

Synthesis of enantiomerically pure 1,3-diols by stereoselective reduction of β-ketosulfoxides. Influence of a stereogenic hydroxylic centre at the δ-position

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Abstract: The influence of the stereogenic hydroxylic carbon at the δ -position of the carbonyl group in 1,5-bis(*p*-tolylsulfinyl)-4-hydroxy-2-pentanone 1 and 2,6-bis(*p*-tolylsulfinyl)-5-hydroxy-3-hexanones 2 on the stereochemical course of DIBALH and DIBALH/ZnBr₂ reductions has been studied. In contrast with the DIBALH reductions of β -hydroxyketones, that are monitored by the hydroxylic stereogenic carbon, the presence of the sulfinyl group determines a complete 1,3-induction of the sulfur centre. © 1997 Elsevier Science Ltd

One of the most versatile methods to obtain enantiomerically pure secondary methyl carbinols involves the reduction of the corresponding enantiomerically pure β -ketosulfoxides with DIBALH or DIBALH/ZnCl₂,¹ followed by hydrogenolysis of the carbon-sulfur bond of the resulting β hydroxysulfoxides. The scope of this methodology has been recently extended by us to the synthesis of other secondary alcohols, using α -alkyl- β -ketosulfoxides as the starting compounds.² The high stereoselectivity observed in DIBALH reduction was related to the ability of the aluminum to associate with the unshared electron pair at the sulfinylic group, previously to the intramolecular hydride attack.³ Therefore, it could be expected that the presence in the same molecule of other groups able to compete with the sulfinyl one for the association to the metal had a significant negative influence on the stereoselectivity. In order to expand the scope of the Solladie's methodology to highly functionalized substrates, the influence of different groups had to be evaluated. In this sense, several papers concerning reduction of β -ketosulfoxides bearing additional alkoxy,⁴ keto,⁵ ester,⁶ and carboxylic⁷ groups have been published, which demonstrates the predominant role of the sulfinyl group in the stereoselectivity. Nevertheless, the situation could be different with hydroxy ketosulfoxides because the hydroxy group has proved to be highly efficient in the control of the stereoselectivity of the DIBALH reductions of β -hydroxyketones and thus this reagent has become one of the most interesting choices with which to synthesize enantiomerically pure syn-1,3-diols.⁸ The great interest of these 1,3-diols (and their corresponding anti isomers)⁹ prompted us to investigate the behaviour of β -keto- δ -hydroxysulfoxides, in order to evaluate the relative influence of the OH and SO groups in the control of the stereoselectivity of DIBALH reductions. Herein we report our results on the synthesis and reduction of 1,5-bis(p-tolylsulfinyl)-4-hydroxy-2-pentanone 1 and 2,6-bis(p-tolylsulfinyl)-5-hydroxy-3-hexanone 2 with DIBALH and DIBALH/ZnBr₂¹⁰ yielding an stereochemically defined 1,3-diol moiety, with high potential synthetic applicability.

The synthesis of the starting bis-sulfinylhydroxyketones 1 and 2 (Scheme 1) was carried out by treatment of (R)-methyl (or ethyl) p-tolylsulfoxide, 3 (or 4), with LDA and further addition to the lithium salt of compound $5^{6a,11}$ by the usual experimental procedure.^{1b,12} It is well known that all these reactions require an additional equivalent of base to be consumed by the obtained β -ketosulfoxides. In this sense, the use of methyl (or ethyl) p-tolylsulfoxide lithium anion as both nucleophile and base (instead of LDA), improved the yield of ketosulfoxides 1 (from 45% to 63%) and 2 (from 29% to 60%).

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Compound 2 was obtained as a 56:44 mixture of epimers 2a and 2b at the new stereogenic center, which was used without prior separation in the subsequent reduction reactions. Configurations of 2a and 2b were tentatively assigned as indicated in Scheme 1, from the relative values of the chemical shifts (δ values) observed for their methine and methyl protons, according to the rules established for other α -methyl- β -ketosulfoxides of known configuration.^{4b,4c,12b}



Scheme 1.

The reduction of compound 1 with DIBALH in the usual conditions (THF as solvent at -78° C) took place with very high stereoselectivity (de=90%), affording anti-(R_S , S_2 , S_4 , R_S)-bis(p-tolylsulfinyl)-2,4-pentanediol **6B** in 82% yield. It was readily attained as a pure epimer by column chromatography. DIBALH reduction conducted on the substrate previously chelated with ZnBr₂ (2.4 eq) is less stereoselective, yielding a ca 83:18 diastereoisomeric mixture (80% yield) of syn and anti diols **6A** and **6B** (Scheme 2). It is noteworthy that an high excess of the reduction agent (4 eq) was necessary to complete both reactions.



Scheme 2.

The DIBALH reduction of a 56:44 epimeric mixture of compounds 2a and 2b, previously chelated with ZnBr₂ (2.4 eq) yielded a 57:43 mixture (by ¹H-NMR) of the dihydroxysulfoxides 7aA and 7bA respectively (Scheme 3, Table 1).¹³ This ratio suggests that the reduction of both epimeric ketosulfoxides is completely stereoselective using the zinc halide as the chelating agent (compounds 7aA and 7bA must derive from 2a and 2b respectively). Otherwise, the stereochemical course of these reactions^{2-4b} allows us to assign the *R* configuration to the hydroxylic center created in these reductions (Scheme 3, Table 1).

A less favourable situation was observed in the absence of zinc halide. In these conditions, only epimer 2b evolved with almost complete stereoselectivity into 7bB, whereas 2a yielded an epimeric mixture of 7aA and 7aB (Table 1). This different behaviour of 2a and 2b had been evidenced in other α -methyl- β -ketosulfoxides,^{2a,4b,4c,7} which allowed us to assign tentatively the configuration of each diastereomer, as it is indicated in Scheme 3.

The relative configurational assignment of the α -methyl- β -hydroxysulfoxides can usually be deduced from the value of their vicinal coupling constants between methinic CH-OH and CH-Me



Scheme	3.
Scheme	Э.

Table 1. Reduction of ketosulfoxide 2a and 2b with DIBALH and DIBALH/ZnBr2

Ketosulfoxide	Н	Yield (%)	7aA	7bA	7aB	7bB	C*-OH (R/S)
2a (56) +2b (44)	DIBALH/ZnBr ₂	90	57	43	0	0	100/0
2a (56) +2b (44)	DIBALH	72	15	0	40	45	15/85

protons.¹⁴ Unfortunately, diastereomers 7 exhibit a very complex spectra precluding the measure of such constants. However, from the study of the ¹H-NMR spectra of several α -methyl- β hydroxysulfoxides of known configuration (Table 2) we could deduce the following rules: (a) For **aA** and **bB** diastereomers, $\delta(CH-OH)$ values are higher and $\delta(CH-Me)$ are lower than those of their corresponding **aB** and **bA** ones; (b) $\delta(CH_3CH)$ values are higher for **aA** and **bB** than for **aB** and **bA** diastereomers. According to the above statements, we could tentatively assign the relative configurations of the different α -methylated dihydroxy bis-sulfoxides 7 (see Table 2). This assignment is totally consistent with that suggested on the basis of other DIBALH or DIBALH/ZnX₂ reductions on different α -methyl- β -ketosulfoxides.

To accomplish the unequivocal configurational assignment of bis-hydroxysulfoxides 6 and 7 it was necessary to establish unambiguously the configuration of the new hydroxylic carbon relative to the known absolute S configuration of the hydroxylic carbon in starting β -hydroxyester 5.^{6a} The ¹³C chemical shift of the acetonide methyl groups of 1,3-diols can be used as a valuable tool for the determination of the relative configuration of 1,3-diols hydroxylic carbons,¹⁵ as it has been indicated by Rychnovsky and Evans¹⁶ on the basis of *syn* and *anti* acetonides conformations. Therefore, we transformed 1,3-diols 6 and 7 into the corresponding acetonides 8 and 9 respectively by treatment with 2,2-dimethoxypropane and catalytic CSA in acetone (Scheme 4). According to the formulated rules, the ¹³C- δ values observed for acetonides 8A, 9aA, and 9bA, respectively derived from 6A, 7aA and 7bA (those obtained as major diastereomers in DIBALH/ZnBr₂ reductions), indicate that they must exhibit a *syn* stereochemistry, whereas the opposite *anti* one was deduced for acetonides 8B, 9aB and 9bB, respectively derived from 6B, 7aB, and 7bB (which are the predominant epimers in DIBALH reductions).

This result indicated that the presence of the stereogenic hydroxylic center in the starting β -ketosulfoxide has a scarce influence in the stereoselectivities of DIBALH reductions. The sulfur configuration completely controls the stereochemical course of these reductions on the non methylated substrates, which afford exclusively the corresponding *anti* diol **6B**. In the reduction of ketosulfoxide **2**, the presence of the methyl substituent determines a lower stereoselectivity when the reaction is carried out without the zinc halide,¹⁷ but again *anti* 1,3-diols **7aB** and **7bB** are the major ones. It is noteworthy that for a 1,3-induction controlled by the stereogenic hydroxylic carbon the *syn* diols were expected.^{8a} The presence of the chelating agent determines the formation of *syn* diols, as it was expected according to a complete 1,3- induction of the sulfur atom. In these conditions, the methyl subtituent does not affect the stereoselectivity, and as expected, exclusively *syn* 1,3 diols **7aA** and

Table 2. ¹H-NMR significant parameters of α -methyl- β -hydroxysulfoxides RCH_{β}(OH)CH_{α}(CH₃)SOTol



R	δΗβ				δΗα			$J_{\alpha,\beta}$ (Hz)			δ CH ₃				Ref.		
Compound	aA	bB	bA	aB	aA	bB	bA	aB	aA	bB	bA	aB	aA	bB	bA	aB	
Ме	4.56		4.22		2.54		2.87		2.5		9.1		1.34		1.28		2a
		4.34		4.07		2.54	_	2.83		1.8		8.2		1.37		1.29	
nPr	4.33		4.05		2.56		2.90		2.5		8.6		1.05		0.93	1	2a
		4.17		3.90		2.56		2.79		1.8		8.0		1.30		0.89	
iPr	3.87		3.79		2.73		2.96		2.2		9.3		0.86		0.88		2a
		3.73		3.72		2.71		2.96		1.8		8.9		1.3		0.9	
tBu	4.65		4.43		2.89		3.07		1.2		7.5		1.08		1.03		2a
		3.76		3.53		2.76		2.85		0.9		4.6		1.52		1.11	
Ph	5.53		4.86		2.78		3.05		2.7		9.1		0.94		0.68		2a
		5.32				2.69				1.7				1.27			
p-MeOPh	5.37		4.86		2.74		3.10		3.4		9.2		0.97		0.63		2a
		5.30				2.68				1.8				1.18			
CH ₂ CH(OMe) ₂	4.30		4.01		2.62		3.00		3.3		7.8		1.07		0.94		4c
		4.40		4.10		2.56		2.62		1.9		7.1		1.21		0.94	
(7)	4.37		4.50		2.66		3.05		3.5				1.03		0.87		
		4.68		4.30		2.70		2.70						1.10		0.89	



Scheme 4.

7bA are obtained. However, competitive chelation of the basic hydroxylic center leads to a lower stereoselectivity in the reduction of 1 and a 18% of the *anti* isomer 6B is obtained.

The stereochemical course of these reactions can be rationalized by assuming that the presence of the hydroxy group has scarce influence on the stereoselectivitivy of the DIBALH reduction (the observed results for 1, 2a, and 2b are practically the same to those obtained from other β -ketosulfoxides lacking of additional hydroxy groups), which is mainly controlled by the sulfur configuration.

The reaction of DIBALH with the hydroxy group of the studied ketosulfoxides would yield the alkoxydialkylalane I_1 (Scheme 5) with hydrogen evolution. These intermediates must be stabilized by association with the sulfinyl oxygen (species I_2) or with the carbonyl one (species I_3), the first one being the most stable due to its higher basicity. In both cases, the stereoselectivity of the reaction

would be determined by the intramolecular attack of a second molecule of DIBALH (an excess of the reagent is used), associated previously to the sulfinyl group, on the next carbonyl group. Therefore the DIBALH reduction of substrates 1, 2a, and 2b must exhibit identical restrictions to those observed for other previously studied β -ketosulfoxides.^{1,2} From this assumption, the almost exclusive synthesis of the *anti*-1,3-diols 6B or 7bB (from 1 and 2b, respectively) as well as the formation of a 40:15 mixture of *anti* 7aB and *syn* 7aA diols (from 2a) are both expected. The intermolecular DIBALH attack on species like I₂ (the expected pathway for β -hydroxyketones lacking of sulfinyl groups),^{8a} affording the *syn*-1,3-diols, apparently does not compete with the above intramolecular evolution



Scheme 5.

When reactions are carried out in the presence of $ZnBr_2$, the formation of chelated species like II, must be expected. The intermolecular DIBALH attack on such a species would yield the *syn*-1,3-diols **6A** (from 1), **7aA**, and **7bA** (both from the mixture **2a** and **2b**).

This situation could be complicated by the DIBALH reaction with the OH group, forming the species III₁ able to evolve, by shifting of $ZnBr_2$, into III₂ and III₃. The stereochemical course of the DIBALH reduction of the species III₃ must be identical to that of II, whereas III₂ could evolve into the anti-1,3 diol (previous shifting by DIBALH of the $ZnBr_2$ joined to the sulfinyl group) and thus decreasing the stereoselectivity (Scheme 6). This fact could explain the behaviour of compound 1 affording a 83:18 mixture of 6A and 6B, syn-1,3-diol being the major one. The almost complete stereoselectivity observed in reduction of 2a and 2b is intriguing and it could be related to the influence of the methyl group at C- α on the stability of the TS involved in the intramolecular hydride transfer.

In summary, the influence of the stereogenic hydroxylic carbon at δ -position on the stereochemical course of the β -ketosulfoxide reduction is scarce or non-existant in the DIBALH reductions. We obtain even better results than when using certain substrates lacking this basic center. The ability of the hydroxy moiety to coordinate with the electrophilic aluminum hydride, merely determines the need of using an excess of the reagent. It seems that only DIBALH molecules associated to the sulfinyl group, are efficiently converted into a nucleophilic hydride, able to give the intramolecular hydride transfer postulated for other β -ketosulfoxides.

Experimental

Diastereoisomeric ratios were established by integration of well separated signals of the diastereoisomers in the crude reaction mixtures. NMR spectra were recorded on a *Brucker WP-200-SY* instrument in CDCl₃ solutions. Optical rotations were measured on a *Perkin–Elmer 241-MC* polarimeter. Mass spectra were obtained in the electron impact mode (EI) at 70 eV unless stated otherwise. IR spectra were obtained in a Philips PU-9716 in CHCl₃ solutions. All reactions were monitored by TLC, that was performed on precoated sheets of silica gel 60 (F_{254}), and flash chromatography was effected with silica gel 60 (230–400 mesh). The apparatus for inert atmosphere experiments were



Scheme 6.

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 was distilled from potassium hydroxide.

Synthesis of β -ketosulfoxides

General procedure

A solution of *n*-butyllithium 2.38 M in hexane (0.546 ml, 1.3 mmol, 2.2 eq) was added to a solution of diisopropylamine (0.198 ml, 1.42 mmol, 2.4 eq) in 1.3 ml of dry THF at -78° C under argon. The mixture was stirred for 30 min at the same temperature and then a solution of the corresponding (+)-(*R*)-alkyl-*p*-tolylsulfoxide in 2.9 ml of dry THF at -78° C was added. It was stirred for 30 min at the same temperature. Another solution of *n*-butyllithium 2.38 M in hexane (0.273 ml, 0.65 mmol, 1.1 eq) was added to a solution of diisopropylamine (0.099 ml, 0.71 mmol, 1.2 eq) in 0.7 ml of dry THF at -78° C under argon. The mixture was stirred for 30 min at the same temperature and then a solution of hydroxysulfoxide (151 mg, 0.59 mmol, 1.0 eq) in 1.5 ml of dry THF at -78° C was added. This solution was immediately added dropwise to the solution of (*R*)-alkyl-*p*-tolylsulfoxide anion. The reaction was stirred overnight at -78° C under argon. A saturated solution of ammonium chloride was then added. The mixture was acidified to pH 3–4 with H₂SO₄ 5%, 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 anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to yield the crude product.

(R_S,S₄,R_S)-1,5-Bis(p-tolylsulfinyl)-4-hydroxy-2-pentanone 1

It was prepared following the general procedure from methyl 3-hydroxy-4-*p*-tolylsulfinylpentanoate and (+)-(*R*)-methyl-*p*-tolylsulfoxide (1.18 mmol, 2 eq). The crude product was purified by flash chromatography (acetone/hexane 2/3) to yield compound 1 (63%). $[\alpha]_D$ =+296 (c=1, CHCl₃). mp 134–135°C. ¹H-NMR δ : 2.41 (s, 3H, CH₃Ar), 2.42 (s, 3H, CH₃Ar), 2.73 (AB of ABX, 2H, J_{AB}=17 Hz, J_{AX}=7.3 Hz, J_{BX}=4.8 Hz, $\Delta \nu$ =26 Hz, H-5), 2.82 (AB of ABX, 2H, J_{AB}=13.3 Hz, J_{AX}=9.7 Hz J_{BX}=2.7 Hz, $\Delta \nu$ =53 Hz, H-3), 3.86 (s, 2H, H-1), 4.46 (s broad, 1H, OH), 4.59 (X of ABX, m, 1H, H-4), 7.50–7.20 (AA'BB', 8H, Tol). ¹³C-NMR δ : 21.3 (CH₃Ar), 51.0 (C-3), 62.1 (C-5), 62.7 (C-4), 68.0 (C-1), 142.2, 141.5, 139.5, 139.0, 130.0, 124.0, 123.8 (arom 8 C), 200.4 (CO). IR ν_{max} : 3346, 2980, 2913, 1705, 1593, 1490, 1086, 1036 cm⁻¹.

2,6-Bis(p-tolylsulfinyl)-5-hydroxy-3-hexanone 2a and 2b

It was prepared following the general procedure from methyl 3-hydroxy-4-*p*-tolylsulfinylpentanoate and (+)-(R)-ethyl-*p*-tolylsulfoxide (1.3 mmol, 2.2 eq) as a mixture 56:44 (¹H-NMR) of diastereomers 2a and 2b. The crude was purified by flash chromatography (diethyl ether/acetone 2/1). Yield: 60%.

 $(R_{S}, S_{2}, S_{5}, R_{S})$ -2a ¹H-NMR δ : 1.26 (d, 3H, J=7.0 Hz, H-1), 2.40 (s, 3H, CH₃Ar), 2.42 (s, 3H, CH₃Ar), 3.05–2.50 (m, 4H, H-4 and H-6), 3.84 (c, 1H, J=7.0 Hz, H-2), 4.50 (s, 1H, OH), 4.60–4.55 (m, 1H, H-5), 7.50–7.30 (m, 16H, Tol). ¹³C-NMR δ : 8.3 (C-1), 21.1 (CH₃Ar), 50.1 (C-4), 62.4 (C-6), 70.0 (C-5 and C-2), 142.0, 141.3, 136.9, 129.7, 129.6, 124.8, 124.4, 123.6 (arom), 203.3 (CO).

 $(R_{S},R_{2},S_{5},R_{S})$ -2b¹H-NMR δ : 1.24 (d, 3H, J=7.0 Hz, H-1), 2.40 (s, 3H, CH₃Ar), 2.42 (s, 3H, CH₃Ar), 3.05–2.50 (m, 4H, H-6 and H-4), 3.86 (c, 1H, J=7.0 Hz, H-2), 4.30 (s, 1H, OH), 4.60–4.55 (m, 1H, H-5), 7.50–7.30 (m, 16H, Tol). ¹³C-NMR δ : 9.5 (C-1), 21.1 (CH₃Ar), 50.1 (C-4), 62.4 (C-6), 70.0 (C-5 and C-2), 142.0, 141.3, 136.9, 129.7, 129.6, 124.8, 124.4, 123.6 (arom), 203.7 (CO). **IR** ν max: 3346, 2950, 2920, 1710, 1610, 1505, 1445, 1395, 1370, 1300, 1080, 1040, 1010, 805 cm⁻¹.

Reduction of β -ketosulfoxides

DIBALH reduction

To a solution of the corresponding β -ketosulfoxide (0.375 mmol, 1 eq) in dry THF (9.5 ml) at -78° C, diisobutylaluminium hydride (DIBALH) 1M in hexane (1.5 ml, 1.5 mmol, 4 eq) was added. After 1 h the reaction was shown to be completed and the excess of DIBALH was decomposed with 1.2 ml of methanol. The solvents were removed *in vacuo* and the residue was dissolved with H₂SO₄ 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.

DIBALH/ZnBr₂ reduction

A solution of the corresponding β -ketosulfoxide (0.13 mmol, 1 eq) in dry THF (2 ml) at rt was added to a solution of ZnBr₂ (71.4 mg, 0.32 mmol, 2.4 eq) in dry THF (1 ml) under argon. The mixture was stirred for 2 h. After that, the solution was cooled at -78° C and a solution of DIBALH 1M in hexane (0.53 ml, 0.53 mmol, 4 eq) was dropwise added. The reaction was stirred till completion at the same temperature (*ca.* 1h) and the excess of DIBALH was decomposed with 0.45 ml of methanol. The solvents were removed *in vacuo* and the residue was disolved with H₂SO₄ 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.

(R_S, R₂, S₄, R_S)1,5-Bis(p-tolylsulfinyl)-2,4-pentanediol 6A

It was obtained by DIBALH/ZnBr₂ reduction starting from β-ketosulfoxide 1 (80%, de 65%). [α]_D=+406 (c=1.7, CHCl₃). MS (EI): m/z: 380 (0.4), 241 (9), 223 (3), 139 (100), 123 (34), 91 (70). HRMS: Calcd for C₁₉H₂₄O₄S₂: 380,1110. Found: 380.1105. ¹H-NMR (300 MHz, CDCl₃): δ: 1.79 (AB of ABXY, 2H, J_{AB}=14.2 Hz, J_{AX}=8.9 Hz, J_{BX}=8.9 Hz, J_{AY}=3.4 Hz and J_{BY}=3.4 Hz, $\Delta\nu$ =45.0 Hz, H-3), 2.39 (s, 3H, CH₃Ar), 2.40 (s, 3H, CH₃Ar), 2.90 (AB of ABX, 2H, J_{AB}=13.4 Hz, J_{AX}=10.5 Hz and J_{BX}=3.8 Hz, $\Delta\nu$ =64.4 Hz, H-1), 2.88 (AB of ABX, 2H, J_{AB}=13.2 Hz, J_{AX}=7.8 Hz, J_{BX}=2.2 Hz, $\Delta\nu$ =87.6 Hz, H-5), 4.50–4.39 (X of the two ABX systems, m, 2H, H-3), 7.50 and 7.30 (AA'BB', 4H, Tol), 7.51 and 7.32 (AA'BB', 4H, Tol). ¹³C-NMR δ: 21.3 (CH₃Ar), 42.3 (C-3), 62.6, 63.1 (C-1, C-5), 65.5, 67.3 (C-2, C-4), 141.8, 141.6, 141.5, 139.9, 139.3, 130.0, 124.0, 123.9 (8 C arom). IR ν_{max} : 3360, 2906, 2226, 1593, 1490, 1423, 1303, 1083, 1033, 1006, 806 cm⁻¹.

(R_S, S₂, S₄, R_S) 1,5-Bis(p-tolylsulfinyl)-2,4-pentanediol 6B

It was obtained by DIBALH reduction starting from β -ketosulfoxide 1. The crude product was chromatographed (acetone/diethyl ether 3/1) to yield compound **6B** (82%, de 90%). [α]_D=+332 (c=1,

CHCl₃). Mp 127–128°C. MS (EI): m/z: 380 (1), 241 (10), 223 (3), 139 (100), 123 (51), 105 (7), 91 (82), 77 (21). HRMS: Calcd for $C_{19}H_{24}O_4S_2$: 380.1110. Found: 380.1121. ¹H-NMR δ : 1.68–1.62 (m, 2H, H-3), 2.40 (s, 6H, CH₃Ar), 3.10–2.70 (m, 4H, H-2 and H-5), 4.60 (s br, 2H, H-2 and H-4), 5.30 (s br, 2H, OH), 7.54 and 7.32 (AA'BB' systems, 8H, Tol). ¹³C-NMR δ : 21.2 (CH₃Ar), 43.5 (C-3), 62.2 (C-2 and C-4), 65.1 (C-1 and C-5), 141.3, 140.0, 129.9, 123.8 (8 C arom). IR ν_{max} : 3366, 2890, 1493, 1303, 1233, 1086, 1033, 1010, 806 cm⁻¹.

2,6-Bis(p-tolylsulfinyl)-3,5-hexanediol 7

DIBALH reduction of β -ketosulfoxide 2 afforded compound 7 as a mixture of diastereomers 15 **7aA**: 40 **7aB**: 45 **7bB**. that was purified by flash chromatography (diethyl ether/acetone, 2/1). Global yield: 72%. The diastereoisomeric mixture, obtained by DIBALH/ZnBr₂, 57 **7aA**: 43 **7bA**, was chromatographed (acetone/diethyl ether, 3/1) to yield pure diastereomers. Overall yield: 90%. The diastereomers could not be separated by flash chromatography.

 $(R_S, R_2, S_3, S_5, R_S)$ -7bB ¹H-NMR. δ : 1.10 (d, 3H, J=7.0 Hz, H-1), 1.85–1.40 (m, 2H, H-4), 2.41 (s, 3H, CH₃Ar), 2.76–2.65 (m, 1H, H-2), 2.91 (X of ABX, 2H, J_{AB}=13.2 Hz, J_{AX}=9.8 Hz, J_{BX}=2.7 Hz, Δv =28.7 Hz, H-6), 4.60–4.48 (m, 1H, H-5), 4.75–4.60 (m, 1H, H-3), 7.59–7.30 (AA'BB' systems, m, 8H, Tol).

 $(R_{S}, S_{2}, S_{3}, S_{5}, R_{S})$ -**7aB**¹H-NMR. δ : 0.89 (d, 3H, J=6.8 Hz, H-1), 1.85–1.40 (m, 2H, H-4), 2.41 (s, 3H, CH₃Ar), 2.76–2.65 (m, 1H, H-2), 2.91 (X of ABX, 2H, J_{AB}=13.2 Hz, J_{AX}=9.8 Hz and J_{BX}=2.7 Hz, Δv =28.7 Hz, H-6), 4.38–4.22 (m, 1H, H-3), 4.60–4.48 (m, 1H, H-5), 7.59–7.30 (AA'BB' systems, m, 8H, Tol). IR v_{max} : 3370, 2920, 1085, 1045, 1010 cm⁻¹.

(R_S , S_2 , R_3 , S_5 , R_S)-**7aA** ¹H-NMR. δ: 1.03 (d, 3H, J=7.0 Hz, H-1), 1.60–2.00 (m, 2H, H-4), 2.39 (s, 3H, CH₃Ar), 2.41 (s, 3H, CH₃Ar), 2.66 (cd, 1H, J=7.0 Hz, 3.5 Hz, H-2), 2.90 (AB of ABX, 2H, J_{AB}=13.5 Hz, J_{AX}=9.7 Hz and J_{BX}=2.2 Hz, $\Delta \nu$ =78.3 Hz, H-6), 4.37 (ddd, 1H, J=9.5 Hz, 3.5 Hz and 3.5 Hz, H-3), 4.60–4.40 (X of ABX, m, 1H, H-5), 7.65–7.30 (m, 8H, Tol). ¹³C-NMR δ: 4.6 (C-1), 21.4 (CH₃Ar), 39.8 (C-4), 63.9 (C-6), 64.0 (C-2), 66.9 (CHOH), 71.8 (CHOH), 141.7, 141.1, 139.1, 138.0, 130.1, 129.9, 129.7, 128.7, 127.9, 125.7, 124.9, 124.2, 123.9 (arom C).

(R_5 , R_2 , R_3 , S_5 , R_5)-**7bA** ¹H-NMR. δ : 0.87 (d, 3H, J=7.1 Hz, H-1), 1.60–2.00 (m, 2H, H-4), 2.39 (s, 3H, CH₃Ar), 2.41 (s, 3H, CH₃Ar), 3.20–2.70 (m, 2H, H-6), 3.10–3.00 (m, 1H, H-2), 4.20–4.00 (m, 1H, H-5), 4.60–4.40 (m, 1H, H-3), 7.65–7.30 (m, 8H, arom). ¹³C-NMR δ : 8.8 (C-1), 21.4 (CH₃Ar), 39.5 (C-4), 61.9 (C-6), 66.1 (C-2), 66.6 (CHOH), 72.5 (CHOH), 141.7, 141.1, 139.1, 138.0, 130.1, 129.9, 129.7, 128.7, 127.9, 125.7, 124.9, 124.2, 123.9 (arom C). MS **7aA** and **7bA** (EI): m/z: 255 (13), 139 (100), 124 (31), 91 (98), 77(25). IR **7aA** and **7bA** (CHCl₃ sol): ν_{max} : 3350, 2920, 1087, 1035, 1010, 810 cm⁻¹.

Synthesis of 1,3-acetonides

General procedure: To a solution of corresponding dihydroxysulfoxide (0.1 mmol, 1 eq) in 1ml of acetone were added 2,2-dimethoxypropane (5 mmol, 50 eq) and catalytic CSA (2mg) at rt. The mixture was stirred for 30 min and an aqueous NaHCO₃ 15% solution was added. The aqueous layer was extracted with diethyl ether 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*.

(R_S,R₂,S₄,R_S)-1,5-Bis(p-tolylsulfinyl)-2,4-O-isopropyliden-2,4-pentanediol 8A

It was prepared following the general procedure from **6A**. Yield: 90%. ¹H-NMR δ : 1.38 (s, 3H, CH₃C), 1.42 (s, 3H, CH₃C), 1.40–1.65 (m, 2H, H-3), 2.41 (s, 3H, CH₃Ar), 2.42 (s, 3H, CH₃Ar), 2.74 (d, 2H, J=6.3 Hz, CH₂CHO), 2.90 (AB of ABX, 2H, J_{AB}=13.0 Hz, J_{AX}=6.8 Hz, J_{BX}=4.0 Hz, $\Delta\nu$ =71.6 Hz, CH₂CHO), 4.14–4.00 (m, 1H, CHO), 4.57–4.36 (m, 1H, CHO), 7.52, 7.51, 7.32, 7.31 (AA'BB', 8H, arom). ¹³C-NMR δ : 19.7 (CH₃C), 21.4 (CH₃Ar), 29.7 (CH₃C), 35.6 (C-3), 63.3, 62.7 (C-1, C-5), 64.5, 64.2 (C-2, C-4), 99.7 (C(CH₃)₂), 141.5, 130.0, 124.4, 123.7 (arom C). **IR** (CHCl₃) ν_{max} : 3390, 2910, 1600, 1490, 1380, 1265, 1160, 1085, 1035, 1015, 810 cm⁻¹.

(R_S,S₂,S₄,R_S)-1,5-Bis(p-tolylsulfinyl)-2,4-O-isopropyliden-2,4-pentanediol 8B

It was prepared following the general procedure from **6B**. The crude product was purified by flash chromatography (ethyl acetate/hexane 3/1). Yield: 40%. ¹H-NMR δ : 1.53 (s, 6H, CH₃C), 1.72 (dd, 2H, J=7.8 Hz and 7.8 Hz, H-3), 2.41 (s, 6H, CH₃Ar), 2.80 (d, 4H, J=6.3 Hz, H-1, H-5), 4.40–4.60 (m, 2H, H-2, H-4), 7.54 and 7.32 (AA'BB', 8H, arom). ¹³C-NMR δ : 21.3 (CH₃Ar), 24.5 ((CH₃)₂C), 36.9 (C-3), 61.0 (C-2, C-4), 63.8 (C-1, C-5), 101.9 (C(CH₃)₂), 141.4, 141.2, 129.9, 123.7 (C arom).

(R_S,S_2,R_3,S_5,R_S) and $(R_S,R_2,R_3,S_5,R_S)-2,6$ -Bis(p-tolylsulfilnyl)-3,5-O-isopropyliden-3,5-hexanediol **9aA** and **9bA**

They were prepared following the general procedure from a mixture 60:40 of 7aA and 7bA. By ¹H-NMR two diastereomers (9aA and 9bA) in proportion 55:45 were observed. The crude product was chromatographed (ethyl acetate/hexane 3/1). Yield: 60%.

 $(R_{S},R_{2},R_{3},S_{5},R_{S})$ -**9bA** 1^H-NMR. δ : 0.98 (d, 3H, J=7.2 Hz, H-1), 1.45 (s, 3H, CH₃C), 1.49 (s, 3H, CH₃C), 1.70–1.50 (m, 2H, H-4), 2,41 (s, 3H, CH₃Ar), 2.42 (s, 3H, CH₃Ar), 2.81–2.74 (m, 2H, H-6), 3.06 (cd, 1H, J=7.2 Hz and 7.2 Hz, H-2), 3.83 (ddd, 1H, J=10.6 Hz, 7.2 Hz and 3.2 Hz, H-3), 4.54–4.34 (m, 1H, H-5), 7.55–7.28 (AA'BB', m, 8H, arom).

 $(R_5, S_2, R_3, S_5, R_5)$ -**9a**A ¹H-NMR. δ : 1.13 (d, 3H, J=7.0 Hz, H-1), 1.44 (s, 3H, CH₃C), 1.49 (s, 3H, CH₃C), 1.72–1.51 (m, 2H, H-4), 2.41 (s, 6H, CH₃Ar), 2.6 (cd, 1H, J=7.0 Hz and 5.2 Hz, H-2), 2.81–2.78 (m, 2H, H-6), 4.14–4.00 (m, 1H, H-3), 4.53–4.40 (m, 1H, H-5), 7.55–7.28 (AA'BB', m, 8H, aroma). ¹³C-NMR (50 MHz, CDCl₃) **9a**A and **9b**A δ : 6.3, 5.8 (C-1), 20.0, 19.8 (CH₃C), 21.6 (CH₃Ar), 29.3, 29.6 (CH₃C), 32.2, 33.4 (C-4), 63.2, 63.4, 64.5, 64.8 (C-6 and C-2), 68.5, 68.6 (C-5, C-3), 99.3, 99.6 (C(CH₃)₂), 141.5, 141.1, 129.9, 129.6, 129.4, 125.7, 124.6, 123.7 (arom C). MS (EI) **9a**A and **9b**A: m/z: 434 (M⁺), 419, 404, 295, 203, 139, 123, 91. HRMS: Calcd for C₂₃H₃₀O₄S₂: 434.1585. Found: 434.1579.

 (R_S,S_2,S_3,S_5,R_S) and $(R_S,R_2,S_3S_5,R_S)-2,6$ -Bis(p-tolylsulfinyl)-3,5-O-isopropyliden-3,5-hexanediol **9aB** and **9bB**

They were prepared following the general procedure from a mixture 53:47 of **7aB** and **7bB**. By ¹H-NMR was observed two diastereomers **9aB** and **9bB** in proportion 52:48. The two diastereomers could be separated by flash chromatography (ethyl acetate/hexane 3/1). Yield: 100%.

 $(R_{s}, S_{2}, S_{3}, S_{5}, R_{s})$ -**9aB** ¹H-NMR. δ : 0.83 (d, 3H, J=6.9 Hz, H-1), 1.52 (s, 3H, CH₃C), 1.54 (s, 3H, CH₃C), 1.76 (dd, 2H, J=7.0 Hz and 2.4 Hz, H-4), 2.41 (s, 6H, CH₃Ar), 2.56 (dc, 1H, J=9.8 Hz and 6.9 Hz, H-2), 2.80–2.84 (m, 2H, H-6), 4.10–4.24 (m, 1H, H-3), 4.45–4.59 (m, 1H, H-5), 7.26–7.56 (AA'BB', m, 8H, arom).

 $(R_{S},R_{2},S_{3},S_{5},R_{5})$ -**9bB** ¹H-NMR. δ : 0.93 (d, 2H, J=7.0 Hz, H-1), 1.50 (s, 3H, CH₃C), 1.51 (s, 3H, CH₃C), 1.76 (AB of ABXY, 2H, J_{AB}=12.6 Hz, J_{AX}=10.1 Hz, J_{AY}=9.5 Hz, J_{BX}=5.9 Hz, J_{BY}=6.8 Hz, H-4), 2.41 (s, 3H, CH₃Ar), 2.59 (cd, 1H, J=7.0 Hz and 2.4 Hz, H-2), 2.83–2.79 (m, 2H, H-6), 4.39–4.53 (m, 1H, H-5), 4.71 (ddd, 1H, J=9.5Hz, 6.8 Hz and 2.4 Hz, H-3), 7.29–7.59 (AA'BB', m, 8H, arom). ¹³C-NMR δ : 4.3, 7.2 (C-1), 21.5 (CH₃Ar), 24.6, 24.5, 24.4, 24.2 (CH₃C), 34.4 (C-4), 36.4 (C-4), 64.0 (C-6), 65.9, 64.9, 63.9, 62.2, 61.5, 61.2 (C-2, C-3, C-5), 102.1, 101.8 (C(CH₃)₂), 142.2, 141.5, 141.3, 140.6, 139.9, 138.9, 130.1, 129.8, 129.7, 125.6, 124.1, 123.7 (arom C).

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- 11. DIBALH reduction of methyl (*R*)-*p*-tolylsulfinyl-3-oxobutanoate yielded compound (S_3,R_S)-5 with high optical purity (de>95%). Lower stereoselectivity (78% de) was reported for DIBALH/ZnCl₂ reduction affording the corresponding (R_3,R_S)-5 epimer. See Solladié and Almario^{6a}
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- 13. We have designated as **aA** or **bB** those diastereoisomers exhibiting opposite configuration at the methylated carbon and the contiguous hydroxylic center, and as **aB** or **bA** those with the same configuration in both carbons.
- 14. See García Ruano et al.4b,c and references cited therein.
- 15. As a syn-acetonide adopts a well defined chair conformation, geminal methyls resonate at two different chemical shift values (ca 20 and ca 30 ppm). However, both methyl groups of the anti isomers resonate very close to ca 25 ppm, due to the twist-boat conformation adopted by the sixmembered heterocycle. On the other hand, acetonide quaternary carbon appears at $\delta < 100$ ppm in syn diasteromers and at $\delta > 100$ ppm in the anti ones.¹⁶ Additionally, the two carbinol carbons in anti 1,3-diols always resonate more upfield than those in syn compounds because 1,3-diols exist in an intramolecularly hydrogen-bonded form as six-membered ring derivatives (see Kiyooka et al.^{8a} and the references cited therein)
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- 17. This is the usual behaviour in C- α substituted β -ketosulfoxides.^{2a,4b,4c,7}

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