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Jacobsen-type enantioselective hydrolysis of aryl glycidyl ethers. ^{31}P NMR analysis of the enantiomeric composition of oxiranes

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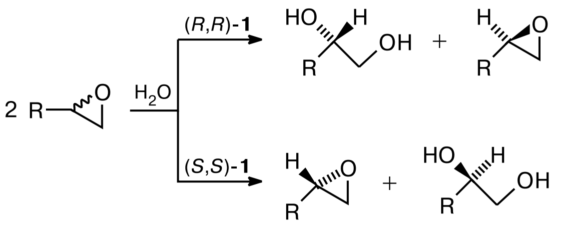
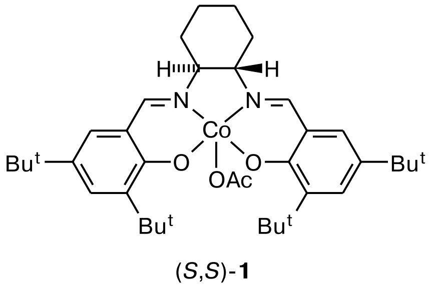
The enantioselective partial hydrolysis of a number of racemic aryl glycidyl ethers in the presence of chiral Co(salen)-catalyst was studied. The enantiomeric composition of the isolated (*R*)-aryl glycidyl ethers was analyzed by ^{31}P NMR using optically active substituted 2-chloro-1,3,2-dioxaphospholanes. A synthesis of β-adrenoblocking agents (*S*)-toliprolol and (*S*)-moprolol based on the simultaneously obtained (*S*)-3-aryloxypropane-1,2-diols was proposed.

Key words: enantioselective hydrolysis, chiral Co(salen)-catalyst, aryl glycidyl ethers, enantiomeric purity, ^{31}P NMR, 3-aryloxypropane-1,2-diols, toliprolol, moprolol.

Among various approaches to nonracemic compounds, of special value are those permitting the preparation of broad ranges of target compounds within a single experimental strategy. An example of such approach is enantioselective hydrolysis of terminal epoxides in the presence of chiral Co^{III} (salen) complexes (Scheme 1), which was recently proposed by Jacobsen.[1]

Scheme 1





(*S*,*S*)-**1**

If racemic aryl glycidyl ethers **2** are used as substrates, this reaction gives scalemic 3-aryloxypropane-1,2-diols (**3**) and unreacted aryl glycidyl ethers enriched in the enantiomer with the opposite configuration of the chiral center. The overall stereochemical outcome of the reaction (*i.e.*, predominant configurations of the diol and the epoxide) depends on the configuration of the chiral catalyst.

Both nonracemic products **2** and **3** obtained by the Jacobsen reaction are of considerable interest. For example, aryl glycidyl ethers are valuable intermediates in the synthesis of β-adrenoblocking agents of the 1-alkylamino-3-aryloxypropan-2-ol class.[2] Aryloxypropanediols **3** themselves exhibit a clear-cut biological activity; at least three of these compounds, mephenesin (Ar = 2-MeC$_6$H$_4$), guaifenesin (Ar = 2-MeOC$_6$H$_4$), and chlorphenesin (Ar = 4-ClC$_6$H$_4$) are registered pharmaceuticals.[3]

Recently, we found that some compounds of this class, in particular, mephenesin and guaifenesin, undergo spontaneous resolution of enantiomers upon crystallization.[4] This phenomenon is of interest from the practical standpoint, because it can underlie the development of efficient methods for large-scale production of nonracemic compounds.[5] The theoretical aspects of spontaneous resolution, a boundary phenomenon between the chemistry of enantioselective processes and supramolecular chemistry, are equally important.[6] To extend the studies along this line and to develop new ways of preparing nonracemic biologically active compounds, we needed a broad range of nonracemic aryloxypropanediols **3**.

Previously, scalemic aryloxypropanediols have been prepared from enantiopure natural feedstock[7] or by partial alkaline hydrolysis of racemic esters by means of enzymes[8] or living microbes.[9] The method used most widely is catalytic regioselective addition of phenols to

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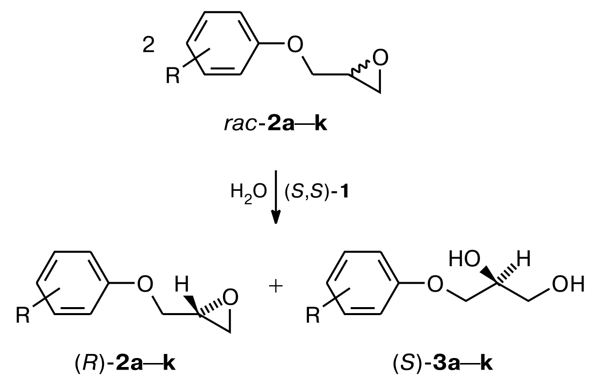
scalemic glycidols.[10,11] Partial enantioselective hydrolysis of racemic aryl glycidyl ethers according to Jacobsen has substantial advantages over all known methods, as it uses readily available racemic starting compounds and the procedure is simpler and better reproducible than those used in biotechnology. In an original study,[1c] this method was used to prepare scalemic 3-phenyloxy- and 3-(1-naphthyl)oxypropane-1,2-diols from the corresponding racemic ethers **2**.

In this study, we carried out partial hydrolysis of aryl glycidyl ethers **2a—k** in the presence of (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)cyclohexane-1,2-diaminocobalt(III) ((*S*,*S*)-**1**) (Scheme 2).

Scheme 2



R = H (**a**), 2-Me (**b**), 3-Me (**c**), 4-Me (**d**), 2-MeO (**e**), 3-MeO (**f**), 4-MeO (**g**), 2-Cl (**h**), 3-Cl (**i**), 4-Cl (**j**), 2-($CH_2CH=CH_2$) (**k**)

Table 1. Yields and physicochemical characteristics of (*R*)-aryl glycidyl ethers **2**

Compound	Yield (%)	B.p. /°C (Torr)	$-[\alpha]_D^{20}$	*ee* (%)
2a	40	69—70 (0.05)	4.8 (*c* 7.38, $CHCl_3$)[a]	>89 (92)[b]
2b	50	65—68 (0.05)	7.7 (*c* 0.89, EtOH)	53
2c	50	70—73 (0.05)	8.0 (*c* 1.91, MeOH)[c]	>80
2d	41	65—70 (0.05)	7.3 (*c* 0.88, EtOH)	71
2e	38	90 (0.1)	11.9 (*c* 0.87, EtOH)	89
2f	48	79—80 (0.05)	10.0 (*c* 0.93, EtOH)	>94
2g	50	90—94 (0.1)	11.3 (*c* 1.36, MeOH)[d]	80
2h	47	75—77 (0.05)	9.1 (*c* 1.91, EtOH)	89
2i	45	76—80 (0.05)	9.7 (*c* 1.45, EtOH)	91
2j	46	90—94 (0.1)	8.2 (*c* 0.37, EtOH)	63
2k	68	82—85 (0.05)	2.6 (*c* 1.25, EtOH)	29

[a] Lit. data[1c] for (*S*)-**2a**, $[\alpha]_D^{20}$ +5.2 (*c* 7.5, $CHCl_3$).

[b] Determined by polarimetry.

[c] Lit. data[15] for (*S*)-**2c**, $[\alpha]_D^{20}$ +13.2 (*c* 1.4, MeOH).

[d] Lit. data:[16] $[\alpha]_D^{25}$ −10.2 (*c* 1.29, MeOH) (25 °C).

The starting compounds were prepared by the reactions of the corresponding sodium phenoxides with racemic epichlorohydrin by a known procedure.[12] The catalyst (*S*,*S*)-**1** was synthesized by published procedures.[1c,13] The catalyst configuration was chosen deliberately for the preparation of diols (*S*)-**3**, because (*S*)-enantiomers act as eutomers both in the series of compounds **3** and in the series of β-adrenoblocking agents that can be obtained from **3**.[14] The yields, the enantiomeric purity, and some characteristics of the isolated products are summarized in Tables 1, 2. The specific rotation values of the diols we obtained were always measured after a single recrystallization from CCl_4. The optical purity might increase due to partial enrichment in one enantiomer. Although the reaction conditions were not optimized for each case, the data of Tables 1 and 2 show satisfactory results as regards

Table 2. Yields, physicochemical characteristics, and optical purity (*ee*) of (*S*)-3-aryloxypropane-1,2-diols **3**

Compound	Yield (%)	M.p./°C		$[\alpha]_D^{20}$		*ee* (%)	
		experiment	published data	experiment	published data	experiment[a]	published data
3a	40	64—65	62.5—64.5 [10c]	+10.1 (*c* 1.0, EtOH)	−10.8 (*c* 1.0, EtOH)[b,8a]	88.8	95 [8a]
3b	23	91.5—92.5	90.9—92.9 [10c]	−19.3 (*c* 1.15, hexane—Pr^iOH, 4 : 1)	−19.3 (*c* 0.9, hexane—Pr^iOH, 4 : 1)[8a]	>99	>99 [8a]
3c	42	59—60	60—62 [4]	+9.2 (*c* 0.94, EtOH)	+9.3 (*c* 1.0, EtOH)[8a]	97.9	>99 [8a]
3d	40	64—65	64—65 [4]	+8.4 (*c* 1.01, EtOH)	−9.2 (*c* 1.0, EtOH)[b,8a]	88.5	97 [8a]
3e	34	98—99	96.8—99.1 [10c]	+12.9 (*c* 0.96, EtOH)	+12.9 (*c* 1.2, EtOH)[17]	>99	99 [17]
3f	40	40—43	—	+8.8 (*c* 1.18, EtOH)	+10.4 (*c* 1.0, EtOH)[8a]	82.9	98 [8a]
3g	46	78—79	79—80 [4]	+7.3 (*c* 1.28, EtOH)	+7.9 (*c* 1.0, EtOH)[8a]	88.7	96 [8a]
3h	48	86—88	91.8 [10b]	−12.3 (*c* 1.3, hexane—EtOH, 4 : 1)	−13.4 (*c* 1.0, hexane—EtOH, 4 : 1)[8a]	90.8	99 [8a]
3i	49	74—74.5	74—76 [4]	+12.1 (*c* 1.15, EtOH)	+12.7 (*c* 1.0, EtOH)[8a]	94.3	>99 [8a]
3j	39	80—81	83.5—84.5 [10c]	+9.4 (*c* 1.37, MeOH)	−10.2 (*c* 1.0, MeOH)[b,10c]	91.4	99.4 [10c]
3k	20	50—51	47—49 [11]	−2.1 (*c* 2.18, EtOH)	−2.1 (*c* 2.8, EtOH)[11]	>90	>90 [11]

[a] Determined by polarimetry.

[b] For the (*R*)-enantiomer.

both the chemical yields and the enantiomeric purity of the products. The method used to determine the latter characteristics deserves special consideration.

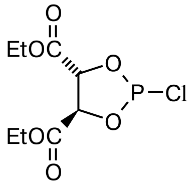
The optical purity checked using published data on the specific rotations of appropriate prototypes served as a measure of enantiomeric purity of diols **3a—k**. Unfortunately, such data for glycidyl ethers **2** are virtually missing. However, even when they are available (for compounds **2a**,**c**,**g**), only in the case of **2a**, can they be compared with the enantiomeric excess determined by an independent method.[1c]

Previously, we demonstrated the possibility of determining the enantiomeric composition of terminal epoxides using their reactions with enantiopure cyclic chlorides of phosphorus acids.[18] These reactions give two regioisomeric adducts, one usually predominating. In the case of aryl glycidyl ethers, the predominant product is the so-called β-adduct in which the P atom is linked to the chiral center of the starting epoxide through the O atom. The configuration and the enantiomeric composition of the adduct remain the same as in the epoxide. If the P atom in the starting acid chloride occurs in a chiral environment (it is not necessary and even undesirable that this atom itself is the chirality center), the β-adduct is formed as a mixture of two diastereomers, whose ^{31}P NMR chemical shifts differ by a Δδ value called diastereomeric dispersion of chemical shift (DDCS). The ratio of the signals of the adduct diastereomers reflects the ratio of enantiomers in the epoxide under interest. Thus, if the organophosphorus reagent has a high degree of enantiomeric purity (regarded as enantiopure), then the enantiomeric excess of the substrate can be described by the following formula

$$ee = (I_1 - I_2)/(I_1 + I_2),$$

where I_1 and I_2 are the integral intensities of the signals of individual diastereomers.

Both the quality and the mere possibility of analysis of the enantiomeric composition of the substrate is dictated by the DDCS, which depends, first of all, on the nature of the phosphorus reagent. Practically, cyclic chlorides **4**[19] and **5**,[20] derived from diethyl ester or bis-*N*,*N*′-dimethylamide of natural tartaric acid are most readily available in an enantiopure form.



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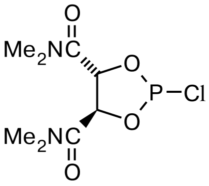

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The choice of the reagent for analysis was due to the fact that the reaction of chiral reagent **4** with racemic epoxide **2d** gives regioisomeric adducts whose ^{31}P NMR signals are not resolved, *i.e.*, the DDCS is close to zero. A similar situation is observed in the spectrum of the reaction mixture of reagent **4** and oxirane **2a**. Meanwhile, the reaction mixture obtained from chiral reagent **5** and *rac*-**2d** exhibits a pair of signals with equal intensities for the diastereomeric phosphites corresponding to the major regioisomer (δ$_P$ 139.90 and 139.69), which are suitable for integration. Therefore, we used amide **5** for the quantitative analysis of the aryl glycidyl ethers **2** we obtained. Thus, in the simplified form (with the minor regioisomer being neglected), the chemical meaning of the method we propose can be represented by Scheme 3.

Scheme 3

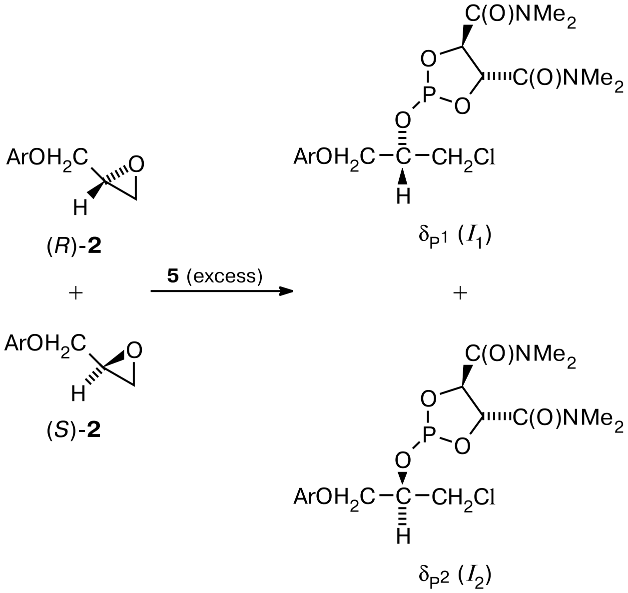


Figure 1 shows fragments of the ^{31}P NMR spectrum of the reaction mixtures obtained by reactions of racemic (*rac*) (*a*) and scalemic (*scal*) (*b*) glycidyl ethers **2h** with reagent **5**. It can be seen that one of the two signals (which are identical for *rac*-**2h**) markedly decreases in the case of *scal*-**2h**. Besides mere illustration, this Figure should demonstrate that adequate analysis, especially of substrates with high enantiomeric purities, requires preliminary recording of the spectrum for the racemic substrate. Otherwise, the signal of the minor diastereomer (corresponding to the minor enantiomer of the initial substrate) may be either lost among the noise, or another signal (for example, that for the regioisomeric α-adduct with δ$_P$ 142.09 in the case of epoxide **2h**) may be misidentified as being due to this product.

Table 3 gives the chemical shifts characterizing the individual diastereomeric phosphites shown in Scheme 3, the relative integral intensities, and the DDCS between their signals. It can be seen from Table 3 that the Δδ values

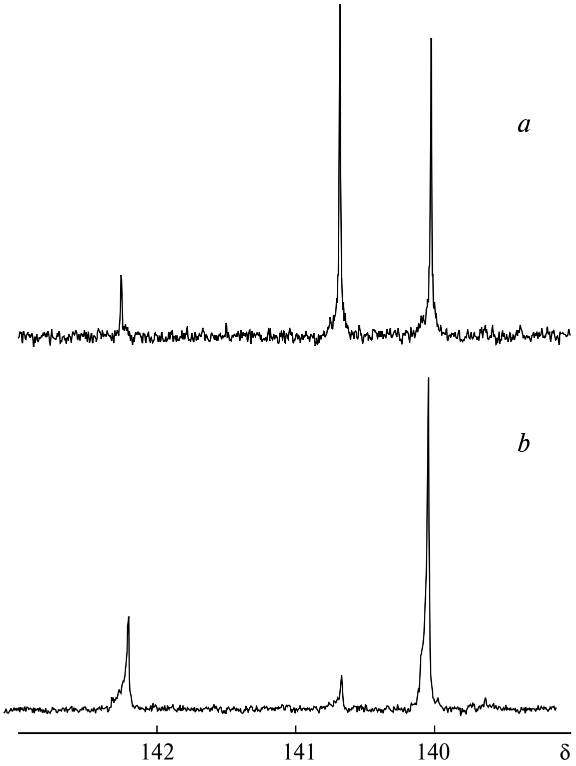


Fig. 1. ^{31}P NMR spectra of the reaction mixtures obtained from racemic (*a*) and scalemic (*b*) glycidyl ethers **2h** and compound **5**.

for oxiranes **2a—k** vary in the range of 0.10—0.76 ppm. Actually, too small DDCS values result in an overestimated integral intensity of the minor signal (integrated against the background of the major one) and, as a consequence, to an underestimated enantiomeric excess. This is reflected by the characters ">" placed ahead of the enantiomeric excess values calculated from the integral intensities and listed in Table 1. For phenylglycidyl ether **2a**, the enantiomeric compositions determined by two independent methods are given, namely, by polarimetry resorting to published data and by a known ^{31}P NMR procedure. The values are in good agreement with each other.

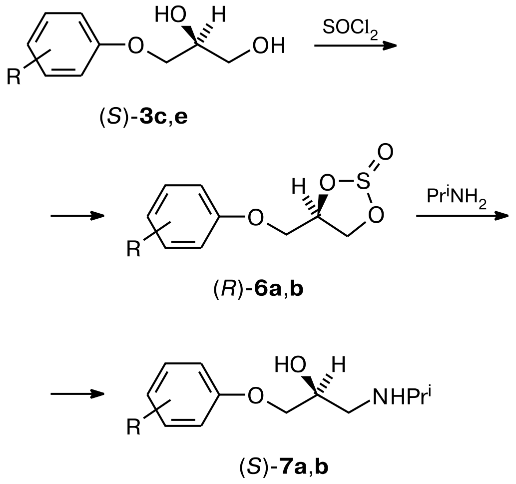
Table 3. Chemical shifts (δ_P), relative integral intensities (*I*), and diastereomic dispersion of chemical shift ($\Delta\delta$) for diastereomic phosphites formed from oxiranes **2a—k** (see Scheme 3)

Substrate	δ_P (*I*)	$\Delta\delta$
2a	140.28 (0.06), 140.08 (1.00)	0.20
2b	140.94 (0.31), 140.30 (1.00)	0.64
2c	140.60 (0.11), 140.50 (1.00)	0.10
2d	139.84 (1.00), 139.60 (0.17)	0.24
2e	140.43 (1.00), 140.09 (0.06)	0.34
2f	140.74 (0.03), 140.55 (1.00)	0.19
2g	140.30 (1.00), 140.06 (0.11)	0.24
2h	140.53 (0.06), 140.90 (1.00)	0.63
2i	141.80 (0.05), 141.60 (1.00)	0.20
2j	140.20 (0.23), 140.00 (1.00)	0.20
2k	141.06 (0.55), 140.30 (1.00)	0.76

As noted above, scalemic aryl glycidyl ethers are extensively used in organic synthesis. We believe that aryloxypropanediols, having become readily available, would be equally popular. Apart from the evident use as final products (recall that **3b,e,j** are pharmaceuticals[3]), noteworthy are the prospects of transforming them into cyclic sulfites **6** with subsequent opening of the epoxide-like heterocycle by nucleophiles. If primary amines are used as the nucleophiles, β-adrenoblocking agents will be formed as the products. A few examples of this approach have been reported.[21,11]

To summarize our study, consider examples of synthesis, according to Scheme 4, of the (*S*)-isomers of two registered drugs, toliprolol[22a] (**7a**) and moprolol[22b] (**7b**), whose (*S*)-isomer has its own name levotensin. Both nonracemic β-adrenoblocking agents were prepared in yields of >80% and with satisfactory enantiomeric purities.

Scheme 4



R = 3-Me (**3c**, **6a**, **7a**), 2-OMe (**3e**, **6b**, **7b**)

Thus, the strategy proposed for the transition from racemic aryl glycidyl ethers to a broad range of nonracemic compounds including β-adrenoblocking agents and the proposed ^{31}P NMR method for the analysis of the enantiomeric purity of the resulting epoxides using organophosphorus derivatizing reagents are quite operative.

Experimental

NMR spectra were recorded on Bruker WM-250 (250.1 (^{1}H) and 62.9 MHz (^{13}C)) and Bruker MSL-400 (100.6 MHz (^{31}P)) spectrometers relative to the internal (Me$_4$Si (^{1}H and ^{13}C)) or external (H$_3$PO$_4$ (^{31}P)) standards in CDCl$_3$. Optical rotation was measured on a Perkin—Elmer 341 polarimeter. Mass spectra were run on a MAT-212 mass spectrometer (resolution 1000, voltage 60 V, emission current 0.1 mA, direct sample introduction into the ion source with a gradual temperature rise). The purity grade of the products was estimated by GC/MS using a Varian 3700 chromatograph. Recording conditions: a 50-m long SE 54 column; injector temperature 240 °C; initial temperature of the column 100 °C; heating rate 6 °C$\cdot$min^{-1}; final temperature of the column 240 °C.

Complex (*S*,*S*)-**1** was prepared from (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)cyclohexane-1,2-diaminocobalt(II).[1c] The latter was synthesized by a known procedure,[13] $[\alpha]_D^{20}$ +1150 (*c* 0.02, CH_2Cl_2) (*cf.* Ref. 13, for (*R*,*R*)-**1**: $[\alpha]_D^{20}$ −1100 (*c* 0.01, CH_2Cl_2)). The purity was additionally checked by mass spectrometry. Substituted aryl glycidyl ethers **2** were prepared from epichlorohydrion and aromatic alcohols.[12]

Kinetic hydrolytic resolution of epoxides 2 (general procedure). A mixture of oxirane **2** (30 mmol), complex (*S*,*S*)-**1** (0.1 g, 0.15 mmol), and water (0.27 mL, 15 mmol) in 0.5 mL (or 3 mL for **2e—g**) of THF was stirred for 4—30 h (for **2e**,**k**, 80 h). The reaction was monitored by GC/MS. The unreacted oxirane was evaporated *in vacuo*. The residue was dissolved in hot water and the catalyst was separated by repeated extraction of the aqueous phase with light petroleum. The solid residue formed after removal of water *in vacuo* was purified by a single recrystallization from CCl_4. Characteristics of the reaction products are summarized in Tables 1 and 2. The catalyst isolated from the solution in light petroleum can be reused.

Analysis of the enantiomeric composition of oxiranes 2a—k (general procedure). Pyridine (0.12 g, 1.52 mmol) was added at 5—10 °C in a dry nitrogen atmosphere to 2.0 mL of a THF solution containing (4*R*,5*R*)-bis(*N*,*N*-dimethylaminocarbonyl)-2-chloro-1,3,2-dioxaphospholane (**5**) (0.13 g, 0.48 mmol) obtained by a known procedure.[20] The reaction mixture was kept for 10 min, and the required oxirane **2** (0.44 mmol) in 0.3 mL of THF was added at the same temperature. The solution was kept for at least 1 h, filtered, and concentrated *in vacuo*. Several drops of C_6D_6 were added and the solution was placed in a tube for recording ^{31}P NMR spectrum. The spectral data are given in Table 3.

(4*R*)-4-[(3-Methylphenoxy)methyl]-1,3,2-dioxathiolan-2-one (6a) was prepared by the reaction of diol **3c** (0.77 g, 4.64 mmol) with $SOCl_2$ (0.55 g, 4.64 mmol) in 3 mL of CH_2Cl_2 similarly to the previously described procedure[11] as a mixture of *cis*- and *trans*-isomers (yield 0.96 g (quantitative), oil). ^1H NMR, δ: 2.32 (s, 3 H, Me); 3.84—4.00 (m, 1.2 H, CH_2OAr (*trans*)); 4.19—4.71 (m, 2.8 H, CH_2OAr (*cis*), CH_2OS (*cis*, *trans*)); 4.79—4.90 (m, 0.4 H, CHOS (*cis*)); 5.06—5.15 (m, 0.6 H, CHOS (*trans*)); 6.58—7.29 (m, 4 H, Ar). ^{13}C NMR, δ: 21.2 (CH_3 (*trans*)); 21.6 (CH_3 (*cis*)); 66.3 (CH_2OS (*trans*)); 67.9 (CH_2OS (*cis*)); 68.6 (CH_2O (*trans*)); 69.2 (CH_2O (*cis*)); 78.0 (CHOS (*trans*)); 80.0 (CHOS (*cis*)); 111.5, 111.8, 115.5, 115.6, 122.5, 122.9, 129.3, 129.7 (CH, Ar); 139.5 ($\underline{C}$—Me (*trans*)); 140.1 ($\underline{C}$—Me (*cis*)); 157.8 (*i*-C (*trans*)); 158.1 (*i*-C (*cis*)).

(2*S*)-1-Isopropylamino-3-(3-methylphenoxy)propan-2-ol (7a). A solution of dioxathiolane **6a** (0.78 g, 3.67 mmol) and Pr^iNH_2 (7.0 g) in 25 mL of DMF was kept for 45 h at 60—70 °C. After the reaction, excess amine and DMF were removed *in vacuo*, 30 mL of a 1 *M* solution of NaOH was added, the mixture was extracted with AcOEt (3×30 mL), and the extract was dried with Na_2SO_4. After removal of the solvent *in vacuo*, the residue was dissolved in 30 mL of Et_2O and gaseous HCl was passed through the resulting solution to give 0.76 g (85.4%) of (2*S*)-1-isopropylamino-3-(3-methylphenoxy)propan-2-ol hydrochloride (**7a**$\cdot$HCl), m.p. 118—119 °C (from a 1 : 1 Et_2O—EtOH mixture), $[\alpha]_D^{20}$ −24.5 (*c* 1.06, EtOH) (*cf.* Ref. 23: m.p. 119 °C, $[\alpha]_D^{20}$ −27.4 (*c* 1.01, EtOH)).

(4*R*)-4-[(2-Methoxyphenoxy)methyl]-1,3,2-dioxathiolan-2-one (6b) was prepared from diol **3e** (1.4 g, 7.69 mmol) similarly to **6a** in a quantitative yield, equal to 1.72 g (oil), as a mixture of *cis*- and *trans*-isomers. ^1H NMR, δ: 3.85 (s, 3 H, OMe); 3.99—4.19 (m, 1.14 H, $C\underline{H}_2OAr$ (*trans*)); 4.25—4.46 (m, 0.86 H, $C\underline{H}_2OAr$ (*cis*)); 4.53—4.59, 4.68—4.71, 4.79—4.85 (all m, totally 2 H, CH_2OS (*cis*, *trans*)); 4.90—4.95 (m, 0.43 H, CHOS (*cis*)); 5.23—5.32 (m, 0.57 H, CHOS (*trans*)); 6.89—7.05 (m, 4 H, Ar). ^{13}C NMR, δ: 56.2 (CH_3); 68.8 (CH_2OS (*cis*)); 69.0 (CH_2OS (*trans*)); 70.2 ($\underline{C}H_2OAr$ (*trans*)); 70.9 ($\underline{C}H_2OAr$ (*cis*)); 78.1 (CHOS (*trans*)); 80.2 (CHOS (*cis*)); 112.8, 112.8, 116.4, 116.6, 112.2, 121.2, 123.2, 123.4 (CH, Ar); 147.7 (*i*-C, Ar); 150.4 (*i*-C, Ar); 150.5 (*i*-C, Ar).

(2*S*)-1-Isopropylamino-3-(2-methoxyphenoxy)propan-2-ol (7b) was prepared from dioxathiolane **6b** (1.08 g, 4.45 mmol) by a procedure similar to that reported for aminopropanol **7a** in a yield of 1.13 g (87.6%), m.p. 75—80 °C (*cf.* Ref. 22b: m.p. 78—80 °C). (2*S*)-1-Isopropylamino-3-(2-methoxyphenoxy)propan-2-ol hydrochloride was prepared by passing gaseous HCl through a solution of **7b** base in Et_2O (30 mL). Yield **7b**$\cdot$HCl 0.95 g (82.1%), m.p. 124—125 °C (from a mixture Et_2O—EtOH, 3 : 1), $[\alpha]_D^{20}$ −16.5 (*c* 5.00, EtOH) (*cf.* Ref. 22b: m.p. 121—123 °C, $[\alpha]_D^{20}$ −16.3 (*c* 5.00, EtOH)).

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