Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 9, pp. 2299-2312, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00306-1

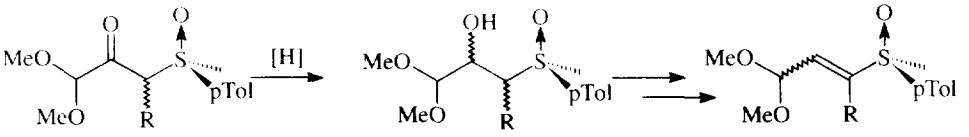
Enantiomerically pure 3-*p*-Tolylsulfinyl Acrolein and Crotonaldehyde Dimethylacetals. Stereoselective Reduction of β–Keto-γ,γ–Dialkoxysulfoxides.

José L. García Ruano,* M. Carmen Maestro,* Francisco Sánchez-Sancho
Departamento de Química Orgánica(C-I). Universidad Autónoma, 28049-Madrid, Spain

Abstract: The synthesis of the title compounds by basic elimination on the O-derivatives of unsubstituted and α–methylated β–hydroxy-γ,γ-dialkoxysulfoxides is reported. The study of the stereoselectivity of DIBAL and DIBAL/ZnI_2 reductions of the starting β–ketosulfoxides and their α–methylated derivatives is also presented.

Enantiomerically pure vinylsulfoxides have received considerable attention because of their usefulness in asymmetric cycloadditions[1] and conjugated addition reactions.[2] Different methods have been used to synthesize these substrates[3] according to the availability of stereochemically pure starting compounds, the stereoselectivity of the reactions involved in their preparation and the configurational stability of the products. Vinylsulfoxides containing an acetalated formyl group in the β–position are very interesting intermediates because they can be used as precursors of the corresponding aldehydes.[4] The synthesis of these unsaturated sulfinylacetals from glyoxal dimethyl monoketal using the Horner-Wittig reaction[5] with sulfinylphosphonates or condensation[6] with alkyl *p*-tolylsulfoxides is complicated mainly by difficulties associated to the synthesis of the precursor,[7] and by the presumably lack of stereoselectivity yielding mixtures of Z and E compounds.[8]

The stereoselective reduction of β–ketosulfoxides with DIBAL and DIBAL/ZnX_2 has been one of the research interests of our group in recent years.[9] The good results obtained from this hydride derive from its electrophilic character determining its association with some basic centre of the sulfinyl group as a preceding step to intramolecular hydride transfer. The presence of an alkyl substituent in α–position maintains this behaviour and the configuration of the new stereogenic centre is governed mainly by the sulfur chirality. However, though a high stereoselectivity is obtained in the DIBAL/$ZnBr_2$ reduction when appropriate conditions[10] are used, only a moderate induction is attained in the absence of the chelating agent[10b]. In continuation with our studies on α–alkylated β–ketosulfoxides, we are interested in establishing the additional influence of heteroatomic functions next to the carbonyl group on the stereoselectivity of the reduction processes, because the coordinating ability of these functions could modify the expected results by interaction

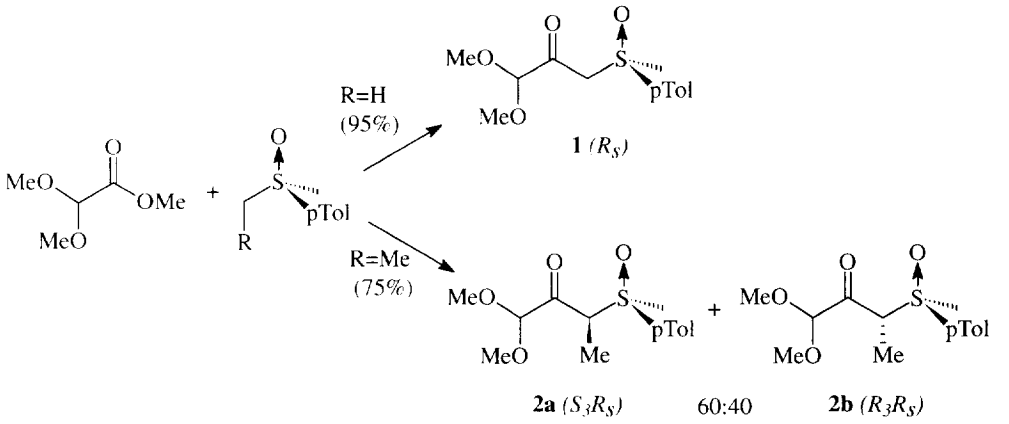


R=H **1**
R=Me **2a +2b**

Scheme 1

with DIBAL or with the Lewis acid[11]. In this sense, methylated 2-oxo-3-sulfinyl acetals are very interesting substrates because their structure contains heteroatomic functions and the alkyl substituent at the two diastereotopic α positions of the carbonyl group. On the other hand, reduction of 2-oxo-3-sulfinyl acetals would allow the stereoselective synthesis of α–hydroxy-β–sulfinylaldehydes and in addition could be used to obtain unsaturated sulfinylaldehyde dimethylacetals. In this paper we report the results of the DIBAL and DIBAL/ZnX_2 reduction of (***R***)-3-*p*-tolylsulfinyl pyruvaldehyde dimethylacetal (**1**) and its 3-methylderivatives (**2a** and **2b**), as well as those concerning the basic elimination of some of the O-substituted derivatives of the obtained hydroxyacetals in order to achieve the stereoselective synthesis of the corresponding vinylsulfoxides (Scheme 1).[12]

The synthesis of the starting β-ketosulfoxides **1** and **2** was performed by reaction of the commercially available methyl dimethoxyacetate with methyl and ethyl *p*-tolylsulfoxide respectively (Scheme 2), following the previously described methods.[13] Compound **2** was obtained as a 60:40 mixture of diastereomers **2a+2b**, which was used without prior separation in the subsequent reduction reactions. The configurational assignment of **2a** and **2b** was made by comparison of the ^{1}H-δ values observed for their methine and methyl protons with those of other α-methyl-β-ketosulfoxides of known configuration.[14] On this basis, the configuration S_3R_S was assigned to **2a** and R_3R_S to **2b**.

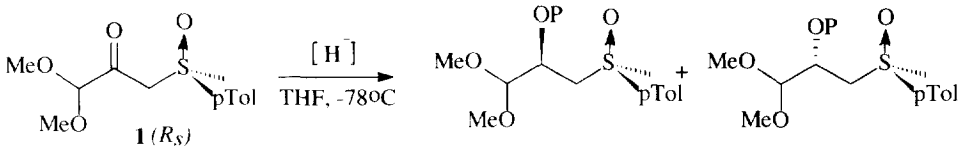


Scheme 2

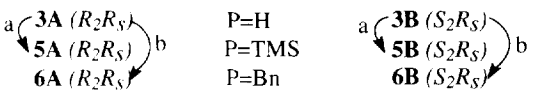
The DIBAL and DIBAL/ZnX_2 reductions of β-ketosulfoxides are well-known highly stereoselective reactions that yield β-hydroxysulfoxides. Thus, enantiomerically pure **3B** (de>97% by 200 MHz ^{1}H-NMR) was obtained by DIBAL reduction of compound **1**[15](Scheme 3), an excess of the hydride (3 eq) being necessary to achieve a high yield.

In the presence of ZnX_2, the DIBAL reduction is less stereoselective, yielding a mixture of **3A** and **3B** epimers at hydroxylic carbon (Scheme 3). It was necessary therefore, to carry out a detailed study of the reaction conditions in order to achieve high diastereomeric excess. The inverse addition mode (addition of the substrate, previously chelated with the Lewis acid, on the solution of DIBAL at -78°C), the use of 1.9 eq of Lewis acid, minimum chelation time (<1 min.), low chelation temperature (-50°C) and an excess of DIBAL (4-5 eq) allowed us to obtain a 92:8 mixture of **3A**:**3B** (84% *de*) that was separated by column chromatography

yielding **3A** in high optical purity (96% *de*, by 200 MHz ^{1}H-NMR). In these reactions ZnI_2 seems to produce better results than $ZnBr_2$, the $ZnCl_2$ being the least efficacious.[16]



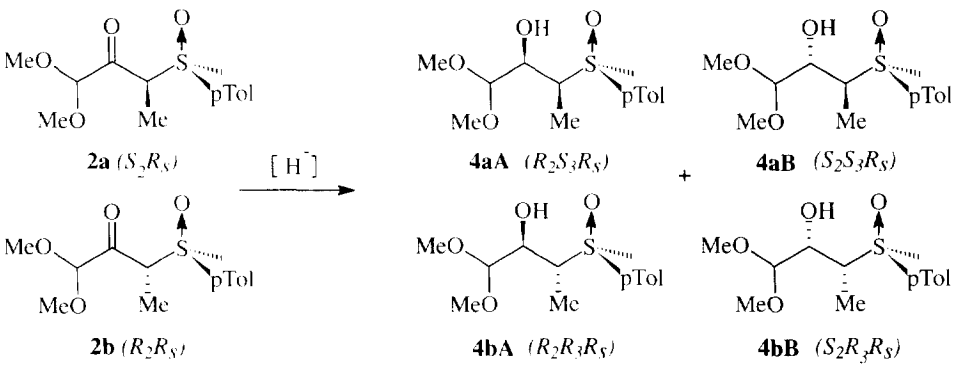
[H⁻]	Yield(%)	3A	3B
DIBAL/ZnI_2	60	92	8
DIBAL	85	0	100



a: TMSOTf (1.5 eq), Et$_3$N (1.7 eq), 0 °C, CH_2Cl_2; from **3A** (85%) or **3B** (80%);
b: BnBr (1.1 eq), NaH (1.05 eq), TBAI (0.01 eq), rt, THF; from **3A** or **3B** (80%).

Scheme 3

The configurational assignment of the compounds **3A** and **3B** was deduced from their ^{1}H-NMR parameters and those of their trimethylsilyloxy or benzyloxy derivatives **5A, 5B** or **6A, 6B**, easily obtained by **3A** and **3B** silylation or benzylation under standard conditions. Taking into account the relative value of the vicinal coupling constants $J_{2,3a}$ and $J_{2,3b}$ for these compounds and the chemical shift differences between H_{3a} and H_{3b},[17] compounds **B** must exhibit opposite configurations at the hydroxylic carbon and the sulfur (***S*$_2$*R*$_S$**), whereas compounds **A** must have the same configuration in both stereogenic centres (***R*$_2$*R*$_S$**), as indicated in Scheme 3.



Ketosulfoxide	[H⁻]	Yield (%)	4aA	4aB	4bA	4bB	C*-OH (*R/S*)
2a(60)+**2b**(40)	DIBAL/ZnI_2	65	62	0	28	10	90/10
2a(60)+**2b**(40)	DIBAL	98	20	39	0	41	20/80

Scheme 4

The DIBAL reduction of the 60:40 epimeric mixture of α–methyl-β–ketosulfoxides **2a+2b** yielded a 39:20:41 mixture (by ^{1}H-NMR) of the hydroxysulfoxides **4aB**, **4aA** and **4bB** respectively (Scheme 4), which

suggests that the reduction of **2b** is completely stereoselective affording exclusively **4bB**, whereas **2a** yields a mixture of epimers at the hydroxylic carbon **4aB** and **4aA**. This situation is inverted in the presence of ZnI_2, **2a** being now the sole epimer evolving with high stereoselectivity. Thus, the reduction of the above mixture of ketosulfoxides **2a+2b**, in THF solution a -78 °C in the optimised conditions for compound **1** (the chelation of the substrate with the Lewis acid must be effected at -50 °C in the previous instant to its addition on 5 eq of DIBAL) afforded a 62:10:28 mixture of **4aA**, **4bB** and **4bA** (Scheme 4). Different reaction conditions such as longer chelation times, higher chelation temperatures, direct addition mode, etc, produce a significant decrease in stereoselectivity, yielding mixtures of the four possible diastereomeric hydroxysulfoxides.

The treatment of the diastereomeric mixtures of the hydroxysulfoxides **4** with trimethylsilyl triflate at 0 °C in CH_2Cl_2, afforded the corresponding O-trimethylsilyl derivatives **7**, allowing an easy separation by column chromatography of epimers at the hydroxylic carbon (**A** and **B** epimers).

Table 1. Coupling constants and configuration of α-methyl-β-hydroxysulfoxides **4** and their O-TMS derivatives **7**

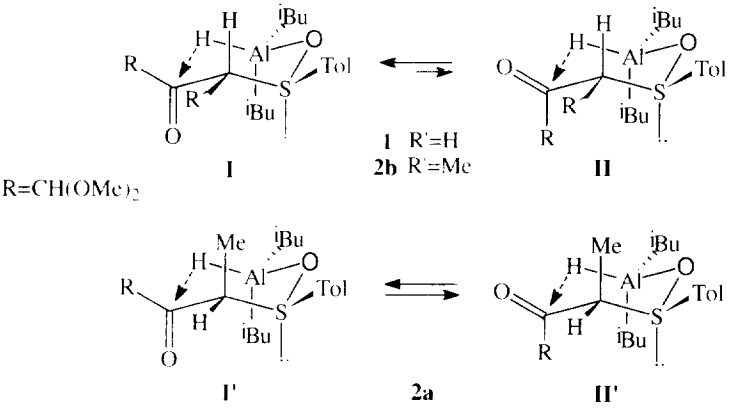
Compound N°	$^3J_{2,3}$ Hz	Relative Configuration	Starting Compound	Absolute Configuration
4aB	6.8	*anti*	**2a** (S_3R_S)	($S_2S_3R_S$)
4aA	1.0	*syn*	**2a** (S_3R_S)	($R_2S_3R_S$)
4bB	1.0	*syn*	**2b** (R_3R_S)	($S_2R_3R_S$)
4bA	7.5	*anti*	**2b** (R_3R_S)	($R_2R_3R_S$)
7aB	7.0	*anti*	**4A** ($S_2S_3R_S$)	($S_2S_3R_S$)
7aA	2.3	*syn*	**4A** ($R_2S_3R_S$)	($R_2S_3R_S$)
7bB	1.8	*syn*	**4B** ($S_2R_3R_S$)	($S_2R_3R_S$)
7bA	4.0	*anti*	**4B** ($R_2R_3R_S$)	($R_2R_3R_S$)

The configurational assignments of the α-methyl-β-hydroxysulfoxides **4**, as well as those of their O-trimethylsilyl derivatives **7**, were deduced from the value of their vicinal coupling constants $J_{2,3}$ taking into account the data obtained from compounds with related structures (2-hydroxy-3-methylsulfinylbutanes). It was established that sulfoxides with an *anti* configuration between the OR and Me groups have a higher $^3J_{2,3}$ values than those with the *syn* stereochemistry.[18]

According to this rule, we could tentatively assign the relative configurations of the different hydroxysulfoxides (see Table 1) assuming the stereochemistry of the starting ketosulfoxides. The rule is also applicable to the O-TMS derivatives, whose configuration will be identical to that of the starting alcohols.

In order to confirm this assignment, we performed the MCPBA oxidation of different mixtures of hydroxysulfoxides into their corresponding sulfones **8**. This reaction was carried out in the NMR sample tube. As we can see in Scheme 4, the two sulfoxides which exhibit the same *syn* or *anti* stereochemistry, would yield enantiomeric sulfones with identical ^1H-NMR spectra, and therefore only two different sets of signals would be observed in the spectra, being their relative intensities related to the composition of the starting mixture. Accordingly, the oxidation of a 39:20:41 mixture of **4aB**, **4aA** and **4bB** (obtained by DIBAL

reduction of the ketosulfoxides **2**) yielded a 39:61 mixture of sulfones **8** (*anti*) and **8** (*syn*) respectively, whereas the oxidation of a 62:10:28 mixture of **4aA**, **4bB** and **4bA** (derived from the DIBAL/ZnI_2 reduction) afforded a 72:28 mixture of **8** (*syn*) and **8** (*anti*). Finally, the reaction of a 5:61:15:19 mixture of **4aB**, **4aA**, **4bB** and **4bA** (obtained from the DIBAL/ZnI_2 reduction in the direct addition mode) with MCPBA yielded a c.a. 25:75 mixture of **8** (*anti*) and **8** (*syn*).

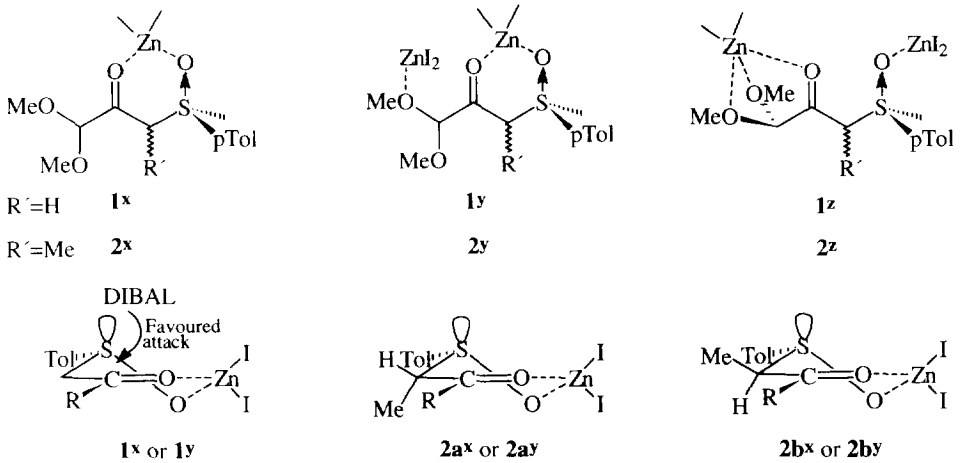


Scheme 5

Concerning to the influence of the acetal group on the stereochemical course of the reduction of the β–ketosulfoxides, the results reported in this paper, which are identical to others previously reported for substrates lacking in the acetal group, reveal that it is minimal or non-existant in the DIBAL reductions[10, 13a]. The ability of the acetal moiety to coordinate with the electrophilic aluminium hydride, simply determines the need for using an excess of the reagent. It seems that only DIBAL molecules associated to the sulfinyl group, are efficiently converted into nucleophilic hydride, able to give the intramolecular hydride transfer postulated for other β–ketosulfoxides. Taking into account that the presumably most stable transition states **I** and **II** (Scheme 5) yield different epimers at the hydroxylic carbon, the stereochemical results can be explained as follows. In the case of **1** and **2b**, TS **I** (exhibiting a $(^tBu/O)_{1,3\text{-syndiaxial}}$ interaction) is much more stable than TS **II** (with a $(^tBu/R)_{1,3\text{-syndiaxial}}$ interaction) and the reaction is highly stereoselective. By contrast, the stability of the transition states **I'** and **II'** must be similar in **2a** (the interactions $(R/Me)_{gauche}$ + $(^tBu/O)_{1,3\text{-syndiaxial}}$ present in TS **I'**, counterbalance the $(Me/O)_{gauche}$+ $(R/^tBu)_{1,3\text{-syndiaxial}}$ present in TS **II'**), which would explain the formation of both epimers in similar ratio.

The lower selectivity observed in the DIBAL/ZnI_2 reductions of compound **1** and **2** can be explained as follows. All these substrates exhibit three different oxygens, the sulfinyl oxygen being presumably the strongest base. Therefore, the addition of ZnI_2 will afford associated species containing one, two or even more molecules of the Lewis acid (Scheme 6). Considering that the best stereochemical results were obtained by addition of 1.9 eq. of ZnI_2, it can be expected that species such $\mathbf{1}^{y}$ and $\mathbf{1}^{z}$, containing two Lewis acid molecules were predominant. Species $\mathbf{1}^{y}$ must be immediately formed from $\mathbf{1}^{x}$ (monoassociated species initially formed), whereas $\mathbf{1}^{z}$, slowly formed from $\mathbf{1}^{y}$, must be the most stable one because it exhibits three stabilising Zn-O interactions and involves five membered rings. As it was the case of other systems lacking the acetal group, the DIBAL reduction of the species $\mathbf{1}^{x}$ and $\mathbf{1}^{y}$, with the sulfinyl and carbonyl oxygens joined to the metal, must be highly stereoselective according to steric (chair like transition state) and stereoelectronic factors (stabilising

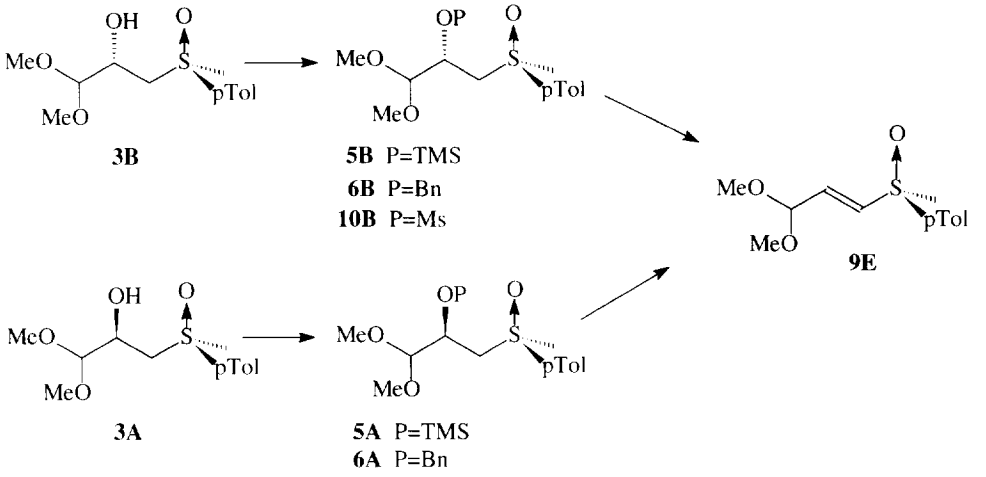
interactions between the lone electron pair at sulfur and electrophilic hydride).[19] On the contrary, low stereoselectivity can be expected from the DIBAL intermolecular attack on $\mathbf{1}^{z}$.[20] Therefore, experimental conditions favouring the equilibration between $\mathbf{1}^{y}$ and $\mathbf{1}^{z}$ (longer chelation times and higher temperatures) would determine a decrease in the observed stereoselectivity, whereas those minimising formation of $\mathbf{1}^{z}$ would increase such stereoselectivity. These predictions agree with the experimental evidences. In order to explain the results obtained in the DIBAL/ZnI_2 reduction of compounds **2a+2b,** it must be additionally considered that the formation of the chelated species $\mathbf{2}^{x}$or $\mathbf{2}^{y}$ is easier in compound **2a** (such species will be destabilised in **2b** by steric Tol/Me and Me/R interactions), this epimer being the sole one which evolves with high stereoselectivity.[10]



Scheme 6

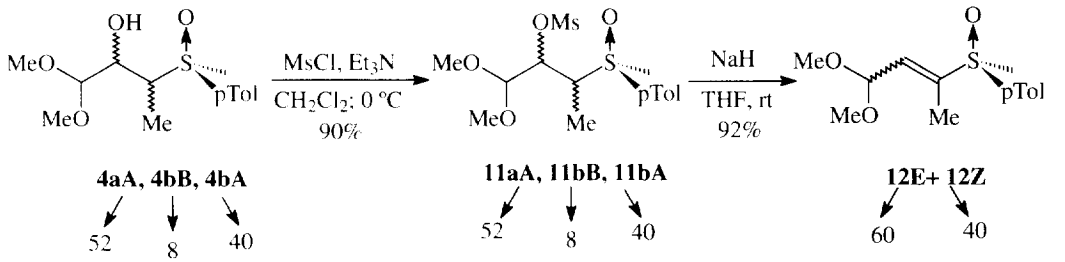
Once the reduction conditions were optimised to obtain α–hydroxy–β–sulfinyl acetals **3** and **4** with the higher asymmetric induction, our interest was focused in the synthesis of enantio- and diastereoisomerically pure vinylsulfoxides with an acetal group in β–position by basic elimination reaction on the corresponding O-protected derivatives. Therefore, hydroxysulfoxides **3A** and **3B** were separately submitted to O-benzylation, O-trimethylsilylation or O-mesylation in the usual conditions, to afford the corresponding derivatives **5**, **6** and **10** (Scheme 7). Treatment of trimethylsilyl derivatives **5A** or **5B** with 2 eq of methyllithium at -78°C in tetrahydrofuran to attain fast elimination of the oxygenated function, yields exclusively *E*-vinylsulfoxide **9E**, regardless of the configuration of the hydroxylic carbon. The same result was obtained by treatment of the benzylated hydroxysulfoxide **6A** with NaH, but incomplete conversion was attained despite the use of a large excess of the hydride (4 eq). These last conditions, however, allowed the total transformation of mesylate **10B** in vinylsulfoxide **9E** in high yield (90% from **3B**)[4b]. Accordingly the best way to obtain compound **9E** is the DIBAL reduction of ketosulfoxide **1** at low temperature (-78°C) followed of trimethylsilylation or mesylation and final basic elimination. Sulfur configuration is not affected during elimination process (methyllithium

treatment), yielding enantiomerically pure vinylsulfoxide **9E** as was confirmed by ^{1}H-NMR using Pr(hfc)$_3$ as chiral shift reagent.[21]



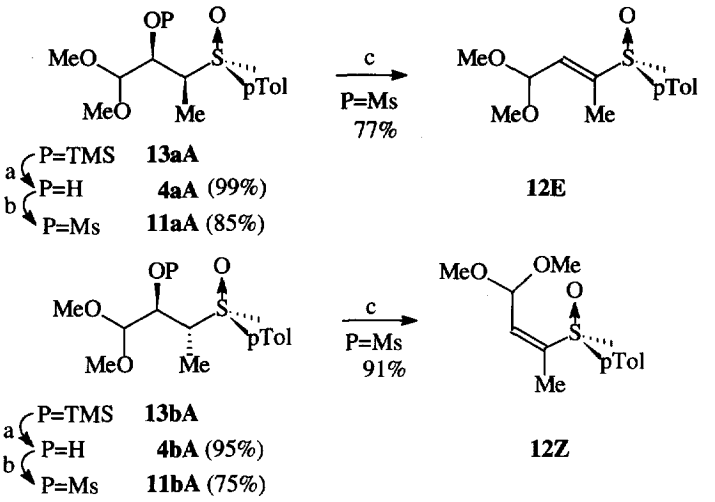
Scheme 7

The above sequence (mesylation and basic elimination) was also applied to a 52:8:40 diastereomeric mixture of **4aA**, **4bB** and **4bA** respectively, yielding a 60:40 mixture of vinylsulfoxides **12E** and **12Z** (Scheme 8). The obtained **Z/E** ratio strongly suggests a diastereoselective basic elimination of mesylates **11**.



Scheme 8

To confirm this assumption, it was necessary to carry out the reaction separately on the two major diastereomers (**11aA** and **11bA**) of the above mixture, both with ***R*** configuration in the hydroxylic stereogenic centre. The separation of these mesylates as well as that of the starting hydroxy compounds was not possible. Therefore, we effected chromatographic separation of the corresponding O-TMS derivatives **13aA** and **13bA**, but unfortunately, the elimination reaction failed on these silyl derivatives[22]. Then, a desilylation-mesylation sequence was readily effected to obtain diastereoisomerically pure mesylates **11aA** and **11bA,** that were independently treated with NaH to afford respectively α–methyl vinylsulfoxides **12E** and **12Z,** as was expected assuming the *anti* elimination of hydrogen and mesyloxy groups (Scheme 9).



a: TBAF (2.5 eq), THF, rt; b: MsCl (1.5 eq), Et_3N (1.7 eq), CH_2Cl_2, rt; c: NaH (4eq), THF, rt.

Scheme 9

In summary, the study reported herein have led to a efficient entry to formyl derivatives of ***E***-vinyl sulfoxides unsubstituted in α–position. Application of the same strategy to diastereoisomerically pure α–alkyl-β–hydroxysulfoxides proceeds diastereospecifically to afford enantiomerically pure ***E*** or ***Z*** isomers of the corresponding α–alkylated vinylsulfoxides.

Acknowledgements. We thank DGICYT (PB-92-0162) for financial support. F. Sánchez-Sancho thanks Universidad Autónoma de Madrid for a scholarship.

Experimental Section

Melting points were determined on a *Gallenkamp* apparatus and are uncorrected. NMR spectra were recorded on a *Bruker WP-200-SY* instrument and *Bruker AMX-300.* Optical rotations were mesured on a *Perkin-Elmer 241-MC* polarimeter. Mass spectra were registered on a *VG AutoSpec* instrument in the electron impact mode (EI) at 70 eV. IR spectra were obtained in a *Philips PU-9716.* TLC analysis and flash chromatography were performed on silica gel Merck (230-400 mesh ASTM for flash chromatography). Triethylamine and diisopropylamine were distilled from potassium hydroxide. THF and diethyl ether were distilled from sodium-benzophenone under argon and CH_2Cl_2 over P_2O_5.

Synthesis of β-ketosulfoxides.

General procedure: A solution of *n*-Butyllithium 2.34M in hexane (17.5ml, 40.9mmol, 2.1eq) was added to a solution of diisopropylamine (6ml, 42.8mmol, 2.2eq) in 100ml of dry THF at -78°C under argon. The mixture was stirred for 30 minutes at the same temperature and then a solution of the corresponding (+)-(*R*)-alkyl-*p*-tolylsulfoxide (19.5mmol, 1eq) in 40ml of dry THF at -40°C was added. After 30 minutes, net methyl dimethoxyacetate (2.7ml, 22.4mmol, 1.1eq) was added. The reaction was stirred at -78°C until completion (1h). A saturated solution of ammonium chloride was then added. The mixture was acidified to pH 3-4 with

H_2SO_4 10%, the aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with a saturated solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed (eluent: ethyl acetate/hexane 1/1) to obtain the pure product.

(*R*)-2-oxo-3-(*p*-tolylsulfinyl)propanal dimethyl acetal (1). It was prepared following the general procedure from methyl dimethoxyacetate and (+)-(*R*)-methyl-*p*-tolylsulfoxide. The product was obtained as an orange oil and used without further purification. Yield: 95%, de >97%. $[\alpha]_D$ = +201 (c=1, $CHCl_3$). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 2.42 (s, 3H, CH_3Ar), 3.38 (s, 6H, 2 CH_3O), 3.95, 4.08 (AB system, 2H, J_{AB}=14Hz, CH_2), 4.42 (s, 1H, CH), 7.34, 7.56 (AA'BB', 4H, Tol). **^{13}C NMR** ($CDCl_3$): δ: 21.1 (CH_3Ar), 54.6 (2 CH_3O), 63.9 (C-3), 103.6 (C-1), 123.9, 129.7 (arom. CH), 139.7, 141.8 (arom. C), 196.5 (CO). **IR** (CH_2Cl_2 sol.): ν_{max}: 2930, 2830, 1725, 1595, 1495, 1085, 1070, 810 cm^{-1}.

2-oxo-3-(*p*-tolylsulfinyl)butanal dimethyl acetal (2a+2b). It was obtained, following the general procedure from methyl dimethoxyacetate and (+)-(*R*)-ethyl-*p*-tolylsulfoxide, as a mixture 60:40 (^{1}H NMR) of diastereomers **2a+2b**. The crude was purified by flash chromatography to yield 70% of **2a+2b** as a yellow oil.
(S_S,R_S)-2a.- ^{1}H NMR (200 MHz, $CDCl_3$): δ: 1.34 (d, 3H, J=7Hz, CH_3-CH), 2.41 (s, 3H, CH_3Ar), 3.35, 3.36 (2s, 6H, 2 CH_3O), 4.23 (c, 1H, J=7Hz, CH-CH_3), 4.44 (s, 1H, CH-O), 7.32, 7.48 (AA'BB', 4H, Tol).
(R_S,R_S)-2b. ^{1}H NMR (200 MHz, $CDCl_3$): δ: 1.20 (d, 3H, J=7Hz, CH_3-CH), 2.43 (s, 3H, CH_3Ar), 3.39, 3.40 (2s, 6H, 2 CH_3O), 4.37 (c, 1H, J=7Hz, CH-CH_3), 4.45 (s, 1H, CH-O), 7.34, 7.52 (AA'BB', 4H, Tol).**^{13}C NMR** (50MHz, $CDCl_3$) (**2a+2b**).- δ: 8.4, 9.5 (2 C-4), 21.1 (2 CH_3Ar), 54.2, 54.4, 54.8, 54.9 (4 CH_3O), 65.4, 65.9 (2 C-3), 103.6, 103.8 (2 C-1), 124.5, 125.0, 129.5 (arom. CH), 137.5, 138.1, 141.9, 142.2 (arom. C), 199.8 (CO). **IR** ($CHCl_3$ sol.): ν_{max}: 2990, 2930, 1720, 1595, 1495, 1445, 1305, 1085, 1050, 810 cm^{-1}.

Reduction of β-ketosulfoxides.

DIBAL reduction: To a solution of the corresponding β-ketosulfoxide (3.2mmol, 1eq) in dry THF (80ml) at -78°C, diisobutylaluminium hydride (DIBAL) 1M in hexane was added (9.6 ml, 3eq). After 5 minutes the reaction was shown to be completed and the excess of DIBAL was decomposed with 5ml of methanol. The solvents were removed at vacuo and the residue was dissolved with HCl 5% and extracted with ethyl acetate. The organic phase was washed with a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. Finally, the solvent was evaporated under reduced pressure to yield the crude product.

DIBAL/ZnI_2 reduction: A solution of the corresponding β-ketosulfoxide (3.9mmol, 1eq) in 15ml of dry THF at -78°C was added to a solution of ZnI_2 (2.4g, 7.41mmol, 1.9eq) in 15ml of dry THF at -50°C (ZnI_2 precipitates below this temperature) under argon. This mixture was quickly and immediately added to a solution of DIBAL 1M in hexane (20ml, 20mmol, 5eq) in 100ml of dry THF at -78°C. The reaction was stirred till completion at -78°C (c.a. 1h) and then 2ml of methanol were added. Once the solution reached room temperature, 50ml of a saturated solution of potassium sodium tartrate and 50ml of ethyl acetate were added. The mixture was stirred for 20 minutes, the organic layer was separated and the aqueous one was extracted with ethyl acetate. The organic phases were combined and washed with a sodium thiosulfate solution and with a saturated sodium chloride solution. After drying over sodium sulfate, the solvent was eliminated under reduced pressure. The residue was chromatographed (eluent: ethyl acetate/hexane 3/1) to obtain the pure product.

[R_S,R_S]-2-Hydroxy-3-(*p*-tolylsulfinyl) propanal dimethyl acetal (3A). It was obtained by DIBAL/ZnI_2 reduction starting from β-ketosulfoxide **1** (80%, de 84 %). The crude product was chromatographed (ethyl acetate/hexane 3/1) to yield compound **3A** (96%, de >97%) as a yellow orange oil. $[\alpha]_D$= +178 (c=1, $CHCl_3$). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 2.41 (s, 3H, CH_3Ar), 3.3 (m, 2H, CH_2), 3.44, 3.46 (2s, 6H, 2 CH_3O), 3.53 (d,

1H, J=2.5Hz, OH), 4.18 (m, 1H, H-2),4.34 (d, 1H, J=5.1Hz, H-1), 7.32, 7.55 (AA'BB', 4H, Tol). **^{1}H NMR** (300 MHz, $CDCl_3$): δ: 2.41(s, 3H, CH_3Ar), 3.00 (AB of ABXY, 2H, J_{AB}=13.4Hz, J_{AX}=3.6Hz, J_{BX}=8.0Hz, Δν=20Hz, CH_2), 3.43, 3.46 (2s, 6H, 2 CH_3O), 4.17 (X of ABXY, 1H, J_{XY}=5.0Hz, J_{AX}=3.6Hz, J_{BX}=8.0Hz, H-2), 4.33 (Y of ABXY, 1H, J_{XY}=5.0Hz, H-1), 7.32, 7.55 (AA'BB', 4H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 21.2 (CH_3Ar), 55.1, 56.0 (2 CH_3O) 58.6 (C-3), 68.4 (C-2), 105.7 (C-1), 124.0, 129.8 (arom. CH), 140.3, 141.6 (arom. C). **IR** ($CHCl_3$ sol.): ν_{max}: 3600-3200, 2970, 2940, 1600, 1495, 1445, 1380, 1130, 1080, 1035, 810cm^{-1}.

[S_2,R_S]-2-Hydroxy-3-(*p*-tolylsulfinyl) propanal dimethyl acetal (3B). It was obtained diastereomerically pure (^{1}H NMR) by DIBAL reduction starting from β-ketosulfoxide **1**. The crude product was purified by flash chromatography (ethyl acetate/hexane 3/1), yielding hydroxysulfoxide **3B** as a white solid (80%, de >97%). $[\alpha]_D$= +261 (c=0.75, $CHCl_3$). **m.p.** 70-71°C (hexane). **Anal.** Calc. for $C_{12}H_{18}O_4S$: C 55.83; H 6.97. Found: C 56.18; H 7.07. **MS** (EI): m/z: 183(3), 139(18), 123(3), 91(8), 87(11), 75(100), 85(3), 59(2). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 2.41(s, 3H, CH_3Ar), 2.95 (m, 2H, CH_2), 3.40, 3.41 (2s, 6H, 2 CH_3O), 4.25 (m, 2H, H-1, H-2), 4.43 (d, 1H, J=4Hz, OH), 7.32, 7.54 (AA'BB', 4H, Tol). **^{1}H NMR** (300MHz, $CDCl_3$): δ: 2.40(s, 3H, CH_3Ar), 2.92 (AB of ABXY, 2H, J_{AB}=13.6Hz, J_{AX}=2.4Hz, J_{BX}=9.3Hz, Δν=32Hz, CH_2), 3.38, 3.39 (2s, 6H, 2 CH_3O), 3.78 (d, 1H, J=3.6Hz, OH), 4.23 (XY of ABXY, 2H, H-1, H-2), 7.32, 7.52 (AA'BB', 4H, Tol). **^{1}H NMR** (200MHz, C_6D_6): δ: 1.90(s, 3H, CH_3Ar), 3.05 (m, 2H, CH_2), 3.14, 3.21 (2s, 6H, 2 CH_3O), 4.24 (d, 1H, J=4.5Hz, H-1), 4.64 (dt, 1H, J=9Hz, J=4.5Hz, H-2), 6.79, 7.36 (AA'BB', 4H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 21.2 (CH_3Ar), 55.0, 56.6 (2 CH_3O) 58.8 (C-3), 66.2 (C-2), 105.8 (C-1), 123.9, 129.8 (arom. CH), 140.0, 141.3 (arom. C). **IR** ($CHCl_3$ sol.): ν_{max}: 3400-3300, 2990, 2930, 1600, 1495, 1445, 1380, 1085, 1040, 810 cm^{-1}.

2-Hydroxy-3-(*p*-tolylsulfinyl) butanal dimethyl acetal (4). DIBAL reduction afforded compound **4** as a mixture of three diastereomers in proportion: 39(**4aB**): 20(**4aA**): 41(**4bB**) pure enough to be used without further purification. Global yield: 98%. The diastereoisomeric mixture, obtained by DIBAL/ZnI_2, 62(**4aA**): 10(**4bB**): 28(**4bA**), was chromatographed (ethyl acetate/hexane 3/1) to yield pure diastereomers **4** Global yield: 60%. The diastereomers couldn't be separated by flash chromatography.

(**S_2,S_3,R_S)-4aB.**- **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 1.03 (d, 3H, $J_{3,4}$=7Hz, C$\underline{H}_3$-CH), 2.42 (s, 3H, CH_3Ar), 2.89 (dc, 1H, $J_{2,3}$=6.8Hz, $J_{3,4}$=7Hz, H-3), 3.49, 3.52 (2s, 6H, 2 CH_3O), 3.94 (m, 1H, H-2), 4.50 (d, 1H, $J_{1,2}$=4.4Hz, H-1), 7.32, 7.45 (AA'BB', 4H, Tol). **^{13}C NMR** ($CDCl_3$): δ: 5.2 (C-4), 21.4 (CH_3Ar), 56.1, 55.6 (2 CH_3O) 59.9 (C-3), 72.7 (C-2), 105.2 (C-1), 124.5, 129.8 (arom. CH), 141.1, 148.7 (arom. C).

(**R_2,S_3,R_S)-4aA.**- **$[\alpha]_D$** = +150 (c=1, $CHCl_3$). **m.p.** 104-106°C. **MS** (EI): m/z: 151(4), 139(10), 123(7), 101(16), 91(6), 75(100), 59(11). **HRMS**: Calcd for $C_{13}H_{20}O_4S$: 272.1082. Found: m/z: M, 272.1090. **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 1.14 (d, 3H, $J_{3,4}$=7.1Hz, C$\underline{H}_3$-CH), 2.36 (s, 3H, CH_3Ar), 2.85 (dc, 1H, $J_{2,3}$=2.7Hz, $J_{3,4}$=7.1Hz, H-3), 3.19 (d, 1H, J=3.2Hz, OH), 3.30, 3.41 (2s, 6H, 2 CH_3O), 4.00 (ddd, 1H, $J_{2,3}$=2.7Hz, J=3.2Hz, $J_{1,2}$=6.4Hz, H-2), 4.32 (d, 1H, $J_{1,2}$=6.4Hz, H-1), 7.27, 7.46 (AA'BB', 4H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 5.1 (C-4), 21.2 (CH_3Ar), 54.7 (2 CH_3O) 60.4 (C-3), 70.3 (C-2), 104.1 (C-1), 124.5, 129.9 (arom. CH), 138.1, 141.3 (arom. C). **IR** ($CHCl_3$ sol.): ν_{max}: 3560-3300, 2980, 2925, 1600, 1490, 1445, 1085, 1065, 970, 810 cm^{-1}.

(**S_2,R_3,R_S)-4bB.**- **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 1.35 (d, 3H, $J_{3,4}$=7Hz, C$\underline{H}_3$-CH), 2.42 (s, 3H, CH_3Ar), 2.82 (dc, 1H, $J_{2,3}$=1.0Hz, $J_{3,4}$=7Hz, H-3), 3.25, 3.38 (2s, 6H, 2 CH_3O), 3.47 (broad s, 1H, H-2), 4.27 (broad s, 1H, H-1), 7.33, 7.55 (AA'BB', 4H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 8.8 (C-4), 21.5 (CH_3Ar), 54.8 (2 CH_3O) 59.3 (C-3), 68.1 (C-2), 104.1 (C-1), 125.0, 130.0 (arom. CH), 138.2, 141.9 (arom. C).

(**R_2,R_3,R_S)**-4bA.-**^{1}H NMR** (200 MHz, $CDCl_3$): δ: 1.05 (d, 3H, $J_{3,4}$=7Hz, C$\underline{H}_3$-CH), 2.42 (s, 3H, CH_3Ar), 2.93 (dc, 1H, $J_{2,3}$=7.5Hz, $J_{3,4}$=7.0Hz, H-3), 3.36, 3.47 (2s, 6H, 2 CH_3O), 4.60 (d, 1H, $J_{1,2}$=4.8Hz, H-1), 4.75 (dd, 1H, $J_{1,2}$=4.8Hz, $J_{2,3}$=7.5Hz, H-2), 7.32, 7.61 (AA'BB', 4H, Tol).

Synthesis of benzyloxy derivatives.

General procedure: To a stirred suspension of NaH (48mg, 2.04mmol, 1.05eq) in 15ml of dry THF, at room temperature under argon, the corresponding hydroxysulfoxide in THF (1ml) was added. The mixture was stirred for 30 min. and then benzyl bromide (0.25ml, 2.13mmol, 1.1eq) and tetrabutylammonium iodide (7mg, 0.02mmol, 0.01eq) were added. The reaction was stirred at room temperature until completion (12h). Then it was diluted with dichloromethane and filtered through celite (washing several times with CH_2Cl_2). Solvents were evaporated in vacuo and the residue was chromatographed (ethyl acetate/hexane 1/2) to afford the corresponding pure compound **6**.

[R_2,R_S]-2-Benzyloxy-3-(*p*-tolylsulfinyl)propanal dimethyl acetal (6A). Yield: 80%. de >97%. $[\alpha]_D$= +67 (c=1.95, $CHCl_3$). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 2.38(s, 3H, CH_3Ar), 3.15 (d, 2H, $J_{2,3}$=5.5Hz, CH_2), 3.40, 3.41 (2s, 6H, 2 CH_3O), 3.75 (dq, 1H, $J_{1,2}$=4.9Hz, $J_{2,3}$=5.5Hz, H-2), 4.40 (d, 1H, $J_{1,2}$=4.9Hz, H-1), 4.46, 4.64 (AB system, 2H, J_{AB}=11.6Hz, CH_2Ph), 7.30-7.60 (AA'BB', 4H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 21.2 (CH_3Ar), 55.6 (2 CH_3O) 58.2 (C-3), 72.3 (CH_2Ph), 77.9 (C-2), 105.6 (C-1), 124.1, 127.6, 127.7, 128.2, 129.7 (arom. CH), 137.6, 140.9 141.2 (arom. C). **IR** ($CHCl_3$ sol.): ν_{max}: 2990, 2930, 2840, 1600, 1495, 1445, 1350, 1190, 1030, 1090, 1040, 970, 915, 810 cm^{-1}.

[S_2,R_S]-2-Benzyloxy-3-(*p*-tolylsulfinyl) propanal dimethyl acetal (6B). Yield: 80%. de >97%. $[\alpha]_D$= +146 (c=0.75, $CHCl_3$). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 2.40(s, 3H, CH_3Ar), 2.95 85 (AB of ABXY, 2H, J_{AB}=13.3Hz, J_{AX}=3.0Hz, J_{BX}=10.2Hz, Δν=31Hz, CH_2), 3.40 (s, 6H, 2 CH_3O), 4.11 (X of ABXY, 1H, J_{XY}=4.4Hz, J_{AX}=3.0Hz, J_{BX}=10.2Hz, H-2), 4.30 (Y of ABXY, 1H, J_{XY}=4.4Hz, H-1), 4.83 (s, 2H, CH_2Ph), 7.30-7.60 (AA'BB', 4H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 20.9 (CH_3Ar), 55.4 (2 CH_3O) 59.6 (C-3), 73.7 (C-2, CH_2Ph), 105.2 (C-1), 123.4, 127.5, 127.9, 128.0, 129.5 (arom. CH), 137.5, 140.8, 141.1 (arom. C). **IR** ($CHCl_3$ sol.): ν_{max}: 2930, 2840, 1600, 1495, 1445, 1375, 1210, 1130, 1085, 1040, 810 cm^{-1}.

Synthesis of trimethylsilyl derivatives.

General procedure: To a solution of the corresponding hydroxysulfoxide (0.25mmol, 1eq) in 2ml of dry dichloromethane at 0°C under argon, were added successively 0.06ml of triethylamine (0.43mmol, 1.7eq) and 0.07ml of trimethylsilyl trifluoromethanesulfonate (0.38mmol, 1.5eq). When the reaction was shown to be completed (20min), was diluted with 20 ml of cold water, extracted with diethyl ether and dried over anhydrous magnesium sulfate. Column chromatography (ethyl acetate/hexane 1/2.5) of the residue afforded the pure silyl derivatives.

[R_2,R_S]-2-Trimethylsilyloxy-3-(*p*-tolylsulfinyl) propanal dimethyl acetal (5A). It was obtained from hydroxysulfoxide **3A** (85%, de>97%). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 0.13 (s, 9H, $(CH_3)_3Si$), 2.41(s, 3H, CH_3Ar), 3.06 (AB of ABXY, 2H, J_{AB}=13.5Hz, J_{AX}=6.0Hz, J_{BX}=6.6Hz, Δν=16Hz, CH_2), 3.43, 3.45 (s, 6H, 2 CH_3O), 3.97 (X of ABXY, 1H, J_{XY}=5.3Hz, J_{AX}=6.0Hz, J_{BX}=6.6Hz, H-2), 4.33 (Y of ABXY, 1H, J_{XY}=5.3Hz, H-1), 7.30, 7.55 (AA'BB', 4H, Tol).

[S_2,R_S]-2-Trimethylsilyloxy-3-(*p*-tolylsulfinyl) propanal dimethyl acetal (5B). It was obtained from hydroxysulfoxide **3B** (80%, de>97%). **^{1}H NMR** (200 MHz, $CDCl_3$): δ: 0.25 (s, 9H, $(CH_3)_3Si$), 2.40(s, 3H, CH_3Ar), 2.85 (AB of ABXY, 2H, J_{AB}=3.0Hz, J_{AX}=2.5Hz, J_{BX}=10.0Hz, Δν=37Hz, CH_2), 3.41 (s, 6H, 2 CH_3O), 4.17 (Y of ABXY, 1H, J_{XY}=4.3Hz, H-1), 4.27 (X of ABXY, 1H, J_{XY}=4.3Hz, J_{AX}=2.5Hz, J_{BX}=10.0Hz, H-2), 7.29, 7.53 (AA'BB', 4H, Tol).

2-Trimethylsilyloxy-3-(*p*-tolylsulfinyl) butanal dimethyl acetal (13). The treatment of a mixture of hydroxysulfoxides **4** (obtained from DIBAL or DIBAL/ZnI_2 reduction) affords the diastereomeric mixtures of TMS-derivatives **13**. The ratio of the starting hydroxysulfoxides is mantained in the corresponding silyl

derivatives. The diastereomers could be separated by flash chromatography (ethyl acetate/hexane 1/2.5). Global yield: 87%.

(S_2,S_3,R_S)-13aB. ^{1}**H NMR** (200 MHz, $CDCl_3$): δ: 0.20 (s, 9H, $(CH_3)_3Si$), 1.02 (d, 3H, $J_{3,4}$=7Hz, C$\underline{H}_3$-CH), 2.40 (s, 3H, CH_3Ar), 2.82 (dc, 1H, $J_{2,3}$=7Hz, $J_{3,4}$=7Hz, H-3), 3.46, 3.48 (2s, 6H, 2 CH_3O), 3.86 (dd, 1H, $J_{1,2}$=4Hz, $J_{2,3}$=7Hz, H-2), 4.33 (d, 1H, $J_{1,2}$=4Hz, H-1), 7.35, 7.46 (AA'BB', 4H, Tol).

(R_2,S_3,R_S)-13aA. ^{1}**H NMR** (200 MHz, $CDCl_3$): δ: 0.12 (s, 9H, $(CH_3)_3Si$), 0.88 (d, 3H, $J_{3,4}$=7.1Hz, C$\underline{H}_3$-CH), 2.39 (s, 3H, CH_3Ar), 3.17 (dc, 1H, $J_{2,3}$=2.3Hz, $J_{3,4}$=7.1Hz, H-3), 3.51, 3.56 (2s, 6H, 2 CH_3O), 3.82 (dd, 1H, $J_{1,2}$=7Hz, $J_{2,3}$=2.3Hz, H-2), 4.76 (d, 1H, $J_{1,2}$=7Hz, H-1), 7.27, 7.56 (AA'BB', 4H, Tol).

(S_2,R_3,R_S)-13bB. ^{1}**H NMR** (200 MHz, $CDCl_3$): δ: 0.23 (s, 9H, $(CH_3)_3Si$), 0.89 (d, 3H, $J_{3,4}$=7Hz, C$\underline{H}_3$-CH), 2.41 (s, 3H, CH_3Ar), 2.86 (dc, 1H, $J_{2,3}$=1.8Hz, $J_{3,4}$=7Hz, H-3), 3.34, 3.43 (2s, 6H, 2 CH_3O), 4.23 (d, 1H, $J_{1,2}$=6.8Hz, H-1), 4.51 (dd, 1H, $J_{1,2}$=6.8Hz, $J_{2,3}$=1.8Hz, H-2), 7.35, 7.59 (AA'BB', 4H, Tol).

(R_2,R_3,R_S)-13bA. ^{1}**H NMR** (200 MHz, $CDCl_3$): δ: 0.15 (s, 9H, $(CH_3)_3Si$), 1.18 (d, 3H, $J_{3,4}$=7Hz, C$\underline{H}_3$-CH), 2.40 (s, 3H, CH_3Ar), 2.90 (dc, 1H, $J_{2,3}$=4Hz, $J_{3,4}$=7Hz, H-3), 3.31, 3.44 (2s, 6H, 2 CH_3O), 3.89 (dd, 1H, $J_{1,2}$=5.6Hz, $J_{2,3}$=4Hz, H-2), 4.30 (d, 1H, $J_{1,2}$=5.6Hz, H-1), 7.30, 7.49 (AA'BB', 4H, Tol).

Silyl deprotection.*General procedure.* The corresponding O-trimethylsilyl derivative (60mg, 0.17mmol, 1eq) was disolved in dry dichloromethane at room temperature under argon. Then, a solution of tetrabutylammonium fluoride 1.1M in THF (0.5ml, 042mmol, 2.5 eq) was added dropwise and the mixture was stirred until completion (c.a. 15 min). It was diluted with water, extracted with ethyl acetate and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the corresponding desilylated product (99% from **13aA**; 95% from **4bA**), that could be used without further purification.

Synthesis of mesyl derivatives.

General procedure. To a solution of the corresponding hydroxysulfoxide (50mg, 0.18mmol, 1eq) at 0°C in 4ml of dry dichloromethane, under argon, was added methanesulfonyl chloride (0.02ml, 0.27mmol, 1.5eq) and Et_3N (0.04ml, 0.31mmol, 1.7eq). The reaction mixture was stirred at 0°C until completion (c.a. 1h). It was diluted with cold water, extracted with ethyl acetate and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo affording the corresponding diastereomer of **11,** pure enough to be used without further purification.

[R_2,S_3,R_S]-2-mesyloxy-3-(*p*-tolylsulfinyl)butanal dimethyl acetal (11aA). It was synthesized from hydroxysulfoxide **4aA.** Yield: 85%. ^{1}**H NMR** (200 MHz, $CDCl_3$):δ: 1.22 (d, 3H, $J_{3,4}$=7.1Hz, C$\underline{H}_3$-CH), 2.42 (s, 3H, CH_3Ar), 3.04 (dc, 1H, $J_{2,3}$=3.5Hz, $J_{3,4}$=7.1Hz, H-3), 3.18 (s, 3H, CH_3-SO_3), 3.37, 3.48 (2s, 6H, 2 CH_3O), 4.59 (d, 1H, $J_{1,2}$=5.3Hz, H-1), 4.96 (dd, 1H, $J_{2,3}$=3.5Hz, $J_{1,2}$=5.3Hz, H-2), 7.34, 7.53 (AA'BB', 4H, Tol). **[R_2,R_3,R_S]-2-mesyloxy-3-(*p*-tolylsulfinyl)butanal dimethyl acetal (11bA).** It was synthesized from hydroxysulfoxide **4bA**. Yield: 75%. ^{1}**H NMR** (200 MHz, $CDCl_3$): δ: 1.02 (d, 3H, $J_{3,4}$=7.1Hz, C$\underline{H}_3$-CH), 2.42 (s, 3H, CH_3Ar), 3.00 (dc, 1H, $J_{2,3}$=2.5Hz, $J_{3,4}$=7.1Hz, H-3), 3.16 (s, 3H, CH_3-SO_3), 3.52, 3.60 (2s, 6H, 2 CH_3O), 4.84 (dd, 1H, $J_{2,3}$=2.5Hz, $J_{1,2}$=7.0Hz, H-2), 5.11(d, 1H, $J_{1,2}$=7.0Hz, H-1), 7.34, 7.61 (AA'BB', 4H, Tol).

Basic elimination.

Method I (MeLi). To a stirred solution of the corresponding O-trimethylsilyl derivative (15mg, 0.048mmol, 1 eq) in dry THF (1ml) at -78°C, MeLi 1.5M (64 µl, 0.096 mmol, 2 eq) was added under argon. The mixture was stirred for 2 hours until completion and then, a saturated solution of ammonium chloride was added. The aqueous layer was extracted with ethyl acetate and dried with anhydrous sodium sulfate to yield pure compound **9**.

Method II (NaH). To a stirred suspension of NaH (15mg, 0.63mmol, 4eq) in dry THF (5ml) at room temperature under argon, a solution of the corresponding O-mesyl derivative (55mg, 0.16mmol, 1eq) in 2ml of dry THF was added. The mixture was stirred overnight, diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with a saturated solution of sodium chloride and dried with anhydrous sodium sulfate. The crude product was chromatographed (ethyl acetate/hexane 1/2.5) to obtain pure compound **12**.

(2*E*, R_S)-3-*p*-tolylsulfinylpropenal dimethyl acetal (9E). It was synthesized following method I from **5A**. (91%) or from **5b** (90%).ee > 97% $[\alpha]_D$=+292 (c=1, $CHCl_3$); **^{1}H NMR** (200MHz, $CDCl_3$): δ: 7.46, 7.26 (AA'BB', 4H, Tol), 6.62 (dd, 1H, J=15.0, J=1.0, H-1); 6.43 (dd, 1H, J=15, J=3.0, H-2); 5.01 (dd, 1H, J=3.0, J=1.0, H-3); 3.30 (s, 6H, OMe); 2.41 (s, 3H, Tol). **^{13}C NMR** (50MHz, $CDCl_3$,): δ: 141.7, 139.8 (C arom.), 139.1, 132.4, 129.9 (CH arom.), 124.5 (2 CH=), 99.7 (C<u>H</u>$(OMe)_2$), 52.4, 52.3 (OMe), 21.2 (Me-Ar).

(2*Z*, R_S)-3-*p*-tolylsulfinyl-2-butenal dimethyl acetal (12Z). It was synthesized following method II from **11bA** Yield: 91%). ee >97%. $[\alpha]_D$ = -212 (c=0.4, $CHCl_3$); **^{1}H NMR** (200MHz, $CDCl_3$): δ: 7.53, 7.30 (AA'BB', 4H, Tol), 5.98 (dc, 1H, J=5.6, J=1.1, H-2); 5.62 (d, 1H, J=5.6, C<u>H</u>$(OMe)_2$); 3.45, 3.40 (2s, 6H, OMe); 2.40 (s, 3H, Tol); 1.77 (d, 3H, J=1.1, Me). **IR** (BrK): ν_{max}: 2970, 2930, 2840, 1790, 1645, 1495, 1450, 1410, 1260, 1115, 1085, 1050, 1015, 950, 865, 810 cm^{-1}.

(2*E*, R_S)-3-*p*-tolylsulfinyl-2-butenal dimethyl acetal (12E). It was synthesized following method II from **11aA** Yield: 77%. ee >97%. $[\alpha]_D$=+76 (c=1.1, $CHCl_3$); **^{1}H NMR** (200MHz, $CDCl_3$): δ: 7.50, 7.30 (AA'BB', 4H, Tol), 6.45 (dc, 1H, J=5.6, J=1.3, H-2); 5.11 (d, 1H, J=5.6, C<u>H</u>$(OMe)_2$); 3.34, 3.32 (2s, 6H, OMe); 2.40 (s, 3H, Tol); 1.71(d, 3H,J=1.3, Me). **^{13}C NMR** (50MHz, $CDCl_3$): δ: 9.6 (C-4), 21.4 (CH_3Ar), 52.3, 52.4 (2 CH_3O), 78.7 (C-3), 99.2 (C-2), 105.2 (C-1), 129.2, 129.9 (arom. CH), 137.9, 143.1 (arom. C). **IR** (BrK): ν_{max}: 3040, 3000, 2940, 2840, 1660, 1600, 1495, 1450, 1370, 1195, 1125, 1080, 1050, 965, 910, 810 cm^{-1}. **Anal.** calc. for $C_{13}H_{18}O_3S$: 61.43% C; 7.08% H; 12.61%S. Found: 61.36%C; 6.79%H; 12.16% S.

References and Notes:

[1] Vinylsulfoxides: a) as enophiles (Hiroi, K., Umemura, M.; *Tetrahedron Lett.*, **1992**, *33*, 3343), b) as dienes (Arce, E.; Carreño, M.C.; Cid, M.B. García Ruano,J.L. *J. Org. Chem.* **1994**, *59*, 3421.; Gosselin, P.; Bonfard, E.; Hayes, P; Retoux, R; Maignan, C; *Tetrahedron: Asymmetry*, **1994**, 5, 781; Aversa, M.C.; Bonaccorsi, P. Giannetto, P.; Jones, D.N.; *Tetrahedron: Asymmetry*, **1994**, 5, 805);c) as dienophiles (Alonso, I.; Carretero, J.C.; García-Ruano, J.L.; *J. Org. Chem.*, **1994**, *59*, 1499, and references cited therein); d) as dipolarophiles (Takahashi, T; Fujii, A, Sugita, J. Hagi, T.; Kitano, K; Arai, Y. Koizumi, T.; Shiro, M.; *Tetrahedron: Asymmetry*, **1991** 2, 1379).

[2] Vinylsulfoxides:a) as Michael acceptors (Posner, G. H. in *The Chemistry of Sulfones and Sulfoxides*, Patai, S.; Rappoport, Z.; Stirling, C.J.M. De.; Wiley, J.& Sons Ltd.; 1988, p. 823; Pyne, S. G.; Bloem, P.; Chapman,. S.L.; Dixon, C.E.; Griffith, R.; *J. Org. Chem.*, **1990**, 55, 1086); b) in cyclopropane synthesis (Hamdouchi, C.; *Tetrahedron Lett.*, **1992**, *33*, 1701.; Hiroi, K. Arinaga, Y.; *Tetrahedron Lett.*, **1994**, *35*, 153); c) in asymmetric radical addition (Toru, T., Watanabe, Y., Tsusaka, M.; Ueno, Y.; *J. Am., Chem. Soc.*; **1993**, *115*, 10464); d) in Marino lactonizations (Marino, J.P.; *Pure Appl. Chem.*, **1993**, *65*, 667).

[3] Solladié, G. "Synthesis of Sulfides, Sulfoxides and Sulfones". Eds. Trost, B and Fleming, I., *vol. 6*, p. 150. Pergamon Press, Oxford (1991).

[4] a) Solladié, G.; Moine, , G. *J. Am., Chem. Soc.*; **1984**, *106*, 6097. For an application in the synthesis of a sulfinyldiene: b) Arce, E.; Carreño, M.C.; Cid, M.B. García Ruano, J.L.; *Tetrahedron: Asymmetry, in press.*

[5] Mikolajczyk, M.; Midura W.; Slawomir, G.; Zatorski, A; Chefczynska, A; *J. Org. Chem.*, **1978**, *43*, 473.

[6] Tsuchihashi, G.; Mitamura, S.; Inoue, S; Ogura, K.; *Tetrahedron Lett.*, **1973**, *13*, 323.

[7] It is known that glyoxal dimethyl monoketal exist as hydrated and polymerised forms in variable extent. The described synthetic methods for this compound, for instance, acrolein diethyl acetal ozonolysis (Stetter, H.; s, K.H.; *Synthesis*, **1981**, 129) or direct synthesis from glyoxal (Sangsari, F.H.; Chastrette, F.; Chastrette, M.; Synth. Comm. **1988**, *18(2)*, 1343), failed in affording good yields.

[8] As it was described in the preparation of ethyl *(R)-p*-tolylsulfinylprop-3-enoates: Maignan, C; Guessous, A. Rouessac,F; *Tetrahedron Lett.*, **1984**, 25, 1727.

[9] García Ruano, J.L. *Phosphorus, Sulfur and Silicon*, **1993**, *74*, 233 (and references cited therein)

[10] a) Barros, D; Carreño, M.C.; García Ruano, J.L.; Maestro, M.C.; *Tetrahedron Lett.*, **1992**, *33*, 2733; b) García Ruano, J.L.; Fuerte, A.; Maestro, M.C.; *Tetrahedron: Asymmetry*, **1994**, 5, 1443.

[11] DIBAL reductions of O-protected γ–hydroxy–β–ketosulfoxides have been reported and it is remarkable the decrese of the stereoselectivity in the presence of $ZnBr_2$:a) Solladié, G.; Almario, A. ; *Tetrahedron Lett.*, **1994**, *35*, 1937; b) Solladié, G.; Almario, A.; *Tetrahedron: Asymmetry*, **1994**, *5*, 1717 ; c) Solladié, G.; Almario, A.; *Tetrahedron: Asymmetry*, **1995**, *6*, 559.

[12] Preliminary communication: García Ruano, J.L.; González-Vadillo, A.; Maestro, M.C.; Sánchez-Sancho, F.; *8th European Symposium on Organic Chemistry*. Barcelona. Spain (1993).

[13] a) Solladié, G.; Frèchou, C; Greck, C.; *J. Org. Chem.*, **1986**, *51*, 1912. b) Annunziata, R; Cinquini, M; Cozzi, F. *J. Chem. Soc. Perkin Trans. 1*, **1979**, 1687.; c) Bravo, P.; Piovosi, E.; Resnati, G.; *Synthesis.*, **1986**, 579. d) García Ruano, J.L.; Martín Castro, A.M.; Rodriguez, J. H.; *J. Org. Chem.*, **1992**, *57*, 7235.

[14] Compounds displaying the same configuration at sulfur and C-α ($\boldsymbol{R_3R_S}$ in our substrates because of the ***R*** configuration of the starting sulfoxide) exhibit a higher δ-value for methine proton and a lower δ-value for the methyl protons than those of the corresponding diastereoisomers with different configuration at the mentioned stereogenic centres ($\boldsymbol{S_3R_S}$). This behaviour is shown in the following table. See ref. 10, 13d. and Sato, T.; Otera, J.; *Synlett.*, **1995**, 365.

Significant ^{1}H-NMR data for configurational assignment of α-methyl, β-ketosulfoxides. R-CO-CH(CH_3)-SOTol

R	δ–CH (ppm) Epimer $\boldsymbol{S_3R_S}$	δ–CH (ppm) Epimer $\boldsymbol{R_3R_S}$	δ–CH_3 (ppm) Epimer $\boldsymbol{S_3R_S}$	δ–CH_3 (ppm) Epimer $\boldsymbol{R_3R_S}$	Reference
Ph	4.62	4.89	1.66	1.30	13d
Me	3.69	3.76	1.35	1.27	13d
n-Pr	3.69	3.78	1.39	1.21	13d
i-Pr	3.88	4.01	1.50	1.14	13d
t-Bu	4.02	4.22	1.66	1.07	13d
$(MeO)_2CH$	4.23 (**2a**)	4.37 (**2b**)	1.34 (**2a**)	1.20 (**2b**)	This report

[15] After finishing this part, we knew that the DIBAL and DIBAL/$ZnCl_2$ reduction of 3-*p*-tolylsulfinyl pyruvaldehyde diethylacetal (very similar to compound **1**) had been previously studied. (Hamdouchi, C. Ph. D. Thesis. Université Louis Pasteur . Strasbourg, 1990. Director: Solladié, G.). Diastereomeric excesses of 95% and 42% were respectively obtained by this author.

[16] It seems that the efficiency of the different ZnX_2 as catalysts is related to their solubility in the reaction medium, very low for zinc chloride and bromide at the low chelation temperatures required to achieve the best stereochemical results.

[17] Conformational studies of numerous β-hydroxysulfoxides (R-CHOH-CH_2-SOMe) show that both, the difference between the two vicinal coupling constants of the CH-CH_2 grouping ($\Delta^3J = {}^3J_{2,3a} - {}^3J_{2,3b}$ in our substrates) and the chemical shift difference between the two methylene protons ($\Delta\delta=\delta(H_{3a})-\delta(H_{3b})$) were lower for epimers with the same configuration at both stereogenic centres ($\boldsymbol{R_2R_S}$ in our substrates) than for epimers with different configuration ($\boldsymbol{S_2R_S}$). On the other hand, the Δ^3J values strongly decreased in the β-alkoxy sulfoxides derived from the $\boldsymbol{R_2R_S}$ epimers, whereas they are scarcely modified in those derived from the $\boldsymbol{S_2R_S}$ ones. (see: a) Brunet, E.; García Ruano, J.L.; Hoyos, M.A.; Rodriguez, J.H.; Prados, P.; Alcudia, F. *Org. Magn. Reson.*, **1983**, *21*, 643 and b) Alcudia, F; Brunet, E.; García Ruano, J.L.; Rodriguez, J.H.; Prados, P; Sánchez, F. *J. Chem. Research*, **1982**,*(S)* 284; *(M)* 2826). Significant ^{1}H-NMR parameters of compounds **3A**, **3B** (alcohols); **5A, 5B** (silyl derivatives) and **6A, 6B** (benzyl derivatives) used in configurational assignment are collected in the following table.

Compound	$^3J_{2,3a}$ (Hz)	$^3J_{2,3b}$ (Hz)	Δ^3J (Hz)	Δδ (Hz)	Configuration
3A	3.6	8.0	4.4	20	$\boldsymbol{R_2R_S}$
5A	6.0	6.6	0.6	16	$\boldsymbol{R_2R_S}$
6A	5.5	5.5	0.0	0	$\boldsymbol{R_2R_S}$
3B	2.4	9.3	6.9	32	$\boldsymbol{S_2R_S}$
5B	2.5	10.0	7.5	37	$\boldsymbol{S_2R_S}$
6B	3.0	10.2	7.2	31	$\boldsymbol{S_2R_S}$

[18] Carretero, J.C.; García Ruano, J.L.; Martinez, M.C.; Rodriguez, J.H.; Alcudia, F. *Tetrahedron*, **1985**, *41*, 2419.

[19] 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, 2121.

[20] If we assume that DIBAL become associated to sulfinyl oxygen (interchanging with ZnI_2) before an intramolecular hydride transfer, the induced configuration at hydroxylic carbon would be the opposite to that obtained by reduction on species $\mathbf{1}^x$ or $\mathbf{1}^y$ which would decrease the stereoselectivity.

[21] The use of 0.1 eq of the chiral shift reagent allowed a good separation of four methoxy signals for racemic compound (δ: 2.97; 3.01; 3.04; 3.06). In the same conditions, ^{1}H-NMR of **9** showed exclusively signals at 3.01 ppm and 3.06 ppm, assuring its enantiomeric purity. In contrast, it has been established that a loss of optical rotation occurs if (Z)-*p*-tolylsulfinylpropenoate is obtained *via* Horner-Wadsworth-Emmons reaction (see: Cardellicchio, C.; Naso, F; Scilimati, A., *Tetrahedron Letts.*, **1994**, *35*, 4635.

[22] These trimethylsilyl derivatives, failed to yield compounds **12**. Elimination reaction is precluded at low temperature (-78°C), probably as a consequence of higher steric hindrance in these α–methylated compounds in comparison with the α–unsubstituted ones. A complex mixture of compounds was obtained increasing the temperature. On the other hand attempts of benzyloxy group elimination using NaH were unsuccessful, because hydroxy group deprotection was observed in some extent.

(*Received in UK* 26 *July* 1995; *accepted* 5 *September* 1995)