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Synthesis of α,β-Epoxysulfoxides: Thermodynamic Control in Base-induced Cyclization of Chlorohydrins Derived from α-Chlorobenzyl Phenyl Sulfoxide and Alkyl Aldehydes

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Dedicated to Prof. Pedro Joseph Nathan on the occasion of his 65th birthday

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Abstract. The preparation, purification and characterization of new sulfinylchlorohydrins and α,β-epoxy sulfoxides are reported. Sulfinylchlorohydrins were prepared by addition of lithium α-chlorobenzyl phenyl sulfoxide to acetaldehyde, propanaldehyde and butanaldehyde. Each aldehyde produced two diastereomeric chlorohydrins, which were characterized by IR and NMR. Relative configurations of the sulfinylchlorohydrins derived from acetaldehyde were established by X-ray diffraction. Experiments carried out at -70, -30, 0 and 25°C, showed that *t*-BuOK in THF induced isomerization of sulfinyl chlorohydrins faster than cyclization. Thus, *trans*- to *cis*-ratio of α,β-epoxy sulfoxides (85/15) was proportional to relative stability of sulfinylchlorohydrins.
Key Words: sulfinylchlorohydrins; Darzens reaction; α,β-epoxy sulfoxides; α-chlorobenzyl phenyl sulfoxide.

Resumen. Se reporta la preparación, purificación y caracterización estructural de nuevas sulfinilclorohidrinas vecinales y α,β-epoxisulfóxidos. Las clorohidrinas se obtuvieron por adición del carbanión de α-clorobencilfenilsulfóxido al acetaldehido, propanaldehido y butanaldehido. Cada aldehido produjo un par de clorohidrinas diastereoméricas, las cuales se caracterizaron estructuralemente por IR y RMN. La configuración relativa de las dos clorohidrinas derivadas de acetaldehido, se estableció por difracción de rayos X. La experimentación realizada a -70, -30, 0 y 25°C mostró que el *t*-BuOK en THF induce la isomerización de sulfinilclorohidrinas más rápido que la ciclización y por lo tanto, la composición diastereomérica de α,β-epoxisulfóxidos de 85/15, es atribuible a la estabilidad relativa de las sulfinilclorohidrinas.
Palabras clave: sulfinilclorohidrinas; reacción de Darzens; α,β-epoxisulfóxidos; α-clorobencilfenilsulfóxido.

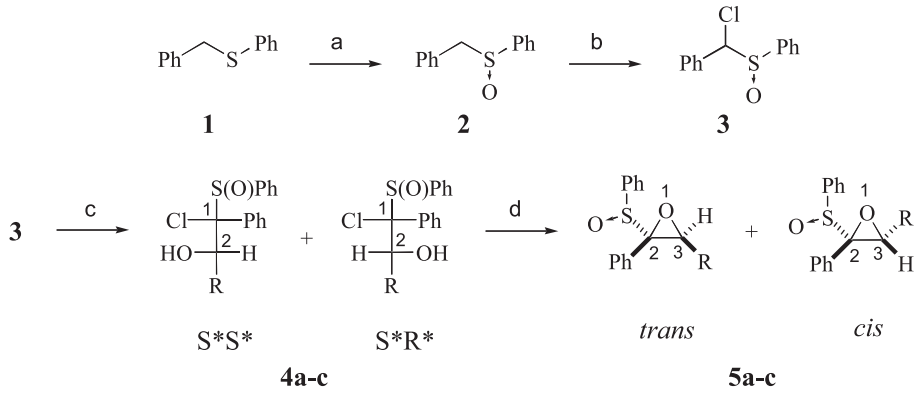
Introduction

Acyclic α,β-epoxy sulfoxides are important synthetic intermediates. The epoxy and sulfinyl groups of these intermediates can be rearranged under thermal and acidic conditions to give α-sulfinyl aldehydes, ketones and unsaturated carbonyl compounds [1]. On the other hand α,β-epoxy sulfoxides can be transformed to ketones and allylic alcohols by the action of nucleophiles on β-carbon [2] and to epoxides either by the action of nucleophiles on β-carbon [2,3] or electrophiles on α-carbon [4]. α,β-Epoxy sulfoxides may also be converted to aldol derivatives by the action of lithium dimethyl cuprate followed by quenching with ketones [5].

As part of our studies of small chiral molecules containing aromatic rings [6], we have prepared six new α,β-epoxy sulfoxides through base-mediated cyclization [7] of the new sulfinylchlorohydrins **4a-c** (Scheme 1). Although sulfinylchlorohydrins were first reported [7] in 1969 and since then used as synthetic precursors of α,β-epoxy sulfoxides, little attention has been devoted to their stereochemistry. The aim of the present work is to examine the relative configuration of sulfinylchlorohydrins **4a-c** and to rationalize the stereochemical preference of their base-mediated cyclization.

Results

Chlorohydrins **4a-c** were prepared as it is shown in Scheme 1. The starting material benzyl phenyl sufide (**1**), was prepared in almost quantitative yield from thiophenol, potassium carbonate and benzyl bromide in dimethylformamide at 25°C [8]. Sulfide **1** was oxidized with sodium metaperiodate in methanol-water at 25°C [9]. The resulting benzyl phenyl sulfoxide (**2**, 95% yield) was transformed to α-chlorobenzyl phenyl sulfoxide (**3**, 44% average yield) with *N*-chlorosuccinimide and K_2CO_3 in dichloromethane under reflux [10]. The ^{1}H NMR spectrum of compound **3** in deuterated chloroform showed two single signals at 5.50 and 5.49 ppm in approximately 3/7 ratio, indicating that **3** consisted of two diastereomers, whose relative configuration have been proposed by Tsuchihashi and coworkers [11]. Deprotonation of diastereomeric mixture of **3** in tetrahydrofuran at -70°C, was carried out with lithium diisopropylamide. Reaction of metalated **3** with acetaldehyde, propanaldehyde and butanaldehyde at -70°C gave after the hydrolysis, the chlorohydrins **4a-c**, respectively in good yields. Thin layer chromatography (CH_2Cl_2-heptane-acetone 2:2:1) of crude **4a** showed two main spots of $_{Rf}$ 0.36 and 0.25 corresponding to a pair of diastereomeric chlorohydrins (in nearly 1:1 ratio). The structural characterization and relative configuration of these diastere-



4a, **5a**: R= CH_3; **4b**, **5b**: R = CH_3CH_2; **4c**, **5c**: R = $CH_3CH_2CH_2$

(a) $NaIO_4$, MeOH, 29 h, 25°C; (b) NCS, K_2CO_3, CH_2Cl_2, 24 h, 32°C; (c) LDA, CH_3COH or CH_3CH_2COH or $CH_3CH_2CH_2COH$, THF, 0.5 h, -70°C, then NH_4Cl/H_2O; (d) *t*-BuOK, THF, 0.25 h, 0°C, then HCl 20%.

Scheme 1. Synthesis of diastereomeric sulfinylchlorohydrins and α,β-epoxy sulfoxides showing the numbering system adopted for NMR data. Experimental conditions are given at the bottom.

omers were established by X-ray diffraction studies (Figure 1). Pertinent crystal data and information about intensity collection are listed in Table 2.

The "more polar" diastereomer **4a**, was identified as (1S*,2S*)-1-chloro-1-phenyl-1-[(S*)-phenylsulfinyl]-2-propanol and the "less polar" one as (1S*,2R*)-1-chloro-1-phenyl-1-[(S*)-phenylsulfinyl]-2-propanol; from here on labeled as **4a**S*S* and **4a**S*R*, respectively. Relative configuration of diastereomeric sulfinylchlorohydrins **4b** and **4c**, were assigned by comparison of their $_{Rf}$ values, melting points and NMR data with those of **4a**S*S* and **4a**S*R*. As a rule, configuration S*S* were assigned to the "more polar" and high melting sulfinylchlorohydrins **4b** and **4c**, and S*R* to the "less polar" and low melting ones.

Regarding the stereoselectivity of sulfinylchlorohydrins cyclization [1,2,22], we started from the logic expectation that cyclization of **4a**S*S* by internal S_N2 mechanism would lead to *trans*-α,β-epoxy sulfoxide while derivative **4a**S*R* would lead to the corresponding *cis*-epoxide [13]. The cyclization of **4a**S*S* carried out with potassium *tert*-butoxide (*t*-BuOK) in THF at 25°C, gave the mixture of *trans*- and *cis*-α,β-epoxy sulfoxides in 85/15 molar ratio. Attempts to separate these products were fruitless because they are oils of similar relative polarities; therefore, they were analyzed as binary mixtures. Efforts to separate the pure diastereomers for elemental analysis are in progress. In line with the stereoselective cyclization of 2-chloro-3-aryl-3-hydroxypropionates [14], we carried out the cyclization of **4a**S*S* and **4a**S*R* in separate flasks with *t*-BuOK in THF at -70, -30 and 0°C, followed by neutralization with aqueous ammonium chloride. The results are presented in Table 1.

Table 1. Results of base induced cyclization of diastereomeric chlorohydrins **4a** at different temperatures and **4b**S*S*, **4c**S*S* at 0°C. Composition determined by signal integration of the main components identified by ^{1}H NMR.

substrate	T(°C)	time (h)	reaction mixture composition (%)	*trans*/*cis* ratio	yield(%)
4aS*S*	-70	3.0	98% of **4a**S*S* and 2% of **4a**S*R*	—	0
4aS*R*	-70	3.0	15% of **4a**S*S* and 85% of **4a**S*R*	—	0
4aS*S*	-30	3.0	33.4% **4a**S*S*, 12.1% **4a**S*R*, 43.6% **5a**-*trans*, 5.2% **5a**-*cis* and 5.7% of **3**.	89/11	not detd.
4aS*R*	-30	3.0	64.8% **4a**S*S*, 9.9% **4a**S*R*, 18.5% **5a**-*trans*, 2.2% **5a**-*cis* and 4.6% of 3.	89/11	not detd.
4aS*S*	0	2.0	79.1% **5a**-*trans*, 13.9% **5a**-*cis* and 7% of **3**.	85/15	75
4aS*R*	0	2.0	59% **5a**-*trans*, 11.3% **5a**-*cis*, and 29.7% of **3**.	84/16	73
4aS*S*	0	0.25	69.3% **5a**-*trans*, 12.5% **5a**-*cis*-epoxide, and 18.2% of **3**.	84/15	80
4bS*S*	0	0.25	69.6% **5b**-*trans*, 13% **5b**-*cis*, and 17.4% of **3**.	84/16	86
4cS*S*	0	0.25	75.2% **5c**-*trans*, 13.2% **5c**-*cis*, and 11.6% of **3**.	85/15	88

Table 2. Crystal data and intensity collection for studied sulfinylchlorohydrins.

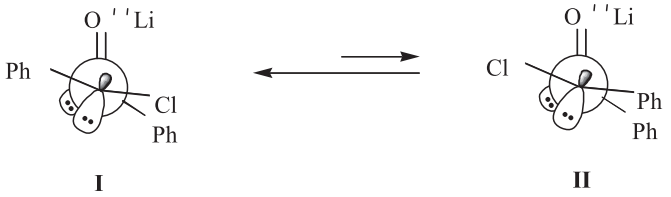
compound	**4a**S*S*	**4a**S*R*
Empirical formula	$C_{15}H_{15}ClO_2S$	$C_{15}H_{15}ClO_2S$
Formula weight	294.78	294.78
Crystal system	Monoclinic	Orthorhombic
Space group	P2(1)/n	Pbca
a (Å)	6.5223(5)	7.6971(18)
b (Å)	20.6133(15)	16.056(4)
c (Å)	11.2515(8)	22.839(5)
Volume (Å^3)	1 489.61	2 822.6
Z	4	8
D (calc. mg / m^3)	1.314	1.387
Reflections collected	10 613	11 216
Independent reflections	2 628 [Rint 0.0246]	2 481 [Rint 0.0288]
Goodness-of-fit	1.051	1.170

Crystallographic data for the structures of sulfinylchlorohydrins **4a**S*S* and **4a**S*R* reported in this paper, have been deposited with the Cambridge Crystallographic Data Centre (CCDC # 295982 and 295983, respectively). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (Fax: 44-1223-336033 or e-mail: deposit@ccdc.cam.uk).

Discussion

Simple stereochemical rules anticipate that in the absence of stereocontrolled conditions, four diastereomers might arise when forming sulfinylchlorohydrins of type **4a-c**. In practice however, the addition of α-metallated chloroalkyl aryl sulfoxide to aldehydes [2,3,13] and symmetrical ketones [2,7] give two and one diastereomer, respectively. The number of diastereomeric sulfinylchlorohydrins obtained by us is congruent with published results [2,3]. Our diastereomeric ratio (nearly 1:1) is close to that obtained by Yamakawa and coworkers [2] (1:1.3), who used (-)-α-chloroalkyl *p*-tolyl sulfoxide of high enantiomeric excess. Accordingly, the diastereofacial selectivity of chiral sulfoxide on the kinetic addition to carbonyl is poor. In contrast, the X-ray structures of **4a**S*S* and **4a**S*R* indicate that the addition is highly diastereoselective with respect to the α-sulfinyl carbon. Although we used the diastereomeric mixture of α-chlobenzyl phenyl sulfoxide, in the products, the segment that comes from metalated α-chlorobenzyl phenyl sulfoxide, has relative configuration S*,S*. This implies that the two possible α-sulfinyl carbanions are not isoenergetic. Since addition usually occurs on the same side of S-O bond [15], conformer I shown in scheme 2, should be more stable than II; therefore the transformation of II to I by α-carbon inversion [16], causes the observed stereoselectivity.

In order to facilitate visual analysis, structures of Figure 1 are drawn with similar orientation. The angle between planes formed by aromatic rings is approximately 45° and the torsion angle chlorine-C1-C4-C5 of 1.8°, indicates that the aromatic ring attached to C1 is almost coplanar with the bond C1-chlorine. Newman projection of segments S1-C1 and C1-C2 in the two X-ray structures, shows the maximum number of *gauche* interactions [14] between adjacent chlorine and sulfinyl-oxygen: torsion angles of the segment O2-S1-C1-chlorine are -51.6° and -59.3° for **4a**S*S* and **4b**S*R*, respectively. On the structure of **4a**S*,S* hydroxyl group is observed in *anti* relation to the chlorine while in the structure of **4a**S*R* they are *syn* (torsion angle of the segment chlorine-C1-C2-O1 are 167.4° and 52.1°, respectively). Moreover, hydroxyl hydrogen is oriented towards sulfinyl oxygen and in **4a**S*R*, atoms O2-



Scheme 2. Newman projection of C1-Sulfur of metalated α-chlorobenzyl phenyl sulfoxides. Conformers I and II assume metalation of S*-α-chlorobenzyl phenyl (S*)-sulfoxide and R*-α-chlorbenzyl phenyl (S*)-sulfoxide, respectively.

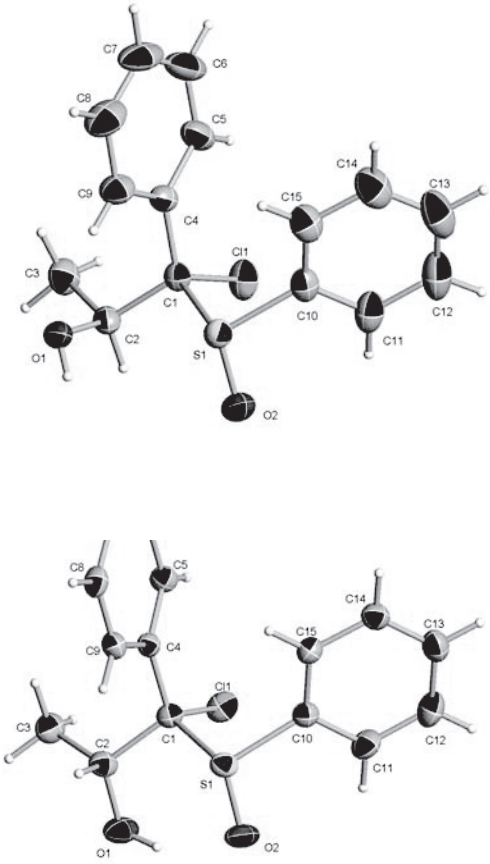


Fig. 1. ORTEP drawing of sulfinylchlorohydrins **4a**S*S* (above) and **4a**S*R* (below). The open chain of three carbons keeps the numbering system used for NMR data.

S1-C1-C2-O1-hydroxyl hydrogen have the ideal conformation required for intramolecular hydrogen bond [17].

The chemical shifts of methine hydrogen at C2 and the methyl C3 observed for diastereomeric sulfinylchlorohydrins **4a-c** can readily be explained by assuming that their main conformations in $CDCl_3$ solution are similar to those shown in Figure 1. For instance, diastereomer **4a**S*R* shows the methine hydrogen in the paramagnetic zone of phenyl attached to C1 and the methyl close to the diamagnetic zone; thus in agreement with the downfield and upfield shifts observed on its 300 MHz NMR spectrum. The relative signal intensities of the respective methine hydrogen of **4a**S*S* and **4a**S*R* can be used to determine the diastereomeric composition of the mixture.

Potassium hydroxide and *t*-BuOK induce cyclization of sulfinylchlorohydrins to afford α,β-epoxisulfoxides. Yamakawa and his coworkers [2] reported the cyclization of diastereomeric *p*-tolyl sulfinylchlorohydrins with 30% aqueous KOH in methanol at room temperature. Previously, Durst and coworkers [1b] observed that KOH promoted cyclization and fragmentation of sulfinylchlorohydrins. In our hands, the derivative **4a**S*S* with KOH gave diastereomeric **3** as the only product. However, by mixing **4a**S*S* with *t*-BuOK, in anhydrous THF at 25°C we obtained the mixture of *trans*- and *cis*-α,β-epoxy sulfoxides in 85:15 ratio, respectively. The relative configuration of α,β-epoxy sulfoxides was determined by NMR. *trans*-Isomer has the methyl group in front of phenyl ring, so an upfield shift is expected for methyl signal; accordingly, the doublet at 1.18 ppm was assigned to this isomer. The same conclusion can be drawn by comparison of the chemical shifts of methine hydrogen of epoxide ring. Along with the signals of α,β-epoxy sulfoxides, the NMR spectra of the reaction mixture contained the signals of benzylic hydrogen of **3** in 1:1 diastereomeric ratio and small amounts of other unidentified by-products. The presence of **3** in this mixture implies that in the absence of a protic solvent, retroaddition and cyclization are competing reactions. Experiments conducted at -70°C, showed that *t*-BuOK induced isomerization of **4a**S*S* and **4a**S*R*. After 3 h with vigorous stirring, pure **4a**S*R* underwent 15% isomerization whereas under identical conditions, **4a**S*S* underwent only 2% isomerization. Since no signals due to cyclized products were observed on the NMR spectra of these mixtures, it was concluded that under above-mentioned conditions, isomerization rate was faster than cyclization. Experiments conducted at -30 and 0°C, confirmed that diastereomer **4a**S*S* is thermodynamically more stable than **4a**S*R*. This fact anticipates that the final diastereomeric ratio of sulfinylchlorohydrins prepared by the method described in this paper will depend of the mixing time of oxyanions and temperature of hydrolysis. Accordingly, isomerization rate might also explain irregular diastereomeric ratios of sulfinylchlorohydrins observed by other authors [3]. Although cyclization of chlorohydrins **4a**S*S* and **4a**S*R* occurred at -30°C and 0°C, diastereomeric composition of α,β-epoxy sulfoxides was practically independent of the temperature. In all experiments, the *trans*-α,β-epoxy sulfoxide was formed in higher amount. Internal S_N2 mechanism of this base-promoted cyclization, explains the direct correlation between the more stable chlorohydrin **4a**S*S* and *trans*-α,β-epoxysulfoxide; therefore we consider the cyclization process to be thermodynamically controlled. High yields of α,β-epoxy sulfoxides were obtained in 15 minutes at 0°C.

Table 1 show that base-promoted cyclization of chlorohydrins **4b**S*S* and **4c**S*S* followed the path described above for **4a**S*S* and **4a**S*R*, so further experimentation with diastereomers **4b**S*R* and **4c**S*R* was unnecessary.

Conclusion

In this study we have demonstrated that *t*-BuOK in anhydrous THF induces retroaddition and cyclization of chlorohydrins **4a-c**. Retroaddition occurs faster than cyclization and promotes isomerization of chlorohydrins. Base-induced isomerization of chlorohydrins S*R* in THF, occurs faster than with their corresponding S*S* because the latter are thermodynamically more stable. Cyclization of the more stable chlorohydrins produce mainly the *trans*-α,β-epoxy sulfoxides by internal S_N2 mechanism by means of a thermodynamically controlled process.

Experimental

General. Commercial THF was evaporated from sodium-benzophenone, and hexane, AcOEt, CH_2Cl_2 and MeOH were distilled in conventional glass apparatus before used. The following chemicals purchased from Aldrich, were used without further purification: thiophenol, NCS, $NaIO_4$, *tert*-butanol, propanaldehyde and butanaldehyde. Acetaldehyde and diisopropylamine (from Merck) were distilled before used. Alufolien® sheets and silica gel 230-400 mesh were used for tlc and column chromatography, respectively.

A Julabo immersion cooler FT901 was used to reach temperatures below 25°C. MeOH was used as cooling fluid. Melting points were measured in a Fisher-Jones apparatus and are uncorrected. Infrared spectra were recorded on a FT Vector 33 equipped with horizontal ATR accessory having a 45° ZnSe crystal. Proton and ^{13}C NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer equipped with a 5 mm ^1H probe at 25°C. Proton NMR spectra were obtained from 0.03 M solutions in $CDCl_3$ using pulse width of 11.5 ms (45°), a pulse delay of 5 s, 16 transients in a spectral width of 3592 Hz digitized into 32K data points. $^{13}C\{^1H\}$ NMR spectra were obtained from ~ 0.1 M solutions in $CDCl_3$. All chemical shifts are from internal TMS signal and data are given in standard format: δ units, integration, signal multiplicity, coupling constants in Hertz and assignment. X-ray diffraction analysis were carried out with an APEX-Bruker diffractometer with graphite-monochromatized Mo-Ka radiation (l = 0.71069 Å). Intensity data were collected at 25°C. The structures were solved by SHELXS97 method (Sheldrick, G. M., program for

Crystals Structure Analysis, release 97-2) and refined by full-matrix least squares. For each crystal, heavy atoms were refined anisotropically while hydrogen atoms were located in the calculated positions. CH analysis was performed on an Elementar vario EL III elemental analyzer.

Preparation of benzyl phenyl sulfide (**1**). This compound was prepared with some modifications of a published method [8]. In a round bottom flask, thiophenol was mixed with powdered K_2CO_3 in DMF at 25°C followed by careful addition of benzyl bromide (15% excess). After 4 h of vigorous stirring, the reaction mixture was filtered to remove the solids, and the solvent was evaporated under reduced pressure. The concentrate was dissolved in hexane and left on standing at room temperature for spontaneous crystallization. The yellowish leaflets (mp 33-34°C, 93% yield, lit. [8] mp 40-41°C), were filtered off, dried under reduced pressure and analyzed. IR and NMR spectra of this compound were identical to those of authentic **1**. This result was reproduced with 15 and 60 g of thiophenol.

Preparation of benzyl phenyl sulfoxide (**2**). With some modifications of a published method [9], this compound was prepared in the following way: In a round bottom flask of 500 mL were placed a 2 inch-long stirring bar, sulfide **1** (12.0 g, 59.9 mmol) and MeOH (220 mL). A suspension of $NaIO_4$ (12.8 g, 59.9 mmmol in 50 mL water), was added to the methanolic solution of **1**. The resulting white suspension was stirred 29 h at 25°C, then filtered off by suction. After careful work up of the filtrate, we obtained 12.2 g (94% yield) of colorless crystals (EtOAc, mp 123-125°C, lit.[8] mp 122-123°C). From ^{1}H NMR, it was found that this material consisted of 95% of sulfoxide **2** and about 5% of benzyl phenyl sulfone. The chemical shifts of its ^{13}C NMR spectra, were in agreement with published data [18], therefore above-mentioned crystals were used without further purification.

Preparation of α-chlorobenzyl phenyl sulfoxide (**3**). This compound was prepared with the following modified procedure [10]: In a round bottom flask of 500 mL were placed a 2 inch-long stirring bar, **2** (10 g, 46.2 mmol), K_2CO_3 (6.4 g, 46.3 mmol, fine powder), 90% NCS (13.7 g, 92.3 mmol) and CH_2Cl_2 (200 mL). A condenser and a drying tube filled with calcium oxide were assembled to the reaction flask, and the mixture was heated under reflux for 24 h with stirring. The mixture was filtered by suction and the solid was thoroughly washed with CH_2Cl_2. Organic solution was poured into a separatory funnel and washed with cold 1 M NaOH solution (3 × 40 mL) to remove succinimide. After work up, flash chromatography (hexane-EtOAc 7:3) of the yellow concentrate and recrystallization of the component that gives the spot of $_{Rf}$ 0.34 (hexane-EtOAc 3:2), we obtained 4.98 g (43% yield) of yellowish small needles that melted between 117-118 °C, lit.[11] mp 101-123°C. From NMR analysis it was found that this material consisted of two diastereomers of **3** of approximately 3:7 ratio. IR (neat) ν_{max} 638.9, 689, 744.1, 840.6, 1051.7, 1085.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.49-7.21 (8H, m, aromatic hydrogens), 7.04 (2H, dm, J_d = 7.2 Hz, H*o*-phenyl sulfinyl), 5.50 and 5.49 (1H, s, benzylic hydrogen); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 78.56 and 78.14 (C benzylic, in nearly 3:7 ratio), and sixteen signals of aromatic carbons at δ 140.07, 139.12, 132.09, 132.01, 131.06, 130.71, 129.96, 129.88, 128.79, 128.61, 128.58, 128.44, 128.40, 128.17, 125.82, and 125.78 ppm.

Preparation of (1S*,2S*)- and (1S*,2R*)-1-benzyl-1-chloro-1-[phenyl-(S*)-sulfinyl]-2-propanol (**4a**S*S* and **4a**S*R*, respectively). General procedure: In a three-neck round-bottom flask of 250 mL was placed a 1.5 inch-long stirring bar. One neck was stopped with a septum, other with alcohol thermometer and the third with an addition funnel stopped with latex septum. The air contained into the flask was permanently purged with a small flux of nitrogen. By means of hypodermic syringes, the flask was charged with anhydrous THF (40 mL), cooled to -70 °C, charged with 1.75 M n-BuLi (7.9 mL) and diisopropylamine (1.9 mL) distilled from barium oxide. The colorless solution was stirred 50 min. Meanwhile, in a clean and dried flask were placed **3** (3.0 g, 11.96 mmol), dissolved with THF (30 mL), and transferred with canula into the addition funnel. This solution was added slowly and with stirring to LDA solution at -70°C. The addition funnel was washed with THF (10 mL) and the resulted solution was added to the reaction flask. The brownish reaction mixture, containing the carbanion, was stirred at -70°C for 1 h. With a cold syringe, 2.8 mL of acetaldehyde were added to the reaction mixture. The yellowish solution was stirred 30 min at -70°C and then hydrolyzed at this temperature with saturated NH_4Cl solution (2 mL). The solvent was evaporated under reduced pressure and the yellowish oil was partially dissolved in CH_2Cl_2 (50 mL) and transferred to a separatory funnel. The organic layer was washed with NH_4Cl solution (20 mL), filtered through anhydrous sodium sulfate and concentrated in rotavapor. The yellowish oil was subjected to flash chromatography (CH_2Cl_2-heptane-acetone, 2:2:1), to obtain 0.25g of compound **3**, 2.10g of the "more polar" chlorohydrin and 2.57g of the "less polar" chlorohydrin (73% yield). By means of spectroscopy and X-ray diffraction analysis, the "more polar" and the "less polar" chlorohydrins were identified as **4a**S*S* and **4a**S*R*, respectively. Chlorohydrin **4a**S*S* was isolated as colorless prisms-like from EtOAc: mp 148-150°C; IR (neat) ν_{max} 664.3, 687.0, 700.5, 745.3, 865.7, 1041.9, 1083.4, 3261.6 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (2H, dm, *J* = 6.5 Hz, H*o*-benzyl), 7.43 to 7.31 (4H, m, aromatic hydrogens), 7.22 (2H, tm, *J* = 7.7 Hz, H*m*-phenyl sulfinyl), 6.95 (2H, dm, *J* = 8.4 Hz, H*o*-phenyl sulfinyl), 5.08 (1H, δ, *J* = 5.9, OH), 4.85, (1H, c, *J* = 6.2 Hz, CH), 1.21 (3H, δ, *J* = 5.9, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.98 (C1), 72.12 (C2), 18.49 (C3) and eight signals of aromatic carbons at δ 137.91, 131.80, 131.42, 129.43, 129.28, 128.19, 127.67, and 126.86. *Anal*. C 60.87%, H 5.13%, calcd. for $C_{15}H_{15}ClSO_2$, C 61.11%, H 5.13%. Chlorohydrin **4a**S*R* was isolated as colorless prisms-like from AcOEt: mp 98-101°C;

IR (neat) ν_{max} 692.8, 727.4, 753.0, 792.6, 1029.7, 1131.4, 1289.9, 1410.8, 1441.6, 3397.1 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 to 7.23 (8H, m, aromatic hydrogens), 6.92 (2H, dm, *J* = 8.4 Hz, H*o*-phenyl sulfinyl), 4.69 (1H, s, OH), 5.20 (dc, *J* = 2.0 and 6.1 Hz, CH), 1.07 (3H, δ, *J* = 6.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.35 (C1), 73.90 (C2), 18.71 (C3) and eight signals of aromatic carbons at δ 137.41, 132.31, 132.06, 129.62, 128.65, 127.91, 127.87, and 126.42. *Anal*. C 60.88%, H 5.18%, calcd. for $C_{15}H_{15}ClSO_2$, C 61.11%, H 5.13%.

Preparation of (1S*,S*)- and (1S*,2R*)-1-benzyl-1-chloro-1-[phenyl-(S*)-sulfinyl]-2-butanol (**4b**S*S* and **4b**S*R*, respectively). These compounds were prepared from lithio carbanion of **3** and propanaldehyde according to the procedure described above. Products were partially purified by a combination of recrystallization from EtOAc and flash chromatography (CH_2Cl_2-heptane-acetone 2:2:1). The "more polar" and the "less polar" chlorohydrins were identified as **4b**S*S* and **4b**S*R*, respectively. Isolated amounts of these diastereomers corresponded to 75% yield of 1:1 ratio. Chlorohydrin **4b**S*S* was isolated as colorless prisms-like from AcOEt: mp 137-139°C; IR (neat) ν_{max} 684.2, 700.9, 747.8, 870.1, 997.4, 1031.6, 1443.6, 3259.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, dm, *J* = 7.5 Hz, H*o*-benzyl), 7.43 to 7.32 (4H, m, aromatic hydrogens), 7.26 (2H, tm, *J* = 7.7 Hz, H*m*-phenyl sulfinyl), 6.94 (2H, dm, *J* = 8.3 Hz, H*o*-phenyl sulfinyl), 4.47 (1H, ddd, *J* = 1.9, 6.3 and 10.0, CH), 4.12 (1H, δ, *J* = 6.3 Hz, OH), 1.70 (1H, m, H_A of CH_2), 1.18 to 1.06, (1H, m, H_B of CH_2), 1.02 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.88 (C1), 77.69 (C2), 25.33 (C3), 10.85 (C4) and eight signals of aromatic carbons at δ 137.89, 132.31, 131.37, 129.34, 129.13, 128.17, 127.65 and 126.82. *Anal*. C 62.0%, H 5.56%, calcd. for $C_{16}H_{17}ClSO_2$, C 62.23%, H 5.55%. Chlorohydrin **4b**S*R* was isolated as colorless prisms-like from EtOAc: mp 121-123°C; IR (neat) ν_{max} 645.2, 695.6, 753.4, 884.8, 994.3, 1020.1, 1043.9, 1077.6, 1442.4, 3391.9 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 to 7.22 (8H, m, aromatic hydrogens), 6.91 (2H, dm, *J* = 8.3 Hz, H*o*-benzyl), 4.86 (1H, dt, *J* = 2.5 and 9.8, CH), 4.57 (1H, dd, *J* = 2.6 and 1.8 Hz, OH), 1.49 (1H, m, H_A of CH_2), 1.20 (1H, m, H_B of CH_2), 0.96 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.27 (C1), 78.87 (C2), 25.85 (C3), 10.23 (C4), and eight signals of aromatic carbons at δ 137.51, 132.28, 132.01, 129.56, 128.60, 127.93, 127.88, and 126.46. *Anal*. C 61.79%, H 5.58%, calcd. for $C_{16}H_{17}ClSO_2$, C 62.23%, H 5.55%.

Preparation of (1S*,2S*)- and (1S*,2R*)-1-benzyl-1-chloro-1-[phenyl-(S*)-sulfinyl]-2-pentanol (**4c**S*S* and **4c**S*R*, respectively). These compounds were prepared from metalated **3** and butanaldehyde according to the procedure described above. Products were partially purified by a combination of recrystallization from EtOAc and flash chromatography (CH_2Cl_2-heptane-acetone 2:2:1). The "more polar" and the "less polar" chlorohydrins were identified as **4c**S*S* and **4c**S*R*, respectively. Isolated amounts of these diastereomers corresponded to 58% yield of 1:1 ratio. Chlorohydrin **4c**S*S* was colorless prisms-like from AcOEt: mp 146-148°C; IR (neat) ν_{max} 701.1, 748.4, 869.0, 1004.9, 1044.4, 1080.1, 1442.9, 3327.2 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, dm, *J* = 7.5 Hz, H*o*-benzyl), 7.44 to 7.33 (4H, m, aromatic hydrogens), 7.23 (2H, tm, *J* = 7.7 Hz, H*m*-phenyl sulfinyl), 6.93 (2H, dm, *J* = 8.3 Hz, H*o*-phenyl sulfinyl), 4.56 (1H, ddd, *J* = 1.3, 6.2 and 10.3, CH), 4.00 (1H, δ, *J* = 6.2 Hz, OH), 1.68 to 1.33, (3H, m, CH_2), 1.21 to 1.07 (1H, m, CH_2), 0.88 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.79 (C1), 76.05 (C2), 34.20 (C3), 19.45 (C4), 13.79 (C5), and eight signals of aromatic carbons at 137.93, 132.30, 131.40, 129.38, 129.13, 128.21, 127.68, and 126.82 ppm. *Anal*. C 63.08%, H 5.98%, calcd. for $C_{17}H_{19}ClSO_2$, C 63.24%, H 5.93%. Chlorohydrin **4c**S*R* was isolated as small colorless needles from EtOAc: mp 120-121°C; IR (neat) ν_{max} 697.4, 752.7, 886.5, 997.5, 1019.1, 1032.3, 1077.8, 1137.6, 1445.0, 3338.8 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 to 7.22 (8H, m, aromatic proton), 6.91 (2H, dm, *J* = 8.4 Hz, H*o*-benzyl), 4.97 (1H, dt, *J* = 2.4 and 9.6 Hz, CH), 4.56 (1H, dd, *J* = 1.9 and 2.5, OH), 1.68 to 1.24 (3H, m, CH_2), 1.13 to 1.02 (1H, m, CH_2), 0.82 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 95.36 (C1), 77.04 (C2), 34.61 (C3) 18.63 (C4), 13.67 (C5), and eight signals of aromatic carbons at δ 137.55, 132.28, 132.01, 129.56, 128.61, 127.91, 127.88, and 126.47. *Anal*. C 63.20%, H 5.93%, calcd. for $C_{17}H_{19}ClSO_2$, C 63.24%, H 5.93%.

Preparation of diastereomeric 2-phenyl-3-methyl-2-sulfinyl oxirane (**5a**-*trans* and **5a**-*cis*). General procedure: In a three-neck round-bottom flask of 100 mL was placed a 1 inch-long stirring bar. One neck was stopped with a septum, other with alcohol thermometer and the third with a stopcock connected to a bubbling tube containing glycerin. The air contained into the flask was permanently purged with a small flux of nitrogen. The flask was charged with chlorohydrin **4a**S*S* (250 mg, 0.848 mmol) and anhydrous THF (25 mL). The resulted solution was tempered to the desired temperature (-70, -30, 0, and 25°C) and five min latter, 1.1 mL of *t*-BuOK 0.81 M in THF were added with hypodermic syringe, with stirring (*t*-BuOK was prepared from dry *tert*-butanol and a weighed amount of potassium. When the metal disappeared, *tert*-butanol was evaporated under reduced pressure and the white powder of *t*-BuOK was mixed, under nitrogen atmosphere, with a known volume of anhydrous THF. The resulting suspension was transferred with canula into a glass bottle where it was kept under nitrogen). The reaction was followed with tlc. At 0 and 25°C, conversion was completed within 0.25 h; therefore, the mixture was hydrolyzed with 20% HCl (2.5 mL). THF was evaporated in rotavapor and the concentrated was extracted with CH_2Cl_2 (40 mL), the organic layer was filtered trough anhydrous Na_2SO_4 and the solvent evaporated in rotavapor. The yellowish oil (crude product) was analyzed by proton NMR and then purified by flash chromatography (hexane-EtOAc 7:3) to obtain the mixture of **5a**-*trans* and **5a**-*cis* in 85/15 ratio (80% global yield for the reaction

carried out at 0°C). Mixture of **5a**-*trans* / **5a**-*cis*, yellowish oil: IR (neat) ν_{max} 690.0, 745.8, 975.0, 1053.9, 1087.0, 1444.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (1H, dm, *J* = 1.4 and 7.2 Hz, H*p*-phenyl sulfinyl), 7.36 to 7.18 (7H, aromatic hydrogens), 6.94 (2H, dm, *J* = 1.3 and 8.3 Hz, H*o*-phenyl sulfinyl), 3.99 (1H, q, *J* = 5.4, CH **5a**-*trans*), 3.47 (1H, q, *J* = 5.5 Hz, CH **5a**-*cis*), 1.18 (3H, δ, *J* = 5.4, CH_3 **5a**-*trans*), 1.93 (3H, δ, *J* = 5.5, CH_3 **5a**-*cis*); ^{13}C NMR (**5a**-*trans*, $CDCl_3$, 75 MHz) δ 78.30 (C2), 60.44 (C3), 14.84 (C3) and eight signals of aromatic carbons at δ 139.75, 131.40, 129.23, 128.69, 128.42, 127.61, 127.11, and 125.09.

Preparation of diastereomeric 2-phenyl-3-ethyl-2-sulfinyl oxirane (**5b**-*trans* and **5b**-*cis*). These compounds were prepared at 0°C from chlorohydrin **4b**S*S* by the general procedure described above. Crude product (yellowish oil) was analyzed by ^1H NMR and partially purified by flash chomatography (hexane-EtOAc 7:3) to obtain the mixture of **5b**-*trans* and **5b**-*cis* in 87/13 ratio. Mixture of **5b**-*trans* / **5b**-*cis*, colorless oil: IR (neat) ν_{max} 690.2, 745.9, 942.6, 1052.5, 1087.7, 1444.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 to 7.14 (8H, m, aromatic hydrogens), 6.95 (2H, dm, *J* = 1.3 and 8.3 Hz, H*o*-phenyl sulfinyl), 3.84 (1H, dd, *J* = 5.6 and 6.7 Hz, CH **5b**-*trans*), 3.31 (1H, t, *J* = 6.5 Hz, CH **5b**-*cis*), 1.49 to 1.18 (2H, m, CH_2 **5b**-*trans*), 2.36 to 2.16 (2H, m, CH_2 **5b**-*cis*), 1.02 (3H, t, *J* = 7.5 Hz, CH_3 **5b**-*trans*), 1.30 (3H, t, *J* = 7.5 Hz, CH_3 **5b**-*cis*);^{13}C NMR (**5b**-*trans*, $CDCl_3$, 75 MHz) δ 78.45 (C2), 65.53 (C3), 22.60 (C4), 9.99(C5), and eight signals of aromatic carbons at δ 139.78, 131.39, 129.18, 128.54, 128.39, 127.56, 127.31 and 125.11.

Preparation of diastereomeric 2-phenyl-3-propyl-2-sulfinyl oxirane (**5c**-*trans* and **5c**-*cis*). These compounds were prepared at 0°C from chlorohydrin **4c**S*S* by the general procedure described above. Crude product (yellowish oil) was analyzed by ^1H NMR and partially purified by flash chromatography (hexane-EtOAc 7:3) to obtain the mixture of **5c**-*trans* and **5c**-*cis* in 85/15 ratio. Mixture of **5c**-*trans* / **5c**-*cis*, colorless oil: IR (neat) ν_{max} 695.6, 745.6, 939.8, 1052.9, 1088.3, 1444.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 to 7.17 (8H, m, aromatic hydrogens), 6.95 and 6.97 (2H, dm, *J* = 8.0 Hz, H*o*-phenyl sulfinyl), 3.88 (1H, dd, *J* = 4.4 and 7.3 Hz, CH, **5c**-*trans*), 3.35 (1H, t, *J* = 6.3 Hz, CH **5c**-*cis*), 1.57 to 1.39 (3H, CH_2CH_2, **5c**-*trans*), 2.22 (2H, m, CH_2 **5c**-*cis*), 1.15 (1H, CH_2 **5c**-*trans*), 1.75 (2H, sextet, *J* = 7.4 Hz, CH_2 **5c**-*cis*), 0.91 (3H, t, *J* = 7.2 Hz, CH_3 **5c**-*trans*), 1.13 (3H, t, *J* = 7.4, CH_3 **5c**-*cis*); ^{13}C NMR (**5c**-*trans*, $CDCl_3$, 75 MHz) δ 78.14 (C2), 64.34 (C3), 31.17 (C4), 19.42 (C5), 13.80 (C6), and eight signals of aromatic carbons at δ 139.79, 131.37, 129.16, 128.55, 128.39, 127.55, 127.40 and 125.10.

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References

1. a) Tavares, D. F.; Estep, R. E.; Blezard, M. *Tetrahedron Lett*. **1970**, 2373-2376; b) Durst, T.; Tin, K. C.; Reinach-Hirtzbach, F.; Decesare J. M.; Ryan, M. D. *Can. J. Chem.* **1979**, *57*, 258-266; c) Taber, D. F.; Gunn, B. P. *J. Org. Chem.* **1979**, *44*, 450-452.
2. Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130-3136.
3. Satoh, T.; Motohashi, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1988**, *36*, 1169-1173.
4. Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horiguchi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515-2528.
5. Satoh, T.; Sugimoto, A.; Ito, M.; Yamakawa, K. *Tetrahedron Lett.* **1989**, 1083-1089.
6. García-Martínez, C.; Cervantes-Cuevas, H.; Escalante-García, J. *Chirality* **2003**, *15*, S74-S81.
7. Durst, T. *J. Am. Chem. Soc.* **1969**, *91*, 1034-1035.
8. Shriner, R. L.; Struck, H. C.; Jorison, W. J. *J. Am. Chem. Soc.* **1930**, *52*, 2060-2069.
9. Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282-284.
10. Tsuchihashi, G.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1726.
11. Iriuchijima, S.; Tsuchihashi, G. *Tetrahedron Lett*. **1969**, 5259-5262.
12. Tsuchihashi G.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2023-2027.
13. Satoh, T.; Kaneko, Y.; Izawa, T.; Sakata, K.; and Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1983-1990.
14. Roux-Schmitt, M. C.; Seyden-Penne, J.; Wolfe, S. *Tetrahedron* **1972**, *28*, 4965-4979.
15. a) Marsh, M.; Massa, W.; Harms, K.; Baum, G.; Boche, G. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1011-1012; b) Pyne, S. G.; Boche, G. *J. Org. Chem.* **1989**, *54*, 2663-2667; c) Casey, M.; Mukherjee, I.; Trabsa, H. *Tetrahedron Lett.* **1992**, 127-130.
16. Dress, R. K.; Roelle, T.; Hofmann, R. W. *Chem. Ber.* **1995**, *128*, 673-677.
17. March, J.; Smith, M. B. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons, Inc.: N.Y., 2001; pp 98-102.
18. Shapiro, M. J. *J. Org. Chem.* **1978**, *43*, 742-743.