. A (solid + liquid) diagram of the melting temperature against composition was obtained for this system. Thermodynamic data on binary mixtures of enantiomers are useful, for instance 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.

The temperature data were determined according to the method of Höhne et al.,[13] following the procedure described by Gallis et al.[14] The solidus values correspond to the extrapolated peak onset temperatures T_E. The determination of the liquidus points T_L requires a correction for the shift of the peak temperature due to the heating of the sample and due to the distortions of the peak shape, using the correct angle γ. The angle is obtained from a melting experiment using a pure standard substance (doubly sublimed naphthalene in our case) at the respective heating rate; the slope of the linear front section of the curve determines γ. For a pure (chemically and enantiomerically) component, the extrapolated peak onset temperature and the corrected peak temperature almost coincide (Fig. 2a); and in all cases corrected values have been used (Fig. 2a and b).

For the right evaluation of the binary phase diagram 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 $[\alpha_i]/[\alpha_{max}] = op \approx ee = |(n_R - n_S)|/$

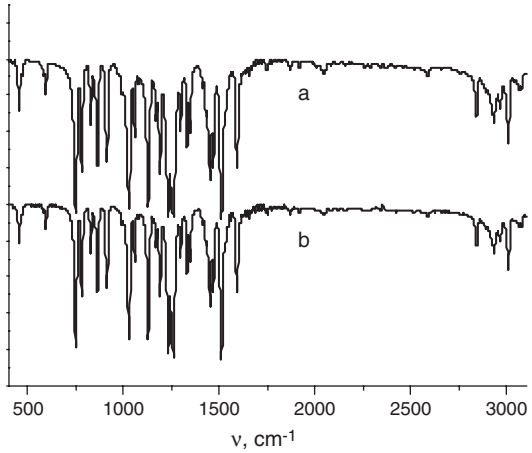

Figure 1. IR spectra of the crystalline 1,2-epoxy-3-(2-methoxyphenyloxy)-propane **1** [(a), (*S*)-(+); (b), racemic].

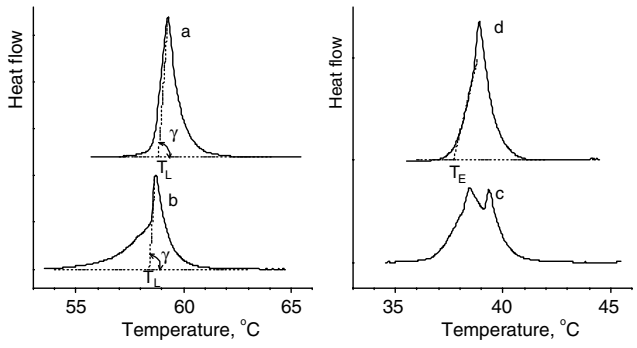

Figure 2. Thermal curves for 1,2-epoxy-3-(2-methoxyphenyloxy)-propane **1** [(a), (*S*)-(+)-, op ≈ 100%; (b), (*S*)-(+)-, op ≈ 99.0%; (c), *rac*-, as obtained after recrystallization; (d), *rac*-, after grinding].

Table 1. D.s.c. measured melting point and enthalpy of fusion of racemic (low index *R*) and (*S*)-(+) (low index *A*) 1,2-epoxy-3-(2-methoxyphenyloxy)-propane **1**

T'^{f}_{A} (°C)	T'^{f}_{R} (°C)	ΔH^{f}_{A} (J mol^{-1})	ΔH^{f}_{R} (J mol^{-1})	ΔS^{m}_{l} (J K^{-1} mol^{-1})	ΔG^{0} (J mol^{-1})
58.8	37.6	25,400	21,300	4.79	−165

($n_R + n_S$). The closer is the value [α_{max}] used in the calculations to the value of the specific rotation for enantiopure sample, the better is equivalence between the optical purity and the enantiomeric excess. We believe that enantiopure samples of (*S*)-**1** are characterized by the values $[\alpha]^{20}_{D} = +13.0 \pm 0.1$ (*c* 0.61, EtOH) or $[\alpha]^{20}_{D} = +16.0 \pm 0.1$ (*c* 1.02, MeOH). The following reasons were taken into account to establish enantiomeric purity of such a sample. (1) The value of specific rotation was constant after several consecutive crystallizations. Running ahead, it can be mentioned that for conglomerate forming substances (only) this is a solid evidence for the enantiomeric purity. (2) The ^{31}P NMR control of the enantiomeric purity of this sample with the use of our developed derivatizing phosphorus reagent based upon bis-*N*,*N*′-dimethylamide of natural tartaric acid[9,15] reveals no traces of the second enantiomer. (3) The d.s.c. heating curve for this sample has virtually ideal shape (Fig. 2a), with a base line and a linear front part of the curve constitutes a nearly perfect angle. In an effort to test this criterion we demonstrate another curve for the sample with op ≈ 0.99 {$[\alpha]^{20}_{D} = +12.9$ (*c* 0.6, EtOH)} (Fig. 2b); one can see dramatically changed front, which is evidence of enantiomeric impurities.

The results obtained for the temperature and the enthalpy of fusion of the pure enantiomer and the pure racemate are presented in Table 1. From the d.s.c. data the melting temperature against composition diagram was drawn and is depicted in Figure 3.

Experimental points in Figure 3 form an obvious single eutectic V-shape curve typical to a racemic conglomerate.[10] Figure 3 presents also the theoretical liquidus curve (dashed line) deduced for conglomerate from the Schröder–Van Laar equation $\ln(n) = (\Delta H^{f}_{A}/R)(1/T^{f}_{A} - 1/T^{f})$. Both experimental and theoretical sets correlate quite well. The calculated[10,16] entropy of mixing for enantiomeric **1** in the liquid state is equal to 4.79 J K^{-1} mol^{-1}, which is slightly less but close to the ideal value of 5.77 J K^{-1} mol^{-1} (Rln2) for conglomerates.

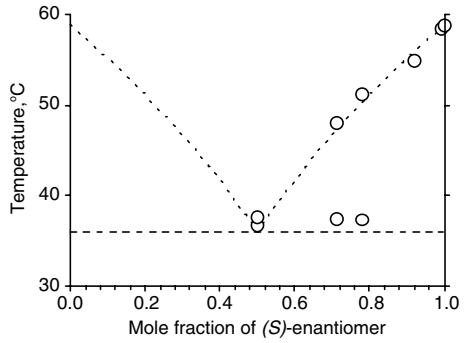

Figure 3. Experimental (circles) and calculated (dashed lines) melting point phase diagram of **1**.

One other circumstance is worthy of notice. Whereas the endothermic event for routinely prepared polycrystalline sample of highly enantioenriched epoxide **1** is depicted by smooth unimodal curve (Fig. 2a), analogous events for the similar racemic samples are depicted by remarkable polymodal comb-shaped curves (Fig. 2c). For the carefully ground samples the heating curve changes its shape to a relatively broad unimodal one (Fig. 2d).

We believe that these peculiarities of the racemic sample heating curves are diagnostic indicators for a conglomerate forming substances. The thermally induced event for such a substance is not a proper melting. The process begins from the formation of a limited amount of a liquid (eutectic) phase promoted by microscopic contaminations followed by the dissolution of scalemic crystals in racemic melt. As the entrapped crystals dissolve in this portion of a melt, the endothermic process ceases. The expansion of liquid zones through the sample is restrained by surface tension, so it is realized as intermittent advance. If the sample consists of the rather coarse individual crystals, this succession of distinct events of near complete dissolution of the solid in the one part of the sample and stepwise growth of the liquid drops encapsulating new portions of crystals leading to new endothermic events would generate a comb-shaped thermal curve. If the sample consists of the thin-grinded crystals, these consequences will lead to smooth but rather broad thermal curve as compared with the curve for enantiopure sample of the same mass.

2.3. X-ray investigations

The X-ray studies of single crystals picked up from a racemic sample of **1** revealed that all crystals belong to the 'chiral' space group $P2_12_12_1$, $Z = 4$. This fact implies that epoxide **1** crystallizes as a racemic conglomerate, and homochiral molecules only are present in the single crystal elementary cell. The geometry of **1** is depicted in Figure 4. Structural parameters (bond lengths and angles) of **1** have normal values, usually observed in similar compounds. The methoxyphenyl fragment of the molecule is planar, the oxypropyl fragment also has nearly planar *trans*-conformation with the torsions C(1A)O(2)C(3)C(2) = 172.1(3) and O(2)C(3)C(2)C(1) = 156.5(5)°.

Analysis of the intermolecular interactions in the homochiral crystal of **1** showed no pronounced π–π interactions between benzene rings. Dihedral angles between the planes of the neighboring benzene rings are about 84.7°. Two short intermolecular contacts were observed between hydrogen atoms of methyl and methylene groups and the center of gravity [Cg(2)] of the neighboring extramolecular benzene ring: C(4)–H(4B)···Cg(2) [$x - 1, y, z$], the distance H···Cg(2) 2.69 Å, the angle C(4)–H(4B)···Cg(2) 152°, and C(3)–H(3B)···Cg(2)

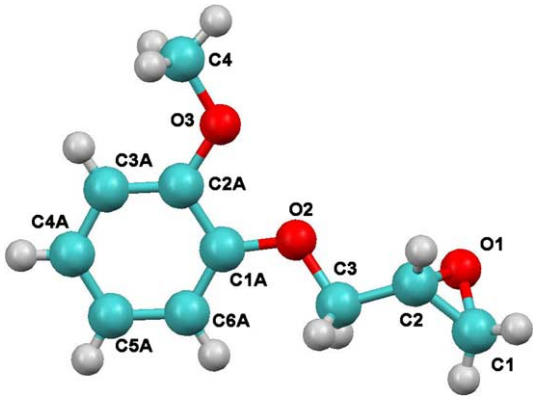

Figure 4. Geometry of the molecule **1** in crystal, and atomic numbering scheme.

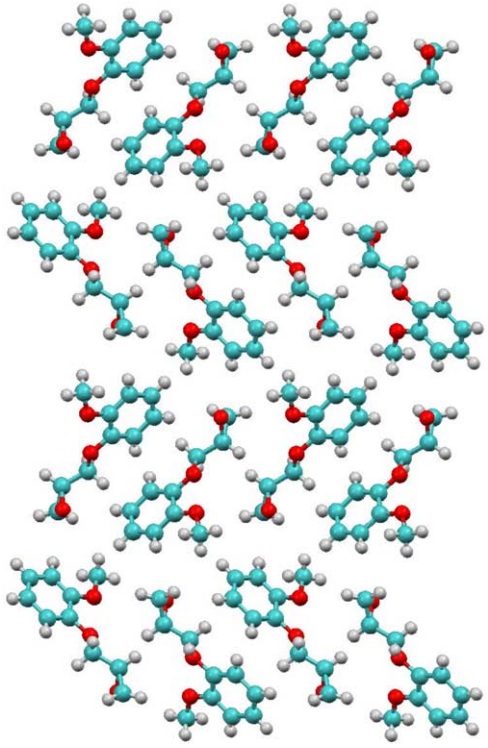

Figure 5. Packing diagram of crystal **1**. View along *OZ* axis.

$[1/2 + x, 1/2 - y, 1 - z]$, H···Cg(2) 3.19 Å, C(3)–H(3B)···Cg(2) 155°. Another type of week intermolecular interactions, the hydrogen bond C(1)–H(1A)···O(3)′ $[1/2 + x, 1/2 - y, 2 - z]$ characterized by the distances C(1)–H(1A) 0.97, H(1A)···O(3)′ 2.58, C(1)···O(3)′ 3.347(7) Å, and angle C(1)–H(1A)···O(3)′ 136° have been observed. The general hydrogen bond motif is zigzag chains along *OX* axis. As a whole crystalline epoxide **1** has a lamellar type of the packing (Fig. 5).

2.4. Resolution of the glycidyl ether 1 by preferential crystallization

The above mentioned material created a solid evidence that 1,2-epoxy-3-(2-methoxyphenyloxy)-propane **1** crystallizes as a racemic conglomerate. Although a stable conglomerate is a necessary condition for the application of preferential crystallization, it can be insufficient to ensure a practical entrainment effect under some circumstances.[17] So we tried to realize the experimental resolution of racemic **1** through entrainment procedure, having in mind to demonstrate the effect of entrainment first of all, and making no effort to achieve an optimum condition for the process. We employed rectified ethanol as the solvent.

A supersaturated solution of *rac*-**1** including a small excess of (*R*)-(−)-**1** was prepared by heating, and then cooled to 10 °C. A small number of seeds of (*R*)-(−)-**1** were added and the stirred solution was allowed to crystallize for 30 min. The weight of (*R*)-(−)-**1** obtained after filtration was more than the common weight of initial excess of (*R*)-enantiomer and seed added, although the op of the precipitate was only 83%. To the mother liquor, *rac*-**1** was added in order that the quantity of **1** in the solution could be recovered. The mixture was heated until the solid was completely dissolved and then cooled to 10 °C. After the solution had been seeded with (*S*)-(+)-**1** and stirred for 30 min, the precipitated (*S*)-(+)-**1** was collected in a similar manner.

The current degree of resolution is low as yet, but it certainly might be improved by a future detailed examination of the resolution conditions.

3. Conclusion

To the best of our knowledge the glycidyl ether **1** is only a third conglomerate forming representative among the broad class of epoxides. The two others are glycidyl 3-nitrobenzenesulfonate[18] and (2*RS*, 3*SR*)-3-(4-methoxyphenyl)glycidic acid 4-chloro-3-methylphenyl ester.[19] The last compound resolved by entrainment procedure was already used in the synthesis of single enantiomer coronary vasodilator diltiazem. We believe that more intent search for conglomerates within this highly reactive class of chemicals would lead to more intent practical use of the unappreciated potential of spontaneous resolution phenomenon.

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker MSL-400 (400.13 MHz for ^{1}H; 100.6 MHz for ^{13}C) 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*-**1** and (*R*)- or (*S*)-**1** in KBr pellets were recorded on an Bruker IFS-66v Fourier-transform spectrometer. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration *c* is given as g/100 mL). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected.

The melting curves of the samples of 1,2-epoxy-3-(2-methoxyphenyloxy)-propane 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.[14]

4.2. Synthesis

Racemic epichlorohydrin and guaiacol were commercially available. (*R*)- and (*S*)-epichlorohydrin were prepared according to Jacobsen method without modifications.[20] Racemic 1,2-epoxy-3-(2-methoxyphenyloxy)-propane *rac*-**1** was prepared from racemic epichlorohydrin and guaiacol by known procedure,[21] bp 88–90 °C at 0.05 mmHg, mp 38–40 °C (colorless needles from ethanol) [lit.[21] bp 120 °C/0.9 mmHg; lit.[22] mp 36 °C (light petroleum)]; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.97$–6.86 (m, 4H–Ar), 4.23 (dd, $^2J = 11.44$, $^3J = 3.27$, 1H, CH_2), 4.02 (dd, $^2J = 11.44$, $^3J = 5.45$, 1H, CH_2), 3.85 (s, 3H, CH_3), 3.39–3.36 (m, 1H, CH), 2.87 (dd, $^2J = 4.63$, $^3J = 4.36$, 1H, CH_2), 2.72 (dd, $^2J = 4.91$, $^3J = 2.72$, 1H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 149.93$, 148.25, 122.11, 121.01, 114.70, 112.33, 70.45, 55.99, 50.29, 44.88 [lit.[23,21]].

4.2.1. (*S*)-1,2-Epoxy-3-(2-methoxyphenyloxy)-propane. (*S*)-**1** used as seed was obtained from the (*R*)-epichlorohydrin {6.33 g, 0.07 mol; $[\alpha]_D^{20} = -24.4$ (*c* 1.7, MeOH), op 70%} and guaiacol (2.80 g, 0.025 mol) as described for racemic compound.[21] The configuration of the product is inverted as against the configuration of the starting epichlorohydrin. The crude (*S*)-**1** was crystallized four times from EtOH to give colorless needles {1.43 g (35%); mp 59–60 °C; $[\alpha]_D^{20} = +13.0$ (*c* 0.61, EtOH), $[\alpha]_D^{20} = +16.0$ (*c* 1.02, MeOH), ee > 99%}; [lit.[5] mp 56–57 °C]; {lit.[6] mp 43–47 °C, $[\alpha]_D^{20} = +13.6$ (*c* 0.997, MeOH) (ee 98 ± 1%, NMR)}.

4.2.2. (*R*)-1,2-Epoxy-3-(2-methoxyphenyloxy)-propane. (*R*)-**1** used as seed was synthesized analogously from the (*S*)-epichlorohydrin. The colorless needles; mp 59–60 °C (EtOH), $[\alpha]_D^{20} = -12.9$ (*c* 0.53, EtOH) {lit.[6] mp 52–54 °C, $[\alpha]_D = -11.7$ (*c* 0.995, MeOH) (ee 98 ± 1%, NMR)}.

4.3. Resolution of racemic 1,2-epoxy-3-(2-methoxyphenyloxy)-propane 1 by preferential crystallization (entrainment)

Racemic 1,2-epoxy-3-(2-methoxyphenyloxy)-propane *rac*-**1** (1.9 g) and (*R*)-**1** {0.15 g, $[\alpha]_D^{20} = -12.7$ (*c* 0.94, EtOH)} were dissolved in 20 ml of ethanol at 30 °C. The solution of this specially prepared sample (op ≈ 7%) was cooled to 10 °C and seeded with finely-pulverized (*R*)-**1** (13 mg). After stirring the mixture for 30 min at 5–6 °C, precipitated (*R*)-**1** was collected by filtration {0.22 g after drying; $[\alpha]_D^{20} = -11.1$ (*c* 1.1, EtOH), op 83%}. The extra portion of *rac*-**1** (0.22 g) was then dissolved in the mother liquor at 30 °C; the resulting solution was cooled to 10 °C. After addition of (*S*)-**1** {13 mg, $[\alpha]_D^{20} = +13.0$ (*c* 0.61, EtOH)} as seed crystals to the solution, and stirring the mixture for 30 min at 5–6 °C, (*S*)-**1** {0.12 g after drying; $[\alpha]_D^{20} = +11.1$ (*c* 1.1, EtOH), op 83%} was collected by filtration.

A high degree of enantiomeric purity of collected 1,2-epoxy-3-(2-methoxyphenyloxy)-propanes can be achieved by slow crystallization from ethanol. Thus crop of crude (*R*)-**1** {200 mg; $[\alpha]_D^{20} = -11.1$ (*c* 1.07, EtOH)} was dissolved in 0.7 ml of ethanol at 50–60 °C. The solution was cooled to 7 °C and left standing at this temperature overnight; 155 mg of enantiomerically pure (*R*)-**1** {$[\alpha]_D^{20} = -13.1$ (*c* 1.22, EtOH)} was collected by filtration.

4.4. X-ray analysis

4.4.1. X-ray crystallography of 1. $C_{10}H_{12}O_3$, $M = 180.21$, orthorhombic, space group $P2_12_12_1$, $a = 5.068(2)$, $b = 18.169(7)$, $c = 10.128(7)$ Å, $V = 932.5(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.28$ Mg m^{-3}. Cell parameters and intensities of 2751 independent reflections were measured on an Enraf-Nonius CAD-4 diffractometer in the $\omega/2\theta$-scan mode, $\theta \leqslant 64.8°$, using Cu K_α radiation (graphite monochromator, λ 1.54184 Å). The stability of crystals and experimental conditions were checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. Linear decay correction of intensities of reflections was applied, because 74% decay of intensity control reflections were observed. Absorption corrections were not applied (μCu 7.41 cm^{-1}). Corrections for Lorentz and polarization effects were applied. The structure was solved by direct method using the SIR program[24] and refined by the full matrix least-squares using SHELXL97 program.[25] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were solved from difference Fourier maps and its contribution on structural factors was included with fixed positional and thermal parameters in the last cycles. The absolute crystal structure and absolute molecule configuration were determined by the Flack parameter (absolute structure parameter 0.0035(15)). The final residuals were $R = 0.057$, $Rw = 0.112$, goodness-of-fit on $F^2 = 0.945$ on 1331 observed reflections with $F^2 \geqslant 2\sigma$.

Cell parameters, data collection, and data reduction were performed on Alpha Station 200 computer using MolEN program.[26]

Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number CCDC 275429.

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