Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 6, pp. 1819-1828, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00217-0

Synthesis of Enantiomerically Pure β–Hydroxy–γ–Sulfinylaldehyde Dimethyl Acetals

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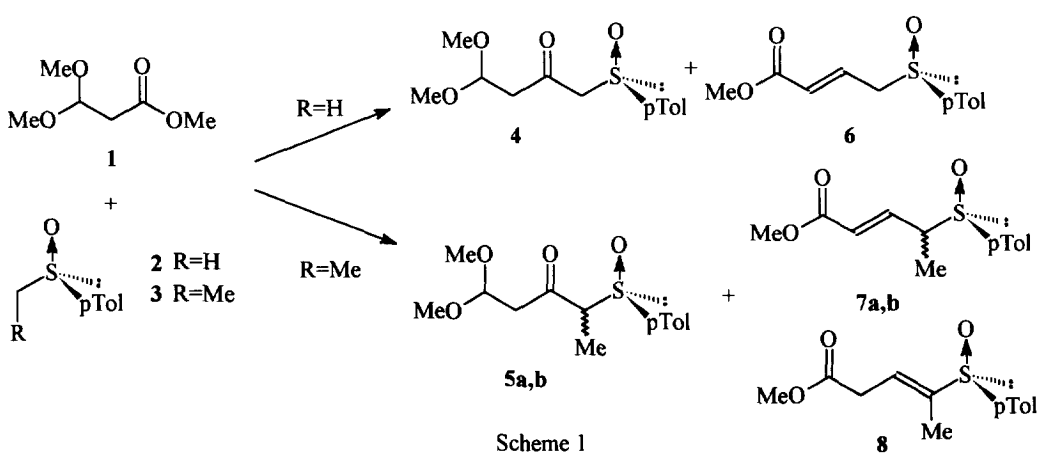
Abstract: Lithium alkyl *p*-tolylsulfinyl anions generated from **2** or **3** react with methyl 3,3-dimethoxypropanoate (**1**) yielding the corresponding β-ketosulfoxides **4** and **5** respectively. The presence of two methoxy groups in the δ–position of these β–ketosulfoxides has little or no influence on the stereoselectivity of DIBAL and DIBAL/ZnX_2 reductions, allowing the synthesis of the title acetals in high diastereoisomeric excess.

The synthesis and stereoselective reactions of β-ketosulfoxides have been one of the subject of our interest in the last years.[1] In the reductions with DIBAL and DIBAL/ZnX_2, the stereogenicity of the sulfur atom controls the hydride approach to the carbonyl group because the electrophilic character of the aluminium atom determines its association with the sulfinyl group as a previous stage of the intramolecular hydride transfer.[2] The presence of an α–alkyl substituent[3] and/or acetal moieties in γ[4]– or ε–position[5] maintains basically this behaviour but with limitations in some cases. The very recent paper of Blase et. al[6] on the reduction of β-keto-δ-dioxolane sulfoxide derived from 1-*p*-tolylsulfinyl-2,4-pentanedione prompted us to report our results on the synthesis and the reduction of *(R_S)*-3-oxo-4-*p*-tolylsulfinylbutanal and *(R_S)*-3-oxo-4-*p*-tolylsulfinyl pentanal dimethyl acetals **4** and **5** with DIBAL and DIBAL/ZnX_2. These reductions were carried out to complete our studies concerning the stereoselectivity of the reaction of α–alkylated-β–ketosulfoxides with heteroatomic functions next to the carbonyl group[3b,4,7,8] and with the aim of synthesizing homochiral β-hydroxy aldehyde derivatives, which have received considerable attention recently as chiral building blocks in the synthesis of natural products[9] and as versatile key intermediates in the synthesis of 1,3-diols[10] or homoallyl alcohols.[11]



Scheme 1

Moreover, in the case of the title compounds, the presence of an easily transformable sulfinyl moiety on the acetalated aldol structures broadens their potential synthetic applicability. The synthesis of the starting ketosulfoxides **4** and **5** was effected by the usual approach[12] (Scheme 1), consisting of the treatment of the commercially available methyl 3,3-dimethoxypropanoate **1** with the appropriate lithium anion previously generated by reaction of the enantiomerically pure alkyl *p*-tolylsulfoxide (methyl and ethyl respectively) with LDA. However, besides the expected ketosulfoxides, the condensation reactions afford the corresponding ***E***-allylsulfoxides **6**[13] and **7** (Scheme 1). The formation of the α–methylvinylsulfoxide **8**[14] is also observed in the reaction of the sulfoxide **3** (Scheme 1, Table 1).

Table 1.- Reaction of ester **1** with methyl and ethyl *p*-tolylsulfoxides **2** and **3**

Entry	Starting sulfoxide	Molar Ratio ester **1**:sulfoxide: LDA	Product Ratio
1	**2**	1 : 1 : 2	**4** : **6** (55 : 45)
2	**2**	1 : 2 : 2	**4** : **6** (96 : 4)
3	**3**	1 : 1 : 2	**5a,b** : **7a,b** : **8** (31 : 39 : 30)
4	**3**	1 : 2 : 2	**5a,b** : **7a,b** : **8** (73 : 13 : 14)
5	**3**	1 : 2 : 2*	**5a,b** : **7a,b** : **8** (95 : 2 : 3)

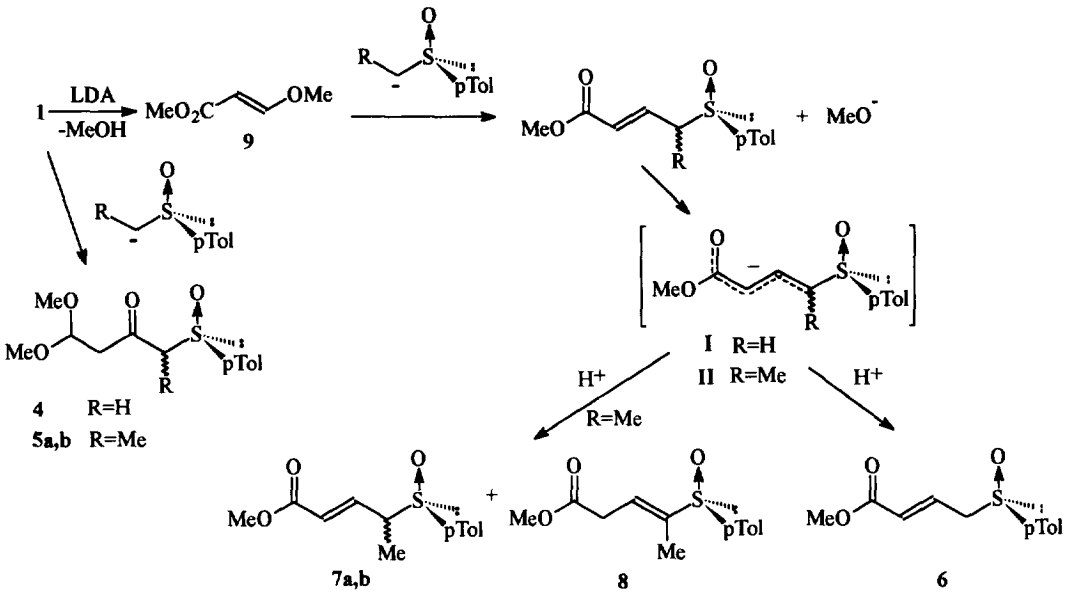
*t-BuLi is used as base instead of LDA.

A well known fact is that all these reactions require two equivalents of base because the resulting β–ketosulfoxides consume one of them. However, in the reaction conditions shown in entries 1 and 3 (1 eq. of LDA + 1 eq. of sulfinyl carbanion), the expected ketosulfoxides were obtained in a moderated or low ratio. It is also observed that the formation of the allylic sulfoxide **6** was almost precluded when the reaction was effected using 2 equivalents of the sulfinyl carbanion derived from **2** (entry 2). However, though ketosulfoxides **5a,b** were the major compounds starting from **3** in the same conditions, a significant amount of unsaturated esters **7a,b** and **8** were still obtained (entry 4). The best way to minimise the formation of the undesired products is attained using t-BuLi as base (entry 5) instead of LDA, which allows diastereoisomers **5a,b** to be obtained nearly as the sole products. Nevertheless, under these conditions, **5a,b** is obtained in less than 30% yield.

This behaviour can be explained as indicated in Scheme 2. The ester **1** reacts with the lithium derivatives obtained from sulfoxides **2** or **3** yielding the expected β–ketosulfoxides **4** or **5a,b** respectively, whereas **1** with LDA affords methyl 3-methoxyacrylate **9** (Scheme 2)[15]. Compounds **6**, **7a,b** and **8**[16] result in the attack of the sulfinylcarbanion on compound **9**. Consequently, the condensation must be performed in the absence of LDA in order to avoid the formation of the undesired products and to increase the amount of β–ketosulfoxides in the reaction mixture.

Considering the data shown in Table 1, the equilibrium between the sulfoxide **2** and the LDA must be totally shifted towards the sulfinylcarbanion because high yields of β–ketosulfoxide **4** are obtained under the indicated conditions (entry 2, Table 1). However, the lower stability of the anion derived from **3** would determine the presence of a substantial amount of LDA in the equilibrium when equimolar quantities of base and sulfoxide

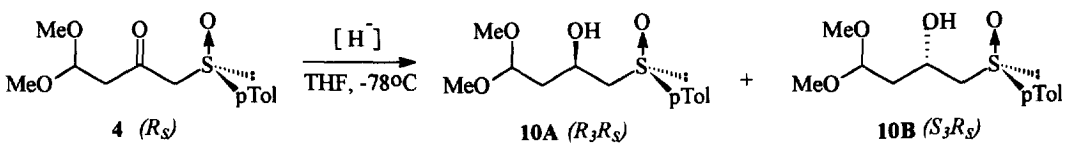
were used, which would explain the obtention of significant amounts of **7a,b** and **8** in the conditions of the entry 4 (Table 1). The use of a stronger base, such as t-BuLi (whose low nucleophilic character preclude the transformation of **1** into **9**) allows the exclusive formation of the lithium derivative of **3**, thus preventing the generation of significant amounts of the unsaturated sulfoxides **7a,b** and **8** (entry 5, Table 1).



Scheme 2

Compound **5** was obtained as a 60:40 mixture of diastereoisomers **5a**+**5b**, that was used without previous separation in the subsequent reduction reactions. The configurational assignment of **5a** and **5b** was made, as usual, comparing the ^{1}H-NMR δ values observed for their methine and methyl protons with those of other α–methyl–β–ketosulfoxides of known configuration.[17]

Compound **7** is also obtained as a mixture of two diastereoisomers **7a**+**7b**, epimers at the allylic stereogenic centre. No separation attempts were carried out on these sulfoxides. In no case, were allylic sulfoxides of ***Z*** configuration detected in the reaction mixtures. The formation of the unexpected unsaturated sulfoxides **6**[18] and **7**, is a result of a great interest, considering that stable stereogenic allyl sulfoxides[19] are valuable synthetic intermediates[20].

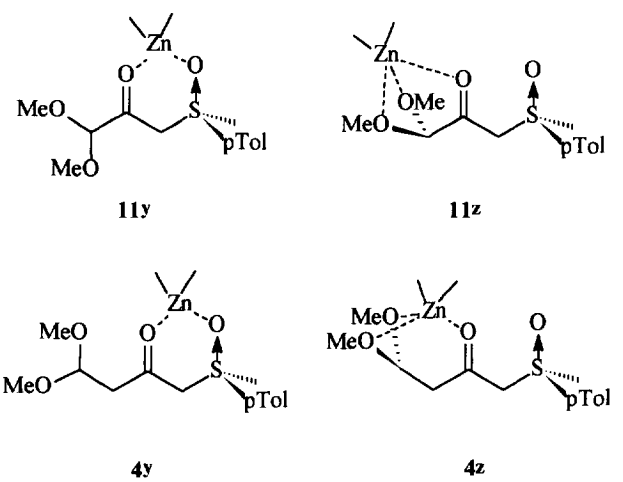


H⁻	Yield (%)	10A	10B
DIBAL/ZnI_2	84	98	2
DIBAL	80	0	100

Scheme 3

Once the Andersen reaction conditions were optimised to obtain β–ketosulfoxides **4** and **5a,b**, we accomplished their DIBAL and DIBAL/ZnX_2 reductions to obtain the corresponding hydroxy sulfinylacetals. The reactions were carried out in the same conditions that provided the highest asymmmetric induction in the reduction of the related sulfinylpyruvaldehyde dimethylacetal **11**[21]. DIBAL/ZnI_2 reduction of ketosulfoxide **4** affords the hydroxysulfoxide **10A** of ***R*** configuration at the hydroxylic carbon with a good yield (84%) and high diastereoselectivity (96% de), when 1.9 eq of the Lewis acid and 5 eq of DIBAL were used. The DIBAL reduction is even more stereoselective in the absence of ZnI_2 and the *(S₃R_S)*-3-hydroxy-4-*p*-tolylsulfinylbutanal dimethylacetal **10B** is the sole diastereoisomer obtained in a 80% yield. (Scheme 3). Acetal moiety was easily hydrolized into the free aldehyde by reaction of the corresponding benzyl derivative with pyridinium *p*-toluenesulfonate[22]

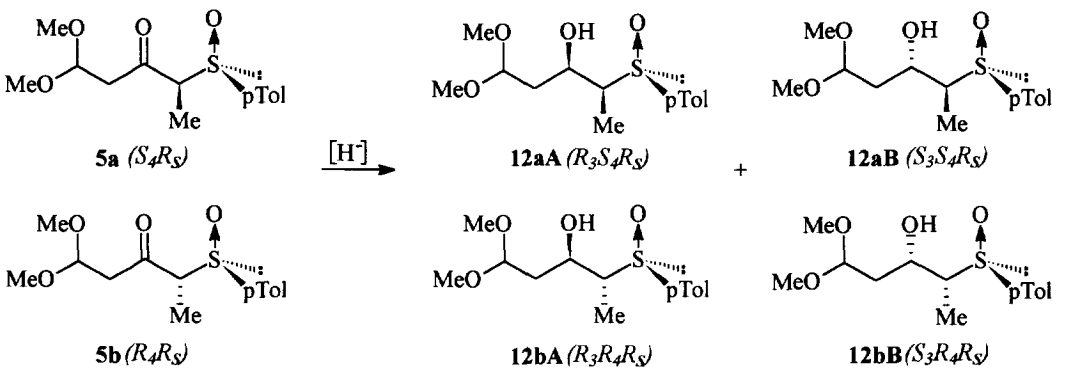
The configurational assignment of **10A** and **10B** was deduced from the relative value of the vicinal coupling constants $J_{2,3a}$ and $J_{2,3b}$. The lowest value of Δ^3J ($\Delta^3J = {}^3J_{2,3a} - {}^3J_{2,3b}$) corresponds to the epimer with the same configuration in both stereogenic centres (Δ^3J has a value of 4.7 Hz for *(R₃R_S)*-**10A** and 7.3 Hz for its epimer *(S₃R_S)*-**10B**, according to the rule previously established for many β–hydroxysulfoxides exhibiting the RCHOH-CH_2-SOR structure.[23]



Scheme 4

The high stereoselectivity observed in the DIBAL/ZnI_2 reduction of **4** (96% *de*) contrasts with the lower one obtained in the recently described reduction of the *(Rs)*-3-*p*-tolylsulfinylpyruvaldehyde dimethyl acetal **11** (84% *de*).[4] This lower stereoselectivity was explained by assuming that ZnI_2 forms a five member chelate **11z**, with the carbonyl and methoxy oxygens, which competes with the six membered one **11y**, generated by the association of the Lewis acid with the sulfinyl and carbonyl oxygens (Scheme 4). Taking into account that the stereochemical course of the DIBAL reduction of **11y** and **11z** is different, such competition determines a notable decrease in *de* unless the equilibration between **11y** and **11z** was prevented.[424] The lower stability of the **4z** chelate (six membered ring) than of the **11z** chelate (five membered ring) could explain that **4z** did not became in equilibrium with **4y**.

The reduction of the 60:40 epimers mixture of α–methyl-β–ketosulfoxides **5a**+**5b** was effected in the same conditions that for the non methylated sulfoxide **4** in order to evaluate the influence of the alkyl group on the reduction stereoselectivity. In the presence of ZnI_2 the above mixture basically yields the hydroxysulfoxides **12aA** and **12bA**, epimers at C-4, in a ratio similar to the starting mixture. This result indicates that **5a** and **5b** evolve with high stereoselectivity under these conditions, the induced configuration at the hydroxylic carbon



Ketosulfoxide	H⁻	Yield (%)	**12aA**	**12bA**	**12aB**	**12bB**	C*-OH *(R/S)*
5a (60) +**5b** (40)	DIBAL/ZnI_2	78	59	35	3	3	94/6
5a (60) +**5b** (40)	DIBAL	90	21	0	41	38	21/79

Scheme 5

being *R* in both cases. However, the presence of the methyl group at C-4 decreases significantly the stereoselectivity of the DIBAL reduction in the absence of the Lewis acid as is shown in Scheme 5. The diastereoisomer **5b** reacts stereoselectively yielding **12bB** as the sole product, whereas the epimer **5a** affords a ca. 1:2 mixture of the corresponding hydroxysulfoxides **12aA** and **12aB** (Scheme 5). This behaviour had been observed and rationalised for other α–alkyl-β–ketosulfoxides previously reported.[1,3,4]

Table 2. Coupling constants and configuration of α–methyl–β–hydroxysulfoxides **12.**

Compound N°	$^3J_{2,3}$ Hz	Relative Configuration	Starting Compound	Absolute Configuration
12aB	7.1	*anti*	**5a** *(S4RS)*	*(S3S4RS)*
12aA	3.3	*syn*	**5a** *(S4RS)*	*(R3S4RS)*
12bB	1.9	*syn*	**5b** *(R4RS)*	*(S3R4RS)*
12bA	7.8	*anti*	**5b** *(R4RS)*	*(R3R4RS)*

The relative configuration of the α–methyl-β–ketosulfoxides **12** was accomplished from the value of the vicinal coupling constants $J_{2,3}$. Taking into account the data obtained from compounds with related structure (2-hydroxy-3-methylsulfinylbutanes[25], 2-hydroxy-3-*p*-tolylsulfinylbutanal dimethyl acetals[4] and 4-hydroxy-5-*p*-tolylsulfinylhexanoic acid derivatives[3b]) it can be deduced that compounds with an *anti* relationship between the OH and Me groups (Scheme 5) have higher $^3J_{2,3}$ values than those with the *syn* stereochemistry[23]. According to

the configuration assigned to the starting β–ketosulfoxide, the above rule allows us to establish the absolute configuration of hydroxysulfoxides **12** (see Table 2). This assignment is totally consistent with that suggested by the well established mechanistic considerations.

As conclusion, the results reported in this paper indicate that two methoxy groups in a δ–position have little or no influence on their DIBAL and DIBAL/ZnI_2 reductions of β–ketosulfoxides and α–alkyl, β–ketosulfoxides, which take place according to the stereochemical course proposed for other β–ketosulfoxides without heteroatomic functions.[1,2] On the other hand, we also report the suitable conditions to obtain ketosulfoxides **4** and **5** in good yields, starting from the ester-acetal **1**.

Acknowledgements. We thank DGICYT (PB-93-0257) and Comunidad Autónoma de Madrid (AE-00144/94) for financial support. D. Barros also thanks C.A.M. for a fellowship.

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* in $CDCl_3$ solution. Optical rotations were measured 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). Diisopropylamine was 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

***(R_S)*-3-oxo-4-(*p*-tolylsulfinyl)butanal dimethyl acetal 4** .- A solution of *n*-butyllithium 2.36M in hexane (2.7 ml, 6.4 mmol) was added to a solution of diisopropylamine (0.969 ml, 6.9 mmol) in 6.4 ml of dry THF at -78°C under argon. The mixture was stirred for 30 minutes at the same temperature and then a solution of (+)-(*R*)-methyl-*p*-tolylsulfoxide **2** (900 mg, 5.8 mmol) in 22 ml of dry THF at -78°C was added. After 30 minutes, methyl 3,3-dimethoxypropanoate (394 mg, 2.66 mmol) was added without solvent. The reaction mixture was stirred at -78°C under argon until completion and a saturated solution of ammonium chloride was added at the same temperature. The salts were solved by water addition and the aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over anhydrous sodium sulphate. The solvent was evaporated in vacuo to yield a mixture 96:4 of compounds **4**:**6**. Separation by column chromatography (acetone:hexane:diethyl ether 3:8:4) affords pure ketosulfoxide **4**. $[\alpha]_D$= +178 (c=1.48, $CHCl_3$). Mp: 46.4-47 °C. Yield: 68%. **^{1}H NMR**: δ: 7.56 and 7.44 (AA'BB', 4H, Ar), 4.71 (t, 1H, J=5.4, H-1), 3.89 (AB system, 2H, J_{AB}=13,8, Δν=16.5 Hz, H-4), 3.33 (s, 3H, CH_3O), 3.32 (s, 3H, CH_3O), 2.80 (ABX system, 2H, J_{AB}=15.4, J_{AX}=5.4 and J_{BX}=5.4, Δν= 19.9 Hz, H-2), 2.42 (s, 3H, CH_3Ar). **^{13}C NMR**: δ: 198.2 (CO), 141.2, 139.1, 129.3, 123.4 (arom), 100.2 (C-1), 68.0 (C-4), 53.1 (C-2), 47.9 (2 CH_3O), 20.6 (CH_3Ar). **IR** ($CHCl_3$): ν_{max}: 2993, 2926, 1706, 1443, 1226, 1193, 1116, 1080, 1053 cm^{-1}. **MS** (EI): m/z: 270 (0.3) M^+, 239 (12), 238(10), 139 (20), 131 (100), 100 (22).**HRMS** calcd for $C_{13}H_{18}O_4S$; 270.09258. Found: 270.9320.

Methyl *(2E,R_S)*-4-*p*-tolylsulfinyl-2-butenoate 6 - A 55:45 mixture of compounds **4** and **6** respectively is obtained starting from LDA (5.46 mmol), methyl sulfoxide **2** (400 mg, 2.6 mmol) and ester **1** (443 mg, 2.99 mmol), following the above procedure. The crude was chromatographed (eluent: diethyl ether:hexane:ethyl acetate 3.5:2:1)to afford pure allylsulfoxide **6** (40 % yield). $[\alpha]_D$= +173 (c=1, CH_2Cl_2). **^{1}H-NMR:** 7.47 and

7.33 (AA'BB', 4H, arom), 6.69 (dt, J=15.6 and 8.0, 1H, H-3), 5.89 (dd, J=15.6 and 0.9, 1H, H-2), 3.73 (s, 3H, CH_3O), 3.63 (ABXY sistem, J=12.8, 8.0, 0.9 and 0.9, 2H, H-4), 2.42 (s, 3H, CH_3Ar). **^{13}C-NMR:** 165.2 (CO), 142.0, 139.0, 129.9, 124.1 (arom C), 134.5 (C-3), 128.2 (C-2), 58.9 (C-4), 51.7 (CH_3O), 21.4 (CH_3Ar). **MS** (EI, 35 eV): m/z: 238 (4) M^+, 139 (100), 123 (7), 99 (19), 91 (24), 77 (7).

A solution of *n*-butyllithium 2.42 M in hexane (0.983 ml, 2.38 mmol) was added to a solution of diisopropylamine (0.367 ml, 2.62 mmol) in 2.4 ml of dry THF at -78°C under argon. The mixture was stirred for 30 minutes at the same temperature and then a solution of (+)-(*R*)-ethyl-*p*-tolylsulfoxide (400 mg, 2.38 mmol) in 8.6 ml of dry THF at -78°C was added. After 30 minutes, methyl 3,3-dimethoxypropanoate **1** (0.176 ml, 1.2 mmol) was added without solvent. The reaction was stirred at -78°C under argon until completion and quenched by a saturated solution of ammonium chloride at the same temperature. The reaction mixture was treated as above to yield a mixture 73:13:14 of compounds **5**:**7**:**8**. Separation by column chromatography affords pure **5** as a 60: 40 (^{1}H NMR) mixture of diastereomers **5a**:**5b** (60 % yield) and a ca. 1:1 mixture of the allylsulfoxide **7** and the isomeric vinylsulfoxide **8**, being 60:40 the diastereoisomeric ratio for **7a** and **7b** respectively. Chromatographic separation of compounds **7** and **8** have not been accomplished

3-oxo-4-(*p*-tolylsulfinyl)pentanal dimethyl acetal 5a+5b .- (S_4,R_S)-5a.- ^{1}H NMR: δ: 7.51-7.30 (m, 8H, Ar), 4.68 (dd, 1H, J=5.8 and 5.0, H-1), 3.85 (c, 1H, J=7.0, H-4), 3.35 (s, 3H, CH_3O), 3.30 (s, 3H, CH_3O), 2.76 (AB of ABX, 1H, J_{AB}=15.6, J_{AX}=5.8 and J_{BX}=5.0, Δν= 29.4 Hz, H-2), 2.41 (s, 3H, CH_3Ar), 1.32 (d, 3H, J=7.0, H-5).**(R_4,R_S)-5b.- ^{1}H NMR**: δ: 7.51-7.30 (m, 8H, arom), 4.76 (dd, 1H, J=5.3 and 5.4, H-1), 3.92 (c, 1H, J=6.8, H-4), 3.35 (s, 3H, CH_3O), 3.33 (s, 3H, CH_3O), 2.85 (m, 2H, H-2), 2.41 (s, 3H, CH_3Ar), 1.20 (d, 3H, J=6.8, H-5). **^{13}C NMR 5a+5b**.- δ: 201.9, 201.8 (2 CO), 142.2, 141.9, 137.5, 137.2, 129.6, 124.8 124.5 (Ar), 101.0, 100.9 (2 C-1), 70.5, 70.4(2 C-4), 54.0, 53.3 (2 C-2), 47.7, 47.2 (4 CH_3O), 21.2 (2 CH_3Ar), 9.1, 8.4 (2 C-5). **IR** (KBr) ν_{max}: 2960, 2826, 1706, 1446, 1380, 1116, 1086, 1053, 813 cm^{-1}. . **MS** (EI, 15 eV): m/z: 284 (2) M^+, 253 (15), 252(13), 145 (100), 140 (43), 139 (51), 113 (60), 114 (82).**HRMS** Calcd for $C_{14}H_{20}O_4S$; 284.10823. Found: 284.10788.

Methyl *(2E R_S)*-4-*p*-tolylsulfinyl-2-pentenoate 7a+7b .- 7a: **^{1}H-NMR**: 7.50-7.20 (m, 8H, arom), 6.69 (dd, J=15.7 and 3.1, 1H, H-3), 5.79 (dd, J=15.7 and 1.1, 1H, H-2), 3.72 (s, 3H, CH_3O), 3.59 (m, 1H, H-4), 2.39 (s, 3H, CH_3Ar), 1.39 (d, J=7.0, 3H, H-5). **7b: ^{1}H-NMR**: 7.50-7.20 (m, 8H, arom), 6.65 (dd, J=15.6 and 3.2, 1H, H-3), 5.84 (dd, J=15.6 and 1.1, 1H, H-2), 3.73 (s, 3H, CH_3O), 3.59 (m, 1H, H-4), 2.41 (s, 3H, CH_3Ar), 1.33 (d, J=7.0, 3H, H-5).

Methyl *(2E R_S)*-4-*p*-tolylsulfinyl-3-pentenoate 8 .- ^{1}H-NMR: 7.50-7.20 (m, 4H, arom), 6.63 (tc, J=7.1 and 1.5, 1H, H-3), 3.72 (s, 3H, CH_3O), 3.25 (d, J=7.1, 2H, H-2), 2.39 (s, 3H, CH_3Ar), 1.63 (d, J=1.5, 3H, H-5). **^{13}C-NMR**: **7a+7b+8**: 169.8 165.2 (CO), 144.0, 141.5, 140.8, 140.6, 138.7, 136.8, 136.6, 129.3, 129.1, 125.7, 124.9, 124.7, 124.5, 124.3 (arom C, C-2 and C-3), 61.4, 60.7 (C-4), 51,6 ,51.1 (CH_3O), 32.9 (C-5, **8**), 20.8 (CH_3-Ar), 11.8 and 11.2 (C-5, **7a+7b**). **IR** (KBr): 3460, 1720, 1640, 1433, 1273, 1260, 1173, 1086, 1053, 816 cm^{-1}. **MS** (EI): m/z: 252 (11) M^+, 236 (3), 139 (46), 123 (31), 113 (100), 91 (65).

REDUCTION OF β-KETOSULFOXIDES

DIBAL reduction: A solution of the corresponding β-ketosulfoxide (0.14 mmol) in dry THF (0.5 ml) at -78°C was dropwise added to a solution of diisobutylaluminium hydride (DIBAL) 1M in hexane (0.56 ml, 0.56 mmol) in 5.6 ml of dry THF at the same temperature. After a reaction time of 45 minutes, 0.04 ml of methanol, 2.8 ml of ethyl acetate and 2.8 ml of saturated solution of potassium sodium tartrate were added. The mixture was

stirred for 30 minutes at room temperature, the organic layer was separated and the aqueous one was extracted with ethyl acetate. The extracts were combined, washed with brine and dried over anhydrous sodium sulphate. Finally, the solvent was removed at vacuo to yield the corresponding hydroxysulfoxides.

DIBAL /ZnI_2 reduction: A solution of the corresponding β-ketosulfoxide (0.14 mmol) in 1 ml of dry THF at -78°C was added to a solution of ZnI_2 (85 mg, 0.266 mmol) in 0.5 ml 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 (0.7 ml, 0 7 mmol) in 3.6 ml of dry THF at -78°C. Once the reaction was completed (45 minutes), 0.05 ml of methanol, 3 ml of ethyl acetate and 3.6 ml of saturated solution of potassium sodium tartrate were added. The work-up was effected as above and the residue was chromatographed (ethyl acetate:hexane 3:1) to obtain the corresponding pure hydroxysulfoxides.

(*R*$_S$,*R*$_S$)-3-hydroxy-4-(*p*-tolylsulfinyl)butanal dimethyl acetal 10A .- It was obtained by DIBAL/ZnI_2 reduction starting from β-ketosulfoxide **4** (84%, de > 95%). $[\alpha]_D$= +176 (c=2, $CHCl_3$). **^{1}H NMR**: δ: 7.56 and 7.34 (AA'BB', 4H, Ar), 4.59 (dd, 1H, J=5.7, J=5.2, H-1), 4.07 (s, 1H, OH), 4.40-4.30 (X of ABX, m, 1H, H-3), 3.38 (s, 3H, CH_3O), 3.35 (s, 3H, CH_3O), 2.93 (AB of ABX, 2H, J_{AB}=13.1, J_{AX}=8.3 and J_{BX}=3.6, Δν = 41.5Hz, H-4), 2.42 (s, 3H, CH_3), 1.87 (AB of ABXY, 2H, J_{AB}=14.1, J_{AX}=8.5, J_{BX}=5.7, J_{BY}=5.2, J_{AY}=4.1, Δν=22.2 Hz, H-2). **^{13}C NMR**: δ: 141.8, 140.3, 130.03, 124.0 (Ar), 102.7 (C-1), 65.2 (C-3), 62.9 (C-4), 53.8 (CH_3O), 53.7 (CH_3O), 39.4 (C-2), 21.3 (CH_3Ar).**IR** ($CHCl_3$) ν_{max}: 3426, 2980, 2920, 2826, 1440, 1416, 1380, 1233, 1183, 1123, 1083, 1058, 1036, 806 cm^{-1}. **MS** (EI, 15 ev): m/z: 272 (1) M^+, 255.1(13), 223 (10), 139 (41), 133 (32), 115 (100), 101 (43). **HRMS** Calcd for $C_{13}H_{20}O_4S$; 272.10823. Found: 272.10873. **Analysis** Calcd. for $C_{13}H_{20}O_4S$; C, 57.33; H, 7.41; S, 11.75. Found ; C, 57.32; H, 7.43; S, 12.26.

(*S*$_S$,*R*$_S$)-3-hydroxy-4-(*p*-tolylsulfinyl)butanal dimethyl acetal 10B .- It was obtained by DIBAL reduction starting from β-ketosulfoxide **4** (80%, de>97%). $[\alpha]_D$= +241 (c=1.17, $CHCl_3$).**^{1}H NMR**: δ: 7.53 and 7.34 (AA'BB', 4H, Ar), 4.59 (t, 1H, J=5.5, H-1), 4.50-4.30 (X of ABX, m, 1H, H-3), 3.34 (s, 3H, CH_3O), 3.31 (s, 3H, CH_3O), 2.86 (AB of ABX, 2H, J_{AB}=13.3, J_{AX}=9.7 and J_{BX}=2.4, Δν=41.9 Hz, H-4), 2.40 (s, 3H, CH_3Ar), 1.81 (AB of ABXY, 2H, J_{AB}=14.1, J_{AX}=8, J_{BX}=5.5, J_{BY}=5.5 and J_{AY}=3.9, Δν=22.9Hz, H-2). **^{13}C NMR**: δ: 141.4, 140.0, 130, 123.9 (Ar), 102.8 (C-1), 65.2 (C-3), 63.4 (C-4), 53.7 (CH_3O), 53.3 (CH_3O), 39.3 (C-2), 21.3 (CH_3Ar). **IR** ($CHCl_3$) ν_{max}: 3440, 2950, 2910, 2830, 1445, 1380, 1125, 1085, 1055, 1035, 810 cm^{-1}. **MS** (EI, 15 eV): m/z: 272 (1) M^+, 255.1(20), 223 (11), 139 (44), 133 (46), 115 (100), 101 (44). **HRMS** Calcd for $C_{13}H_{20}O_4S$; 272.10823. Found: 272.10834.

3-hydroxy-4-(*p*-tolylsulfinyl)pentanal dimethyl acetal 12 .- DIBAL reduction yielded compound **12** as a mixture of three diastereoisomers 21 (**12aA**): 41 (**12aB**): 38 (**12bB**). Global yield: 90%. DIBAL/ZnI_2 reduction afforded the four diastereoisomers of compound **12** in a ratio 59 (**12aA**): 35 (**12bA**): 3 (**12aB**): 3 (**12bB**). Global yield: 78%. Diastereomers separation have not been accomplished. **(*R*$_3$,*S*$_4$,*R*$_S$)-12aA.- ^{1}H NMR**: δ: 7.62-7.30 (m, 4H, Ar), 4.59 (t, 1H, J=5.3, H-1), 4.30 (dt, 1H, J=9.4 and 3.3, H-3), 3.39 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3O), 2.62 (cd, 1H, J=7 and 3.3, H-4), 2.41 (s, 3H, CH_3Ar), 2.10-1.70 (m, 2H, H-2), 1.07 (d, J=7.0, 3H, H-5). **^{13}C NMR** δ: 142.1, 141.1, 138.5, 129.7, 125.7, 124.2 (Ar), 103.5 (C-1), 68.9 (C-3), 63.7 (C-4), 53.9 (CH_3O), 53.6 (CH_3O), 37.0 (C-2), 21.3 (CH_3Ar), 4.4 (C-5). **(*S*$_3$,*S*$_4$,*R*$_S$)-12aB.- ^{1}H NMR**: δ: 7.61-7.27 (m, 4H, Ar), 4.53 (dd, 1H, J=6.5 and 4.8, H-1), 4.10 (td, 1H, J=7.1 and 3.3, H-3), 3.90 (s broad, 1H, OH), 3.37 (s, 3H, CH_3O), 3.28 (s, 3H, CH_3O), 2.62 (cd, 1H, J=7.1 and 7.1, H-4), 2.42 (s, 3H, CH_3Ar), 2.12-1.76 (m, 2H, H-2), 0.94 (d, 3H, J=7, H-5).**IR** ($CHCl_3$) **12aB+12bB** ν_{max}: 3400, 2905, 2820, 1480, 1440, 1370, 1115, 1075, 1050, 800 cm^{-1}. **MS** (EI, 15 eV) **12aB+12bB:** m/z: 255 (7), 196(8), 147(42), 140 (38), 139 (19), 129 (100), 115 (86). **(*R*$_3$,*R*$_4$,*R*$_S$)-12bA. ^{1}H NMR**: δ: 7.62-7.30 (m, 4H, Ar), 4.64 (t, 1H, J=5.4, H-1), 4.01

(ddd, 1H, J=9.3Hz, 7.8Hz and 2.9Hz, H-3), 3.49 (s, 3H, CH_3O), 3.39 (s, 3H, CH_3O), 3.00 (dc, 1H, J=7.8Hz and 7.0Hz, H-4), 2.41 (s, 3H, CH_3Ar), 2.10-1.70 (m, 2H, H-2), 0.94 (d, J=7.0, 3H, H-5).**^{13}C NMR**: δ: 142.1, 141.1, 138.5, 129.7, 125.7, 124.2 (Ar), 103.3 (C-1), 69.5 (C-3), 64.1 (C-4), 53.9 (CH_3O), 53.6 (CH_3O), 36.9 (C-2), 21.3 (CH_3Ar), 8.6 (C-5).**IR** ($CHCl_3$) **12aA+12bA** ν_{max}: 3450, 2930, 2840, 1450, 1370, 1120, 1080, 1050, 810 cm^{-1}. **MS** (EI, 15 eV) **12aA+12bA**: m/z: 255 (6), 196(5), 147(35), 140 (40), 139 (30), 129 (100), 115 (89). **12bB.- ^{1}H NMR**: δ: 7.61-7.27 (m, 4H, Ar), 4.67 (t, 1H, J=5.0, H-1), 4.40 (ddd, 1H, J=9.4, 3.4 and 1.9, H-3), 3.90 (s broad, 1H, OH), 3.40 (s, 3H, CH_3O), 3.32 (s 3H, CH_3O), 2.56 (cd, 1H, J=7.0 and 1.9, H-4), 2.41 (s, 3H, CH_3Ar), 2.15-1.55 (m, 2H, H-2), 1.21 (d, 3H, J=7.0, H-5).

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13. The formation of compounds with a similar structure to that of **6** must be responsible of the low yields obtained by Page in similar reactions reported in reference 6
14. E configuration is tentatively assigned to compound **8** by comparison of its ^{1}H-NMR data and those of the **E** and **Z** isomers of 3-*p*-tolylsulfinyl-2-butenal dimethyl acetal (see ref. 4).
15. We have checked that in the presence of LDA, compound **1** readily evolves into compound **9.**
16. The formation of a vinylsulfoxide (compound **8**) from dienolate **II** and not from **I** must presumably be attributed to the higher stability of a trisubstituted double bond in comparison with a disubstituted one.
17. ^{1}H-NMR data for configurational assignment of α–methyl-β–ketosulfoxides.R-CO-CH(CH_3)-SOTol

R	δ–CH (ppm) Epimer S_3R_S	δ–CH (ppm) Epimer R_3R_S	δ–CH_3 (ppm) Epimer S_3R_S	δ–CH_3 (ppm) Epimer R_3R_S	Reference
Ph	4.62	4.89	1.66	1.30	12c
Me	3.69	3.76	1.35	1.27	12c
n-Pr	3.69	3.78	1.39	1.21	12c
i-Pr	3.88	4.01	1.50	1.14	12c
t-Bu	4.02	4.22	1.66	1.07	12c
$CH(OMe)_2$	4.23	4.37	1.34	1.20	4
$CH_2CH(OMe)_2$	3.85 (**5a**)	3.92 (**5b**)	1.32 (**5a**)	1.20 (**5b**)	This report

Compounds displaying the same configuration at sulfur and C-α (R_3R_S in our substrates because of the *R* configuration of the starting sulfoxide) -named as **b** in this report- 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 (S_3R_S). This behaviour is shown in the above table. See ref. 3, 4, 12c and: Sato, T.; Otera, J.; *Synlett.*, **1995**, 365.

18. Sulfur configuration is not affected either by the condensation reaction or by prolonged storage of compound **6** in a freezer, as was confirmed by ^{1}H-NMR using Eu(tfc)$_3$ as chiral shift reagent. The use of 0.25eq of the above reagent allowed a good separation of methyl ester signals for the racemic sulfoxide (δ: 3.40 and 3.37 ppm). In the same conditions, ^{1}H-NMR of compound **6** showed the signal of the single R_S enantiomer at 3.37 ppm.
19. Usually, the preparation of optically active allyl aryl sulfoxides is complicated by its configurational instability.See: a) Bickart, P. Carson, F.V.; Jacobus, J.; Miller, E.G.; Mislow, K.; *J. Amer. Chem. Soc.*, **1968**, *90*, 4869. b): Mislow, K.; Tang, R.; *J. Amer. Chem. Soc.*, **1970**, *92*, 2100. In addition, the obtained allylsulfoxides are stable compounds presumably because sulfoxide-sulfenate rearrangement is unfavourable by the withdrawing effect of the methoxycarbonyl group.
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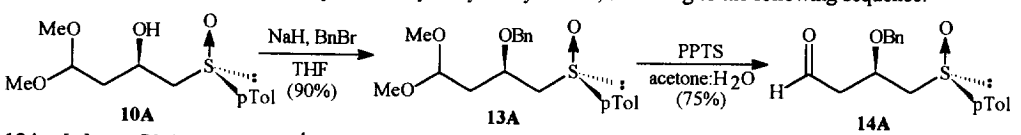
21. In reference 4 we reported that the reduction with DIBAL of the α-unsubstituted γ,γ-dimethoxy-β-ketosulfoxide is less selective when a zinc halide as chelating agent was added, than in the absence of this Lewis acid. However, the stereoselectivity increases by the use of special conditions as: inverse addition mode (addition of thesubstrate,previously chelated with the ZnX_2, on the solution of DIBAL at -78 °C), a minimum chelation period before adding the reduction agent, low chelation temperature and the use ofZnI_2 as Lewis acid. These same conditions were used to reduce compounds **4** and **5a,b**.
22. a) Sterzycki, R. *Synthesis*, **1979**, 724; b) Parrinello, G; Stille, J.K. *J. Amer. Chem. Soc.*, **1987**, *109*, 7122. We have used this procedure to obtain the O-protected hydroxyaldehyde **14A**, according to the following sequence:



10A **13A** **14A**

13A.- $[\alpha]_D$= +79 (c=1, $CHCl_3$). **^{1}H NMR**: δ: 7.46-7.29 (m, 9H, Ar), 4.55 (dd, 1H, J=6.0 and 5.3 Hz, H-1), 4.40 (s, 2H, C$\underline{H}_2$Ph), 3.9 (m, 1H, H-3), 3.29 (s, 3H, CH_3O), 3.26 (s, 3H, CH_3O), 3.07 (part AB of and $ABXM_2$ system, 2H, J_{AX}= 6.7, J_{BX}=5.0 and J_{AB}=13.4, Dn=22 Hz, H-4), 2.40 (s, 3H, CH_3Ar), 2.20-1.90 (m, 2H, H-2).**^{13}C NMR**: δ: 141.6, 141.0, 130.1, 128.5, 128.0, 127.9, 124.3 (Ar), 101.5 (C-1),71.2 (C$\underline{H}_2$-Ph) 71.1 (C-3), 62.5 (C-4), 53.1 (CH_3O), 52.8 (CH_3O), 37.4 (C-2), 21.5 (CH_3Ar)..**IR** ($CHCl_3$) n_{max}: 2930, 2840, 1450, 1370, 1120, 1080, 1050, 1010 cm^{-1}. **MS** (EI): m/z: 239 (3), 223 (4), 140 (15), 139 (21), 91 (100). **HRMS** Calcd for $C_{20}H_{26}O_4S$: 362.15518. Found: 362.15494.

14A.- $[\alpha]_D$= +109 (c=0.7, $CHCl_3$). **^{1}H NMR**: δ:9.75 (d, 1H, 7.49-7.26 (m, 9H, Ar), 4.47 (s, 2H, C$\underline{H}_2$Ph), 4.30 (m, 1H, H-3), 3.02 (part AB of and $ABXM_2$ system, 2H, J_{AX}= 5.4, J_{BX}=6.8 and J_{AB}=13.6, Dn=25 Hz, H-4), 3.20-2.90 (m, 2H, H-2), 2.40 (s, 3H, CH_3Ar). **^{13}C NMR**: δ: 199.8 (CHO), 141.8, 140.3, 137.6, 130.1, 128.5, 128.0, 127.9, 124.0 (Ar),71.5 (C$\underline{H}_2$-Ph) 69.4 (C-3), 60.7 (C-4), 48.2 (C-2), 21.4 (CH_3Ar).**IR** ($CHCl_3$) n_{max}: 2930, 1720, 1600, 1450, 1370, 1120, 1080, 1050. cm^{-1}. **MS** (EI): m/z: 208 (2), 193(7), 140(43), 139 (67), 108 (23), 107 (21), 91 (100). **HRMS** Calcd for $C_{18}H_{20}O_3S$: 316.11332. Found: 316.11282.

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(*Received in UK* 2 *April* 1996)