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Stereochemistry of Nucleophilic Epoxidation of (S)-2-*p*-Tolylsulfonyl-2-cyclohexenol and O-Derivatives.

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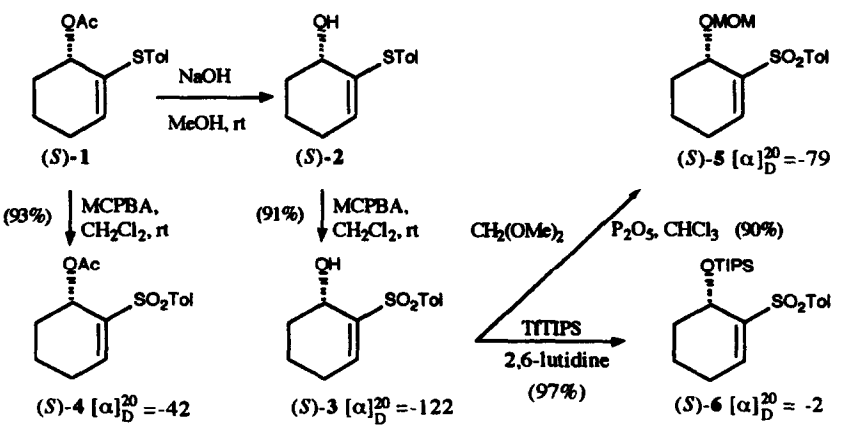
Abstract: Epoxidation of 2-*p*-tolylsulfonyl-2-cyclohexenol **3** and its OAc (**4**) and OMOM (**5**) derivatives with LiOO*t*-Bu and $NaOOH/H_2O$ proceeds with high stereoselectivity to give the *syn* epoxy alcohols **7-9**. The O-triisopropylsilyl derivative (OTIPS, **6**) evolves into a 63:37 mixture of *syn:anti* epoxides. A rationalization of these results, based on the conformational preferences of the starting substrates, is proposed.

Vinyl sulfones have been widely used as building blocks in synthetic organic chemistry.[1] The utility of these substrates as starting materials to synthesize highly functionalized systems has been explored in cyclic[1a,2] and acyclic[3] vinyl sulfones. Whereas many results have been published about Michael additions to γ-oxygenated α,ß-unsaturated sulfones,[1a,2,4,5] less work has been made on the α-hydroxyalkyl vinylsulfones, despite their potential synthetic interest. With respect to the nucleophilic epoxidation of these substrates, to our knowledge, only one example, concerning acyclic vinylsulfones, has been recently reported.[6] The synthetic utility of these reactions, derived from their high stereoselectivity, make the study of the corresponding cyclic sulfones of great interest. We describe hereby the results obtained in the epoxidation of the chiral 2-*p*-tolylsulfonyl-2-cyclohexenol **3** and of its O-derivatives **4-6** (Scheme 1) with two different nucleophilic epoxidation reagents, LiOO*t*-Bu/THF and $NaOOH/H_2O$.

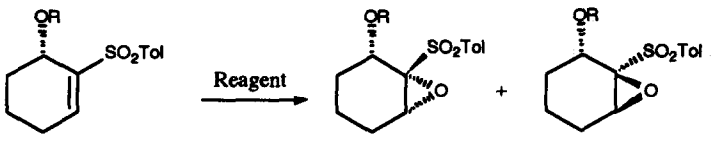


Scheme 1

Vinyl sulfones **3-6** are readily available from 2-*p*-tolylthiocyclohexenyl acetate **1**[7,8] (it can be obtained as (R) and (S) enantiomers, but in Scheme 1, only the (S) one has been represented). Thus, the MCPBA oxidation of **1** and **2** (obtained from **1** by basic hydrolysis) yielded the corresponding sulfones **4** and **3**. Reactions of **3** with $CH_2(OMe)_2/P_2O_5$ and with triisopropylsilyl trifluoromethanesulfonate/lutidine afforded **5** or **6** respectively.[9]

The results obtained in the nucleophilic epoxidation of compounds **3-6** with LiOO*t*-Bu/THF at room temperature or $NaOOH/H_2O$ in acetone at 45-50°C, are collected in Table 1. The *syn*-epoxides **7-10** are the only diastereomers detected except in the case of the reaction of **6** with LiOO*t*-Bu/THF (entry 4), which yields a 63:37 mixture of the **10**-*syn*:**10**-*anti* oxiranes.[10] It is of interest to point out that the reactivity decreases by introducing protecting groups.Compound **3** was shown to be the most reactive. This effect is more evident when the $NaOOH/H_2O$ is used as nucleophile which is much less reactive (mainly due to the solvent). In these conditions, the conversion of the O-acetyl (**4**) and O-TIPS (**6**) derivatives is very low and even after 13 hours c.a.70% of starting material was recovered (see reaction times, entries 6 and 8). The composition of these reaction mixtures (^{1}H-NMR) also indicated the presence of hydroxy-epoxide **7**-*syn* resulting from direct epoxidation of **4** or **6**, or from deprotection to **3** and further epoxidation. The optical purity of epoxyalcohol (S)-**7**-*syn* was determined as 98% ee by ^{1}H-NMR [Pr(hfc)$_3$].

Table 1: Epoxidation of cyclohexenylsulfones **3-6** with LiOO*t*-Bu/THF and $NaOOH/H_2O$



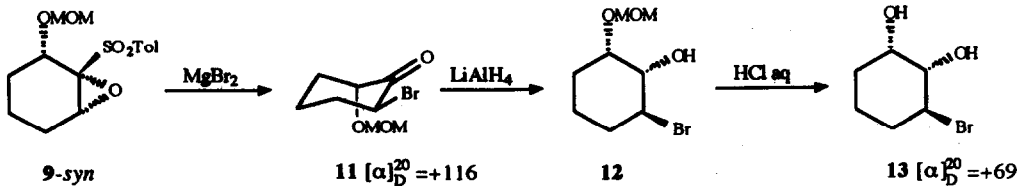
syn *anti*

Entry	Substrate	Reagent[a,b]			Yield (%)
1	**3** (R=H)	A (2h)	**7**-*syn*		72
2	**4** (R=Ac)	A (4h)	**8**-*syn*		52
3	**5** (R=MOM)	A (4h)	**9**-*syn*		65
4	**6** (R=TIPS)	A (4h)	**10**-*syn* (63%)	**10**-*anti* (37%)	66
5	**3** (R=H)	B (2h)	**7**-*syn*		70
6	**4** (R=Ac)	B (13h)	**7**-*syn*[c]		e
7	**5** (R=MOM)	B (4h)	**9**-*syn*		65
8	**6** (R=TIPS)	B (13h)	**10**-*syn*[d]		e

[a]A: LiOO*t*-Bu/THF, rt; B: H_2O_2/NaOH 2.2N/acetone, 45-50°C. [b]Reaction time in brackets. [c]Only epoxide **7**-*syn* was formed. [d]Significant amount of compound **7**-*syn* was also isolated. [e]A complex mixture was formed after 13h and c.a.70% of the starting material was recovered

The relative configuration of the resulting epoxides was assigned as follows. Compound **9**-*syn* was chemically correlated with the known bromocyclohexanediol **13**[11] (Scheme 2). The opening of **9**-*syn* with $MgBr_2$[12] produced compound **11** (68% yield) whose reduction with $LiAlH_4$ is highly stereoselective affording compound **12**. The exclusive axial attack of the hydride must be due to the axial arrangement of the O-MOM group.[13] The treatment of **12** with aqueous HCl gave **13**[14] diastereomerically pure (40% overall yield). The stereochemistry of **13** was unambiguosly established from its ^{1}H-NMR spectrum.[11]

Chemical correlations of **7**-*syn* with **9**-*syn* (**7**-*syn* reacts with $CH_2(OMe)_2/P_2O_5$ yielding **9**-*syn*), **8**-*syn* (which evolves into **7**-*syn* by hydrolysis with NaOH/MeOH) and **10**-*syn* (which yields **7**-*syn* by treatment with TBAF/THF) allowed us to establish the *syn*-stereochemistry of all these epoxides, and indirectly that of the compound **10**-*anti*, which was obtained in the reaction of **6** with LiOO*t*-Bu. Compound **7**-*anti* was obtained by reaction of **10**-*anti* with TBAF/THF at 0°C.

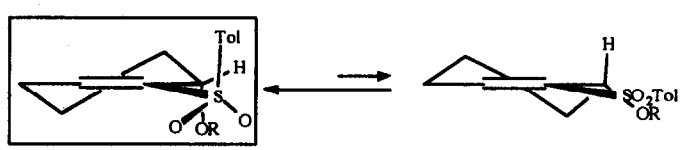


9-*syn* **11** $[\alpha]_D^{20}$ =+116 **12** **13** $[\alpha]_D^{20}$ =+69

Scheme 2

A comparison of our results with those reported by Jackson *et al* [6] on acyclic hydroxy sulfones indicates a similar or even higher diastereoselectivity in the formation of the cyclic substrates. Nevertheless, none of the explanations suggested by these authors to rationalize the stereoselectivity observed in the epoxidation of the free alcohols with LiOO*t*-Bu (coordination of the lithium atom with the oxygens at substrate and reagent, or hydrogen bond formation from the alcohol proton and the *t*-butylperoxide anion[6]) are consistent with our results. Thus, the fact that the stereoselectivity of the epoxidation of the free alcohol **3** with lithium *t*-butylperoxide was identical to those observed from its derivatives **4** and **5**, excludes the hydrogen bond formation as determining factor in the stereochemical control. Additionally, the similar results obtained in the reactions of **3** with LiOO*t*-Bu/THF and $NaOOH/H_2O$ allowed us to exclude the coordination of the lithium atom as the major directing influence.

The stereochemical outcome of the epoxidations of our substrates can be rationalized on the basis of the conformational behaviour of the starting cyclic vinyl sulfones. The most stable half-chair conformation must be that exhibits the oxygenated function in pseudoaxial arrangement (**A**), in order to avoid the strong torsional strain OR/SO_2Tol which destabilizes the **B** conformation (Scheme 3). The nucleophilic attack from the lower face in the **A** conformation must be favoured because it would yield a chair-like T.S., much more stable than the twist-like T.S. generated in the attack from the upper face.[15] There is another factor, concerning the conformational equilibrium around the C-S bond, which reinforces this tendency. Thus, the *p*-tolyl group, the bulkiest one around the sulfur atom, would mainly be oriented toward the upper face of the double bond, in order to minimize the steric interactions with the oxygenated function at C-1. This disposition prevents the approach of the reagent from the upper face and determines the favoured attack *syn* to the oxygenated function. The decrease of the stereoselectivity observed in the epoxidation of O-TIPS derivative **6** can be explained considering that this bulky substituent is hindering the attack from the lower face.



A **B**

Scheme 3

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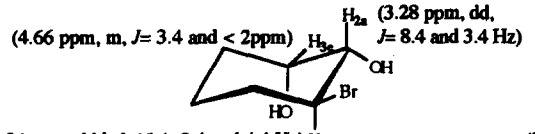
9.- All new compounds gave satisfactory analysis and spectral data. As a representative example, we indicate the ^{1}H-NMR data of **3** (200 MHz, $CDCl_3$): δ 7.77 and 7.34 (AA'BB' system, 4H, Tol); 7.15 (dd, 1H, *J*=2.7 and 4.9Hz, H_3); 4.31 (t, 1H, *J*=3.0Hz, H_1); 2.44 (s, 3H, CH_3); 2.48-1.39 (m, 6H).

10.- **7-*syn***: ^{1}H-NMR ($CDCl_3$) δ 7.82 and 7.37 (AA'BB' system, 4H, Tol); 4.78 (t, 1H, *J*=4.8Hz, H_1); 4.02 (dd, 1H, *J*=1.6 and 2.7Hz, H_3); 2.45 (s, 3H, CH_3); 2.17-1.29 (m, 6H).**8-*syn*** : ^{1}H-NMR ($CDCl_3$) δ 7.77 and 7.36 (AA'BB' system, 4H, Tol); 5.88 (t, 1H, *J*=5.0Hz, H_1); 4.15 (dd, 1H, *J*=1.6 and 2.8Hz, H_3); 2.45 (s, 3H, CH_3); 2.20-1.25 (m, 6H); 1.54 (s, 3H, CH_3-CO). **9-*syn***: ^{1}H-NMR ($CDCl_3$) δ 7.79 and 7.34 (AA'BB' system, 4H, Tol); 4.64 (t, 1H, *J*=5.8Hz, H_1); 4.54 and 4.31 (AB system, 2H, *J*=6.9Hz, $C\underline{H}_2$-OMe); 4.01 (dd, 1H, *J*=1.6 and 3.1Hz, H_3); 3.26 (s, 3H, OCH_3); 2.44 (s, 3H, CH_3); 2.02-1.25 (m, 6H). **10-*syn***: ^{1}H-NMR ($CDCl_3$) δ 7.81 and 7.31 (AA'BB' system, 4H, Tol); 5.08 (t, 1H, *J*=4.5Hz, H_1); 3.83 (dd, 1H, *J*=1.4 and 3.2Hz, H_3); 2.43 (s, 3H, CH_3); 2.10-0.80 (m, 6H); 1.10-0.90 (m, 21H); **10-*anti*** ^{1}H-NMR ($CDCl_3$) δ 7.77 and 7.31 (AA'BB' system, 4H, Tol); 4.90 (t, 1H, *J*=3.9 Hz, H_1); 3.27 (d, 1H, *J*=3.6Hz, H_3); 2.43 (s, 3H, CH_3); 2.10-0.80 (m, 6H); 1.20-1.10 (m, 21H).

11.- Although bromocyclohexanediol **13** is described in the literature, neither its NMR spectrum nor its $[\alpha]_D^{20}$ value was specified (see Alvarez A., Nuñez M.T. and Martín V.S., *J. Org. Chem.*, **1990**, *55*, 3429 and references cited therein). The stereochemical assignment had to be based in the the ^{1}H-NMR, mainly the multiplicity and *J* values of H-1, H-2 and H-3 signals shown below which are only consistent with this stereochemical arrangement. As can be seen, these parameters are very similar to those of its MOM precursor **12** and to those of 3-iodo-1,2-cyclohexanediol of the same relative configuration (see Bognini A., Cardillo G., Orena M., Porzi G. and Sandri S.; *J. Org. Chem.*, **1982**, *47*, 4626).



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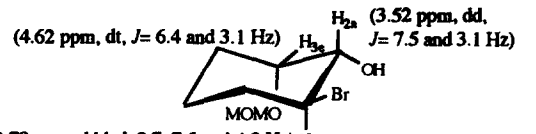

12

Taking into account the absolute (S)-configuration of C-1 in the 2-*p*-tolylthio cyclohexenol **2**, used as starting material, we could assign the (S1,S2,S3) configuration to the resulting bromocyclohexanediol **13** which could be thus obtained in enantiomerically pure form.

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14.- The same compound **13** was obtained in two steps from **7-*syn*** (reaction with $MgBr_2$ and further $LiAlH_4$ reduction) but the unstability of the intermediate 2-hydroxy-6-bromo cyclohexanone, that could not be isolated, determined an overall yield for this sequence of only 12%.

15.- This factor itself is unable to explain the observed high stereoselectivity (de>95%). Thus, the reaction of the 2-(1-hydroxyethyl)-2-cyclohexen-1-one with H_2O_2/MeOH/NaOH at 0°C yielded a 4:1 mixture of syn and anti epoxides (de=60%) (see Bailey M., Staton I., Ashton P.R., Markó I.E.; David Ollis W.; *Tetrahedron Asymmetry*, **1991**, *2*, 495).

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