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Stereoselective Hydride Reductions of Chiral 2-*p*-Tolylsulfinylcycloalkanones

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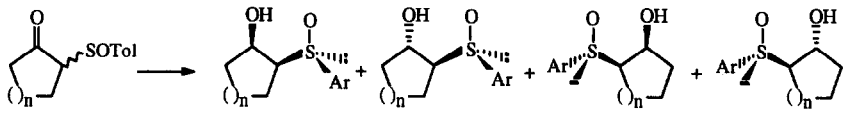
Abstract: The highly stereoselective hydride reductions of chiral 2-*p*-tolylsulfinyl-cyclopentanones and -cycloheptanones are described. With DIBAL (electrophilic hydride) the configuration induced at C-1 is controlled by the sulfinyl group (1,3-asymmetric induction), and it can be inverted by using $ZnCl_2$ as catalyst. With L-selectride the stereoselectivity is directed by the C-2 chiral groups (1,2-asymmetric induction). Other nucleophilic hydrides gave results which depend on the reagents and the size of the rings.

The stereoselective reduction of acyclic chiral ß-ketosulfoxides with DIBAL and DIBAL/$ZnCl_2$ is a very useful method to obtain optically pure secondary methylcarbinols.[1] This reaction has been successfully used as key step in the enantioselective synthesis of several interesting natural products.[2] Further studies on α–alkyl β–ketosulfoxides showed a non stereoselective process with DIBAL, whereas in the presence of an excess of $ZnBr_2$ their reduction was highly stereoselective,[3] being mainly controlled by the sulfur configuration.[4] With respect to cyclic β-ketosulfoxides, the reports concerning their reduction were only related to the synthesis of cyclohexanol derivatives.[1,5] Thus, the reactions of 2-*p*-tolylsulfinylcyclohexanones with DIBAL and DIBAL/$ZnCl_2$ were highly stereoselective[5] giving rise to the synthesis of enantiomerically pure cyclohexenols[6] and 4-hydroxy-2-cyclohexenones[7] utilized as starting material in total synthesis of biologically active compounds.[8] DIBAL reductions of cyclic β–ketosulfoxides were as stereoselective as those with DIBAL/$ZnCl_2$. This fact revealed some differences between the behaviour of cyclic and acyclic substrates, which could probably be attributed to the conformational restrictions of the rings and/or to the lower stability of the bicyclic chelates generated in the presence of $ZnCl_2$. Therefore, in spite of the synthetic success obtained from cyclohexanone derivatives, no studies related to other sulfinylcycloalkanones have so far been published. In order to check the general scope of the method to obtain other enantiomerically pure cyclic carbinols, we undertook the study of the reduction of 2–*p*-tolylsulfinyl-cyclopentanones (**1**) and -cycloheptanones (**3**) with different hydrides (Scheme 1). We report herein the results of this study and discuss their possible stereochemical course.

Results and Discussion

The starting β–ketosulfoxides **1** and **3** were obtained as mixtures of epimers at C-α (**a+b**) by reaction of the corresponding cycloalkanone enolates or cycloalkanone imine enolates[9] with (S)-(-)-menthyl *p*-toluenesulfinate in the previously reported conditions. The isomers **1a** and **3a**, which were the major components of the mixtures, were isolated diastereomerically pure by crystallization and therefore they could be independently characterized.[10] The separation of diastereomerically pure samples of the minor components (**1b** and **3b**) was not possible and the study of their reductions was carried out on mixtures of epimers **a+b**, where **a** were the major components, once the behaviour of the **a** epimers had been independently established.

Table **- Reductions of 2-*p*-tolylsulfinylcyclopentanone (1), 2-phenylsulfinylcyclohexanone (2) and 2-*p*-tolylsulfinylcycloheptanone (3)**



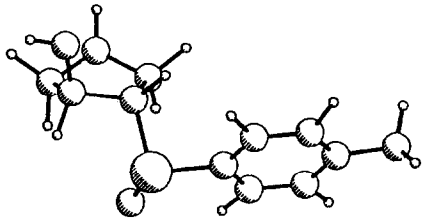
		$(R_1S_2R_S)$	$(S_1S_2R_S)$	$(S_1R_2R_S)$	$(R_1R_2R_S)$
n=1 (R=*p*-Tol)	**1a, 1b**	^{c}**5a (cis)**	^{t}**5a (trans)**	^{c}**5b (cis)**	^{t}**5b (trans)**
n=2 (R=Ph)	**2a*, 2b***	^{c}**6a* (cis)**	^{t}**6a*(trans)**	^{c}**6b* (cis)**	^{t}**6b* (trans)**
n=3 (R=*p*-Tol)	**3a, 3b**	^{c}**7a (cis)**	^{t}**7a (trans)**	^{c}**7b (cis)**	^{t}**7b (trans)**

Entry	[a]	Subs.	yield[b]	Products[c]	Subs.	yield[b]	Products[c]	Subst.	yield[b]	Products[c]
				^{c}**5a** : ^{t}**5a**			^{c}**6a***:^{t}**6a***			^{c}**7a** : ^{t}**7a**
1	A	**1a**	91	<2:>98	**2a***	97	<2:>98[d]	**3a**	98	7:93
2	B	**1a**	83	>98:>2	**2a***	94	80:20[d]	**3a**	98	>98:<2
3	C	**1a**	85	>98:<2	**2a***	68	82:18[d]	**3a**	73	90:10
4	D	**1a**	90	>98:>2	**2a***	99	81:19[d]	**3a**	68	92:8
5	E	**1a**	81	>98:<2	**2a***	82	>98:<2	**3a**	70	>98:<2
6	F	**1a**	60	>98:<2	**2a***	78	>98:<2			
				^{c}**5a**:^{t}**5a**/^{c}**5b**:^{t}**5b**			^{c}**6b***:^{t}**6b***			^{c}**7a**:^{t}**7a**/^{c}**7b**:^{t}**7b**
7	A	**1a+1b**	80	0:89/0:11	**2b***	96	94: 6[d]	**3a+3b**	84	4:57 / 32:7
8	B	**1a+1b**	83	82:0/0:18	**2b***	84	5 :95[d]	**3a+3b**	83	61:0 / 5:34
9	C	**1a+1b**	85	>96:0/traces	**2b***	81	26:74[d]	**3a+3b**	90	55:6 / 12:27
10	D	**1a+1b**	90	>96:0/traces	**2b***	90	54:46[d]	**3a+3b**	95	56:5/39:0
11	E	**1a+1b**	84	93:0/ 7:0	**2b***	84	33:67	**3a+3b**	83	61:0 / 31:8
12	F	**1a+1b**	57	87:0/13:0	**2b***	80	>98:<2			

[a]Hydride: A=DIBAL, B=DIBAL/$ZnCl_2$, C=$LiAlH_4$, D=$NaBH_4$, E=$LiEt_3BH$, F=Li(*s*-Bu)$_3$BH; [b] after chromatographic isolation (%); [c] Diastereomeric ratio determined by ^{1}H-nmr ; [d] From reference 1

The results obtained in the reduction of the 2-*p*-tolylsulfinylcycloalkanones **1** and **3** are collected in the table. The data corresponding to racemic 2-phenylsulfinylcyclohexanones **2*** have been taken from reference 1 and are considered for comparison purposes. Results on enantiomerically pure 2-*p*-tolylsulfinylcyclohexanones **4**[5] are similar to those of 2-phenyl derivatives **2**. Thus, reaction of (**S2RS**)-**4a** with DIBAL afforded *trans*-hydroxysulfoxide (**S1S2RS**)-^{t}**8a** (d.e. > 98%) whereas the reduction with the system DIBAL/$ZnCl_2$ gave carbinol (**R1S2RS**)-^{c}**8a** (d.e. = 80%).[5,11] Reactions on (**R2RS**)-**4b** yielded (**S1R2RS**)-^{c}**8b** (d.e. > 98%) and (**R1R2RS**)-^{t}**8b** (d.e. = 72%) upon treatment with DIBAL and DIBAL/$ZnCl_2$ respectively.[5]

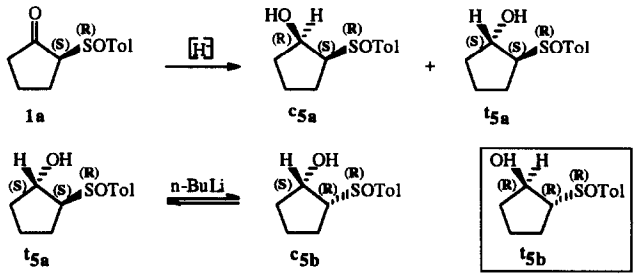
Figure: ORTEP plot of (**S1S2RS**)-2-*p*-tolylsulfinylcyclopentanol (^{t}**5a**)



Optically pure cyclopentanols ^{c}**5a** and ^{t}**5a**, were readily isolated by crystallization from the reactions carried out on pure **1a** or from **1a+1b** mixtures, where **1a** was predominant. Alcohols ^{c}**5b** and ^{t}**5b**, which are always the minor components of the reaction mixtures, could not be isolated diastereomerically pure. Their ^{1}H-nmr data were deduced from the spectra of the mixtures containing them. All the possible cycloheptanols **7** could be isolated in diastereomerically pure form, by crystallization or chromatographic separation from their respective mixtures (see experimental).

The similarity of nmr parameters corresponding to the four different cyclopentanols **5** prevented their configurational assignment (see experimental). X-ray diffraction of ^{t}**5a** allowed us to determine its absolute configuration as (**S1S2RS**)[12] and its stereochemistry in solid state is depicted in the figure. As it can be seen, the configurations at C-2 (**S**) and sulfur (**R**) are coincident with those assigned by nmr to the starting ketosulfoxide **1a** (**S2RS**), and the relative stereochemistry of the vicinal heteroatomic substituents is *trans*. Considering that compound ^{c}**5a** was also derived from (**S2RS**)-**1a**, we assigned the absolute configuration (**R1S2RS**) to the chiral centers, only differing from that of ^{t}**5a** in the configuration at C-1. On this base, compound ^{c}**5a** must be the *cis*-isomer.

The configurational assignment of ^{c}**5b** was established by chemical correlation. Thus, the treatment of the *trans*-alcohol ^{t}**5a** with n-BuLi (2 eq.) determined the epimerization at C-2, yielding a 3:1 mixture of ^{t}**5a** and ^{c}**5b** allowing us to assign the (**S1R2RS**) configuration to compound ^{c}**5b** (epimer at C-2 of ^{t}**5a**), and therefore the (**R1R2RS**) one to diastereoisomer ^{t}**5b**.



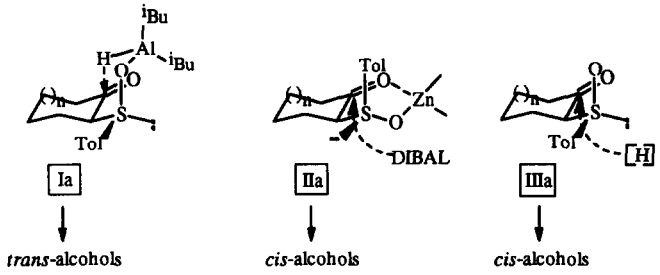
Scheme 1

The relative stereochemistry of the heteroatomic substituents in the sulfinylcycloheptanols **7**, was easily deduced from the values of the vicinal coupling constants $^3J_{1,2}$ which are higher than 9Hz for compounds exhibiting *trans* arrangement (**^{t}7a** and **^{t}7b**) but smaller than 3Hz for those with a *cis* relationship (**^{c}7a** and **^{c}7b**). Taking into account the configuration of the starting ketosulfoxides **3a** and **3b**, previously established as ($\mathbf{S_2R_S}$) for **3a** and ($\mathbf{R_2R_S}$) for **3b**,[9] and considering that the reduction of each one yields alcohols differing in the configuration of the hydroxylic carbon (*cis* or *trans* arrangement of their heteroatomic functions), we can assign the configurations ($\mathbf{R_1S_2R_S}$) and ($\mathbf{S_1S_2R_S}$) to compounds **^{c}7a** (*cis*) and **^{t}7a** (*trans*), derived from ($\mathbf{S_2R_S}$)-**3a**, and ($\mathbf{R_1R_2R_S}$) and ($\mathbf{S_1R_2R_S}$) to compounds **^{t}7b** (*trans*) and **^{c}7b** (*cis*), generated from ($\mathbf{R_2R_S}$)-**3b** (see table).

As we can see in the table, the behaviour of the epimers **a** is very similar regardless of the ring size. Thus, their reactions with DIBAL (entry 1) afforded only *trans*-sulfinylcycloalkanol (**^{t}5a** and **^{t}6a**) in the cases of **1a** and **2a**, or as major component of the reaction mixture in the case of **3a** (**^{t}7a**, d.e.= 86%). In the reductions with other hydrides (entries 2-6) the corresponding *cis*-derivatives are mainly formed. Many of these stereochemical results were rationalized in the case of the six membered rings[1] taking into account the conformational preferences of the starting β–ketosulfoxides and the possible associations of the metals present in the reagents with the oxygens of the substrates. In the case of DIBAL reductions, we can assume the formation of a tetracoordinated species (**Ia**, Scheme 2) by association of the aluminium with the sulfinyl oxygen, which is the most basic center of the starting β-ketosulfoxides. This species is now able to act as nucleophilic hydride reducing the carbonyl group by intramolecular hydride transfer. A chair-like transition state without serious steric strain, such as $\mathbf{I_a}$ (Scheme 2), can be invoked to explain the main formation of *trans* alcohols. In the presence of the ZnX_2, the evolution of a chelated species such as $\mathbf{II_a}$ (Scheme 2), with the tolyl group arranged in pseudo axial position which precludes the axial approach of the DIBAL, could justify the major formation of the *cis* carbinols.[13]

The stereoselectivity observed in the reductions of **a** epimers with nucleophilic hydrides can be explained taking into account that **IIIa** (Scheme 2) must be the most favoured and reactive conformer in all these substrates. The high stability of conformer **IIIa** could be attributed to the stabilizing donor-acceptor interaction existing between the unshared electron pair of the carbonyl oxygen and the empty d orbital on sulfur,[14] which is only possible from the spatial arrangement shown in **IIIa** (a more detailed discussion about

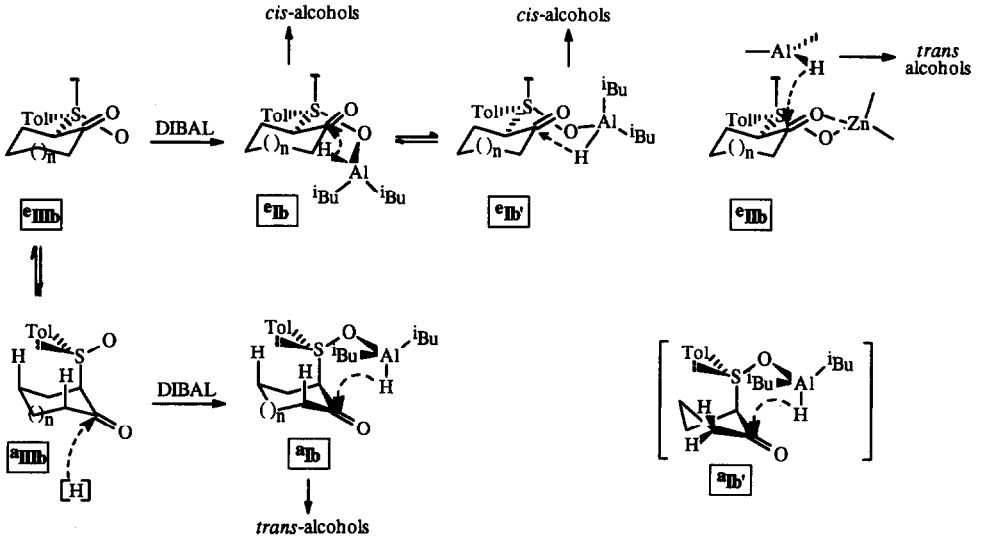
this point can be seen in reference 1). The orientation of the sulfinylic oxygen in conformation **IIIa** makes difficult the axial approach of the nucleophilic hydrides from both steric and stereoelectronic grounds. Therefore, the equatorial attack resulting in the formation of the *cis* alcohols must be favoured in all cases, the stereoselectivity being higher when the size of the hydride became larger. The possibility that the Li^+ could act as chelating agent does not modify these predictions.



Scheme 2

The stereochemical evolution of the **b** epimers is more complex. None of the rotamers around the C-S bond in the chair conformation ^{e}**IIIb** (Scheme 3) (**e** superscript indicates that the SOTol group is in equatorial arrangement) can be stabilized by the donor-acceptor interaction before mentioned because they do not fulfil the stereochemical requirements. This fact determines a non negligible participation of rotamers ^{a}**IIIb** (**a** superscript indicates the axial arrangement of the SOTol group in the conformational equilibria). The stereoselectivity observed in the DIBAL reduction of **2b*** can be explained by assuming the intramolecular hydride transfer from the associated species ^{e}**Ib**. Although a chair-like transition state (^{e}**Ib'**) was initially proposed for this transfer,[1] a twist-like transition state (^{e}**Ib**), similar to that depicted in Scheme 3, could also be favoured due to the absence of significant steric interactions. Furthermore the hydride approach to the carbonyl group in ^{e}**Ib** takes place with an orientation which agrees with the predicted as the most stable by both experimental data[15] and theoretical calculations (non perpendicular nucleophilic approach).[14] Both of them would yield the *cis*-hydroxy sulfoxide, ^{c}**6b***. The formation of the *trans*-isomer ^{t}**6b*** can be a consequence of the intramolecular transfer from ^{a}**Ib** (Scheme 3) through a chair-like transition state. In the case of the cyclohexanone derivatives, both the larger stability (and therefore population) of ^{e}**IIIb** with the sulfinyl group in equatorial arrangement, and the 1,3-*syn*-diaxial interactions between the *i*-Bu group and the hydrogens of the CH_2 group, unstabilizing the transition state resulting from ^{a}**Ib**, determined the major formation of compound ^{c}**6b***. The situation must be similar for the corresponding sulfinylcycloheptanone **3b**, where the *cis*-isomer ^{c}**7b** is also favoured. By the contrary, the reaction of sulfinylcyclopentanone **1b** with DIBAL only yielded the *trans*-isomer ^{t}**5b**, suggesting that the evolution through a transition state like ^{a}**Ib** must be now clearly favoured with respect to the evolution through ^{e}**Ib**. Considering that the 1,3-*syn*-diaxial interactions unstabilizing both the conformation ^{a}**IIIb** and the transition state resulting from ^{a}**Ib** in

cyclohexanone derivatives, must be absent in the five membered rings (see **^{a}IIb'** in Scheme 3) the highly stereoselective and apparently anomalous evolution of **1b** with DIBAL is not surprising.



Scheme 3

The results of the DIBAL/$ZnCl_2$ reduction of the **b** epimers can be explained assuming the formation of the chelated species **IIb** (Scheme 3). The axial approach of the DIBAL, which yields the *trans*-isomer, must be favoured from steric (chair-like T.S.) and stereoelectronic grounds (stabilizing interaction between the lone electron pair at sulfur and the empty orbital at the aluminium).[1]

As in the case of **a** epimers, only steric interactions justify the stereoselectivity observed in the reductions of **1b** and **2b*** with L-selectride, determining the exclusive formation of the *cis*-alcohols, **^{c}5b** and **^{c}6b***, during the intermolecular attack of the bulky reagent on **^{e}IIIb** (equatorial approach) and **^{a}IIIb** (axial approach) (Scheme 3). As we can see, the configuration induced at C-1 with this hydride is the opposite to that of C-2 ($\mathbf{R_1}$ starting from the ($\mathbf{S_2R_S}$)-**a** epimers and $\mathbf{S_1}$ from the ($\mathbf{R_2R_S}$)-**b** ones), regardless of the configuration at sulfur, which indicates that these reductions are 1,2-asymmetric induction processes.

Finally, the less stereoselective evolution of the substrates with other nucleophilic hydrides, as well as the differences observed depending on the size of the rings, are not easy to explain and must be related to the conformational preferences of each substrate and to the chelating properties of the involved metals.

In conclusion, we can state that the stereoselectivity of the DIBAL reductions of chiral sulfinylcycloalkanones is mainly controlled by the configuration of the sulfur (1,3-asymmetric induction process) and it can be inverted by use of $ZnCl_2$ as catalyst, whereas that observed with L-selectride is only dependent of the configuration at C-2 (1,2-asymmetric induction process).

Experimental

Melting points were determined on a Gallen Kamp apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with the Bruker WP-200-SY instrument. Chemicals shifts are given in parts per million (δ), using tetramethylsilane as an internal standard. Diastereomeric ratios were established by integration of well-separated signals of the diastereomers in the mixtures of the hydroxysulfoxides resulting from hydrolysis and are collected in Table I. Eluting solvents are indicated in the text. Opticals rotations were measured on a Perkin-Elmer 241 MC polarimeter. TLC analysis were performed on Merck (art. 554) silice gel plates and silica gel (230-400 mesh ASTM) from Merck was used for flash chromatography.

General Procedures for Hydride Reductions. Reductions were carried out following the procedures described in reference 1: **Method A: (*i*-Bu)$_2$AlH. Method B: (*i*-Bu)$_2$AlH/ZnCl$_2$. Method C: LiAlH$_4$. Method D: NaBH$_4$.**

Method E: Li(*s*-Bu)$_3$BH and LiEt$_3$BH. To a solution of the ß-ketosulfoxide (0.2 mmol) in 2 ml of THF 0.3 ml (0.3 mmol) of a 1M hexane solution of Li(*s*-Bu)$_3$BH or LiEt$_3$BH were added at -78°C, under N_2. Stirring was maintained until completion of the reaction and then this mixture was poured over 20 ml of ethyl acetate and 10 ml of HCl (10%). The organic layer was extracted with methylene chloride and washed with saturated sodium bicarbonate (4x20 ml). Drying and evaporation of organic solvents in vacuo afforded the hydroxysulfoxides.

($S_1S_2R_S$)-2-*p*-tolylsulfinylcyclopentanol (^{t}5a). Reduction of a 79:21 mixture of compounds **1a** and **1b** following method B, yielded a mixture of diastereomers ^{t}**5a** and ^{t}**5b**. Pure ^{t}**5a** was obtained by crystallization (hexane-ethyl acetate) of the resulting mixture; mp 93-94°C; $[\alpha]_{20}^{D}$ = +99.5 (c=1, acetone); MS m/z 224(2) M^+, 208(11), 191(1), 179(2), 140(100), 92(61); ^{1}H NMR 7.49 and 7.31 (AA'BB' system, 4H, Tol), 4.55 (c, 1H, J=5.5 Hz, CHOH), 3.0 (dt, 1H, J=5.5 and 7.8 Hz, CHSO), 2.42 (s, 3H, CH_3), 2.0-1.5 (m, 6H); ^{13}C NMR 141.2, 138.8, 129.8 (2C), 124.3 (2C), 73.3, 70.7, 35.0, 22.0, 21.3, 21.0; IR (KBr) 3330, 1090, 1030, 1020, 820. Anal. calcd for $C_{12}H_{16}SO_2$: C, 64.24; H, 7.20. Found: C, 64.53; H, 7.26.

($R_1S_2R_S$)-2-*p*-tolylsulfinylcyclopentanol (^{c}5a). Reduction of a 79:21 mixture of compounds **1a** and **1b** following methods A, C, D and E, yielded a mixture of diastereomers ^{c}**5a**, ^{c}**5b** and ^{t}**5b**. Pure ^{c}**5a** was obtained from the mixture by crystallization (hexane-ethyl acetate); mp 105-106°C; $[\alpha]_{20}^{D}$ = +207 (c=1, acetone); MS m/z 224(2) M^+, 207(3), 140(100), 92(70); ^{1}H-NMR 7.50 and 7.31 (AA'BB' system, 4H, Tol), 4.50 (m, 1H, CHOH), 2.94 (dt, 1H, J=5.4 and 8.6 Hz, CHSO), 2.41 (s, 3H, CH_3) 2.50-1.40 (m, 6H); ^{13}C-NMR 140.8, 139.2, 129.8 (2C), 124.1 (2C), 73.6, 68.4, 35.1, 21.3 (2C), 21.0; IR (KBr) 3350, 1120, 1020, 1010, 805. Anal. calcd. for $C_{12}H_{16}SO_2$: C, 64.24; H, 7.20. Found: C, 64.42; H, 7.13.

($R_1R_2R_S$)-2-*p*-tolylsulfinylcyclopentanol (^{t}5b). Reduction of a 79:21 mixture of compounds **1a** and **1b** following method A and separation by flash chromatography of the resulting mixture (eluent ethyl acetate/hexane 2:1) gave ^{t}**5b** contaminated with traces of ^{t}**5a**; ^{1}H NMR 7.56 and 7.32 (AA'BB' system, 4H, Tol), 4.63 (c, 1H, J=6.4 Hz, CHOH), 2.96 (m, 1H, CHSO), 2.41 (s, 3H, CH_3), 2.10 (m, 1H), 1.85-1.60 (m, 5H); ^{13}C-NMR 142.1, 139.9, 130.0 (2C), 124.6 (2C), 74.7, 71.0, 34.1, 25.0, 21.9, 21.4.

($S_1R_2R_S$)-2-*p*-tolylsulfinylcyclopentanol (^{c}5b). Reduction of compounds a 79:21 mixture of **1a** and **1b** following method E and chromatographic separation of the resulting mixture (eluent ethyl acetate/hexane 2:1) gave ^{c}**5b** contaminated with traces of ^{c}**5a**; ^{1}H NMR 7.61 and 7.34 (AA'BB' system, 4H, Tol), 4.63 (m, 1H, CHOH), 2.89 (dt, 1H, J= 4.2 and 9.2 Hz, CHSO), 2.43 (s, 3H, CH_3), 2.15-1.50 (m, 6H); ^{13}C NMR 141.9, 139.6, 130.0 (2C), 124.8 (2C), 73.9, 68.4, 34.6, 24.1, 22.3, 21.4.

($S_1S_2R_S$)-2-*p*-tolylsulfinylcycloheptanol (^{t}7a). Reduction of compound **3a** and **3b** following method B yielded a mixture of diastereomers ^{t}**7a**, ^{c}**7b** y ^{t}**7b**. Pure ^{t}**7a** by crystallization (cyclohexane) from the resulting mixture; mp 98-100°C; $[\alpha]_{20}^{D}$ = +156 (c=1, acetone); MS m/z 140(100), 139(11), 92(50); ^{1}H NMR 7.55 and 7.35 ((AA'BB' system, 4H, Tol), 4.80 (bs, 1H, OH), 4.15 (ddd, 1H, J=3.8, 5.4 and 9.0 Hz, CHOH), 3.12 (ddd, 1H, J=2.4, 8.7 and 9.6 Hz,CHSO), 2.41 (s, 3H, CH_3), 1.90-1.08 (m, 10H); ^{13}C-NMR 141.1, 136.7, 129.4 (2C), 124.9 (2C), 70.5, 69.5, 36.2, 28.6, 26.8, 21.7, 21.5, 21.1; IR (KBr) 3300, 1085, 1040, 1035, 1020.

($R_1S_2R_S$)-2-*p*-tolylsulfinylcycloheptanol (^{c}7a). Reduction of compound **3a** following method C yielded only one diastereomer purified by crystallization (acetone); mp 126-128°C; $[\alpha]_{20}^{D}$ = +121° (c=1, acetone); MS m/z 140(100), 113(10), 92(59); ^{1}H NMR 7.50 and 7.35 (AA'BB' system, 4H, Tol), 4.60 (dt, 1H, J= 2.3 and 5.6 Hz, CHSO), 2.80 (d, 1H, OH), 2.63 (ddd, 1H, J= 1.9, 3.6 and 10.8, CHSO), 2.41 (s, 3H, CH_3), 2.10-1.90 (m, 6H); ^{13}C NMR 141.1, 138.5, 129.5 (2C), 124.6 (2C), 69.6, 69.1, 35.8, 27.4, 26.2, 22.4, 21.2, 18.8; IR (KBr) 3320, 1090, 1070, 1030.

($R_1R_2R_S$)-2-*p*-tolylsulfinylcycloheptanol (^{t}7b): Reduction of a 55:45 mixture of **7a** and **7b** following method B yielded a mixture of alcohols ^{c}**7a**, ^{c}**7b** and ^{t}**7b**. Diastereomer ^{t}**7b** was isolated by flash chromatography (eluent hexane/acetone 2:1) and purified by crystallization (cyclohexane); mp 150-151°C; $[\alpha]_{20}^{D}$ = +55 (c=0.5, acetone); MS m/z 140(100), 139(9), 92(57); ^{1}H NMR 7.65 and 7.34 (AA'BB' system, 4H, Tol), 4.60 (bs, 1H, OH), 4.30 (dt, 1H, J=4.5 and 8.5 Hz, CHOH), 2.80 (ddd, 1H, J=3.8, 7.5 and 8.6, CHSO), 2.43 (s, 3H, CH_3), 1.90-1.20 (m, 10H); ^{13}C NMR 142.5, 139.3, 129.9 (2C), 126.0 (2C), 73.2, 71.7, 35.8, 29.4, 26.7, 23.1, 22.8, 21.4; IR (KBr) 3360, 1060, 1025, 1015.

($S_1R_2R_S$)-2-*p*-tolylsulfinylcycloheptanol (^{c}7b): Reduction of a 55:45 mixture of **7a** and **7b** following method D gave a mixture of alcohols ^{c}**7a**, ^{c}**7a** and ^{c}**7b**. Diastereomer ^{c}**7b** was separated by flash chromatography (eluent acetonitrile/chloroform 1:2) and purified by crystallization (hexane); mp 123-124°C; $[\alpha]_{20}^{D}$ = +206° (c=0.5, acetone); MS m/z 140(100), 113(11), 92(72); ^{1}H NMR 7.55 and 7.36 (AA'BB' system, 4H, Tol), 4.45 (m, 1H, CHOH), 3.95 (bs, 1H, OH), 2.50 (ddd, 1H, J=1.8, 2.3 and 10.7, CHSO), 2.43 (s, 3H, CH_3), 2.0-1.30 (m, 10H); ^{13}C NMR 141.7, 138.9, 129.9 (2C), 124.9 (2C), 67.6, 67.2, 35.8, 27.1, 26.1, 23.4, 21.7, 21.4; IR (KBr) 3340, 1085, 1035, 1015.

($S_1S_2R_S$)-2-*p*-tolylsulfinylcyclohexanol (^{t}8a). Reduction of (S_2R_S)-2-*p*-tolylsulfinylcyclohexanone (**4a**) following method A gave ^{t}**8a** pure, mp 152-153°C ; $[\alpha]_{20}^{D}$ = +238° (c=1, chloroform); MS m/z 238(4)M^+, 140(100), 92(35); ^{1}H NMR 7.59 and 7.44 (AA'BB' system, 4H, Tol), 4.62 (d, 1H, J=3.0 Hz, OH), 3.91 (tdd, 1H, J=2.5, 4.7 and 9.9 Hz, CHOH), 2.67 (ddd, 1H, J=3.7, 9.9 and 11.9 Hz, CHSO), 2.43 (s, 3H, CH_3), 2.15-1.07 (m, 8H); ^{13}C NMR 141.4, 136.5, 129.7 (2C), 125.2 (2C), 69.3, 67.1, 35.4, 24.8, 23.7, 21.4, 21.2; IR (KBr) 3500, 1020, 1005, 805.

($R_1S_2R_S$)-2-*p*-tolylsulfinylcyclohexanol (^{c}8a). Reduction of **4a** following method B gave a mixture of ^{c}8a and ^{t}8a from which ^{c}8a was separated by flash chromatography (eluent acetonitrile/ carbon tetrachloride 1:3) ; mp 119-120°C (from carbon tetrachloride-methanol); $[\alpha]_{20}^{D}$ = +174° (c=1, chloroform); MS m/z 238(2)M^+, 140(100), 92(34); ^{1}H NMR 7.49 and 7.33 (AA'BB' system, 4H, Tol), 4.39 (m, 1H, CHOH), 3.21 (bs, 1H, OH), 2.49 (ddd, 1H, J= 2.1, 3.8 and 12.5 Hz, CHSO), 2.43 (s, 3H, CH_3), 2.13-1.05 (m, 8H); ^{13}C NMR 141.4, 137.6, 129.7 (2C), 124.6 (2C), 67.0, 66.2, 33.3, 25.2, 21.3, 18.9, 18.1; IR (KBr) 3300, 1000, 805.

($R_1R_2R_S$)-2-*p*-tolylsulfinylcyclohexanol (^{t}8b). Reduction of a 75:25 mixture of (S_2R_S)-2-*p*-tolylsulfinylcyclohexanone (**4a**) and (R_2R_S)-2-*p*-tolylsulfinylcyclohexanone (**4b**) following method B gave a mixture of ^{c}8a, ^{t}8b and ^{c}8b from which ^{t}8b and ^{c}8b were separated by flash chromatography (eluent acetonitrile/ carbon tetrachloride 1:3). ^{t}8b was crystallized from hexane-acetone; mp 146-147°C ; $[\alpha]_{20}^{D}$ = +167° (c=1, chloroform); MS m/z 238(2)M^+, 140(100), 92(41); ^{1}H NMR 7.62 and 7.35 (AA'BB' system, 4H, Tol), 4.50 (bs, 1H, OH), 4.10 (td, 1H, J=4.9 and 9.6 Hz, CHOH), 2.73 (ddd, 1H, J=4.5, 9.6 and 12.0 Hz, CHSO), 2.43 (s, 3H, CH_3), 2.12 (m, 1H), 1.73 (m, 1H), 1.50-0.96 (m, 5H); ^{13}C NMR 142.6, 139.1, 130.0 (2C), 125.5 (2C), 72.2, 68.4, 34.6, 27.1, 24.6, 23.7 (2C), 21.4; IR (KBr) 3330, 1020, 1000, 815.

($S_1R_2R_S$)-2-*p*-tolylsulfinylcyclohexanol (^{c}8b). mp 186-188°C (acetone-hexane); $[\alpha]_{20}^{D}$ = +330° (c=0.6, chloroform); MS m/z 238(2)M^+, 140(100), 92(47); ^{1}H NMR 7.55 and 7.36 (AA'BB' system, 4H, Tol), 4.33 (m, 1H, CHOH), 3.04 (bs, 1H, OH), 2.44 (s, 3H, CH_3), 2.43-2.13 (m, 2H), 1.96-1.11 (m, 7H); ^{13}C NMR 141.8, 138.1, 130.0 (2C), 124.7 (2C), 65.5, 64.7, 33.2, 25.5, 22.5, 21.4, 19.3; IR (KBr) 3300, 1000, 815.

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10. Following the procedure described in reference 9, compound **1a** could not be isolated diastereomerically pure. A slight modification of the experimental procedure (a very slow addition of the imine on the LDA) gave a cleaner reaction mixture from which **1a** could be crystallized (ethyl acetate-hexane) after chromatography. m.p. 63-65°C, $[\alpha]_{20}^{D}$ = +668 (c = 1, $CHCl_3$)

11. The use of an excess of $ZnBr_2$ instead $ZnCl_2$ improved the stereoselectivity in the case of **4a** reduction (**^{t}8a**:**^{c}8a** <3:>97 was now obtained). According to reference 5, this suggests an unefficient chelation of the substrate in the presence of $ZnCl_2$ as the reason of the decreased stereoselectivity.
12. Crystals of **^{t}5a** belong to the orthorhombic space group $P2_12_12_1$, and accurate lattice constants of a = 10.161 (3), b = 11.600 (2), c = 9.869 (2). All unique diffraction maxima [range of hkl, -11 11, -13 13, -11 11] were collected using 2θ:θ scans and CuKα radiation. Of the 2321reflections measured in this fashion, 2297 were judged observed [I>2σ(I)] and used in subsequent calculations. The structure, solved by direct methods was refined to R = 0.077 and Rw = 0.093 (refinement by least square). The absolute configuration was determined by comparing *xyz* and *-x-y-z* refinements. Computer and programs : Vax 750, Multan80, Dirdif, Xray 76System, Pesos, Parst. Tables of atomic coordinates, bond lengths and angles, and thermal parameters (supplementary material) are available on request from the Cambridge Crystallographic Data Center.
13. The different stability of the bicyclic chelates is related to the size of the cycloalkanone rings, and must be important in the control of the stereoselectivity observed for the different ring sizes. The higher stability of cyclopentanone/ZnX_2 chelates, where the interactions between the *p*-Tolyl group and the axial proton at C-3 must be lower than in higher rings (see **IIa** in Scheme 2), could explain the better results achieved in the case of sulfinyl cyclopentanones **1a** and **1b** (compare the diastereomers ratios corresponding to entries 2 and 8).
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