Highly Stereoselective Aldol Reactions of Lithium Ester Enolates with (R_S)-2-(*p*-Tolylsulfinyl)cyclohexanones

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Aldol reactions lithium alkyl acetates (LiCRR″CO_2R′) with (R_S)-2-(*p*-tolylsulfinyl)cyclohexanone (**1**) (as an epimeric mixture at C-2) take place with very efficient control of the configuration at the tertiary hydroxylic carbon (C-1). Stereoselectivity becomes complete if R and/or R″ are not hydrogen. Only carbinols derived from (S_2,R_S)-1 epimer were obtained, the major ones being those exhibiting *S* configuration (opposite to that of the sulfur) at the hydroxylic carbon. When LiCHRCO_2R′ is used, mixtures of the two epimers at the new stereogenic center C-1′ are obtained (∼10−82% de), their proportion being dependent on the size of R. The use of lactone enolates avoids the formation of epimeric mixtures, affording only one diastereoisomer with an ($R_{3'}$,S_1,S_2,R_S) configuration at the four adjacent chiral centers. Tricoordinated lithium species, which involve the enolate and the sulfinyl and carbonyl oxygens of the substrates, are invoked to explain the stereoselectivity observed in these aldol reactions with sulfinyl ketones as electrophiles.

Asymmetric aldol reactions are among the most powerful methods for the stereochemical control in natural products synthesis. Absolute and relative stereochemistries of these reactions can be controlled by the use of chiral enolates, substrates, or catalysts, with hundreds of papers and some excellent comprehensive reviews[1] covering this topic. Most of these reports are related to the aldehydes, the number of papers concerning the use of ketones being significantly lower. In these cases, chiral ketones have been mainly used as a source of enolate, whereas very few stereoselective reactions have been reported with ketones acting as electrophiles. In this sense, the results attained in reactions of chiral enolates with ketones[2] or achiral enolates with chiral ketones[3] usually show moderate stereoselectivity.

The sulfinyl group has been used as a chiral auxiliary in asymmetric aldol reactions. Thus, it has been reported by Solladié *et al.* that reactions of magnesium enolates derived from α-sulfinyl acetates (lithium enolates do not react) with aldehydes and some ketones take place with very high diastereofacial selectivity.[4] Several synthetic applications of these chiral enolates have been developed.[5] Nevertheless, attempts to extend the methodology to α-sulfinyl[6] and *β*-sulfinyl[7] derivatives of other esters have achieved only moderate success. Solladié's method has been extended to *N*,*N*-dimethylacetamide derivatives with good results[8] (only in the case of aldehydes), whereas reaction of magnesium enolates of α-sulfinyl ketones with several aldehydes proceeds with modest stereoselectivity.[9] Our experience in the field of asymmetric synthesis mediated by sulfoxides[10] has allowed us to show the high efficiency of the sulfinyl group in the stereochemical control of the reduction,[11] alkylation,[11a,12] and hydrocyanation[11a,13] processes of α-sulfinyl ketones. Additionally, other authors have been able to perform reactions of enolates with *N*-sulfinylimines with high selectivity.[14] Despite this efficiency, no studies concerning the use of α-sulfinyl ketones as chiral electrophiles in aldolic reactions have been reported as far as we know. This has prompted us to investigate the behavior of optically pure *β*-keto sulfoxides with enolates. In this paper we report the results obtained in the aldol reactions of 2-(*p*-tolylsulfinyl)cyclohexanone (**1**) with the lithium enolates derived from different esters and lactones. Our results reveal that the sulfinyl group on the electrophilic moiety is also a very effective chiral auxiliary that produces highly stereoselective aldol reactions.

Results and Discussion

The synthesis of the starting sulfinylcyclohexanone **1** was performed by sulfinylation of cyclohexanone *N*-

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Scheme 1

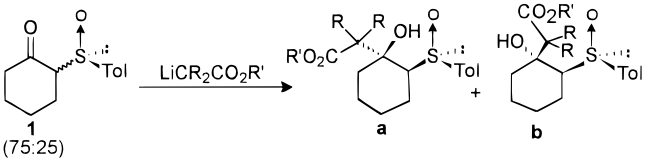


Table 1. Addition of R_2CHCO_2R' Lithium Enolates to 1

entry	compd	R	R′	a:b	yield (%)
1	**3**	H	Me	91:9	88
2	**2**	H	Et	93:7	92
3	**4**	H	t-Bu	96:4	81
4	**8**	Me	Et	100:0	90

phenylimine, according to the previously reported method,[15] to yield a 75:25 mixture of the two epimers at C-2. The above mixture was used, without previous separation, in all the reactions with enolates reported herein. The results obtained in reactions of **1** with lithium enolates from alkyl acetates and ethyl 2-methylpropanoate are shown in Scheme 1 and Table 1.

The addition of keto sulfoxide **1** (as a 75:25 epimeric mixture at C-2) over a THF solution of 2 equiv of ethyl acetate lithium enolate[16] affords a 93:7 mixture of the two diastereoisomeric hydroxy esters **2a** and **2b**. The use of methyl or *tert*-butyl acetates as the source of the corresponding enolates slightly modifies the stereoselectivity of the reaction (Table 1, entries 1−3). The major diastereoisomer of each mixture can be obtained in optically pure form by a single crystallization (de > 97% by ^{1}H NMR). Chromatographic separation of the 96:4 mixture of the hydroxy esters **4a** and **4b**, obtained from *tert*-butyl acetate, allowed the isolation and characterization of the minor component **4b**.[17]

The configurational assignment of the diastereoisomers **a** and **b** was ascertained from their ^{1}H NMR parameters, assuming that the sulfur configuration remains unaltered under the reaction conditions. The equatorial arrangement of the sulfinyl group in the favored conformation of both isomers could be deduced from the axial orientation of their C-2 protons [$^3J_{vic}$(CDCl$_3$) ≈ 12.5 and 3.8 Hz]. The hydroxy group signal [δ (CDCl$_3$) ∼4.25 ppm] of the major isomers **2a**−**4a** appears as a doublet due to the long-range coupling with the axial C-6 proton ($^4J_{OH,6}$ ≈ 1.4). These data indicate a relative *W* planar arrangement and suggest a strong intramolecular hydrogen bond between the hydroxy and sulfinyl groups.[18] In Figure 1, we have depicted the presumably most stable conformations around the C-S bond in the four possible diastereoisomers of compounds **2**−**4**, assuming unaltered sulfur configuration. From this figure, it can be deduced that the above mentioned hydrogen bonding can be exclusively formed for the (S_1,S_2,R_S) isomers, because the conformation required for such an association in the (R_1,R_2,R_S) isomers, would be strongly destabilized by the steric interaction between the *p*-tolyl and -CH_2CO_2R' groups in a 1,3-parallel arrangement. Therefore the (S_1,S_2,R_S) configuration must be assigned to the major diastereoisomers **2a**−**4a** obtained in these reactions.

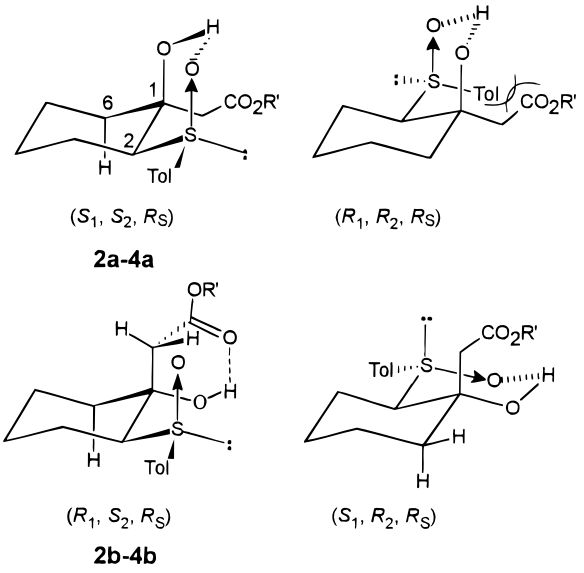
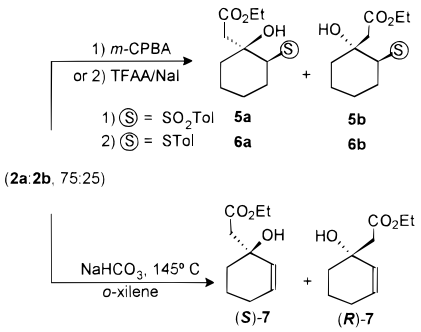


Figure 1. Significant conformations around the C−S bond for diastereomers of compounds **2**−**4**.

Scheme 2



In order to know the configuration of the minor isomers **2b**−**4b**, we have effected the following transformations (Scheme 2). A 75:25 mixture of **2a** + **2b**[19] was oxidized with *m*-CPBA, yielding a mixture of diastereomeric sulfones **5a** + **5b**, in the same proportion as the starting sulfoxides. Since both sulfones have different ^{1}H NMR spectra, they must be epimers in only one of their chiral centers, either C-1 or C-2. The same must be true for their precursor sulfoxides. The reduction of the **2a** + **2b** mixture with TFAA/NaI, yielding the corresponding diastereoisomeric sulfides **6a** + **6b**, confirms the above statement. The pyrolytic sulfinyl elimination from the same mixture of **2a** + **2b** yielded compound **7** as a mixture of enantiomers, in the same proportion as the starting sulfoxides.[20] This fact demonstrates that sulfoxides **2a** and **2b** have the opposite configuration at C-1 and, therefore, identical configurations at C-2 and sulfur. Thus, the (R_1,S_2,R_S) configuration must be assigned to the minor diastereoisomer **2b** and, accordingly, to the minor components of the mixtures obtained from methyl and *tert*-butyl acetates **3b** and **4b**, respectively. It is remarkable that only the hydroxy sulfoxides derived from diastereoisomer (S_2,R_S)-**1** were obtained in these reactions. The ^{1}H NMR spectrum of compound **4b** strongly supports the stereochemical assignment depicted in

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(16) When the reaction was carried out on direct addition mode (ester enolate was added over the keto sulfoxide), the yield diminished drastically.

(17) Starting from **2a** + **2b** or **3a** + **3b** diastereoisomeric mixtures, only the the major component can be isolated by chromatography.

(18) Jochins, J. G.; Taigel, G.; Seeliger, A.; Lutz, P.; Driesen, H. E. *Tetrahedron Lett.* **1967**, 4363.

(19) This mixture, enriched in the minor diastereoisomer **2b**, was prepared from the original mixture by repeated crystallizations of the major one **2a**.

(20) This was established from the ^{1}H NMR spectrum of a sample containing **7** and Eu(tfc)$_3$ as chiral shift reagent.

Figure 1. The most significant datum is the long-range coupling constant ($^4J_{CH2,H6} = 1.5$) between the H-6 axial and one proton of the methylene group next to the ester group. This coupling evidences a *W* planar arrangement of both protons, which can be maintained due to the hydrogen bond between the hydroxy and the ester group.

Starting from α,α-dimethyl-substituted acetate, the stereoselectivity of the reaction became complete at the carbonyl center. Thus, the epimeric mixture of keto sulfoxides **1** yields exclusively the (S_1,S_2,R_S)-**8a** isomer (similar spectroscopic parameters than those of **2a**−**4a**), indicating again that only the (S_2,R_S)-**1** epimer evolves under these conditions, and in a completely stereoselective manner (Scheme 1).

In order to propose a mechanistic model to explain the obtained results, it is important to point out the essential role of the lithium, acting as a template for these aldol reactions. In fact, they do not work with sodium or potassium enolates. The same is true for lithium enolates in the presence of HMPA, which acts by removing the metal. On the other hand, the reactivity and stereoselectivity of these reactions decreased in the presence of $ZnBr_2$ (which had proved to be an efficient catalyst in many other nucleophilic additions to β-keto sulfoxides), presumably due to the strong association of the metal with the carbonyl and sulfinyl oxygens, making the chelating effect of the lithium atom more difficult.

On the basis of steric grounds, the equatorial approach of the enolates on the carbonyl group of the sulfinylcyclohexanones **1** was expected to be favored. Thus, the formation of **2a**−**4a** and **8a** as major or exclusive products was not unexpected. The alternative axial approach on the presumably favored conformation of the substrate (the sulfinyl group in equatorial arrangement[21]) must be unstabilized by the interaction of the nucleophile with the *syn*-diaxial protons at C-3 and C-5. This would justify the high stereoselectivity obtained in the reactions with different alkyl acetates (~95:5 ratio of epimers), which become complete with α-alkyl-substituted esters (higher size of the nucleophilic carbon). Nevertheless, it has been reported that the attack of ethyl acetate lithium enolates on 2-methyl-5-isopropenylcyclohexanone (with the methyl group equatorially arranged) mainly yields the equatorial tertiary alcohol (axial attack).[22] The fact that our substrates **1** exhibit an inverted stereoselectivity in their reactions with ester enolates suggests the important role of the sulfinyl group in the stereochemical course of these reactions. From a steric and stereoelectronic point of view, the axial arrangement of the sulfinyl oxygen in the presumably most populated conformation around the C−S bond[23] (Figure 2) must contribute to make even more difficult the axial approach of the electrophilic enolate. Otherwise, the much higher reactivity of the (S_2,R_S)-**1** epimer, with respect to that of the (R_2,R_S)-**1** one (carbinols derived from the first one are exclusively formed in these reactions), can be explained by assuming a lithium chelate additionally stabilized by the sulfinyl oxygen, forming a tricoordinated species. This is not possible from the (R_2,R_S) epimer because the spatial arrangement of the tolyl group strongly destabilizes such a tricoordination (Figure 2).

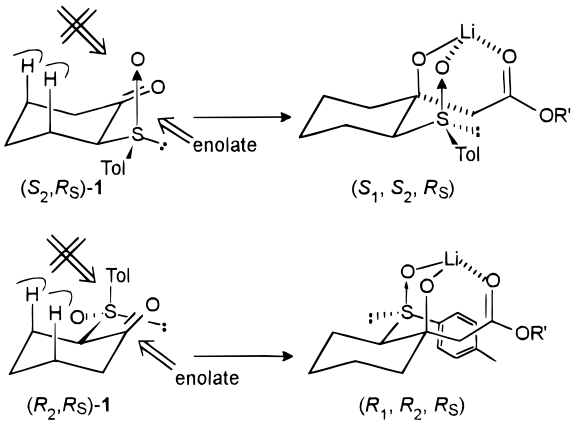


Figure 2. Favored approach of acyclic ester enolates in aldol reactions of 2-(*p*-tolylsulfinyl)cyclohexanone.

Scheme 3

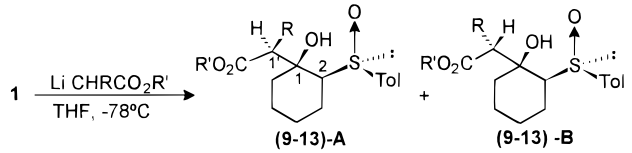


Table 2. Addition of RCH_2CO_2R' Lithium Enolates to 1

entry	compd	R	R′	A:B	yield (%)
1	**9**	Me	Et	55:45	88
2	**13**	Me	*t*-Bu	60:40	92
3	**10**	Et	Et	66:34	92
4	**11**	*i*-Pr	Et	74:26	88
5	**12**	*t*-Bu	Et	91:9	75

According to all the above data, we can conclude that the addition of lithium enolates derived from esters to the carbonyl group of the 2-(*p*-tolylsulfinyl)cyclohexanone (**1**) is highly or completely stereoselective, yielding the β-hydroxy esters that result of the enolate equatorial approach, in high diastereoisomeric excess.

Additionally, reactions of ethyl α-alkylacetate lithium enolates present a supplementary interest because of the formation of a second stereogenic center in the aldolic process. Thus, reactions of RCH_2CO_2Et (propanoate, butanoate, 3-methylbutanoate, and 3,3-dimethylbutanoate) enolates with keto sulfoxide **1** (as an epimeric mixture in C-2) afforded mixtures of two diastereoisomers, the stereoselectivity being higher as the size of R becames larger (R = Me, 55:45 of **9A** and **9B**; R = Et, 66:34 of **10A** and **10B**; R = *i*-Pr, 74:26 of **11A** and **11B**; and R = *t*-Bu, 91:9 of **12A** and **12B**) (Scheme 3). As in the case of unsubstituted enolates, the reaction with *tert*-butyl propanoate enolate illustrates that a bulkier group in the ester moiety produces only a slight increase in the stereoselectivity (R = Me, R′ = *t*-Bu 60:40 of **13A** and **13B**).

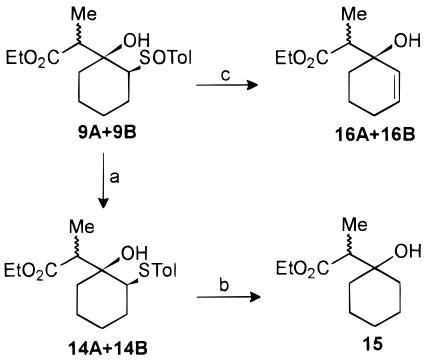
The components of the above mixtures are epimers at C-1′, as could be deduced from the following facts: (a) Reduction of the hydroxy sulfoxides **9A** + **9B** yielded a mixture of two nonenantiomeric thioethers **14A** and **14B** with different ^{1}H NMR spectra. Treatment of **14A** + **14B** with NiB_2 produces the reductive cleavage of C−S bond,[24] affording a mixture of the two enantiomers at C-1′ of the

(21) The axial approach on the cyclohexanone ring must be favored when the attack of the reagent takes place on the presumably minor conformations of these cyclohexanones (those arranging the sulfinyl group in axial position), because the steric interactions with the substituent must be more severe than those with the *syn*-diaxial protons. Nevertheless, the diastereoisomer formed from this attack would be the same as that obtained by the equatorial approach on the major conformation of the substrates.

(22) Maestro, M. A.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1992**. *57*, 5208.

(23) Carreño, M. C.; García Ruano, J. L.; Martín , A. M.; Pedregal, C; Rodriguez, J. H.; Rubio, A; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.

Scheme 4[a]



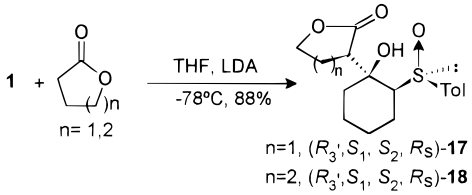
[a] (a) TFAA/NaI, −60 °C; (b) Ni_2B; (c) $NaHCO_3$, 145 °C.

desulfenylated compound **15**[25] (identical ^{1}H NMR spectra, which became different in the presence of a chiral shift reagent). The ee of compound **15** was identical to the de of the starting hydroxy sulfoxides. This demonstrates that **9A** and **9B** exhibit opposite configurations at C-1′. (b) Pyrolytic elimination of the sulfinyl group from the initial mixture of **9A** + **9B** yielded a diastereoisomeric mixture of **16A** and **16B** (they show different ^{1}H NMR spectra). Thus, **16A** and **16B** must exhibit a different relative configuration and therefore are epimers at C-1′. As a consequence, we can conclude that hydroxy sulfoxides **9A** and **9B** have the same configuration at C-1, C-2, and sulfur, but differ in configuration at C-1′ (Scheme 4).

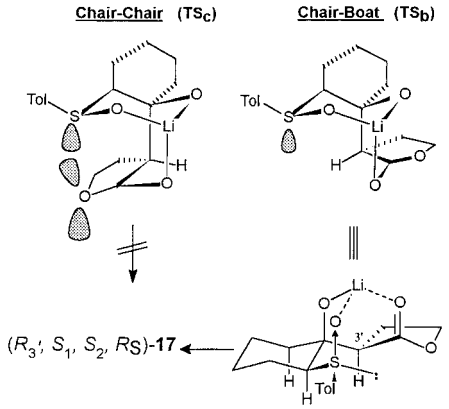
Once this point is clarified, we are sure that the stereoselectivity of the aldol reaction of R-CH_2-CO_2R′ with **1** is complete on the electrophilic center (keto sulfoxide) but only moderated on the nucleophilic one (lithium ester enolates). This behavior could be explained by assuming a totally stereoselective attack of each one of the two isomeric enolates (*E* and *Z*)[26] on the less hindered face of the carbonyl group (equatorial approach). Since the highly favored formation of the *E*-enolates[27] was expected under our experimental conditions, the hydroxy sulfoxides ratios, which in some cases was not very much different (Table 2), suggested to us that equilibration between *E* and *Z* enolates must take place in the reaction conditions. This is not surprising if the strong acidic character of the *β*-keto sulfoxide protons is taken into account. Therefore, diastereoisomeric ratio of the obtained *β*-hydroxy esters would depend on both the reactivity of each enolate and their relative proportion in the equilibrium.

In order to confirm this assumption, we have made the reaction of the keto sulfoxides **1** with the lithium enolates derived from *γ*-butyrolactone and *δ*-valerolactone, the cyclic structure of which precludes the mentioned equilibration. Only one diastereoisomer was obtained in both cases (**17** and **18**, respectively, Scheme 5), indicating that these reactions are completely stereoselective either in the electrophilic carbonyl or in the nucleophilic center. The absolute configuration of **17** was unequivocally established as (R_3′,S_1,S_2,R_S) by X-ray diffraction studies[28]

Scheme 5



Scheme 6



and the same configuration was assigned to **18** by comparison of the ^{1}H NMR spectra of both hydroxy lactones. The complete stereocontrol observed in the later cases, strongly supports a highly stereoselective attack of the enolates.

Two different bicyclic structures can be postulated for the tricoordinated lithium species, depending on the chairlike (TS_c) or boatlike (TS_b) transition states adopted by the six-membered ring containing the lactone enolate fragment (Scheme 6). The results obtained in their reactions with the keto sulfoxide **1** (exclusive formation of diastereoisomer with *R* configuration at C-3′) suggest that TS_b must be much more stable than TS_c. The electronic repulsion between the lone electron pairs at sulfur and alkoxy oxygen could account for the strong destabilization of TS_c (presumably favored from a steric point of view), which would explain that only TS_b was the operative transition state in all these reactions. The spatial restrictions imposed by the cyclic structure of the lactone are determinant of the strong stereoelectronic destabilization, because this interaction can be easily diminished by opening of the lactone ring, as can be seen from proper molecular models (see later).

From the spectroscopic data of hydroxy esters **9**−**12**, obtained from acyclic enolates (Table 3), we can establish that the relative configuration of diastereoisomers **A**, obtained as the major isomers in all cases, must be identical. The same is true for the minor **B** ones, which must be epimers at C-1′ of the hydroxy esters **A**. Nevertheless, these spectroscopic parameters cannot be used to carry out their unambiguous configurational assignment. Unfortunately, neither was conclusive the comparison of the spectroscopic parameters of these **A** and **B** epimers with those of compounds of known absolute configuration **17** and **18**, obtained from lactones, because the cyclic and acyclic structures of the ester

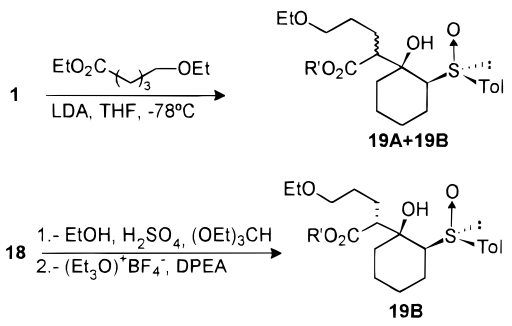
(24) Back, T. G.; Baron, D. L.; Yang K. *J. Org. Chem.* **1993**, *58*, 2407.
(25) Direct reduction of the sulfoxides **9A** + **9B** into **15** failed with NiB_2 or Raney nickel.
(26) We refer to the stereoisomeric enolates as *Z* or *E*, assigning to the "OLi" a higher priority than "OR" group.
(27) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.
(28) The crystal structure of compound **17** reinforces the previous configurational assignment, based on ^{1}H NMR parameters. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 3. Significant ^{1}H NMR Parameters of Compounds 9−12 and 19 (A and B Epimers)

		^{1}H NMR						^{13}C NMR
compd	R	$J_{2,3}$ ($CDCl_3$)	J_{OH} ($CDCl_3$)	δ H-2 (C_6D_6)	δ H-1′ (C_6D_6)	δ OH (C_6D_6)	$\Delta\delta$ AA′BB′ [a] (C_6D_6)	δ CAr[b] ($CDCl_3$)
9A	Me	12.4, 3.7	2	3.13	3.81	4.68	0.63	136.8
9B	Me	11.2, 3.9		2.36	3.72	4.77	0.41	138.8
10A	Et	12.5, 3.8	1.7	2.68	3.67	4.85	0.65	136.9
10B	Et	11.6, 4.0	2.2	2.27	3.57	4.78	0.40	137.8
11A	*i*-Pr	12.6, 3.6		2.86	3.60	4.76	0.54	136.8
11B	*i*-Pr	10.0, 3.9		2.62	3.53	4.93	0.51	138.8
12A	*t*-Bu	12.0, 3.6	1.3	2.71	3.85	4.80	0.53	137.2
12B	*t*-Bu	9.1, 4.3		2.71	3.80	5.05	0.50	139.4
19A	$(CH_2)_3OEt$	12.5, 3.8	2.0	2.80	3.85	4.79	0.62	136.8
19B	$(CH_2)_3OEt$	11.6, 3.8	1.9	2.47	3.87	4.84	0.47	137.4

[a] Observed chemical shift differences between p-tolyl protons. [b] Chemical shift of upper field quaternary aromatic carbon.

Scheme 7



moieties induce important differences in the considered parameters. Therefore, we have carried out the chemical correlation depicted in Scheme 7. The reaction of the ethyl 5-ethoxypentanoate lithium enolate with keto sulfoxide **1** yielded a 60:40 mixture of compounds **19A** and **19B**. As we can see, the relative proportion of the epimers is almost identical to that obtained from ethyl butanoate (Table 2), as it can be expected by assuming a scarce influence of the ethoxy group on the stereochemical course of the reaction and a similar size of the involved R groups (ethyl and 4-ethoxypropyl). Otherwise, the ethanolysis of the lactone **18**, followed by the *O*-alkylation of the resulting carbinol,[29] yielded a single δ-alkoxyester, which could be spectroscopically identified as **19B**, the minor diastereoisomer of the above mentioned aldol reaction. This correlation allowed us to assign the absolute configuration ($R_{3'},S_1,S_2,R_S$) exhibited by the compounds attained from lactones to the minor adducts obtained from acyclic esters lithium enolates.

In order to explain the stereochemical results obtained from acyclic esters, we must consider the evolution of the two stereoisomeric enolates. None of the two possible transition states derived from the *Z*-enolates [TS_b-(*Z*) and [TS_c-(*Z*)] is affected by important stereoelectronic interactions; therefore, the steric effects are the main factors controlling their relative stability, which must be higher for the chairlike [TS_c-(*Z*)], thus explaining the formation of the *R* configuration at C-1′ (Scheme 8). A similar situation takes place in the attack of the *E*-enolate. The chairlike transition state [TS_c-(*E*)] must be favored with respect to the boatlike one [TS_b-(*E*)] (the stereoelectronic repulsion unstabilizing the first one is much less restrictive than in lactones), and the formation of the *S* configuration at C-1′ results from this approach. The steric interactions in [TS_c-(*Z*)] are lower than those for [TS_c-(*E*)], which would explain the faster evolution of the reagents through the first one and, therefore, the formation of a higher proportion of isomer **B** than expected from the low ratio of *Z*-enolate generated in the experimental conditions used.

(29) In the reported conditions for lactone simultaneous cleavage and *O*-alkylation (King, S. A. *J. Org. Chem.* **1994**, *59*, 2253), compound **18** afforded exclusively cleavage.

Conclusions

In summary, we have described the aldol reactions of α-sulfinylcyclohexanones with different esters. They evolve with a complete control of the stereoselectivity in both the carbonyl and enolate prochiral centers. The equilibration of the enolates determines the formation of mixtures of two diastereoisomers, epimers at C-1′, the proportion of which is related with the nature of the starting ester. The use of lactones as reagents, which are unable to equilibrate, yields only one isomer. The key of the stereoselectivity is the formation of a tricoordinated lithium species with the sulfinyl oxygen of the chiral auxiliary. Studies related to the use of other cyclic and acyclic ketones as well as other compounds as sources of nucleophiles (nitriles, amides, acids, sulfones, sulfoxides, etc.) are been investigated in our laboratory, and the results obtained will be reported in due course.

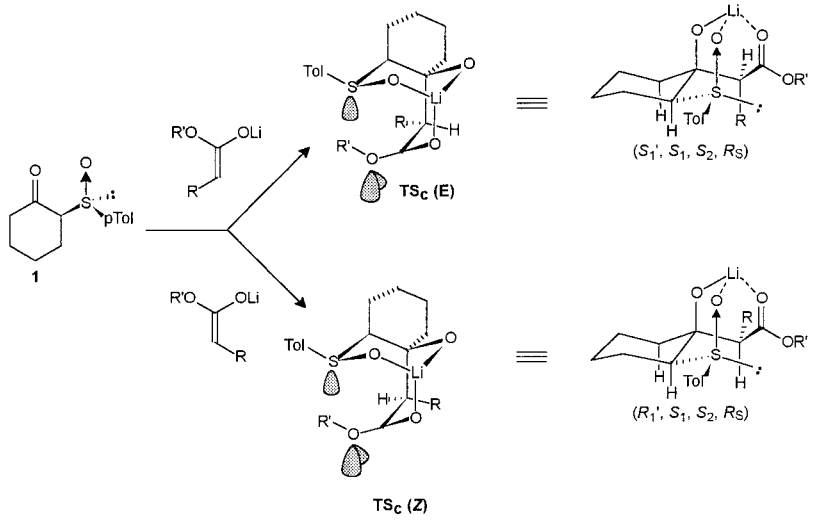
Experimental Section

Diastereoisomeric aldols ratios were established by integration of well-separated signals of the diastereoisomers in the crude reaction mixtures and are listed in Tables 1 and 2. Mass spectra were obtained in the electron impact (EI) mode at 70 eV unless stated otherwise. All reactions were monitored by TLC, which was performed on precoated sheets of silica gel 60 (F_{254}), and flash chromatography was effected with silica gel 60 (230−400 mesh). The apparatuses for inert atmosphere experiments were dried by flaming in a stream of dry argon. THF was distilled from sodium/benzophenone under argon and CH_2Cl_2 over P_2O_5. Diisopropylamine and diisopropylethylamine were distilled from potassium hydroxide.

A. Condensation of Lithium Ester Enolates and *β*-Keto Sulfoxides. General Procedure. A solution of butyllithium (5.9 mL of a 2.5 M solution in hexanes, 14.9 mmol) was dropwise added to a cooled (−78 °C) THF solution of diisopropylamine (2.2 mL, 15.7mmol in 60 mL of THF). After 20 min of stirring, a solution of the corresponding ester (14.9 mmol) in 5 mL of THF at −78 °C was added via cannula. The mixture was maintained 30 min at the same temperature, and a solution of 2-(*p*-tolylsulfinyl)cyclohexanone (**1**, 1.75 g, 7.4 mmol) in 25 mL of THF was added via cannula. After 20 min at −78 °C, the reaction was quenched with a NH_4Cl saturated solution (40 mL) and the mixture extracted with ethyl acetate (2 × 40 mL). The organic extracts were washed with brine (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed under vacuum and the crude product purified by flash chromatography to afford the corresponding hydroxy ester.

1-[(Ethoxycarbonyl)methyl]-2-(*p*-tolylsulfinyl)cyclohexanol (2) was obtained following the general procedure from ethyl acetate (1.31ml, 14.9 mmol) as a 93:7 mixture of diastereomers **2a:2b** (global yield 92%). Column chromatog-

Scheme 8



raphy on silica gel (hexane−ethyl acetate, 3:1) and recrystallization (benzene) afford pure **2a** (82%) as a white solid. Isolation of diastereomer **2b** has not been accomplished: **[1*S*,2*S*,(S)*R*]-2a:** mp 95−96 °C; $[\alpha]^{25}_D$ +156 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.42 and 7.33 (4H, AA′BB′ system), 4.25 (1H, d, *J* = 1.8 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 3,31 and 2.94 (2H, AB system, *J* = 15.3 Hz), 2.95 (1H, dd, *J* = 12.5 and 3.8 Hz), 2.42 (3H, s), 2.20−1.10 (8H, bm), 1.32 (3H, t, *J* = 7.1 Hz); ^{13}C NMR δ 171.1, 141.0, 137.3, 129.8, 124.2, 72.9, 64.9, 60.6, 45.9, 37.6, 24.6, 21.2, 20.4, 16.4, 14.1; IR ($CHCl_3$) 3390, 1705, 1170, 1020, 1010, 800. Anal. Calcd for $C_{17}H_{24}SO_4$: C, 62.94; H, 7.46; S, 9.86. Found: C, 62.98; H, 7.30; S, 9.82.

1-[(Methoxycarbonyl)methyl]-2-(*p*-tolylsulfinyl)cyclohexanol (3) was obtained following the general procedure from methyl acetate (1.18 mL, 14.9 mmol) as a 91:9 mixture of diastereomers **3a:3b** (global yield 88%). Column chromatography on silica gel (hexane−ethyl acetate, 3:1) and subsequent recrystallization (benzene) afford pure **3a** (74%) as a white solid. Isolation of diastereomer **3b** has not been accomplished.

[1*S*,2*S*,(S)*R*]-3a: mp 156−157 °C; $[\alpha]^{25}_D$ +176 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.42 and 7.33 (4H, AA′BB′ system), 4.27 (1H, d, *J* = 1.4 Hz), 3.75 (3H, s), 3.34 and 2.96 (2H, AB system, *J* = 16.4 Hz), 2.95 (1H, dd, *J* = 12.5 and 3.8 Hz), 2.42 (3H, s), 2.20−1.10 (8H, bm), 1.32 (3H, t, *J* = 7.1 Hz); ^{13}C NMR δ 171.6, 141.1, 137.1, 129.8, 124.3, 73.1, 64.6, 51.7, 45.8, 37.7, 24.7, 21.4, 20.4, 16.4; IR ($CHCl_3$) 1720, 1180, 1040, 1030, 810. Anal. Calcd for $C_{16}H_{22}SO_4$: C, 61.91; H, 7.15; S, 10.31. Found: C, 61.75; H, 6.98; S, 10.04.

1-[*tert*-Butoxycarbonyl)methyl]-2-(*p*-tolylsulfinyl)cyclohexanol (4) was obtained following the general procedure from *tert*-butyl acetate (2.0 mL, 14.9 mmol) as a 96:4 mixture of diastereomers **4a:4b** (global yield 81%). Both diastereomers were separated by column chromatography on silica gel (hexane−ethyl acetate, 3:1).

[1*S*,2*S*,(S)*R*]-4a: mp 143−145 °C; $[\alpha]^{25}_D$ +140 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.39 and 7.28 (4H, AA′BB′ system), 4.22 (1H, d, *J* = 1.3 Hz), 3,13 and 2,86 (2H, AB system, J_{AB} = 15.2 Hz), 2.87 (1H, dd, *J* = 12.1 and 2.1 Hz), 2.39 (3H, S), 2.20−1.10 (8H, bm), 1.47 (9H, s); ^{13}C NMR δ 170.5, 140.9, 137.7, 129.7, 124.2, 81.3, 72.9, 65.4, 46.9, 37.5, 28.1, 24.7, 21.3, 20.5, 16.5; IR ($CHCl_3$) 3400, 1705, 1150, 1020, 1010, 840; MS *m*/*z* 296(2) M^+, 279 (14), 213 (4), 157 (80), 140 (100), 123 (17), 97 (73); HRMS calcd for $C_{19}H_{28}SO_4$ 352.17083, found 352.17136. Anal. Calcd for $C_{19}H_{28}SO_4$: C, 64.74; H, 8.01; S, 9.08. Found: C, 64.17; H, 7.87; S, 8.84.

[1*S*,2*R*,(S)*R*]-4b: mp 136−137 °C; $[\alpha]^{25}_D$ +101 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.46 and 7.30 (4H, AA′BB′ system), 4.96 (1H, s), 3.08 (1H, part A of and ABX system, *J* = 1.4, *J* = 16.2 Hz) and 2.79 (1H, part B of an ABX system), 2.40 (1H, m), 2.39 (3H, s), 2.20−1.10 (8H, bm), 1.49 (9H, s); ^{13}C NMR δ 172.6, 140.5, 140.0, 129.7, 124.3, 82.2, 76.4, 72.6, 39.4, 38.5, 28.1, 24.6, 23.0, 21.3, 17.7; IR ($CHCl_3$) 3340, 1690, 1150, 1020, 1010, 830; MS *m*/*z* 296(1) M^+, 279 (18), 213 (10), 157 (72), 140 (100), 123 (19), 97 (60); HRMS calcd for $C_{19}H_{28}SO_4$ 352.17083, found 352.17081. Anal. Calcd for $C_{19}H_{28}SO_4$: C, 64.74; H, 8.01; S, 9.08. Found: C, 63.20; H, 7.81; S, 8.15.

[1*S*,2*S*,(S)*R*]-1-[2′-(Ethoxycarbonyl)prop-2′-yl]-2-(*p*-tolylsulfinyl)cyclohexanol (8A) was obtained as the sole diastereomer (ed >97%) following the general procedure from ethyl 2-methylpropanoate (1.99 mL, 14.9 mmol). Column chromatography (hexane−ethyl acetate, 3:1) affords pure **8A** as a white solid: yield 90%; mp 84−86 °C; $[\alpha]^{25}_D$ +101 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.42 and 7.33 (4H, AA′BB′ system), 4.83 (1H, d, *J* = 2 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 2.60 (1H, dd, *J* = 12.5 and 3.7 Hz), 2.43 (3H, s), 2.08 (1H, m), 1.9−1.1 (7H, bm), 1.36 and 1.35 (3H, t), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR δ 178.3, 140.6, 138.9, 129.6, 123.9, 76.8, 66.6, 61.5, 49.1, 33.6, 24.9, 23.1, 21.5, 21.2, 20.6, 16.6, 13.7; IR ($CHCl_3$) 3510, 3410, 1690, 1240, 1150, 1040. Anal. Calcd for $C_{19}H_{28}SO_4$: C, 64.74; H, 8.01; S, 9.08. Found: C, 64.93; H, 8.02; S, 9.11.

1-[1′-(Ethoxycarbonyl)ethyl]-2-(*p*-tolylsulfinyl)cyclohexanol (9) was obtained from ethyl propanoate (1.70 mL, 14.9 mmol) as a 55:45 mixture of C-1′ epimers **9A:9B** (yield 88%). Separation of both epimers was effected by column chromatography (hexane−acetone, 4:1).

[1′*S*,1*S*,2*R*,(S)*R*]-9A: mp 102−103 °C; $[\alpha]^{25}_D$ +111 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.41 and 7.33 (4H, AA′BB′ system), 4.23 (2H, q, *J* = 7.1 Hz), 4.09 (1H, d, *J* = 2 Hz), 3.69 (1H, q, *J* = 7.2 Hz), 2.89 (1H, dd, *J* = 12.4 and 3.7 Hz,), 2.42 (3H, s), 2.20−1.10 (8H, bm), 1.38 (3H, d, *J* = 7.1 Hz)., 1.33 (3H, t, *J* = 7.2 Hz); ^{13}C NMR δ 173.5, 140.5, 136.8, 129.4, 123.8, 74.3, 64.5, 60.1, 47.6, 31.7, 24.3, 20.9, 19.9, 16.2, 13.9, 10.6; IR ($CHCl_3$) 3390, 1705, 1140, 1040, 1010, 870. Anal. Calcd for $C_{18}H_{26}SO_4$: C, 63.88; H, 7.77; S, 9.45. Found: C, 63.94; H, 7.64; S, 9.32.

[1′*R*,1*S*,2*R*,(S)*R*]-9B: mp 140−142 °C; $[\alpha]^{25}_D$ +104 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.48 and 7.30 (4H, AA′BB′ system), 4.20 (2H, q, *J* = 7.2 Hz), 4.07 (1H, bs), 3.53 (1H, q, *J* = 7.2 Hz), 2.56 (1H, dd, *J* = 11.2 and 3.9 Hz), 2.42 (3H, s), 2.20−1.10 (8H, bm), 1.29 (3H, d, CH_3CH, *J* = 7.1 Hz), 1.27 (3H, t, *J* = 7.2 Hz); ^{13}C NMR δ 174.4, 141.0, 138.8, 129.7, 124.1, 75.1, 65.0, 60.6, 47.2, 32.5, 24.3, 21.2, 20.2, 17.1, 14.0, 12.6; IR ($CHCl_3$) 3400, 1710, 1175, 1040, 1010, 850. Anal. Calcd for $C_{18}H_{26}SO_4$: C, 63.88; H, 7.77; S, 9.45. Found: C, 63.99; H, 7.70; S, 9.33.

1-[1′-(Ethoxycarbonyl)propyl]-2-(*p*-tolylsulfinyl)cyclohexanol (10) was obtained from ethyl butanoate (1.97 mL, 14.9 mmol) following the general procedure as 66:34 mixture of C-1′ epimers **10A:10B** (yield 92%). Purification and separation of both epimers was effected by column chromatography on silica gel (hexane−acetone, 4:1). The isomer **10A**, obtained as solid, was crystallized (CH_2Cl_2−hexane) to white plates, whereas the isomer **10B** was obtained as a colorless oil.

[1′*S*,1*S*,2*R*,(S)*R*]-10A: mp 115−116 °C; $[\alpha]^{25}_D$ +138 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.37−7.31 (4H, m), 4.24 (2H, m), 4.08 (1H,

d, J = 1.7 Hz), 3,41 (1H, dd, J = 3.0 and 11.3 Hz), 2.54 (1H, dd, J = 12.5 and 3.8 Hz), 2.41 (3H, s), 2.20−0.9 (8H, bm), 1.33 (3H, t, J = 7.1 Hz), 0.98 (3H, d, CH_3CH, J = 7.3 Hz); ^{13}C NMR δ 173.8, 141.1, 136.9, 129.8, 124.3, 75.1, 64.9, 60.5, 57.4, 32.8, 24.7, 21.4, 20.3, 19.2, 16.7, 14.4, 12.9; IR ($CHCl_3$) 3390, 1710, 1150, 1020.

[1′*R*,1*S*,2*R*,(S)*R*]-10B: $[\alpha]^{25}_D$ +105 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.39 and 7.33 (4H, AA′BB′system), 4.20 (2H, m), 4.08 (1H, d, J = 2.2 Hz), 3.35 (1H, dd, J = 3.0 and 8.9 Hz), 2.57 (1H, dd, J = 11.6 and 4.0 Hz), 2.41 (3H, s), 2.30−0.8 (8H, bm), 1.29 (3H, t, J = 7.0 Hz), 0.98 (3H, d, CH_3CH, J = 7.3 Hz); ^{13}C NMR δ 173.9, 141.2, 137.8, 129.8, 124.4, 75.4, 64.8, 60.5, 56.4, 33.4, 24.6, 21.4, 21.3, 20.3, 19.2, 17.6, 14.3, 12.8; IR ($CHCl_3$) 34000, 1700, 1150, 1090.

1-[1′-(Ethoxycarbonyl)-2′-methylpropyl]-2-(*p*-tolylsulfinyl)cyclohexanol (11) was obtained from ethyl 3-methylbutanoate (2.28 mL, 14.9 mmol) following the general procedure as a 74:26 mixture of the epimers in C-1′, **11A:11B** (yield 88%). Purification and separation of both epimers were effected by column chromatography (hexane−ethyl acetate, 7:2).

[1′*S*,1*S*,2*R*,(S)*R*]-11A: mp 79−81 °C; $[\alpha]^{25}_D$ +106 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.27 (4H, m), 4.20 (2H, m), 3.99 (1H, s), 3.24 (1H, d, J = 6.8 Hz), 2.59 (1H, dd, J = 12.6 and 3.6 Hz), 2.37 (3H, S), 2.34 (1H, m), 2.50−1.1 (8H, bm), 1.30 (3H, t, J = 6.8 Hz), 1.18 and 0.92 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 173.5, 141.0, 136.8, 129.8, 124.1, 75.8, 65.1, 60.7, 60.1, 32.5, 26.5, 24.5, 23.9, 21.2, 20.4, 16.8, 14.4; IR ($CHCl_3$) 3480, 1700, 1170, 1100, 1010, 820. Anal. Calcd for $C_{19}H_{28}SO_4$: C, 65.54; H, 8.26; S, 8.73. Found: C, 65.43; H, 8.24; S, 8.93.

[1′*R*,1*S*,2*R*,(S)*R*]-11B: mp 72−74 °C; $[\alpha]^{25}_D$ +86 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.38 and 7.29 (4H, AA′BB′ system), 4.12 (1H, bs), 3.27 (1H, d, J = 7.2 Hz), 2.66 (1H, dd, J = 10.0 and 3.9 Hz), 2.38 (3H, s), 2.17 (1H, m), 2.50−1.1 (8H, bm), 1.24 (3H, t, J = 7.2 Hz), 1.13 and 1.0(3H, d, J = 6.8 and 6.7 Hz, respectively); ^{13}C NMR δ 173.4, 141.0, 138.8, 129.7, 124.4, 75.5, 67.1, 60.2, 58.3, 32.9, 27.2, 24.0, 23.4, 21.3, 20.9, 20.6, 18.3, 14.2; IR ($CHCl_3$) 3420, 1710, 1160, 1070, 1030, 810. Anal. Calcd for $C_{19}H_{28}SO_4$: C, 65.54; H, 8.26; S, 8.73. Found: C, 65.44; H, 8.21; S, 8.92.

1-[1′-(Ethoxycarbonyl)-2′,2′-dimethylpropyl]-2-(*p*-tolylsulfinyl)cyclohexanol (12) was obtained from ethyl 3,3-dimethylbutanoate (2.14 g, 14.9 mmol) following the general procedure as a 91:9 mixture of the epimers in C-1′ **12A:12B** (yield 75%). Purification and separation of both epimers was effected by column chromatography (hexane−acetone, 4:1).

[1′*S*,1*S*,2*R*,(S)*R*]-12A: $[\alpha]^{25}_D$ +115 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.34 (4H, s) 4.23 (2H, m), 4.05 (1H, d, J = 1.6 Hz), 3.54 (1H, s), 2.55 (1H, dd, J = 12.0 and 3.6 Hz), 2.41 (3H, s), 2.35−0.8 (8H, bm), 1.34 (3H, t, J = 7.1 Hz), 1.23 (9H, s); ^{13}C NMR δ 173.6, 141.0, 137.2, 129.8, 124.2, 77.5, 66.1, 62.3, 60.1, 35.1 (2C), 30.7, 24.4, 21.3, 20.6, 16.9, 14.3; HRMS calcd for $C_{21}H_{32}SO_4$ 380.20213, found 380.20236; MS *m*/*z* 322 (0.3) M^+, 363 (3), 241 (32), 237 (24) 185 (100), 139 (82), 97 (65).

[1′*R*,1*S*,2*R*,(S)*R*]-12B: $[\alpha]^{25}_D$ +91 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.44 and 7.31 (4H, AA'BB' system), 4.30 (1H, s), 4.03 (2H, q, J = 7.0 Hz), 3.46 (1H, s), 2.85 (1H, dd, J = 9.1 and 4.3 Hz), 2.41 (3H, s),2.50−1.1 (8H, bm), 1.23 (3H, t, J = 6.8 Hz), 1.26 (9H, s); ^{13}C NMR δ 173.4, 141.2, 139.4, 129.8, 124.5, 77.0, 68.2, 60.1 (2C), 34.3, 34.2,, 30.5, 23.8, 21.4, 21.1, 19.6, 14.2; MS *m*/*z* 322 (0.4) M^+, 363 (4), 241 (15), 237 (33) 185 (100), 139 (63), 97 (69).

1-[1′-(*tert*-butoxycarbonyl)ethyl]-2-(*p*-tolylsulfinyl)cyclohexanol (13) was obtained from *tert*-butyl propanoate (2.24 mL, 14.9 mmol) following the general procedure as 60:40 mixture of C-1′ epimers **13A:13B** (yield 92%). Purification and separation of both epimers was effected by column chromatography on silica gel (hexane−acetone, 4:1).

[1′*S*,1*S*,2*R*,(S)*R*]-13A: mp 121−123 °C; $[\alpha]^{25}_D$ +143 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.39 and 7.32 (4H, AA′BB′ system), 4.05 (1H, d, J = 2.1 Hz), 3,54 (1H, q, J = 7.2 Hz), 2.91 (1H, dd, J = 12.4 and 3.8 Hz), 2.41 (3H, s), 2.20−0.9 (8H, bm), 1.50 (9H, s), 1.18 (3H, d, CH_3CH, J = 7.2 Hz); ^{13}C NMR δ 173.7, 141.0, 136.9, 129.8, 124.3, 80.8, 75.0, 64.3, 49.0, 32.1, 28.1, 24.9, 21.4, 20.4, 17.1, 11.4; IR ($CHCl_3$) 3400, 1710, 1370, 1150, 1030, 1010, 840; MS *m*/*z* (35 eV): 366 (0.2) M^+, 293 (11), 237 (16), 171 (75), 140 (76), 123 (15), 97 (100); HRMS calcd for $C_{20}H_{30}SO_4$ 366.18648, found 366.18701. Anal. Calcd for $C_{20}H_{30}SO_4$: C, 65.54; H, 8.26; S, 8.73. Found: C, 65.27; H, 8.07; S, 8.86.

[1′*R*,1*S*,2*R*,(S)*R*]-13B: mp 141−142 °C; $[\alpha]^{25}_D$ +105 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.43 and 7.33 (4H, AA′BB′ system), 4.0 (1H, s), 3.34 (1H, q, J = 7.1 Hz), 2.59 (1H, dd, J = 10.2 and 4.1 Hz), 2.40 (3H, s), 2.30−0.80 (8H, bm), 1.45 (9H, s), 1.23 (3H, d, CH_3CH, J = 7.2 Hz); ^{13}C NMR δ 174.1, 141.0, 129.8, 128.3, 124.5, 81.7, 74.9, 66.8, 47.4, 32.5, 28.1, 24.1, 21.4, 20.6, 17.8, 12.5; IR ($CHCl_3$) 3420, 1710, 1370, 1150, 1040, 1010, 840; MS *m*/*z* (35 eV) 366 (0.4) M^+, 293 (14), 237 (29), 171 (80), 140 (84), 123 (18), 97 (100). Anal. Calcd for $C_{20}H_{30}SO_4$: C, 65.54; H, 8.26; S, 8.73. Found: C, 64.97; H, 8.14; S, 8.99.

[3′*R*,1*S*,2*S*,(S)*R*]-1-(2′-Oxotetrahydrofuran-3′-yl)-2-(*p*-tolylsulfinyl)cyclohexanol (17) was obtained as a sole diastereomer (ed >97%) following the general procedure from γ-butyrolactone (1.14 mL, 14.9 mmol). Purification by column chromatography (hexane−ethyl acetate, 3:1) afforded compound **17** as a white solid: yield 88%; mp 170 °C (benzene); $[\alpha]^{25}_D$ +108 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.41 and 7.32 (4H, AA′BB′ system), 4.52 and 4.36 (2H, AB from an ABX_2 system, J_{AB} = 9.5, J_{AX} = 2.5, and J_{BX} = 7.0 Hz), 4.14 (1H, d, J = 1.3 Hz), 3.6 (1H, dd, J = 11.6 and 9.6 Hz), 2.57−2.34 (4H, m), 2.42 (3H, s), 2.0−1.0 (8H, m); ^{13}C NMR δ 178.2, 141.2, 138.7, 129.9, 124.1, 74.1, 66.8, 66.2, 47.9, 34.3, 25.3, 24.4, 21.3, 20.4, 16.4; IR ($CHCl_3$) 3480, 1740, 1360, 1170, 1040, 1010. Anal. Calcd for $C_{17}H_{22}SO_4$: C, 63.33; H, 6.88; S, 9.93. Found: C, 63.10; H, 6.64; S, 9.71.

[3′*R*,1*S*,2*S*,(S)R]-1-(2′-Oxotetrahydropyran-3′-yl)-2-(*p*-tolylsulfinyl)cyclohexanol (18) was obtained as a sole diastereomer (ed >97%) from δ-valerolactone (1.38 mL, 14.9 mmol), yield 88%. Column chromatography of the crude product (hexane−ethyl acetate, 3:1) affords compound **18** as a white solid: mp 152−153 °C; $[\alpha]^{25}_D$ +129 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.46 and 7.35 (4H, AA′BB′ system), 4.71 (1H, d, J = 0.7 Hz), 4.60−4.42 (2H, m, OCH_2CO), 3.49 (1H, dd, J = 11.5 and 7.8 Hz), 2.64 (1H, ddd, J = 0.7 Hz, 4.3, 11.6 Hz), 2.41 (3H, s), 2.4−0.7 (12H, m); ^{13}C NMR δ 173.2, 141.0, 137.6, 129.8, 124.3, 92.3, 69.2, 65.7, 48.6, 34.5, 24.6, 22.7, 22.2, 21.3, 20.5, 16.4; IR ($CHCl_3$) 340, 1700, 1165, 1080, 1040. Anal. Calcd for $C_{18}H_{24}SO_4$: C, 64.26; H, 7.20; S, 9.51. Found: C, 64.26; H, 6.93; S, 9.9.59.

1-[1′-(Ethoxycarbonyl)-4′-ethoxybutyl]-2-(*p*-tolylsulfinyl)cyclohexanol (19) was obtained from ethyl 5-ethoxypentanoate[27] (2.59 g, 14.9 mmol) as a 60:40 mixture of C-1′ epimers **19A:19B** (yield 85%). Purification and separation of both epimers was effected by column chromatography on silica gel (CH_2Cl_2−ethyl acetate−acetone, 9:0.5:0.5).

[1′*S*,1*S*,2*R*,(S)*R*]-19A: $[\alpha]^{25}_D$ +121 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 7.28 (4H, m), 4.12 (2H, m), 4.06 (1H, J = 2 Hz), 3.42 (5H, m), 2.34 (3H, s), 2.1−0.8 (12 H, m), 1.26 (3H, t, J = 7.1 Hz), 1.13 (3H, t, J = 7.0 Hz);^{13}C NMR δ 173.7, 141.1, 136.8, 129.8, 124.3, 75.1, 70.4, 66.0, 64.8, 60.6, 55.2, 32.8, 28.6, 24.7, 22.8, 21.3, 20.3, 16.7, 15.2, 14.3; IR ($CHCl_3$) 3400, 1720, 1100, 1000.

[1′*R*,1*S*,2*R*,(S)*R*]-19B: $[\alpha]^{25}_D$ +99 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.41 and 7.32 (4H, AA′BB′ system), 4.19 (2H, q, J = 7.1 Hz), 3.94 (1H, J = 1.9 Hz), 3.51 (5H, m), 2.41 (3H,s), 2.1−0.8 (12 H, m), 1.27 (3H, t, J = 7.1 Hz), 1.18 (3H, t, J = 7.0 Hz); ^{13}C NMR: δ 173.4, 140.8, 137.4, 129.8, 124.3, 76.4, 69.1, 65.8, 64.4, 60.3, 53.7, 32.9, 27.9, 24.2, 22.6, 21.3, 20.3, 17.0, 15.0, 14.1; IR ($CHCl_3$) 3370, 1700, 1100, 1060.

Diastereoisomer **19B** was also obtained as a sole diastereoisomer, in two steps, from lactone **18** following the next procedure.

[1′*R*,1*S*,2*S*,(S)*R*]-1-[1′-(Ethoxycarbonyl)-4′-hydroxybutyl]-2-(*p*-tolylsulfinyl)cyclohexanol (20). To a stirred solution of hydroxylactone **18** (300 mg, 0.89 mmol) and trimethyl orthoformate (296 μL, 1.78 mmol) in dried ethanol (4 mL) was added H_2SO_4 (0.06 equiv). The reaction mixture was heated at 50 °C for 6 h. The solvent was carefully removed and the residue partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The aqueous layer was twice extracted with ethyl acetate (20 mL), the combined organic layers were washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (acetone−hexane, 1:2.5) to obtain pure **20** as a white solid: yield 78%; mp 119−

121 °C; $[\alpha]^{25}_D$ +112 (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 7.41 and 7.32 (4H, AA′BB′system), 4.21 (2H, q, J = 7.1 Hz), 4.01 (1H, d, J = 2 Hz), 3.82− 3.51 (2H, m), 3.50 (1H, dd, J = 2.4 and 11.9 Hz), 2.59 (1H, dd, J = 11.8 and 3.7 Hz), 2.42 (3H, s), 2.30−0.8 (8H, bm), 1.30 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 173.8, 141.2, 137.3, 129.9, 124.4, 64.4, 61.8, 60.7, 54.0, 33.3, 31.0, 24.7, 24.0, 21.4, 20.3, 17.4, 14.3.

[1′*R*,1*S*,2*R*,(S)*R*]-1-[1′-(Ethoxycarbonyl)-4′-ethoxybutyl]-2-(*p*-tolylsulfinyl)cyclohexanol (19B). Into a flame-dried flask was placed diisopropylethylamine (0.94 mmol, 158 μL), and a solution of 0.3 g of hydroxy ester **20** (0.76 mmol) in 5 mL of CH_2Cl_2 and 1 mmol of triethyloxonium tetrafluorborate (1 M solution in CH_2Cl_2 from Aldrich) were added via syringe. The resulting solution was stirred at room temperature for 3 h before it was quenched with ice water and extracted with ethyl acetate (2 × 20 mL). The organic extracts were washed twice with 5% aqueous $NaHCO_3$ and once with water and dried over Na_2SO_4. The solvent was removed and the crude product purified by flash chromatography (acetone−hexane, 1:2.5) to afford pure **19B** (0.22 g, 68%).

B. Sulfinyl Group Oxidation. (1*S*,2*S*)-1-[(Ethoxycarbonyl)methyl]-2-(*p*-tolylsulfonyl)cyclohexanol (5a). To a solution of hydroxy sulfoxide **2a** (200 mg, 0.62 mmol) in dichloromethane (15 mL) was dropwise added a solution of *m*-CPBA (50−60% in water, 282 mg, 0.75 mmol) in chloroform (15 mL). After 30 min, a saturated solution of $NaHCO_3$ (5 mL) was added and stirring was maintained during 30 min. The layers were separated and the organic one was washed with saturated $NaHCO_3$ solution (2 × 30 mL) and dried ($MgSO_4$). Removal of the solvent afford pure **5a** as a colorless solid which was recrystallized from acetone−hexane: yield 90%; mp 90−92 °C; $[\alpha]^{25}_D$ −11 (*c* 1, $CHCl_3$); ^{1}H NMR δ 7.74 and 7.34 (4H, AA′BB′ system), 4.12 (2H, q, J = 7.1 Hz), 3.64 (1H, dd, J = 12.6 and 3.6 Hz), 3.25 and 3.02 (2H, AB system, J = 17.2 Hz), 2.45 (3H, s), 2.20−1.10 (8H, bm), 1.27 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 171.5, 144.7, 135.7, 129.6, 128.8, 71.3, 66.3 ,60.4, 45.4, 38.1,24.8, 23.8, 21.6, 20.2, 14.1; IR ($CHCl_3$) 3500, 1705, 1280, 1270, 1160, 1110, 1060, 1010. Anal. Calcd for $C_{17}H_{24}SO_5$: C, 59.98; H, 7.11; S, 9.40. Found: C, 60.14; H, 6.82; S, 9.32.

C. Sulfinyl Group Reduction. General Procedure. A cooled (−40 °C) solution of TFAA (0.97 mL, 6.85 mmol) in acetone (5 mL) was dropwise added via cannula to a stirred suspension of the corresponding hydroxy sulfoxide (1.71 mmol) and sodium iodide (778 mg, 5.14 mmol) in acetone (25 mL) at the same temperature. The solution turned to dark red, and after 15 min of stirring, a saturated sodium carbonate solution and a 5% sodium thiosulfate solution were sequentially added. The reaction mixture was allowed to reach room temperature, and the organic solvent was evaporated, The residue was extracted with ethyl acetate (2 × 40 mL), washed with brine (2 × 20 mL), and dried ($MgSO_4$). The extracts were evaporated in vacuo to yield the crude product.

(1*S*,2*S*)-1-[(Ethoxycarbonyl)methyl]-2-(*p*-tolylsulfenyl-)cyclohexan-1-ol (6a) was obtained from **2a** following the general procedure. The crude product was chromatographed (hexane−acetone, 6:1) to afford pure **6a** (474 mg, 90%) as a pale yellow oil: $[\alpha]^{25}_D$ +2 (*c* 2, $CHCl_3$); ^{1}H NMR δ 7.31 and 7.05 (4H, AA′BB′ system), 4.10 (2H, q, J = 7.1 Hz), 3.53 (1H, s), 3.17 and 2.48 (2H, AB system, J = 15.3 Hz), 3.02 (1H, t, J = 8.0 Hz), 2.28 (3H, s), 2.0−1.40 (8H, bm), 1.22 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 172.4, 135.5, 132.0, 129.4, 130.3, 72.1, 60.3,-57.6, 44.3, 36.9, 30.1, 23.7, 20.7 (two peaks), 13.8; MS *m*/*z* 308 (62) M^+, 290 (15), 221 (19), 167 (77), 1398 (44), 124 (100), 97 (59), 91 (55); HRMS calcd for $C_{17}H_{24}SO_3$ 308.14462, found 322.14422.

(1′*S*,1*S*,2*S*)-1-[1′-(Ethoxycarbonyl)ethyl]-2-(*p*-tolylsulfenyl)cyclohexan-1-ol (14A) was obtained from **9A** following the general procedure. Column chromatography on silica gel (hexane−acetone, 6:1) afforded pure **14A** (473 mg, 86%) as a pale yellow oil: $[\alpha]^{25}_D$ +1.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR δ 7.35 and 7.08 (4H, AA′BB′ system), 4.08 (2H, m), 3.45 (1H, t, J = 8.0 Hz,), 3,14 (1H, q, J = 7.3 Hz), 2.73 (1H, s), 2.32 (3H, s), 1.90−1.20 (8H, bm), 1.23 (3H, d, J = 7.3 Hz), 1.20 (3H, t, J = 7.1 Hz); ^{13}C NMR δ 174.8, 137.0, 132.8, 131.4, 129.5, 74.2, 60.3, 55.6, 45.9, 32.7, 30.2, 24.8, 21.1, 13.9, 11.4; IR ($CHCl_3$) 3480, 1710, 1180, 1030, 960; MS *m*/*z* 322 (76) M^+, 304 (4), 221 (22), 181 (55), 153 (37), 124 (100), 97 (62), 91(50); HRMS calcd for $C_{18}H_{26}SO_3$ 322.16026, found 322.15973

(1′*R*,1*S*,2*S*)-1-[1′-(Ethoxycarbonyl)ethyl]-2-(*p*-tolylsulfenyl)cyclohexan-1-ol (14B) was obtained from **9B** following the general procedure. The crude was chromatographed (hexane−acetone, 7:1) to afford pure **14B** (457 mg, 83%) as a pale yellow oil: $[\alpha]^{25}_D$ +10 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 7.34 and 7.10 (4H, AA′BB′ system), 4.19 (2H, q, J = 7.1 Hz), 3.62 (1H, d, J = 1), 3,38 (1H, q, J = 7.3 Hz), 3.01 (1H, dd, J = 10 and 5.7 Hz), 2.32 (3H, s), 2.0−1.0 (8H, bm), 1.28 (3H, t, J = 7.1 Hz), 1.20 (3H, d, J = 7.1 Hz); ^{13}C NMR δ 175.5, 137.0, 132.5, 131.7, 129.6, 75.0, 60.8, 55.2, 46.7, 32.1, 30.2, 25.9, 21.0, 20.8, 14.1, 11.8; IR ($CHCl_3$) 3480, 1710, 1180, 1030, 960; MS *m*/*z* 322(85) M^+, 304 (10), 221 (22), 181 (55), 153 (41), 124 (100), 97 (65), 91 (52); HRMS calcd for $C_{18}H_{26}SO_3$ 322.16026, found 322.16016

D. Sulfinyl Group Reductive Elimination. 1-[1′-(Ethoxycarbonyl)ethyl]cyclohexanol (15). $NaBH_4$ (516 mg, 13.5 mmol) was added in small portions to a cooled (0 °C) and vigorously stirred suspension of $NiCl_2 \cdot 6H_2O$ (1.16 g, 4.86 mmol) in a THF−MeOH (1:3) solution containing a 60:40 mixture of diastereomers **14A:14B** (198 mg, 0.63 mmol). A black precipitate appeared with H_2 evolution. Stirring was continued during 30 min, and the reaction was monitored by TLC (hexane−ethyl acetate, 5:1). The crude was filtered through Celite and washed with the solvent mixture. The organic extracts were concentrated in vacuo, and the residue was diluted with CH_2Cl_2−H_2O (1:1). The two layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 60 mL), washed with brine, and dried ($MgSO_4$). The solvents were evaporated under reduced pressure, and the crude was purified by chromatography (hexane−CH_2Cl_2, 3:1) to afford **15**[30] as a mixture of enantiomers: yield 71%; ^{1}H NMR δ 4.15 (2H, q, J = 7.1 Hz), 3.0 (1H, d, J = 1.8 Hz), 2.40 (1H, c, J = 7.2 Hz), 1.75−1.35 (10H, m), 1.20 (3H, t, J = 7.1 Hz), 1.11 (3H, d, J = 7.1 Hz); ^{13}C NMR δ 176.8, 71.1, 60.3, 47.8, 36.8, 25.6, 21.8, 21.5, 14.0, 11.3. Starting from pure **14A**, enantiomerically pure **(*S*)-15** was obtained as an oil, $[\alpha]^{25}_D$ +20 (*c* 0.5, $CHCl_3$).

E. Sulfinyl Group Pyrolysis. General Procedure. To a flame-dried flask equipped with a reflux condenser containing sodium bicarbonate (3.5 g, 40.6 mmol) was added via cannula a solution of the corresponding hydroxy sulfoxide (1.06 mmol) in *o*-xylene (10 mL) . The mixture was vigorously stirred and heated in an oil bath at the tempeature indicated in each case. The reaction progress was monitored by TLC (ethyl acetate−hexane, 1:4). The mixture was cooled to room temperature, and the crude product was filtered over Celite and washed with a saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous one was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were finally washed with brine and dried ($MgSO_4$). To prevent any reaction product evaporation, ethyl acetate was eliminated under reduced pressure without heating. Cycloalkenol isolation was effected by flash chromatography using successively hexane (to remove remaining *o*-xylene) and the eluent indicated in each case.

(1*S*)-1-[(Ethoxycarbonyl)methyl]cyclohex-2-en-1-ol (7) was obtained from **2a** by heating during 3 h at 150 °C. Chromatographic purification (ethyl acetate−hexane, 1:5) affords compound **(**1*S*)-**7** (132 mg, 68%) as an oil: $[\alpha]^{25}_D$ +13 (*c* 0.3 $CHCl_3$); ^{1}H NMR δ 5.71(1H, dt, J = 10.0 and 3.7 Hz) 5.57 (1H, bd, 10) 4.09 (2H, q, CH_3CH_2, J = 7.2 Hz), 3.64 (1H, s), 2.46 (2H, s), 2.40−1.40 (6H, bm), 1.32 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 172.3, 130.7, 130.0, 67.9, 60.4, 45.3, 35.5, 24.8, 18.7, 14.0; IR($CHCl_3$) 3500, 1700, 1180, 1030, 1000; MS *m*/*z* 184(1) M^+, 166 (14), 156 (17), 121 (11), 83 (37); HRMS calcd for $C_{10}H_{16}$-SO_3 184.10995, found 184.11017.

(1′*R*,1*R*)-1-[1′-(Ethoxycarbonyl)ethyl]cyclohex-2-en-1-ol (16A) was obtained from **9B** by heating during 3 h at 145 °C. Chromatographic purification (CH_2Cl_2−hexane, 2:1) affords **16B** (143 mg, 82%) as an oil: $[\alpha]^{25}_D$ +68 (*c* 1, $CHCl_3$); ^{1}H

(30) Diem, M. J.; Burow, D. F.; Fry, J. L. *J. Org. Chem.* **1977**, *42*, 1801.

NMR δ 5.88 (1H, ddd, J = 10.2, 3.9, and 2.6 Hz) 5.57 (1H, d, J = 10.2 Hz), 4.16 (2H, q, J = 6.9 Hz), 3.02 (1H, s), 2.57 (1H, c), 2.20−1.10 (6H, bm), 1.27 (3H, t, J = 6.9 Hz), 1.22 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 176.1, 131.4, 129.0, 70.1, 60.5, 48.2, 34.7, 25.0, 18.7, 14.2, 12.1; IR($CHCl_3$) 3480, 1750, 1150, 960; IR ($CHCl_3$) 3460, 1710, 1190, 960; HRMS calcd for $C_{10}H_{16}SO_3$ 184.10995, found 184.11017.

(1′*S*,1*R*)-1-[1′-(Ethoxycarbonyl)ethyl]cyclohex-2-en-1-ol (16B) was obtained from **9A** by heating during 5 h at 125 °C. Chromatographic purification (CH_2Cl_2−hexane, 2:1) affords **16A** (157 mg, 75%) as an oil: $[\alpha]^{25}_D$ +40 (*c* 2, $CHCl_3$); ^{1}H NMR δ 5.7 (1H, m), 5.47 (1H, d, J = 9.8 Hz), 4.12 (2H, q, J = 6.9 Hz), 3.38 (1H, s), 2.50 (1H, q, J = 7.1 Hz), 2.20−1.40 (6H, bm), 1.22 (3H, t, J = 7.1 Hz), 1.11 (3H, t, J = 7.2 Hz); ^{13}C NMR δ 176.1, 131.0, 130.8, 70.1, 60.6, 48.1, 31.6, 25.0, 18.4, 14.1, 12.1.

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Supporting Information Available: X-ray experimental data of compound **17**. ^{1}H NMR spectral data of compounds **9A**−**12A** and **9B**−**12B** recorded in benzene-d_6 solution (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS; see any current masthead pages for ordering instructions.

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