



## Synthesis and Reactions of Enantiomerically Pure Chloromethyl Oxiranes

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**Abstract:** The reactivities of 1-chloro-3-*p*-tolylsulfinyl acetone (*R<sub>S</sub>*)-**1** towards diazomethane and of the resulting diastereoisomeric 1-chloromethyl-1-sulfinylmethyl oxiranes **2** towards *O*-, *N*- and *C*-centred nucleophiles are investigated. The synthesis of differently functionalized homochiral chlorinated sulphur-free oxiranes (*R*)-**15**, (*S*)-**16** and (*R*)-**17** has been accomplished in good chemical yields.

Carbonyl epoxidation reactions are of considerable importance: Not only do they involve formation of a new carbon-carbon bond but the epoxide can be manipulated further in a variety of synthetically useful reactions.<sup>1</sup> In particular, the reaction of diazomethane with ketones has been a rich source of chemistry: in addition to homologation products, substantial amounts of epoxides are formed, while with enolizable ketones *O*-methyl enol ethers may be the prevailing products.<sup>1,2</sup>

Enantiomerically pure sulfinyl-epoxides have been obtained by addition of  $\alpha$ -metallated  $\alpha$ -chloromethyl sulfoxides to carbonyl compounds. This modified Darzens reaction can occur with high diastereoface selection, due to the sulfinyl moiety, but with low simple diastereoselection, delivering mixtures of *syn* and *anti* diastereoisomers.<sup>3</sup> Sulfinylmethyl-oxiranes have been synthesised from enantiomerically pure  $\gamma$ -chloro- $\beta$ -ketosulfoxides. Reduction to  $\gamma$ -chloro- $\beta$ -hydroxysulfoxides and intramolecular displacement of a chloride ion afforded these useful building blocks in highly stereoselective fashion.<sup>4</sup> Enantiomerically pure  $\beta$ -hydroxysulfoxides have been transformed also in the corresponding desulphurized oxiranes, by reduction of the sulfinyl group to sulfide and treatment with trimethyloxonium fluoroborate, followed by  $S_N2$  ring closure.<sup>5</sup>

Recently we reported a new entry to sulfinylmethyl-oxiranes, in which the key-step was the one carbon addition across the C=O bond of  $\beta$ -ketosulfoxides, achieved by treatment of the latter with diazomethane. Preparation of chiral and enantiomerically pure 1-sulfinylmethyl-1-fluoromethyl oxirane was accomplished by this route with high diastereoselection, starting from  $\gamma$ -fluoro- $\beta$ -ketosulfoxides.<sup>6</sup> This strategy was successful in generating, with high asymmetric induction, compounds capable of further manipulation due to the three membered ring, the sulfinyl functionality and a variety of fluoro-substituted carbons, but it was less suitable for unsubstituted- and  $\gamma$ -hydroxy-substituted  $\beta$ -keto-sulfoxides, because of a much lower stereoselection.<sup>7</sup>

Our continuing efforts are directed towards the development of this methodology for the efficient formation of chiral and enantiomerically pure epoxides from sulfoxides and for their use in asymmetric synthesis.

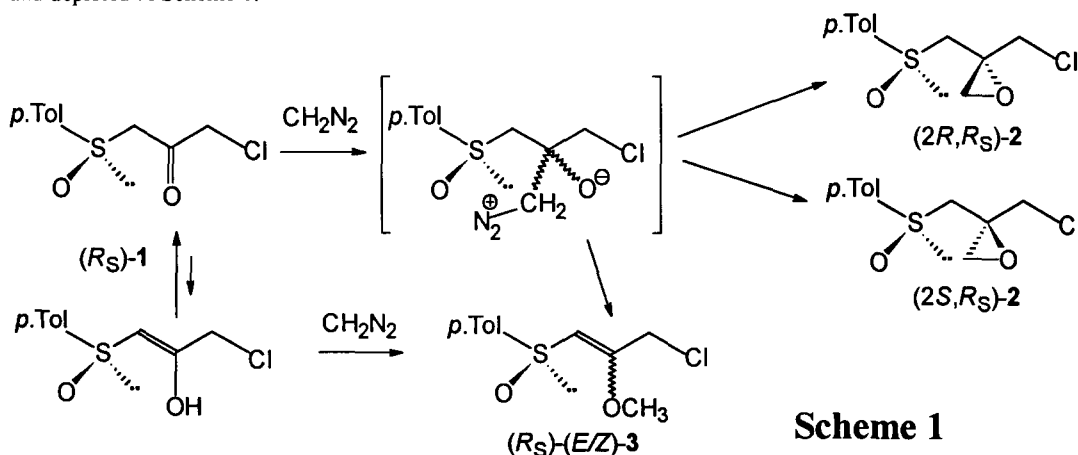
In line with this strategy, this paper describes the full details of the preparation of 1-sulfinylmethyl-1-chloromethyl oxiranes and of a number of chemoselective elaborations of this useful C-4 chiron.<sup>8</sup>

The reaction between diazomethane and carbonyl compounds forming epoxides entails attack of the methylene carbon on the carbonyl to form a betaine under kinetic control, which then collapses with expulsion of molecular nitrogen.<sup>9</sup> Before oxirane ring closure, electron rich substituents can migrate from the central carbon to the methylene, forming homologous ketones.<sup>1c</sup> Moderately stable 1,3-cycloadducts form when strong electron withdrawing substituents are present on the carbonyl.<sup>2d</sup> Enolizable ketones give rise to methyl enoethers and seldom to C-methylated compounds through attack of the methylene on the acidic enol form; diazomethane itself promotes the keto-enol equilibration.<sup>10</sup> Solvents play an important role in directing the reaction. In particular, polar solvents like methanol, and higher alcohols to a minor extent, are known to speed up the epoxide formation.

## RESULTS AND DISCUSSION

The starting  $\beta$ -keto-sulfoxide, 1-chloro-3-*p*-tolylsulfinyl acetone ( $R_S$ )-1, can be easily obtained through acylation of ( $R_S$ )-methyl-*p*-tolylsulfoxide with ethyl chloroacetate.<sup>11</sup> The electron-poor character of the carbonyl group is enhanced by the two electron withdrawing substituents at the  $\alpha$ -carbons, namely the sulfinyl group and the chlorine atom. Therefore, the methylene addition across the C=O bond giving the corresponding oxirane is highly favoured, while the formation of homologous ketones is inhibited by the low migratory aptitude of the electron poor  $\alpha$ -carbons. Moreover, the keto/enol equilibrium is by far shifted towards the carbonyl form.

The reactions were run adding an ethereal solution (*c.a.* 0.5 M) of diazomethane to the solution of the ketone ( $R_S$ )-1 in different solvents kept at the appropriate temperature. Solvent removal and flash chromatography provided the products in enantiomerically pure form. The results are summarised on Table 1 and depicted in Scheme 1.



The reaction showed a remarkable solvent effect. The best results were obtained in methanol at  $-15^\circ\text{C}$ : after a few minutes ( $2R, R_S$ )-2 and ( $2S, R_S$ )-2 were obtained in 71% and 17% yields, respectively. In the same media, at  $0^\circ\text{C}$ , the epoxides were isolated in lower yield, and traces of ( $R_S$ )-(E) and ( $R_S$ )-(Z) enoethers 3 were detected. In ethyl ether, the best result regarding the diastereoselection was achieved, but the worst

regioselection was observed, with the ratio between oxiranes **2** and enolethers **3** equal to 1.6. The reaction rate was lower in ethyl ether, benzene and DMF at 0°C. In these conditions the process was complete in four/five hours (five minutes in methanol). Finally, in DMF, after five hours at -15°C, the reaction mixture did not contain any epoxide, but only (*R<sub>S</sub>*)-(*E*)- and (*R<sub>S</sub>*)-(*Z*)-enolethers **3** in 43% yield and in a 3 : 1 ratio, along with unreacted ketone (*R<sub>S</sub>*)-**1** that was recovered in 32% yield.

**Table 1.** Reaction conditions, chemical yields, face- and regio-selectivity.

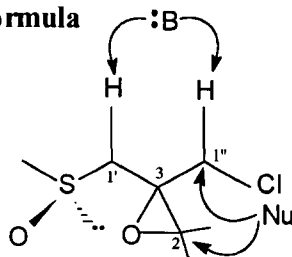
|                | Solvent     | Temperature (°C) | Reaction time (min.) | Oxiranes <b>2</b> yield (%) | <i>R/S</i> - <b>2</b> Ratio | Enolether <b>3</b> yield (%) |
|----------------|-------------|------------------|----------------------|-----------------------------|-----------------------------|------------------------------|
| <b>Entry 1</b> | methanol    | 0                | 5                    | 75.6                        | 5:1                         | 1.4 <sup>a</sup>             |
| <b>Entry 2</b> | methanol    | - 15             | 5                    | 88.0                        | 4.2:1                       | 0                            |
| <b>Entry 3</b> | ethyl ether | 0                | 240                  | 36.0                        | 17:1                        | 22.7 <sup>a</sup>            |
| <b>Entry 4</b> | benzene     | 0                | 270                  | 64.0                        | 8.1:1                       | 23.0 <sup>a</sup>            |
| <b>Entry 5</b> | DMF         | 0                | 300                  | 0                           | —                           | 43.0 <sup>b</sup>            |

<sup>a</sup> Only (*Z*) enolether **3** was detected. <sup>b</sup> Enolethers **3** were obtained in (*Z*)/(*E*) = 2.9 : 1.0 ratio.

It is interesting to note that, as already reported for  $\gamma$ -fluorosubstituted- $\beta$ -keto-sulfoxides<sup>6</sup> and in general also for hydride addition reactions on  $\beta$ -keto-sulfoxides,<sup>12</sup> diazomethane preferentially attacks the *Si* face of the carbonyl group of (*R<sub>S</sub>*)-**1**. The diastereoselection of the process could be ascribed to an initial interaction of the partially positively charged nitrogen atom of diazomethane with the sulfinyl group of (*R<sub>S</sub>*)-**1**. The subsequent methylene attack occurs from the less hindered carbonyl face. The presence of the electron withdrawing substituent on the  $\gamma$ -carbon seems to be necessary to have a high difference in the population of the reactive rotamers and therefore to have a high diastereoface selectivity in the reaction with diazomethane.<sup>13</sup> This is shown by a 97 : 3 diastereoface selection in the case of  $\gamma$ -fluoro-substitution,<sup>6</sup> 89 : 11 for  $\gamma$ -chloro-substitution and 85 : 15 for  $\gamma$ -bromo-substitution,<sup>14</sup> 70 : 30 for  $\gamma$ -hydroxy-substitution<sup>7a</sup> and negligible diastereoselection observed for  $\gamma$ -unsubstituted  $\beta$ -keto-sulfoxides.<sup>7b</sup>

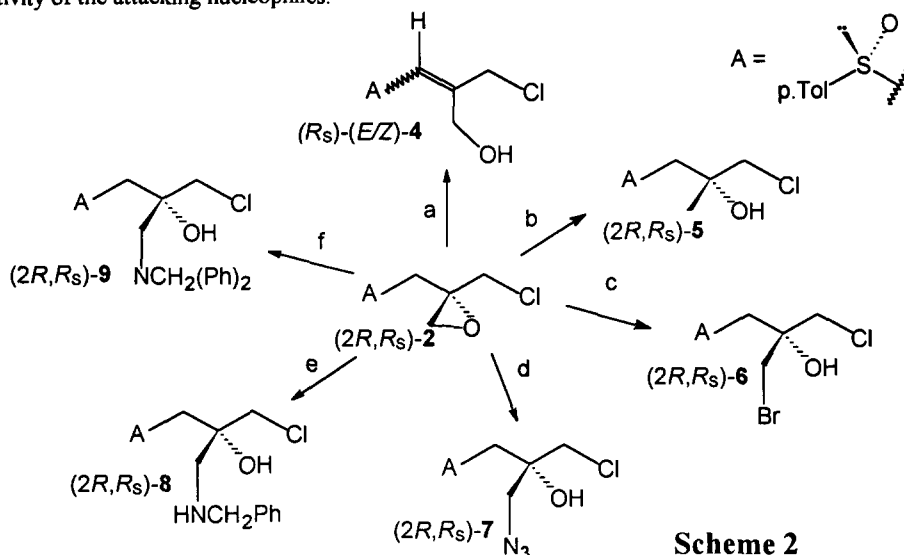
The synthetic value of chloromethyl methylene oxides has been demonstrated in a collection of synthetic transformations, reported below. We had already successfully employed the nucleophilic addition of carbon-, nitrogen- and oxygen-centred nucleophiles as a convenient means of preparing a large number of the corresponding tertiary alcohols from 1-*p*-tolylsulfinyl-1-fluoroalkyl oxiranes.<sup>15</sup> Therefore, since the chlorine atom is much more reactive than fluorine, especially as a leaving group, it seemed logical to us to explore the feasibility of the same reactions on the chloromethyl oxiranes **2**.

### Formula



As shown in the Formula, enhanced and multiple reactivity of chlorosulfinyl oxirane **2** is associated to the presence of different active sites: a) the hydrogens on C-1' and C-1'' are activated by the electron withdrawing

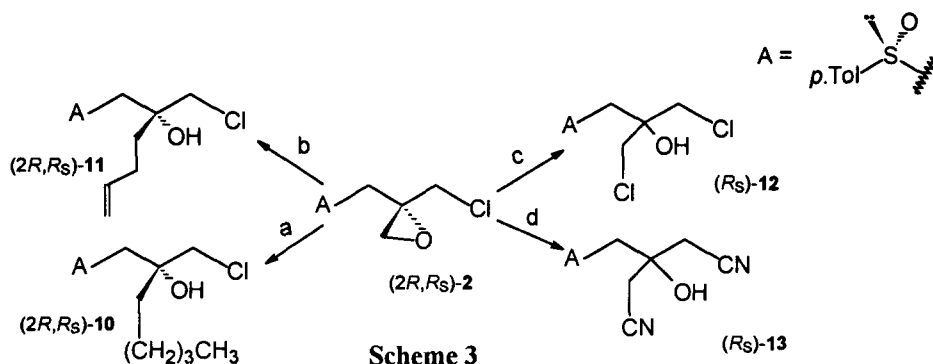
sulfinyl and chlorine substituents respectively and can be abstracted by bases: through a push-pull mechanism, the resulting anions can give rise to the corresponding allyl alcohol, more stable because of strain release;<sup>16</sup> b) on the other hand, the C-2 carbon of the oxirane ring and the C-1" carbon represent suitable sites of attack for nucleophilic species,<sup>17</sup> because of the strain of the three-membered ring and of the capacity of the mobile chlorine atom to act as a leaving group; c) the sulfinyl moiety itself is a suitable site of reaction, whilst the attack of nucleophiles on C-3 seems much less favourable due to the steric hindrance. Moreover, electrophilic assistance by protic acids or Lewis acids coordination on the oxirane oxygen can modify the kinetics and the regioselectivity of the attacking nucleophiles.<sup>18</sup>



**Reagents and conditions:** a) NaOH, THF/H<sub>2</sub>O, r.t. (51%); b) LiAlH<sub>4</sub>, THF, -70°C (50%); c) CuBr<sub>2</sub>, LiBr, THF, r.t. (79%); d) NaN<sub>3</sub>, NH<sub>4</sub>Cl, THF, r.t. (74%); e) benzylamine, THF, r.t. (88%); f) dibenzylamine, THF, r.t. (48%).

As shown in Scheme 2, the action of the base NaOH gave rise to an inseparable mixture of (*E*) and (*Z*) isomers of the allylic alcohol (*R<sub>S</sub>*)-4, as already observed for the fluorinated analogue.<sup>6b</sup> Successful nucleophilic ring opening of the oxirane ring by hydride-releasing species, by bromide<sup>19</sup> and azide<sup>15a</sup> anions and by benzyl and dibenzyl amines<sup>20</sup> gave the corresponding chloromethyl tertiary alcohol (*2R,R<sub>S</sub>*)-5, bromosubstituted tertiary alcohol (*2R,R<sub>S</sub>*)-6, azido derivative (*2R,R<sub>S</sub>*)-7 and benzyl- and dibenzylamino derivatives (*2R,R<sub>S</sub>*)-8 and (*2R,R<sub>S</sub>*)-9.

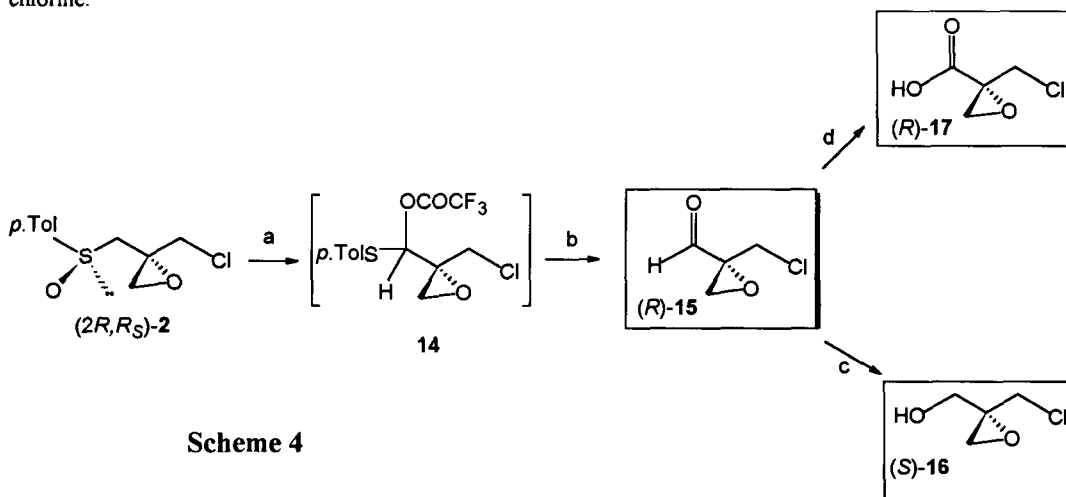
On the other hand, the reactions with carbon-centred nucleophiles were less chemo- and regio-selective. In fact, as shown in Scheme 3, only the addition of a butyl cuprate,<sup>21</sup> was selectively directed to the oxirane ring, affording the tertiary alcohol (*2R,R<sub>S</sub>*)-10 in good yield. Allylmagnesium chloride still produced the oxirane ring opening, affording in good yield the tertiary alcohol (*2R,R<sub>S</sub>*)-11, but unidentified by-products also formed in the reaction. Interestingly, using methylmagnesium chloride as nucleophile on (*2R,R<sub>S</sub>*)-2, the dichloro carbinol (*R<sub>S</sub>*)-12 was the main reaction product, along with a 10% yield of the allylic alcohol (*E*)/(*Z*)-4. This unusual outcome should be explained with the already observed competitive nucleophilic attack of the chloride counterion to the oxirane ring, that produces the main product (*R<sub>S</sub>*)-12.<sup>6b</sup> The formation of the minor product (*R<sub>S</sub>*)-4 should arise from hydrogen abstraction from the sulfinyl-bearing carbon atom, owing to the basic properties of the Grignard reagent.<sup>22</sup>



**Reagents and conditions:** a) CuI, *n*-butyl lithium, THF,  $-20^{\circ}\text{C}$  (80%); b) allylmagnesium chloride, THF,  $0^{\circ}\text{C}$  (76%); c) methylmagnesium chloride, THF,  $5^{\circ}\text{C}$  (80%); d) KCN,  $\text{LiClO}_4$ ; acetonitrile,  $60^{\circ}\text{C}$  (23%).

When the epoxide  $(2R,RS)\text{-2}$  was submitted to the reaction with cyanide anion,<sup>23</sup> the glutaronitrile derivative  $(RS)\text{-13}$  was the only recoverable product. An attempt to introduce regiospecifically the cyanide group by reacting  $(2R,RS)\text{-2}$  with trimethylsilylcyanide<sup>24</sup> under  $\text{BF}_3\cdot\text{OEt}_2$  catalysis was unsuccessful.

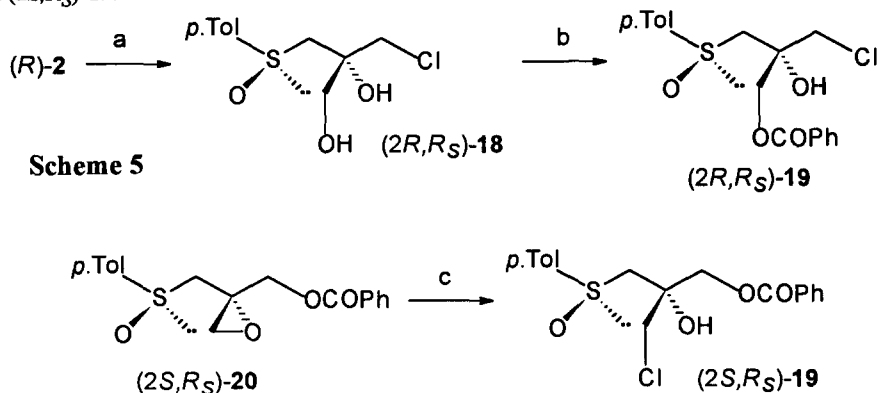
To exploit the reactivity of the sulfinyl moiety, the Pummerer rearrangement<sup>25</sup> was chosen in order to remove the auxiliary sulfinyl group with the introduction of an oxygen functionality in its place. As shown in Scheme 4, the  $(2R,RS)\text{-2}$  oxirane was treated with an acetonitrile solution of trifluoroacetic anhydride to give the labile *p*-tolylthio/trifluoroacetoxy intermediate **14** that was converted into the formyl/chloromethyl oxirane  $(R)\text{-15}$ . The reduction of the formyl group with sodium borohydride to give the hydroxymethyl oxirane  $(S)\text{-16}$ , and the oxidation with sodium chlorite to give the glycidyl acid  $(R)\text{-17}$ , were performed without affecting the chlorine.



**Reagents and conditions:** a)  $(\text{CF}_3\text{CO})_2\text{O}$ , *sym*-collidine, acetonitrile,  $-10^{\circ}\text{C}$ ; b)  $\text{HgCl}_2$ ,  $\text{K}_2\text{CO}_3$ , acetonitrile,  $0^{\circ}\text{C}$  (80%); c)  $\text{NaBH}_4$ ,  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ , r.t. (89%); d)  $\text{NaClO}_2$ ,  $\text{K}_2\text{HPO}_4$ , *tert*.butanol, 2-methyl-2-propene, r.t. (85%).

Finally, a chemical correlation with a compound of known absolute stereochemistry was performed to establish unequivocally the absolute configuration at C-2 of the molecules described in the present paper. The

major diastereoisomeric oxirane **2** was treated with a diluted solution of perchloric acid, affording in high yield the diol derivative **18**, as shown in Scheme 5. The subsequent protection of the primary hydroxy group as benzoate afforded the sulfinyl/chloromethyl tertiary alcohol **19**. On the other hand, the sulfinyl oxirane (*2S,R<sub>S</sub>*)-**20**, whose C-2 absolute configuration has been previously established by X-ray analysis of the corresponding bromohydrin derivative,<sup>5b</sup> was submitted to reaction with cupric chloride/lithium chloride<sup>26</sup> to give the chlorohydrin (*2S,R<sub>S</sub>*)-**19**.



**Reagents and conditions:** a)  $\text{HClO}_4$ ,  $\text{THF}/\text{H}_2\text{O}$  (70%); b)  $\text{PhCOOH}$ , DCC,  $\text{CH}_2\text{Cl}_2$ , DMAP, r.t. (90%); c)  $\text{CuCl}_2$ , LiCl, THF, r.t. (96%).

Comparison between the specific rotation values and, in particular, proton NMR spectra showed the diastereoisomeric relationship between the compound **19** obtained from the major diastereoisomeric oxirane **2** and the one produced by (*2S,R<sub>S</sub>*)-**20**, thus confirming the anticipated (*R*) stereochemistry at C-2.

## CONCLUSIONS

The addition of diazomethane to the  $\beta$ -keto- $\gamma$ -chloro-sulfoxide (*R<sub>S</sub>*)-**1** gives the  $\alpha$ -sulfinylmethyl- $\alpha$ -chloromethyl-oxiranes **2** in moderate to good chemical yields, with diastereomeric excesses ranging from 62% to 95%; the face- and regioselectivity of the reaction is solvent-dependent. The reactivity of the  $\alpha$ -chloromethyl  $\alpha$ -sulfinylmethyl oxiranes **2** towards different nucleophilic species has been studied and the chemoselectivity seems to be higher for the *O*- and *N*-centred nucleophiles than for the *C*-centred ones. Starting from the enantiomerically pure (*2R,R<sub>S</sub>*)-**2**, through a Pummerer reaction, small homochiral chloromethyl oxiranes, like the  $\alpha$ -formyl-, the  $\alpha$ -hydroxymethyl- and the  $\alpha$ -carboxy- derivatives (*R*)-**15**, (*S*)-**16** and (*R*)-**17** have been readily obtained.

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## EXPERIMENTAL

**General Details.**  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC 250L spectrometer. Optical rotations were obtained on a Jasco DIP-181 polarimeter. Melting points are uncorrected and were obtained on a capillary apparatus. Mass spectra were registered on a Hitachi-Perkin-Elmer ZAB 2F instrument. Flash

chromatographies were performed with silica gel 60 (60–200  $\mu\text{m}$ , Merck) and preparative TLC separations were performed on Merck 60F<sub>254</sub> precoated plates. All reactions were monitored by TLC performed on analytical Merck silica gel 60F<sub>254</sub> TLC plates. Tetrahydrofuran (THF) was freshly distilled from sodium and diisopropylamine was distilled from calcium hydride and stored on 4 Å molecular sieves. In other cases, commercially available reagent-grade solvents and reagents were employed without purification. Accurate mass measurements were performed on a VG ZAB 2F instrument operating in EI conditions (70 eV, 200  $\mu\text{A}$ ). For compounds for which the  $\text{M}^+$  ion abundance was lower than 0.1% the measurements were carried out on the  $[\text{M}-\text{OH}]^+$  ion.

**Synthesis of (*R<sub>S</sub>*)-1-chloro-3-[4-(methylphenyl)sulfinyl]propan-2-one 1.**<sup>11</sup> To a solution of LDA (0.054 mmol) in THF (70 ml) at  $-60^\circ\text{C}$  under nitrogen, a solution of methyl-*p*-tolyl-sulfoxide (0.045 mmol, 7.0 g) in THF (40 ml) was added dropwise. The resulting yellow solution was cooled at  $-75^\circ\text{C}$  and a solution of ethyl chloroacetate (0.058 mmol, 5.2 ml) in THF (10 ml) was added dropwise. After 10 min., the reaction was quenched with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution (30 ml) at  $-70^\circ\text{C}$ , then pH was adjusted to 3 adding aqueous HCl solution and the temperature was allowed to reach room temperature. The organic layers were extracted with ethyl acetate (30 ml x 3) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was obtained as a pale yellow solid that was purified by crystallization: hot ethyl acetate (200 ml) was added up to complete solution, then cool *n*-hexane (20 ml) was slowly added. After one night at  $0^\circ\text{C}$ , the white precipitate was filtered to obtain purified product (5.5 g) as white needles. The mother liquor was dried under *vacuum* and purified by flash chromatography (ethyl acetate/*n*-hexane 3 : 2) to give another portion of pure compound (2.5 g) in 77% global yield:  $[\alpha]_{\text{D}}^{20} + 222.2$  (c 1.1,  $\text{CHCl}_3$ ); m.p.  $128\text{--}129^\circ\text{C}$  (ethyl acetate/*n*-hexane 3 : 2);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.42 (s, 3H,  $\text{ArCH}_3$ ), 3.92 (d, 1H,  $\text{CH}_a\text{S}$ ,  $^2J_{\text{H-H}} = 13.0$  Hz); 4.04 (d, 1H,  $\text{CH}_b\text{S}$ ), 4.16 (s, 2H,  $\text{CH}_2\text{Cl}$ ), 7.32–7.55 (m, 4H,  $\text{ArH}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 21.5 (s, 1C,  $\text{ArCH}_3$ ), 49.9 (s, 1C,  $\text{CH}_2\text{Cl}$ ), 64.6 (s, 1C,  $\text{CH}_2\text{S}$ ), 123.9 and 130.3 (s, 4C,  $\text{ArCH}$ ), 138.7 (s, 1C,  $\text{CH}_3\text{CAr}$ ), 142.6 (s, 1C,  $\text{SCAr}$ ); IR (nujol)  $\nu$  ( $\text{cm}^{-1}$ ): 2920, 1720, 1082, 1037, 921, 809; Mass (C.I., %): 231 ( $\text{M}^+$ , 100), 197 [ $\text{M}^+-\text{Cl}$ ], 10], 139 (*p*.  $\text{ToISO}^+$ , 45). HRMS: Found 230.01695; calculated for  $\text{C}_{10}\text{H}_{11}\text{O}_2\text{S}^{35}\text{Cl}$  230.01652.

**Synthesis of oxiranes 2. a) Methanol.** To a solution of ketone (*R<sub>S</sub>*)-1 (13.0 mmol, 3 g) in methanol (150 ml) at  $0^\circ\text{C}$  a solution of diazomethane (c.a. 0.5 M in ethyl ether, 100 ml) was added portionwise. After 5 min., excess  $\text{CH}_2\text{N}_2$  was destroyed by adding some drops of acetic acid and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/*n*-hexane 1 : 1) to give (2*R*,*R<sub>S</sub>*)-2-chloromethyl-2-[[4-(methylphenyl)sulfinyl]methyl]oxirane 2 in 63% yield, (2*S*,*R<sub>S</sub>*)-2 in 12.6% yield, (*R<sub>S</sub>*)-(Z)-1-[4-(methylphenyl)sulfinyl]-2-methoxy-3-chloro-propene 3 in 1.4% yield. (2*R*,*R<sub>S</sub>*)-2:  $[\alpha]_{\text{D}}^{20} + 245.4$  (c 1.0,  $\text{CHCl}_3$ ); m.p.  $105\text{--}106^\circ\text{C}$  (isopropylether);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.44 (s, 3H,  $\text{ArCH}_3$ ), 2.92 (d, 1H,  $\text{CH}_a\text{S}$ ,  $^2J_{\text{H-H}} = 14.0$  Hz); 2.98 (dd, 1H,  $\text{CH}_a\text{O}$ ,  $^2J_{\text{H-H}} = 4.2$ ,  $^4J_{\text{H-H}} = 0.96$  Hz), 3.26 (d, 1H,  $\text{CH}_b\text{O}$ ), 3.51 (dd, 1H,  $\text{CH}_b\text{S}$ ,  $^4J_{\text{H-H}} = 0.96$  Hz), 3.52 (d, 1H,  $\text{CH}_a\text{Cl}$ ,  $^2J_{\text{H-H}} = 12.0$  Hz), 3.75 (d, 1H,  $\text{CH}_b\text{Cl}$ ), 7.32–7.60 (m, 4H,  $\text{ArH}$ ); IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 2923, 1494, 1401, 1085, 1045, 811, 745; Mass (EI/*m/z*, %): 245 ( $\text{M}^+$ , 90), 209 [ $\text{M}^+-\text{Cl}$ ], 10], 139 (*p*.  $\text{ToISO}^+$ , 100); HRMS: Found 244.0333; calculated for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}^{35}\text{Cl}$  244.0321. (2*S*,*R<sub>S</sub>*)-2:  $[\alpha]_{\text{D}}^{20} + 181.2$  (c 1.4,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.45 (s, 3H,  $\text{ArCH}_3$ ), 2.82 (dd, 1H,  $\text{CH}_a\text{S}$ ,  $^2J_{\text{H-H}} = 13.6$  Hz,  $^4J_{\text{H-H}} = 1.2$  Hz); 2.92 (dd, 1H,  $\text{CH}_a\text{O}$ ,  $^2J_{\text{H-H}} = 4.4$ ,  $^4J_{\text{H-H}} = 1.6$  Hz), 3.00 (d, 1H,  $\text{CH}_b\text{O}$ ), 3.40 (dd, 1H,  $\text{CH}_b\text{S}$ ,  $^4J_{\text{H-H}} = 1.6$  Hz), 3.71 (dd, 1H,  $\text{CH}_a\text{Cl}$ ,  $^2J_{\text{H-H}} = 12.0$  Hz,  $^4J_{\text{H-H}} = 1.2$  Hz), 4.03 (d, 1H,  $\text{CH}_b\text{Cl}$ ), 7.30–7.55 (m, 4H,  $\text{ArH}$ ); (*R<sub>S</sub>*)-(Z)-3:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.40 (s, 3H,  $\text{ArCH}_3$ ), 4.00 (d, 1H,  $\text{CH}_a\text{Cl}$ ,  $^2J_{\text{H-H}} = 12.5$  Hz), 4.02 (s, 3H,  $\text{OCH}_3$ ), 4.14 (d, 1H,  $\text{CH}_b\text{Cl}$ ), 5.68 (s, 1H,  $\text{CHS}$ ), 7.26–7.54 (m, 4H,  $\text{ArH}$ ); HRMS: Found 244.0308; calculated for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}^{35}\text{Cl}$  244.0321. The same reaction was performed on (*R<sub>S</sub>*)-1 dissolved in the same

solvent, at the same reagents concentration, but decreasing the temperature to  $-15^{\circ}\text{C}$ : after 5 min., (2*R*,*R*<sub>S</sub>)-2 was formed in 71% yield along with (2*S*,*R*<sub>S</sub>)-2 in 17% yield, whilst no enol ethers were detected.

**b) Ethyl ether.** Following the above described procedure, dissolving 1 in ethyl ether, after 4 hours at  $0^{\circ}\text{C}$ , the following compounds were obtained: (2*R*,*R*<sub>S</sub>)-2 in 34% yield, (2*S*,*R*<sub>S</sub>)-2 in less than 2% yield (only detectable in traces from  $^1\text{H}$  NMR spectrum of the crude reaction mixture), (*R*<sub>S</sub>)-(Z)-3 in 22.7% yield.

**c) Benzene.** Following the same procedure, dissolving (*R*<sub>S</sub>)-1 in benzene, after 4.5 hours at  $0^{\circ}\text{C}$ , the following products were obtained: (2*R*,*R*<sub>S</sub>)-2 in 57% yield, (2*S*,*R*<sub>S</sub>)-2 in 7% yield, (*R*<sub>S</sub>)-(Z)-3 in 23% yield.

**d) Dimethylformamide.** Dissolving (*R*<sub>S</sub>)-1 in DMF at  $0^{\circ}\text{C}$ , after 5 hours, the following compounds were isolated: (*R*<sub>S</sub>)-(Z)-3 in 32% yield, (*R*<sub>S</sub>)-(E)-3 in 11% yield, starting ketone 1 in 32% yield. (*R*<sub>S</sub>)-(E)-3:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.42 (s, 3H, ArCH<sub>3</sub>), 3.95 (d, 1H, CH<sub>a</sub>Cl,  $^2J_{\text{H-H}} = 12.5$  Hz), 4.05 (d, 1H, CH<sub>b</sub>Cl), 4.10 (s, 3H, OCH<sub>3</sub>), 5.52 (s, 1H, CHS), 7.30-7.60 (m, 4H, ArH).

**Reaction of epoxide 2 with bases.** To a solution of (2*R*,*R*<sub>S</sub>)-2 (100 mg, 0.41 mmol) in THF (1 ml), a 1M NaOH aqueous solution (1 ml) was added dropwise at  $0^{\circ}\text{C}$ . After 1 hour, aqueous HCl was added up to pH 7 and the organic layers were extracted with ethyl acetate (3 x 1 ml). After the usual procedures, the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 2 : 3) to give (Z)-2-chloromethyl-1-[4-(methylphenyl)sulfinyl]-prop-1-en-3-ol (*R*<sub>S</sub>)-4 (51 mg, 51% yield):  $R_f$  0.35;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.42 (s, 3H, ArCH<sub>3</sub>), 3.77 (d, 1H, CH<sub>a</sub>Cl,  $^2J_{\text{H-H}} = 13.1$  Hz), 3.90 (d, 1H, CH<sub>b</sub>Cl), 4.10 (brs, 2H, CH<sub>2</sub>O), 4.38 (brs, 1H, OH), 6.40 (s, 1H, CHS), 7.30-7.60 (m, 4H, ArH); and (*R*<sub>S</sub>)-(E)-4 (28 mg, 28% yield):  $R_f$  0.25;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.40 (s, 3H, ArCH<sub>3</sub>), 3.20 (brs, 1H, OH), 4.32 (d, 2H, CH<sub>2</sub>O,  $^4J_{\text{H-H}} = 1.6$  Hz), 4.33 (d, 1H, CH<sub>a</sub>Cl,  $^2J_{\text{H-H}} = 11.5$  Hz), 4.70 (d, 1H, CH<sub>b</sub>Cl), 6.49 (t, 1H, CHS,  $^4J_{\text{H-H}} = 1.6$  Hz), 7.30-7.60 (m, 4H, ArH).

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-chloro-2-[[4-(methylphenyl)sulfinyl]methyl]-propan-2-ol 5.** To a suspension of  $\text{LiAlH}_4$  (40 mg, 1.05 mmol) in THF (5 ml) at  $-70^{\circ}\text{C}$  under nitrogen atmosphere, a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in THF (5 ml) was added dropwise at the same temperature. After 2.5 hours at  $-70^{\circ}\text{C}$ , the reaction was carried out overnight at room temperature, then quenched with a saturated  $\text{NH}_4\text{Cl}$  aqueous solution (2 ml), pH was adjusted to 2 by adding a diluted aqueous HCl solution and the organic phases were extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was purified by flash chromatography (chloroform/ethyl acetate 9 : 1) to give (2*R*,*R*<sub>S</sub>)-5 (100 mg, 50% yield):  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} + 212.0$  (c 1.0,  $\text{CHCl}_3$ ); m.p.  $78-79^{\circ}\text{C}$  (isopropylether);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 1.4 (s, 3H, CH<sub>3</sub>), 2.42 (s, 3H, ArCH<sub>3</sub>), 2.96 (dd, 1H, CH<sub>a</sub>S,  $^2J_{\text{H-H}} = 13.2$ ,  $^4J_{\text{H-H}} = 1.2$  Hz); 3.05 (d, 1H, CH<sub>b</sub>S), 3.66 (dd, 1H, CH<sub>a</sub>Cl,  $^2J_{\text{H-H}} = 11.4$ ,  $^4J_{\text{H-H}} = 1.2$  Hz), 4.00 (d, 1H, CH<sub>b</sub>Cl), 5.58 (s, 1 OH), 7.30-7.60 (m, 4H, ArH); Mass (C.I., %): 245 ( $\text{M}^+$ , 100), 139 ( $\text{p.TolSO}^+$ , 20); HRMS: Found 246.0603; calculated for  $\text{C}_{11}\text{H}_{15}\text{O}_2\text{S}^{35}\text{Cl}$  246.0477.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-bromo-3-chloro-2-[[4-(methylphenyl)sulfinyl]methyl]-propan-2-ol 6.** A suspension of  $\text{CuBr}_2$  (146 mg, 0.65 mmol) and LiBr (113 mg, 1.31 mmol) in THF (5 ml) was cooled at  $0^{\circ}\text{C}$  and stirred up to green colour. After 2 min., the temperature was fast increased up to room temperature and a solution of (2*R*,*R*<sub>S</sub>)-2 (100 mg, 0.41 mmol) was added dropwise in 3 min. After 30 min., the reaction was quenched with a 5% aqueous  $\text{Na}_2\text{HPO}_4$  solution (2 ml, pH = 7), the organic phases were extracted with ethyl acetate (3 x 10 ml), dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/ethyl acetate 3 : 2) to give (2*R*,*R*<sub>S</sub>)-6 in 79% yield:  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} + 219.0$  (c 1.0,  $\text{CHCl}_3$ ); m.p.  $90-91^{\circ}\text{C}$  (isopropylether);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.45 (s, 3H, ArCH<sub>3</sub>), 3.07 (d, 1H, CH<sub>a</sub>S,  $^2J_{\text{H-H}} = 13.5$  Hz); 3.15 (dd, 1H, CH<sub>b</sub>S,  $^4J_{\text{H-H}} = 1.25$  Hz), 3.64 (d, 1H, CH<sub>a</sub>Cl,  $^2J_{\text{H-H}} = 11.0$  Hz), 3.70 (d, 1H, CH<sub>b</sub>Cl), 3.93 (dd, 1H, CH<sub>a</sub>Br,  $^2J_{\text{H-H}} = 11.8$  Hz,  $^4J_{\text{H-H}} = 1.25$  Hz), 4.02

(d, 1H, CH<sub>2</sub>Br), 4.75 (s, 1H, OH), 7.34-7.60 (m, 4H, ArH); Mass (C.I., %): 325 (M<sup>+</sup>, 100), 246 (M<sup>+</sup>-Br, 40), 139 (*p*.TolSO<sup>+</sup>, 10); HRMS: Found 323.9557; calculated for C<sub>11</sub> H<sub>14</sub> O<sub>2</sub> S<sup>35</sup> ClBr<sup>79</sup> 323.9583.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-azido-3-chloro-2-([4-(methylphenyl)sulfinyl]methyl)-propan-2-ol 7.** To a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in anhydrous ethanol (5 ml) stirred at room temperature under nitrogen, a solution of NaN<sub>3</sub> (63.6 mg, 0.98 mmol) and NH<sub>4</sub>Cl (45.2 mg, 0.82 mmol) in the same solvent (2 ml) was added dropwise. After 24 hours, the solvent was evaporated and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 1 : 1) to give (2*R*,*R*<sub>S</sub>)-7 (173 mg, 73.6% yield): R<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 300.1 (c 1.5, CHCl<sub>3</sub>); m.p. 90-91°C (*n*-hexane/ethyl acetate 1 : 1); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 2.45 (s, 3H, ArCH<sub>3</sub>), 2.98 (d, 1H, CH<sub>2</sub>S, <sup>2</sup>J<sub>H-H</sub> = 13.0 Hz); 3.10 (dd, 1H, CH<sub>2</sub>S, <sup>4</sup>J<sub>H-H</sub> = 1.2 Hz), 3.47 (s, 2H, CH<sub>2</sub>N), 3.83 (dd, 1H, CH<sub>2</sub>Cl, <sup>2</sup>J<sub>H-H</sub> = 11.5 Hz, <sup>4</sup>J<sub>H-H</sub> = 1.2 Hz), 4.00 (d, 1H, CH<sub>2</sub>Cl), 4.92 (s, 1H, OH), 7.30-7.60 (m, 4H, ArH); IR (nujol) ν (cm<sup>-1</sup>): 3300 (ν<sub>O-H</sub>), 2100 (ν<sub>N<sub>3</sub></sub>), 1050, 805; Mass (C.I., %): 288 (M<sup>+</sup>, 100), 139 (*p*.TolSO<sup>+</sup>, 40); HRMS: [M-OH]<sup>+</sup> Found 270.0473; calculated for C<sub>11</sub> H<sub>13</sub> O<sub>2</sub> S<sup>35</sup> ClN<sub>3</sub> 270.0465.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-*N*-(benzyl)amino-3-chloro-2-([4-(methylphenyl)sulfinyl]methyl)-propan-2-ol 8.** To a solution of (2*R*,*R*<sub>S</sub>)-2 (100 mg, 0.41 mmol) in anhydrous THF (0.8 ml), neat benzylamine (67 μl, 0.61 mmol) was added and stirring under nitrogen at room temperature was continued for 24 hours. Then THF was evaporated and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 3 : 7) to give (2*R*,*R*<sub>S</sub>)-8 (143 mg, 88% yield): R<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 149.3 (c 1.2, CHCl<sub>3</sub>); m.p. 87.5-88.5°C (isopropylether); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 2.40 (s, 3H, ArCH<sub>3</sub>), 2.80 (d, 1H, CH<sub>2</sub>N, <sup>2</sup>J<sub>H-H</sub> = 12.4 Hz), 2.90 (d, 1H, CH<sub>2</sub>N), 2.88 (d, 1H, CH<sub>2</sub>S, <sup>2</sup>J<sub>H-H</sub> = 13.9 Hz); 3.10 (d, 1H, CH<sub>2</sub>S), 3.68 (d, 1H, CH<sub>2</sub>Cl, <sup>2</sup>J<sub>H-H</sub> = 13.9 Hz), 3.77 (d, 1H, CH<sub>2</sub>Cl), 7.20-7.60 (m, 9H, ArH); IR (KBr) ν (cm<sup>-1</sup>): 3290, 1454, 1019, 1001, 890, 741; Mass (C.I., %): 245 (M<sup>+</sup>-C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>NH<sub>2</sub>, 100), 139 (*p*.TolSO<sup>+</sup>, 40); HRMS: [M-OH]<sup>+</sup> Found 334.1069; calculated for C<sub>18</sub> H<sub>21</sub> O S<sup>35</sup> ClN 334.1072.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-*N*-(dibenzyl)amino-3-chloro-2-([4-(methylphenyl)sulfinyl]methyl)-propan-2-ol 9.** To a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in anhydrous THF (4 ml), neat dibenzylamine (0.31 ml, 1.63 mmol) was added and stirring under nitrogen at room temperature was continued for two weeks. Then THF was evaporated and the residue was purified by flash chromatography (petroleum ether/ethyl acetate 7 : 3) to give (2*R*,*R*<sub>S</sub>)-9 (173 mg, 48% yield): R<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 96.0 (c 1.1, CHCl<sub>3</sub>); m.p. 139-141°C (*n*-hexane/ethyl acetate 1 : 1); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 2.43 (s, 3H, ArCH<sub>3</sub>), 2.55 (d, 1H, CH<sub>2</sub>N, <sup>2</sup>J<sub>H-H</sub> = 14.0 Hz), 2.78 (d, 1H, CH<sub>2</sub>S, <sup>2</sup>J<sub>H-H</sub> = 14.4 Hz), 3.00 (d, 1H, CH<sub>2</sub>N), 3.08 (d, 1H, CH<sub>2</sub>S), 3.60 (d, 1H, CH<sub>2</sub>Cl, <sup>2</sup>J<sub>H-H</sub> = 10.8 Hz), 3.65 (d, 1H, CH<sub>2</sub>Ar, <sup>2</sup>J<sub>H-H</sub> = 13.2 Hz), 3.74 (d, 1H, CH<sub>2</sub>Cl), 3.82 (d, 1H, CH<sub>2</sub>Ar), 4.60 (brs, 1H, OH), 7.15-7.50 (m, 14H, ArH); Mass (C.I., %): 442 (M<sup>+</sup>, 100), 406 (M<sup>+</sup>-HCl, 30), 139 (*p*.TolSO<sup>+</sup>, 30); HRMS: [M-OH]<sup>+</sup> Found 424.1471; calculated for C<sub>25</sub> H<sub>27</sub> O S<sup>35</sup> ClN 424.1495.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-chloro-2-([4-(methylphenyl)sulfinyl]methyl)-eptan-2-ol 10.** CuI (264 mg, 1.39 mmol) was suspended in anhydrous THF (7 ml) at -20°C, *n*-Buthyllithium (2.5 M solution in *n*-hexane, 1.1 ml, 2.78 mmol) was added dropwise by syringe. The solution became black and, after 15 min., the temperature was decreased to -70°C and a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in the same solvent (7 ml) was added dropwise. Temperature was allowed to raise up to -20°C in 2.5 hours. Then the reaction was quenched by adding a saturated NH<sub>4</sub>Cl aqueous solution, the organic layers were extracted with ethyl acetate (3 x 10 ml), dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give a residue that was purified by flash chromatography (*n*-hexane/ethyl acetate 3 : 2) to give (2*R*,*R*<sub>S</sub>)-10 (197 mg, 79.5% yield): R<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 186.0 (c 1.0, CHCl<sub>3</sub>); m.p. 89-90°C (ethyl ether); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 0.89 (t, 3H, CH<sub>3</sub>CH<sub>2</sub>, <sup>3</sup>J<sub>H-H</sub> = 5.7 Hz), 1.20-1.70 (m, 8H, CH<sub>2</sub>), 2.43 (s, 3H, ArCH<sub>3</sub>), 3.00 (s, 2H, CH<sub>2</sub>S),

3.73 (d, 1H,  $\text{CH}_2\text{Cl}$ ,  $^2J_{\text{H-H}} = 11.5$  Hz), 4.00 (d, 1H,  $\text{CH}_2\text{Cl}$ ), 4.58 (s, 1H, OH), 7.30-7.60 (m, 4H, ArH); HRMS:  $[\text{M-OH}]^+$  Found 285.1088; calculated for  $\text{C}_{15}\text{H}_{22}\text{O S}^{35}\text{Cl}$  285.1074.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-chloro-2-[[4-(methylphenyl)sulfinyl]methyl]-hex-5-en-2-ol 11.** Allyl-magnesium chloride (2.0 M solution in THF, 0.5 ml, 0.98 mmol) was diluted in anhydrous THF (2 ml) at 5°C and a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in the same solvent (2 ml) was added dropwise at the same temperature. After 15 min., a saturated  $\text{NH}_4\text{Cl}$  aqueous solution was added dropwise and pH was adjusted to 3 by adding some drops of aqueous hydrochloric acid. The organic layers were extracted with ethyl acetate (3 x 5 ml), dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give a residue that was purified by flash chromatography (petroleum ether/ethyl acetate 4 : 1) to give (2*R*,*R*<sub>S</sub>)-11 (178 mg, 75.6% yield):  $R_f$  0.25;  $[\alpha]_{\text{D}}^{20} + 196.0$  (c 1.0,  $\text{CHCl}_3$ ); m.p. 93-94°C (isopropylether);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  : 1.80 (t, 2H,  $\text{C}(\text{OH})\text{CH}_2\text{C}$ ,  $^3J_{\text{H-H}} = 8.0$  Hz), 2.10-2.30 (m, 2H,  $\text{CH}_2\text{C}=\text{CH}_2$ ), 2.45 (s, 3H,  $\text{ArCH}_3$ ), 3.00 (s, 2H,  $\text{CH}_2\text{S}$ ), 3.73 (d, 1H,  $\text{CH}_2\text{Cl}$ ,  $^2J_{\text{H-H}} = 12.0$  Hz), 4.04 (d, 1H,  $\text{CH}_2\text{Cl}$ ), 4.70 (s, 1H, OH), 4.92-5.10 (m, 2H,  $\text{CH}=\text{CH}_2$ ), 5.62-5.90 (m, 1H,  $\text{CH}=\text{CH}_2$ ), 7.30-7.60 (m, 4H, ArH); HRMS: Found 286.0793; calculated for  $\text{C}_{14}\text{H}_{19}\text{O}_2\text{S}^{35}\text{Cl}$  286.0789.

**Reaction of (2*R*,*R*<sub>S</sub>)-2 with methyl magnesium chloride.** To a solution of methyl magnesium chloride (22% solution in THF, 0.33 ml, 0.98 mmol) in anhydrous THF (1 ml) at 5°C, a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in the same solvent (4 ml) was added dropwise at the same temperature. The solution became yellow and, after 30 min., the reaction was quenched as described above. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 2 : 3) to give (*R*<sub>S</sub>)-1,3-dichloro-2-[[4-(methylphenyl)sulfinyl]methyl]-propan-2-ol 12 (177 mg, 88.2% yield):  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} + 170.4$  (c 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  : 2.43 (s, 3H,  $\text{ArCH}_3$ ), 3.03 (d, 1H,  $\text{CH}_2\text{S}$ ,  $^2J_{\text{H-H}} = 13.6$  Hz), 3.12 (d, 1H,  $\text{CH}_2\text{S}$ ), 3.74 (d, 1H,  $\text{CH}_2\text{Cl}$ ,  $^2J_{\text{H-H}} = 10.6$  Hz), 3.84 (d, 1H,  $\text{CH}_2\text{Cl}$ ), 3.88 (d, 1H,  $\text{CH}_2\text{Cl}$ ,  $^2J_{\text{H-H}} = 10.6$  Hz), 4.00 (d, 1H,  $\text{CH}_2\text{Cl}$ ), 5.73 (brs, 1H, OH), 7.35-7.60 (m, 4H, ArH); HRMS: Found 280.00516; calculated for  $\text{C}_{11}\text{H}_{14}\text{O}_2\text{S}^{35}\text{Cl}$  280.00877. along with (*E/Z*)-2-chloromethyl-1-[4-(methylphenyl)sulfinyl]-prop-1-en-3-ol 4 (20 mg, 10% yield):  $R_f$  0.20;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  : 2.40 (s, 3H,  $\text{ArCH}_3$ ), 3.00 (m, 1H, OH), 3.80 (d, 1H,  $\text{CH}_2\text{OH}$ ,  $^2J_{\text{H-H}} = 12.0$  Hz), 4.10 (d, 1H,  $\text{CH}_2\text{OH}$ ), 4.12 (s, 2H,  $\text{CH}_2\text{Cl}$ ), 3.84 (d, 1H,  $\text{CH}_2\text{Cl}$ ), 6.38 (s, 1H, CHS), 7.30-7.60 (m, 4H, ArH).

**Reaction of (2*R*,*R*<sub>S</sub>)-2 with potassium cyanide.** KCN (98 mg, 1.53 mmol) was suspended in anhydrous  $\text{CH}_3\text{CN}$  (2 ml) at 50-55°C. Neat  $\text{LiClO}_4$  (162.7 mg, 1.53 mmol) was added and, after 10 min., a solution of (2*R*,*R*<sub>S</sub>)-2 (250 mg, 1.02 mmol) in the same solvent (2 ml) was added dropwise. Temperature was allowed to raise up to 60°C in 0.5 hours and the colour of the solution became brown. After 1.5 hours, the starting material disappeared: the solvent was evaporated to half the volume, washed with water and extracted with ethyl acetate (3 x 10 ml). After the usual procedures, the residue was purified by flash chromatography (chloroform/ethyl acetate 7 : 3) to give (*R*<sub>S</sub>)-3-[[4-(methylphenyl)sulfinyl]methyl]-3-hydroxy-pentan-1,5-dinitrile 13 (65 mg, 23% yield):  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} + 214.0$  (c 0.9,  $\text{CHCl}_3$ ); m.p. 135-136°C (*n*-hexane/ethyl acetate 1 : 1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  : 2.45 (s, 3H,  $\text{ArCH}_3$ ), 2.88 (d, 1H,  $\text{CH}_2\text{S}$ ,  $^2J_{\text{H-H}} = 17.0$  Hz), 2.95 (d, 1H,  $\text{CH}_2\text{S}$ ), 3.06 (d, 1H,  $\text{CH}_2\text{CN}$ ,  $^2J_{\text{H-H}} = 13.5$  Hz), 3.07 (d, 1H,  $\text{CH}_2\text{CN}$ ,  $^2J_{\text{H-H}} = 17.0$  Hz), 3.19 (d, 1H,  $\text{CH}_2\text{CN}$ ), 3.21 (d, 1H,  $\text{CH}_2\text{CN}$ ), 5.50 (s, 1H, OH), 7.35-7.60 (m, 4H, ArH); IR (nujol)  $\nu$  ( $\text{cm}^{-1}$ ): 3200 ( $\nu_{\text{O-H}}$ ), 2240 ( $\nu_{\text{C-N}}$ ), 1600, 1495, 810; Mass (C.I., %): 263 ( $\text{M}^+ + 1$ , 100), 247 ( $\text{M}^+ - \text{CN}$ , 15), 139 (*p*. TolSO<sup>+</sup>, 18), 92 ( $\text{C}_7\text{H}_8^+$ , 15); HRMS: Found 262.1479; calculated for  $\text{C}_{13}\text{H}_{14}\text{O}_2\text{S}^{35}\text{N}_2$  262.0773.

**Reaction of (2*R*,*R*<sub>S</sub>)-2 with trimethylsilylcyanide.** To a solution of (2*R*,*R*<sub>S</sub>)-2 (200 mg, 0.82 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3 ml) stirred at room temperature under nitrogen, neat trimethylsilylcyanide (98%, 0.1 ml,

0.822 mmol) was added dropwise by syringe. No reaction occurred in 45 min.:  $\text{BF}_3 \cdot \text{OEt}_2$  (five drops) was added by syringe and no reaction occurred in 20 min.  $\text{BF}_3 \cdot \text{OEt}_2$  was added again following the same procedure up to the stoichiometric amount (50% solution, 0.2 ml, 0.82 mmol,) and the solution became brown. After 2 hours at room temperature, all starting epoxide disappeared, the reaction was quenched by adding phosphoric buffered solution ( $\text{pH} = 8$ ) and the organic layers were extracted with methylene chloride ( $3 \times 10$  ml), dried over anhydrous sodium sulfate and evaporated to give a residue that, upon flash chromatographic purification (chloroform / ethyl acetate 3 : 2) gave: (*R*<sub>S</sub>)-1-chloro-3-[4-(methylphenyl)sulfinyl]-propan-2-one **1** (73 mg, 33% yield), whose  $[\alpha]_{\text{D}}^{20}$  value was identical and whose  $^1\text{H}$  NMR, IR and Mass spectra were overimposable to those of the above described ketone **1** obtained by condensation of methyl-*p*-tolylsulfoxide with ethyl chloroacetate.

**Synthesis of (2*R*)-2-chloromethyl-2-formyl-oxirane 15.** To a solution of (2*R*,*R*<sub>S</sub>)-**2** (630 mg, 2.57 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (7 ml) neat *sym*.collidine (0.75 ml, 5.65 mmol) was added and the solution was cooled at  $-25^\circ\text{C}$ . A solution of trifluoroacetic anhydride (1.05 ml, 5.14 mmol) in the same solvent (2 ml) was added dropwise. The solution became yellow and the temperature was kept at  $-20^\circ\text{C}$  for 20 min. Then, the solution was allowed to reach room temperature and stirring was continued for 10 min. Neat  $\text{K}_2\text{CO}_3$  was added up to  $\text{pH} = 7$  and a suspension of  $\text{HgCl}_2$  (1.05 g, 3.85 mmol) in  $\text{CH}_3\text{CN}$  (3 ml) was added portionwise. A white precipitate formed and stirring was continued for 3 hours at room temperature. Then, the white solid was filtered off on celite pad, the clear pale yellow solution was concentrated and the residue was purified by flash chromatography (chloroform / ethyl acetate 9 : 1) to give (2*R*)-**15** (247 mg, 79.4% yield):  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} + 9.13$  (c 2.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 3.22 (d, 1H,  $\text{CH}_a\text{O}$ ,  $^2J_{\text{H-H}} = 4.6$  Hz), 3.30 (d, 1H,  $\text{CH}_b\text{O}$ ), 3.80 (d, 1H,  $\text{CH}_a\text{Cl}$ ,  $^2J_{\text{H-H}} = 13.2$  Hz), 3.95 (d, 1H,  $\text{CH}_b\text{Cl}$ ), 8.98 (s, 1H, CHO); HRMS: Found 119.9970; calculated for  $\text{C}_4\text{H}_5\text{O}_2\text{Cl}$  119.9976.

**Synthesis of (S)-2-chloromethyl-2-hydroxymethyl oxirane 16.** To a solution of (*R*)-**15** (200 mg, 1.65 mmol) in  $\text{CH}_3\text{CN}$  (3 ml) at  $0^\circ\text{C}$ , a suspension of  $\text{NaBH}_4$  (125 mg, 3.3 mmol) in  $\text{CH}_3\text{CN} / \text{H}_2\text{O}$  10 : 1 (2.2 ml) was added portionwise. After 20 min., the solvent was evaporated and the residue was purified by flash chromatography (chloroform / ethyl acetate 1 : 1) to give (2*S*)-**16** (181 mg, 89% yield):  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} - 22.8$  (c 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 2.86 (d, 1H,  $\text{CH}_a\text{O}$ ,  $^2J_{\text{H-H}} = 4.7$  Hz), 3.05 (dd, 1H,  $\text{CH}_b\text{O}$ ,  $^4J_{\text{H-H}} = 1.0$  Hz), 3.52 (d, 1H,  $\text{CH}_a\text{Cl}$ ,  $^2J_{\text{H-H}} = 11.7$  Hz), 3.78 (dd, 1H,  $\text{CH}_b\text{Cl}$ ,  $^4J_{\text{H-H}} = 1.0$  Hz), 3.80 (brd, 1H,  $\text{CH}_a\text{OH}$ ,  $^2J_{\text{H-H}} = 12.6$  Hz), 3.98 (brd, 1H,  $\text{CH}_b\text{OH}$ ).

**Synthesis of (R)-2-carboxy-2-chloromethyl oxirane 17.** To a solution of (*R*)-**15** (200 mg, 1.65 mmol) in  $\text{CH}_3\text{CN}$  (3 ml) at  $-10^\circ\text{C}$ , neat *tert*.buthanol (2.2 ml) and 2-methyl-2-butene (1.8 ml) were added. A solution of  $\text{NaClO}_2$  (222 mg, 2.48 mmol) and  $\text{KH}_2\text{PO}_4$  (506 mg, 3.80 mmol) in  $\text{H}_2\text{O}$  (2 ml) was added dropwise at the same temperature. Then, the reaction mixture was allowed to reach room temperature and the colour of the solution became pale yellow. After 1.5 hours under stirring, sodium citrate buffered solution ( $\text{pH} = 5$ ) was added (2 ml), then water (3 ml) and the organic layers were extracted with ethyl ether ( $3 \times 3$  ml), dried over anhydrous sodium sulfate and evaporated to give a residue that was purified by flash chromatography (*n*-hexane / ethyl acetate / acetic acid 1 : 4 : 0.1) to give (2*R*)-**17** (192 mg, 85% yield):  $R_f$  0.35;  $[\alpha]_{\text{D}}^{20} + 9.4$  (c 0.4,  $\text{CHCl}_3$ ); m.p.  $40\text{--}42^\circ\text{C}$  (ethyl ether);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$ : 3.14 (d, 1H,  $\text{CH}_a\text{O}$ ,  $^2J_{\text{H-H}} = 5.6$  Hz), 3.28 (d, 1H,  $\text{CH}_b\text{O}$ ), 3.72 (d, 1H,  $\text{CH}_a\text{Cl}$ ,  $^2J_{\text{H-H}} = 12.2$  Hz), 4.12 (d, 1H,  $\text{CH}_b\text{Cl}$ ), 10.88 (brs, 1H, COOH); IR (film)  $\nu$  ( $\text{cm}^{-1}$ ): 2920, 1745 ( $\nu\text{C=O}$ ), 1430, 1270, 1199, 921, 760; Mass (EI/*m/z*): 136 ( $\text{M}^+ - 1$ ), 118 ( $\text{M}^+ - \text{H}_2\text{O}$ ), 106 ( $\text{M}^+ - \text{HCHO}$ ), 92 ( $\text{M}^+ - \text{CO}_2$ ), 83 ( $\text{M}^+ - 1 - \text{CH}_3\text{Cl}$ ).

**Synthesis of (2*R*,*R*<sub>S</sub>)-3-chloro-2-[[4-(methylphenyl)sulfinyl]methyl]-propan-1,2-diol 18.** (2*R*,*R*<sub>S</sub>)-**2** (100 mg, 0.41 mmol) was dissolved in a THF/H<sub>2</sub>O 1 : 1 solution (2 ml) and HClO<sub>4</sub> (70%, 180 µl) was added at room temperature. After two days at the same temperature, the reaction was quenched with an aqueous NaHCO<sub>3</sub> saturated solution (up to pH 7), the organic phase was extracted with ethyl acetate (2 x 15 ml), washed with water (5 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate 1 : 4) to give (2*R*,*R*<sub>S</sub>)-**18** in 70% yield: *R*<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 194.6 (c 0.3, CHCl<sub>3</sub>); m.p. 112–113°C (isopropylether); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 2.44 (s, 3H, ArCH<sub>3</sub>), 2.98 (d, 1H, CH<sub>a</sub>S, <sup>2</sup>*J*<sub>H-H</sub> = 13.8 Hz); 3.15 (d, 1H, CH<sub>b</sub>S), 3.42 (brt, 1H, CH<sub>2</sub>OH), 3.70 (d, 1H, CH<sub>a</sub>Cl, <sup>2</sup>*J*<sub>H-H</sub> = 11.4 Hz), 3.75 (brd, 2H, CH<sub>2</sub>OH, <sup>3</sup>*J*<sub>H-H</sub> = 7.0 Hz), 3.83 (d, 1H, CH<sub>b</sub>Cl), 7.30–7.60 (m, 4H, ArH); <sup>1</sup>H NMR (CDCl<sub>3</sub> + D<sub>2</sub>O), δ: 2.44 (s, 3H, ArCH<sub>3</sub>), 2.98 (d, 1H, CH<sub>a</sub>S, <sup>2</sup>*J*<sub>H-H</sub> = 13.8 Hz); 3.15 (d, 1H, CH<sub>b</sub>S), 3.70 (d, 1H, CH<sub>a</sub>Cl, <sup>2</sup>*J*<sub>H-H</sub> = 11.4 Hz), 3.75 (s, 2H, CH<sub>2</sub>OH), 3.83 (d, 1H, CH<sub>b</sub>Cl), 7.30–7.60 (m, 4H, ArH); Mass (C.I., %): 263 (M<sup>+</sup>, 100), 245 (M<sup>+</sup>–H<sub>2</sub>O, 20), 139 (*p*.TolSO<sup>+</sup>, 80); HRMS: Found 262.0384; calculated for C<sub>11</sub> H<sub>15</sub> O<sub>3</sub> S<sup>35</sup> Cl 262.0426.

**Synthesis of (2*R*,*R*<sub>S</sub>)-1-chloro-2-[[4-(methylphenyl)sulfinyl]methyl]-3-*O*-benzoyl-2,3-propan-diol 19.** To a solution of (2*R*,*R*<sub>S</sub>)-**18** (30 mg, 0.114 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) stirred at r.t., neat DCC (25 mg, 0.125 mmol) and benzoic acid (15.2 mg, 0.125 mmol) were added. After 5 min., neat dimethylaminopyridine (1.4 mg, 0.011 mmol) was added. A white precipitate immediately formed and, after 10 min., white dicyclohexylurea was filtered off, the volume of the collected solution reduced under vacuum and the resulting solution was poured into a flash chromatography column. Elution with *n*-hexane / ethyl acetate 1 : 1 allowed the obtainment of (2*R*,*R*<sub>S</sub>)-**19** (38 mg, 90% yield): *R*<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 137.6 (c 0.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 2.45 (s, 3H, ArCH<sub>3</sub>), 3.16 (s, 2H, CH<sub>2</sub>S), 3.96 (d, 1H, CH<sub>a</sub>Cl, <sup>2</sup>*J*<sub>H-H</sub> = 11.8 Hz), 4.09 (d, 1H, CH<sub>b</sub>Cl), 4.45 (d, 1H, CH<sub>a</sub>O, <sup>2</sup>*J*<sub>H-H</sub> = 11.7 Hz), 4.59 (d, 1H, CH<sub>b</sub>O), 4.94 (s, 1H, OH); 7.34–8.10 (m, 9H, ArH); HRMS: Found 366.07085; calculated for C<sub>18</sub> H<sub>19</sub> O<sub>4</sub> S<sup>35</sup> Cl 366.06872.

**Synthesis of (2*S*,*R*<sub>S</sub>)-19.** To a suspension of CuCl<sub>2</sub> (33.1 mg, 0.25 mmol) in THF (0.3 ml) stirred at 0°C, neat LiCl (20.5 mg, 0.50 mmol) was added. The colour of the slurry became orange. Temperature was allowed to reach 25°C (r.t.) and a solution of (2*S*,*R*<sub>S</sub>)-2-benzyloxymethyl-2-[[4-(methylphenyl)sulfinyl]methyl]oxirane **20** (50 mg, 0.16 mmol) in THF (0.3 ml) was added dropwise. After 5 min., the solution became yellow and the reaction was complete in 2 hours. A 5% solution of Na<sub>2</sub>HPO<sub>4</sub> (2 ml) was added (pH = 7), the organic layers were extracted with ethyl acetate (3 x 1 ml), dried over anhydrous sodium sulfate and evaporated to give a residue that was purified by flash chromatography (chloroform / ethyl acetate 7 : 3) to give (2*S*,*R*<sub>S</sub>)-**19** (54 mg, 96% yield): *R*<sub>f</sub> 0.35; [α]<sub>D</sub><sup>20</sup> + 128.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ: 2.42 (s, 3H, ArCH<sub>3</sub>), 3.02 (d, 1H, CH<sub>a</sub>S, <sup>2</sup>*J*<sub>H-H</sub> = 13.7 Hz), 3.16 (d, 1H, CH<sub>b</sub>S), 3.70 (d, 1H, CH<sub>a</sub>Cl, <sup>2</sup>*J*<sub>H-H</sub> = 11.6 Hz), 3.84 (d, 1H, CH<sub>b</sub>Cl), 4.64 (d, 1H, CH<sub>a</sub>O, <sup>2</sup>*J*<sub>H-H</sub> = 11.8 Hz), 4.69 (d, 1H, CH<sub>b</sub>O), 4.80 (s, 1H, OH); 7.30–8.10 (m, 9H, ArH).

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